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2018 Novel Synthetic Methodology and Total Syntheses of Highly Functionalized Carbazoles and Benzo[c]cinnolines • Vijayaragavan Elumalai

Novel Synthetic Methodology and Total Syntheses of Highly Functionalized Carbazoles and Benzo[*c*]cinnolines

Vijayaragavan Elumalai

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2018

UNIVERSITY OF BERGEN

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Bergen 22-11-2017

Abstract

This dissertation discloses a project encompassing a synthetic strategies and new methods for the synthesis of some functionalized N-heterocyclic compounds. Much attention have been focused to synthesize N-heterocyclic compounds due to their interesting biological properties in medicinal chemistry. Among the various N-heterocycles, carbazole and its derivatives are frequently embedded in numerous natural products and active pharmaceutical ingredients in various drug structures. In this thesis, carbazomycin G, a carbazole alkaloid owns a special interest due to their versatile biological properties. We have developed a methodology for the synthesis of carbazomycin G through 12-steps involving several new method development for the key intermediates via Suzuki cross coupling, indium reduction and especially Pd-catalyzed intramolecular ring closing reaction to obtain the carbazole moiety.

Furthermore, we have developed a methodology to synthesize few particular N-heterocyclic compounds such as benzo[*c*]cinnoline and Boscalid® due to their attractive biological features and their applications in medicinal chemistry. Benzo[*c*]cinnoline and its derivatives are known for their various pharmacological activities and particularly anticancer property. The synthesis consists of two steps involving Suzuki cross coupling reaction followed by a redox process that leads to cyclic compound benzo[*c*]cinnoline. Another notable compound Boscalid® that is an important class of fungicide synthesized by means of three optimized steps and often applied to protect the agricultural crops. Moreover, a high rate and new reduction method based on sodium borohydride and cobalt sulfate was developed and optimized for the reduction of various reducible functional groups. The outline of the thesis including different synthetic strategies and new methodologies are summarized in graphical abstract.

Graphical Abstract

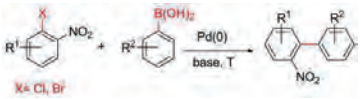
Chapter 1: Introduction

N-heterocyclic compounds are very important structural motifs widely found in numerous natural products and known as potentially active pharmaceutical ingredients (APIs). Synthetic strategies and new methodology for the synthesis of several N-heterocyclic compounds are discussed. An overview of these new methods is presented in this thesis.

Chapter 2: Statistical Experimental Design and Multivariate Modelling

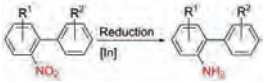
Statistical experimental design was utilized in this thesis and discussed briefly. This important technique determines the variables for method development and process optimization in synthetic organic chemistry.

Chapter 3 (Paper I): A Highly Efficient $Pd(PPh_3)_4$-Catalyzed Suzuki Cross-Coupling Method for the Preparation of 2-Nitrobiphenyls from 1-Chloro-2-nitrobenzenes and Phenylboronic Acids



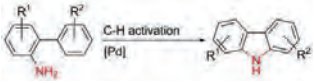
A highly efficient method for Suzuki cross coupling between congested 1-chloro-2-nitrobenzene and phenylboronic acid was developed and optimized for the synthesis of 2-nitrobiphenyl. The optimized reaction condition was developed by means of statistical experimental design and multivariate analysis. The developed method was tested with various substituted chloro and bromo nitroarenes and obtained medium to excellent yield of the corresponding 2-nitrobiphenyls.

Chapter 4 (Paper II): Indium Powder as the Reducing Agent in the Synthesis of 2-Aminobiphenyls



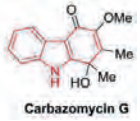
A method was developed for reduction of 2-nitrobiphenyls to 2-aminobiphenyls using In-powder as the reductant in acidic medium. The developed method was proven tolerant to various functional groups and resulted medium to excellent yields.

Chapter 5 (Paper III): Synthesis of the Carbazole Scaffold Directly from 2-Aminobiphenyl by Means of Tandem C–H Activation and C–N Bond Formation



An efficient and rapid method for the synthesis of carbazole moiety was developed and investigated using 2-aminobiphenyl.The method involves tandem Pd(II)-catalyzed intramolecular C-H activation and C-N bond formation and showed good functional group tolerance. This method was also suitable with corresponding 2-acetaminobiphenyls to obtain the N-acetyl carbazoles.

Chapter 6: Total Synthesis of Carbazomycin G



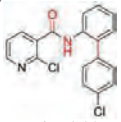
Carbazomycin G

A concise total synthesis of natural product, carbazomycin G was achieved through 12-synthetic steps. The synthesis involves several new methodologies for the synthesis of important intermediate that utilized to further to obtain the natural product.

Chapter 7 (Paper IV): A Concise Synthesis to Benzo[*c*]cinnolines via 2,2'-Dinitro-1,1'-Biphenyls Attained from a Novel Tailored Suzuki Cross-Coupling

An efficient two step synthesis leading to benzo[*c*[cinnoline scaffold was developed. The method involves the synthesis of 2,2'-nitrobiphenyls and subsequently the nitro group is partially reduced and directly cyclized into benzo[*c*]cinnoline.

Chapter 8: A novel synthesis of Boscalid®



Boscalid® is an important fungicide used commonly in the agriculture. We have developed a novel three step synthesis leading to Boscalid® compound.

Chapter 9: A High Rate and Efficient Reduction Method Based on Sodium Borohydride and Cobalt sulfate

A fast and high yielding reduction method was developed using sodium borohydride and cobalt sulfate heptahydrate. The method showed high rate and selectivity for the reduction of various functionalities.

List of Publications

Published Papers

1. **Vijayaragavan Elumalai**, Alexander H. Sandtorv and Hans-René Bjørsvik. *A Highly Efficient $Pd(PPh_3)_4$-Catalyzed Suzuki Cross-Coupling Method for the Preparation of 2-Nitrobiphenyls from 1-Chloro-2-nitrobenzenes and Phenylboronic Acids, Eur. J. Org. Chem.* **2016**, 1344-1354.

2. **Vijayaragavan Elumalai** and Hans-René Bjørsvik. *Indium powder as the reducing agent in the synthesis of 2-amino-1,1'-biphenyls. Tetrahedron Lett.* **2016**, 57, 1224-1226.

3. Hans-René Bjørsvik and **Vijayaragavan Elumalai**. *Synthesis of the Carbazole Scaffold Directly from 2-Aminobiphenyl by Means of Tandem C–H Activation and C–N Bond Formation*. *Eur. J. Org. Chem*. **2016**, 5474-5479.

4. **Vijayaragavan Elumalai** and Hans-René Bjørsvik. *A Concise Synthesis to Benzo[c]cinnolines via 2,2'-Dinitro-1,1'-Biphenyls Attained from a Novel Tailored Suzuki Cross-Coupling. ChemistrySelect*. **2017**, 2, 9387– 9390.

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Appendices

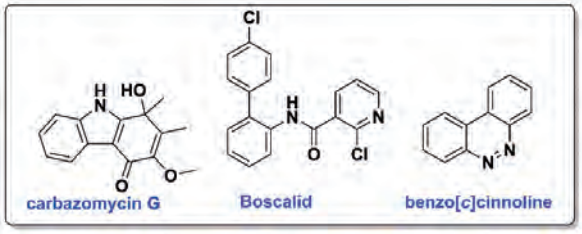
Chapter 1
Introduction

Heterocyclic chemistry is a fascinating branch and paramount importance in organic chemistry. Heterocyclic compounds played a major role in biological processes and appear as essential structural moiety in several natural products includes plant alkaloids, vitamins, carbohydrates, amino acids, nucleic acids and many natural and synthetic dyes. Typically, heterocycles possess promising structural activity for the design of new medicines.[1] Therefore, much attention have been focused in our group to synthesize functionalized N-heterocyclic compounds such as imidazole,[2] carbazole[3] and benzo[*c*]cinnoline[4] due to their promising biological properties.[5] Several research work on imidazole have been reported by our research group concerns the design and development of functionalized imidazole and imidazole backbone in particular.[6]

In this thesis, we focused mainly the synthetic strategies and new methodologies for the synthesis of functionalized carbazoles, and benzo[*c*]cinnolines. We have utilized the Pd-catalyzed Suzuki cross-coupling reactions [7] as a key step for developing the methodology towards the functionalized heterocyclic compounds. Pd-catalyzed cross-coupling reactions are powerful tools in organic chemistry to form carbon-carbon and carbon-heteroatom bonds.[8] Significant achievements in this field have been made in last decades in connection with numerous publications and patents.[9] The important class of synthetic transformation are valuable in both academia and industry for the synthesis of fine chemicals and provide key steps for building complex bioactive molecules and in total synthesis.[10] The award of 2010 Nobel Prize in chemistry was a monumental accomplishment and jointly given to Richard Heck, Ei-ichi Negishi and Akira Suzuki for their discoveries and developments in Pd-catalyzed cross coupling reactions.[11]

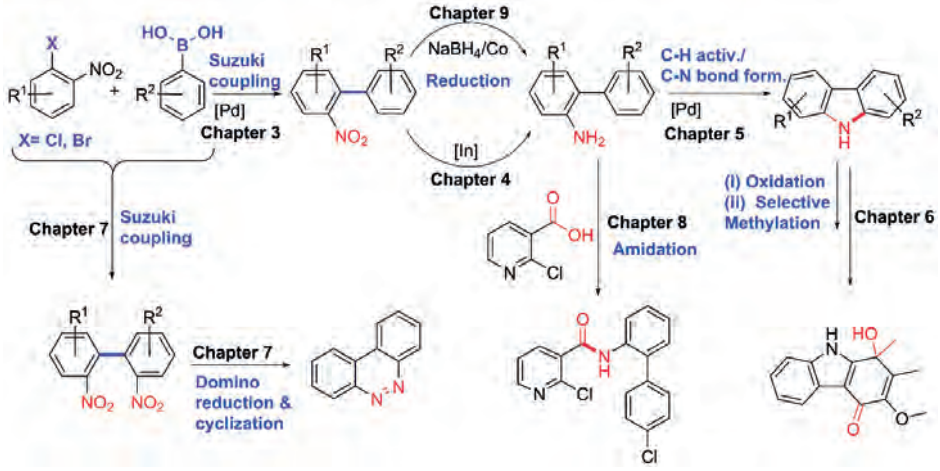
Carbazole is an important aromatic heterocyclic compound consisting dibenzo-pyrrole system. Carbazole and its derivatives are of special interest in medicinal chemistry and appears as an essential structural framework in several natural products [12] and potential active pharmaceutical ingredients (APIs) in numerous drugs such as anti-inflammatory,[13] antibacterial,[14] antifungal,[15] antiviral,[16] and anticancer.[17] My current group have developed a novel methodology by means of transition metal catalyzed C-H bond functionalization. Number of synthetic methods have been reported previously.[3] Nevertheless, This method is associated with several major shortcomings including requires protecting/auxiliary group, prolonged reaction time, and use of expensive catalysts. Moreover, lack of substrate availability and generality in intermediates synthesis. In order to address the limitations discussed, we have developed a straightforward and rapid method for the synthesis of carbazole, discussed more detail in chapter 5. The developed method is a valuable key step in various applications including several natural products, pharmaceuticals and agrochemicals. In particular, we have utilized this novel methodology for the synthesis of antibiotic carbazole alkaloid, carbazomycin G (discussed in Chapter 6), a fungicide, Boscalid® (discussed in Chapter 8) and biologically important moiety benzo[*c*]cinnoline (discussed in Chapter 7) are shown in Figure 1.1.

Figure 1.1 Biologically active important synthetic targets



Our novel methodology for the synthesis of various N-heterocyclic compounds are summarized in Scheme 1.1, illustrates the outline of my research projects in a well connecting manner.

Scheme: 1.1. Overview of the project description



Chapter 2 details the importance of statistical experimental design and its applications in synthetic organic chemistry. We have utilized this technique in Chapter 3 (**paper I)** in order to explore the important parameters in a chemical reaction.

Chapter 3 (Paper I) designates the method development for the synthesis of highly congested and substituted 2-nitrobiphenyls using Suzuki cross-coupling reaction with chloronitroarenes and phenylboronic acid. Coupling with chloroarenes using simple catalytic system is still remains challenging in organic chemistry. It is often require a bulky ligand and complex catalyst in order to facilitate the reaction. Therefore, we have investigated and optimized a method using Statistical experimental design and multivariate modelling. The developed method was suitable with number of different functionality on chloronitroarene. We also tested with various bromonitrarenes and afforded excellent yield and selectivity of the corresponding 2-Nitrobiphenyls.

Chapter 4 (Paper II) describes the method for the reduction of nitro to amino groups. In the previous chapter, we have synthesized a series of 2-nitrobiphenyls. We wanted to develop an efficient method to reduce the nitro group into corresponding amino compounds. Though numerous methods were reported to the reduction of nitro

to amino groups, we have simplified and improved a method using Indium powder as the reductant in acidic condition. The improved method afforded excellent yield of the corresponding 2-aminobiphenyls.

Chapter 5 (Paper III) illustrates the direct ring closing reaction of 2-aminobiphenyls into carbazole scaffold. The developed method involves tandem intramolecular C-H activation and C-N bond formation that leads to the cyclized product. The presented method was suitable with several of electron withdrawing and donating groups and afforded medium to excellent yield. Moreover, the method is also suitable with 2-acetaminobiphenyls to obtain the corresponding N-acetyl carbazoles.

Chapter 6 depicts the total synthesis of natural product carbazomycin G. We have developed a methodology for the synthesis of carbazomycin G using twelve synthetic steps starting from commercially available compound. We have developed novel synthetic methodology for the synthesis of several intermediates and afforded medium to good yields.

Chapter 7 (Paper IV) represents the two-step synthesis of unsymmetrically substituted benzo[c]cinnolines. The first step involves a Suzuki cross coupling reaction to synthesize a key intermediate 2,2'-dinitrobiphenyls followed by redox reaction that leads to cyclized product, benzo[*c*]cinnoline. We have developed a method that is suitable for both symmetrical and unsymmetrical substituted benzo[c]cinnolines via Suzuki cross coupling reaction based on Chapter 3.

Chapter 8 describes a method development for the synthesis of boscalid. We have optimized and investigated the synthesis of Boscalid® by in 3-steps. First step involves the 2-nitrobiphenyl via Suzuki cross coupling reaction (based on Chapter 3), followed by reduction of nitro to amino group (based on Chapter 4) and finally an amide coupling with nicotinic acid. The presented method is very rapid and highly selective and suitable for the industrial synthesis using flow chemistry.

Chapter 9 details a reduction method using stoichiometric amount of sodium borohydride and copper sulfate heptahydrate. The method is very rapid and produce hydrogen in-situ for the reduction of various functional groups in a short time. Through this method, numerous functionalities are reduced and excellent yields and selectivity were obtained.

Chapter 10 describes the summary and outlook of my thesis

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Chapter 2

Statistical Experimental Design and Multivariate Modeling

2.1 Introduction

Statistical experimental design (DoE) and optimization is a powerful technique in synthetic chemistry to identify the various types of problems in the research and industrial field. Ronald Fisher developed the statistical approach in 1958[1]. This approach is largely applied for optimizing the chemical processes in industry [2,3] and less frequently applied in academics, [4,5] is mainly due to the lack of experts to use this technique in academia. Thus, many research papers are fail to discover the substrate scope of new reactions.[6] Previously, the traditional method one factor/variable at a time (OFAT also called OVAT) [7] was often used for reaction optimization. However, the method proceeded completely via trial and error approach and difficult to identify the optimum conditions for a certain process. Moreover, OVAT method ignores the interaction between the variables or factors of the reaction.

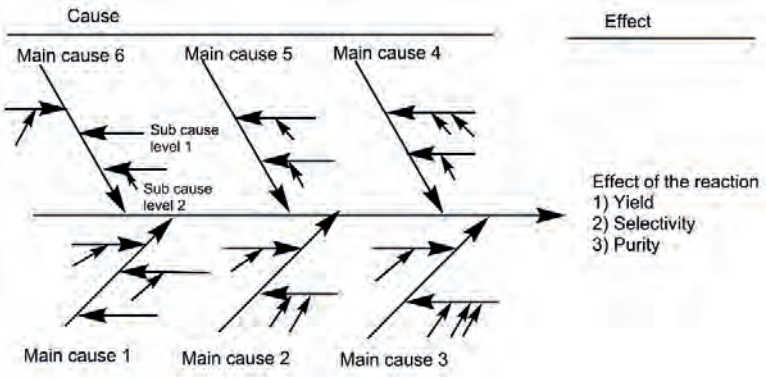
In the past decades, the application of DoE has been greatly increased to the field of process developments and optimization. This is evidenced by the number of publications related to the field.[8] In this chapter, we describes the importance of the statistical experimental design to optimize the chemical reaction that allows the variation of multiple factors and instantly monitor the reaction variables for a particular process. Furthermore, this method allows the evaluation of a large number of reaction variables with shorter number of experiments. DoE has a significant advantage to detect the interactions between the factors or variables that affect the product yield and quality. In compare with the OVAT method, DoE method is more efficient and effective to determine the highest yielding conditions. Additionally, it gives more information about the performance of the reaction with the similar or potentially reduced number of experiments than in the OVAT method.

2.2 Screening experiments and Ishikawa diagram

In synthetic organic chemistry, many factors or experimental variables that may affect the result of a reaction. A screening of the experiments are required in order to determine the variables and their interaction that might have significant effect on the result of the reaction, which is measured by using one or more responses. A pre-experimental design is necessary in order to identify a root cause to the problem of the reaction. For these reasons, a useful diagram was developed by a Japanese quality control expert, Kaoru Ishikawa that can be applied in reviewing the experimental variables. It is a simple problem analysis tool, which often-called cause and effect diagram (Figure 2.1).[9]

The diagram is useful to determine the cause and effect of the reaction and helps to identify the root cause of the problem in an easy way. Moreover, it gives better understanding of complex problems by means of visual analysis.[10] In general, Ishikawa diagrams have a box at the right hand side represents the effect of the reaction known as responses. This diagram demonstrates the experimental variables of the reaction symbolizes the horizontal line in which the stem denotes the general causes, namely bones. These bones should draw at the left hand side, which are labelled with the cause to be investigated. Each of the larger bones having smaller bones, which indicates the more specific aspects of a certain cause, and sometimes there might be third level of bones or more. When most of the probable causes are identified, it has written in the box along with the original effect.

Figure 2.1. General outline of the Ishikawa diagram



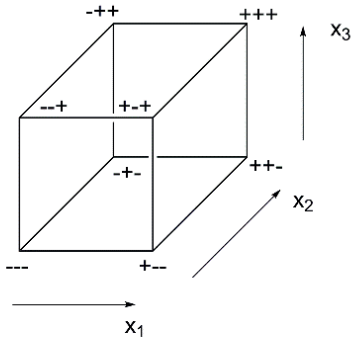
2.3 Selection of variable and design of experiments

When the experimental variables were selected to do the experimental design based on the Ishikawa diagram Figure 2.1.), it is also important that the other variables should be at a fixed level in an experimental design. The subsequent step is to choose the experimental design in order to estimate the influence of the different experiment variables on the result. There are several experimental design methods are available, and some of them are full factorial, fractional factorial, saturated design, central composite design and mixture design. The most common screening methods are full factorial or fractional factorial designs. These designs are useful to determine the linear influence of the variables and the interaction between the experimental variables, especially the variable with maximum influence can be identified. The fractional factorial design is particularly useful when there are many variables are needed to be analyzed in order to optimize the reaction and there is not much time and the raw materials available. Moreover, it reduce the number of experiments compared to the full factorial design. However, with the poor accuracy of the design, the method could able to identify the important variables and their interaction in a less time.

2.4 Factorial design

In a factorial design, the impact of all the experimental variables and the interaction effects are investigated. For example, the 2^k design is a major set of building block and frequently used for many experimental designs. The 2^k design refer the number of K factors (number of experimental variables) and each factors with two level. The level of each factor is assigned by minus (–) for low level and plus (+) for high level. In addition, a 'center point' experiment, a zero level (0) must include in the design with all the variables at their middle value. It allows determining the confidence intervals and the risk of nonlinear relationships is minimized. The geometrical view and design matrix for 2^3 factorial design shown in Figure 2.2.

Figure.2.2. An example of 2^3 factorial design



a) Geometrical view

Run	Factors		
	X_1	X_2	X_3
1	-	-	-
2	+	-	-
3	-	+	-
4	+	+	-
5	-	-	+
6	+	-	+
7	-	+	+
8	+	+	+
9	0	0	0
10	0	0	0

b) Design matrix

In chapter 3 (paper I) the experimental design with four variables at two levels were discussed for the Suzuki cross coupling reaction. The design matrix for 2^4 factorial design is illustrated in Figure 2.3.

Figure 2.3. Design Matrix for 2^4 factorial design

Run	Factors			
	X_1	X_2	X_3	X_4
1	-	-	-	-
2	+	-	-	-
3	-	+	-	-
4	+	+	-	-
5	-	-	+	-
6	+	-	+	-
7	-	+	+	-
8	+	+	+	-
9	-	-	-	+
10	+	-	-	+
11	-	+	-	+
12	+	+	-	+
13	-	-	+	+
14	+	-	+	+
15	-	+	+	+
16	+	+	+	+
17	0	0	0	0
18	0	0	0	0

2.4.1 Interpretation and response surface analysis

For each experiment in the factorial design, various responses (y_1, y_2, …y_n) are measured. Based on the statistical experimental design in Figure 2.3, a model matrix equation (1) was created. This matrix was multivariate modelling correlated to the response vector y (yield of the target compound) to accomplish a model equation as shown in equation 2.

$$M = [1 \;\; x_1 \;\; x_2 \;\; x_3 \;\; x_4 \;\; x_1x_2 \;\; x_1x_3 \;\; x_1x_4 \;\; x_2x_3 \;\; x_2x_4 \;\; x_3x_4 \;\; x_1x_2x_3 \;\; x_1x_2x_4 \;\; x_1x_3x_4 \;\; x_2x_3 \;\; x_4 \;\; x_1x_2x_3x_4] \quad (1)$$

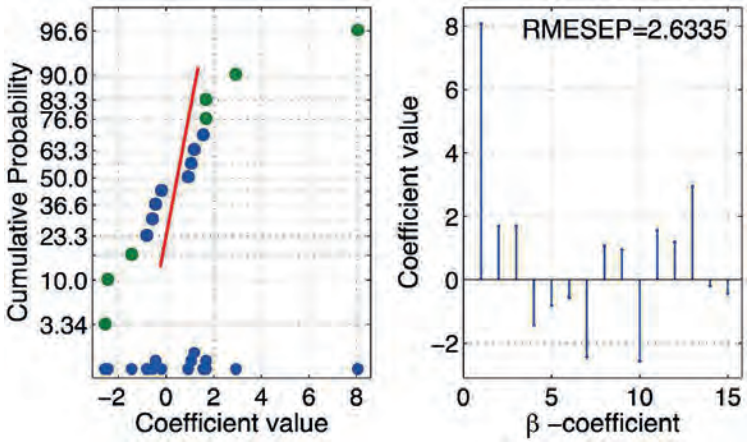
$$y = f(x_1, x_2, x_3, x_4) = \beta_0 + \sum_{i=1}^{4} \beta_i x_i + \sum_{i=1}^{3} \sum_{j=2}^{4} \beta_{ij} x_i x_j \quad (2)$$

The experimental variables used in a coded arrangement, see equation (3) to enable both the model building as well as the consequent model interpretation.

$$x_i = \frac{z_i - \{z_{i,L} + \frac{1}{2} \times (z_{i,H} - z_{i,L})\}}{z_{i,H} - \{z_{i,L} + \frac{1}{2} \times (z_{i,H} - z_{i,L})\}}, \qquad i = 1, \ldots, 4 \tag{3}$$

The model parameters, (theβ's) were studied using cumulative normal probability plot (Figure 2.4). Using the cumulative normal distribution plot, which illustrates that the model appears to be collected by the following main model parameters β_1, β_2, β_3 (positive signs) and β_4 (negative sign). Furthermore, the interaction terms β_{14} and β_{34} (negative sign) and β_{134} (positive sign) contributes significantly in the model. By using a multivariate model composed of these regression coefficients, the *iso*-contour projections of the response surfaces were produced.

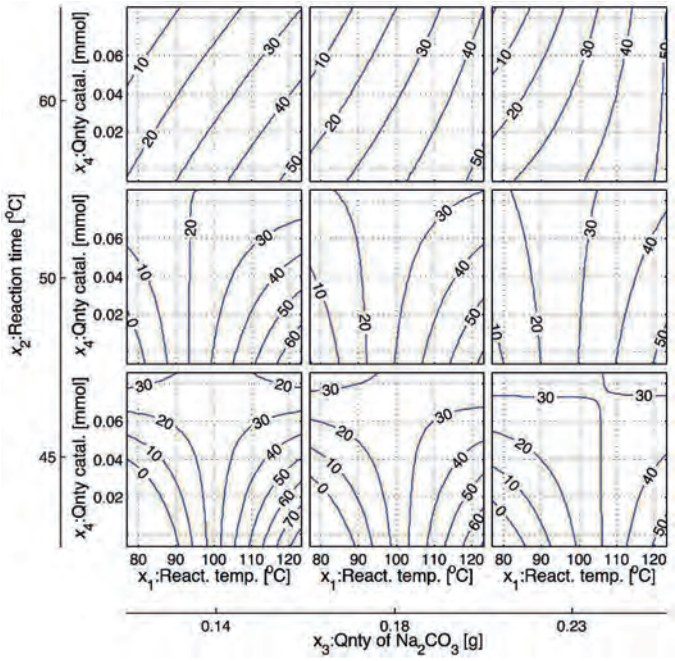
Figure 2.4. Cumulative normal distribution (CND) plot with the regression coefficients plot



Response surface methodology (RSM) is an important tool for analyzing and optimizing reaction products and processes. It is a set of mathematical and statistical techniques for empirical model building used for the development of functional relationship between the response variables and the number of control variables. The

iso-contour projections of the response surfaces (Figure 2.5), predict the experimental conditions to generate maximum yield.

Figure 2.5. Iso-contour projections



2.5 Conclusions

The various applications and importance of the experimental design compared to the OVAT method were discussed in this chapter. The DoE and the response analysis interpretation could be very useful to reaction optimization for the development of novel synthetic methodology. It can able to predict the optimum experimental condition with high yielding product. The method has been very useful in industrial chemistry for the development of novel reaction methodology and improving methods with the existing transformations. We have utilized this technique (chapter 3) for the optimization of Suzuki cross coupling reaction with highly congested chloro-substituents. We believe that the reported design of experiments will be a general tool for scientific community for reaction optimization and methodology developments.

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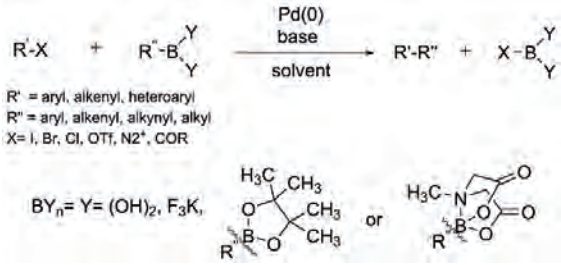
Chapter 3

Suzuki Cross Coupling: Synthesis of 2-Nitrobiphenyls

3.1 Introduction

Suzuki cross coupling [1] is an important carbon-carbon bond forming method used in organic synthesis of both academic and industrial interest, frequently used in the production of series of valuable compounds. Typically, the biphenyl scaffold are prepared by means of the Pd-catalyzed Suzuki cross coupling of aryl halides and arylboronic acids. [2] In particular, the unsymmetrically substituted biphenyl constitutes an important building blocks of herbicides,[3] liquid crystals,[4], ligands,[5] agrochemicals,[6] polymers [7] natural products and numerous biologically active pharmaceuticals.[8] Akira Suzuki discovered the Suzuki reaction (Scheme 3.1) in 1979. In recognition of this valuable approach, Suzuki received a Nobel Prize in 2010, together with Negishi and Heck for their discoveries in Pd-catalyzed cross coupling reactions.[9] A selection of an important targets[10] prepared by using the Suzuki cross coupling is shown in Figure 3.1.

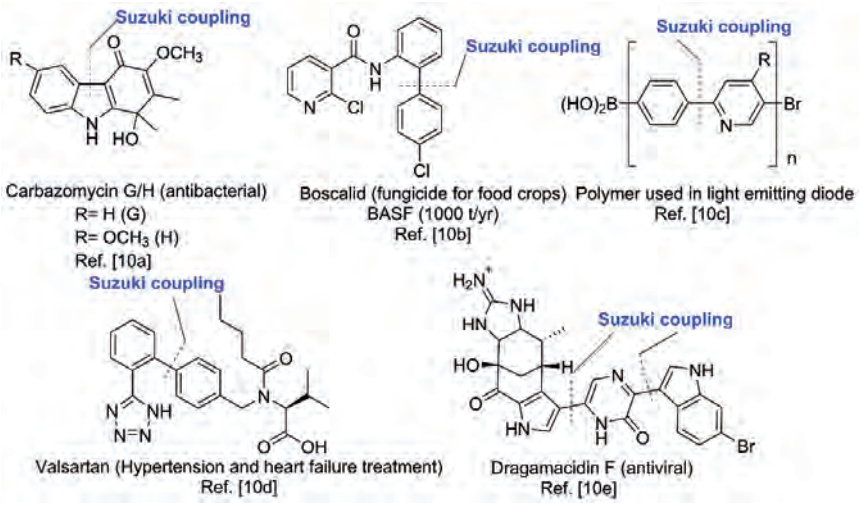
Scheme 3.1. General Outline of Suzuki cross-coupling reaction



There exist a series of Pd-catalyzed cross-coupling reactions, the Negishi coupling,[11] the Stille coupling,[12] the Hiyama coupling[13] and the Kumada coupling[14] are available for the preparation of biphenyl moiety. In compare with the other coupling methods, Suzuki cross-coupling reaction has recognized the most popular in recent times and provides an attractive features including mild reaction conditions, readily availability of boronic acids and its derivatives (MIDA esters,[15] trifluoroborates[16]

and boronic esters[17]) which are easy to prepare and environmentally safer than the other organometallic reagents and could be used for the scope and utility of Suzuki coupling. Moreover, the boron containing by-products are non-toxic and can be easy to remove even in large-scale synthesis. Based on these viewpoints, it is clear that the Suzuki cross coupling is a more sustainable reaction and are applicable in the industry for the preparation of biologically active pharmaceuticals and fine chemicals.

Figure 3.1. Important synthetic targets produced using Suzuki cross-coupling reaction

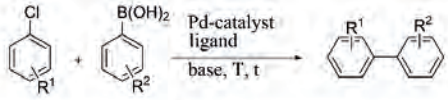


Among several biphenyl scaffold, synthesis of 2-nitrobiphenyl by means of the Suzuki cross coupling have attracted our attention and constitutes in several N-heterocyclic compounds thus utilized as an important synthetic targets in medicinal chemistry. Several synthetic methods has been described earlier for the synthesis of 2-nitrobiphenyls. In 2005, Freeman and collaborators [18] revealed a method for the synthesis of 2-nitrobiphenyls using $Pd(PPh_3)_4$ as a catalyst. However, the method required long reaction time (up to 42 h) and a huge excess of base in order to synthesize the target 2-nitrobiphenyls. Recently, Gooßen and collaborators [19] reported a method for the synthesis of 2-nitrobiphenyls by using a decarboxylative Hiyama coupling reaction, which operate using a trimetallic Pd/Cu/Ag catalytic system at high temperatures.

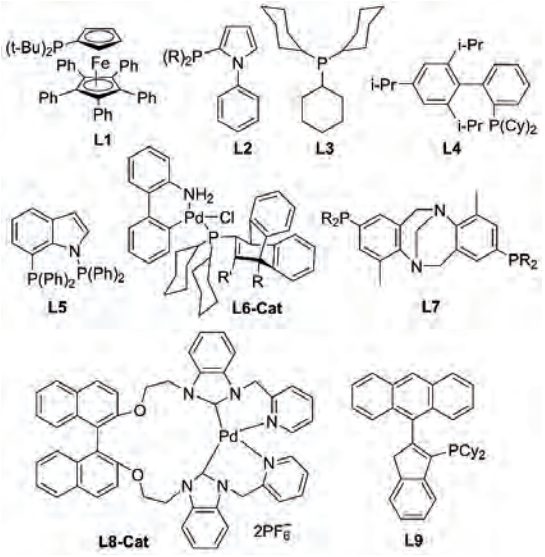
Nevertheless, the Suzuki cross coupling reaction has appeared as the method with the most attractive features for the preparation of biphenyls, includes the mild reaction conditions and its tolerance towards water and in general high functional group tolerance and high regio and stereoselectivities.

Previously, the Suzuki cross-coupling reaction was achieved by reacting organoboronic acids with aryl halides in the presence of a base and $Pd(PPh_3)_4$ as catalyst.[20] Aryl halides such as Iodides, Bromides and triflates are well known coupling partner for Suzuki cross coupling reaction. However, the coupling with aryl chlorides remains a challenging task in organic chemistry due to the bond strength of C-Cl, which is highly reluctance towards the oxidative addition. The chloro compounds are cheaper than bromo and iodo compounds that motivate for using chloroarenes. Previously, some Suzuki coupling methods has been described involving chloroarenes as coupling partner.[21] Further substantial improvement were not revealed until various palladium complexes were introduced as catalysts to facilitate the Suzuki cross-coupling reaction.[22] In order to extend the scope and utility of the Suzuki cross coupling with aryl chlorides, one strategy involves the introduction of expensive ligands,[23] which increase the electron density around the Pd-center and thus facilitate the cleavage of the C-Cl bond to enable cross coupling.[24, 25] (Table 3.1). However, these ligands are usually expensive and not feasible in the large-scale reactions. Herein, we have reported an efficient Pd-catalyzed ligandless method for the synthesis of substituted 2-nitrobiphenyls under microwave irradiation. This method was successfully adapted for the synthesis of the congested biphenyl intermediate in a new total synthesis of carbazomycin G.

Table 3.1. Disclosed Suzuki coupling with chloroarenes as substrate.



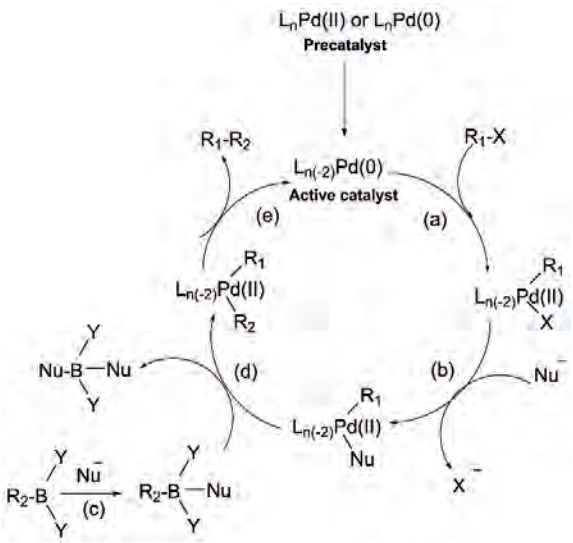
#	Author	Year	Ref	Catalyst	Ligand	Base	Temp (^{0}C)	Time (h)
1	Hartwig et al	2002	[23a]	$Pd(dba)_2$	**L1**	KF/K_3PO_4	45-100	15-72
2	Beller et al	2003	[23b]	$Pd_2(dba)_3$	**L2**	K_3PO_4	60-100	20
3	Fu et al	2006	[23c]	$Pd_2(dba)_3$	**L3**	K_3PO_4	100	18
4	Buchwald et al	2007	[23d]	$Pd_2(dba)_3$	**L4**	K_3PO_4	100	5-24
5	Sarkar et al	2010	[23e]	$Pd(CH_3CN)_2Cl_2$	**L5**	NaOH	125	3.5-8
6	Doherty et al	2013	[23f]	L6-Cat	**L6**	K_3PO_4	50-80	0.5-14
7	Cvengros et al	2013	[23g]	$Pd(OAc)_2$	**L7**	K_3PO_4	90	0.16-24
8	Liu et al	2015	[23h]	L8-Cat	**L8**	K_2CO_3	40	6-12
9	Yu et al	2017	[23i]	$Pd(OAc)_2$	**L9**	K_3PO_4	90	16



3.2 General mechanism of Suzuki cross coupling reaction

The general mechanism [26] of Suzuki cross coupling is outlined in Figure 3.2. It involves four main steps, oxidative addition, ligand exchange, transmetallation and reductive elimination. The mechanism of each step has been described in detail. The oxidative addition is the rate-determining step of the catalytic cycle,[27] involves the palladium catalyst coupled with organic halide to form the organopalladium complex (path a), in which the palladium is oxidized from Pd(0) to Pd(II). The next step is the displacement of the halide with base to form the more reactive species (path b) depending on the base used. The third step (path d) involves the transmetallation with boron ate complex (which is formed by activation of boronicacid with base in path c) to form the organopalladium species. The final step of the mechanism is the reductive elimination (path e) to achieve the target-coupled product and regenerates the palladium catalyst and thus completing the catalytic cycle.

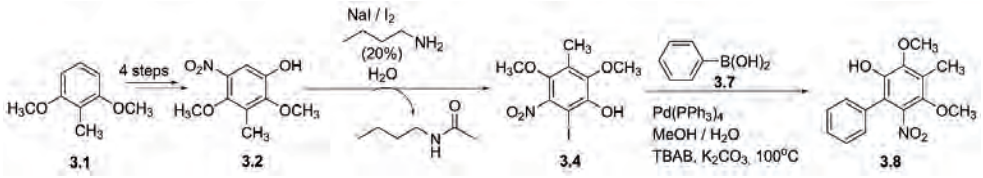
Figure 3.2. General mechanism of Suzuki cross-coupling reaction



3.3 Methods and discussion

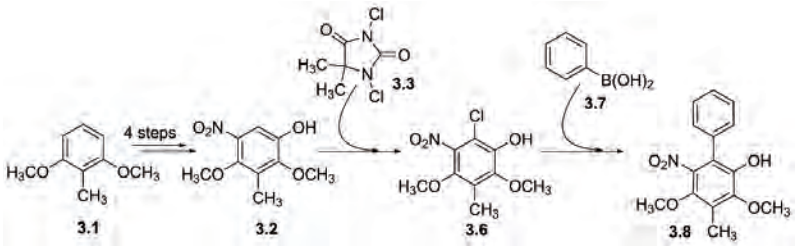
For our total synthesis of the natural product Carbazomycin G [28] (discussed in Chapter 6), we needed an appropriate methodology to synthesize the highly congested substituted 2-nitrobiphenyls. Previously a Suzuki cross-coupling method [29] was developed in our group, using the 1-iodo-2-nitrobenzene with phenylboronic acid. The method afforded 2-nitrobiphenyls in good to excellent yield with $Pd(PPh_3)_4$ as catalyst. In order to extend the scope of this available method, attempts to prepare the congested 1-iodo-2-nitrobenzene **3.4** using a disclosed method by Crich and collaborators.[30] The method afforded only 30% yield of the desired iodo compound **3.4 (**Scheme 3.2). However, reproducibility of the reaction was an additional problem. We assumed that it might occur due to the presence of unknown impurity in the Iodine. Therefore, this strategy was abandoned.

Scheme 3.2. Attempt to Suzuki cross coupling reaction



Few years ago, we have developed a novel method for the fast halogenation of some heterocyclic compounds by means of *N,N′*-dihalo-5,5-dimethyl-hydantoinin as the halogenating agent.[31] We wanted to utilize this method and attempted for the preparation of congested 1-halo-2-nitrobenzenes with different halogenating agent such as DIH, DBH and DCH. As a result, the method failed for bromination using DBH and iodination using DIH. Surprisingly, the method works excellently with DCH **3.3** reacting with compound **3.2** to afford the quantitative conversion to provide the congested 1-chloro-2-nitrobenzene **3.6**. Subsequently, the chloro compound **3.6** was attempted to Suzuki cross coupling with phenylboronic acid **3.7** using the method disclosed previously in our group,[29] attained only 30% conversion yield of the desired biphenyl compound **3.8** (Scheme 3.3).

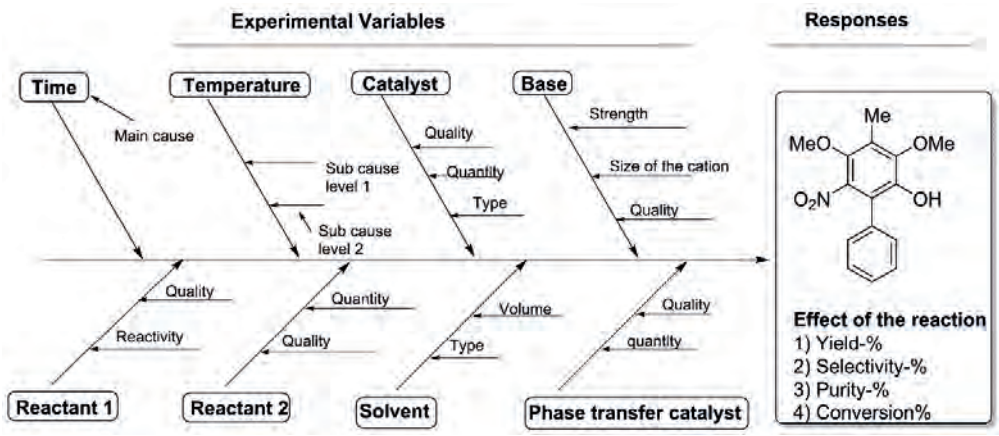
Scheme 3.3. Optimization of Suzuki cross coupling strategy



3.4 Optimization of Suzuki cross-coupling reaction

The outcome of the Suzuki cross-coupling reaction (Scheme 3.3) was encouraged us to investigate to optimize the Suzuki cross-coupling reaction using the statistical experimental design,[32] multivariate analysis,[33] and response surface methodology.[34] The importance of this technique in organic synthesis has been discussed briefly in chapter 2. A primary thing is to figure out the possible variables that could affect the rate of the reaction, which could be predictable by using the Ishikawa diagram (cause and effect diagram).[35] The Ishikawa diagram for Suzuki cross coupling of chlorinated compound for the synthesis of congested 2-nitrobiphenyl is shown in Figure 3.3.

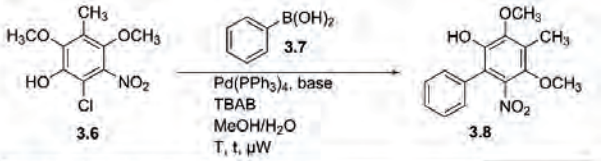
Figure 3.3. Ishikawa diagram for Suzuki cross coupling reaction



3.4.1 Statistical experimental design

In this viewpoint based on the reaction profile, (Figure 3.3). We assumed that the four variables namely, reaction temperature (x_1), reaction time (x_2), quantity of base (x_3) and amount of catalyst loading (x_4) that could affect the reaction rate in terms of yield and selectivity. For the four experimental variables x_1-x_4, we have created a statistical experimental design with 18 experiments using the formula. $2^k+c = 2^4+2= 18$, where k, is the number of variables and c, is the center experiment. The summarized results of the experimental design are shown in Table. 3.2.

Table 3.2 Optimization of the Suzuki Cross Coupling reaction using statistical experimental design



Experimental variables and selected levels

	Experimental variables	-1 (L)	0	+1 (H)
x_1	Reaction temperatures [°C]	90	100	110
x_2	Reaction time (min)	45	60	75
x_3	Quantity of Na_2CO_3 (g)	0.15	0.19	0.23
x_4	Loading of $Pd(PPh_3)_4$ (mmol)	0.022	0.0435	0.065

Experimental design: $2^k + c$, k = 4, c = 2 $\Longrightarrow$ $2^4 + 2 = 18$

#[a]	Experimental variables [b]				Responses [c]
	x_1 [°C]	x_2 [min]	x_3 [g]	x_4 [mmol]	y [%]
1	90	45	0.15	0.022	8
2	110	45	0.15	0.022	44
3	90	75	0.15	0.022	15
4	110	75	0.15	0.022	35
5	90	45	0.23	0.022	25
6	110	45	0.23	0.022	39
7	90	75	0.23	0.022	29
8	110	75	0.23	0.022	43
9	90	45	0.15	0.065	22
10	110	45	0.15	0.065	30
11	90	75	0.15	0.065	27
12	110	75	0.15	0.065	32
13	90	45	0.23	0.065	16
14	110	45	0.23	0.065	29
15	90	75	0.23	0.065	20
16	110	75	0.23	0.065	39
17	100	60	0.19	0.0435	19
18	100	60	0.19	0.0435	21
Opt. [d]	120	30	0.10	0.025	53

(a) The list of experiments were carried out in a random order.
(b) The substrate, 2-Chloro-4,6-dimethoxy-5-methyl-3-nitrophenol **3.6** (0.21 g, 0.85 mmol) was used in all of the experiments.
(c) Measured response from each of the experiment, y = measured yield of target product **3.8** using GC-MS.
(d) Optimized conditions based on the response surface methodology expressed in a coded format. x_1 = +2, x_2 = -2, x_3 = -2, x_4 = -1

3.4.2 Multivariate Modelling

In order to simplify the estimation of the model terms, the experimental variables x_1-x_4 were scaled using the equation (1) which produced the design matrix **D** for the scaled variables x_1-x_4, and then used to produce the model matrix **M** by using equation (2). In these equations, z_k is the experimental variable in which k expressed in real units and variable x_k is the same variable provided in scaled units. $z_{k,}L$ and $z_{k,}H$ are the selected low (L) and high (H) level experimental values expressed in real units of the experimental variable z_k. The selected levels (L, 0, H) are provided above in the Table 1. The scaling using the equation (1) gives all the experimental variables of low values in $x_{k,}L = -1$ and correspondingly the high values $x_{k,}H = +1$.

$$x_k = \frac{z_k - \left[z_{k,L} + \frac{1}{2}\times(z_{k,H} - z_{k,L})\right]}{z_{k,H} - \left[z_{k,L} + \frac{1}{2}\times(z_{k,H} - z_{k,L})\right]},\ k = 1, \ldots, 4 \qquad (1)$$

Model matrix **M** can be obtained based on design matrix **D** as follows,

$$\mathbf{M} = [\mathbf{1}\ \overbrace{x_1\ x_2\ x_3\ x_4}^{y}\ x_1x_2\ x_1x_3\ x_1x_4\ x_2x_3\ x_2x_4\ x_3x_4\ x_1x_2x_3\ x_1x_2x_4\ x_1x_3x_4\ x_2x_3x_4\ x_1x_2x_3x_4] \qquad (2)$$

Multiple linear regression,[36] expressed in equation (3) used to estimate the model shown in equation (4) by means of MATLAB[37] computer software and in-house coded routines that has been benchmarked earlier against the commercial software, such as SAS.[38]

$$y = \mathbf{M}b \Rightarrow b = (\mathbf{M}^T\mathbf{M})^{-1}\mathbf{M}^T y \qquad (3)$$

This matrix was multivariate correlated to the response vector y (yield of target biphenyl compound) to achieve a model of the form as shown in equation (4)

$$y = f(x_1, x_2, x_3, x_4) = 27.389 + 8.063x_1 + 1.688x_2 + 1.688x_3 - 1.438x_4 - 0.813x_1x_2 - 0.563x_1x_3 - 2.437x_1x_4 + 1.063x_2x_3 + 0.937x_2x_4 - 2.563x_3x_4 + 1.562x_1x_2x_3 + 1.188x_1x_2x_4 + 2.937x_1x_3x_4 - 1.188x_2x_3x_4 - 0.437x_1x_2x_3x_4$$

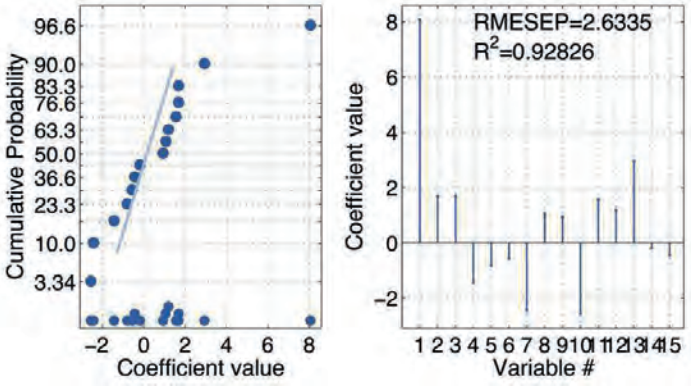
$$R^2 = 0.928,\ R^2_{adj} = 0.390,\ RMSEP = 2.634,\ RSD = 2.793 \quad (4)$$

The estimated regression coefficients were studied with a cumulative normal distribution (CND) plot (Figure 3.4). Based on the CND plot, the model appears to be composed by the following main model parameters β_1, β_2, β_3 (positive signs) and β_4 (negative sign). Moreover, the interaction terms β_{14} and β_{34} (negative sign): and β_{134} (positive sign) contributes substantially in the model. The final multivariate model, see Equation (5), By using a multivariate model composed of these regression coefficients, the *iso*-contour projections of the response surfaces were produced and presented in Figure 3.5.

$$y = f(x_1, x_2, x_3, x_4) = 27.389 + 8.063x_1 + 1.688x_2 + 1.688x_3 - 1.438x_4 - 2.437x_1x_4 - 2.563x_3x_4 + 2.937x_1x_3x_4$$

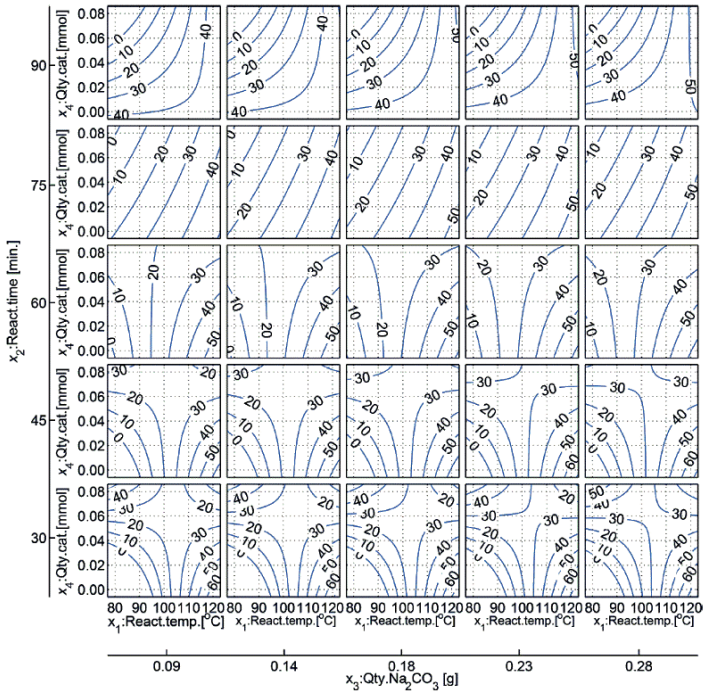
$$R^2 = 0.862,\ R^2_{adj} = 0.768,\ RMSEP = 3.635,\ RSD = 3.856 \quad (5)$$

Figure 3.4 Cumulative normal distribution (CND) plot with the regression coefficients plot adjacent of the right hand side for the Suzuki cross-coupling reaction



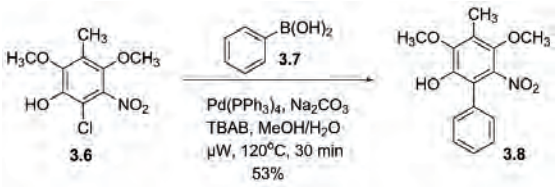
The *iso*-contour projections of the response surfaces (Figure 3.5), predict that the following experimental conditions will provide an improved yield: a low quantity of base (Na_2CO_3) [0.10 g], a short reaction time [30 min.], a high reaction temperature [120 ^oC], and a low catalyst loading [0.022 mmol]. The following up experiment using the predicted conditions revealed a yield of 53%, which represent the best yield for this cross-coupling reaction (Scheme 3.4).

Figure 3.5 Iso-contour projections of the response surface describing the yield of the biphenyl **3.8** from the Suzuki cross-coupling reaction between congested aryl chloride **3.6** and the phenylboronic acid **3.7.**



Iso-Contour projection of the response surface prepared for predictive purposes. The iso-contour lines made by the model Equation (4) show the predicted yield (*y*) of target 2-nitrobiphenyl **3.8**. How to read the graphic: the outer horizontal frame line shows the variation in the quantity of the sodium carbonate (x_3), and the vertical frame line displays the effect of the reaction time (x_2). Each variable has five discrete levels [–2 –1 0 +1 +2]. The 25 subplots within the outer frame lines show the *iso*-contour lines projections of the response surfaces when the two experimental variables — reaction temperature (x_1) and quantity of Pd catalyst (x_4) — are continuously varied within a range that corresponds to [–2 +2].

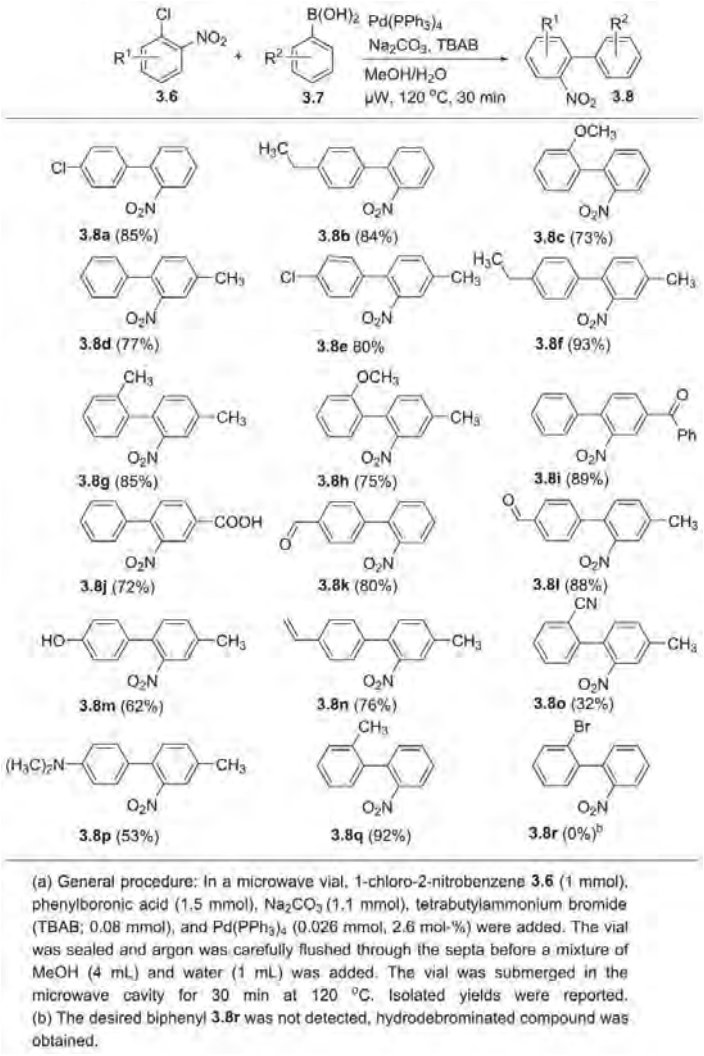
Scheme 3.4 Optimized Suzuki cross coupling reaction



3.5 Scope and limitation of optimized Suzuki cross coupling reaction

Herein, we have developed and optimized a simple and efficient $Pd(PPh_3)_4$-catalyzed Suzuki cross coupling method for the highly congested chloroarene with phenylboronic acid. (Scheme 3.4). These results encouraged us to investigate whether this method could be a general method for the synthesis of 2-nitrobiphenyls using the Suzuki cross coupling reaction. The scope and limitation of the developed method were examined with variety of substituted chloroarenes and bromoarenes. The method tolerates with both electron withdrawing and donating groups. Table 3.3 illustrates the coupling of variety of chloroarenes and phenylboronic acid with different functionality. The only change in the experimental condition was the reduced amount of phenylboronic acid (1.5 eq) was used compared to the optimized conditions of Suzuki coupling (2.3 eq). We have tested 18 different functionality of chloroarenes underwent for Suzuki cross coupling reaction afforded medium to excellent yield and good selectivity of corresponding biphenyl compounds in almost all the cases. The method attained low yield in case with electron withdrawing group in the ortho positions. (Table 3.3, compound **3.8o**). Moreover, we obtained the hydrodebrominated compound during the reaction instead of the desired bromonitro biphenyl compound (Table 3.3, compound **3.8r**).

Table 3.3 Scope and limitation of the Suzuki cross-coupling method with chloroarenes[a]

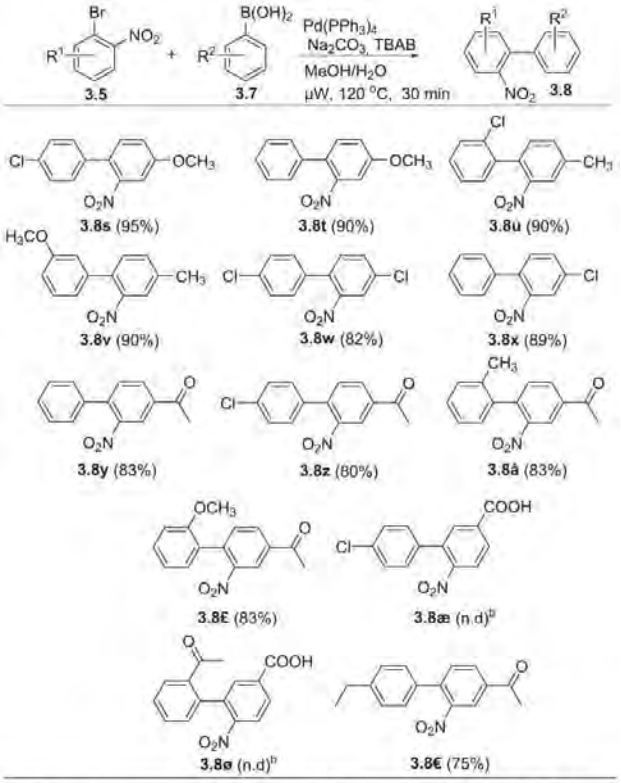


(a) General procedure: In a microwave vial, 1-chloro-2-nitrobenzene **3.6** (1 mmol), phenylboronic acid (1.5 mmol), Na_2CO_3 (1.1 mmol), tetrabutylammonium bromide (TBAB; 0.08 mmol), and $Pd(PPh_3)_4$ (0.026 mmol, 2.6 mol-%) were added. The vial was sealed and argon was carefully flushed through the septa before a mixture of MeOH (4 mL) and water (1 mL) was added. The vial was submerged in the microwave cavity for 30 min at 120 °C. Isolated yields were reported. (b) The desired biphenyl **3.8r** was not detected, hydrodebrominated compound was obtained.

We have also tested with different substituted bromoarenes **3.5** in order to see how the developed method works with these substrates. As a result, the method gave excellent yield of biphenyl product **3.8** in all the cases except the reaction with carboxyl group substrate, desired biphenyl product was not detected for compounds **3.8æ** and **3.8ø** (Table 3.4). Overall, the optimized Suzuki cross-coupling strategy was operated very well for variety of functionalities for both the aryl halides and phenylboronic acids. In general, it might be suitable method for the preparation of 2-

nitrobiphenyls via Suzuki cross-coupling reaction with different aryl halides, more specific with less reactive aryl chlorides. The desired 2-nitrobiphenyl is an important intermediate in several biologically active compounds and natural products.

Table 3.4 Scope and limitation of the Suzuki cross-coupling method with bromoarenes[a]



(a) General procedure: In a microwave vial, 1-bromo-2-nitrobenzene **3.5** (1 mmol), phenylboronic acid (1.5 mmol), Na_2CO_3 (1.1 mmol), tetrabutylammonium bromide (TBAB; 0.08 mmol), and $Pd(PPh_3)_4$ (0.026 mmol, 2.6 mol-%) were added. The vial was sealed and argon was carefully flushed through the septa before a mixture of MeOH (4 mL) and water (1 mL) was added. The vial was submerged in the microwave cavity for 30 min at 120 °C. Isolated yields were reported. (b) the desired biphenyl was not detected

3.6 Conclusion

We have developed and optimized an efficient Suzuki cross-coupling method for the synthesis of 2-nitrobiphenyls using 1-chloro-2-nitrobenzenes and phenylboronic acids as reaction partners. The method exhibits high functional group tolerance with both 1-chloro-2-nitrobenzenes and the phenylboronic acids and afforded medium to excellent yield and good selectivity of the desired 2-nitrobiphenyls. The method was initially developed to couple highly congested aryl halides with phenylboronic acid. In compare with the previously disclosed studies by using chlorobenzenes as a reactant in the Suzuki cross-coupling reaction, we utilized a simple and readily available catalyst $Pd(PPh_3)_4$. The optimized study demonstrates the importance of multivariate design and modeling in explorative synthesis to develop new synthetic methodology. In the present case, the DoE methodology replaced the need for expensive and complex catalyst ligands.

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Chapter 4

Indium Reduction: Synthesis of 2-Aminobiphenyls

4.1. Introduction

Reduction reaction plays an important role in organic synthesis. A variety of organic synthesis involves the reduction at some point to accomplish towards the target molecule. A large number of organic functionalities are reduced into various useful functional groups. Several synthetic methods have been reported earlier for the reduction of different functionalities. Among them, catalytic hydrogenation and reduction with metal hydrides reveals the most important reduction reaction. The other reduction methods involves various metals, metal salts and other organic compounds.

In this chapter, we mainly focused the synthesis of aromatic amines from nitro compounds. Aromatic amines are extensively used as starting materials and important intermediates for the production of variety of compounds such as dye materials, agrochemicals, medicines, polymer surfactants, and chelating agents. [1] Number of methods exist for the transformation of nitro to amino group, includes catalytic hydrogenation using Palladium on carbon [2] and Raney Nickel, [3] is the most important and used method for the industrial processes where no side product was occurred except water. The major problem of this method involves the reduced selectivity in the presence of other reducible functionalities. In such cases, the other methods involves using the $NaBH_4$-$CuSO_4$ system [4] and Pd-catalyzed reduction with silicon hydrides [5] as well as with Bechamp reduction with Fe and HCl [6] are to be used. Moreover, methods incorporating with $SnCl_2$, [7] Sm, [8] Zn, [9] $TiCl_3$, [10] sodium dithionite [11] and Indium powder with NH_4Cl [12] for the selective reduction of nitro compounds into corresponding amine compounds.

A project devoted to synthesize the carbazole [13] (Chapter 5) and Boscalid® [14] (Chapter 8) scaffold, we needed access to synthesize the 2-aminobiphenyls, which is an important intermediates in several natural products and fungicides.[1] A method has been reported previously in our group for the synthesis of the intermediates 2-nitrobiphenyls by means of Suzuki cross coupling reaction. [15]

We needed a simple and efficient method for the reduction of 2-nitrobiphenyls into 2-aminobiphenyls.The method involves indium powder with NH_4Cl solution [12] is attracted our attention due to their simplicity of the reaction with nitroarenes. Indium is one of the low valent metal and used as reducing agents.[16] It has several applications including the mild conditions, non-toxic and unreactive towards the air and water made the reagent suitable in organic synthesis for the reduction of different functionalities. The first ionization potential of Indium (5.8 eV) is lower than the other reducible groups such as, Sn (7.3 eV), Zn (9.4 eV) and close to alkali metal Na (5.1 eV). These data suggests that the metal indium contribute readily in single electron transfer reaction.

4.2 Method and discussions

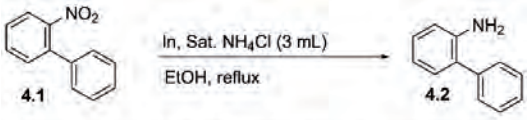
Several reduction methods have been described earlier using Indium metal for different functional group hydrogenation. For example, selective reduction of nitro compounds into their corresponding anilines, [12] heterocyclic ring reduction in quinolones and isoquinolines, [17] reductive elimination of 1,2-dibromides,[18] ketone deoxygenation,[19] pinacol coupling.[20] Furthermore, the selective reduction of alkenes [21] and azides [22] into corresponding reduced products are achieved by using the Indium metal. Table 4.1 shows the list of previously described reduction methods of nitro compounds into corresponding amine by means of Indium powder under different experimental conditions. [23]

Table 4.1. Previously disclosed Indium reduction method

#	Authors	Year	Ref	Substrate	Solvent	Indium [equiv]	Temp [°C]	Time [h]
1	Banik et al	2000	23b	NO_2	EtOH	2.75	80	5-22
2	Lee et al	2001	23a	NO_2	aq.THF (3:1)	4	rt	0.5-2
3	Moody et al	2001	23f	NO_2	EtOH	7	reflux	1-3
4	Lee et al	2001	23a	N_3	aq.THF (3:1)	2	rt	2-8
5	Goti et al	2003	23g	NH_2OH	EtOH	1.25	reflux	3-13
6	Becker et al	2005	23d	NO_2	EtOH	4	reflux	2.5
7	Yoo et al	2012	23e	NO_2	THF	8	rt	0.5-4

However, in order to utilize indium reduction method reported by Moddys and collaborators,[12] we need a very high dilution of the substrates in solvent medium, excess of indium powder and long reaction time up to 72 hours. It prompted us to re-investigate the method to explore and simplify towards our biphenyl compound application. We have performed the reduction with our substrate 2-nitrobiphenyl **4.1** afforded full conversion of substrate **4.1** into desired amine compound **4.2** based on GC analysis (Table 4.2. entry 1). However, these trials gave only 41% of the isolated amine compound **4.2**. The obstacles involves several steps in the workup procedure. Such as filtration, pH adjustment, extraction, solvent removal and finally silica gel chromatography.

Table 4.2. Screening of Indium reduction producing 2-aminobiphenyls



4.1 4.2

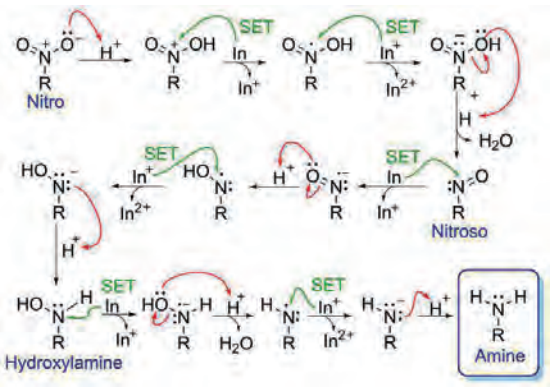
#	In (equiv)	Time (h)	Yield (%)[a]
1	7	90	100
2	3.5	90	100
3	2	90	87
4	2	150	100

a) Yield measured by using GC

4.3 Proposed mechanism of Indium reduction

The mechanism of the indium reduction has not been clearly examined in the described literature procedures. We proposed a mechanism parallel with Zinc reduction (Figure 4.1). Our proposed mechanism shows that we need three equivalents of indium to carry out the reduction depending on the oxidation state of indium. The desired amine product was achieved via nitroso and hydroxylamine as intermediates. We wanted to investigate the reaction with reduced amount of indium powder from 7 equiv to 3.5 equiv, afforded quantitative conversion (Table 4.2. entry 2) and further reduced the quantity of indium to 2 equiv, gave 87% conversion yield in 90 min (entry 3). The prolonged reaction time from 90 min to 150 min afforded full conversion. (entry 4). These results suggests that we need two or three equivalents of indium powder for each nitro group based on the final oxidation state of the indium.

Figure.4.1. Proposed mechanism for Indium reduction of the nitro group



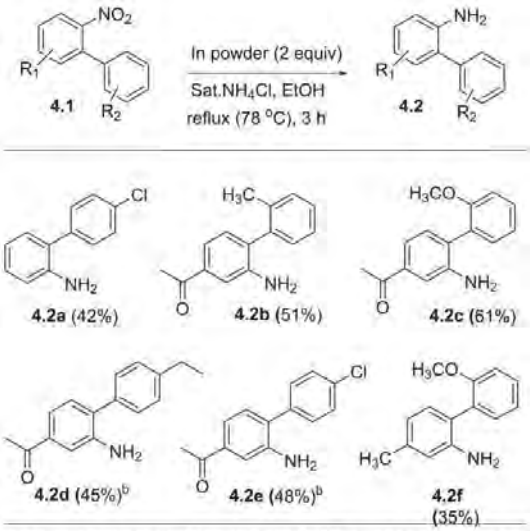
During the indium reduction methods, we also observed that the particle size was crucial relevant to the reaction rate and performance of the reaction. We used freshly opened bottle of indium powder (100 mesh, 99.99% purity) in order to accomplish quantitative conversion. Nevertheless, the reactivity of indium was impaired after

some days in storage under room temperature, which might be due to the surface oxidation.

4.4 Scope and Limitations

We have investigated the scope of the reaction with different nitro compounds under the same experimental conditions. (Scheme 4.1) All of the trials afforded only low to medium isolated yield and turn into decomposition of products after sometimes.

Scheme 4.1. Initial investigation of Indium reduction for the synthesis of 2-aminobiphenyls[a]

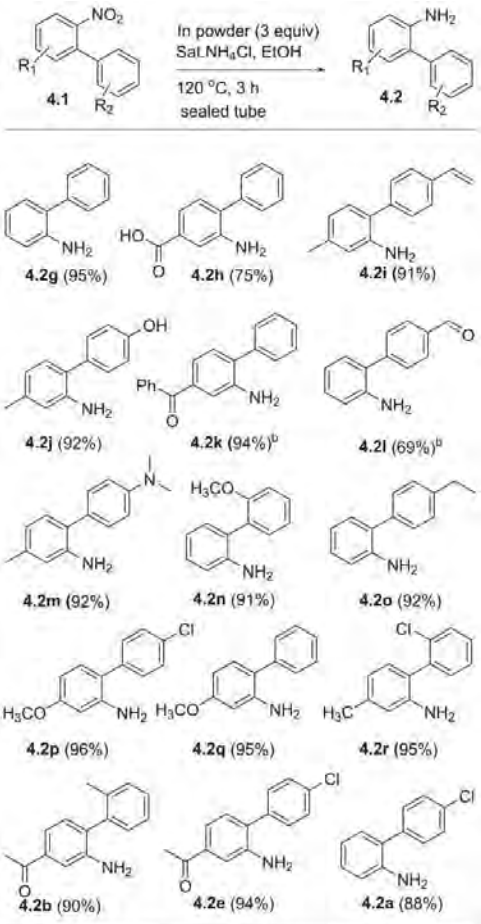


(a) General procedure: 2-Nitrobiphenyl **4.1** (1 mmol) was dissolved in EtOH (10 mL) To the stirred solution, mixture of NH_4Cl (16 mmol) in H_2O (1.2 mL) and indium powder (2 mmol) were added. The reaction mixture was stirred under reflux 3 h. Isolated yield were reported b) Additional In powder and NH_4Cl was added after 3 h to attain high conversion

Therefore, we wanted to explore the method with experimental variables to improve the outcome of the reaction. For example, altering the reaction temperature from 78 ^oC to 120 ^oC in a sealed tube reactor, reduce the volume of solvent from 10 mL to 4 mL and lowered the quantity of NH_4Cl from (16 mmol to 1.03 mmol). These conditions provide a quantitative conversion yield of the desired amine product. (Scheme 4.2, **4.2g**). These results suggested that it required three equivalent of indium and the mechanism based on In^{2+} oxidation state.

We then examined a scope of the reaction with different substituted 2-nitrobiphenyls **4.1**, afforded 2-aminobiphenyls in excellent isolated yield and high purity in all the cases except in **4.2k** and **4.2l** compound, which is measured by GC-analysis. In contrast to other methods, the major advantage of the improved method includes simple work-up procedure that leads to desired product in high purity and selective reduction of nitro group in presence of other reducible groups.

Scheme 4.2. Scope and limitations of Indium reduction for the synthesis of 2-aminobiphenyls using the improved protocol[a]



(a) General procedure: In a tube reator, 2-Nitrobiphenyl **4.1** (1 mmol) was dissolved in EtOH (4 mL). Then, a mixture of NH_4Cl (2 mmol) in H_2O (1.2 mL) and indium powder (3 mmol, 99.99% 100 mesh, use preferably a freshly opened bottle or stored under Ar) were added. The tube was then sealed and the reaction mixture was heated at 120°C for 3h. Isolated yield were reported
(b) Yield measured by GC

4.5 Conclusion

We have developed and improved an indium reduction method for the synthesis of 2-aminobiphenyls from corresponding 2-nitrobiphenyls. The improved method utilizes 3 equivalent of Indium powder and reduced amount of solvent and NH_4Cl solution. In contrast with previous reported methods, our improved method works very simple, requires only filtration of the post reaction mixture followed by the evaporation of the solvent afforded the desired target molecule. It also provides selective reduction of nitro compounds in the presence of other reducible groups and high functional group tolerance afforded high purity of the product. The mechanistic proposal illustrates clearly the three equivalent of Indium is necessary to achieve the high conversion yield.

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Chapter 5
Synthesis of the Carbazole Scaffold Directly from 2-Aminobiphenyls

5.1 Introduction

Carbazole is an important N-heterocyclic compound appear as an essential structural motif in numerous biologically active natural products and potentially active pharmaceutical ingredients (APIs) [1] (Figure 5.1) as well as in dye industry and material science. It is one of the important nitrogen containing aromatic compound possessing innumerable biological activities such as anticancer, [2] antiviral, [3] antibiotic [4] antifungal [5] and anti-inflammatory properties. [6] Carbazole has been isolated from various natural sources over the past few decades. [7] In 1965, Chakraborty et al reported the first antibiotic carbazole alkaloid murrayanine isolated from stem bark of murraya koenigii [8] (curry leaf tree) (Figure 5.1a), a richest source of carbazole alkaloids from the terrestrial plants.

Figure 5.1. Biologically active carbazole alkaloids

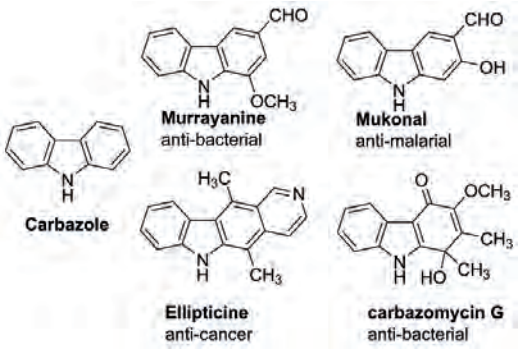
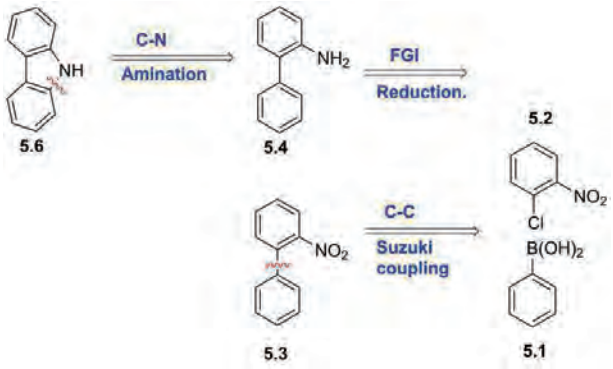


Figure 5.1a. Murraya Koenigii (curry leaf tree) (Knölker 2005) [1]

5.2 Retrosynthetic route

The outline of our retrosynthetic pathway leading to carbazole is illustrated in Figure 5.2. The target carbazole **5.6** was achieved through direct ring closing of 2-aminobiphenyls **5.4** using intramolecular C-H activation and C-N bond formation. [10] The subsequent compound **5.4** was accessed via functional group interconversion (FGI) using reduction of biphenyl compound **5.3**. The biphenyl moiety was obtained via Suzuki cross coupling of chloroarenes **5.2** with phenylboronic acid **5.1**. In this viewpoint, we have developed a more straightforward and rapid method for the synthesis of the target molecule.

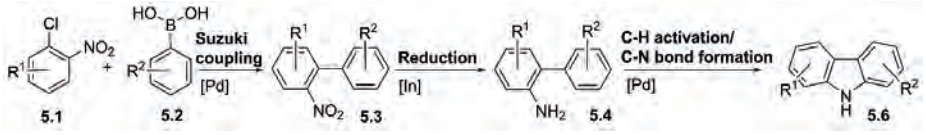
Figure.5.2. Retrosynthetic route to Carbazole



5.3 Methods

Owing to the tremendous application of carbazoles **5.6**, considerable attention has been focused to construct the carbazole scaffold. Several research groups have been involved earlier to synthesize the carbazole scaffold **5.6** using different synthetic methodology.[9] In this chapter, we have reported a novel synthetic methodology for the synthesis of carbazole **5.6** (scheme 5.1). [10] The new strategy involves three important synthetic steps, Step 1 involves Suzuki cross-coupling reaction to prepare different derivatives of 2-nitrobiphenyls **5.3** using 1-chloro-2-nitroarenes **5.1** and phenylboronic acid **5.2** followed by reduction of nitro group into amine compound **5.4** using Indium powder in step 2. We have discussed more elaborately the Suzuki cross coupling reaction and Indium reduction in Chapter 3 and 4. In this chapter, we mainly focus the intramolecular C-H bond activation followed by C-N bond formation leads to carbazole **5.6** framework.

Scheme 5.1. Carbazole three step novel synthesis



Transition metal catalyzed C-H bond activation[11] has emerged as an efficient methodology for the synthesis of several biologically active N-heterocyclic compounds and enables widespread application in organic synthesis especially using Pd-catalyzed intramolecular C-H activation combined with C-N bond formation. Several methods have been reported earlier for synthesis of carbazole using protected 2-aminobiphenyls.[12,10a] A decade ago, Buchwald and collaborators[12a,13] described a method that allowed to the synthesis of the carbazole scaffold by means of tandem C–H functionalization and C–N bond formation (Scheme 5.2, path a). The major drawbacks of this method includes long reaction time and require protecting or auxiliary group for 2-amino group in order to facilitate the reaction. During the last

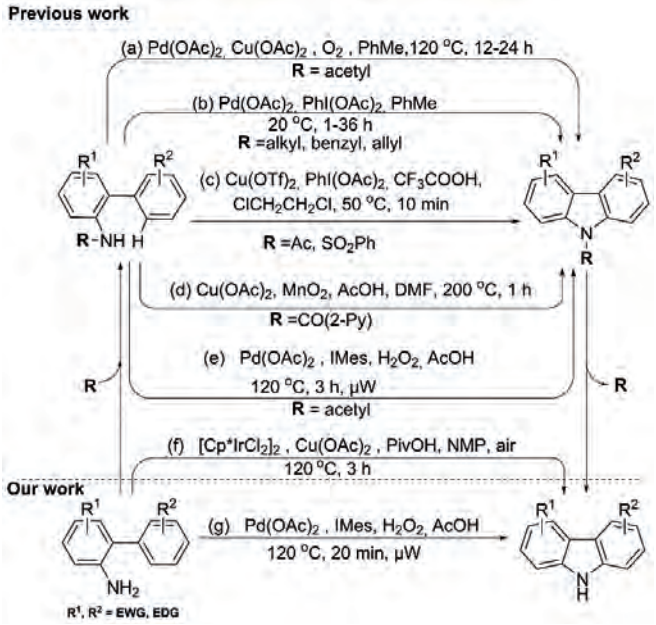
decade, a few additional methods for the synthesis of carbazoles have been described based on tandem C–H activation and C–N bond formation.

Gaunt and collaborators [12b] disclosed a Pd-catalyzed method with hypervalent iodine compound, phenyliodosyl diacetate as the reoxidant for the palladium catalyst $Pd(OAc)_2$ (Scheme 5.2, path b). A significant improvement of this method involved the low reaction temperature. However, the method suffer with drawbacks, specifically, the need of protecting group and the formation of stoichiometric quantities of the reduced oxidant as the side product. Subsequently, Chang and collaborators [14] and Hirano, Miura, and collaborators [12d] described two additional methods for the carbazole involving copper as the catalyst (Scheme 5.2, path c and d). Both of these methods also require protecting group and stoichiometric quantities of oxidants, such as $PhI(OAc)_2$, and MnO_2 were used.

Recently, a direct ring closing method disclosed by Satoh, Miura and collaborators [12e] using Ir(III)/Cu-based catalytic system with air as the terminal oxidant (Scheme 5.2, path f). Until now, this is the only method involved intramolecular amination to the preparation of the carbazole scaffold from unprotected 2-aminobiphenyl, but this process requires an expensive iridium based catalyst along with several other additives to facilitate the ring-closing reaction.

Compared with protected amino group, a free amine group has been less frequently used owing to its tight coordination with metal complex that suppress the catalytic activity. However, the major drawbacks of these reported methods includes, need of protecting/auxiliary group, long reaction time, and needs of expensive catalyst. We wanted to develop a more straightforward and practical procedure for the synthesis of carbazole which is highly required. Herein, we have developed a direct method for ring closing of 2-aminobiphenyls by means of intramolecular C-H functionalization followed by ring closing C-N bond formation to produce carbazole. (Scheme 5.2, path g). We have also developed a ring closing method using N-protected 2-aminobiphenyls to attain corresponding N-acetylcarbazoles (Scheme 5.2, path e).

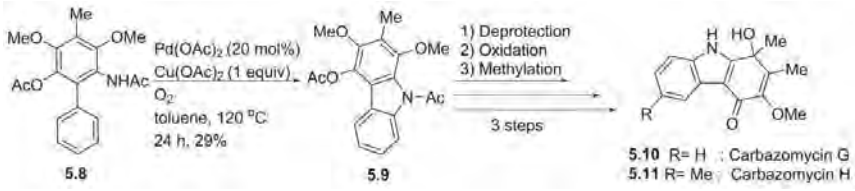
Scheme 5.2. Carbazole synthesis using intramolecular C-H activation and C-N bond formation



5.3 Results and Discussion

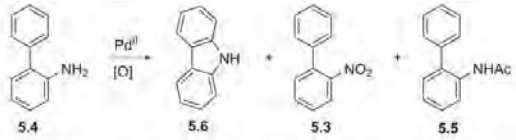
The project discussed in chapter 6, the total synthesis of Carbazomycin G, [15] several new synthetic reaction were required, such as preparation of congested 2-nitrobiphenyl by means of Suzuki coupling and required efficient reduction method to convert nitro into amino group. Initially, we attempted the ring closing reaction using the Buchwald method [13] for our substrates **5.8**. However, the method not operated well and afforded only 29% conversion yield of compound **5.9** based on GC analysis (Scheme 5.3). We have also performed several trial reactions with varying the experimental conditions and parameters. However, these trails not improved the yield of the target product, nevertheless attained different unidentified compounds. It might be due to the congested substitution pattern of the substrate molecule under oxidative conditions.

Scheme 5.3 Attempt to produce carbazole scaffold leading to Carbazomycin G/H



In order to improve the method, we investigated the ring closing protocol using the free amine as a substrate. The free amine can be oxidized with different reaction conditions.[16] However, we wanted to develop a direct cyclization method using 2-aminobiphenyl **5.4** as a substrate to achieve the target molecule. Table 5.1 shows the screening of the ring closing reaction of 2-aminobiphenyl **5.4** with altering the reaction time and the catalytic systems. We observed the target carbazole **5.6** combined with two different side products **5.3** & **5.5** (Table 5.1, entry 1-7). Evidently the catalytic system with $Pd(OAc)_2$ and IMes.HCl (1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride) ligand operated reasonably well towards the desired target product (Table 5.1, entry 7) and obtained 67% of the target product **5.6**. This reaction condition as a starting point to determine the high yielding protocol.

Table.5.1 Screening of ring closing reaction to produce carbazole scaffold[a]

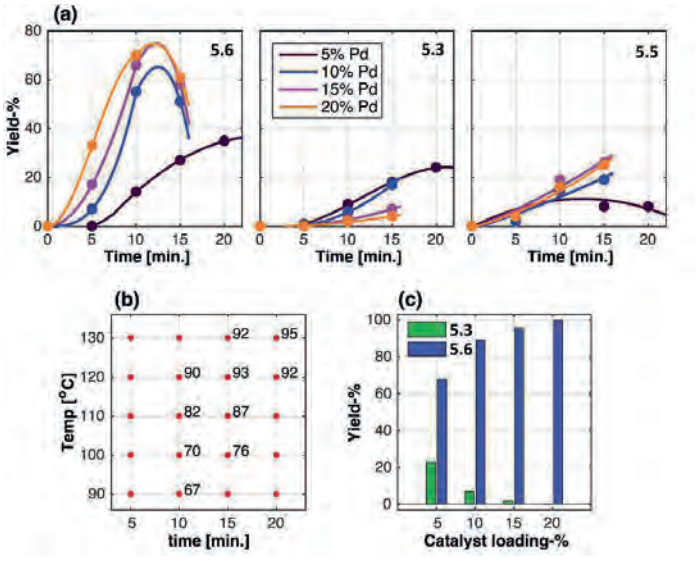


Entry	Catalyst/Ligand	t (min)	Measured response yield (%)[b]			
			Conv.	5.4	5.3	5.5
1	$Pd(OAc)_2$	90	93	39	26	20
2	$Pd(OAc)_2$	60	86	48	30	nd
3	$Pd(OAc)_2$	20	67	30	10	24
4	$Pd(OAc)_2$/IMes.HCl	20	84	45	18	15
5	$Pd(tfa)_2$	20	77	49	9	16
6	$Pd(tfa)_2$/IMes.HCl	20	83	43	15	21
7[c]	$Pd(OAc)_2$/IMes.HCl	10	97	67	2	28

(a) Procedure: To a solution of 2-aminobiphenyl **5.4** (84.5 mg, 0. 5 mmol) in glacial acetic acid (5 mL), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%) or $Pd(TFA)_2$ (8.3 mg, 0.025 mmol, 5 mol%), IMes. HCl (8.5 mg, 0.025 mmol) and H_2O_2 (0.128 mL) were added to perform under microwave irradiation at a temperature T=90 °C. The reaction mixture was monitored by means GC-MS using response factor to determine the various reaction products. (b) Conversion of compound **5.4**, measured yields of compound **5.3** and **5.6** were corrected based on the response factors (2-aminobiphenyl, F=1), (2-Nitrobiphenyl, F=1.29) and (Carbazole, F=1). The yield of compound **5.5** was uncorrected with response factor (c) 20 mol% $Pd(OAc)_2$ was used

A number of experiments were conducted and monitored by GC analysis after a period of 5-20 min. As a result, increased amount of palladium catalyst from 5-20 mol% revealed a major effect towards the target carbazole **5.6** compound. However, the target product yield was decreased after a time of 10-15 min in addition with formation of side products **5.3 & 5.5** (Figure 5.3a). Further optimizations were conducted by using the systematic variation with reaction temperature and time (Figure 5.3b). High yielding reaction condition was found based on the reaction profile and provided almost a quantitative conversion of the substrate. The optimized protocol was then repeated with different amount of catalyst varying from 5-20 mol% using the freshly opened bottle of catalyst and ligand (Figure 5.3c). The results illustrates that using 20 mol% of Pd at 120 ^{o}C under microwave irradiation afforded quantitative conversion yield of carbazole. The reduced quantity of Pd loading yielded the corresponding oxidized product 2-nitrobiphenyl. Using 5 mol% of Pd, afforded 23% yield of the oxidized product. The formation of the oxidized product is less when the amount of Pd loading is increased from 5-20 mol%. The developed method was also suitable with 2-acetaminobiphenyl **5.5** to produce corresponding N-acetylcarbazoles **5.7**.

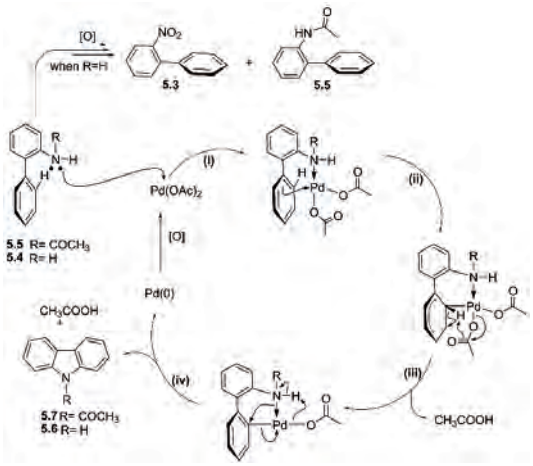
Figure 5.3. Reaction profile, screening and variation of the ring closing reaction



5.4 Proposed reaction mechanism

Based on previous mechanistic studies,[12a,13] we have proposed a reaction mechanism for ring closing of both the protected and un-protected 2-aminobiphenyls **5.4 & 5.5** leading to corresponding carbazole compounds **5.6 & 5.7** via intramolecular C-H activation and subsequent C-N bond formation (Figure 5.4). Pre-association of the substrates **5.4 & 5.5** to palladium acetate enables the ortho-palladation (Figure 5.4, step i) followed by the production of six-membered palladacycle with concomitant release of acetic acid (step ii and iii). The final step involves the reductive elimination leads to the target product with reduced palladium species Pd(0) (Figure 5.4, step iv). The Pd (0) is reoxidized to Pd(II) by means of hydrogen peroxide and thus completing the catalytic cycle. The side product **5.3** and **5.5** can also be obtained under the experimental conditions.

Figure 5.4 Proposed mechanism for the carbazole framework

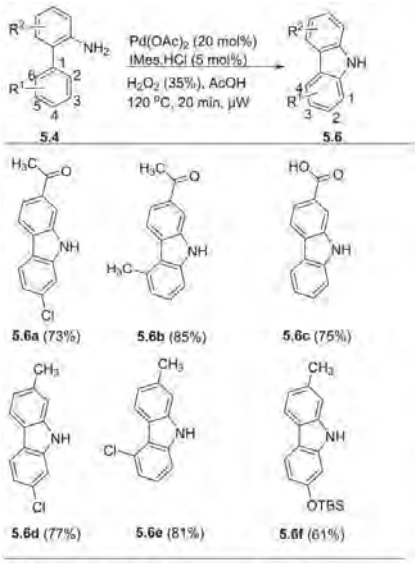


In overall, we have developed an efficient method for the synthesis of carbazoles **5.6** via Palladium catalyzed ring closing reactions. The method involves direct ring closing of 2-aminobiphenyls **5.4** using intramolecular C-H functionalization and C-N bond formation under microwave irradiation for shorter time afforded medium to excellent yield of the carbazole derivatives.

5.5 Scope and limitations

A scope and limitation of the developed method has been investigated with different derivatives of 2-aminobiphenyls **5.4** with substitution on both the rings, As a result, the method compatible with both protected and unprotected 2-aminobiphenyls involving different electron donating and withdrawing groups. The Table 5.4 shows different derivatives of carbazoles were synthesized using oxidative cyclization reactions of 2', 4' and 4-substituted 2-aminobiphenyls. The method tolerates both electron withdrawing and donating groups for the synthesis of carbazoles at 120 ^{o}C for 20 minutes, resulting moderate to good yield were obtained (Scheme 5.4, **5.6a-5.6f**). The reaction was unsuccessful without protection of the hydroxy group. However, attempt to protect the -OH with TBS-Cl (Scheme 5.4, **5.6f**) was successful, obtained 61% isolated yield of the desired carbazole product. However, the product has been decomposed based on the NMR studies.

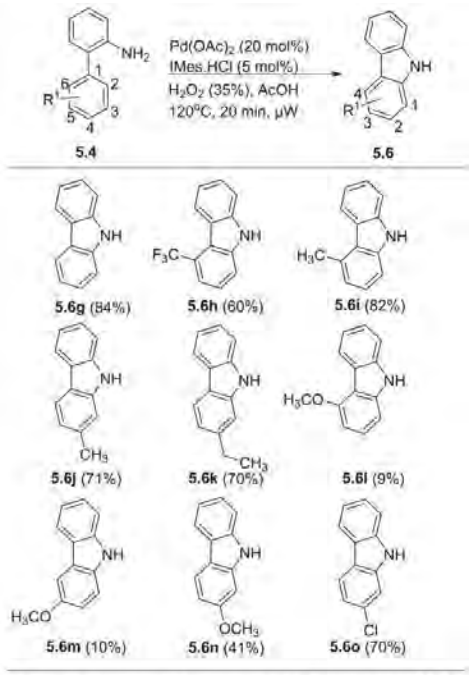
Scheme 5.4 Scope and limitation of the ring closing reaction of 2', 4' and 4-substituted 2-aminobiphenyls[a]



(a) General procedure: In a microwave tube, 2-aminobiphenyl **5.4** (1 mmol) in glacial acetic acid (5 mL) and then $Pd(OAc)_2$ (0.2 mmol), IMes·HCl (0.05 mmol), and H_2O_2 (35 %, 2.9 mmol) were added. The vial was sealed and submerged in the microwave cavity for 20 min at 120 ^{o}C. Isolated yields are reported

For substrates with 2', 3' and 4' substituted 2-aminobiphenyls, we also attained a moderate to good yield of the desired carbazole except with methoxy substituent (Scheme 5.4). For example, we obtained only 10% of product with methoxy substituents at ortho and meta positions (**5.6l** and **5.6m**) and moderate yield obtained at para position (**5.6n**). This might be due to the inductive effect of methoxy substituent that would disrupt the intermediate and the expected methoxy group would be oxidized in presence of the oxidative conditions. The same applies to the hydroxy substituents. Furthermore, this method could be suitable and efficient for the synthesis of unsymmetrical carbazoles. In general, electrophilic substitution on carbazole favours the position 3 and 6. However, in our method it allows substitution also at position 2 and 4 that might be useful for the synthesis of different carbazole containing natural products.

Scheme 5.5 Scope and limitation of the ring closing reaction of 2', 3' and 4'-substituted 2-aminobiphenyls[a]

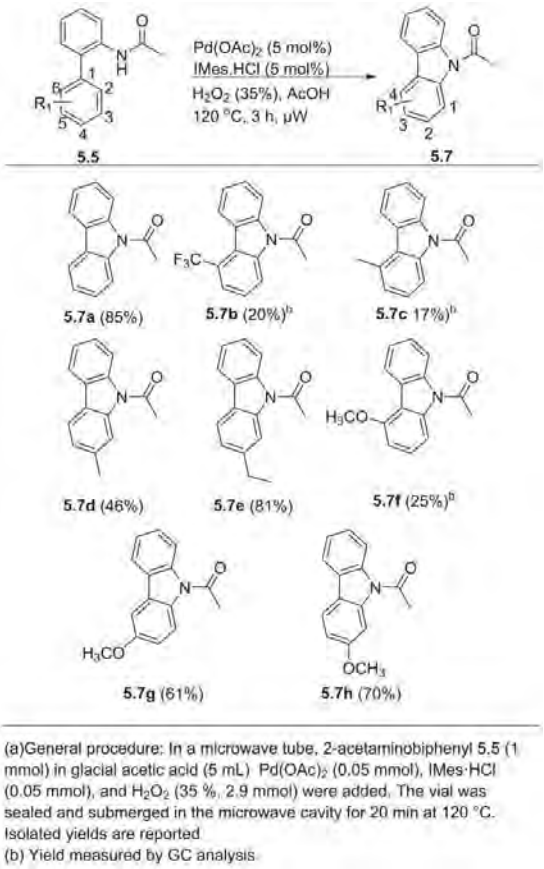


(a) General procedure: In a microwave tube, 2-aminobiphenyl **5.4** (1 mmol) in glacial acetic acid (5 mL) and then $Pd(OAc)_2$ (0.2 mmol), IMes·HCl (0.05 mmol), and H_2O_2 (35 %, 2.9 mmol) were added. The vial was sealed and submerged in the microwave cavity for 20 min at 120 °C. Isolated yields are reported

We have attempted whether our method would tolerate for the protected 2-aminobiphenyls **5.5** (Scheme 5.6) to synthesize N-acetylcarbazoles **5.7**. The substrate, 2-acetaminobiphenyl **5.5** was synthesized via acetylation of 2-aminobiphenyls **5.4** using acetyl chloride, followed by ring closing reaction under the same conditions as in Scheme 5.4 and 5.5, except the Pd-catalyst loading (5 mol%) and the reaction time (3 h). Using this method, the reaction with methoxy substituent at meta and para position (Scheme 5.6, **5.7g** and **5.7h**) was successful and only 25 % conversion yield was obtained at ortho position (**5.7f)**. The substituent at meta position (Scheme 5.6, compound **5.7g**) provided two regioisomer, the major isomer 7'-methoxy derivative obtained in 61% isolated and the 5'-methoxy substituted compound in 12% yield due to the steric hindrance of the substituent. Substrates with methyl group at ortho and para position gave low to moderate yield (Scheme 5.6, **5.7c** and **5.7d)** and ethyl group at para position afforded good yield **(5.7e)** Additionally, only 20% conversion yield was obtained with strong electron withdrawing groups (CF_3) (**5.7b**).

Eventually, the ring closing reaction of both the protected and unprotected 2-aminobiphenyls were investigated with various substitution pattern on both the ring with different substituent pattern. The rapid method for the synthesis of carbazole under the mild conditions could be useful for the synthesis of different natural products drugs and important dye compounds.

Scheme 5.6 Scope and limitation of the ring closing reaction of 2', 3' and 4'-substituted 2-acetaminobiphenyls[a]



(a)General procedure: In a microwave tube, 2-acetaminobiphenyl 5.5 (1 mmol) in glacial acetic acid (5 mL) $Pd(OAc)_2$ (0.05 mmol), IMes·HCl (0.05 mmol), and H_2O_2 (35 %, 2.9 mmol) were added. The vial was sealed and submerged in the microwave cavity for 20 min at 120 °C. Isolated yields are reported
(b) Yield measured by GC analysis

5.6 Conclusion

We have developed a novel synthetic route to carbazole by means of three synthetic steps especially the step involves Pd(II)-catalyzed intramolecular C-H activation and C-N bond formation is noteworthy. The developed methods operated excellently, tolerated with variety of electron releasing and withdrawing groups, and obtained good to excellent yield of the target carbazole scaffold. Moreover, the novel described method is used to synthesize the carbazomycin G, a carbazole 1,4-quinone alkaloid. Further development and synthesis of various biologically active natural products using transition metal catalyzed reactions is under progress in our laboratory.

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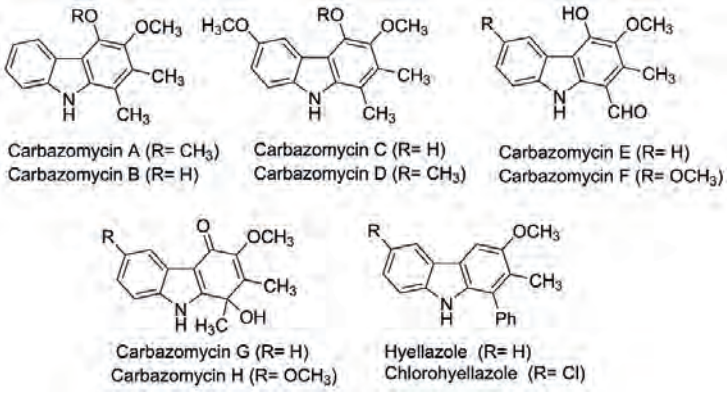
Chapter 6

Total Synthesis of Carbazomycin G

6.1 Introduction

Carbazomycin is one of the important class of carbazole alkaloid isolated from *Streptoverticillium ehimense,* have possessing numerous biological properties involving anticancer,[1] antibacterial[2] and antifungal[3] activities. Carbazomycin alkaloids A–H (Figure 6.1) were first discovered and structure elucidated by Nakamura and co-workers.[4] The other type of carbazole alkaloid, hyellazoles (Figure 6.1) were isolated from blue green alga *(Hyella cae~pifosa)* [5]. These naturally occurring carbazole alkaloids are highly challenging target molecule to organic chemists to develop novel synthetic methodologies due to their enormous application in medicines. In compare with the other carbazomycins, several research groups have interested in total synthesis of carbazomycin G, because of its interesting substitution pattern with chiral center and important biological applications.

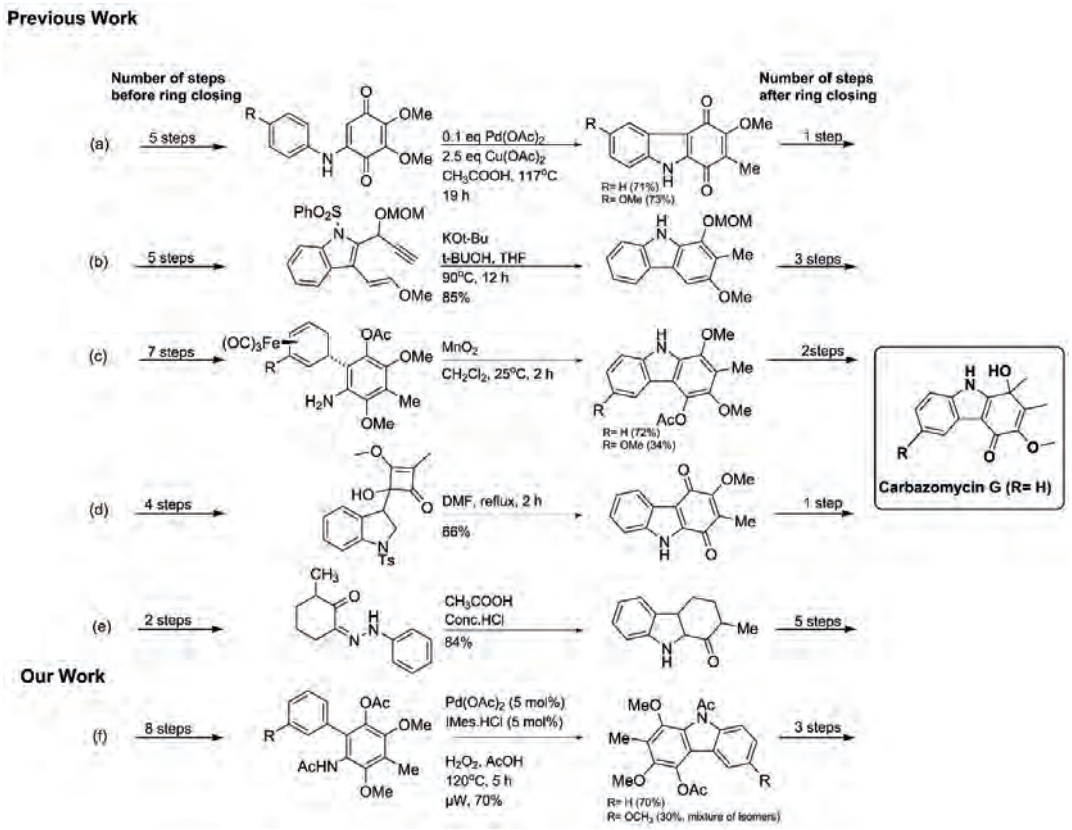
Figure 6.1. Structure of naturally occurring carbazomycin and hyellazole derivatives



Several synthetic approach of Carbazomycin G **6.15** were already reported. [6] Particularly using a consecutive transition metal-mediated C-C and C-N bond formations is noteworthy. (Scheme 6.1). This methodology was applied in total synthesis of carbazomycins including A, [7] B, [7] C, [8] D, [8] and E. [9] and other important carbazole alkaloids. [10] Knölker et al [11] developed the first iron-mediated total synthesis of carbazomycin G and H (Scheme 6.1, path c). Knölker et al also reported another method [12] involving Pd-catalyzed oxidative cyclization of arylamino-1,4-benzoquinone for the synthesis of carbazomycin G and H (Scheme 6.1, path a). In 2000, Hibino and co-workers [13] reported a synthesis of carbazomycin G through an allene mediated electrocyclic reaction (Scheme 6.1, path b). In 2014, Hu et al [14] described a method involving thermal ring expansion and self-redox cascade reaction (Scheme 6.1, path d). Additionally, total synthesis of carbazomycin G synthesized by means of Fischer indole cyclization method [15] was also reported (Scheme 6.1, path e).

Here, we reported a method involves several synthetic schemes for the synthesis of novel intermediates in order to obtain the target molecule. Our approach is based on the Pd-catalyzed intramolecular C-H activation followed by C-N bond formation to attain the congested carbazole [16] moiety in order to synthesize the target molecule carbazomycin G/H (Scheme 6.1, path f).

Scheme 6.1. Previously described synthetic methods leading to carbazomycin G

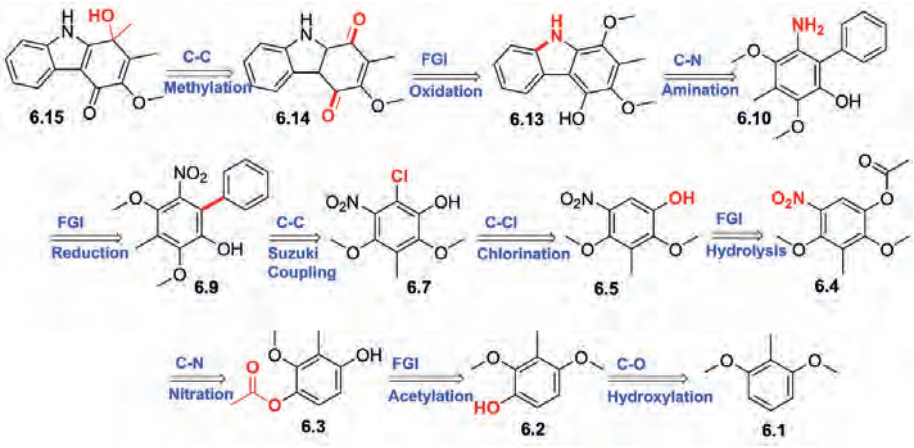


6.2 Retrosynthetic pathway

Our retrosynthetic analysis leading to carbazomycin G is shown in Figure 6.2. The target natural product **6.15** was accessible via regioselective methylation of 1,4-quinone **6.14**. The quinone moiety **6.14,** the key intermediate, prepared by oxidation of the novel carbazole compound **6.13** with nitric acid. The required carbazole moiety **6.13** can be synthesized through Pd-catalyzed intramolecular C-H activation and subsequent C-N bond formation of aminobiphenyl **6.10**, which can be prepared via reduction of nitrobiphenyl **6.9**. Furthermore, the central biphenyl moiety **6.9** was obtained by Suzuki cross coupling of crowded chloro compound **6.7**. To obtain the

highly substituted chloro compound, needed access to synthesize the nitrophenol **6.5,** which can be prepared in four steps from 2,6-dimethoxy toluene **6.1** using the previously disclosed procedure.[17]

Figure 6.2 Retrosynthetic route for carbazomycin G

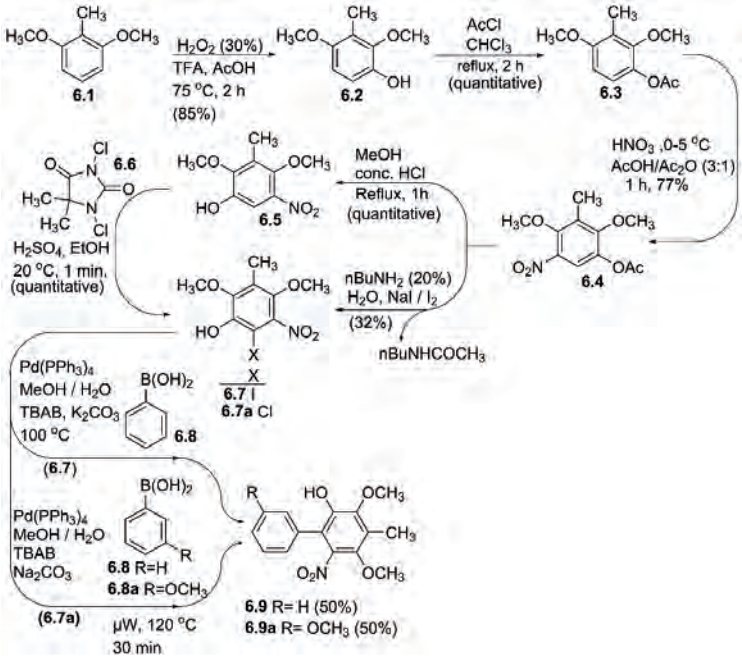


6.3 Method and discussion

Our approach for the total synthesis of carbazomycin G involves twelve synthetic steps, starting from commercially available 2,6-dimethoxy toluene **6.1**. A nitro phenol **6.5** intermediate compound was synthesized earlier in our group [17] in 4-steps involving oxidation, acetylation, nitration and de-protection. Attempts to introduce the iodide to compound **6.5** was successful following literature procedure. [18] However, the reaction was hardly reproducible. We assumed that it might be of impure iodine. Therefore, we abandoned this strategy to proceed further to do Suzuki cross coupling reaction with congested iodoarene **6.7**. Later on, a novel method was developed in our group for the fast halogenation of heterocycles using *N*,*N*′-dihalo-5,5-dimethylhydantoin.[19] The developed method made us wonder whether this could operate for the iodination with *N*,*N*′-diiodo-5,5-dimethylhydantoin (DIH) as iodinating reagent. Nevertheless, a trial of iodination of compound **6.5** was failed. Afterwards, we attempted to perform bromination of compound **6.5** with the corresponding *N*,*N*′-

dibromo-5,5-dimethylhydantoin (DBH) as brominating agent. However, this attempt was also not successful. Attempts with *N*,*N*′-dichloro-5,5-dimethylhydantoin (DCH) successfully afforded chlorinated compound **6.7a** in quantitative yield. Subsequently, we established a Suzuki cross coupling reaction of congested chloroarene **6.7a** with phenylboronic acid **6.8**. We have attempted the Suzuki cross coupling reaction with our previously reported methodology [20], however low yields (29%) of the coupled product **6.9** were only obtained. Therefore, we have optimized and developed a novel method for the synthesis of congested 2-nitrobiphenyls [21] (discussed in chapter 3) (Scheme 6.2).

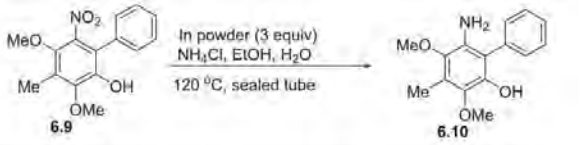
Scheme 6.2. Suzuki cross coupling method to produce congested 2-nitrobiphenyls



Intermediate 2-nitrobiphenyl compound (**6.9)** was synthesized in 50% yield to synthesis the carbazomycin G **6.15**. For synthesis of carbazomycin H, we have performed a reaction with 3-methoxy phenylboroinc acid **6.8a** under the same Suzuki cross coupling conditions afforded **6.9a** in 50% yield. Reduction of nitro group yielded **6.10**. Several synthetic methods were available for nitro group reduction. [22] However, we screened the reaction with various experimental conditions using indium powder

based on a method reported by Moody et al.[23] We initially tested the indium method using from two different suppliers (Aldrich and Alfa Aesar). Both methods afforded only 3% yielded at 100 ºC. Increased reaction duration (3 h) and temperature (120 ºC) resulted quantitative yield of desired amine compound **6.10** (Table 6.1, entry 7).

Table 6.1. Screening of reduction method using In/NH_4Cl[a]

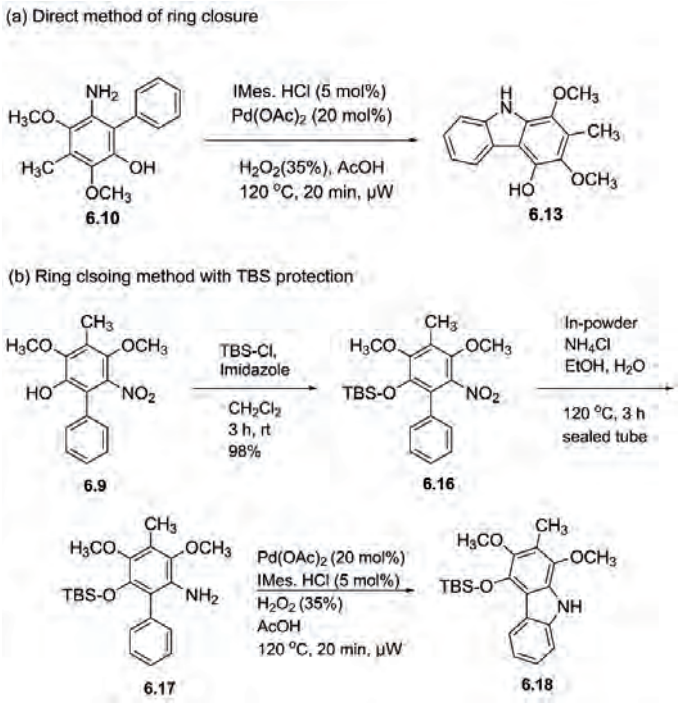


#	In (equiv)	Sonication time (min)	Temp (°C)	Time (h)	Conv.(%) 6.9	Selec.(%)	Yield(%) 6.10
1[b]	3	-	100	3	0	0	0
2[b]	3	30	100	3	3	100	3
3	3	-	100	3	3	100	3
4	3	60	100	1	1	100	1
5	3	-	78 (reflux)	2	3	100	3
6	3	30	120	3	>99	100	>99
7	3	-	120	3	>99	100	>99

(a) General procedure: 2-Nitrobiphenyl **6.9** (1 mmol) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (2 mmol) in H_2O (1.2 mL) and indium powder (3 mmol, 99.99% 100 mesh (purchased from Alfa Aesar), use preferably a freshly opened bottle or stored under Ar) were added. The tube was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h.
(b) Indium powder (99.99%) was used (Purchased from sigma aldrich)

Both nitro compounds **6.9 & 6.9a** were successfully converted into their corresponding amines using Indium mediated reduction method. Amine **6.10** underwent direct cyclization using our new method involves intramolecular C-H activation and C-N bond formation (discussed in Chapter 5). [16] However, this method was not successful to compounds bearing oxidizible functional groups such as methoxy and hydroxyl groups. Compounds with protected hydroxyl groups in **6.9** using tetrabutyl dimethylsilylchloride (TBS-Cl) resulted in 98% yield of compound **6.16** followed by reduction of nitro compound of **6.16** afforded compound **6.17**. However, the subsequent ring closing reaction was failed (Scheme 6.3), resulting decomposition of products.

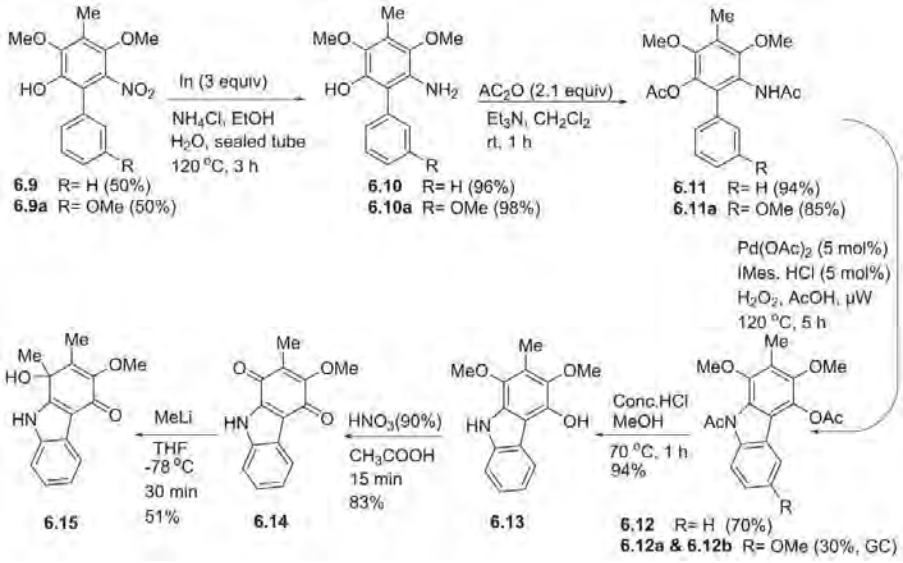
Scheme 6.3. Attempts to produce carbazole moiety via ring closing reaction



Subsequent acetylation (both hydroxyl and amine) was carried out of **6.10** using acetic anhydride to obtain compound **6.11**, followed by next step with ring closing reaction afforded medium yield (37 %) of the ring-closed product **6.12** after 3 hours. However, prolonged reaction time from 3 hours to 5 hours gave 70% isolated yield of compound **6.12**. In the case of carbazomycin H intermediates, the protection step to obtain compound **6.11a** was successful and followed by the ring-closing step afforded two structural isomers of compound, 9-acetyl-1, 3, 6-trimethoxy-2-methyl-9*H*-carbazol-4-yl acetate **6.12a** and 9-acetyl-1, 3, 8-trimethoxy-2-methyl-9*H*-carbazol-4-yl acetate **6.12b**. The separation of these two isomers were unsuccessful. Therefore, we abandoned the strategy to continue further with the synthesis of Carbazomycin H. From this point, we focused only the total synthesis of carbazomycin G. We could able to achieve the congested novel carbazole moiety **6.13** in 94% yield after the de-

protection of the acetyl groups. The last two steps involves oxidation of the compound **6.13** followed by regioselective methylation. The oxidation of methoxy phenol compound **6.13** into 1,4-quinone **6.14** was successfully synthesized in 83% yield based on the oxidation method reported in our group[24] using nitric acid. The final step involves the regioselective methylation [6c] (1,2-addition at C-1) of 1,4-quinone compound **6.14** with methyl lithium afforded the carbazomycin G **6.15** in 51% yield (Scheme 6.4) with addition of some unidentified products.

Scheme 6.4. Synthetic route leading to carbazomycin G



6.4 Conclusion

We have developed a novel synthetic methodology to synthesis a carbazole alkaloid Carbazomycin G in twelve-step synthesis with medium to excellent yields in each step. Thus, the total synthesis afforded an overall yield of 8.1%. This total synthesis is associated with a couple of fascinating transition metal catalyzed organic reactions, including Suzuki cross coupling of congested chloroarenes and intramolecular C-H activation followed by C-N bond formation for the synthesis of novel congested intermediates.

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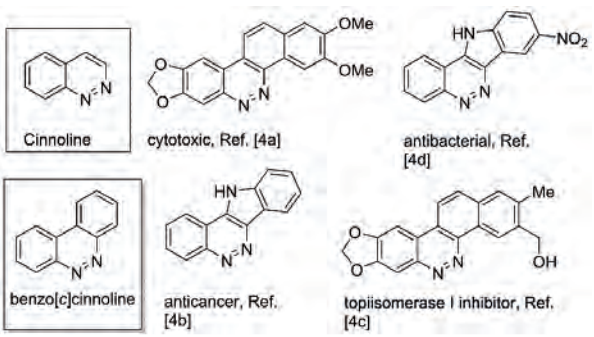
Chapter 7

Synthesis of Benzo[*c*]cinnolines by means of the Suzuki Cross Coupling

7.1 Introduction

Cinnolines are an important heterocyclic compound and the structural moiety are often found in various potentially active pharmaceutical compounds.[1] Cinnoline and its derivatives are known to display interesting biological properties such as anti-cancer,[2a] antibacterial,[2b] antimicrobial,[2c] antifungal,[2d] anti-inflammatory,[2e] antiulcer,[2f] anti-hypertensive,[2f] topoisomerase inhibitor[2g] and cytotoxic activities.[2h] Among various cinnoline derivatives, benzo[c]cinnolines are of particular interest in medicinal chemistry due to their promising anticancer properties.[3] Subsequently, various important cinnoline derivatives have been identified as biologically active compounds and shown in Figure. 7.1.[4]

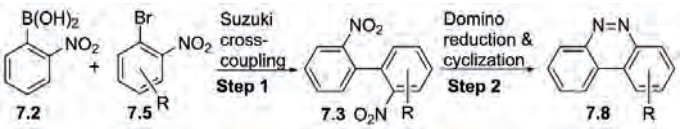
Figure 7.1. Biologically active Cinnoline derivatives



Previously in our research group, reported a synthetic method for the synthesis of symmetrical benzo(*c*)cinnolines[5] by means of the 2, 2'-dinitro-1-1'-biphenyls which were synthesized via Ullmann coupling.[6] The method using the Suzuki cross coupling[7] reaction to synthesize the symmetrically substituted 2, 2'-dinitro-1-1'-biphenyls[8] was not very successful which afforded low yields only. Recently, for a

project related to the synthesis of carbazole scaffold [9] (discussed in Chapter 5), we needed access to synthesize 2-nitrobiphenyls that we could able to produce via our previously disclosed Suzuki cross coupling reaction of 2-nitro-1-iodobenzenes with phenylboronic acid.[8] We revisited the method and improved a protocol using optimization study that allows 2-nitro-chlorobenzenes as well as 2-nitro-bromobenzenes as reaction partners with phenylboronic acid for the synthesis of 2-nitrobiphenyls[10] in excellent yield and selectivity. By these encouraging results we wanted to explore the developed method could also be suitable for the synthesis of 2, 2'-dinitrobiphenyls **7.3** and thereby access to synthesize the corresponding unsymmetrically substituted benzo(*c*)cinnolines **7.8**. The important features of benzo[*c*]cinnoline **7.8** derivatives incited to synthesize the moiety based on the efficient methodology by means of two steps (Scheme 7.1).

Scheme.7.1. Two step synthesis of benzo[*c*]cinnoline



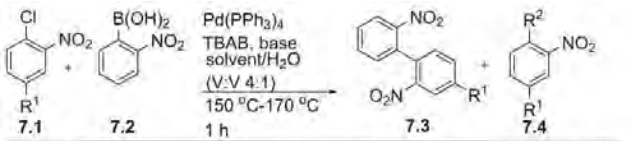
In addition to our method, benzo(*c*)cinnolines **7.8** were synthesized previously by using different synthetic methodologies. In 2007, Scobie et al reported a three-step synthesis involving a base catalyzed condensation of 2-amino-2'-nitrobiaryls.[11] Recently, Pal and collaborators described a method using photocatalytic reduction of 2, 2'-dinitro-1-1'-biphenyls.[12] Simultaneously, Sridhar et al reported a method via consecutive C-C and C-N bond formation.[13] These reported methods required several additives were necessary in order to carry out the reaction as well as require long reaction time and several synthetic steps were needed to produce the benzo(*c*)cinnoline moiety.

7.2 Results and discussion

We initially attempted a Suzuki cross coupling reaction to synthesize 2, 2'-dinitrobiphenyls **7.3** using 2-nitrochlorobenzenes **7.1** and 2-nitro phenylboronic acid **7.2** as reaction partners. However, the method was unsuccessful and obtained only the homocoupled product of the 2-nitro phenylboronic acid **7.2**. Therefore, we wanted to investigate the rate of the reaction in the presence of electron withdrawing substituent. For example, we have performed a reaction with CF_3 group, afforded the desired coupled product although in low yield only. Interestingly, an ipso-type nucleophilic substitution was observed at high temperature with solvent as the nucleophile. Therefore, we abandoned the strategy to further investigate the reaction. The screening of the reaction with 2-nitrochlorobenzenes **7.1** was shown in Table. 7.1.

Widdowson and Wilhelm[14] stated that the nitro group in the ortho position is not only acting as an electron withdrawing group, but also as a coordinating group for incoming palladium in the Suzuki cross coupling and thereby act a significant influence on the C–C coupling. Moreover, the recent study by Sakaki, Nakao, and collaborators [15] described that the NO_2 group of nitroarenes, even operated as the leaving group in the Suzuki cross coupling. These observations exemplifies the difficulties of using ortho-nitro substituted reagents in the Suzuki cross-coupling experiments.

Table 7.1. Screening of Suzuki cross coupling reaction to produce 2-nitrobiphenyls[a]

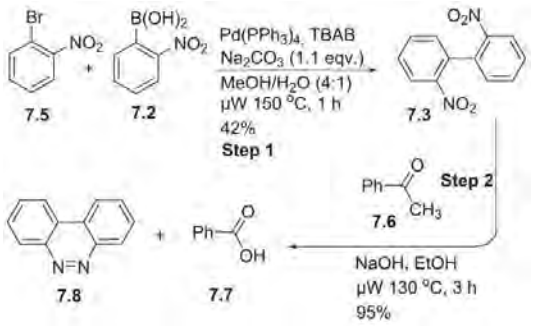


#	R^1	Base	[equiv]	Solvent	R^2	T[°C]	Conversion Yield (%) 7.3	7.4
1	H	Na_2CO_3	1.1	MeOH	OMe	150	nd	nd
2	CF_3	Na_2CO_3	1.1	MeOH	OMe	150	nd	nd
3	CF_3	Cs_2CO_3	2.0	MeOH	OMe	150	14	35
4	CF_3	NaOH	2.0	MeOH	OMe	150	19	70
5	CF_3	NaOH	2.0	DMF	NMe_2	160	8	78
6	CF_3	NaOH	2.0	DMF	NMe_2	170	nd	91

(a) General procedure: 1-chloro-2-nitrobenzene **7.1** (1 mmol), 2-nitrophenylboronic acid **7.2** (1.5 mmol), Na_2CO_3 (1.1 mmol), TBAB (0.08 mmol), and $Pd(PPh_3)_4$ (0.026 mmol, 2.6 mol-%) MeOH (4 mL) and H_2O (1 mL) under microwave heating for 60 min. at temperature range of 150 °C-170 °C
(b) Yield measured by GC

Furthermore, we started to examine the Suzuki cross coupling reaction with 2-nitrobromo benzenes **7.5** and phenylboronic acid **7.2** as reaction partner. The reaction afforded a moderate yield of the unsubstituted coupled product 2,2'-dinitro-1,1'-biphenyl **7.3** (Scheme 7.2, Step 1). The subsequent step (Scheme 7.2, Step 2) involves the redox process involving a partial nitro group reduction using acetophenone **7.6** followed by intramolecular cyclization leads to benzo[*c*]cinnoline scaffold **7.8** in excellent yield with acetic acid **7.7** as a side product. The mechanism of the reductive cyclization of 2,2'-dinitro-1,1'- biphenyl **7.3** into corresponding benzo[*c*]cinnolines **7.8** has been discussed previously in our group.[5]

Scheme 7.2. Two step synthesis of benzo[*c*]cinnoline involving Suzuki cross coupling reaction and domino reductive cyclization.

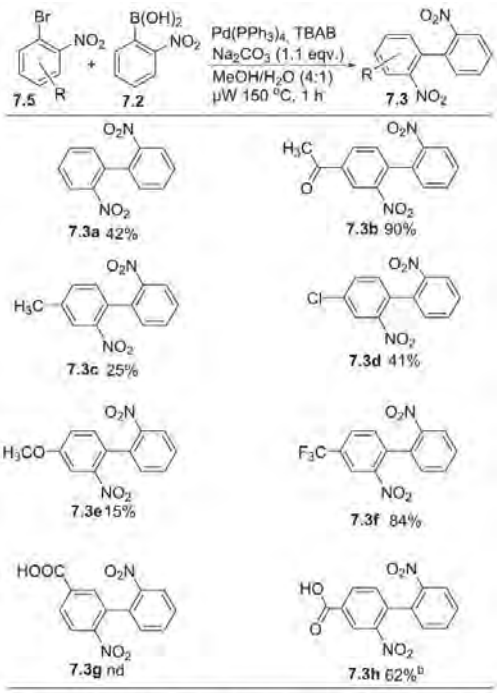


7.3 Scope and limitations

A scope and limitation of the Suzuki cross coupling reaction has been investigated with different functionality on the 1-bromo-2-nitrobenzenes **7.5** with various electron withdrawing and donating groups. As a result, all of these reactions except the 3-bromo-4-nitrobenzoic acid (**7.5g**) afforded the corresponding 2,2'-dinitrobiphenyls (**7.3a-h**) in a moderate to excellent yield. (Scheme 7.3). For example, protecting carboxylic acid group as a methyl ester (methyl 4-bromo-3-nitrobenzoate) afforded a moderate yield of the benzo[*c*]cinnoline carboxylic acid (**7.3h**) due to the ester hydrolysis under the basic conditions. The substrates bearing with electron-donating

groups provided low yield (**7.3c** and **7.3e**) and high yield were obtained with strong electron-withdrawing substituents such as $COCH_3$ and CF_3 (**7.3b** and **7.3f**). In case of weak deactivating group, it gave moderate yield (**7.3d**). These results revealed that the electron withdrawing groups deactivate the aromatic ring, decrease the electron density on C-Br bond towards the oxidative addition and facilitates the transmetallation with boronicacid even in the presence of strong deactivating groups. With the low yield of biphenyl, we obtained the hydrodebrominated compound and nitrobenzene in range of 40-50% yield via protodeboration under basic conditions.

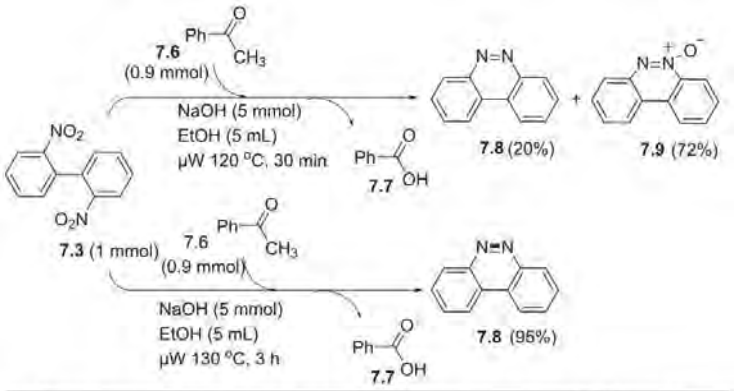
Scheme 7.3. Suzuki cross coupling reaction for the preparation of 2,2'-dinitro-1,1'-biphenyls[a]



(a) General procedure: 1-Bromo-2-nitrobenzene **7.5** (1 mmol), 2-nitrophenylboronic acid **7.2** (1.5 mmol), Na_2CO_3 (1.1 mmol), TBAB (0.08 mmol), and $Pd(PPh_3)_4$ (0.026 mmol, 2.6 mol-%) MeOH (4 mL) and H_2O (1 mL) under microwave heating for 1 h. at 150 °C. Isolated yields were reported
(b) **7.3h** was formed when the ester substrate (**7.5h**) was hydrolysed under the basic conditions. The product yield was estimated by means of ^{1}H-NMR.

We have initially attempted to synthesize the target benzo[c]cinnolines **7.8** from 2,2'-dinitrobiphenyls **7.3** using shorter time (30 min) at 120°C under microwave irradiation. As a result, the reaction afforded the benzo[*c*]cinnoline-*N*-oxide **7.9** (less reduced form of product) as the major product and benzo[*c*]cinnoline **7.8** (expected product) as the minor product (scheme 7.4). We wanted to attain the benzo[c]cinnoline as our target molecule. Therefore, we have examined the rate of the reaction by increasing the reaction time from 30 min to 3 hours and slightly increased the temperature from 120 °C to 130 °C that attained an excellent yield (95%) of the target benzo[*c*]cinnoline **7.8**.

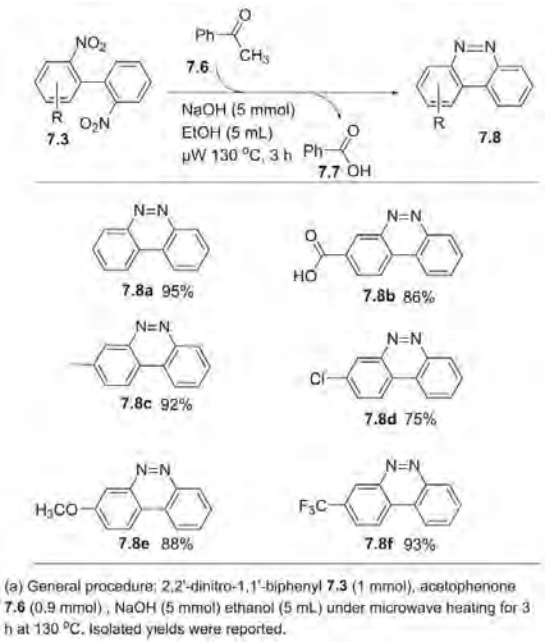
Scheme 7.4. Screening reaction conditions for the domino reductive cyclization[a]



(a) General procedure: 2,2'-dinitro-1,1'-biphenyl **7.3** (1 mmol), acetophenone **7.6** (0.9 mmol), NaOH (5 mmol) ethanol (5 mL) under microwave heating for 30 min at 120 °C and 3 h at 130 °C. Isolated yields were reported.

We examined the scope of the reaction with different functionality as we made in the Suzuki cross coupling which afforded high to excellent yield in all the cases and the method was compatible with both the activating and deactivating substituents such as $–CH_3$, $-OCH_3$, -Cl, $-CF_3$, -COOH and the developed method was not suitable in the redox process with easily oxidizable groups such as aldehyde and alcohol etc.

Scheme 7.5. Scope and limitation of the domino reductive intramolecular cyclization for the synthesis of Benzo[*c*]cinnolines[a]



(a) General procedure; 2,2'-dinitro-1,1'-biphenyl **7.3** (1 mmol), acetophenone **7.6** (0.9 mmol) , NaOH (5 mmol) ethanol (5 mL) under microwave heating for 3 h at 130 °C. Isolated yields were reported.

Benzo[*c*]cinnolines carboxylic acid **7.8b** has been synthesized in two different substrates. One strategy involves from the corresponding 2,2'-dinitro-1,1'-biphenyl carboxylic acid methyl ester **7.5h** , since the ester group was hydrolyzed under the basic conditions. The second strategy was synthesized from the analogous 1-(2,2'-dinitro-[1,1'-biphenyl]-4-yl)ethan-1-one **7.3b**. In this substrate, the acetyl group functioned as a reducing agent intramolecularly (in the place of acetophenone **7.6**) for the two-nitro groups that leads to the formation of the cyclized product benzo[*c*]cinnoline carboxylic acid (**8b**). When an experiment performed with identical conditions in the presence of acetophenone **7.6**, the identical benzo[*c*]cinnoline-3-carboxylic acid **7.8b** was obtained due to the intramolecular reaction of the acetyl group. Moreover, the added acetophenone **7.6** has no effect on the reaction outcome.

7.4 Conclusion

In summary, we have developed an efficient two-step protocol for the synthesis of un-symmetrically and symmetrically substituted benzo[*c*]cinnolines. The key intermediate 2,2'-dinitro-biphenyls were successfully synthesized by means of a Suzuki cross coupling protocol of 1-bromo-2-nitrobenzenes with 2-nitro phenylboronic acid as a coupling partner followed by a domino reductive intramolecular cyclization leads to the target molecule. Overall, the method was compatible with both electron withdrawing and donating groups except the presence of easily oxidizable groups.

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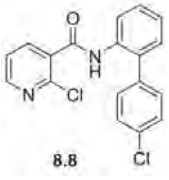
Chapter 8

A Novel Synthesis of Boscalid®

8.1 Introduction

Boscalid® is a widely used carbaxamide-based fungicide in agricultural sector.[1] It was launched by BASF in 2003 and approved as a fungicide in many countries.[2] Globally, more than 1,000 tons of Boscalid® is produced in a year.[3] Synthesis/production of Boscalid® **8.8** were reported in numerous patents and publications[4,5]

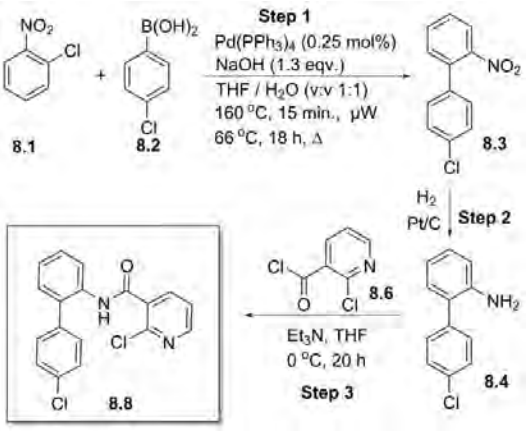
Figure 8.1. Structure of Boscalid®



8.8

The industrial synthesis of Boscalid® is shown in Scheme 8.1. The most important step (Step 1) is the formation of carbon-carbon bond using Pd-catalyzed Suzuki cross-coupling of 1-chloro-2-nitrobenzene **8.1** and 4-chloro phenylboronic acid **8.2** for the production of 4'-chloro-2-nitro-1,1'-biphenyl **8.3.** Subsequent hydrogenation of nitro group into amino group afforded compound **8.4** followed by amide coupling with 2-chloro-nicotinyl chloride **8.6** afforded the fungicide Boscalid® **8.8.**[4] However, this synthetic route requires long reaction times and high reaction temperatures to achieve the desired target molecule. In this viewpoint, we mainly focused to develop a method to minimize the reaction durations and optimized mild temperatures for each step involving the synthesis of the Boscalid® **8.8** in the above route itself.

Scheme 8.1. Industrial synthesis of Boscalid®

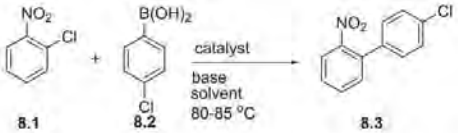


8.2 Methods and discussion

8.2.1 Suzuki cross coupling reaction (step 1)

We have initially investigated the Suzuki cross coupling reaction[6] between the 1-chloro-2-nitrobenzene **8.1** and 4-chlorophenyl boronic acid **8.2** based on previously disclosed methods from our group.[7] We have performed a number of reactions by varying the quantity of boronic acid **8.2**, reaction temperature, base, catalyst and solvent towards the biphenyl product. Table.8.1 depicts the screening of Suzuki cross-coupling reaction and afforded low to medium yield. The reaction using $Pd(PPh_3)_4$ and methanol/water solvent system attracted our attention (Table.8.1, entry 3) to further develop the method. Therefore, we have continued the process to optimize the reaction at high temperature. The rate of the reaction has been increased steadily from 1 hour to 8 hours and obtained almost a quantitative conversion with high yield and good selectivity after 8 hours under reflux conditions (Table 8.2.)

Table. 8.1. Screening of Suzuki cross coupling producing 2-nitrobiphenyls[a]



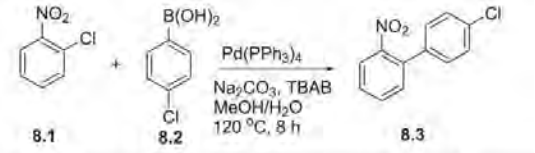
8.1 8.2 8.3

#	Base	Catalyst	Solvent	Time (h)	Conv.y(%)[b]
1	Na_2CO_3	$Pd(PPh_3)_4$	DMF/H_2O	6	29
2	Na_2CO_3	$IMesPd(TFA)_2$	DMF/H_2O	3	18
3	Na_2CO_3	$Pd(PPh_3)_4$	$MeOH/H_2O$	2	41[c]
4	K_2CO_3	$Pd(PPh_3)_4$	DMF/H_2O	5	8
5	K_3PO_4	$Pd(OAc)_2$	$MeOH/H_2O$	5	nd
6	KH_2PO_4	$Pd(PPh_3)_4$	DMF/H_2O	6	3
7	tBuOK	$IMesPd(TFA)_2$	DMF	1	20

(a) General procedure: 1-Chloro-2-Nitrobenzene **8.1** (0.2 g, 1.27 mmol), 4-Chloro phenylboronicacid **8.2** (0.3 g, 1.92 mmol), Na_2CO_3 (0.15 g, 1.44 mmol), TBAB (0.032 g, 0.010 mmol) , $Pd(PPh_3)_4$ (0.038 g, 0.033 mmol) and $MeOH/H_2O$ (3:1) ratio. The reaction mixture was heated under reflux at 120 °C for 8 hours. (b) Yield measured by GC. (c) 2.3 equiv of 4-chloro-phenylboronic acid **8.2** was used

Recently, we have developed an efficient Suzuki cross coupling method for the synthesis of 2-nitro-1,1'-biphenyls using 1-chloro-2-nitrobenzene **8.1** and 1-bromo-2-nitrobenzene as a coupling partner with phenylboronic acid.[8] The established method was developed by optimization process for the highly congested 1-chloro-2-nitrobenzenes. The new method was examined with variety of substituted 1-chloro-2-nitro and 1-bromo-2-nitrobenzenes in short time (30 min) under microwave heating (120 ˚C) and afforded excellent yields of various 2-nitro-1,1'-biphenyl **8.3** compounds. The 2-nitro-1,1'-biphenyl **8.3** derivatives are an important intermediate and act as a precursor for the synthesis of carbazole framework.[9]

Table.8.2. Attempts to produce the 2-nitro-1,1'-biphenyls[a]



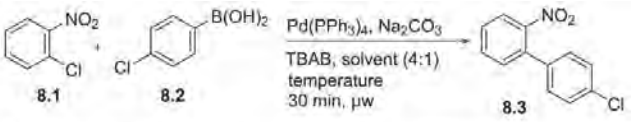
8.1 8.2 8.3

Run #	Time (h)	Conv. (%)	Selec. (%)	Yield (%)[b]
1	1	2	100	2
2	2	15	100	15
3	3	39	100	39
4	4	66	100	66
5	5	71	100	71
6	6	78	100	78
7	7	88	100	88
8	8	95	100	95

(a) General procedure: 1-Chloro-2-Nitrobenzene **8.1** (0.2 g, 1.27 mmol), 4-Chloro phenylboronicacid **8.2** (0.46 g, 2.94 mmol), Na_2CO_3 (0.15 g, 1.44 mmol), TBAB (0.032 g, 0.010 mmol) , $Pd(PPh_3)_4$ (0.038 g, 0.033 mmol) and $MeOH/H_2O$ (3:1) ratio. The reaction mixture was heated under reflux at 120 ^{0}C for 8 hours. (b) Yield measured by GC analysis

For example, 4'-chloro-2-nitrobiphenyl **8.3** was prepared in high yield under microwave heating. The method also works under thermal heating (120 $^\circ$C) with sealed tube for 30 min afforded a quantitative conversion yield of 2-nitro-1,1'-biphenyl **8.3**. In compare with the patents by BASF, our method is suitable in both thermal and microwave heating in short time (30 min) and could be useful for the industrial method of preparation. The Suzuki cross coupling method also worked very well with various solvents (Table.8.3) in order to use them in flow reactor technology [10] in our group that is under progress.

Table.8.3 Screening of Suzuki coupling with different solvent system



#	Solvent	Temeprature (°C)	Conv.(%)	Yield (%)
1	$MeOH/H_2O$	120	100	85
2	$EtOH/H_2O$	120	100	85
3	$PrOH/H_2O$	90	75	64
4	$BuOH/H_2O$	110	100	83

Reaction procedure: In a microwave vial, 1-chloro-2-nitrobenzene **8.1** (1 mmol), 4-chloro-phenylboronic acid (1.5 mmol), Na_2CO_3 (1.1 mmol), tetrabutylammonium bromide (TBAB; 0.08 mmol), and $Pd(PPh_3)_4$ (0.026 mmol, 2.6 mol-%) were added. The vial was sealed and argon was flushed through the septa before a mixture of MeOH (4 mL) and water (1 mL) was added. The vial was submerged in the microwave cavity for 30 min at 120 °C

8.2.2 Reduction method (Step 2)

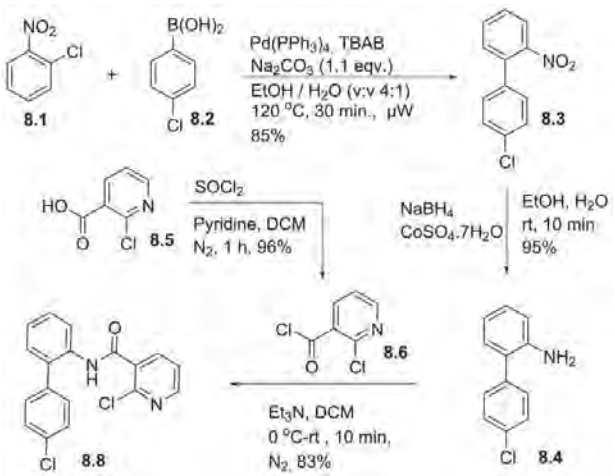
Previously, numerous methods were reported to the reduction of nitro to amino compounds.[11] We have chosen an indium powder reduction method for this transformation due to the inflammable nature, easy handling and non-toxic properties. Recently, we have developed a reduction method for the synthesis of 2-amino-1,1'-biphenyls **8.4** from 2-nitro-1,1'-biphenyls **8.3** using an indium powder.[12] The method required only simple filtration to remove the residue of the metal since the quantitative conversion yield of desired amine compounds were obtained in almost all the cases. The method is suitable for selective reduction of nitro compound in presence of several other reducible groups. In our synthetic route, the Boscalid® intermediate 4'-chloro-2-nitro-1,1'-biphenyl **8.3** was reduced to 4'-chloro-2-amino-1,1'-biphenyl compound **8.4** (88% isolated yield) using indium powder as the reductant in sealed tube for 3 hours at 120ºC. In view of the industrial application of Boscalid® **8.8**, we have developed a novel and efficient method for the reduction of nitro to amino compound using the $NaBH_4$ and cobalt sulfate heptahydrate as the reductant system. Previously there are some existed methods for the reduction of different functionalities using the $NaBH_4$ in presence of various additives. [13] We focused mainly to reduce the nitro group into amino group. The developed method is very rapid under thermal heating and about 10 min reaction time the reaction has been completed and afforded

an excellent yield of the corresponding amine compound. We used this method to synthesize the intermediate and obtained 95% isolated yield of 4'-chloro-2-aminobiphenyl **8.4**. Due to the high rate and good selectivity of the method, we wanted to elaborate the reduction step using different functionalities, which has been discussed in Chapter 9.

8.2.3 Amide bond formation (Step 3)

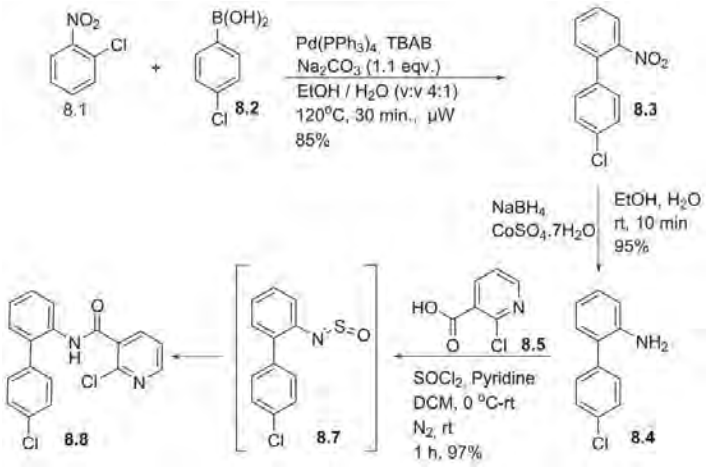
The final step of the synthesis is the amide bond formation between the amine with either acid or acid chloride. Amide bond formation is well known reaction in organic synthesis.[14] Several synthetic methods has been described earlier for this formation. For our target molecule, we have developed a two different method for amide bond formation. **Method 1** involves the coupling between the synthesized amine (via two steps) with the 2-chloro-nicotinyl chloride **8.6** (synthesized from 2-chloro-nicotinic acid **8.5** using $SOCl_2$) in the presence of trimethylamine as base in short time (10 min) afforded Boscalid® **8.8** in 92% yield. (Scheme 8.2).

Scheme 8.2. Three step synthesis of Boscalid® via acid chloride



Method 2 describes the coupling of the amine **8.4** with less reactive 2-chloronicotinic acid **8.5** in the presence of thionyl chloride and pyridine, a stable intermediate sulfinylaniline was formed in situ during the reaction [15] and simultaneously react with the acid compound to obtain the target Boscalid® compound. (Scheme 8.3).

Scheme 8.3. Three step synthesis of Boscalid® via Sulfinylaniline intermediate



8.3 Conclusion

In summary, we have developed a synthetic route to minimize the reaction times and reduced temperatures in synthesis of Boscalid® in a reported industry method. Our methodology comprised a much higher reaction rate in all the three synthetic steps and provided excellent outcomes of the reaction. We are presently exploiting the batch process method into continuous flow process for the industrial application, which is under progress in our laboratory.

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Chapter 9

A High Rate and Efficient Reduction Method Based on Sodium Borohydride and Cobalt sulfate

9.1. Introduction

Reduction reactions are of paramount importance in organic synthesis. In particular, reduction of nitro compounds into corresponding amines are one of the essential synthetic transformations used heavily in synthetic organic chemistry.[1]Aromatic amines are an important starting materials and extensively used as key intermediates for the production of various chemical substances such as agrochemicals, dye stuffs, drugs, polymers and pigments. [2] Furthermore, aromatic amines might be easily converted into different groups such as H, OH, F, Cl, Br, I, etc by means of the diazotization reactions.[3]

Numerous synthetic methods were previously reported for direct conversion of nitro to amino groups. The catalytic hydrogenation [4] involving palladium on carbon with hydrogen gas is one of the most commonly used method in industry and no side products are formed except water. However, these existing methods suffers from number of limitations involving using expensive and highly flammable nature of the reagents. Moreover, this method also suffers in reducing the selectivity in the presence of other functional groups and required high purity of the substrates in order to facilitate the reduction reaction. In this viewpoint a new facile, chemo selective and sustainable reduction method is a subject of interest and still highly demanded.

In order to implement our process leading to boscalid (Chapter 8), we needed a reduction method that could be implemented as a continuous flow operation. Recently, we have developed and improved a method for reduction of nitro group into corresponding amine using indium powder.[5] However, indium method is partially not suitable to our current flow reactor process due to the solubility and difficult to feed

the substrate into the reactor.[6] Therefore, it is required a suitable method to solve these type of problems.

In the past decades, metal hydrides are considered valuable reagents in modern organic synthesis.[7] Among the metal hydrides, $NaBH_4$ is one of the most frequently used hydride due to its mild conditions, and inexpensive reagent brings innovative changes in reduction of different functional groups, more commonly, aldehydes, [8] and ketones, [9]. Moreover, the functional groups such as nitro ($-NO_2$), carboxylic acid (-COOH), ester ($-CO_2R$), nitriles (-CN) and amides ($-CONH_2$) are more resistant towards $NaBH_4$ reduction. It is well known that using $NaBH_4$ alone, the reducing power is rather limited. However, the reducing power is drastically enhanced when combined with metal halides. Reduction of nitro and several other functional groups have been reduced by using $NaBH_4$ in the presence of various transition metals and other additives, for example $CoCl_2$,[10] $NiCl_2$,[11] $CuCl_2$,[12] $SnCl_2$,[13] $BiCl_3$,[14] $ZrCl_4$,[15] SbF_3,[16] $CuSO_4$,[17] Raney nickel,[18] and charcoal.[19]

The approach using sodium borohydride combined with transition metals have attracted our attention. Herein, we have described a simple and efficient reduction method using readily available $NaBH_4$ and cobalt sulfate heptahydrate for the reduction of several functional groups. The developed method enables the workup process easier and afforded a high yield of the desired product by simple filtration. In addition, the rate of the reaction enriched considerably to reduce groups such as nitro, nitrile, and azide. The method has been elaborated extensively in our group and examined the reduction of several aromatic and aliphatic alkene and alkyne compounds under slightly different reaction conditions. Overall, the method is suitable for reduction of variety of functional groups using $NaBH_4$ and cobalt sulfate heptahydrate system.

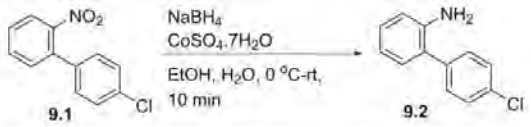
9.2 Results and discussion

We set out to investigate the $NaBH_4/Co^{II}$ reduction system using cobalt (II) heptasulfate and $NaBH_4$. $CoSO_4.7H_2O$ is readily available and cheap material compared to other cobalt counter ions. Based on the previous study with $NaBH_4$/cobalt chloride,[10a] attempted a reduction reaction of compound **1** with 5 equivalents of $NaBH_4$ and 2 equivalents of cobalt sulfate, afforded a quantitative yield of the desired amine compound in 10 minutes. Despite of its frequent use for reduction of various functionality using these combinations of $NaBH_4$ and cobalt source,[10] the nature of the reducing species in these reaction mixtures remains unclear. For example, observed a black granular precipitate (Co_2B) when mixing $NaBH_4$ and cobalt sulfate in ethanol as a solvent, it is an exothermic reaction evolving hydrogen gas steadily during the reaction. Cobalt boride is a cheap inorganic material and has been considered as an effective hydrogenation catalyst in organic synthesis and useful for hydrogen storage in fuel cell technologies.[20]

The mechanism of the reaction is somewhat not clearly understood based on the previous work.[10c] We supposed that the cobalt boride was formed in situ with the reaction mixture of $NaBH_4$ and Cobalt source. The cobalt boride act as a true catalyst in the reaction mixture and coordinating with the functional group that need to reduce and activating them towards the reduction reaction. A large excess of $NaBH_4$ was required to carry out the reduction reaction. It reacted with the alcoholic solvent and cobalt borides further accelerated to the decomposition of $NaBH_4$.

We examined the reaction rate using reduced amount of $NaBH_4$ and catalytic amount of cobalt source. It gave only trace amount of the amine product **9.2** (entry 2), increased amount of $NaBH_4$ (4 equiv) and catalytic amount of cobalt afforded only 23% yield. Additional trials with stoichiometric amount, gave almost quantitative conversion yield. (entry 5) Only negligible amount (1%) of hydrodechlorinated compound was observed. The optimized condition was developed for the reduction of nitro to amino compounds (entry 5) and shown in Table 9.1.

Table 9.1. Optimization of reduction of NO_2 group using $NaBH_4$/Co system[a]

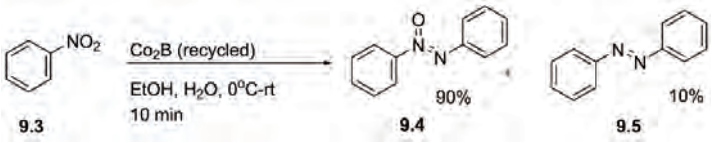


#	$NaBH_4$ (mol. eqv)	$CoSO_4.7H_2O$ (mol. eqv)	Conv. yield **9.2** (%)[b]
1[c]	5	2	100
2	2	20 mol%	traces
3	2	1	19
4	3	1	89
5[a,d]	4	1	99
6	4	20 mol%	23

(a) Reaction procedure :Nitro compound **9.1** (119 mg, 0.51 mmol), $CoSO_4.7H_2O$ (143 mg, 0.51 mmol) , ethanol (5 mL) and water (0.7 mL) was added. Cooled to 0°C. $NaBH_4$ (77 mg, 2.04 mmol) dissolved in ethanol (1.5 ml) was added. The reaction mixture was stirred at ambient temperature for 10 min.
(b) Conversion yield estimated by GC
(c) Starting point to investigate optimized conditions
(d) optimized condition yield with 1% of dechlorinated product was observed

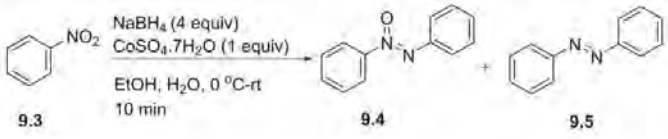
In addition, reduction of nitro benzene with recycled cobalt boride (Co_2B) was also performed to study the reaction rate compared with cobalt sulfate. The method works very well in a small-scale (0.5 mmol) and afforded 90% conversion yield of azoxy product **9.4**, (Scheme 9.1). The results of the reaction was encouraged further to explore with recycled catalyst (cobalt boride) in order to scale up the reaction. When we scaled up to ten times (5 mmol), the reaction rate becomes slower and gave only 23% yield after 10 minutes reaction time. Prolonged the reaction period (up to 1 hour) did not improve the yield. To conclude with this viewpoint, the cobalt boride is not suitable catalyst with large-scale reduction of nitro compound. It might be due to the presence of impurities formed in the reaction and stability of the catalyst. However, it requires a fresh mixture of $NaBH_4$ and cobalt system in order to perform in large-scale synthesis.

Scheme 9.1 Attempt to reduction using recycled cobalt boride



Furthermore, needed to explore the reduction reaction using $NaBH_4$ in the presence of several other cobalt counter ions. The reaction rate with counter ions such as, sulfate, chloride, nitrate and acetate were tested. The method works almost similar in all the cases except the cobalt sulfate that afforded nearly quantitative yield. Moreover, the cobalt sulfate is much cheaper than the other counter ions. The list of reaction study is shown in Table 9.2.

Table 9.2 Screening of the reduction reaction with different cobalt source[a]

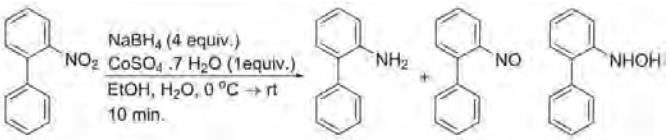


#	Co(II) (1 eqv)	Yield **9.4** (%)[b]	Yield **9.5** (%)[b]
1	$CoSO_4$. 7 H_2O	98	2
2	$CoCl_2$	95	5
3	$Co(NO_3)_2$.6 H_2O	94	6
4	$Co(OAc)_2$. 4 H_2O	94	6

(a) General procedure: Substrate **9.3** (1 mmol) was dissolved in ethanol (5 mL). To the stirred solution, cobalt salt (1 mmol) dissolved in water (0.7 mL) was added. The reaction mixture was cooled to 0°C and then $NaBH_4$ (4 mmol) was added gradually and instantly observed a black granular precipitate of cobalt boride (Co_2B) and copious quantities of hydrogen. The reaction mixture was stirred at ambient temperature for 10 min
(b) Yield estimated by GC

In addition to this screening (Table 9.2), the reduction method was established with several protic solvents under three different reaction times (Table 9.3). The solvent ethanol, methanol are suitable for the transformation of 2-nitrobiphenyl **9.6** to 2-aminobiphenyl **9.7** with complete conversion after 10 minutes (entry 1& 2, Table 9.3). The method was failed in propanol and butanol as solvent due to the poor solubility of substrates. Then adding catalytic amount (20 mol%) of phase transfer catalyst (TBAB) to the reaction mixture (entry 3 & 4, Table 9.3) resulted quantitative conversion of nitrobiphenyl compound **9.6**. However, the desired product **9.7** was obtained in low yield with additional side products (**9.8** & **9.9**).

Table 9.3 Screening of the reduction reaction with different solvents[a]



9.6 **9.7** **9.8** **9.9**

#	Solvent	Time [min.]	Conv.(%)	Selec. (%)			Yield (%)[b],[c]		
			9.6	**9.7**	**9.8**	**9.9**	**9.7**	**9.8**	**9.9**
1	MeOH	5	86	46	40	0	41	36	0
		10	>99	>99	0	0	>99	0	0
2	EtOH	5	18	57	26	0	10	5	0
		10	>99	>99	0	0	>99	0	0
3[d]	PrOH	5	0	0	0	0	0	0	0
		10	0	0	0	0	0	0	0
3[e]	PrOH	5	26	21	34	39	5	9	10
		10	96	33	40	17	32	39	16
		20	99	17	55	23	17	54	23
4[f]	BuOH	5	76	21	73	0	16	56	0
		10	76	29	63	0	22	47	0
		20	>99	40	23	0	40	23	0

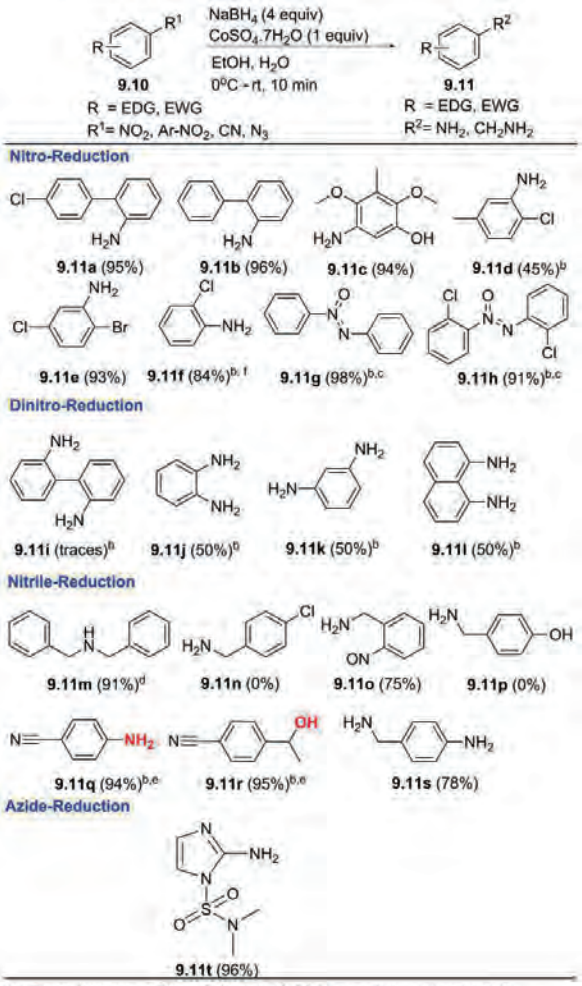
[a] General procedure: Nitro compound **9.6** (1 mmol) was dissolved in ethanol (5 mL). To the stirred solution, $CoSO_4.7H_2O$ (1 mmol) dissolved in water (0.7 mL) was added. The reaction mixture was cooled to 0 °C and then $NaBH_4$ (4 mmol) was added. The reaction mixture was stirred at ambient temperature for 10 min.
[b] Yield measured by GC
[c] Trace amount of carbazole was observed in all the cases
[d] Repeated reaction under the same conditions afforded the same results
[e] 20 mol% TBAB was used
[f] 25% yield of carbazole was observed with 20 mol% TBAB at 20 min

9.3 Scope and limitation

Using this optimized procedure (Table 9.1), several functional groups such as NO_2, CN, and N_3 were examined. The scope and limitation of the method was shown in Scheme 9.2. The reduction of nitro biphenyl and highly congested nitro compound afforded excellent yield of corresponding amino compounds (**9.11a-9.11c**, Scheme 9.2). The method is compatible with both electron withdrawing and donating groups. Reduction of nitro compound in the presence of bromo and chloro substituents is compatible with this method and obtained the amine compound (**9.11e**) in excellent yield. In case with reduction of nitrobenzene and chloronitrobenzene, mainly observed the azoxy benzene instead of the desired amine compound under the optimized conditions (**9.11g** & **9.11h**). This is due to the reductive coupling of nitrobenzene in aqueous medium and evidenced by previous published results.[21] However, increased amount of $NaBH_4$ (5 equiv) gave the amine only with chloronitrobenzene (**9.11f**).

Reduction of dinitro compounds is also challenging with this method. We have tested with different dinitro compound with the same conditions as nitro reduction. However, it gave only approximately 50 % of the desired diamine compound (**9.11j** & **9.11l**, Scheme 9.2). Increased amount of $NaBH_4$ (8 equiv.) didn't improve the yield of desired product instead some unidentified compounds were obtained. Synthesis of secondary amines is challenging reaction using the reduction of nitrile compounds. With our method, benzonitrile was reduced and afforded secondary amine in 91% yield (**9.11m**). Further scope of the method was unsuccessful with chloro and hydroxyl substituents in the para position, no reaction was occurred (**9.11n** & **9.11p)**. However, the method work with nitro group in ortho position, it reduced the nitrile into primary amine and partially reduced the nitro group into nitrozo group evidenced by HR-MS analysis (**9.11o**). Additionally, it was also selectively reduced the nitro to amine and ketone into secondary alcohol in presence of nitriles (**9.11q** & **9.11r).** It also reduced the azide in protected 2-azidoimidazole into corresponding amine in excellent yield (**9.11t**).

Scheme 9.2. Scope of the reduction reaction using $NaBH_4$/Co system[a]



(a) **Reaction procedure:** Substrate **9.10** (1 mmol) was dissolved in ethanol (5 mL). To the stirred solution, $CoSO_4.7H_2O$ (1 mmol) dissolved in water (0.7 mL) was added. The reaction mixture was cooled to 0°C and then $NaBH_4$ (4 mmol) was added. The reaction mixture was stirred at room temperature for 10 min

(b) Yield measured by GC

(c) 2% of diazo product **9.5** was formed

(d) Secondary amine **9.11m** was detected under same the experimental conditions

(e) Selective reduction of functional groups in presence of nitrile

(f) 5 equiv of $NaBH_4$ was used

9.4 Conclusions

In summary, we have developed a rapid and efficient method for the reduction of reducible groups, NO_2, CN and N_3. This method well tolerated with various functional groups and afforded medium to excellent yield. Moreover, the method is compatible for selective reduction in presence of halogen and nitriles. We believe that the reported method could be useful as a general method in organic synthesis for reduction of various functionalities.

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Chapter 10

Summary and Outlook

10.1 Summary

In this dissertation, we have addressed the synthetic strategies and novel methodologies to the functionalization of some of the heterocyclic compounds. The main contribution of my project involved in total synthesis of natural product, carbazomycin G. Several novel synthetic methods have been presented in this thesis for the synthesis of intermediates to achieve the natural product. In particular, the carbazole framework is the fundamental structural unit of the target molecule. A new approach was designed for the synthesis of carbazole framework through three synthetic steps such as Suzuki cross coupling for the synthesis of 2-nitrobiphenyls followed by reduction of nitro into amine and finally the intramolecular C-H activation and subsequent C-N bond formation of 2-aminobiphenyl leading to carbaozle moiety.

We have developed and optimized a highly efficient Pd-catalyzed Suzuki cross coupling method for the synthesis of unsymmetrical 2-nitrobiphenyls using highly crowed chloroarenes as challenging coupling partner, which is summarized in chapter 3 (Paper I). Based on the scope and utility, the developed method could be suitable as a general synthetic protocol for the synthesis of 2-nitrobiphenyls. The reaction optimization study was elaborated in chapter 2 and discussed mainly the importance and various application of the statistical experimental design and multivariate modeling in synthetic organic chemistry.

The Suzuki cross coupling protocol have attracted our attention and utilized in synthesis of 2, 2'-dinitrobiphenyls, an important intermediate for the preparation of both the symmetrically and unsymmetrically substituted benzo[*c*]cinnolines. The synthesis of benzo[c]cinnolines and different scope of the method were described in chapter 7 (Paper IV)

Furthermore, two different reduction methods were disclosed in this thesis. Indium powder reduction method described in chapter 4 (Paper II) for converting mainly the various substituted 2-nitrobiphenyls into 2-aminobiphenyls. The method shown very simple workup procedure and selective reduction afforded excellent yield of the target product. Another method involved the cobalt catalyzed $NaBH_4$ reduction reported in chapter 9 for the reduction of numerous functional groups for example, nitro, nitrile, and azide. The method displayed a high reaction rate and broad scope of the reaction was investigated.

In chapter 5 (Paper III), we have reported a direct ring closing method for the synthesis of carbazole using 2-aminobiphenyls. The method involves combined C-H activation and C-N bond formation using Palladium catalyst. The developed method was suitable for the synthesis of various substituted carbazoles on both the rings. Moreover, the method could also appropriate for the synthesis of N-acetyl carbazoles from corresponding 2-acetaminobiphenyls. We have utilized this methodology for the synthesis of natural product carbazomycin G, discussed in chapter 6. Our methodology contains distinct novel synthetic intermediates and substantial transition metal catalyzed reactions were utilized.

Additionally, an improved 3-step synthesis of Boscalid® was discussed in chapter 8. We have used our synthetic methodology (from chapter 3 and chapter 9) for the synthesis of intermediates towards the Boscalid® synthesis. The final step involves the amidation using amine and acid or acid chloride. We have developed one pot reaction for amidation via sulfinylaniline intermediate using acid and amine in the presence of thionyl chloride.

To conclude, the project has been described in a well-connected arrangement. The 2-nitrobiphenyl via Suzuki coupling is the central structural moiety. The developed methodology of the project can be used for variety of applications including in natural product synthesis, agrochemicals and several biologically important compounds.

10.2 Outlook

There are significant numbers of experiments; thoughts and adaptations in related to this dissertation have been left for future work due to the inadequate time period to carry out. Future work might involve in study of reaction mechanisms of particular reactions and trying various methods with new approaches. First, it could be interesting to try optimized Suzuki cross coupling method (Chapter 3) using heterocyclic substrates as coupling partners to synthesize the heterocyclic compounds. Many natural products contain heterocyclic core moieties and they are invaluable sources for medicinal chemistry. In addition, it could also be useful to try to develop and optimize the Suzuki coupling with deactivated boronic acid for the synthesis of various important intermediates as only few particular examples have been examined with deactivated boronic acid. Further developments in this area could be beneficial.

The other attention could be the study on mechanism of reduction using $NaBH_4/Co^{II}$ system in chapter 9. The mechanism of this reaction is still unclear with the reported methods. Additional improvements with the previous methods could be valuable. Moreover, the direct ring closing method for the synthesis of carbazole is highly important in organic synthesis for the variety of natural products and several other drug candidates. The method is not very suitable with the substrates bearing easily oxidizable functional groups, gave only low yield under the oxidative condition with strong oxidant hydrogen peroxide. Further developments with different approaches could be useful with this method. Several novel intermediates were synthesized in the total synthesis of carbazomcyin G (Chapter 6). The intermediates are of particular interest and tested the cytotoxic effect with HL-60 and MOLM-13 leukemia cells. Further activity analysis is in progress.

Furthermore, we have utilized the amidation method for the synthesis of Boscalid® via sulfiniyaniline intermediate in chapter 8. The methods worked very well in one pot reaction with less reactive acid as a substrate. Further analysis of the reaction mechanism of the amidation would be highly desirable and could be useful method for synthesis of numerous substituted amides.

The research results presented in chapter 6 about the carbazomycin G synthesis, chapter 8 about a new industrial synthesis of the agrochemical Boscalid®, and chapter 9 that concern a new efficient high rate reduction method based on the sodium borohydride reduction of Co^{2+} forming in-situ hydrogen and the nanoparticle material Co_2B, are currently under preparation as manuscripts and will be submitted for evaluation in due time.

Paper I

A Highly Efficient $Pd(PPh_3)_4$-Catalyzed Suzuki Cross-Coupling Method for the Preparation of 2-Nitrobiphenyls from 1-Chloro-2-nitrobenzenes and Phenylboronic Acids

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Full Paper

Suzuki Cross-Coupling

A Highly Efficient $Pd(PPh_3)_4$-Catalyzed Suzuki Cross-Coupling Method for the Preparation of 2-Nitrobiphenyls from 1-Chloro-2-nitrobenzenes and Phenylboronic Acids

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Abstract: A simple and efficient method for Suzuki cross-coupling of highly substituted and congested 1-chloro-2-nitrobenzene with phenylboronic acid was developed, investigated, and optimized. The reaction conditions comprises a mixture of MeOH and water (4:1) as the reaction medium, readily available and cheap $Pd(PPh_3)_4$ as catalyst, sodium carbonate as base, and microwave heating, which affords a fast reaction rate with good outcomes. The procedure was proven to have high functional group tolerance with phenylboronic acid and for 1-chloro-2-nitrobenzene and thus is a general method for the synthesis of 2-nitrobiphenyl. The target scaffold, 2-nitrobiphenyls, was produced in excellent yields with excellent selectivities in all cases.

Introduction

The biphenyl scaffold constitutes a fundamental structural moiety for several application areas, which includes herbicides,[1] fungicides[2] catalyst ligands,[3] liquid crystals,[4] active pharmaceutical ingredients, and drug candidates.[5] Moreover, 2-*N*-substituted biphenyls are of notable interest because such frameworks can act as precursors for the essential 1*H*-carbazole framework.[6]

Methods, such as the Ullmann,[7] Gomberg–Bachmann,[8] and Suzuki cross-coupling reactions[9] are used for the preparation of biphenyls, of which the latter is the most efficient method for the construction of $C(sp^2)$–$C(sp^2)$ bonds in organic synthesis and in the fine chemical industry.[10]

Freeman and collaborators[6d] disclosed in 2005 a method for the synthesis of 2-nitrobiphenyls by using $Pd(PPh_3)_4$ as a catalyst. In contrast to the method we disclose herein, their method required long reaction times (up to 42 h) and a large surplus of base to synthesize the target 2-nitrobiphenyls. Recently, Gooßen and collaborators[11] disclosed a method for the synthesis of 2-nitrobiphenyls by means of a decarboxylative Hiyama coupling reaction, which uses a trimetallic Pd/Cu/Ag catalytic system at high temperatures. However, the Suzuki cross-coupling reaction has emerged as the method with the most attractive features for the purpose of preparation of biphenyls, which includes mild reaction conditions, tolerance of water, generally high functional group tolerance, and high selectivity and yields.

Originally, the Suzuki cross-coupling reaction was performed by reacting organic boronic acids with bromo- and iodoarenes in the presence of a base and $Pd(PPh_3)_4$ as catalyst.[12] However, because the C–Cl bond is less activated towards oxidative addition, a general application of chlorobenzenes as one of the reaction partners in the Suzuki cross-coupling reaction has been a long-standing and challenging task for the Suzuki cross-coupling method. Although some of the first examples to involve chloro-arenes[13] as reaction partners in this cross-coupling reaction were disclosed about forty years ago, further significant advances were not revealed until various palladium complexes were introduced as catalysts to facilitate the Suzuki cross-coupling reaction.[14] Even if simple catalysts, such as $Pd(OAc)_2$ have been shown to operate to some extent with chlorobenzenes in the Suzuki cross-coupling reaction,[15] the greatest successes were obtained when ingenious and dedicated ligands[16] were installed on Pd to form the catalyst. In this context, particularly complex elaborated phosphorus ligand have been devised, synthesized, and used for the purpose.[17] These ligands have, among other features, increased electron density around the Pd center, which helps to facilitate the C–Cl oxidative cleavage and assist cross-coupling,[3a,18–23] but due to their high degree of elaboration, such ligands are expensive and not achievable for larger scale reactions.

Results and Discussion

For our project, we needed access to unusually congested biphenyl **5** (Scheme 1), which we devised as a key intermediate in a new total synthesis for the carbazole alkaloids carbazomycin G and H.[24]

One of the key steps in this synthesis was devised and developed in our group several years ago, namely a Suzuki cross-coupling reaction[25] that was needed to join congested 1-iodo-2-nitrobenzene (**3l**) and phenylboronic acid. An accompanying scope and limitation study revealed that the method operated to provide 2-nitrobiphenyls in high yields by reacting 1-iodo-2-

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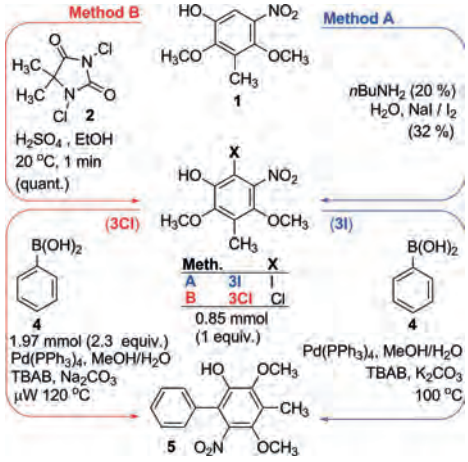


Scheme 1. Chlorination or iodination followed by Suzuki coupling reaction steps that lead to 3,5-dimethoxy-4-methyl-6-nitro-1,1′-biphenyl-2-ol.

nitrobenzenes with phenylboronic acids by using Pd(PPh$_3$)$_4$ as catalyst, with any of the solvent pairs, dimethylformamide/water, acetone/water, methanol/water, or methanol, as reaction medium. To implement the cross-coupling step for congested 1-iodo-2-nitrobenzene (**3I**), which we attempted by means of an iodination method disclosed by Crich and collaborators.[26] This method afforded **3I** but only in a low yield (≈ 30 %). Nevertheless, a much larger problem arose, because we were not able to reproduce the iodination step **1** → **3I** in accordance with this method (Scheme 1, Method A). We assumed the obstacle in this process to be due to the iodine purity. We were about to abandon the outlined strategy to lead to 1*H*-carbazole scaffold through the 2-nitro-1,1′-biphenyl, at which point we discovered a halogenating method suitable for various *N*-heterocycles.[27] These results made us wonder whether this method could operate for the iodination **1** → **3I** with *N*,*N*′-diiodo-5,5-dimethylhydantoin as iodination reagent (similar to Scheme 1, Method B), however, iodination trials failed. Subsequently, we attempted to perform bromination with the corresponding *N*,*N*′-dibromo-5,5-dimethylhydantoin, however, this also did not work. Attempts with *N*,*N*′-dichloro-5,5-dimethylhydantoin (DCH) **2Cl** reacted smoothly to provide chlorinated benzene **3Cl** (Scheme 1, Method B) in quantitative yield. With chlorinated product **3Cl** in hand, we wanted to establish a Suzuki cross-coupling reaction **3Cl** + **4** → **5**. We attempted our previously disclosed Suzuki cross-coupling method developed for iodobenzenes,[25] which successfully afforded target molecule 3,5-dimethoxy-4-methyl-6-nitro-1,1′-biphenyl-2-ol (**5**), but only in low yield (≈ 30 %). This encouraging result prompted us to perform a systematic optimization by means of statistical experimental design,[28] multivariate regression analysis,[29,30] and response surface methodology.[31] In this context, we assumed that the reaction temperature (z_1), the reaction time (z_2), the quantity of base (z_3), and the amount of catalyst (z_4) were the variables that affected the performance of the reaction in terms of yield and selectivity. By using the experimental variables z_1–z_4 a statistical experimental design $2^k + c = 2^4 + 2 = 18$ was created, which is listed in standard order in Table 1, but it was performed in random order in the laboratory.

Table 1. Statistical experimental design used for the investigation and optimization of the Suzuki cross-coupling with Pd(PPh$_3$)$_4$ as catalyst.

Experimental variables and selected levels

	Experimental variables	−1 (L)	0	+1 (H)
z_1	Reaction temperature [°C]	90	100	110
z_2	Reaction time [min]	45	60	75
z_3	Quantity Na_2CO_3 [g]	0.15	0.19	0.23
z_4	Loading Pd(PPh$_3$)$_4$ [mmol]	0.022	0.0435	0.065

Experimental design: $2^k + c$, $k = 4$, $c = 2 \Rightarrow 2^4 + 2 = 18$

#[a]	Experimental variables[b]				Response[c]
	z_1 [°C]	z_2 [min]	z_3 [g]	z_4 [mmol]	y [%]
1	90	45	0.15	0.022	8
2	110	45	0.15	0.022	44
3	90	75	0.15	0.022	15
4	110	75	0.15	0.022	35
5	90	45	0.23	0.022	25
6	110	45	0.23	0.022	39
7	90	75	0.23	0.022	29
8	110	75	0.23	0.022	43
9	90	45	0.15	0.065	22
10	110	45	0.15	0.065	30
11	90	75	0.15	0.065	27
12	110	75	0.15	0.065	32
13	90	45	0.23	0.065	16
14	110	45	0.23	0.065	29
15	90	75	0.23	0.065	20
16	110	75	0.23	0.065	39
17	100	60	0.19	0.0435	19
18	100	60	0.19	0.0435	21
Opt.[d]	120	30	0.10	0.025	53

[a] The experiments were carried out in a random order. [b] 2-Chloro-4,6-dimethoxy-5-methyl-3-nitrophenol (**3Cl**; 0.21 g, 0.85 mmol) was used as a substrate in all of the experiments. [c] Measured response from each experiment y = GC–MS measured yield of target product 3,5-dimethoxy-4-methyl-6-nitro-1,1′-biphenyl-2-ol (**5**). [d] Optimized conditions expressed in coded format: reaction temperature (x_1) = +2, reaction time (x_2) = −2, quantity of base (x_3) ≈ −2, and Pd-catalyst loading (x_4) ≈ −1.

The results of the experiments were evaluated by analyzing the post-reaction mixture by means of GC–MS, the results of which are given in the right hand column of Table 1.

Modeling

To facilitate the estimation of the model terms, the experimental variables z_1–z_4 were scaled in accordance with Equation (1) that produced design matrix **D** in the scaled variables x_1–x_4, which were then used to produce model matrix **M** by using Equation (2). In these equations, z_k is the experimental variable k expressed in real units and variable x_k is the identical variable provided in scaled units. $z_{k,L}$ and $z_{k,H}$ are the selected low (L) and high (H) experimental values expressed in the real units of the experimental variable z_k. The selected levels (L, 0, H) are provided in the upper part of Table 1. The scaling by means of Equation (1) gives all the experimental variables low values $x_{k,L} = -1$ and correspondingly the high values $x_{k,H} = +1$.

$$x_k = \frac{z_k - \left[z_{k,I} + \frac{1}{2} \times (z_{k,II} - z_{k,I})\right]}{z_{k,H} - \left[z_{k,I} + \frac{1}{2} \times (z_{k,II} - z_{k,I})\right]}, \quad k = 1, \ldots, 4 \tag{1}$$

$$\mathbf{M} = [\overbrace{1\ x_1\ x_2\ x_3\ x_4\ x_1x_2\ x_1x_3\ x_1x_4\ x_2x_3\ x_2x_4}^{\mathbf{D}}\ x_3x_4\ x_1x_2x_3\ x_1x_2x_4\ x_1x_3x_4\ x_2x_3x_4\ x_1x_2x_3x_4] \tag{2}$$

Multiple linear regression,[29] Equation (3), was used to estimate the model shown in Equation (4) by means of MATLAB[32] computer software and in-house coded routines that previously have been benchmarked against commercial software, such as SAS.[33]

$$y = \mathbf{Mb} \Rightarrow b = (\mathbf{M}^T\mathbf{M})^{-1}\mathbf{M}^T y \tag{3}$$

$$\begin{aligned} y = f(x_1, x_2, x_3, x_4) &= 27.389 + 8.063x_1 + 1.688x_2 + 1.688x_3 - 1.438x_4 \\ &- 0.813x_1x_2 - 0.563x_1x_3 - 2.437x_1x_4 + 1.063x_2x_3 + 0.937x_2x_4 \\ &- 2.563x_3x_4 + 1.562x_1x_2x_3 + 1.188x_1x_2x_4 + 2.937x_1x_3x_4 \\ &- 1.188x_2x_3x_4 - 0.437x_1x_2x_3x_4 \end{aligned}$$
$$R^2 = 0.928,\ R^2_{adj} = 0.390,\ RMSEP = 2.634,\ RSD = 2.793 \tag{4}$$

The estimated regression coefficients were analyzed with a cumulative normal distribution plot (Figure 1), which suggest that the regression coefficients β_1, β_2, β_3 (positive signs) and β_4 (negative sign) should be included in the model. Moreover, the interaction terms β_{14} and β_{34} (negative signs) and β_{134} (positive sign) might also be included. The final multivariate model, see Equation (5), was subsequently used to produce the iso-contour response surface projections of the Suzuki cross-coupling reaction (Figure 2).

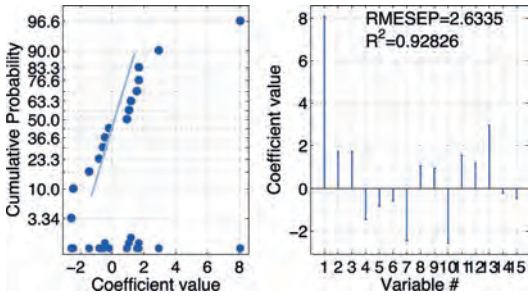


Figure 1. Cumulative normal distribution plot and regression coefficient spectrum estimated for the Suzuki cross-coupling reaction: **3Cl** + **4** → **5**.

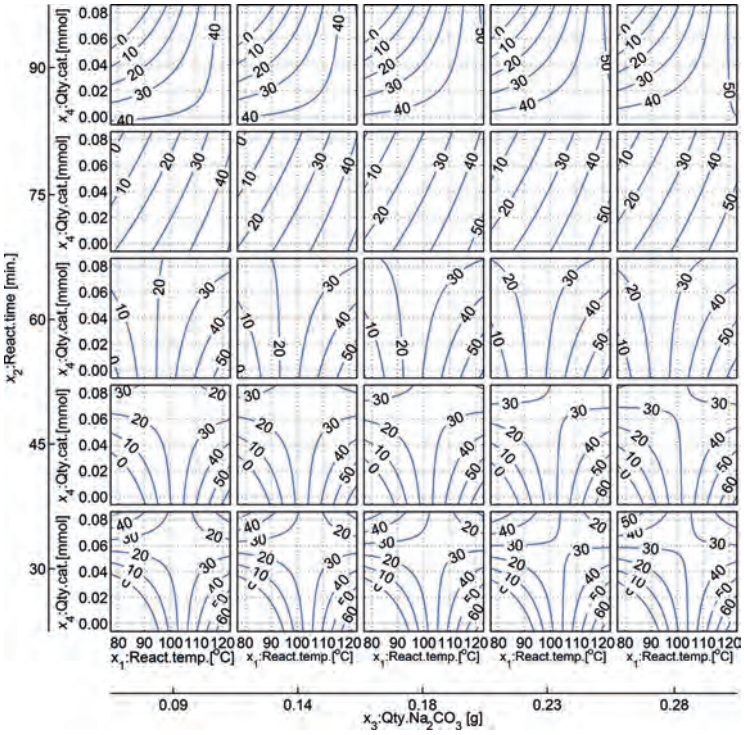


Figure 2. iso-Contour projection of the response surface prepared for predictive purposes. The iso-contour lines created by the model Equation (4) display the predicted yield (*y*) of target molecule 2-nitrobiphenyl **7**. How to read the graphic: the outer horizontal frame line shows the variation in the quantity of the sodium carbonate (x_3), and the vertical frame line displays the effect of the reaction time (x_2). Each variable has five discrete levels [–2 –1 0 +1 +2]. The 25 subplots within the outer frame lines show the *iso*-contour lines projections of the response surfaces when the two experimental variables — reaction temperature (x_1) and quantity of Pd catalyst (x_4) — are continuously varied within a range that corresponds to [–2 +2].

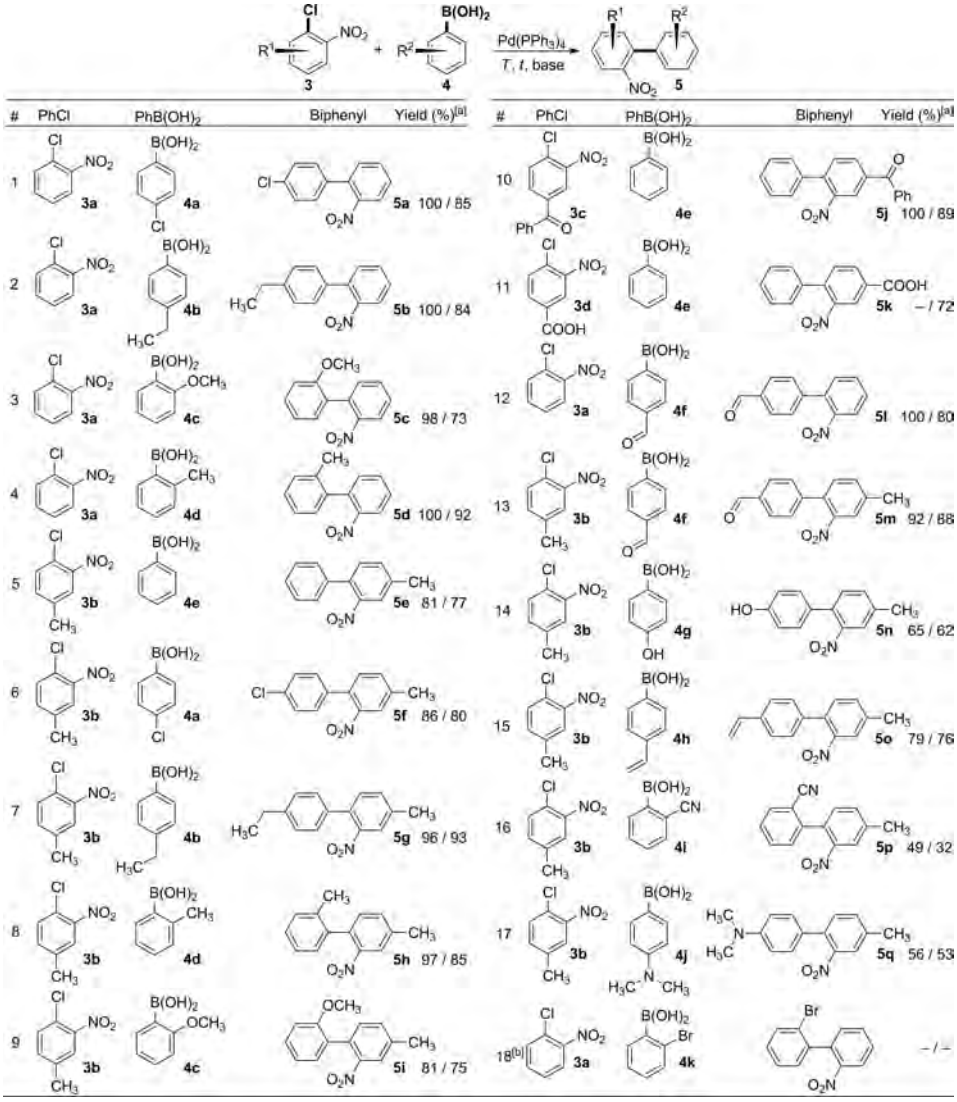
$$y = f(x_1, x_2, x_3, x_4) = 27.389 + 8.063x_1 + 1.688x_2 + 1.688x_3 - 1.438x_4 - 2.437x_1x_4 - 2.563x_2x_4 + 2.937x_1x_2x_4$$
$$R^2 = 0.862,\ R^2_{Adj} = 0.768,\ RMSEP = 3.635,\ RSD = 3.856 \quad (5)$$

The plots within Figure 2 were subsequently used to predict the conditions of a higher yielding procedure for the Suzuki cross-coupling reaction. The optimized conditions were taken from the sub plot found in the lower left-hand corner of the Figure 2.

The model predicts that a low quantity of base (z_3; 0.10 g), short reaction time (z_2; 30 min), high reaction temperature (z_1; 120 °C), and low Pd-catalyst loading (z_4; 0.022 mmol) are optimal.

These selections were made to simultaneously obtain optimized yields and to minimize inputs (that is amounts of rea-

Table 2. Library for the investigation of the scope and limitation of the $Pd(PPh_3)_4$-catalysed Suzuki cross-coupling reaction that involves 1-chloro-2-nitrobenzenes (**3**) and phenylboronic acids (**4**) as reaction partners.



#	PhCl	$PhB(OH)_2$	Biphenyl	Yield (%)[a]
1	**3a**	**4a**	**5a**	100 / 85
2	**3a**	**4b**	**5b**	100 / 84
3	**3a**	**4c**	**5c**	98 / 73
4	**3a**	**4d**	**5d**	100 / 92
5	**3b**	**4e**	**5e**	81 / 77
6	**3b**	**4a**	**5f**	86 / 80
7	**3b**	**4b**	**5g**	96 / 93
8	**3b**	**4d**	**5h**	97 / 85
9	**3b**	**4c**	**5i**	81 / 75
10	**3c**	**4e**	**5j**	100 / 89
11	**3d**	**4e**	**5k**	– / 72
12	**3a**	**4f**	**5l**	100 / 80
13	**3b**	**4f**	**5m**	92 / 88
14	**3b**	**4g**	**5n**	65 / 62
15	**3b**	**4h**	**5o**	79 / 76
16	**3b**	**4i**	**5p**	49 / 32
17	**3b**	**4j**	**5q**	56 / 53
18[b]	**3a**	**4k**		– / –

[a] Conversion yield based on GC/isolated yield after column chromatography; n.d.: not detected. [b] The isolated product in this reaction was the 2-nitrobiphenyl that resulted from a dehydrodebromination reaction.

gents and Pd catalyst, and shorten reaction times). This was possible to achieve by means of the sub-plot in the lower left corner of Figure 2. This sub-plot predicts a yield of ≥ 50 %.

The predicted reaction conditions were used in following-up experiments to achieve a maximum yield of 53 % of target molecule **5**. This result corresponds to an increased yield of (53 – 32) 21 %-point and is a relative improvement of > 65 % by using only a simple $Pd(PPh_3)_4$ as catalyst in the Suzuki cross-coupling reaction.

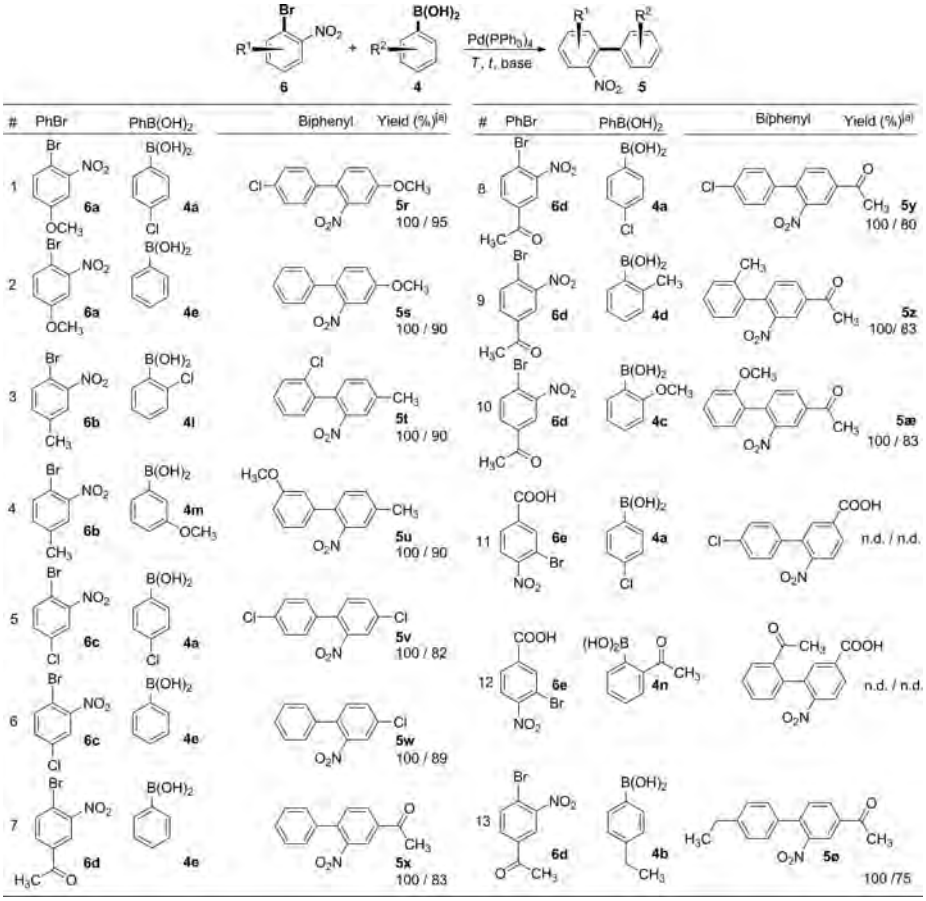
Owing to the good result we attained with congested chloroarene **3Cl**, we were eager to explore whether the developed and optimized reaction conditions could operate as a general method for the coupling of 1-chloro-2-nitrobenzenes and phenylboronic acids with $Pd(PPh_3)_4$ as the only catalyst.

Investigation of the Scope and Limitation of the Method

A test library (Table 2) composed of 18 various combinations of phenylboronic acids and 1-chloro-2-nitrobenzenes with a variety of electron-donating and electron-withdrawing functional groups was outlined and tested by means of the established procedure for the **3Cl** + **4** → **5** cross-coupling reaction.

The only change to the method made was to reduce quantity of phenylboronic acid used (2.3 equiv. → 1.5 equiv.). As Table 2 reveals, the developed method proceeds with excellent yields in most cases and demonstrates high functional group tolerance. In addition to these advantages, the method takes place at a significantly faster rate than previously published methods that involve chlorobenzenes. Furthermore, the method was also investigated by using a similar library that contained bromobenzenes in place of chlorobenzenes as the coupling partner to phenylboronic acid. A library composed of 13 entries (Table 3) of 1-bromo-2-nitrobenzenes and phenylboronic acids was explored to evaluate the scope and limitations of the method by using 1-bromo-2-nitrobenzenes as the haloarene.

Table 3. Library for the investigation of the scope and limitation of the $Pd(PPh_3)_4$-catalysed Suzuki cross-coupling reaction that involves 1-bromo-2-nitrobenzenes (**6**) and phenylboronic acids (**4**) as reaction partners.



[a] Conversion yield based on GC/Isolated yield after column chromatography; n.d.: not detected.

Conclusions

In summary, we have designed, developed, and optimized a fast and efficient Suzuki cross-coupling reaction for the synthesis of 2-nitro-1,1′-biphenyls in high to excellent yield by using 1-chloro-2-nitrobenzenes and phenylboronic acids as reaction partners. The method demonstrates high functional group tolerance with both 1-chloro-2-nitrobenzenes and the phenylboronic acids. The method was originally developed to couple a highly congested halo-arene with phenylboronic acid. In contrast to previously disclosed studies that relate to chlorobenzenes as a reactant in the Suzuki cross-coupling reaction, we utilized cheap, simple, and commonly exploited catalyst tetrakis(triphenylphosphine)-palladium(0). This was made possible by fine-tuning the experimental conditions assisted by multivariate design and modeling to inform a fast, selective, and high-yielding cross-coupling method. This study demonstrates how multivariate design and modeling might be used in explorative synthesis to develop new catalyzed synthetic methods and, as in this case, replace the need for dedicated and sophisticated catalyst ligands.

Experimental Section

Experimental Details: All reagents and solvents were purchased from commercial sources and used as received. Melting points were determined in open capillaries. Reagent grade chemicals were purchased from commercial sources and used without further purification. All reaction mixtures and column eluents were monitored by TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 nm and λ = 365 nm. IR spectra were recorded as KBr discs with a Shimadzu FTIR-8300 spectrophotometer, and ^{1}H and ^{13}C NMR spectra were recorded with Bruker AV 400 MHz and 500 MHz instruments. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument.

General Methods: GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d.,0.33 mm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. DART-mass spectra were obtained by using PEG as an internal standard in positive ionization mode with a TOF mass analyzer. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature at a frequency of 400 and 100 MHz, respectively.

The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ = 7.26 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm) with tetramethylsilane as an external reference. Flash chromatography was performed by using the indicated solvent system and silica gel (230–400 mesh). All reagents used were commercially available from Aldrich Chemical Co. For new compounds HRMS data were also recorded.

The microwave-assisted experiments were performed by means of a Biotage Initiator Sixty EXP Microwave System, that operates at 0–400 W at 2.45 GHz, in the temperature range of 40–250 °C, a pressure range of 0–20 bar (2 MPa, 290 psi), and with reactor vial volumes of 0.2–20 mL.

General Procedure for the Suzuki Cross-Coupling Reaction: Into a microwave vial, 1-chloro (or bromo)-2-nitrobenzene (1 mmol), phenylboronic acid (1.5 mmol), Na_2CO_3 (1.1 mmol), tetrabutylammonium bromide (TBAB; 0.08 mmol), and $Pd(PPh_3)_4$ (0.026 mmol, 2.6 mol-%) were added. The vial was sealed and argon was carefully flushed through the septa before a mixture of MeOH (4 mL) and water (1 mL) was added. The vial was submerged in the microwave cavity for 30 min at 120 °C. The post-reaction mixture was cooled to room temperature, and methanol was removed under reduced pressure. The reaction mixture was diluted with diethyl ether (30 mL) and washed with water (40 mL). The aqueous phase was extracted with diethyl ether (2 × 50 mL) and the organic phases were combined and dried with Na_2SO_4. The drying agent was filtered off and the crude product purified by flash chromatography [ethyl acetate/hexane (mixture of isomers)] to afford 2-nitrobiphenyls.

Suzuki Cross-Coupling Reaction with Chlorobenzenes

2,4-Dimethoxy-3-methyl-5-nitrophenol (1) [136763-93-3]: A solution of conc. HCl (13 mL) in MeOH (25 mL) was added to 2,4-dimethoxy-3-methyl-5-nitrophenyl acetate (1.9 g, 7.45 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 70 °C at reflux temperatures. After cooling to r.t. the solvent was removed under reduced pressure. The crude product was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The organic layers were combined and dried with Na_2SO_4 to afford the title compound as an orange solid (1.40 g, 88 %), m.p. 53–55 °C. R_f = 0.65 (EtOAc/hexane, 40:60). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (s, 1 H), 5.56 (s, 1 H), 3.79 (s, 6 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 146.4, 145, 140.2, 127.4, 109.3, 62.1, 61.1, 10 ppm. MS (EI): *m/z* (%) = 213 (100) [M$^+$], 183 (7), 166 (53), 152 (21), 137 (40), 125 (40), 122 (26), 77 (30), 53 (45). IR: $\tilde{\nu}$ = 3404, 3083, 2929, 2846, 1500 cm^{-1}.

2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol (3Cl): To a solution of 2,4-dimethoxy-3-methyl-5-nitrophenol (0.311 g, 0.145 mmol) in EtOH (15 mL), DCH (146 mg, 0.0741 mmol) was added followed by conc. H_2SO_4 dropwise (≈ 24 drops) with good stirring. After the addition was completed, the reaction mixture was quenched with NaOH (4.1 M, 5 mL). A heavy red precipitation was observed during the addition of NaOH, which was neutralized with acetic acid (pH ≈ 4), and the resulting mixture was diluted with water (25 mL) and extracted with diethyl ether (3 × 40 mL). The organic layers were combined and dried with Na_2SO_4. The crude product was isolated by flash chromatography (CH_2Cl_2/hexane, 40:60) to afford the title compound as pale yellow crystals (0.34 g, 95 %), m.p. 118.5 °C. R_f = 0.29 (CH_2Cl_2/hexane, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (s, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5, 144.0, 142.7, 125.6, 109.3, 62.9, 61.0, 9.9 ppm. MS (EI): *m/z* (%) = 247 (100) [M$^+$], 217 (5), 213 (16), 186 (25), 171 (27), 138 (26), 108 (20), 83 (22), 77 (48), 67 (32). HRMS (EI): calcd. for $C_9H_{10}ClNO_5$ 247.0248; found 247.0248. IR: $\tilde{\nu}$ = 3406, 3083, 2970, 2929, 2846, 1500, 1108 cm^{-1}.

2-Iodo 4,6-dimethoxy-5-methyl-3-nitrophenol (3I): A solution of KI (0.332 g, 2 mmol) and iodine (0.295 g, 1.16 mmol) in H_2O (1 mL) was added dropwise to an aqueous solution of $BuNH_2$ (20 %; 1.5 mL) and acetic acid 2,4-dimethoxy-3-methyl-5-nitrophenyl (**4;** 0.170 g, 0.67 mmol), for 1–2 min at room temperature. The resulting dark mixture was stirred for 30 min at room temperature, and then poured into CH_2Cl_2 (50 mL). The organic layer was washed with aqueous sodium thiosulfate (10 %; 30 mL), dried with anhydrous Na_2SO_4, and filtered. After removal of the solvent in vacuo, the final crude (0.100 g) contained **5** as major product in 32 % yield (81 % purity), and 2,4-dimethoxy-3-methyl-5-nitrophenol as a major impurity. $C_9H_{10}NO_5I$ MW 339.09. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.85 [s, 3 H, -OMe], 3.79 [s, 3 H, -OMe], 2.26 [s, 3 H, -Me] ppm. ^{13}C NMR

(200 MHz, $CDCl_3$): δ = 146.7, 146.0, 144.3, 127.0, 71.1, 62.9, 61.1, 10.1 ppm. MS: *m/z* (%) = 339 (100), 324 (3), 278 (14), 263 (19), 248 (6), 235 (6), 207 (8), 179 (14), 167 (19), 151 (13), 136 (22), 123 (15), 108 (39), 93 (13), 79 (38), 67 (47), 53 (40), 43 (16).

3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (5): In a microwave tube, 2-chloro-4,6-dimethoxy-5-methyl-3-nitrophenol (**6;** 0.21 g, 0.85 mmol), phenyl boronic acid (0.24 g, 1.97 mmol), Na_2CO_3 (0.10 g, 0.94 mmol), TBAB (0.021 g, 0.065 mmol) and $Pd(PPh_3)_4$ (0.025 g, 0.022 mmol) were added. The reaction mixture was carefully flushed with argon before adding a mixture of MeOH (4 mL) and water (1 mL), The tube was sealed and placed into the microwave cavity for 30 min at 120 °C. Then the reaction mixture was washed with water (40 mL) and extracted with diethyl ether (2 × 25 mL). The organic extracts were combined and dried with Na_2SO_4. The crude product was isolated by flash chromatography (CH_2Cl_2/hexane, 15:85) to afford the title compound as a white powder (0.125 g, 51 %), m.p. 102.5 °C. R_f = 0.49 (CH_2Cl_2/hexane, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.45 (m, 5 H), 5.57 (s, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 143.2, 142.9, 130.8, 129.4, 128.9, 128.8, 125.6, 119.4, 62.8, 61.0, 10.0 ppm. MS (EI): *m/z* (%) = 289 (100) [M$^+$], 272 (7), 246 (20), 207 (24), 199 (13), 169 (13), 141 (20), 129 (40), 115 (33), 102 (12), 83 (23), 77 (20). HRMS (ESI): calcd. for $C_{15}H_{15}NO_5$ [M + Na$^+$] 312.0848; found 312.0846. IR: $\tilde{\nu}$ = 3481, 2927, 2850, 1530, 1370 cm^{-1}.

4′-Chloro-2-nitro-1,1′-biphenyl (5a) [6271-80-3]: 1-Chloro-2-nitrobenzene (0.25 g, 1.59 mmol), 4-chlorophenylboronic acid (0.373 g, 2.39 mmol), Na_2CO_3 (0.185 g, 1.75 mmol), TBAB (0.041 g, 0.13 mmol), and $Pd(PPh_3)_4$ (0.048 g, 0.042 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as a yellow crystalline solid (0.315 g, 85 %), m.p. 59 °C. R_f = 0.58 (EtOAc/hexane, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.82 (dd, *J* = 1.2, 8 Hz, 1 H), 7.53–7.57 (td, *J* = 1.2, 7.6 Hz, 1 H), 7.41–7.45 (td, *J* = 1.2, 8 Hz, 1 H), 7.31–7.34 (m, 3 H), 7.16–7.19 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 135.9, 135.2, 134.5, 132.5, 131.9, 129.3, 128.9, 128.6, 124.3 ppm. MS (EI): *m/z* (%) = 237.2 (1), 236.1 (8), 233.3 (99) [M$^+$], 215.9 (42), 198 (48), 168.3 (98), 149.9 (100), 139.2 (98), 115.1 (94), 97.7 (35), 74.23 (99), 62.3 (87). IR: $\tilde{\nu}$ = 1521, 1347, 827 cm^{-1}. The recorded spectroscopic data were in accordance with the literature.[34]

4′-Ethyl-2-nitro-1,1′-biphenyl (5b) [166589-62-4]: 1-Chloro-2-nitrobenzene (0.25 g, 1.59 mmol), 4-ethylphenylboronic acid (0.358 g, 2.39 mmol), Na_2CO_3 (0.185 g, 1.75 mmol), TBAB (0.041 g, 0.127 mmol), and $Pd(PPh_3)_4$ (0.048 g, 0.042 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as a yellow liquid (0.301 g, 84 %). R_f = 0.66 (EtOAc/hexane, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.75 (dd, *J* = 1.2, 7.2 Hz, 1 H), 7.49–7.53 (td, *J* = 1.2, 7.6 Hz, 1 H), 7.35–7.39 (m, 2 H), 7.15–7.19 (m, 4 H), 2.62 (q, *J* = 7.6 Hz, 2 H), 1.19 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 134.7, 133, 130.6, 130.4, 126.7, 126.3, 126.2, 122.7, 122.4, 27, 13.7 ppm. MS (EI): *m/z* (%) = 228.2 (4), 227 (35) [M$^+$], 210 (19), 198 (27), 181.9 (54), 164.9 (100), 151.6 (61), 129.1 (21), 115 (27), 88.8 (16), 82 (33), 76 (20). IR: $\tilde{\nu}$ = 2964, 1521, 1351 cm^{-1}.

2-Methoxy-2′-nitro-1,1′-biphenyl (5c) [6460-92-0]: 1-Chloro-2-nitrobenzene (0.25 g, 1.59 mmol), 2-methoxyphenylboronic acid (0.362 g, 2.38 mmol), Na_2CO_3 (0.185 g, 1.75 mmol), TBAB (0.041 g, 0.13 mmol), and $Pd(PPh_3)_4$ (0.048 g, 0.042 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a pale green solid (0.264 g, 73 %), m.p. 78.9 °C. R_f = 0.53 (EtOAc/hexane, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.94 (dd, *J* = 1.2, 8 Hz, 1 H), 7.63–7.66 (td, *J* = 1.2, 7.6 Hz, 1 H), 7.45–7.49 (td, *J* = 1.6, 8 Hz, 1 H), 7.37–7.43 (m, 4 H), 7.31–7.33 (dd, *J* = 1.6, 7.2 Hz, 1 H), 7.01–7.11 (td, *J* = 1.2, 7.6 Hz, 1 H), 6.90–6.93 (dd, *J* = 0.8, 8.4 Hz, 1 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 149.7, 133.1, 132.8, 132.5, 129.8, 129.7, 128, 127, 123.9, 121.2, 110.6, 55.2 ppm. MS (EI): *m/z* (%) = 231.2 (3), 230.2 (25), 229 (98) [M$^+$], 197.9 (47), 184 (33), 170 (82), 168 (99), 152 (50), 139 (100), 115 (86), 89 (26), 77 (35), 63 (45). IR: $\tilde{\nu}$ = 2950, 1500, 1355 cm^{-1}. The recorded spectroscopic data were in accordance with the literature.[35]

2-Methyl-2′-nitro-1,1′-biphenyl (5d) [67992-12-5]: 1-Chloro-2-nitrobenzene (0.25 g, 1.59 mmol), 2-methylphenylboronic acid (0.324 g, 2.38 mmol), Na_2CO_3 (0.185 g, 1.75 mmol), TBAB (0.041 g, 0.127 mmol), and $Pd(PPh_3)_4$ (0.048 g, 0.042 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as a yellow liquid (0.3112 g, 92 %). R_f = 0.53 (EtOAc/hexane, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.93 (dd, *J* = 1.2, 8.4 Hz, 1 H), 7.53–7.58 (td, *J* = 1.2, 7.6 Hz, 1 H), 7.42–7.46 (td, *J* = 1.6, 8 Hz, 1 H), 7.24–7.27 (dd, *J* = 1.6, 8 Hz, 1 H), 7.13–7.23 (m, 3 H), 7.01–7.03 (dd, *J* = 0.8, 7.6 Hz, 1 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 137.5, 136.5, 135.6, 132.6, 132.2, 130, 128.3, 128.2, 125.8, 124.1, 19.9 ppm. MS (EI): *m/z* (%) = 214.2 (2), 213 (15) [M$^+$], 195.9 (48), 166.1 (64), 164.9 (100), 151.6 (39), 139 (19), 115 (28), 88.9 (12), 82.2 (43), 63 (18). IR: $\tilde{\nu}$ = 3062, 2360, 2342, 1521, 1346 cm^{-1}. The recorded spectroscopic data were in accordance with the literature.[25]

4-Methyl-2-nitro-1,1′-biphenyl (5e) [39554-87-5]: 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), phenylboronic acid (0.267 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.12 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a pale orange liquid (0.239 g, 77 %). R_f = 0.63(EtOAc/hexane, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.39–7.44 (m, 4 H), 7.30–7.34 (m, 3 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 138.7, 137.4, 133.5, 133.1, 131.8, 128.7, 128, 127.9, 124.4, 20.9 ppm. MS (EI): *m/z* (%) = 214.2 (7), 212.8 (52) [M$^+$], 184.5 (81), 164 (98), 151.4 (100), 127.1 (99), 1149 (52), 90.7 (31), 88.8 (41), 82 (68), 76.5 (71). IR: $\tilde{\nu}$ = 3028, 1523, 1351 cm^{-1}. The recorded spectroscopic data were in accordance with the literature.[36]

4′-Chloro-4-methyl-2-nitro-1,1′-biphenyl (5f): 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 4-chlorophenylboronic acid (0.342 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.12 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a yellow liquid (0.291 g, 80 %). R_f = 0.63 (EtOAc/hexane, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.41–7.44 (dd, *J* = 1.2, 8 Hz, 1 H), 7.37–7.40 (m, 2 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.21–7.24 (m, 2 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 139.2, 136, 134.2, 133.3, 132.4, 131.6, 129.3, 128.9, 124.6, 20.9 ppm. HRMS (EI): calcd. for $C_{13}H_{10}ClNO_2$ 247.0400; found 247.0400. IR: $\tilde{\nu}$ = 2924, 1525, 1347, 817 cm^{-1}.

4′-Ethyl-4-methyl-2-nitro-1,1′-biphenyl (5g): 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 4-ethylphenylboronic acid (0.328 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.12 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a yellow solid (0.327 g, 93 %), m.p. 53.6 °C. R_f = 0.73(EtOAc/hexane, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1 H), 7.44–746 (dd, *J* = 1.2, 8 Hz, 1 H), 7.36–7.38 (d, *J* = 8 Hz, 1 H), 7.26–7.31 (m, 4 H), 2.74 (q, *J* = 7.6 Hz, 2 H), 2.51 (s, 3 H), 1.32 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 144.2, 138.4, 134.6, 133.4, 133, 131.7, 128.2, 127.9, 124.3, 28.6, 20.9, 15.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO_2Na$ [M + Na$^+$] 264.1000; found 260.1001. IR: $\tilde{\nu}$ = 2969, 2932, 1525, 1354 cm^{-1}.

2′,4-Dimethyl-2-nitro-1,1′-biphenyl (5h): 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 2-methylphenylboronic acid (0.298 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.12 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a yellow liquid (0.280 g, 85 %). R_f = 0.71 (EtOAc/hexane, 20:80). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 7.35–7.37 (dd, J = 1.2, 7.2 Hz, 1 H), 7.12–7.22 (m, 4 H), 7.00–7.01 (dd, J = 1.2, 8.4 Hz, 1 H), 2.41 (s, 3 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 138.7, 137.5, 135.8, 133.6, 133.4, 132, 129.9, 128.4, 128, 125.7, 124.4, 21, 19.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}NO_2Na$ [M + Na^+] 250.0844; found 250.0845. IR: $\tilde{\nu}$ = 2923, 1524, 1349 cm^{-1}.

2′-Methoxy-4-methyl-2-nitro-1,1′-biphenyl (5i): 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 2-methoxyphenylboronic acid (0.333 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.12 mmol) and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a pale-yellow solid (0.265 g, 75 %), m.p. 101 °C. R_f = 0.61 (EtOAc/hexane, 20:80). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.43–7.45 (dd, J = 0.8, 7.6 Hz, 1 H), 7.35–7.39 (td, J = 1.6, 8 Hz, 1 H), 7.28–7.31 (m, 2 H), 7.05–7.09 (td, J = 1.2, 7.6 Hz, 1 H), 6.90 (d, J = 8 Hz, 1 H), 3.70 (s, 3 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 149.5, 138.5, 133.5, 132.3, 130.1, 129.7, 129.6, 127, 124.3, 121.2, 110.6, 55.2, 20.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}NO_3Na$ [M + Na^+] 266.0793; found 266.0795. IR: $\tilde{\nu}$ = 2963, 2835, 1501, 1356 cm^{-1}.

(2-Nitro-1,1′-biphenyl-4-yl)(phenyl)methanone (5j) [857493-17-5]: 4-Chloro-3-nitrobenzophenone (0.25 g, 0.96 mmol), phenylboronic acid (0.176 g, 1.44 mmol), Na_2CO_3 (0.112 g, 1.06 mmol), TBAB (0.025 g, 0.08 mmol), and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a pale yellow crystalline solid (0.260 g, 89 %), m.p. 115.8 °C. R_f = 0.61 (EtOAc/hexane, 20:80). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 1.6 Hz, 1 H), 8.05–8.07 (dd, J = 2, 8 Hz, 1 H), 7.84–7.86 (dd, J = 0.8, 8 Hz, 2 H), 7.64–7.68 (m, 1 H), 7.53–7.61 (m, 3 H), 7.45–7.48 (m, 3 H), 7.36–7.39 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 149.1, 139.8, 137.5, 136.4, 136.4, 133.3, 133.2, 132.2, 130, 128.9, 128.8, 127.8, 125.6 ppm. MS (EI): m/z (%) = 304.3 (1), 302.9 (9) [M^+], 274.8 (28), 258 (6), 225.9 (7), 207 (9), 197.9 (6), 170 (16), 150.6 (22), 138.9 (8), 105 (98), 78.3 (5), 76.9 (100), 62.7 (5), 50.9 (17). IR: $\tilde{\nu}$ = 1661, 1515, 1360 cm^{-1}. The recorded spectroscopic data were in accordance with the literature.[6d]

2-Nitro-1,1′-biphenyl-4-carboxylic Acid (5k) [99847-12-8]: 4-Chloro-3-nitrobenzoic acid (0.25 g, 1.24 mmol), phenylboronic acid (0.226 g, 1.85 mmol), Na_2CO_3 (0.145 g, 1.37 mmol), TBAB (0.032 g, 0.10 mmol), and $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) were added. The reaction mixture was carefully flushed with argon before adding a mixture of MeOH (4 mL) and water (1 mL). The tube was sealed and placed into the microwave cavity for 30 min at 120 °C. After this time, the reaction mixture was cooled to room temp. and the solvent was removed under reduced pressure. Then the reaction mixture was washed with water (40 mL) and acidified with HCl (1 N, pH = 1–2) and filtered. The obtained solid contains both acid compound and biphenyl (impurity). Water (5 mL) was added to the flask, which contained the obtained solid. The solid was basified with NaOH (4 M; pH = 10–12) and extracted with CH_2Cl_2 (2 × 40 mL). The aqueous layer was then acidified with HCl (1 N; pH = 1–2) and filtered to afford compound **5k** as a pale yellow solid (0.215 g, 72 %), m.p. 189.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, J = 1.6 Hz, 1 H), 8.33–8.36 (dd, J = 1.6, 8.0 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.45–7.49 (m, 3 H), 7.35–7.37 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 149.4, 141.3, 136.2, 133.4, 132.5, 129.5, 129.1, 129, 127.7, 125.9 ppm. HRMS (ESI^-): calcd for $C_{13}H_8NO_4$ [M^+ – H] 242.0453; found 242.0455. IR: $\tilde{\nu}$ = 2515, 1693, 1537, 1350 cm^{-1}. The recorded spectroscopic data were in accordance with the literature.[6d]

2′-Nitro-1,1′-biphenyl-4-carbaldehyde (5l) [169188-17-4]: 1-Chloro-2-nitrobenzene (0.25 g, 1.59 mmol), 4-formylphenylboronic acid (0.358 g, 2.39 mmol), Na_2CO_3 (0.185 g, 1.75 mmol), TBAB (0.041 g, 0.127 mmol), and $Pd(PPh_3)_4$ (0.048 g, 0.042 mmol). The title compound was isolated by chromatography (CH_2Cl_2/hexane, 50:50) as yellow crystals (0.287 g, 80 %), m.p. 102.3 °C. R_f = 0.33 (CH_2Cl_2/hexane, 50:50). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.01 (s, 1 H), 7.93–7.96 (m, 3 H), 7.66–7.70 (td, J = 1.2, 7.2 Hz, 1 H), 7.54–7.58 (td, J = 1.2, 8 Hz, 1 H), 7.48–7.50 (dd, J = 1.6, 6.4 Hz, 2 H), 7.44–7.46 (dd, J = 1.6, 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 148.8, 143.8, 135.8, 135.4, 132.9, 131.7, 130, 129.1, 128.7, 124.5 ppm. MS (EI): m/z (%) = 226.7 (95) [M^+], 210 (62), 198.6 (100), 168.5 (99), 150.1 (100), 113.8 (99), 101.2 (92), 74.3 (99). IR: $\tilde{\nu}$ = 2859, 1693, 1505, 1351 cm^{-1}.

4′-Methyl-2′-nitro-1,1′-biphenyl-4-carbaldehyde (5m): 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 4-formylphenylboronic acid (0.328 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.117 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (CH_2Cl_2/hexane, 40:60) as yellow crystals (0.309 g, 88 %), m.p. 106 °C. R_f = 0.29 (CH_2Cl_2/hexane, 50:50). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.05 (s, 1 H), 7.91–7.93 (m, 2 H), 7.76 (s, 1 H), 7.45–7.48 (m, 3 H), 7.32 (d, J = 8 Hz, 1 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 148.6, 143.9, 139.8, 135.7, 133.5, 132.5, 131.5, 129.8, 128.7, 124.9, 21 ppm. HRMS (ESI): calcd. for $C_{14}H_{11}NO_3Na$ (MeOH) [M + Na^+] 296.0899; found 296.0899. IR: $\tilde{\nu}$ = 2854, 2750, 1696, 1521, 1351 cm^{-1}.

4′-Methyl-2′-nitro-1,1′-biphenyl-4-ol (5n) [1620094-10-1]: 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 4-hydroxyphenylboronic acid (0.302 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.117 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (CH_2Cl_2/hexane, 80:20) as a dark yellow liquid (0.208 g, 62 %). R_f = 0.26 (CH_2Cl_2/hexane, 90:10). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (s, 1 H), 7.38–7.40 (dd, J = 0.8, 8 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.15–7.19 (m, 2 H), 6.84–6.88 (m, 2 H), 5.52 (s, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 149.2, 138.3, 133, 131.7, 129.6, 129.3, 124.3, 115.7, 20.8 ppm. MS (EI): 231.2 (1), 230.2 (10), 228.9 (100) [M^+], 212 (26), 196 (8), 183.9 (57), 167.9 (35), 151.7 (49), 127.4 (56), 114.9 (32), 77 (22), 75.6 (30). IR: $\tilde{\nu}$ = 3284, 1701, 1520, 1355 cm^{-1}.

4-Methyl-2-nitro-4′-vinyl-1,1′-biphenyl (5o): 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 4-vinylphenylboronic acid (0.324 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.117 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (CH_2Cl_2/hexane, 40:60) as yellow crystals (0.265 g, 76 %), m.p. 73.6 °C. R_f = 0.69 (CH_2Cl_2/hexane, 50:50). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 1 H), 7.32–7.38 (m, 3 H), 7.24 (d, J = 8 Hz, 1 H), 7.17–7.20 (m, 2 H), 6.63–6.70 (m, 1 H), 5.69–5.74 (dd, J = 0.4, 17.6 Hz, 1 H), 5.20–5.23 (m, 1 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 138.7, 137.3, 136.8, 136.2, 133.1, 133.1, 131.6, 128.1, 126.5, 124.5, 114.6, 20.9 ppm. HRMS (ESI): calcd. for $C_{15}H_{13}NO_2Na$ [M + Na^+] 262.0844; found 262.0845. IR: $\tilde{\nu}$ = 3064, 1514, 1359 cm^{-1}.

4′-Methyl-2′-nitro-1,1′-biphenyl-2-carbonitrile (5p): 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 2-cyanophenylboronic acid (0.322 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.117 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (CH_2Cl_2/hexane, 50:50) as pale-yellow crystals (0.110 g, 32 %), m.p. 97.6 °C. R_f = 0.39 (CH_2Cl_2/

hexane, 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.74–7.77 (dd, J = 1.2, 8 Hz, 1 H), 7.61–7.65 (td, J = 1.6, 8 Hz, 1 H), 7.48–7.54 (m, 2 H), 7.31–7.34 (m, 2 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148, 142.2, 140.7, 134.1, 132.9, 132.7, 132, 130.5, 129, 128.3, 125.4, 117.6, 112.3, 21.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{10}N_2O_2Na$ [M + Na$^+$] 261.0640; found 261.0641. IR: $\tilde{\nu}$ = 2919, 2360, 2340, 2233, 1519, 1351 cm^{-1}.

***N*,*N*-4′-Trimethyl-2′-nitro-1,1′-biphenyl-4-amine (5q):** 4-Chloro-3-nitrotoluene (0.25 g, 1.46 mmol), 4-(dimethylamino)phenylboronic acid (0.361 g, 2.19 mmol), Na_2CO_3 (0.170 g, 1.60 mmol), TBAB (0.038 g, 0.117 mmol), and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol). The title compound was isolated by chromatography (CH_2Cl_2/hexane, 30:70) as dark orange crystals (0.201 g, 53 %), m.p. 136 °C. R_f = 0.24 (CH_2Cl_2/hexane, 30:70). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 7.31–7.38 (m, 2 H), 7.17–7.21 (m, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 2.99 (s, 6 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 149.2, 137.4, 133.4, 132.8, 131.6, 128.7, 124.8, 124.3, 112.5, 40.5, 20.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}N_2O_2H$ [M + H$^+$] 257.1290; found 257.1291. IR: $\tilde{\nu}$ = 2880, 2811, 1610, 1521, 1361 cm^{-1}.

Suzuki Cross-Coupling Reaction with Bromobenzenes

4′-Chloro-4-methoxy-2-nitro-1,1′-biphenyl (5r) [41734-95-6]: 1-Bromo-4-methoxy-2-nitrobenzene (0.25 g, 1.08 mmol), (4-chlorophenyl)boronic acid (0.253 g, 1.62 mmol), Na_2CO_3 (0.126 g, 1.19 mmol), TBAB (0.028 g, 0.087 mmol), and $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a yellow solid (0.275 g, 95 %), m.p. 77.8 °C. R_f = 0.40 (EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.39 (m, 2 H), 7.36 (s, 1 H), 7.30 (d, J = 8.5 Hz, 1 H), 7.20–7.21 (m, 2 H), 7.14–7.16 (dd, J = 2.5, 8.5 Hz,1 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 149.5, 135.9, 134.0, 132.7, 129.4, 128.8, 127.5, 118.8, 109.2, 56.0 ppm. MS (EI): m/z (%) = 265 (38), 263 (87) [M$^+$], 246 (15), 228 (28), 200 (36), 182 (45), 170 (37), 139 (100), 113 (14), 75 (13), 69 (31). IR: $\tilde{\nu}$ = 3084, 3017, 2983, 2942, 2841, 1529, 1358, 817 cm^{-1}.

4-Methoxy-2-nitro-1,1′-biphenyl (5s) [16098-16-1]: 1-Bromo-4-methoxy-2-nitrobenzene (0.25 g, 1.08 mmol), phenylboronic acid (0.198 g, 1.62 mmol), Na_2CO_3 (0.126 g, 1.19 mmol), TBAB (0.028 g, 0.087 mmol), and $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as dark yellow crystals (0.223 g, 90 %), m.p. 72.1 °C. R_f = 0.45 (EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.42 (m, 4 H), 7.34 (d, J = 8.5, 7.6 Hz, 1 H), 7.27–7.29 (m, 2 H), 7.14–7.16 (dd, J = 2.5, 8.5 Hz,1 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 149.7, 137.3, 132.8, 128.7, 128.6, 128.0, 127.9, 118.7, 109.0, 55.9 ppm. MS (EI): m/z (%) = 229 (85) [M$^+$], 212 (58), 201 (34), 184 (53), 168 (74), 139 (100), 128 (78), 102 (23), 63 (36). IR: $\tilde{\nu}$ = 2917, 2849, 1526, 1346 cm^{-1}.

2′-Chloro-4-methyl-2-nitro-1,1′-biphenyl (5t): 1-Bromo-4-methyl-2-nitrobenzene (0.25 g, 1.16 mmol), (2-chlorophenyl)boronic acid (0.272 g, 1.74 mmol), Na_2CO_3 (0.135 g, 1.27 mmol), TBAB (0.030 g, 0.09 mmol), and $Pd(PPh_3)_4$ (0.035 g, 0.030 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as light brown crystals (0.256 g, 90 %), m.p. 72.6 °C. R_f = 0.55 (EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.47–7.49 (dd, J = 0.5, 7.5 Hz, 1 H), 7.44–7.45 (m, 1 H), 7.32–7.34 (m, 2 H), 7.24–7.26 (m, 2 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.4, 139.6, 137.2, 133.7, 132.9, 132.2, 131.5, 130.0, 129.4, 129.3, 126.9, 124.8, 21.0 ppm. HRMS (DART): calcd. for $C_{13}H_{11}{}^{35}ClNO_2$ [M + H$^+$] 248.0478; found 248.0478, calcd. for $C_{13}H_{11}{}^{37}ClNO_2$ 250.0478; found 248.0449 IR: $\tilde{\nu}$ = 3057, 2922, 1522, 1352, 754 cm^{-1}.

3′-Methoxy-4-methyl-2-nitro-1,1′-biphenyl (5u) [943620-21-1]: 1-Bromo-4-methyl-2-nitrobenzene (0.25 g, 1.16 mmol), (3-methoxyphenyl)boronic acid (0.264 g, 1.74 mmol), Na_2CO_3 (0.135 g, 1.27 mmol), TBAB (0.030 g, 0.09 mmol), and $Pd(PPh_3)_4$ (0.035 g, 0.030 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as a yellow liquid (0.255 g, 90 %). R_f = 0.48 (EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (s, 1 H), 7.40–7.41 (dd, J = 1, 8 Hz, 1 H), 7.30–7.33 (m, 2 H), 6.91–6.93 (m, 1 H), 6.86–6.88 (dd, J = 1, 7.5 Hz, 1 H), 6.83–6.84 (m, 1 H), 3.81 (s, 3 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7, 149.2, 138.8, 138.7, 133.3, 133.0, 131.6, 129.7, 124.3, 120.3, 113.7, 113.5, 55.3, 20.9 ppm. MS (EI): m/z (%) = 243 (73) [M$^+$], 215 (65), 184 (41), 172 (54), 152 (100), 144 (55), 115 (52), 76 (28), 63 (33), 55 (66). IR: $\tilde{\nu}$ = 2938, 2836, 1525, 1355 cm^{-1}.

4,4′-Dichloro-2-nitro-1,1′-biphenyl (5v) [192942-45-3]: 1-Bromo-4-chloro-2-nitrobenzene (0.25 g, 1.06 mmol), (4-chlorophenyl)-boronic acid (0.249 g, 1.59 mmol), Na_2CO_3 (0.124 g, 1.17 mmol), TBAB (0.027 g, 0.084 mmol), and $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as a yellow solid (0.232 g, 82 %), m.p. 87.1 °C. R_f = 0.56 (EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, J = 2.5 Hz, 1 H), 7.59–7.61 (dd, J = 2, 8.5 Hz, 1 H), 7.39–7.41 (dd, J = 2, 6.5 Hz, 2 H), 7.36 (d, J = 8 Hz, 1 H), 7.21–7.22 (dd, J = 2, 6.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.3, 134.9, 134.8, 134.4, 133.7, 132.9, 132.6, 129.2, 129.1, 124.4 ppm. MS (EI): m/z (%) = 269 (28), 267 (43) [M$^+$], 232 (31), 204 (54), 186 (100), 176 (43), 150 (89), 139 (51), 93 (45), 75 (94). IR: $\tilde{\nu}$ = 3091, 1518, 13548, 815 cm^{-1}.

4-Chloro-2-nitro-1,1′-biphenyl (5w) [29608-78-4]: 1-Bromo-4-chloro-2-nitrobenzene (0.25 g, 1.06 mmol), phenylboronic acid (0.194 g, 1.59 mmol), Na_2CO_3 (0.124 g, 1.17 mmol), TBAB (0.027 g, 0.084 mmol), and $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 5:95) as a yellow liquid (0.220 g, 89 %). R_f = 0.69(EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, J = 2 Hz, 1 H), 7.58–7.60 (dd, J = 2.5, 8.5 Hz, 1 H), 7.38–7.43 (m, 4 H), 7.28–7.29 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.5, 136.3, 134.8, 133.0, 132.4, 129.2, 128.8, 128.6, 127.8, 124.2 ppm. MS (EI): m/z (%) = 235 (10), 233 (30) [M$^+$], 216 (40), 205 (48), 188 (26), 168 (52), 152 (100), 115 (60), 75 (56), 63 (40). IR: $\tilde{\nu}$ = 3063, 3028, 1529, 1349, 773 cm^{-1}.

1-(2-Nitro-1,1′-biphenyl-4-yl)ethan-1-one (5x) [42771-77-7]: 1-(4-bromo-3-nitrophenyl)ethan-1-one (0.25 g, 1.02 mmol), phenylboronic acid (0.187 g, 1.59 mmol), Na_2CO_3 (0.119 g, 1.12 mmol), TBAB (0.026 g, 0.080 mmol), and $Pd(PPh_3)_4$ (0.031 g, 0.027 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a yellow solid (0.246 g, 83 %), m.p. 106.7 °C. R_f = 0.17(EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39 (d, J = 1.5 Hz, 1 H), 8.17–8.19 (dd, J = 2, 8 Hz, 1 H), 7.57 (d, J = 8 Hz, 1 H), 7.44–7.46 (m, 3 H), 7.32–7.34 (m, 2 H), 2.68 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.4, 149.5, 140.4, 136.8, 136.3, 132.5, 131.4, 129.0, 128.9, 127.7, 124.0, 26.7 ppm. MS (EI): m/z (%) = 241 (31) [M$^+$], 224 (35), 213 (54), 198 (39), 170 (46), 151 (100), 142 (47), 139 (35), 115 (33), 76 (25), 63 (31). IR: $\tilde{\nu}$ = 3095, 1683, 1519, 1352 cm^{-1}. The recorded spectroscopic data were in accordance with the previously disclosed ^{1}H NMR spectroscopic data.[6d]

1-(4′-Chloro-2-nitro-1,1′-biphenyl-4-yl)ethan-1-one (5y) [52806-84-5]: 1-(4-Bromo-3-nitrophenyl)ethan-1-one (0.25 g, 1.02 mmol), (4-chlorophenyl)boronic acid (0.239 g, 1.59 mmol), Na_2CO_3 (0.119 g, 1.12 mmol), TBAB (0.026 g, 0.080 mmol) and $Pd(PPh_3)_4$ (0.031 g, 0.027 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as a yellow solid (0.220 g, 80 %), m.p. 101.3 °C. R_f = 0.14(EtOAc/hexane, 10:90). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, J = 2 Hz, 1 H), 8.18–8.20 (dd, J = 1.5, 8 Hz, 1 H), 7.54 (d, J = 8 Hz, 1 H), 7.43–7.44 (dd, J = 1.5, 6.5 Hz, 2 H), 7.26–7.28 (dd, J = 1.5, 6.5 Hz, 2 H), 2.69 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$):

δ = 195.2, 149.3, 139.2, 137.1, 135.3, 134.8, 132.4, 131.5, 129.2, 129.1, 124.1, 26.7 ppm. MS (EI): *m/z* (%) = 277 (36), 275 (94) [M^+], 260 (47), 240 (69), 214 (48), 186 (72), 179 (91), 170 (58), 151 (100), 139 (55), 75 (98). IR: $\tilde{\nu}$ = 3073, 1698, 1521, 1350, 817 cm^{-1}.

1-(2′-Methyl-2-nitro-1,1′-biphenyl-4-yl)ethan-1-one (5z): 1-(4-Bromo-3-nitrophenyl)ethan-1-one (0.25 g, 1.02 mmol), 2-methylphenylboronic acid (0.208 g, 1.53 mmol), Na_2CO_3 (0.119 g, 1.12 mmol), TBAB (0.026 g, 0.080 mmol), and $Pd(PPh_3)_4$ (0.031 g, 0.027 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 15:85) as a yellow solid (0.216 g, 83 %), m.p. 59.5 °C. R_f = 0.22(EtOAc/hexane, 10:90). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 2 Hz, 1 H), 8.12–8.15 (dd, *J* = 2, 10 Hz, 1 H), 7.40 (d, *J* = 9.5 Hz, 1 H), 7.16–7.28 (m, 3 H), 7.00–7.02 (dd, *J* = 1, 9.5 Hz, 1 H), 2.64 (s, 3 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 149.3, 140.9, 137.0, 136.5, 135.3, 132.9, 131.6, 130.2 128.7, 127.9, 125.9, 124.0, 26.7, 19.9 ppm. HRMS (DART): calcd. for $C_{15}H_{14}NO_3$ [M + H^+] 256.0974; found 256.0974. IR: $\tilde{\nu}$ = 2923, 1689, 1529, 1351 cm^{-1}.

1-(2′-Methoxy-2-nitro-1,1′-biphenyl-4-yl)ethan-1-one (5æ): 1-(4-Bromo-3-nitrophenyl)ethan-1-one (0.25 g, 1.02 mmol), (2-methoxyphenyl)boronic acid (0.232 g, 1.53 mmol), Na_2CO_3 (0.119 g, 1.12 mmol), TBAB (0.026 g, 0.080 mmol), and $Pd(PPh_3)_4$ (0.031 g, 0.027 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 15:85) as a yellow solid (0.216 g, 83 %), m.p. 113.1 °C. R_f = 0.14(EtOAc/hexane, 10:90). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 2 Hz, 1 H), 8.12–8.14 (dd, *J* = 2, 10 Hz, 1 H), 7.46 (d, *J* = 10 Hz, 1 H), 7.33–7.37 (m, 1 H), 7.25–7.27 (dd, *J* = 2, 9 Hz, 1 H), 7.02–7.06 (td, *J* = 1, 9.5 Hz, 1 H), 6.85 (d, *J* = 10 Hz, 1 H), 3.63 (s, 3 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.7, 155.7, 149.8, 137.5, 136.6, 133.0, 131.8, 130.6, 129.6, 126.0, 123.8, 121.4, 110.7, 55.2, 26.7 ppm. HRMS (DART): calcd. for $C_{15}H_{14}NO_4$ [M + H^+] 272.0923; found 272.0923. IR: $\tilde{\nu}$ = 2910, 1689, 1537, 1363 cm^{-1}.

1-(4′-Ethyl-2-nitro-1,1′-biphenyl-4-yl)ethan-1-one (5ø): 1-(4-Bromo-3-nitrophenyl)ethan-1-one (0.25 g, 1.02 mmol), (4-ethylphenyl)boronic acid (0.229 g, 1.53 mmol), Na_2CO_3 (0.119 g, 1.12 mmol), TBAB (0.026 g, 0.080 mmol), and $Pd(PPh_3)_4$ (0.031 g, 0.027 mmol). The title compound was isolated by chromatography (EtOAc/hexane, 10:90) as yellow crystals (0.205 g, 75 %), m.p. 79.3 °C. R_f = 0.19(EtOAc/hexane, 10:90). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 1.5 Hz, 1 H), 8.15–8.17 (dd, *J* = 1.5, 8 Hz, 1 H), 7.57 (d, *J* = 8 Hz, 1 H), 7.25–7.29 (m, 4 H), 2.71 (q, *J* = 7.5 Hz, 2 H), 2.67 (s, 3 H), 1.28 (t, *J* = 8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.4, 149.5, 145.3, 140.4, 136.5, 133.5, 132.4, 131.3, 128.5, 127.7, 123.9, 28.6, 26.7, 15.3 ppm. HRMS (DART): calcd. for $C_{16}H_{16}NO_3$ [M + H^+] 270.1130; found 270.1130. IR: $\tilde{\nu}$ = 2965, 2929, 2870, 1689, 1532, 1356 cm^{-1}.

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SUPPORTING INFORMATION

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Title: A Highly Efficient Pd(PPh_3)$_4$-Catalyzed Suzuki Cross-Coupling Method for the Preparation of 2-Nitrobiphenyls from 1-Chloro-2-nitrobenzenes and Phenylboronic Acids
Author(s): Vijayaragavan Elumalai, Alexander H. Sandtorv, Hans-René Bjørsvik*

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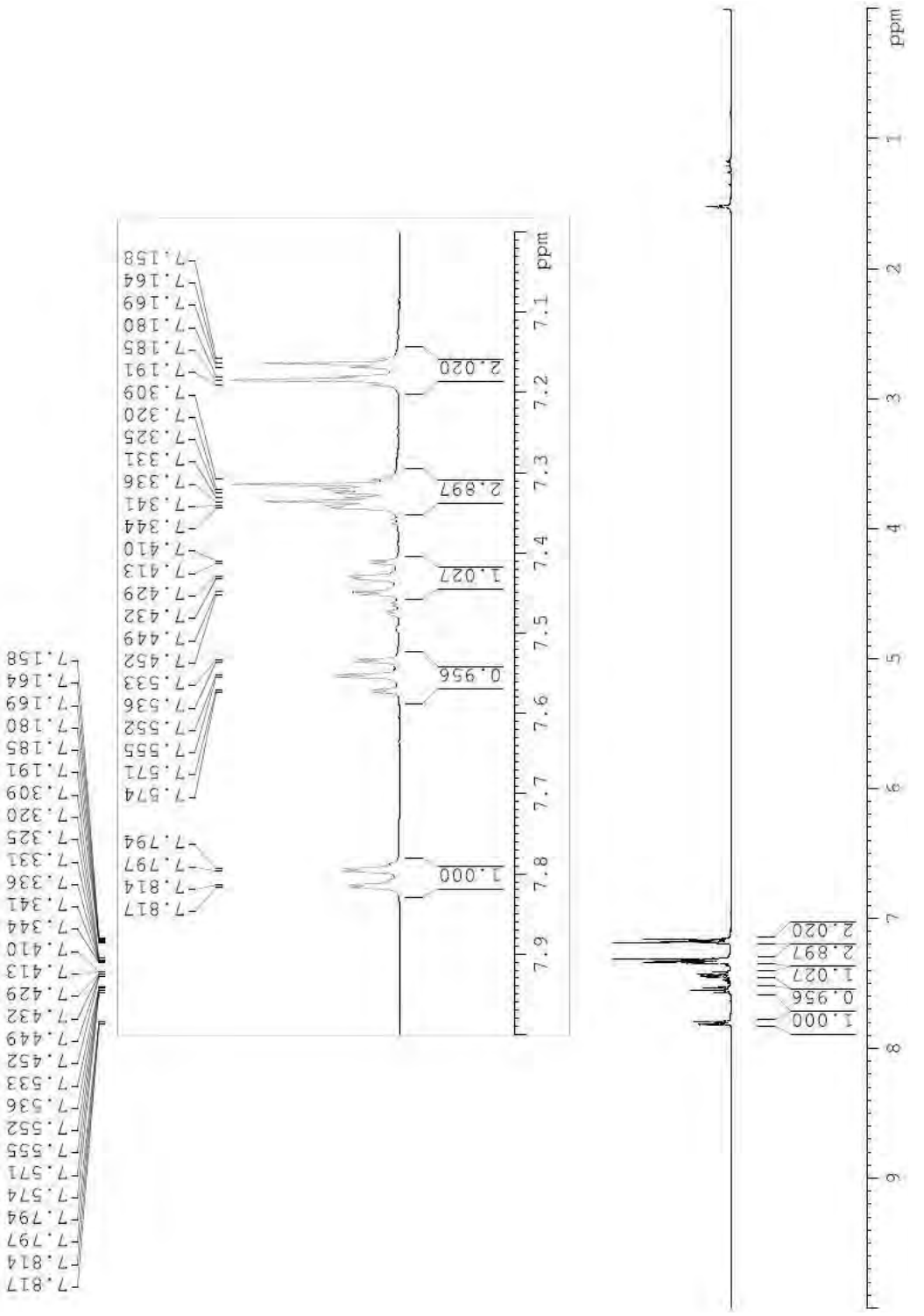

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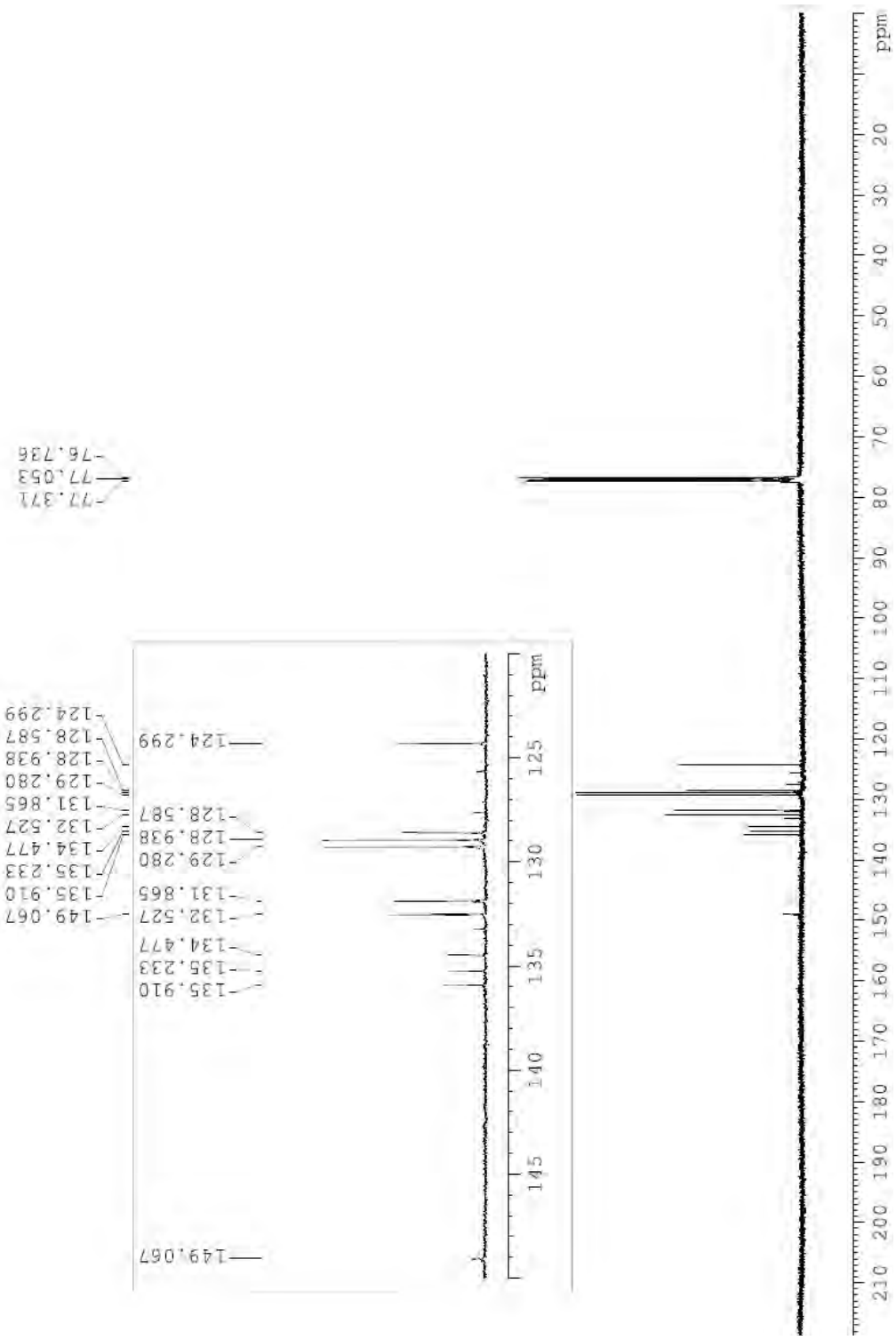

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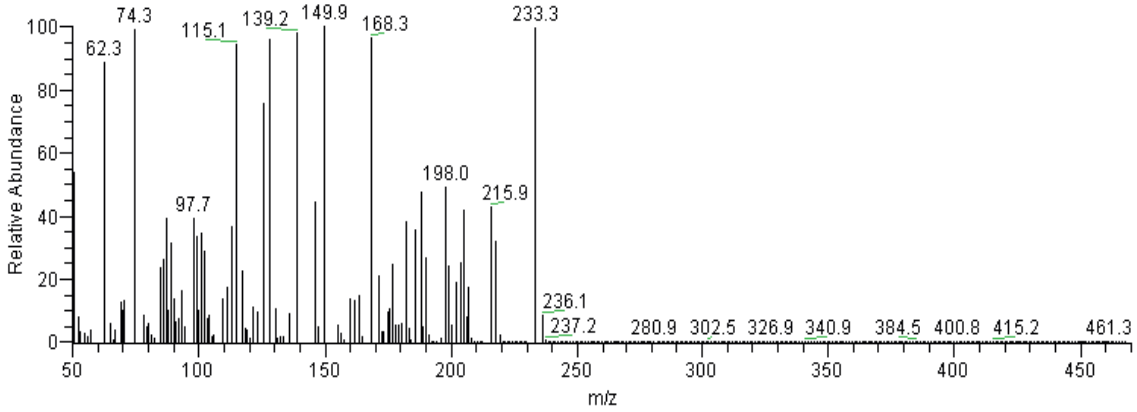

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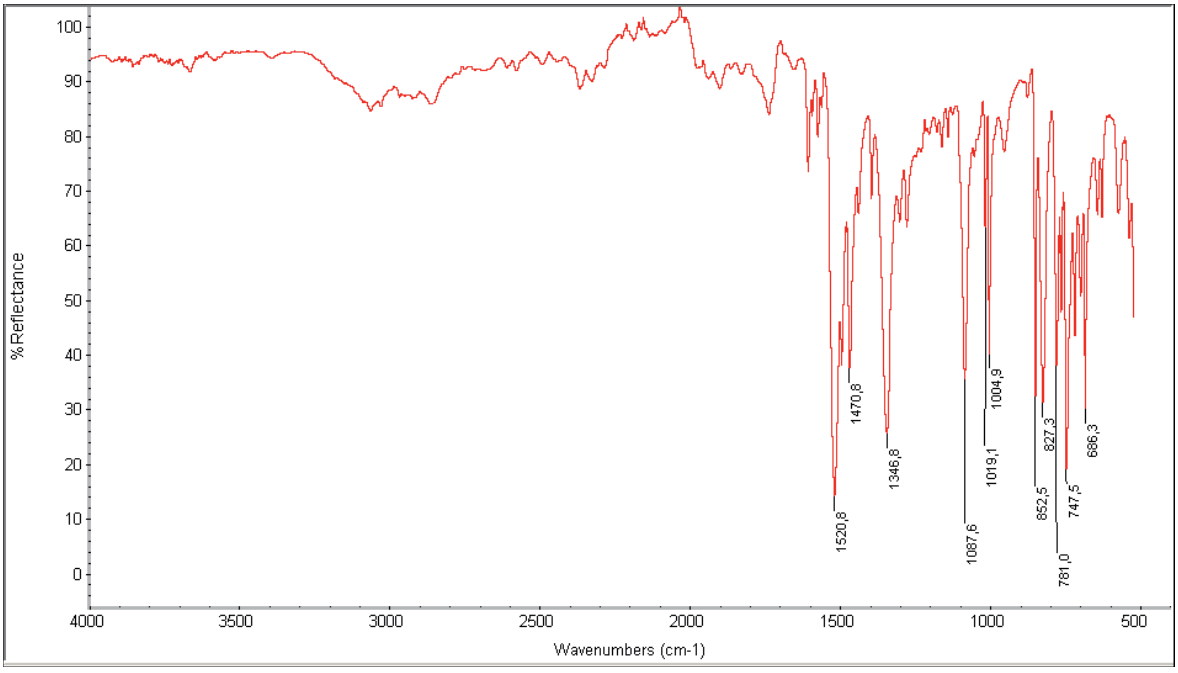

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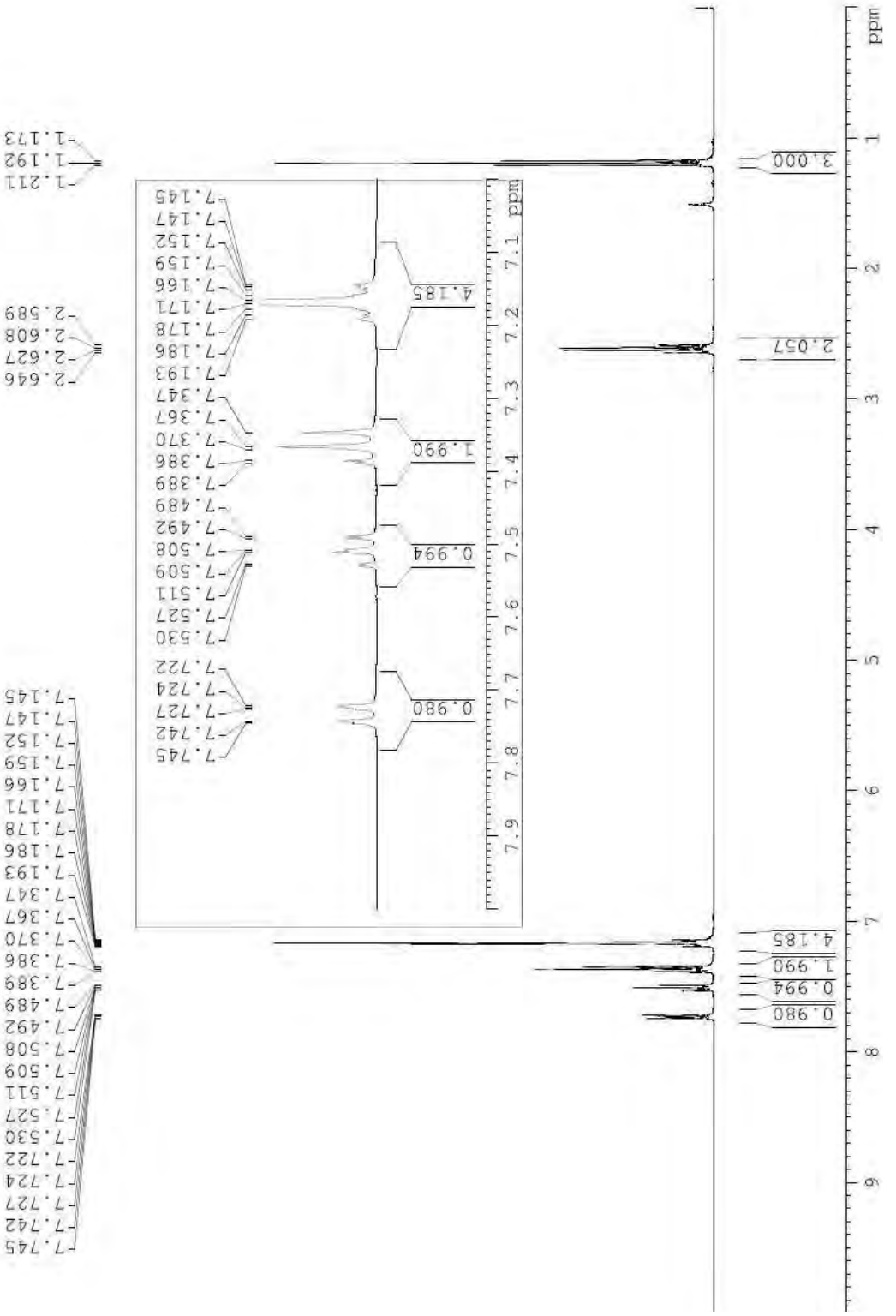

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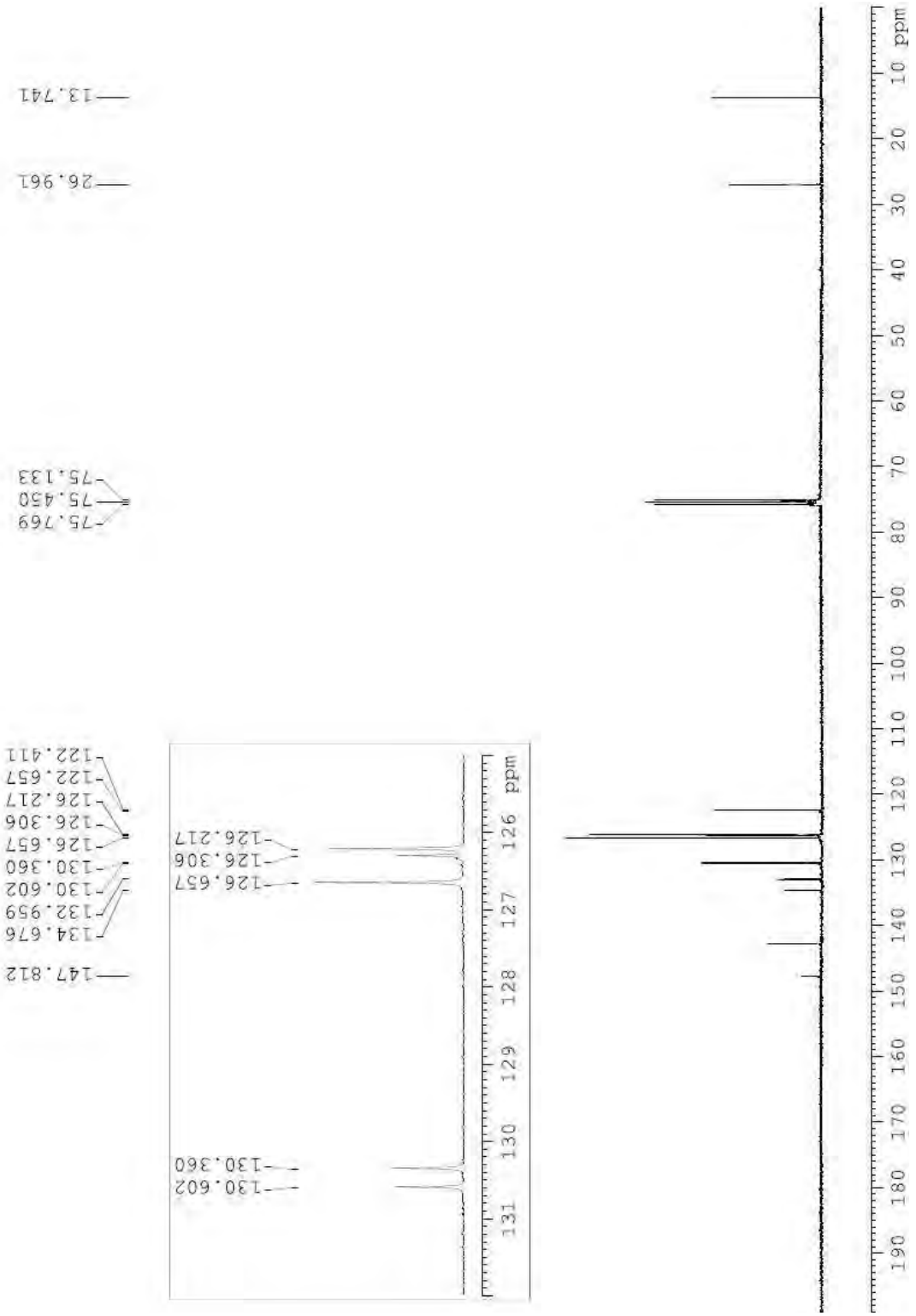

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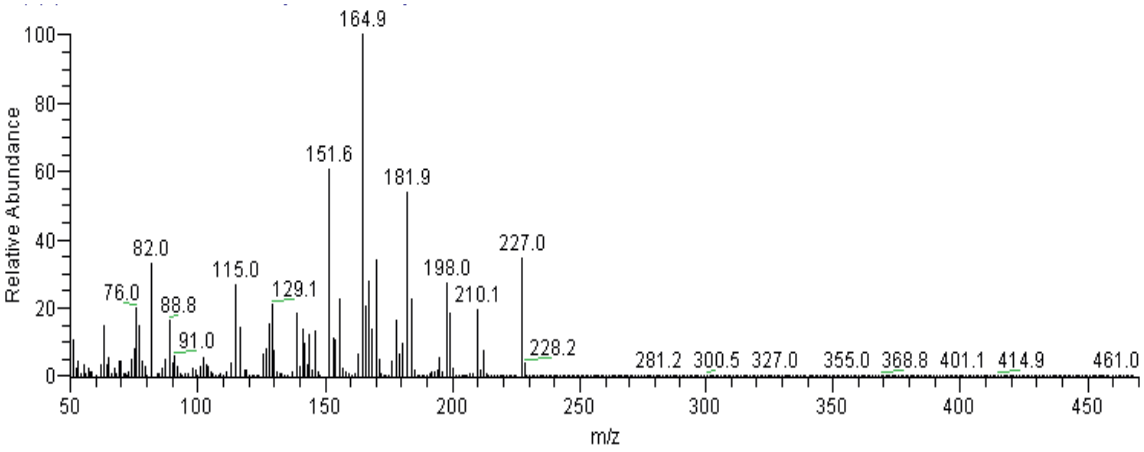

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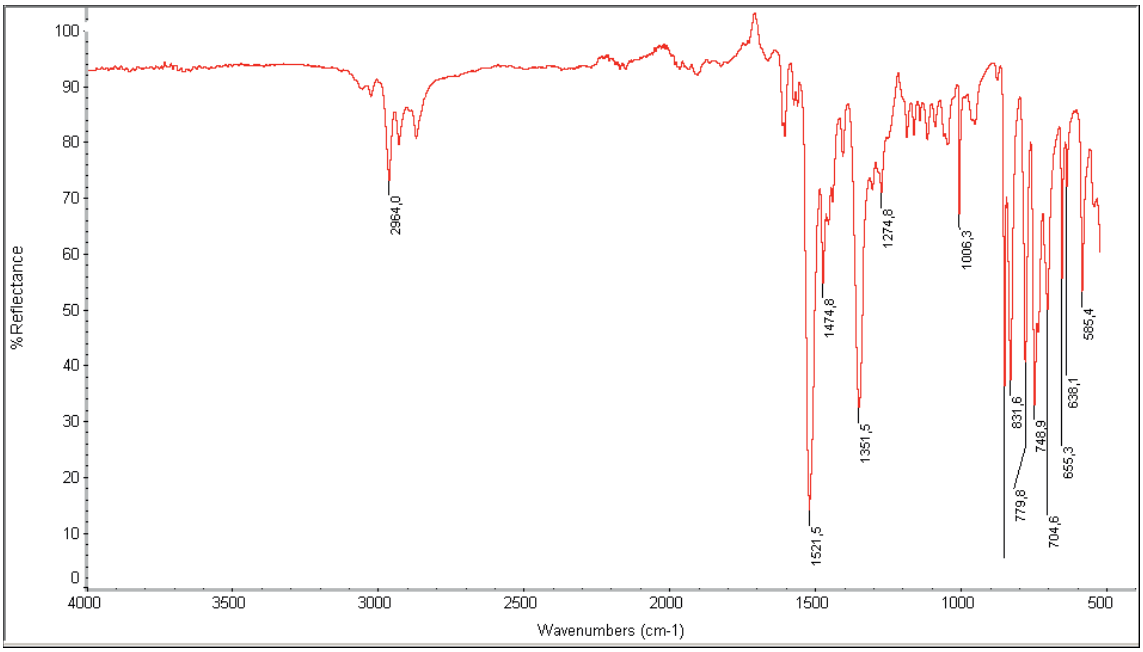

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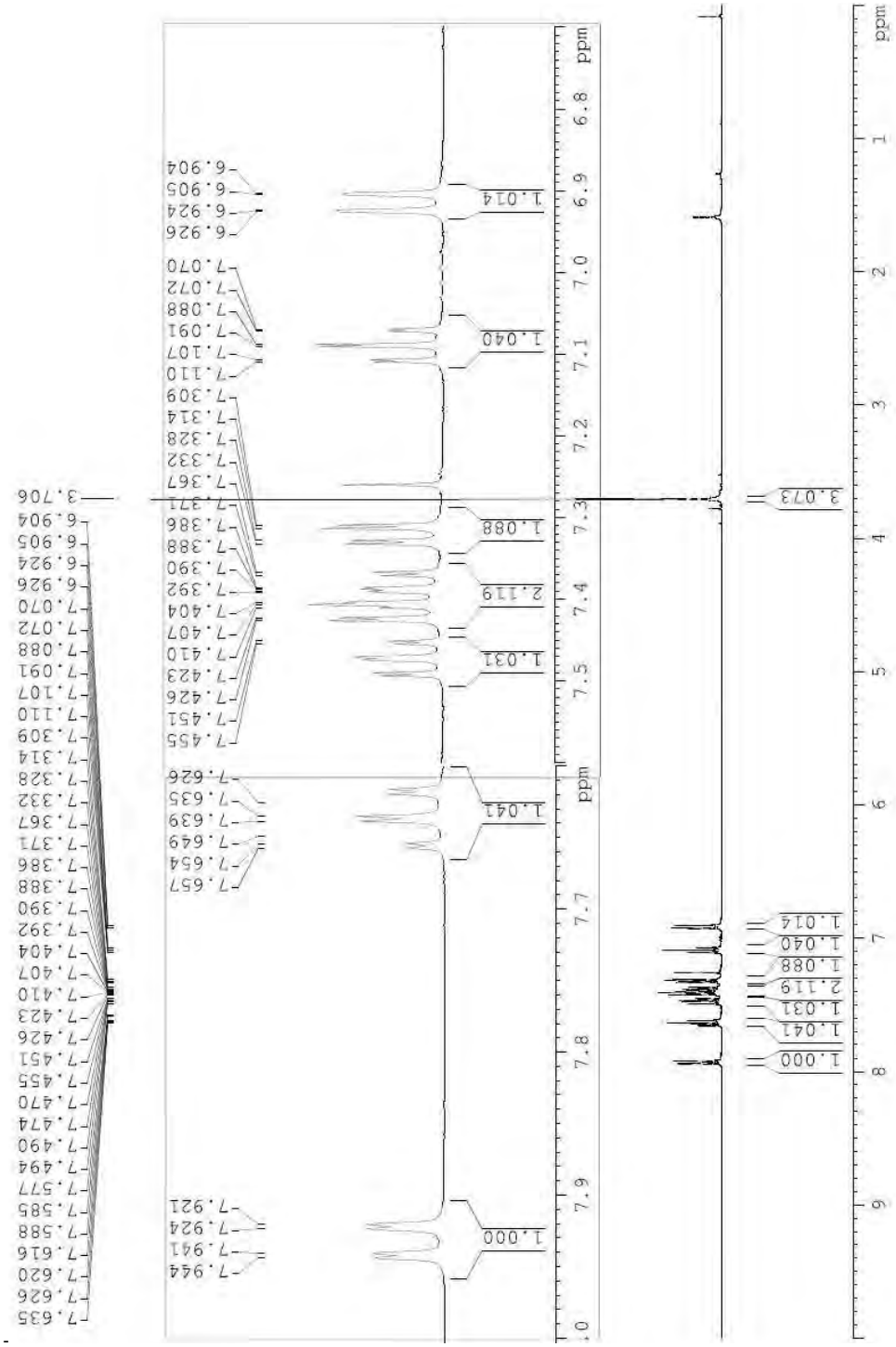

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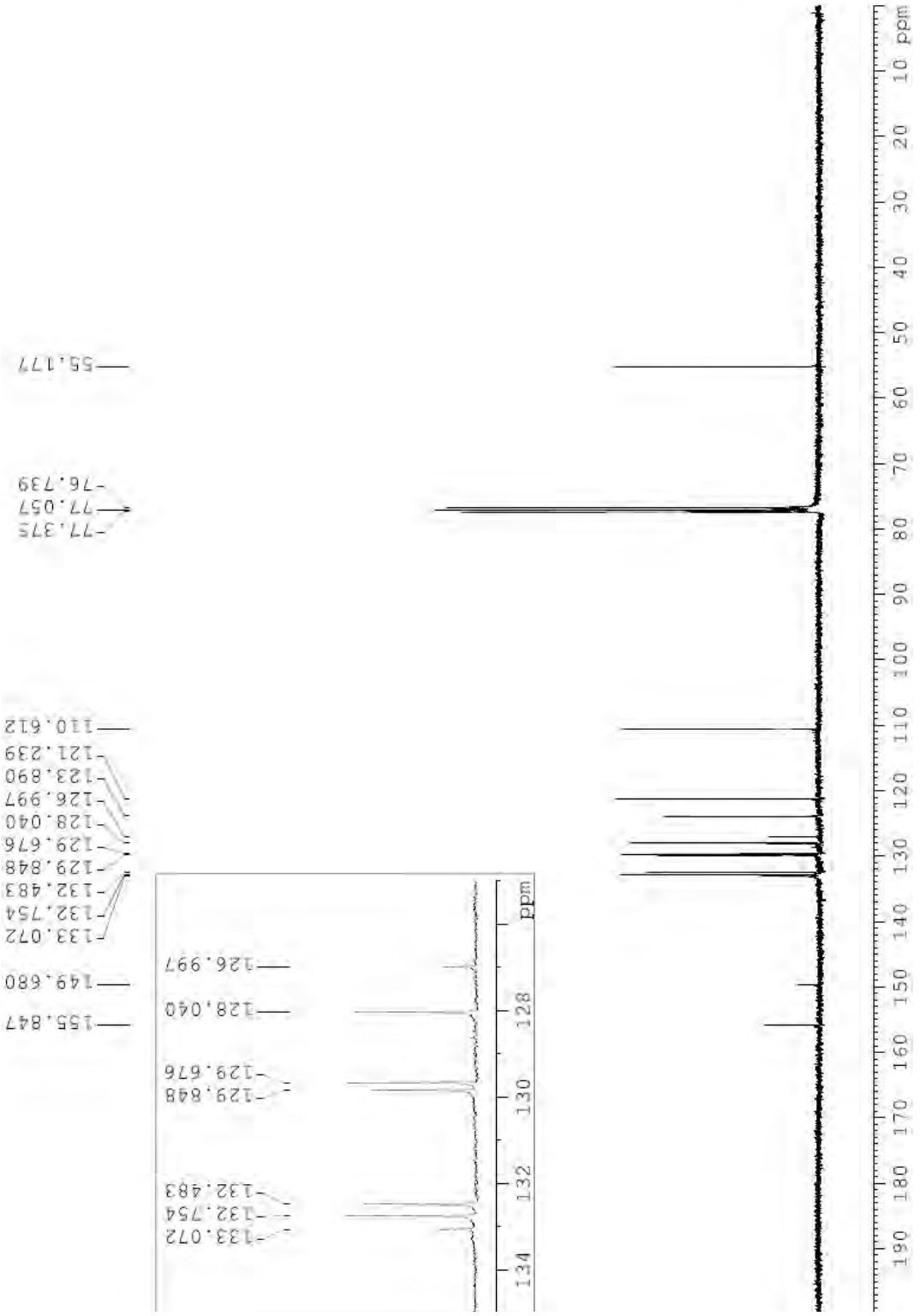

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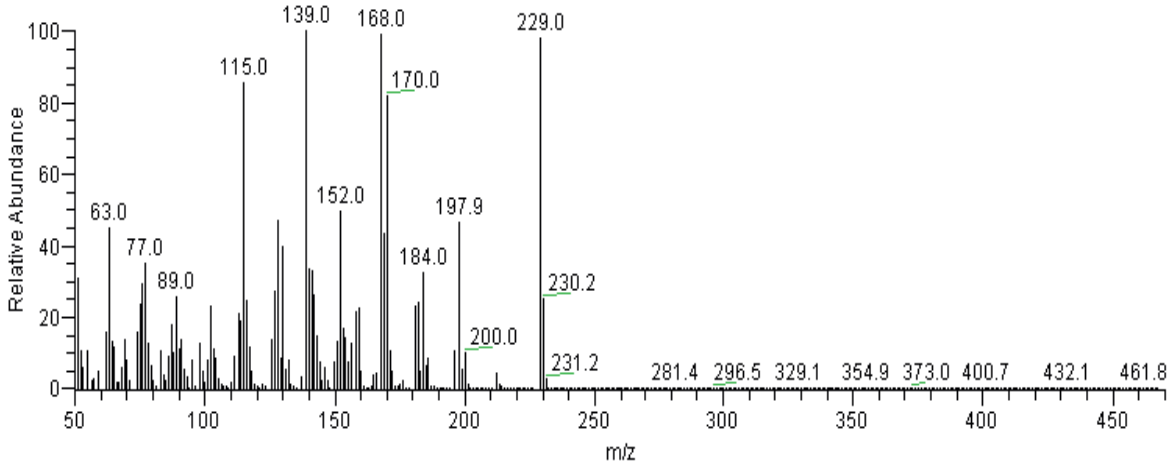

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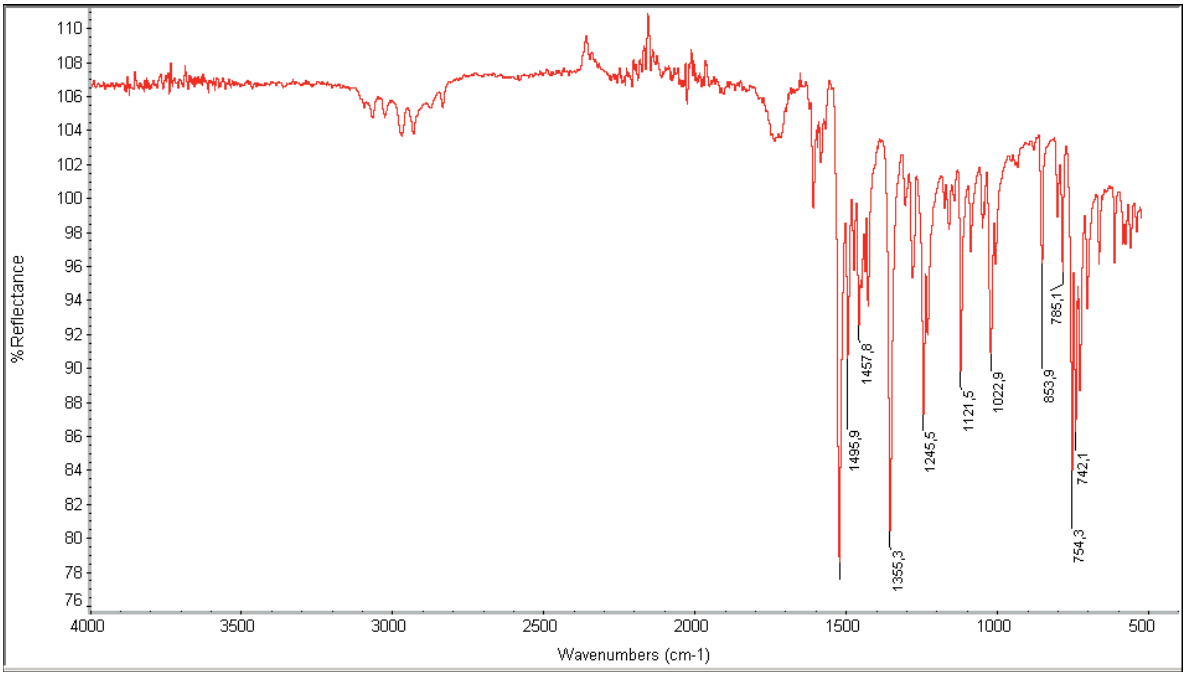

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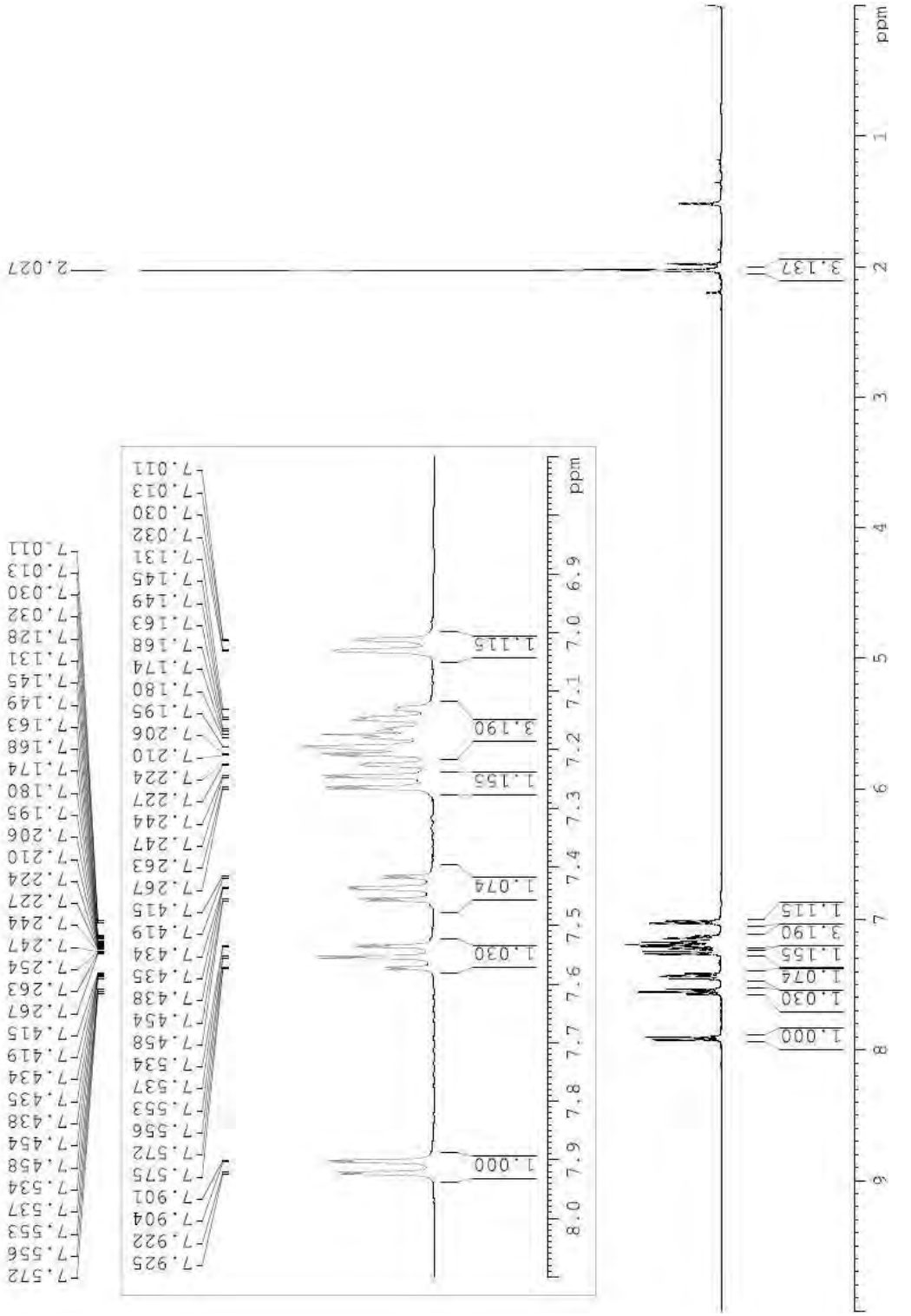

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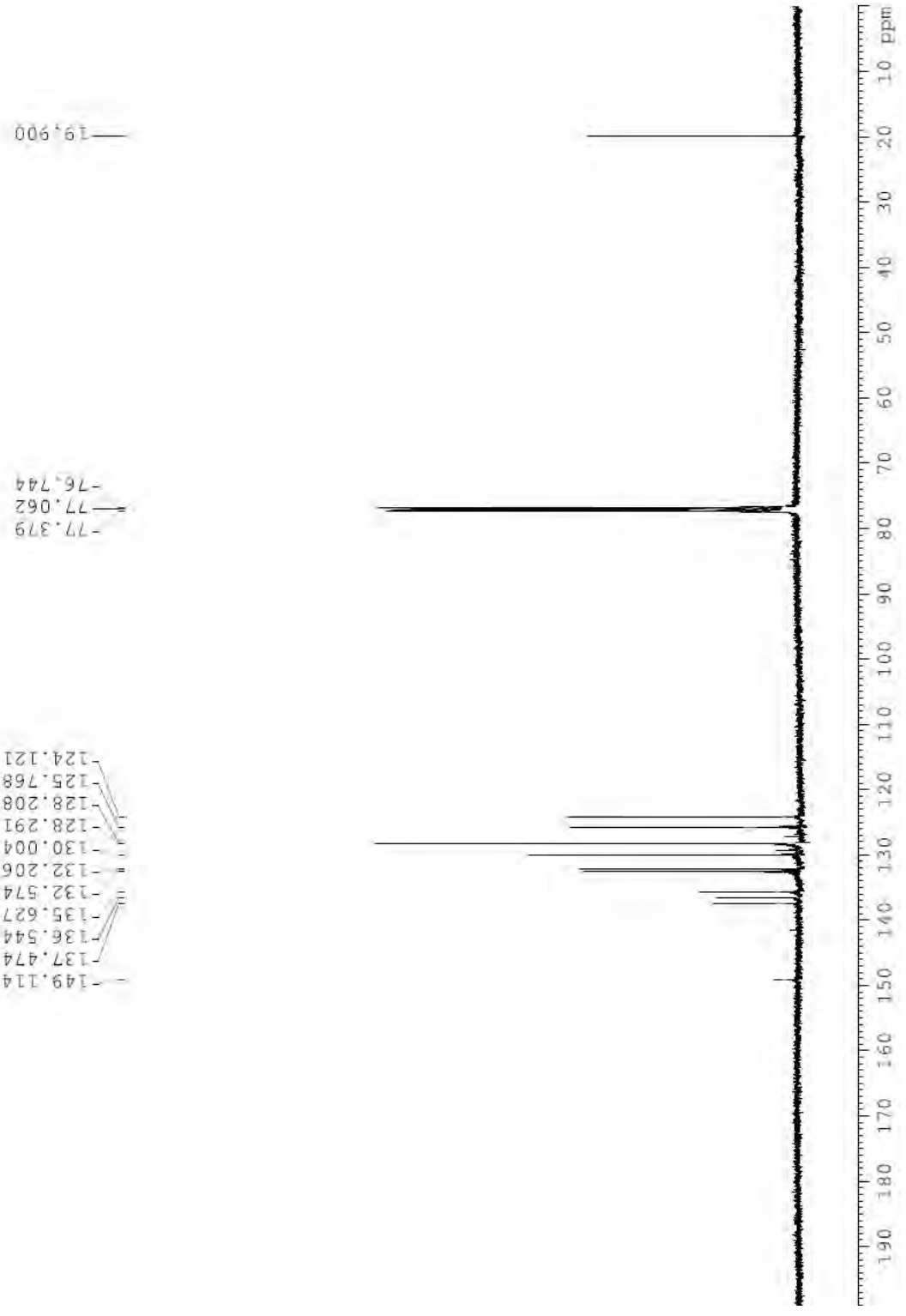

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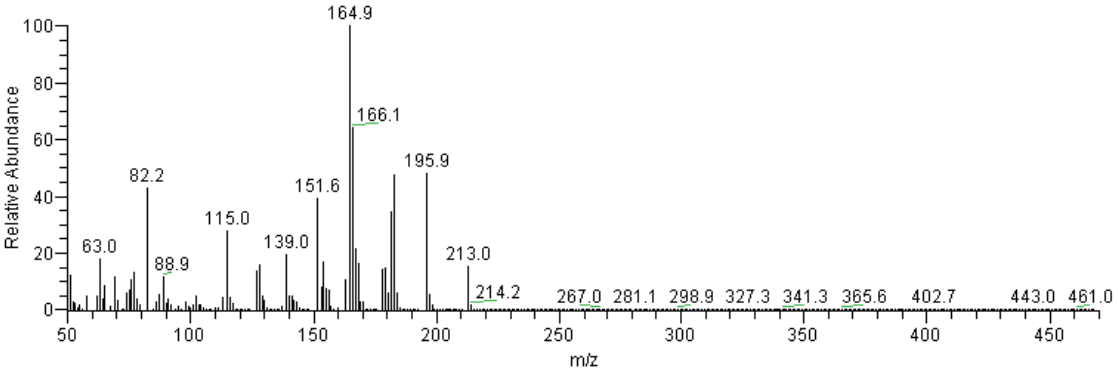

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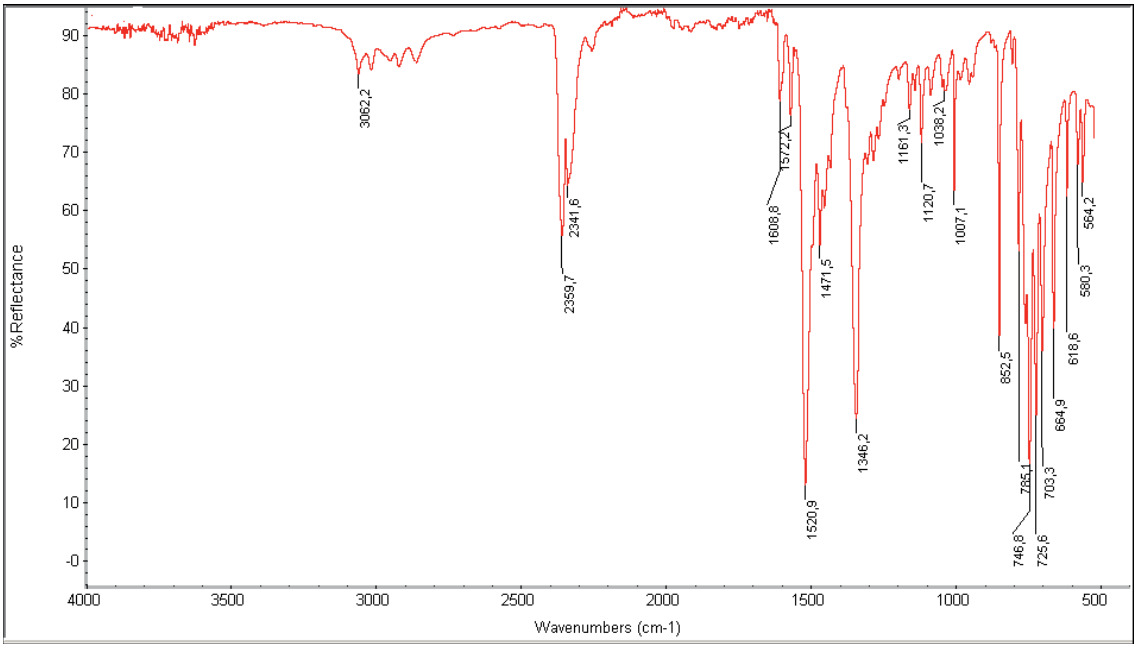

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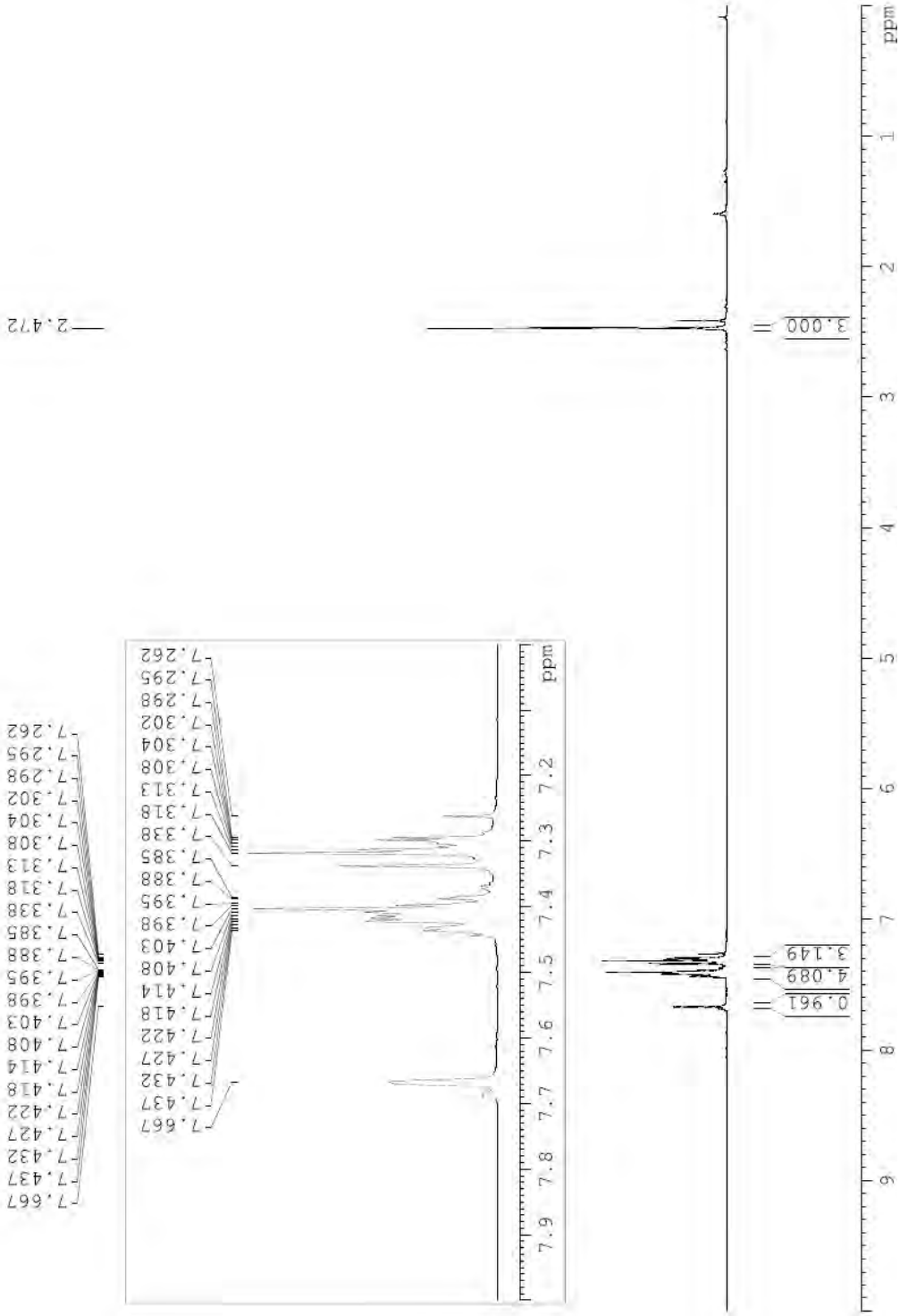

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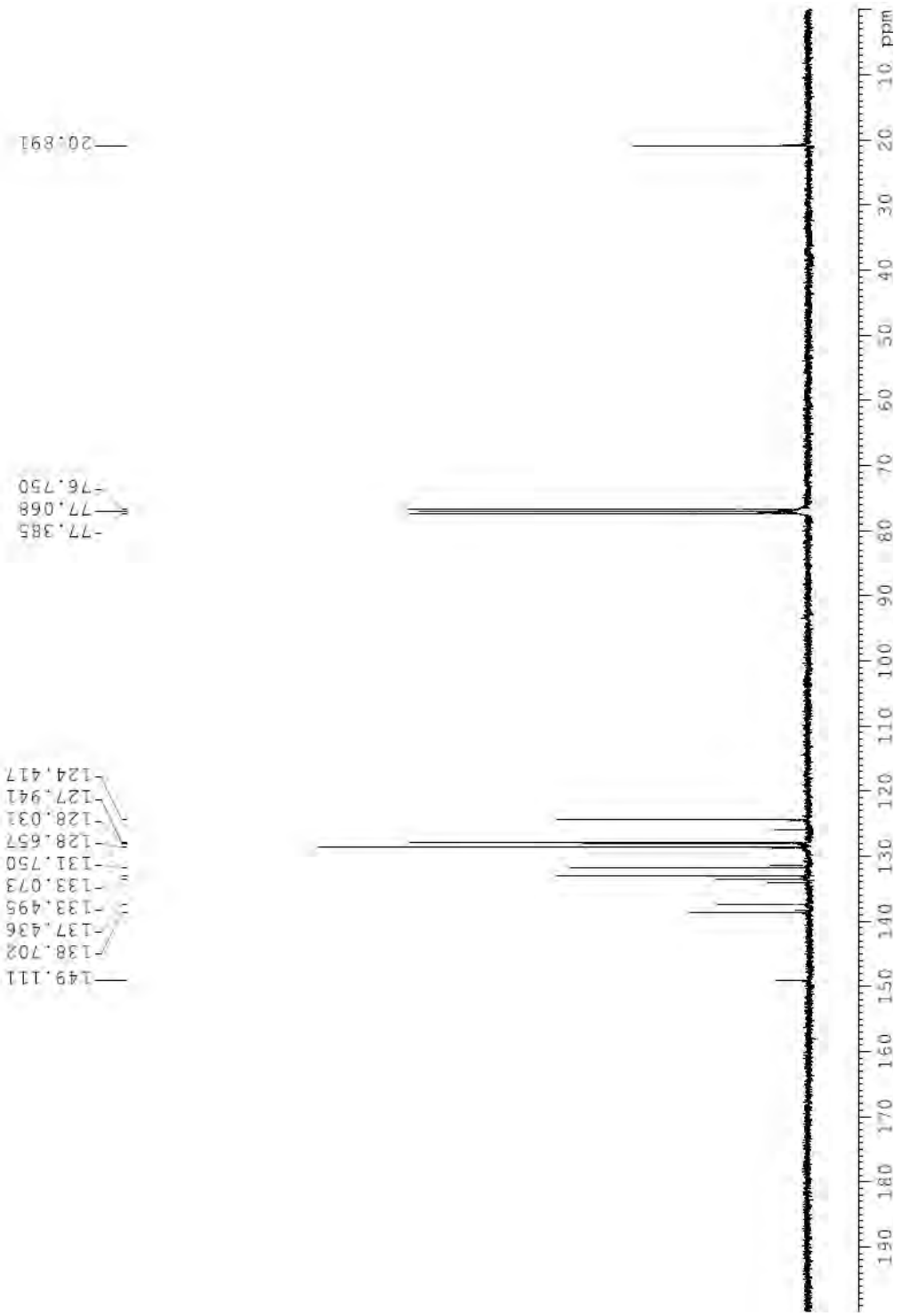

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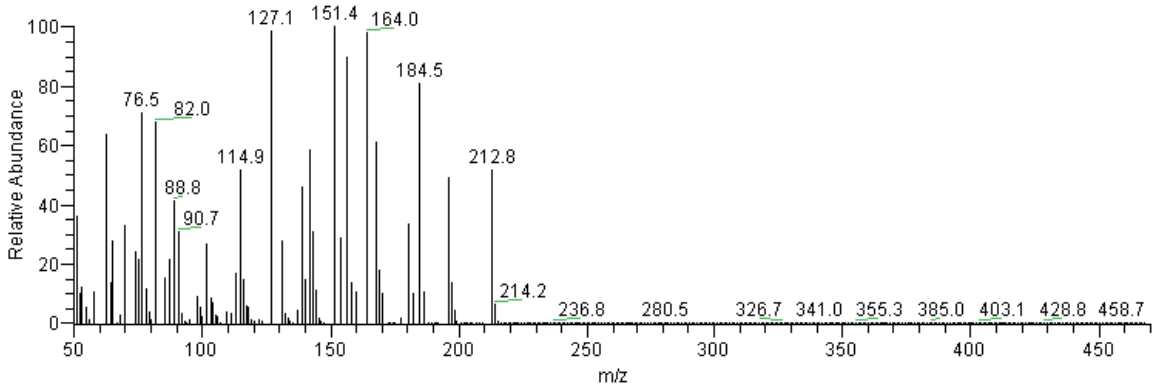

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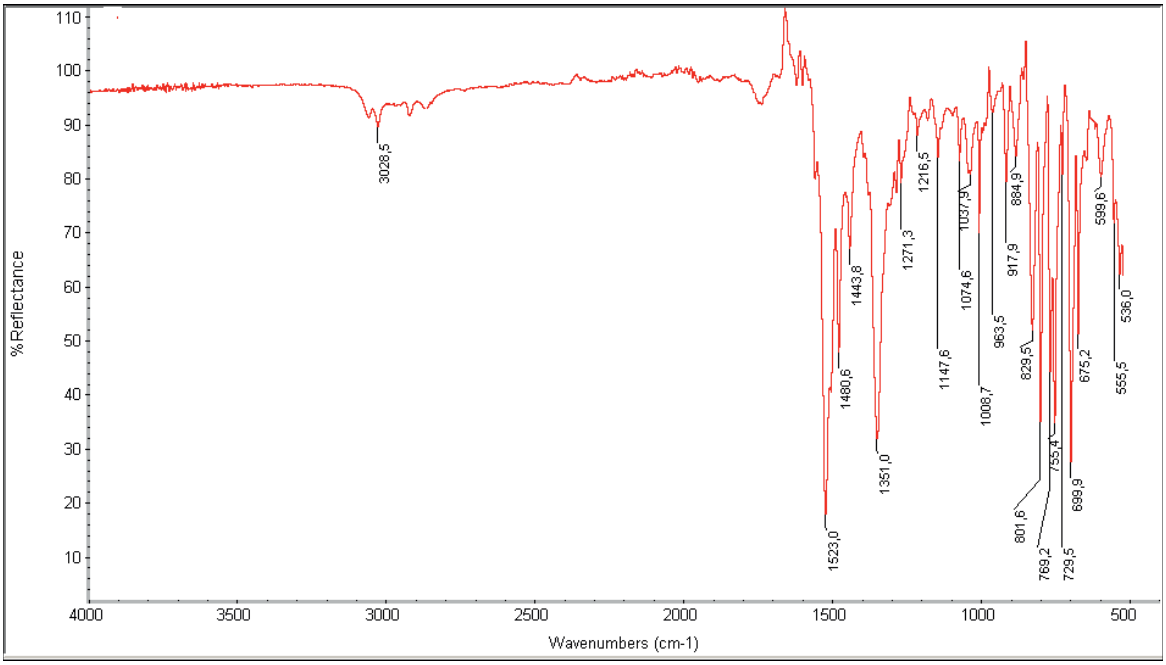

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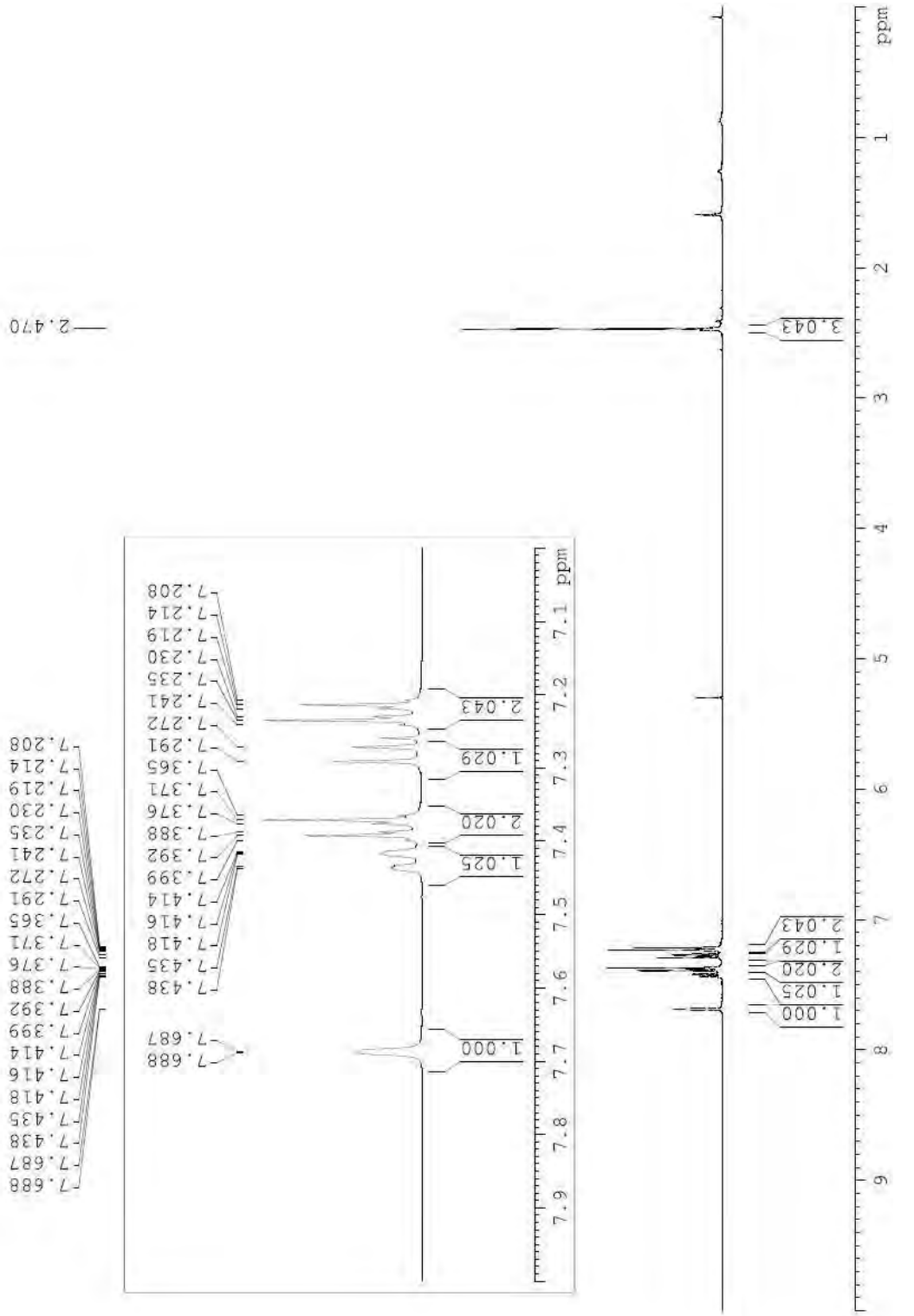

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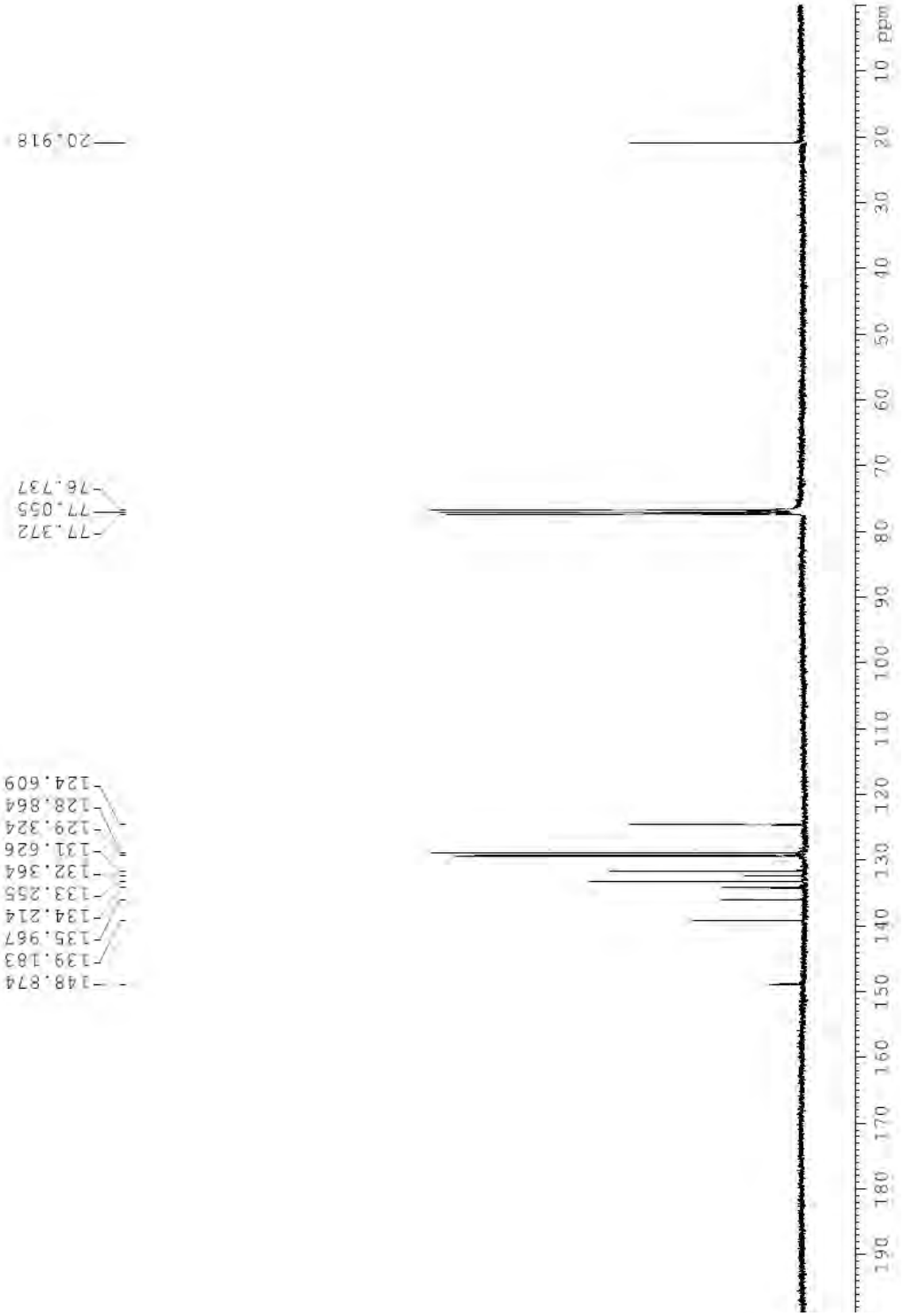

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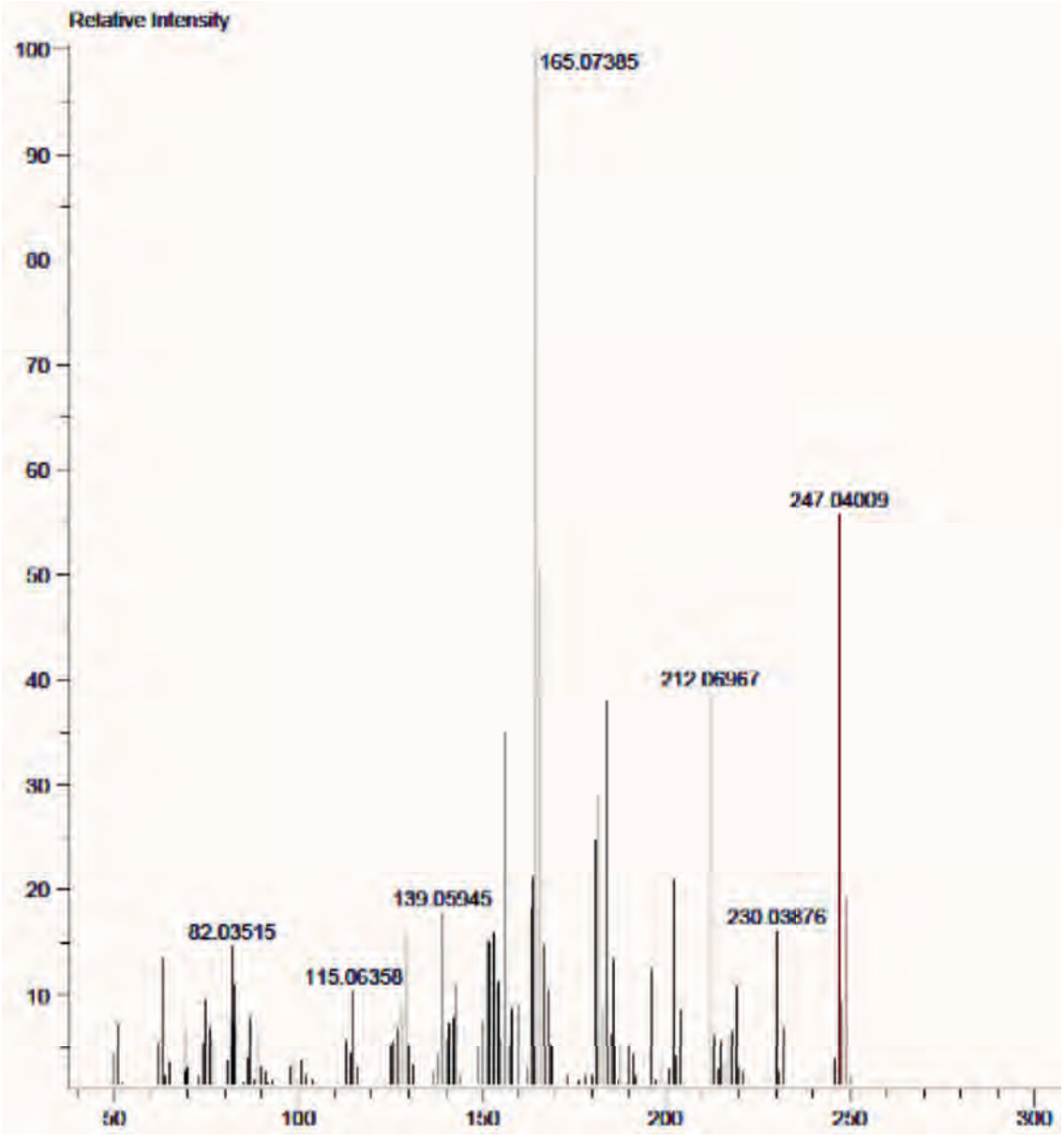

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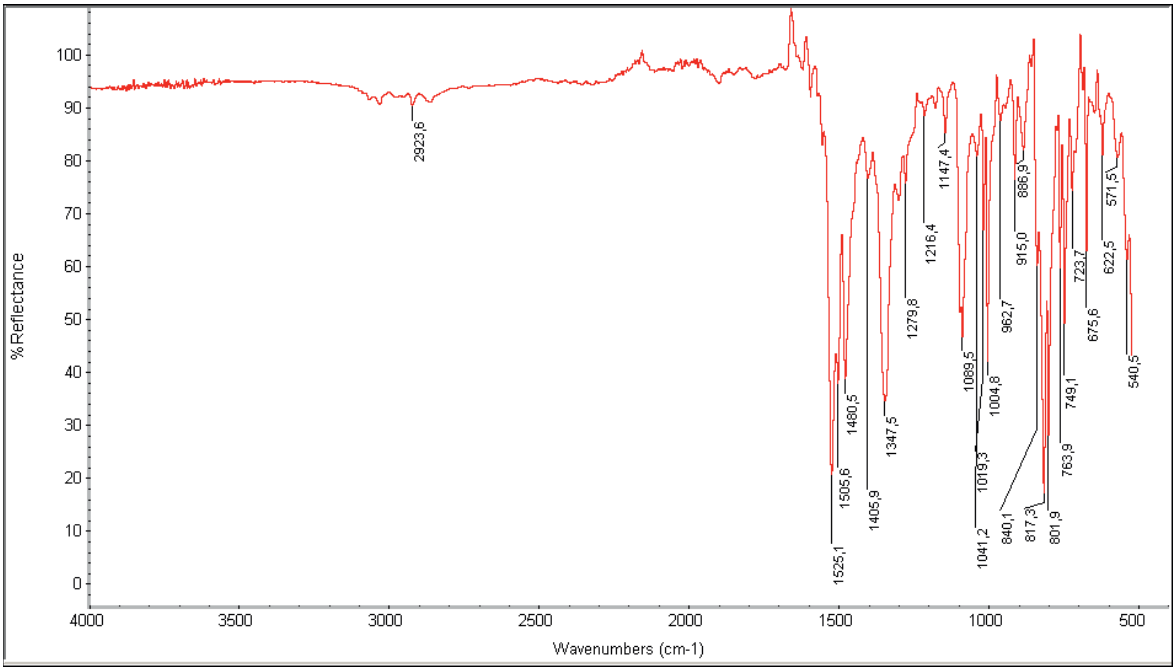

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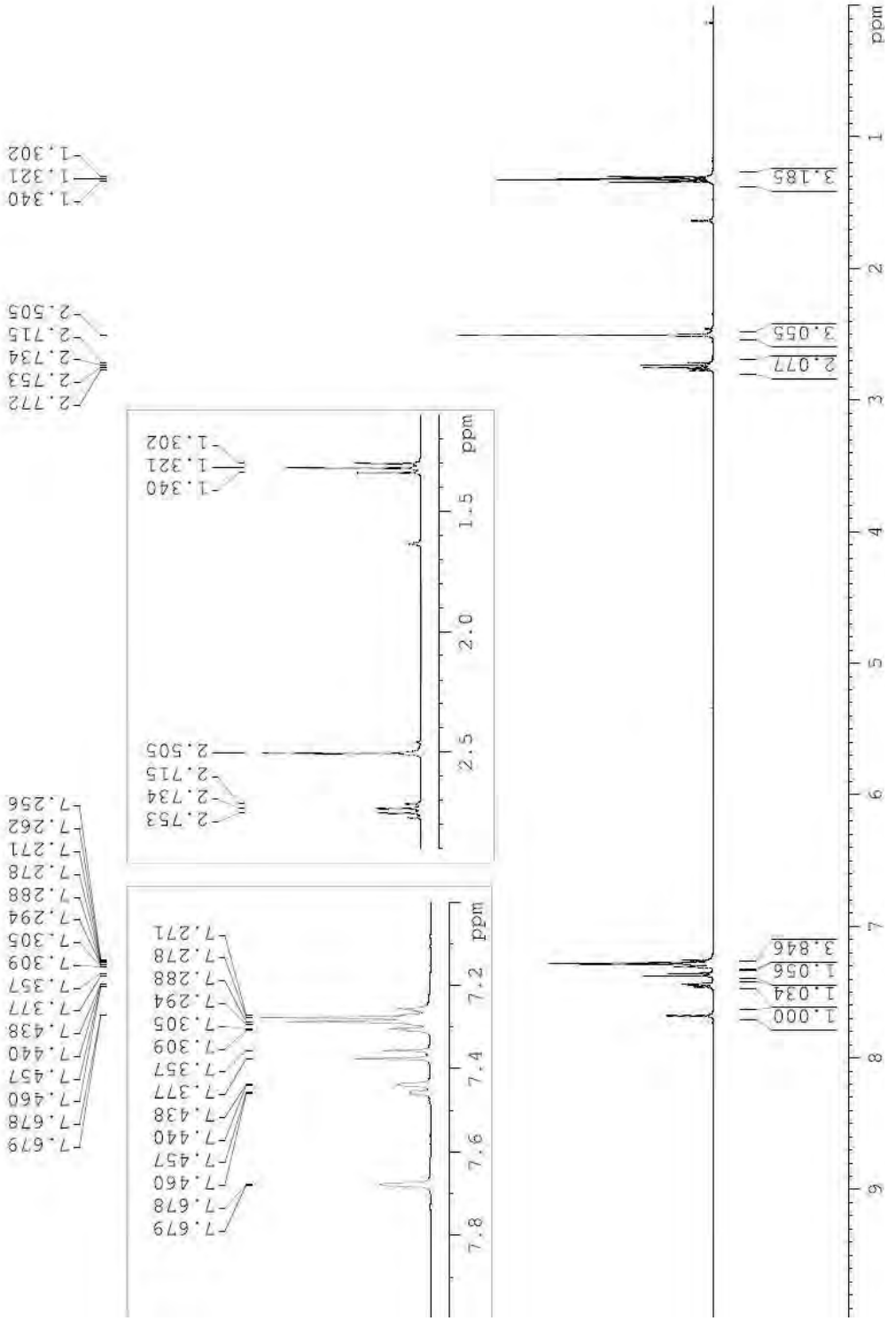

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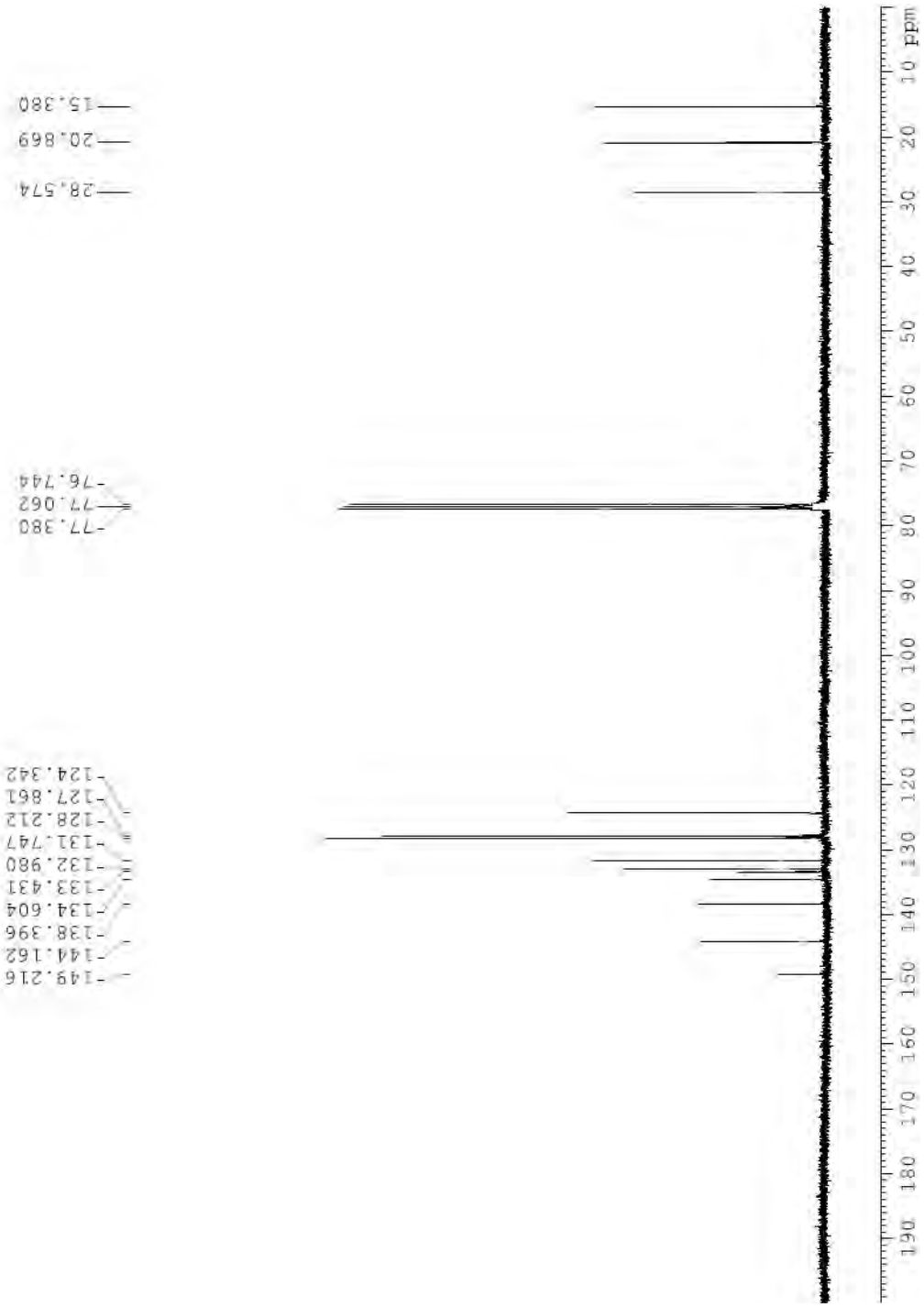

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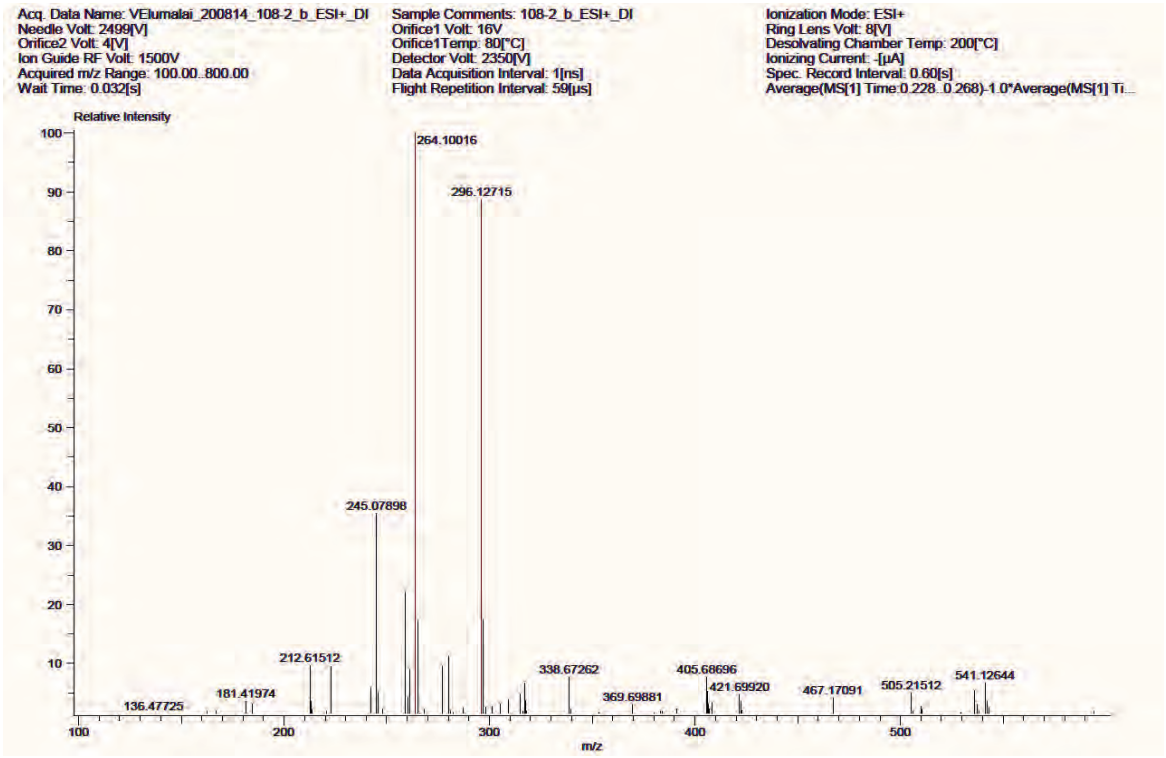
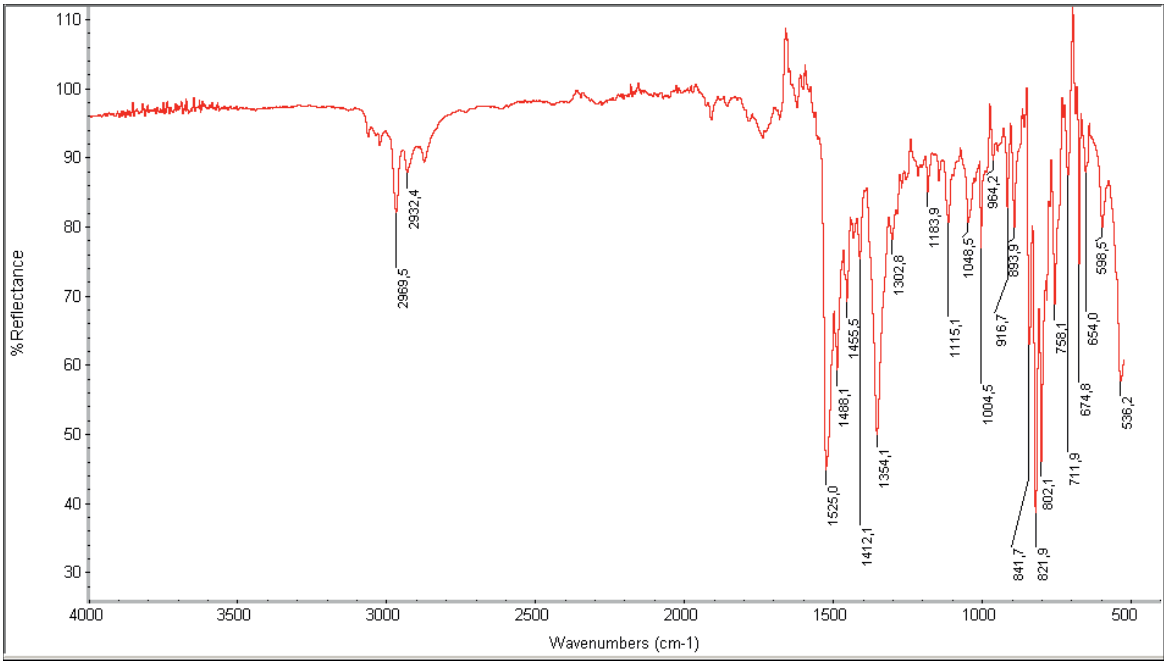
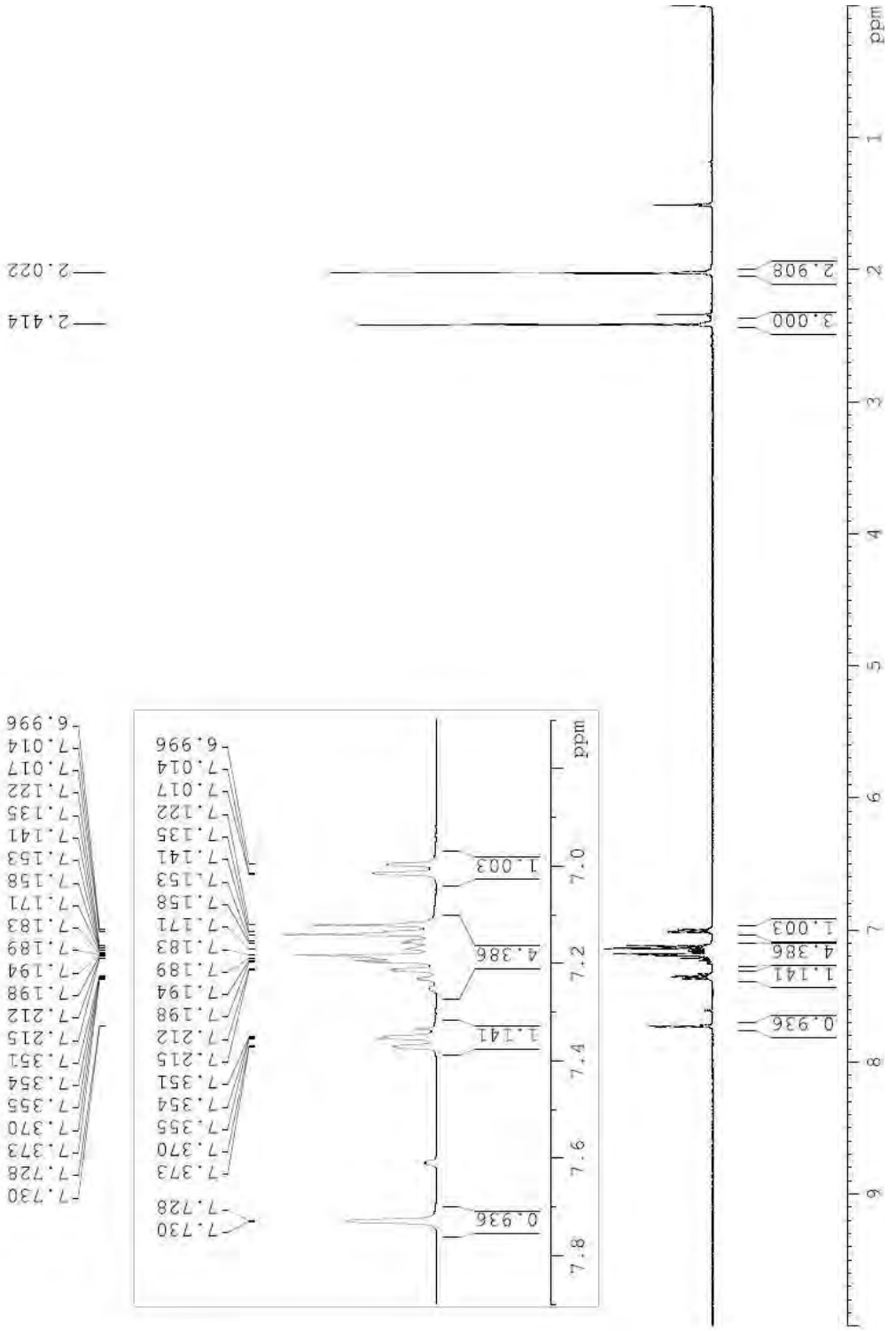


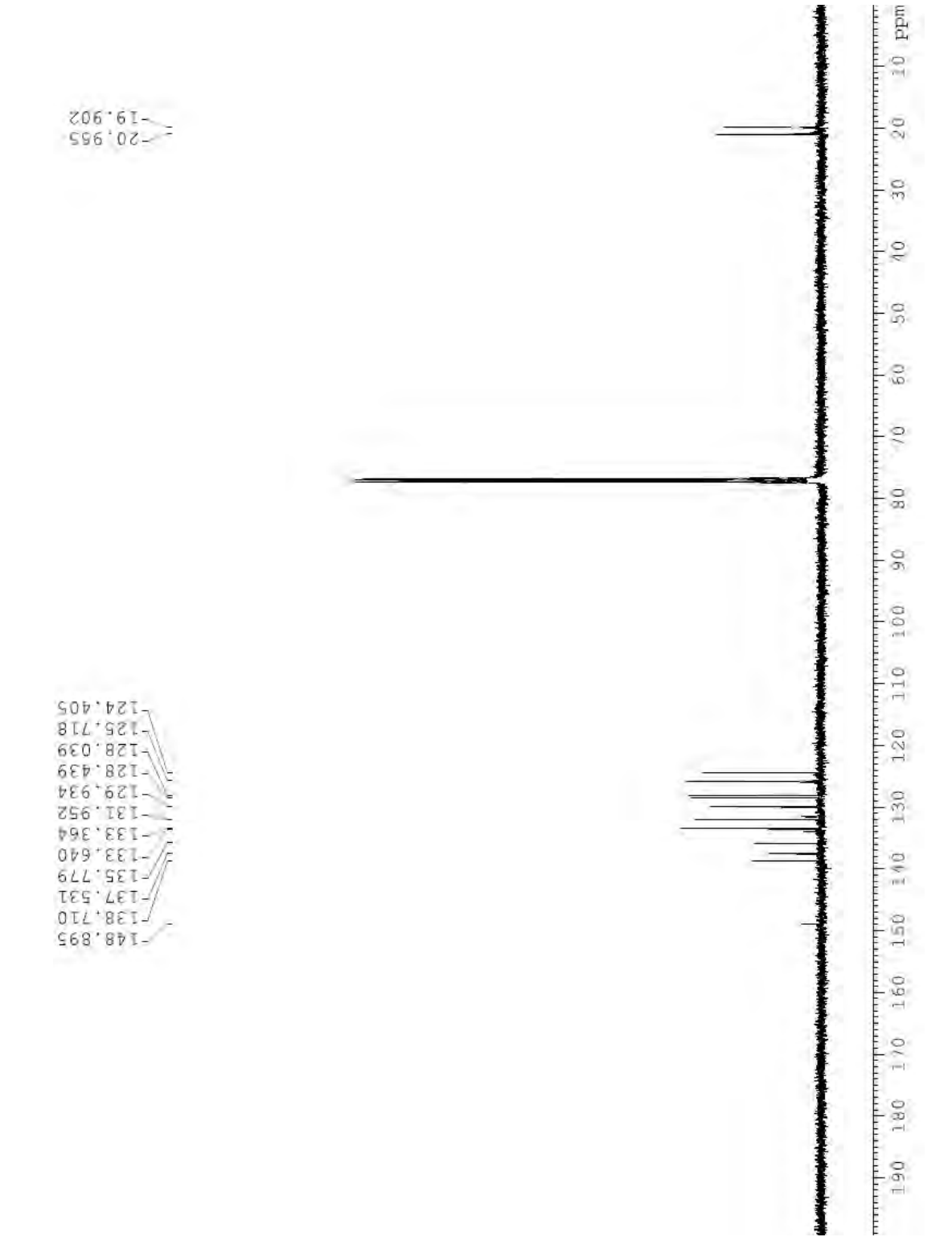
IR of 4'-ethyl-4-methyl-2-nitro-1,1'-biphenyl (5g)



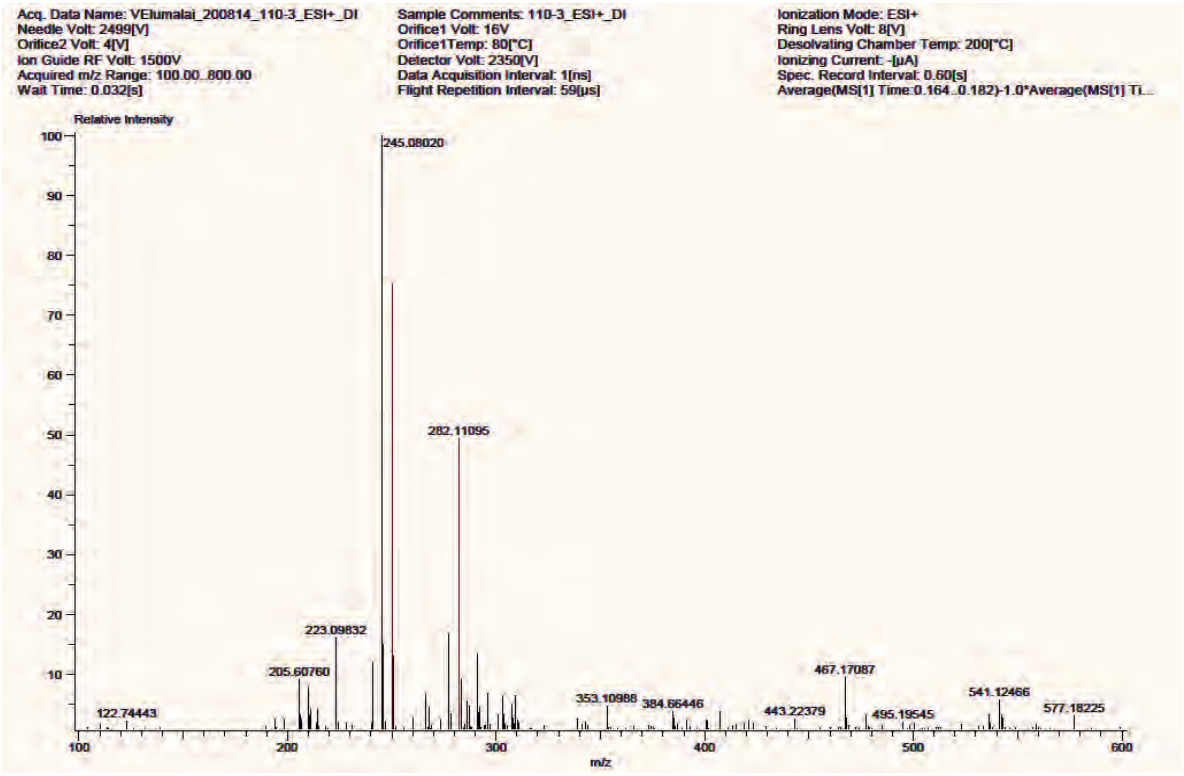
^{1}H-NMR of 2',4-dimethyl-2-nitro-1,1'-biphenyl (5h) in $CDCl_3$



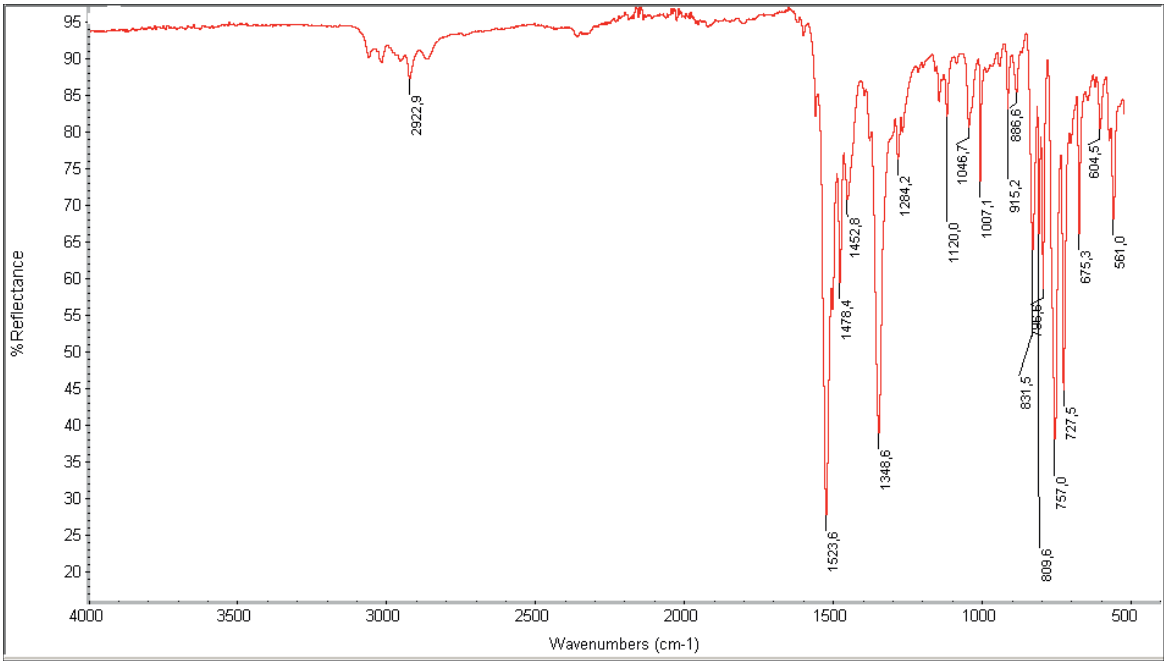
^{13}C-NMR of 2',4-dimethyl-2-nitro-1,1'-biphenyl (5h) in $CDCl_3$



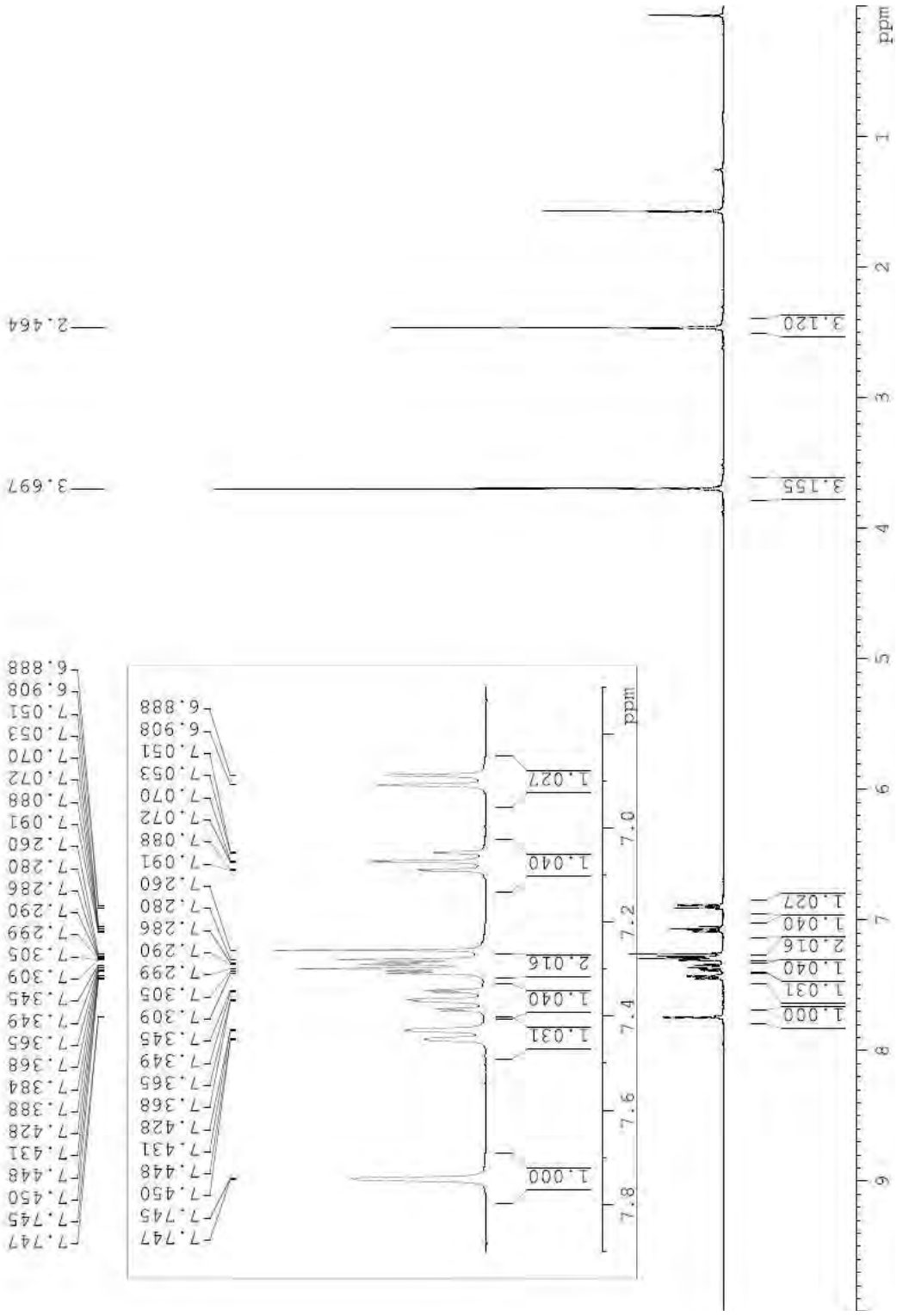
HR-MS of 2',4-dimethyl-2-nitro-1,1'-biphenyl (5h)



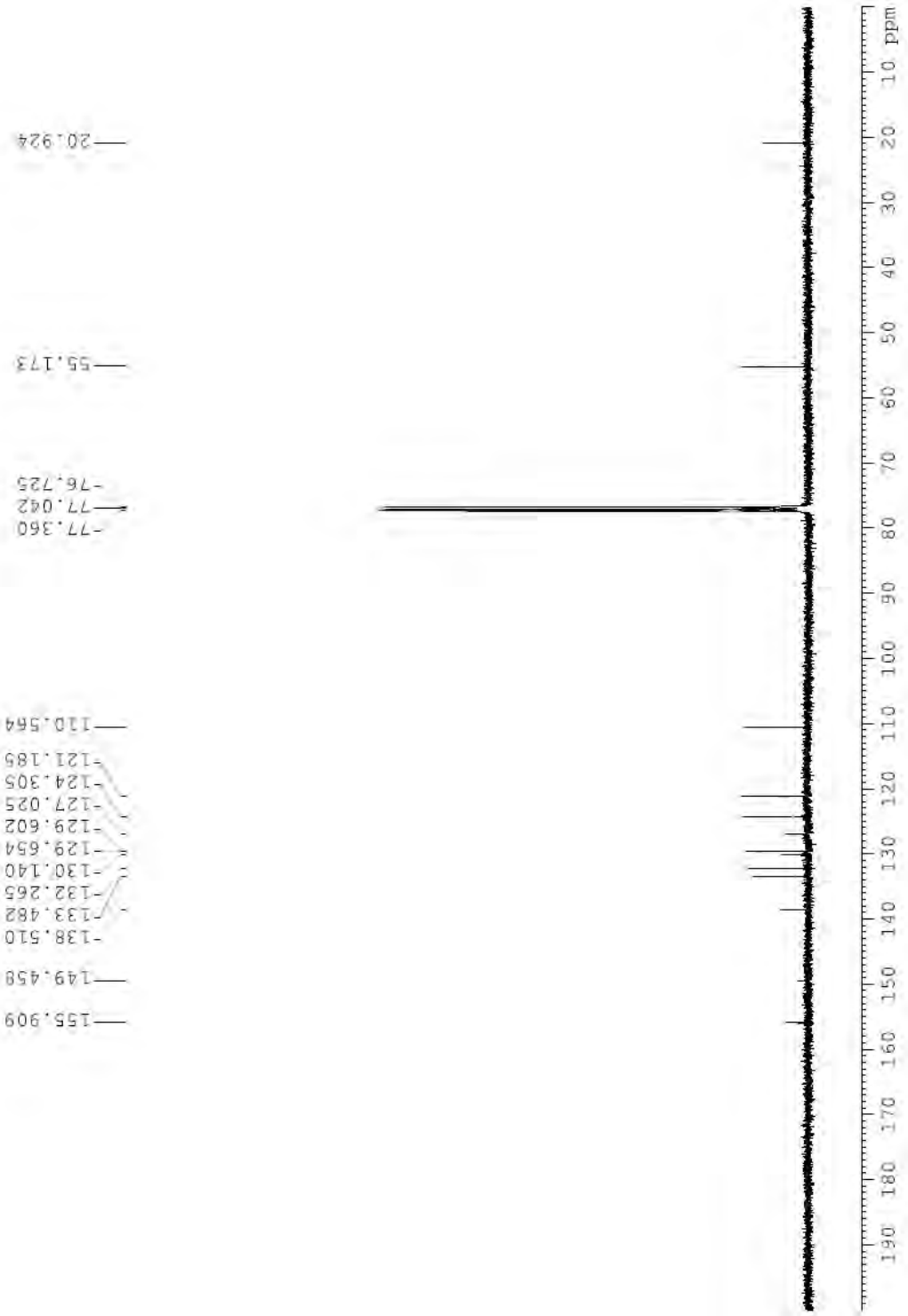
IR of 2',4-dimethyl-2-nitro-1,1'-biphenyl (5h)



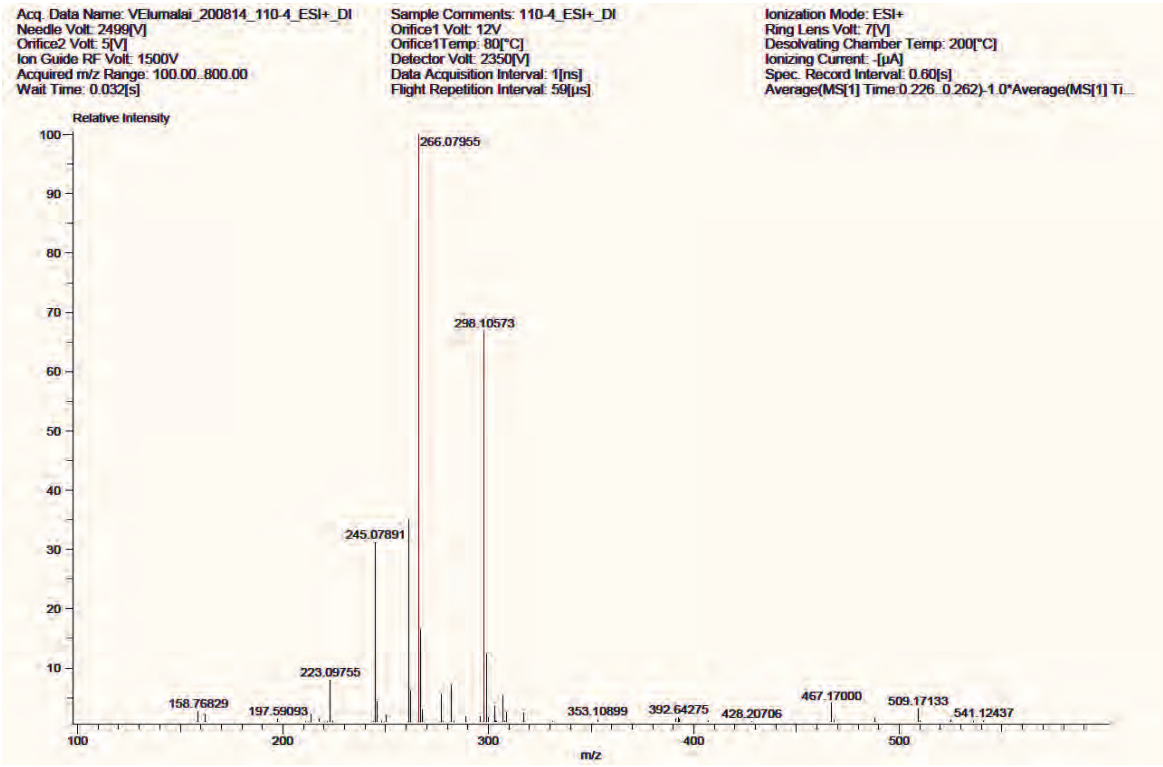
^{1}H-NMR of 2'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5i) in $CDCl_3$



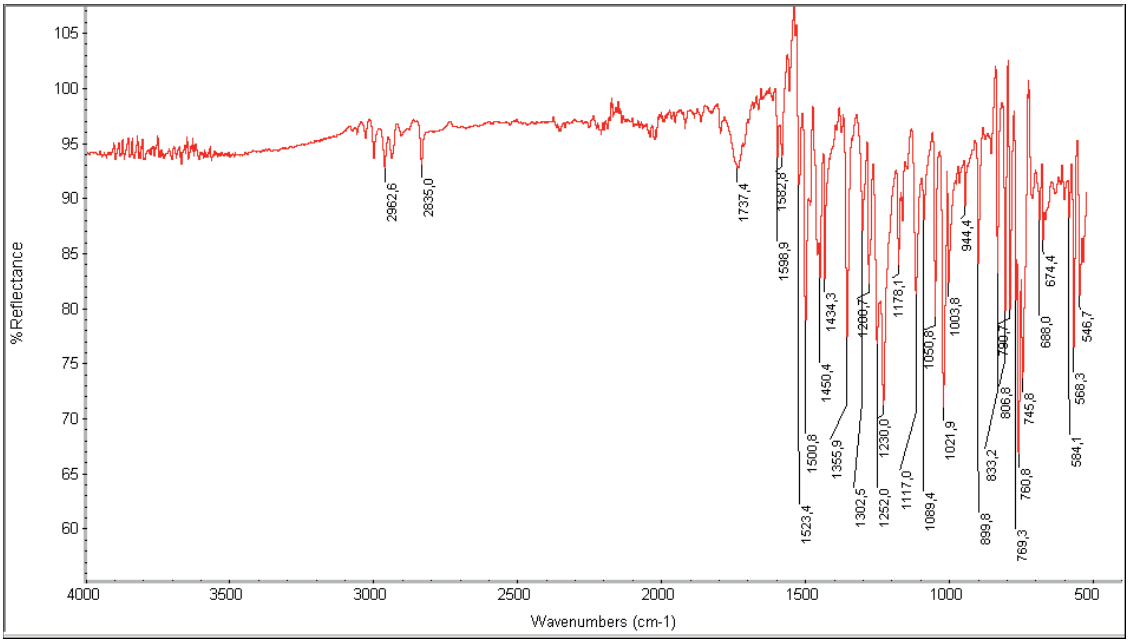
^{13}C-NMR of 2'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5i) in $CDCl_3$



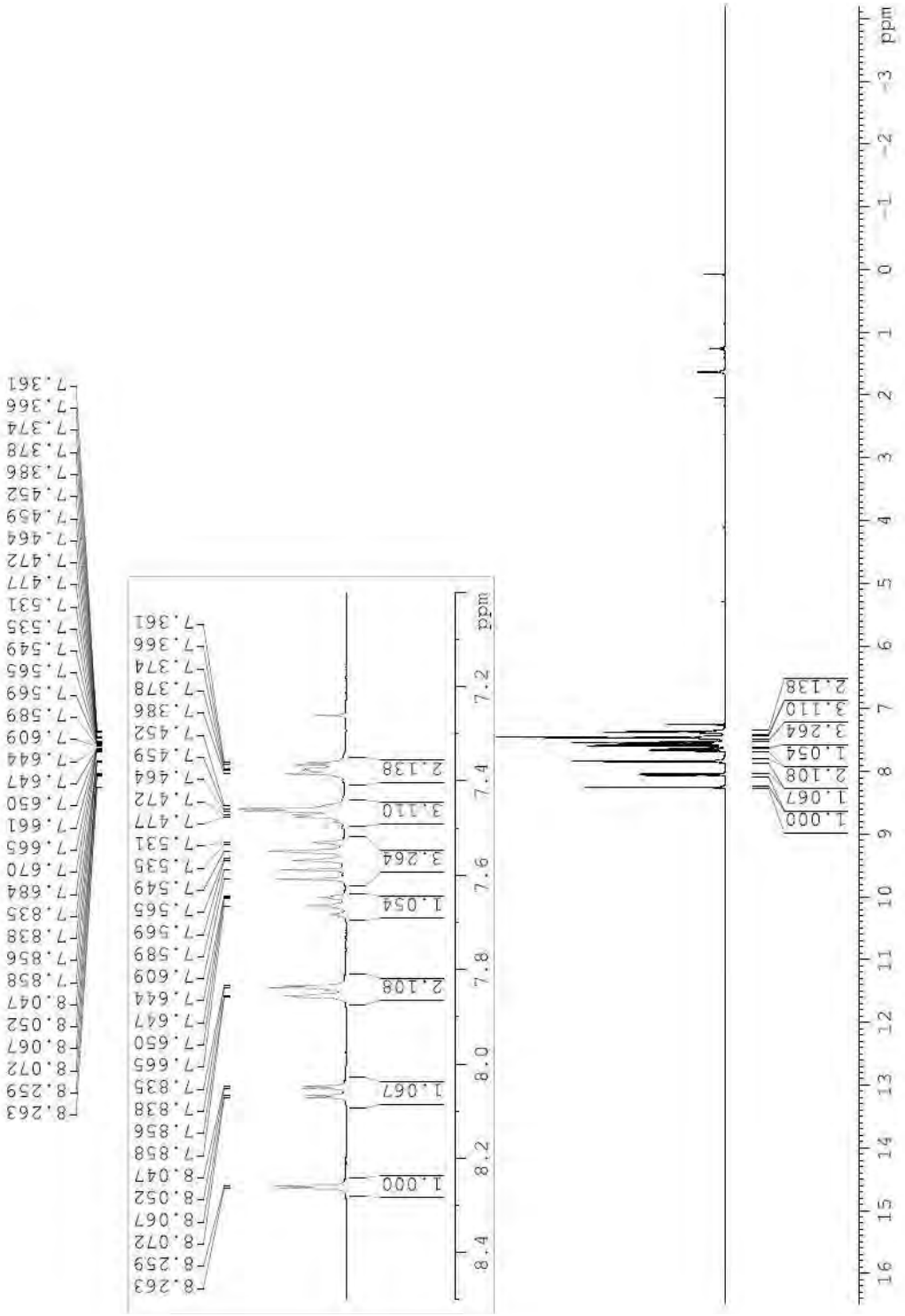
HR-MS of 2'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5i)



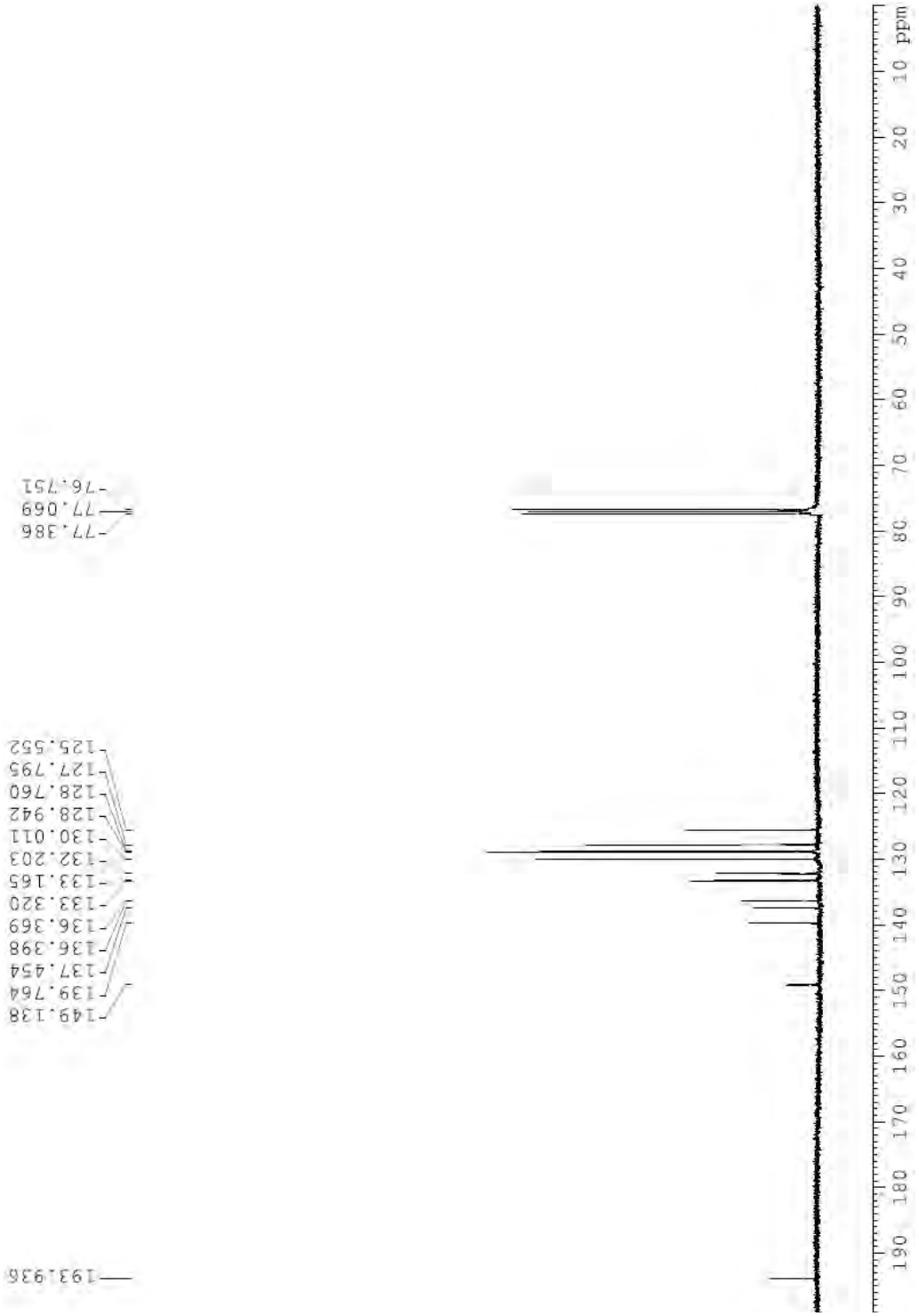
IR of 2'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5i)



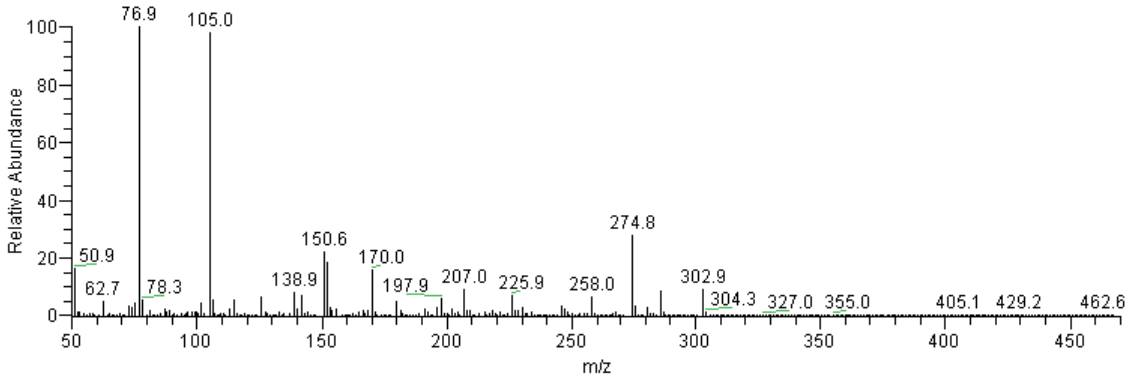
^{1}H-NMR of (2-nitro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (5j) in $CDCl_3$



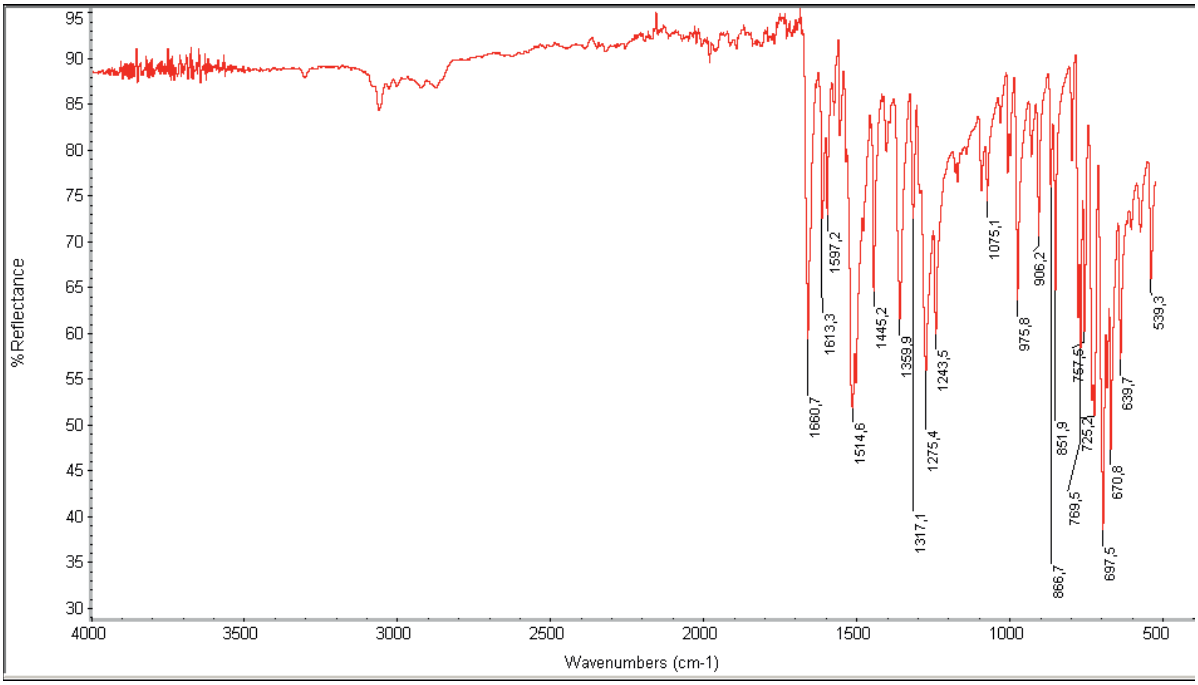
^{13}C-NMR of (2-nitro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (5j) in $CDCl_3$



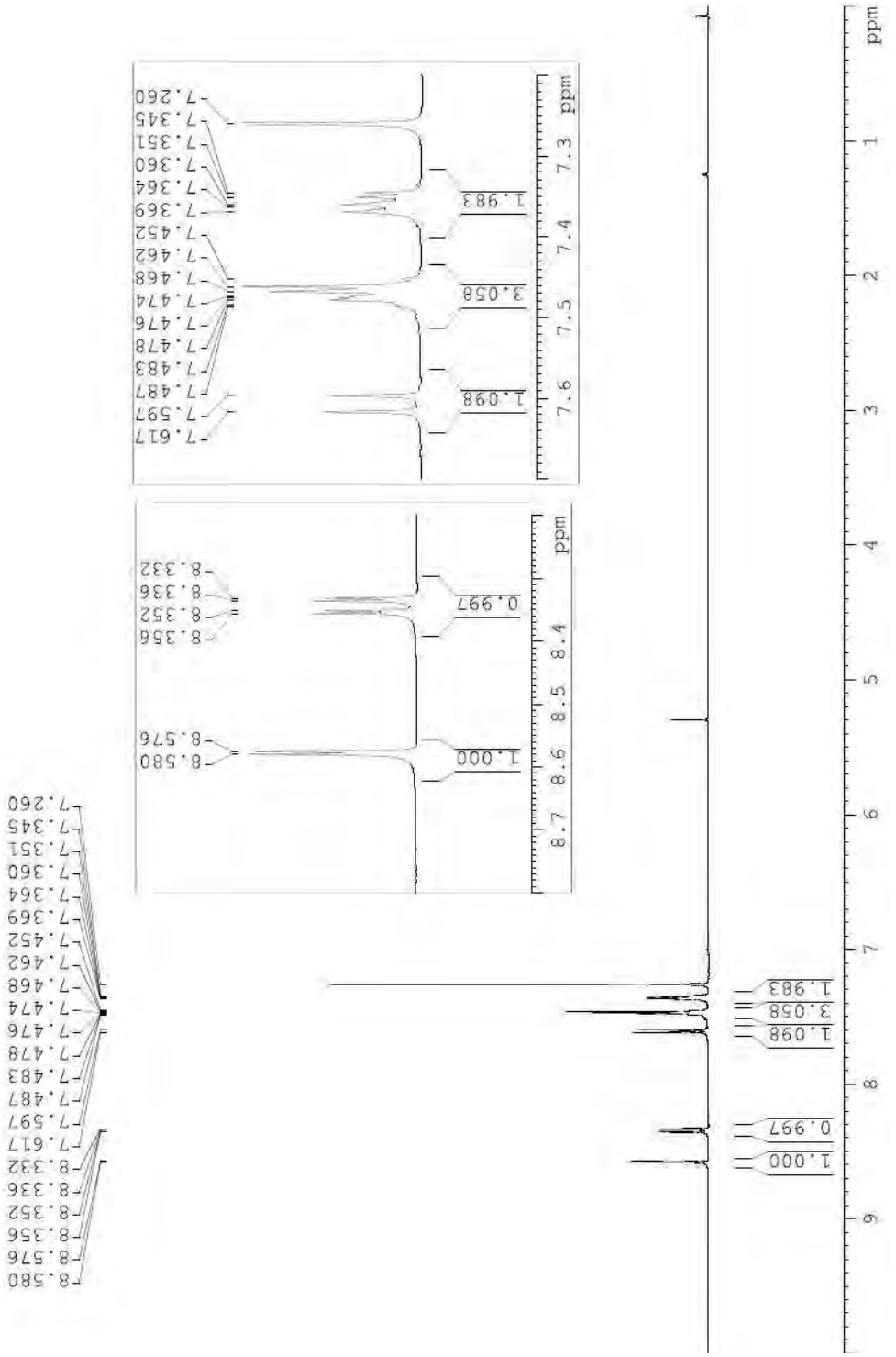
MS (EI) of (2-nitro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (5j)



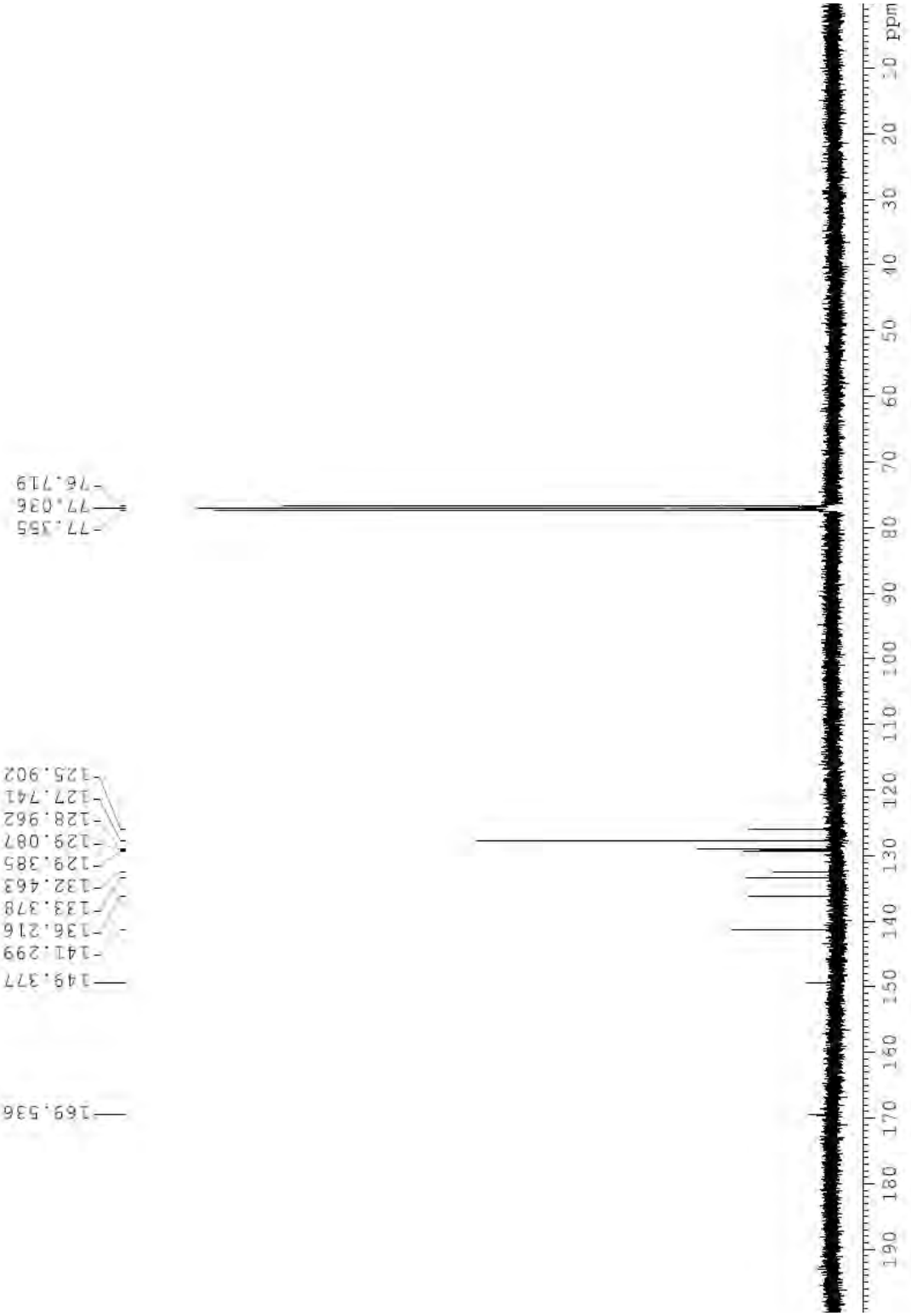
IR of (2-nitro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (5j)



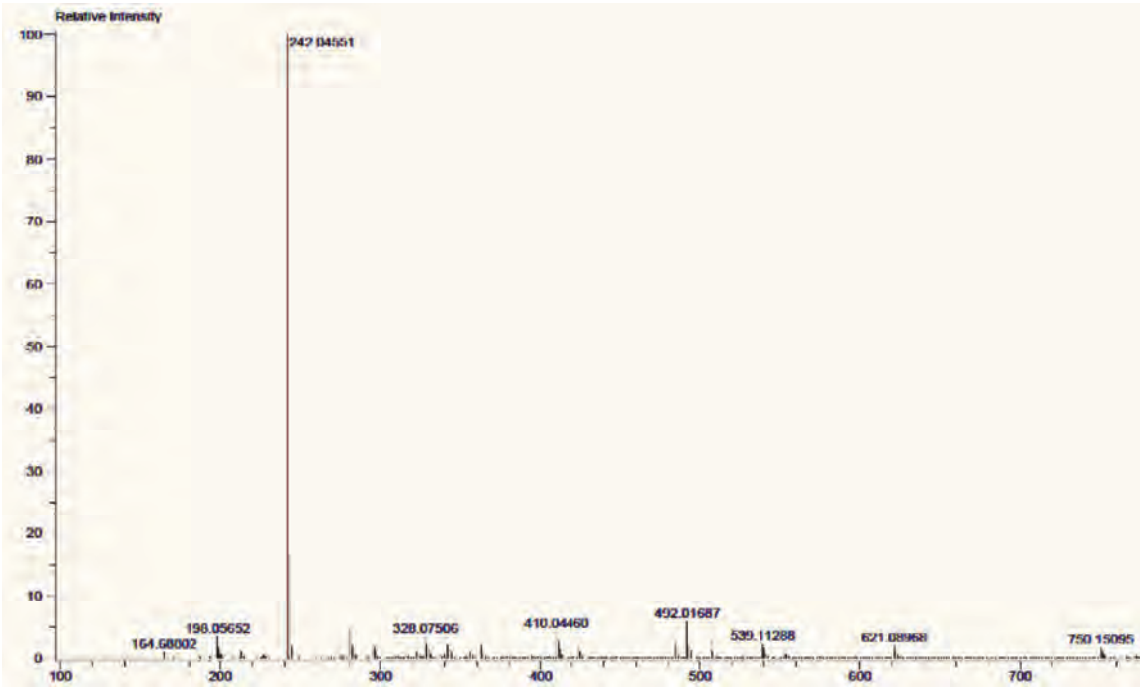
^{1}H-NMR of 2-nitro-[1,1'-biphenyl]-4-carboxylic acid (5k) in $CDCl_3$



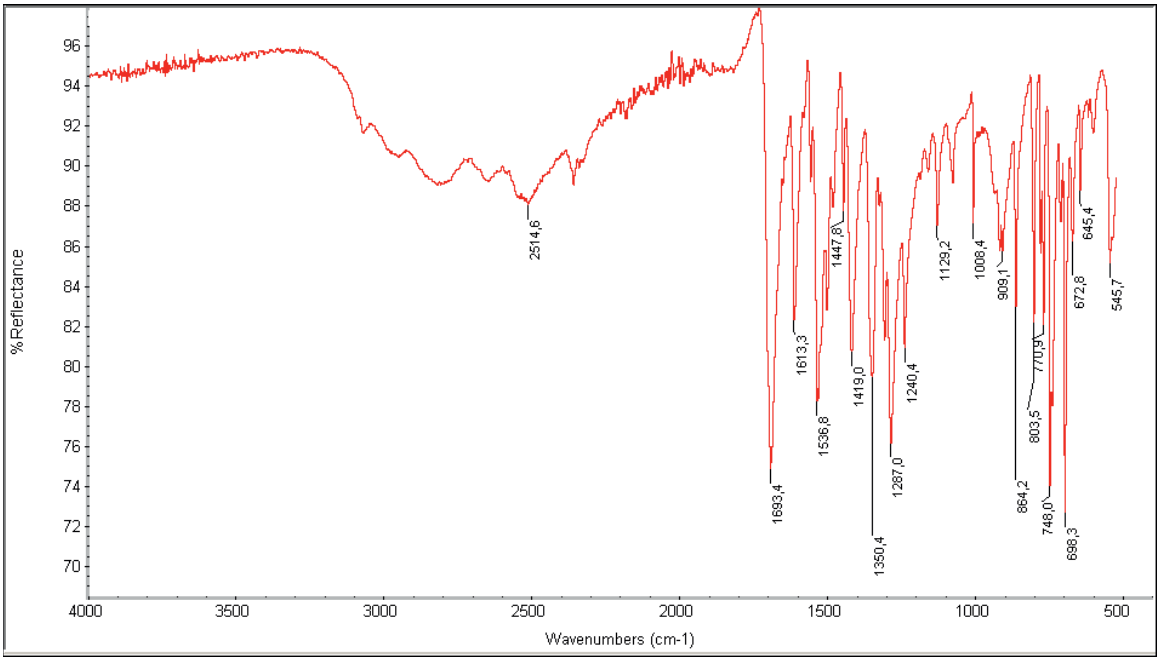
^{13}C-NMR of 2-nitro-[1,1'-biphenyl]-4-carboxylic acid (5k) in $CDCl_3$



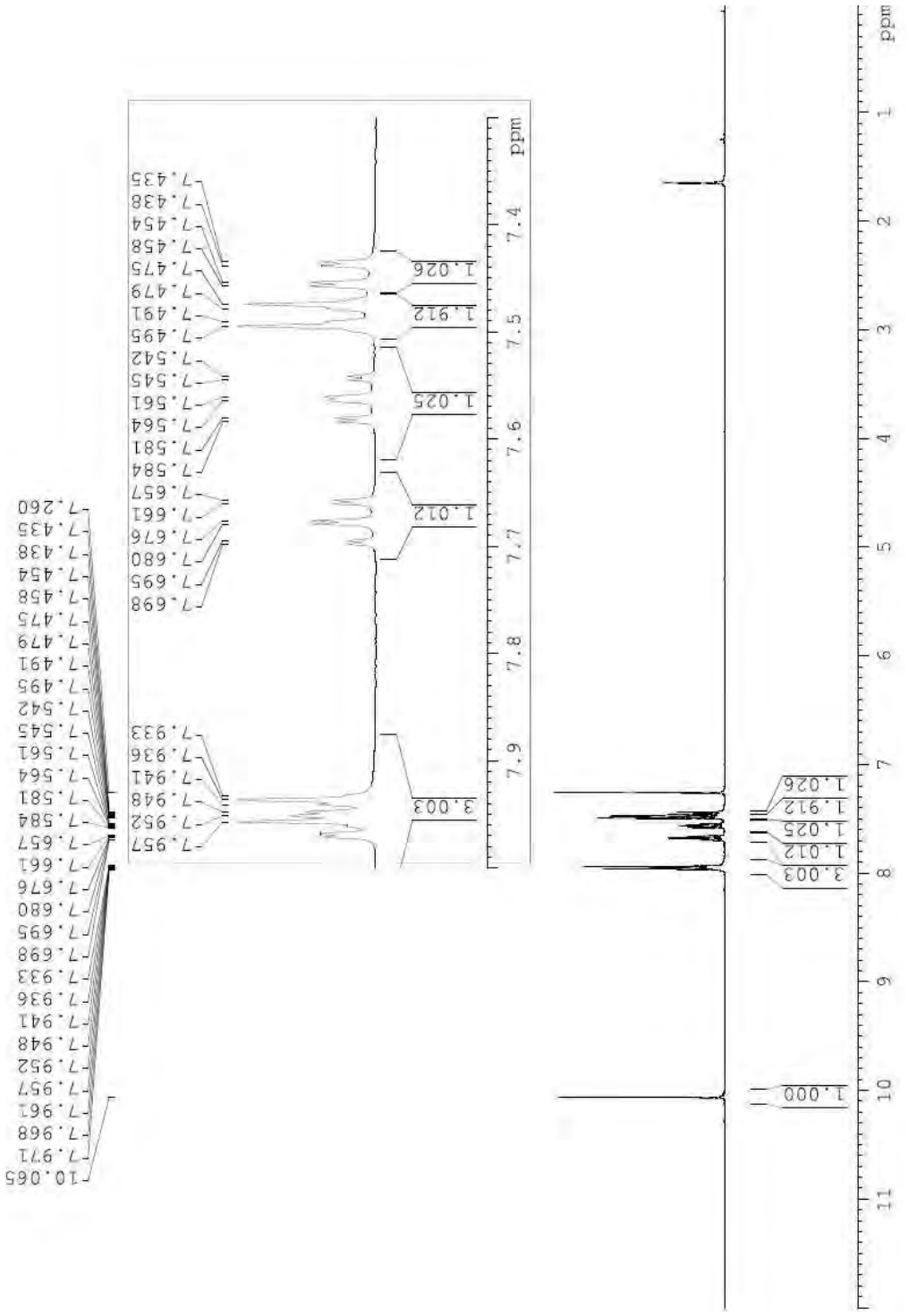
HR-MS of 2-nitro-[1,1'-biphenyl]-4-carboxylic acid (5k)



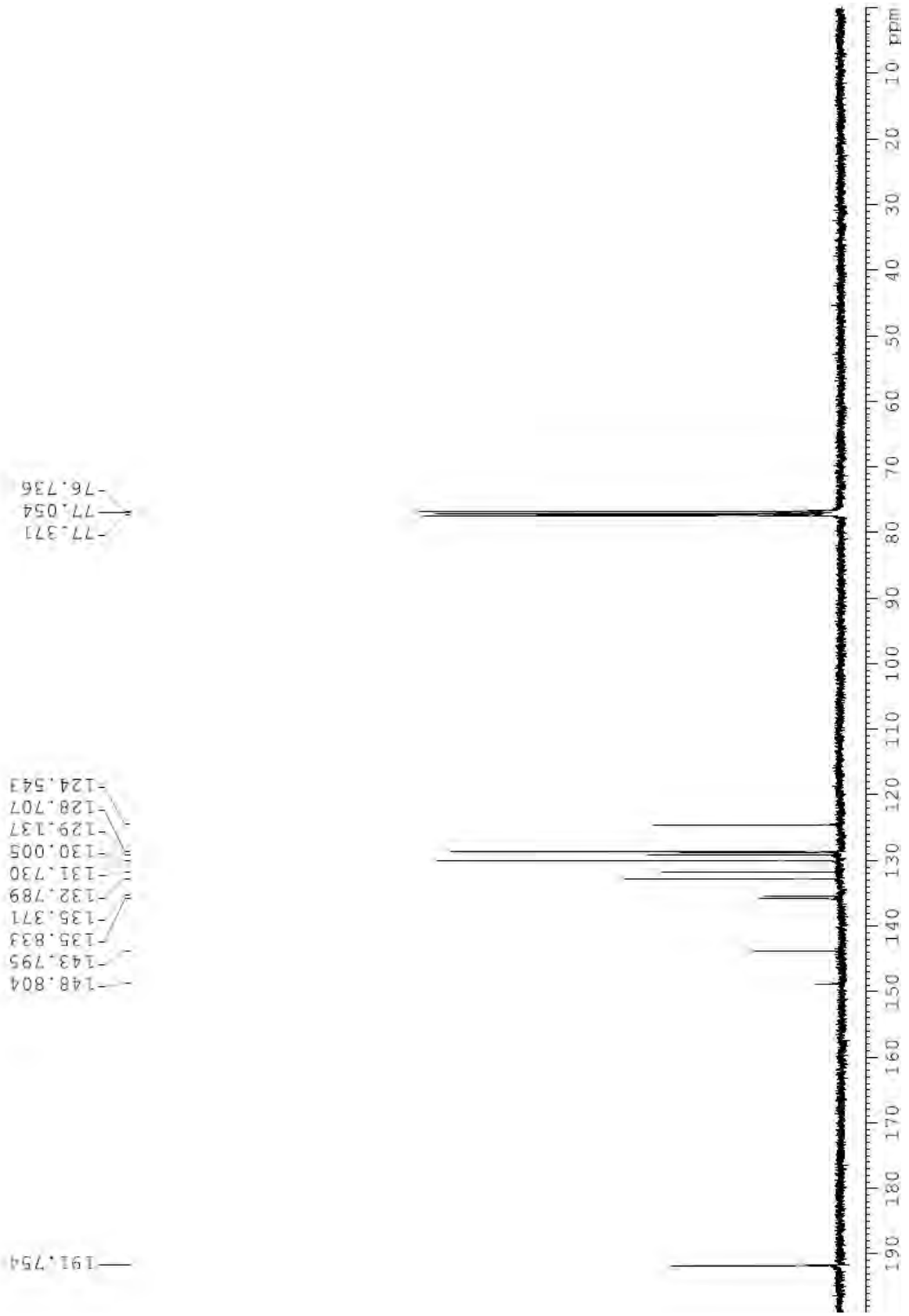
IR of 2-nitro-[1,1'-biphenyl]-4-carboxylic acid (5k)



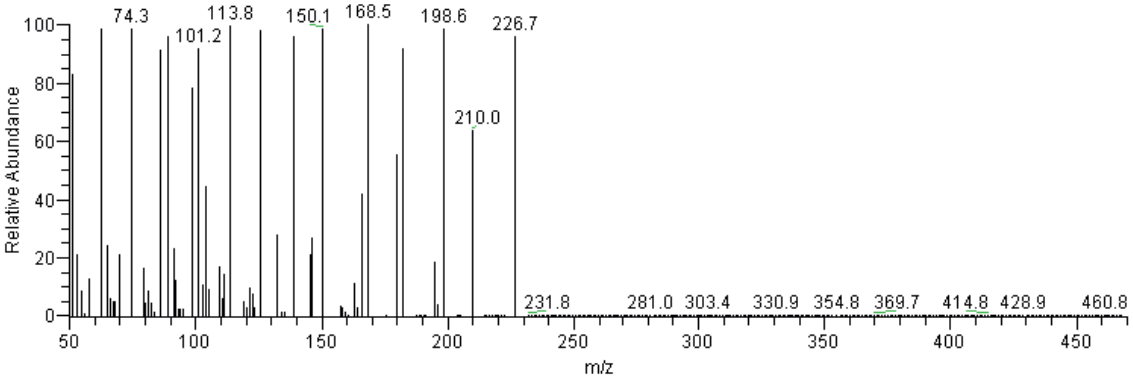
^{1}H-NMR of 2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5l) in $CDCl_3$



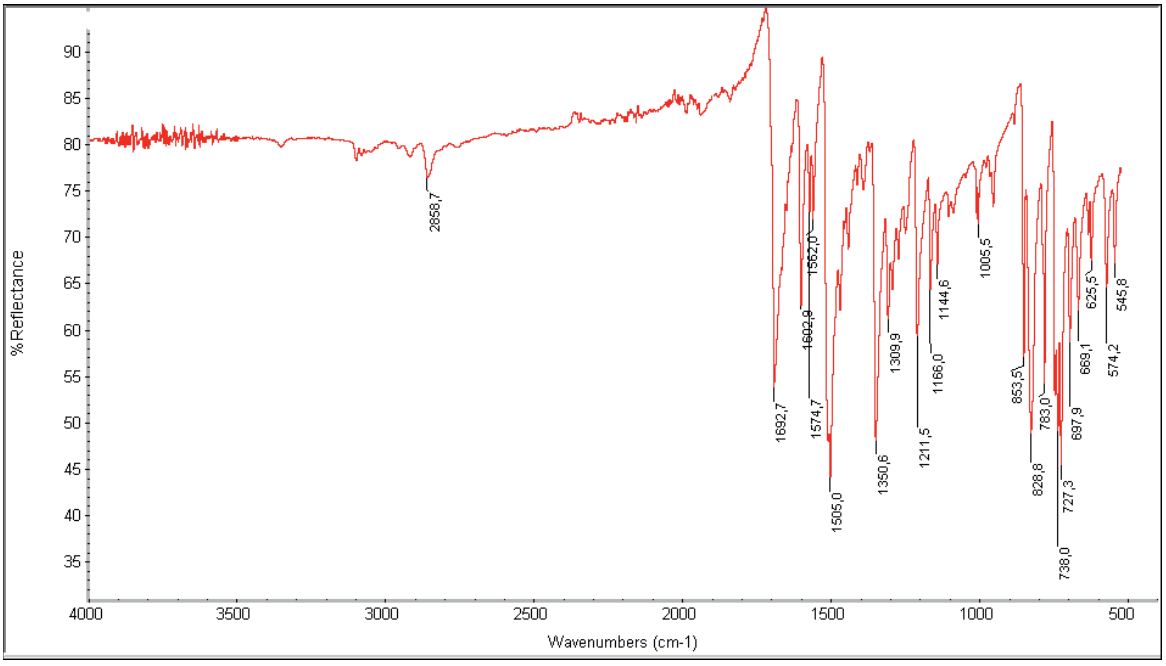
^{13}C-NMR of 2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5l) in $CDCl_3$



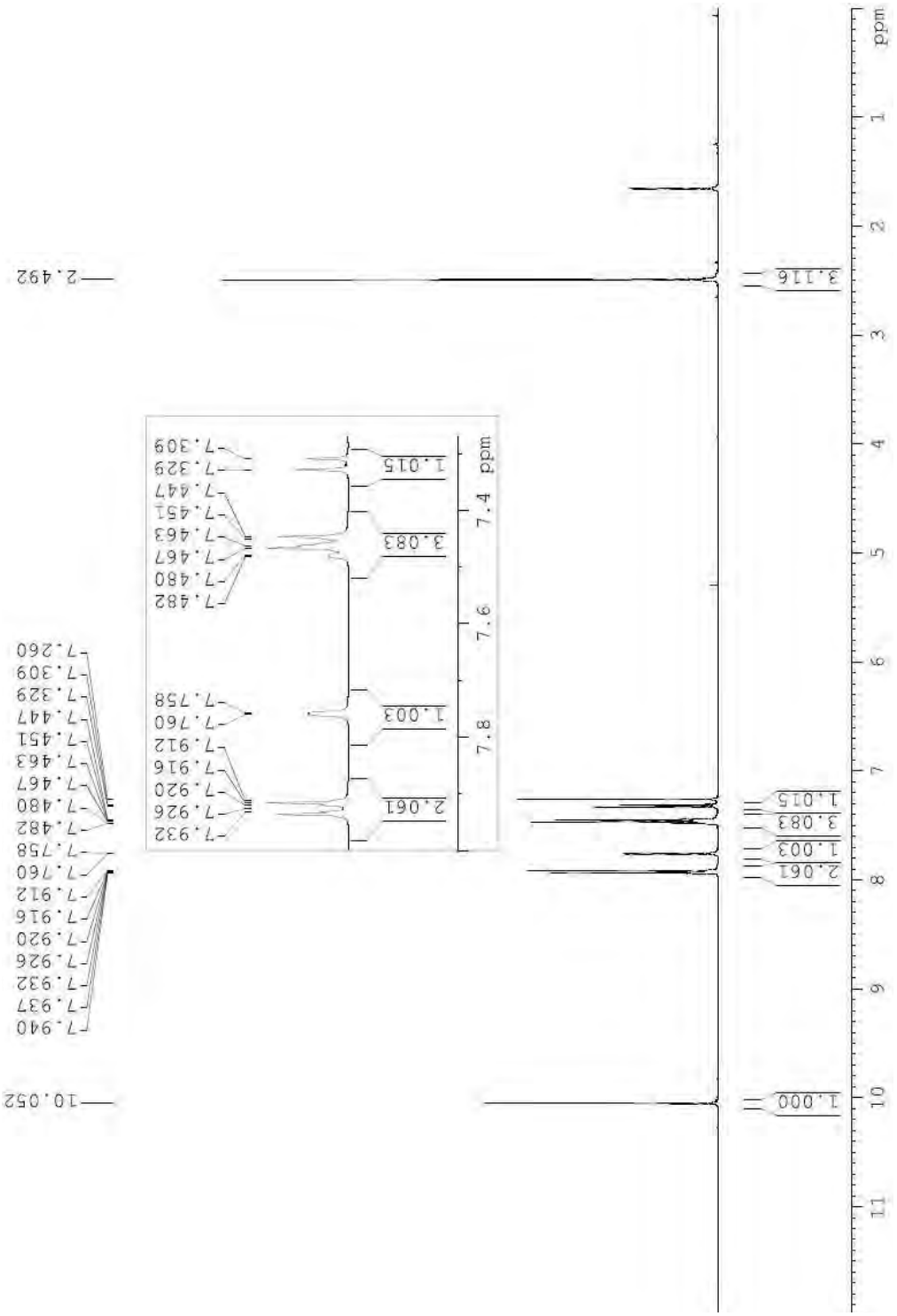
MS (EI) of 2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5l)



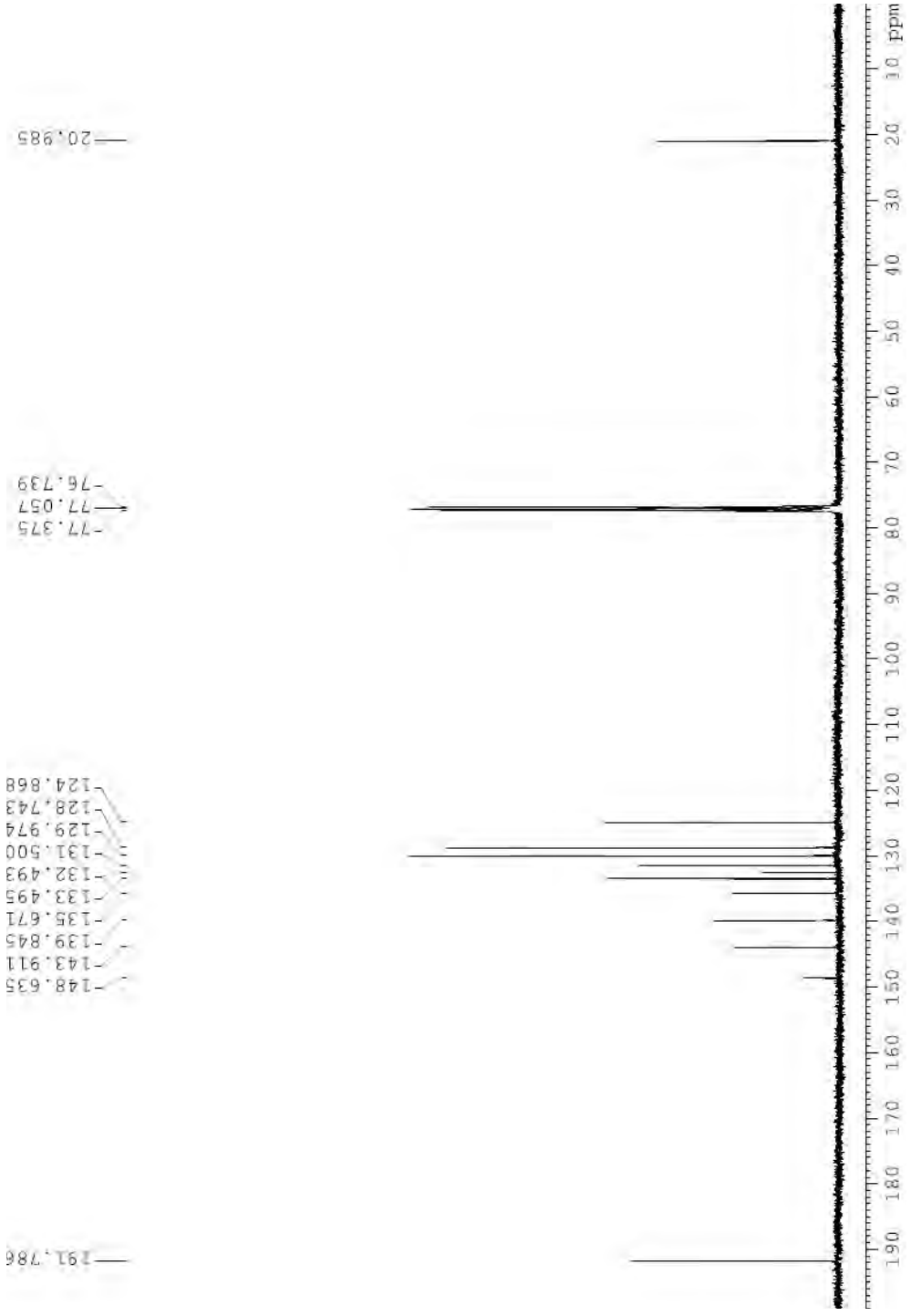
IR of 2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5l)



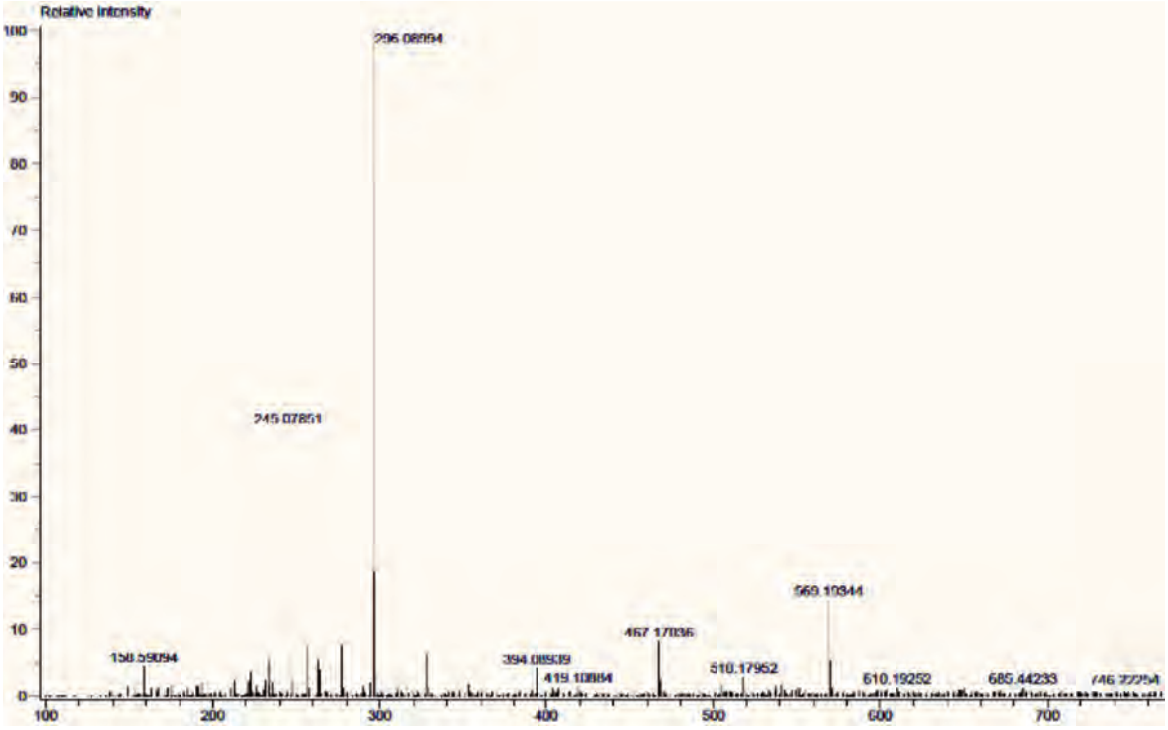
^{1}H-NMR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5m) in $CDCl_3$



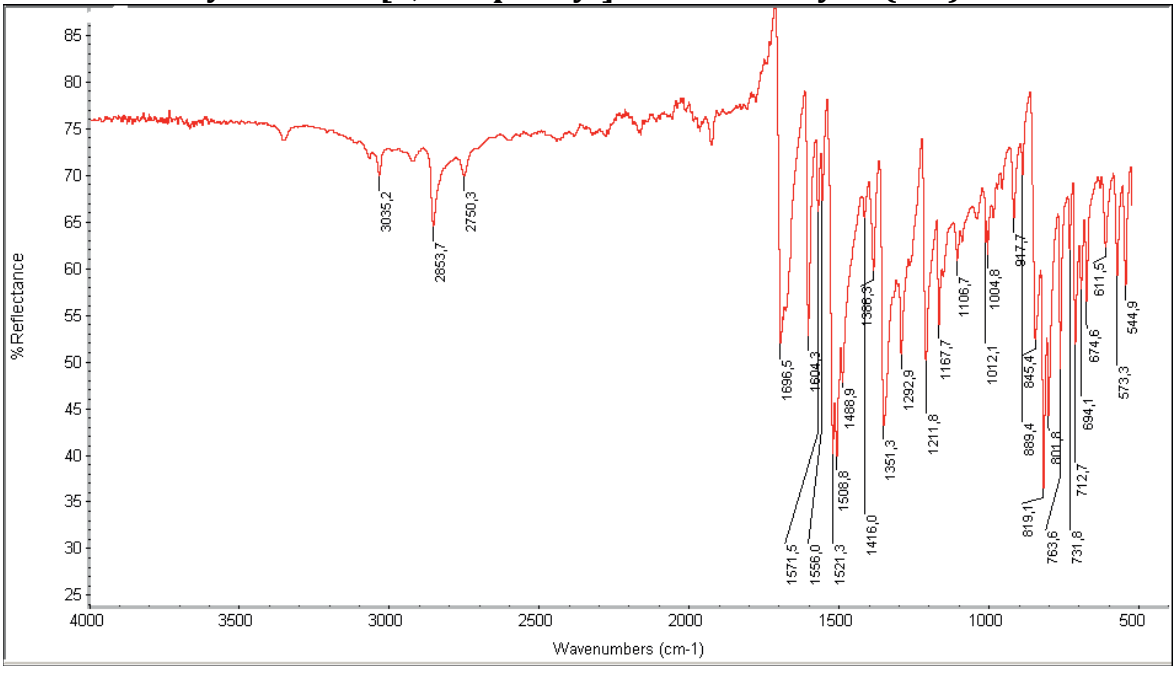
^{13}C-NMR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5m) in $CDCl_3$



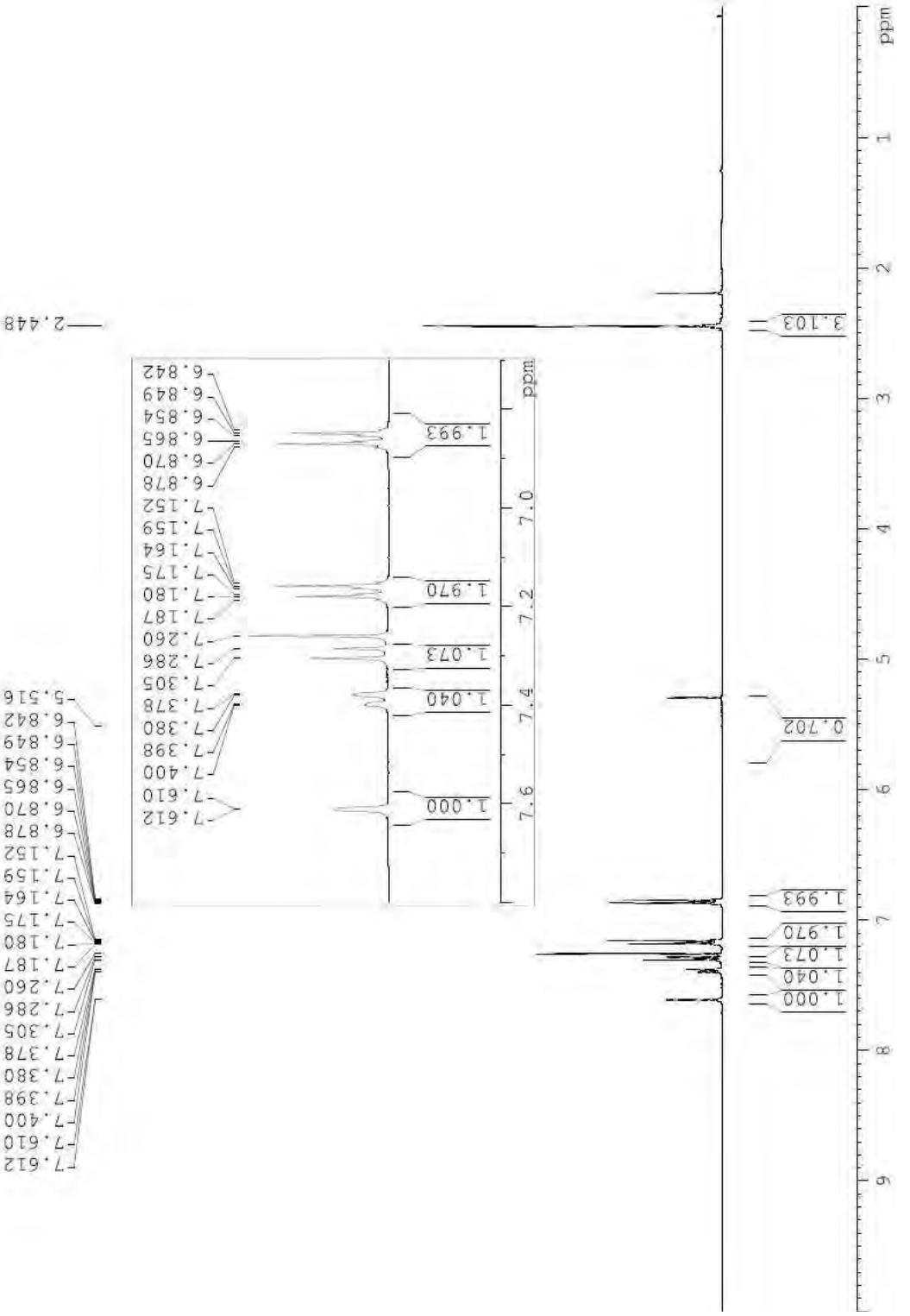
HR-MS of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5m)



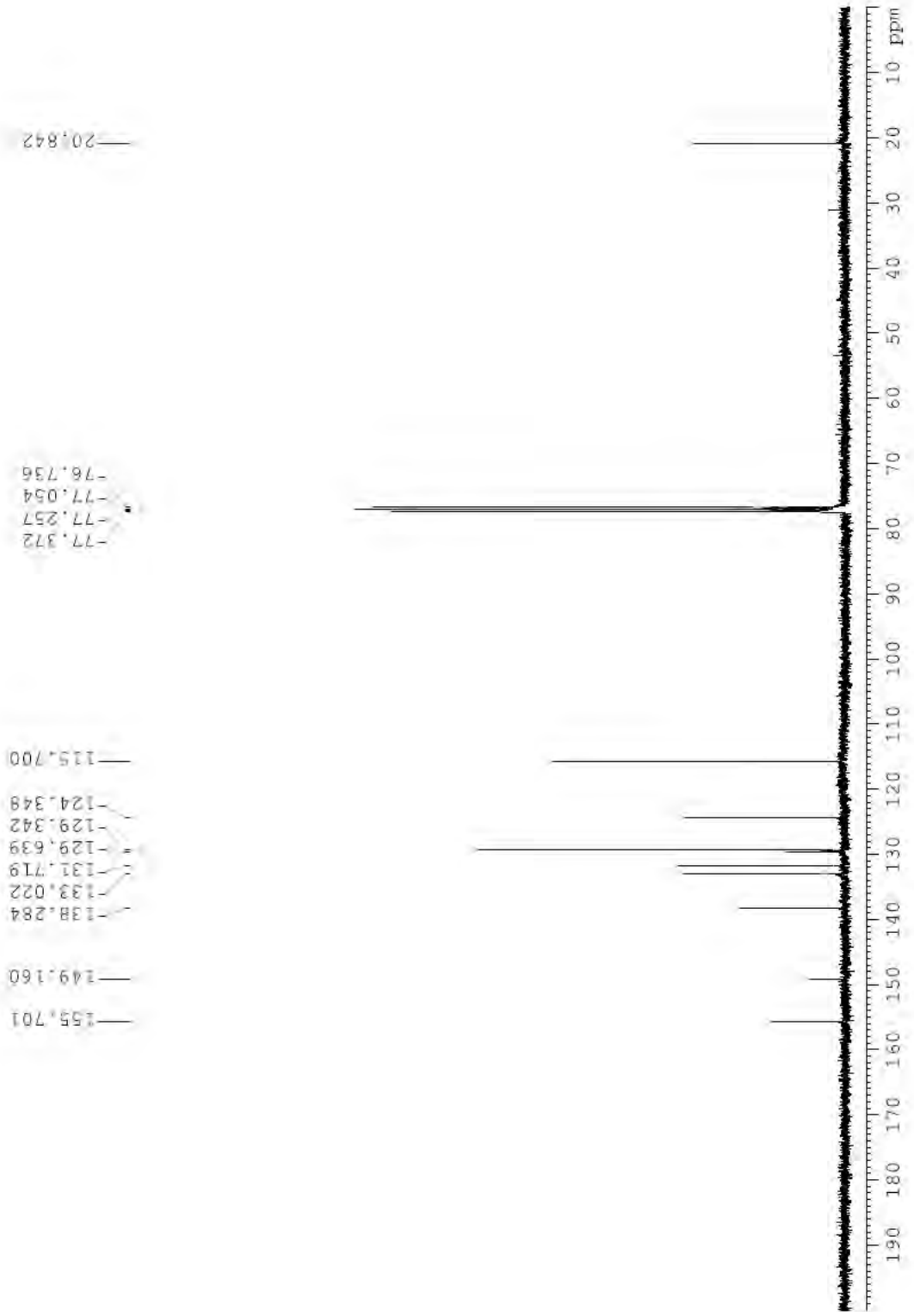
IR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-carbaldehyde (5m)



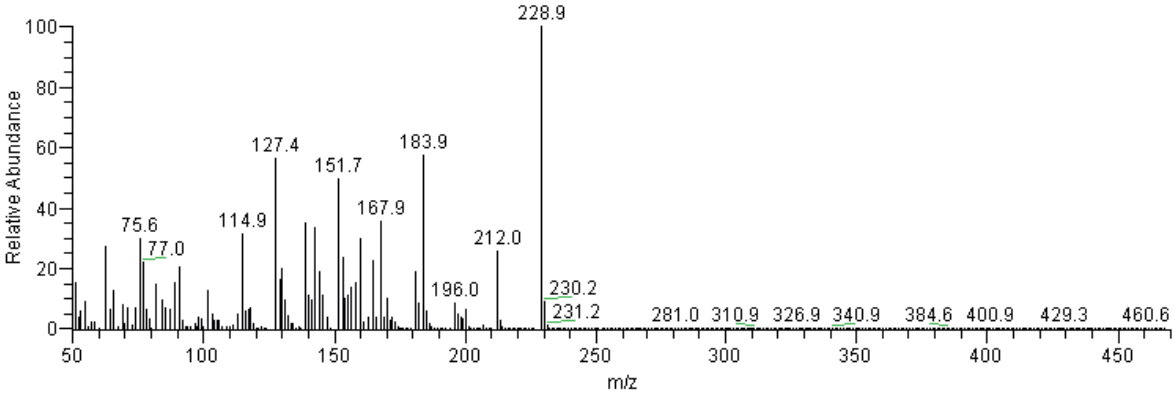
^{1}H-NMR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-ol (5n) in $CDCl_3$



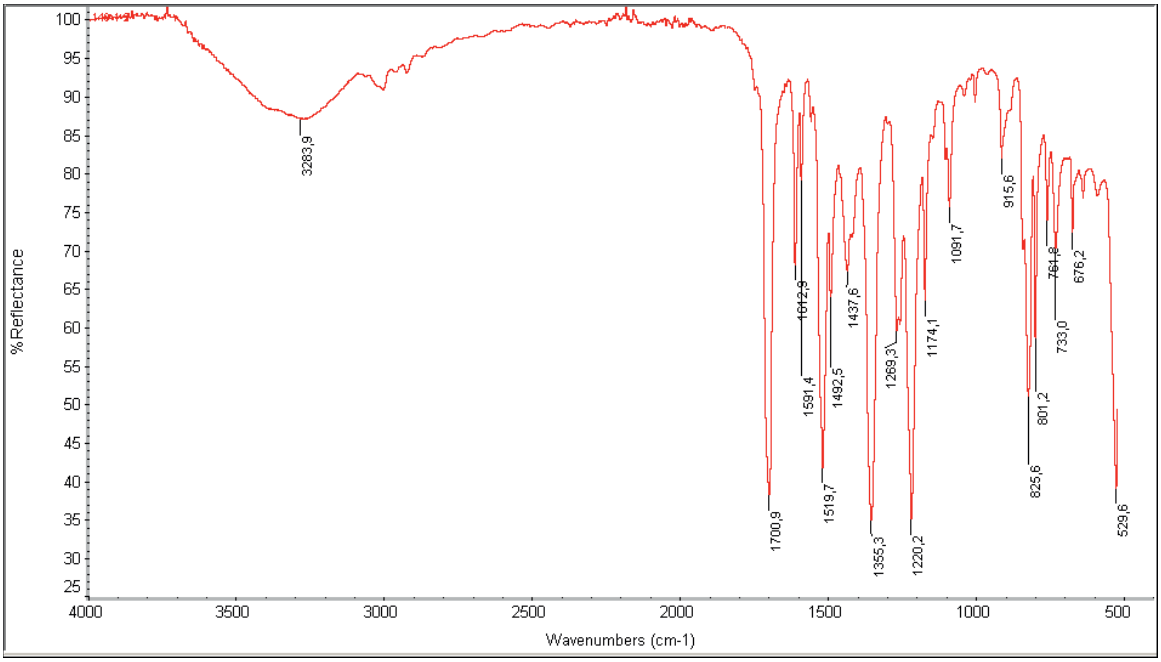
^{13}C-NMR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-ol (5n) in $CDCl_3$



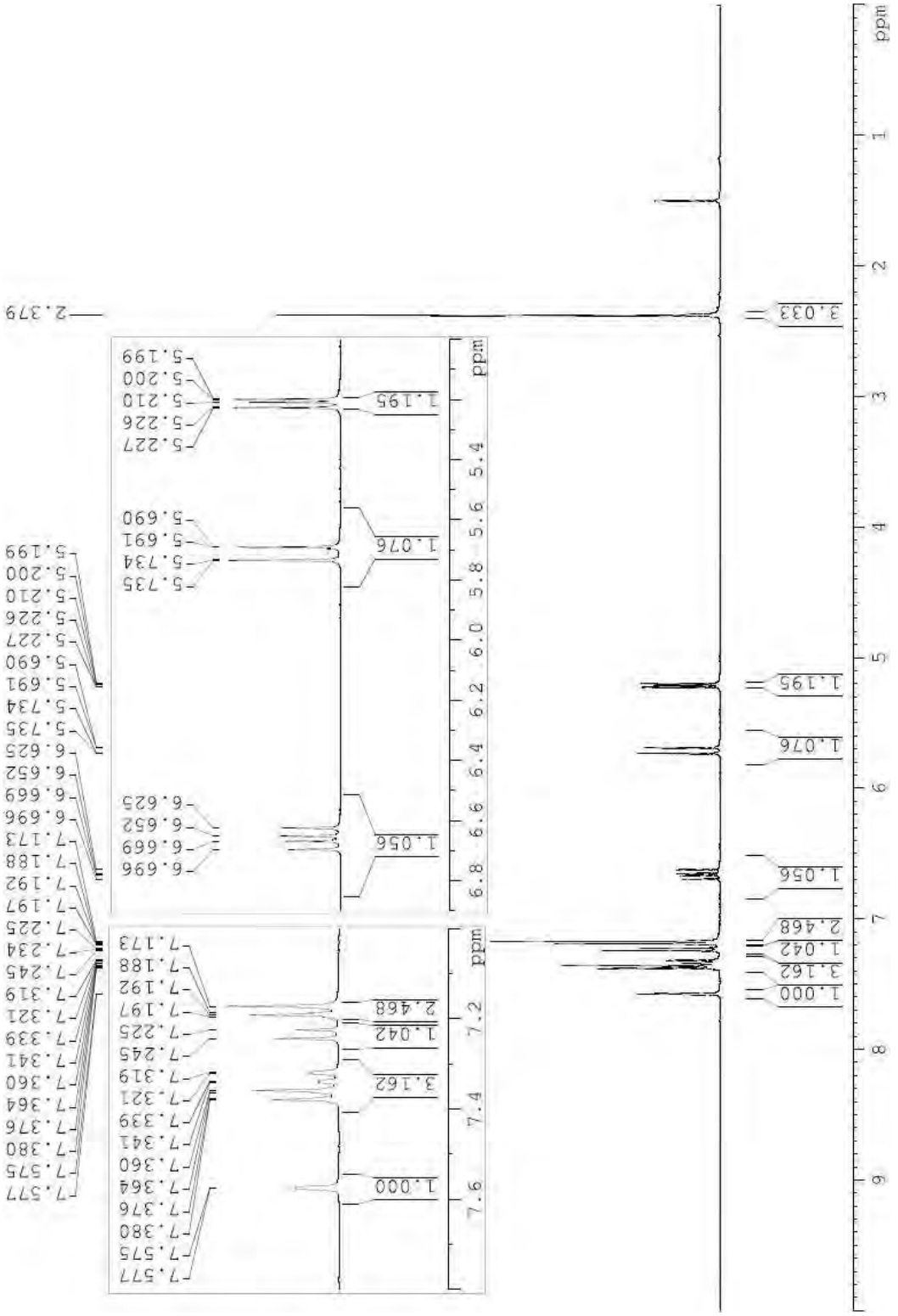
MS (EI) of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-ol (5n)



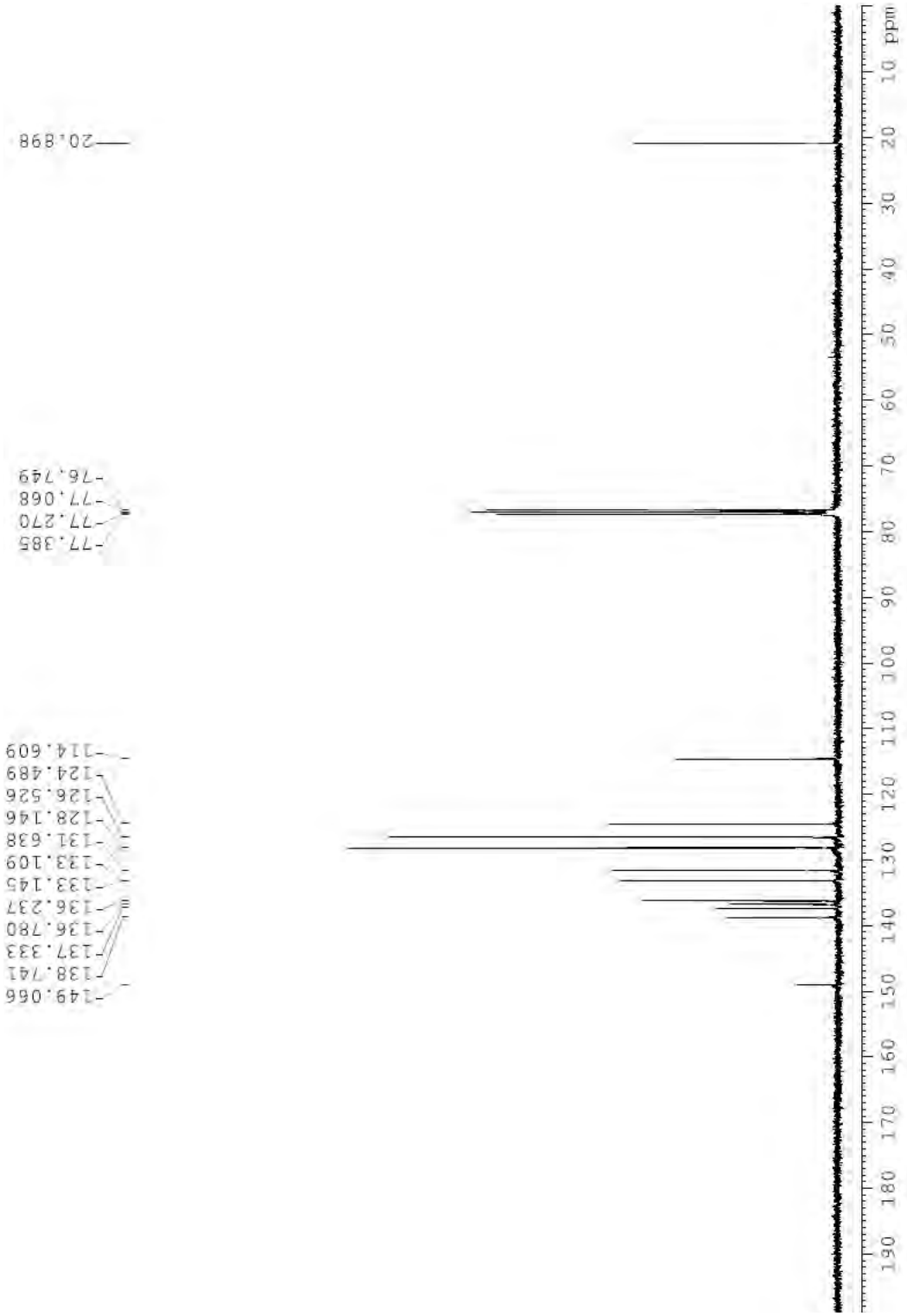
IR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-4-ol (5n)



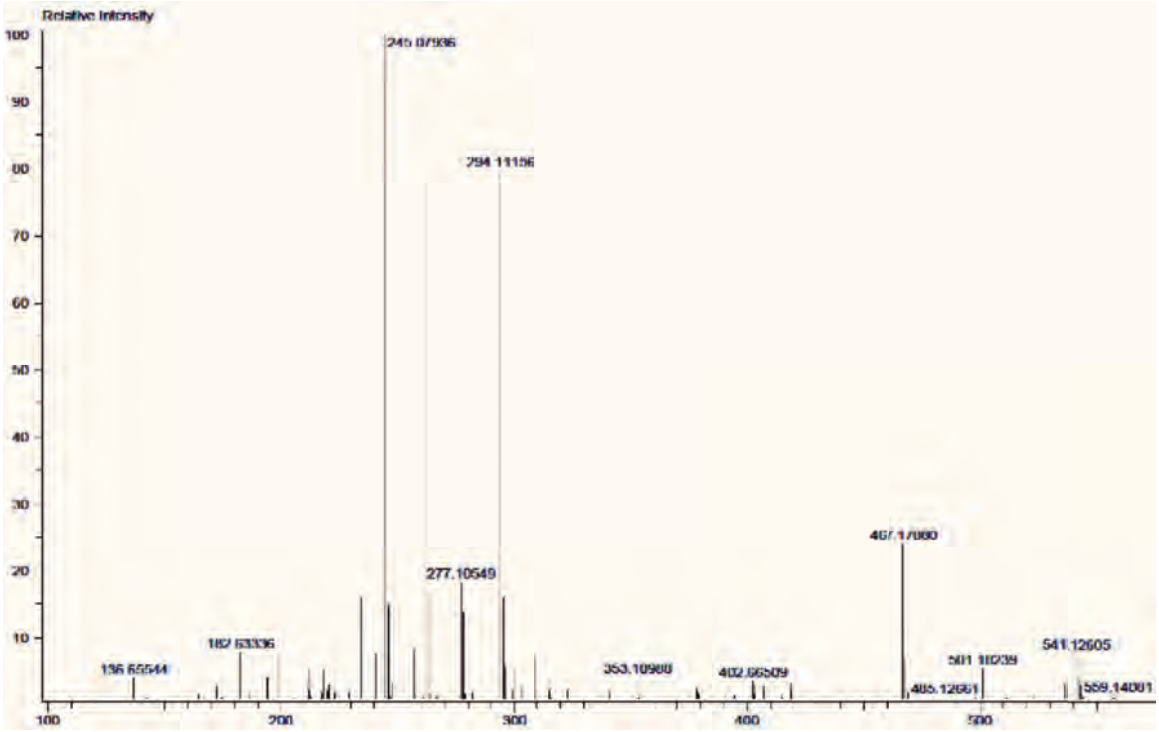
^{1}H-NMR of 4-methyl-2-nitro-4'-vinyl-1,1'-biphenyl (5o) in $CDCl_3$



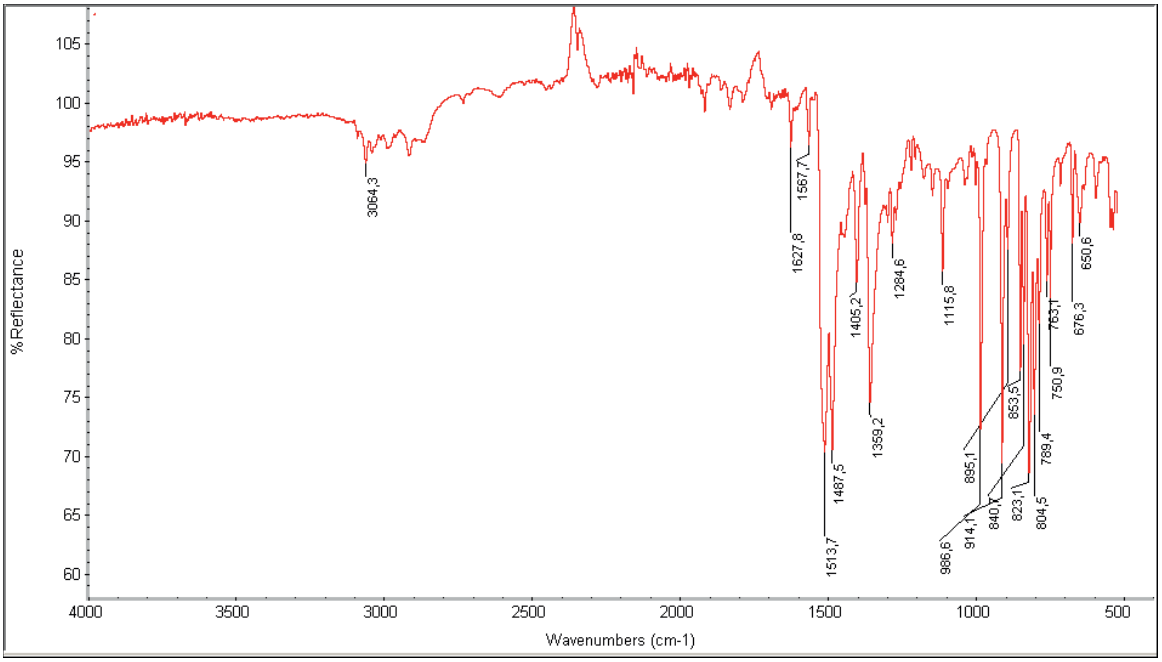
^{13}C-NMR of 4-methyl-2-nitro-4'-vinyl-1,1'-biphenyl (5o) in $CDCl_3$



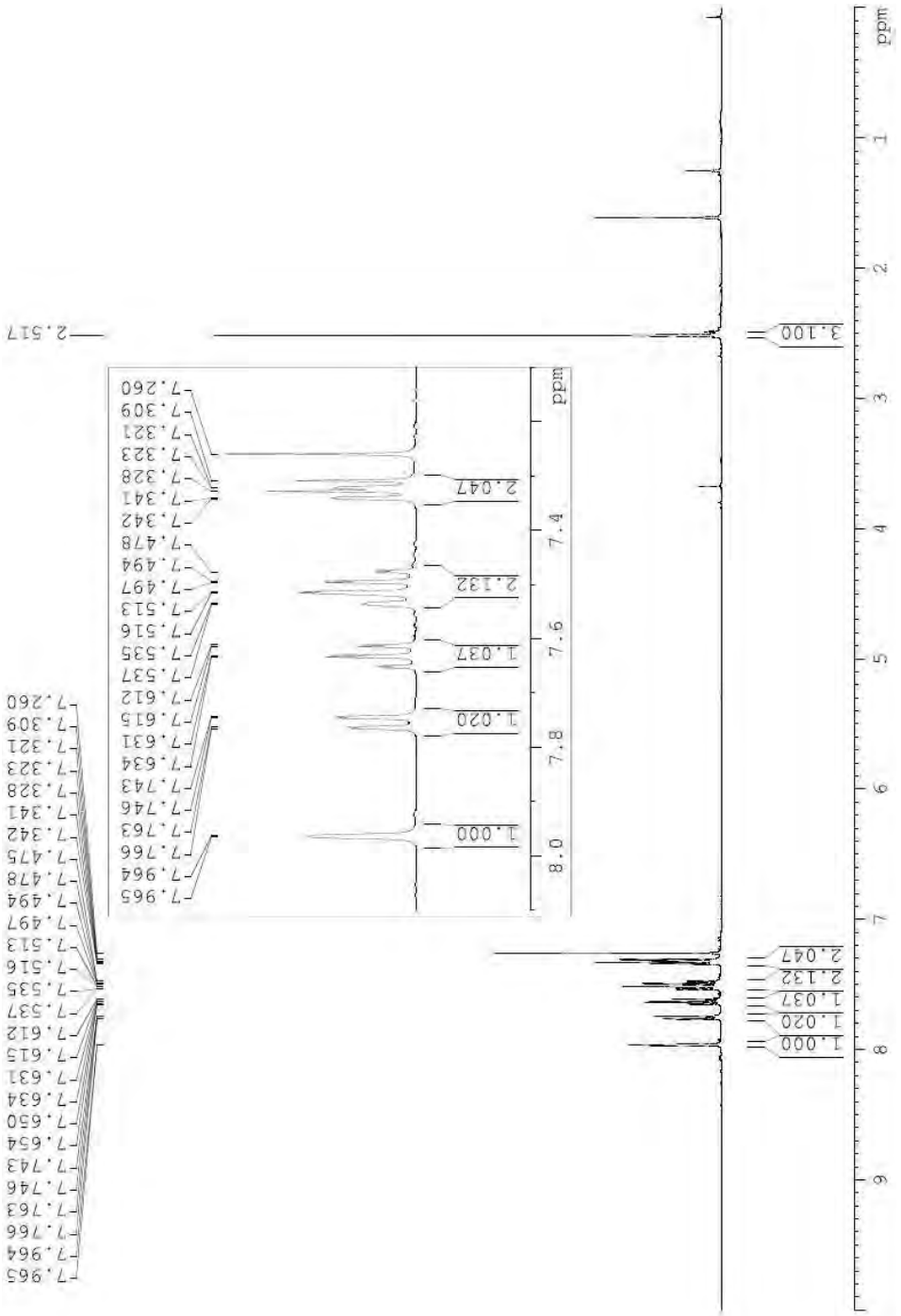
HR-MS of 4-methyl-2-nitro-4'-vinyl-1,1'-biphenyl (5o)



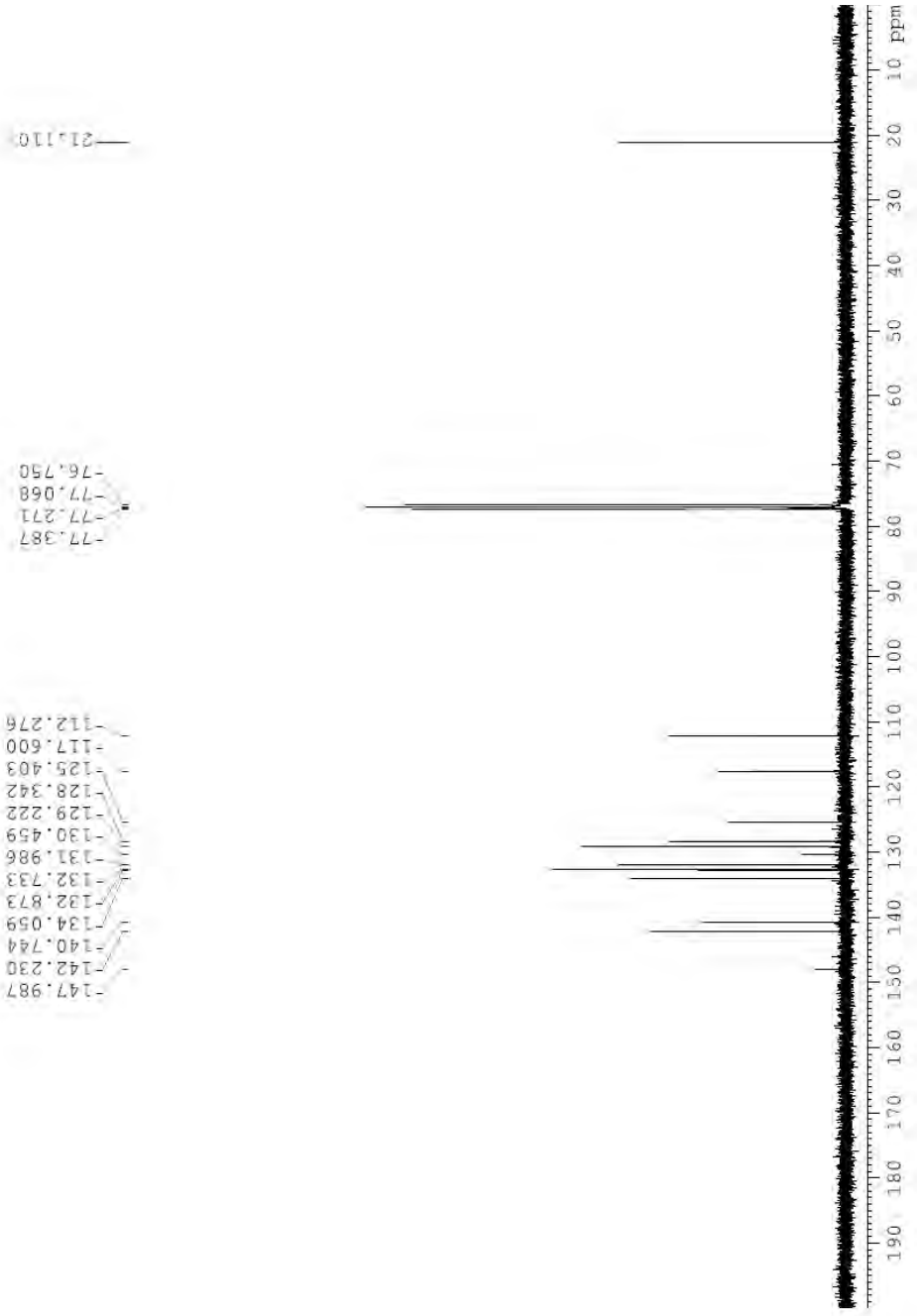
IR of 4-methyl-2-nitro-4'-vinyl-1,1'-biphenyl (5o)



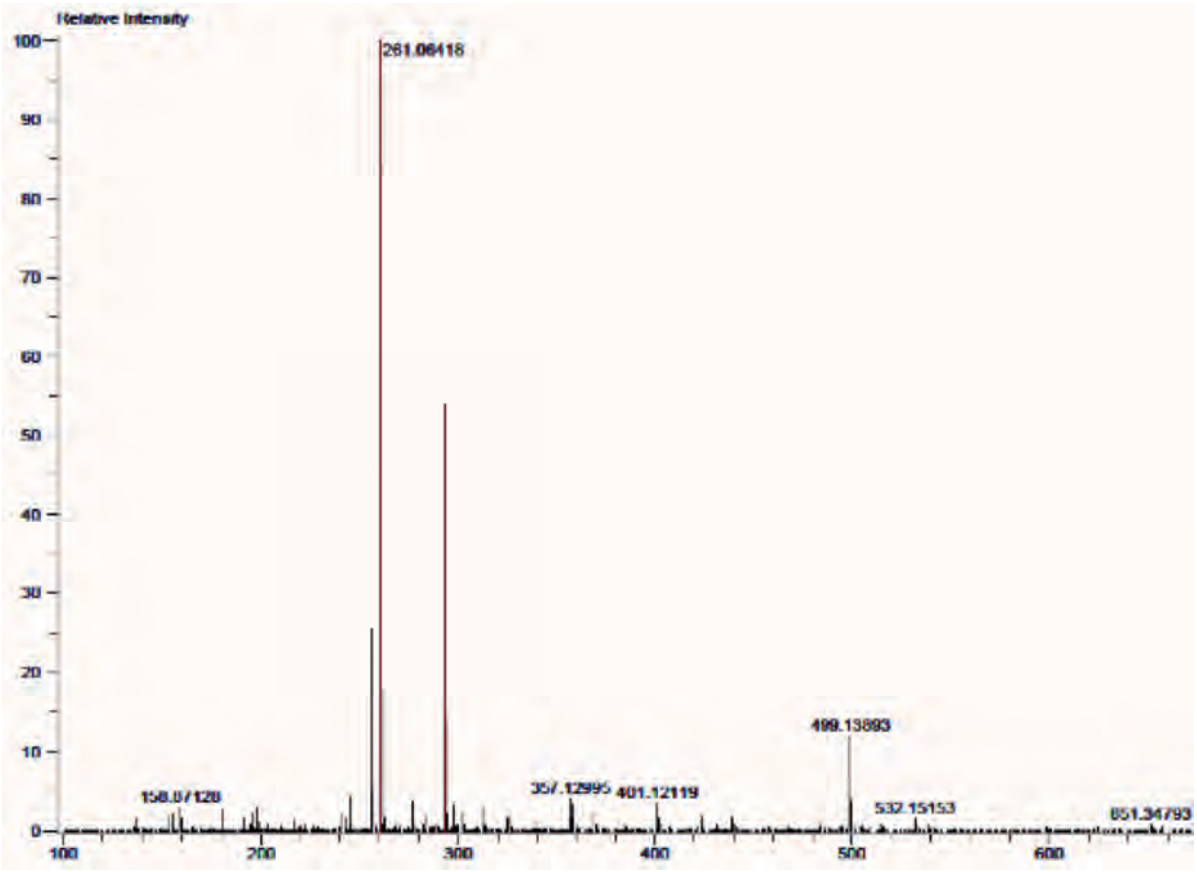
^{1}H-NMR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-2-carbonitrile (5p) in $CDCl_3$



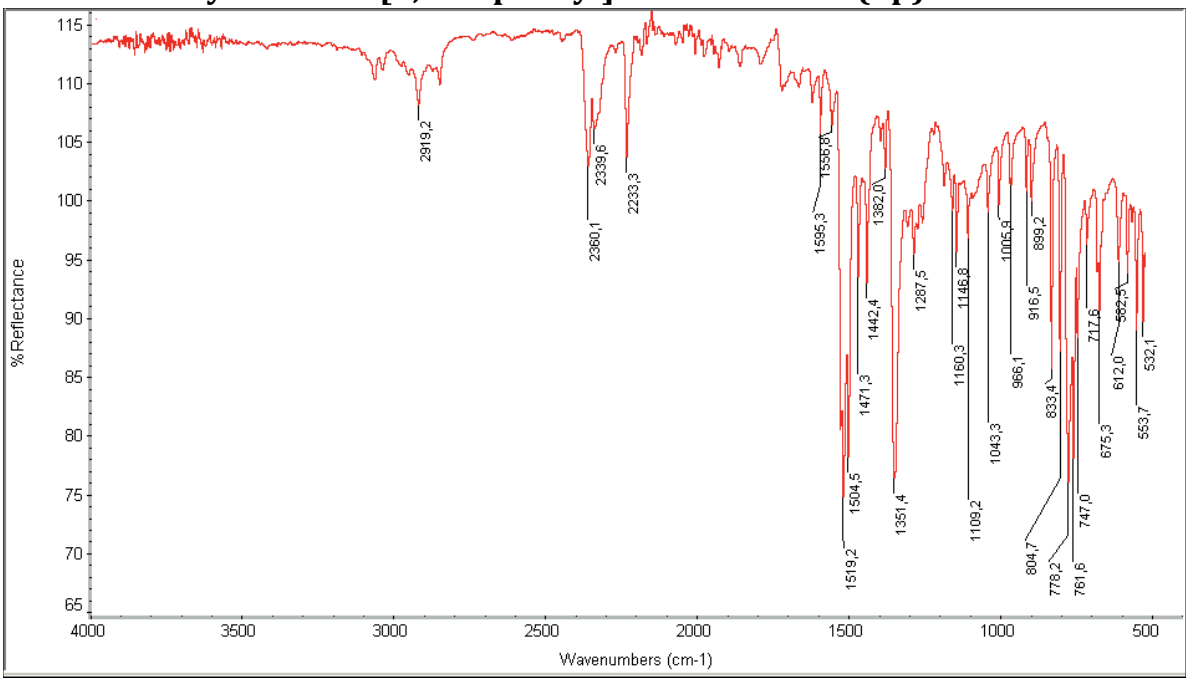
^{13}C-NMR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-2-carbonitrile (5p) in $CDCl_3$



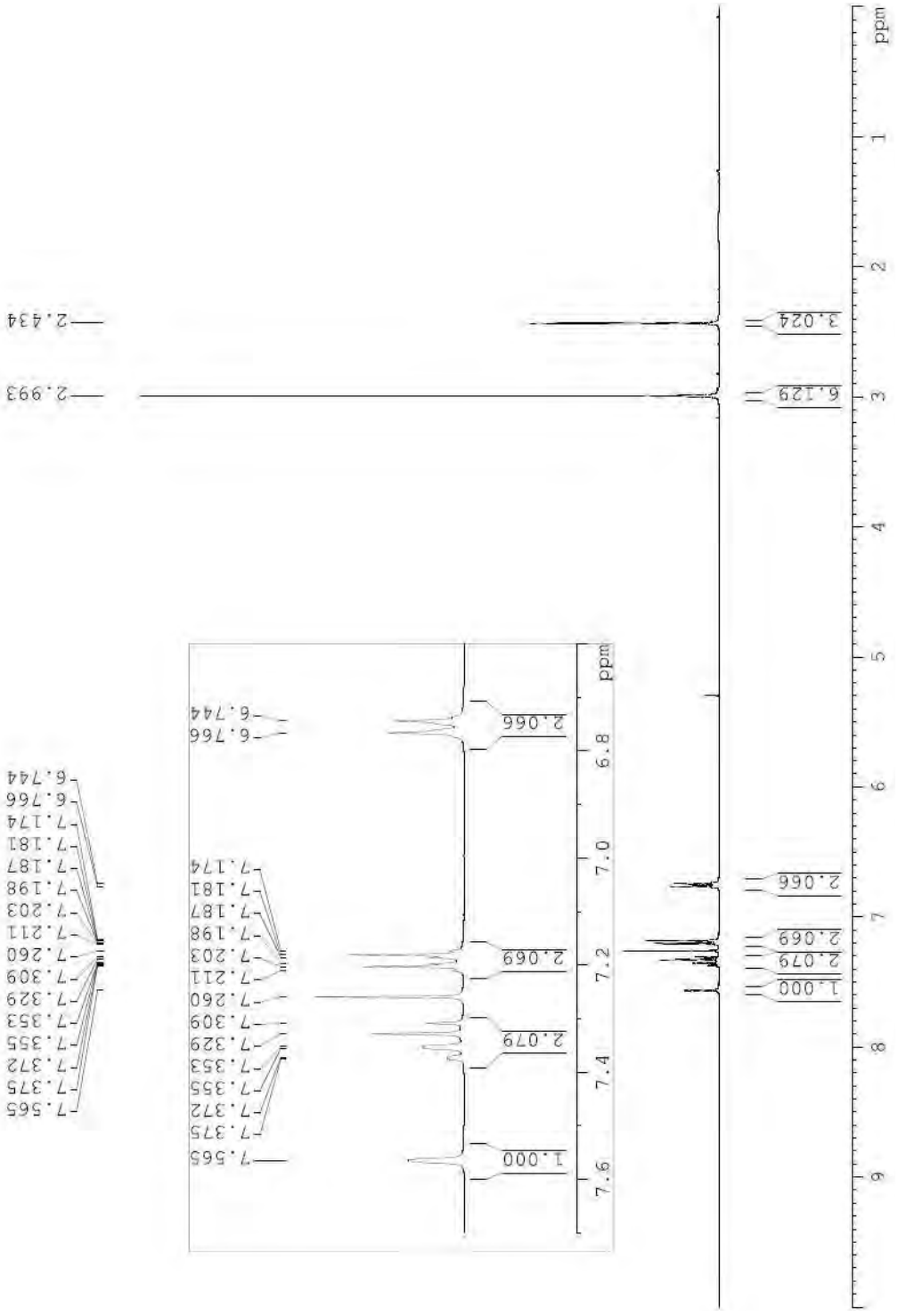
HR-MS of 4'-methyl-2'-nitro-[1,1'-biphenyl]-2-carbonitrile (5p)



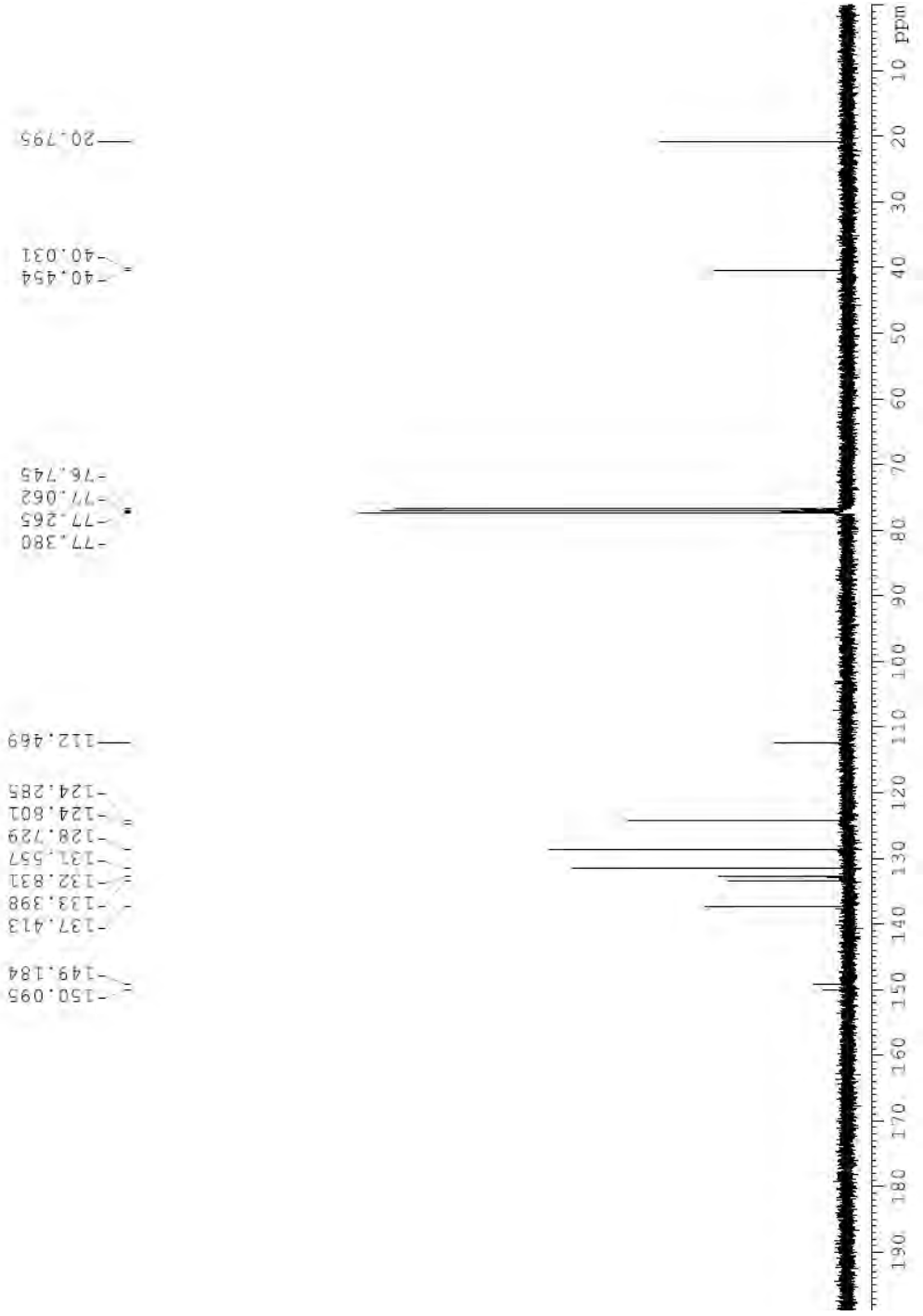
IR of 4'-methyl-2'-nitro-[1,1'-biphenyl]-2-carbonitrile (5p)



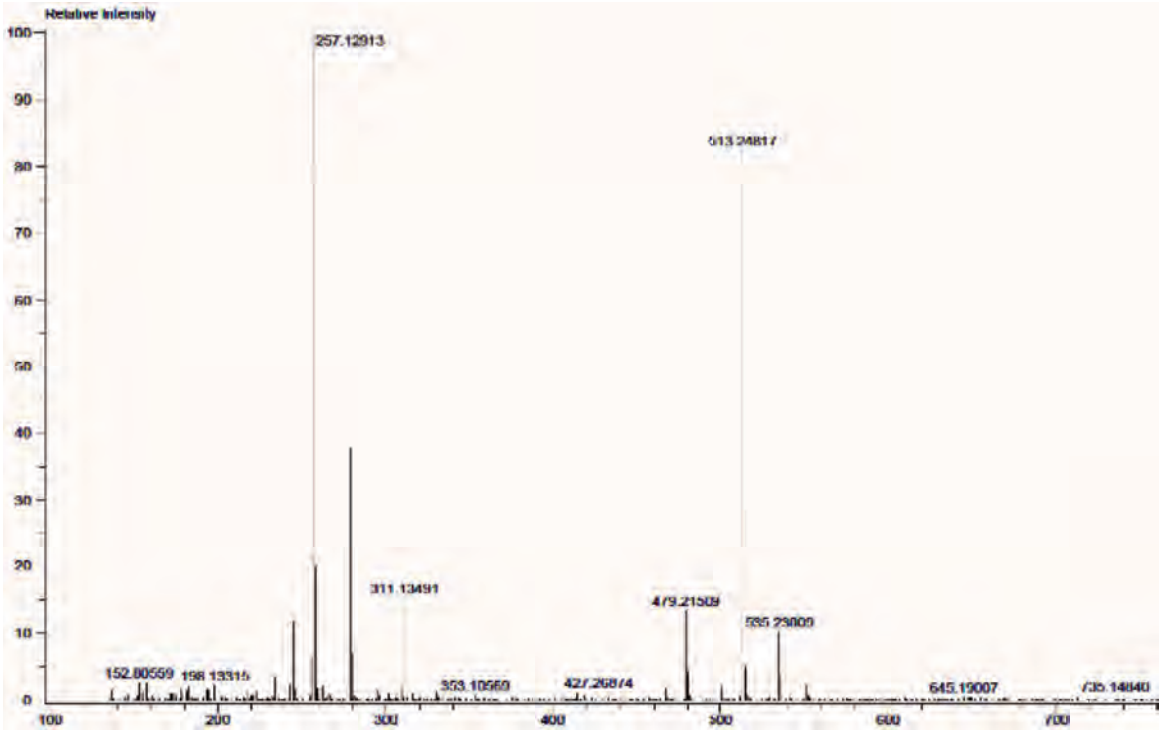
^{1}H-NMR of *N,N*,4'-trimethyl-2'-nitro-[1,1'-biphenyl]-4-amine (5q) in $CDCl_3$



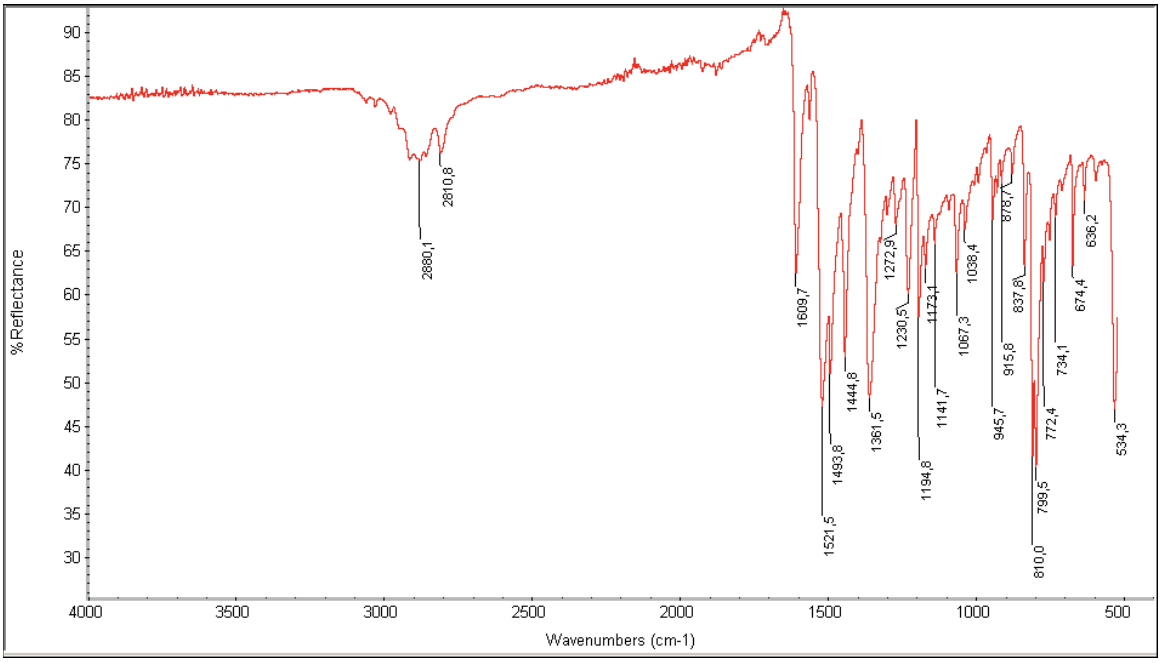
^{13}C-NMR of *N,N*,4'-trimethyl-2'-nitro-[1,1'-biphenyl]-4-amine (5q) in $CDCl_3$



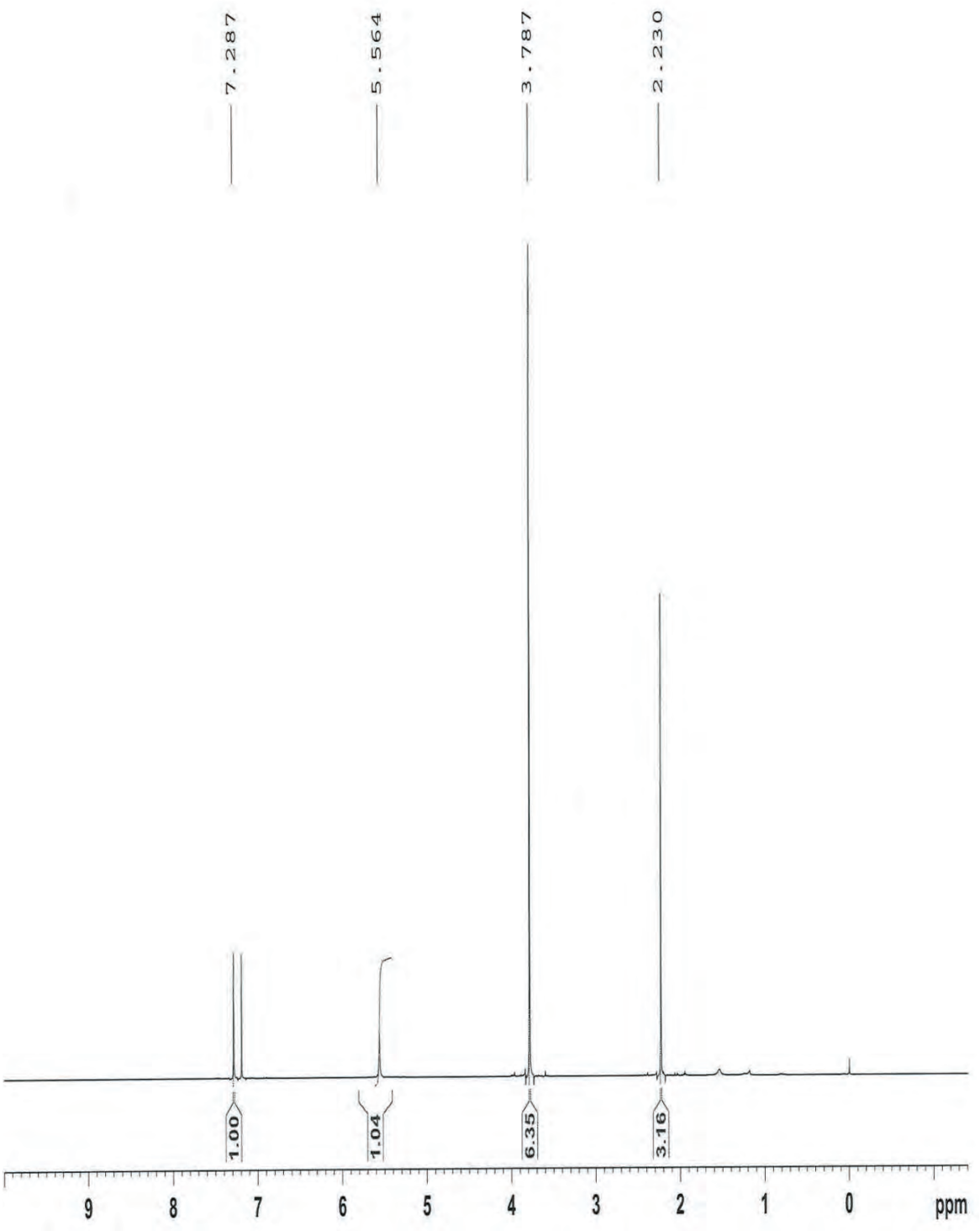
HR-MS of *N,N*,4'-trimethyl-2'-nitro-[1,1'-biphenyl]-4-amine (5q)



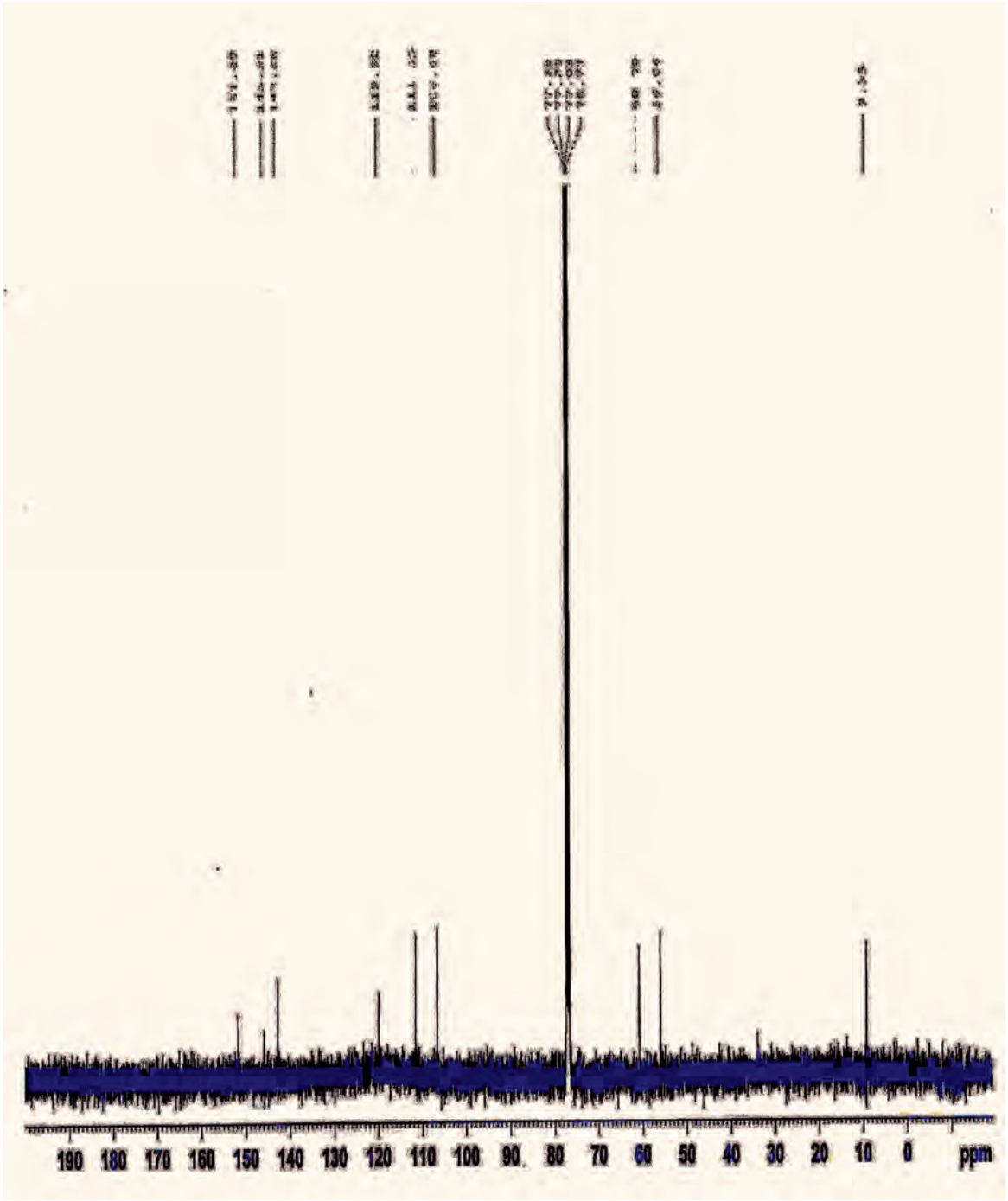
IR of *N,N*,4'-trimethyl-2'-nitro-[1,1'-biphenyl]-4-amine (5q)



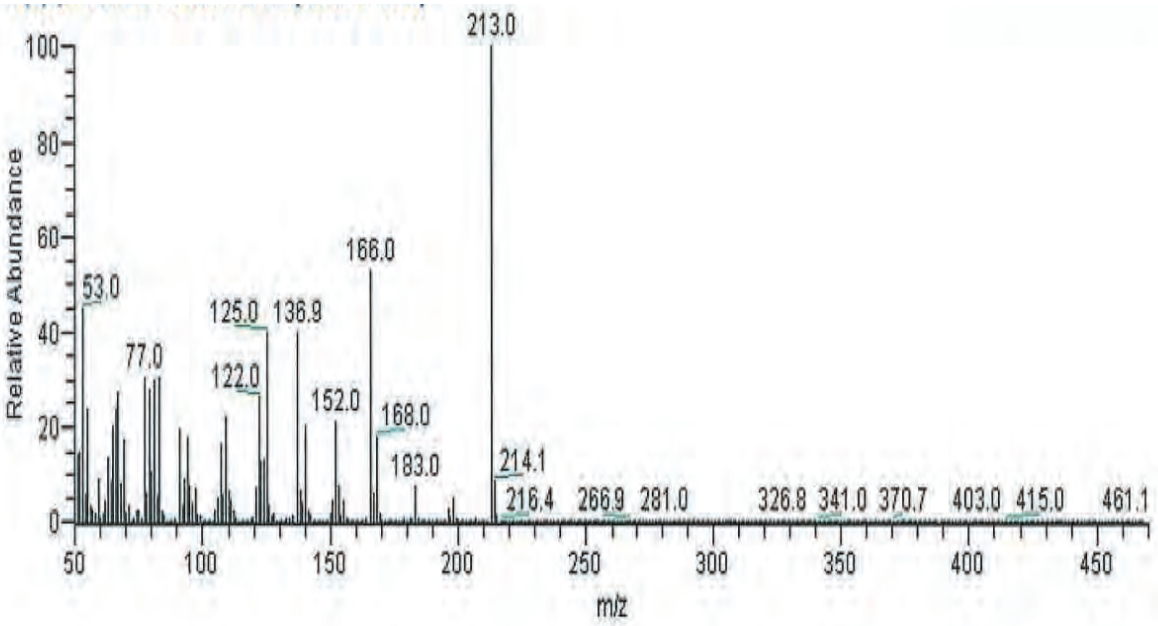
^{1}H-NMR of 2,4-Dimethoxy-3-methyl-5nitrophenol (1) in $CDCl_3$



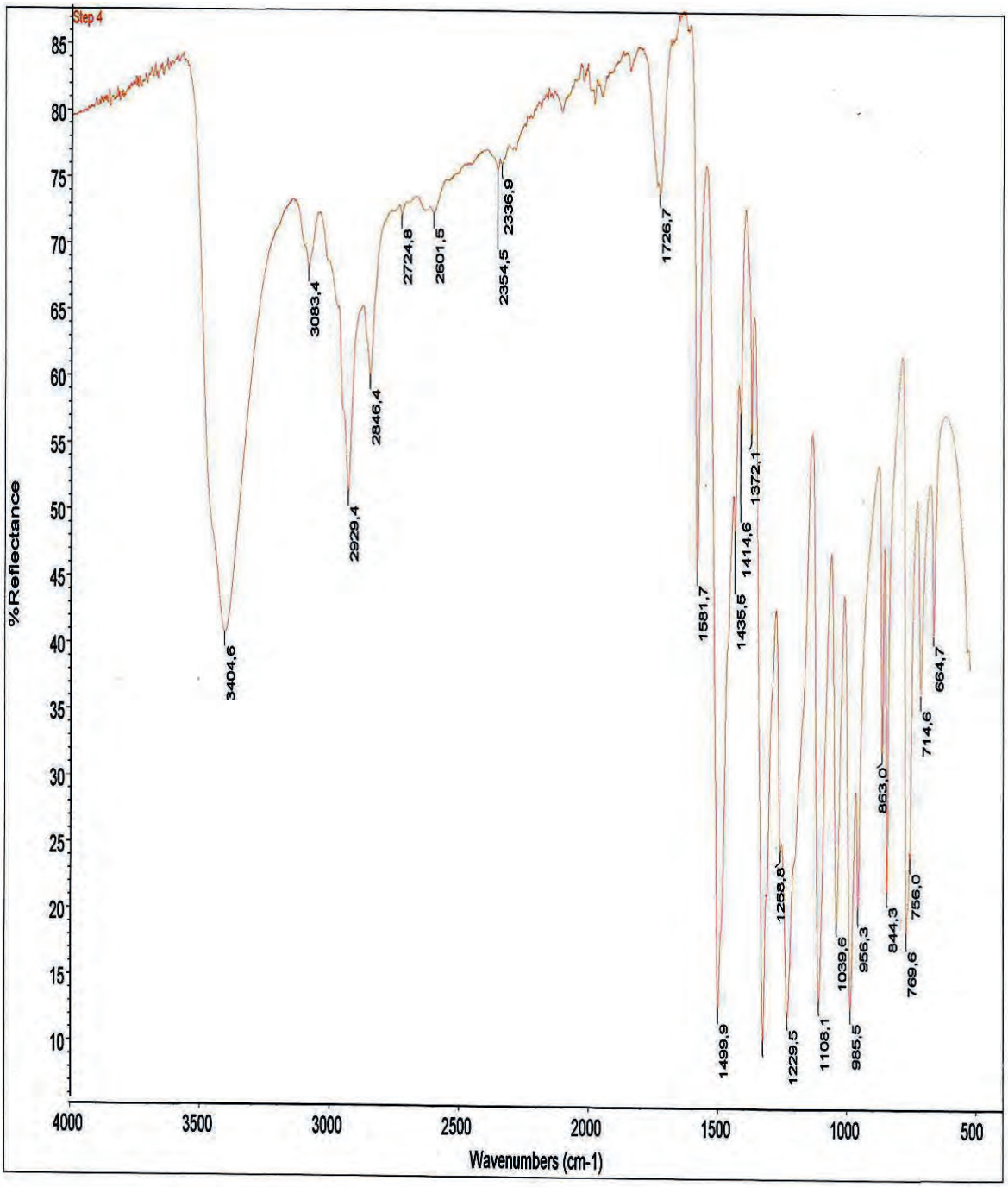
^{13}C-NMR of 2,4-Dimethoxy-3-methyl-5-nitrophenol (1) in $CDCl_3$



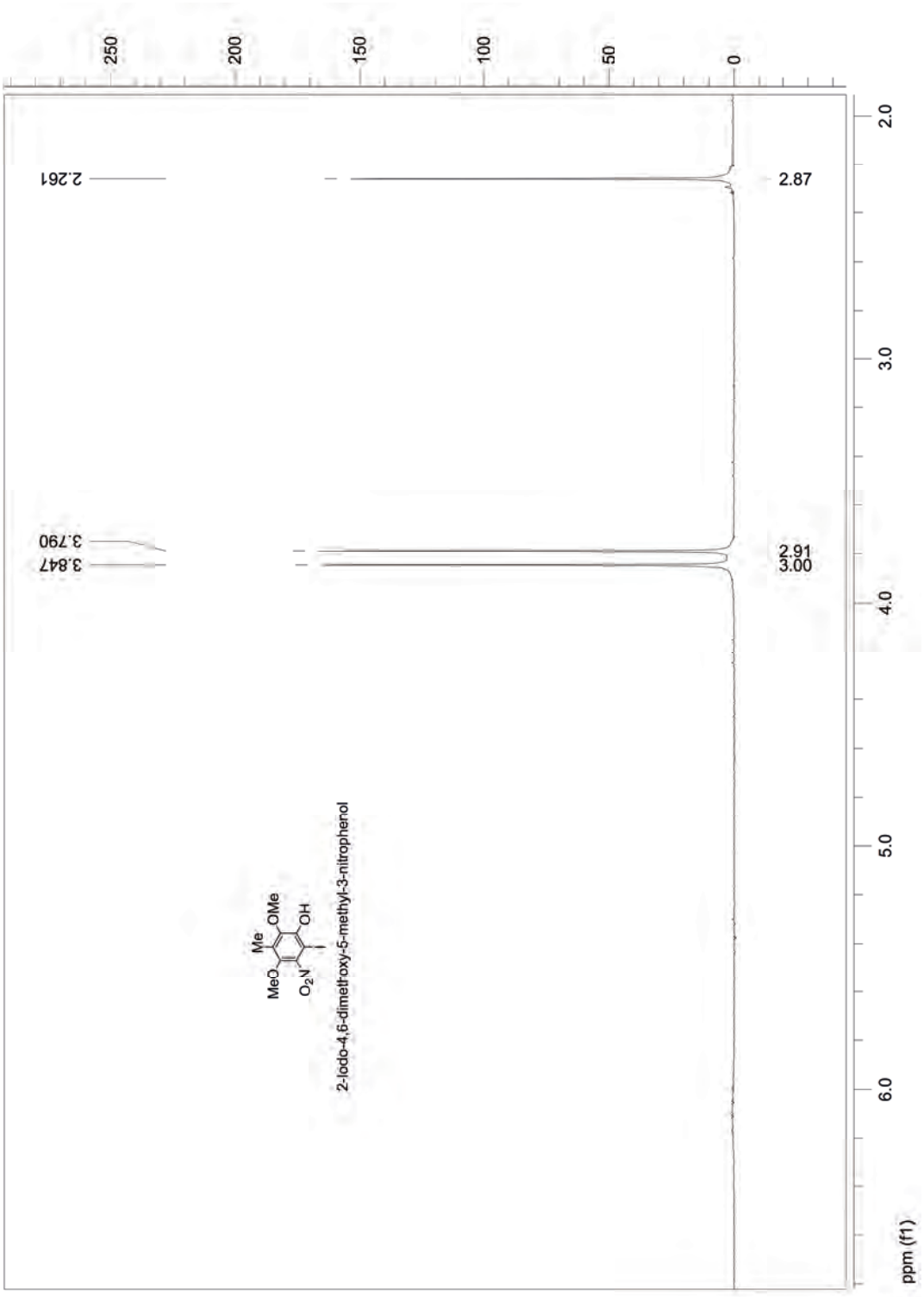
MS (EI) of 2,4-Dimethoxy-3-methyl-5nitrophenol (1)



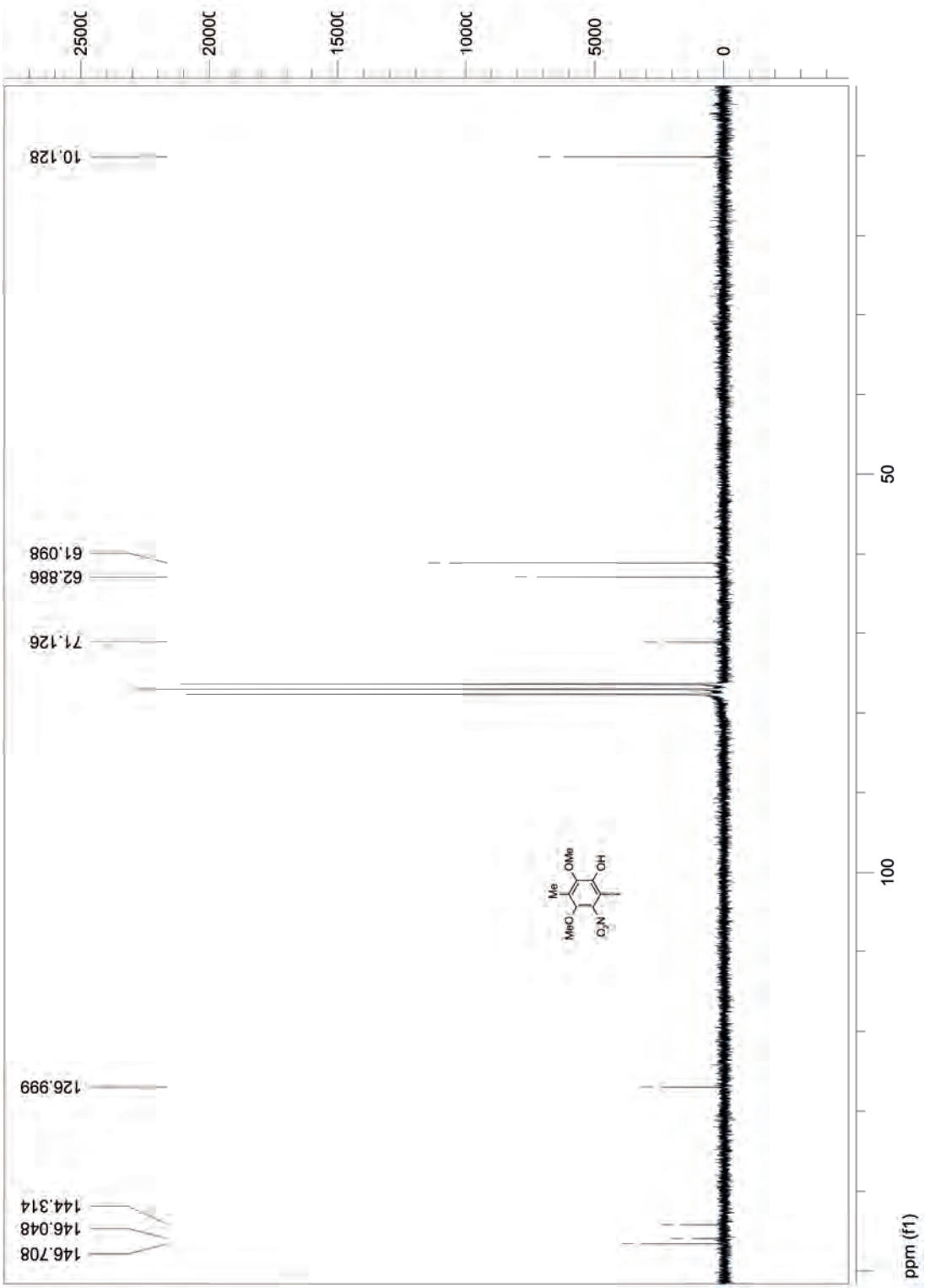
IR of 2,4-Dimethoxy-3-methyl-5nitrophenol (1)



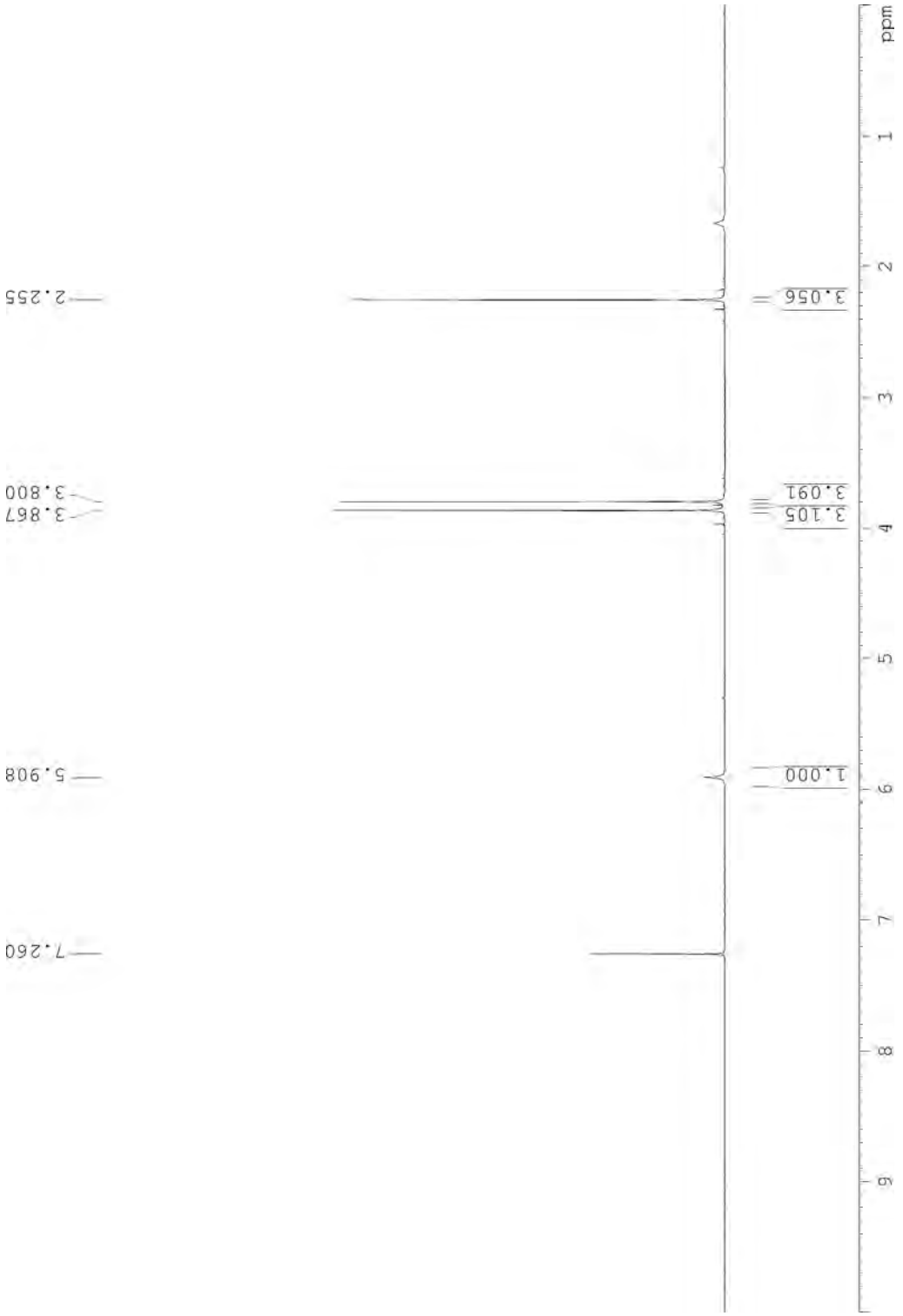
^{1}H-NMR of 2-Iodo-4,6-dimethoxy-5-methyl-3-nitrophenol (3I) in $CDCl_3$



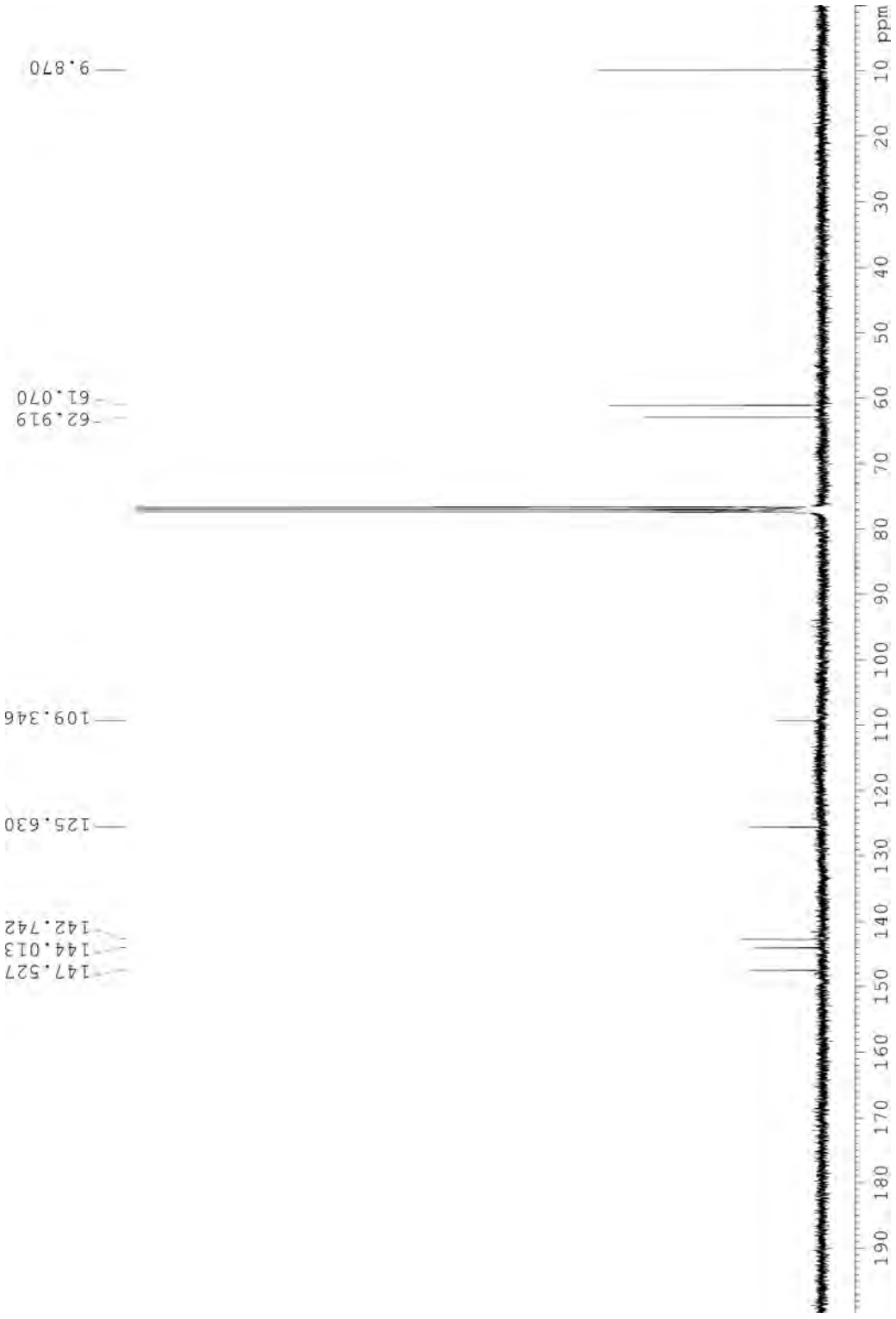
^{13}C-NMR of 2-Iodo-4,6-dimethoxy-5-methyl-3-nitrophenol (3I)



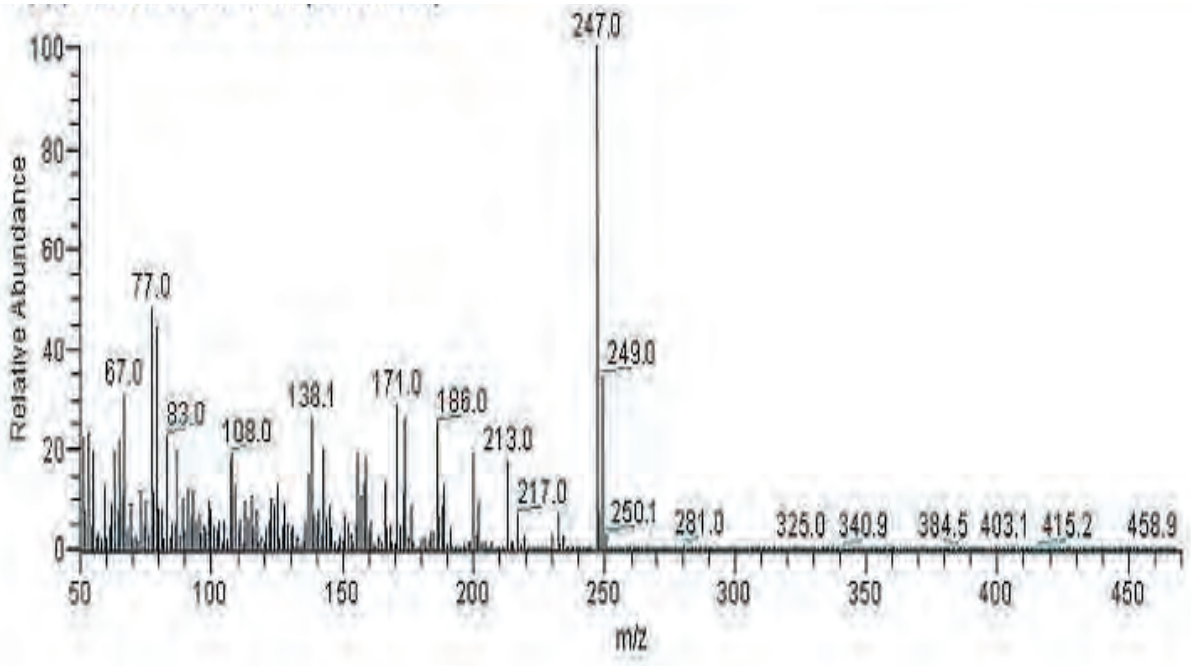
^{1}H-NMR of 2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol (3Cl) in $CDCl_3$



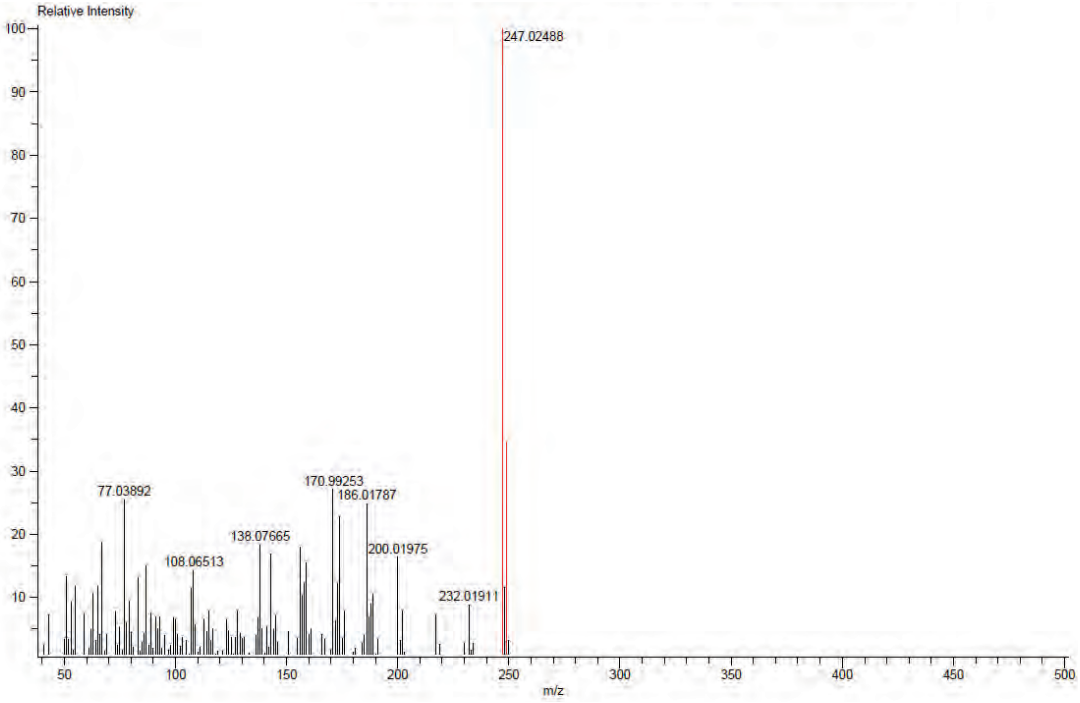
^{13}C-NMR of 2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol (3Cl) in $CDCl_3$



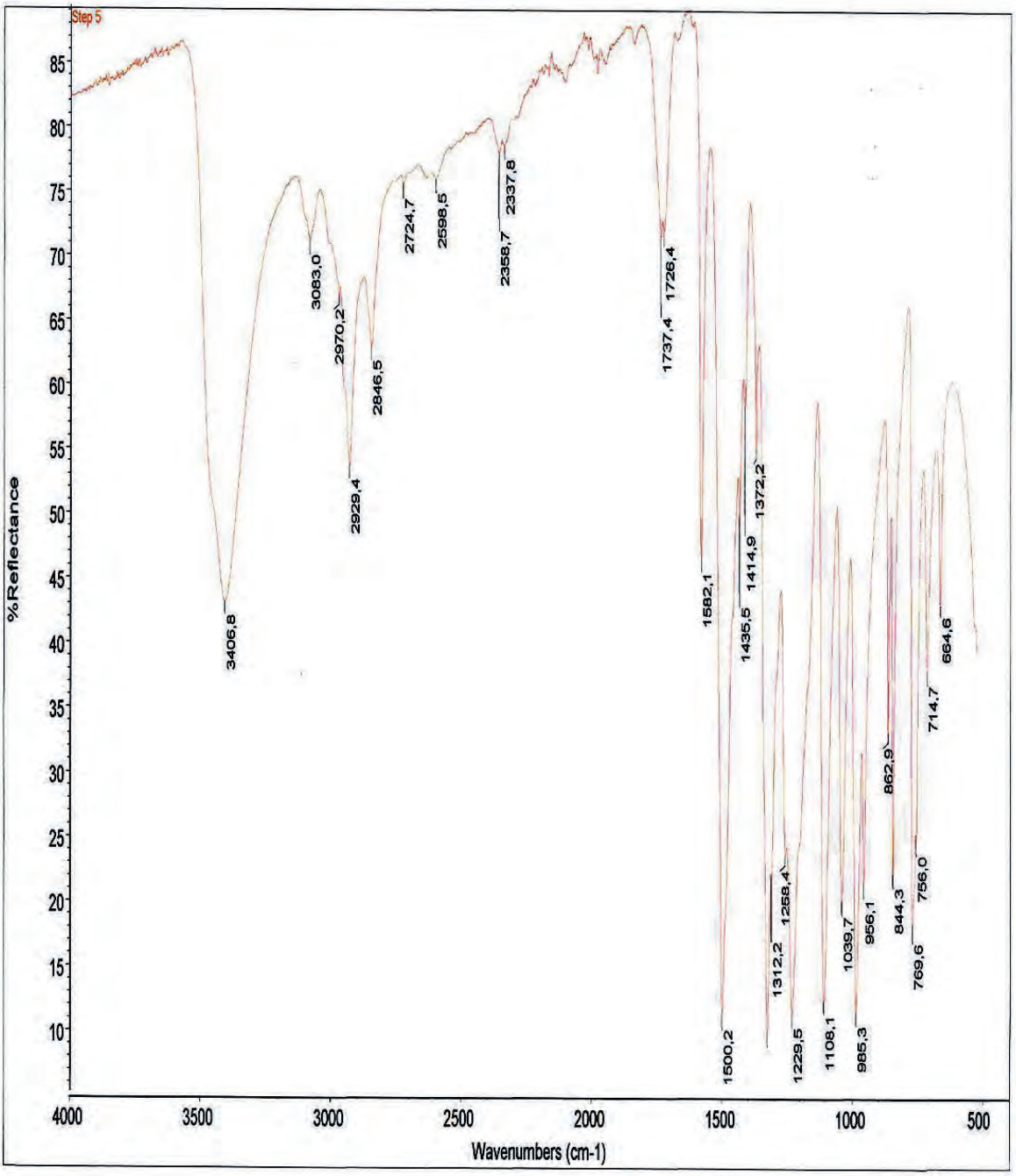
MS (EI) of 2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol (3Cl)



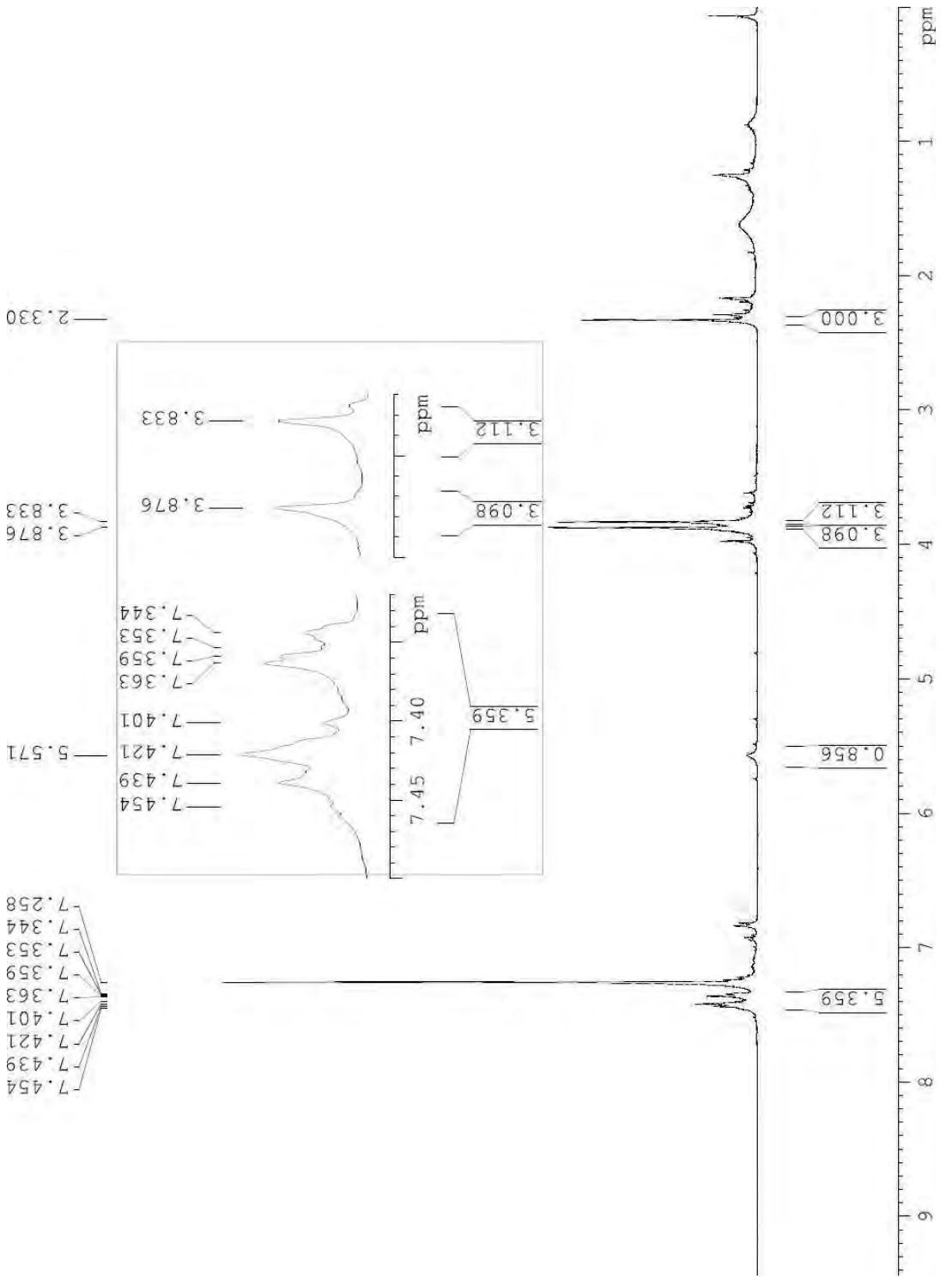
HR-MS (EI) of 2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol (3Cl)



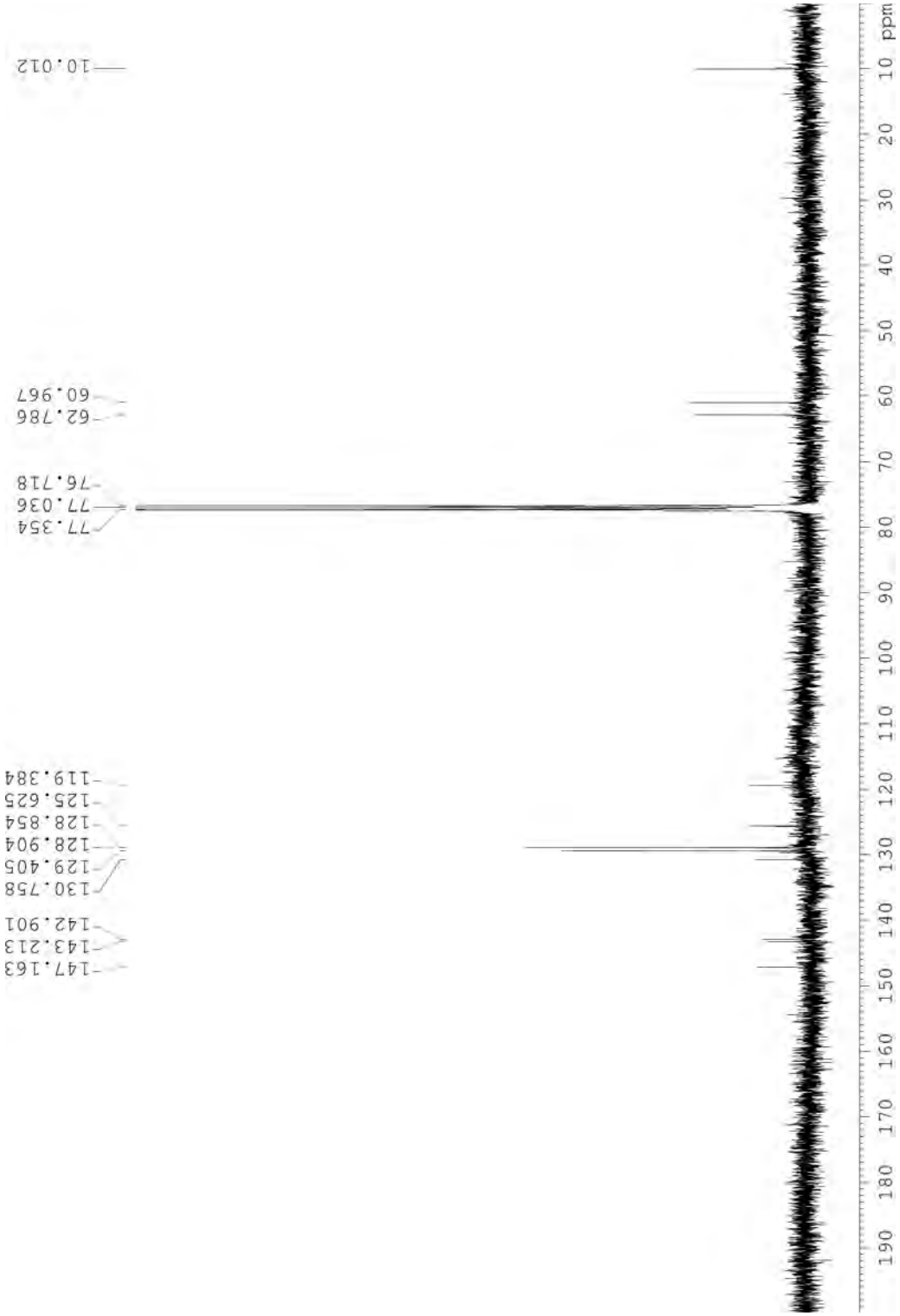
IR of 2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol (3Cl)



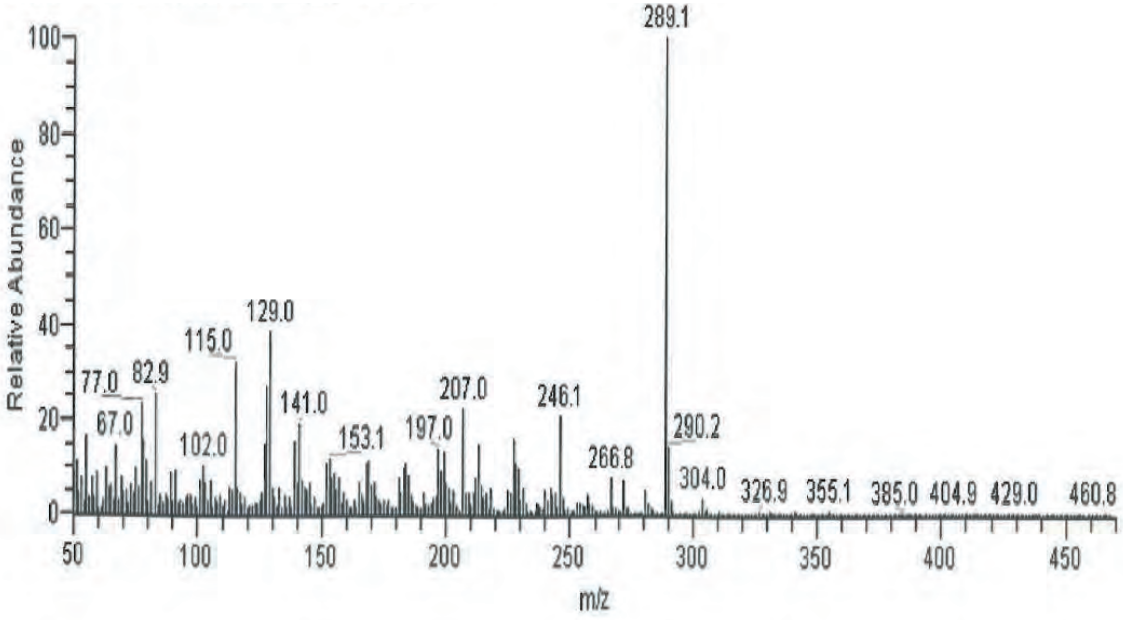
^{1}H-NMR of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (5) in $CDCl_3$



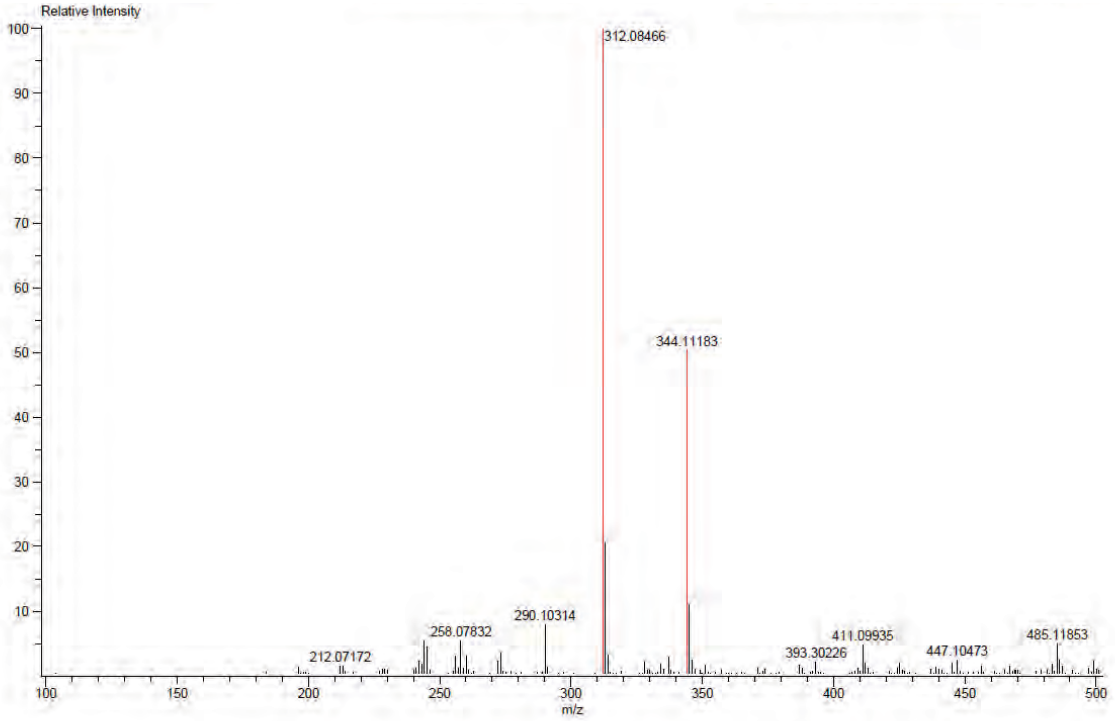
^{13}C-NMR of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (5) in $CDCl_3$



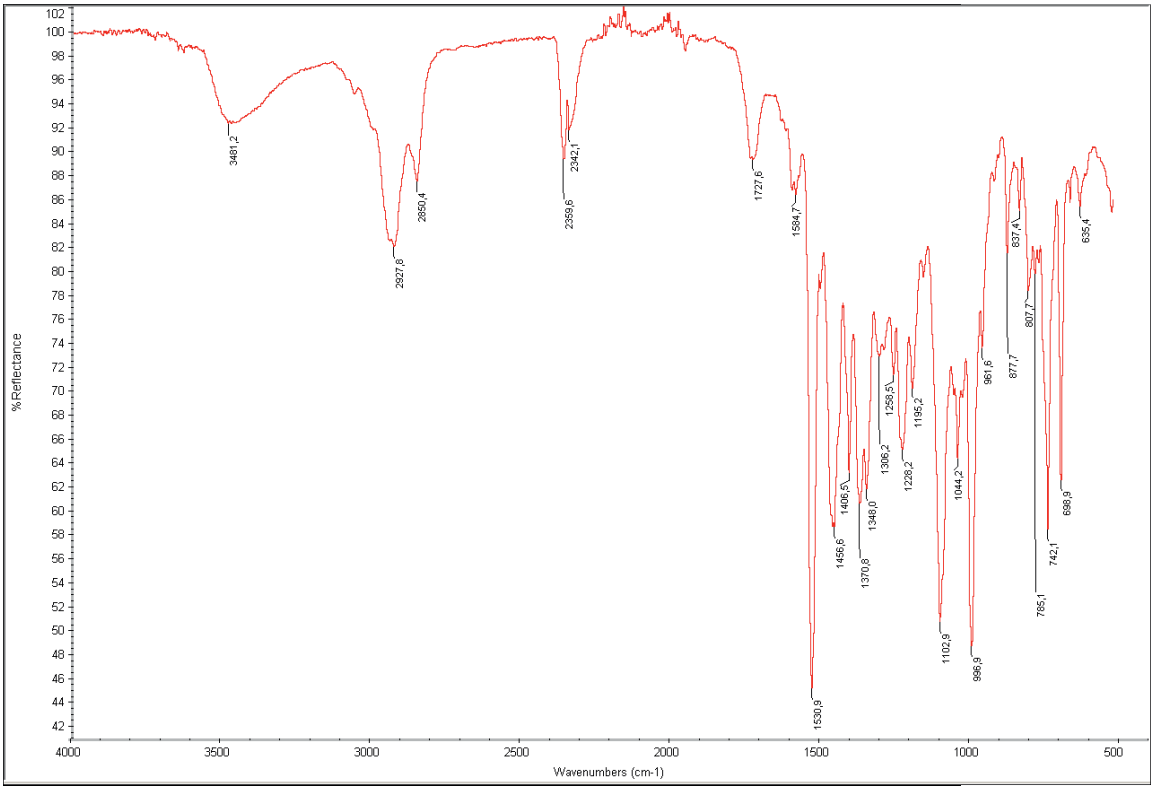
MS (EI) of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (5) in $CDCl_3$



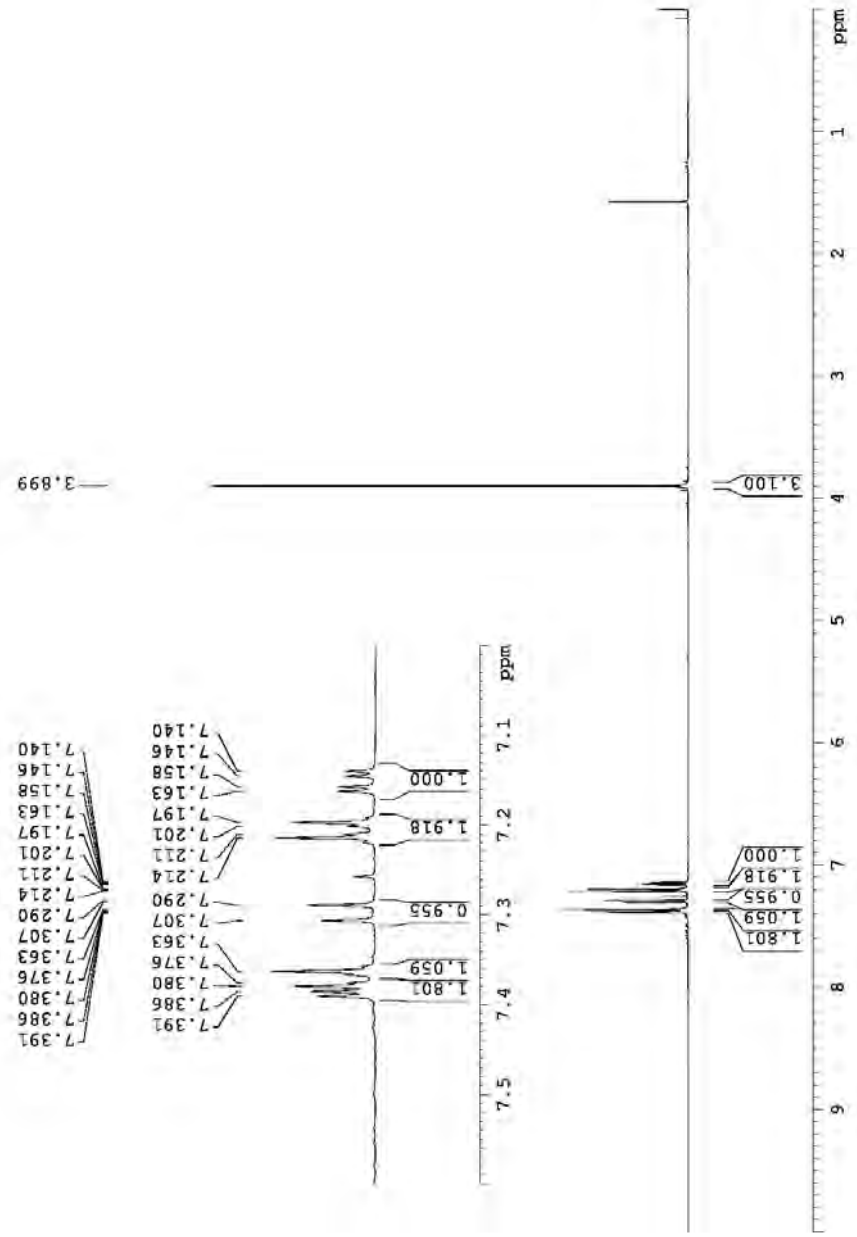
HR-MS of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (5)



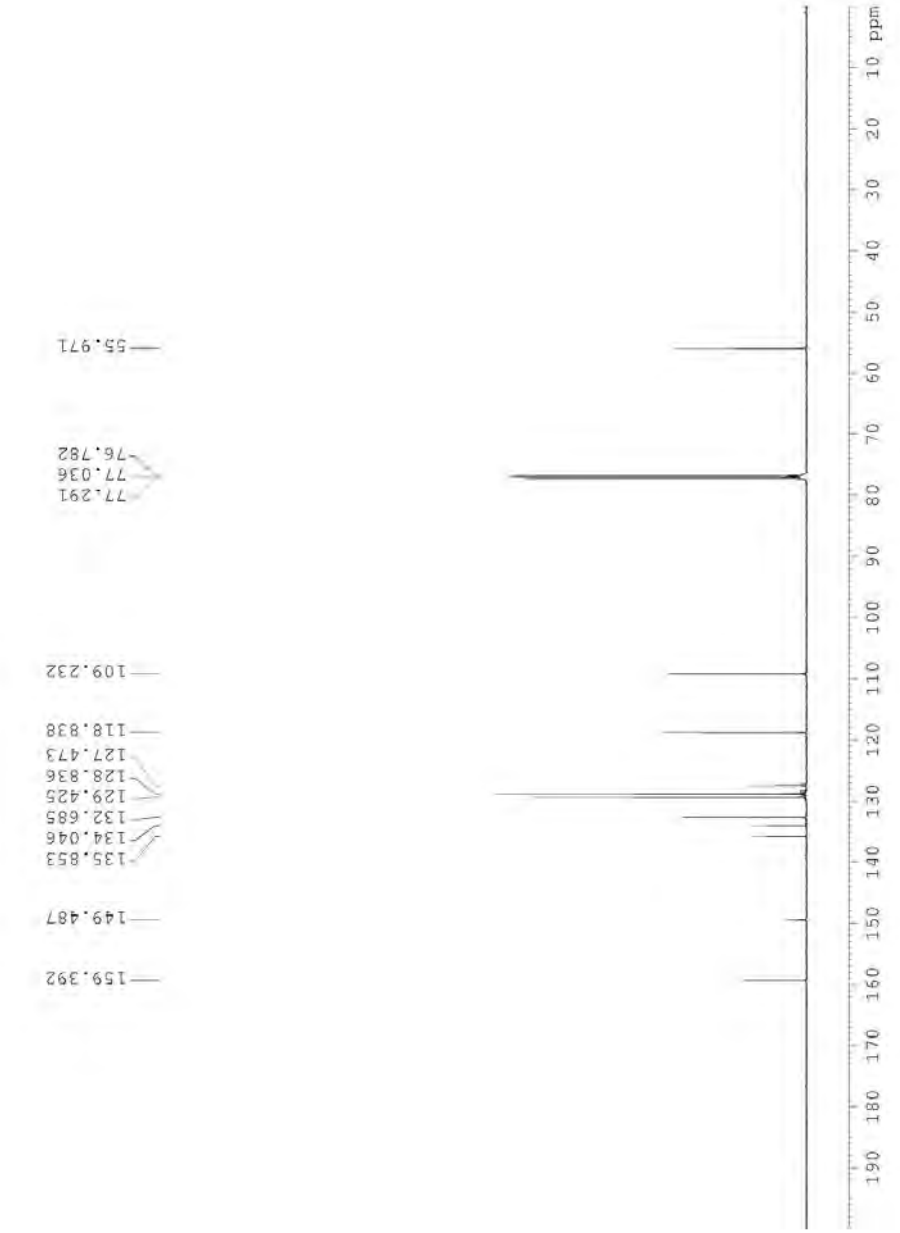
IR of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (5)



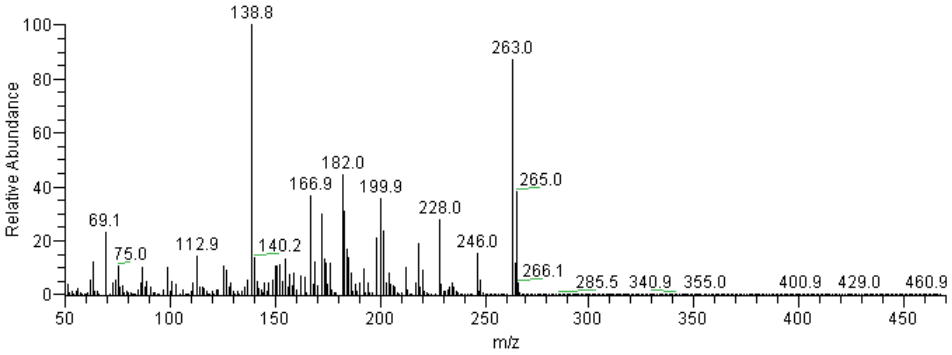
^{1}H-NMR of 4'-chloro-4-methoxy-2-nitro-1,1'-biphenyl (5r) in $CDCl_3$



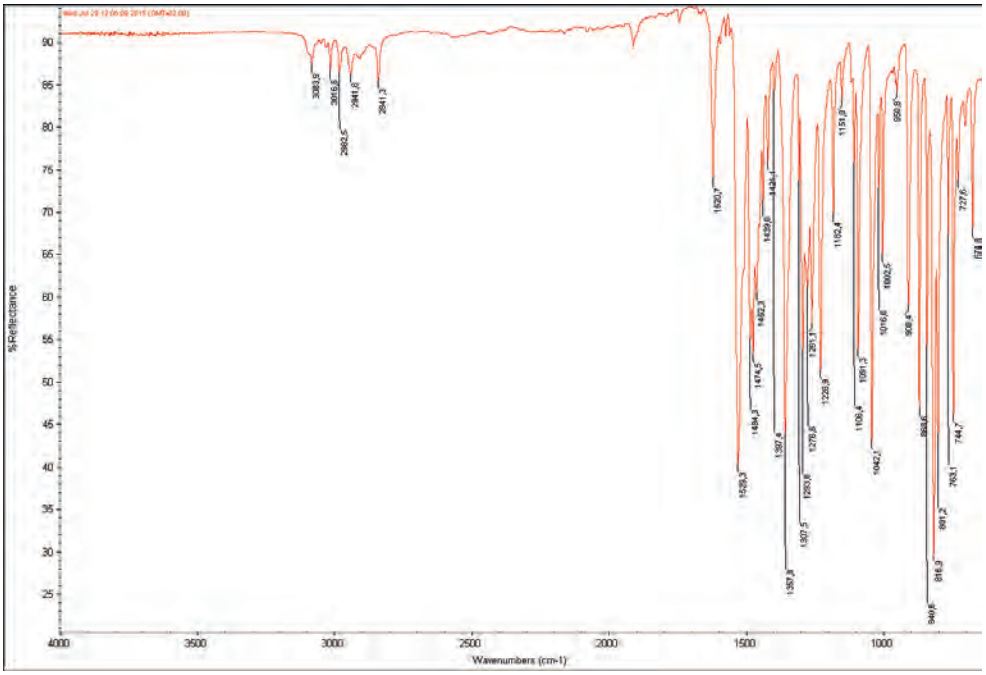
^{13}C-NMR of 4'-chloro-4-methoxy-2-nitro-1,1'-biphenyl (5r) in $CDCl_3$



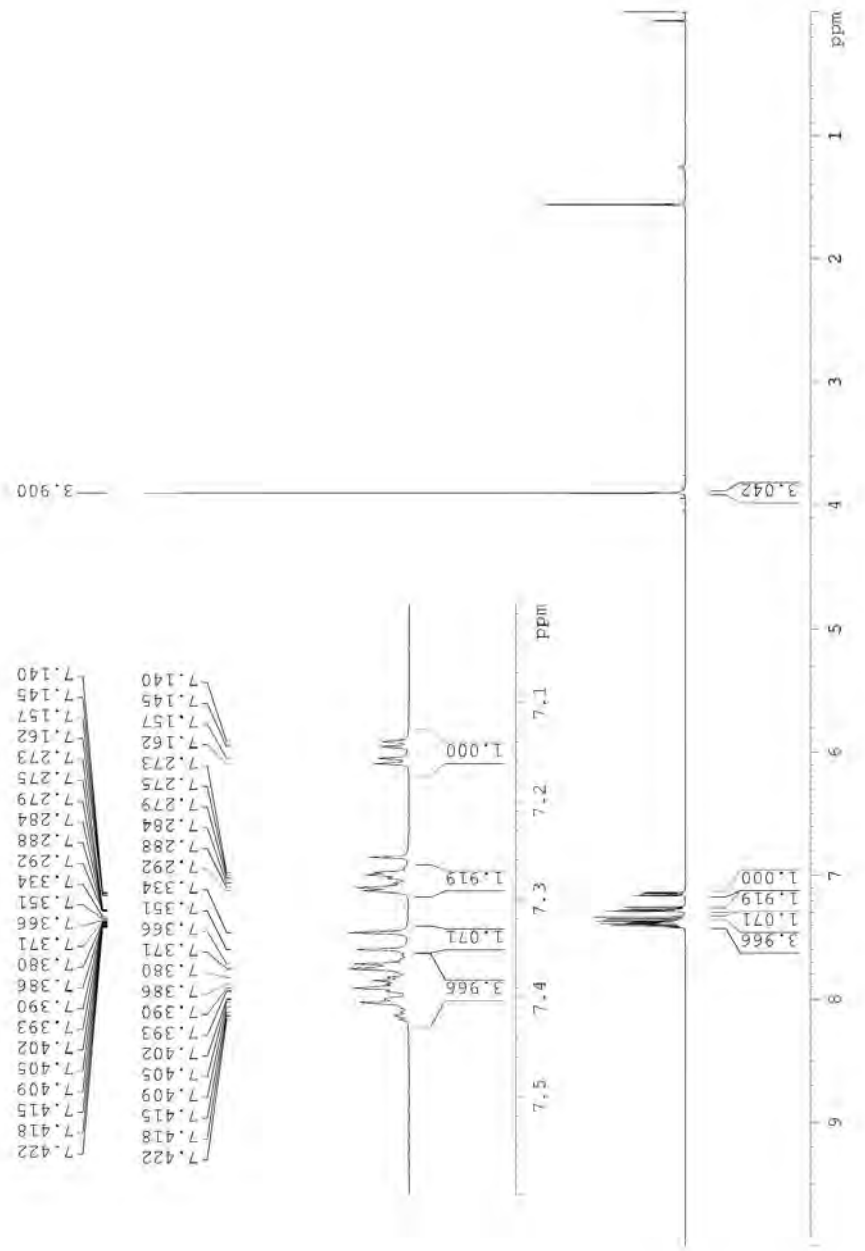
MS (EI) spectrum of 4'-chloro-4-methoxy-2-nitro-1,1'-biphenyl (5r)



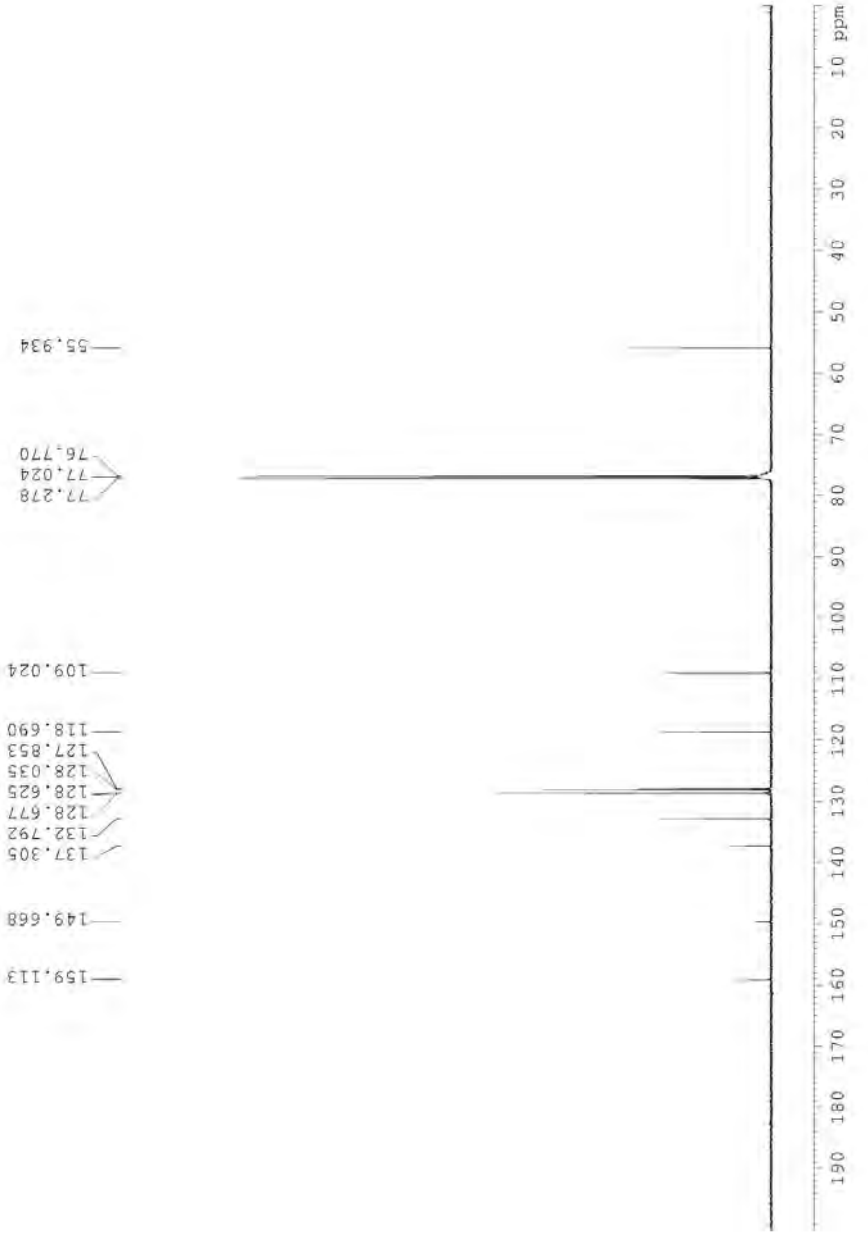
IR spectrum of 4'-chloro-4-methoxy-2-nitro-1,1'-biphenyl (5r)



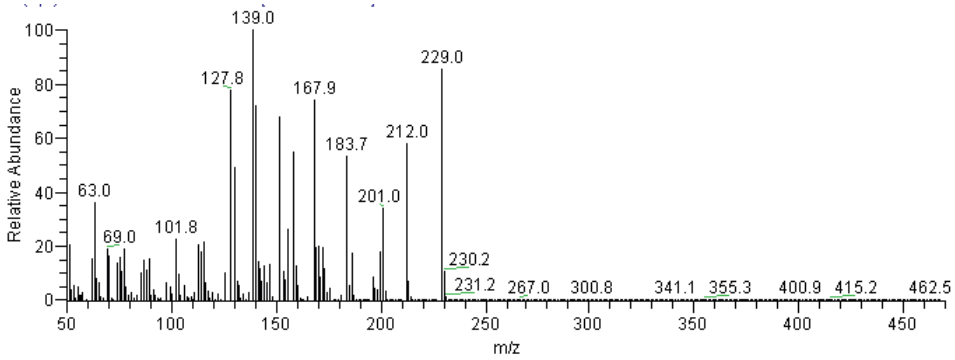
^{1}H-NMR spectrum of 4-methoxy-2-nitro-1,1'-biphenyl (5s) in $CDCl_3$



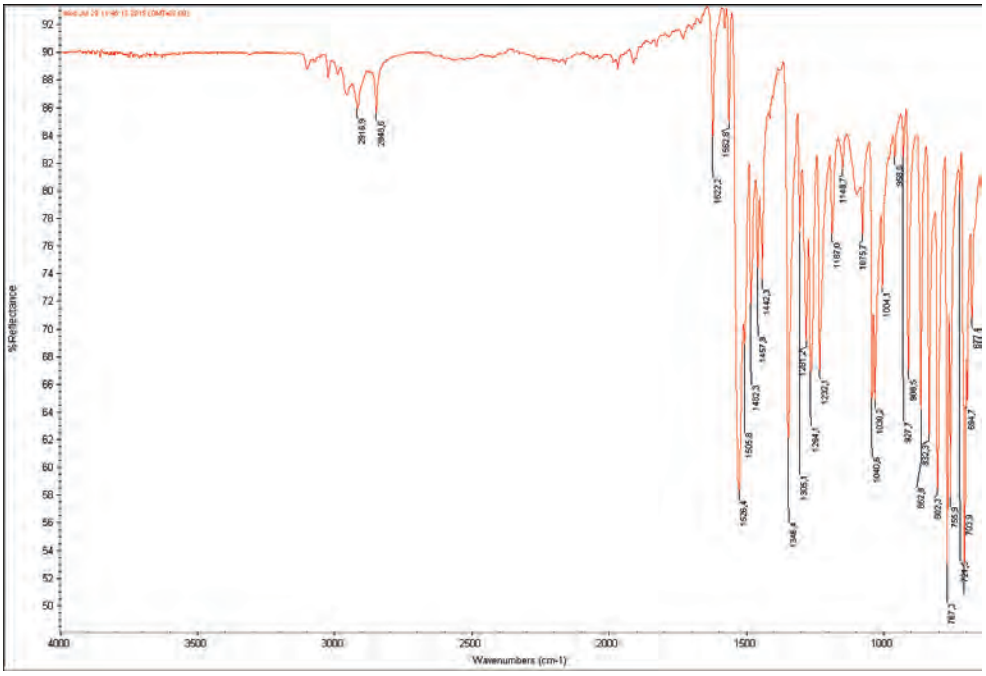
^{13}C-NMR spectrum of 4-methoxy-2-nitro-1,1'-biphenyl (5s) in $CDCl_3$



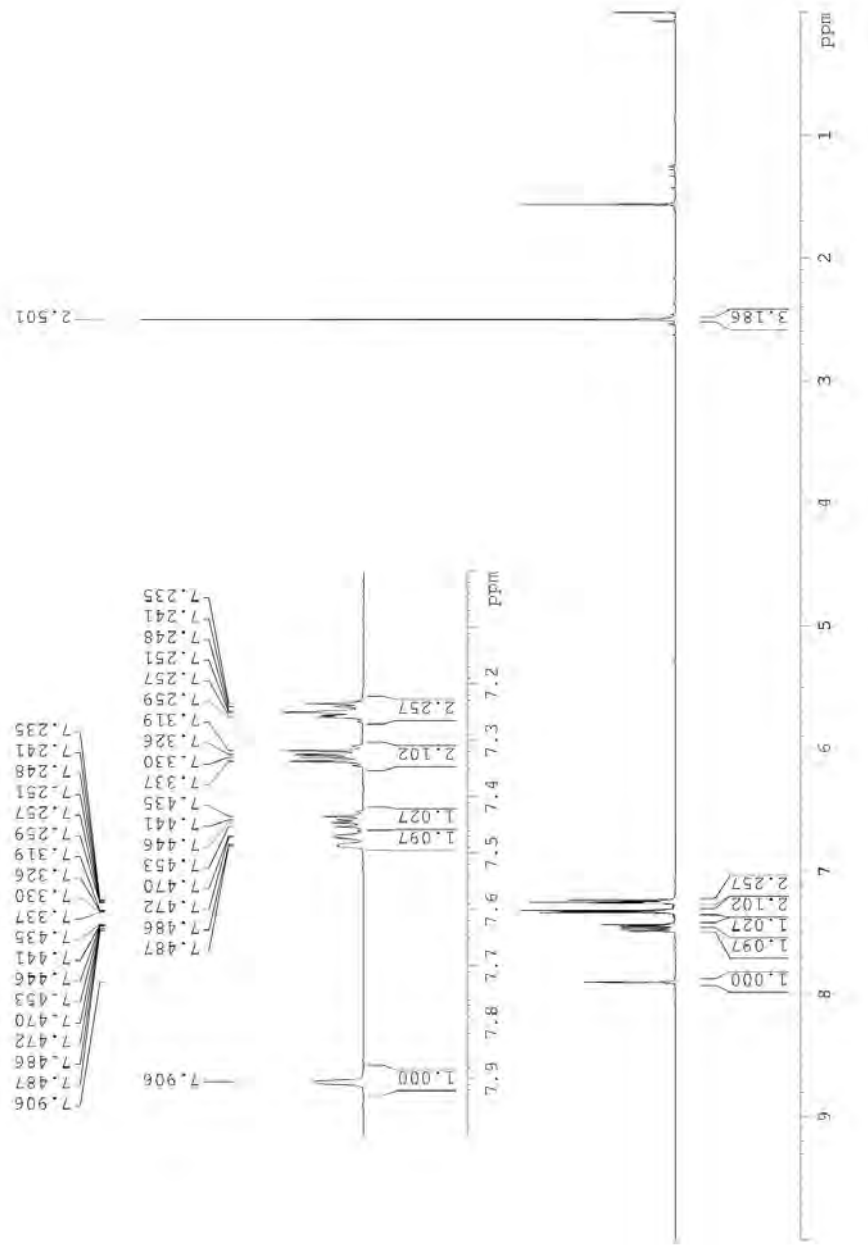
MS (EI) spectrum of 4-methoxy-2-nitro-1,1'-biphenyl (5s)



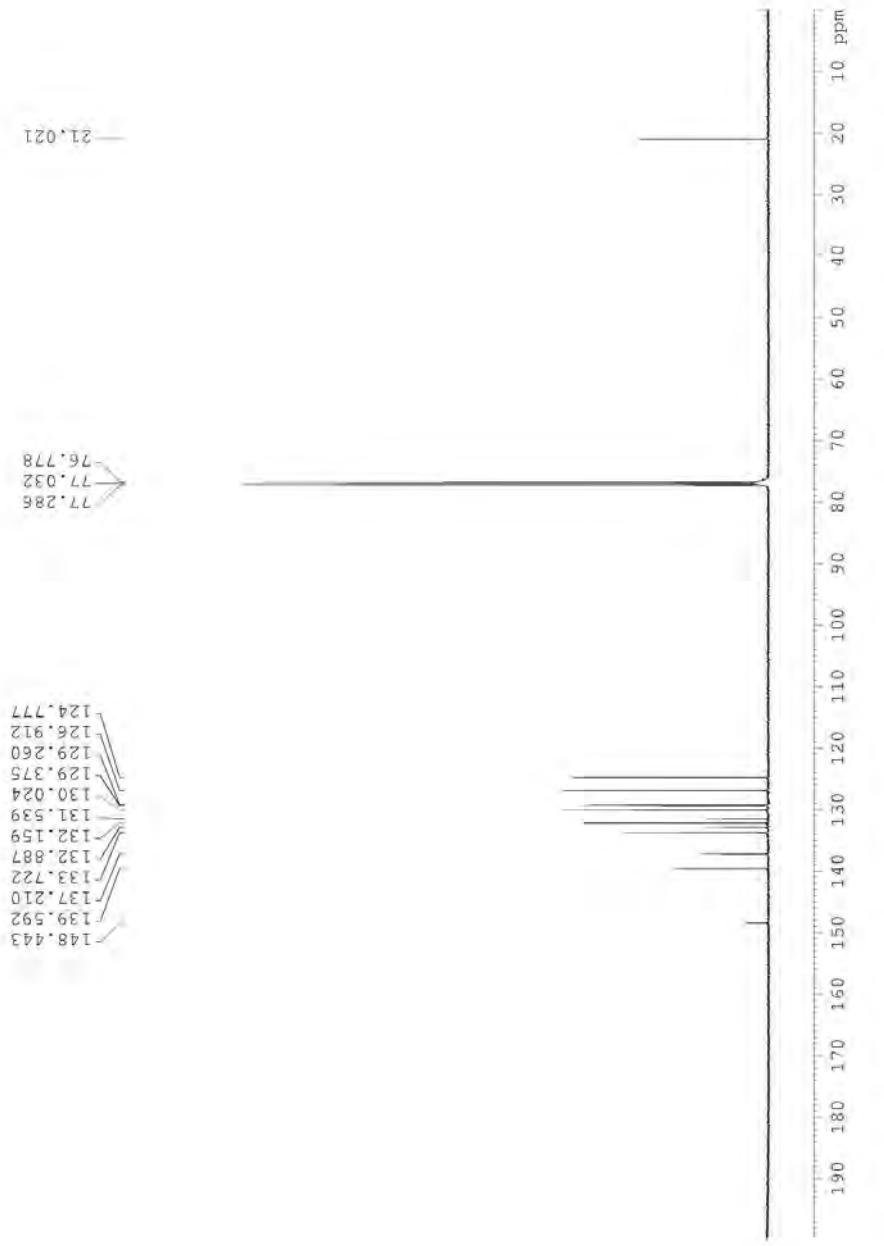
IR spectrum of 4-methoxy-2-nitro-1,1'-biphenyl (5s)



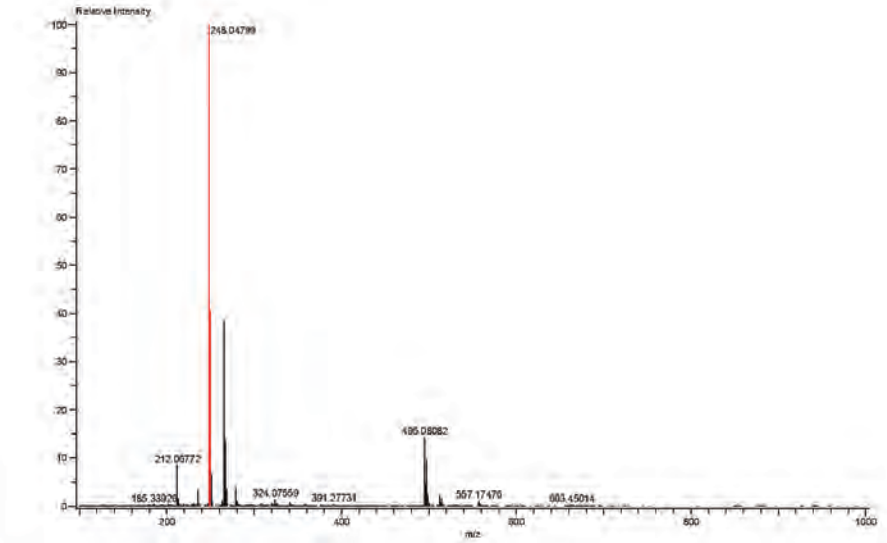
^{1}H-NMR of 2'-chloro-4-methyl-2-nitro-1,1'-biphenyl (5t) in $CDCl_3$



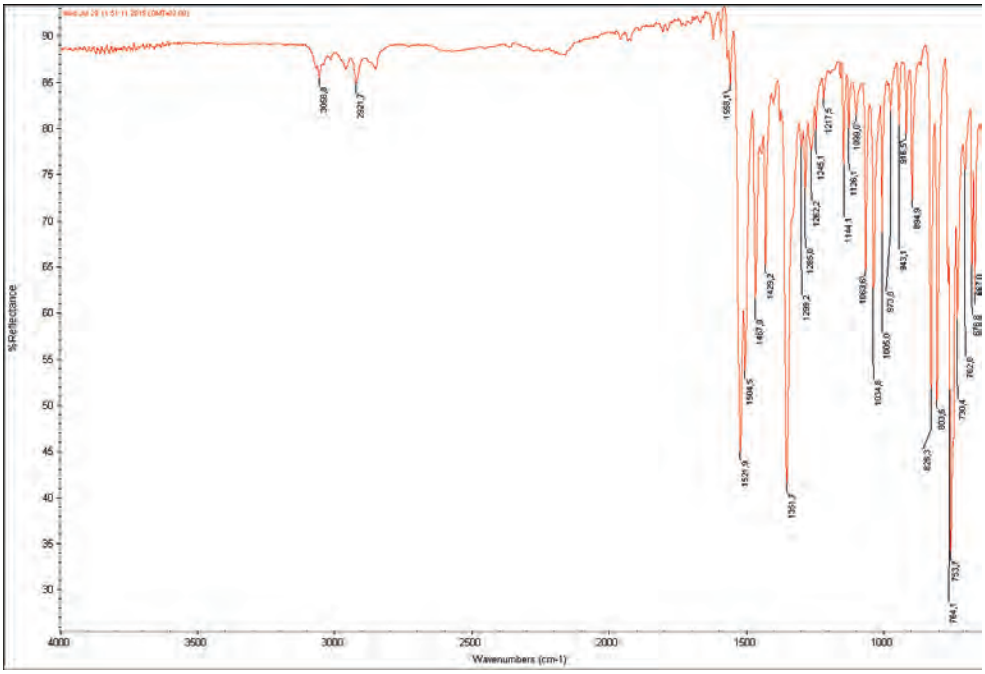
^{13}C-NMR of 2'-chloro-4-methyl-2-nitro-1,1'-biphenyl (5t) in $CDCl_3$



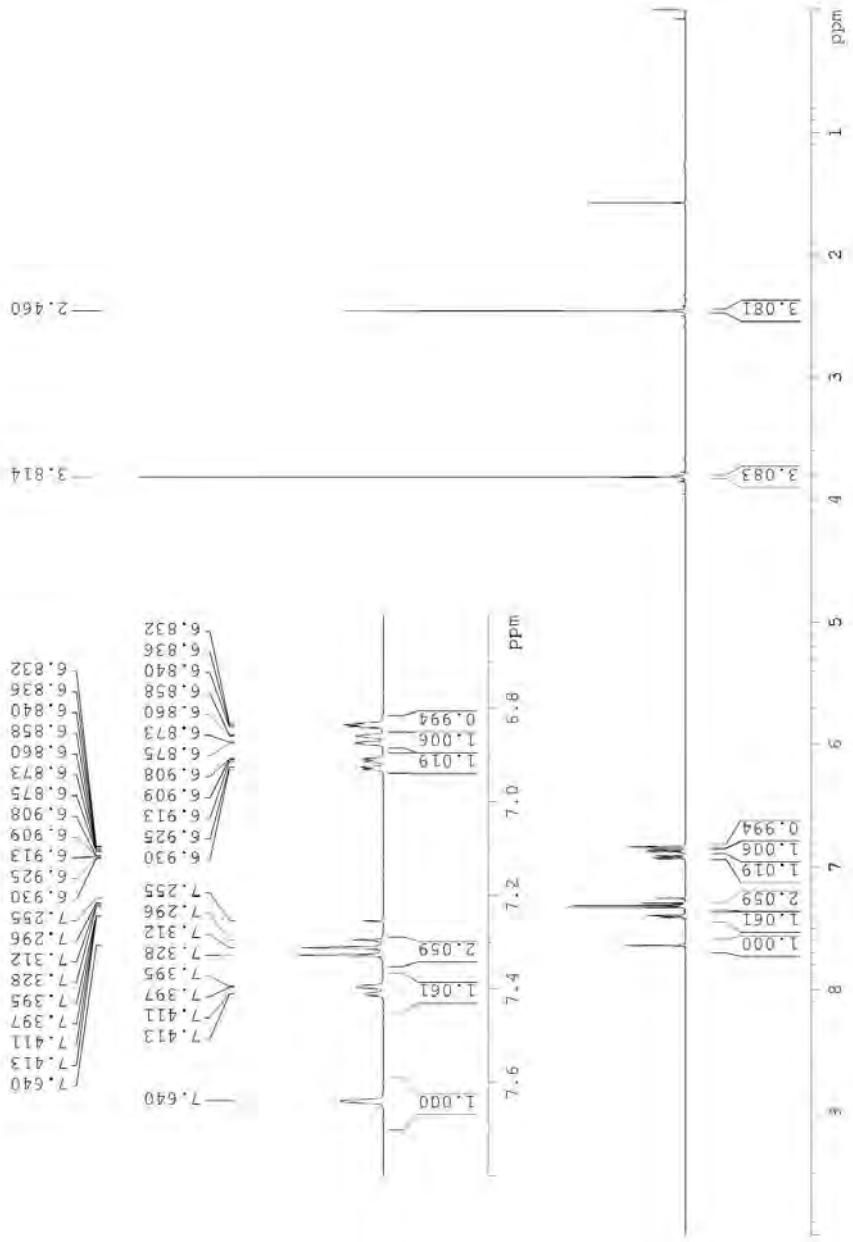
HR-MS of 2'-chloro-4-methyl-2-nitro-1,1'-biphenyl (5t)



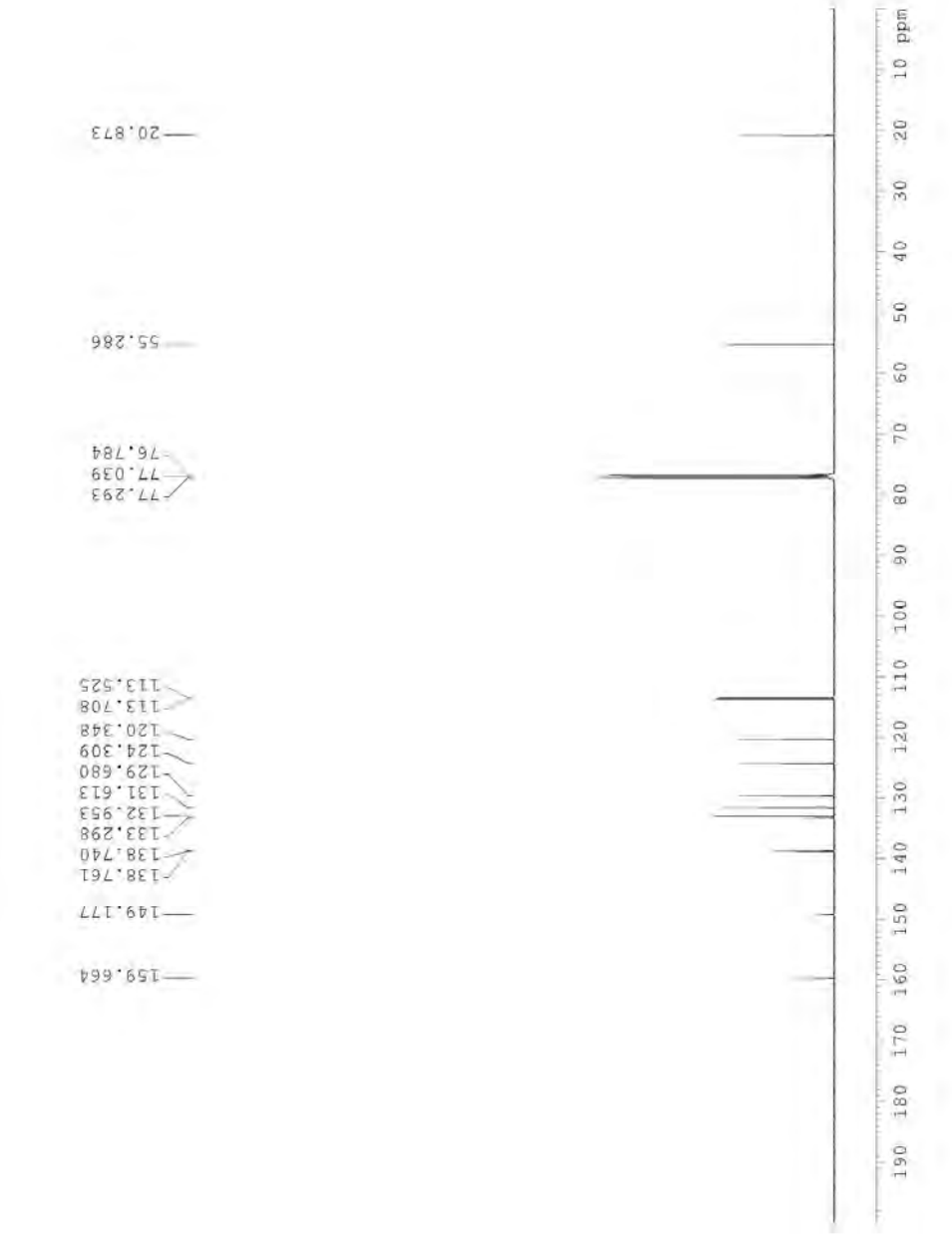
IR of 2'-chloro-4-methyl-2-nitro-1,1'-biphenyl (5t)



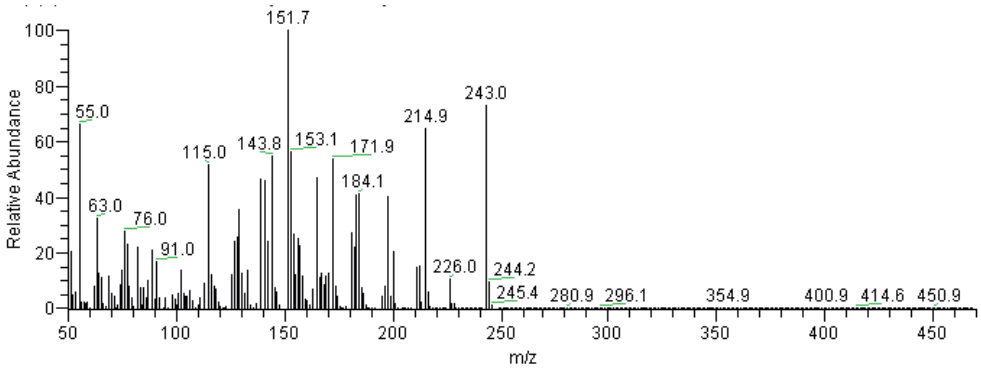
^{1}H-NMR of 3'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5u) in $CDCl_3$



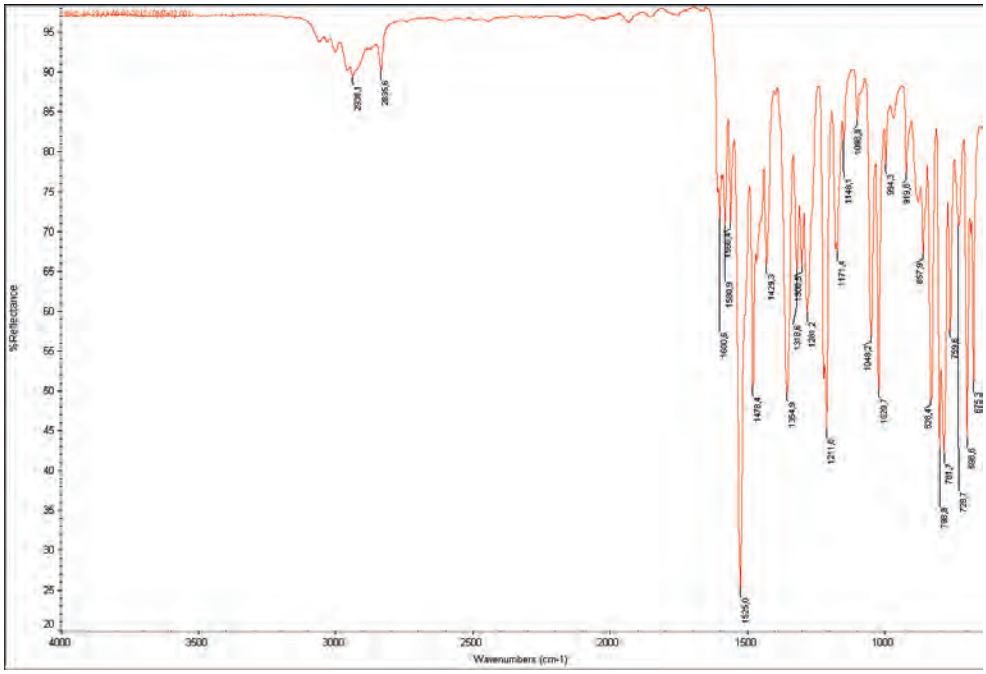
^{13}C-NMR of 3'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5u) in $CDCl_3$



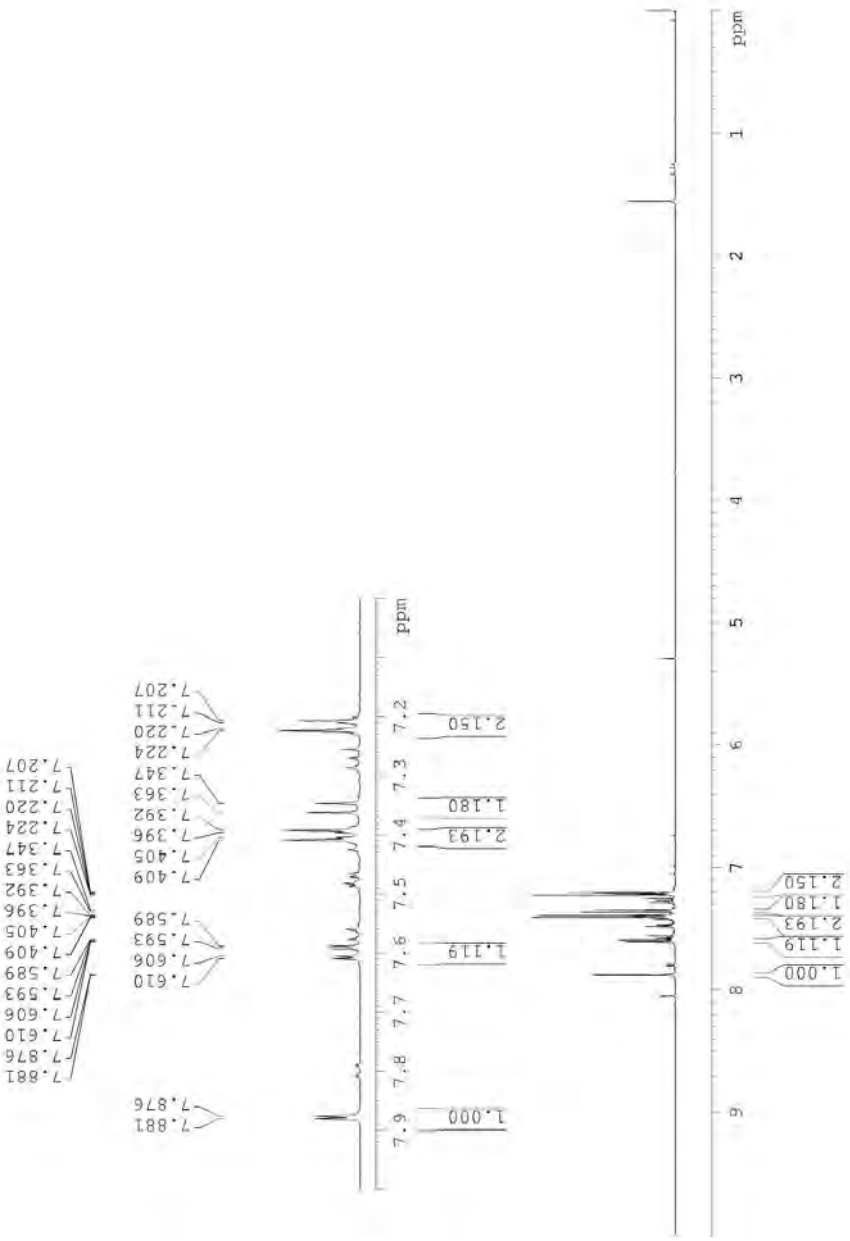
MS (EI) of 3'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5u)



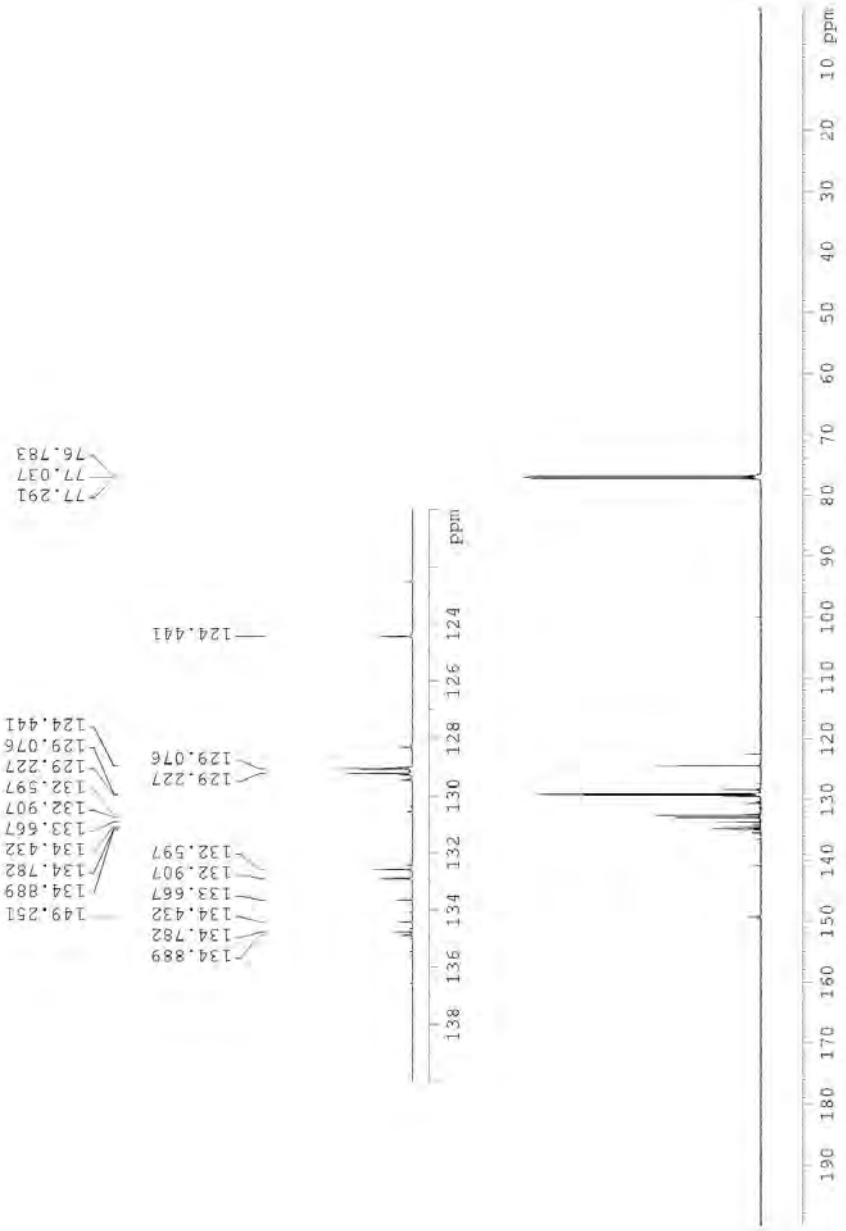
IR spectrum of 3'-methoxy-4-methyl-2-nitro-1,1'-biphenyl (5u)



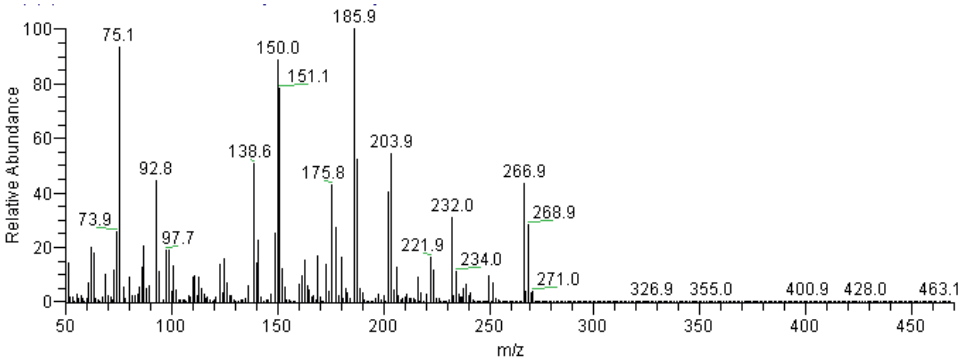
^{1}H-NMR of 4,4'-dichloro-2-nitro-1,1'-biphenyl (5v) in $CDCl_3$



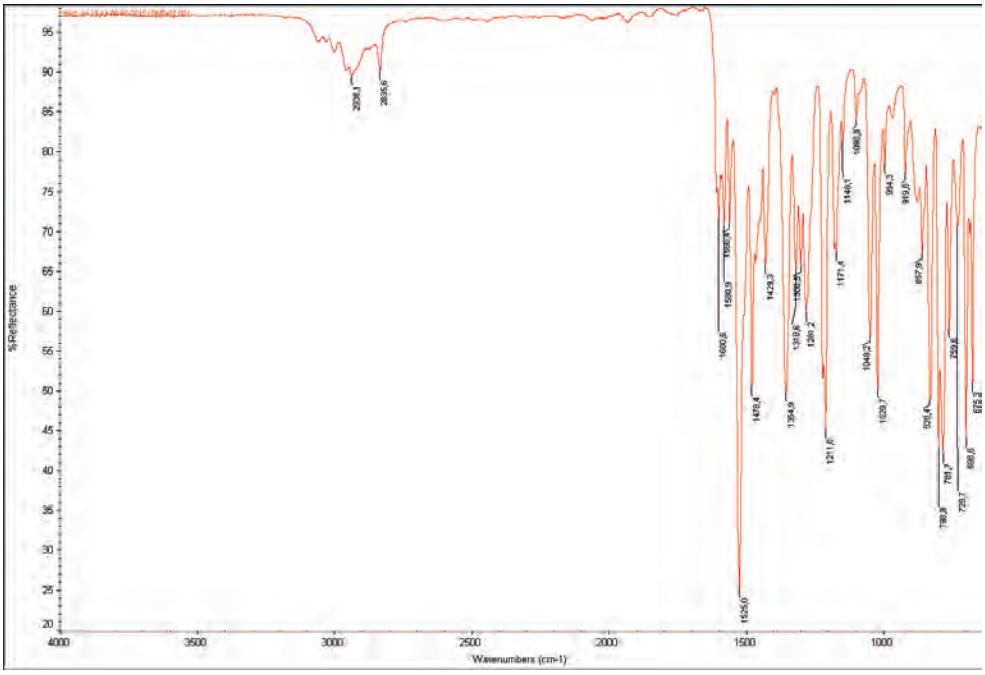
^{13}C-NMR of 4,4'-dichloro-2-nitro-1,1'-biphenyl (5v) in $CDCl_3$



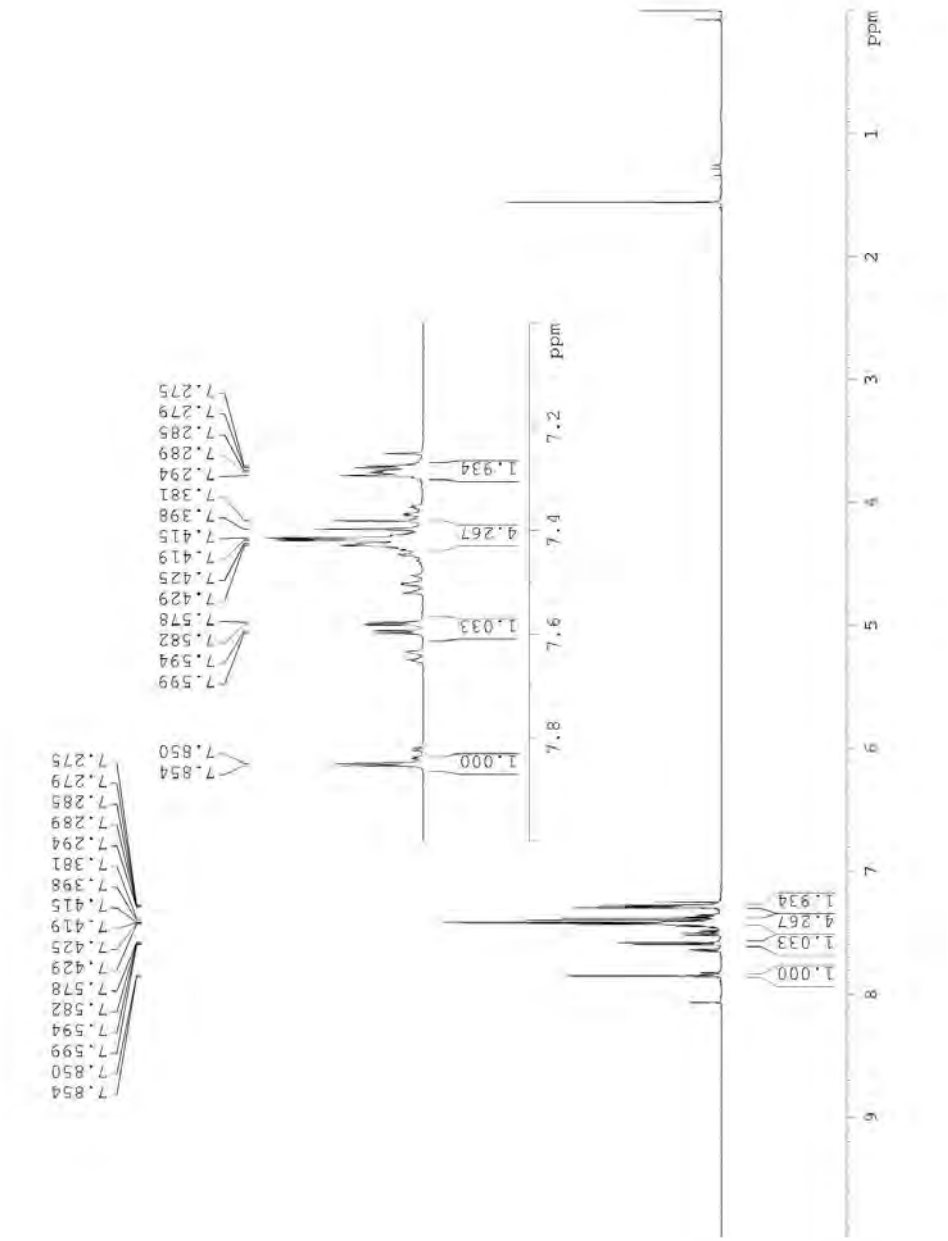
MS (EI) of 4,4'-dichloro-2-nitro-1,1'-biphenyl (5v)



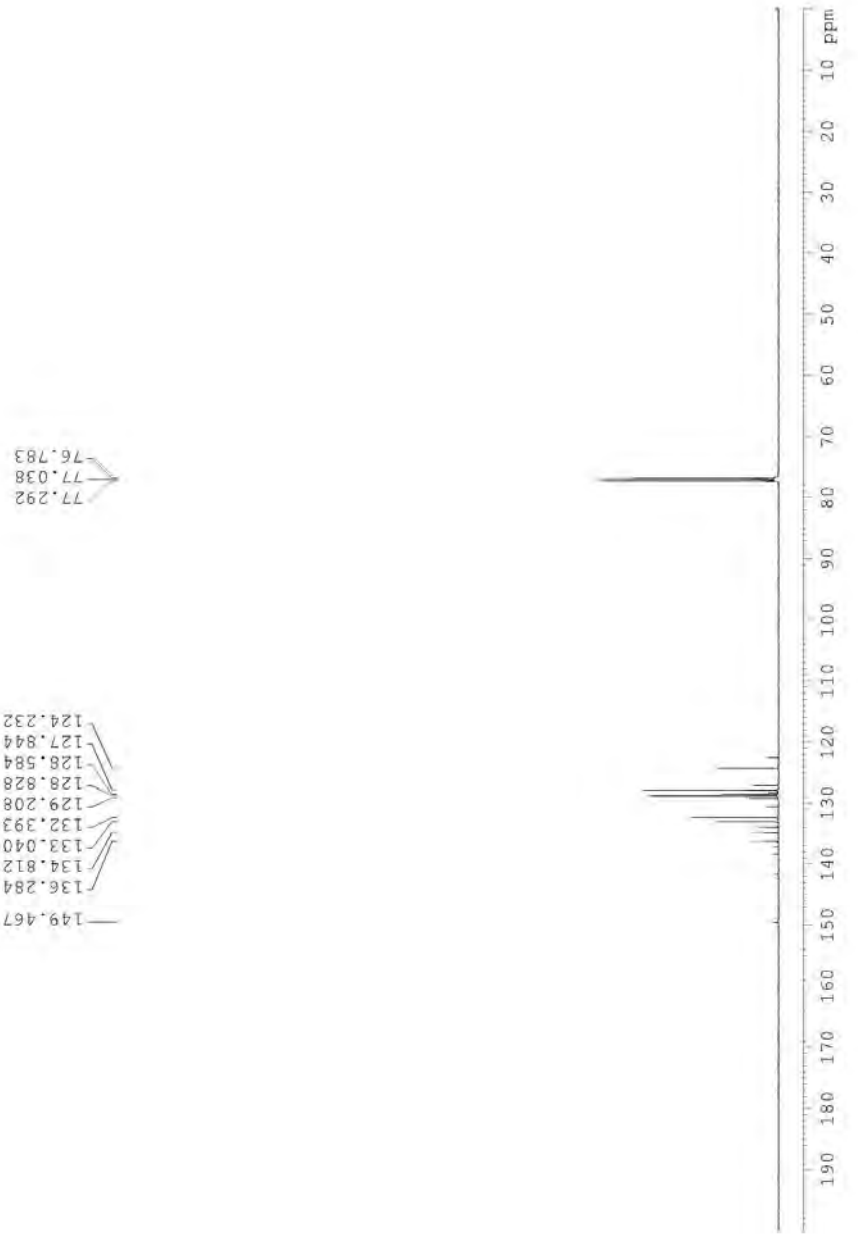
IR spectrum of 4,4'-dichloro-2-nitro-1,1'-biphenyl (5v)



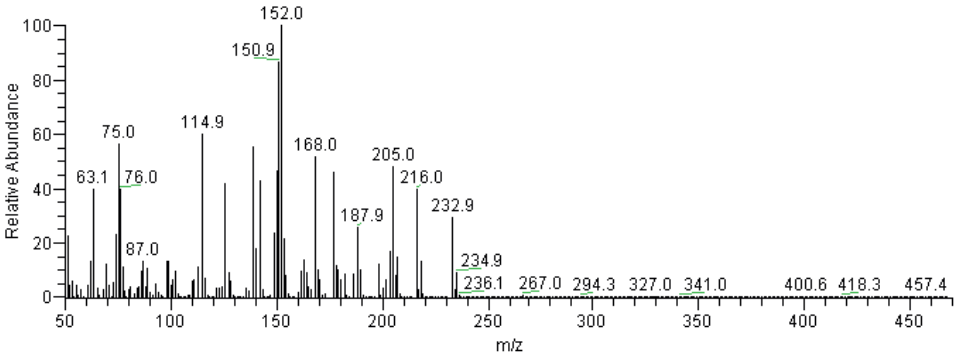
^{1}H-NMR spectrum of 4-chloro-2-nitro-1,1'-biphenyl (5w) in $CDCl_3$



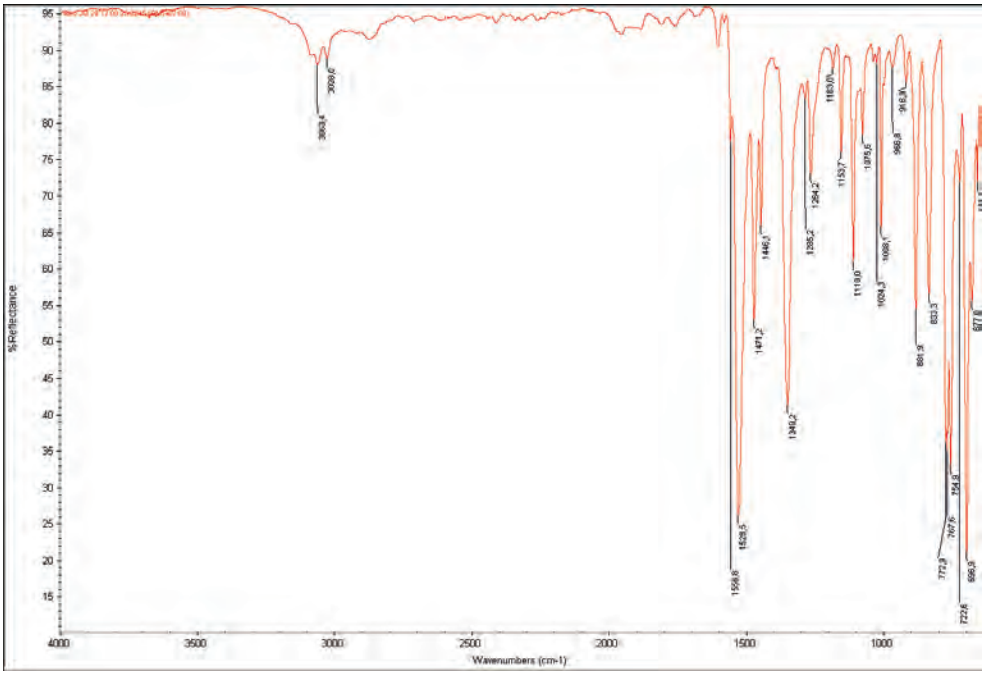
^{13}C-NMR of 4-chloro-2-nitro-1,1'-biphenyl (5w) in $CDCl_3$



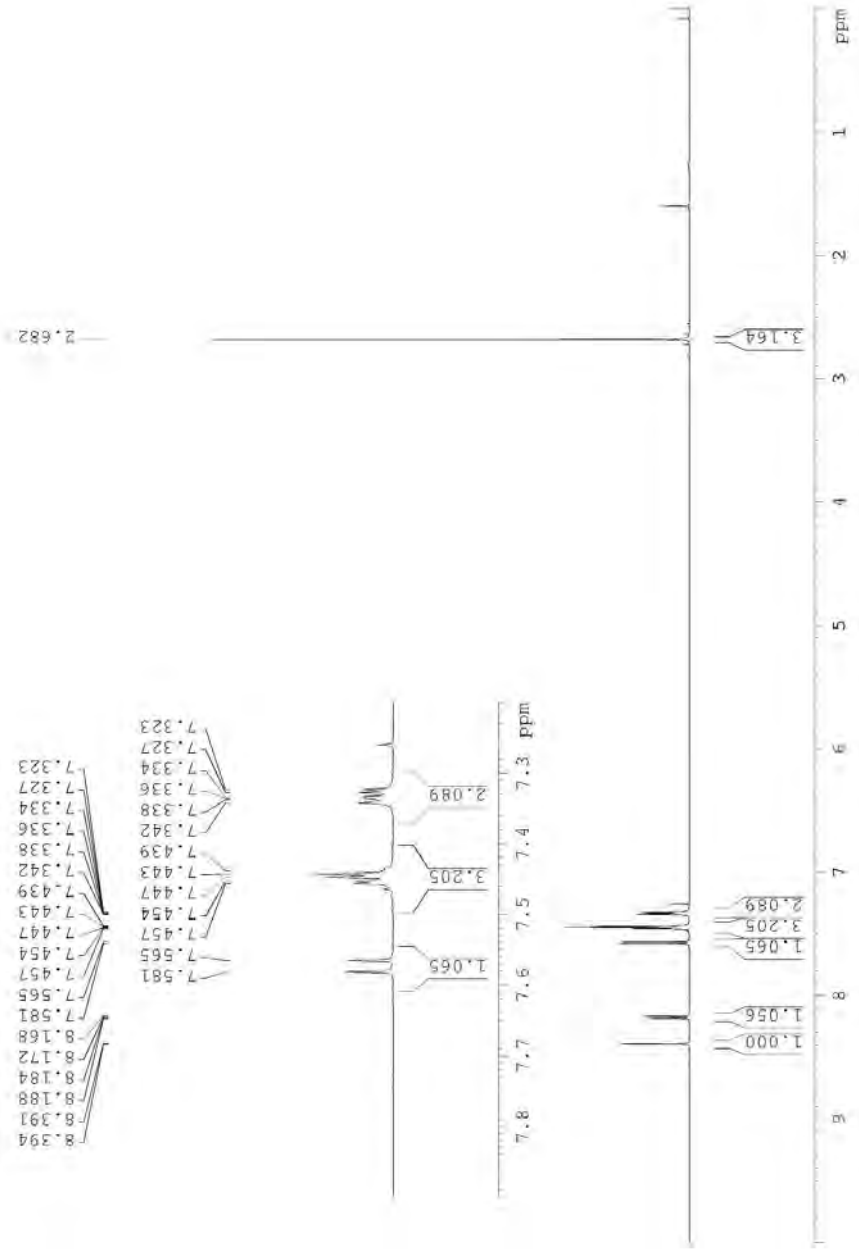
MS (EI) of 4-chloro-2-nitro-1,1'-biphenyl (5w)



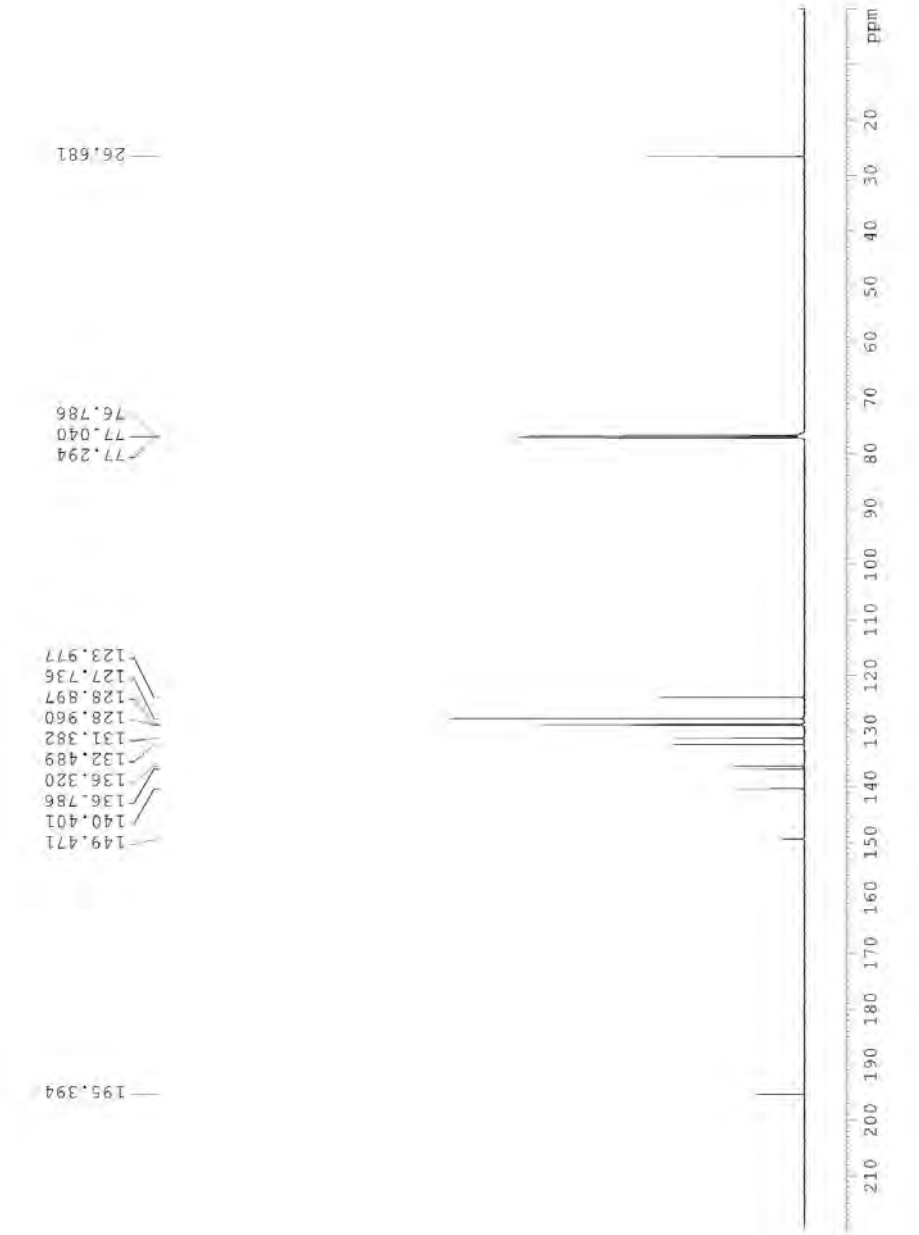
IR spectrum of 4-chloro-2-nitro-1,1'-biphenyl (5w)



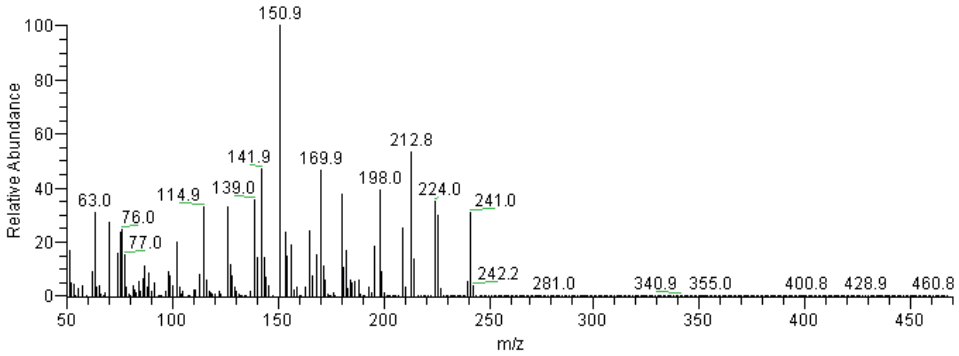
^{1}H-NMR of 1-(2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5x) in $CDCl_3$



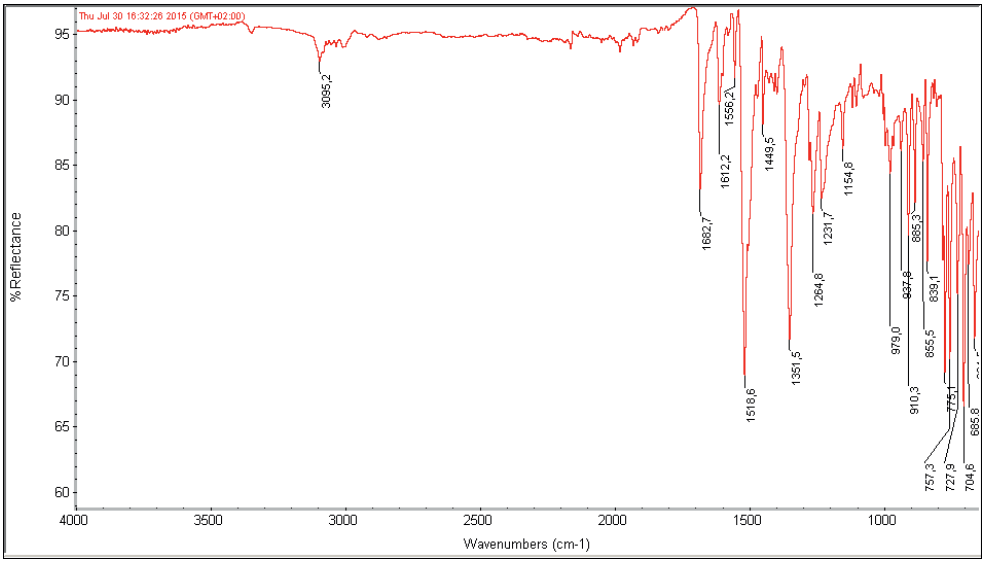
^{13}C-NMR of 1-(2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5x) in $CDCl_3$



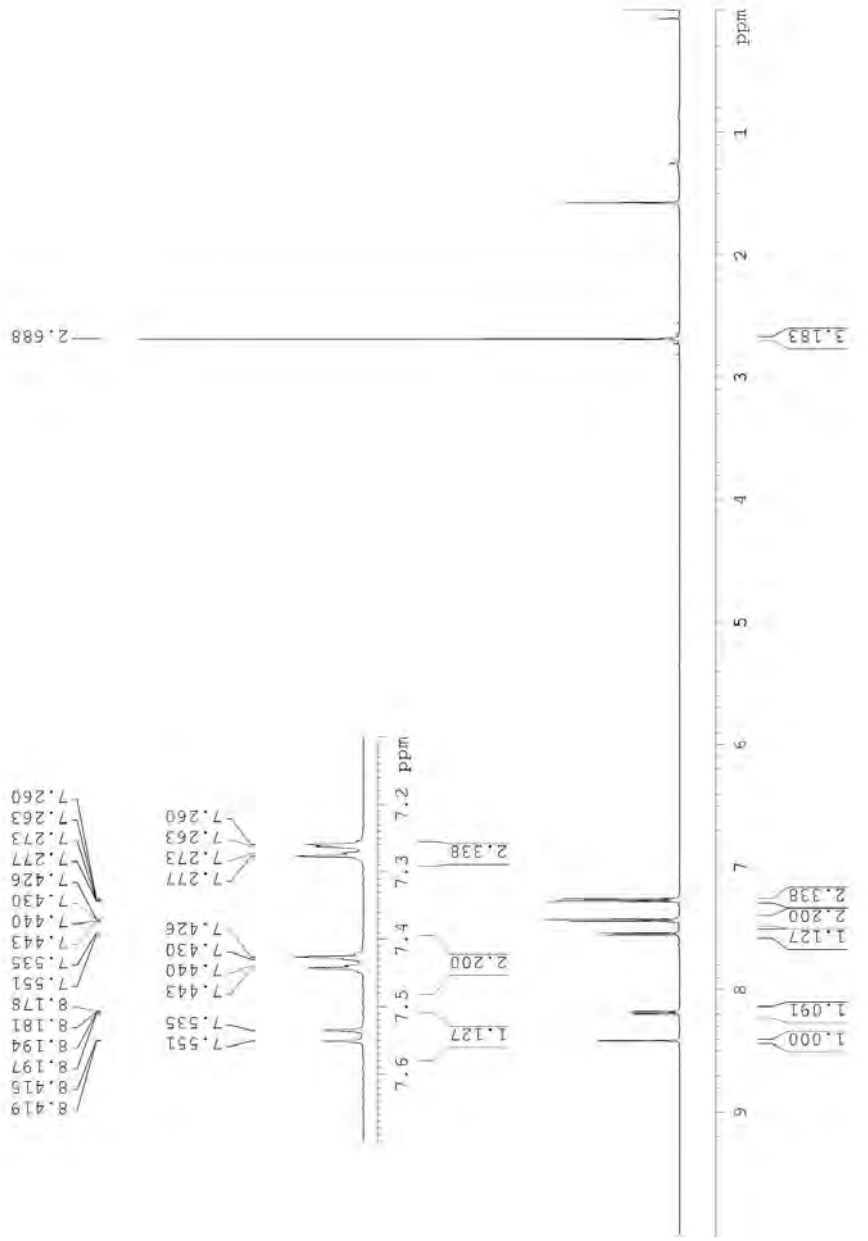
MS (EI) of 1-(2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5x)



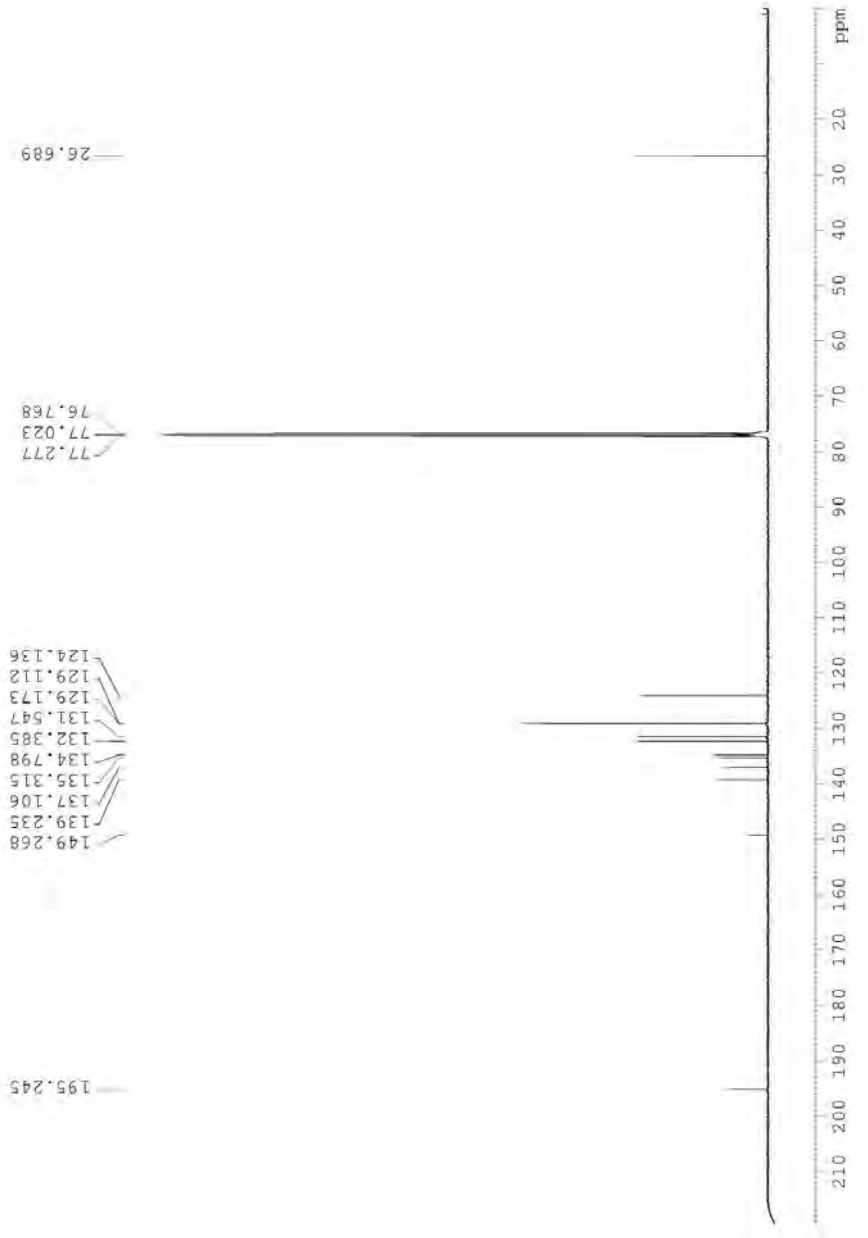
IR of 1-(2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5x)



^{1}H-NMR of 1-(4'-chloro-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5y) in $CDCl_3$



^{13}C-NMR of 1-(4'-chloro-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5y) in $CDCl_3$



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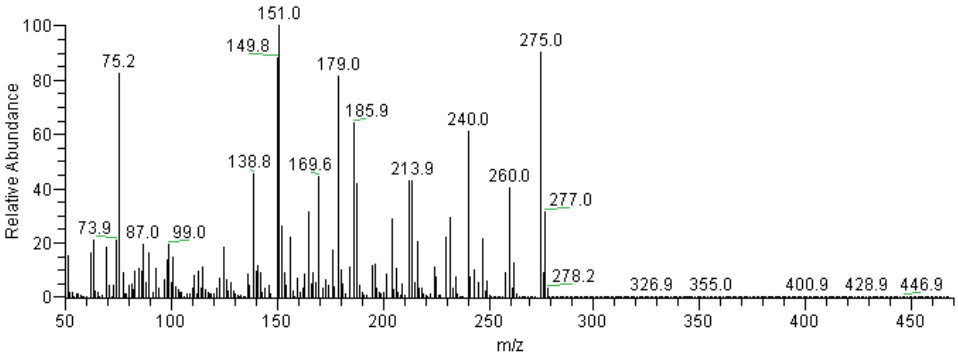
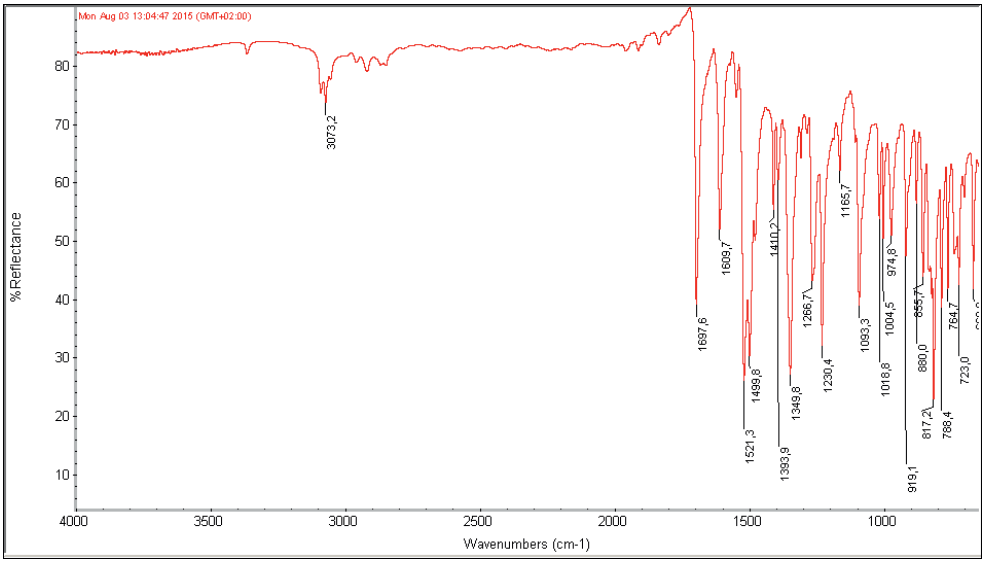
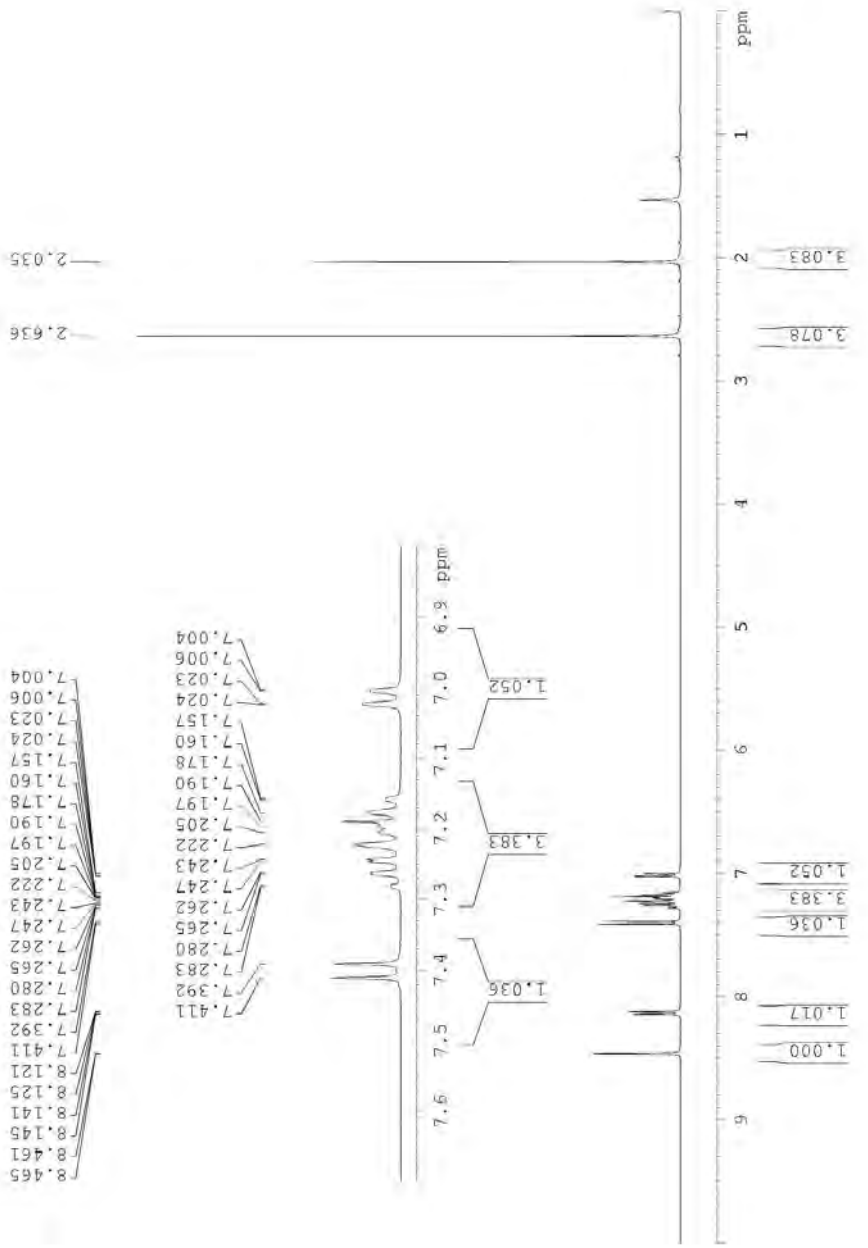


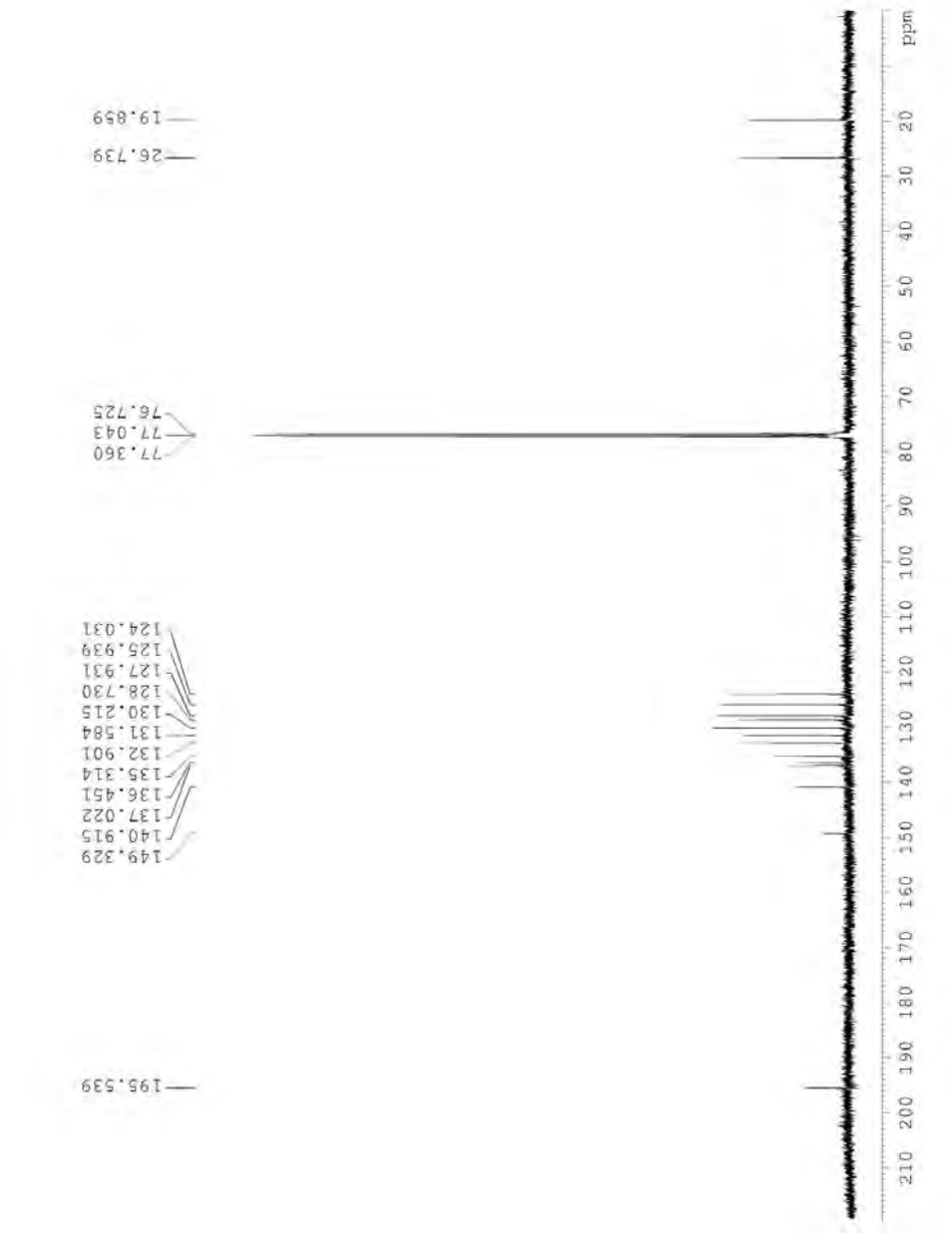
IR of 1-(4'-chloro-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5y)



^{1}H-NMR of 1-(2'-methyl-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5z) in $CDCl_3$



^{13}C-NMR of 1-(2'-methyl-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5z) in $CDCl_3$



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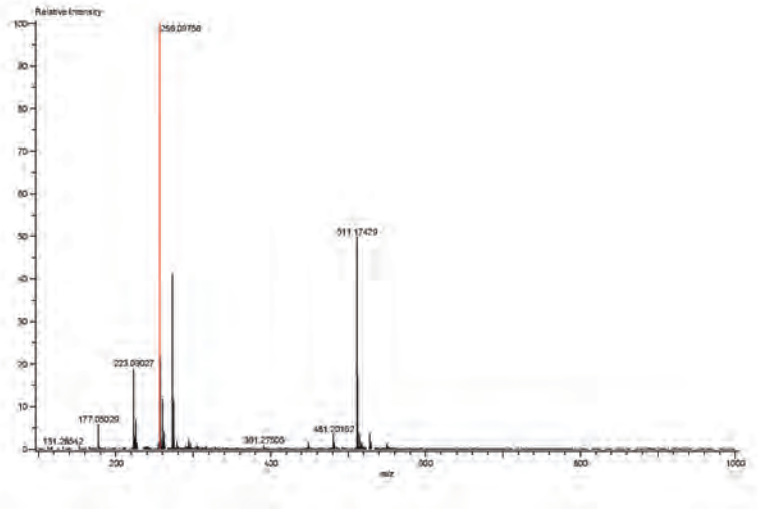

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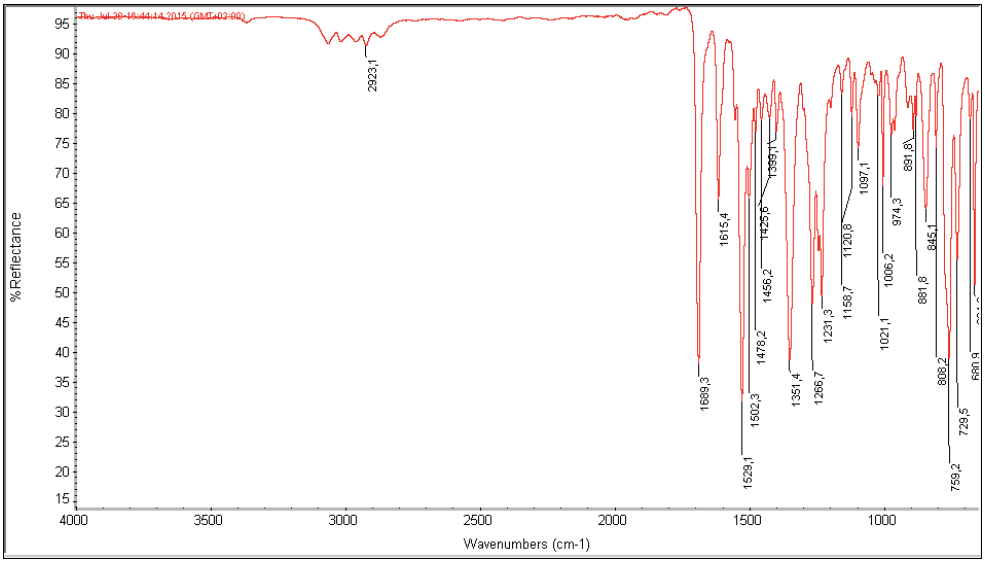
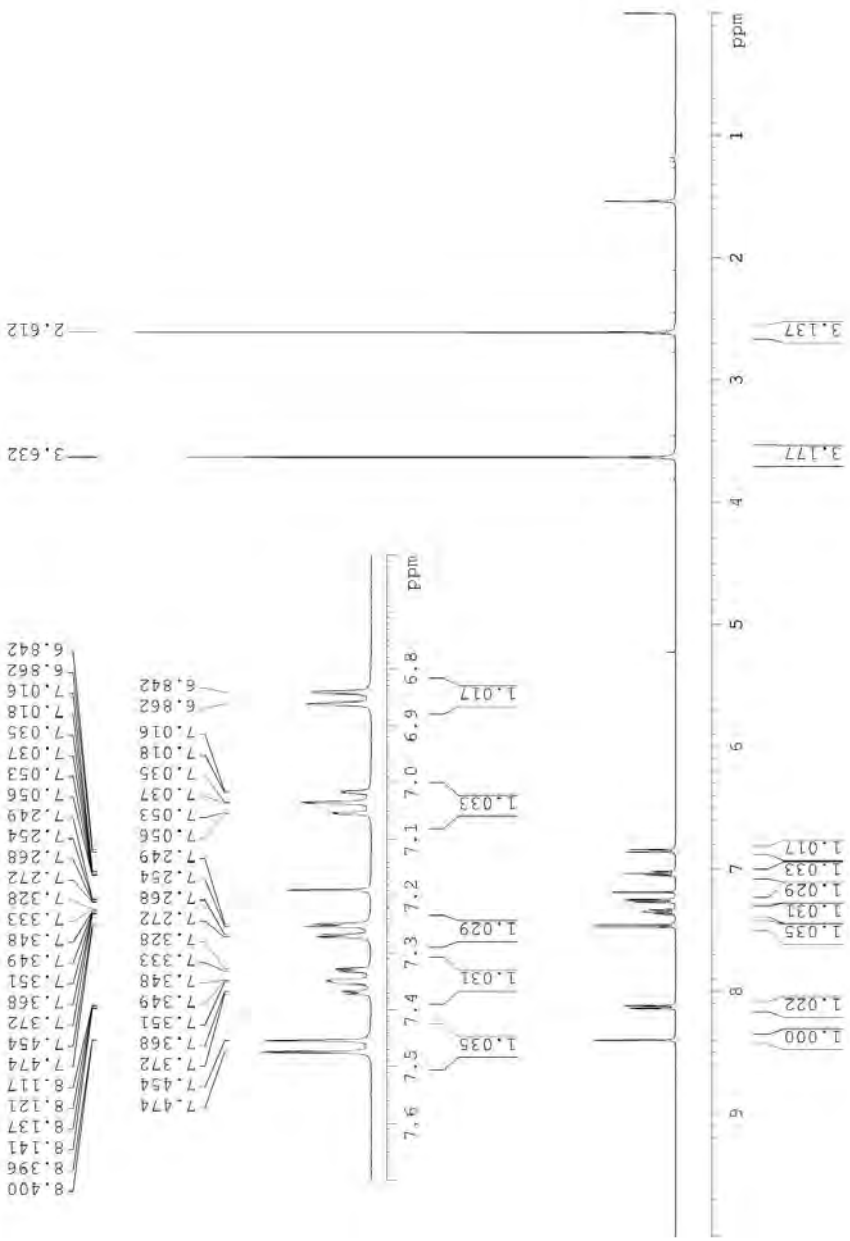
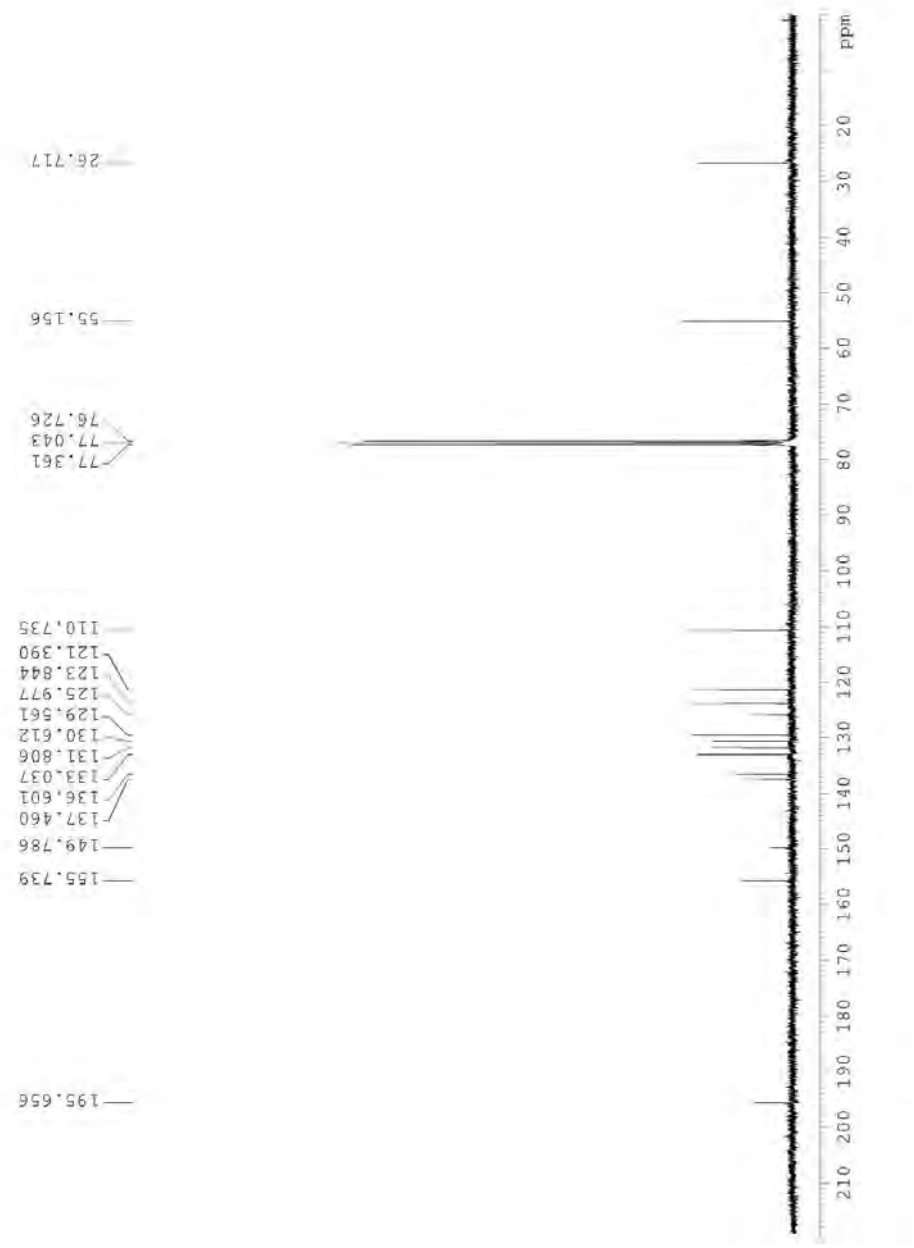


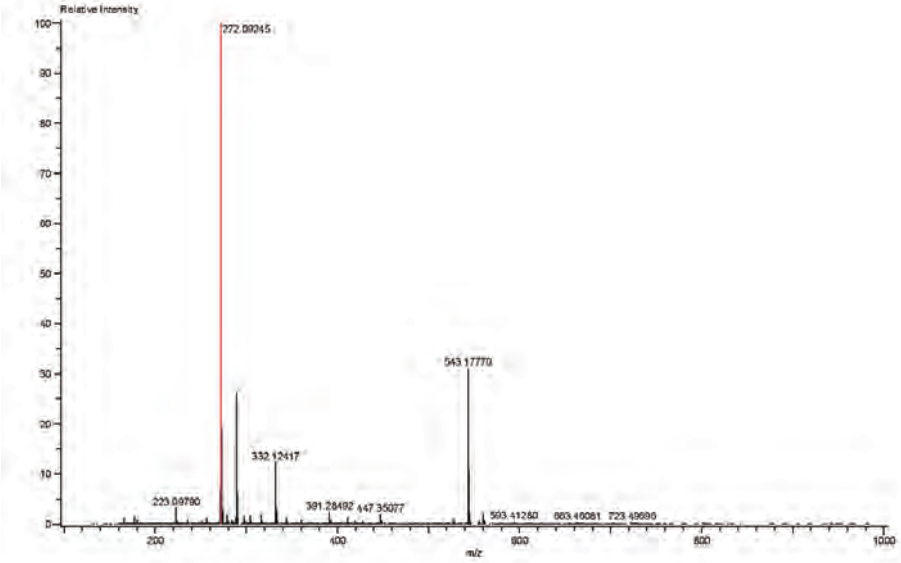
^{1}H-NMR of 1-(2'-methoxy-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5æ) in $CDCl_3$



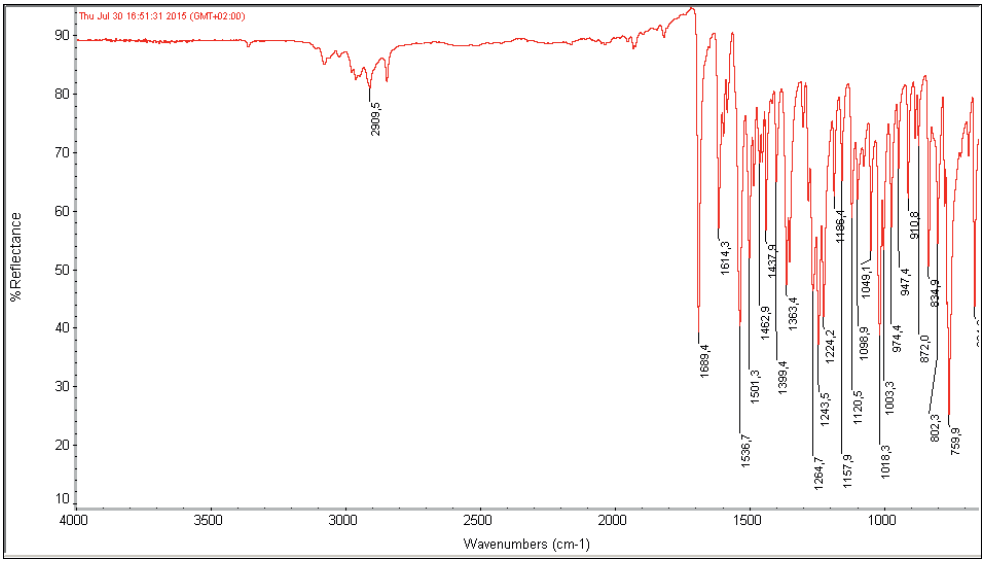
^{13}C-NMR of 1-(2'-methoxy-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5æ) in $CDCl_3$



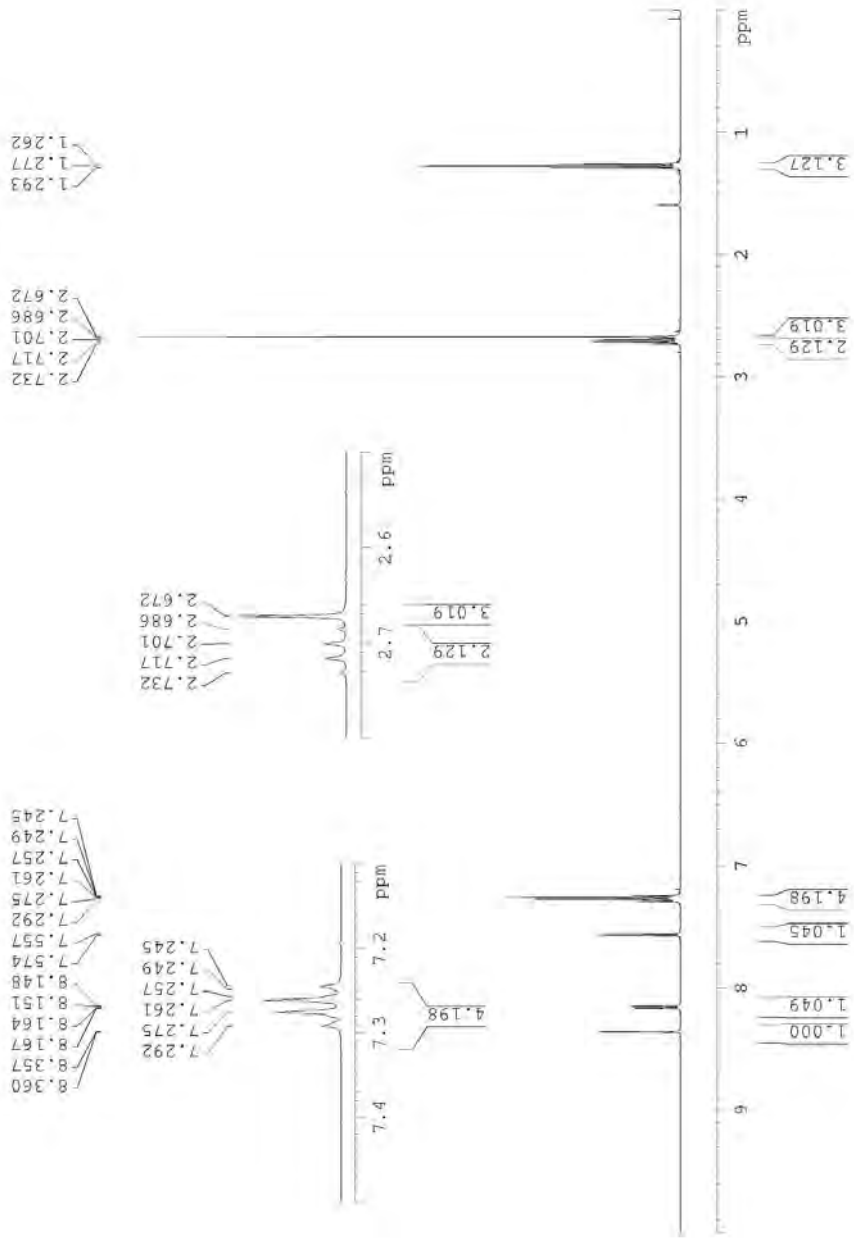
HR-MS of 1-(2'-methoxy-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5æ)



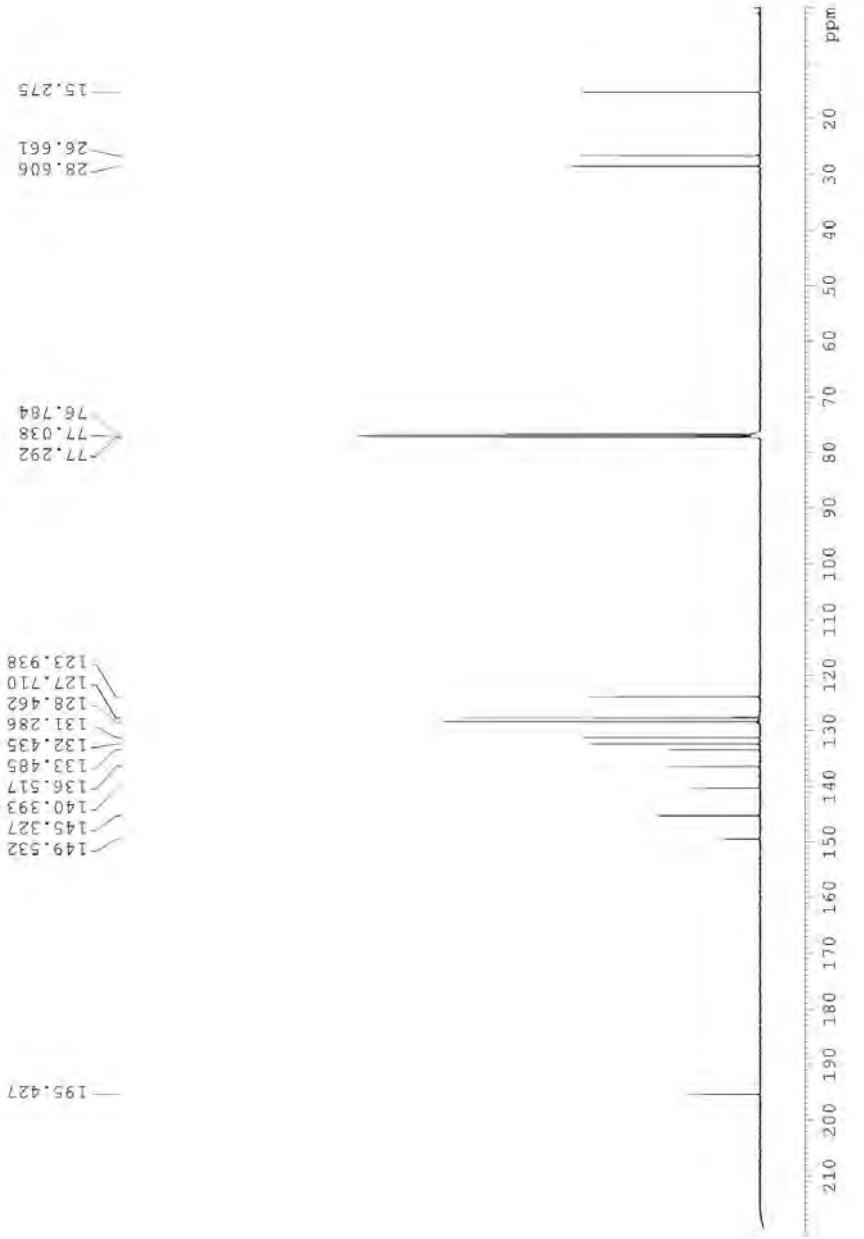
IR of 1-(2'-methoxy-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5æ)



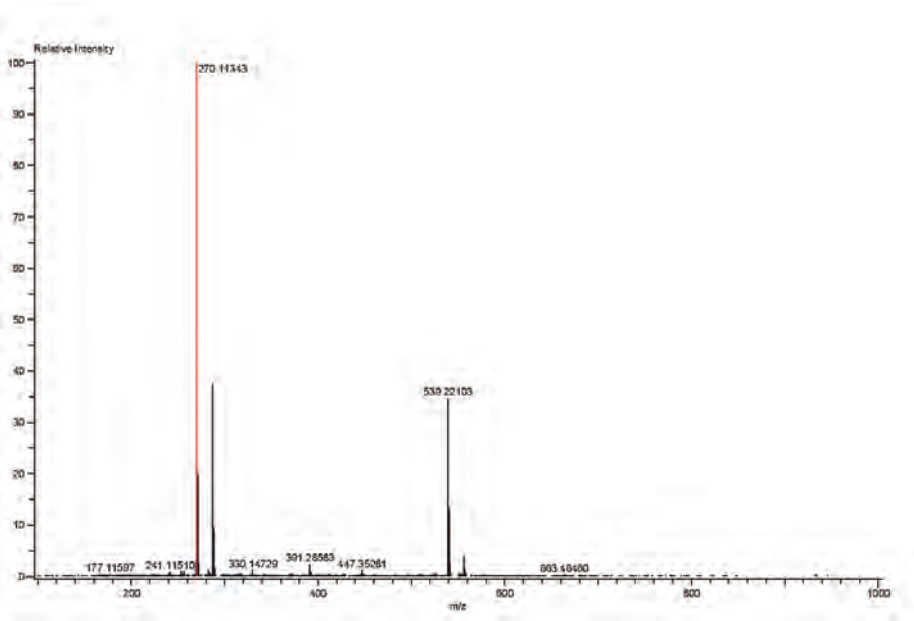
^{1}H-NMR of 1-(4'-ethyl-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5ø) in $CDCl_3$



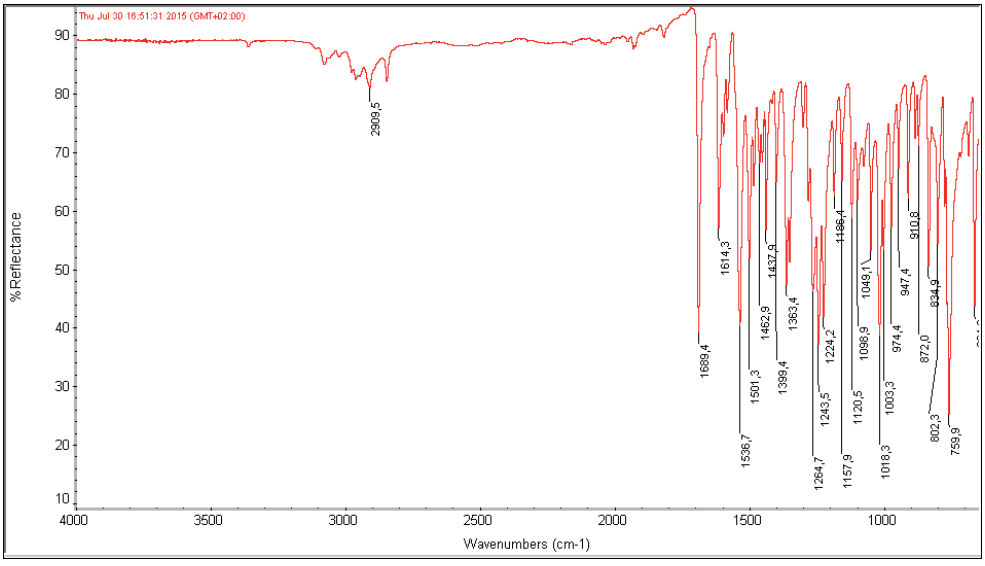
^{13}C-NMR of 1-(4'-ethyl-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5ø) in $CDCl_3$



HR-MS of 1-(4'-ethyl-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5ø)



IR spectrum of 1-(4'-ethyl-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (5ø)



Paper II

Indium powder as the reducing agent in the synthesis of 2-amino-1,1'-biphenyls.

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Indium powder as the reducing agent in the synthesis of 2-amino-1,1′-biphenyls

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ABSTRACT

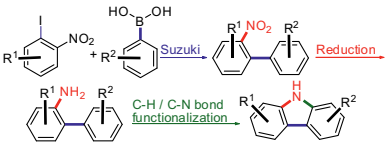
An improved and simplified In-based protocol for the reduction of 2-nitro-1,1′-biphenyls to the corresponding 2-amino-1,1′-biphenyls is disclosed. The method utilizes only a stoichiometric quantity of indium powder as the reducing reagent along with a stoichiometric quantity of ammonium chloride. The work-up is very simple, it requires only a simple filtration of the post-reaction mixture whereupon the reaction medium is removed under reduced pressure. The method was also proven to operate with a variety of functional groups to provide high to excellent yields of the target 2-amino-1,1′-biphenyls. A proposal for a reaction mechanism is also provided.

Introduction

For a project dedicated to the synthesis of the 1*H*-carbazole scaffold, we have previously disclosed a highly efficient method for the synthesis of 2-nitro-1,1′-biphenyls by means of the Suzuki cross coupling reaction (Scheme 1).[1] For the subsequent step, which encompasses reduction of the 2-nitro-1,1′-biphenyl intermediate to the corresponding 2-amino-1,1′-biphenyl, we were searching for a reliable, simple, and efficient reduction method. To approach the target 1*H*-carbazole frameworks, we planned to use the combined C–H functionalization and C–N bond formation as disclosed by Buchwald and collaborators,[2] or the newly reported iridium(III) catalyzed intramolecular C–H amination method by Miura and collaborator.[3]

Numerous methods exist for the Ph—NO_2 → Ph—NH_2 transformation, including catalytic hydrogenation with Pd/C[4] or Raney nickel,[5] Pd catalyzed reduction using silicon hydride as the reducing agent,[6] and the Bechamp reduction that involves treatment of the nitroaromatic with iron and hydrochloric acid.[7]

Additionally, protocols encompassing either $SnCl_2$,[9] $TiCl_3$,[10] Zn,[11] Sm,[12] or sodium dithionite ($Na_2S_2O_4$)[13] as reducing agents constitute functioning methods developed for the nitroarene to aniline transformation. A method disclosed by Moody and collaborators[14] attracted our attention due to its simplicity involving the treatment of nitroarene with elemental In in an ammonium chloride solution.



Scheme 1. Outline for the synthesis of 2-amino-1,1′-biphenyls,[8] a key intermediate for the synthesis of 1*H*-carbazoles.

Results and discussion

In order to utilize the Moody method,[14] a highly diluted substrate mixture in ethanol should be treated with a large excess of indium powder and a saturated solution of aqueous ammonium chloride for a long reaction time, up to 72 h. We began to investigate this method with our substrate 2-nitro-1,1′-biphenyl, trials that proved to function perfectly well. Chromatographic analysis of the post-reaction mixture revealed full conversion of the substrate to the desired 2-amino-1,1′-biphenyl (Scheme 2, entry 1). However, the subsequent workup procedure required several steps including filtration, pH adjustment, extraction, solvent removal, and finally column chromatography, which only provided a low isolated yield (41%) of our target 2-amino-1,1′-biphenyl.

It turned out that the work-up procedure resulted in decomposition or other loss of the target reduction product and in some occasions we also observed ring closure to give the 1*H*-carbazole frameworks, but only in small quantities. Although, with considerable challenges to implement this reduction method, we found

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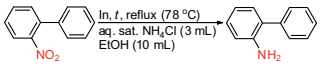


Entry	In [equiv.]	t [min.]	Yield (%)[a]
1	7	90	quant.
2	3.5	90	quant.
3	2	90	87
4	2	150	quant.

a Yield based on GC

Scheme 2. Indium reduction of 2-nitro-1,1′-biphenyls to 2-amino-1,1′-biphenyls.

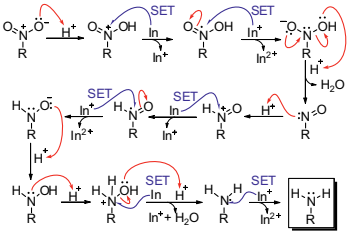
that it looked attractive due to its simplicity, which spurred us to explore, adapt, and simplify the Moody method for our amino-biphenyl application.

To the best of our knowledge, the In reduction method has not been thoroughly investigated from a mechanistic point of view. Nevertheless, for us it was reasonable to draw a parallel to the Zn powder reduction method, which would require two or three equivalents of In for each nitro group depending on the final oxidation state of the oxidized indium.

Therefore, we reduced the amount of indium, 7 → 3.5 equiv, an alteration that still provided quantitative yields (measured with GC) of the 2-amino-biphenyl. Further lowering the quantity of In to only 2 equiv afforded a yield of 87% (GC). This experiment was repeated with prolonged reaction time, 150 min (Scheme 2, entry 4), which successfully provided the target molecule in quantitative yields (GC). The achieved results suggested a mechanism where In ends up at an oxidation state of +3, see our proposal for a mechanism in Scheme 3. During this experimentation we also observed that the particle size of the indium powder was important in relation to the reaction rate and overall performance of the reaction. For the reduction experiments, we utilized a freshly opened container of indium powder (100 mesh, 99.99%) to achieve a quantitative conversion in almost all trials. However, the reactivity of the indium as a reductant was observed to be impaired even at few days of storage when stored under a normal atmosphere at room temperature, which we believe is due to surface oxidation.

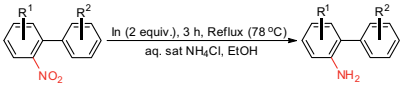
A scope and limitation of the reduction method was evaluated by means of a small library of various substituted 2-nitro-1,1′-biphenyls (Table 1). Unfortunately, the hitherto developed method was revealed to operate in low to medium yields only.

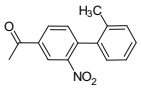
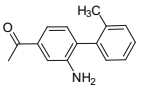
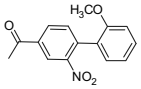
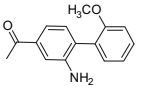
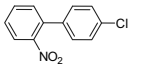
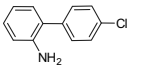
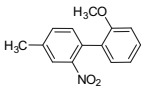
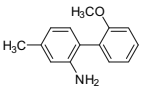
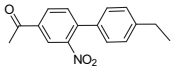
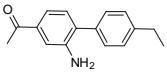
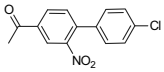
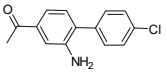
These results (Table 1) encouraged us to further explore the experimental variables with the goal to improve the outcome. The reaction temperature was raised (78→120 °C) and for this purpose the reaction was conducted in a sealed tube reactor. The solvent (EtOH) volume was lowered (10→4 mL) and a lowered quantity of ammonium chloride was utilized [16 mmol (0.85 g)[15] → 1.03 mmol (0.055 g)]. These conditions were explored with a library composed of fifteen 2-nitro-1,1′-biphenyls (Table 2). The results show that the method provides high to excellent yields in all cases and displays a good functional group tolerance. The achieved results also suggest that the developed method is consistent with the proposed mechanism resulting in an oxidation of In to In^{+2} and thus requiring 3 equiv of elemental In.



Scheme 3. Mechanism proposal for the In promoted reduction of the Ar-NO_2 group.

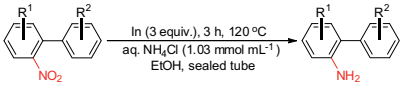
Table 1
Introductory exploration of an improved procedure for the reduction of 2-nitro-1,1′-biphenyl to 2-amino-1,1′-biphenyl

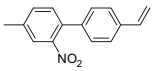
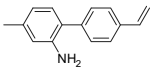
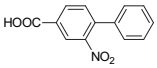
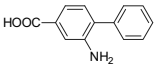
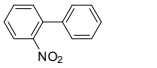
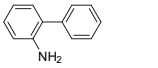
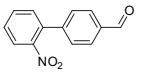
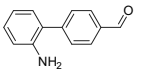
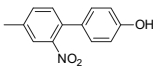
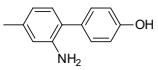
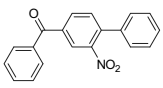
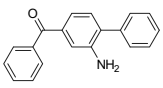


Entry	2-Nitrobiphenyl	2-Aminobiphenyl	Yield[a] (%)
1			100 (51)
2			100 (61)
3			100 (42)
4			100 (35)
5			100 (45)[b]
6			100 (48)[b]

[a] Yield based on GC (isolated yield after column chromatography).
[b] Additional In powder (2 equiv) and aq satd NH_4Cl (3 mL) was added after 3 h in an attempt to attain higher conversion and yield.

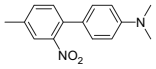
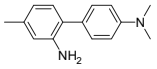
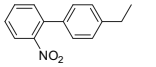
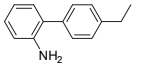
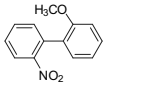
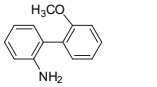
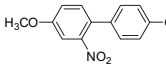
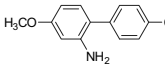
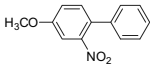
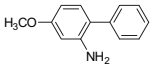
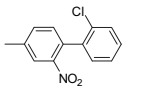
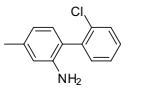
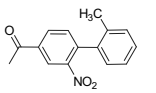
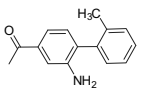
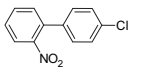
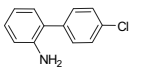
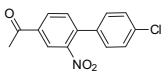
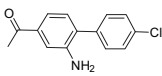
Table 2
Exploration of the scope and limitation of the In promoted reduction of 2-nitro-1,1′-biphenyl to 2-amino-1,1′-biphenyl[8]



Entry	2-Nitro-biphenyl	2-Amino-biphenyl	Yield[a] (%)
1			91
2			75
3			95
4			69[b]
5			92
6			94[b]

(*continued on next page*)

Table 2 (*continued*)

Entry	2-Nitro-biphenyl	2-Amino-biphenyl	Yield[a] (%)
7			92
8			92
9			91
10			96
11			95
12			95
13			90
14			88
15			94

[a] Isolated yield.
[b] Product was not isolated, measured by GC.

Advantages of the improved indium reduction method comprise a considerably simplified work-up and high purity of target product. When the reduction was completed at 3 h, ethyl acetate was added to the post reaction mixture and the solid inorganics could be filtered off. The resulting filtrate was dried over Na_2SO_4 and the solvent was removed under reduced pressure using a rotary evaporator. The target 2-amino-1,1-biphenyls were isolated in yields in the range of 69–96%.

Conclusions

In conclusion, we have explored and improved a method suitable for the preparation of 2-amino-1,1′-biphenyls by reduction of the corresponding 2-nitro-1,1′-biphenyls. A stoichiometric quantity of indium powder (3 In: 1 substrate) with ethanol as the reaction medium was revealed to be necessary. The lowered reduction reagent loading gives rise to a simple work-up, namely only filtration of the post reaction mixture followed by evaporation of the solvent. This is in contrast to previous methods, which required column chromatography for purification of the reaction product. Furthermore, the method displays a high functional group tolerance to provide high to excellent yields, demonstrated with a series of 2-nitro-1,1′-biphenyls. A proposal for a reaction mechanism is described based on analogy with the Zn reduction and experimental observations, namely the required quantities of the elemental In as reduction reagent.

Acknowledgment

V.E. gratefully acknowledges the Department of Chemistry at the University of Bergen – Norway for funding his research fellowships. Dr. Bjarte Holmelid is acknowledged for excellent technical support with the HRMS analyses.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.007.

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8. *General procedure:* 2-Nitrobiphenyl (1 mmol, 0.2 g) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (2 mmol, 0.107 g) in H_2O (1.2 mL) and indium powder (3 mmol, 0.344 g, 99.99% 100 mesh, use preferably a freshly opened bottle or stored under Ar) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The resulting mixture was filtered through a pad of celite to remove the catalyst. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting transparent organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the target compound.
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15. *The Merck Index*, 12th ed.; Merck & Co.: Whitehouse Station, NJ, USA, 1996. Monograph number 537, p 89. Ammonium chloride solubility in water: 28.3 w/w-% (0.283 g mL^3) at 25 °C.

Indium powder as the reducing agent in the synthesis of 2-amino-1,1'-biphenyls

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EXPERIMENTAL SECTION

General Methods

GC analysis were performed on a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d.,0.33mm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained on a GC-MS instrument, using a gas chromatograph equipped with fused silica column (l30 m, 0.25 mm i.d., 0.25mm film thickness) and helium as carrier gas. DART-mass spectra are obtained using PEG as an internal standard in the positive ionization mode with a TOF mass analyzer. ^{1}H NMR and ^{13}C NMR were recorded at ambient temperature at a frequency of 500 and 125 MHz, respectively. The Chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton ($\delta = 7.26$) and $CDCl_3$ for carbon ($\delta = 77.0$) using TMS as an external reference. Melting points are reported uncorrected. All reagents used were commercially available from Aldrich Chemical Co. HR-MS data were also collected for all compounds.

4-methyl-4'-vinyl-[1,1'-biphenyl]-2-amine (1) (NEW)

4-methyl-2-nitro-4'-vinyl-1,1'-biphenyl (0.25 g, 1.05 mmol), NH_4Cl (0.110 g, 2.10 mmol) and indium powder (0.362 g, 3.15 mmol) . The title compound was obtained as a orange solid (0.20 g, 91%). R_f = 0.32 [(EtOAc:Hx, 10:90)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.45-7.48 (m, 2H), 7.40-7.42 (m, 2H), 7.02 (d, *J*= 7.5 Hz, 1H), 6.72-6.78 (m, 1H), 6.64-6.66 (dt, *J*= 1Hz, 8.5 Hz, 1H), 6.59 (s, 1H), 5.76-5.78 (dd, *J*=1 Hz, 17.5 Hz, 1H), 5.25-5.28 (dd, *J*= 1Hz, 11Hz, 1H), 3.71 (s, br, 2H), 2.30 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.3, 139.1, 138.5, 136.5, 136.3, 130.3, 129.3, 126.6, 124.6, 119.7, 116.3, 113.8, 21.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}N$ 210.1283; Found 210.1285); IR (cm^{-1}): 3452.2, 3368.4, 3005.4, 2918.0, 1608.8, 1496.1.

2-amino-[1,1'-biphenyl]-4-carboxylic acid (2) (856797-75-6)

2-nitro-[1,1'-biphenyl]-4-carboxylic acid (0.125 g, 0.515 mmol), NH_4Cl (0.055 g, 1.03 mmol) and indium powder (0.178 g, 1.55 mmol) .The title compound was obtained as a yellow liquid (0.082 g, 75%). R_f = 0.17 [(EtOAc:Hx, 30:70)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.56 (d, *J*= 7.5 Hz, 1H), 7.44-7.51 (m, 5H), 7.37-7.41 (m, 1H), 7.21 (d, *J*= 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 171.9, 143.7, 138.5, 132.7, 130.6, 129.0, 128.8, 127.9, 120.4, 116.9; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{12}NO_2$ 214.0868; Found 214.0869); IR (cm^{-1}): 3481.5, 3387.3, 3024.5, 2525.9, 2358.8, 1677.3, 1407.8.

[1,1'-biphenyl]-2-amine (3) (90-41-5)

2-nitro-1,1'-biphenyl (0.1 g, 0.50 mmol), NH_4Cl (0.055 g, 1.03 mmol) and indium powder (0.172 g, 1.50 mmol).The title compound was obtained as a brown solid (0.080 g, 95%). R_f = 0.29 [(EtOAc:Hx, 10:90)]; m.p 50-51^{o}C; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.43-7.45 (m, 4H), 7.33-7.36 (m, 1H), 7.12-7.17 (m, 2H), 6.81-6.84 (td, *J*= 1 Hz, 7.5Hz, 1H), 6.75-6.77 (dd, *J*= 1 Hz, 8 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.5, 139.5, 130.5, 129.1, 128.8, 128.5, 127.7, 127.2,118.7, 115.6 : HR-MS (DART): $(M+H)^+$: Calcd for $C_{12}H_{12}N$ 170.0970; Found 170.0970); IR (cm^{-1}): 3457.4, 3368.6, 3023.4, 1613.6, 1481.4.

2'-amino-4'-methyl-[1,1'-biphenyl]-4-ol (5) (NEW)

4'-methyl-2'-nitro-[1,1'-biphenyl]-4-ol (0.115 g, 0.50 mmol), NH_4Cl (0.055 g, 1.00 mmol) and indium powder (0.172 g, 1.50 mmol).The title compound was obtained as a pale-yellow solid (0.092 g, 92%). R_f = 0.36 [(EtOAc:Hx, 30:70)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.29-7.31 (dd, *J*= 2 Hz, 6.5 Hz, 2H), 7.00 (d, *J*= 7.5 Hz, 1H), 6.88-6.89 (dd, *J*= 2 Hz, 6.5Hz, 2H), 6.64-6.65(m, 1H), 6.60 (s, 1H), 3.72 (s, 2H), 2.30 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 154.7, 143.3, 138.1, 131.8, 130.4, 130.4, 124.8, 119.7, 116.3, 115.6, 21.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{14}NO$ 200.1075; Found 200.1078); IR (cm^{-1}): 3384.1, 3292.6, 2917.6, 1609.6, 1495.0

(2-amino-[1,1'-biphenyl]-4-yl)(phenyl)methanone (6) (NEW)

(2-nitro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (0.152 g, 0.50 mmol), NH_4Cl (0.055 g, 1.00 mmol) and indium powder (0.172 g, 1.50 mmol). The title compound was obtained as a dark yellow liquid (0.129 g, 94 %). R_f = 0.54 [(EtOAc:Hx, 30:70)]; MS (EI): m/z (%)=274.1(24), 273.1 (M^+,100), 196.0 (82), 168.0 (50), 139.0 (17), 115.0 (23), 105.0 (58), 77.0 (86), 51.0 (19); IR (cm^{-1}): 3370.5, 3059.0, 3027.7, 2248.3, 1652.4.

N4',N4',4-trimethyl-[1,1'-biphenyl]-2,4'-diamine (7) (1548736-07-7)

N,N,4'-trimethyl-2'-nitro-[1,1'-biphenyl]-4-amine (0.128 g, 0.50 mmol), NH_4Cl (0.055 g, 1.00 mmol) and indium powder (0.172 g, 1.50 mmol) .The title compound was obtained as a brown liquid (0.104 g, 92%). R_f = 0.54 [(EtOAc:Hx, 30:70)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.25-7.33 (dd, *J*= 2.5 Hz, 7 Hz, 2H), 7.01 (d, *J*= 8 Hz, 1H), 6.79-6.81 (dd, *J*= 2.5 Hz, 7 Hz, 2H), 6.62-6.64 (dt, *J*= 1 Hz, 7.5 Hz, 1H), 6.58 (s, 1H), 3.72 (s, br, 2H), 2.98 (s, 6H), 2.29 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 149.6, 143.6, 137.6, 130.3, 129.8, 127.5, 125.3, 119.5, 116.2, 112.8, 40.6, 21.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{19}N_2$ 227.1548; Found 227.1549); IR (cm^{-1}): 3442.4, 3359.6, 2916.7, 2796.8, 1605.6, 1499.8.

4'-ethyl-[1,1'-biphenyl]-2-amine (8) (55258-95-2)

4'-ethyl-2-nitro-1,1'-biphenyl (0.25 g, 1.1 mmol), NH_4Cl (0.117 g, 2.2 mmol) and indium powder (0.379 g, 3.3 mmol) . The title compound was obtained as a dark brown liquid (0.20 g, 92%): R_f = 0.77 [(EtOAc:Hx, 30:70)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.37 (d, *J*= 8 Hz, 2H), 7.27 (d, *J*= 8 Hz, 2H), 7.12-7.16 (m, 2H), 6.81 (t, *J*= 7.5 Hz, 1H), 6.76 (d, *J*= 7.5 Hz, 1H), 3.75 (s, br, 2H), 2.70 (q, *J*= 7.5 Hz, 2H), 1.28 (t, *J*= 7.5 Hz, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.6, 143.2, 136.8, 130.5, 129.0, 128.3, 127.7, 118.6, 115.6, 28.6, 15.5; HR-MS (DART): $(M+H)^+$: Calcd for $C_{14}H_{16}N$ 198.1283; Found 198.1285); IR (cm^{-1}): 3457.4, 3369.3, 3021.4, 2962.5, 2929.4, 2870.4, 1612.4, 1487.7.

2'-methoxy-[1,1'-biphenyl]-2-amine (9) (1206-76-4)

2-methoxy-2'-nitro-1,1'-biphenyl (0.234 g, 1.02 mmol), NH_4Cl (0.108 g, 2.04 mmol) and indium powder (0.351 g, 3.06 mmol) .The title compound obtained as a dark brown solid (0.185 g, 91%). R_f = 0.49 [(EtOAc:Hx, 30:70)]; m.p 80-82^{o}C; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.33-7.37 (td, *J*= 1.2 Hz, 8 Hz, 1H), 7.25-7.27 (dd, *J*= 1.5 Hz, 7.5 Hz, 1H), 7.17(t, *J*= 7.5 Hz, 1H), 7.09-7.11 (dd, *J*= 1 Hz, 7.5 Hz, 1H), 7.04 (t, *J*= 7.5 Hz, 1H), 6.99 (d, *J*= 8 Hz, 1H), 6.83(t, *J*= 7.5 Hz, 1H), 6.77 (d, *J*= 8 Hz, 1H), 3.80 (s, 3H), 3.19 (s, br, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 156.7, 144.3, 131.8, 131.1, 129, 128.5, 128.3, 125.0, 121.2, 118.5, 115.7, 111.3, 55.8; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{14}NO$ 200.1075; Found 200.1078); IR (cm^{-1}): 3448.8, 3368.3, 3020.5, 2937.0, 2833.6, 1614.7, 1482.3.

4'-chloro-4-methoxy-[1,1'-biphenyl]-2-amine (10) (1175861-91-2)

4'-chloro-4-methoxy-2-nitro-1,1'-biphenyl (0.225 g, 0.86 mmol), NH_4Cl (0.091 g, 1.72 mmol) and indium powder (0.296 g, 2.58 mmol) .The title compound was obtained as a dark yellow liquid (0.191g, 96%); R_f = 0.63 [(EtOAc:Hx, 30:70)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.35-7.38 (m, 4H), 7.0 (d, *J*= 8.5 Hz, 1H), 6.39-6.41 (dd, *J*= 2.5Hz, 8 Hz, 1H), 6.30 (d, *J*= 2.5Hz, 1H), 3.79 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 160.3, 144.6, 137.8, 132.7, 131.3, 130.6, 128.9, 119.5, 104.5, 101.2, 55.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{13}{}^{35}ClNO$ 234.0686; Found 234.0687); Calcd for $C_{13}H_{13}{}^{37}ClNO$ 236.0656; Found 236.0642; IR (cm^{-1}): 3467.6, 3371.8, 2934.9, 2834.4, 1608.1, 1482.0.

4-methoxy-[1,1'-biphenyl]-2-amine (11) (38088-00-5)

4-methoxy-2-nitro-1,1'-biphenyl (0.217 g, 0.95 mmol), NH_4Cl (0.101 g, 1.90 mmol) and indium powder (0.327 g, 2.85 mmol) .The title compound was obtained as a pale-brown solid (0.180 g, 95%). R_f = 0.47 [(EtOAc:Hx, 30:70)]; m.p 41-42^{o}C; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.42 (d, *J*= 4 Hz, 4H), 7.29-7.33 (m, 1H), 7.05 (d, *J*= 8.5 Hz, 1H), 6.39-6.42 (dd, *J*= 2.5 Hz, 8.5 Hz, 1H), 6.32 (d, *J*= 2.0 Hz, 1H), 3.80 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 160.1, 144.6, 139.4, 131.3, 129.2, 128.8, 126.8, 120.9, 104.3, 101.1, 55.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{14}NO$ 200.1075; Found 200.1076); IR (cm^{-1}): 3459.5, 3371.4, 3026.4, 2934.7, 2833.1, 1610.0, 1484.5.

2'-chloro-4-methyl-[1,1'-biphenyl]-2-amine (12) (1552980-85-4)

2'-chloro-4-methyl-2-nitro-1,1'-biphenyl (0.24 g, 0.97mmol), NH_4Cl (0.103 g, 1.94 mmol) and indium powder (0.334 g, 2.90 mmol). The title compound was obtained as a brown liquid (0.20 g, 95%). R_f = 0.71 [(EtOAc:Hx, 30:70)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.48-7.50 (m, 1H), 7.29-7.33 (m, 3H), 6.94 (d, *J*= 7.5 Hz, 1H), 6.66 (d, *J*= 7.5 Hz, 1H), 6.62 (s, 1H), 2.32 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.6, 139.1, 138, 134.0, 132.1, 130.3, 129.9, 128.9, 127.2, 122.7, 119.3, 116.2, 21.4: HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{13}{}^{35}ClN$ 218.0737; Found 218.0738); Calcd for $C_{13}H_{13}{}^{37}ClN$ 220.0707; Found 220.0655); IR (cm^{-1}): 3458.0, 3374.4, 2917.9, 1618.9, 1467.0.

1-(2-amino-2'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (13) (NEW)

1-(2'-methyl-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (0.24 g, 0.94 mmol), NH_4Cl (0.10 g, 1.89 mmol) and indium powder (0.324 g, 2.82 mmol). The title compound was obtained as a pale-yellow solid (0.19 g, 90%). R_f = 0.37 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.28-7.31 (m, 2H), 7.22-7.23 (m, 2H), 7.17-7.20 (m, 1H), 7.09-7.10 (m, 1H), 7.02 (d, *J*= 8 Hz, 1H), 3.46 (s, br, 2H), 2.51 (s, 3H), 2.08 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 198.3, 144.1, 137.6, 137.4, 136.6, 132.3, 130.5, 130.3, 129.5, 128.2, 126.3, 118.6, 114.2, 26.7, 19.6; HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO$ 226.1232; Found 226.1233); IR (cm^{-1}): 3482.4, 3453.4, 3381.9, 3361.3, 2921.3, 1670.6, 1659.0, 1619.9, 1424.5, 1291.7.

4'-chloro-[1,1'-biphenyl]-2-amine (14) (1204-44-0)

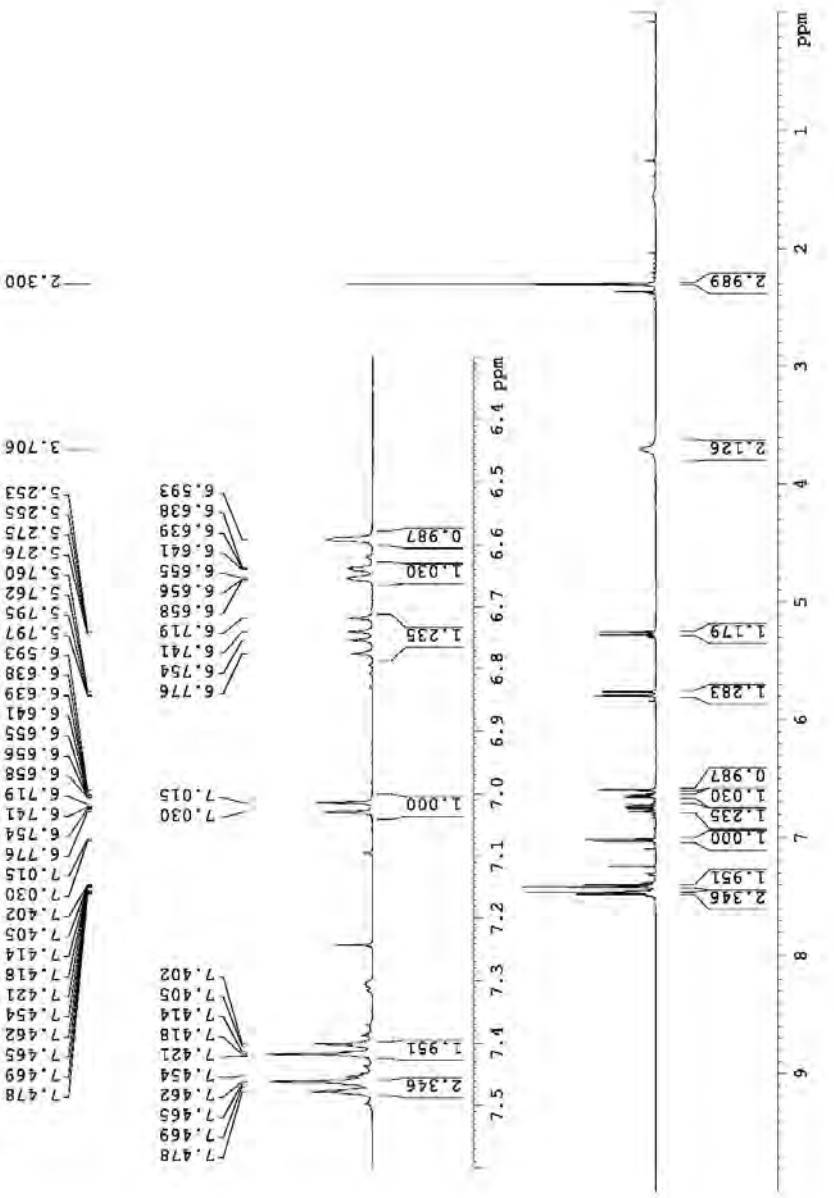
4'-chloro-2-nitro-1,1'-biphenyl (0.25 g, 1.07 mmol), NH_4Cl (0.113 g, 2.13 mmol) and indium powder (0.369 g, 3.21 mmol) . The title compound was obtained as a light brown liquid (0.192 g, 88%). R_f = 0.63 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.28-7.31 (m, 4H), 7.03-7.07 (td, *J*= 1.5Hz, 8 Hz, 1H), 6.97-6.99 (dd, *J*= 1.5Hz, 7.5 Hz, 1H), 6.70-6.73 (td, *J*= 1Hz, 7.5 Hz, 1H), 6.63-6.65 (dd, *J*= 1Hz, 8 Hz, 1H), 3.56 (s, br, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.5, 138.0, 133.1, 130.5, 130.4, 129.0, 128.9, 126.4, 118.8, 115.8; HR-MS (DART): $(M+H)^+$: Calcd for $C_{12}H_{11}{}^{35}ClN$ 204.0580; Found 204.0582); Calcd for $C_{12}H_{11}{}^{37}ClN$ 206.0551; Found 206.0522); IR (cm^{-1}): 3455.1, 3370.2, 3026.4 , 1614.0, 1480.3, 1291.4.

1-(2-amino-4'-chloro-[1,1'-biphenyl]-4-yl)ethan-1-one (15) (52806-85-6)

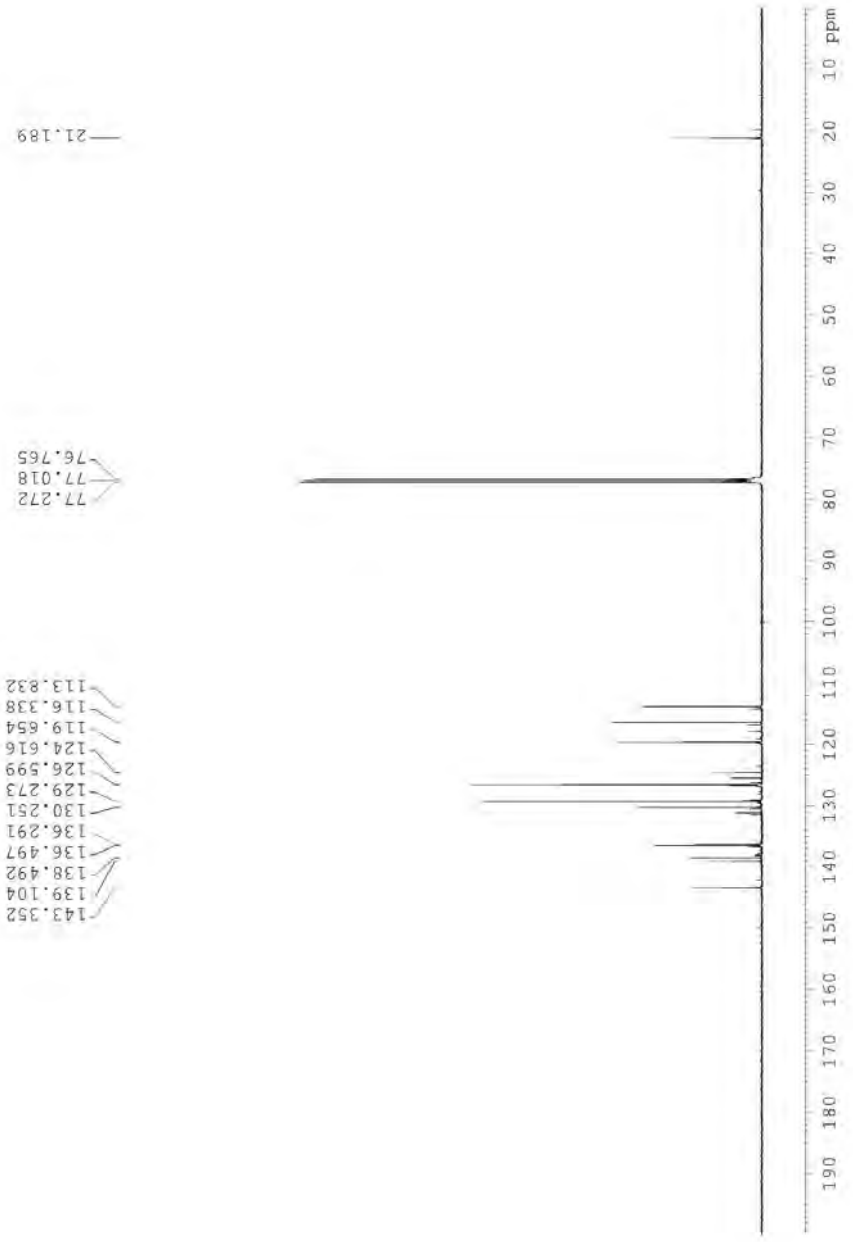
1-(4'-chloro-2-nitro-[1,1'-biphenyl]-4-yl)ethan-1-one (0.21 g, 0.76 mmol), NH_4Cl (0.081 g, 1.53 mmol) and indium powder (0.262 g, 2.28 mmol) . The title compound was obtained as a yellow solid (0.17 g, 94%). R_f = 0.32 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.34 (d, *J*= 2Hz, 2H), 7.32-7.33 (m, 1H), 7.30-7.31 (m, 1H), 7.25-7.27 (m, 2H), 7.06 (d, *J*= 7.5 Hz, 1H), 3.74 (s, br, 2H), 2.48 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 198.1, 143.8, 137.5, 136.9, 133.8, 130.5, 130.2, 129.4, 129.2, 118.9, 114.9, 26.7; HR-MS (DART): $(M+H)^+$: Calcd for $C_{14}H_{13}{}^{35}ClNO$ 246.0686; Found 246.0688); Calcd for $C_{14}H_{13}{}^{37}ClNO$ 248.0656; Found 248.0668); IR (cm^{-1}): 3497.3, 3379.7, 3302.1 , 1671.9, 1420.3, 1289.6.

SPECTRA

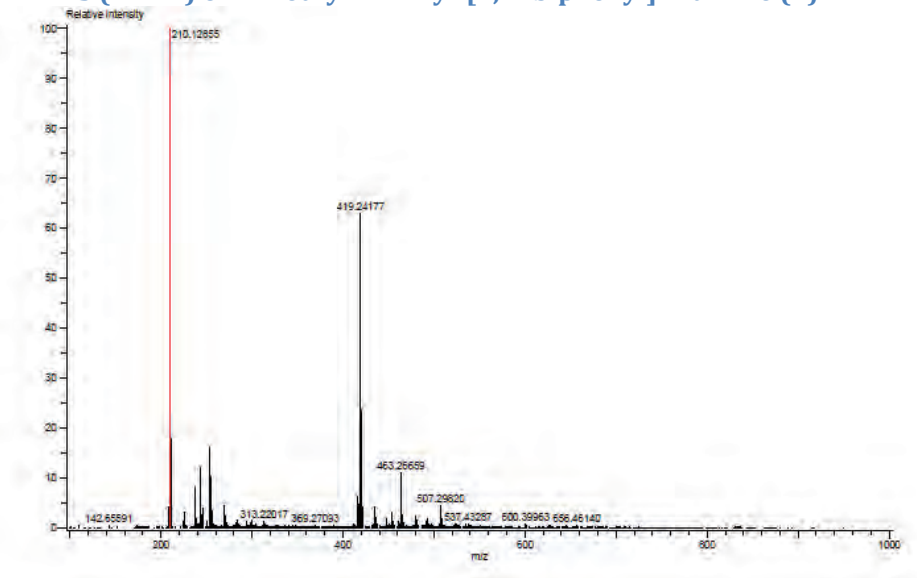
^{1}H-NMR of 4-methyl-4'-vinyl-[1,1'-biphenyl]-2-amine (1)



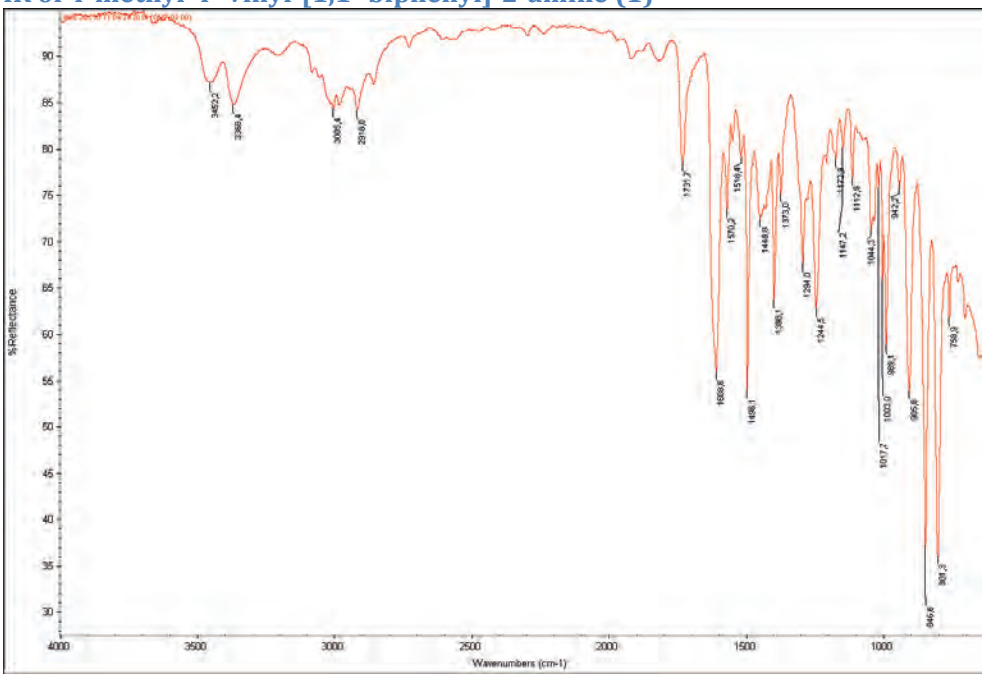
^{13}C-NMR of 4-methyl-4'-vinyl-[1,1'-biphenyl]-2-amine (1)



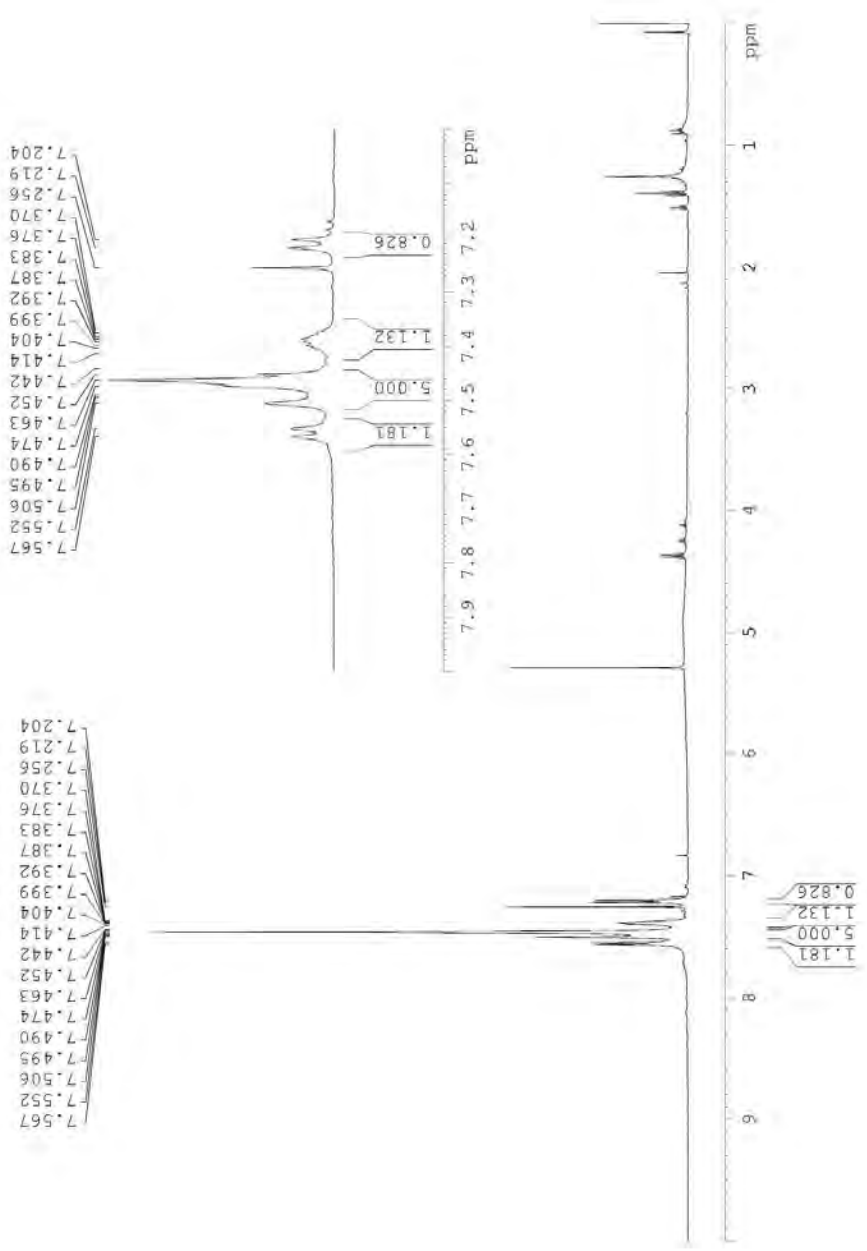
HR-MS (DART) of 4-methyl-4'-vinyl-[1,1'-biphenyl]-2-amine (1)



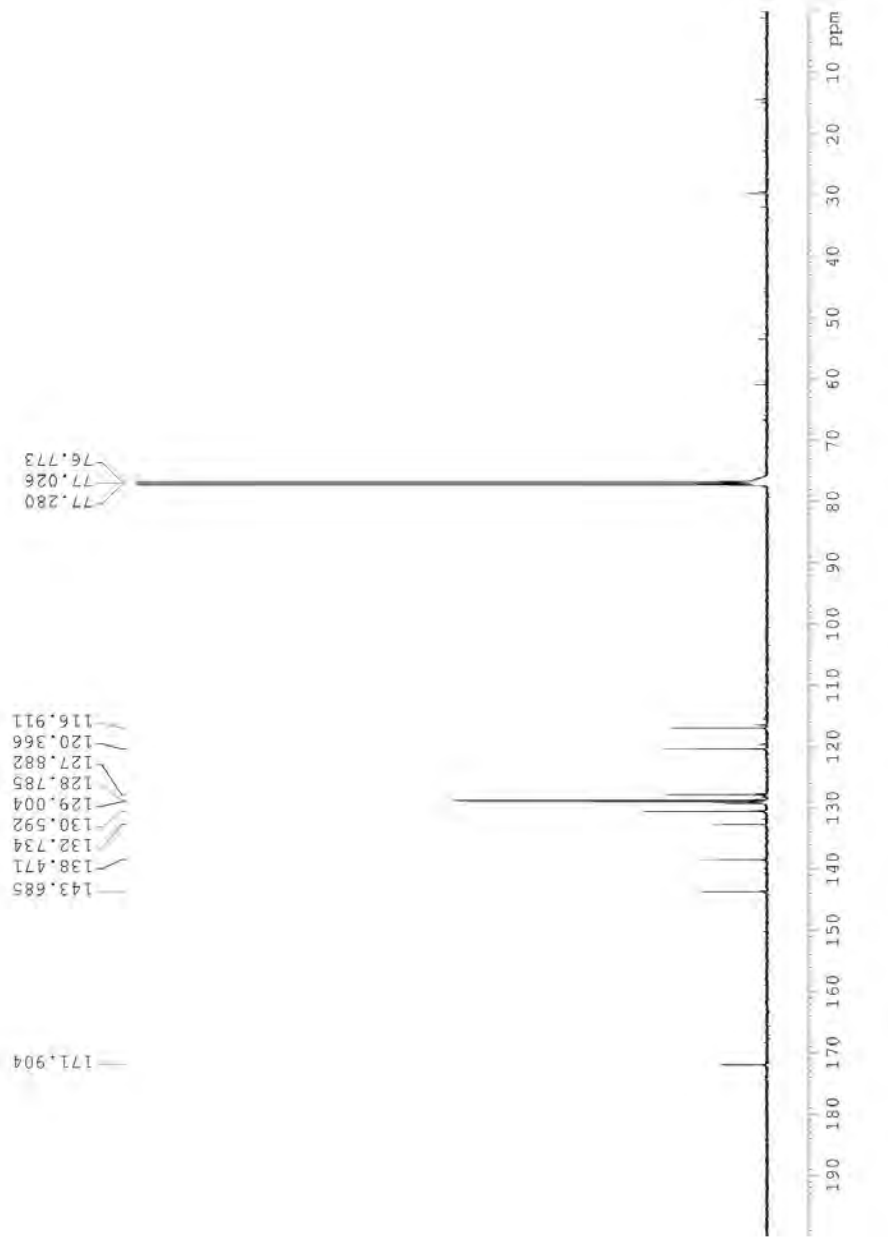
IR of 4-methyl-4'-vinyl-[1,1'-biphenyl]-2-amine (1)



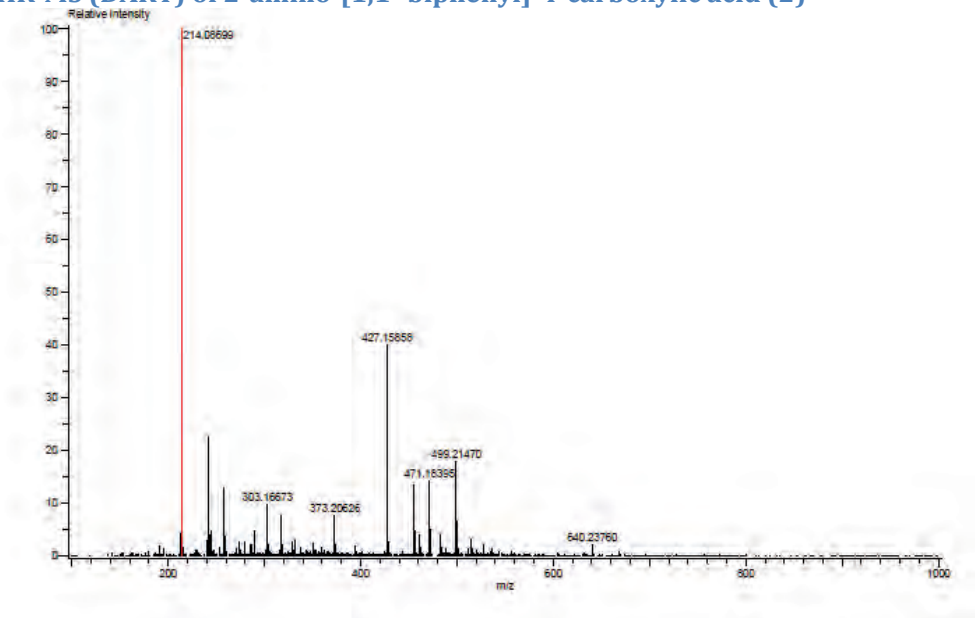
^{1}H-NMR of 2-amino-[1,1'-biphenyl]-4-carboxylic acid (2)



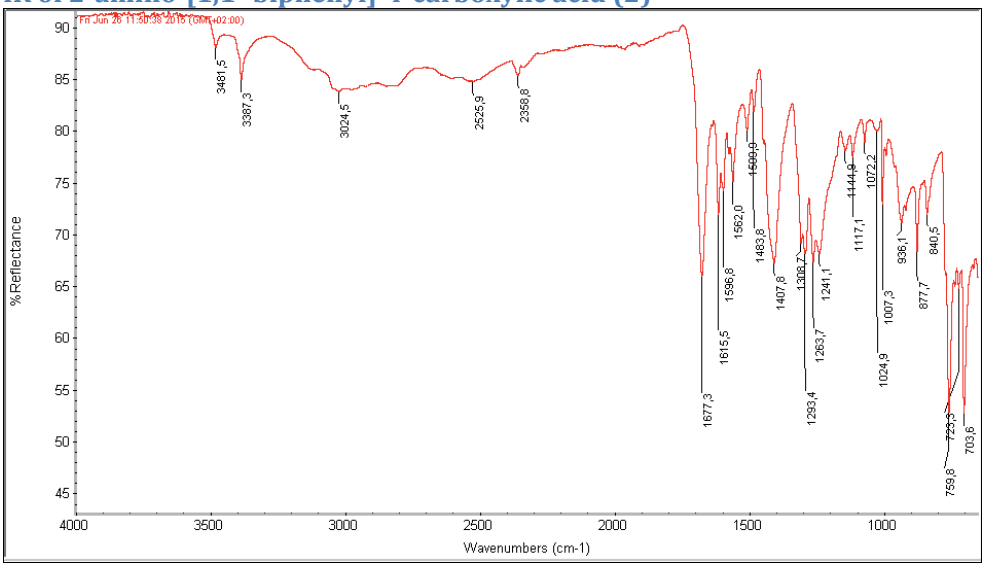
^{13}C-NMR of 2-amino-[1,1'-biphenyl]-4-carboxylic acid (2)



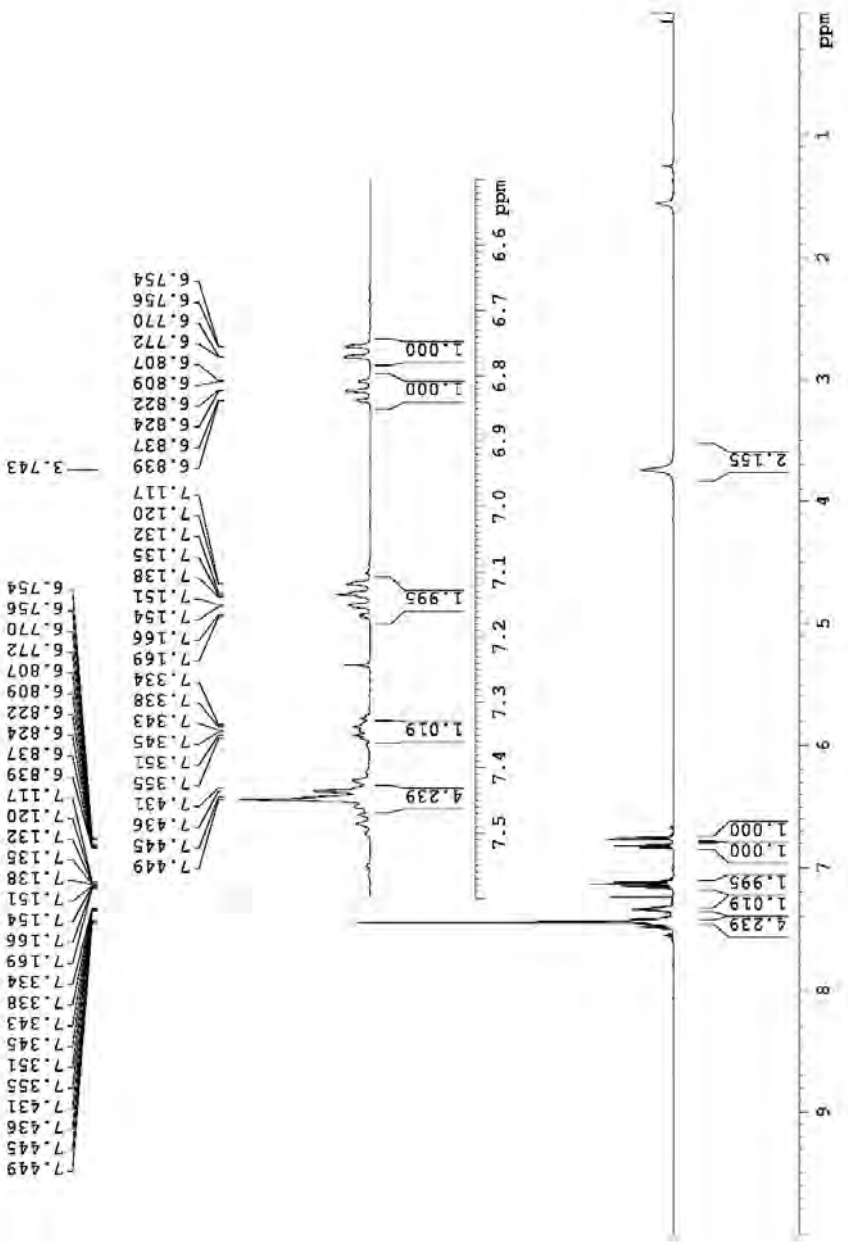
HR-MS (DART) of 2-amino-[1,1'-biphenyl]-4-carboxylic acid (2)



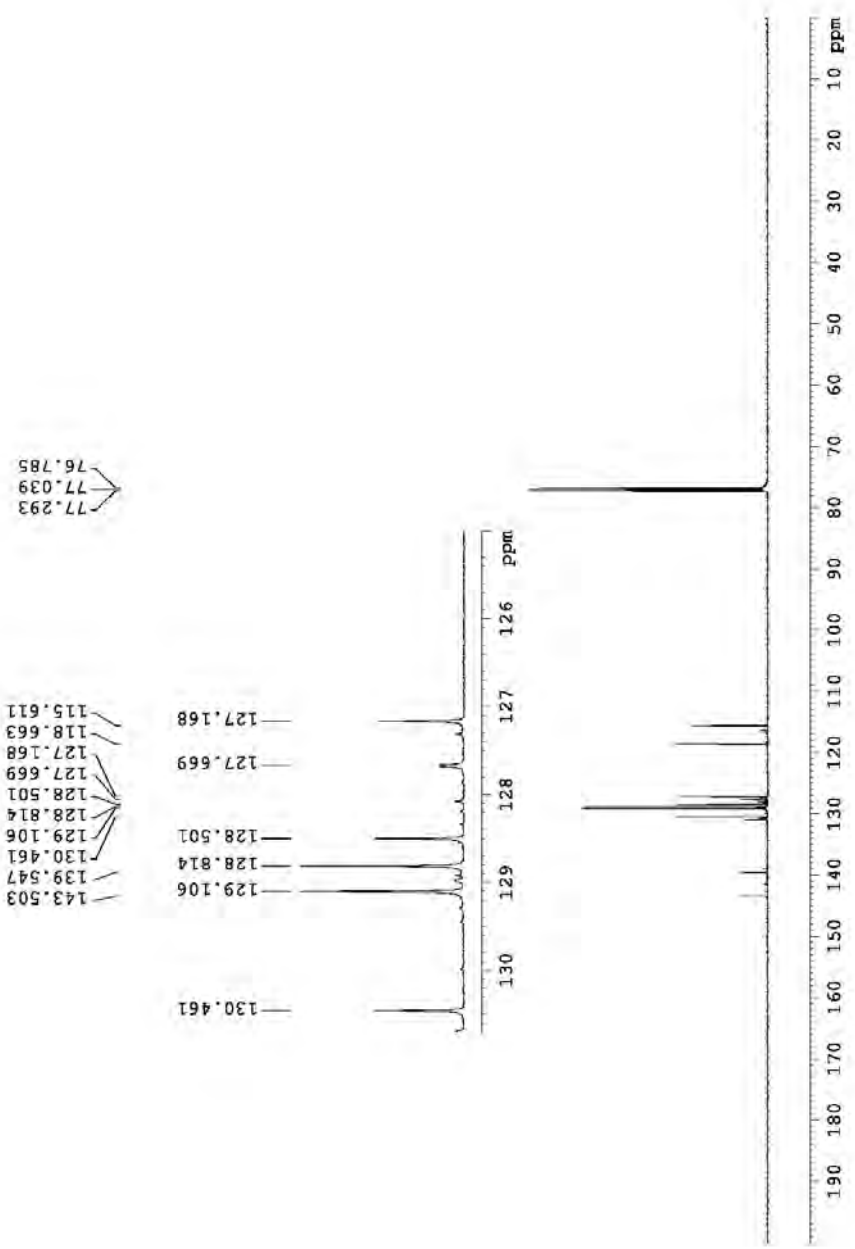
IR of 2-amino-[1,1'-biphenyl]-4-carboxylic acid (2)



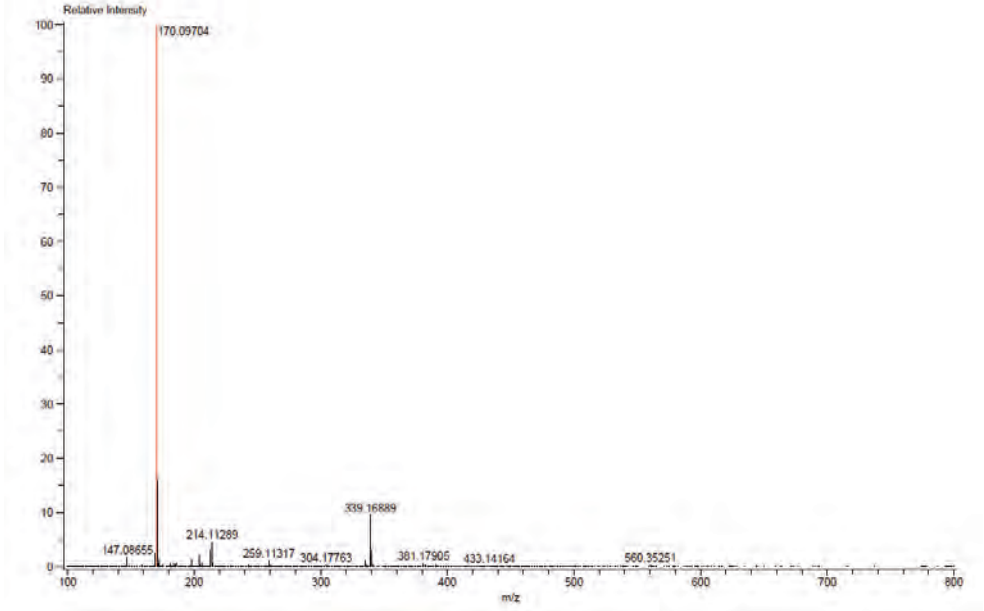
^{1}H-NMR of [1,1'-biphenyl]-2-amine (3)



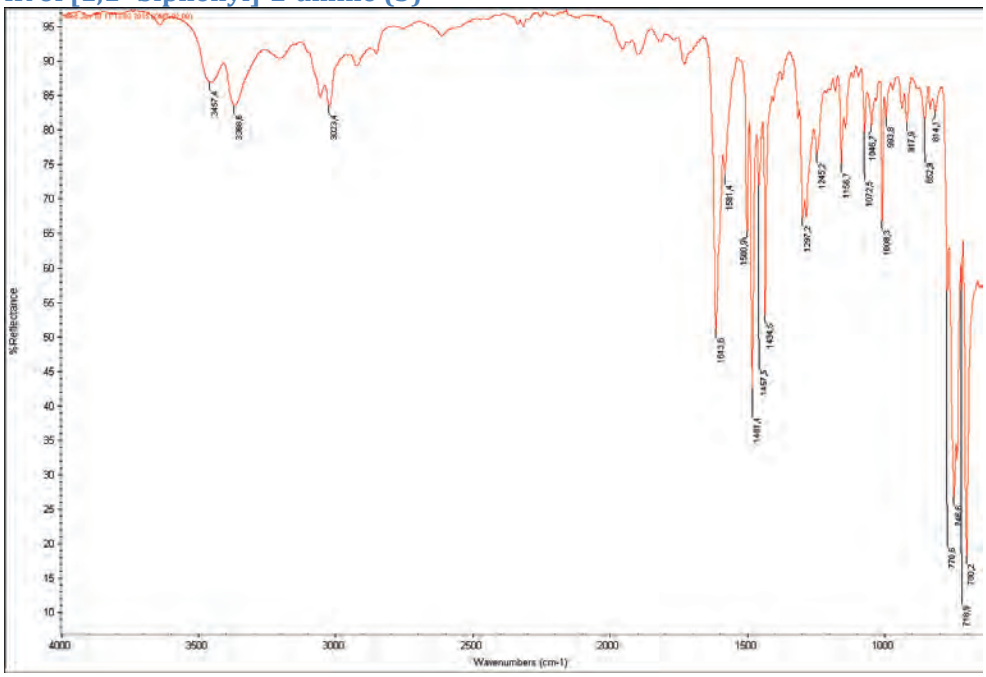
^{13}C-NMR of [1,1'-biphenyl]-2-amine (3)



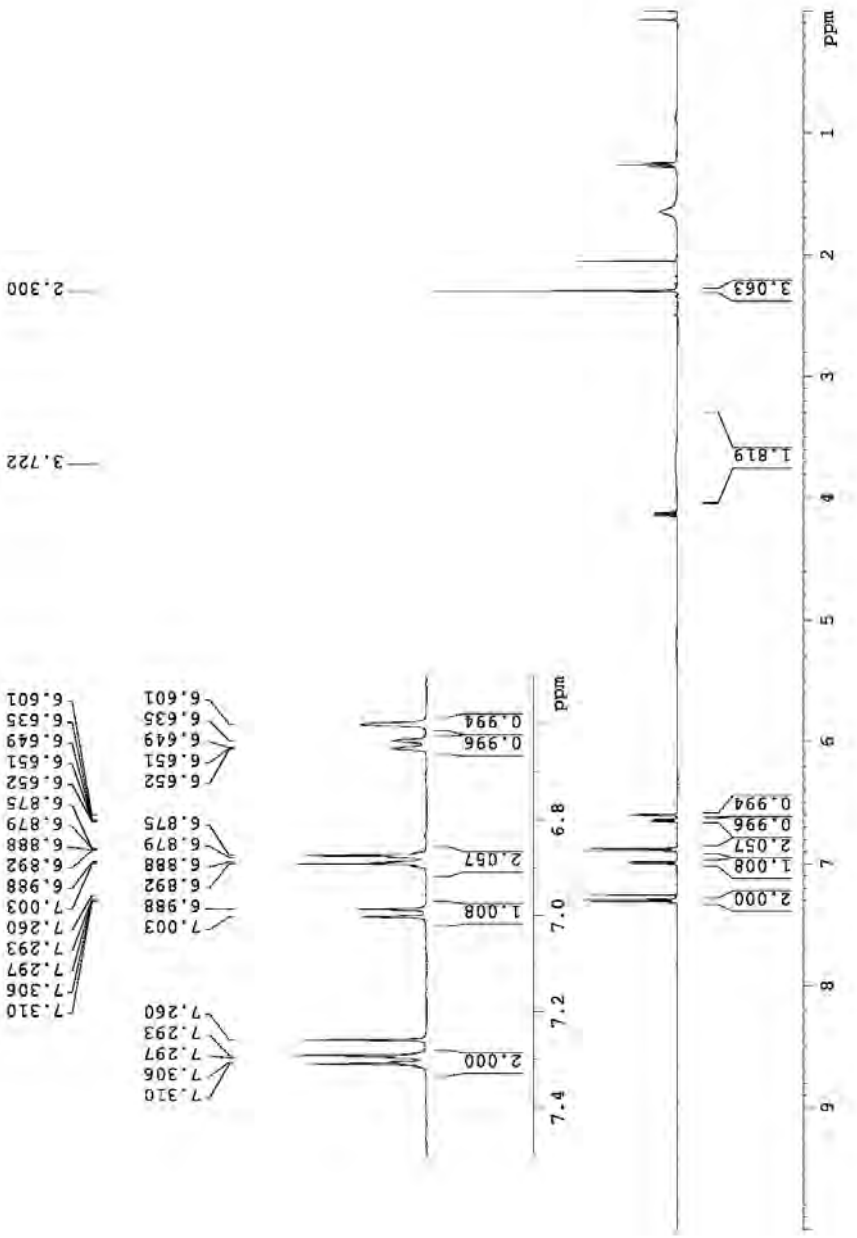
HR-MS (DART) of [1,1'-biphenyl]-2-amine (3)



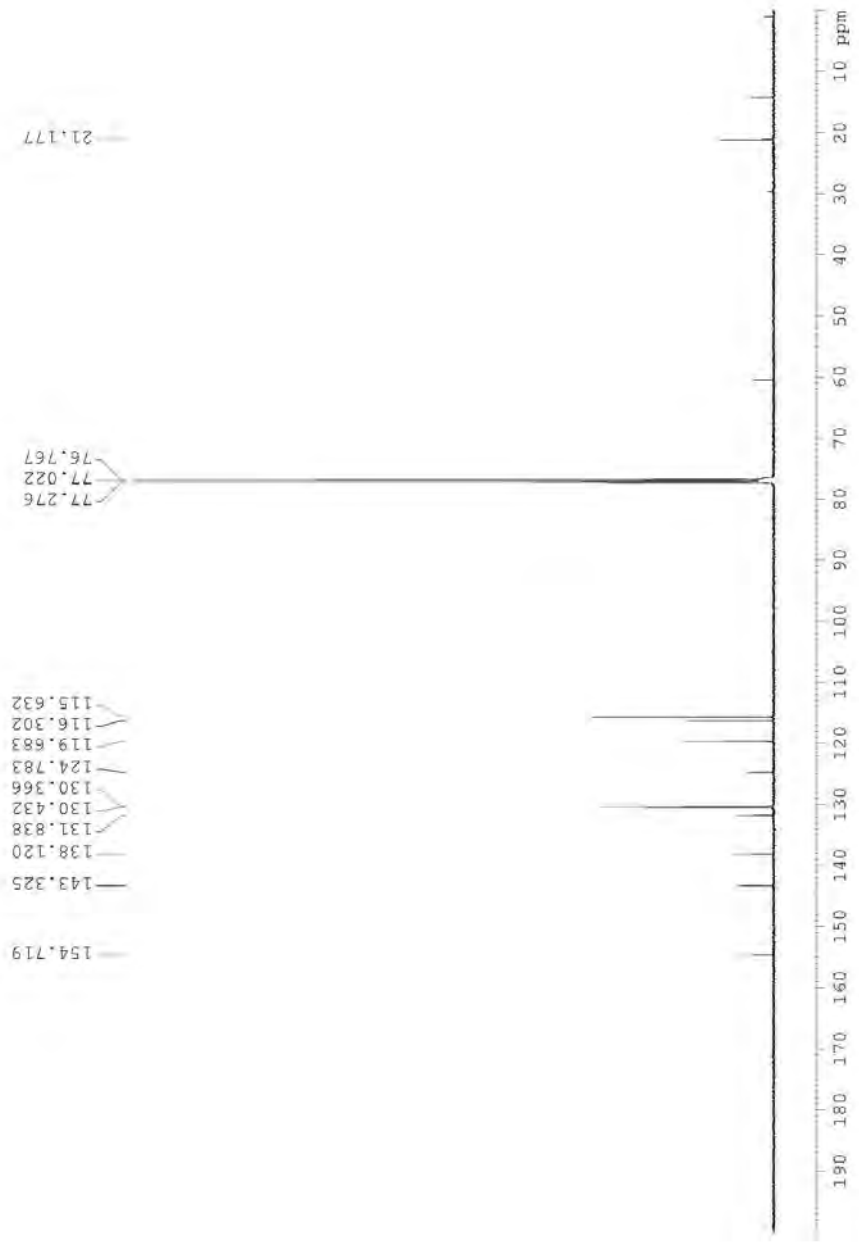
IR of [1,1'-biphenyl]-2-amine (3)



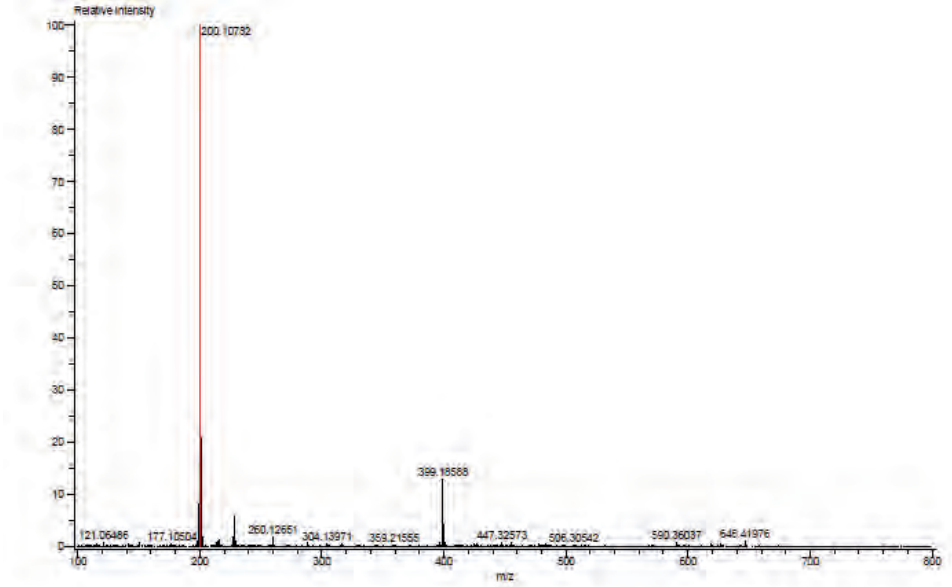
^{1}H-NMR of 2'-amino-4'-methyl-[1,1'-biphenyl]-4-ol (5)



^{13}C-NMR of 2'-amino-4'-methyl-[1,1'-biphenyl]-4-ol (5)

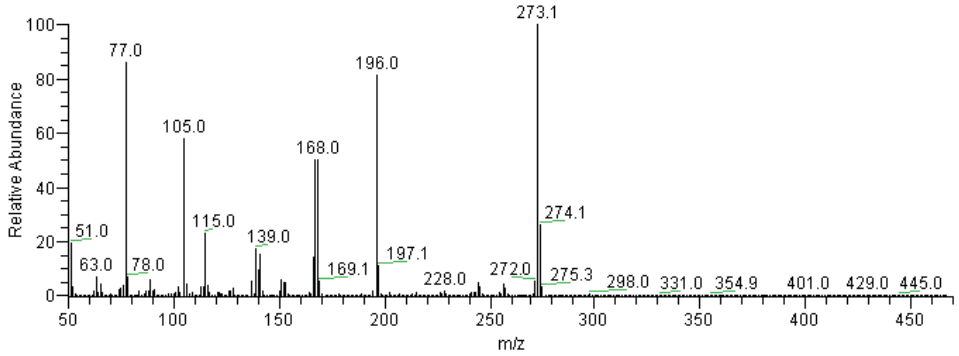


HR-MS (DART) of 2'-amino-4'-methyl-[1,1'-biphenyl]-4-ol (5)

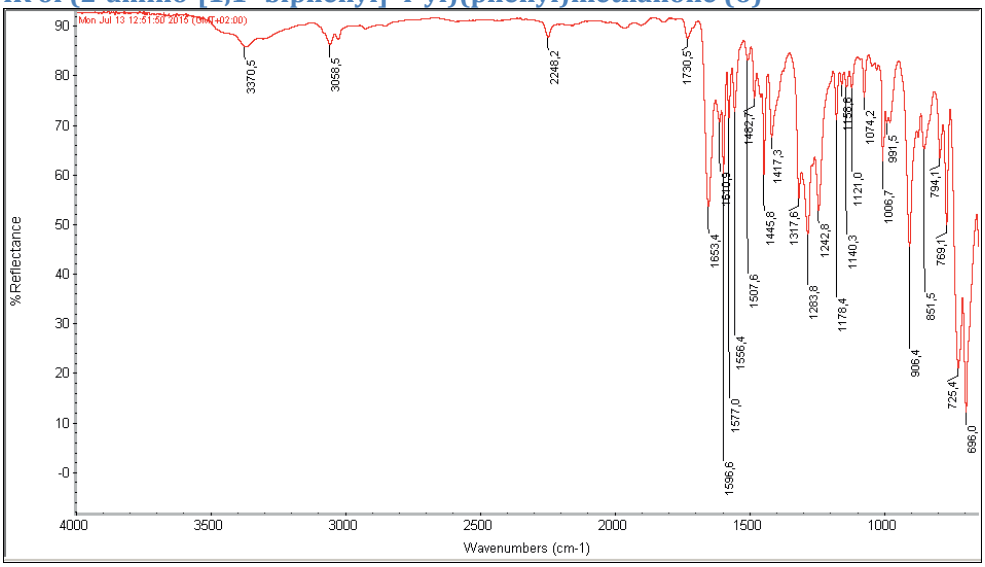


IR of 2'-amino-4'-methyl-[1,1'-biphenyl]-4-ol (5)

MS (EI) (2-amino-[1,1'-biphenyl]-4-yl)(phenyl)methanone (6)



IR of (2-amino-[1,1'-biphenyl]-4-yl)(phenyl)methanone (6)



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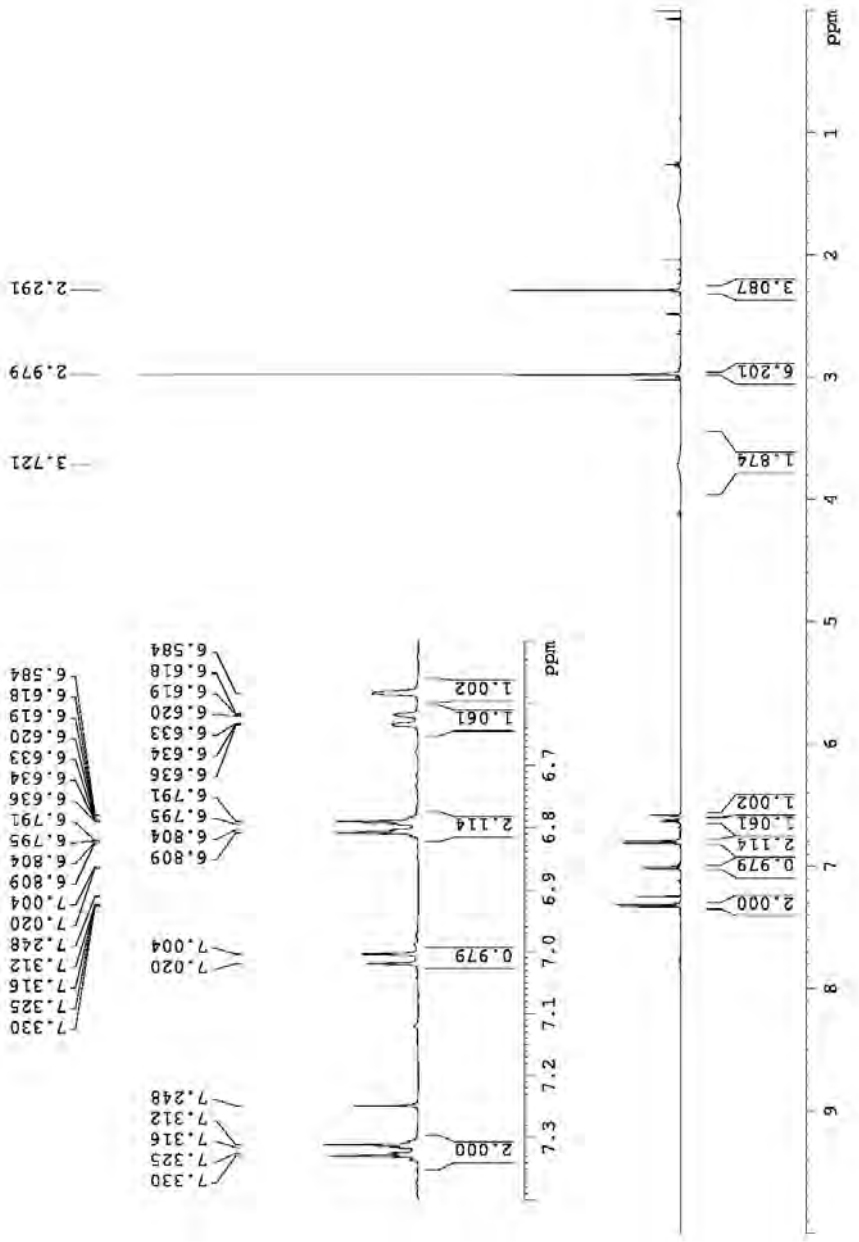

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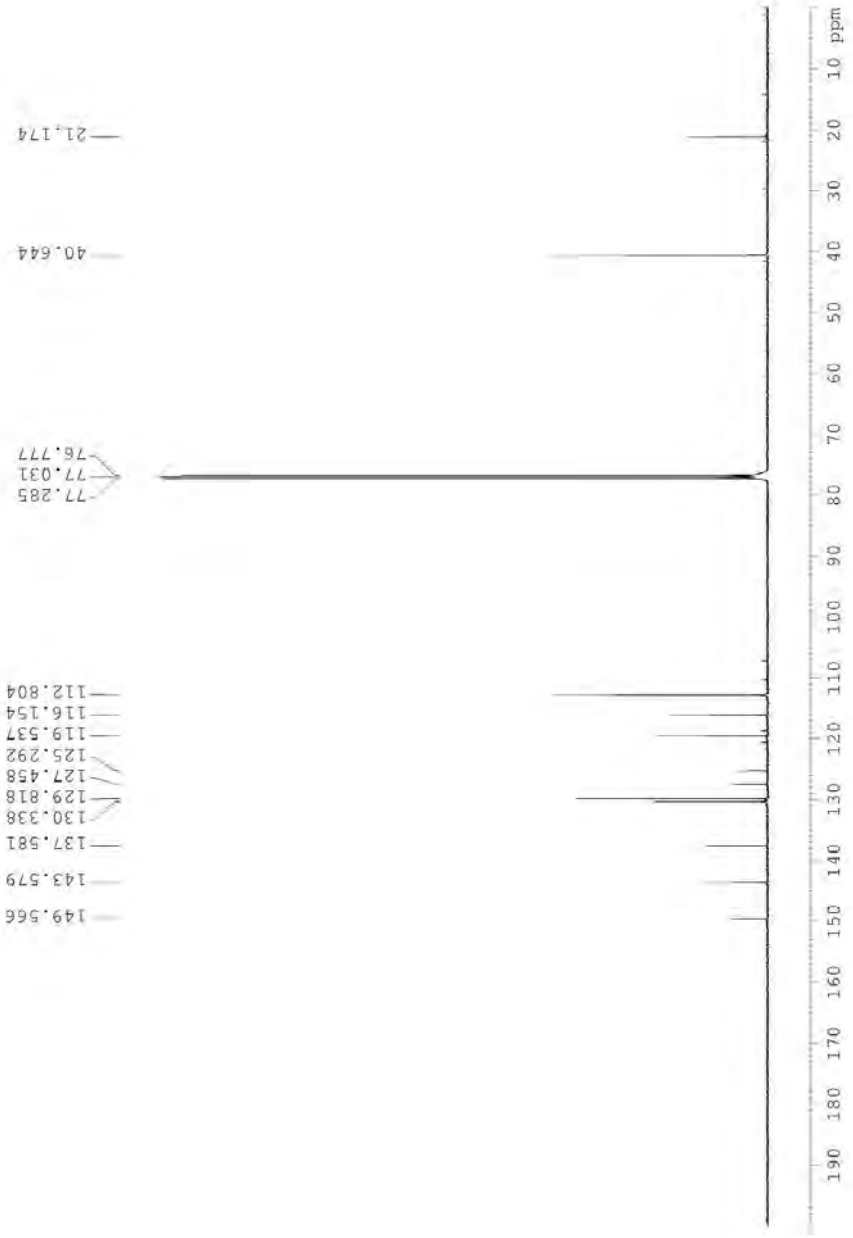

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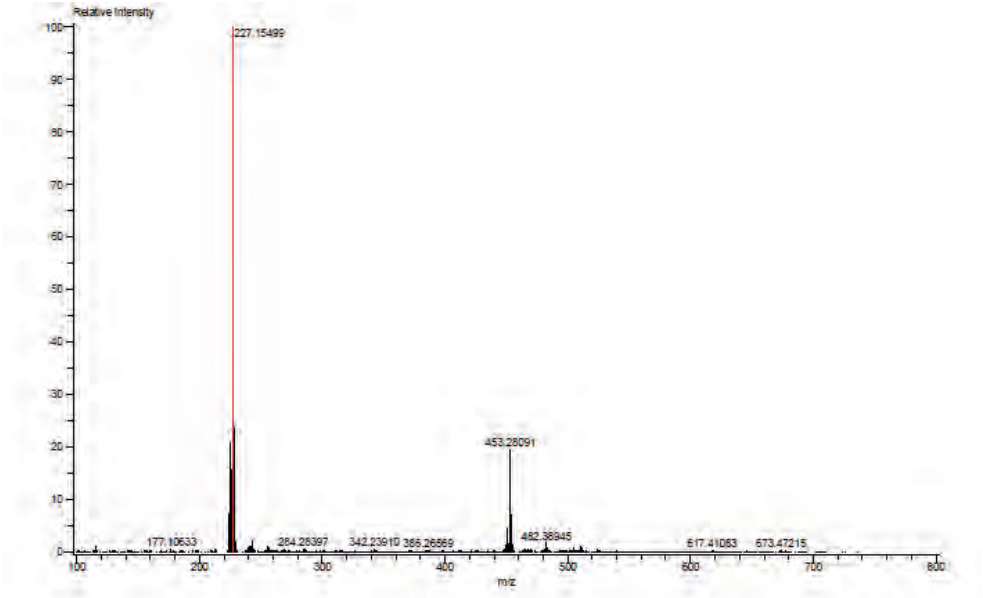
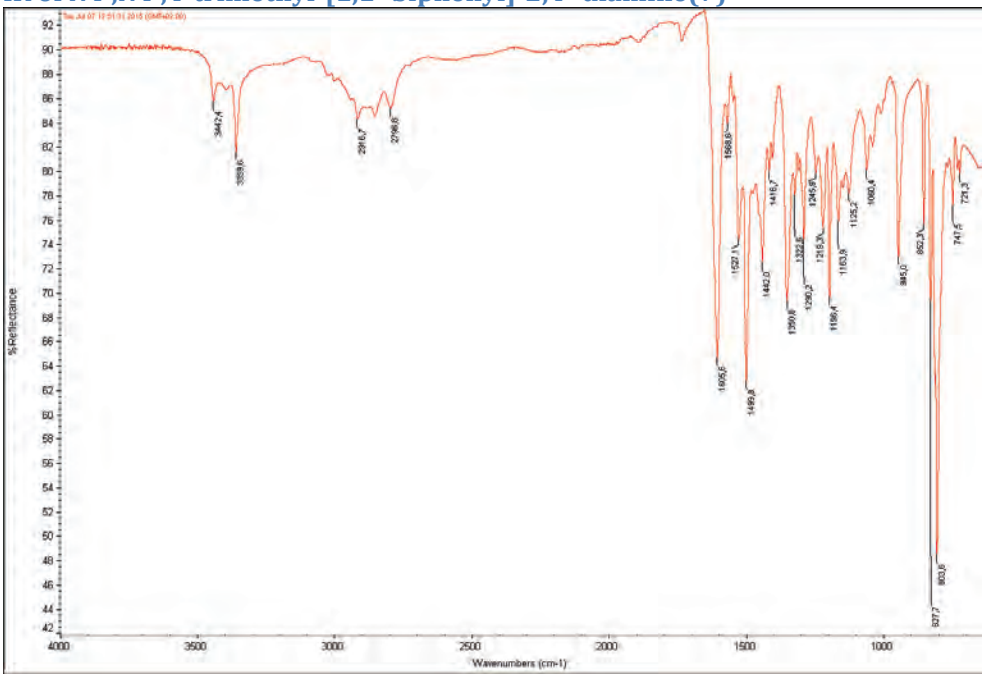


IR of N4',N4',4-trimethyl-[1,1'-biphenyl]-2,4'-diamine(7)



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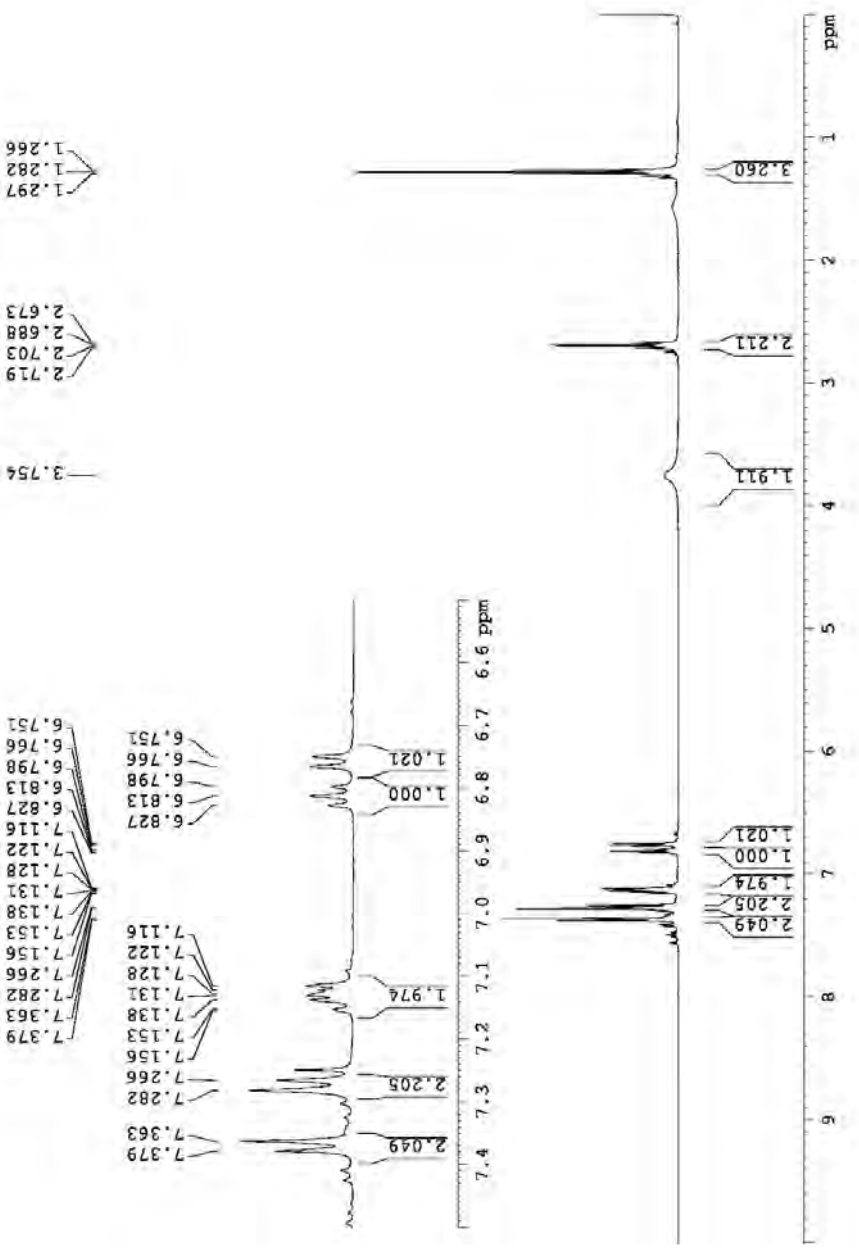

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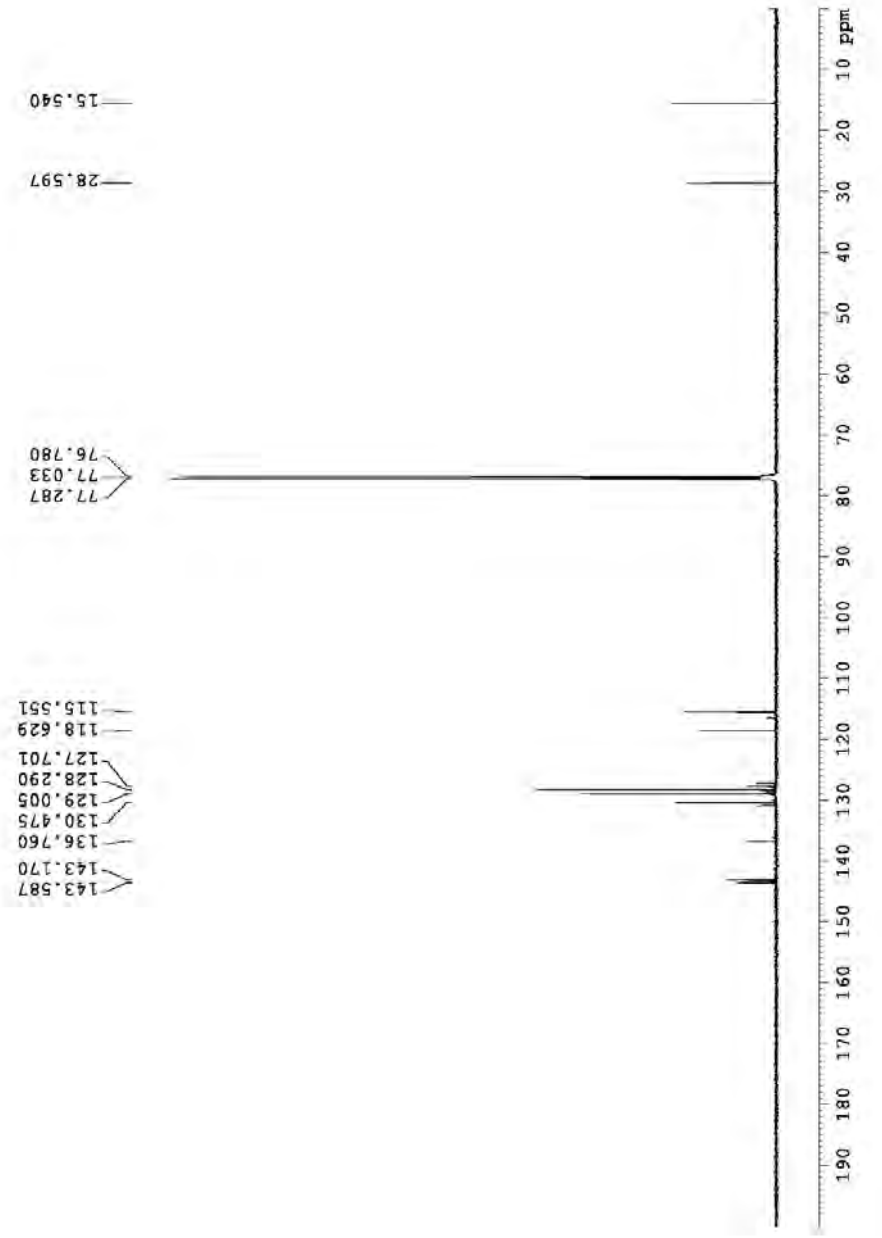

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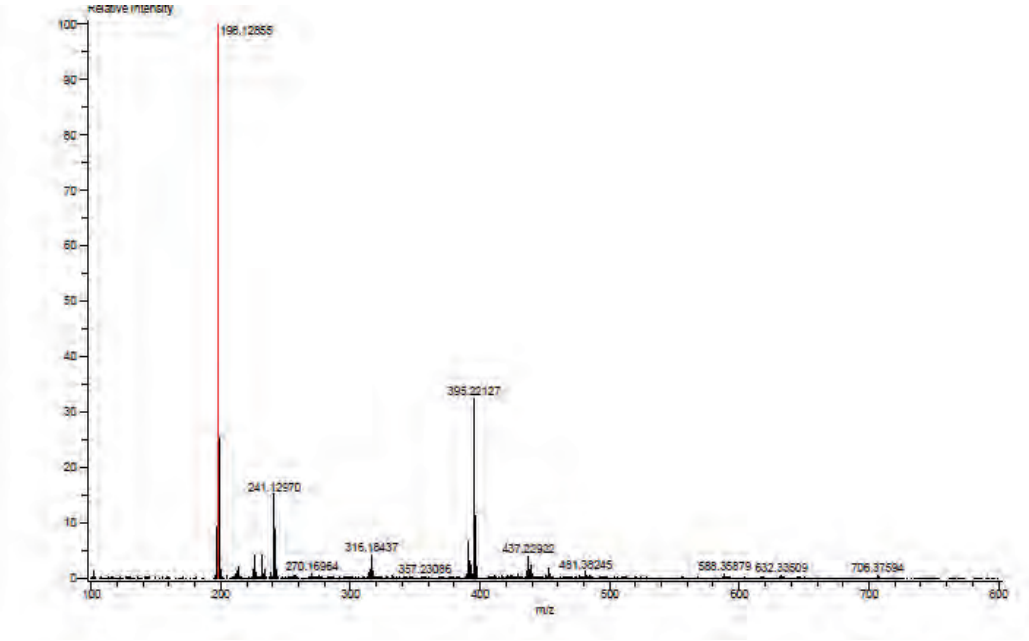

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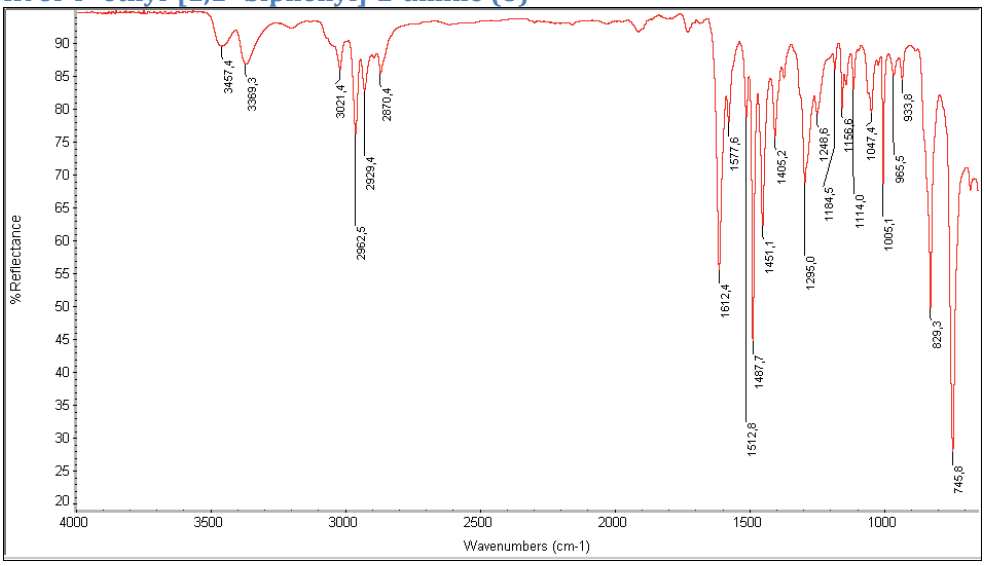
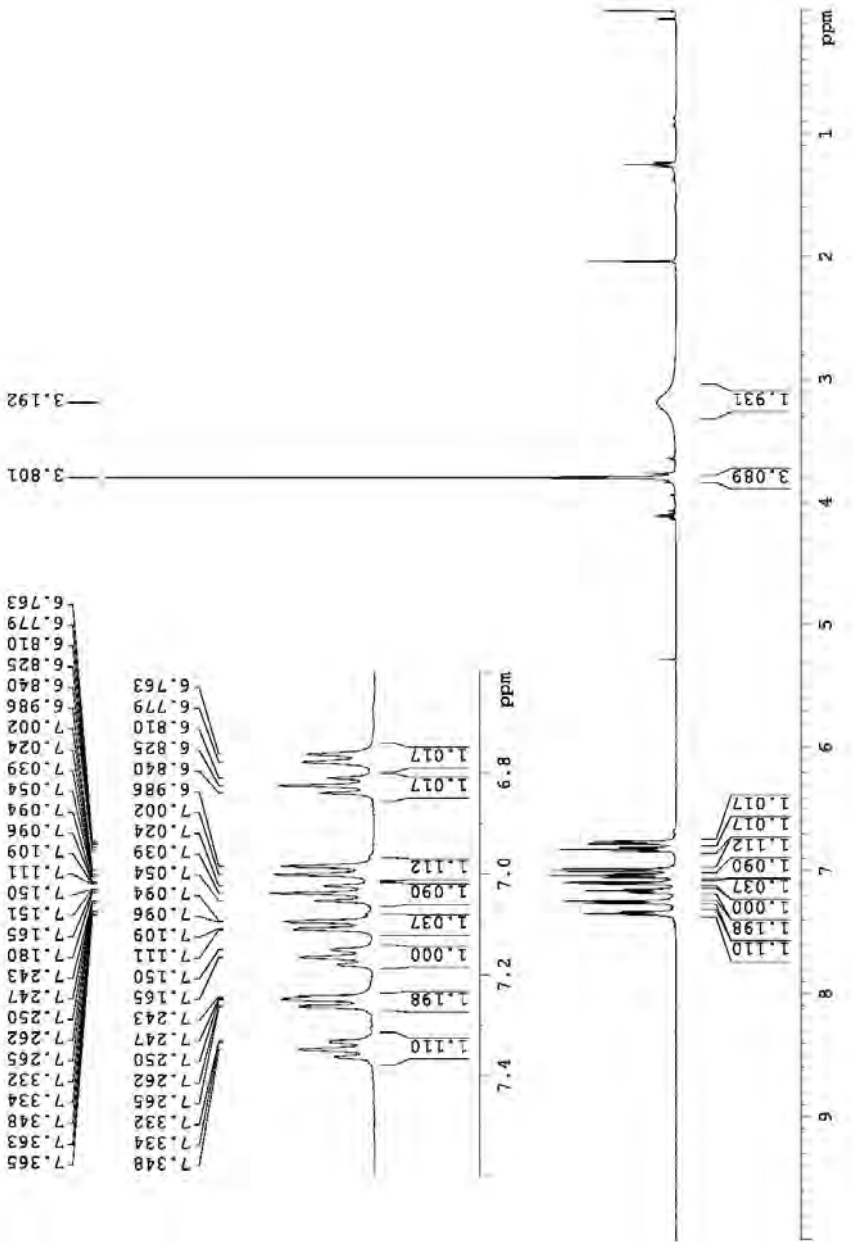


^{1}H-NMR of 2'-methoxy-[1,1'-biphenyl]-2-amine (9)



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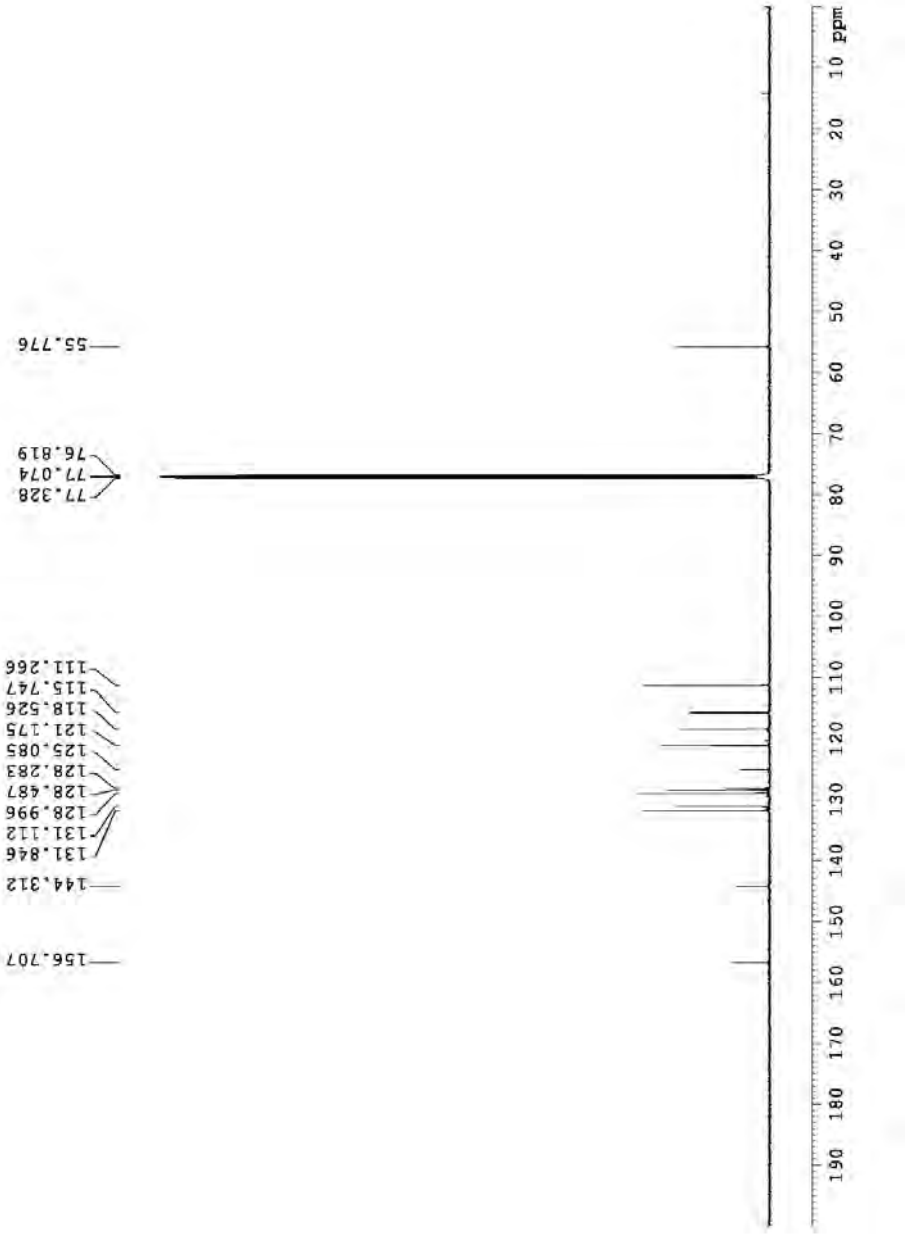

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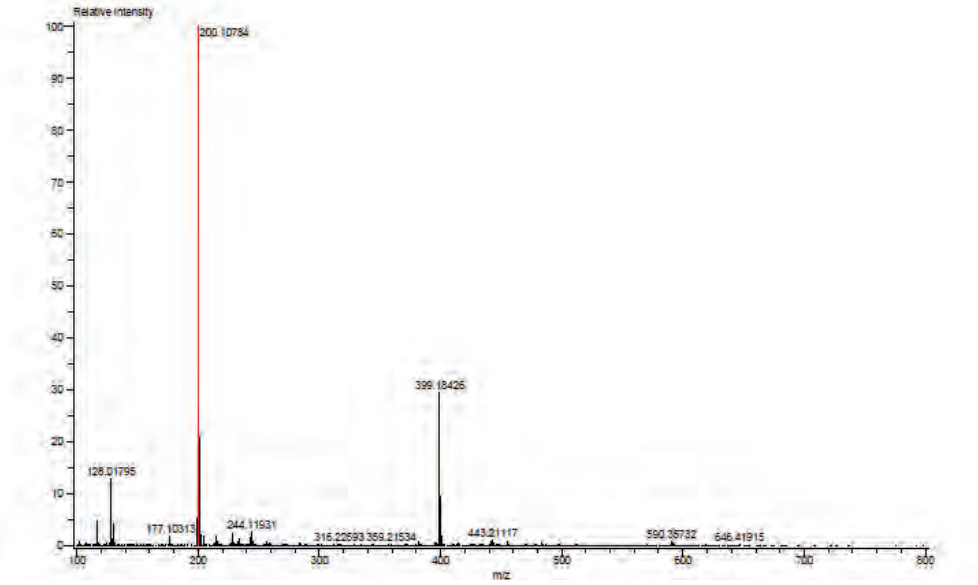

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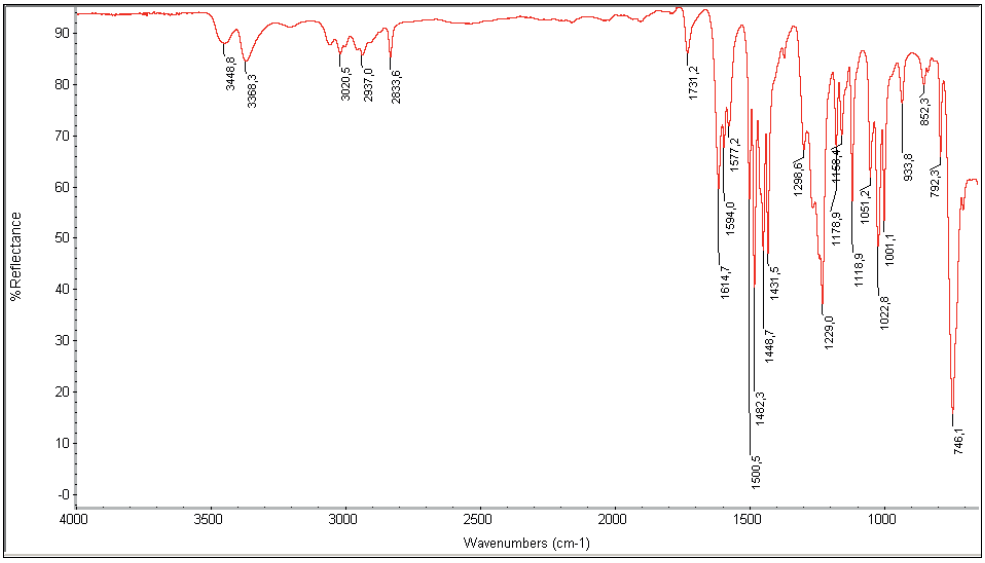

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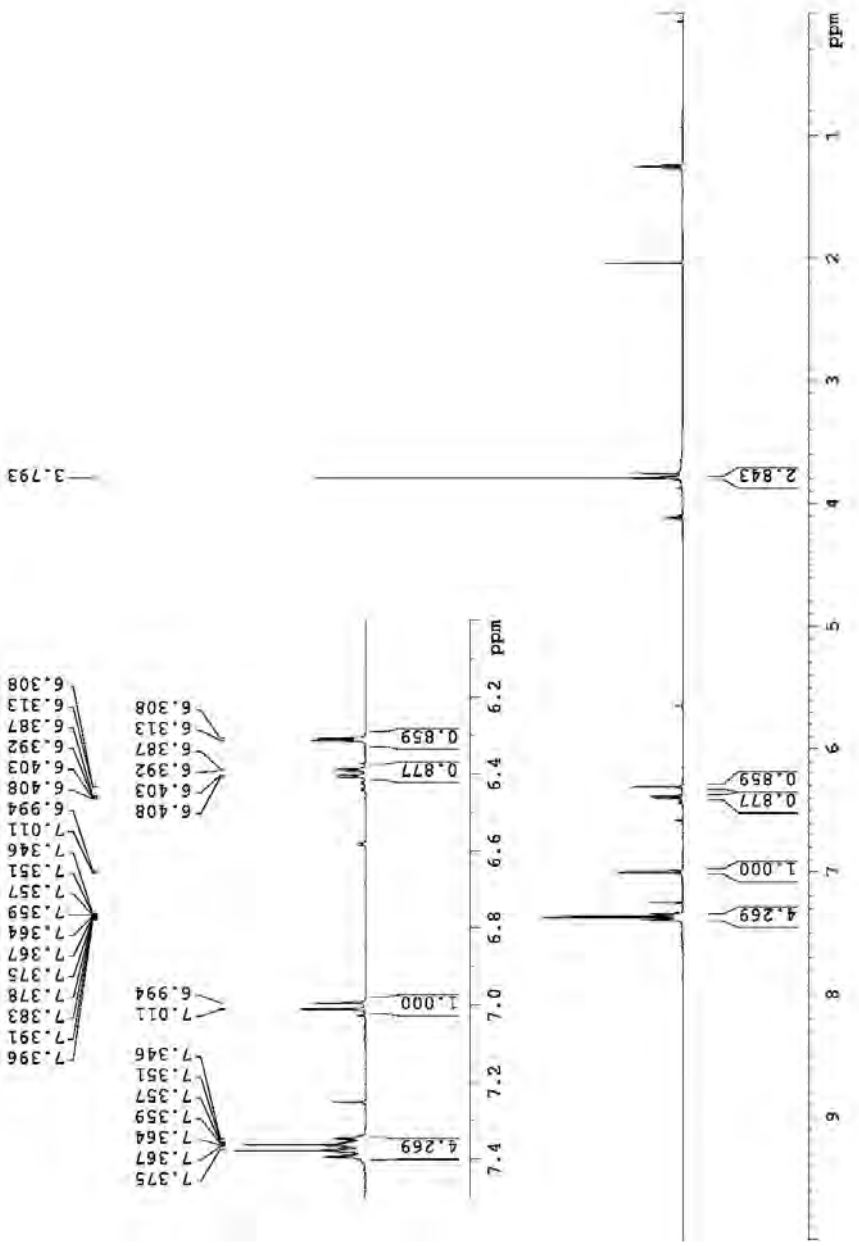

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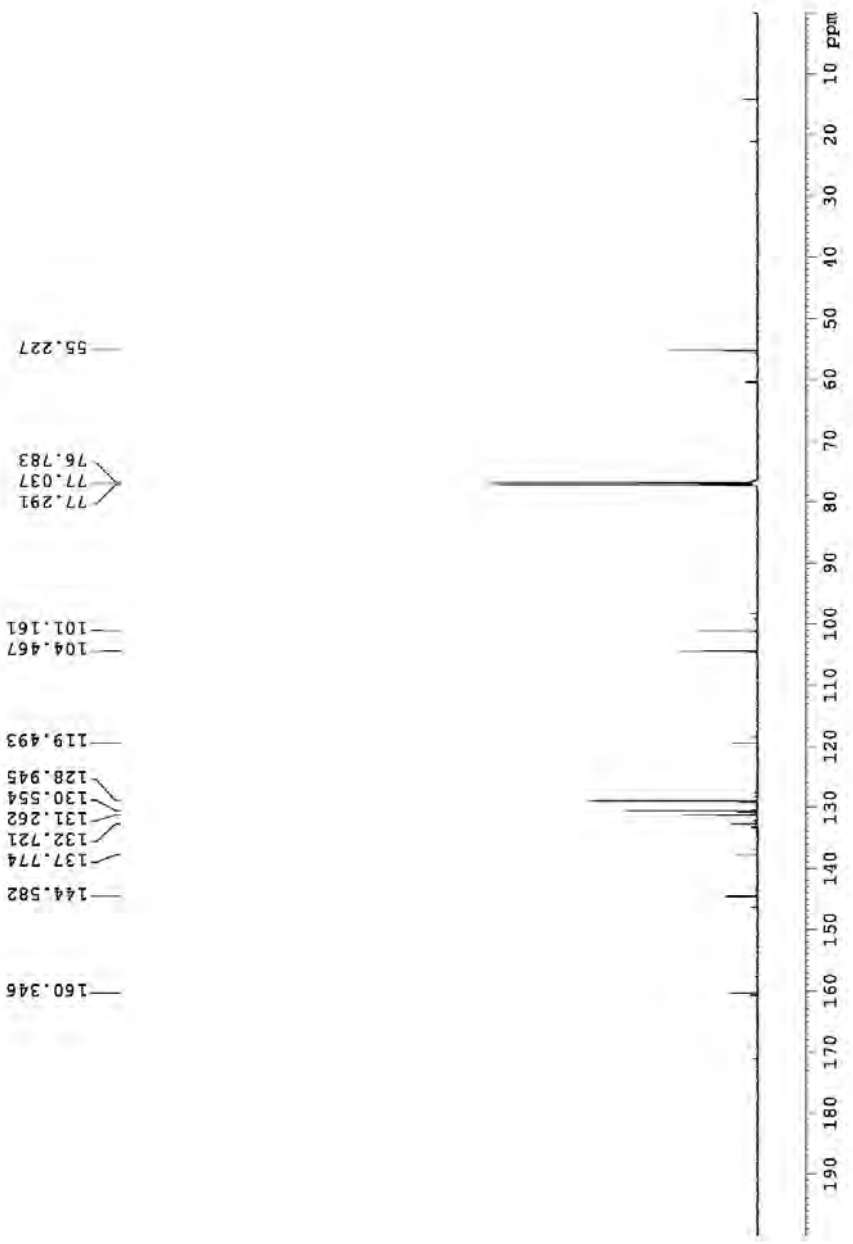

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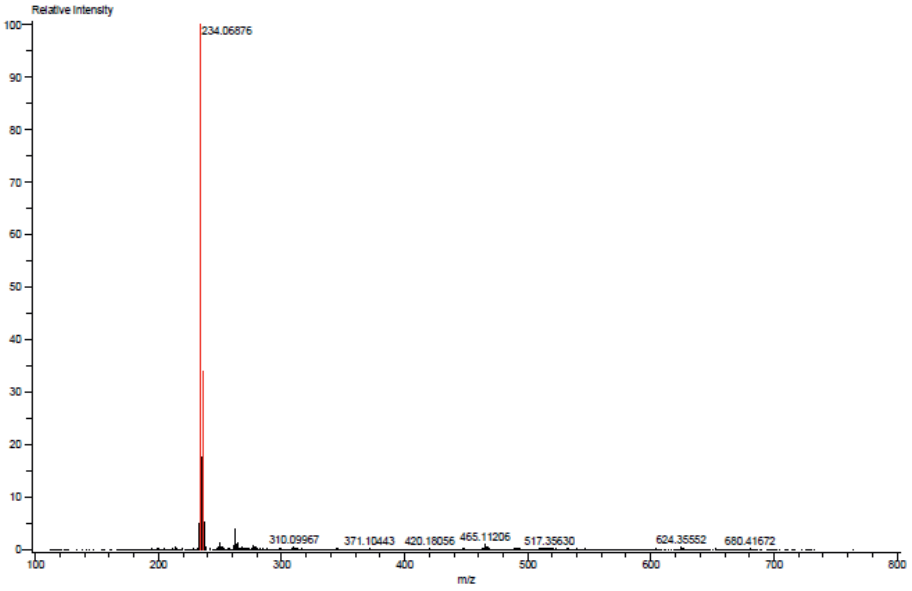
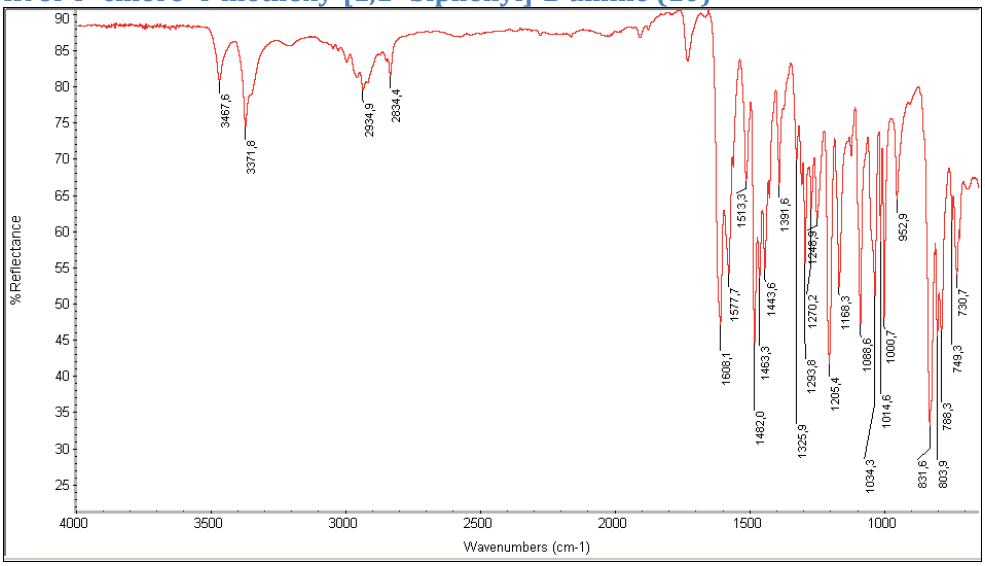
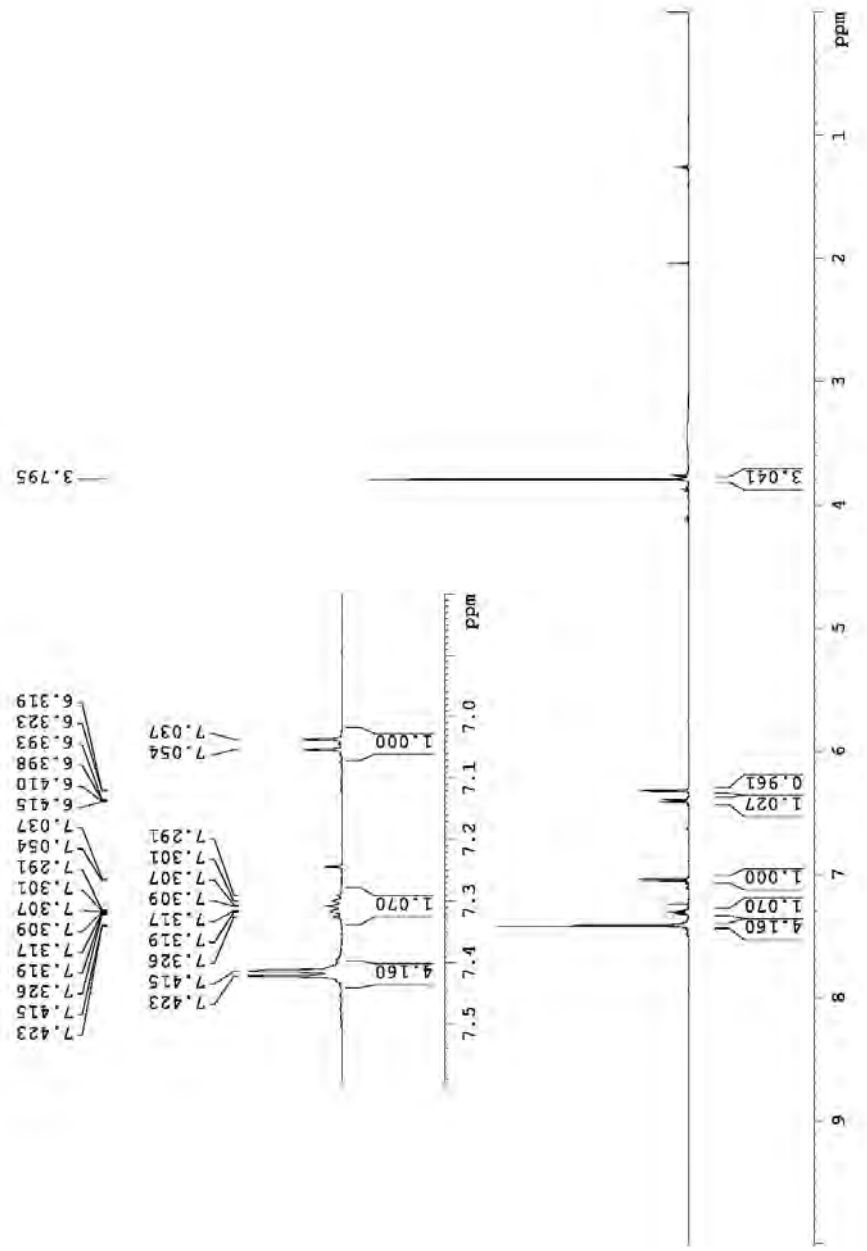


IR of 4'-chloro-4-methoxy-[1,1'-biphenyl]-2-amine (10)



^{1}H-NMR of 4-methoxy-[1,1'-biphenyl]-2-amine (11)



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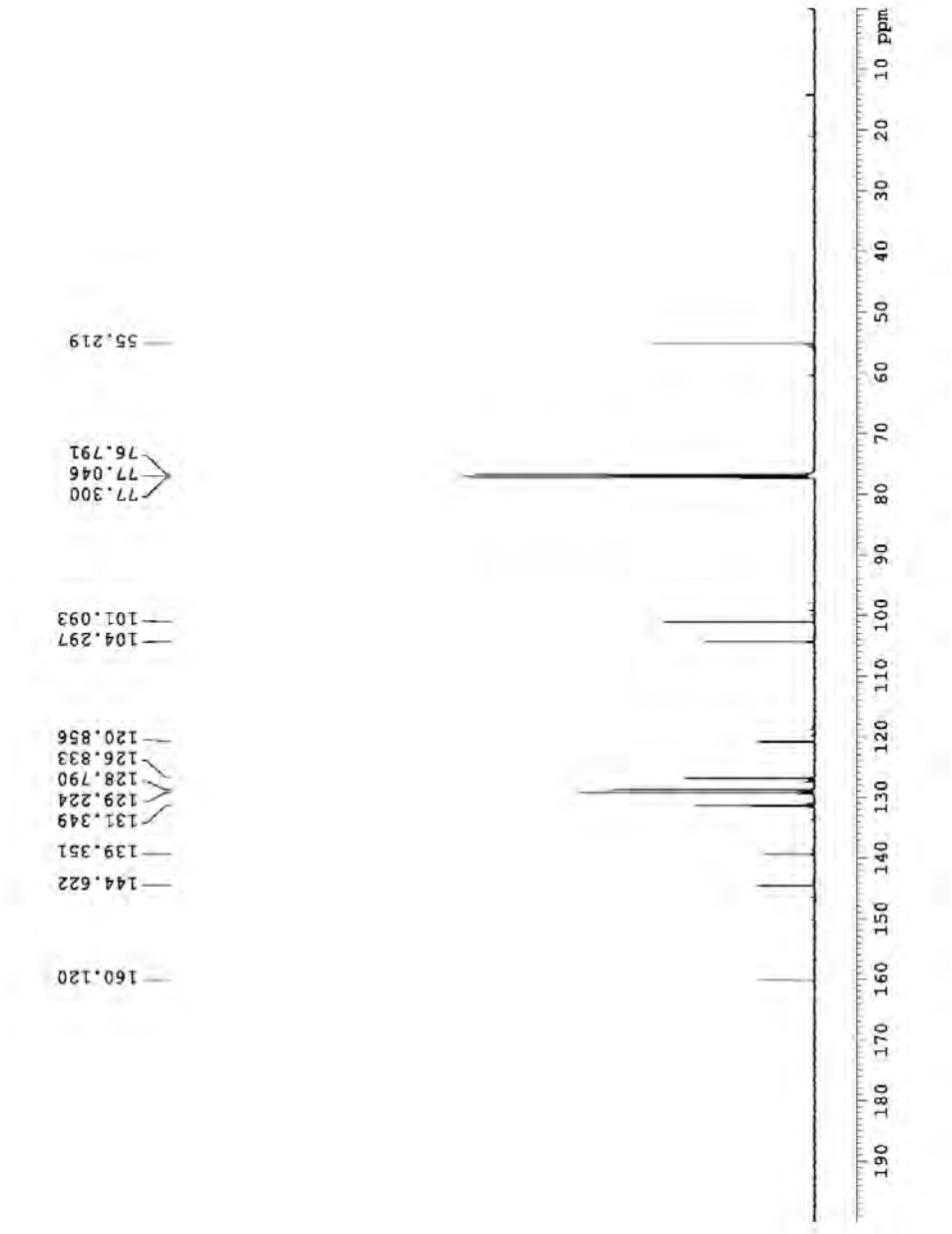

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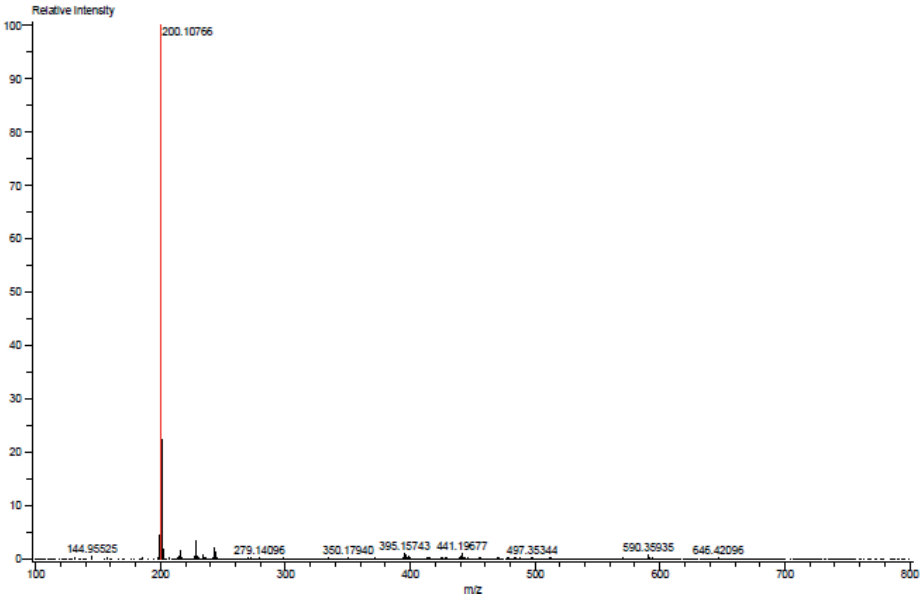
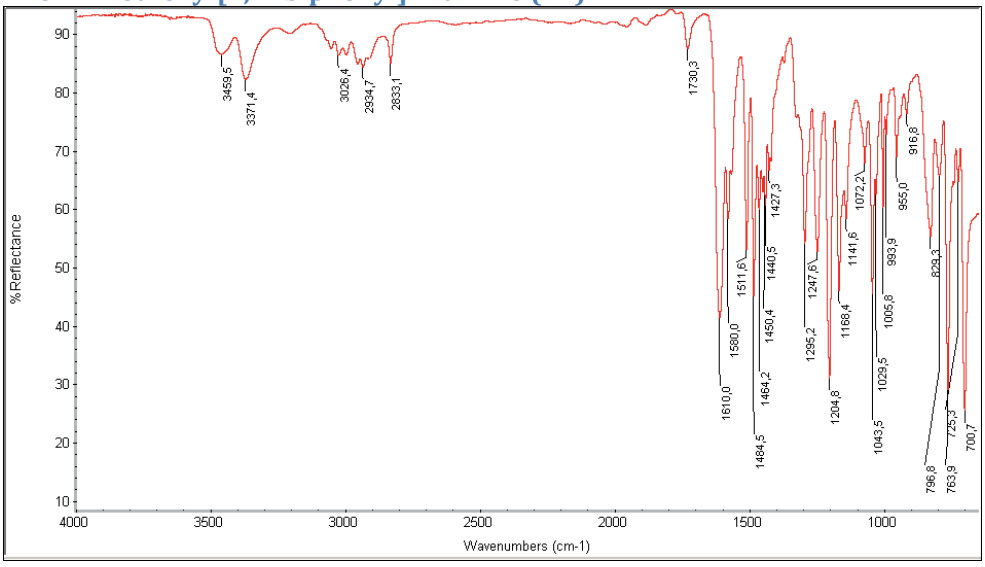


IR of 4-methoxy-[1,1'-biphenyl]-2-amine (11)



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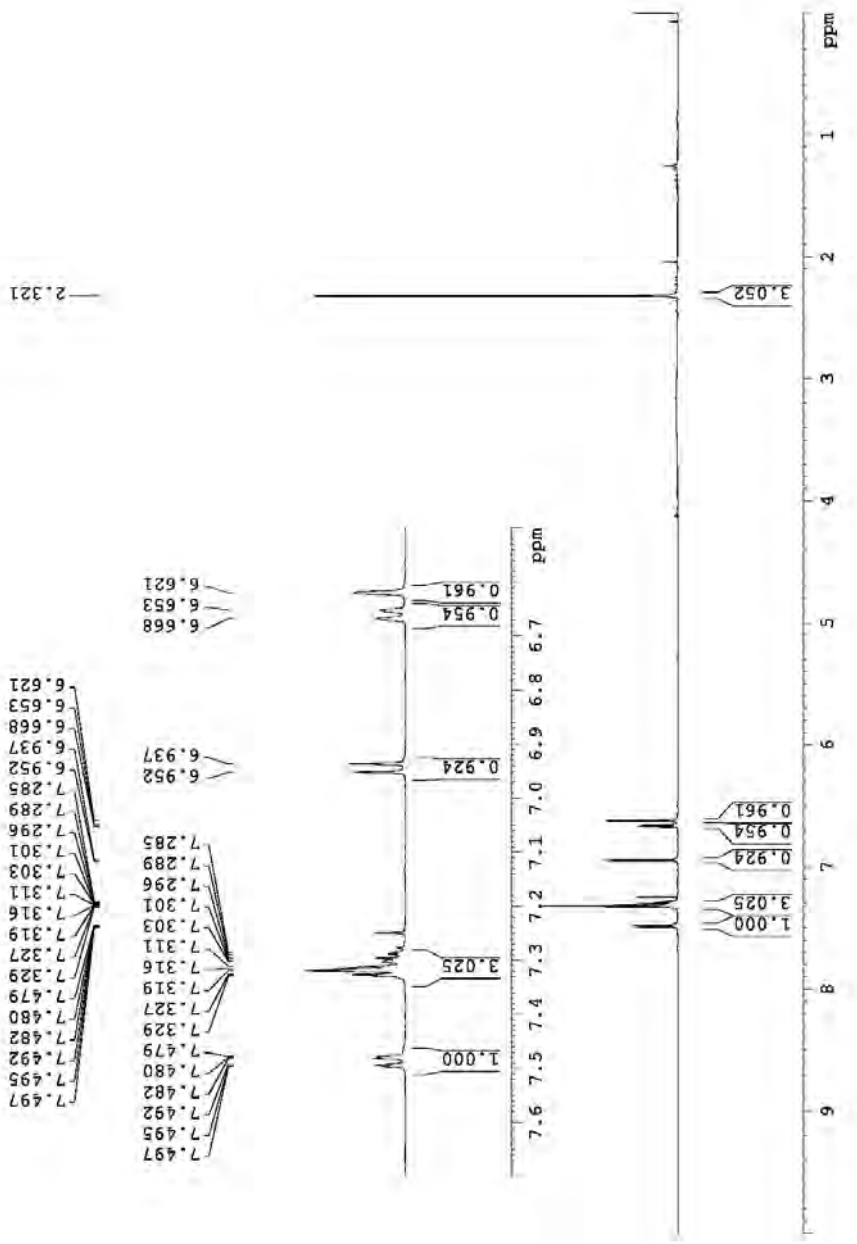

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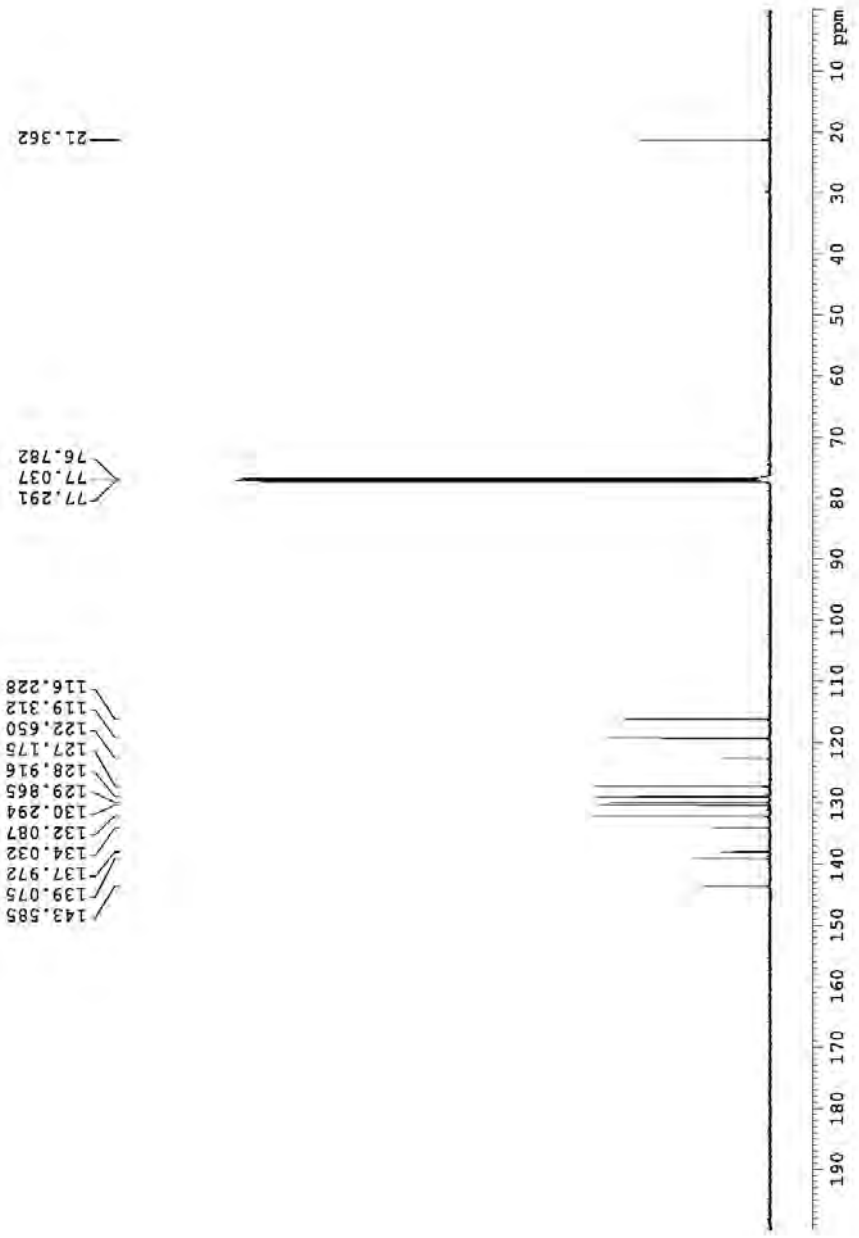

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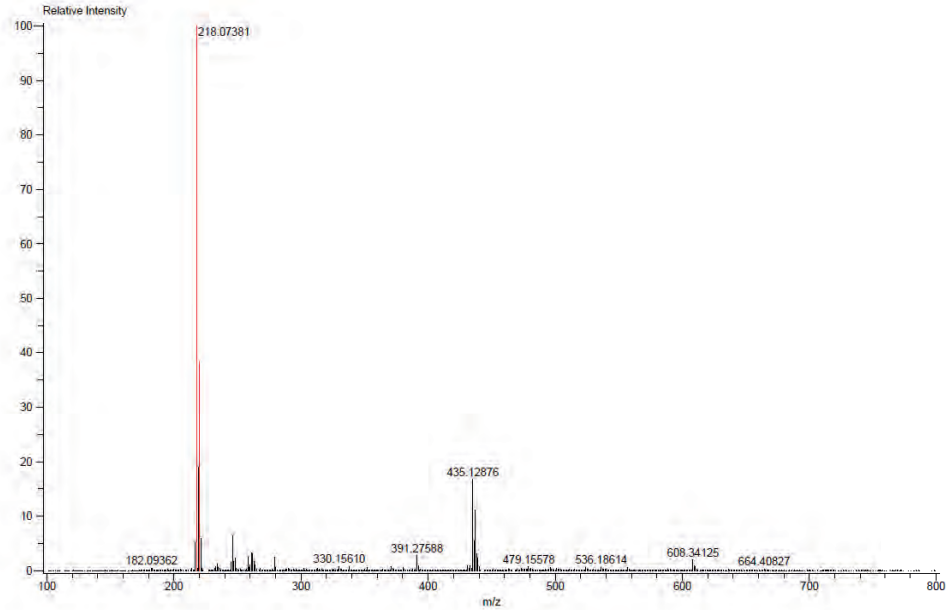

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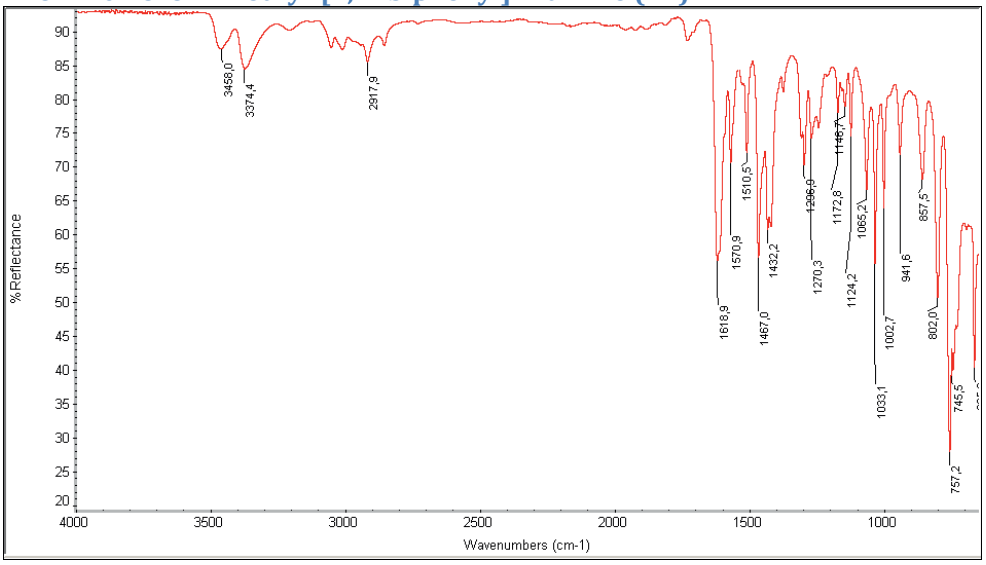

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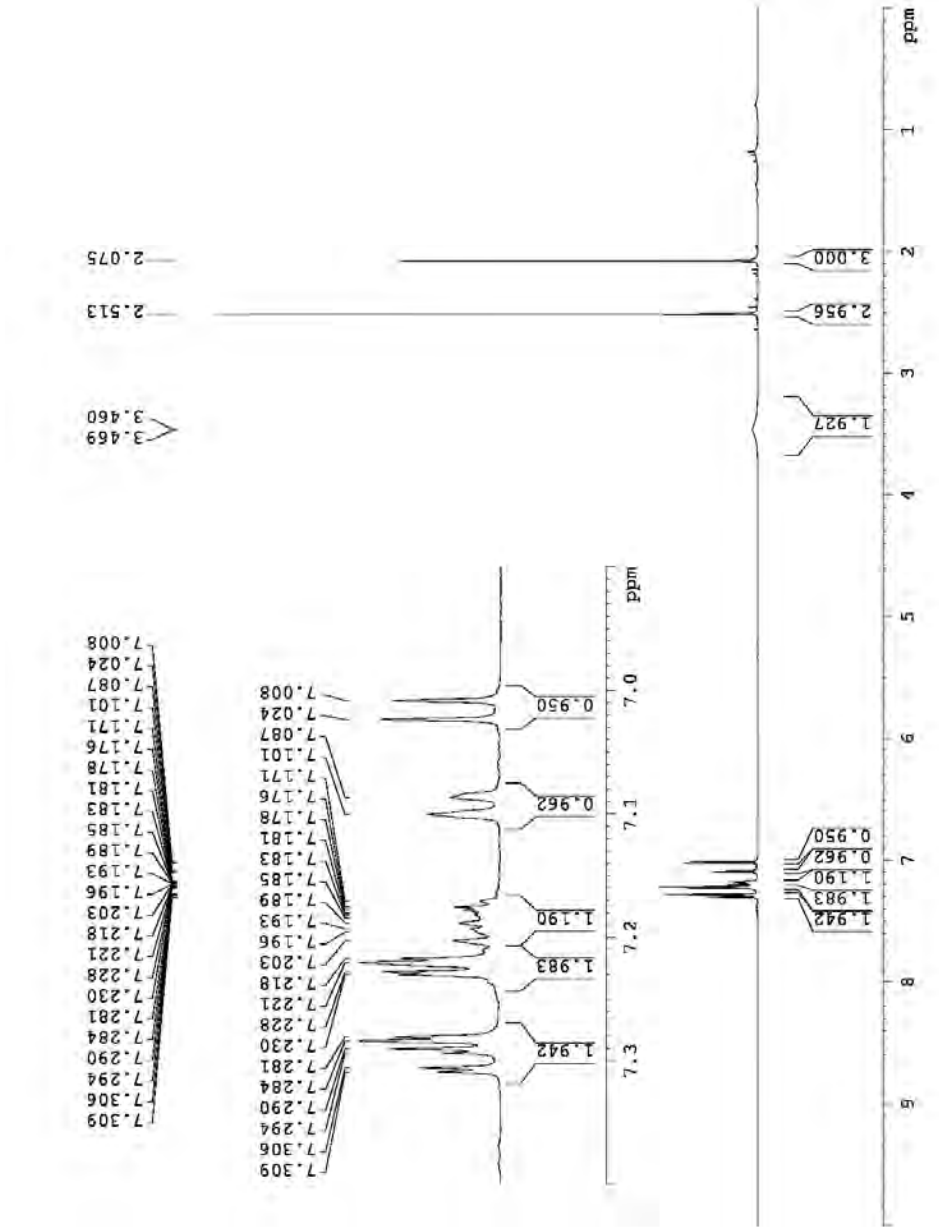

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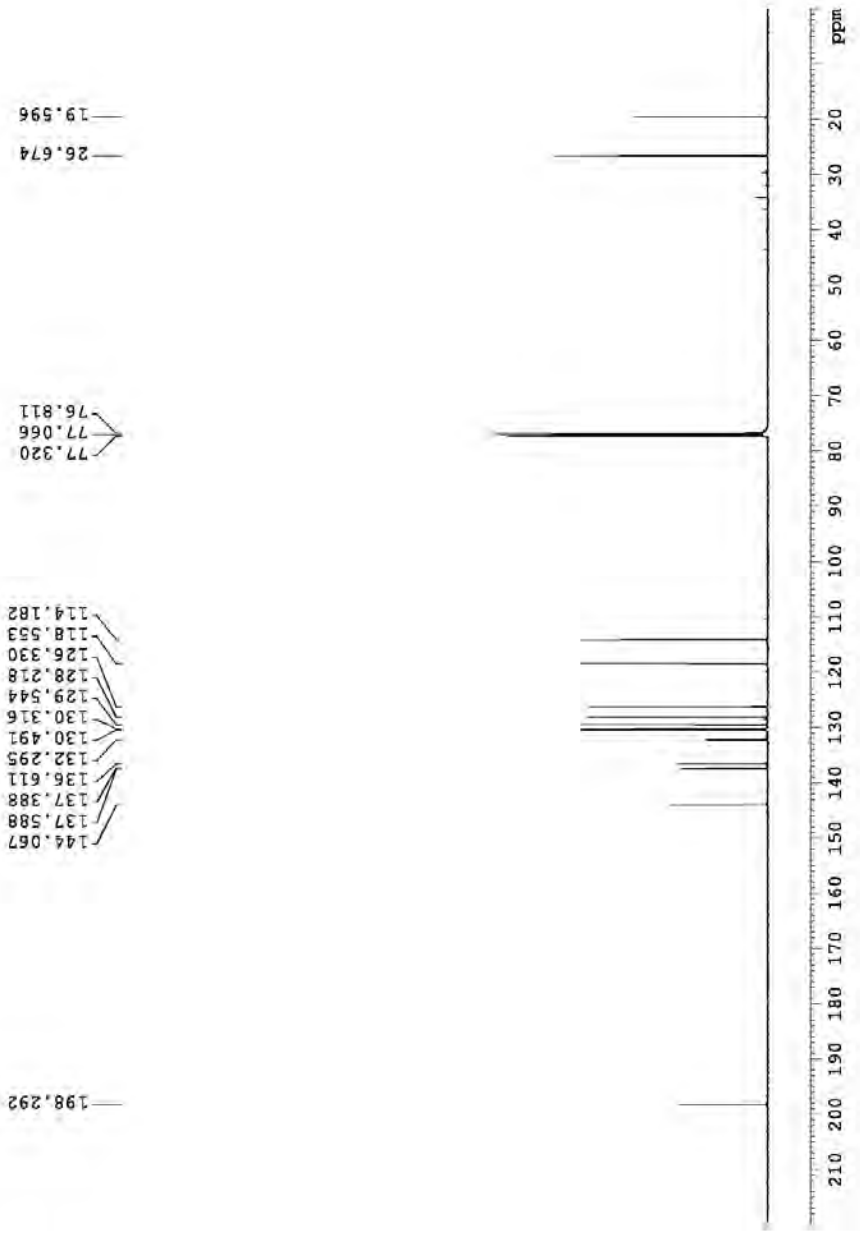

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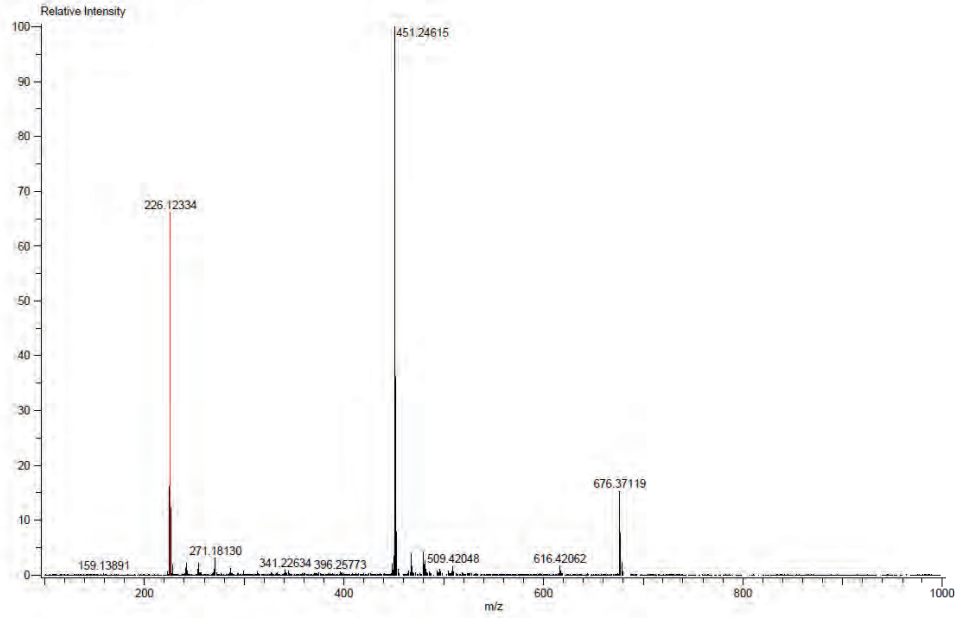
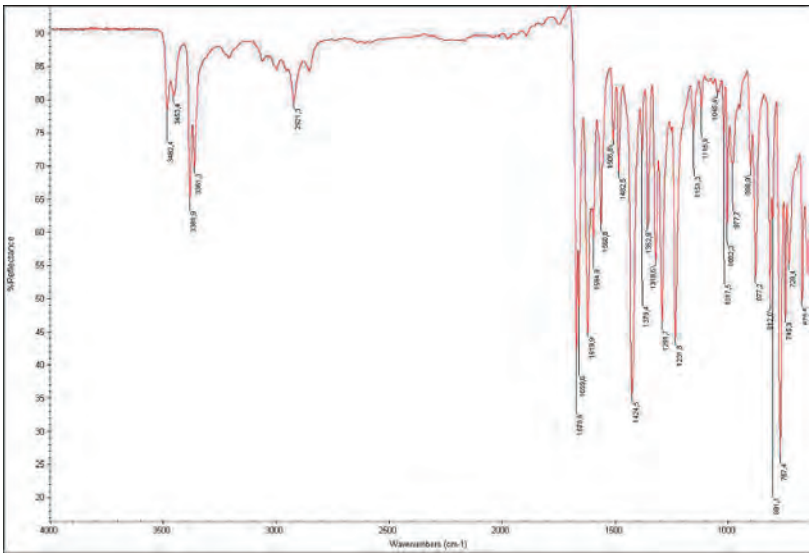
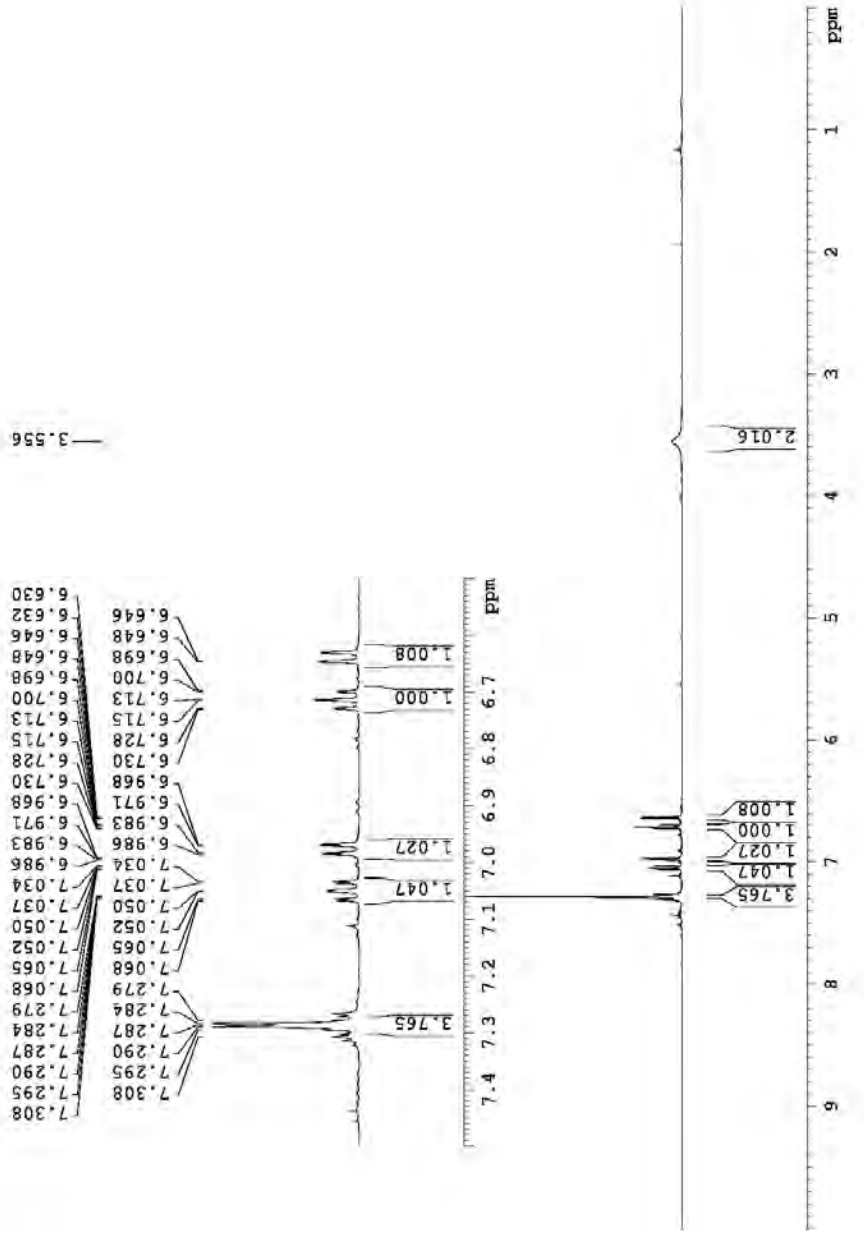


IR of 1-(2-amino-2'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (13)



^{1}H-NMR of 4'-chloro-[1,1'-biphenyl]-2-amine (14)



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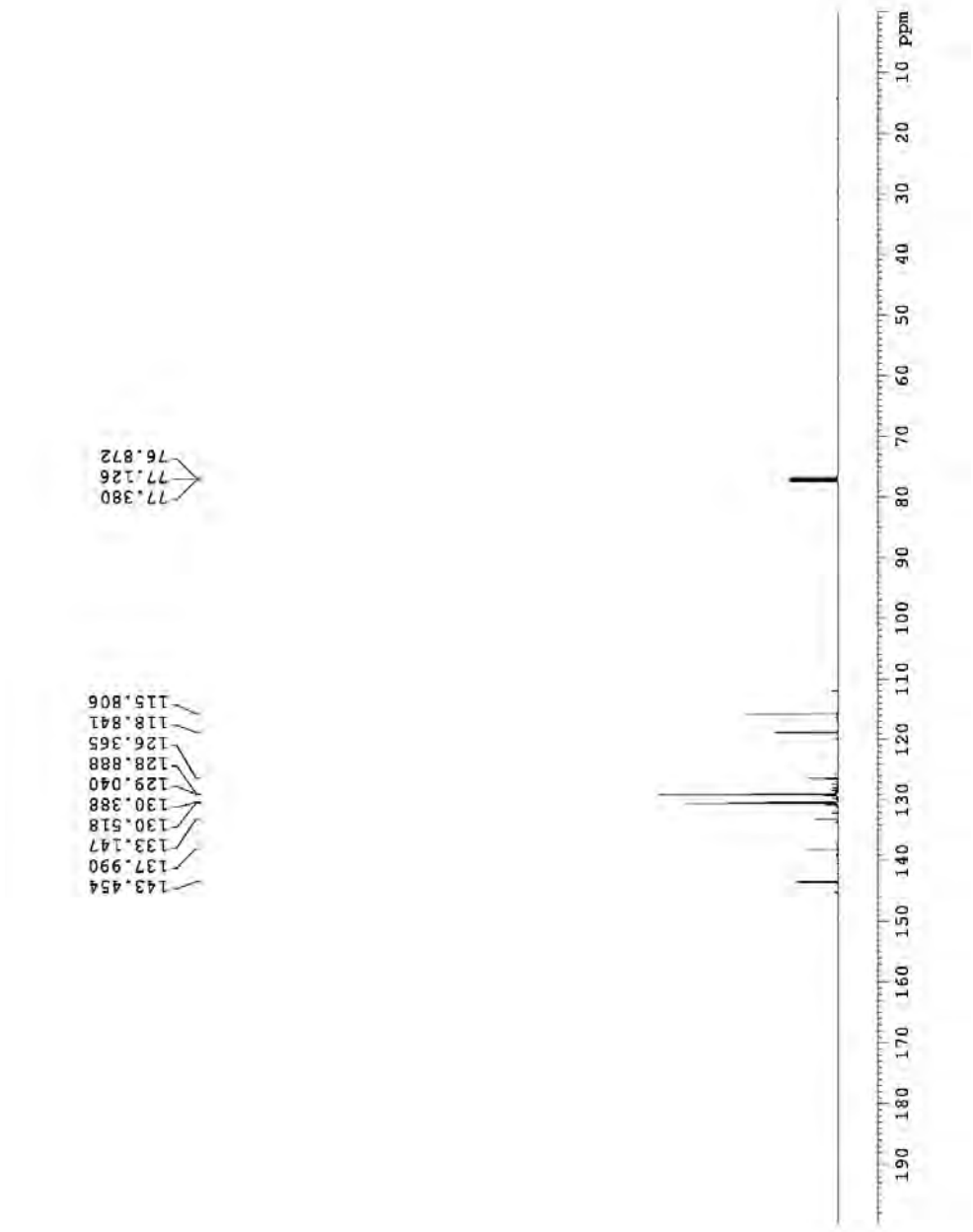

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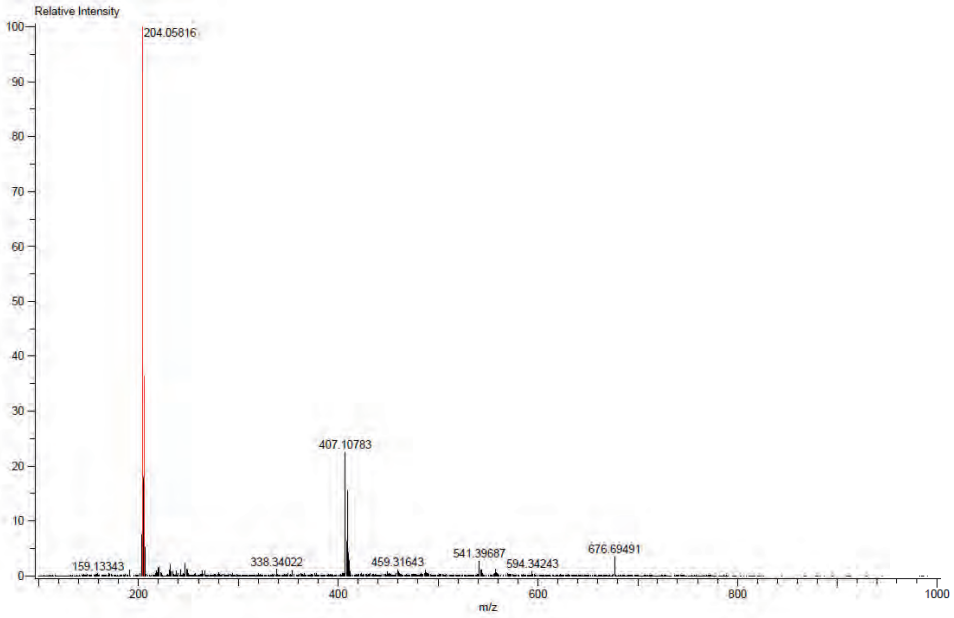
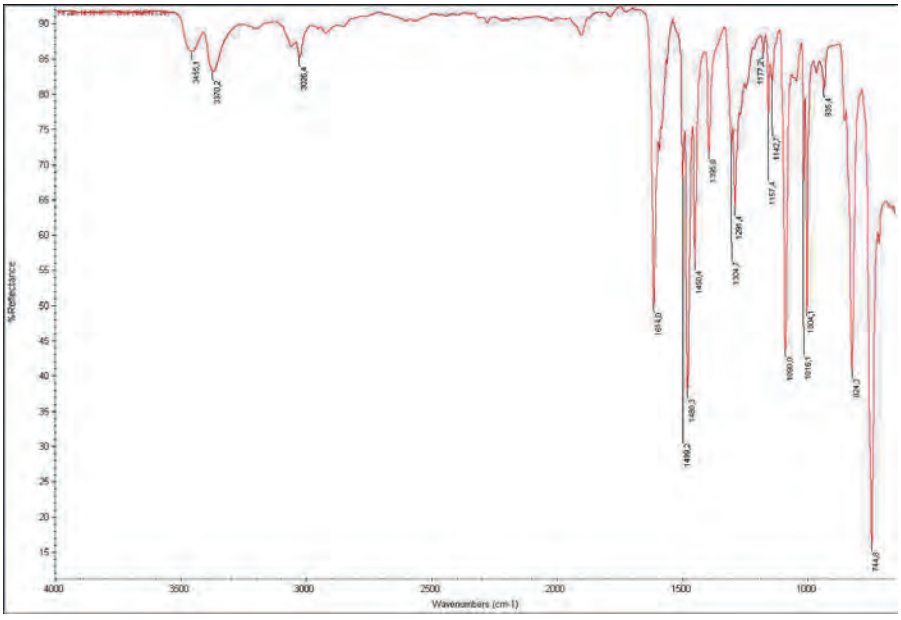
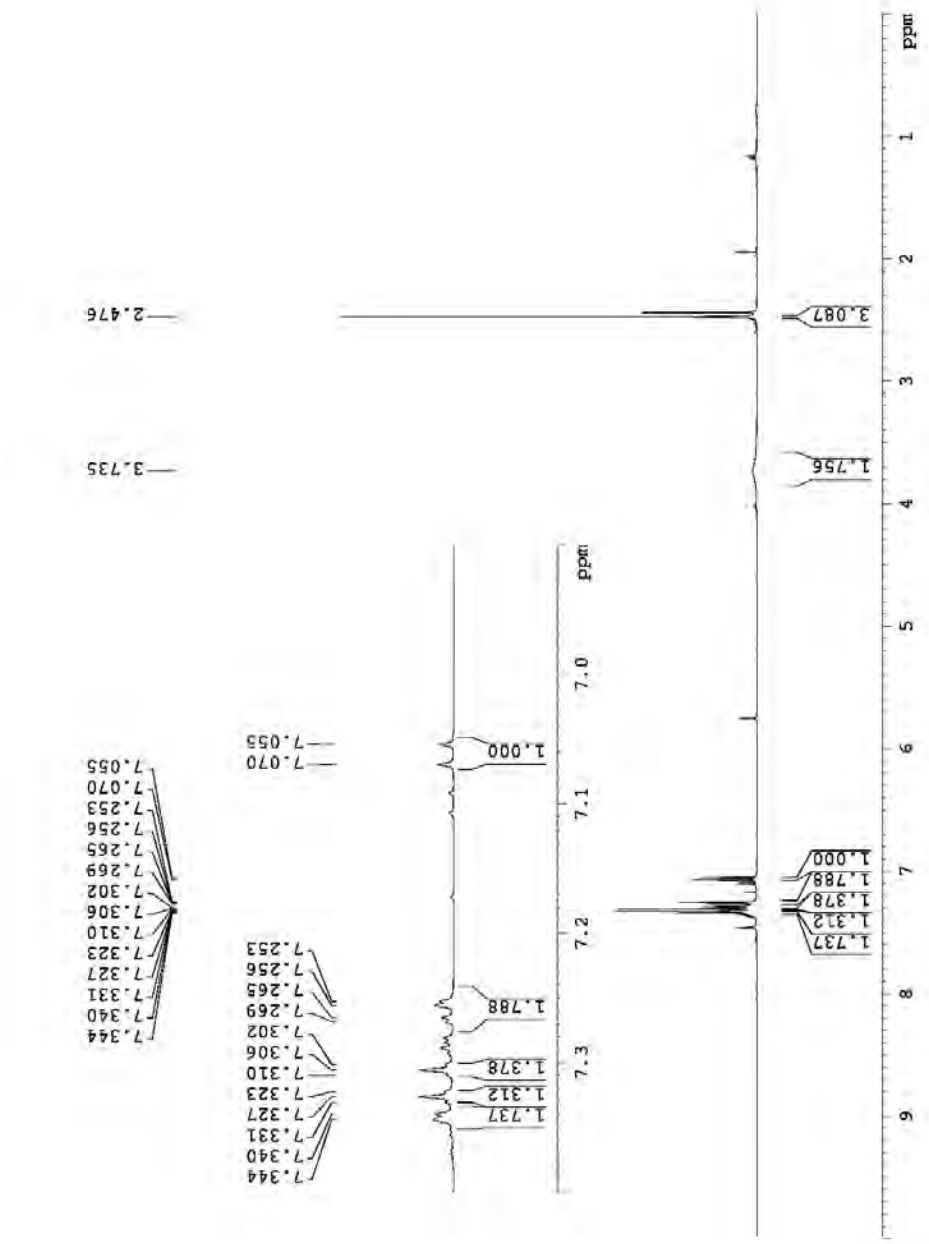


IR of 4'-chloro-[1,1'-biphenyl]-2-amine (14)



^{1}H-NMR of 1-(2-amino-4'-chloro-[1,1'-biphenyl]-4-yl)ethan-1-one (15)



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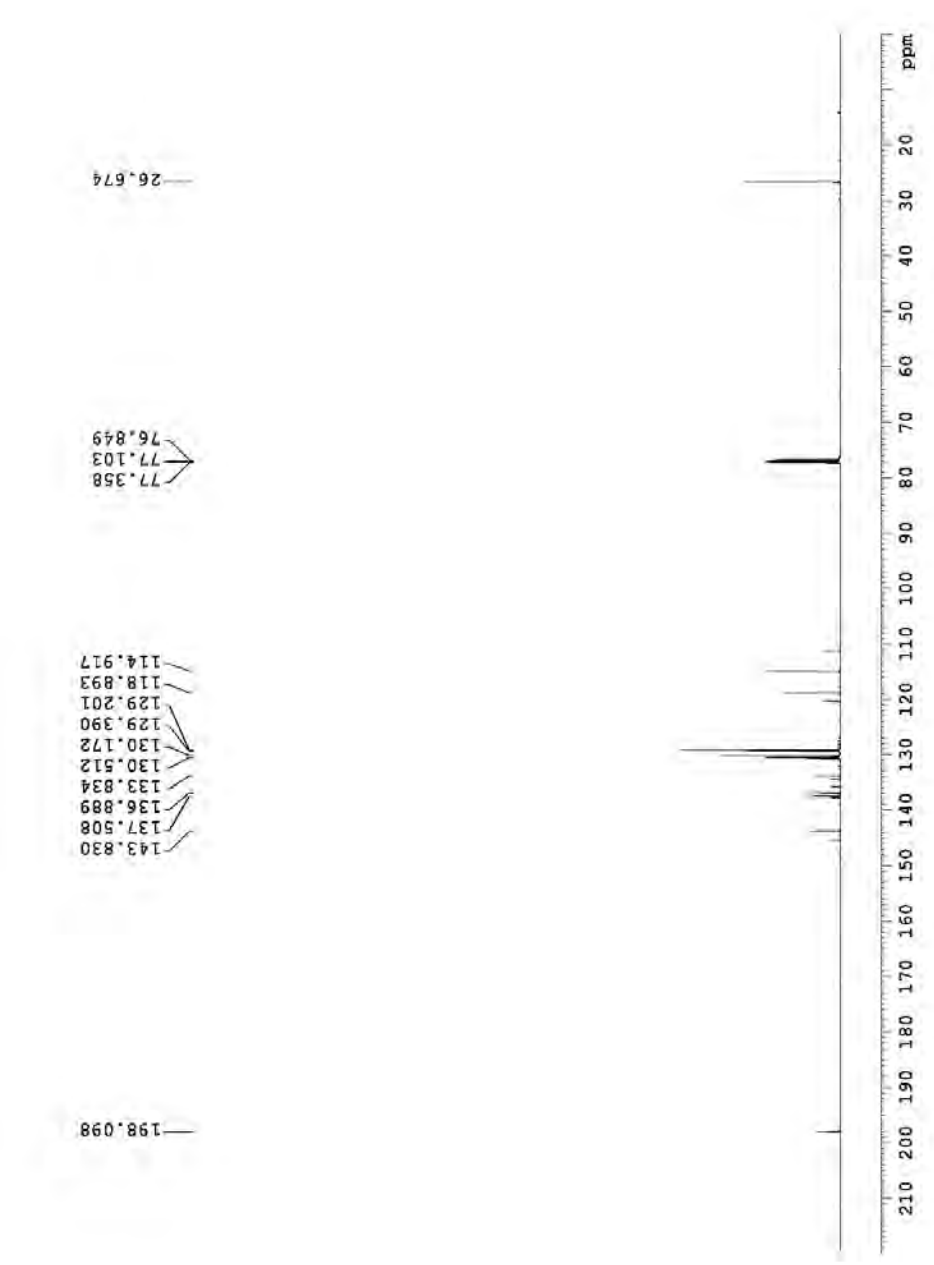

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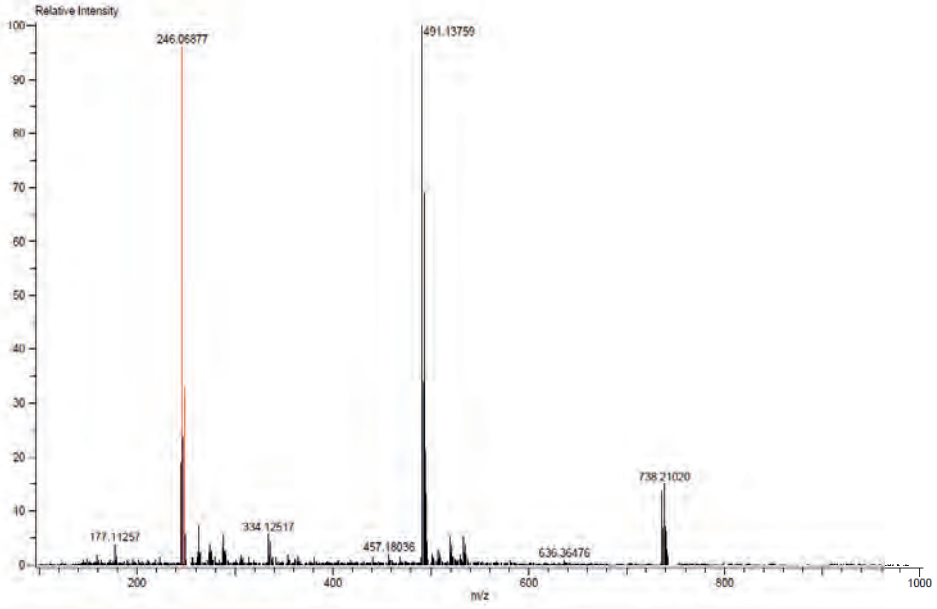
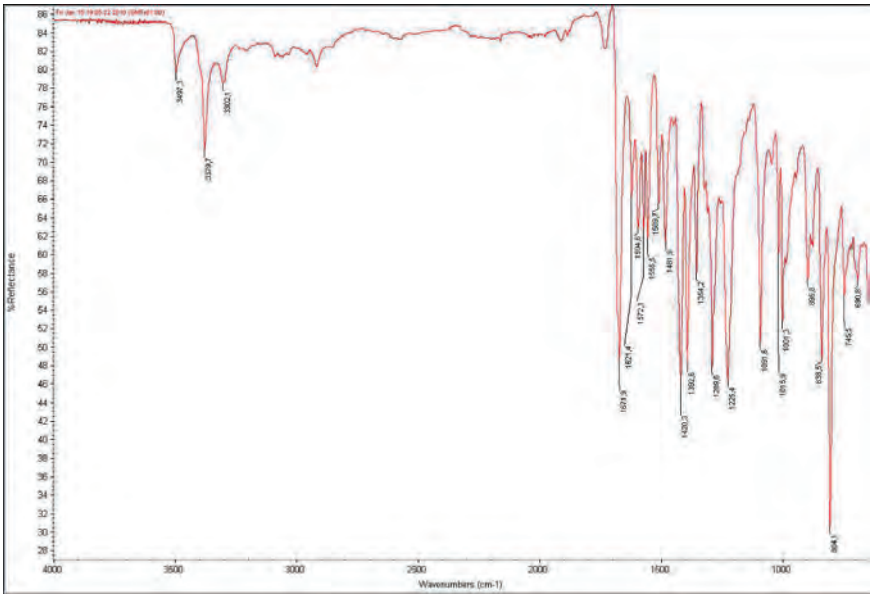


IR of 1-(2-amino-4'-chloro-[1,1'-biphenyl]-4-yl)ethan-1-one (15)



Paper III

Synthesis of the Carbazole Scaffold Directly from 2-Aminobiphenyl by Means of Tandem C–H Activation and C–N Bond Formation.

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EurJOC European Journal of Organic Chemistry

Communication

C–H Activation

Synthesis of the Carbazole Scaffold Directly from 2-Aminobiphenyl by Means of Tandem C–H Activation and C–N Bond Formation

Hans-René Bjørsvik*[a] and Vijayaragavan Elumalai[a]

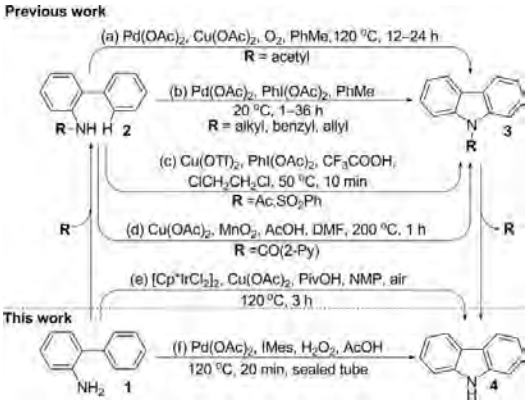
Abstract: An efficient method for the synthesis of the carbazole scaffold was designed and investigated. The method was developed to produce substituted carbazoles by an intramolecular combination of a free amine group and an arene. The steps of the method involved tandem Pd-catalyzed C–H activation and intramolecular C–N bond formation. The method showed good functional group tolerance, and substituent(s) could be on either of the two rings or on both of the two rings of the 2-aminobiphenyl substrate. After ring closure, the reduced Pd catalyst was oxidized to Pd^{II} by hydrogen peroxide. The novel method was also demonstrated to operate excellently with the corresponding 2-*N*-acetylaminobiphenyls.

Introduction

The carbazole framework constitutes an essential kernel of numerous indispensable applications in society and industry. Therefore, considerable effort has been devoted to the development of efficient methods exploitable for the synthesis of such molecular motifs.[1] A decade ago, Buchwald and collaborators[2] disclosed seminal work that described an attractive strategy and methodology that permitted the synthesis of the carbazole framework through tandem C–H activation and C–N bond formation (Scheme 1, path a). This strategy involved 2-*N*-acetylaminobiphenyl **2** as the substrate, and it was exposed to C–H activation at the 2′-position assisted by a Pd^{II} moiety coordinated to the 2-*N*-acetylamino group. The subsequent step resulted in C–N bond formation that afforded the carbazole scaffold concomitant with the release of Pd^0. Pd^0 was oxidized to Pd^{II} by O_2, which allowed recycling of Pd as the catalyst (Scheme 2). The major drawbacks of this method[2] comprise a rather long reaction time and the need for a protecting or auxiliary group attached to the 2-amino group, provoked by the fact that the oxidative conditions can also support the parasite oxidation reaction **1** → **5**.

During the last decade, a few more methods based on tandem C–H activation and C–N bond formation have been revealed.

Gaunt and collaborators[3] disclosed a process that also involved $Pd(OAc)_2$ as the catalyst, but with the hypervalent iodine compound phenyliodosyl diacetate in DMF as the reoxidant for the palladium catalyst (Scheme 1, path b). An important improvement offered by this method is the low reaction temperature (20 °C), although the method is still saddled with drawbacks, namely, the need of a protecting or auxiliary group and the production of stoichiometric quantities of the reduced oxidant as a byproduct.



Scheme 1. Intramolecular C–H activation and C–N bond formation resulting in the carbazole framework. $Cu(OTf)_2$ = copper(II) trifluoromethanesulfonate, 2-Py = 2-pyridyl, Cp* = pentamethylcyclopentadienyl, PivOH = pivalic acid, NMP = 1-methylpyrrolidin-2-one, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

Satoh, Miura, and collaborators[4] communicated lately a method that encompassed an Ir^{III}/Cu-based catalytic system with air as the terminal oxidant (Scheme 1, path e). To date, this method is the only intramolecular amination method allowing the preparation of the carbazole scaffold from unprotected 2-aminobiphenyl, but this protocol requires an expensive Ir-based catalyst along with several other additives to operate the ring-closing reaction. Two other methods involving copper as the catalyst were disclosed by Chang and collaborators[5a] and

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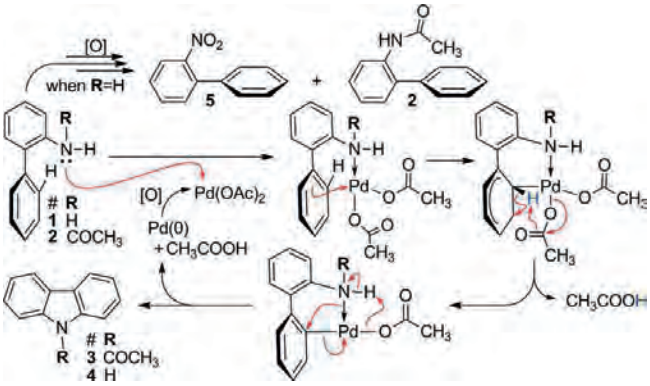
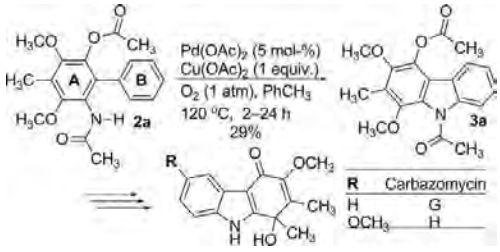


Scheme 2. Reaction mechanism proposed for tandem Pd-catalyzed C–H activation and C–N bond formation resulting in the carbazole scaffold by using 2-aminobiphenyl as the substrate.

Hirano, Miura, and collaborators[5b] (Scheme 1, paths c and d). Both of these methods also require supporting/auxiliary groups installed on the amino group and stoichiometric quantities of oxidants, $PhI(OAc)_2$, and MnO_2.

Results and Discussion

For a project in progress in our group dedicated to a novel total synthesis of the natural products carbazomycins G and H,[6] several new methods were needed: preparation of the functionalized benzene moieties[7] needed for the 2-aminobiphenyl precursor, Suzuki cross-coupling methods suitable for the preparation of 2-nitrobiphenyls,[8] and an efficient method for reduction of the nitro group.[9] Moreover, we aimed to utilize the C–H activation and intramolecular C–N formation strategy disclosed by Buchwald and collaborators.[2] Thus, we initiated the use of the Buchwald protocol in attempts to accomplish the intramolecular amidation with biphenyl **2a** (Scheme 3).

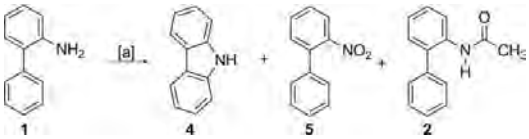


Scheme 3. Intramolecular C–H activation and C–N formation leading to carbazole precursor **3a** (29 %) for carbazomycin G (R = H) and carbazomycin H (R = OCH_3).

However, probably because of the highly congested substitution pattern of the A ring combined with the acetyl group attached to the 2-amino group, the ring-closing reaction afforded target carbazole **3a** in a yield of only 29 %. This somewhat disappointing result spurred us to undertake further investigations of the ring-closing protocol. Even though the amino group can be oxidized to the nitro group under various conditions,[10] we wanted to investigate the ring closure by using the nonprotected 2-aminobiphenyl framework. 2-Nitrobiphenyl (**5**) might be the product of a parasite reaction occurring under the oxidative conditions used in the Pd-catalyzed intramolecular amination. Indeed, we observed this oxidation product as soon as unprotected 2-aminobiphenyl (**1**) was used as the substrate (Table 1).

Alteration of the reaction time, reaction temperature, and the composition of the catalytic system was revealed to affect

Table 1. Screening experiments for the ring closing of 2-aminobiphenyl to achieve the carbazole scaffold.[a]



Entry	Catalyst/Ligand	*t* [min]	Measured response[b] [%] Conv.	*y*4	*y*5	*y*2
1	$Pd(OAc)_2$	90	93	39	26	20
2	$Pd(OAc)_2$	60	86	48	30	nd
3	$Pd(OAc)_2$	20	67	30	10	24
4	$Pd(OAc)_2$/IMes•HCl	20	84	45	18	15
5	$Pd(tfa)_2$	20	77	49	9	16
6	$Pd(tfa)_2$/IMes•HCl	20	83	43	15	21
7[c]	$Pd(OAc)_2$/IMes•HCl	10	97	67	2	28

[a] Reaction conditions: A reactor tube was charged with a solution of 2-aminobiphenyl (**1**; 84.5 mg, 0.5 mmol) in glacial acetic acid (5 mL), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol-%) or $Pd(TFA)_2$ (8.3 mg, 0.025 mmol, 5 mol-%), IMes•HCl (8.5 mg, 0.025 mmol) if specified, and H_2O_2 (35 %, 0.128 mL, 1.45 mmol), and the tube was immersed into the cavity of a microwave oven for the specified time at *T* = 90 °C. tfa = trifluoroacetic acid. [b] The reaction was monitored by means of GC–MS; Conv. = conversion of **1**. Yields (*y*) of compound **4** and **5** were corrected by using the following response factors: 2-aminobiphenyl (**1**), *rf***1** = 1.00; carbazole, *rf***4** = 1.00; 2-nitrobiphenyl, *rf***5** = 1.29. The selectivities and yields of compounds **2** and **5** are uncorrected with response factor. nd = not detected. [c] $Pd(OAc)_2$ (22.4 mg, 0.100 mmol, 20 mol-%) was used.

not only the yield of target carbazole **4** but also the distribution of side products **2** and **5**. Evidently, the N-heterocyclic carbene ligand IMes with $Pd(OAc)_2$ operated reasonably well as the catalyst for the ring-closing reaction. Moreover, the reaction time also appeared to be of paramount importance. The reaction trial of entry 7 (Table 1) was used as a basis in an attempt to discover a higher yielding protocol. A series of experiments with various Pd loadings (5–20 mol-%) were conducted and monitored over a period of 20 min. Alteration of the Pd loading revealed a great effect on the outcome of the reaction (Figure 1a). Moreover, after a reaction time of 10–15 min, the target molecule started to depredate concomitantly as parasite products **2** and **5** were produced.

Further optimization of the method was conducted by means of systematic variation (in a grid pattern) of the reaction temperature and time (Figure 1b).

High-yielding conditions were located at a reaction time of 15–20 min with a temperature of 120–130 °C. The so-far-optimized protocol (Figure 1a,b) was then repeated under various Pd loadings (5–20 %, Figure 1c). A high conversion (≥97 %) of the 2-aminobiphenyl (**1**) substrate was achieved for all of these experiments. If the Pd loading was <20 mol %, oxidation of the amino group to the nitro group occurred. In fact, as much as 23 % of 2-nitrobiphenyl (**5**) was formed by using 5 mol % Pd, and **5** was formed in only about 2 % yield with a Pd loading of 15 mol %. With a Pd loading of 20 mol %, the carbazole scaffold was obtained in 97 % yield.

A scope and limitations study of our new method was then undertaken by means of examining a series of substituted 2-aminobiphenyls (Table 2). Overall, the method tolerated both electron-withdrawing and electron-donating groups to afford the target carbazole scaffolds in moderate to excellent yields. However, a few exceptions were observed: 2′-methoxy-2-aminobiphenyl and 3′-methoxy-2-aminobiphenyl afforded yields of around 10 % only (Table 2, entries 6 and 7) and 4′-methoxy-2-aminobiphenyl provided a moderate yield (Table 2, entry 8). These observations might be due to the inductive effect of the methoxy substituent that would disrupt the intermediate, but the oxidative conditions present for the catalytic cycle might also give rise to oxidation of the aromatic kernel into a demethoxylated quinoid framework,[11] which could be followed by additional degradation reactions. Moreover, as expected, the method did not operate with substrates that contained a free hydroxy group; nevertheless, by means of standard protection (*tert*-butyldimethylsilyl chloride) of the hydroxy group, a high yield of the target carbazole was obtained (Table 2, entry 15).

The method was also explored with 2-*N*-acetylaminobiphenyls as substrates (Table 3). In this context, minor alterations to the experimental conditions were found to be beneficial, namely, a lower Pd loading (5 mol-%) and an extended reaction time (3 h). Under these conditions with 3′-methoxy-2-*N*-acetylaminobiphenyl and 4′-methoxy-2-*N*-acetylaminobiphenyl, the corresponding carbazoles were achieved in high yields (Table 3, entries 7 and 8). However, the 2′-methoxy-substituted substrate provided a low yield (25 %) only. The 3′-methoxy-substituted substrate (Table 3, entry 7) provided two regioisomers, namely, 1-(3-methoxy-9*H*-carbazol-9-yl)ethan-1-one (**3g**, major) and 1-(2-methoxy-9*H*-carbazol-9-yl)ethan-1-one (minor). The methylated substrates (Table 3, entries 3 and 4) provided low to mod-

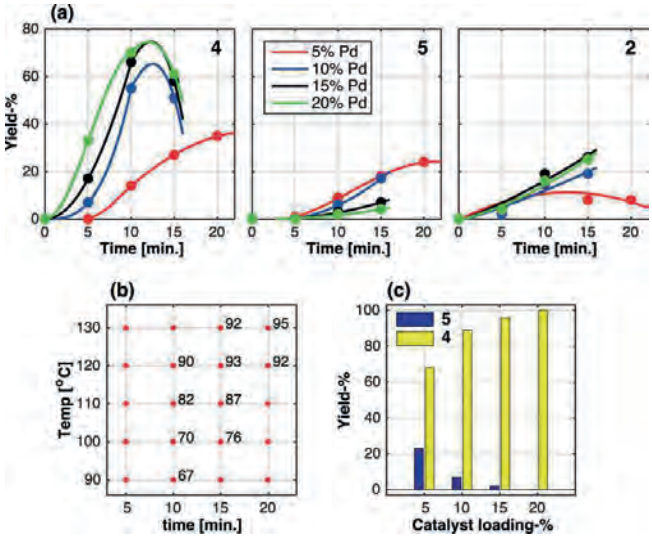
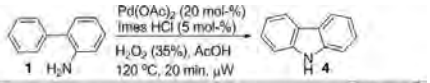


Figure 1. (a) Reaction profiles showing the outcomes of **4**, **5**, and **2** at various Pd loadings. To a solution of 2-aminobiphenyl (84.5 mg, 0.5 mmol) in glacial acetic acid (5 mL) was added $Pd(OAc)_2$ (5–20 mol-%), IMes•HCl (8.5 mg, 0.025 mmol), and H_2O_2 (35 %, 0.128 mL, 1.45 mmol) to perform the above reactions under microwave irradiation for 15–20 min at 90 °C. (b) Screening of the reaction time (5–20 min) vs. reaction temperature (90–130 °C) revealed optimized conditions at higher temperatures and longer reaction times. (c) Variation (5–20 %) of the catalyst loading (using 20 min and 120 °C) afforded a high conversion (≥97 %) of 2-aminobiphenyl (**1**) with **4** and **5** as reaction products.

Table 2. Scope of the reaction by using 2-aminobiphenyls **1** as the substrate.

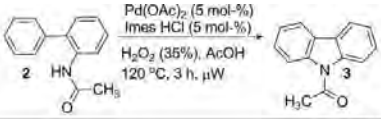


#	2-Aminobiphenyls	Carbazole	Responses[a] y [%]	yi [%]
1	**1**	**4**	92	84
2	**1b**	**4b**	na	60
3	**1c**	**4c**	>99	82
4	**1d**	**4d**	na	71
5	**1e**	**4e**	>99	70
6[b]	**1f**	**4f**	na	9
7	**1g**	**4g**	na	10
8	**1h**	**4h**	na	41
9	**1i**	**4i**	90	70
10	**1j**	**4j**	na	75
11	**1k**	**4k**	94	73
12	**1l**	**4l**	98	85
13	**1m**	**4m**	91	77
14	**1n**	**4n**	>99	81
15[c]	**1o**	**4o**	82	61

[a] *y* = conversion yield based on GC, *yi* = yield of isolated product after column chromatography (silica gel), na = not analyzed on GC. [b] An additional experiment by using 20 mol-% IMes was also conducted. The outcome was similar to that obtained in the experiment for which 5 mol-% IMes was used. [c] An experiment without the *tert*-butyldimethylsilyl (TBS) protecting group installed did not afford the target carbazole.

erate yields; this applied also to a substrate with a strong electron-withdrawing group (Table 3, entry 2). The observed results are consistent with previous observations.[2]

Table 3. Scope of the reaction by using 2-*N*-acetylaminobiphenyl (**2**) as the substrate.



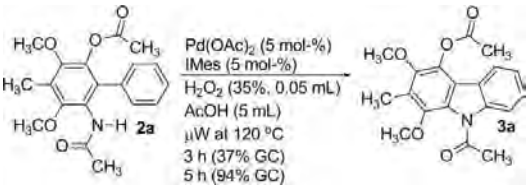
#	2-Aminobiphenyls	Carbazole	Responses[a] y [%]	yi [%]
1	**2**	**3**	91	85
2	**2b**	**3b**	20	ni
3	**2c**	**3c**	17	ni
4	**2d**	**3d**	51	46
5	**2e**	**3e**	100	81
6	**2f**	**3f**	25	ni
7[b]	**2g**	**3g**	75	61
8	**2h**	**3h**	82	70

[a] *y* = conversion yield based on GC, *yi* = yield of isolated product after column chromatography (silica gel), ni = not isolated. [b] In addition to major product **3g**, a minor quantity (12 %) of the 5′-methoxy derivative was obtained.

Electrophilic substitution on the carbazole scaffold normally occurs at the 3- and 6-positions. However, our new method allowed functionalization in the 2- and 4-positions, which might be valuable for the synthesis of natural products that contain the carbazole scaffold.

As an ultimate test of the new protocol, we attempted to perform the transformation **2a** → **3a** previously performed with the Buchwald method[2] (Scheme 2). Only a minor change to the conditions of our new method was needed: whereas 3 h

afforded the product in 37 % yield, a reaction time of 5 h provided the product in an excellent yield of 94 %. The conditions and results are summarized in Scheme 4.



Scheme 4. Intramolecular C–H activation and C–N formation leading to carbazole **3a** (94 %) as a precursor of carbazomycin G. µW = microwave.

Conclusion

In summary, we developed a new, highly efficient and high-rate method for the synthesis of the carbazole framework by means of Pd-catalyzed tandem C–H activation and intramolecular C–N bond formation by using the 2-aminobiphenyl scaffold as the substrate. In general, the method tolerated both electron-withdrawing and electron-donating groups on one or both of the two aromatic rings of the substrate. Even substrates labile for oxidation such as aromatics that contained hydroxy and/or the methoxy groups could be converted into their corresponding carbazoles. However, if the 2-aminobiphenyl scaffold was substituted with a methoxy group, an acetyl group needed to be introduced on the 2-amino group as an auxiliary group. Free hydroxy groups needed protection.

Experimental Section

General Methods: All reagents and solvents were purchased from commercial sources and were used as received. Melting points were determined in open capillaries. Reagent-grade chemicals were purchased from commercial sources and were used without further purification. All reactions and column eluates were monitored by TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 and 365 nm. IR spectra were recorded as KBr discs with a Shimadzu FTIR-8300 spectrophotometer, and ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AV 400 MHz and 500 MHz instruments. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument. GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d., 0.33 mm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. DART mass spectra were obtained by using PEG as an internal standard in positive ionization mode with a TOF mass analyzer. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature at frequencies of 400/500 and 100/125 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for ^{1}H (δ = 7.26 ppm) and $CDCl_3$ for ^{13}C (δ = 77.0 ppm) and residual DMSO for ^{1}H (δ = 2.50 ppm) and [D_6]DMSO for ^{13}C (δ = 39 ppm) with tetramethylsilane as an external reference. Flash chromatography was performed by using the indicated solvent system and silica gel (230–400 mesh). All reagents used were commercially available from Aldrich Chemical Co. For new compounds, HRMS data were also recorded. The microwave-assisted experiments were performed by means of a Biotage Initiator Sixty EXP Microwave System that operated at 0–400 W and 2.45 GHz in the temperature range of 40 to 250 °C, a pressure range of 0 to 20 bar (2 MPa, 290 psi), with reactor vial volumes of 0.2 to 20 mL.

General Procedure for 2-Aminobiphenyl Derivatives 1–1o: 2-Nitrobiphenyl (1 mmol, 0.2 g) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (2 mmol, 0.107 g) in H_2O (1.2 mL) and indium powder (3 mmol, 0.344 g, 99.99 % 100 mesh, used preferably a freshly opened bottle or stored under an atmosphere of argon) were added, whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed, and the mixture was stirred and heated at 120 °C for 3 h. The mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The resulting mixture was filtered through a pad of Celite to remove the catalyst. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting transparent organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the 2-aminobiphenyl compound.

2′-Methyl-[1,1′-biphenyl]-2-amine (1c): 2′-Methyl-2-nitro-1,1′-biphenyl (0.324 g, 1.52 mmol), NH_4Cl (0.161 g, 3.04 mmol), and indium powder (0.523 g, 4.56 mmol). The title compound was obtained as a yellow liquid (0.259 g, 93 %). R_f = 0.66 (hexanes/EtOAc, 80:20). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.22 (m, 3 H), 7.12–7.14 (m, 1 H), 7.08–7.11 (td, J = 1.5, 7.5 Hz, 1 H), 6.93–6.95 (dd, J = 1, 7 Hz, 1 H), 6.72–6.75 (td, J = 1, 7 Hz, 1 H), 6.68–6.70 (dd, J = 1, 8 Hz, 1 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.6, 138.6, 137.0, 130.3, 130.1, 130.0, 128.4, 127.7, 127.5, 126.2, 118.3, 115.1, 19.7 ppm. IR: $\tilde{\nu}$ = 3465, 3375, 3018, 2921, 1612, 1480, 1447, 1296 cm^{-1}. HRMS (DART): calcd. for $C_{13}H_{13}N$ [M + H]$^+$ 184.1126; found 184.1127.

General Procedure for 2-Acetaminobiphenyl Derivatives 2–2h: Acetyl chloride (0.04 mL, 0.62 mmol) was added dropwise to a solution of 2-aminobiphenyl (0.1 g, 0.59 mmol) and triethylamine (0.09 mL, 0.65 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. Then, the solvent was evaporated under reduced pressure. The residue was dissolved in ether (20 mL) and washed with water (20 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure obtain the *N*-acetylated compound.

***N*-([1,1′-Biphenyl]-2-yl) Acetamide:** 2′-Amino-[1,1′-biphenyl] (**1a**) (0.10 g, 0.59 mmol), acetyl chloride (0.04 mL, 0.62 mmol), and triethylamine (0.09 mL, 0.65 mmol). The title compound was obtained as a pale-white solid (0.115 g, 93 %). M.p. 119.8–120 °C. R_f = 0.24 (hexanes/EtOAc, 80:20). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, J = 8.5 Hz, 1 H), 7.49 (t, J = 7 Hz, 2 H), 7.38 (m, 3 H), 7.24 (d, J = 7 Hz, 1 H), 7.18 (d, J = 7.5 Hz, 1 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 138.2, 134.7, 132.2, 130.1 129.2, 129.1, 128.4, 128.0, 124.4, 121.7, 24.6 ppm. IR: $\tilde{\nu}$ = 3286, 3027, 1658, 1531, 1433, 1301 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{13}NNaO$ [M + Na]$^+$ 234.0895; found 234.0896;

General Procedure for Carbazole Derivatives 4–4o: In a microwave tube, 2-aminobiphenyl (84.5 mg, 0.5 mmol) was dissolved in glacial acetic acid (5 mL) and then $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), IMes•HCl (8.5 mg, 0.025 mmol), and H_2O_2 (35 %, 0.128 mL, 1.45 mmol) were added. The vial was sealed, whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in

the microwave cavity for 20 min at 120 °C. Then, the acetic acid solvent was removed under reduced pressure. The crude product was dissolved in EtOAc (25 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with aqueous $NaHCO_3$ (20 mL). The organic layer was filtered through a pad of Celite and dried with Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; hexanes/EtOAc, gradient 90:10 to 50:50) to obtain the target compound.

9*H*-Carbazole (4): 2-Amino-1,1′-biphenyl (**1a**; 0.085 g, 0.50 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), IMes·HCl (8.5 mg, 0.05 mmol), and H_2O_2 (35 %, 0.128 mL, 1.45 mmol). The title compound was obtained as a pale-brown solid (0.070 g, 84 %). M.p. 242–243 °C. R_f = 0.49 (hexanes/EtOAc, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8 Hz, 2 H), 7.42–7.47 (m, 4 H), 7.22–7.26 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 125.8, 123.4, 120.3, 119.4, 110.6 ppm. IR: $\tilde{\nu}$ = 3415, 3050, 1599, 1449, 1325, 722 cm^{-1}. HRMS (DART): calcd. for $C_{12}H_{10}N$ $[M + H]^+$ 168.0813; found 168.0814.

Acknowledgments

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Keywords: Biaryls · C–H activation · C–N bond formation · Nitrogen heterocycles · Palladium

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SUPPORTING INFORMATION

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Title: Synthesis of the Carbazole Scaffold Directly from 2-Aminobiphenyl by Means of Tandem C–H Activation and C–N Bond Formation
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Experimental section

General Procedure 2-aminobiphenyl derivatives

Experimental Details: All reagents and solvents were purchased from commercial sources and used as received. Melting points were determined in open capillaries. Reagent grade chemicals were purchased from commercial sources and used without further purification. All reaction mixtures and column eluents were monitored by TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 nm and λ = 365 nm. IR spectra were recorded as KBr discs with a Shimadzu FTIR-8300 spectrophotometer, and ^{1}H and ^{13}C NMR spectra were recorded with Bruker AV 400 MHz and 500 MHz instruments. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument.

General Methods: GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d., 0.33 mm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. DARTmass spectra were obtained by using PEG as an internal standard in positive ionization mode with a TOF mass analyzer. ^{1}H and ^{13}CNMR spectra were recorded at ambient temperature at a frequency of 400, 500 MHz and 100, 125 MHz respectively. The chemical shifts are reported in ppm relative to residual $CDCl_3$ for proton (δ = 7.26 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm) and DMSO-d_6 for proton (δ = 2.50 ppm) and carbon (δ = 39 ppm) with tetramethylsilane as an external reference. Flash chromatography was performed

by using the indicated solvent system and silica gel (230–400 mesh). All reagents used were commercially available from Aldrich Chemical Co. For new compounds HRMS data were also recorded.

The microwave-assisted experiments were performed by means of a Biotage Initiator Sixty EXP Microwave System, that operates at 0–400 W at 2.45 GHz, in the temperature range of 40–250 °C, a pressure range of 0–20 bar (2 MPa, 290 psi), and with reactor vial volumes of 0.2–20 mL.

2-aminobiphenyl derivatives:

General Procedure. 2-Nitrobiphenyl (1 mmol, 0.2 g) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (2 mmol, 0.107 g) in H_2O (1.2 mL) and indium powder (3 mmol, 0.344 g, 99.99% 100 mesh, use preferably a freshly opened bottle or stored under Ar) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The resulting mixture was filtered through a pad of celite to remove the catalyst. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting transparent organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the 2-aminobiphenyl compound.

2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-amine (1b) [438-84-6]

2-nitro-2'-(trifluoromethyl)-1,1'-biphenyl (0.283 g, 1.06 mmol), NH_4Cl (0.112 g, 2.11 mmol) and indium powder (0.365 g, 3.22 mmol) .The title compound was obtained as a yellow liquid (0.236 g, 94%).; R_f = 0.81 [(Hx:EtOAc, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.80 (d, *J*= 8 Hz, 1H), 7.59-7.62 (td, *J*= 0.5 Hz, 7.5 Hz, 1H), 7.50 (t, *J*= 7.5 Hz, 1H), 7.38 (d, *J*= 8 Hz, 1H), 7.19-7.22 (td, *J*= 1.5 Hz, 7.5 Hz, 1H), 7.03 (d, *J*= 7.5 Hz, 1H), 6.80-6.83 (td, *J*= 1 Hz, 7.5 Hz, 1H), 6.77-6.78 (dd, *J*= 1 Hz, 8 Hz, 1H), 3.34 (s, br, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.7, 138.0, 137.9, 132.5, 132.0, 130.3, 129.1, 127.9, 126.6(q, CF_3), 125.0, 124.9, 117.9, 115.3 ; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{11}F_3N$ 238.0844; Found 238.0845); IR (cm^{-1}): 3462, 3399, 3360, 3340, 1616, 1452, 1312, 1106.

2'-methyl-[1, 1'-biphenyl]-2-amine (1c) [1203-41-4]

4'-methyl-2-nitro-1, 1'-biphenyl (0.324 g, 1.52 mmol), NH_4Cl (0.161 g, 3.04 mmol) and indium powder (0.523 g, 4.56 mmol). The title compound was obtained as a yellow liquid (0.259 g, 93%): R_f = 0.66 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.17-7.22 (m, 3H), 7.12-7.14(m, 1H), 7.08-7.11 (td, *J*= 1.5 Hz, 7.5 Hz, 1H), 6.93-6.95 (dd, *J*= 1.5 Hz, 7 Hz, 1H), 6.72-6.75 (td, *J*= 1 Hz, 7 Hz, 1H), 6.68-6.70 (dd, *J*= 1 Hz, 8 Hz, 1H), 2.10 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.6, 138.6, 137.0, 130.3, 130.1, 130.0, 128.4, 127.7, 127.5, 126.2, 118.3, 115.1, 19.7; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{13}N$ 184.1126; Found 184.1127); IR (cm^{-1}): 3465, 3375, 3018, 2921, 1612, 1480, 1447, 1296.

4'-methyl-[1, 1'-biphenyl]-2-amine (1d) [1204-43-9]

4'-methyl-2'-nitro-1,1'-biphenyl (0.235 g, 1.10 mmol), NH_4Cl (0.117 g, 2.20 mmol) and indium powder (0.379 g, 3.30 mmol) .The title compound obtained as an orange liquid (0.192 g, 96%); R_f = 0.61[(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.27 (d, *J*= 8.5 Hz, 2H), 7.17 (d, *J*= 8 Hz, 2H), 7.03-7.08 (dddd, *J*= 1.5 Hz, 7.5 Hz, 2H), 6.72-6.75 (td, *J*= 1.5 Hz, 7.5 Hz, 1H), 6.67-6.69 (dd, *J*= 1 Hz, 8 Hz, 1H), 2.32 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.5, 136.9, 136.5, 130.5, 129.5, 129.0, 128.3, 127.7, 118.7, 115.6, 21.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{13}N$ 184.1126; Found 184.1128); IR (cm^{-1}): 3455, 3368, 3021, 2919, 1613, 1488, 1449, 1293.

4'-ethyl-[1, 1'-biphenyl]-2-amine (1e) [55258-95-2]

4'-ethyl-2-nitro-1,1'-biphenyl (0.300 g, 1.32 mmol), NH_4Cl (0.140 g, 2.64 mmol) and indium powder (0.455 g, 3.96 mmol) .The title compound was obtained as an orange liquid (0.240 g, 92%); R_f = 0.63 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.37-7.39 (m, 2H), 7.28-7.30 (dd, *J*= 2 Hz, 7.5 Hz, 2H), 7.13-7.17 (m, 2H), 6.81-6.85 (td, *J*= 1Hz, 7.5 Hz, 1H), 6.77-6.78 (dd, *J*= 1Hz, 8 Hz, 1H), 2.71 (q, *J*= 8 Hz, 2H), 1.30 (t, *J*= 7.5Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.5, 143.2, 136.8, 130.5, 129.0, 128.3, 127.7, 118.7, 115.6, 28.6, 15.5; HR-MS (DART): $(M+H)^+$: Calcd for $C_{14}H_{15}N$ 198.1283; Found 198.1284); IR (cm^{-1}): 3460, 3370, 3022, 2963, 2929, 2871, 1613, 1488, 1452, 1295.

2'-methoxy-[1, 1'-biphenyl]-2-amine (1f) [1206-76-4]

2'-methoxy-2-nitro-1, 1'-biphenyl (0.284 g, 1.24 mmol), NH_4Cl (0.131 g, 2.47 mmol) and indium powder (0.427 g, 3.72 mmol) .The title compound was obtained as a pale-brown liquid (0.238 g, 96%). R_f = 0.40 [(Hx:EtOAc, 80:20)]; ^{1}HNMR (500 MHz, $CDCl_3$): δ= 7.26-7.29 (td, *J*= 1.5 Hz, 8 Hz, 1H), 7.17-7.19 (dd, *J*= 2 Hz, 7.5 Hz, 1H), 7.08-7.11 (td, *J*= 1.5 Hz, 8 Hz, 1H), 7.02-7.04 (dd, *J*= 1.5 Hz, 7.5 Hz, 1H), 6.95-6.98 (td, *J*= 1 Hz, 7.5 Hz, 1H), 6.92 (d, *J*= 8.5 Hz, 1H), 6.74-6.77 (td, *J*= 1 Hz, 7.5 Hz, 1H), 6.69-6.71 (dd, *J*= 1Hz, 8Hz, 1H), 3.73 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 156.7, 144.3, 131.8, 131.1, 129.0, 128.5, 128.3, 125.1, 121.2, 118.5, 115.7, 111.3, 55.7; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{14}NO$ 200.1077; Found 200.1077); IR (cm^{-1}): 3449, 3368, 3021, 2934, 2834, 1615, 1483, 1449, 1229.

3'-methoxy-[1, 1'-biphenyl]-2-amine (1g) [38089-02-0]

3'-methoxy-2-nitro-1,1'-biphenyl (0.329 g, 1.44 mmol), NH_4Cl (0.153 g, 2.88 mmol) and indium powder (0.496 g, 4.32 mmol) .The title compound was obtained as a pale-yellow liquid (0.250 g, 87%); R_f = 0.48 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.36 (t, *J*= 8 Hz, 1H), 7.14-7.18 (m, 2H), 7.04-7.06 (dt, *J*= 1.5 Hz, 7.5 Hz, 1H), 7.00-7.01 (m, 1H), 6.89-6.91 (dddd, *J*= 1 Hz, 2.5 Hz, 1H), 6.82-6.85 (td, *J*= 1 Hz, 7.5 Hz, 1H), 6.77-6.79 (dd, *J*= 1 Hz, 8 Hz, 1H), 3.84 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 159.9, 143.3, 140.9, 130.3, 129.8, 128.6, 127.6, 121.4, 118.6, 115.7, 114.5, 112.9, 55.3; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{14}NO$ 200.1077; Found 200.1077); IR (cm^{-1}): 3412, 3340, 3010, 2961, 2933, 2835, 1605, 1568, 1475, 1421, 1291, 1206, 1048.

4'-methoxy-[1, 1'-biphenyl]-2-amine (1h) (38089-03-1)

4'-methoxy-2-nitro-1,1'-biphenyl (0.284 g, 1.24 mmol), NH_4Cl (0.131 g, 2.48 mmol) and indium powder (0.427 g, 3.72 mmol) .The title compound was obtained as an orange liquid (0.235 g, 95%); R_f = 0.40 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.38-7.40 (m, 2H), 7.11-7.16 (m, 2H), 6.97-7.00 (m, 2H), 6.81-6.84 (td, *J*= 1.5 Hz, 7.5 Hz, 1H), 6.76-6.78 (dd, *J*= 1 Hz, 8 Hz, 1H), 3.86 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 158.8, 143.6, 131.8, 130.5, 130.2, 128.2, 127.4, 118.7, 115.6, 114.2, 55.3; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{14}NO$ 200.1077; Found 200.1077); IR (cm^{-1}): 3461, 3368, 3001, 2934, 2835, 1709, 1610, 1488, 1240, 1032.

4'-chloro-[1, 1'-biphenyl]-2-amine (1i) [1204-44-0]

4'-chloro-2-nitro-1, 1'-biphenyl (0.25 g, 1.07 mmol), NH_4Cl (0.113 g, 2.13 mmol) and indium powder (0.369 g, 3.21 mmol). The title compound was obtained as a light brown liquid (0.192 g, 88%). R_f = 0.63 [(Hx:EtOAc, 70:30)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.28-7.31 (m, 4H), 7.03-7.07 (td, *J*= 1.5Hz, 8 Hz, 1H), 6.97-6.99 (dd, *J*= 1.5Hz, 7.5 Hz, 1H), 6.70-6.73 (td, *J*= 1Hz, 7.5 Hz, 1H), 6.63-6.65 (dd, *J*= 1Hz, 8 Hz, 1H), 3.56 (s, br, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 143.5, 138.0, 133.1, 130.5, 130.4, 129.0, 128.9, 126.4, 118.8, 115.8; HR-MS (DART): $(M+H)^+$: Calcd for $C_{12}H_{11}{}^{35}ClN$ 204.0580; Found 204.0582); Calcd for $C_{12}H_{11}{}^{37}ClN$ 206.0551; Found 206.0522); IR (cm^{-1}): 3455, 3370, 3026 , 1614, 1480, 1291.

2-amino-[1, 1'-biphenyl]-4-carboxylic acid (1j) [856797-75-6]

2-nitro-[1, 1'-biphenyl]-4-carboxylic acid (0.125 g, 0.515 mmol), NH_4Cl (0.055 g, 1.03 mmol) and indium powder (0.178 g, 1.55 mmol) .The title compound was obtained as yellow liquid (0.082 g, 75%). R_f = 0.17 [(Hx:EtOAc, 70:30)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.56 (d, *J*= 7.5 Hz, 1H), 7.44-7.51 (m, 5H), 7.37-7.41

(m, 1H), 7.21 (d, *J*= 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$); *δ*= 171.9, 143.7, 138.5, 132.7, 130.6, 129.0, 128.8, 127.9, 120.4, 116.9; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{12}NO_2$ 214.0868; Found 214.0869); IR (cm^{-1}): 3482, 3387, 3025, 2526, 2359, 1677, 1408.

1-(2-amino-4'-chloro-[1, 1'-biphenyl]-4-yl) ethan-1-one (1k) [52806-85-6]

1-(4'-chloro-2-nitro-[1, 1'-biphenyl]-4-yl) ethan-1-one (0.21 g, 0.76 mmol), NH_4Cl (0.081 g, 1.53 mmol) and indium powder (0.262 g, 2.28 mmol). The title compound was obtained as a yellow solid (0.17 g, 94%). R_f = 0.32 [(Hx:EtOAc, 70:30)]; ^{1}H-NMR (500 MHz, $CDCl_3$): *δ*= 7.34 (d, *J*= 2Hz, 2H), 7.32-7.33 (m, 1H), 7.30-7.31 (m, 1H), 7.25-7.27 (m, 2H), 7.06 (d, *J*= 7.5 Hz, 1H), 3.74 (s, br, 2H), 2.48 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): *δ*= 198.1, 143.8, 137.5, 136.9, 133.8, 130.5, 130.2, 129.4, 129.2, 118.9, 114.9, 26.7; HR-MS (DART): $(M+H)^+$: Calcd for $C_{14}H_{13}{}^{35}ClNO$ 246.0686; Found 246.0688); Calcd for $C_{14}H_{13}{}^{37}ClNO$ 248.0656; Found 248.0668); IR (cm^{-1}): 3497, 3380, 3302 , 1672, 1420, 1290.

1-(2-amino-2'-methyl-[1, 1'-biphenyl]-4-yl) ethan-1-one (1l) [NEW]

1-(2'-methyl-2-nitro-[1, 1'-biphenyl]-4-yl) ethan-1-one (0.24 g, 0.94 mmol), NH_4Cl (0.10 g, 1.89 mmol) and indium powder (0.324 g, 2.82 mmol). The title compound was obtained as a pale-yellow solid (0.19 g, 90%). R_f = 0.37 [(Hx:EtOAc, 70:30)]; ^{1}H-NMR (500 MHz, $CDCl_3$): *δ*= 7.28-7.31 (m, 2H), 7.22-7.23 (m, 2H), 7.17-7.20 (m, 1H), 7.09-7.10 (m, 1H), 7.02 (d, *J*= 8 Hz, 1H), 3.46 (s, br, 2H), 2.51 (s, 3H), 2.08 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): *δ*= 198.3, 144.1, 137.6, 137.4, 136.6, 132.3, 130.5, 130.3, 129.5, 128.2, 126.3, 118.6, 114.2, 26.7, 19.6; HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO$ 226.1232; Found 226.1233); IR (cm^{-1}): 3482, 3453, 3382, 3361, 2921, 1671, 1659, 1620, 1425, 1292.

4'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1m) [1555774-70-3]

4'-chloro-4-methyl-2-nitro-[1, 1'-biphenyl] (0.124 g, 0.50 mmol), NH_4Cl (0.055 g, 1.00 mmol) and indium powder (0.172 g, 1.50 mmol) .The title compound was obtained as a dark brown liquid (0.102 g, 94%). R_f = 0.75 [(Hx:EtOAc, 70:30)]; ^{1}H-NMR (500 MHz, $CDCl_3$): *δ*= 7.37-7.41 (m, 4H), 6.98 (d, *J*= 7.5 Hz, 1H), 6.65 (d, *J*= 7.5 Hz, 1H), 6.60 (s, 1H), 3.64 (s, br, 2H), 2.30 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); *δ*= 143.2, 138.8, 138.0, 132.9, 130.5, 130.2, 128.9, 127.8, 119.8, 116.4, 21.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{13}{}^{35}ClN$ 218.0737; Found 218.0738); Calcd for $C_{13}H_{13}{}^{37}ClN$ 220.0707; Found 220.0701); IR (cm^{-1}): 3463,3377, 2917, 1608, 1478, 1090, 803.

2'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1n) [1552980-85-4]

2'-chloro-4-methyl-2-nitro-1, 1'-biphenyl (0.24 g, 0.97mmol), NH_4Cl (0.103 g, 1.94 mmol) and indium powder (0.334 g, 2.90 mmol). The title compound was obtained as a brown liquid (0.20 g, 95%). R_f = 0.71 [(Hx:EtOAc, 70:30)]; ^{1}H-NMR (500 MHz, $CDCl_3$): *δ*= 7.48-7.50 (m, 1H), 7.29-7.33 (m, 3H), 6.94 (d, *J*= 7.5 Hz, 1H), 6.66 (d, *J*= 7.5 Hz, 1H), 6.62 (s, 1H), 2.32 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): *δ*= 143.6, 139.1, 138, 134.0, 132.1, 130.3, 129.9, 128.9, 127.2, 122.7, 119.3, 116.2, 21.4: HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{13}{}^{35}ClN$ 218.0737; Found 218.0738); Calcd for $C_{13}H_{13}{}^{37}ClN$ 220.0707; Found 220.0655); IR (cm^{-1}): 3458, 3374, 2918, 1619, 1467, 1033.

4'-((tert-butyldimethylsilyl) oxy)-4-methyl-[1, 1'-biphenyl]-2-amine (1o) [NEW]

4'-((tert-butyldimethylsilyl) oxy)-4-methyl-2-nitro-[1, 1'-biphenyl] (0.365 g, 1.06 mmol), NH_4Cl (0.113 g, 2.12 mmol) and indium powder (0.365 g, 3.18 mmol) .The title compound was obtained as a yellow solid (0.312 g, 94%). R_f = 0.69 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): *δ*= 7.29-7.30 (m, 2H), 7.09 (d, *J*= 7.5 Hz, 1H), 6.89-6.91 (m, 2H), 6.63-6.65 (m, 1H), 6.60 (s, 1H), 2.30 (s, 3H), 1.01 (s, 9H), 0.24 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$); *δ*= 154.7, 143.4, 138.0, 132.3, 130.4, .130.2 124.9, 120.3, 119.6, 116.2, 25.7, 21.2, 18.2, -4.4; MS(EI): m/z(%): 314.2(21), 313.1(89, M+), 257.2(42), 256.1(100), 240.1(24), 198.1(9), 182.1(21), 167.1(22), 127.6(27), 75.1(30), 57.1(8); HR-MS (DART): $(M+H)^+$: Calcd for $C_{19}H_{28}NOSi$ 314.1940; Found 314.1942); IR (cm^{-1}): 3447, 3363, 2929, 2857, 1601, 1495, 1252.

2-acetaminobiphenyl derivatives

General procedure. To a solution of 2-aminobiphenyl (0.1 g, 0.59 mmol) and triethylamine (0.09 mL, 0.65 mmol) in 10 mL anhydrous of dichloromethane at 0°C, acetyl chloride (0.04 mL, 0.62 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h. After the reaction time, the solvent was evaporated under reduced pressure. The residue was dissolved in ether (20 ml) washed with water (20 ml). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the N-acetylated compound.

N-([1, 1'-biphenyl]-2-yl) acetamide (2a) [2113-47-5]

2'-amino-[1, 1'-biphenyl] **(1a)** (0.10 g, 0.59 mmol), Acetyl chloride (0.04 mL, 0.62 mmol) and Triethylamine (0.09 mL, 0.65 mmol). The title compound was obtained as a pale- white solid (0.115 g, 93%). mp 119.8-120 ^oC; R_f = 0.24 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.26 (d, *J*= 8.5 Hz, 1H), 7.49 (t, *J*= 7 Hz, 2H), 7.38(m, 3H), 7.24 (d, *J*= 7 Hz, 1H), 7.18 (d, *J*= 7.5 Hz, 1H), 2.02 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 168.3, 138.2, 134.7, 132.2, 130.1 129.2, 129.1, 128.4, 128.0, 124.4, 121.7, 24.6; HR-MS (ESI): $(M+Na)^+$: Calcd for $C_{14}H_{13}NNaO$ 234.0895; Found 234.0896); IR (cm^{-1}): 3286, 3027, 1658, 1531, 1433, 1301.

N-(2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-yl)acetamide(2b) [869631-32-3]

2'-trifluoromethyl-[1, 1'-biphenyl]-2-amine **(1b)** (0.105 g, 0.443 mmol), Acetyl chloride (0.03 mL, 0.46 mmol) and Triethylamine (0.07 mL, 0.48 mmol). The title compound was obtained as pale- yellow solid (0.122 g, 98%). mp 87.2-88.4 ^oC; R_f = 0.42 [(Hx:EtOAc, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.15 (d, *J*= 8Hz, 1H), 7.82 (d, *J*= 7.5Hz, 1H), 7.63 (t, *J*= 7.5Hz, 1H), 7.56 (t, *J*= 7.5Hz, 1H), 7.40-7.43 (m, 1H), 7.32 (d, *J*= 7.5Hz, 1H), 7.16 (m, 2H), 6.51 (s, br, 1H), 1.92 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 167.1, 135.5, 134.1, 131.2, 131.0 129.0, 128.9, 128.1, 127.5, 125.6 (q, CF_3), 122.9, 121.1, 23.3; HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO$ 280.0949; Found 280.0950); IR (cm^{-1}): 3237, 3031, 1659, 1529, 1312, 1109.

N-(2'-methyl-[1, 1'-biphenyl]-2-yl)acetamide (2c) [1616966-63-2]

2'-methyl-[1, 1'-biphenyl]-2-amine **(1c)** (0.12 g, 0.66 mmol), Acetyl chloride (0.05 mL, 0.69 mmol) and Triethylamine (1.0 mL, 0.72 mmol). The title compound was obtained as pale- brown liquid (0.146 g, 94%). R_f = 0.15 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.34 (d, *J*= 7.5 Hz, 1H), 7.36-7.39 (m, 1H), 7.32-7.34 (m, 2H), 7.29-7.31 (m, 1H), 7.14-7.19 (m, 3H), 6.78 (s, br, 1H), 2.10 (s, 3H), 1.95 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 168.1, 137.0, 135.3, 130.6, 130.0 129.7, 128.5, 128.4 126.4, 125.5, 123.9, 120.7, 24.7, 19.7; MS(EI): m/z(%); 226.1(8), 225.1(70, M+), 184.1(12), 183.1(100), 168.1(48), 167.1(52), 166.1(50), 152.1(14), 139(10), 115(11), 89.1(8), 63(6); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO$ 226.1232; Found 226.1233); IR (cm^{-1}): 3413, 3294, 3019, 2923, 1686, 1518, 1443, 1301, 1181.

N-(4'-methyl-[1, 1'-biphenyl]-2-yl)acetamide (2d) [76472-82-7]

4'-methyl-[1, 1'-biphenyl]-2-amine **(1d)** (0.085 g, 0.460 mmol), Acetyl chloride (0.03 mL, 0.48 mmol) and Triethylamine (0.07 mL, 0.50 mmol). The title compound was obtained as pale- brown liquid (0.094 g, 90%). R_f = 0.16 [(Hx:EtOAc, 80:20)]; MS(EI): m/z (%): 226.2(6), 225.1(39, M^+), 184.2(14), 183.1(100), 182.1(40), 168.1(23), 167.1(36), 153.1(5), 152.1(14), 139.1(6), 115.1(7), 77.1(6), 63.1(5);

N-(4'-ethyl-[1, 1'-biphenyl]-2-yl)acetamide (2e) [NEW]

4'-ethyl-[1, 1'-biphenyl]-2-amine **(1e)** (0.112 g, 0.570 mmol), Acetyl chloride (0.04 mL, 0.60 mmol) and Triethylamine (0.09 mL, 0.62 mmol). The title compound was obtained as pale- yellow oil (0.131 g, 96%). R_f = 0.19 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.27 (d, *J*= 8 Hz, 1H), 7.35-7.37 (m, 1H), 7.28-7.34 (m, 4H), 7.23 (d, *J*= 7 Hz, 1H), 7.16 (t, *J*= 7.5 Hz, 1H), 2.73 (q, *J*= 7.5 Hz, 2H), 2.03 (s, 3H), 1.31 (t, *J*= 7.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 168.2, 144.1, 135.4, 134.8, 130.1, 129.2, 128.6, 128.4 128.2, 124.3, 121.5, 28.6, 24.7, 15.4; HR-MS (DART): $(M+H)^+$: Calcd for $C_{16}H_{18}NO$ 240.1388; Found 240.1389);

N-(2'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2f) [141540-23-0]

2'-methoxy-[1, 1'-biphenyl]-2-amine **(1f)** (0.11 g, 0.55 mmol), Acetyl chloride (0.04 mL, 0.57 mmol) and Triethylamine (0.08 mL, 0.60 mmol). The title compound was obtained as pale- brown liquid (0.128 g, 96%). R_f = 0.31 [(Hx:EtOAc, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.28 (d, J= 8.5 Hz, 1H), 7.35-7.41 (m, 2H), 7.24 (d, J= 7.5 Hz, 1H), 7.17 (t, J= 7.5 Hz, 1H), 6.94-6.97 (m, 2H), 6.90 (m, 1H), 3.84 (s, 3H), 2.03 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 168.2, 156.1, 135.5, 132.2, 130.9, 129.7, 128.3, 124.5 122.5, 121.7, 117.5, 110.6, 55.9, 24.6; MS(EI): m/z(%): 241.1(22, M^+), 199.1(21), 181.1(26), 168.1(100), 167.1(82), 166.1(16), 139.1(18), 128.1(16), 115.1(10), 77.1(19), 51.1(24); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO_2$ 242.1181; Found 242.1182); IR (cm^{-1}): 3415, 3057, 2933, 2836, 1688, 1515, 1443, 1234, 1022.

N-(3'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2g) [94028-76-9]

3'-methoxy-[1, 1'-biphenyl]-2-amine **(1g)** (0.115, 0.577 mmol), Acetyl chloride (0.043 mL, 0.605 mmol) and Triethylamine (0.088 mL, 0.632 mmol). The title compound was obtained as pale- brown liquid (0.137 g, 99%). R_f = 0.41 [(Hx:EtOAc, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.08 (d, J= 8.5 Hz, 1H), 7.38-7.41 (m, 2H), 7.22-7.25 (m, 2H), 7.18 (t, J= 7.5 Hz, 1H), 7.09 (t, J= 7.5 Hz, 1H), 7.03-7.06 (m, 1H), , 3.83 (s, 3H), 1.99 (s, 3H); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO_2$ 242.1181; Found 242.1182); IR (cm^{-1}): 3306, 2930, 2836, 1691, 1516, 1443, 1240, 1020.

N-(4'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2h) [1217-87-4]

4'-methoxy-[1, 1'-biphenyl]-2-amine **(1h)** (0.112, 0.563 mmol), Acetyl chloride (0.042 mL, 0.586 mmol) and Triethylamine (0.087 mL, 0.623 mmol). The title compound was obtained as pale- yellow oil (0.135 g, 99%). R_f = 0.38 [(Hx:EtOAc, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.26 (d, J= 8 Hz, 1H), 7.33-7.36 (m, 1H), 7.28-7.30 (m, 2H), 7.22 (d, J= 7 Hz, 1H), 7.15-7.17 (m, 1H), 7.01-7.02 (m, 2H), 3.87 (s. 3H), 2.03 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 168.2, 159.4, 134.9, 130.4, 130.3, 130.1, 128.1, 124.3, 121.5, 114.5, 55.4, 24.7; MS(EI): m/z(%): 242.1(7), 241.1(41, M^+), 200.1(15), 199.1(100), 184.1(33), 167.1(14), 154.1(30), 139.1(9), 128.1(22), 127.1(17), 102.1(7), 77.1(11), 63.1(8); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO_2$ 242.1181; Found 242.1181; IR (cm^{-1}): 3350, 2932, 2838, 1689, 1512, 1240, 1032.

N-acetyl Carbazole derivatives

General procedure. In a microwave tube, 2-acetaminobiphenyl (106 mg, 0.51 mmol) dissolved in glacial acetic acid (5mL), $Pd(OAc)_2$ (5.7 mg, 0.025 mmol), Imes.HCl (8.7 mg, 0.025 mmol) and H_2O_2 (35%, 0.130 mL, 1.48 mmol) were added. The vial was sealed whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in the microwave cavity for 3 h at 120^{o}C. After the reaction time, the solvent acetic acid was removed under reduced pressure. The crude product was dissolved in EtOAc (25 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layer was washed with aqueous $NaHCO_3$ (20 mL). The organic layer was filtered off and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by silica gel chromatography using hexane (mixture of isomers) and ethyl acetate (gradient; 90:10 to 70:30) to obtain the N-acetyl Carbazole compound.

1-(9H-carbazol-9-yl) ethan-1-one (3a) [574-39-0]

N-([1, 1'-biphenyl]-2-yl)acetamide **(2a)** (0.106 g, 0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), IMes.HCl (8.5 mg, 0.025 mmol) and H_2O_2 (35%, 0.128 mL, 1.45 mmol). The title compound was obtained as a pale- yellow solid (0.090 g, 85%). mp 77.5-78.5 ^{o}C; R_f = 0.70 [(Hx:EtOAc, 70:30)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.22 (d, J= 8.5 Hz, 2H), 7.99-8.01 (m, 2H), 7.47-7.50 (m, 2H), 7.38-7.41 (td, J= 7.5 Hz, 1 Hz, 2H), 2.89 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 170.1, 138.7, 127.4, 126.4, 123.7, 119.9, 116.3, 27.8; MS(EI): m/z(%): 210.1(5), 209.1(32, M^+), 168.1(20), 167.1(100), 166.1(25), 140.1(11), 139.1(11), 138.1(3), 113.1(3), 89.1(2), 63.1(3); HR-MS (DART): $(M+H)^+$: Calcd for $C_{14}H_{12}NO$ 210.0919; Found 210.0920; IR (cm^{-1}): 3417, 3043, 2919, 1678, 1444, 1367, 1297, 1014.

1-(4-(trifluoromethyl)-9*H*-carbazol-9-yl) ethan-1-one (3b) [3932-32-9]

N-(2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-yl) acetamide **(2b)** (0.105 g, 0.376 mmol), $Pd(OAc)_2$ (4.2 mg, 0.019 mmol), IMes.HCl (8.5 mg, 0.019 mmol) and H_2O_2 (35%, 0.096 mL, 1.09 mmol). MS (EI): m/z (%): 278.1(2), 277(12, M^+), 258(1), 236.1(12), 235.1(100), 216.1(4), 185.1(7), 166.1(9), 139.1(4), 87(1), 75(1), 63(1)

1-(4-methyl-9*H*-carbazol-9-yl) ethan-1-one (3c) [1616966-64-3]

N-(2'-methyl-[1, 1'-biphenyl]-2-yl)acetamide **(2c)** (0.140 g, 0.62 mmol), $Pd(OAc)_2$ (7.0 mg, 0.031 mmol), IMes.HCl (11.0 mg, 0.031 mmol) and H_2O_2 (35%, 0.16 mL, 1.79 mmol). MS (EI): m/z (%): 224.2(4), 223.1(23, M+), 182.1(15), 181.1(100), 180.1(68), 179.1(8), 152.1(19), 127.1(5), 89.1(3), 77.1(7), 63.1(5).

1-(2-methyl-9*H*-carbazol-9-yl) ethan-1-one (3d) [433287-20-8]

N-(4'-methyl-[1, 1'-biphenyl]-2-yl)acetamide **(2d)** (0.087 g, 0.390 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), IMes.HCl (7.0 mg, 0.02 mmol) and H_2O_2 (35%, 0.10 mL, 1.11 mmol). The title compound was obtained as an orange liquid (0.040 g, 46%). R_f = 0.55 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.15 (d, *J*= 8.5 Hz, 1H), 8.05 (s, 1H), 7.93-7.95 (m, 1H), 7.85 (d, *J*= 8 Hz, 1H), 7.42-7.45 (td, *J*= 1 Hz, 7 Hz, 1H), 7.34-7.37 (td, *J*= 1 Hz, 7.5 Hz, 1H), 7.20-7.21 (dd, *J*= 0.5, 8 Hz, 1H), 2.87 (s, 3H), 2.54 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 170.2, 139.1, 138.6, 137.6, 126.8, 126.6, 124.9, 124.0, 123.6, 119.6, 27.8, 22.4; MS(EI): m/z(%): 224.1(5), 223.1(27, M+), 182.1(15), 181.1(100), 180.1(70), 179.1(8), 152.1(18), 151.1(8), 127.1(5), 77.1(6), 63.1(5); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{14}NO$ 224.1075; Found 224.1077.

1-(2-ethyl-9*H*-carbazol-9-yl) ethan-1-one (3e) [NEW]

N-(4'-ethyl-[1, 1'-biphenyl]-2-yl) acetamide **(2e)** (0.058 g, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), IMes.HCl (4.2 mg, 0.012 mmol) and H_2O_2 (35%, 0.062 mL, 0.70 mmol). The title compound was obtained as pale- orange oil (0.047 g, 81%). R_f = 0.71 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.14 (d, *J*= 8 Hz, 1H), 8.08 (s, 3H), 7.93-7.95 (m, 1H), 7.88 (d, *J*= 7.5 Hz, 1H), 7.41-7.45 (td, *J*= 1.5 Hz, 7.5 Hz, 1H), 7.34-7.37 (td, *J*= 1 Hz, 7.5 Hz, 1H), 7.23-7.24 (dd, *J*= 1.5 Hz, 8 Hz, 1H), 2.87 (s, 3H), 2.82 (q, *J*= 7.5 Hz, 2H), 1.33 (t, *J*= 8 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 170.2, 144.2, 139.1, 138.7, 126.8, 126.6, 124.3, 123.8, 123.6, 119.6, 119.5, 116.1, 115.7 29.8, 27.8, 16.2; MS(EI): m/z(%): 238.2(4), 237.1(28, M+), 196.1(10), 195.1(65), 181.1(14), 180.1(100), 179.1(13), 168.1(12), 152.1(13), 75(4), 63(5); HR-MS (DART): $(M+H)^+$: Calcd for $C_{16}H_{16}NO$ 238.1232; Found 238.1233; IR (cm^{-1}): 2963, 2928, 2870, 1690, 1421, 1366, 1293, 1192.

1-(4-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3f) [869631-38-9]

N-(2'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide **(2f)** (0.115 g, 0.477 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol), IMes.HCl (8.1 mg, 0.024 mmol) and H_2O_2 (35%, 0.120 mL, 1.38 mmol). MS (EI): m/z(%): 240.1(4), 239.1(41, M^+), 198.1(13), 197.1(100), 182(41), 154.1(76), 153.1(27), 139.1(10), 128.1(17), 127.1(25), 126.1(18), 77(9). 63(8).

1-(3-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3g) [173312-32-8]

N-(3'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide **(2g)** (0.108 g, 0.448 mmol), $Pd(OAc)_2$ (5.0 mg, 0.022 mmol), IMes.HCl (8.0 mg, 0.022 mmol) and H_2O_2 (35%, 0.11 mL, 1.29 mmol). The title compound was obtained as pale- yellow oil (0.065 g, 61%). R_f = 0.77 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.15 (t, *J*= 7.5 Hz, 1H), 7.94 (d, *J*= 8 Hz, 1H), 7.47-7.49 (m, 1H), 7.43-7.45 (dd, *J*= 1 Hz, 7 Hz, 1H), 7.37 (t, *J*= 8 Hz, 2H), 7.04-7.06 (dd, *J*= 3 Hz, 9 Hz, 1H), 3.93(s, 3H), 2.85 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 169.7, 156.5, 139.1, 133.1, 127.4, 126.5, 123.5, 119.9, 117.3, 116.3, 114.9, 103.2, 55.8, 27.6; MS(EI): m/z(%): 240.1(4), 239.1(33, M+), 198.1(11), 197.1(78), 183(13), 182(100), 154.1(36), 139(6), 128.1(15), 127.1(27), 126.1(20), 101(7), 75(13), 51(8); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{14}NO_2$ 240.1025; Found 240.1024; IR (cm^{-1}): 3346, 2935, 2833, 1684, 1487, 1433, 1300, 1200, 1033.

1-(2-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3h) [92552-65-3]

N-(4'-methoxy-[1, 1'-biphenyl]-2-yl) acetamide **(2h)** (0.115 g, 0.477 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol), IMes.HCl (8.1 mg, 0.024 mmol) and H_2O_2 (35%, 0.120 mL, 1.38 mmol). The title compound was obtained as pale- yellow solid (0.080 g, 70%). mp 108.7-109.9 ^oC; R_f = 0.83 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.93 (d, *J*= 8.5 Hz, 1H), 7.77-7.80 (m, 2H), 7.73 (d, *J*= 8.5 Hz, 1H), 7.23-7.31 (m, 2H), 6.86-6.89 (dd, *J*= 2.5 Hz, 8.5 Hz, 1H), 3.82 (s, 3H), 2.75 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 170.2, 159.8, 140.1, 138.4, 126.7, 125.9, 123.7, 120.2, 119.7, 119.2, 115.7, 111.4, 102, 55.8, 27.7; MS(EI): m/z(%): 240.1(8), 239(50, M^+), 198.1(15), 197.1(100), 182(71), 155(8), 154.1(64), 153.1(36), 139(7), 128(17), 127.1(27), 126(20), 101.1(7), 75912), 63(9); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{14}NO_2$ 240.1025; Found 240.1023; IR (cm^{-1}): 3386, 2925, 2838, 1693, 1461, 1432, 1038.

Carbazole derivatives

General procedure. In a microwave tube, 2-aminobiphenyl (84.5 mg, 0.5 mmol) was dissolved in glacial acetic acid (5mL), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), IMes.HCl (8.5 mg, 0.025 mmol) and H_2O_2 (35%, 0.128 mL, 1.45 mmol) were added. The vial was sealed whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in the microwave cavity for 20 min at 120^{o}C. After the reaction time, the solvent acetic acid was removed under reduced pressure. The crude product was dissolved in EtOAc (25 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layer was washed with aqueous $NaHCO_3$ (20 mL). The organic layer was filtered off via pad of celite and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexanes (mixture of isomers) and ethyl acetate (gradient; 90:10 to 50:50) to obtain the target compound.

9*H*-carbazole (4a) [86-74-8]

2-amino-1, 1'-biphenyl **(1a)** (0.085 g, 0.50 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), IMes.HCl (8.5 mg, 0.05 mmol) and H_2O_2 (35%, 0.128 mL, 1.45 mmol). The title compound was obtained as a pale- brown solid (0.070 g, 84 %). mp 242-243 ^oC ;R_f = 0.49 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 8.09 (d, *J*= 8 Hz, 2H), 7.42-7.47 (m, 4H), 7.22-7.26 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$); δ= 139.5, 125.8, 123.4, 120.3, 119.4, 110.6; HR-MS (DART): $(M+H)^+$: Calcd for $C_{12}H_{10}N$ 168.0813; Found 168.0814; IR (cm^{-1}): 3415, 3050, 1599, 1449, 1325, 722.

4-(trifluoromethyl)-9*H*-carbazole (4b) [2586-09-6]

2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-amine **(1b)** (0.100 g, 0.422 mmol), $Pd(OAc)_2$ (19.0 mg, 0.084 mmol), IMes.HCl (7.2 mg, 0.021 mmol) and H_2O_2 (35%, 0.11 mL, 1.23 mmol). The title compound was obtained as a brown liquid (0.060 g, 60 %). R_f = 0.42 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.25 (d, *J*= 8 Hz, 1H), 8.23 (s, br, 1H), 7.52 (d, *J*= 8.5 Hz, 1H), 7.47 (d, *J*= 7.5 Hz, 1H), 7.36-7.43 (m, 3H), 7.20-7.24 (td, *J*= 1.5 Hz, 8 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 140.1, 139.8, 126.9, 126.0, 124.9, 123.8, 123.5 (q, *J*= 18 Hz), 120.5, 120.3, 119.4, 117.1 (q, *J*= 22.5 Hz), 114.5, 110.8; MS(EI): m/z(%): 236.1(14), 235.1(100, M^+), 216(9), 185.1(12), 166.1(16), 139(11), 117.4(52), 107.7(12), 93(25), 69.1(12); HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_9F_3N$ 236.0687; Found 236.0686; IR (cm^{-1}): 3415, 1327, 1293, 1112, 726.

4-methyl-9*H*-carbazole (4c) [3770-48-7]

2'-methyl-[1, 1'-biphenyl]-2-amine **(1c)** (0.12 g, 0.66 mmol), $Pd(OAc)_2$ (30.0 mg, 0.13 mmol), IMes.HCl (11.0 mg, 0.032 mmol) and H_2O_2 (35%, 0.17 mL, 1.91 mmol). The title compound was obtained as a pale- brown solid (0.097 g, 82 %). mp 126 ^oC ;R_f = 0.66 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.16-8.18 (dd, *J*= 0.5 Hz, 8 Hz, 1H), 8.05(s, br, 1H), 7.41-7.43 (m, 2H), 7.30-7.33 (m, 1H), 7.25-7.28 (m, 2H), 7.00-7.02 (dd, *J*= 1 Hz, 7 Hz, 1H), 2.88 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 139.5, 133.4, 125.7, 125.2, 124.0, 122.6, 121.9, 121.0, 119.4, 110.4, 108.1, 20.8; MS(EI): m/z(%): 182.1(13), 181.1(100, M+), 180.1(80), 179.1(7), 152.1(17),

127.1(5), 90.5(34), 77.1(30), 63.1(10); HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{12}N$ 182.0970; Found 182.0969; IR (cm^{-1}): 3384, 3053, 2918, 2849, 1600, 1454, 1324.

2-methyl-9*H*-carbazole (4d) [3652-91-3]

4'-methyl-[1, 1'-biphenyl]-2-amine **(1d)** (0.086 g, 0.47 mmol), $Pd(OAc)_2$ (22.4 mg, 0.09 mmol), IMes.HCl (8.0 mg, 0.023 mmol) and H_2O_2 (35%, 0.120 mL, 1.35 mmol). The title compound was obtained as brown solid (0.060 g, 71 %). mp 233.5-234.4 ^oC; R_f = 0.58 [(Hx:EtOAc, 80:20)]; ^1H-NMR (500 MHz, $CDCl_3$): δ= 8.03 (d, *J*= 8 Hz, 1H), 7.95 (d, *J*= 8 Hz, 1H), 7.38-7.40 (m, 2H), 7.23 (s, 1H), 7.20-7.22 (m, 1H), 7.06 (d, *J*= 8 Hz, 1H), 2.53 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 140.0, 139.5, 136.0, 129.3, 129.2, 125.3, 123.5, 121.0, 120.0, 119.3, 110.7, 110.5, 22.1; MS(EI): m/z(%): 182.1(16), 181.1(100, M+), 153.1(10), 152.1(25), 96.1(18), 90.5(45), 77.1(54), 60.1(77); HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{12}N$ 182.0970; Found 182.0968; IR (cm^{-1}): 3397, 3049, 2916, 2852, 1607, 1460, 1326, 1243, 807, 726.

2-ethyl-9*H*-carbazole (4e) [106551-62-6]

4'-ethyl-[1, 1'-biphenyl]-2-amine **(1e)** (0.112 g, 0.569 mmol), $Pd(OAc)_2$ (25.0 mg, 0.11 mmol), IMes.HCl (11.0 mg, 0.029 mmol) and H_2O_2 (35%, 0.15 mL, 1.65 mmol). The title compound was obtained as brown solid (0.082 g, 75 %). mp 222-224 ^oC ;R_f = 0.66 [(Hx:EtOAc, 80:20)]; ^1H-NMR (500 MHz, $CDCl_3$): δ= 8.02-8.04 (dd, *J*= 0.5 Hz, 7.5 Hz, 1H), 7.97 (d, *J*= 8 Hz, 1H), 7.38-7.42 (m, 2H), 7.28 (d, *J*= 8.5 Hz, 1H), 7.24 (s, 1H), 7.08-7.10 (dd, *J*= 1.5 Hz, 8 Hz, 1H), 2.81(q, *J*= 7.5 Hz, 2H), 1.32 (t, *J*= 7.5 Hz, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 142.6, 136.2, 132.1, 129.3, 128.2, 125.3, 121.4, 120.0, 119.9, 119.3, 110.5, 29.5, 16.1; MS(EI): m/z(%): 195.1(52, M+), 180.1(100), 133(19), 96(58), 77(36), 60(57); HR-MS (DART): $(M+H)^+$: Calcd for $C_{14}H_{14}N$ 196.1126; Found 196.1128; IR (cm^{-1}): 3396, 2960, 2927, 1654, 1461, 1247.

4-methoxy-9*H*-carbazole (4f) [6933-50-2]

2'-methoxy-[1, 1'-biphenyl]-2-amine **(1f)** (0.110 g, 0.55 mmol), $Pd(OAc)_2$ (25.0 mg, 0.11 mmol), IMes.HCl (9.0 mg, 0.028 mmol) and H_2O_2 (35%, 0.128 mL, 1.45 mmol). The title compound was obtained as a pale- brown solid (0.010 g, 9 %). mp 132-133 ^oC; R_f = 0.71 [(Hx:EtOAc, 80:20)]; ^1H-NMR (500 MHz, $CDCl_3$): δ= 8.31 (d, *J*= 8 Hz, 1H), 8.07 (s, br, 1H), 7.36-7.40 (m, 2H), 7.33 (d, *J*= 8 Hz, 1H), 7.22-7.24 (m, 1H), 7.05 (d, *J*= 8 Hz, 1H), 6.68 (d, *J*= 8 Hz, 1H), 4.08 (s. 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 151.0, 133.4, 127.2, 125.6, 123.6, 121.4, 119.7, 117.8, 114.4, 104.6, 98.2, 95.1, 50.2; MS(EI): m/z(%): 198.1(11), 197.1(84, M^+), 182(37), 155.1(11), 154(100), 128(24), 127(32), 126(17), 99(30), 77(29), 63.1(23); HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{12}NO$ 198.0919; Found 198.0920; IR (cm^{-1}): 3401, 2956, 2919, 2850, 1718, 1455, 1261, 1101, 752.

3-methoxy-9*H*-carbazole (4g) [18992-85-3]

3'-methoxy-[1, 1'-biphenyl]-2-amine **(1g)** (0.115 g, 0.578 mmol), $Pd(OAc)_2$ (26.0 mg, 0.116 mmol), IMes.HCl (10 mg, 0.029 mmol) and H_2O_2 (35%, 0.148 mL, 1.676 mmol). The title compound was obtained as brown solid (0.013 g, 10 %). mp 145-147 ^oC; R_f = 0.71 [(Hx:EtOAc, 80:20)]; ^1H-NMR (500 MHz, $CDCl_3$): δ= 8.03 (d, *J*= 7.5 Hz, 1H), 7.93 (s, br, 1H), 7.56 (m, 1H), 7.39-7.42 (m, 2H), 7.34(d, *J*= 8.5 Hz, 1H), 7.19-7.22 (m, 1H), 7.05-7.08 (dd, *J*= 2.5 Hz, 9 Hz, 1H), 3.93 (s. 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 153.9, 140.3, 134.4, 128.8, 125.8, 123.8, 120.3, 119.1, 115.1, 111.3, 110.7, 103.2, 56.1; MS(EI): m/z(%): 197.1(79, M^+), 182(100), 154(65), 133(25), 128(31), 127(41), 96(63), 77(53), 51(52); HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{12}NO$ 198.0919; Found 198.0920; IR (cm^{-1}): 3399, 2917, 2848, 1460, 1172, 1031, 817, 726.

2-methoxy-9*H*-carbazole (4h) (6933-49-9)

4'-methoxy-[1, 1'-biphenyl]-2-amine **(1h)** (0.112 g, 0.563 mmol), $Pd(OAc)_2$ (25 mg, 0.11 mmol), IMes.HCl (9.6 mg, 0.028 mmol) and H_2O_2 (35%, 0.14 mL, 1.61 mmol). The title compound was obtained as a pale- brown solid (0.045 g, 41 %). mp 236.5-237.5 ^oC; R_f = 0.72 [(Hx:EtOAc, 80:20)]; ^1H-NMR (500 MHz, DMSO-d_6): δ= 11.1 (s, 1H), 7.95-7.99 (m, 2H), 7.42 (d, *J*= 8.5 Hz, 1H), 7.27-7.30 (td, *J*= 1 Hz, 7 Hz, 1H), 7.09-7.12 (td, *J*= 1 Hz, 8 Hz, 1H), 6.97 (d, *J*= 2.5 Hz, 1H), 6.76-6.78(dd, *J*= 2 Hz, 8.5 Hz, 1H) 3.83 (s, 3H);; ^{13}C-NMR (125 MHz,

DMSO-d_6); δ= 158.4, 141.0, 139.6, 124.1, 122.6, 120.9, 119.2, 118.5, 116.1, 110.6, 107.7, 94.4, 55.2; HR-MS (DART): $(M+H)^+$: Calcd for $C_{13}H_{12}NO$ 198.0919; Found 198.0919; IR (cm^{-1}): 3386, 2930, 2837, 1602, 1511, 1460, 1303, 1245, 1178, 1030.

2-chloro-9*H*-carbazole (4i) [10537-08-3]

4'-chloro-[1, 1'-biphenyl]-2-amine **(1i)** (0.13 g, 0.090 mmol), $Pd(OAc)_2$ (29 mg, 0.129 mmol), IMes.HCl (11.0 mg, 0.032 mmol) and H_2O_2 (35%, 0.160 mL, 1.85 mmol). The title compound was obtained as pale- brown solid (0.090 g, 70 %). mp 233.1-235 ^oC ;R_f = 0.61 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.92 (s, 1H), 7.86 (d, *J*= 7.5 Hz, 1H), 7.80 (d, *J*= 8.5 Hz, 1H), 7.23-7.25 (m, 3H), 7.08-7.10 (m, 1H), 7.02-7.04 (dd, *J*= 1.5 Hz, 8.0 Hz, 1H); ^{13}C-NMR (125 MHz, DMSO-d_6); δ= 140.3, 140.0, 129.9, 126.0, 121.8, 121.5, 121.3, 120.3, 119.0, 118.6, 111.2, 110.6; MS(EI): m/z(%): 203(30), 201(100, M^+), 167.1(6), 166.1(61), 140(20), 139(30), 102(23), 101(65), 87.1(23), 83(62), 69.2(49), 63.1(30); HR-MS (EI): $(M)^+$: Calcd for $C_{12}H_8{}^{35}ClN$ 201.0345; Found 201.0348; Calcd for $C_{12}H_8{}^{37}ClN$ 203.0316; Found 203.0323; IR (cm^{-1}): 3413, 3061, 2952, 2853, 1595, 1437, 1327, 1090, 812, 726.

9*H*-carbazole-2-carboxylic acid (4j) [51094-28-1]

2-amino-[1, 1'-biphenyl]-4-carboxylic acid **(1j)** (0.11 g, 0.52 mmol), $Pd(OAc)_2$ (23 mg, 0.102 mmol), IMes.HCl (9.0 mg, 0.026 mmol) and H_2O_2 (35%, 0.13 mL, 1.50 mmol). The title compound was obtained as a pale- white solid (0.082 g, 75 %). mp 316-318 ^oC; R_f = 0.63 [(Hx:EtOAc, 50:50)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 11.53 (s, 1H), 8.20 (t, *J*= 7.5 Hz, 2H), 8.11 (s, 1H), 7.77-7.79 (dd, *J*= 1 Hz, 8 Hz, 1H), 7.56 (d, *J*= 8 Hz, 1H), 7.45-7.48 (td, *J*= 1 Hz, 7 Hz, 1H), 7.20-7.23 (td, *J*= 1 Hz, 8 Hz, 1H); ^{13}C-NMR (125 MHz, DMSO-d_6); δ= 168.1,140.9, 139.0, 127.7, 126.8, 125.8, 121.6, 120.9, 119.8, 119.5, 119.0, 112.4, 111.3; HR-MS (DART): $(M-H)^+$: Calcd for $C_{13}H_8NO_2$ 210.0555; Found 210.0552; IR (cm^{-1}): 3415, 3391, 2923, 1670, 1260, 1000.

1-(7-chloro-9*H*-carbazol-2-yl) ethan-1-one (4k) [NEW]

1-(2-amino-4'-chloro-[1, 1'-biphenyl]-4-yl) ethan-1-one **(1k)** (0.125 g, 0.510 mmol), $Pd(OAc)_2$ (23 mg, 0.102 mmol), IMes.HCl (8.7 mg, 0.026 mmol) and H_2O_2 (35%, 0.130 mL, 1.47 mmol). The title compound was obtained as brown solid (0.090 g, 73 %). mp 218-220 ^oC; R_f = 0.69 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 11.67 (s, 1H), 8.21-8.25 (m, 2H), 8.11 (s, 1H), 7.81-7.83 (dd, *J*= 1.5 Hz, 8 Hz, 1H), 7.62 (d, *J*= 2Hz, 1H), 7.22-7.24 (dd, *J*= 2 Hz, 8.5 Hz, 1H), 2.68 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6); δ= 197.8, 141.7, 139.5, 134.4, 131.4, 125.5, 122.6, 120.5, 120.2, 119.4, 119.1, 111.6, 111.0, 26.9; MS(EI): m/z(%): 245(18), 243(57, M^+), 230(32), 228(100), 208(69), 200(82), 173(42), 164(56), 138(29), 114(47), 96(44), 86(60), 83(69), 82(52), 63(50); HR-MS (DART): $(M+H)^+$: Calcd for $C_{14}H_{10}{}^{35}Cl$ NO 243.0451; Found 243.0453, Calcd for $C_{14}H_{10}{}^{37}Cl$ NO 245.0451; Found 245.0454; IR (cm^{-1}): 3307, 2962, 2919, 1660, 1621, 1429, 1250, 801.

1-(5-methyl-9*H*-carbazol-2-yl) ethan-1-one (4l) [NEW]

1-(2-amino-2'-methyl-[1, 1'-biphenyl]-4-yl) ethan-1-one **(1l)** (0.095 g, 0.422 mmol), $Pd(OAc)_2$ (19.0 mg, 0.085 mmol), IMes.HCl (7.0 mg, 0.021 mmol) and H_2O_2 (35%, 0.11 mL, 1.23 mmol). The title compound was obtained as pale white solid (0.080 g, 85 %). mp 180-182 ^oC ;R_f = 0.70 [(Hx:EtOAc, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.39 (s, br, 1H), 8.20 (d, *J*= 8 Hz, 1H), 8.09 (s, 1H), 7.85-7.87 (dd, *J*= 1.5 Hz, 8.5 Hz, 1H), 7.37-7.40 (m, 1H), 7.33 (d, *J*= 8 Hz, 1H), 7.05 (d, *J*= 7 Hz, 1H), 2.90 (s, 3H), 2.72 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 198.5, 141.2, 139.1, 134.3, 134.0, 127.9, 127.2, 122.2, 121.4, 121.2, 119.9, 110.6, 108.5, 27.0, 20.8; MS(EI): m/z(%): 223.1(61, M^+), 208(100), 207(17), 180(68), 178(20), 152(32), 151(17), 127(16), 104(60), 89.1(35), 77(67), 63(25); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{14}NO$ 224.1075; Found 224.1077; IR (cm^{-1}): 3261, 2918, 2849, 1660, 1618, 1441, 1274, 1205.

2-chloro-7-methyl-9*H*-carbazole (4m) [NEW]

4'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine **(1m)** (0.085 g, 0.391 mmol), $Pd(OAc)_2$ (18.0 mg, 0.080 mmol), IMes.HCl (7.0 mg, 0.021 mmol) and H_2O_2 (35%, 0.10 mL, 1.14 mmol). The title compound was obtained as

yellow solid (0.065 g, 77 %). mp 85-87 ^{o}C ;R_f = 0.58 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ=11.27 (s, 1H), 8.06 (d, J= 8.5 Hz, 1H), 7.98 (d, J= 8.0 Hz, 1H), 7.54 (m, 1H), 7.49 (s, 1H), 7.48 (m, 1H), 7.30 (s, 1H), 2.47 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6); δ= 140.5, 140.3, 135.6, 131.2, 128.3, 121.1, 120.6, 120.0, 119.5, 118.5, 111.1, 110.4, 21.6; MS(EI): m/z(%): 216(24), 215(71, M^+), 214(38), 180.1(44), 179.1(22), 151(20), 133(11), 107(15), 96(26), 90(81), 76(100), 75.1(61), 63(44), 57(39); HR-MS (EI): $(M)^+$: Calcd for $C_{13}H_{10}{}^{35}ClN$ 215.0502; Found 215.0503; Calcd for $C_{13}H_{10}{}^{37}ClN$ 217.0472; Found 217.0564; IR (cm^{-1}): 3406, 2920, 2851, 1600, 1002, 798.

5-chloro-2-methyl-9*H*-carbazole (4n) [NEW]

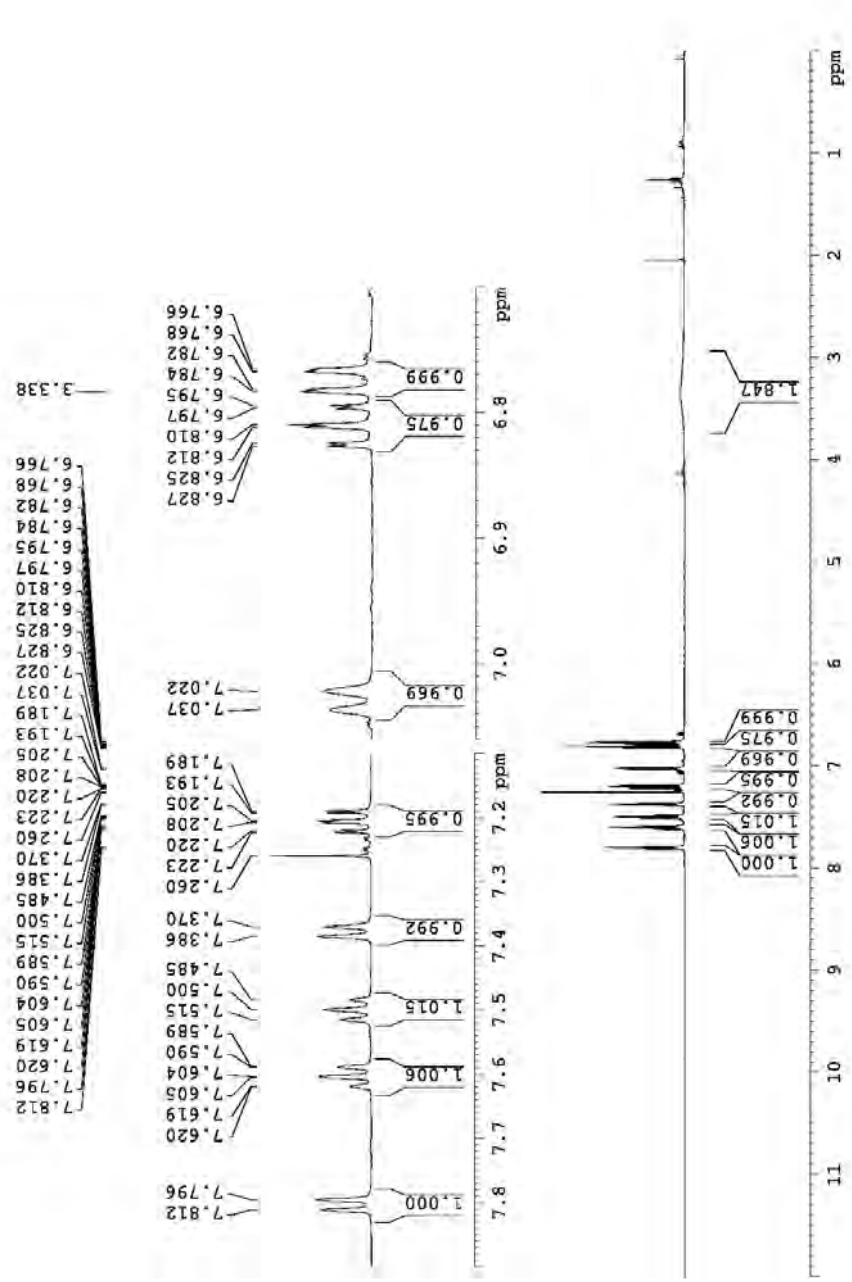
2'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine **(1n)** (0.089 g, 0.410 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol), IMes.HCl (7.0 mg, 0.021 mmol) and H_2O_2 (35%, 0.10 mL, 1.18 mmol). The title compound was obtained as orange solid (0.071 g, 81 %). mp 70-71 ^{o}C; R_f = 0.40 [(Hx:EtOAc, 80:20)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.35 (d, J= 8 Hz, 1H), 7.90 (s, 1H), 7.16-7.19 (m, 2H), 7.09-7.11 (m, 2H), 7.01-7.03 (dd, J= 0.5 Hz, 8 Hz, 1H), 2.44 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$); δ= 140.5, 140.0, 136.7, 128.3, 125.6, 122.7, 121.4, 120.8, 120.1, 120.0, 110.5, 108.8, 22.1; MS(EI): m/z(%): 217(31), 216(30), 215(100, M^+), 180.1(44), 178(22), 152.1(20), 108(17), 90(64), 89.1(92), 76(84), 75.1(45), 63(31); HR-MS (EI): $(M)^+$: Calcd for $C_{13}H_{10}{}^{35}ClN$ 215.0502; Found 215.0503; Calcd for $C_{13}H_{10}{}^{37}ClN$ 217.0472; Found 217.0507; IR (cm^{-1}): 3384, 2917, 2850, 1609, 1432, 1317, 808, 753.

2-((tert-butyldimethylsilyl) oxy)-7-methyl-9*H*-carbazole (4o) [NEW]

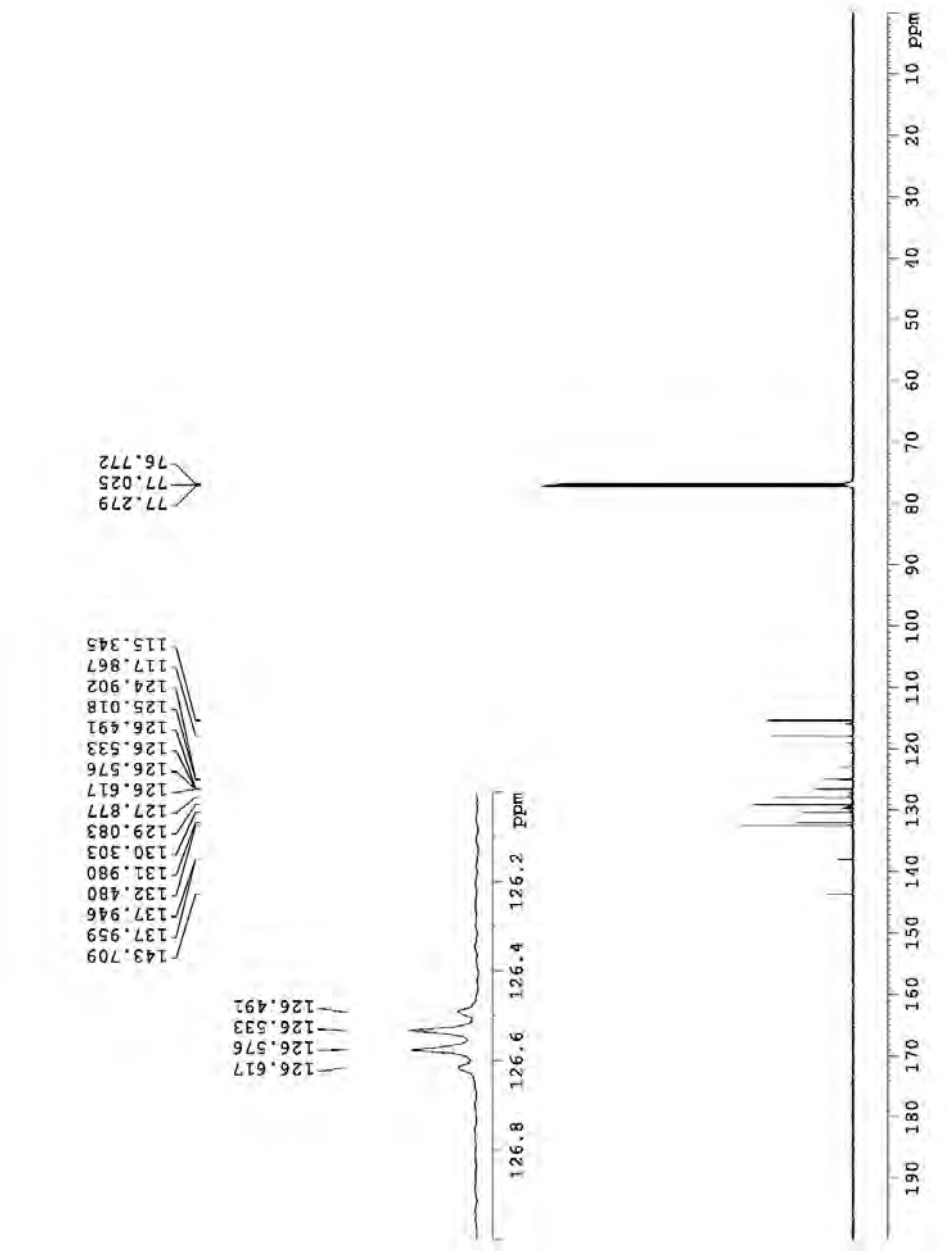
4'-((tert-butyldimethylsilyl) oxy)-4-methyl-[1, 1'-biphenyl]-2-amine **(1o)** (0.070 g, 0.23 mmol), $Pd(OAc)_2$ (10 mg, 0.045 mmol), IMes.HCl (4 mg, 0.01 mmol) and H_2O_2 (35%, 0.06 mL, 0.64 mmol). MS(EI): m/z(%): 312.1(9), 311.1(38, M+), 255.1(36), 254(100), 239(16), 226(23), 207(25), 196(12), 180(22), 152(14), 126.7(99), 111.6(14), 96(15), 75(31), 73(79), 59(22), 57(39).

Spectral data

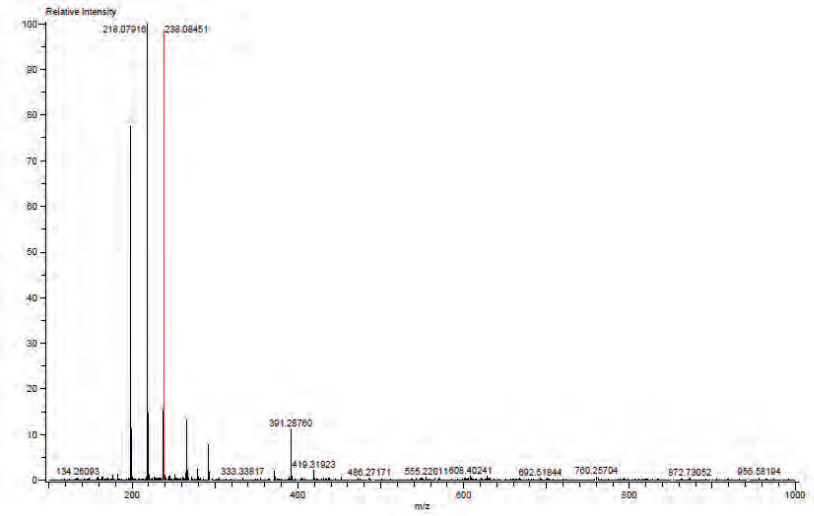
^{1}H-NMR of 2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-amine (1b) in $CDCl_3$



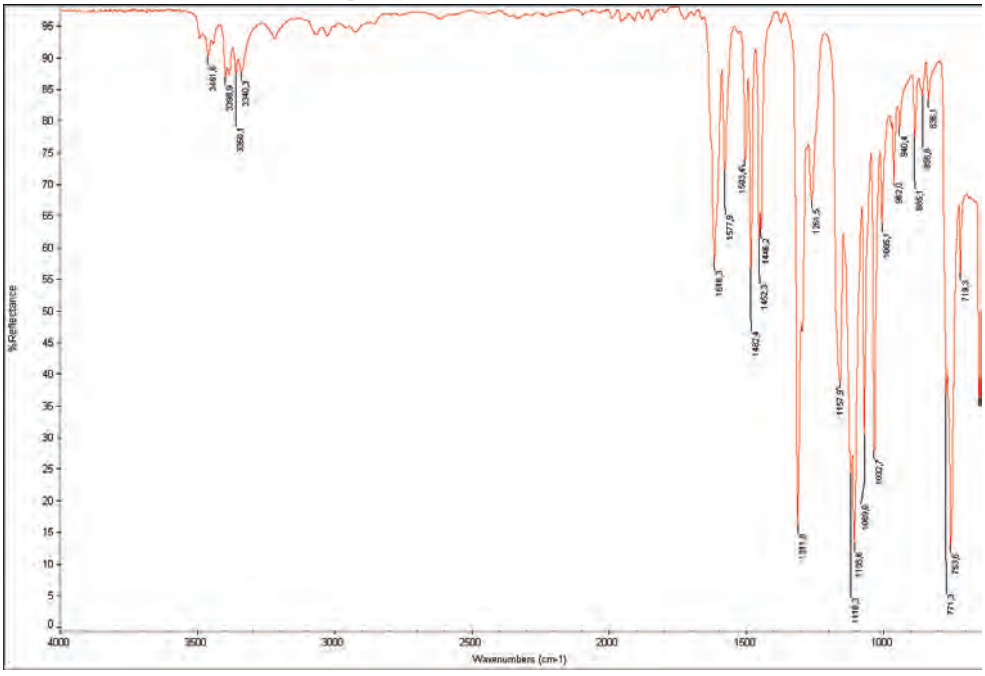
^{13}C-NMR of 2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-amine (1b) in $CDCl_3$



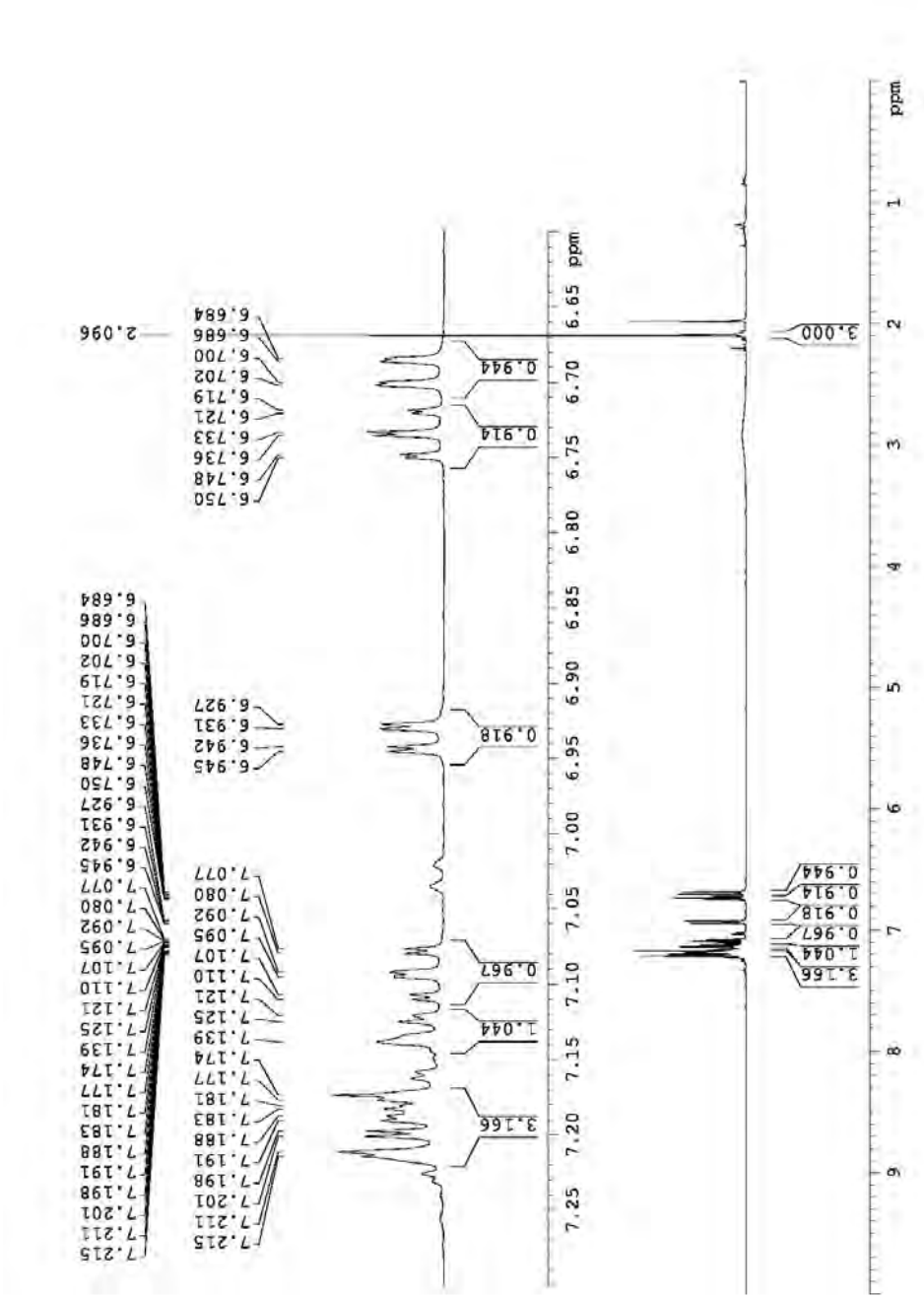
HRMS (DART+) of 2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-amine (1b)



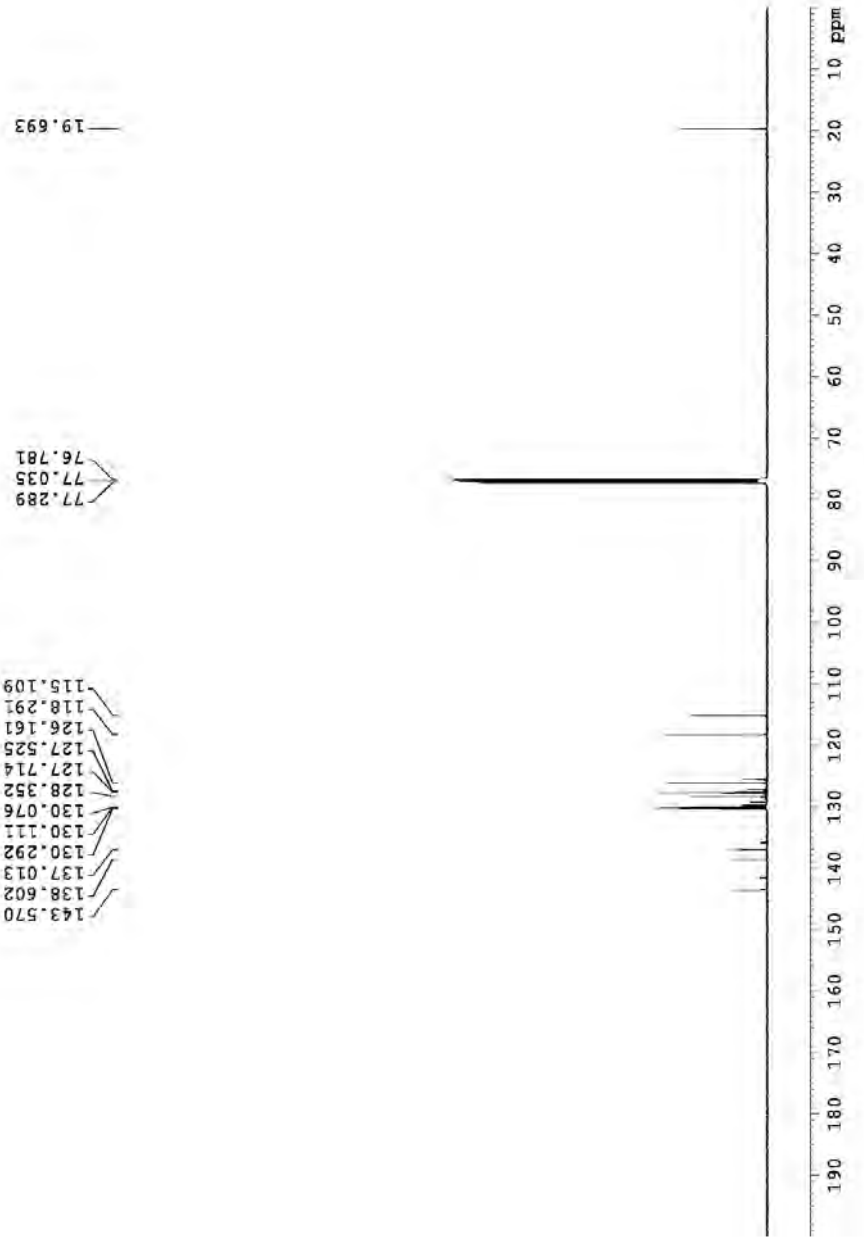
IR of 2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-amine (1b)



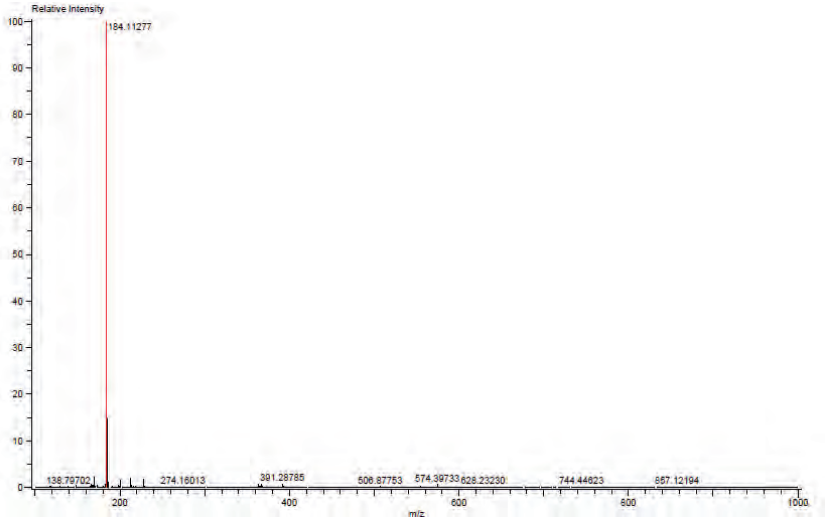
^{1}H-NMR of 2'-methyl-[1, 1'-biphenyl]-2-amine (1c) in $CDCl_3$



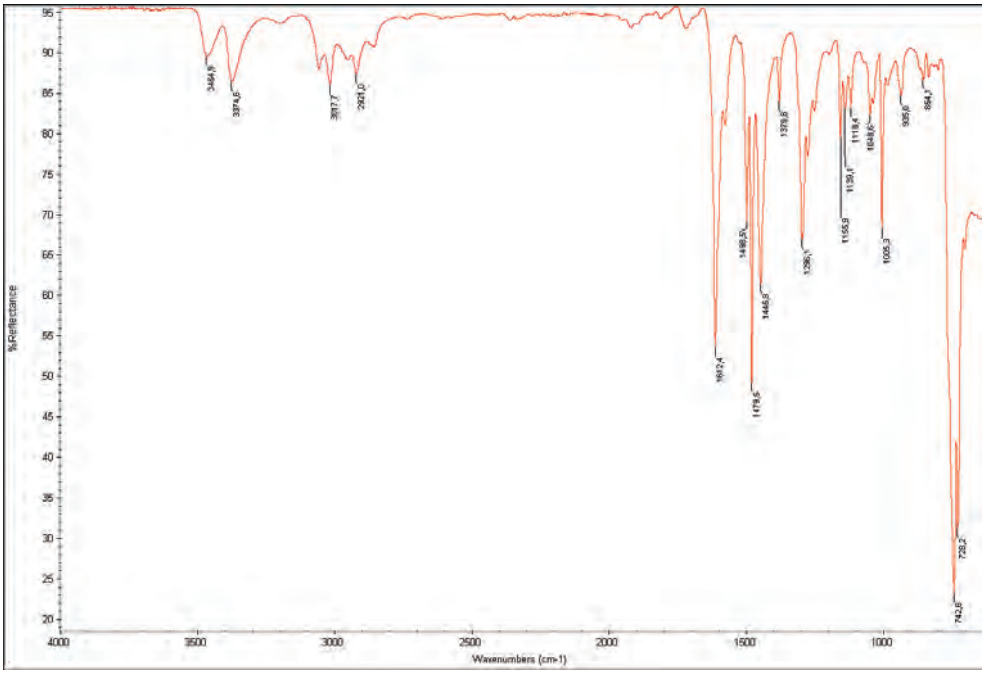
^{13}C-NMR of 2'-methyl-[1, 1'-biphenyl]-2-amine (1c) in $CDCl_3$



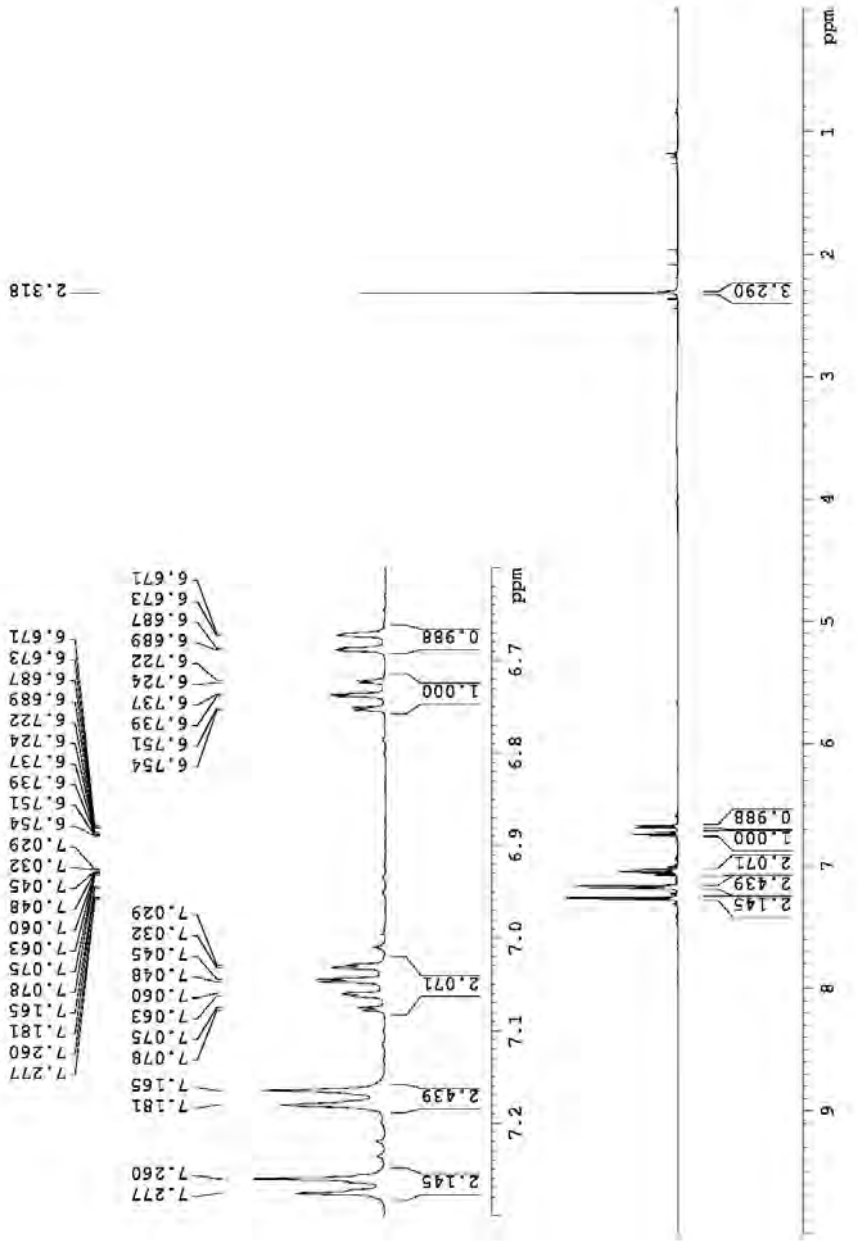
HRMS (DART+) of 2'-methyl-[1, 1'-biphenyl]-2-amine (1c)



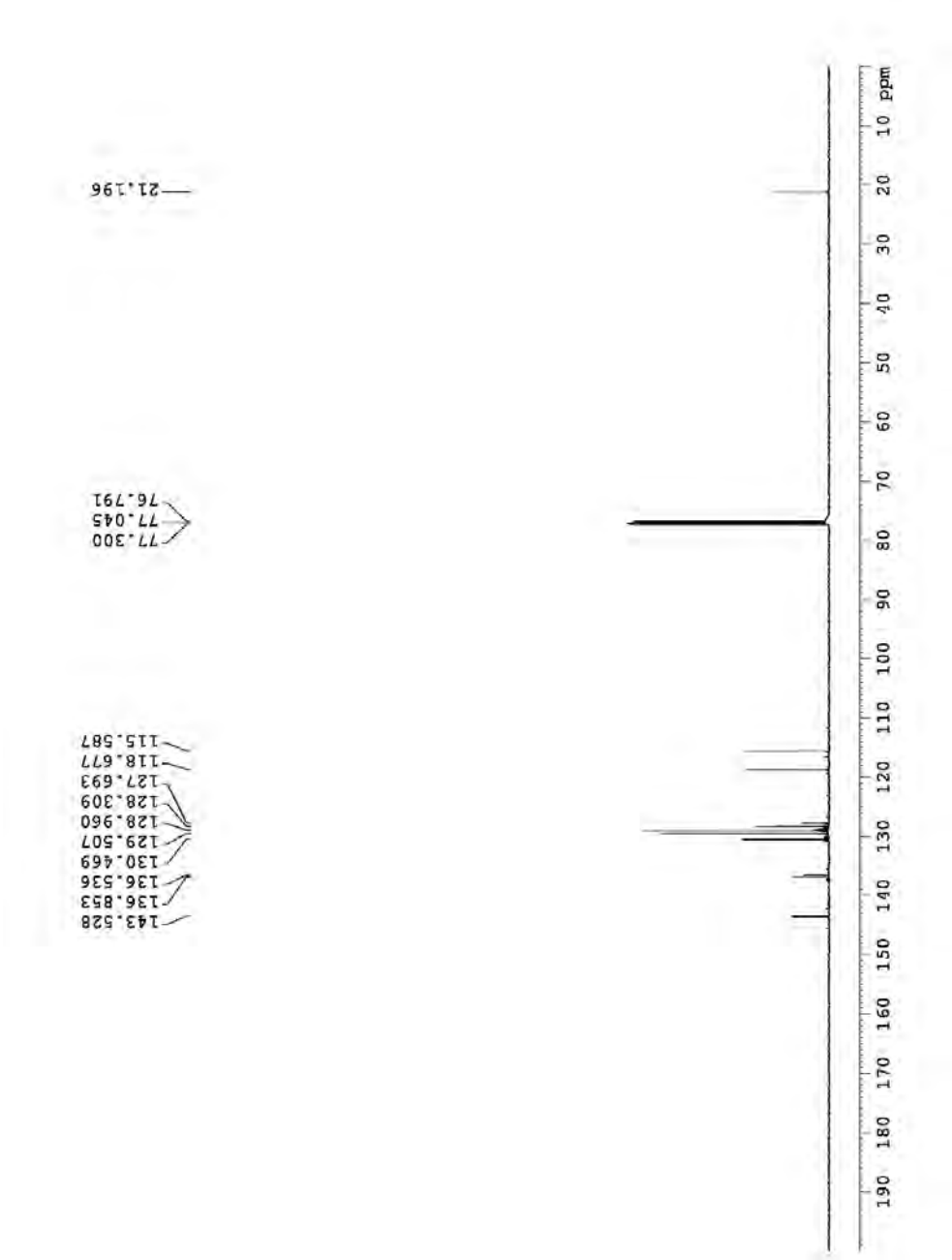
IR of 2'-methyl-[1, 1'-biphenyl]-2-amine (1c)



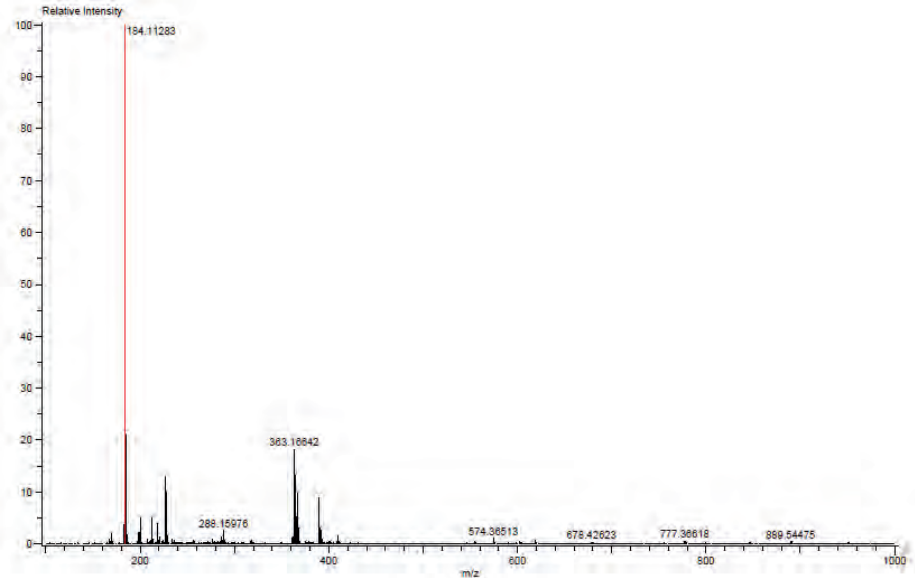
^{1}H-NMR of 4'-methyl-[1, 1'-biphenyl]-2-amine (1d) in $CDCl_3$



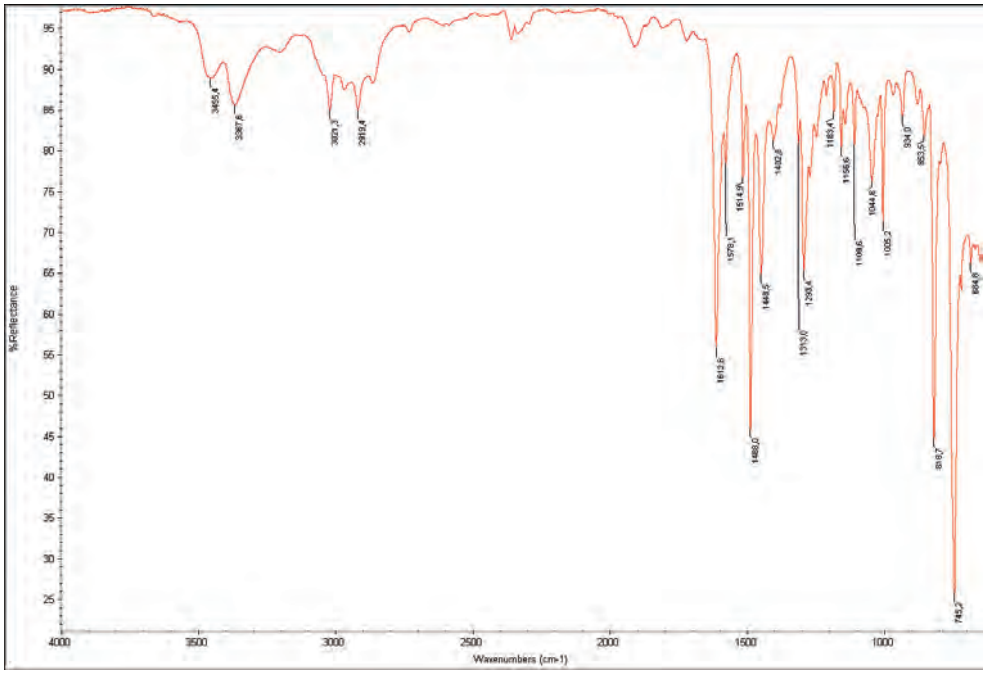
^{13}C-NMR of 4'-methyl-[1, 1'-biphenyl]-2-amine (1d) in $CDCl_3$



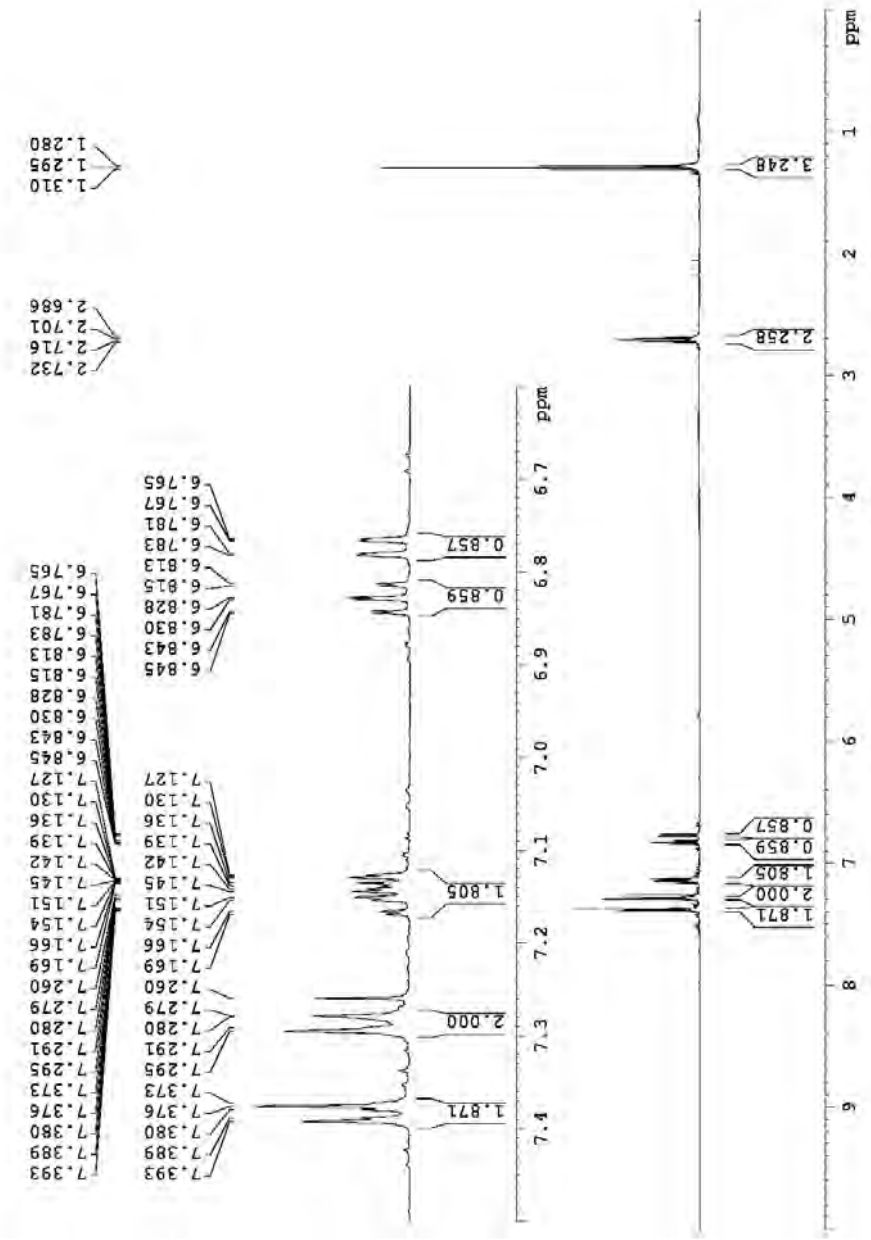
HRMS (DART+) of 4’-methyl-[1, 1’-biphenyl]-2-amine (1d)



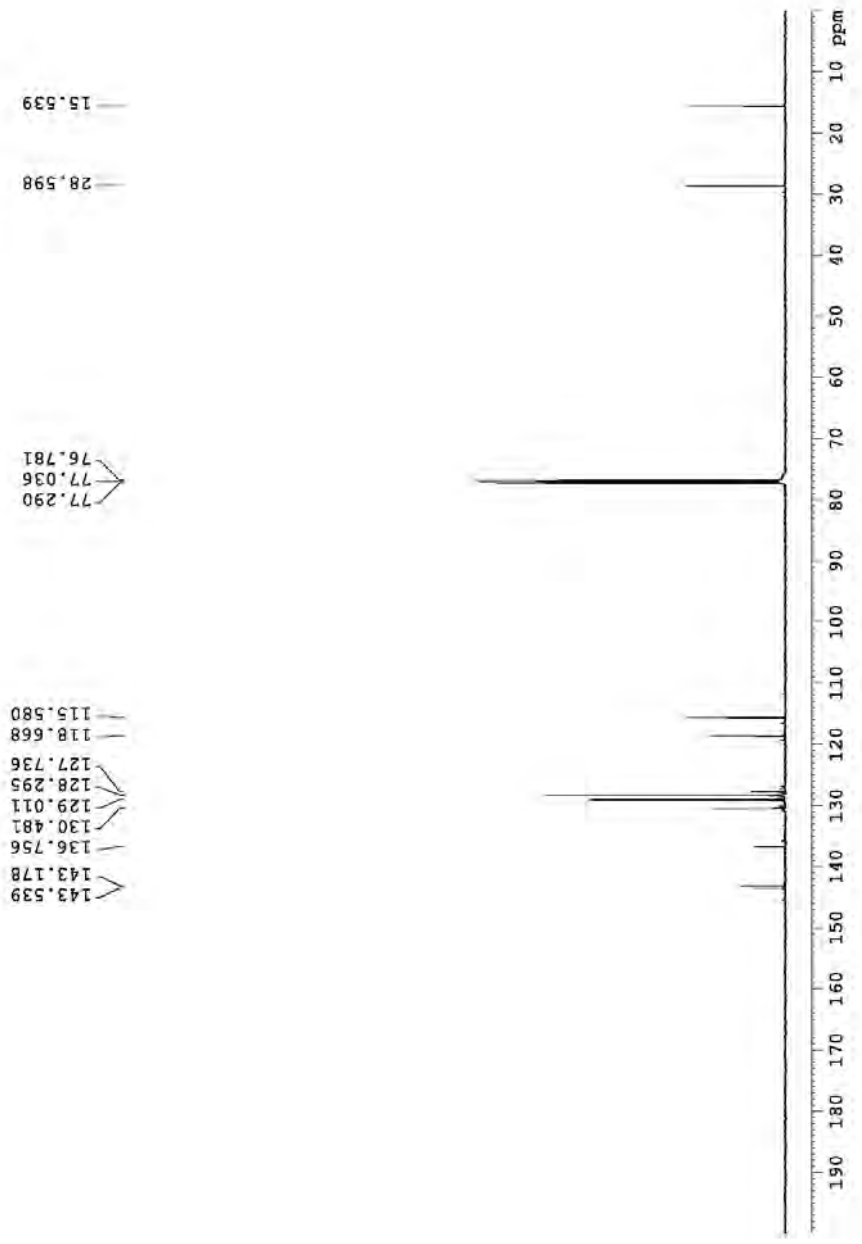
IR of 4’-methyl-[1, 1’-biphenyl]-2-amine (1d)



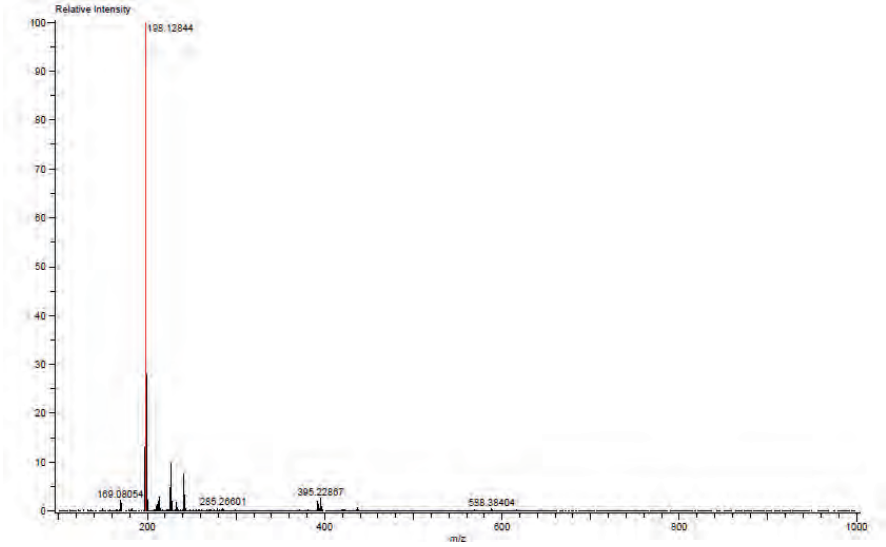
^{1}H-NMR of 4'-ethyl-[1, 1'-biphenyl]-2-amine (1e) in $CDCl_3$



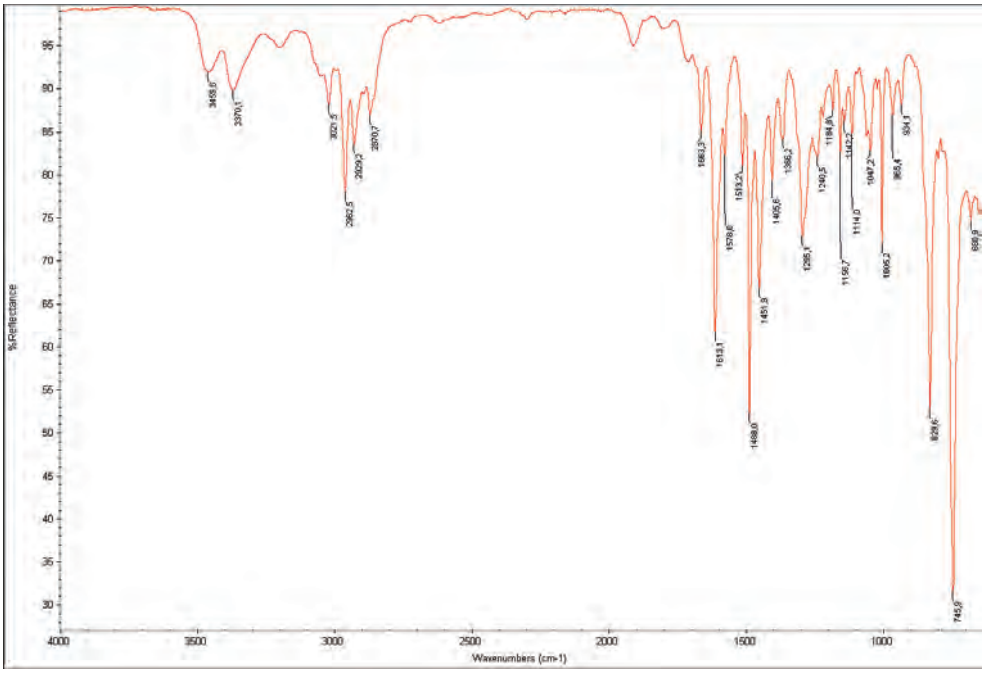
^{13}C-NMR of 4'-ethyl-[1, 1'-biphenyl]-2-amine (1e) in $CDCl_3$



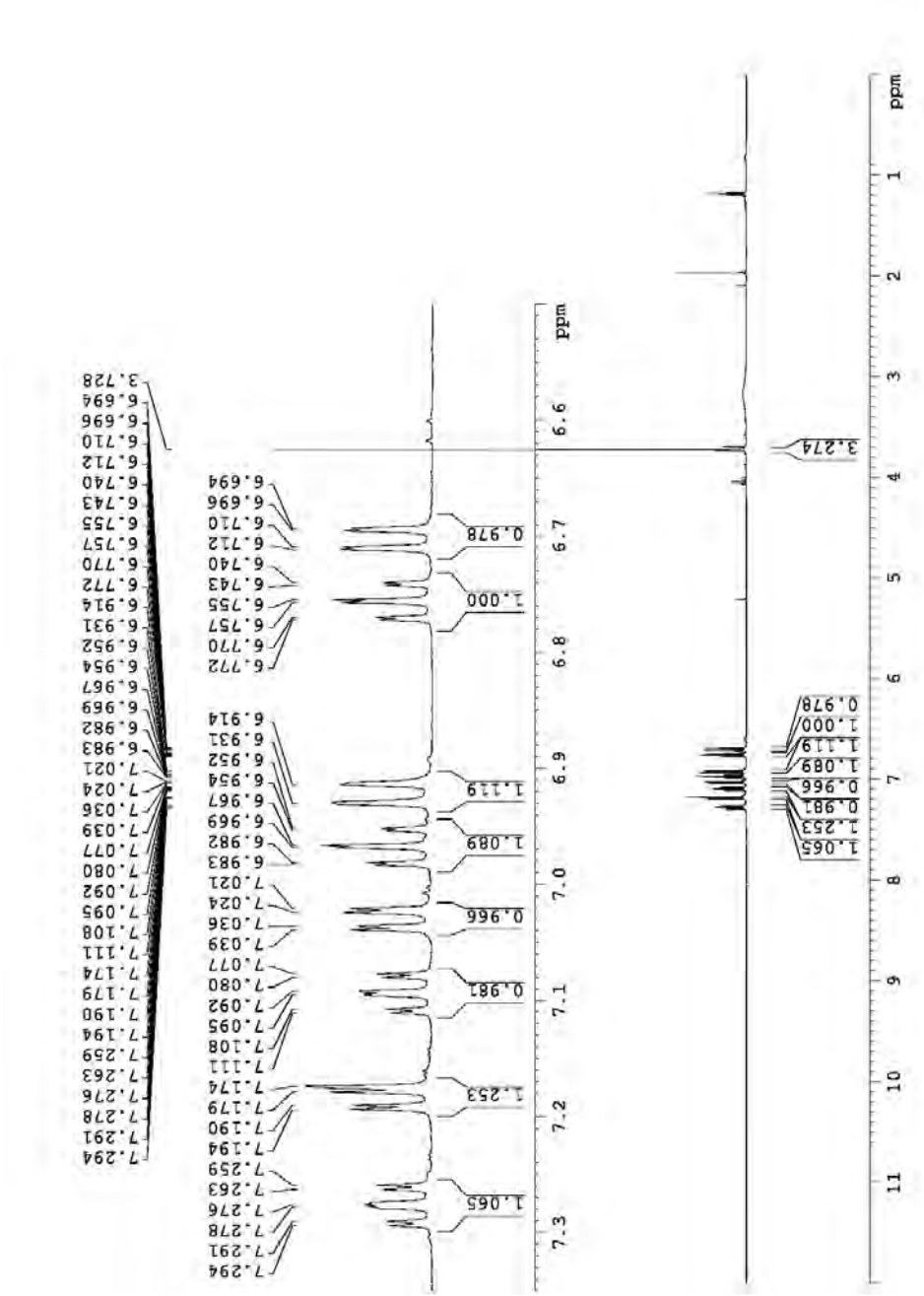
HRMS (DART+) of 4'-ethyl-[1, 1'-biphenyl]-2-amine (1e)



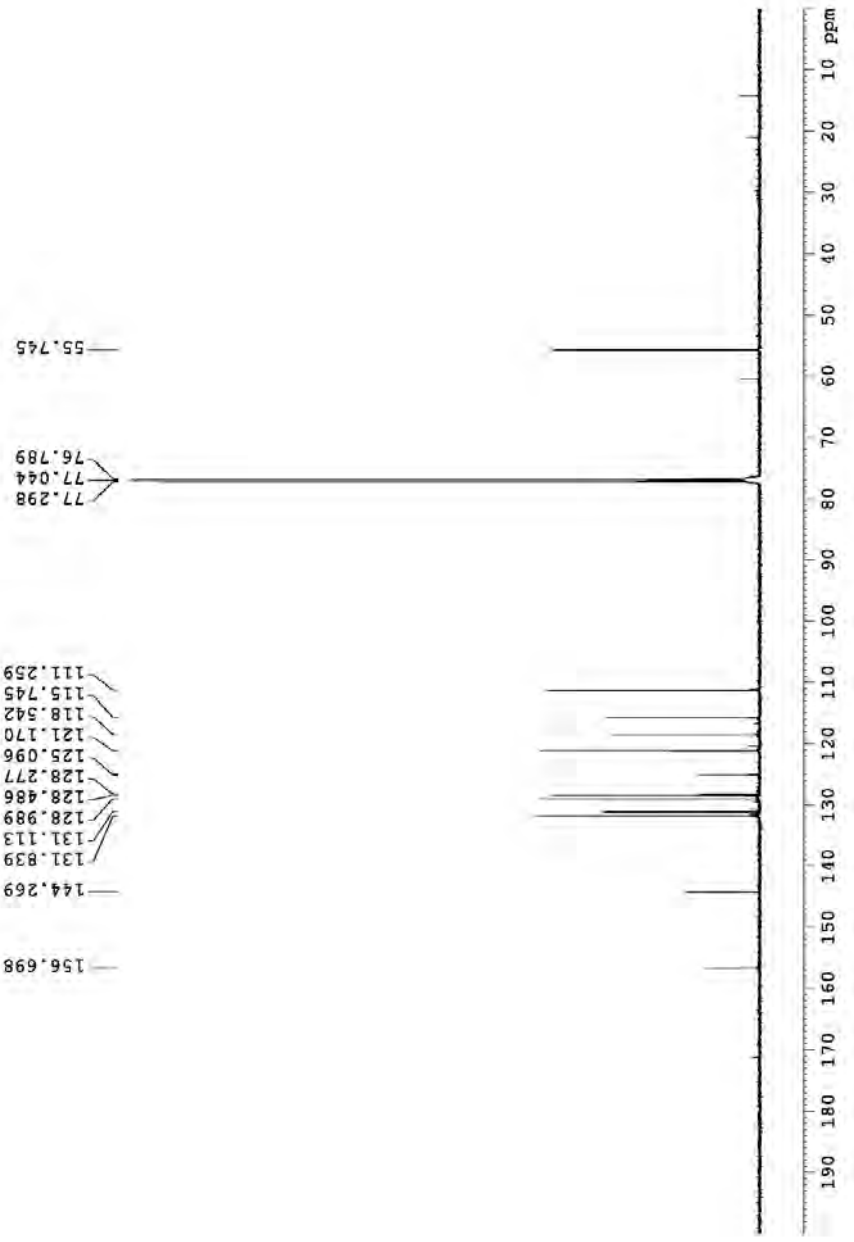
IR of 4'-ethyl-[1, 1'-biphenyl]-2-amine (1e)



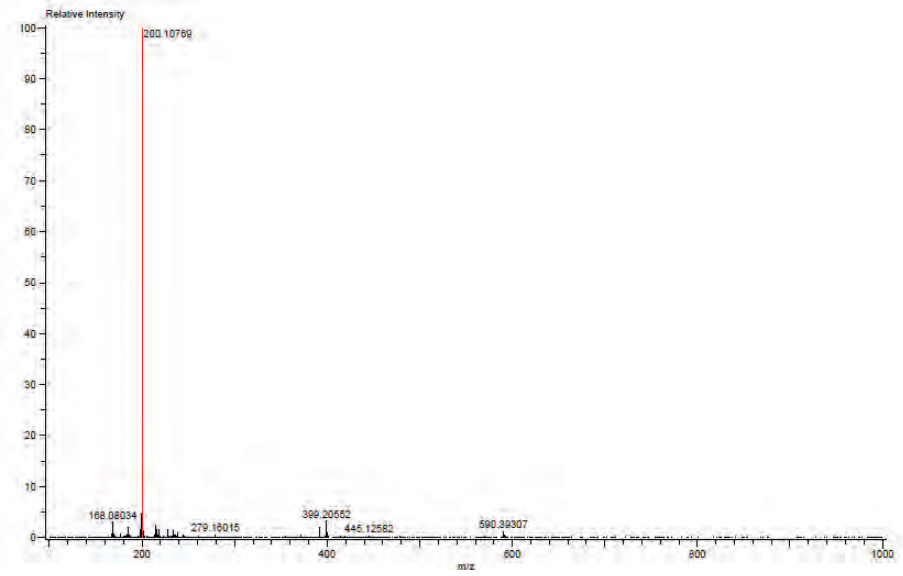
^{1}H-NMR of 2'-methoxy-[1, 1'-biphenyl]-2-amine (1f) in $CDCl_3$



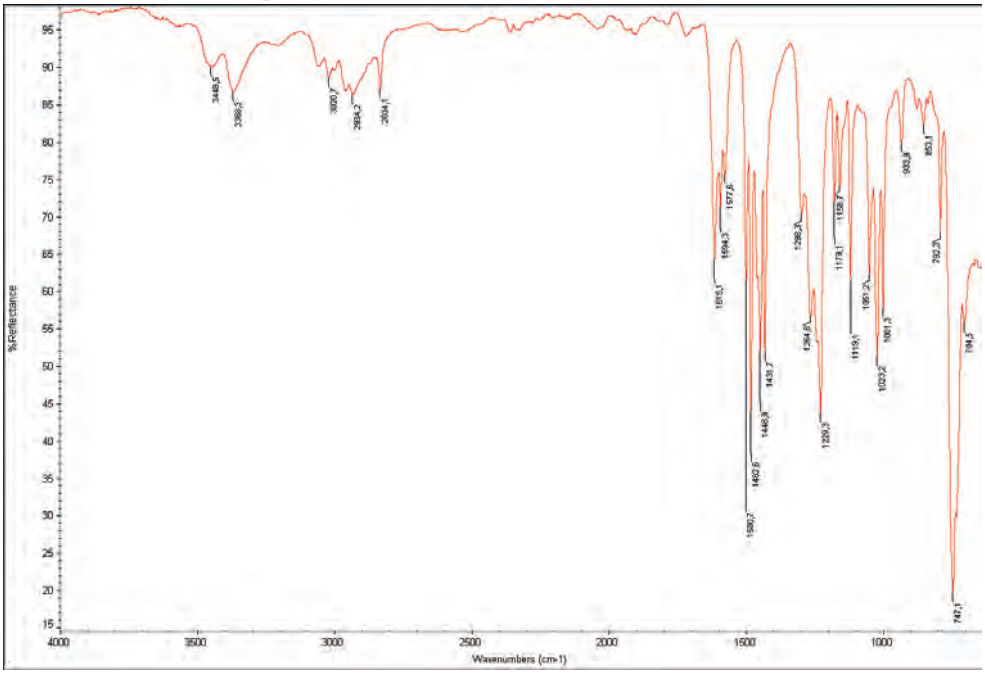
^{13}C-NMR of 2'-methoxy-[1, 1'-biphenyl]-2-amine (1f) in $CDCl_3$



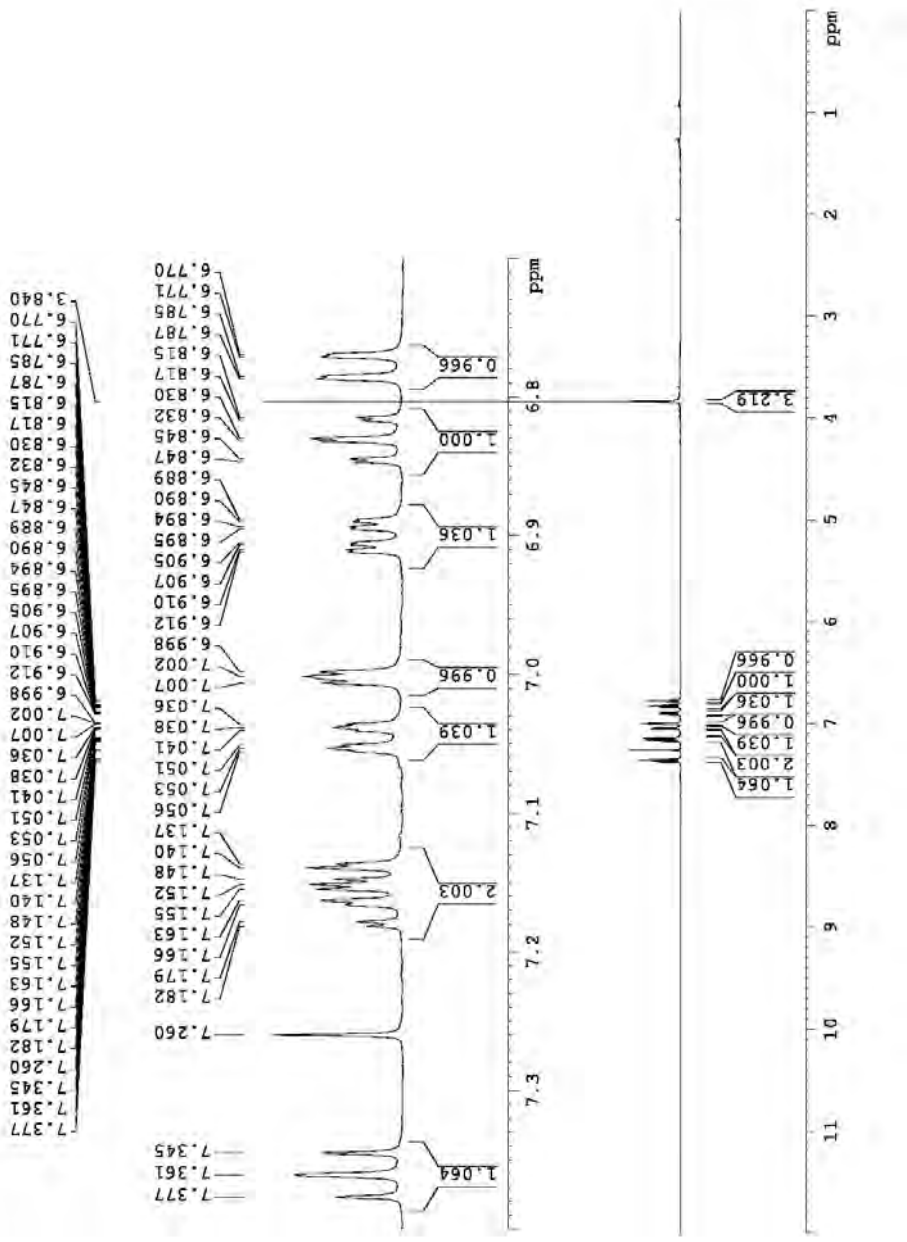
HRMS (DART+) of 2'-methoxy-[1, 1'-biphenyl]-2-amine (1f)



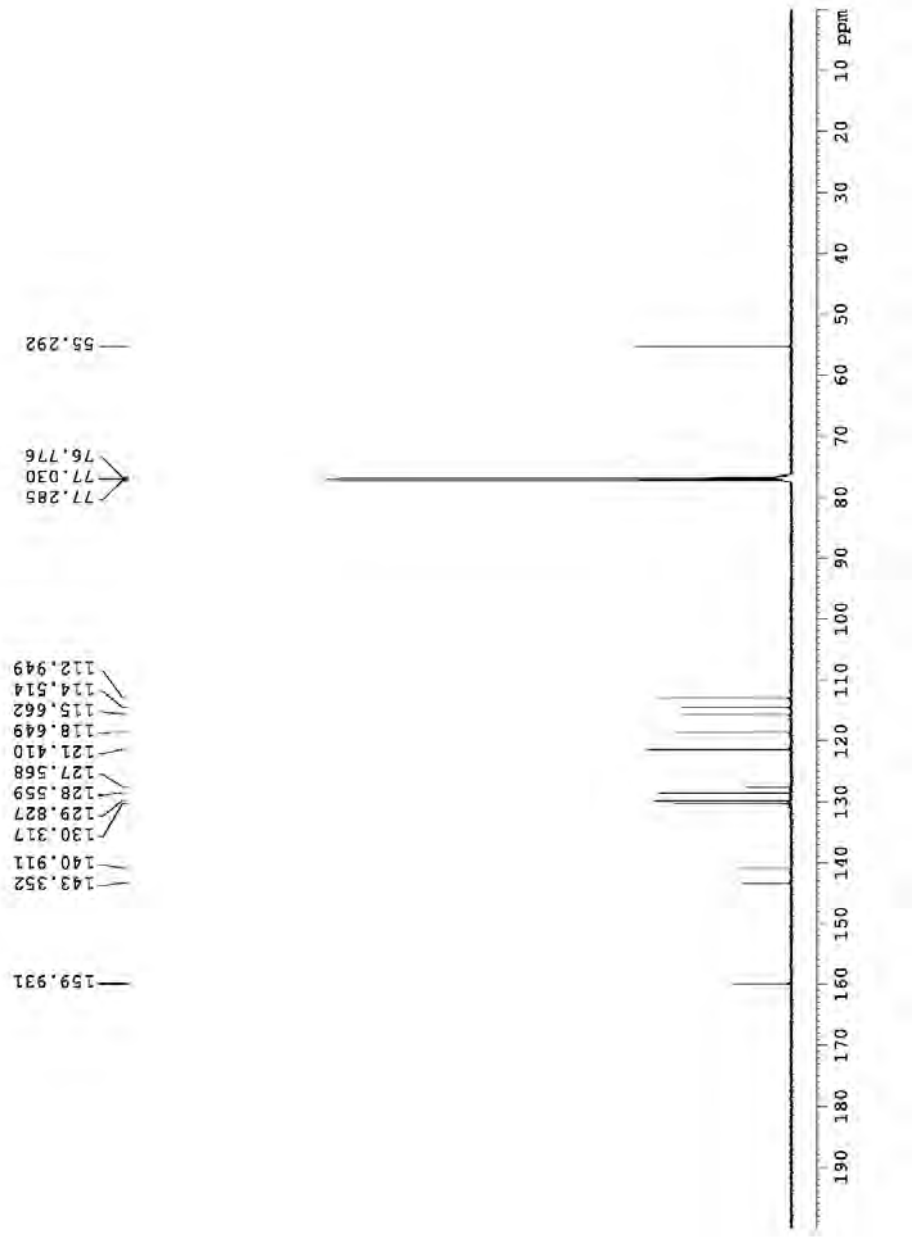
IR of 2'-methoxy-[1, 1'-biphenyl]-2-amine (1f)



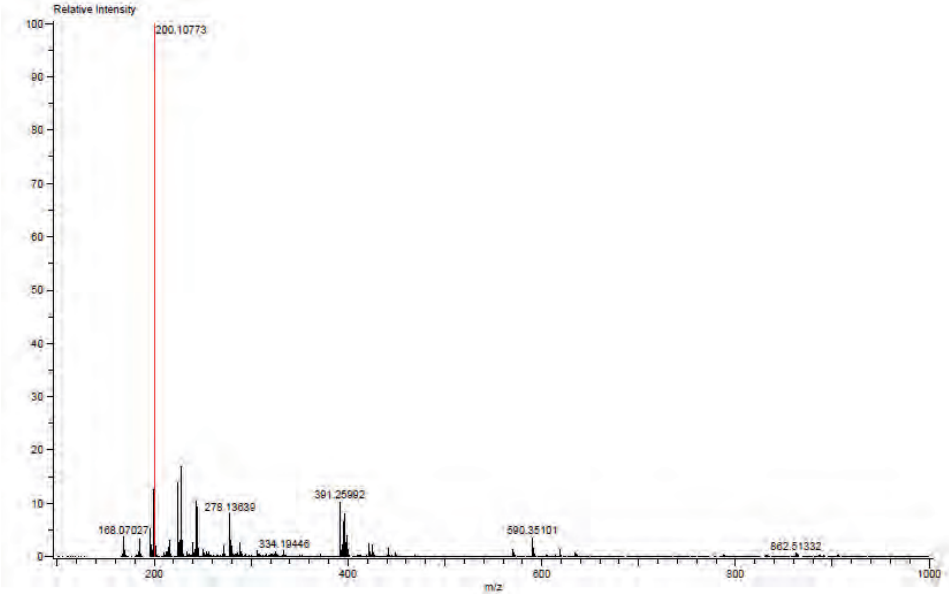
^{1}H-NMR of 3'-methoxy-[1, 1'-biphenyl]-2-amine (1g) in $CDCl_3$



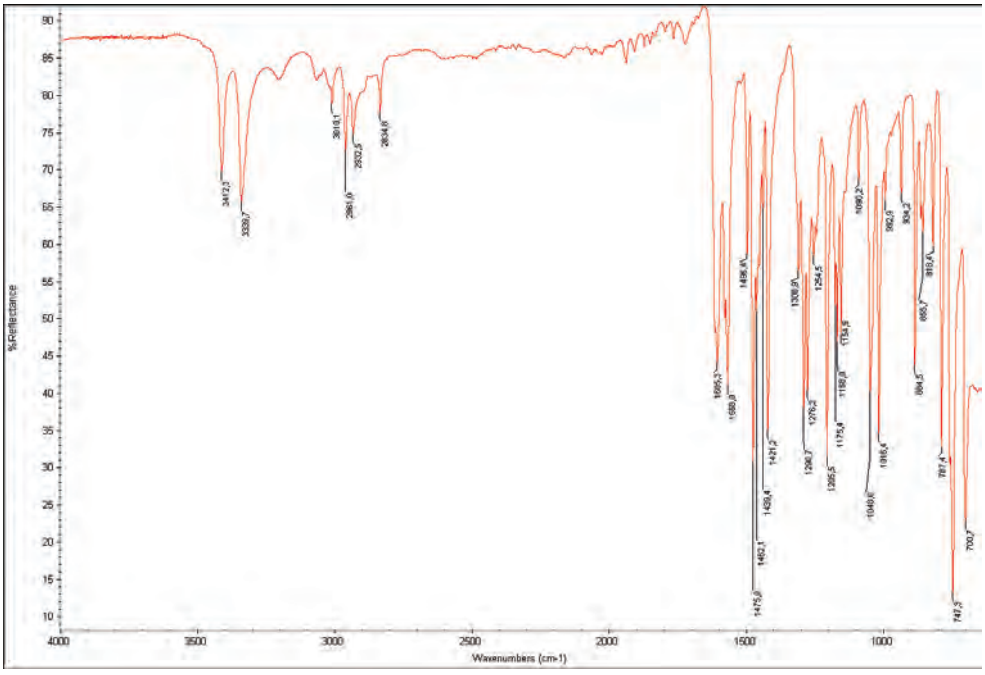
^{13}C-NMR of 3'-methoxy-[1, 1'-biphenyl]-2-amine (1g) in $CDCl_3$



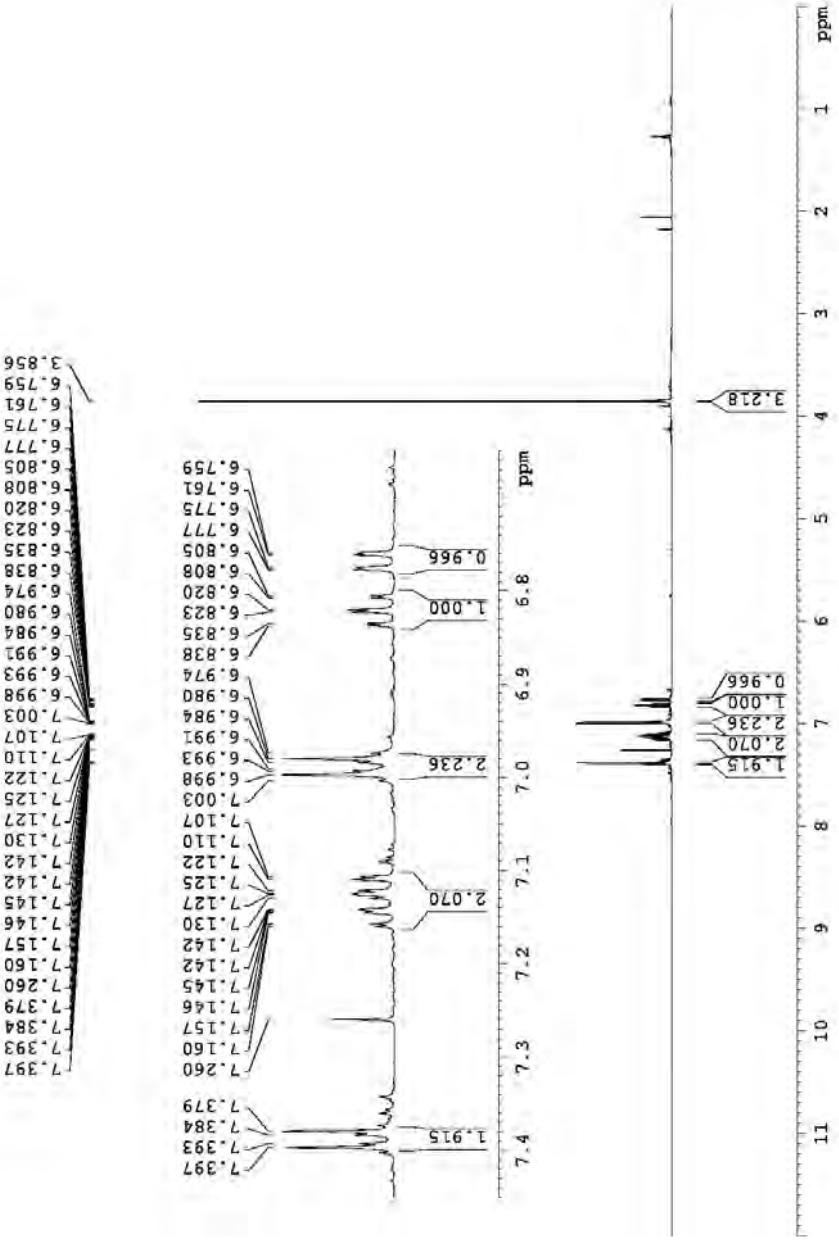
HRMS (DART+) of 3'-methoxy-[1, 1'-biphenyl]-2-amine (1g)



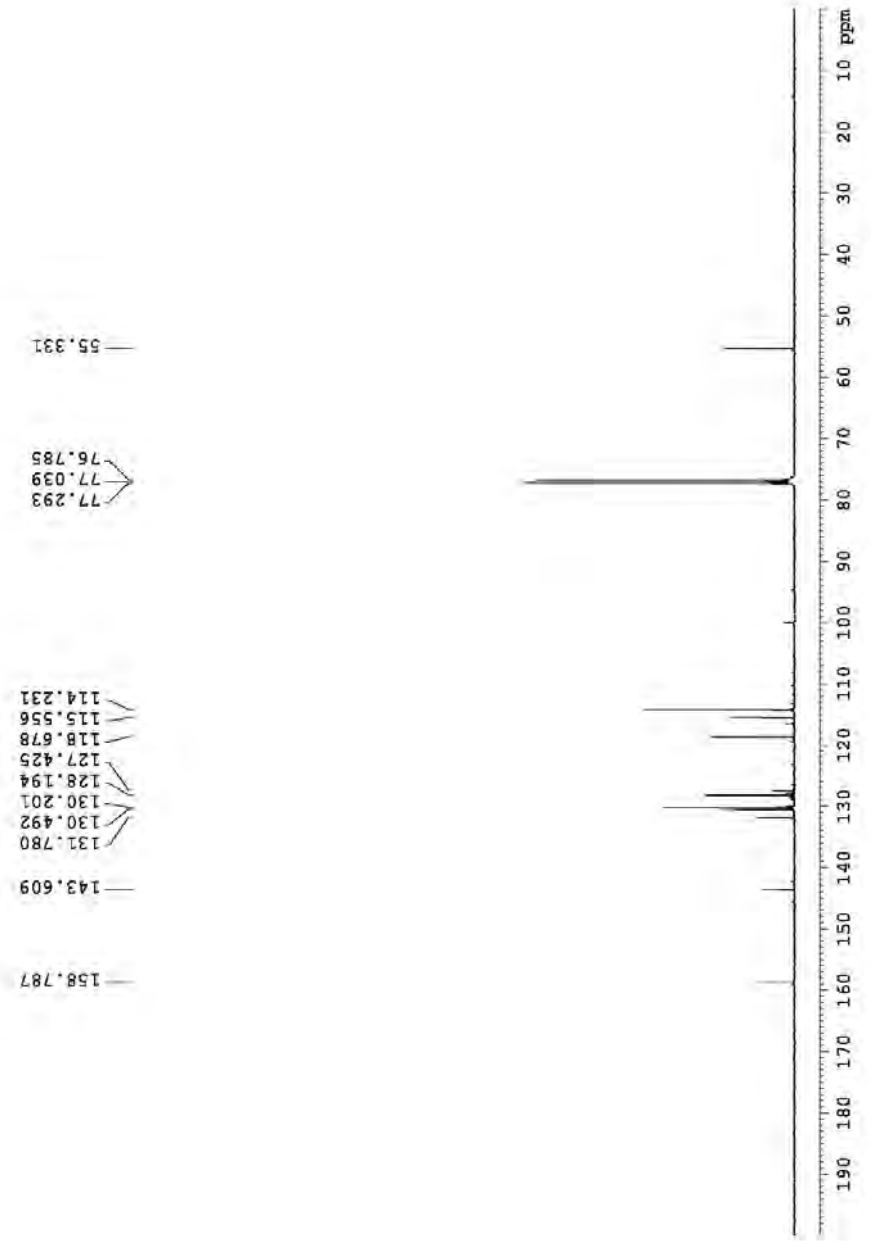
IR of 3'-methoxy-[1, 1'-biphenyl]-2-amine (1g)



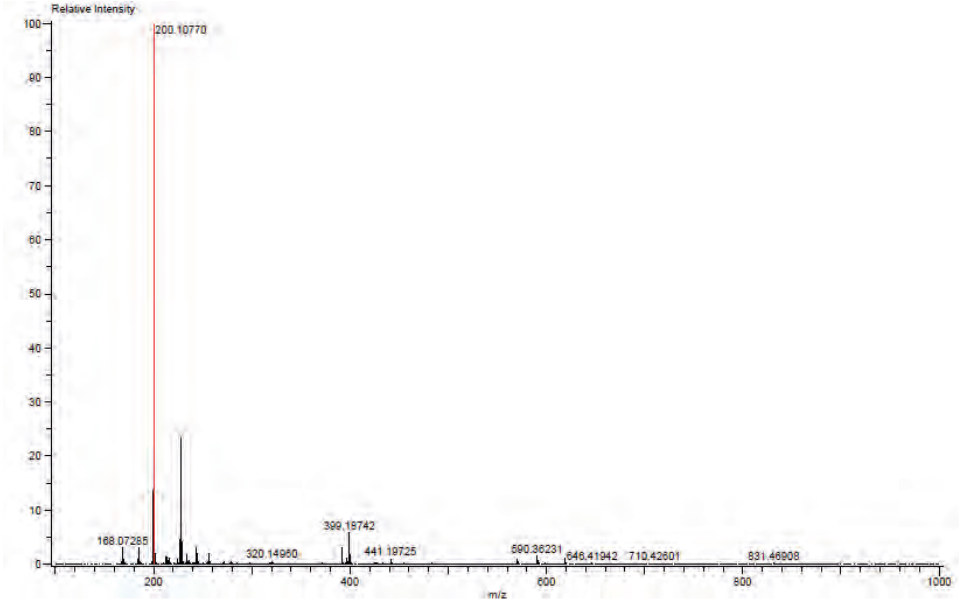
^{1}H-NMR of 4'-methoxy-[1, 1'-biphenyl]-2-amine (1h) in $CDCl_3$



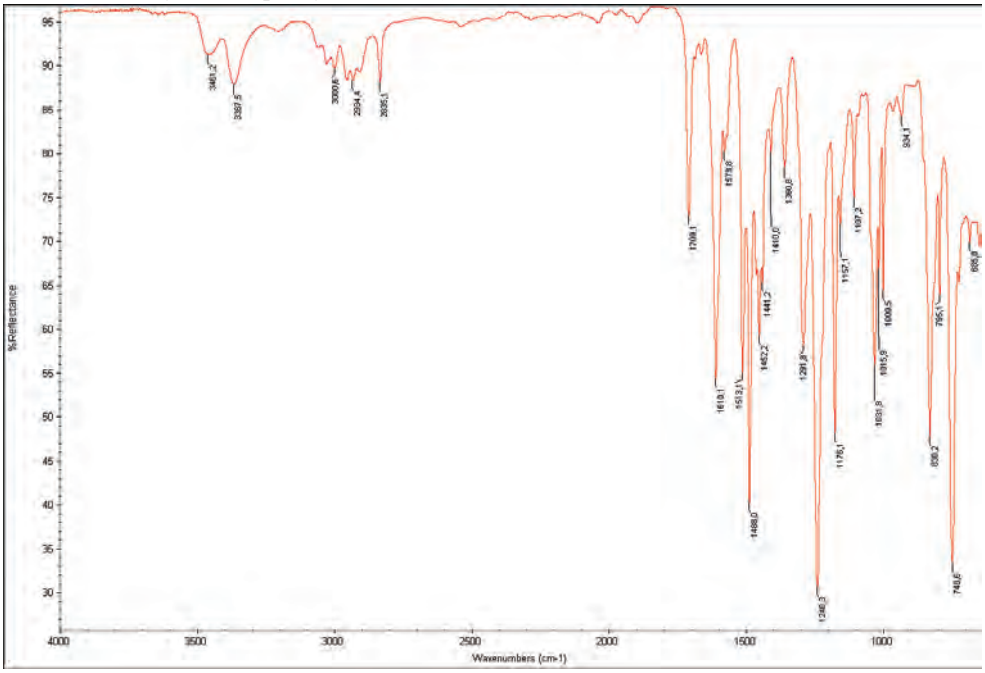
^{13}C-NMR of 4'-methoxy-[1, 1'-biphenyl]-2-amine (1h) in $CDCl_3$



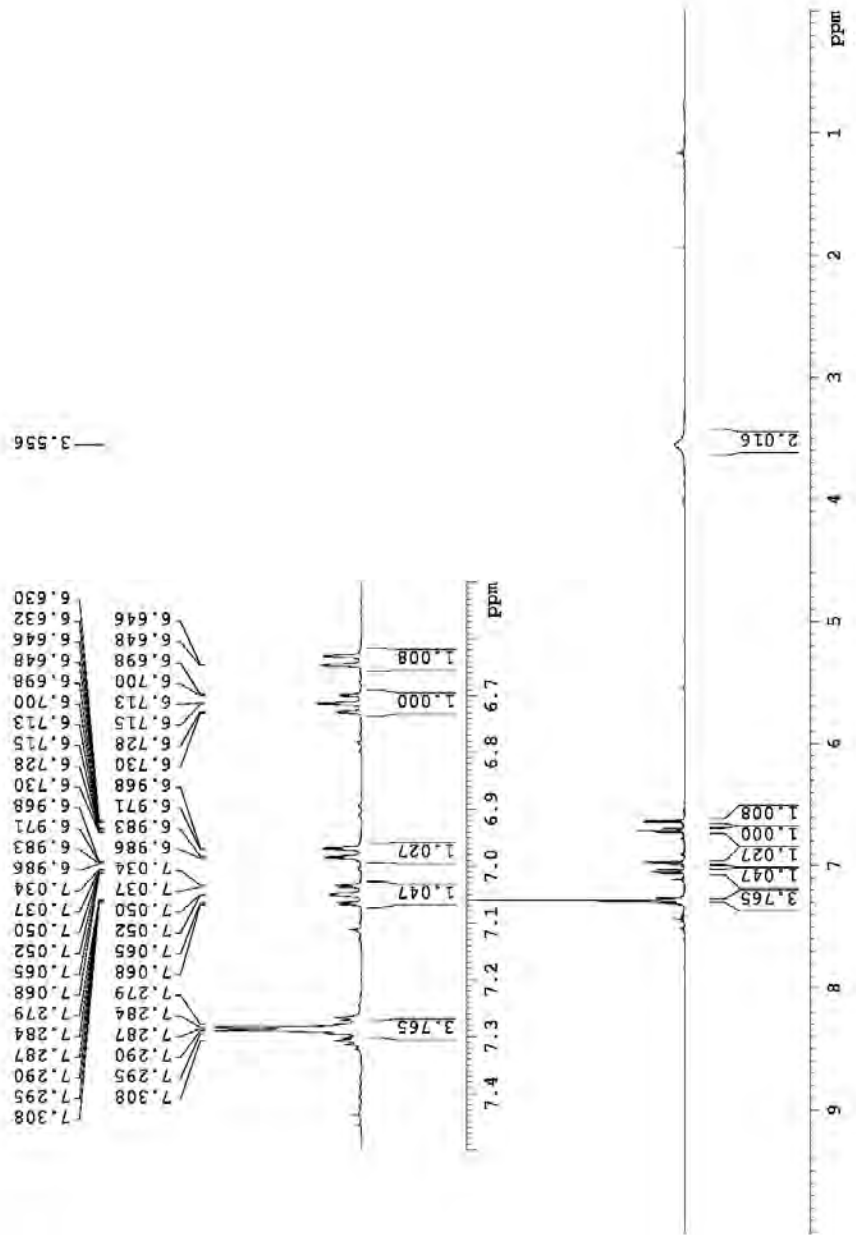
HRMS (DART+) of 4'-methoxy-[1, 1'-biphenyl]-2-amine (1h)



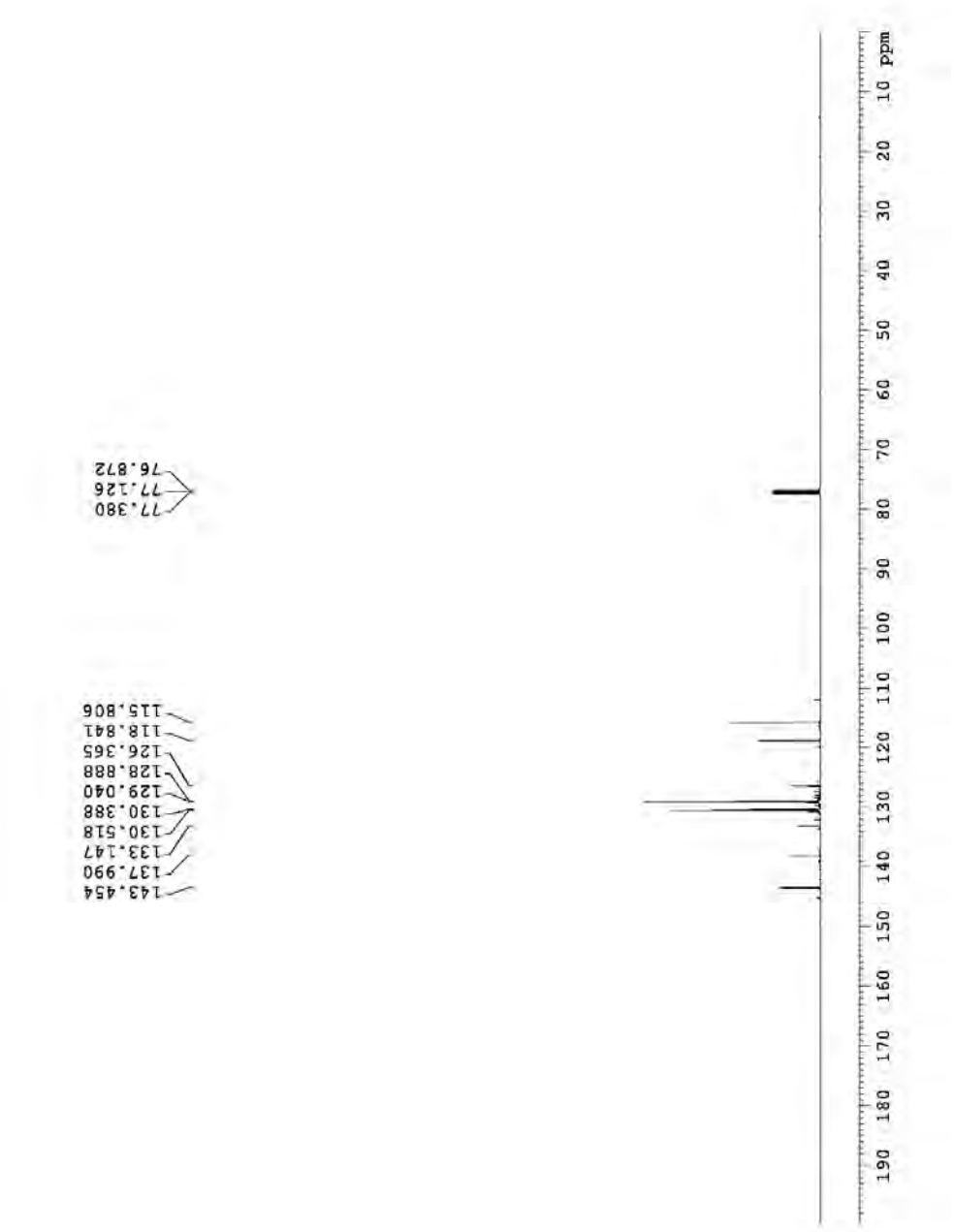
IR of 4'-methoxy-[1, 1'-biphenyl]-2-amine (1h)



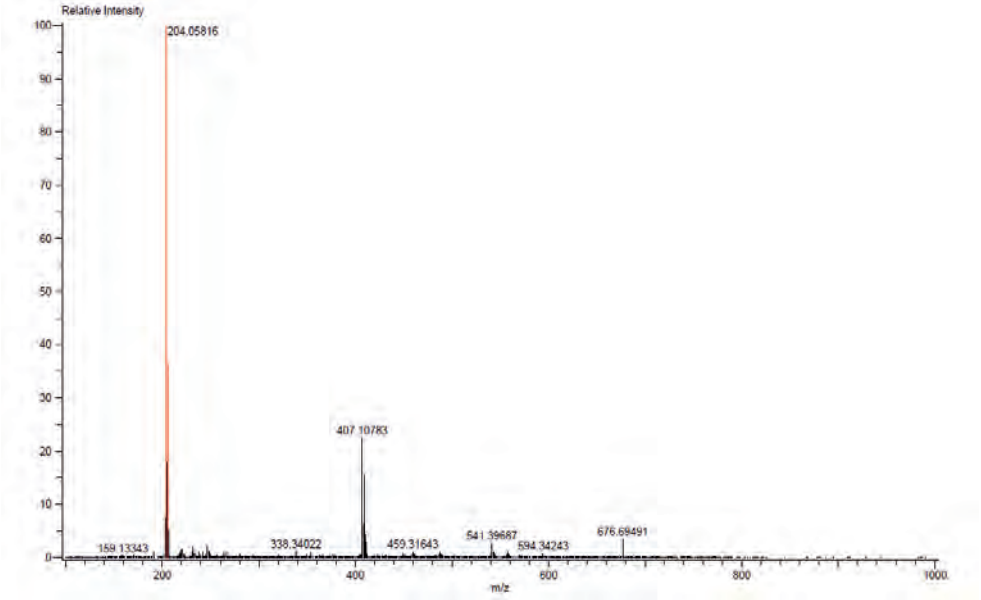
^{1}H-NMR of 4'-chloro-[1, 1'-biphenyl]-2-amine (1i) in $CDCl_3$



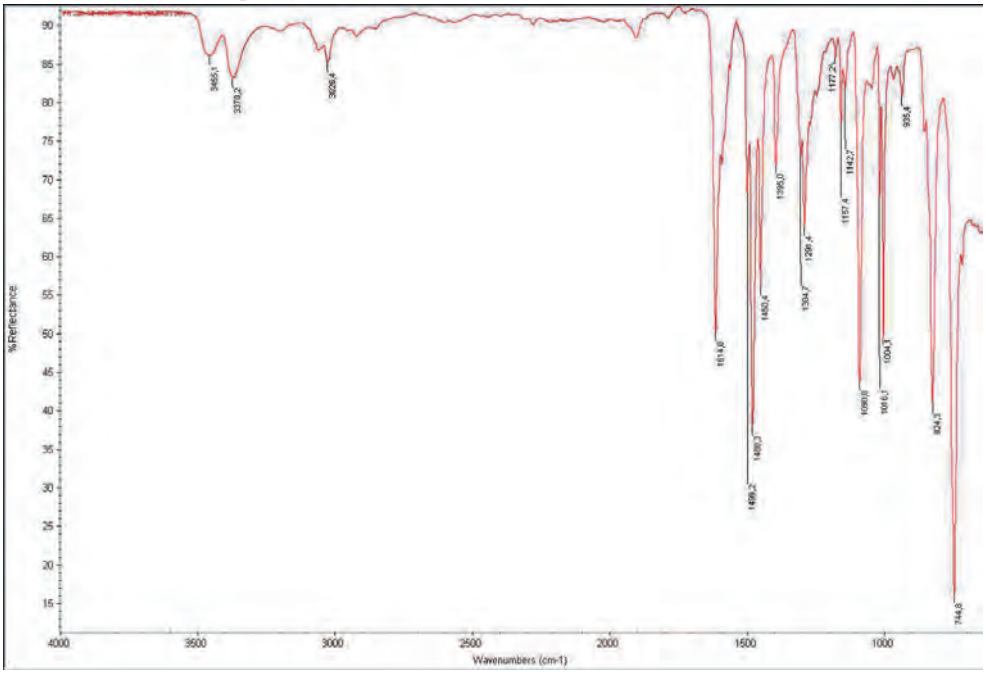
^{13}C-NMR of 4'-chloro-[1, 1'-biphenyl]-2-amine (1i) in $CDCl_3$



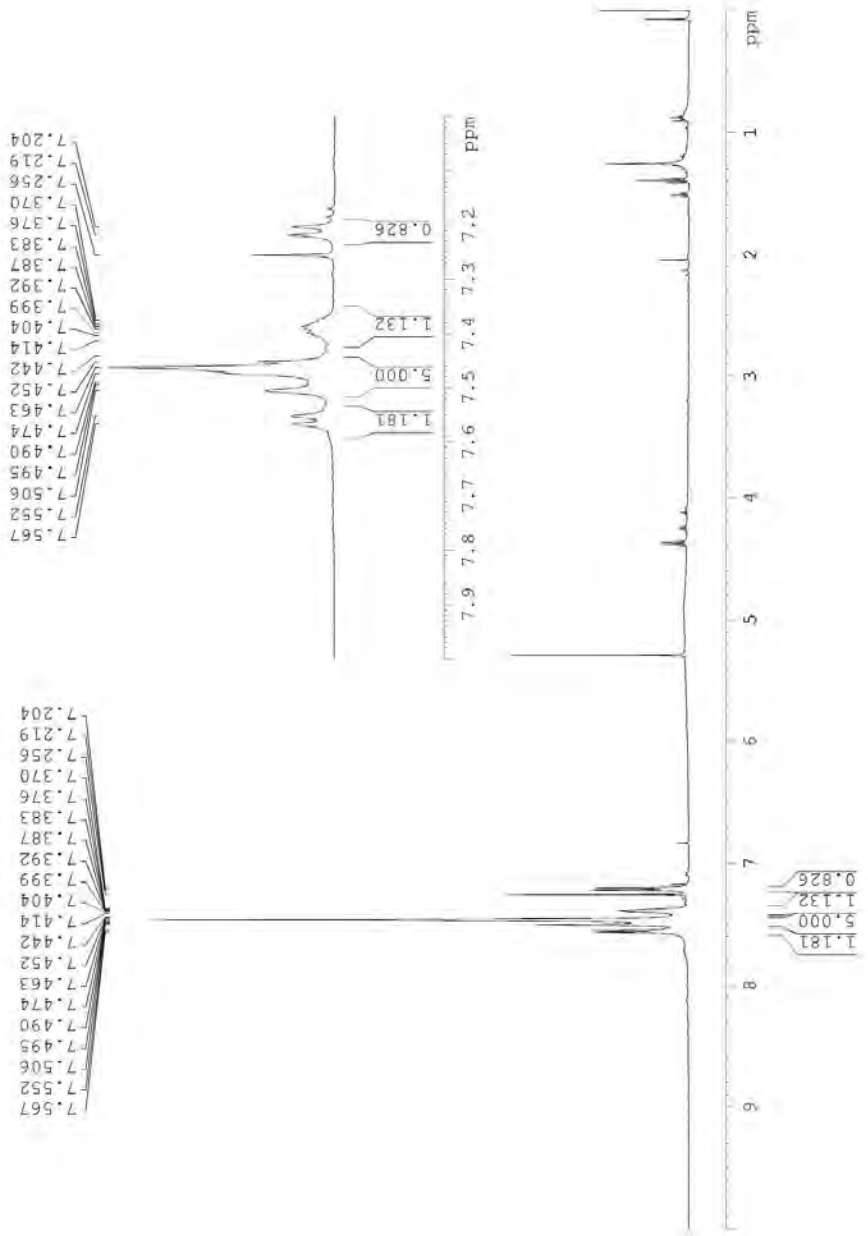
HRMS (DART+) of 4'-chloro-[1, 1'-biphenyl]-2-amine (1i)



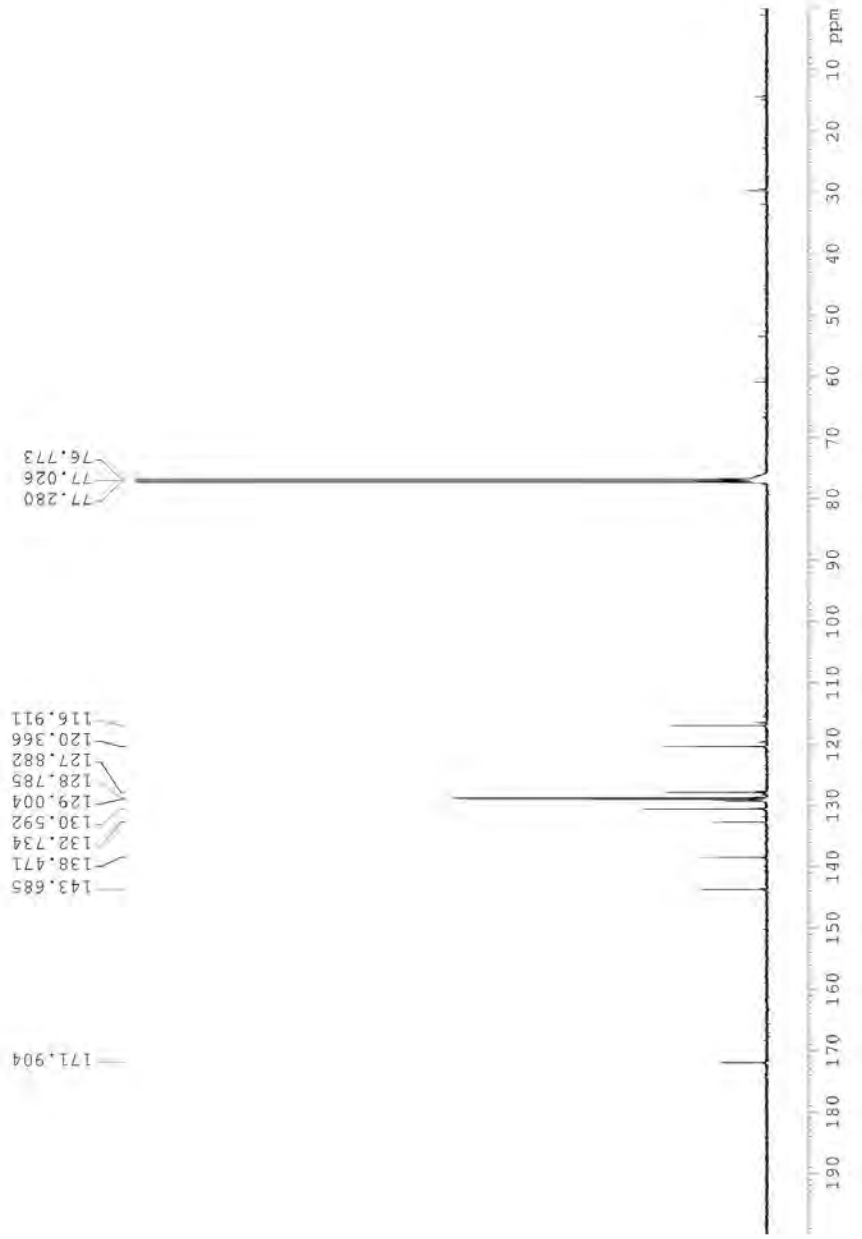
IR of 4'-chloro-[1, 1'-biphenyl]-2-amine (1i)



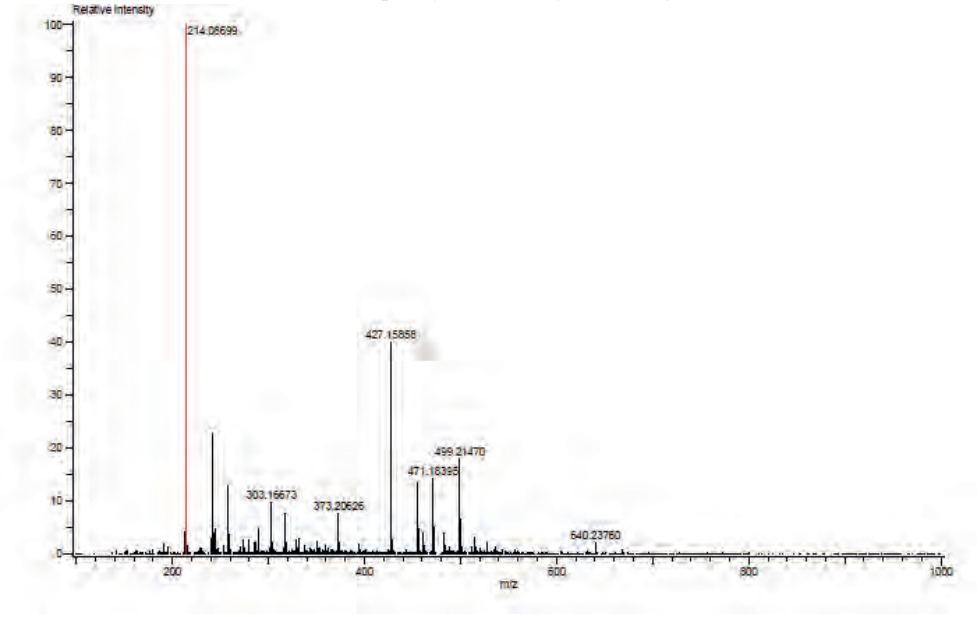
^{1}H-NMR of 2-amino-[1, 1'-biphenyl]-4-carboxylic acid (1j) in $CDCl_3$



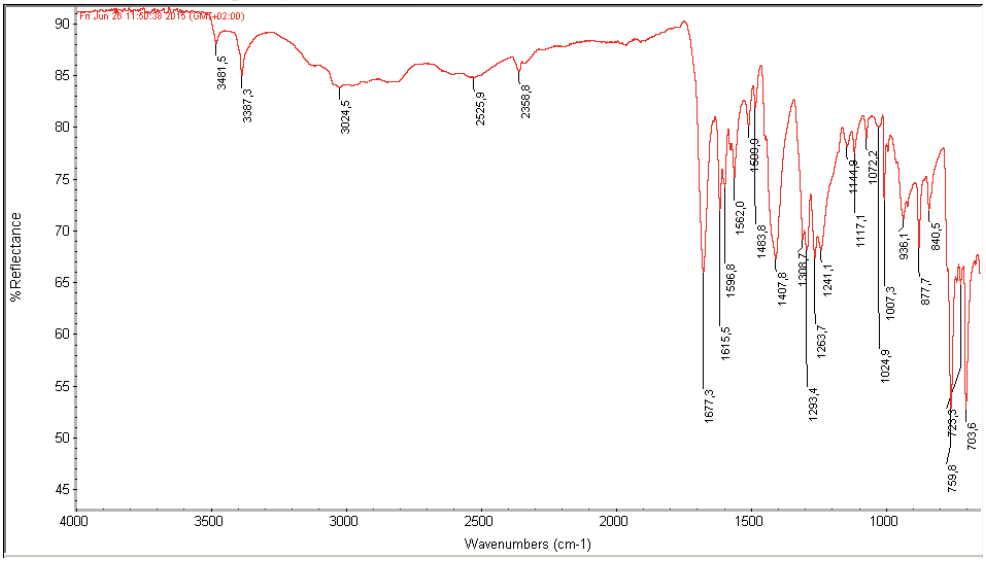
^{13}C-NMR of 2-amino-[1, 1'-biphenyl]-4-carboxylic acid (11j) in $CDCl_3$



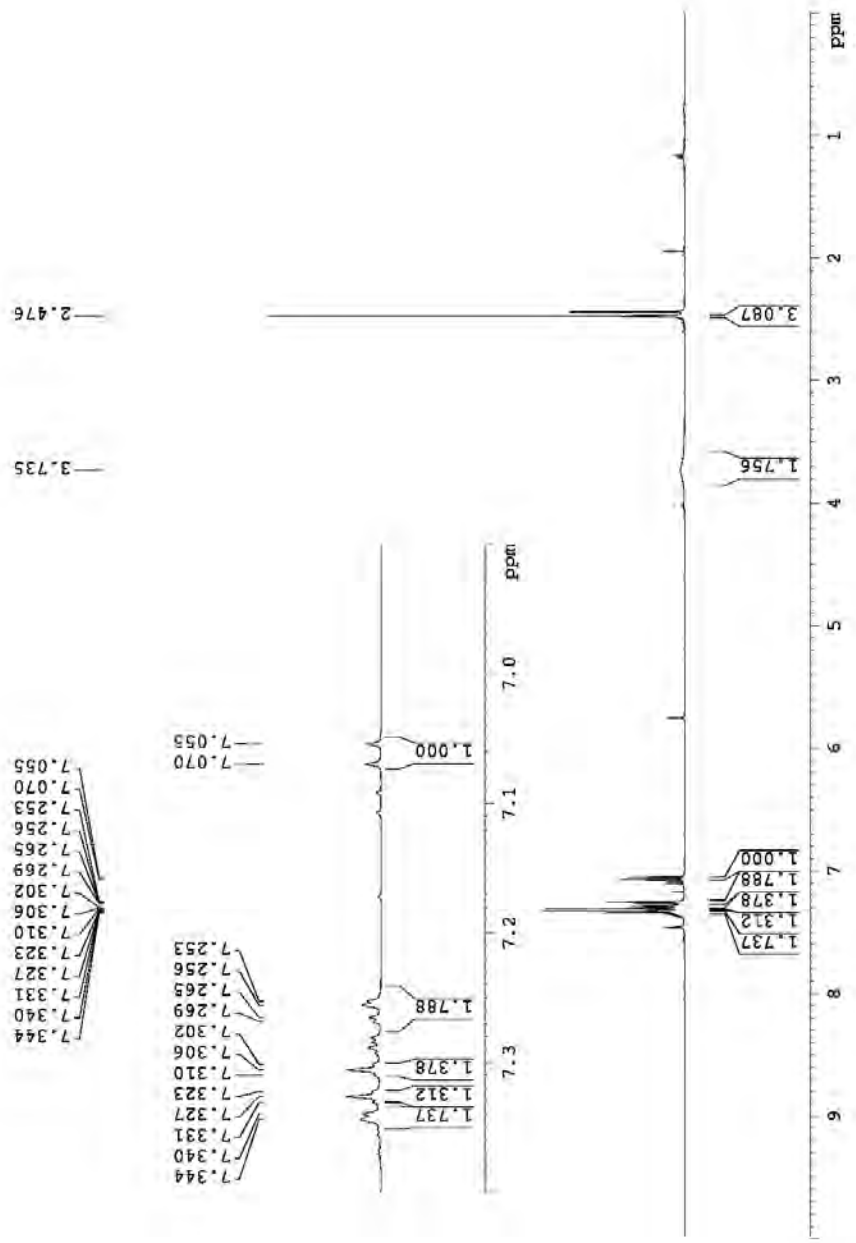
HRMS (DART+) of 2-amino-[1, 1'-biphenyl]-4-carboxylic acid (1j)



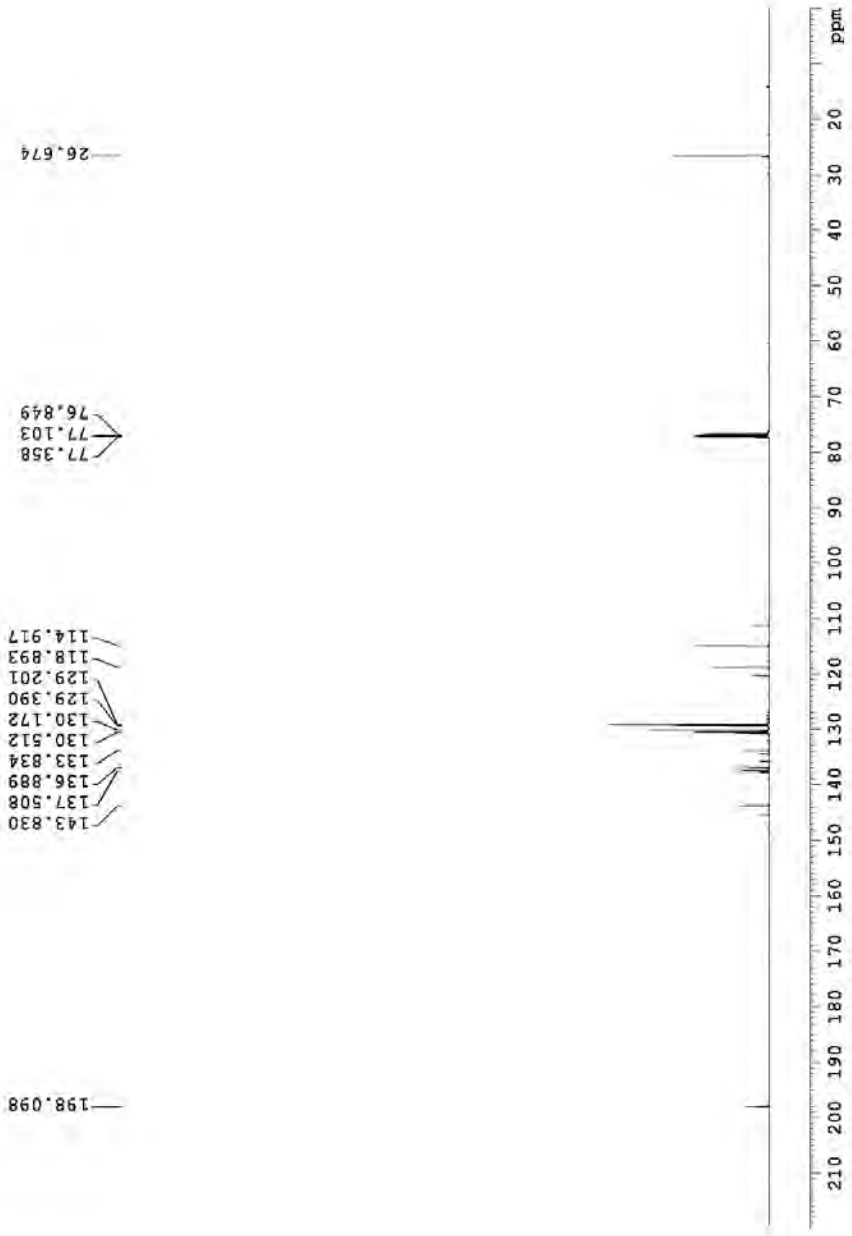
IR of 2-amino-[1, 1'-biphenyl]-4-carboxylic acid (1j)



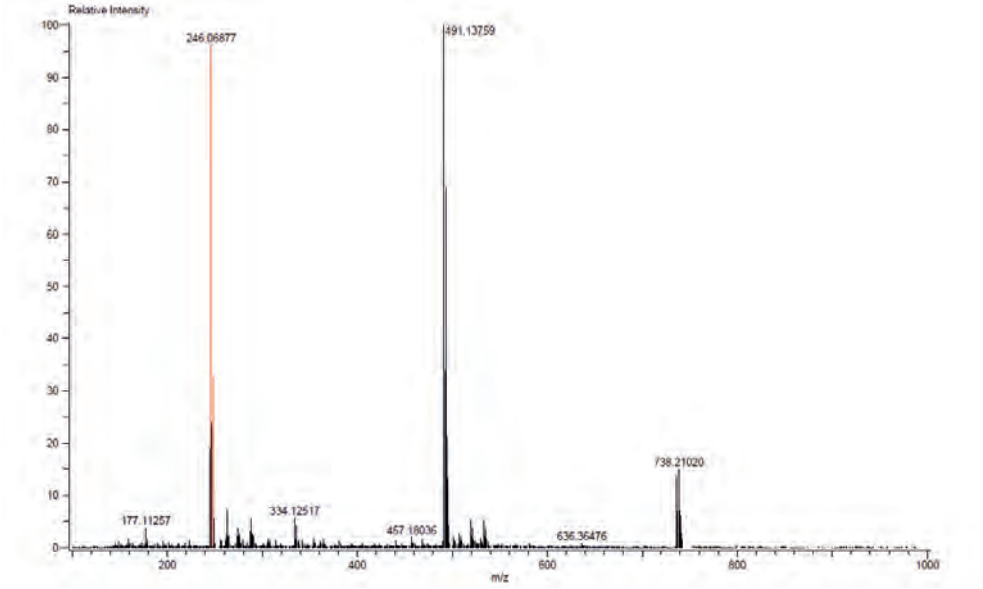
^{1}H-NMR of 1-(2-amino-4'-chloro-[1, 1'-biphenyl]-4-yl) ethan-1-one (1k) in $CDCl_3$



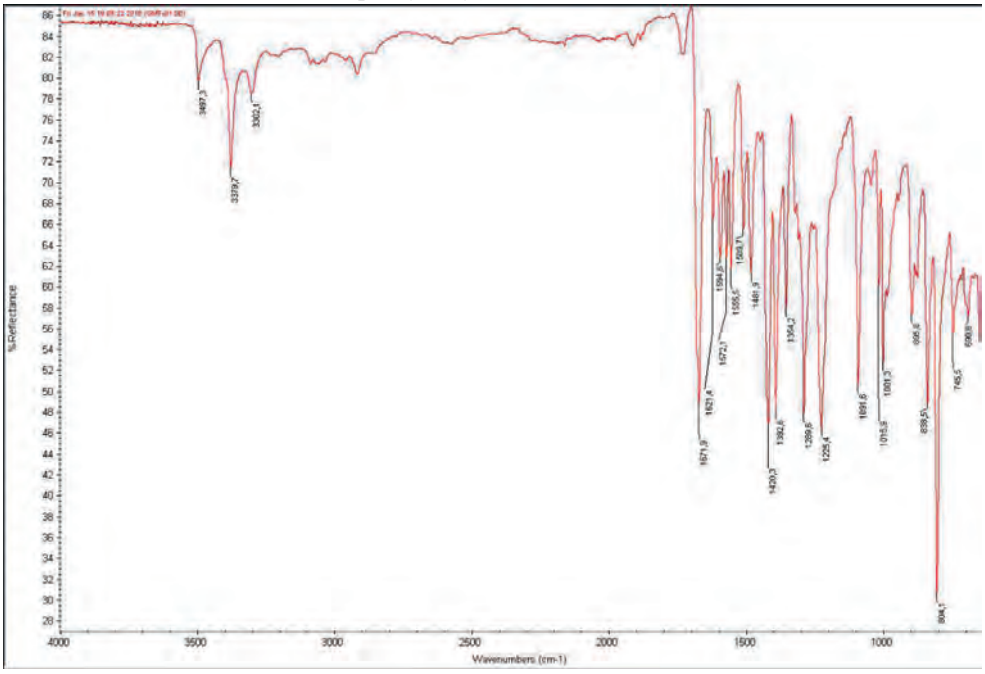
^{13}C-NMR of 1-(2-amino-4'-chloro-[1, 1'-biphenyl]-4-yl) ethan-1-one (1k) in $CDCl_3$



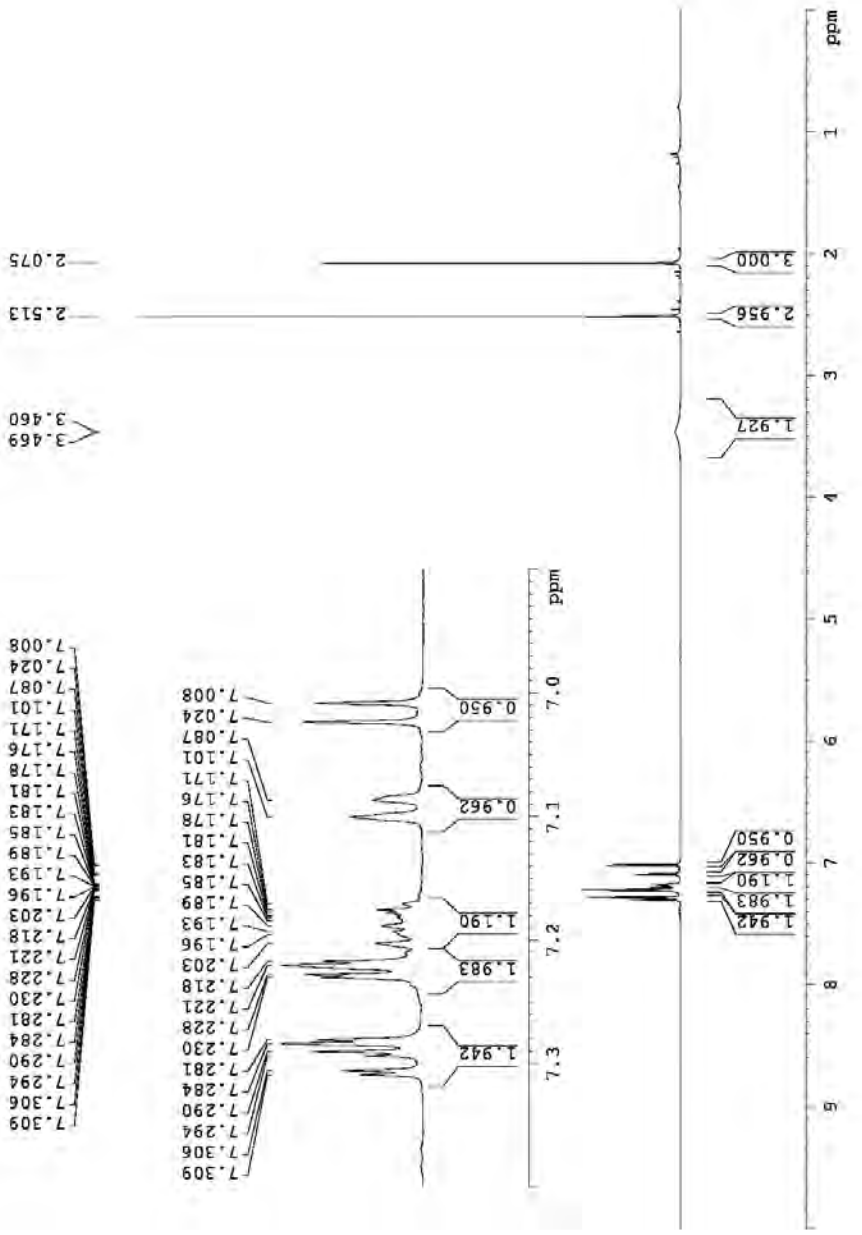
HRMS (DART+) of 1-(2-amino-4'-chloro-[1, 1'-biphenyl]-4-yl) ethan-1-one (1k)



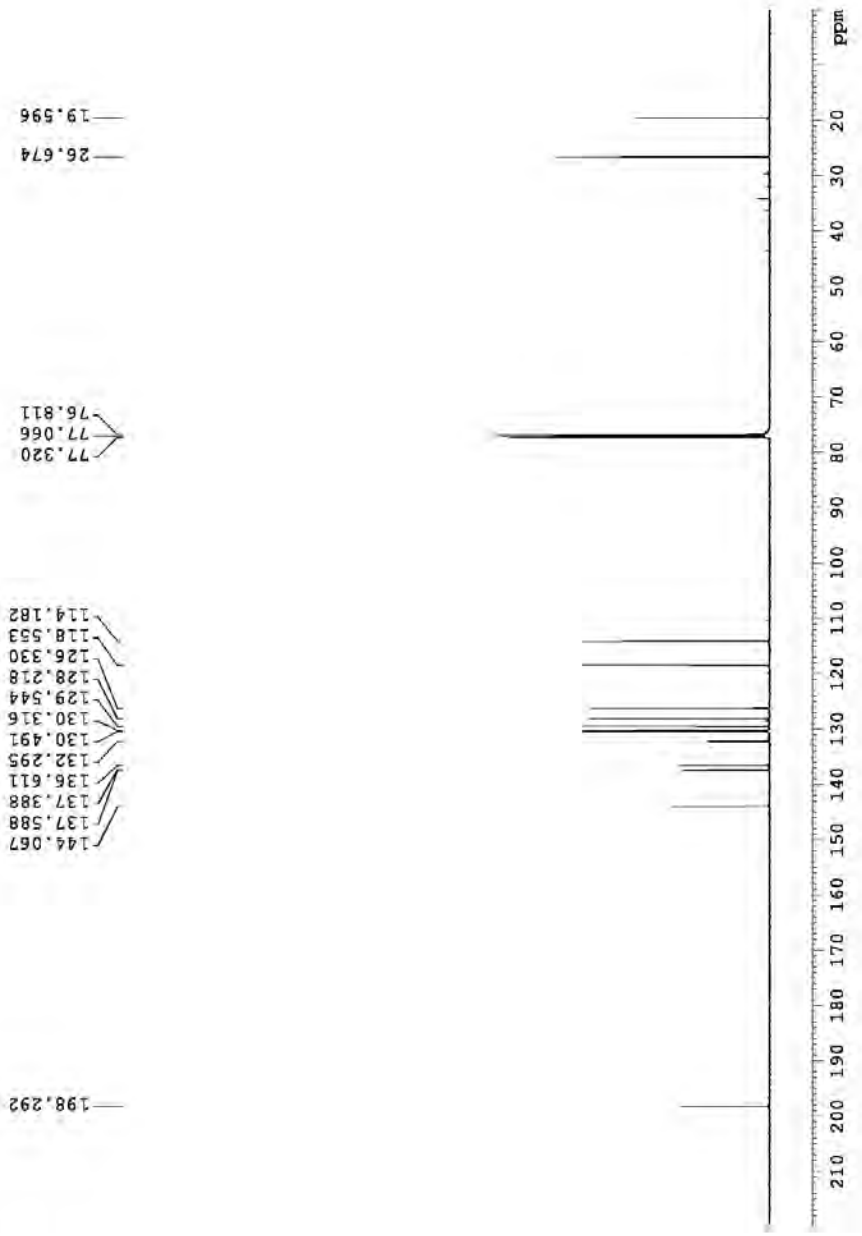
IR of 1-(2-amino-4'-chloro-[1, 1'-biphenyl]-4-yl) ethan-1-one (1k)



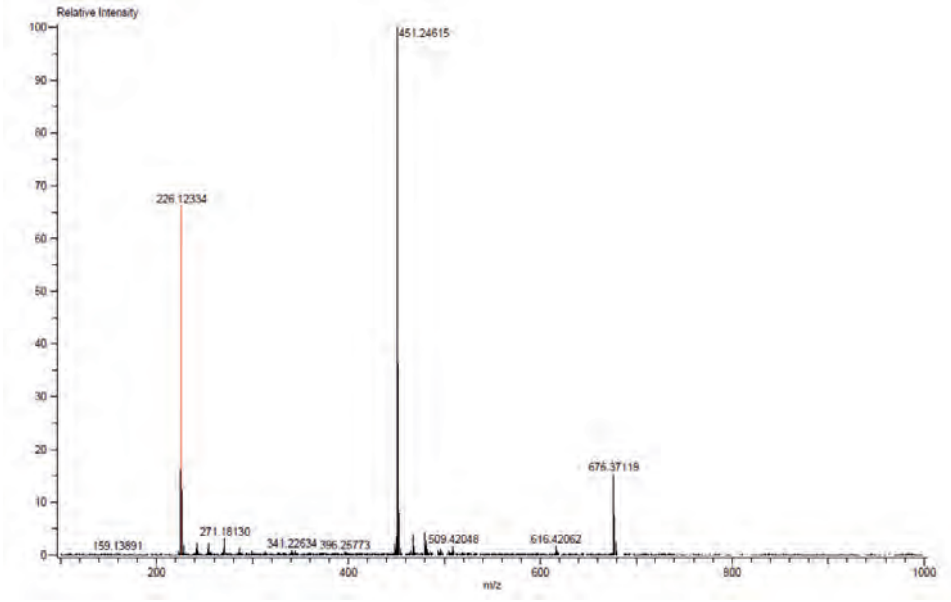
[1]H-NMR of 1-(2-amino-2'-methyl-[1, 1'-biphenyl]-4-yl) ethan-1-one (1l) in $CDCl_3$



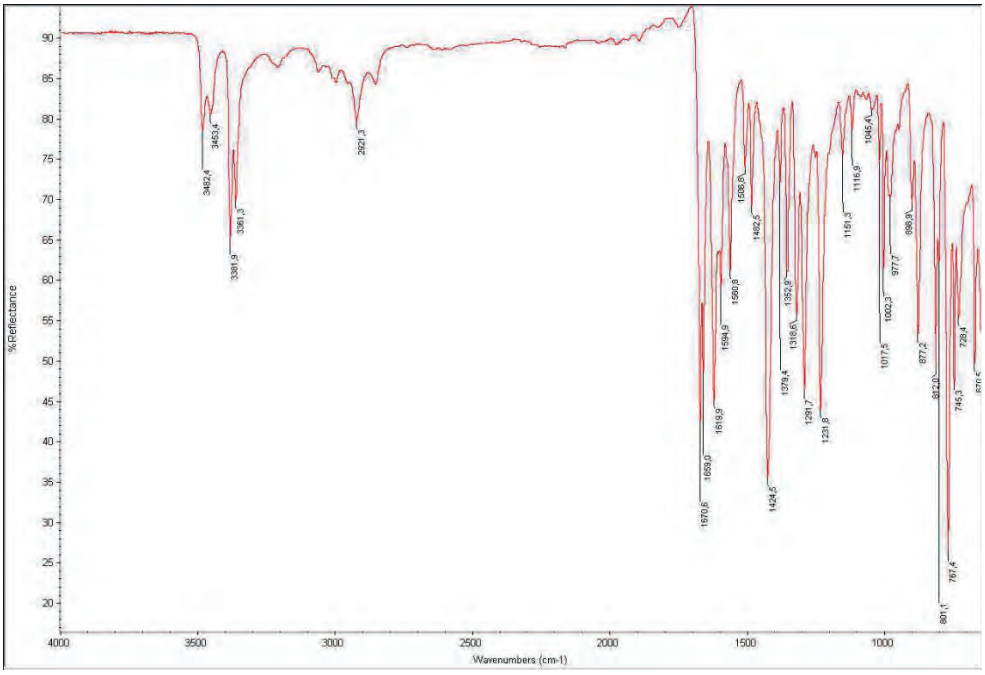
^{13}C-NMR of 1-(2-amino-2'-methyl-[1, 1'-biphenyl]-4-yl) ethan-1-one (1l) in $CDCl_3$



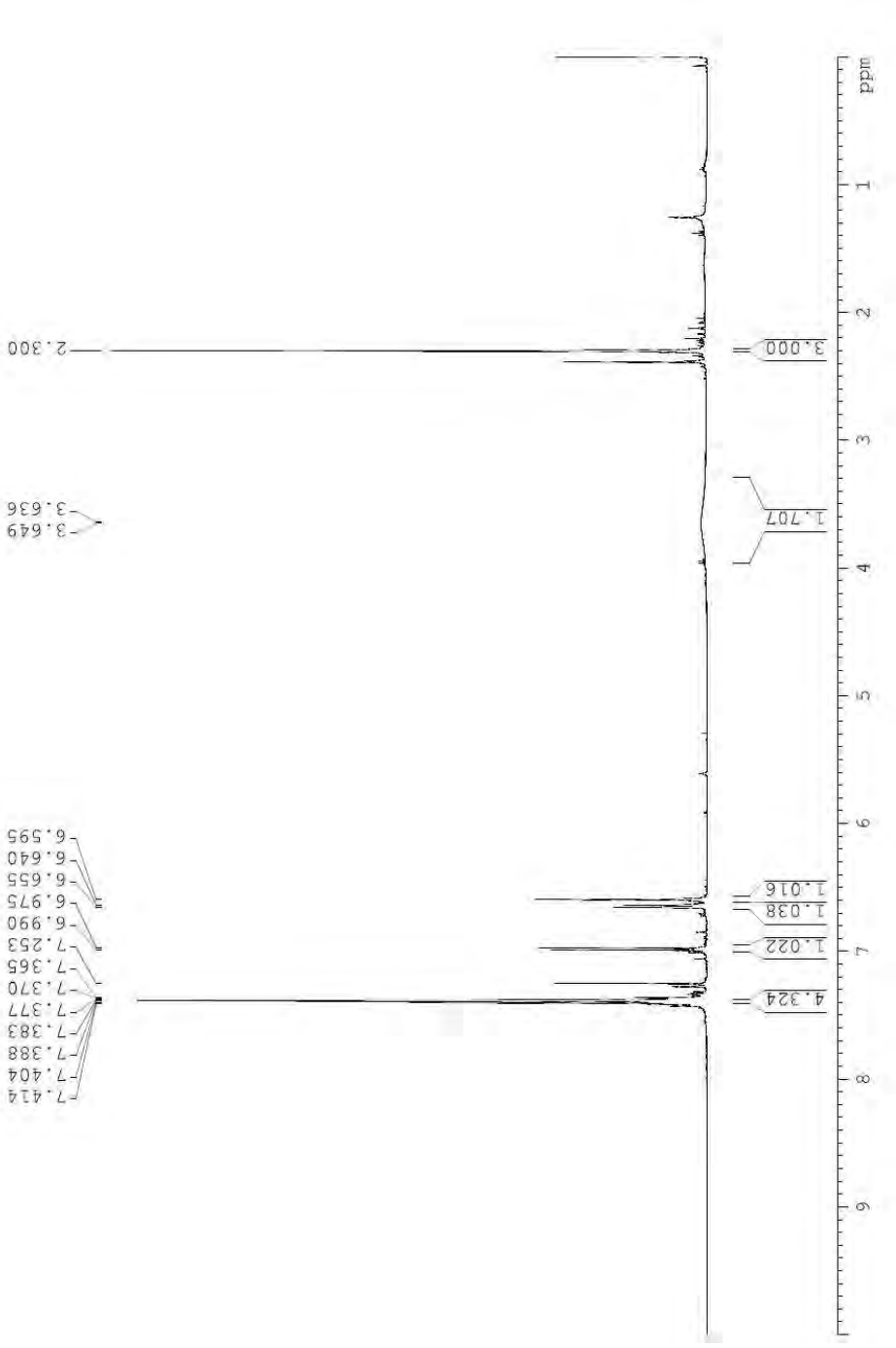
HRMS (DART+) of 1-(2-amino-2'-methyl-[1, 1'-biphenyl]-4-yl) ethan-1-one (1l)



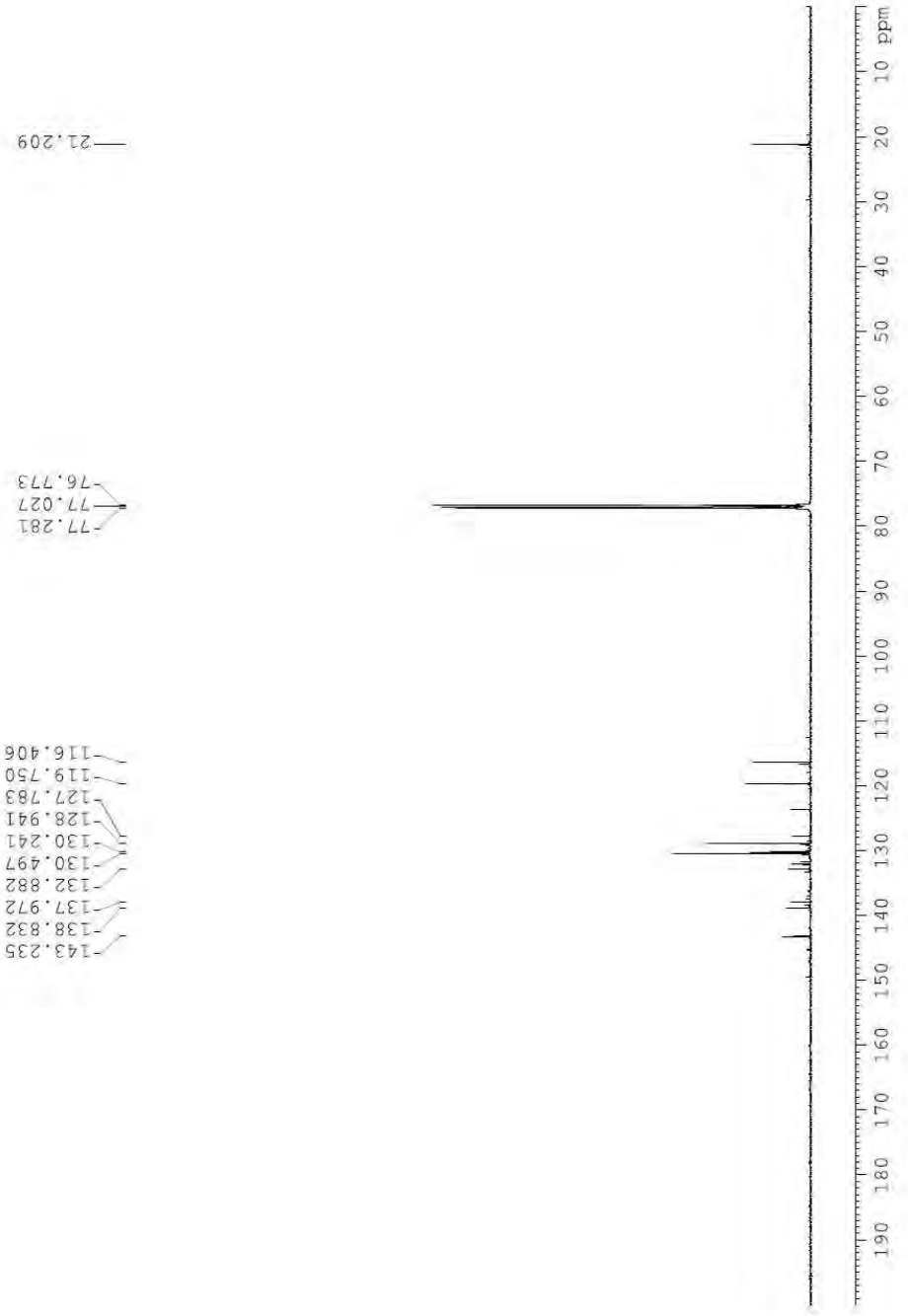
IR of 1-(2-amino-2'-methyl-[1, 1'-biphenyl]-4-yl) ethan-1-one (1l)



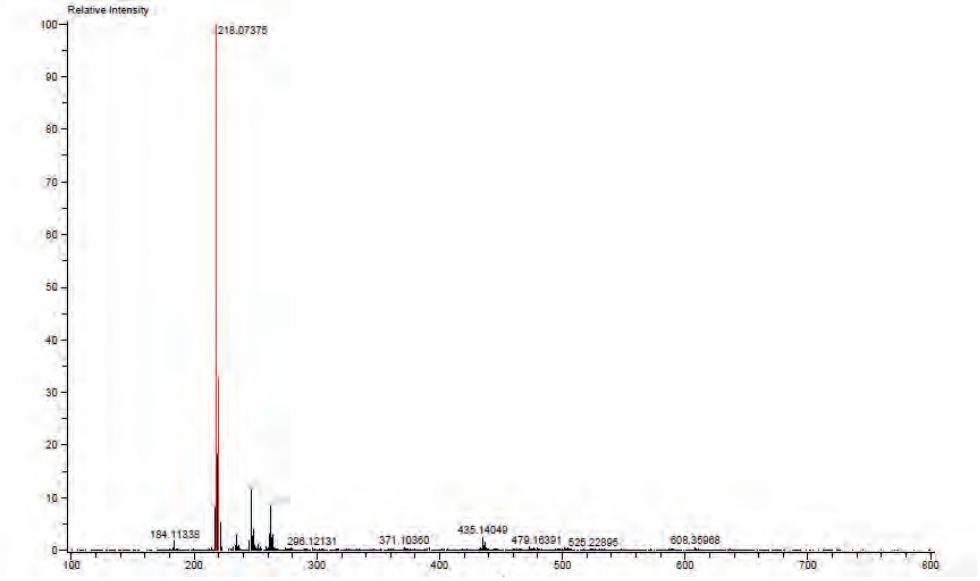
^{1}H-NMR of 4'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1m) in $CDCl_3$



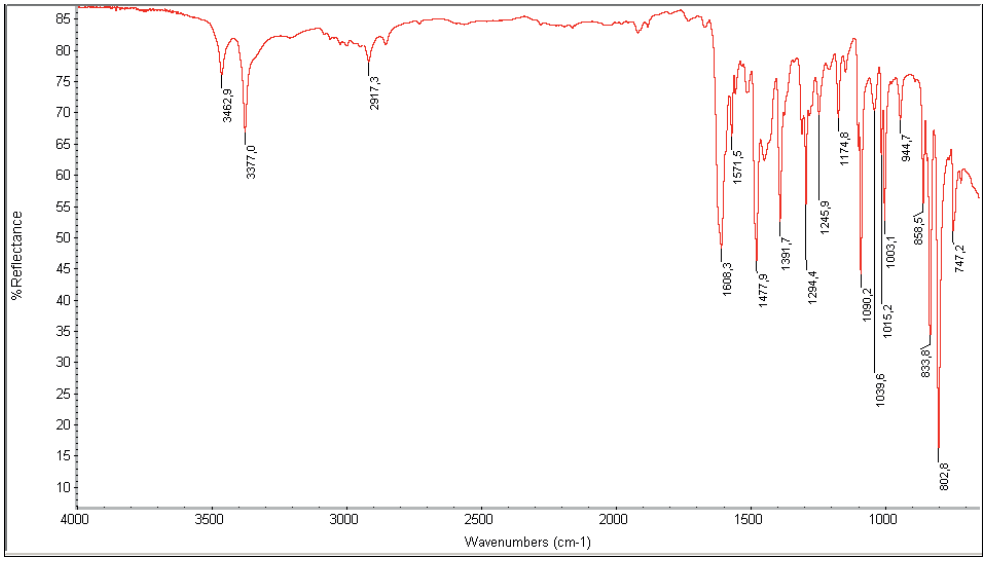
^{13}C-NMR of 4'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1m) in $CDCl_3$



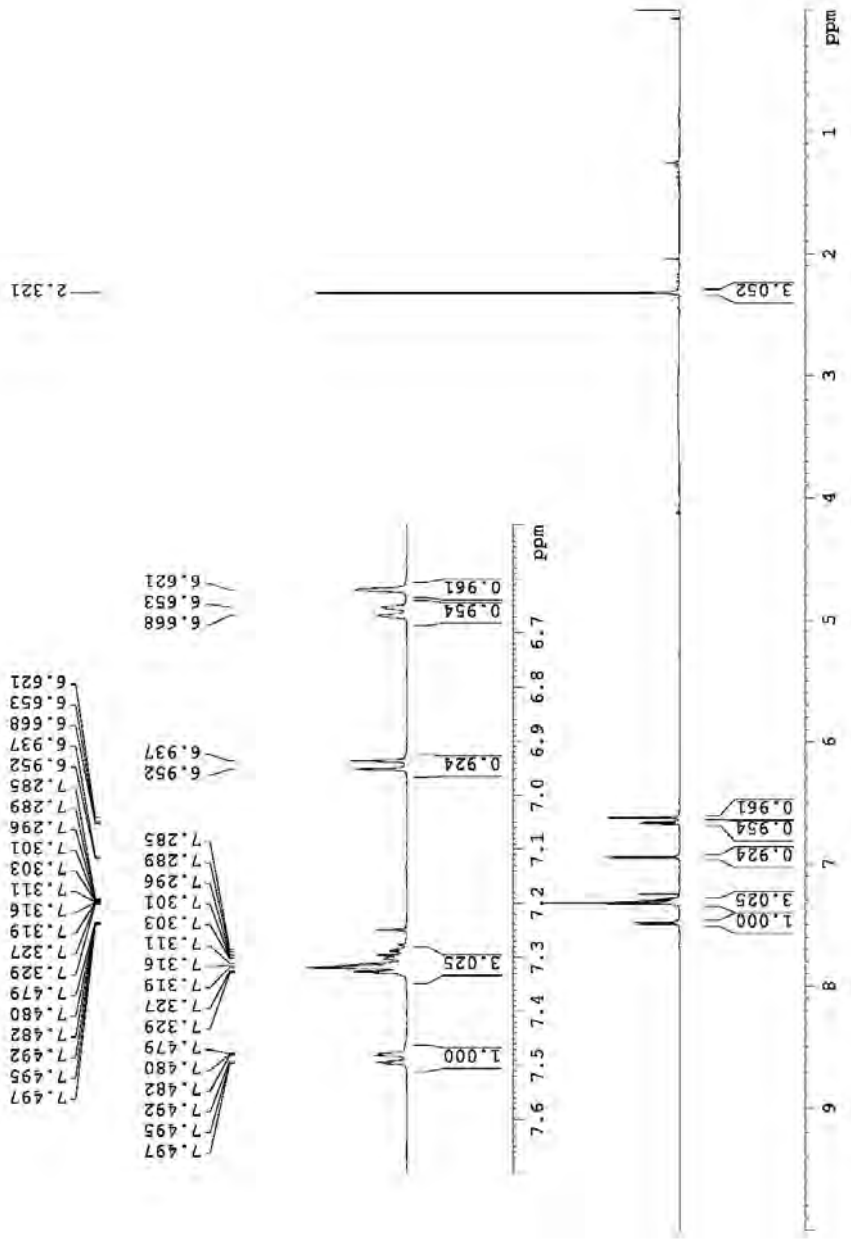
HRMS (DART+) of 4'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1m)



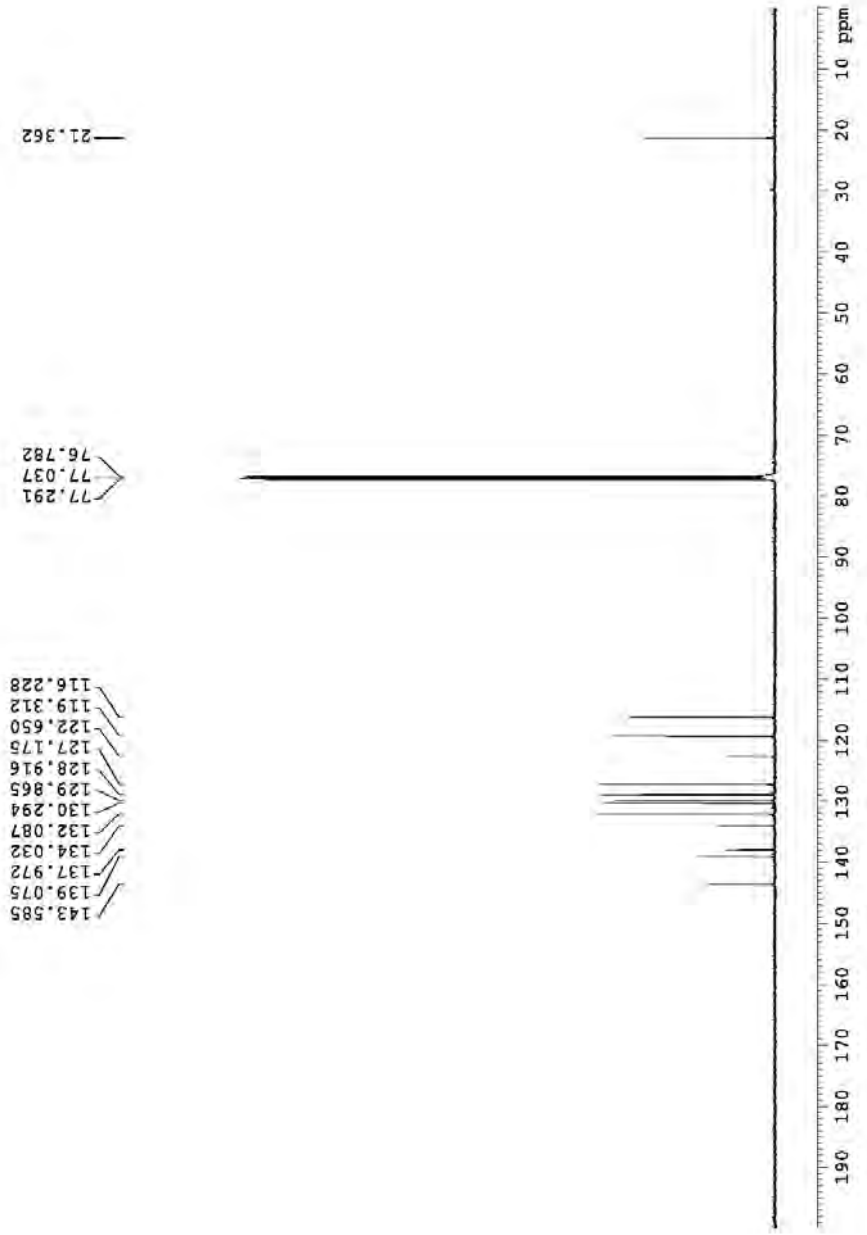
IR of 4'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1m)



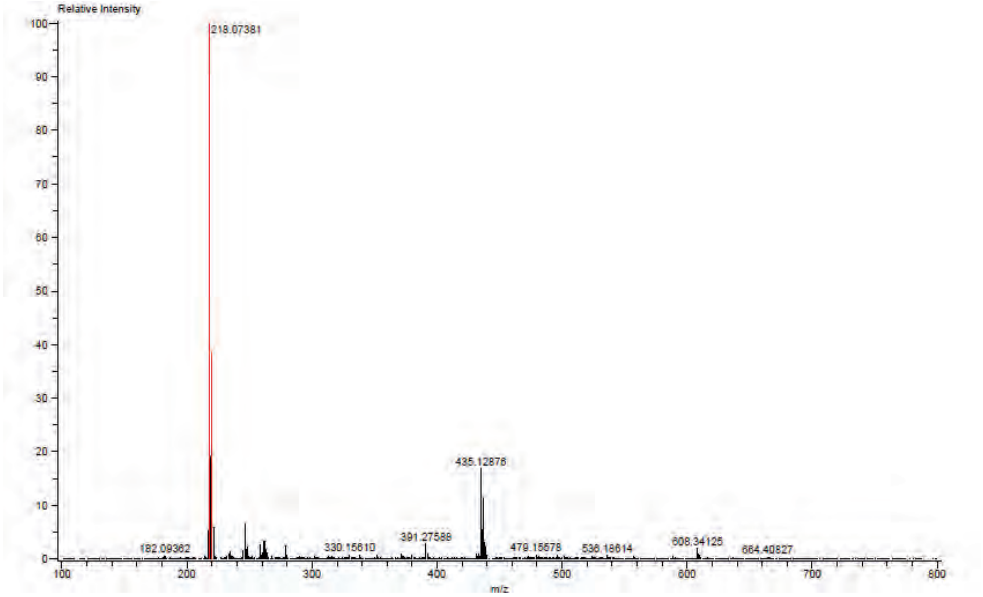
^{1}H-NMR of 2'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1n) in $CDCl_3$



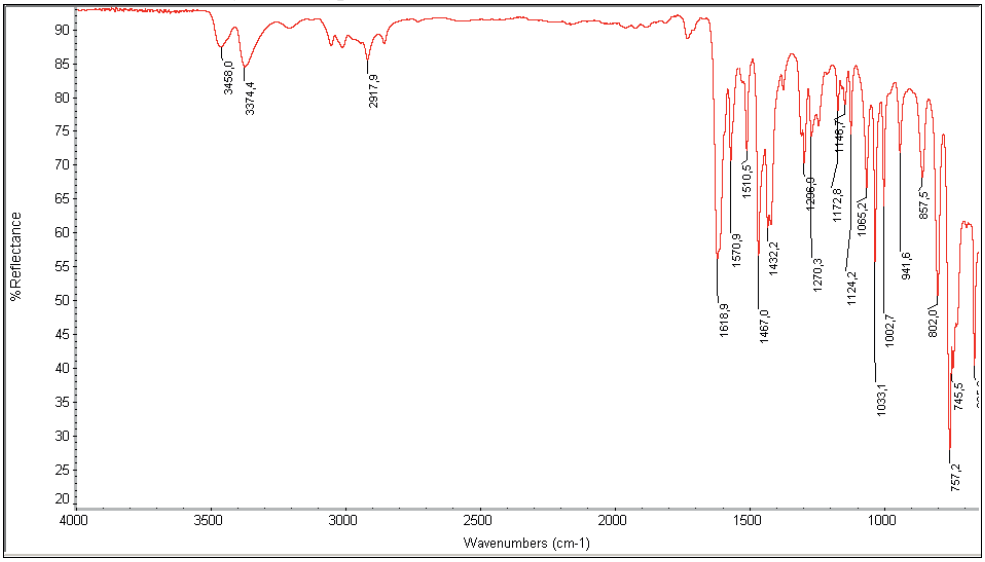
^{13}C-NMR of 2'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1n) in $CDCl_3$



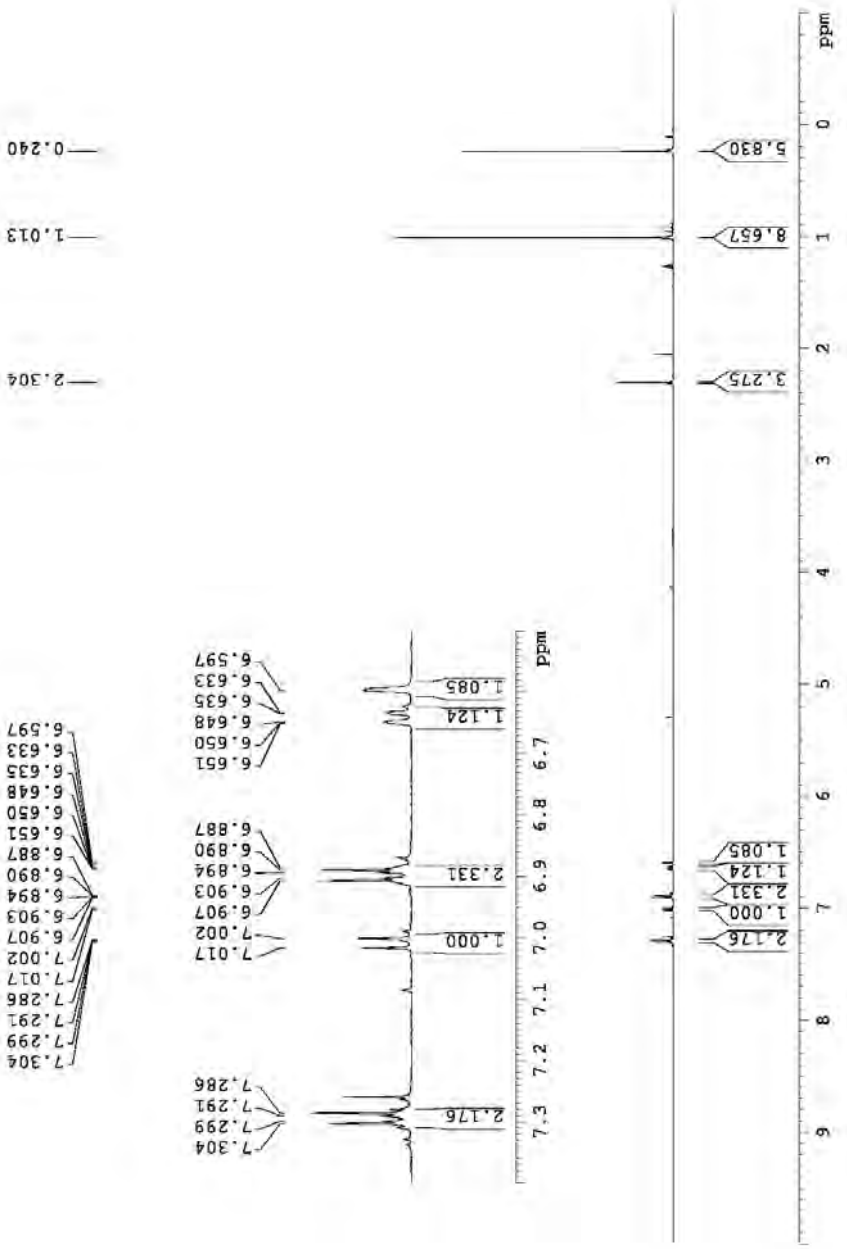
HRMS (DART+) of 2'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1n)



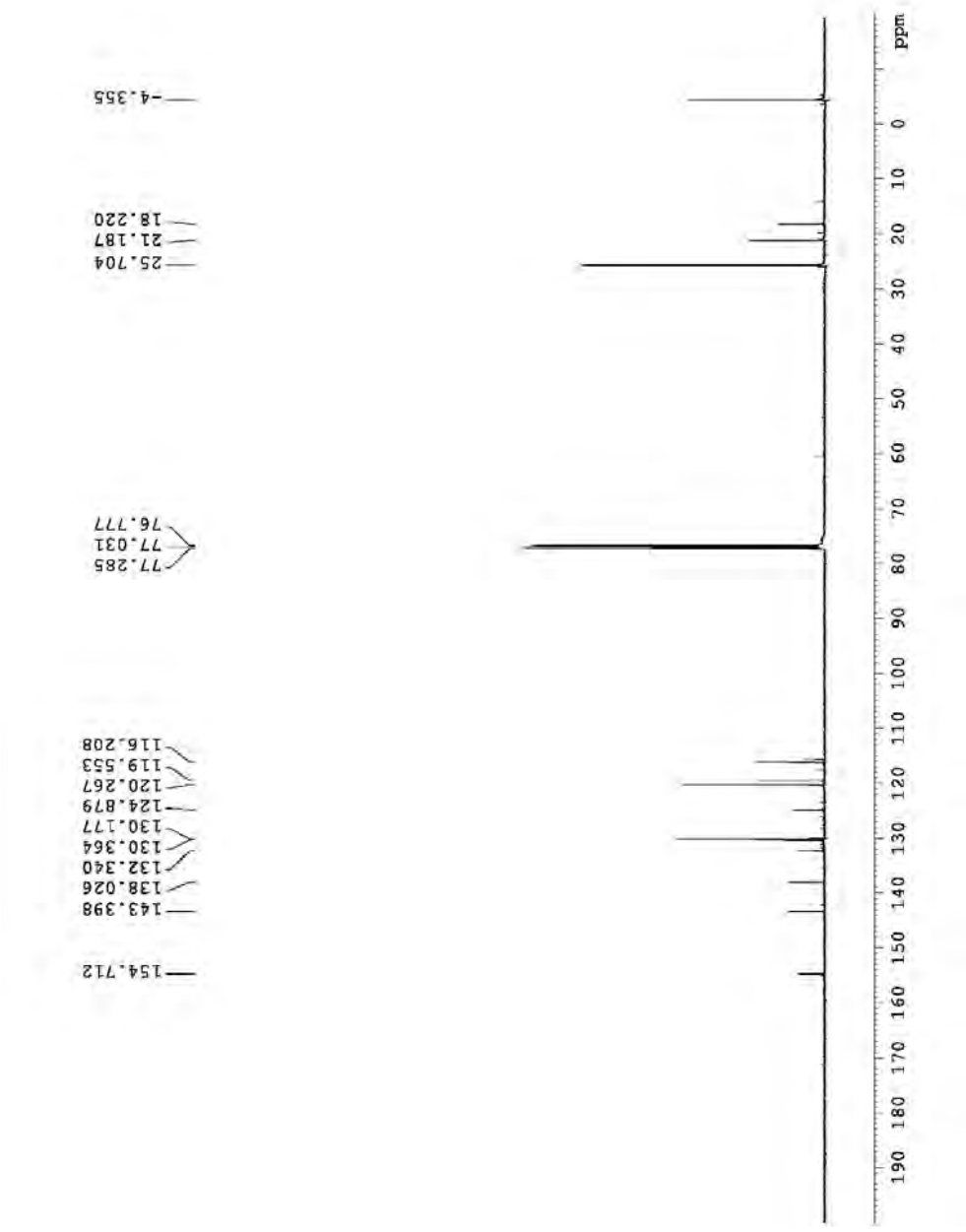
IR of 2'-chloro-4-methyl-[1, 1'-biphenyl]-2-amine (1n)



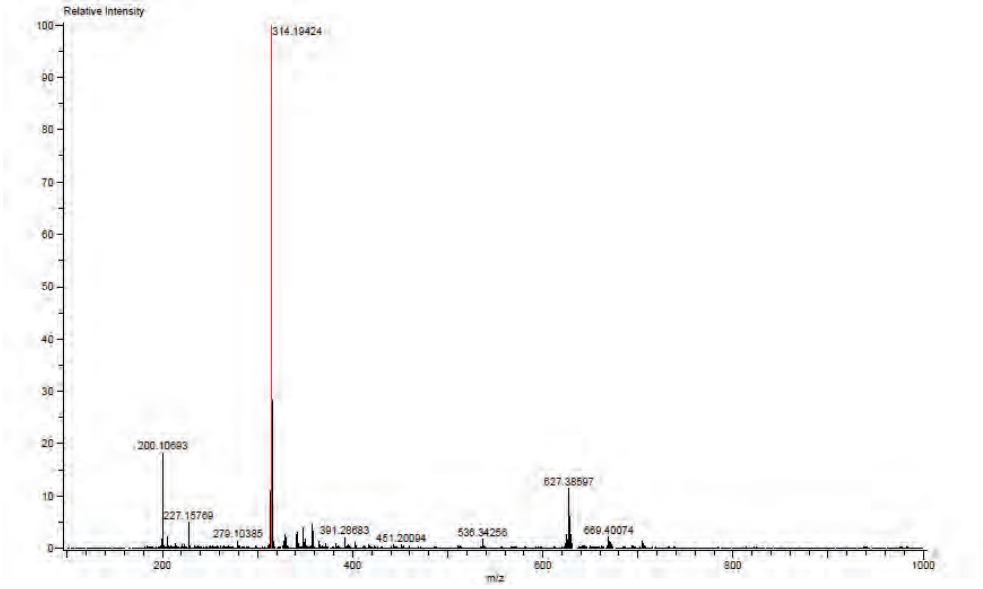
^{1}H-NMR of 4'-((tert-butyldimethylsilyl) oxy)-4-methyl-[1, 1'-biphenyl]-2-amine (1o) in $CDCl_3$



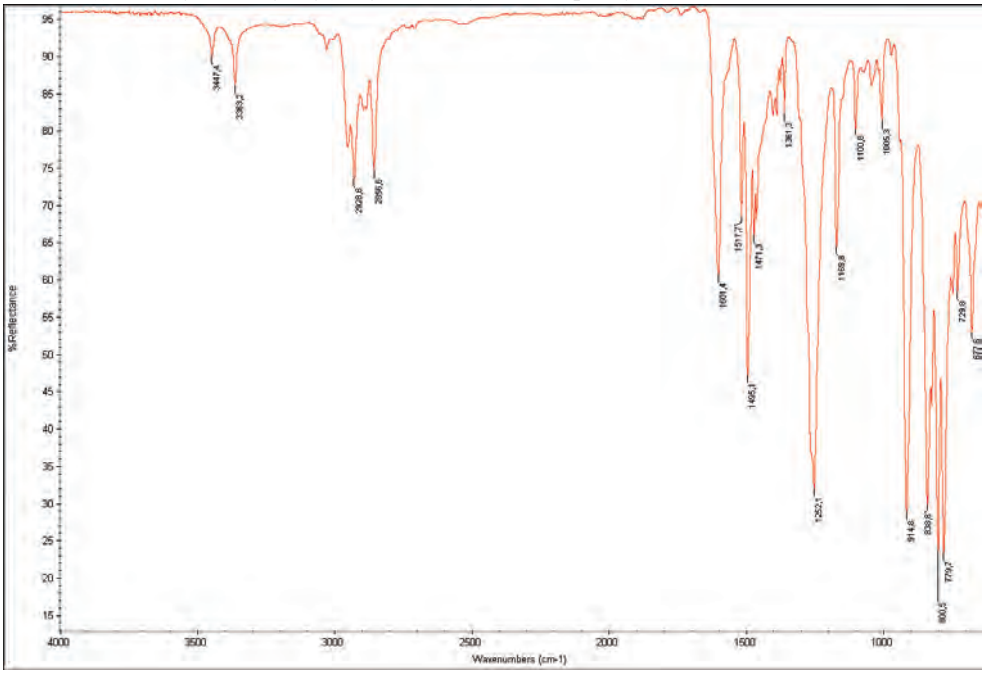
^{13}C-NMR of 4'-((tert-butyldimethylsilyl) oxy)-4-methyl-[1, 1'-biphenyl]-2-amine (1o) in $CDCl_3$



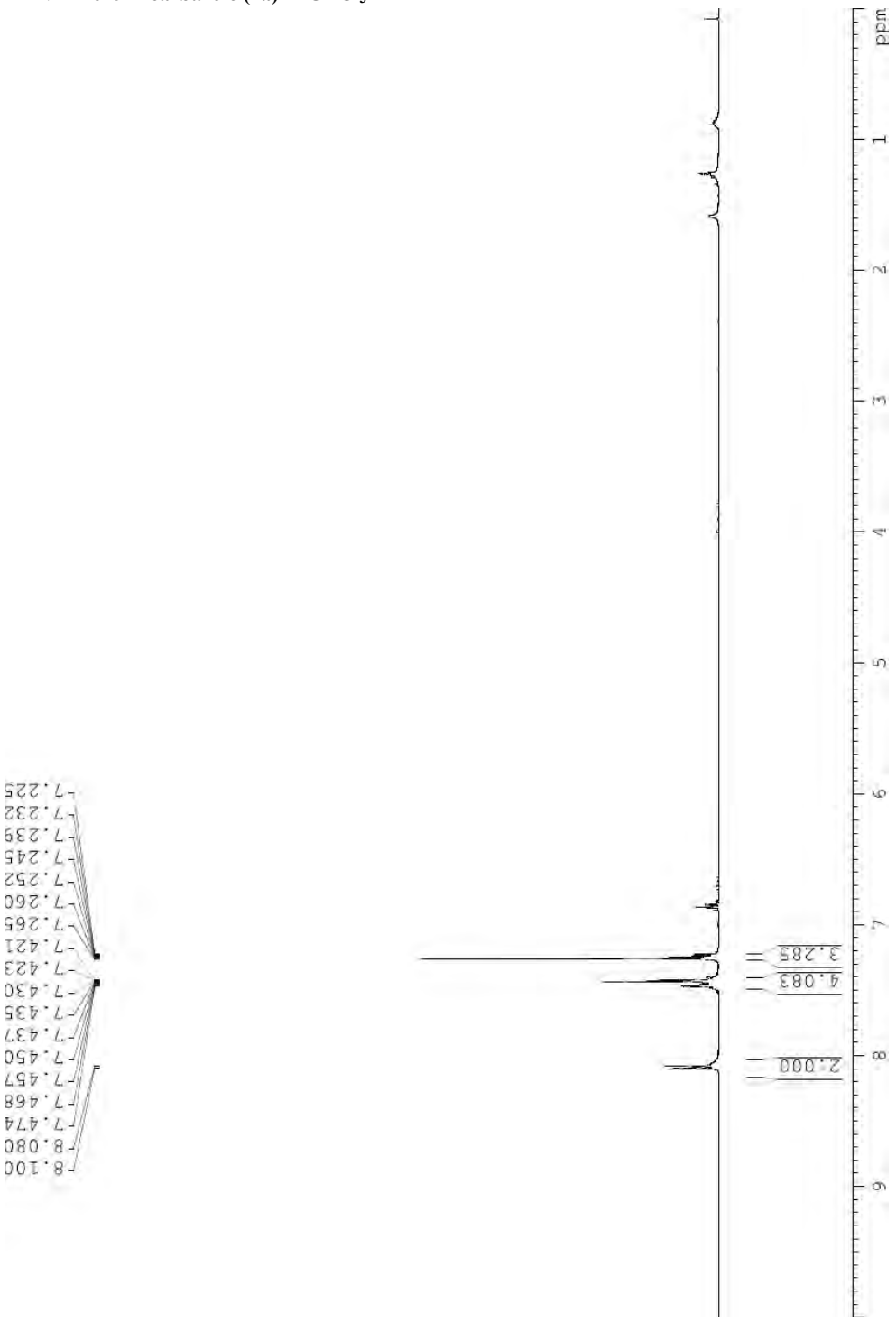
HRMS (DART+) of 4'-((tert-butyldimethylsilyl) oxy)-4-methyl-[1, 1'-biphenyl]-2-amine (1o)



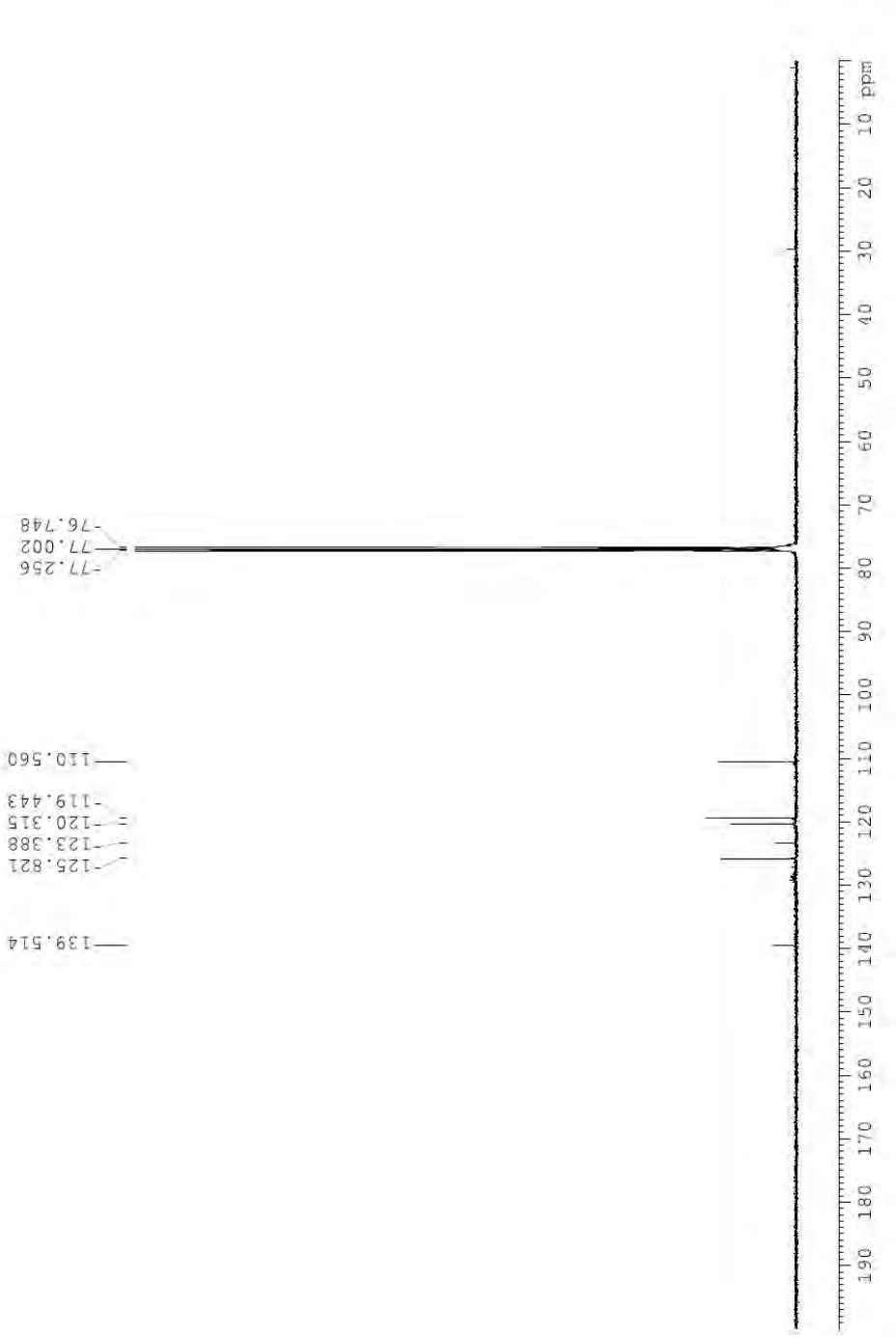
IR of 4'-((tert-butyldimethylsilyl) oxy)-4-methyl-[1, 1'-biphenyl]-2-amine (1o)



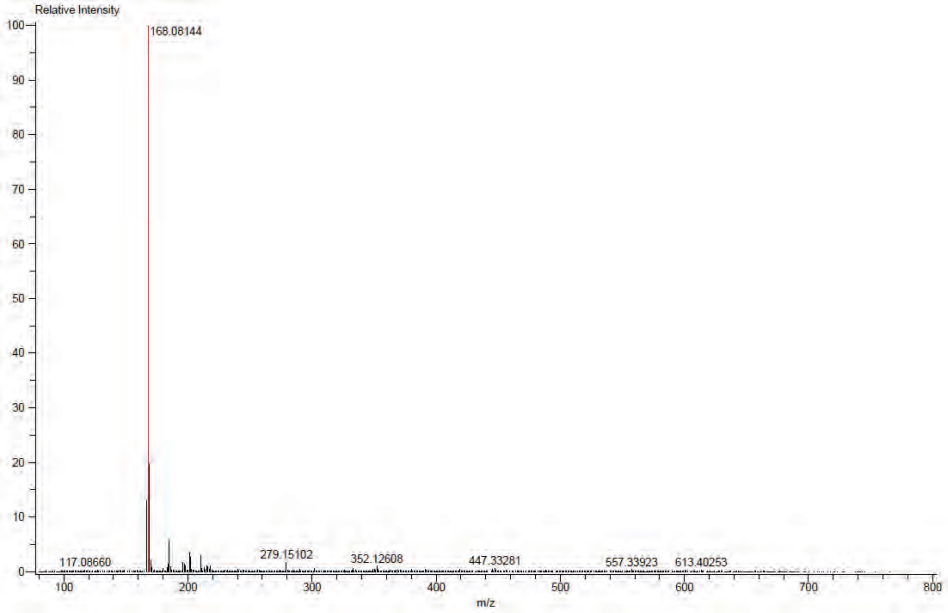
^{1}H-NMR of 9*H*-carbazole (4a) in $CDCl_3$



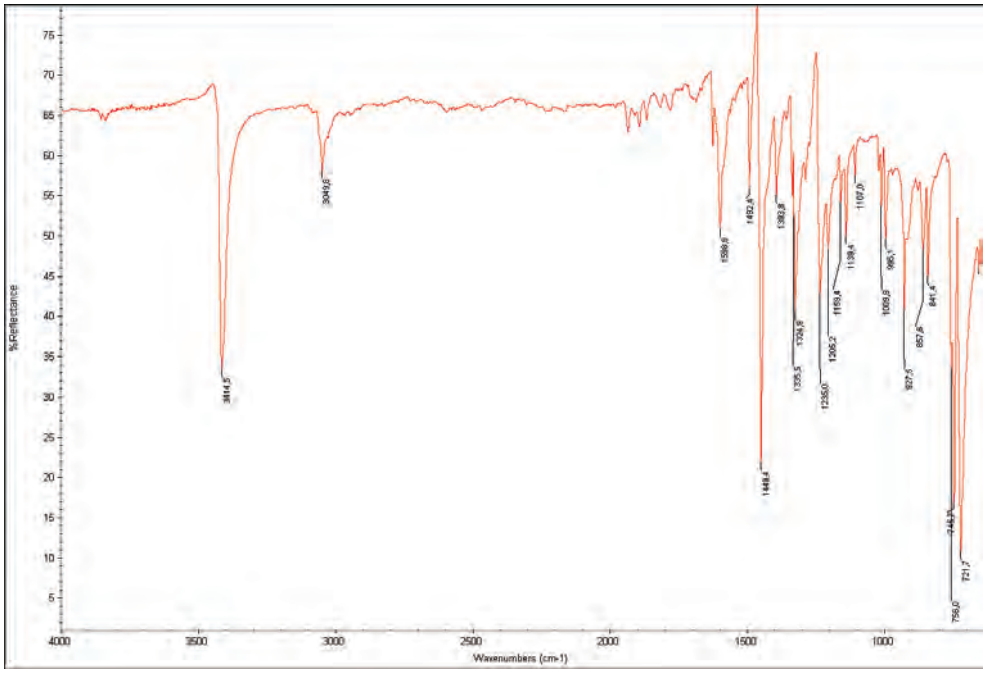
^{13}C-NMR of 9*H*-carbazole (4a) in $CDCl_3$



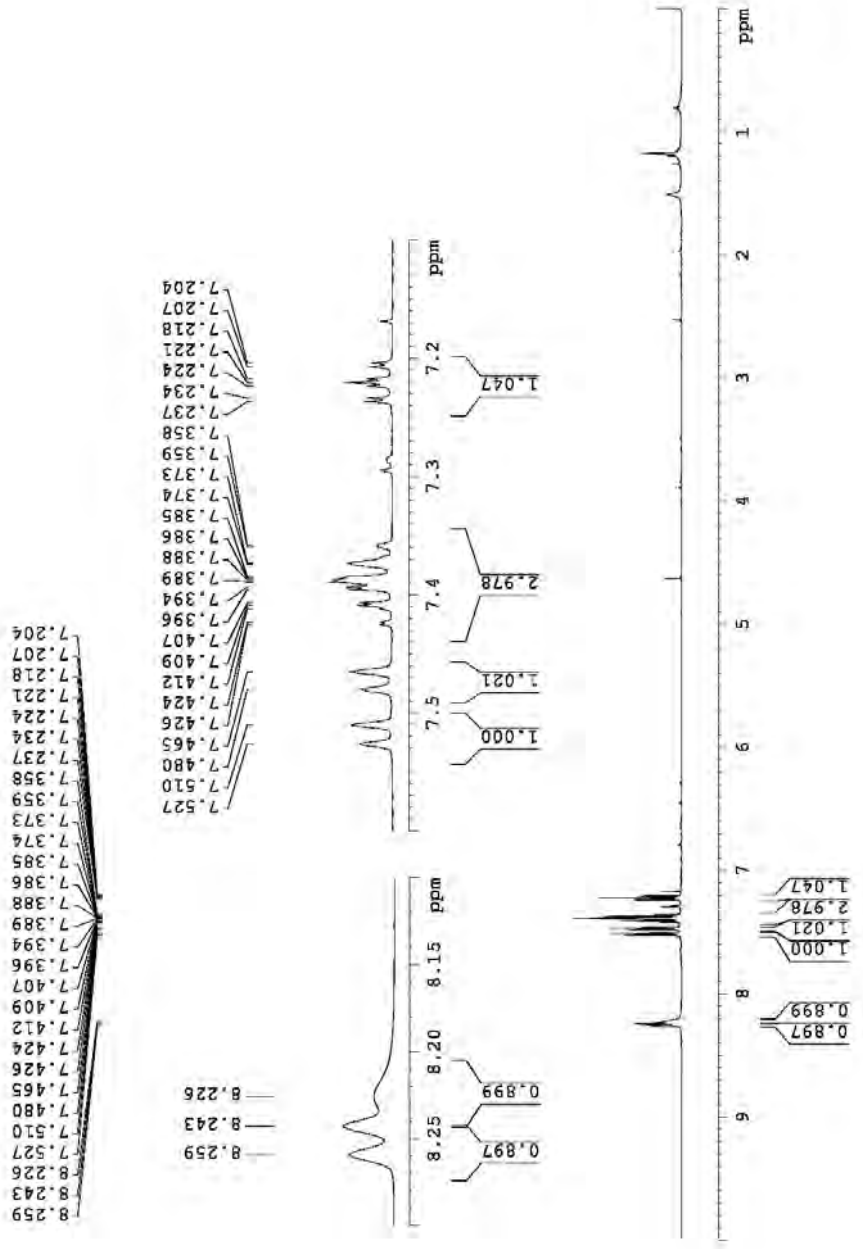
HRMS (DART+) of 9*H*-carbazole (4a)



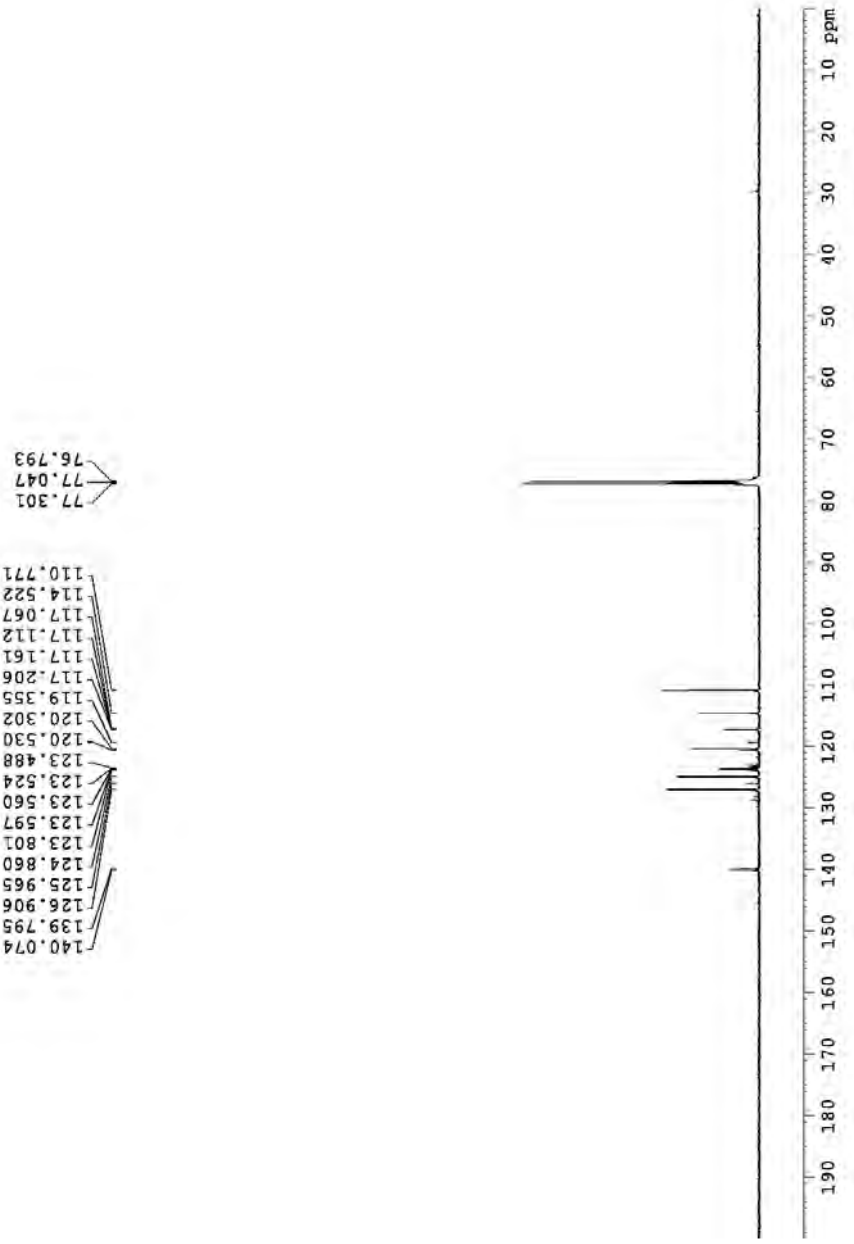
IR of 9*H*-carbazole (4a)



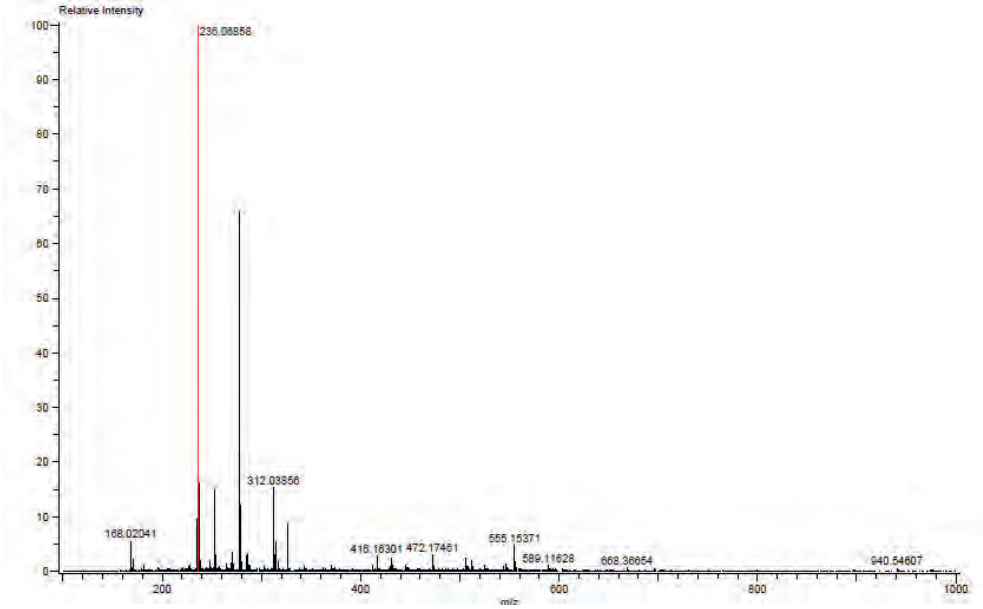
^{1}H-NMR of 4-(trifluoromethyl)-9*H*-carbazole (4b) in $CDCl_3$



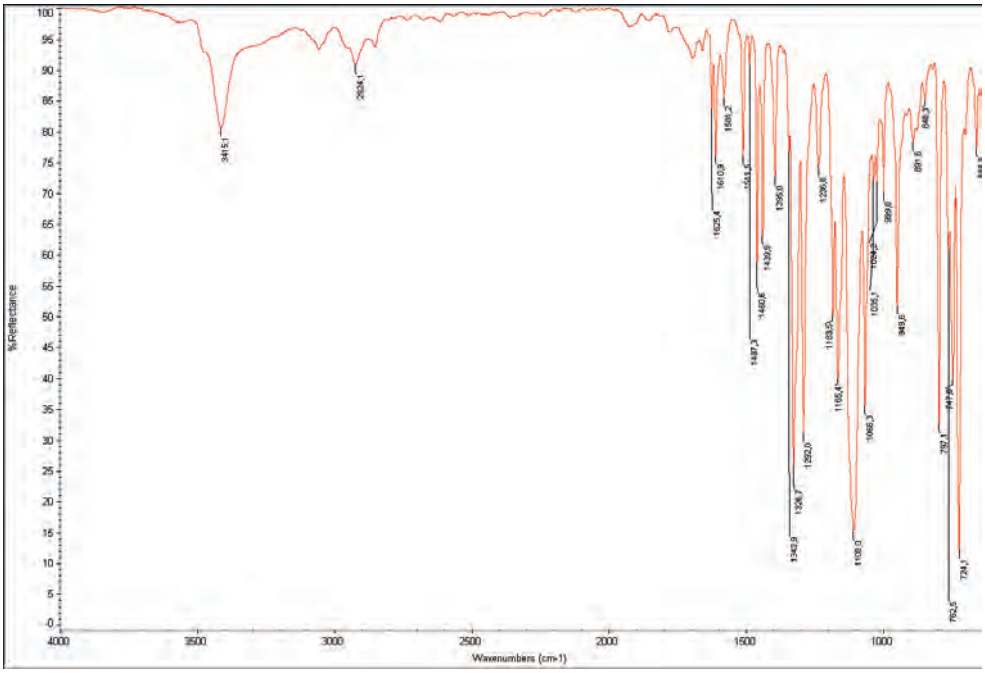
^{13}C-NMR of 4-(trifluoromethyl)-9*H*-carbazole (4b) in $CDCl_3$



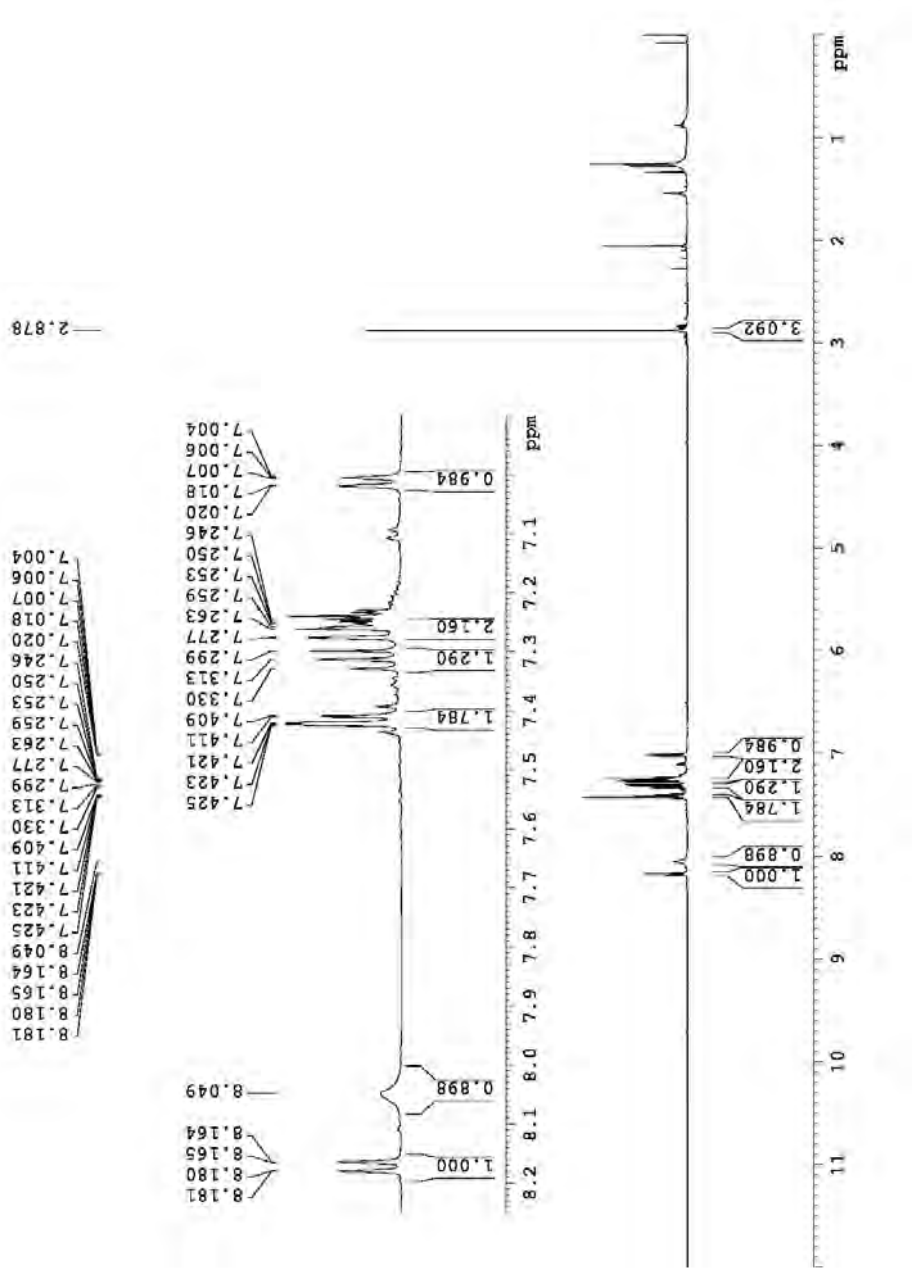
HRMS (DART+) of 4-(trifluoromethyl)-9*H*-carbazole (4b)



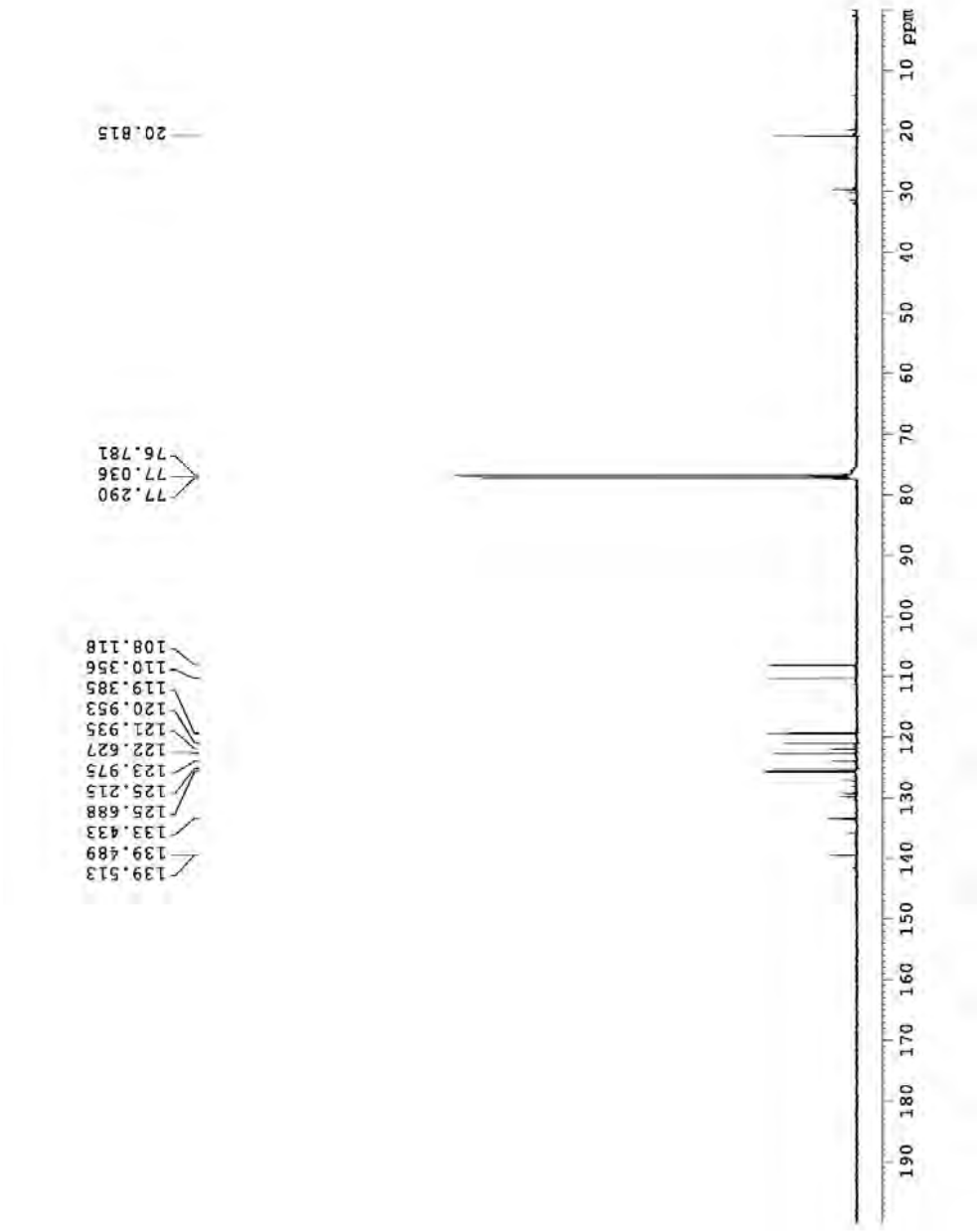
IR of 4-(trifluoromethyl)-9*H*-carbazole (4b)



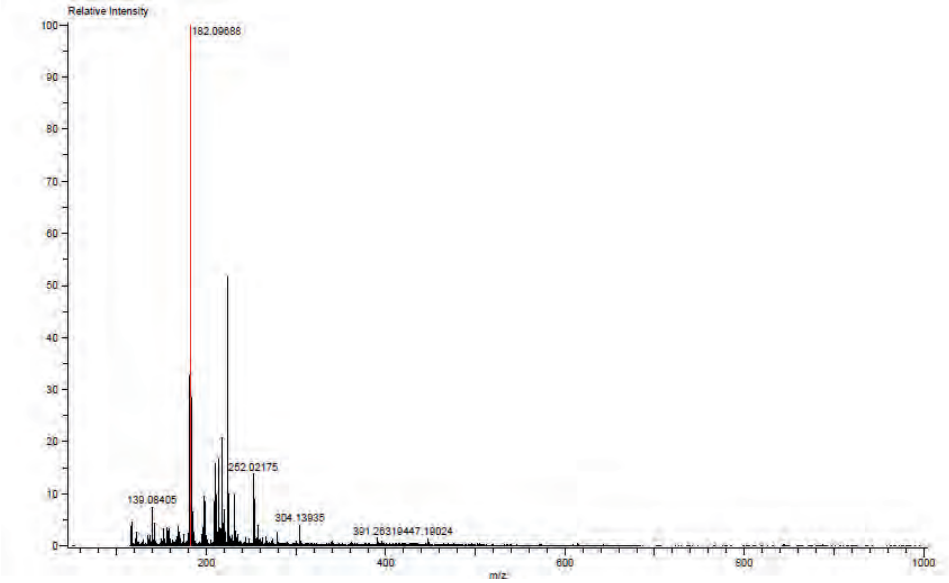
^{1}H-NMR of 4-methyl-9*H*-carbazole (4c) in $CDCl_3$



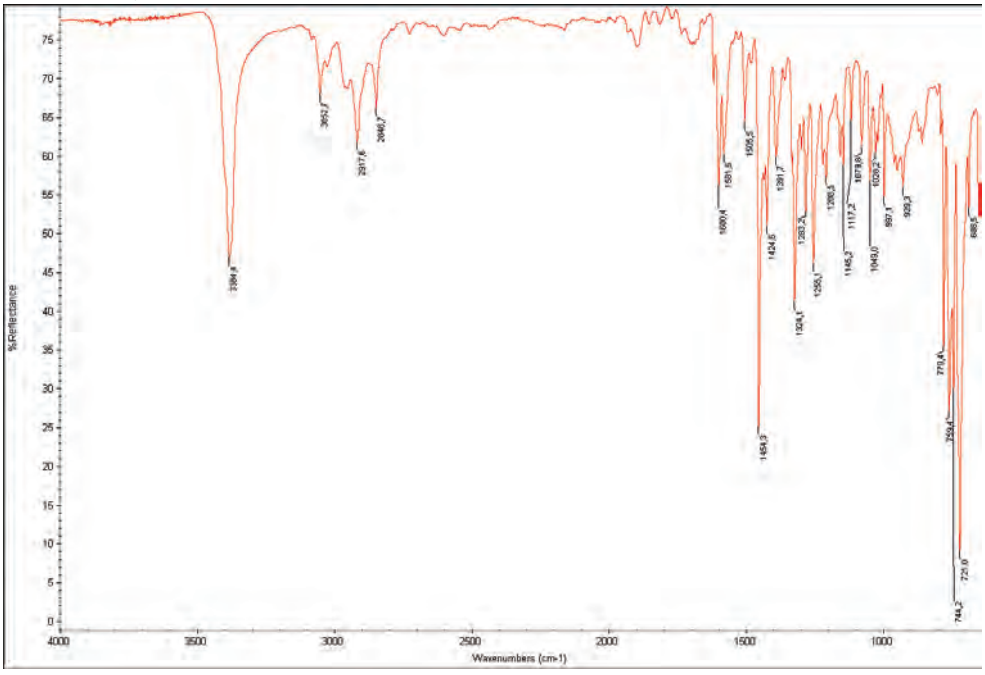
^{13}C-NMR of 4-methyl-9*H*-carbazole (4c) in $CDCl_3$



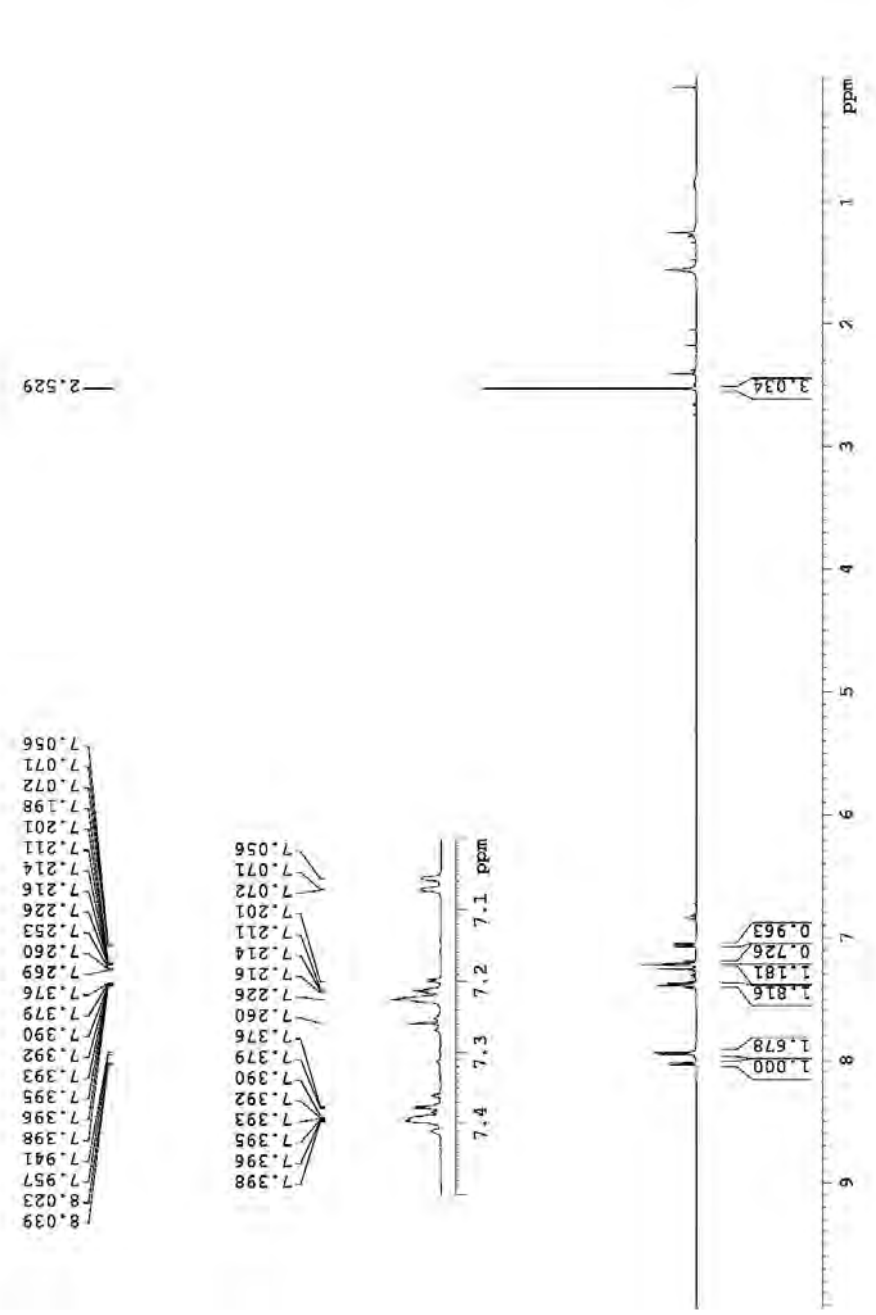
HRMS (DART+) of 4-methyl-9*H*-carbazole (4c)



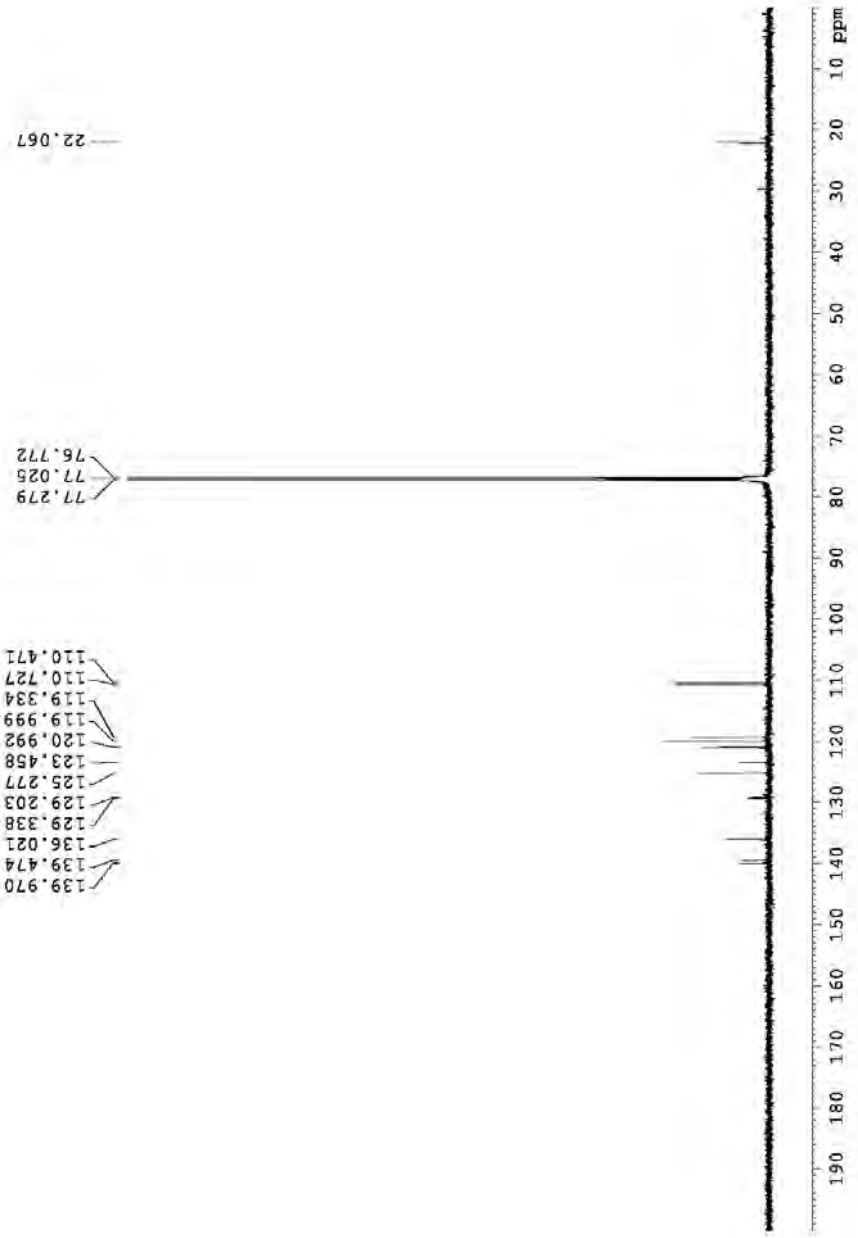
IR of 4-methyl-9*H*-carbazole (4c)



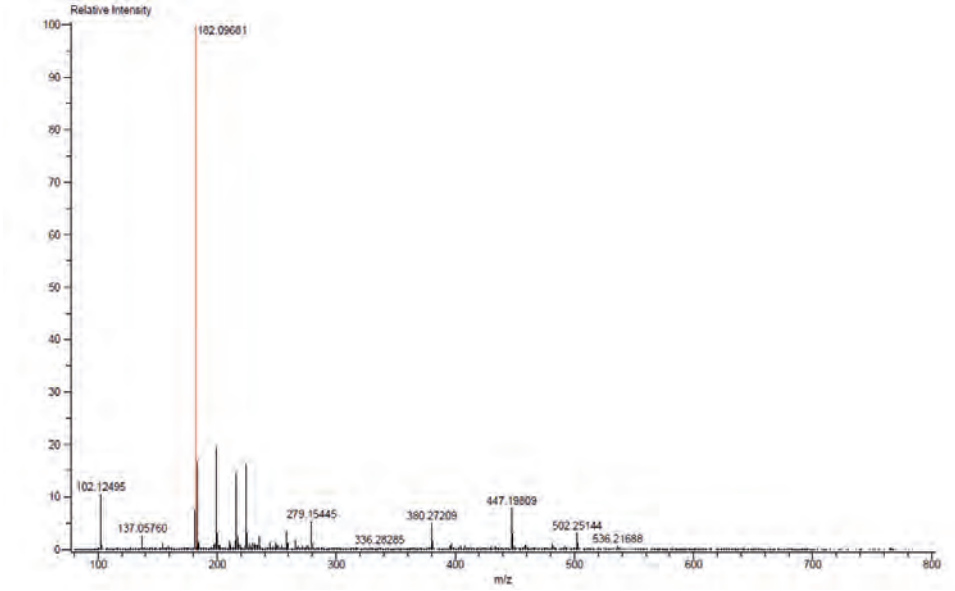
^{1}H-NMR of 2-methyl-9*H*-carbazole (4d) in $CDCl_3$



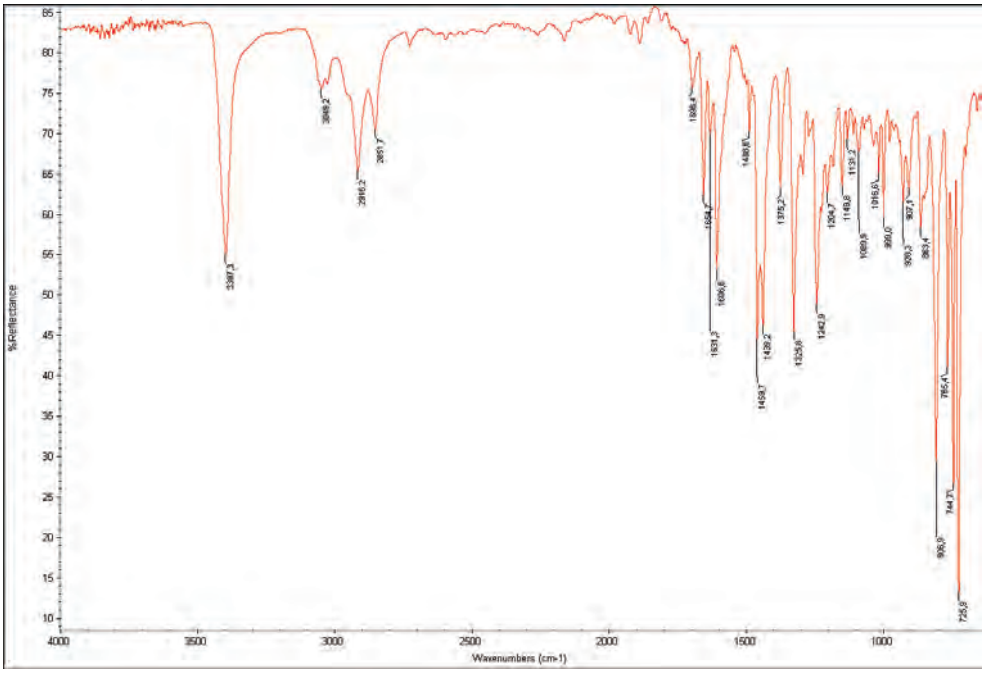
^{13}C-NMR of 2-methyl-9*H*-carbazole (4d) in $CDCl_3$



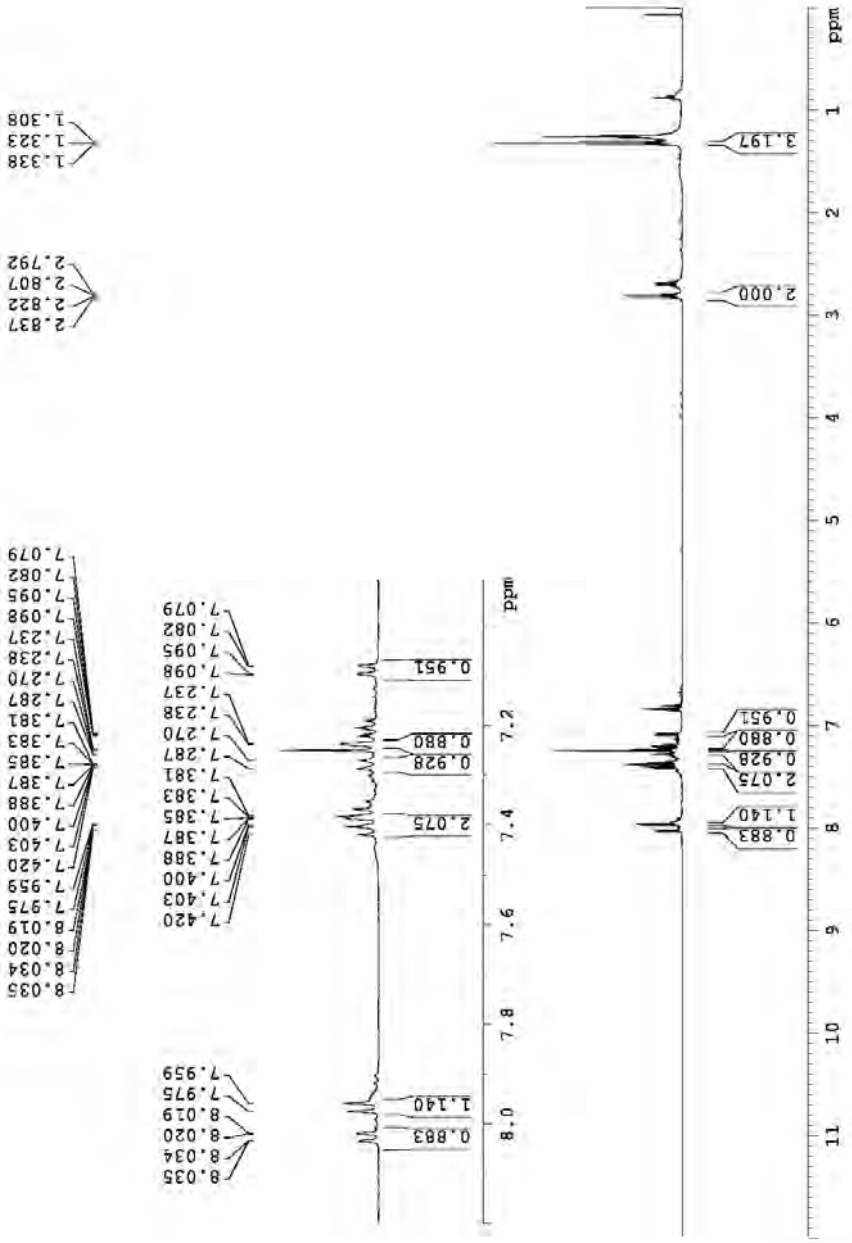
HRMS (DART+) of 2-methyl-9*H*-carbazole (4d)



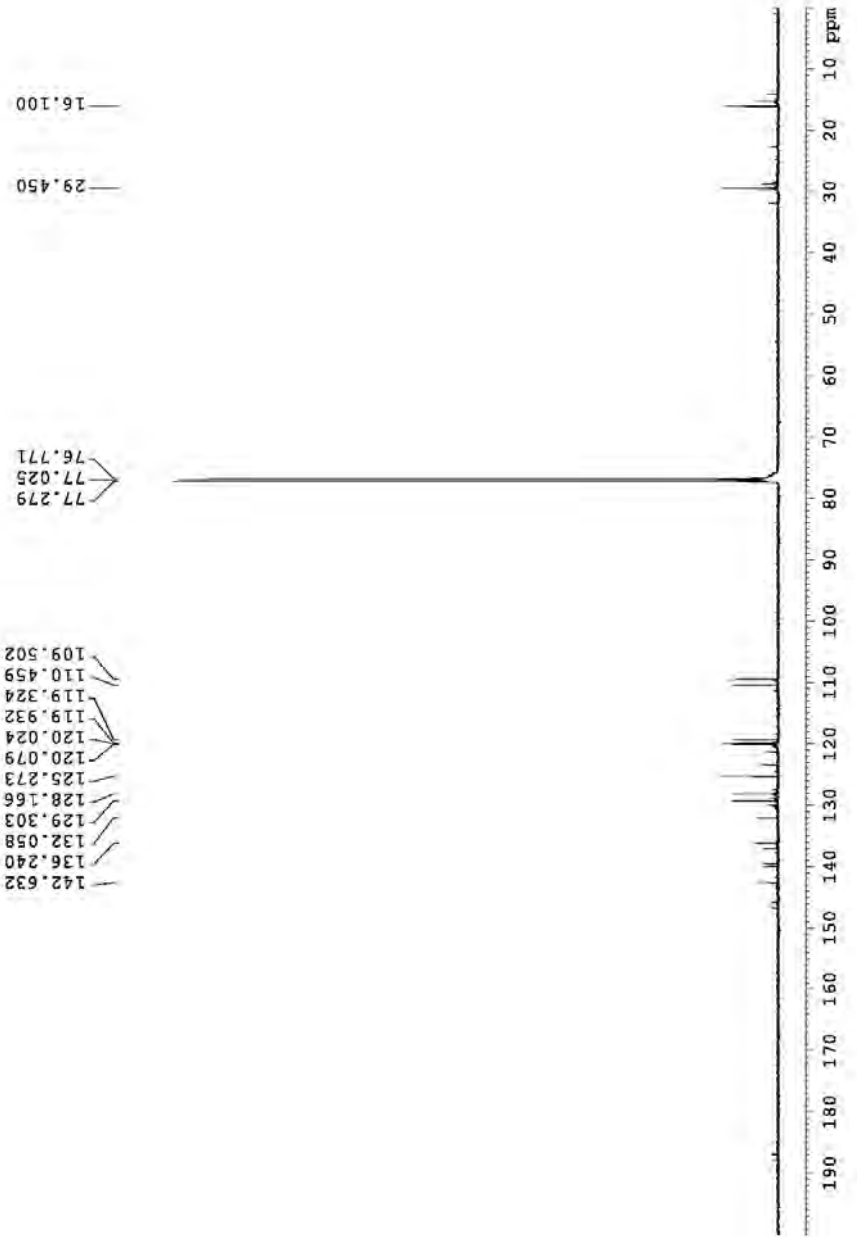
IR of 2-methyl-9*H*-carbazole (4d)



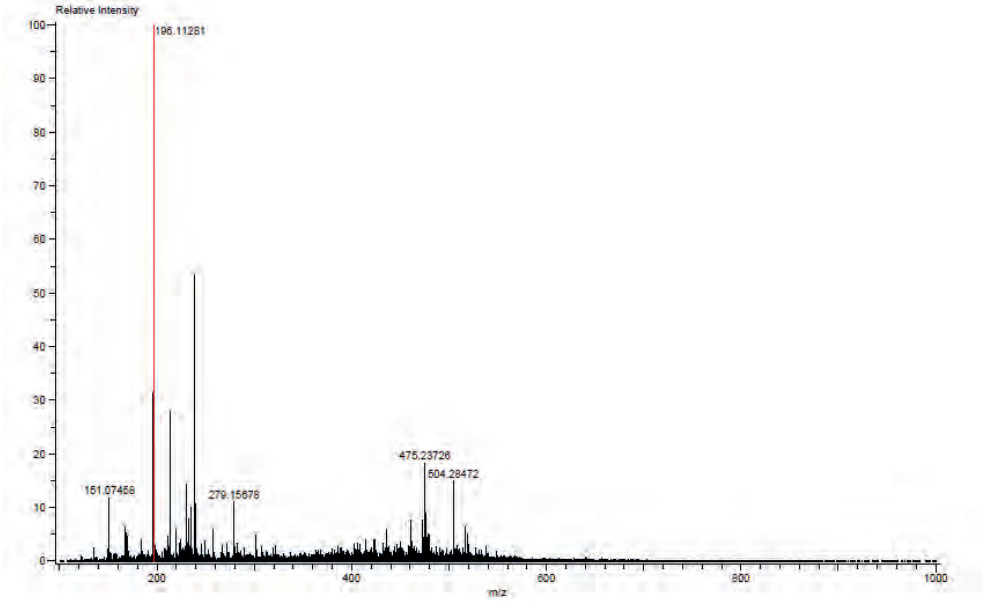
^{1}H-NMR of 2-ethyl-9*H*-carbazole (4e) in $CDCl_3$



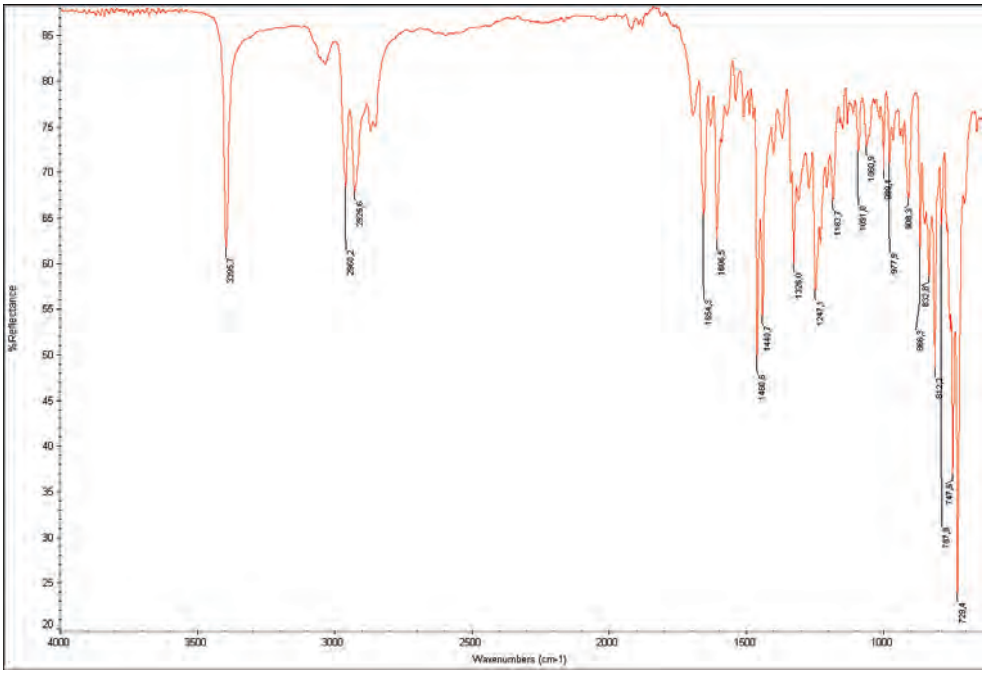
^{13}C-NMR of 2-ethyl-9*H*-carbazole (4e) in $CDCl_3$



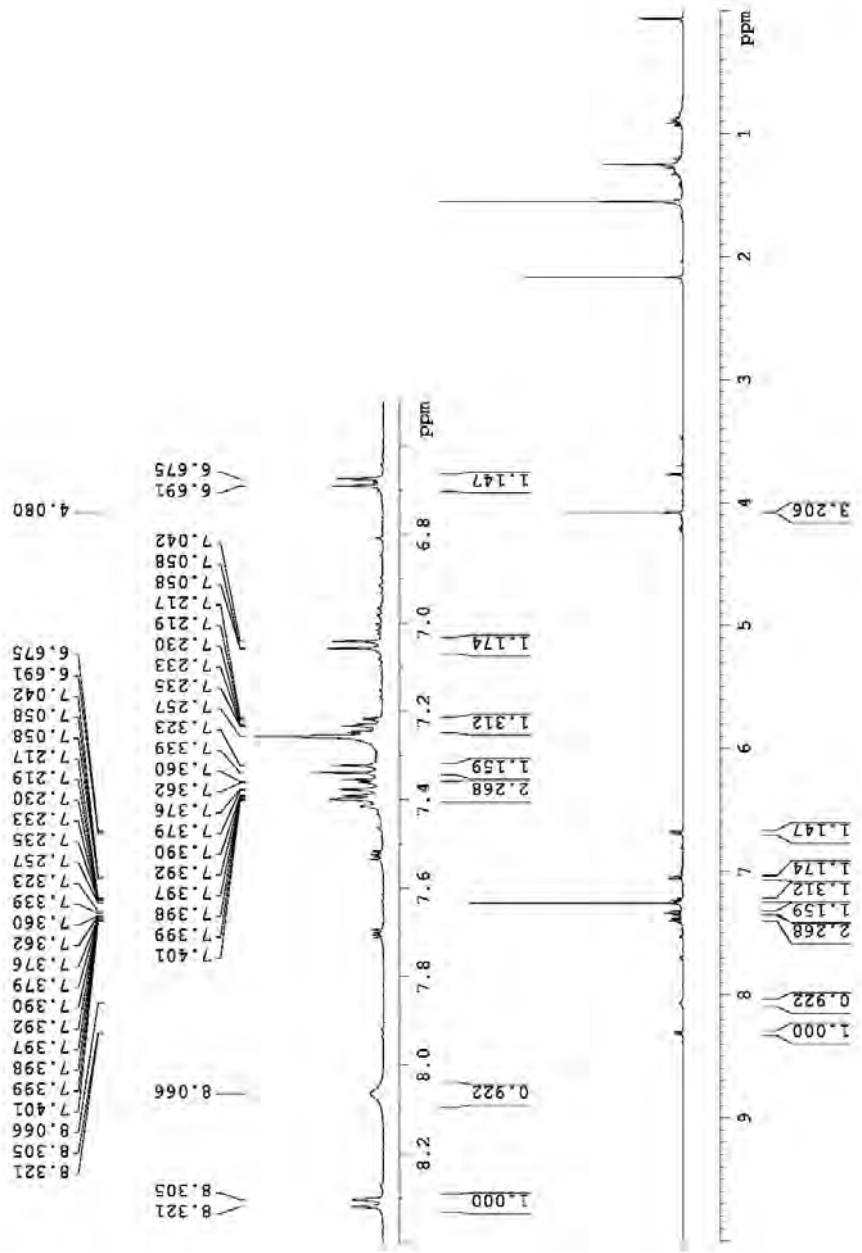
HRMS (DART+) of 2-ethyl-9*H*-carbazole (4e)



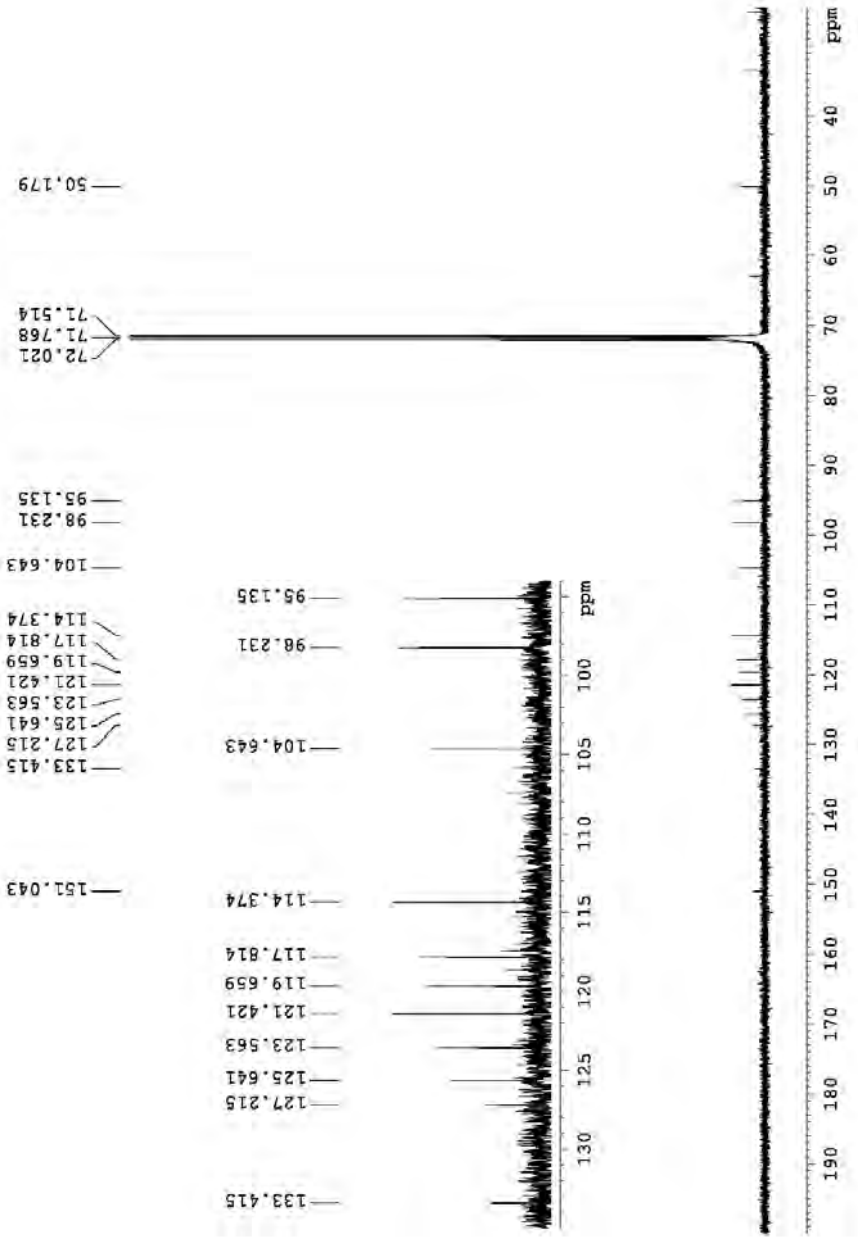
IR of 2-ethyl-9*H*-carbazole (4e)



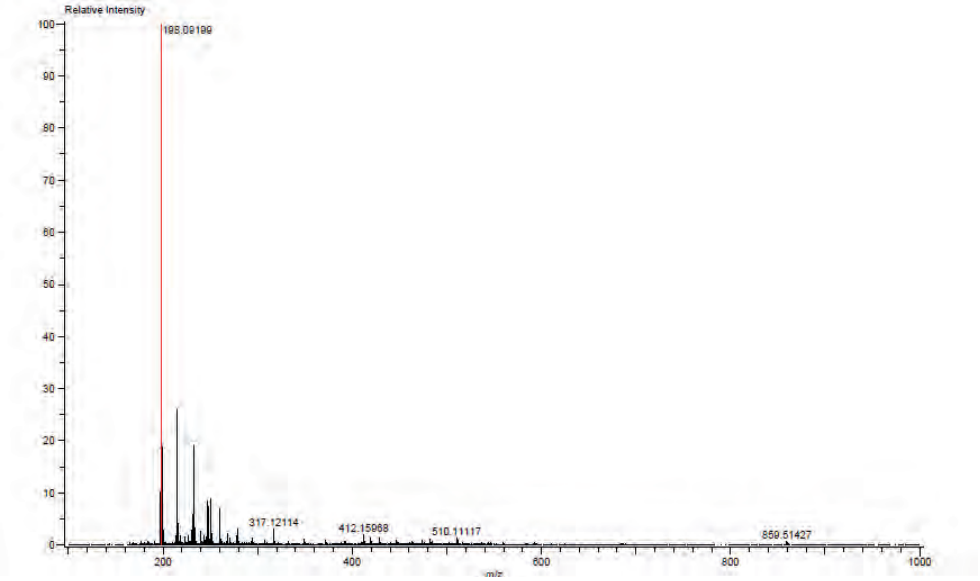
^{1}H-NMR of 4-methoxy-9*H*-carbazole (4f) in $CDCl_3$



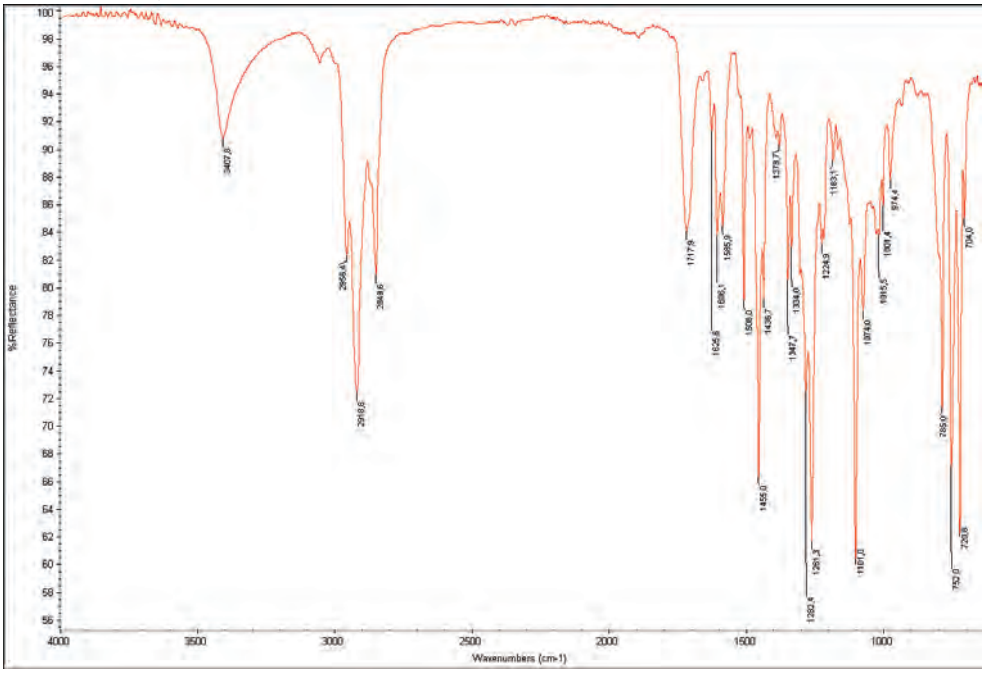
^{13}C-NMR of 4-methoxy-9*H*-carbazole (4f) in $CDCl_3$



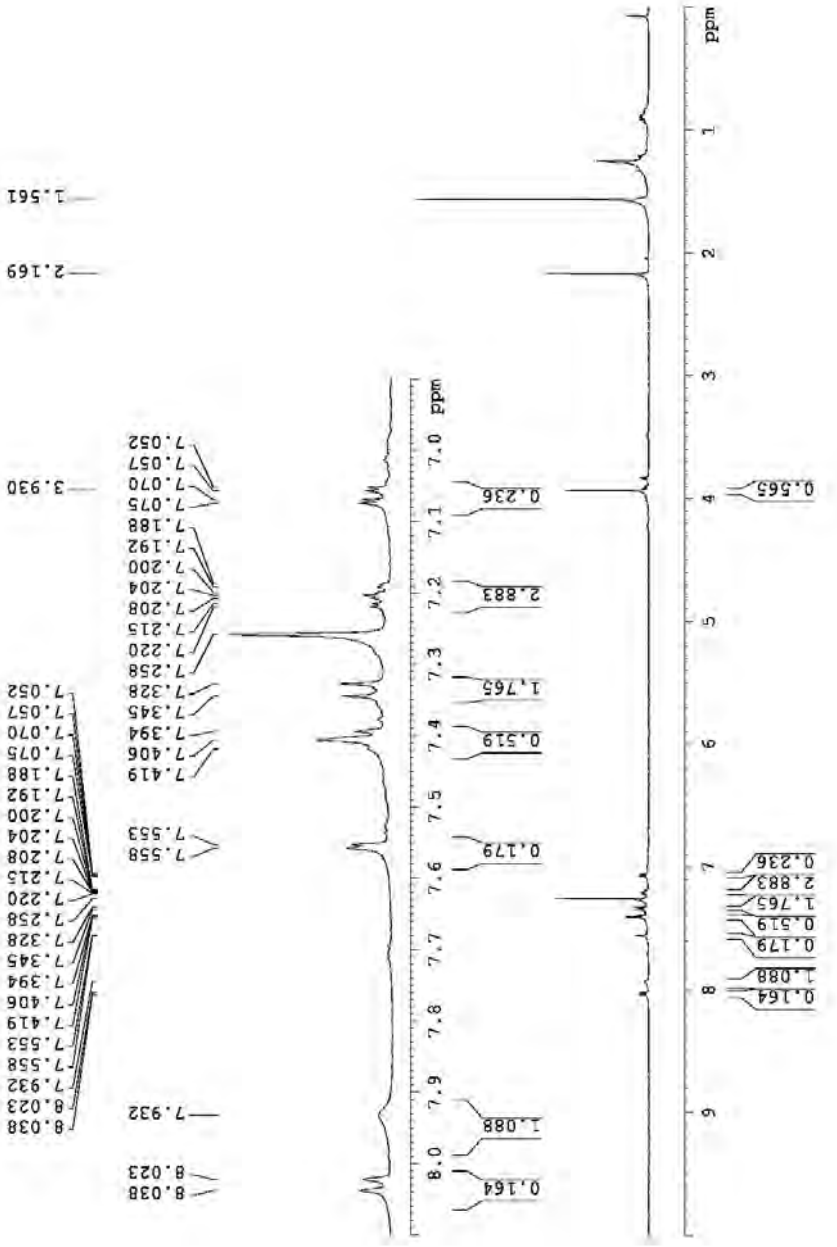
HRMS (DART+) of 4-methoxy-9*H*-carbazole (4f)



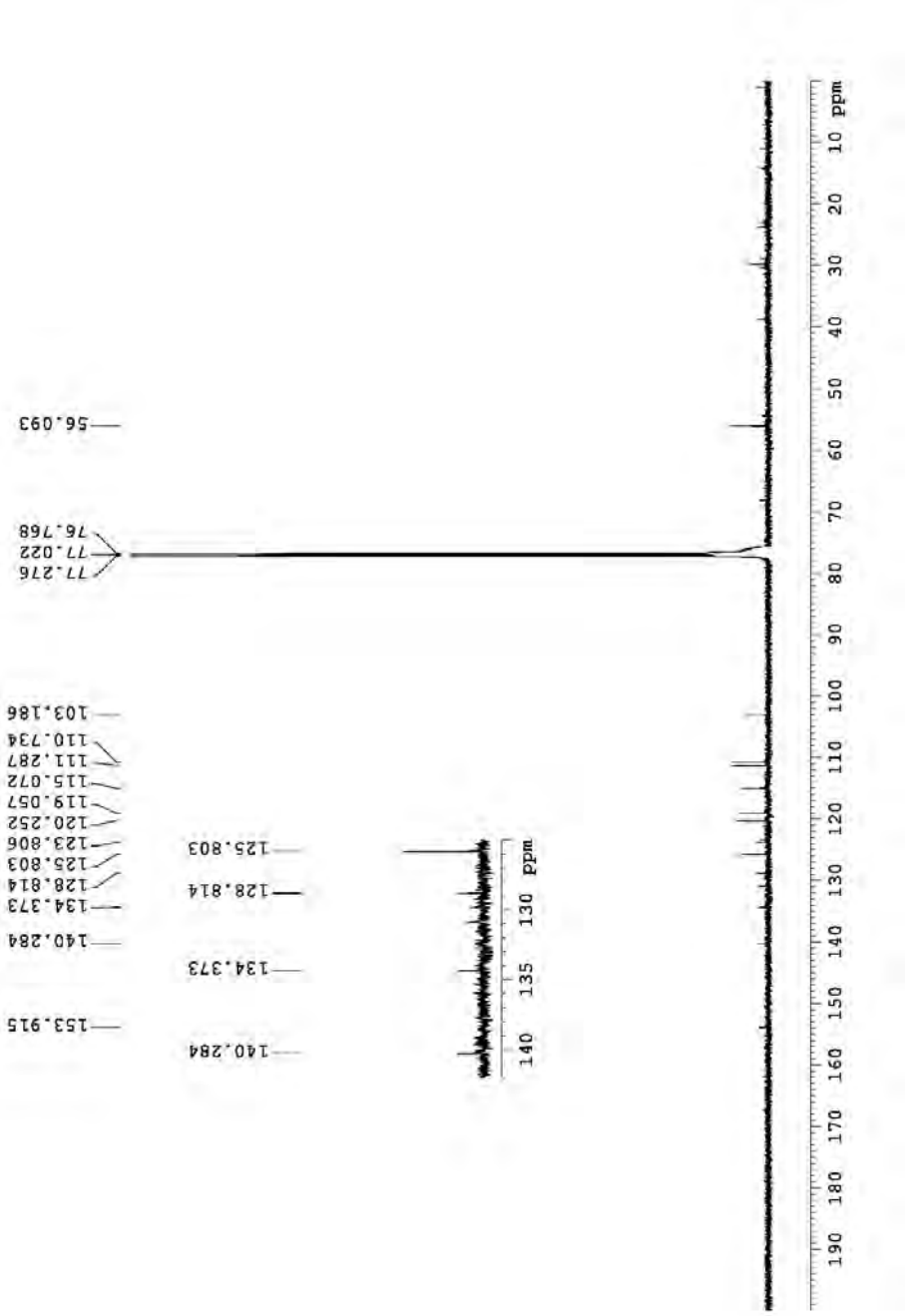
IR of 4-methoxy-9*H*-carbazole (4f)



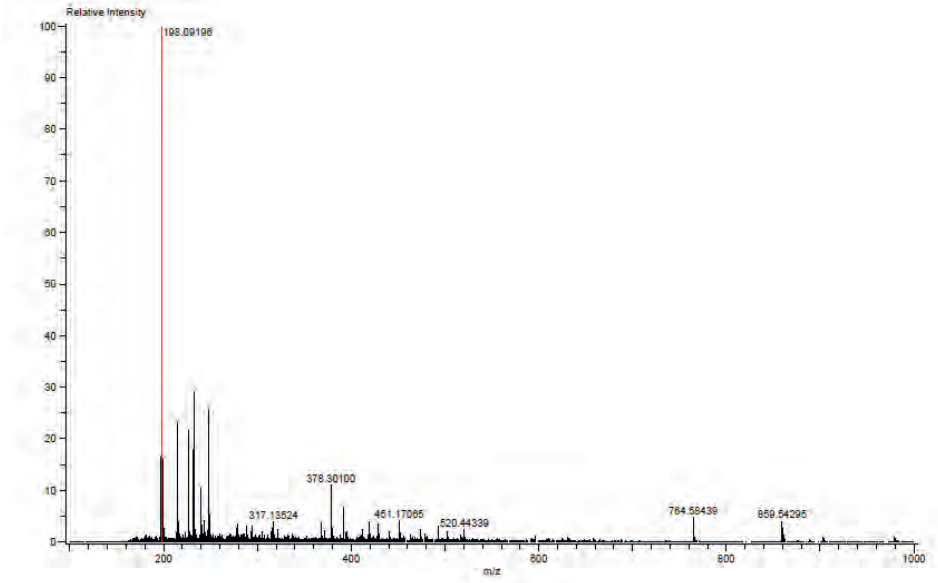
^{1}H-NMR of 3-methoxy-9*H*-carbazole (4g) in $CDCl_3$



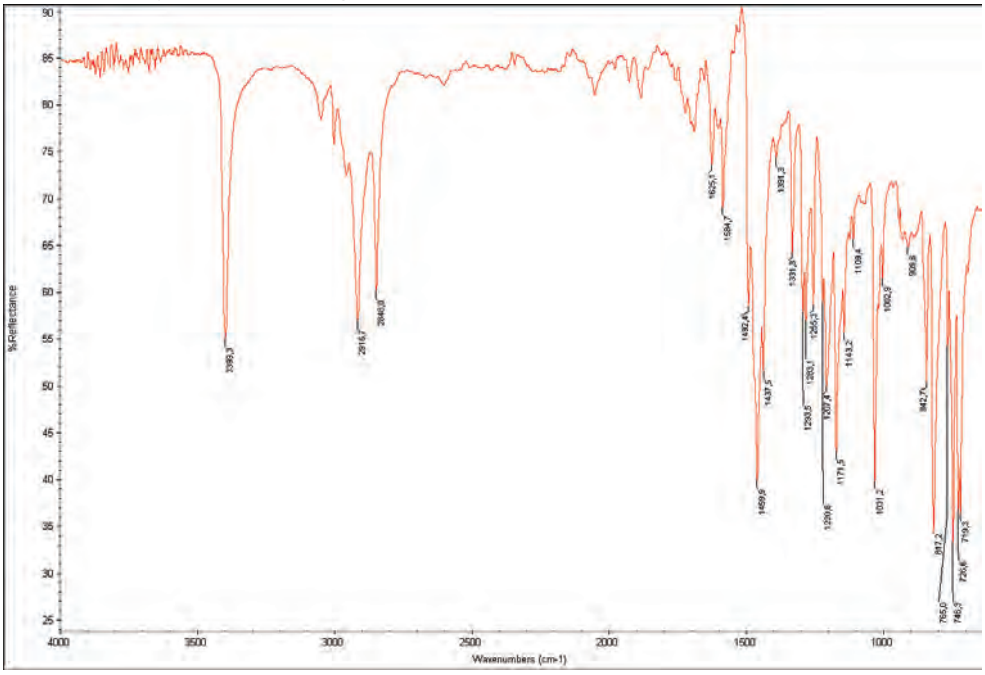
^{13}C-NMR of 3-methoxy-9*H*-carbazole (4g) in $CDCl_3$



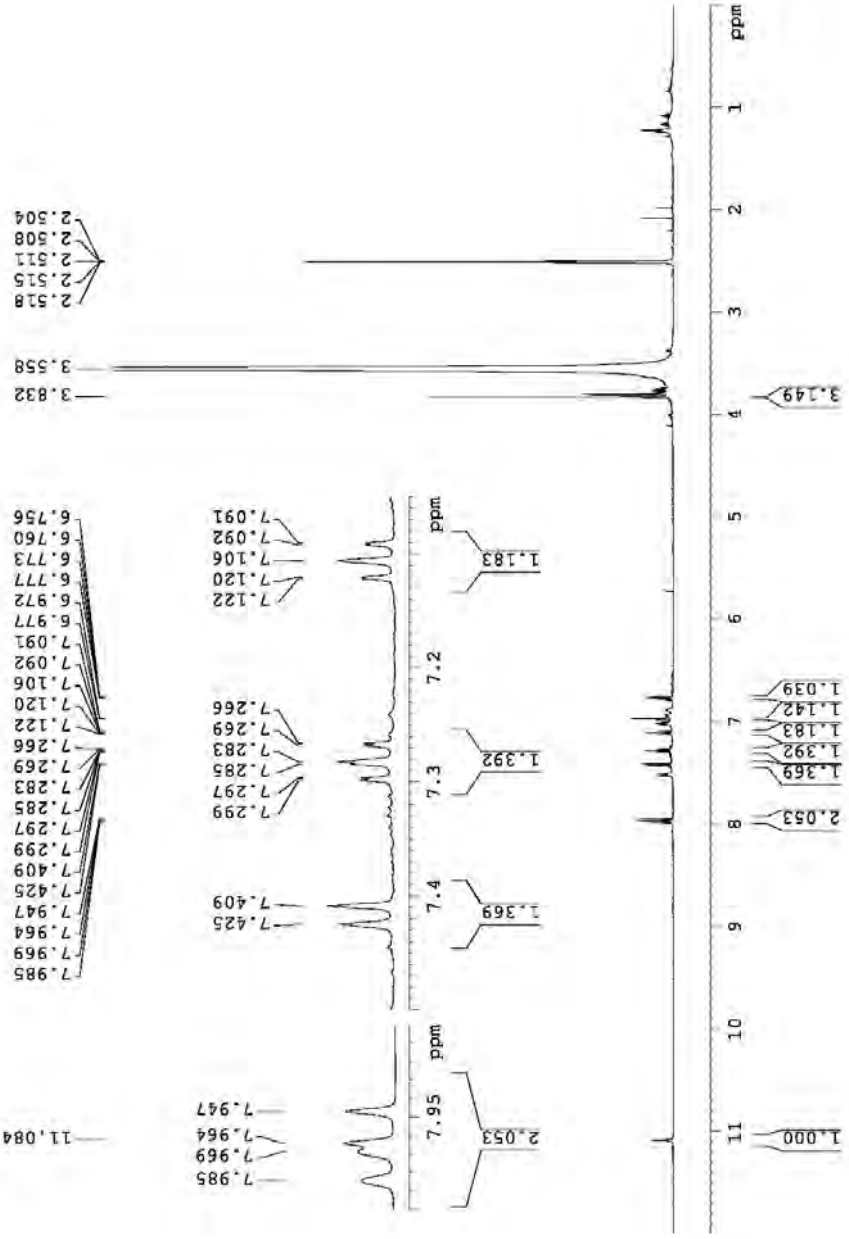
HRMS (DART+) of 3-methoxy-9*H*-carbazole (4g)



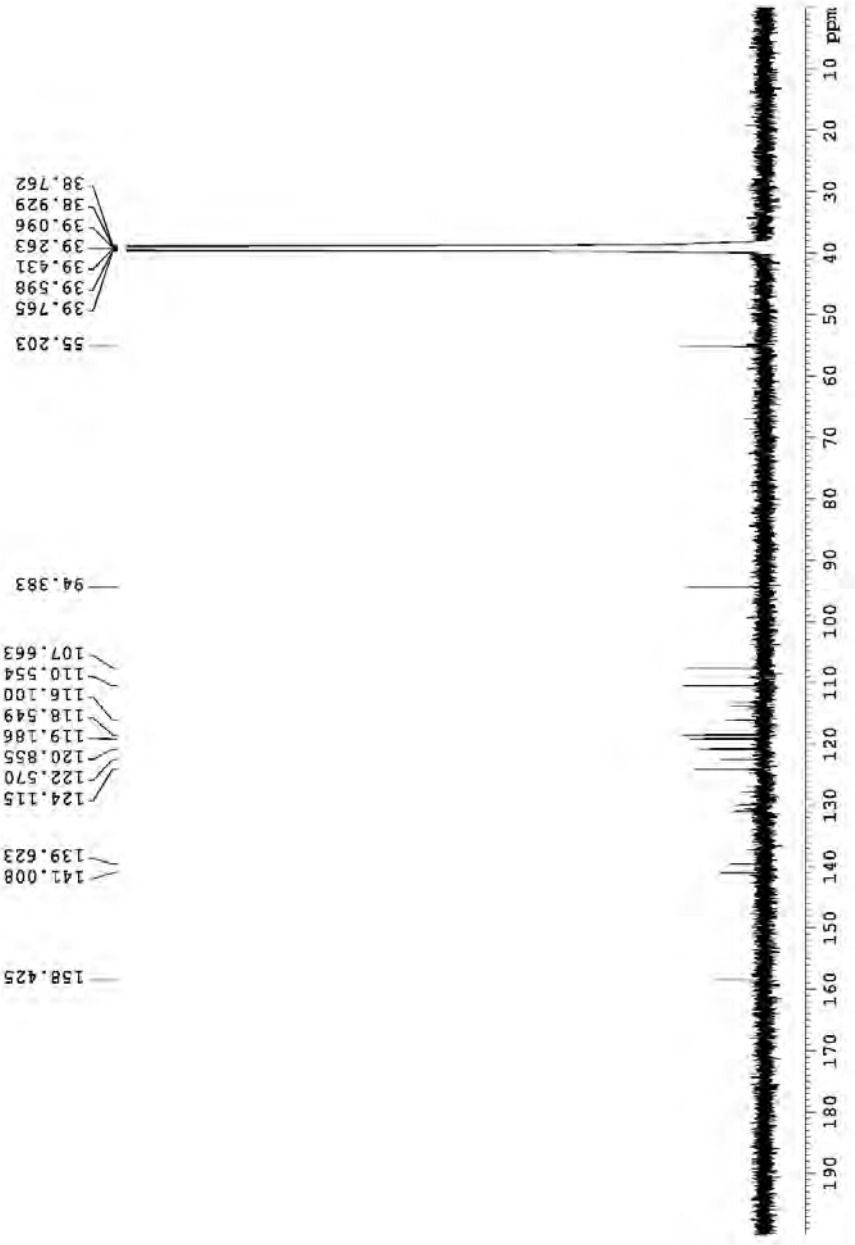
IR of 3-methoxy-9*H*-carbazole (4g)



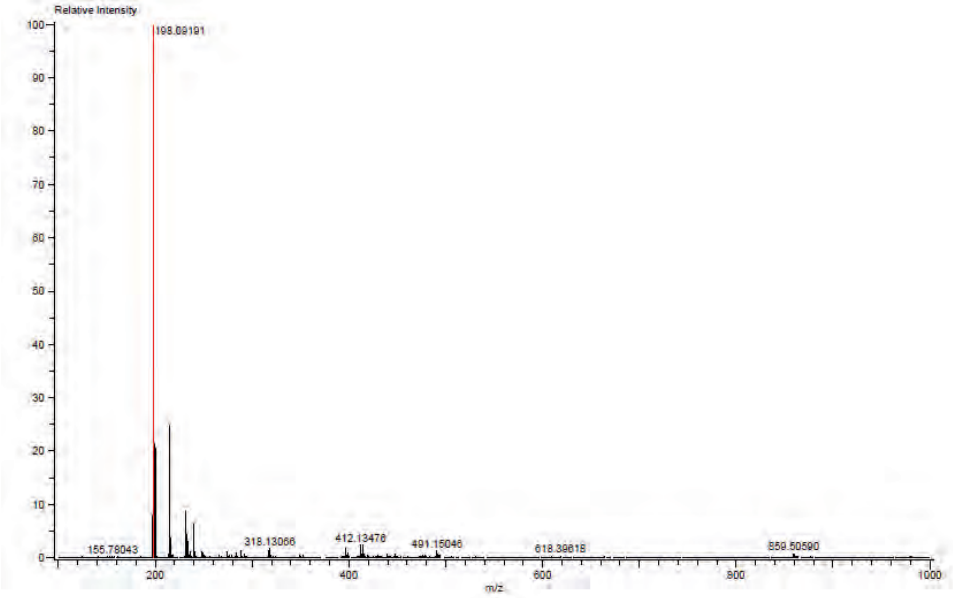
[1]H-NMR of 2-methoxy-9*H*-carbazole (4h) in DMSO-d_6



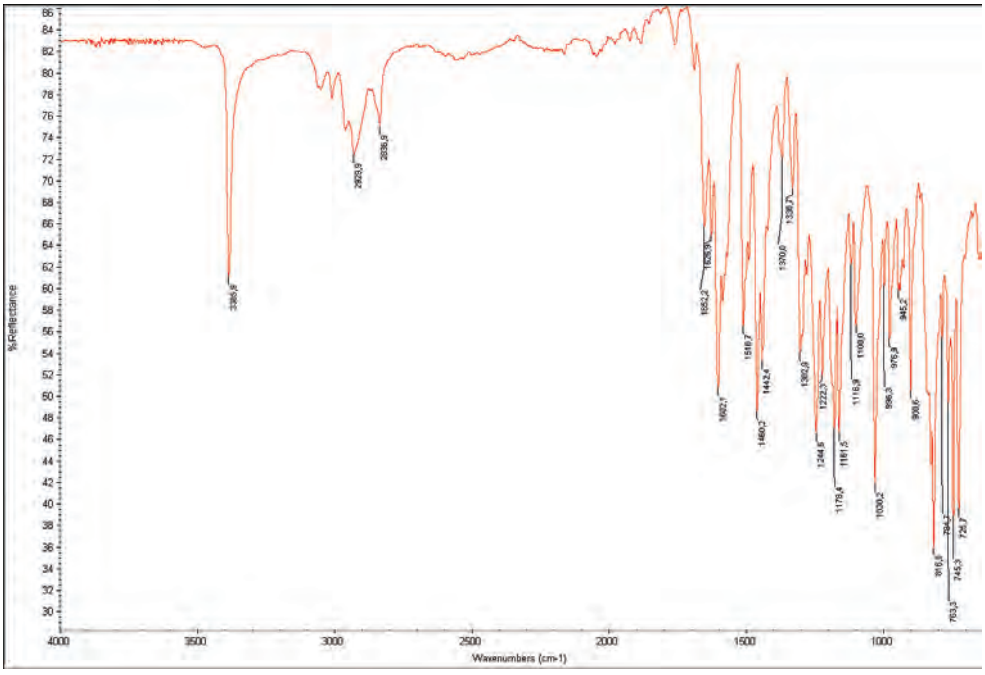
^{13}C-NMR of 2-methoxy-9*H*-carbazole (4h) in DMSO-d_6



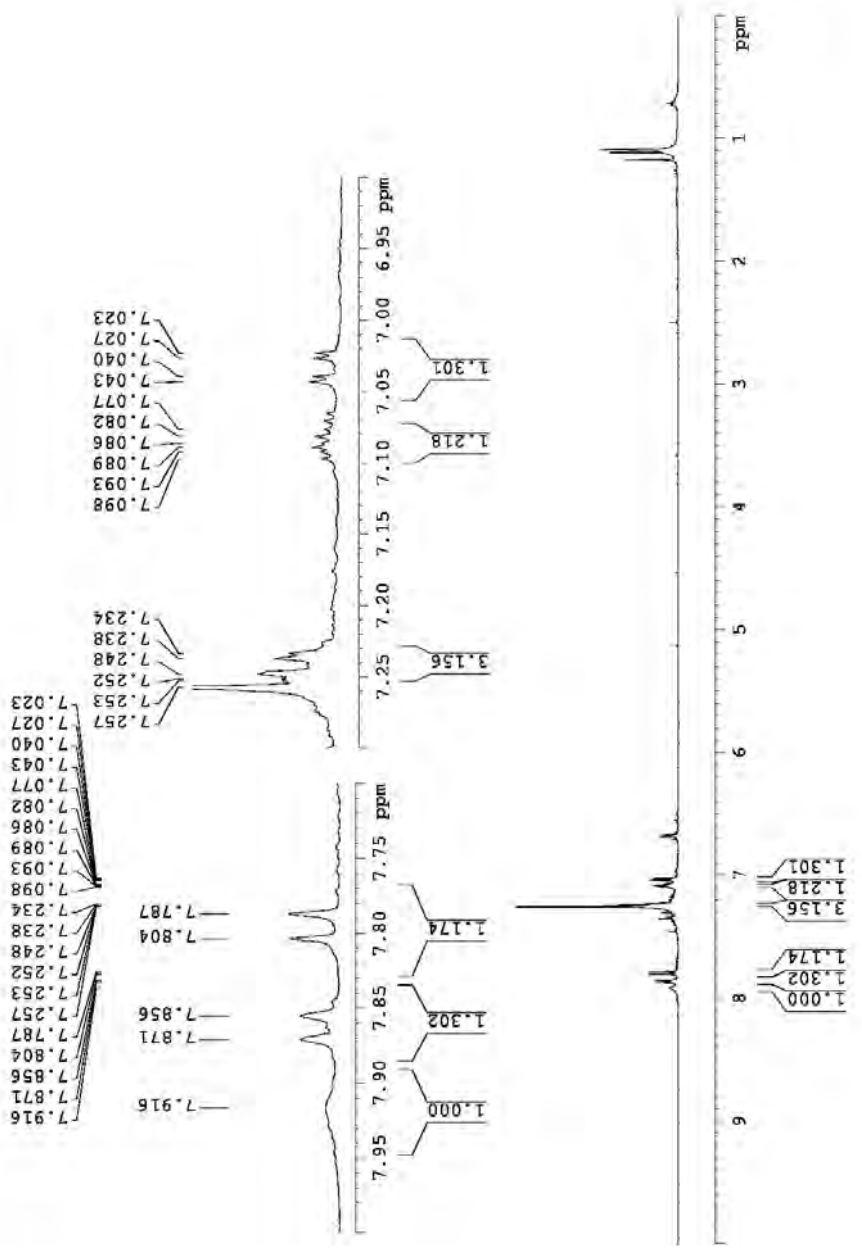
HRMS (DART+) of 2-methoxy-9*H*-carbazole (4h)



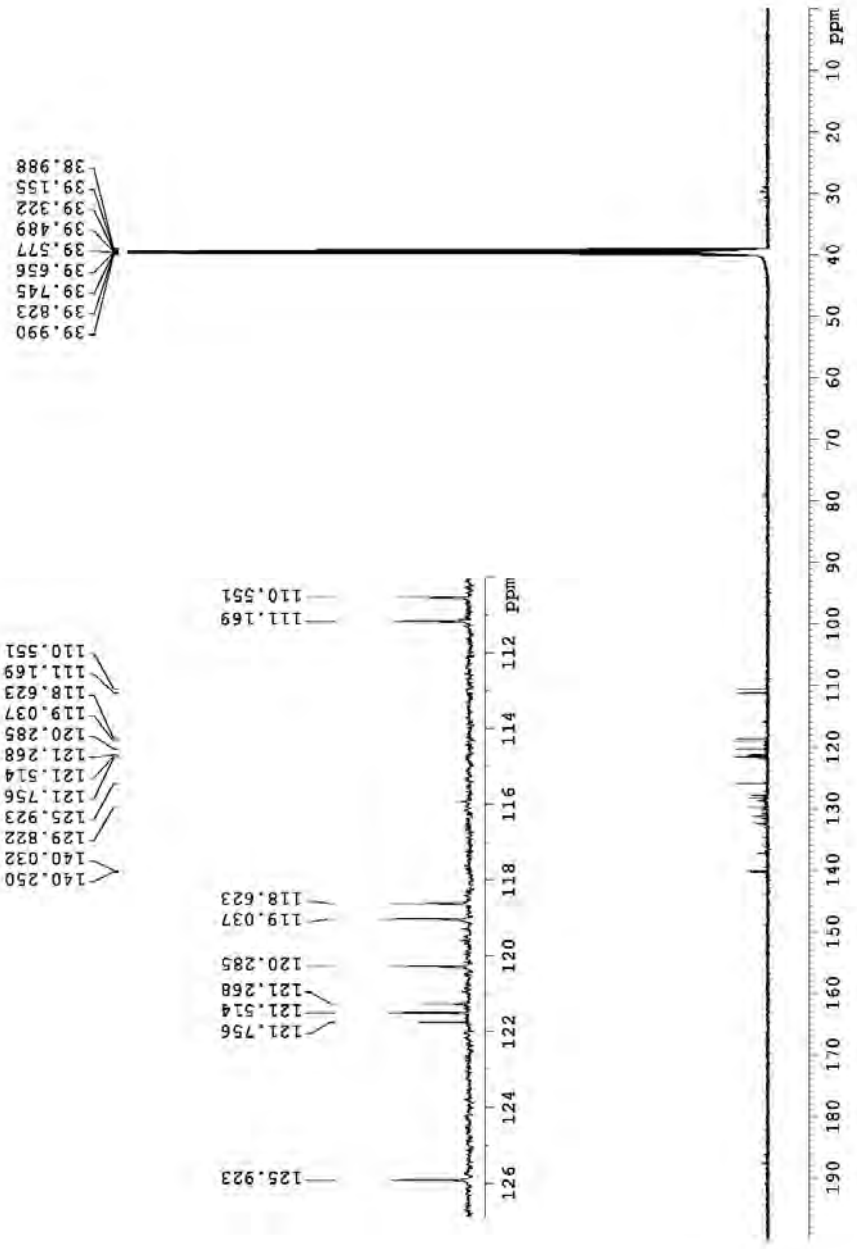
IR of 2-methoxy-9*H*-carbazole (4h)



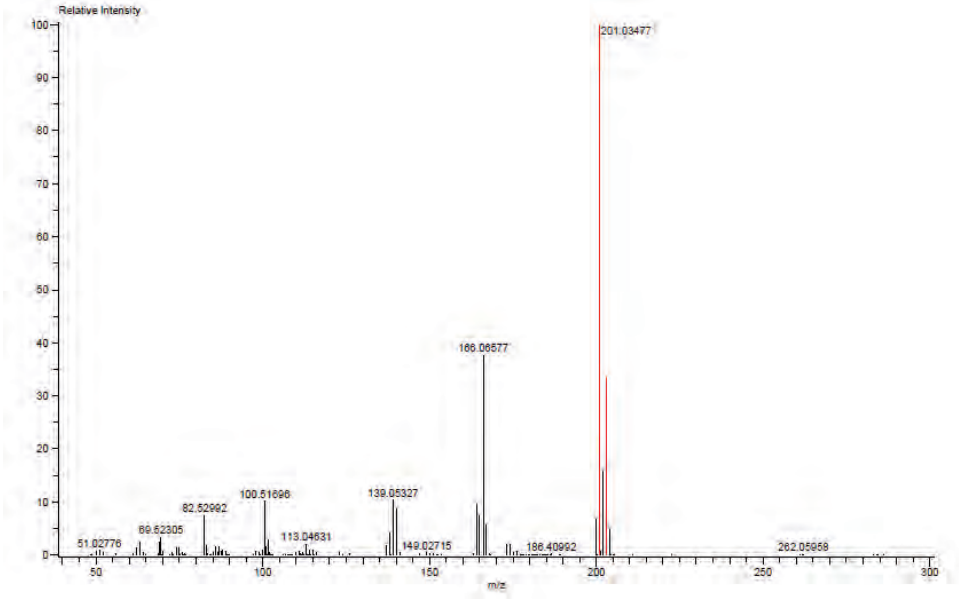
^{1}H-NMR of 2-chloro-9*H*-carbazole (4i) in $CDCl_3$



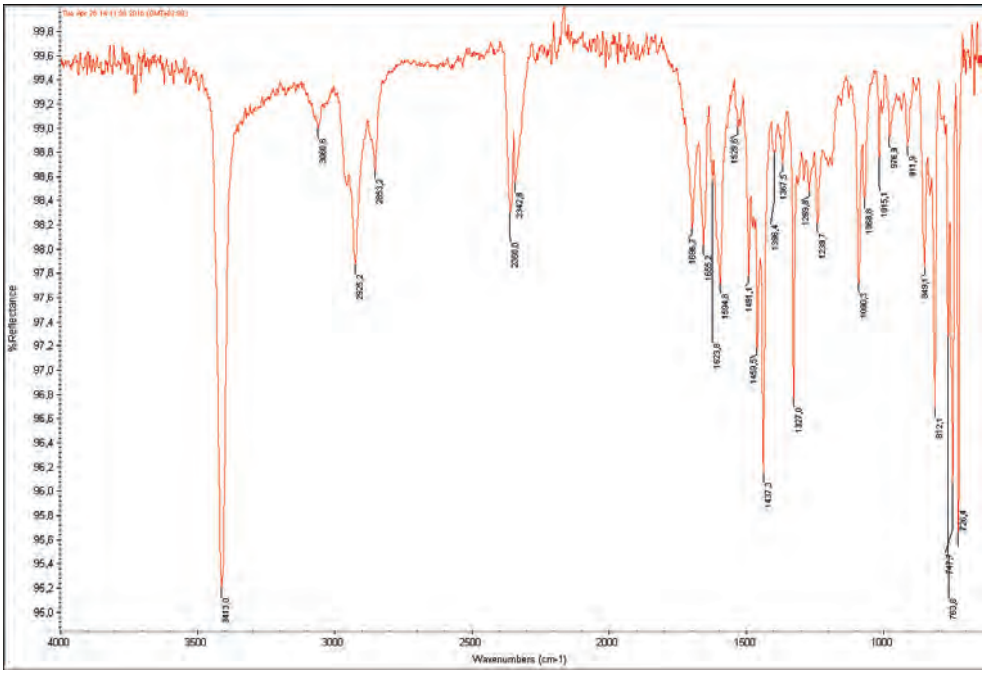
^{13}C-NMR of 2-chloro-9*H*-carbazole (4i) in DMSO-d$_6$



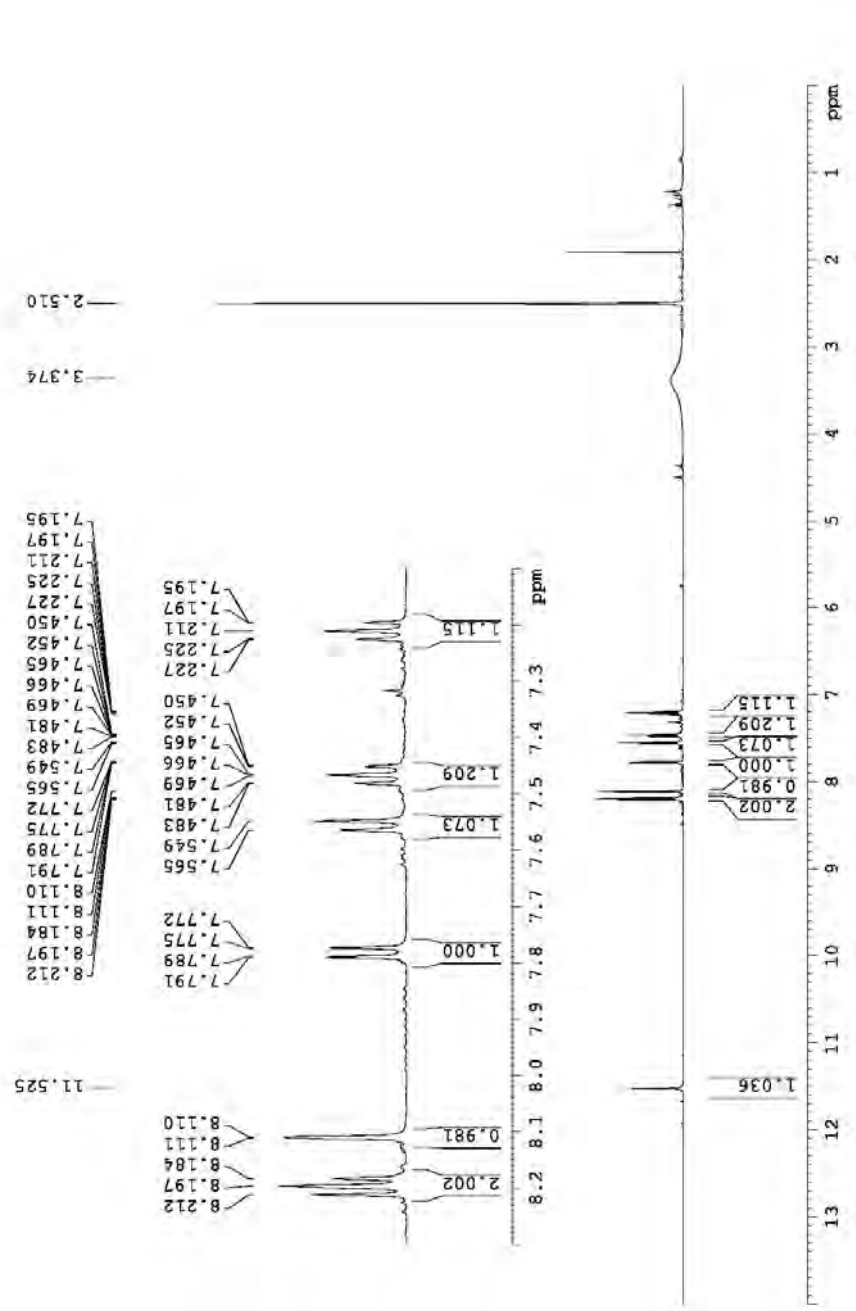
HRMS (EI) of 2-chloro-9*H*-carbazole (4i)



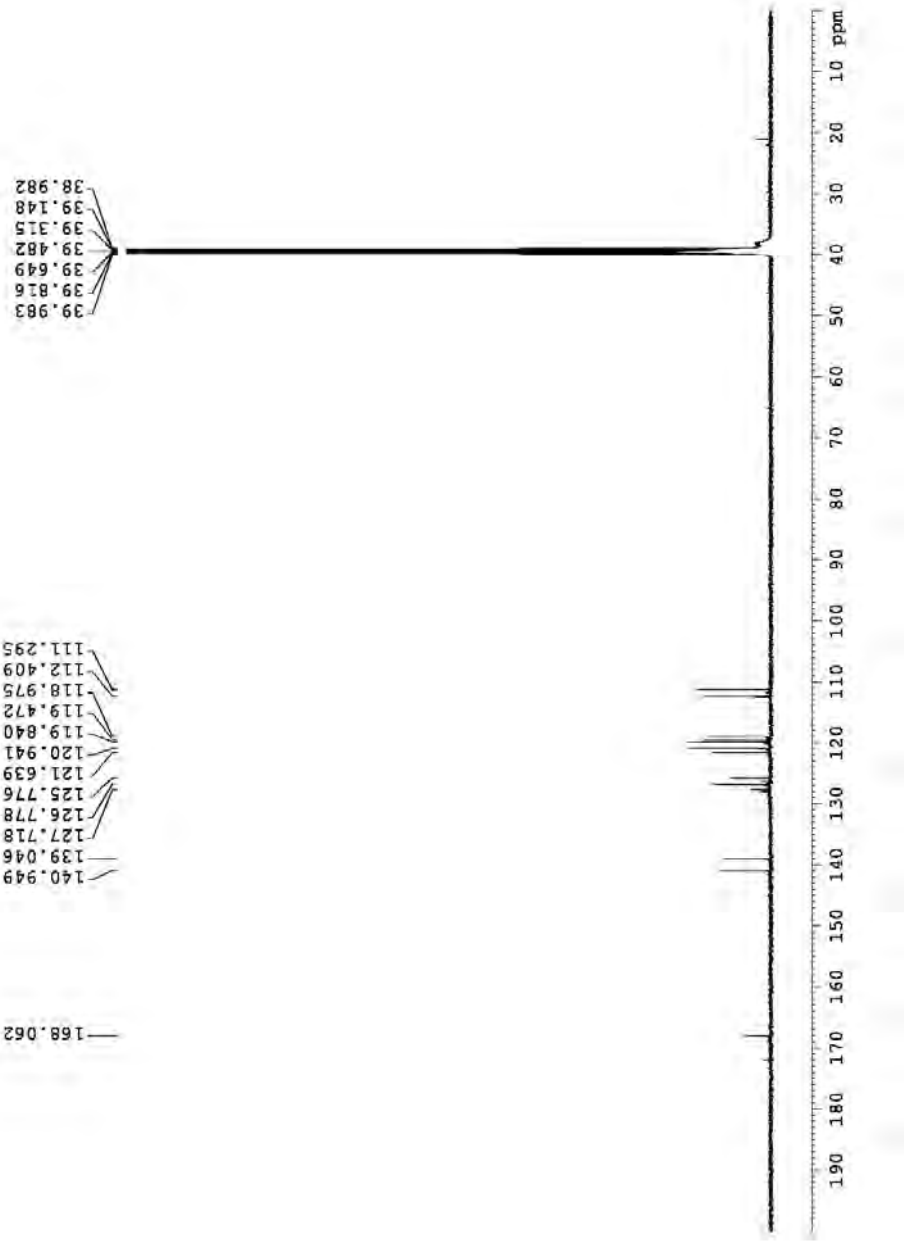
IR of 2-chloro-9*H*-carbazole (4i)



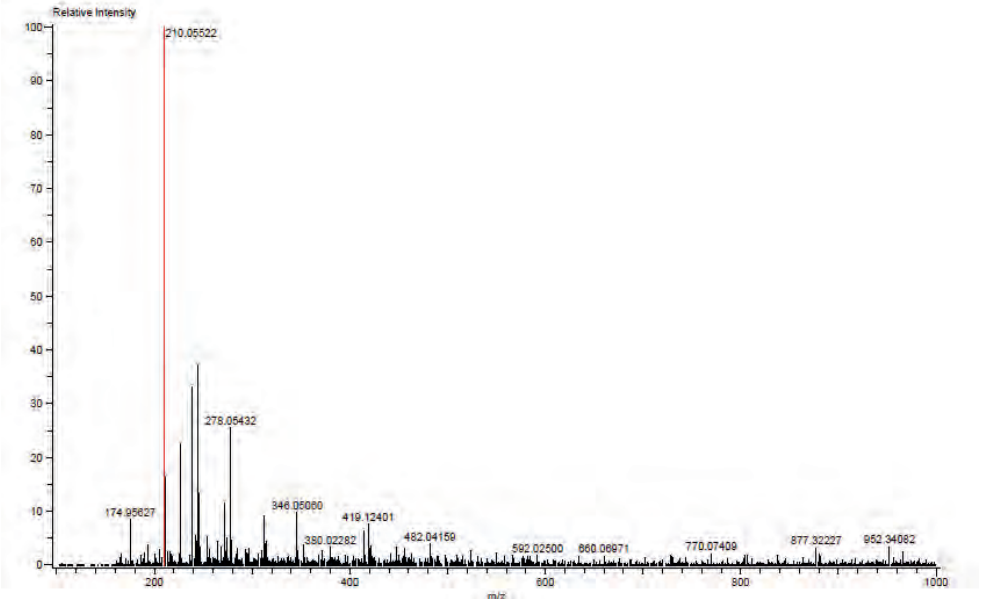
^{1}H-NMR of 9*H*-carbazole-2-carboxylic acid (4j) in DMSO-d_6



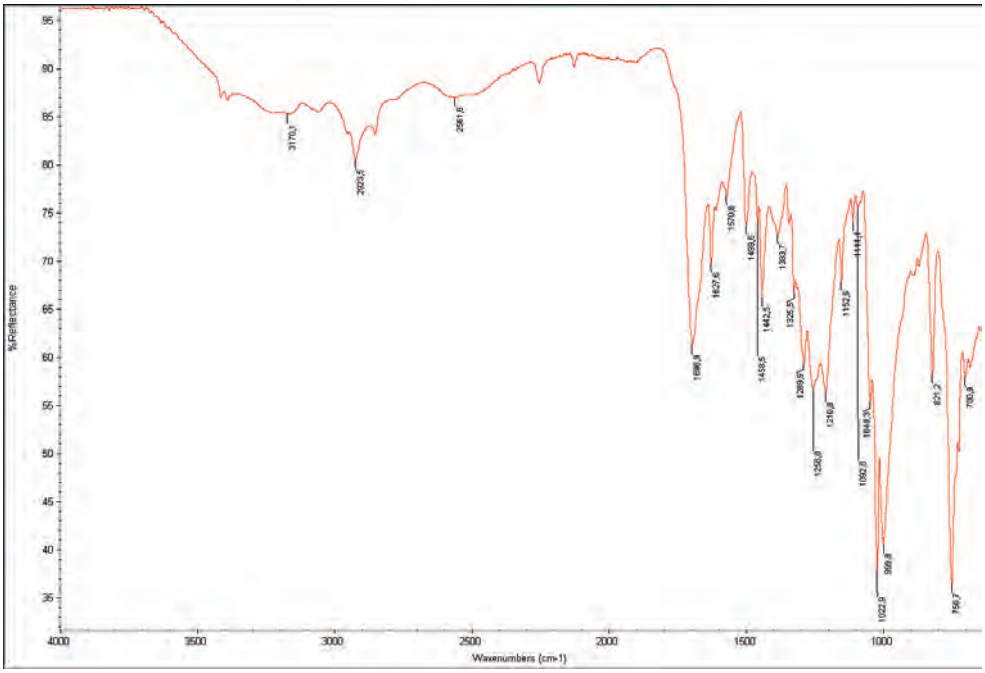
^{13}C-NMR of 9*H*-carbazole-2-carboxylic acid (4j) in DMSO-d_6



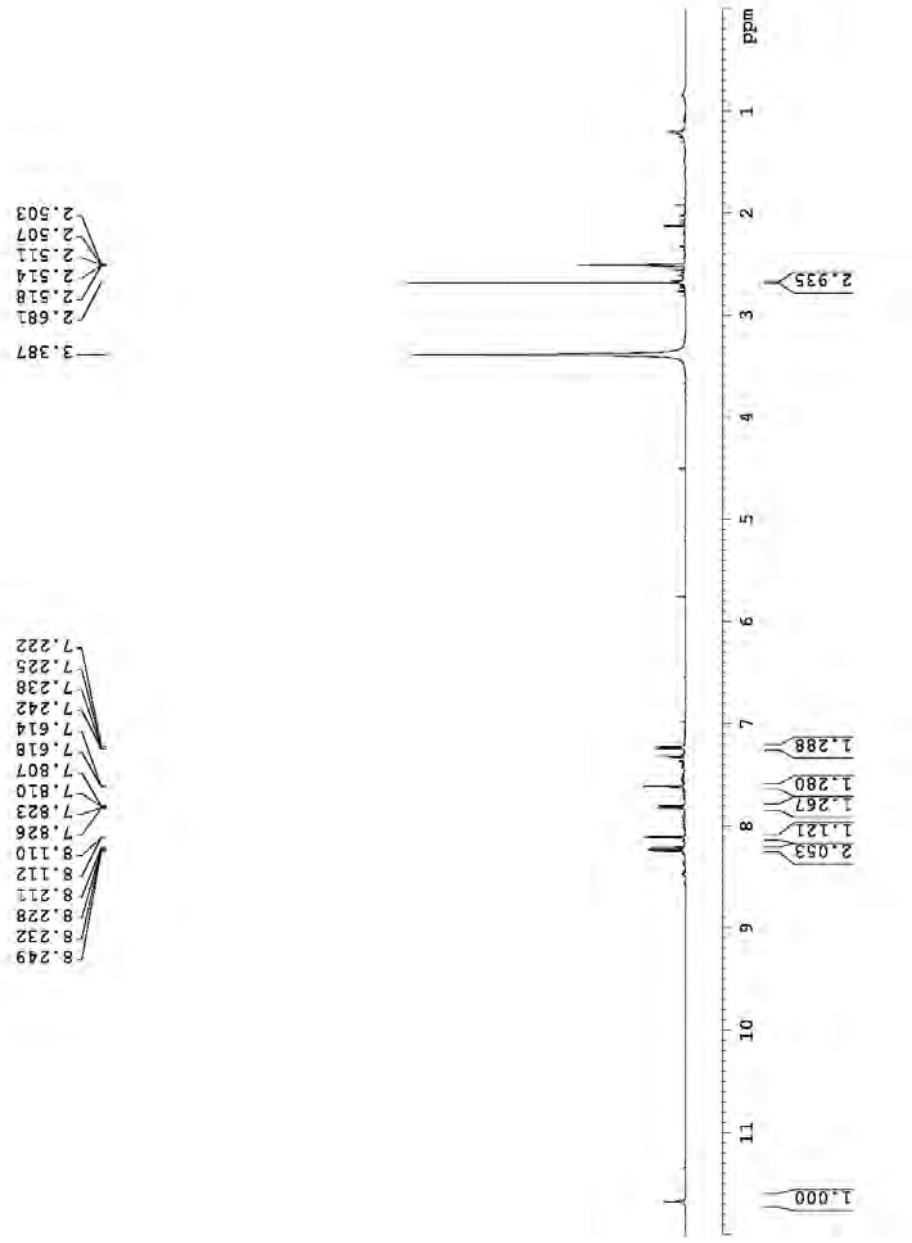
HRMS (DART-) of 9*H*-carbazole-2-carboxylic acid (4j)



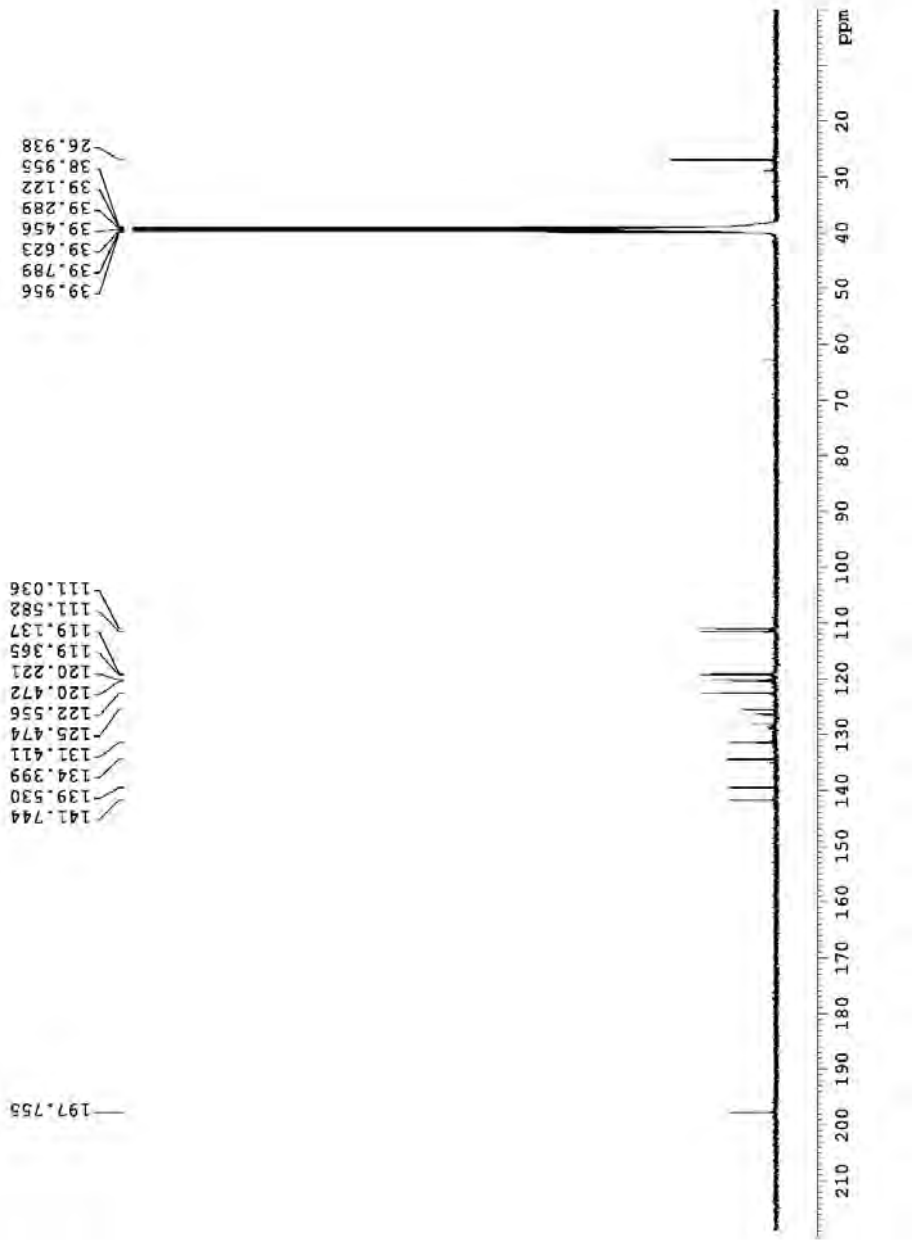
IR of 9*H*-carbazole-2-carboxylic acid (4j)



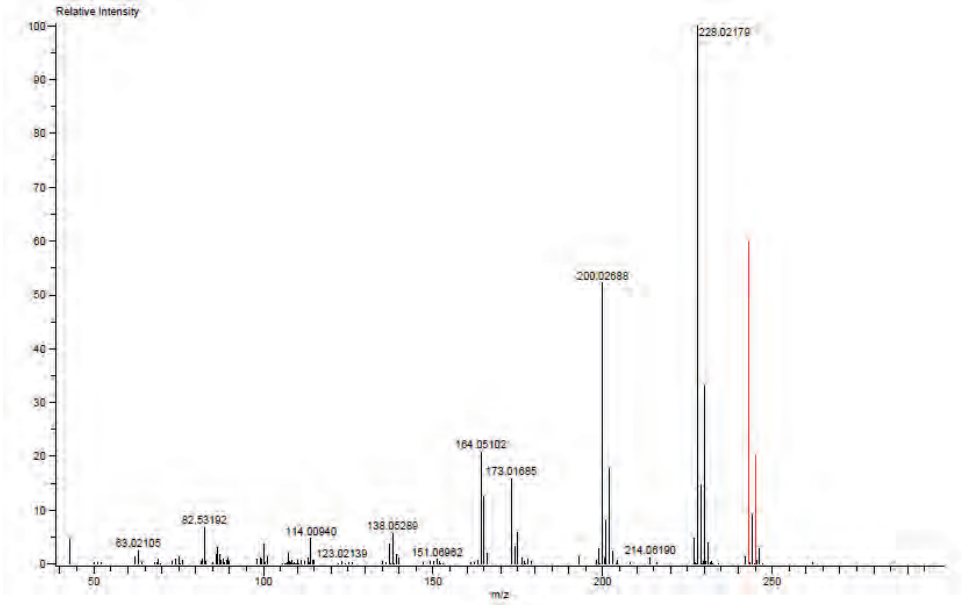
[1]H-NMR of 1-(7-chloro-9*H*-carbazol-2-yl) ethan-1-one (4k) in DMSO-d_6



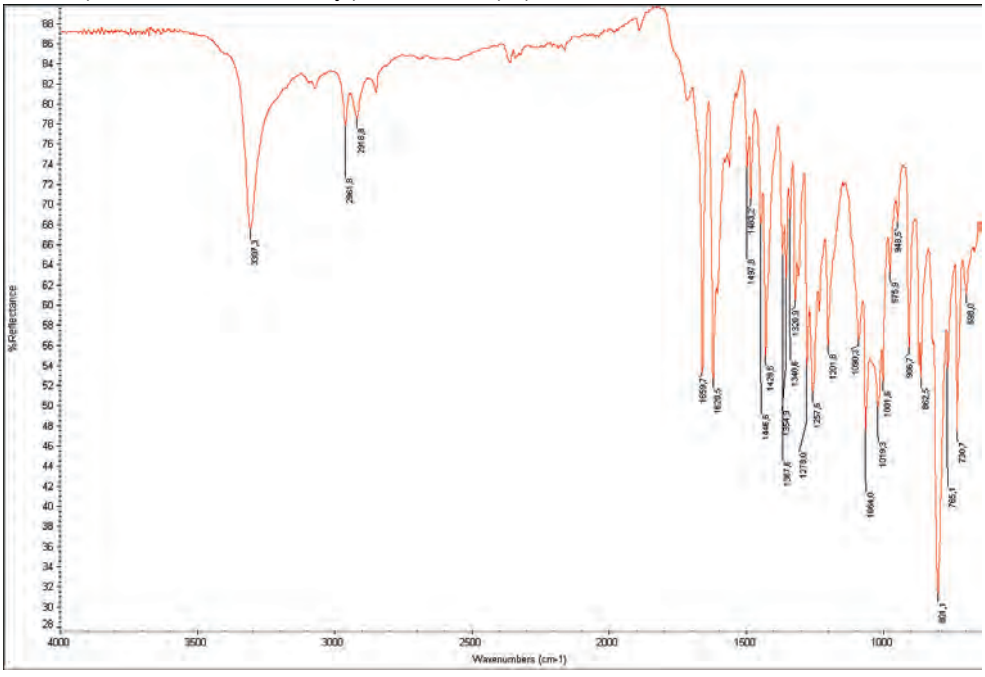
^{13}C-NMR of 1-(7-chloro-9*H*-carbazol-2-yl) ethan-1-one (4k) in DMSO-d$_6$



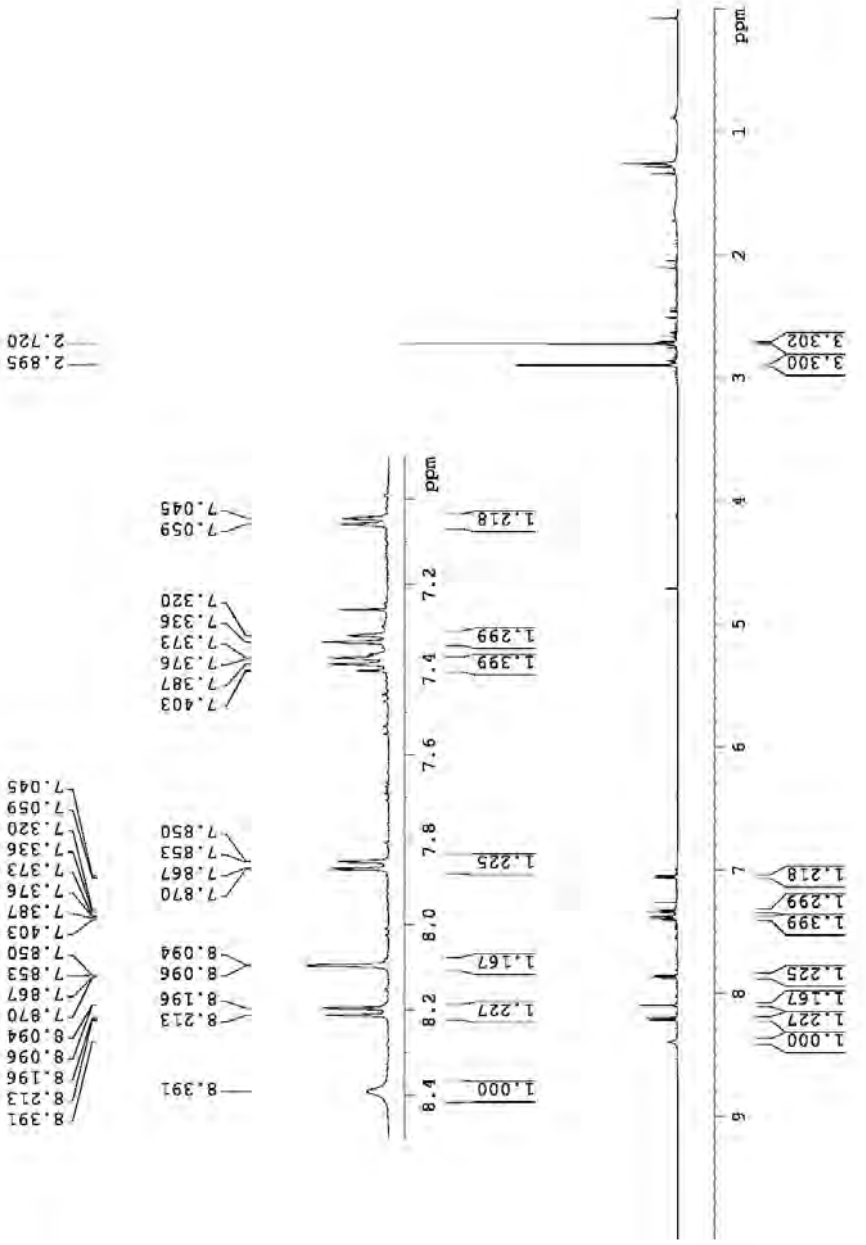
HRMS (EI) of 1-(7-chloro-9*H*-carbazol-2-yl) ethan-1-one (4k)



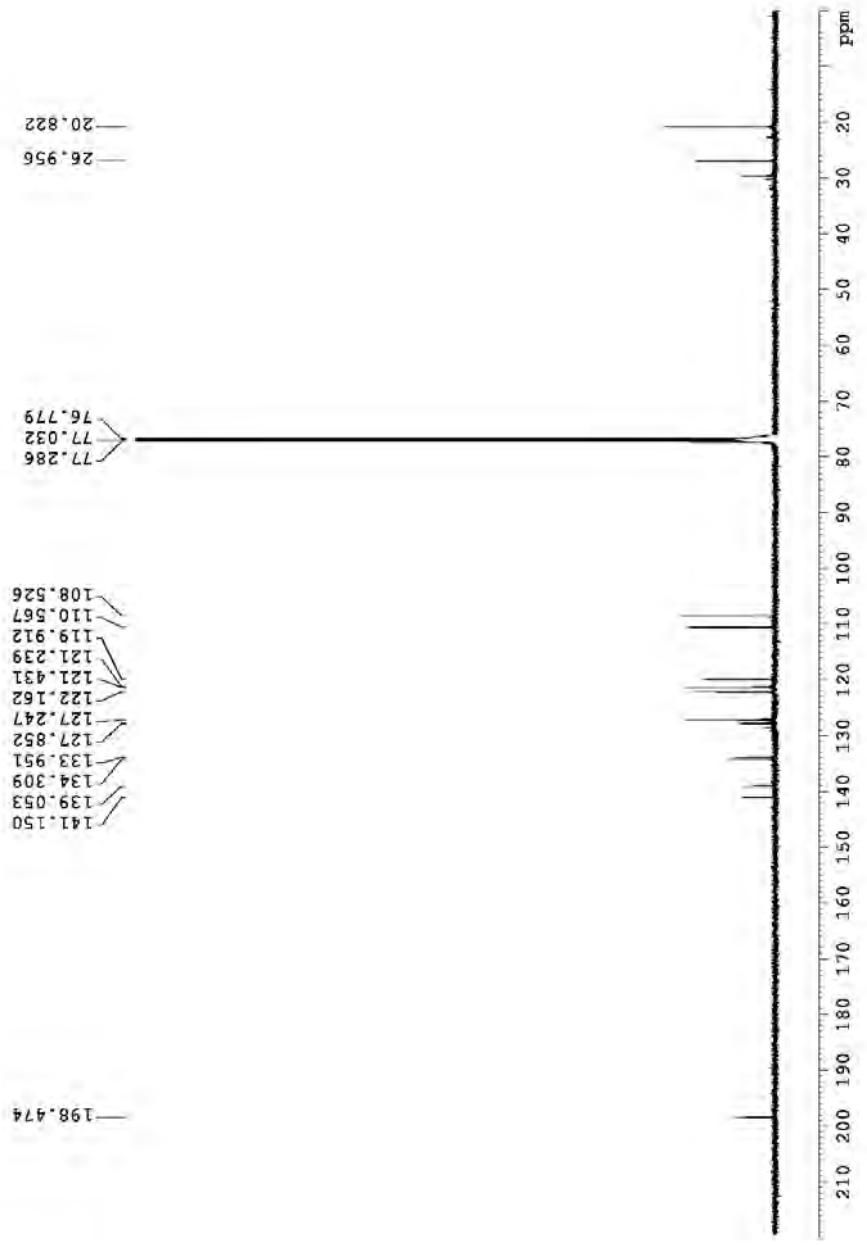
IR of 1-(7-chloro-9*H*-carbazol-2-yl) ethan-1-one (4k)



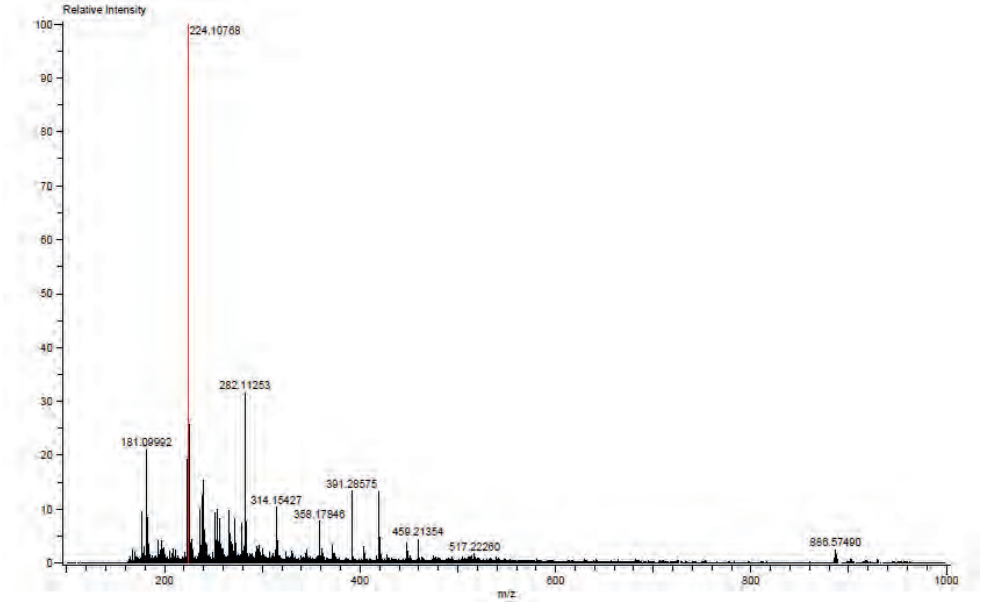
^{1}H-NMR of 1-(5-methyl-9*H*-carbazol-2-yl) ethan-1-one (4l) in $CDCl_3$



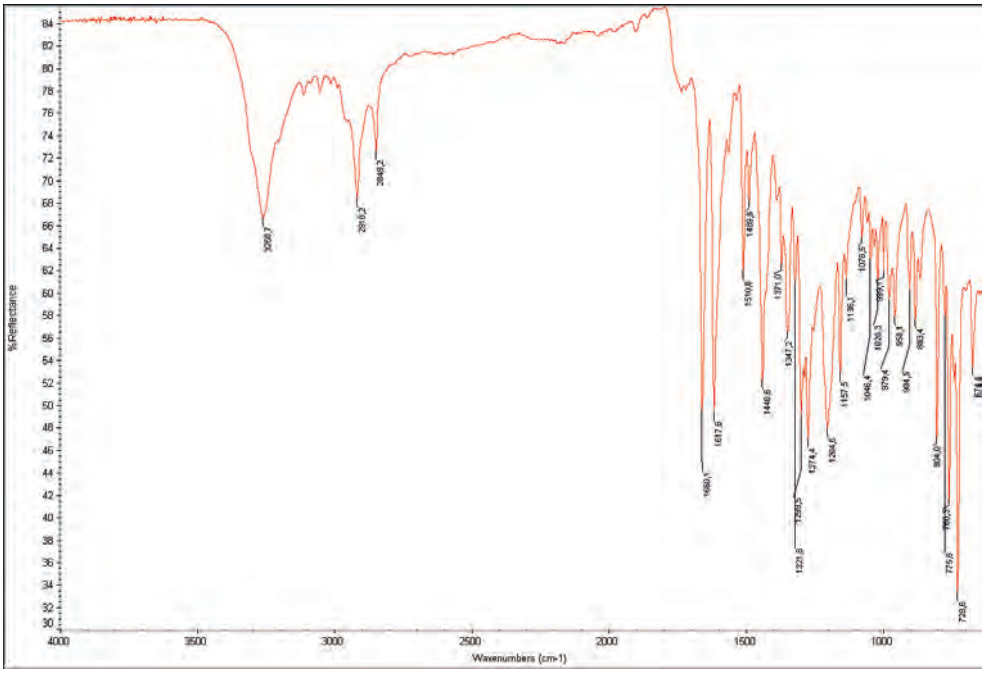
^{13}C-NMR of 1-(5-methyl-9*H*-carbazol-2-yl) ethan-1-one (4l) in $CDCl_3$



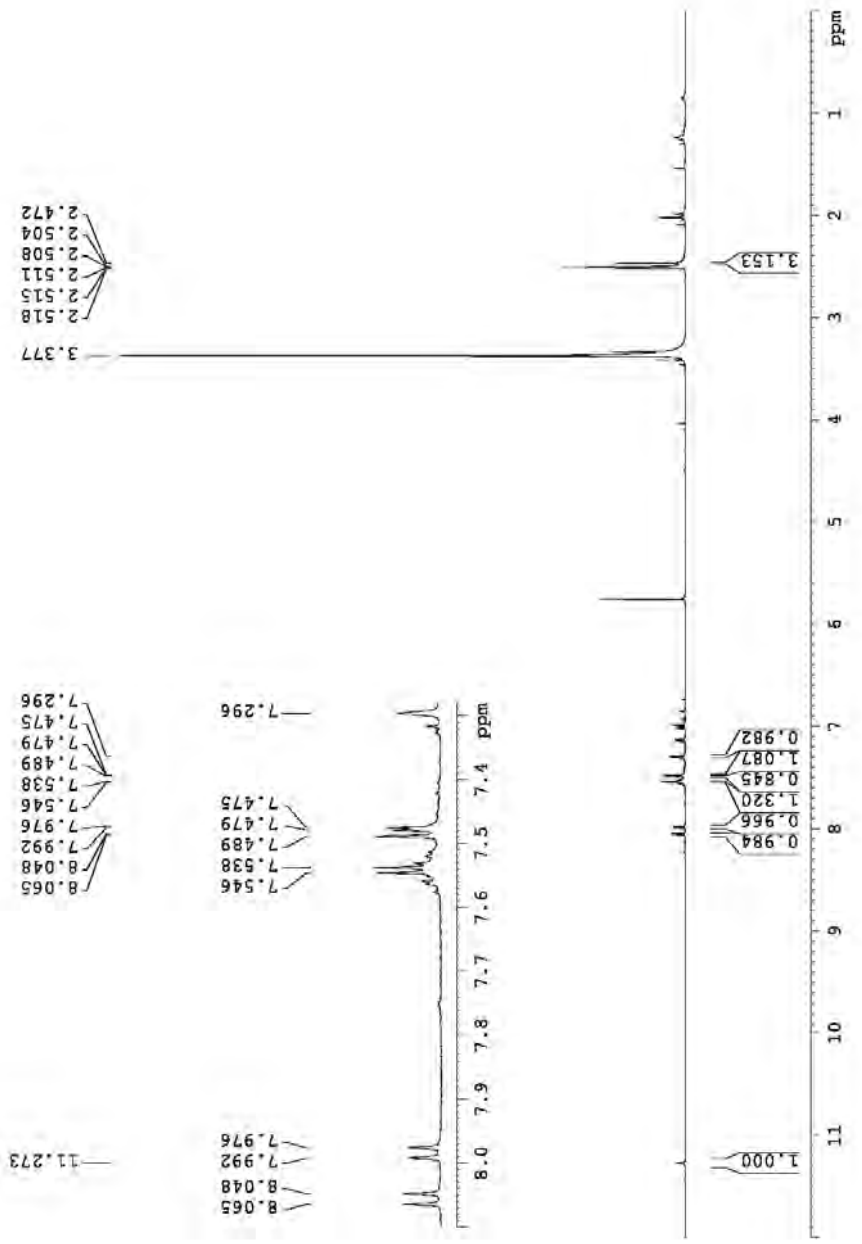
HRMS (DART+) of 1-(5-methyl-9*H*-carbazol-2-yl) ethan-1-one (4l)



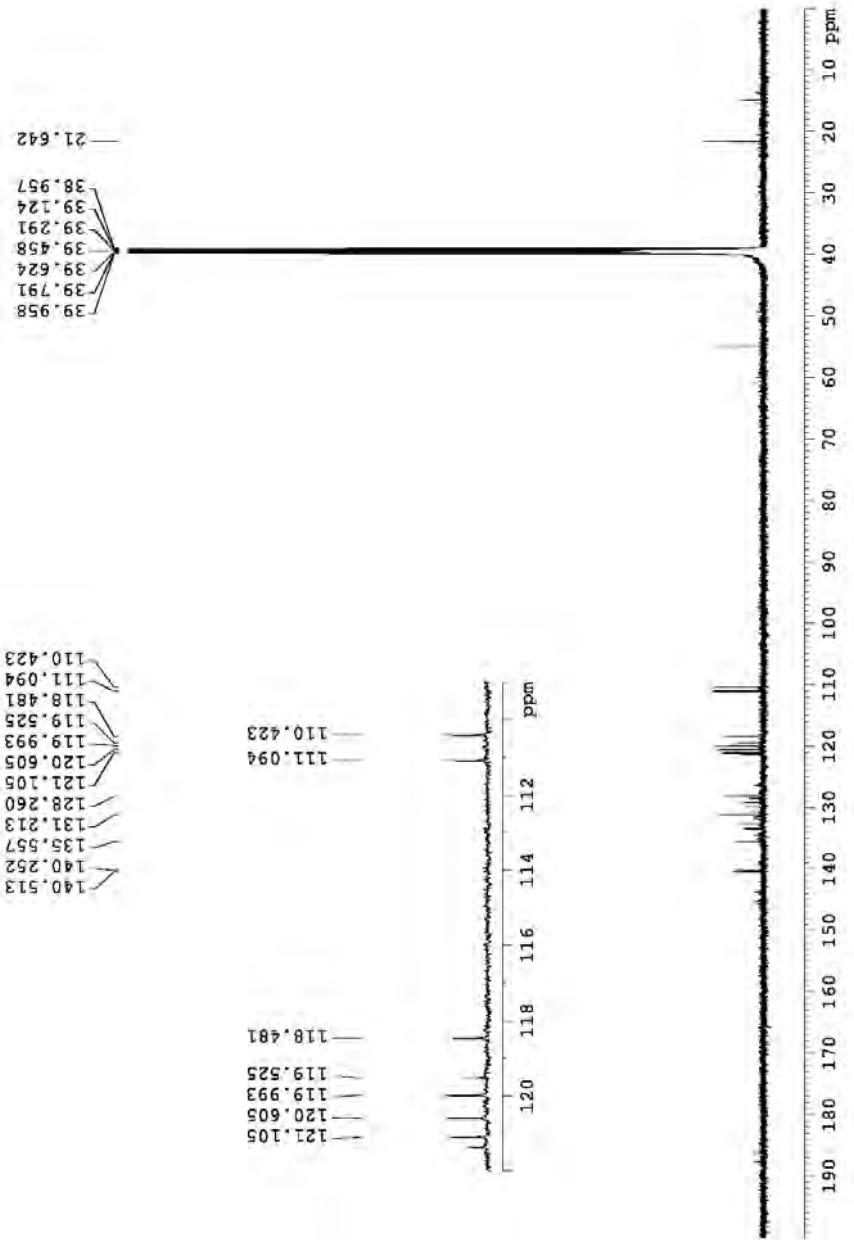
IR of 1-(5-methyl-9*H*-carbazol-2-yl) ethan-1-one (4l)



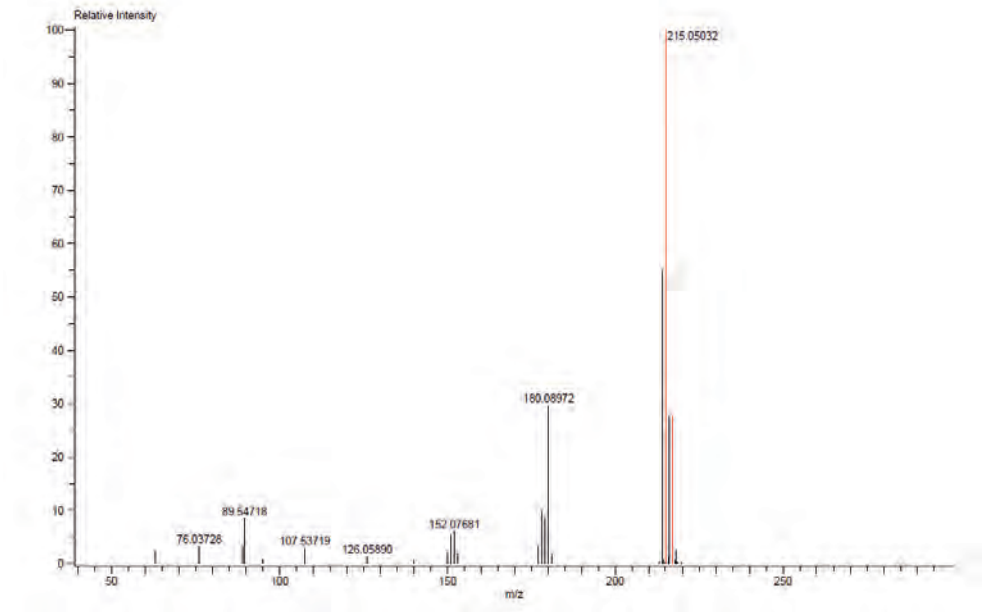
[1]H-NMR of 2-chloro-7-methyl-9*H*-carbazole (4m) in DMSO-d_6



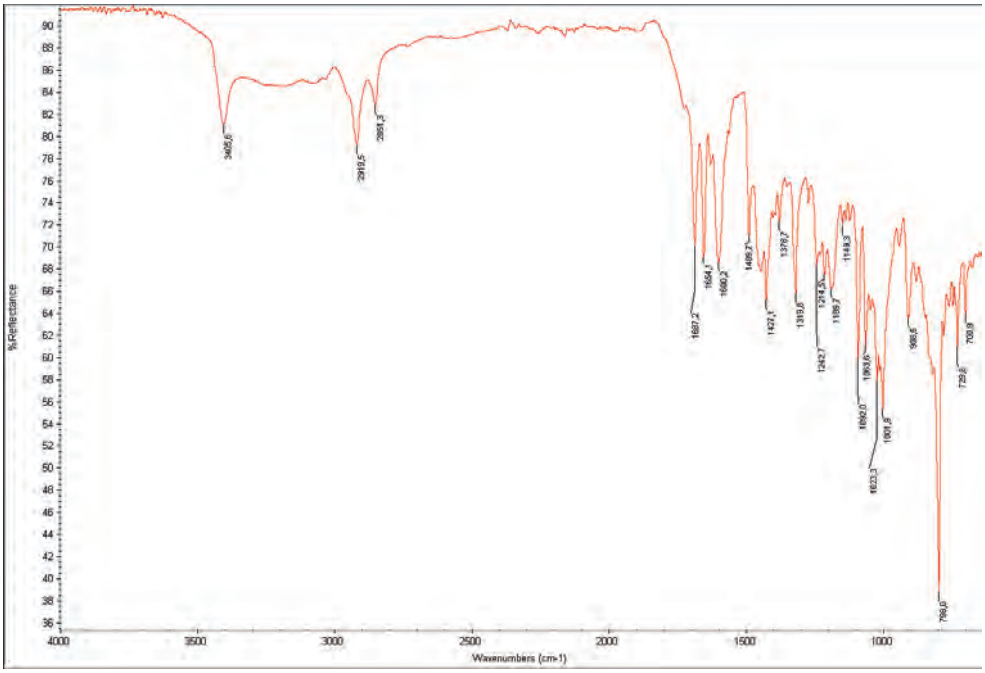
^{13}C-NMR of 2-chloro-7-methyl-9*H*-carbazole (4m) in DMSO-d$_6$



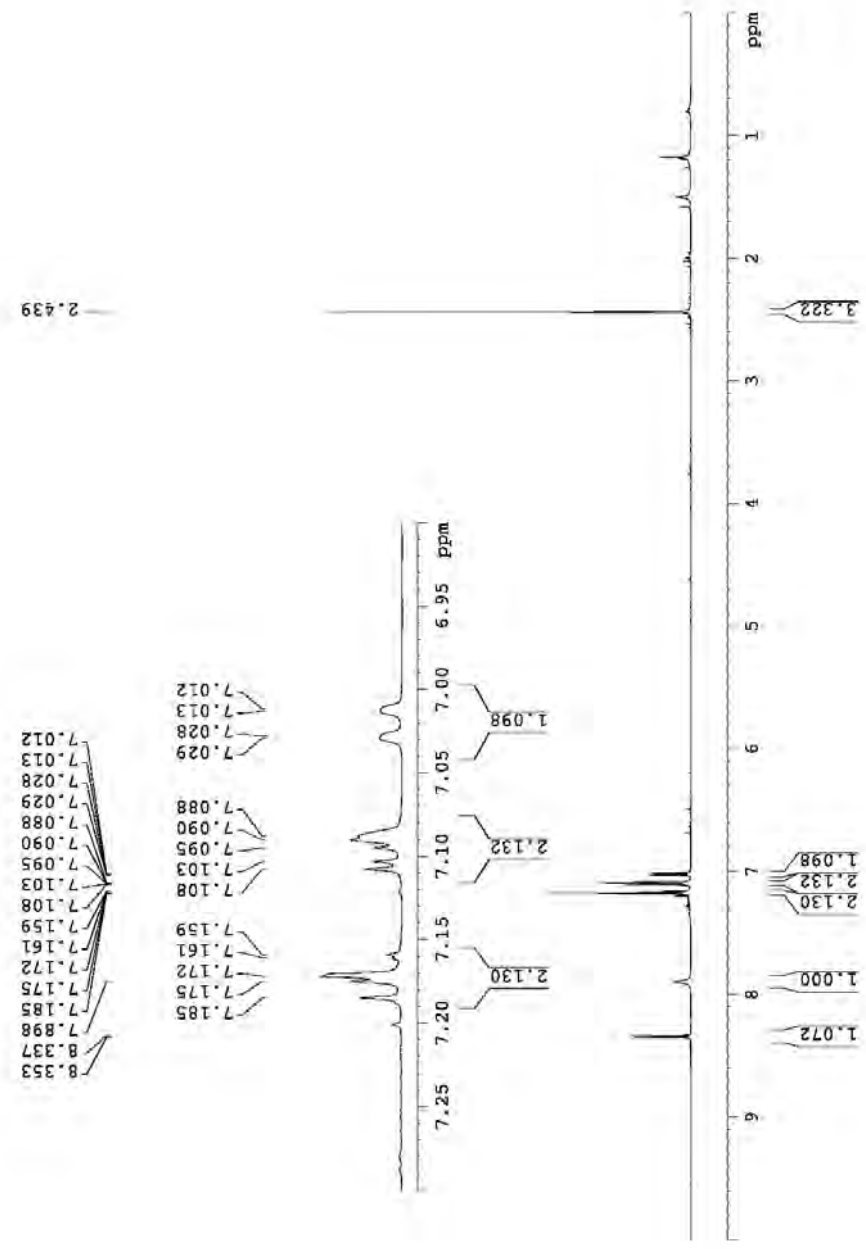
HRMS (EI) of 2-chloro-7-methyl-9*H*-carbazole (4m)



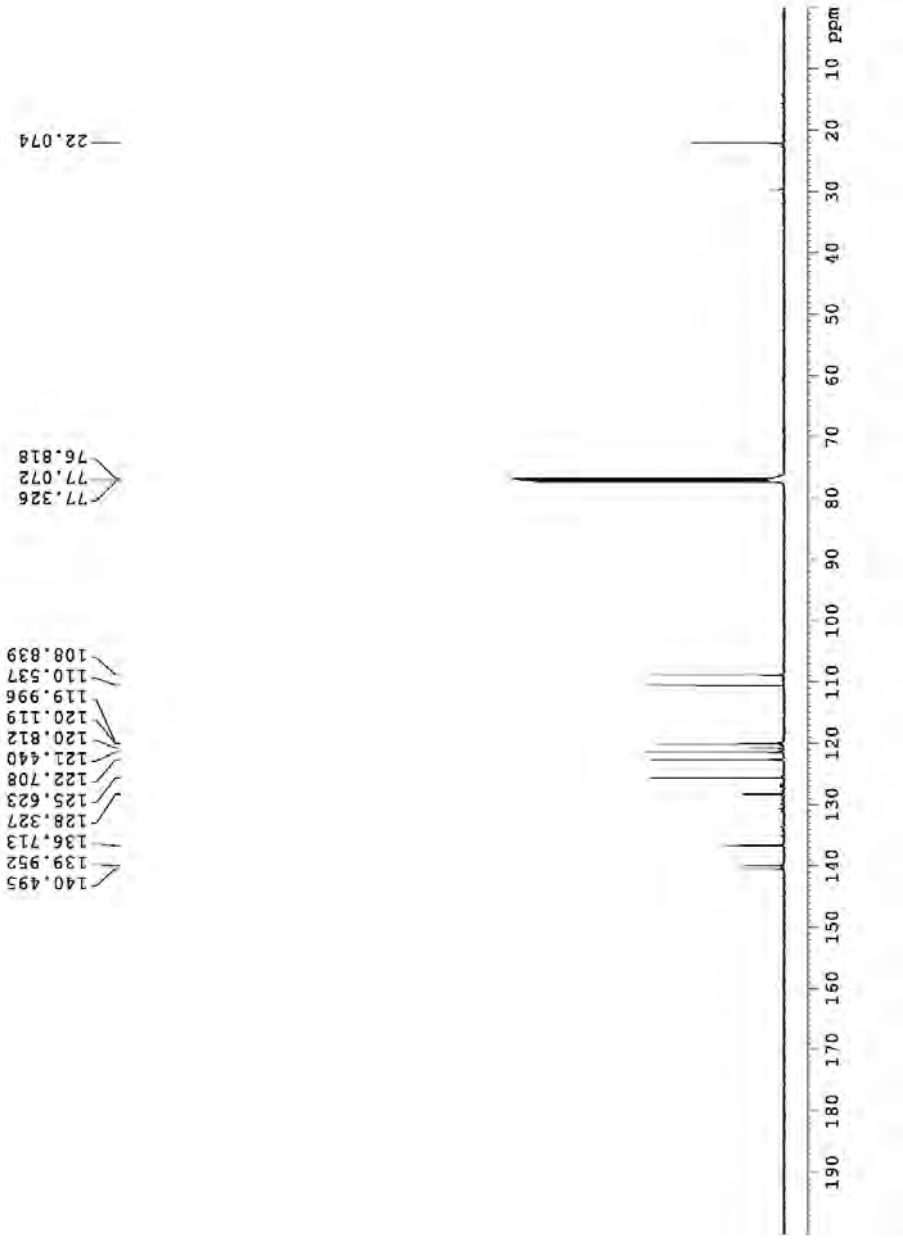
IR of 2-chloro-7-methyl-9*H*-carbazole (4m)



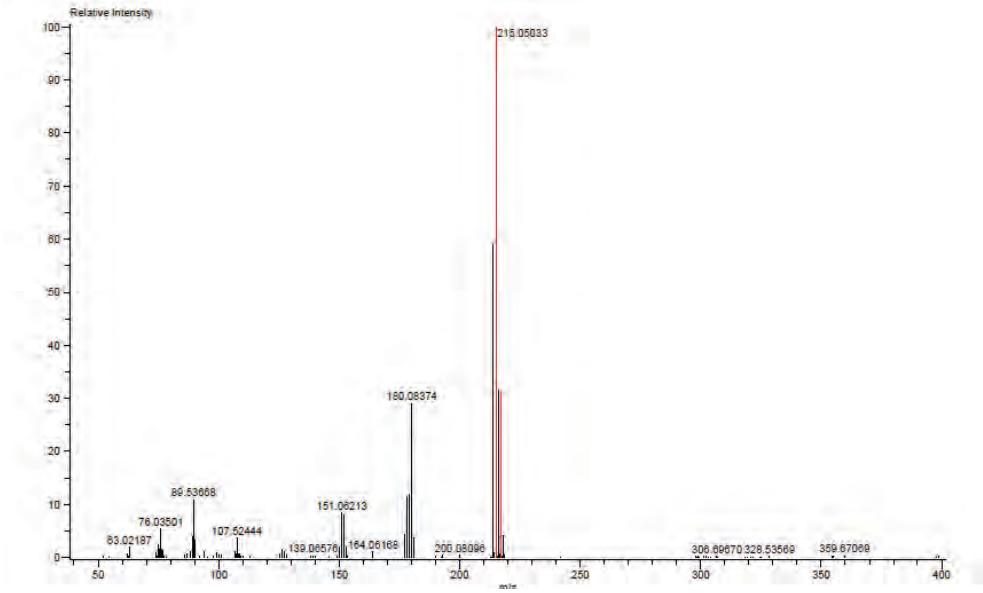
^{1}H-NMR of 5-chloro-2-methyl-9*H*-carbazole (4n) in $CDCl_3$



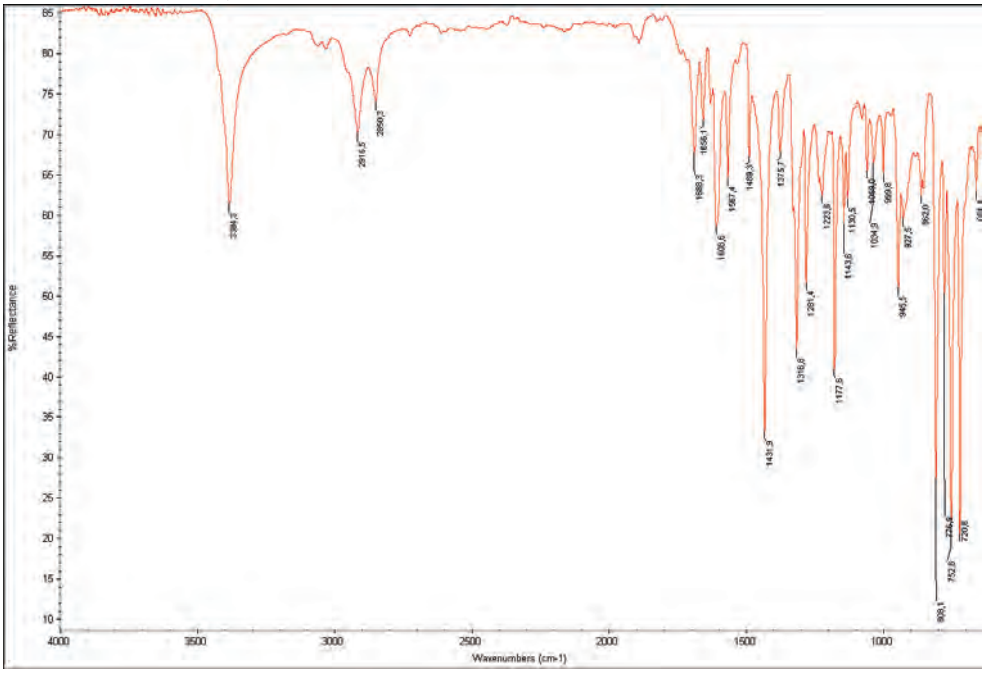
^{13}C-NMR of 5-chloro-2-methyl-9*H*-carbazole (4n) in $CDCl_3$



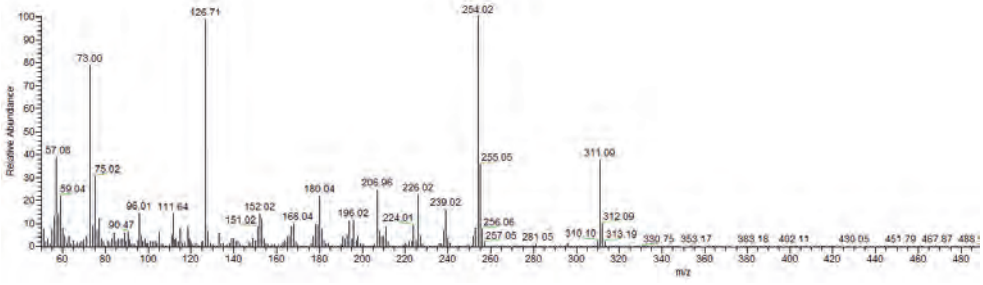
HRMS (EI) of 5-chloro-2-methyl-9*H*-carbazole (4n)



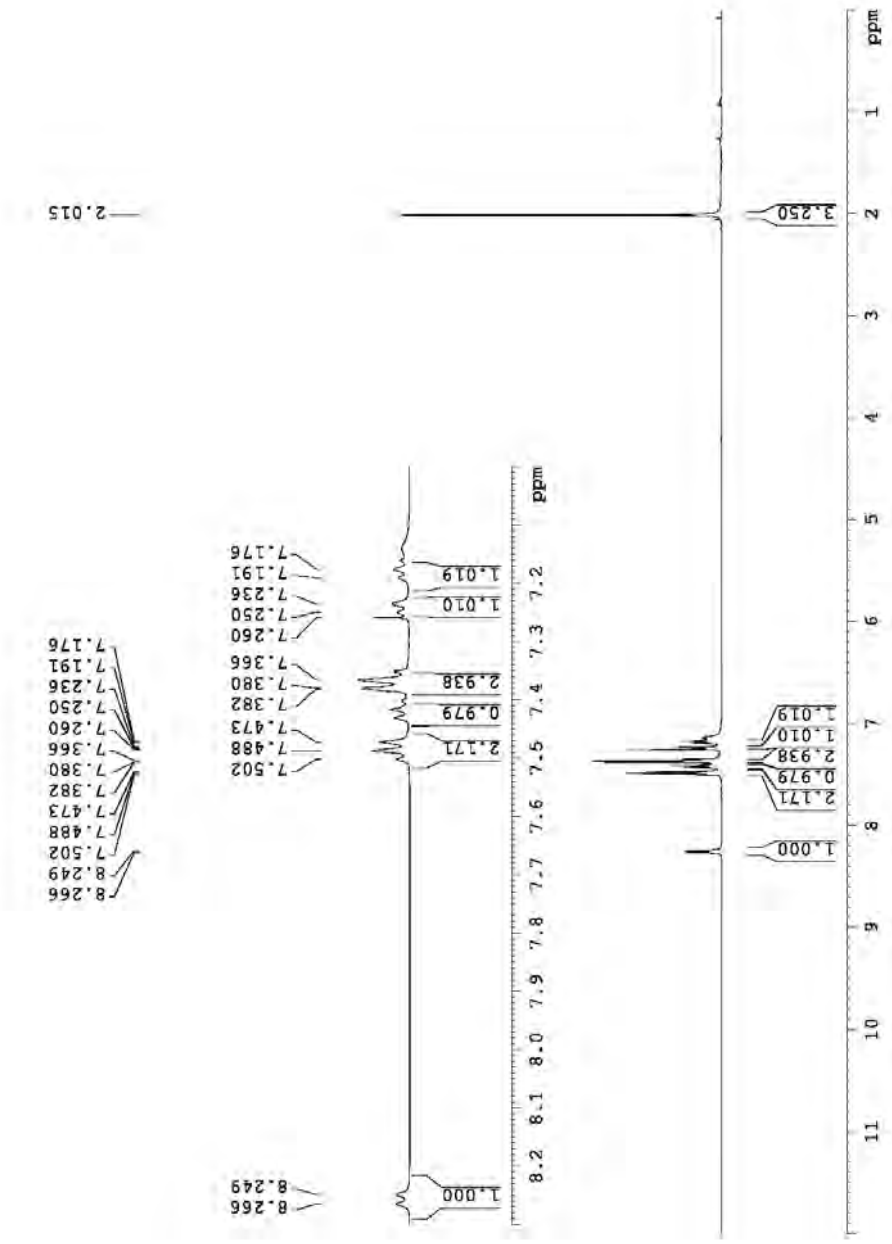
IR of 5-chloro-2-methyl-9*H*-carbazole (4n)



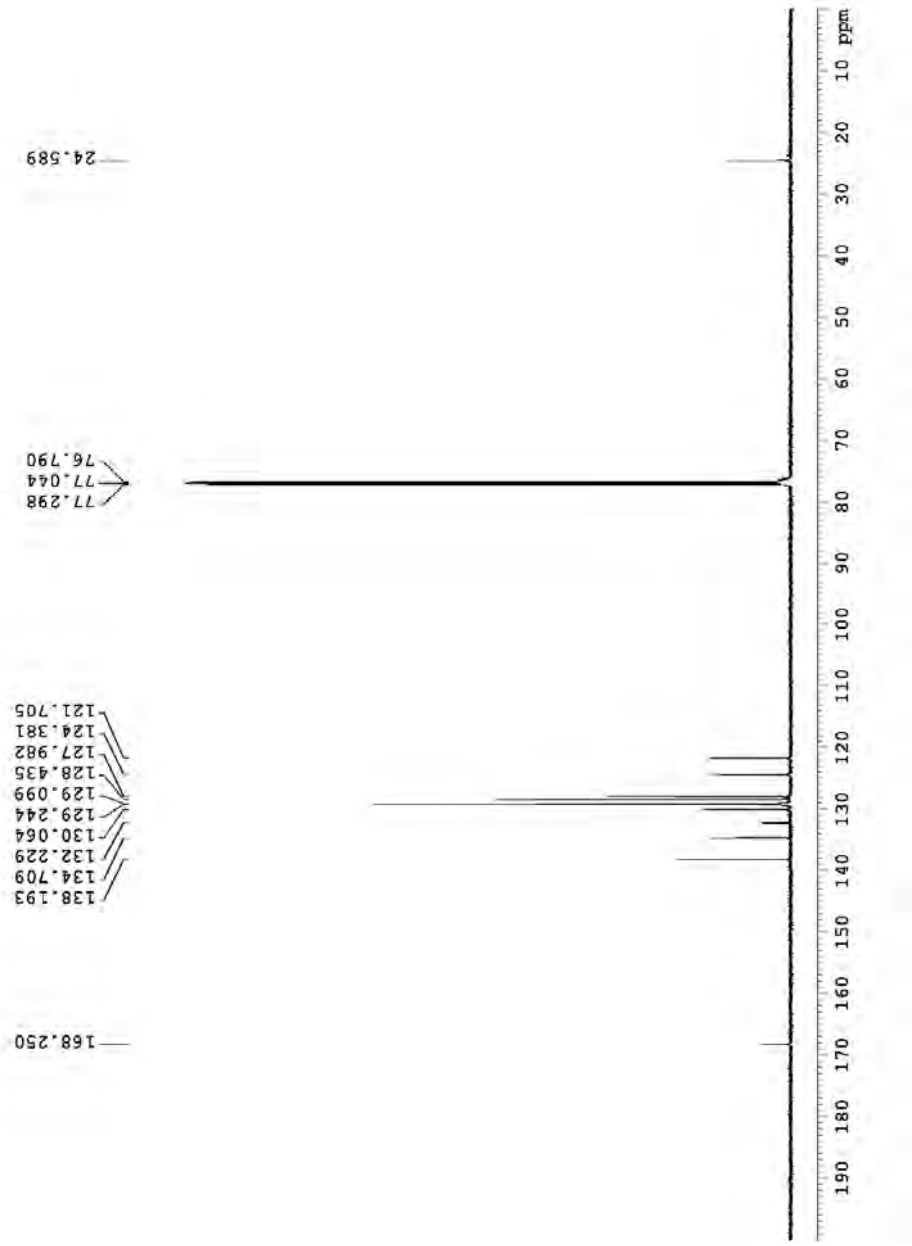
MS (EI) of 2-((tert-butyldimethylsilyl) oxy)-7-methyl-9*H*-carbazole (4o)



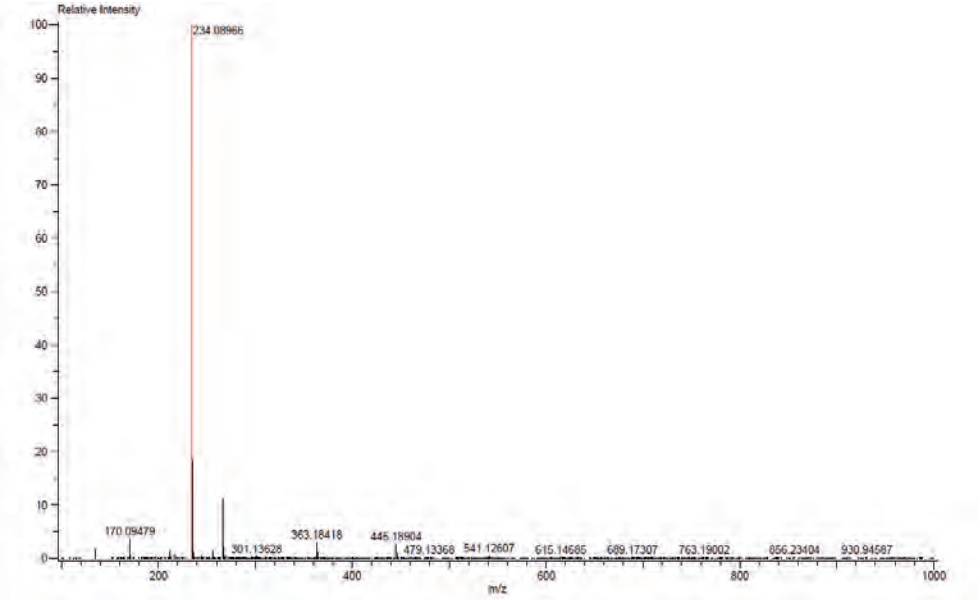
^{1}H-NMR of N-([1, 1'-biphenyl]-2-yl) acetamide (2a) in $CDCl_3$



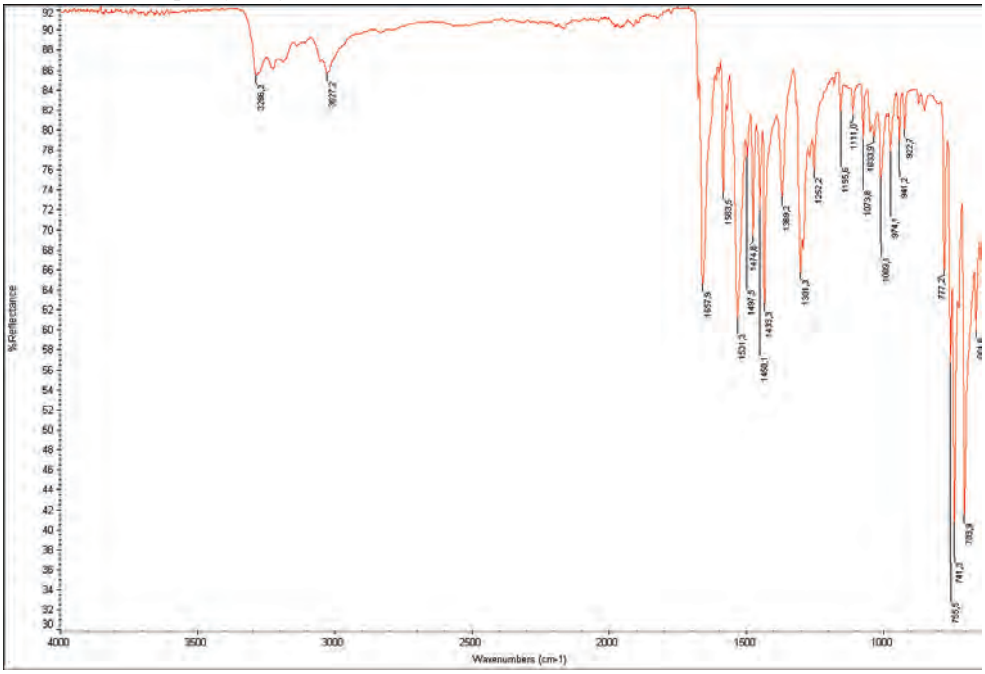
^{13}C-NMR of N-([1, 1'-biphenyl]-2-yl) acetamide (2a) in $CDCl_3$



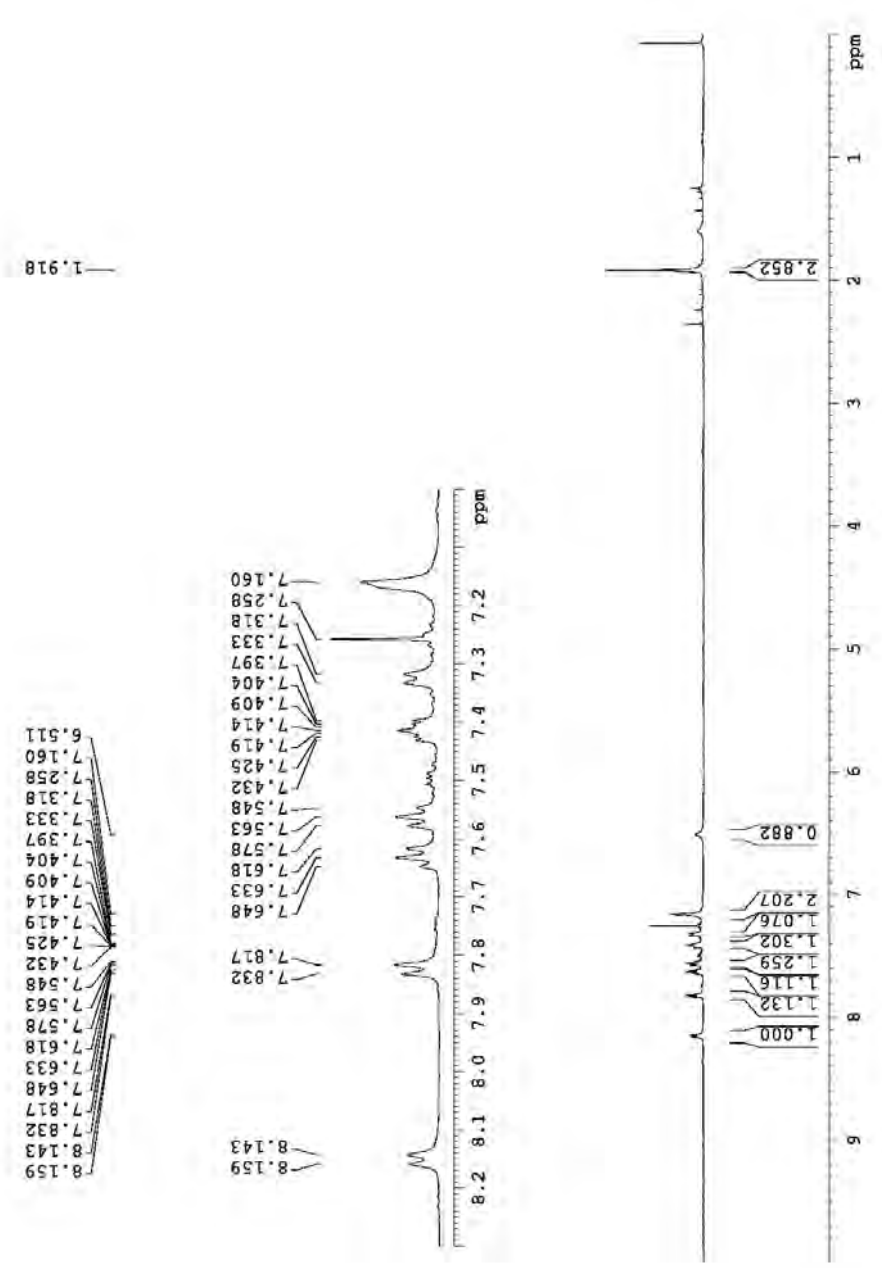
HRMS (ESI) of N-([1, 1'-biphenyl]-2-yl) acetamide (2a)



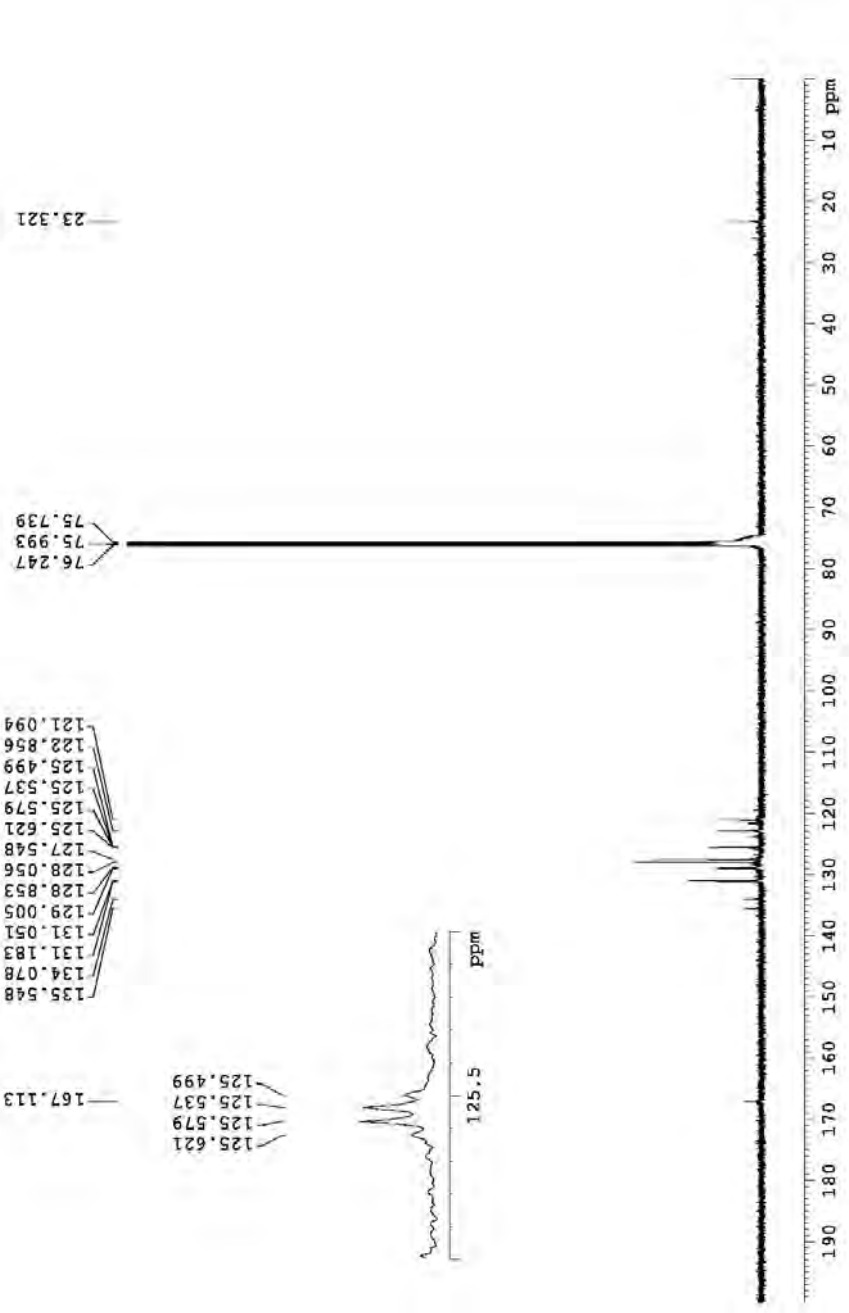
IR of N-([1, 1'-biphenyl]-2-yl) acetamide (2a)



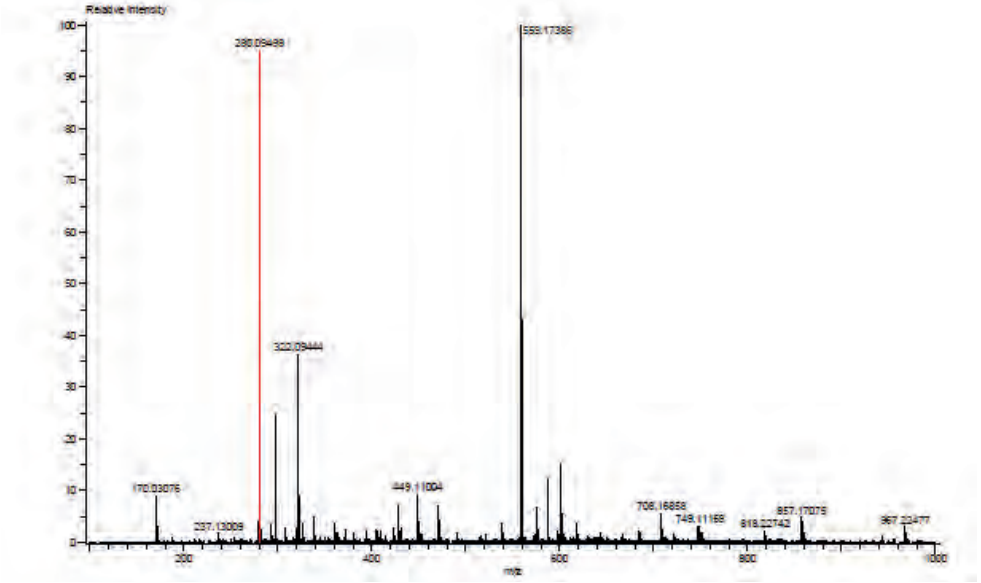
^{1}H-NMR of *N*-(2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-yl)acetamide(2b) in $CDCl_3$



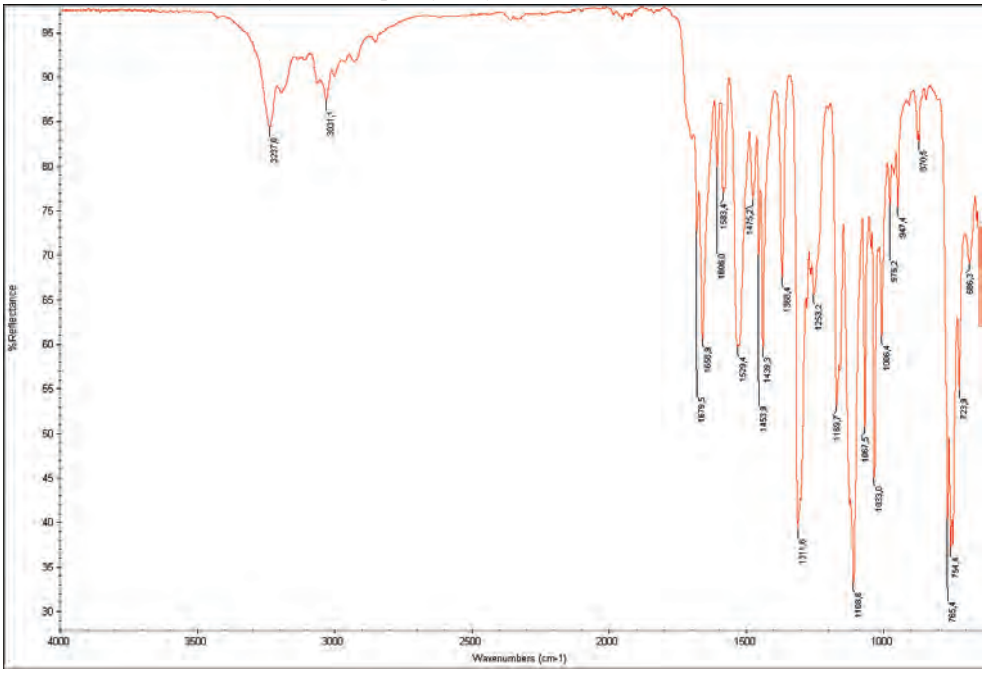
^{13}C-NMR of *N*-(2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-yl)acetamide(2b) in $CDCl_3$



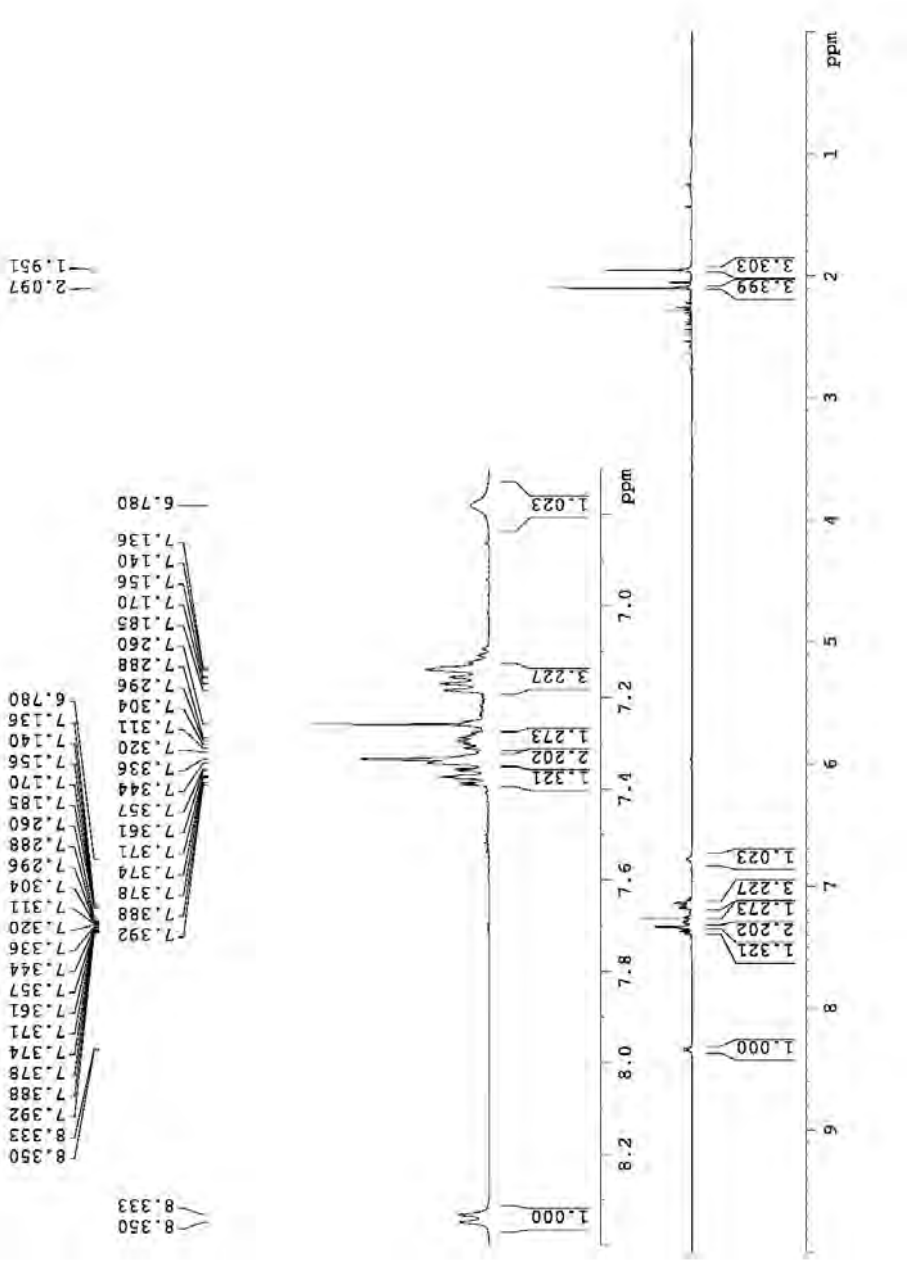
HRMS (DART+) of *N*-(2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-yl)acetamide(2b)



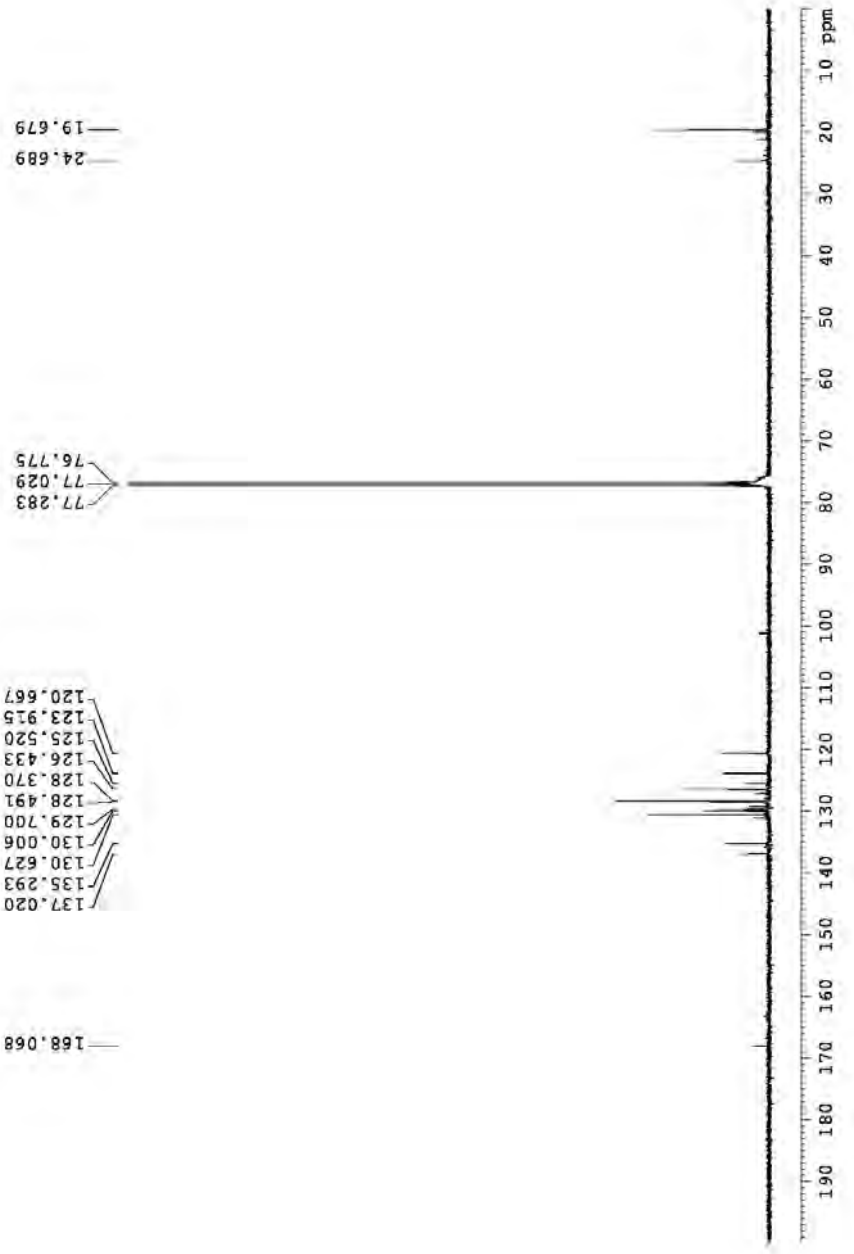
IR of *N*-(2'-(trifluoromethyl)-[1, 1'-biphenyl]-2-yl)acetamide(2b)



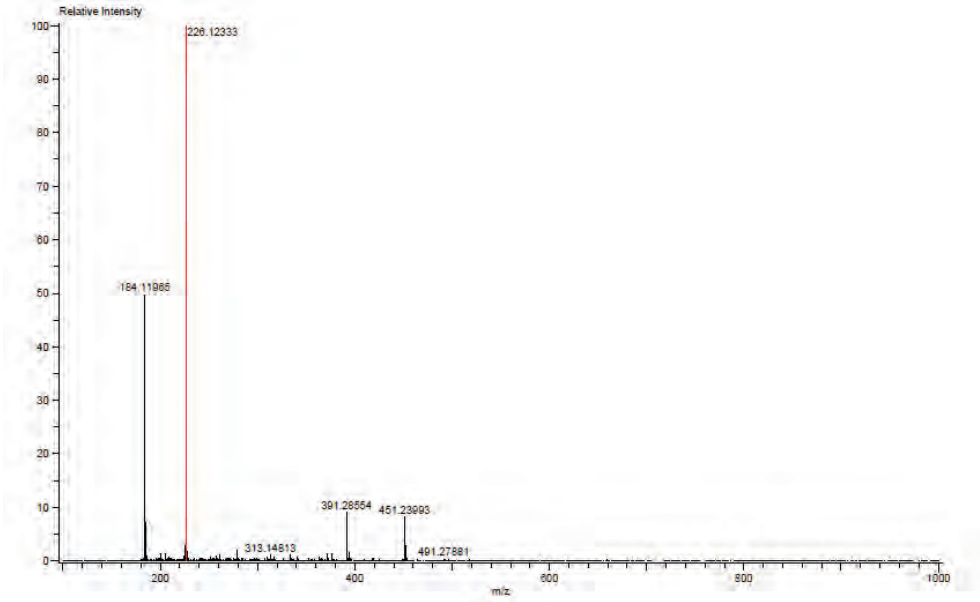
^{1}H-NMR of N-(2'-methyl-[1, 1'-biphenyl]-2-yl)acetamide (2c) in $CDCl_3$



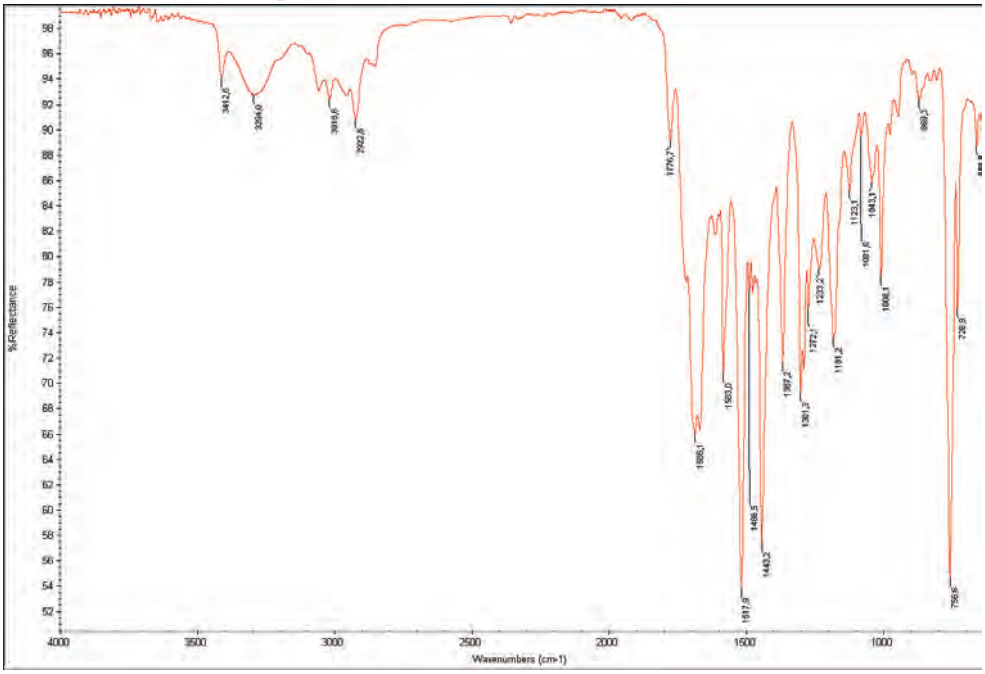
^{13}C-NMR of N-(2'-methyl-[1, 1'-biphenyl]-2-yl)acetamide (2c) in $CDCl_3$



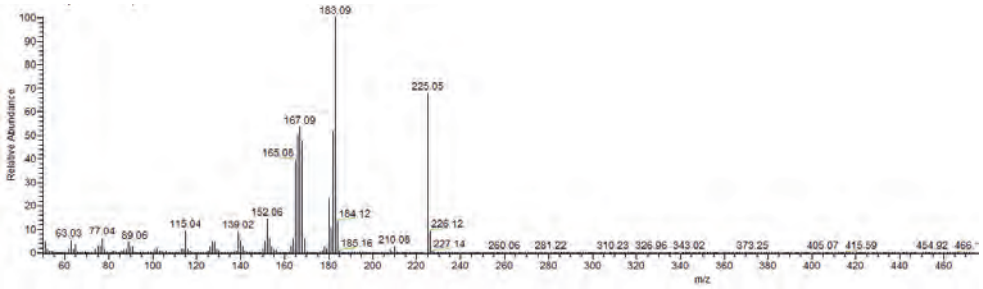
HRMS (DART+) of N-(2'-methyl-[1, 1'-biphenyl]-2-yl)acetamide (2c)



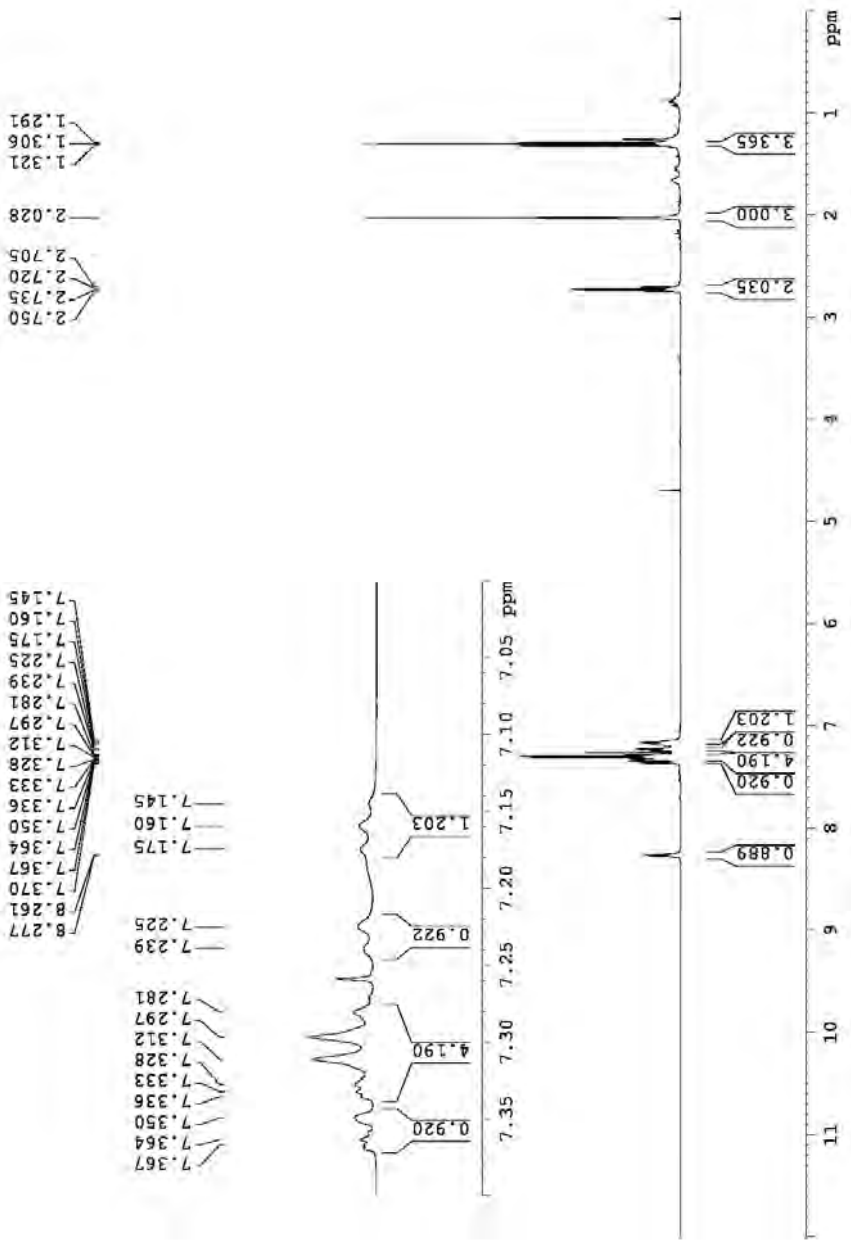
IR of N-(2'-methyl-[1, 1'-biphenyl]-2-yl)acetamide (2c)



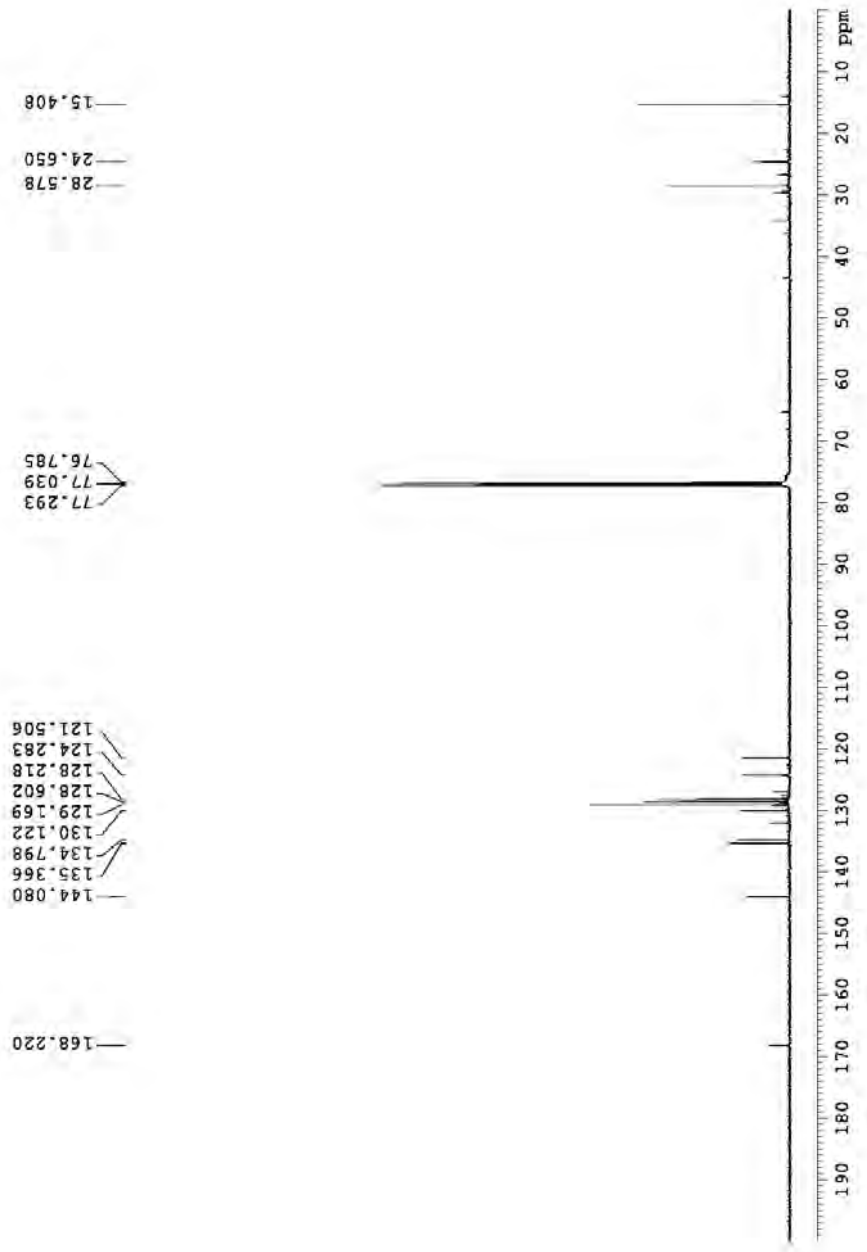
MS (EI) of N-(4'-methyl-[1, 1'-biphenyl]-2-yl)acetamide (2d)



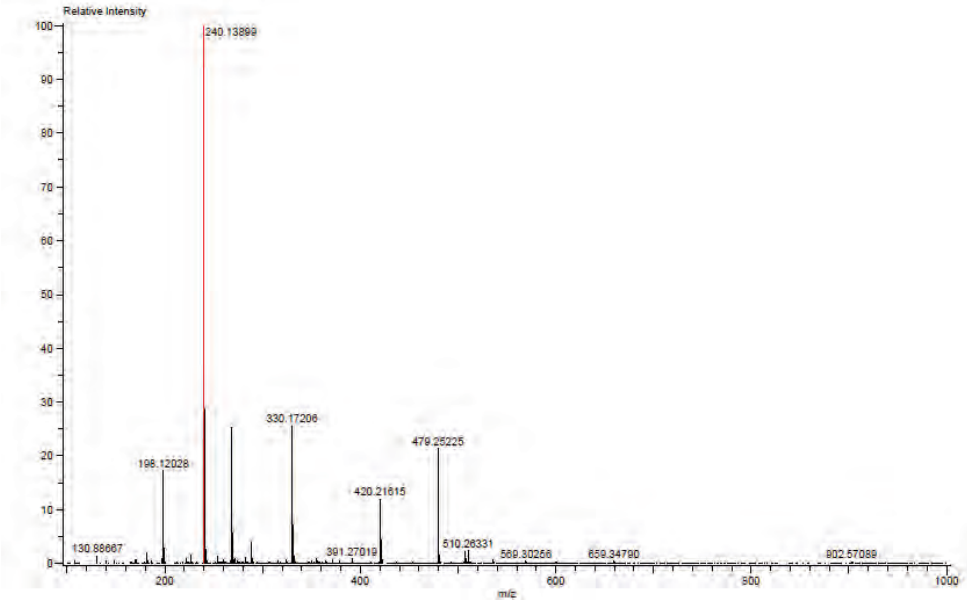
^{1}H-NMR of N-(4'-ethyl-[1, 1'-biphenyl]-2-yl)acetamide (2e) in $CDCl_3$



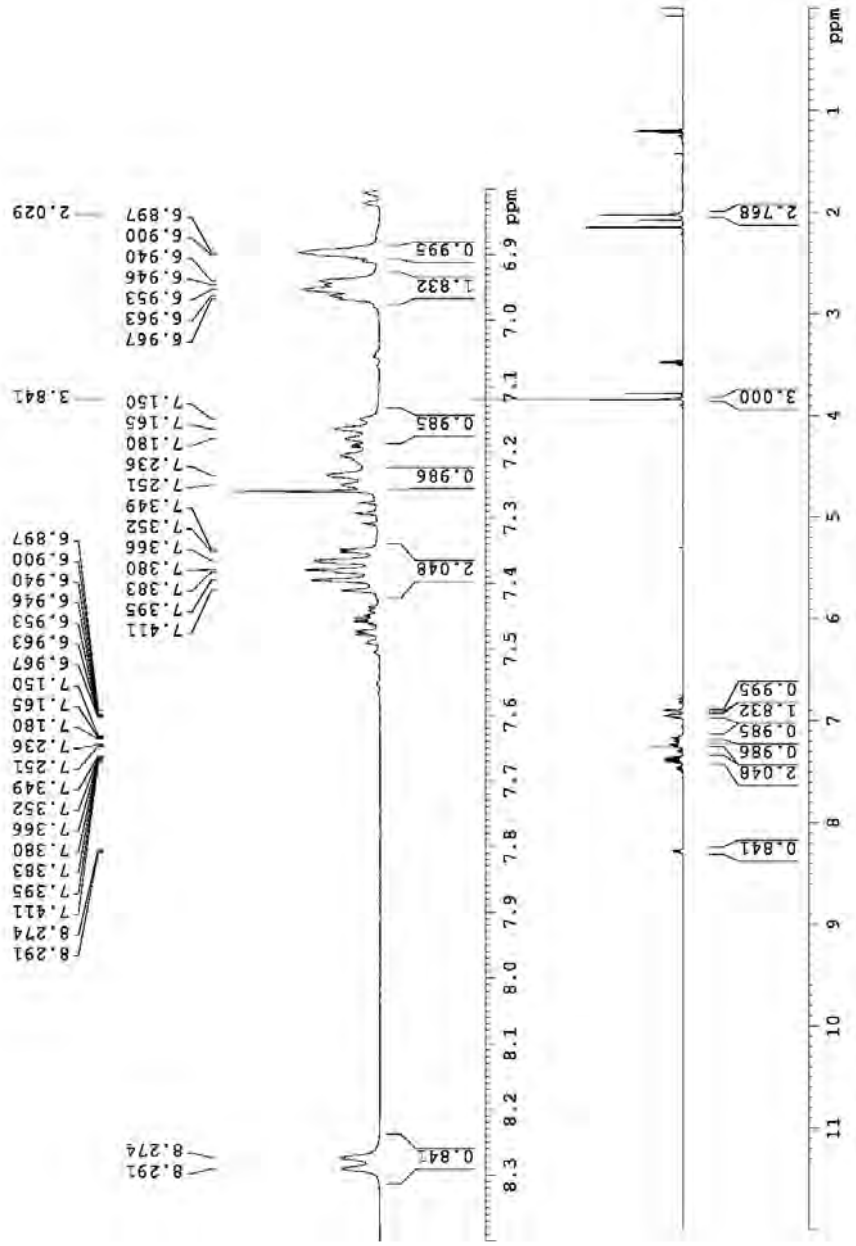
^{13}C-NMR of N-(4'-ethyl-[1, 1'-biphenyl]-2-yl)acetamide (2e) in $CDCl_3$



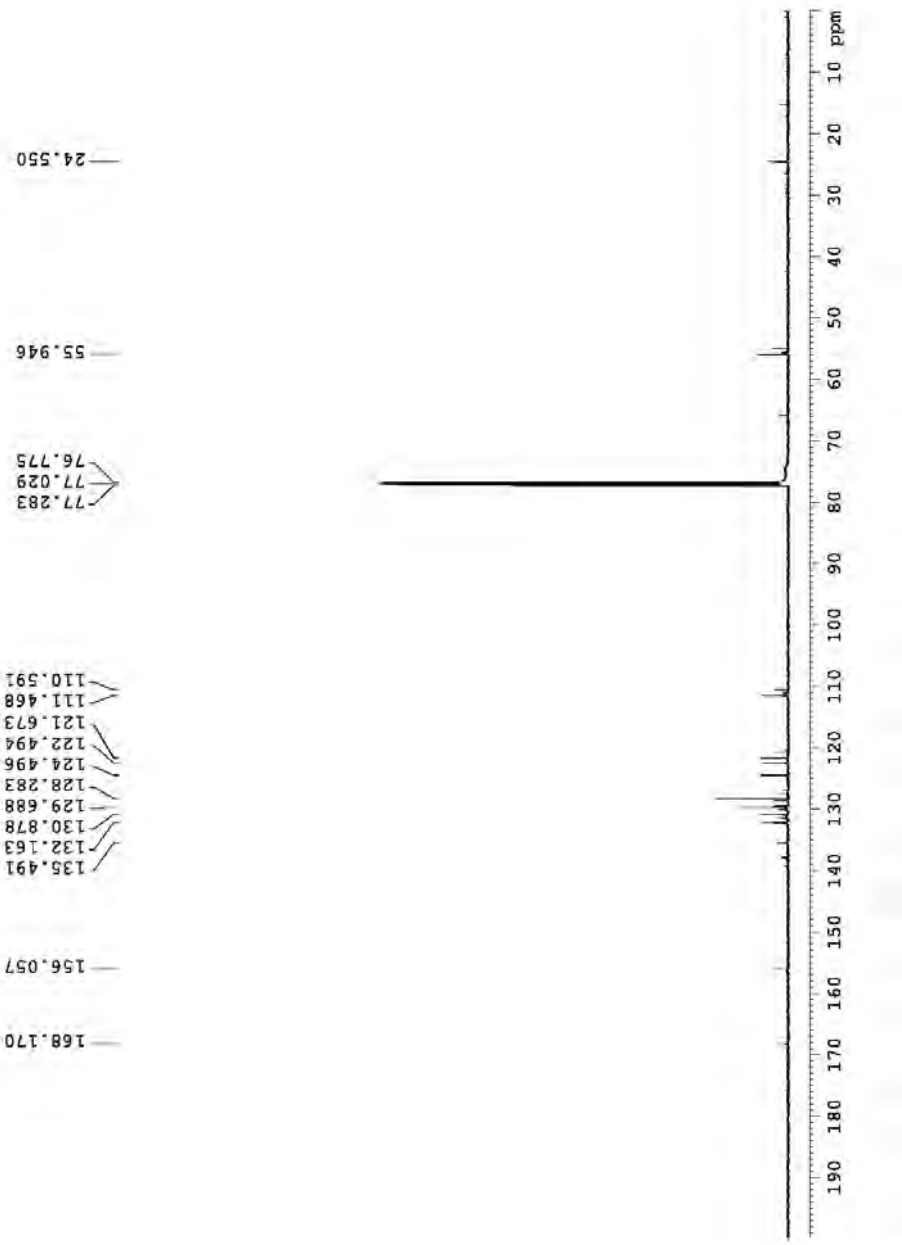
HRMS (DART+) of N-(4'-ethyl-[1, 1'-biphenyl]-2-yl)acetamide (2e)



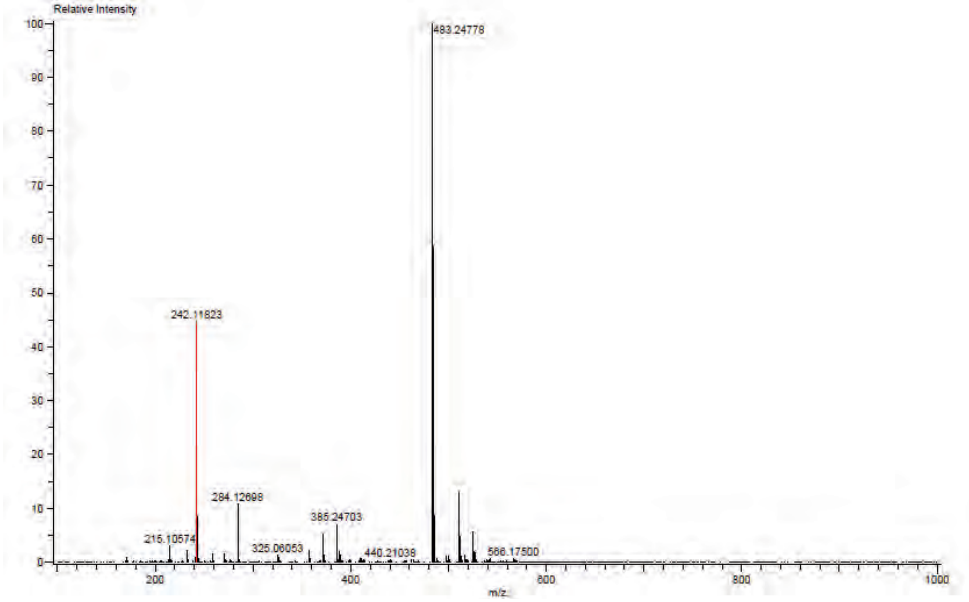
^{1}H-NMR of N-(2'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2f) in $CDCl_3$



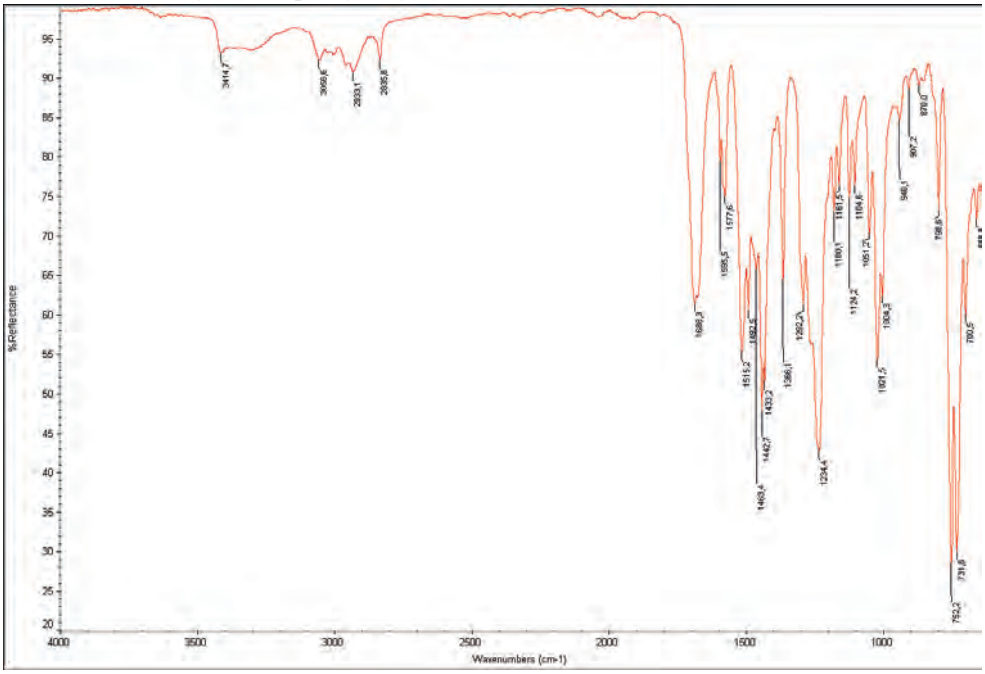
^{13}C-NMR of N-(2'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2f) in $CDCl_3$



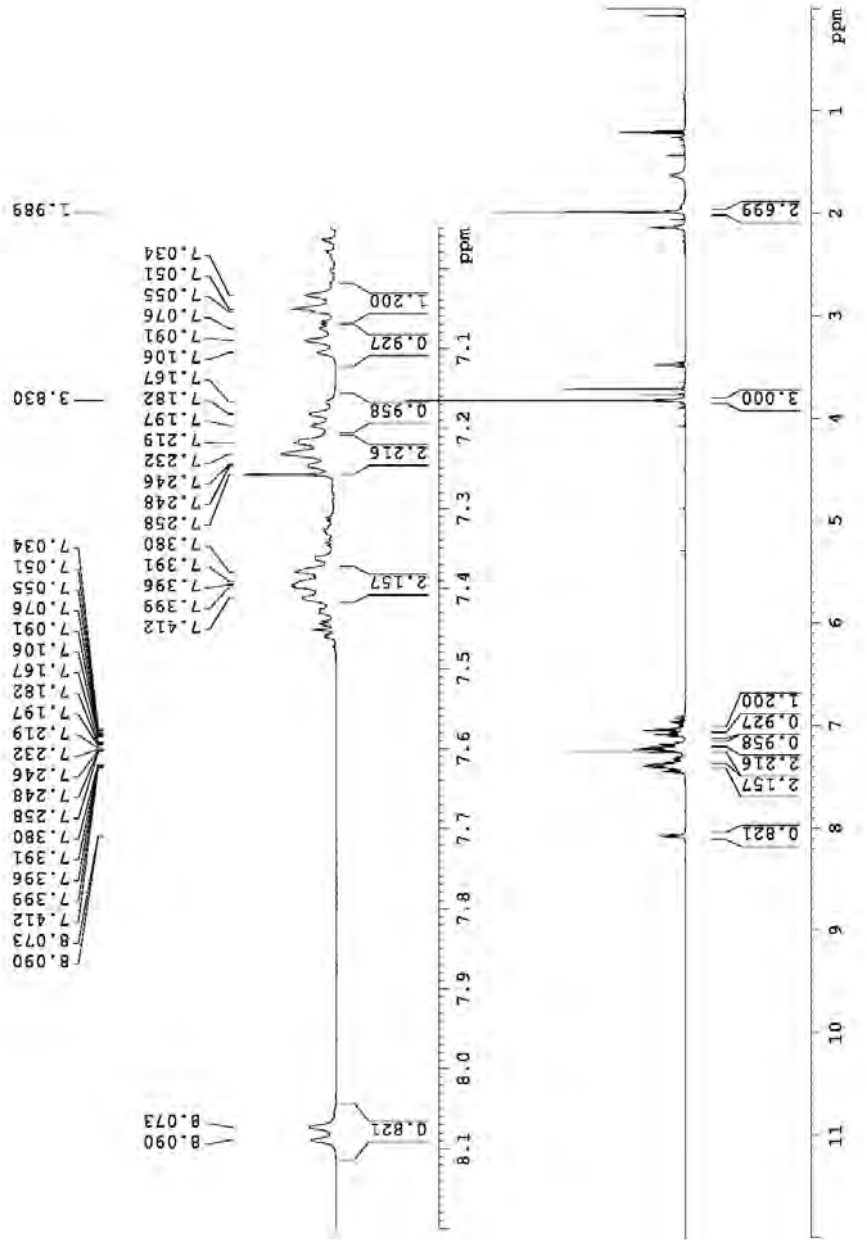
HRMS (DART+) of N-(2'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2f)



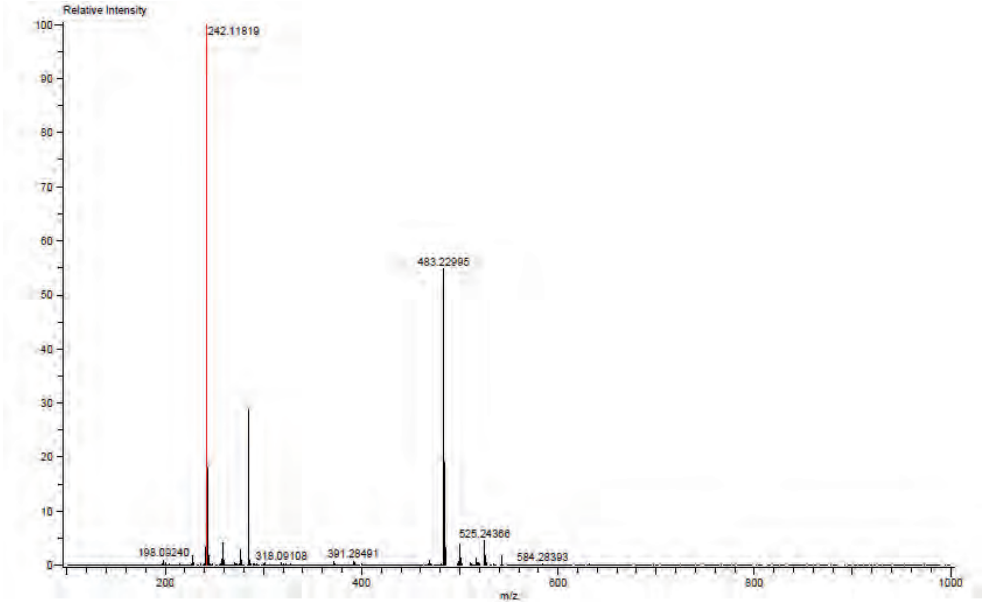
IR of N-(2'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2f)



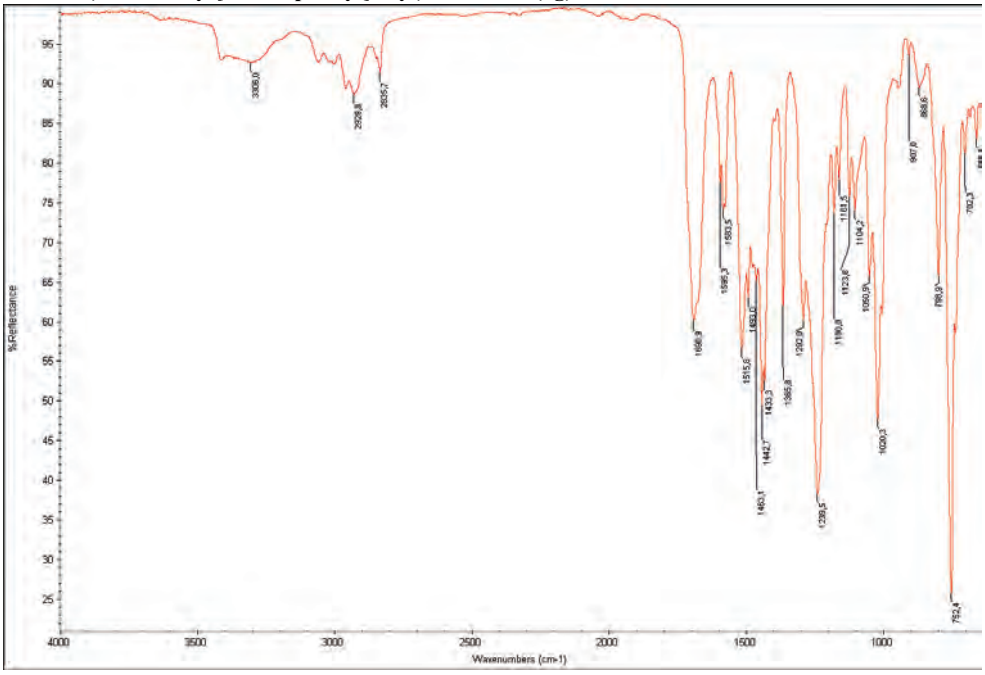
^{1}H-NMR of N-(3'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2g) in $CDCl_3$



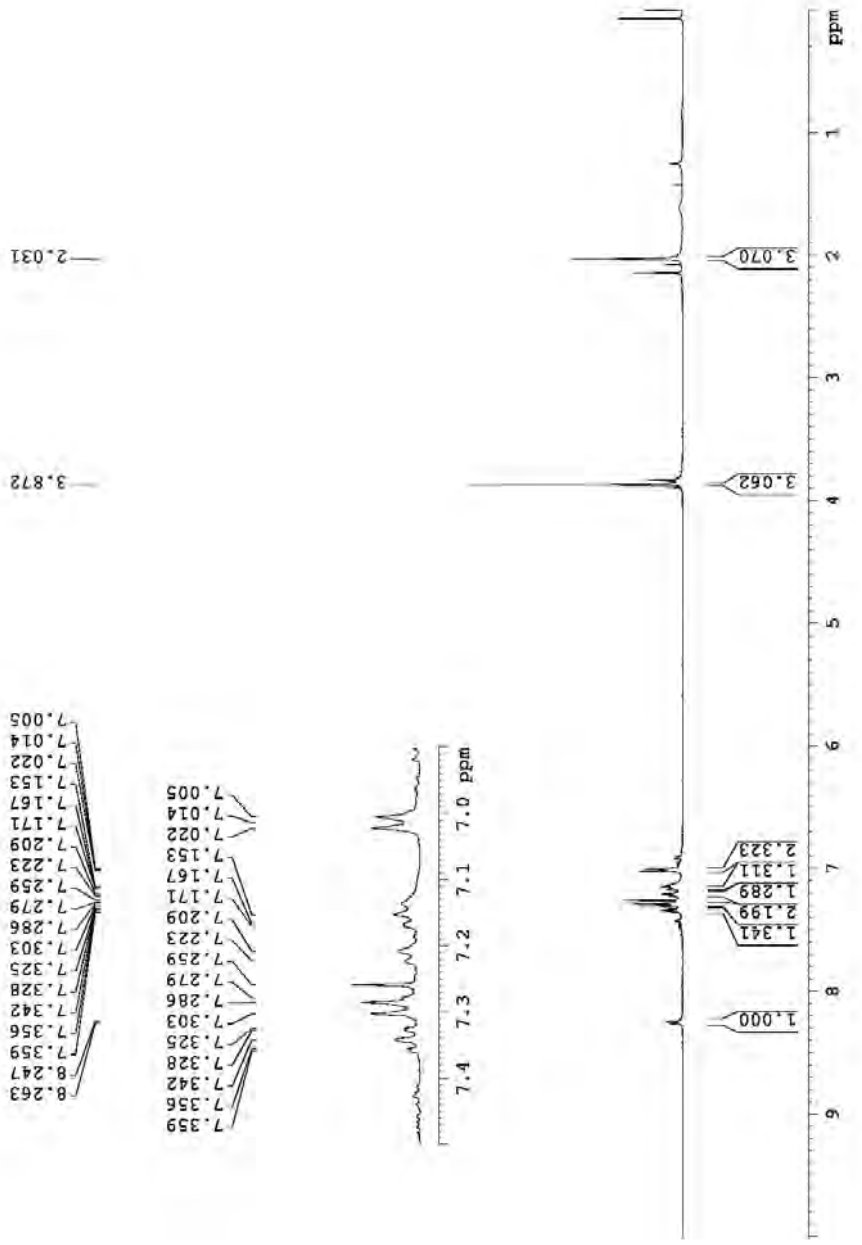
HRMS (DART+) of N-(3'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2g)



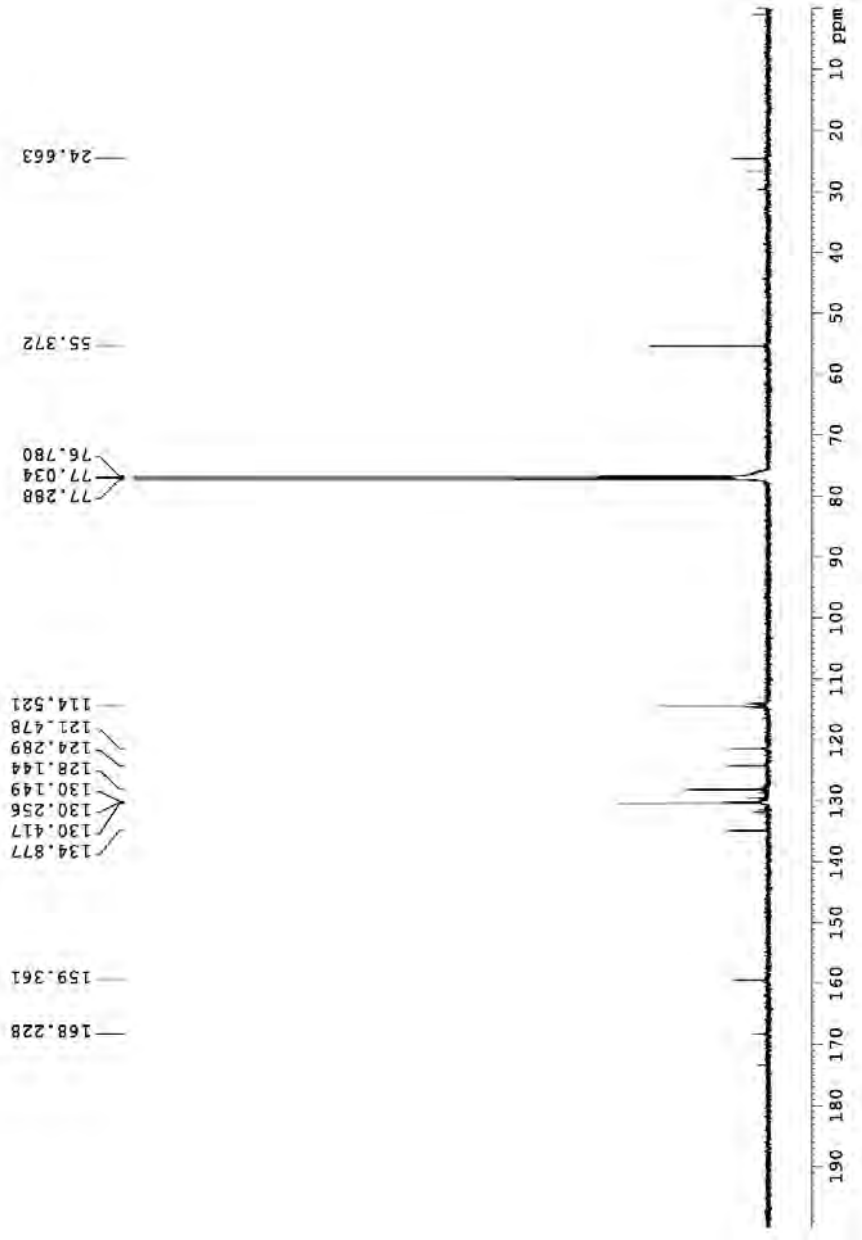
IR of N-(3'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2g)



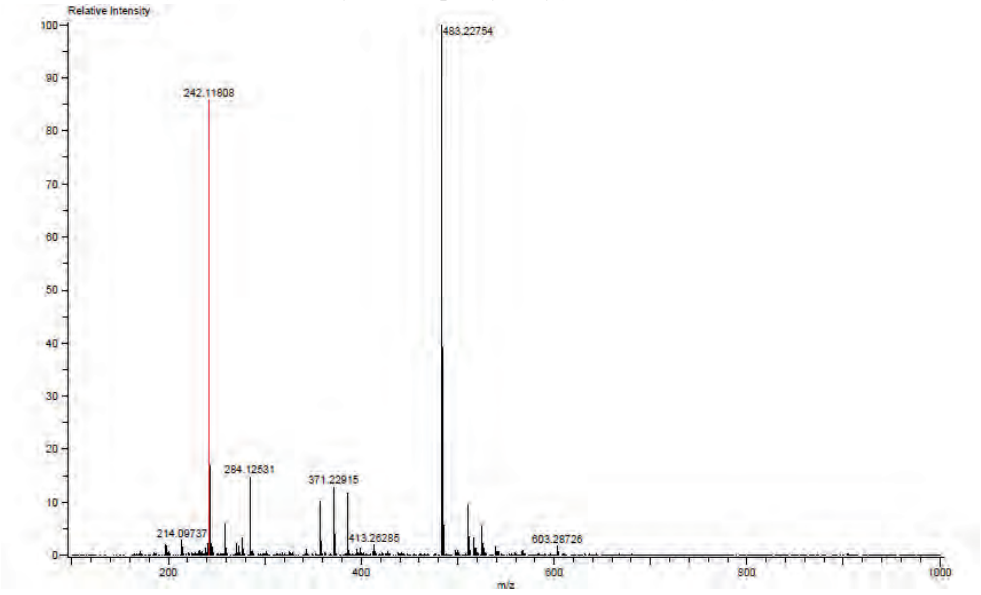
^{1}H-NMR of N-(4'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2h) in $CDCl_3$



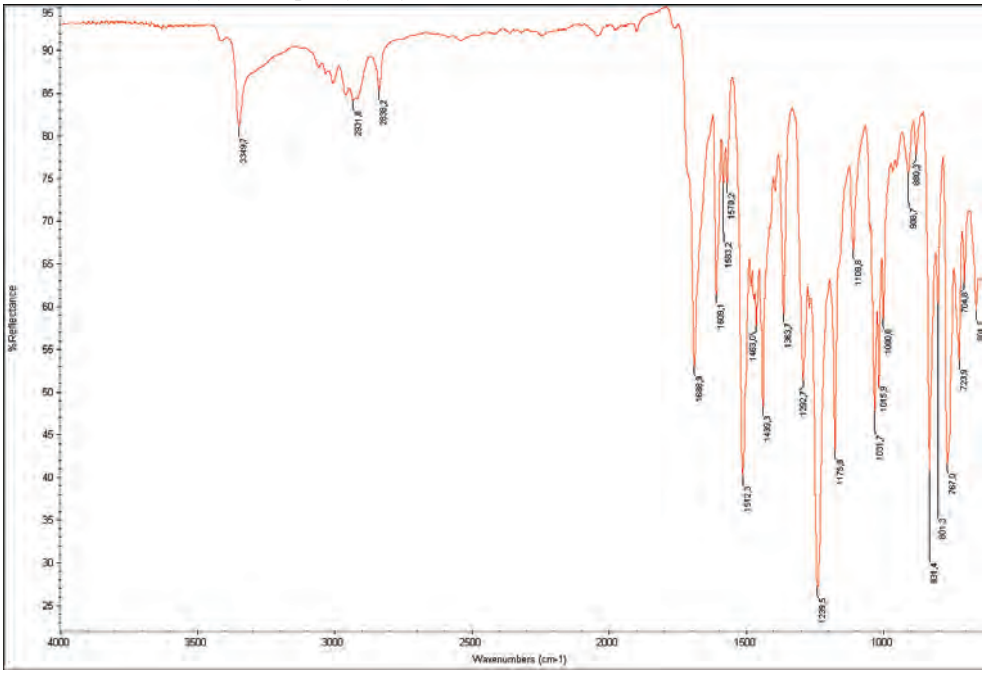
^{13}C-NMR of N-(4'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2h) in $CDCl_3$



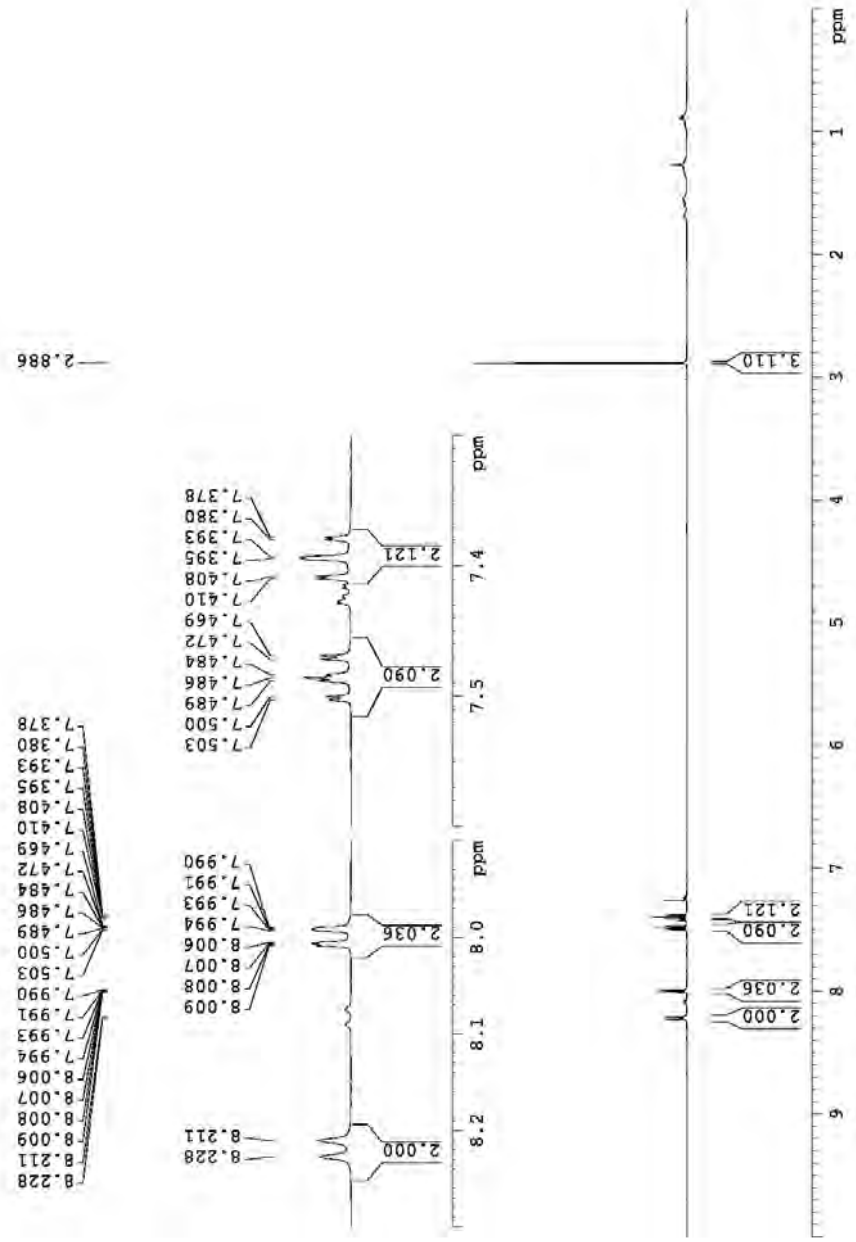
HRMS (DART+) of N-(4'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2h)



IR of N-(4'-methoxy-[1, 1'-biphenyl]-2-yl)acetamide (2h)



^{1}H-NMR of 1-(9H-carbazol-9-yl) ethan-1-one (3a) in $CDCl_3$



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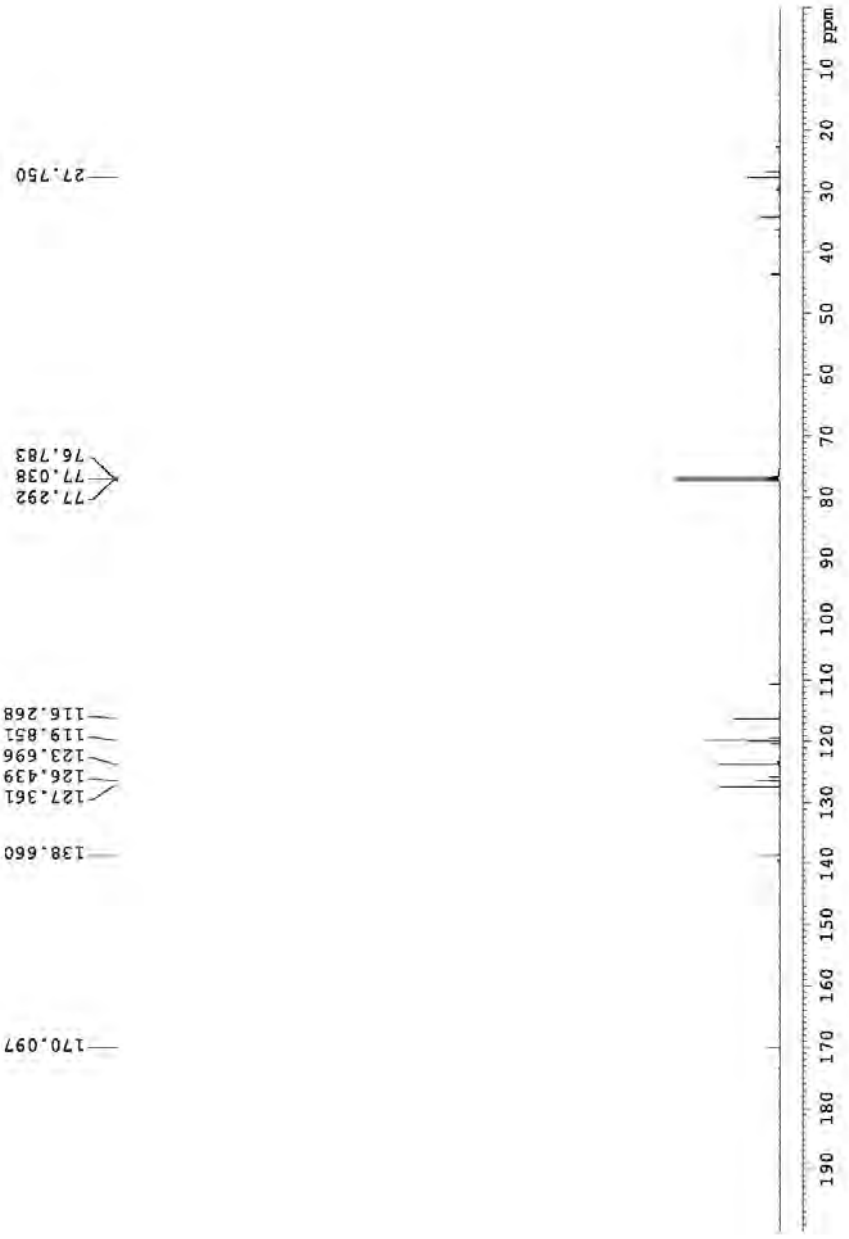

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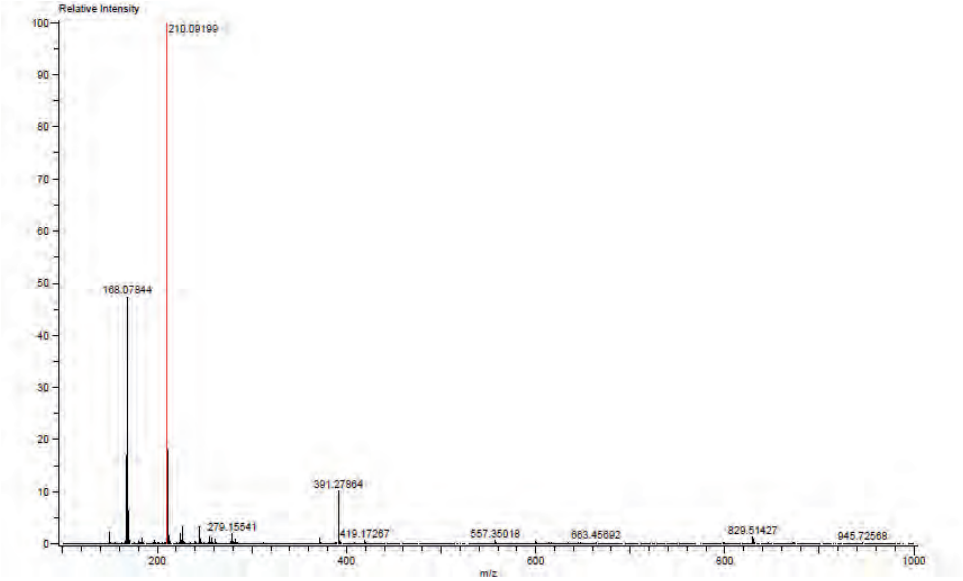
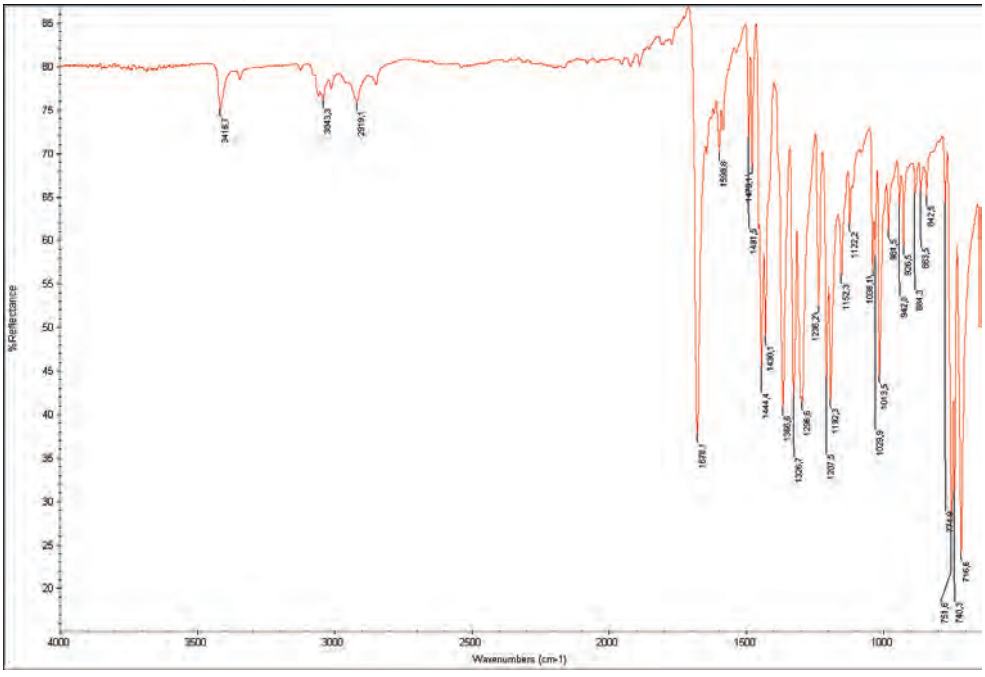
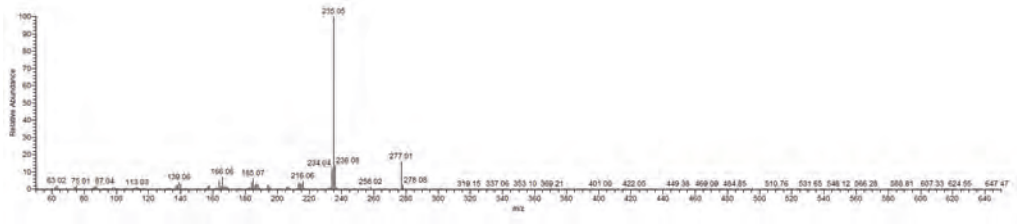


IR of 1-(9H-carbazol-9-yl) ethan-1-one (3a)



MS (EI) of 1-(4-(trifluoromethyl)-9*H*-carbazol-9-yl) ethan-1-one (3b)



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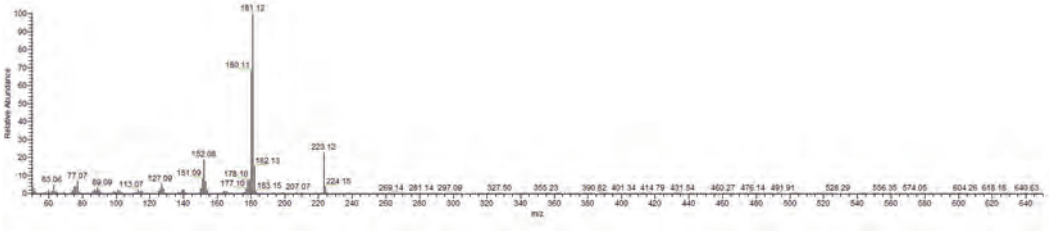

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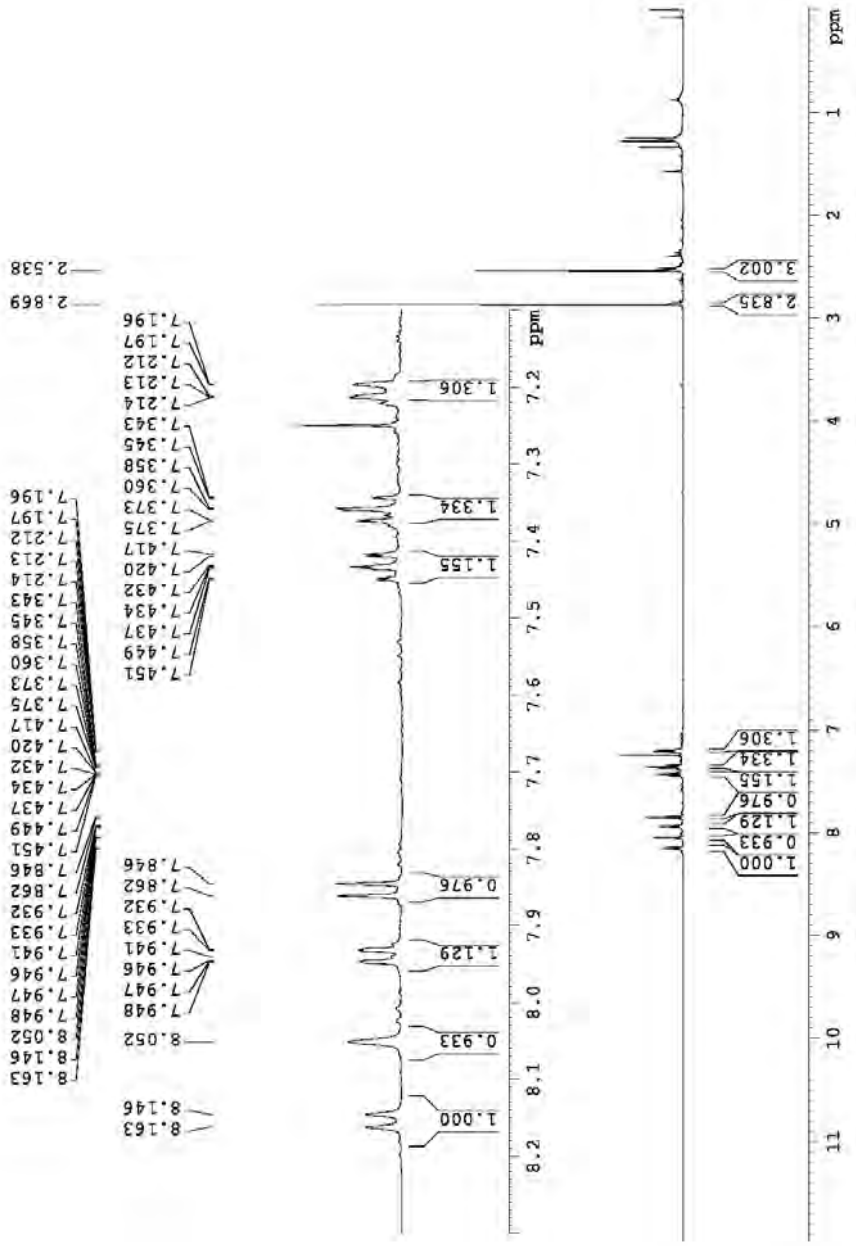

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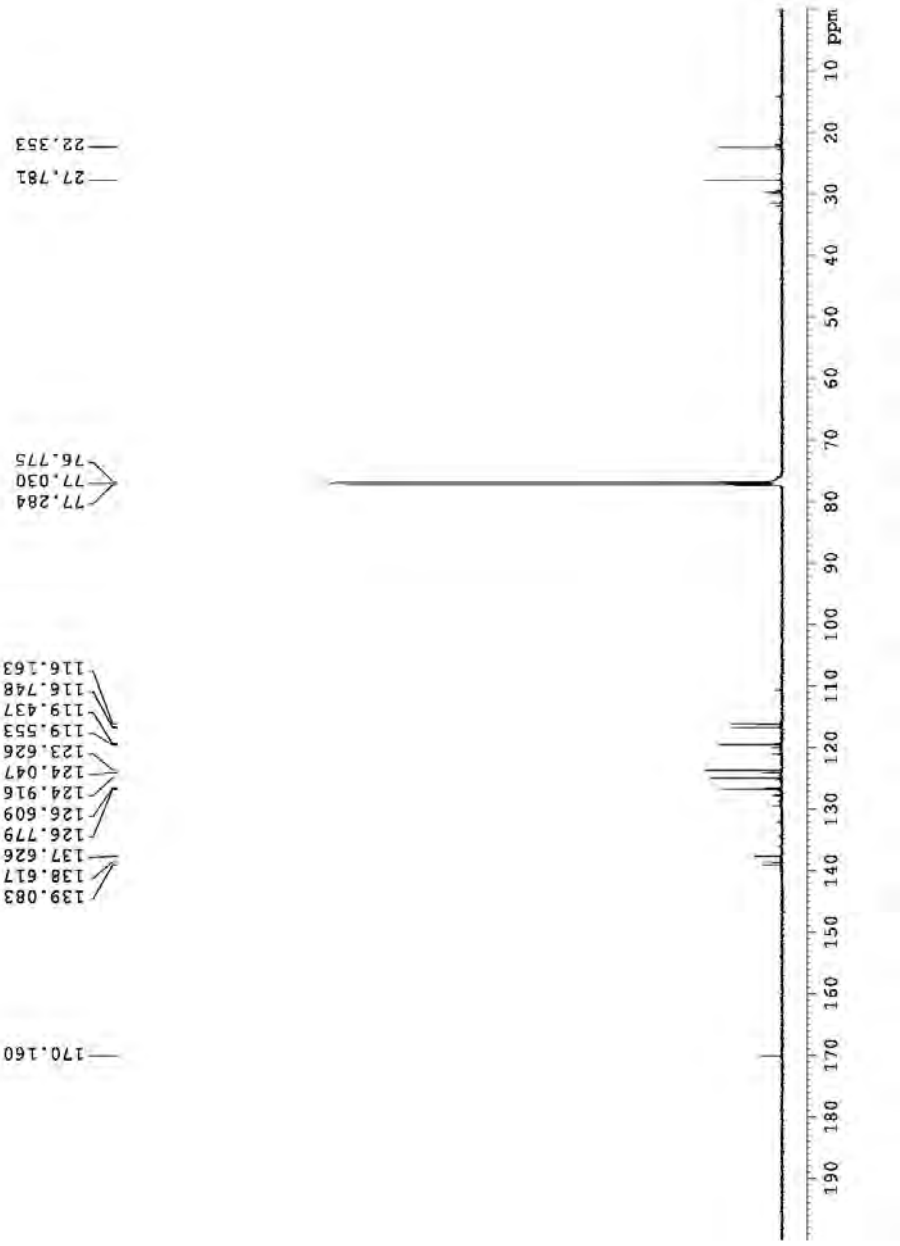
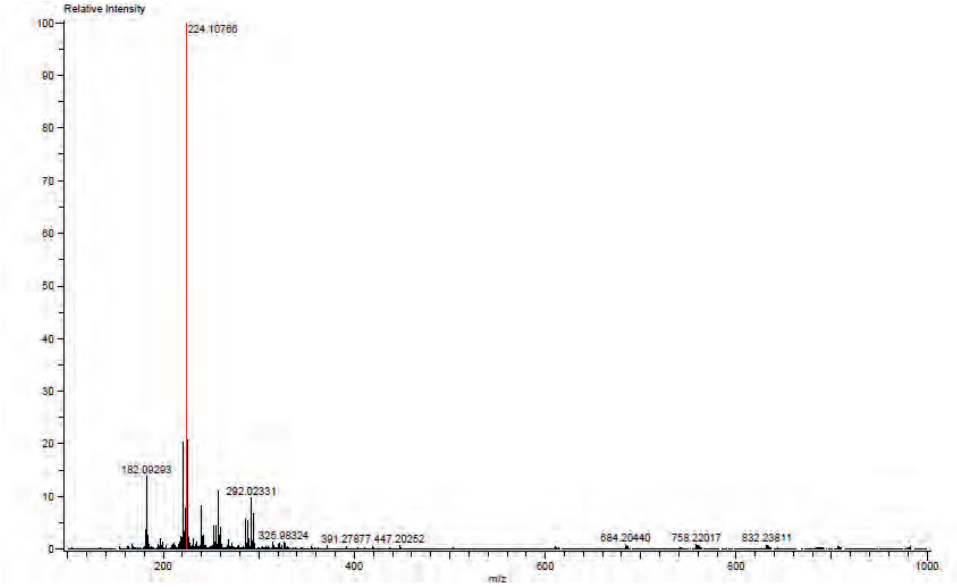


HRMS (DART+) of 1-(2-methyl-9*H*-carbazol-9-yl) ethan-1-one (3d)



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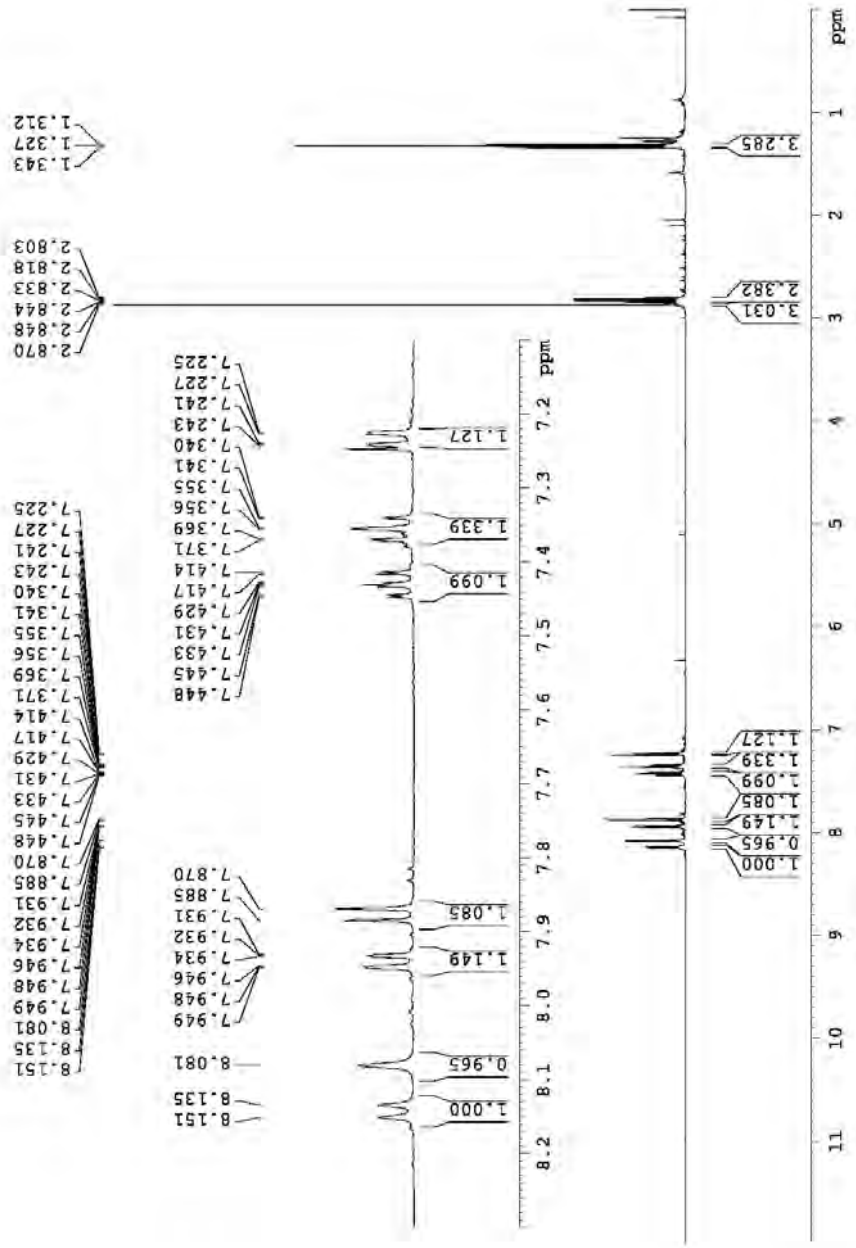

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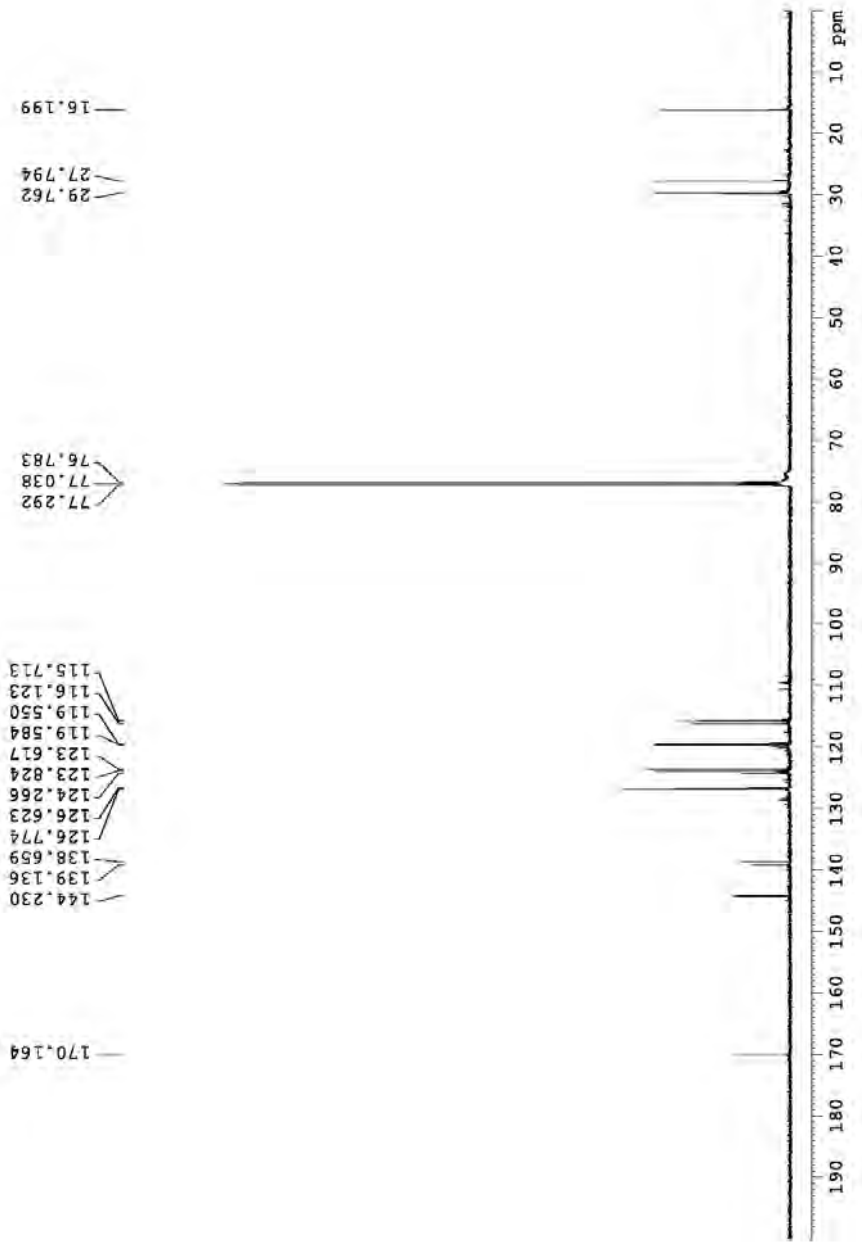
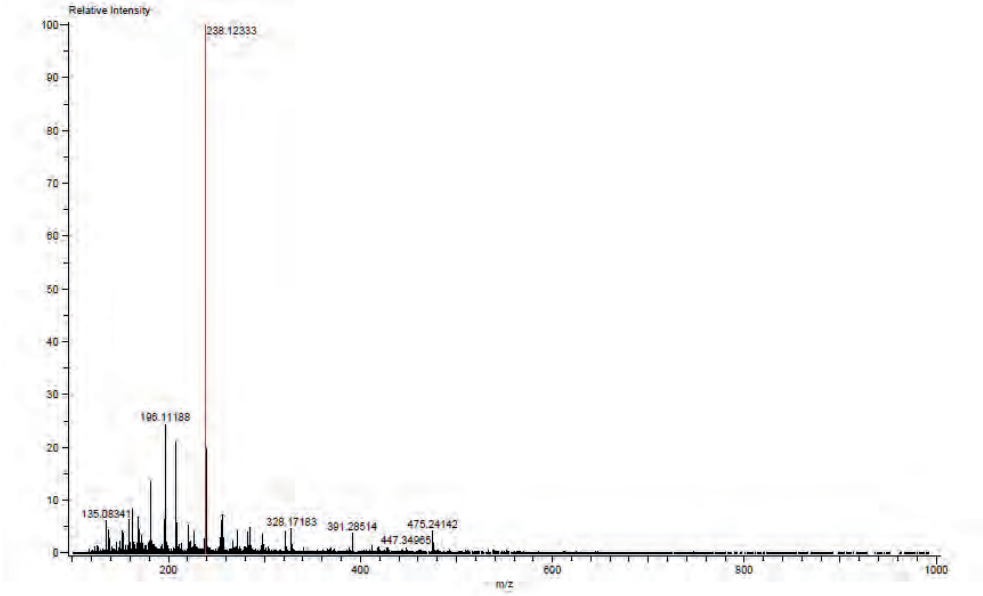
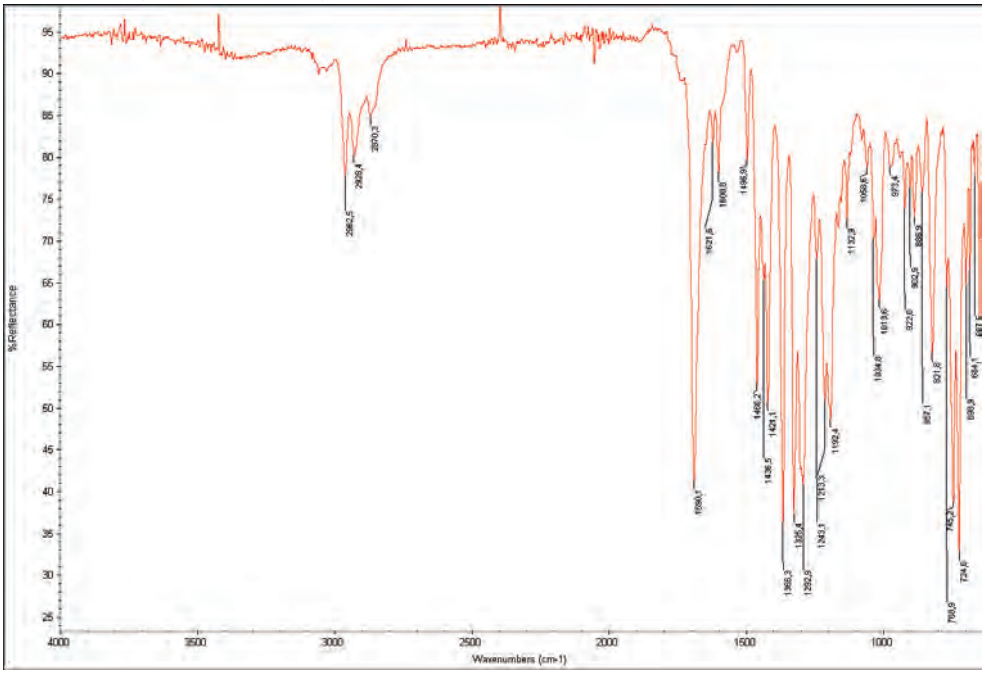


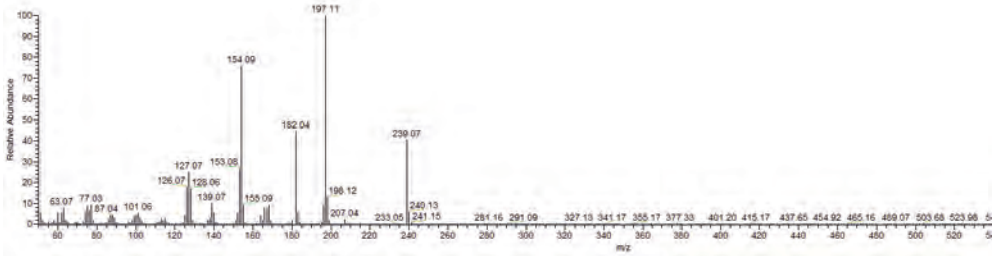
HRMS (DART+) of 1-(2-ethyl-9*H*-carbazol-9-yl) ethan-1-one (3e)



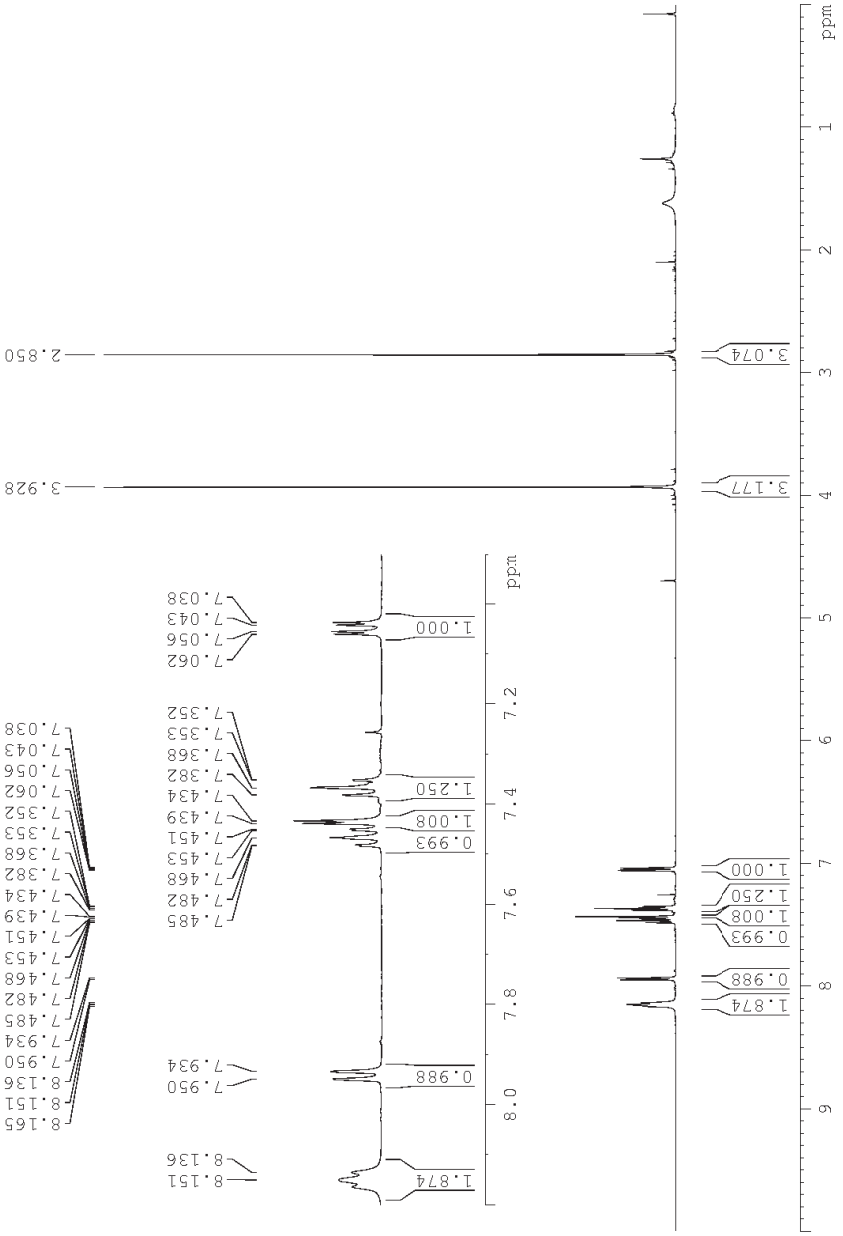
IR of 1-(2-ethyl-9*H*-carbazol-9-yl) ethan-1-one (3e)



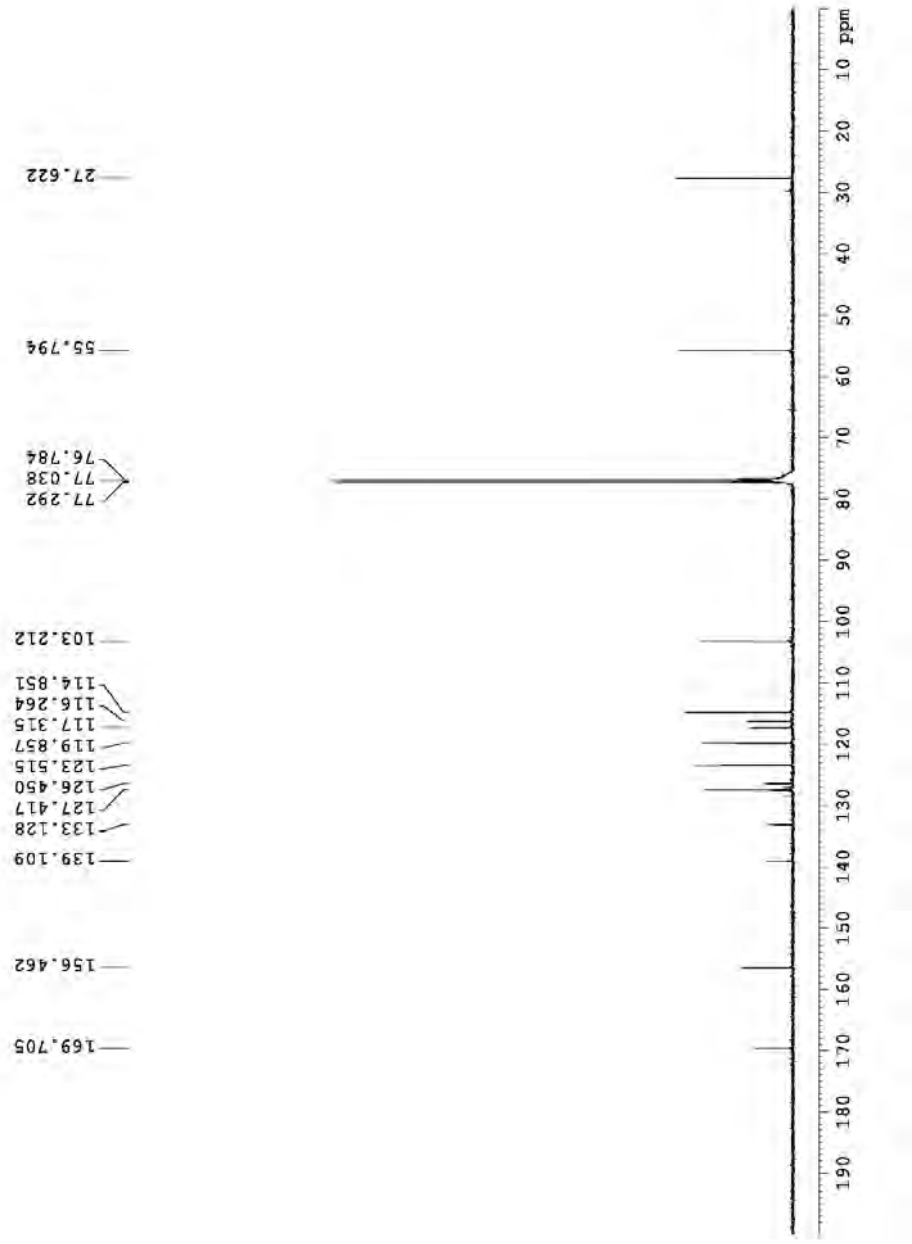
MS (EI) of 1-(4-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3f)



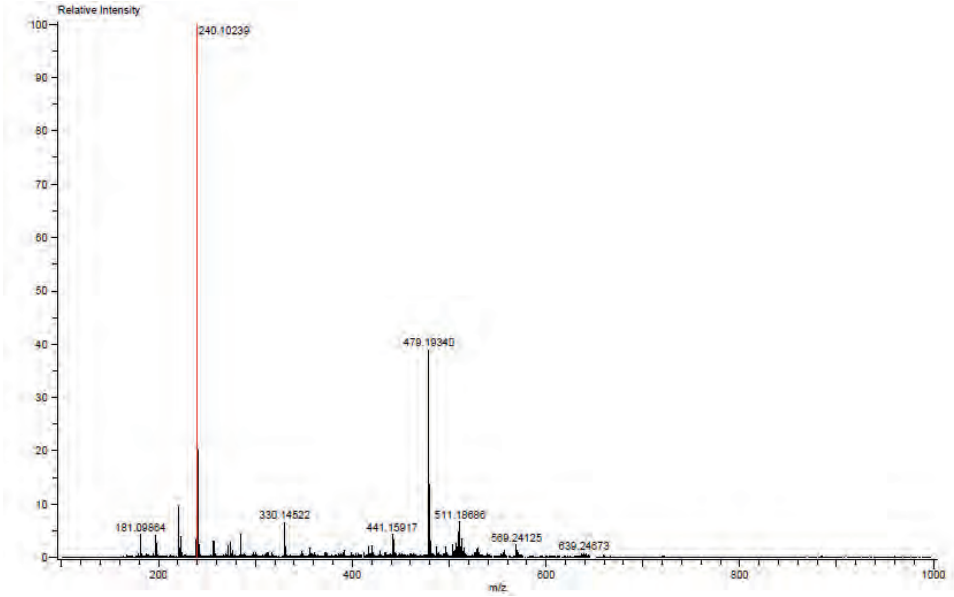
[1]H-NMR of 1-(3-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3g) in $CDCl_3$



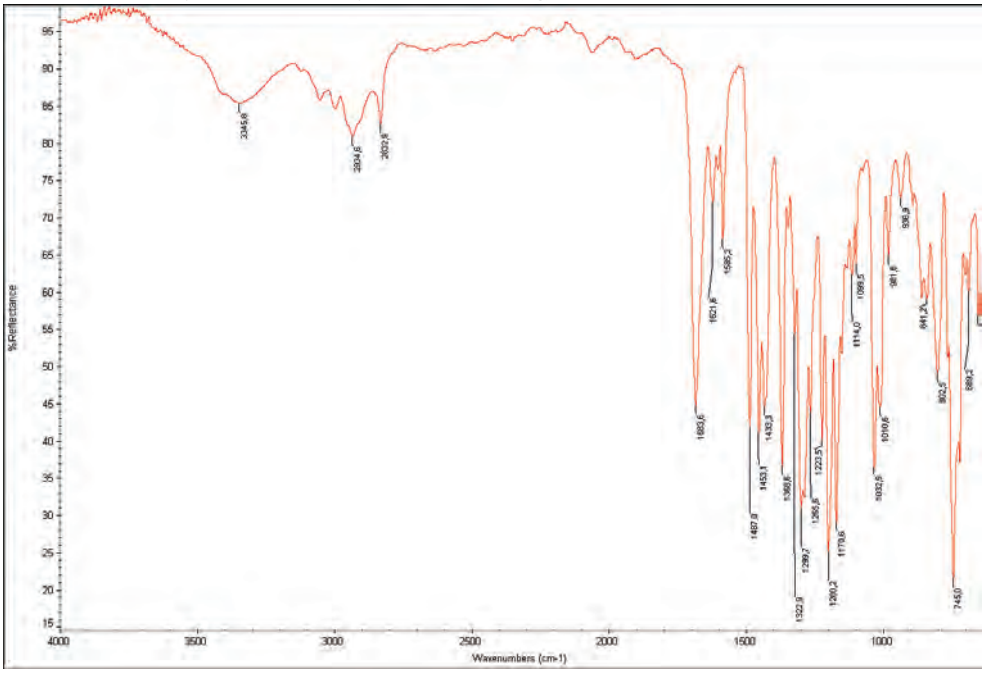
^{13}C-NMR of 1-(3-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3g) in $CDCl_3$



HRMS (DART+) of 1-(3-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3g)



IR of 1-(3-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3g)



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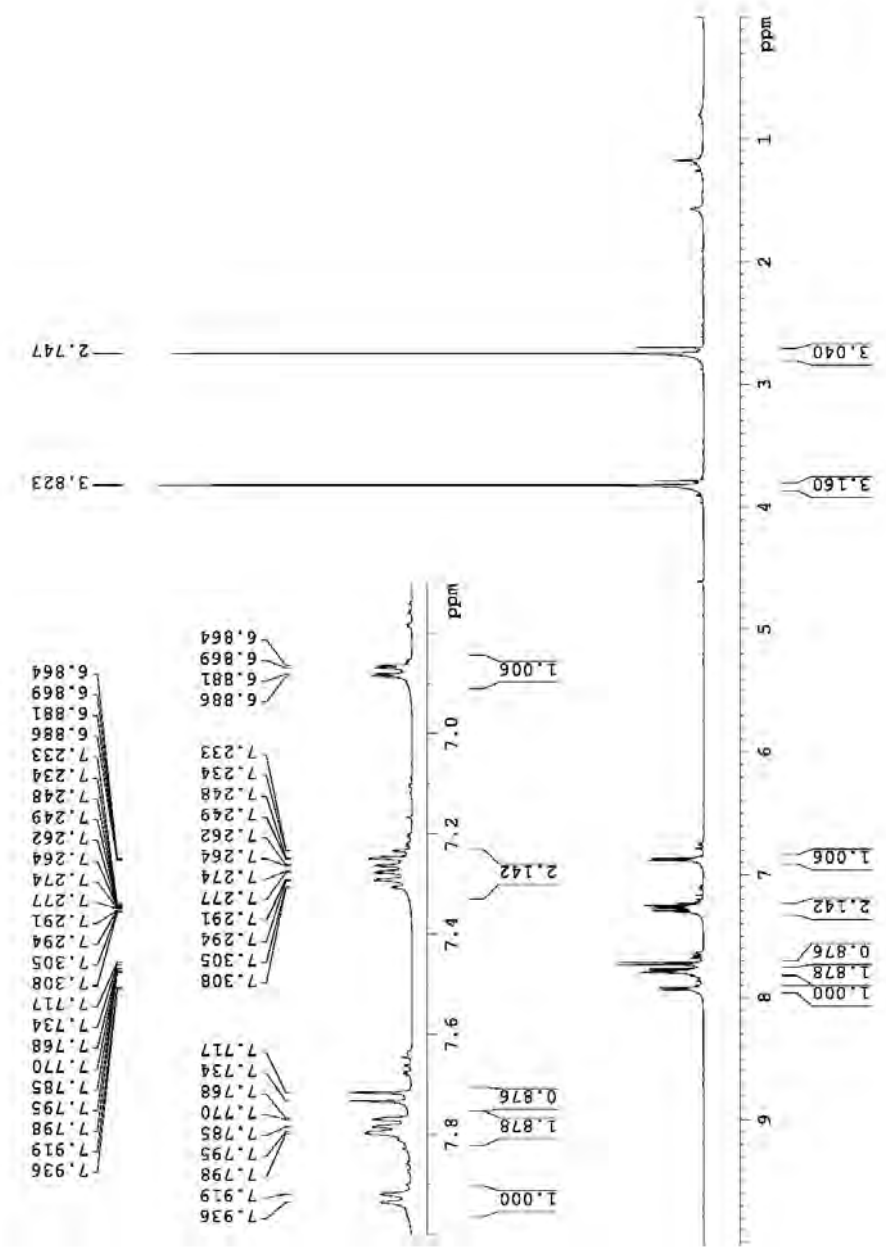
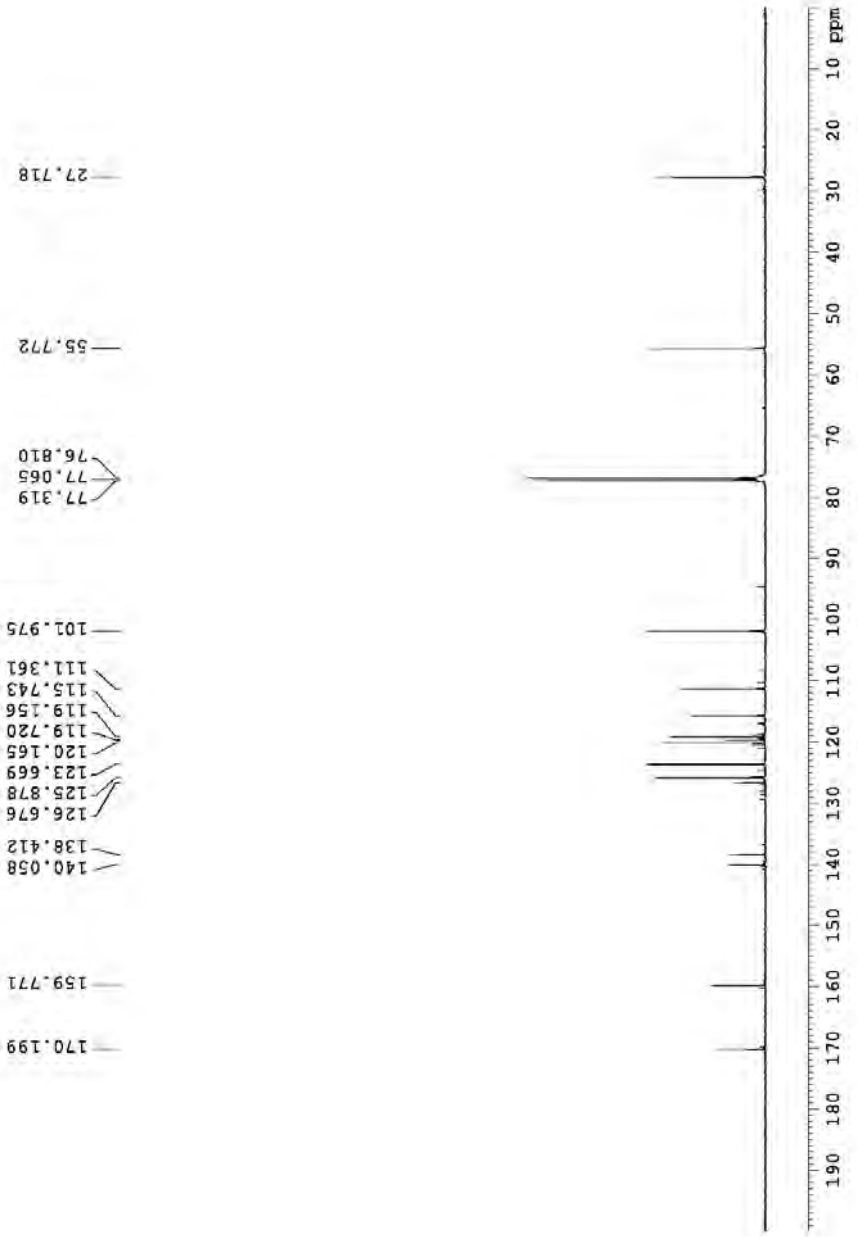
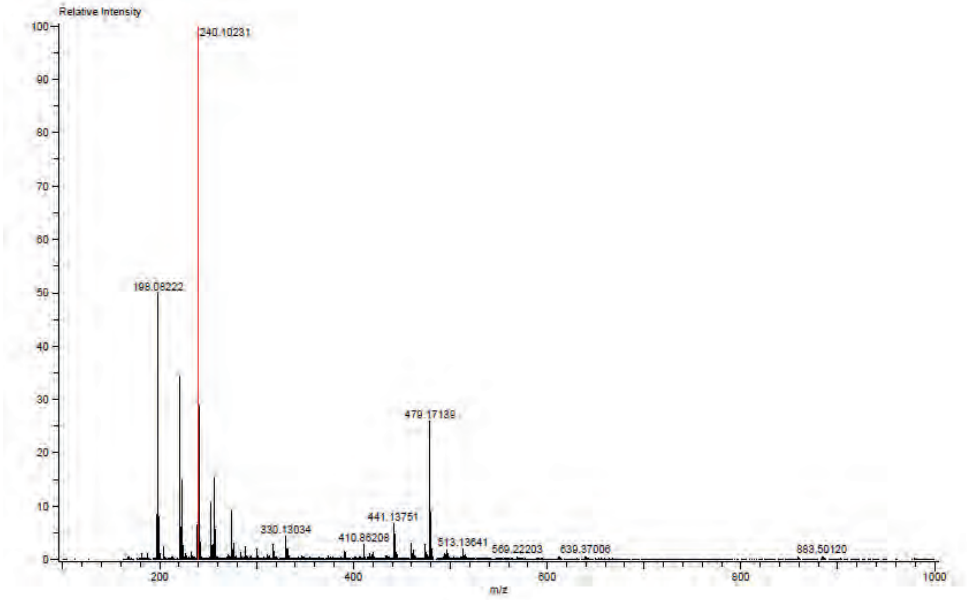


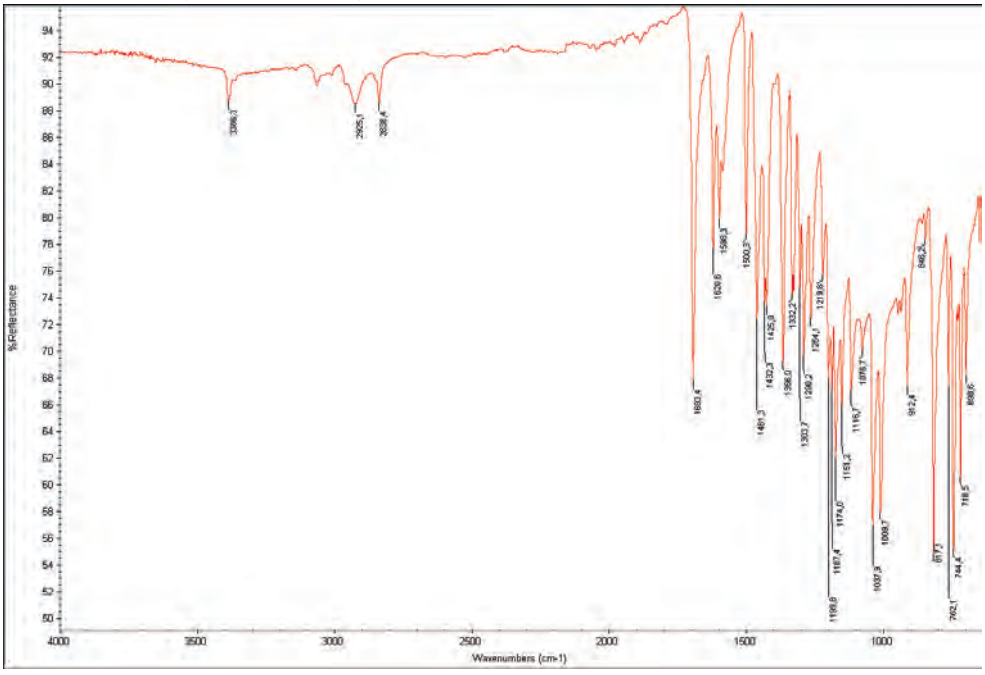
^{13}C-NMR of 1-(2-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3h) in $CDCl_3$



HRMS (DART+) of 1-(2-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3h)



IR of 1-(2-methoxy-9*H*-carbazol-9-yl) ethan-1-one (3h)



Paper IV

A Concise Synthesis to Benzo[c]cinnolines via 2,2'-Dinitro-1,1'-Biphenyls Attained from a Novel Tailored Suzuki Cross-Coupling.

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A Concise Synthesis to Benzo[*c*]cinnolines via 2,2′-Dinitro-1,1′-Biphenyls Attained from a Novel Tailored Suzuki Cross-Coupling

Vijayaragavan Elumalai and Hans-René Bjørsvik*[a]

A new two-step synthetic process for the preparation of unsymmetrically substituted benzo[*c*]cinnolines was developed. The key intermediate 2,2′-dinitro-1,1′-biphenyl was prepared by means of an unprecedented tailored Suzuki cross-coupling protocol. The subsequent step is constituted by a domino partial nitro group reduction and intramolecular diazo bond formation, a process that afford target benzo[*c*]cinnoline scaffold. The disclosed method tolerates both electron-withdrawing- and electron-donating groups.

Cinnoline moieties are frequently found in biologically active molecules,[1] whereof numerous with attractive pharmacological properties such as antibacterial,[2a] anticancer,[2b] antimicrobial,[2c] anti-inflammatory,[2d] antifungal,[2e] antihypertensive,[2f] antiulcer,[2f] cytotoxic,[2g] and topoisomerase inhibitor,[2h] see Figure 1.

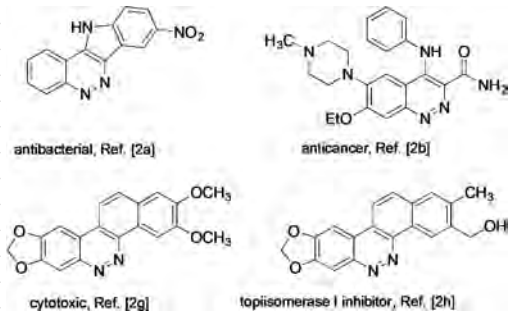
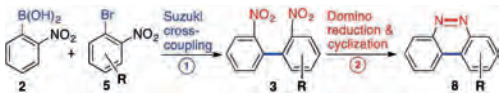


Figure 1. Biologically active cinnoline derivatives.

In a previous disclosure, we envisioned, established a synthetic pathway, and process for the preparation of the benzo[*c*]cinnoline scaffold.[3] However, this process was limited to the synthesis of symmetrically substituted benzo[*c*]cinnolines via 2,2′-dinitro-1,1′-biphenyls obtained via the Ullmann coupling.[4] 2,2′-Dinitro-1,1′-biphenyl was also prepared by means of a Suzuki cross-coupling protocol, although in low yield only. This cross-coupling protocol requested high temperature and long reaction time (150 °C, 20 h).[5] Widdowson and Wilhelm[6] reported that the nitro group in the *ortho* position to the halo atom of the haloarene **5** (Scheme 1) is not only acting as an



Scheme 1. A two step process to the benzo[c]cinnoline. ① A tailored Suzuki cross-coupling protocol allowing the preparation of 2,2′-dinitro-1,1′-biphenyls **3**. ② A domino partial nitro group reduction and intramolecular diazo bond formation that provides the benzo[c]cinnoline scaffold **8**.

electron withdrawing group, but also as a coordinating group for incoming palladium in the Suzuki cross-coupling and thereby act a significant influence on the C–C coupling. This was recently supported by a study disclosed by Sakaki, Nakao, and collaborators,[7] which revealed that the NO_2 group of nitroarenes even operated as the leaving group in the Suzuki cross-coupling. These observations explain the difficulties of using *ortho*-NO_2 substituted reagents in the Suzuki cross-coupling experiments.

For a project in progress in our laboratory related to the synthesis of the carbazole scaffold,[8] we needed access to 2-nitro-1,1′-biphenyls that we only partly could produce by means of our previously disclosed Suzuki cross-coupling protocol that encompasses 2-nitro-1-iodobenzenes with phenylboronic acids as reaction partners.[5]

We undertook therefore a revisit to this reaction protocol, which afforded a new method allowing the use of both 1-chloro-2-nitrobenzenes and 1-bromo-2-nitrobenzenes as reaction partners to phenylboronic acids.[9] Propelled by these encouraging results we sought to explore whether this method could be further extended to prepare 2,2′-dinitro-1,1′-biphenyl derivatives **3** and thereby offer an easy access to un-symmetrically substituted benzo[*c*]cinnolines **8**, as outlined in Scheme 1.

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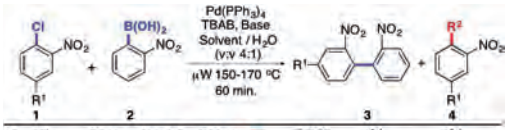
At the outset of the study whose results are disclosed herein, we commenced exploring 2-nitro-chlorobenzenes **1** as the coupling partner to 2-nitro-phenylboronic acid **2** in attempts to approach our target key intermediate 2,2′-dinitro-1,1′-biphenyls **3** using our recently disclosed Suzuki cross-coupling protocol.[9] The subsequent step that involves the domino partial nitro group reduction and intra-molecular diazo bond formation that results in the cyclization and thus the forming of the benzo[*c*]cinnoline scaffold was based on a redox process firstly developed for oxidation of aromatics containing an oxygen functionalized benzylic moiety.[3,10]

In addition to our method for the preparation of the benzo[*c*]cinnoline scaffold, only few other methods have been disclosed based on a strategy that involves 2,2′-nitro/amino-1,1′-biphenyls.[11] However, our initial trials operated poorly or not at all with 2-nitro-chlorobenzenes **1**. Even with a deactivating substituent present, low yields only were achieved of target coupling product **3** (entries 3–5 of Table 1).

Table 1. Screening of reaction conditions for the synthesis of 2,2′-dinitro-1,1′-biphenyls.



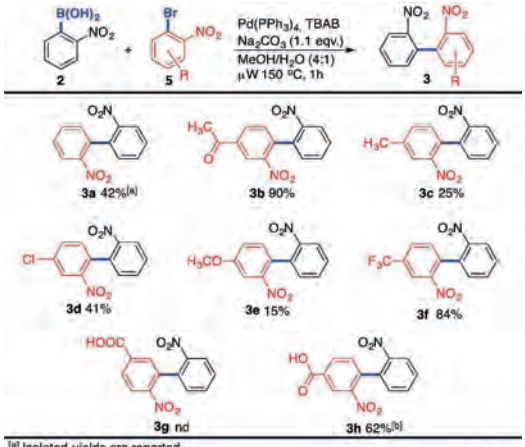
1 2 3 4

#	R^1	Base	[equiv.]	Solvent	R^2	T [°C]	3[a]	4[a]
1	H	Na_2CO_3	1.1	MeOH	OMe	150	nd	nd
2	CF_3	Na_2CO_3	1.1	MeOH	OMe	150	nd	nd
3	CF_3	Cs_2CO_3	2.0	MeOH	OMe	150	14	35
4	CF_3	NaOH	2.0	MeOH	OMe	150	19	70
5	CF_3	NaOH	2.0	DMF	NMe_2	160	8	78
6	CF_3	NaOH	2.0	DMF	NMe_2	170	nd	91

[a] Measured by GC, nd = not detected

Interestingly, an unexpected product **4** was formed via an *ipso*-type nucleophilic substitution of the chlorine atom with the solvent as the nucleophile. However, we abandoned further investigation using 1-chloro-2-nitrobenzenes as reaction partner in the cross-coupling step due to unfavourable selectivity towards target biphenyl (**3**).

In the following, we continued to examine 1-bromo-2-nitrobenzenes **5** in the place of 1-chloro-2-nitrobenzenes **1** as reaction partner for 2-nitro-phenylboronic acid **2**, Scheme 2. Initial experiments involved un-substituted reaction partners, which afforded target product **3a**, although in a moderate yield only. A library composed of different 1-bromo-2-nitrobenzenes **5** with a variety of electron-donating and electron-withdrawing functional groups (**R** ∈ [$COCH_3$, CH_3, Cl, OCH_3, CF_3, COOH]) were successively reacted with 2-nitro-phenylboronic acid **2** using the established Suzuki cross-coupling procedure. All of these trials except for the experiment that involved 3-bromo-4-nitrobenzoic acid **5g** afforded target intermediate 2,2′-dinitro-1,1′-biphenyl derivative **3** (**3a–h**), Scheme 2. Attempts to protect the carboxylic acid group as a methyl ester (methyl 4-bromo-3-nitrobenzoate) afforded a moderate yield of the expected benzo[*c*]cinnoline scaffold, but the methyl ester was



[a] Isolated yields are reported.
[b] **3h** was formed when methyl 4-bromo-3-nitrobenzoate (**5h**) was hydrolysed due to the basic reaction conditions. The product was quantified by means of ^{1}H NMR

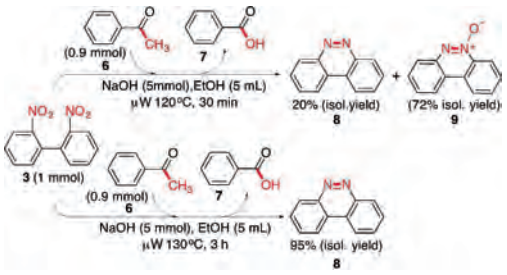
Scheme 2. A tailored Suzuki cross-coupling leading to 2,2′-dinitro-1,1′-biphenyls.

hydrolysed to carboxylic acid (**3h**). Substrates that possessed electron-donating groups afforded low yields only (**3c** and **3e**). With electron-withdrawing substituents present, e.g. $COCH_3$ and CF_3 (**3b** and **3f**), high to excellent yields were obtained. In the case with a weak deactivating group present (**3d**), a moderate yield was obtained.

These results reveal that the electron withdrawing groups deactivate the aromatic ring, decrease the electron density around the C–Br bond and thus facilitates the oxidative addition and the transmetallation with phenylboronic acid even in the presence of the strong deactivating NO_2 group. In the experiments that afforded low to moderate yield of target 2,2′-dinitro-1,1′-biphenyl **3**, substantial quantities ($\lesssim$50%) of hydrodebrominated **5** was observed. Furthermore, the method appeared not to operate with a free carboxyl acid group present, as revealed for the expected product **3g**.

The second step of the process, the domino partial nitro group reduction and intramolecular diazo bond formation is constituted by a principal redox process that ultimately afford the benzo[*c*]cinnoline framework **8** and the by-product **7**. Previously, this process was comprehensively investigated and disclosed by our group.

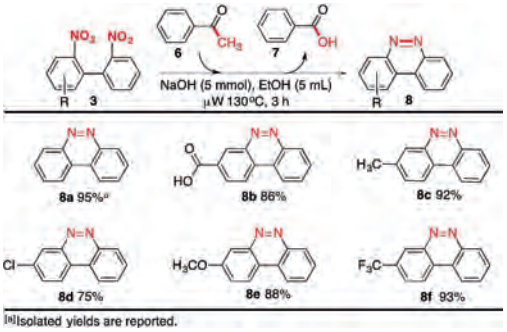
For the present study, initially, we attempted to synthesize target benzo[*c*]cinnoline framework **8** by treating 2,2′-dinitro-1,1′-biphenyl **3** for a short period (30 min.), under microwave irradiation at elevated temperature (120°C) in the place of thermal heating, Scheme 3. However, benzo[*c*]cinnoline-*N*-oxide **9** was obtained as the major product and the expected benzo[*c*]cinnoline **8** as the minor product. Since the major product **9** of this reaction experiment constitutes a less reduced form of target molecule **8**. Increased reaction time (3 h) and reaction temperature (130 °C) were attempted, which



Scheme 3. Optimization of the reaction conditions for the domino nitro group reduction and intramolecular diazo bond formation.

successfully afforded target molecule benzo[*c*]cinnoline **8** in an excellent yield (95%).

The established method for the synthesis of the benzo[*c*] cinnoline scaffold was then utilized on a selection of 2,2′-dinitro-1,1′-biphenyls. The trials demonstrated that the ring formation, that is the domino partial nitro group reduction and intramolecular diazo bond formation (providing the benzo[*c*] cinnoline scaffold) operates successfully for both the activating and deactivating substituents including $-CH_3$, $-OCH_3$, –Cl, $-CF_3$, and –COOH, see Scheme 4. In line with our previous findings



Scheme 4. Scope and limitation of the domino nitro group reduction and intramolecular diazo bond formation yielding the benzo[*c*]cinnoline scaffold.

for the symmetrically substituted 2,2′-dinitro-1,1′-biphenyls the domino partial nitro group reduction and intramolecular diazo bond formation does not operate successfully with oxidisable functional groups such as $-COCH_3$, –CHO, and –OH.

Benzo[*c*]cinnolines that shall possess the carboxylic acid group, might be synthesized from the corresponding 2,2′-dinitro-1,1′-biphenyl carboxylic acid methyl ester. Benzo[*c*] cinnoline-3-carboxylic acid was synthesized from the analogous 1-(2,2′-dinitro-[1, 1′-biphenyl]-4-yl)ethan-1-one **3b**. In this molecule, the acetyl group acted as the reducing agent (in the place of acetophenone **6**) for the two nitro groups that lead to formation of the benzo[*c*]cinnoline scaffold bearing the carboxylic acid group (**8b**). When an experiment with identical conditions was conducted, but with acetophenone **6** present, benzo[*c*]cinnoline-3-carboxylic acid **8b** was formed, which revealed that the acetyl group of the substrate **3b** again operated as the reductant.

In summary, we have developed an unprecedented Suzuki cross-coupling protocol for the synthesis of 2,2′-dinitro-1,1′-biphenyls that taken together with an substantially improved domino partial nitro group reduction and intramolecular diazo bond formation process constitutes a two-step synthesis applicable for the preparation of un-symmetrically (and symmetrically) benzo[*c*]cinnolines. Overall, the disclosed process operates with both electron withdrawing and electron donating groups present in the molecular scaffold. Functional groups susceptible to SET oxidation such as free hydroxyl and carboxylic acid need to be protected before subjected for the experimental conditions of the revealed procedure.

Supporting Information Summary

The supporting information provides complete experimental procedures and spectral data (^{1}H, ^{13}C and HRMS) of synthesised compounds **3a-3f**, **8a-8f** and **9**.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Benzo[*c*]cinnoline · 2,2′-Dinitro-1,1′-biphenyl · *N*-heterocycle · Palladium · Suzuki cross-coupling

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All the ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent, except for compound **4b** for which DMSO-*d*6 was used. The spectra were recorded by using a NMR instrument at 500 MHz for ^{1}H and 125 MHz for ^{13}C.

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Experimental Section

Chemicals. Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without being purified. All the reaction mixtures and the column fractions samples were monitored by means of TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 nm and λ = 365 nm. ^{1}H and ^{13}C NMR spectra were recorded with BrukerAV 500 MHz. High-resolution mass spectrometry (HRMS) were performed with a Q-TOF Micro YA263 instrument.

Analyses. GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m,0.20 mm i.d.,0.33 mm film thickness) at a helium pressure of200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. DART mass spectra were obtained by using PEG as an internal standard in positive ionization mode with a TOF mass analyzer. ^{1}H and ^{13}C-NMR spectra were recorded at ambient temperature at a frequencyof 500 and 125 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ = 7.26 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm) and with DMSO-d_6 for proton (δ = 2.50 ppm) and for carbon (δ = 39.0 ppm) with tetramethylsilane as an external reference. Flash chromatography was performed by using the indicated solvent system and silicagel (230–400 mesh).

Microwave reactor. The microwave-assisted experiments were performed by means of a Biotage Initiator Sixty EXP Microwave System, that operates at 0–400 W at 2.45 GHz, in the temperature range of 40–250 °C, a pressure range of 0–20 bar (2 MPa, 290 psi), and with reactor vial volumes of 0.2–20 mL.

General procedure to 2,2'-dinitro-1,1'-biphenyls. 1-Bromo-2-nitrobenzene (1 mmol), 2-nitrophenylboronic acid (1.5 mmol), Na_2CO_3 (1.1 mmol), tetrabutylammonium bromide (TBAB; 0.08 mmol), and $Pd(PPh_3)_4$ (0.026 mmol, 2.6 mol-%) were transferred to a microwave vial (10 mL), which was sealed and flushed with Ar whereupon a mixture of MeOH (4 mL) and water (1 mL) was added. The mixture was stirred for 10-15 s and then placed into the microwave cavity for 60 min. at 150 °C. The solvent (methanol) was then removed under reduced pressure. The residue was diluted with diethyl ether (50 mL) and washed with water (50 mL). The aqueous phase was extracted with diethyl ether (2 × 40 mL). The organic layers were combined and dried over Na_2SO_4. The drying agent was filtered off and the crude product was purified by silica-gel flash chromatography [ethyl acetate/hexane (mixture of isomers)] to obtain the 2,2'-dinitro-1,1'-biphenyl.

2,2'-dinitro-1,1'-biphenyl (3a) [2436-96-6]. 1-bromo-2-nitrobenzene **5a** (0.100 g, 0.495 mmol), (2-nitrophenyl)boronic acid **2** (0.124 g, 0.743 mmol), Na_2CO_3 (0.058 g, 0.547 mmol), TBAB (0.013 g, 0.040mmol) and $Pd(PPh_3)_4$ (0.015 g, 0.013 mmol) The title compound was isolated using [(EtOAc:Hx, 10:90)] eluent as a pale-brown solid (0.051 g, 42 %). R_f = 0.22 [(EtOAc:Hx, 10:90)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.21-8.23 (dd, *J*= 1.0 Hz, 8 Hz, 2H), 7.67-7.70 (td, *J*= 1.5 Hz, 8.0 Hz, 2H), 7.58-7.61 (m, 2H), 7.29-7.31 (dd, *J* = 1.0 Hz, 7.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 147.2, 134.2, 133.4, 130.9, 129.1, 124.8.; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{12}H_9N_2O_4^+$ 245.05568; Found 245.05677.

1-(2,2'-dinitro-[1,1'-biphenyl]-4-yl)ethan-1-one (3b) [NEW]. 1-(4-bromo-3-nitrophenyl)ethan-1-one **5b** (0.100 g, 0.410 mmol), (2-nitrophenyl)boronic acid **2** (0.103 g, 0.617 mmol), Na_2CO_3 (0.048 g, 0.453 mmol), TBAB (0.011 g, 0.034 mmol) and $Pd(PPh_3)_4$ (0.013 g, 0.011 mmol). The title compound was isolated using [(EtOAc:Hx, 20:80)] eluent as a yellow solid (0.105 g, 90 %). R_f = 0.30 [(EtOAc:Hx, 20:80)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.75 (s, 1H), 8.27-8.29 (dd, *J* = 1.0 Hz, 8.0 Hz, 1H), 8.24-8.26 (dd, *J* = 2 Hz, 8 Hz, 1H), 7.71-7.74 (td, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.63-7.65 (m, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.28-7.30 (dd, *J* = 1.5 Hz, *J* = 8 Hz, 1H), 2.72 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 195.2, 147.4, 146.9, 138.6, 137.7, 133.7, 133.4, 132.4, 131.5, 130.5, 129.7, 125.1, 124.6, 26.7.; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{14}H_{11}N_2O_5^+$ 287.06625; Found 287.06699.

4-methyl-2,2'-dinitro-1,1'-biphenyl (3c) [106164-07-2]. 1-bromo-4-methyl-2-nitrobenzene **5c** (0.100 g, 0.463 mmol), (2-nitrophenyl)boronic acid **2** (0.115 g, 0.689 mmol), Na_2CO_3 (0.054 g, 0.509 mmol), TBAB (0.012 g, 0.037 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol). The title compound was isolated using [(EtOAc:Hx, 10:90)] eluent as a pale-orange solid (0.030 g, 25%). R_f = 0.25 [(EtOAc:Hx, 10:90)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.19 (d, *J*= 8.5 Hz, 1H), 8.03 (s, 1H), 7.67 (t, *J*= 7.5 Hz, 1H),

7.56-7.59 (m, 1H), 7.48 (d, *J*= 7.5 Hz, 1H), 7.28-7.29 (m, 1H), 7.17 (d, *J*= 8 Hz, 1H), 2.52 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 147.5, 147.1, 139.8, 134.3, 134.1, 133.3, 131.2, 131.1, 130.7, 129.0, 125.2, 124.8, 21.0.; HR-MS (DART+): *m/z* $[M+H_2O]^+$: Calcd for $C_{13}H_{12}N_2O_5^+$ 276.07407; Found 276.07918.

4-chloro-2,2'-dinitro-1,1'-biphenyl (3d) [72005-81-3]. 1-bromo-4-chloro-2-nitrobenzene **5d** (0.100 g, 0.423 mmol), (2-nitrophenyl)boronic acid **2** (0.106 g, 0.635 mmol), Na_2CO_3 (0.049 g, 0.462 mmol), TBAB (0.011 g, 0.034 mmol) and $Pd(PPh_3)_4$ (0.013 g, 0.011 mmol)The title compound was isolated using [(EtOAc:Hx, 10:90)] eluent as a pale-yellow solid (0.048 g, 41%). R_f = 0.28 [(EtOAc:Hx, 10:80)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.15-8.18 (m, 2H), 7.64 (t, *J*= 7.5 Hz, 1H), 7.59-7.61 (dd, *J*= 2 Hz, 8 Hz, 1H), 7.53-7.57 (m, 1H), 7.18-7.22 (m, 2H), ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 147.6, 147.2, 135.1, 133.6, 133.5, 133.1, 132.7, 132.0, 130.9, 129.5, 125.1, 125.0. ; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{12}H_8ClN_2O_4^+$ 279.01671; Found 279.01744.

4-methoxy-2,2'-dinitro-1,1'-biphenyl (3e) [55324-17-9]. 1-bromo-4-methoxy-2-nitrobenzene **5e** (0.25 g, 1.08 mmol), (2-nitrophenyl)boronic acid **2** (0.270 g, 1.62 mmol), Na_2CO_3 (0.126 g, 1.19 mmol), TBAB (0.029 g, 0.09 mmol) and $Pd(PPh_3)_4$ (0.032 g, 0.028 mmol). The title compound was isolated using [(EtOAc:Hx, 15:85)] eluent as a pale-brown solid (0.045 g, 15%). R_f = 0.24 [(EtOAc:Hx, 15:75)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.16-8.18 (dd, *J*= 1 Hz, 8 Hz, 1H), 7.72 (s, 1H), 7.64-7.68 (m, 1H), 7.55-7.58 (m, 1H), 7.28-7.30 (dd, *J*= 1.5 Hz, 7.5 Hz, 1H), 7.19-7.20 (m, 2H), 3.93 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 159.8, 148.0, 147.6, 134.0, 133.3, 131.8, 131.4, 128.9, 125.9, 124.7, 119.8, 109.6, 56.0.; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{13}H_{11}N_2O_5^+$ 275.06625; Found 275.06699.

2,2'-dinitro-4-(trifluoromethyl)-1,1'-biphenyl (3f) [NEW]. 1-bromo-2-nitro-4-(trifluoro-methyl)benzene **5f** (0.100 g, 0.370 mmol), (2-nitrophenyl)boronic acid **2** (0.093 g, 0.557 mmol), Na_2CO_3 (0.043 g, 0.406 mmol), TBAB (0.010 g, 0.031 mmol) and $Pd(PPh_3)_4$ (0.011 g, 0.010 mmol) The title compound was isolated using [(EtOAc:Hx, 10:90)] eluent as a yellow solid (0.098 g, 84 %). R_f = 0.31 [(EtOAc:Hx, 10:90)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.49 (s, 1H), 8.28-8.30 (dd, *J*= 1.0 Hz, 8 Hz, 1H), 7.94-7.96 (dd, *J*= 1.0 Hz, 8.0 Hz, 1H), 7.72-7.76 (td, *J*= 1.5 Hz, 7.5 Hz, 1H), 7.64-7.68 (td, J= 1.5 Hz, 8.0 Hz, 1H), 7.48 (d, *J*= 8 Hz, 1H), 7.28-7.30 (dd, *J*= 1.5 Hz, 7.5 Hz, 1H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 147.2, 146.9, 138.0, 133.8, 132.9, 132.0, 131.9, 130.5 129.9 (q), 129.8, 125.1, 123.8, 122.2 (q). HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{13}H_8F_3N_2O_4^+$ 313.04307; Found 313.04388.

2,2'-dinitro-[1,1'-biphenyl]-3-carboxylic acid (3g) [NEW]. 3-bromo-4-nitrobenzoic acid **5g** (0.100 g, 0.406 mmol), (2-nitrophenyl)boronic acid **2** (0.103 g, 0.617 mmol), Na_2CO_3 (0.048 g, 0.453 mmol), TBAB (0.011 g, 0.034 mmol) and $Pd(PPh_3)_4$ (0.012 g, 0.010 mmol). The title compound was not observed instead only obtained nitrobenzoic acid (hydrodebrominated compound) after acidic workup (pH 1-2).

2,2'-dinitro-[1,1'-biphenyl]-4-carboxylic acid (3h) [NEW]. methyl 4-bromo-3-nitrobenzoate **5h** (0.100 g, 0.385 mmol), (2-nitrophenyl)boronic acid **2** (0.096 g, 0.575 mmol), Na_2CO_3 (0.045 g, 0.425 mmol), TBAB (0.010 g, 0.031 mmol) and $Pd(PPh_3)_4$ (0.012 g, 0.010 mmol) were transferred to the microwave reactor tube, that was sealed and flushed with Ar. Then methanol (4 mL) and water (1 mL) were added. The reactor tube was submerged into the microwave cavity for 1 h at a temperature of 150 °C. After completion of the reaction, the solvent methanol was removed under reduced pressure. The residue was diluted with diethyl ether (50 mL) and washed with water (50 mL). The product was in the aqueous phase since it was hydrolysed and form sodium salt under the basic conditions. The aqueous layer was acidified with Conc., HCl (pH 1-2) and extracted with ethyl acetate (40 mL). The aqueous phase was extracted with ethyl acetate (2 × 40 mL). The organic extracts were combined and dried over sodium sulfate. The drying agent was filtered off and the crude product contains the desired acid compound with 62% purity based on NMR data (hydrolysed product from the ester) and also the hydrodebrominated compound (3-nitrobenzoic acid) with 38% estimated by NMR data (total of 0.050 g). It was difficult to separate both the acid containing products, the crude product was proceeded next step without further purification.The spectral data for the crude product as follows: ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 10.91 (s, br, 2H), 8.95 (m, 1H), 8.92 (d, 1H), 8.47-8.49 (m, 1H), 8.44-8.46 (m, 1H), 8.40-8.42 (dd, *J*=1.5 Hz, 8.0 Hz, 1H), 8.28-8.30 (dd, *J*= 1.5 Hz, 8.0 Hz, 1H), 7.70-7.75 (m, 2H), 7.64-7.67 (m, 1H), 7.46 (d, *J*= 8.0 Hz, 1H), 7.30-7.32 (dd, *J*= 1.0 Hz, 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ=170.0, 169.7, 148.4, 147.3, 146.8, 139.6, 135.8, 134.5, 133.8, 133.3, 131.5, 131.0, 130.5, 129.9, 129.8, 128.4, 126.6, 125.3, 125.1.

General procedure for the synthesis of benzo[*c*]cinnolines. 2,2'-dinitro-1,1'-biphenyl (1 mmol), acetophenone (0.9 mmol) and NaOH (5 mmol) were transferred to a microwave vial (10 mL), which was sealed and flushed with Ar whereupon ethanol (5 mL) was added. The mixture was stirred for 10-15 s and then placed into the microwave cavity for 3 h at 130 °C. The solvent ethanol was then removed under reduced pressure. The residue was diluted with ethyl acetate (30 mL) and washed with water (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL). The organic layers were combined and dried over Na_2SO_4. The drying agent was filtered off and the crude product was purified by silica-gel flash chromatography [ethyl acetate/hexane (mixture of isomers)] to obtain the target benzo[*c*]cinnoline.

benzo[*c*]cinnoline (8a) [230-17-1]. 2,2'-dinitro-1,1'-biphenyl **3a** (0.200 g, 0.818 mmol), acetophenone **6** (0.09 mL, 0.74 mmol), NaOH (0.164 g, 4.10 mmol) and ethanol (5 mL) were added. The title compound was isolated using [(EtOAc:Hx, 20:80)] eluent as a yellow crystalline solid (0.140 g, 95 %). R_f = 0.29 [(EtOAc:Hx, 20:80)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.74-8.75 (m, 2H), 8.56-8.58 (m, 2H), 7.89-7.91 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 145.3, 131.6, 131.3, 129.2, 121.4, 120.9.; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{12}H_9N_2^+$ 181.07602; Found 181.07654.

benzo[*c*]cinnoline-3-carboxylic acid (8b) [20684-47-3].

Method 1 – intramolecular reaction without acetophenone present. To a microwave vial, 1-(2,2'-dinitro-[1,1'-biphenyl]-4-yl)ethan-1-one **3b** (0.030 g, 0.105 mmol), NaOH (0.021 g, 0.525 mmol) were added. The vial was sealed and flushed with Ar and solvent ethanol (5 mL) was added. The tube was submerged into microwave cavity for 3 h at 130 °C. The reaction proceeded via an intramolecular cyclization using the acetyl group as reductant in the molecule and the product should be an acid instead of ketone. Under the basic conditions it should form the sodium salt. After the reaction time, the solvent ethanol was removed under reduced pressure. The residue was diluted with ethyl acetate (40 mL) and washed with water (40 mL). The aqueous phase was acidified with Conc., HCl (pH 1-2) and extracted with ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL). The organic extracts were combined and dried over Na_2SO_4. The drying agent was filtered off and the crude product contains the desired acid compound as a dark brown solid (0.020 g, 86 %). R_f = 0.33 [(100%, EtOAc)]. ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 13.6 (s, br, 1H), 9.18 (s, 1H), 9.03 (d, *J*= 7.5 Hz, 1H), 8.96-8.98 (m, 1H), 8.75-8.77 (m, 1H), 8.48-8.50 (dd, *J*= 1.5 Hz, 8.5 Hz, 1H), 8.11-8.13 (m, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ= 166.4, 145.1, 144.1, 132.6, 132.0, 131.8, 131.2, 131.0, 130.6, 123.3, 123.2, 123.0, 119.6. HR-MS (DART-): *m/z* $[M-H]^-$: Calcd for $C_{13}H_7N_2O_2^-$ 223.05130; Found 223.05099.

Method 2 – Using acetophenone as reductant. 2,2'-dinitro-[1,1'-biphenyl]-4-carboxylic acid (**3h**) (24.8 mg, 0.086 mmol), acetophenone **6** (0.009 mL, 0.077 mmol) and NaOH (0.017 g, 0.425 mmol) were added into the microwave tube (10 mL). The tube was sealed and flushed with Ar and solvent ethanol (5 mL) was added. The tube was submerged into microwave cavity for 3 h at 130 °C. After the reaction time, the solvent ethanol was removed under reduced pressure. The residue was diluted with ethyl acetate (30 mL) and washed with water (40 mL). The expected product was in the aqueous phase since it form sodium salt under the basic conditions The aqueous phase was acidified with Conc., HCl (pH 1-2) and extracted with ethyl acetate (40 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL). The organic extracts were combined and dried over Na_2SO_4. The drying agent was filtered off and the crude product was washed with DCM (10 mL) to remove the impurities and obtained the title compound as a pale-yellow solid ((0.016 g, 81%); ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 13.5 (s, br, 1H), 9.17 (d, 1H), 9.02 (d, *J*= 8.5 Hz, 1H), 8.96-8.97 (m, 1H), 8.75-8.77 (m, 1H), 8.47-8.49 (dd, *J*= 1.5 Hz, 8.5 Hz, 1H), 8.11-8.13 (m, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ= 166.4, 145.1, 144.1, 132.6, 132.0, 131.8, 131.2, 130.9, 130.6, 123.3, 123.2, 123.0, 119.6.

3-methylbenzo[*c*]cinnoline (8c) [79580-34-0]. 4-methyl-2,2'-dinitro-1,1'-biphenyl **3c** (0.036 g, 0.140 mmol), acetophenone **6** (0.015 mL, 0.125 mmol), NaOH (0.028 g, 0.70 mmol) and ethanol (5 mL) were added. The title compound was isolated using [(EtOAc:Hx, 10:90)] eluent as a yellow solid (0.025 g, 92 %). R_f = 0.11 [(EtOAc:Hx, 10:90)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.70-8.72 (m, 1H), 8.51-8.53 (m, 2H), 8.45 (d, *J*= 8.5 Hz, 1H), 7.85-7.88 (m,2H), 7.72-7.74 (dd, *J*= 1.5 Hz, 8.5 Hz, 1H), 2.68 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 145.6, 145.2, 139.7, 133.5, 131.4, 131.3, 130.4, 128.7, 121.3, 121.2, 121.1, 118.7, 21.7. HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{13}H_{11}N_2^+$ 195.09167; Found 195.09277.

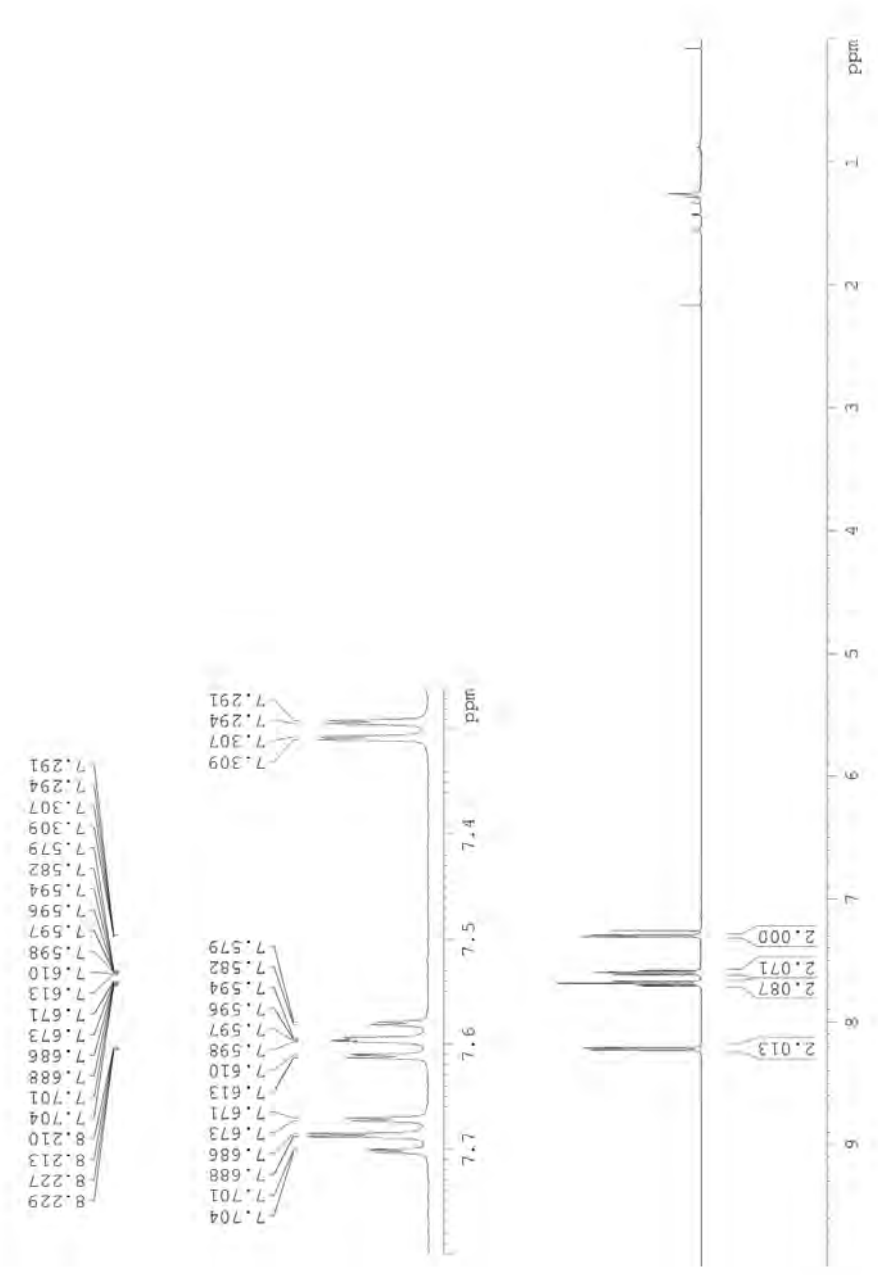
3-chlorobenzo[*c*]cinnoline (8d) [57880-67-8]. 4-chloro-2,2'-dinitro-1,1'-biphenyl **3d** (0.035 g, 0.126 mmol), acetophenone **6** (0.013 mL, 0.116 mmol), NaOH (0.025 g, 0.625 mmol) and ethanol (5 mL) were added. The title compound was isolated using [(EtOAc:Hx, 10:90)] eluent as a yellow solid (0.020 g, 75 %). R_f = 0.19 [(EtOAc:Hx, 10:90)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.75-8.78 (m, 2H), 8.53-8.57 (m, 2H), 7.94-7.96 (m, 2H), 7.86-7.89 (dd, *J*= 2.0 Hz, 8.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 145.6, 145.4, 135.1, 132.3, 132.1, 131.6, 130.3, 129.6, 128.5, 125.4, 123.2, 121.3. HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{12}H_8{}^{35}ClN_2{}^+$ 215.03705; Found 215.03799; Calcd for $C_{12}H_8{}^{37}ClN_2{}^+$ 217.03410; Found 217.03561.

3-methoxybenzo[*c*]cinnoline (8e) [55324-18-0]. 4-methoxy-2,2'-dinitro-1,1'-biphenyl **3e** (0.040 g, 0.416 mmol), acetophenone **6** (0.015 mL, 0.133 mmol), NaOH (0.029 g, 0.730 mmol) and ethanol (5 mL) were added. The title compound was isolated using [(EtOAc:Hx, 15:85)] eluent as a yellow solid (0.027 g, 88 %). R_f = 0.13 [(EtOAc:Hx, 15:85)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.69-8.71 (dd, *J*= 1.0 Hz, 8.0 Hz, 1H), 8.46-8.49 (m, 2H), 8.08 (d, 1H), 7.85-7.88 (m, 1H), 7.81-7.84 (m, 1H), 7.53-7.55 (dd, *J*= 3.0 Hz, 9.0 Hz, 1H), 4.07 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 159.3, 146.0, 144.1, 130.6, 130.2, 127.2, 122.7, 121.7, 120.2, 120.0, 114.4, 108.5, 54.8.; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{13}H_{11}N_2O^+$ 211.08659; Found 211.08736.

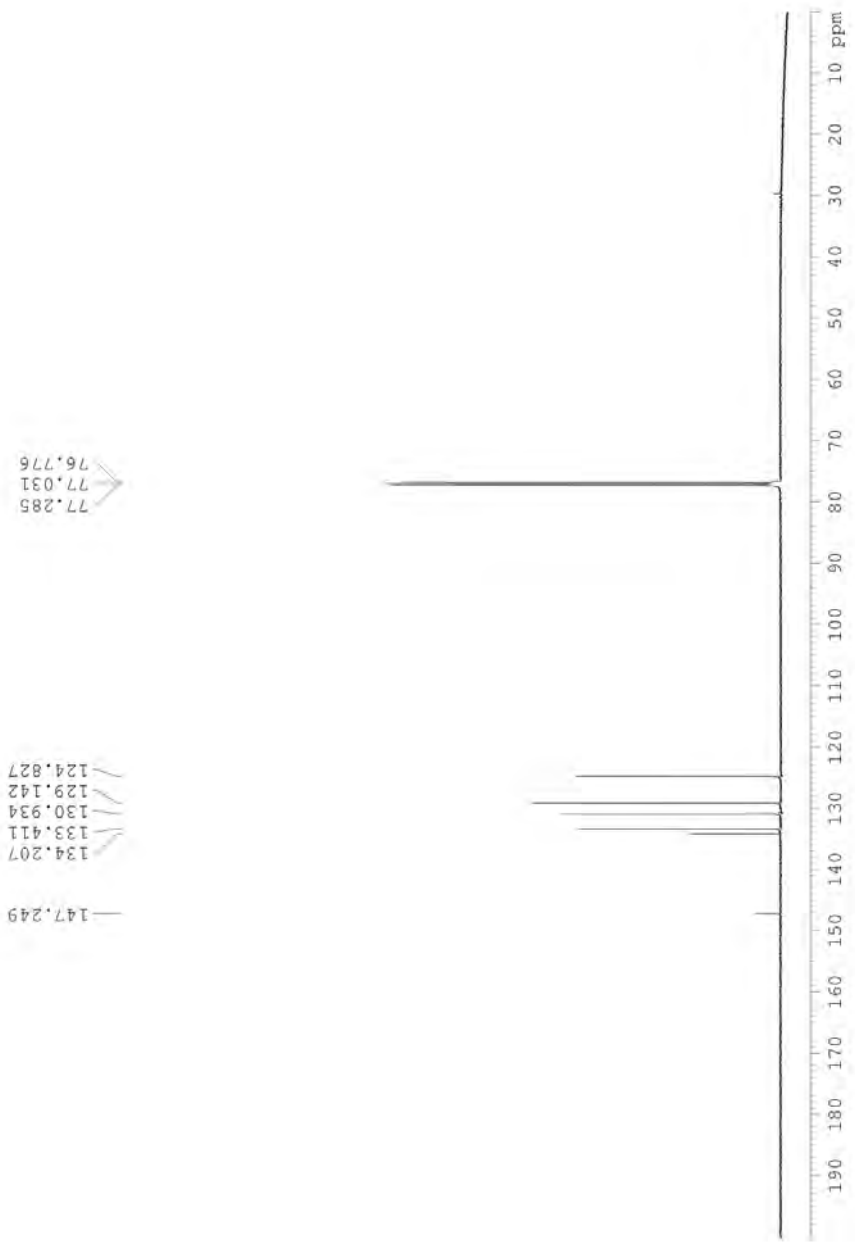
3-(trifluoromethyl)benzo[*c*]cinnoline (8f) [945927-97-9]. 2,2'-dinitro-4-(trifluoromethyl)-1,1'-biphenyl **3f** (0.080 g, 0.256 mmol), acetophenone **6** (0.027 mL, 0.233 mmol), NaOH (0.051 g, 1.275 mmol) and ethanol (5 mL) were added. The title compound was isolated using [(EtOAc:Hx, 10:90)] eluent as a yellow solid (0.059 g, 93 %). R_f = 0.17 [(EtOAc:Hx, 10:90)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 9.06 (s, 1H), 8.81-8.83 (m, 1H), 8.72 (d, *J*= 8.5 Hz, 1H), 8.61-8.63 (m, 1H), 8.09-8.11 (dd, *J*= 2.0 Hz, 8.5 Hz, 1H), 8.00-8.02 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 145.9, 144.1, 132.3, 131.7, 130.5, 129.1(q), 127.3 (q), 123.0, 121.7, 119.9.; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{13}H_8F_3N_2{}^+$ 249.06341; Found 249.06419.

benzo[*c*]cinnoline-N-oxide (9) [6141-98-6]. To a microwave vial (10 mL), 2,2'-dinitro-1,1'-biphenyl **3a** (0.20 g, 0.82 mmol), acetophenone **6** (0.09 mL, 0.74 mmol) and NaOH (0.164 g, 4.10 mmol) were added. The vial was sealed and flushed with Ar and then ethanol (5 mL) was added. The solution was stirred for 10 s before being subjected into microwave heating for 30 min. at 120 °C. The solvent ethanol was removed under reduced pressure. The residue was diluted with diethyl ether (50 mL) and washed with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL). The organic extracts were combined and dried over Na_2SO_4. The drying agent was filtered off and the crude product was purified by silica-gel flash chromatography [ethyl acetate/hexane (mixture of isomers)] [20:80] to obtain the title compound as dark brown solid (0.115 g, 72 %). R_f = 0.24 [(EtOAc:Hx, 20:80)]^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.83-8.85 (dd, *J*= 1.0 Hz, 8 Hz, 1H), 8.49-8.51 (dd, *J*= 1.0 Hz, 8.5 Hz, 1H), 8.36-8.38 (m, 1H), 7.99-8.00 (dd, *J*= 1.0 Hz, 8.5 Hz, 1H), 7.92-7.95 (m, 1H), 7.79-7.83 (m 1H), 7.74-7.77 (m 1H) , 7.68-7.70 (m 1H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 142.4, 137.3, 132.7, 130.6, 130.0, 128.9, 128.8, 126.5, 122.5, 122.4, 121.3, 118.4.; HR-MS (DART+): *m/z* $[M+H]^+$: Calcd for $C_{12}H_9N_2O^+$ 197.07094; Found 197.07248.

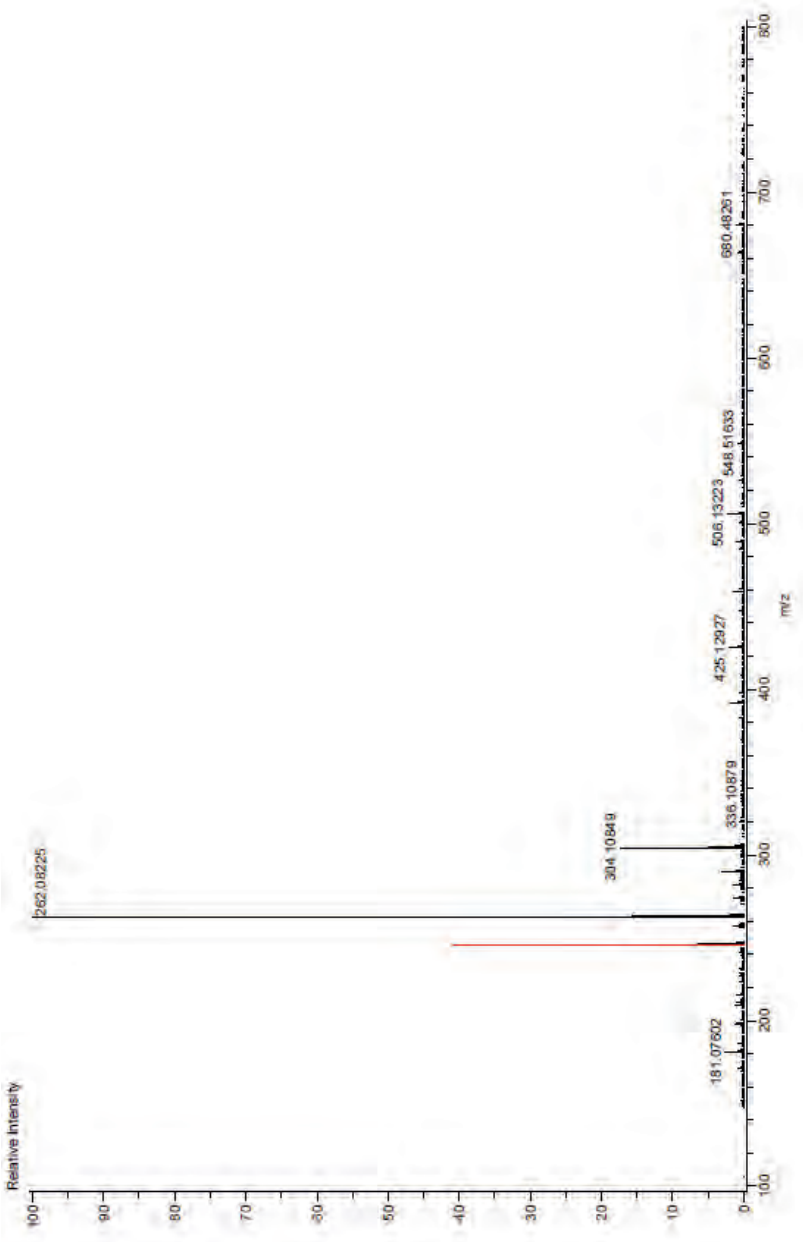
^{1}H-NMR of 2,2'-dinitro-1,1'-biphenyl (3a)



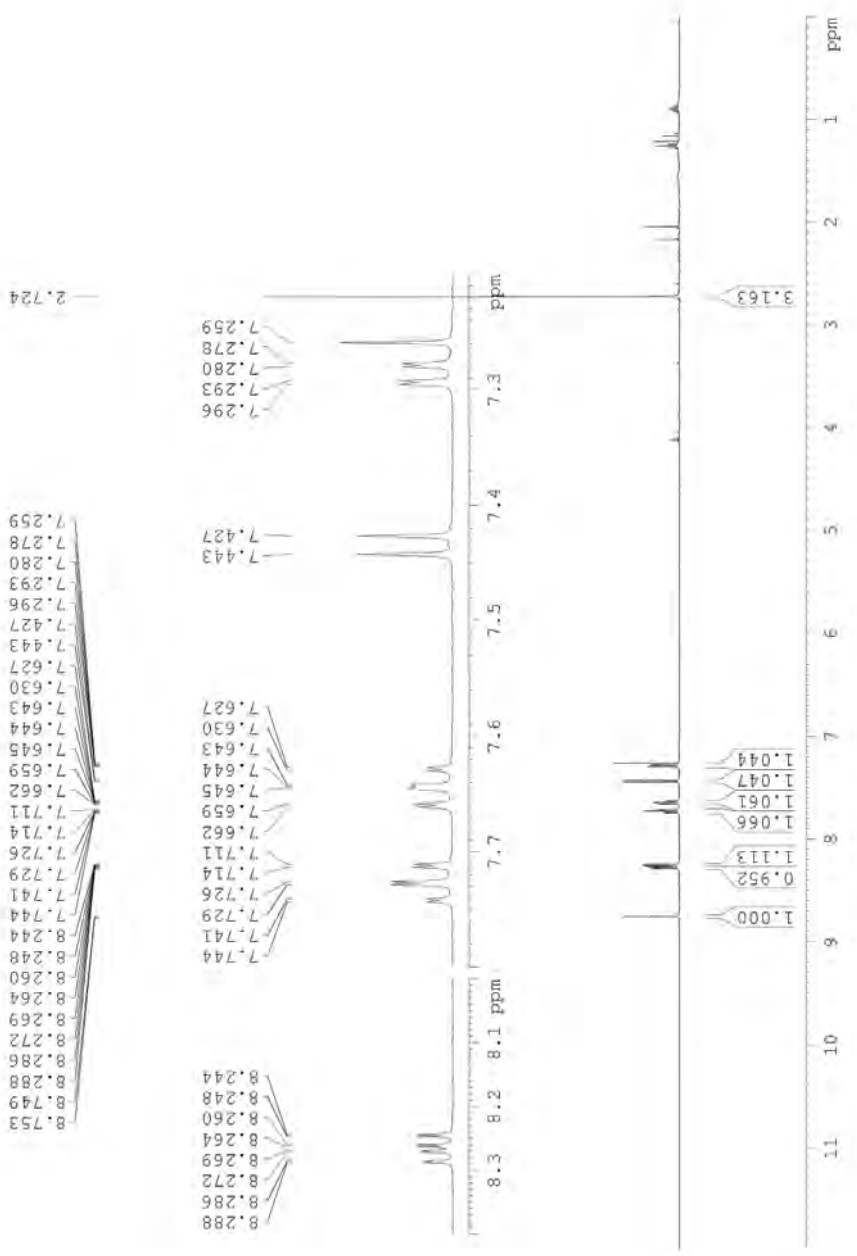
^{13}C-NMR of 2,2'-dinitro-1,1'-biphenyl (3a)



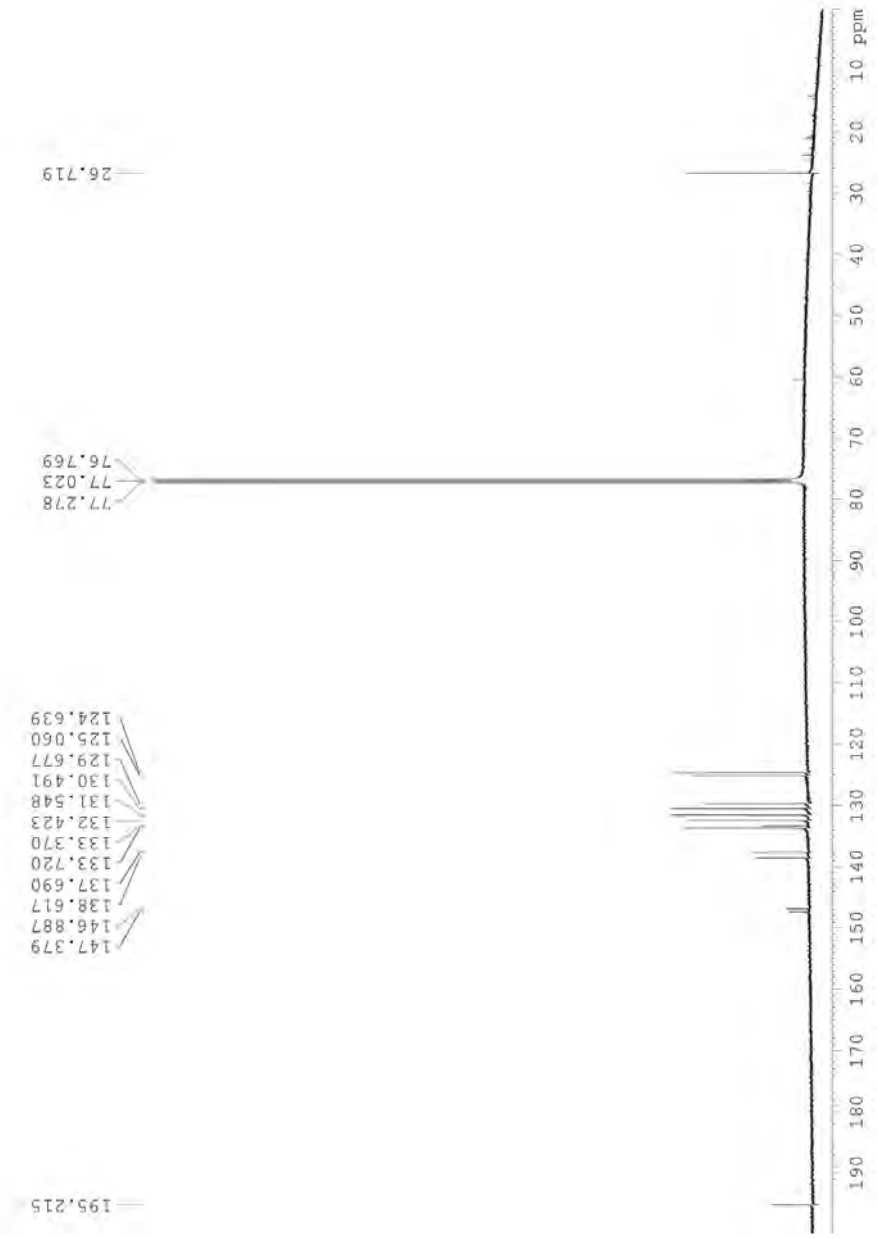
HR-MS (DART) of 2,2'-dinitro-1,1'-biphenyl (3a)



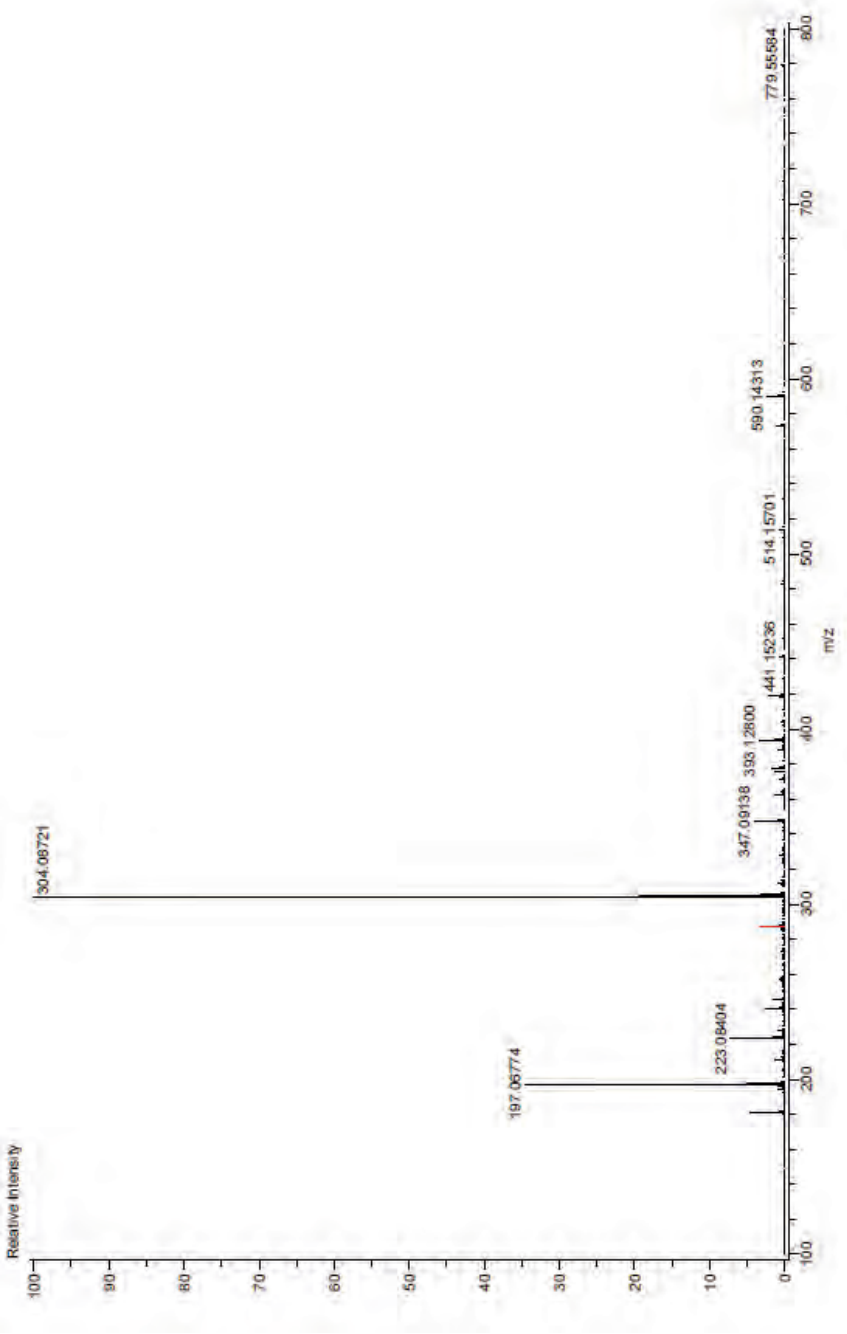
^{1}H-NMR of 1-(2,2'-dinitro-[1,1'-biphenyl]-4-yl)ethan-1-one (3b)



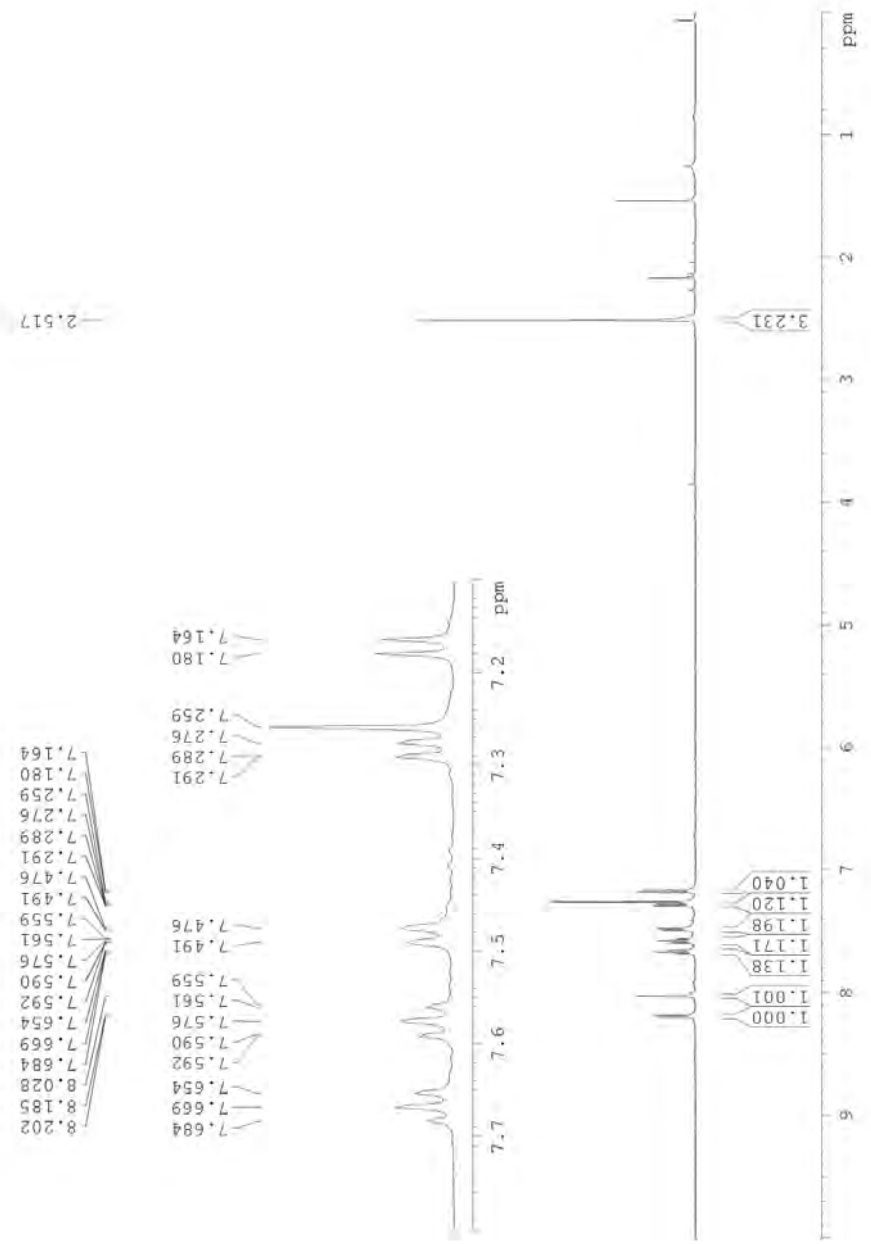
^{13}C-NMR of 1-(2,2'-dinitro-[1,1'-biphenyl]-4-yl)ethan-1-one (3b)



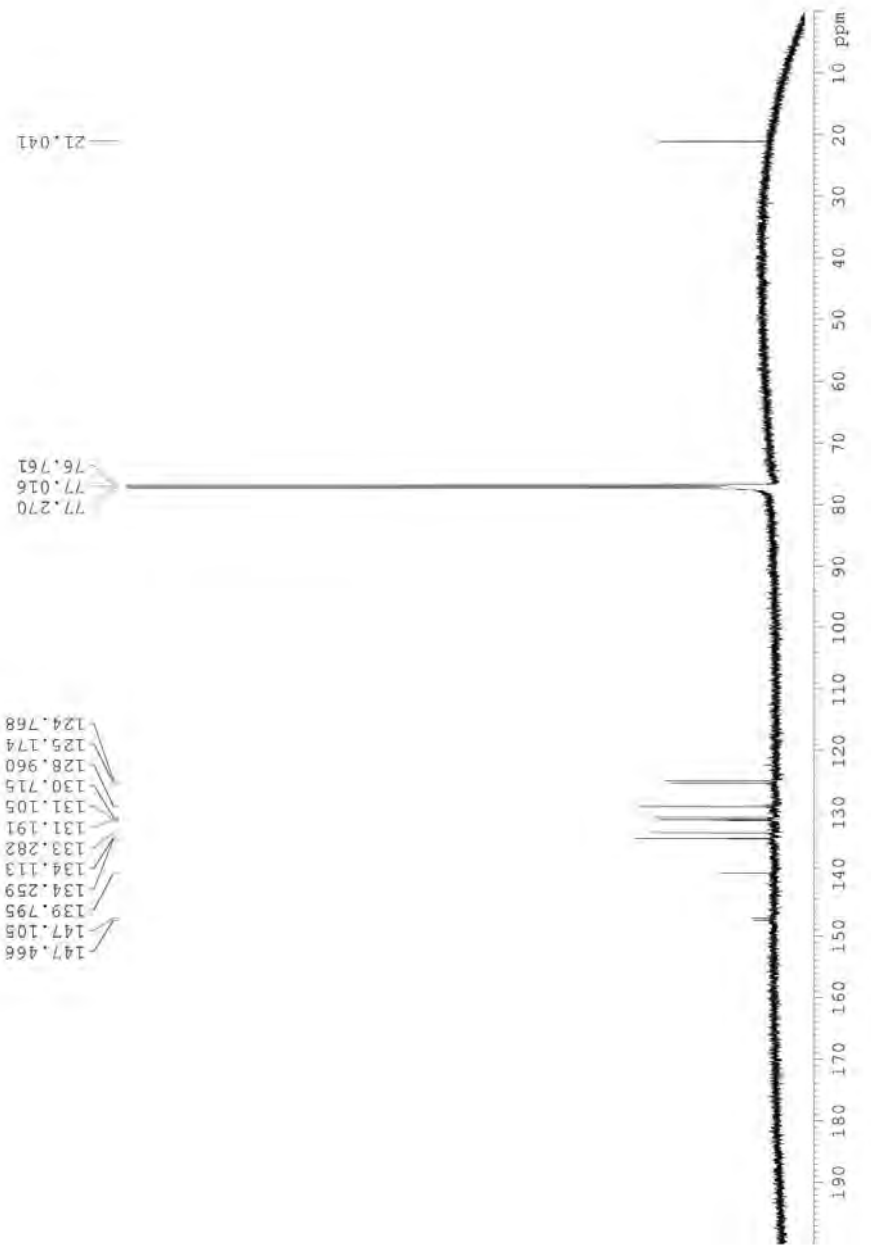
HR-MS (DART) of 1-(2,2'-dinitro-[1,1'-biphenyl]-4-yl)ethan-1-one (3b)



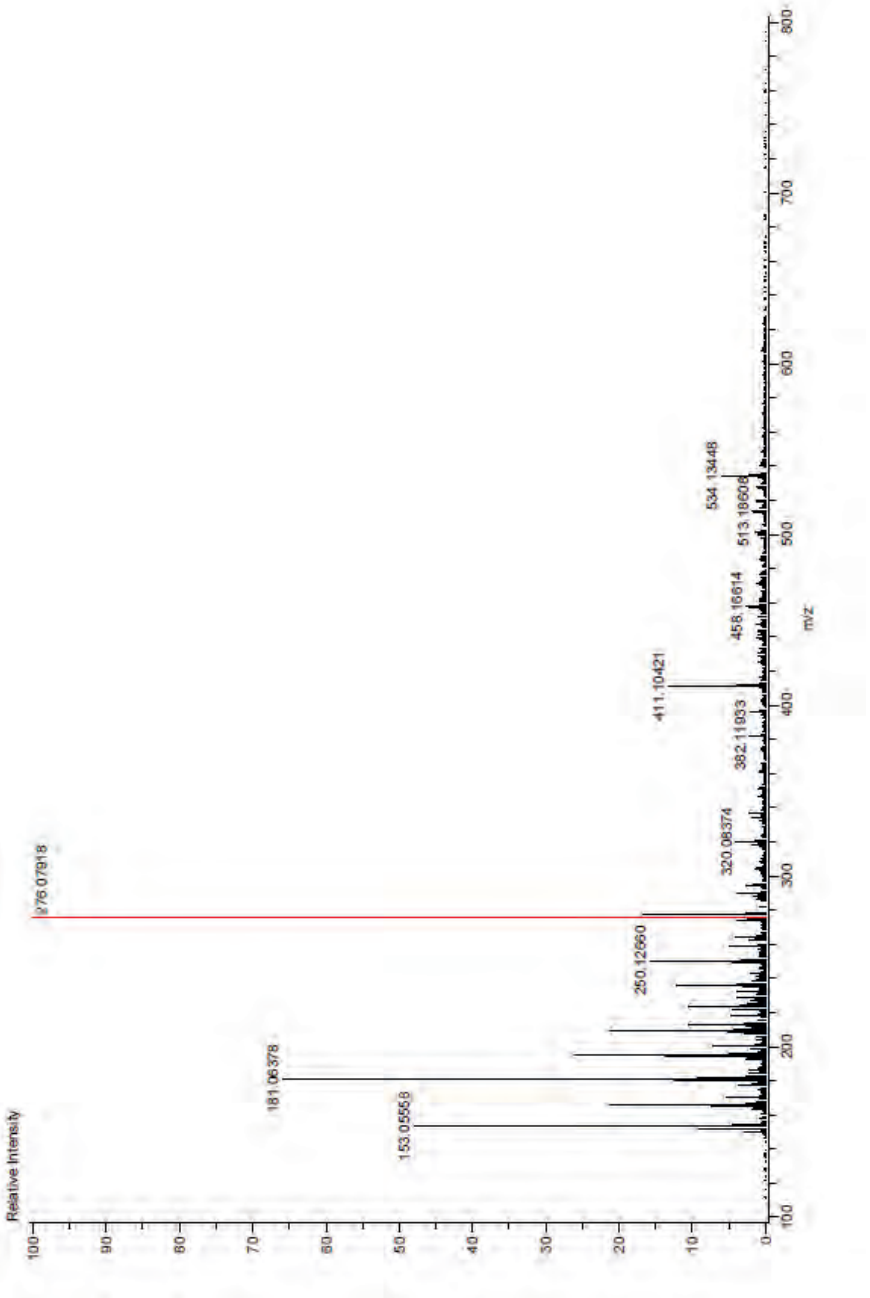
^{1}H-NMR of 4-methyl-2,2'-dinitro-1,1'-biphenyl (3c)



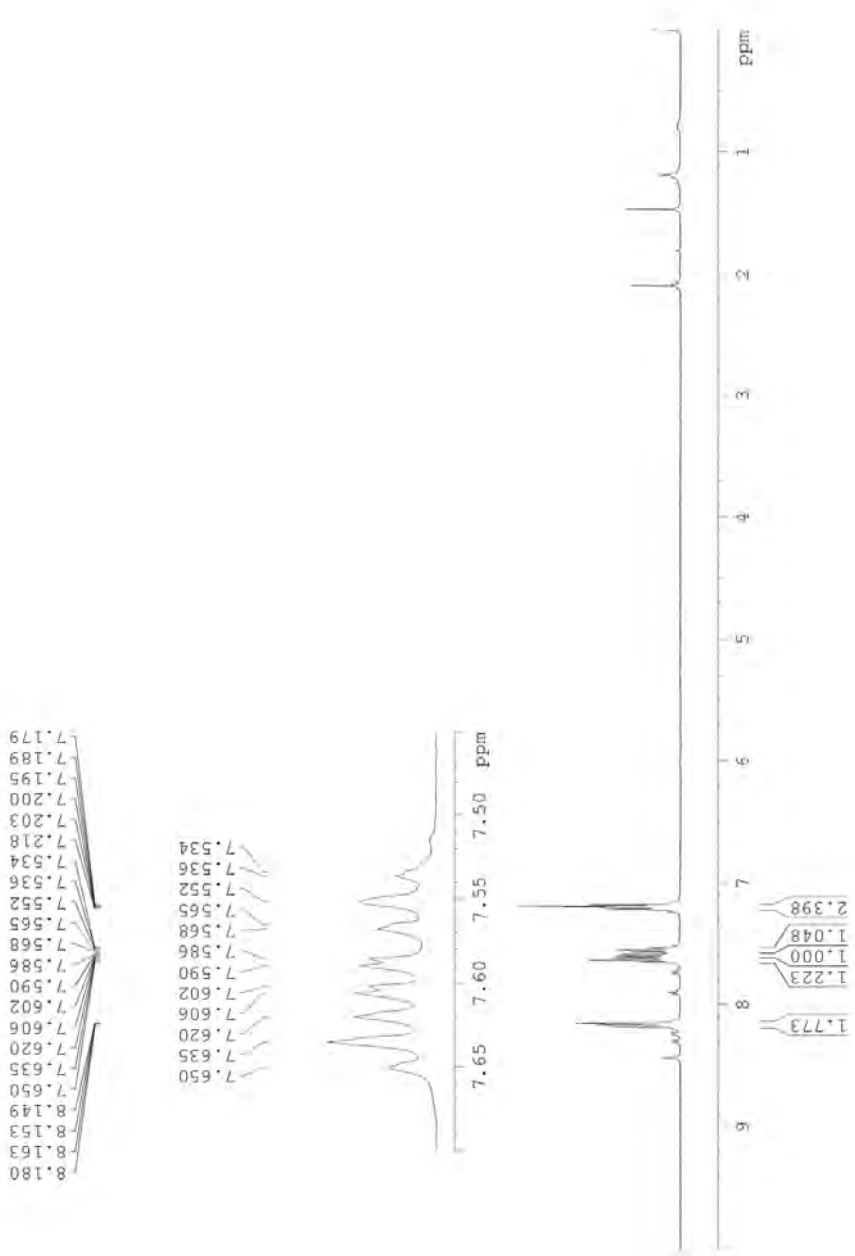
^{13}C-NMR 4-methyl-2,2'-dinitro-1,1'-biphenyl (3c)



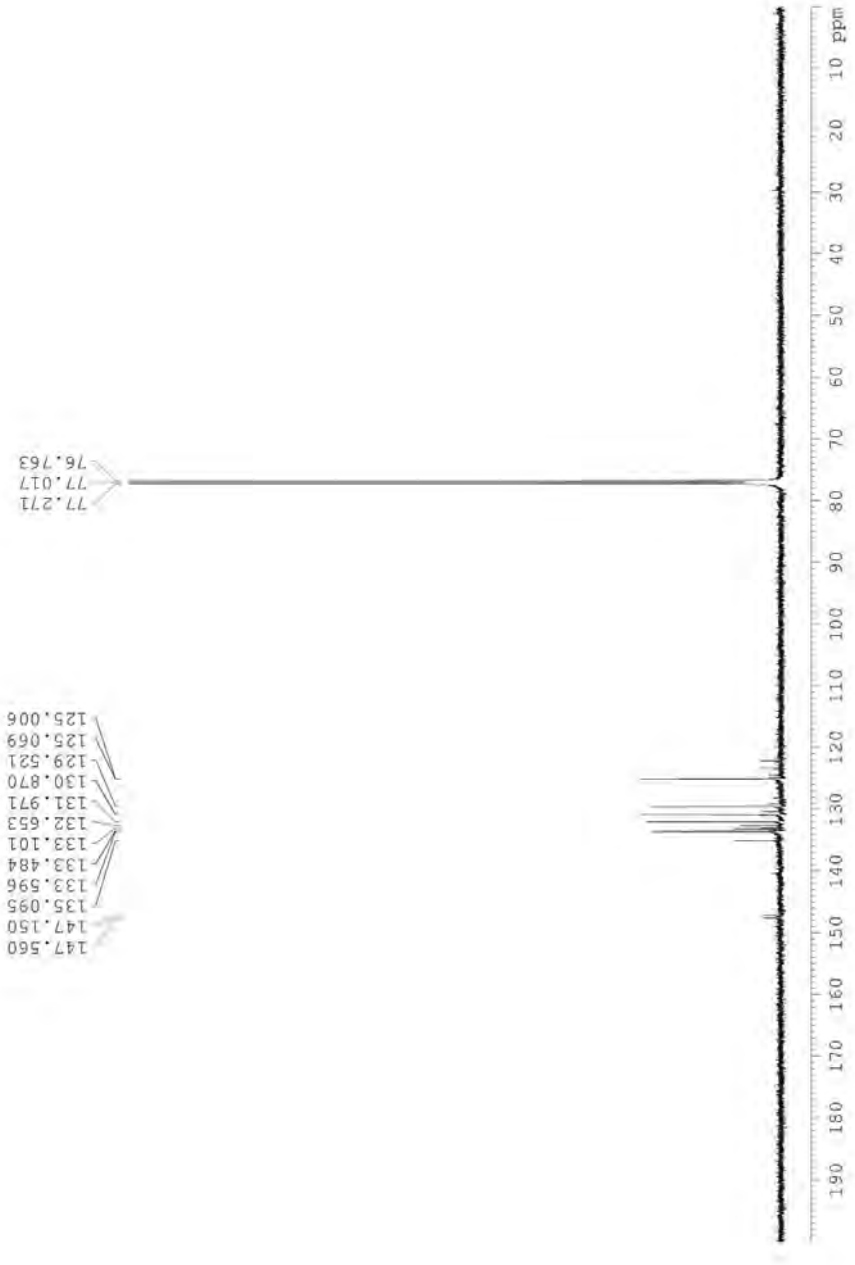
HR-MS (DART) of 4-methyl-2,2'-dinitro-1,1'-biphenyl (3c)



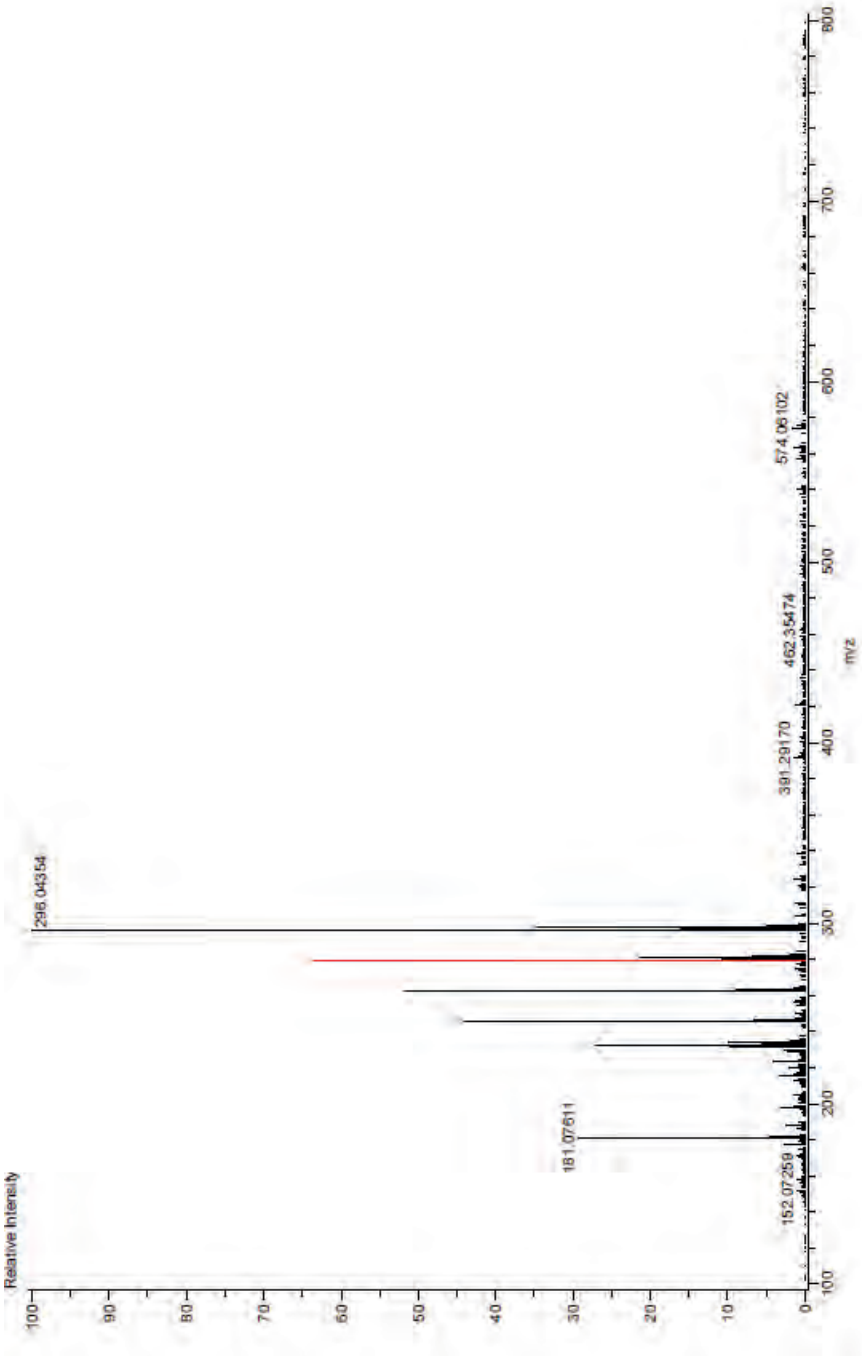
^{1}H-NMR of 4-chloro-2,2'-dinitro-1,1'-biphenyl (3d)



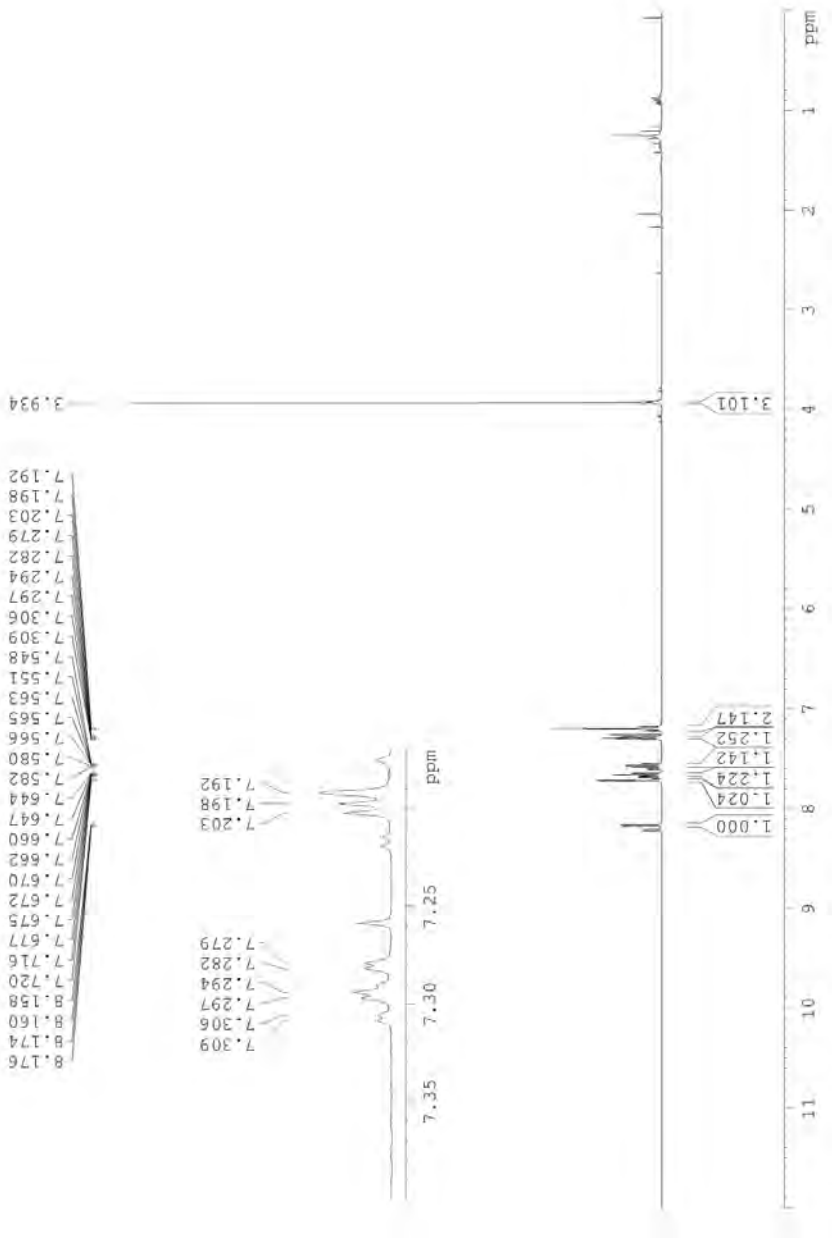
^{13}C-NMR of 4-chloro-2,2'-dinitro-1,1'-biphenyl (3d)



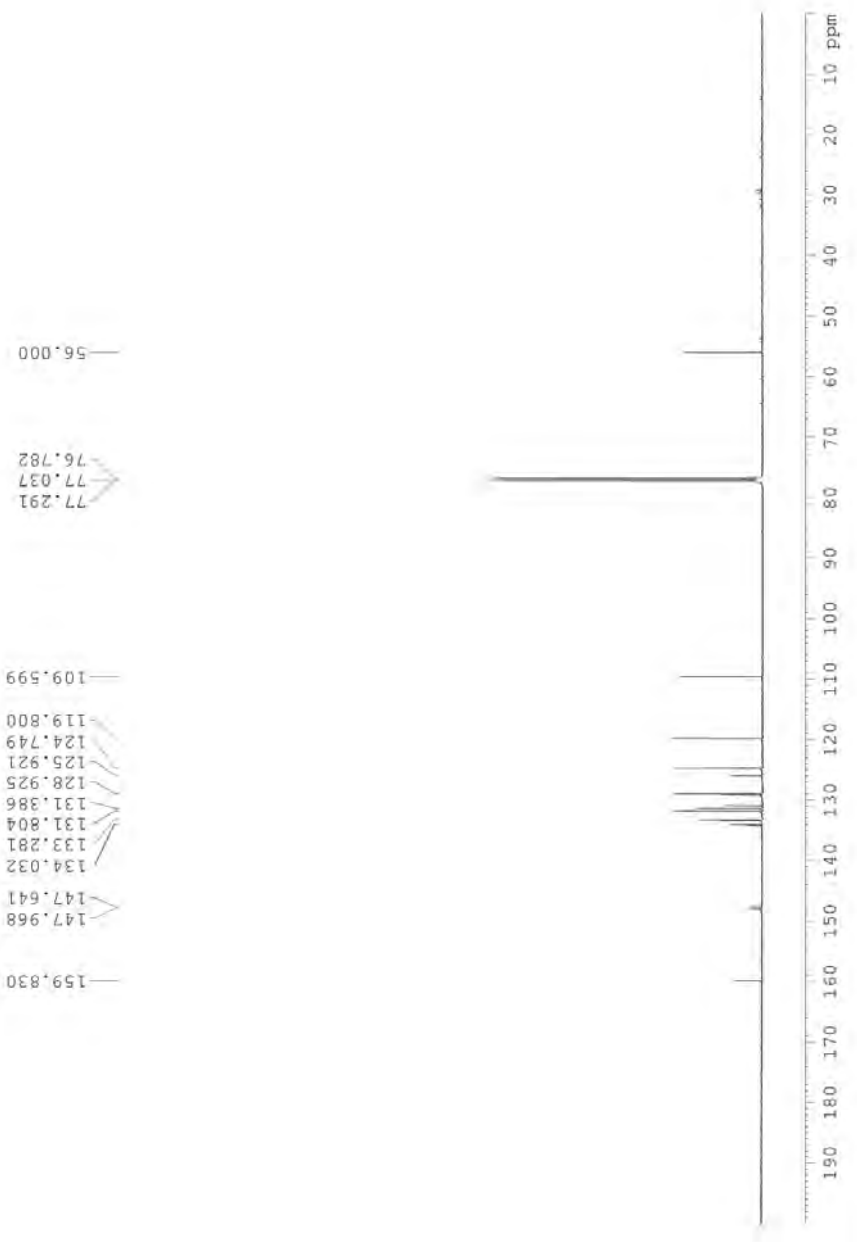
HR-MS (DART) of 4-chloro-2,2'-dinitro-1,1'-biphenyl (3d)



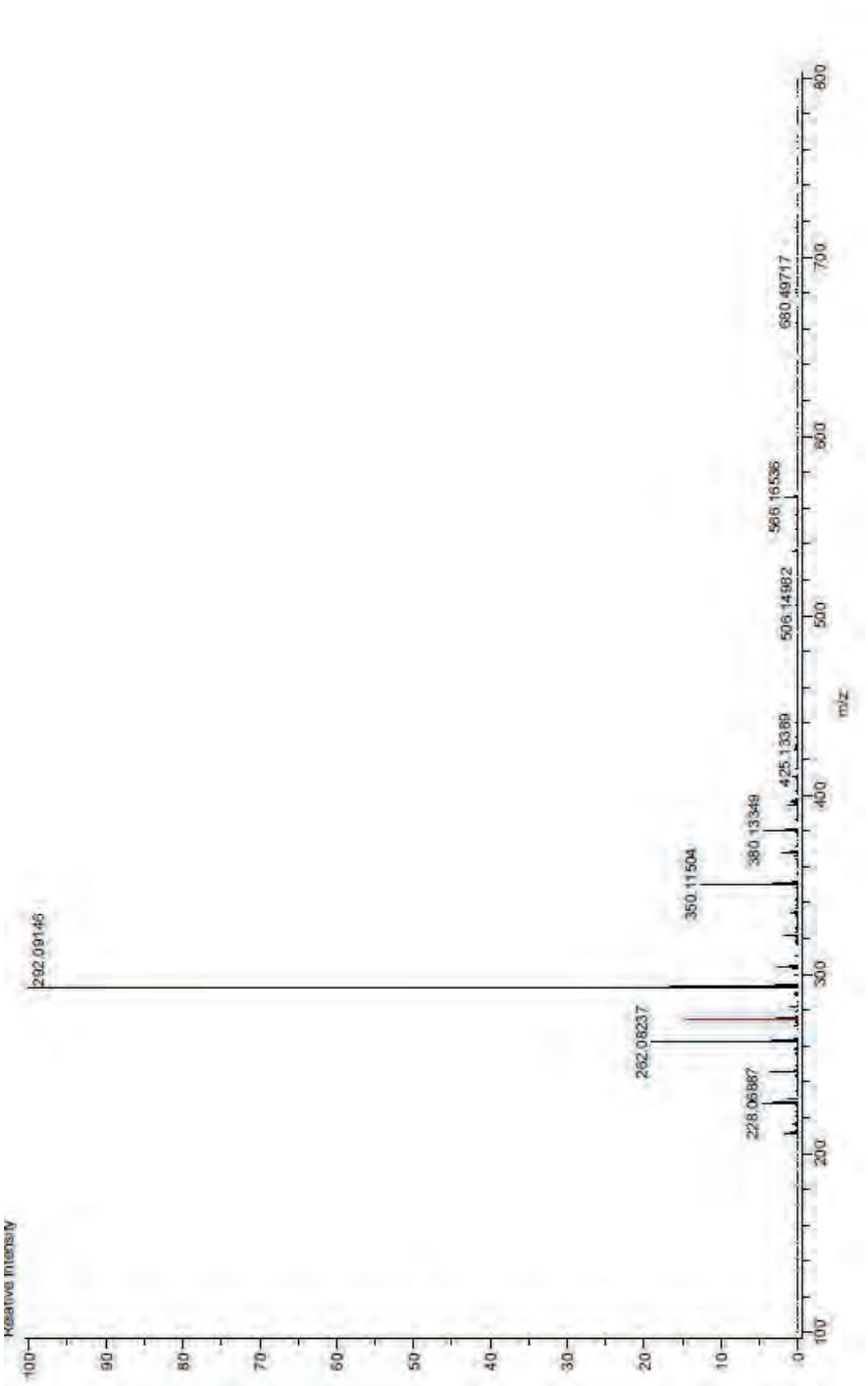
^{1}H-NMR of 4-methoxy-2,2'-dinitro-1,1'-biphenyl (3e)



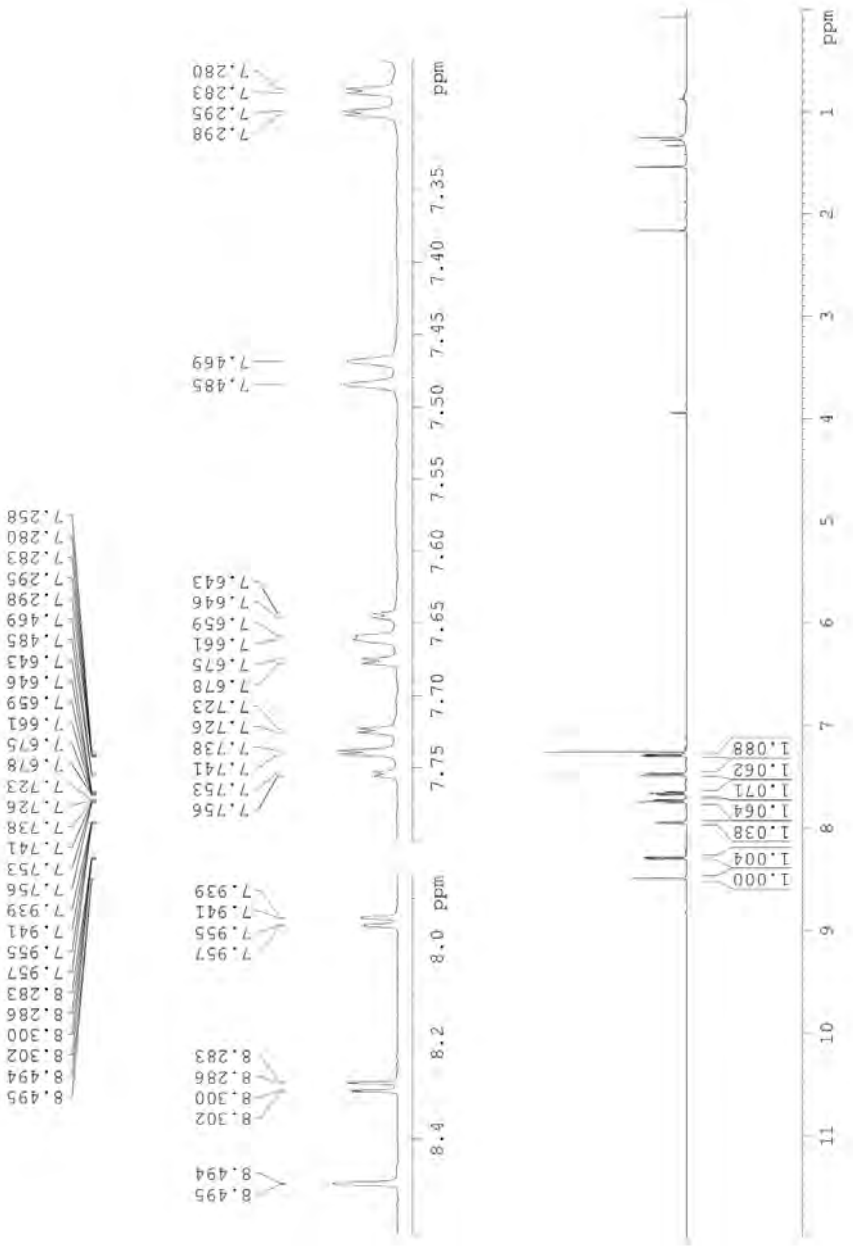
^{13}C-NMR of 4-methoxy-2,2'-dinitro-1,1'-biphenyl (3e)



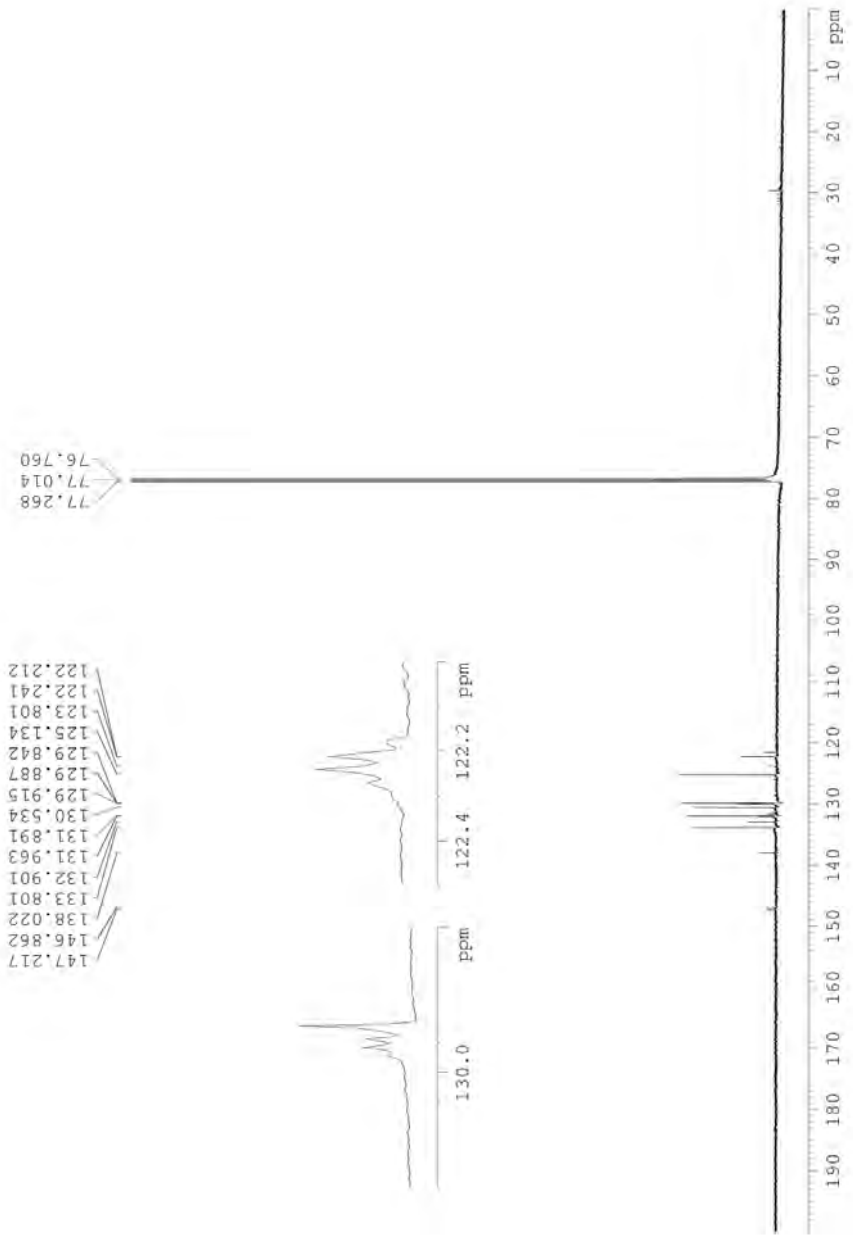
HR-MS (DART) of 4-methoxy-2,2'-dinitro-1,1'-biphenyl (3e)



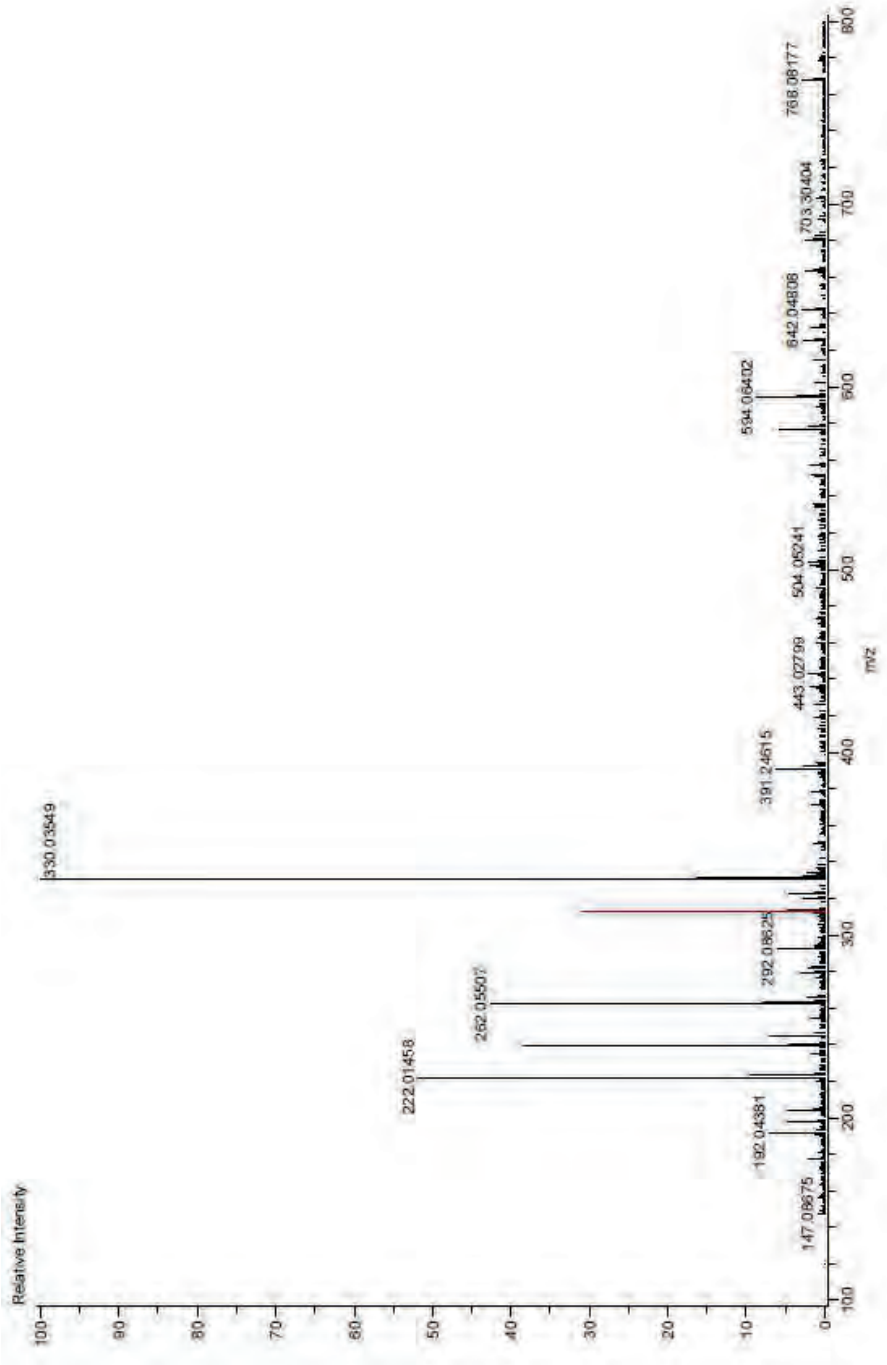
^{1}H-NMR of 2,2'-dinitro-4-(trifluoromethyl)-1,1'-biphenyl (3f)



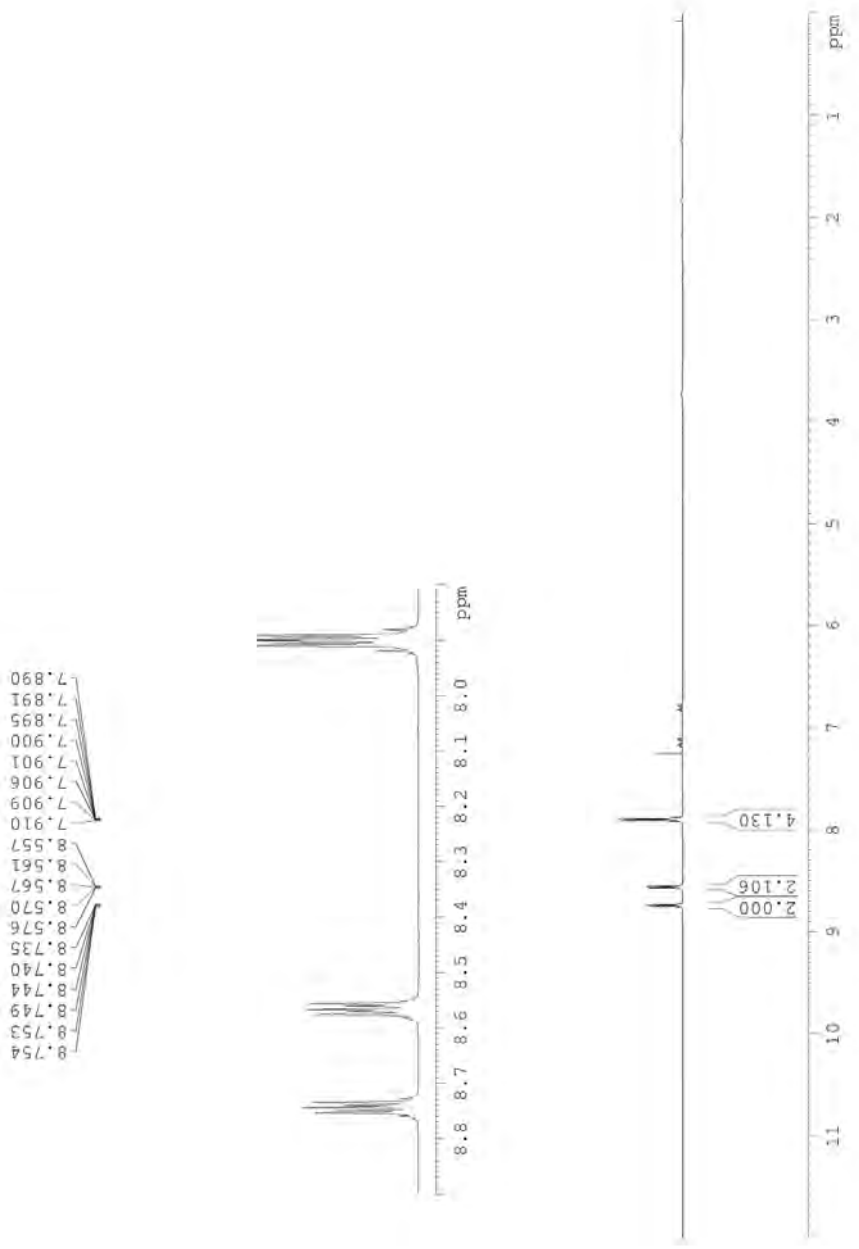
^{13}C-NMR of 2,2'-dinitro-4-(trifluoromethyl)-1,1'-biphenyl (3f)



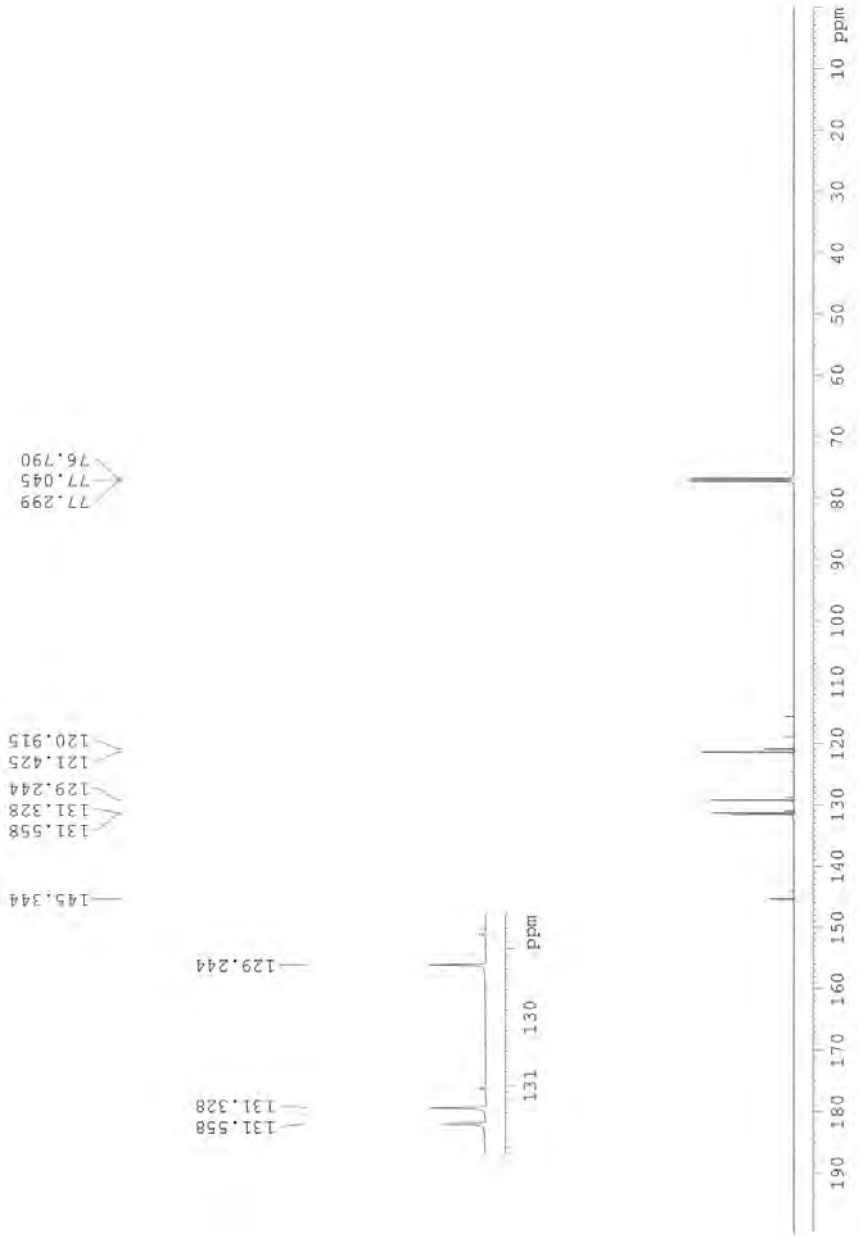
HR-MS (DART) of 2,2'-dinitro-4-(trifluoromethyl)-1,1'-biphenyl (3f)



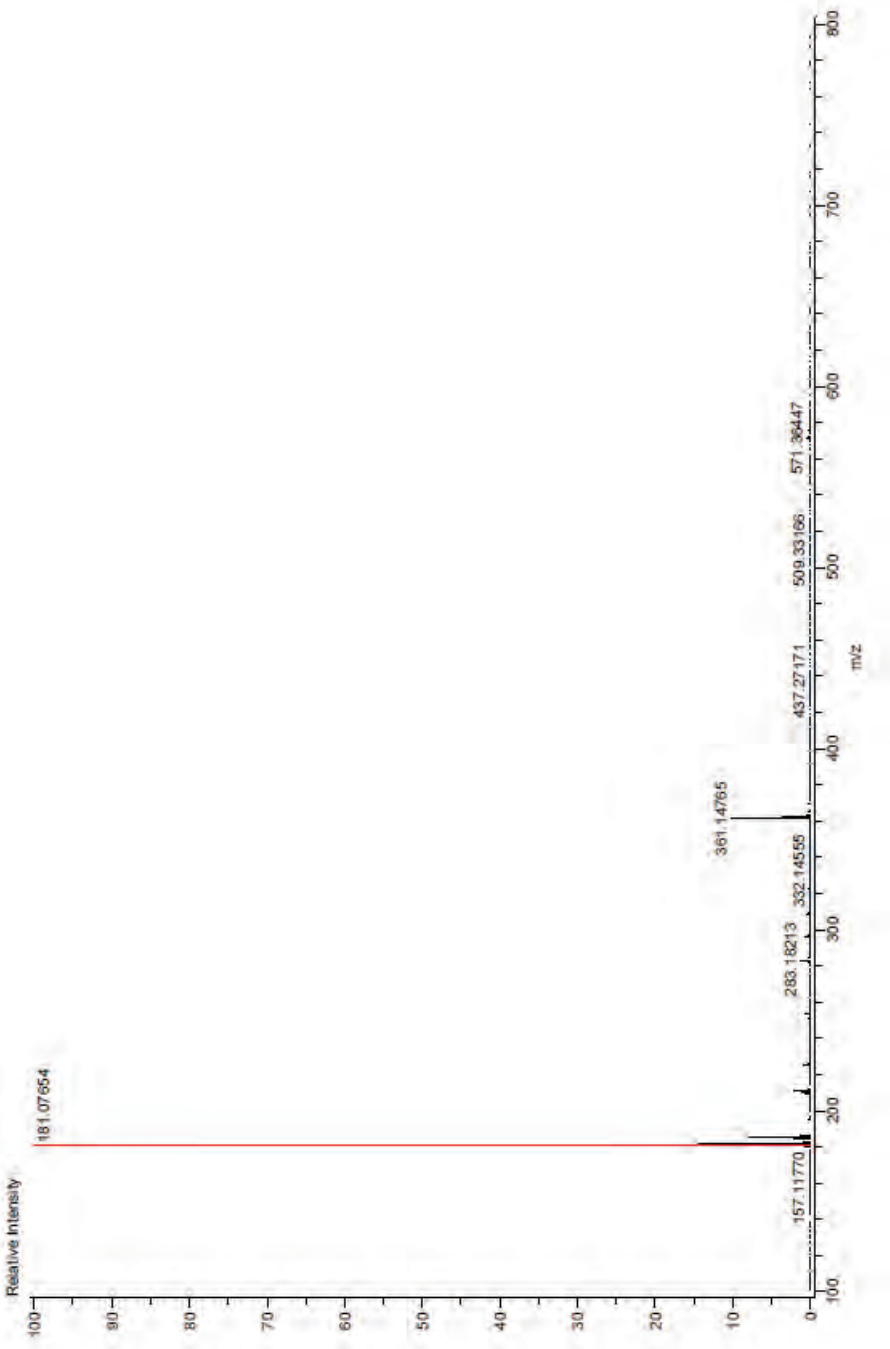
^{1}H-NMR of benzo[*c*]cinnoline (8a)



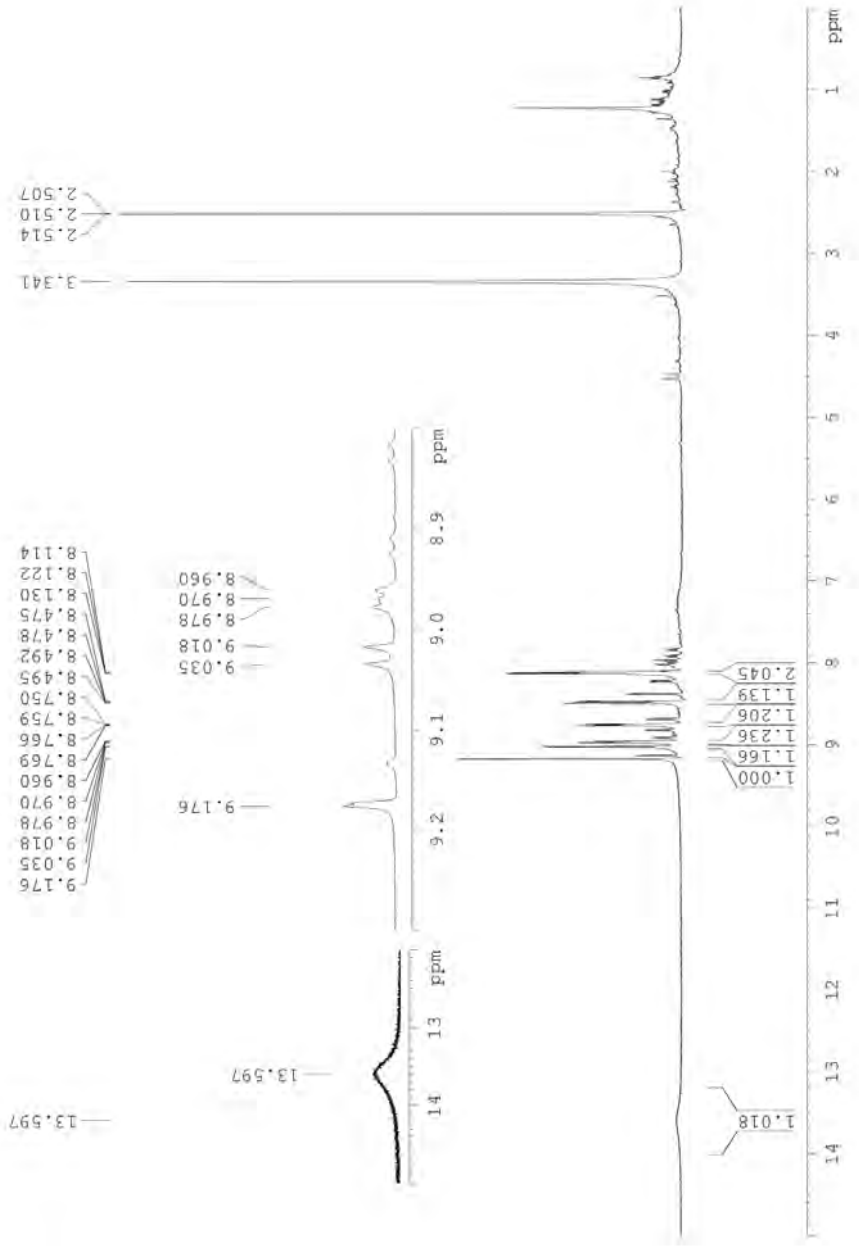
^{13}C-NMR of benzo[*c*]cinnoline (8a)



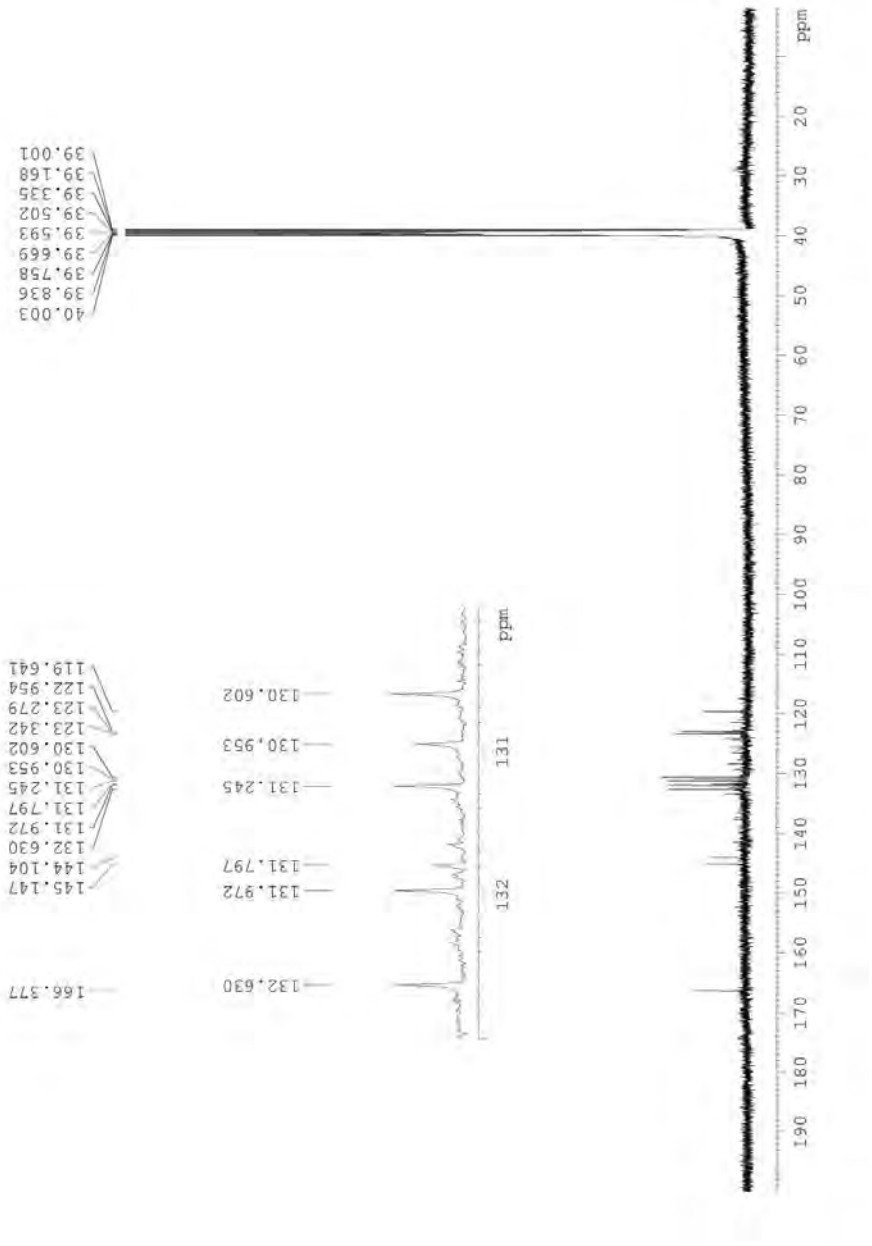
HR-MS (DART) of benzo[*c*]cinnoline (8a)



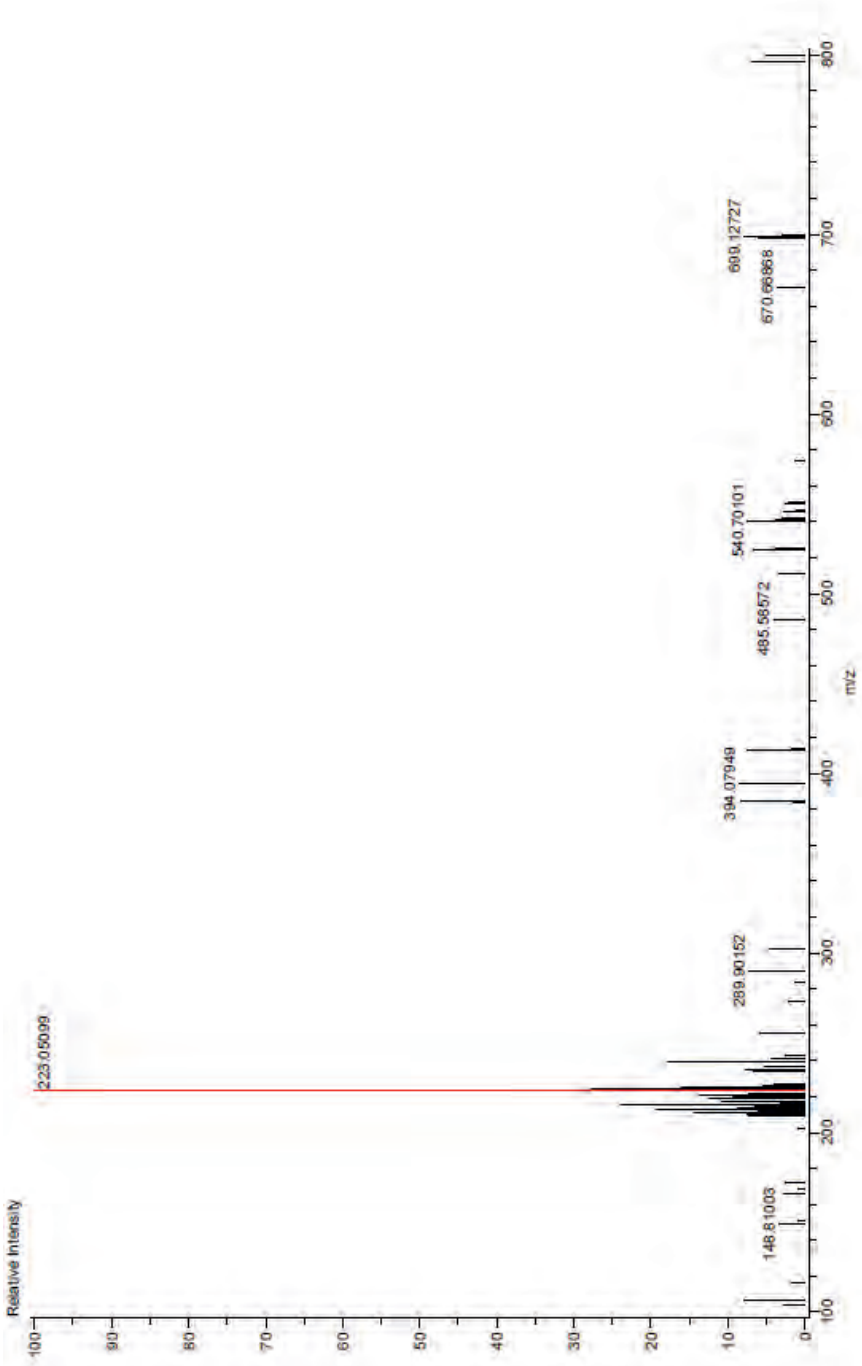
^{1}H-NMR of benzo[*c*]cinnoline-3-carboxylic acid (8b)



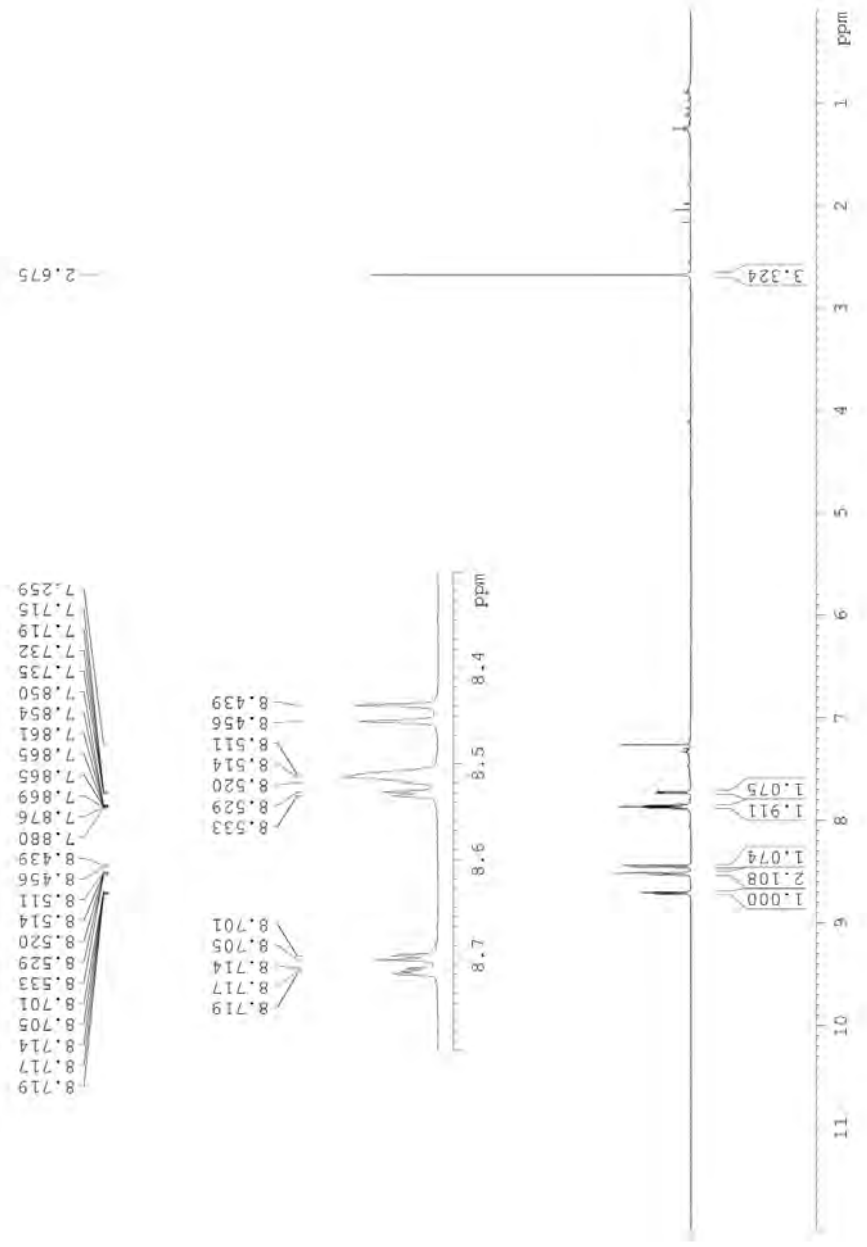
^{13}C-NMR of benzo[*c*]cinnoline-3-carboxylic acid (8b)



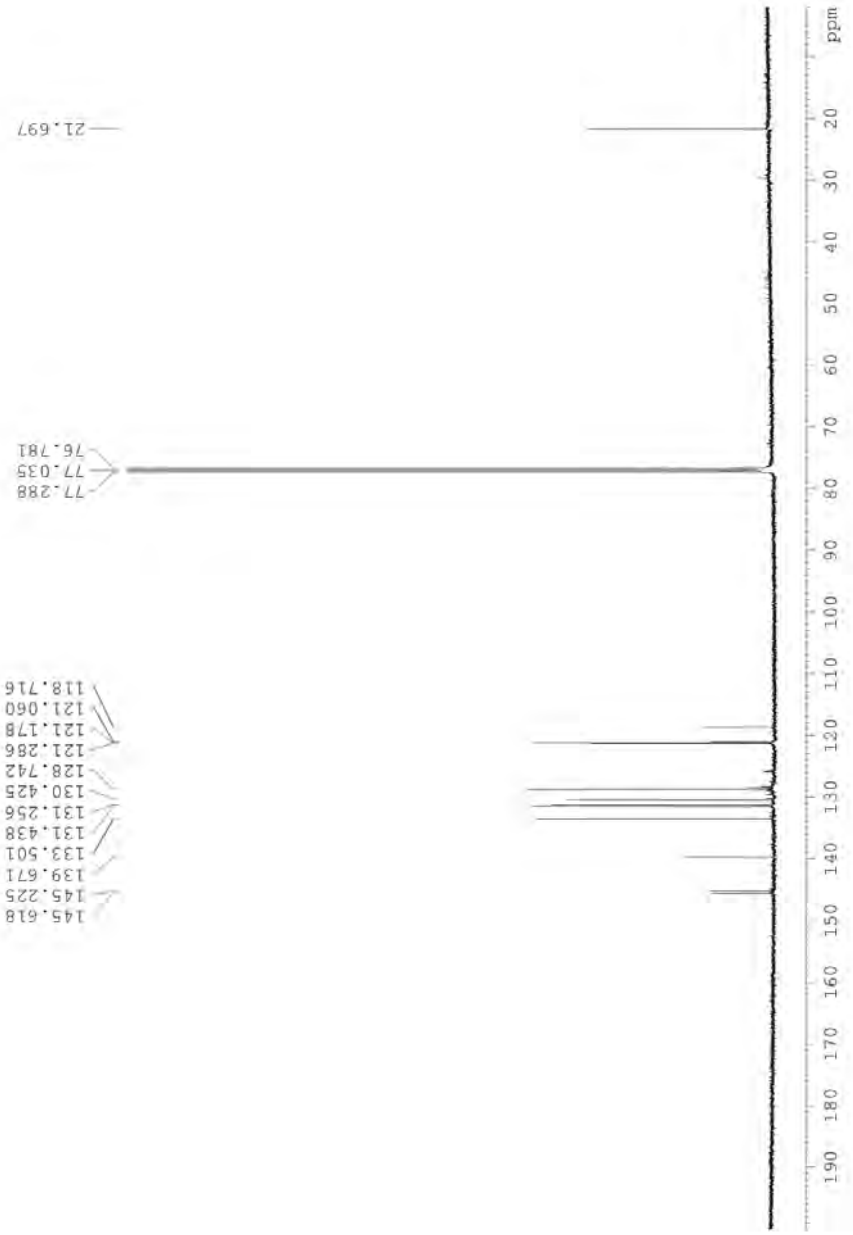
HR-MS (DART) of benzo[*c*]cinnoline-3-carboxylic acid (8b)



^{1}H-NMR of 3-methylbenzo[*c*]cinnoline (8c)

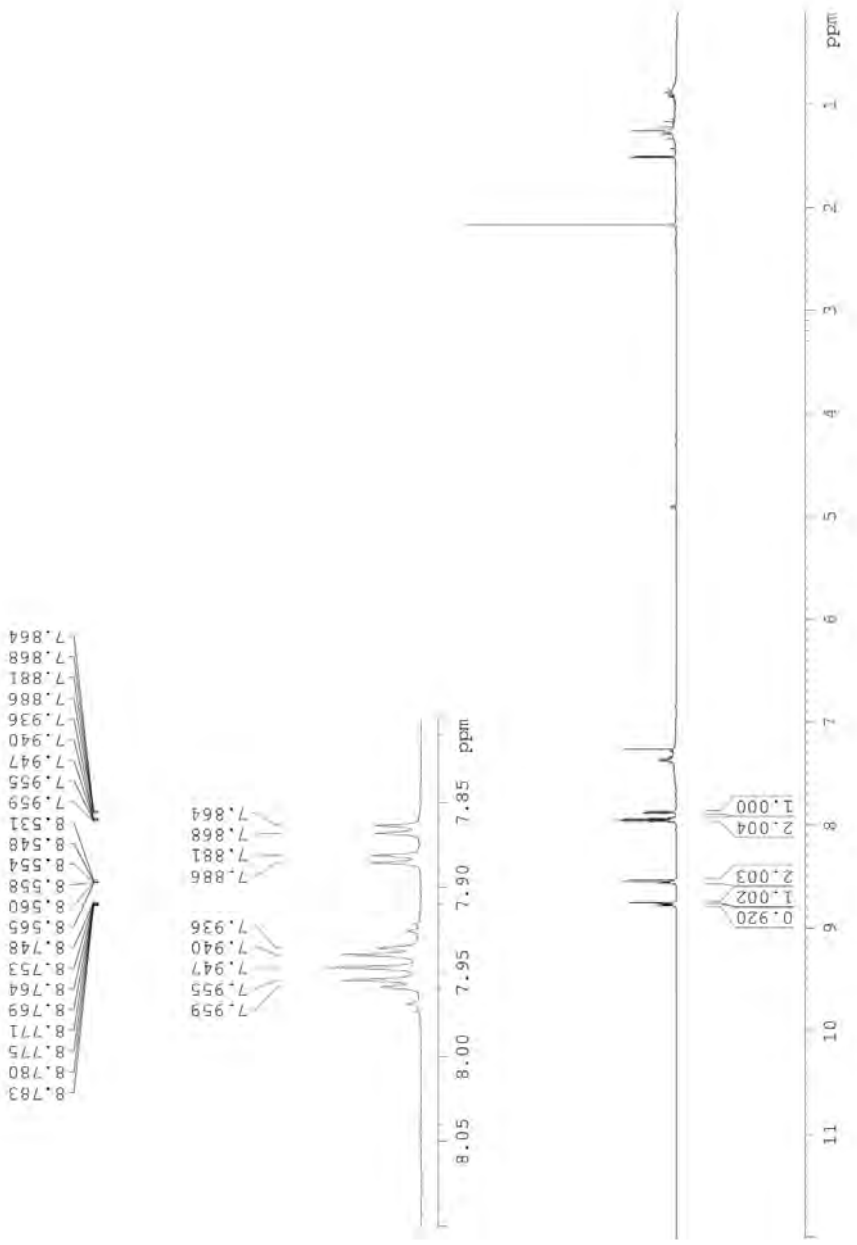


^{13}C-NMR of 3-methylbenzo[*c*]cinnoline (8c)

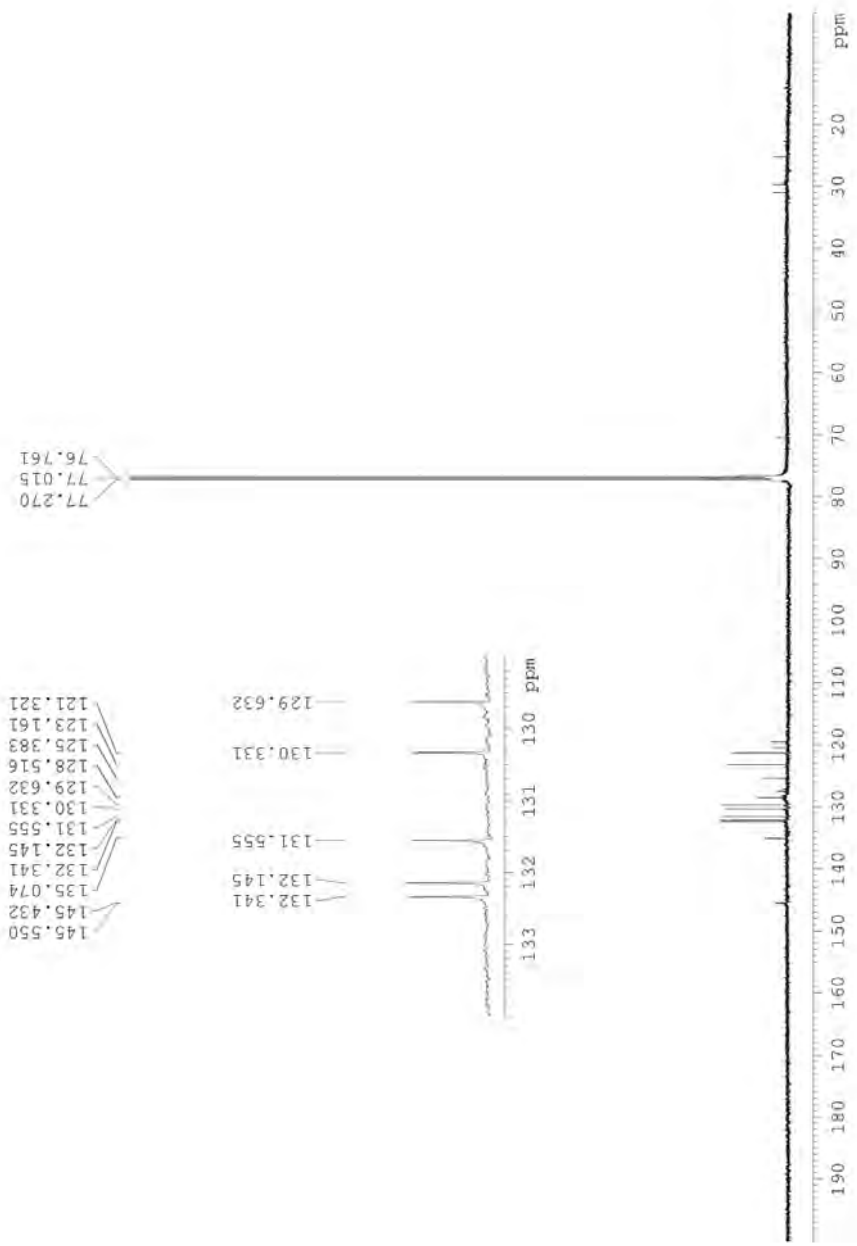


HR-MS (DART) of 3-methylbenzo[*c*]cinnoline (8c)

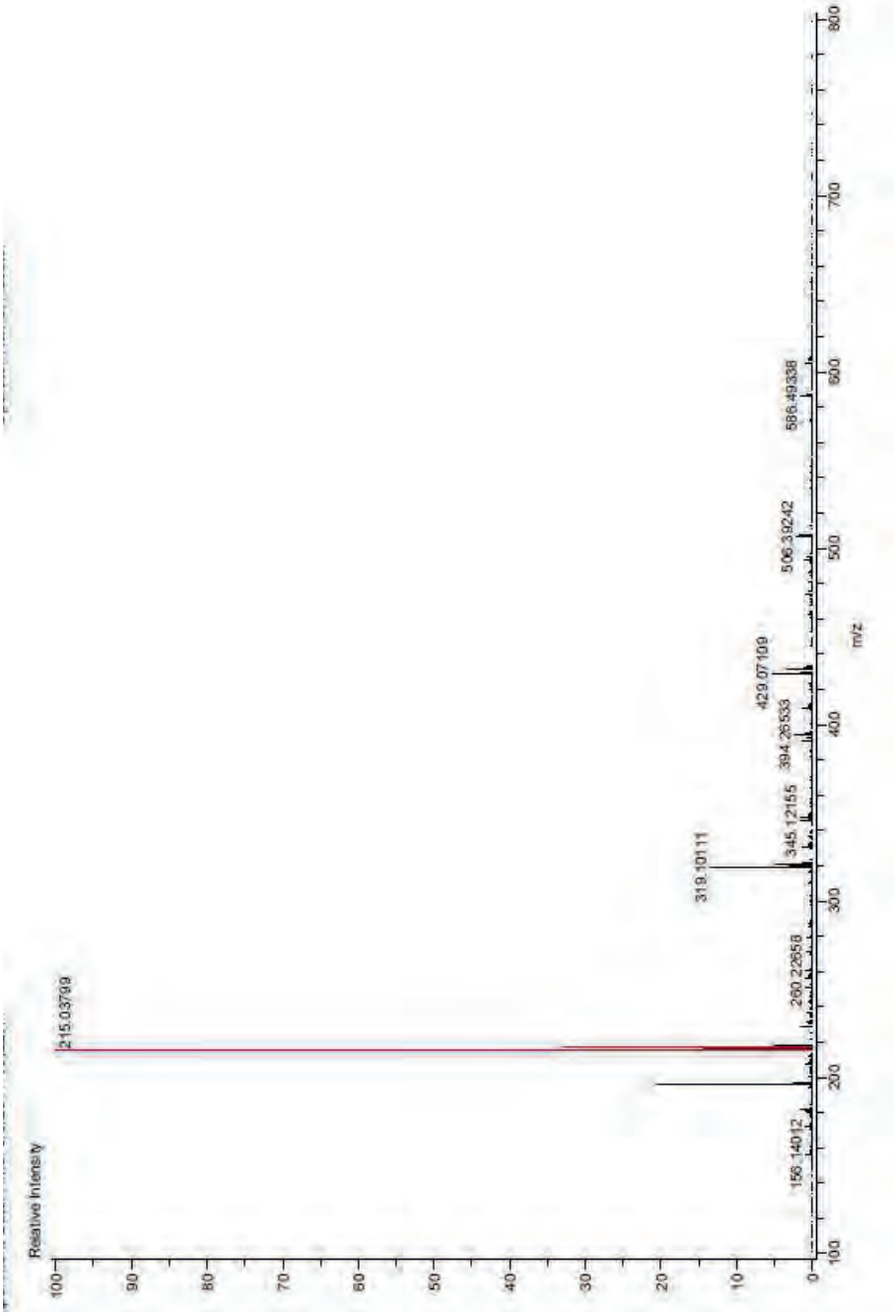
^{1}H-NMR of 3-chlorobenzo[*c*]cinnoline (8d)



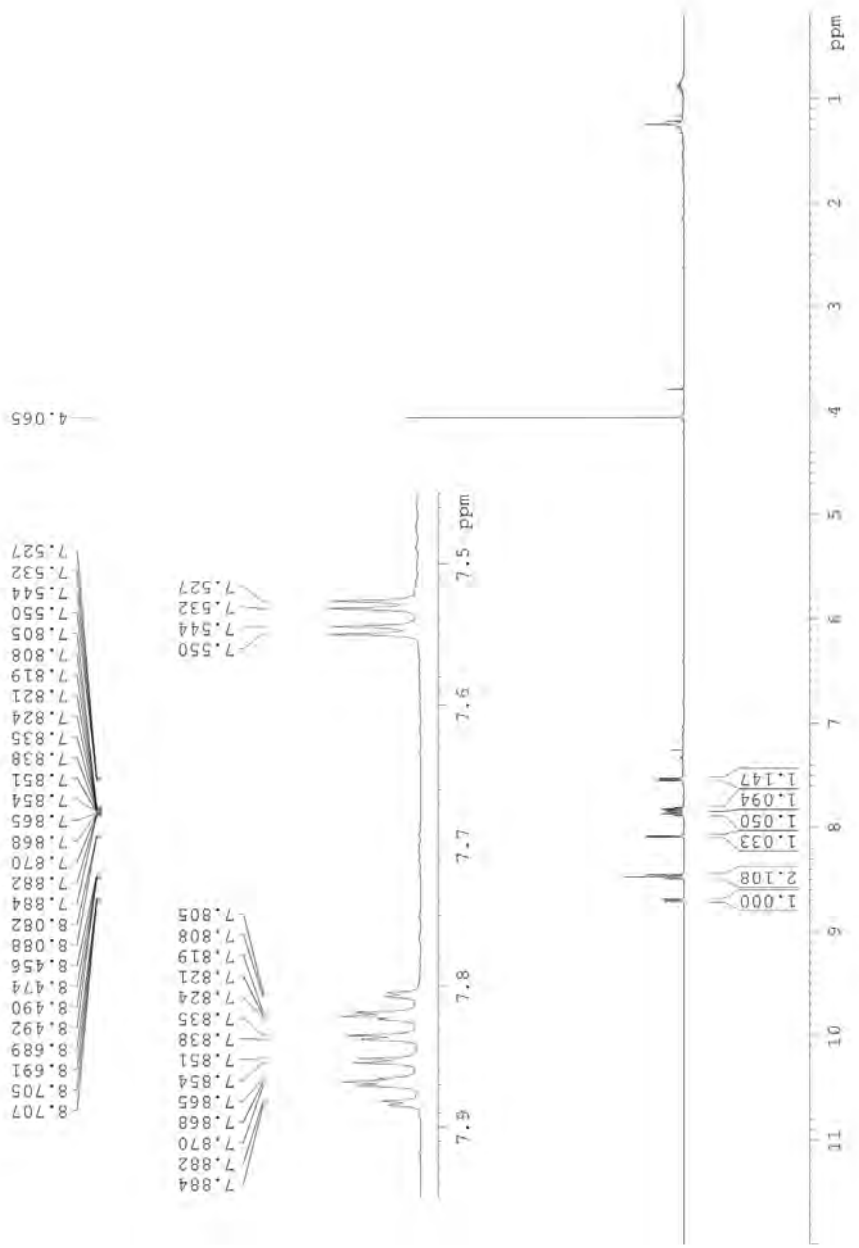
^{13}C-NMR of 3-chlorobenzo[*c*]cinnoline (8d)



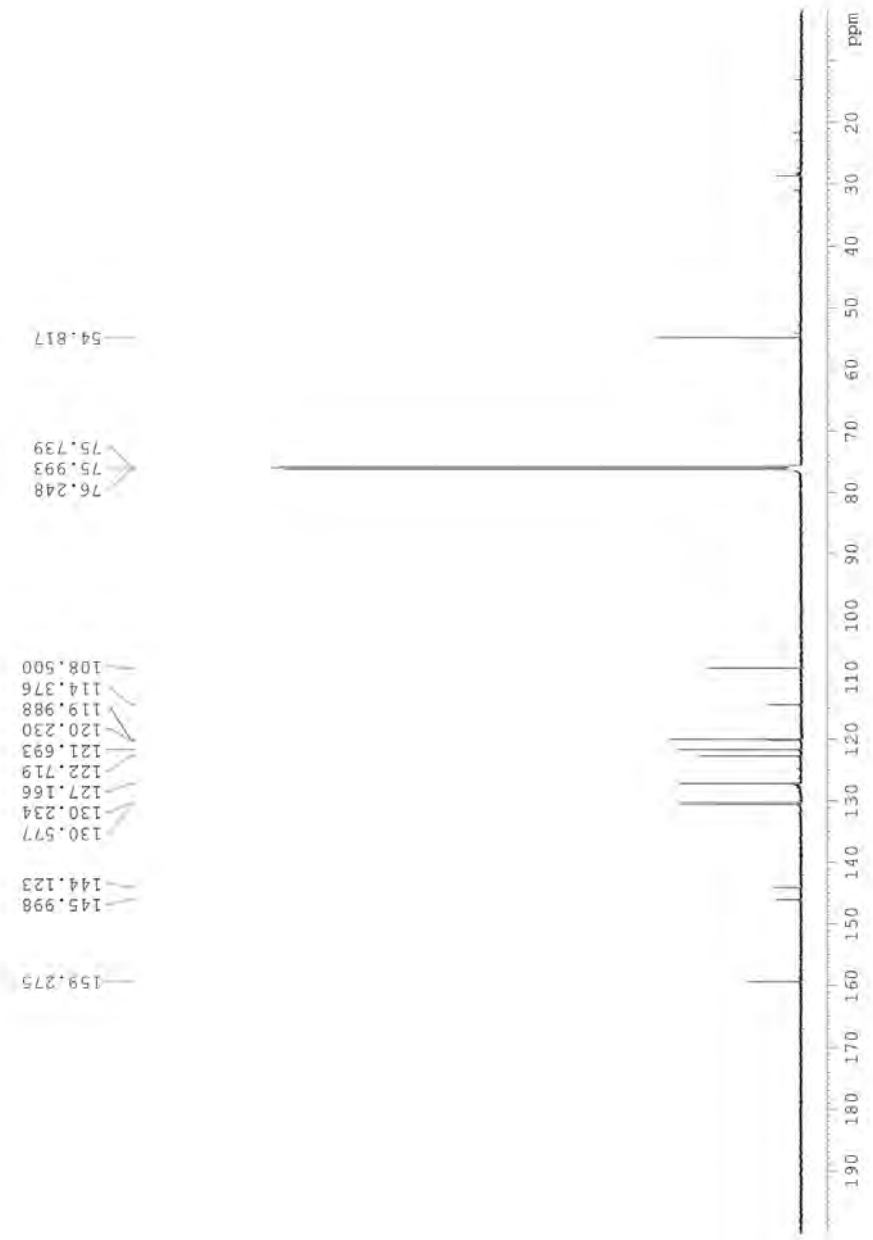
HR-MS (DART) of 3-chlorobenzo[*c*]cinnoline (8d)



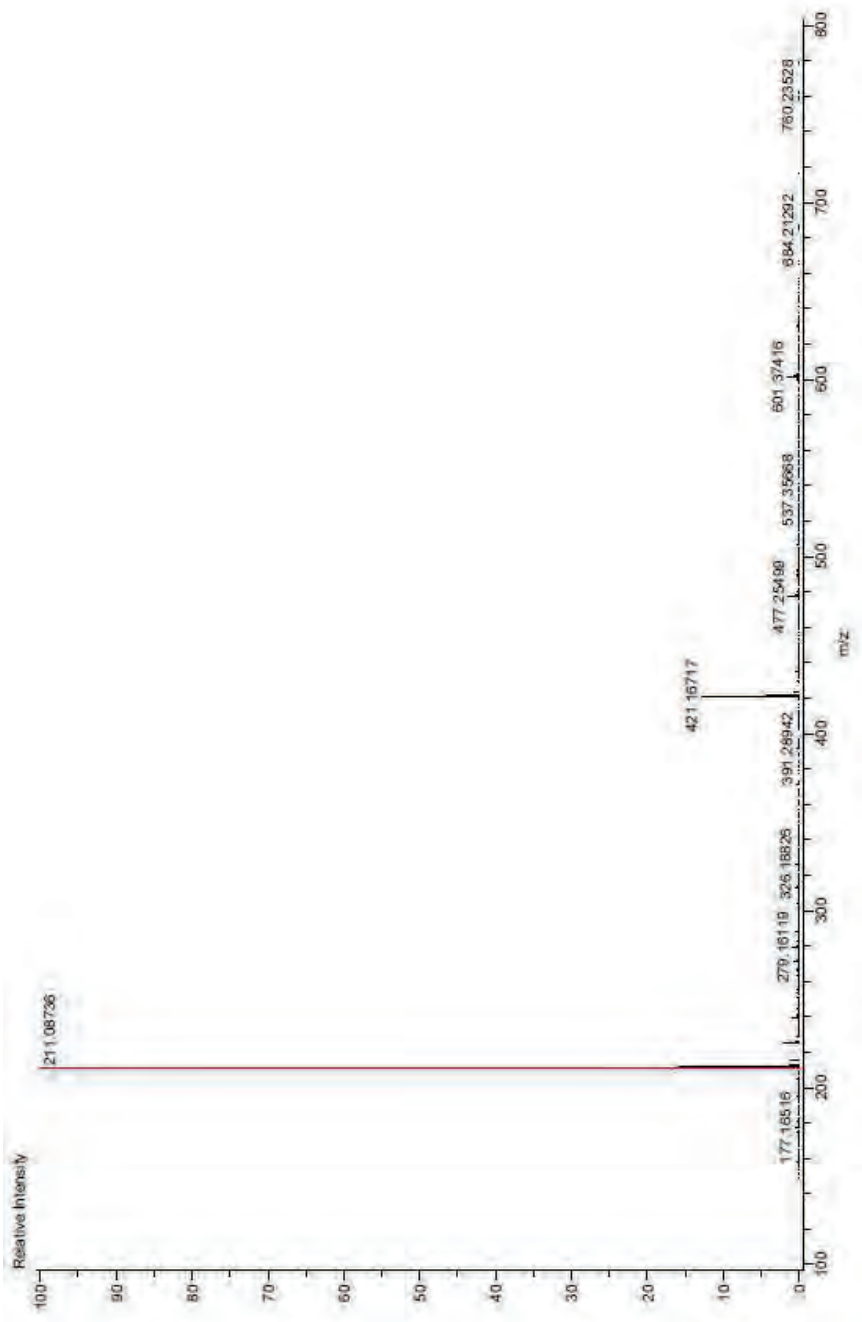
^{1}H-NMR of 3-methoxybenzo[*c*]cinnoline (8e)



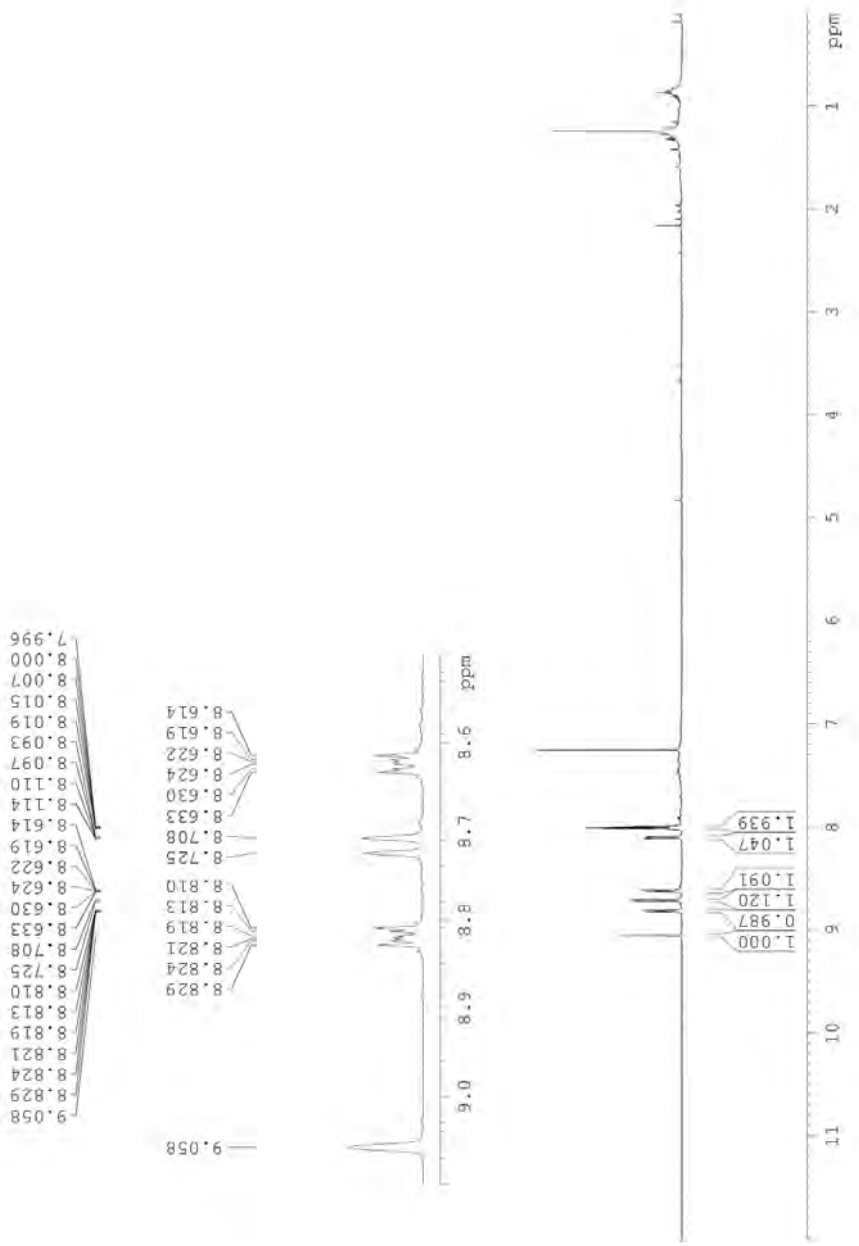
^{13}C-NMR of 3-methoxybenzo[*c*]cinnoline (8e)



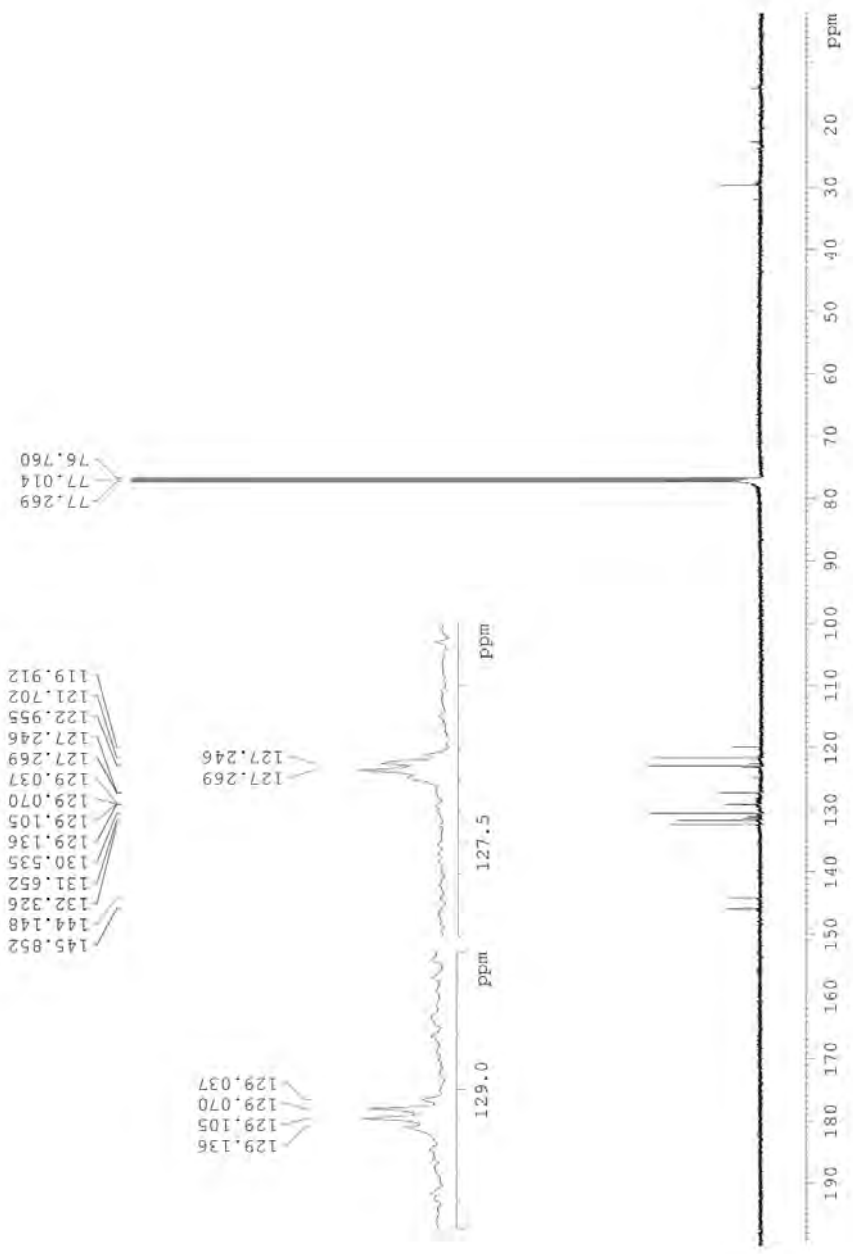
HR-MS (DART) of 3-methoxybenzo[*c*]cinnoline (8e)



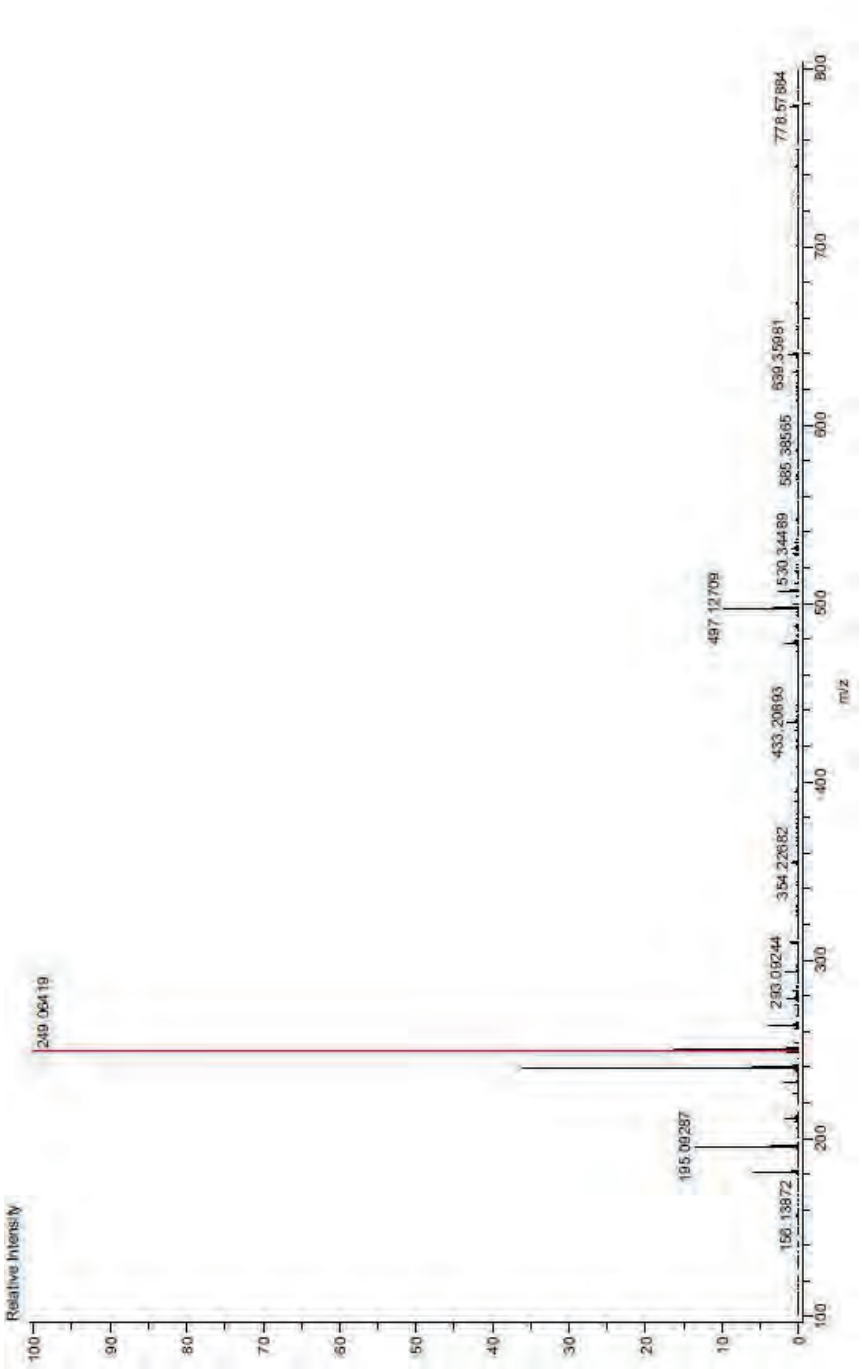
^{1}H-NMR of 3-(trifluoromethyl)benzo[*c*]cinnoline (8f)



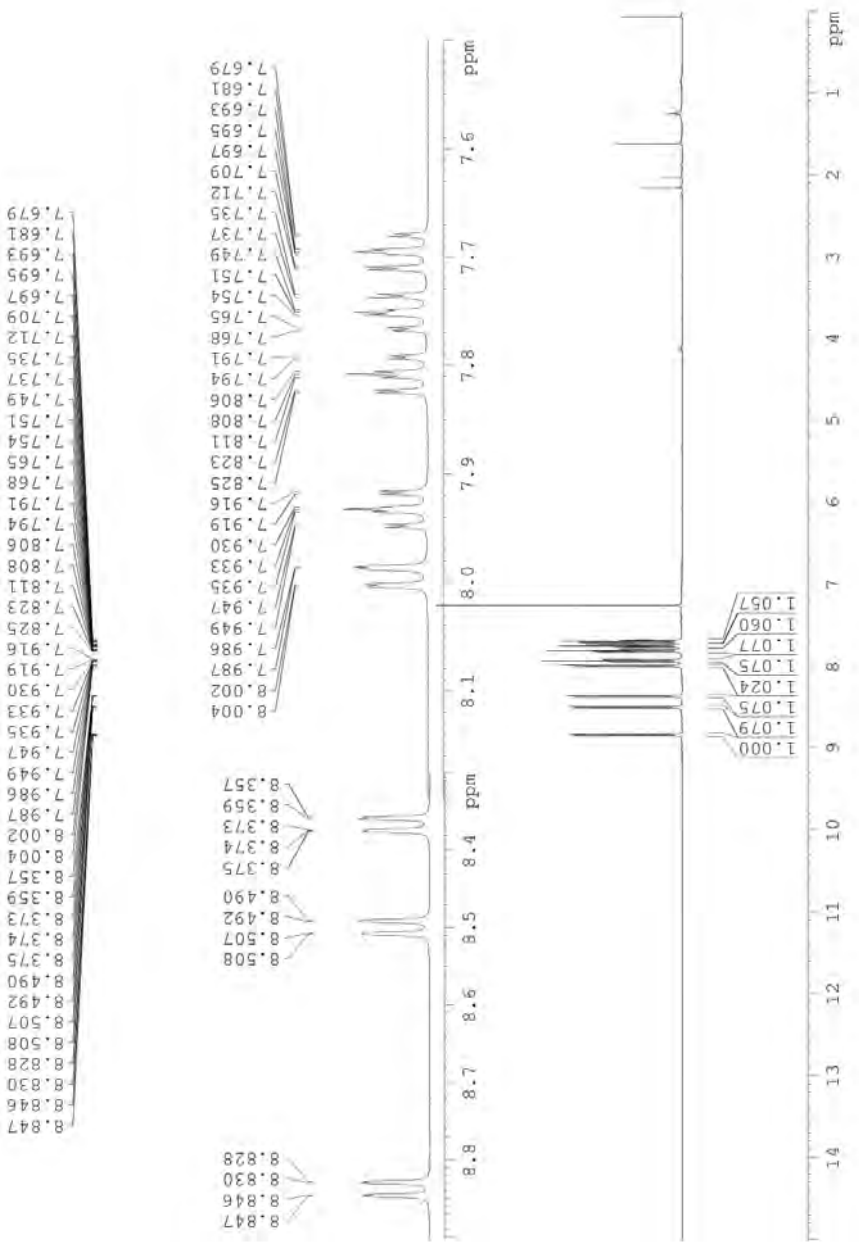
^{13}C-NMR of 3-(trifluoromethyl)benzo[*c*]cinnoline (8f)



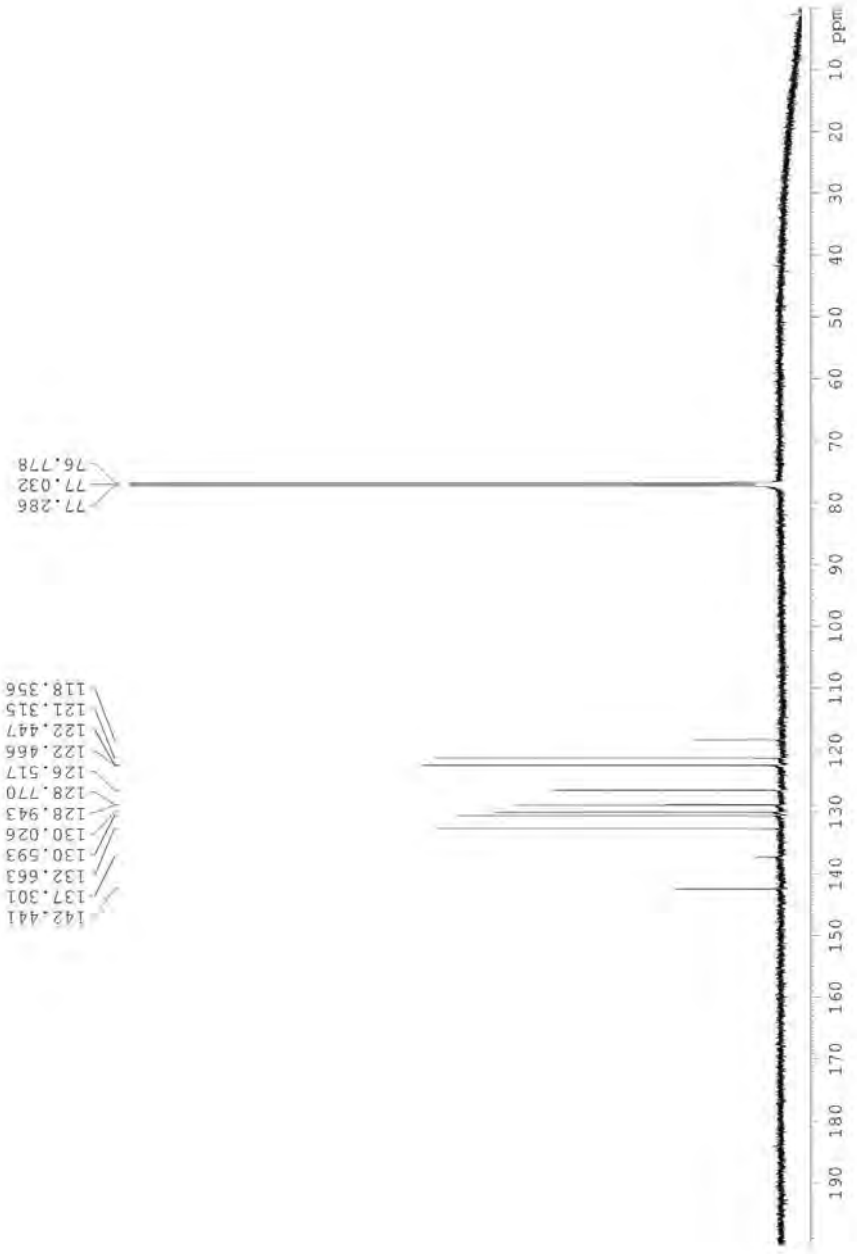
HR-MS (DART) of 3-(trifluoromethyl)benzo[*c*]cinnoline (8f)



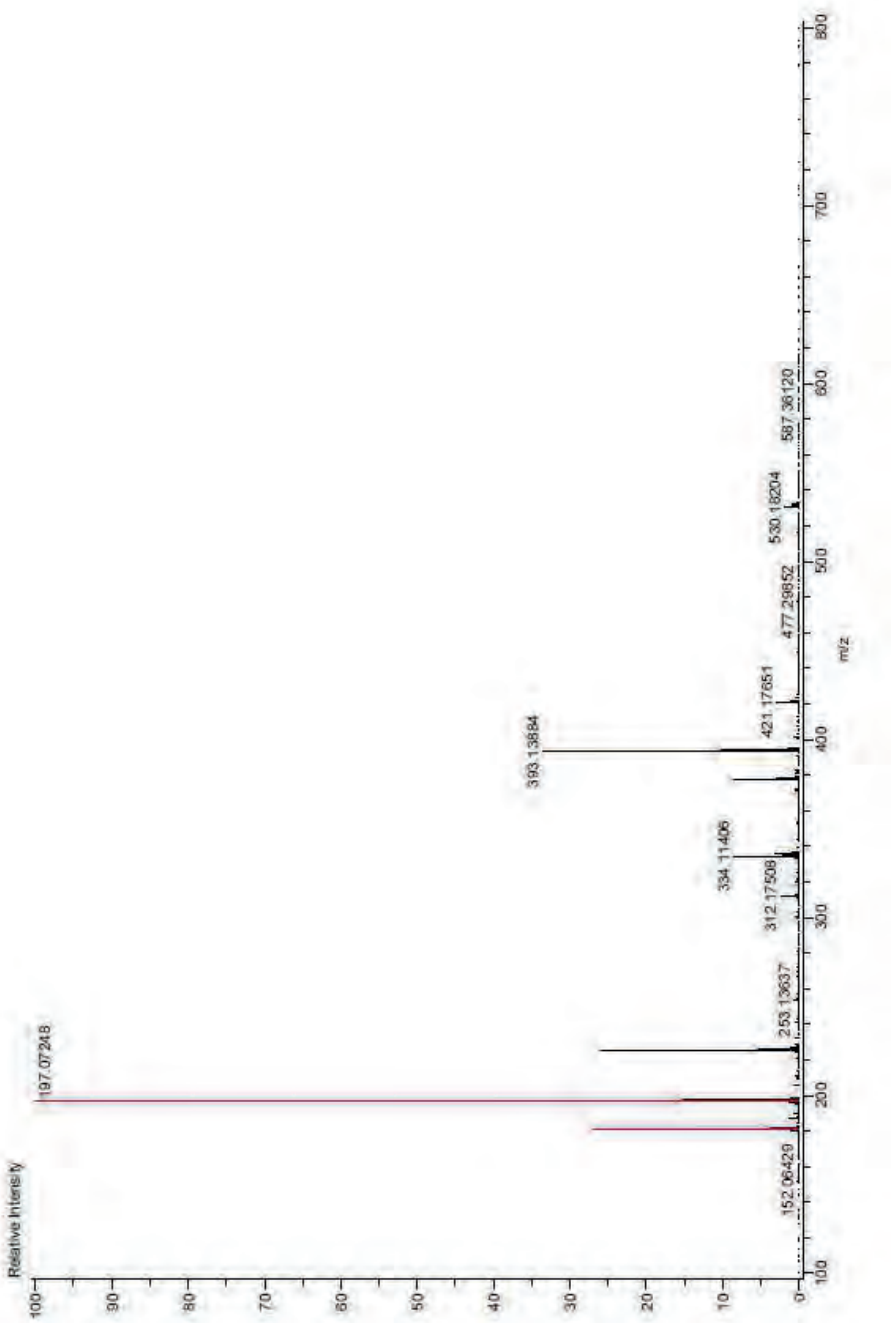
^{1}H-NMR of benzo[*c*]cinnoline-*N*-oxide (9)



^{13}C-NMR of benzo[*c*]cinnoline-*N*-oxide (9)



HR-MS (DART) of benzo[*c*]cinnoline-*N*-oxide (9)



Supporting Information for Chapter 6

Total Synthesis of Carbazomycin G

Experimental section

Experimental Details: All reagents and solvents were purchased from commercial sources and used as received. Melting points were determined in open capillaries. Reagent grade chemicals were purchased from commercial sources and used without further purification. All reaction mixtures and column eluents were monitored by TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 nm and λ = 365 nm. IR spectra were recorded as KBr discs with a Shimadzu FTIR-8300 spectrophotometer, and ^{1}H and ^{13}C NMR spectra were recorded with Bruker AV 400 MHz and 500 MHz instruments. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument.

General Methods: GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d., 0.33 mm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. DARTmass spectra were obtained by using PEG as an internal standard in positive ionization mode with a TOF mass analyzer. ^{1}H and ^{13}CNMR spectra were recorded at ambient temperature at a frequency of 400, 500 MHz and 100, 125 MHz respectively. The chemical shifts are reported in ppm relative to residual $CDCl_3$ for proton (δ = 7.26 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm) with tetramethylsilane as an external reference. Flash chromatography was performed by using the indicated solvent system and silica gel (230–400 mesh). All reagents used were commercially available from Aldrich Chemical Co. For new compounds, HRMS data were also recorded.

The microwave-assisted experiments were performed by means of a Biotage Initiator Sixty EXP Microwave System, that operates at 0–400 W at 2.45 GHz, in the temperature range of 40–250 °C, a pressure range of 0–20 bar (2 MPa, 290 psi), and with reactor vial volumes of 0.2–20 mL.

2,4-Dimethoxy-3-methyl phenol (6.2) [19676-67-6]. To a solution of 2, 6-dimethoxy toluene **6.1** (3 g, 19.7 mmol) in acetonitrile (25 mL), was added trifluoroacetic acid (1.3 mL, 19.7 mmol) and hydrogen peroxide (35%, 3.5 mL, 39.4 mmol). The reaction mixture was stirred for 2 h at 75 ºC. The reaction mixture was cooled to room temperature and the solvent acetonitrile was removed under reduced pressure. The crude mixture was diluted with water (30 mL) and extracted with EtOAc (2x40 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The title compound was isolated by silica gel column chromatography [(EtOAc:Hx, 20:80)] as orange liquid (1.75 g, 53%); R_f =0.49 [(EtOAc:Hx, 20:80)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.67 (d, *J*= 9 Hz, 1H), 6.46 (d, *J*= 9 Hz, 1H), 5.10 (s, br, 1H), 3.69 (s, 6H), 2.09 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$,): δ =151.9, 145.9, 142.8, 120.1, 111.8, 106.9, 60.9, 56.1, 9.3; MS (EI): m/z (%); 168

(100, M^+), 153 (61), 125 (49), 107 (23), 93 (9), 79 (11), 65 (21), 53 (12); IR (cm^{-1}): 3406, 2996, 2940, 2834, 1486, 1259, 1098, 730.

2, 4-Dimethoxy-3-methylphenyl acetate (6.3) [96502-90-8]. To a solution of 2, 4-Dimethoxy-3-methyl phenol **6.2** (1.5 g, 8.9 mmol) in $CHCl_3$ (15 mL), was added acetyl chloride (1.3 mL, 17.8 mmol). The reaction mixture was heated for 2 h under reflux. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure to afford the title compound as a dark- orange liquid (1.75 g, 94 %); R_f =0.78 [(EtOAc:Hx, 40:60)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.86 (d, *J*= 9 Hz, 1H), 6.60 (d, *J*= 8.5 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.7, 156.4, 150.5, 137.6, 121.2, 119.7, 105.6, 60.8, 55.7, 20.7, 9.2; MS (EI): m/z (%): 210 (9, M^+), 168 (100), 153 (53), 139 (4), 125 (19), 107 (12), 79 (6), 65 (8), 53 (7); IR (cm^{-1}): 2940, 2838, 1759, 1484, 1199, 1106, 728.

2,4-Dimethoxy-3-methyl-5-nitrophenyl acetate (6.4) [192188-84-4]. 2,4-Dimethoxy-3-methylphenyl acetate **6.3** (1.6g, 7.6 mmol) was dissolved in a solution of AcOH/Ac_2O (1:3 ratio, 12 mL) at 0-5 ºC. A solution of HNO_3 (65 %, 1.0 mL, 14.5 mmol) in AcOH/Ac_2O (1:3 ratio, 12 mL) was added dropwise to the reaction mixture under vigorous stirring at 0-5 ºC. When the addition was completed, the reaction mixture was stirred for 30 minutes at ambient temperature. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic layers were combined and washed with $NaHCO_3$ (2×50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the title compound as a yellow liquid (1.45 g, 75 %); R_f = 0.70 [(EtOAc:Hx, 40:60)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 3.87 (s, 3H,), 3.83 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 168.7, 155.2, 151.3, 139.1, 138.8, 129, 118, 62.1, 60.9, 20.6, 10; MS (EI): m/z (%): 255 (4, M^+), 213 (100), 166 (26), 152 (8), 137 (8), 123 (11), 107 (10), 77 (14), 53 (14); IR (cm^{-1}): 2946,1770, 1522, 1343, 1187, 88, 729.

2,4-Dimethoxy-3-methyl-5nitrophenol (6.5) [136763-93-3]. A solution of Conc.HCl (12 mL) in MeOH (25 mL) was added dropwise to 2, 4-Dimethoxy-3-methyl-5-nitrophenyl acetate **6.4** (1.5 g, 5.9 mmol) at 0 ºC . The reaction mixture was stirred for 1 h at 70 ºC under reflux. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The crude product was diluted with water (40 mL) and extracted with EtOAc (2× 40 mL). The organic layers were combined and dried over Na_2SO_4 to afford the title compound as orange solid (1.05 g, 83 %); R_f = 0.34 [(EtOAc:Hx, 20:80)]; mp 53-55 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (s, 1H), 3.78 (s, 6H), 2.21 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ = 150.2, 146.3, 145.1, 140.0, 127.5, 109.4, 62.1, 61.0, 10; MS (EI): m/z (%): 213 (100, M^+), 166 (59), 152 (21), 137 (36), 125 (43), 122 (28), 91(23), 83(40), 77 (32), 53 (49); IR (cm^{-1}): 3418, 2944, 1519, 1338, 1245, 1102, 988, 733.

2-Chloro 4, 6-dimethoxy-5-methyl-3-nitrophenol (6.7a) [NEW]. To a solution of 2,4-dimethoxy-3-methyl-5-nitrophenol **6.5** (0.311 g, 0.145 mmol) in EtOH (15 mL), DCH **6.6** (146 mg, 0.074 mmol) was added followed by conc. H_2SO_4 dropwise (≈ 24 drops) with good stirring. After the addition was completed, the reaction mixture was quenched with NaOH (4.1 M, 5 mL). A heavy red precipitation was observed during the addition of NaOH, which

was neutralized with acetic acid (pH≈ 4), and the resulting mixture was diluted with water (25 mL) and extracted with diethyl ether (3 × 40 mL). The organic layers were combined and dried with Na_2SO_4. The crude product was isolated by silica gel column chromatography (CH_2Cl_2/hexane, 40:60) to afford the title compound as pale yellow crystals (0.34 g, 95 %), m.p. 118.5 °C. *R*f =0.29 (CH_2Cl_2/hexane, 60:40). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.91 (s, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.5, 144.0, 142.7, 125.6, 109.3, 62.9, 61.0, 9.9 ppm. MS (EI): *m/z* (%) = 247 (100, M+), 217 (5), 213 (16), 186 (25), 171 (27), 138 (26), 108 (20), 83 (22), 77 (48), 67 (32). HRMS (EI): calcd. For $C_9H_{10}ClNO_5$ 247.0248; found 247.0248. IR (cm^{-1}) = 3406, 3083, 2970, 2929, 2846, 1500, 1108.

3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (6.9) [NEW]. In a microwave tube, 2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol **6.7a** (0.21 g, 0.85 mmol), phenylboronic acid **6.8** (0.155 g, 1.27 mmol), Na_2CO_3 (0.10 g, 0.97 mmol), TBAB (0.021 g, 0.065 mmol) and $Pd(PPh_3)_4$ (0.025 g, 0.022 mmol) were added. The reaction mixture was carefully flushed with argon before adding a mixture of MeOH (4 mL) and water (1 mL), The tube was sealed and submerged in the microwave cavity for 30 min at 120 ºC. The reaction mixture was diluted with water (40 mL) and extracted with diethyl ether (2×30 mL). The organic layers were combined and dried over Na_2SO_4. The crude product was isolated by silica gel column chromatography [(DCM:Hx, 40:60)] eluent to afford the title compound as yellow solid (0.122 g, 50 %); *R*f =0.1 (CH_2Cl_2/hexane, 40:60); mp: 102.7ºC; ^{1}H- NMR (500 MHz, $CDCl_3$): δ = 7.46-7.40 (m, 3H), 7.37 -7.35 (m, 2H), 5.55 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.33 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 147.2, 143.2, 142.9, 142.6, 130.8, 129.4, 128.9, 128.8, 125.6, 119.4, 62.8, 61.0, 10; MS (EI): m/z (%): 289 (100, M^+), 272 (7), 246 (20), 207 (24), 199 (13), 169 (13), 141 (20), 129 (40), 115 (33), 102 (12), 83 (23), 77 (20); HR-MS (EI): $(M+Na)^+$: Calcd for $C_{15}H_{15}NNaO_5$ 312.0848; Found 312.0846);: IR (cm^{-1}) = 3413, 2937, 2929, 2849, 1528, 1101, 991, 748.

3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol (6.9a) [NEW]. In a microwave tube, 2-Chloro 4,6-dimethoxy-5-methyl-3-nitrophenol **6.7a** (0.168 g, 0.68 mmol), 3-methoxy phenylboronic acid **6.8a** (0.155 g, 1.02 mmol), Na_2CO_3 (0.079 g, 0.75 mmol), TBAB (0.019 g, 0.05 mmol) and $Pd(PPh_3)_4$ (0.020 g, 0.018 mmol) were added. The reaction mixture was carefully flushed with argon before adding a mixture of MeOH (4 mL) and water (1 mL), The tube was sealed and submerged in the microwave cavity for 30 min at 120 ºC. The reaction mixture was diluted with water (40 mL) and extracted with diethyl ether (2×30 mL). The organic layers were combined and dried over Na_2SO_4. The crude product was isolated by silica gel column chromatography [(DCM:Hx, 40:60)] eluent to afford the title compound as yellow oil (0.109 g, 50 %); *R*f =0.1 (CH_2Cl_2/hexane, 40:60); ^{1}H- NMR (500 MHz, $CDCl_3$): δ = 7.28 (t, J= 8Hz, 1H), 6.88-6.85 (m, 2H), 6.82 (s, 1H), 5.48 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 2.25 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 159.8, 147.2, 143.2, 142.8, 142.4, 131.9, 130, 125.7, 121.6, 119.2, 114.9, 114.8, 62.8, 60.9, 10; MS (EI): m/z (%): 320 (17), 319 (100, M^+), 276 (33), 257 (15), 244 (22), 159 (32), 128 (35), 115 (45), 83 (38), 55 (22); HR-MS (DART): $(M+H)^+$: Calcd for $C_{16}H_{18}NO_6$ 320.1134; Found 320.1136)IR (cm^{-1}) = 3450, 2942, 2837, 1530, 1238, 1103, 997, 765.

6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10) [NEW]. 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol **6.9** (0.20 g, 0.69 mmol) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (0.073 g, 1.38 mmol) in H_2O (1.2 mL) and indium powder (0. 238 g, 2.01 mmol) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed and the reaction mixture was

stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL) and filtered through a pad of celite. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to obtain title compound in purple oil (0.175 g, 98%).; R_f = 0.44 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.50-7.47 (m, 3H), 7.43-7.40 (m, 2H), 5.30 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.27 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 142.8, 138.5, 137.2, 134.4, 134.0, 130.5, 129.1, 127.7, 123.3, 113.0, 61.1, 59.5, 9.5; MS (EI): m/z (%): 260 (9), 259 (58, M^+), 244 (100), 229 (9), 216 (22), 201 (36), 184 (11), 144 (14), 128(11), 89 (8), 77(9); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{18}NO_3$ 260.1287; Found 260.1287); IR (cm^{-1}): 3458, 3334, 3057, 2933, 2849, 1580, 1460, 994, 727.

6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10a) [NEW]. 3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol **6.9a** (0.08 g, 0.25 mmol) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (0.027 g, 0.50 mmol) in H_2O (1.2 mL) and indium powder (0. 086 g, 0.75 mmol, 99.99% 100 mesh, use preferably a freshly opened bottle or stored under Ar) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL) and filtered through a pad of celite. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the title compound in purple oil (0.071 g, 98%).; R_f = 0.36 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.40 (t, J= 8 Hz, 1H), 6.99-6.97 (m, 1H), 6.95-6.94 (m, 1H), 6.93-6.91 (m, 1H), 5.29 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 2.27 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 160.1, 142.8, 138.5, 137.1, 135.3, 134.4, 130.2, 123.4, 122.7, 115.8, 113.6, 112.8, 61.0, 59.5, 55.3, 9.5; MS (EI): m/z (%): 290 (12), 289 (74, M^+), 274 (100), 259 (12), 246 (26), 231 (25), 137 (14), 130 (32), 115 (15), 83 (14), 77(10);HR-MS (DART): $(M+H)^+$: Calcd for $C_{16}H_{20}NO_4$ 290.1392; Found 290.1395); IR (cm^{-1}): 3458, 3341, 3057, 2933, 2849, 1580, 1360, 994, 727.

6-acetamido-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate (6.11) [NEW]. In a 50 mL RB-flask, 6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol **6.10** (0.12 g, 0.46 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under inert atmosphere. To the stirred solution added triethylamine (0.14 mL, 0.97 mmol). The solution was cooled under ice bath and added acetic anhydride (0.09 mL, 1.01 mmol) dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 1 hour. The residue was diluted in EtOAc (50 mL) and washed with water (40 mL). The organic layer was washed with $NaHCO_3$ (30 mL) and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the title compound (0.148 g, purple liquid) in 94 % crude yield. R_f = 0.74 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.34 (m, 3H), 7.20 (m, 2H), 6.50 (s, br, 1H), 3.76 (d, J=8.5Hz, 6H), 2.29 (s, 3H), 2.17 (s, 3H), 1.99 (s, 3H); MS (EI): m/z (%): 343 (11, M^+), 301 (46), 270 (24), 244 (100), 201 (24), 144 (51), 128 (39), 115 (60), 89 (72), 83(94), 77(47), 55(43); HR-MS (DART): $(M+H)^+$: Calcd for $C_{19}H_{22}NO_5$ 344.14980; Found 344.14999; IR (cm^{-1}): 2928, 2552, 1669, 1603, 1451, 1422, 1290, 1205, 707.

6-acetamido-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate (6.11a) [NEW]. In a 50 mL RB-flask, 6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol **6.10a** (0.13 g, 0.45 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under inert atmosphere. To the stirred solution added triethylamine (0.13 mL, 0.97 mmol). The solution was cooled under ice bath and added acetic anhydride (0.09 mL, 1.01 mmol) dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 1 hour. The residue was diluted in EtOAc (50 mL) and washed with water (40 mL). The organic layer was washed with $NaHCO_3$ (30 mL) and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the title compound (0.131 g, purple liquid) in 85% (crude yield). R_f = 0.67 [(EtOAc:Hx, 50:50)]; MS (EI): m/z (%): 373 (16, M^+), 332 (12), 331 (68), 316(7), 300 (26), 274 (100), 256 (11), 242 (13), 231 (11), 174 (12), 115 (9), 83 (15);

9-acetyl-1,3-dimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12) [NEW]. 6-acetamido-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate **6.11** (0.063 g, 0.183 mmol) was dissolved in glacial acetic acid (5mL), $Pd(OAc)_2$ (2.1 mg, 0.009 mmol), Imes.HCl (3.2 mg, 0.009 mmol) and H_2O_2 (35%, 0.05 mL, 0.53 mmol) were added. The vial was sealed whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in the microwave cavity at 120ºC for 5 hours. The reaction mixture was monitored by GC (94% yield). The crude product was dissolved in EtOAc (20 mL) and washed with water (25 mL). The water phase was extracted with EtOAc (2×15 mL). The combined layer was washed with aq.$NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4 and filtered off. The solvent was evaporated under reduced pressure. The crude product was purified by using silica gel column chromatography (20:80, EtOAc:Hx) to attain the title compound (0.043 g, brown liquid) in 70% yield. R_f = 0.33 [(EtOAc:Hx, 20:80)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, *J*= 8.5 Hz, 1H), 7.83 (d, *J*= 7.5 Hz, 1H), 7.45 (t, *J*= 7.5 Hz, 1H), 7.33 (t, *J*= 7.5 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 2.62 (s, 3H), 2.54 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 172.8, 168.6, 147.4, 144.0, 140.4, 134.8, 128.5, 127.7, 124.9, 123.7, 123.6, 121.1, 119.7, 115.1, 61.1, 60.0, 26.8, 20.8, 10.2; MS (EI): m/z (%): 341 (11, M^+), 299 (19), 257 (46), 242 (100), 226 (11), 196 (12), 168 (22), 154 (23), 127 (22), 115 (27), 89(12), 77(12), 55(12);HR-MS (DART): $(M+H)^+$: Calcd for $C_{19}H_{20}NO_5$ 342.1341; Found 342.1343); IR (cm^{-1}): 2935, 1766, 1702, 1445, 1398, 1367, 1269, 1254, 1183, 1082, 1002, 749.

9-acetyl-1, 3, 6-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12a) & 9-acetyl-1, 3, 8-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12b) [NEW]. 6-acetamido-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate **6.11a** (0.130 g, 0.348 mmol) was dissolved in glacial acetic acid (5 mL), $Pd(OAc)_2$ (8 mg, 0.024 mmol), Imes.HCl (12 mg, 0.024 mmol) and H_2O_2 (35%, 0.09 mL, 1.0 mmol) were added. The vial was sealed whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in the microwave cavity at 120ºC for 5 hours. The reaction mixture was monitored by GC (50% conversion yield). Acetic acid was removed under reduced pressure. The crude product was dissolved in EtOAc

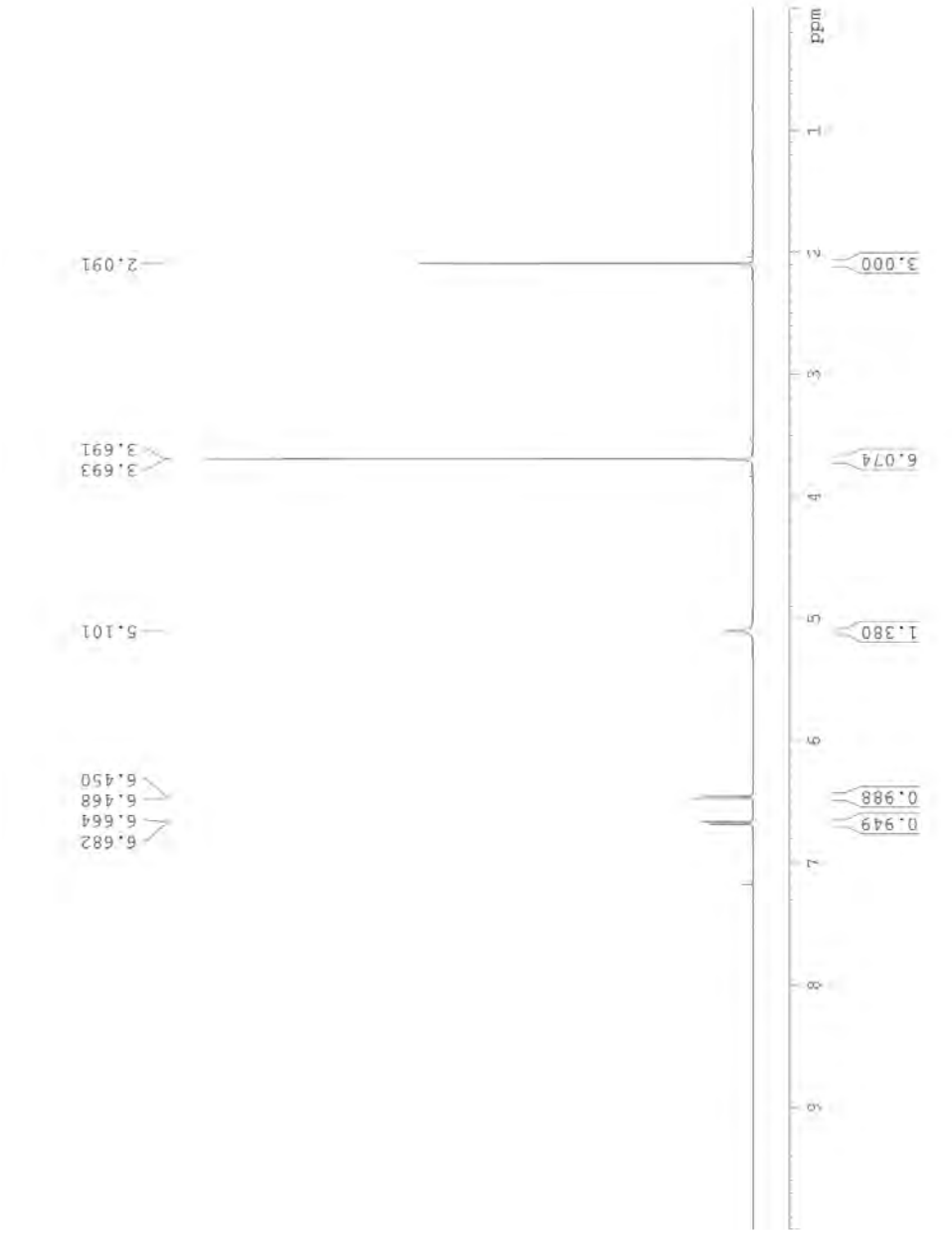
(40 mL) and washed with water (25 mL). The water phase was extracted with EtOAc (2×40mL). The combined organic layer was washed with aq.$NaHCO_3$ (30 mL). The organic layer was dried over Na_2SO_4 and filtered off. The solvent was evaporated under reduced pressure. The crude product was purified by using silica gel column chromatography (20:80, EtOAc:Hx) afforded a mixture of isomers in 30% yield. ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 8.13 (d, *J*= 9 Hz, 1H), 7.64 (d, *J*= 7.5 Hz, 1H), 7.54-7.55 (m, 1H), 7.32 (t, *J*= 8 Hz, 1H), 7.25 (m, 1H), 6.96-6.98 (dd, *J*= 2.5, 9 Hz, 1H), 3.82 (s, 1H), 3.79 (s, 3H), 3.77 (s, 1H), 3.65 (s, 3H), 2.54 (s, 3H), 2.47 (s, 3H), 2.31 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 172.5, 168.6, 159.6, 156.3, 147.4, 144.2, 135.1, 134.7, 130.5, 129.5, 129.1, 125.1, 124.6, 122.6, 120.4, 119.7, 116.2, 114.4, 114.3, 105.5, 61.1, 59.9, 55.8, 55.5, 26.6, 20.8, 10.2; MS (EI): m/z (%): 371 (7, M^+), 331 (11), 287 (28), 272 (62), 207 (69), 115 (34), 96 (38), 83 (42), 77(76)

1,3-dimethoxy-2-methyl-9H-carbazol-4-ol (6.13) [NEW]. To a stirred solution of 9-acetyl-1,3-dimethoxy-2-methyl-9H-carbazol-4-yl acetate **6.12** (0.023 g, 0.07 mmol) in methanol (10 mL) at 0 ^{o}C , was added a solution of conc.HCl (2 mL) in MeOH(5 mL) dropwise. The reaction mixture was stirred for 1 h at 70^{o}C. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (2x 20 mL). The combined organic layer was dried over Na_2SO_4. The solvent was filtered off to obtain the title compound as a brown solid (0.017 g, 94%). R_f = 0.42[(EtOAc:Hx, 20:80)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm)= 8.24 (d, *J*= 8 Hz, 1H), 8.10 (s, br, 1H), 7.41 (m, 1H), 7.39-7.35 (td, *J*= 1.0 Hz, 6.5 Hz, 1H), 7.24-7.20 (m, 1H), 6.03 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 2.42 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm)= 140.7, 139.1, 137.6, 135.8, 130.7, 125.0, 123.2, 122.6, 121.0, 119.5, 110.6, 110.2, 61.3, 60.8, 9.8; HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO_3$ 258.1130; Found 258.1133); IR (cm^{-1}): 3309, 3244, 2973, 2924, 2896, 1624, 1321, 1087, 1046, 879.

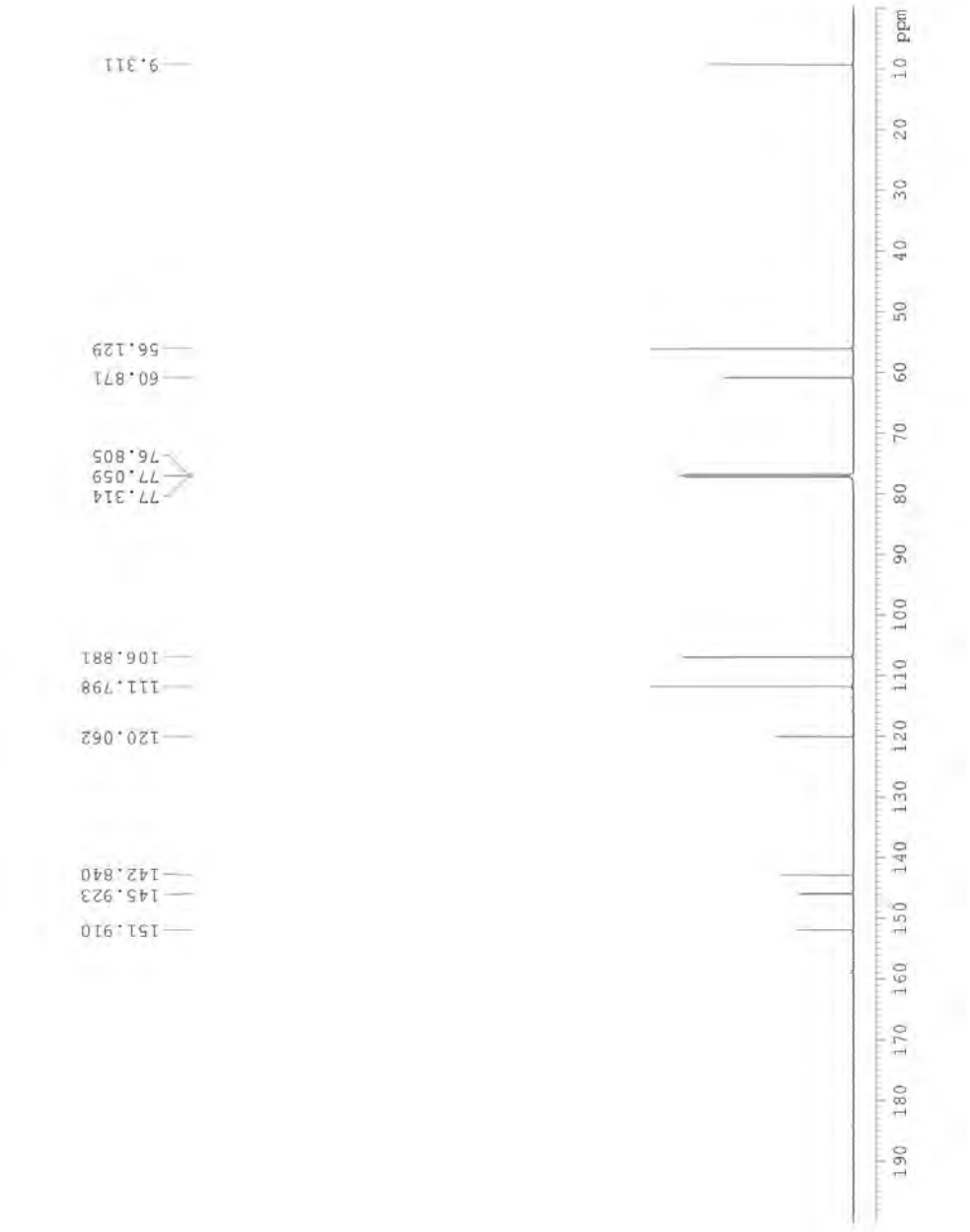
3-methoxy-2-methyl-1H-carbazole-1,4 (9H)-dione (6.14) [192188-88-8]. To a solution of 1, 3-dimethoxy-2-methyl-9H-carbazol-4-ol **6.13** (40 mg, 0.155 mmol) in glacial acetic acid (3 mL), HNO_3 (90%, 0.01 ml, 0.186 mmol) was added slowly at 0-5^{o}C. Then, the reaction mixture was stirred at ambient temperature for 15 min. After the reaction time, H_2O (20 ml) was added to the solution and extracted with EtOAc (3 × 30 ml). The combined organic extracts were washed with H_2O (2 × 40 ml) and dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by using silica gel column chromatography (50:50, DCM:Hx) to obtain the title compound as a pale-green solid (36 mg, 0.124 mmol) R_f = 0.86[(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ(ppm)= 12.85 (s, br, 1H), 8.01 (d, *J*= 8 Hz, 1H), 7.53 (d, *J*= 8.5 Hz, 1H), 7.35-7.38 (td, *J*= 1.0, 8.0 Hz, 1H), 7.29-7.32 (td, *J*= 1.0 Hz, 8.0 Hz, 1H), 4.03 (s, 3H), 1.92 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ(ppm)= 180.5, 178.7, 157.8, 137.6, 136.4, 129.3, 128.4, 126.6, 126.0, 123.8, 121.4, 113.7, 61.2, 8.4; HR-MS (ESI-): $(M-H)^+$: Calcd for $C_{14}H_{10}NO_3$ 240.06606; Found 240.06632); IR (cm^{-1}): 3257, 2958, 2923, 2853, 1639, 1258, 1094, 1022, 794.

Carbazomycin G (1-hydroxy-3-methoxy-1,2-dimethyl-1,9-dihydro-4*H*-carbazol-4-one) (6.15) [115920-44-0]. In a vacuum dried Schlenk tube, the solution of compound **6.14** (0.022 g, 0.091 mmol) dissolved in THF (10 mL) was added under Ar atmosphere. The solution was cooled to -78 ºC (dry ice and acetone mixture). A solution of methyllithium (1.6 M in Et_2O, 0.26 mL, 0.42 mmol) was added dropwise at -78 ºC. The reaction mixture was warmed to room temperature for about 30 minutes, then quenched with NH_4Cl (10%, 10 mL). The reaction mixture was extracted with EtOAc (2× 50 mL). The organic extracts were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by using silica gel column chromatography (50:50, EtOAc:Hx) to obtain the target compound as a pale-yellow solid (51%, 12 mg, 0.047 mmol) R_f = 0.41[(EtOAc:Hx, 50:50)]; ^{1}H-NMR (850 MHz, DMSO-d_6): δ(ppm)= 12.19 (s, br, 1H), 8.01 (d, *J*= 7.7 Hz, 1H), 7.44 (d, *J*= 7.7 Hz, 1H), 7.22 (t, *J*= 7.7 Hz, 1H), 7.17 (t, *J*= 7.7 Hz, 1H), 5.92 (s, 1H), 3.69 (s, 3H), 1.98 (s, 3H), 1.57 (s, 3H); ^{13}C-NMR and DEPT (212.5 MHz, DMSO-d_6): δ(ppm)= 177.6 (C=O), 154.4 (C), 147.7 (C), 140.8 (C), 136.5 (C), 123.9 (C), 122.9 (CH), 121.4 (CH), 120.5 (CH), 112.0 (CH), 108.4 (C), 67.4 (C), 59.2 (CH_3), 27.9 (CH_3), 10.1 (CH_3); HR-MS (ESI-): $(M-H)^+$: Calcd for $C_{15}H_{14}NO_3$ 256.09737; Found 256.09799); IR (cm^{-1}): 3255 br, 2924, 2853, 1719, 1643, 1618, 1468, 1375, 1289, 1138, 1092, 1011, 961, 804, 748.

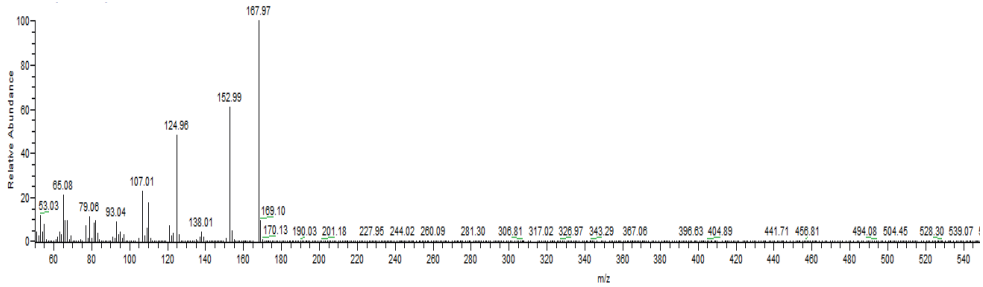
^{1}H-NMR of 2,4-Dimethoxy-3-methyl phenol (6.2) in $CDCl_3$



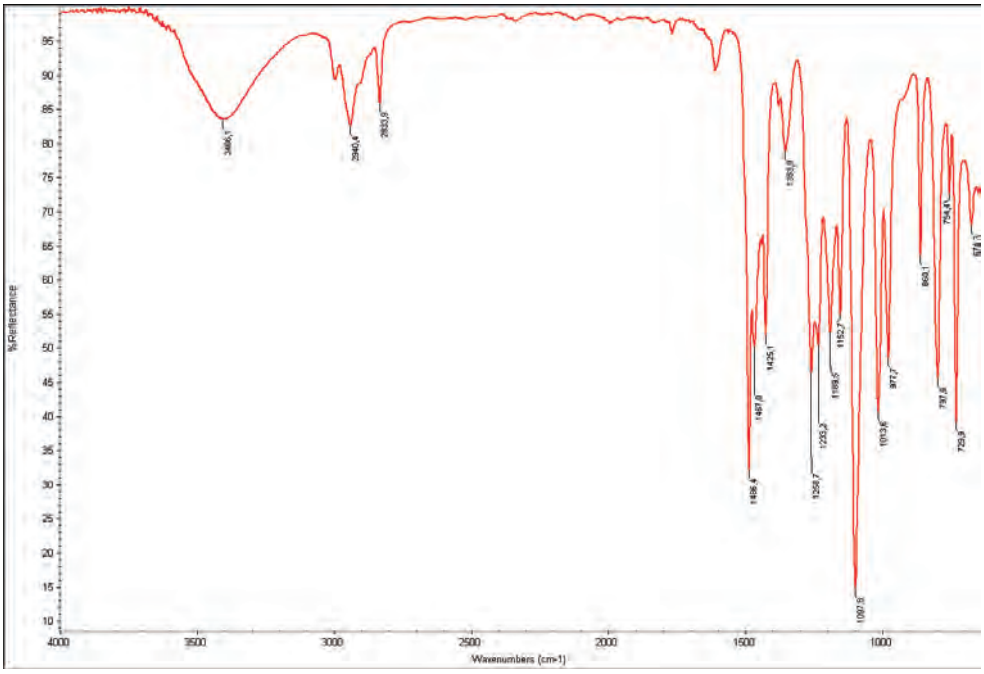
^{13}C-NMR of 2,4-Dimethoxy-3-methyl phenol (6.2) in $CDCl_3$



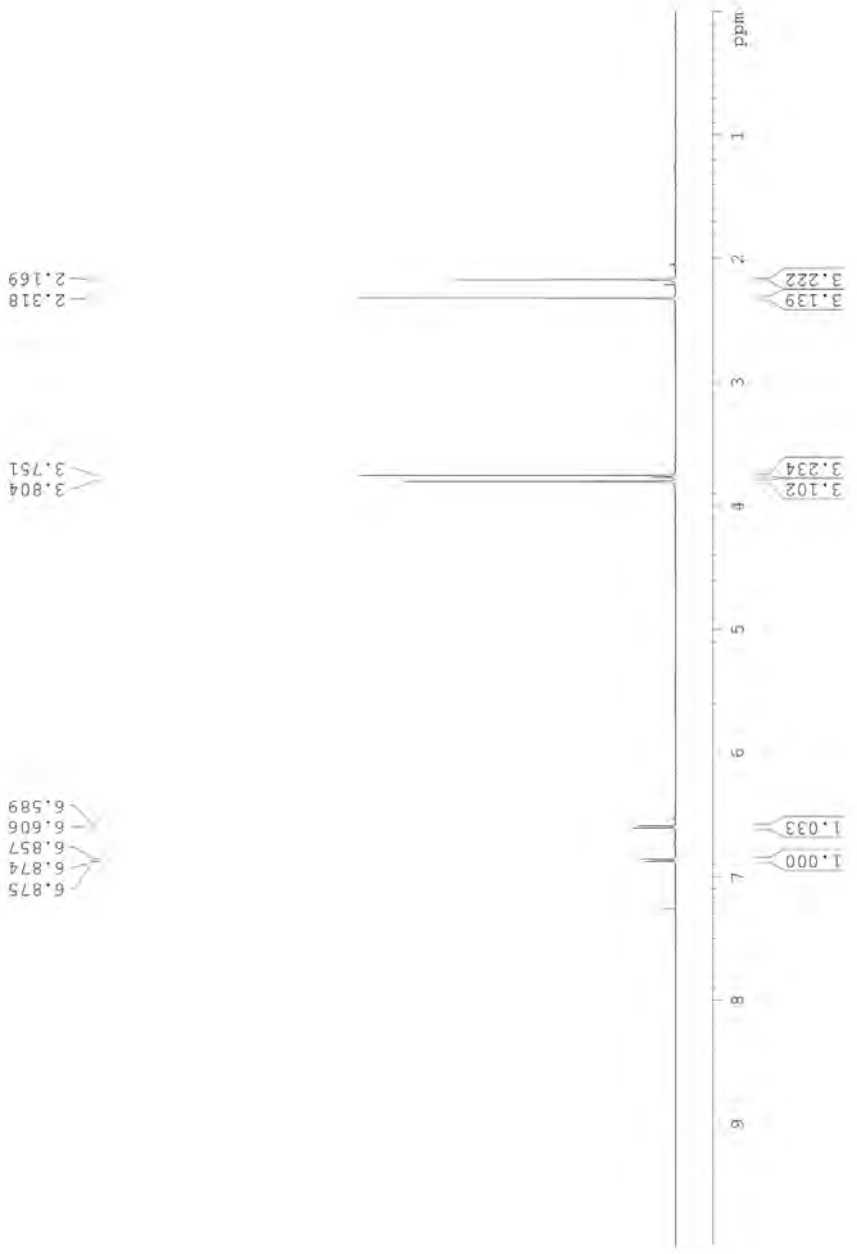
MS(EI) of 2,4-Dimethoxy-3-methyl phenol (6.2)



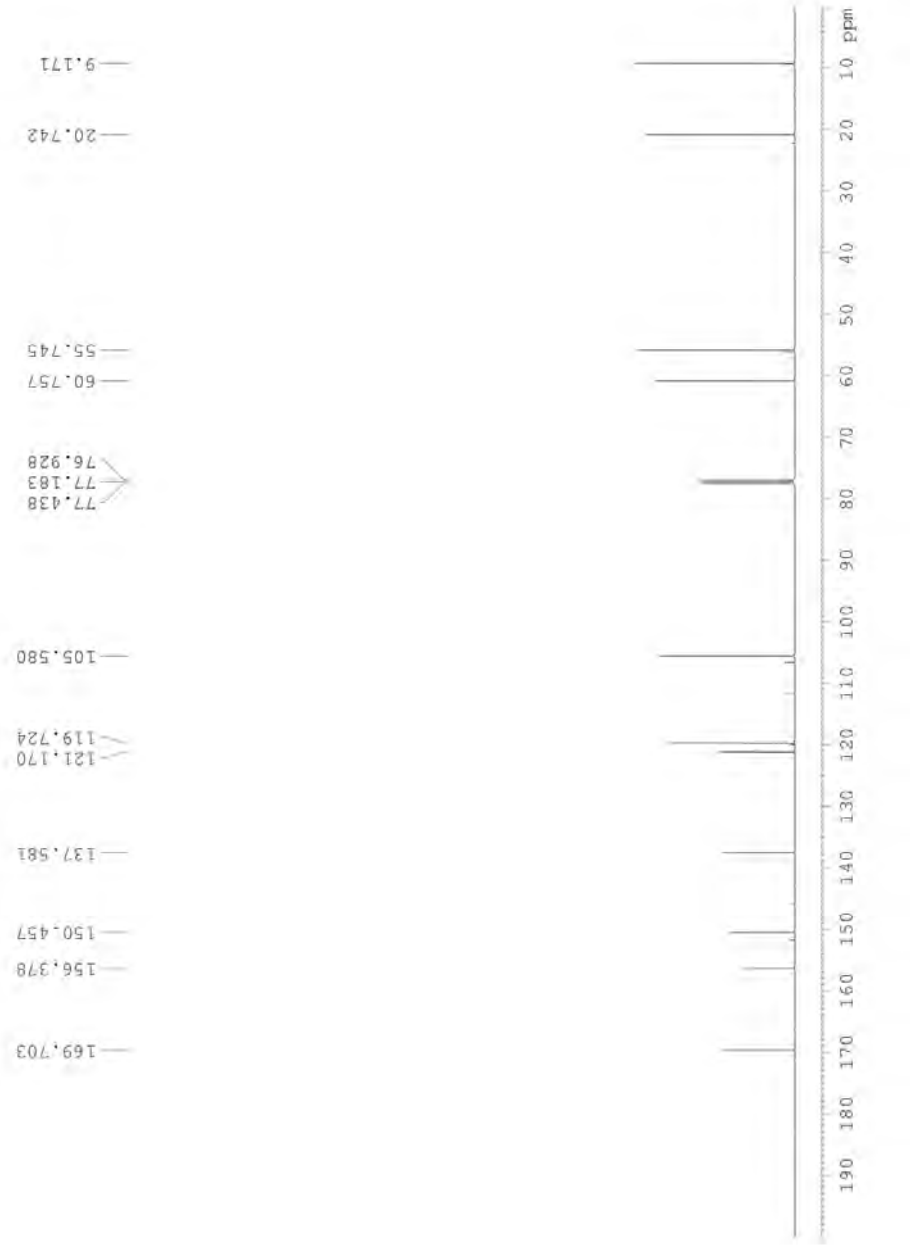
IR of 2,4-Dimethoxy-3-methyl phenol (6.2)



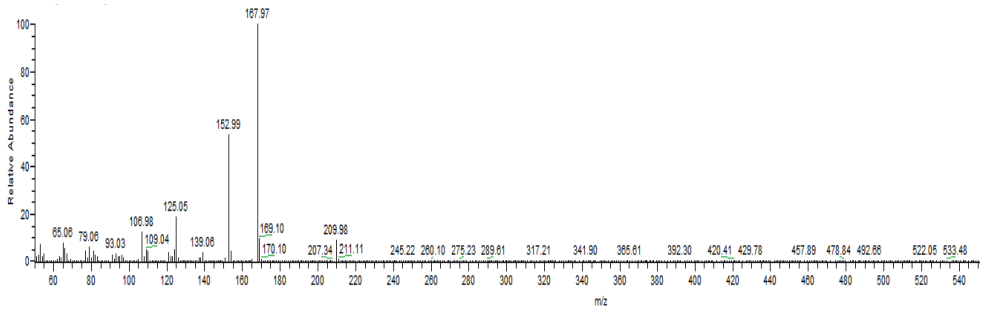
[1]H-NMR of 2, 4-Dimethoxy-3-methylphenyl acetate (6.3) in $CDCl_3$



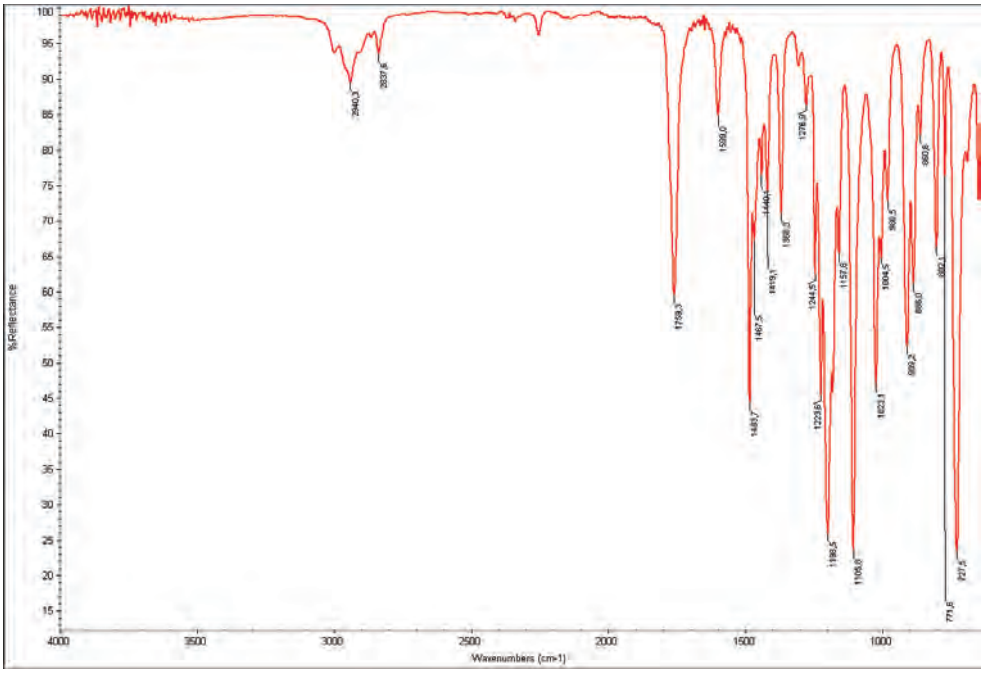
^{13}C-NMR of 2, 4-Dimethoxy-3-methylphenyl acetate (6.3) in $CDCl_3$



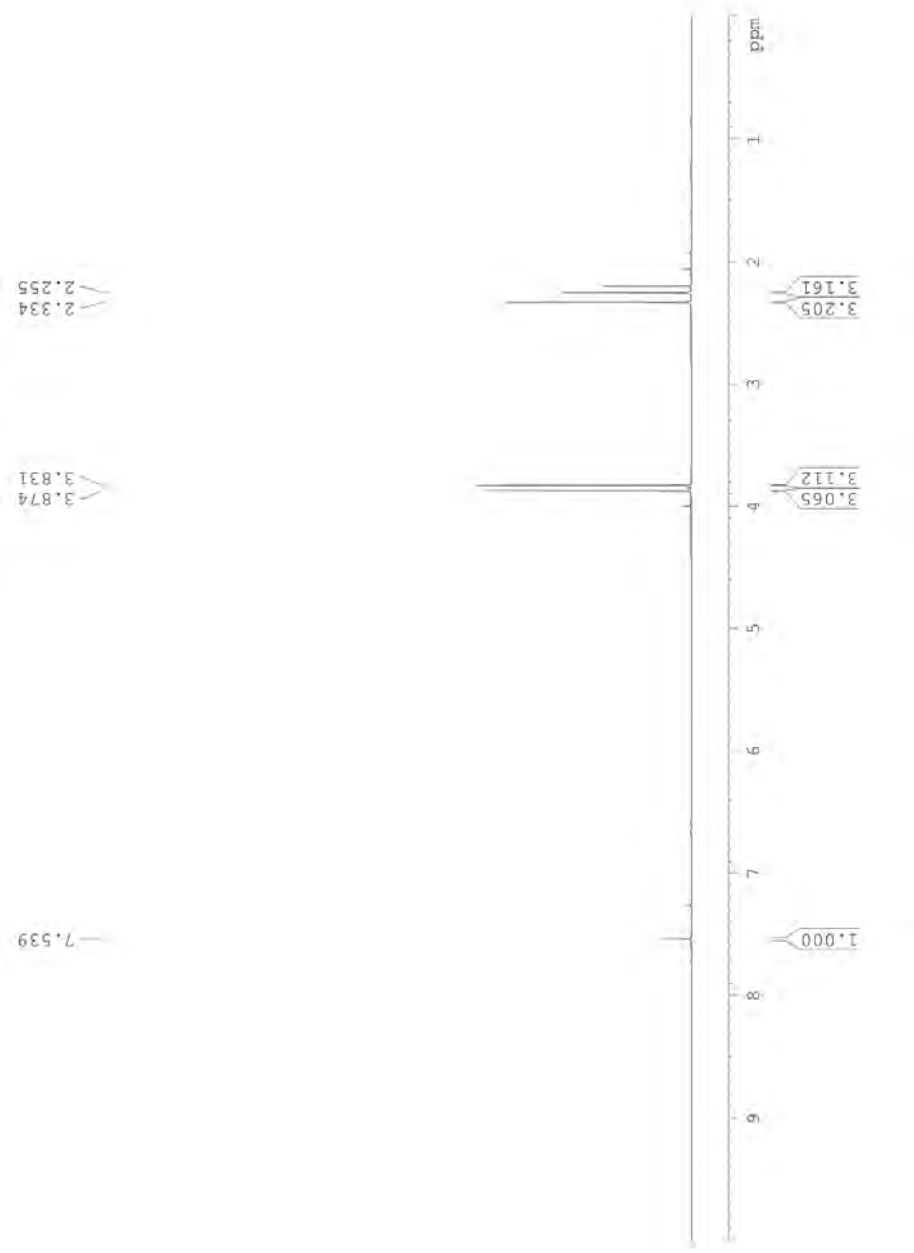
MS (EI) of 2, 4-Dimethoxy-3-methylphenyl acetate (6.3)



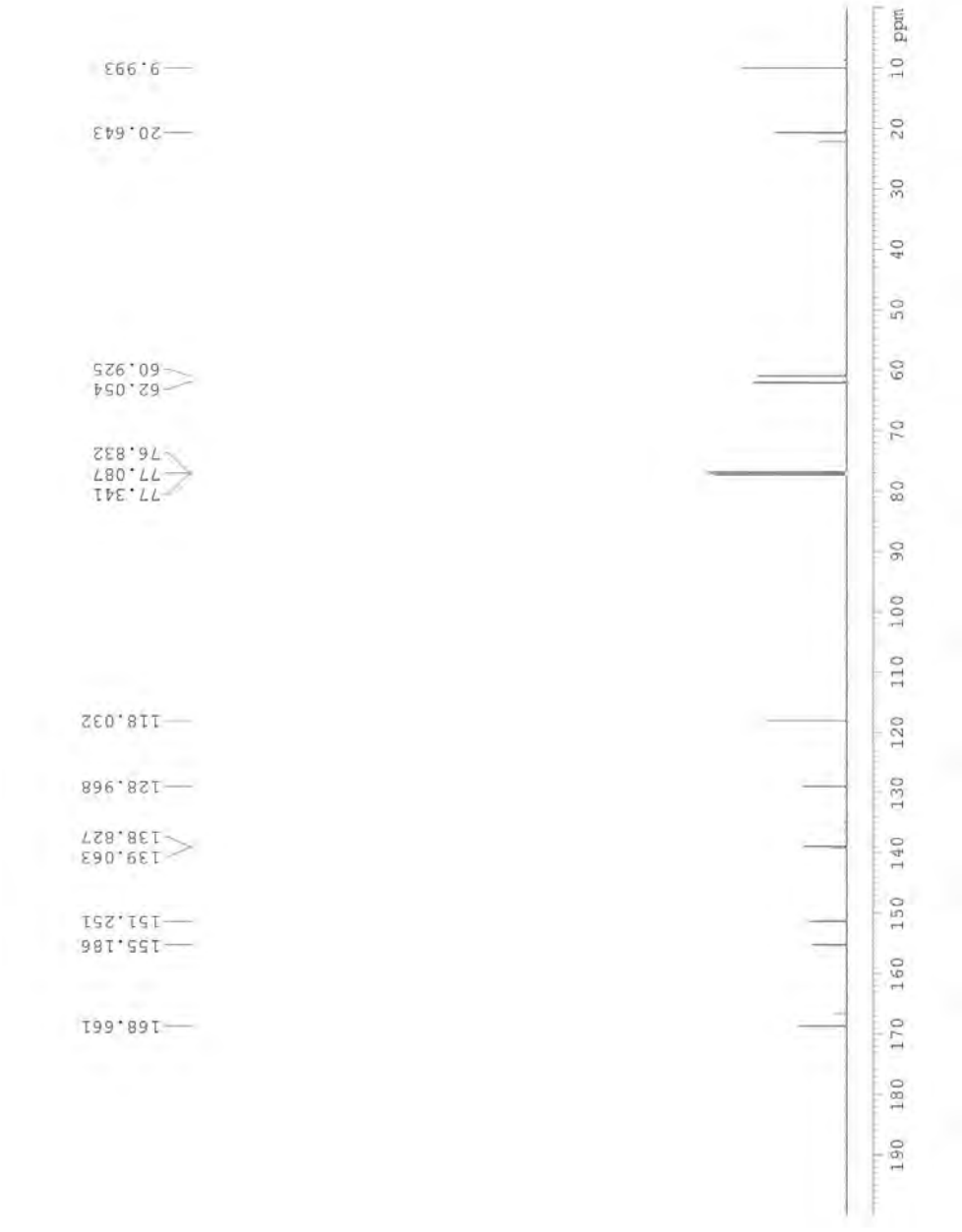
IR of 2, 4-Dimethoxy-3-methylphenyl acetate (6.3)



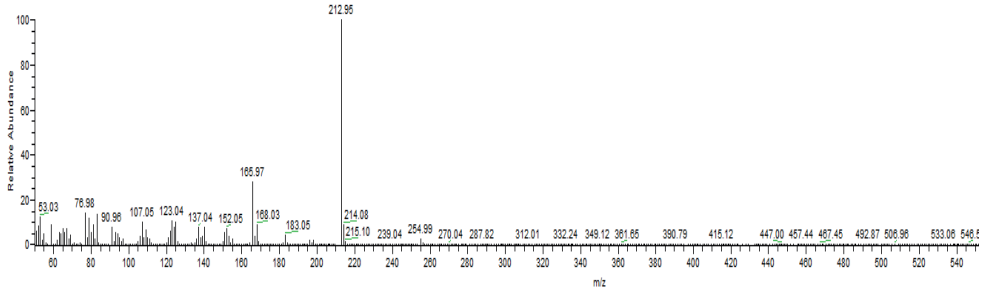
^{1}H-NMR of 2,4-Dimethoxy-3-methyl-5-nitrophenyl acetate (6.4) in $CDCl_3$



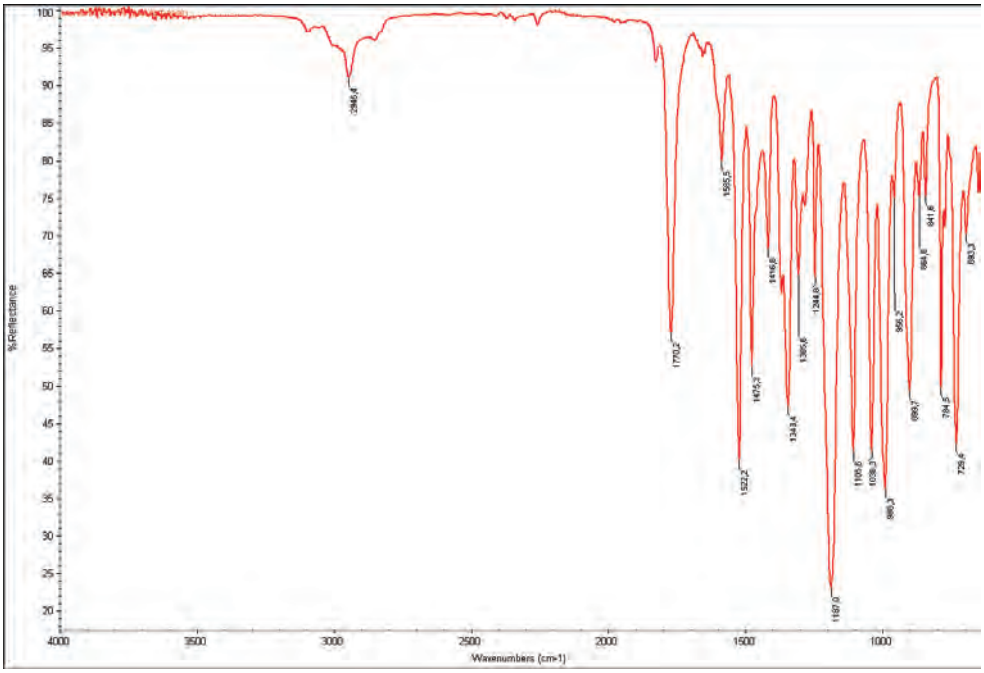
^{13}C-NMR of 2,4-Dimethoxy-3-methyl-5-nitrophenyl acetate (6.4) in $CDCl_3$



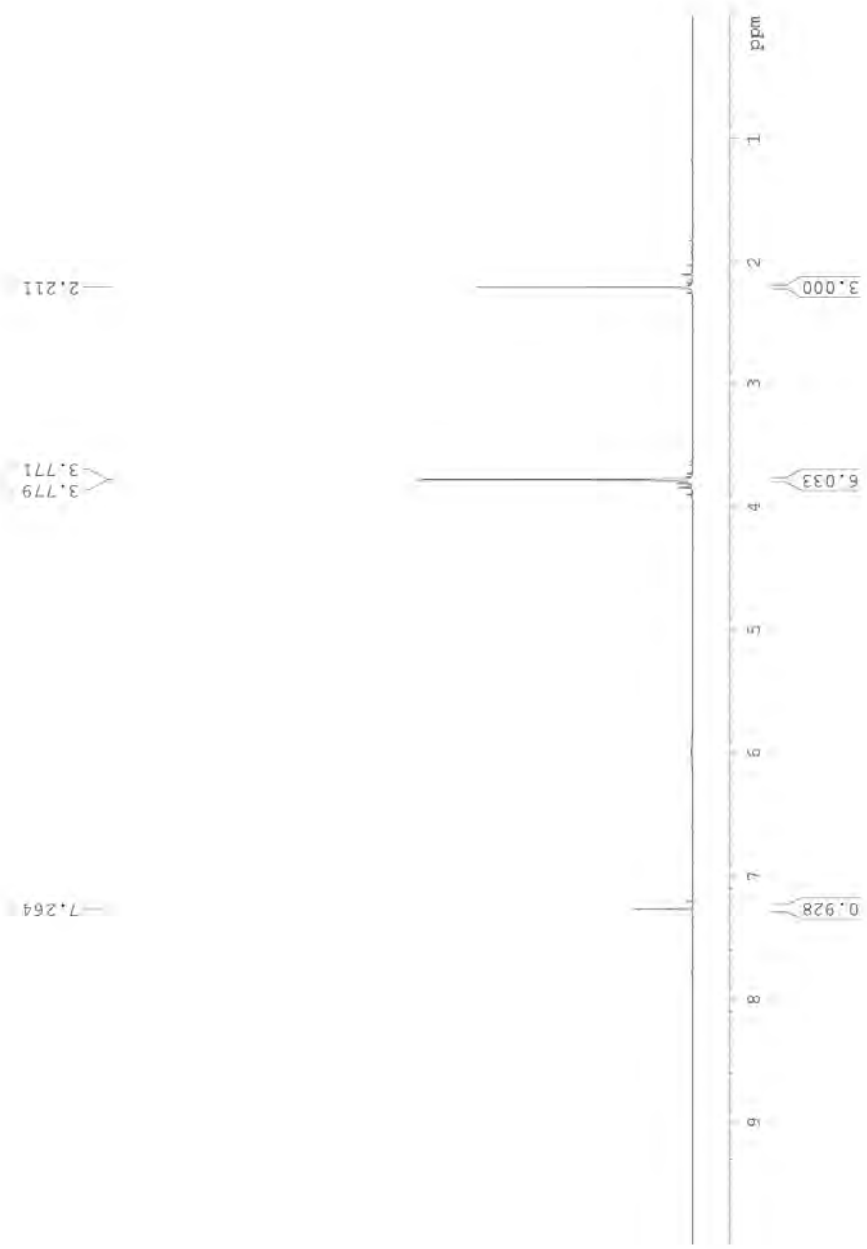
MS (EI) of 2,4-Dimethoxy-3-methyl-5-nitrophenyl acetate (6.4)



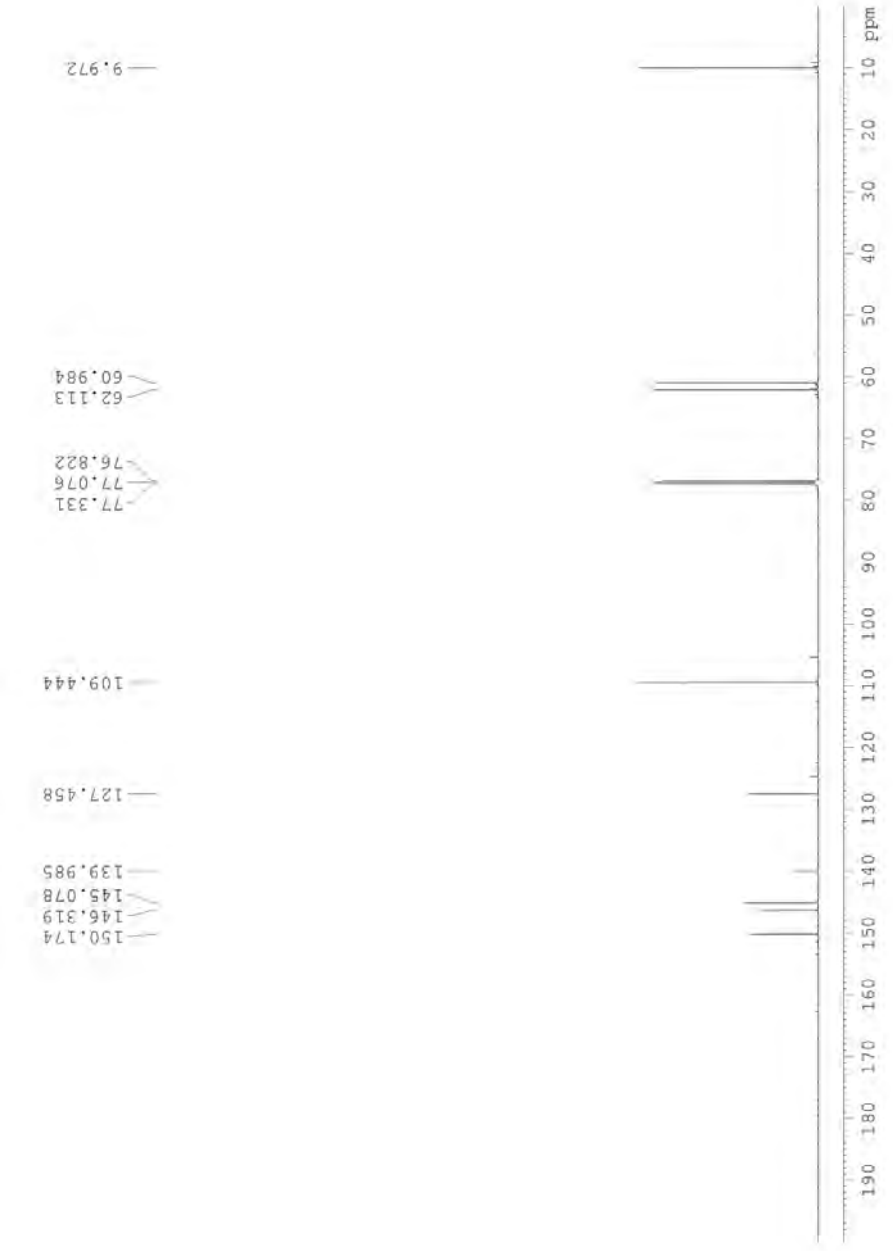
IR of 2,4-Dimethoxy-3-methyl-5-nitrophenyl acetate (6.4)



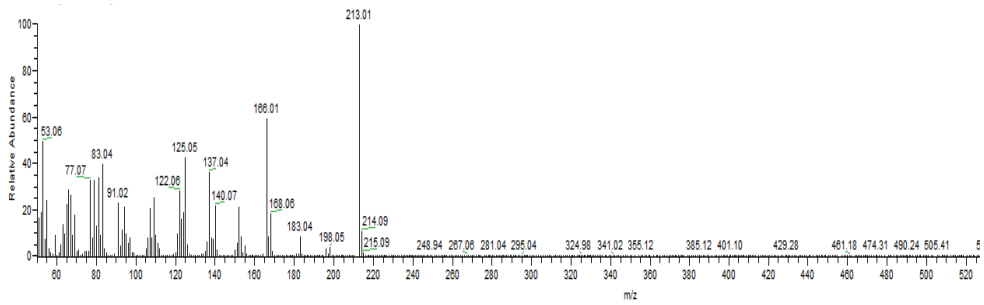
[1]H-NMR of 2,4-Dimethoxy-3-methyl-5nitrophenol (6.5) in $CDCl_3$



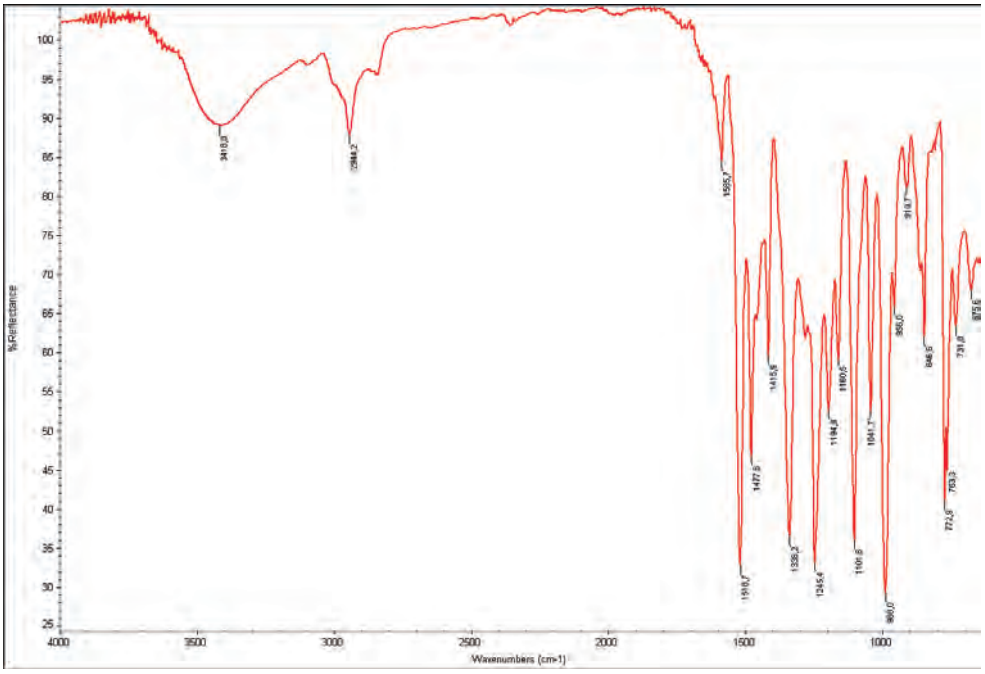
^{13}C-NMR of 2,4-Dimethoxy-3-methyl-5nitrophenol (6.5) in $CDCl_3$



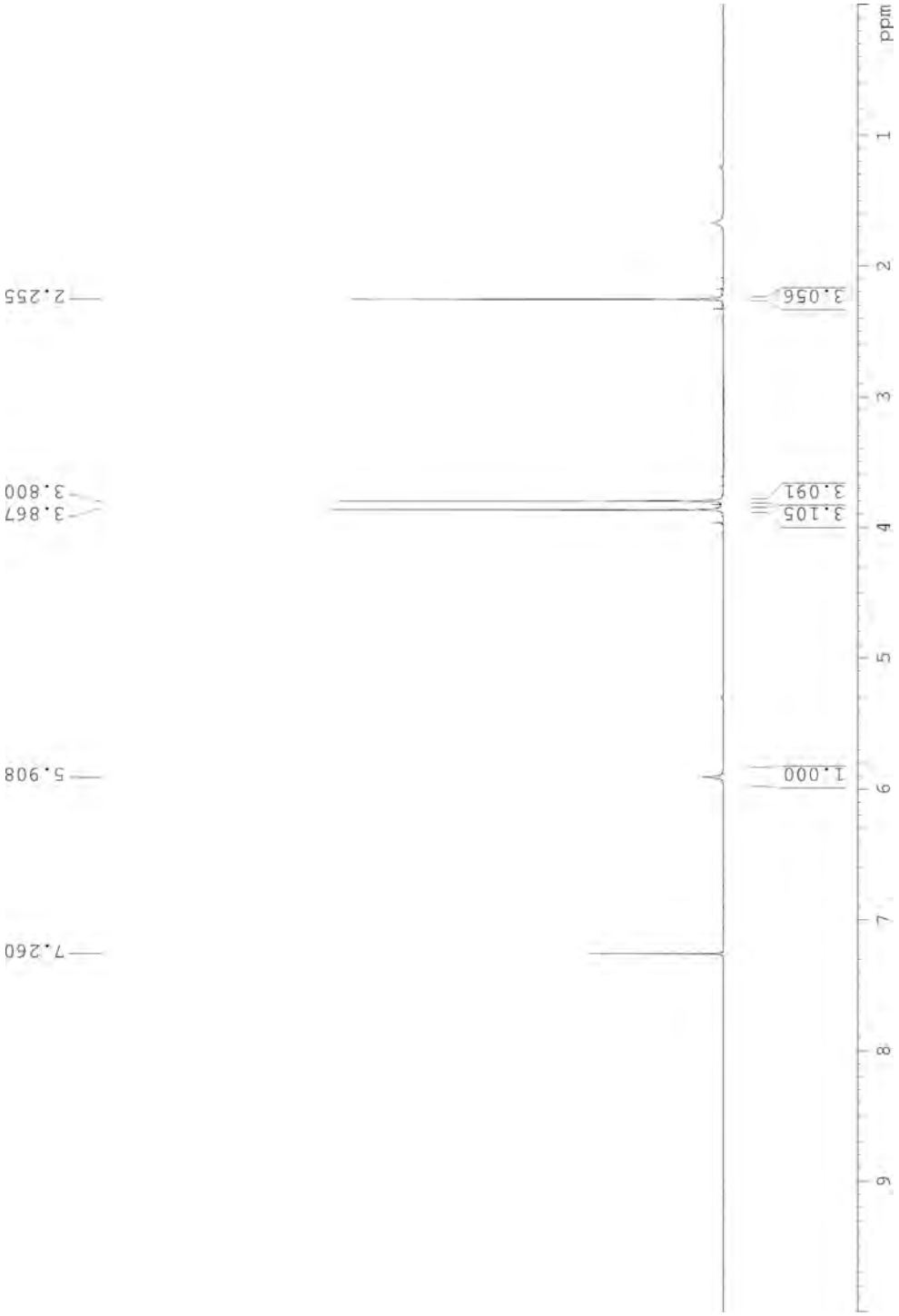
MS (EI) of 2,4-Dimethoxy-3-methyl-5nitrophenol (6.5)



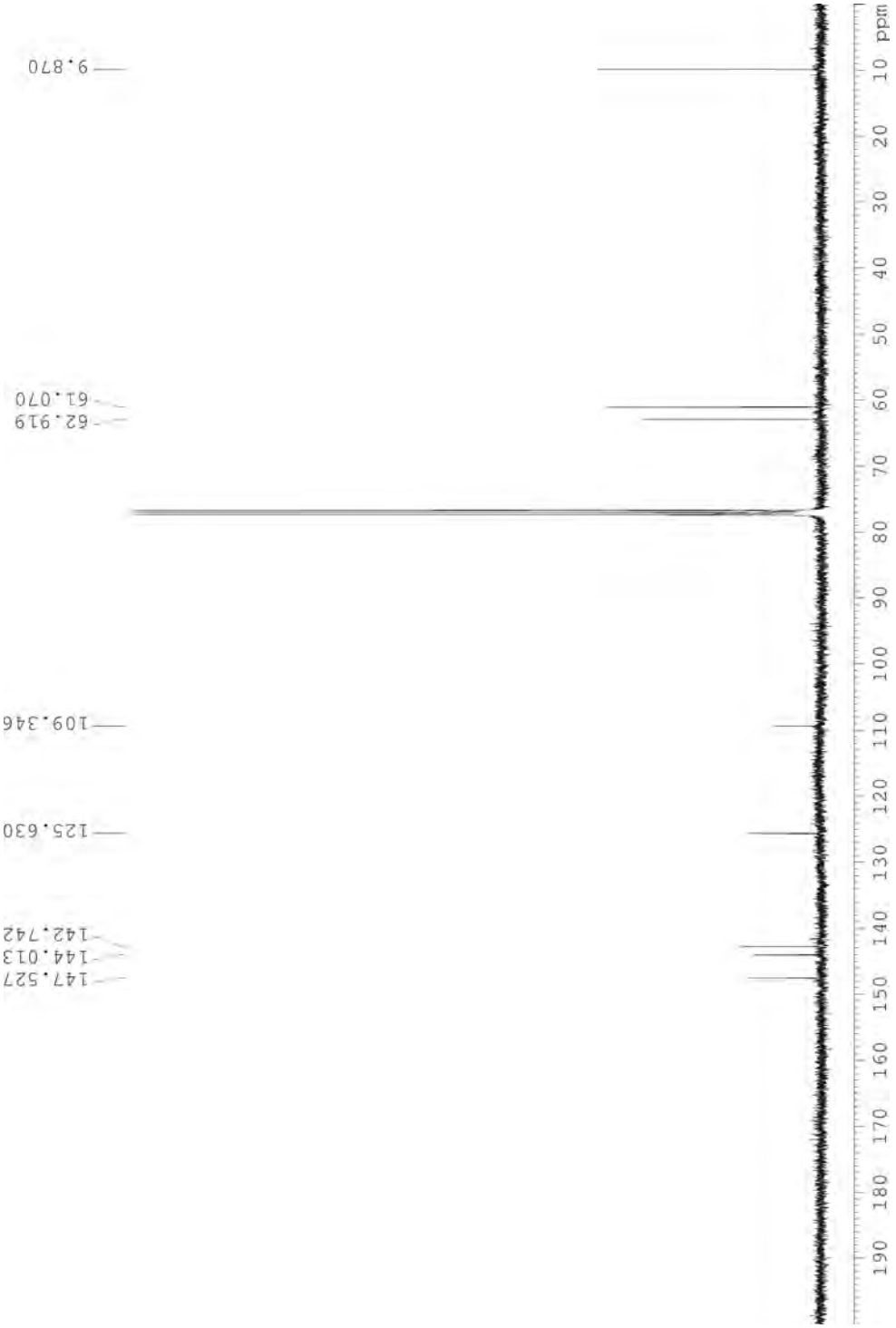
IR of 2,4-Dimethoxy-3-methyl-5nitrophenol (6.5)



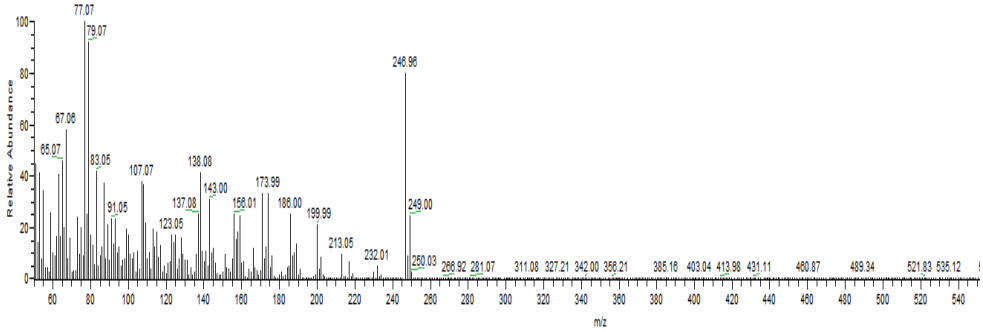
[1]H-NMR of 2-Chloro 4, 6-dimethoxy-5-methyl-3-nitrophenol (6.7a) in $CDCl_3$



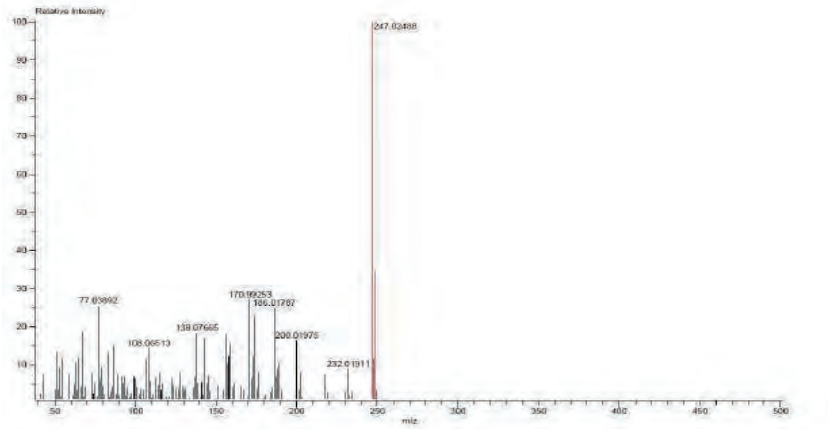
^{13}C-NMR of 2-Chloro 4, 6-dimethoxy-5-methyl-3-nitrophenol (6.7a) in $CDCl_3$



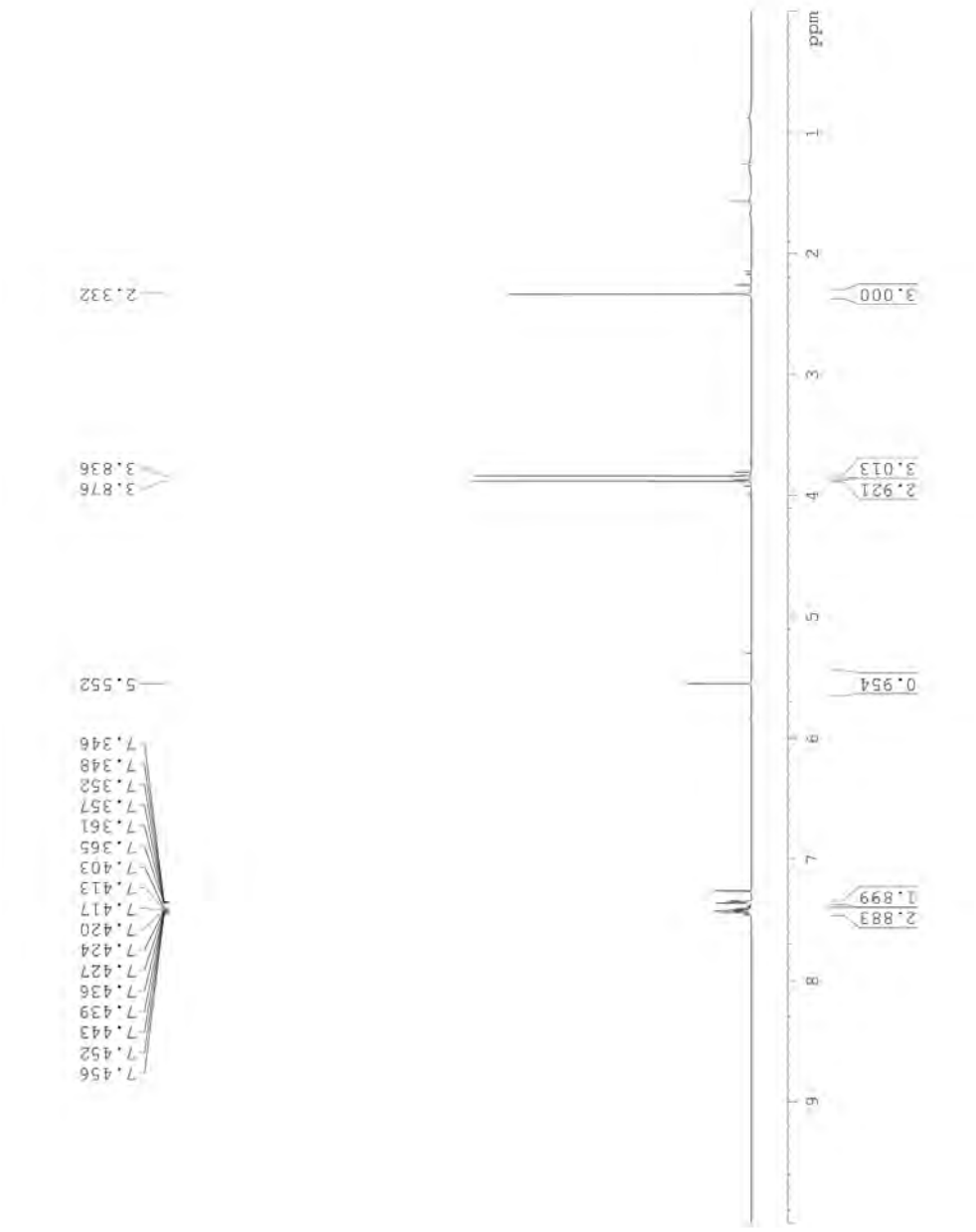
MS (EI) 2-Chloro 4, 6-dimethoxy-5-methyl-3-nitrophenol (6.7a)



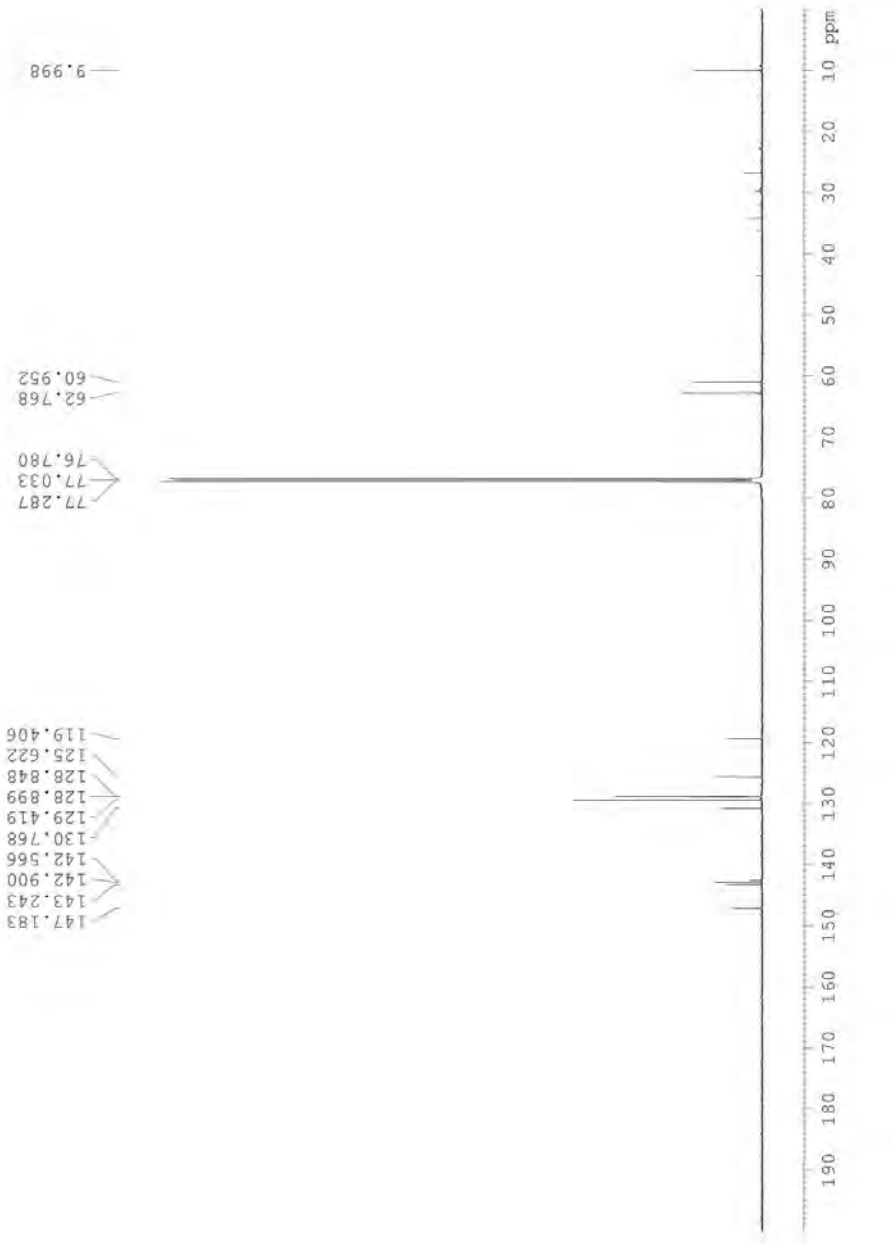
HRMS (EI) 2-Chloro 4, 6-dimethoxy-5-methyl-3-nitrophenol (6.7a)



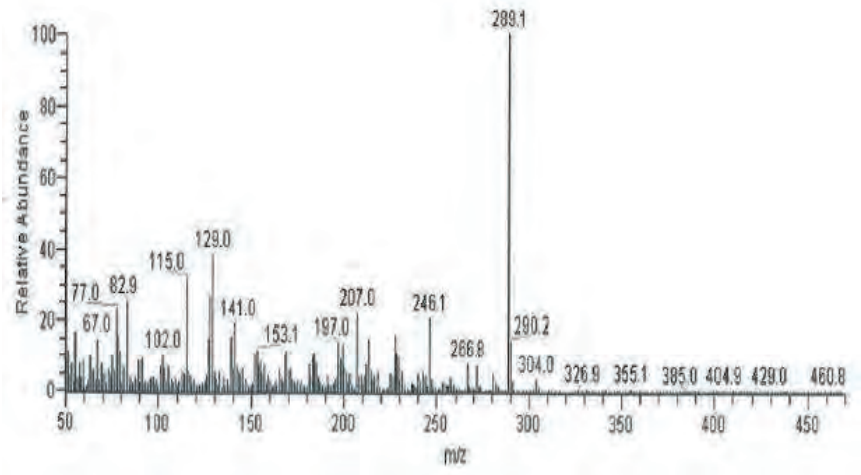
^{1}H-NMR of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (6.9) in $CDCl_3$



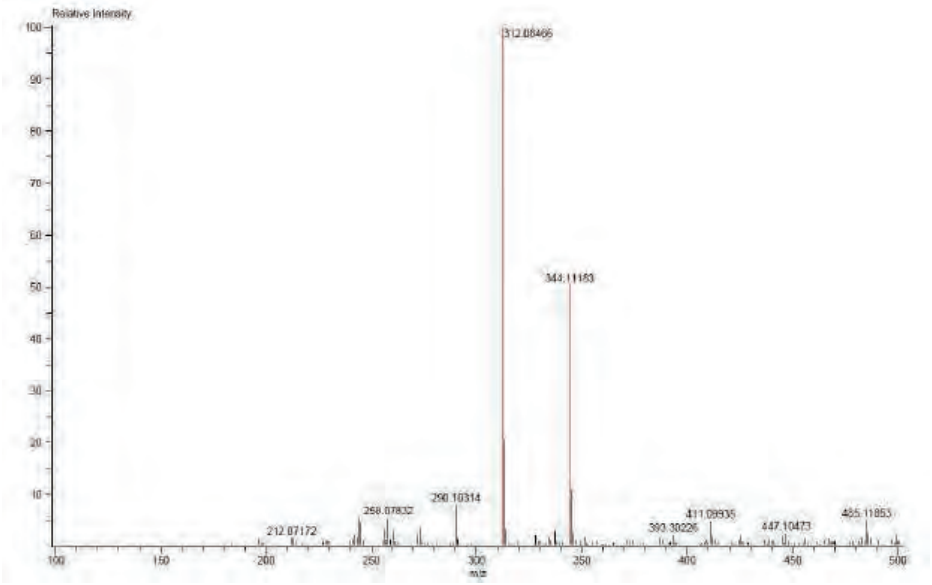
^{13}C-NMR of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (6.9) in $CDCl_3$



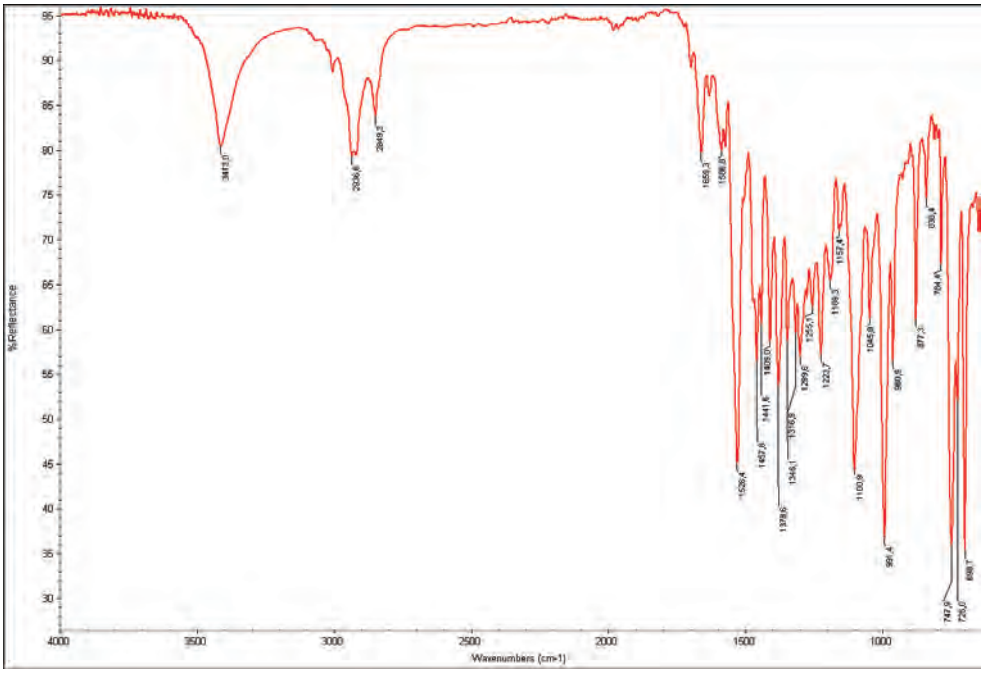
MS (EI) of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (6.9)



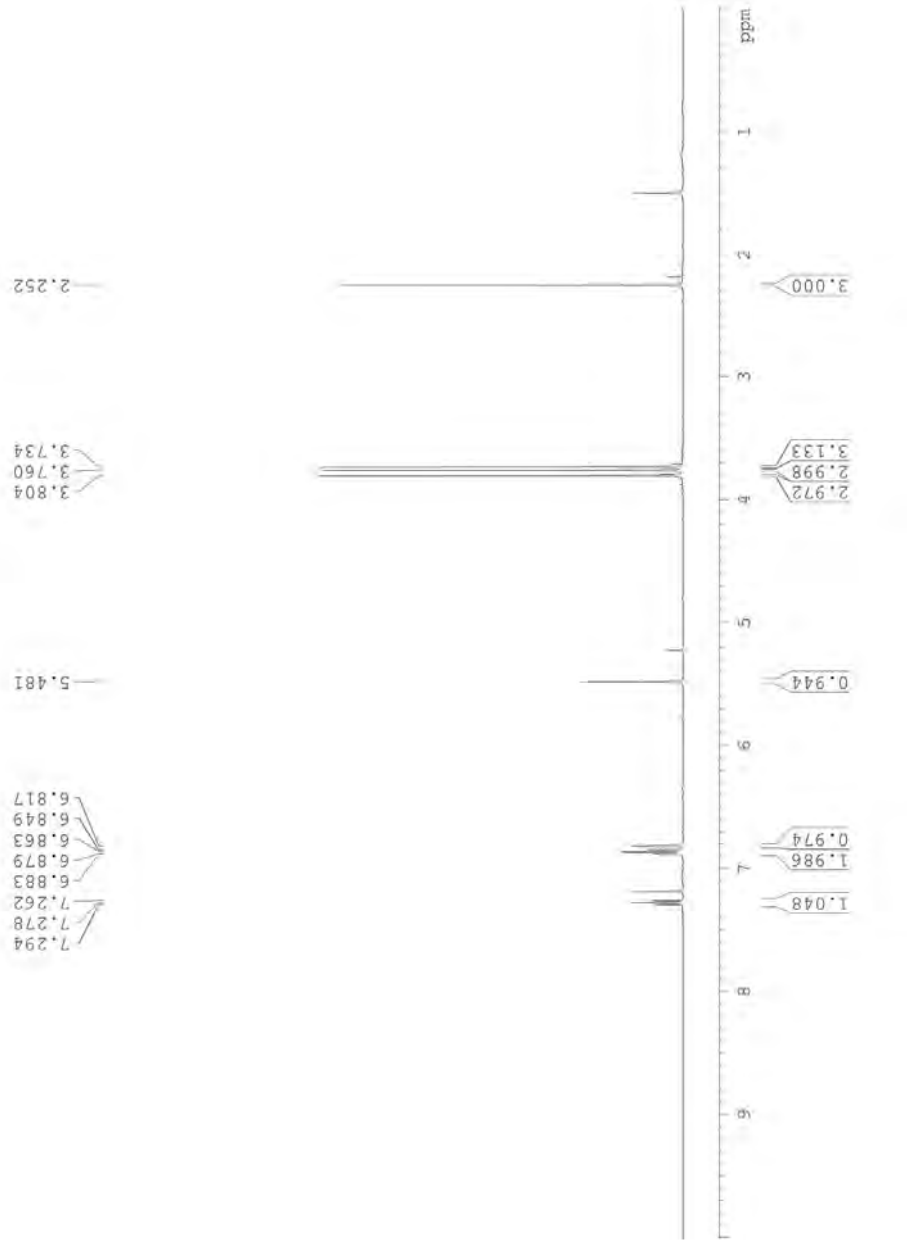
HRMS (EI) of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (6.9)



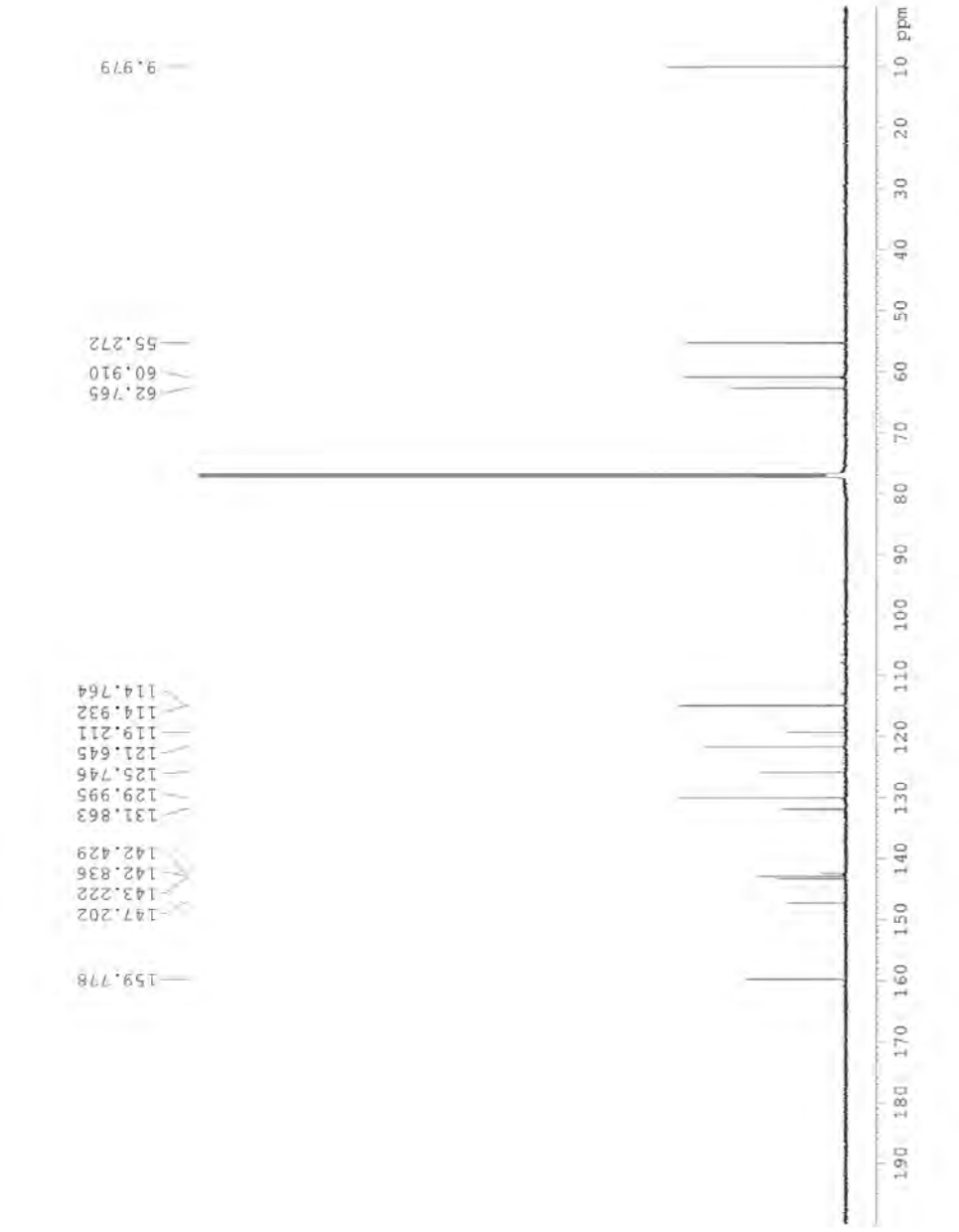
IR of 3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (6.9)



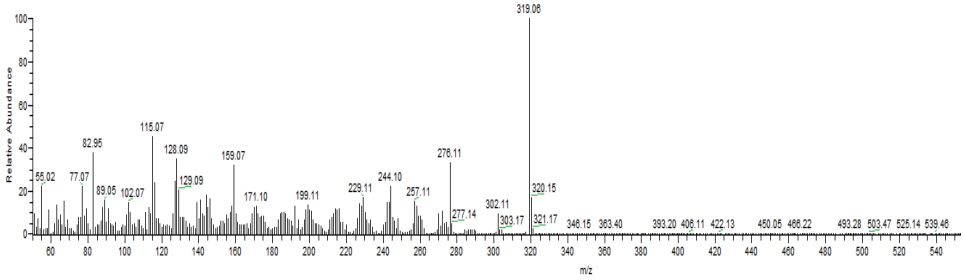
^{1}H-NMR of 3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol (6.9a) in $CDCl_3$



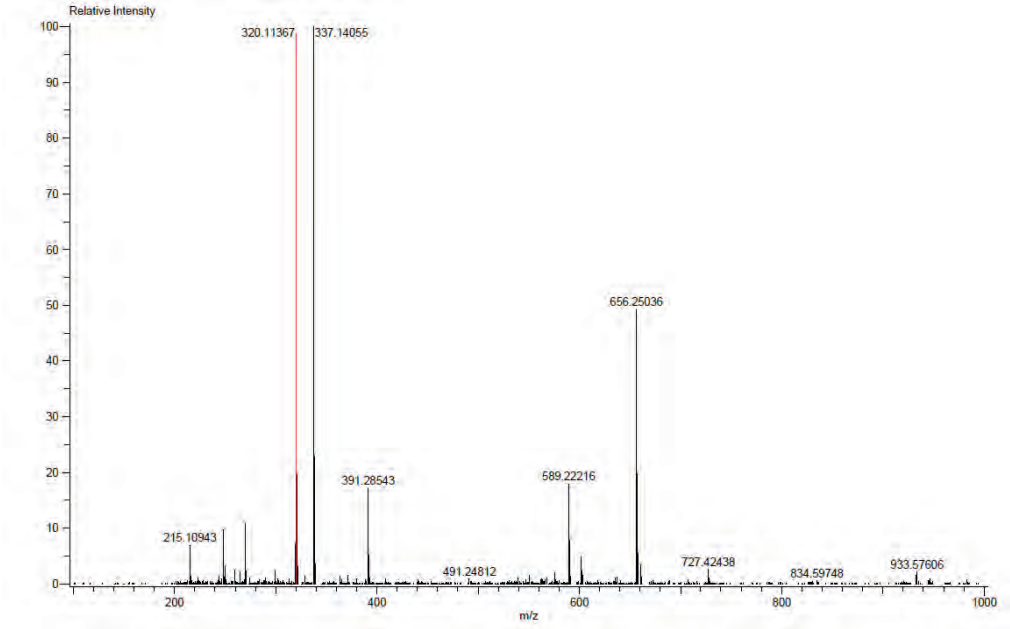
^{13}C-NMR of 3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol (6.9a) in $CDCl_3$



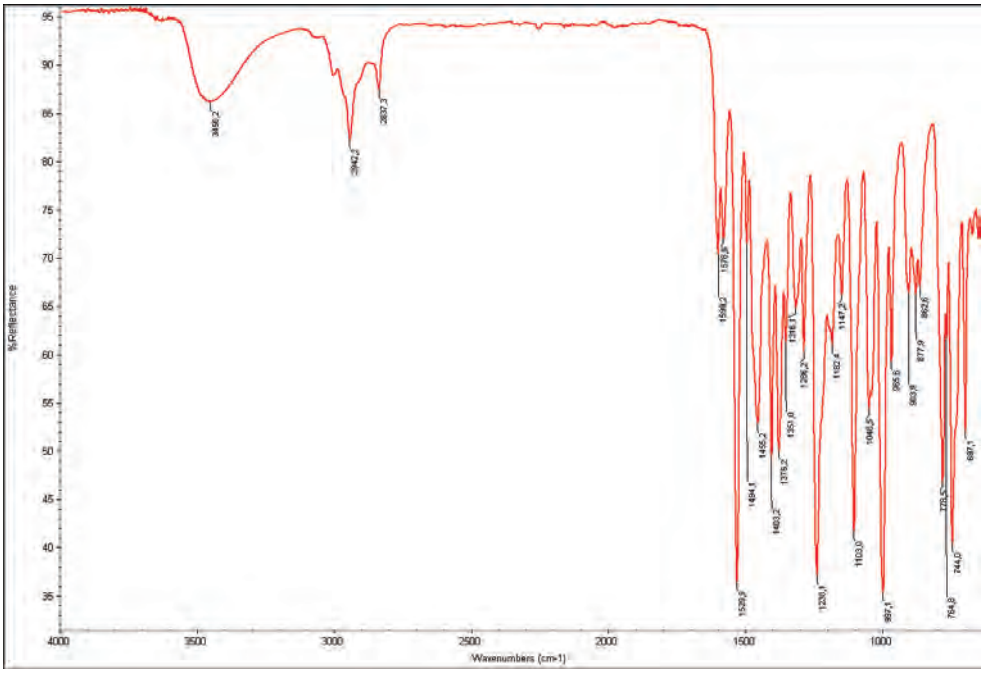
MS (EI) of 3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol (6.9a)



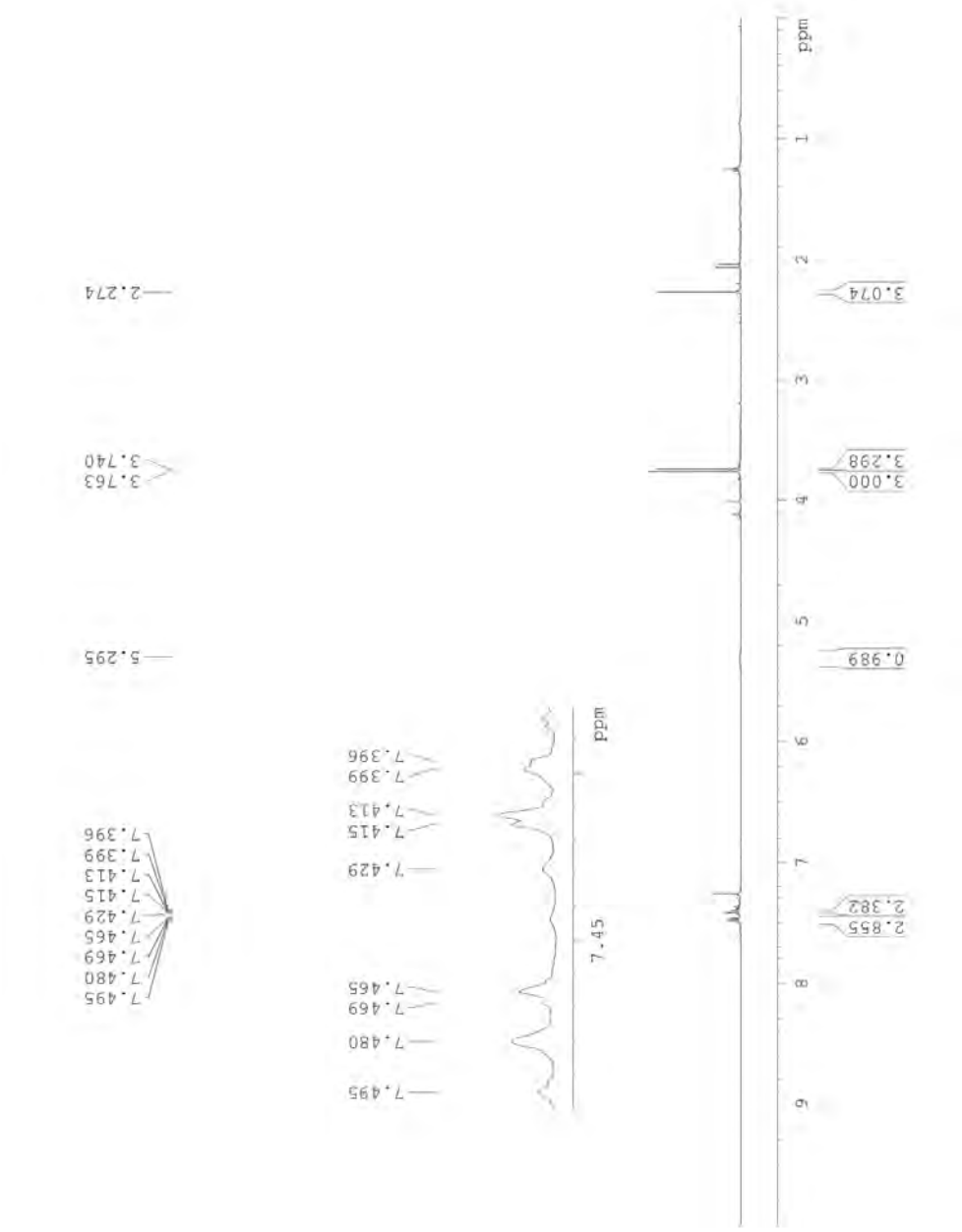
HRMS (EI) of 3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol (6.9a)



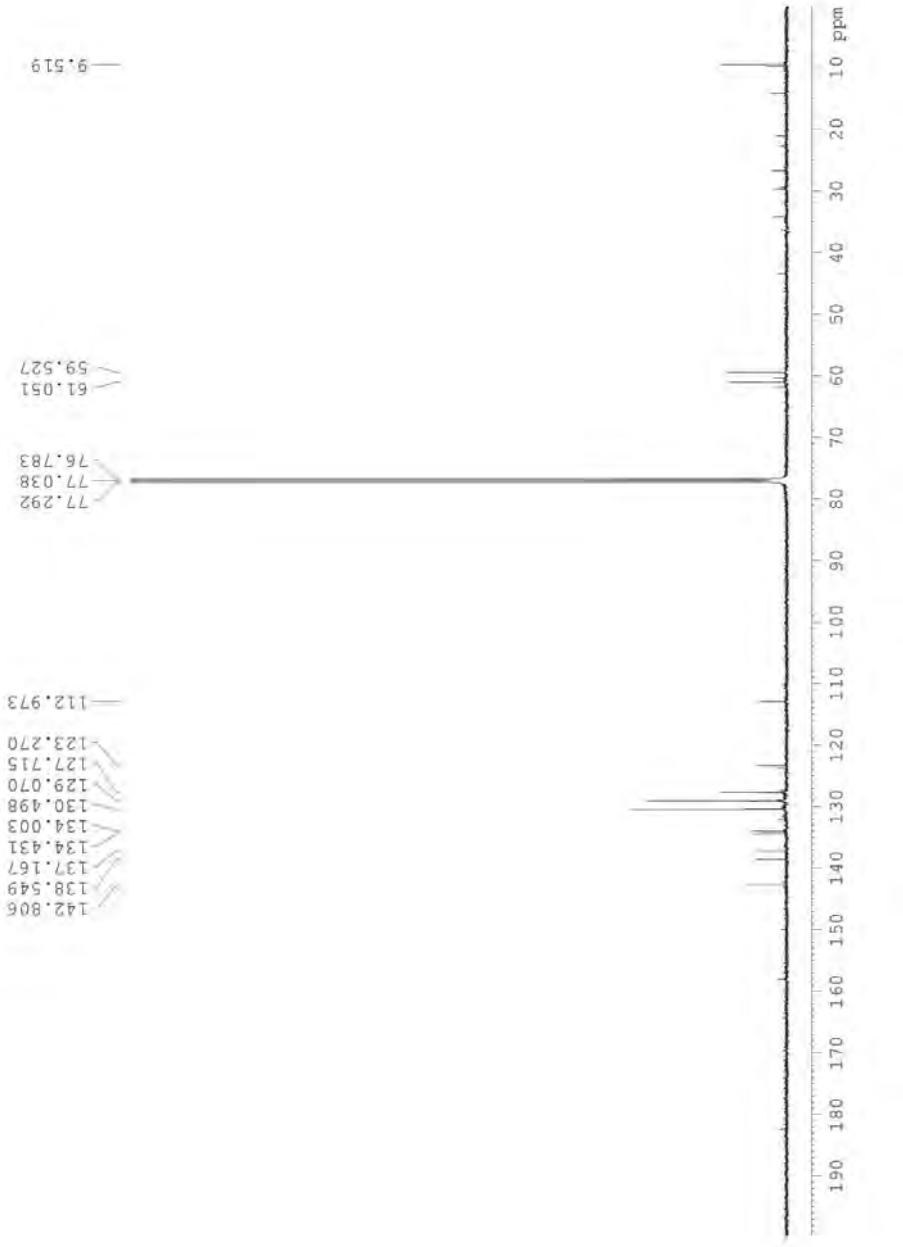
IR of 3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol (6.9a)



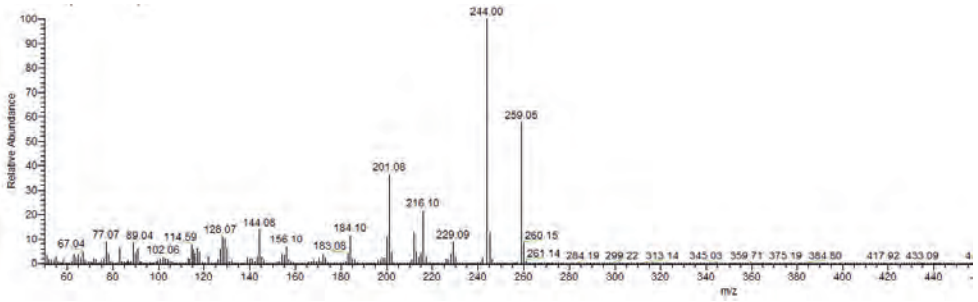
^{1}H-NMR of 6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10) in $CDCl_3$



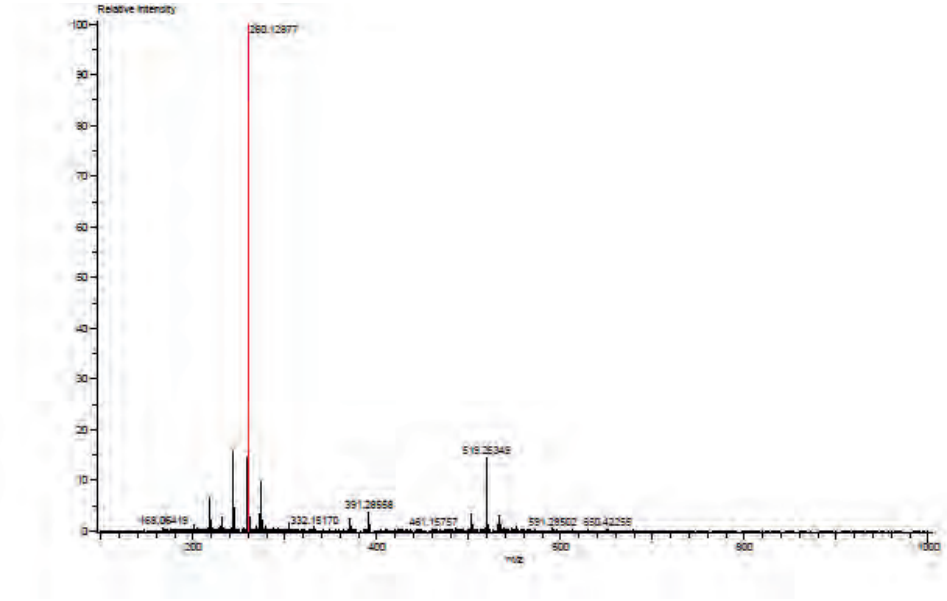
^{13}C-NMR of 6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10) in $CDCl_3$



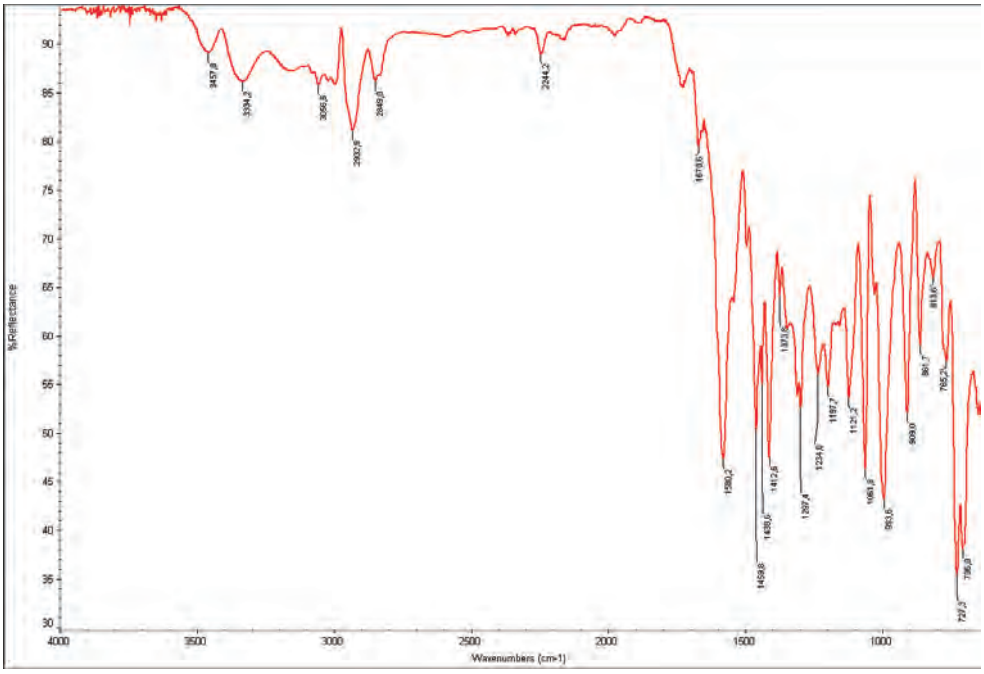
MS (EI) of 6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10)



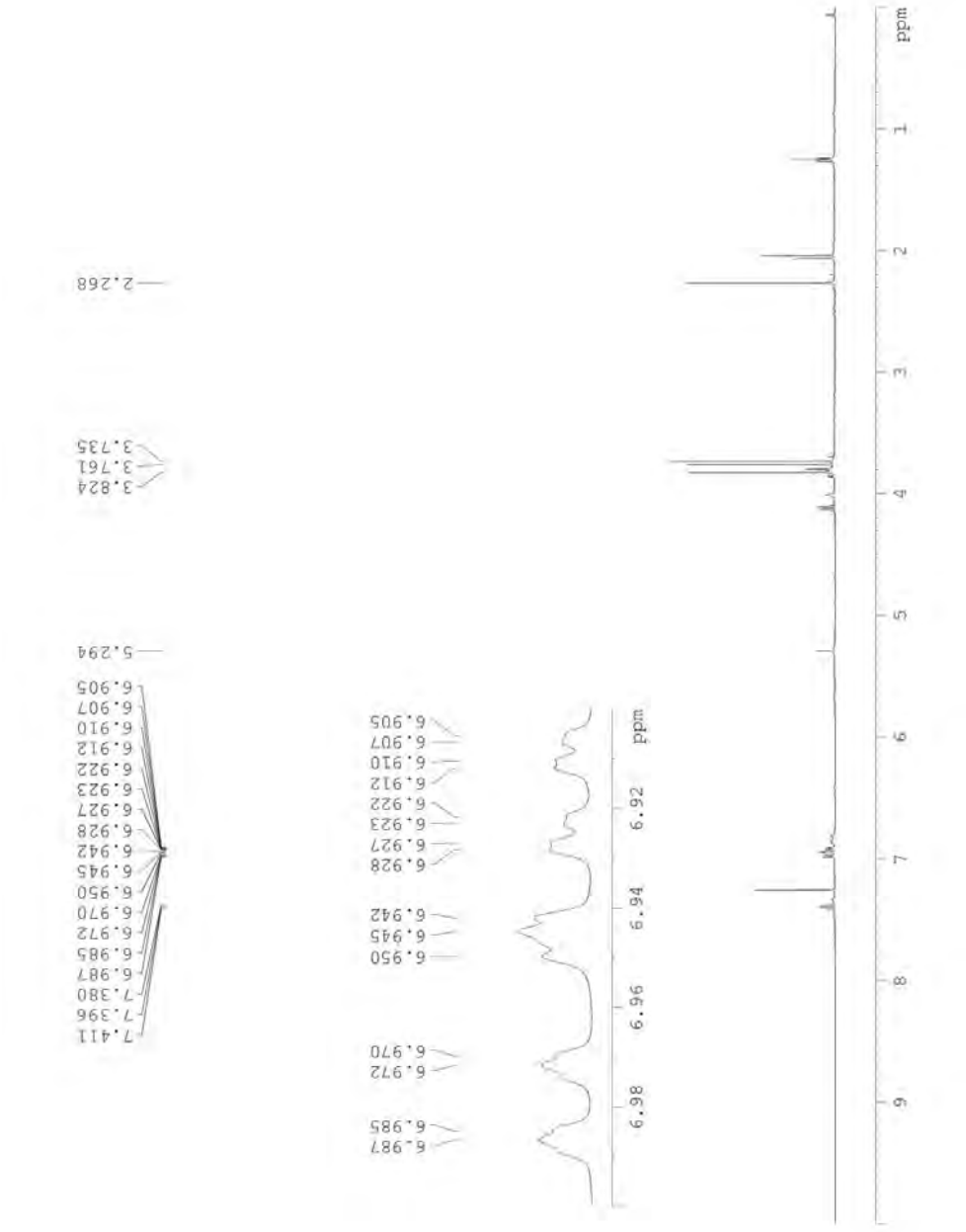
HRMS (DART^{+}) of 6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10)



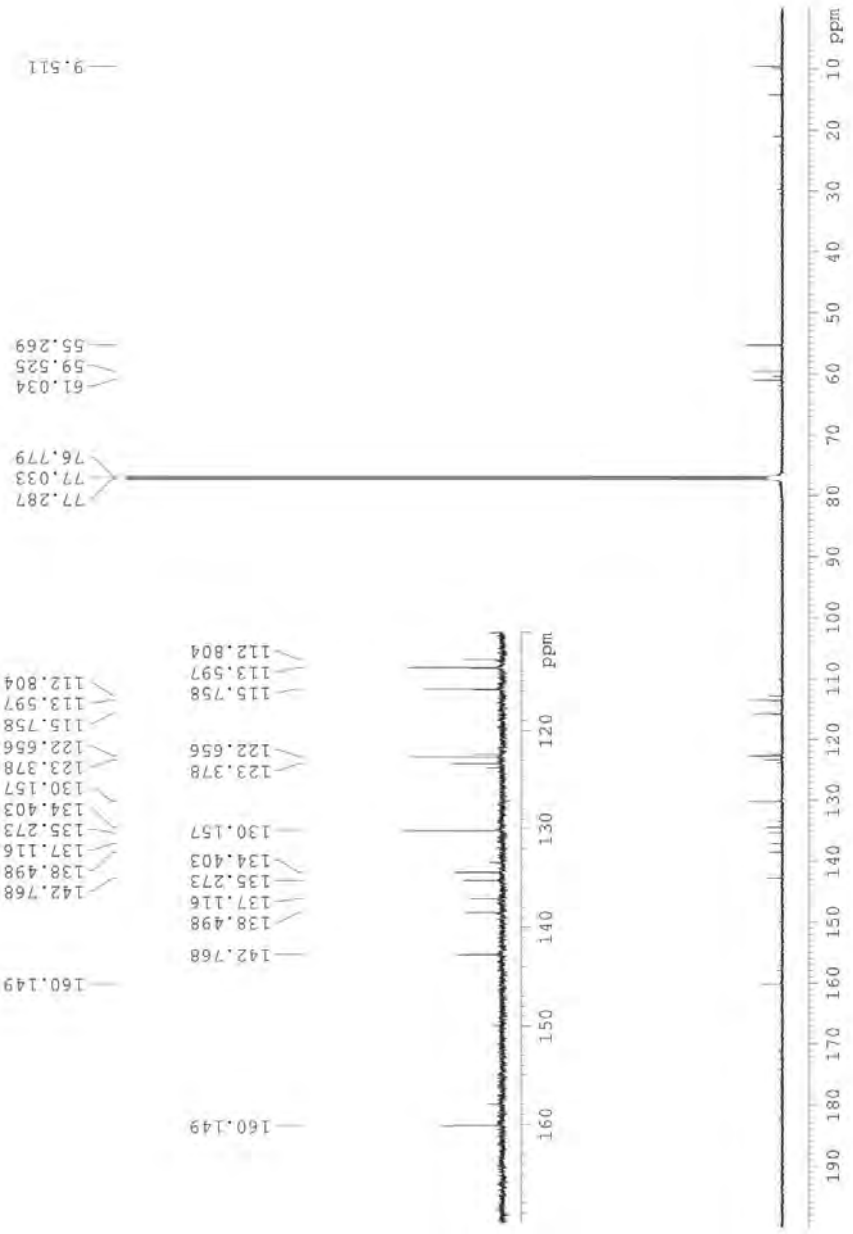
IR of 6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10)



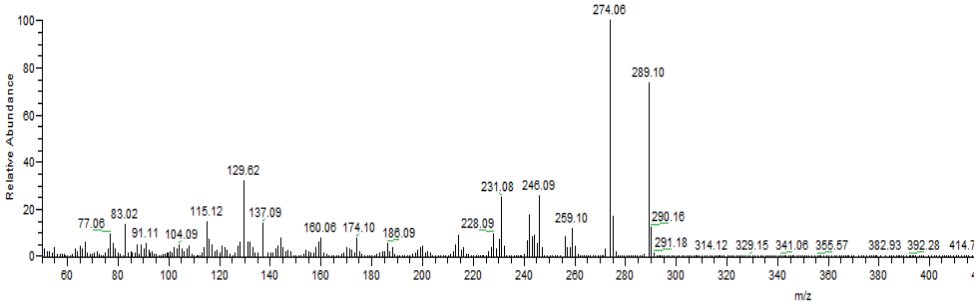
^{1}H-NMR of 6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10a) in $CDCl_3$



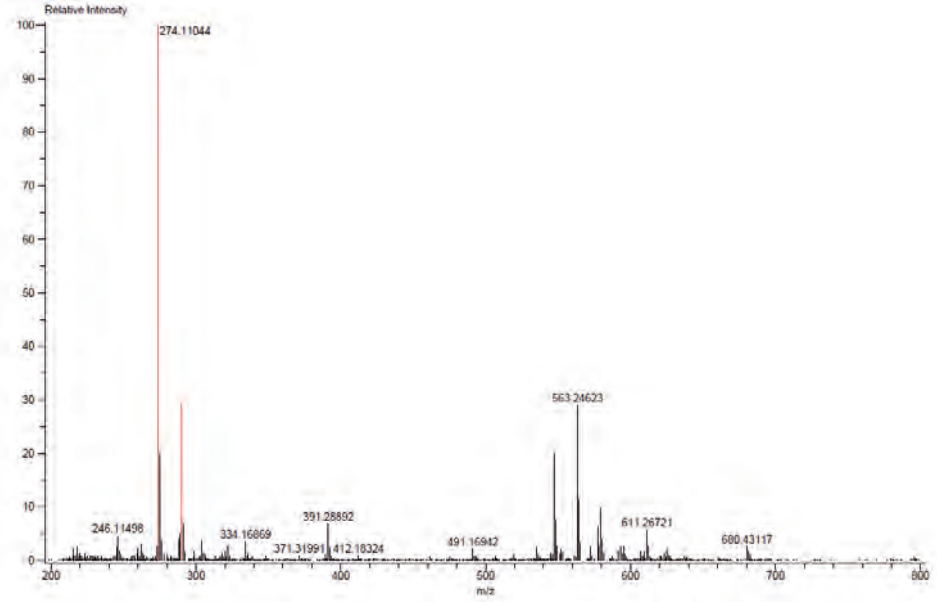
^{13}C-NMR of 6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10a) in $CDCl_3$



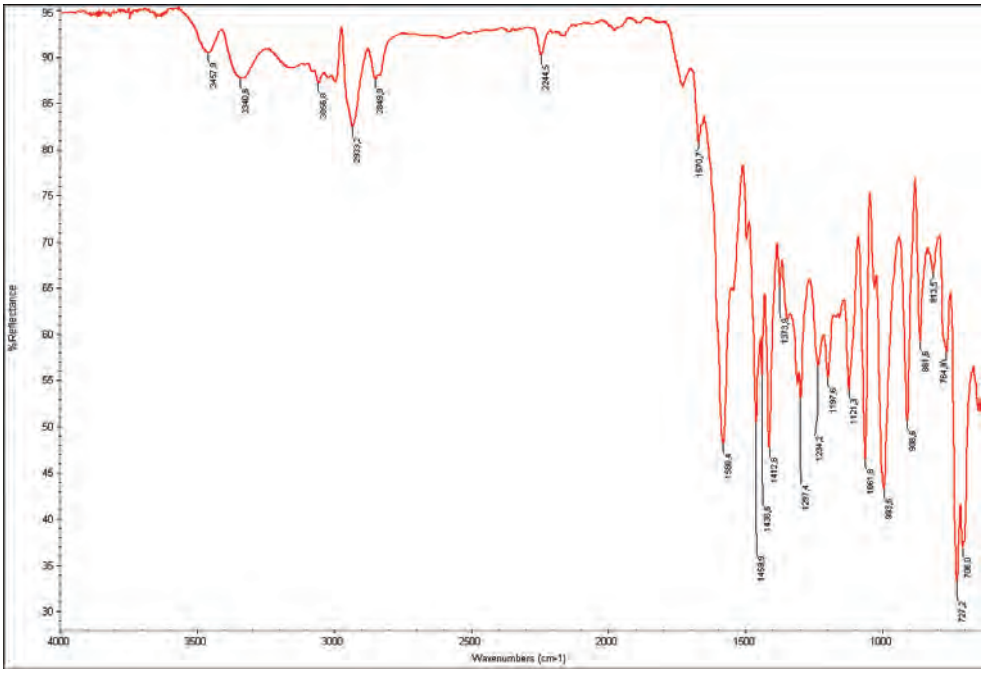
MS (EI) of 6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10a)



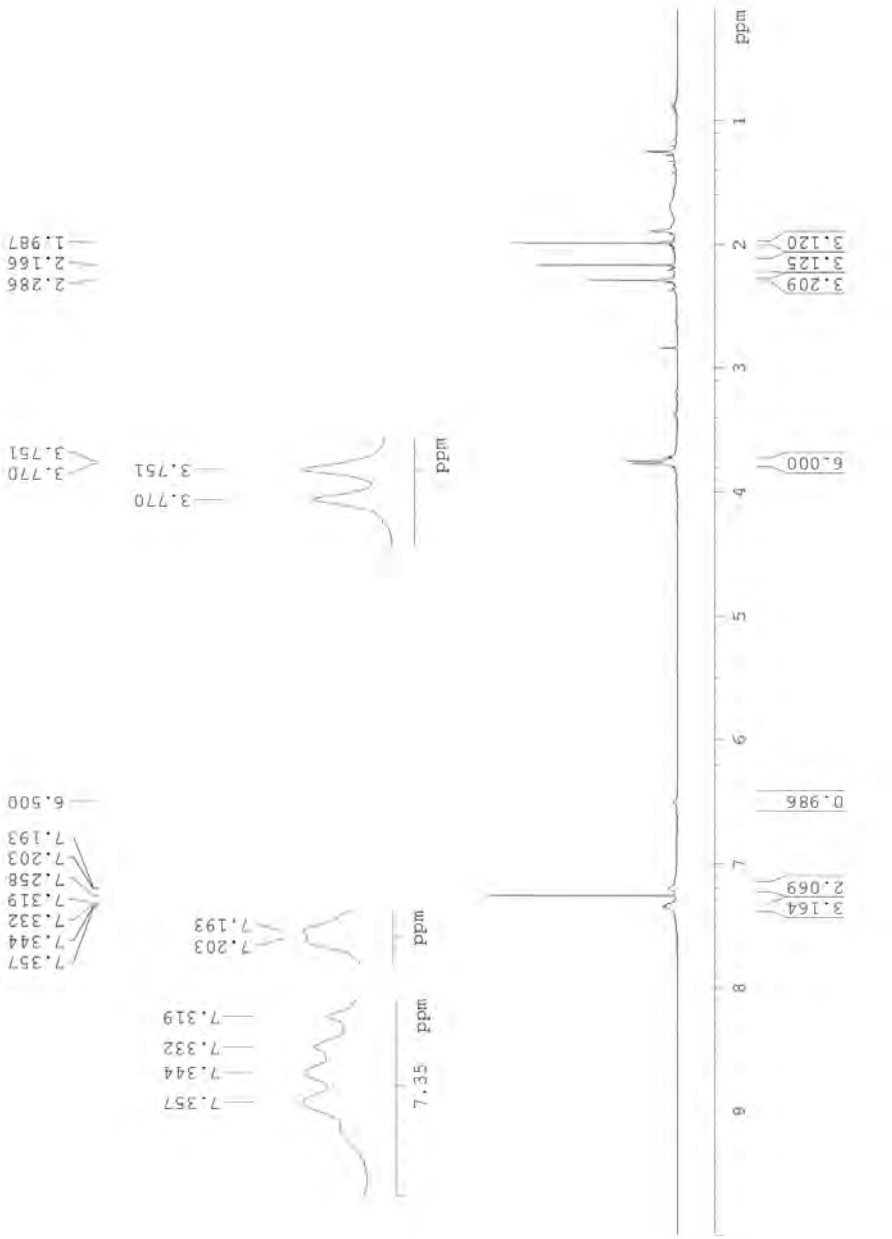
HRMS (EI) of 6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10a)



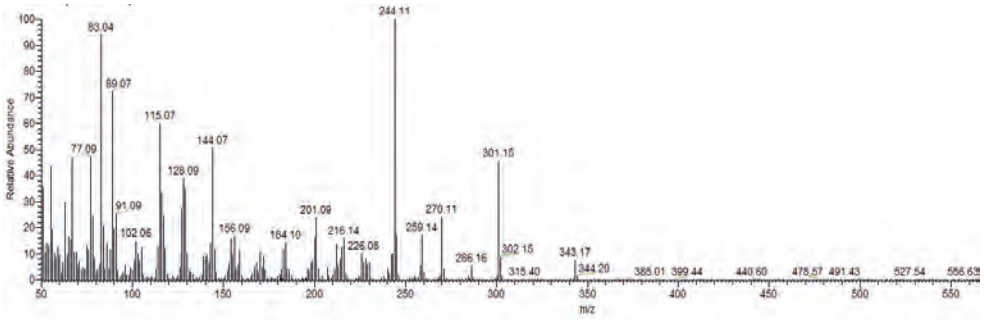
IR of 6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (6.10a)



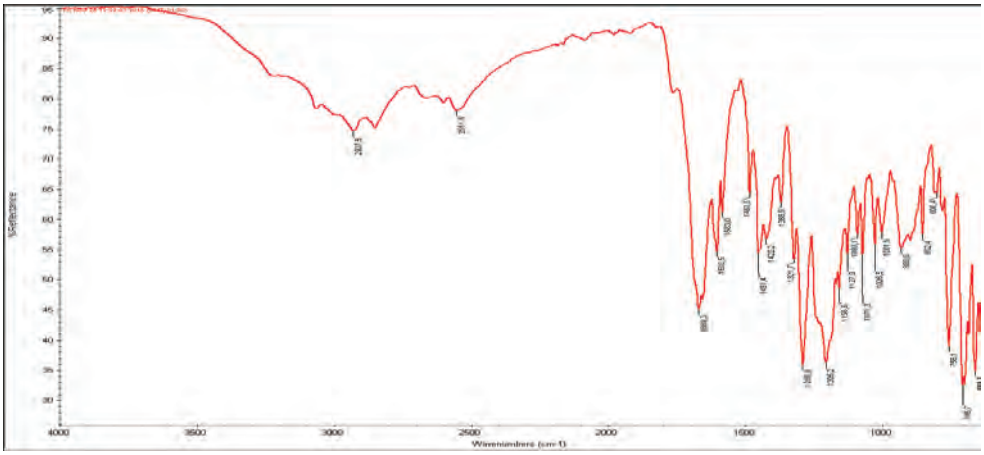
^{1}H-NMR of 6-acetamido-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate (6.11) in $CDCl_3$



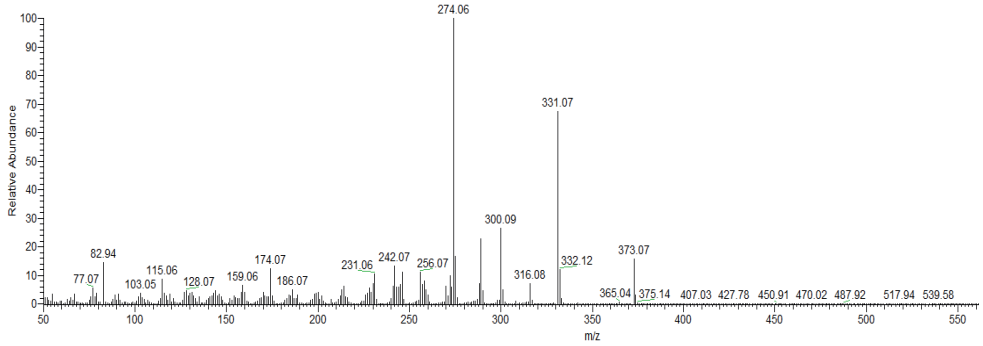
MS(EI) of 6-acetamido-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate (6.11)



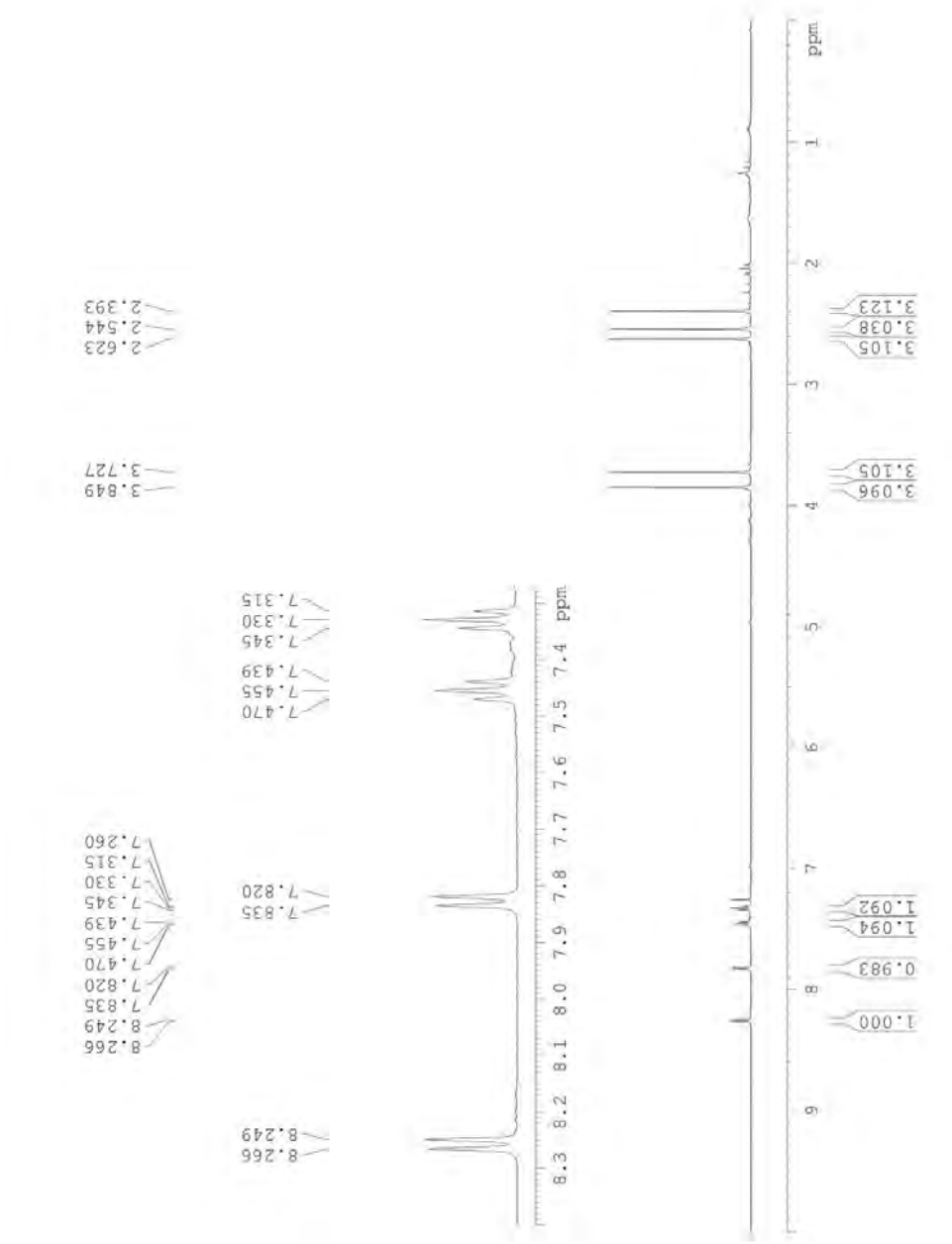
IR of 6-acetamido-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate (6.11)



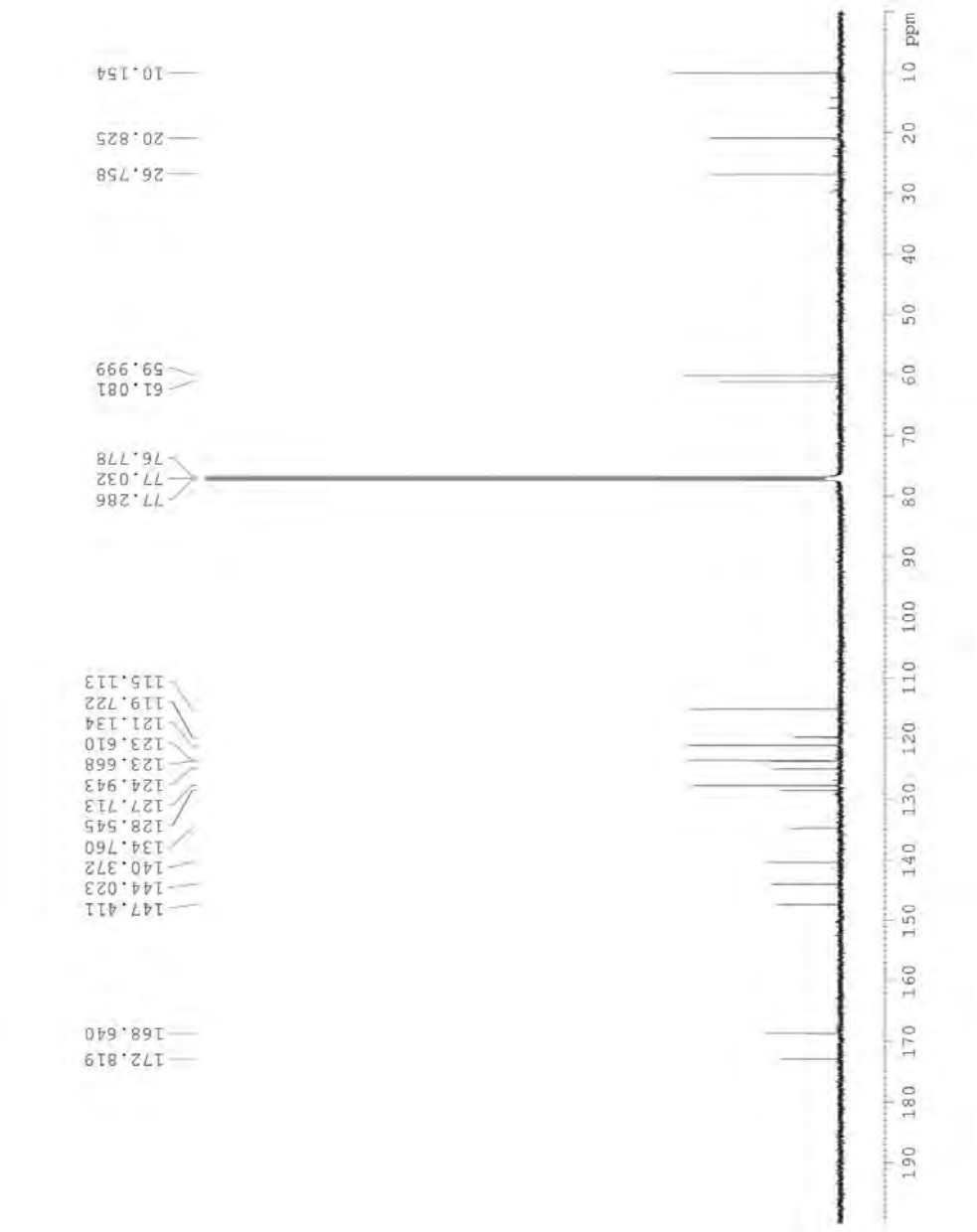
MS(EI) of 6-acetamido-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate (6.11a)



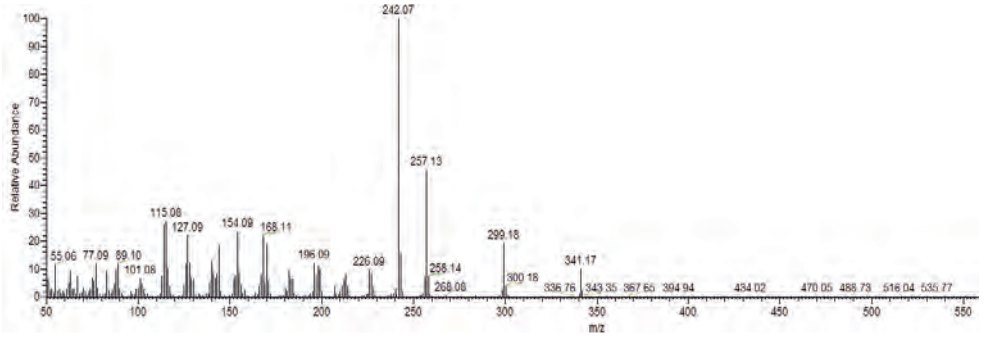
^{1}H-NMR of 9-acetyl-1,3-dimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12) in $CDCl_3$



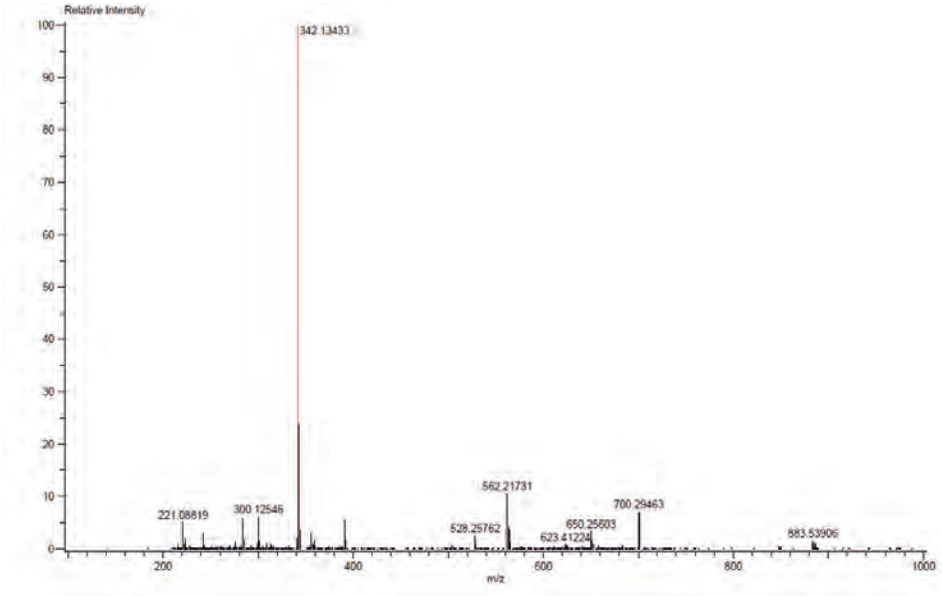
^{13}C-NMR of 9-acetyl-1,3-dimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12) in $CDCl_3$



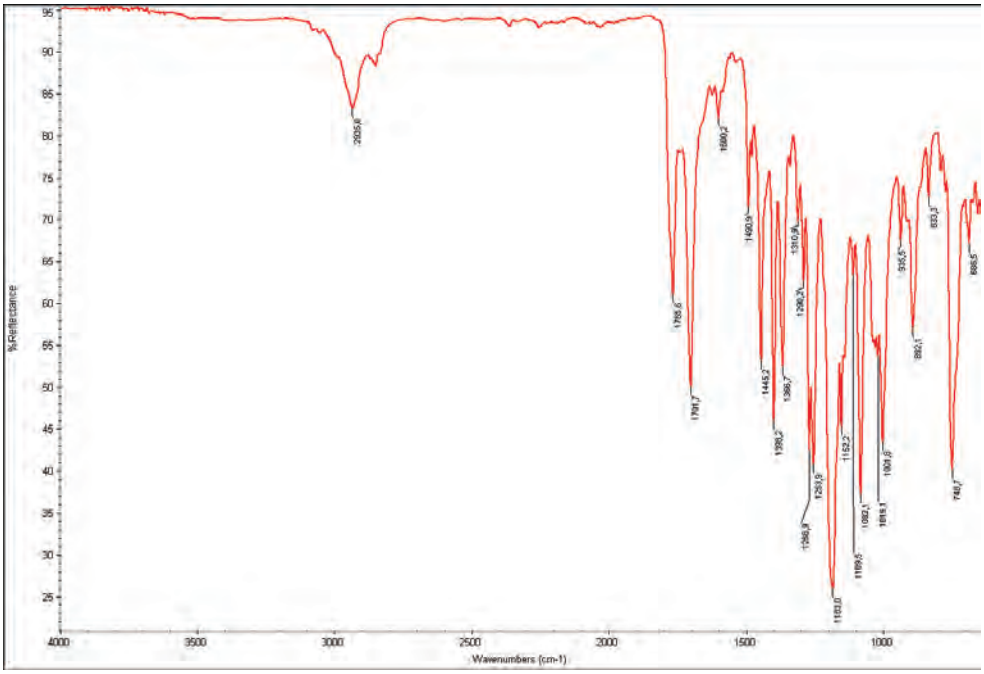
MS (EI) of 9-acetyl-1,3-dimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12)



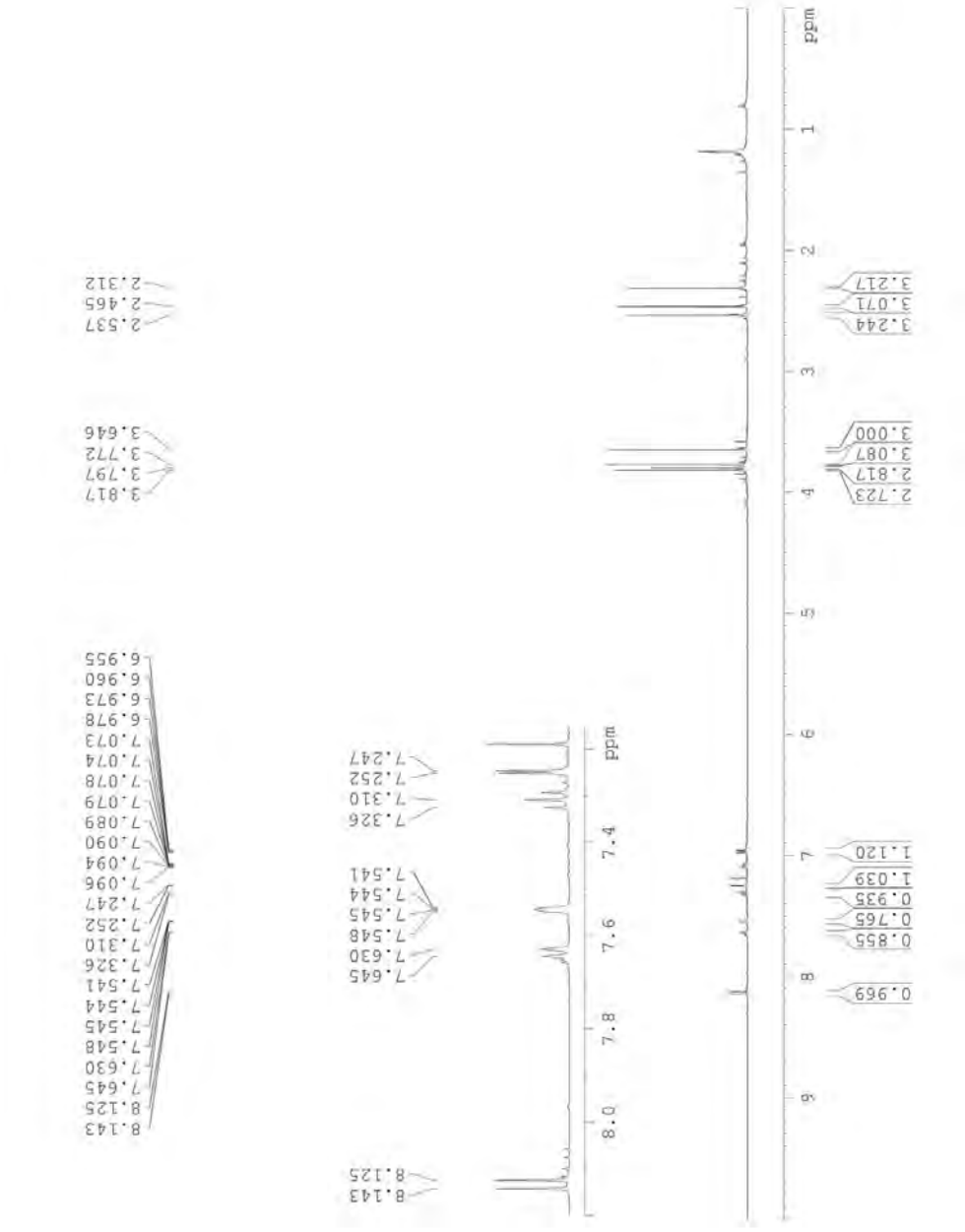
HRMS (EI) of 9-acetyl-1,3-dimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12)



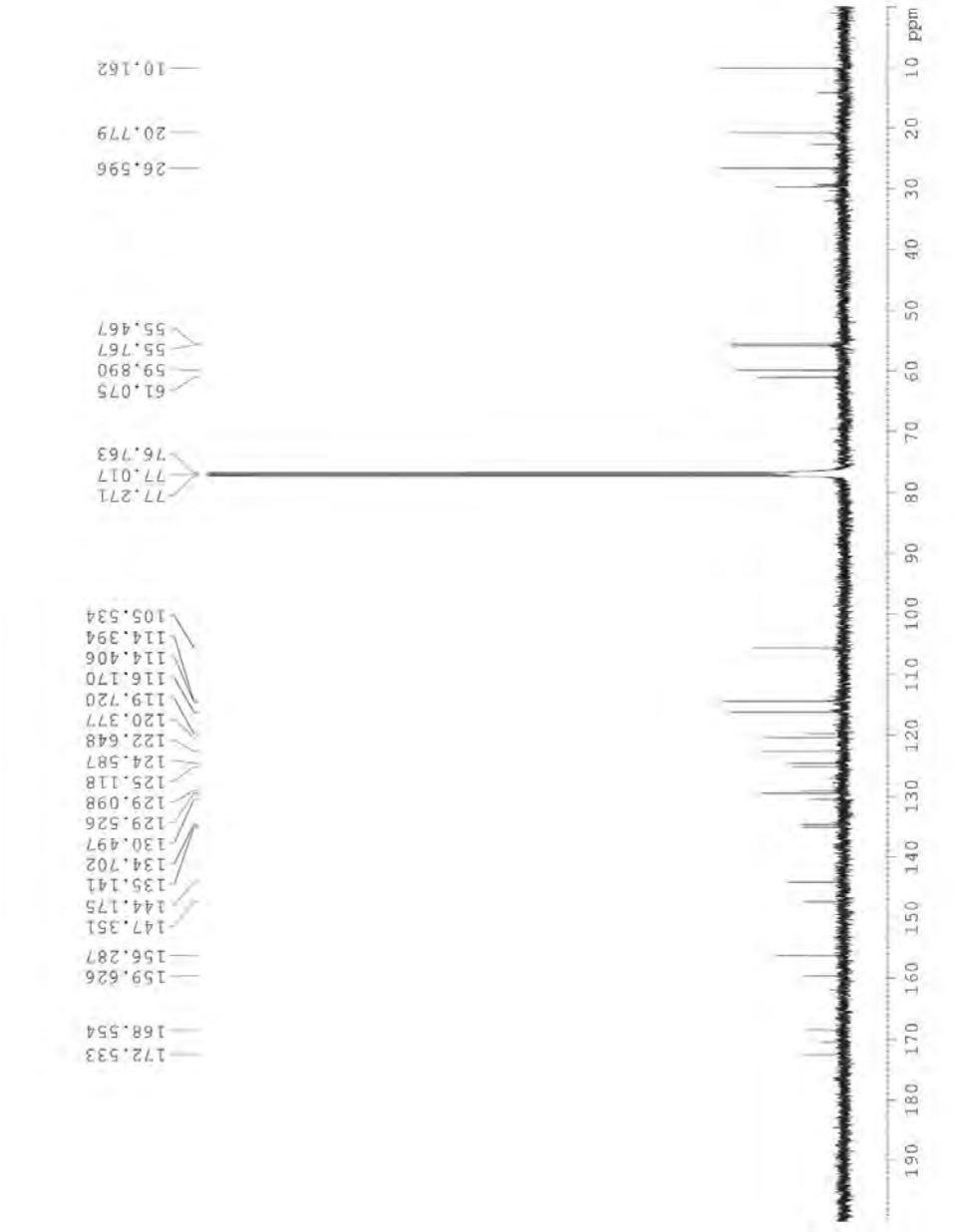
IR of 9-acetyl-1,3-dimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12)



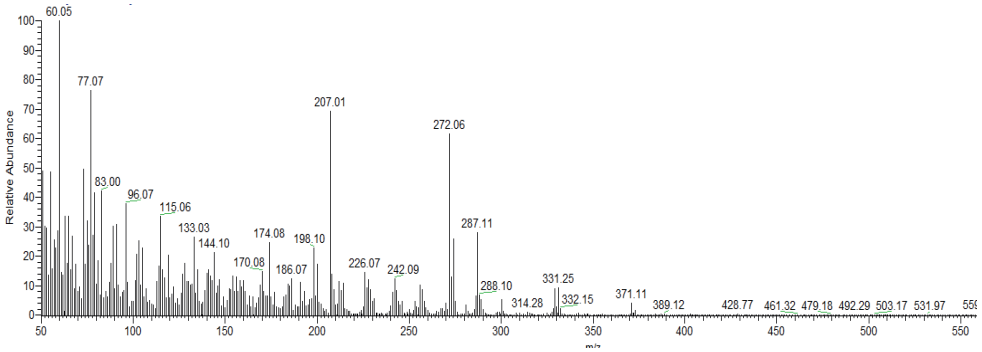
^{1}H-NMR of 9-acetyl-1,3,6-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12a) & 9-acetyl-1,3,8-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12b) in $CDCl_3$



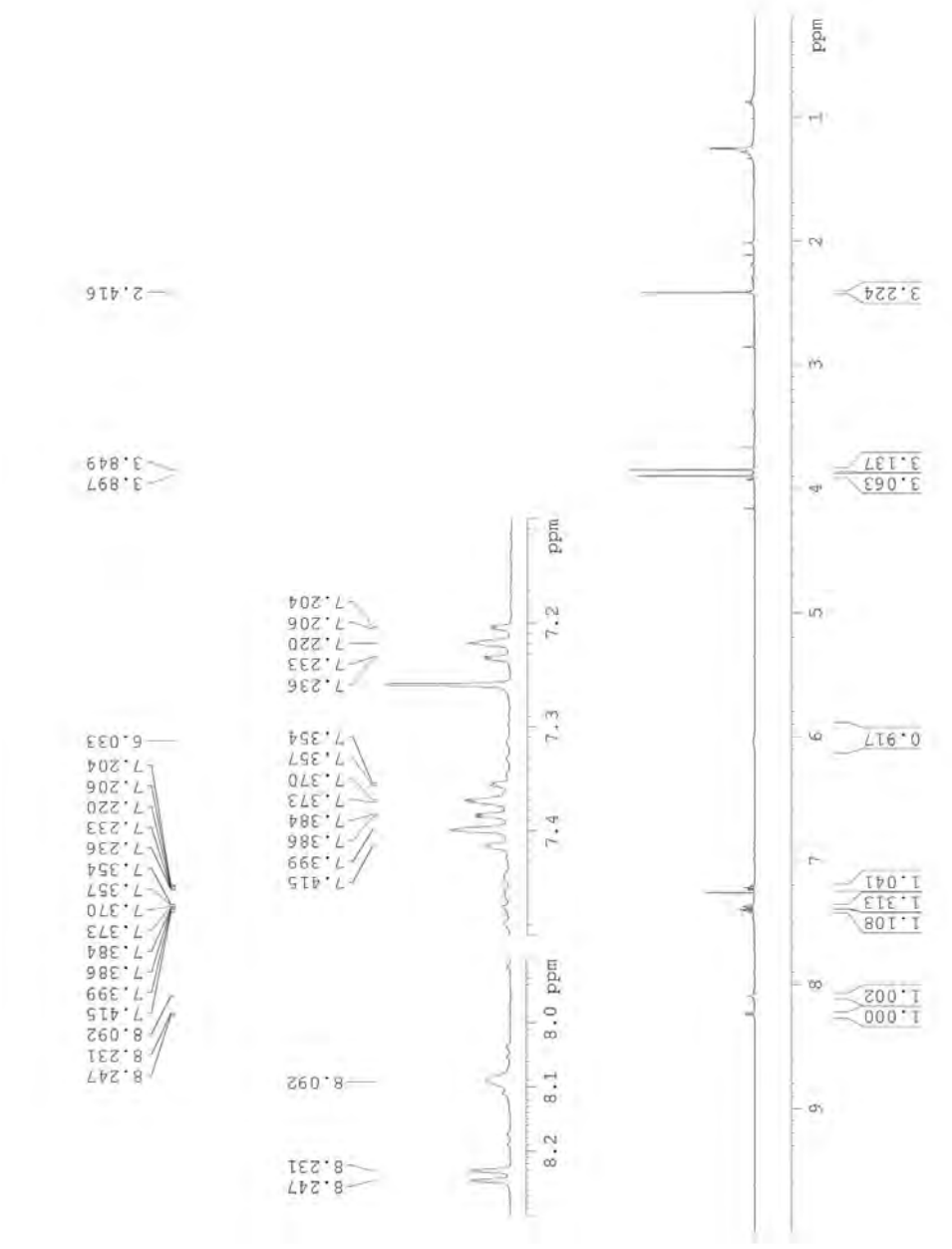
^{13}C-NMR of 9-acetyl-1,3,6-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12a) & 9-acetyl-1,3,8-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12b) in $CDCl_3$



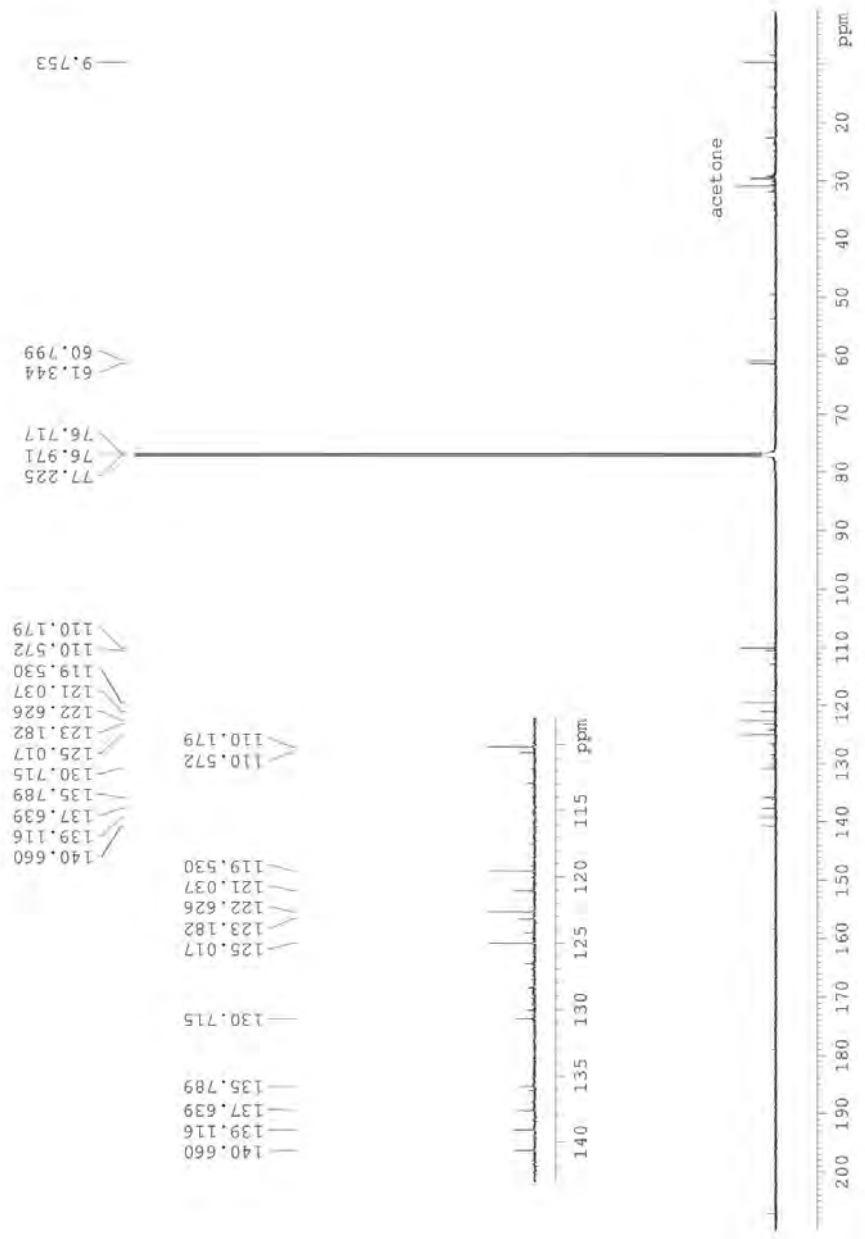
MS (EI) of 9-acetyl-1,3,6-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12a) & 9-acetyl-1,3,8-trimethoxy-2-methyl-9H-carbazol-4-yl acetate (6.12b)



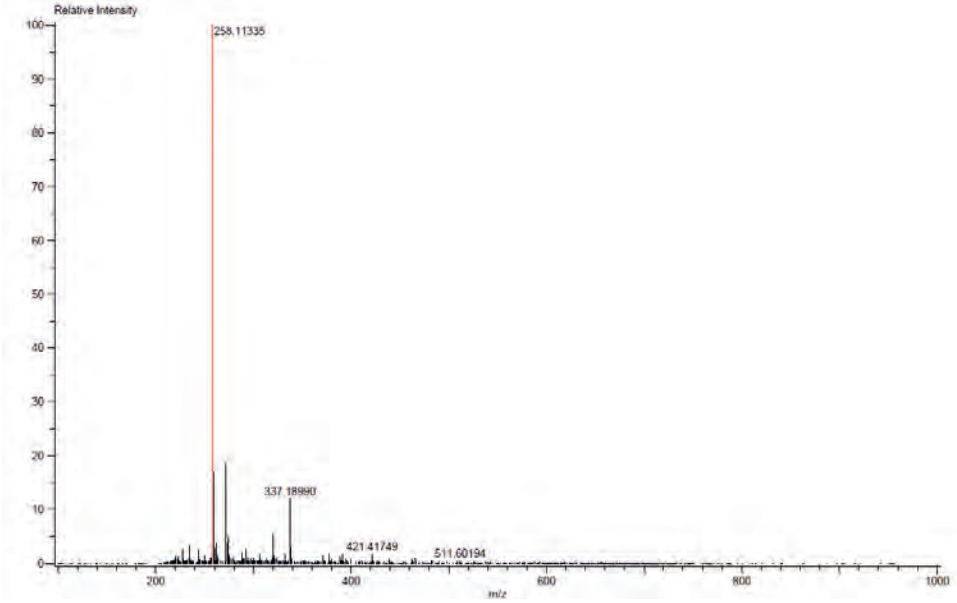
^{1}H-NMR of 1,3-dimethoxy-2-methyl-9H-carbazol-4-ol (6.13) in $CDCl_3$



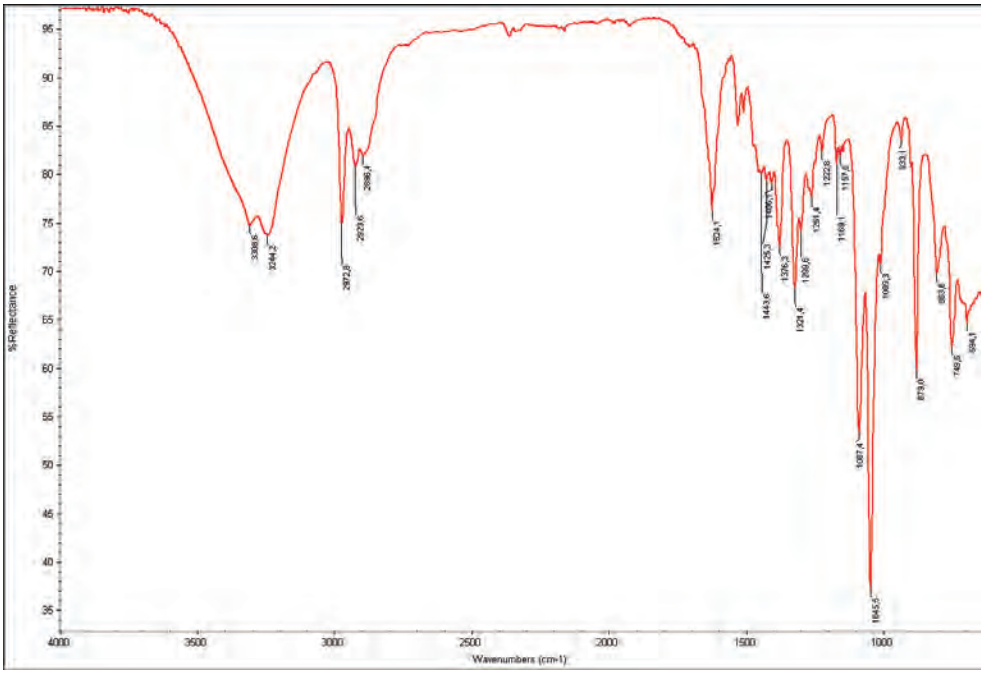
^{13}C-NMR of 1,3-dimethoxy-2-methyl-9H-carbazol-4-ol (6.13) in $CDCl_3$



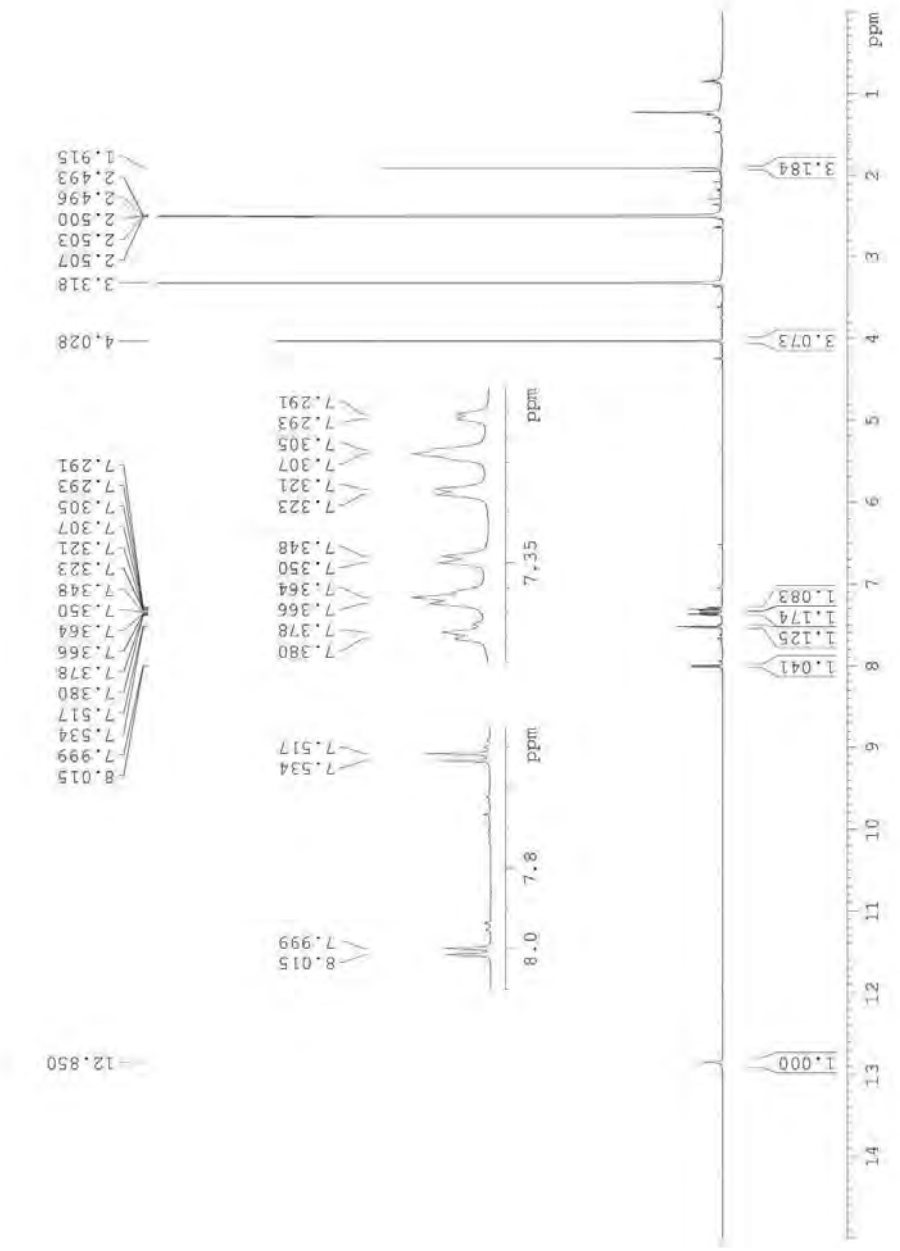
HRMS (DART+) of 1,3-dimethoxy-2-methyl-9H-carbazol-4-ol (6.13)



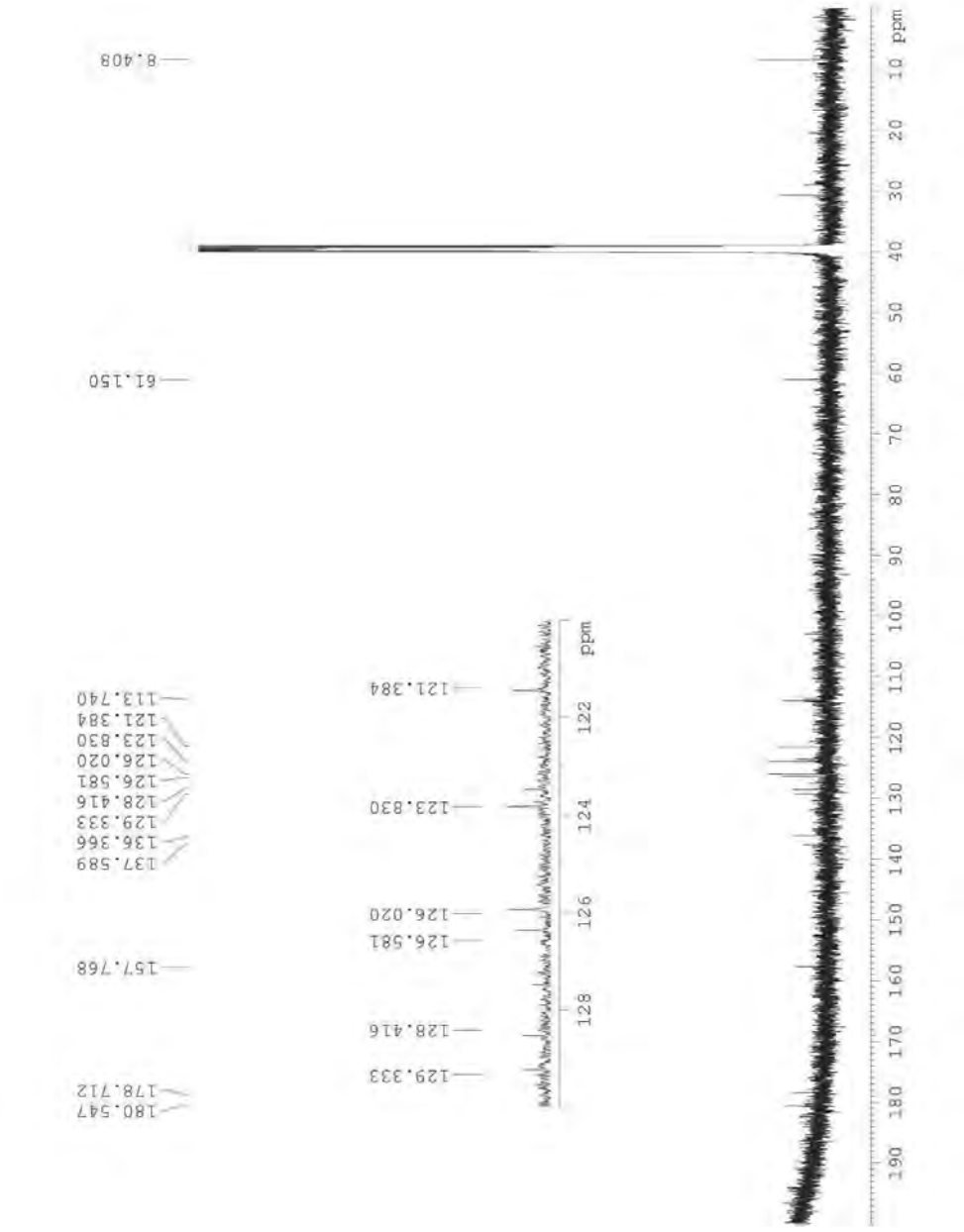
IR of 1,3-dimethoxy-2-methyl-9H-carbazol-4-ol (6.13)



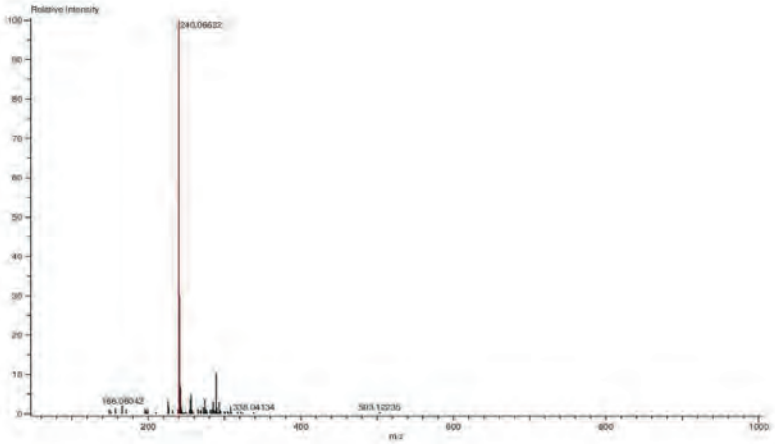
^{1}H-NMR of 3-methoxy-2-methyl-1H-carbazole-1,4(9H)-dione (6.14) in DMSO-d_6



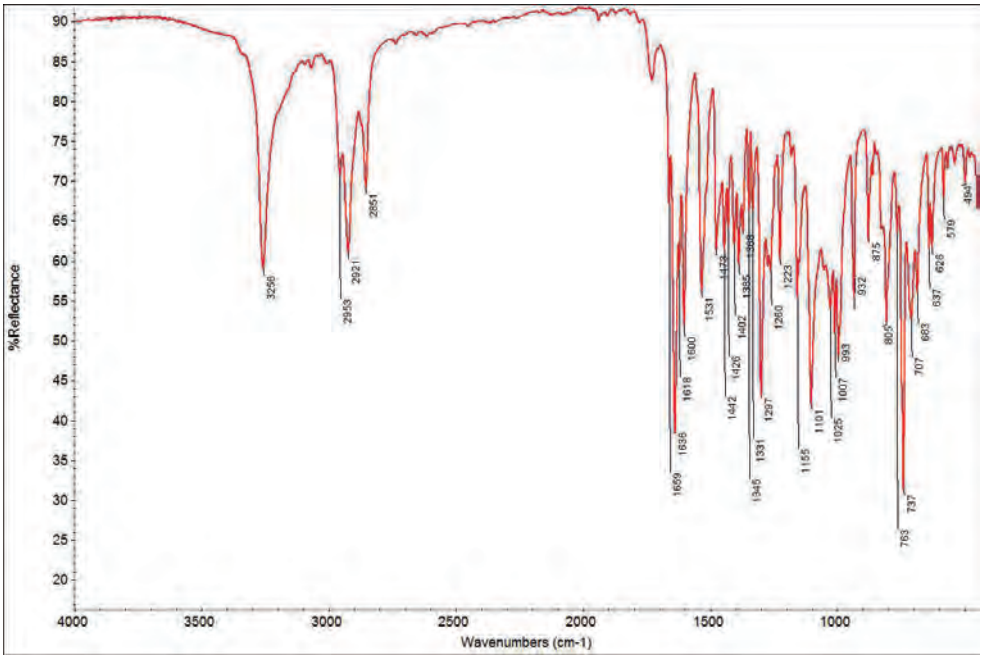
^{13}C-NMR of 3-methoxy-2-methyl-1H-carbazole-1,4(9H)-dione (6.14) in DMSO-d_6



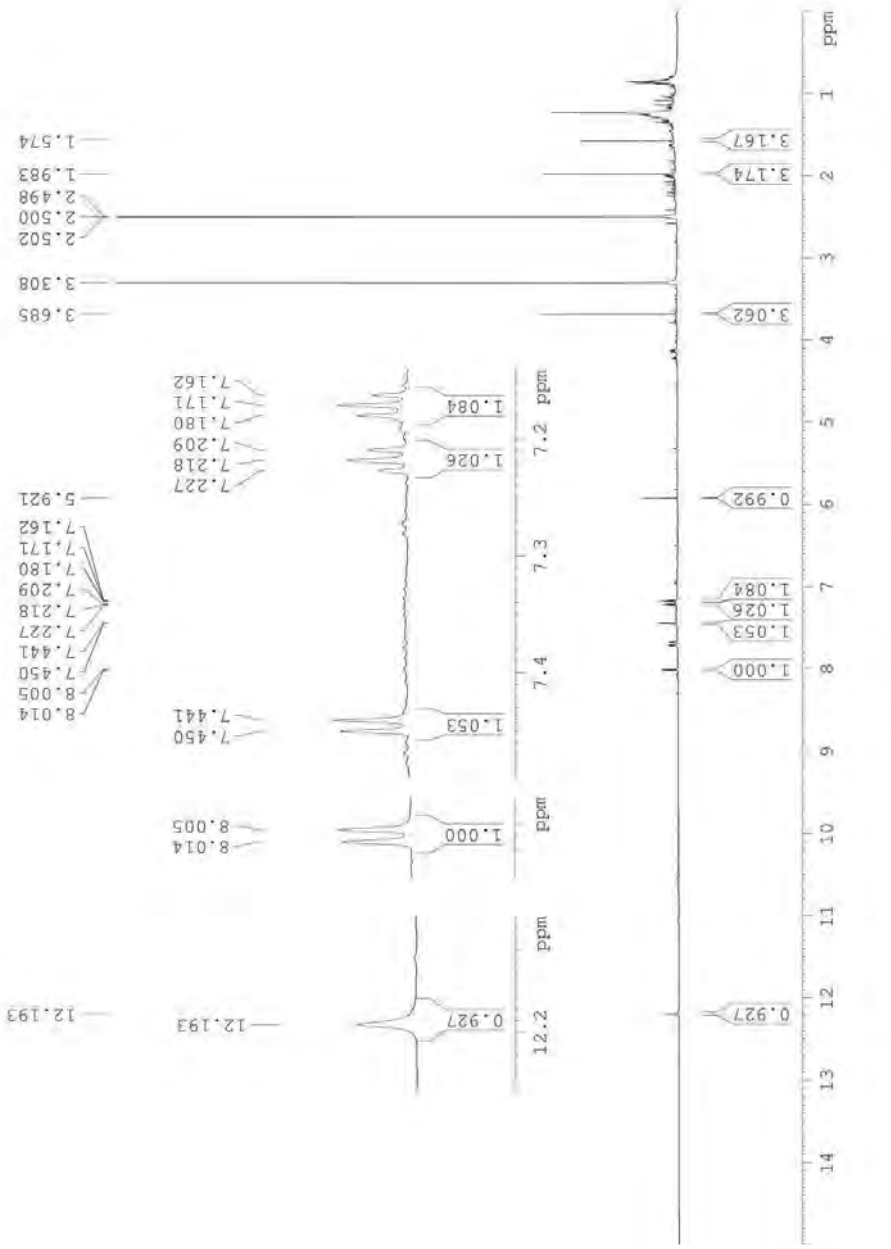
HRMS (ESI-) of 3-methoxy-2-methyl-1H-carbazole-1,4(9H)-dione (6.14)



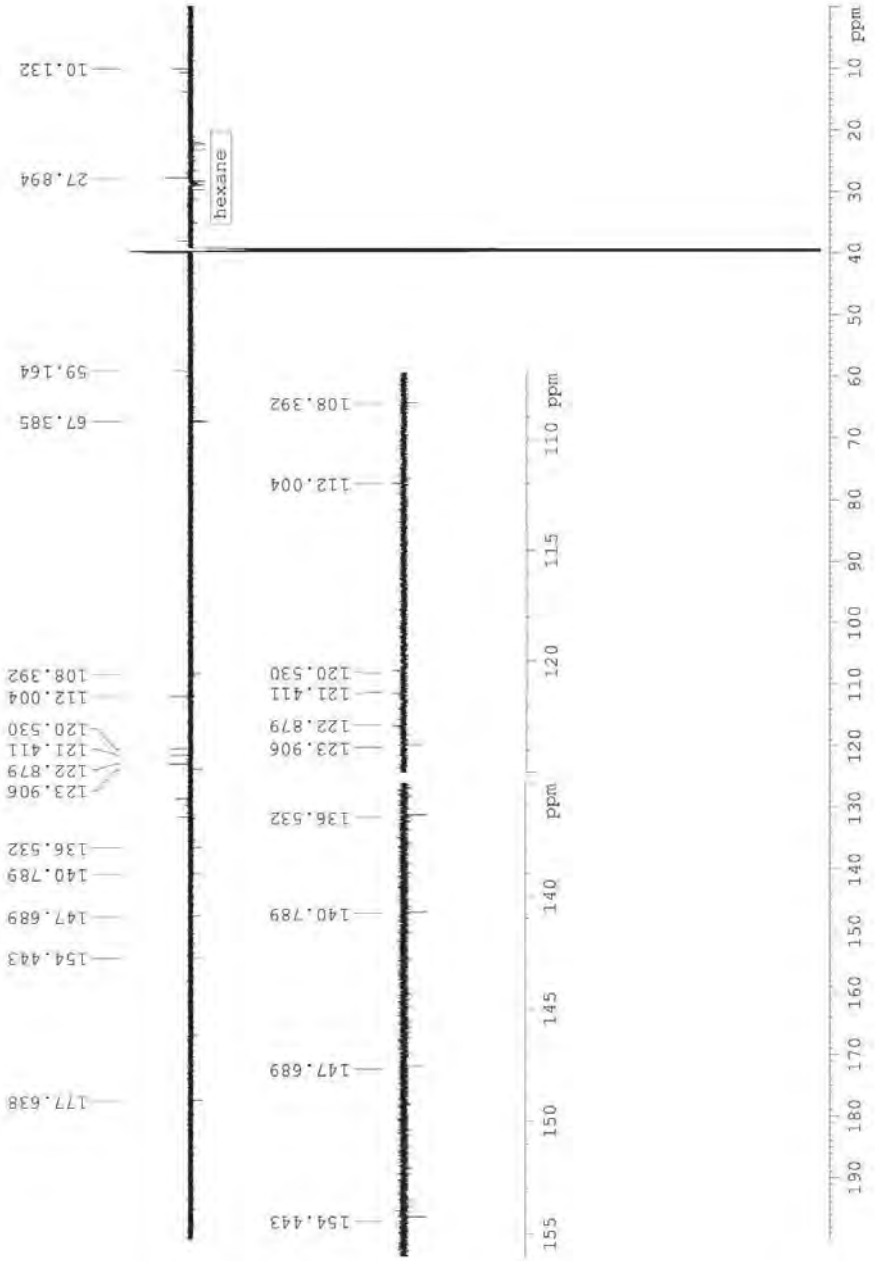
IR of 3-methoxy-2-methyl-1H-carbazole-1,4(9H)-dione (6.14)



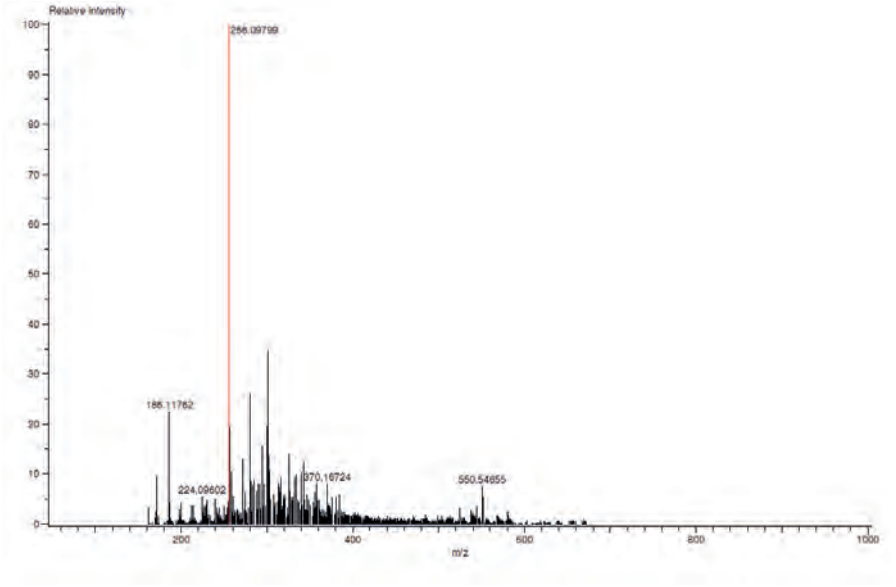
^{1}H-NMR of 1-hydroxy-3-methoxy-1,2-dimethyl-1,9-dihydro-4H-carbazol-4-one (6.15) in DMSO-d_6 (Carbazomycin G)



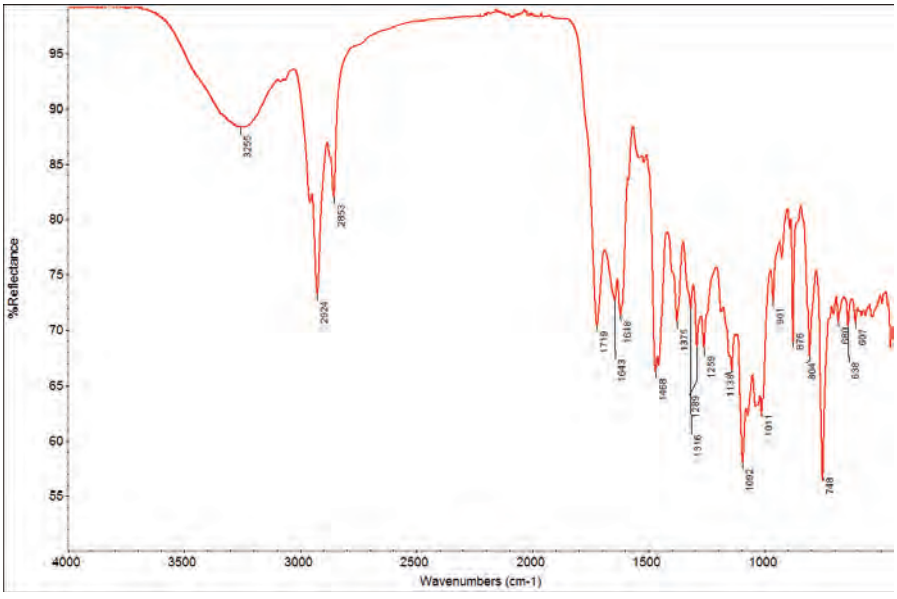
^{13}C-NMR (DEPT) of 1-hydroxy-3-methoxy-1,2-dimethyl-1,9-dihydro-4H-carbazol-4-one (6.15) (Carbazomycin G)



HRMS (ESI-) of 1-hydroxy-3-methoxy-1,2-dimethyl-1,9-dihydro-4H-carbazol-4-one (6.15) (Carbazomycin G)



IR of 1-hydroxy-3-methoxy-1,2-dimethyl-1,9-dihydro-4H-carbazol-4-one (6.15) (Carbazomycin G)



Supporting Information for Chapter 8

A novel synthesis of Boscalid®

Experimental Section

General methods: All chemicals were used as received. GC analysis were performed on a capillary gas chromatograph equipped with a fused silica column (L 25 m, 0.20 mm i.d.,0.33mm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained on a GC-MS instrument, using a gas chromatograph equipped with fused silica column (l30 m, 0.25 mm i.d., 0.25mm film thickness) and helium as carrier gas. DART-mass spectra were obtained using PEG as an internal standard in the positive ionization mode with a TOF mass analyzer. ^{1}H-NMR and ^{13}C-NMR were recorded at ambient temperature at a frequency of 500 and 125 MHz, respectively. The Chemical shifts were reported in ppm relative to residual $CHCl_3$ for proton (δ = 7.26) and $CDCl_3$ for carbon (δ = 77.0) and residual DMSO-d_6 for proton (δ = 2.50) and for carbon (δ = 39.51) using TMS as an external reference. Flash chromatography was perrmed by means of the hexane (mixture of isomers) and ethyl acetate solvent system using silica gel (230-400 mesh).
The microwave-assisted experiments were performed by means of Biotage Initiator Sixty EXP Microwave System, that operates at 0–400 W at 2.45 GHz, in the temperature range of 40–250 °C, a pressure range of 0–20 bar (2 MPa, 290 psi), and with reactor vial volumes of 0.2–20 mL.

4'-chloro-2-nitro-1,1'-biphenyl (8.3) [6271-80-3]

To a microwave vial, 1-Chloro-2-nitrobenzene **(8.1)** (0.25 g, 1.58 mmol), 4-chlorophenylboronic acid **(8.2)** (0.373 g, 2.39 mmol), Na_2CO_3 (0.184 g, 1.75 mmol), TBAB (0.041 g, 0.13 mmol), and $Pd(PPh_3)_4$ (0.047 g, 0.042 mmol) were added. The vial was sealed and argon was flushed through the septa and then a mixture of EtOH (4 mL) and water (1 mL) were added. After stirring for 10s, the vial was submerged in the microwave cavity for 30 min at 120 ºC. After the reaction time, the solvent methanol was removed under reduced pressure. The reaction mixture was diluted in diethyl ether (50 mL) and washed with water (50 mL). The aqueous phase was extracted with diethyl ether (2 × 50 mL) and the organic phases were combined and dried over Na_2SO_4. The drying agent was filtered off and the crude product was purified by flash column chromatography using [EtOAc:Hx, 10:90] to afford the title compound as a pale-yellow solid (0.315 g, 85 %). R_f = 0.55 (EtOAc/hexane, 10:90). ^{1}H -NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.79–7.82 (dd, J =1.0, 8.0 Hz, 1 H), 7.54–7.57 (td, J = 1.5, 8.0 Hz, 1 H), 7.41–7.45 (td, J =1.5, 8 Hz, 1 H), 7.32–7.34 (m, 3 H), 7.17–7.18 (m, 2 H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 149.1, 135.9, 135.2, 134.5, 132.5, 131.9, 129.3,128.9, 128.6, 124.3; HR-MS (EI): $(M)^+$: Calcd for $C_{12}H_8{}^{35}ClNO_2{}^+$ 233.02381; Found 233.02417); Calcd for $C_{12}H_{18}{}^{37}ClNO_2$ 235.02086; Found 235.02146); MS (EI): *m/z* (%) = 232.8 (22, M+), 198.0 (24), 170.0 (29), 168.0 (30), 153.0 (16), 152.0 (100), 151.0 (52), 142.0 (41), 139.0 (39), 126.0 (29), 115 (52), 87 (18),76 (55), 75 (53), 74 (30), 63 (38), 62 (16).

4'-chloro-[1, 1'-biphenyl]-2-amine (8.4) [1204-44-0]

4'-chloro-2-nitro-1, 1'-biphenyl **(8.3)** (119 mg, 0.51 mmol) was dissolved in ethanol (5 mL). To the stirred solution, $CoSO_4.7H_2O$ (143 mg, 0.51 mmol) dissolved in water (0.7 mL) was added. The reaction mixture was cooled to 0ºC. After cooling at 0ºC, $NaBH_4$ (77 mg, 2.04 mmol) was dissolved in ethanol (1.5 ml) was added slowly and instantly observed a black granular precipitate (Co_2B) and copious quantities of hydrogen. The reaction mixture was

stirred at ambient temperature for 10 min. After the reaction time, the reaction mixture was filtered using Buchner funnel to remove the precipitate. The filtered solution was diluted with EtOAc (50 mL) and washed with water (50 mL). The aqueous layer was then extracted with EtOAc (2×50 mL). The organic layers were combined and dried over Na_2SO_4. The drying agent was filtered off and the solvent was evaporated under reduced pressure to obtain the title compound as a brown solid (0.099 g, 95%). R_f = 0.63 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm)= 7.41-7.42 (m, 4H), 7.16-7.19 (td, *J*= 1.5 Hz, 8 Hz, 1H), 7.09-7.11 (dd, *J*= 1.5 Hz, 7.5 Hz, 1H), 6.82-6.85 (td, *J*= 1 Hz, 7.5 Hz, 1H), 6.76-6.78 (dd, *J*= 1 Hz, 8 Hz, 1H), 3.73 (s, br, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 143.4, 138.0, 133.1, 130.5, 130.3, 129.0, 128.8, 126.3, 118.8, 115.7; HR-MS (DART+): $(M+H)^+$: Calcd for $C_{12}H_{11}{}^{35}ClN^+$ 204.05745; Found 204.05764); Calcd for $C_{12}H_{11}{}^{37}ClN$ 206.05450; Found 206.05148); MS (EI): *m/z* (%) = 205. (29), 204 (16), 203 (95, M+), 168 (56), 167 (100), 141 (10), 140 (12), 139 (20), 115 (12), 89 (7), 84 (12), 83.4 (19), 70.5 (12).

2-chloronicotinoyl chloride (8.6) [49609-84-9]

To the stirred solution of 2-chloronicotinic acid **(8.5)** (0.30 g, 1.59 mmol) in diethyl ether (10 mL), Pyridine (0.16 ml, 3.18 mmol) and thionyl chloride (0.24 ml, 3.18 mmol) were added slowly under N_2 atmosphere at 0^{o}C . After the addition, the reaction mixture was stirred at ambient temperature for 60 minutes. After the reaction time, water (20 ml) was added and extracted with diethyl ether (2 ×50 mL). The organic layers were combined and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure to afford the title compound as a white powder (0.270 g, 96%). ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm)= 8.55-8.56 (dd, *J*= 2 Hz, 5 Hz, 1H), 8.22-8.24 (dd, *J*= 2 Hz, 7.5 Hz, 1H), 7.53-7.55 (m, 1H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm)= 165.7, 151.7, 147.7, 140.0, 128.1, 123.1.

2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) (Boscalid) [188425-85-6]

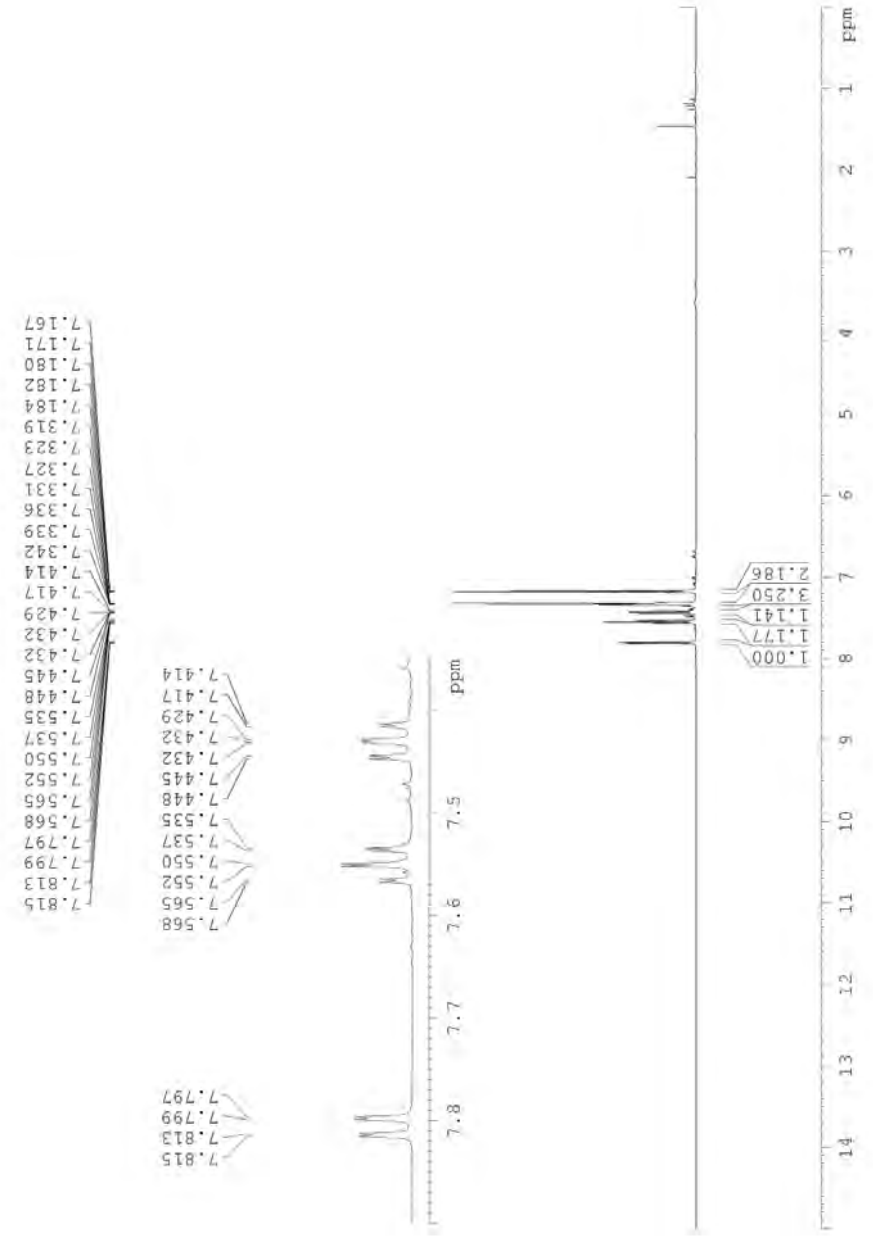
Method 1: Amide coupling using amine (8.4) and acid chloride (8.6)

To the stirred solution of 2-amino-4'-chlorobiphenyl **(8.4)** (0.050 g, 0.246 mmol) in CH_2Cl_2 (10 mL), triethylamine (0.068 mL, 0.492 mmol) and 2-chloronicotinoyl chloride **(8.6)** (0.043 g, 0.246 mmol) were added slowly at 0^{o}C under inert atmosphere. After the addition, the reaction mixture was stirred at room temperature for 10 minutes. After the reaction time, the reaction mixture was quenched with water (40 ml) and extracted with CH_2Cl_2 (2 × 40 mL). The organic extracts were combined and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed using rotary evaporator. The crude product was purified by using flash chromatography using [EtOAc:Hx, 15:85] eluent to afford title compound as a white solid (0.070 g, 83%). R_f = 0.13 [(EtOAc:Hx, 15:85)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm)= 8.38-8.39 (dd, *J*= 2Hz, 5 Hz, 1H), 8.34-8.36 (d, *J*= 8 Hz, 1H), 8.07-8.09 (m, 2H), 7.36-7.38 (m, 2H), 7.26-7.30 (m, 3H), 7.19-7.20 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm)= 162.5, 151.4, 146.7, 140.2, 136.3, 134.5, 134.4, 132.2, 131.1, 130.8, 130.2, 129.3, 128.9, 125.3, 122.9, 122.1; HR-MS (DART+): $(M+H)^+$: Calcd for $C_{18}H_{13}Cl_2N_2O^+$ 343.03994; Found 343.03789); Calcd for $C_{18}H_{13}{}^{35}Cl^{37}ClN_2O^+$ 345.03699; Found 345.03581); Calcd for $C_{18}H_{13}{}^{37}Cl_2N_2O^+$ 347.03404; Found 347.03422); MS (EI): m/z (%)= 341.9 (3, M+), 204.0 (3), 167.0 (11), 166.0 (10), 142.0 (30), 141.0 (8), 140.0 (100), 139.0 (12), 138.0 (3), 114.0 (31), 111.9 (44), 76.0 (12).

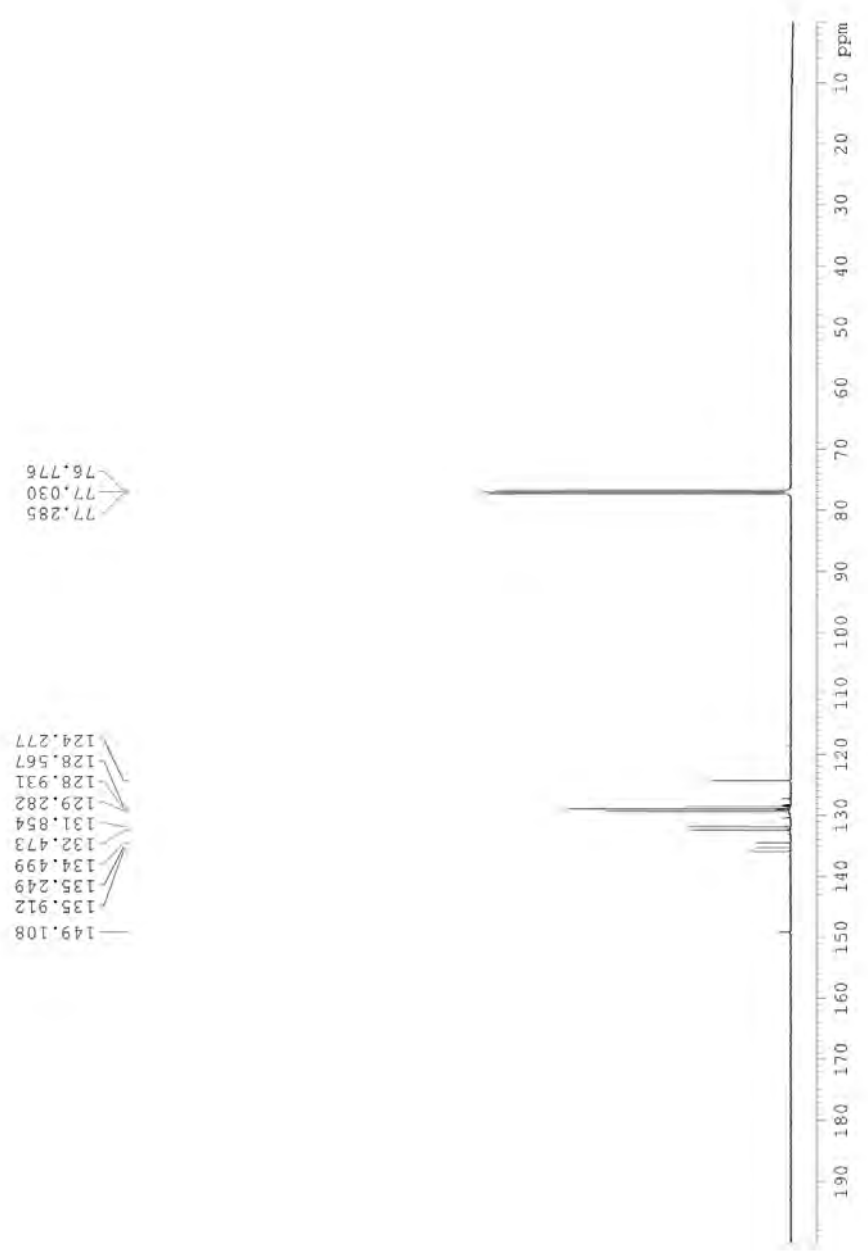
Method 2: Amide coupling using amine (8.4) and acid (8.5) via sulfiniylaniline (8.7)

To the stirred mixture of 2-chloronicotinic acid **(8.5)** (0.050 g, 0.317 mmol) in CH_2Cl_2 (10 mL), thionyl chloride (0.047 mL, 0.630 mmol) and pyridine (0.077 ml, 0.951 mmol) were added slowly to the reaction mixture at 0°C under inert atmosphere, followed by the solution of 4'-chloro-[1, 1'-biphenyl]-2-amine **(8.4)** (0.064 g, 0.317 mmol) in CH_2Cl_2 (5 mL) was added to the reaction mixture. The reaction mixture was stirred for 10 min at room temperature and monitored by using GC-MS, observed a quantitative conversion yield of sulfiniylaniline intermediate **(6a)** after 10 min. Then prolonged a reaction to 60 minutes at room temperature afforded a title compound in quantitative yield based on GC-MS. After the reaction time, the reaction mixture was quenched with water (40 ml) and extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure to afford the title compound as a pale-white solid (0.105 g, 97%). R_f = 0.30 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 10.15 (s, 1H), 8.47-8.48 (dd, *J*= 2 Hz, 4.5 Hz, 1H), 7.86-7.88 (dd, *J*= 1.5 Hz, 7.5 Hz, 1H), 7.59 (d, *J*= 8 Hz, 1H), 7.50-7.52 (m, 3H), 7.45-7.48 (m, 3H), 7.39-7.40 (m, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ= 164.2, 150.3, 146.5, 137.8, 137.7, 136.4, 133.9, 132.9, 132.1, 130.7, 130.2, 128.3, 127.8, 127.4, 126.9, 123.0; HR-MS (ESI+DI): $(M+H)^+$: Calcd for $C_{18}H_{13}Cl_2N_2O^+$ 343.03994; Found 343.04098); Calcd for $C_{18}H_{13}{}^{35}Cl^{37}ClN_2O^+$ 345.03699; Found 345.03881); Calcd for $C_{18}H_{13}{}^{37}Cl_2N_2O^+$ 347.03404; Found 347.08921; $(M+Na)^+$: Calcd for $C_{18}H_{12}Cl_2N_2NaO^+$ 365.02189; Found 365.02277); Calcd for $C_{18}H_{12}{}^{35}Cl^{37}ClN_2NaO^+$ 367.01894; Found 367.02042); Calcd for $C_{18}H_{12}{}^{37}Cl_2N_2NaO^+$ 369.01599; Found 369.02030; MS (EI): m/z (%)= 343.9 (9), 342.9 (3), 341.9 (14, M+), 204 (5), 201.0 (3), 167.0 (13), 166.0 (13), 142 (30), 141.0 (8), 140.0 (100), 139.0 (12), 138.0 (4), 114.0 (30), 111.9 (43), 76.0 (13).

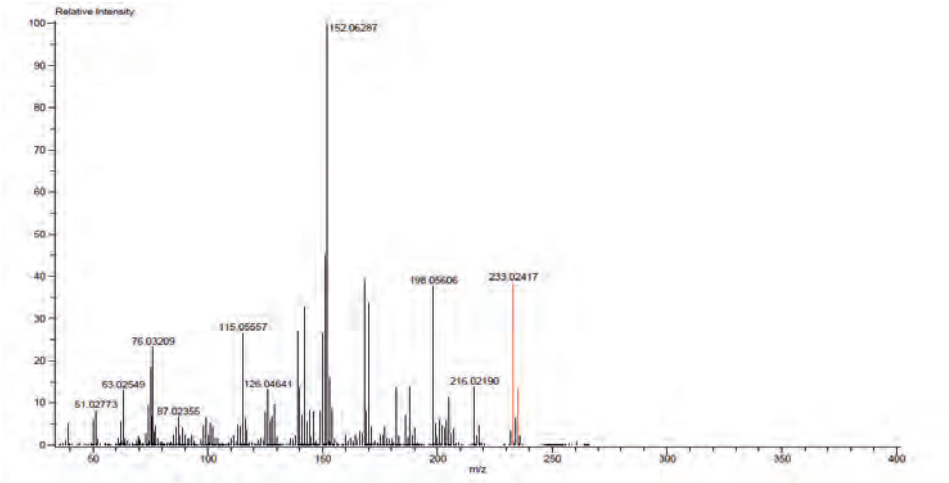
^{1}H-NMR of 4'-chloro-2-nitro-1,1'-biphenyl (8.3) in $CDCl_3$



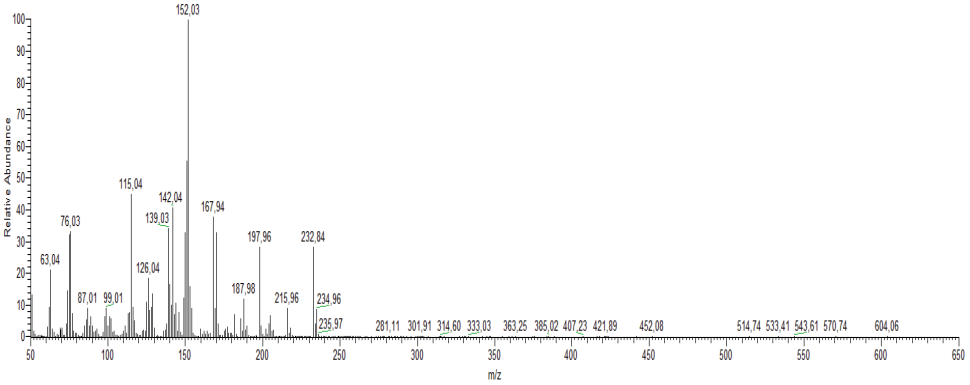
^{13}C-NMR of 4’-chloro-2-nitro-1,1'-biphenyl (8.3) in $CDCl_3$



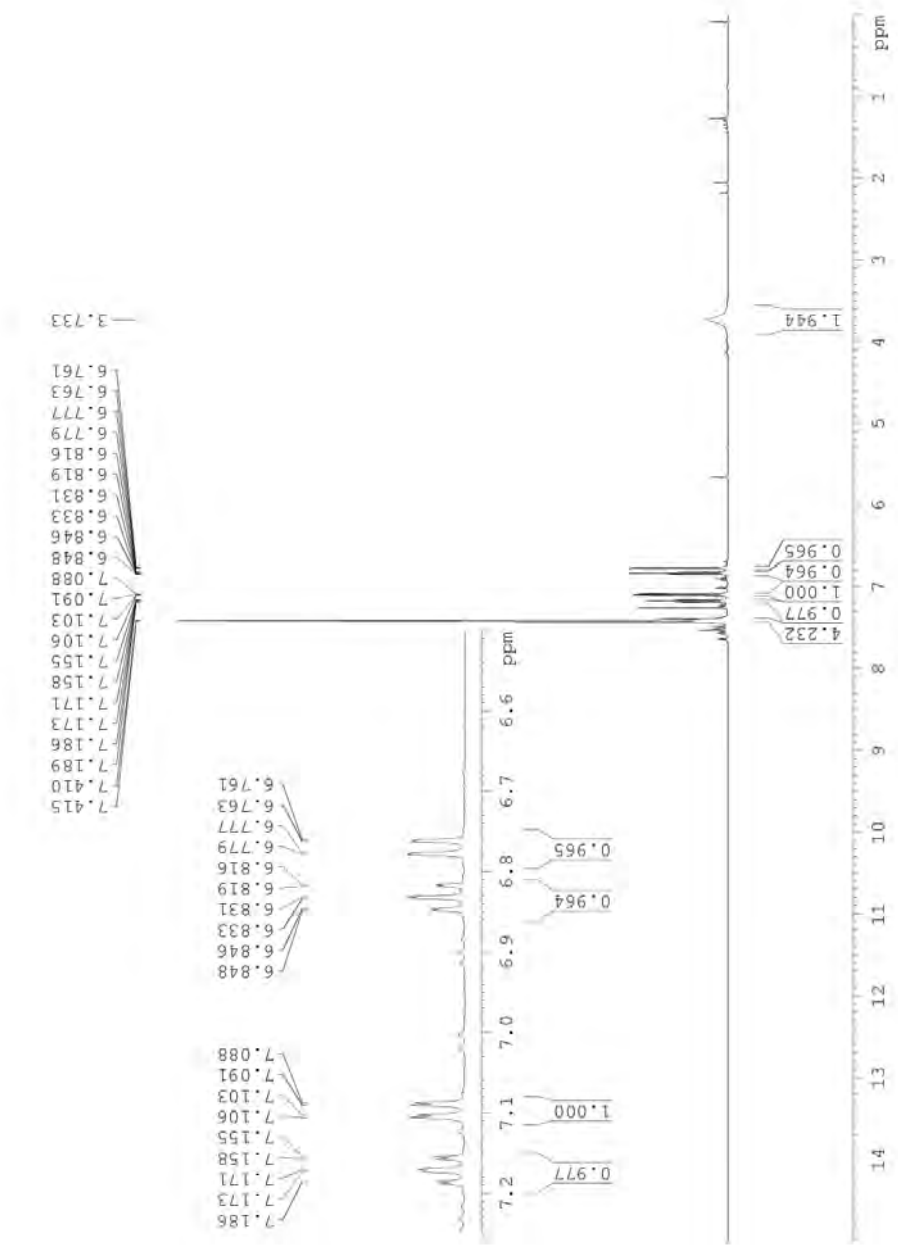
HR-MS (EI) of 4’-chloro-2-nitro-1,1'-biphenyl (8.3)



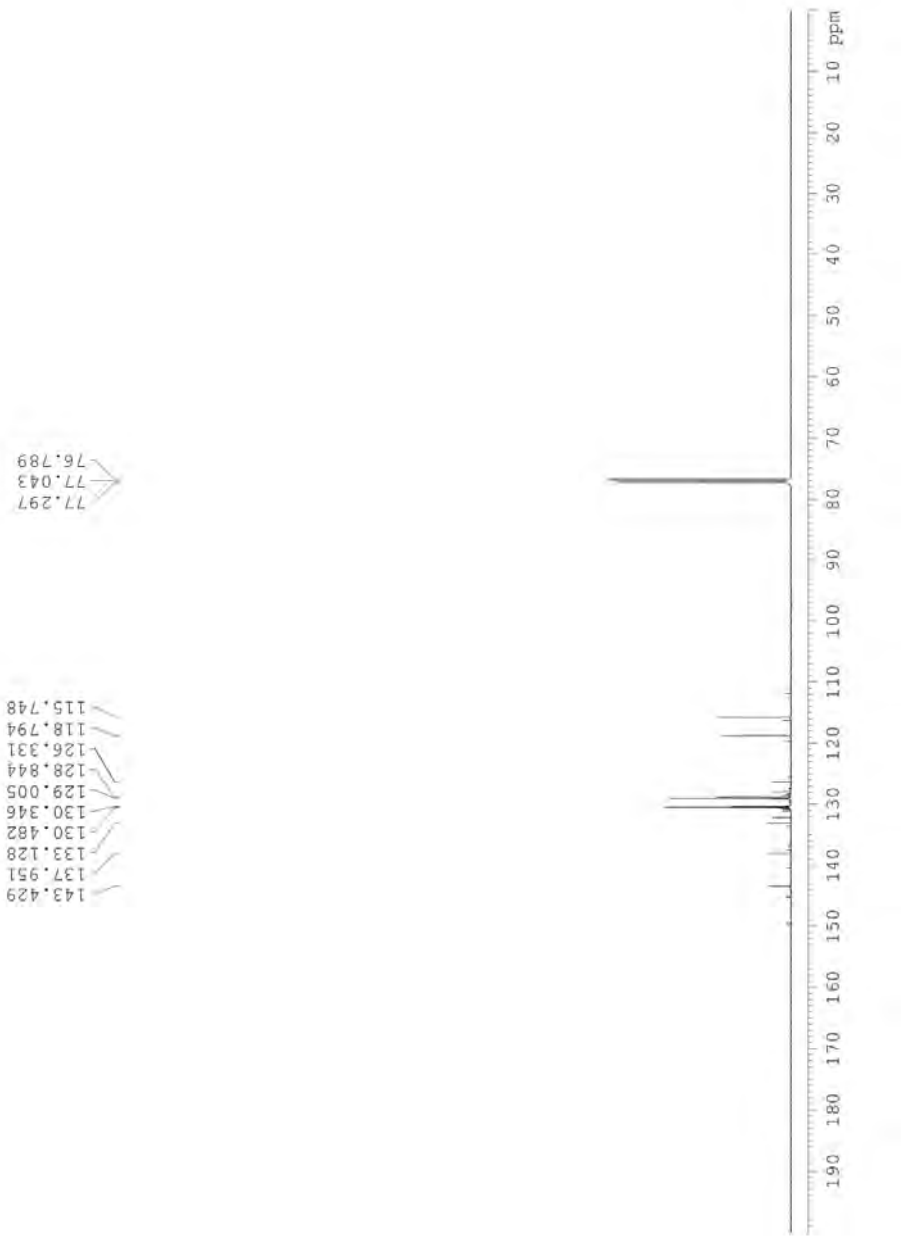
MS (EI) of 4’-chloro-2-nitro-1,1'-biphenyl (8.3)



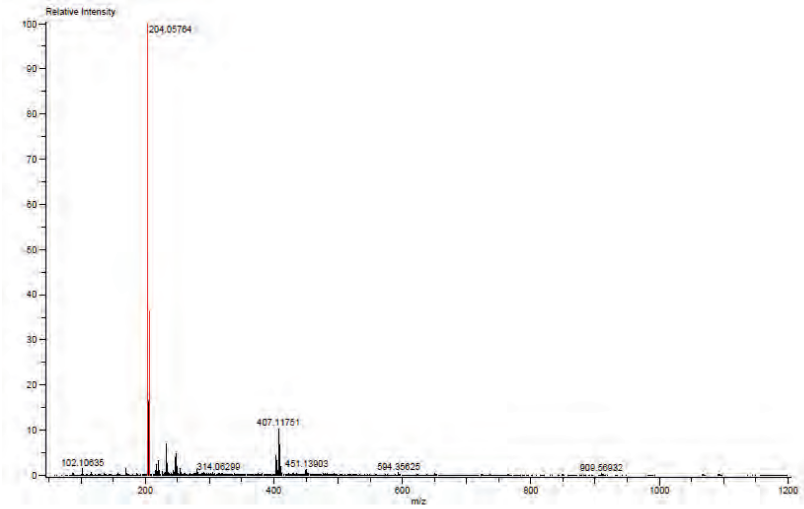
^{1}H-NMR of 4'-chloro-[1,1'-biphenyl]-2-amine (8.4) in $CDCl_3$



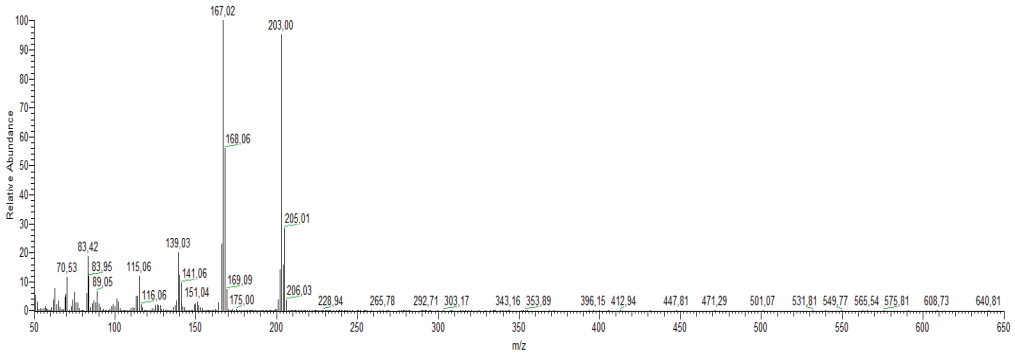
^{13}C-NMR of 4'-chloro-[1,1'-biphenyl]-2-amine (8.4) in $CDCl_3$



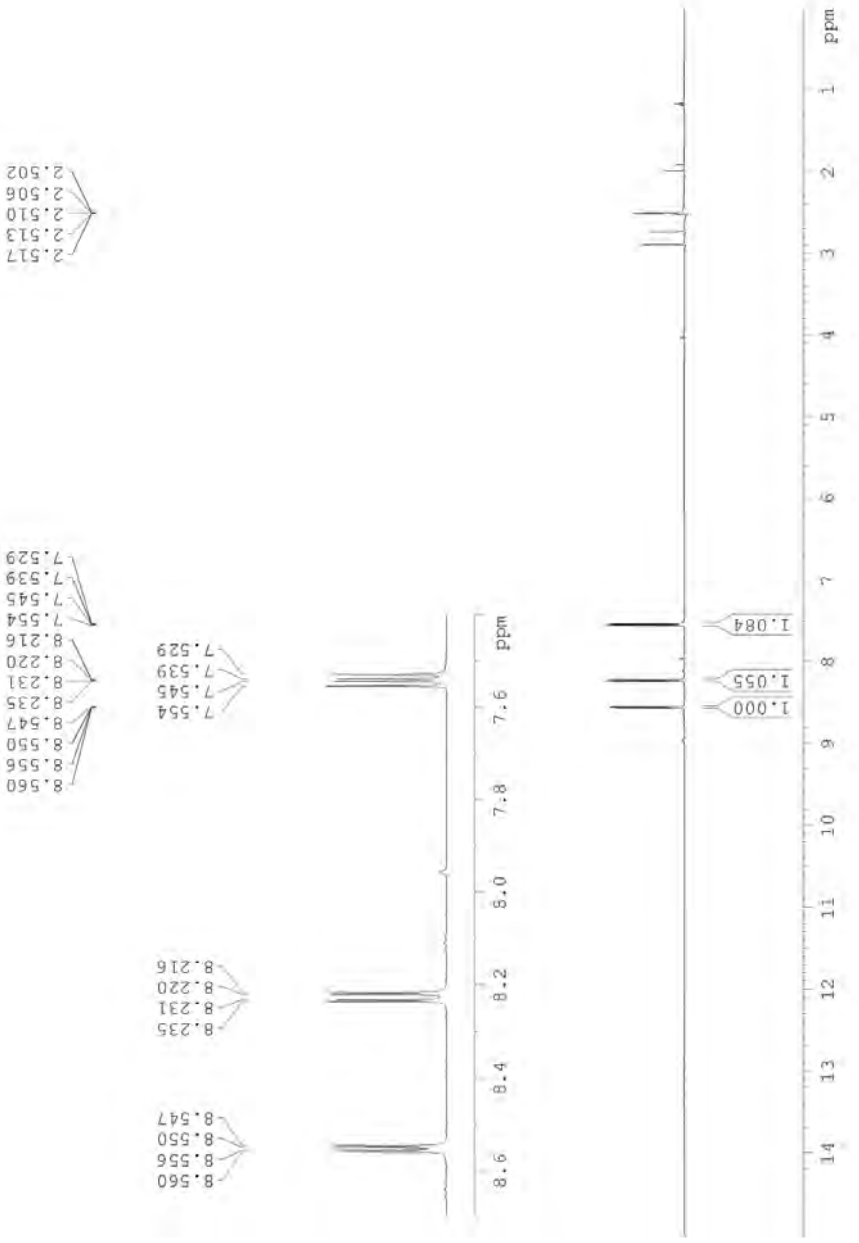
HR-MS (DART+) of 4'-chloro-[1,1'-biphenyl]-2-amine (8.4)



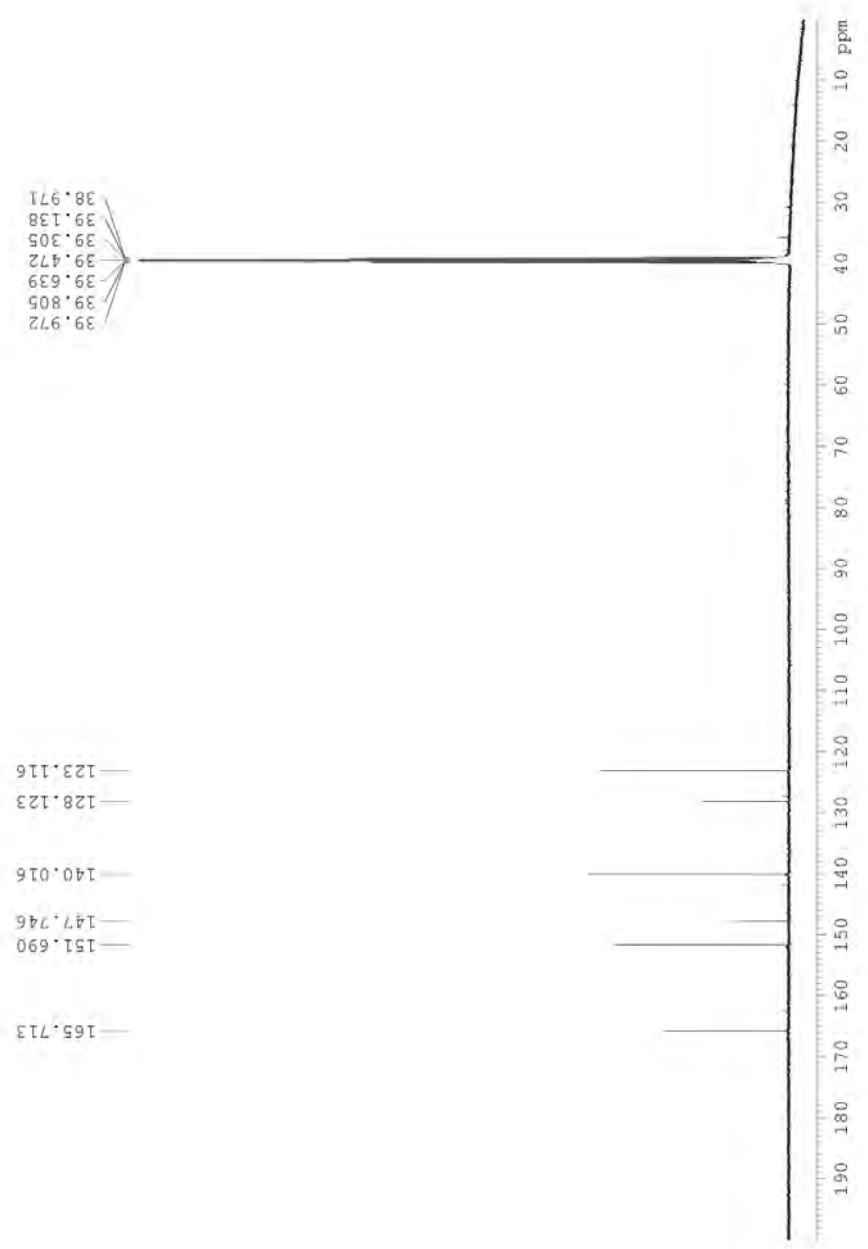
MS (EI) of 4'-chloro-[1,1'-biphenyl]-2-amine (8.4)



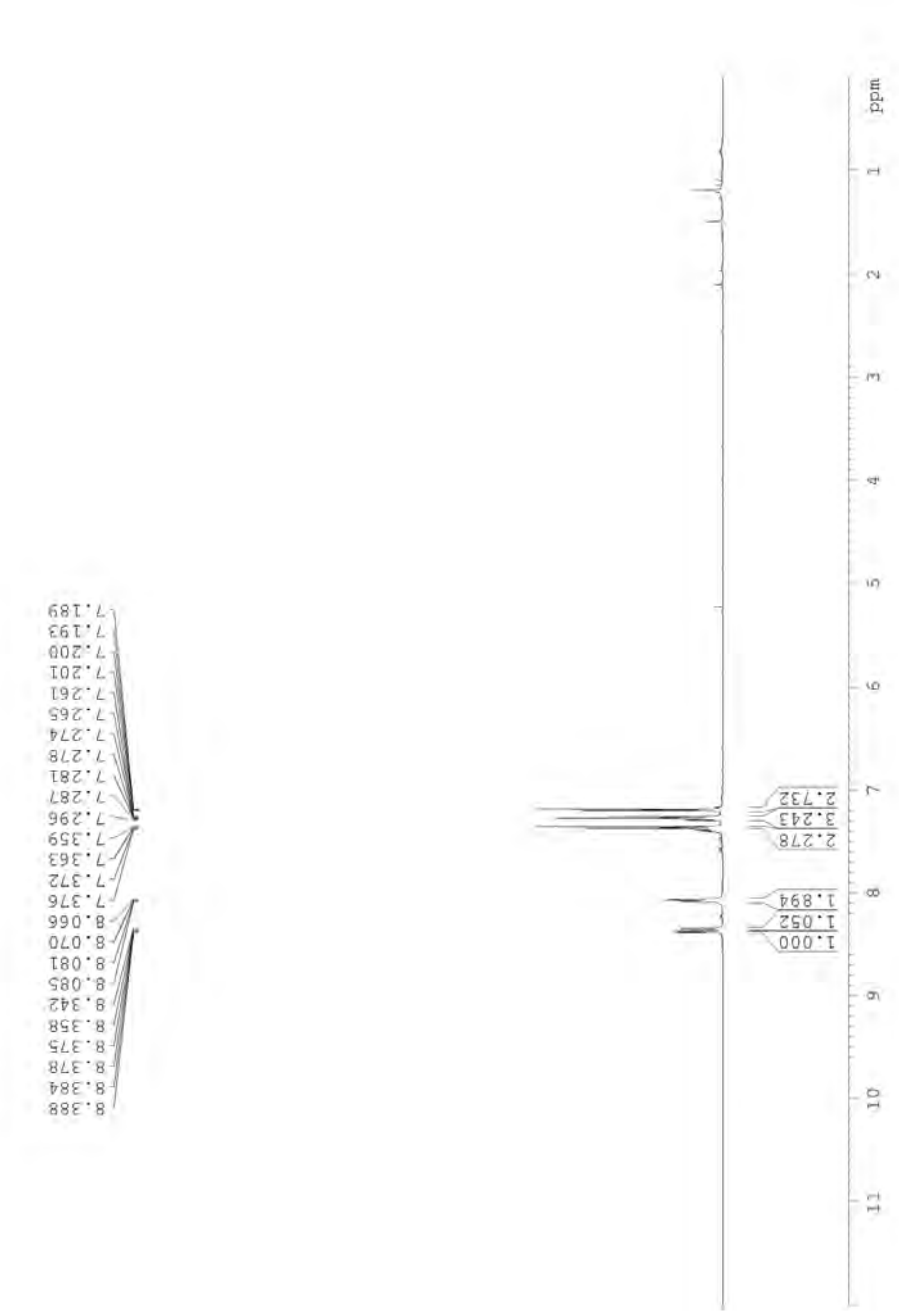
^{1}H-NMR of 2-chloronicotinoyl chloride (8.6) in DMSO-d_6



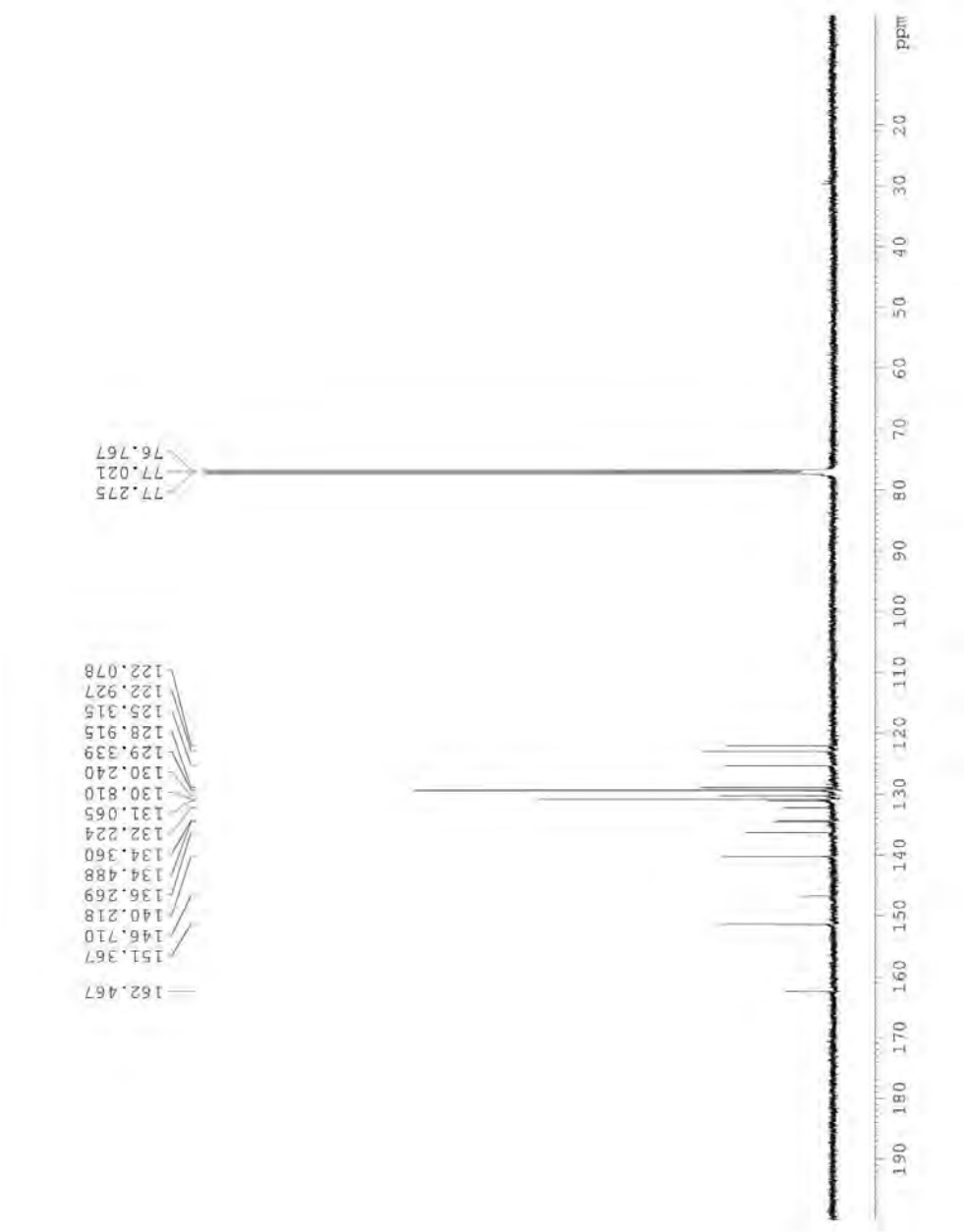
^{13}C-NMR of 2-chloronicotinoyl chloride (8.6) in DMSO-d$_6$



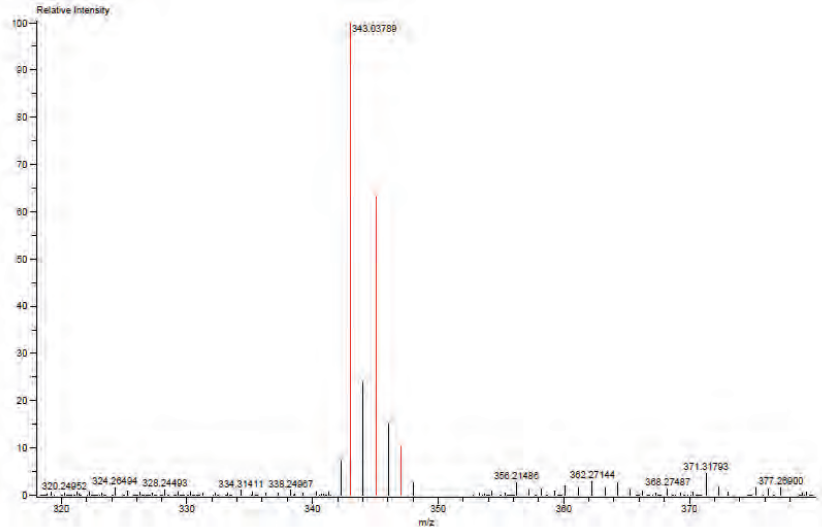
^{1}H-NMR of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) in $CDCl_3$ [method 1]



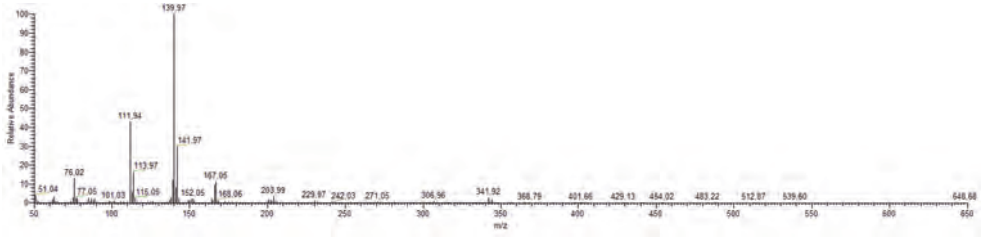
^{13}C-NMR of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) in $CDCl_3$ [method 1]



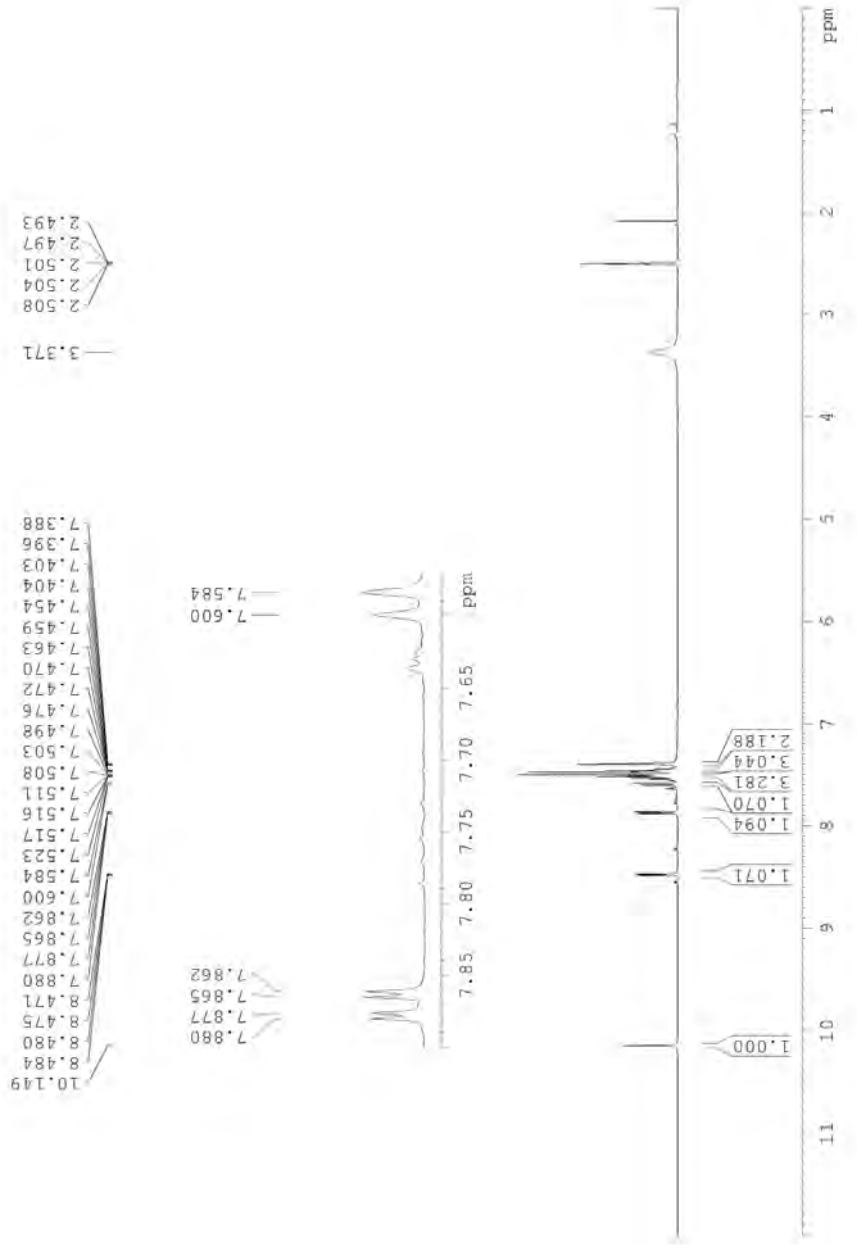
HR-MS (DART+) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) [method 1]



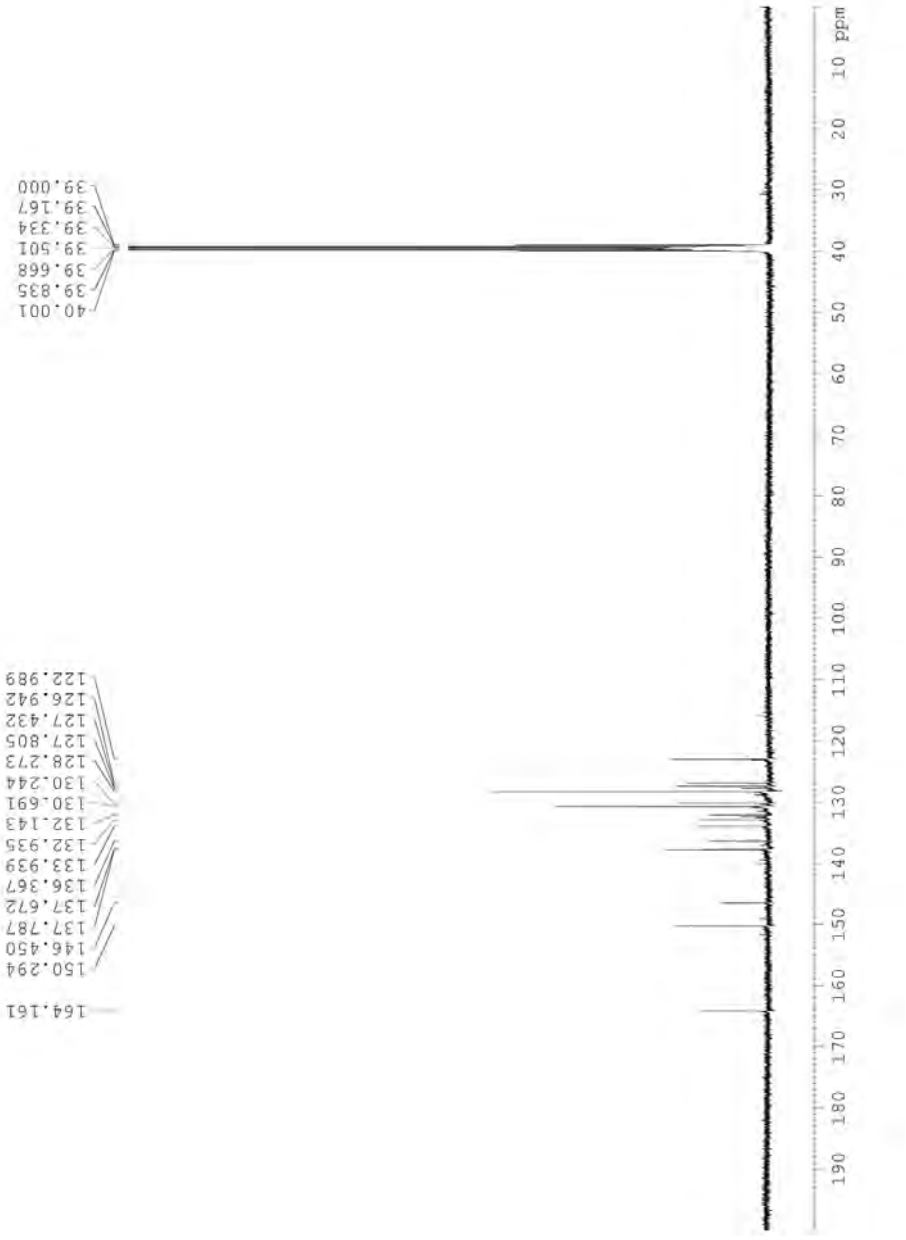
MS (EI) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) [method 1]



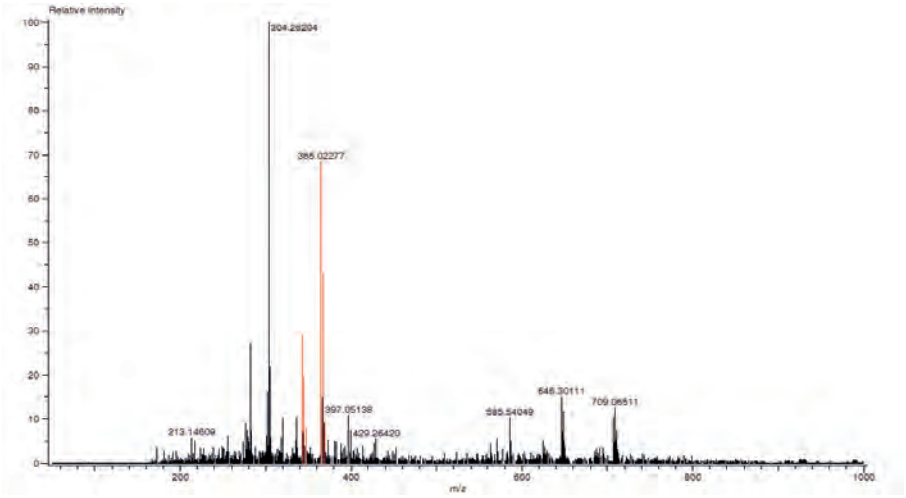
^{1}H-NMR of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) in DMSO-d_6 [method 2]



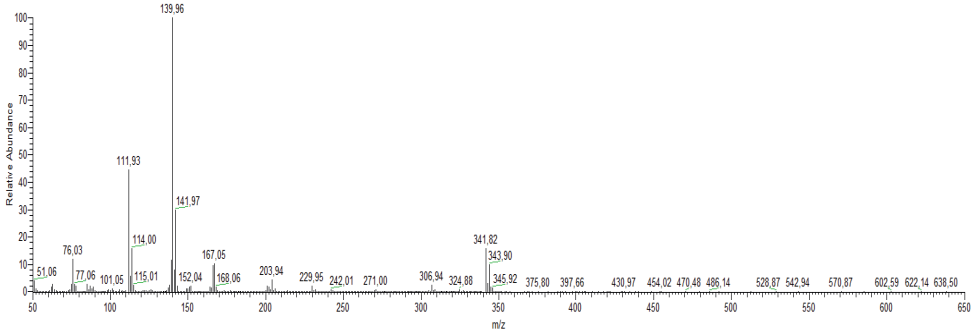
^{13}C-NMR of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) in DMSO-d_6 [method 2]



HR-MS (ESI+DI) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) [method 2]



MS (EI) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (8.8) [method 2]



Supporting Information for Chapter 9

A High Rate and Efficient Reduction Method Based on Sodium Borohydride and Cobalt sulfate

Experimental Section

Chemicals. All reagents and solvents were purchased commercially and used without being purified. All the reaction mixtures were monitored by means of TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 nm and λ = 365 nm. ^{1}H and ^{13}C NMR spectra were recorded with BrukerAV 500 MHz.

Analyses. GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d., 0.33 mm film thickness) at a helium pressure of200 kPa, split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. ^{1}H and ^{13}C-NMR spectra were recorded at ambient temperature at a frequency of 500 and 125 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ = 7.26 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm) and with DMSO-d_6 for proton (δ = 2.50 ppm) and for carbon (δ = 39.0 ppm) with tetramethylsilane as an external reference.

General procedure for the reduction of nitro/nitrile/azide compounds. Substrate (1 mmol) was dissolved in ethanol (5 mL). To the stirred solution, $CoSO_4.7H_2O$ (1 mmol) dissolved in water (0.7 mL) was added. The reaction mixture was cooled to 0^{o}C and then $NaBH_4$ (4 mmol) was added gradually and instantly observed a black granular precipitate of cobalt boride (Co_2B) and copious quantities of hydrogen. The reaction mixture was stirred at ambient temperature for 10 min. The reaction mixture was quenched with water (15 mL) and filtered by using Buchner funnel to remove the precipitate. The filtered solution was diluted with EtOAc (100 mL) and washed with water (50 mL). The aqueous phase was then extracted with EtOAc (2×50 mL). The organic phase was combined and dried over sodium sulfate, the drying agent was filtered off and the solvent was evaporated using Rota vapor to obtain the amine compound.

4'-chloro-[1,1'-biphenyl]-2-amine (9.11a) [1204-44-0]. 4'-chloro-2-nitro-1,1'-biphenyl (0.119 g, 0.510 mmol), $NaBH_4$ (0.077 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.143 g, 0.510 mmol). The title compound was isolated as a pale-brown solid (0.104 g, 95 %). R_f = 0.76 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.48-7.50 (m, 2H), 7.43-7.45 (m, 2H), 7.04-7.08 (m, 1H), 6.97-6.99 (dd, J = 1.5 Hz, 7.5 Hz, 1H), 6.76-6.78 (dd, J = 1.0 Hz, 8 Hz, 1H), 6.62-6.6.66 (td, J = 1.0 Hz, 7.5 Hz, 1H), 4.83 (s, br, 2H) ; ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 145.1, 138.5, 131.3, 130.5, 129.9, 128.6, 128.5, 124.4, 116.7, 115.4. MS(EI): m/z(%): 205(33), 204(19), 203(100, M+), 169(8), 168(65), 167(94), 141(9), 140(12), 139(20), 115(12), 89(29), 83.6(44), 69.4(11); IR (cm-1): 3433, 3338, 2921, 2851, 1616, 1481, 1025, 1004, 826, 749.

[1,1'-biphenyl]-2-amine (9.11b) [90-41-5]. 2-nitro-1,1'-biphenyl (0.10 g, 0.50 mmol), $NaBH_4$ (0.076 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.141 g, 0.510 mmol). The title compound was isolated as a yellow solid (0.081 g, 96 %). R_f = 0.74 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.42-7.46 (m, 4H), 7.32-7.35 (m, 1H), 7.12-7.17 (m, 2H), 6.81-6.84 (td, J = 1.0 Hz, 7.0 Hz, 1H), 6.75-6.77 (dd, J = 1.0 Hz, 8 Hz, 1H), 3.74 (s, br, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 143.5, 139.6, 130.5, 129.1, 128.8, 128.5, 127.7, 127.2, 118.7, 115.6. MS(EI): m/z(%): 170.1(13), 169.1(100, M+), 168.1(55), 167(44),

154(4), 139(7), 115(10), 89(2), 83.5(14), 77(23), 63(5), 51(4); IR (cm-1): 3480, 3386, 3194, 1611, 1479, 1434, 1284, 1156, 749.

5-amino-2,4-dimethoxy-3-methylphenol (9.11c) [111223-14-4]. 2,4-dimethoxy-3-methyl-5-nitrophenol (0.150 g, 0.704 mmol), $NaBH_4$ (0.107 g, 2.04 mmol), $CoSO_4.7H_2O$ (0.198 g, 0.510 mmol), ethanol (5 mL) and water (1 mL). The title compound was isolated as a dark blue liquid (0.121 g, 94 %). R_f = 0.5 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.23 (s, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 2.20(s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.5, 138.9, 137.5, 136.5, 124.2, 100.1, 61.0, 59.6, 9.5; MS(EI): m/z(%): 184(4), 183(45, M+), 169(11), 168(100), 153(24), 140(22), 125(38), 96.9(19), 83(25), 69(25), 54.9(28); IR (cm-1): 3327, 2973, 2927, 2882, 1380, 1087, 1045, 879.

2-chloro-5-methylaniline (9.11d) [95-81-8]. 1-chloro-4-methyl-2-nitrobenzene (0.086 g, 0.500 mmol), $NaBH_4$ (0.076 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.141 g, 0.510 mmol). m/z(%): 143.1(35), 142.1(26), 141.1(100, M+), 139.1(31), 113(7), 107.1(9), 106.1(100), 89.1(5), 79.1(27), 77.1(34), 63.1(6), 51.1(8).

2-bromo-5-chloroaniline (9.11e) [823-57-4]. 1-bromo-4-chloro-2-nitrobenzene (0.118 g, 0.500 mmol), $NaBH_4$ (0.076 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.141 g, 0.510 mmol). The title compound was isolated as a brown solid (0.096 g, 93 %). R_f = 0.88 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.30 (d, J = 8.5 Hz, 1H), 6.74 (s, 1H), 6.58-6.60 (dd, J = 2.5 Hz, 8.5 Hz, 1H), 4.15 (s, br, 2H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 145.0, 133.9, 133.3, 119.3, 115.2, 107.0; MS(EI): m/z(%): 208.9(21), 206.9(100, M+), 205(74), 128(11), 126(33), 99(24), 90(34), 73(6), 63(27), 52(11); IR (cm-1): 3188, 2922, 1416, 1193, 720, 642.

1,2-diphenyldiazene 1-oxide (9.11g) [495-48-7]. Nitrobenzene (0.126 g, 1.02 mmol), $NaBH_4$ (0.154 g, 2.04 mmol), $CoSO_4.7H_2O$ (0.254 g, 0.510 mmol), ethanol (6 mL) and water (1.5 mL). MS(EI): m/z(%): 198.1(12, M+), 169.1(13), 141.1(8), 105(11), 91(24), 77(100), 65.1(23), 51.1(29).

1,2-bis(2-chlorophenyl)diazene 1-oxide (9.11h) [13556-84-8]. 1-chloro-2-nitrobenzene (0.080 g, 0.510 mmol), $NaBH_4$ (0.077 g, 2.04 mmol) dissolved in ethanol (3 mL), $CoSO_4.7H_2O$ (0.143 g, 0.510 mmol), ethanol (3 mL) and water (1.5 mL). MS(EI): m/z(%): 233(18), 231(25, M+), 168.1(12), 139(16), 113(31), 111(100), 99(17), 90.1(32), 75(65), 63.1(21).

2-chloroaniline (9.11f) [95-51-2]. 1-chloro-2-nitrobenzene (0.080 g, 0.510 mmol), $NaBH_4$ (0.077 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.143 g, 0.510 mmol). MS(EI): m/z(%): 129(32), 128(8), 127(100, M+), 100(8), 92(20), 73(5), 65(26), 52(8), 45.6(5).

naphthalene-1,8-diamine (9.11l) [479-27-6]. 1,8-dinitronaphthalene (0.112 g, 0.51 mmol), $NaBH_4$ (0.077 g, 2.04 mmol), $CoSO_4.7H_2O$ (0.141 g, 1.02 mmol), TBAB (0.032, 0.1 mmol). MS(EI): m/z(%): 159.1(9), 158.1(100, M+), 140(7), 130.1(32), 114.1(6), 103.1(8), 77.1(32), 65.1(5), 51(4).

[1,1'-biphenyl]-2,2'-diamine (9.11i) [1454-80-4]. 2,2'-dinitro-1,1'-biphenyl (0.125 g, 0.510 mmol), $NaBH_4$ (0.077 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.143 g, 0.510 mmol). MS(EI): m/z(%): 185(13), 184.1(100, M+), 183(37), 167.1(77), 166(31), 154(9), 139(14), 128(14), 105(13), 91.1(26), 77.1(32), 65(16), 58.1(38).

benzene-1,2-diamine (9.11j) [95-54-5]. 1,2-dinitrobenzene (0.171 g, 1.02 mmol), $NaBH_4$ (0.154 g, 4.08 mmol), $CoSO_4.7H_2O$ (0.287 g, 1.02 mmol), ethanol (6 mL) and water (1.5

mL). MS(EI): m/z(%): 109.1(8), 108.1(100, M+), 107.1(25), 91(4), 81.1(22), 80(57), 54.1(9), 53.1(13).

benzene-1,3-diamine (9.11k) [108-45-2]. 1,3-dinitrobenzene (0.086 g, 0.510 mmol), $NaBH_4$ (0.144 g, 4.08 mmol) and $CoSO_4.7H_2O$ (0.246 g, 1.02 mmol). MS(EI): m/z(%): 109.1(7), 108(100, M+), 91(6), 81(34), 80(52), 73(17), 53(12).

dibenzylamine (9.11m) [103-49-1]. benzonitrile (0.105 g, 1.02 mmol), $NaBH_4$ (0.154 g, 4.08 mmol), $CoSO_4.7H_2O$ (0.286 g, 1.02 mmol), ethanol (6 mL) and water (1.5 mL) . The title compound was isolated as a pale-yellow solid (0.183 g, 91 %). R_f = 0.85 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.34 (s, 10H), 3.81 (s, 4H), 1.57 (s, br, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 140.3, 128.4, 128.2, 127.0, 53.2; MS(EI): m/z(%): 197(9), 196.1(13, M+), 120.1(8), 106(55), 92(21), 91(100), 77(7), 65(16), 51(6); IR (cm-1): 3061, 3026, 1494, 1452, 731, 694.

(2-nitrosophenyl)methanamine (9.11o) [NEW]. 2-nitrobenzonitrile (0.056 g, 0.510 mmol), $NaBH_4$ (0.057 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.106 g, 0.510 mmol). The title compound was isolated as a pale-brown solid (0.038 g, 75 %). R_f = 0.15 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.56-7.58 (dd, J = 1.5 Hz, 8 Hz, 1H), 7.16-7.20 (m, 1H), 6.71-6.73 (dd, J = 1.0 Hz, 8.5 Hz, 1H), 6.60 (s, br, 2H), 6.52(m, 1H) ; ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 171.3, 150.2, 131.8, 128.7, 116.4, 114.3, 113.7, 40.0; MS(EI): m/z(%): 137(6), 136(73, M+), 119(100), 107(3), 92(66), 80(3), 65(32), 52(8); IR (cm-1): 3393, 1660, 1621, 1023, 994, 824, 761; HRMS (ESI): m/z $[M+H]^+$: Calcd. for $C_7H_9N_2O^+$ 137.07094; Found 137.07177.

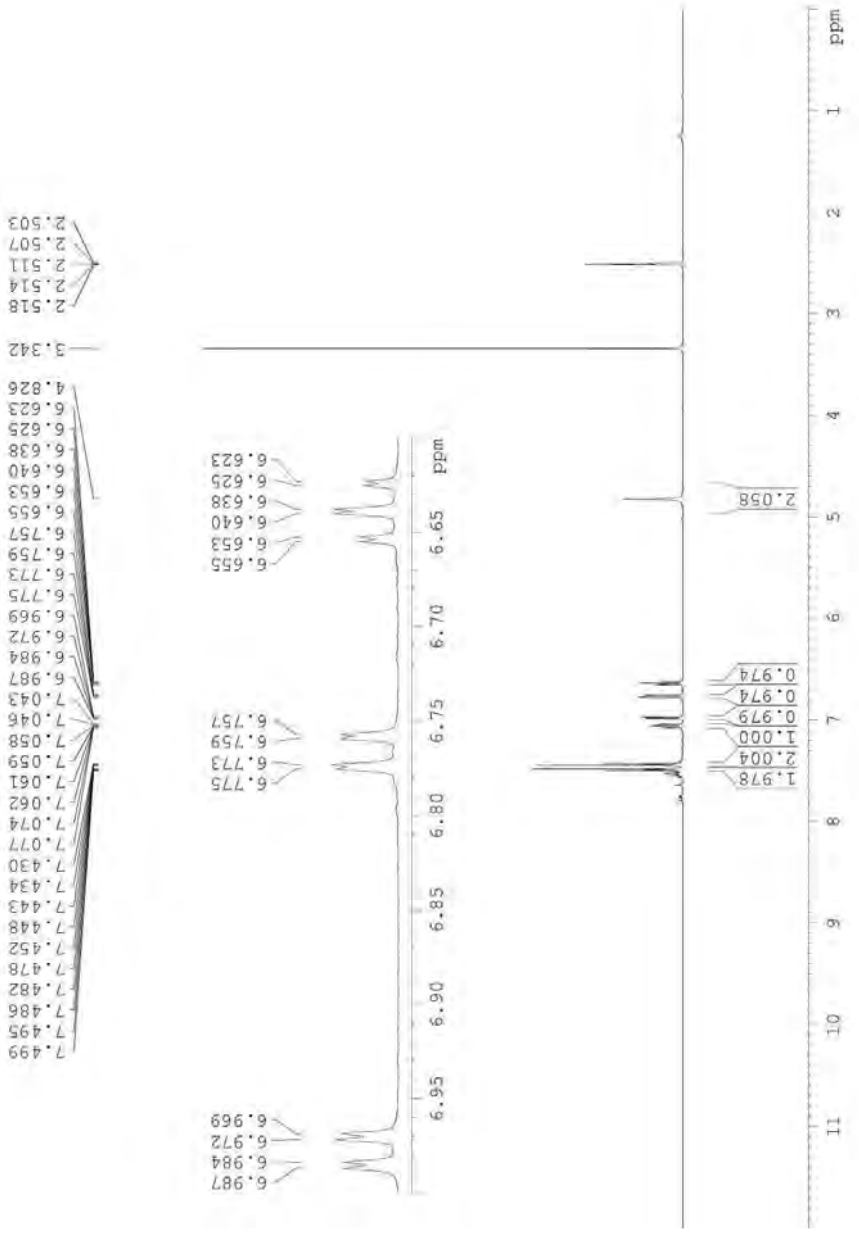
4-aminobenzonitrile (9.11q) [873-74-5]. 4-nitrobenzonitrile (0.074 g, 0.510 mmol), $NaBH_4$ (0.077 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.143 g, 0.510 mmol). MS(EI): m/z(%): 119(9), 118(100, M+), 91(34), 64(11), 154(13), 52(6).

4-(1-hydroxyethyl)benzonitrile (9.11r) [52067-35-3]. 4-acetylbenzonitrile (0.073 g, 0.510 mmol), $NaBH_4$ (0.077 g, 2.04 mmol) and $CoSO_4.7H_2O$ (0.143 g, 0.510 mmol). MS(EI): m/z(%):147(8, M+), 130(17), 132(100), 116(3), 105(13), 103(12), 104(99), 103(12), 89(3), 77(33), 63(5), 51(15); IR (cm-1): 3312, 2972, 2879, 1379, 1087, 1046, 880.

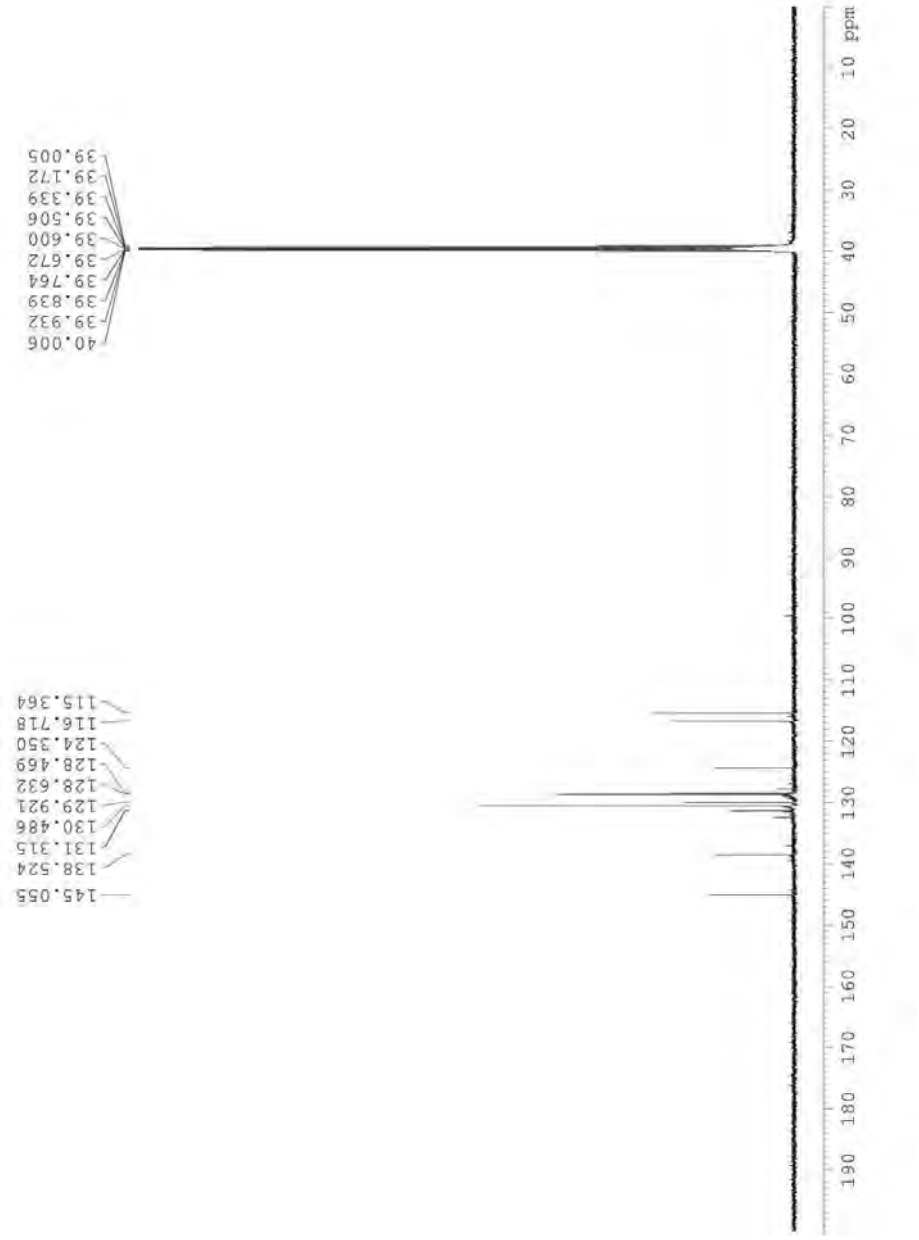
4-(aminomethyl) aniline (9.11s) [4403-71-8]. 4-aminobenzonitrile (0.118 g, 1.00 mmol), $NaBH_4$ (0.151 g, 4.00 mmol) and $CoSO_4.7H_2O$ (0.281 g, 1.00 mmol). The title compound was isolated as a pale-brown solid (0.095 g, 78 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.16-7.17 (m, 2H), 6.66-6.68 (m, 2H), 4.56 (s, 2H), 3.68 (s, br, 2H), 1.59 (s, br, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 131.0, 128.2, 118.0, 113.5, 49.5.

2-amino-N,N-dimethyl-1H-imidazole-1-sulfonamide (9.11t) [1258289-36-9**].** 2-azido-N,N-dimethyl-1H-imidazole-1-sulfonamide (0.054 g, 0.250 mmol), $NaBH_4$ (0.038 g, 1.00 mmol) and $CoSO_4.7H_2O$ (0.070 g, 0.249 mmol). The title compound was isolated as a yellow solid (0.046 g, 96 %). R_f = 0.12 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.77 (d, J = 1.5 Hz, 1H), 6.59 (d, J = 1.0 Hz, 1H), 5.24 (s, br, 2H), 2.91 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 148.5, 125.6, 113.4, 38.6; MS(EI): m/z(%): 190(23, M+), 108(8), 99.1(6), 83(24), 82(100), 63.9(7), 55(29), 45.1(12); IR (cm-1): 3456, 3286, 3118, 2920, 1640, 1374, 1161, 1047, 963, 710, 594.

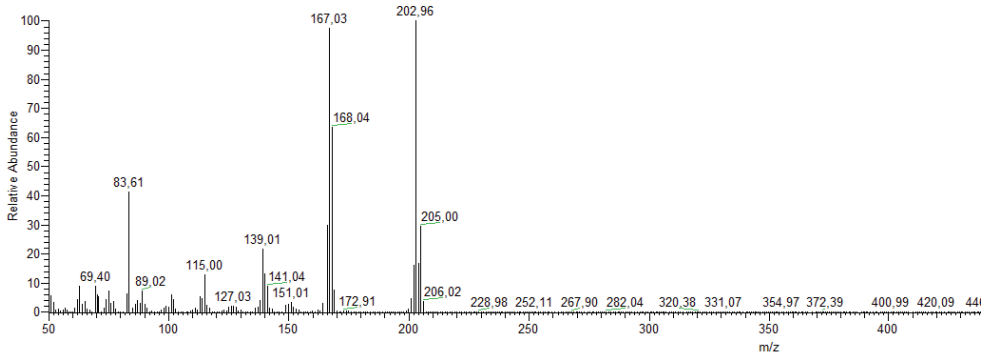
^{1}H-NMR of 4'-chloro-[1,1'-biphenyl]-2-amine (9.11a) in DMSO-d$_6$



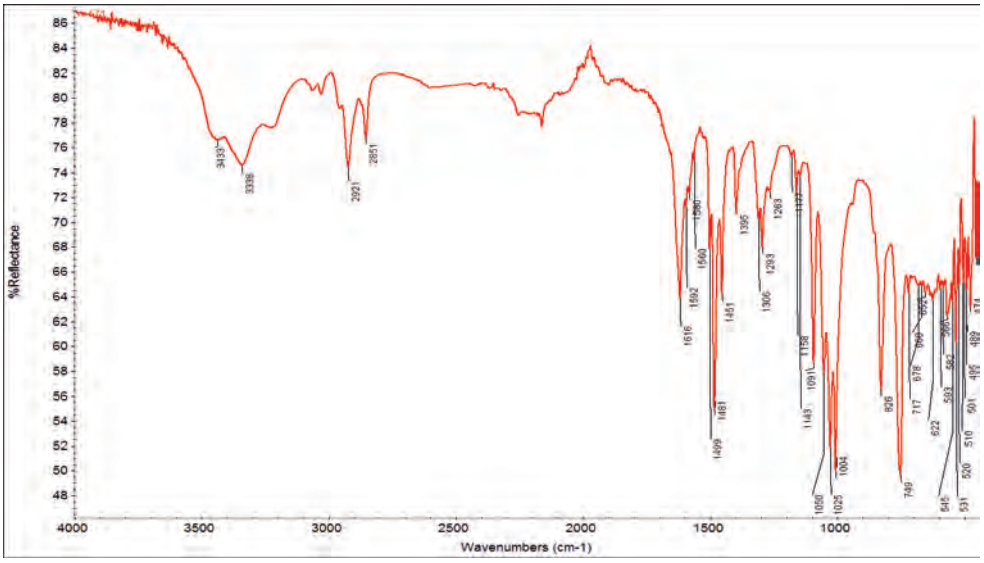
^{13}C-NMR of 4'-chloro-[1,1'-biphenyl]-2-amine (9.11a) in DMSO-d$_6$



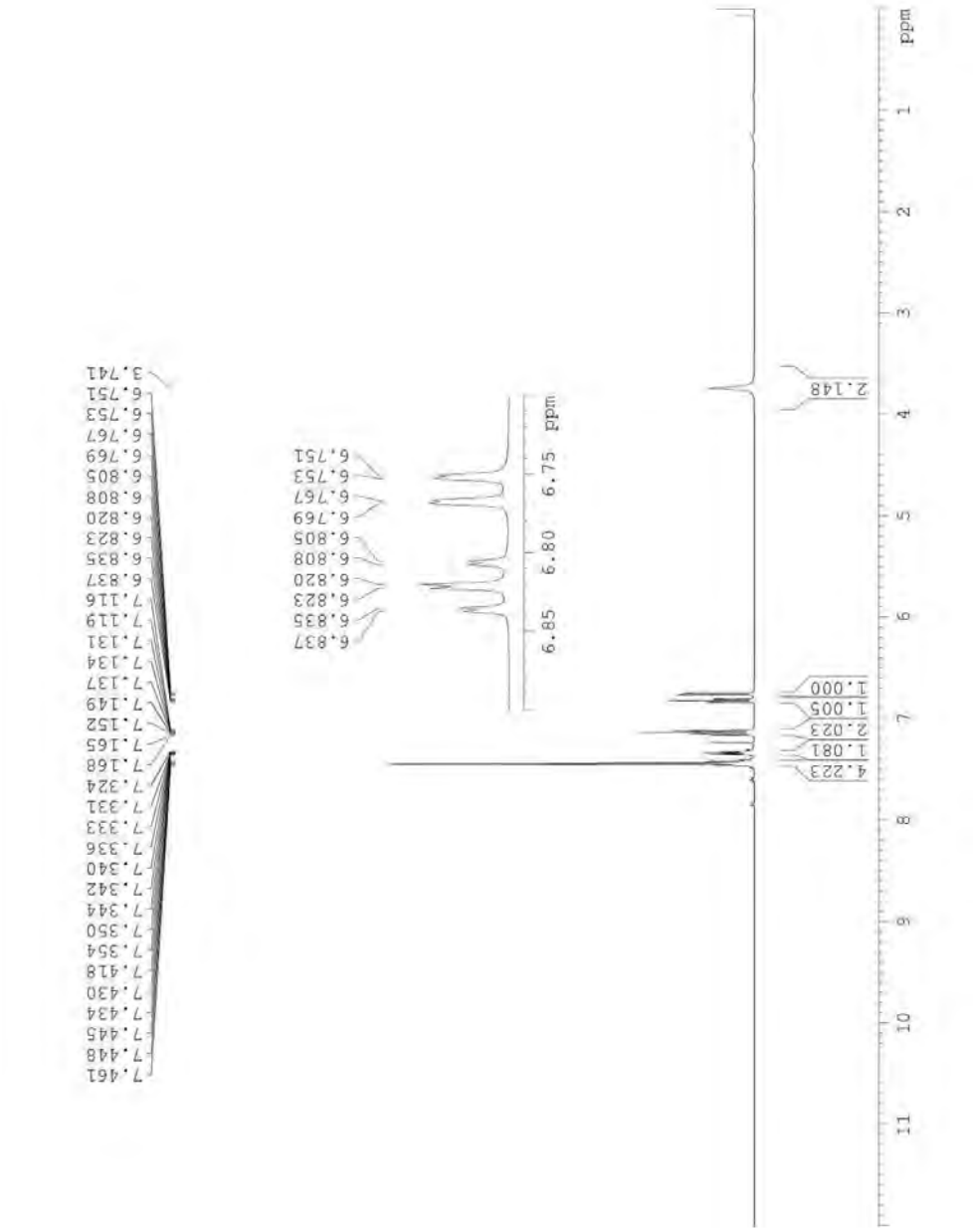
MS (EI) of 4'-chloro-[1,1'-biphenyl]-2-amine (9.11a)



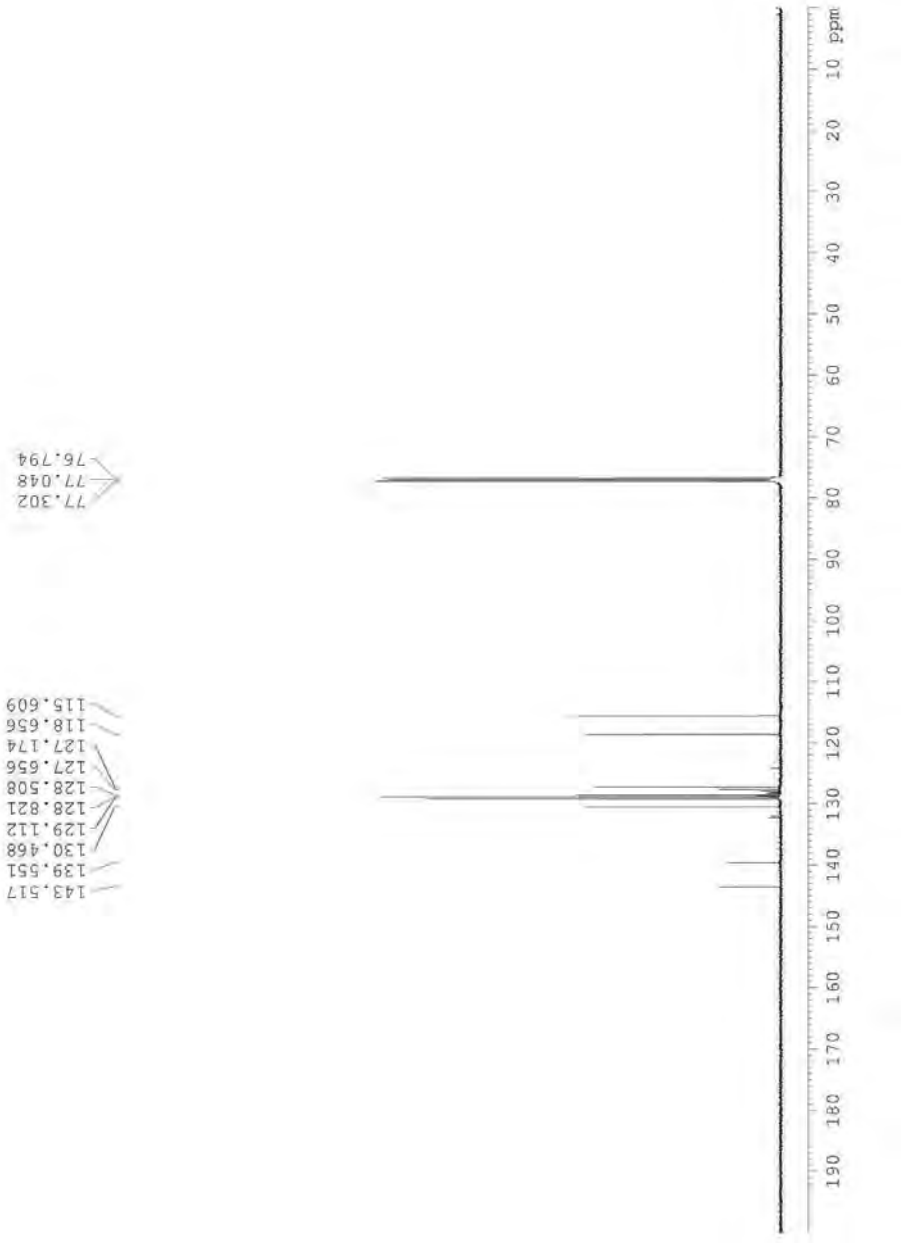
IR of 4'-chloro-[1,1'-biphenyl]-2-amine (9.11a)



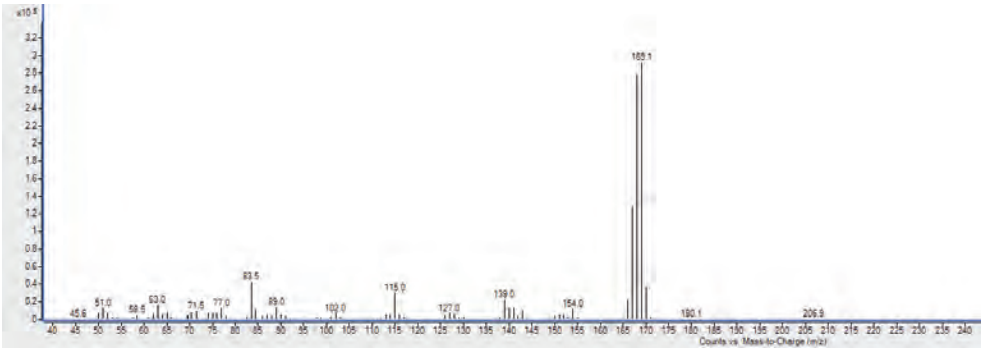
^{1}H-NMR of [1,1'-biphenyl]-2-amine (9.11b) in $CDCl_3$



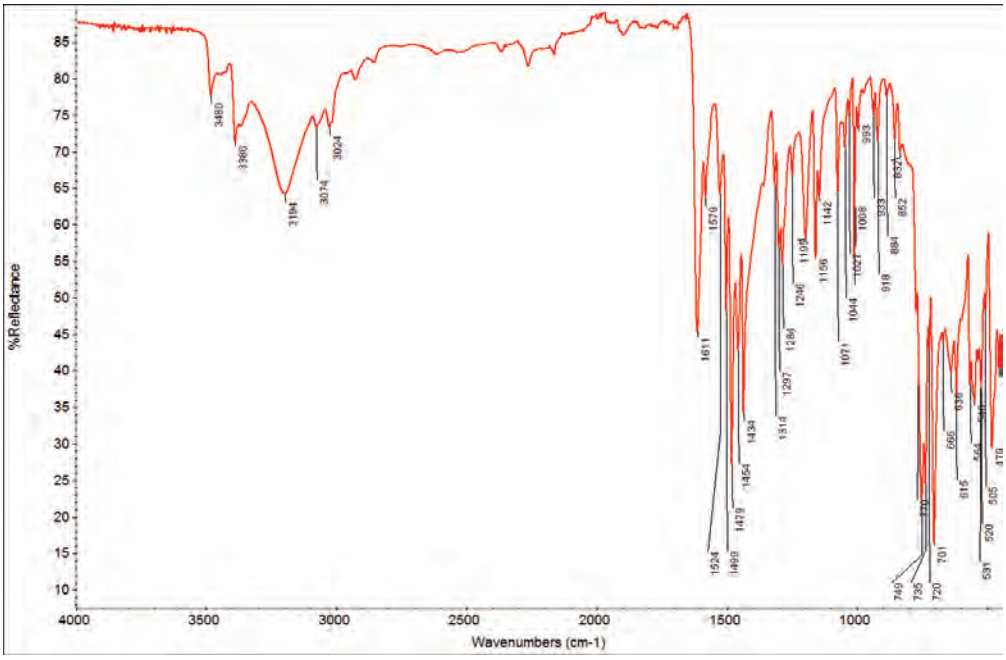
^{13}C-NMR of [1,1'-biphenyl]-2-amine (9.11b) in $CDCl_3$



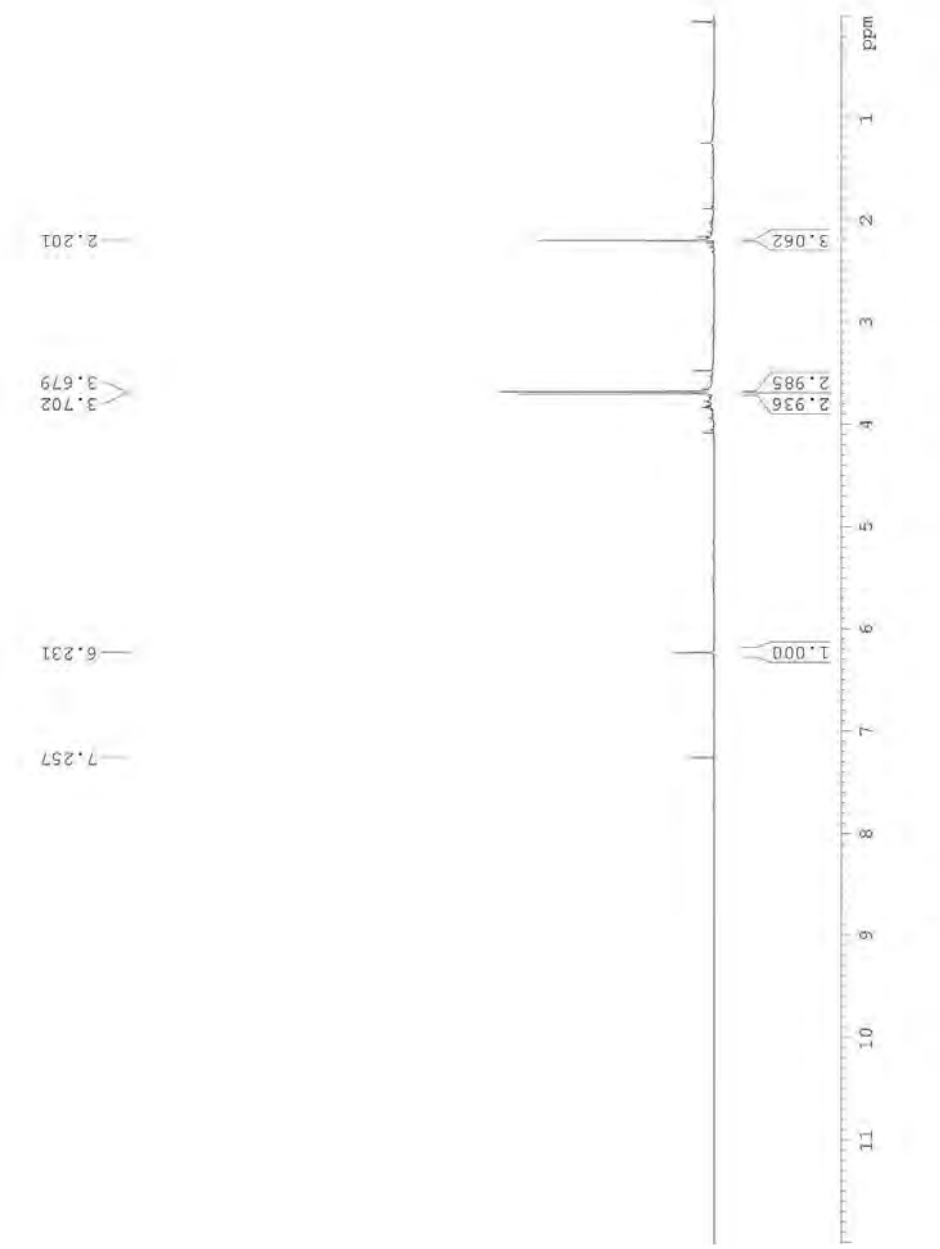
MS (EI) of [1,1'-biphenyl]-2-amine (9.11b)



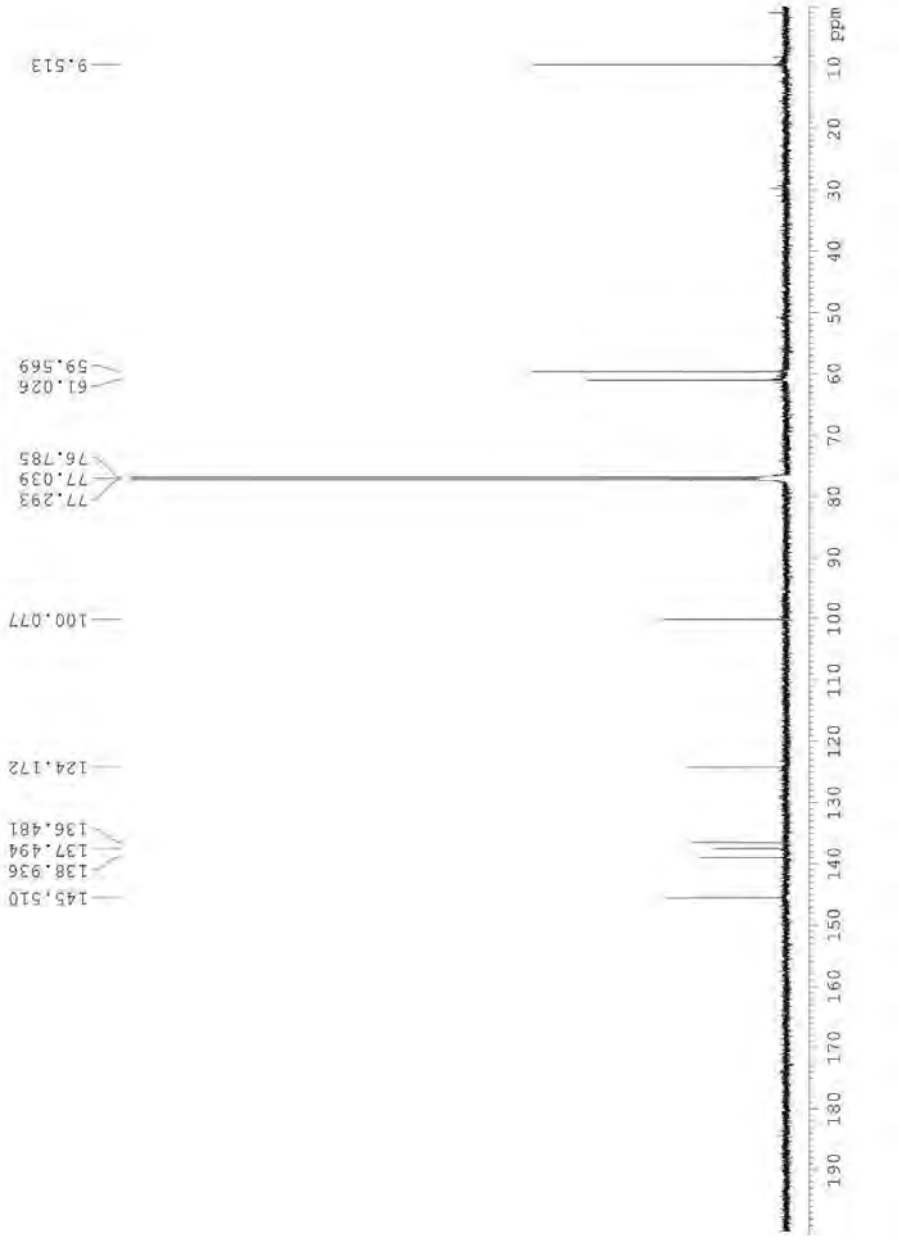
IR of [1,1'-biphenyl]-2-amine (9.11b)



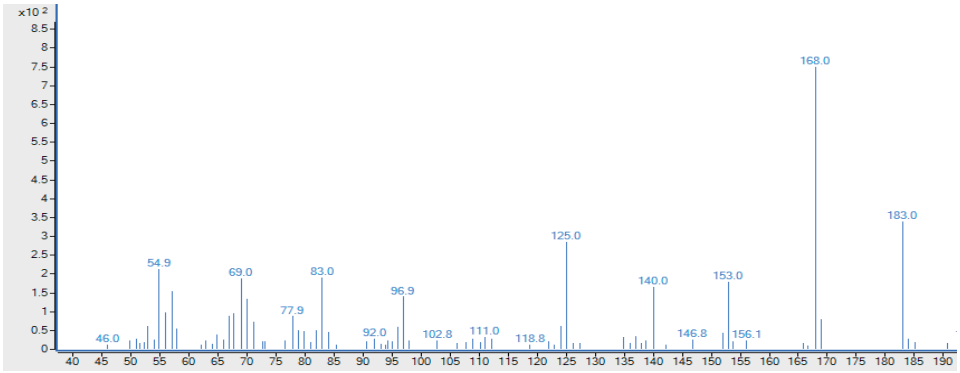
^{1}H- NMR of 5-amino-2,4-dimethoxy-3-methylphenol (9.11c) in $CDCl_3$



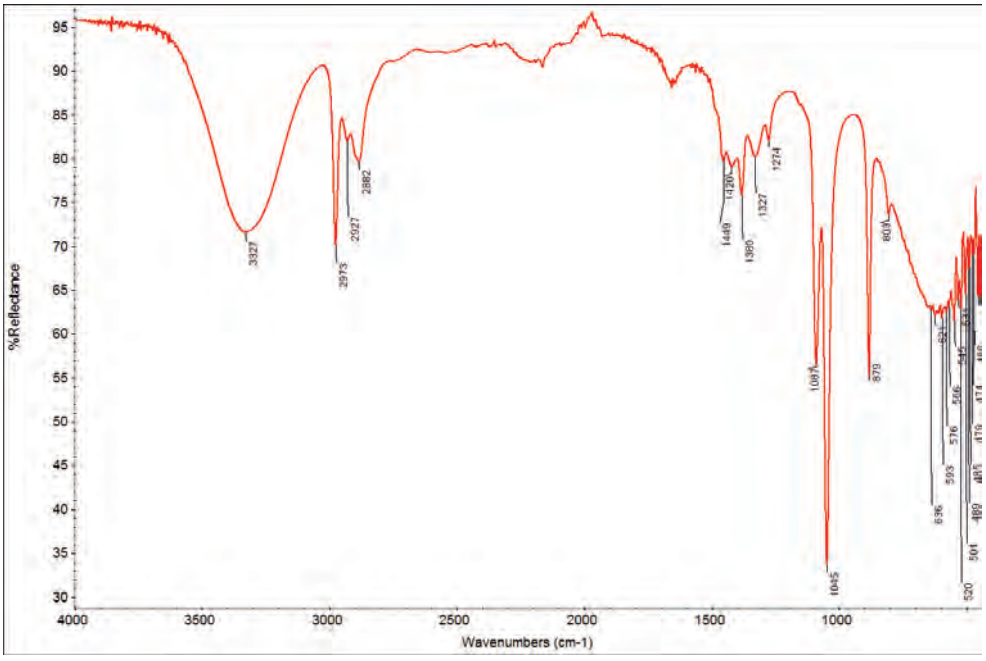
^{13}C- NMR of 5-amino-2,4-dimethoxy-3-methylphenol (9.11c) in $CDCl_3$



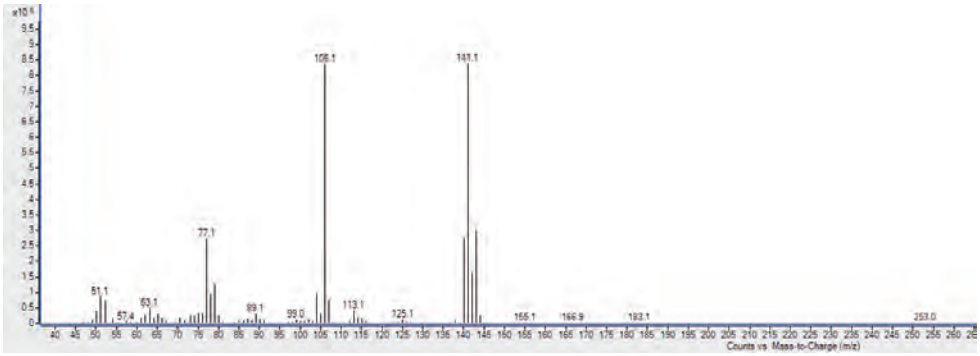
MS (EI) of 5-amino-2,4-dimethoxy-3-methylphenol (9.11c)



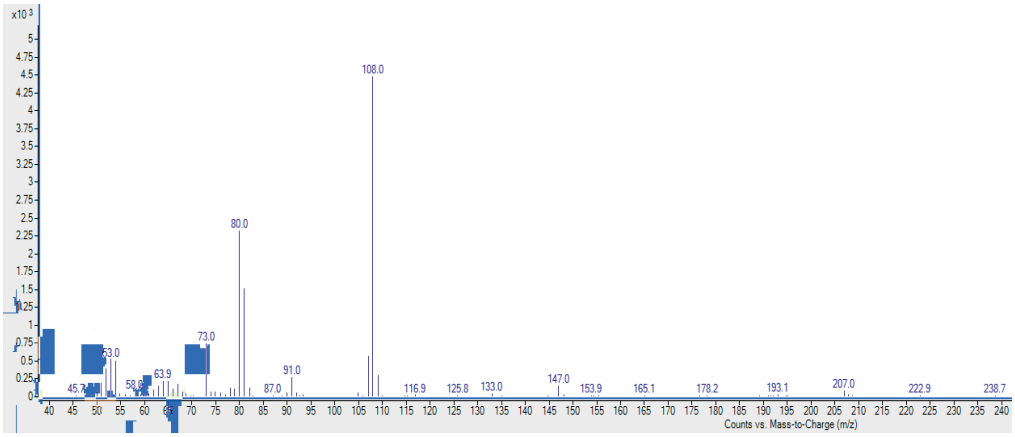
IR of 5-amino-2,4-dimethoxy-3-methylphenol (9.11c)



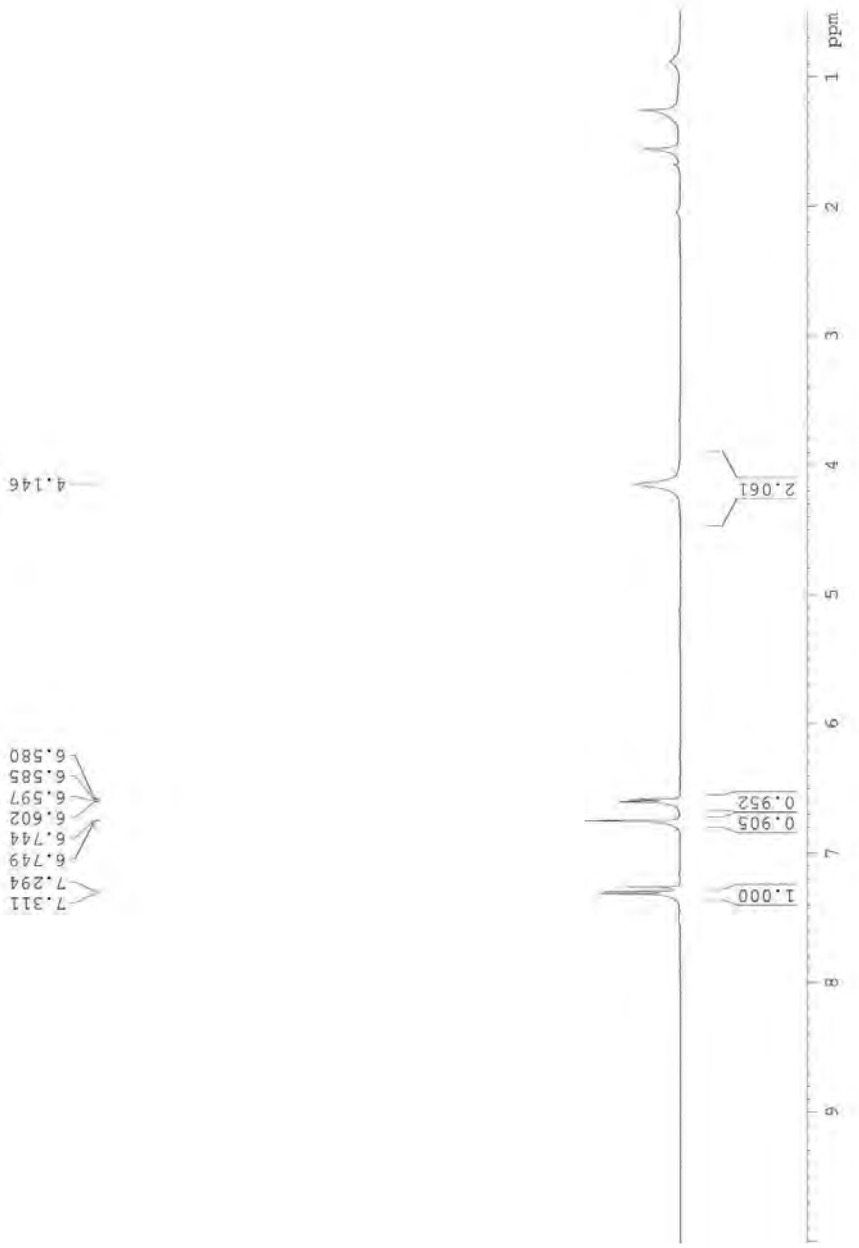
MS (EI) of 2-chloro-5-methylaniline (9.11d)



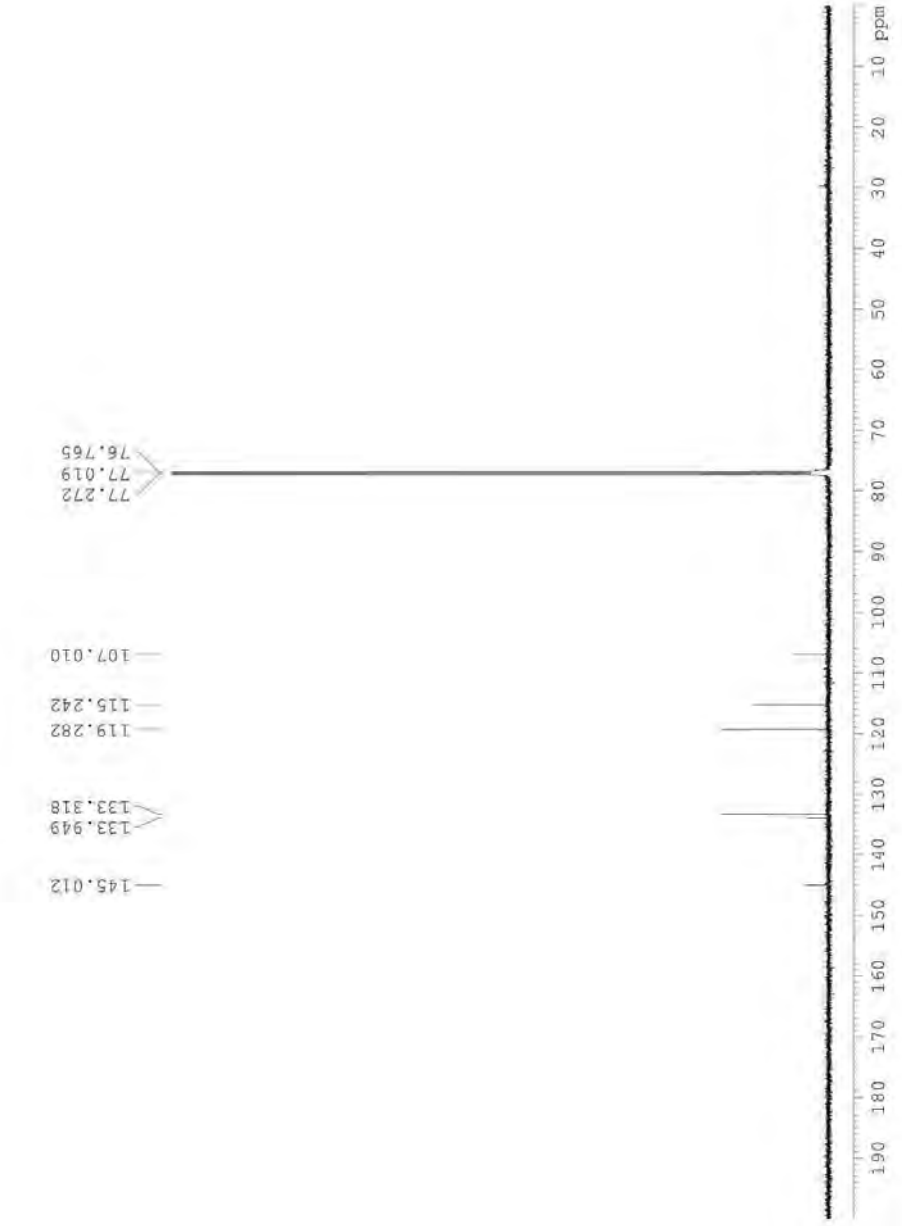
MS (EI) of benzene-1,3-diamine (9.11k)



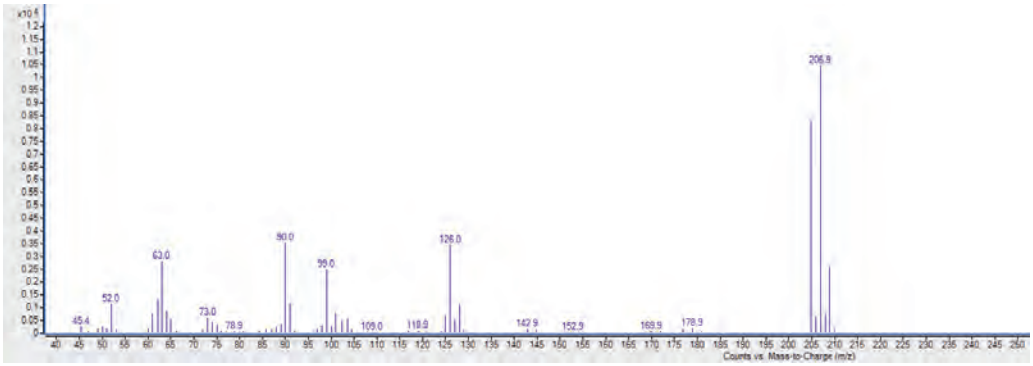
^{1}H-NMR of 2-bromo-5-chloroaniline (9.11e) in $CDCl_3$



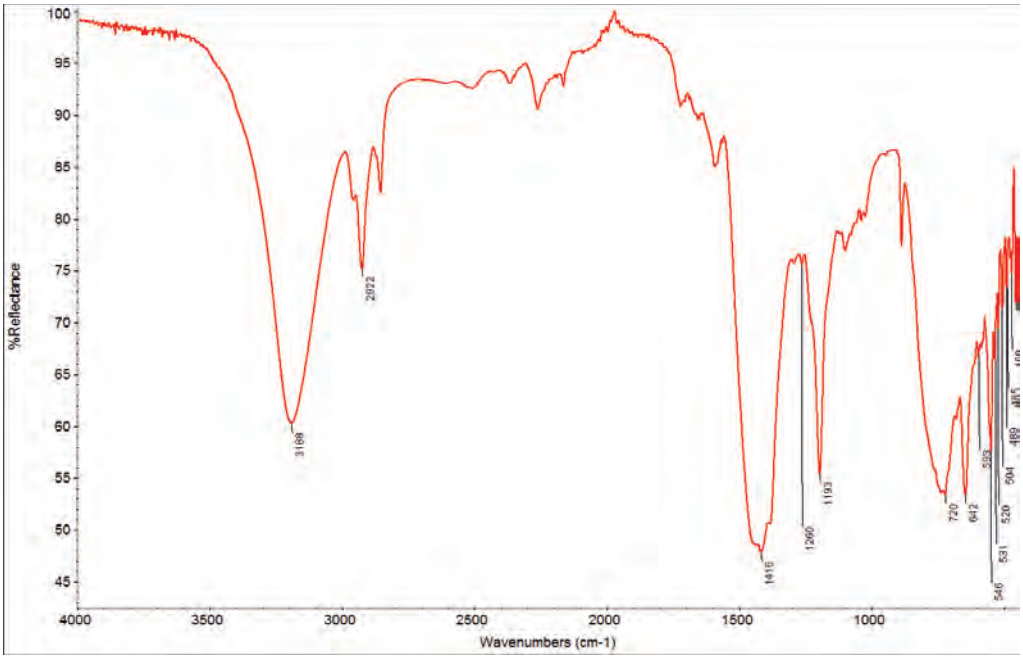
^{13}C-NMR of 2-bromo-5-chloroaniline (9.11e) in $CDCl_3$



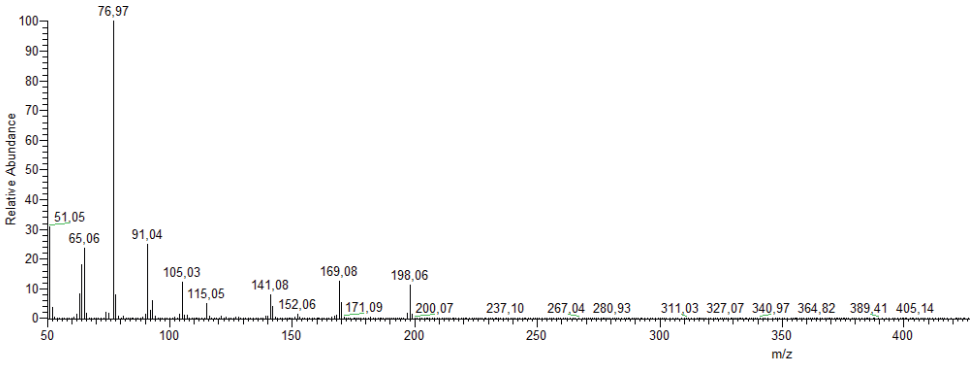
MS (EI) of 2-bromo-5-chloroaniline (9.11e)



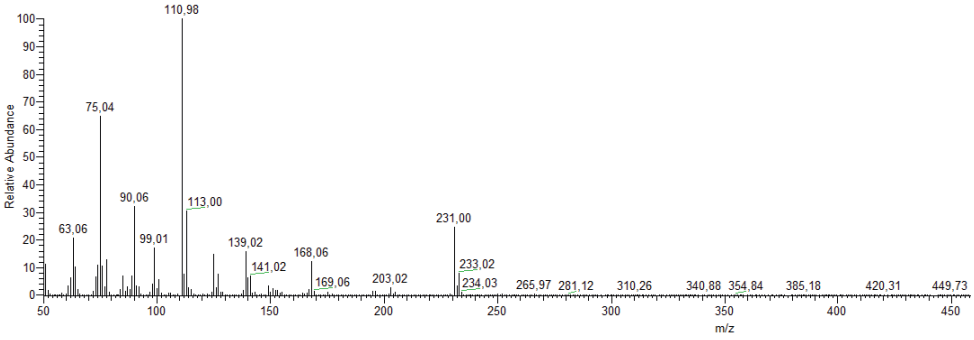
IR of 2-bromo-5-chloroaniline (9.11e)



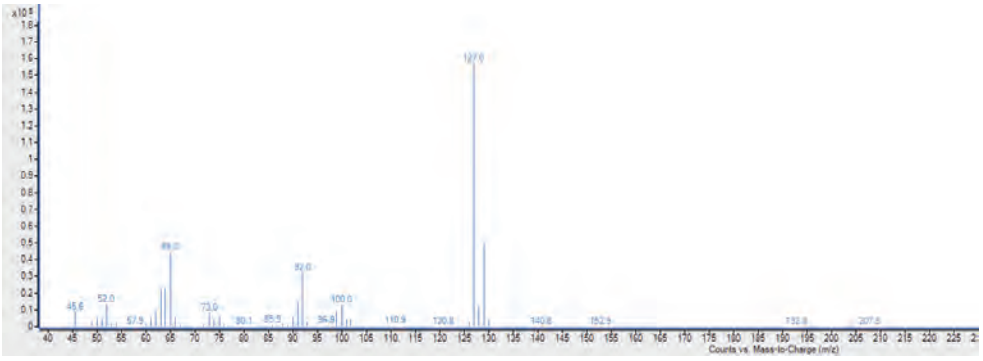
MS (EI) of 1,2-diphenyldiazene 1-oxide (9.11g)



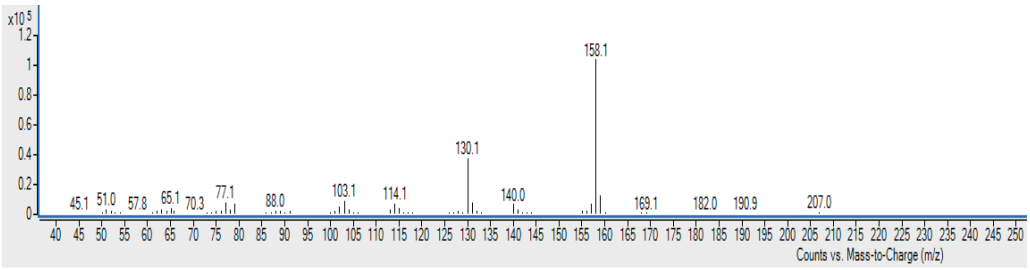
MS (EI) of 1,2-bis(2-chlorophenyl)diazene 1-oxide (9.11h)



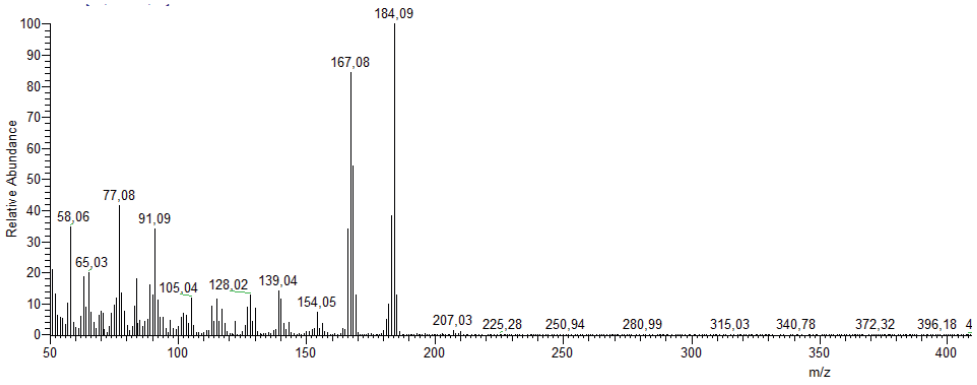
MS (EI) of 2-chloroaniline (9.11f)



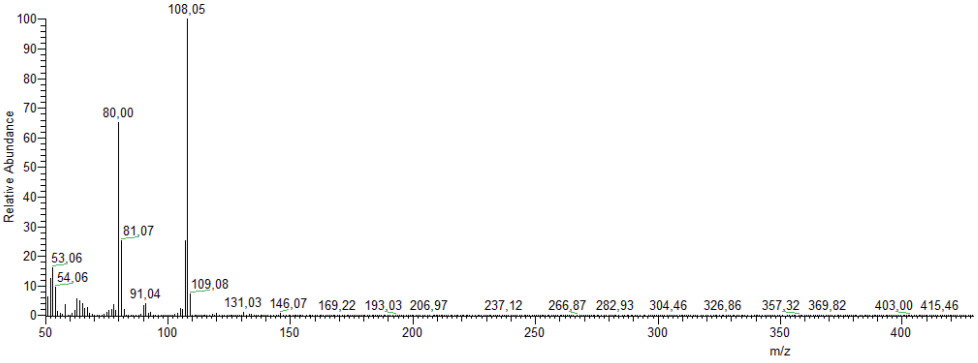
MS (EI) of naphthalene-1,8-diamine (9.11l)



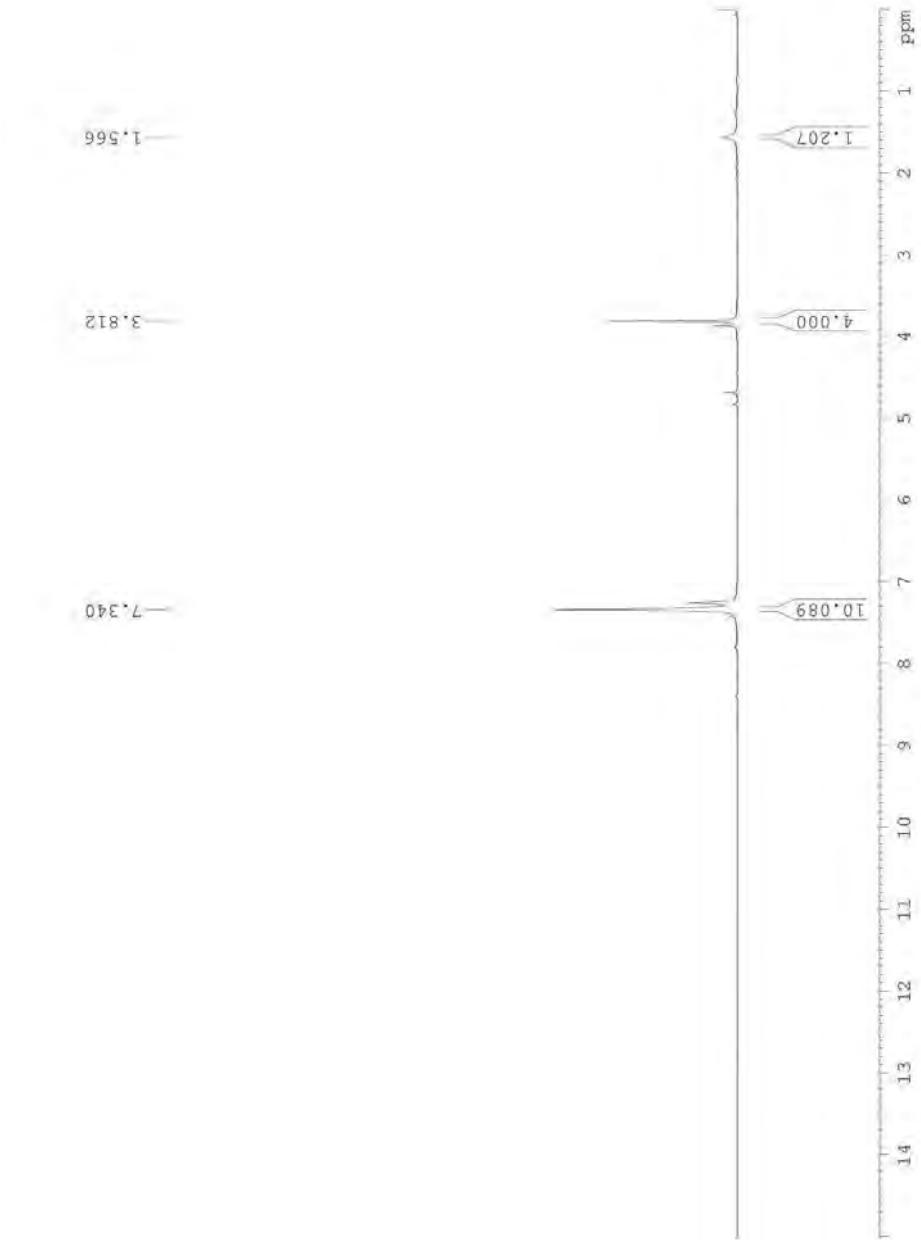
MS (EI) of [1,1'-biphenyl]-2,2'-diamine (9.11i)



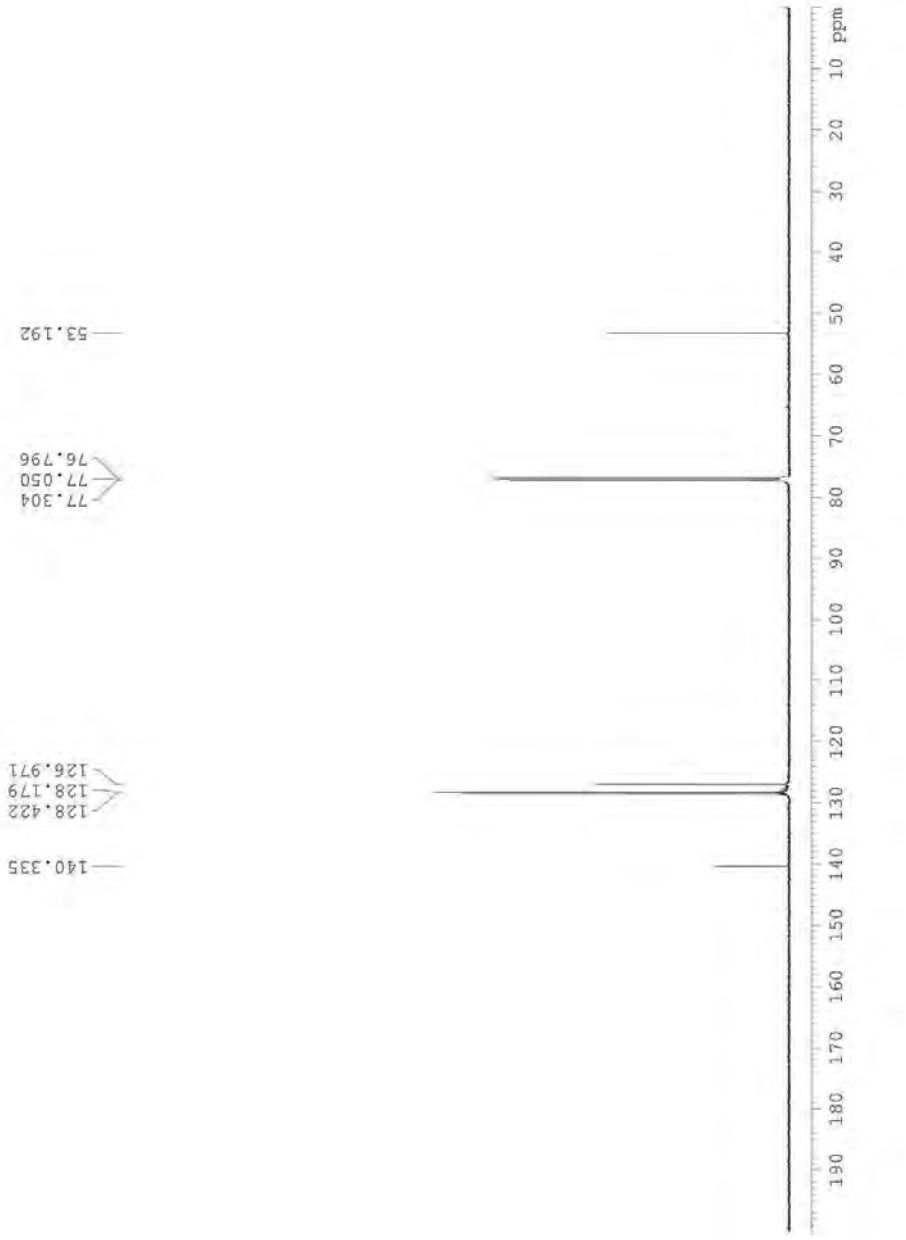
MS (EI) of benzene-1,2-diamine (9.11j)



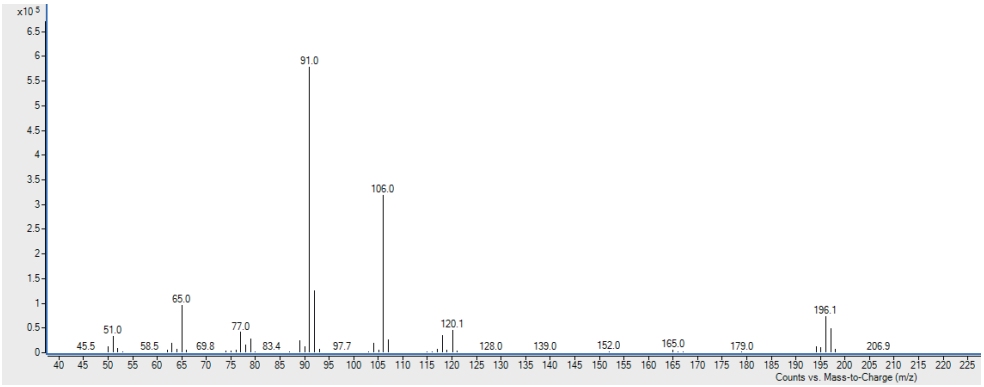
^{1}H-NMR of dibenzylamine (9.11m) in $CDCl_3$



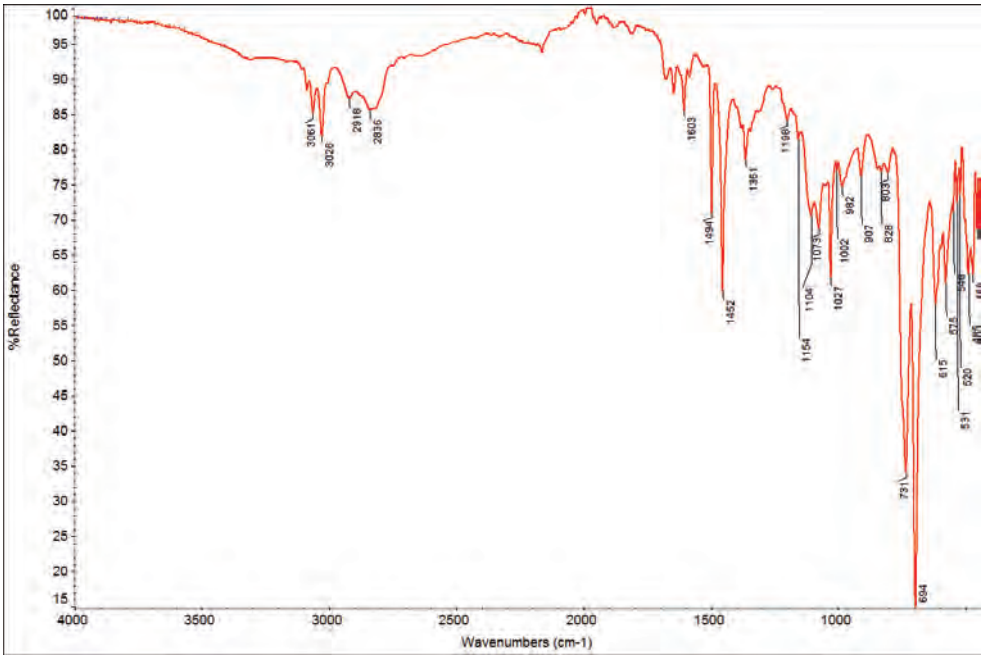
^{13}C-NMR of dibenzylamine (9.11m) in $CDCl_3$



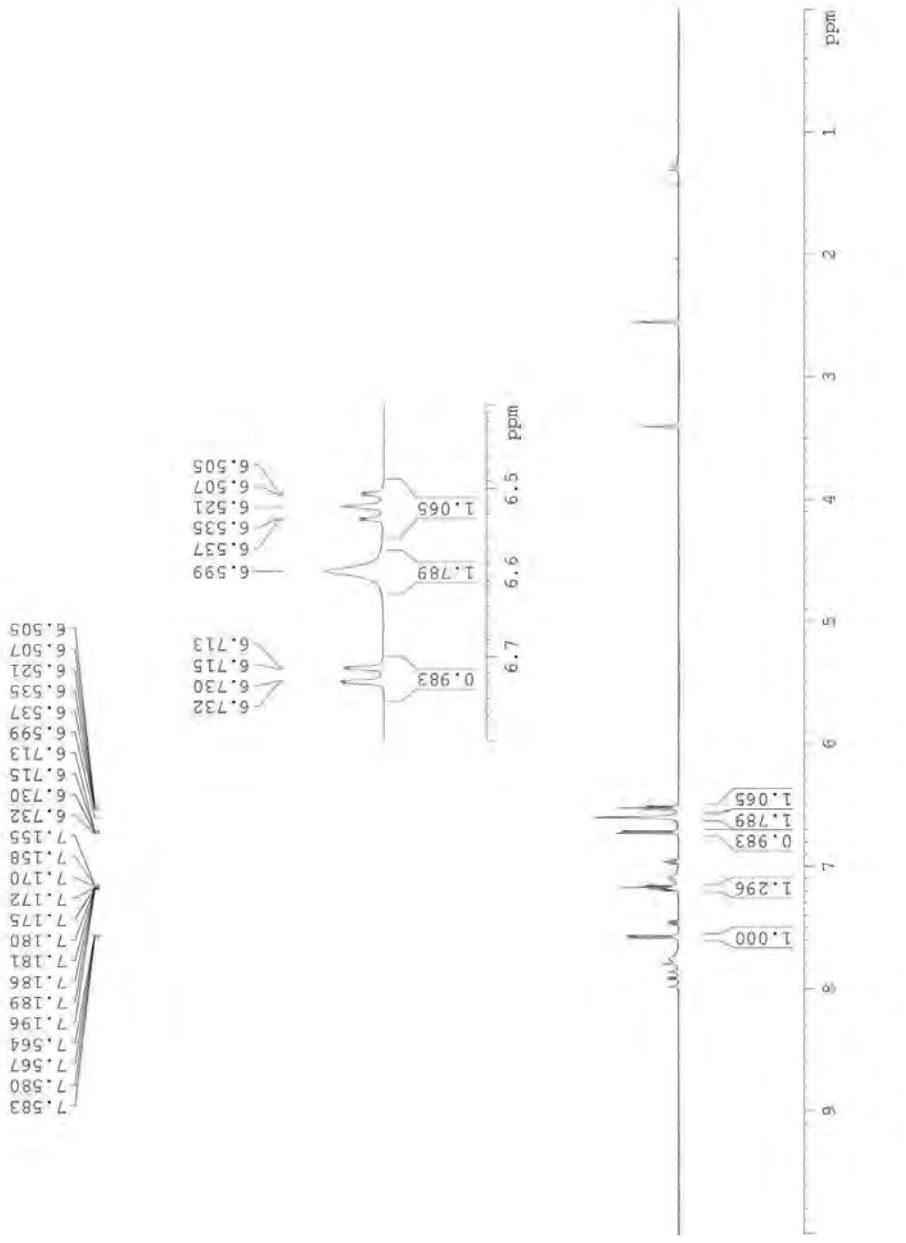
MS (EI) of dibenzylamine (9.11m)



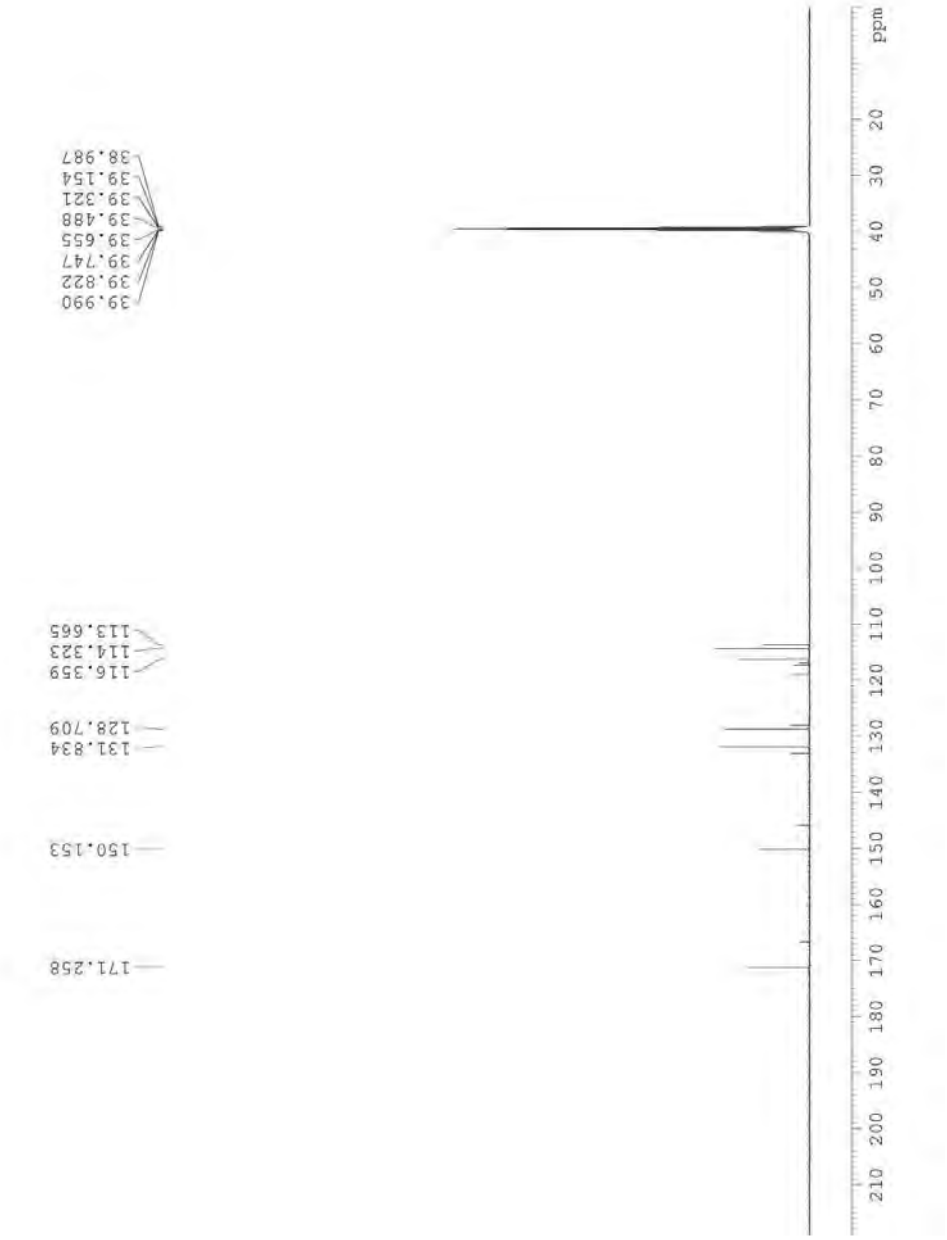
IR (EI) of dibenzylamine (9.11m)



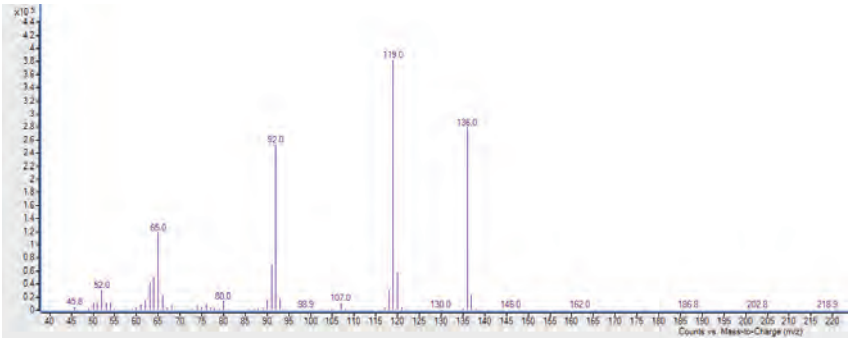
^{1}H-NMR of (2-nitrosophenyl)methanamine (9.11o) in DMSO-d$_6$



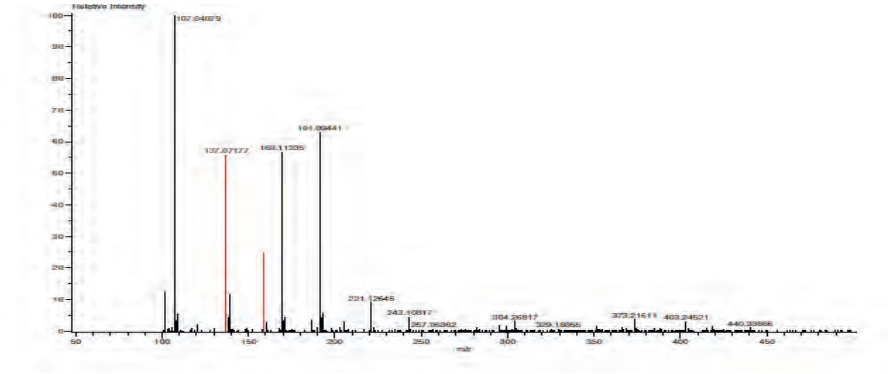
^{13}C-NMR of (2-nitrosophenyl)methanamine (9.11o) in DMSO-d$_6$



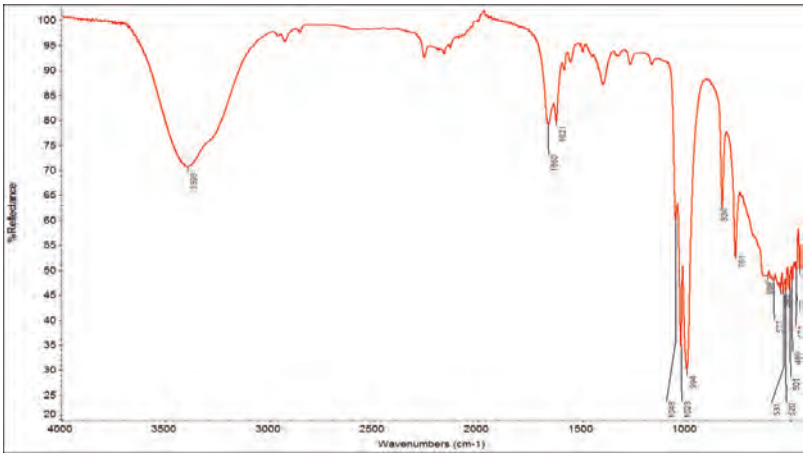
MS (EI) of (2-nitrosophenyl)methanamine (9.11o)



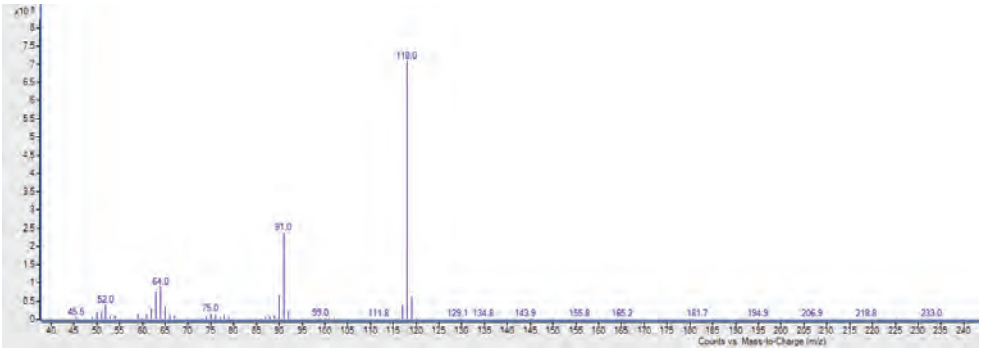
HRMS of (2-nitrosophenyl)methanamine (9.11o)



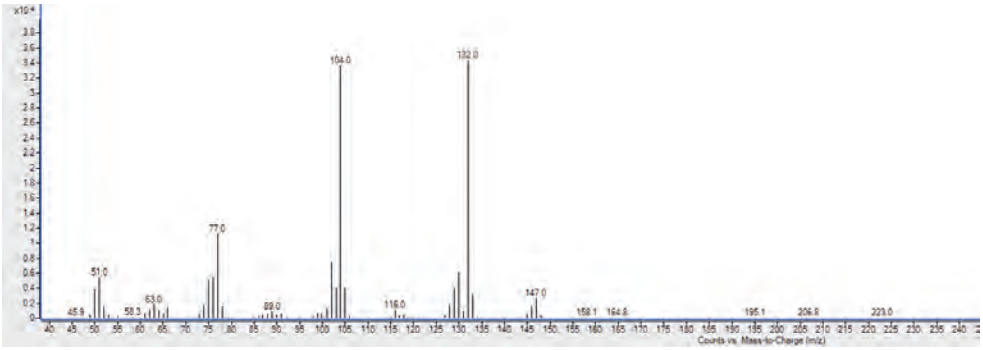
IR of (2-nitrosophenyl)methanamine (9.11o)



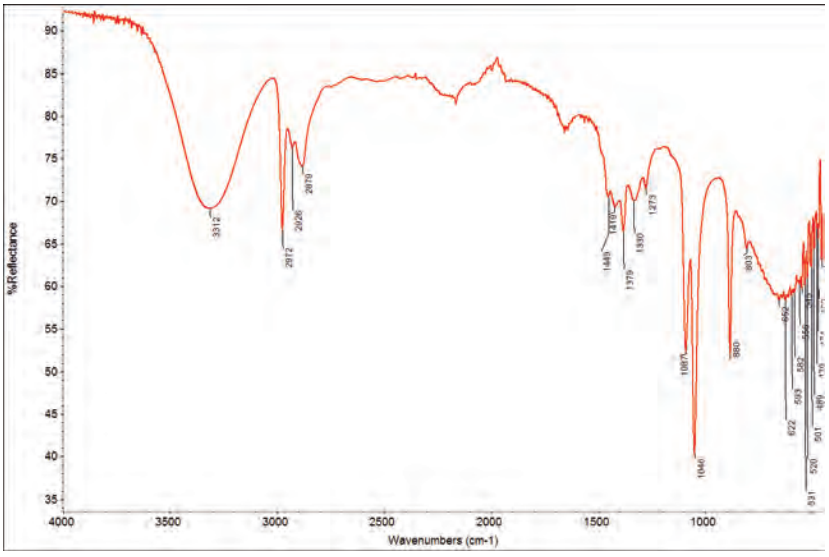
MS (EI) of 4-aminobenzonitrile (9.11q)



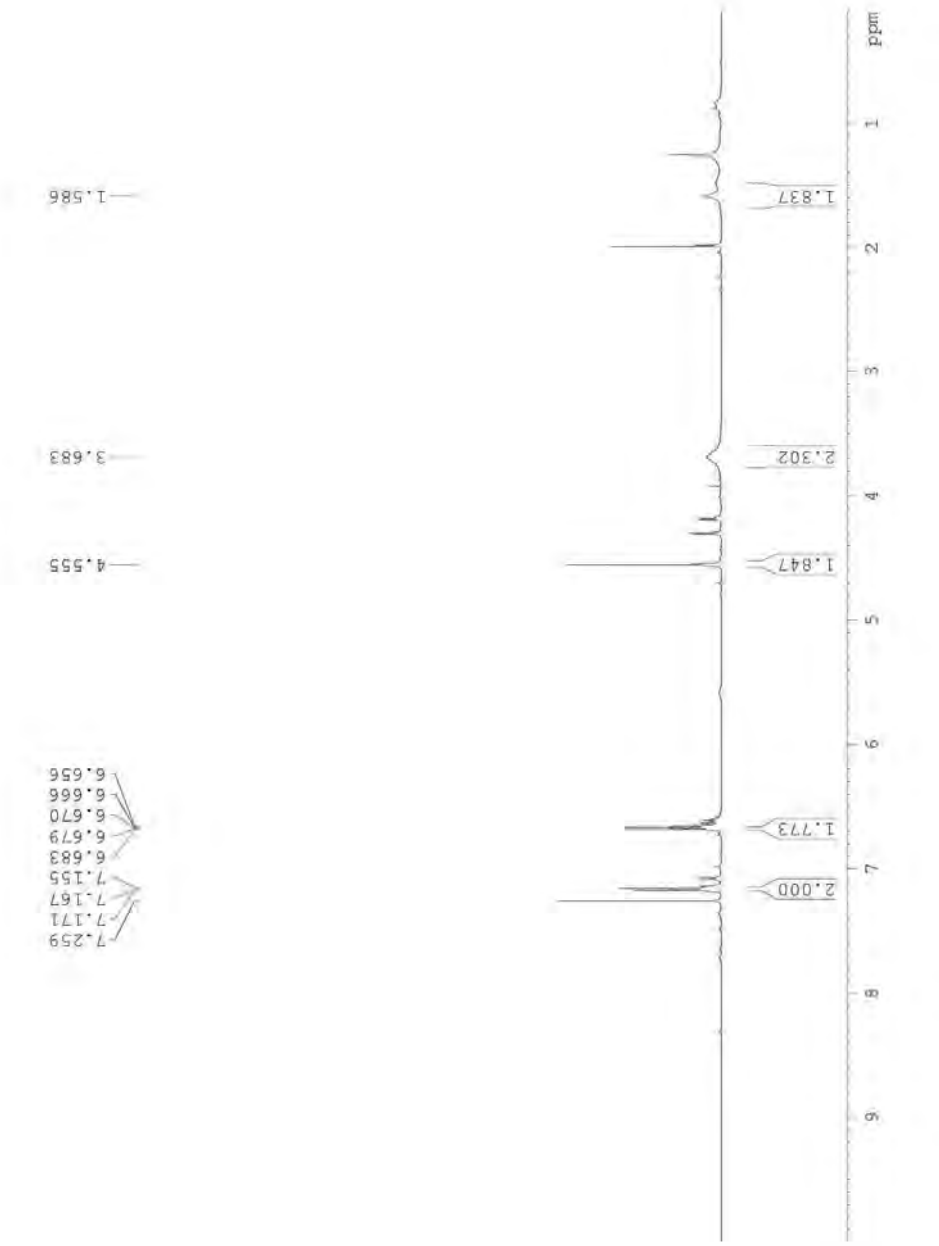
MS (EI) 4-(1-hydroxyethyl)benzonitrile (9.11r)



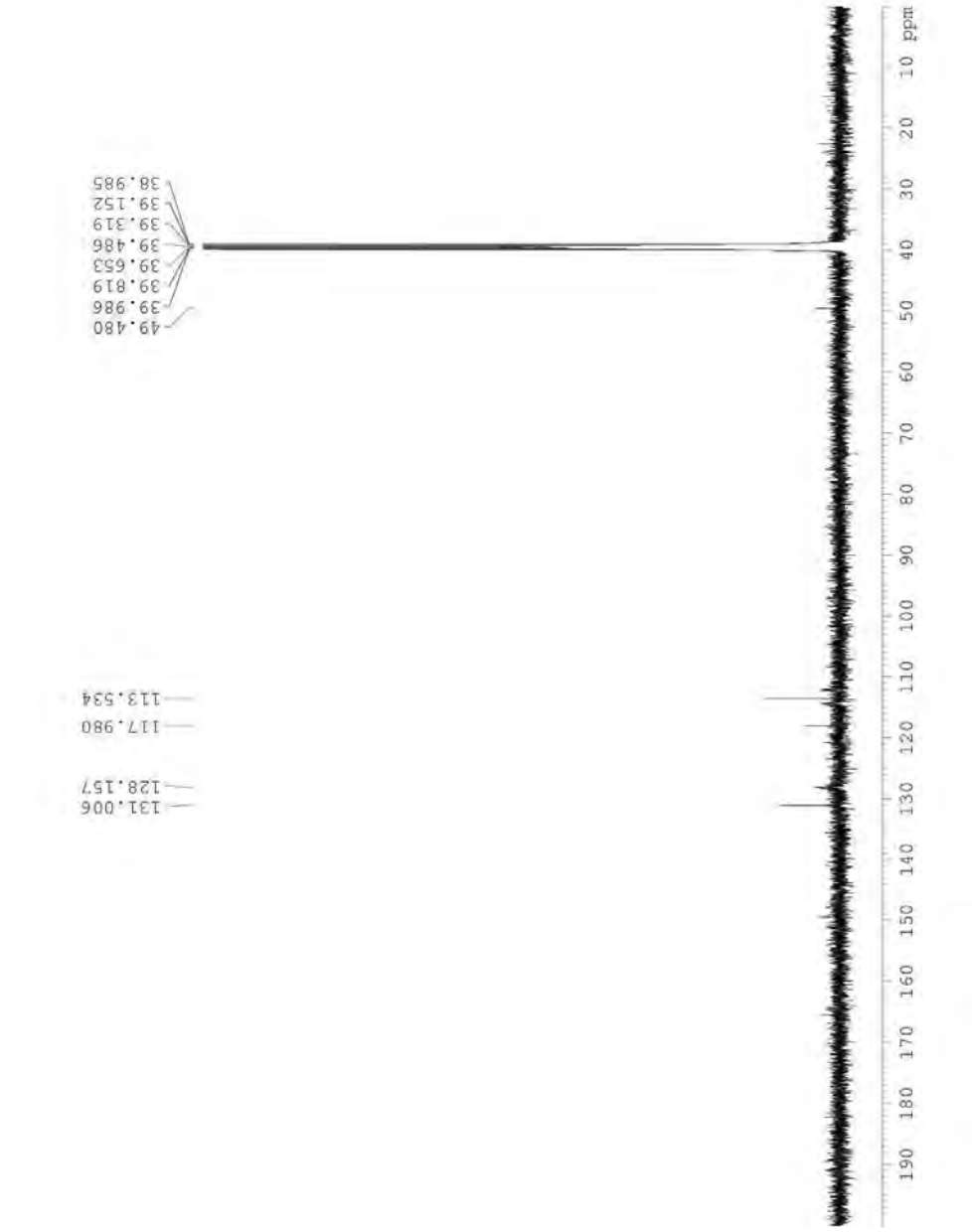
IR 4-(1-hydroxyethyl)benzonitrile (9.11r)



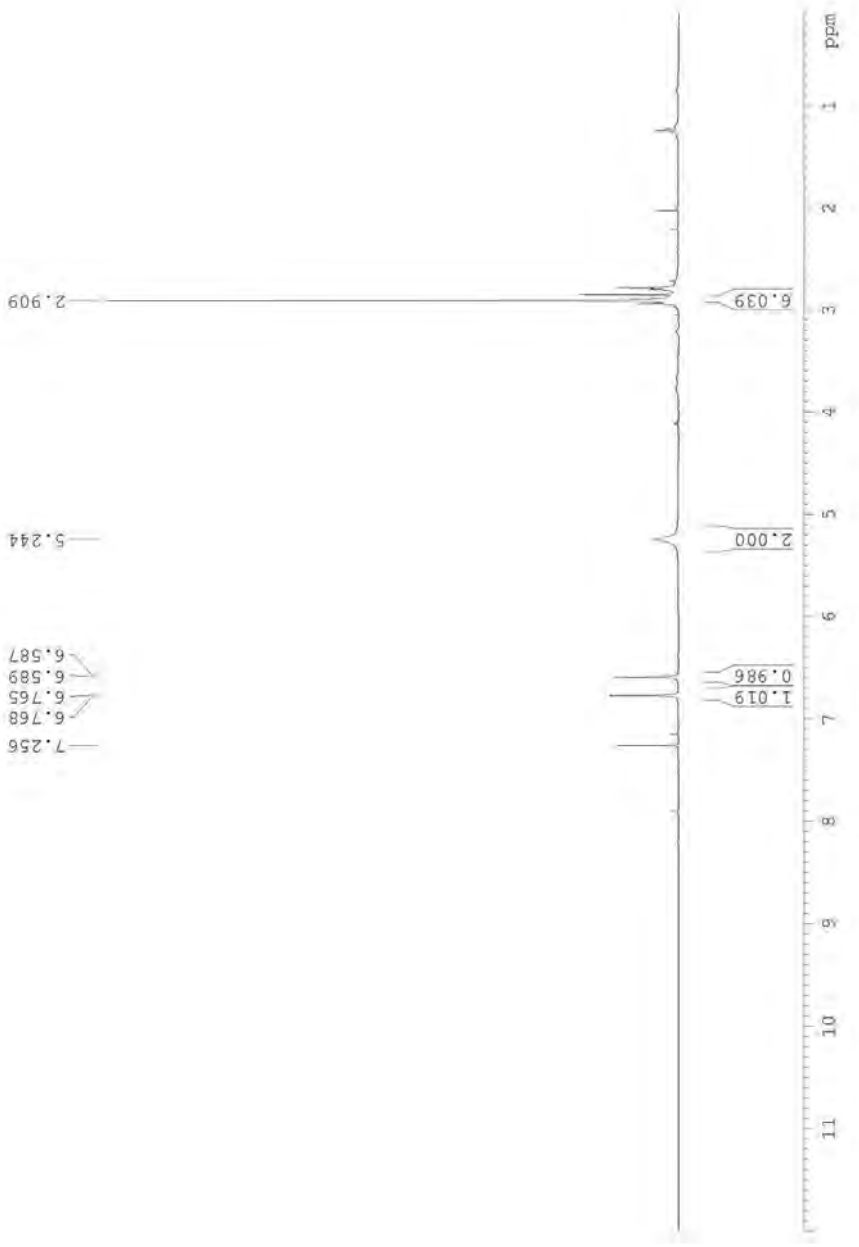
^{1}H-NMR of 4-(aminomethyl)aniline (9.11s) in $CDCl_3$



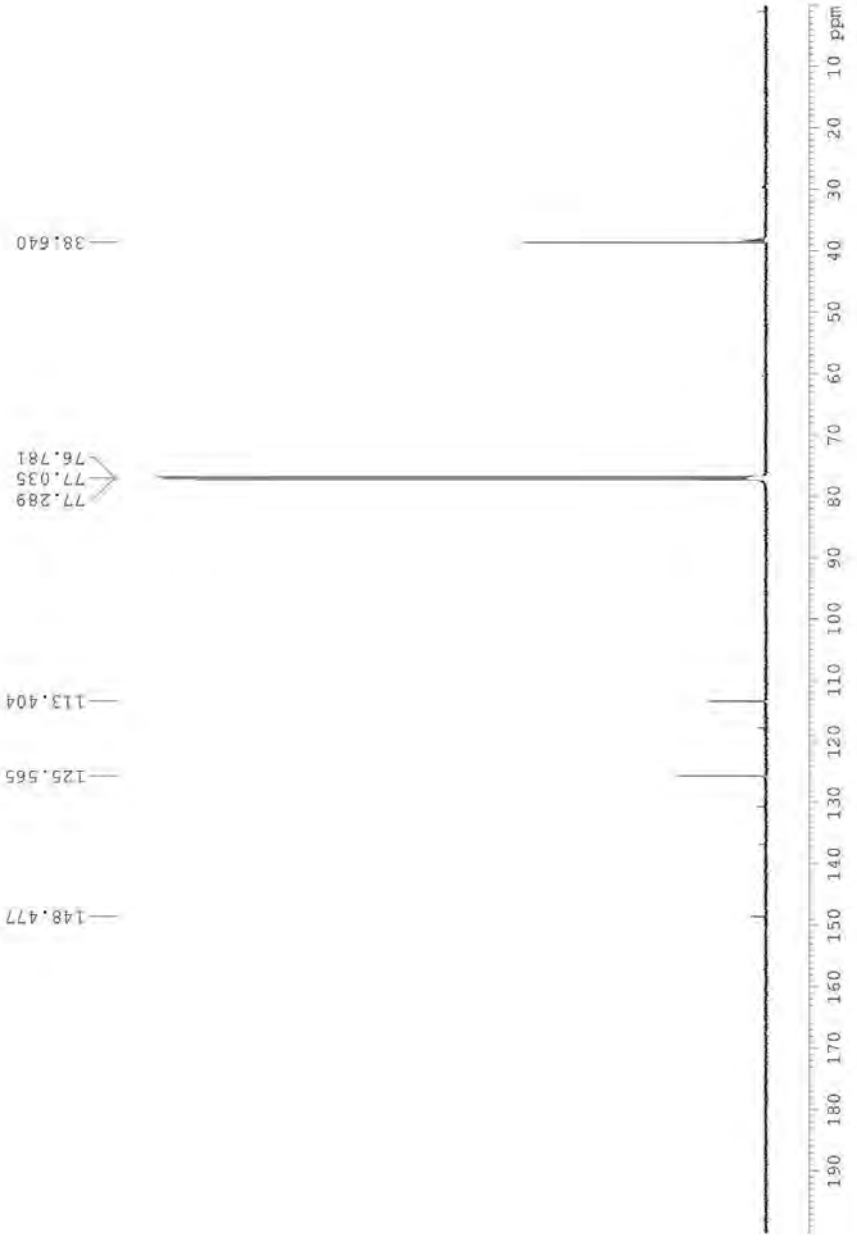
^{13}C-NMR of 4-(aminomethyl)aniline (9.11s) in DMSO-d$_6$



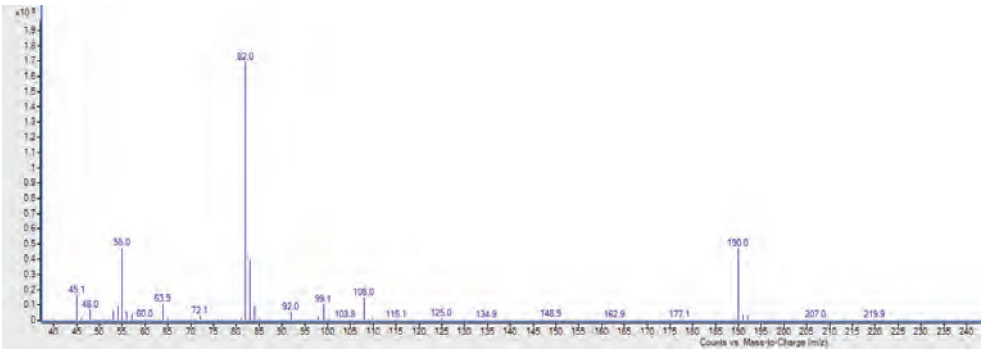
^{1}H-NMR of 2-amino-N,N-dimethyl-1H-imidazole-1-sulfonamide (9.11t) in $CDCl_3$



^{13}C-NMR of 2-amino-N,N-dimethyl-1H-imidazole-1-sulfonamide (9.11t) in $CDCl_3$



MS (EI) of 2-amino-N,N-dimethyl-1H-imidazole-1-sulfonamide (9.11t)



IR of 2-amino-N,N-dimethyl-1H-imidazole-1-sulfonamide (9.11t)