CONSTRUCTION OF PYRROLO[1,2-*a*]PYRAZINE STRUCTURE BY METAL CATALYZED CYCLIZATION OF *N*-PROPARGYL SUBSTITUTED PYRROLES

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Approval of the thesis:

CONSTRUCTION OF PYRROLO[1,2-*a*]PYRAZINE STRUCTURE BY METAL CATALYZED CYCLIZATION OF *N*-PROPARGYL SUBSTITUTED PYRROLES

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

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February 2013, 95 pages

Pyrrolo[1,2-*a*]pyrazine is one of the isomers of pyrolodiazine family. Pyrrolo[1,2-*a*]pyrazine possesses a bicyclic heteroaromatic structure that have 10 electrons. It has various biological importances in synthetic chemistry; therefore, many different approaches to generate this skeleton have been developed so far. In this study, our prior aim was to develop a new synthetic methodology for the formation of pyrrolo[1,2-*a*]pyrazine moiety. In the first part of this focus, the starting compound, methyl 2-(2-methoxy-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate was successfully synthesized, then the conversion of the ester group at the lower arm to the amine group was carried out. Heteroatom cyclization catalyzed by CuI afforded the desired substituted pyrrolo[1,2-*a*]pyrazine structure. In the second part, it was aimed to synthesize new compounds with unusual structures which are not described in the literature; namely, as pyrrolo[1,2-*a*]pyrazine *N*-oxide. In this direction, first pyrrole was submitted to Vilsmeier-Haack reaction to attach a formyl group at C-2. Substitution reaction then effectively gave 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde, which was a key molecule to synthesize the aldoxime. $AuCl_3$ catalyzed cyclization of the corresponding oxime afforded pyrrolo[1,2-*a*]pyrazine *N*-oxide. In the next step, Sonogashira coupling reactions were carried out to obtain terminal alkynes (RC≡CR') starting from 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde. The aim of this part was to study the effect of aryl groups to the activated alkyl functional group by a metal catalyst. In this case, unexpected oxime-oxime transformation was observed, which is unprecedented in the literature.

Keywords: Pyrrolodiazine, pyrrolo[1,2-*a*]pyrazine, pyrrolo[1,2-*a*]pyrazine *N*-oxide, oxime-oxime transformation.

ÖZ

METAL KATALİZÖRLER EŞLİĞİNDE *N*-PROPARGİL SÜBSTİTÜE PİROL TÜREVLERİNİN HALKALAŞMASI SONUCUNDA PİROLO[1,2-*a*]PİRAZİN İSKELETİNİN OLUŞUMU

GÜVEN, Sinem
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Şubat 2013, 95 sayfa

Pirolodiazin ailesinin üyelerinden biri olan pirolo[1,2-*a*]pirazin bisiklik aromatik bir bileşiktir. Bazı önemli biyolojik özellik göstermeleri nedeniyle uzun yıllardır bu iskeletin oluşumu için farklı sentetik metotlar geliştirilmektedir. Bu çalışmada hedeflenen temel nokta pirolo[1,2-*a*]pirazin halkasının oluşumu için yeni bir yöntem geliştirmektir. Çalışmanın ilk kısmında, çıkış maddesi olan *N*-sübsütie 2,3-dikarboksilat pirolü başarıyla sentezlendikten sonra alt koldaki ester fonksiyonel grubu amin grubuna dönüştürüldü. Ardından CuI katalizörü eşliğinde aktive olmuş üçlü bağdaki karbon atomuna, azot atomunun molekül içi saldırısı sonucunda hedeflenen yapı sentezlendi. Çalışmanın ikinci kısmında ise literatürde henüz bilinmeyen pirolo[1,2-*a*]pirazin *N*-oksit halkasının oluşturulması hedeflenmiştir. Bu nedenle pirolden başlayarak Vilsmeier-Haack reaksiyonu sonucunda pirolun C-2 karbon atomuna formil grubu takıldı, propargil bromür eşliğinde sübstitüsyon reaksiyonu gerçekleştirildi ve anahtar molekül olan azot atomuna propargil grubu bağlı pirol-2-karboksialdehit sentezlendi. Hemen ardından aldoksim türevi başarıyla elde edildi ve sentezlenen aldoksimin $AuCl_3$ katalizörü eşliğindeki reaksiyonu sonucunda pirolo[1,2-*a*]pirazin *N*-oksit yapısı etkili ve basit bir yöntemle sentezlendi. Böylelikle literature yeni bir heterosiklik *N*-oksit molekülü kazandırıldı. Ardından, propargil grubuna Sonogashira kenetlenme reaksiyonuyla farklı aril grupları takıldı ve aldoksim olusturuldu. $AuCl_3$ katalizörlüğünde gerçekleşen halkalaşma reaksiyonu sonucunda beklenen ürünün aksine, oksim-oksim düzenlenmesi sonucu farklı bir oksim ürünü elde edildi. Literatüre yeni bir düzenlenme tepkimesi kazandırıldı.

Anahtar kelimeler: Pirolodiazine, pirolo[1,2-*a*]pirazin, pirolo[1,2-*a*]pirazin *N*-oksit, oksim-oksim değişimi.

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No hell below us
above us only sky

John Lennon

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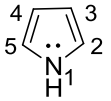
CHAPTER 1

INTRODUCTION

1.1 Pyrrole

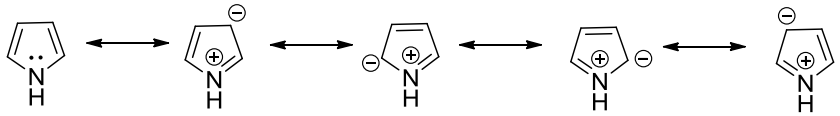
1.1.1 General Properties of Pyrrole

Pyrrole (**1**) is a five-membered heterocyclic molecule that contains sp^2 hybridized nitrogen atom. Highly privileged pyrrole molecule possesses aromaticity; six π-electrons can delocalize around each empty p orbital of each atom, all of which are definitely coplanar. The nonbonding electrons participate to the delocalization; thus, weak acid behavior of pyrrole ring can be explained by its aromatic character.



Pyrrole
1

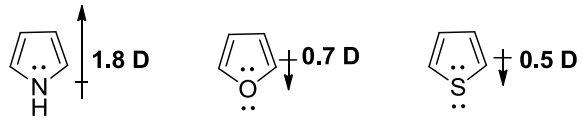
The carbon-carbon bond and the carbon-nitrogen bond distances do not show typical characteristics of single bonds or double bonds.[1] Therefore, pyrrole must be regarded with the hybrid resonance structures (**1-1d**) of which major contributors are shown below (Scheme 1).



1 **1a** **1b** **1c** **1d**

Scheme 1

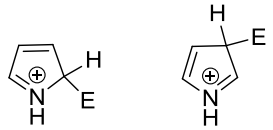
The dipole moment of the pyrrole ring is 1.80 D in benzene solution and the positive end of the dipole is directed toward the nitrogen atom[1]; on the other hand, in the case of furan (**2**) and thiophene (**3**), these heteroaromatic molecules have much more lower dipole moments in the opposite direction than the dipole moment of pyrrole, 0.7 D and 0.5 D respectively (Scheme 2).[2]



Pyrrole **1** Furan **2** Thiophene **3**

Scheme 2

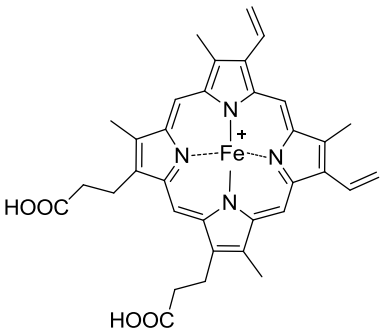
The orientation of the electrophilic substitution reaction in pyrrole ring is more selective by forming intermediate A than intermediate B since the positive charge on nitrogen atom can delocalize more in intermediate A than the case of B. However, this pattern could change depending upon the substituents on the pyrrole ring (Scheme 3).[3]



A **B**

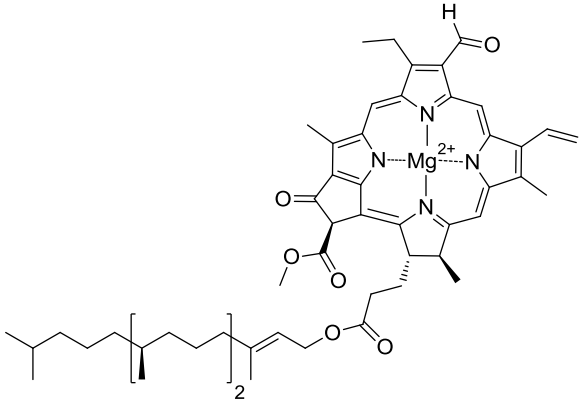
Scheme 3

Pyrrole rings are found in porphyrins that involve the vital blood pigments e.g. heme B (**4**), in which four substituted pyrrole rings are connected to each other with four methine groups and Fe^{+} substitutes two –NH group to form complex molecule, and also the essential pigment chlorophyll has porphyrin unit itself e.g. chlorophyll b (**5**).[4]



Heme B

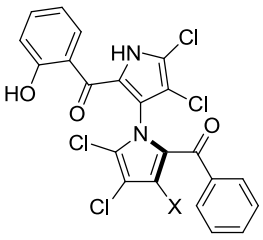
4



Chlorophyll b

5

Furthermore some natural products containing pyrrole moiety display various biological activities; Hughes and his coworkers isolated a bispyrrole compound, named as Marinopyrroles A and B (**6**) for the first time despite its synthesis as well as other examples of chiral bispyrroles were known in the literature. These axially chiral molecules show activity against metacillin-resistant *Staphylococcus Aureus* stains.[5] Permethyl Storniamide (**7**), isolated from some marine species, has sensitizing property of antitumor agents in those cases of multidrug resistance (MDR) according to Boger and his collobrators' study.[6] The importance of pyrrole skeleton in material sciences is also prominent. 4,4-Difluoro-4-boradipyrrin units (**8**), known as BODIPY, possessing various biological and electrochemical applications.[7]



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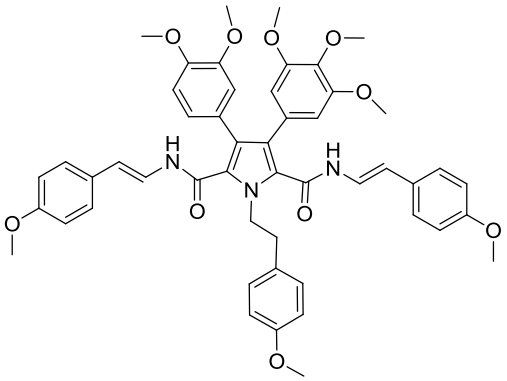

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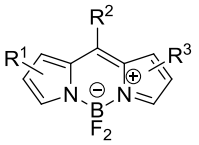
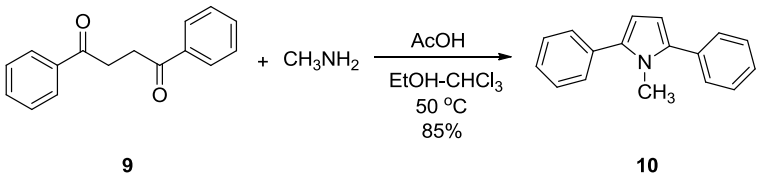


8

Due to its fundamental significance in chemistry, a number of efficient synthetic approaches have been developed.

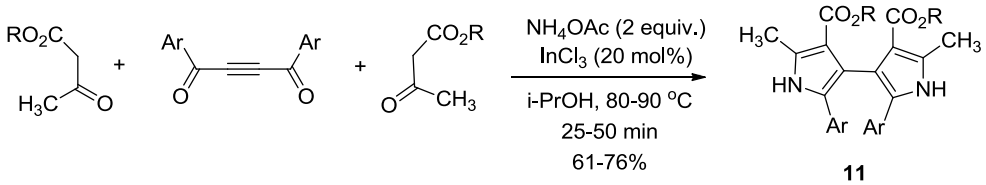
1.1.2 Pyrrole Synthesis

In 1884, Paal and Knorr separately reported a condensation reaction between 1,4-dicarbonyl compounds with excess primary amines or ammonia to yield substituted pyrroles. When γ-diketone **9** was treated with methyl amine, 2,5-disubsituted pyrrole **10** was formed successfully (Scheme 4). However, the pH of the reaction affects the product formation as Amarnath *et al*.[8] showed. When the pH was below 3, the furan ring was formed as a major product. Axially chiral 3,3- bispyrrole dervatives **11** formation also can be achieved by Michael addition cascaded with Paal- Knorr type condensation (Scheme 5).[9]



9 **10**

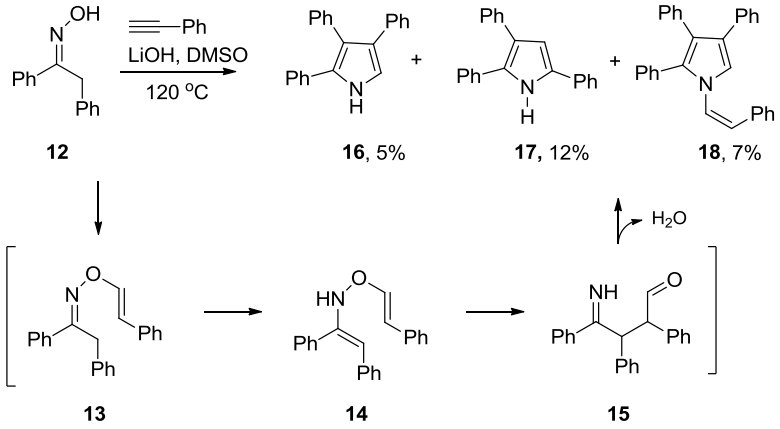
Scheme 4



11

Scheme 5

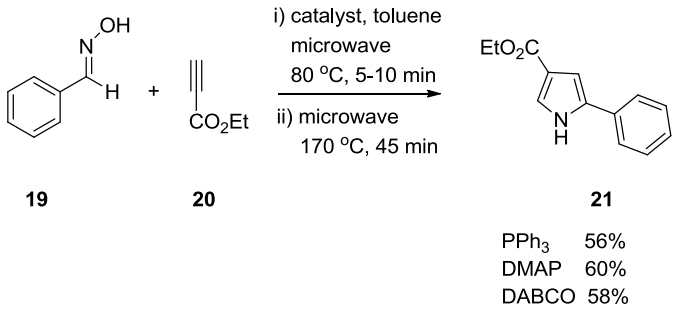
Trofimov reaction is another route for the synthesis of pyrroles. Under the quite strong alkali conditions, ketoxime **12** reacts with acetylene to give vinyl oxime **13** then subsequently vinyl oxime **13** tautomerizes to diene **14** which undergoes a sigmatropic rearrangement to form corresponding imine **15** (Scheme 6). Intramolecular cyclization affords substituted pyrroles **16**, **17**, **18**. Trofimov reaction offers an easy route to generate aryl, alkyl, hetaryl substituted pyrroles (Scheme 5). However harsh reaction conditions resulted in the formation of regioisomers and disfavored Trofimov Reaction. Therefore, Ngwerume and Camp provided a regioselective milder reaction conditions under microwave assisted nucleophilic catalysis as a modified Trofimov reaction (Scheme 7).[10]



12 **16**, 5% **17,** 12% **18**, 7%

13 **14** **15**

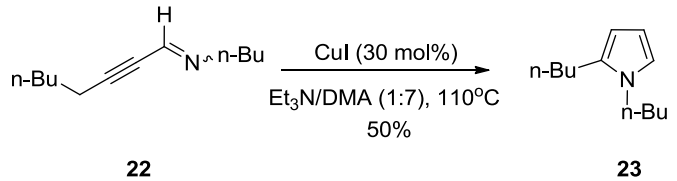
Scheme 6



19 **20** **21**

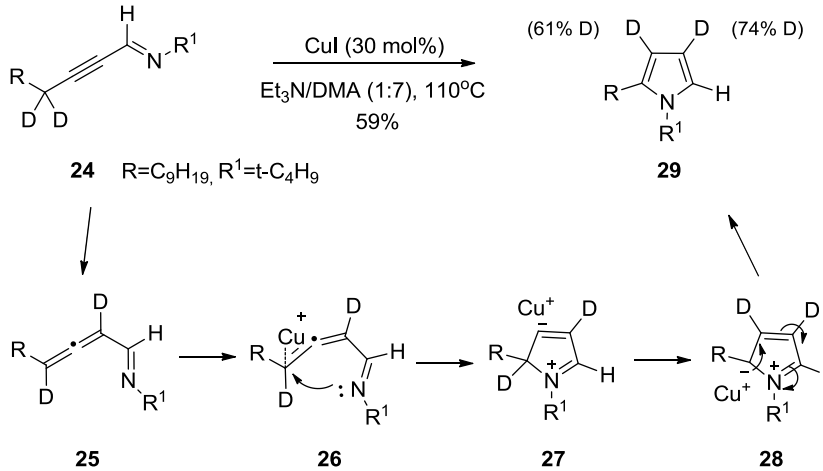
Scheme 7

Alkynes are frequently found as a key functional group in a series of construction of pyrrole skeleton. One or one of the most crucial methodologies for it was reported in 2001. It included a Cu-(I) assisted heteroatom cyclization of alkynyl imines to generate 2-substituted or 2,5-disubstituted pyrrole fused heteroaromatic molecules (Scheme 8).[11] One of the acidic protons of alkynyl imines was abstracted by NEt_3 which was then subjected to propargyl-allenyl isomerization to generate allene **25** in situ as Kel'in and his collaborators proposed.[11] Subsequent to the coordination of Cu-(I) to the terminal double bond creating an electrophilic carbon, nucleophilic attack by non-bonding electrons on nitrogen atom occurred to that carbon to generate zwitter ion intermediate **27**. Isomerization to the more stable zwitter ion intermediate **28** gave the product **29** successfully (Scheme 9). Deuterium shift during propargyl-allenyl isomerization strengthened the group's theory on the reaction mechanism.



22 **23**

Scheme 8

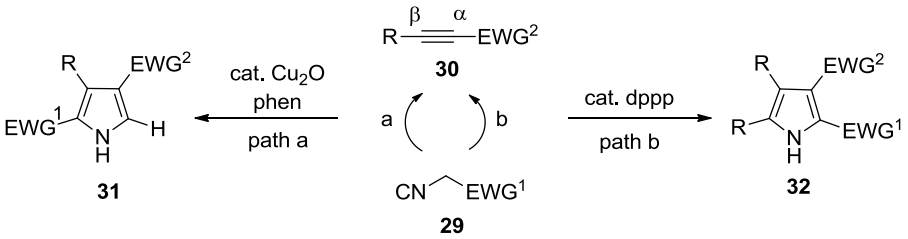


24 R=C_9H_{19}, R^1=t-C_4H_9 **29**

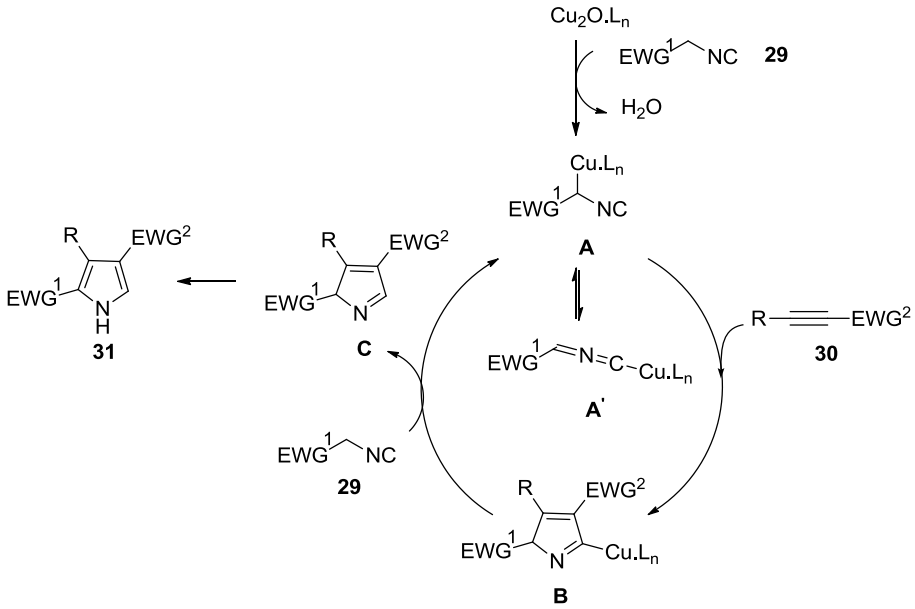
25 **26** **27** **28**

Scheme 9

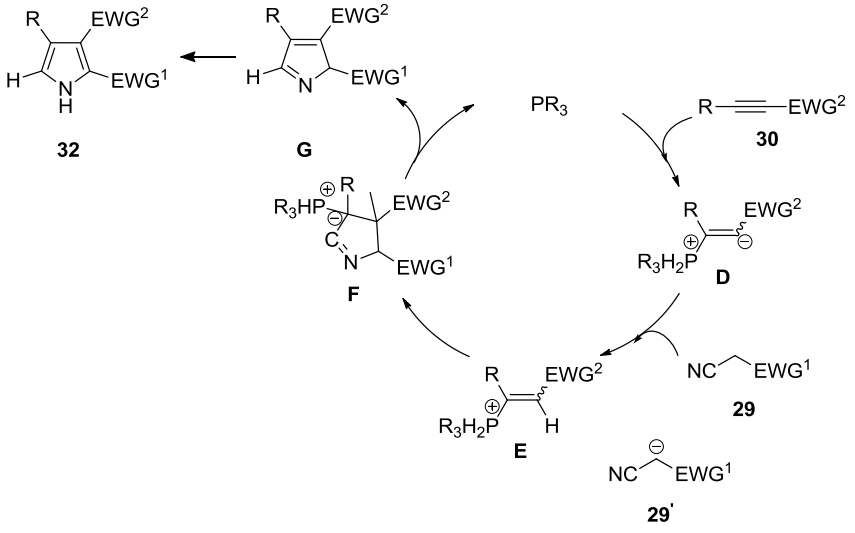
The number of studies on synthesizing pyrrole ring starting from alkynes is very broad and there are so many different approaches present in the literature. Another method on this area was represented by Kamijo, Kanazawa and Yamamoto.[12] They indicated that regioselectivity of the product depends on the catalyst used. (Scheme 10) If the reaction between isocyanate **29** and activated alkyne **30** are catalyzed by Cu_2O (Scheme 11), it yields 2,4-substituted pyrrole **31**; on the other hand, if phosphine catalyzes this reaction, the formation of 2,3-disubstituted product **32** occurs (Scheme 12).



Scheme 10



Scheme 11

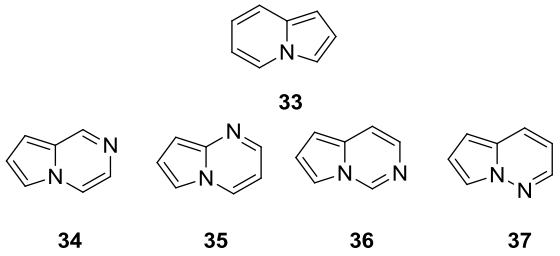


Scheme 12

1.2 Pyrrolodiazine

Pyrrolodiazine is a class of pyrrole fused heteroaromatic molecules. They are also aza analogous of indolizine (**33**) moiety. The four isomers of pyrrolodiazines are known in the literature, namely as pyrrolo[1,2-*a*]pyrazine (**34**), pyrrolo [1,2-*a*]pyrimidine (**35**), pyrrolo[1,2-*c*]pyrimidine (**36**) and

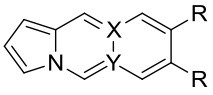
pyrrolo [1,2-*b*]pyridazine (**37**).[13] The nonbonding electrons on the pyrrole type nitrogen atom make contribution to the total number of π electrons of the aromatic system (Scheme 13).



33 **34** **35** **36** **37**

Scheme 13

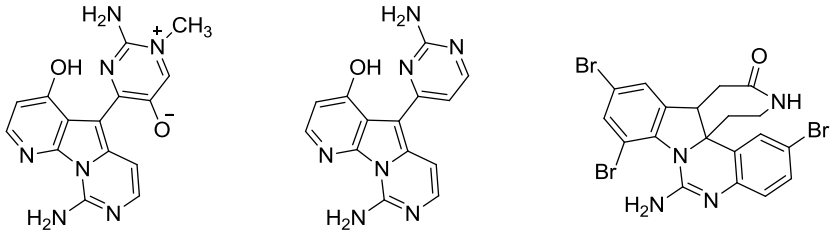
Pyrrolodiazines are the precursors for the synthesis of DNA intercalating agents.[14] Molecules **38** that intercalate the DNA are crucial due to their behaving role as antitumor agents. These molecules are generally found in heterocyclic molecules containing two or four aromatic systems fused to each other having a quaternary nitrogen atom for the activity according to the studies of Pastor *et al.*[14]



38

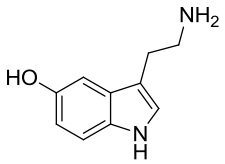
X = N; Y = C
X = C; Y = N

Moreover, pyrrolodiazine skeleton are found in many naturally isolated products. For instance Variolins[15,16] (**39**, **40**), alkaloid family isolated from Antarctic sponge specie *Kirkpatrickia varialosa*, exhibit activity against some tumor cells and virus-related diseases. Alkaloid Hinckdentine[17] (**41**) contains dihydro derivative of pyrrolo[1,2-*c*] structure, which are known as cataleptogens.



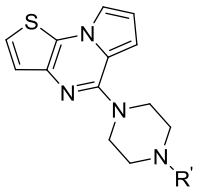
Variolin A **39** Variolin B **40** Hinckdentine **41**

There is a strong connection between mood-related disorders and reduced serotonin (**42**) levels in the brain; therefore, new drug designs have been made for the development of new molecules targeted the specific serotonin receptors, also known as 5-hydroxytryptamine or generally 5-HT receptors. One of the designed 5-HT_3 receptor was tricyclic piperazinopyrrolothienopyrazine (PPTP) core (**43**).[18]



Serotonin

42

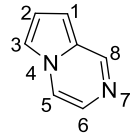


43

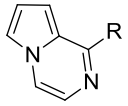
This thesis only focuses on pyrrolo[1,2-*a*]pyrazine (**34**) skeleton; hence, the other isomers of pyrrolodiazine are not elaborated for the rest of this thesis.

1.2.1 Properties of pyrrolo[1,2-*a*]pyrazine

Theoretical calculations by Paudler and Dunham[19] on pyrrolo[1,2-*a*]pyrazine structure show that C-1 and C-3 atoms have the highest electron density; on the other hand, the electron density on the C-8 is the least among other atoms. These theoretical calculations were verified with the experiments carried out with pyrrolo[1,2-*a*]pyrazine (**34**).



Pyrrolo[1,2-*a*]pyrazine
34



44: R= Ph
45: R= NH_2
46: R= Cl
47: R= OMe

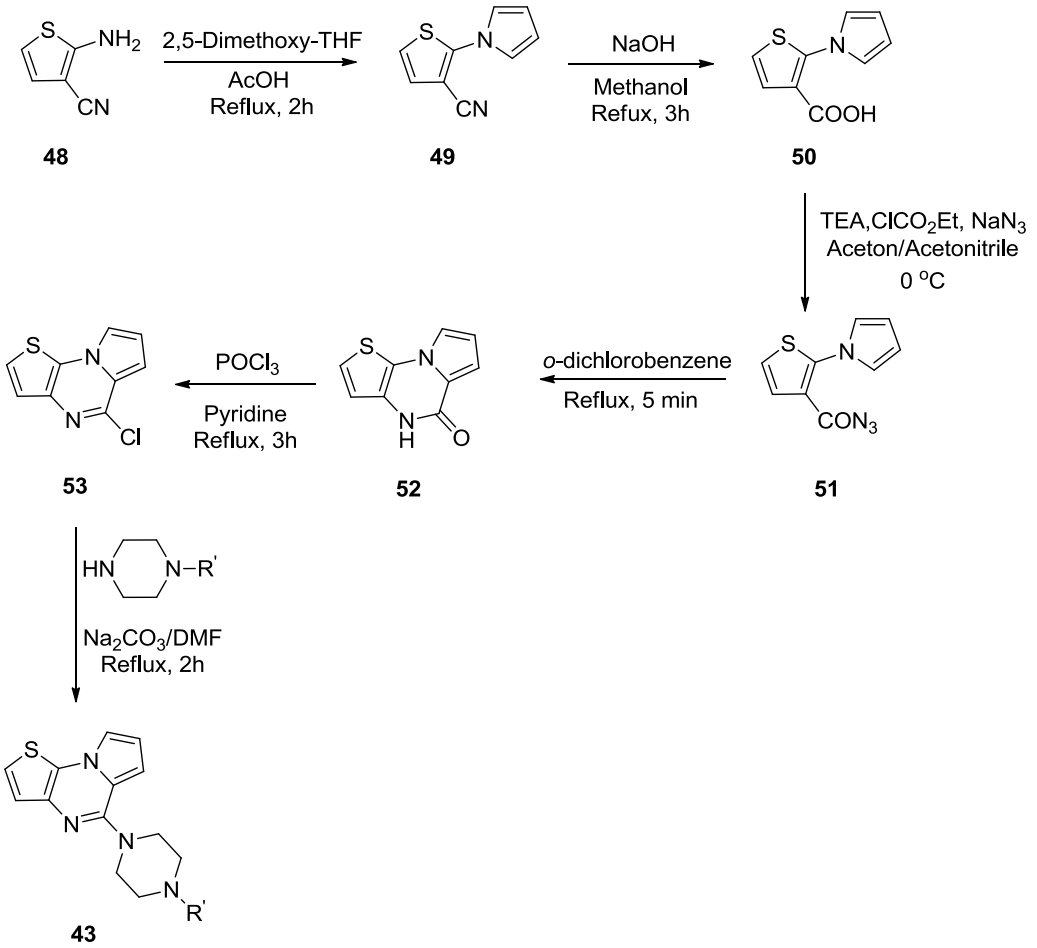
Electrophilic aromatic bromination and nitration to pyrrolo[1,2-*a*]pyrazine (**34**) occured at the position 1 and 3 and furthermore when it was treated with phenyllithium, 8-phenylpyrrolo[1,2-*a*]pyrazine (**44**) was formed, which were in consistent with the theoretical calculations. Buchan and his coworkers[20] further extended Paudler and Dunham's study on the reactivity of pyrrolo[1,2-*a*]pyrazines. Only the nonbridged nitrogen atom was subject to protonation or alkylation for the formation of a quaternary nitrogen atom. Moreover, pyrrolo[1,2-*a*]pyrazines failed to undergo electrophilic substitution reactions with weak electrophiles such as nitroso compounds to obtain aza-coupled product. Vilsmeier-Haack formylation, in addition, did not work with pyrrolo[1,2-*a*]pyrazines although indolizines successively gave formylation via Vilsmeier reaction.

Nucleophilic substitution reaction is another case for pyrrolo[1,2-*a*]pyrazines. Phenyllithium successively attacked to the C-8 carbon to produce 8-phenylpyrrolo[1,2-*a*]pyrazines (**44**); however, pyrrolo[1,2-a]pyrazine did not undergo amination to give **45** by Chichibabin reaction though the harsh reaction conditions. While hydride departure did not occur, chlorine group at C-8 in **46** was effectively substituted with amine or methoxy group to give **45** and **47** under the reported reaction conditions.

1.2.2 Synthesis of pyrrolo[1,2-*a*]pyrazine derivatives

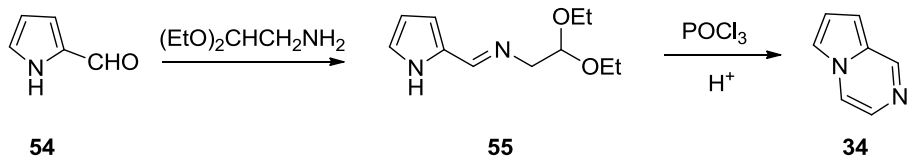
Rault and coworkers[18] studied on the derivatives of piperazinopyrrolothienopyrazine (PPTP) (**43**) some of which resulted in having great affinity to the specific 5-HT_3 receptor; hence, the group achieved to synthesize this substituted PPTP core in different pathways. One of their synthetic pathways included that first 2-amino-3-thiophenecarbonitrile (**48**) was treated with 2,5-dimethoxytetrahydrofuran in acetic acid at reflux temperature afforded pyrrole derivative **49**, and then hydrolysis of nitrile group by NaOH gave the carboxylic acid **50**. The conversion of carboxylic acid group to acyl azide group **51** was done with ethyl chloroformate and sodium azide in acetone at 0 °C. Curtius rearrangement in situ made the intermediate subject to afford the cyclization product **52**, and subsequently treatment with phosphoryl chloride in pyridine at reflux temperature gave the

chlorinated product **53**. The chlorinated product in DMF solution was treated with the corresponding piperazine derivative in the presence of a base to yield 5-substituted pyrrolo[1,2-*a*]thieno[3,2-*e*]pyrazines (**43**) (Scheme 14).



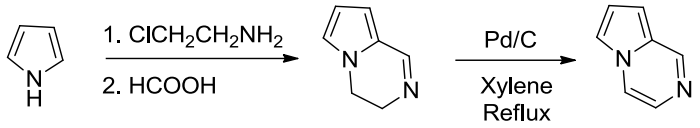
Scheme 14

The oldest approach for the formation of pyrrolo[1,2-*a*]pyrazine (**34**) was reported by Herz and Tocker.[21] 2-Pyrrolocarboxaldehyde (**54**) was condensed with aminoethylacetal to give pyrrole acetal **54**. Treatment of pyrrole acetal **54** with phosphorous oxychloride and polyphosphoric acid resulted in the desired pyrrolo[1,2-*a*]pyrazine (**34**) in overall yield of 18% (Scheme 15).



Scheme 15

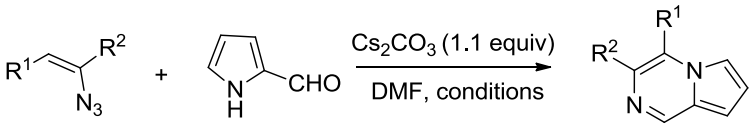
Minguez *et al.*[13] developed a much better synthetic approach for the synthesis pyrrolo[1,2-*a*]pyrazine (**34**). First starting from pyrrole (**56**), the 3,4-dihdyropyrrolo[1,2-*a*]pyrazine (**57**) was synthesized and then the oxidation by Pd/C catalyst in xylene at reflux temperature afforded the product **34** with a total yield of 59% (Scheme 16).



56 **57** **34**

Scheme 16

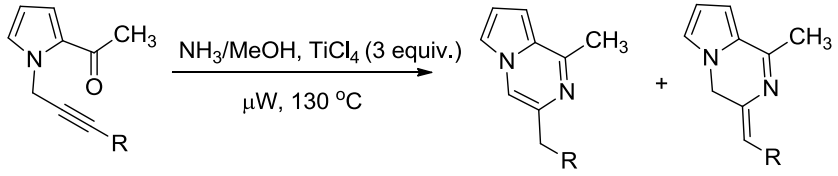
An efficient and versatile approach for generation of pyrazine scaffold was enhanced by Chen and his coworkers.[22] The cyclization between 2-pyrrolocarboxaldehyde (**54**) and vinyl azide **58** in the presence of base resulted in pyrrolo[1,2-*a*]pyrazine derivative **59** in high yield. According to the proposed mechanism, the reaction started with a proton abstraction from **54** by base to create a nucleophilic nitrogen atom, which attacked to the double bond in **58** according to a Michael-type addition reaction and to a release of N_2. Finally, intramolecular condensation gave the cyclization product **59** successfully (Scheme 17).



58 **54** **59**

Scheme 17

Another cascade synthetic route consisted of $TiCl_4$ catalyzed heteroatom cyclization of *N*-alkynyl pyrroles under microwave-assisted conditions. The reaction was carried out with different *N*-alkynyl pyrroles as starting compounds. According to Alfonsi *et al*. reported[23], some *N*-alkynyl pyrrole derivatives **60** afforded pyrrolo[1,2-*a*]pyrazine derivative **61** along with its isomer dihydropyrrolo[1,2-*a*]pyrazine **62**. In this concise cascade reaction, first NH_3 readily reacted with ketone to yield the corresponding imine, and then the coordination of $TiCl_4$ to the triple bond created an electrophilic carbon atom. Intramolecular nucleophilic attack by the nitrogen atom to the electrophilic carbon caused 6-*exo*-*dig* type cyclization to give pyrrolo[1,2-*a*]pyrazine dervatives **61** (Scheme 18).

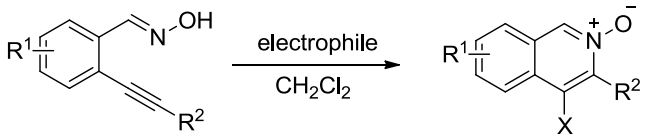


60 **61** **62**

Scheme 18

1.2.3 Synthesis of new class of compounds: Pyrrolo[1,2-*a*]pyrazine *N*-oxides

Different classes of polycyclic heteroaromatic *N*-oxide molecules and their synthesis are described in the literature. One of the examples for generating heterocyclic *N*-oxides is that 2-alkynylbenzaldoxime **63** underwent electrophilic cyclization to generate isoquinoline *N*-oxide derivative **64** (Scheme 19).The importance of this class of compounds was reported in the literature. Some of them are used as organocatalysis in organic chemistry and they also play an important role at charge-transfer, metal (Li^+/Mg^{2+}) sensor effects and initiators for radical polymerization reaction in material science.[24]

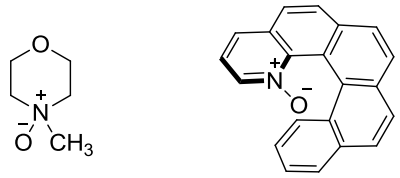


63 **64**

electrophile= I_2, ICl, NIS,; X= I, Br; R^1= H, F;
R^2= Ph, *p*-MeO-C_6H_4, n-Bu, *c*-Pr

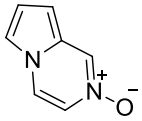
Scheme 19

Additionally, some heterocyclic *N*-oxides have got a reputation for being excellent catalysts for the asymmetric synthesis. A very well-known N-methylmorpholine *N*-oxide (**65**) stoichiometrically assists as an oxidant in Sharpless asymmetric dihydroxylation [25]; another example is polycyclic pyridine *N*-oxide (**66**) which is used as a catalyst for the formation of homopropargylic alcohols with a good enantioselectivity.[26]



65 **66**

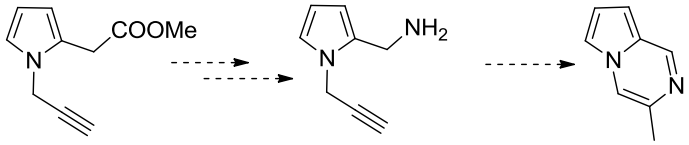
However, the synthesis of pyrrolo[1,2-*a*]pyrazine *N*-oxide (**67**) and its properties have not been investigated yet in the literature.



67

1.3 Aim of the study

In this thesis, we aimed to develop a new synthetic methodology leading to pyrrolo-fused new heterocycles using electrophilic heteroatomic cyclization

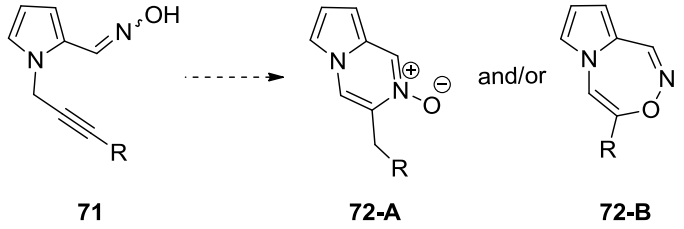


68 **69** **70**

Scheme 20

The first part of this research dealt with the construction of the desired *N*-alkynyl 2-substituted methylamine pyrrole derivative **70** yet we needed to develop a concise method for the synthesis of compound **68**. In the light of this purpose, we offered an efficient way for the generation of substituted pyrrole ring to get the molecule **68**. Then it was aimed to convert the ester group to the amine group using Curtius rearrangement. Electrophilic cyclization by using π-acid catalyst was planned to perform to obtain the desired molecule **70** from which we totally intended to offer a new methodology to construct the pyrrolo[1,2-*a*]pyrazine moiety (Scheme 20).

The goal of the second part was to investigate the product resulted from metal-catalyzed cyclization of pyrrole aldoxime substrates **71**. Two possible nucleophilic attacks to the activated carbon were possible as shown in Scheme 21, which was intriguing for us to study on it.



71 **72-A** **72-B**

Scheme 21

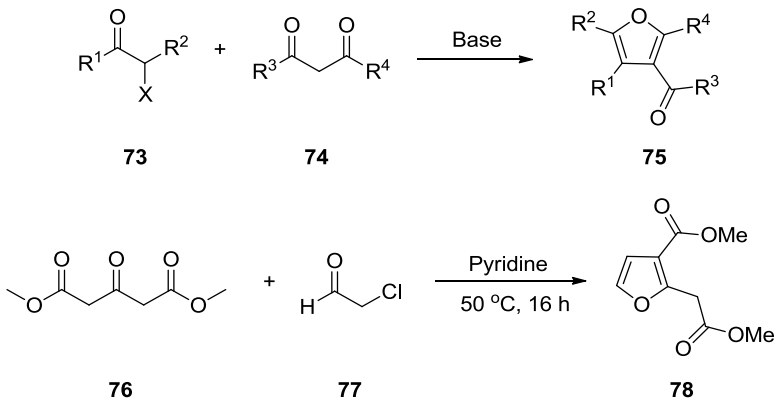
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of pyrrolo[1,2-*a*]pyrazine moiety

2.1.1 Synthesis of the starting compound: methyl 2-(2-methoxy-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate

During the investigations on the synthesis of *N*-alkynl-2-substituted pyrrole derivative, it was aimed to develop a simple route for its formation. In this direction, Hantzsch synthesis of pyrroles was seemed a conceivable way for the construction of pyrrole ring in the presence of ammonia or a primary amine when considering the condensation mechanism behind 1,3-diketone **74** and halo carbonyl compounds in the presence of a base. In 1994, Tada, Otsu and Chiba[27] reported that the synthesis of methyl 2-(2-methoxy-2-oxoethyl)-3-furoate (**78**) was accomplished by condensation of dimethyl-1,3-acetonedicarboxylate (**76**) with chloroacetaldehyde (**77**) in pyridine under the mild conditions (Scheme 22), namely as Feist-Benary furan synthesis.

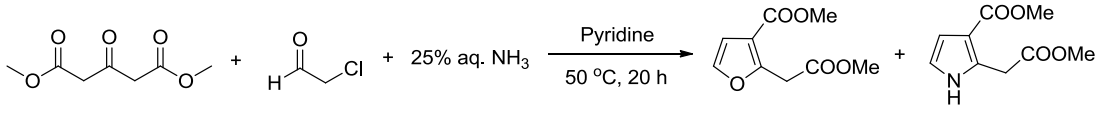


73 **74** **75**

76 **77** **78**

Scheme 22

In the light of afore-mentioned information, it was planned to search whether presence of ammonia or a primary amine could provide a pyrrole ring and/or with a furan ring. Our results showed that dimethyl-1,3-acetonedicarboxylate (**76**), chloroacetaldehyde (**77**) and 25% solution of NH_3 in pyridine at 50 °C yielded methyl 3-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate (**79**) in 17% crude yield and methyl 2-(2-methoxy-2-oxoethyl)-3-furoate (**78**) in 57% crude yield (Scheme 23).



57% 17%

76 **77** **78** **79**

Scheme 23

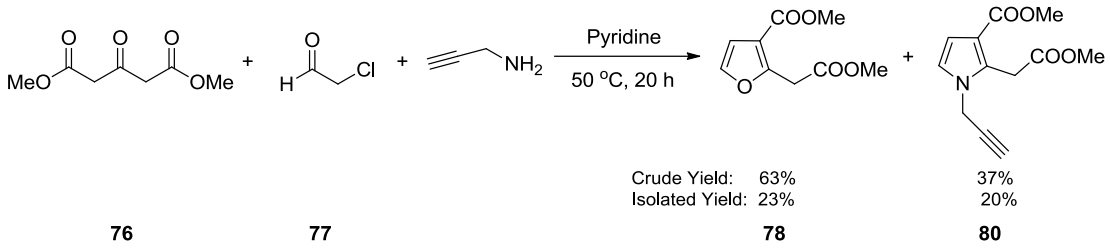
In order to improve the yield of the desired product **79**, same reaction was also carried out in the presence of ammonia gas and ammonium acetate, separately. The crude yield of each compound is shown in the Table 1. The yield of pyrrole derivative **79** was increased up to 32% by using ammonium acetate.

Table 1: Yields of furan diester **78** and pyrrole diester **79** with different nitrogen sources

	%Yield of **78**[a]	%Yield of **79**[a]
$NH_{3(g)}$	61%	12%
25% aqueous NH_3	57%	17%
CH_3COONH_4	40%	32%

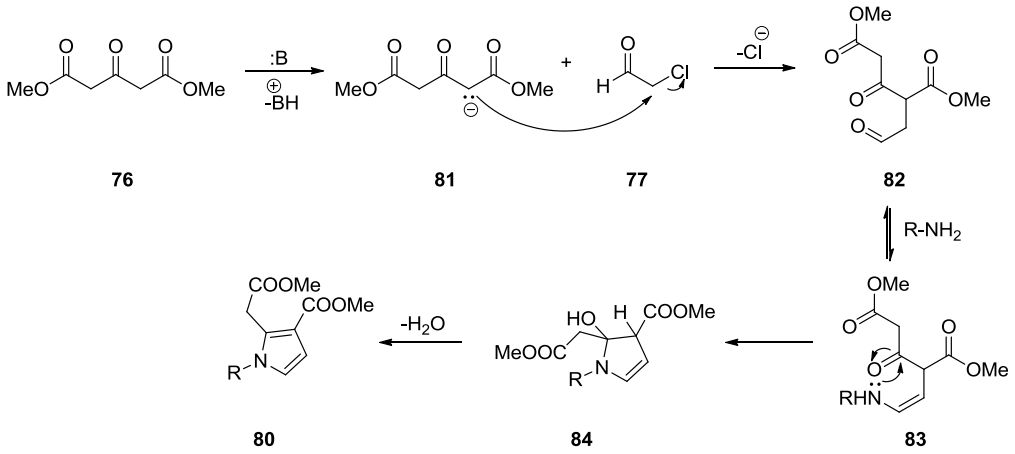
a: crude yield

Next, we carried out the same reaction with propargyl amine as an amine source to construct the key compound, methyl 2-(2-methoxy-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**80**) (Scheme 24).



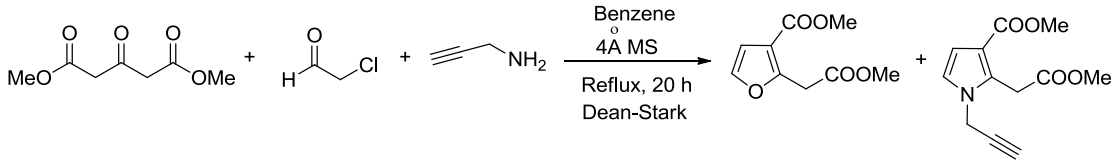
Scheme 24

Although haloaldehyde **77** was added after the addition of 1,3-dicarboxylate **76** and primary amine, it still may be suggested that the reaction mechanism for the formation of pyrrole diester **80** proceeded initially proton abstraction from 1,3-dicarbonyl compound **76** in the presence of a base to create a carbanion which attacks chloroacetaldehyde (**77**) with an S_N2 fashion to generate **82**. Enamine **83** formation and subsequently annulation gave pyrrole diester **80** (Scheme 25).



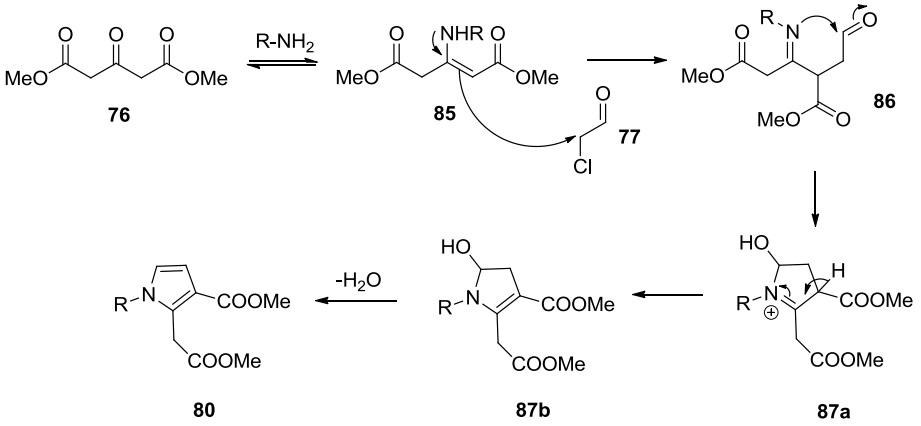
Scheme 25

However, when this reaction was carried out without a base, furan diester **78** and pirol diester **80** were formed as a mixture. In this case, Feist furan product **78** was again predominated Hantzsch pyrrole product **80** (Scheme 26).



Scheme 26

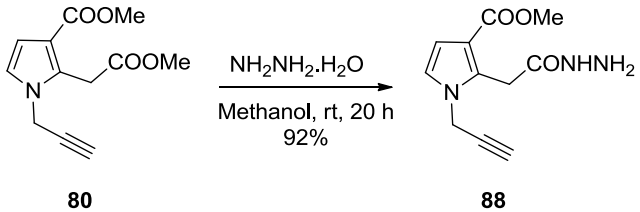
This result showed that without a need for base, pyrrole **80** formation proceeded via enamine **85** then nucleophilic substitution reaction resulted in the formation of **86** which underwent intramolecular annulation to give **87**, and finally elimination of H_2O afforded pyrrole **80** (Scheme 27). The formation of furan **78** was probably due to the hydrolysis of enamine **86**.



Scheme 27

2.1.2 Synthesis of methyl 2-(2-hydrazinyl-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate

After synthesis of the diester **80**, the attention was turned to convert the ester functional group at the lower arm of **80** to the amine group. For this purpose, we first planned to generate an acyl azide functional group, which can be easily converted into the corresponding amine using Curtius rearrangement in situ. To do so, hydrazide molecule **88** was chosen as a starting material to synthesize the acyl azide (Scheme 28).



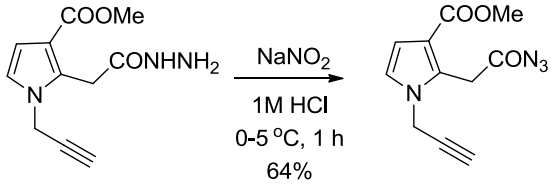
Scheme 28

Two different ester groups exist in the compound **80**; however, reactivity difference provides regioselectivity under the certain reaction conditions. In the case of furan, it was reported[28] that the corresponding furan diester **78** was successively converted to furan dihydrazide in methanol at reflux temperature. However, when **80** was treated with hydrazine monohydrate at room temperature, hydrazide formation was regioselectively occurred at the lower arm to furnish **88** since the ester group of the upper arm is conjugated with the pyrrole ring; thus, the reactivity of carbonyl carbon of the

upper arm is lower than that of lower arm. Methyl 2-(2-hydrazinyl-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**88**) was generated as the sole product in a 92% yield.

2.1.3 Synthesis of 1-{[3-(methoxycarbonyl)-1-prop-2-ynyl-1*H*-pyrrol-2-yl]acetyl}triaza-1,2-dien-2-ium

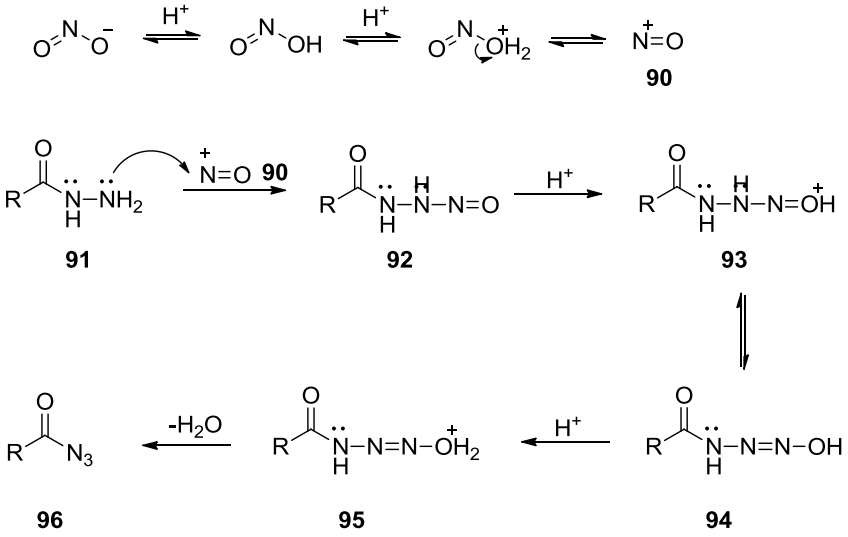
The reaction shown in Scheme 29 was performed for the formation of 1-{[3-(methoxycarbonyl)-1-prop-2-ynyl-1*H*-pyrrol-2-yl]acetyl}triaza-1,2-dien-2-ium (**89**) (Scheme 29).



88 **89**

Scheme 29

In the presence of acid, nitrite was protonated and nitrosonium ion **90** was formed in situ. Electron pair on β-nitrogen of the hyrazide **91** was available to attack to positively charged nitrosonium ion **90** to form β-nitroso hydrazine intermediate **92**. Then tautomerization of β-nitroso hydrazine and removal of one mole H_2O generated the desired acyl azide **94** (Scheme 30).



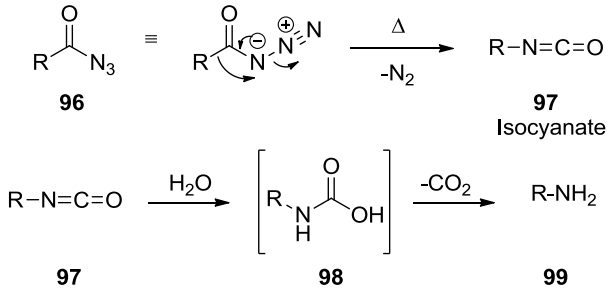
91 **92** **93** **94** **95** **96**

Scheme 30

NMR spectra as well as the IR spectrum were compatible with the structure. Frequency at 2148 cm^{-1} was arising from the azide group in the molecule **89**.

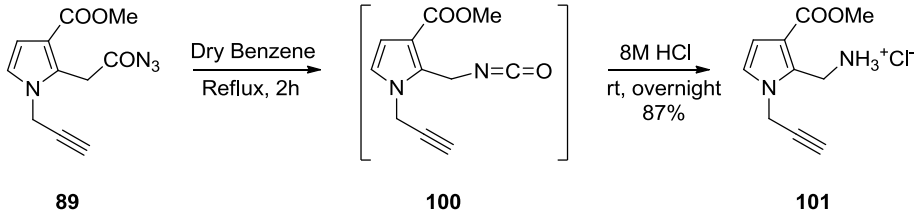
2.1.4 Synthesis of methyl 2-[2-(chloroamino)-2-oxoethyl]-1-prop-2-ynyl-1*H*-pyrrole-3-carboxylate

Curtius rearrangement[29] is one way to produce amine from acyl azide **96**. Heating acyl azide in a dry aprotic solvent **96** leads to isocyanate **97** formation and N_2 evolution. Isocyanates are not so stable and they prefer to react with other nucleophiles to generate stable compounds. Water can attack the carbon group of isocyanate functionality to give carbamic acid **98**, which undergoes decorboxylation to produce amine **99** (Scheme 31).



Scheme 31

Acyl azide **89** was submitted to Curtius rearrangement in dry benzene at reflux temperature and the corresponding isocyanate was formed in situ and addition of 8M HCl to the reaction mixture at room temperature gave the desired amine **101** in 87% yield (Scheme 32).

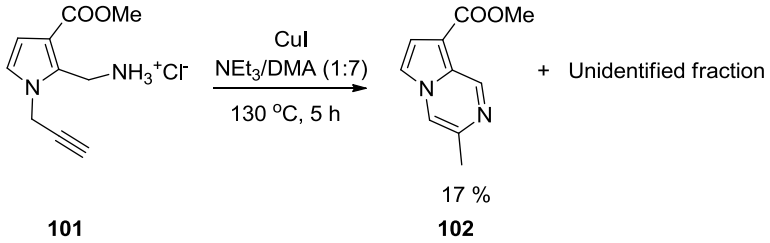


Scheme 32

Attempts to deprotonate **101** with 10% NaOH solution were failed. Therefore further reactions were carried out with the ammonium chloride salt **101**.

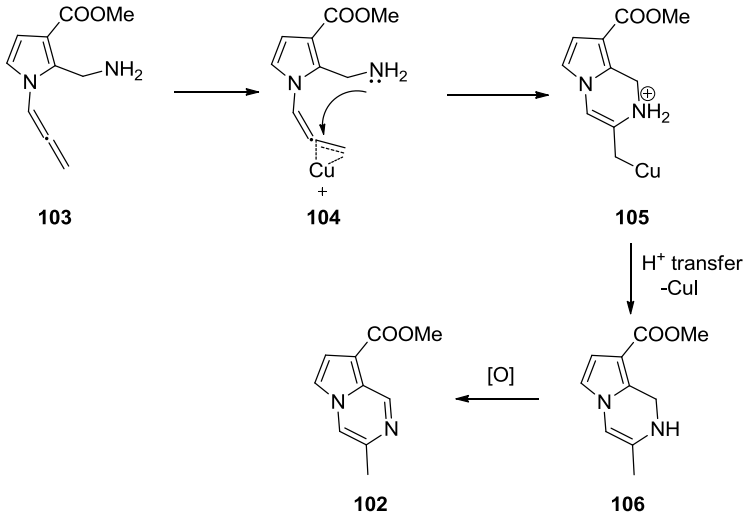
2.1.5 Synthesis of methyl 3-methylpyrrolo[1,2-*a*]pyrazine-8-carboxylate

In the course of the cyclization reactions, a base needed to abstract proton from compound **101** to generate amine in situ and also it was required to use apolar solvent with higher dipole moment to dissolve the starting compound **101**. Therefore, Kel'in, Sromek and Gevorgyan's study[11] of Cu (I) catalyzed cyclization of alkynyl imines to generate pyrrole was applied cyclization reaction of **101** to generate pyrrolo[1,2-*a*]pyrazine moiety **102** (Scheme 33).



Scheme 33

The reaction mechanism emphasizes that presence of base is important not only for the generation of amine in the reaction but also it renders propargyl-allene isomerization to yield allene **103**. Coordination of Cu-(I) to the terminal double bond increases the electrophilicity of the middle carbon of allene, which makes it susceptible to intramolecular nucleophilic attack through nonbonding electrons on nitrogen. Proton transfer and subsequently air oxidation of the compound **106** afforded pyrrolo[1,2-*a*]pyrazine derivative **102** in yield of 17% (isolated yield) (Scheme 34).



Scheme 34

6-*exo*-dig and 7-*endo*-dig ring closure are favorable according to Baldwin's rule[30] as long as nucleophile attacks to the electrophile from an ideal angle. In our case, 6-*exo*-dig ring closure occurred due to electrophilic character of C-2 carbon in allene unit and aromaticity of pyrrolo[1,2-*a*]pyrazine.

The ^{1}H-NMR spectrum of 3-methylpyrrolo[1,2-*a*]pyrazine-8-carboxylate (**102**) was shown in Figure 1. Protons belonging to pyrazine ring resonated at 8.04 ppm and 9.19 ppm and protons attached to the pyrrole ring appeared at 7.48 ppm and 7.10 ppm. The other spectral data was also in agreement with the proposed structure.

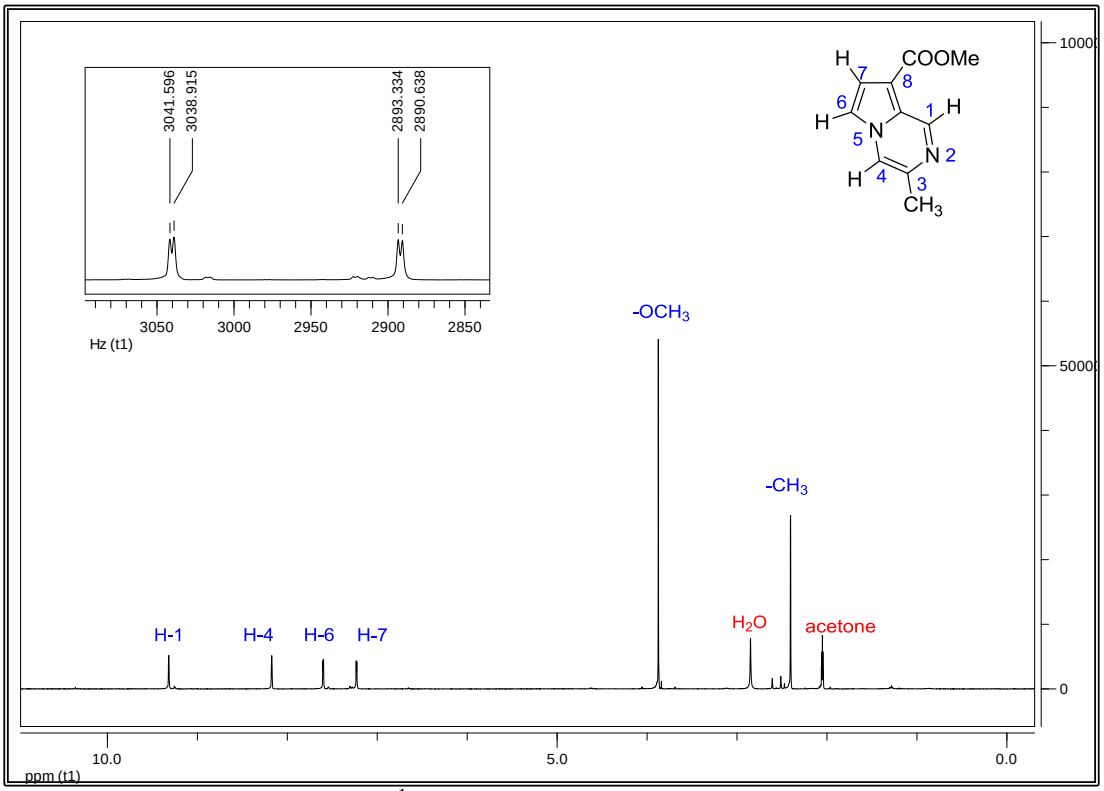


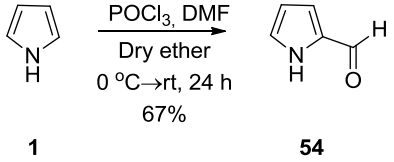
Figure 1 ^{1}H-NMR Spectrum of compound **102**

Unfortunately, the yield of the product **102** was low, 17 %. This reaction was performed at very high temperature, 130 °C, avoiding light; hence, that high reaction temperature may cause polymerization of the pyrrole ring. As a matter of the fact that the crude product was dark and very viscous that polymerization could be conceived here.

2.2 Synthesis of pyrrolo[1,2-*a*]pyrazine *N*-oxide moiety

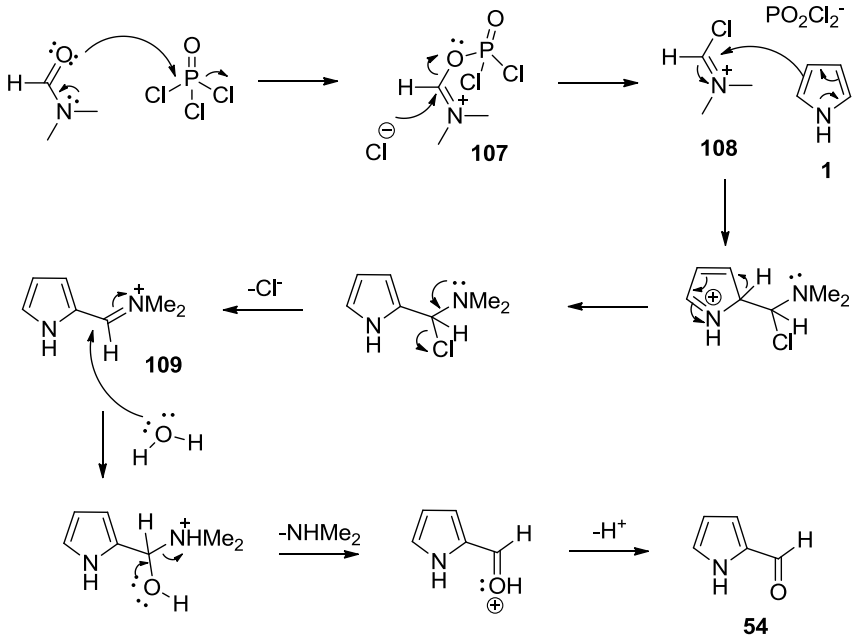
2.2.1 Synthesis of 1*H*-pyrrole-2-carbaldehyde

Pyrrole ring is an electron rich heterocyclic aromatic compound. Electrophilic aromatic substitution occurred at the C-2 site where positive charge was stabilized more by resonance, as it was already mentioned. In the direction of our aim for this part, Vilsmeier-Haack reaction was applied for the formylation of pyrrole (**1**) to give 1*H*-pyrrole-2-carbaldehyde (**54**) (Scheme 35).[31]



Scheme 35

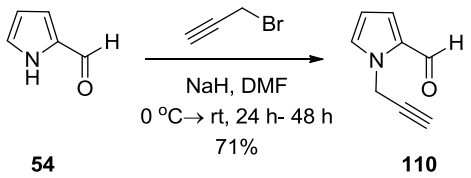
First, dimethyl formamide and phosphorus oxychloride were reacted to generate imminium ion **108**. Electrophilic aromatic substitution occurred at the C-2 position of pyrrole. Hydrolysis of imminium intermediate **109** during the work up gave 1*H*-pyrrole-2-carbaldehyde (**54**) (Scheme 36).



Scheme 36

2.2.2 Synthesis of 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde

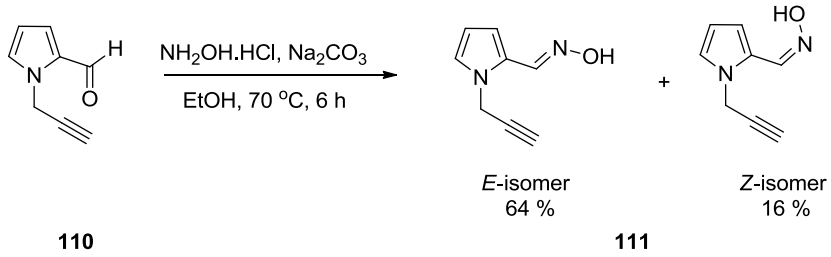
Lack of basicity of pyrrole ring and it's even slightly acidic character can be explained by participation of nonbonding electrons on nitrogen atom to the conjugation; therefore, substitution reaction can take place after base abstracts proton attached to nitrogen. In the presence of NaH and propargyl bromide, an S_N2 reaction took place to afford 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde in 71% yield (Scheme 37).[32]



Scheme 37

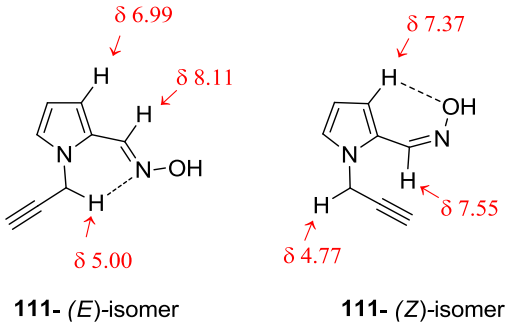
2.2.3 Synthesis of 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde oxime

In this part of this thesis, we planned to synthesize the oxime **111** derived from **110** to perform cyclization reaction between the propargyl group and oxime hydroxyl group. For the synthesis of oxime, hydroxylamine was added to aldehydes or ketones to form aldoxime HRC=NOH or ketoxime R_2R_1C=NOH. 1-(Prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde oxime (**111**) was successively formed starting from the corresponding carbaldehyde **110** (Scheme 38).[33]



Scheme 38

Karabatsos[34,35] reported that the aldoxime proton of the *anti*-configurated oxime resonates at lower field than that of *syn*- configurated oxime. Afonin *et al*. investigated ^{1}H and ^{13}C-NMR spectra of 1-vinylpyrrole-2-carbaldehyde oxime isomers' in which all spectroscopic finding were in consistent with Karabatsos'. Therefore, the assignments of the configuration *E*- and *Z*-isomers were made from ^{1}H-NMR spectra. The intramolecular hydrogen bonding for both *E*-isomer and *Z*-isomer of **111** are shown below (Scheme 39). As expected, intramolecular hydrogen bondings decreased the electron density around those corresponding protons and made them shifted to downfield. On the basis of the different chemical shifts of the relevant protons, we assigned the *E*- and *Z*- configuration of the formed oximes.

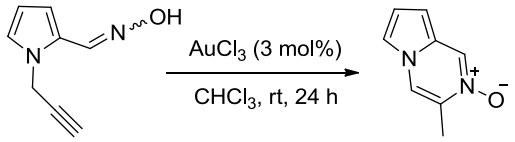


Scheme 39

2.2.4 Synthesis of 3-methylpyrrolo[1,2-*a*]pyrazine 2-oxide

In the formation of pyrrolo[1,2-*a*]pyrazine skeleton, we showed that ring closure occurred in a 6-*exo*-dig fashion due to electrophilic character of middle carbon atom of allene unit and the aromatic character of the formed six-membered ring. In the case of cyclization with oximes, there are two possible nucleophilic attacks to the activated carbon exist; either nitrogen or oxygen can attack to the electrophile whereas nitrogen is better nucleophile than oxygen.

The cyclization reaction of oxime **111** was carried out with $AuCl_3$ as a catalyst at room temperature. Its resistance to air and moisture makes $AuCl_3$ very preferable catalyst among other transition metal catalysts. According to our result, 3-methylpyrrolo[1,2-*a*]pyrazine 2-oxide (**112**) was formed as the sole product with an excellent yield of 97% (Scheme 40).



111 **112**

Scheme 40

A mixture of oxime isomers of **111** was used to give pyrrolo[1,2-*a*]pyrazine *N*-oxide **112.** When this reaction was carried out with *E*- and *Z*-isomers separately, regardless of the configuration of oximes, the same product **112** was formed as the single product.

The structure of this compound was determined by 1D and 2D NMR spectral data. DEPT-90 spectrum showed the presence of five CH carbon resonances in the sp^2 region of compound **112** (Figure2). The presence of methyl carbon resonating at 20.7 ppm was established by DEPT-135 spectrum (Figure 3). The HMBC spectrum totally proved the proposed structure of **112** (Figure 4). The important part here was the correlation between H-1 proton and C-3 atom shown in Figure 4.

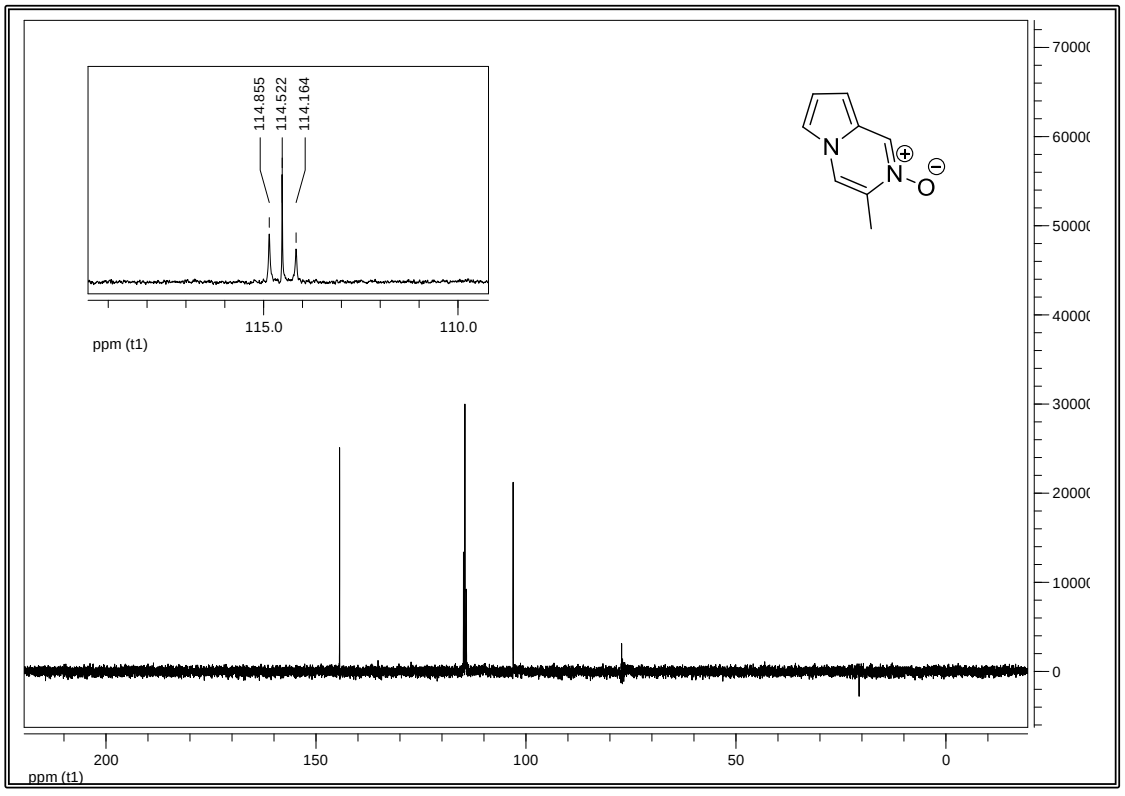


Figure 2 DEPT-90 Spectrum of compound **111**

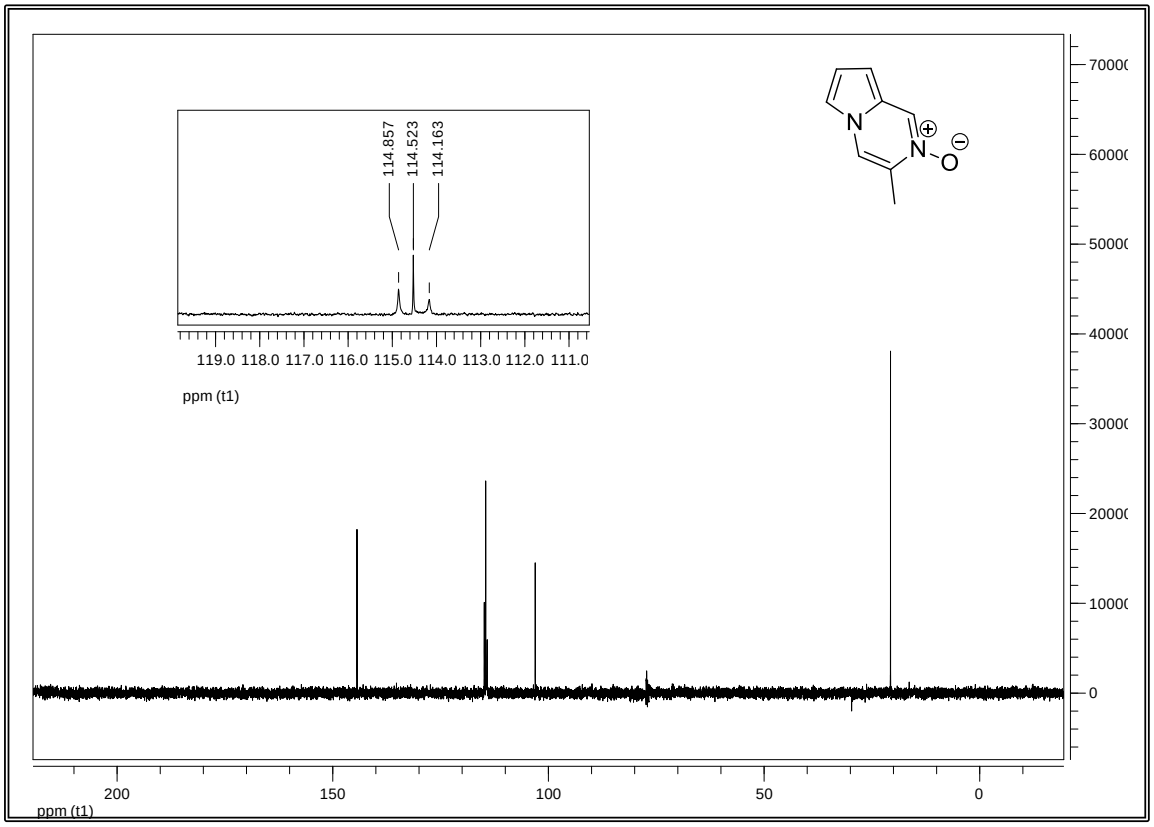


Figure 3 DEPT-135 Spectrum of compound **112**

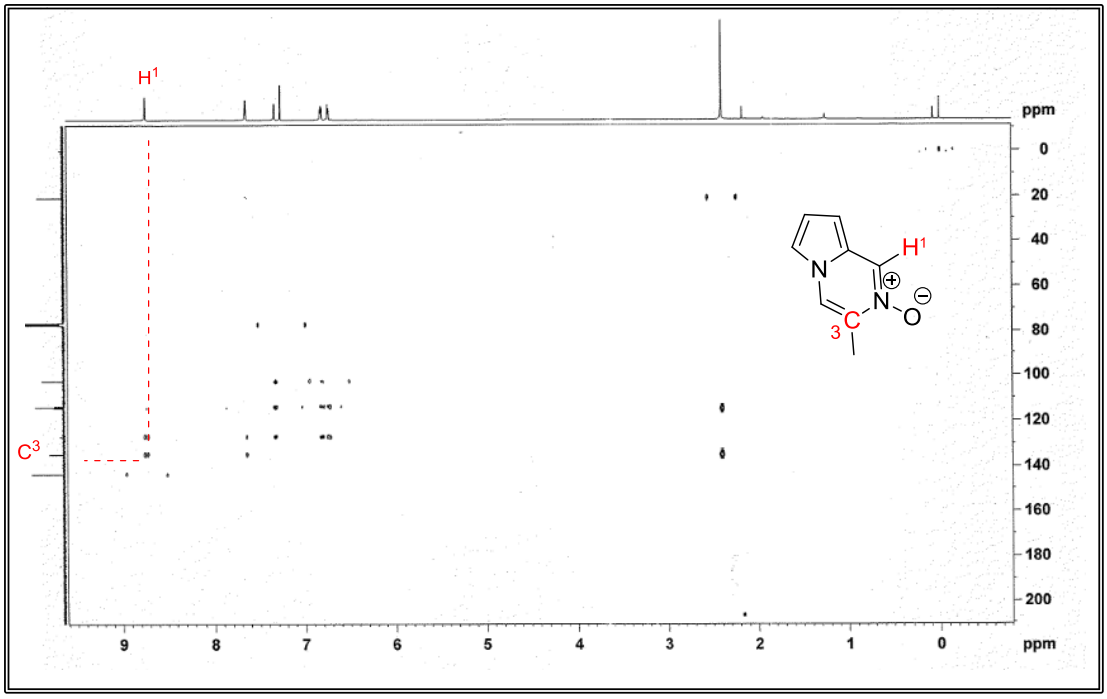


Figure 4 HMBC Spectrum of compound **112**

Proposed catalytic cycle for this reaction is shown in Scheme 41. Coordination of $AuCl_3$ to the triple bond makes it susceptible to intramolecular nucleophilic attack by nitrogen via the 6-*exo*-dig

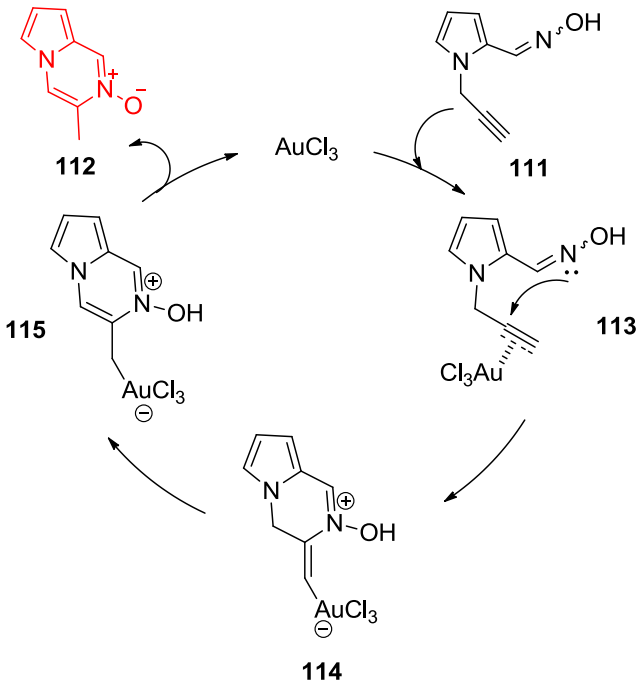
cyclization to give zwitter ion intermediate **114**. Proton transfer and regeneration of catalyst affords the product **112** (Scheme 41). Careful examination of the reaction mixture did not reveal the formation of a seven-membered ring where hydroxyl oxygen was involved in the cyclization reaction.

Furthermore, it was desired to investigate whether different metal catalysts would render *exo*/*endo* selectivity in the activation of alkyne. None of metal catalysts provided any selectivity; the same product was formed with yield shown in Table 2.

Table 2: Yields of **112** with different metal catalysts

Catalyst (3 mol%)	Crude Yield %
$AuCl_3$	97%
LnAuCl*/ AgOTf	92%
CF_3SO_2OAg	82%
CuI	45%

LnAuCl*: Chloro[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]gold(I)



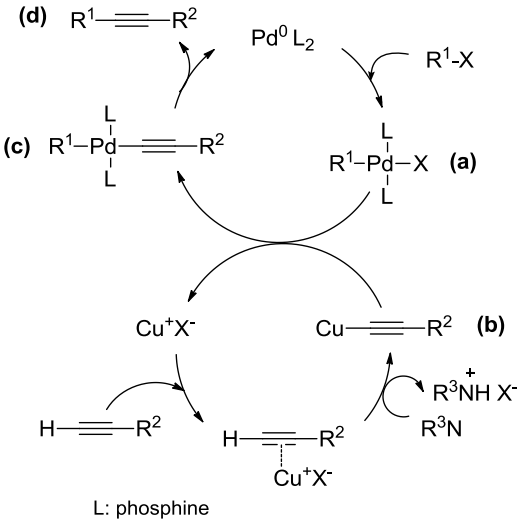
Scheme 41

2.3 Oxime-Oxime Transformation

2.3.1. Synthesis of 1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde, 1-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde and 1-(3-(3-nitrophenyl)prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde

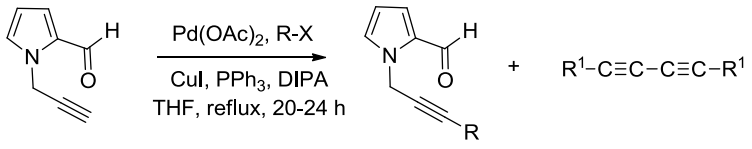
Sonogashira coupling is a convenient method so as to construct new C-C bonds. Some variations of cross-coupling Sonogashira have been reported in the literature, yet copper-cocatalyzed Sonogashira coupling was going to be emphasized here. One modification of Sonogashira couplings uses Pd catalyst and CuI cocatalyst in the presence of a base, in which terminal alkynes and aryl halides undergo coupling reaction. The exact mechanism behind this catalytic cycle has been still remained unclear; however, it was thought that palladium(II) diacetate was reduced by phosphine, amines and

ethers. Oxidative addition of R^1-X (aryl, hetaryl, vinyl) took place to form (**a**). Cu catalytic cycle provided copper acetylide (**b**), which then participated to ligand substitution step to generate (**c**). Finally reductive elimination provided coupling product (**d**) and regeneration of palladium catalyst (Scheme 42).[36]

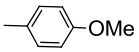
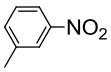


Scheme 42

We applied Sonogashira coupling to 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde (**102**) to generate **116**, **117**, and **118** (Scheme 43). The scope of having these coupling products was to investigate the activity of alkyne carbon atoms during cyclization reaction.



102

Entry	R-X	R	Yield% of Product[a]	Yield% of Side Product[a]
116	Iodobenzene		71%	-
117	4-iodoanisole		68%	23%
118	1-bromo-3-nitrobenzene		66%	21%

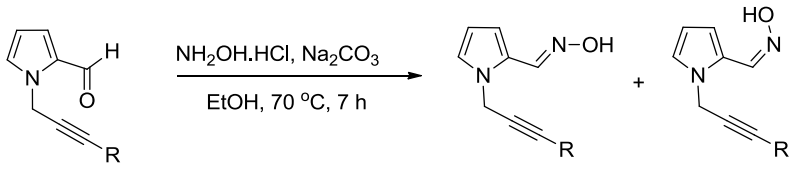
a: Crude yield
R^1: **102**-

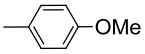
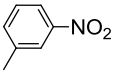
Scheme 43

We desired to get higher yields for Sonogashira couplings; however, homocoupling products were formed in significant amounts. The reaction conditions should be completely oxygen-free, yet for our reaction conditions it was not unfortunately. Here, in the presence of oxygen, it oxides Pd(0) to Pd(II)[37], which alternately catalyze homocoupling product since Pd(II) is formed only over the formation of bicoupling product.

2.3.2 Synthesis of 1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde oxime, 1-(3-(3-nitrophenyl)prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde oxime, 1-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde oxime

Oximes of corresponding aldehydes **116**, **117** and **118** were successfully generated (Scheme 44). ^{1}H-NMR spectra of those oximes guided us to assign *E*- and *Z*-isomers.



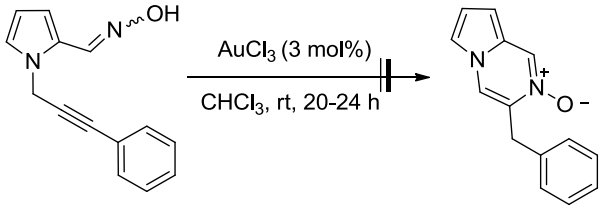
Entry	R	Yield% (*E*-isomer)[a]	Yield% (*Z*-isomer)[a]
119		62%	31%
120		56%	28%
121		60%	30%

a: Crude yield

Scheme 44

2.3.3 New Type of Rearrangement Arising: Oxime-oxime transformation

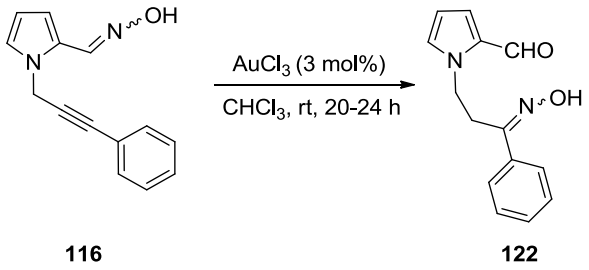
During the investigation of $AuCl_3$-assisted cyclization reaction of 1-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde oxime (**119**), we were expecting basically 6-*exo*-dig type cyclization to give pyrrolo[1,2-*a*]pyrazine skeleton without considering any electron donating or electron withdrawing property of phenyl ring, yet the expected product did not form (Scheme 45).



116 **119**

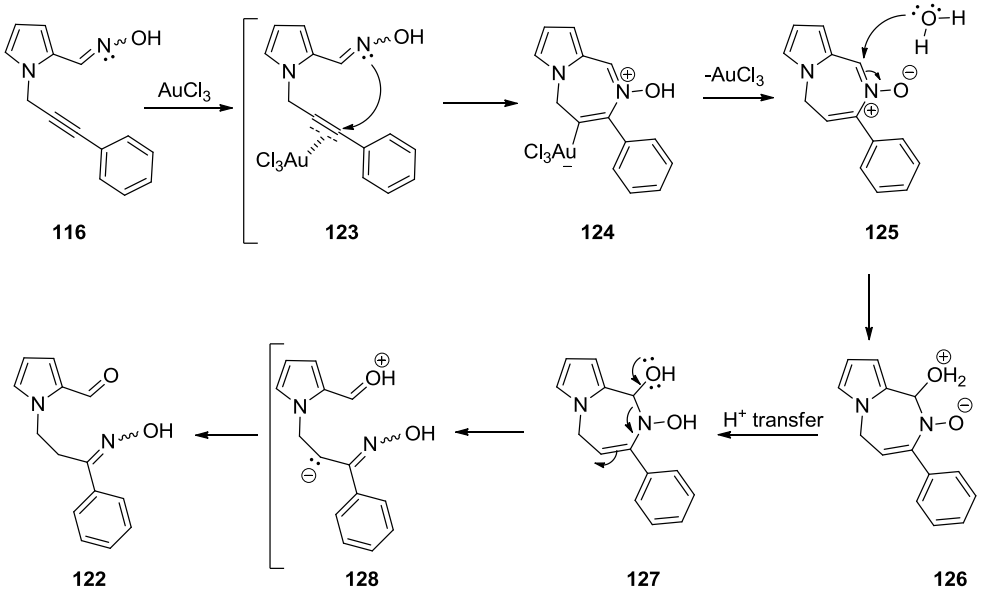
Scheme 45

We are glad to report a new type of oxime-oxime transformation for the first time, which is unprecedented in the literature. The intramolecular heteroatom cyclization catalyzed by $AuCl_3$ resulted in different direction apart from our expectations (Scheme 46).



Scheme 46

Although the oxime-oxime transformation mechanism is still being studied in detail, it seemed probable that the mechanism proceeded via the formation seven-membered ring. 7-*Endo*-dig type attack was in case since phenyl group could stabilize the partial positive charged localized on the α-carbon, where the electron density at β-carbon was increased. Thus nucleophilic attack occurred to the more electrophilic α-carbon, which generated 7-membered ring zwitter ion intermediate **124**. Here an attack of oxygen is probably disfavored to the formation of eight-membered ring. After formation of **124**, water molecule present in the reaction media can attack the activated imine carbon to cause subsequent ring-opening of the seven-membered ring to generate aldehyde structure. The oxime will be formed on the carbon atom next to the benzene ring. The overall reaction is the intermolecular transfer of oxime functionality from one carbon atom to another via a seven-membered ring formation as an intermediate to form **122** (Scheme 47).



Scheme 47

The proposed structure was fully confirmed by 1D NMR as well as by 2D NMR spectra. DEPT-135 spectrum of compound **122** clearly showed the presence of two methylene carbon atoms. Furthermore, COSY spectrum proved that these methylene groups are connected to each other. An isomeric oxime was also formed. Careful examination of the ^{1}H-NMR spectrum revealed the presence of two methylene functionalities in the minor isomer of **122** (Figure 5).

In the HMBC spectrum of compound **122**, characteristic oxime carbon resonating at 155.8 ppm correlates with two methylene protons and it also correlates with phenyl protons. This finding clearly supports that the oxime functionality was transferred from aldehyde to the propargyl carbon. Aldehyde carbon correlates only with pyrrole protons clearly indicating the attachment of aldehyde to pyrrole ring (Figure 6).

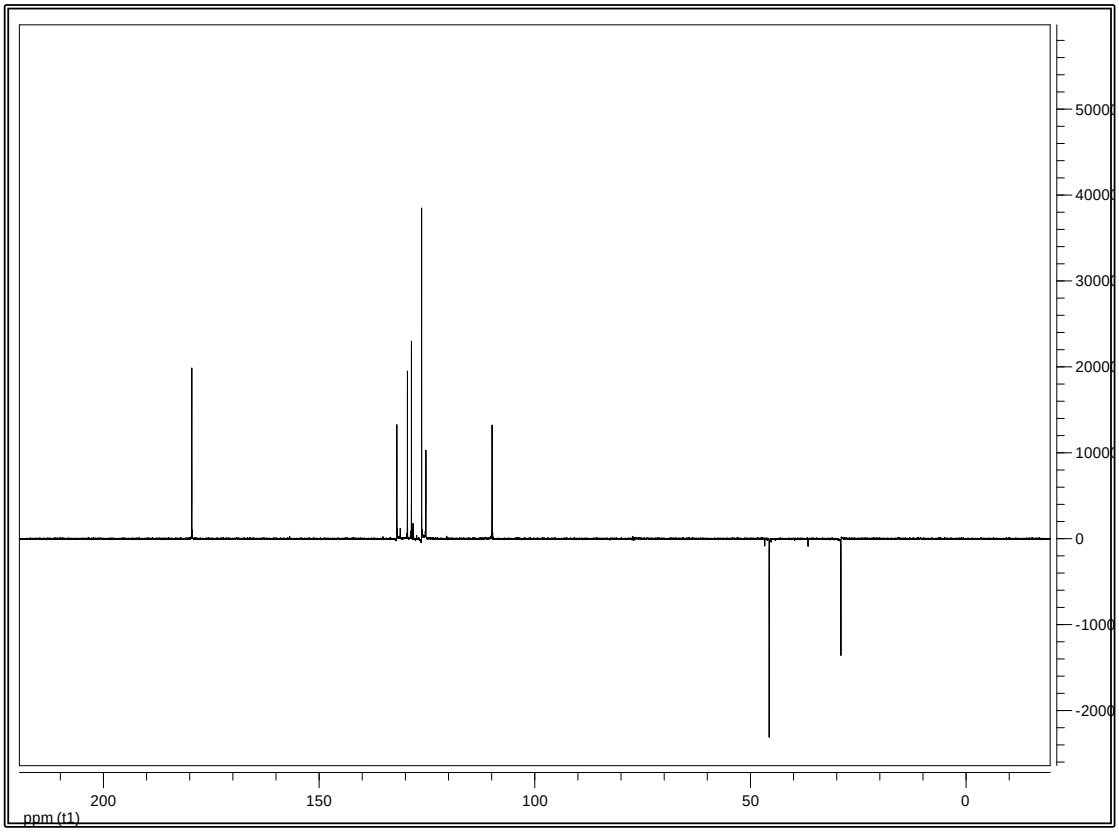


Figure 5 DEPT-135 Spectrum of compound **122**

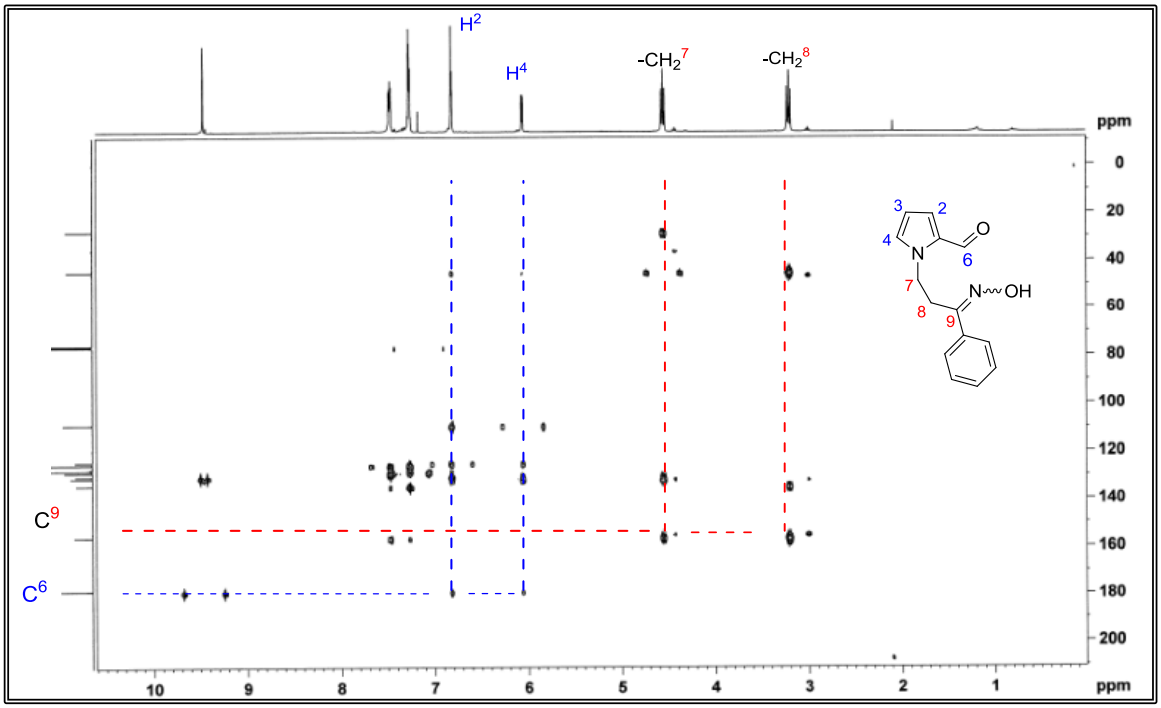
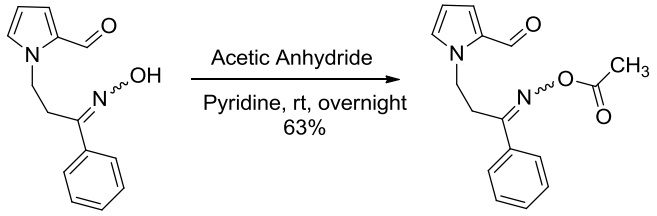


Figure 6 HMBC Spectrum of compound **122**

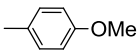
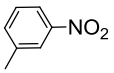
We also proved the presence of hydroxyl group. The compound **122** underwent acetylation reaction, and fortunately, in ^{1}H-NMR there was a peak at 2.14 ppm which was arising from methyl of acetyl group (Scheme 48).



122 **129**

Scheme 48

We further studied how activating or deactivating group on phenyl ring affected the activation of alkyne during our cyclization reaction. Starting from compounds **130** and **131**, oxime-oxime transfer processes were also observed for both cases (Scheme 49).

Entry	R	Yield% (*E*-isomer)	(*Z*-isomer)
122		83%	6%
130		38%	38%
131		73%	15%

Scheme 49

CHAPTER 3

EXPERIMENTAL

3.1 General

Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in $CDCl_3$, CD_3OD, DMSO-*d6*, and acetone-*d6* with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Bruker Platinum ATR FT-IR spectrometer and Thermo Scientific Nicolet iS10 FT-IR spectrometer. Band positions were reported in reciprocal centimeters (cm^{-1}).

Gallenkamp electronic melting point apparatus was used to obtain melting points.

Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

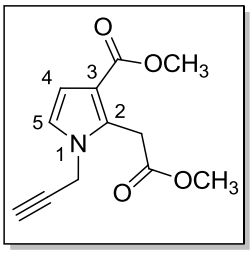
ACD NMR (Name generator) was used for the nomenclature of the compounds.

Purification of solvents were performed as reported in the literature.[38]

3.2 Synthesis of methyl 2-(2-methoxy-2-oxoethyl)-1-prop-2-ynyl-1*H*-pyrrole-3-carboxylate (80)

To a solution of dimethyl 1,3-acetonedicarboxylate (**76**) (15 g, 086 mol) in pyridine (30 ml), propargyl amine (7,1 g, 0.129 mol) was added at room temperature. While reaction mixture is stirring at room temperature for 10 min, the solution of chloroacetaldehyde (**77**) (22.5 g, 45%, 0,129 mol) was added slowly to this mixture. After completion of the addition, reaction mixture was heated to 50 °C for 20 h. Then the reaction mixture was extracted with water and ethyl acetate. The organic phase was washed with 2M HCl, 5% $NaHCO_3$, and brine, respectively and dried over $MgSO_4$. Reaction crude was 14.65 g after evaporation. According to ^{1}H-NMR of crude, yield of furan diester **78** was 63% and pyrrole diester **80** was 37%. The products were successively separated by column chromatography over silica gel (400 g) eluated with hexane-ethyl acetate (4:1) gave first fraction, methyl [3-(1-methoxyethenyl)furan-2-yl]acetate (**78**) as a yellowish liquid (4.0 g, 23%), and second fraction, methyl 2-(2-methoxy-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**80**) which was further purified with recrystallization from hexane-ethyl acetate (6:1) to give as a white powder (4.5 g, 20%), mp 93-94 °C.

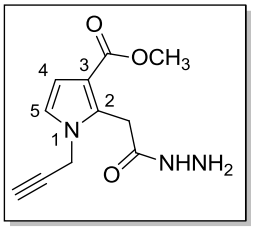
Procedure 2 for the synthesis of **80**: To a solution of dimethyl 1,3-acetonedicarboxylate (**76**) (0.5 g, 2.87 mmol) in benzene (10 ml), propargyl amine (0.316 g, 5.74 mmol) was added at room temperature. While reaction mixture is stirring at room temperature for 10 min, the solution of chloroacetaldehyde (**77**) (0.751 g, 45%, 4.31 mmol) was added slowly to this mixture. After completion of the addition, reaction mixture was heated to reflux temperature for 20 h with using Dean-Stark apparatus and 4Å molecular sieve. After reaction completion, reaction solvent was removed under the reduced pressure. Then the residue was extracted with EtOAc. (3x 30 ml), and dried over $MgSO_4$. Removal of solvent under the reduced pressure gave crude (0.543 g). According to ^{1}H-NMR of crude, yield of furan diester **78** was 57% and pyrrole diester **80** was 32%.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J_{54} = 3.1 Hz, 1H, H-5), 6.58 (d, J_{45} = 3.1 Hz, 1H, H-4), 4.67 (d, J = 2.6 Hz, 2 H, -CH_2), 4.21 (s, 2H, -CH_2), 3.79 (s, 3H, -OCH_3), 3.71 (s, 3H, -OCH_3), 2.43 (t, J = 2.6 Hz, 1H, -CH);
^{13}C-NMR (100 MHz, CDO_3D) δ 172.1, 167.3, 132.7, 122.6, 115.1, 110.7, 78.6, 75.5, 52.7, 51.4, 37.4, 31.5;
IR (ATR) 3277, 1725, 1686, 1557, 1501, 1436, 1346, 1271, 1230, 1201, 1138, 1054, 1034, 991, 929, 900, 780;
Anal. Calcd. for $C_{12}H_{13}NO_4$: C 61.27, H 5.57, N 5.95. Found: C 61.23, H 5.55, N 6.00.

3.3 Synthesis of methyl 2-(2-hydrazino-2-oxoethyl)-1-prop-2-ynyl-1*H*-pyrrole-3-carboxylate (88)

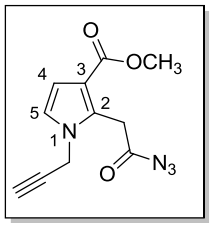
To a solution of methyl 2- (2-methoxy-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**80**) (1.52 g, 6.46 mmol) in methanol (15 ml), hydrazine monohydrate (1.62 g, 32 mmol) was added at room tempareture. The reaction was stirred for 20 h at room temperature. Precipitate was filtrated and washed with 5 ml of methanol, which afforded methyl 2-(2-hydrazinyl-2-oxoethyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**88**) (1.41 g, 6.0 mmol) as a white solid (1.41 g, 92%), mp 149-150 °C.



^{1}H-NMR (400 MHz, DMSO-*d6*) δ 9.08 (br t, 1H, -NH), 6.86 (d, J_{54} = 3.1 Hz, 1H, H-5), 6.39 (d, J_{45} = 3.1 Hz, 1H, H-4), 4.87 (d, J = 2.6 Hz, 2H, -CH_2), 4.19 (br d, J = 3.97 Hz, 2H, -CH_2), 3.90 (br s, 2H, -NH_2), 3.68 (s, 3H, -OCH_3), 3.50 (t, J = 2.6, 1H, -CH);
^{13}C-NMR (100 MHz, DMSO-*d6*) δ 167.7, 164.6, 132.6, 121.2, 112.7, 108.8, 78.4, 76.5, 50.6, 36.2, 29.6;
IR (ATR) 3269, 1686, 1643, 1557, 1498, 1433, 1342, 1274, 1222, 1189, 1136, 1037, 987;
HRMS calcd for $C_{11}H_{13}N_3O_3$ $[M+H]^+$: 236.10297. Found: 236.1054

3.4 Synthesis of 1-{[3-(methoxycarbonyl)-1-prop-2-ynyl-1*H*-pyrrol-2-yl]acetyl}triaza-1,2-dien-2-ium (89)

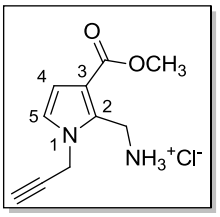
To a hydrazide **88** (1.41 g, 6.46 mmol) solution in 1M HCl (15 ml) cooled to 0-5 °C in an ice-bath, aqueous solution of $NaNO_2$ (0.60 g, 7.72 mmol) was added dropwise. The reaction was stirred for 1 h at 0-5 °C. The resulting solution was extracted with EtOAc (3 x 30 ml), and then the organic layer was washed with sat. Na_2CO_3 and brine, respectively. Evaporation of the solvent under reduced pressure gave orange colored crude (1.225 g). The purification of the reaction crude by column chromatography with hexane:ethyl acetate (3:1) gave 1-{[3-(methoxycarbonyl)-1-prop-2-ynyl-1*H*-pyrrol-2-yl]acetyl}triaza-1,2-dien-2-ium (**89**), as a white powder (1.02 g, 64%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J_{54} = 3.1 Hz, 1H, H-5), 6.58 (d, J_{45} = 3.1 Hz, 1H, H-4), 4.66 (d, J = 2.6 Hz, 2H, -CH_2), 4.22 (s, 2H, -CH_2), 3.80 (s, 3H, -OCH_3), 2.46 (t, J = 2.6 Hz, 1H, -CH);
^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.7, 165.2, 129.7, 121.6, 114.9, 110.1, 76.7, 74.6, 51.0, 36.8, 33.0;
IR (ATR) 3266, 2149, 1711, 1682, 1561, 1496, 1438, 1336, 1266, 1227, 1185, 1136, 1076, 1046, 1032.

3.5 Synthesis of methyl 2-[2-(chloroamino)-2-oxoethyl]-1-prop-2-ynyl-1*H*-pyrrole-3-carboxylate (101)

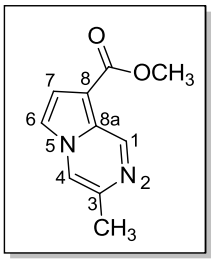
Azide **89** (1.02 g, 4.16 mmol) was dissolved in dry benzene (10 ml), and the solution was heated to reflux temperature, and stirred for 2.5 h. The solution was allowed to cool to room temperature, and then 8M HCl was added to this solution at room temperature through overnight stirring. After the completion of the reaction, aqueous layer was separated, and evaporation of water under reduced pressure provided methyl 2-[2-(chloroamino)-2-oxoethyl]-1-prop-2-ynyl-1*H*-pyrrole-3-carboxylate (**101)**, as a white-greyish solid (0.83 g, 87%), mp 183-184 °C.



^{1}H-NMR (400 MHz, DMSO-*d6*) δ 8.39 (br s, 3H, -NH_3), 7.03 (d, J_{54} = 3.0 Hz, 1H, H-5), 6.50 (d, J_{45} = 3.0 Hz, 1H, H-4), 5.18 (br d, *J* = 2.5, 2H, -CH_2), 4.29 (br q, 2H, -CH_2), 3.75 (s, 3H, -OCH_3), 3.60 (t, *J*= 2.5, 1H, -CH);
^{13}C-NMR (100 MHz, DMSO-*d6*) δ 164.1, 129.4, 123.0, 115.3, 109.3, 78.2, 77.1, 51.0, 36.6, 31.6
IR (ATR) 3268, 1686, 1643, 1558, 1497, 1435, 1341, 1219, 1191, 1049, 989, 931
HRMS calcd for $C_{10}H_{13}N_2O_2$ $[M+H]^+$: 194.10498. Found: 193.0983.

3.6 Synthesis of methyl 3-methylpyrrolo[1,2-*a*]pyrazine-8-carboxylate (102)

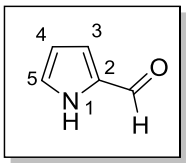
The corresponding salt **101** (0.260 g, 1.14 mmol) was dissolved in anhydrous DMA, then CuI (0.072 g, 0.38 mmol) and NEt_3 (0.9 ml) was added to the mixture, respectively. The temperature was brought to 130 °C with the protection the reaction from the light. The reaction was monitored via TLC. After reaction was stirred for 5 h, reaction mixture was cooled to the room temperature. Extraction was performed with ethyl acetate (15 ml) and water (25 ml); however, shaking resulted in an emulsion formation due to Cu^+. The middle and upper layer were separated from lower layer. The emulsion layer and aqueous layer were individually washed with ethyl acetate (2 x 10 ml). The combination of organic phases that was dried over MgSO4 was evaporated under reduced pressure gave dark-viscous crude (0.33 g). Column chromatography over silica gel eluted with ethyl acetate gave the unidentified fraction (6 mg) first and the second isolated product was the desired pyrrolo[1,2-*a*]pyrazine **102** as a brownish solid (35 mg, 17%), 110-111 °C.



^{1}H-NMR (400 MHz, acetone-*d6*) δ 9.32 (s, 1H, H-1), 8.17 (s, 1H, H-4), 7.60 (d, J_{67} = 2.7 Hz, 1H, H-6), 7.23 (d, J_{76} = 2.7 Hz, 1H, H-7), 3.87 (s, 3H, -OCH_3), 2.40 (s, 3H, -CH_3);
^{13}C-NMR (100 MHz, acetone-*d6*) δ 165.6, 145.9, 139.7, 129.8, 118.5, 118.0, 117.3, 108.6, 52.4, 21.7;
IR (ATR) 1688, 1532, 1449, 1357, 1273, 1243, 1201, 1150, 1079, 1044, 943, 817, 738;
HRMS calcd for $C_{10}H_{10}N_2O_2$ $[M+H]^+$: 191.0815. Found: 191.0850.

3.7 Synthesis of 1*H*-pyrrole-2-carbaldehyde (54)

To a solution of $POCl_3$ (34.25 g, 0.2234 mol) and DMF (19.61 g, 0.2683 mol) in dry ether (60 ml), pyrrole (15.0 g, 0.2234 mol) was added dropwise in an ice-bath. After the reaction was stirred for 24 h, the mixture was quenched with sat. $NaHCO_3$ solution until pH was brought around 7. Then the extraction was performed with ethyl acetate. (Each 200 ml aqueous phase was washed with 250 ml ethyl acetate with 3 times.) Dried over $MgSO_4$ and then the evaporation of solvent under the reduced pressure gave residue. Separation by column chromatography eluted with hexane:ethyl acetate (3:1) gave successively 1*H*-pyrrole-2-carbaldehyde (**54**) as a needle shaped colorless crystals (13.5 g, 64%), mp 44-45°C.

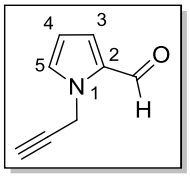


^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.47 (br s, 1H, -NH), 9.51 (d, *J* = 1.0, 1H, -CH), 7.18 (br s, 1H, H-3), 7.01 (ddd, J_{54} = 3.8 Hz, J_{53} = 2.3 Hz, ^{4}J =1.5 Hz, 1H, H-5), 6.35 (ddd, J_{45} = 3.8 Hz, J_{43} =2.4 Hz, ^{4}J = 2.0 Hz, 1H, H-4);
^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.4, 132.8, 126.9, 121.8, 111.3.

3.8 Synthesis of 1-prop-2-ynyl-1*H*-pyrrole-2-carbaldehyde (110)

To a solution of 1*H*-pyrrole-carbaldehyde (**54**) (10.0 g, 0.1051 mol) in DMF (70 ml), NaH (4.08 g, 0.17 mol) was added slowly to this solution cooled in an ice-bath. After the completion of addition, the reaction mixture was stirred for 30 min, whereupon propargyl bromide (16.2 g, 0.14 mol) was carefully added drop by drop to the solution. The reaction mixture was stirred for 24 h-48 h. Extraction with ethyl acetate (3 x 150 ml) afforded the residue, which was then separated by column

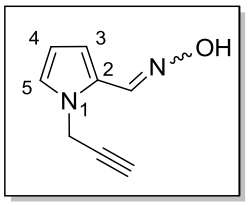
chromatography on silica gel eluted with hexane:ethyl acetate (3:1) to yield 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde (**110**) as on orange liquid (9.94 g, 71%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J* = 1.0 Hz, 1H, -CH), 7.25 Hz (br s, 1H, H-3), 6.95 (dd, J_{54} = 4.0 Hz, J_{53} = 1.7 Hz, 1H, H-5), 6.27 (dd, J_{45} = 4.0 Hz, J_{43} = 2.6 Hz, 1H, H-4), 5.20 (d, *J* = 2.6 Hz, 2H, -CH_2), 2.46 (t, *J* = 2.6 Hz, 1H, -CH);
^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.5, 131.0, 130.3, 124.9, 110.1, 77.4, 74.3, 38.1.

3.9 Synthesis of 1-prop-2-ynyl-1*H*-pyrrole-2-carbaldehyde oxime (111)

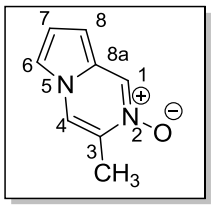
To the mixture of $NH_2OH.HCl$ and anhydrous Na_2CO_3 in ethanol (10 ml), a solution of 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde (**101**) (0.5 g, 3.76 mmol) in ethanol (10 ml) was added. The reaction mixture was heated to 70 °C for 6 h. After the completion of reaction, ethanol was removed under reduced pressure. H_2O (20 ml) was added and the mixture was extracted with ethyl acetate (3 x 20 ml). Organic layers were combined and dried over $MgSO_4$ and finally evaporation of solvent under reduced pressure gave 0.46 g the mixture of *E*- and *Z*-isomers of 1-prop-2-ynyl-1*H*-pyrrole-2-carbaldehyde oxime **111** as a light orange crystals. (*E*-isomer 0.356 g, 64 % and *Z*-isomer 0.089 g, 16%. The corresponding yields were calculated according to isomers' ratio in NMR.)



^{1}H-NMR (*E*-isomer) (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, -CH), 6.99 (br dd, J_{34} = 3.6 Hz, J_{35} = 1.7 Hz, 1H, H-3), 6.45 (dd, J_{54} = 3.7 Hz, J_{53} = 1.7 Hz, 1H, H-5), 6.21 (br dd, J_{45} = 3.6 Hz, J_{43}= 3.6 Hz, 1H, H-4), 5.00 (d, *J* = 2.5 Hz, 2H, -CH_2), 2.43 (t, *J* = 2.5 Hz, 1H, -CH);
^{1}H-NMR (*Z*-isomer) (400 MHz, $CDCl_3$) δ 7.56 (s, 1H, -CH), 7.37 (dd, J_{34} = 3.9 Hz, J_{35} = 1.6 Hz, 1H, H-3), 6.87 (br dd, J_{54} = 3.5 Hz, J_{53}= 1.7 Hz, 1H, H-5), 6.28 (dd, J_{45} = 3.5 Hz, J_{43} = 3.1 Hz, 1H, H-4), 4.78 (d, *J* = 2.5 Hz, 2H, -CH_2), 2.48 (t, *J* = 2.5 Hz, 1H, -CH);
^{13}C-NMR (*E*-isomer) (100 MHz, $CDCl_3$) δ 143.2, 125.8, 124.4, 115.7, 109.2, 78.2, 73.7, 38.4;
^{13}C-NMR (*Z*-isomer) (100 MHz, $CDCl_3$) δ 135.6, 124.6, 122.4, 119.7, 109.6, 77.2, 74.6, 37.0;
IR (ATR) 3225, 1730, 1630, 1047, 1295, 1244, 1078, 933, 818, 725, 665, 504;
HRMS for $C_8H_8N_2O$ $[M+H]^+$: 149.07094. Found: 149.072.1.

3.10 Synthesis of 3-methylpyrrolo[1,2-*a*]pyrazine 2-oxide (112)

E/*Z*-isomer of the corresponding oxime **111** (100 mg, 0.675 mmol) was dissolved in $CHCl_3$ (3 ml) and $AuCl_3$ (6.1 g, 3 mol%) was added in this solution. Reaction mixture was stirred for 20-24 h at room temperature. Then reaction solvent was evaporated under the reduced pressure. The crude gave the *N*-oxide **112** (97 mg, 97%). In order to obtain the analytically pure sample, purification column chromatography eluted with ethyl acetate was performed, which afforded **112** as a yellow solid, 62 mg. (62%) **112** was further purified by recrystallization from $CHCl_3$ into the diethyl ether atmosphere to give snowflake type colorless crystals, mp 78-79 °C.



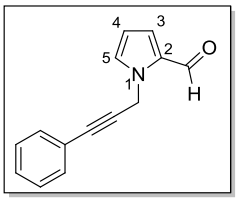
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.74 (br s, 1H, H-1), 7.65 (m, 1H, H-4), 7.33 (m, 1H, H-8), 6.81 (dd, J_{67} = 4.1 Hz, J_{68} = 2.5 Hz, 1H, H-6), 6.73 (m, 1H, H-7), 2.40 (d, *J* = 0.9 Hz, 3H, -CH_3);
^{13}C-NMR (400 MHz, $CDCl_3$) δ 144.4, 135.2, 127.4, 114.8, 114.5, 114.2, 103.0, 20.7;
IR (ATR) 1629, 1302, 1036, 926, 721, 421;
HRMS for $C_8H_8N_2$ $[M+H]^+$: 133.07602. Found: 133.0760.

3.11 General procedure for Sonogashira couplings (116, 117, 118)

Cuprous iodide (17.05 mg, 0.089 mmol), triphenylphosphine (89 mg, 0.339 mmol), palladium acetate (17.05 mg, 0.076 mmol) and dry diisopropylamine (14 ml, 0.138 mmol) were added in a solution of aryl halide (6.83 mmol) in dry THF (50 ml) under nitrogen atmosphere. Then 1-(prop-2-yn-1-yl)-1*H*-

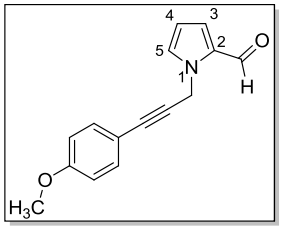
pyrrole-2-carbaldehyde (**107**) (1 g, 7.51 mmol) diluted in dry THF (5 ml) was added in this reaction mixture at room temperature. The mixture was heated to reflux temperature and stirred for 24 h. After cooling, solvent was removed under reduced pressure. H_2O (50 ml) was added to the residue and extracted with ethyl acetate (3 x 50 ml) and lastly the combined organic layers washed with brine. Dried over $MgSO_4$ and removal of solvent under reduced pressure gave the crude. Separation of the product with column chromatography on silica gel eluted with hexane:ethyl acetate (3:1) afforded the compounds **116-118**.

1-(3-Phenylprop-2-ynyl)-1*H*-pyrrole-2-carbaldehyde (116): obtained as a yellowish liquid (0.943 g, 66 % isolated yield).



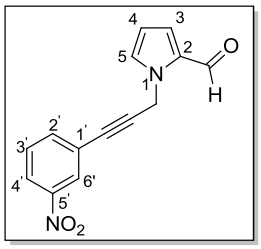
^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J =0.9 Hz, 1H, -CH), 7.47-7.43 (m, 5H, -CH), 7.37 (br s, 1H, H-3), 6.98 (dd, J_{54} = 4.0 Hz, J_{53} = 1.7 Hz, 1H, H-5), 6.30 (dd, J_{45} = 4.0 Hz, J_{43}= 2.7 Hz, 1H, H-4), 5.43 (s, 1H, -CH_2);
^{13}C-NMR (400 MHz, $CDCl_3$) δ 179.5, 131.7, 131.1, 130.4, 128.7, 128.3, 124.9, 122.1, 110.0, 86.0, 82.6, 38.9.

1-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-1*H*-pyrrole-2-carbaldehyde (117): obtained as a yellowish liquid (0.434 g, 27% isolated yield).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 0.9 Hz, 1H, -CH), 7.47-7.43 (m, 5H, -CH), 7.37 (br s, 1H, H-3), 6.98 (dd, J_{54} = 4.0 Hz, J_{53} = 1.7 Hz, 1H, H-5), 6.30 (dd, J_{45} = 4.0 Hz, J_{43} = 2.7 Hz, 1H, H-4), 5.43 (s, 1H, -CH_2);
^{13}C-NMR (400 MHz, $CDCl_3$) δ 179.4, 160.0, 133.2, 131.0, 130.3, 124.8, 114.1, 113.8, 109.8, 86.0, 81.2, 55.1, 38.9;
IR (ATR) 2928, 1604, 1508, 1465, 1298, 1244, 1172, 1075, 1027, 939, 829, 723, 604, 534;
HRMS for $C_{15}H_{13}NO_2$ $[M+H]^+$: 240.10191. Found: 240.1037.

1-[3-(3-Nitrophenyl)prop-2-yn-1-yl]-1*H*-pyrrole-2-carbaldehyde (118): obtained as a pale yellow powder (0.733 g, 42% isolated yield), mp 107-108 °C.



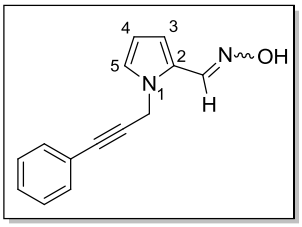
^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 0.9 Hz, 1H, -CH), 8.26 (br dd, $J_{6'4'}$ = 3.5 Hz, $J_{6'3'}$ = 1.8 Hz, 1H, H-6'), 8.17 (ddd, $J_{4'3'}$ = 8.3 Hz, $J_{4'2'}$ = 2.2 Hz, $J_{4'6'}$ = 1.0 Hz, 1H, H-4'), 7.73 (br ddd, $J_{3'4'}$ = 8.3 Hz , $J_{3'2'}$ = 7.7 Hz, $J_{3'6'}$ = 1.1 Hz, 1H, H-3'), 7.50 (br t, J = 8.0, 1H, H-), 7.28 (br s, 1H, H-3), 7.00 (ddd, J_{54} = 4.3 Hz, J_{53}= 1.9 Hz, J = 0.7 Hz, 1H, H-5), 6.32 (ddd, J_{45}= 3.8 Hz, J_{43} = 2.8 Hz, J = 0.7 Hz, 1H, H-4), 5.45 (s, 2H, -CH_2);

^{13}C-NMR (400 MHz, $CDCl_3$) δ 179.6, 148.0, 137.4, 131.1, 130.4, 129.4, 126.6, 125.0, 123.9, 123.4, 110.3, 85.7, 83.1, 38.7;
IR (ATR) 1648, 1526, 1473, 1401, 1369, 1348, 1311, 1216, 1073, 904, 874, 805, 770, 732, 671, 606, 522.

3.12 General procedure for oxime generation (119 ,120, 121)

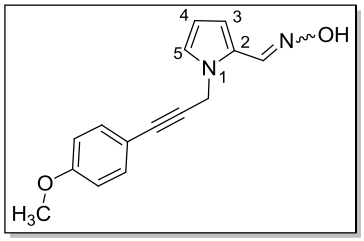
A solution of the starting compound **116** to **118** (1 equiv.) in ethanol was added to the mixture of $NH_2OH.HCl$ (2 equiv.) and anhydrous Na_2CO_3 (2 equiv.) in ethanol. The reaction mixture was heated to 70 °C for 7 h. After the completion of reaction, ethanol was removed under the reduced pressure, then H_2O (20 ml) was added to the residue. The mixture was extracted with ethyl acetate (3 x 20 ml). Organic layers were combined, washed with brine, dried over $MgSO_4$ and finally evaporation of solvent under reduced pressure gave the mixtures of *E*- and *Z*-isomers of the corresponding oximes **119** to **121**.

1-(3-phenylprop-2-ynyl)-1*H*-pyrrole-2-carbaldehyde oxime (119): obtained as a pale yellow powder (0.841 g, 3.75 mmol), *E*-isomer in a 62% yield and *Z*-isomer in a 31% yield.



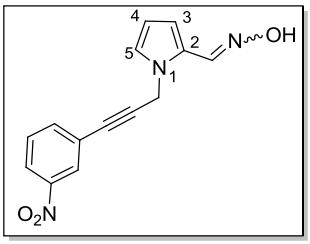
^{1}H-NMR (*E*-isomer) (400 MHz, $CDCl_3$) δ 8.16 (s, 1H, -CH), 7.49-7.42 (m, 2H), 7.33-7.30 (m, 3H), 7.09 (br dd, J_{34} = 2.8 Hz, J_{35}= 1.7 Hz, 1H, H-3), 6.49 (dd, J_{54} = 3.7 Hz, J_{53} = 1.7 Hz, 1H, H-5), 6.23 (dd, J_{45} = 3.7 Hz, J_{43} = 2.8 Hz, 1H, H-4), 5.21 (s, 2H, -CH_2);
^{1}H-NMR (*Z*-isomer) (400 MHz, $CDCl_3$) δ 7.66 (s, 1H, -CH), 7.49-7.42 (m, 2H), 7.39 (dd, J_{34} = 3.8 Hz, J_{35} = 1.5 Hz, 1H, H-3), 7.33-7.30 (m, 3H), 6.95 (br dd, J_{54} = 2.8 Hz, J_{53} = 1.7 Hz, 1H, H-5), 6.29 (dd, J_{43} = 3.8 Hz, J_{45} = 2.8 Hz, 1H, H-4), 5.00 (s, 2H, -CH_2);
^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3, 131.8 (br), 128.8, 128.6, 128.3, 128.2, 125.8, 124.6, 124.5, 122.3, 121.9, 119.6, 109.4, 109.0 115.5, 86.0, 85.5, 83.4, 82.5, 39.2;
IR (ATR) 2844, 1637, 1479, 1405, 1328, 1289, 1227, 1128, 1075, 924, 846;
HRMS for $C_{14}H_{12}N_2O$ $[M+H]^+$:225.10224. Found: 225.1062.

1-[3-(4-Methoxyphenyl)prop-2-ynyl]-1*H*-pyrrole-2-carbaldehyde oxime (120): obtained as a yellowish viscous liquid (0.388 g, 1.52 mmol), *E*-isomer in a 56 % yield, *Z*-isomer in a 28 % yield.



^{1}H-NMR (*E*-isomer) (400 MHz, $CDCl_3$) δ: 8.15 (s, 1H, -CH), 7.68 (d, *J* = 8.7 Hz, 2H, -CH), 7.08 (br dd, J_{34} = 2.8 Hz, J_{35} = 1.7 Hz, 1H, H-3), 6.83 (d, *J* = 8.8 Hz, 2H, -CH), 6.47 (dd, J_{54} = 3.8 Hz, J_{53} = 1.7 Hz, 1H, H-5), 6.21 (dd, J_{45} = 3.7 Hz, J_{43}= 2.8 Hz, 1H, H-3), 5.17 (s, 2H, -CH_2), 3.80 (s, 3H, -OCH_3);
^{1}H-NMR (*Z*-isomer) (400 MHz, $CDCl_3$) δ 7.65 (s, 1H, -CH), 7.38 (d, *J* = 4.8 Hz, 2H, -CH), 7.40 (br dd, J_{34} = 2.9 Hz , J_{35} = 1.8 Hz, 1H, H-3), 6.94 (br dd, J_{54} =3.7 Hz, J_{53} = 1.8, 1H, H-5), 6.28 (dd, J_{45} = 3.7 Hz, J_{43} = 2.9 Hz, 1H, H-4), 4.97 (s, 2H, -CH_2), 3.80 (s, 3H, -OCH_3);
^{13}C-NMR (100 MHz, aceton-*d6*) δ 162.0, 161.9, 143.7, 136.9, 135.0, 134.9, 134.9, 127.2, 127.1, 125.6, 125.2, 120.0, 116.3, 116.0, 115.9, 115.9, 115.9, 86.6, 86.2, 84.9, 84.5, 56.6, 40.3, 39.0, 31.9;
IR (ATR) 2928, 1604, 1508, 1465, 1289, 1244, 1172, 1075, 1027, 939, 829, 723, 604, 534.

1-[3-(3-nitrophenyl)prop-2-ynyl]-1*H*-pyrrole-2-carbaldehyde oxime (121): obtained as pale yellow solid (0.690 g, 2.83 mmol), *E* isomer in a 60 % yield, *Z* isomer in a 30 % yield.

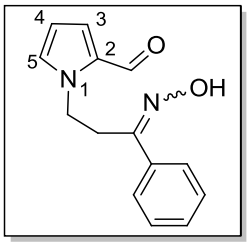


^{1}H-NMR (*E*-isomer) (400 MHz, $CDCl_3$) δ 8.27 (br s, 1H, -CH), 8.17 (m, 1H), 8.12 (m, 1H), 7.72 (m, 1H), 7.49 (m, 1H), 7.02 (br s, 1H, H-3), 6.45 (br dd, J_{54} = 2.1 Hz, 1H, H-5), 6.23 (br dd, J_{45} =2.1 Hz, 1H, H-4), 5.27 (s, 1H, -CH_2);
^{1}H-NMR (*Z*-isomer) (400 MHz, $CDCl_3$) δ: 8.26 (br s, 1H, -CH), 8.18 (m, 1H), 7.72 (m, 1H), 7.50 (m, 1H), 7.44 (br s, 1H, H-3), 7.01 (br s, 1H, H-5), 6.34 (br dd, 1H, H-4), 5.07 (s, 1H, -CH_2);
^{13}C-NMR (100 MHz, aceton-*d6*) δ: 150.2, 143.7, 139.4, 139.4, 132, 132, 128.0, 127.9, 127.5, 127.4, 126.5, 126.0, 125.7, 125.4, 125.2, 125.1, 120.6, 116.3, 110.8 (br), 89.4, 88.6, 84.3, 83.7, 40.3, 38.9;
IR(ATR) 3080, 1646, 1527, 1451, 1390, 1346, 1099, 932, 899, 871, 834, 784, 734, 670, 531, 408;
HRMS for $C_{14}H_{11}N_3O_3$ $[M+H]^+$:270.08732. Found: 270.0900.

3.13 General procedure for oxime-oxime transformation reactions (122, 130, 131)

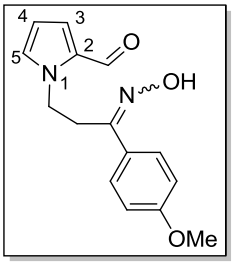
Starting material **119** to **121** (2.0 mmol) was dissolved in $CHCl_3$ (5 ml). $AuCl_3$ (3 mol%) was added in this solution and the reaction mixture was stirred for 24 h at room temperature. Evaporation of the solvent under reduced pressure gave the residue. Mixture of *E*/*Z*-isomers of **122** to **131** was purified with column chromatography on silica gel eluted with indicated solvent systems below.

1-[(3*E*/*Z*)-3-(Hydroxyimino)-3-phenylpropyl]-1*H*-pyrrole-2-carbaldehyde (122): Ratio of isomers according to ^{1}H-NMR gave the formation of *E*-isomer yielded as 85% and the formation of *Z*-isomer yielded as 6%. Purification of the residue (0.288 g) by column chromatography on silica gel with hexane:ethyl acetate (3:1) was carried out to afford **122** as a pale yellow solid.



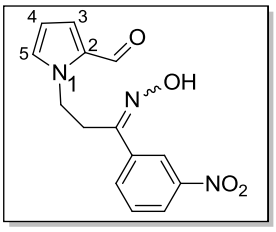
^{1}H-NMR (*E*-isomer) (400 MHz, $CDCl_3$) δ 9.56 (br s, 1H, -CH), 7.58-7.54 (m, 2H), 7.36-7.34 (m, 3H), 6.91-6.89 (m, 2H), 6.15 (dd, J_{45} = 3.8 Hz, J_{43}= 2.7 Hz, 1H, H-4), 4.64 (t, *J* = 7.1 Hz, 2H, -CH_2), 3.29 (t, *J* = 7.1 Hz, 2H, -CH_2);
^{1}H-NMR (*Z*-isomer) (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 0.7 Hz, 1H, -CH), 7.53-7.50 (m, 2H), 7.43-7.39 (m, 3H), 6.95-6.92 (m, 2H), 6.19 (dd, J_{45} = 4.0 Hz, J_{43} = 2.5 Hz, 1H, H-3), 4.51 (t, *J* = 7.1 Hz, 2H, -CH_2), 3.09 (7.1 Hz);
^{13}C-NMR (*E*-isomer) (100 MHz, $CDCl_3$) δ 179.4, 157.0, 134.9, 131.9, 131.2, 129.6, 128.6, 126.2, 125.1, 109.8, 45.6, 29.0;
IR (ATR) 3063, 1659, 1480, 1403, 1362, 1321, 1213, 1068, 1026, 937, 743, 681, 609, 466.

1-[(3*E*/*Z*)-3-(Hydroxyimino)-3-(4-methoxyphenyl)propyl]-1*H*-pyrrole-2-carbaldehyde (130): Ratio of isomers according to ^{1}H-NMR gave the formation of *E*-isomer yielded as 38% and the formation of *Z*-isomer yielded as 38%. Purification of the residue (0.228 g) by column chromatography on silica gel with hexane:ethyl acetate (3:1) was carried out to afford **122** as a viscous yellow liquid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H, -CH), 9.53 (s, 1H, -CH), 7.93-7.89 (m, 2H), 7.55-7.52 (m, 2H), 7.14 (br s, 1H, -CH), 6.93 (dd, *J* = 4.0 Hz, *J* = 1.6 Hz, 1H), 6.92-6.89 (m, 4H), 6.89-6.87(m, 3H), 6.85 (m, 1H), 6.18 (dd, *J* = 4.0 Hz, *J* = 2.5 Hz, 1H, -CH), 6.14 (dd, *J* = 4.0 Hz, *J* = 2.7 Hz, 1H, -CH), 4.70 (t, *J* = 6.4 Hz, 2H, -CH_2), 4.61 (t, *J* = 7.2 Hz, 1H, -CH), 3.84 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 3.43 (t, *J* = 6.4 Hz, 2H, -CH), 3.24 (t, *J* = 7.2 Hz);
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 178.4, 178.3, 162.7, 159.6, 155.1, 133.0, 131.0, 130.0, 129.4, 129.1, 128.6, 126.7, 126.5, 126.3, 124.4, 124.1, 113.0, 112.9, 112.7, 108.8, 54.4, 54.2, 44.7, 43.4, 38.3, 27.8;
IR (ATR) 2838, 1654, 1598, 1512, 1402, 1364, 1320, 1249, 1169, 1077, 1027, 832, 745, 594;
HRMS for $C_{15}H_{16}N_2O_3$ $[M+H]^+$:273.12337. Found: 273.1236.

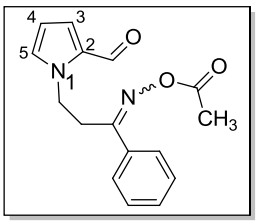
1-[(3*E*/*Z*)-3-(hydroxyimino)-3-(3-nitrophenyl)propyl]-1*H*-pyrrole-2-carbaldehyde (131): Ratio of isomers according to ^{1}H-NMR gave the formation of *E*-isomer yielded as 73% and the formation of *Z*-isomer yielded as 15%. Purification of the residue (0.134 g) by column chromatography on silica gel with hexane:ethyl acetate (2:1) was carried out to afford **131** as a pale yellow solid.



^{1}H-NMR (*E*-isomer**)** (400 MHz, $CDCl_3$) δ 9.55 (s, 1H, -CH), 8.31-8.29 (m, 1H), 8.15 (m, 1H), 7.92-7.88 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 1H, -CH), 6.90-6.88 (m, 2H), 6.12 (br dd, *J* = 3.2 Hz, 1H, -CH), 4.65 (t, *J* = 7.0 Hz, 2H, -CH_2), 3.31 (t, *J* = 7.0 Hz, 2H, -CH_2);
^{1}H-NMR (*Z*-isomer) (400 MHz, $CDCl_3$) δ 9.49 (s, 1H, -CH), 8.21 (m, 2H), 7.81-7.77 (m, 1H), 7.58 (m, 1H), 6.93-6.91 (m, 2H), 6.19 (br dd, *J* = 3.3 Hz, 1H, H-4), 4.54 (t, *J* = 7.1 Hz, 2H, -CH_2), 3.1 (t, *J* = 7.1 Hz, 2H, -CH_2);
^{13}C-NMR (*E*-isomer) (100 MHz, $CDCl_3$) δ: 179.7, 155.0, 137.0, 132.0, 131.8, 131.1, 129.4, 126.0, 125.5, 123.8, 121.0, 110.1, 45.5, 28.5;
IR (ATR) 2920, 1625, 1524, 1476, 1401, 1343, 1077, 1030, 966, 733, 678, 605;
HRMS for $C_{14}H_{13}N_3O_4$ $[M-H]^-$:286.08333. Found: 286.0847.

3.14 Synthesis of 1-{(3*E*/*Z*)-3-[(acetyloxy)imino]-3-phenylpropyl}-1*H*-pyrrole-2-carbaldehyde (129)

129 (72 mg, 0.29 mmol) was successively dissolved in pyridine (5 ml) and then acetic anhydride (88 mg, 0.87 mmol) was introduced to the solution. The reaction mixture was stirred overnight at room temperature. Then H_2O (10 ml) was added in the reaction mixture, which was extracted with ethyl acetate (3 x 10 ml). The combined organic phases was washed with 2M HCl, 5% $NaHCO_3$, and brine, respectively, and dried over $MgSO_4$. Removal of the solvent under the reduced pressure gave *E*/*Z*-isomers as a yellow viscous liquid (52 mg, 62%). Ratio of isomers according to ^{1}H-NMR gave the formation of *E*-isomer yielded as 59% and the formation of *Z*-isomer yielded as 3%.



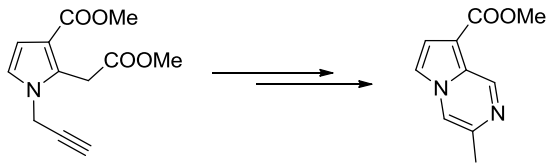
^{1}H-NMR (*E*-isomer) (400 MHz, $CDCl_3$) δ: 9.54 (br s, 1H, -CH), 7.70-7.67 (m, 2H, -CH), 7.43-7.35 (m, 3H, -CH), 6.90 (dd, J_{34} = 4.0 Hz, J_{35} = 1.7 Hz, 1H, H-3), 6.77 (br s, 1H, H-5), 6.14 (dd, J_{45} = 4.0 Hz, J_{43} = 2.5 Hz, 1H, H-4), 4.53 (t, *J* = 6.9 Hz, -CH_2), 3.34 (t, *J* = 6.9 Hz, -CH_2), 2.21 (s, 3H, -CH_3)
^{13}C-NMR (*E*-isomer) (100 MHz) δ: 179.2, 168.4, 162.6, 133.2, 131.5, 131.1, 130.1, 128.6, 127.1, 125.2, 109.9, 46.0, 30.0, 19.6;
IR (ATR) 1764, 1654, 1479, 1404, 1365, 1321, 1195, 997, 930, 748, 693, 607;
HRMS for $C_{16}H_{16}N_2O_3$ $[M+Na]^+$: 307.1053. Found 307.1085.

CHAPTER 4

CONCLUSION

Pyrrole skeleton has attracted chemists not only for its vital role in natural products but also for its broad applications in material sciences and playing as a key role for the construction of some polycyclic heteroaromatic molecules. A large number of studies concerning pyrroles present in the literature. For the last decades, particularly, using alkyne functionality substituted pyrrole ring, have gained significance among diverse synthetic approaches for the generation of heterobicyclic aromatic molecules. In this manner, we aimed obtaining pyrrolo[1,2-*a*]pyrazine moiety, a pyrrole fused heterocyclic molecule, starting from *N*-propargylic substituted pyrroles by metal-catalyzed heteroatom cyclization.

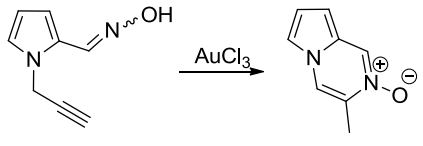
In the first part of this thesis, we pursued a purpose for the development of pyrrole[1,2-*a*]pyrazine derivatives starting from *N*-propargylic substituted pyrroles. To do so, we first achieved to synthesize our key compound *N*-propargylic substituted pyrrole dicarboxylate **80**, inspiring from a well-known substituted furan diester formation reaction, namely as Feist-Benary reaction. We modified Feist-Benary reaction by introducing ammonia or a primary amine to the mixture of 1,3-dicarboxylate **76**, chloroacetone **77** and a base, from which we successively got the desired product **80**. Then the proceeding reaction steps included conversion of ester group attached to C-2 of pyrrole ring to the amine group. We successfully performed this conversion via Curtius rearrangement to furnish our key compound amine **101**. Lastly, Cu-(I) catalyzed and base-assisted heteroatom 6-*exo*-dig cyclization afforded pyrrole[1,2-*a*]pyrazine derivative **102** (Scheme 50).



80 **102**

Scheme 50

6-Membered ring closure occurred to form **102** due to its possessing aromaticity and electrophilicity of the middle carbon of allene, which was formed via propargyl-allene isomerization in the presence of base. Therefore second part of this thesis was aimed to investigate how the presence of two different nucleophiles affected the ring formation. We chose 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde oxime (**111**) as a key molecule. According to our result, $AuCl_3$ assisted cyclization gave solely 6-*exo*-dig cyclization product, pyrrolo[1,2-*a*]pyrazine *N*-oxide derivative **112**, which is not described in the literature (Scheme 51).

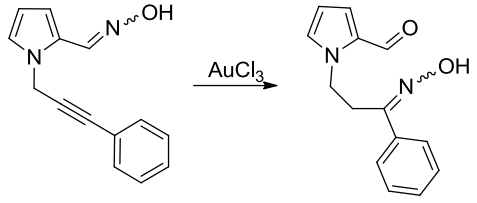


111 **112**

Scheme 51

We also performed the reaction shown in Scheme 49 with other metal catalysts, such as Ag^+, Cu^+ and Au^+ to search whether some other metal catalyst would provide different product rather than **112**. According to our results, pyrrolo[1,2-*a*]pyrazine *N*-oxide derivative **112** was the only product that was formed.

For the above reaction shown in Scheme 49, Au^{3+} which is a π electrophile, coordinated to triple bond for the activation of β-carbon. In the last part of this thesis, we tested the effect of an electron donating or withdrawing group attached to the terminal alkyne. We chose to perform Sonogashira coupling to introduce phenyl group to the terminal alkyne. After we successively obtained coupling product **116**, which was reacted with hydroxyl amine to give **119**. The formed oxime **119** underwent $AuCl_3$-catalyzed cyclization reaction. The reaction, however, went in a different side. We observed that oxime group attached to C-2 of the pyrrole ring moved to the β-carbon of propargyl group after a series of steps, which gave **122** (Scheme 52). The mechanism of this transformation has not been enlightened yet. Our future direction primarily includes conducting a mechanistical study on this transformation, and trying same reaction with an alkynyl substituted *N*-propargyl pyrrole oximes to study the effect of alkyl group to the activation of triple bond by a metal catalyst.



119 **122**

Scheme 52

In this way, we developed a new concise methodologies for the construction of pyrrolo[1,2-*a*]pyrazine derivatives, and we presented a new type of transformation, which is called oxime transformation, to the literature.

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APPENDIX A

SPECTRAL DATA

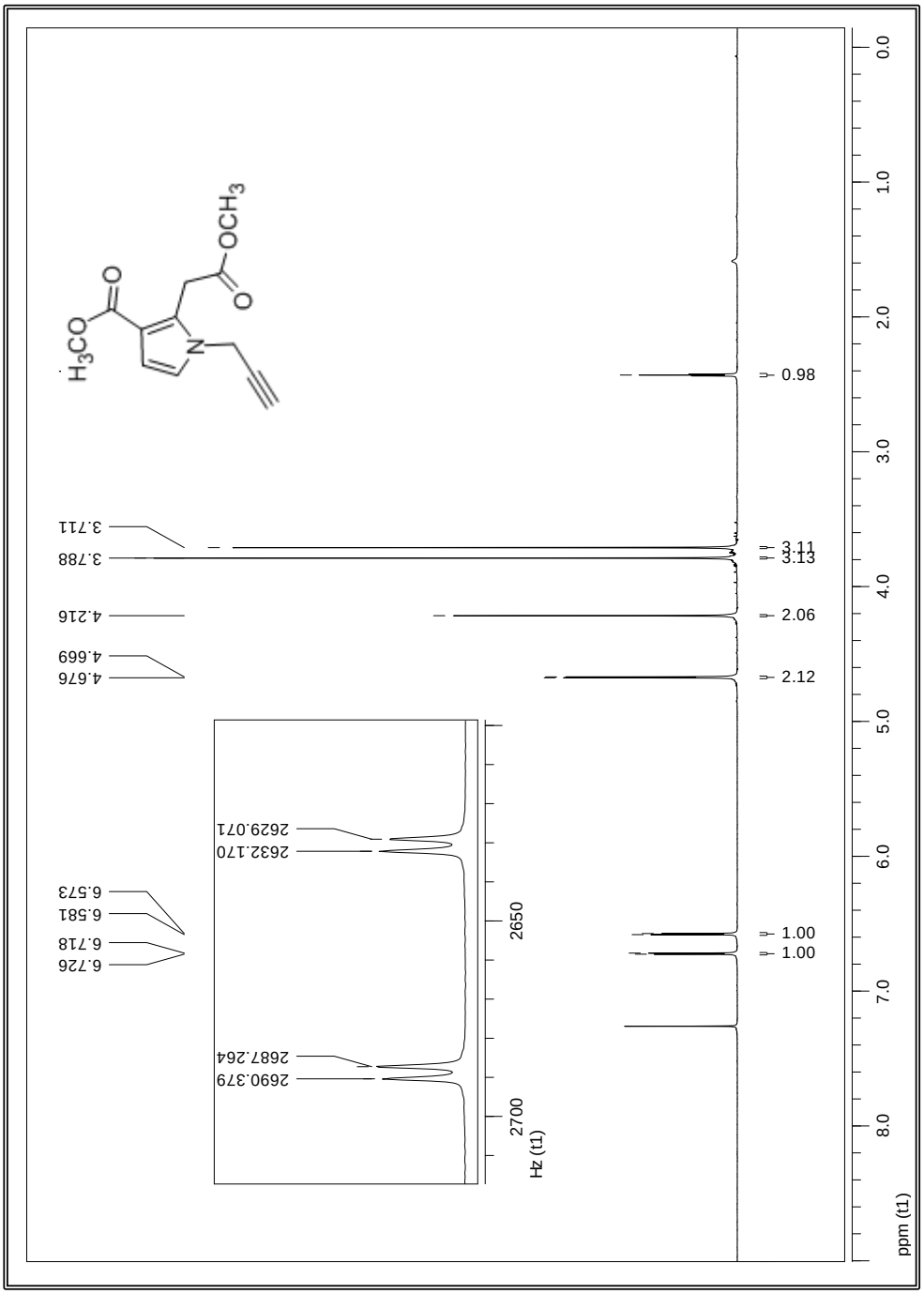

Figure 7 ^{1}H-NMR Spectrum of Compound **80**

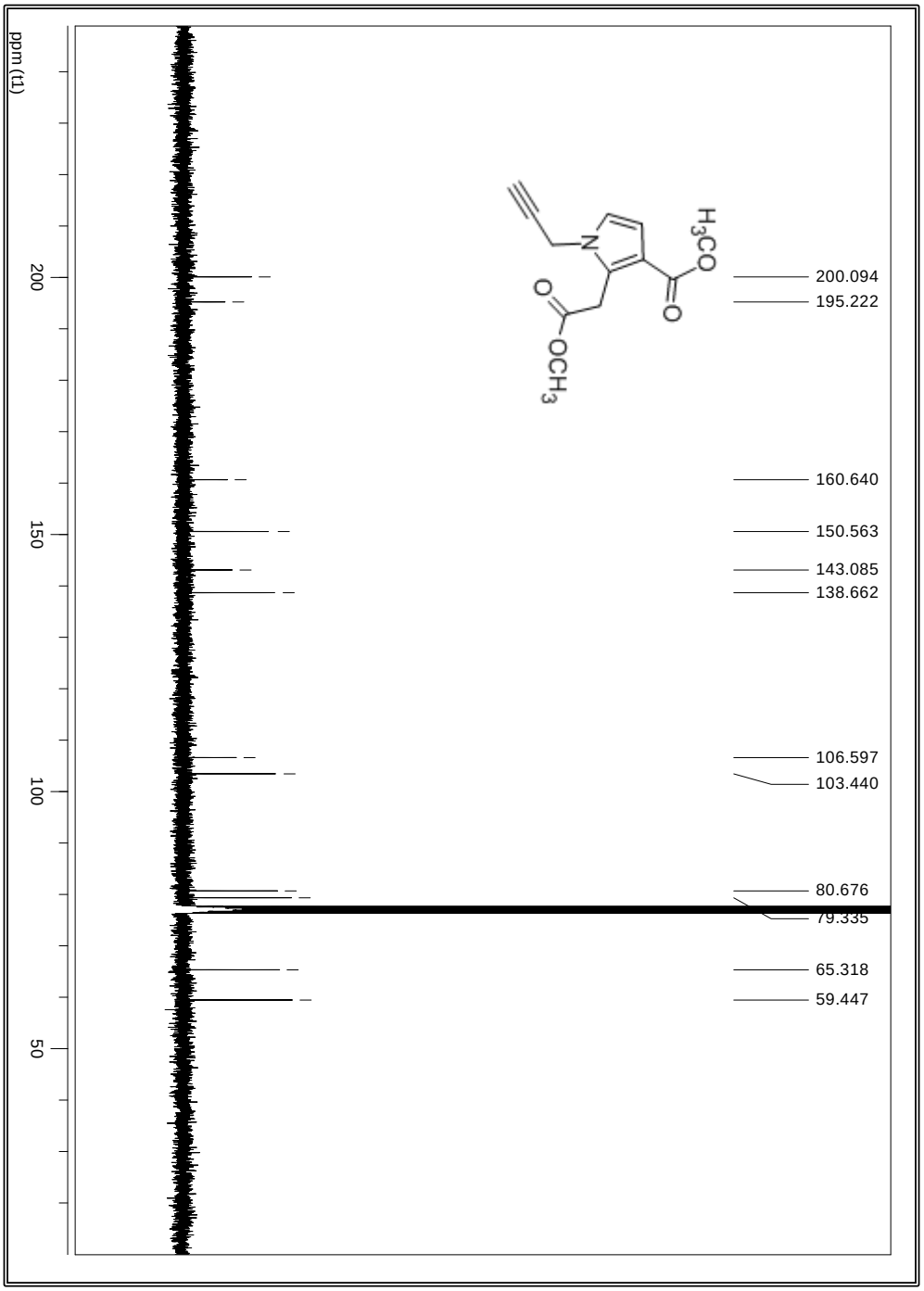

Figure 8 ^{13}C-NMR Spectrum of Compound **80**

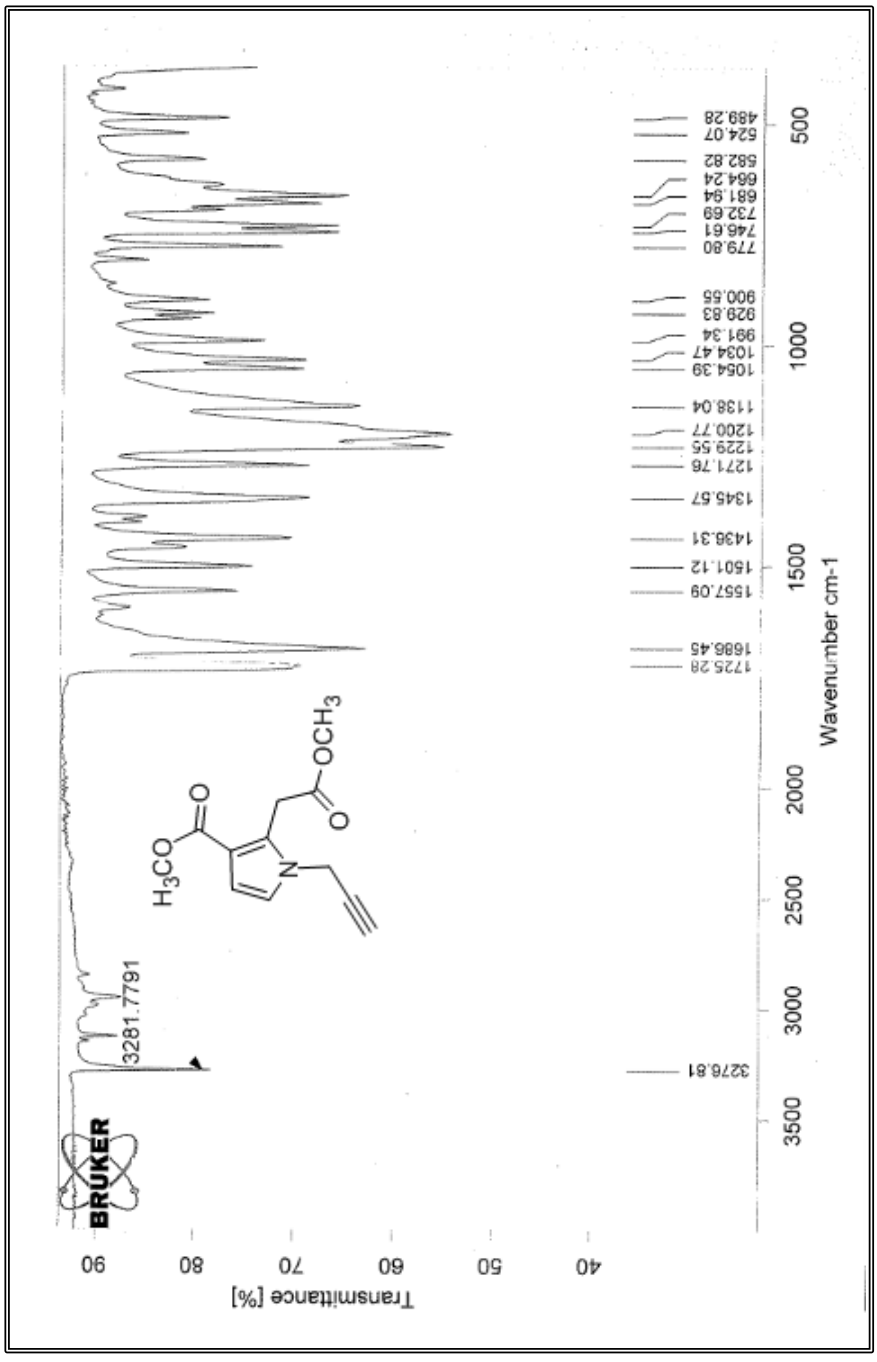

Figure 9 IR Spectrum of Compound **80**

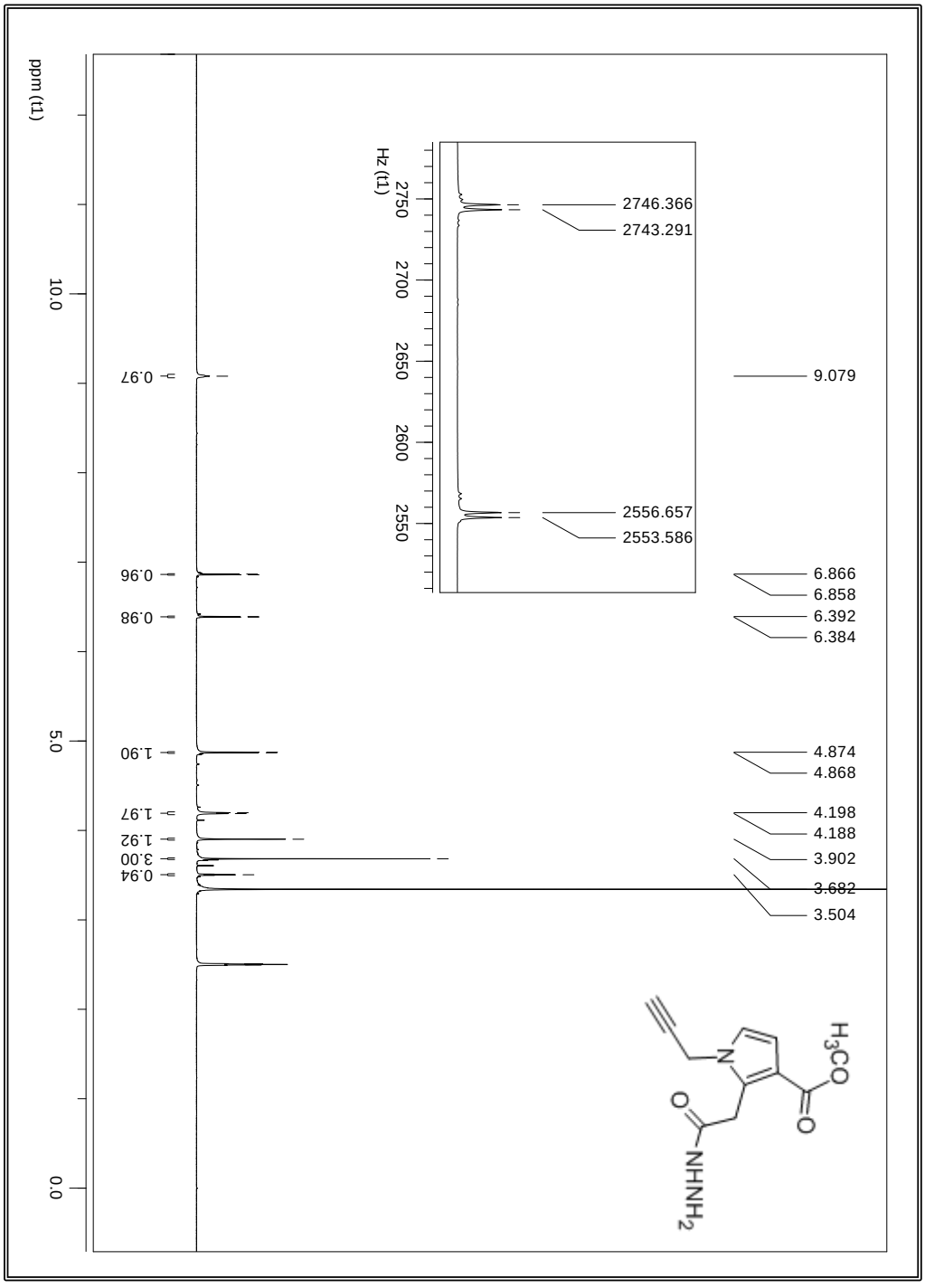

Figure 10 ^{1}H-NMR Spectrum of compound **88**

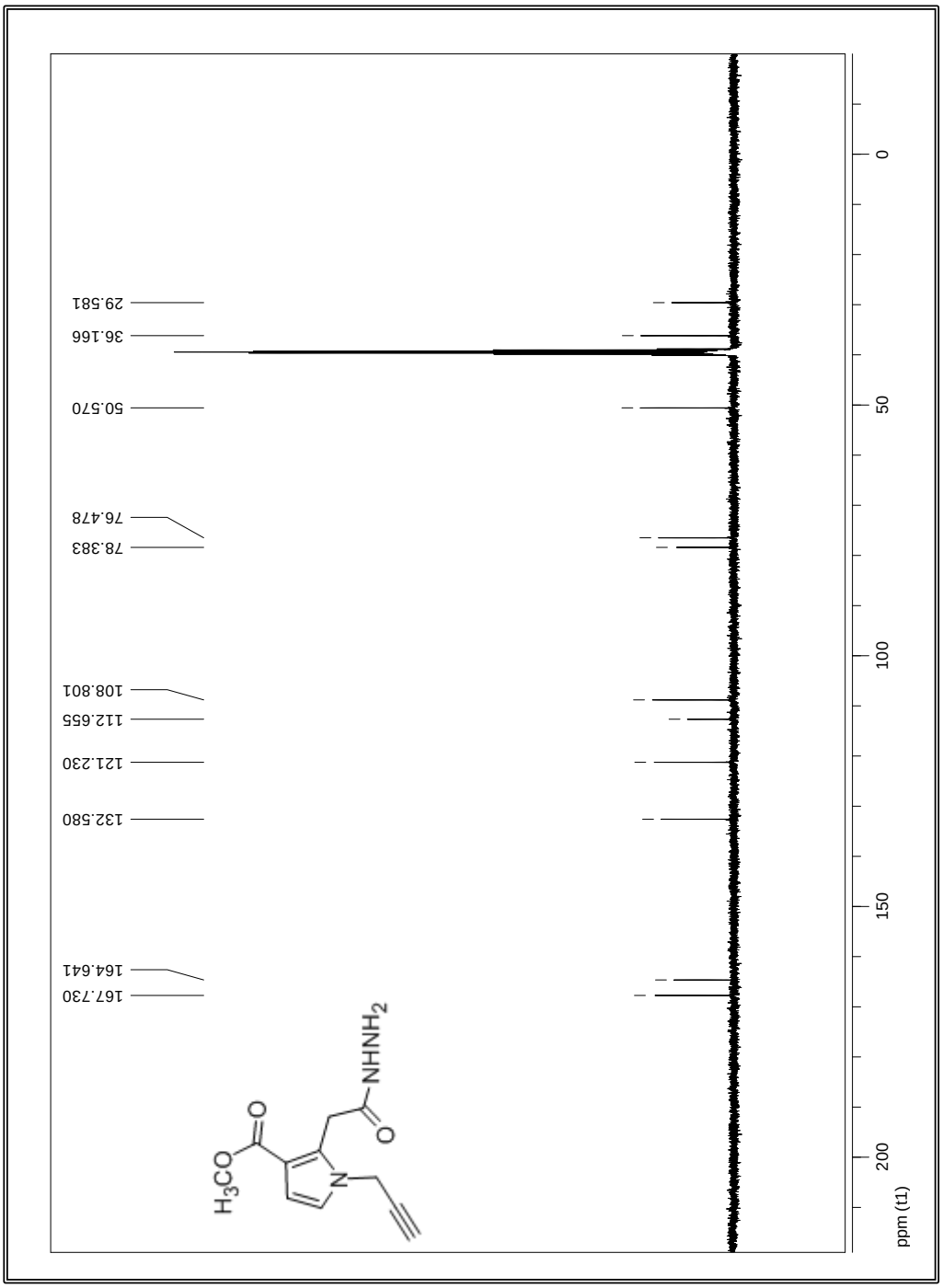

Figure 11 ^{13}C-NMR Spectrum of compound **88**

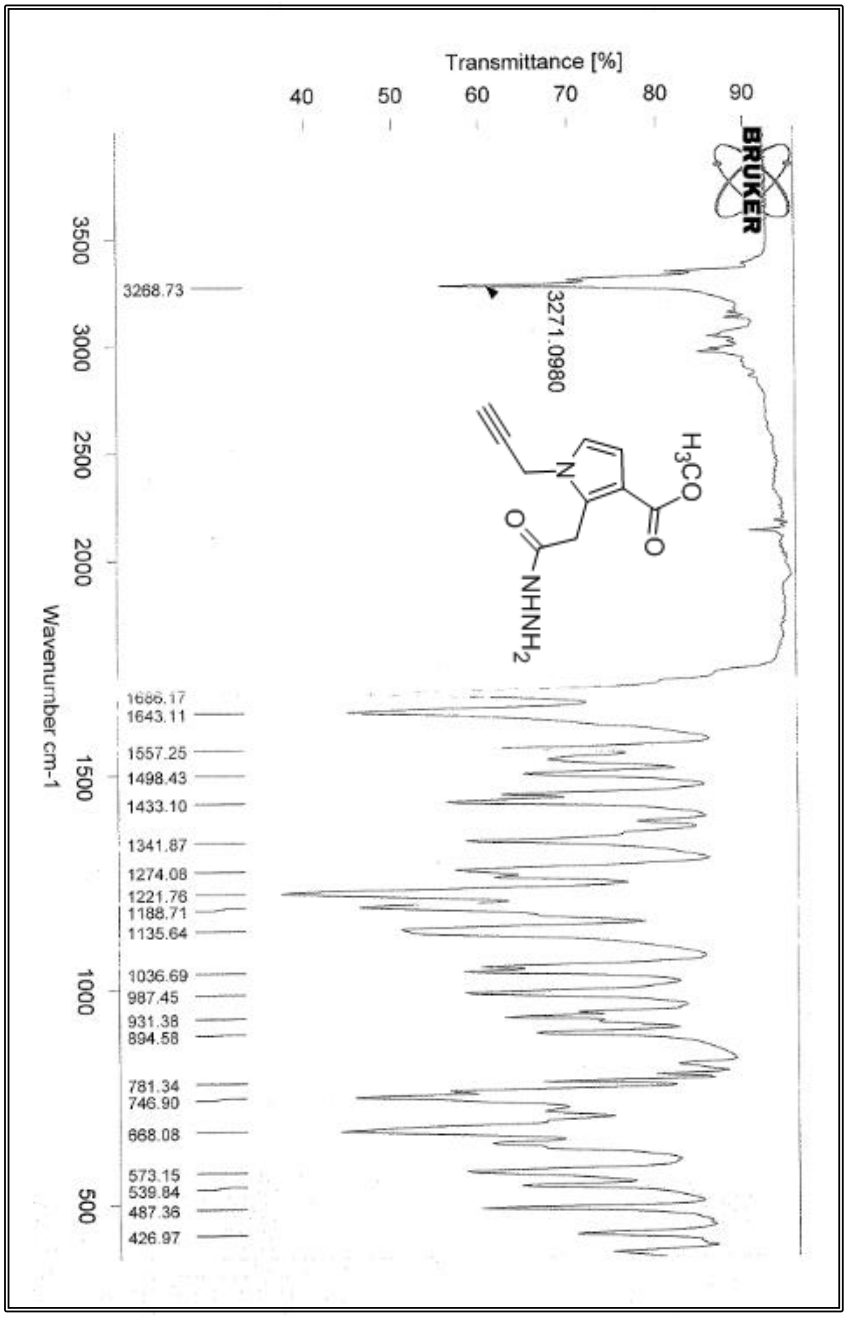

Figure 12 IR Spectrum of compound **88**

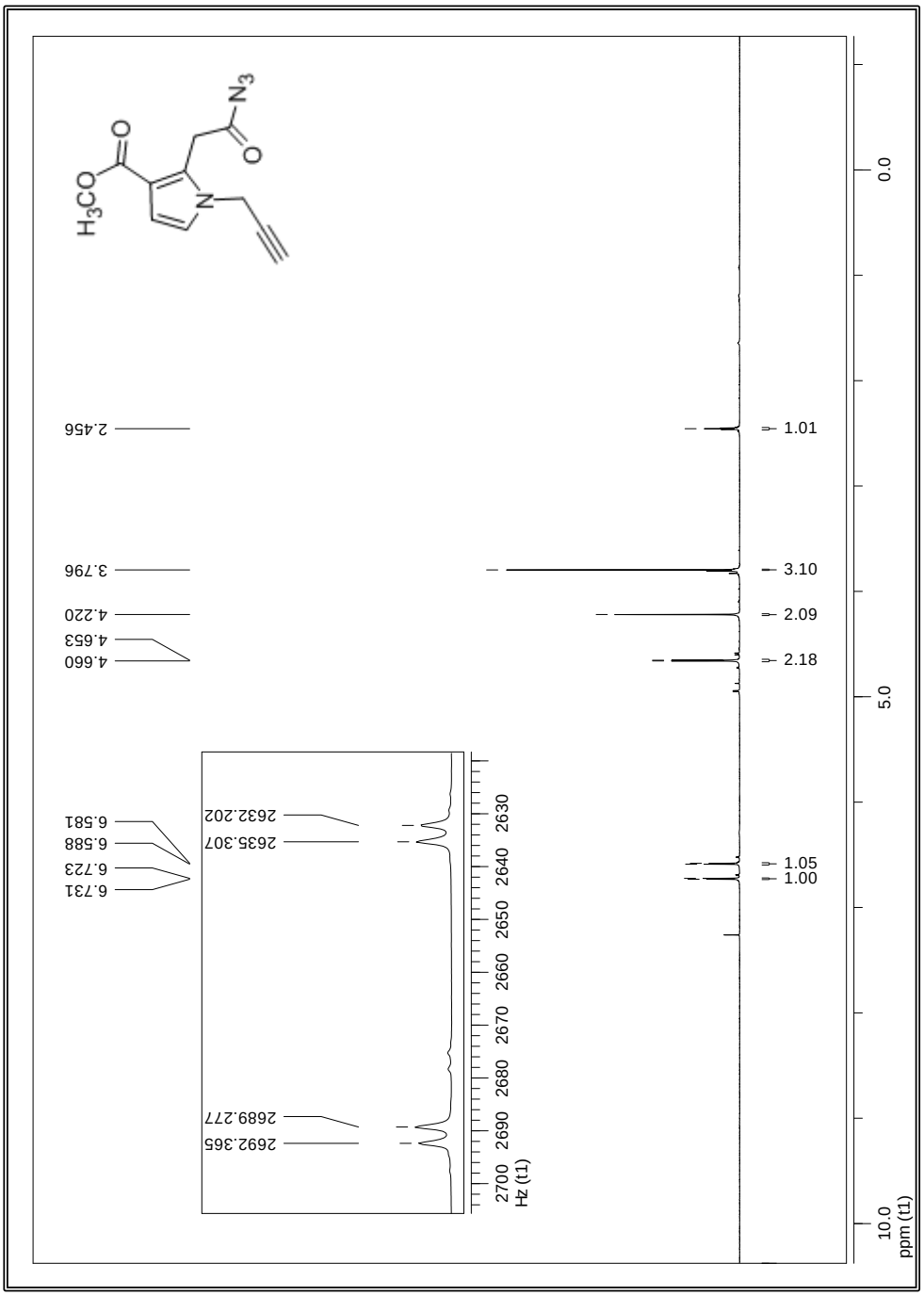

Figure 13 ^{1}H-NMR Spectrum of Compound **89**

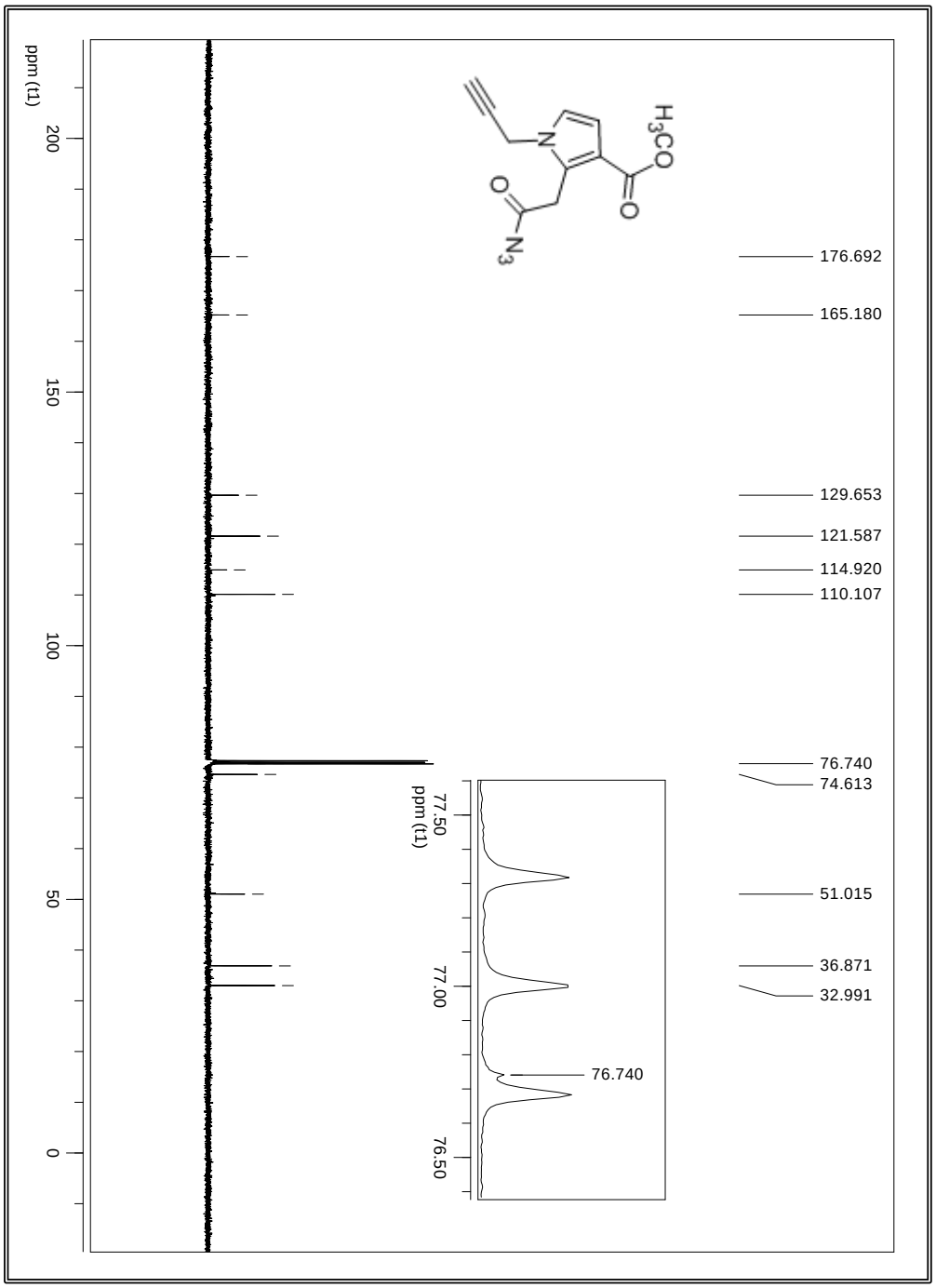

Figure 14 ^{13}C-NMR Spectrum of Compound **89**

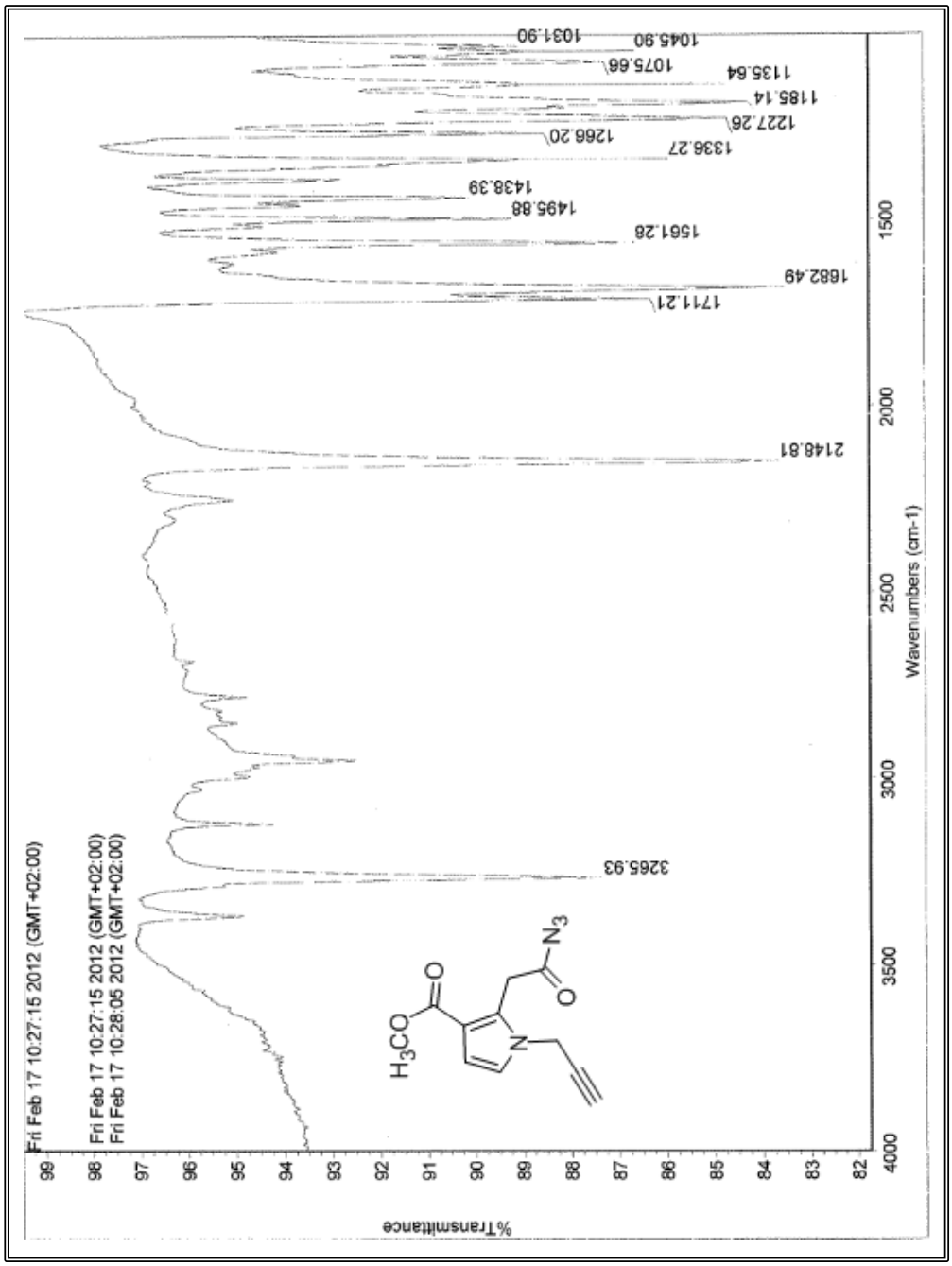

Figure 15 IR Spectrum of Compound **89**

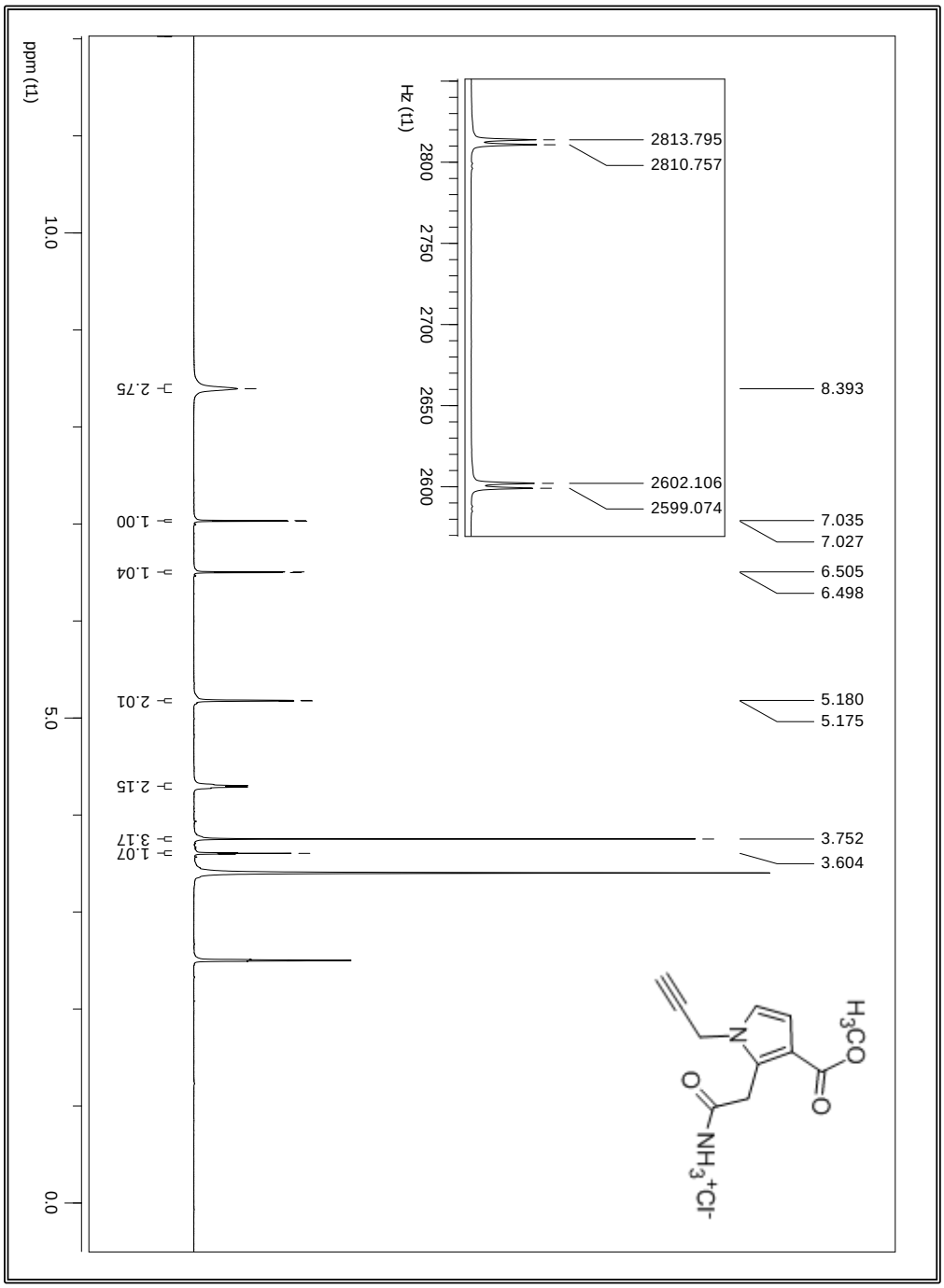

Figure 16 ^{1}H-NMR Spectrum of Compound **101**

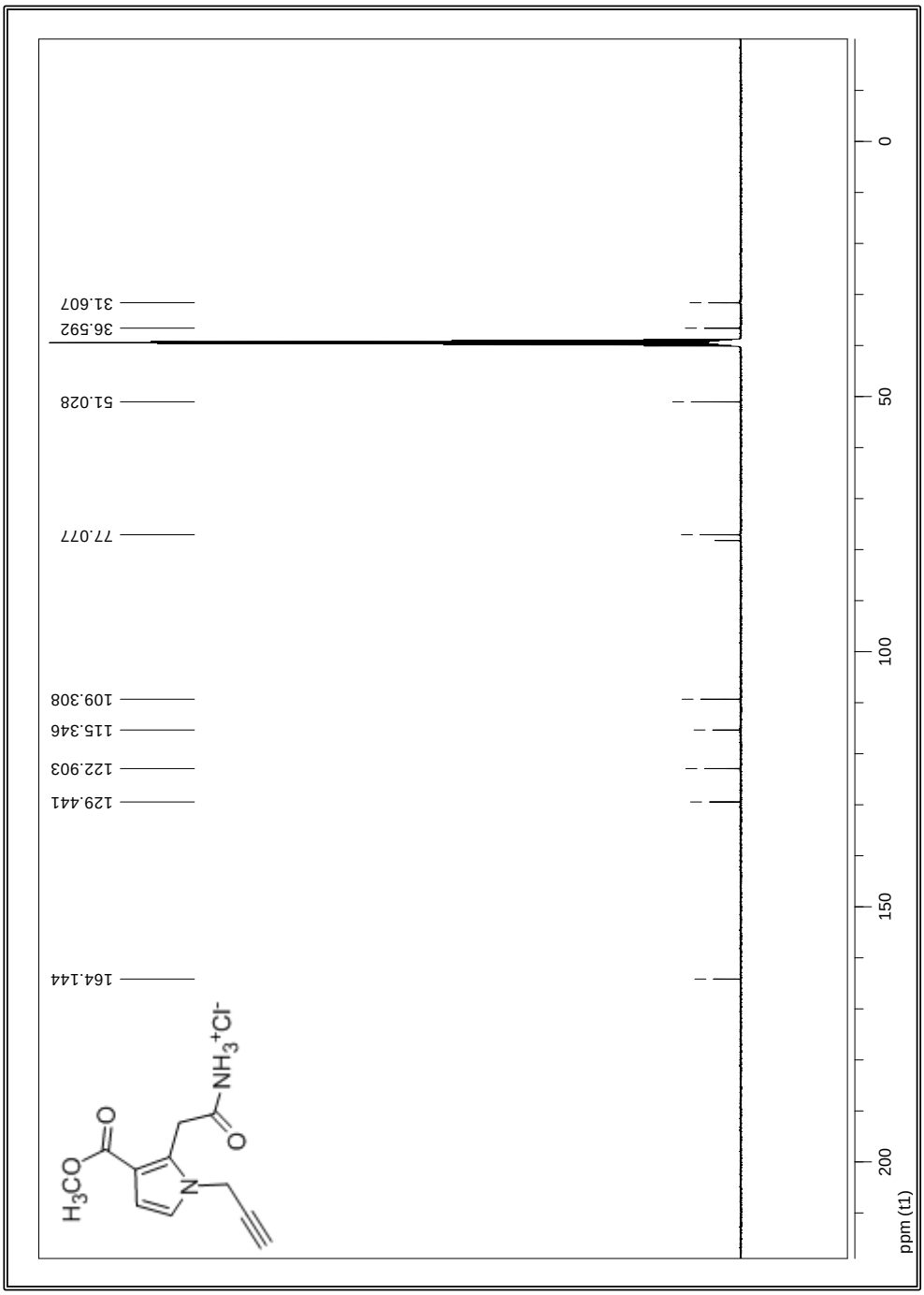

Figure 17 ^{13}C-NMR Spectrum of Compound **101**

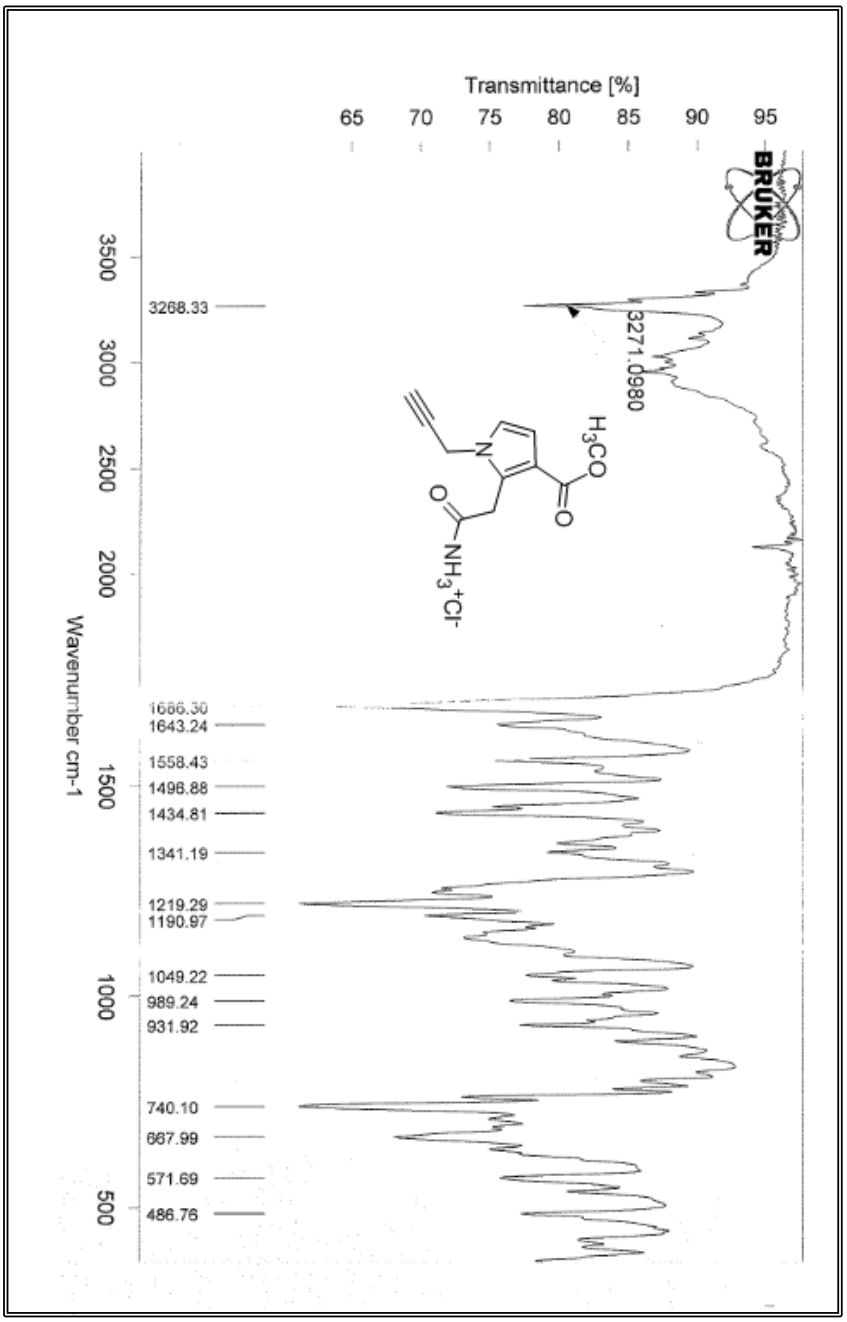

Figure 18 IR Spectrum of Compound **101**

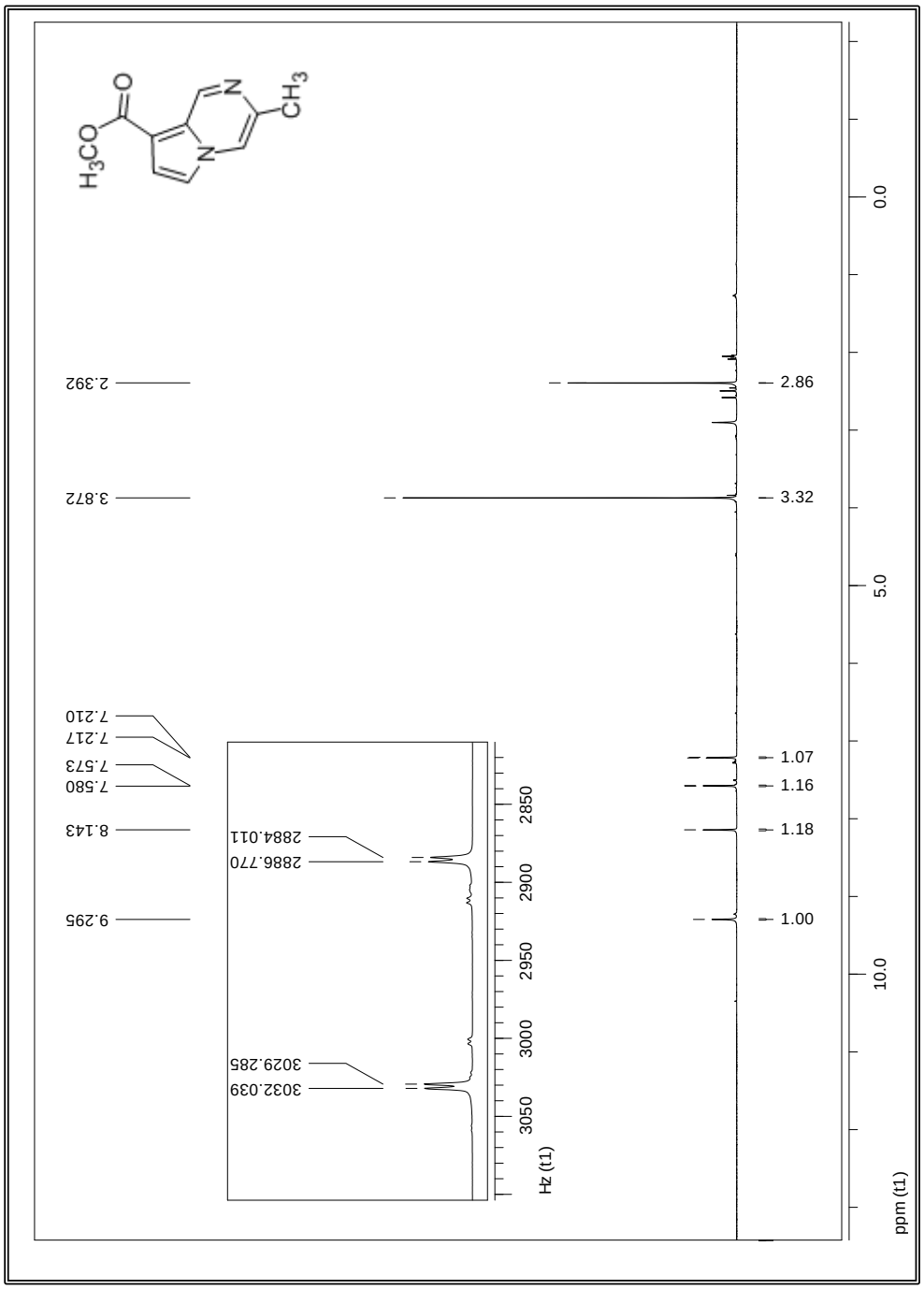

Figure 19 ^{1}H-NMR Spectrum of Compound **102**

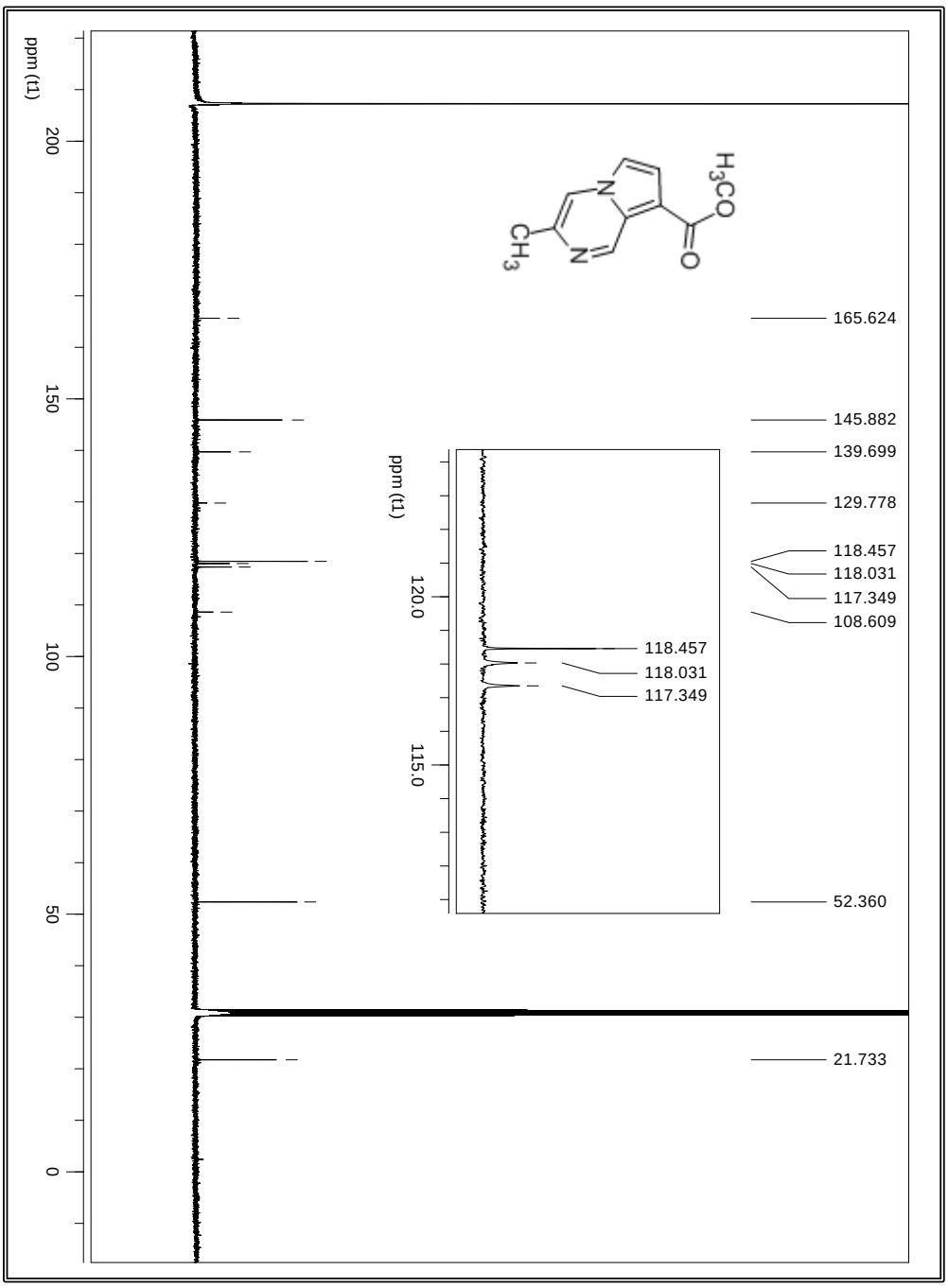

Figure 20 ^{13}C-NMR Spectrum of Compound **102**

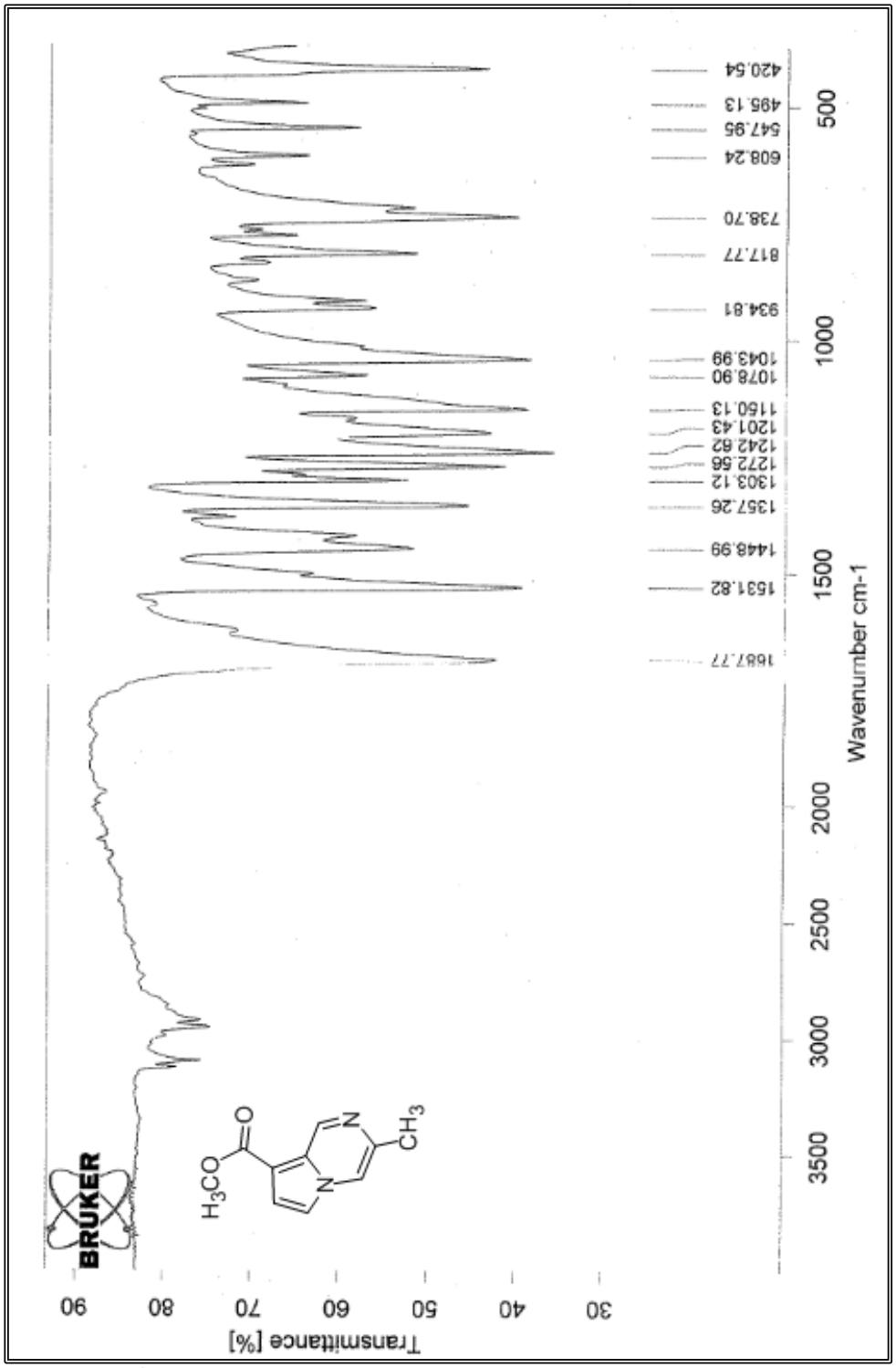

Figure 21 IR Spectrum of Compound **102**

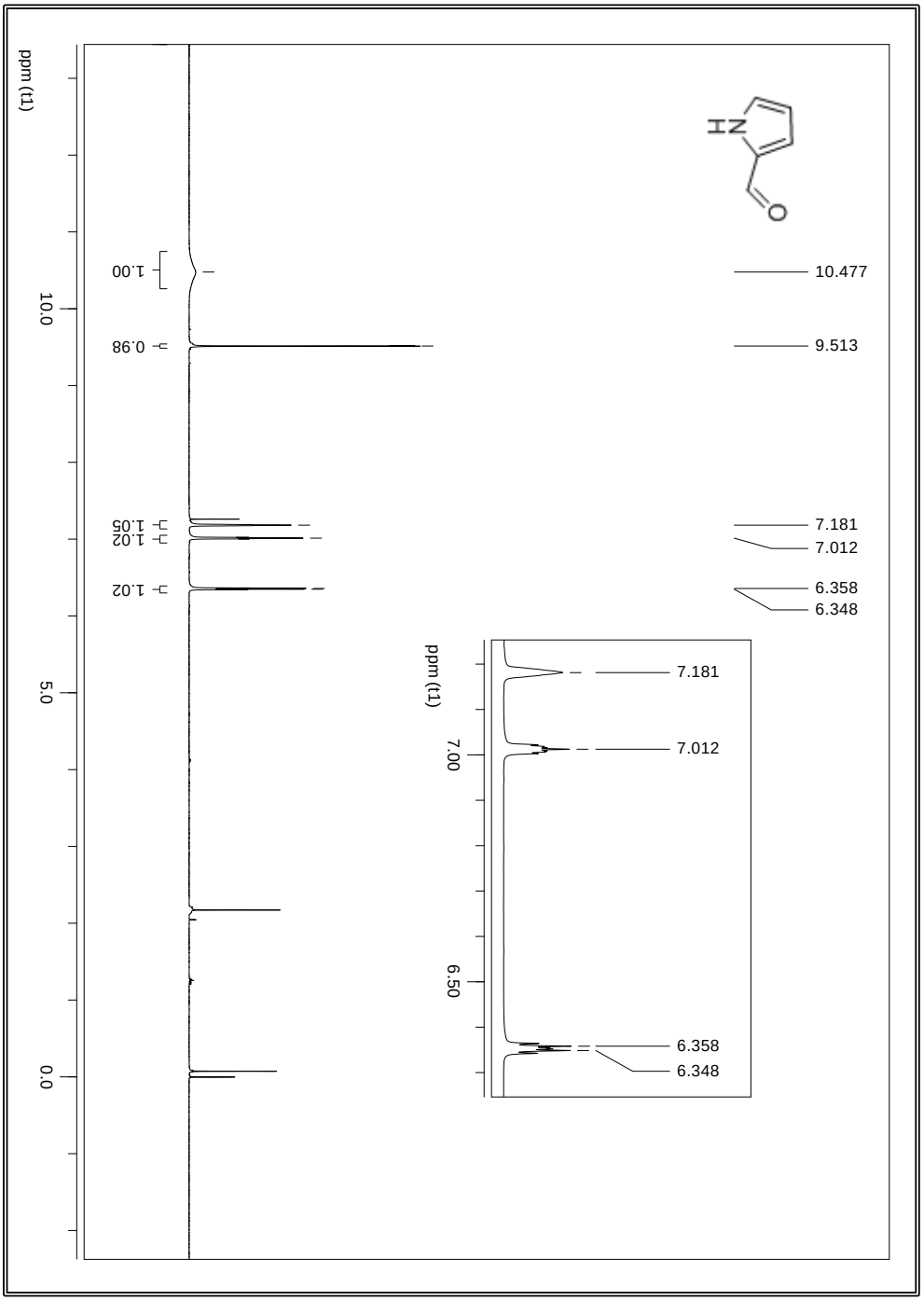

Figure 22 ^{1}H-NMR Spectrum of Compound **54**

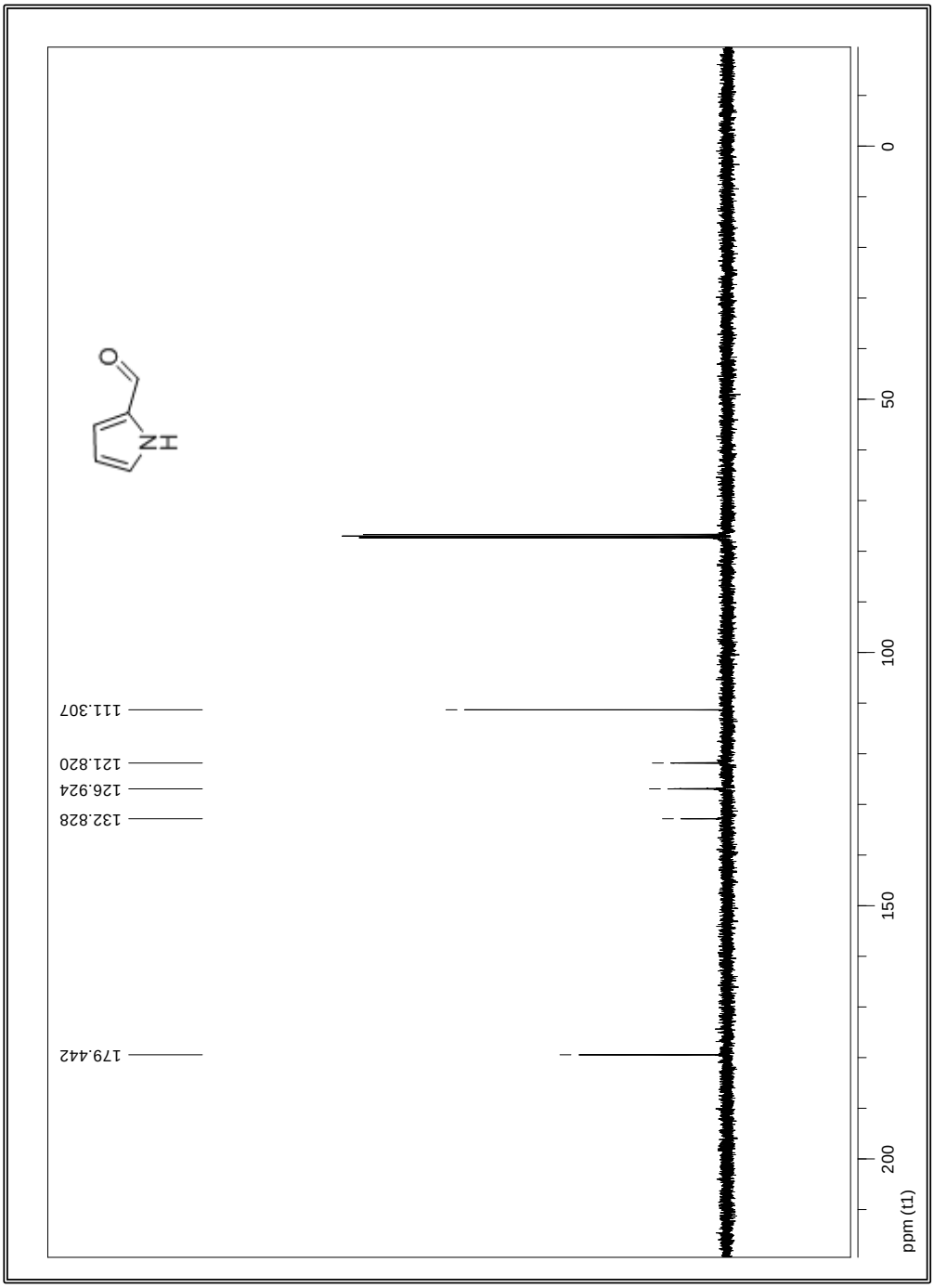

Figure 23 ^{13}C-NMR Spectrum of Compound **54**

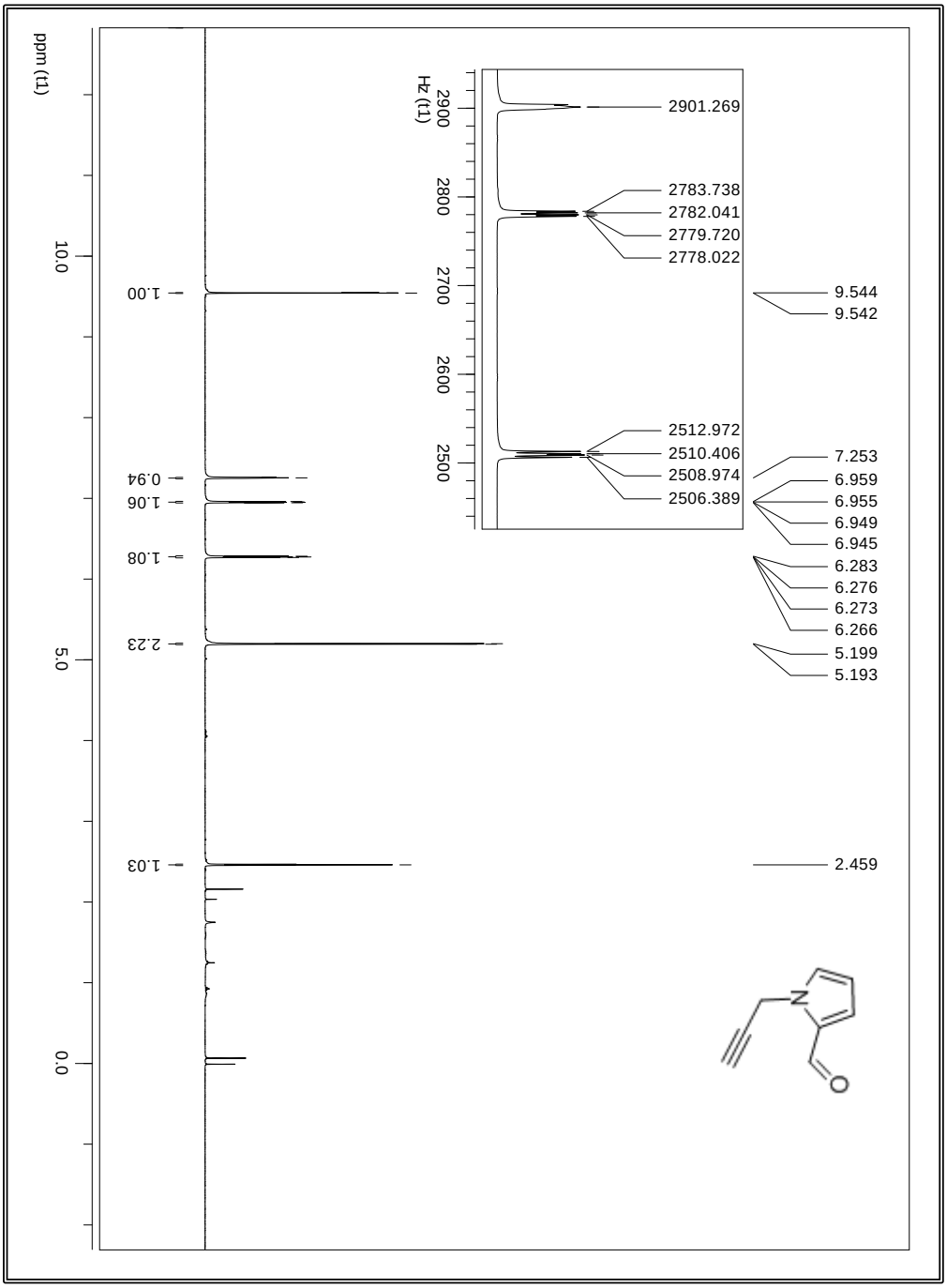

Figure 24 ^{1}H-NMR Spectrum of Compound **110**

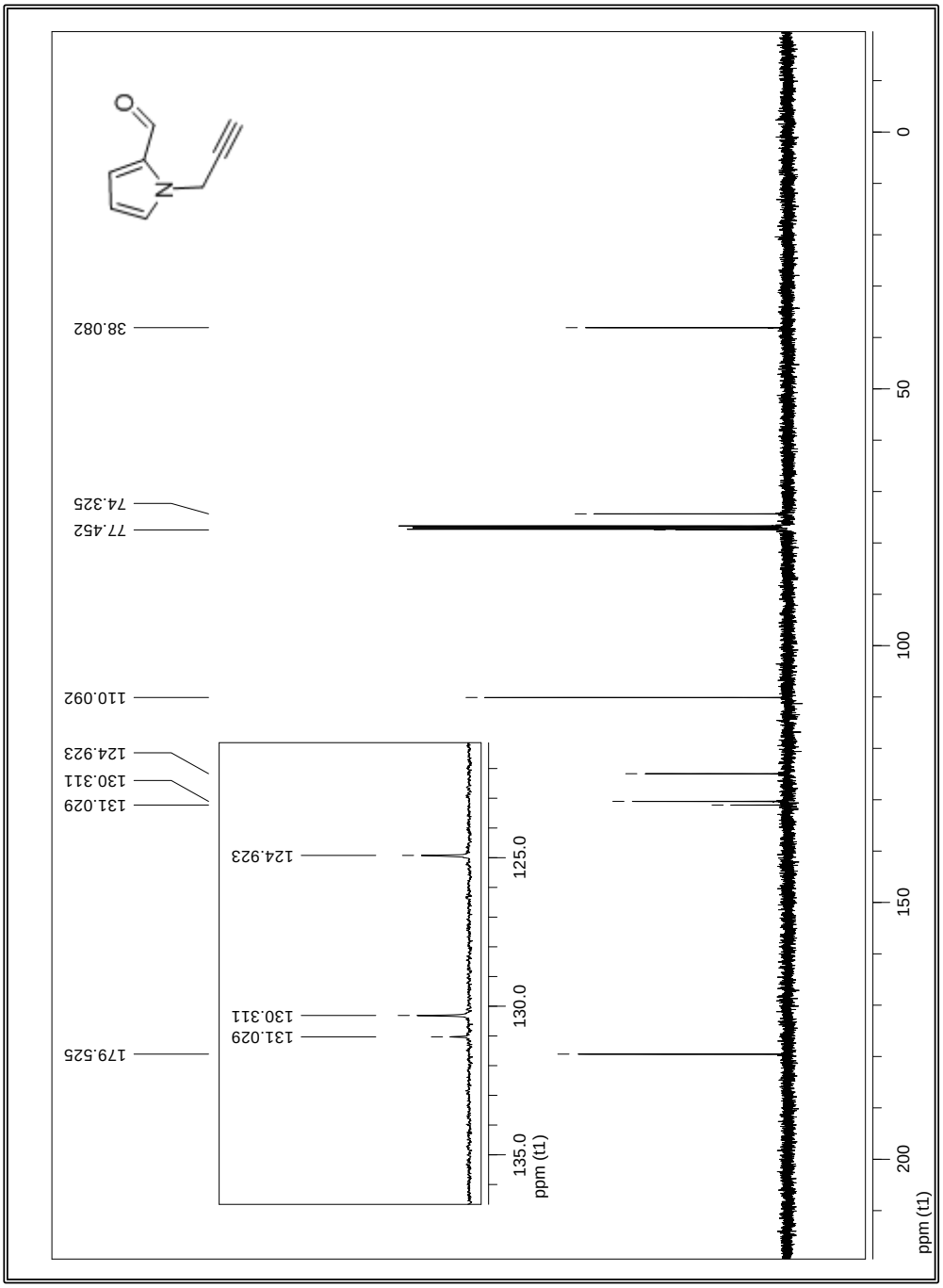

Figure 25 ^{13}C-NMR Spectrum of Compound **110**

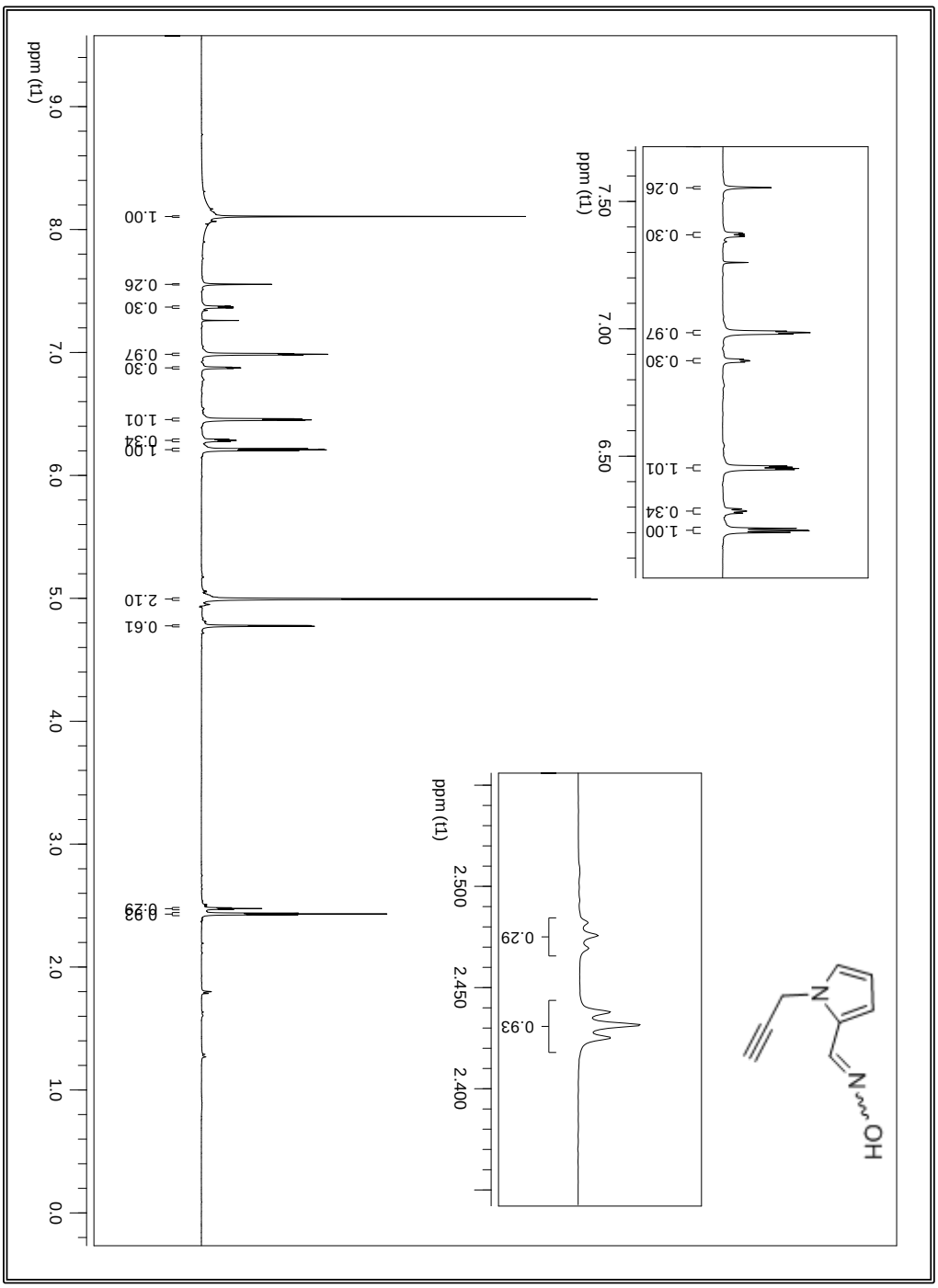

Figure 26 ^{1}H-NMR Spectrum of Compound **111**

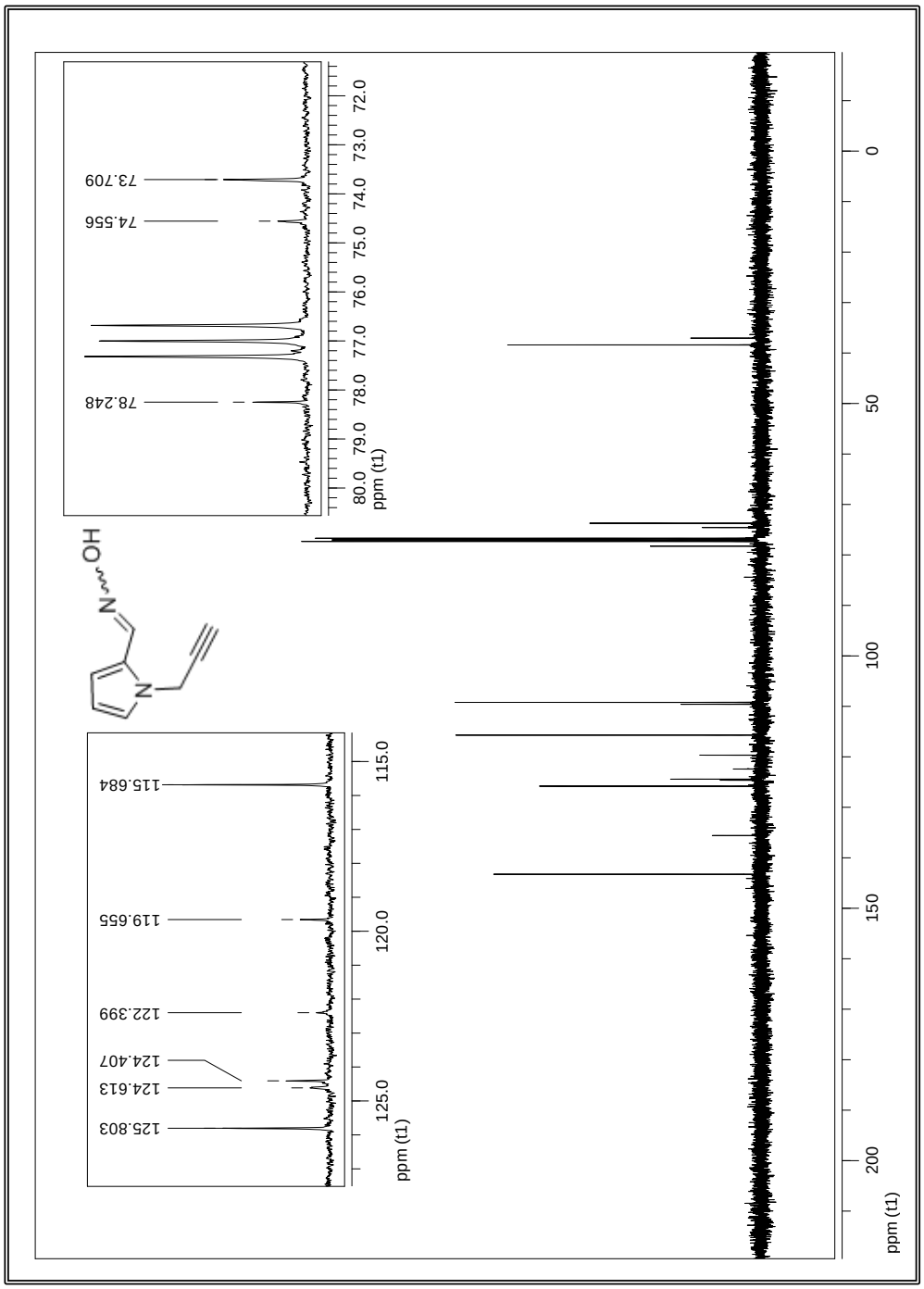

Figure 27 ^{13}C-NMR Spectrum of Compound **111**

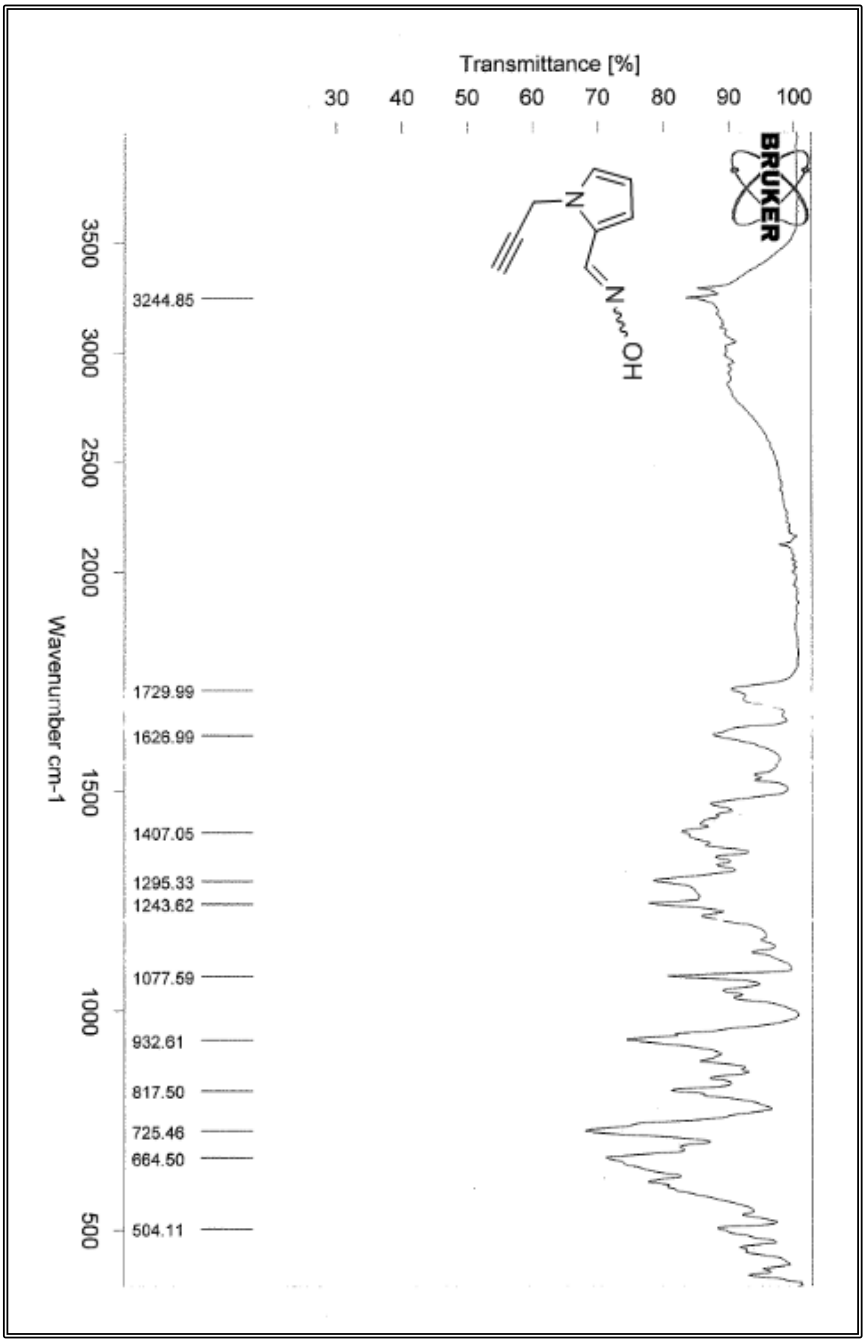

Figure 28 IR Spectrum of Compound **111**

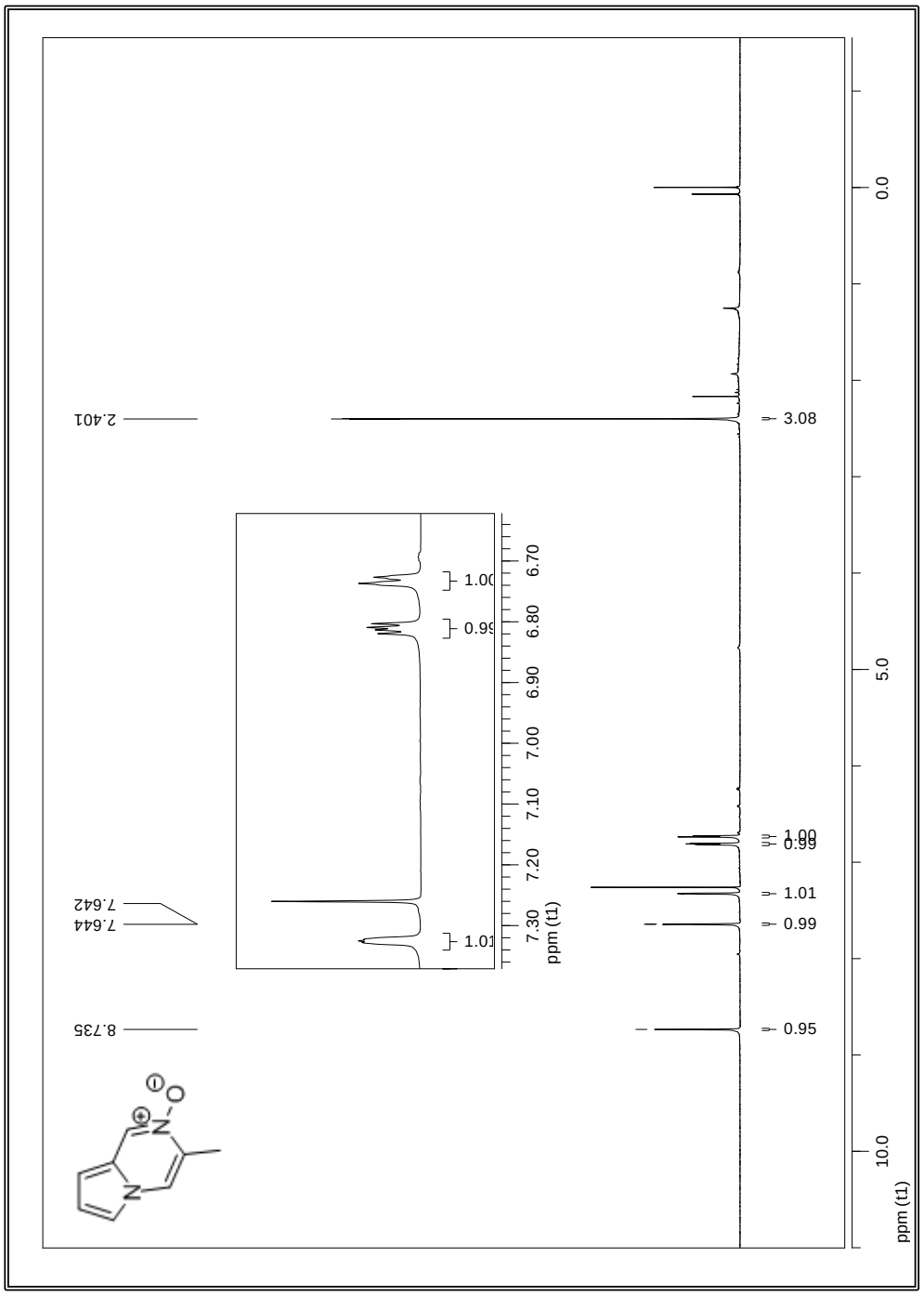

Figure 29 ^{1}H-NMR Spectrum of Compound **112**

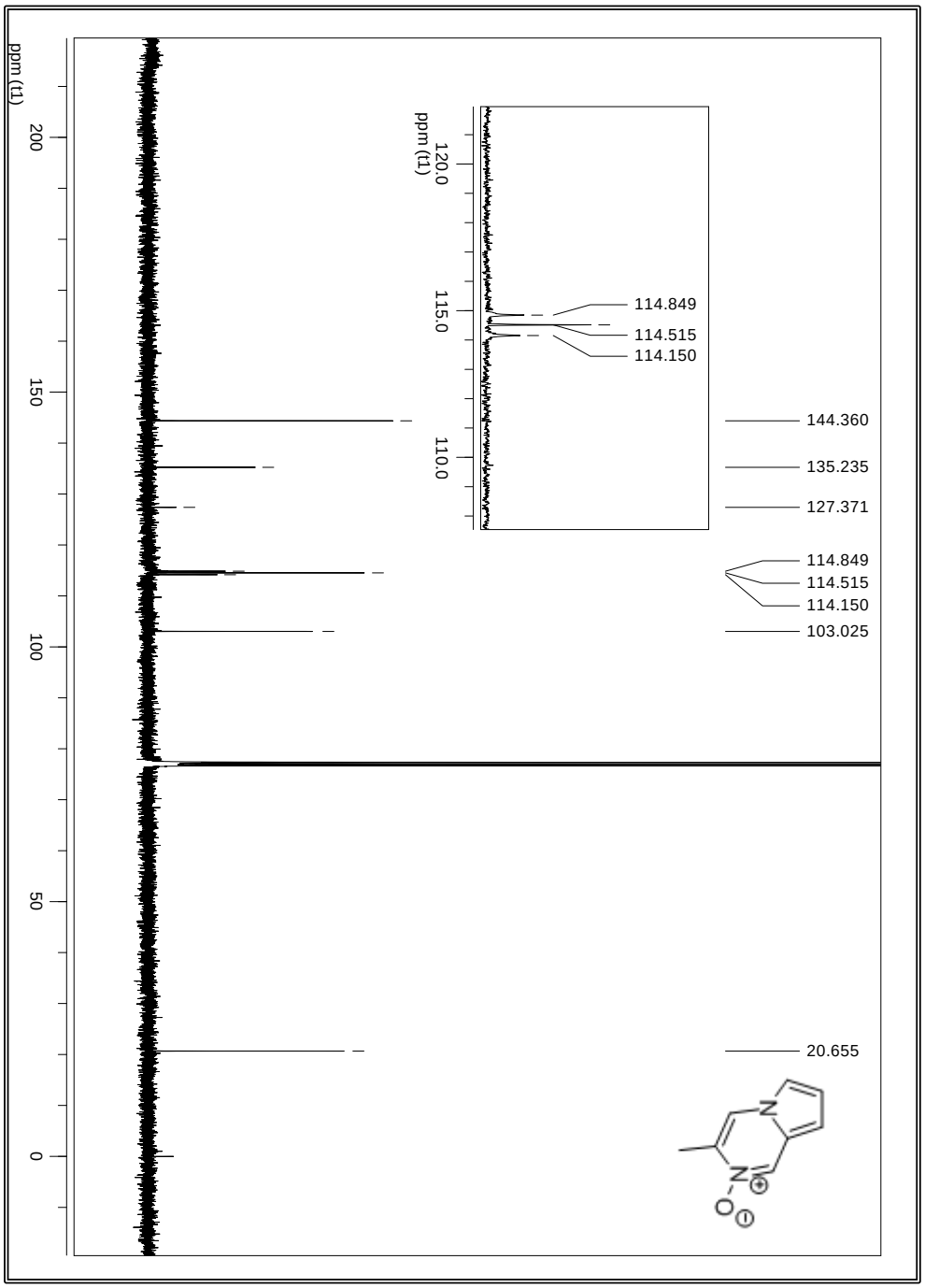

Figure 30 ^{13}C-NMR Spectrum of Compound **112**

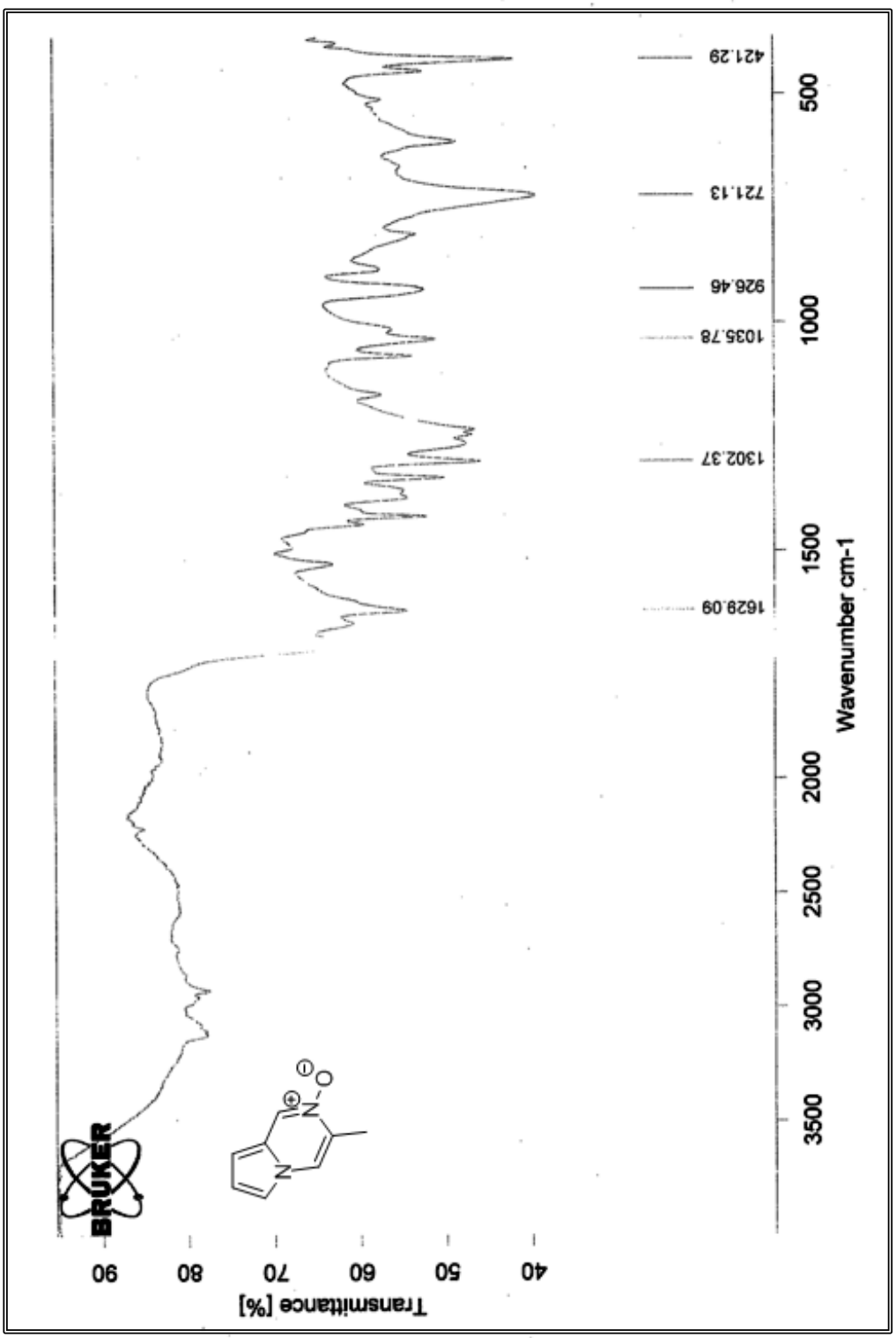

Figure 31 IR Spectrum of Compound **112**

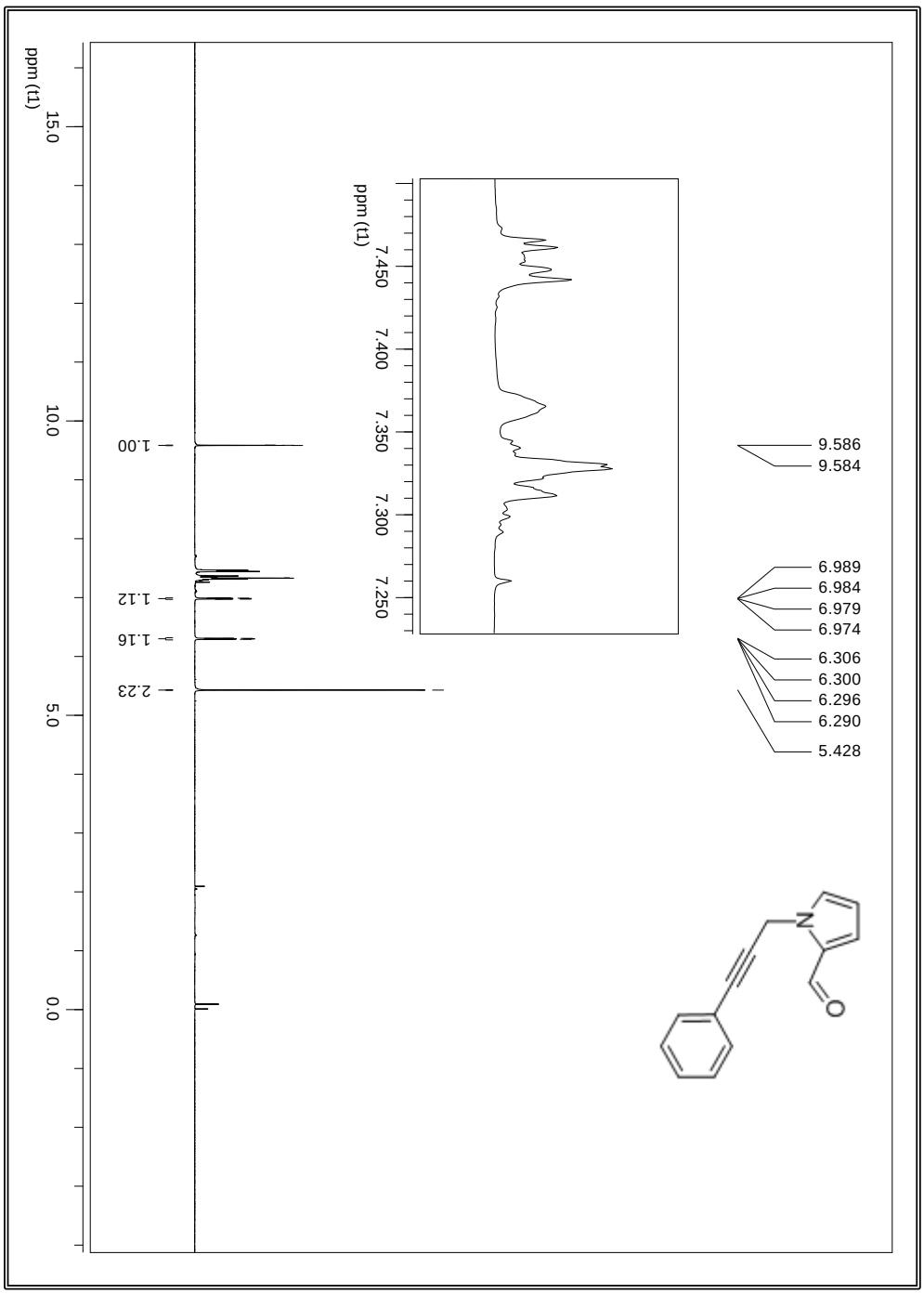

Figure 32 ^{1}H-NMR Spectrum of Compound **116**

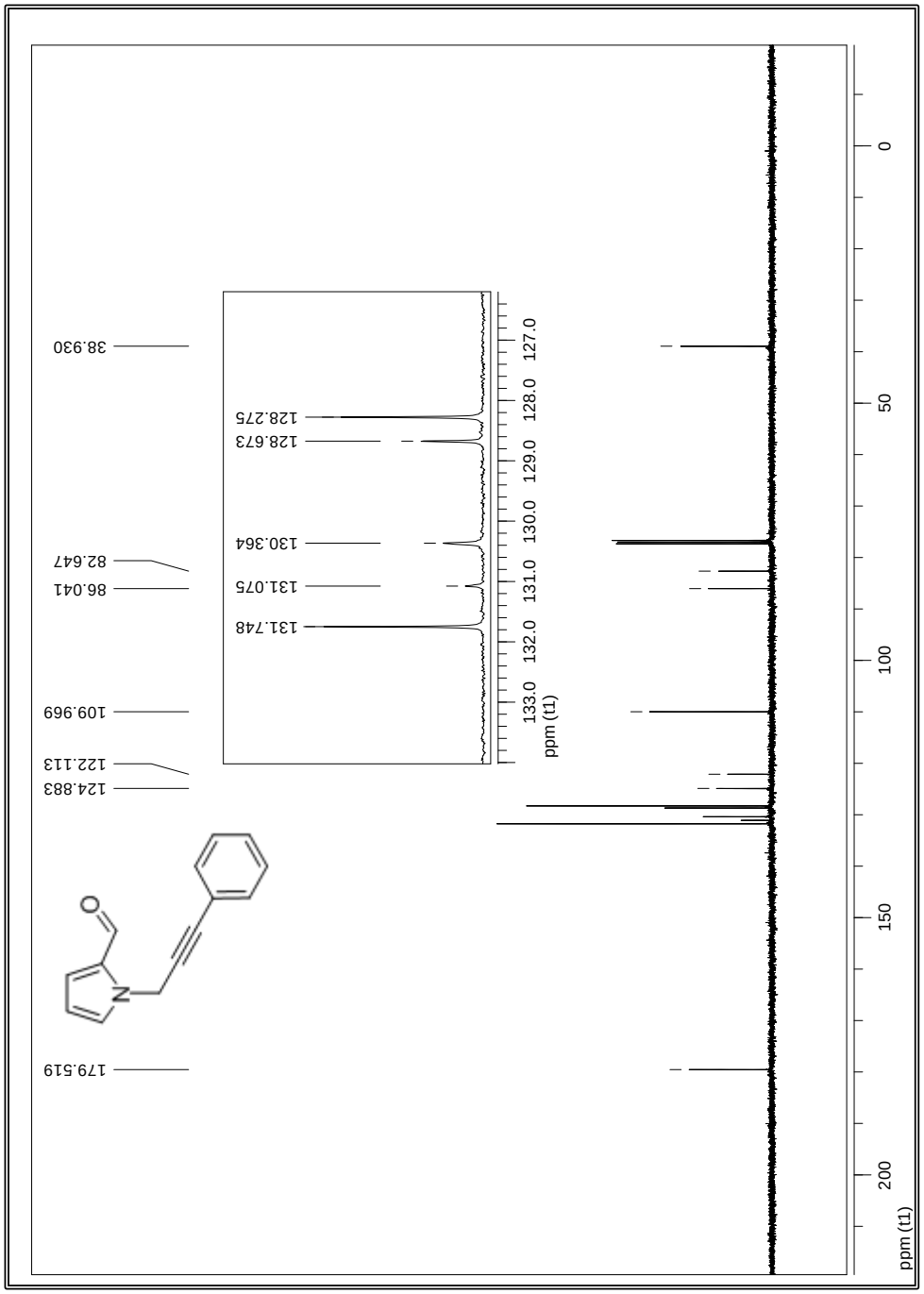

Figure 33 ^{13}C-NMR Spectrum of Compound **116**

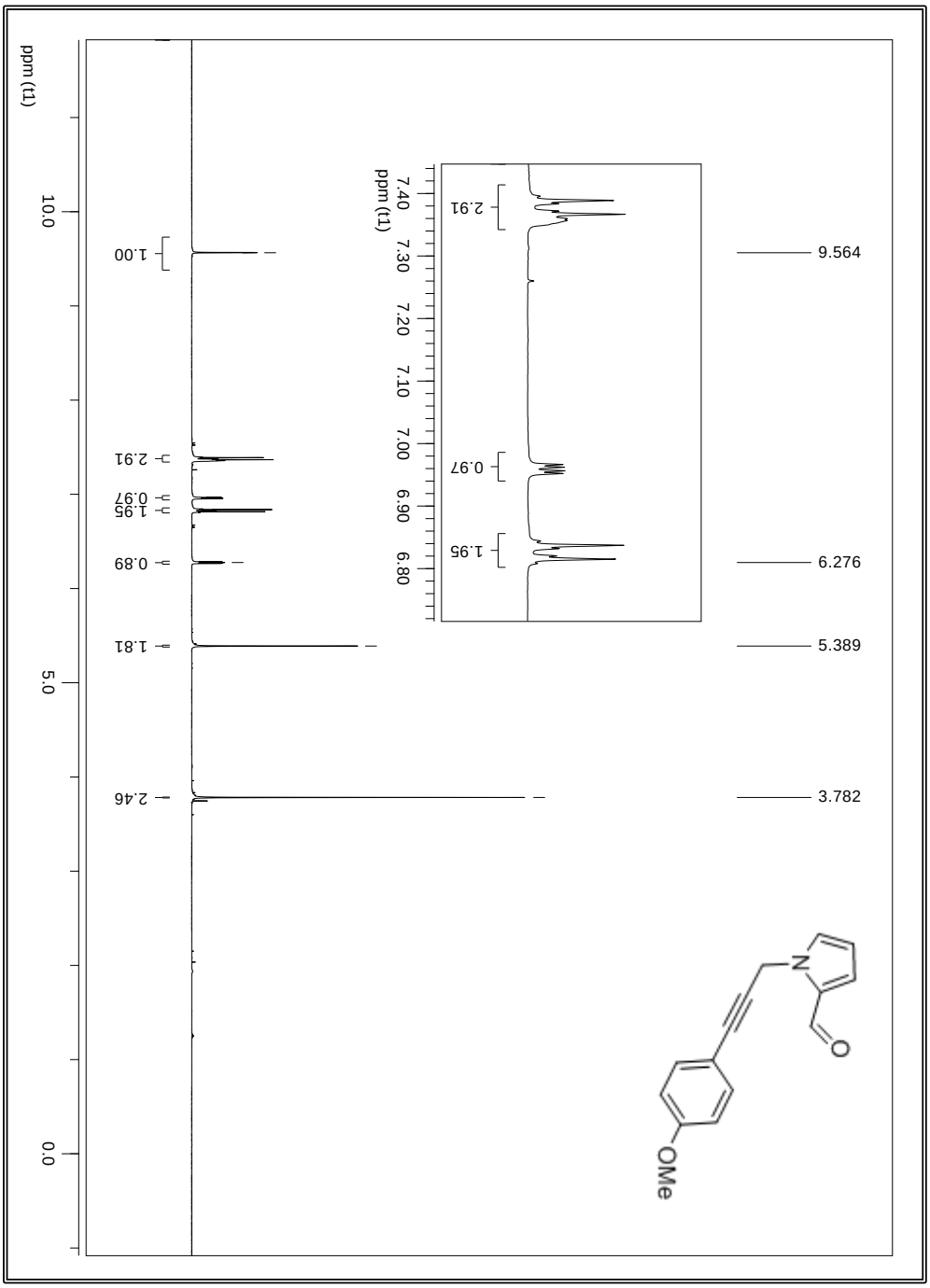

Figure 34 ^{1}H-NMR Spectrum of Compound **117**

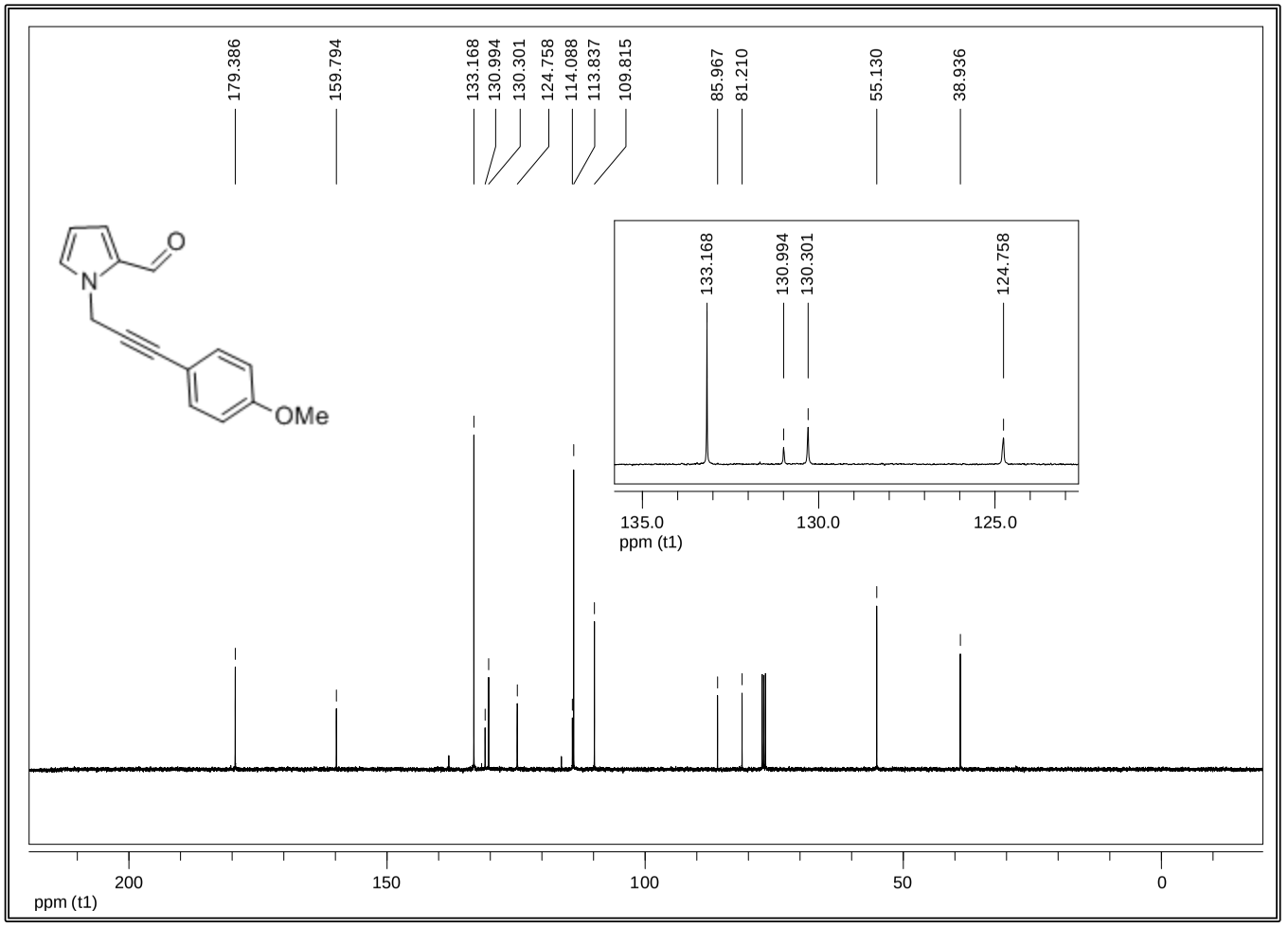

Figure 35 ^{13}C-NMR Spectrum of Compound **117**

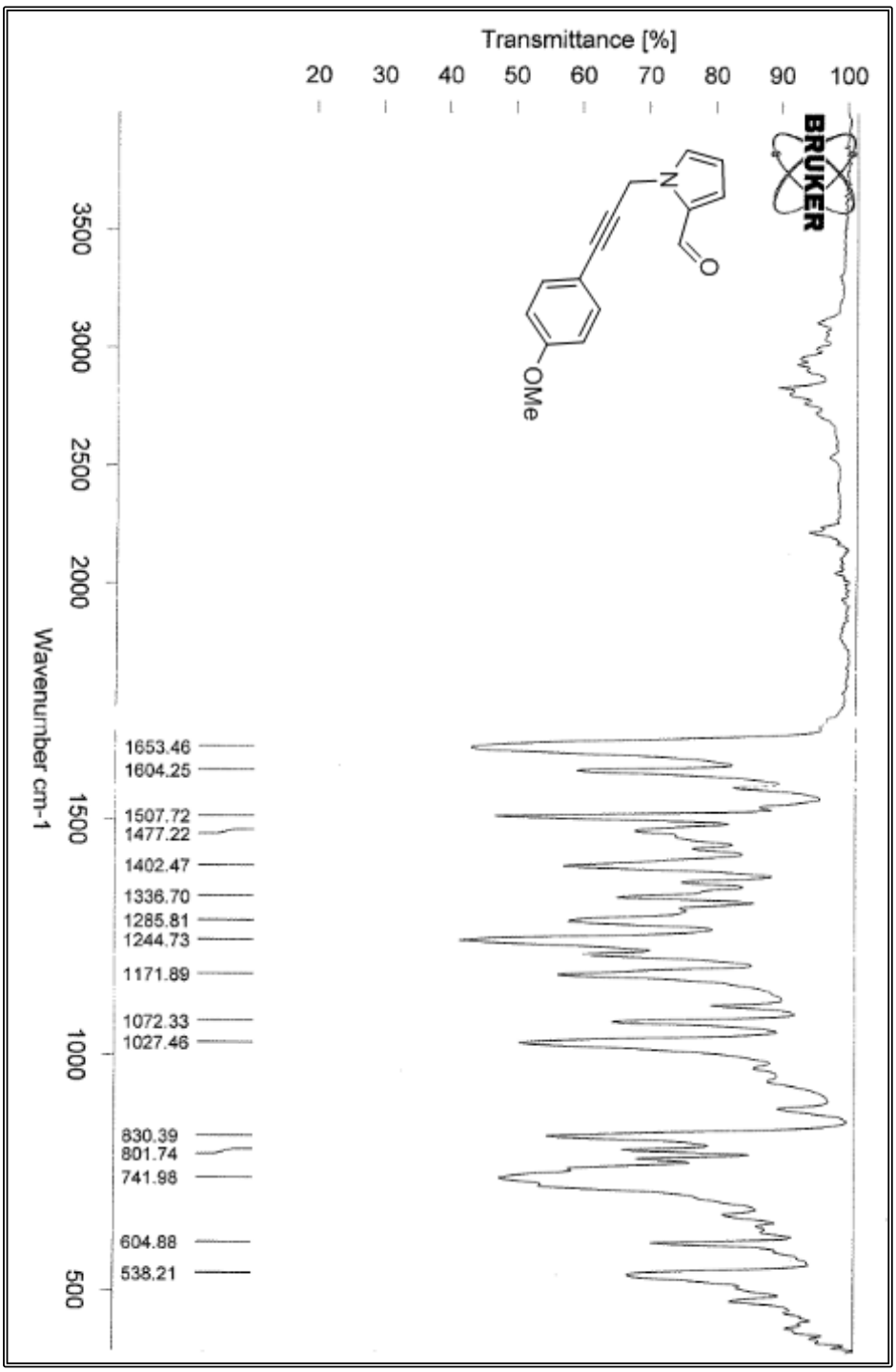

Figure 36 IR Spectrum of Compound **117**

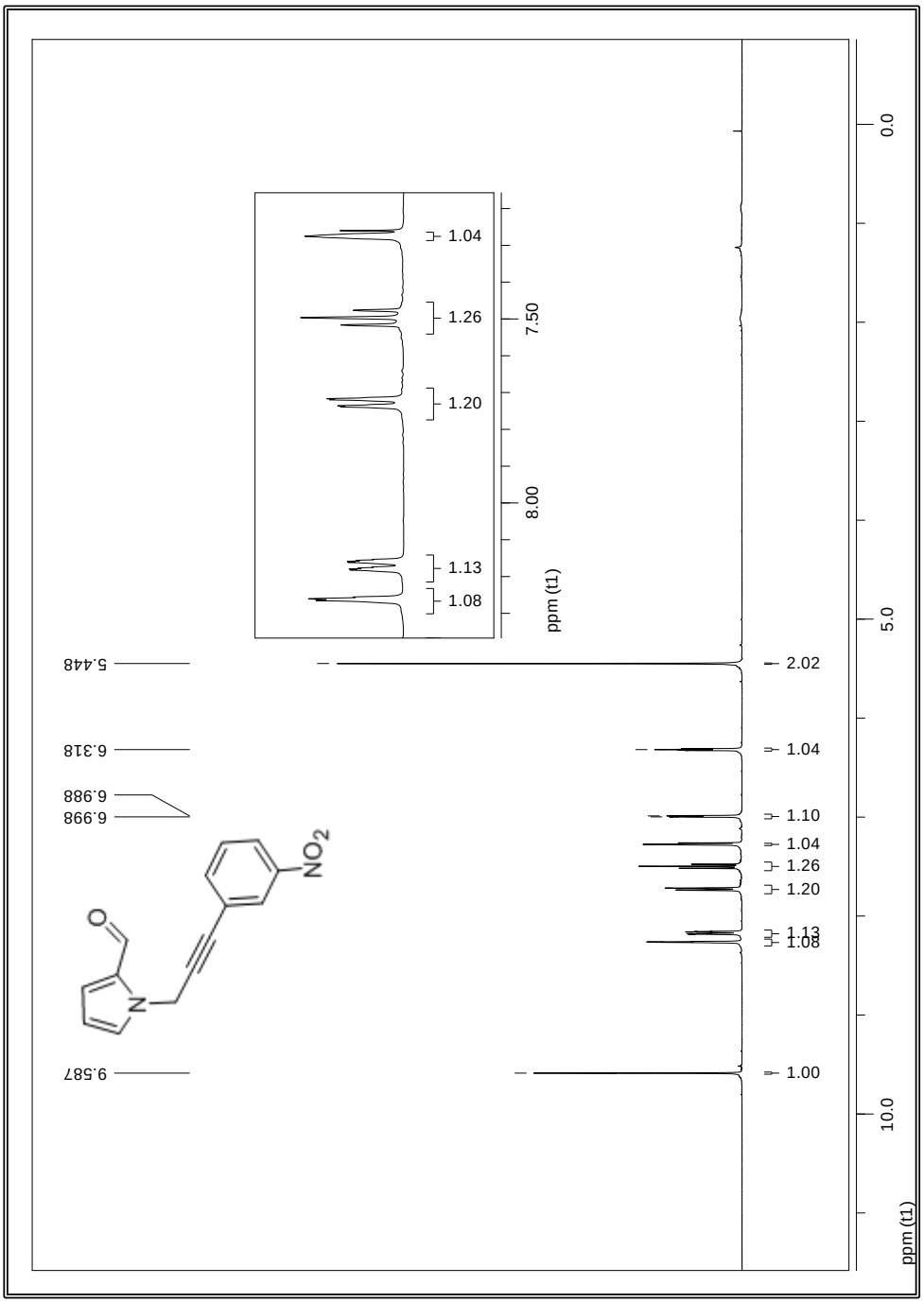

Figure 37 ^{1}H-NMR Spectrum of Compound **118**

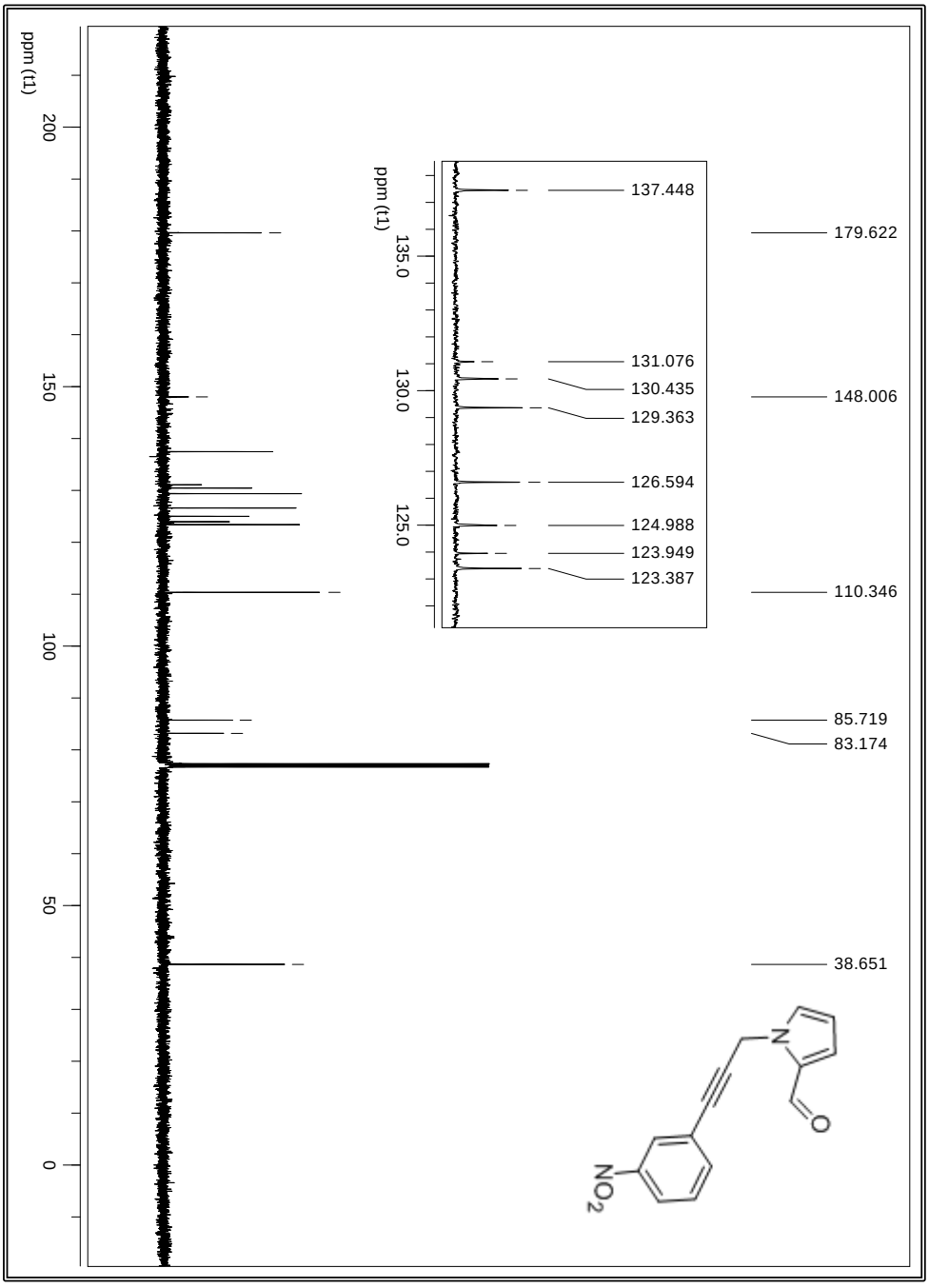

Figure 38 ^{13}C-NMR Spectrum of Compound **118**

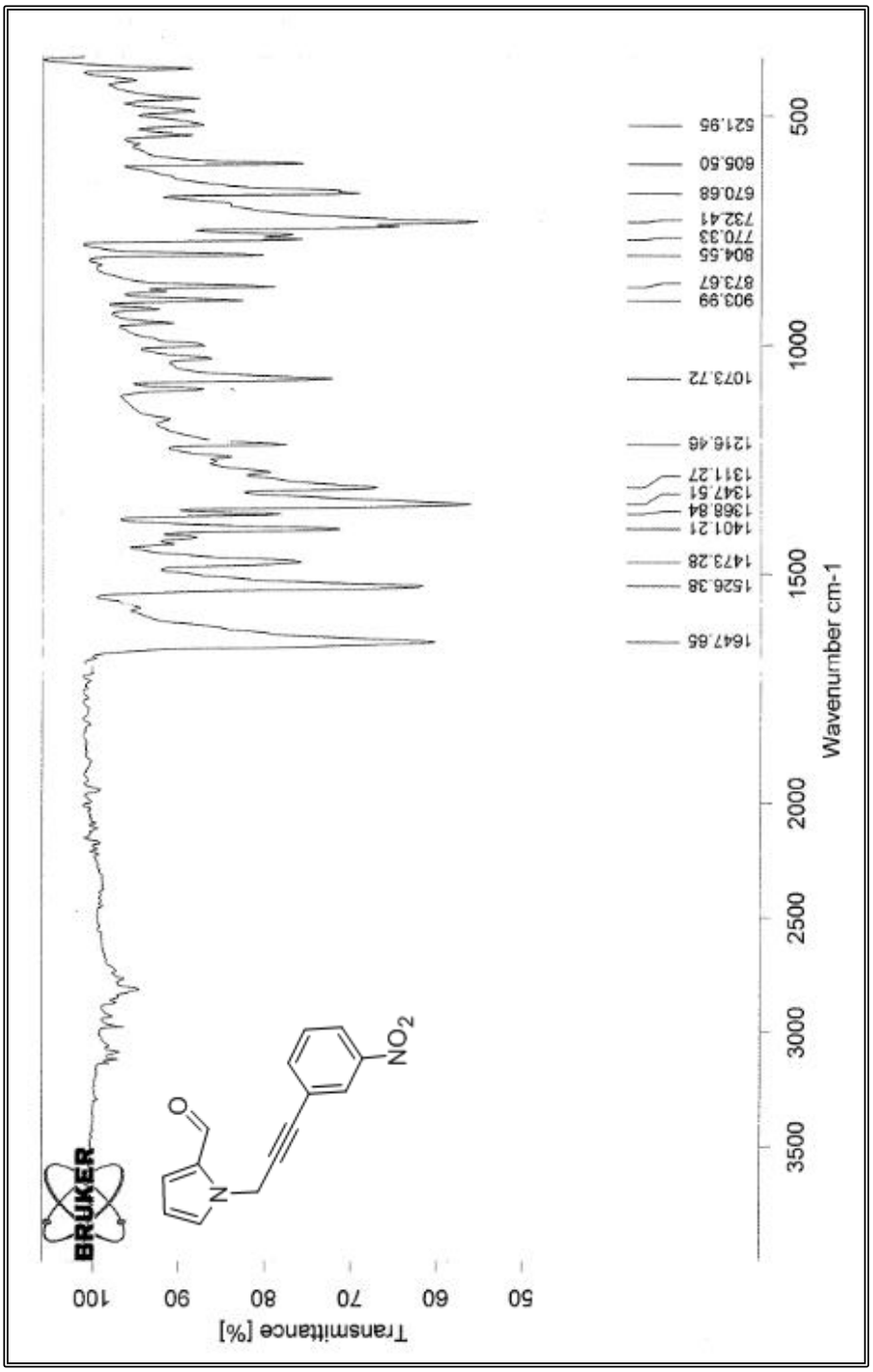

Figure 39 IR Spectrum of Compound **118**

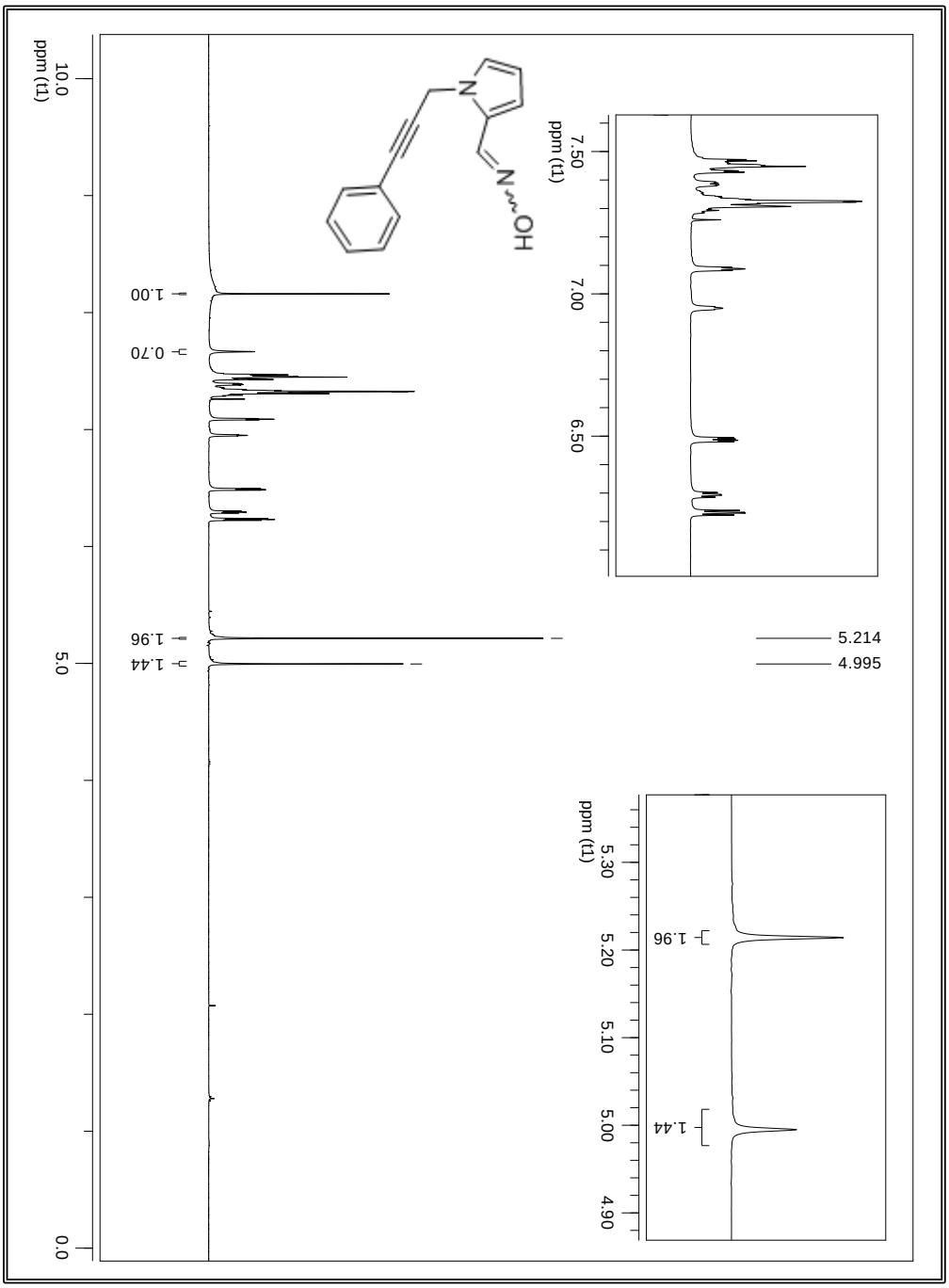

Figure 40 ^{1}H-NMR Spectrum of Compound **119**

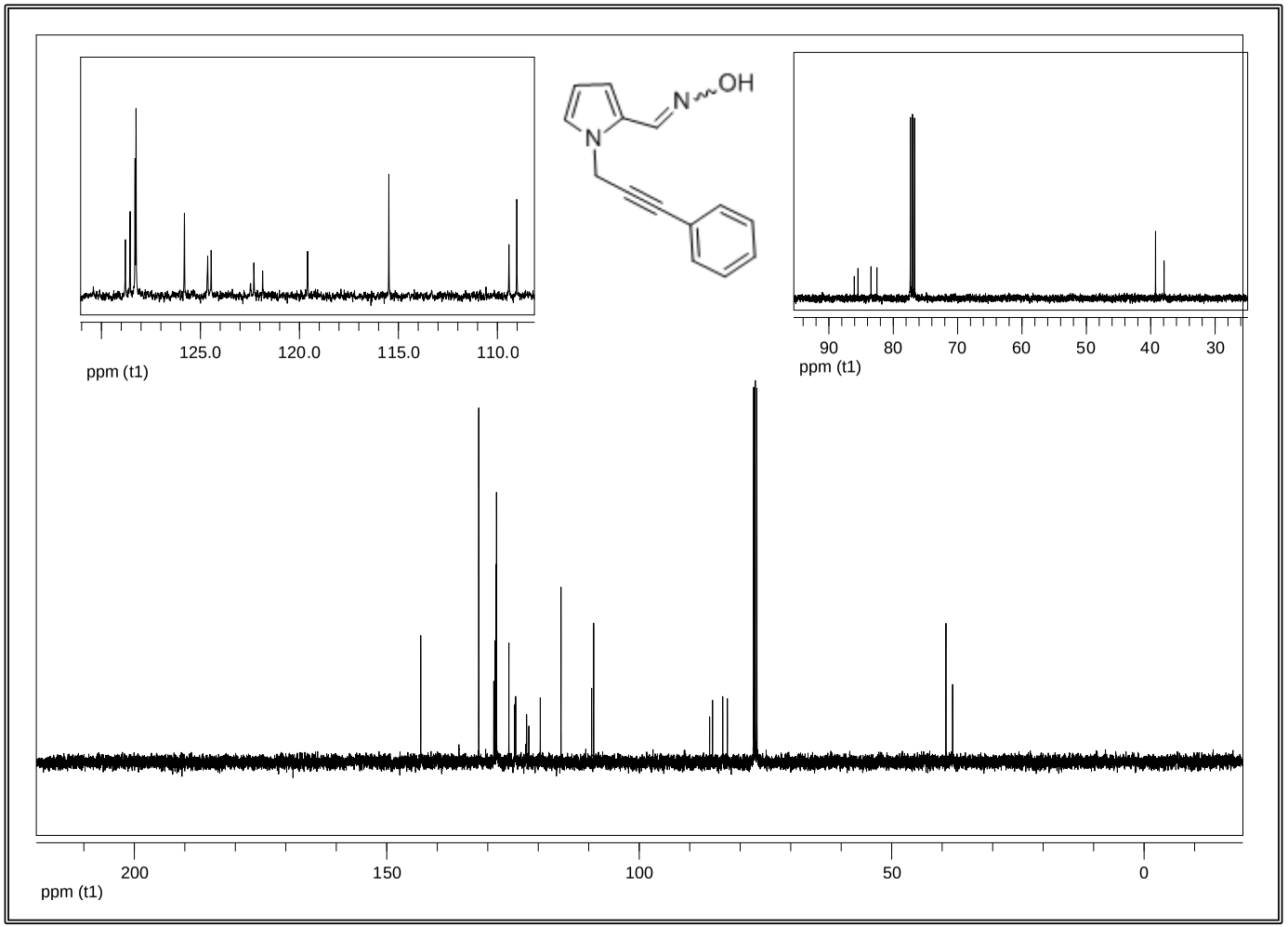

Figure 41 ^{13}C-NMR Spectrum of Compound **119**

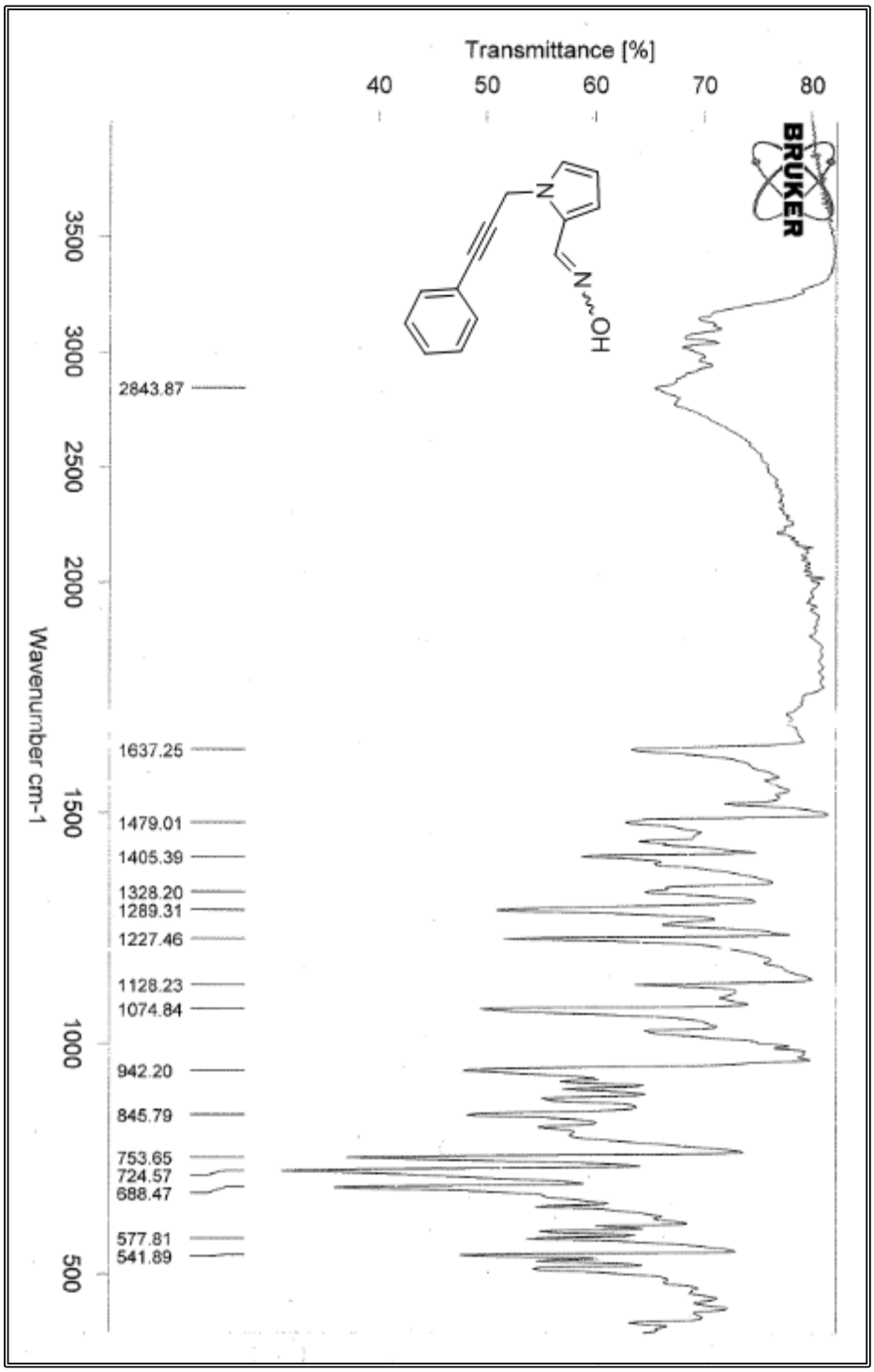

Figure 42 IR Spectrum of Compound **119**

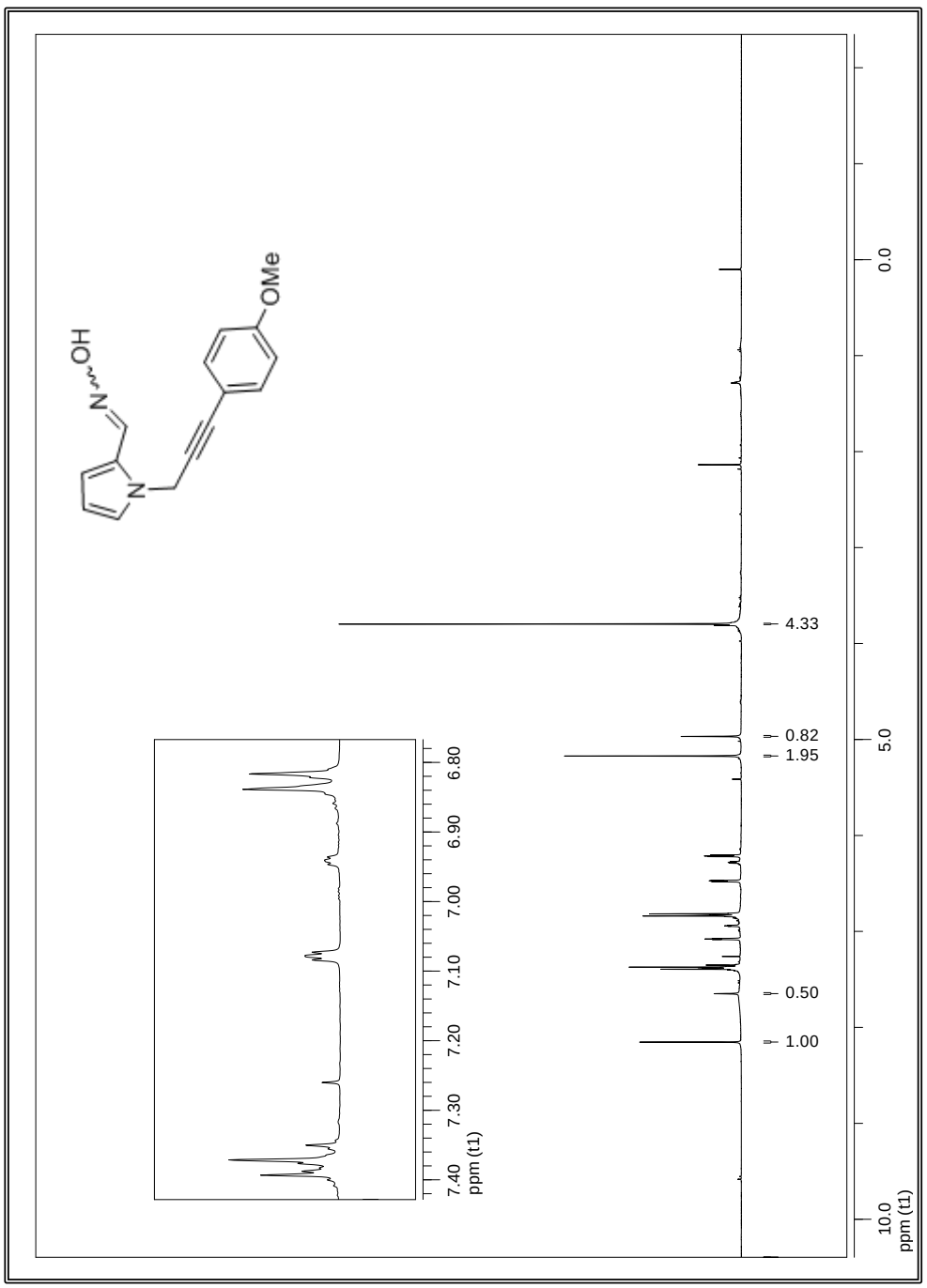

Figure 43 ^{1}H-NMR Spectrum of Compound **120**

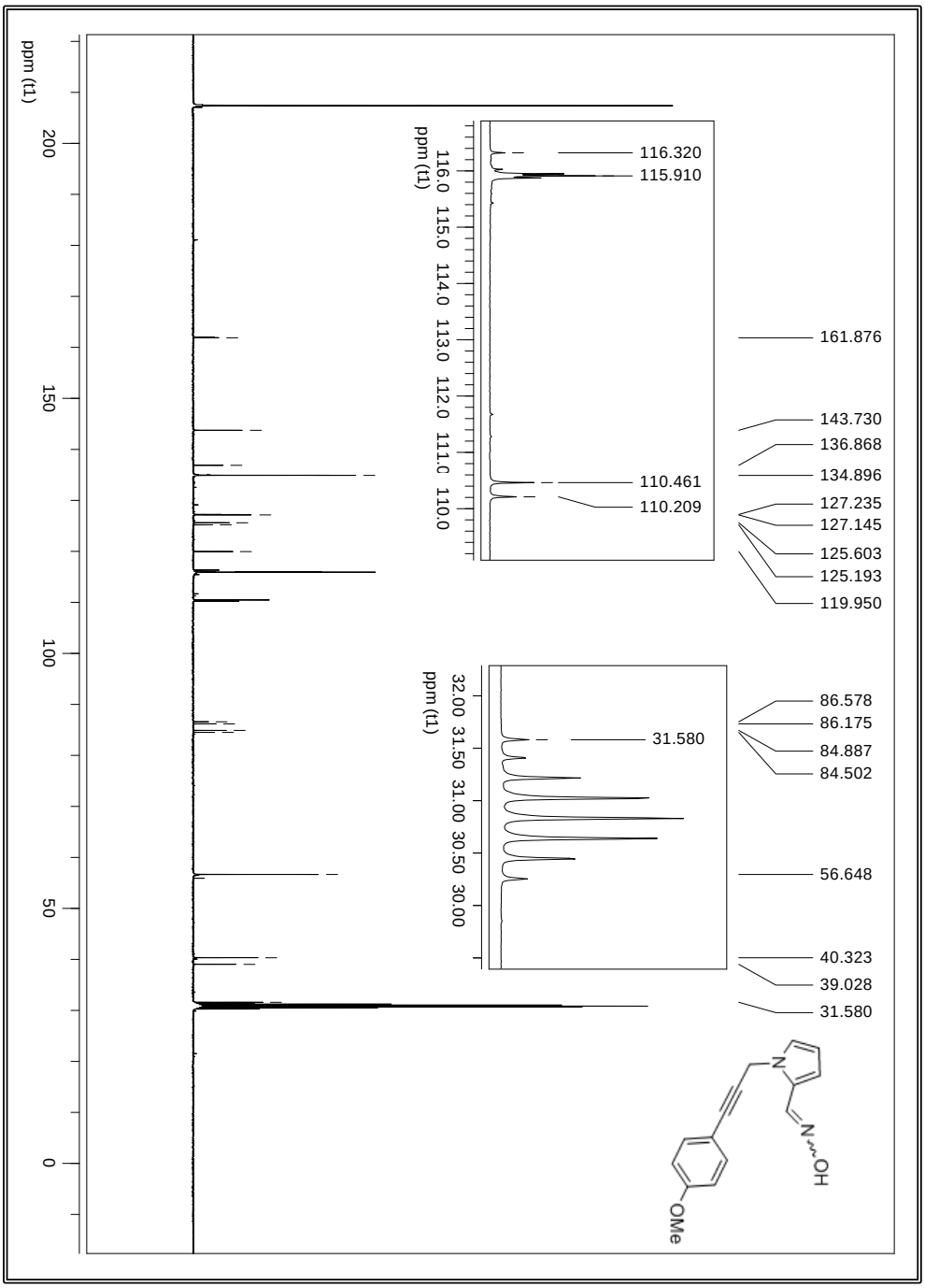

Figure 44 ^{13}C-NMR Spectrum of Compound **120**

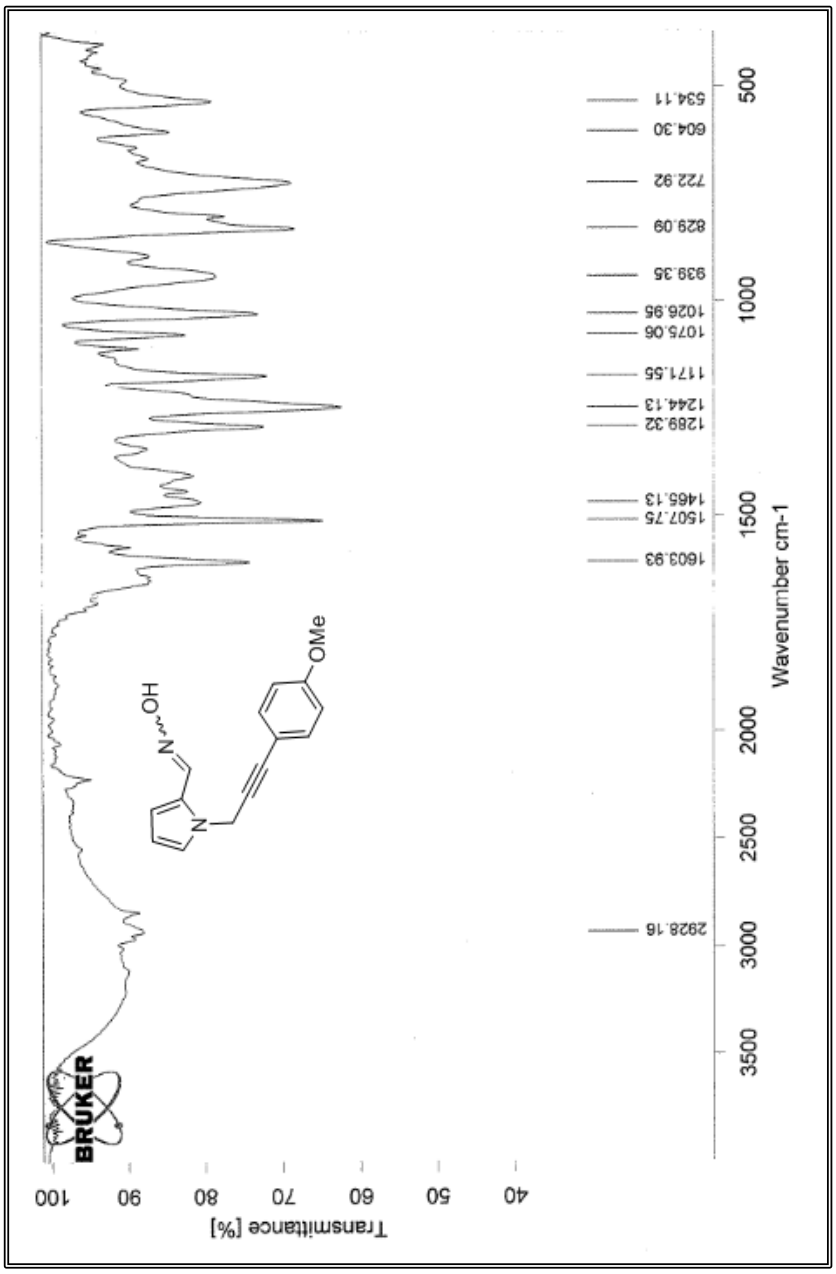

Figure 45 IR Spectrum of Compound **120**

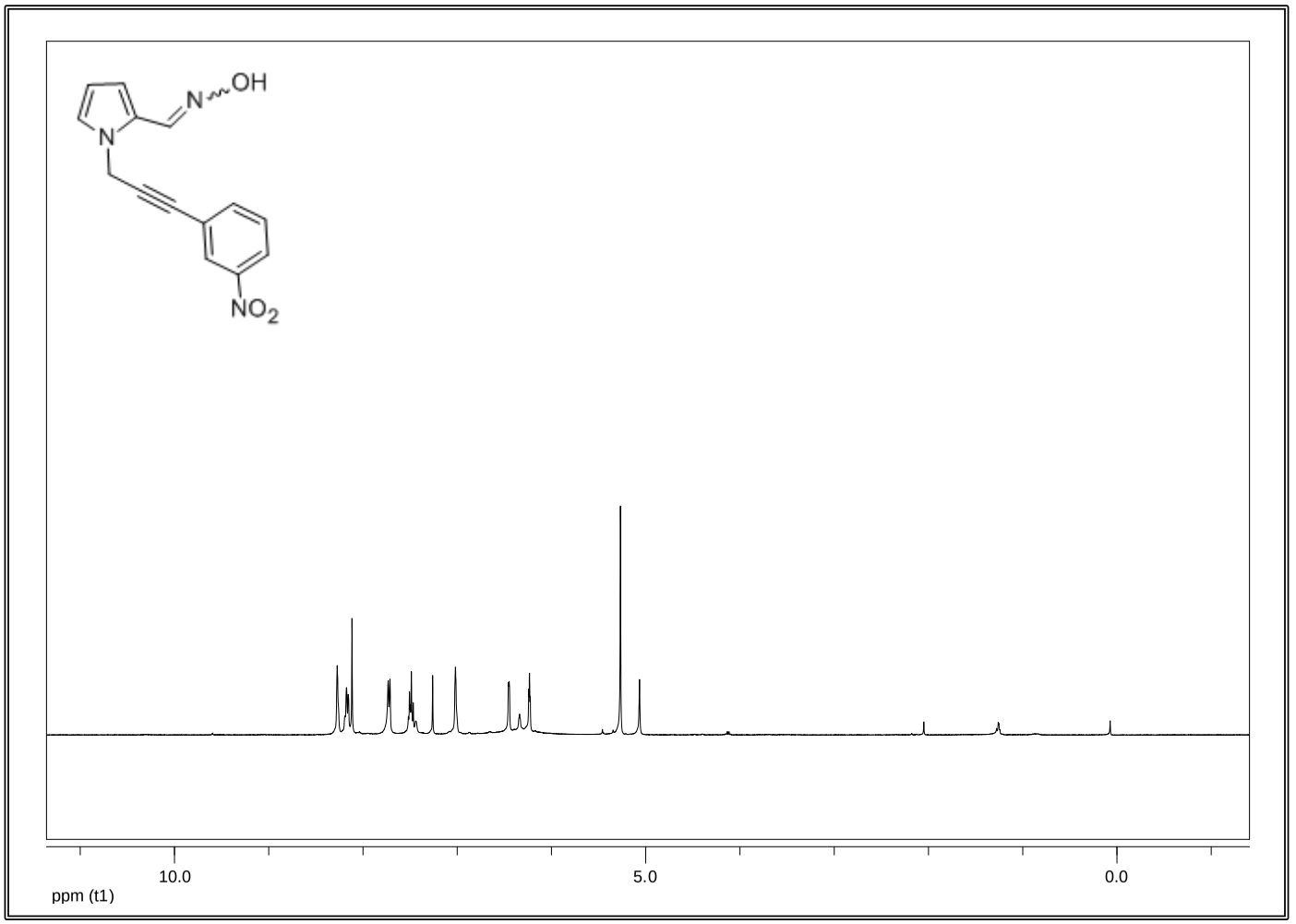

Figure 46 ^{1}H-NMR Spectrum of Compound **121**

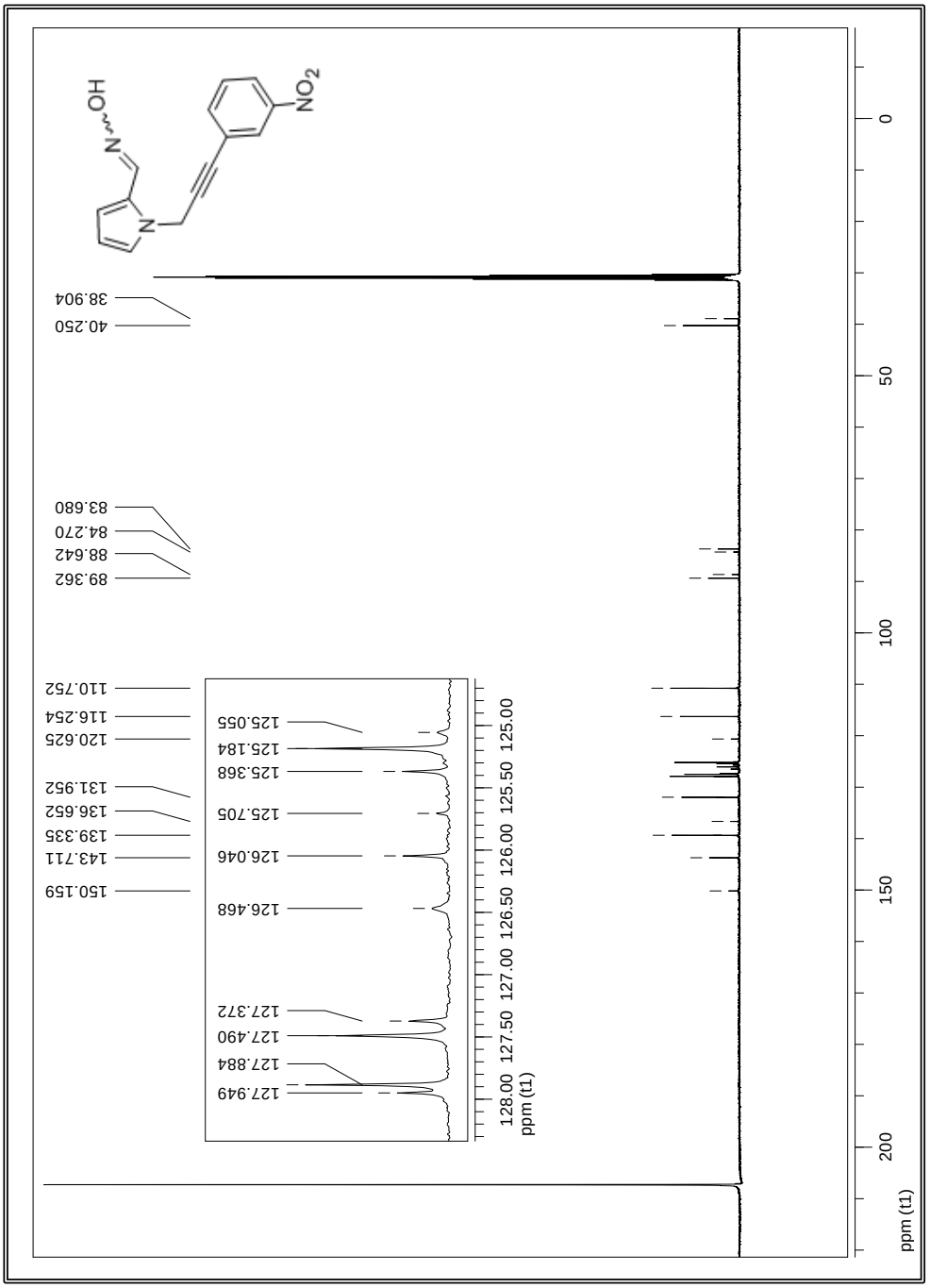

Figure 47 ^{13}C-NMR Spectrum of Compound **121**

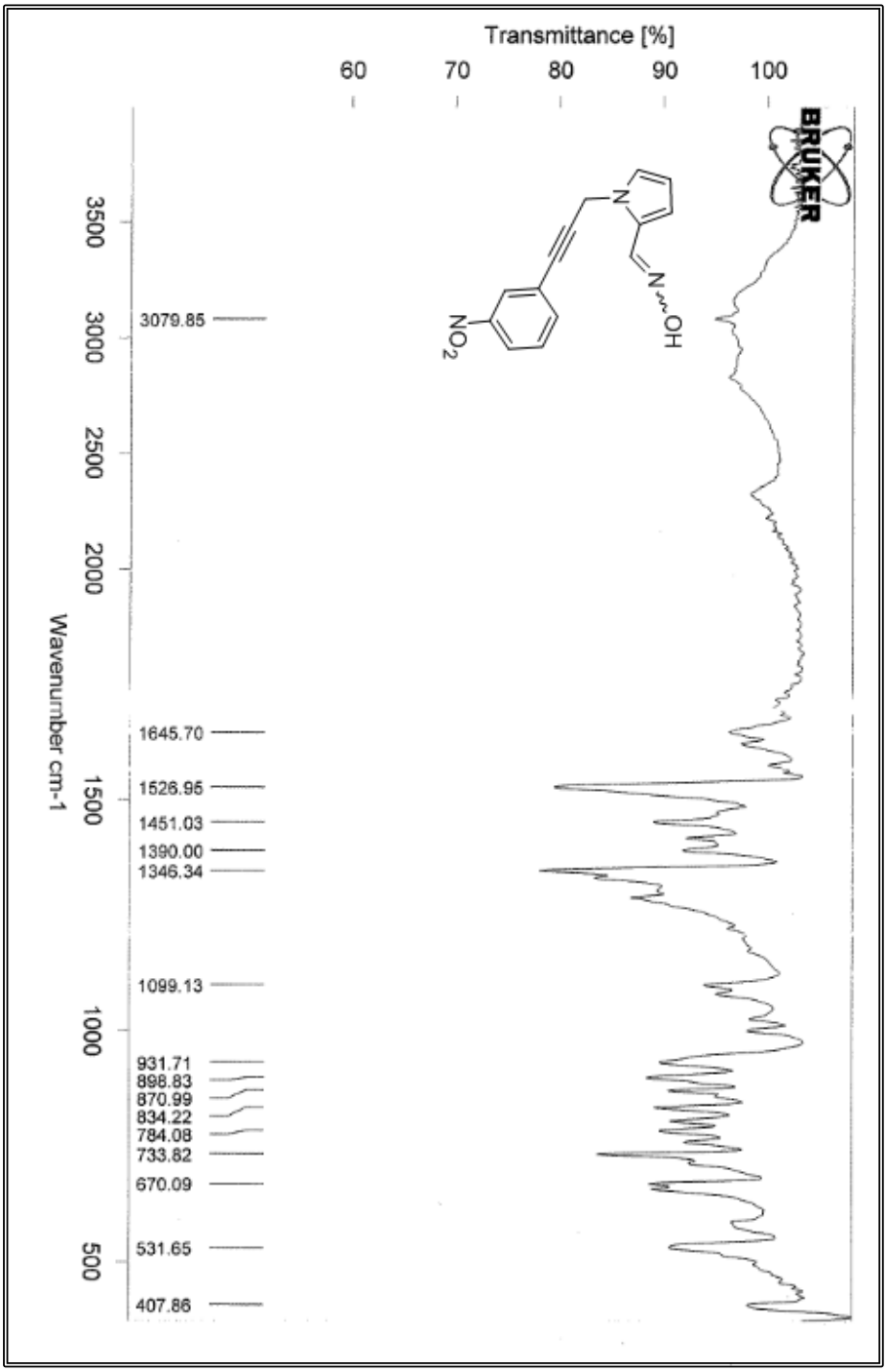

Figure 48 IR Spectrum of Compound **121**

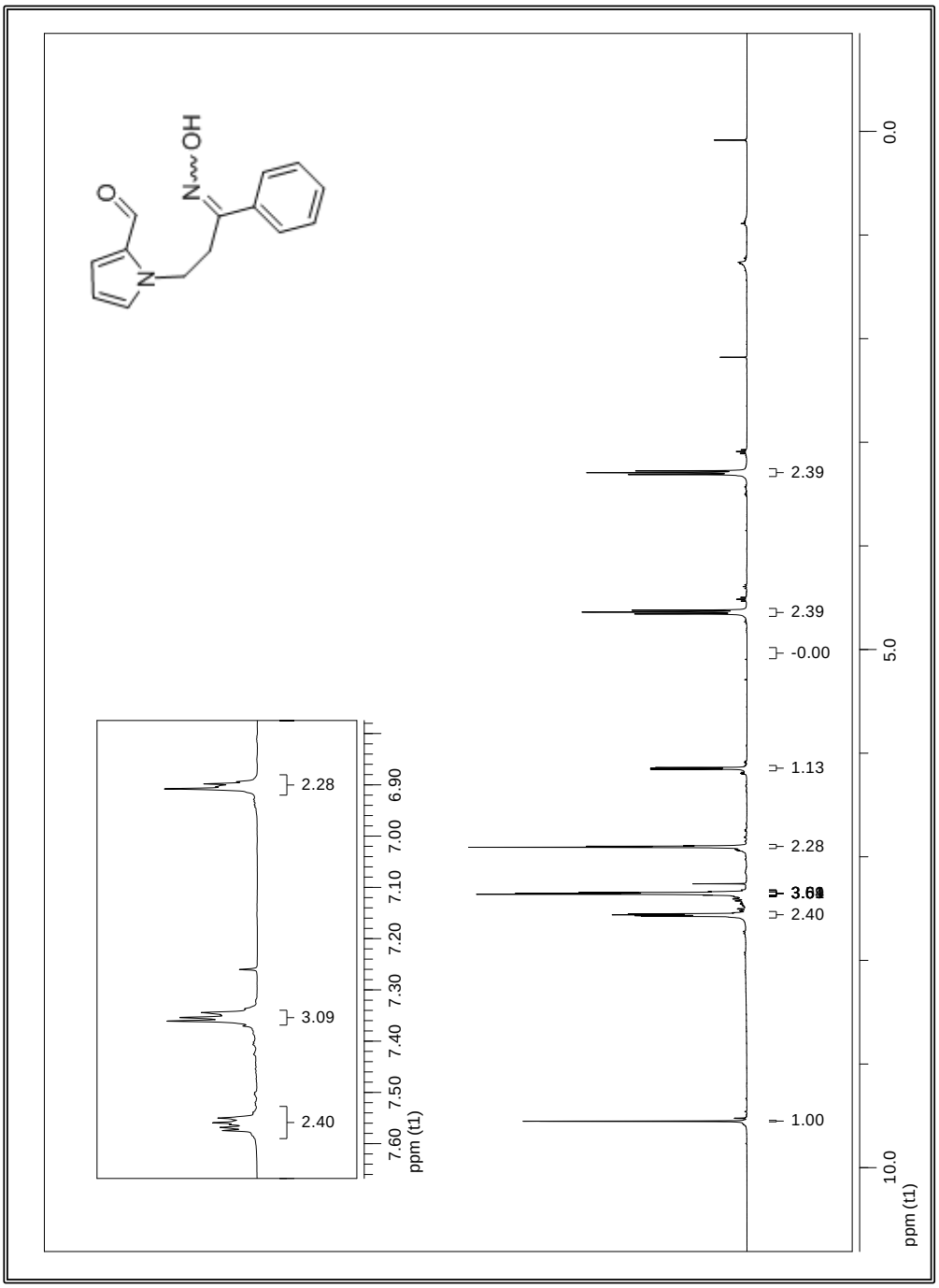

Figure 49 ^{1}H-NMR Spectrum of Compound **122**

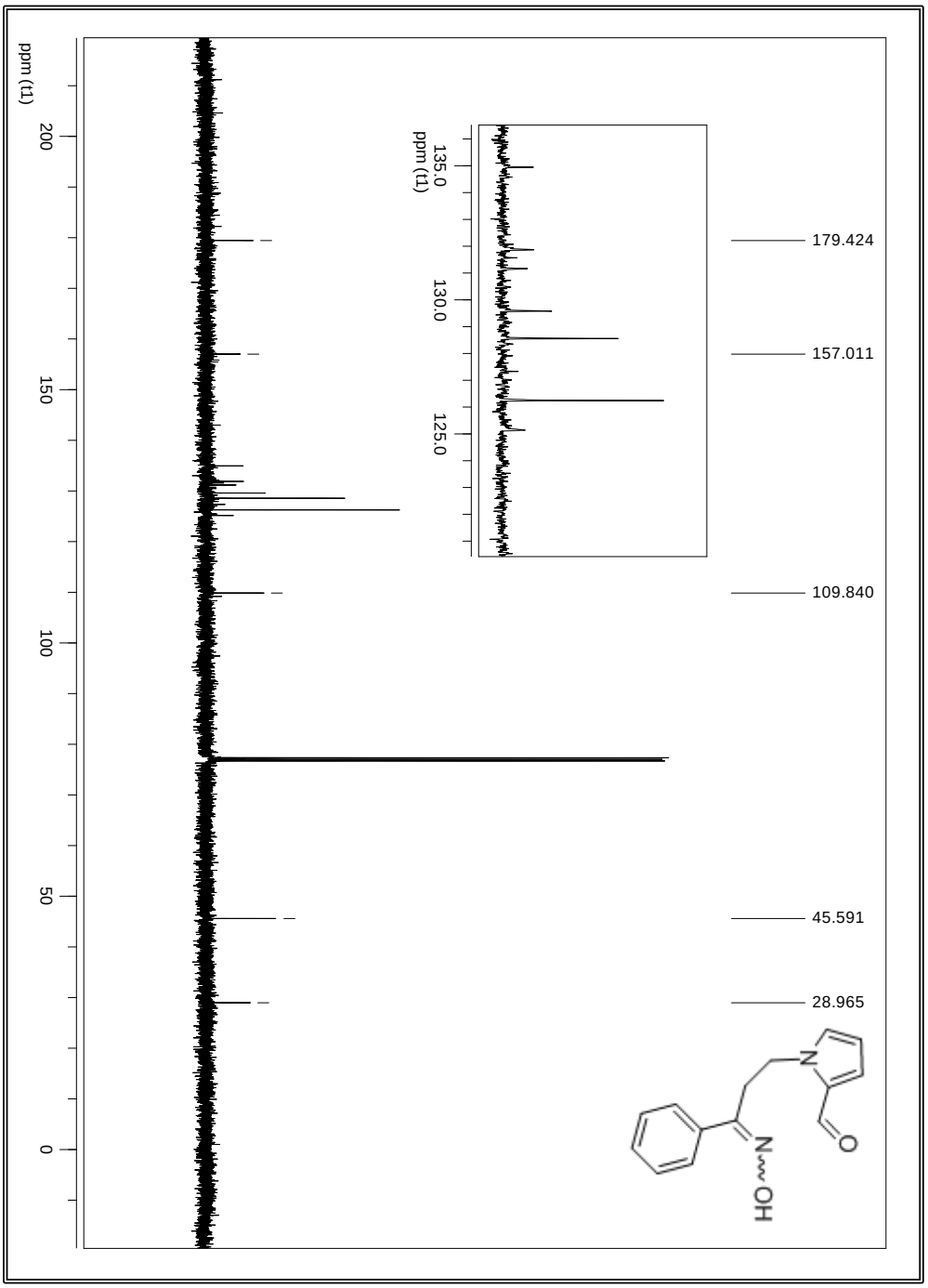

Figure 50 ^{13}C-NMR Spectrum of Compound **122**

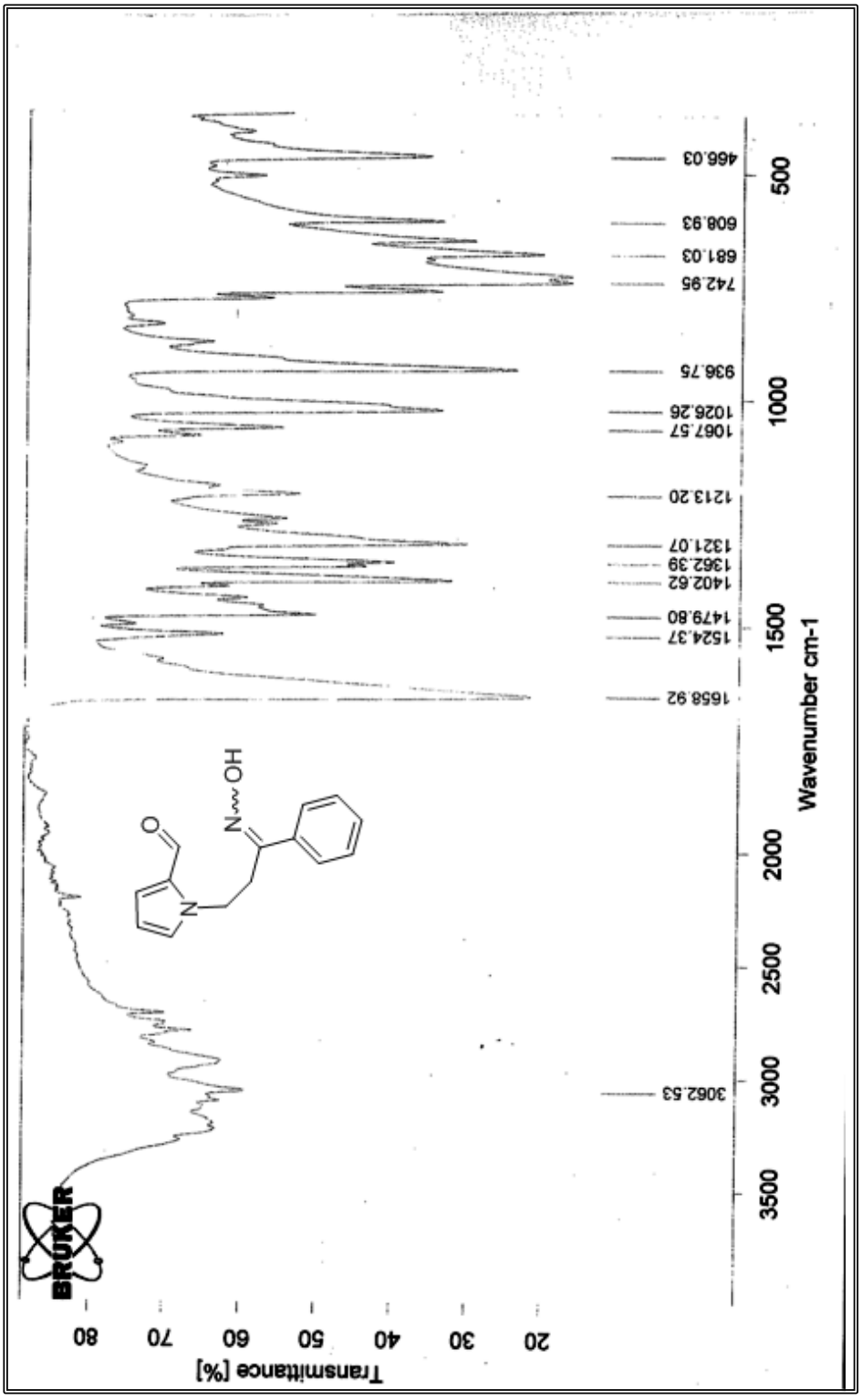

Figure 51 IR Spectrum of Compound **122**

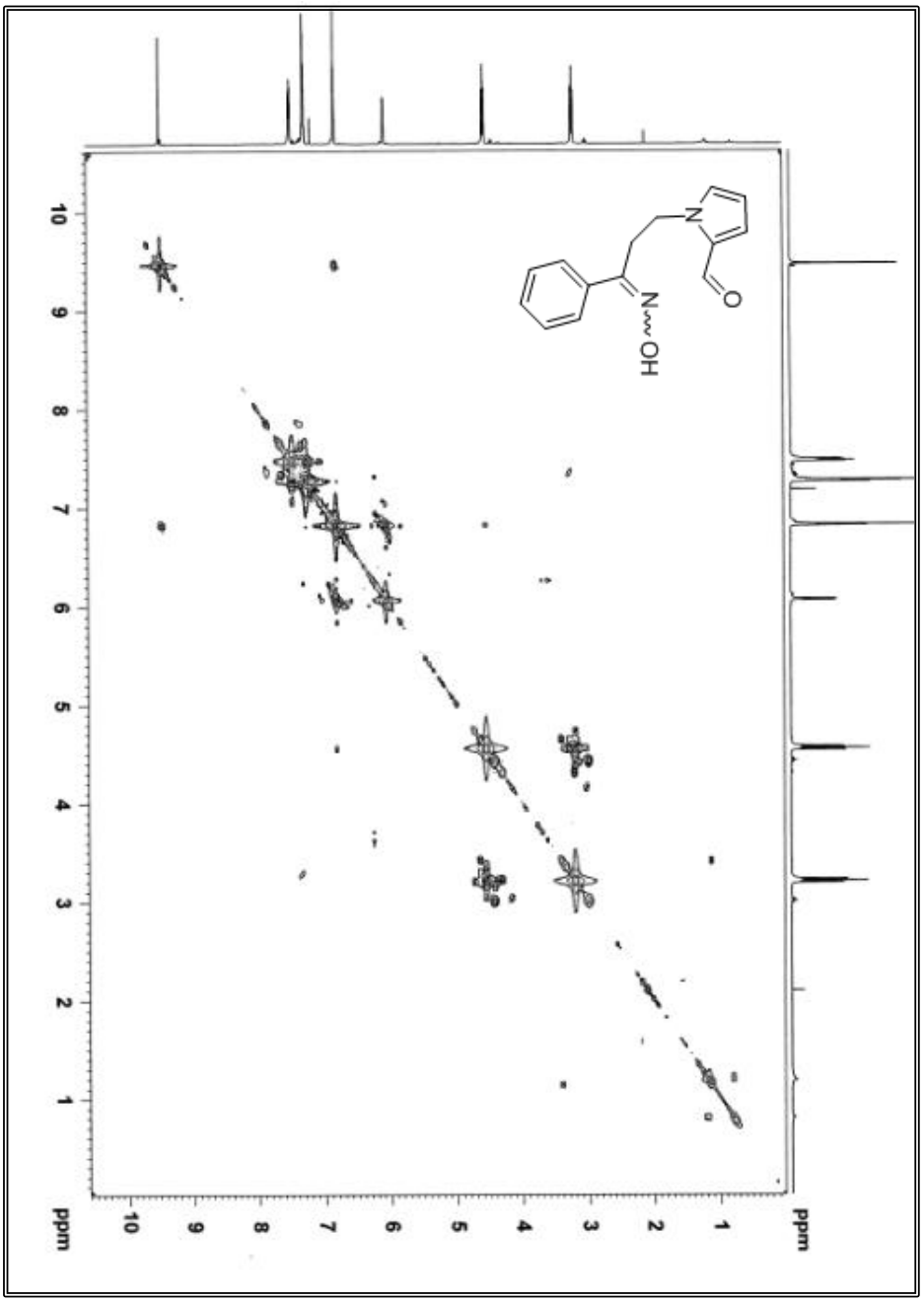

Figure 52 COSY Spectrum of Compound **122**

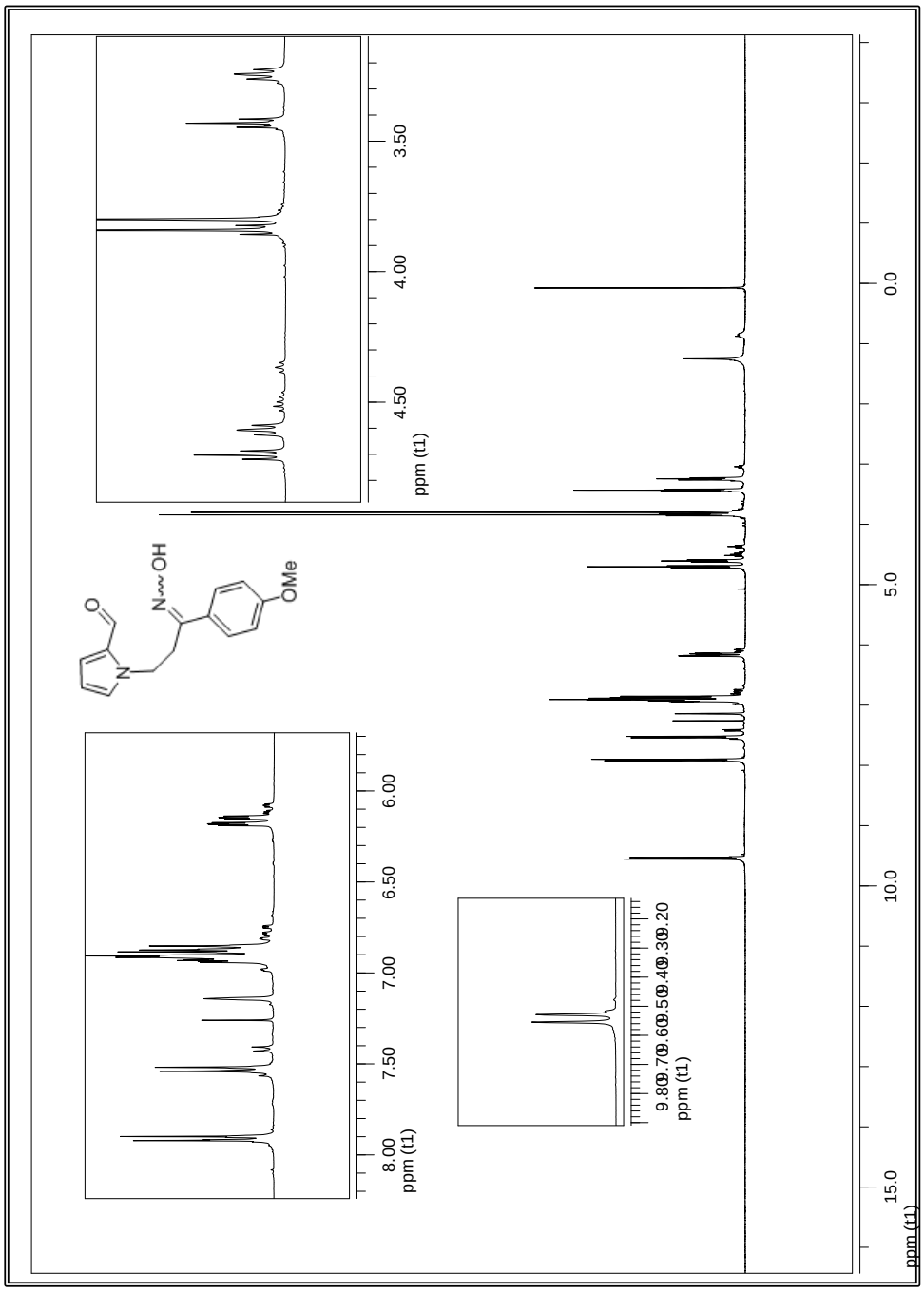

Figure 53 ^{1}H-NMR Spectrum of Compound **130**

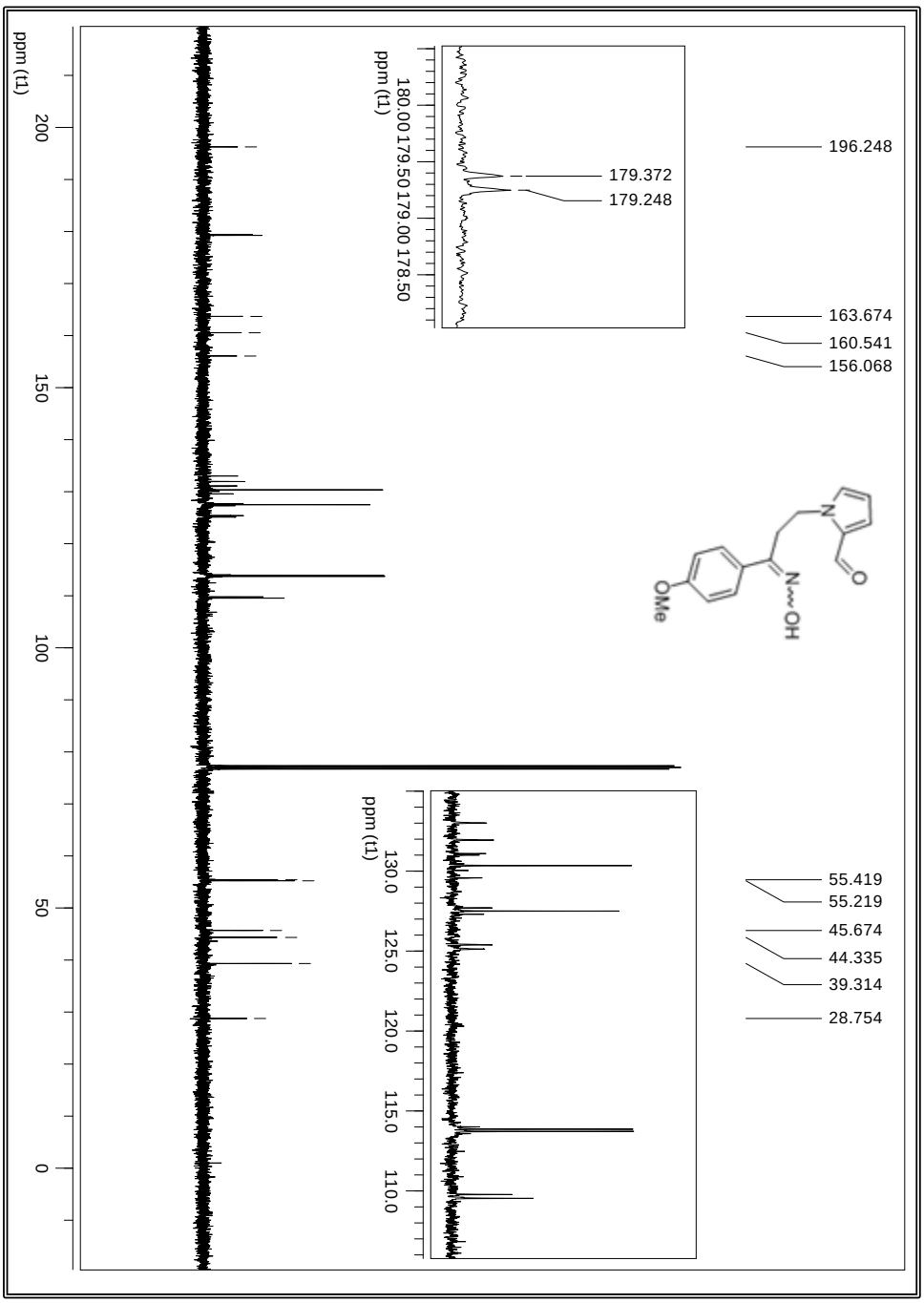

Figure 54 ^{13}C-NMR Spectrum of Compound **130**

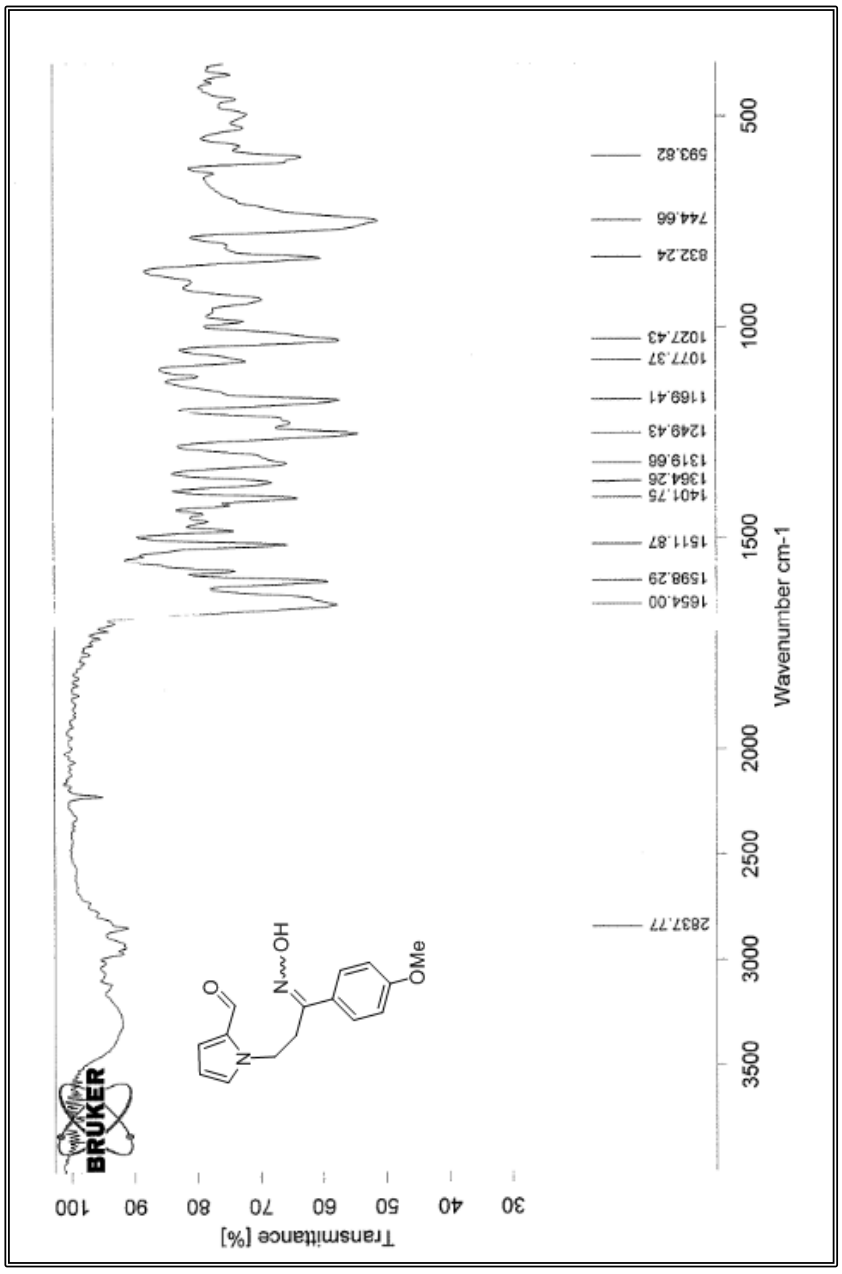

Figure 55 IR Spectrum of Compound **130**

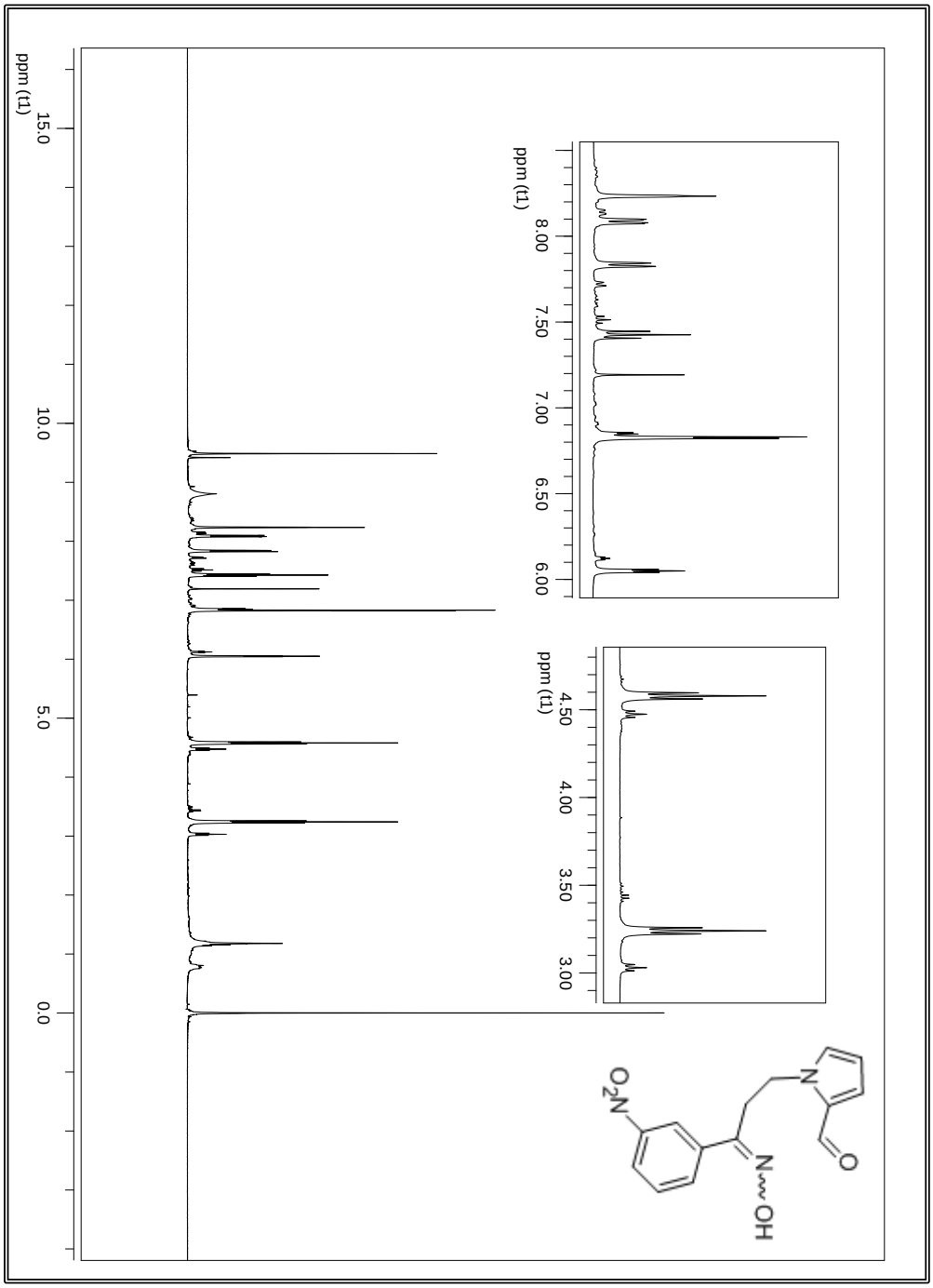

Figure 56 ^{1}H-NMR Spectrum of Compound **131**

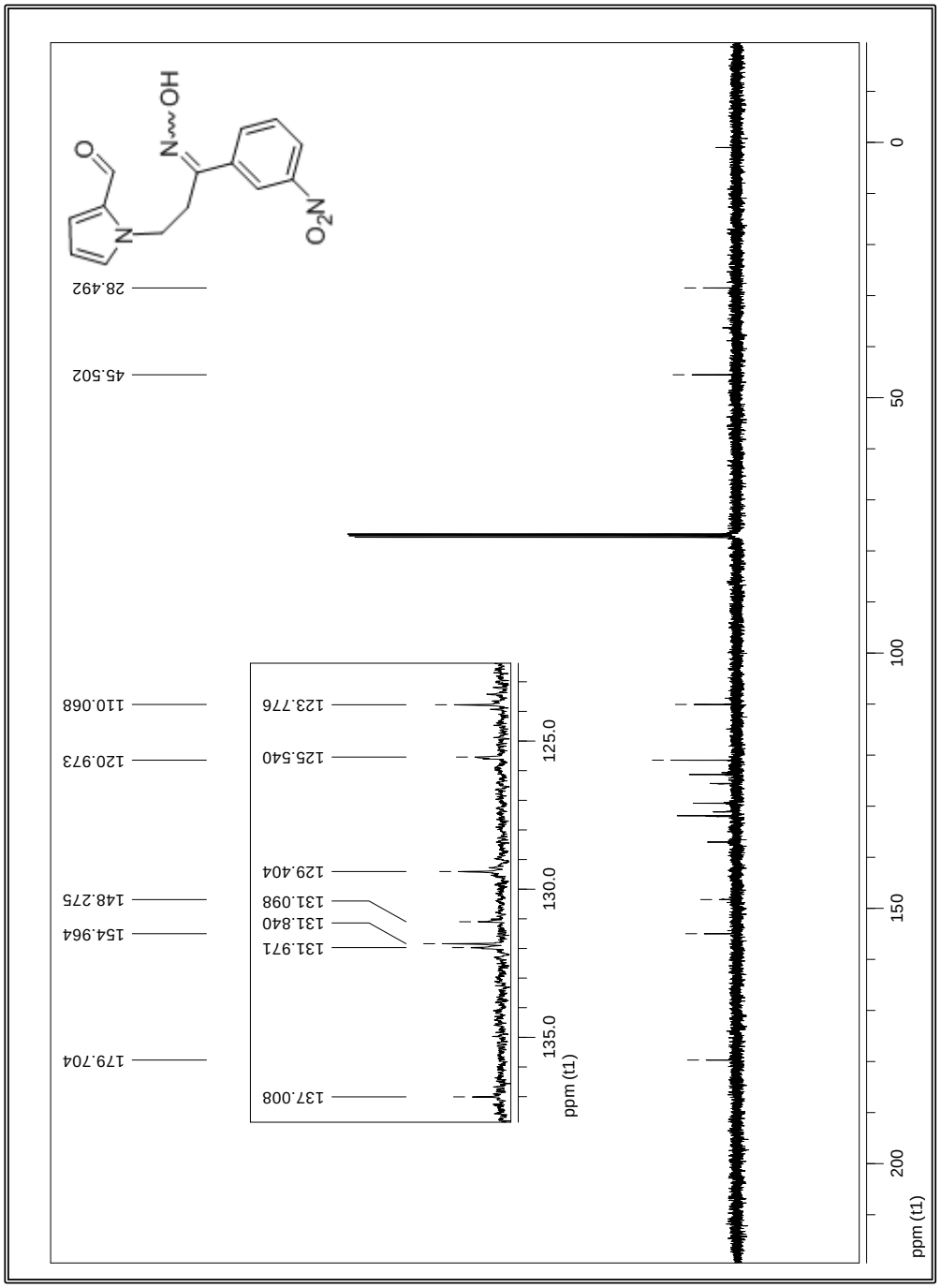

Figure 57 ^{13}C-NMR Spectrum of Compound **131**

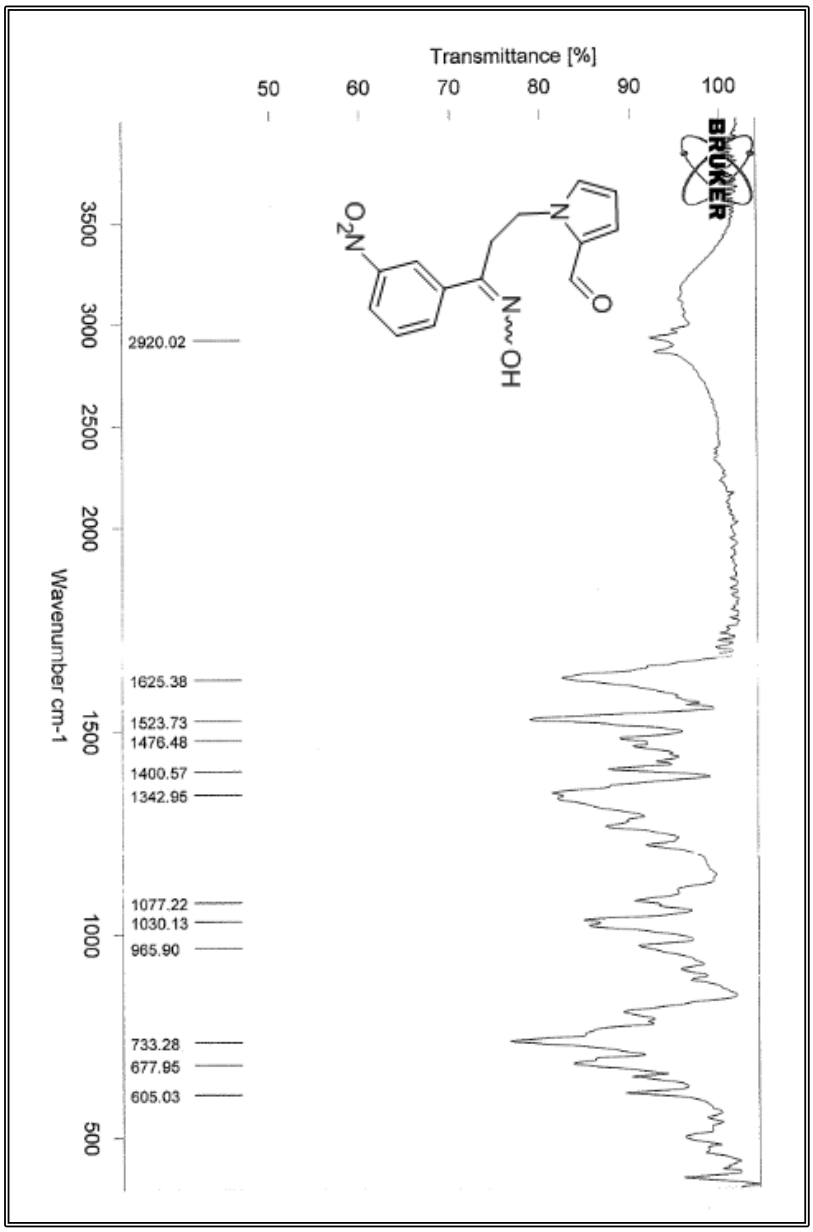

Figure 58 IR Spectrum of Compound **131**

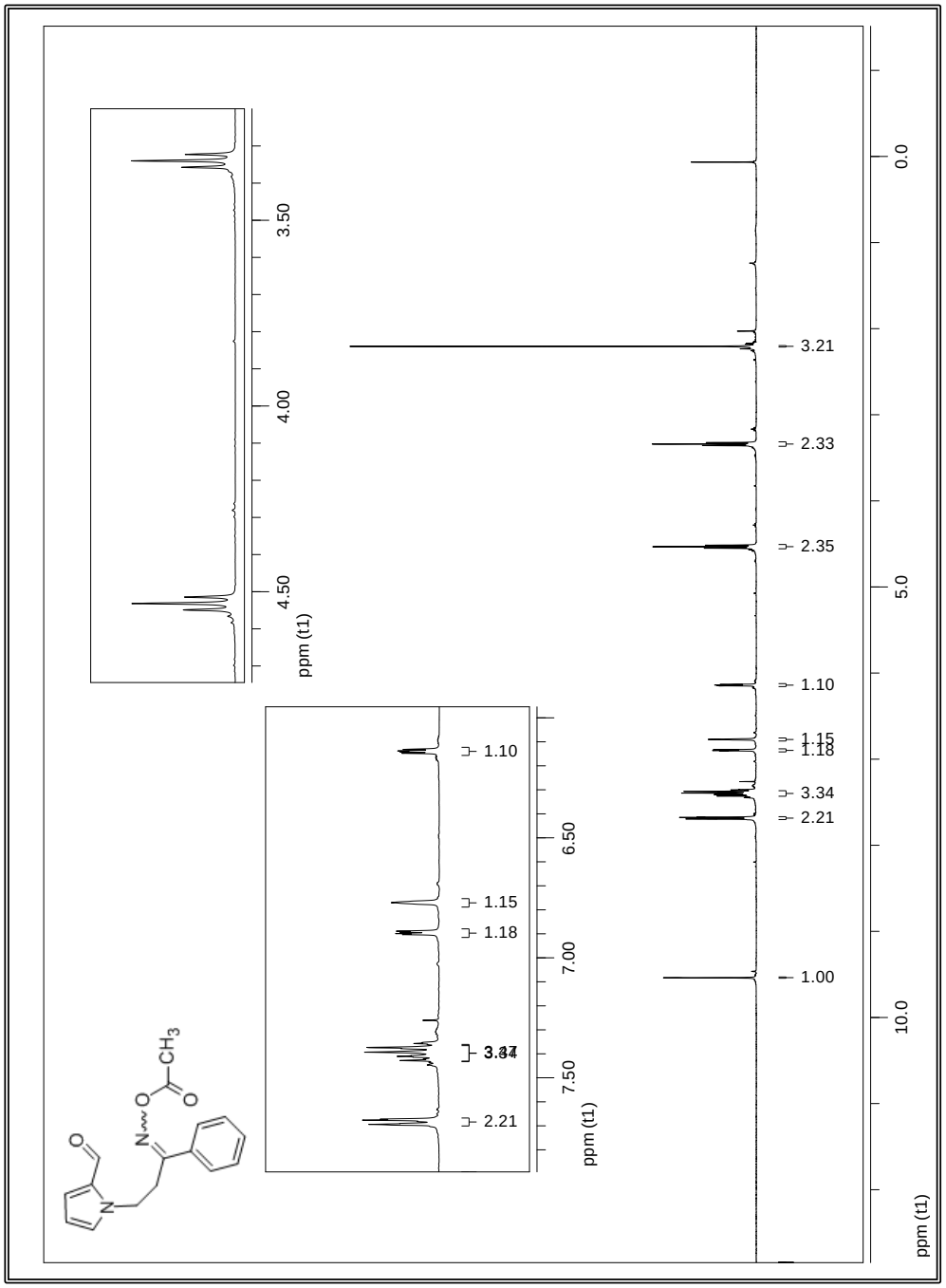

Figure 59 ^{1}H-NMR Spectrum of Compound **122**

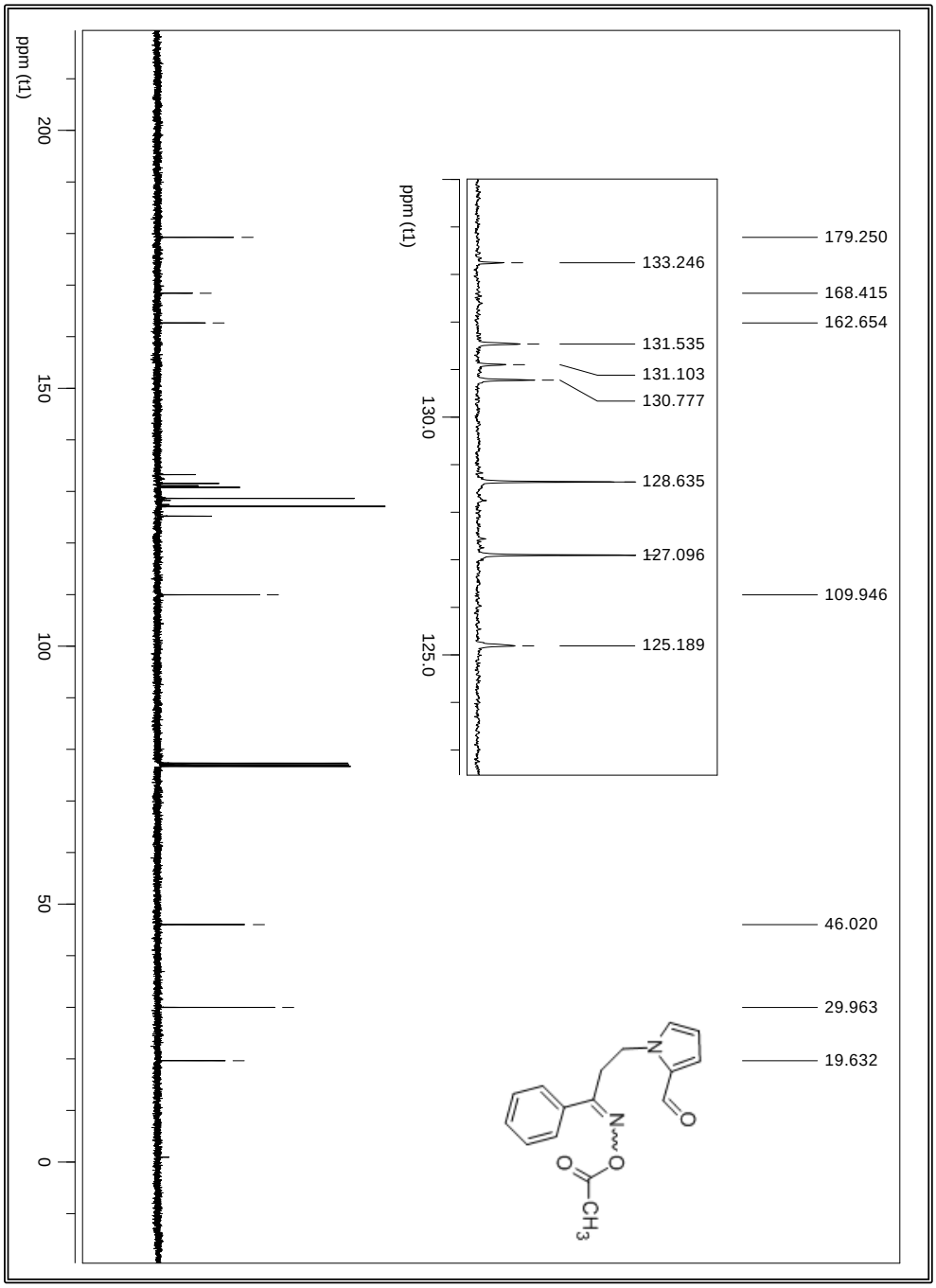

Figure 60 ^{13}C-NMR Spectrum of Compound **122**

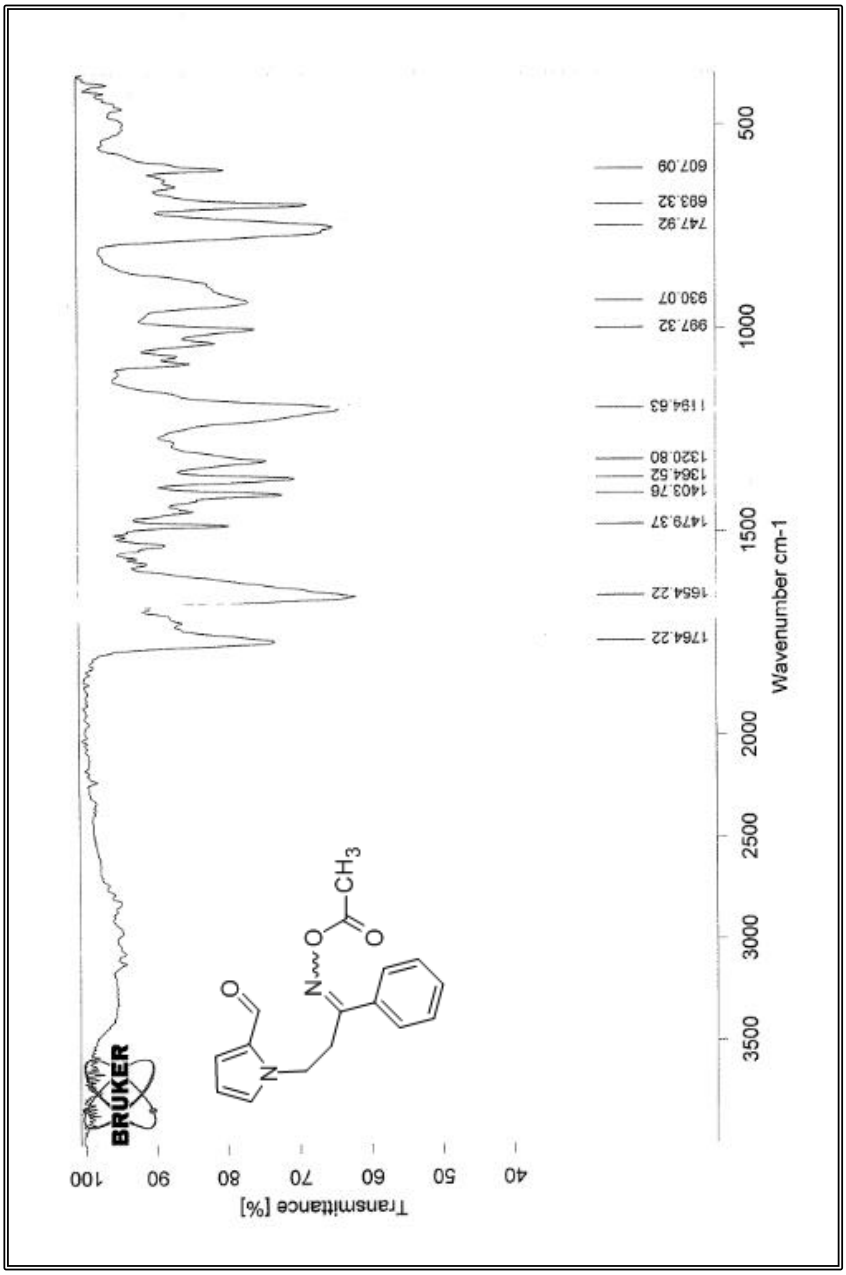

Figure 61 IR Spectrum of Compound **122**