BRØNSTED ACID-CATALYZED INVERSE ELECTRON-DEMAND DIELS-ALDER REACTIONS OF 1,2-DIAZINES

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By

Hatice Seher Korkmaz

September 2023

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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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Yunus Emre TÜRKMEN (Advisor)

_____

Halil İbrahim OKUR

_____

Çağatay DENGİZ

Approved for the Graduate School of Engineering and Science

_____

Orhan ARIKAN

Director of the Graduate School

ABSTRACT

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INVERSE ELECTRON-DEMAND DIELS-ALDER

REACTIONS OF 1,2-DIAZINES

Hatice Seher Korkmaz

M.Sc. in Chemistry

Advisor: Yunus Emre Türkmen

September 2023

The discovery of Diels-Alder reaction by Otto Diels and Kurt Alder in 1928 marked an important development in synthetic organic chemistry. This [4+2] cycloaddition reaction has been used in a variety of ways over the years, from natural product synthesis to medicinal chemistry. The process produces derivatives of cyclohexane by the coordinated addition of a conjugated diene and a dienophile. As a subclass of Diels-Alder reactions, inverse electron-demand Diels-Alder (IEDDA) reactions are covered in this thesis, along with their intricate mechanisms and applications. IEDDA cycloaddition reactions have become more well-known recently, especially in the fields of chemical biology, bio-orthogonal reactions and the synthesis of complex molecules. These reactions generally have excellent regio- and stereoselectivity and they occur between electron-poor dienes and electron-rich dienophiles. They have

been crucial in the synthesis of bioactive substances with potential use for the cancer treatment, such as halenaquinone and rhodexin A. Catalysts have become an effective means of promoting IEDDA reactions in the search for milder reaction conditions and higher yield. To modify the energy levels of dienes and increase reactivity, Brønsted acid catalyst has been used in this project. This study involves the investigation of pyridinium salts as Brønsted acid catalyst intended to reduce the LUMO energy levels of 1,2-diazines. The goal is to make diazines more reactive in IEDDA reactions, creating new pathways for the synthesis of a variety of complex molecules. By bridging the gap between difficult reaction conditions and effective IEDDA reactions, this project aims to increase the usefulness of this potent synthetic method in contemporary organic chemistry.

Key Words: Diels-Alder (DA), Inverse Electron-Demand Diels-Alder (IEDDA) reactions, Brønsted acid catalyst

ÖZET

1,2-DİAZİNLERİN BRØNSTED

ASİT KATALİZLİ İNVERS

DIELS-ALDER REAKSİYONLARI

Hatice Seher Korkmaz

Kimya Bölümü, Yüksek Lisans

Tez Danışmanı: Yunus Emre Türkmen

Eylül 2023

1928'de Otto Diels ve Kurt Alder tarafından Diels-Alder reaksiyonunun keşfi, sentetik organik kimya alanında önemli bir gelişmeye neden oldu. Bu [4+2] halkasal katılma reaksiyonu, yıllar boyunca doğal ürünlerin sentezinden farmasötik kimyaya kadar çeşitli şekillerde kullanılmıştır. Bu işlem, konjuge bir dien ve bir dienofilin eklenmesiyle sikloheksan türevleri üretir. Diels-Alder reaksiyonunun bir alt sınıfı olan invers Diels-Alder reaksiyonu (IEDDA), karmaşık mekanizmaları ve uygulamalarıyla birlikte bu tezde ele alınacaktır. IEDDA siklokatılma reaksiyonları son zamanlarda özellikle kimyasal biyoloji, biyo-ortogonal reaksiyonlar ve karmaşık moleküllerin sentezi alanlarında daha iyi bilinmektedir. Bu reaksiyonlar mükemmel yer-seçiciliğine ve stereo-seçiciliğe sahiptir ve elektronca fakir dienler ve elektronca zengin dienofiller arasında gerçekleşir. Halenakinon ve rodeksin A gibi kanser tedavisinde kullanılabilecek biyoaktif maddelerin

sentezinde çok önemli bir rol oynamışlardır. Katalizörler, daha ılımlı IEDDA reaksiyon koşullarının araştırılmasında etkili bir araç haline gelmiştir. Bu projede dienin enerji seviyesini değiştirmek ve reaktiviteyi arttırmak için Brønsted asit katalizörü kullanıldı. Bu çalışma, 1,2-diazin'in LUMO enerji seviyesini düşürmeyi amaçlayan ve Brønsted asit katalizörü olan piridinyum tuzlarının katalitik aktivitelerinin incelenmesini içermektedir. Amaç, 1,2-diazini IEDDA reaksiyonlarında daha reaktif hale getirerek farklı kompleks moleküller için yeni sentez yolları oluşturmaktır. Zorlu reaksiyon koşulları ile verimli IEDDA reaksiyonları arasındaki boşluğu dolduran bu proje, bu etkili sentez yönteminin modern organik kimyadaki kullanımını artırmayı hedefliyor.

Anahtar Kelimeler: Diels-Alder (DA), İnvers Diels-Alder reaksiyonu (IEDDA), Brønsted asit katalizörü

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Dedicated to KORKMAZ family…

LIST OF ABBREVIATIONS

BH_3.THF	Borane-tetrahydrofuran
CAN	Ceric ammonium nitrate
DA	Diels-Alder
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density Functional Theory
DIEA	N, N-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EAS	Electrophilic aromatic substitution
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_3N	Triethylamine
FMO	Frontier molecular orbitals
HFIP	Hexafluoroisopropanol
HOMO	Highest occupied molecular orbital
KOtBu	Potassium tert-butoxide
MeOH	Methanol
2-Me-THF	2-Methyl tetrahydrofuran
NBS	N-Bromosuccinimide
NEDDA	Normal Electron-Demand Diels-Alder
NMR	Nuclear Magnetic Resonance
***o*-tol**	Ortho-toluidine

IEDDA	Inverse Electron-Demand Diels-Alder
TES	Triethylsilyl
TFE	Trifluoroethanol
Tf_2NH	Bistriflimide
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-Layer Chromatography
TMS	Trimethylsilyl
PMP	p-Methoxyphenyl
Ph	Phenyl
$PhCF_3$	Trifluorotoluene
Phen	Phenanthroline

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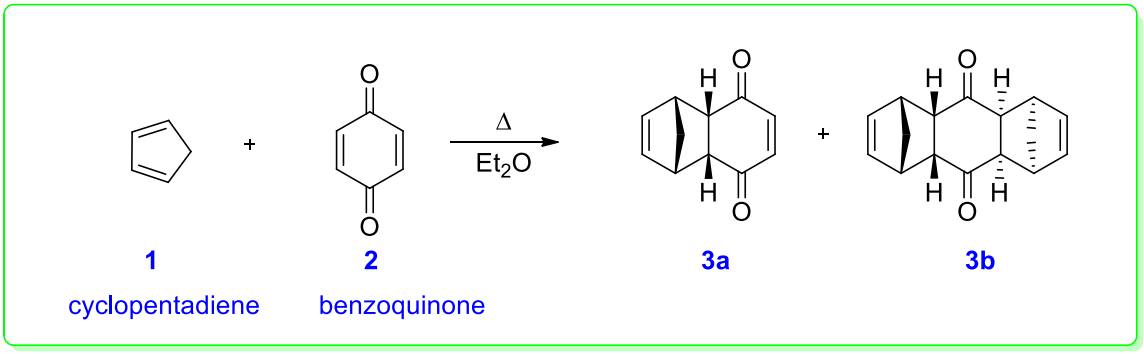
1 INTRODUCTION

1.1. Diels-Alder Reactions and Their General Applications

Diels-Alder reactions date back to 1928, and were discovered by Otto Diels and Kurt Alder who were awarded Nobel Prize in Chemistry for their pioneering work on this reaction in 1950.[1] Subsequently, it has captured focus over following decades and open windows to a great research area in synthetic organic chemistry.[2,3] They have widespread applications in medicinal chemistry and drug discovery.[4,5] Furthermore, Diels-Alder (DA) reactions constitute a very important subclass of pericyclic reactions and they are categorized as a thermally-allowed [4+2] cycloaddition, which originates from a cyclic transition state in concerted manner and encompasses cycloaddition of a conjugated diene with dieonophile.[6] Therefore, they facilitate the generation of cyclohexane derivatives. Cyclopentadiene (**1**) and benzoquinone (**2**) exemplify a prominent instance of DA reactions giving mono- and di-adducts (Scheme 1, compounds **3a** and **3b**).[7]



Scheme 1: Diels-Alder reaction of cyclopentadiene and benzoquinone

The mechanism of DA reaction is considered as a concerted pericyclic reaction, and proceeds with a single cyclic transition state.[8] Accordingly, normal electron demand Diels-Alder (NEDDA) reactions are controlled by orbital symmetry considerations and they are categorized as a $[_{\pi}4_{s} + _{\pi}2_{s}]$ cycloaddition, eventuating between 4π electron system (electron rich diene) and 2π electron system (electron poor dienophile). Frontier molecular orbitals (FMO) articulate the rationale behind this phenomenon. In the case of ubiquitous NEDDA reaction, the major interaction takes place between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile (Figure 1).[8] To exemplify, electron rich butadiene and electron poor dienophile stand as a compelling illustration of NEDDA reaction.[9]

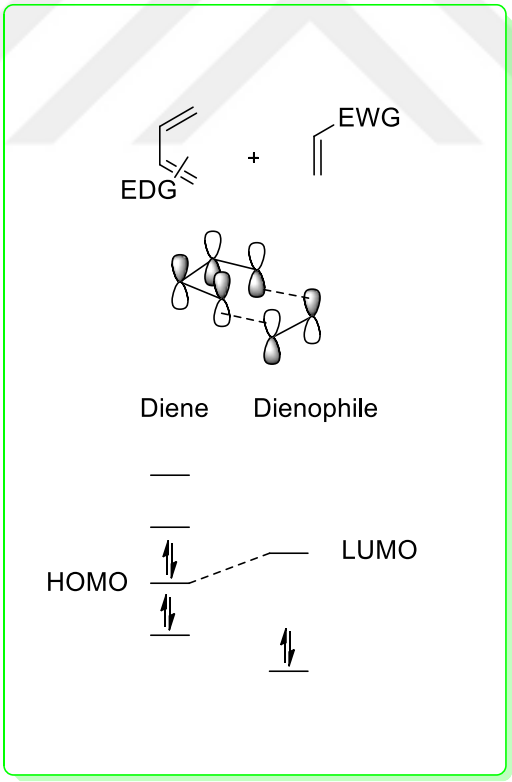
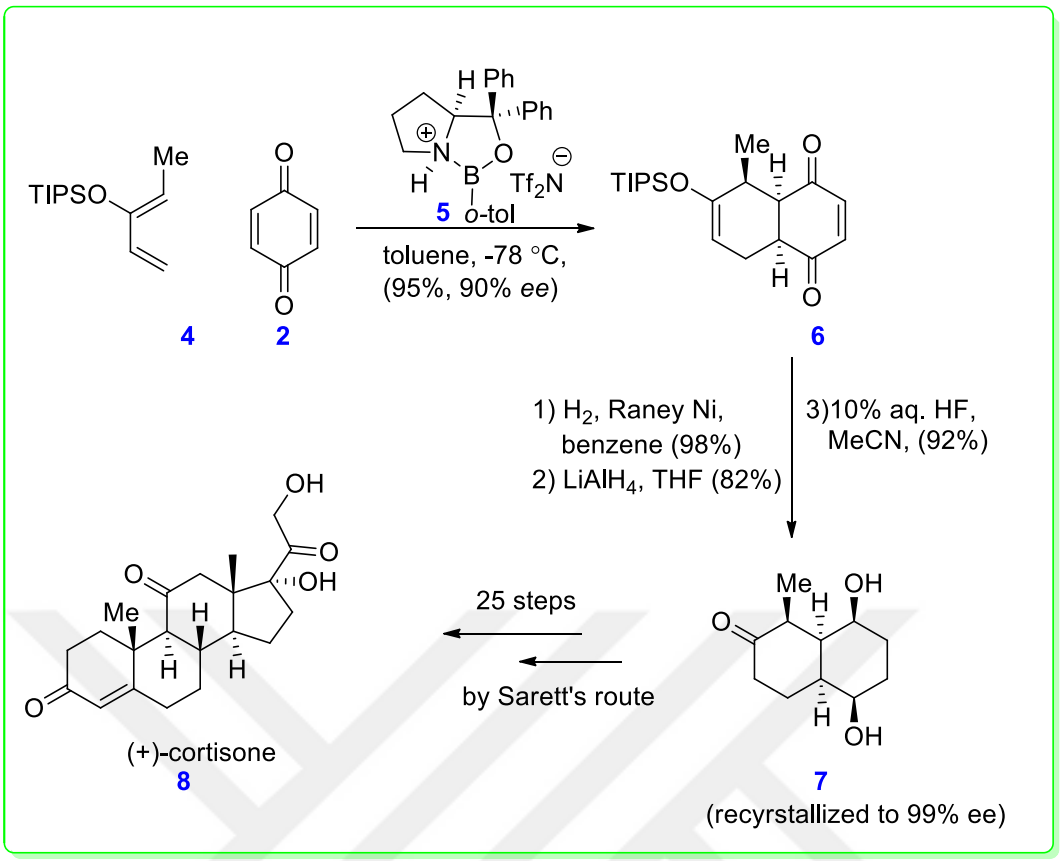


Figure 1: FMO analysis of NEDDA reaction.

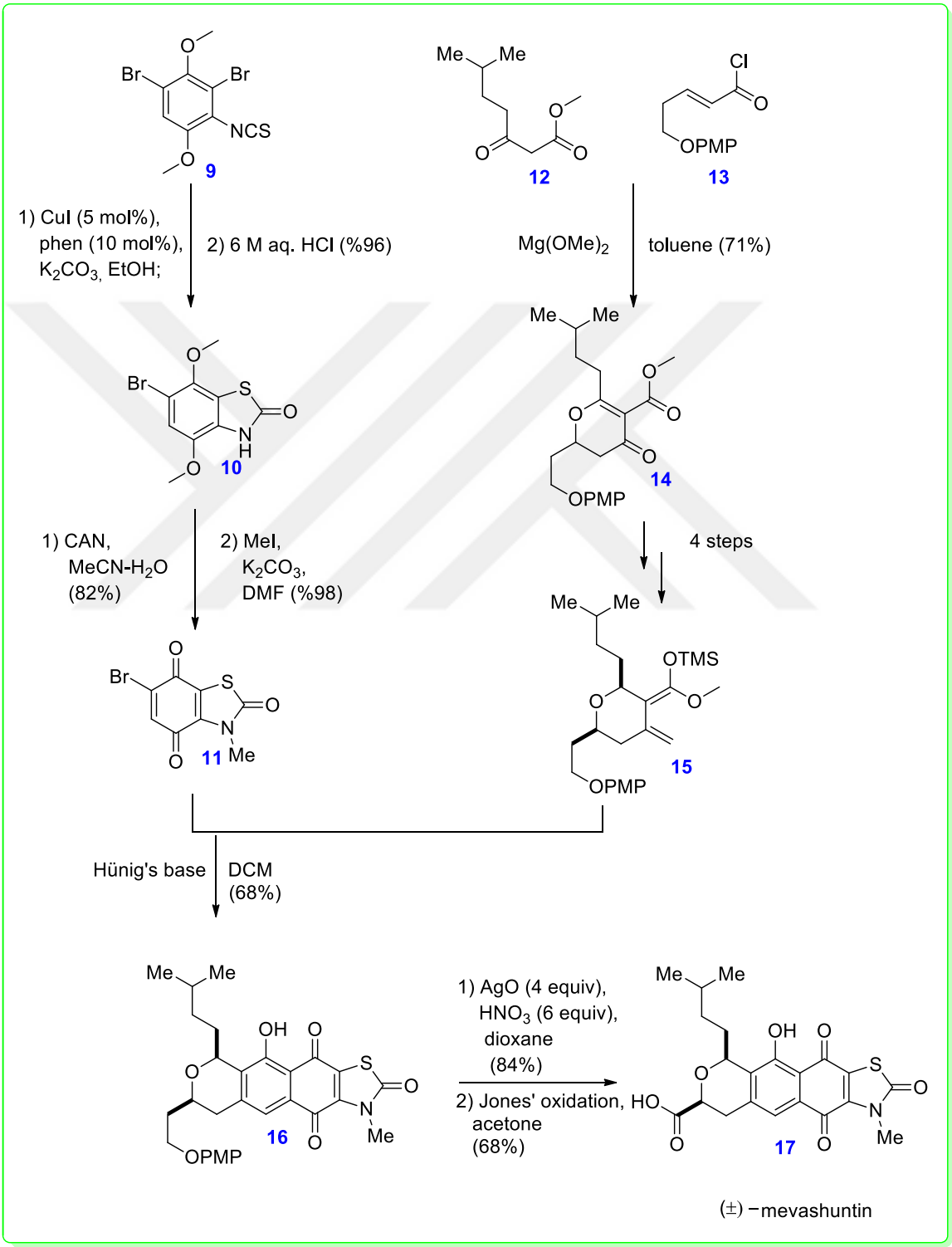
Due to DA reaction's concerted mechanism, it guarantees incorporation of the majority of atoms from starting materials into final products and demonstrates remarkable diversity.[10,11] In a retrosynthetic analysis, it is critical to plan disconnections in molecules, and in this respect, DA reactions furnish strategic bond formation, rapid construction of ring systems, which renders it a versatile transformation in the synthesis of complex molecules.[12] Substantively, they have been playing vital role in the total synthesis of natural products since they are commonly stereoselective and regioselective.[13] In 2004, E. J. Corey and co-workers conducted research accomplishing the formal synthesis of (+)-cortisone through building up a chiral cationic oxazaborolidinium catalyst **5**, and they used an initial DA reaction parallel to method achieved by Sarett (Scheme 2).[14,15] Diene **4** and benzoquinone (**2**) were used to initiate reaction the synthetic route in the presence of chiral catalyst **5**, which gave compound **6** in high yield with excellent regioselectivity. Hydrogenation of diketone **6** followed by reduction resulted in diol **7**. Consequently, the formal total synthesis of (+)-cortisone (**8**) was accomplished by using similar synthetic route with Sarett.[15]



Scheme 2: Enantioselective synthesis of diol **7**.

In 2012, Nawrat and Moody established a highly efficient synthetic pathway to the natural product mevashuntin.[16] When considering the retrosynthetic disconnections to break down this complex molecule, the combination of quinone **11** and diene **15** emerges as a particularly favorable selection in the key late-stage DA reaction (Scheme 3). The most remarkable aspect is that this reaction gives compound **16** in high yield as a single regio-isomer.[17] The synthetic route started with copper-mediated cyclization of compound **9** resulting in the formation of compound **10**. Subsequent to this, the resultant compound **10** underwent methylation and oxidation process, leading to targeted quinone **11**. Diene **15** was generated by condensation of ketoester **12** with acryloyl chloride **13**, which is followed by a parallel sequence of steps to Brassard's synthetic route for ventilagone.[18] Finally, the two components were combined to give the expected DA product **16** in high

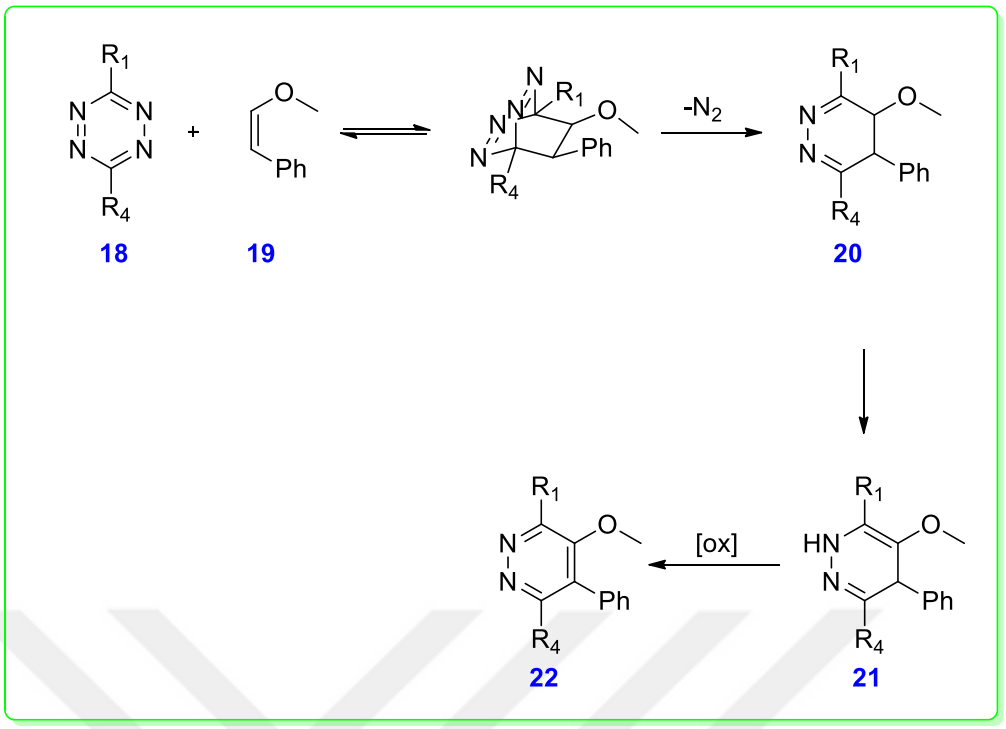
yield. Afterwards, it is followed by deprotection and oxidation of primary alcohols resulting in natural product **17** called mevashuntin.[17]



Scheme 3: Synthesis of mevashuntin (**17**).

1.2. Inverse Electron Demand Diels-Alder Reactions and Their General Applications

Inverse electron-demand Diels-Alder (IEDDA) reactions have garnered significant attention in modern synthetic chemistry and are widely employed in the field of chemical biology.[19,20] They enable to achieve controlled and site-specific modifications of proteins and they are extensively utilized in biorthogonal reactions and click chemistry, offering diversity for the rapid construction of complex molecules.[21,22] Unlike NEDDA reactions, the inception date of IEDDA reactions remains unknown because chemists encountered a challenge in distinguishing between NEDDA and IEDDA reactions before the emergence of modern computational techniques.[23] As a mechanistic approach, it stands as a significant topic whether IEDDA reactions are concerted but it is mostly agreed upon occurrence of [4+2] cycloaddition via single transition state.[24] Many heterocycles can be synthesized through application of IEDDA reactions and addition of tetrazine **18** and alkene **19** is well-known example of them (Scheme 4).[25] After IEDDA addition of reactants, followed by nitrogen extrusion via a retro-Diels-Alder reaction culminated in pyridazine **20**. Isomerization of this resulting compound led to a formation of compound **21**, which was subsequently oxidized to the final product **22**.[26]



Scheme 4: IEDDA reaction between tetrazine **18** and alkene **19**.

FMO theory should be considered to gain a more distinct insight into the mechanism of IEDDA reactions.[27] As a subclass of pericyclic reactions, they are widely accepted as a concerted, asynchronous and [4+2] cycloaddition.[28] Additionally, stereoelectronic effects such as molecular geometry and orbital interactions cannot be disregarded.[29] In contrast to NEDDA reactions, electron poor diene and electron rich dienophile are highly favourable since LUMO of diene and HOMO of dienophile are essential for achieving enhanced orbital overlap in IEDDA reactions.[30] For illustrative purposes, electron poor butadiene and electron rich dienophile are the most common example of IEDDA reactions.[31] As evident from Figure 2, the energy levels of LUMO of the diene and HOMO of the dienophile facilitate optimal orbital overlap.

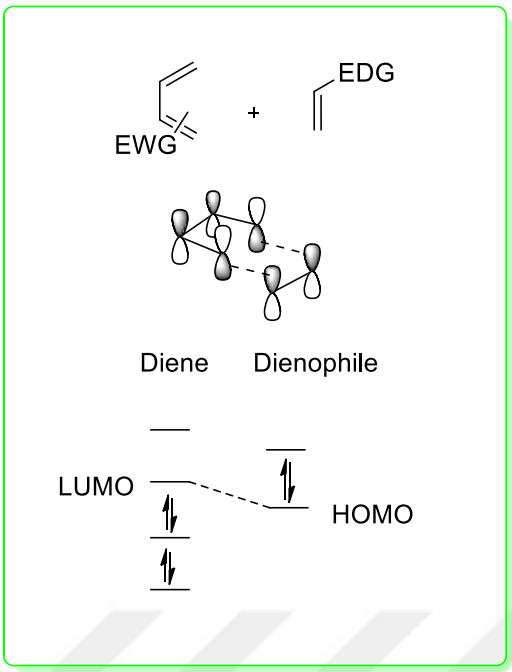
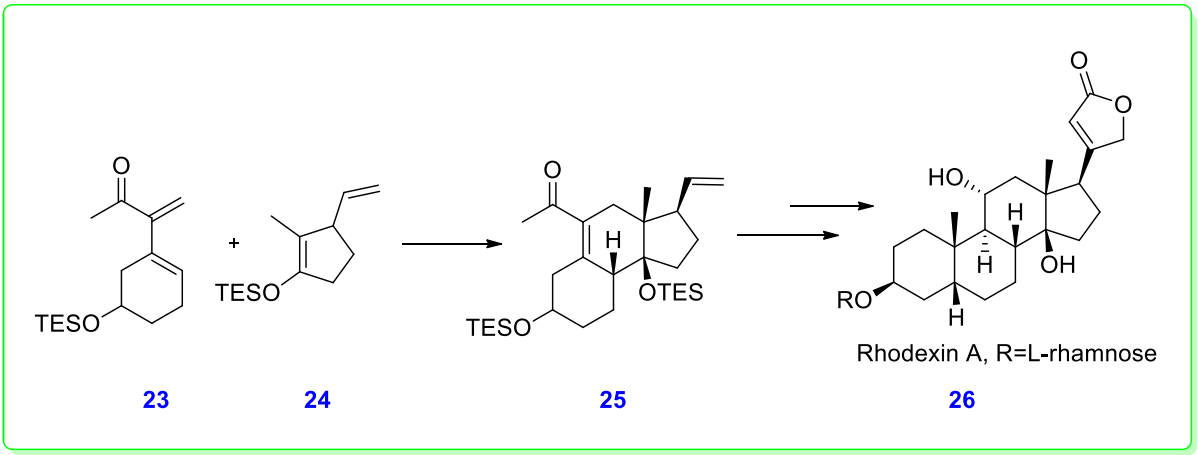


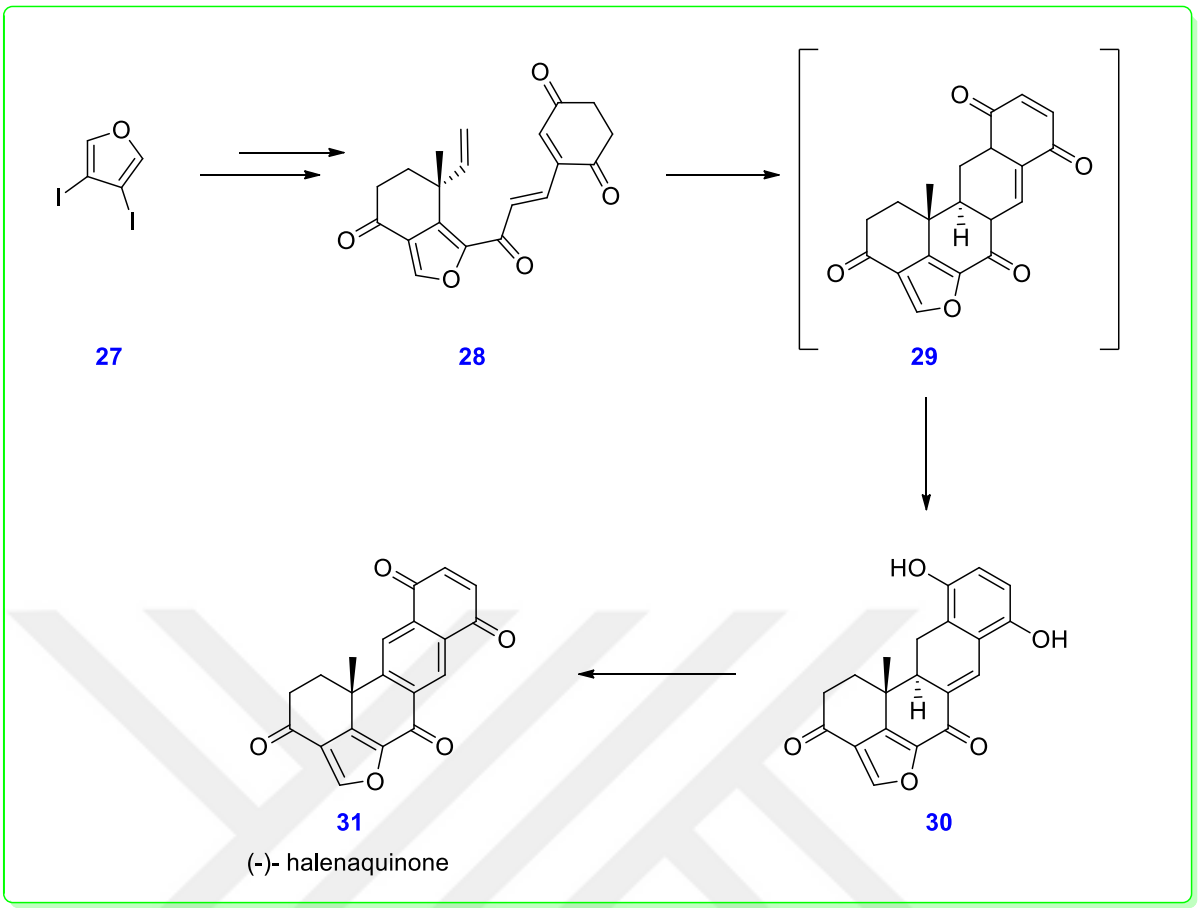
Figure 2: FMO analysis of IEDDA reaction.

In chemical biology, IEDDA reactions represent a fascinating subclass of pericyclic reactions, serving as a fundamental component in the synthetic route culminating in the integration of pyridazine derivatives onto the DNA framework and they exhibit noteworthy efficiency for the synthesis of natural products such as Rhodexin A holding a potential for application in cancer treatment.[32,27] In 2011, M. E. Jung and co-workers reported the total synthesis of Rhodexin A initiated by IEDDA reaction (Scheme 5).[33] This natural product differs from the common steroid scaffold by virtue of its -*cis* fused ring and tertiary hydroxyl group, thereby acquiring distinct stereochemistry and attaining bioactive compound. Addition of diene **23** and dienophile **24** leads to key intermediate tricyclic compound **25** in high yield. After several steps, Rhodexin A (**26**) was smoothly synthesized.[33]



Scheme 5: Synthesis of the key intermediate of Rhodexin A by an IEDDA reaction

Another significant natural product is halenaquinone, known for its capacity to inhibit tumor cells.[34] IEDDA reaction was used to achieve simultaneous construction of two rings, exhibiting slow rate at room temperature and accelerated at high temperature, without an observable variance in yield, resulting in a single isomer.[35] The synthetic route started with diiodofuran **27** followed by several steps in order to give key intermediate **28** (Scheme 6). Then, extensive optimization experiments were undertaken under several conditions to identify the most suitable medium to produce cycloadduct **29**. According to experimental results, compound **28** demonstrated enhanced reactivity under high pressure condition, which resulted in vinyl hydroquinone **30** followed by oxidation and aromatization to afford (-)-halenaquinone (**31**).[35]

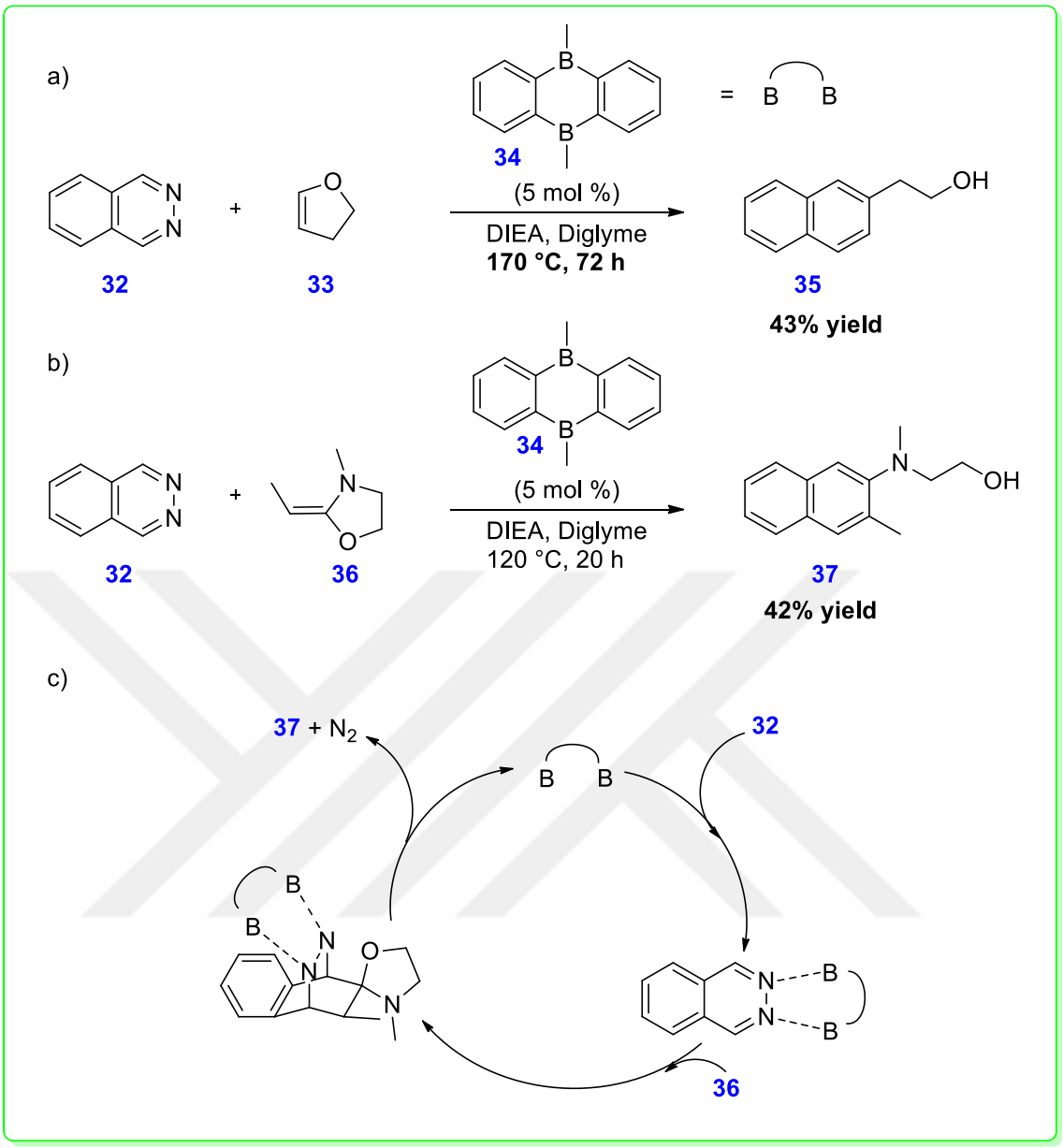


Scheme 6: Synthesis of the key intermediate of (-)-halenaquinone by an IEDDA reaction.

1.3. Lewis Acid and Solvent Hydrogen Bonding-Mediated Inverse Electron-Demand Diels-Alder Reactions

As mentioned in the previous section, the rate of IEDDA reactions depend on the electron richness of the dienophile and electron deficiency of the diene components. In this respect, 1,2,4,5-tetrazines are excellent dienes for IEDDA reactions due to their highly electron deficient nature. On the other hand, reactivity decreases as the number of nitrogens decreases on the azadiene component, and diazines are poor dienes which undergo IEDDA reactions only at high temperatures.[36] As such, the employment of catalysis is demanded for such substrates due to their low reactivity.[37] When reconsidering the FMO analysis, manipulating the energy levels of the LUMO of the diene and HOMO

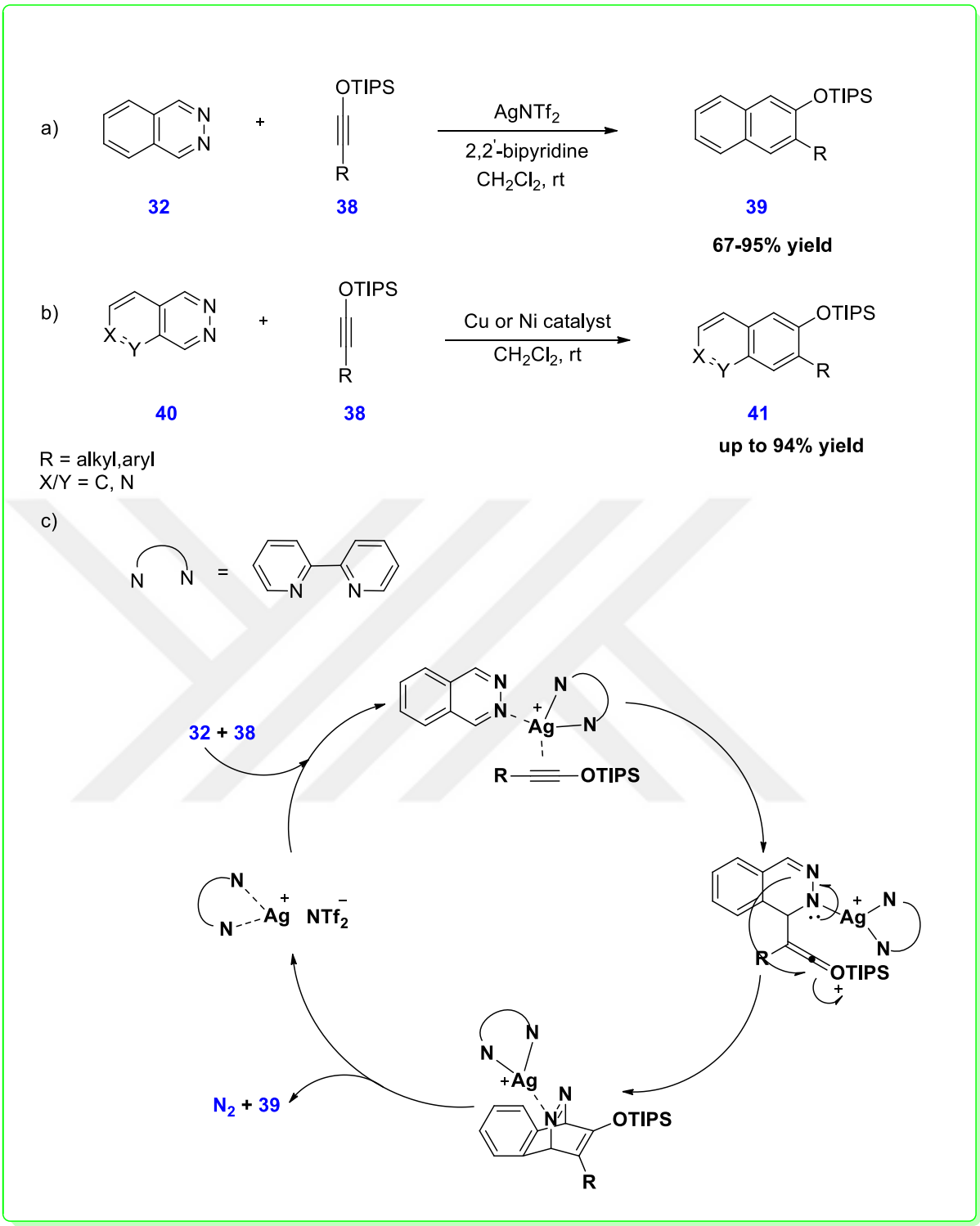
of dienophile comes to the forefront as a suitable strategy to introduce catalytic activity into IEDDA reactions.[38] To exemplify, 1,2 diazines demonstrate low reactivity in IEDDA reactions due to their high energy level of LUMO and Lewis acid is a potential choice to lower LUMO of diene as a catalytic activation.[39] In 2010, Wegner and Kessler established bidentate Lewis acid **34** to activate phthalazine (**32**) by lowering its LUMO energy, and it was employed as a catalyst in a variety of IEDDA reactions (Scheme 7a and 7b). However, a notable drawback lies in strict requirements of the procedure, requiring continuous 3 days of stirring and a high reaction temperature of 170 °C, which resulted in only 43% and 42% yields of products **35** and **37**, respectively (Scheme 7a and 7b). Additionally, these reactions do not work without catalyst **34**. By depending on DFT calculations, part c exhibits the plausible reaction mechanism for IEDDA reaction of diazine with oxazolidine **36**.[39]



Scheme 7: Lewis acid-catalyzed IEDDA reaction of 1,2-diazines.

In last few decades, metal catalysis has gained tremendous interest due to its diversity as a mode of activation and it has been also utilized in IEDDA reactions. With the help of computational methods, plausible reaction mechanisms were proposed.[40,41] In 2012, Rawal, Kozmin and co-workers developed a strategy for IEDDA reactions of diazine derivatives in the presence of metal catalyst and they considered silver catalysts due to their pronounce affinity for alkynes.[42] In Scheme 8a, a silver-catalyzed IEDDA

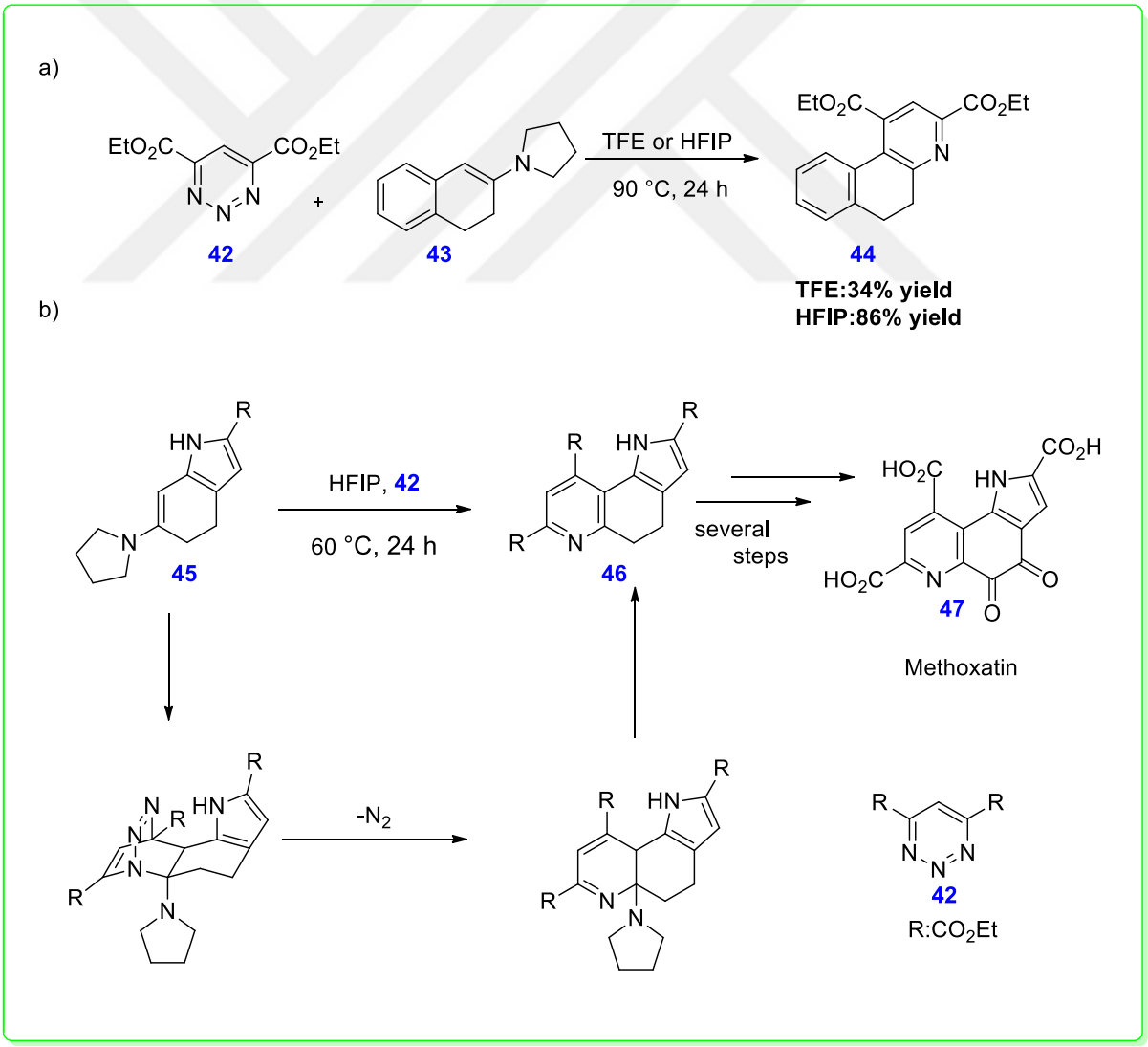
reaction of phthalazine (**32**) and siloxy alkyne **38** is shown, and plausible reaction mechanism for this reaction shown in Scheme 8c. Two years later, the Rawal group succeeded in developing a non-precious metal catalyst for the same type of IEDDA reaction shown in Scheme 8b since silver is precious and expensive material.[43]



Scheme 8: Silver-catalyzed IEDDA reactions of diazines

In spite of extensive investigation, a comprehensive method for catalyzing IEDDA reactions including heterocyclic azadienes remained absent until 2016. In this year, Boger

and co-workers constructed an excellent methodology to activate low LUMO of azadienes in IEDDA reactions.[44] Instead of employing additional catalyst, they exploited solvent itself to catalyze the reaction by using hydrogen bonding solvents such as 2,2,2-trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP). In scheme 9, part a illustrates IEDDA reaction of azadiene **42** and enamine **43**, concluded in the formation cycloaddition product **44**. Additionally, part b highlights a key step, identified as a IEDDA reaction between enamine **45** and azadiene **42** in the total synthesis of methoxatin (**47**).[44] In should be noted that 1,2-diazines were not used as dienes in this work, possibly due to their lower reactivity.

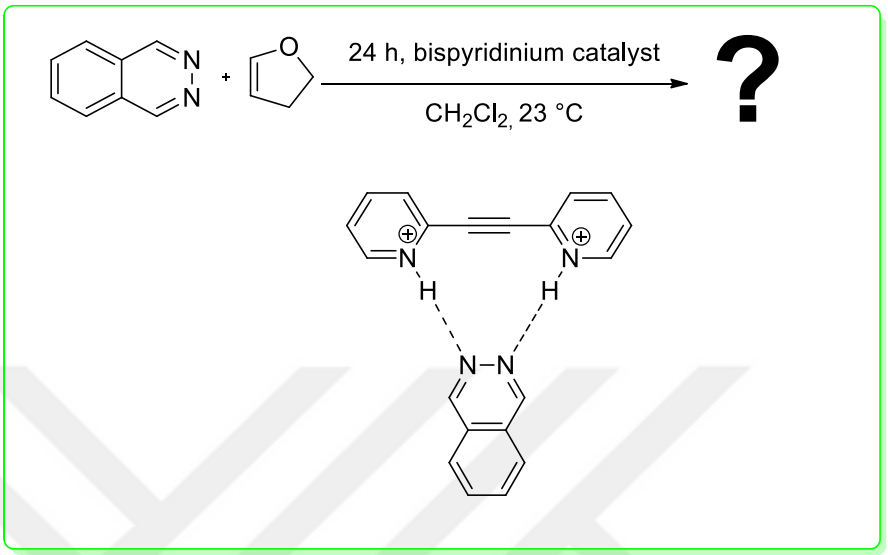


Scheme 9: IEDDA reactions of triazines in H-bonding solvent.

1.4. Aim of this Project

IEDDA reactions have become extremely important in many areas of synthetic organic chemistry, but many of the methods that have been developed to facilitate them suffer from the notable drawback of being dependent on harsh reaction conditions, such as high temperatures and extended reaction times**.** As it was previously mentioned, Wegner and Kesler developed a bidentate Lewis acid strategy to allow phthalazine to participate in an IEDDA reaction with 2,3-dihydrofuran by activating its LUMO. However, a significant drawback of their methodology is the requirement for high reaction temperatures-more specifically, 170 °C-and an extended experimentation period of three days with stirring.[39] These requirements fall under the category of being overly demanding. Afterwards, in order to facilitate the activation of phthalazine and siloxyalkyne, Rawal, Kozmin, and co-workers then introduced a novel method using a silver catalyst. This tactic made it possible to produce the corresponding IEDDA product at room temperature in good yields.[42] Drawing inspiration from their research, the objective of this project was determined. The goal of this research is to create a Brønsted acid catalyst that can successfully lower the LUMO of 1,2-diazines. This modulation is meant to make it easier for dienes to engage in subsequent IEDDA reactions with dienophiles, such as dihydrofurans, dihydropyrans, ynamides, and similar compound classes. An alkyne based bispyridinium salt was developed by Rawal and Türkmen with the purpose of activating phthalazine via two hydrogen bonds as shown in Scheme 10.[45] This strategy is based on the fact that phthalazine structure has two adjacent nitrogen atoms available to form hydrogen bonding interactions with the proposed bispyridinium catalyst. It was hypothesized that this interaction will lower the LUMO energy level of phthalazine, facilitating the desired level of reactivity in order to engage in a variety of IEDDA reactions with electron rich dienophiles. Using this strategy, only a preliminary

result was obtained by Rawal and Türkmen,[45] but a detailed study remained elusive. In this work, we opted to check the generality of this approach and test Brønsted acid catalysis for the activation of phthalazine and related 1,2-diazines in IEDDA reactions.



Scheme 10: Proposed activation of phthalazine.

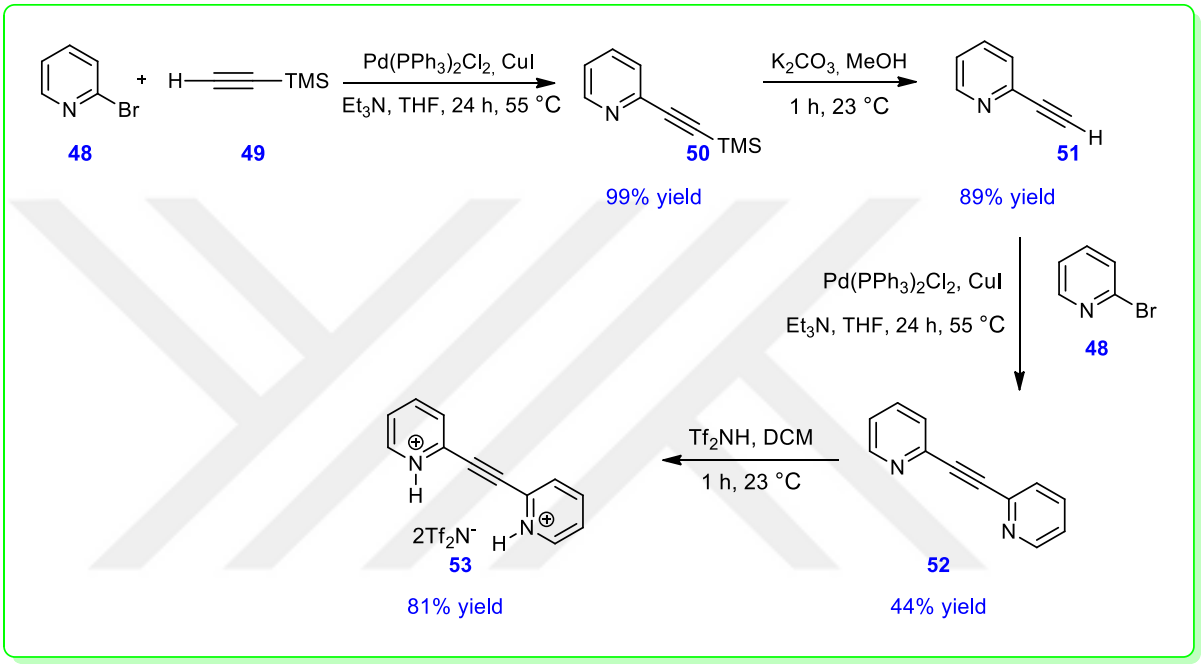
2 RESULTS & DISCUSSION

2.1.Synthesis of the Brønsted-Acid Catalyst 53

The conditions for the Inverse Electron-Demand Diels-Alder (IEDDA) reaction were cautiously optimized by screening different solvents, temperature, and Brønsted acid catalysts. The optimal conditions were settled by the determination of the isolated product yields using flash column chromatography. The optimized conditions have shown the first example of a Brønsted acid-catalyzed IEDDA reaction of 1,2-diazines. With this design, Brønsted acid catalysts were synthesized, and phthalazine (**32**) was used as a model 1,2-diazine substrate throughout the optimization.

To optimize the reaction conditions, our research was initiated with the synthesis of catalyst **53** which was reported by Rawal and Türkmen.[45] For this purpose, 2-((trimethylsilyl)ethynyl)pyridine (**50**) was synthesized first. As it is well known, Sonogashira cross coupling reactions are widely used to form carbon-carbon bond between terminal alkynes and aryl halides.[46] On this basis, the commercially available ethynyltrimethylsilane (**49**) reacts with 2-bromopyridine (**48**) to give 2-((trimethylsilyl)ethynyl)pyridine (**50**) by Sonogashira cross-coupling reaction in 99% yield and it was followed by removal of TMS group by methanolysis brought forth 2-ethynylpyridine (**51**) in 89% yield. Under similar reaction conditions, ethynylpyridine **51** reacts with 2-bromo pyridine (**48**) by a second Sonogashira coupling in order to give bispyridine derivative **52** in 44% yield. Supposably, decrease in the yield may result from electronic effect. Once and for all, bispyridinium derivative **53**, which will be tested as a Brønsted acid catalyst, was prepared by protonation of bispyridine derivative **52** (1.0 eq.) with the help of super acid namely, bistriflimide (Tf_2NH, 2.0 equiv.) in anhydrous DCM (3 mL) under nitrogen (Scheme 11). At the end of the reaction, cold DCM (waited on ice

bath) was used to wash reaction mixture and liquid part was removed by syringe. This process was implemented three times in total for purification. Then, solid part was in contact with vacuum for 2 hours gave compound **53** in 81% yield, and its characterization was done by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy.

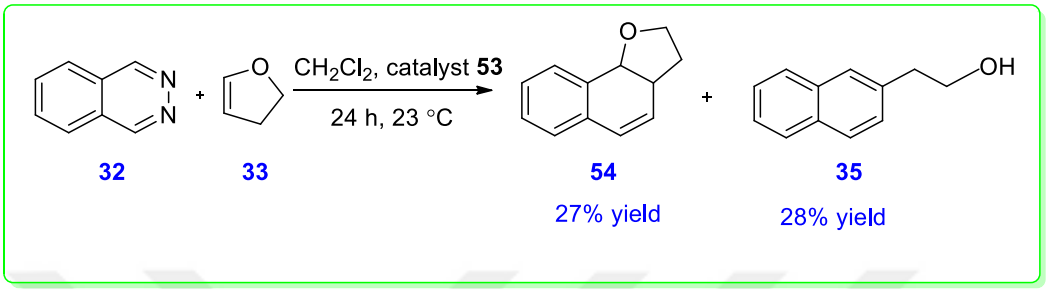


Scheme 11: Synthesis of bispyridinium derivative (catalyst) **53**.

2.2.Brønsted Acid-catalyzed IEDDA reaction of 1,2-Diazines

With the catalyst **53** in hand, viable reaction conditions were set for the IEDDA reaction of phthalazine. As it is known, interaction between LUMO of diene and HOMO of dienophile is essential in IEDDA reactions. Additionally, the best IEDDA reaction occurs between electron-poor diene and electron-rich dienophile.[47] With this objective in mind, phthalazine is an excellent choice as a diene because it holds two vicinal nitrogen on the naphthalene ring and it is electron deficient heterocycle, which makes hydrogen

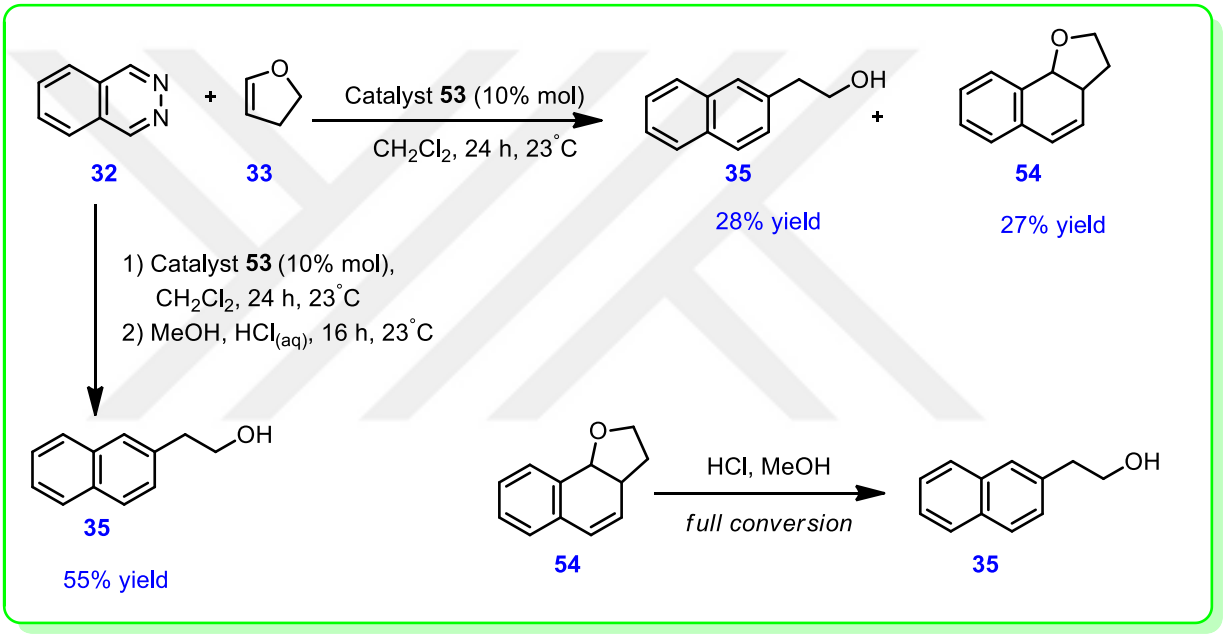
bonding with catalyst **53**. By the aid of hydrogen bonding, LUMO of diene is low enough to interact HOMO of electron rich dienophile such as 2,3-dihydrofuran (**33**) in order to give [4+2] cycloaddition product under mild conditions (Scheme 12).



Scheme 12: IEDDA reaction of phthalazine with 2,3-dihydrofuran

Compound **32** (1.0 equiv.), dihydrofuran **33** (2.0 equiv.) and catalyst **53** (0.1 equiv.) were stirred for 24 h at room temperature by using DCM as a solvent. After work-up procedure and flash silica column chromatography, two products were identified and isolated in similar yields as it is shown in Scheme 12. At the end of the reaction, naphthalene-2-ethanol (**35**) was desired product while the other product **54** is a structural isomer of naphthalene-2-ethanol. Our aim was to obtain single product over other possibilities since this is mostly desired to control selectivity and reactivity in organic synthesis.[48] Supportively, acid treatment was considered to open up the five membered ring on the product **54** since our main product **35** was not acid-sensitive. Then, phthalazine and 2,3-dihydrofuran were reacted with the help of catalyst **53**. At the end of 24 h, solvent was evaporated and work-up procedure was implemented. Without a further purification, the resulting reaction mixture was directly treated with HCl in methanol and stirred for 16 h at room temperature, which culminated in full conversion into compound **35**. Additionally, as a control experiment, isolated compound **54** was undergone acid

treatment by 16 h stirring at room temperature concluded in full conversion into 2-napthalene ethanol (**35**). Conclusively, it is deduced that one-pot IEDDA reaction of phthalazine (**32**) with 2,3-dihydrofuran (**33**) resulted in main product **35** in 55% yield if acid treatment is implemented as a second step. Finally, the first example of a Brønsted acid-catalyzed IEDDA reaction of 1,2-diazines was accomplished as a single product (Scheme 13).

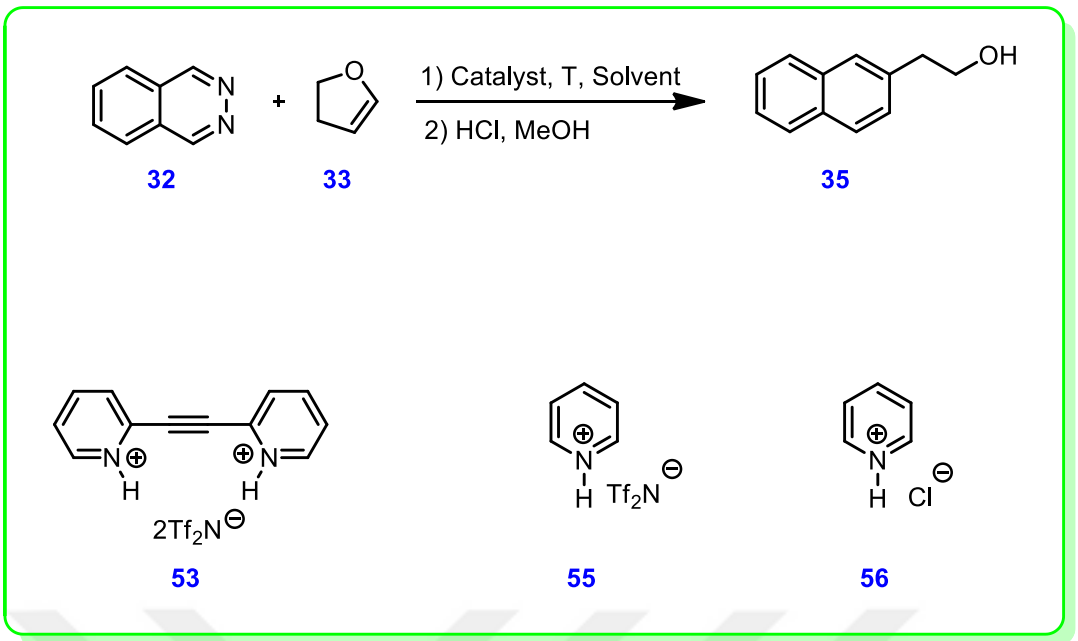


Scheme 13: IEDDA reaction of 1,2 diazines with acid treatment by using catalyst **53**

2.3. Optimization Studies of the IEDDA Reaction

After this achievement, the stage was set for optimization studies such as screening of different solvents and temperature, and designing new catalysts. Initially, our work switched to solvent effect and four different solvents were used for the reaction shown in Table 1 under completely the same conditions at 23 °C by using catalyst **53** (Scheme 14). After flash column chromatography on silica, isolated product yields were comparable as it

can be seen in Table 1. When utilizing catalyst **53** among the solvents acetonitrile, tetrahydrofuran, dichloroethane and dichloromethane (DCM), DCM exhibited the most favorable outcome with a %55 yield (Table1, entry 1-4). Also, we used super acid namely, bistriflimide to catalyze IEDDA reaction, which resulted in 35% yield (Table 1, entry 5). Then, we designed three different Brønsted acid catalysts by considering hydrogen bonding ability of molecule with nitrogen atoms present on the phthalazine (Scheme 14). Additionally, counterion effect is seen in catalyst **56** and **55** by observing the increase in the yield from %55 to %71 (Table 1, entry 6-7). Upon initial assessment of the three catalysts, catalyst **53** was considered as the primary contender. Remarkably, however, catalyst **55** brought forth the highest yield as 71% at 23 °C (Table 1, entries 1,6 and 7). Subsequently, catalyst **55** and DCM were selected as the best catalyst and solvent. With catalyst **55** in hand, reaction temperature was increased with respect to boiling point limitation. To exemplify, solvents 2-Me-THF, DCE, toluene, and trifluorotoluene ($PhCF_3$) were used to see IEDDA reaction at higher temperature. 2-Me-THF is excellent choice instead of using THF since it is environmentally friendly, more stable and having higher boiling point. Also, trifluorotoluene and toluene are similar in structure. The presence of $-CH_3$ group in toluene and the $-CF_3$ group in trifluorotoluene indeed leads to differing electron donating and electron withdrawing effect, which have significant impact on polarity and thus on reactivity. However, none of the solvents provide a superior result compared to that in DCM (Table 1, entries 8-14). Finally, as a control experiment, initial four different solvents were tried for catalyst **55** to compare results with catalyst **53** smoothly (Table1, entries 15-18).



Scheme 14: Three different Brønsted acid-catalysts tested in the IEDDA reaction.

Table 1: Optimization studies with screening catalyst, solvent and temperature.

Entry	Catalyst (mol%)	T (°C)	Solvent	Yield (%)
1	**53** (5)	23	DCM	55
2	**53** (5)	23	CH_3CN	45
3	**53** (5)	23	THF	32
4	**53** (5)	23	DCE	54
5	Tf_2NH (10)	23	DCM	35
6	**55** (10)	23	DCM	71*
7	**56** (10)	23	DCM	56
8	**55** (10)	55	2-Me-THF	52
9	**55** (10)	55	DCE	57
10	**55** (10)	55	$PhCF_3$	52
11	**55** (10)	55	toluene	66
12	**55** (10)	75	DCE	43
13	**55** (10)	35	DCM	71
14	**55** (10)	75	Me-THF	49
15	**55** (10)	23	CH_3CN	55
16	**55** (10)	23	THF	45
17	**55** (10)	23	toluene	32
18	**55** (10)	23	DCE	58

* This reaction was repeated four times. For isolated yields, mean value was calculated as a 70.275 and standard deviation (S.D) was calculated as a 1.517.

For the last step of optimization studies, amount of catalyst **55** was decreased by half and doubled to see the effect of catalyst loading (Table 2). There was no notable change in isolated product yields. Additionally, main reaction was carried out in large scale to see efficiency of the reaction and we obtained %58 yield. As a consequence, 10 mol% was selected as the best catalyst loading.

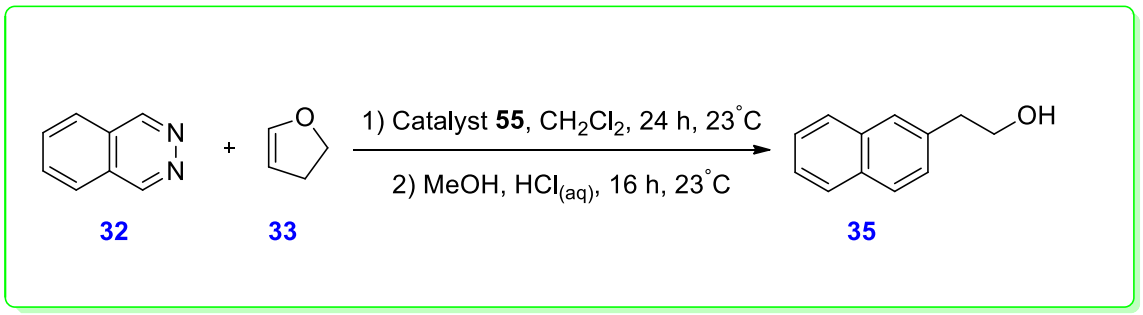
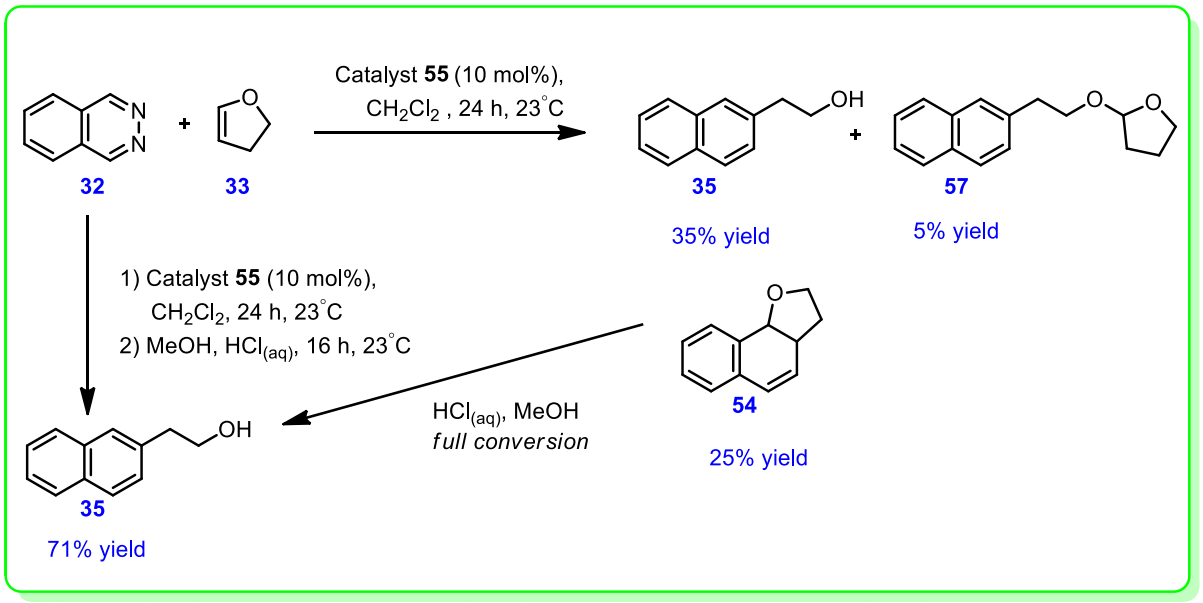


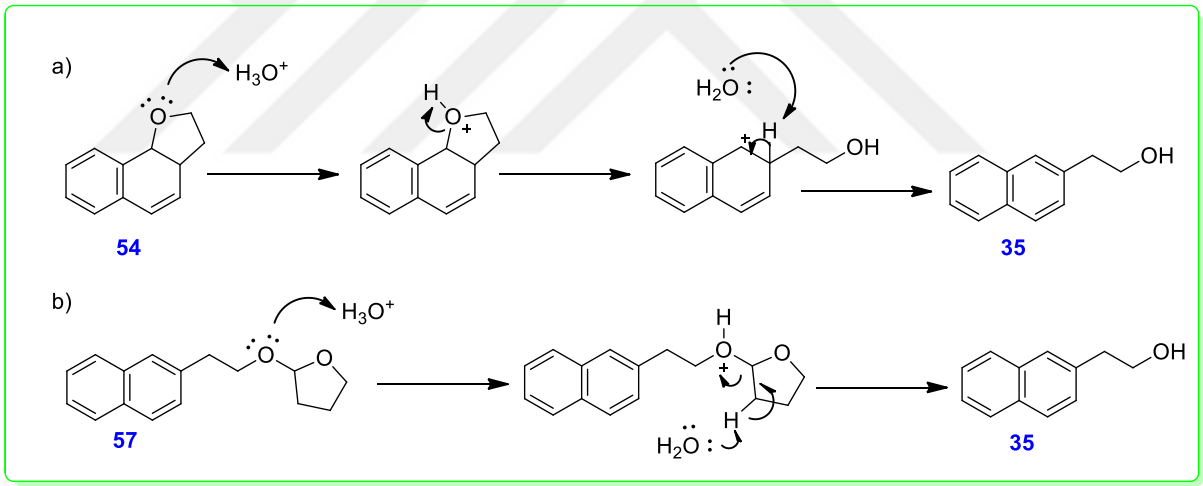
Table 2: Investigation of the effect of catalyst loading.

Entry	Catalyst 55 loading	Amount of Phthalazine	Yield %
1	(5 mol%)	0.38 mmol	68
2	(20 mol%)	0.38 mmol	67
3	(20 mol%)	1 mmol	58

As it is discussed earlier, obtaining a single product has a great importance in organic chemistry reactions. When we use catalyst **55** in IEDDA reaction of phthalazine and 2,3-dihydrofuran, compound **35** was obtained as a single product with 71% yield after acidic work-up (Table 1, entry 6). Subsequently, our focus shifted towards exploring possible products without implementing acidic work-up. Then, three cycloaddition products were observed and isolated in the absence of acidic work-up (Scheme 15). At the first glance, all the products seem that they are related to the main product **35** in structure as it is discussed earlier. To illustrate how three products converted into a single product, we proposed a reaction mechanism to show conversion of products **54** and **57** into compound **35** (Scheme 16).



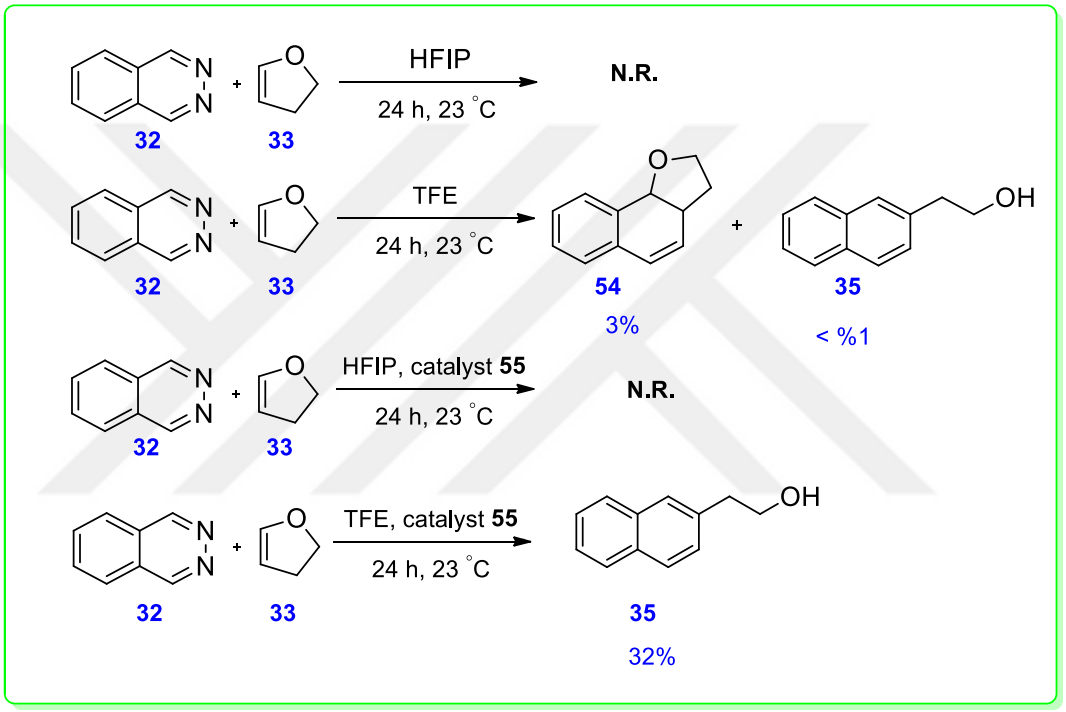
Scheme 15: IEDDA reaction of phthalazine (**32**) with dienophile **33** catalyzed by **55**.



Scheme 16: Proposed reaction mechanism after acidic-work up.

In 2016, Boger and co-workers have demonstrated an innovative strategy aimed at lowering LUMO of azadienes in IEDDA reaction. Instead of introducing additional catalyst, they have used solvent itself to catalyze the reaction by using hydrogen bonding solvent such as 2,2,2-trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP).[44]

Drawing inspiration from this logic, HFIP and TFE were tested in order to see H-bonding effect in our main reaction. Without catalyst **55**, there was no conversion to corresponding IEDDA product for HFIP and conversion was very low for TFE. With catalyst **55** (10% mol), situation was same for HFIP. However, it was increased to 31% yield for TFE (Scheme 17).

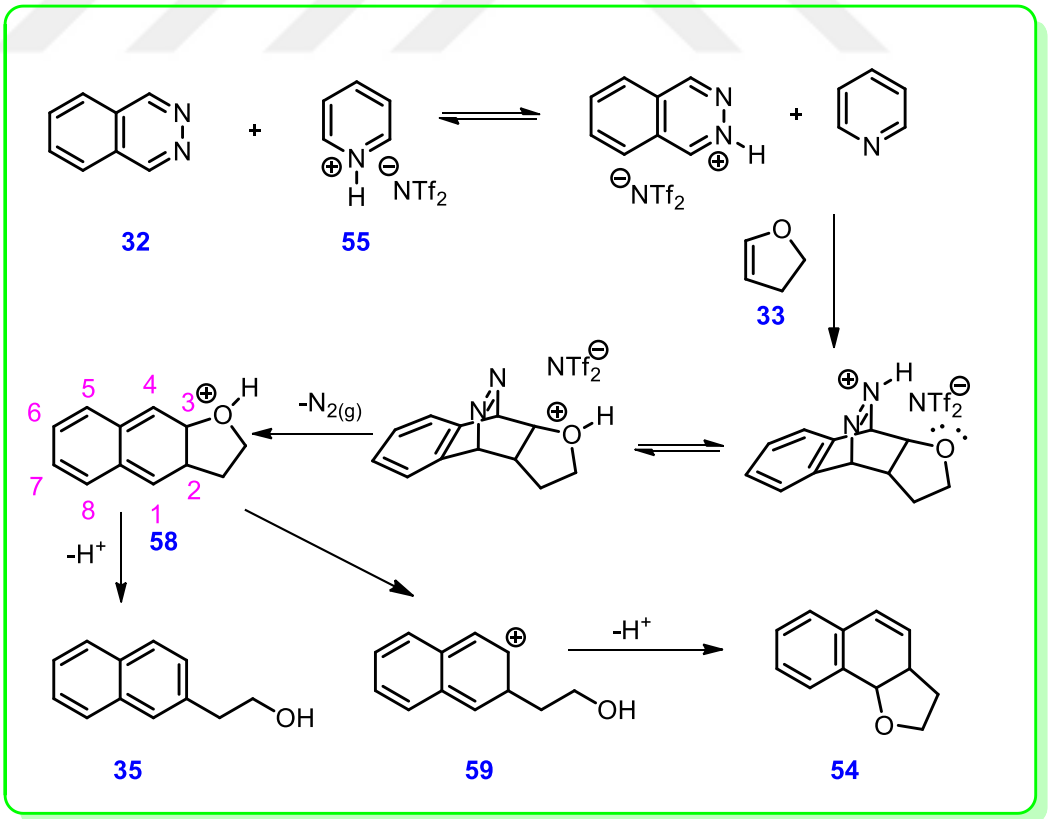


Scheme 17: IEDDA reaction between **32** and **33** in TFE and HFIP.

2.4. Proposed Reaction Mechanism

After an extensive investigation of solvent systems, mechanism of the main reaction has become a question mark. We proposed the most probable reaction mechanism shown below in Scheme 18. More clearly, phthalazine (**32**) can be protonated by catalyst **55**, and compound **33** (dienophile) approaches to the protonated-phthalazine (diene),

which culminated in [4+2] cycloaddition. Then, intramolecular proton transfer followed by nitrogen extrusion would result in intermediate **58**. At this moment, there are two possibilities. For the first one, five membered ring may directly open up and any water molecule picks up hydrogen from third carbon position in the way molecule gains aromaticity, which will result in compound **35**. For the other possibility, five membered ring may open up and first carbon position having carbocation is the most probable resonance contributors. The rationale behind this is resonance contributors of intermediate **59**. If all possible resonance contributors are considered, it would be easily seen that carbocation on the first position gives the most stable resonance contributor thanks to gaining aromaticity. Hence, reaction prefers this resonance structure and oxygen easily attacks carbocation on the first position, which will result in compound **54** (Scheme 18).



Scheme 18: Plausible reaction mechanism of IEDDA reaction.

2.5. Substrate Scope

The next focus was the substrate scope and 3, 4-dihyropyran (**60**) was selected as a corresponding dienophile. To see the effect of the ring strain, compound **60** is a favourable example since five membered ring has a higher ring strain with respect to six membered ring especially with the sp^2 carbons on the ring.[49] Additionally, there is only one -CH_2 difference between **33** and **60**. The results were supportive because isolated yields were considerably low with respect to main reaction using five membered ring namely, 2,3-dihydrofuran (**33**). In fact, there was no conversion to corresponding IEDDA product at room temperature. In consideration of the boiling point limitation related to DCM, we focused on other solvents namely, DCE, toluene, and acetonitrile in order to see corresponding IEDDA product in higher temperatures. The temperature was raised to 75-100 °C. Remarkably, resulting [4+2] cycloaddition product **61**, representative of the IEDDA reaction being studied, manifested its highest yield within the medium of toluene at 100 °C (Table 3, entry 2-5).

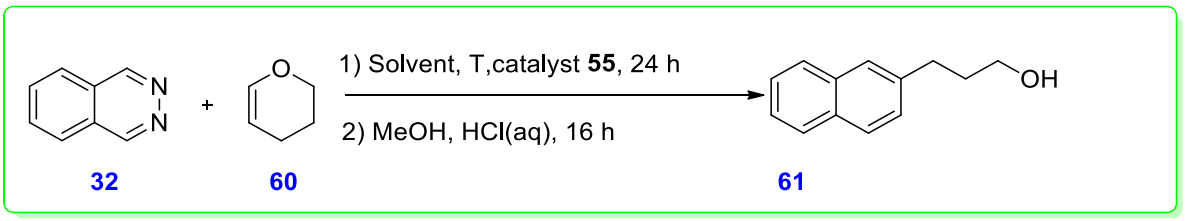
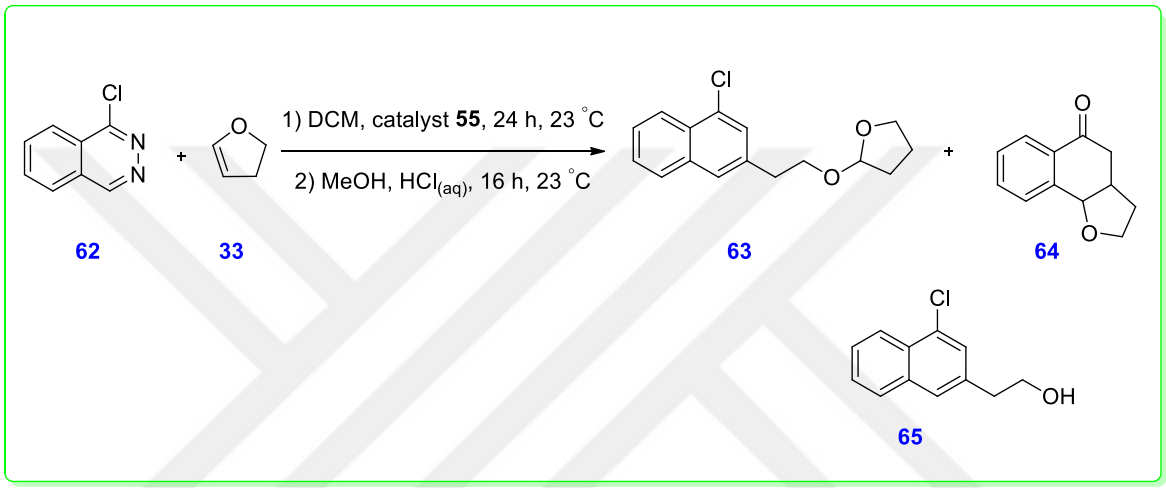


Table 3: IEDDA reaction of phthalazine (**32**) with 2,3-dihyropyran (**60**)

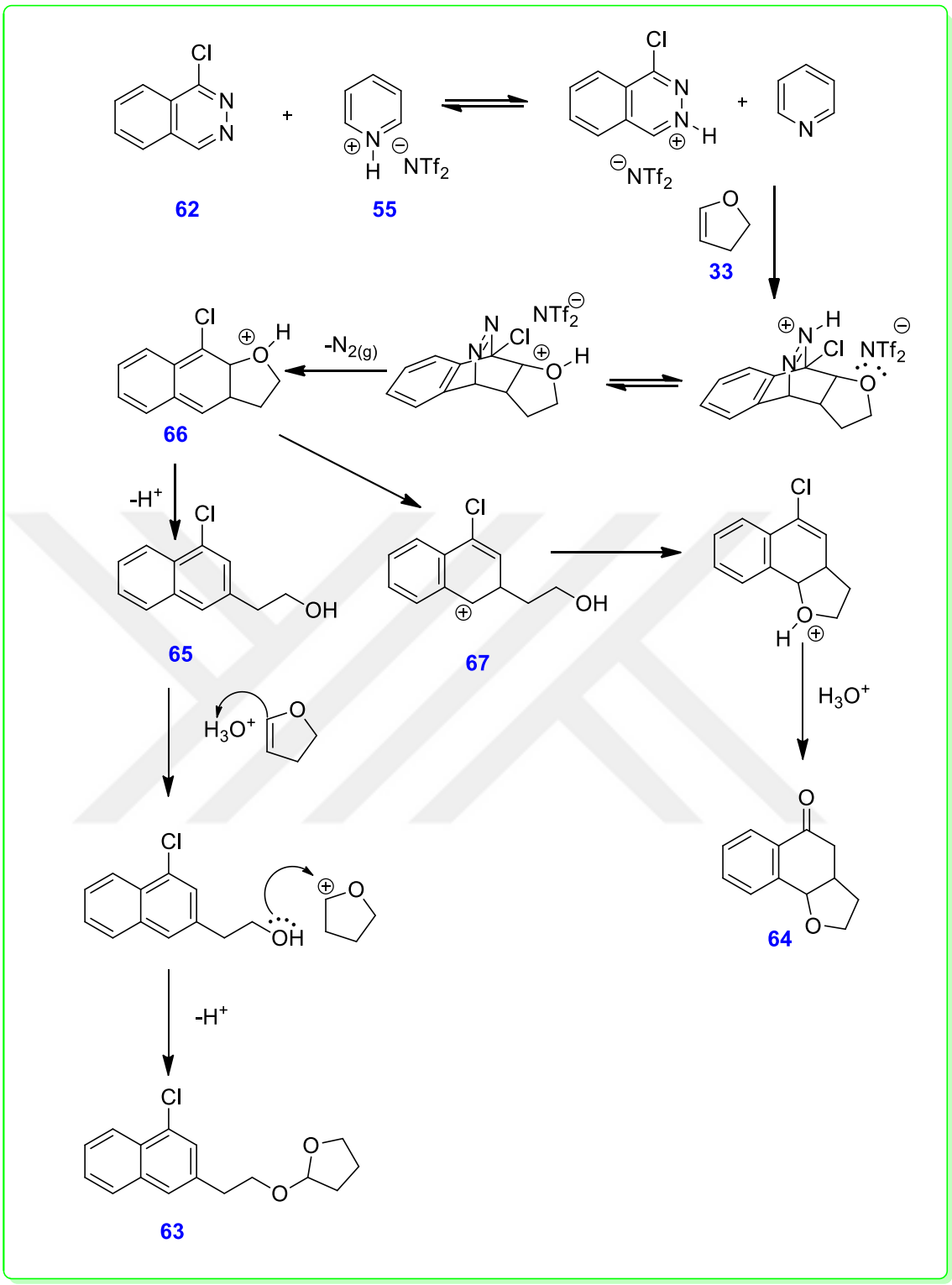
Entry	T (°C)	Solvent	Yield %
1	75	DCE	18
2	77	CH_3CN	13
3	77	toluene	20
4	100	toluene	27
5	23	DCM	N.R.

The next substrate was selected as 1-chlorophthalazine (**62**) since it is more electron deficient than phthalazine. Unlike expectations, this reaction resulted in very less [4+2] cycloaddition products and overall yield was <2%. After flash silica column chromatography, only compound **65** was fully characterized while structures of other two compounds were tentatively assigned depending on ^{1}H-NMR spectroscopy since they could not be obtained in pure form (Scheme 19). We proposed the most probable mechanistic studies for these three products, which is very similar with IEDDA reaction of phthalazine and 2,3-dihydrofuran. Protonation of 1-chlorophthalazine followed cycloaddition and nitrogen extrusion resulted in intermediate **66**. There are two possible pathways. Firstly, as previously discussed, the intermediate **66** has a strong tendency to undergo ring opening, resulting in the formation of compound **67** which is most probable resonance contributor. After this, oxygen may attack carbocation shown in compound **67** and it may result in compound **64** in acidic medium. Secondly, five membered ring on

intermediate **66** may directly open up and any water molecule picks up hydrogen from second carbon position in the way molecule gains aromaticity, which resulted in compound **65**. Finally, 2,3-dihydrofuran is electron rich alkene and it was added into medium as a two equivalence. Hence, protonation of compound **33** creates positive charge on second carbon position of furan. Then, oxygen in 1-chlorophthalazine may attack to the carbocation, generating compound **63** (Scheme 20).

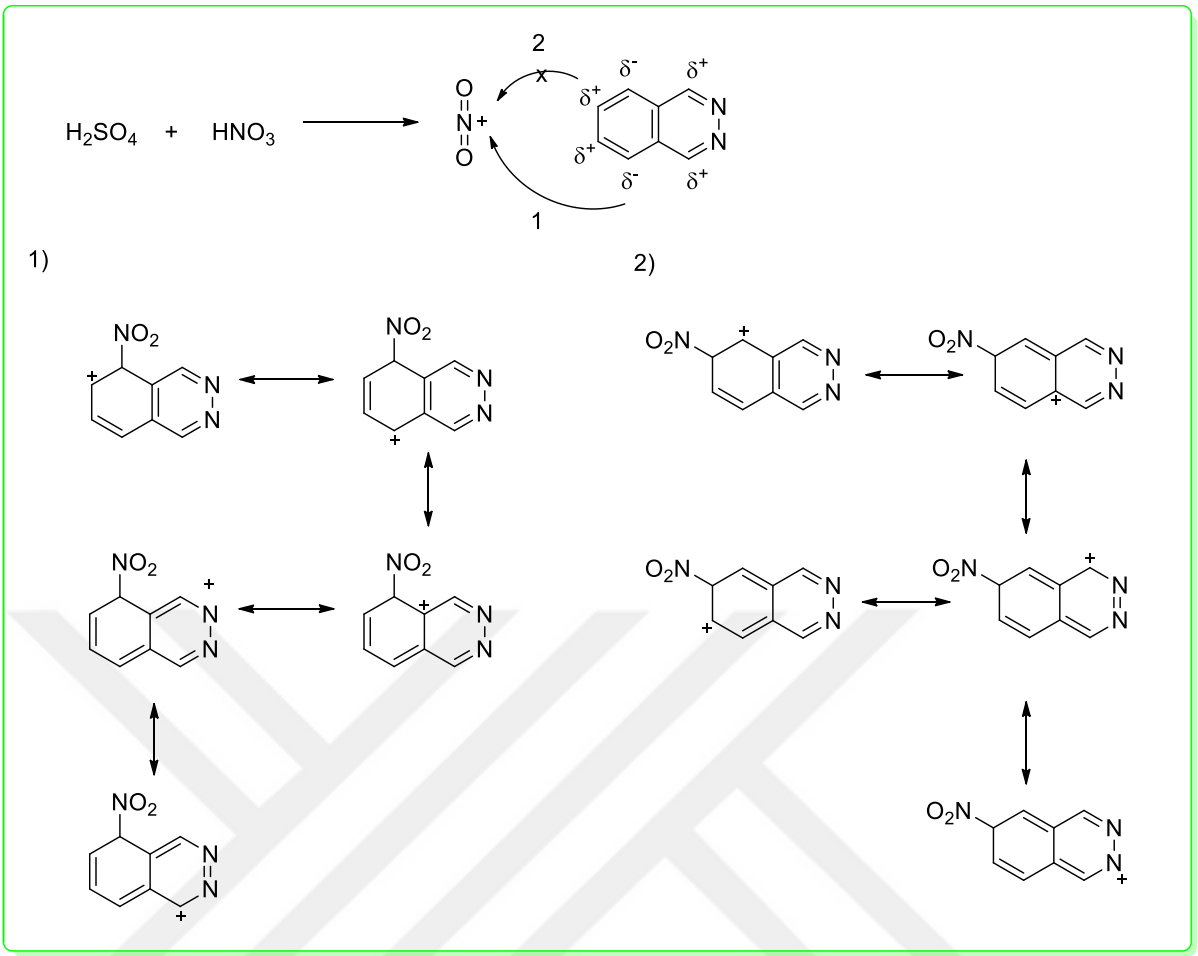


Scheme 19: IEDDA reaction of 1-chlorophthalazine (**62**) with 2,3-dihydrofuran (**33**).



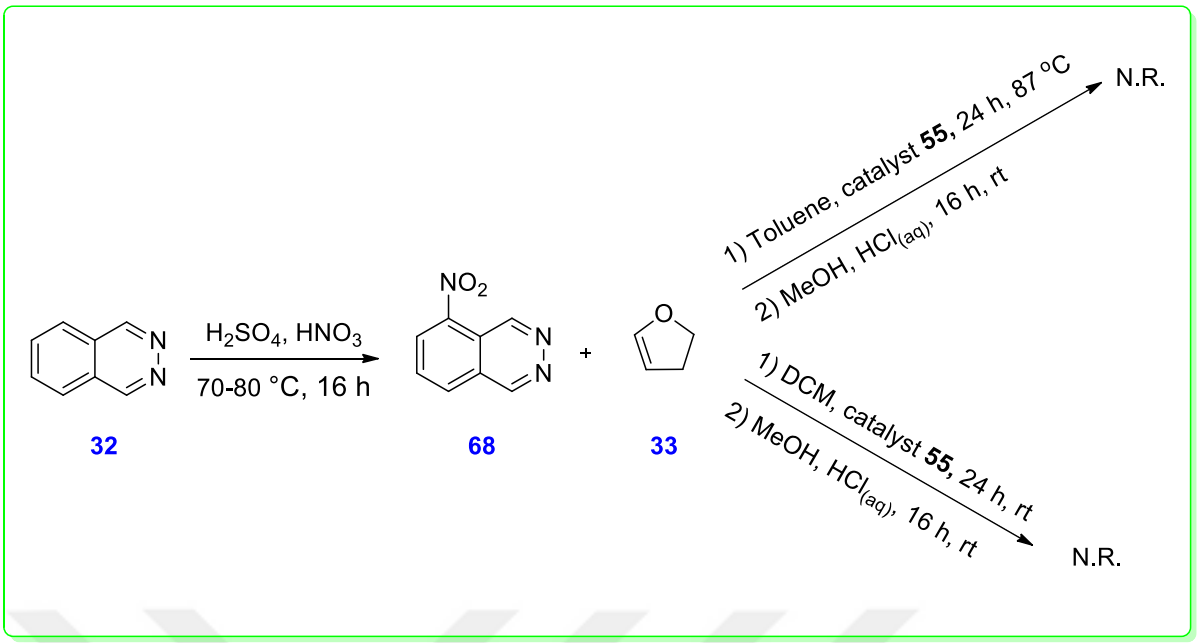
Scheme 20: Plausible reaction mechanism of IEDDA reaction of **62**.

5-nitrophthalazine (**68**) is another electron deficient phthalazine derivative. For the preparation of this compound, the first step was the nitration of phthalazine. Nitric acid is first protonated by sulfuric acid, which produces nitronium ion upon dehydration. Then, nitronium ion was easily accessible for electrophilic aromatic substitution (EAS) since it is known reaction from the literature.[50] Due to the electronegative nature of nitrogen, nitro group does not attach to the adjacent carbon to the nitrogen so nitro group would make a bond with second carbon position or third one. There are two possible paths for EAS. For the first way, there are five resonance contributors and two of them include an aromatic ring. For the second way, there are again five resonance contributors. However, one of them only contains an aromatic ring. Evidently, first path was the most favourable one and 5-nitrophthalazine (**68**) was obtained as a single product (Scheme 21).



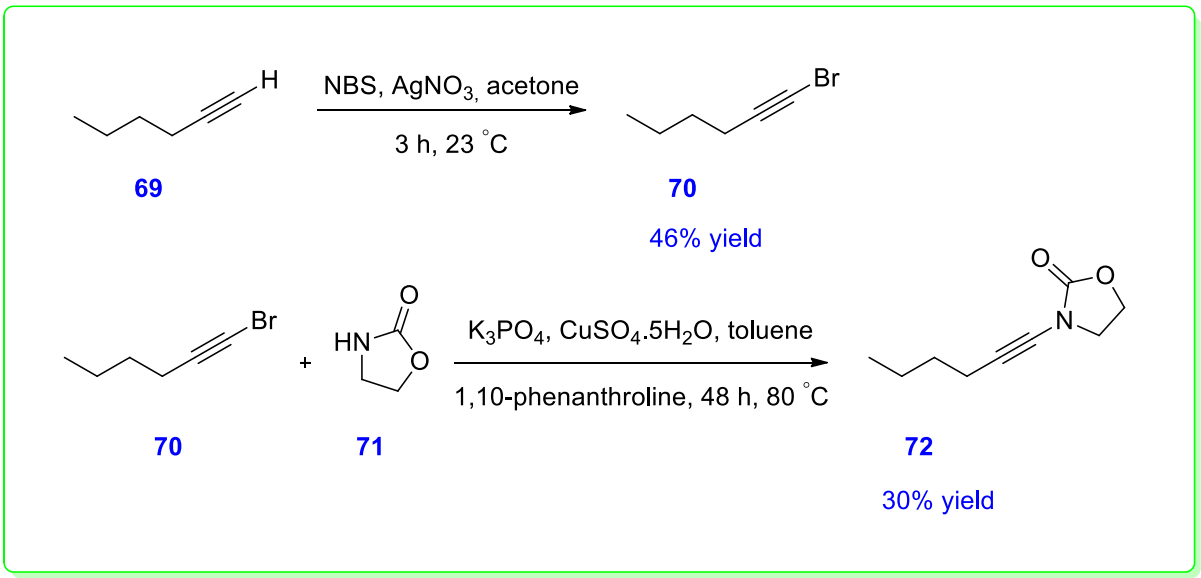
Scheme 21: Regioselectivity of the nitration of phthalazine.

With 5-nitrophthalazine (**68**) in hand, 2,3-dihyrofuran (**33**) was tried for IEDDA reaction in order to get corresponding product in high yield. Unexpectedly, compound **68** did not give any conversion to desired product at room temperature and high temperature as well (Scheme 22). The reason for this observed lack of reactivity might be the lower basicity of **68** due to the presence of the -NO_2 group. In order to react as a diene, **68** needs to get protonated, but because of its lower basicity, pyridinium of catalyst **55** may not be acidic enough to protonate **68**.



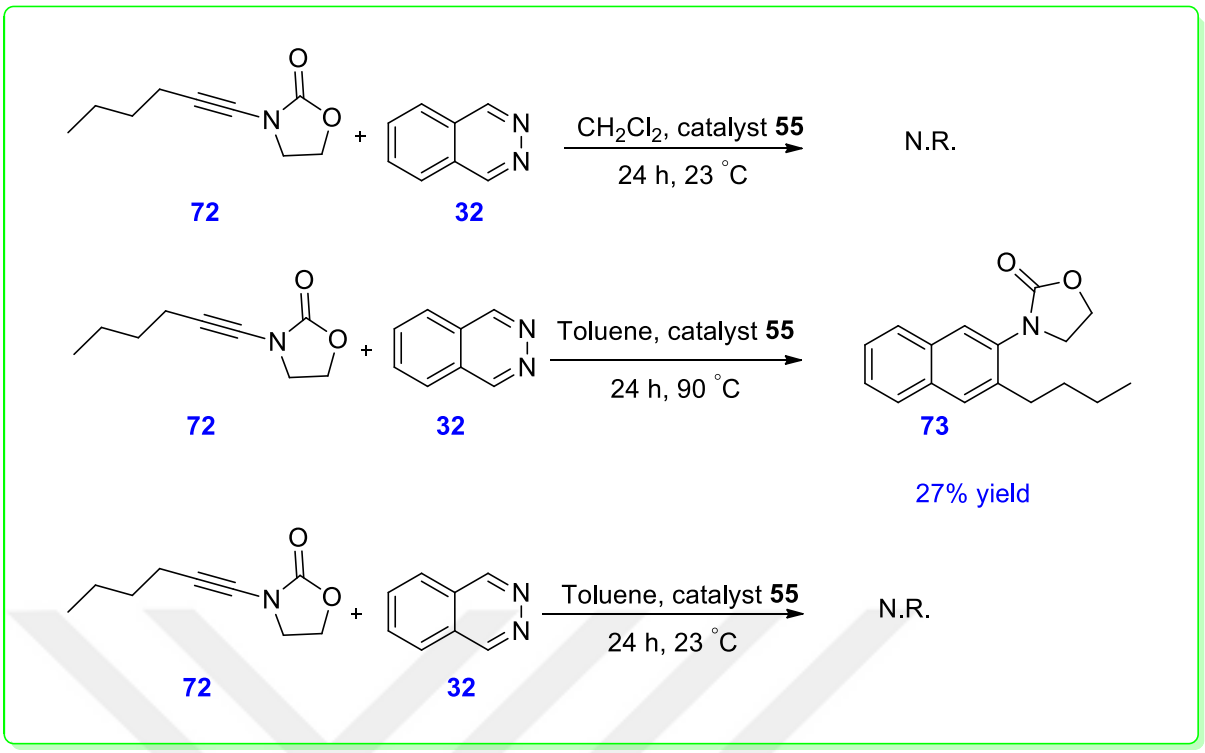
Scheme 22: IEDDA reaction of 5-nitrophthalazine (**68**) with 2,3-dihydrofuran (**33**).

Ynamide derivative **72** is an electron rich dienophile for the main IEDDA reaction. Hence, 1-hexyne (**69**) is a good starting point to synthesize compound **72**. Halogenation of compound **69** followed by copper sulfate-pentahydrate-1,10-phenanthroline-catalyzed amidation of 1-bromo-1-hexyne (**70**) culminated in compound **72** in 30% yield (Scheme 23).



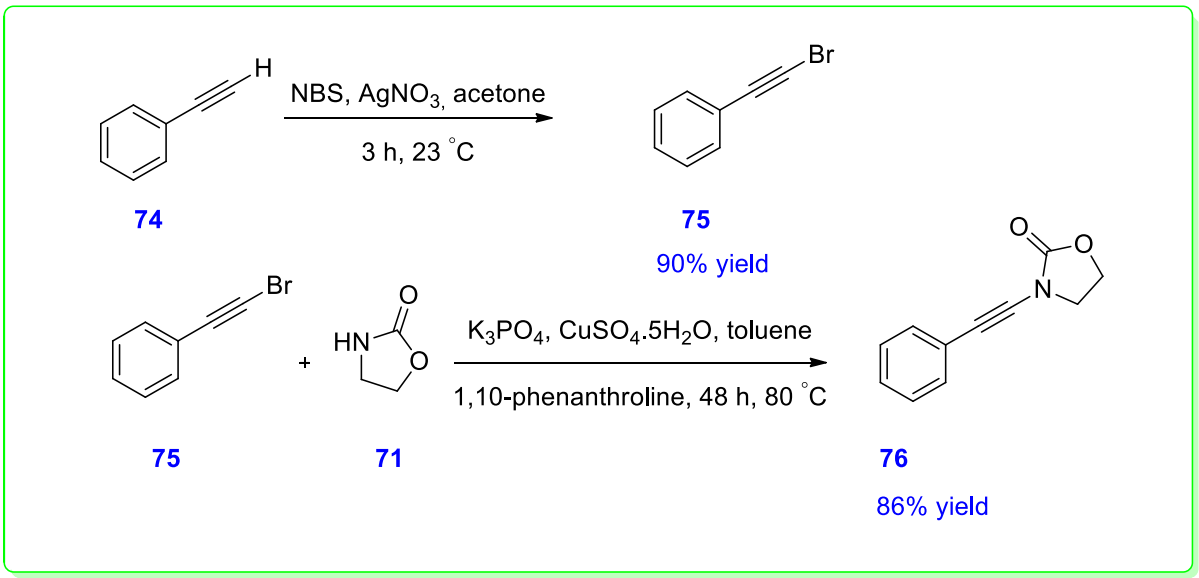
Scheme 23: Synthesis of ynamide **72**.

Compound **72** did not undergo expected IEDDA reaction at room temperature. However, when we heated the reaction to 90 °C, compound **73** was obtained in 27% yield. Even though we replaced DCM with toluene, desired product was not observed at room temperature (Scheme 24).



Scheme 24: IEDDA reaction of phthalazine with compound **72**.

Another ynamide derivative (compound **76**) was considered for IEDDA reaction as an electron rich dienophile. The synthesis of compound **76** is the same as that of compound **72** as it is described above. Bromination of ethynylbenzene (**74**) followed by copper sulfate-pentahdrate-1,10-phenanthroline-catalyzed amidation of (bromoethynyl)benzene (**75**) produced ynamide **76** in 86% yield (Scheme 25).



Scheme 25: Synthesis of ynamide **76**.

Compound **76** is more electron rich than compound **72** as a dienophile since phenyl group has more electron density than butyl group. Hence, it could undergo IEDDA reaction with phthalazine at first glance. However, results had a reverse situation. Unexpectedly, compound **76** did not show any conversion in IEDDA reaction with phthalazine at room temperature and we did a small screening with different solvents at high temperature. Interestingly, it did not give any conversion at high temperature such as 150 °C (Table 4). The plausible explanation behind these results would be steric effect. Due to sterically more crowded nature of the phenyl group compared to butyl group, diene **32** may not be in proper orientation to give corresponding cycloaddition product as it can be seen from the results below.

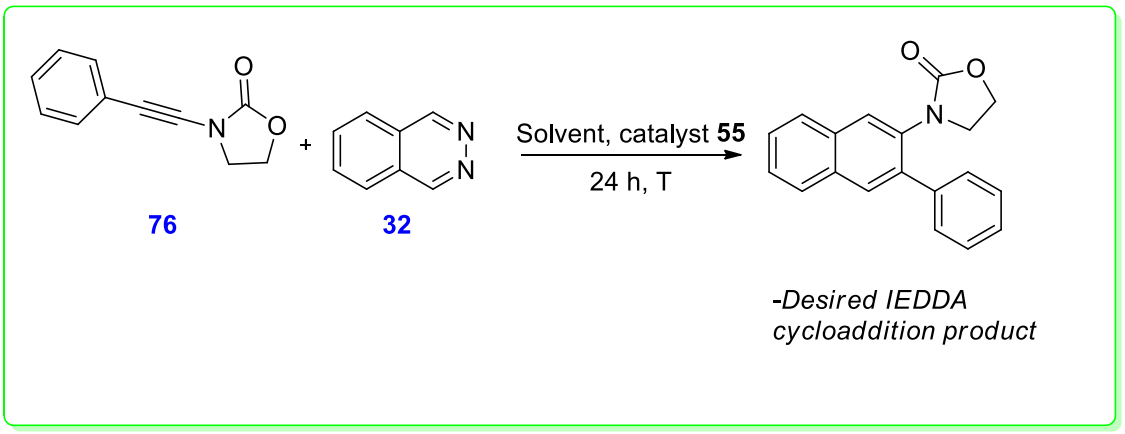
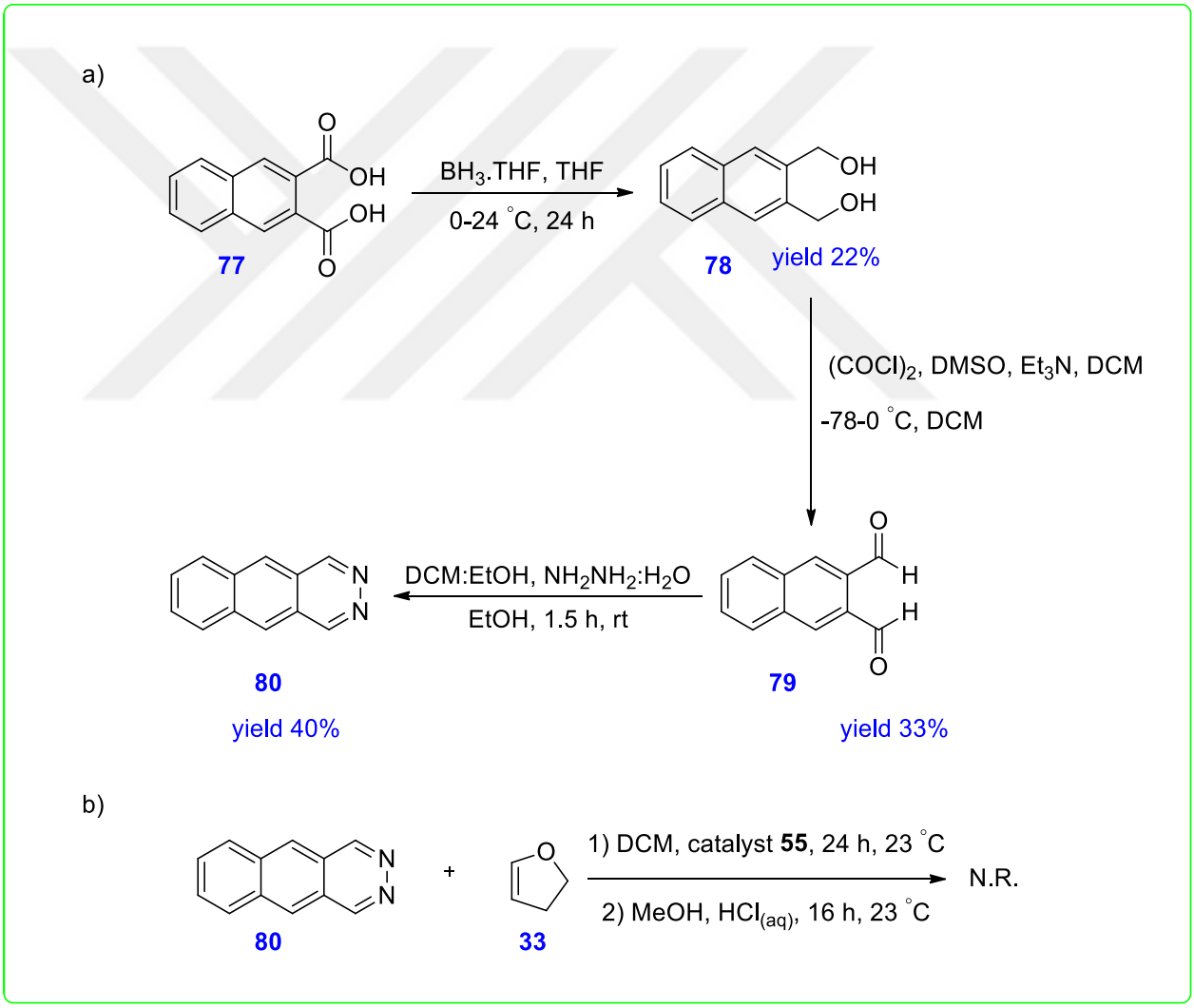


Table 4: IEDDA reaction of phthalazine with compound **76** at high temperature

Entry	T (°C)	Solvent	Yield %
1	23	DCM	N.R.
2	23	mesitylene	N.R.
3	90	toluene	N.R.
4	90	mesitylene	N.R.
5	150	mesitylene	N.R.

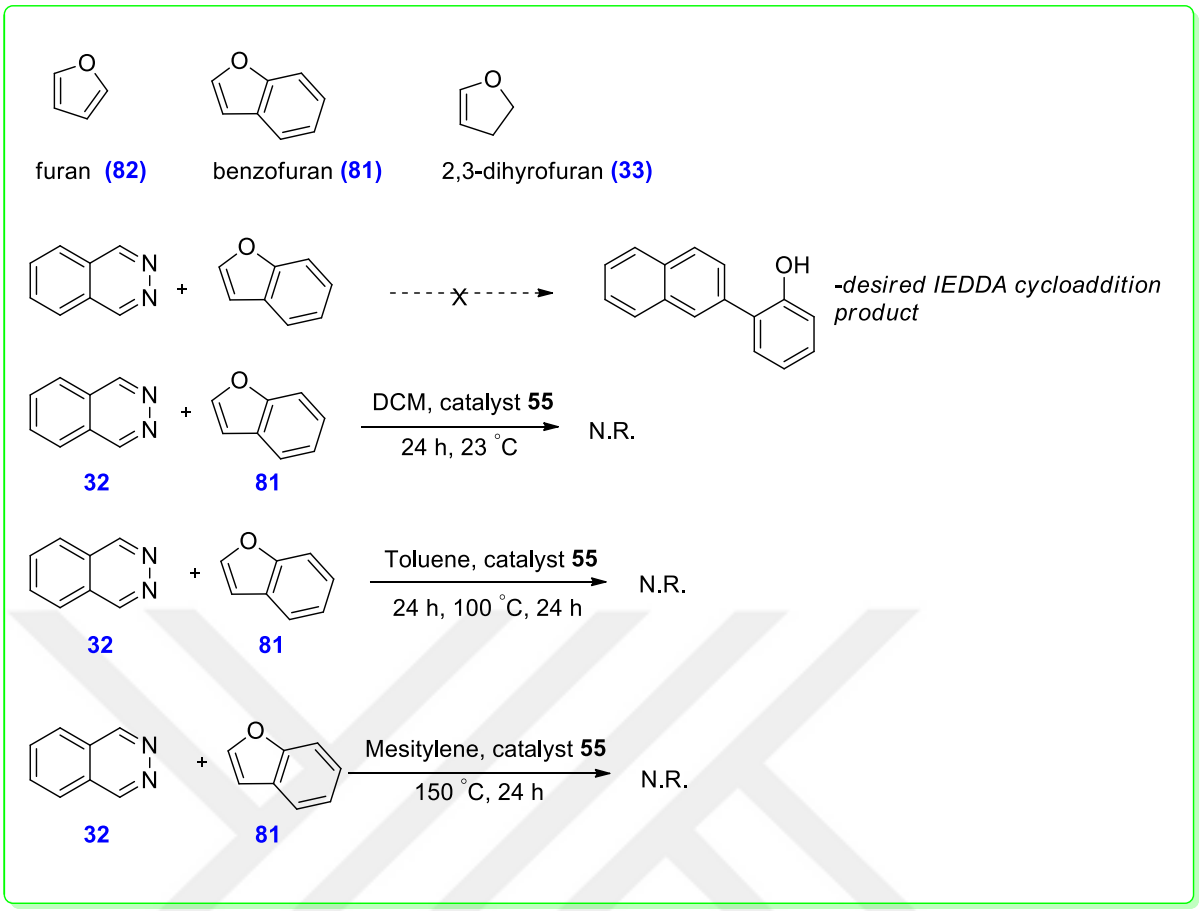
After investigation of dienophile in substrate scope, our focus transitioned toward exploration of phthalazine derivatives namely, benzo[g]phthalazine (**80**). This interest was motivated by similarity in the potential structural and functional attributes exhibited by phthalazine. Compound (**80**), a particular derivative of interest, demonstrates the incorporation of benzene molecule fused to the phthalazine ring system. For the synthesis of compound **80**, the synthetic sequence reported by Rawal, Kozmin and co-workers was followed.[42] This sequence starts with reduction of napthalane-2,3-dicarboxylate (**77**) to naphthalene-2,3-dilyldimethanol (**78**) in 22% yield followed by its oxidation to 2,3-napthalenedialdehyde (**79**), resulted in 33% yield. The following transformation of

compound **79** to **80** was accomplished via treatment with hydrazine. After purification process, isolated yield was 40% yield (Scheme 26a). Unfortunately, the desired cycloaddition product was not observed by IEDDA reaction of 2,3-dihyrofuran with benzo[g]phthalazine (Scheme 26b). This result is puzzling and requires further investigation since diazine **80** is expected to be a competent diene for this targeted transformation.



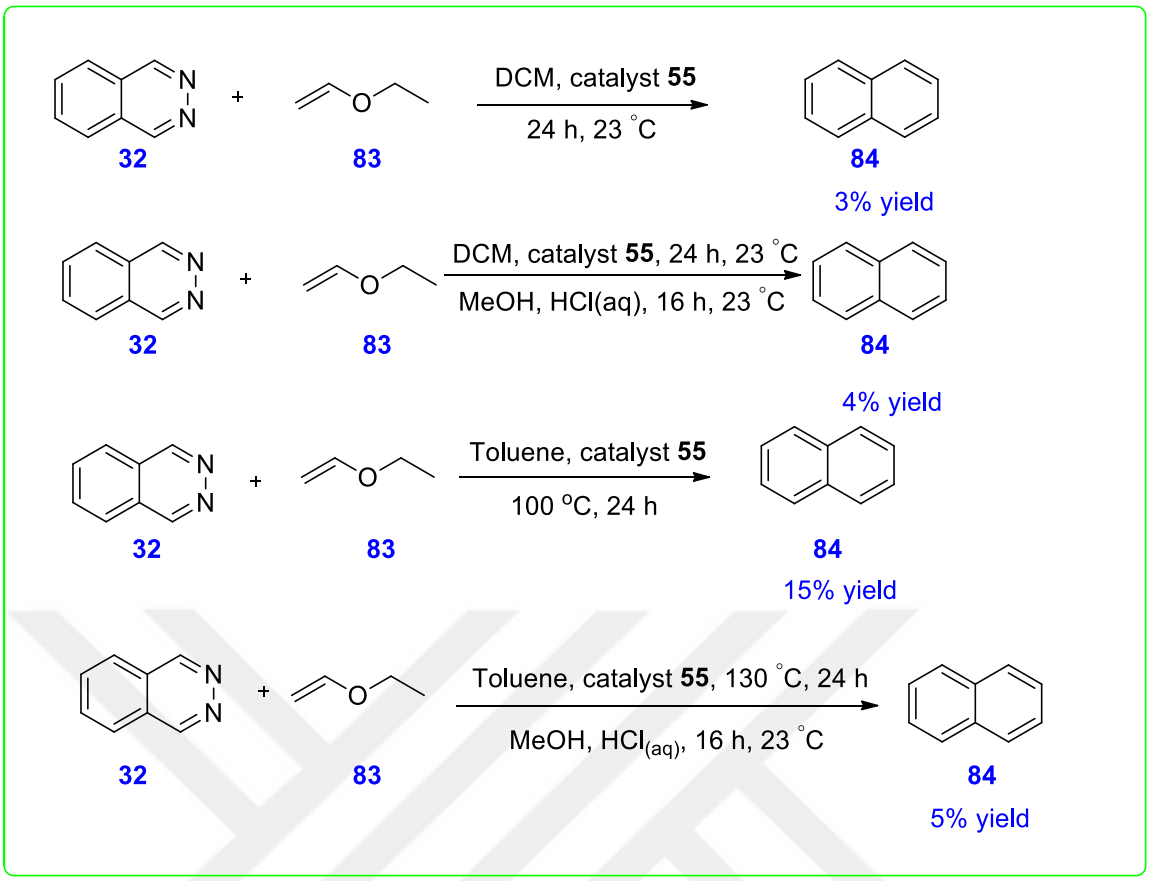
Scheme 26: Synthesis of diazine **80**.

The next substrate was selected as benzofuran (**81**). It would be considerable dienophile due to its moderate reactivity. More clearly, reactivity of benzofuran (**81**) should be between furan (**82**) and 2,3-dihydrofuran (**33**). Furan (**82**) is an aromatic five membered ring and aromaticity of the molecule should be broken to undergo any reaction, which is strongly disfavoured. Compound **33** is non-aromatic five membered ring and it gives IEDDA reaction in 71% yield at room temperature. Benzofuran (**81**) is an aromatic compound consisted of fused benzene and furan rings. Supposably, even if it undergoes IEDDA reaction with phthalazine, benzene ring in furan (**82**) should stay as an aromatic ring at the end of the reaction. Hence, reactivity of benzofuran should be moderate in the way it would give IEDDA reaction. On the contrary, it did not give any desired product at even high temperatures (Scheme 27).



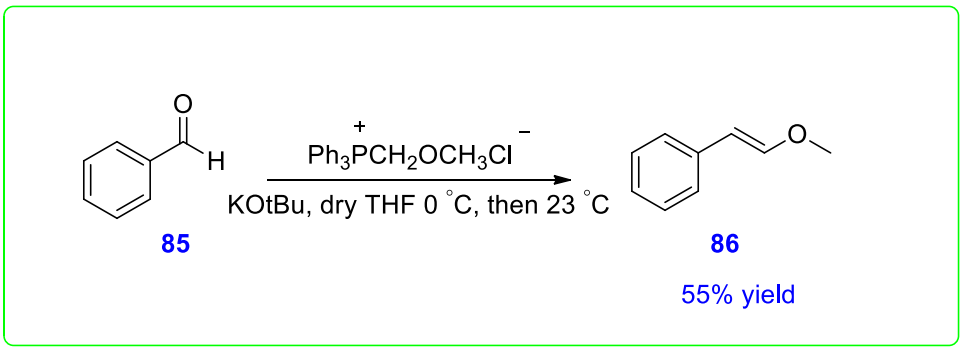
Scheme 27: IEDDA reaction of phthalazine with compound **81**.

After dealing with benzofuran, enol ethers come to the forefront for the substrate scope. Due to lone pairs on oxygen in enol ethers, alkene becomes electron rich in the way IEDDA reaction of phthalazine with ethoxyethene (**83**) would be more probable. At this point, internal standard 1,3,5-trimethoxybenzene was used to predict the yield in the IEDDA reaction of phthalazine (**32**) with ethoxyethene (**83**). The desired product namely, naphthalene (**84**) was occurred in a very small amount at room temperature and we have observed slight enhancement in yield at higher temperature (Scheme 28).



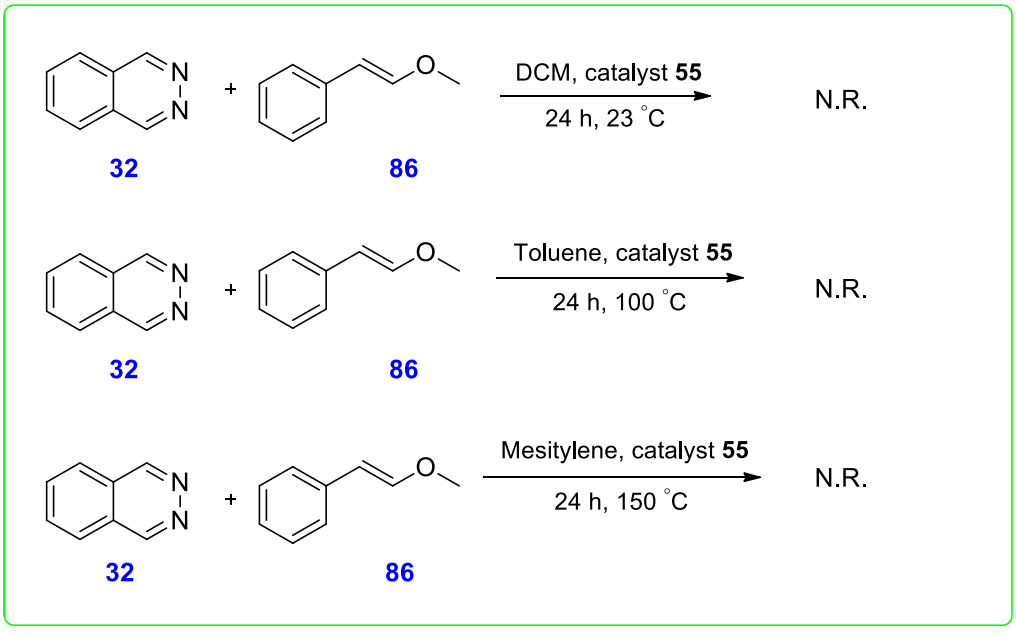
Scheme 28: IEDDA reaction of phthalazine with ethoxyethene (**83**).

By keeping enol ethers in mind, another potential candidate for substrate scope was 2-methoxyvinylbenzene (**86**). Wittig reaction of benzaldehyde (**85**) with methoxymethyltriphenylphosphonium chloride activated by KO*t*-Bu resulted in compound **86** in 55% yield as a mixture of *E* and *Z* isomers (Scheme 29). It should be noted that both *E* and *Z* isomers were expectd to give the same IEDDA cycloaddition product due the reaction mechanism. Hence, having a mixture of them is not an issue in the main reaction.



Scheme 29: Wittig reaction of benzaldehyde (**85**).

Finally, compound **86** was used as a dienophile in IEDDA reaction of phthalazine (**32**). Unfortunately, we could not observe any IEDDA product in despite of electron rich nature of compound **86**. Supposably, the rationale behind this fact may come from the steric effect. Due to phenyl group, compound **86** would be sterically hindered in the way orbitals of the molecules could not properly align to give expected IEDDA product (Scheme 30).



Scheme 30: IEDDA reaction of phthalazine with enol ether **86**.

3 CONCLUSION

In summary, we presented the first example of Brønsted acid-catalyzed IEDDA reaction of 1,2-diazines under mild conditions such as room temperature and a single day of continuous stirring. After optimization studies, we used the pyridinium salt **55** as a highly effective Brønsted acid catalyst that is considered to lower LUMO of diene, thus facilitating the formation of desired cycloaddition product at room temperature. However, despite numerous attempts, we were unable to broaden the substrate scope due to low yield of desired IEDDA products.

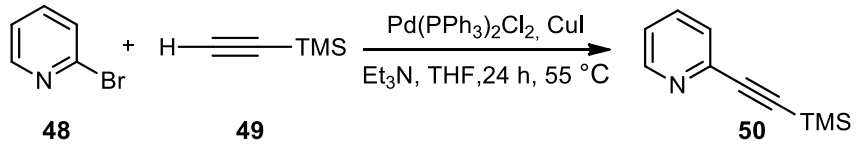
4 EXPERIMENTAL SECTION

4.1. General Information

All air- and moisture-sensitive experiments in this work were carried out using oven-dried glassware. Chemicals were purchased from Acros, Aldrich, Merck, TCI, Thermo Scientific, Alfa Aesar and Carlo Erba. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed plates pre-coated with silica gel (Silicycle). Visualization of TLC plates was conducted by UV light (254 and 365 nm) and/or $KMnO_4$ staining solution. As a purification technique, flash column chromatography was performed on Silicycle 40-63 μm (230-400 mesh) flash silica gel. All organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. NMR spectra were measured on Bruker DPX 400 for ^{1}H-NMR and ^{13}C-NMR and calibrated from internal standard (TMS,0 ppm) or residual solvent signals (chloroform on 7.26 ppm for ^{1}H-NMR spectra and on 77.17 ppm for ^{13}C-NMR spectra). ^{1}H-NMR spectroscopic data are reported as follows: chemical shift (parts per million, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublet, dt = doublet of triplet, tt = triplet of triplet, pd = pentate of doublet, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet), coupling constant (Hz). Infrared (FTIR) spectra were recorded on a Bruker Alpha-Platinum-ATR spectrometer equipped with a diamond ATR crystal module, and a deuterated triglycine sulfate (DTGS) mid-IR detector. Only selected peaks were reported.

4.2. Synthesis of the Brønsted-Acid Catalysts

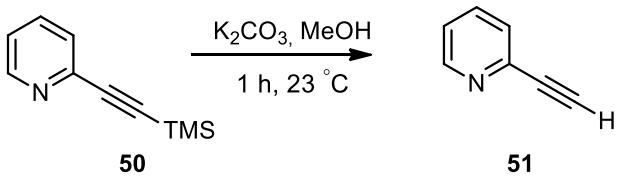
4.2.1. Compound 50



An oven-dried 50 mL, two-neck, round-bottomed flask was cooled under vacuum and refilled with N_2 (×3). Then, flask was fitted with a septum on one neck and connected to the Schlenk line via an adapter on the second neck. Triethylamine (6-8 mL) was added via syringe and it was deoxygenated by purging with nitrogen gas. Sequentially, 2-bromopyridine (**48**) (758 μL, 7.6 mmol), ethynyltrimethylsilane (**49)** (820 mg, 8.4 mmol), bis(triphenylphosphine)- palladium (II) dichloride (53.3 mg, 0.076 mmol) and copper iodide (28.8 mg, 0.15 mmol) were added. The resulting mixture was stirred for 24 h at 50 °C, and the progress of the reaction was monitored by TLC. Afterwards, the reaction mixture was cooled down to ambient temperature and quenched with a saturated aqueous solution of NaCl (10 mL). The aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; EtOAc: hexanes = 1:10 → 1:4) gave product **50** (1.315 g, 99% yield) as a clear liquid. Spectral data for **50** match published reports.[51]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 4.3 Hz, 1H), 7.45 (td, *J* = 7.8, 1.6 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.09 – 6.98 (m, 1H), 0.11 (s, 9H).

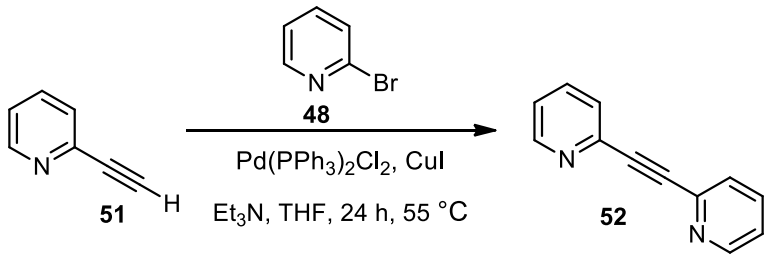
4.2.2. Compound 51



An oven-dried round bottom flask was placed and compound **50** (1.315 g, 7.5 mmol) was added into it. Methanol (8 mL) and potassium carbonate (1140 mg, 8.3 mmol) were added. Reaction mixture was stirred for 30 min at 23 °C. The progress of the reaction was monitored by TLC. Afterwards, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (8 mL). The aqueous phase was extracted with DCM (3×15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; EtOAc: hexanes = 1:5 → 1:1) gave product **51** (650 mg, 89% yield) as a colorless liquid. Spectral data for **51** match published reports.[52]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (d, *J* = 4.8 Hz, 1H), 7.69 – 7.33 m, 1H), 7.42 – 7.03 (m, 1H), 7.23 – 6.95 (m, 1H), 3.07 (s, 1H).

4.2.3. Compound 52

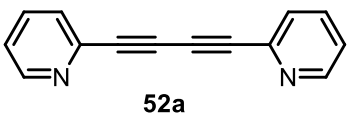


An oven-dried- 50 mL, two-neck, round-bottomed flask was cooled under vacuum and refilled with N_2 (×3). Triethylamine (8 mL) was added via syringe and it was deoxygenated by purging with nitrogen gas. Sequentially, 2-bromopyridine (**48**) (546 µL, 5.7 mmol), compound **51** (650 mg, 6.3 mmol) bis(triphenylphosphine)palladium (II) dichloride (40 mg, 0.057 mmol) and copper iodide (21.9 mg, 0.12 mmol), were added. The resulting mixture was stirred at 50 °C overnight, and the progress of the reaction was monitored by TLC. Afterwards, the reaction mixture was cooled down to ambient temperature and quenched a saturated aqueous solution of NaCl (10 mL). The aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; only EtOAc → 5% MeOH in EtOAc) gave product **52** (417 mg, 44% yield) as a brownish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 2H), 7.63 (td, *J* = 7.7, 1.8 Hz, 2H), 7.54 (dt, *J* = 7.9, 1.1 Hz, 2H), 7.21 (ddd, *J* = 7.5, 4.9, 1.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.1, 142.8, 136.3, 127.9, 123.5, 878.0.

Notes:



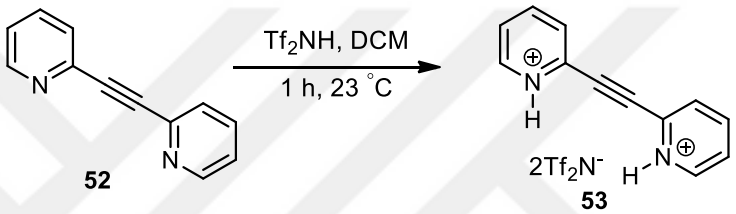
52a

From the purification of compound **52** by flash silica column chromatography, compound **52a** (15 mg, 7% yield) was also isolated as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (dd, *J* = 4.8, 0.9 Hz, 2H), 8.62 (dd, *J* = 4.8, 0.9 Hz, 2H), 7.68 (td, *J* = 7.8, 1.8 Hz, 2H), 7.54 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.29 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.5, 142.1, 136.3, 128.5, 123.9, 81.1, 73.3.

4.2.4. Compound 53



An oven-dried test tube was cooled under vacuum and refilled with N_2 (×3). Compound **52** (100 mg, 0.55 mmol) was dissolved in anhydrous DCM (2 mL) in another flask and it was added to test tube via syringe. Then, Tf_2NH (312 mg, 1.11 mmol) was taken into another vial and dissolved in DCM (1.5 mL). The reaction mixture was stirred for one hour at 23 °C. After 60 min, solid formation and the generation of a biphasic mixture was observed. The supernatant liquid was syringed out. Then the solid was washed with DCM (2 mL) and the solvent was syringed out. This process was repeated three times in total. Solid was stayed under vacuum for one hour. At the end, compound **53** (318 mg, 81% yield) was obtained as a dark-pinkish solid.

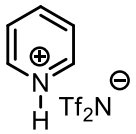
M.P. = 135-137 °C

^{1}H NMR (400 MHz, DMSO-d^6) δ: 12.64 (s, 2H), 8.85 – 8.59 (m, 2H), 8.07 (td, *J* = 7.8, 1.7 Hz, 2H), 7.88 (d, *J* = 7.9 Hz, 2H), 7.63 (ddd, *J* = 7.8, 5.1, 1.1 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-*d*^{6}) δ: 149.6, 140.1, 139.4, 129.1, 125.5, 120.0 (q, $J_{C\text{-}F}$ = 322 Hz), 88.3.

^{19}F NMR (376 MHz, DMSO-*d*^{6}) δ: -75.98.

4.2.5. Compound 55



55

The addition of pyridine (40 mg, 0.5 mmol) was done dropwise at 0 °C under nitrogen to a solution of Tf2NH (0.141 g, 0.5 mmol) in anhydrous DCM (1.5 mL). After 45 minutes of stirring, a clear, colorless solution was produced. After that, it was treated with hexanes (3–4 mL) to produce white solids, and the solution was allowed to sit at 0 °C for about 40 minutes. The liquid portion was syringed out after the white solid had been washed with hexanes. Three times this procedure was carried out. After 2 hours of waiting under vacuum, a white solid yielded product **55** (178 mg, 99% yield). Spectral data for **55** match published reports.[42]

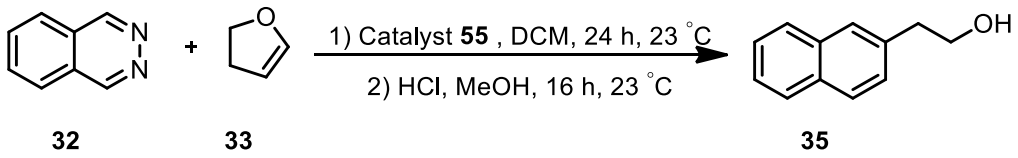
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (dd, *J* = 6.5, 1.3 Hz, 2H), 8.61 (tt, *J* = 8.0, 1.6 Hz, 2H), 8.09 (dd, *J* = 7.7, 6.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.1, 141.8, 127.7, 119.6 (q, $J_{C\text{-}F}$ = 321 Hz).

^{19}F NMR (376 MHz, DMSO-*d*^{6}) δ: -77.66.

4.3. Synthesis of IEDDA Cycloaddition Products

4.3.1. Compound 35



32 **33** **35**

In a clean 2 mL-vial, phthalazine (**32**, 50 mg, 0.38 mmol) was dissolved in anhydrous DCM (1 mL). Then, commercially available 2,3-dihyrofuran (**33**, 58 μL, 0.77 mmol) was added dropwise. Lastly, catalyst **55** (14 mg, 0.038 mmol) was added into the reaction. The reaction mixture was stirred for 24 h at 23 °C. After the reaction was stopped, it was quenched with a saturated aqueous solution of $NaHCO_3$ (15 mL), and the aqueous phase was extracted with EtOAc (3×15 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the resulting reaction mixture was transferred into 20 mL- vial and it was dissolved in MeOH (2 mL) and DCM (1 mL). Afterwards, HCl (36.5-38%, 0.2 mL) was added dropwise and reaction mixture was stirred for 16 h at 23 °C. The reaction mixture was quenched with distilled water (15 mL) and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2; %3 MeOH in EtOAc:hexanes = 1:3) gave product **35** (46.5 mg, 71% yield) as a white solid.

M.P. = 65-67 °C

R_f = 0.30 (3% MeOH in EtOAc:hexanes = 1:3)

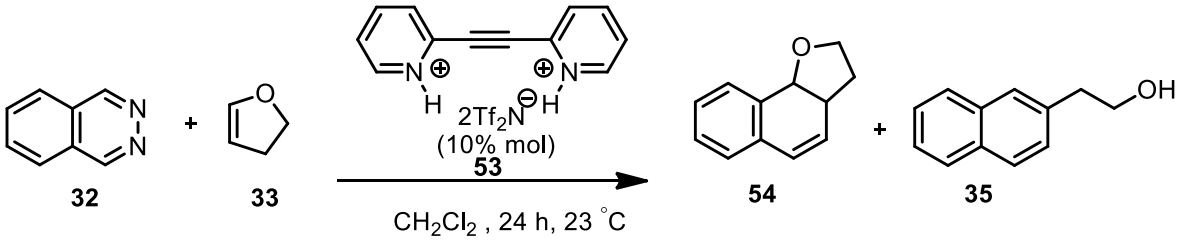
TLC Visualization: UV active; stains with $KMnO_4$ solution

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 – 7.75 (m, 3H), 7.68 (s, 1H), 7.51 – 7.41 (m, 2H), 7.39 – 7.33 (m, 1H), 3.94 (t, *J* = 6.4 Hz, 2H), 3.03 (t, *J* = 6.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.1, 133.7, 132.4, 128.4, 127.83, 127.8, 127.6, 127.5, 126.2, 125.6, 63.7, 39.5.

FTIR ν_{max} (ATR, film)/cm^{-1} 3349 (br), 3054, 3020, 2957, 2923, 2853, 1599, 1506, 1478

4.3.2. Compound 54



To 2 mL-vial, anhydrous DCM (1 mL) was added and phthalazine (**32**) (50 mg, 0.38 mmol) was dissolved in it. Then, commercially available 2,3-dihyrofuran (**33**, 58 μL, 0.77 mmol) was added dropwise. Lastly, catalyst **53** (14 mg, 0.05 mmol) was added. Reaction mixture was stirred for 24 hours at 23 °C. After reaction was stopped, it was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and aqueous phase was extracted with EtOAc (3×10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2; EtOAc: hexanes = 1:6 → EtOAc:hexanes =1:3) gave product **54** (18.4 mg, 28% yield) as a brownish liquid and compound **35** (17 mg, 27% yield) as a white solid.

R_f = 0.69 (3% MeOH in EtOAc:hexanes = 1:3)

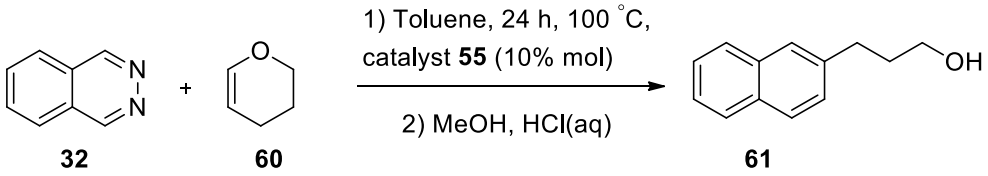
TLC Visualization: UV active; stains with $KMnO_4$ solution

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 – 7.37 (m, 1H), 7.31 – 7.21 (m, 2H), 7.12 (dd, *J* = 7.2, 1.4 Hz, 1H), 6.45 (dd, *J* = 9.7, 2.2 Hz, 1H), 5.78 (dd, *J* = 9.7, 3.1 Hz, 1H), 4.86 (d, *J* = 7.1 Hz, 1H), 3.86 (td, *J* = 8.1, 5.1 Hz, 1H), 3.75 (dd, *J* = 15.3, 7.4 Hz, 1H), 3.16 (ddt, *J* = 10.5, 6.9, 3.4 Hz, 1H), 2.43 (ddd, *J* = 16.0, 12.2, 8.0 Hz, 1H), 2.08 – 1.94 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 132.4, 132.2, 129.7, 129.4, 128.6, 127.6, 126.9, 126.2, 77.00, 65.9, 38.5, 33.5.

FTIR ν_{max} (ATR, film)/cm^{-1} 3376, 3023, 2962, 2925, 2867, 1489, 1452, 1259, 1101, 1086.

4.3.3. Compound 61



To a 2 mL-vial, phthalazine (**32**, 50 mg, 0.38 mmol) was added and it was dissolved in anhydrous Toluene (1 mL). Then, commercially available 2,3-dihyropyran (**60**, 70 μL, 0.77 mmol) was added dropwise. Lastly, catalyst **55** (14 mg, 0.038 mmol) was added. Reaction mixture was stirred for 24 h at 100 °C. Then, it was quenched with a saturated aquesous solution of $NaHCO_3$ (20 mL), and the aqueous phase was extracted with EtOAc (3×20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the resulting reaction mixture was transferred into 20 mL-vial and it was dissolved in MeOH (2 mL) and DCM (1 mL). Afterwards, HCl (36.5-38%, 0.2 mL) was added dropwise and reaction mixture was stirred for 16 h at 23 °C. The reaction mixture was quenched with distilled water (20 mL) and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2; EtOAc:hexanes = 1:3) gave product **61** (20 mg, 28% yield) as a white liquid.

$\mathbf{R}_f$ = 0.25 (EtOAc:hexanes = 1:3)

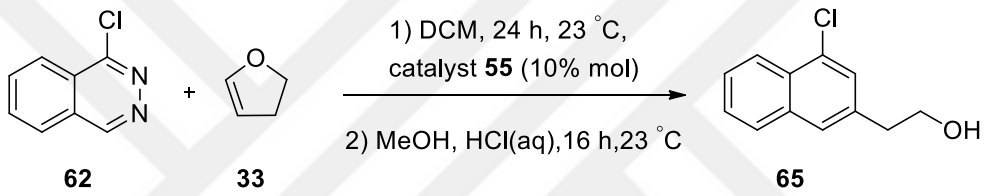
TLC Visualization: UV active; stains with $KMnO_4$ solution

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 – 7.72 (m, 3H), 7.64 (s, 1H), 7.50-7.40 (m, 2H), 7.35 (dd, *J* = 8.4, 1.7 Hz, 1H), 3.71 (t, *J* = 6.4 Hz, 2H), 2.90 – 2.85 (m, 2H), 2.06 – 1.90 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.5, 133.6, 132.2, 128.1, 127.8, 127.6, 127.4, 126.6, 126.1, 125.3, 62.4, 34.3, 32.4.

FTIR ν_{max} (ATR, film)/cm^{-1} 3346.2, 3051.3, 2934.9, 2861.6, 1920.8,1724.7, 1632.8, 1600, 1448.4, 1365.7, 1262

4.3.4. Compound 65



62 33 65

To a clean 2 mL-vial, commercially available 1-chlorophthalazine (**62**, 62.5 mg, 0.38 mmol) was added and it was dissolved in anhydrous DCM (1 mL). Then, 2,3-dihyrofuran **33** (53.5 mg, 0.77 mmol) was added dropwise. Lastly, catalyst **55** (14 mg, 0.038 mmol) was added. Reaction mixture was stirred for 24 h at 23 °C. Then, it was quenched with a saturated aquesous solution of $NaHCO_3$ (10 mL), and the aqueous phase was extracted with EtOAc (3×10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the resulting reaction mixture was transferred into 20 mL-vial and it was dissolved in MeOH (2 mL) and DCM (1 mL). Afterwards, HCl (36.5-38%, 0.2 mL) was added dropwise and reaction mixture was stirred for 16 h at 23 °C. The reaction mixture was quenched with distilled water (10 mL) and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced

pressure. Purification by column chromatography (SiO_2; 4% MeOH in $CHCl_3$) gave product **65** (14 mg, 18% yield) as a greenish liquid.

R_f = 0.48 (EtOAc:hexanes = 1:3)

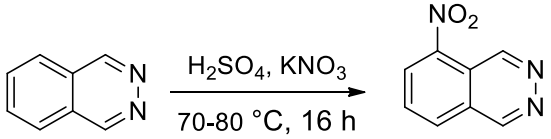
TLC Visualization: UV active; stains with $KMnO_4$ solution

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 – 8.18 (m, 1H), 7.83 – 7.75 (m, 1H), 7.61 (s, 1H), 7.59 – 7.49 (m, 2H), 7.48 (d, *J* = 1.6 Hz, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 3.00 (t, *J* = 6.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.5, 134.6, 132.2, 129.7, 127.9, 127.6, 127.0, 126.8, 126.7, 124.3, 63.3, 39.0.

FTIR ν_{max} (ATR, film)/cm^{-1} 3301, 3053, 2924, 2872, 1629, 1598, 1563, 1498, 1422, 1365, 1258, 1208, 1168, 1150.

4.3.5. Compound 68



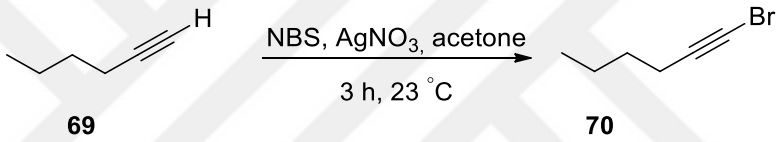
32 **68**

Following procedure was adapted from Shaikh and co-workers.[53] Nitric acid (70%, 3.72 g, 3.68 mmol) was added into round bottom flask and flask was placed in ice bath. Then, a solution of phthalazine (**32**, 1.00 g, 7.68 mmol) in concentrated sulfuric acid (7 mL) was added into it and reaction mixture was heated up to 77 °C. Reaction mixture was stirred for 20 h. Afterwards, it was cooled down to ambient temperature and sodium hydroxide (10 M, around 60 mL) was added very slowly until pH reached 11, which was checked with pH paper. The aqueous phase was extracted with EtOAc (3×80 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated

under reduced pressure. After that, ethanol (15 mL) was added into crude product and heated for 40 seconds with heat-gun. Liquid part was removed with syringe while solid part was stayed under vacuum for one hour. This ethanol treatment process was implemented three times in total, which gave product **68** (650 mg, 50% yield) as a brown-yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 9.68 (s, 1H), 8.74 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.44 – 8.18 (m, 1H), 8.09 (t, *J* = 8.0 Hz, 1H).

4.3.6. Compound 70



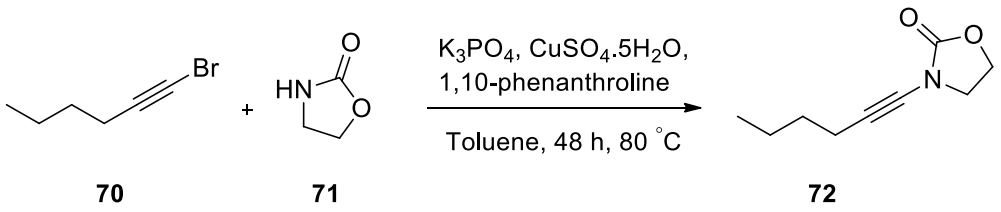
69 **70**

A solution of alkyne **69** (1.16 mL, 829 mg, 10 mmol), NBS (2136 mg, 12 mmol) and silver nitrate (85 mg, 0.5 mmol) was stirred for 3 h at 23 °C. Then, acetone was removed under reduced pressure. The resulting mixture was dissolved in pentane and purified by column chromatography (SiO_2; pentane), which gave product **70** (46% yield, 745 mg) as a colorless liquid. Spectral data for **70** match published reports.[54]

TLC Visualization: UV inactive; stains with $KMnO_4$ solution

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.18 (t, *J* = 7.0 Hz, 2H), 1.52 – 1.43 (m, 2H), 1.43 – 1.32 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

4.3.7. Compound 72

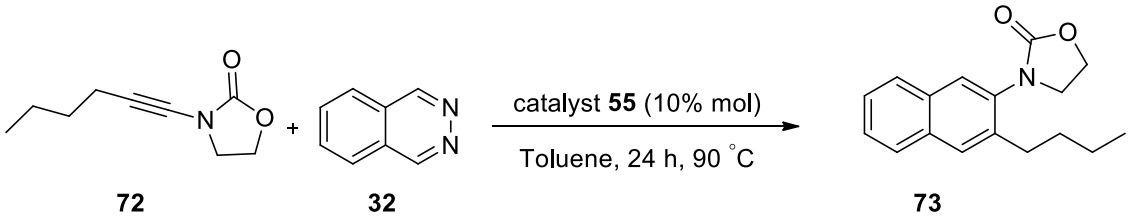


70 **71** **72**

Following procedure was adapted from Zhang and co-workers.[55] An oven-dried-100 mL, two-neck, round-bottomed flask was cooled under vacuum and refilled with N_2 (×3). Sequentially, alkyne **70** (745 mg, 4.63mmol), toluene (25 mL), 2-oxazolidinone **71** (322 mg, 3.7 mmol), K_3PO_4 (1.962 g, 9.3 mmol), $CuSO_4.5H_2O$ (116 mg, 0.46 mmol), and 1,10-phenanthroline (166 mg, 0.93 mmol) were added into round bottom flask, and the resulting mixture was stirred at 80 °C for 48 h. Then, it was cooled down to ambient temperature and all volatile components were evaporated under reduced pressure. Purification by column chromatography (SiO_2; EtOAc:hexanes = 1:3) gave product **72** (227 mg, 30% yield) as a solid product. Spectral data for **72** match published reports.[55]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.40 – 4.23 (m, 2H), 3.88 – 3.62 (m, 2H), 2.19 (t, *J* = 7.0 Hz, 2H), 1.52 – 1.36 (m, 2H), 1.34 – 1.23 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H).

4.3.8. Compound 73



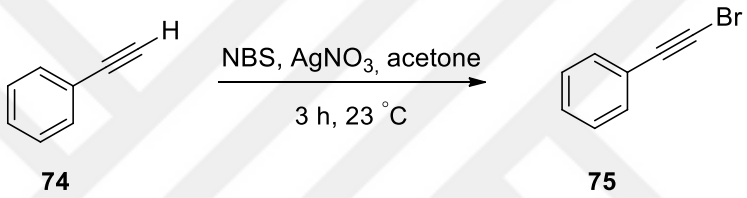
72 **32** **73**

To a clean thin-short vial, phthalazine (23.4 mg, 0.18 mmol) was dissolved in 1 mL of toluene. Then, alkyne **72** (30 mg, 0.18 mmol) was added dropwise. Lastly, catalyst **55** (6.5 mg, 0.02 mmol) was added. The reaction mixture was stirred for 24 hours at 90 °C. After reaction was stopped, it was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL), and the aqueous phase was extracted with EtOAc (3×5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced

pressure. Purification by column chromatography (SiO_2; EtOAc:hexanes = 1:9 → EtOAc:hexanes =1:1) gave product **73** (10 mg, 21% yield) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 – 7.64 (m, 4H), 7.50-7.39 (m, 2H), 4.57 (dd, *J* = 8.6, 7.3 Hz, 2H), 4.04 (dd, *J* = 8.9, 6.8 Hz, 2H), 2.84 – 2.68 (m, 2H), 1.77 – 1.64 (m, 2H), 1.44 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

4.3.9. Compound 75

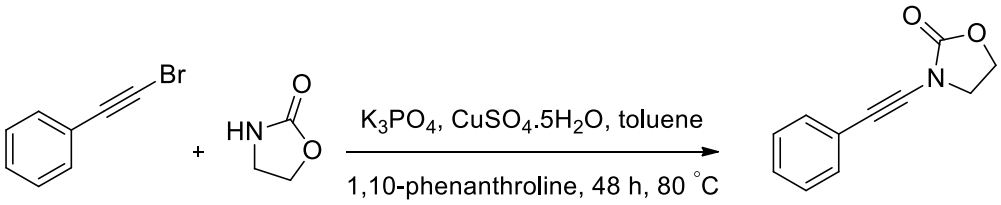


74 **75**

An oven-dried 100 mL, round-bottomed flask was cooled under vacuum and refilled with N_2 (×3). Silver nitrate (170 mg, 1 mmol) was added to a solution of alkyne **74** (2.04 g, 20 mmol) in acetone (50 mL). Then, NBS was added in three portion and reaction mixture was stirred for 3 h at 23 °C. Furthermore, it was concentrated under reduced pressure. Purification by column chromatography (SiO_2; pentane) gave product **75** (3.22 g, 90% yield) as a solid product.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.31 – 7.20 (m, 3H).

4.3.10. Compound 76

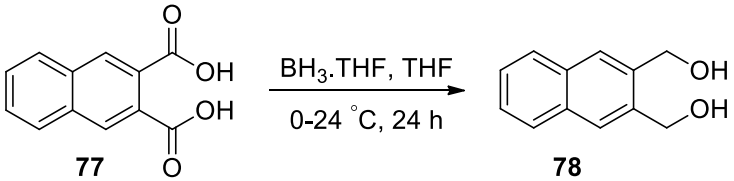


To a clean-100 mL, round-bottomed flask was cooled under vacuum and refilled with N_2 (×3). Sequentially, 2-oxazolidinone (**71**, 1.29 g, 14.8 mmol), $CuSO_4.5H_2O$ (370 mg, 1.48 mmol), 1,10-phenanthroline (544 mg, 3.0 mmol), K_3PO_4 (4.92 g, 35.6 mmol) were added into round bottom flask. Then, toluene (30 mL) and alkyne **75** (3.22 g, 17.8 mmol) were added dropwise. Additionally, toluene (20 mL) was used to clean flask of alkyne **75** and it was added into main reaction. Then, reaction was heated to 80 °C and stirred overnight. Then, it was cooled down to ambient temperature and reaction mixture was evaporated under reduced pressure. Purification by column chromatography (SiO_2; EtOAc:hexanes = 1:6 → 1:2) gave product **76** (2.27 g, 86% yield) as a pale-yellow solid product.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 – 7.40 (m, 2H), 7.35 – 7.28 (m, 3H), 4.54 – 4.44 (m, 2H), 4.05 – 3.96 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.9, 131.6, 128.3, 128.2, 122.2, 78.9, 71.2, 63.0, 47.1.

4.3.11. Compound 78



An oven-dried- 10 mL, two-neck, round-bottomed flask was cooled under vacuum and refilled with N_2 (×3). Subsequently, 2,3-napthalanedicarboxylic acid (**30**, 1000 mg, 4.63 mmol) and anhydrous THF (10 mL) were added under nitrogen. Then, reaction was cooled with ice bath to 0 °C and BH_3.THF (5.40 g, 62.8 mmol) was added through syringe pump for 90 minutes. Reaction mixture was stirred for 24 hours at 23°C. The resulting mixture was cooled down to 0 °C and quenched by dropwise addition of THF:H_2O (1:1, 6 mL). Potassium carbonate was added until the aqueous and organic layers were fully separated. Afterwards, distilled water (5 mL) was added. The resulting mixture was poured into separatory funnel and the aqueous phase was extracted with THF (2×25 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2; 5% MeOH in EtOAc:hexanes = 1:1) gave product **78** (186 mg, 21.4% yield) as a solid product.

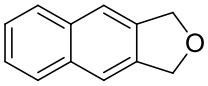
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 – 7.77 (m, 4H), 7.50 (dd, *J* = 6.3, 2.9 Hz, 2H), 7.26 (s, 2H), 4.92 (s, 4H).

Notes:

a)

Anhydrous THF was prepared according to following procedure: 4Å MS was added to 100 mL, round bottom flask. Then, it was heated with heating gun for 15 minutes. After that, it stayed under vacuum for 10 minutes and anhydrous THF was used after one day.

b)

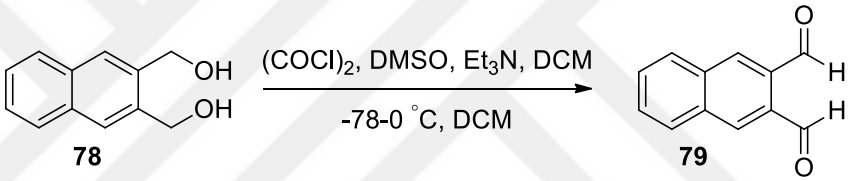


78a

From the purification of compound **78** by flash silica column chromatography, compound **78a** (55 mg, 6% yield) was also isolated as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.68 (s, 2H), 7.52 – 7.35 (m, 2H), 5.23 (d, *J* = 0.5 Hz, 4H).

4.3.12. Compound 79



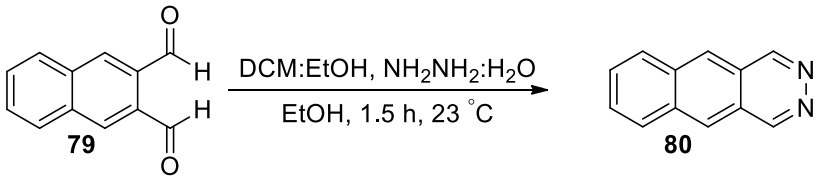
78 **79**

An oven-dried-schlenk tube was cooled under vacuum and refilled with N_2 (×3). Anhydrous DCM (1 mL) and oxalyl chloride (73.13 mg, 0.58 mmol) were added under nitrogen inlet. The resulting solution was cooled to -78 °C. (Temperature was checked by special thermometer to show minus degrees). A solution of DMSO (91.33 mg, 1.17 mmol) in anhydrous DCM (0.5 mL) was added into reaction mixture dropwise. Then, diol **70** (50 mg, 0.28 mmol) was added at once and the resulting mixture was stirred for 30 minutes at -78 °C. Afterwards, triethylamine was added dropwise and reaction mixture was stirred for 20 minutes at -78 °C. Reaction was warmed to 0 °C and was stirred for 2 hours (470 mg, 4.65 mmol). The reaction mixture was quenched with cold distilled water (15 mL) and the aqueous phase was extracted with DCM (3×20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

Purification by column chromatography (SiO_2; EtOAc:hexanes = 1:8 → EtOAc:hexanes = 1:2) gave product **79** (16.8 mg, 33% yield) as a solid product.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.65 (s, 1H), 8.47 (s, 1H), 8.14 – 7.98 (m, 1H), 7.85 – 7.56 (m, 1H).

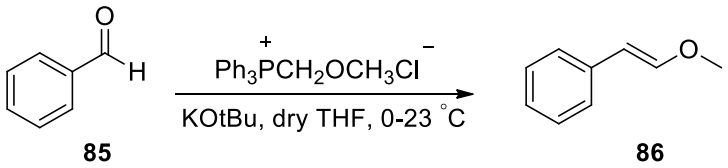
4.3.13. Compound 80



An oven-dried- round-bottomed, a solution of $NH_2NH_2.H_2O$ (142 mg, 2.82 mmol) with EtOH (4 mL) was initially added and solution of dialdehyde **79** (130 mg, 0.71 mmol) in DCM:EtOH (1:1, 6 mL) was secondly added to reaction mixture dropwise at 0 °C. Then, reaction mixture was warmed up to 23 °C and it was stirred for 90 minutes. Then, resulting mixture was evaporated under reduced pressure. It was dissolved in toluene (5 mL) and evaporated under reduced pressure. This process was repeated with DCM three times in total. Purification by column chromatography (SiO_2; EtOAc → EtOAc:isopropanol = 9:1) gave product **80** (51 mg, 40% yield) as a brownish-red solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (s, 2H), 8.52 (s, 2H), 8.27 – 8.06 (m, 2H), 7.81 – 7.53 (m, 2H).

4.3.14. Compound 86



To a two-neck, 100 mL, round bottom flask was cooled under vacuum and refilled with N_2 (×3). Sequentially, (Methoxymethyl)triphenylphosphonium chloride (1.163 g, 3.39 mmol) and anhydrous THF (12 mL) were added. Reaction mixture was cooled to 0 °C. In another flask, under nitrogen, KOtBu (792.9 mg, 7.1 mmol) and THF (15 mL) were mixed, taken by syringe and added into main reaction dropwise under nitrogen at 0 °C in 20 minutes. Afterwards, reaction mixture was stirred for 30 min at 0 °C. Then, benzaldehyde (**85**, 300 mg, 2.8 mmol) was added dropwise. Reaction mixture was stirred for 4 h and warmed up to ambient temperature. The reaction mixture was quenched with distilled water (15 mL), brine (15 mL) and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2; hexanes gave product **86** (215 mg, 57% yield) as a yellowish liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.44 – 7.26 (m, 3H), 7.19 (dddd, *J* = 8.6, 7.5, 3.1, 1.5 Hz, 1H), 7.10 (d, *J* = 13.0 Hz, 1H), 6.18 (d, *J* = 7.0 Hz, 1H), 5.87 (d, *J* = 13.0 Hz, 1H), 5.28 (d, *J* = 7.0 Hz, 1H), 3.81 (s, 2H), 3.72 (s, 2H).

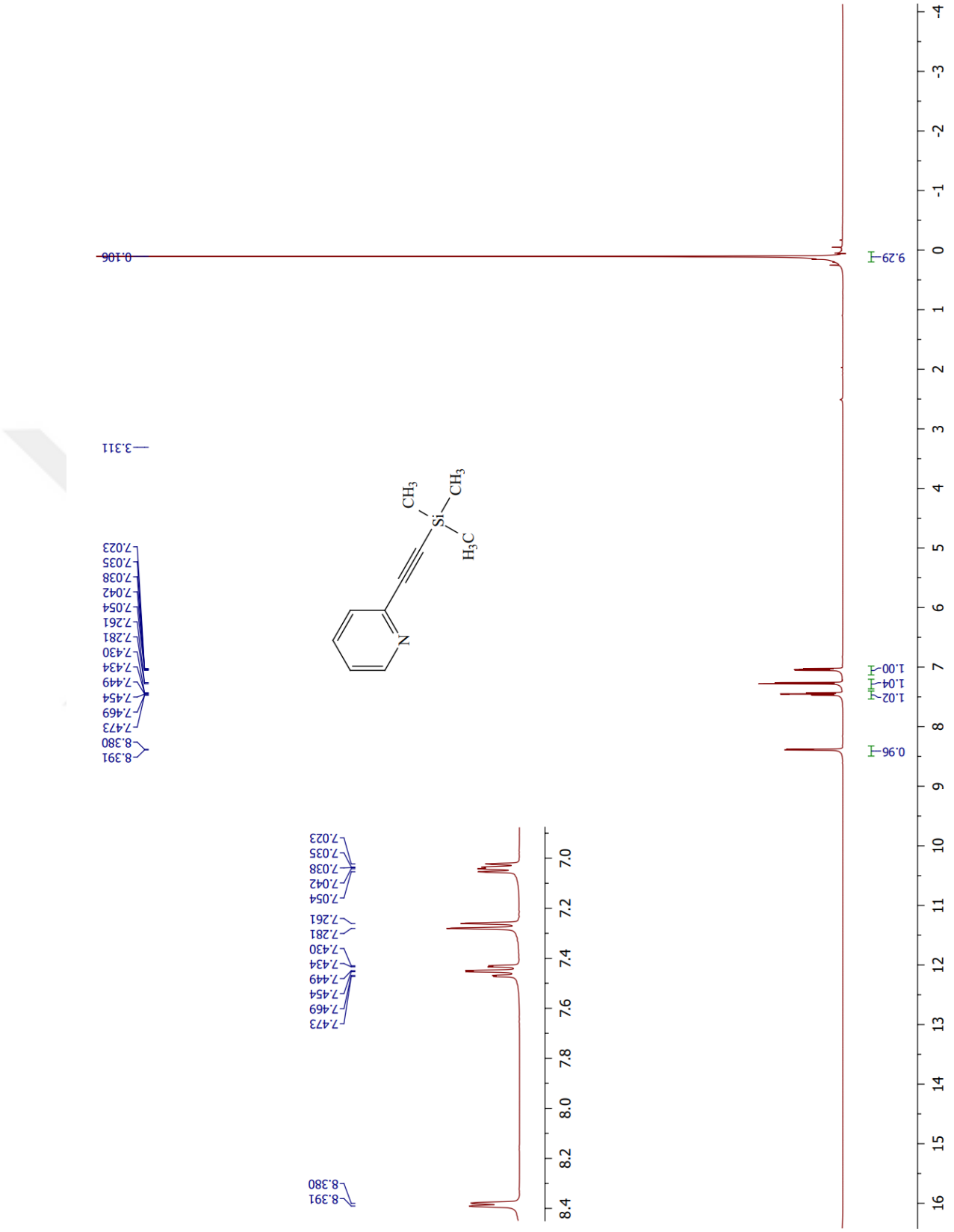


Figure 3: ^{1}H-NMR spectrum of compound **50** in $CDCl_3$

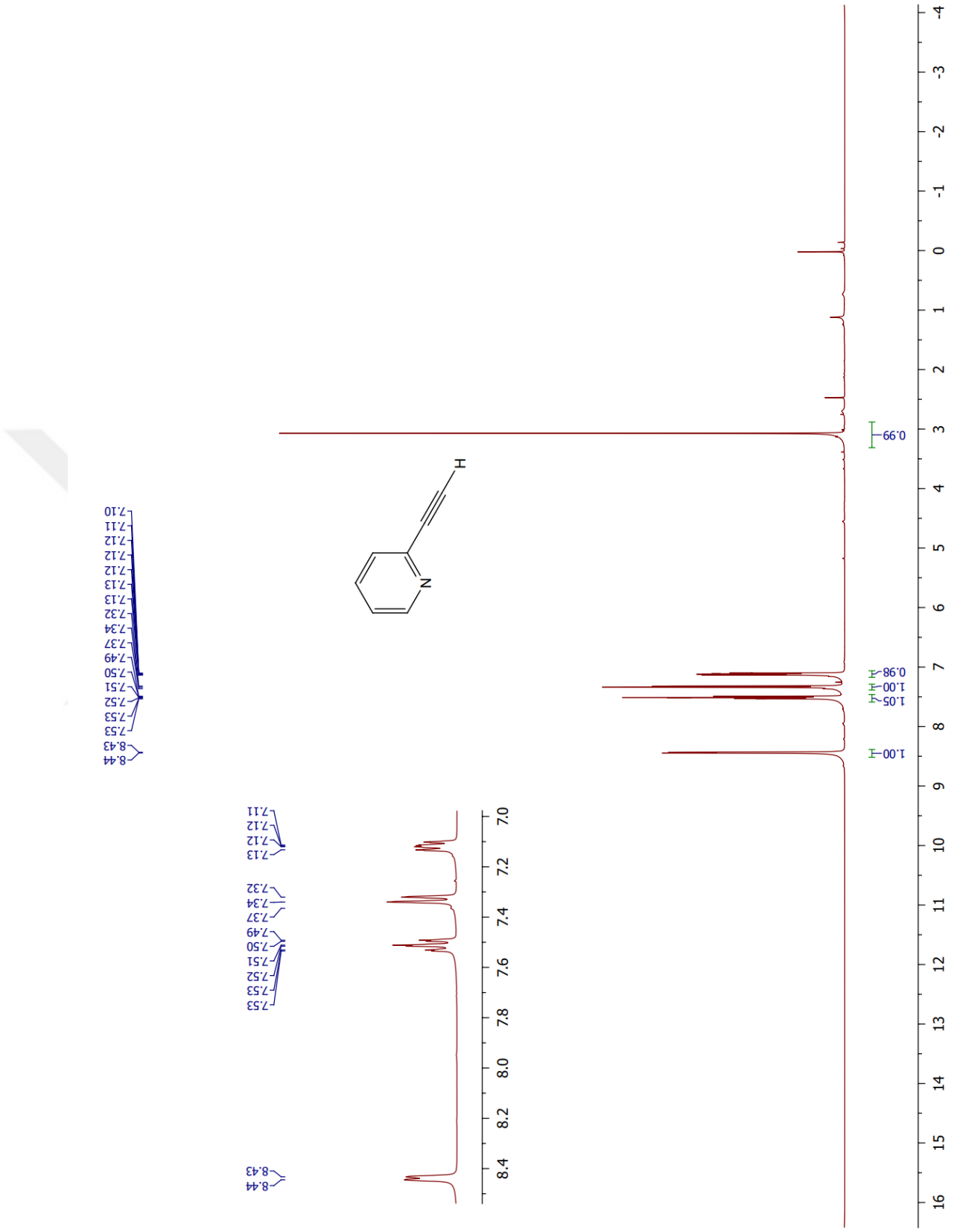


Figure 4: ^{1}H-NMR spectrum of compound **51** in $CDCl_3$

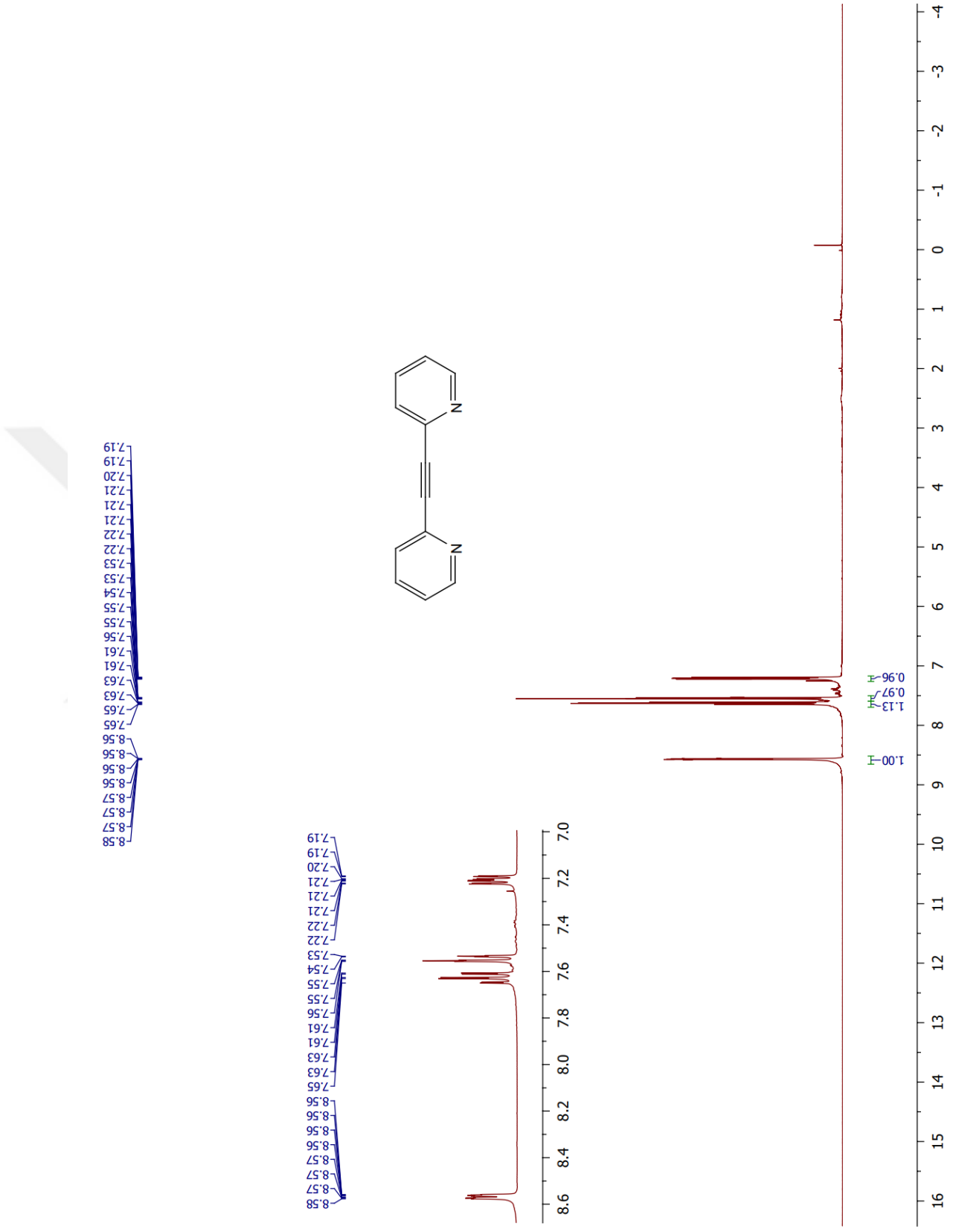


Figure 5: ^{1}H-NMR spectrum of compound **52** in $CDCl_3$

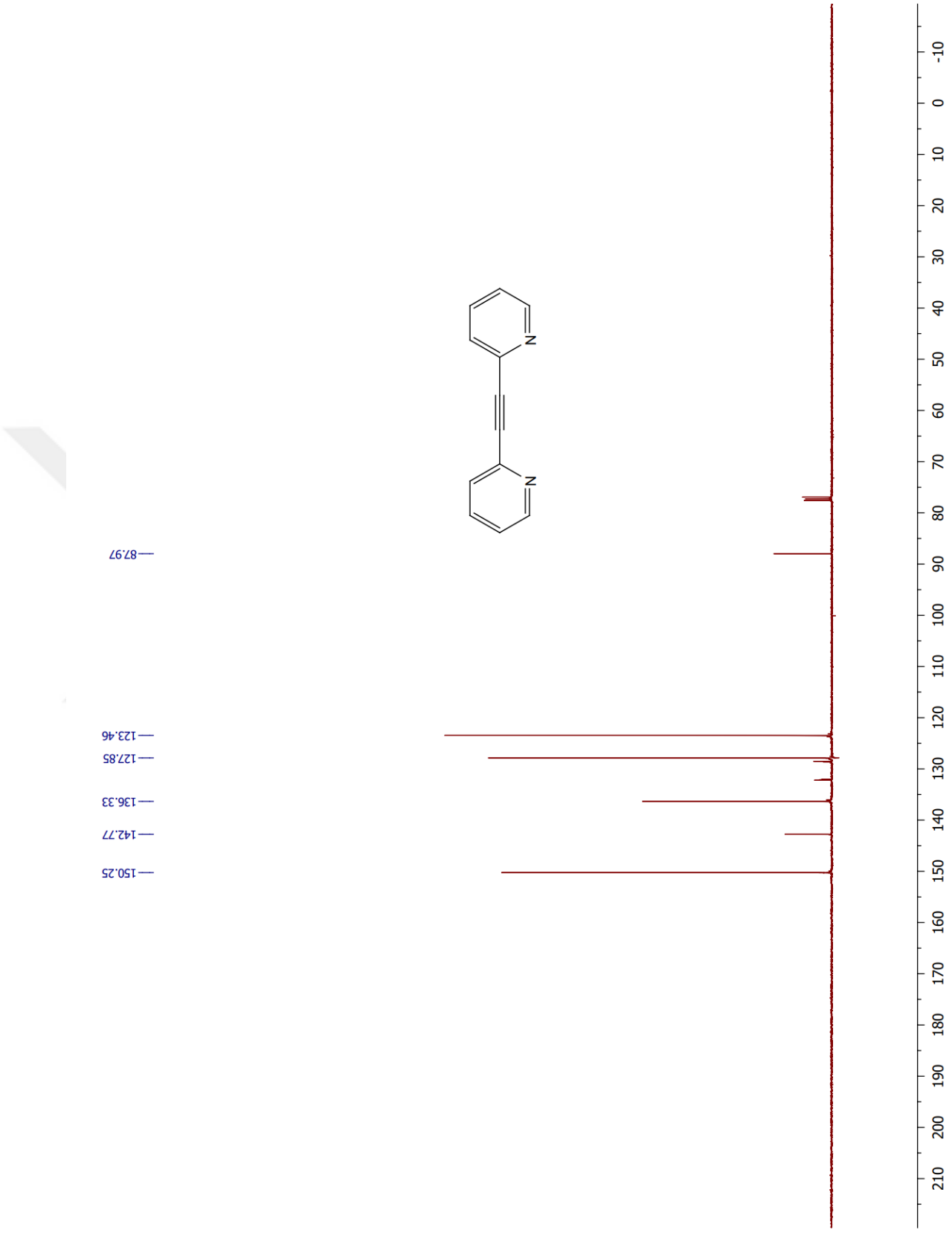


Figure 6: ^{13}C-NMR spectrum of compound **52** in $CDCl_3$

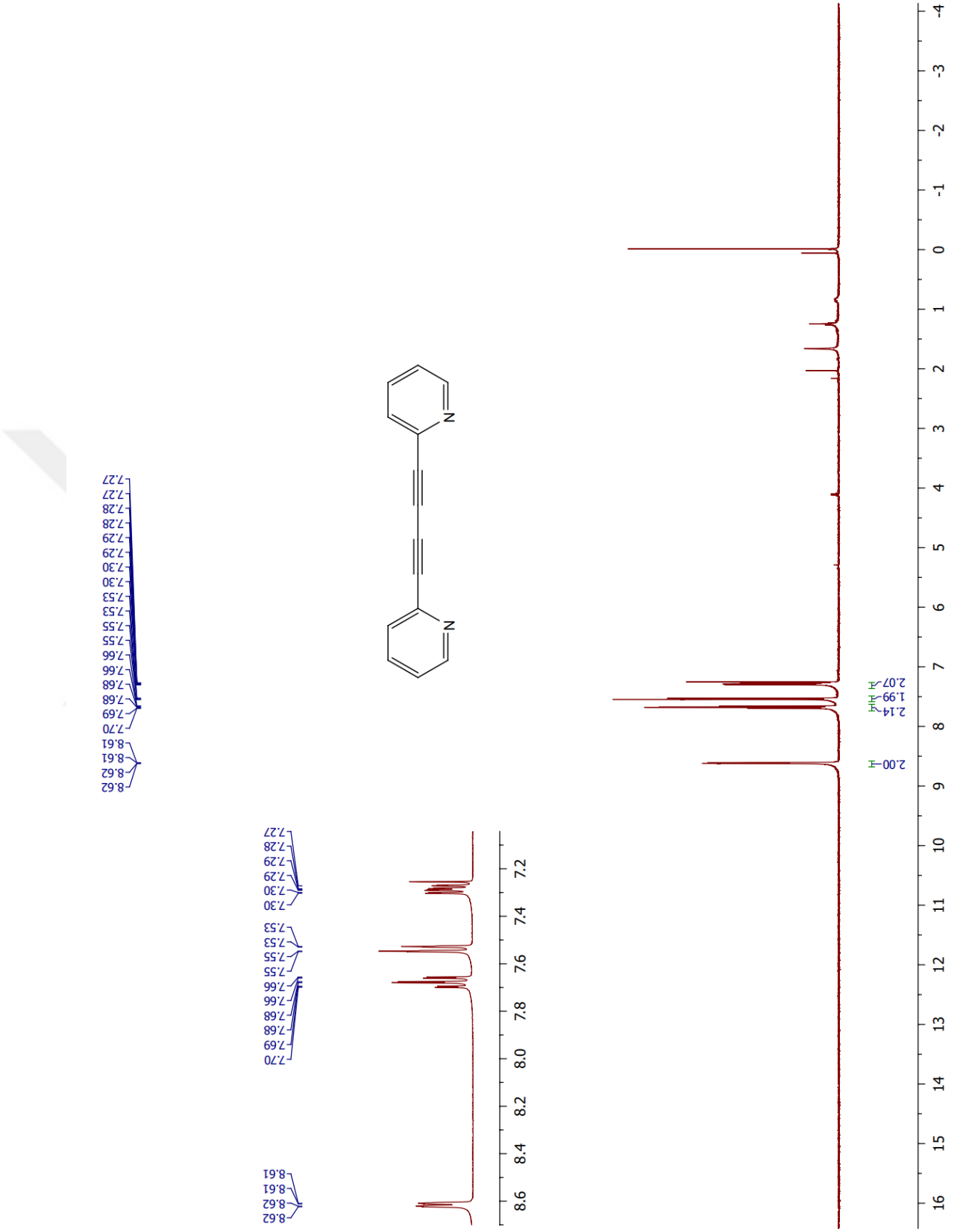


Figure 7: ^{1}H-NMR spectrum of compound **52a** in $CDCl_3$

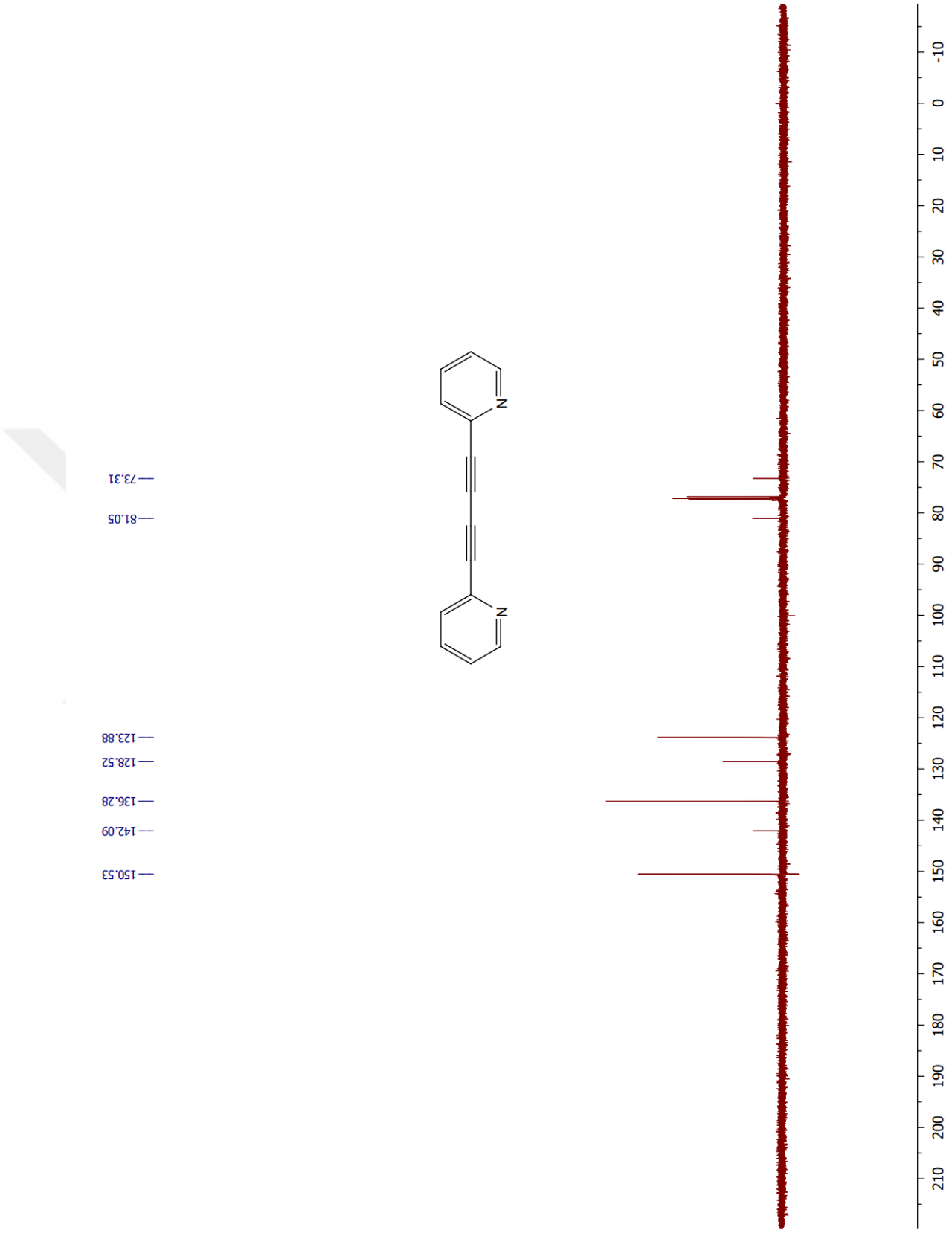


Figure 8: ^{13}C-NMR spectrum of compound **52a** in $CDCl_3$

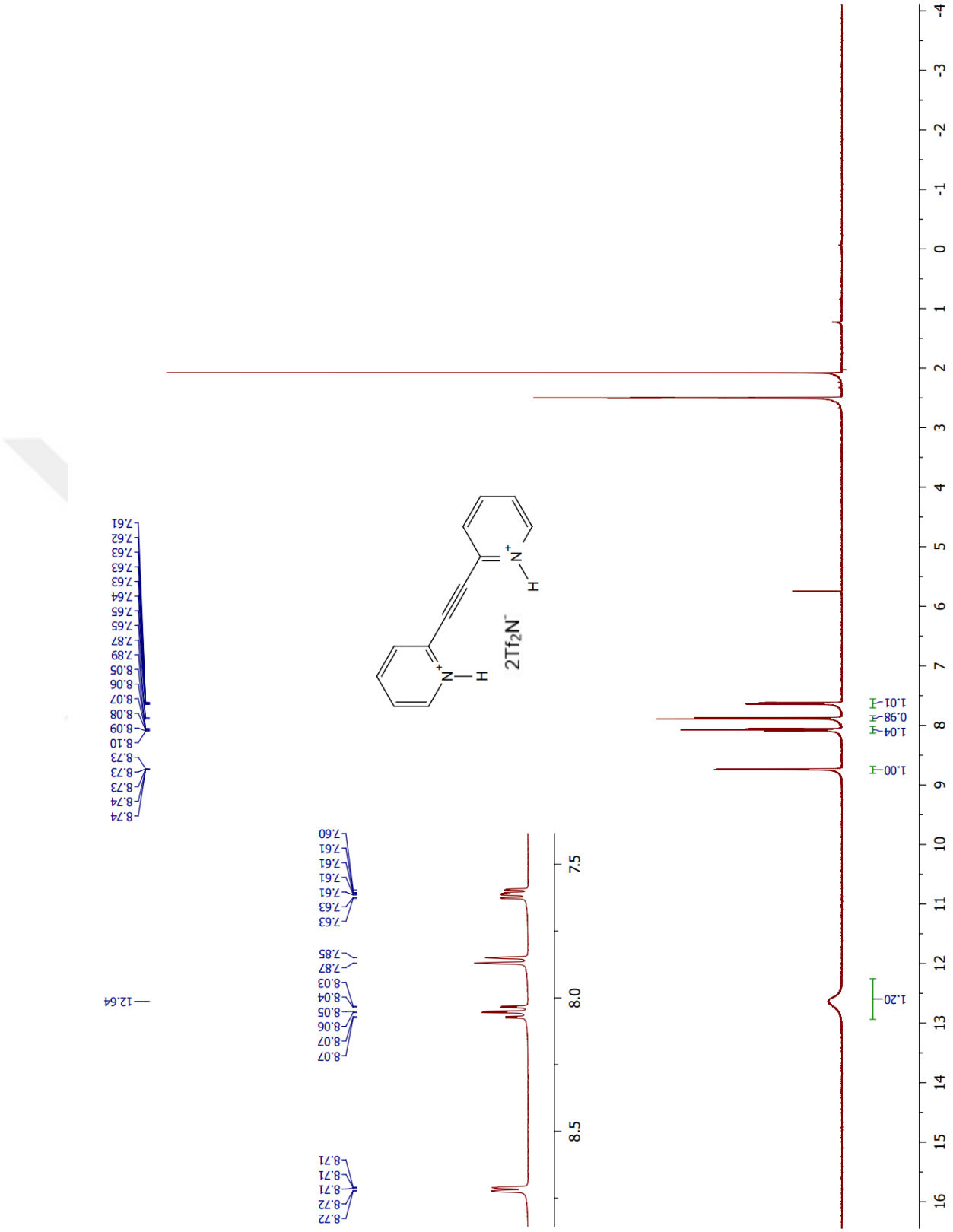


Figure 9: ^{1}H-NMR spectrum of compound **53** in DMSO-d^{6}

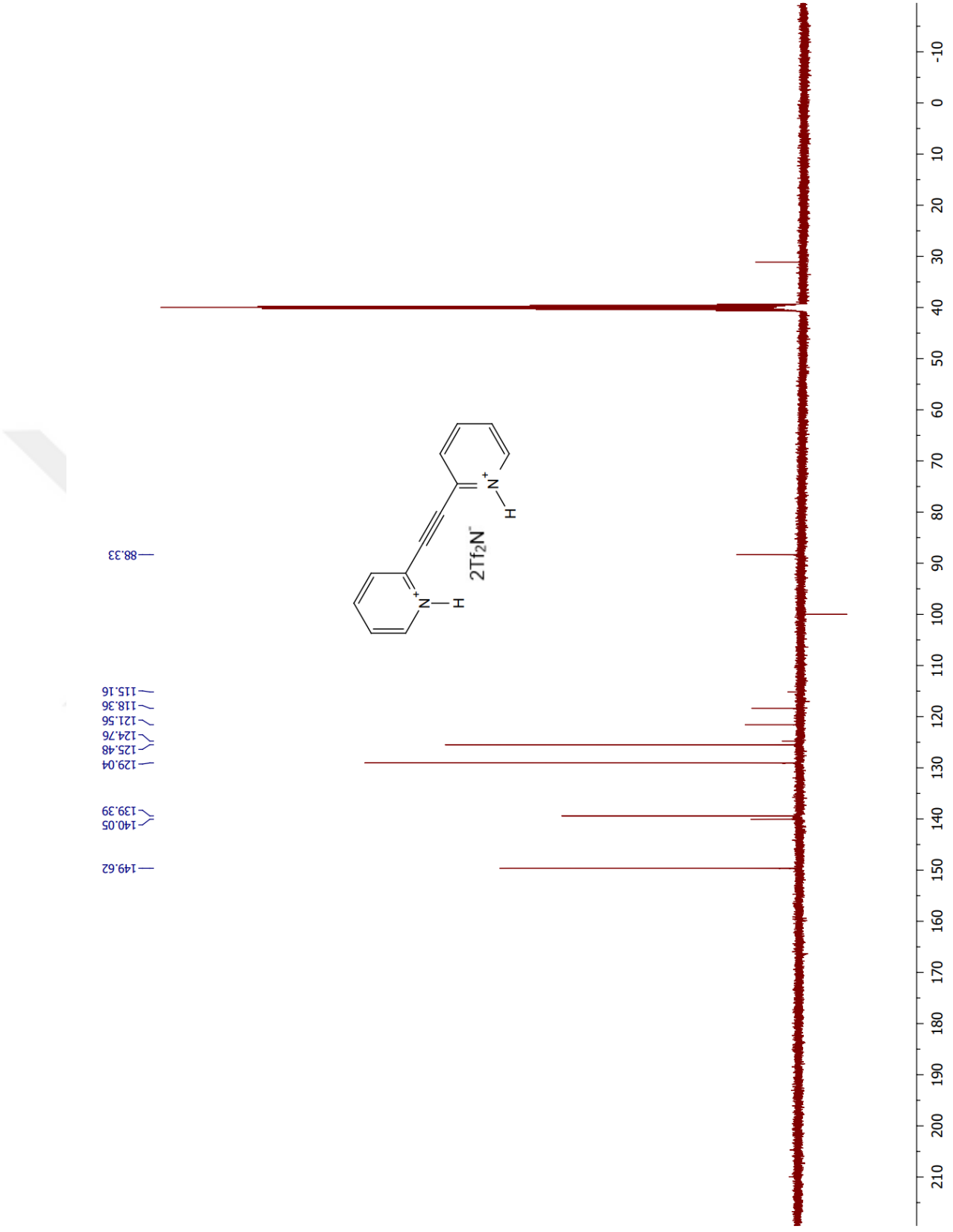


Figure 10: ^{13}C-NMR spectrum of compound **53** in DMSO-d^6

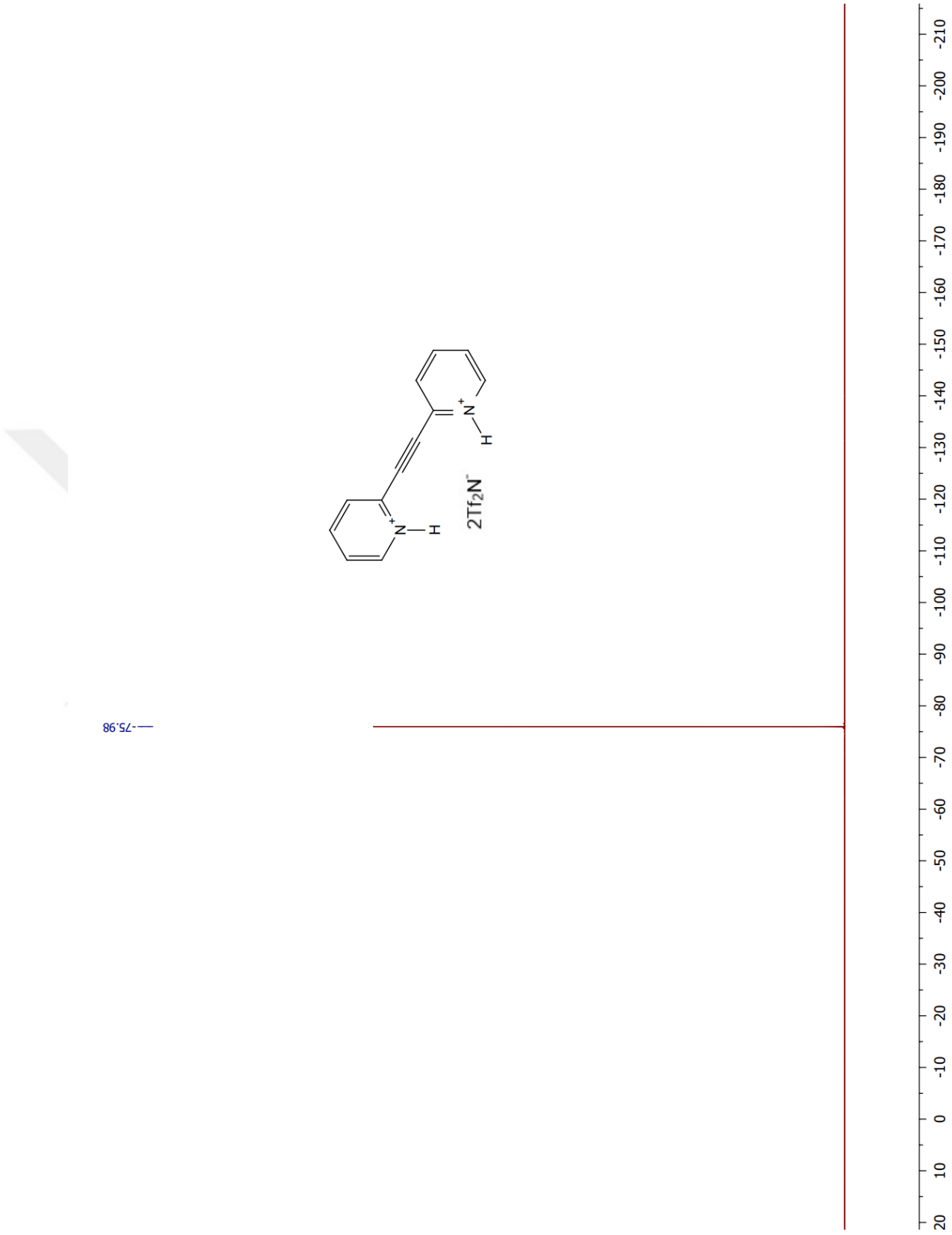


Figure 11: ^{19}F-NMR spectrum of compound **53** in DMSO-*d*^{6}

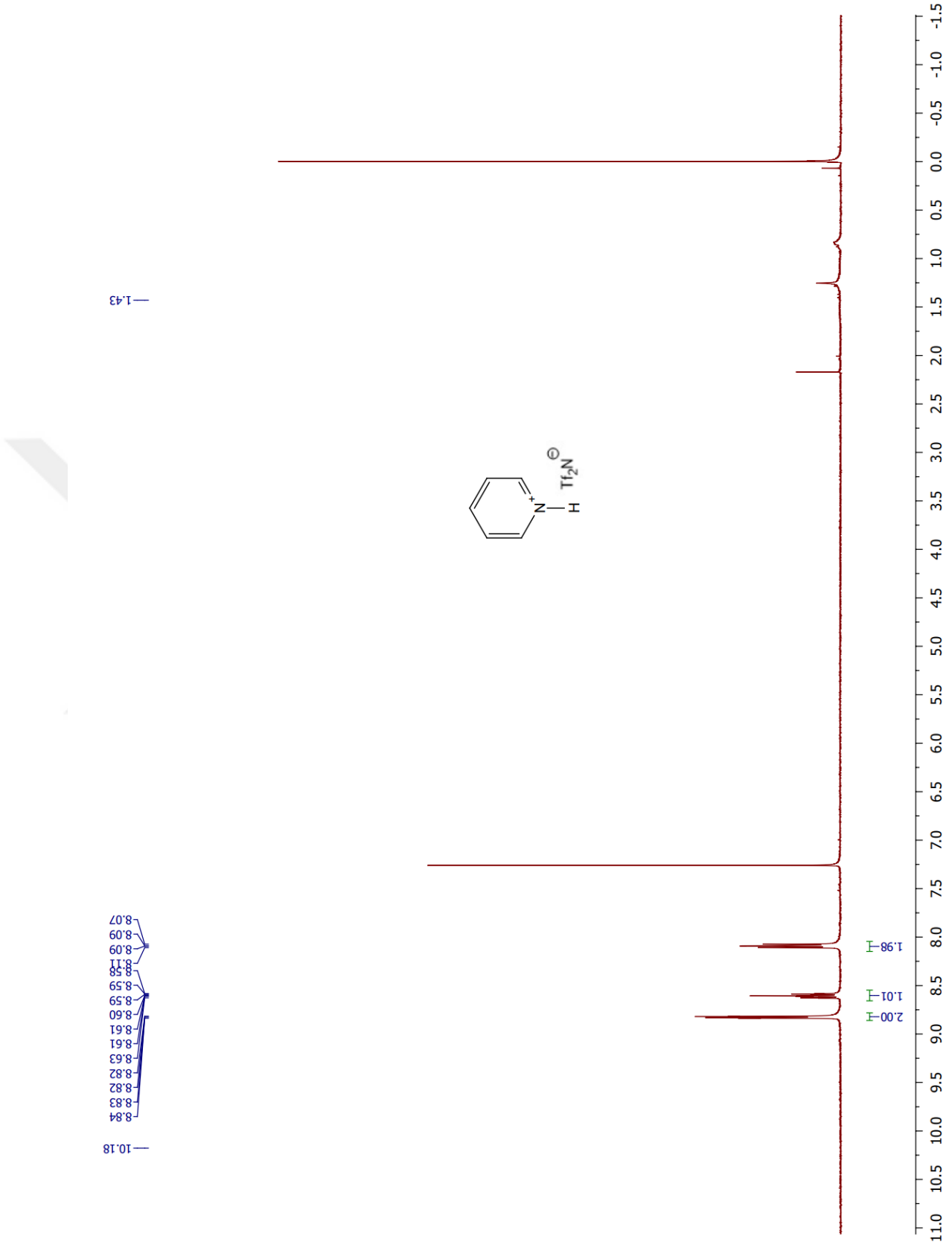


Figure 12: ^{1}H-NMR spectrum of compound **55** in $CDCl_3$

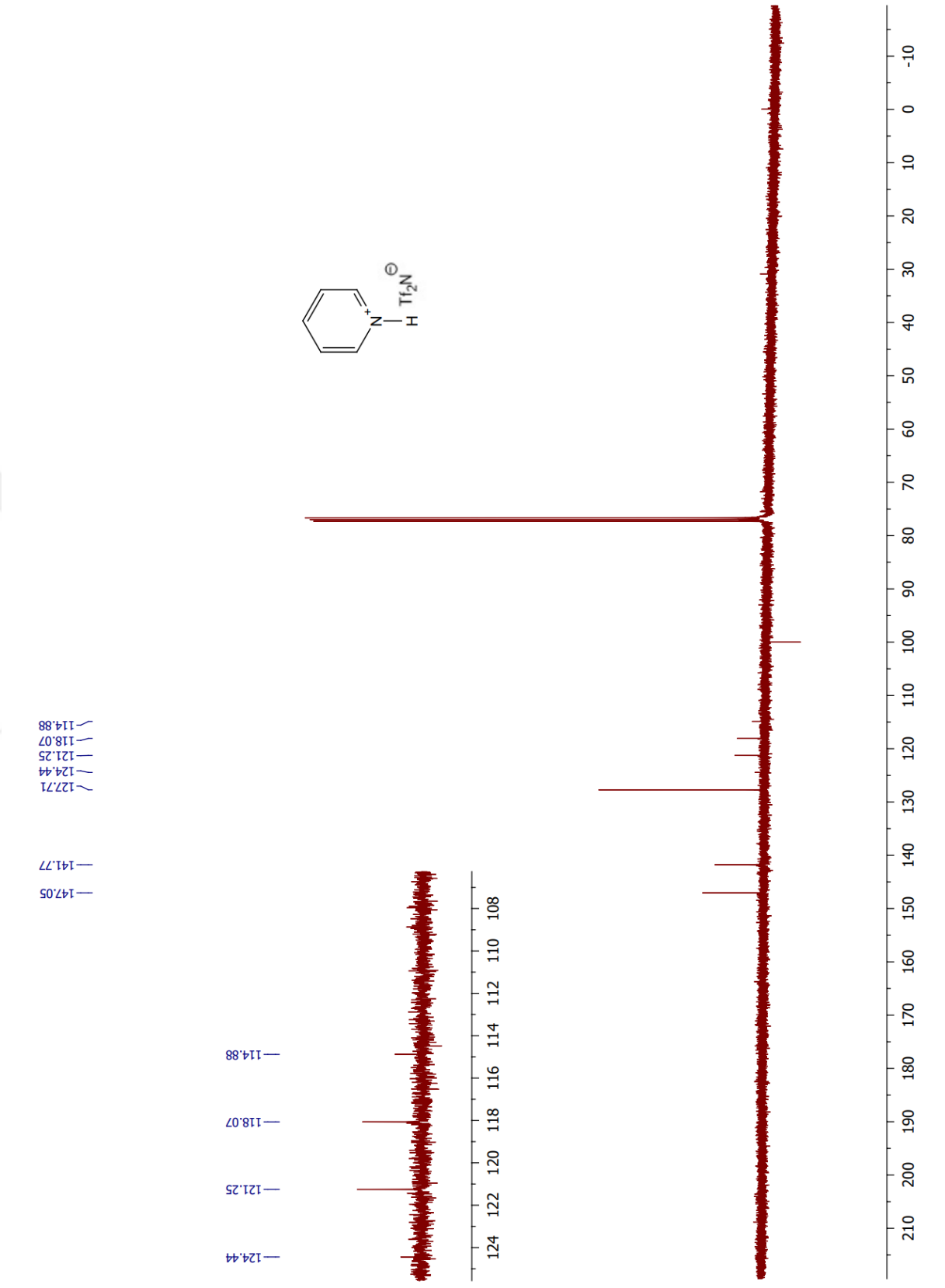


Figure 13: ^{13}C-NMR spectrum of compound **55** in $CDCl_3$

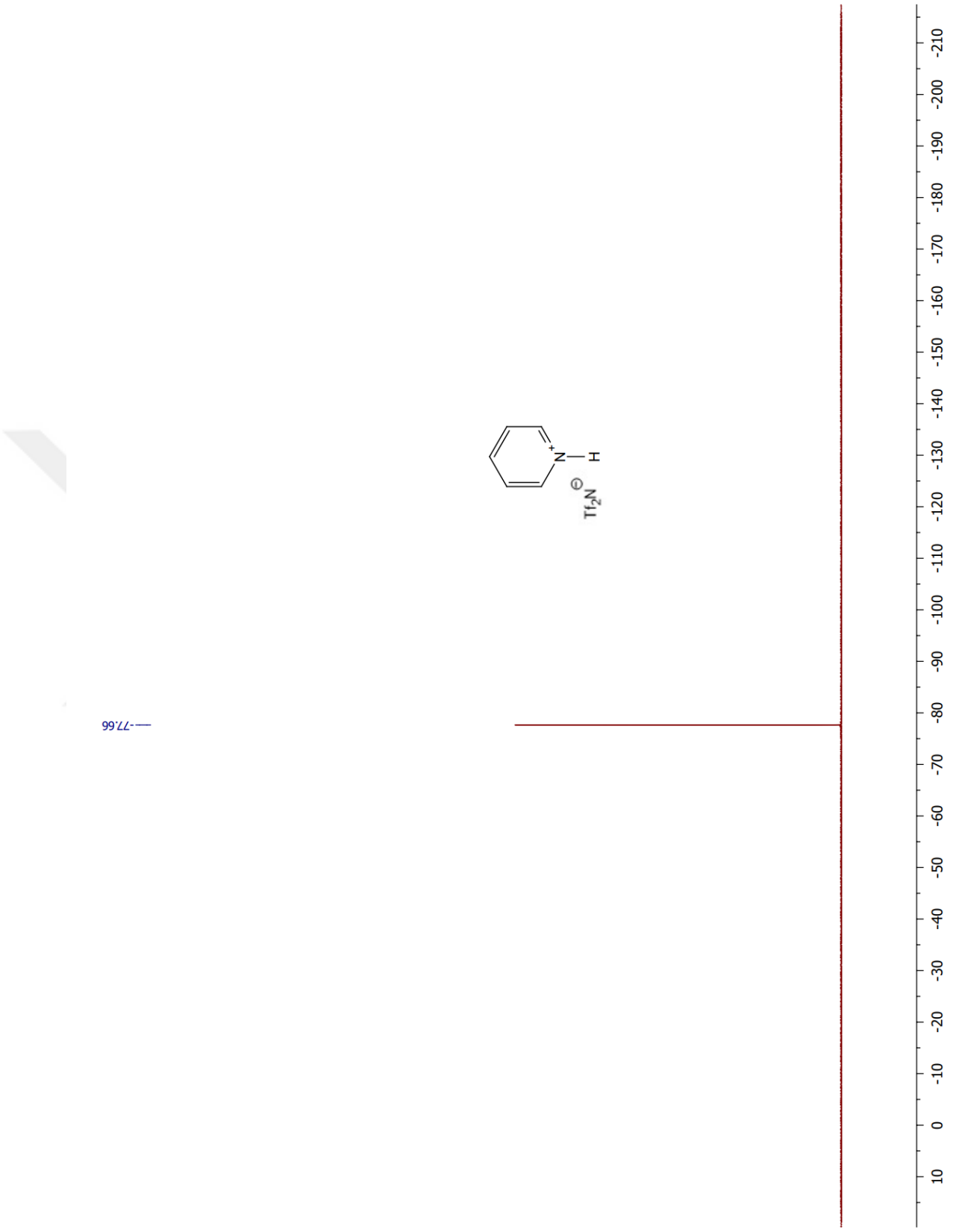


Figure 14: ^{19}F-NMR spectrum of compound **55** in $CDCl_3$

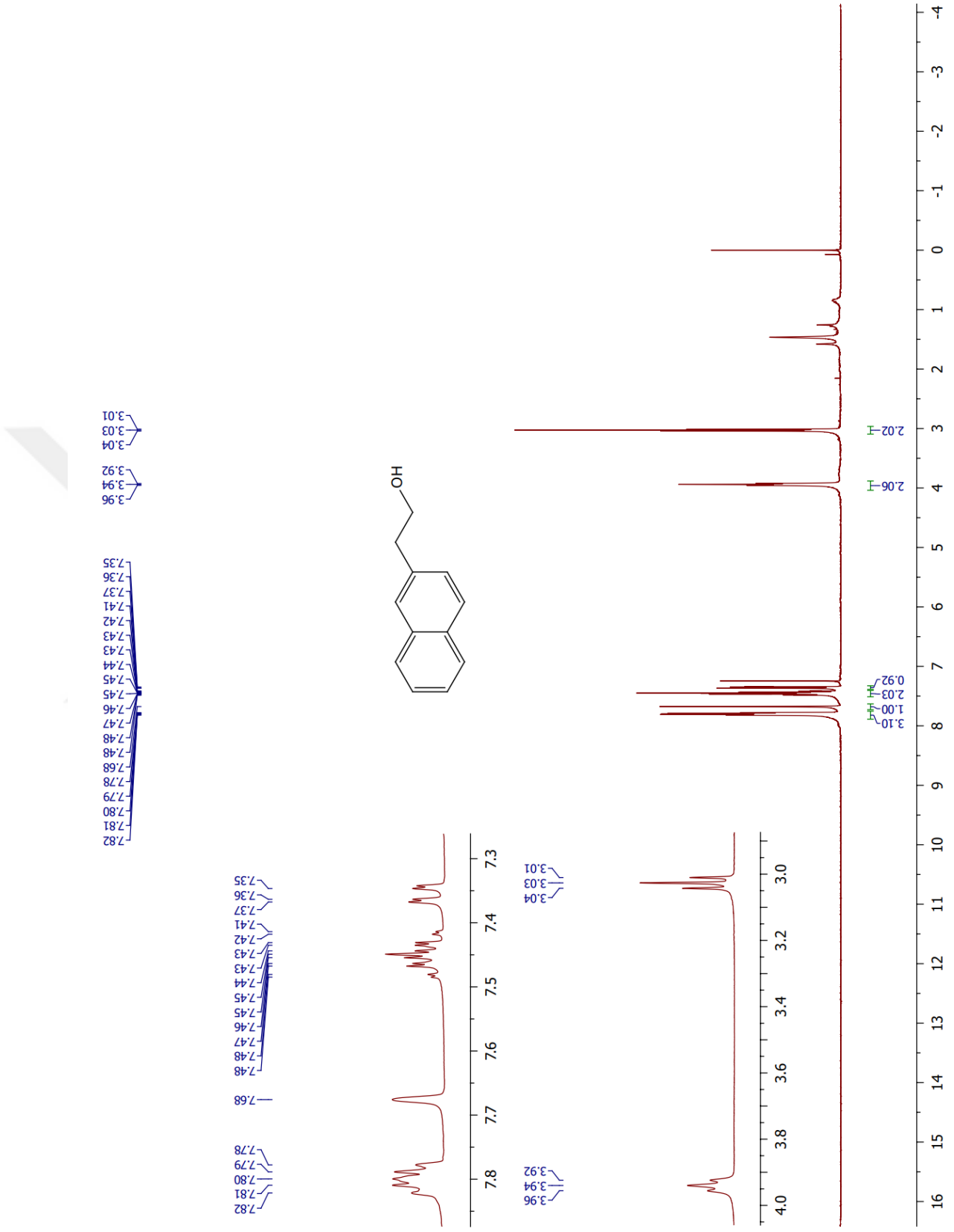


Figure 15: ^{1}H-NMR spectrum of compound **35** in $CDCl_3$

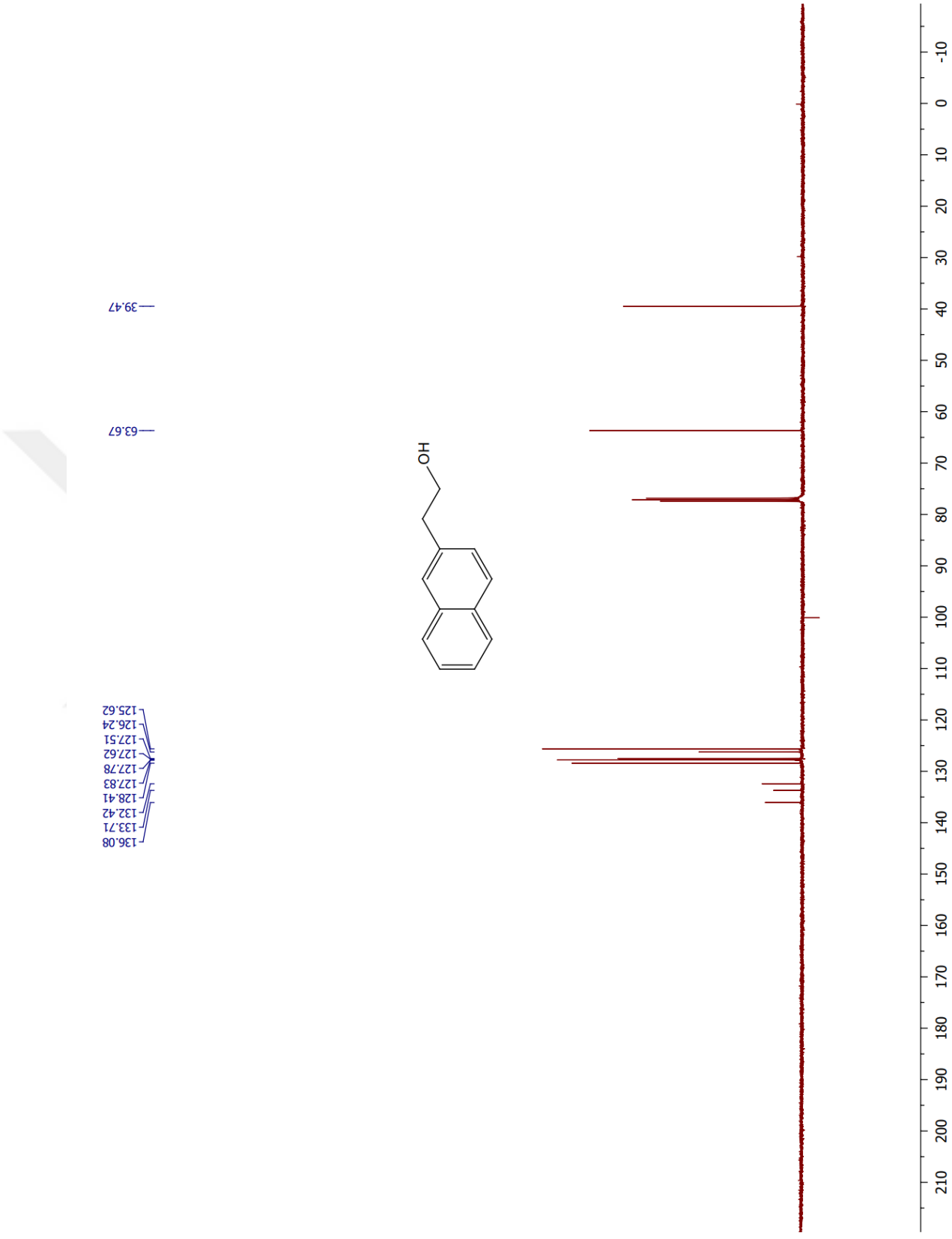


Figure 16: ^{13}C-NMR spectrum of compound **35** in $CDCl_3$

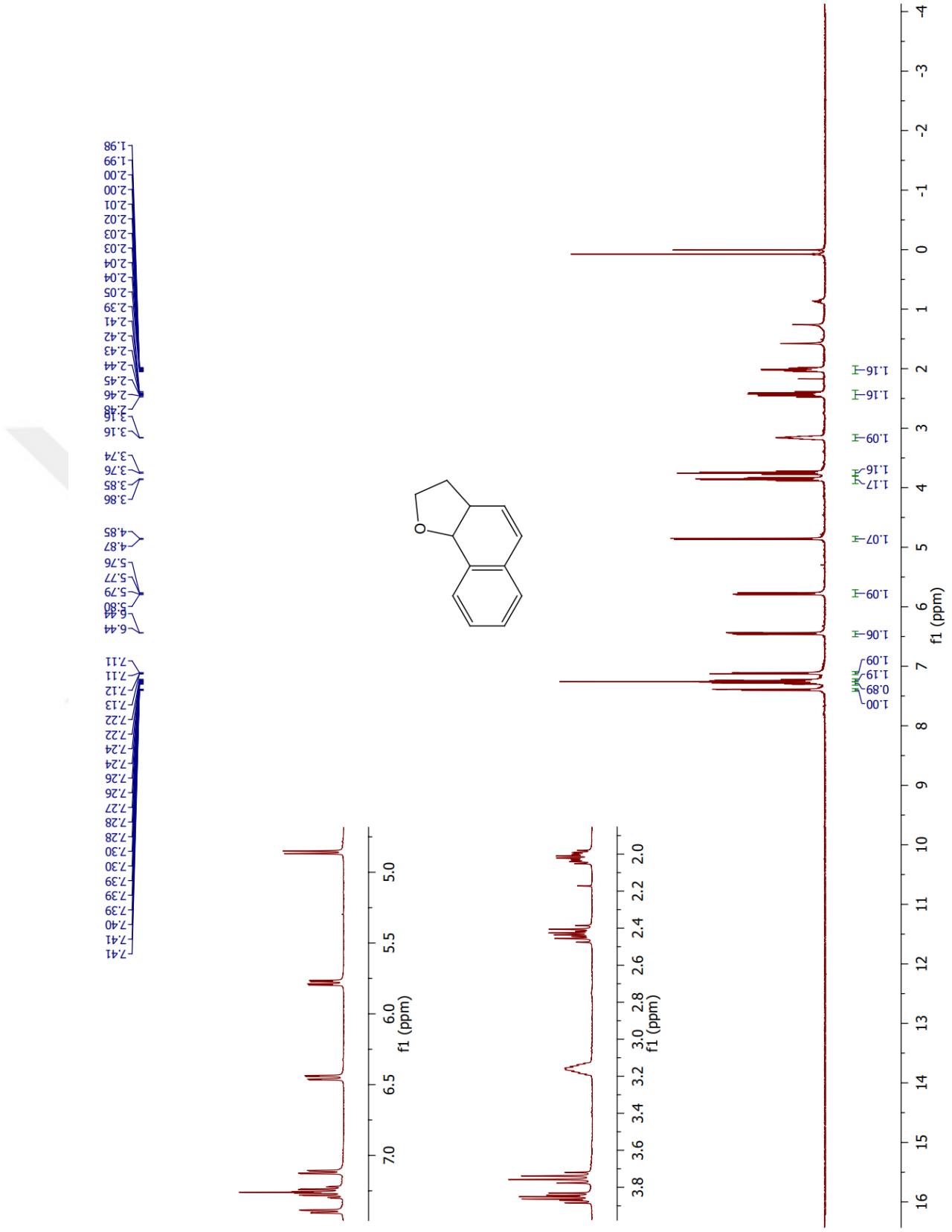


Figure 17: ^{1}H-NMR spectrum of compound **54** in $CDCl_3$

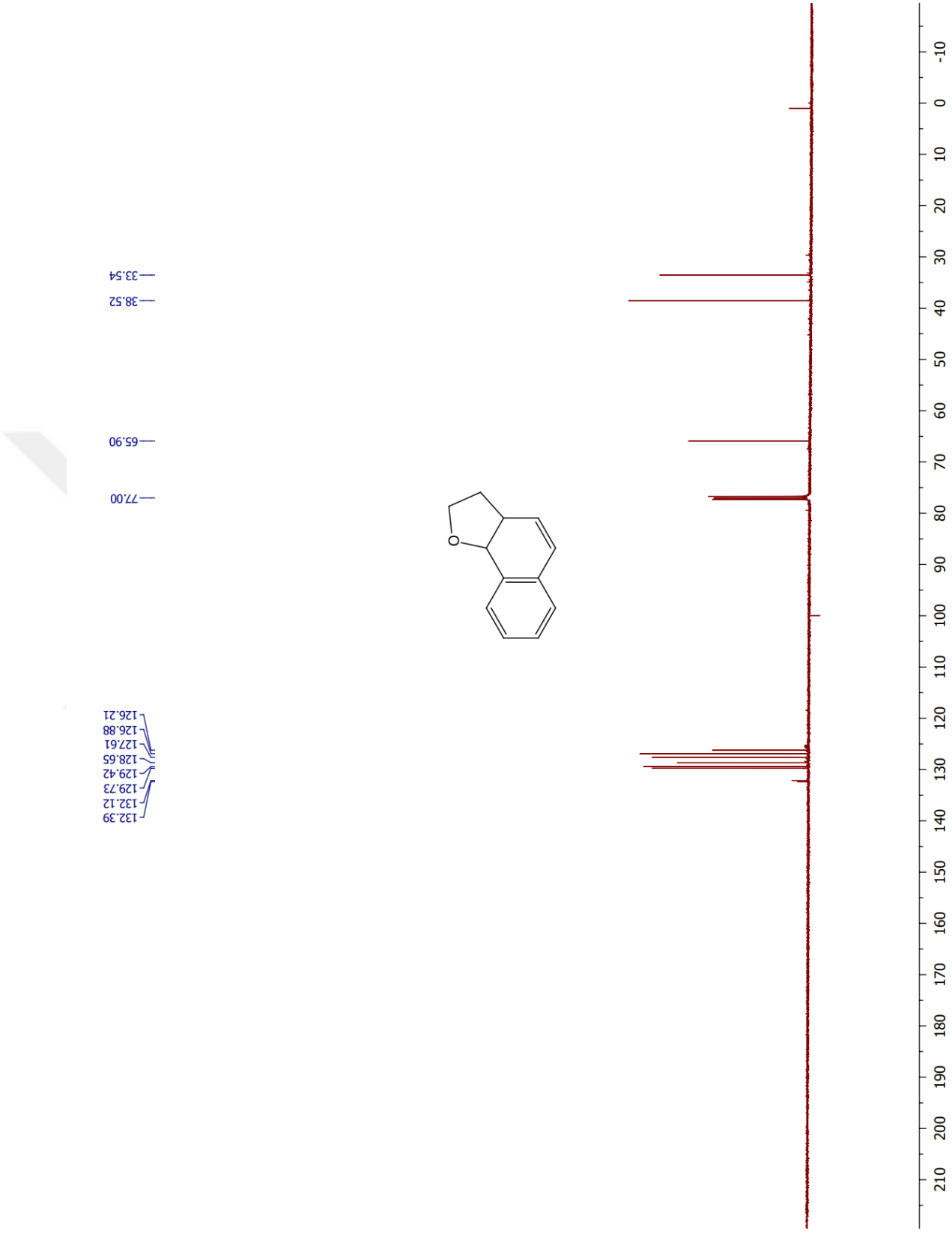


Figure 18: ^{13}C-NMR spectrum of compound **54** in $CDCl_3$

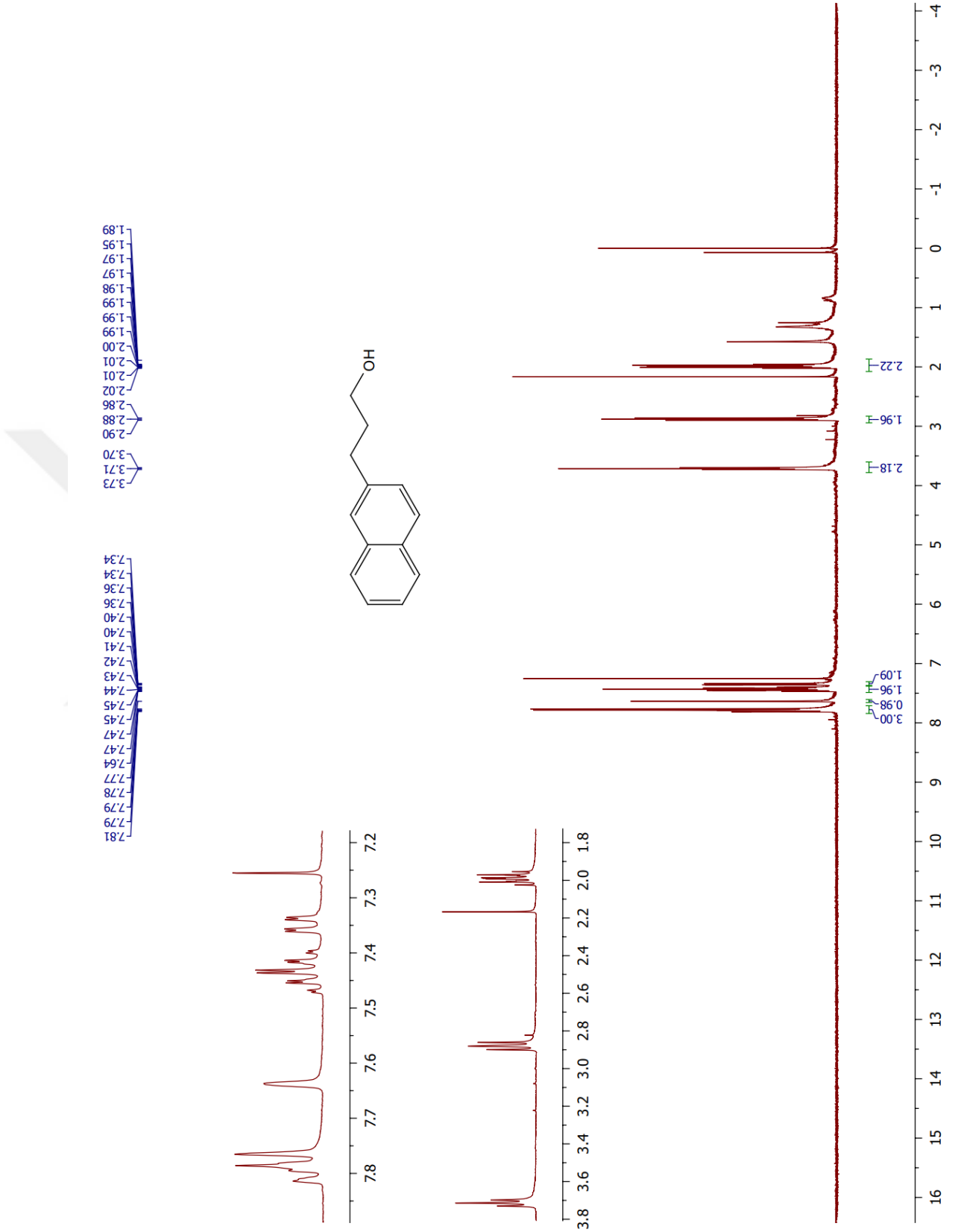


Figure 19: ^{1}H-NMR spectrum of compound **61** in $CDCl_3$

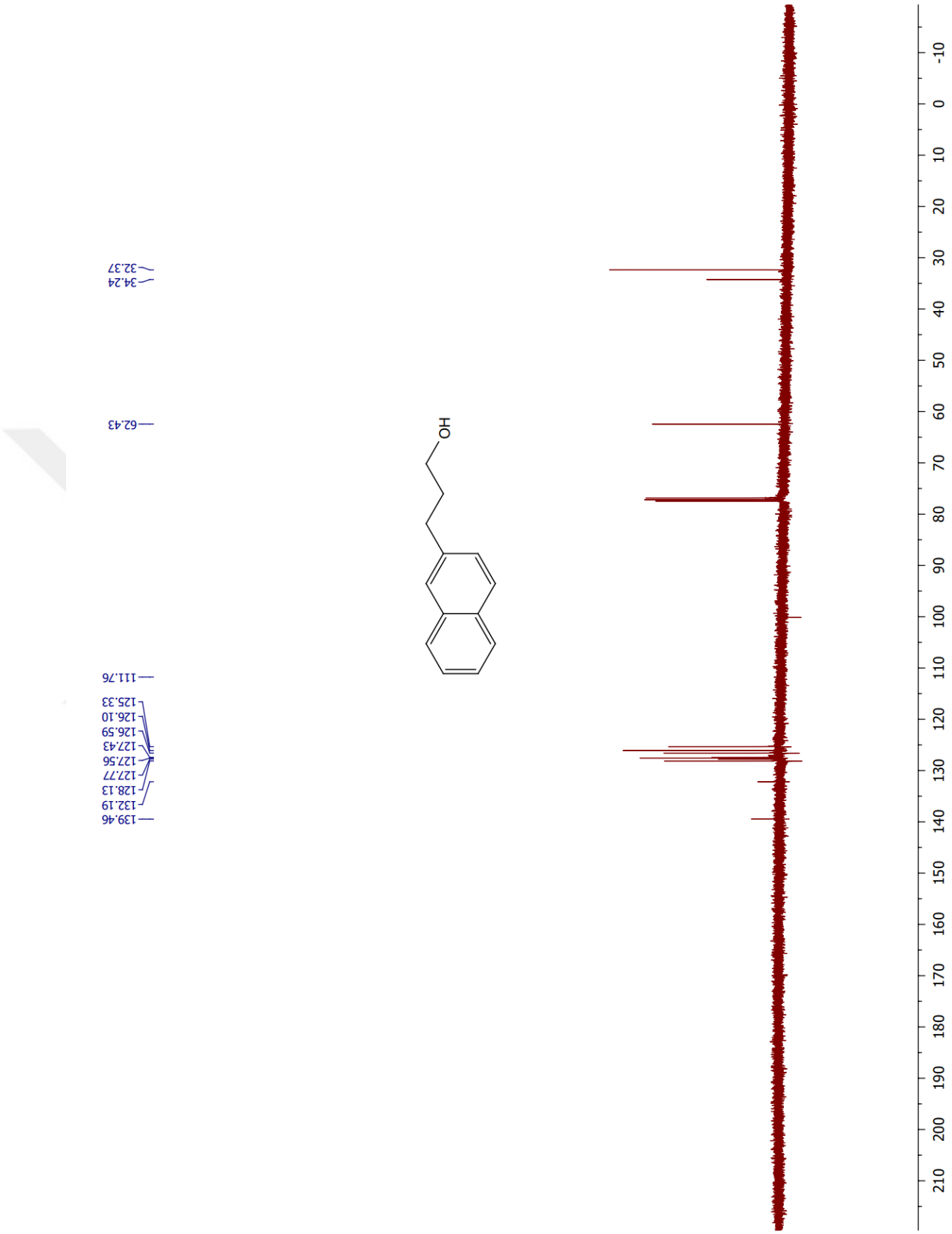


Figure 20: ^{13}C-NMR spectrum of compound **61** in $CDCl_3$

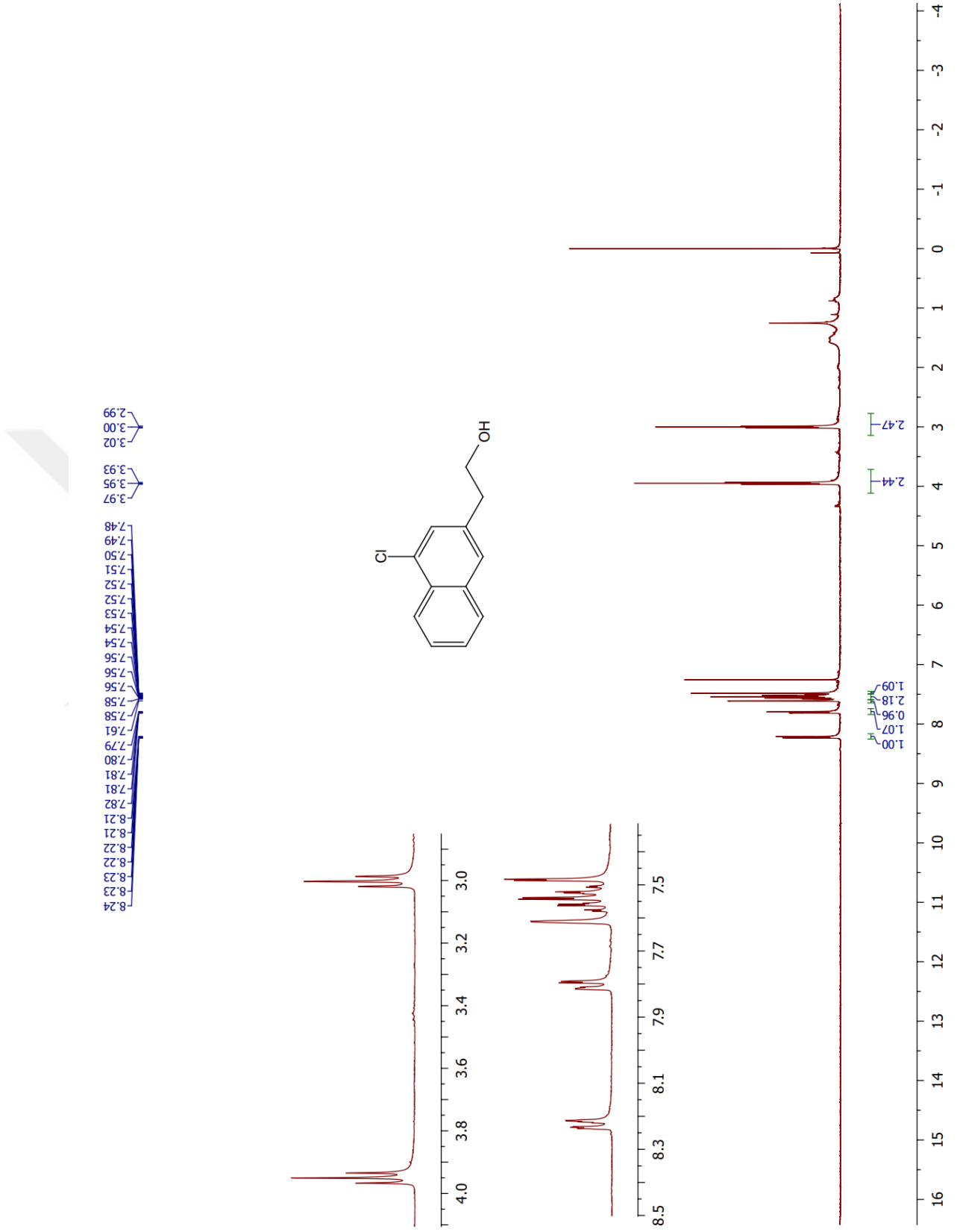


Figure 21: ^{1}H-NMR spectrum of compound **65** in $CDCl_3$

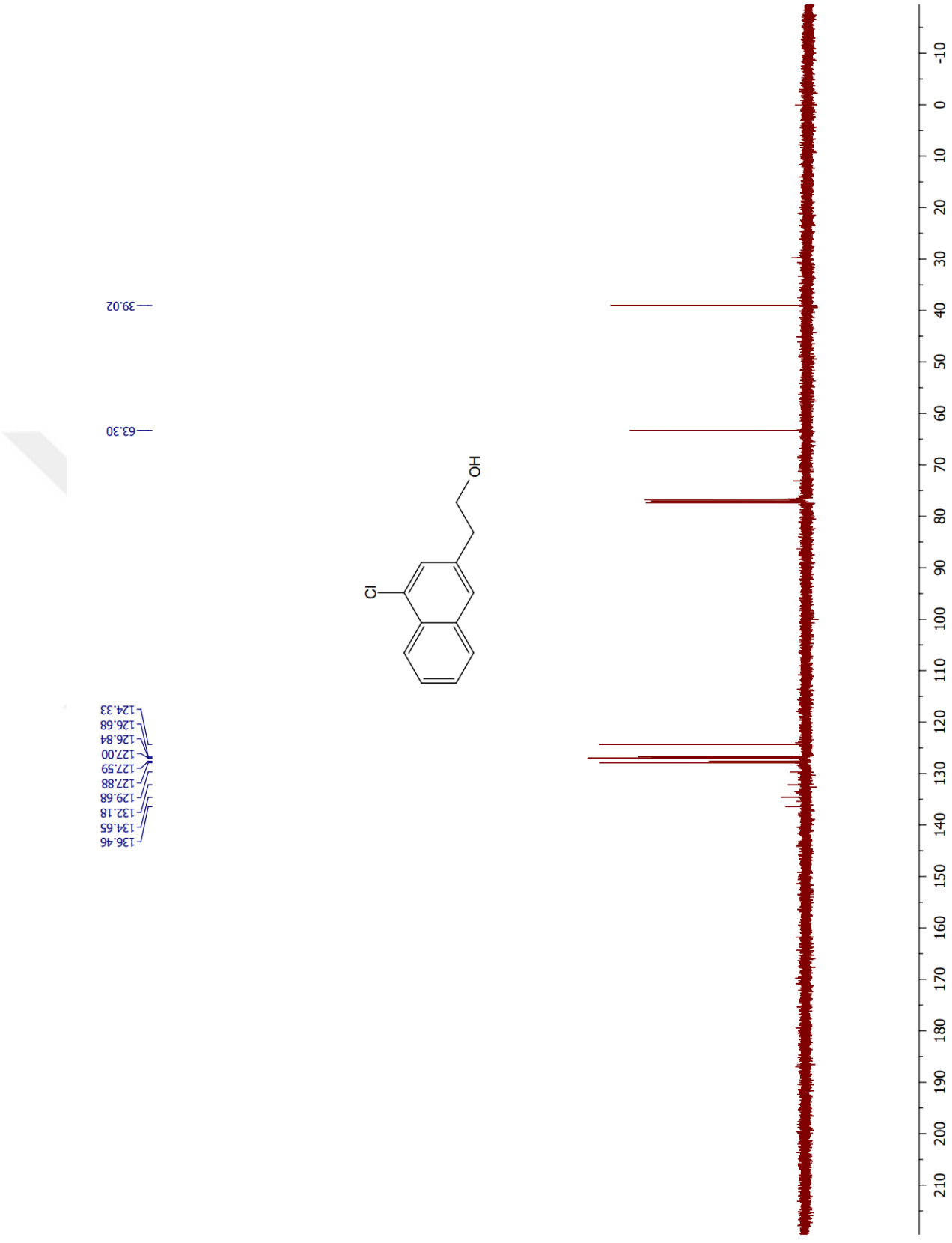


Figure 22: ^{13}C-NMR spectrum of compound **65** in $CDCl_3$

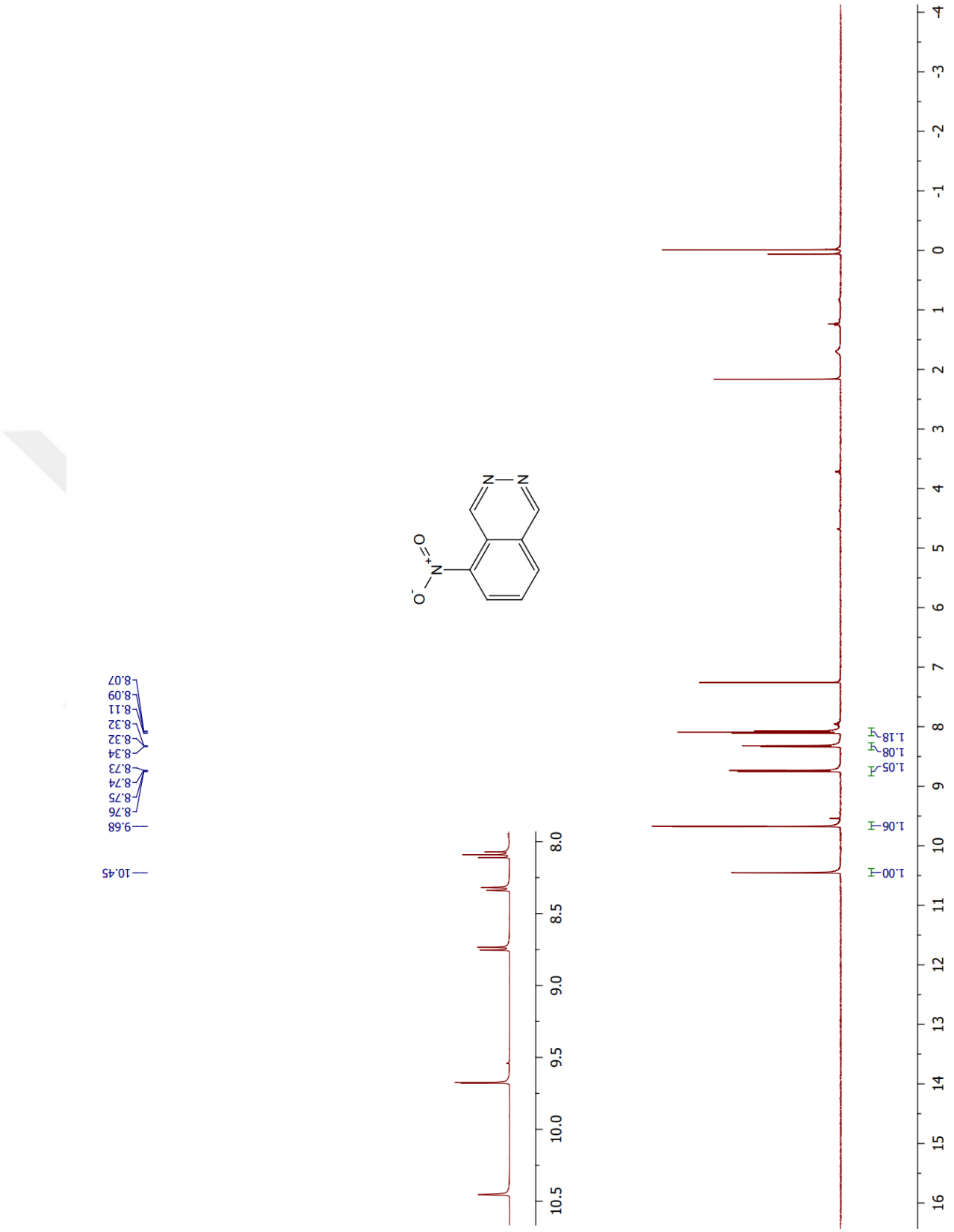


Figure 23: ^{1}H-NMR spectrum of compound **68** in $CDCl_3$

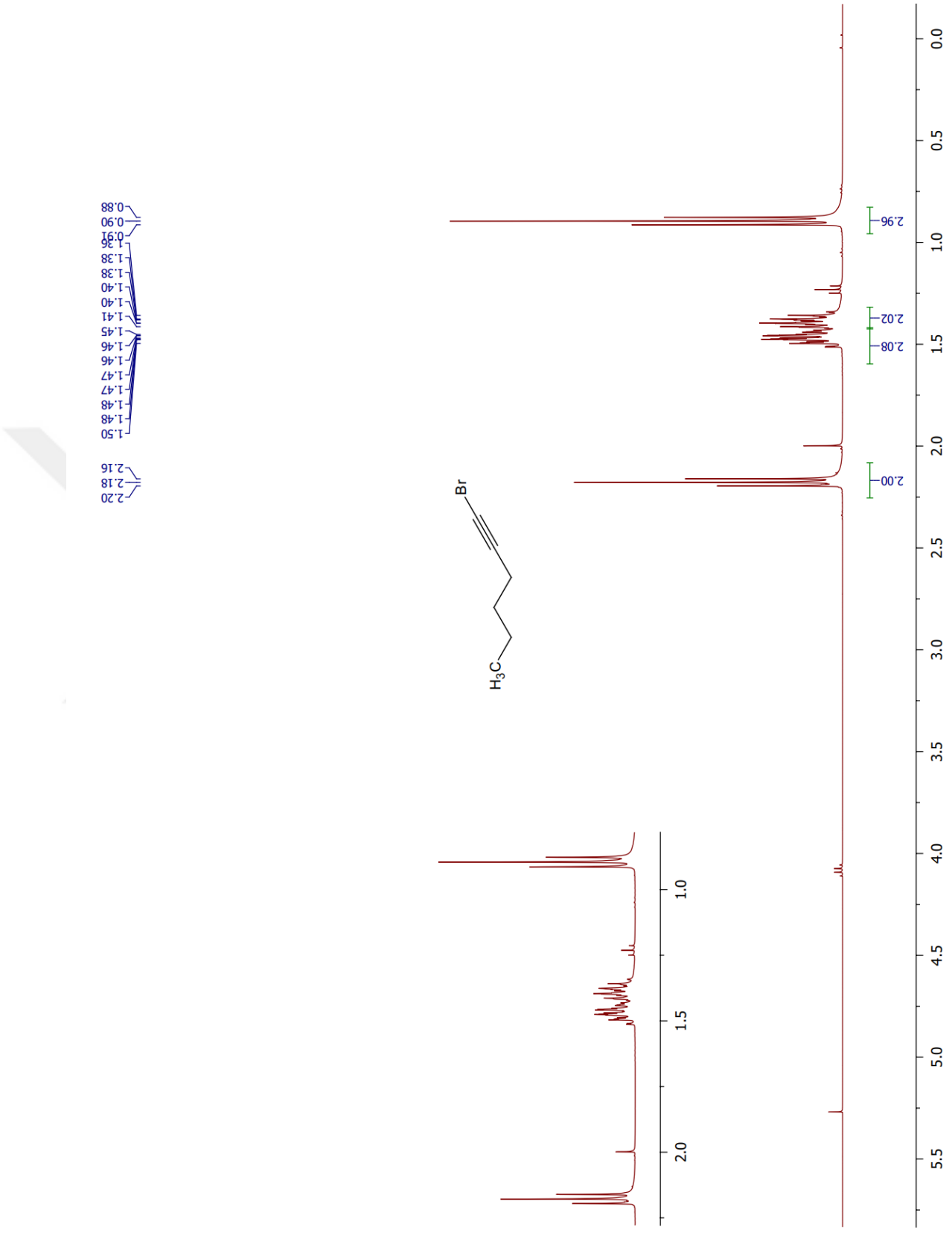


Figure 24: ^{1}H-NMR spectrum of compound **70** in $CDCl_3$

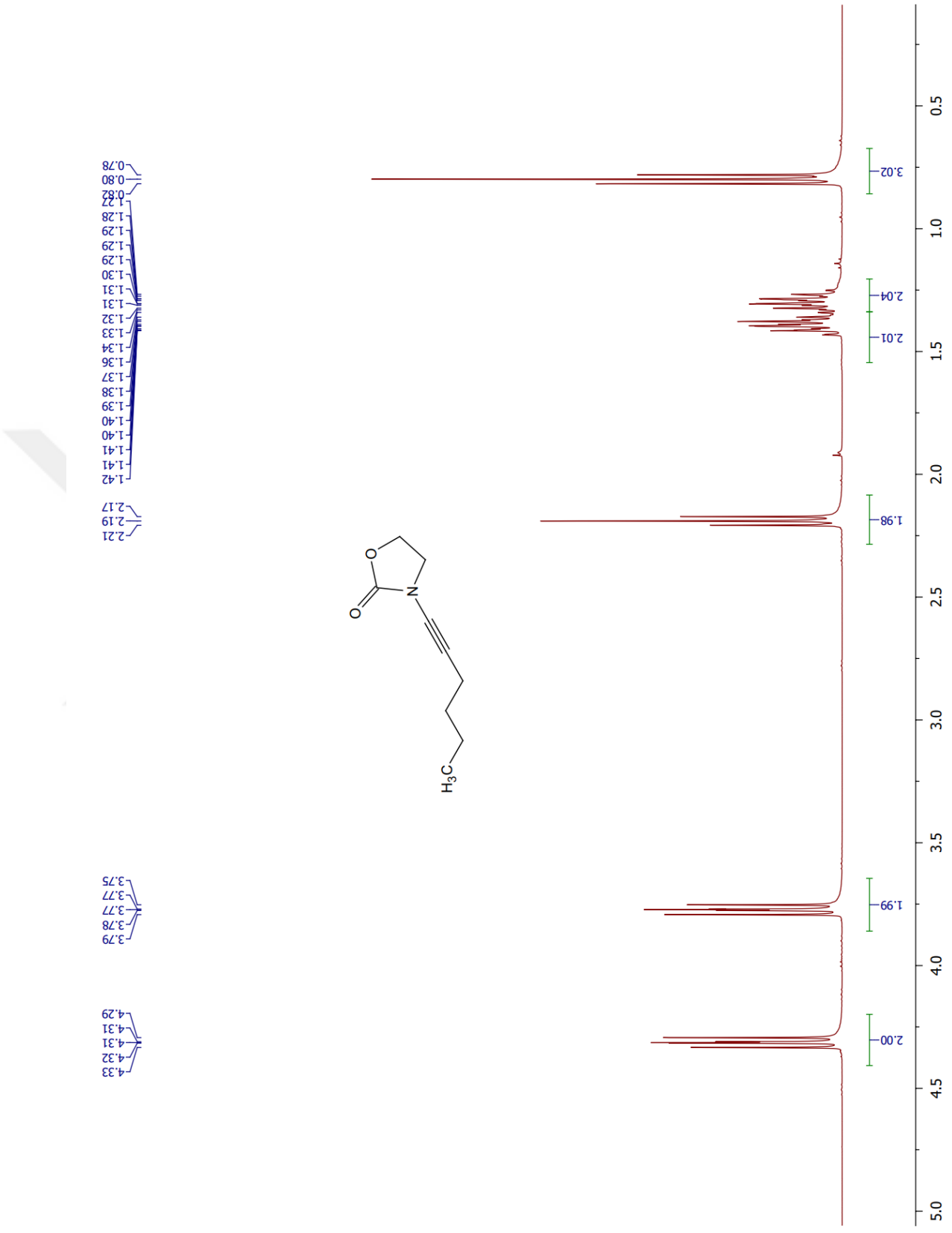


Figure 25: ^{1}H-NMR spectrum of compound **72** in $CDCl_3$

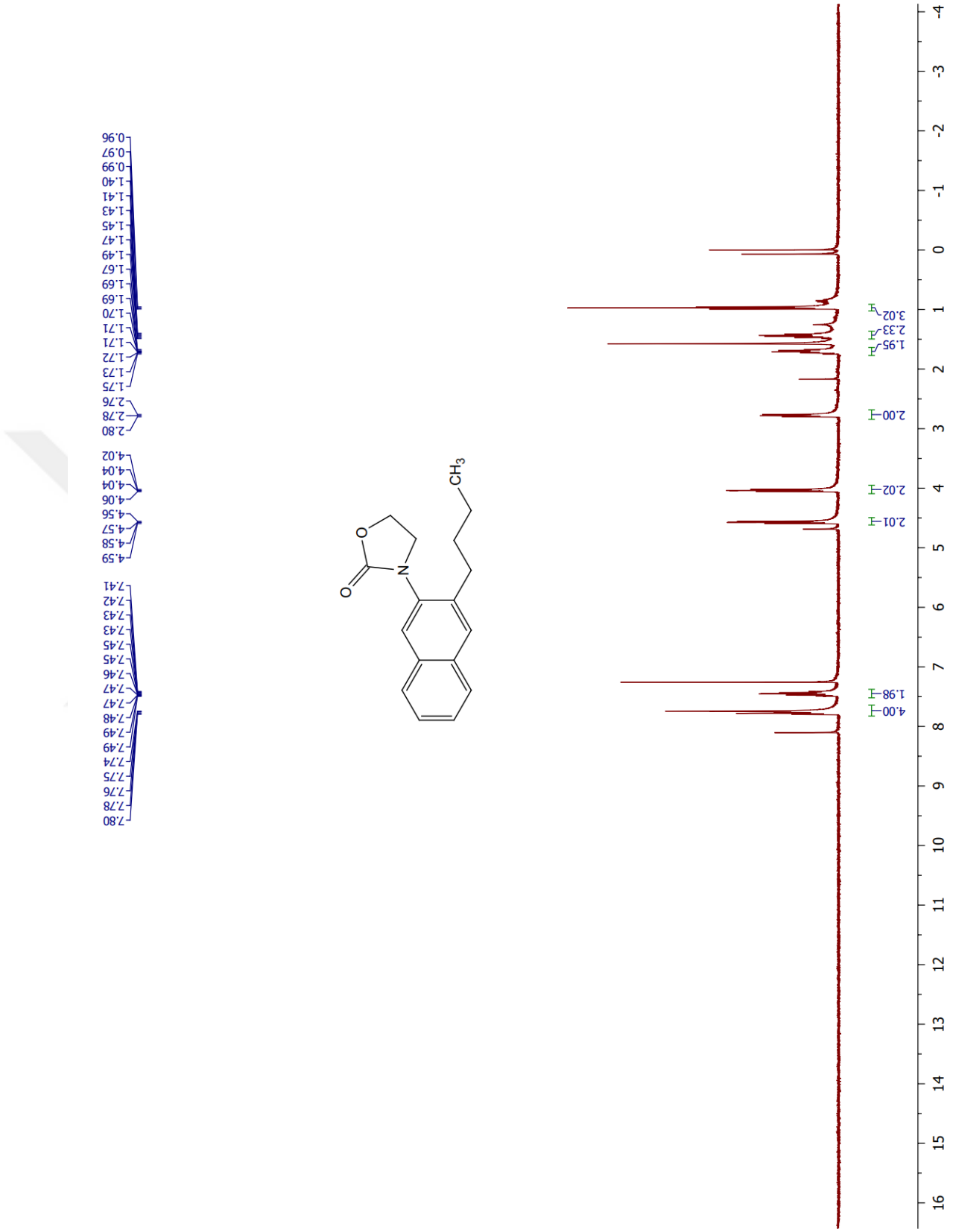


Figure 26: ^{1}H-NMR spectrum of compound **73** in $CDCl_3$

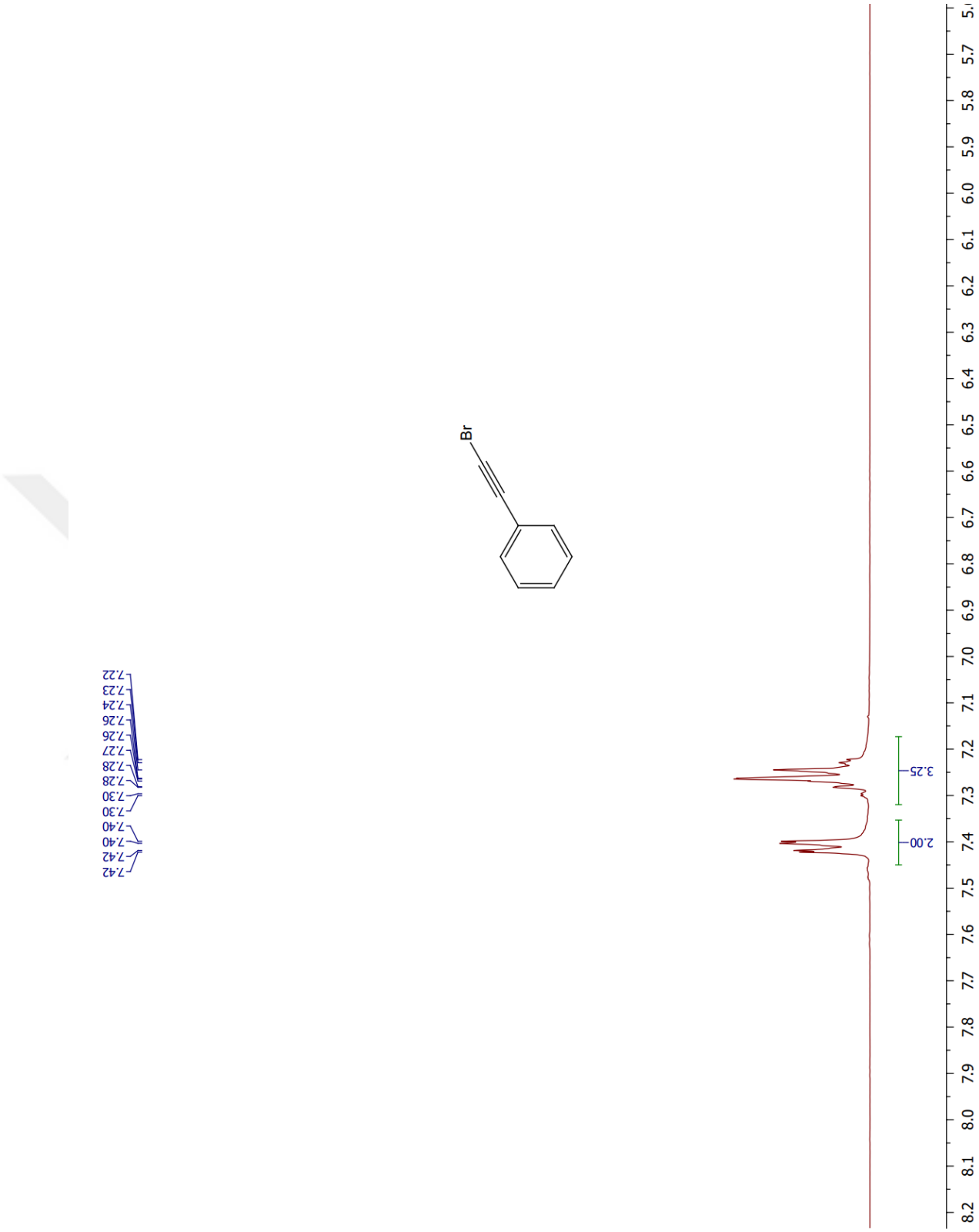


Figure 27: ^{1}H-NMR spectrum of compound **75** in $CDCl_3$

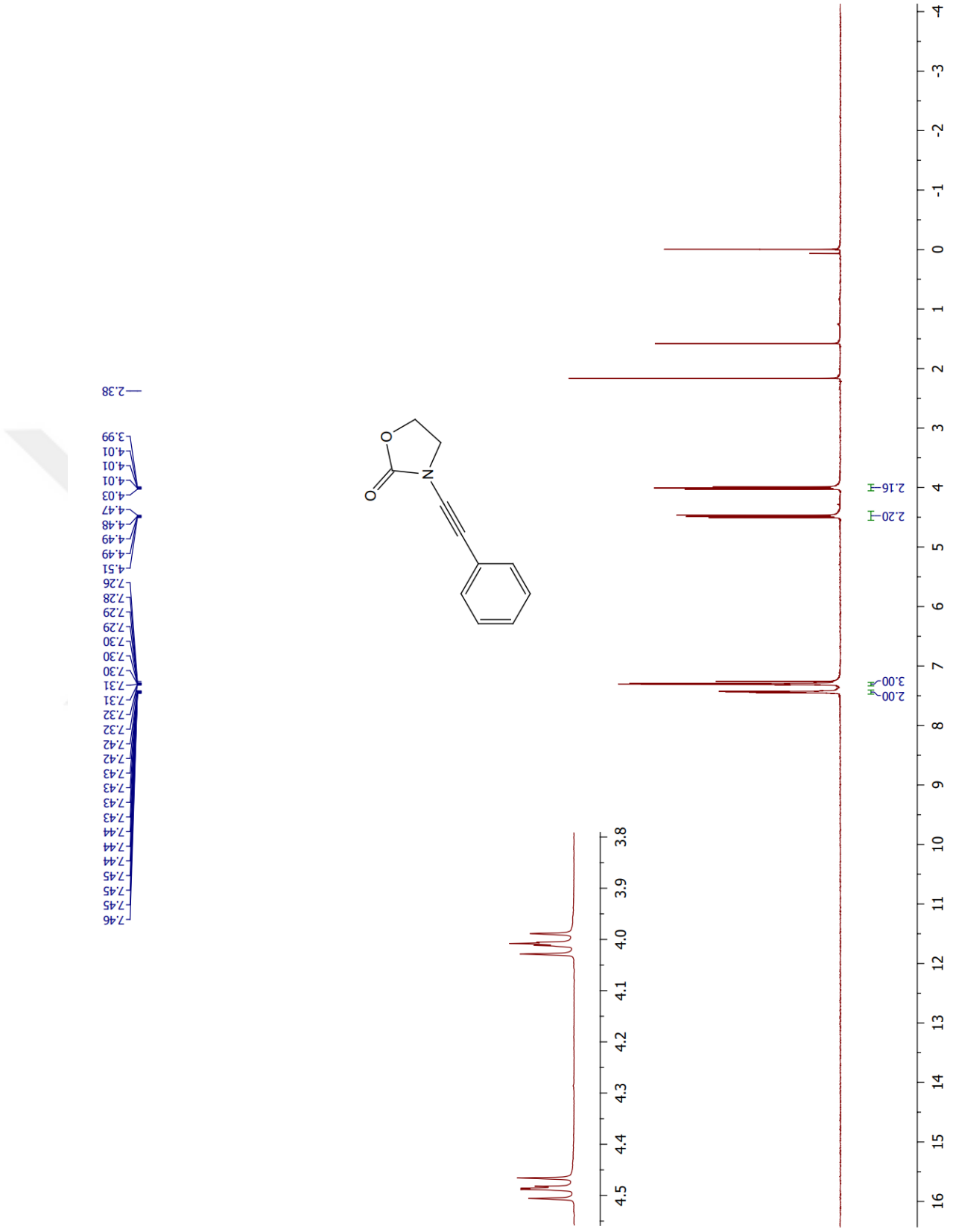


Figure 28: ^{1}H-NMR spectrum of compound **76** in $CDCl_3$

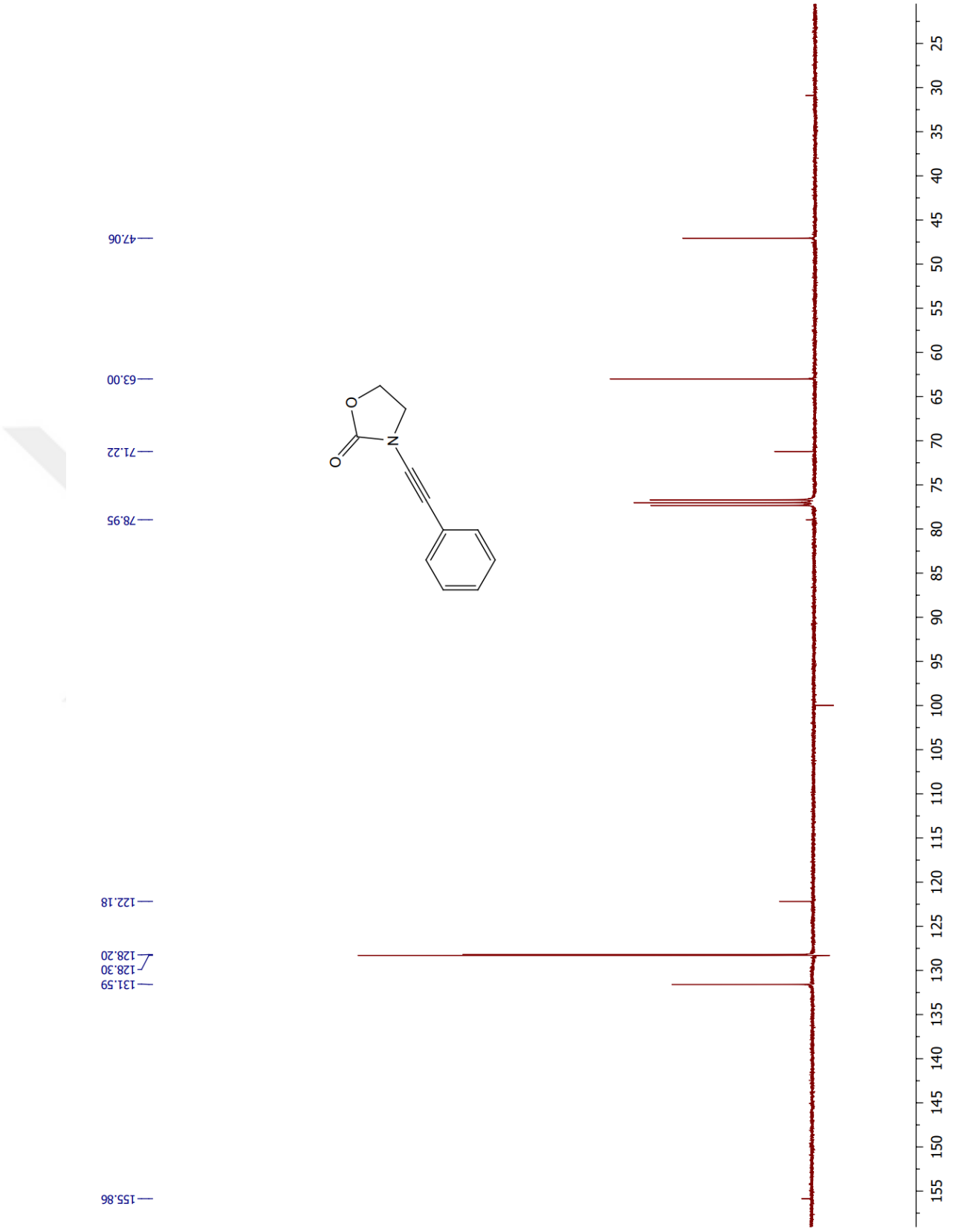


Figure 29: ^{13}C-NMR spectrum of compound **76** in $CDCl_3$

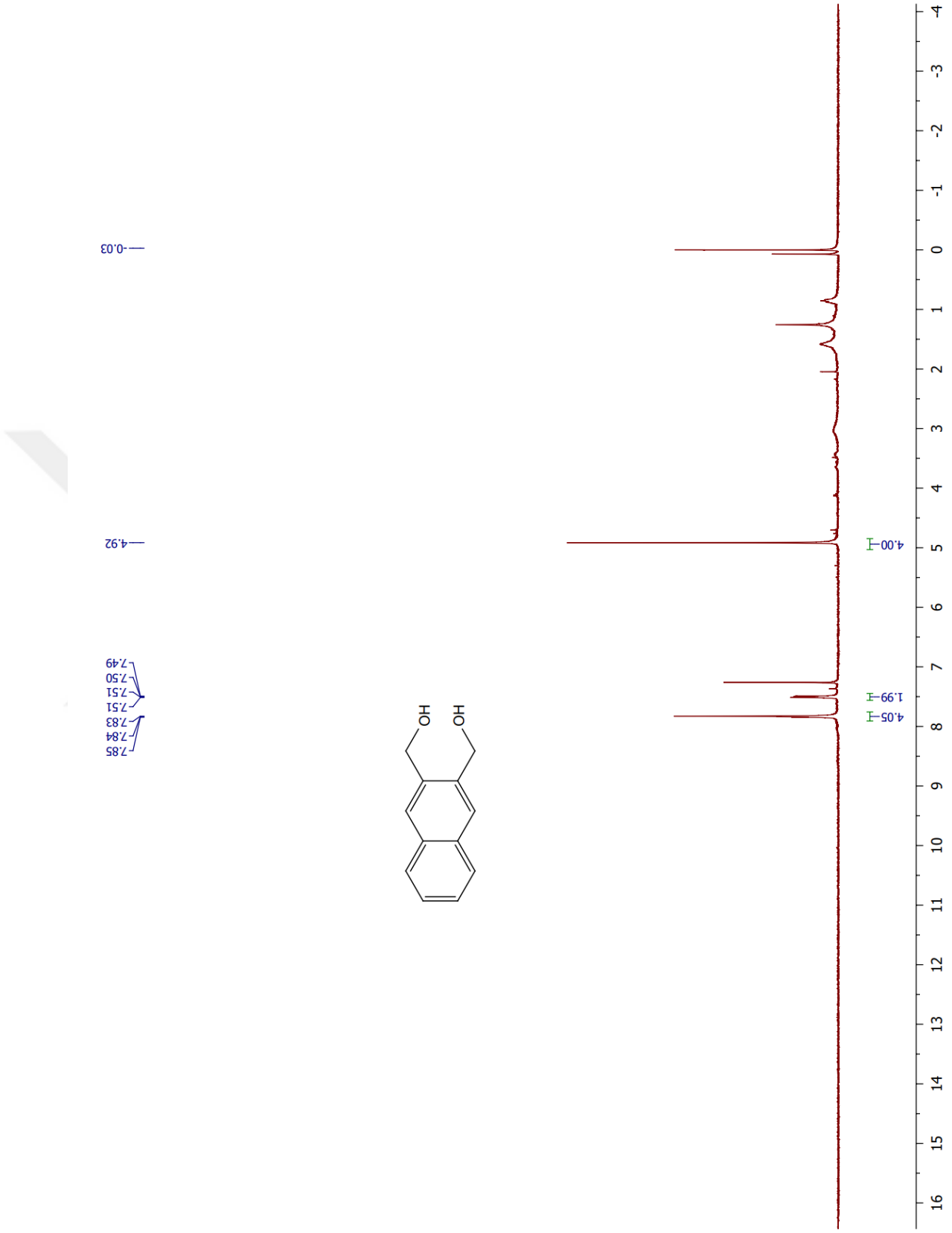


Figure 30: ^{1}H-NMR spectrum of compound **78** in $CDCl_3$

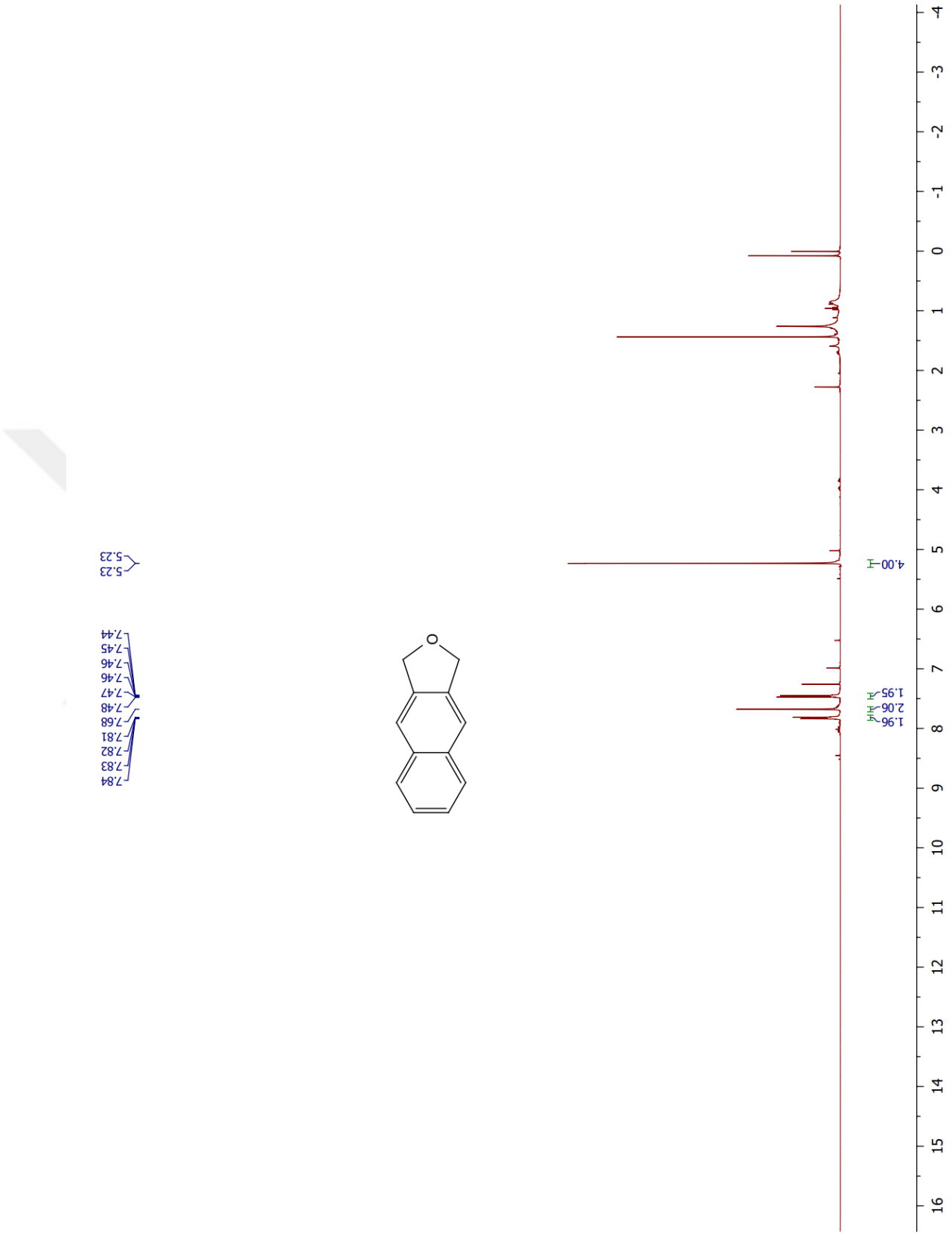


Figure 31: ^{1}H-NMR spectrum of compound **78a** in $CDCl_3$

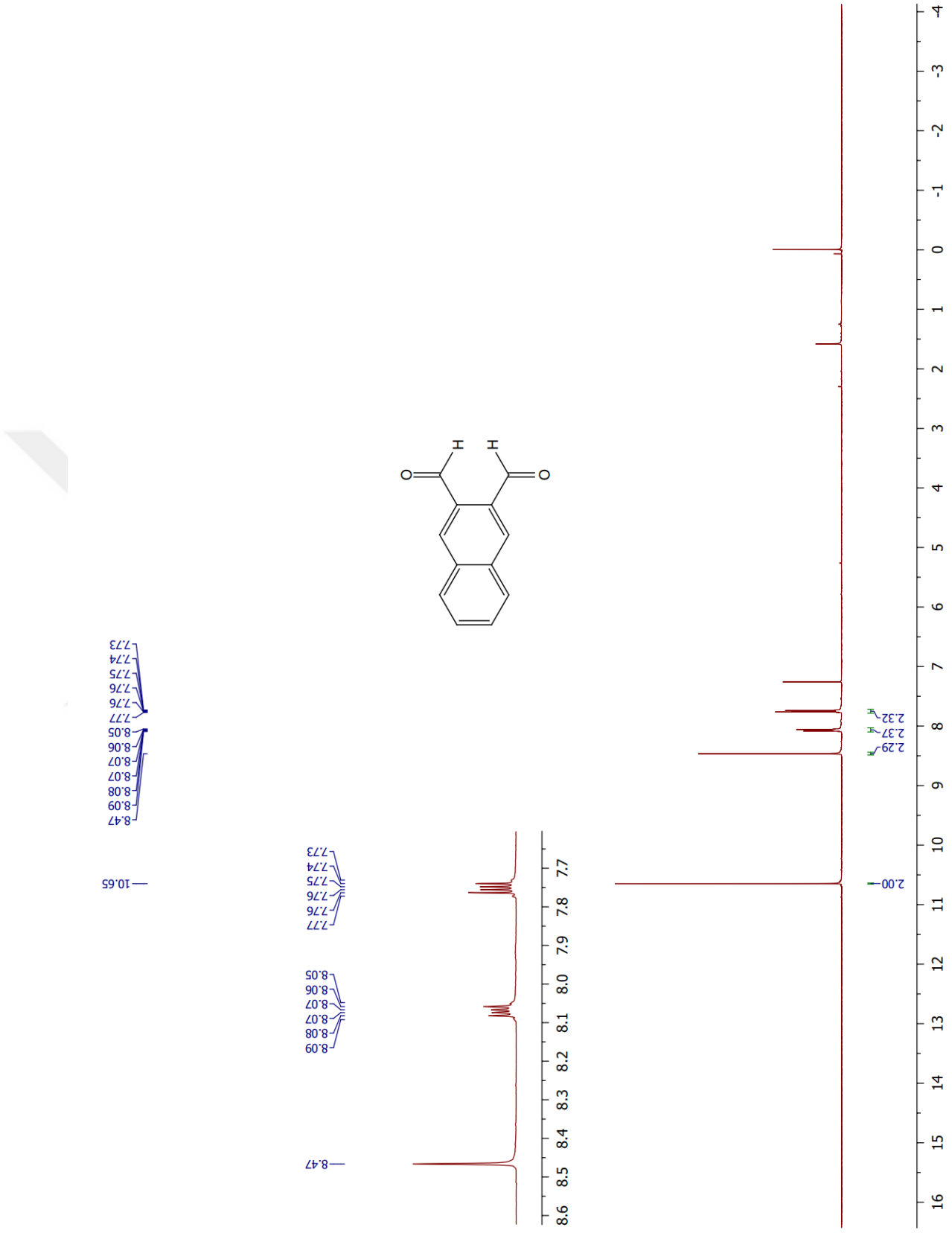


Figure 32: ^{1}H-NMR spectrum of compound **79** in $CDCl_3$

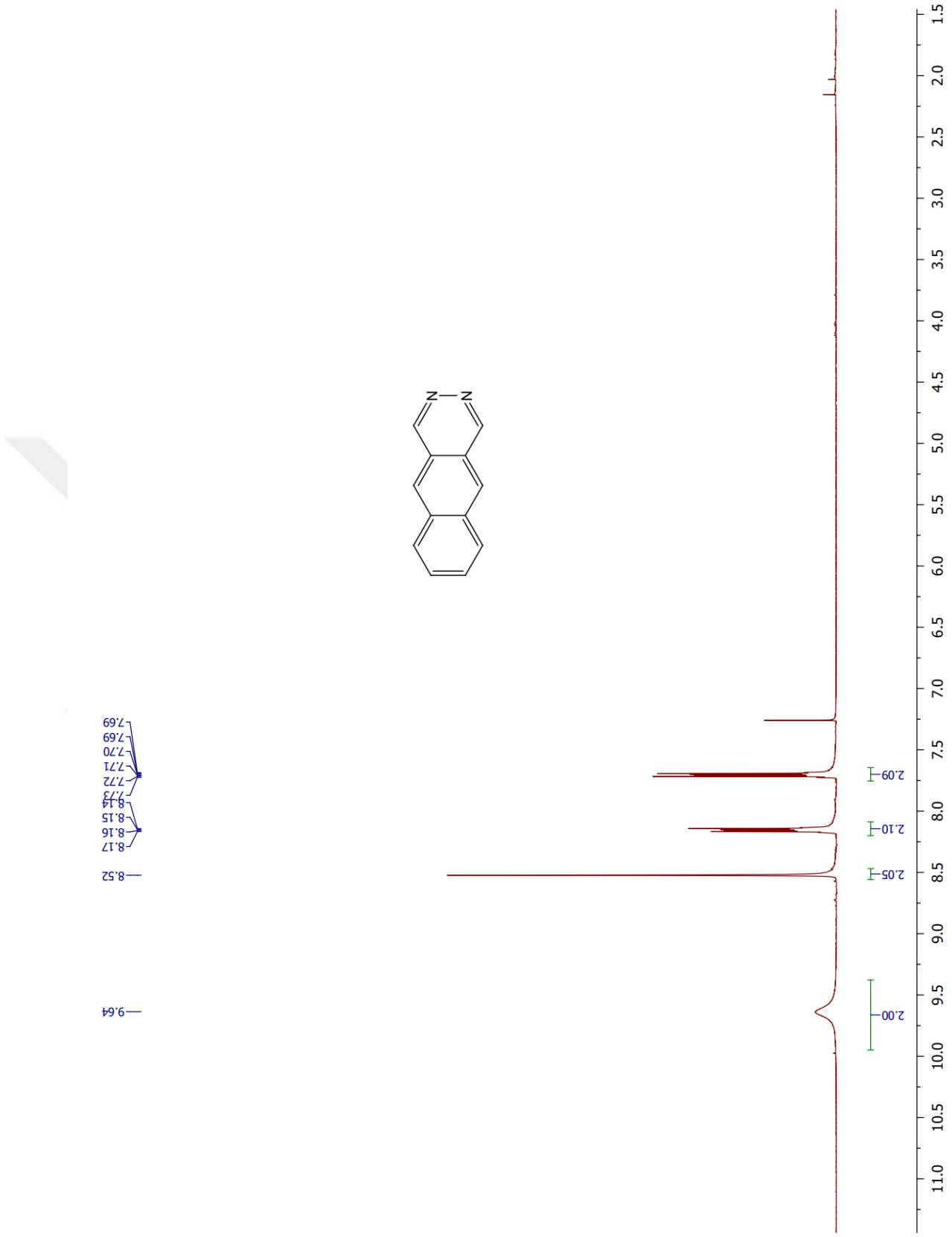


Figure 33: ^{1}H-NMR spectrum of compound **80** in $CDCl_3$

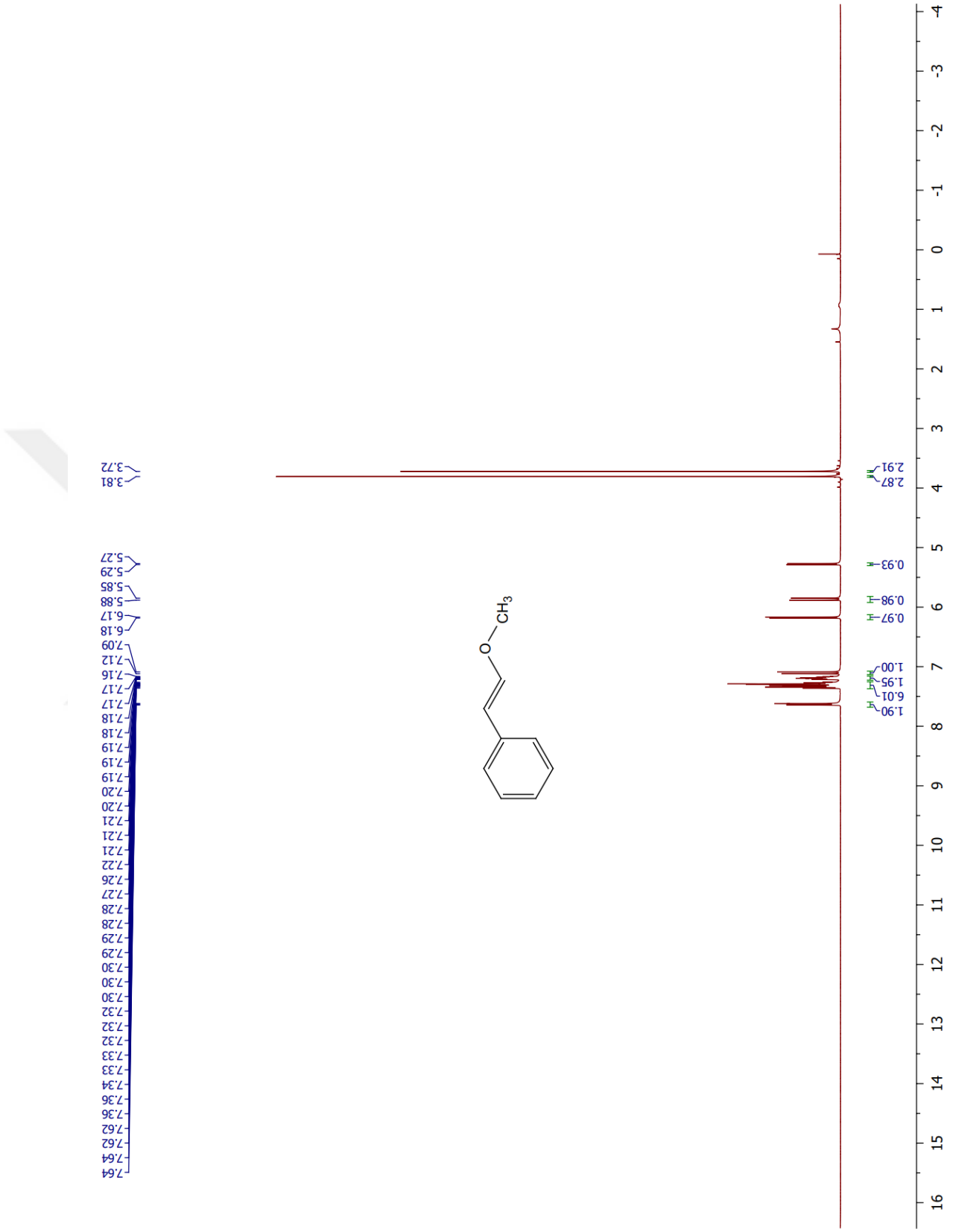


Figure 34: ^{1}H-NMR spectrum of compound **86** in $CDCl_3$

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