REDUCTION OF α, β-ALKYNYL CARBONYL COMPOUNDS USING $SnCl_2$ AND COMPUTATIONAL INVESTIGATION OF THE REACTION MECHANISM

MASTER OF SCIENCE

in

CHEMISTRY

U RALEPELLE

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BY

Ursula Ralepelle

DISSERTATION

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at the

UNIVERSITY OF LIMPOPO

Supervisor: PROF W NXUMALO

Co-supervisors: PROF HR CHAUKE

: PROF I CUKROWSKI (UP)

2023

DECLARATION

I hereby declare that “Reduction of α, β-alkynyl carbonyl compounds using $SnCl_2$ and computational investigation of the reaction mechanism” presented in this dissertation is my own work. It is being submitted in fulfilment of the degree Master of Science at university of Limpopo. It has not been submitted previously by someone at any University. It is my design and all the material for reference within has been fully acknowledged.

Signature..... 

Signed at .....Turfloop.....on ...22.....day of.....September.....2023

DEDICATION

The work developed in this study is dedicated to my mother Hellen Tebogo Phalane, my late father Andria Buti Ralepelle, my siblings Mpho, Meriam, Queen Ralepelle, victor mushwana and my family at large.

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SCIENTIFIC CONTRIBUTIONS

- Conference attended: FSA, SACI -NS Chemist Symposium and 44th SACI National Convention.
- Oral presentation at: 12th Faculty of Sciences and Agriculture, University of Limpopo Research Day Date: 21-23 September 2022 (see appendix)
- Oral presentation at: SACI-NS YOUNG CHEMIST SYMPOSIUM, hosted by the University of Pretoria Tshwane, on the 28th of October 2022.
- Poster and flash presentation at: 44th SACI National Convention at Stellenbosch from 8-13 January 2023.

Awards

Second position in Oral presentation at: 12th Faculty of Sciences and Agriculture, University of Limpopo.

Reduction of α, β-alkynyl carbonyl compounds using $SnCl_2$ and computational investigation of the reaction mechanism

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The development of an efficient method for the reduction of α, β - alkynyl carbonyl compounds, is mostly important in organic synthesis, playing a crucial role in the synthesis of useful intermediates in the manufacturing of medicine, pesticides, production of polymers and other valuable chemicals. From the literature, no reaction was reported when Tin(ii) chloride ($SnCl_2$) was used for the reduction of alkyne to alkane. The aim of this research is to investigate the reduction of conjugated α, β - alkynyl carbonyl compounds into alkanes using commercially available $SnCl_2$ and other metal salts known to reduce the nitro group, such as iron (Fe) and zinc (Zn). Our approach to the synthesis of 1-(6-nitroquinoxaline-2-yl) hex-1-yn-3-one, involves the use of 6-nitroquinoxalin-2-yl-benzenesulfonate compound as a substrate for Sonogashira cross coupling with terminal alkyne to give appreciable yield of 1-(6-nitroquinoxalin-2-yl)hex-1-yn-3-ol compound, followed by oxidizing using PCC or jones reagent to give 1-(6-nitroquinoxalin-2-yl)hex-1-yn-3-one. The oxidised product was used for reduction reaction at different temperatures, time and equivalences of $SnCl_2$. Our desired product was obtained with yields ranging from 17.77 -71.34%. The optimised conditions were extended to other α, β - alkynyl carbonyl compounds such as 1-(pyrimidine-2-yl)hex-1-yn-3-one and 1-(pyrazine-2-yl)hex-1-yn-3-one, and were found to be effective. Computational studies are currently underway to understand the mechanism involved at a molecular level.

Keywords: α, β - alkynyl carbonyl, $SnCl_2$, Sonogashira cross coupling.

Flash presentation at: 44th SACI National Convention at Stellenbosch from Royal Society of Chemistry.

ROYAL SOCIETY OF CHEMISTRY

Flash Presentation Award

This is to certify that

Ursula Ralepelle

has been awarded a Flash Presentation Award from ***Dalton Transactions*** at the

44th SACI National Convention

Stellenbosch, South Africa

8-13 January 2023

Sally Howells
Executive Editor, *Dalton Transactions*

Registered charity number: 207890

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LIST OF ABBREVIATIONS

A	
NH_4Cl	Ammonium chloride
B	
brs	Broad singlet
D	
D	Debye
DFT	Density functional theory
$CDCl_3$	Deuterated Chloroform
D_2O	Deuterium oxide
DMSO	Dimethyl Sulfoxide
DMF	N, N-Dimethylformamide
DCM	Dichloromethane
DMAP	Dimethyl amino pyridine
˚C	Degree Celsius
d	Doublet
dd	Double of doublets
E	
Eq.	Equivalence
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_3N	Triethylamine
E_{gap}	Energy Gap
eV	Electron volts
F	
Fe	Iron
FMOs	Frontier Molecular Orbitals
G	
GC	Gradient Corrected
ΔG	Change in Gibbs energy

H	
HRMS	High resolution mass spectrometry
HCl	Hydrochloric acid
Hz	Hertz
H_2O	Water
HF	Hartree-Fock
J	
J	Coupling constant.
K	
KOH	Potassium hydroxide
K	Kelvin
L	
LDA	Local Density Approximation
M	
MNDO	Modified Neglect of Differential Overlap
mL	Milli litre
Min	Minutes
MP	Melting point
m	Multiplet
$MgSO_4$	magnesium sulphate
N	
NMR	Nuclear magnetic resonance
$NaHCO_3$	Sodium hydrogen carbonate
P	
%	Percentage
ppm	part per million
PCC	Pyridium Chlorochromate
(Ph_2S)	Diphenyl sulphide
R	
RMS	Root mean square
S	
$SnCl_2$	Tin (II) chloride

SCF	Self-Consistent Field method
T	
TB	Tuberculosis
THF	Tetrahydrofuran
TLC	Thin layer chromatography
t	Triplet
Z	
Zn	zinc

ABSTRACT

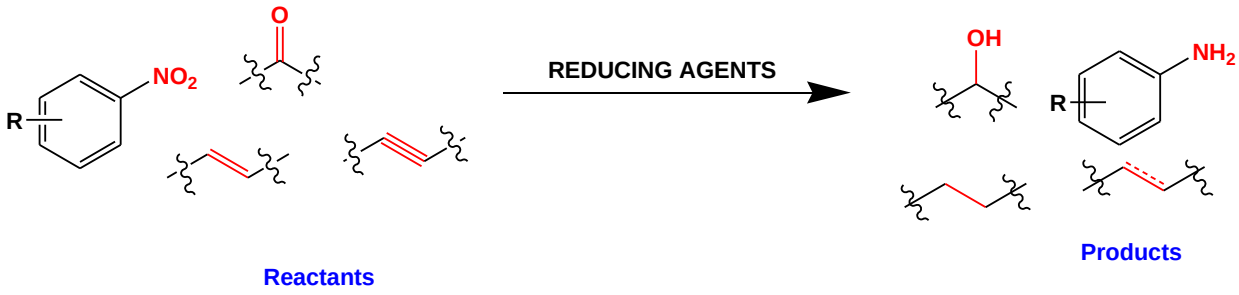
The development of an efficient method for the reduction of α, β-alkynyl carbonyl compounds, is mostly important in organic synthesis, playing a crucial role in the synthesis of pharmaceuticals, pesticides, polymers, and other valuable chemicals. From the literature, no reaction was reported when tin (II) chloride ($SnCl_2$) was used for the reduction of alkyne to alkane. The aim of this research was to investigate the reduction of conjugated α, β-alkynyl carbonyl compounds into alkanes using commercially available $SnCl_2$ and other metal salts known to reduce the nitro group, such as iron (Fe) and zinc (Zn). Our approach to the synthesis of 1-(6-nitroquinoxaline-2-yl)hex-1-yn-3-one **17**, involves the use of 6-nitroquinoxalin-2-yl-benzenesulfonate **34** as a substrate for Sonogashira cross coupling with terminal alkyne to give appreciable yield of 1-(6-nitroquinoxalin-2-yl)hex-1-yn-3-ol **35**, followed by oxidizing using PCC or Jones reagent to give 1-(6-nitroquinoxalin-2-yl)hex-1-yn-3-one **17**. The oxidised product was used to optimise the reduction reaction at different temperatures (˚C), time (hours), and equivalences of $SnCl_2$. Our first desired product **19** was obtained with yields ranging from 18 - 47%, with alkyne and nitro reduced to alkane and amine respectively when using 5 equivalents of $SnCl_2$. During the optimisation, compound **17** also produced compound **36** with yields ranging from 45-80% with only reduced alkyne to alkane and nitro remaining unchanged, when number of equivalences of $SnCl_2$ were reduced to 2 eq. We then introduced the oxidised compound **42** since it contains chloride instead of the nitro and we manage to reduce the alkyne to afford compound **43** with yields ranging from 55-73%. The optimised conditions were extended to other α, β-alkynyl carbonyl compounds such as 1-(pyrazine-2-yl)hex-1-yn-3-one **46**, 1-(pyrimidine-2-yl)hex-1-yn-3-one **51** and 1-(pyridine-2-yl)hex-1-yn-3-one **55**. All the compounds **46**, **51**, successfully reduced to give the corresponding alkanes (**47** & **48**, **52**, **56**). After successful reduction of all the compounds mentioned above using $SnCl_2$, we then introduced other reducing agents such as iron (Fe) and Zinc (Zn) powder, following different methods from the one of $SnCl_2$, they were able to reduce the alkyne from **42** into the alkane **43** and gave the excellent yield of 65-100% when using Zn powder and range of 60-96% when using Fe powder. However, when we introduce compound **17**, the reduction took place only on the nitro instead of alkyne.

Computational studies were carried out to understand the mechanism involved at a molecular level in a relevant ethyl acetate solvent. Geometric optimisation calculations have been performed in gaseous phase by employing density functional theory-based code gaussian with RB3LYP/6-311++G (d. p) basis set. Geometrical, thermodynamical, and molecular orbitals have been calculated to investigate structural and chemical behaviour of the molecules. Among the investigated pyrazine derivatives in gaseous phase, compound **46** was found to have highest negative energy value of -24.866 Hartree/atom with short bond length between $C_{10}{\equiv}C_{11}$ of 1.195 Å as compared to compound **47** and **48**. The results revealed that compound **48** has a superior stability and lower chemical reactivity as compared to compound **46** and **47**, since its corresponding energy gap between HOMO (-0.32937) and LUMO (-0.17780) is lager, having E_{gap} = 0.15157 eV.

CHAPTER 1: INTRODUCTION

1. Introduction

Reduction is the gain of electrons, loss of oxygen or decrease in oxidation state of a chemical or atom within it. In organic chemistry it is defined as a chemical reaction in which hydrogens are added to an unsaturated molecule having a C=X or C≡X, where X= carbon (C), oxygen (O), and nitrogen (N) to give the corresponding saturated molecule in the presence of reducing agents such as lithium aluminum hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$) and transition metals combined with hydrogen H_2 gas as shown in **Scheme 1**[1].



Scheme 1: Reduction of functional group (nitro, carbonyl, alkene, alkyne) in the presence of reducing agents.

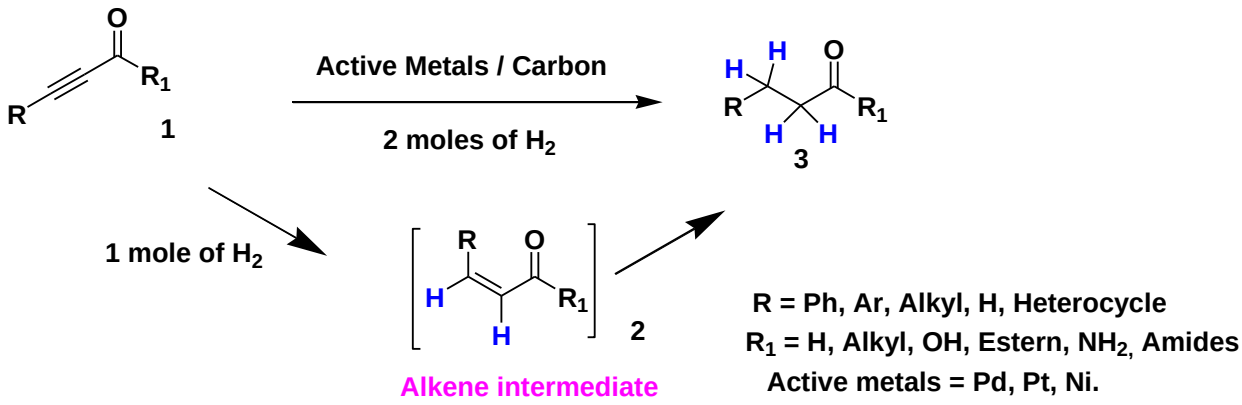
Reduction reaction is one of the most widely used methods for addition of hydrogen to unsaturated hydrocarbons, it is also called catalytic hydrogenation [2]. Unsaturated hydrocarbons including alkynes (C≡C) and alkenes (C=C) can be reduced to corresponding alkanes (single bond) with the use of heterogenous and homogenous catalysts. Reduction reaction is one of the most important reactions in organic chemistry due to its synthetic importance both in the laboratory and in industry, especially with regards to the synthesis of pharmaceutical drugs and fine chemicals [3].

1.1. Heterogenous catalytic hydrogenation

The hydrogenation process of highly unsaturated organic compounds such as alkynes and alkenes can be implemented on supported metal catalyst in which the d-metals serve as active components. The active metals include palladium (Pd), platinum (Pt), and nickel (Ni) [4]. These metals are insoluble in reaction medium and are adsorbed

onto a solid support, such as activated carbon, alumina, calcium carbonate or barium sulphate. Owing to their high capability for hydrogen activation, noble metal supported catalysts, display excellent activity and selectivity. Nevertheless, their exorbitant cost limit their wide applications in the industries [5].

Standard heterogeneous hydrogenation results in complete reduction of alkynes **1** to alkanes **3** in the presence of two molar equivalent of H_2 gas with metal catalyst (Pt, Pd, Ni) [6]. However, using one molar equivalent of H_2 will not prevent hydrogenation of the alkene. Upon the use of one molar equivalent of hydrogen gas, the product of alkenes is produced and the starting material of the molecules' containing alkyne is recovered, since there are not enough hydrogen atoms to react with all the alkyne molecules. For the reduction of alkynes **1** to alkenes **2**, chemo selectivity is required to differentiate between reduction of alkynes and alkene and require the control over cis-or trans- geometry (**Scheme 2**) [7].

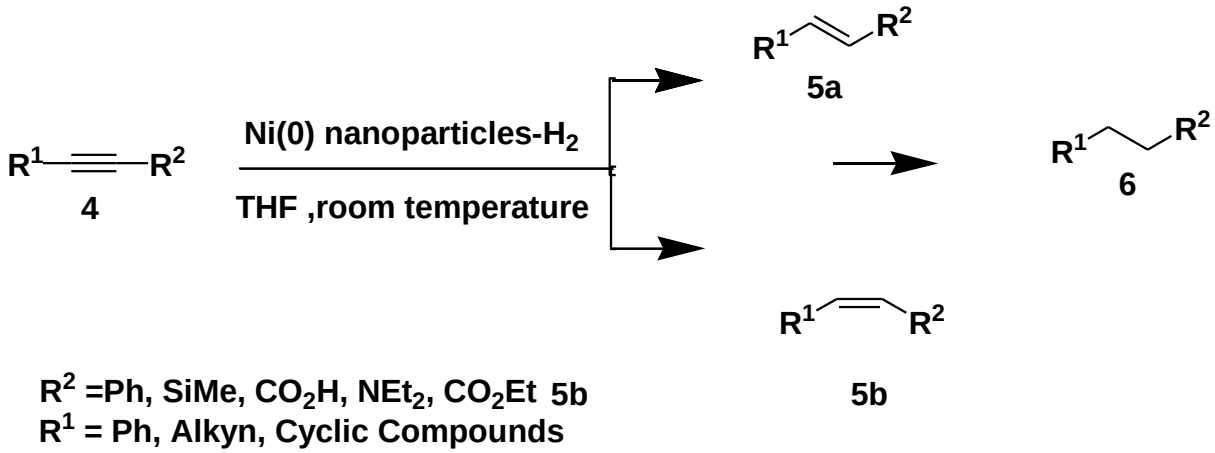


Scheme 2: Heterogeneous hydrogenation results in complete reduction of alkynes **1** to alkane **3** with alkene **2** being an intermediate.

1.1.1. Hydrogens transfer with Nickel (Ni)

In petrochemistry, nickel-based catalysts are among the most used inexpensive heterogeneous catalysts for the selective hydrogenation of poly-unsaturated compounds generated during steam cracking, such as dienes and alkynes, to synthesize other important industrial products such as dyes, pharmaceuticals, and agrochemicals [8]. Raney nickel is considered as being the most used catalyst due to its higher activity and being able to reduce practically any reducible functional groups

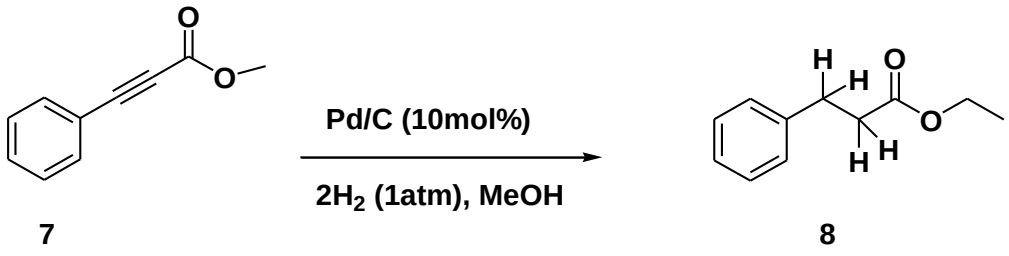
[9, 10]. The disadvantage is to become inactive after prolonged storage. Francisco Alonso *et.al*. reported the fast synthesis of nickel(0) nanoparticles with diameters of 2.5±1.5 nm by reduction of anhydrous nickel (II) chloride with lithium powder and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) in THF at room temperature [11, 12]. The high reactivity of these nanoparticles was demonstrated in the catalytic hydrogenation of a variety of organic compounds, including alkynes **4** and alkenes **5** containing compounds (**Scheme 30)** [13, 14].



Scheme 3: The reduction of alkyne in the presence of Ni(0) nano particles with H_2 to give alkane **6** [12].

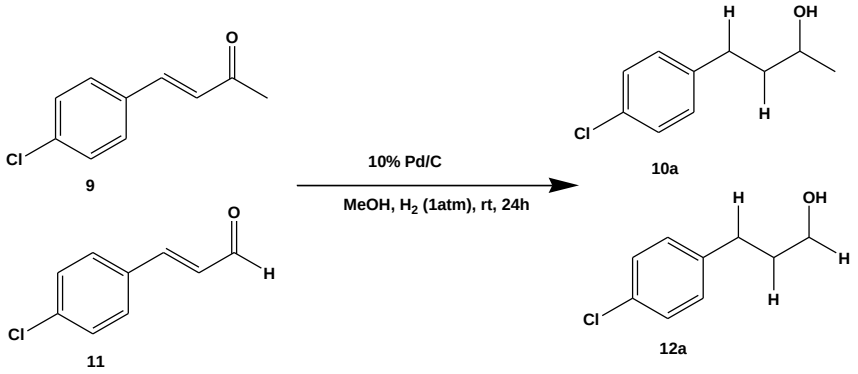
1.1.2. The Hydrogens transfer with palladium (Pd)

Heterogenous catalyst results in complete reduction of alkynes **7** to alkane **8** using Pd/C in combination with H_2 gas as shown in [15] **Scheme 4**.



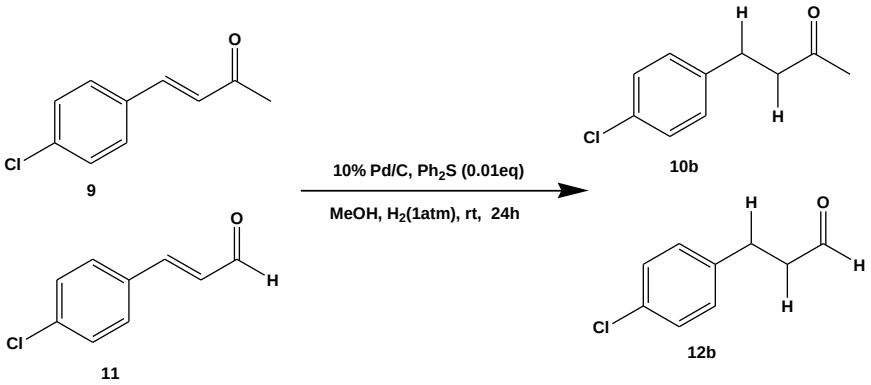
Scheme 4: Reduction of alkyne **7** in the presence of Pd/C with H_2 to give a corresponding alkane [15] **8**.

Palladium-catalysts are fundamental tools of modern organic synthesis. In comparison with all known palladium-based catalysts, palladium supported on carbon (Pd/C) has attracted much attention because of the greatest catalytic activity in a variety of different organic reactions [16]. Palladium tightly bound to the nanoparticle activated carbon has a large surface area with high catalytic efficiency. It can be easily recycled and reused with almost no loss of activity during the filtration process. Chemists have been drawn to reduction methods involving Pd/C. It has already been established for the reduction and hydrogenation of wide range of reducible functional groups, including alkynes, carbonyls, and nitriles [17] .The selective hydrogenation of C=C and C=O groups coexisting in one molecule remain a great challenge. Because at higher catalytic activity of metal (Pd/C), there's an over hydrogenation leading to the poor selectivity of functional groups (C=C, C=O) of compounds **9** and **10**, since they both adsorb on the metal catalyst and reduce to saturated alkane (C-C) and alcohol (C-OH) of compound **10a** and **12a** (**Scheme 5)** [18].



Scheme 5: Poor selectivity of hydrogenation due to higher catalytic activity of Pd/C [18] .

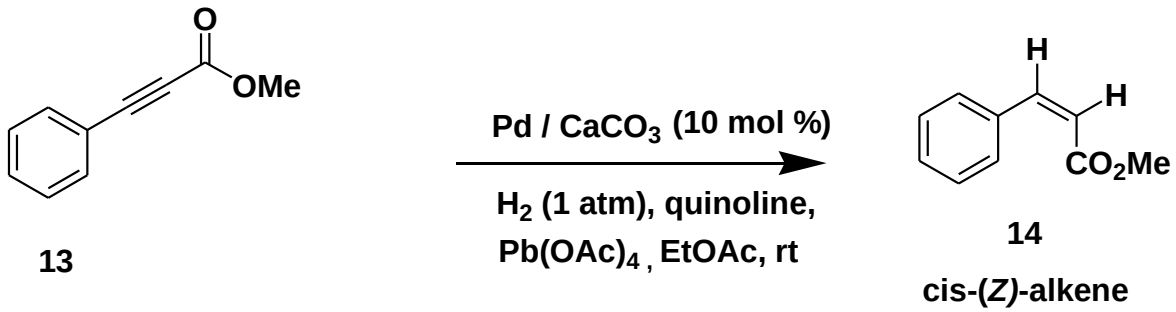
To tackle this challenge, selective poisoning by thiol, amine and diphenyl sulphide molecules is a common and sufficient strategy to reduce the metal ensembles and modify the electronic structure of Pd supported on carbon. Sajiki and co-workers discovered alkene chemoselective hydrogenation in the presence of diphenyl sulphide (Ph_2S) [19]. Furthermore, catalyst poison Ph_2S was introduced into the reaction as a new type of catalyst poison to support Pd/C. In this reaction, alkenes (**9** and **11**) were treated with hydrogen in MeOH at room temperature and gave chemoselective products **10b** and **12b** in good to excellent yield of greater than 90% (**Scheme 6**) [19].



Scheme 6: Chemoselective hydrogenation of alkenes in the presence of diphenyl sulphide and Pd/C to give alkanes [19].

1.1.2.1. Reduction of alkynes to cis- alkenes using Lindlar catalyst

The method that involves the Lindlar catalyst is an alternative which does not require a sophisticated setup like high temperature and pressure. It allows the conversion of alkynes to only alkenes without further reduction to an alkane [20]. The Lindlar catalyst does not adsorb alkenes sufficiently to allow their reduction. But it permits the adsorption and reduction of alkynes **13**. For Lindlar catalyst to afford a cis alkene **14**, Pd is poisoned with Pb and an amine (**Scheme 7**) [21]. This type of reaction is more active towards alkynes than alkenes, but alkene reduction is still possible, so reactions often require careful monitoring. Two hydrogen atoms are added to the same side of alkynes during the reaction mechanism, giving rise to *syn*-addition, in the presence of $CaCO_3$ or $BaSO_4$ for a solid support, $Pb(OAc)_4$ for deactivating the catalyst, and quinoline for binding competitively to the catalyst surface. According to Ibhadon *et al*., it is possible to obtain higher conversion and selectivity of greater that 98% in many cases, using this catalyst. Nevertheless, if water is present in the solvent, the catalyst usually deactivates after one reaction cycle and the catalyst with a modifying agent will require separation from the mixture and this entail additional cost [3].



13 **14**

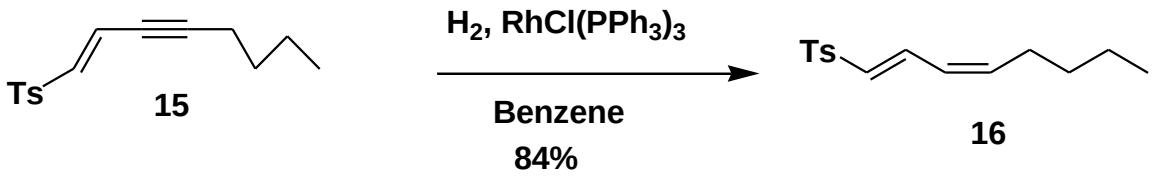
cis-(*Z*)-alkene

Scheme 7: Reduction of alkyne **13** to cis alkene **14** in the presence of Lindlar catalyst [3].

1.2. Homogeneous catalytic hydrogenation

Homogenous catalysts are organometallic compounds, derived from transition metal complex, soluble in common organic solvents such as hydrocarbons, ether, or halo derivatives [22]. For the catalytic hydrogenation of alkynes, homogenous catalysts have been comparatively little used, as compared to heterogenous catalysts. Homogenous catalysts offer an advantage such as milder reaction conditions, higher selectivity, activity, and chemo selective (ketones, carboxylic acids, esters, nitriles, ethers, and nitro groups are inert to reaction conditions) [23]. Wilkinson's catalyst usually gives complete reduction of alkynes (C≡C), since it is the most common hydrogenation reaction with molecular hydrogen [24]. Not only rhodium (Rh), but also iridium (Ir) and ruthenium (Ru) complexes have been studied for the catalytic reduction.

The disadvantage of the homo-catalyst is accompanied by difficulty in separating the catalyst from the product [25]. Although in benzene with acidic co-solvents (2,2,2-trifluoroethanol or phenol), using Wilkinson's catalyst [$RhCl(PPh_3)_3$], alkynes are hydrogenated at a faster rate, while C=C bonds do not change, which allows selective hydrogenation of alkynes [26]. An example of Wilkinson's catalyst in the stereoselective hydrogenation of the *cis*-tosyl-enyne (**15**) to the conjugated (*E*),(*Z*)-diene (**16**) is shown in **Scheme 8**.

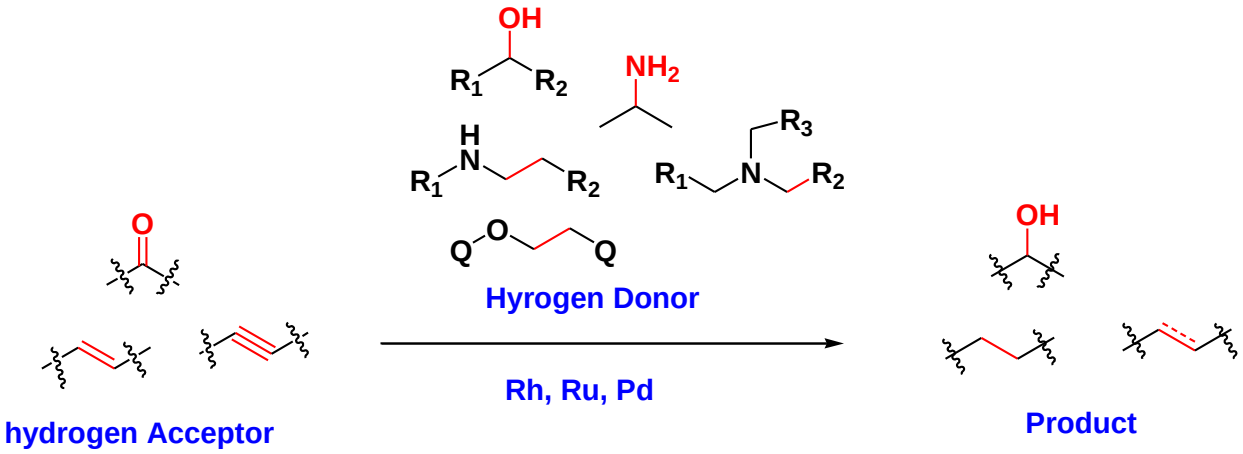


Scheme 8: Reduction of cis-tosyl-enyne **15** to the conjugated (*E*),(*Z*)-diene **16** in the presence of Wilkinson catalyst [27] .

1.3. Addition of hydrogen through hydrogen transfer

This type of hydrogenation involves a reaction in which hydrogen is transferred to an acceptor molecule from another molecule species acting as a donor. Transfer hydrogenation is a movement of protons and electrons that is determined by the catalyst, the substrate, and the reaction conditions. [28, 24]. In 1925, Meerwein and Schmidt discovered the first hydrogenation procedure using alcohols as the source of hydrogen in the presence of aluminum alkoxide as a homogenous catalyst for the reduction of carbonyl compounds [3]. Additional application of the reaction was studied by Verly [29].

Common proton donor includes acids, water, imines, alcohols, amines, and liquid ammonia, that can serve as the hydrogen-source during reduction reaction, allowing the reduction of carbonyl (C=O), alkenes (C=C) and alkynes (C≡C), as represented in [30] **Scheme 9**. For example, commonly used heterocyclic donor molecules such as 1,4-dioxane, ether, and 2,3-dihydrofuran from the saturation reaction of alkene and alkynes, combining with transition metals (Pd, Pt, Ni, Ru, Rh) as catalyst, they can donate a pair of hydrogen atoms [31], while they also acting as solvents [32, 33, 9]. Nitrogen containing compounds such as piperidine, indoline and pyrrolidine are also frequently used as a hydrogen source in combination with transition metals for the reduction of alkynes to alkane [34]. The following parameters are crucial when making a choice for the hydrogen donor: (i) the reaction type, (ii) the nature of targeted functional group, (iii) solubility (ability to act as the solvent for the corresponding reaction), (iv) absent of unwanted formation of side products, (v) requirement of mild conditions, (vi) and the rate of metal and donor molecule exchange.



R_1, R_2, R_3 = H, Alkyl

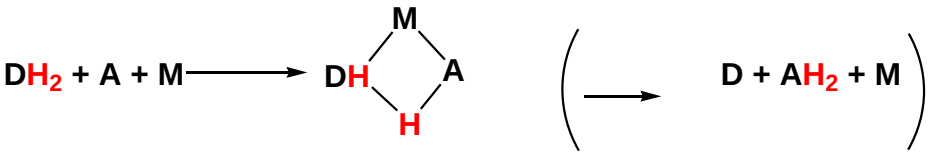
Q = mainly cyclic ethers

Scheme 9: Transfer hydrogenation reaction of alkenes, alkynes, and carbonyls with noble metals in the presence of hydrogen donors [24].

1.3.1. Transfer hydrogenation mechanism

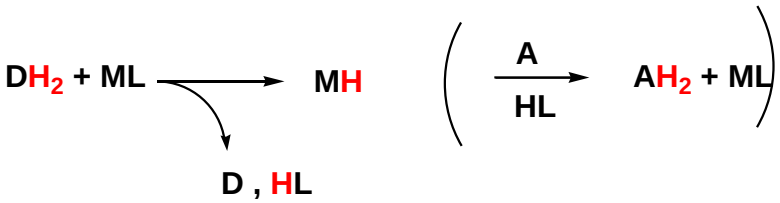
Specific metals and starting materials have a major impact on the mechanism of hydrogen transfer. Direct and indirect processes can be distinguished by their two basic paths. In the direct approach **Scheme 10**, pathway A), H moves straight from the donor to the acceptor molecule; in the indirect pathway **Scheme 10**, pathway B), a metal hydride intermediate develops. The most prominent examples of direct reactions are the Lewis acids Al(III) and Ln(III) [35]. The most catalytically active systems are weak Lewis acids with a high affinity for hydrides, such as Rh, Ru, and Ir [36].

A .Direct transfer pathway

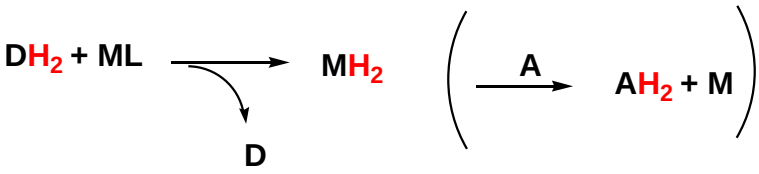


B. Indirect transfere pathway

B1.Formation of a monohydride



B2. Formation of a dihydride

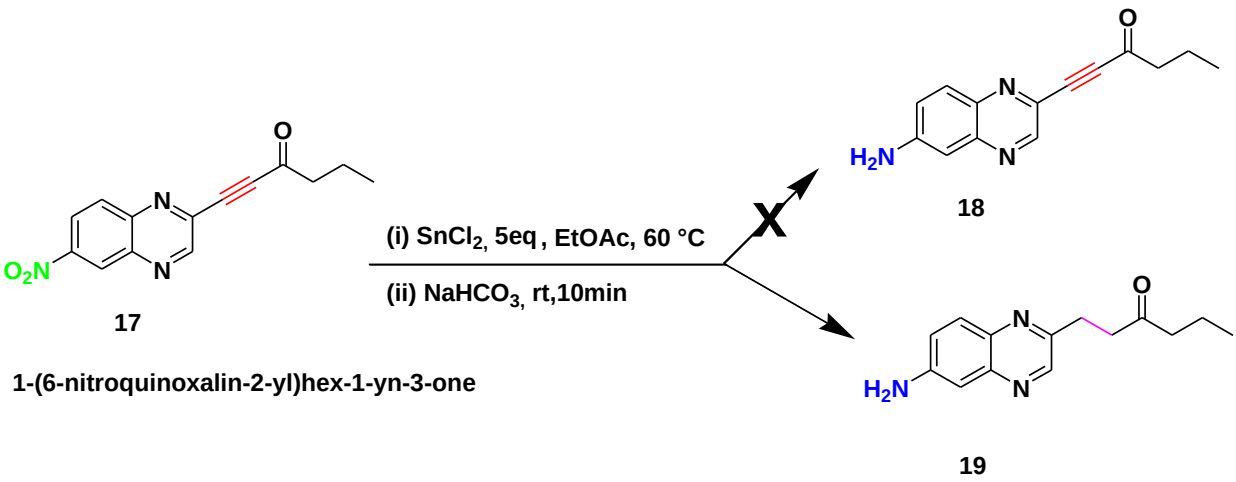


D = donor A = acceptor M = metal

Scheme 10: Hydrogen transfer pathways [36].

1.4. Discovery for reduction of alkyne to alkane using metal salts.

Recently, the organic research group from the University of Limpopo discovered that $SnCl_2$ can be used to reduce an alkyne functional group of 1-(6-nitroquinoxaline-2-yl) hex-1-yn-3-one, which is α, β to a ketone group, to an alkane **19** as shown in **Scheme 11**. This was discovered during the reactions where $SnCl_2$ was used to reduce a nitro group to an amine with α, β-unsaturated carbonyl being present. Interestingly, both the nitro and alkyne groups were reduced [37]. Therefore, this offers an opportunity for $SnCl_2$ to be used as a reducing agent of alkynes to alkanes. From literature, no reaction has been reported for the reduction of alkyne to alkane using $SnCl_2$.



Scheme 11: The reduction of 1-(6-nitroquinoxalin-2-yl)hex-1-yn-3-one **17** in the presence of $SnCl_2$ to give the corresponding compound **19**.

1.5. Background on Tin (Sn)

Tin is a chemical element represented by symbol Sn and atomic number 50 on the periodic table. It is the member of carbon group known as a post transition metal, located in group 14 [38]. Tin consists of two possible oxidation states: +2 (stannous) and +4 (stannic) which are stable. It is characterized as being nontoxic, soft, ductile, malleable, and silvery colored metal. Tin can be found in both organic and inorganic forms in the environment. Organic tin compounds are based on tin with hydrocarbon substituent forming organotin compounds [39]. Inorganic tin compounds are the most important compound formed through the combination of chemicals like sulphur, chloride, or oxide to produce compounds including the tin(II) and tin(IV) chlorides, tin(II) oxide, tin(II) fluoride, and the potassium and sodium stannate. Inorganic tin compounds are used in making toothpaste, perfumes, soaps, coloring agents, food additives, dyes, and in the glass industry [40].

Tin is primarily used in solder alloys for electrical/electronic and general industrial purposes, which accounts for around 34% of annual global production [41]. About 25 to 30% of manufacturing goes toward using tin as a protective covering for other metals, particularly for food containers [41]. Tin(II) chloride is an important inorganic compound and is used mainly as a reducing agent in organic and inorganic synthesis and in the manufacturing of metallized glazing, glass, and pigments [42]. Tin(IV)

chloride is utilized in organic synthesis, in plastics, as intermediate in organotin compounds production and in the manufacturing of tin(IV) oxide film on glass [43]. Tin(II) fluoride is mainly used in preventive dentistry. Under environmental conditions tin and inorganic tin compounds are non-volatile [43]. Tin(II) chloride is soluble in water, whereas other tin compounds tend to be only slightly soluble. Tin compounds are likely to partition to soils and sediments [44].

1.5.1. Chemistry of $SnCl_2$.

Tin (II) chloride is an odourless white crystalline solid with the formular $SnCl_2$ also known as stannous chloride, belonging to the class of inorganic compounds [45]. This is an inorganic compound in which the metal atom is a post-transition metal, and the halogen atom is chlorine. Tin(II) chloride forms a stable hydride, but undergoes hydrolysis in aqueous solution, particularly if hot. Tin(II) chloride should not be confused with the other chloride of tin, tin (IV) chloride ($SnCl_4$). According to its pKa, tin (II) chloride is an acidic compound. Its structure consists of a lone pair of electrons, so the molecule in a gaseous phase has a bend molecular geometry. In its crystalline state, it forms chains linked via chloride bridges. The $SnCl_2$ dihydride with one water coordinated on the tin and second water coordinated to the first water and can react with amines, alcohol, alkali, and oxidizer (**Figure 1**) [46].

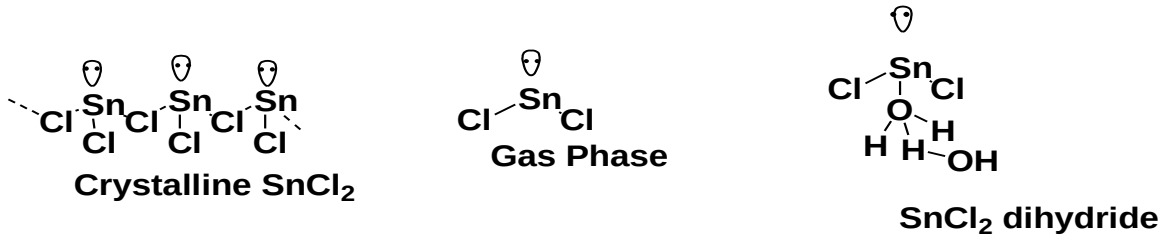


Figure 1: Tin chloride in different form [46].

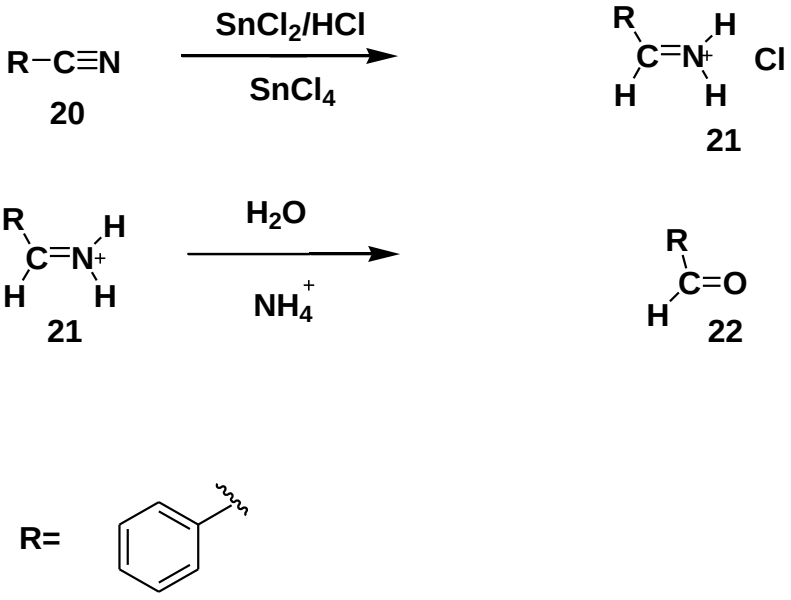
1.5.2. Application of $SnCl_2$ in organic synthesis.

Tin (II) chloride has been regarded as being highly efficient and versatile reducing agent for the reduction and cyclization reaction of nitro compounds, leading to the synthesis of the tertiary and secondary amines through reductive amination of aliphatic and aromatic carbonyl compounds [47, 48]. Tin (II) chloride is prepared from

commercially available metallic tin and hydrogen chloride. Tin (II) chloride has attractive properties such as being a stable solid, highly tolerant of water, easily handled, and less corrosive [49] . It has been widely used in various organic synthetic operations such as manufacturing of pharmaceuticals, production of dyes, reduction of various functional groups, as a catalyst in the production of plastic, additive in lubricants and as a tanning agent. There are many areas of science and technology where $SnCl_2$ is widely used, including the esterification of biodiesel, nuclear medicine, and catalysis. According to Yadav *et al*. [50], evaporation of $SnCl_2$ is accompanied by its oxidation in gas state and deposition of the reaction product on a substrate in the form of SnO_2 film. Tin (II) chloride is used as a reducing agent for labelling ^{99m}Tc-containing radiopharmaceuticals in nuclear medicine and used as an effective catalyst for Stephen reduction [51, 49].

1.5.3. Tin (II) chloride in Stephen's reaction

The Stephen reaction involves the use of $SnCl_2$ as the reducing agent of nitrile in the presence of hydrochloric acid (HCl) to give the corresponding imine, which is easily hydrolyzed to give aldehydes [52]. Subsequently, it has been reported [53, 54] that the reduction in homogeneous solution usually gave better yields of aldehydes, and therefore, diethylene glycol, diethyl ether and ethyl acetate have been recommended as solvents for the reaction [55]. This solution gave efficient conversions of nitriles to aldehydes. For example, when benzonitrile **20** was added to a homogeneous solution, a solid soon separated and benzaldehyde **22** was obtained in good yield (**Scheme 12**). However due to diisobutylaluminium hydride reduction, the Stephen reduction is of less used today.

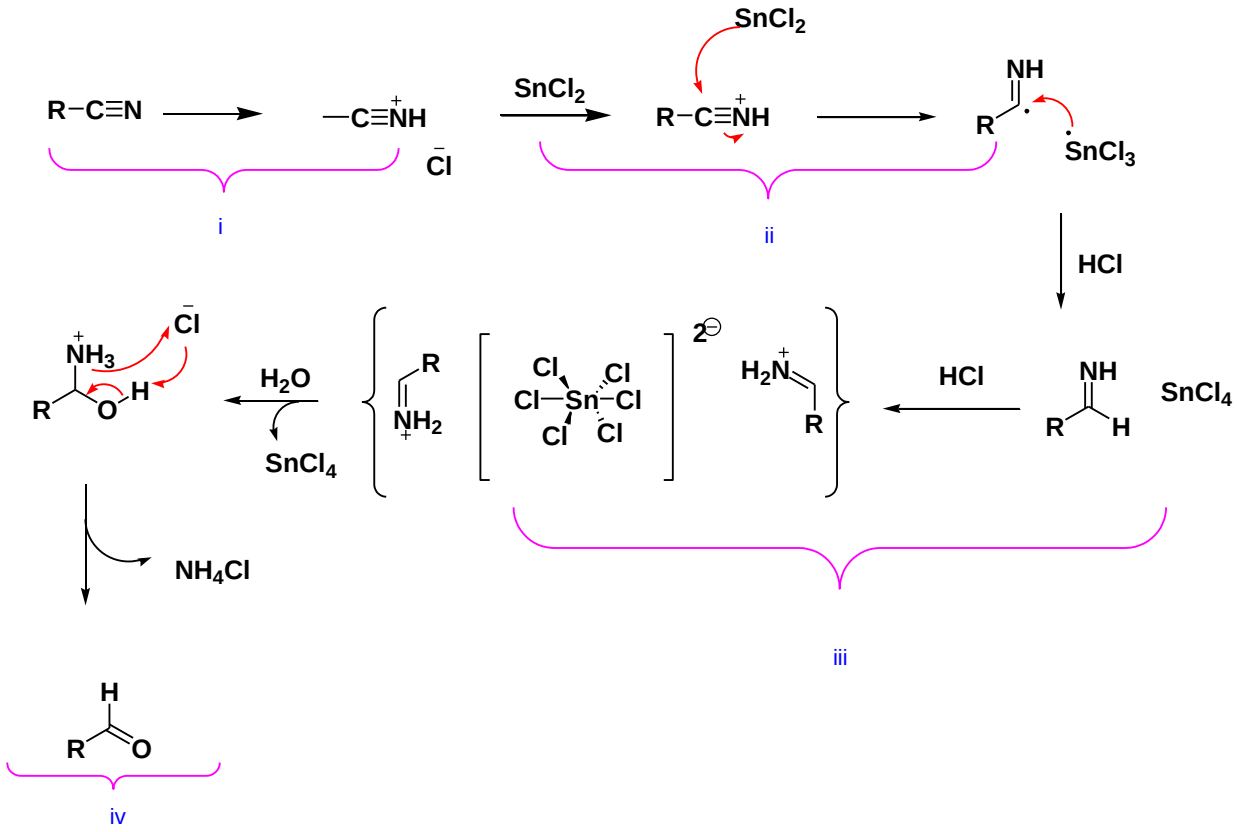


Scheme 12: Reduction reaction of benzonitrile to form benzaldehyde [56].

1.5.4. Stephen's reduction mechanism

The reaction is an organic redox reaction. It is pertinent to note that the reaction is more efficient when aromatic nitriles are used instead of using aliphatic nitriles. Aldimine hydrochloride (also known as stannic chloride) is formed in the reaction, which is unstable, and hydrolyses to give aldehyde [52] (**Scheme 13**). The mechanism steps are as follows:

i. Gaseous hydrogen chloride (HCl) is added to the given nitrile, which reacts to give its corresponding salt.
ii. A single electron transfer from tin (II) chloride reduces this salt. On further reduction with HCl, it forms tin (IV) tetrachloride and amine.
iii. The salt obtained in **step ii** precipitates quickly as aldimine tin chloride.
iv. The hydrolysis of aldimine tin chloride yields an imine. The required aldehyde is formed from this imine. This process results in the formation of ammonium chloride as well.

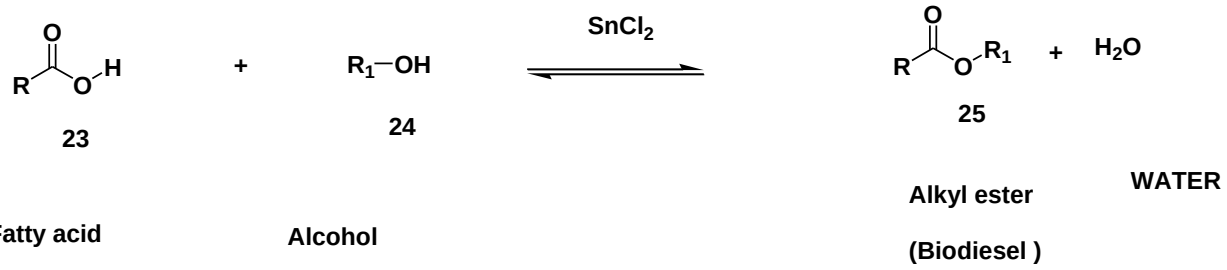


Scheme 13: Stephen's reduction reaction mechanism.

1.5.5. Tin (II) chloride catalysed esterification reaction.

Tin (II) chloride is widely used in the chemical industry, particularly in the plastics industry [57]. Examples are elastic plastic and thermoplastic. In addition, it can also be used as a crosslink catalyst to produce phenolic resins that are found in everyday products such as household appliances [58]. $SnCl_2$ has proven to be a particularly effective catalyst for esterification reactions. As reported in the literature, $SnCl_2$ promotes the esterification of saturated and unsaturated free fatty acids (FFAs) **23** in ethanol solution **24** under mild reaction conditions [59, 60]. The highest yield was achieved using $SnCl_2$ as compared to the common acid catalyst such as sulfuric acid (H_2SO_4) [61]. Therefore, $SnCl_2$ was found to be a potential catalyst for biodiesel production from low-cost raw materials. The high content of FFA will react with the base catalyst, resulting in soap by-product and hindering methyl ester (biodiesel production). Thus, pre-treatment of the feedstock is necessary to reduce its FFA

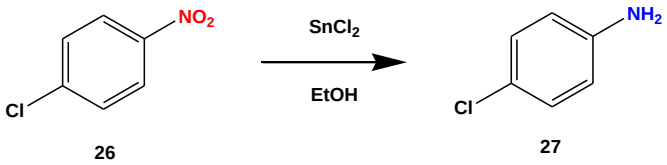
content. Pre-treatment can be achieved by esterifying FFA using alcohol and $SnCl_2$ as shown in the **Scheme 14** [62].



Scheme 14: Esterification of fatty acid **25** in the presence of $SnCl_2$.

1.5.6. The in-situ reduction and cyclization of nitro compounds using $SnCl_2$

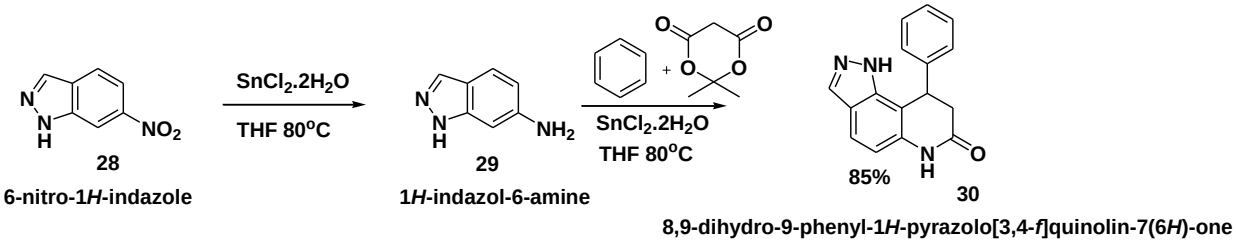
Aromatic nitro groups are selectively reduced by $SnCl_2$ to amines (**Scheme15**). Aromatic compounds are important commercially, and for the synthesis of the variety of organic compounds [63]



Scheme 15: Reduction of nitro benzene **26** to corresponding amine **27** in the presence of $SnCl_2$.

Studies revealed that the reduction of nitro aromatics could lead to different versatile products [64, 65]. A variety of techniques have been developed to reduce aromatic nitro compounds, such as: Pd [66] and Au catalysts [67], and they were reported to work successfully. The methods are characterized as being toxic, require high temperatures and strong acids, and they are too expensive. Therefore, stannous chloride remains an effective catalyst for the reduction of nitro compounds due to its ease of use, mild condition, cheap cost, and ease of operation. For example, quinolin-2(1*H*)-one and acridine derivatives from the in-situ reduction and cyclization reaction

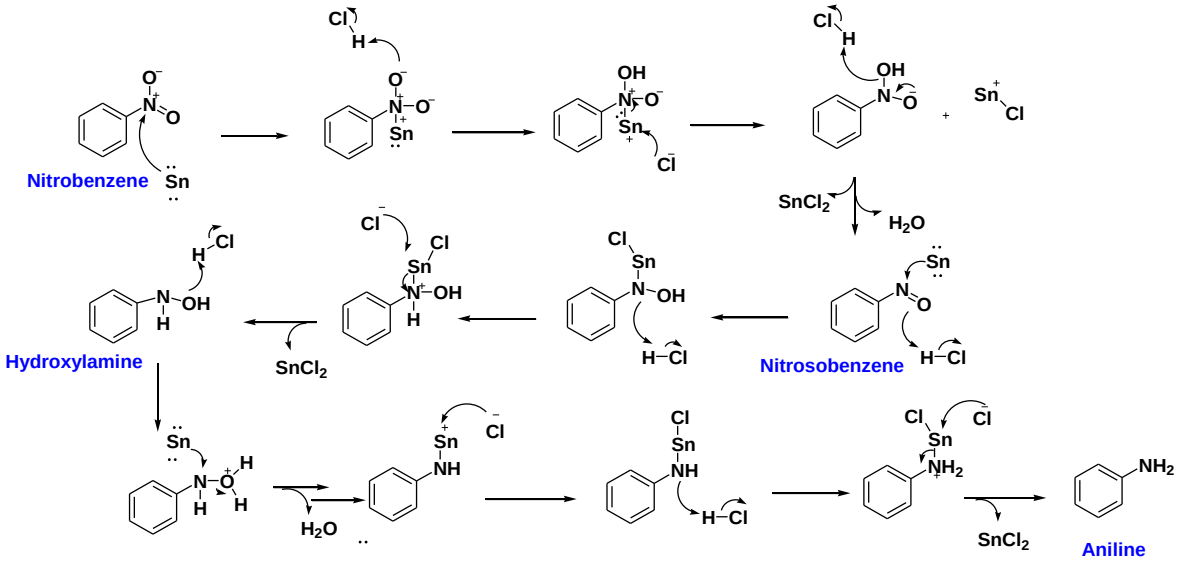
of 6-nitro-1*H*-indazole **28** synthesized under $SnCl_2$ in THF(tetrahydrofuran) to give the corresponding product which is 8,9-dihydro-9-phenyl-1H-pyrazolo[3,4-f]quinoline-7(6H)-one **30** (**Scheme 16)** [68].



Scheme 16: In-situ reduction and cyclization reaction of 6-nitro-1*H*-indazole **28** [68].

1.5.7. Mechanism showing the reduction of nitro to amines using $SnCl_2$

The reduction of aryl nitro compounds is known to proceed via the hydroxylamine, followed by azoxy and azo compounds to its corresponding aryl amine **Scheme 17** [69]. These happen when the proton is introduced into the nitrogen centre, the electrophilicity is enhanced, which prepares the nitrogen centre for the hydride shift. N-H bonds are formed, and N-O bonds are cleaved both by proton attachment and subsequent H_2O elimination.



Scheme 17: Reaction mechanism of nitro to amine using $SnCl_2$ [69].

1.6. Computational studies

Computational chemistry is a branch of chemistry which involves the use of computer simulation to make chemical prediction or solving chemical equation [70, 71]. In this field, various aspects of chemistry can be investigated numerically. This is done by providing data which are difficult to probe experimentally such as energies, transition state structure, reactivity, spectra, and other properties. Computational chemistry has become important in the sense that molecular properties of the system under study can be accessed much quicker than they would through experimental routes [72]. Moreover, computational chemistry is an environmentally friendly approach for chemical studies and does not require expensive reagents that may generate large amount of waste.

Computational chemistry consists of two branches, which are classic mechanics (also known as molecular mechanics) and quantum mechanics [73]. These two methods have similar basic performance but differ in physics law, they are used for calculations performance [74]. Classical mechanics uses classical law of physics (Newtonian mechanics) to predict the properties and structure of the molecules while quantum mechanics law state that the energy and other molecular properties may be accessed through solving the time-independent Schrödinger equation. Quantum mechanical methods can either be classified as semi-empirical method which makes significant approximations to the quantum mechanical laws and then engage a few empirical parameters to alleviate [73, 74] .

Some of the well-known computational methods/ approaches are molecular dynamics (MD) [75] and Ab initio methods [76]. The MD method is a classical mechanical method that is used to model the detailed microscopic dynamical behaviour of many different types of systems, including liquids, gases, solids surfaces and clusters [75]. The Ab initio method is a quantum mechanics method and is referred to as a semi-empirical, it contains no empirical parameters in the computation [76]. These methods include Hartree-Fock (HF) [77] and density functional theory (DFT) [78] amongst others. The current study will employ DFT to predict the reaction mechanism of the reduction of alkynes using $SnCl_2$.The approach has been used in similar studies and can perform ground state properties and gives better prediction on reaction mechanisms [79]. In the following section, a brief description of DFT is given.

1.6.1. Density functional theory

Density Functional Theory (DFT) is a quantum mechanical approach that derives properties of the molecule based on a determination of the electron density of the molecule [80]. DFT was formulated by Hohenberg-Kohn [81] and Kohn-Sham [82] to provide the foundation for accurate calculations. The DFT is based on two mathematical theorems proved by Hohenberg and Kohn, as well as the derivation of a set of equations by Kohn and Sham. They proved that the total ground state energy of a many electrons system is a functional of the electron density [81, 82] .

DFT is a widely used technique because it is computationally more efficient than other quantum techniques with comparable accuracy, and it provides a quantum-mechanical` foundation for most *ab initio* strategies used in computational material science. In DFT, the total electron density is decomposed into one-electron densitie [83].

The attempt to solve the Kohn and Sham equation proved to be difficult, in that the exchange correlation functional is unknown [82, 81]. This is possible by using approximation methods as the local density approximation (LDA) [84] and generalized gradient approximation (GGA) [85] . Within the so-called local density approximation, the exchange-correlation energy density is assumed to be that of a homogeneous electron gas with the same density as that seen locally by the electron. However, when the electron density varies arbitrary, it is difficult to give an exact expression of exchange correlation energy [84].

It has been reported that the LDA typically underestimates bond length cell parameters of system by roughly 10% [84, 86]. Beyond the LDA, the change and correlation in homogenous system is non-local with respect to the electron it surrounds. This is referred to the gradient correction GGA because it add a gradient into experiments. The GGA has been introduced by Perdew and Wang [87] and works accurately for hydrogen bonded crystals and was found to overestimate the bond length and cell parameters.

Generalized gradient approximation functional evolve in two main orientations, the first one is parameter-free, where the new parameters are determined from known

expansion coefficients and other exact theoretical condition. The second is empirical with parameters determined from fits to experimental data or accurately calculated atomic and molecular properties. The most used GGA function in physics is the Perdew, Burke and Ernzerhof (PBE) and Perdew-Wang [88] from 1991 (PW91) and regarded as parameter free.

The PBE function is designed to have a smoother effective potential than PW91, which is prone to numerical instabilities. Most GGA function used in chemistry application is Becke, Lee, Parr and Yang (BLYP) [89], Becke three-parameter hybrid function combined with LYP functional (B3LYP) and there are empirical. The BLYP correlation employs the density's Laplacian and thus formally belongs to the third rung of jacob's ladder, but it is commonly classified as a GGA. B3LYP has been favoured by many organic chemist researchers because of its low computational cost and accuracy when it comes to generating results [90]. The wide range of predefined basis set is offered by Gaussian software which is used to execute all computational calculations.

1.6.2. Gaussian

Gaussian is a powerful computational chemistry software package capable of performing a wide range of *ab initio* quantum mechanical and classical mechanics. It was initially released in 1970 by John Pople and his research group and was developed at Carnegie Mellon University as Gaussian 70 [91]. It has been continuously updated since then, the current version of the program is Gaussian 16 [92], Originally available through the quantum chemistry program exchange and licensed by Gaussian, Inc. The gaussian provide the sum of electronic and thermal enthalpies, and the data generated by Gaussian can be used to calculate heats and free energies of reactions as well as absolute rate information. The versality and user friendly made Gaussian accessible to non-specialist in the computational chemistry field [93]. In this study Gaussian will be employed to evaluate the reaction mechanism of the pyrazine compound derivatives (**46**, **47**, **48**), where the characteristics of these compounds such as geometric and thermodynamics will be determined.

1.7. Aim

The aim of this research was to investigate the reduction of conjugated α, β-alkynyl carbonyl compounds into alkanes using commercially available $SnCl_2$ and other metal salts known to reduce the nitro group, such as iron (Fe) and zinc (Zn).

1.8. Objectives

The objectives of the study were to:

i. optimize the reaction conditions for the reduction of α, β-alkynyl carbonyl compounds to alkane using $SnCl_2$.
ii. investigate the effect of Fe and Zn metal oxide on the reduction of alkynes from α, β-alkynyl carbonyl compounds.
iii. investigate the reaction mechanism involved during the reduction of alkyne both experimentally and computationally.

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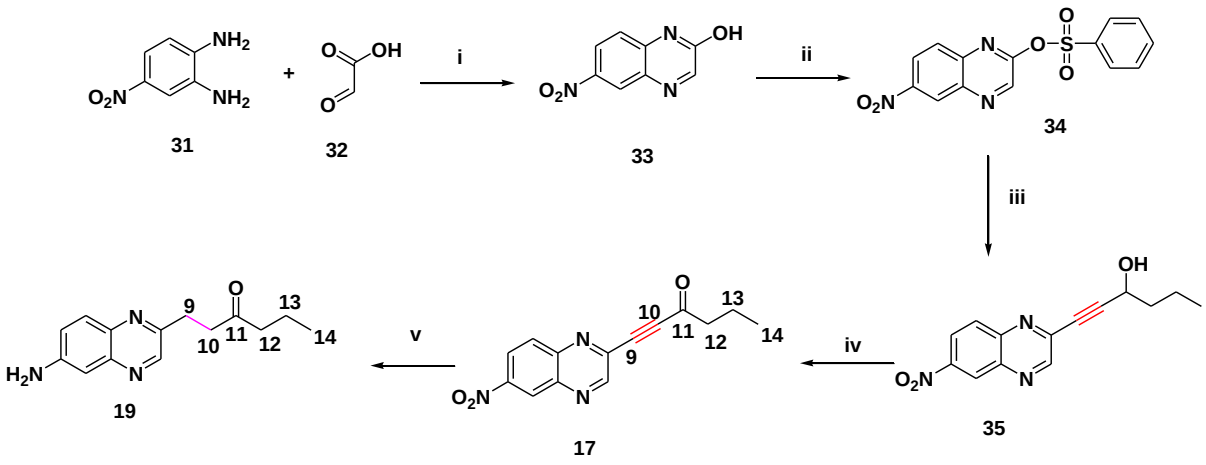
CHAPTER 2:

RESULTS AND DISCUSION

2.1. Introduction in the reduction of 1-(6-nitroquinoxaline-2-yl)hex-1-yn-3-one 17 in the presence of $SnCl_2$

This chapter gives an understanding about the reduction of alkynes to the corresponding alkane using $SnCl_2$ and other salts known to reduce the nitro group such as Fe and Zn. A number of reactions with different compounds were performed to better understand the limitations and versatility of the discovered reaction by Karabo et al. [1] Firstly, we started by reinvestigating the reaction by repeating the reduction reaction of 1-(6-nitroquinoxaline-2-yl)hex-1-yn-3-one **17** in the presence of $SnCl_2$ as a reducing agent to give 1-(6-aminoquinoxaline-2-yl)hexane-3-one **19** to check if $SnCl_2$ can indeed reduce the alkynes to the corresponding alkane.



i = Acetic acid, MeOH, 0°C, 90 min

ii = Benzenesulfonyl Chloride, DMAP, Et_3N, DCM, 0°C , 90 min.

iii = $PdCl_2(PPh_3)_2$ 5mol%, CuI 10mol%, Et_3N 2eq., 1-Hexyn -3-ol , Dry THF, 60°C Overnight

iv = Pyridinium ChloroChromate(PCC) 5eq., DCM

v = $SnCl_2$ 2eq., Ethyl Acetate(EtOAC) , 25°C, 3h, $NaHCO_3$ 10min

Scheme 2.1: Reaction steps to produce 1-(6-aminoquinoxaline-2-yl)hexane-3-one **19**.

To carry on with our investigation, we followed reaction steps as indicated on the reaction **Scheme 2.1** in producing the intermediate **17** for our reduction reaction. We first started by making 6-nitroquinoxaline-2-ol **33** (73%) by cyclocondensation between O-phenylenediamine **31** and glyoxylic acid **32** in a mixture of acetic acid and methanol

following the method reported by Karabo et al., [1] [2] with ^{1}H NMR characterisation showing peaks integrating for 5 protons, at the region which was consistent with what was previously reported.

Having successfully made 6-nitroquinoxaline-2-ol **33** we then converted the OH into benzene sulfonyl to generate a good leaving group by treating **33,** with benzene sulfonyl chloride in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine (Et_3N) in dichloromethane (DCM) [3], to give the corresponding 6-nitroquinoxalin-2-yl benzenesulfonate **34** as a yellow solid (94% yield). The successful incorporation of the benzene sulphonyl group was confirmed by the ^{1}H NMR characterisation, by showing the disappearance of the broad singlet signal resonating around 12 ppm which was consistent with hydroxyl group and the appearance of additional 3 signals which integrated for 5 hydrogens in the aromatic region on the proton NMR spectrum of compound **33**. All the peaks were consistent with what was previously reported [1] [2].

We then introduced Sonogashira coupling between 6-nitroquinoxalin-2-yl benzenesulfonate **34** with hex-1-yn-3-ol in the presence of Et_3N (2 eq.), $PdCl_2(PPh_3)_2$, (5 mol%), and CuI (10 mol%) in THF at 60^{o}C under N_2 atmosphere, in a sealed reaction tube for 16 hours, yielded the corresponding 1-(6-nitroquinoxalin-2yl) hex-1-yn-3-ol **35** in 95% yield. A noticeable triplet signal was observed at 4.7 ppm in the ^{1}H NMR spectrum with a broad singlet signal at around 2.0 ppm integrating for one proton which is consistent with hydroxyl group (OH). The triplet signal at 0.9 ppm is an indicative of the presence of a methyl group (CH_3) next to the methylene group (CH_2) in the compound. The two signals at 1.65 and 1.91 ppm, which both integrated for two protons are consistent with two methylene groups. The ^{13}C NMR spectrum was also in agreement with the compound by showing the presence of the signals at 81.8 and 98.0 ppm which are consistent with carbons of the alkyne group. The NMR analysis were also in agreement with what was previously reported [1].

In an attempt to synthesise the ketone **17** from corresponding alcohol **35** via oxidation reaction using Jones reagent following the method already reported by Mercier et al., [4], a yield of 66% was obtained with ^{1}H NMR showing the trace amount of starting material being present. We improved the yield of reaction, by introducing another oxidising method using pyridium chlorochromate PCC (5 eq.) as oxidising agent in

CH_2Cl_2 (DCM) for 3 hours at room temperature to afford 1-(6-nitroquinoxalin-2yl)hex-1-yn-3-one **17** in a yield of 76% [5].

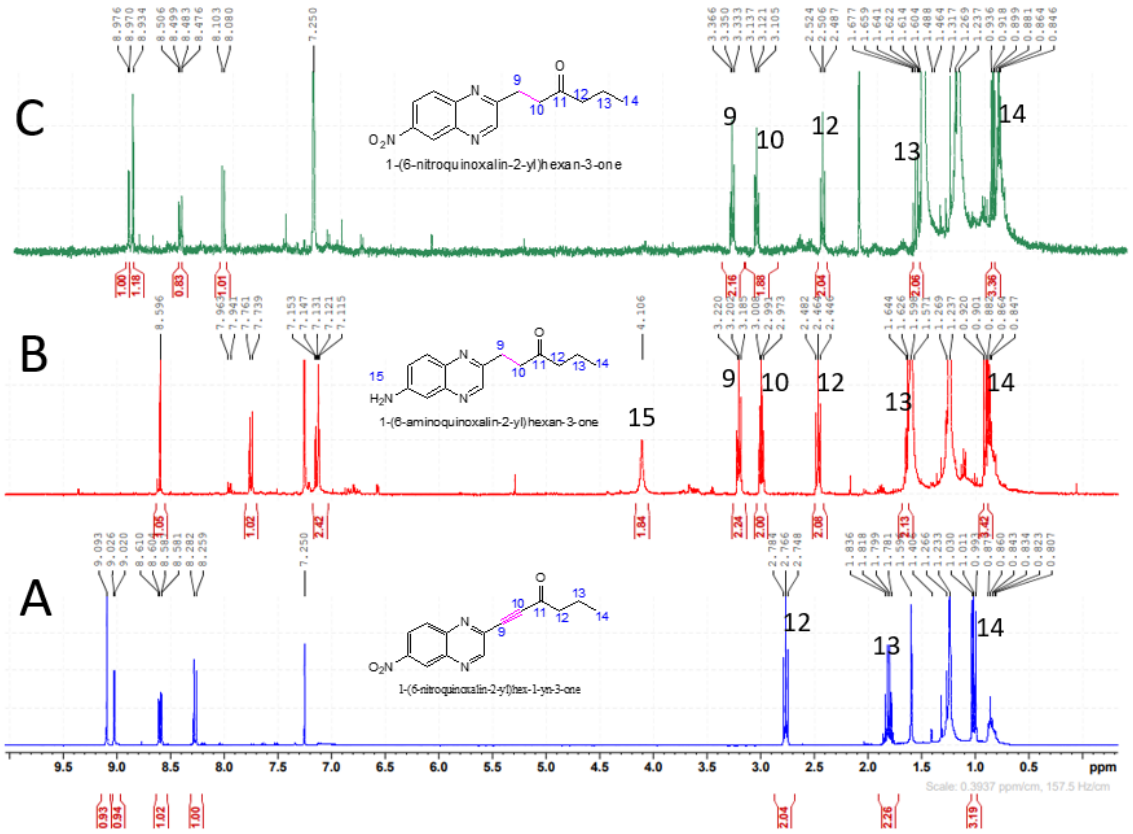


Figure 2.1: ^{1}HNMR of compound **17,19** and **36.**

The ^{1}H NMR spectrum **17** (**Figure 2.1 A**) showed the disappearance of a broad singlet signal resonating around 2.0 ppm, integrating for one hydrogen which was consistent with OH group on compound **35**. The disappearance of the triplet signal integrating for one hydrogen which was at 4.7 ppm on the tertiary carbon with alcohol, triggered the alpha hydrogens signal on carbon (C12) to change its multiplicity from multiplets to triplet. The ^{13}C NMR spectrum of **17** showed a signal at 186.7 ppm which was consistent with the carbonyl carbon at the ketonic region. The ^{1}H and ^{13}C NMR was consistent with the one previously reported [1]. The high-resolution mass spectrum was also in agreement with the molecular weight of structure ($C_{14}H_{12}N_3O_3$ = 270.0880), where $[M + H]^+$ = m/z 270.0883 was observed [1].

Using compound **17**, we repeated the reduction reaction using the same conditions reported by Karabo et al., [1]. In the first condition, 1-(6-nitroquinoxalin-2yl)hex-1-yn-

3-one **17** was reacted with 5 eq. of $SnCl_2$ in ethyl acetate, at 60˚C for 3 hours to give the corresponding 1-(6-aminoquinoxaline-2-yl)hexane-3-one **19** in the low yield of 18%, with both nitro and alkynes being reduced.

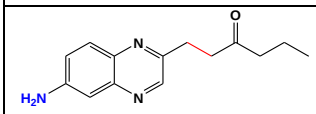
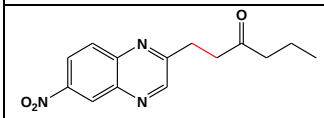
The ^1H NMR spectra of compound **19** (**Figure 2.1 B**) showed a broad singlet signal resonating around 4.11 ppm which integrated for two protons, that was consistent with the amine group -NH_2. The appearance of two triplet signals, each integrating for two hydrogens at 2.97-3.22 ppm suggest the presence of two CH_2's and are consistent with hydrogens at C9 and C10. The ^1H NMR spectrum of compounds **19** also indicated that conversion of -NO_2 to NH_2 group triggered the doublet and doublet of doublet signals of the benzene protons to shift slightly from the lower field because of the less inductive effect of NH_2 as compared to the NO_2 group. The high-resolution mass spectrum was also in agreement with the molecular weight of structure ($C_{14}H_{18}N_3O$ = 244.1372), where $[M + H]^+$ = m/z 244.1440 was observed in **Figure 2.19 (Appendix 1).**

Since our results agreed with what Karabo et al. [1] observed, we then started to optimise the reaction conditions using different parameters such as: time, temperature, and the number of equivalences of $SnCl_2$ to check the optimum conditions responsible for the reduction of the triple bond (**Table 1**).

We also did the reaction using compound **17** with 5 eq. of $SnCl_2$ at 60˚C, but with time changed to 18 hours, and the yield increased to 29%, however, a lot of unrecognized by-products were produced which might have been caused by keeping the reaction for a longer time. Reducing the time to 1 hour using the same conditions, the reaction gave the corresponding compound **19** in 35.1% yield, with TLC and NMR analysis (**Figure 2.1 B**) indicating that the starting material was completely consumed.

Therefore, since other parameters were kept constant during other reactions, we decided to check what will happen if we change the temperature from 60˚C to 25˚C using 5 eq of $SnCl_2$, the reaction proceeded smoothly and quickly within 3 hours. The TLC and NMR analysis indicated that the starting material was completely consumed to generate 1-(6-aminoquinoxaline-2-yl)hexane-3-one **19** in a better yield of 47%, with ^1H NMR indicating the presence of signals same as in **Figure 2.1 B**.

Table 1: The $SnCl_2$-catalysed reduction of alkynes to produce compound 19 and 36.

compound	Run	No. of equivalence of $SnCl_2$	Temperature (˚C)	Time (hours)	%Yield
	1	5	60	3	18
	2	5	60	18	29
	3	5	60	1	35
	4	5	25	3	47
	5	2.5	25	3	80
	6	1	25	3	45
	7	1.5	25	3	60
	8	2	25	1	57
	9	2	25	1:30	70
	10	2	25	3	74
	11	2	60	3	80

When changing the number of equivalence of $SnCl_2$ to 2.5 eq. for 3 hours, at 25˚C, 1-(6-nitroquinoxaline-2-yl)hexane-3-one **36** was isolated in 80% yield. However, the ^1H NMR indicated the presence of product **36** with a lot of impurities which might have an effect in increasing the yield of the final product. On the ^1H NMR we observed that only the alkyne was reduced with the nitro group remain unchanged.

We then reduced the number of equivalence of $SnCl_2$ to 1 eq. for 3 hours at 25˚C, the reaction gave the corresponding 1-(6-nitroquinoxaline-2-yl)hexane-3-one **36** in 45% yield with starting material being recovered.

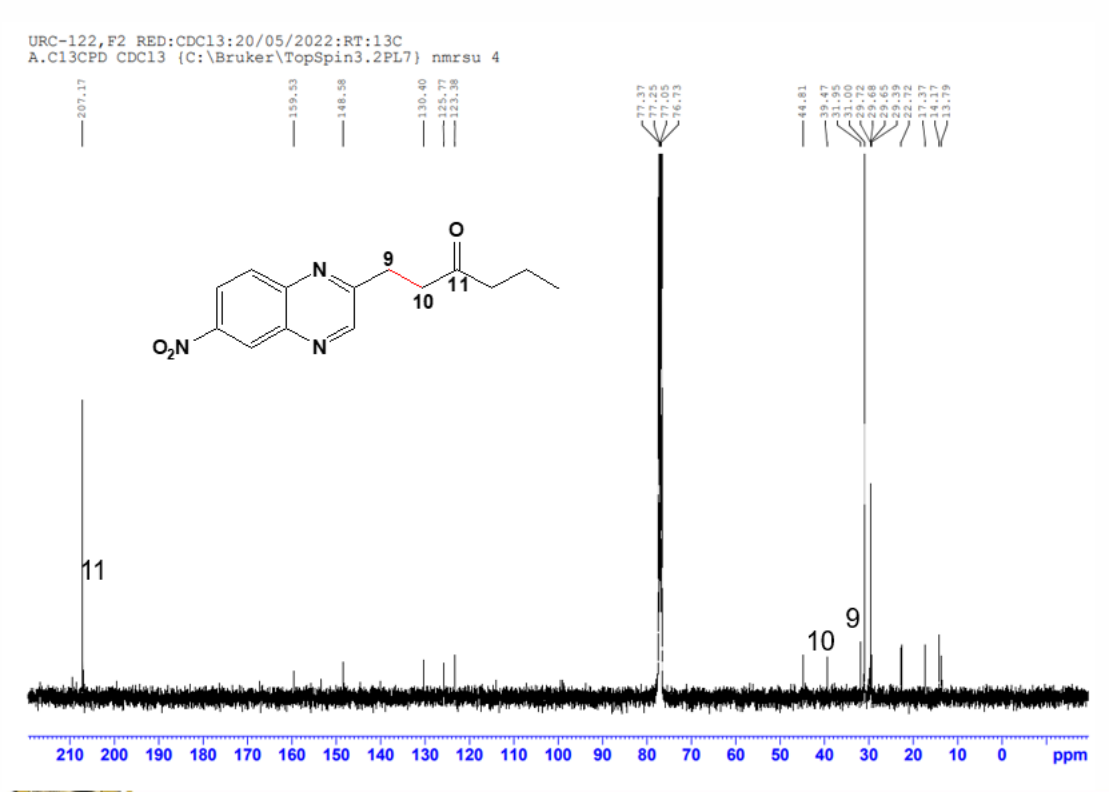


FIGURE 2.2: ^{13}C NMR spectrum of selectively reduced 1-(6-nitroquinoxaline-2-yl) hexan-3-one **36**.

The ^{1}H NMR of compound **36** (**Figure 2.1 C**) showed the presence of two triplets signal around 3.11-3.37 ppm, each integrated for two hydrogens that are consistent with hydrogens at carbon C9 and C10 indicating the presence of two CH_2. The presence of signal C9 and C10, also triggered the shift of signals on nitro quinoxaline, the singlet signal shifted to a lower chemical field at around 8.93 ppm from 9.09 ppm. The other benzene proton signals also show the slight shift from higher to lower chemical field. The ^{13}C NMR spectrum of **36** (**Figure 2.2**) showed the total of 11 carbons instead of 14 carbons, which suggest an overlapping of equivalent carbons. The signal at 209.43 ppm is more intense and is consistent with the carbonyl carbon at ketonic region and other tertiary carbons from benzene side. It also showed the presence of alpha and beta carbons at 39.47 and 29.63 ppm respectively. The cosy spectrum also confirms the corelations of hydrogens on C9 and C10 through ^{3}J-coupling. The high-resolution mass spectrum was also in agreement with the molecular weight of structure ($C_{14}H_{16}N_3O_3$ = 274.1113), where $[M + H]^+$ = m/z 274.1193 was observed in **Figure 2.18 (Appendix 1)**.

In an effort to improve the yield, we increased the number of equivalences of $SnCl_2$ to 1.5 eq. at 25˚C for 3 hours and a better yield of 1-(6-nitroquinoxaline-2-yl)hexane-3-one **36** was isolated in 60%**,** with the recovery of unreacted starting material**.** The ^{1}H NMR and ^{13}C NMR also showed the peaks in **Figure 2.1 C** and **Figure 2.2**.

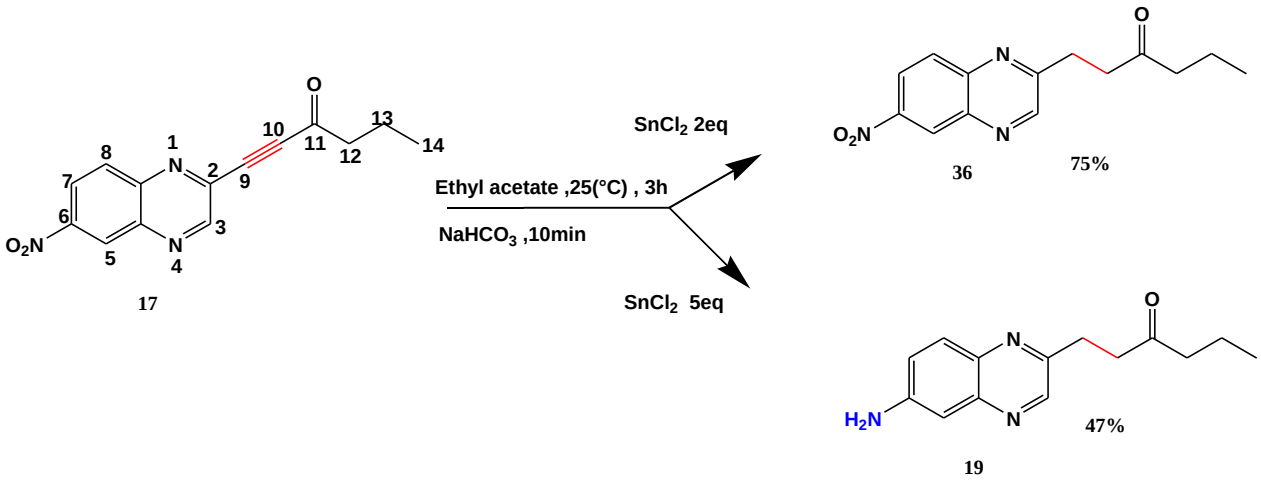
When changing the equivalence of $SnCl_2$ to 2 eq., for 1 hour at 25˚C and 1 and half hour reactions gave the corresponding yields of 57% and 70% respectively, with starting material being recovered. As we increase time to 3 hours, it gave the yield of 74% pure product **36**, confirmed by ^{1}H and ^{13}C N MR in **Figure 2.1 C** and **Figure 2.2** respectively.

By changing the temperature to 60˚C, using 2 eq. of $SnCl_2$ for 3 hours, we were able to isolate 1-(6-nitroquinoxaline-2-yl)hexane-3-one **36** in 80% yield as indicated by NMR analysis, with a lot of impurities. This showed that the high temperature gives the reaction chance to produce the unrecognised by-product. The NMR analysis also contains peaks similar to the ones on **Figure 2.1 C** and **Figure 2.2**.

We also tried to do our reaction in the presence of acid, where compound **17** was treated with HCl and 2 eq. of $SnCl_2$ in ethyl acetate at 25˚C for 3 hours. After the reaction, the work-up was challenging because of the difficult in removing HCl on a large scale. Nuclear magnetic resonance analysis showed the presence of product mixed with a lot of inseparable impurities and there was no recovered stating material. Therefore, we chose not to pursue this route further.

We also did our reduction reaction using compound **17** in the presence of two drops deuterium oxide (D_2O) using the same reduction conditions as of **36**. The purpose was to check if water was the source of hydrogens. During the reaction, the TLC analysis showed the presence of product formation, and the NMR analysis confirmed the consumption of all the starting material to afford compound **36** in yield of 60%, showing the only reduction on alkynes group. From this reaction, our assumption was that if water is the source of additional hydrogens, then there will be a deuterium fast exchange with protons observed around 3.11-3.37ppm on the ^{1}H NMR. However, the expected exchange was not conclusive, since ^{1}H NMR showed the presence of reduced triplet signal. We further characterised the product using HRMS to check the addition of deuterium to mass of compound **36** (M + D_2O), instead only mass of **36** $[M+H]^+$ = m/z 274,1193 was observed. However, the results were not conclusive, we

still need to do more reaction and characterisation for confirmation. Therefore, further characterization was performed to confirm if water is truly the source by checking the presence of masses that contains deuterium is required.



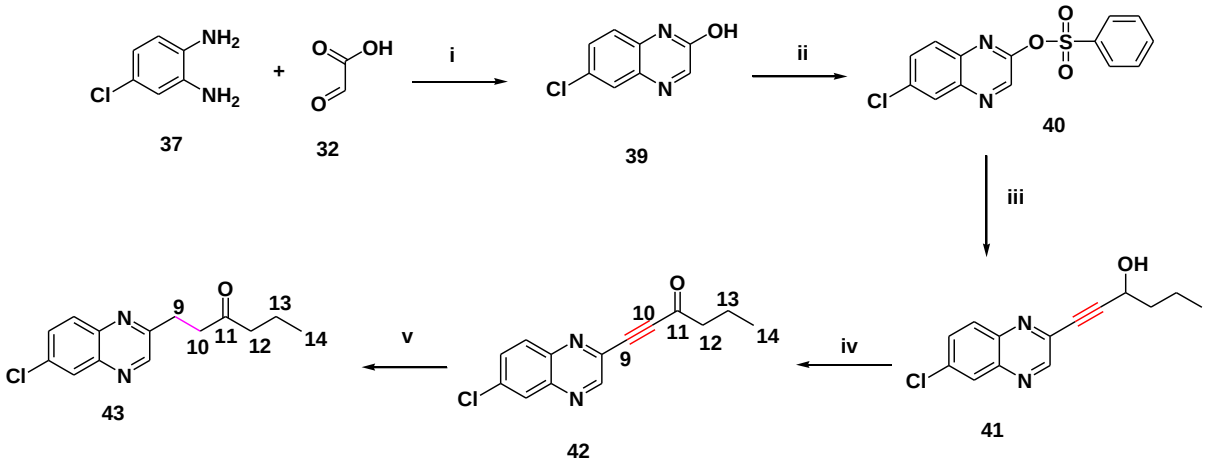
17 36 19

Scheme 2.2: The synthesis of compound **36** and **19**.

From our optimised conditions, we observed that when reacting 1-(6-nitroquinoxalin-2yl)hex-1-yn-3-one **17** with 5 eq. of $SnCl_2$ in ethyl acetate for 3 hours at 25˚C, the isolated compound **19** showed the reduction of both alkynes and nitro group in the yield of 47%. However, when the number of equivalences of $SnCl_2$ changes to 2 eq using the same conditions, an isolated product **36** showed the selectively reduced alkynes with the nitro group remaining unchanged. This was due to the presence of carbonyl (ketone) pulling electrons density towards itself through inductive and resonance effect because it is possible that the conjugated pi system between alkyne and carbonyl groups weakened the triple bond [6]. In that case. it causes the neighbouring alkyne to destabilise and become more reactive towards $SnCl_2$.

Conversely, we noted that when the carbonyl group is replaced with the alcohol (OH) group, the reduction of triple bonds does not happen. This could be because the OH is an electron donating group and will only stabilise the neighbouring alkyne causing it to be unreactive.

2.2. What would happen if we substituted nitro group with chloro on 1-(6-nitroquinoxaline-2-yl)hex-1-yn-3-one 17



i = Acetic acid, MeOH, 0°C, 90 min

ii = Benzenesulfonyl Chloride, DMAP, Et_3N, DCM, 0 °C , 90 min.

iii = $PdCl_2(PPh_3)_2$ 5mol%, CuI 10mol%, Et_3N 2eq. , 1-Hexyn -3-ol , Dry THF, 60°C Overnight

iv = Pyridinium ChloroChromate(PCC) 5eq., DCM

v = $SnCl_2$ 5eq., Ethyl Acetate(EtOAc) , 25 °C, 3h, $NaHCO_3$ 10min

Scheme 2.3: Synthesis steps of compound **43.**

The same procedure as for **33** was followed to make 6-chloroquinoxaline derivatives which was initiated by cyclo-condensation between 4-chloro-1,2-diaminobenzene **37** and glyoxylic acid **32** in methanol and acetic acid following the method reported by Lerato et al. [7] to afford cychloquinoxaline-2-ol **39** in 70% yield. The ^{1}H NMR characterisation showed peaks integrating for 5 protons at the region which was consistent with what was previously reported.

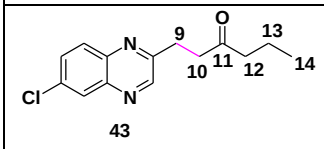
The next step followed was sulphonation of **39** to generate a suitable precursor **40**, with a good leaving group. Compound **39** was reacted in the presence of Et_3N in a DMAP catalysed reaction to afford 6-chloroquinoxalin-3-yl benzenesulfonate **40** in 78% yield. From the ^{1}H-NMR we observed new signals overlapping with signals from the quinoxaline constituent resonating at 7.60, 7.71, 7.82 and 8.12 ppm which integrated for 2:2:1:3 protons of the compound. Furthermore, a characteristic peak of

a singlet resonating at 8.65 ppm (–N=C-H) defining the quinoxaline constituent was observed [7].

followed by Sonogashira cross coupling in which same conditions as of **35** were used and able to produce the corresponding 1-(6-choroquinoxalin-2yl)hex-1-yn-3-ol **41** in 90% yield. The ^{1}HNMR of compound **41** showed the presence of the OH broad peak at around 2.79 ppm integrating for one hydrogen and the triplet signal at around 4.70 ppm integrating for one hydrogen.

After we followed the same procedure as of **17** for oxidation, using PCC (5 eq.) as the oxidising agent in DCM for 3 hours at room temperature, we were able to isolate 1-(6-chloroquinoxalin-2yl)hex-1-yn-3-one **42** in 76% yield. The ^{1}HNMR analysis showed the disappearance of the OH broad singlet signal appeared at 2.79 ppm on the ^{1}H NMR of compound **41**. The disappearance of the triplet signal integrating for one hydrogen which was at 4.70 ppm on the tertiary carbon with alcohol, triggered the signal for hydrogens at alpha carbon (C12) to change its multiplicity from multiplets to triplet.

Table 2: The $SnCl_2$-catalysed reduction of alkynes to produce compound 43.

Compound	Run	No. of equivalence of $SnCl_2$	Temperature (˚c)	Time(hours)	%Yield
 43	1	2	25	3	55
	2	5	25	3	73

The reduction reaction of compound **42** were performed under the same conditions as of **19** and **36.** From the optimised reaction conditions, the most suitable equivalence of $SnCl_2$ was previously found to be 2 and 5 equivalence at 25˚C for 3 hours (**Table1**). When 2 eq of $SnCl_2$ (run 1) reacted with compound **42** in EtOAc, the product of 1-(6-chloroquinoxaline-2-yl)hexane-3-one was isolated in the low yield of 55%, with starting material being recovered to show incomplete reaction. The increase in time and the temperature did not improve the yield, but when the number of equivalences for $SnCl_2$ was increased to 5 eq (run 2), using the same conditions the yield increased to 73%

with no starting material being recovered (**Table 2**). Therefore, we observed that the reduction method works with or without the nitro group.

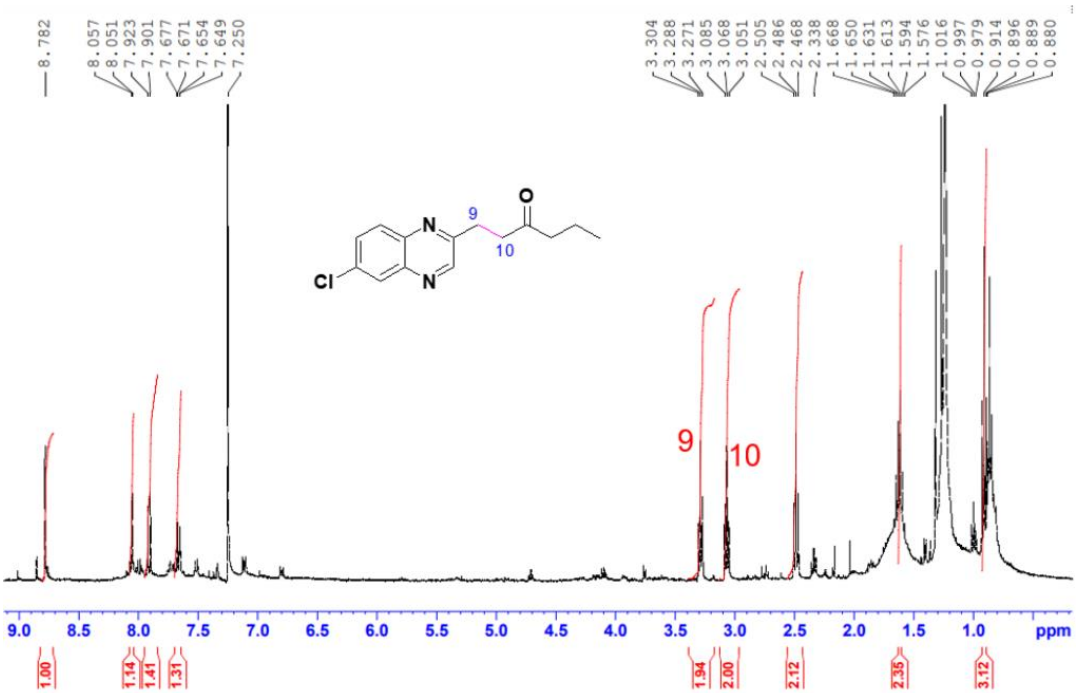


Figure 2.3: The ^{1}HNMR spectrum of 1-(6-chloroquinoxaline -2-yl)hexan-3-one **43**.

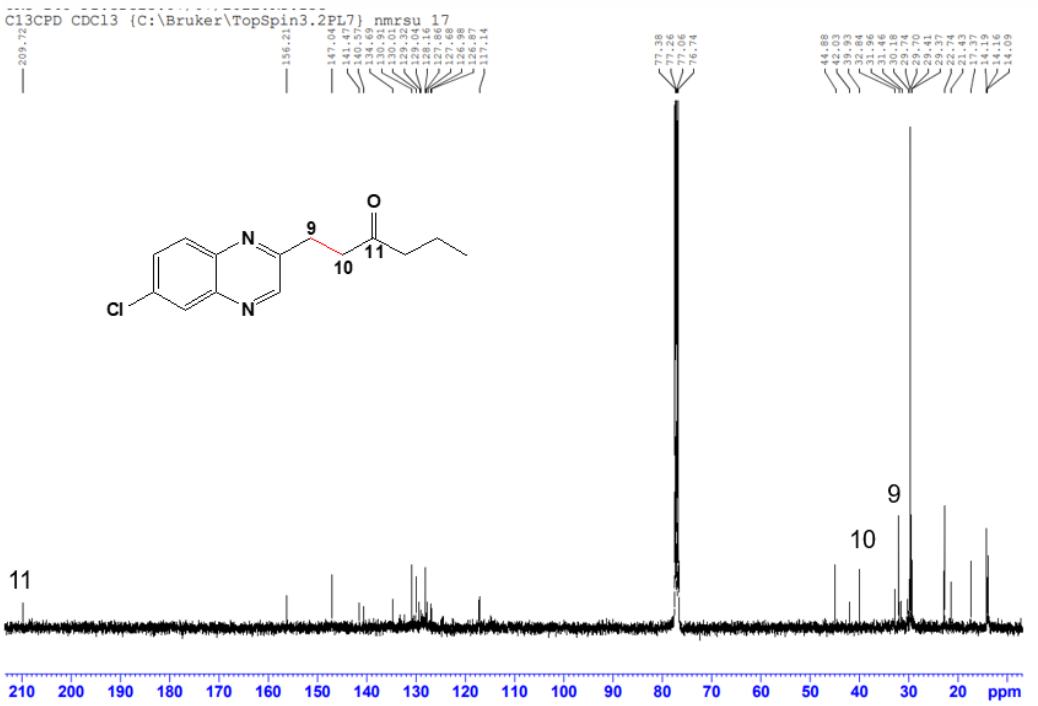


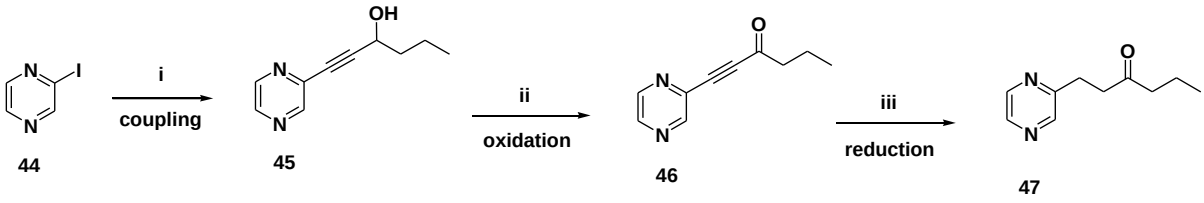
Figure 2.4: The ^{13}CNMR spectrum of 1-(6-nitroquinoxaline -2-yl)hexan-3-one **43**.

The ^{1}H NMR spectra of compound **43** (**Figure 2.3**), shows the presence of two triplet signals resonating from 3.05-3.30 ppm each integrating for two hydrogens suggesting the presence of methylene (CH_2). These two CH_2 are consistent with hydrogens on carbon C9 and C10. The ^{13}C NMR (**Figure 2.4**) also showed the presence of the carbonyl peak at around 209.72 ppm and two methylene peaks at 39.93 ppm for alpha and 31.96 ppm for beta.

2.3. Investigating reactivity of other N-heterocyclic compounds towards the reduction of alkynes using $SnCl_2$.

We increased the scope by investigating other N-heterocyclic compounds (pyrazine, pyrimidine, and pyridine) containing α, β - alkynyl carbonyl for the reduction of alkyne to alkane to confirm whether $SnCl_2$ can also reduce other alkynes attached to different heterocyclic compounds.

2.3.1. Reduction reaction of pyrazine



i = $PdCl_2(PPh_3)_2$ 5mol%, CuI 10mol%, Et_3N 2eq., 1-Hexyn -3-ol , dry THF, 60°C Overnight

ii = Pyridinium ChloroChromate (PCC) 5eq., DCM

iii = $SnCl_2$ 5eq., Ethyl Acetate (EtOAc) , 25°C, 3h, $NaHCO_3$ 10min

Scheme 2.4: Synthesis steps of compound **47**.

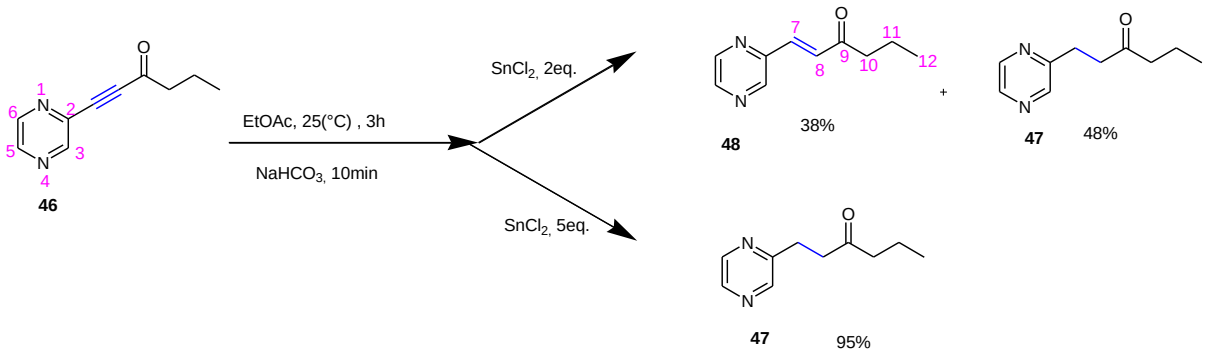
To make the reduction of the pyrazine scaffold we followed the reaction steps showed in **Scheme 2.4.** Firstly, introduced the Sonogashira cross coupling reaction, using compound **44** with hex-1-yn-3-ol in the presence of palladium $PdCl_2(PPh_3)_2$, (5 mol%), Et_3N (2 eq.) and CuI (10 mol%) in THF at 60^{o}C under N_2 atmosphere for 16 hours in a sealed reaction tube. After doing the usual work-up, followed by purification, 1-(pyrazin-2-yl)hex-1-yn-3-ol **45** was obtained in 90% yield. However, there were

challenges we experienced; when doing the reaction in a round bottom flask of small to large size (50-100 ml) at a small scale of less than 200 mg starting material, the reaction ran smoothly and produced the desired product. But when increasing the scale of starting material to 500 mg, under the same conditions, the TLC and NMR analysis showed the recovered starting material with no trace of the desired product. Therefore, we decided to switch from the round bottom flask to the sealed reaction tube and we manage to produce the higher percentage yield of the desired product at any scale of our choice including 1g.

The ^{1}H NMR spectra of compound **45** showed a noticeable triplet signal at 4.52 ppm, integrating for one proton which is consistent with the methine group next to the electron withdrawing oxygen atom. The presence of a broad singlet signal at 2.15 ppm, which integrated for one proton is consistent with hydrogen of the hydroxyl group (OH). The triplet signal at 0.96 ppm is an indicative of the presence of a CH_3 next to the methylene group (CH_2) in the compound. The two multiplets signals at around 1.76-1.89 ppm and 1.51-1.59 ppm, integrated for two protons that are consistent with two methylene groups. The ^{13}C NMR spectrum, also showed the presence of two acetylene group at 94.5 ppm for alpha carbon and 81.3 ppm for beta carbon.

After the successful coupling of compound **45**, it was followed by oxidation reaction by reacting it with PCC (5 eq.) in DCM for 3 hours at room temperature. After filtering through silica gel and the usual work-up, flash column chromatography was used to purify the residue using a mixture of MeOH/DCM to afford the pure brown oily 1-(pyrazin-2-yl)hex-1-yn-3-one **46** in 86% yield.

The ^{1}H NMR spectrum showed the disappearance of the OH broad singlet signal which was at 2.15 ppm on the ^{1}H NMR of compound **45**. The disappearance of the triplet signal at 4.52 ppm on the tertiary carbon with alcohol triggered the signal for hydrogens at alpha carbon (C10) to change its multiplicity from multiplets to triplet at around 2.70 ppm. The ^{13}C NMR spectrum of **45** showed a signal at 186.2 ppm which is consistent with the carbonyl carbon at the ketonic region.



Scheme 2.5: The synthesis of reduced compound **47** and **48**.

The oxidised compound **46 (Figure 2.5 A)**, was then used as a starting material for our investigation in the reduction reaction. The same optimised conditions as for compound **36** were followed using 1-(pyrazin-2-yl)hex-1-yn-3-one **46** and 2 eq. of $SnCl_2$ in ethyl acetate running the reaction at 25˚C for 3 hours and monitoring the reaction on TLC. After the usual work-up using ethyl acetate to extract, flash column chromatography was used to purify the residue in a mixture of hexane/ethyl acetate. To our surprise the reaction gave a mixture of separable products **48** and **47** in the yields of 38% and 48% respectively, both as a yellow oil.

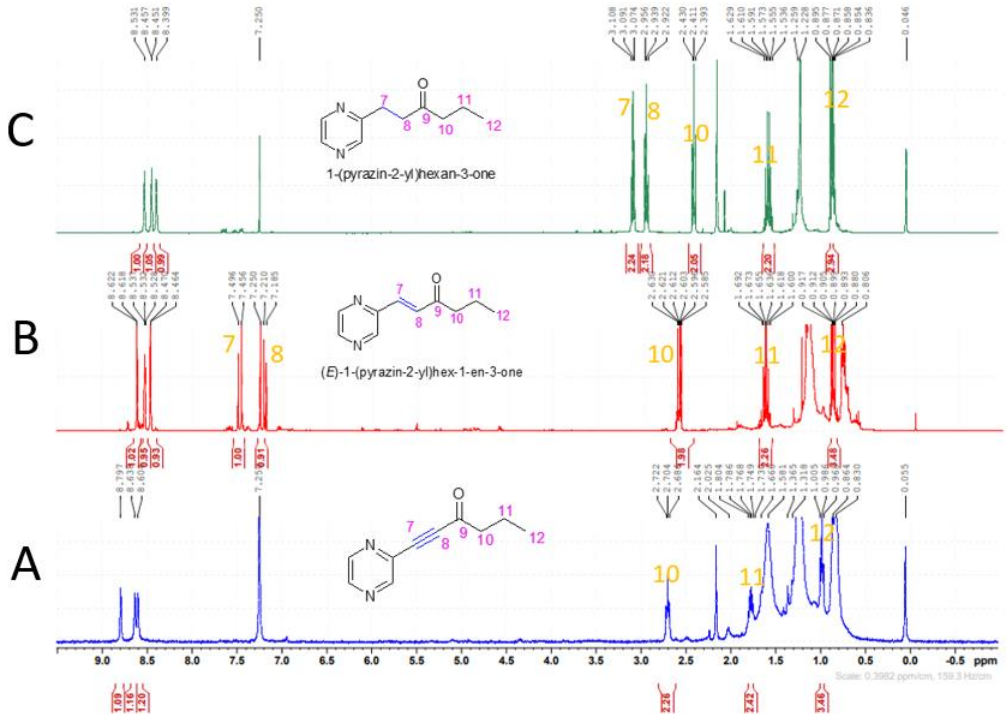


FIGURE 2.5: ^1H NMR spectrums of reduced compounds **47** and **48** from oxidised compound **46**.

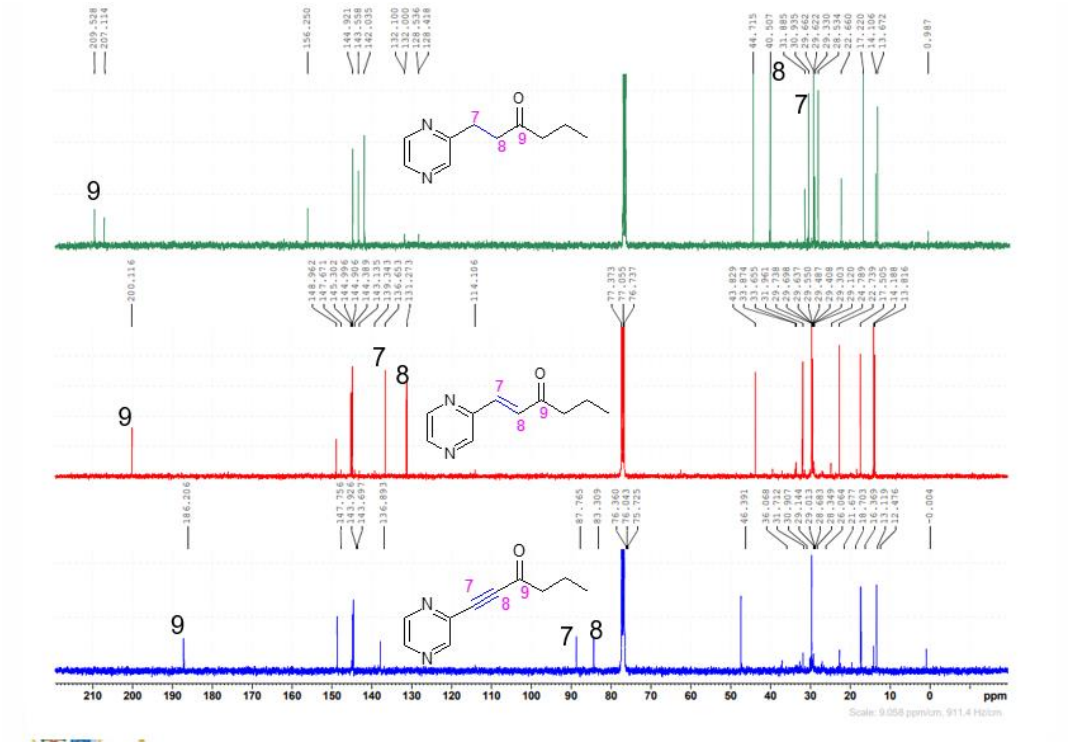


FIGURE 2.6: ^{13}C NMR spectrum spectrums of reduced compounds **47** and **48** from oxidised compound **46**.

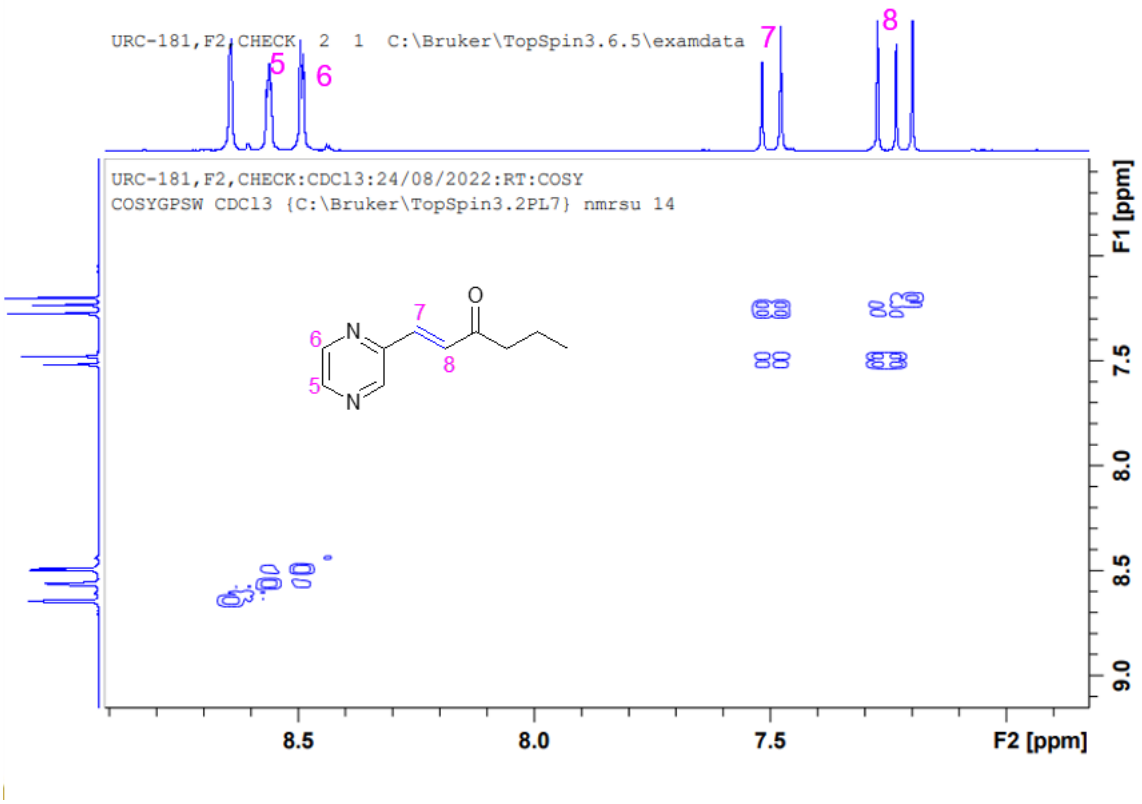


Figure 2.7: The COSY NMR spectrum of compound **48**.

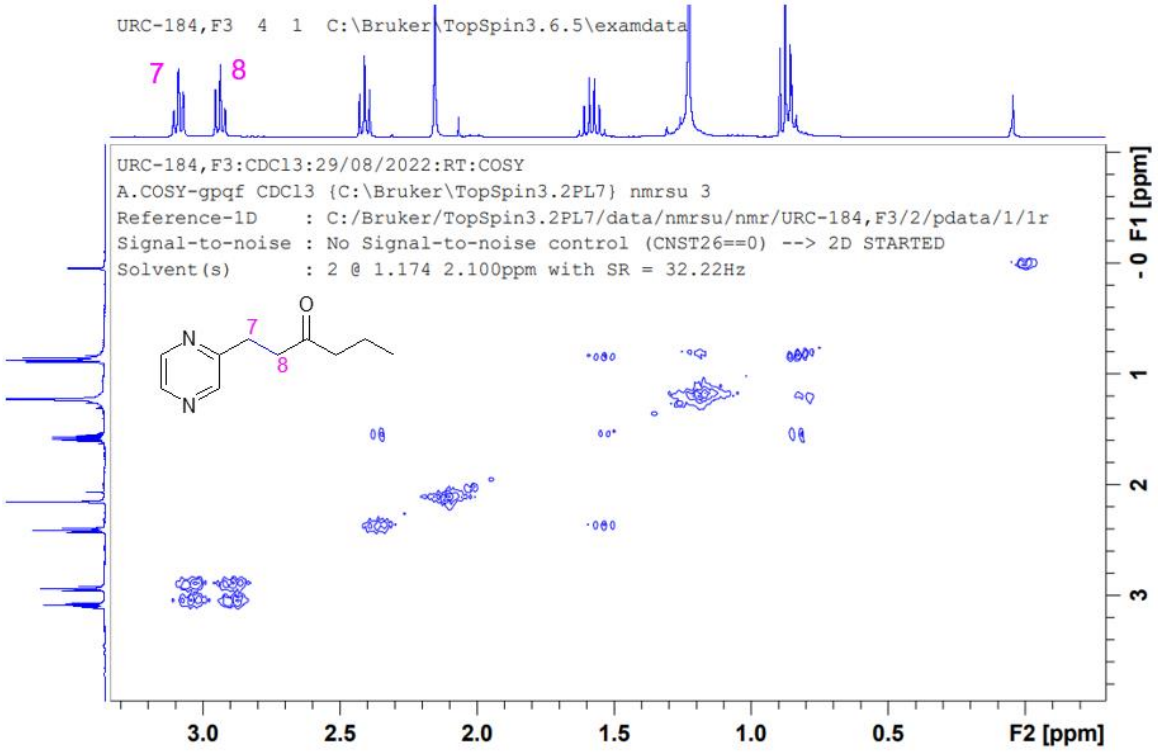


Figure 2.8: The COSY NMR spectrum of compound **47**.

The proton NMR of compound (E)-1-(pyrazin-2-yl)hex-1-en-3-one **48 (Figure 2.5 B)**, showed the presence of two ethylene signals which are trans to each other due to J-value of equal to 15 Hz. These two doublets' signals resonate around 7.55 ppm and 7.30 ppm, and each integrate for one hydrogen which is consistent with beta hydrogen on carbon C7 and alpha hydrogen on C8. The ^{13}C NMR (**Figure 2.6**) also showed the presence of the carbonyl peak at around 200.1 ppm and the two ethylene peaks for C7 at 136.7 ppm and C8 at 131.3 ppm. The cosy spectrum (**Figure 2.7**) also indicated that the hydrogens on C7 only corelate with hydrogens on C8 and hydrogens on carbon C5 only correlate with hydrogens on C6. The high-resolution mass spectrum was also in agreement with the molecular weight of structure (for $C_{14}H_{18}N_3O$ 177.1030), where $[M + H]^+$ = m/z 177.1303 was observed in **Figure 2.22 (Appendix 1)**.

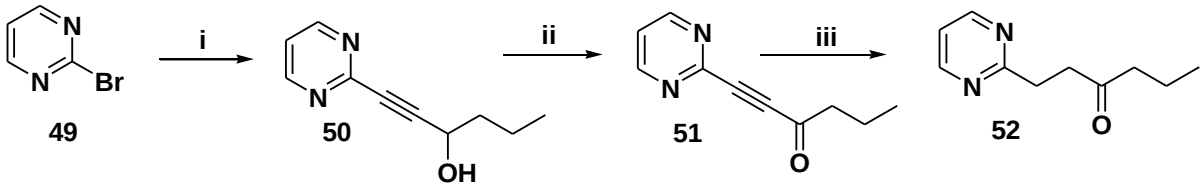
The proton NMR of **47** (**Figure 2.5 C**), showed the presence of two methylene (CH2) signals resonating at 2.94 ppm and 3.09 ppm indicating a complete reduction of alkyne to alkane. Each triplet's signal integrates for two hydrogens which are consistent with

beta hydrogens on C7 and alpha hydrogens on C8. The addition of hydrogens to form alkane, triggered the change in the multiplicity of hydrogens on pyrazine. The hydrogen on C3 changed from doublet to singlet. The ^{13}C NMR spectrum (**Figure 2.6**) also shows the presence of carbonyl peak at 209.98 ppm and two peaks of C7 on 39.8 and C8 at 44.8 ppm. The cosy spectrum (**Figure 2.8**) also indicates the correlation between two methylene through ^{3}J-coupling. The high-resolution mass spectrum was also in agreement with the molecular weight of structure (for $C_{10}H_{15}N_2O$ = 179.1106), where $[M + H]^+$ = m/z 179.1177was observed in **Figure 2.23**.

However, when repeating the reaction using 2 eq. and leave it for overnight, the reaction goes to completion and give the corresponding 1-(pyrazin-2-yl) hexan-1-yn-3-one **47** in 80% yield.

When we repeat the same optimised conditions as for compound **19**, using compound **45** with 5 eq. $SnCl_2$ in ethyl acetate at 25˚C for 3 hours, and monitoring it using TLC and NMR analysis, we isolated a complete pure product of 1-(pyrazin-2-yl) hexan-1-yn-3-one **47** in excellent yield of 95%.

2.3.2. Reduction reaction of pyrimidine.



i = $PdCl_2(PPh_3)_2$ 5mol%, CuI 10mol%, Et_3N 2eq. , 1-Hexyn -3-ol , Dry THF, 60°C Overnight

ii = Pyridinium ChloroChromate(PCC) 5eq., DCM

iii = $SnCl_2$ 5eq., Ethyl Acetate(EtOAc) , 25°C, 3h, $NaHCO_3$ 10min

Scheme 2.6: Synthesis steps of compound **52**.

Turning our attention to pyrimidine, the same coupling reaction procedure as for compound **45** was followed using 2-bromo pyrimidine with hex-1-yn-3-ol in the presence of palladium $PdCl_2(PPh_3)_2$, (5 mol%), Et_3N (2 eq.) and CuI (10 mol%) in THF at 60^{o}C, under N_2 atmosphere for 16 hours in a sealed reaction tube. After the usual

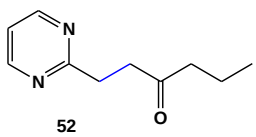
work-up was done, followed by purification by flash chromatography using a mixture of hexane/ethyl acetate 1-(pyrimidine-2-yl)hex-1-yn-3-ol **50** was obtained in 98% yield.

The ^{1}H NMR spectrum of compound **50** showed a noticeable triplet signal at 4.64 ppm, integrating for one proton, which is consistent with the methine group next to the electron withdrawing oxygen atom. The presence of a broad singlet signal at 2.16 ppm, which integrated for one proton is consistent with hydrogen of the hydroxyl group (OH).

With compound **50**, indicating the successful coupling, we then continued with oxidation, following the same procedure as for compound **46**. Compound **50** was reacted with PCC (5 eq) in DCM for 3 hours at room temperature. After filtering through silica gel and the usual work-up, the residue was purified by flash chromatography using a mixture of methanol/DCM to afford the pure brown solid 1-(pyramidine-2-yl) hex-1-yn-3-one **51** in 77% yield.

The ^{1}H NMR spectrum showed the absence of the OH broad singlet signal which was at 2.16 ppm on the ^{1}HNMR of compound **50**. The disappearance of the triplet signal at 4.64 ppm on the tertiary carbon with alcohol, triggered the signal for hydrogens at alpha carbon (C8) to change its multiplicity from multiplets to triplet at around 2.70 ppm. The ^{13}C NMR spectrum of **51** showed a signal at 187.2 ppm which was consistent with the carbonyl carbon at the ketonic region.

Table 3: The $SnCl_2$-catalysed reduction of alkynes to produce compound 52.

Compound	Run	No. of equivalence of $SnCl_2$	Temperature (˚C)	Time (hours)	%Yield
 52	1	2	25	3	51
	2	5	25	3	80

The same procedure as **48** was followed using 1-(pymidine-2-yl) hex-1-yn-3-one with 2 eq. $SnCl_2$ in ethyl acetate running the reaction at 25˚C for 3 hours and monitoring the reaction on TLC. After the usual work-up using ethyl acetate to extract, the residue

was purified by flash chromatography using a mixture of hexane/ethyl acetate to afford a 1-(pyrimidine-2-yl)hexan-1-yn-3-one **52** as brown oil in 51% yield (run 1) as shown on **Table 3**, with starting material being recovered to show incomplete reaction.

When 1-(pymidine-2-yl) hex-1-yn-3-one was treated with 5 eq. $SnCl_2$ in ethyl acetate, using the same conditions as of **48**, after 3 hours of reaction, the TLC and NMR analysis indicated that the starting material was completely consumed and the pure corresponding product of 1-(pyrimidine-2-yl)hexan-1-yn-3-one **52** was produced in good yield of 80% (run 2).

The ^{1}H NMR spectrum of compound **52** (**Figure 2.9**) showed the presence of two triplets signals resonating around 2.96 - 3.29 ppm. Each signal integrates for two hydrogens which are consistent with methylene (CH_2) alpha C8 and beta C7. The ^{13}C NMR (**Figure 2.10**) is also in agreement with ^{1}H NMR by showing the presence of carbonyl peak at 209.98 ppm and the presence of C7 and C8 at 39.8 and 44.8 ppm respectively.

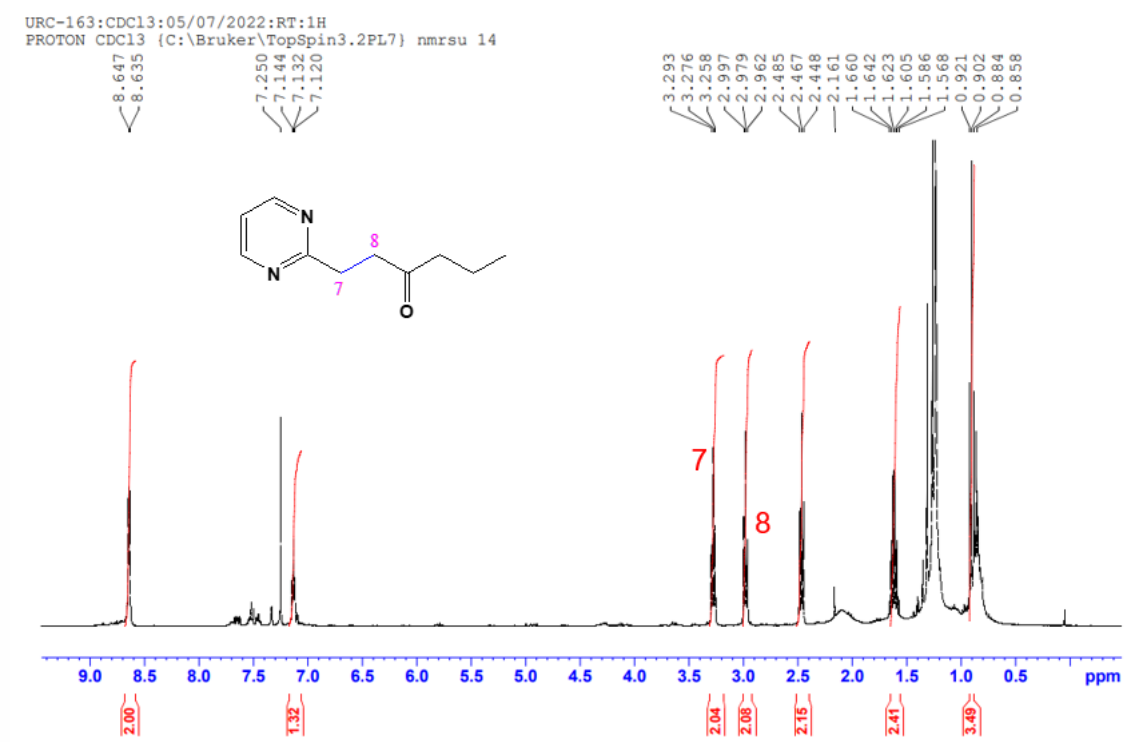


Figure 2.9: ^{1}H NMR spectrum of compound **52**.

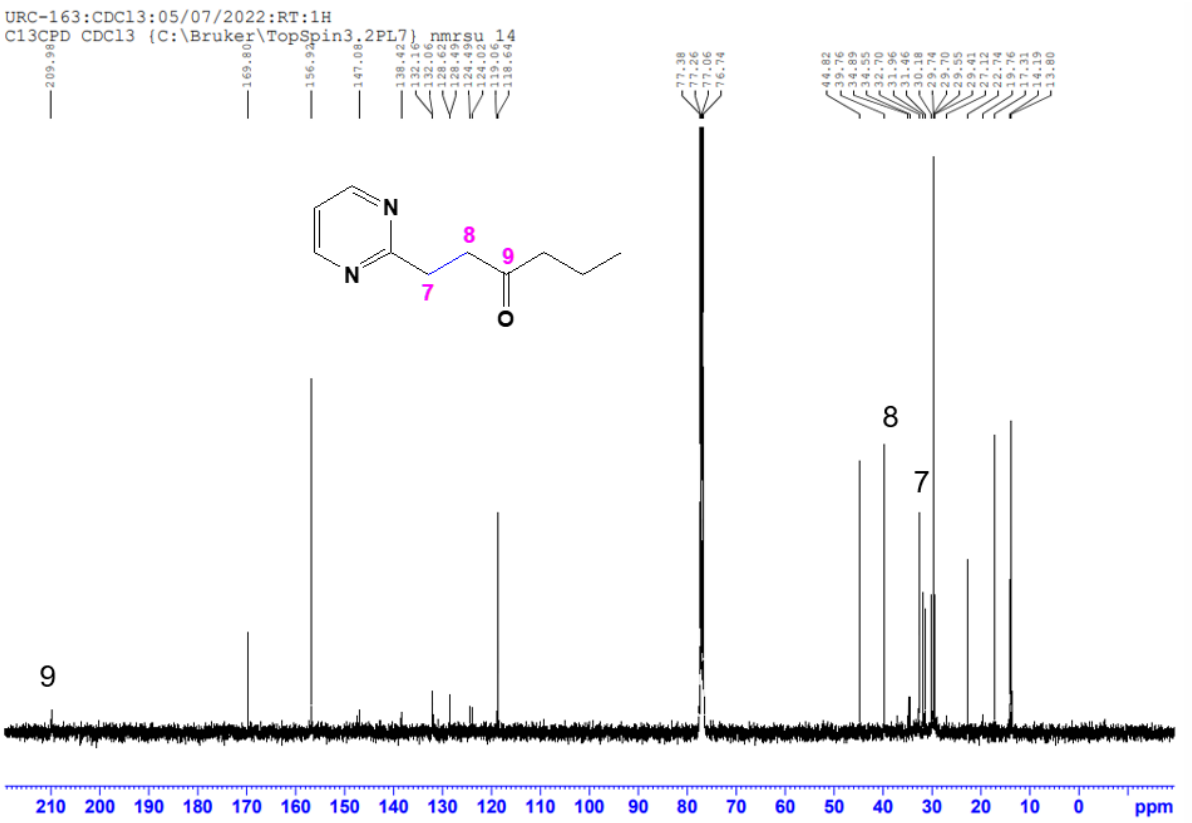
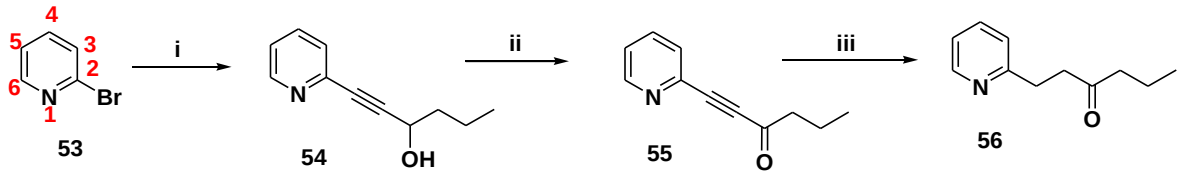


Figure 2.10: ^{13}C NMR spectrum of compound **52**.

2.3.3. Reduction reaction of pyridine



i = $PdCl_2(PPh_3)_2$ 5mol%, CuI 10mol%, Et_3N 2eq., -Hexyn -3-ol , Dry THF, 60°C Overnight

ii = Chromium trioxide 1.5eq., sulfuric acid, acetone, water

iii = $SnCl_2$ 5eq., Ethyl Acetate(EtOAc) , 25°C, 3h, $NaHCO_3$ 10min

Scheme 2.7: Synthesis steps of compound **56**.

After our investigation with pyrimidine and pyrazine, we turned our attention to pyridine. To produce our starting material for the reduction, we firstly followed the same coupling reaction procedure as for compound **45** using 2-bromo pyridine **53** with hex-1-yn-3-ol in the presence of palladium $PdCl_2(PPh_3)_2$, (5 mol%), CuI (10 mol%) and Et_3N (2 eq.) in THF at 60°C under N_2 atmosphere for 16 hours in a sealed reaction

tube. After the usual work-up was done, followed by purification by flash chromatography using a mixture of hexane/ethyl acetate, the pure yellow oil compound 1-(pyridine-2-yl) hex-1-yn-3-ol **54** was obtained 96% yield.

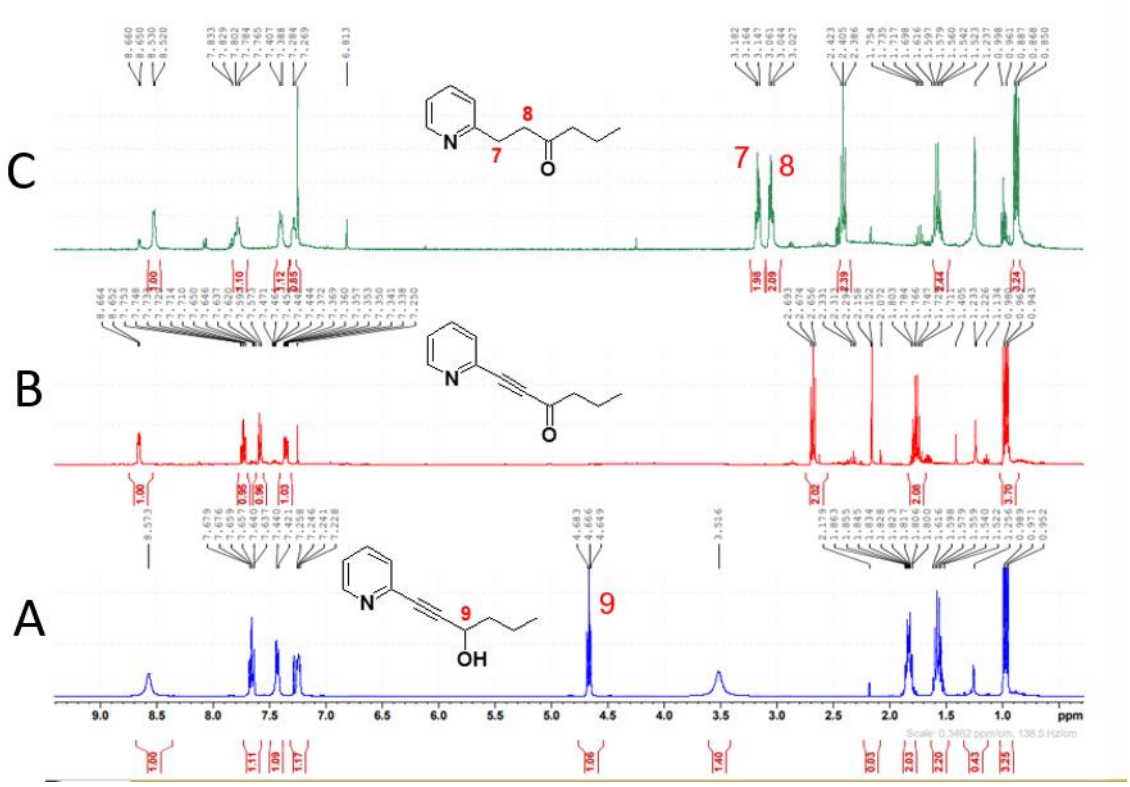


Figure 2.11: Stacked 1H NMR spectrum of compound **54**, **55**, and **56**.

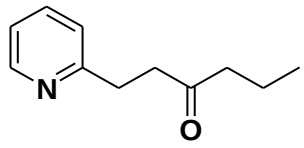
The ^{1}H NMR spectrum of compound **54** (**Figure 2.11 A**) showed a noticeable triplet signal at 4.67 ppm, integrating for one proton which is consistent with the methine group next to the electron withdrawing oxygen atom. The presence of a broad singlet signal at 2.18 ppm, which integrated for one proton is consistent with hydrogen of the hydroxyl group (OH). The ^{13}C NMR showed the total number of 12 carbon which are consistent with the carbons on the compound. The high-resolution mass spectrum was also in agreement with the molecular weight of structure (for $C_{11}H_{14}NO$ is 176.0997), where $[M + H]^+$ = m/z 176.1067was observed in **Figure 2.21 (Appendix 1)**.

After the successful coupling of compound **54**, oxidation reaction was introduced to synthesise ketone from the corresponding alcohol following the same method as of **46** using compound **54** with PCC (5 eq.) as oxidising agent in DCM for 3 hours at 25˚C. However, the method was unsuccessful due to difficult in removal of excess PCC. The NMR spectrum showed a trace amount of the product, together with a large amount of starting material. The crude material was then further reacted with Jones reagent

where compound **54** in acetone was added in the mixture of chromium trioxide, sulfuric acid, and water at room temperature for 16 hours to give the corresponding product of 1-(pyridine-2-yl) hex-1-yn-3-one **55** as brown oil in 73% yield.

The ^{1}H NMR spectrum in **Figure 2.11 B** showed the absence of the OH broad singlet signal which was at 2.18 ppm on the ^{1}H NMR of compound **54**. The disappearance of triplet signal at 4.67 ppm on the tertiary carbon with alcohol, triggered the signal for hydrogens at alpha carbon (C8) to change its multiplicity from multiplets to the triplet at around 2.70 ppm. The ^{13}C NMR spectrum of **55** showed a signal at 209.9 ppm which is consistent with the carbonyl carbon at the ketonic region.

Table 4: The $SnCl_2$-catalysed reduction of alkynes to produce compound 56.

compound	Run	No. of equivalence of $SnCl_2$	Temperature (˚C)	Time(hours)	%Yield
	1	2	60	3	0
	2	5	60	3	60

The results of an attempted reduction of compound **55** are listed in **Table 4**. Compound **55** was subjected to similar optimised reaction conditions as for compound **51**. We firstly reacted compound **55** in the presence of 2 eq. $SnCl_2$ (run 1) in ethyl acetate at 25˚C for 3 hours. After monitoring the reaction on TLC, we observed that no reaction was taking place. Therefore, using the same crude we repeated the reaction by changing temperature to 60 ˚C for 3 hours. The TLC and NMR analysis also showed no product formation with 100% recovered starting material.

Following the same reaction conditions we then reacted compound **55** with 5 eq of $SnCl_2$ (run 2) in ethyl acetate for 3 hours at 60˚C, after monitoring with TLC and the usual work-up using ethyl acetate to extract, the residue was purified by flash chromatography using a mixture of hexane/ethyl acetate, to give the corresponding 1-(pyridine-2-yl) hexane-1-yn-3-one **56** as dark yellow oil in 60%yield.

The proton NMR of **56** (**Figure 2.11 C**), showed the presence of two methylene (CH_2) signals resonating at 3.04 and 3.17 ppm indicating a complete reduction of alkyne to alkane. Each triplet's signal integrates for two hydrogens which are consistent with alpha hydrogens on C8 and beta hydrogens on C8. The ^{13}C NMR spectrum (**Figure 2.12**) also shows the presence of the carbonyl peak at 210.2 ppm and two peaks of C7 at 30.3 ppm and C8 at 41.6 ppm. The cosy spectrum (**Figure 2.13**) showed the correlation between hydrogens on C7 and C8.

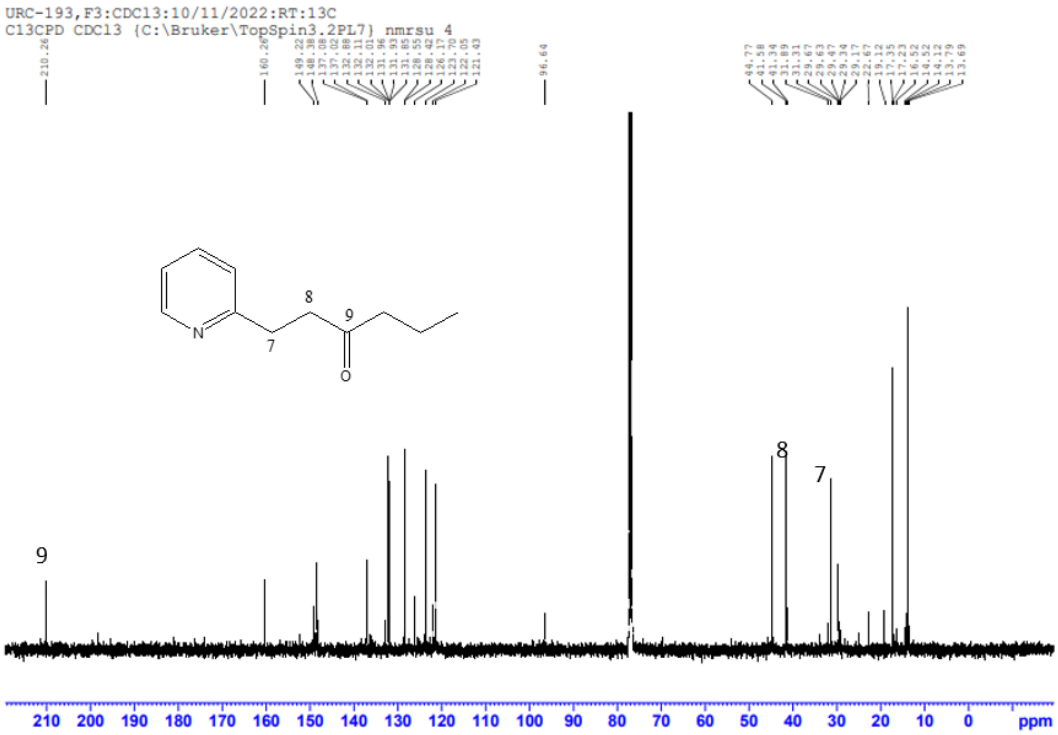


Figure 2.12: The ^{13}C NMR spectrum of compound **56**.

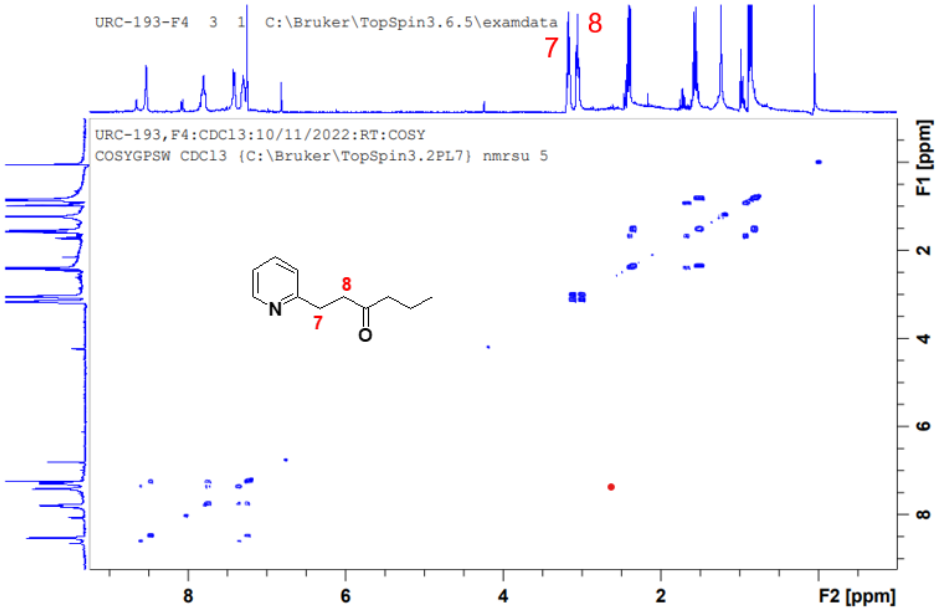
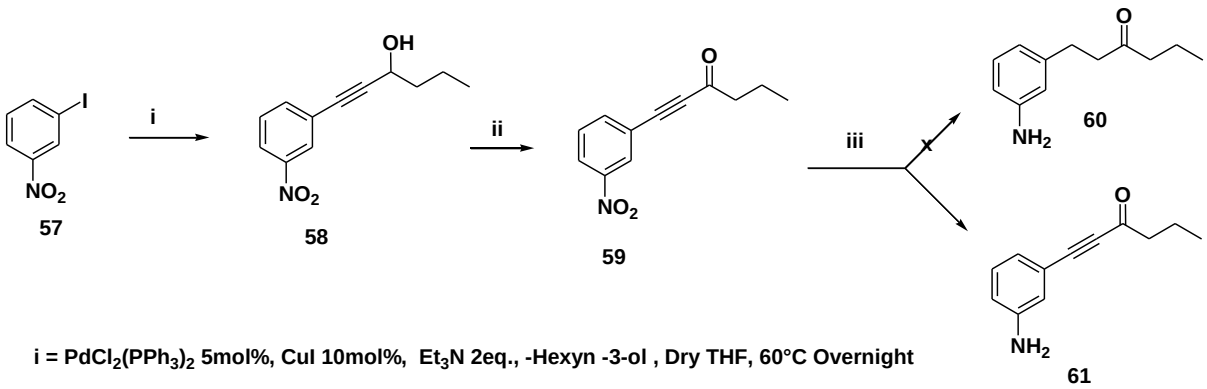


Figure 2.13: The Cosy spectrum of compound **56**.

2.4. Investigating the reduction of alkynes on aromatic compounds using $SnCl_2$ as a reducing agent

Significantly, the procedure worked well in a broad range of 6 membered N-heterocyclic compounds with α, β - alkynyl carbonyl as evident on NMR spectra of compounds **52** and **56**. We therefore decided to try aromatic compounds without heteroatom to check if this method is also applicable to other aromatic systems. We chose to work with various aromatic compounds such as nitrobenzene, iodonisole, 4-phenyl-2-butyn, and bromobenzonitrile.



i = $PdCl_2(PPh_3)_2$ 5mol%, CuI 10mol%, Et_3N 2eq., -Hexyn -3-ol , Dry THF, 60°C Overnight

ii = Pyridinium ChloroChromate(PCC) 5eq., DCM

iii = $SnCl_2$ 5eq. / 2eq., Ethyl Acetate(EtOAc) , 25°C, 3h, $NaHCO_3$ 10min

Scheme 2.8: Synthetic steps of compound **61**.

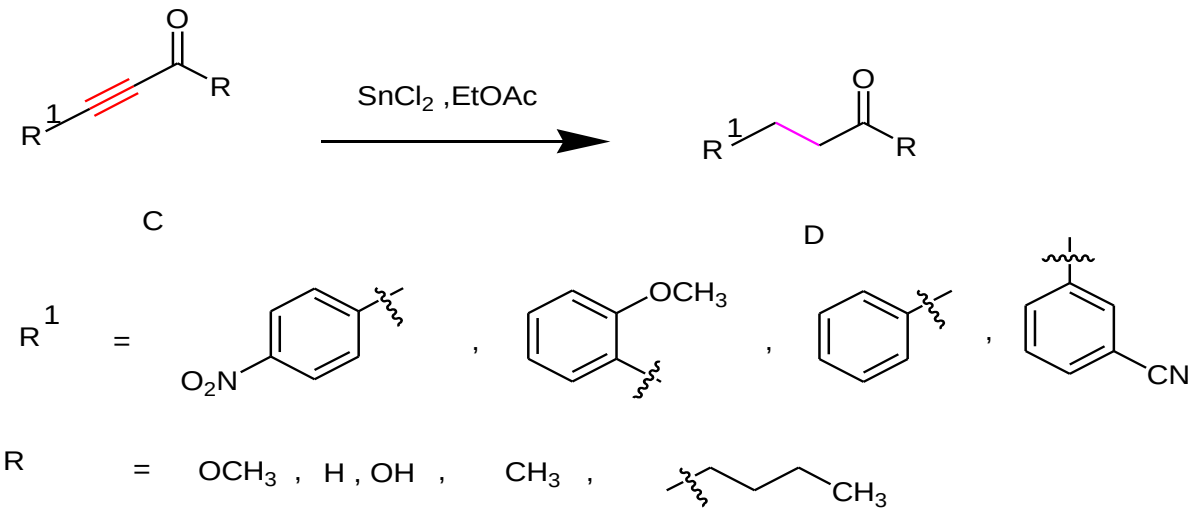
Firstly, we followed the coupling procedures reported by Karabo *et al*., by reacting 1-iodo-3-nitrobenzene with hex-1-yn-3-ol in the presence of palladium ($PdCl_2(PPh_3)_2$, 5 mol%), CuI (10 mol%) and Et_3N (2 eq.) in THF at 60°C under N_2 atmosphere for 16 hours in a sealed reaction tube, to give the corresponding 1-(3-nitrobenzene -2yl)hex-1-yn-3-ol **58** in 100% yield. The ^1H and ^{13}C NMR spectra of the product was consistent with the total number of hydrogens and carbons on the compound. After complete coupling we then continued with oxidation reaction, by reacting compound **58** with PCC (5 eq.) as oxidising agent in DCM for 3 hours at room temperature, to afford a corresponding 1-(3-nitrobenzene -2yl)hex-1-yn-3-one **59** as yellow solid in 80%yield.

The ^1H NMR spectrum showed the absence of the OH broad singlet signal appeared at 2.03 ppm on the ^1H NMR of compound **58**. The disappearance of the triplet signal at 4.61 ppm on the tertiary carbon with alcohol, triggered the signal for hydrogens at alpha carbon to change its multiplicity from multiplets to triplet at around 2.61 ppm.

After oxidation reaction, we did the reduction reaction of compound **59**, hoping to get the same results as of previous reactions. Following the optimised reaction conditions for the reduction we reacted compound **59** with 2 eq. of $SnCl_2$ in ethyl acetate for 3 hours at 60˚C. The TLC and NMR analysis showed the complete reduction of the only nitro group to amine, with the alkynes group remaining unchanged. We then decided to increase the number of equivalences of $SnCl_2$ to 5 eq. under the same conditions we manage to produce a compound **61** of 90% yield with only nitro group being reduced, instead of the expected compound **60** with both nitro and alkyne being reduced. Therefore, after trying with other aromatic system, the method failed to effect

reduction of alkyne to alkane, it only showed the reduction of the nitro group which was already known. The ^{1}H NMR showed a presence of NH_2 signal at around 3.47 ppm and there were not any other signals to show the reduction of the alkyne to alkane.

2.5. The limitations of the reduction using $SnCl_2$



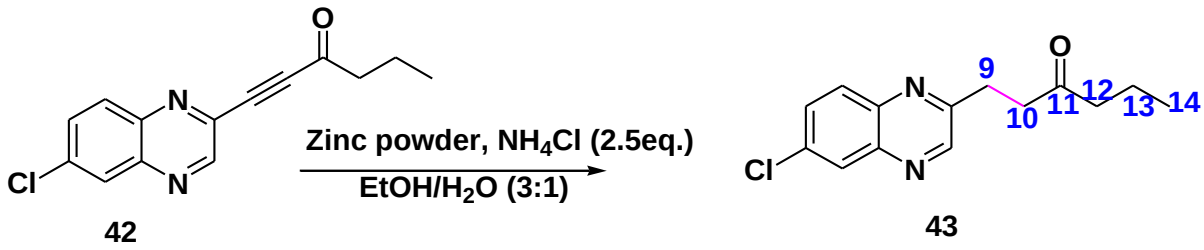
Scheme 2.9: The reduction reaction of aromatic compounds.

The reduction procedure using SnCl2 in the presence of ethyl acetate is limited to the specific heteroaromatic systems (**Figure 2.9**), as the reduction of non-heteroaromatic systems does not occur. The reduction does not take place in the presence of benzene derivatives compound. For the reduction to take place the compound should be N-heterocyclic, with carbonyl attached next to the alkyne. During the optimisation we observed that this reduction method is very sensitive to other experimental conditions such as the type of compounds (aromatic or heterocyclic), temperature (25 and 60˚C), time (3 hours), and the type of functional groups on the compound (ketone). The reduction procedure using SnCl2 in the presence of ethyl acetate is limited to the specific heteroaromatic systems,

2.6. Investigation of the reduction of α, β-alkynyl carbonyl using other metal salts such as zinc (Zn) and iron (Fe)

Further investigation for the reduction of α, β-alkynyl carbonyl compounds was introduced using other metal salts such as Zn and Fe salts. known to reduce nitro group into the amine.

2.6.1. Reduction reaction using Zn as a reducing agent



42 **43**

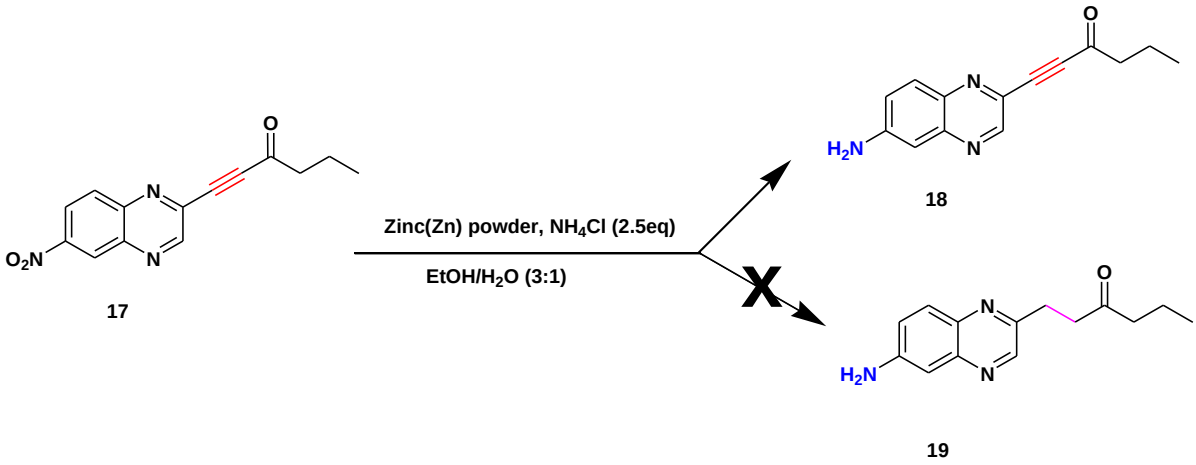
Scheme 2.10: The reduction reaction of compound **43** in the presence of Zinc powder.

Table 5: Zinc as a reducing agent for the reduction of alkynes to produce compound 43.

compound	run	No. of equivalence of Zinc powder	Temperature (˚C)	Time (hours)	%Yield
43	1	2	100	2	65
	2	5	100	2	100

From the oxidised compound **42**, the reduction reaction was conducted following the procedure reported by Gamble et al., [8]. The compound **42** was dissolved in the volume ration of 3:1 of EtOH/H_2O, followed by the addition of 2 eq. zinc powder and NH_4Cl. The reaction was monitored for 2 hours at 100˚C until the reaction was complete as indicated by TLC analysis. The reaction mixture was filtered through

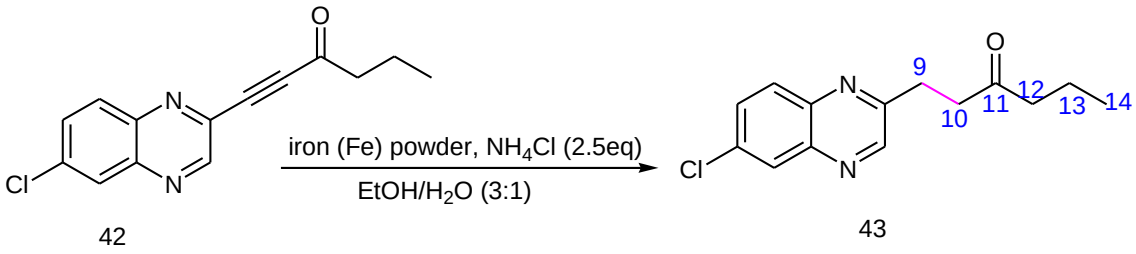
celite, and the solvent was removed under reduced pressure. After the crude was dissolved and extracted with EtOAc, followed by drying with $MgSO_4$ and concentrated under reduced pressure, the crudes were purified by flash chromatography to give the corresponding product **43** as brown solid in 65% yield (**Table 5)** with pure starting material being recovered. Therefore, to increase the yield, we adjusted our reaction conditions by increasing the number of equivalences of zinc powder to 5 eq. Using the same conditions, we were able to isolate compound **43** in an excellent yield of 100%. The ^{1}H and ^{13}C NMR spectra gave the same peaks as the one from reduction using $SnCl_2$ with the two reduced signals in the region 3.1- 3.3 ppm.



Scheme 2.11: The reduction reaction of compound **17** to give compound **18** and **19** in the presence of zinc powder.

When the reduction was done on 1-(6-nitroquinoxaline-2-yl)hex-1-yn-3-one **17** using 2 or 5 eq of Zn powder with NH_4Cl and the mixture of EtOH: H_2O at 100˚C for 2 hours, the reaction took place only on the nitro group to give compound **18**, and no reaction happened on the alkynes to give compound **19** as expected.

2.6.2. Reduction reaction using iron (Fe) powder as a reducing agent



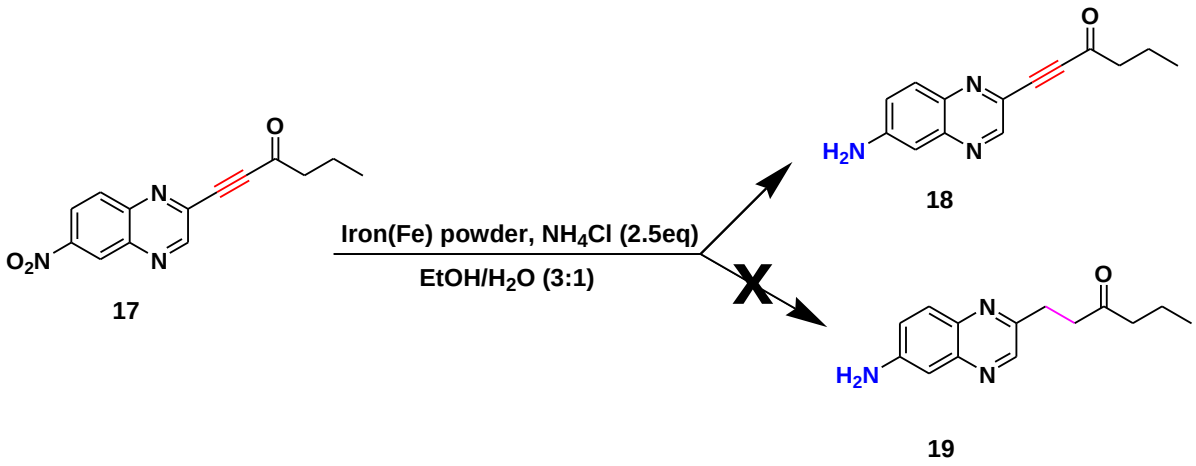
42 43

Scheme 2.12: The reduction reaction of compound **43** in the presence of Fe powder.

Table 5: Iron (Fe) as a reducing agent for the reduction of alkynes to produce compound 43.

Compound	run	No. of equivalence of Fe powder	Temperature (˚C)	Time (hours)	%Yield
43	1	2	100	2	60
	2	5	100	2	96

The same reduction reaction was conducted following the procedure reported by Gamble et al., [8]. The compound **42** was dissolved in the volume ration of 3:1 of EtOH/H_2O, followed by addition of 2 eq. zinc powder and NH_4Cl. The reaction was monitored for 2 hours at 100˚C until the reaction was complete as indicated by TLC analysis. After the work-up and purification by flash chromatography, the corresponding product of compound **43** was produced in 60% yield as shown in **Table 5** with recovered starting material. When we increase the number of equivalences of Fe powder to 5 eq following the same conditions, we were able to isolate compound **43** in excellent yield of 96%. The ^{13}C and ^{1}H NMR was similar to the one of reduction reaction using $SnCl_2$, with proton NMR showing the presence of two triplet signals resonating in the region 3.1-3. 3 ppm.



Scheme 2.13: The reduction reaction of compound **17** to give compound **18** and **19** in the presence of Fe powder.

When the reduction was done on nitro quinoxaline **17** (**Scheme 2.13**), the reaction took place only on the nitro group, but not on the alkyne group and it gave the corresponding compound **18** in 90% yield. The 1H NMR only showed the presence of reduced nitro group to amine group with signal at around 4.0 ppm.

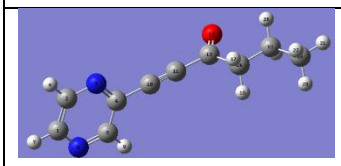
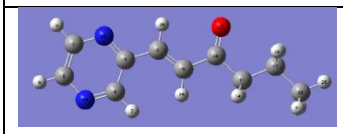
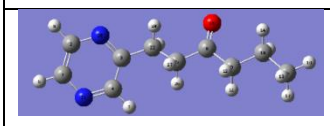
2.7. Computational results

2.7.1. Geometry Optimization

Geometry optimization of pyrazine derivatives in the gaseous phase was performed using DFT method with B3LYP/6-31+G (d, p) hybrid functional [9]. To show that the molecule has converged, the root-mean-square and the force was essentially zero, especially the maximum component of the force was below the cut-off of 0.00045 Newton. The calculated displacement for the next step was smaller than the defined cut-off value of 0. 0018 meter. The root-mean-square of the displacement for the next step was below its cut-off value of 0.0012. Therefore, all the structures for 1-(pyrazin-2-yl) hex-1-yn-3-one **46**, (*E*)-1-(pyrazin-2-yl)hex-1-en-3-one **48**, 1-(pyrazin-2-yl)hexane-1-yn-3-one **47** was converged to a ground state energy (minimum energy). **Table 7** shows the total energy, the dipole moment (D = 1 Debye), bond length and electronic spatial extent (a.u) of the converged structures. It can be clearly seen that the total energy per atoms of the compounds **46**, **48** and **47** shows the order of decreasing energy from the alkyne, alkene to alkane, -24.866, -22.927, -21.274

Hartree/atoms respectively. Note that a compound with the lowest energy value (more negative) is considered favourable otherwise less stable, while a positive energy corresponds to instability of the structure. Compound **46** was found to be more stable since it has highest negative value (-24.866 Hartree/atom). Furthermore, the compound has higher relative dipole moment of 4.6624D, which is the evidence of a molecule with higher binding affinity and hydrogen bond formation. It also has small electronic spatial extent of 4436.752 (a.u) which is the measure of the size of the molecule. From **Table 7,** the bond length of the pyrazine carbons shows an increasing order; alkyne **46**, alkene **48**, and alkane **47** with values 1.195,1.342 and 1.346Å respectively. Compound **46** has the shortest bond length and thus, is the strongest and have higher reactivity since it has a shorter bond length between the triple bonds. Compound **47** contains a weakest bond with lowest reactivity between C-C single bond since it has the longest bond length (1.346Å).

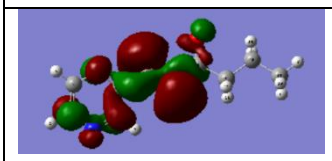
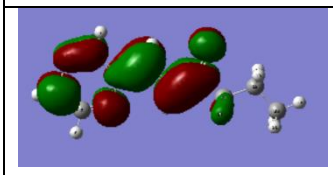
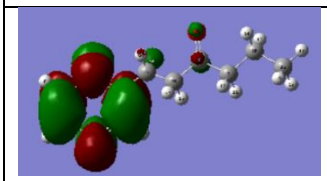
Table 7: The optimised structure of compound 46, 48 and 47 showing bond length(Å), dipole moment and electronic spatial extent (a.u).

structure	No of atoms	Bond length (Å)	SCF energy (A.U) in Hartree / atom	Dipole moment (Debye)	Electronic spatial extent (a.u)
 **46**	23	$C_{10}\equiv C_{11}$ =1.195	-24.866	4.6624	4436.752
 **48**	25	$C_8=C_9$ = 1.342	-22.927	4.076	5169.820
 **47**	27	C_{22}-C_{25} = 1.346	-21.274	3.414	4495.284

2.7.2. Frontier molecular orbitals.

The Frontier Molecular Orbitals (FMOs) of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of chemical species are essential pointers for chemical reactivity together with the kinetic stability of compounds [10]. HOMO is also known as outer orbital electron donating or nucleophilic and LUMO as inner orbital accepter electrons and is thus electrophilic. The energy difference between HOMO and LUMO orbitals is referred to as the energy gap. Note that the Magnitude-HOMO-LUMO energy gap (ΔE_{gap}) has a very significant chemical implication, large gap denoting a good thermodynamic stability of the compound and a small gap indicating easy electronic transition. The results revealed that compound **48** has a superior stability and lower chemical reactivity as compared to compound **46** and **47**, since its corresponding energy gap is lager, having E_{gap} = 0.152 eV. Therefore, as the conjugation increases, the HOMO becomes higher and the LUMO becomes lower. As a result, it is easier to absorb long-wavelength (low energy) light. The order of energy gap of pyrazine increases as hydrogens are added on the compound, the energy gap for compounds **46** and **47** are 0.103 eV and 0.112 eV respectively. From the structure in **Table 8**, note that the red colour lobes represent maximum negative area which are favourable site for electrophilic attack; green colour lobe represents zero potential area and blue colour lobes indicate the maximum positive area which are favourable site for nucleophile attach [11].It is clear that compound 46 display xyz, and is favourable for zyx.

Table 8: Calculated energies of HOMO, LUMO and HOMO- LUMO gap of 1-(pyrazin-2-yl)hex-1-yn-3-one **46,** (E)-1-(pyrazin-2-yl)hex-1-en-3-one **48,** 1-(pyrazin-2-yl) hexane-1-yn-3-one **47** at the rb3lyp/6-311++g (d.p) level of theory.

Structure	HOMO (eV)	LUMO (eV)	HOMO-LUMO gap (eV)
 **46**	-0.32753	-0.22430	0.103
 **47**	-0.32849	-0.21652	0.112
 **48**	-0.32937	-0.17780	0.152

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CHAPTER 3:

CONCLUSION AND FUTURE WORK

3.1. Conclusion

An effective and efficient method for the reduction of selected heterocyclic compounds with α, β - alkynyl carbonyl in the presence of $SnCl_2$ as a reducing agent has been reported. The different N-heterocyclic compounds (**43, 19, 36, 47, 48, 52, 56**) were successfully synthesised in moderate to good yields and their spectroscopic analysis (NMR and HRMS) were in good agreement with the proposed structure.

For the reduction to take place, the compound should be N-heterocyclic with nitrogen being next to the alkynes and the N-heterocyclic compound should have α, β - alkynyl carbonyl. Addition of HCl creates many impurities with no starting material being recovered. The time limit is 3 hours, above that the reaction will start forming unrecognised by-product discovered through higher number of fractions produced during flash purification. The perfect temperature is 25˚C when doing reduction with quinoxaline and the reflux temperature is also good when doing reduction with 6-membered-ring heterocyclic compounds. The short reaction time at low temperature, the use of benign solvent and cheap reagents, make this an attractive and advantageous method for reduction in organic synthesis using $SnCl_2$.

We also did our reduction reaction in the presence of deuterium, to check if water is responsible for the addition of hydrogens to form alkane, since we know that the use of water as the hydrogen source allows a simple and inexpensive way for incorporating deuterium. However, the results from the LC-MS were not conclusive.

Additionally, the easy work-up of the reaction was an advantageous aspect of this method. Other advantages are that this method avoids the use of hydrogen pressure and expensive reducing agents. When using $SnCl_2$ at lower equivalent of less than 5 eq, it selectively reduced alkynes in the presence of other reducible functional groups such as carbonyl and nitro group. The process is simple, safe and can be easily scaled-up to provide large amount of material in excellent yield.

In some instance, higher yields are reported for compound **43**. The reaction of N-heterocyclic compound **43** with Fe and Zn powder in a mixture of ethanol, ammonium chloride and water provide a much more accessible and simpler procedure.

Geometric optimisation has been performed in gaseous phase by employing density functional theory (DFT) with RB3LYP/6-311++G (d. p) basis set. Geometrical,

thermodynamical, and molecular orbitals have been calculated to investigate structural physical and chemical behaviour. Among the investigated pyrazine derivatives, compound **46** has the higher SCF energy of -24.866 Hartree, with lager energy gap of -0.1014 eV and higher dipole moment of 4.6624 D as compared to product **47** and **48.** Larger HOMO-LUMO gaps are associated with higher kinetic stability because the transfer of one electron from HOMO to LUMO occurs under energetically unfavourable circumstances. Due to the ease of electron transition, a lower HOMO-LUMO gap is linked to the lower kinetic stability.

3.2. Future work

- The reduction of alkynes from 5-membered N-heterocyclic ring together with other compounds containing heteroatoms such as oxygen and sulphur in the presence of $SnCl_2$ will be investigated.
- Reactivity and selectivity involved during reduction reaction in the presence of Fe and Zn powder will also be investigated.
- The mechanism involved using computational studies will be investigated.
- Therefore, since our reaction were not performed under ethyl acetate but in gas phase, the same DFT calculations will be used to do all the geometric and thermodynamic calculations to confirm the reduced structure of pyrazine derivatives, physical and chemical properties through computational analysis.

CHAPTER 4: METHODS

4. CHARPTER 4

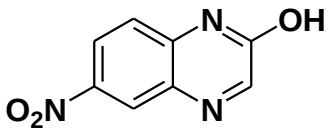
4. Experimental section

4.1. General information

The reactions were conducted in oven-dried (150˚C) glassware, magnetically stirred, and monitored using analytical thin layer chromatography (TLC). The visualization of spots was done using ultraviolet fluorescence (UV) light (254 nm). All the commercially available reagents and solvents were purchased from Merk and Sigma Aldrich and were used without further purification, unless stated otherwise. Tetrahydrofuran (THF) was distilled from sodium benzophenone under nitrogen gas prior to use. Flash column chromatography was carried out on silica gel 60 (230-400 mesh). All reagents were measured at room temperature. The structural properties of compounds were recorded and confirmed by: Nuclear Magnetic Nuclear Magnetic Resonance (NMR) (Bruker Ascend 400 MHz Topspin 3.2) and High-Resolution Mass Spectrometry (HRMS) (Sciex X500R QTOF). All chemical shifts are expressed in part per million (ppm) abbreviated as δ, with respect to an internal standard tetramethyl silane of the ^{1}H and ^{13}C NMR spectra, $CDCl_3$ (^{1}H NMR = 7.25 ppm and ^{13}C NMR = 77.0 ppm). The ^{1}H NMR spectra were reported as follows: δ (position of proton, multiplicity, coupling constant J, and number of protons). The multiplicities are expressed by s = singlet, d = doublets, t = triplets, dd = doublet of doublets, m = multiplets and brs = broad singlet.

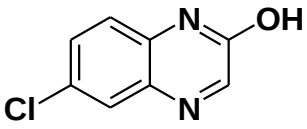
4.2. Synthesis

4.2.1. Synthesis of 6-nitroquinoxalin-2-ol (33)



4-Nitro-O-phenylenediamine **31** (0.0653 mol, 10 g) was dissolved in a mixture of 20 mL acetic acid and 20 mL methanol in a 100 mL flask equipped with a stirrer bar. The solution was cooled to 0 ˚C and treated with glyoxylic acid **32** (1 eq., 0.0653 mol, 7.02 mL) added drop wise over 30 minutes. The reaction was allowed to warm to room temperature and stirred for 90 min. Thereafter, the mixture was filtered and washed with 20 mL water followed by 20 mL methanol. The residues were recrystalised from DMF to give 6-nitroquinoxalin-2-ol **33** as a light brown solid (5.9 g, 73%); M.p = 222–225 °C (Lit 224–226 °C) [1]; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.44 (d, J = 9.0 Hz,1H), 8.32 (s,1H), 8.38 (dd, J = 9.2 and 2.8 Hz, 1H), 8.55 (d, J = 2.5 Hz,1H), 12.95 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm), δ 117.3, 124.9, 125.9, 131.7, 137.8, 143.0, 154.8, 155.4 [1].

4.2.2. Synthesis of 6-chloroquinoxalin-2-ol (39)

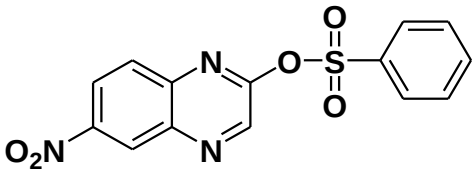


The same procedure as of compound **33** was followed. 4-Chloro-O-phenylenediamine **37** (0.0701 mol, 10 g) was dissolved in a mixture of 20 mL acetic acid and 20 mL methanol in a 100 mL flask equipped with a stirrer bar. The solution was cooled to 0 ˚C and treated with glyoxylic acid **32** (1 eq, 0.0701 mol, 7.02 mL) added drop wise over 30 minutes. The reaction was allowed to warm to room temperature and stirred for 90 min. Thereafter, the mixture was filtered and washed with 20 mL water followed by 20 mL methanol. The residues were recrystalised from DMF to give 6-

chloroquinoxalin2-ol **39** as a purple solid (9.40 g, 70%); M.p = 318 – 320 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.31 (d, J = 8.8 Hz, 1H), 7.61 (d, ^{3}J = 8.8 Hz, 1H and dd, ^{4}J = 2.4 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 12.55 (brs, 1H); ^{13} C NMR (100 MHz, DMSO-d_6, ppm) δ 118.3, 127.9, 128.6, 131.6, 133.3, 141.3, 153.7, 155.6.

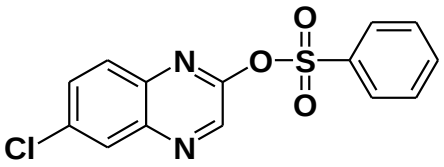
4.3: Sulfonation

4.3.1. Synthesis of 6-nitroquinoxalin-3-yl benzenesulfonate (34)



In a 100 mL round bottom flask, a solution of 6-nitroquinoxaline-2-ol **33** derivatives (5.6 g, 0.0293 mol), DMAP (0.359 g, 0.0029mol, 10 mol %), and benzene sulfonyl chloride (7.48 mL, 0.059 mol, 2 eq), in DCM (70 mL) was stirred at 0˚C for 5 minutes. Then Et_3N (12.5 mL, 0.088 mol, 3 eq) was added dropwise over 5 minutes. The reaction was warmed to room temperature and stirred for 1 hour. Sodium hydrogen carbonate ($NaHCO_3$) was added to the reaction mixture to quench the reaction and the resulting mixture was extracted with DCM. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel using a mixture of methanol and dichloromethane MeOH: DCM (2:3, R_f =0.43), to give the desired 6-nitroquinoxalin-2-yl benzenesulfonate **34** as a yellowish solid (6.5 g, 94 %); M.p 157.1– 160.0 °C (Lit 158.1–160.4 °C) [1]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61-7.66 (m, 2H), 7.72-7.77 (m, 1H), 8.03 (d, J = 9.2 Hz, 1H), 8.18-8.21 (m, 2H), 8.54 (dd, J = 9.2 and 2.5 Hz, 1H), 8.77 (s, 1H), 8.99 (d, J = 2.4 Hz,1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm), δ 124.6, 125.4, 129.2, 129.3, 129.9, 135.1, 136.0, 139.8, 141.4, 142.6, 147.6, 152.7.

4.3.2. Synthesis of 6-chloroquinoxalin-3-yl benzenesulfonate (40)

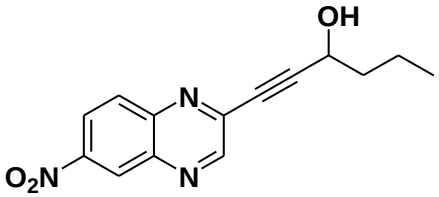


The same procedure as of **34** was followed using 6-chloroquinoxaline-2-ol **33** (4.3 g, 0.0238 mol) with DMAP (0.359 g, 0.0029 mol, 10 mol %), and benzene sulfonyl chloride (7.48 mL, 0.059 mol, 2 eq), in DCM (70 mL) stirred at 0˚C for 5 minutes. Followed by addition of Et_3N (12.5 mL, 0.088mol, 3 eq) dropwise over 5 minutes. Thereafter, the reaction was warmed to room temperature and stirred for 1 hour, followed by the workup and purification by column chromatography using a mixture of MeOH: DCM (2:3, R_f=0.40)as eluent to afford 6- chloroquinoxalin-3-yl benzenesulfonate **40** as a pink solid (2.6 mg, 78%); M.p = 144.0 – 146.5 (Lit 143.7-146.7) [2] ˚C; (400 MHz, $CDCl_3$, ppm) δ 7.60 (m, 2H), 7.71 (m, 2H), 7.82 (d, J = 9.2 Hz, 1H), 8.123 (m, 3H), 8.65 (s, 1H); (100 MHz, $CDCl_3$, ppm) δ 128.2, 129.0, 129.2, 129.6, 132.1, 134.8, 135.7, 136.2, 138.2, 140.1, 141.4, 150.9.

4.4. General procedure for the Sonogashira coupling reaction

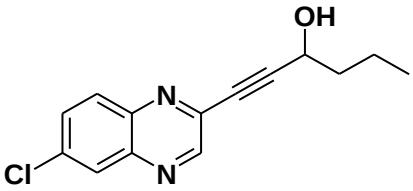
To an oven-dried sealed reaction tube with magnetic stirrer bar, was added 6-nitroquinoxalin-2-yl benzenesulfonate **34,** $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_3N (2 eq) and 1-hexyn-3-ol (1.2 eq) in dry THF (10 mL). The reaction mixture was allowed to stir at 60 ˚C overnight. Upon completion, saturated ammonium chloride solution (10 mL) was added to the reaction mixture to quench the reaction and the resulting mixture was extracted with EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4. The crude mixture was purified by flash column chromatography on silica gel eluting with mixture of EtOAc: n-hexane to give the desired product [3].

4.4.1. Synthesis of 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-ol (35)



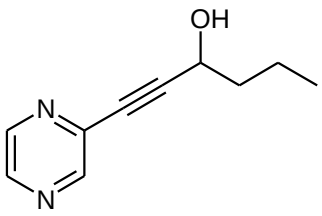
Following procedure for Sonogashira coupling compound **34** (500 mg, 0.0015 mol) was treated with hex-1-yn-3-ol (0.20 mL, 1.2 eq). After purification by flash column chromatography , eluting with mixture of EtOAc: n-hexane (2.3, R_f=0.23) was obtained 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-ol **35** as a brown solid (435.2 mg, 95%); M.p 119.1-121.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.99 (t, J = 7.4 Hz, 3H), 1.56-1.62 (m, 2H), 1.85-1.90 (m, 2H), 2.79 (brs, 1H), 4.74 (t, J = 6.7 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.52 (dd, J = 9.2 and = 2.4 Hz, 1H), 8.95 (d, J = 2.4 Hz,1H), 8.96 (s, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 13.7, 18.4, 39.2, 62.5, 81.8, 98.0, 124.1, 125.5, 130.7, 139.7, 141.8, 144.2, 147.9, 149.0; HRMS (ESI) $[M + H]^+$: m/z 272.1042; Calculated mass for $C_{14}H_{14}N_3O_3$ is 272.1037.

4.4.2. Synthesis of 1-(6-choroquinoxalin-2-yl) hex-1-yn-3-ol (41)



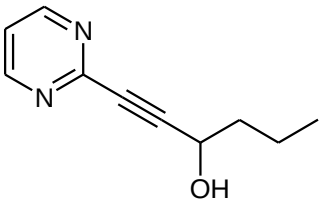
Following procedure for Sonogashira coupling compound **40** (500 mg, 0.0016 mol) was treated with hex-1-yn-3-ol (0.21 mL, 1.2 eq.). After Purification by flash column chromatography, eluting with mixture of EtOAc: n-hexane (2:3, R_f=0.23) was obtained 1-(6-chloroquinoxalin-2-yl) hex-1-yn-3-ol **41** as a brown solid (430 mg, 90%); M.p = 104.1- 108.3˚C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.98 (t, J = 7.4 Hz, 3H), 1.55-1.61 (m, 2H), 1.84-1.90 (m, 2H), 2.79 (brs, 1H), 4.70 (t, J = 6.6 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.70 (dd, J = 9.06Hz, 1H), 8.05 (d, J = 2.4 Hz,1H), 8.83 (s, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 13.7, 18.4, 39.5, 62.6, 80.5, 97.6, 124.1, 125.5, 130.7, 139.7, 141.8, 144.2, 147.9, 149.0.

4.4.3. Synthesis of 1-(pyrazin-2-yl) hex-1-yn-3-ol (45)



Following procedure for Sonogashira coupling compound **44** (200 mg, 0.0009 mol) was treated with hex-1-yn-3-ol (0.27 mL, 1.2 eq). After Purification by flash column chromatography, eluting with mixture of EtOAc: n-hexane (2:3, R_f=0.35) was obtained 1-(pyrazin-2-yl) hex-1-yn-3-ol **45** as a brown oil (318 mg, 90%).^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.84-1.8.49 (m, 2H), 8.56 (d, J = 1.52, 1H), 4.52 (t, J = 9.04 Hz, 1H), 2.15 (brs , 1H), 1.76-1.89 (m, 2H), 1.51-1.59 (m, 2H), 0.96 (t, J = 7.34, 3H). δ ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 13.7, 18.4, 39.4, 62.4, 81.3, 94.5, 139.7, 144.4, 145.9, 147.6, . HRMS (ESI) $[M + H]^+$: m/z 177.1028; Calculated mass for $C_{10}H_{12}N_2O$ is 177.0950.

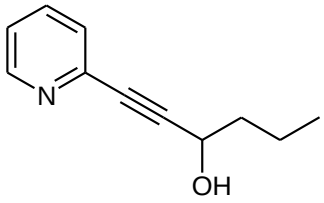
4.4.4. Synthesis of 1-(pyrimidine-2-yl) hex-1-yn-3-ol (50)



Following procedure for Sonogashira coupling compound **49** (200 mg, 0.0013 mol) was treated with hex-1-yn-3-ol (0.17 mL, 1.2 eq). After Purification by flash column chromatography, eluting with mixture of EtOAc: n-hexane (2:3, R_f=0.28) was obtained 1-(pyrimidine-2-yl) hex-1-yn-3-ol **50** as a dark brown oil (252 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.62 (d, J = 4.97 Hz, 2H), 7.30 (t, J = 5.01 Hz, 1H), 4.64 (t, J = 6.72 Hz, 1H), 2.16 (brs, 1H), 1.79-1.85 (m, 2H), 1.51-1.60 (m, 2H), 0.95 (t, J = 7.45 Hz, 3H). δ ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 157.2, 152.5, 119.9, 90.1, 82.9, 62.2,

39.2, 18.4, 13.7. HRMS (ESI) $[M + H]^+$: m/z 177.1026; Calculated mass for $C_{10}H_{13}N_2O$ is 177.0950.

4.4.5. Synthesis of 1-(pyridine-2-yl) hex-1-yn-3-ol (54)

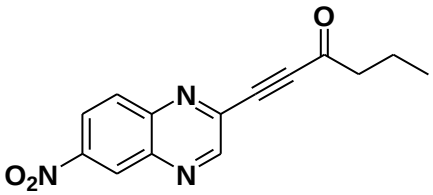


Following procedure for Sonogashira coupling, compound **53** (500 mg, 0.30 mL, 0.0032 mol) was treated with hex-1-yn-3-ol (0.53 mL, 1.5 eq). After Purification by flash column chromatography, eluting with mixture of EtOAc: n-hexane (4:1, R_f=0.47) was obtained 1-(pyridine-2-yl) hex-1-yn-3-ol **54** as a yellow oil (252 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.48 (d, J = 5.25 Hz, 1H), 7.56-7.60 (m, 1H), 7.34 (d, J = 7.89 Hz, 1H), 7.14-7.18 (m, 1H), 4.67 (t, J = 6.89 Hz, 1H), 2.18 (brs, 1H), 1.80-1.86 (m, 2H), 1.54-1.60 (m, 2H), 0.97 (t, J = 7.44 Hz, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 149.8,142.9,136.6, 127.41, 123.2, 91.7, 83.7, 62.4, 39.8, 18.7, 13.9; HRMS (ESI) $[M + H]^+$: m/z 176.1067; Calculated mass for $C_{11}H_{14}NO$ is 176.0997.

4.5. General procedure for oxidation reaction

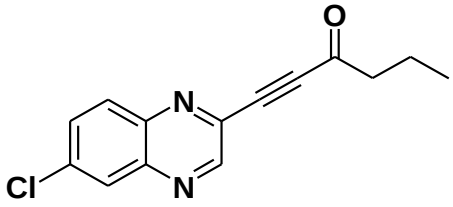
To a solution of 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-ol in 30 mL of DCM was added 5eq. of PCC at 0˚C, and then warmed to room temperature slowly. The mixture was stirred for 2 hours at room temperature and filtered through a short silica gel column. It was washed with 30 mL of DCM. The filtrate was concentrated under vacuum. The resulting crude was further diluted, washed, and extracted using DCM. The crude was purified by flash column chromatography using the mixture of methanol: DCM to afford a pure compound **17** [4].

4.5.1. Synthesis of 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-one (17)



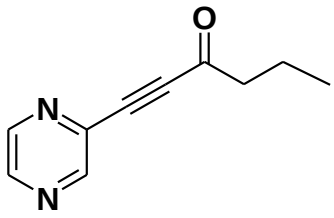
Following procedure for oxidation, compound **35** (197 mg, 0.0073 mol) was treated with PCC (5 eq). After filtering through a short silica gel column and purification by flash column chromatography, eluting with mixture of methanol: DCM (2:3, R_f=0.57) was obtained 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-one **17** as a brown solid (158mg, 80%); M.p = 132.9 -137.2˚C (Lit 135.4-138.0 ˚C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.09 (s, 1H) 9.02 (d, J = 2.4 Hz, 1H) ,8.59 (dd, J = 9.3 and 2.4 Hz, 1H), 8.26 (d, J = 9.2 Hz,1H) 2.76 (t, J = 7.3 Hz, 2H), 1.80 (sext, J = 7.4 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 186.7, 148.9, 148.6, 144.3, 140.5, 140.0, 131.3, 125.7, 124.5, 90.1, 83.7, 47.4, 17.3, 13.5; HRMS (ESI) $[M + H]^+$:m/z 270.0883; Calculated mass for $C_{14}H_{12}N_3O_3$ is 270.0880 [5].

4.5.2. Synthesis of 1-(6-chloroquinoxalin-2-yl) hex-1-yn-3-one (42)



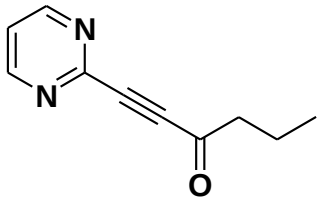
Following procedure for oxidation, compound **41** (450 mg, 0.0017 mol) was treated with PCC (5 eq). After filtering through a short silica gel column and purification by flash column chromatography, eluting with mixture of methanol: DCM (2:3, R_f=0.66) was obtained 1-(6-chloroquinoxalin-2-yl) hex-1-yn-3-one **42** as a brown solid (340 mg, 76%); M.p = 120.6-128.0˚C ;^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.97 (s ,1H) 8.12 (s,1H),8.05 (d, J = 9.22 Hz, 1H), 7.78 (d, J = 9.26 Hz, 1H), 2.74 (t, J = 7.55 Hz, 2H), 1.80 (sext, 2H), 1.00 (t, J = 7.17 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 187.2, 147.9, 141.8, 140.7, 137.8, 137.1, 132.4, 130.7, 128.3, 88.9, 84.0, 47.4, 17.3, 13.5.

4.5.3. Synthesis of 1-(pyrazin-2-yl) hex-1-yn-3-one (46)



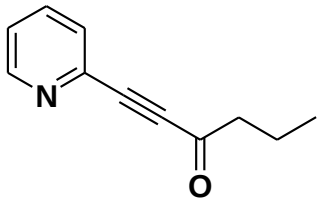
Following procedure for oxidation, compound **45** (317 mg, 0.0018 mol) was treated with PCC (5 eq). After filtered through a short silica gel column and purification by flash column chromatography, eluting with mixture of methanol: DCM(4:1, R_f=0.24) was obtained 1-(pyrazin-2-yl) hex-1-yn-3-one **46** as brown oil (269 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.80 (s, 1H), 8.62 (d, J = 13.97 Hz, 2H), 2.70 (t, J = 7.13 Hz, 2H), 1.78 (sext, 2H), 099 (t, J = 7.30 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 186.2, 147.8, 143.9, 143.7, 136.9, 87.8, 83.3, 46.4, 16.4, 13.1.

4.5.4. Synthesis of 1-(pyrimidine-2-yl) hex-1-yn-3-one (51)



Following procedure for oxidation, compound **50** (154 mg, 0.0009 mol) was treated with PCC (5 eq). After filtering through a short silica gel column and purification by flash column chromatography, eluting with mixture of methanol: DCM(1:4, Rf=0.22) was obtained 1-(pyrimidine-2-yl) hex-1-yn-3-one **51** as brown oil (120 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.79, (d, J = 5.06 Hz, 2H), 7.35 (t, J = 4.97 Hz, 1H), 2.70 (t, J = 7.38 Hz, 2H), 1.77 (sext, 2H), 0.97 (t, J = 7.46 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 187.2, 157.5, 157.5, 151.5, 121.1, 82.7, 78.0, 47.4, 17.2, 13.4.

4.5.4. Synthesis of 1-(pyridine-2-yl) hex-1-yn-3-one (55)

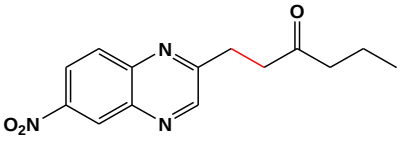


The Jones reagent was used for the oxidation reaction [6] using 1-(pyridin-2-yl) hex-1-yn-3-ol **54** (0.200 g) in acetone (40 mL and added a mixture of chromium trioxide (1.5 eq, 0.170 g), concentrated sulfuric acid (0.073 mL) and water (4 mL) dropwise over a period of 15 min at 0˚C. After stirring at room temperature for 16 hours, the reaction was further diluted with water (15 mL). The product was isolated by extracting with diethyl ether and drying over $NaHSO_4$. The solvent was removed through evaporator vacuum and the crude was purified over flash chromatography in silica gel using a mixture of ethyl acetate: n-hexane (4:1, R_f=0.33) to afford a pure product of 1-(pyrimidin-2-yl) hex-1-yn-3-one **55** as a light brown oil (0.146 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.66 (d, J = 4.74 Hz, 1H), 7.73 (m, 1H), 7.58 (d, J = 7.86 Hz, 1H), 7.36 (m, 1H), 2.68 (t, J = 7.32 Hz, 2H), 1.76 (sext, 2H), 0.96 (t, J = 7.46 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 187.9, 150.5, 140.8, 136.6, 128.6, 124.7, 87.6, 85.8, 47.5, 16.6, 13.7.

4.6. General procedure for reduction reaction on nitro and alkynes group

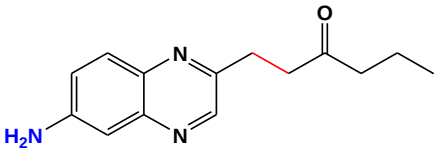
To a suspension of α, β - alkynyl carbonyl compound in EtOAc (10 mL) was added $SnCl_2$ and the reaction mixture refluxed for 3 hours. After cooling to room temperature, $NaHCO_3$ solution (10 mL) was added and stirred for 10 minutes. The suspension was partitioned, and aqueous layer was washed with EtOAc, the combined organic layers were washed with brine and concentrated after drying with anhydrous Na_2SO_4 [7].

4.6.1. Synthesis of 1-(6- nitroquinoxalin-2-yl) hexan-3-one (36)



To a suspension of 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-one **17** (50 mg, 0.00019 mol) in EtOAc (10 mL) was added $SnCl_2$ (84 mg, 0.0004 mol, 2 eq) according to procedure of reduction reaction. Purification on flash column chromatography using a mixture of EtOAc: n-hexane (4:1, R_f=0.50) afforded 1-(6- nitroquinoxalin-2-yl)hexan-3-one **19** as brown solid (21 mg, 47%); M.p = 122.8-160.0˚C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.98 (d, J = 2.51 Hz, 1H), 8.49 (dd, J = 9.13 Hz,1H), 8.09 (d, J = 9.18 Hz, 1H), 8.93 (s, 1H), 3.35 (t, J = 6.70 Hz, 2H), 3.12 (t, J = 6.43 Hz, 2H), 2.51 (t, J = 7.51 Hz, 2H), 1.64 (sext, 2H), 0.92 (t, J = 7.35 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 207.2, 159.5, 148.6, 130.4, 125.7, 123.3, 44.7, 39.42, 31.9, 17.3, 13.7. HRMS (ESI) $[M + H]^+$: m/z 274.1193; Calculated mass for $C_{14}H_{16}N_3O_3$ 274.1113.

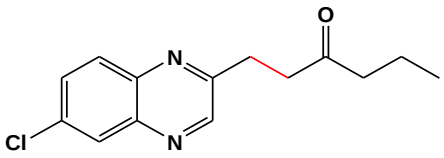
4.6.2. Synthesis of 1-(6- aminoquinoxalin-2-yl) hexan-3-one (19)



To a suspension of 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-one **17** (50 mg, 0.00019 mol) in EtOAc (10 mL) was added $SnCl_2$ (208 mg, 0.0009 mol, 5 eq.) according to procedure of reduction reaction. Purification on flash column chromatography using a mixture of EtOAc: n-hexane (2:3, R_f=0.23) afforded 1-(6- aminoquinoxalin-2-yl)hexan-3-one **19** as yellow solid (21 mg, 47%); M.p = 96.8-98.0˚C (Lit 97.0-97.6 °C) [5] [8]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.60 (s, 1H); 7.75 (d, J = 8.9 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 7.11-7.13 (m, 1H), 4.11 (brs, 2H), 3.20 (t, J = 7.1 Hz, 2H), 2.99 (t, J = 7.1 Hz, 2H), 2.46 (t, J = 7.3 Hz, 2H), 2.46 (t, J = 7.3 Hz, 2H), 1.57-1.66 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 151.8, 147.1, 146.0, 142.9, 136.9,

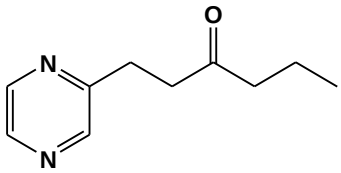
129.6, 121.8, 108.5, 44.9, 40.7, 29.2, 17.3, 13.8; HRMS (ESI) $[M + H]^+$: m/z 244.1440, (Lit $[M + H]^+$:m/z 244.1466); Calculated mass for $C_{14}H_{18}N_3O$ 244.1372

4.6.3 Synthesis of 1-(6-chloroquinoxalin-2-yl) hexan-1-yn-3-one (43)



To a suspension of 1-(6-chloroquinoxalin-2-yl) hex-1-yn-3-one **42** (50 mg, 0.00020 mol) in EtOAc (10 mL) was added $SnCl_2$ (218 mg, 0.00097 mol, 5 eq.) according to procedure of reduction reaction. Purification on flash column chromatography using a mixture of EtOAc: n-hexane (2:3, R_f=0.64) afforded 1-(6- chloroquinoxalin-2-yl) hexan-3-one **43** as brown oil (37 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.78 (s, 1H); 8.05 (d, J = 2.34 Hz, 1H), 7.91 (d, J = 9.02 Hz, 1H), 7.66 (dd, J = 9.13 Hz, 1H), 3.29 (t, J = 6.88 Hz, 2H), 3.07 (t, J = 7.01 Hz, 2H), 2.49 (t, J = 7.53 Hz, 2H), 1.62 (sext, 2H), 0.91 (t, J = 7.59 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 209.7, 156.2, 147.0, 141.5, 140.6, 134.7, 130.9, 130.0, 127.6, 44.9, 39.9, 31.9, 17.3, 13.8.

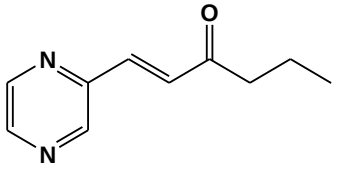
4.6.4. Synthesis of 1-(pyrazin-2-yl) hexane-1-yn-3-one (47)



To a suspension of 1-(pyrazin-2-yl) hex-1-yn-3-one **46** (97 mg, 0.0006 mol) in EtOAc (10 mL) was added $SnCl_2$ (526 mg, 0.0028 mol, 5 eq) according to procedure of reduction reaction. Purification on flash column chromatography using a mixture of EtOAc: n-hexane (2:3, R_f=0.28) afforded 1-(pyrazin-2-yl) hexane-1-yn-3-one **47** as yellow oil in 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (s, 1H), 8.40-8.46 (m, 2H), 3.09 (d, J = 9.18, 1H), 2.94 (t, J = 7.08 Hz, 2H), 2.43 (t, J = 7.40 Hz, 2H), 1.58 (sext, 2H), 0.88 (t, J = 7.40 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 209.5, 156.3,

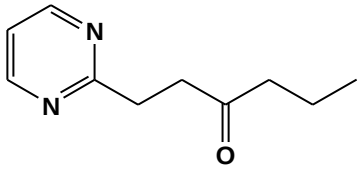
144.9, 143.6, 142.0, 44.7, 40.5, 40.5, 31.9, 17.2, 13.7. HRMS (ESI) $[M + H]^+$: m/z 179.1177; Calculated mass for $C_{10}H_{15}N_2O$ 179.1106.

4.6.5. Synthesis of (E)-1-(pyrazin-2-yl) hex-1-en-3-one (48)



To a suspension of 1-(pyrazin-2-yl) hex-1-yn-3-one **46** (79 mg, 0.0005 mol) in EtOAc (10 mL) was added $SnCl_2$ (204 mg, 0.0009 mol, 2 eq.) according to procedure of reduction reaction. Purification on flash column chromatography using a mixture of EtOAc: n-hexane (2:3, R_f=0.21) afforded (E)-1-(pyrazin-2-yl) hex-1-en-3-one **48** as light yellow oil in 38% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.69 (s, 1H), 8.54-8.61 (m, 2H), 7.55 (d, J = 15.93 Hz,1H), 7.30 (d, J = 15,93 Hz, 1H), 2.67 (t, J = 7.28 Hz, 2H), 1.72 (sext, 2H), 0.97 (t, J = 7.43, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 200.12, 148.9, 145.3, 144.4, 139.3, 136.6, 131.3, 43.8, 17.5, 13.8. HRMS (ESI) $[M + H]^+$: m/z 177.1303; Calculated mass for $C_{14}H_{18}N_3O$ 177.1030.

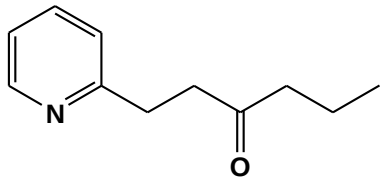
4.6.6. Synthesis of 1-(pyrimidine-2-yl) hexane-1-yn-3-one (52)



To a suspension of 1-(pyrimidine-2-yl) hex-1-yn-3-one **51** (50 mg, 0.0003 mol) in EtOAc (10 mL) was added $SnCl_2$ (324 mg, 0.0014 mol, 5 eq) according to procedure of reduction reaction. Purification on flash column chromatography using a mixture of EtOAc: n-hexane (2:3, R_f=0.26) was done to afford 1-(pyrimidine-2-yl) hexane-1-yn-3-one **52** as light brown oil in 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.64 (d, J = 4.93 Hz, 2H), 7.13 (m, J = 4.79 Hz, 1H), 3.28 (t, J = 7.48 Hz, 2H), 2.98 (t, J = 7.46 Hz,

2H), 2.47 (t, J = 7.38 Hz, 2H), 1.61 (sext, 2H), 0.90 (t, J = 7.40, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 209.9, 169.8, 156.9, 138.4, 118.6, 44.8, 39.8, 22.7, 17.3, 13.8.

4.6.7. Synthesis of 1-(pyridine-2-yl) hexane-1-yn-3-one (56)



To a suspension of 1-(pyridine-2-yl) hex-1-yn-3-one **55** (50 mg, 0.0003 mol) in EtOAc (10 mL) was added $SnCl_2$ (273 mg, 0.0014 mol, 5 eq) according to procedure of reduction reaction. Purification on flash column chromatography using a mixture of EtOAc: n-hexane (4:1, Rf=0.51) was done to afford 1-(pyridine-2-yl) hexane-1-yn-3-one **56** as dark yellow oil (26 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (dd, J = 4.18 Hz, 1H), 7.78 (m, J = 7.20 Hz, 1H), 7.4 (d, J = 7.68 Hz, 1H), 7.28-7.25 (m, J = 5.89 Hz, 1H), 3.16(t, J = 6.84 Hz, 2H), 3.04 (t, J = 6.67 Hz, 2H), 2.40 (t, J = 7.87 Hz, 2H), 1.57 (sext, 2H), 0.87 (t, J = 7.78 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 210.3, 160.3, 148.4, 137.1, 122.1, 121.4, 44.8, 41.6, 31.3, 17.2, 13.7.

4.7. Computational details

Molecules were prepared, following the synthetic steps **44** and **45** to give the interested compounds **46**, **47** and **48**. Gaussian 16 was used to investigate the various properties of the molecules. Computational chemistry software Gaussian 16 capable of predicting many properties of molecules and reactions including the following [9]:

a. Molecular energies and structure
b. Bond and reaction energies
c. Energy and structural transition state
d. Molecular orbitals
e. Atomic charges and electrostatic potential
f. Vibrational frequency

g. Reaction pathway
h. Dipole moments

The computation was carried out on the system to predict the energy and reaction mechanism of the pyrazine derivatives. The Gaussian 16 revision A.03, calculations on the Centre for Higher Performance Computation (CHPC) Cluster was used to calculate molecular properties at the rb31yp/6-311++g (d, p) level of theory with Grimme's D3 empirical dispersion correction (qd3 at 298.15K in vacuum, gas phase). The rb31yp is the method selected with basis set of 6-311++g [10, 11]. Gauss view was used to create inputs and for visualization. The job type used was “opt” for geometry optimisation and “freq” for frequency calculations (thermochemical analysis). To confirm stationary sites and the transitional state along the reaction path, vibrational frequency analysis was employed. The conformation search for products and reactants was performed in Spartan using the Monte Carlo (MC) [12] approach. This was achieved by altering the torsion angle of every rotatable bond in the system by 30°C and the molecular mechanic force field (MMFF) [13]. Calculations of Interacting Quantum Atoms (IQA) [14] was performed using AIMAII software [15]. Data required for computing energy terms were implemented in the REP-FAMSEC method [16]. The XYZ coordinates of all structures considered and a full set of their energies was observed on the output file.

Gaussian takes a text file with a “gjf” in window environment as an input [11]. In this input file the molecular configuration of the molecule is described as well as the specific calculations that were to be performed, such as: geometrical optimization, frequency determination, single point energy, etc. After running Gaussian, a text output file is generated with the extension (.log or .out in window environment) and the same name as the input file. The output file is then browsed to find selected data for analysis. In the current work, gaussian code with the above settings was employed to make predictions of the pyrazine derivatives molecules, in particular the total and binding energy, bond distance, Homo and Lumos [11].

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CHAPTER 5:

APPENDIX 1(EXPERIMENTAL)

APPENDIX 2(COMPUTATIONAL)

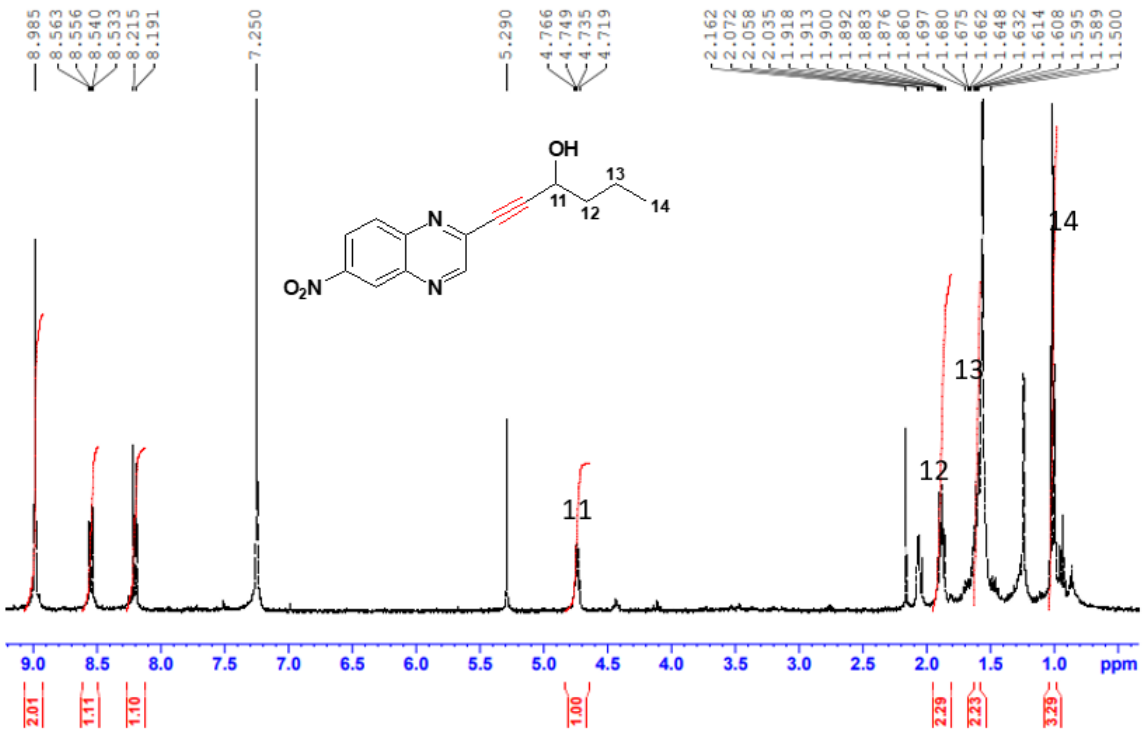

Figure 5.22: ^{13}C NMR spectrum of 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-ol **(35).**

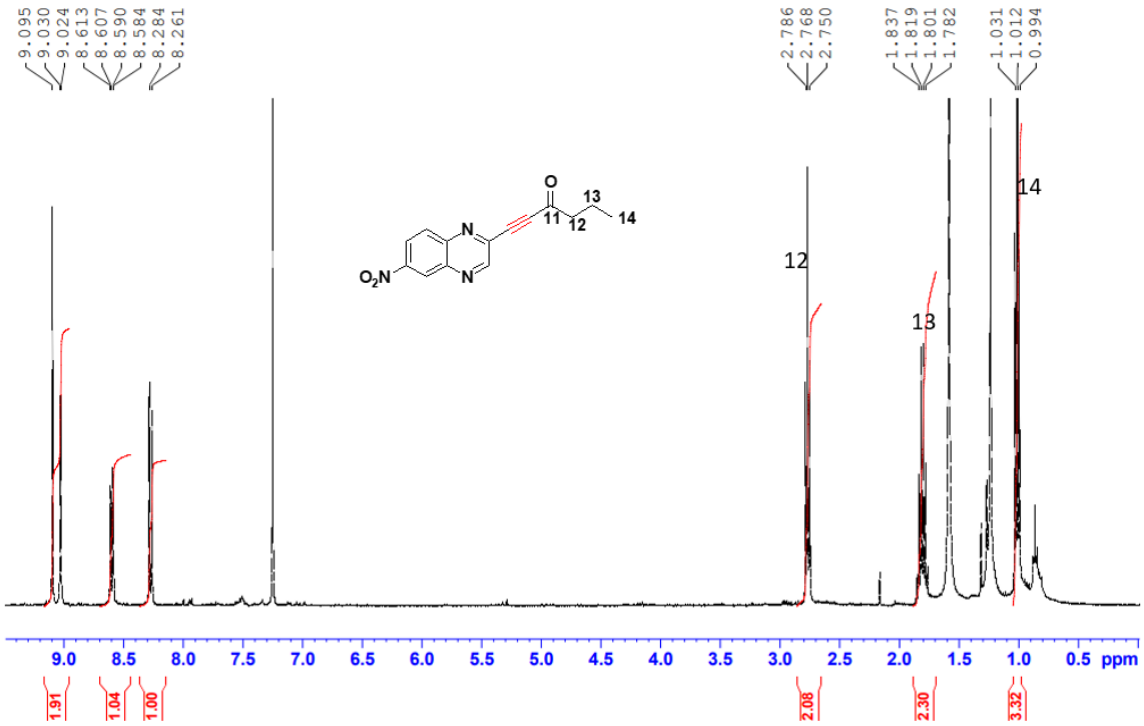

Figure 2.1: ^{1}H NMR spectrum of 1-(6-nitroquinoxalin-2-yl) hex-1-yn-3-one **(17).**

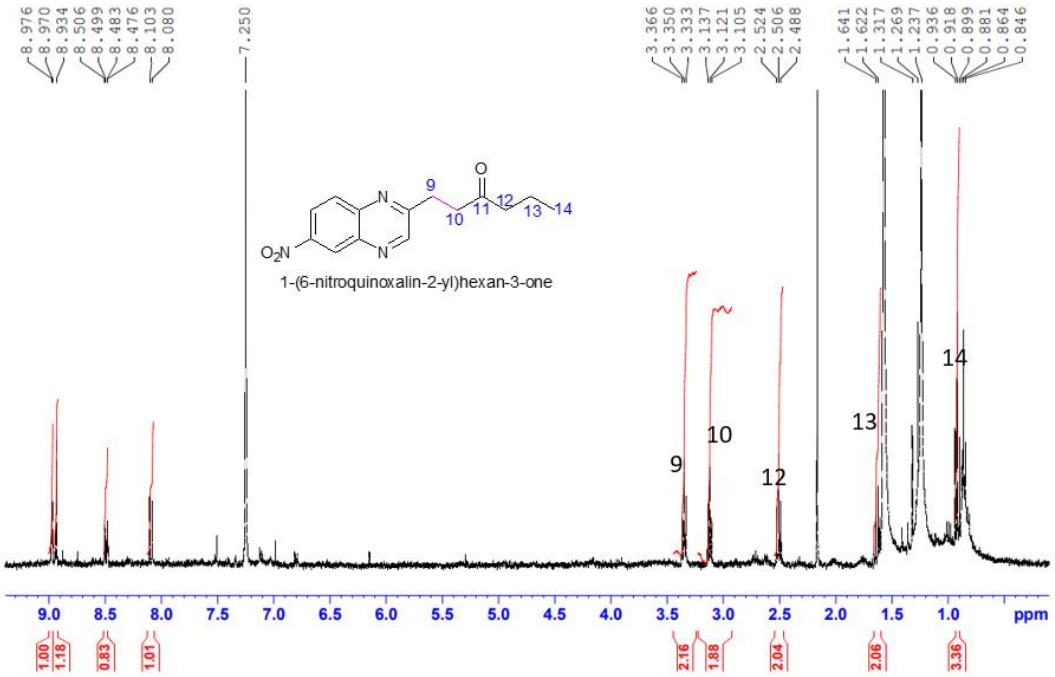

Figure 2.1: ^{1}H NMR spectrum of 1-(6-nitroquinoxalin-2-yl) hexane-1-yn-3-one **(36).**

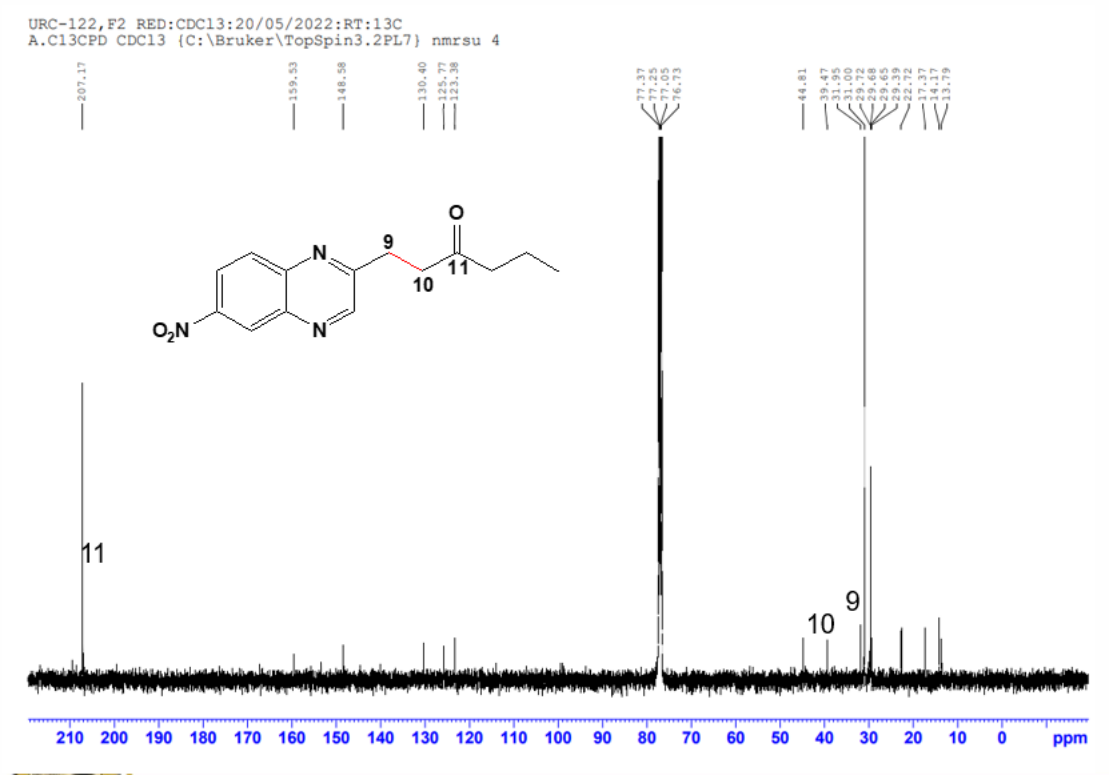

Figure 2.2: ^{13}C NMR spectrum of 1-(6-nitroquinoxalin-2-yl) hexane-1-yn-3-one **(36).**

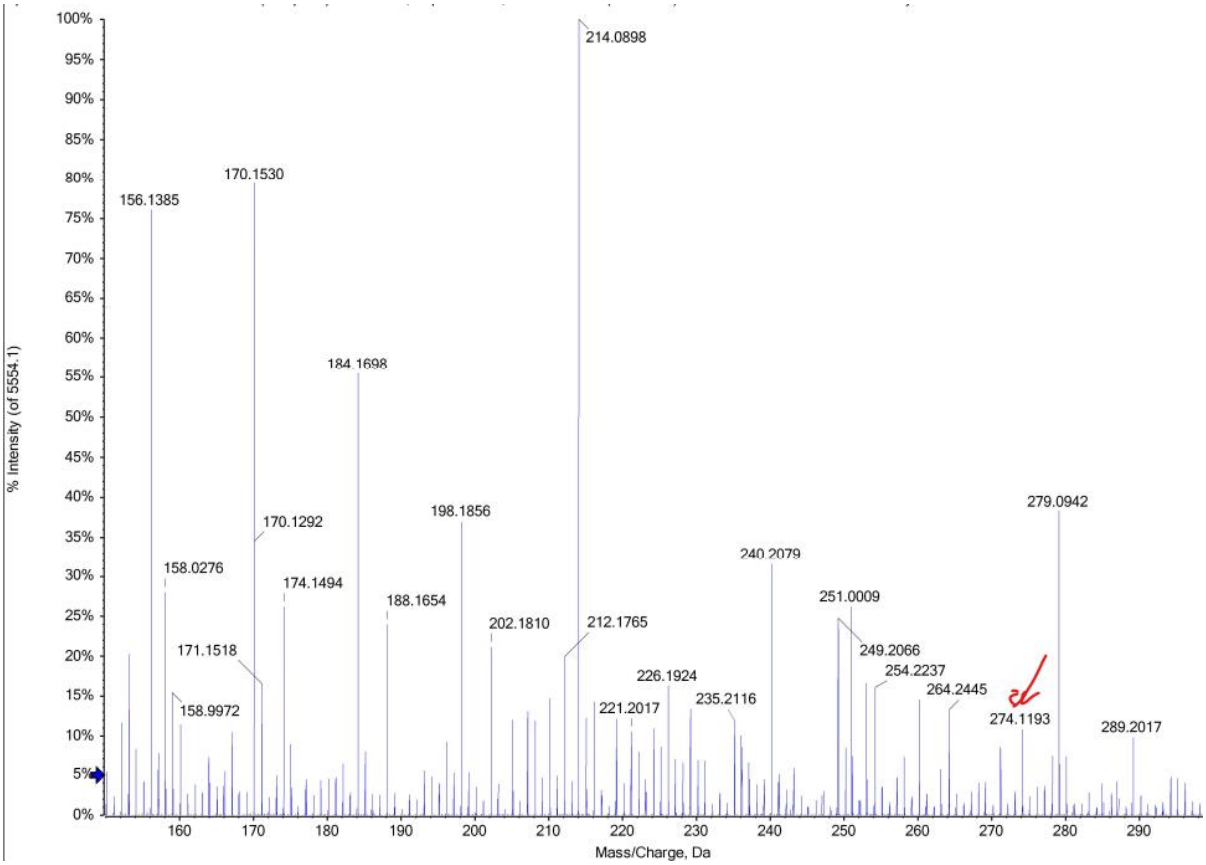

Figure 2.18: Mass spectrum of 1-(6-nitroquinoxalin-2-yl) hexane-1-yn-3-one **(36).**

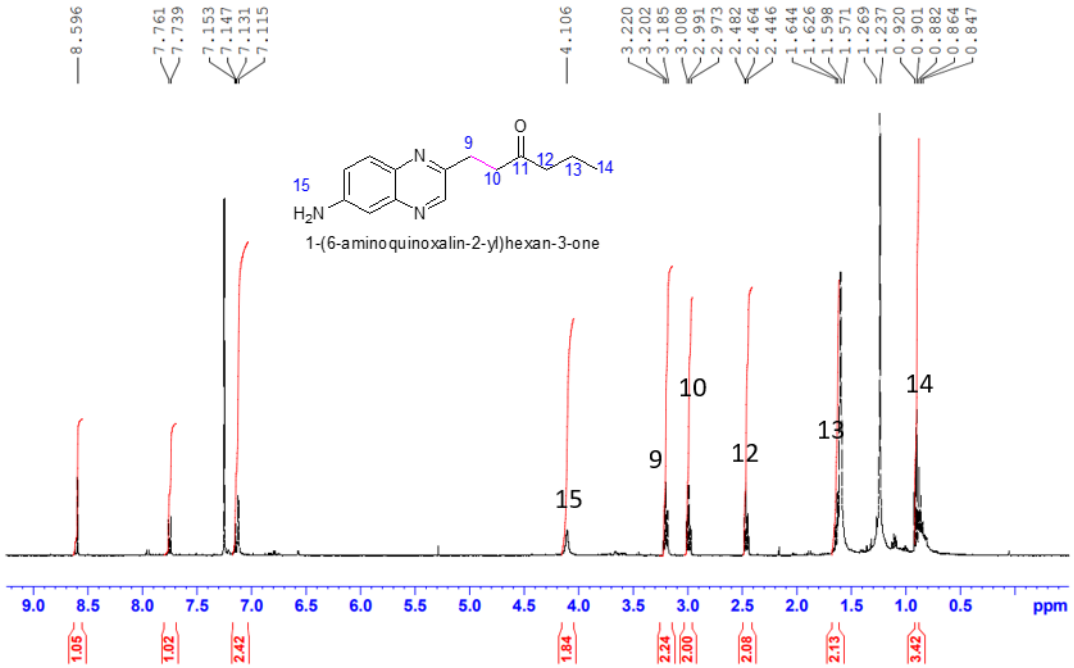

Figure 2.1: ^{1}H NMR spectrum of 1-(6-aminoquinoxalin-2-yl) hexane-1-yn-3-one (**19).**

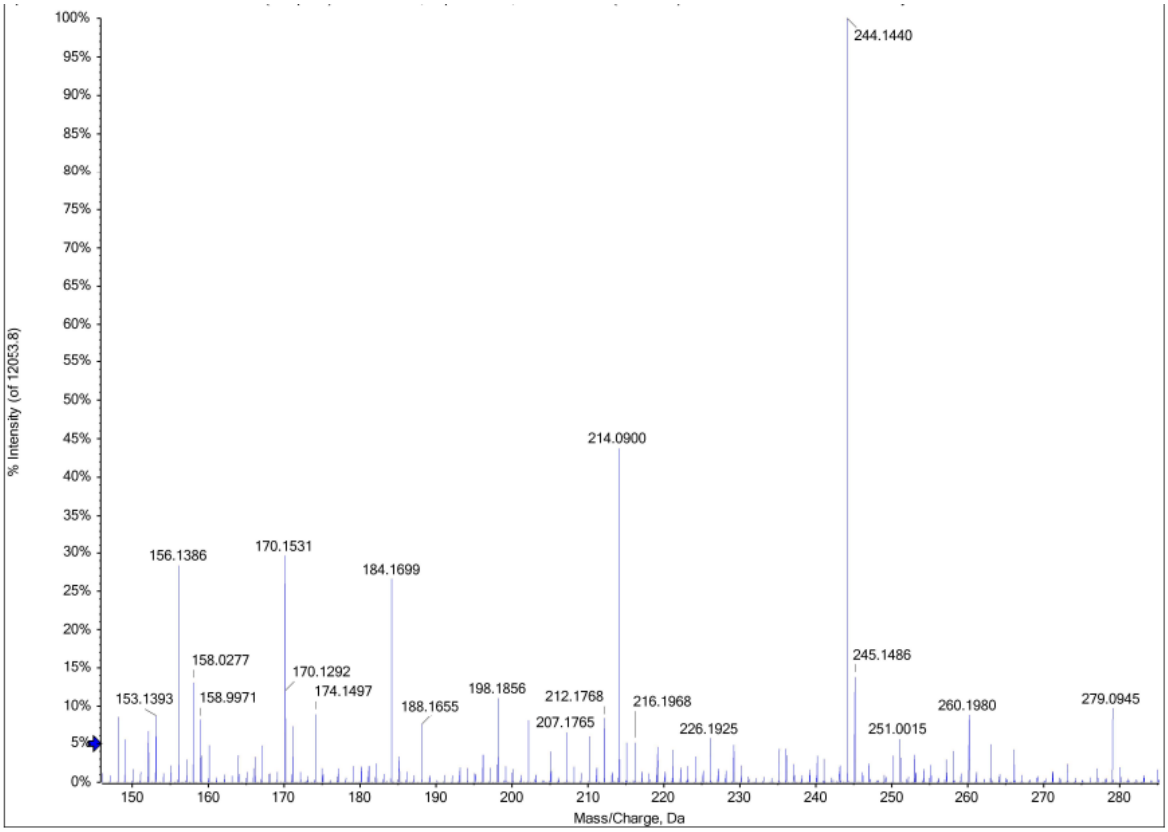

Figure 2.19: Mass spectrum of 1-(6-aminoquinoxalin-2-yl) hexane-1-yn-3-one **19**

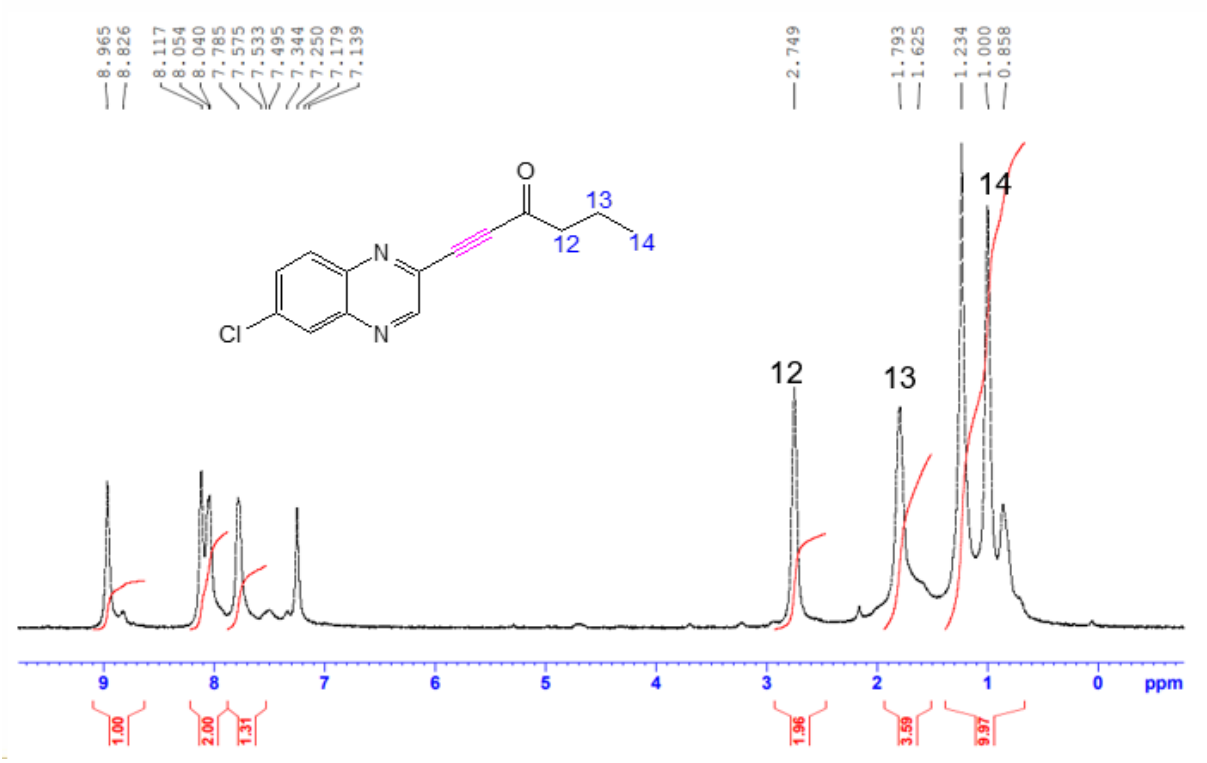

Figure 2.14: [1]H NMR spectrum of 1-(6-chloroquinoxalin-2-yl) hex-1-yn-3-one **(42).**

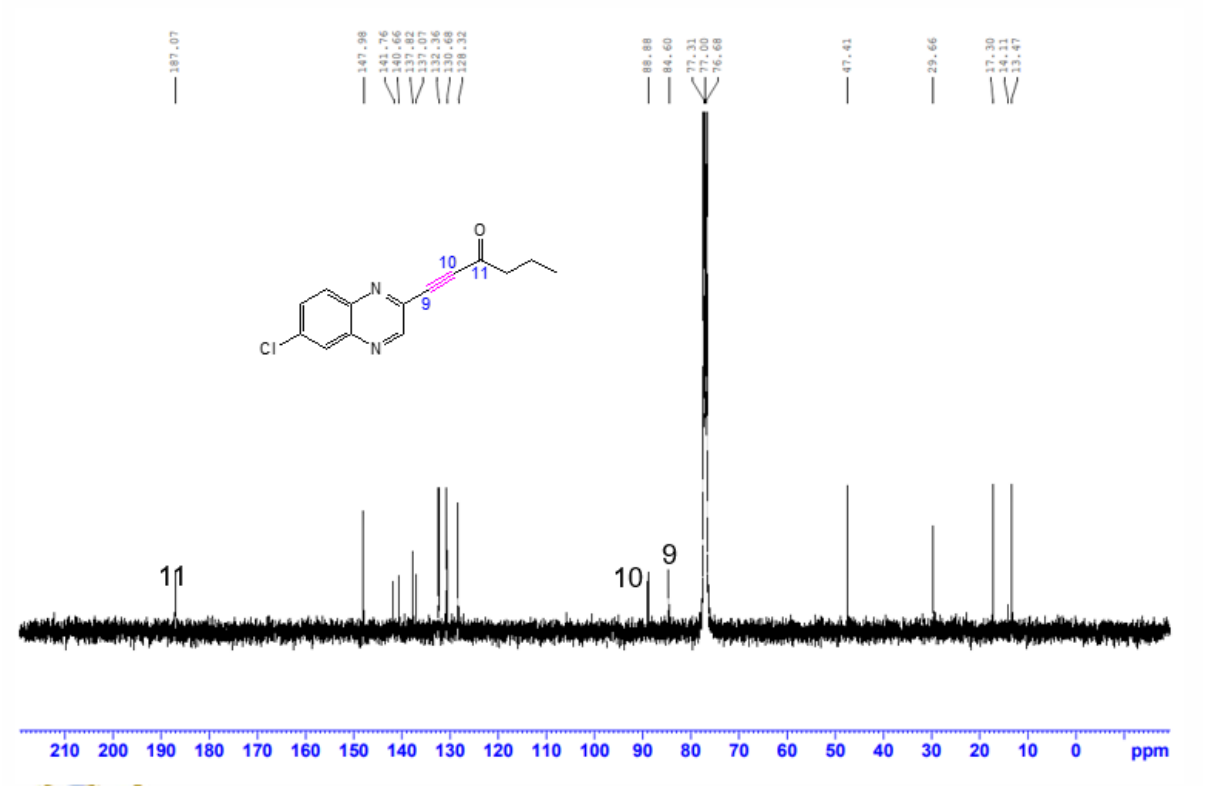

Figure 2.15: [13] C NMR spectrum of 1-(6-chloroquinoxalin-2-yl) hex-1-yn-3-one **(42)**

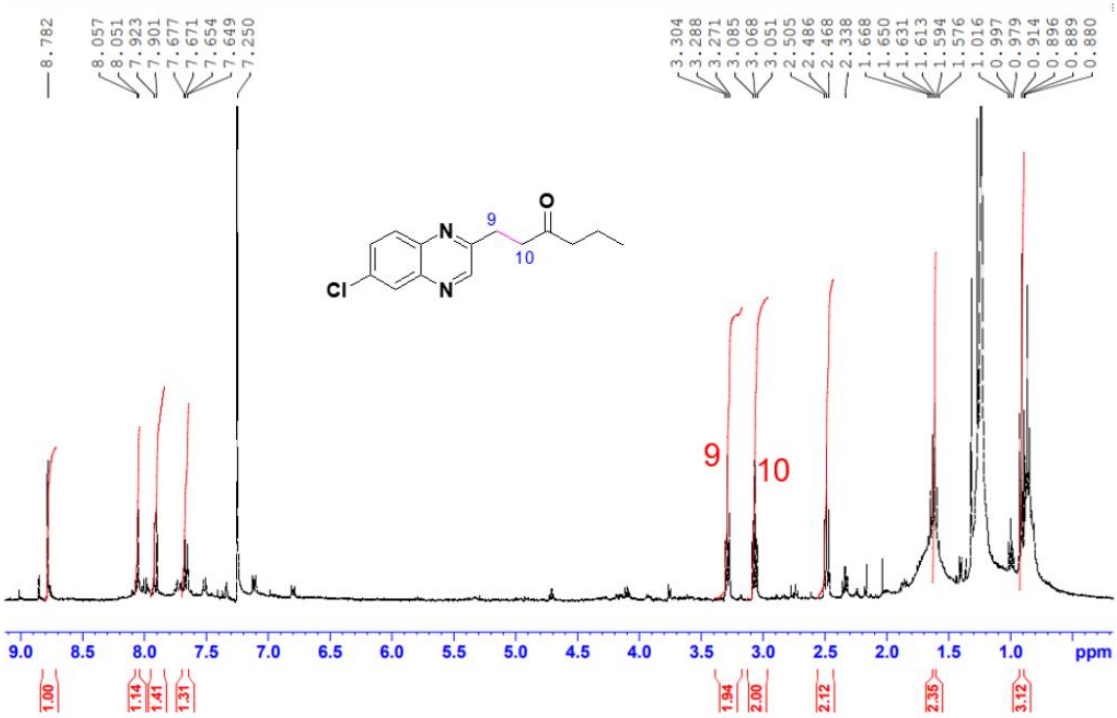

Figure 2.3: [1]H NMR spectrum of 1-(6-chloroquinoxalin-2-yl) hexane-1-yn-3-one **(43).**

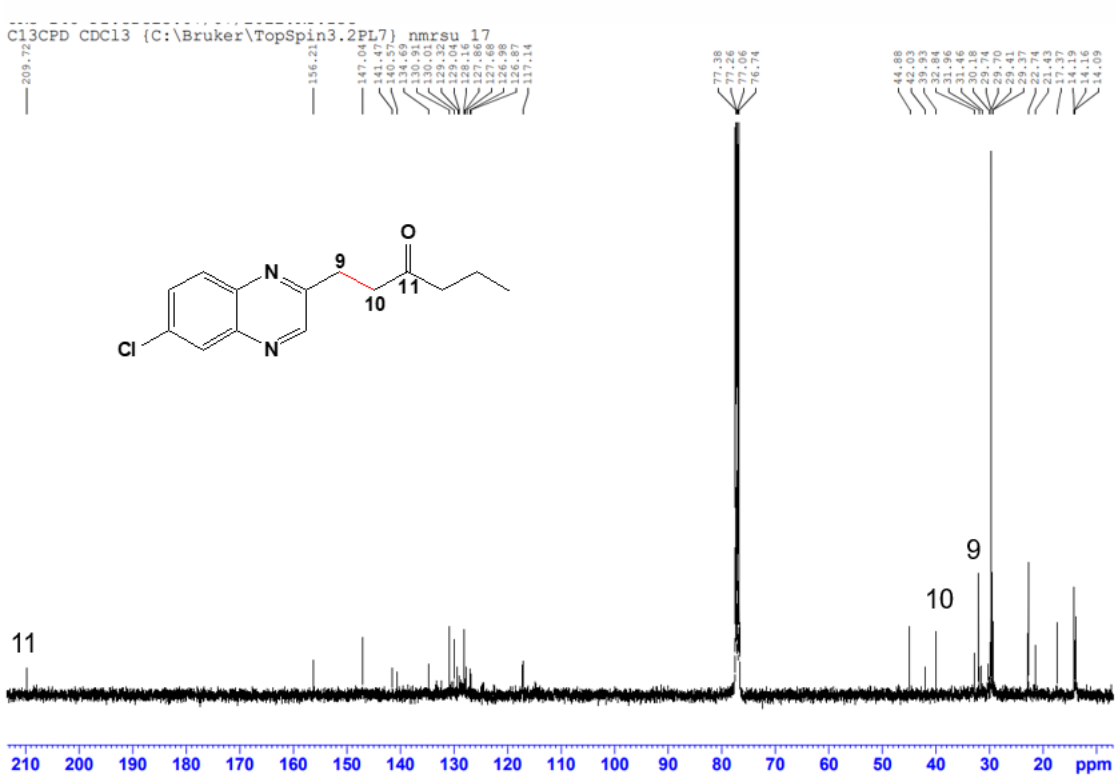

Figure 2.4: [13] C NMR spectrum of 1-(6-chloroquinoxalin-2-yl) hexane-1-yn-3-one **(43).**

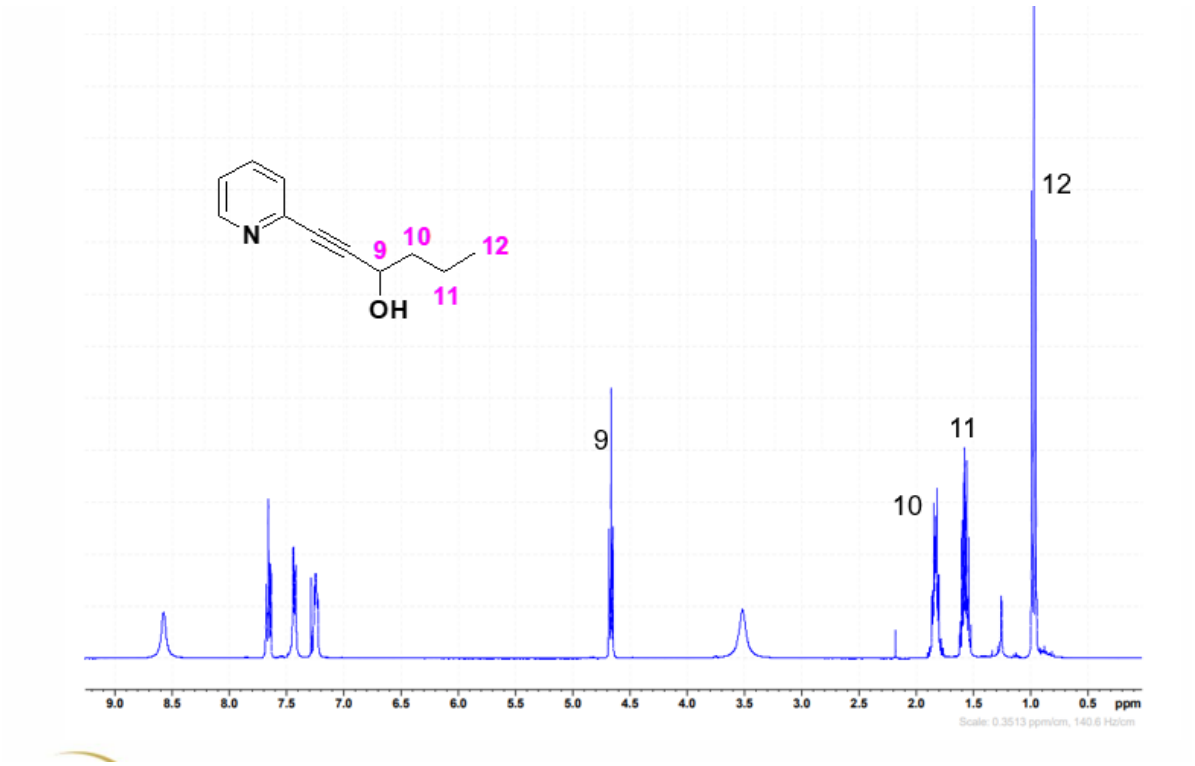

Figure 2.11: ^{1}H NMR spectrum of 1-(pyridine-2-yl) hex-1-yn-3-ol **(54).**

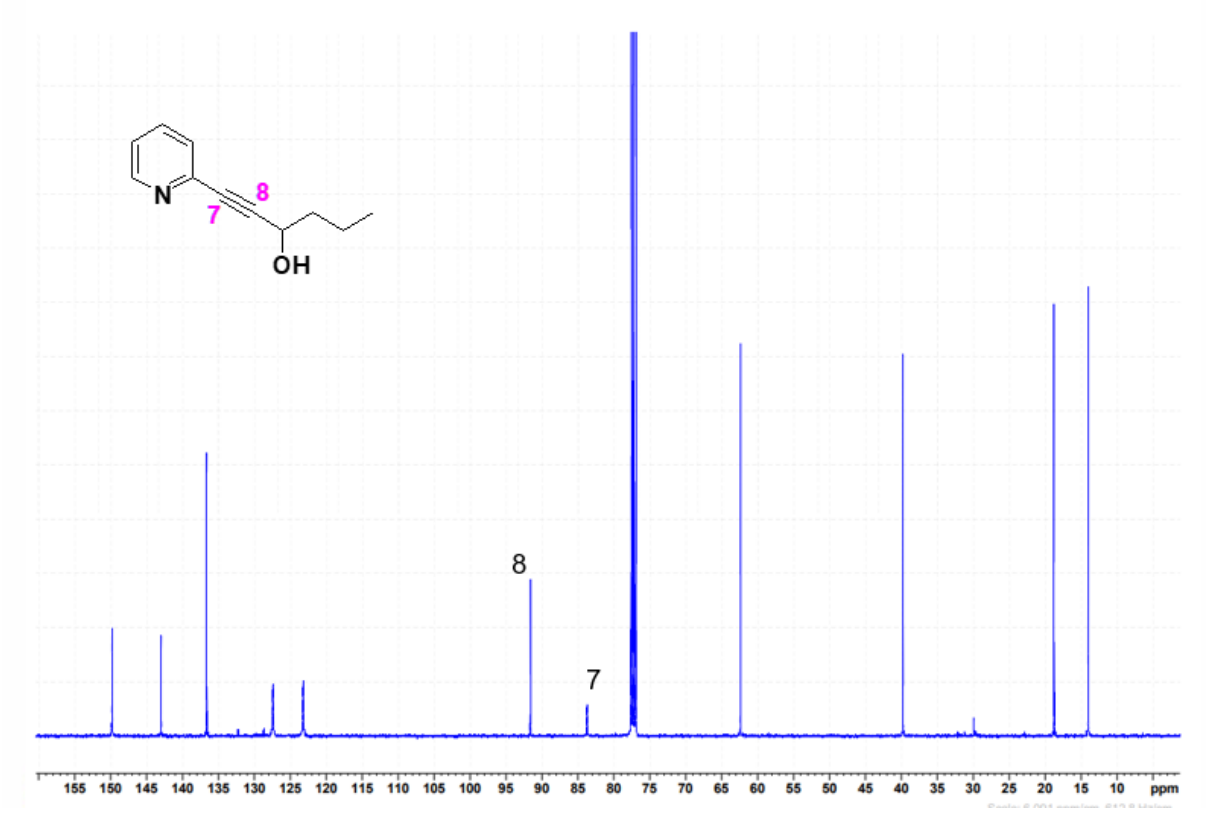

Figure 2.11: ^{13}C NMR spectrum of 1-(pyridine-2-yl) hex-1-yn-3-ol **(54).**

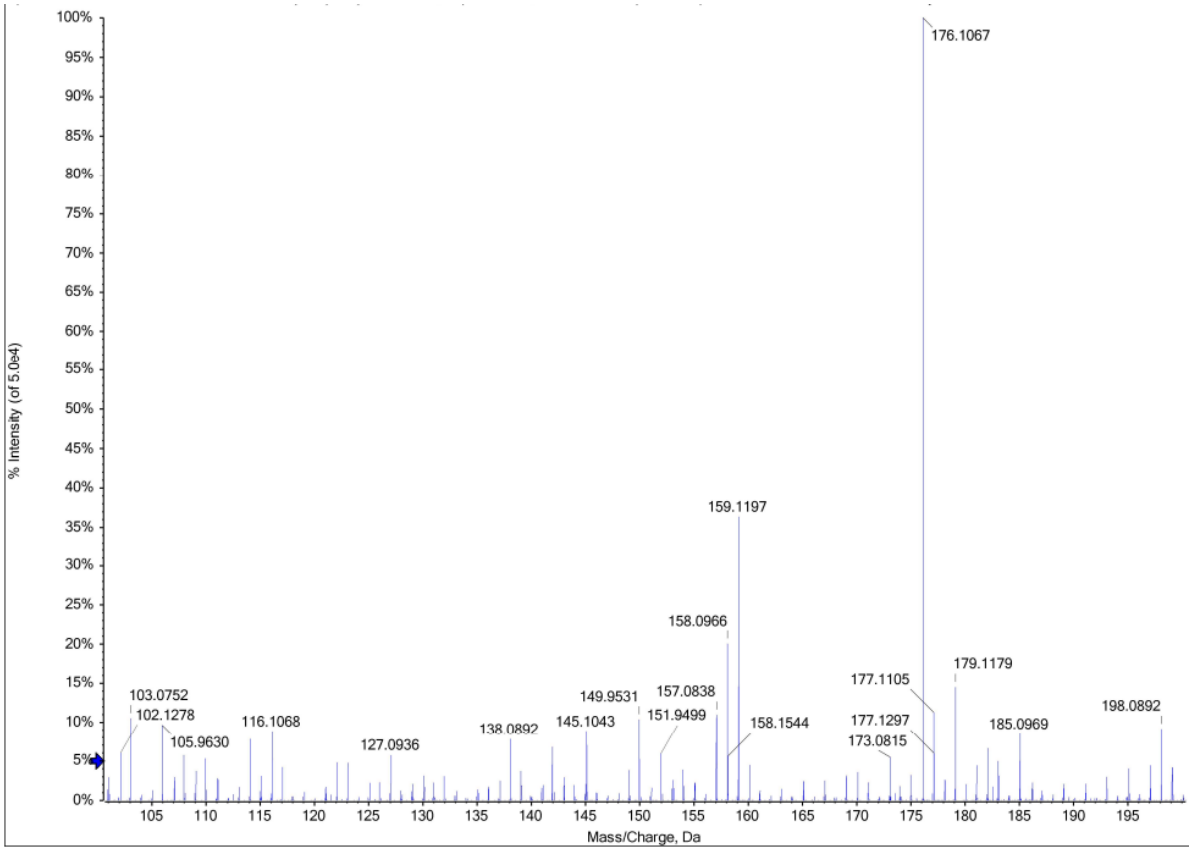

Figure 2.20: Mass spectrum of 1-(pyridine-2-yl) hex-1-yn-3-ol **(54).**

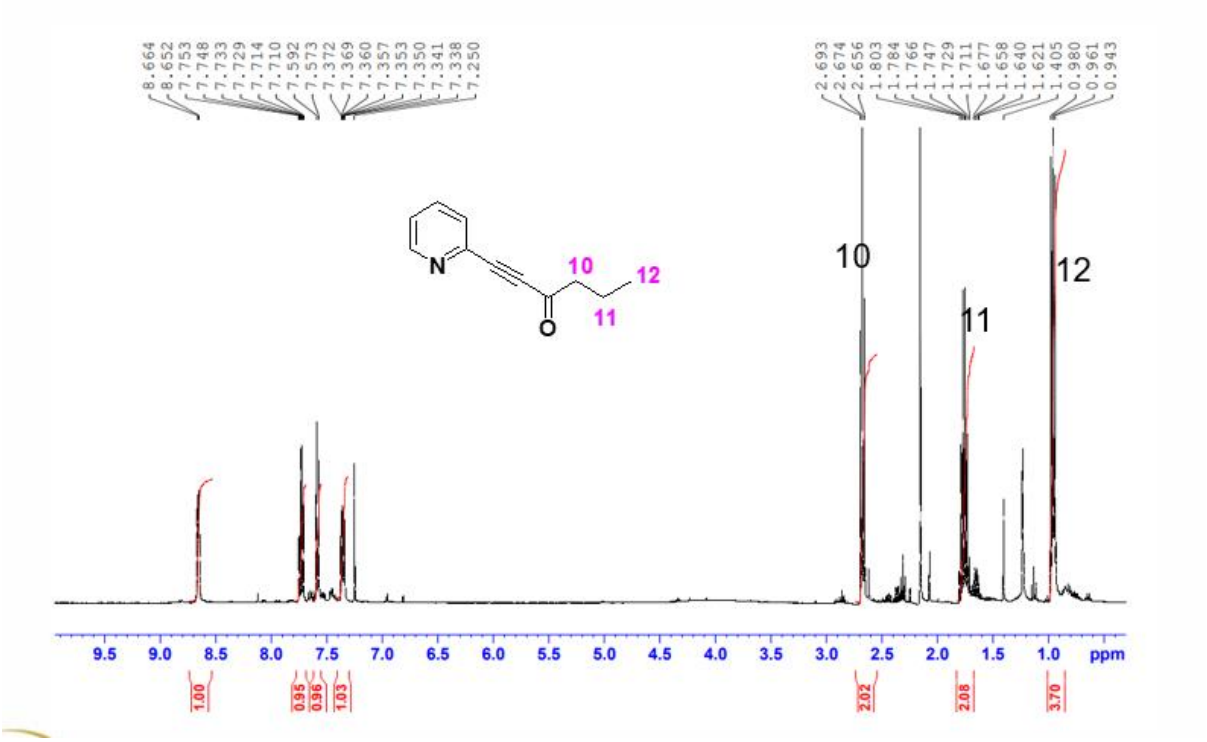

Figure 2.11: ^{1}H NMR spectrum of 1-(pyridine-2-yl) hex-1-yn-3-one **(55).**

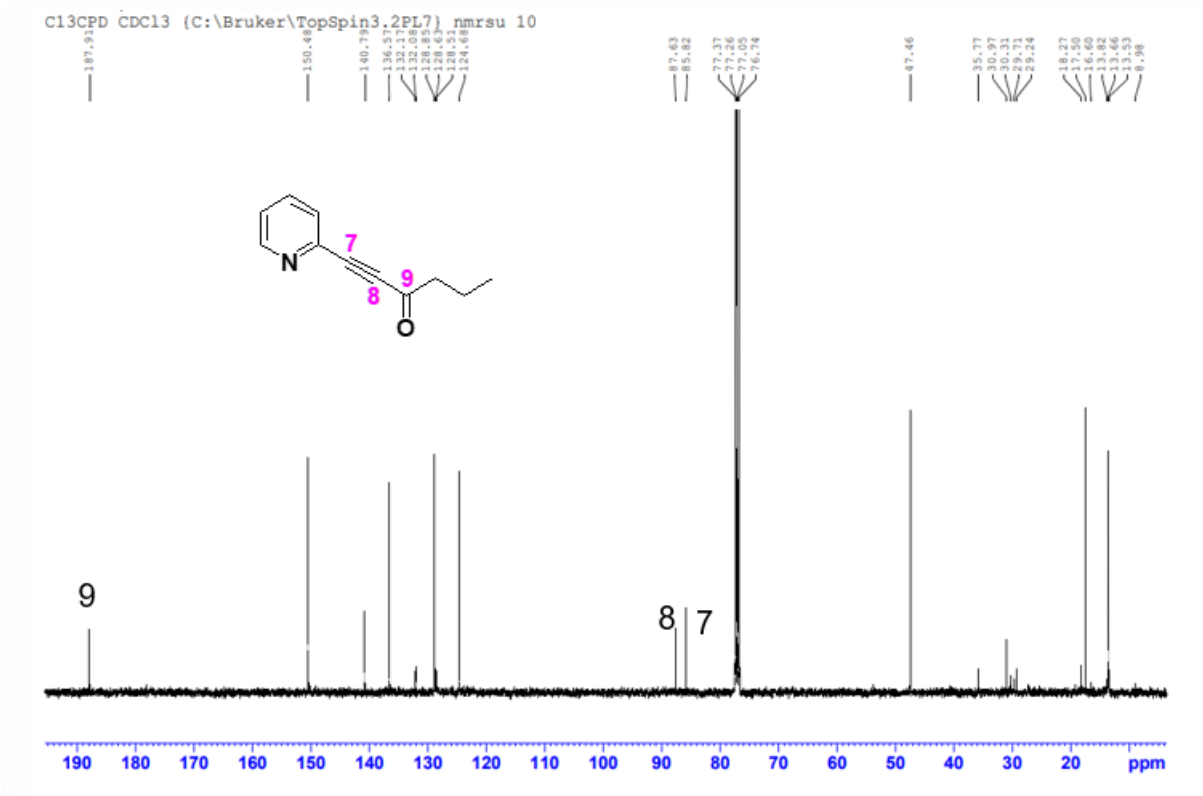

Figure 2.15: ^{13}C NMR spectrum of 1-(pyridine-2-yl) hex-1-yn-3-one **(55).**

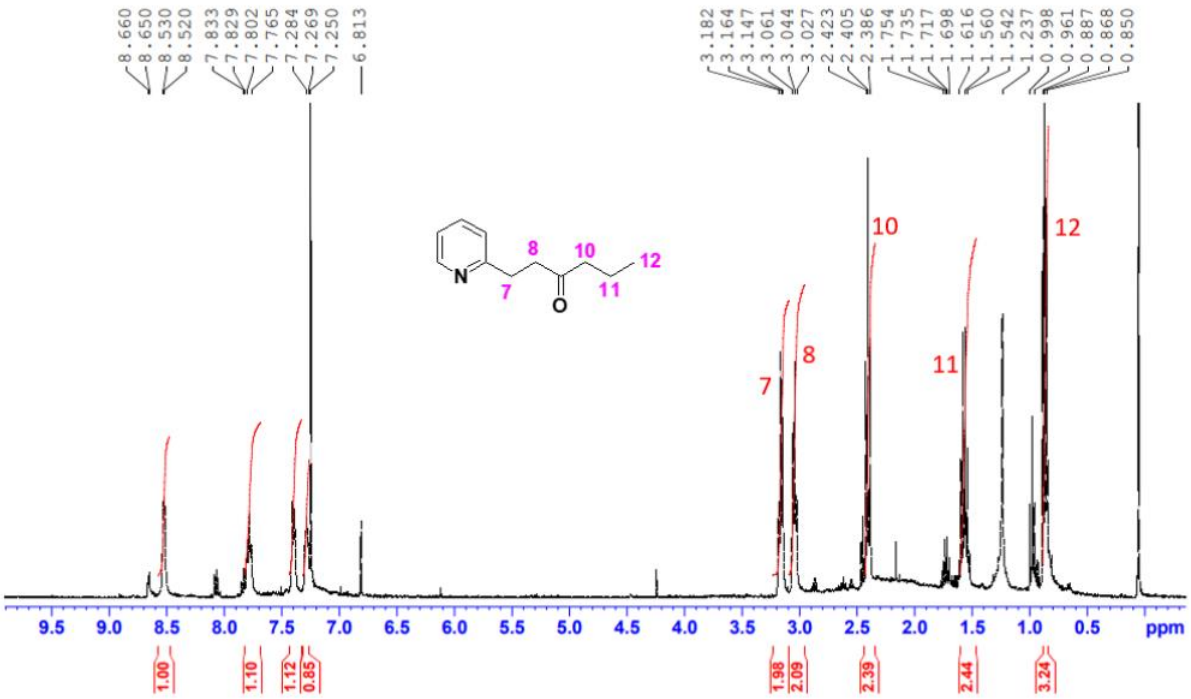

Figure 2.11: ^{1}H NMR spectrum of 1-(pyridine-2-yl) hexane-1-yn-3-one **(56).**

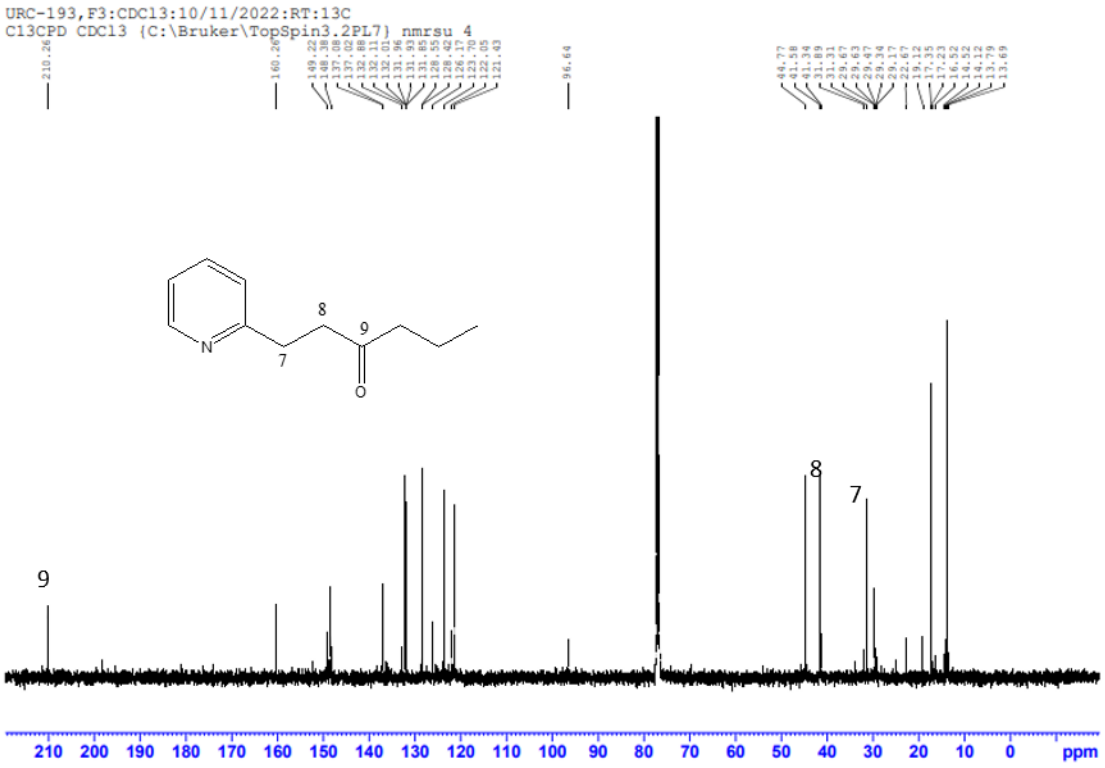

Figure 2.12: ^{13}C NMR spectrum of 1-(pyridine-2-yl) hexane-1-yn-3-one (**56).**

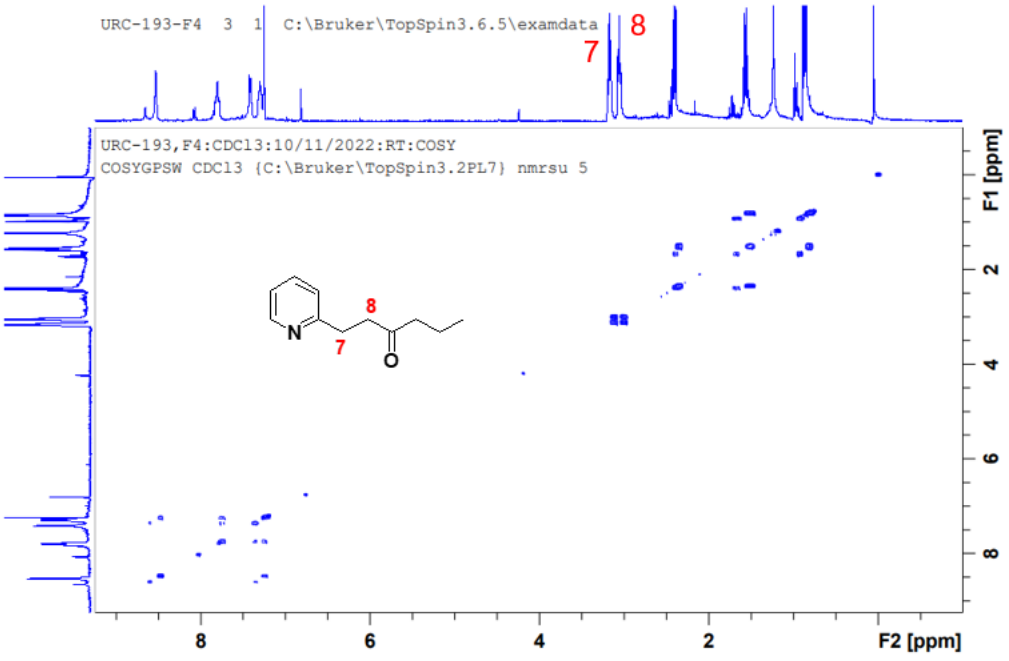

Figure 2.13: Cosy spectrum of 1-(pyridine-2-yl) hex-1-yn-3-one (**56).**

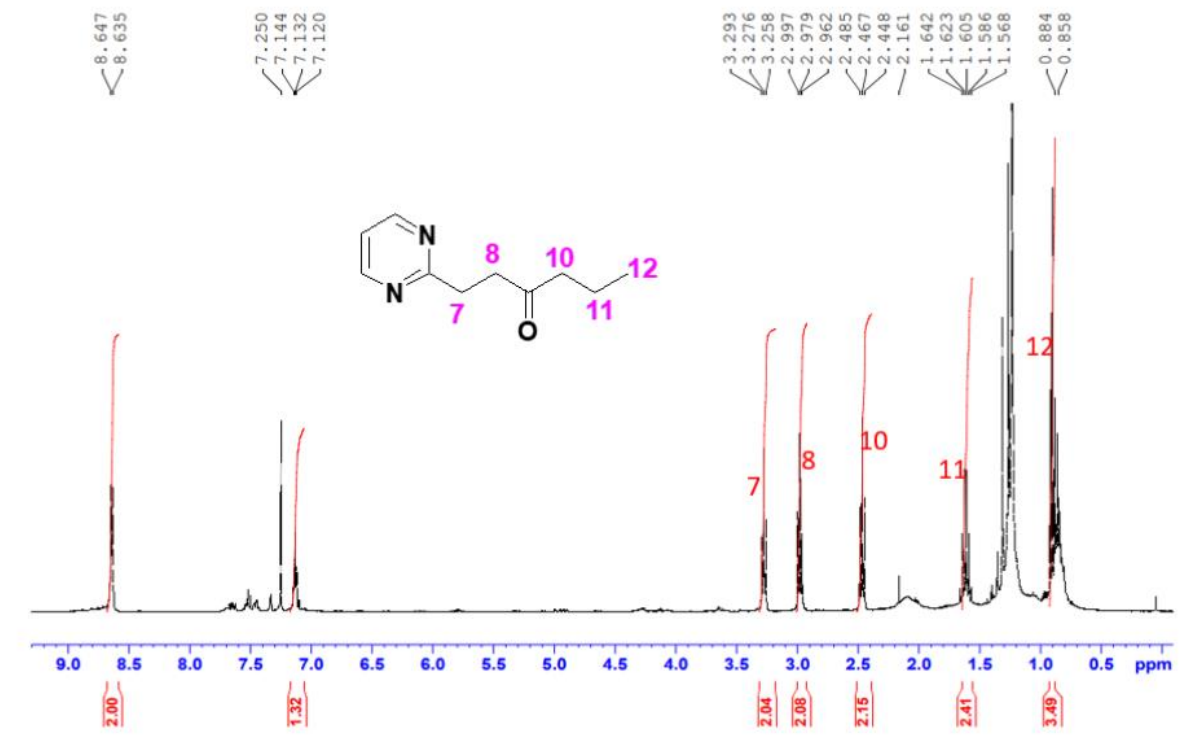

Figure 2.9: ^{1}H NMR spectrum of 1-(pyrimidine-2-yl) hexane-1-yn-3-one (**52).**

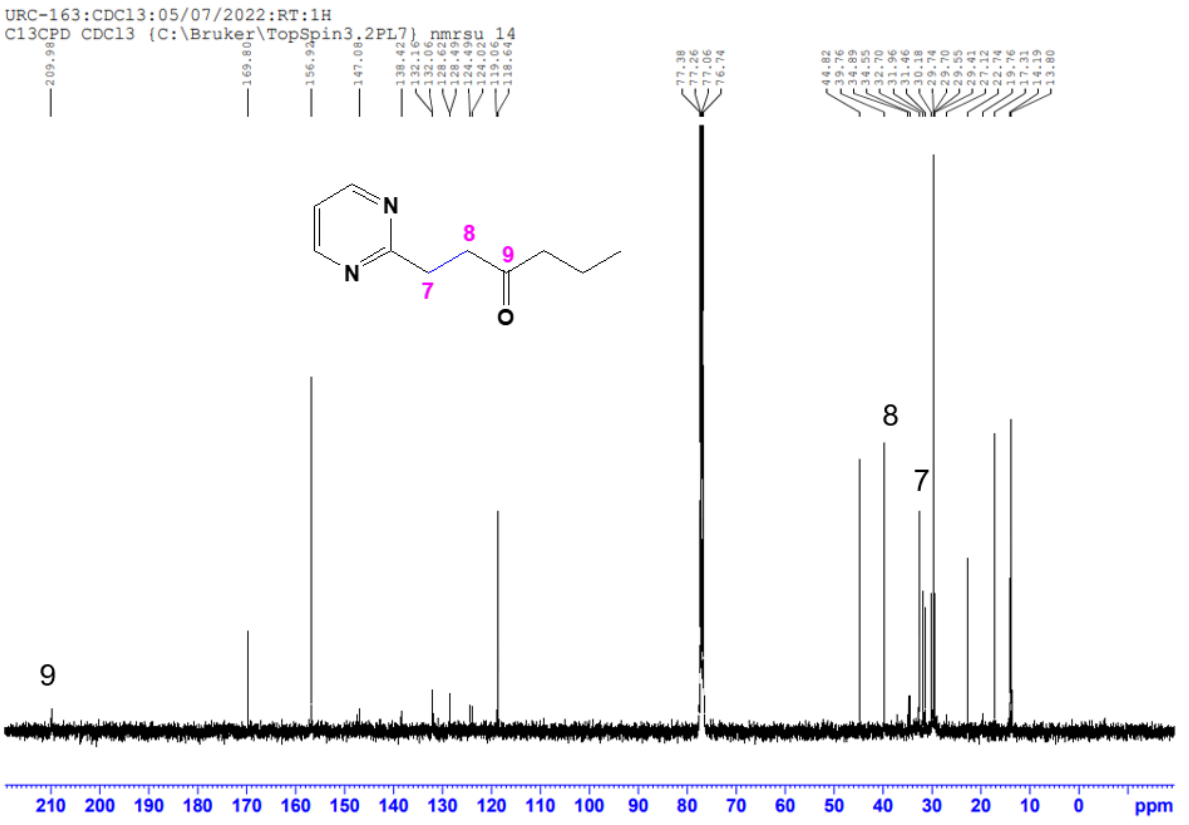

Figure 2.10: ^{13}C NMR spectrum of 1-(pyrimidine-2-yl) hexane-1-yn-3-one **(52).**

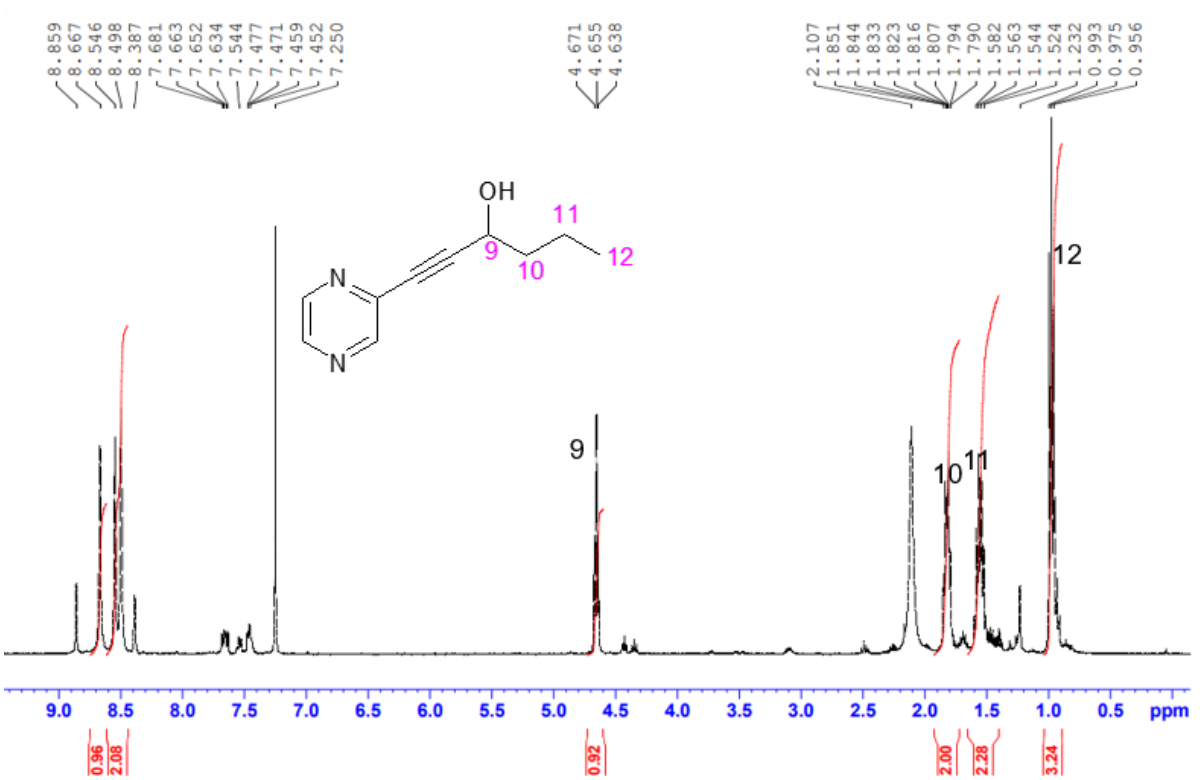

Figure 2.16: ^{1}H NMR spectrum of 1-(pyrazin-2-yl) hex-1-yn-3-ol (**45).**

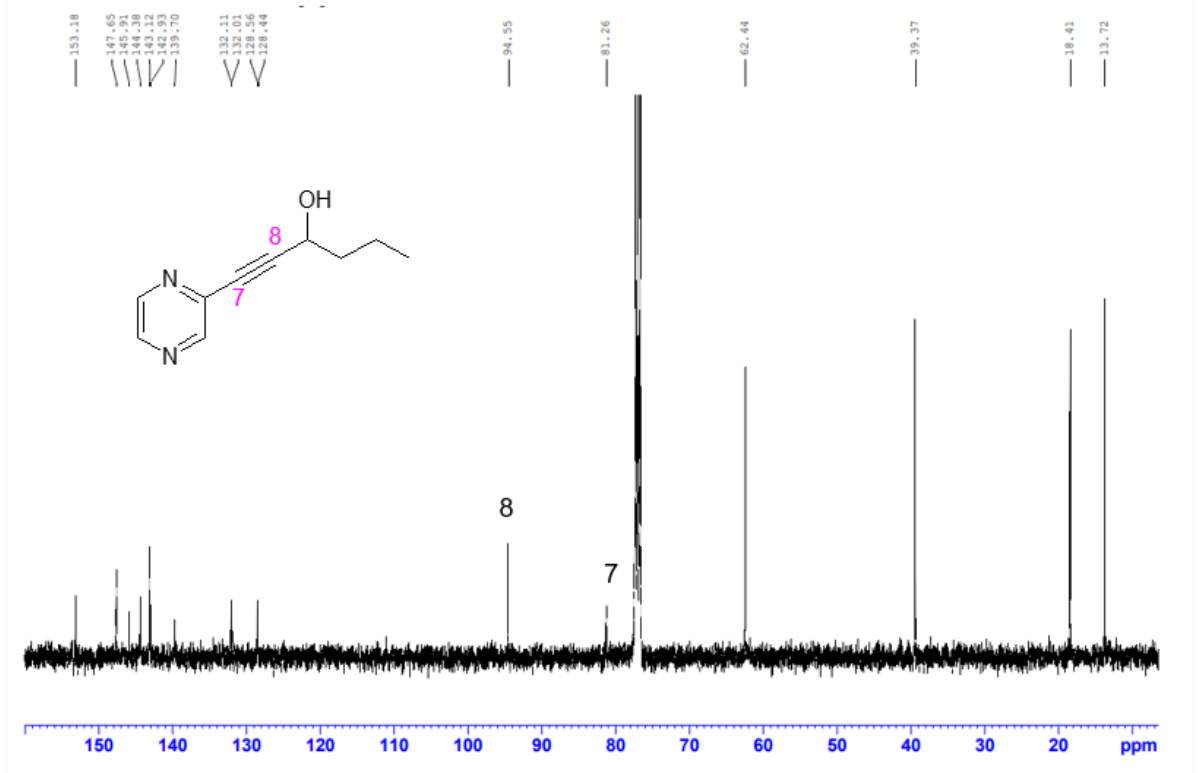

Figure 2.17: ^{13}C NMR spectrum of 1-(pyrazin-2-yl) hex-1-yn-3-ol (**45).**

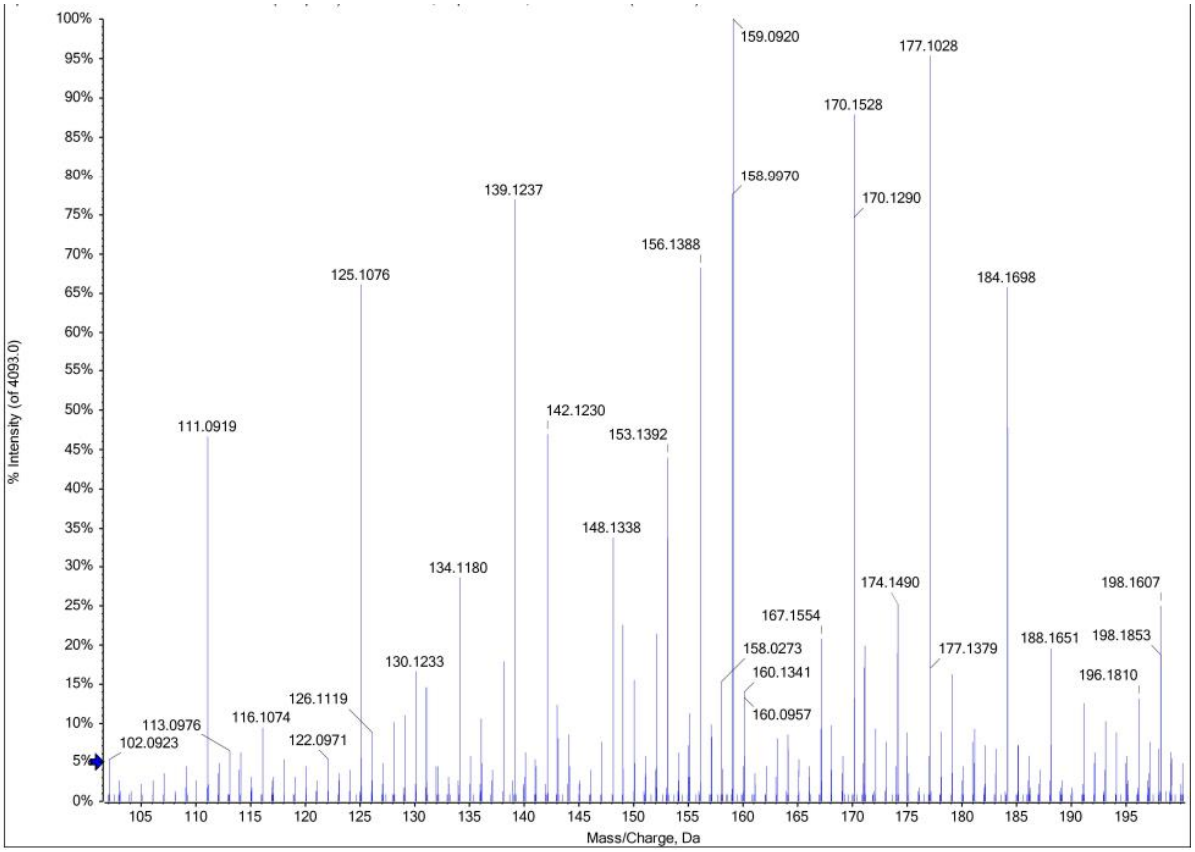

Figure 2.21: Mass spectrum of 1-(pyrazin-2-yl) hex-1-yn-3-ol (**45).**

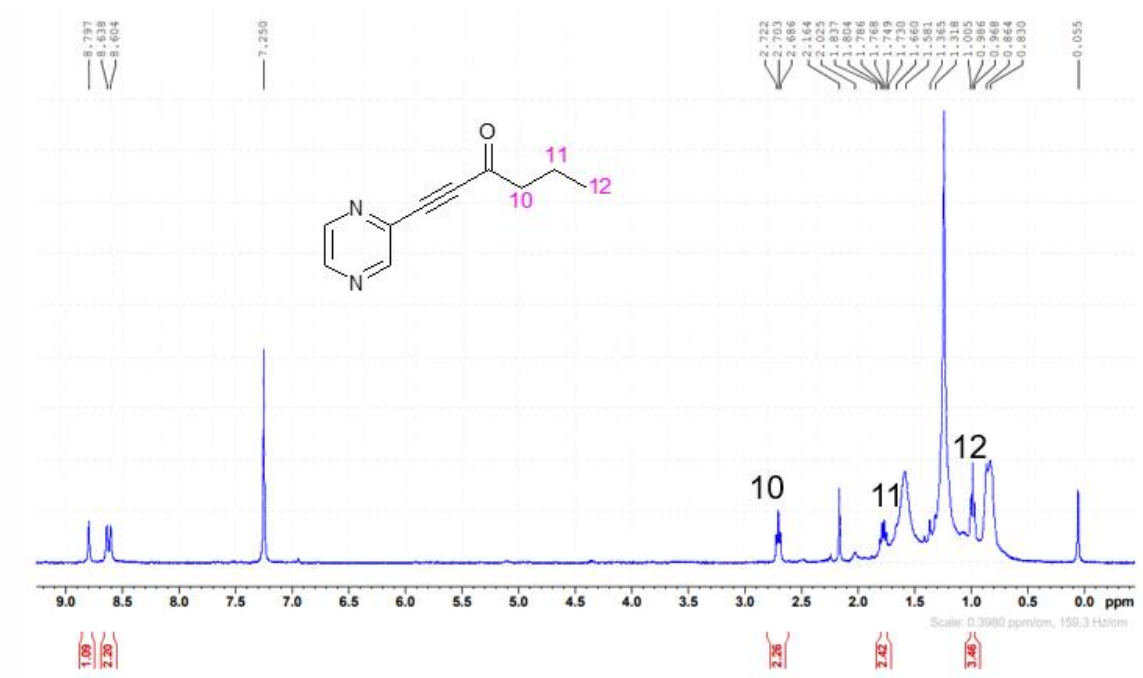

Figure 2.5: [1] H NMR spectrum of 1-(pyrazin-2-yl) hex-1-yn-3-one **46**

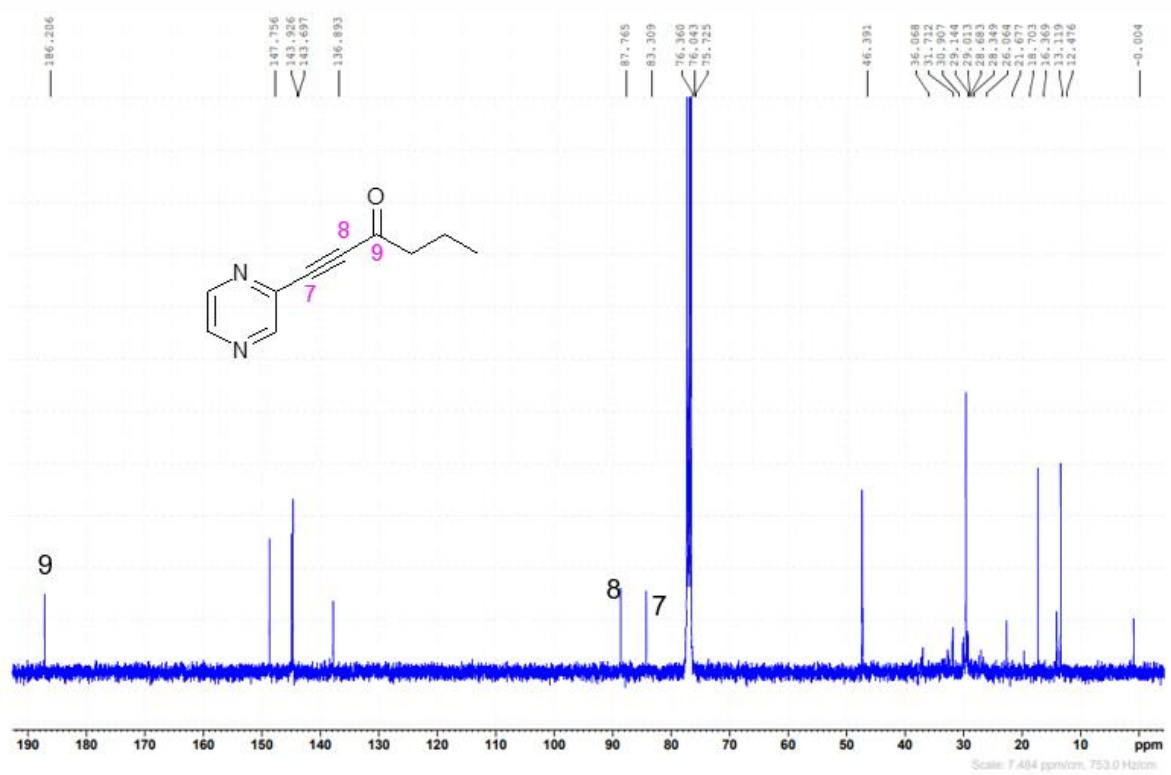

Figure 2.6: ^{13}C NMR spectrum of 1-(pyrazin-2-yl) hex-1-yn-3-one (**46).**

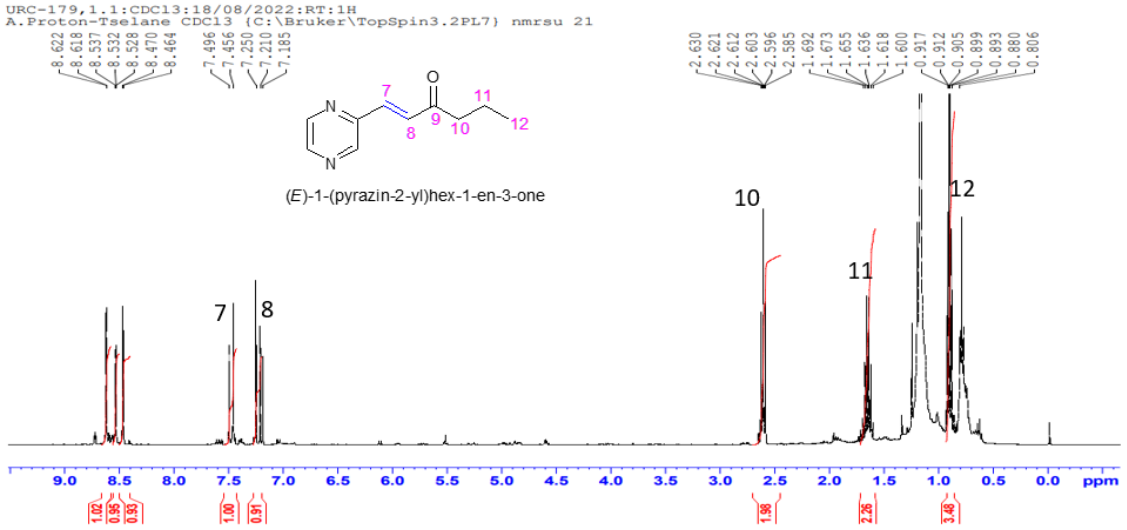

Figure 2.5: ^{1}H NMR spectrum of (E)-1-(pyrazin-2-yl) hex-1-en-3-one (**48).**

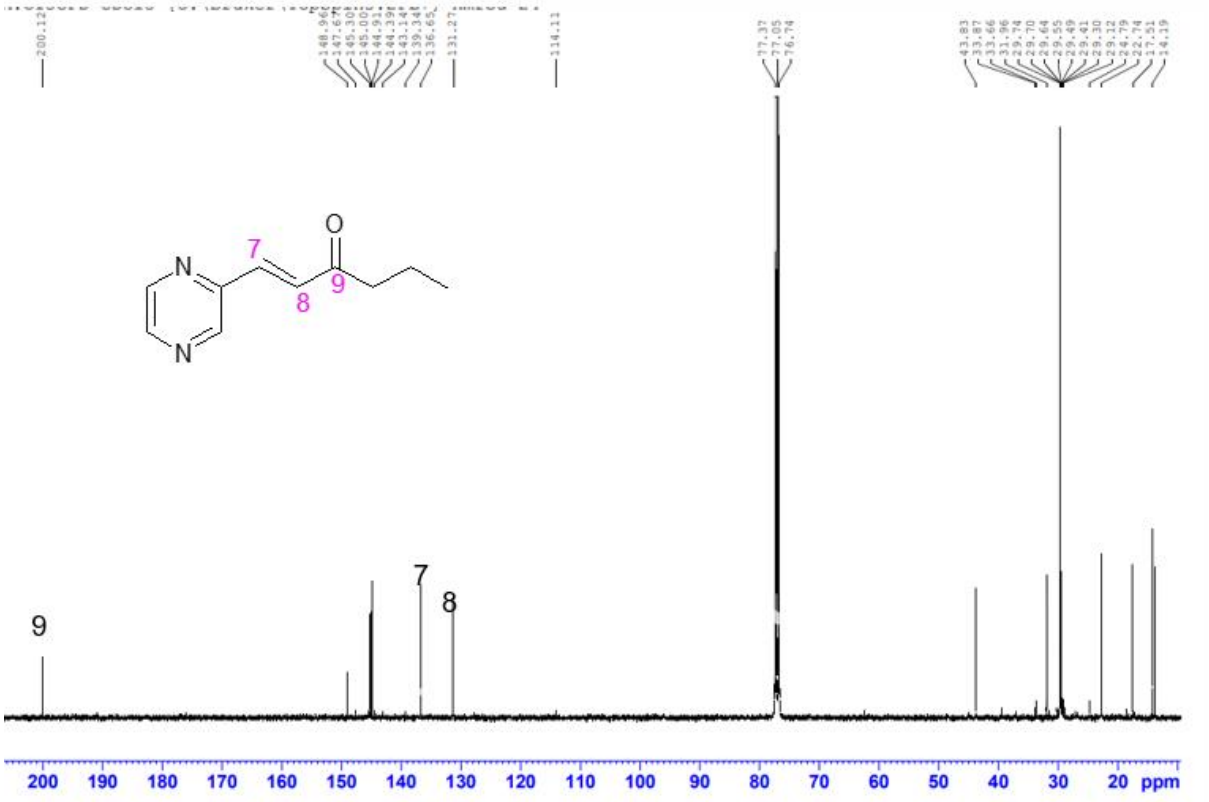

Figure 2.6: ^{13}C NMR spectrum of (E)-1-(pyrazin-2-yl) hex-1-en-3-one (**48).**

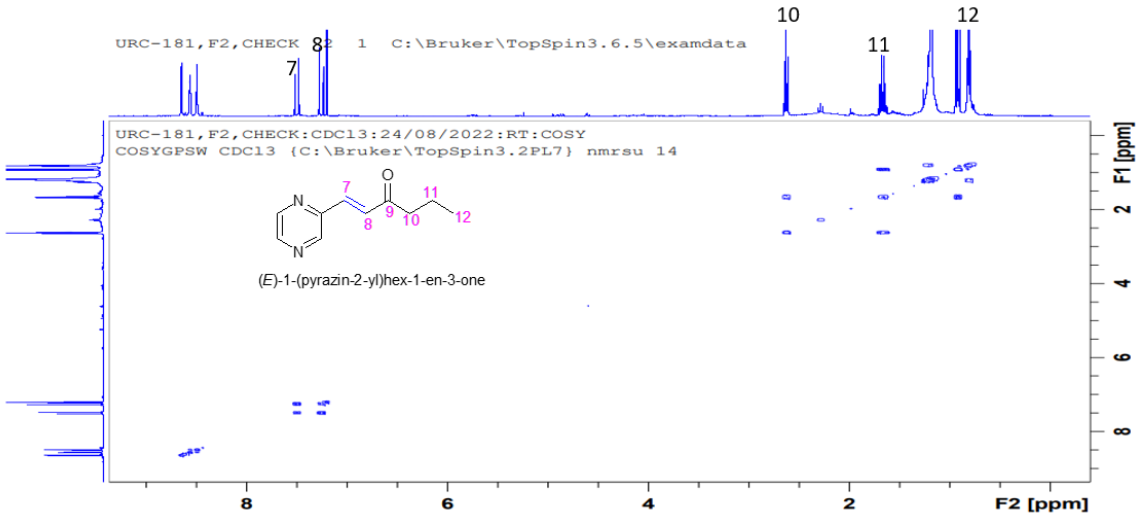

Figure 2.7: Cosy NMR spectrum of (E)-1-(pyrazin-2-yl) hex-1-en-3-one (**48).**

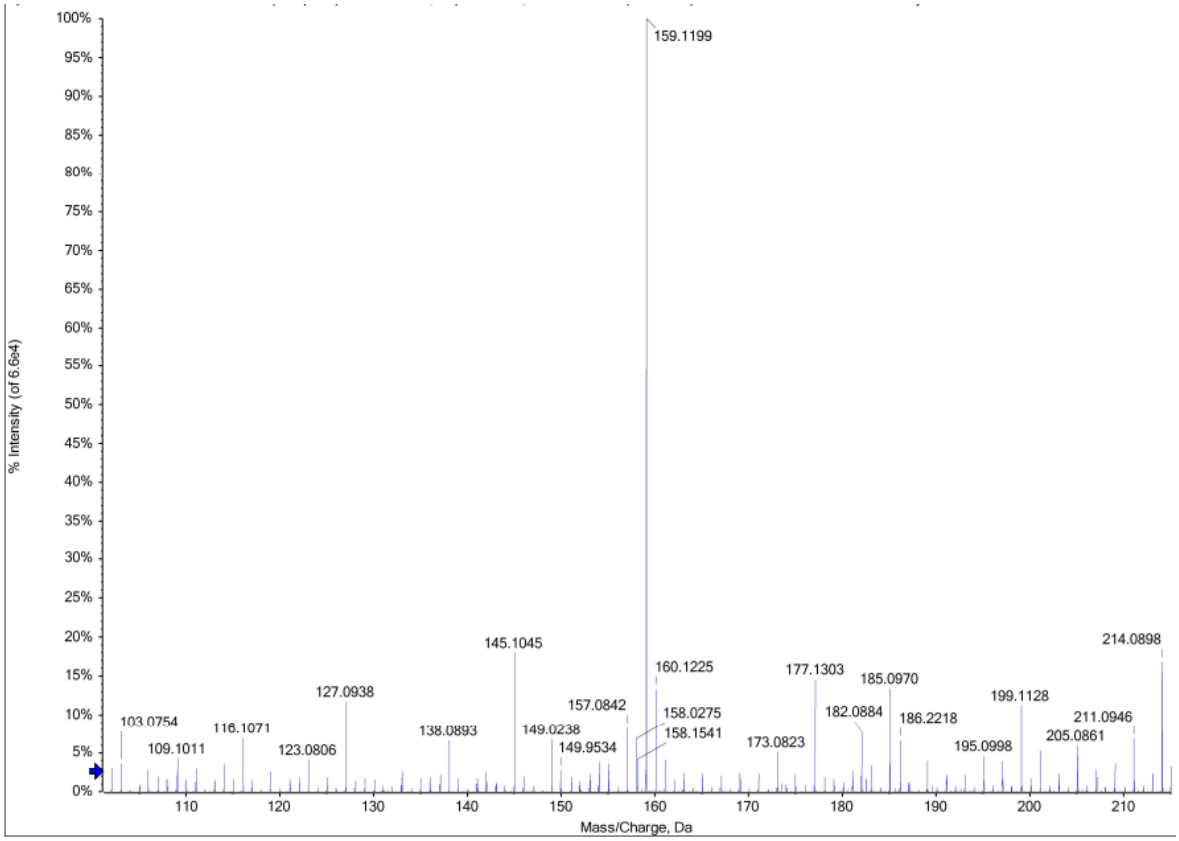

Figure 2.22: Mass NMR spectrum of (E)-1-(pyrazin-2-yl) hex-1-en-3-one (**48).**

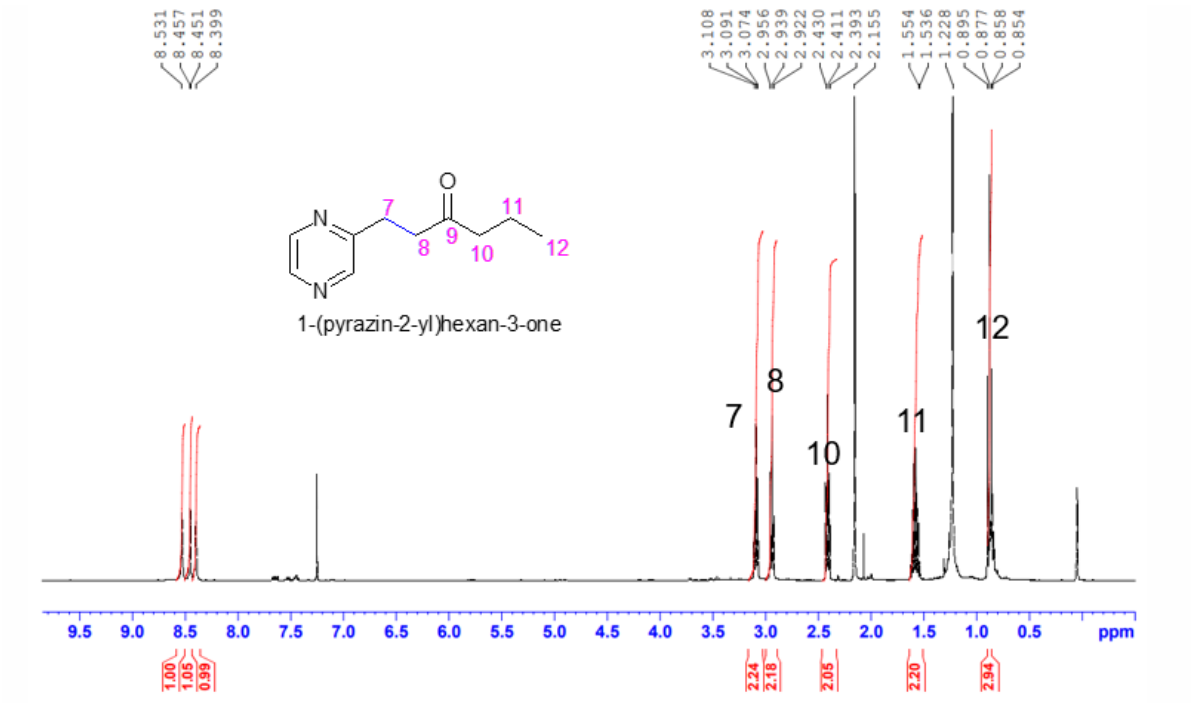

Figure 2.5: [1] H NMR spectrum of 1-(pyrazin-2-yl) hexan-3-one (**47).**

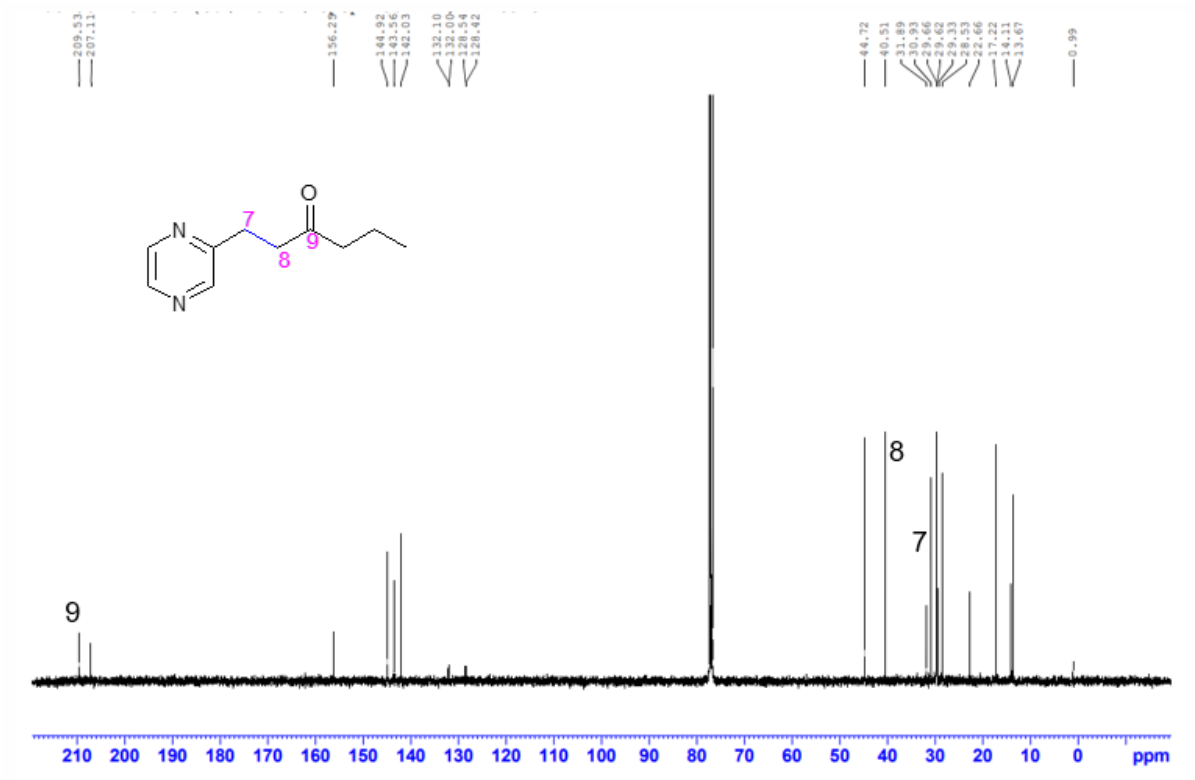

Figure 2.6: ^{13}C NMR spectrum of 1-(pyrazin-2-yl) hexan-3-one (**47).**

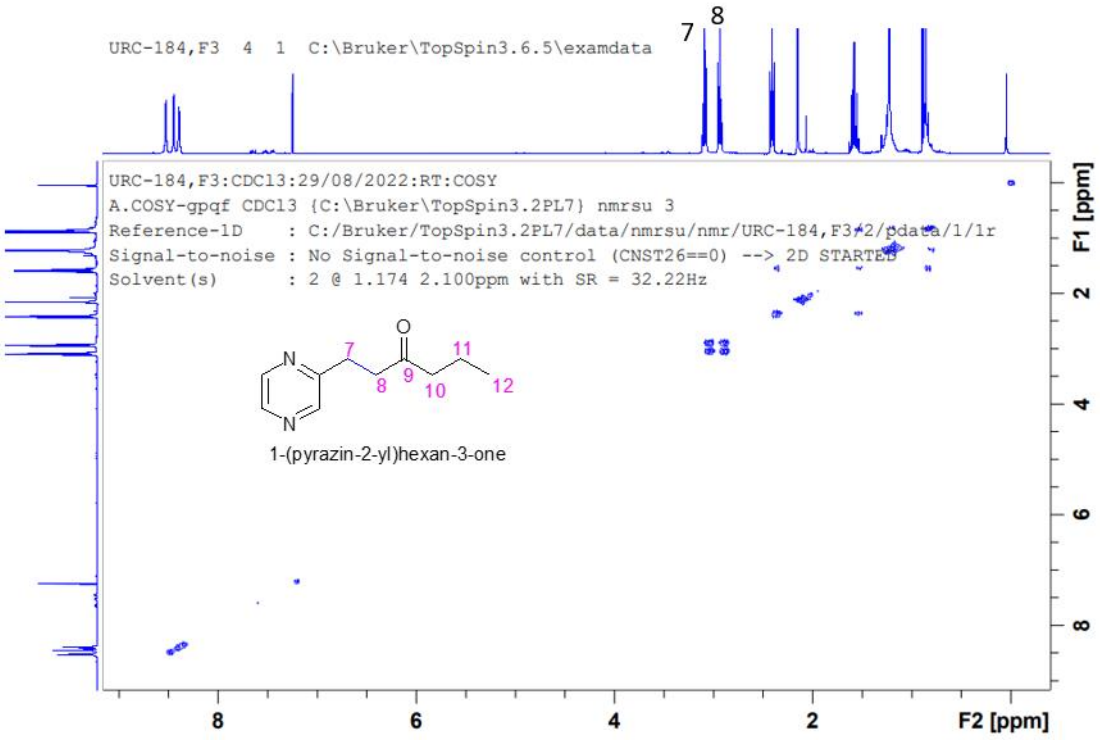

Figure 2.8: Cosy NMR spectrum of 1-(pyrazin-2-yl) hexan-3-one (**47).**

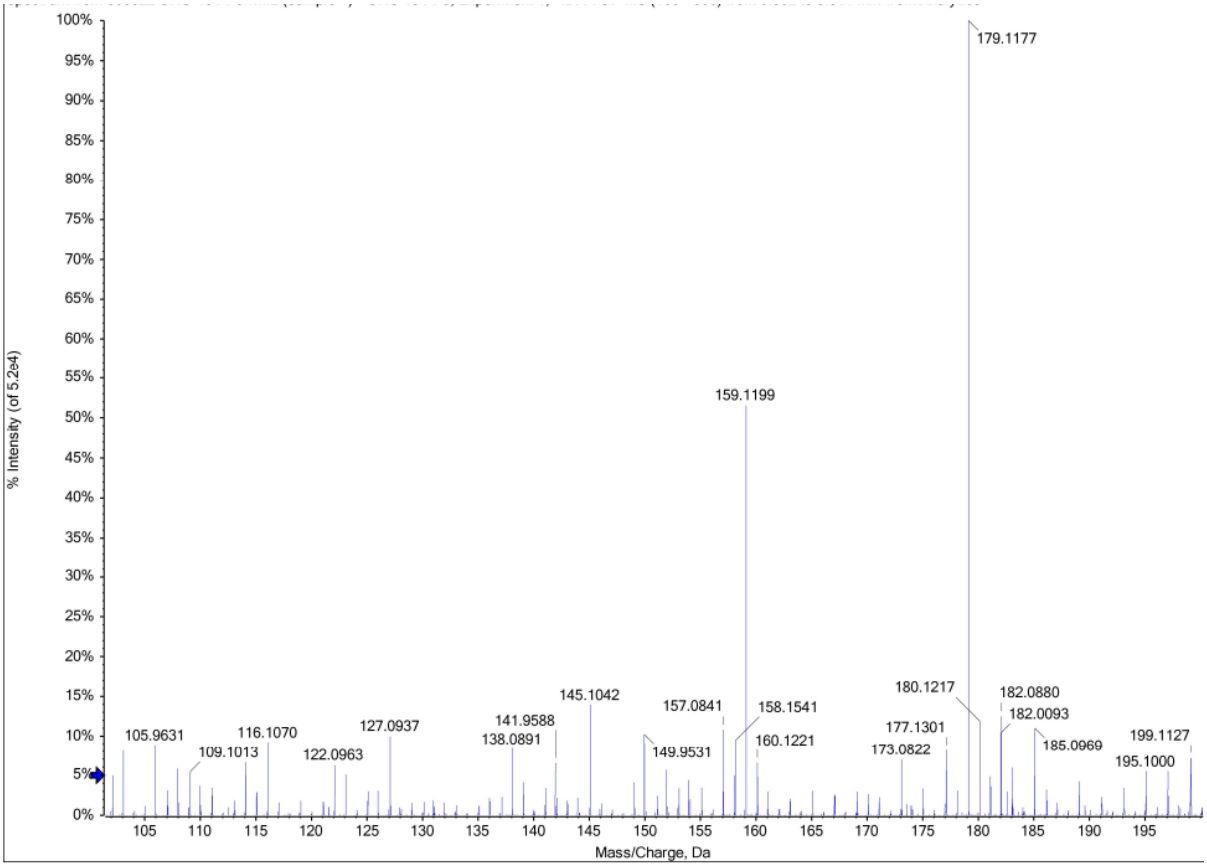

Figure 2.23: Mass NMR spectrum of 1-(pyrazin-2-yl) hexan-3-one (**47).**

APPENDIX 2 (COMPUTATIONAL)

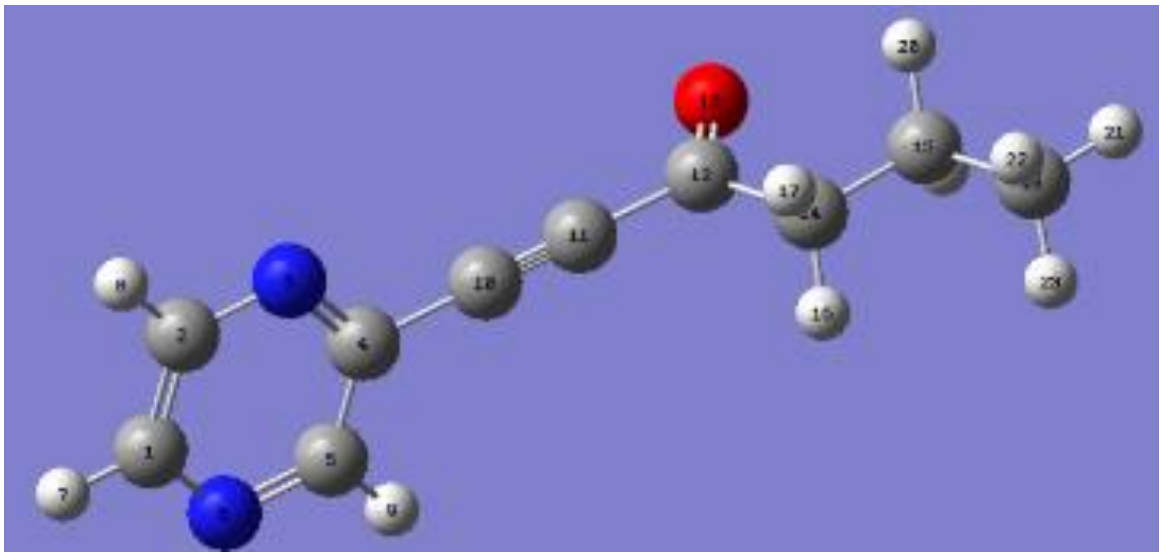

Figure 2.24: Optimized compound **46.**

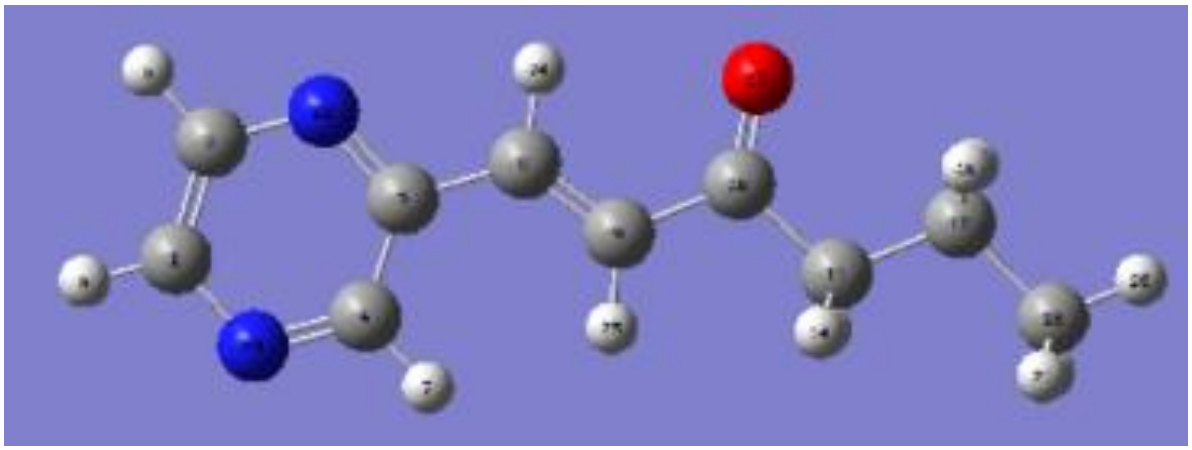

Figure 2.25: Optimized compound **48.**

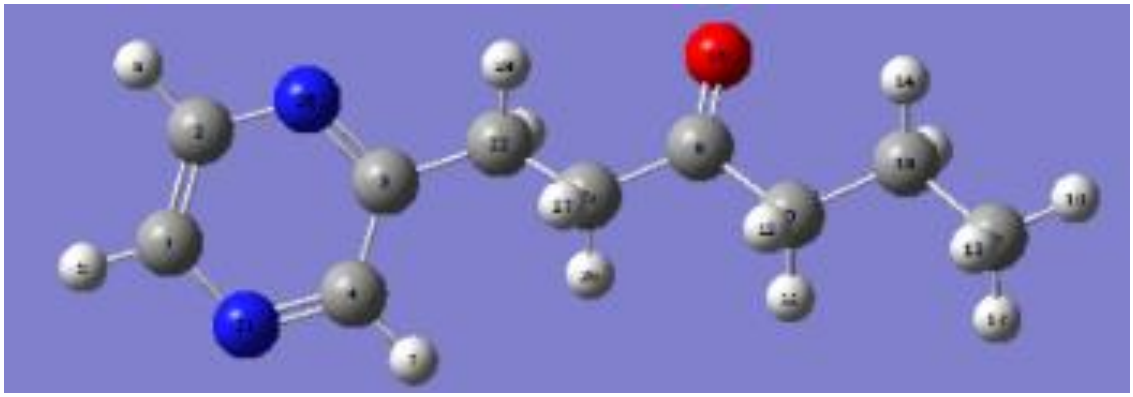

Figure 2.26: Optimized compound **47.**

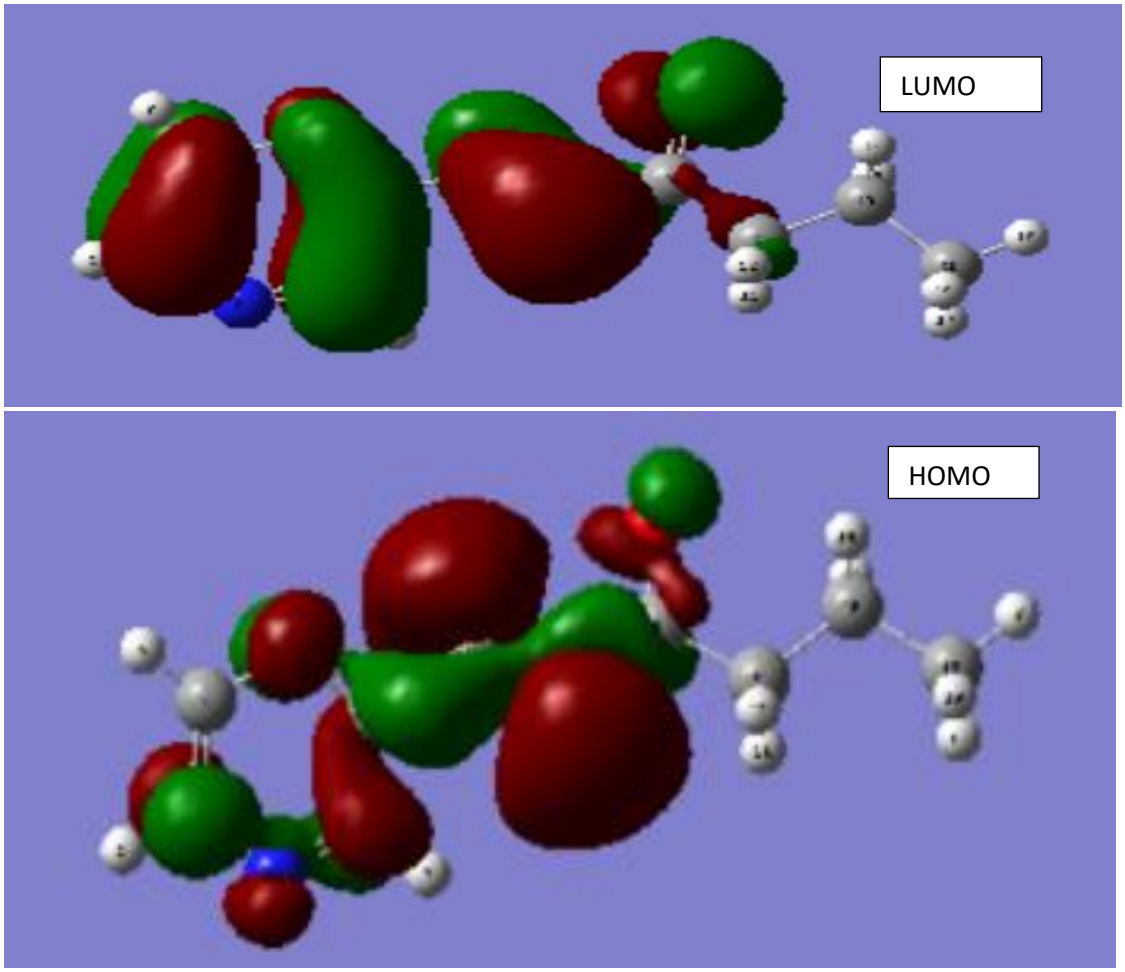

Figure 2.27: The frontier molecular structure of compound **46.**

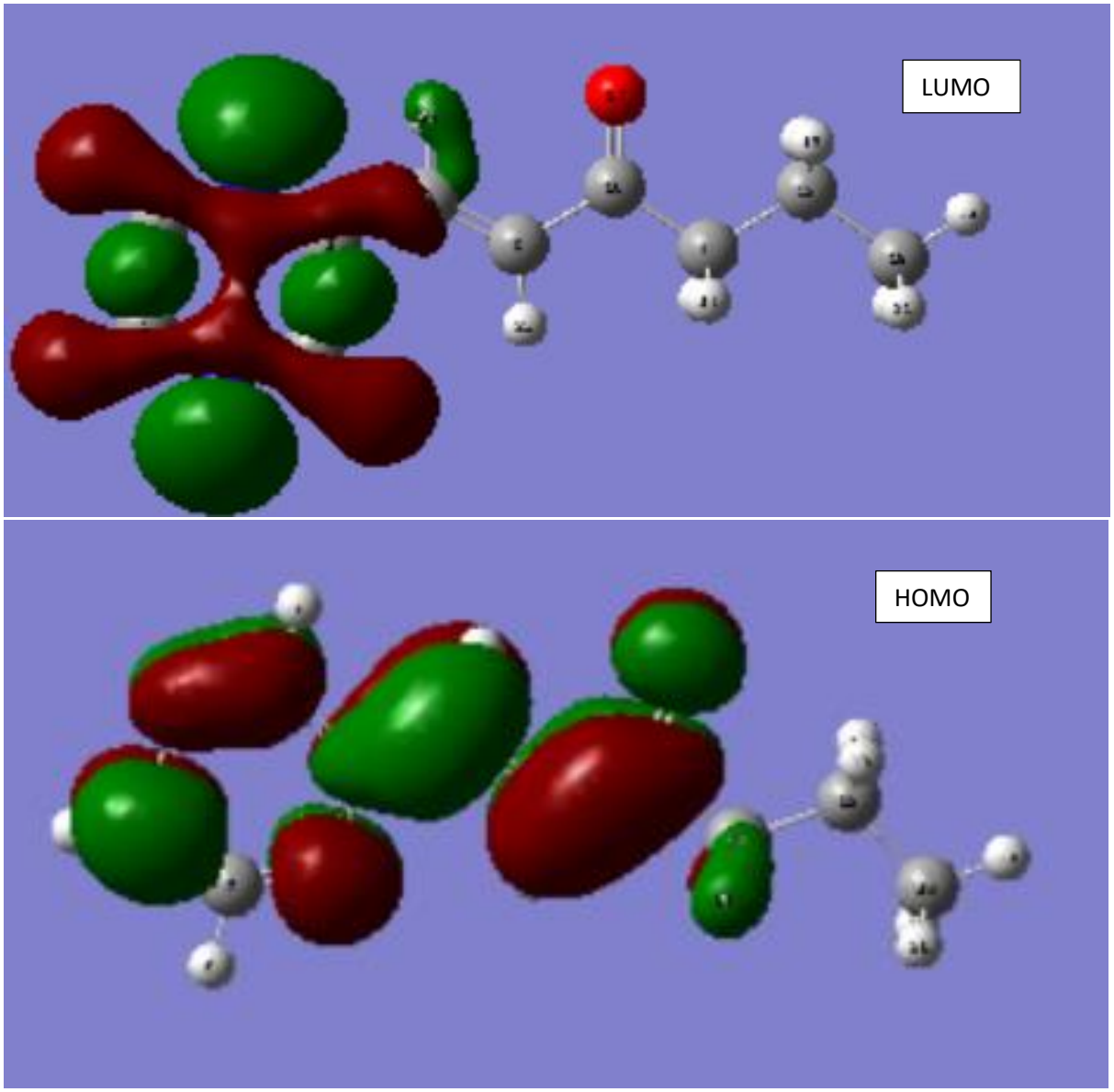

Figure 2.28: The frontier molecular structure of compound **47.**

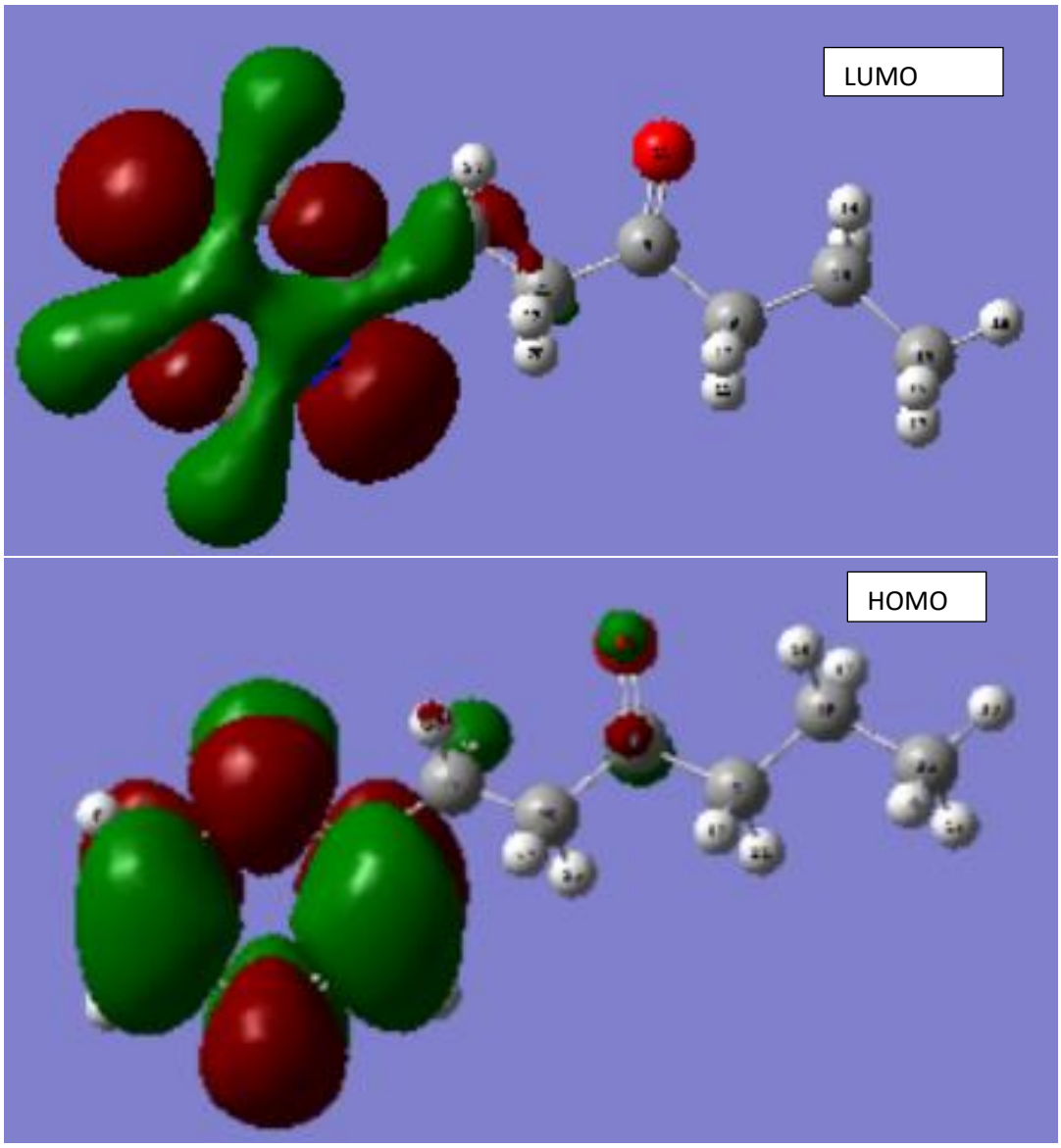

Figure 2.29: The frontier molecular structure of compound **48.**