

**COUPLING OF HALOARENES WITH TERMINAL ALKYNES BY USING
COPPER, IT'S COMPLEXES THEIR SYNTHESIS AND ITS
APPLICATION IN SYNTHETIC ORGANIC CHEMISTRY**

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis, entitled **“Coupling of Haloarenes with Terminal alkynes by using Copper, it's Complexes their synthesis and its Application in Synthetic Organic Chemistry”** in fulfillment of the requirements for the award of the degree of Doctor of Philosophy in Chemistry and submitted in School of Basic and Applied Sciences Galgotias University, Greater Noida is an authentic record of my own work carried out during a period from January, 2014 to December, 2017 under the supervision of Prof.(Dr.) ARVIND KUMAR JAIN and Prof.(Dr.) IMRAN ALI

The matter embodied in this thesis has not been submitted by me for the award of any other degree of this or any other University/Institute.

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ABSTRACT

The first part of my thesis describes the preparation of different copper catalyst for the Sonogashira reaction and exploration of its activity for Sonogashira reaction. It include optimization of reaction condition like right solvent selection for reaction, temperature of reaction, base selection for reaction, purification of product and synthesis or selection of starting materials for reaction. Here in we have prepared following catalyst and explored its activity for Sonogashira reaction. We have developed first time industrial process of preparation for Iodo(tristriphenylphosphine)copper(I). We have prepared 25-30 compounds for each catalyst and characterized using ^1H NMR, C^{13} and C^{13} Dept. Spectroscopy.

1. Iodo (tristriphenylphosphine)copper(I):
2. Bromotris(triphenylphosphine)copper(I)
3. Di- μ -iodidobis[2,2'-bis(diphenylphosphanyl)-1,1'-bina phthyl,]copper(I)
4. (Z)-5-((2-mercaptophenylimino)methyl)-2-methoxy phenol Copper(I)

In addition to this have explored the catalytic activity of copper carbonate for Sonogashira reaction in legand and base free condition (Copper carbonate itself act as base and legand), the specificity of the Sonogashira reaction is the mild reaction condition. Use of copper catalyst for this reaction makes milder condition for this reaction.

The use of copper catalyst in place of palladium catalyst makes this synthesis more economical and environment friendly and closes to green approach.

Second part describes the application of Sonogashira reaction

1. Preparation of 2-Vinyl phenols: This is new protocol we have developed and reporting first time using simple reagent copper powder. Generally in Sonogashira the terminal alkyne proton get substituted by alkyl or aryl group. But here we got addition product. in nucleophilic addition also generally addition takes place according to markovnikov's rule and nucleophile will attach to less substituted carbon atom but Here in reported protocol substitution takes place according to anti markovnikov's rule.
2. Preparation of Isocoumarin: synthesis of isocoumarin involves two steps. Preparation of 2-alkyne benzoic acid from alkyne and 2-Iodobenzoic acid and its cyclization to form

isocumarin. We have prepared isocumarin derivative in single step (one pot synthesis) using simple reagent copper powder and 2-iodobenzoic acid and alkyne as a starting materials. We have also prepared isocumarin 2-iodobenzoate as a starting material using copper powder as a reagent. We have prepared isocumarin using catalyst $\text{CuI}(\text{PPh}_3)_3$.

Third Part describes Industrial application of Sonogashira reaction.

1. Synthesis of Keto and Oxazoline: Developed a new protocol for synthesis of Keto Oxazoline in this protocol formation of oxazoline and oxidation of alkyne group to ketone occur in single step using simple and mild reagent copper powder. We are reporting this new rearrangement with formation of oxazoline ring and oxidation of triple bond for the first time. We have filed Indian patent application for this process and product using copper powder.
2. Induction of Chirality in organic molecule: In literature there is no method available using simple starting material for the preparation of chiral isoindolinone. We have developed the method for preparation of isoindolinone using simple starting material 2-Iodo benzoic acid, and alkynes. Developed a process for chiral purification (chiral resolution) using simple single solvent in single purification up to enantiomeric excess 95%. Here also the copper metal used for coupling and cyclization making this synthesis more economic and approaches towards the green synthesis.

ACKNOWLEDGEMENTS

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I must owe special debt of gratitude to Hon'ble Chancellor **Shri Sunil Galgotia** and **Mr Dhruv Galgotia**, CEO, Galgotias University for their valuable support

I would like to express my deep and sincere gratitude to **Prof. Renu Luthra Vice Chancellor Galgotias University** for all the required permission, support and blessings for this thesis. I would like to thanks **Prof.(Dr.) Bimal Sarkar** Dean School of Basic and Applied Sciences, Galgotias University for his valuable guidance during the duration of my thesis work.

*My Special thanks to my supervisor **Prof. (Dr.) Arvind Kumar Jain** for his support and helping me during my work. He really helped me lot during the course in official hours also and many time on holidays and lot. Without his support I can't able to complete this work within this time span. I am also thankful to his family members; they always treated me as a special guest during every meeting for thesis discussion at his residence. He introduced me with many of his research friends from them I had gain much more knowledge and they helped me lot regarding thesis activities like data analysis, data interpretation raw materials availability and etc.*

I would like to thank my Co- supervisor **Prof. (Dr.) Imran ali** for his guidance and supervision to make this work possible. I really appreciate his patience, help and support throughout this work. *My supervisor and Co- supervisor treated me with great patience so that I have learned a lot throughout this course. I could not have imagined having a better advisor and mentor for my Course.*

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I would like to thanks my friends Mr.R. Vadivelan, Mr. Rupak, Mr. Nadeem Lone, and Mr. Deepak for supporting me for this work.

Last but not list I would like to thank my parents and family members, their love provided me inspiration and driving force, without their support finishing this journey was not possible.

Thanks God for being with me always and providing all the strength and perseverance to carry out this study. I pray to Him that my study be good in all alleviating the pain and suffering of the human race.

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DNYANESHWAR KONDIBHAU NIGHOT

LIST OF PUBLICATIONS

1. Complete **Indian patent**, Application No.201711032188A “Process for preparation of Keto oxazoline.” Date of filing application 12/09/2017, **publication date: 27/10/2017**.
2. Imran Ali, **Dnyaneshwar Nighot**, Arvind Kumar Jain and Nadeem Lone New and Facile Copper Powder Catalyzed Sonoghashira Coupling Reaction of Aromatic Iodoarenes with Terminal Alkynes and their simulation studies, **Synthetic Communications**. (2017), **47, 12, 1175-1184**
3. Arvind Kumar Jain, **Dnyaneshwar Nighot**, Imran Ali, Sunil Jadhav, and Uttam Dhigude, Industrial Scale Process Development of CuI(PPh₃)₃ and its Application in Sonoghashira Coupling reaction, **International Journal of Applied Engineering Research**. (2015), 10, 94, 09-11.
4. Arvind Kumar Jain, **Dnyaneshwar Nighot**, R. Vadivelan, Sunil Jadhav Imran Ali, Di- μ -iodidobis[2,2'-bis(diphenylphosphanyl)-1,1'-bina phthyl,]copper(I) catalyzed Sonoghashira reaction **INROADS** (International Conference **IAET-2016**, **5, 1, 215-217**, DOI: 10.5958/2277-4912.2016.00041.2
5. Arvind Kumar Jain, **Dnyaneshwar Nighot**, Imran Ali, Abstract and poster presentation at IIT Roorkee “Palladium and Phospine free modified Sonoghashira protocol using Copper Carbonate” **International Conference on Advanced materials for energy, environment and health” (ICAM-2016)**.
6. **Dnyaneshwar Nighot**, Arvind Kumar Jain and Imran Ali, Solvent free and base free protocol for Sonoghashira reaction using Bromotris (Triphenylphosphine)Copper(I) **National Conference on Emerging Trends in Applied Sciences” (NCETAS 2016) Galgotias University**.
7. **Dnyaneshwar Nighot**, Arvind Kumar Jain, R. Vadivelan and Imran Ali, Preparation of (Z)-5-((2-mercaptophenylimino)methyl)-2-methoxy phenol Copper complex and its use for Palladium free Coupling of Aryl Iodide and Alkynes “**International Conference on Advancements in Science & Technology ICAST2017**.”
8. R. Vadivelan, **Dnyaneshwar Nighot**, Arvind Kumar Jain and Imran Ali, one pot synthesis for preparation of highly pure 1-(4-Bromobenzyl)-3-Methyl-6-(Piperidin-1-Y1)

Pyrimidine-2,4(1H,3H)-Dione“**International Conference on Advancements in Science & Technology ICAST2017.**”

9. Arvind Kumar Jain, **Dnyaneshwar Nighot**, Imran Ali, Preparation of Biaryle compounds from Iodoarens using Magnesium and Iron metal powder in Solvent free condition. **International Conference on “Changing Technological and Managerial Scenario: Aspect and Prospect” (Ganodaya-2015).**
10. **Dnyaneshwar Nighot**, Arvind Kumar Jain, Imran Ali, New rearrangement: Cyclization and rearrangement of internal substituted alkynes to Form Keto Oxazoline Dnyaneshwar Arvind Imran rearrangement, **Communicated to Journal of Organic chemistry.**
11. **Dnyaneshwar Nighot**, Arvind Kumar Jain and Imran Ali, Copper nanoparticle assisted Base and legend free Approach for synthesis of substituted internal Alkynes Esters and study the effect of alkyl group on rate of reaction. **Communicated.**
12. **Dnyaneshwar Nighot**, Arvind Kumar Jain, Imran Ali, Green protocol for sp-sp² coupling of Aryl Iodide and alkynes using Copper Carbonate: Facile synthesis of Aryl alkynes. **Communicated.**

ABBREVIATIONS

CDCl ₃	deuterated chloroform
d	doublet
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
hr.	hour
m	multiplet
M	molar concentration
MeOH	methanol
t-BuOH	tertiary butanol
min	minute
NMR	nuclear magnetic resonance
t	Triplet
m. moles	Mili moles.

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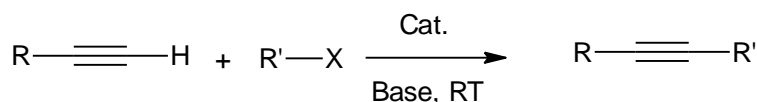
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1. INTRODUCTION

1.1 COPPER CATALYZED MODIFIED SONOGASHIRA REACTION.

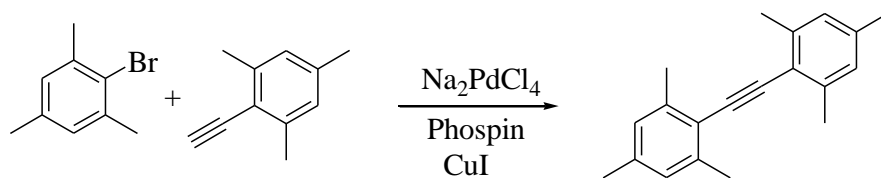
1.1.1 Alkynes general information

Pd-catalyzed coupling of various aryl or alkyl halides with terminal alkynes under mild experimental situation with co catalyst cuprous iodide in solvents such as amines was discovered by Sonogashira in 1975. This reaction applied in various organic syntheses for formation C-C bonds which are the intermediates of various natural products, medicinal compounds, [1-3].



Examples include such as Tazarotene, preparation of SIB-1508Y as a potential medicine for treatment of Parkinson's and Alzheimer's disease and various Cycological dises such as Tourette syndrome/schizophrenia, and (ADHD) disorder [4].

In earlier time Sonogashira coupling has been done using vinyl or aryl halides with terminal alkynes [5].



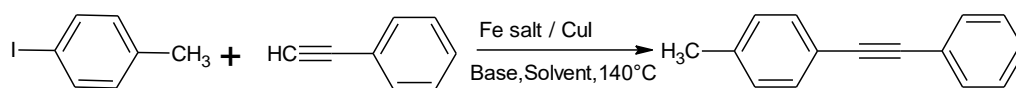
A large amount of research has been done to prepare thousands of different organic products using sonogashira reaction with as discussed conditions [5-6] various researchers modified the experimental reaction condition since its discovery [6] Generally problem with this reaction is that expensive palladium catalyst is to be used in presence of Copper(I) salt. Copper salt favors the dimerisation of aryl halide [7-8].

Many Researchers have developed copper free Sonogashira to avoid dimerisation of aromatic halides this reaction can be done using Ruthenium, Rhodium complexes also but they are also costly metals. Recently more efforts are given on copper catalyzed reaction due to their low cost and many functional group tolerance but the reaction conditions in these reaction are harsh due

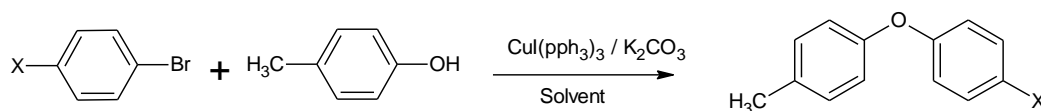
to low solubility, slow reactivity of the catalyst, long reaction time and high temperature leads to many times impurity formation. There is a necessity of development of a good protocol for this reaction. Our aim was to prepare a soluble catalyst and simplify the reaction conditions [9-11]

1.1.3 Methods for preparation of substituted internal Alkynes.

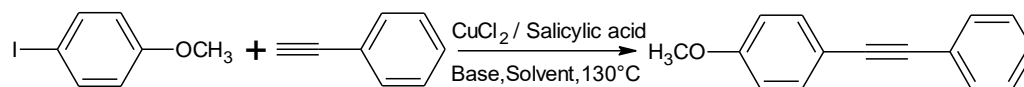
Florian Monnier, et al. [12] developed an inexpensive catalytic system using a copper salt and ligand combination for Sonogashira-type cross-coupling of aryl iodides and phenyl- and hexylacetylene and compared the reactivity of different ligands in the presence of different copper salts. They also studied the effect of different bases on the Sonogashira coupling.



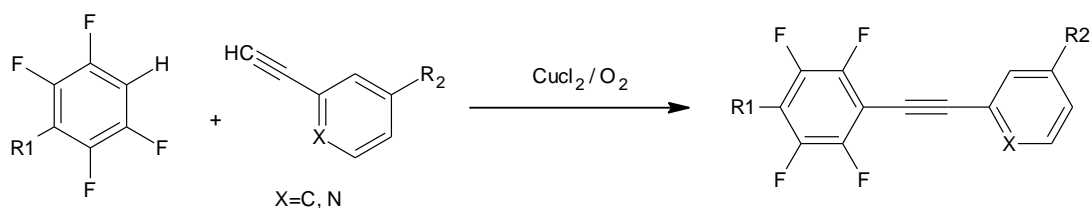
Chandra M. Rao Volla, Pierre Vogel [13] developed a palladium-free protocol in the presence of a Cu salt and iron salt with 94% yield. They used CuI, Fe(OAc)₂, Fe(acac)₃, salt and reaction working well with the combination of CuI and Fe(acac)₃ in DMF solvent with different aryl iodides. The yield obtained was 83-98% and with different alkynes the yield obtained was 91-96%.



Zhenning Yu [14] prepared the catalyst CuI(pPh)₃ by a reported method and used it for the Ullmann reaction with 60% yield.

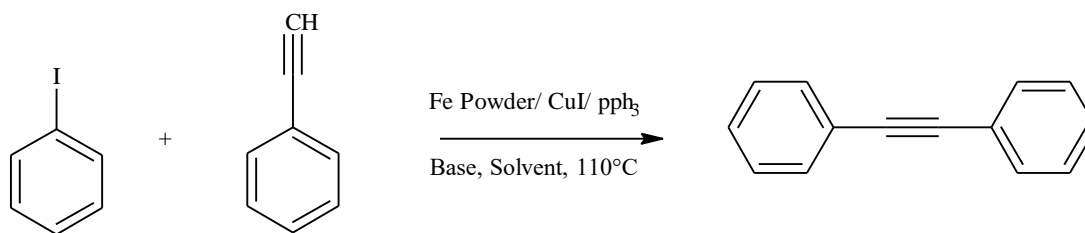


Horung-Jyh [15] used CuCl₂ as a catalyst and salicylic acid as a ligand. They found that the reaction works well in polar solvents such as DMF and DMSO with a yield of ~90%. Iodobenzene containing an electron-withdrawing group gives a good yield than iodobenzene containing an electron-donating group. But the reaction time is more than 24 hours at 130°C.

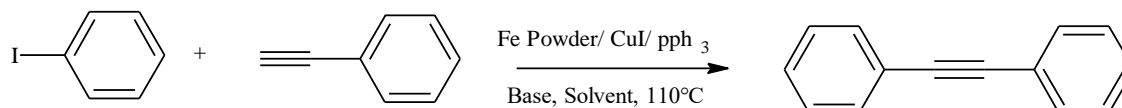


Ye Wei and Co-Worker [16] introduced Oxygen as an oxidant in alkyne coupling of electron-deficient compound polyfluoroarenes and terminal alkynes. They used butyl lithium as a base, Copper Iodide as catalyst and 1,10-phenanthroline (30 mol %), DDQ (15 mol %) and DMSO as a solvent. 5 equiv. of polyfluoroarene used in reaction.

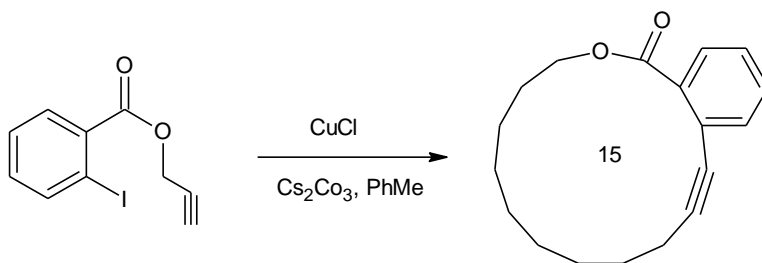
Chu Liu and his Co worker [17] developed a copper catalyst free and phosphine ligand free aerobic aqueous protocol for Sonogashira reaction. They studied different ratio of water with polar solvent and they found 93% yield in 3:1 EtOH water solvent ratio. Iodobenzene containing electron withdrawing group gives good yield than iodobenzene containing electron donating group.



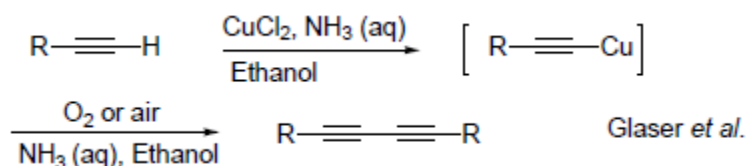
Nagoc Thang Trang and Co worker [18] replaced more costly palladium metal with low costly, environment friendly, most abundant Iron metal and developed same protocol. They studied different substituted Alkynes with Aryl iodide



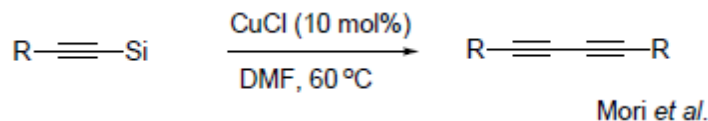
Santandra, Bedard, Collins SK. [19] developed a method for coupling of terminal alkynes with Aryl iodo compound within the molecule to form macro molecule by using Copper Chloride and Ligand in presence of cesium carbonate base in non polar solvent Toluene at 135°C. They also studied the effect of different ligand for this reaction.



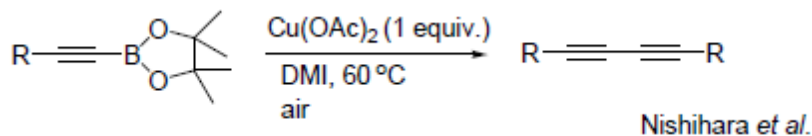
Niranjan Panda and coworker [20-22] reviewed iron and mediated coupling reactions in which they mention formation of diacetylene using stoichiometric amount of copper salt in presence of air or oxygen. (Scheme 1a) [23]. Silicon substituted alkynes used for Glaser homocoupling using CuCl in DMF (Scheme 1b) [24]. Later, Nishihara [25-26] did similar homocoupling reactions using alkynylboronates in the presence of copper acetate (Scheme 1c). Yadav et al. developed ligand- copper-catalyzed dimerization of alkynes in ionic liquid (Scheme 1d). [27]



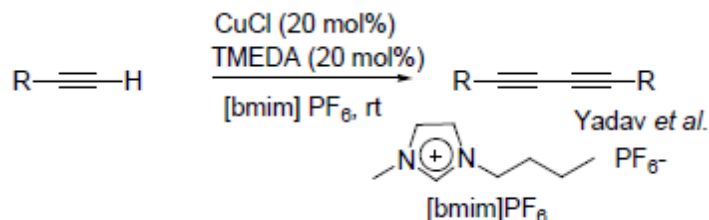
Scheme-1a Cu mediated C(Sp)-C(Sp) coupling presence of oxygen.



Scheme-1b Cu mediated C(Sp)-C(Sp) coupling using silicon substituted alkynes.

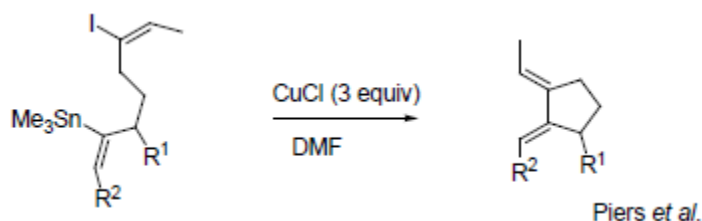


Scheme-1c Cu mediated C(Sp)-C(Sp) coupling alkyl borate.

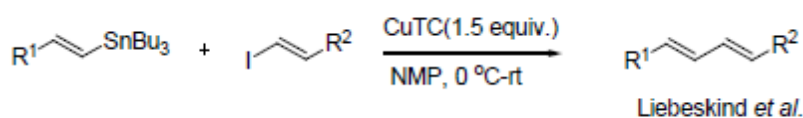


Scheme-1c Cu mediated C(Sp)-C(Sp) coupling in ionic liquid.

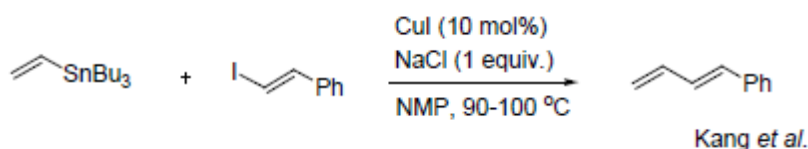
Copper-mediated (sp²)C-C(sp²) bond formation was reported by Piers et al using tin reagent. (Scheme-2a). [28-29] Intermolecular organostannanes and aryl / heteroaryl and vinyl iodides coupling to produce 1,3-dienes in the presence of copper(I)-thiophene carboxylate . (Scheme 2b) [30]. Coupling between organostannanes and aryl iodides using CuI in NMP solvent (Scheme 3a) [31] deactivated aryl bromides also effectively converted to 1, 3-dienes (Scheme 3b). [32]



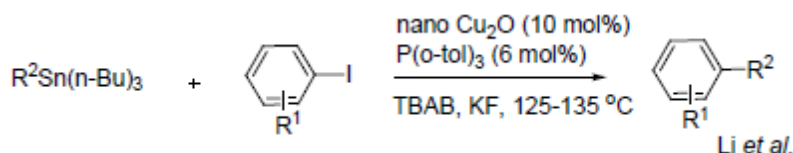
Scheme 2a: Cu-mediated Stille coupling



Scheme 2b: preparation 1,3 diene using Cu-mediated Stille coupling



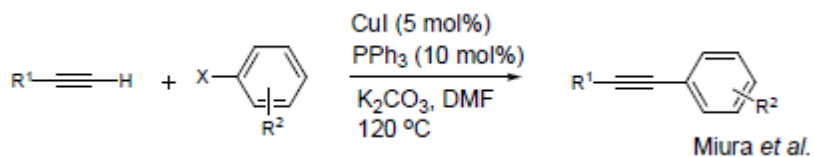
Scheme 3a: Cu-catalyzed Stille coupling.



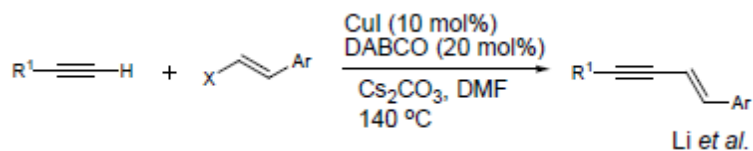
Scheme 3b: Cu-catalyzed Stille coupling of deactivated halides.

The coupling of alkynes with aryles /vinyl halids using copper and ligand reported by Miura et al. (Scheme 4a)[32] Li et al. prepared aryl-alkynes using DABCO and copper salt, here DABCO act as a chelating ligand (Scheme 4b) [33]

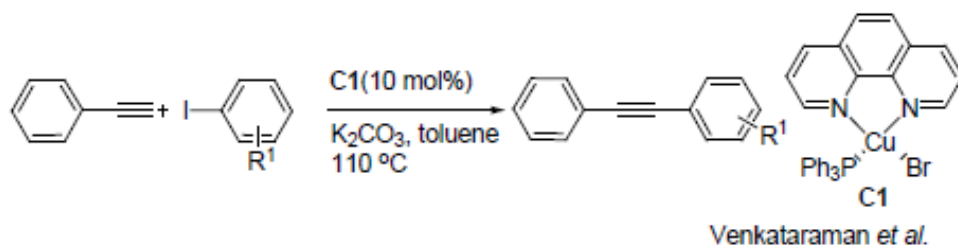
Venkataraman et al. [34] worked on solubility copper salt and prepared soluble complex of copper salt and did C-C coupling reaction in toluene (Scheme 5).



Scheme 4a: Cu-catalyzed Sonagashira coupling.

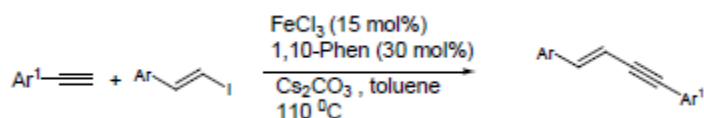


Scheme 4b: Cu-catalyzed Sonagashira coupling using DABCO.

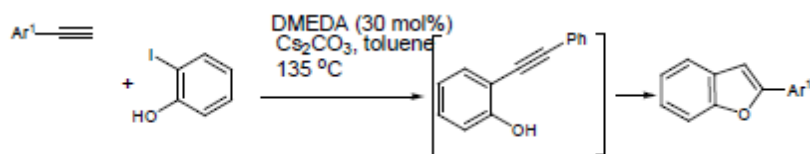


Scheme 5: Cu-catalyzed Sonagashira coupling.

Same way C-C coupling done using FeCl₃ and 1,10-phenanthroline (Scheme 6a), FeCl₃ and DMEDA, FeCl₃ and 2,2'-bipyridine as a ligands (Scheme 6b) [35]

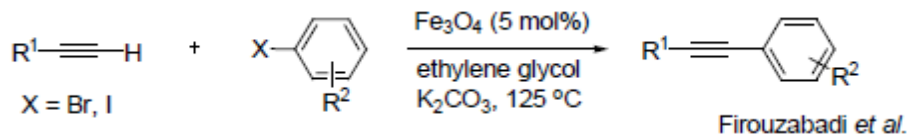


Scheme 6a: Fe-catalyzed Sonagashira coupling using 1,10-phenanthroline .

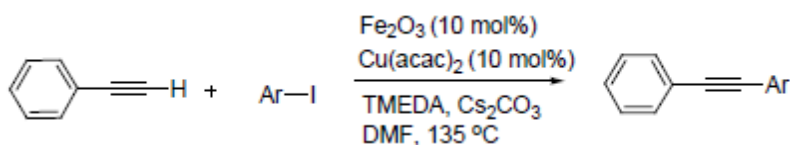


Scheme 6b: Fe-catalyzed Sonagashira coupling using DMEDA.

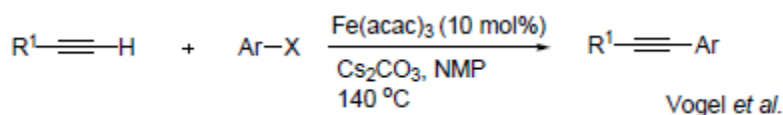
An iron catalyzed Sonogashira and cyclization to produce the 2-arylbenzofuran was also developed (Scheme 6b) [36-37]. Firouzabadi et al. used recyclable Fe₃O₄ nanoparticles for coupling of terminal alkynes and halides (Scheme 7) [38]



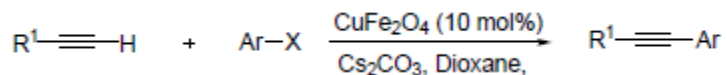
Scheme 7: Heterogeneous Fe-catalyst for Sonogashira coupling.



Scheme 8a: Cu/Fe-co-catalyzed Sonogashira coupling using copper acetylacetonate.



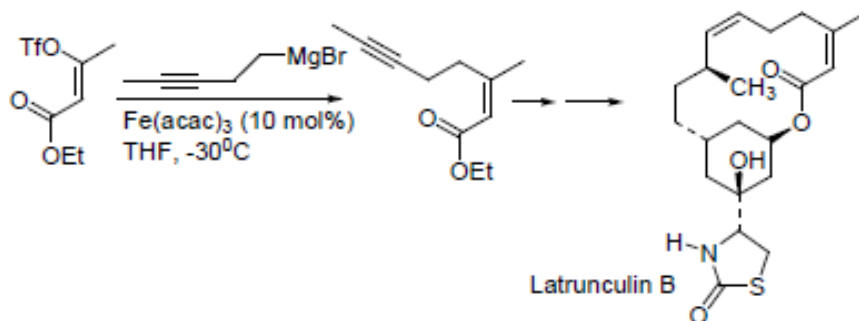
Scheme 8b: Cu/Fe-co-catalyzed Sonogashira coupling using ferrous acetylacetonate.



Scheme 8b: Cu/Fe-co-catalyzed Sonogashira coupling.

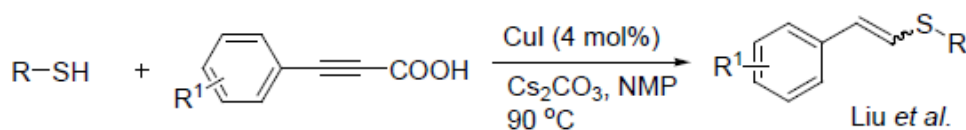
C-C coupling using TMEDA (Scheme 8a), CuI/Fe(acac)₃ catalyzed C-C coupling (Scheme 8b) [39] Niranjana Panda and co-worker used copper ferrite nanoparticle for C-C coupling (Scheme 8c) [40]

Furstner et al. [41] also developed iron catalyst for coupling of alkenyl electrophiles with organomagnesium reagents. Using this method they prepared latrunculin B (Scheme 9).



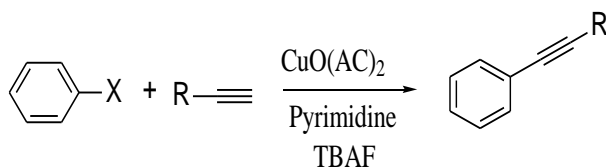
Scheme 9: Fe-catalyzed C(sp²)-C(sp³) coupling.

Liu [42] prepared Vinyl sulfides by decarboxylative C-S coupling of arylpropionic acids and thiols (Scheme 10)

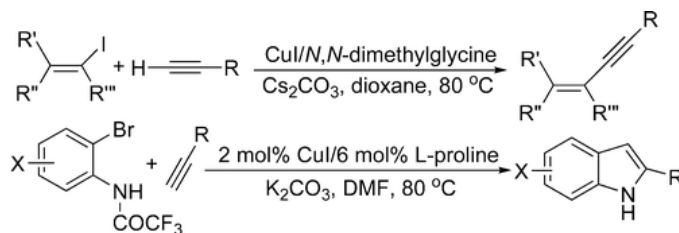


Scheme 10: Decarboxylative C-S cross-coupling

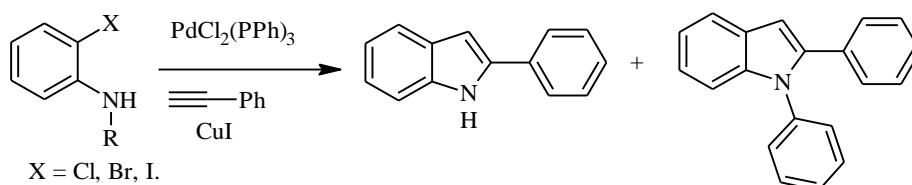
Ye-Xiang Xie prepared internal alkynes using Cu(OAc)₂, TBAF (tetrabutylammoniumfluoride), 4,6-dimethoxypyrimidin-2-amine ligand [43].



C-C coupling using CuI/N, N-dimethylglycine for preparation of conjugated enynes. Also prepared indole from 2-bromotrifluoroacetanilide, 1-alkyne, 2 mol % of CuI, and L-proline in presence of base K₂CO₃ [44].



Hossien A prepared 2-Substituted Indole using terminal alkynes and 2- haloaniline in presence of Pd(PPh₃)₂Cl₂ catalyst and CuI as co-catalyst [45].

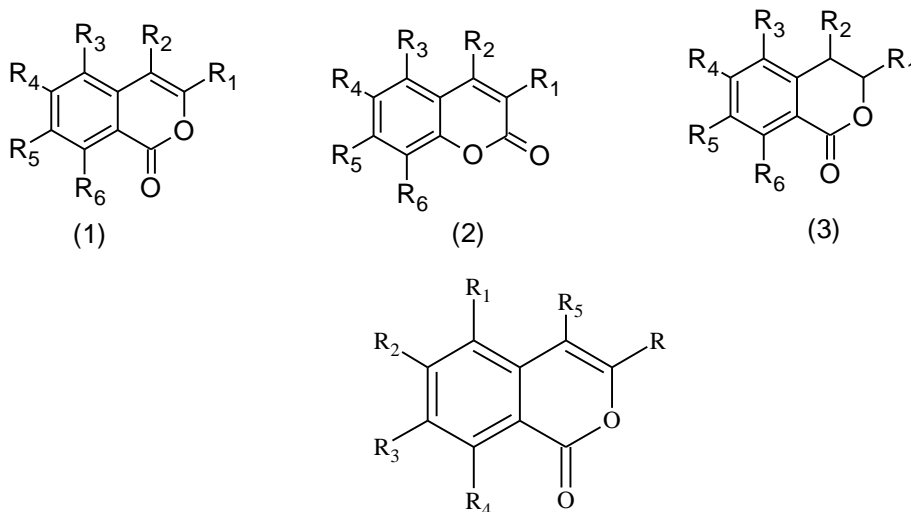


From literature survey it is concluded that Copper salt can be used effectively for Sonogashira reaction, by increasing their solubility and making their soluble complexes. Which get readily dissolve in organic solvent and increase the rate of reaction. Also the method is limited for iodo compounds. Our aim is to accelerate the activity of copper by making different copper complexes and changing the reaction condition so as to obtain good yield.

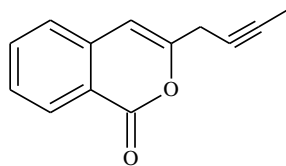
1.2. ISOCUMARINS AND 2-VINYL PHENOLS.

1.2.1. Isocoumarins

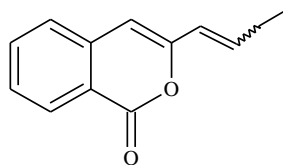
The isocoumarin (1) are the isomer of Coumarin (2) which was isolated from tonka tree. Isocoumarin is a lactonic pyran ring which is fused with benzene ring. Its 3,4-dihydro-analogue (3)



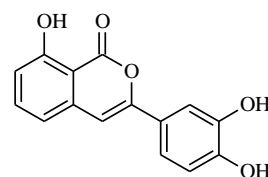
1.2.1.1 General examples of isocoumarins.



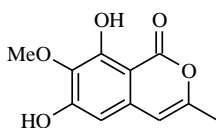
Capillarin



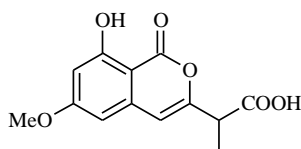
(E) & (Z) Artemidin



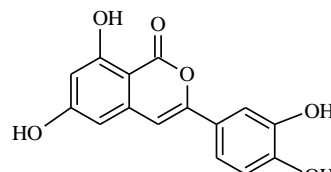
Tunberginol A



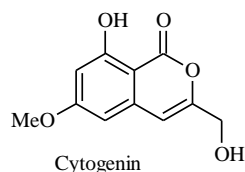
Reaticulol



NM 3

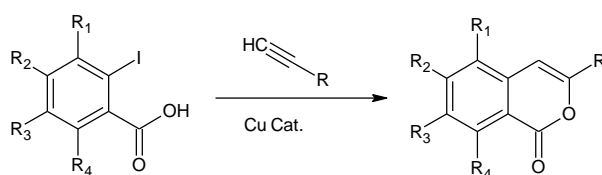


Tunberginol B



Cytogenin

Rubrumycine



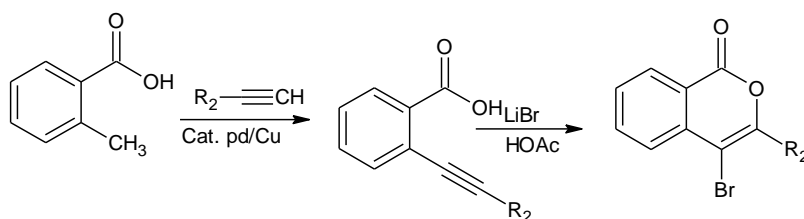
Coumarins are reported as fused benzene and pyrone ring which having biological and therapeutic applications. [46-47].

Cancer has been a fatal disease worldwide in 2008, 13 % of total death occurred due to cancer all deaths worldwide occurred in 2008. [48]. There are so many mechanisms by which anticancer drugs may stop division of cancer cells. [50]. Generally anticancer drugs kill cancer cells by applying apoptosis in cancer cells [51-52]. Coumarin derivatives inhibit the telomerase enzyme, protein kinase activity and down regulating oncogene expression or induce the caspase-9-mediated apoptosis, suppress cancer cell proliferation by arresting cell cycle in G0/G1 phase, G2/M phase and affecting the p-gp of the cancer cell [48-49]. Coumarin derivatives can possess not only cytostatic, but they are having cytotoxic properties also [53]. Coumarin and hydroxycoumarin can stop growth of cancer cell [54], A549 (lung), ACHN (renal), H727 (lung), MCF7 (breast) and HL-60 (leukaemia) and prostate cancer [55], malignant melanoma [56], renal cell carcinoma [57]. Coumarin, itself has cytotoxic effect for Hep2 cells.

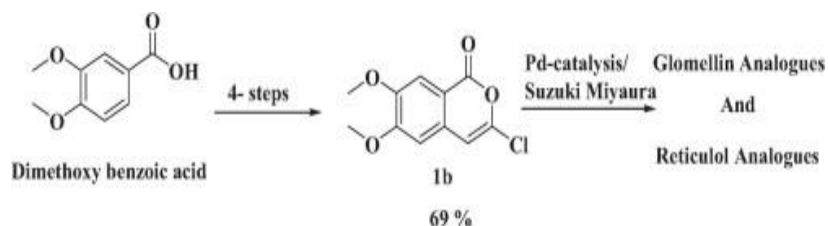
3-substituted isocoumarins, are active scaffolds, [58-60] and intermediates of natural products canesin, a, b-sorigenin methyl ethers, isochromenes, isoquinoline alkaloids.[61-63] 3-substituted isocoumarins traditionally prepared from 2-halobenzoic acid with terminal alkynes [64]. One-pot synthesis done using Pd-catalyzed Sonogashira reaction between terminal alkynes and 2-halobenzoic acids [65]. Over the years Isocoumarins preparation involve noble like Pd, Ru, Rh, and Ir, the reaction conditions are harsh, limited substrate scope, and low yields. Now days, copper salts have great importance as inexpensive, availability and alternatives to noble metals, more specifically palladium. Due to this fact chemist are developing copper catalyzed approach for isocoumarins.[66-68] In 2009, Abarbri, Parrain and coworkers, developed a synthesis of isocoumarin from 2-iodobenzoic acids and terminal alkynes using copper catalyst but this protocol gave a mixture of isocoumarins and phthalides [69] Pal and coworkers used ultrasound for preparation of isocoumarins (60–85%) yield [70]. Lee and coworkers prepared isocoumarin from 2-iodobenzoic acids and terminal alkynes using copper catalyst yield 38-85% [71] Ma and coworkers used 2-bromobenzoic acids, terminal alkyne and CuI/amino acid-catalyst for preparation of isocoumarin [72] Mengli Sun also prepared isocoumarin using 2-bromobenzoic esters and terminal alkynes under mild conditions.

1.2.1.3 Methods for the preparation of Isocoumarin.

Synthesis of Isocoumarine and α -Pyrone via Electrophonic Cyclization

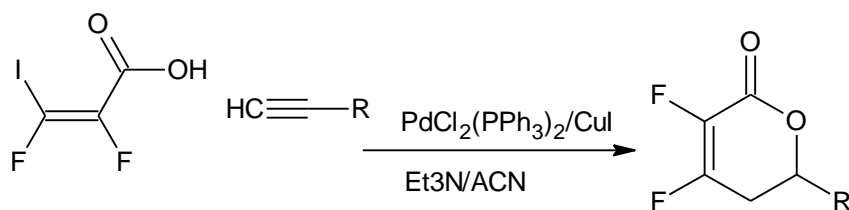


Santandra, Bedard, Collins SK.[73] Prepared isocoumarine derivatives by coupling of aryl iodo compound with terminal alkynes in presence of palladium catalyst and copper Co-Catalyst and Cyclization done in acetic acid in presence of inorganic halides

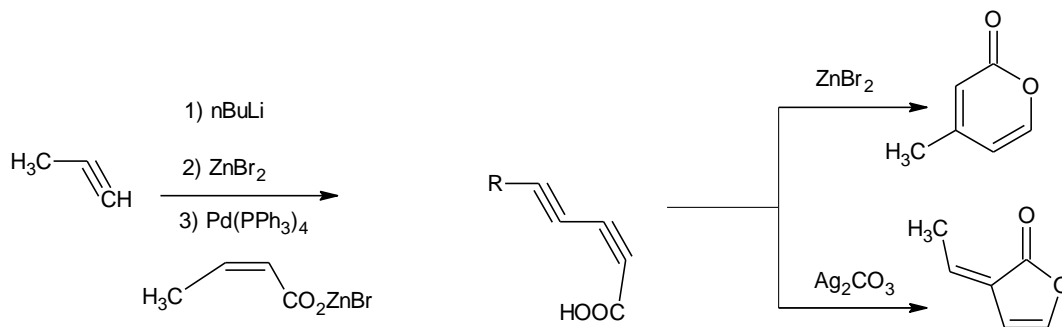


Preparation of isocumarin from 2-Bromo benzoic acid or homophthalic acid using Phosphorous Oxychloride and different substituted boric acid via Suzuki coupling in presence of palladium catalyst with good yield and prepared glomellin and reticulol analogue from this method [74].

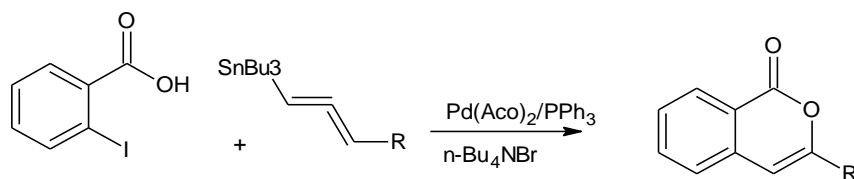
Burton and co-workers [75] used (2*E*)-2, 3-difluoro-3-iodoacrylic acid for preparation of difluorinated 2-pyrones, using terminal acetylenes in presence of using PdCl₂(PPh₃)₂ catalyst and CuI co-catalyst.



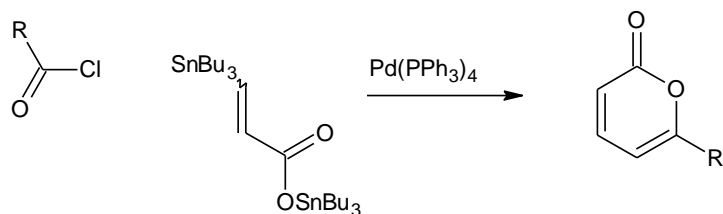
Negishi and co-workers [76] developed method for preparation of pyrons using alkynylzinc-haloacrylic acid and ZnBr₂ [22]. Using Ag₂CO₃ as catalyst they prepared (Z)-5-alkylidenefuran-2(5H)-ones.



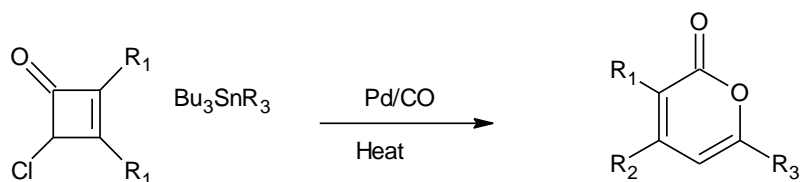
Abarbri and co-workers [77] developed method for preparation of isocumarin using (Z)-β-iodovinyl acids / 2-iodobenzoic acids and various allenyl-tributyltin in presence of palladium acetate, triphenylphosphine, and TBAB.



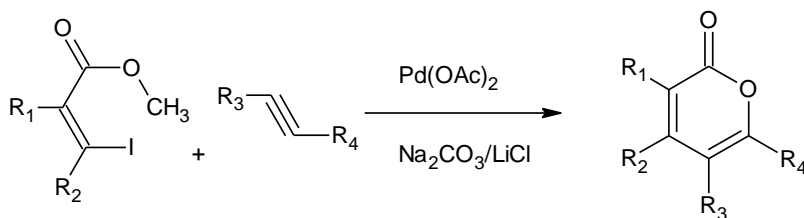
Parrain and co-workers [78] developed synthesis for 2-Pyrone from vinylstannane and acyl chloride via a Stille reaction/cyclization.



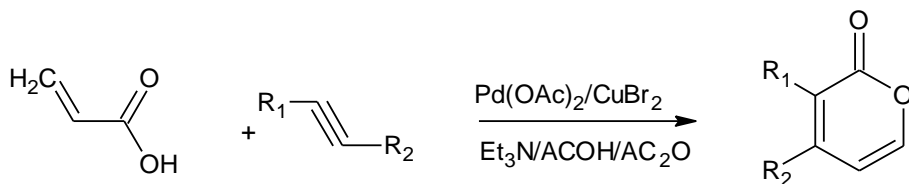
Liebeskind and co-workers [79] developed method for preparation of 2,3,6-trisubstituted-2-pyrones using 4-chloro-2,3-disubstituted-2-cyclo butenones and alkenyl-, aryl-, heteroaryltn followed by thermolysis.



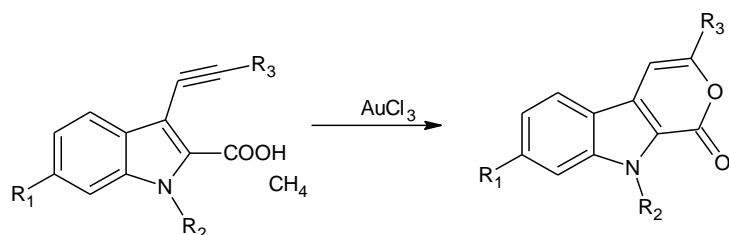
Larock and co-workers [80] developed synthesis of isocoumarins and 2-pyrones having aryl, silyl, ester, tert-alkyl, groups. Using α , β -unsaturated Iodo esters, internal alkynes and palladium catalyst.



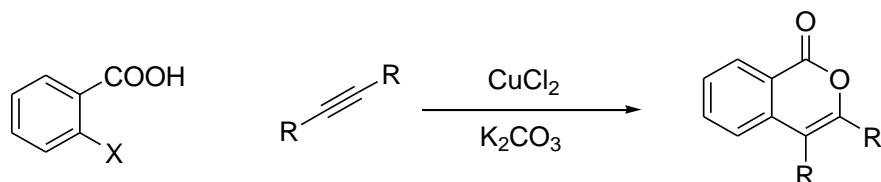
Jiang and co-workers [81] reported synthesis of 2-pyrones and pyridones using Pd-catalyst and acrylic derivatives and internal alkynes as starting materials.



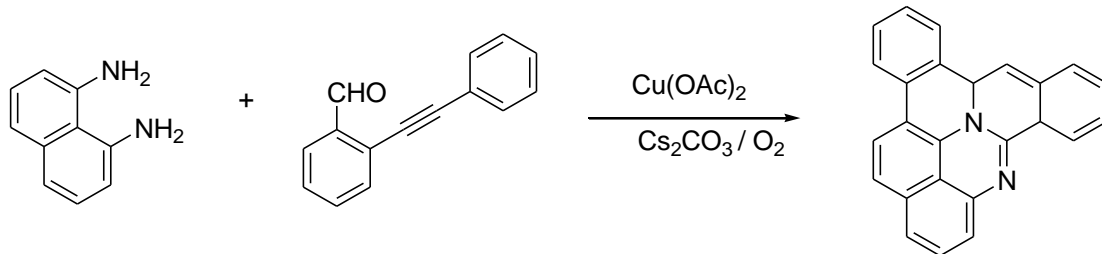
Synthesis of pyrano[3,4-b]indol-1(9H)-ones using gold(III) chloride as a catalyst. Cyclization of 3-ethynyl-indole-2-carboxylic acid to pyrano[3,4-b]indol-1(9H)-ones using gold (III) chloridedonveloped by Perumal and co-workers [82].



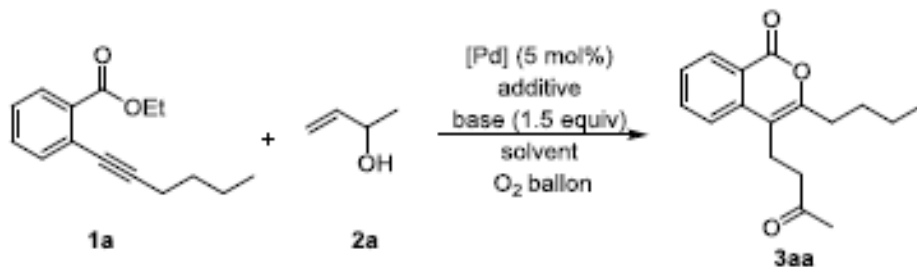
One step preparation of Isocumarin from o-halobenzoic acids and internal alkynes in presence of CuCl_2 catalyst developed with good yield [83].



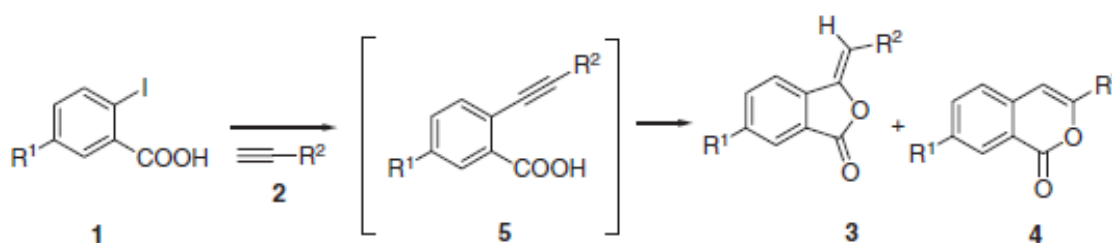
Bin-Bin Feng developed protocol using naphthalene-1,8-diamine, 2-(phenylethynyl)benzaldehyde in presence of Oxygen, Copper acetate as a catalyst and cesium carbonate base for heptacyclic quinolizino[3,4,5,6-kl]perimidines. Three new ring and four new bonds formed in this reaction [84].



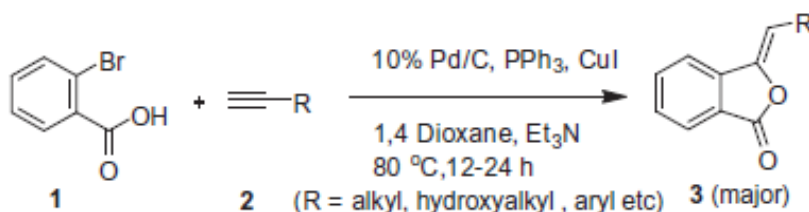
Regioselective nucleophilic oxidative coupling of internal alkynes and alkenyl alcohols in presence of oxygen was investigated. Alkenyl alcohol group is converted to ketonic group and added to carbon-carbon triple bond and molecule cyclized to form substituted isocumarin in presence of palladium catalyst [85].



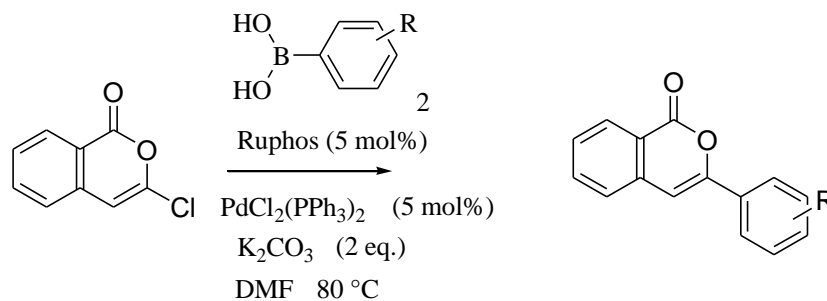
Lie Zou and Huan [86] developed the method for preparation of phthalides as major product. Generally during cyclization of intermediate-5 phthalide-3 and isocoumarin-4 observed as mixture of product but they developed a protocol by using palladium in presence of carbon nanotubes as catalyst and sodium acetate, DABCO (2:0.4) as a base in Solvent DMF water (20:1) at 100°C



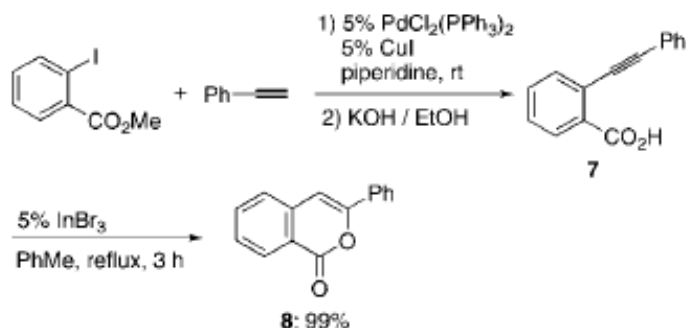
Rabbabu [87] and et al. developed the method for preparation of phthalides as major product with 10- % of corresponding isocoumarin derivative with less expensive starting materials.



Yadavalli and co-workers developed protocol for 3-substituted isochromen-1-ones using Suzuki coupling strategy. 3-chloroisochromen-1-one, reacted with boronic acids in presence of PdCl₂(PPh₃)₂ as catalyst and Ruphos as a ligand and prepared glomellin, reticulol analogues using this method [88].



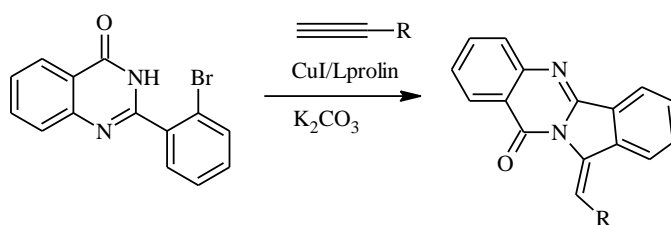
Norio Sakai et al. [89] prepared isocoumarin derivative from esters of iodobenzoic acid and terminal alkynes using palladium catalyst. In first alkynyl ester formed hydrolyzed with base to gives alkynyl acid, which on treatment with indium catalyst get cyclized to isocoumarin using.



Venkataraman et al. developed method for preparation of isocoumarins using *o*-iodobenzoic acid, terminal alkynes and 10% Pd/C–Et₃N–CuI–PPh₃ catalyst system with good yields and regioselectivity in Ethanol [**Error! Reference source not found.**].



Jian-Quan Liu developed a Sonogashira reaction protocol using 2-(2-bromophenyl) quinazolin-4(3H)-ones, terminal alkynes, CuI/L-proline as catalyst system and Cs₂CO₃ as a base to produce isoindolo[1,2-*b*]quinazolin-10(12H)-one derivatives in good yields [90].



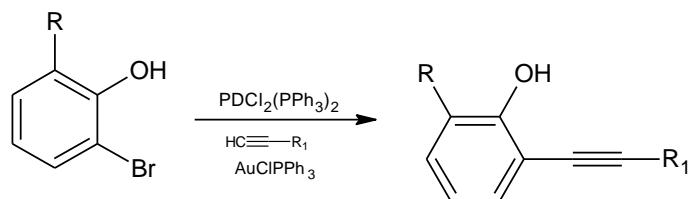
1.2. 2. 2-Vinyl Phenols.

1.2.2.1 General Information.

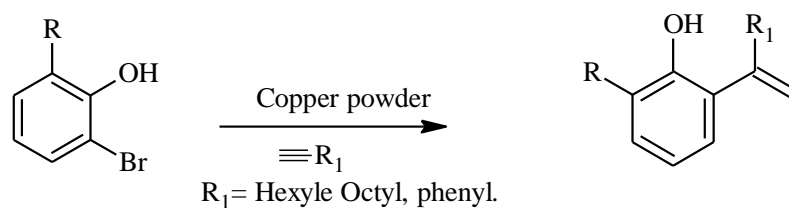
Alkyne phenols are the phenolic compounds containing reactive double bond at Ortho position to phenolic groups hence they are versatile intermediates for preparation of coumarins, 3,4-dihydro-2H-2,4-methanochromans, lactones, cyclic ketons, Chiral *cis*-disubstituted tetra hydro quinolines

While doing work with Sonogashira reaction using 2 bromo phenols as starting material we observed different product formation as compare to normal product using Sonogashira reaction. After optimizing reaction condition, we developed cheap, simple and best protocol as of now reported in the literature.

Generally in Sonogashira the terminal alkyne proton get substituted by alkyl or aryl group. But here we got addition product. Generally in the nucleophilic addition addition takes place according to Markovnikov's rule and nucleophile will attach to less substituted carbon atom but here in reported protocol substitution takes place according to anti Markovnikov's rule. According to current literature we are reporting first time this type of reaction.

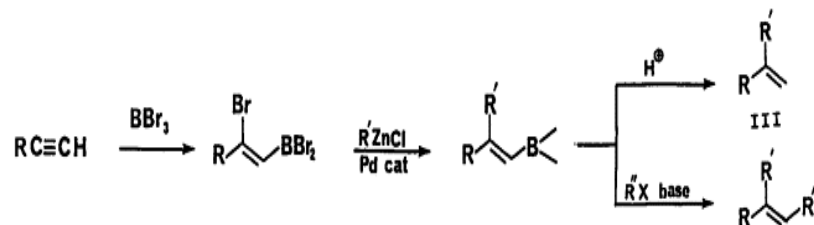


Normal product formation using reported Sonogashira reaction

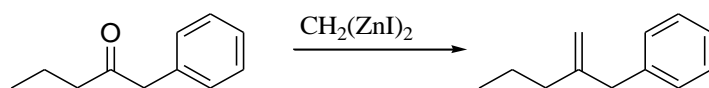


Anti Markovnikov's addition according to our protocol.

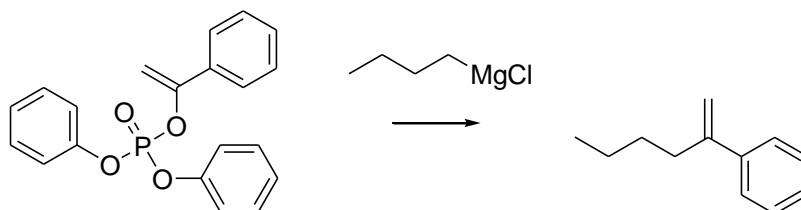
1.2.2.2 Methods of preparation of 2 Vinylphenol.



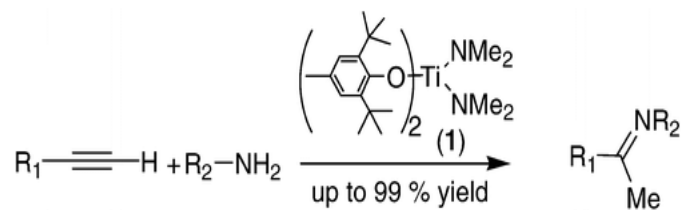
Di- or tri-substituted alkyne prepared in two steps in first step terminal alkyne converted to (Z)-2-bromo-1-alkenylboranes using bromoboration reaction. In second step bromoborane reacted with organozinc chloride to produce substituted alkyne [92].



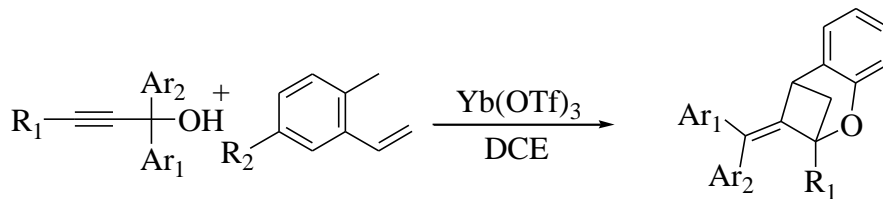
Ketones get converted to alkenes using bis(iodozincio)methane in ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate in the absence of metal salts [93].



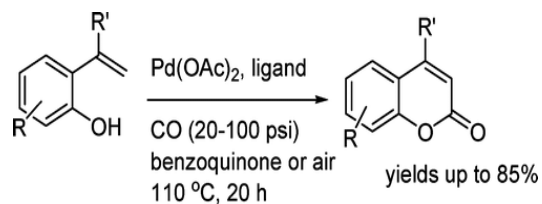
Stereoselectively trisubstituted olefins prepared using enol phosphates using Grignard reagent and $\text{Fe}(\text{acac})_3$ catalyst [94].



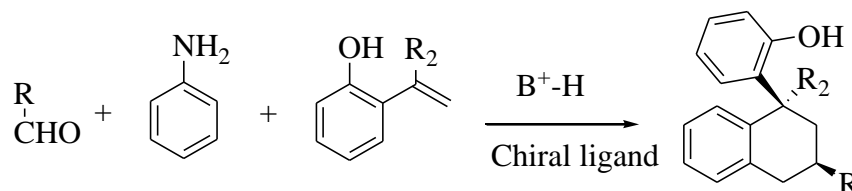
Branched imines prepared using aryloxotitanium, terminal alkyne and aryl amine are obtained in good yield (up to 99%) using primary aromatic and aliphatic amines [95].



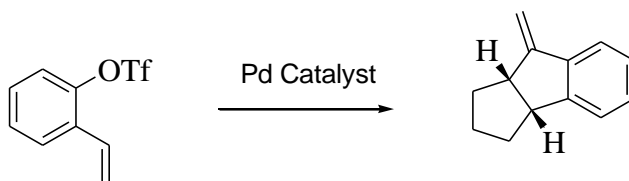
An 2-Vinylphenol used for synthesis of 3,4-dihydro-2H-2,4-methanochromans with propargylic alkynols [**Error! Reference source not found.**]



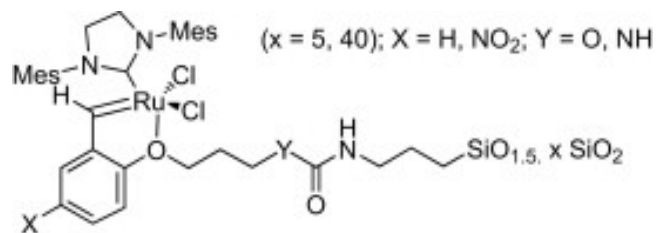
Synthesis of Coumarins using 2-Vinylphenols by using palladium catalyst, 2-vinylphenols and carbon monoxide coumarins prepared up to 85% yield. In this reaction CO, and air or 1,4-benzoquinone used as oxidant [96].



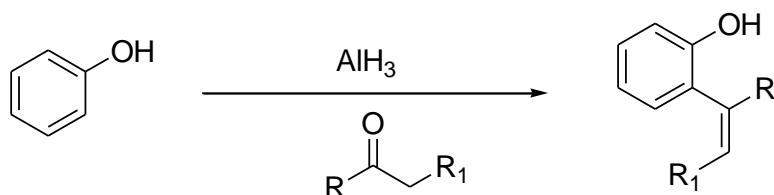
Cis-disubstituted tetrahydroquinolines with high stereoselectivities prepared using 2-Vinylphenols and aromatic amine. Chiral phosphoric acid derivative used as ligand for this chiral synthesis *cis*-disubstituted tetrahydroquinolines which are valuable starting materials tetrahydroquinolines [98].



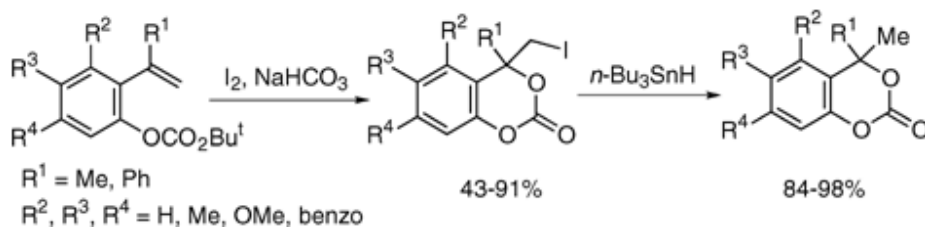
Palladium-Catalyzed Asymmetric Intermolecular Cyclization, developed by Jian Hu, et al. used 2-Vinyl phenol for asymmetric synthesis of (-) martinellie acid [99].



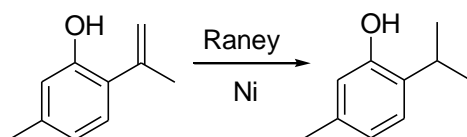
Xavier Elias et. al. prepared hybrid materials using 2-Vinyl phenol. These ruthenium complexes used as catalysts for diene and enyne metathesis [100].



Giovanni Casiraghi et. al. [101] prepared vinyl phenols from aluminum phenoxides and keto compounds in xylene solvent the prepared compound is in isomerically pure form.



Kobayashi Kazuhiro et al [102] prepared 4H-1,3-benzodioxin-2-one from t-butyl 2-vinylphenyl carbonates, iodine using sodium hydrogen carbonate base . In frist step 4-iodomethyl-4H-1,3-benzodioxin-2-one produced on reduction with tributyltin hydride give 4-methyl-4H-1,3-benzodioxin-2-one.

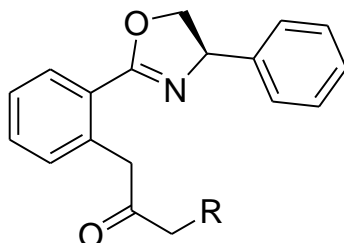


K. J. Divakar et al [103] prepared Thymol 2, a phenolic terpene which is used as an antiseptic, which has been prepared by alkylation of m-cresol via vinyl phenol.

According to literature survey there are two facts during the preparation of 2-vinylphenol either the starting materials are expensive or expensive reagents are used. To solve this problem there is need of simple and economic method for preparation of the 2-vinylphenol.

1.3. KETO OXAZOLINES AND CHIRAL INDUCTION

1.3. 1 Keto Oxazoline



1.3.1.1. Use of Oxazolin for asymmetric catalysis:

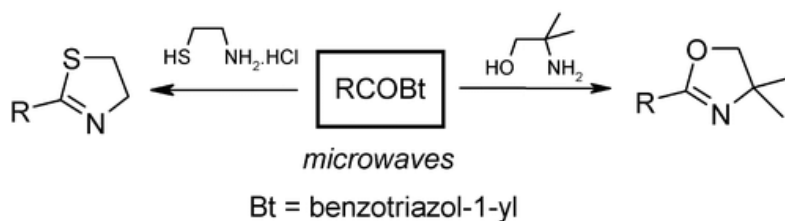
Brunner et al. used oxazoline ligand for enantioselective cyclopropanation. [104] and Schiff bases were commonly used as ligands at that time [105] Brunner's and Noyori worked on this ligand as awarded a nobel prize for asymmetric synthesis. Tadatoshi Aratani, who had worked with Noyori [106] before publishing a number of papers on enantioselective cyclopropanation using Schiff bases [107-109].

During development only 4.9% of enantiomeric excess observed compared to 65.6% using Schiff base ligands. After reinvestigation and development of chiral pyridine oxazoline ligands, 30.2% enantiomeric excess observed in 1986 [110] and 45% in 1989 [111] at the same time Pfaltz et al. reported C2-symmetric semicorrin ligands for cyclopropanations, up to enantiomeric excess 92-97% [112]. Reference was made to both Brunner's and Aratani's work, however the design of the ligands was also largely based on his earlier work with various macrocycles [113]the main drawback of this synthesis was multistep synthesis of ligand and low yield.

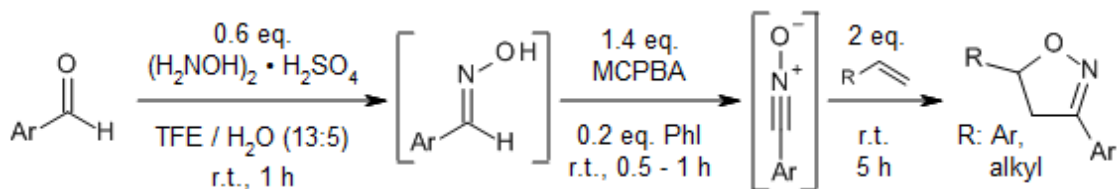
It leads to development of bisoxazolines ligand by Nishiyama et al. synthesised PyBox ligands in 1989. Which gives ee's of up to 93% [114] the first BOX ligands where reported a year later by Masamune et al.[115] and were first used in copper catalysed carbenoid cyclopropanation reactions; achieving ee's of up to 99% with 1% molar loadings. This was a remarkable result for the time (literature reviews in 1949 [116]. and 1971[117]. research proceeded quickly, with

papers from new groups being published within a year [118] and review articles being published by 1996 [119]. Today a considerable number of bis(oxazoline) ligands exist; structurally these are still largely based around the classic BOX and PyBOX motifs, however they also include a number of alternative structures, such as axially chiral compounds [120].

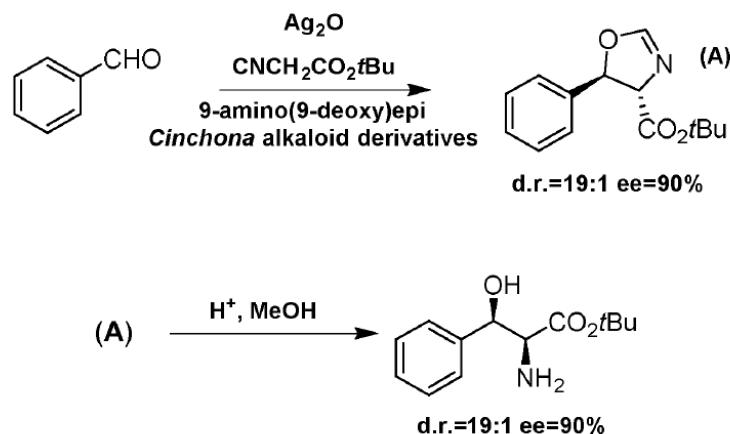
1.3.1.2 Methods of preparation of literature Keto Oxazoline.



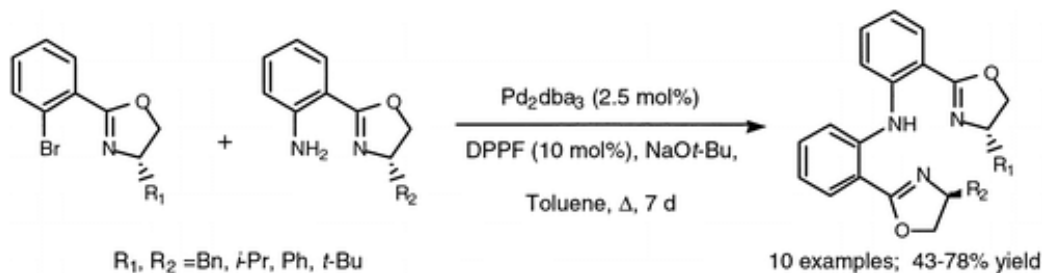
2-amino-2-methyl-1-propanol reacted with N-acylbenzotriazoles and SOCl_2 in presence of microwave 2-substituted 2-oxazolines are produced with 98% yields. 2-substituted thiazolines also prepared by this method by using 2-aminoethanethiol hydrochloride as a starting material with 85–97% yields, [121].



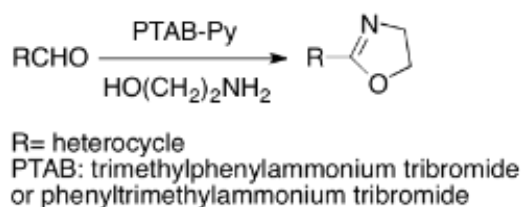
One pot synthesis of isoxazolines using aldehydes, in first step hydroxylamine sulfate produced get converted into aldoximes, aldoximes oxidized to nitrile oxides in next step and finally isoxazolines produced by cycloaddition reaction with good yields [122].



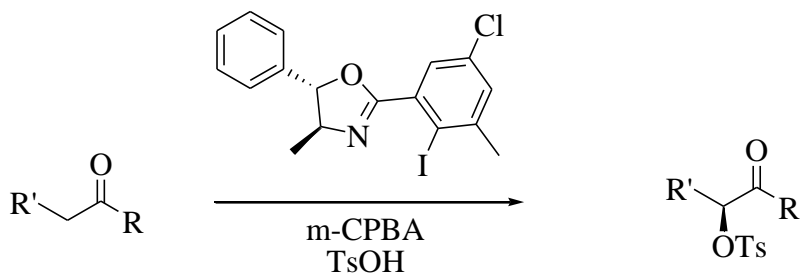
The invention is related to the prepn. of diastereomerically and enantiomerically enriched oxazolines C6-10 aryl or a linear or branched C1-6 alkyl substituted with a C6-10 aryl] using a catalytic system comprising 1-2 9-amino(9-deoxy)epi Cinchona alkaloid derivatives vinyl, ethyl, and a salt or oxide of silver or gold, e.g., Ag_2O , in the aldol reaction of a protected benzaldehyde, with an isocyanoacetate $\text{CNCH}_2\text{COO}_2\text{R}_3$ and cyclization of the resulting aldol an industrially viable and advantageous process for the prepn. of (2S,3R)-2-amino-3-(3,4-dihydroxyphenyl)-3-hydroxypropanoic acid known as droxidopa [123].



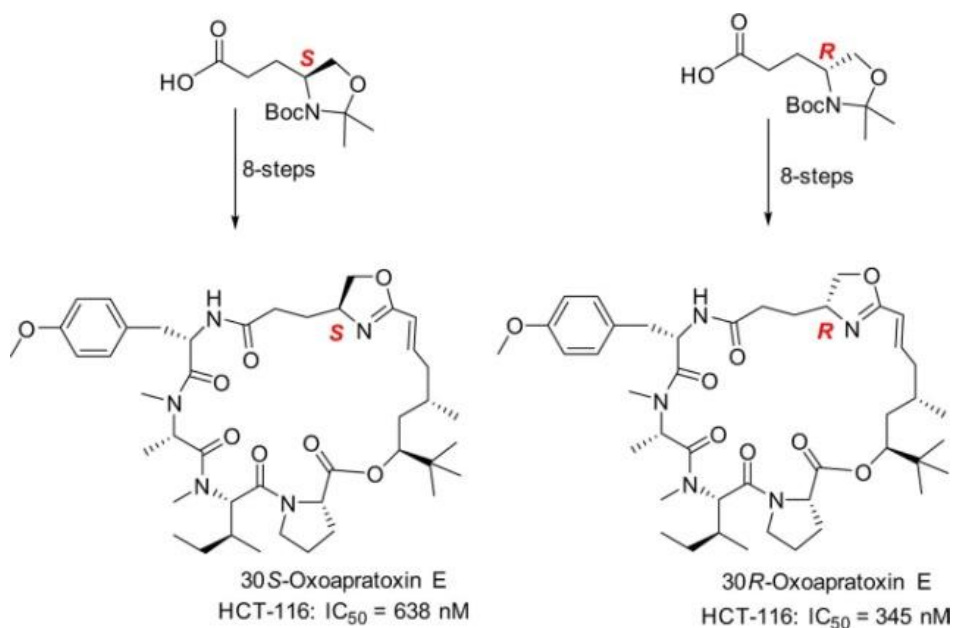
A new bis(oxazoline) ligands prepared using N-Br coupling using Palladium catalyst and DPPF as a legend in presence of sodium tertiary butoxide base , this is a application of Oxazoline [124].



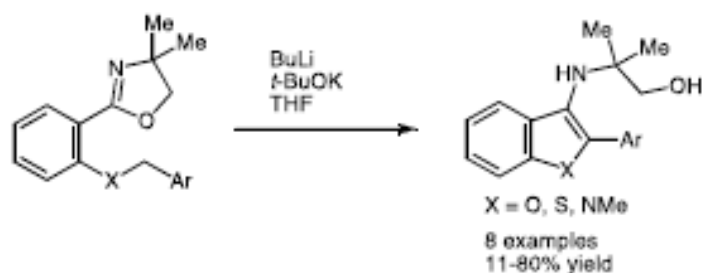
1,3-oxazolines prepared using aldehydes and aminoalcohols in presence of trimethylphenylammonium tribromide at room temperature[125].



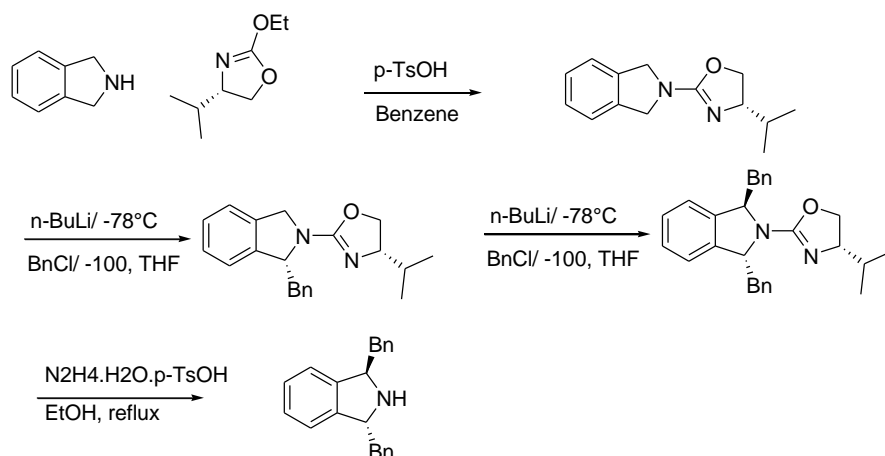
Iodooxazoline catalysts prepared for iodine (III)-mediated α -tosyloxylation of ketone. Using iodooxazoline catalyst α -tosyloxy ketones produced are important chiral synthons. [126].



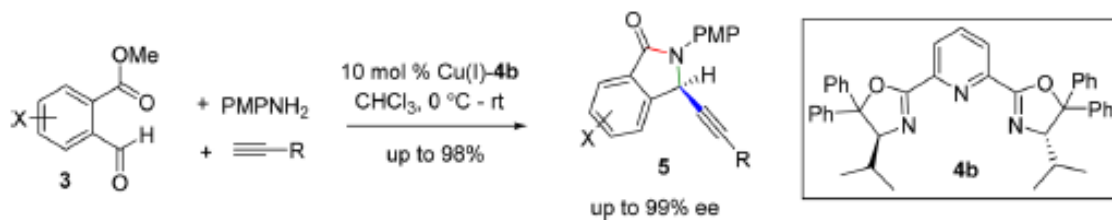
30R- and 30S-oxazoline prepared using oxazolines starting materials this is a good example of application of oxazoline. [127].



Ortho-benzyloxyphenyloxazolines reacted with butyllithium, potassium tert-butoxide to give 2-aryl-3-aminobenzofurans. Using benzylthio, benzylamino compounds as a starting materials we can produce benzothiophenes and indoles by this method [128].

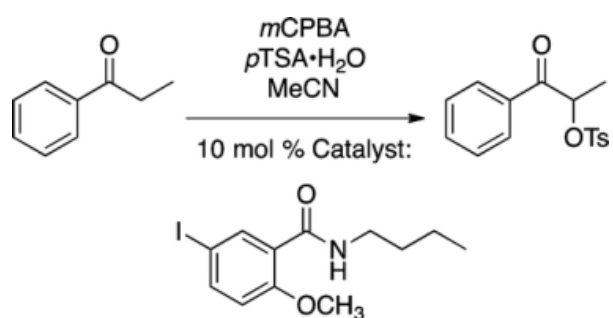


(R,R)-1,3-Dibenzylisoindoline: in this protocol disubstituted chiral isoindoline prepared using asymmetric oxazoline ligand. Using PTSA oxazoline is condensed to isoindoline due to steric effect of oxazoline chiral pure (R,R)-1,3-Dibenzylisoindoline obtained [129].

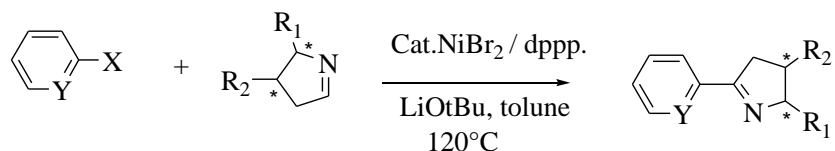


A unified approach for the asymmetric syntheses of medicinally important isoindolinones (S)-PD 172938 and (R)-JM 1232 has been accomplished via a Cu(I)-PYBOX-diPh catalyzed highly enantioselective (up to 99% ee) alkynylation/lactamization sequence in a one-pot fashion. The

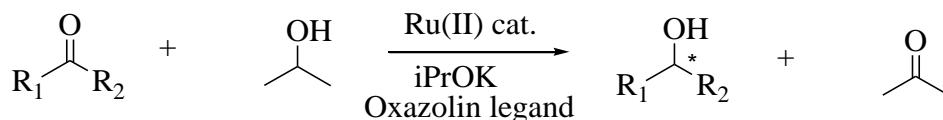
overall sequence involves one C–C and two C–N bond forming events in one pot starting from inexpensive starting material in ambient reaction conditions [130].



A series of rate studies were conducted to evaluate the steric and electronic properties that govern the reactivity of iodoarene amide catalysts in the α -oxytosylation of propiophenone. A meta-substituted benzamide catalyst emerged as the most reactive. This catalyst was employed in the α -oxytosylation of a series of substituted propiophenones, returning the α -tosyloxy ketone products in excellent isolated yield [131].

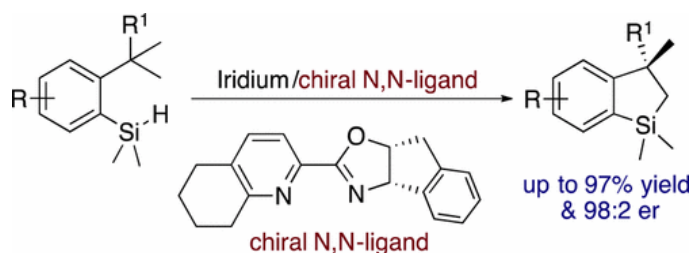


Nickel-catalyzed CH heteroarylation of chiral oxazolines, nickel-catalyzed C–H heteroarylation at the 2 position of oxazolines with heteroaryl halides was developed. Various oxazoline-containing multidentate chiral ligands have been efficiently synthesized. It only costs a nickel! A nickel-catalyzed C–H heteroarylation at the 2 position of oxazolines with heteroaryl halides is described. This method is an efficient synthesis for various oxazoline-containing multidentate chiral ligands [132].

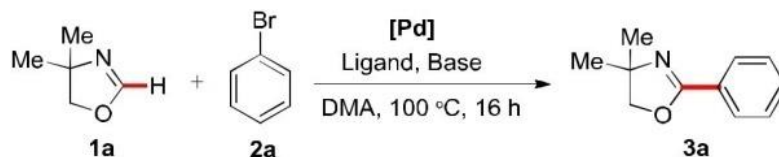


NHTs Effect on the Enantioselectivity of Ru(II) Complex Catalysts Bearing a Chiral Bis(NHTs)-Substituted Imidazolyl-Oxazolanyl-Pyridine Ligand for Asymmetric Transfer Hydrogenation of Ketones. Huining Chai, Pincer-type ruthenium (II)-NNN complex catalysts bearing a chiral

bis(NHTs)-substituted imidazolyl-oxazolanyl-pyridine ligand were synthesized and structurally characterized by NMR, IR, elemental analysis, and X-ray single-crystal crystallographic determinations. The two NHTs groups substituted on the imidazolyl moiety of the chiral NNN ligand exhibited a remarkable effect on the enantioselectivity of the Ru(II)-NNN complexes for the asymmetric transfer hydrogenation (ATH) of ketones. The Ru(II)-NNN complex bearing a chiral (NHTs)₂-substituted imidazolyl-(isopropyl)oxazolanyl-pyridine ligand exhibited excellent catalytic activity, reaching an enantioselectivity up to 99.9% ee for the target alcohol products [133].

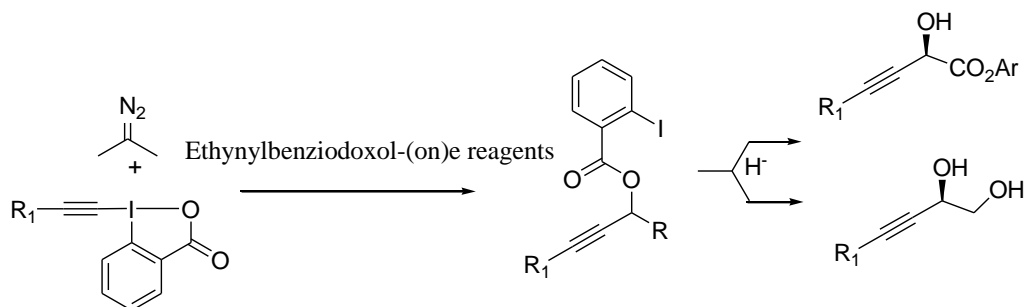


Highly enantioselective intramolecular, silylations of unactivated, primary C(sp³)–H bonds. The reactions form dihydrobenzsiloles in high yields with excellent enantioselectivities by functionalization of enantiotopic methyl groups under mild conditions. The reaction is catalyzed by an iridium complex generated from [Ir(COD)OMe]₂ and chiral dinitrogen ligands that we recently disclosed. The C–Si bonds in the enantioenriched dihydrobenzsiloles were further transformed to C–Cl, C–Br, C–I, and C–O bonds in final products. The potential of this reaction was illustrated by sequential C(sp³)–H and C(sp²)–H silylations and functionalizations, as well as diastereoselective C–H silylations of a chiral, natural-product derivative containing multiple types of C–H bonds. Preliminary mechanistic studies suggest that C–H cleavage is the rate-determining step [134].



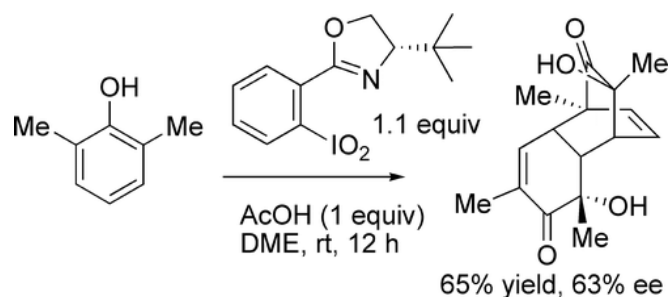
C–H arylations of oxazolines were accomplished with a well-defined palladium catalyst derived from a secondary bisdiamantyl phosphine oxide. The single-component secondary phosphine oxide (SPO)-palladium complex enabled C–H activations with aryl bromides and challenging

aryl chlorides in the absence of directing groups, setting the stage for the step-economical synthesis of pybox ligands under racemization-free reaction conditions [135].

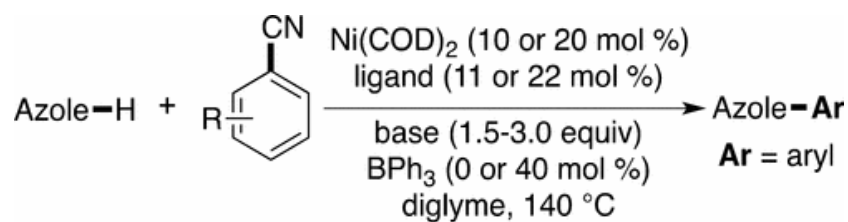


Enantioselective catalytic methods allowing the addition of both a nucleophile and an electrophile onto diazo compounds give a fast access into important building blocks. Herein, we report the highly enantioselective oxyalkynylation of diazo compounds using ethynylbenziodoxol-(on)e reagents and a simple copper bisoxazoline catalyst. The obtained α -benzoyloxy propargylic esters are useful building blocks, which are difficult to synthesize in enantiopure form using other methods. The obtained products could be efficiently transformed into vicinal diols and α -hydroxy propargylic esters without loss in enantiopurity [136].

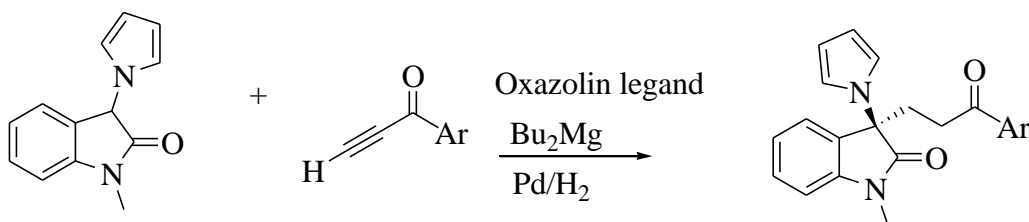
Polyesters have been widely applied owing to their biodegradability and biocompatibility. Recently catalytic ring-opening copolymerization of cyclic anhydrides and epoxides has emerged as an effective approach for the synthesis of polyesters. Herein, we report a series of amido-oxazolinato zinc complexes as highly active catalysts for the ring-opening copolymerization of styrene oxide and cyclic anhydrides. Turnover frequencies up to 4000 h⁻¹ were achieved in the reaction of styrene oxide and maleic anhydride. Analysis of the end groups provides a useful probe for the preference at the electron-poor methine site of styrene oxide for the ring-opening process [137].



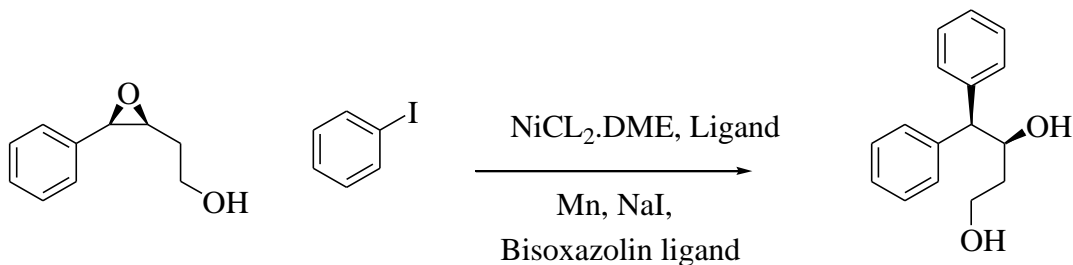
This is application of Iodo oxazoline for preparation of ortho-quinol dimers asymmetrically [138].



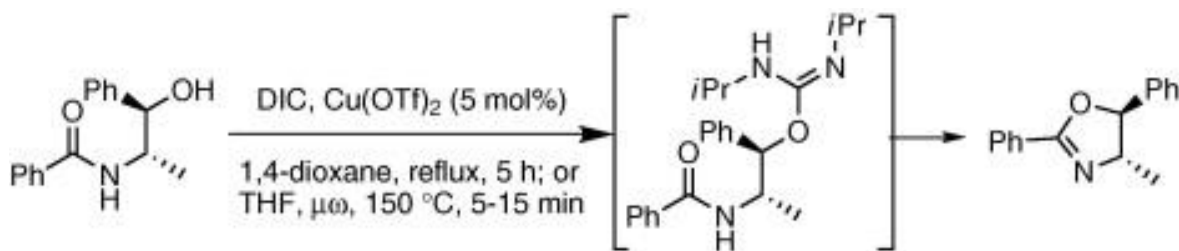
Ni-catalyzed coupling of azoles with aromatic nitriles. The use of BPh₃ promotes these arylations with electronically diverse azoles and benzonitriles. While the nickel catalyst is necessary for the arylations of phenyl oxazoles, arylation of benzoxazoles with some nitriles affords the arylated products even in the absence of the Ni catalyst albeit in lower yield than the catalyzed process. The Ni-catalyzed process exhibits higher rates and a broader scope than the uncatalyzed transformation [139].



Synthesis of chiral pure C3-pyrrolyl-oxindoles using terminal alkynes in presence of oxazoline ligand is presented. The current asymmetric conjugate reaction relies on the development of novel combinational magnesium catalysis involving two chiral ligands [140]. The current protocol proceeds smoothly and gives the corresponding enantioenriched 3,3-disubstituted oxindole skeletons with good enantioselectivities. Furthermore, the conjugate adducts could be transferred to spiro oxindole structures containing an eight-membered ring in high ee values.



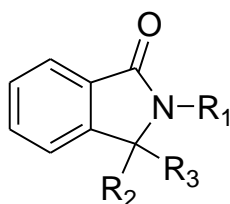
Enantioselective opening of chiral epoxide in presence of bisoxazoline (up to >99.9% ee) is very interesting application of oxazoline [141].



Hydroxy amides reacted with Diisopropylcarbodiimide in presence of copper triflate 2-oxazolidines formed. The reaction condition used is mild and high yield obtained using this method. This reaction also proceeds by microwave irradiation [142].

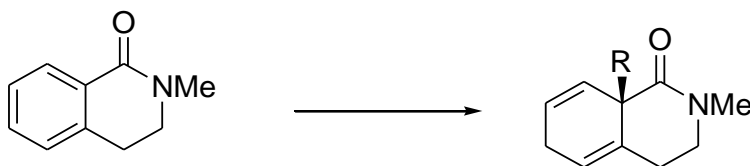
1.3.2 Chiral induction using Sonogashira reaction (Isoindolinons)

Isoindolinons are heterocyclic compounds containing cyclic amide groups represented by structural formula

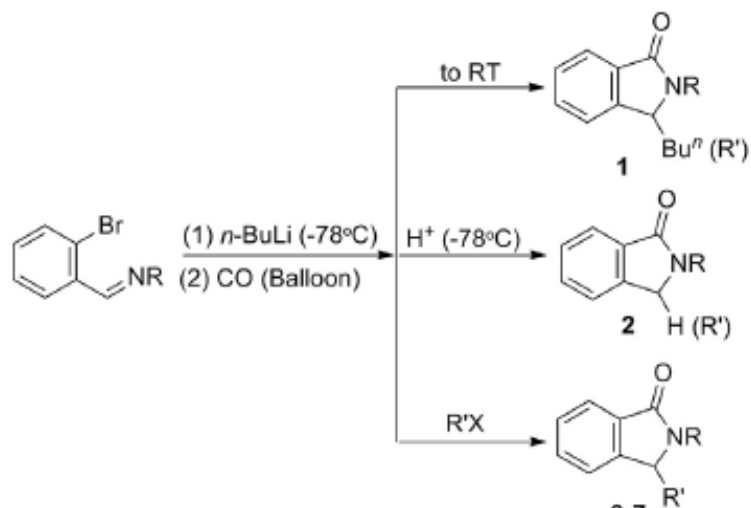


Where R_1 , R_2 , R_3 may be same or different groups. Isoindolinons have received extensive attention in recent years because the isoindolinone skeleton presents in numerous natural products and synthetic pharmaceuticals with a wide range of biological activities. In view of crucial applications of isoindolinone derivatives, their synthetic methodologies have been widely investigated in recent years.

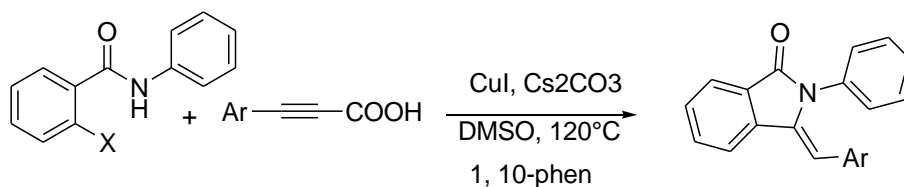
1.3.2.2 Reported literature Isoindolinons.



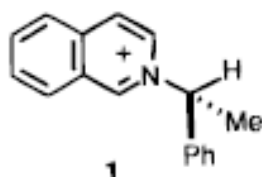
2,3-disubstituted-3,4-dihydro-1(2H)-isoquinolinones were prepared using birch reduction with a diastereoselectivity 35:1 [143]

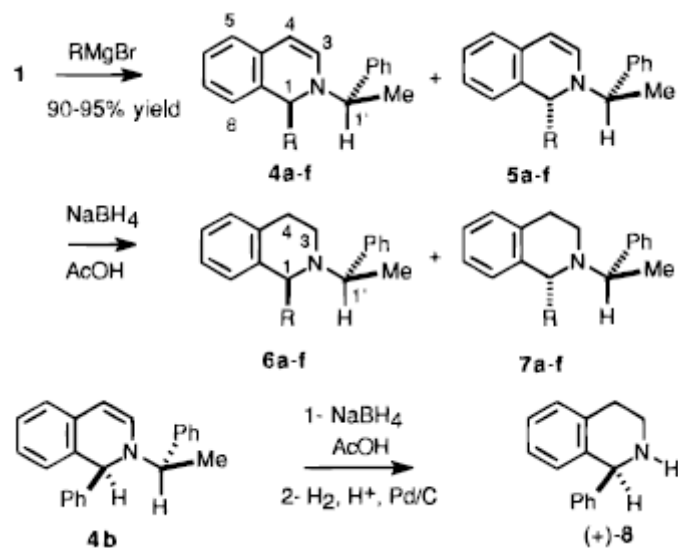


2, 3-disubstituted isoindolinones was prepared using aromatic imines as a starting material in first step n -butyllithium used for induction of R group and carbon monoxide is used in next step for cyclization to form isoindolinones [144].

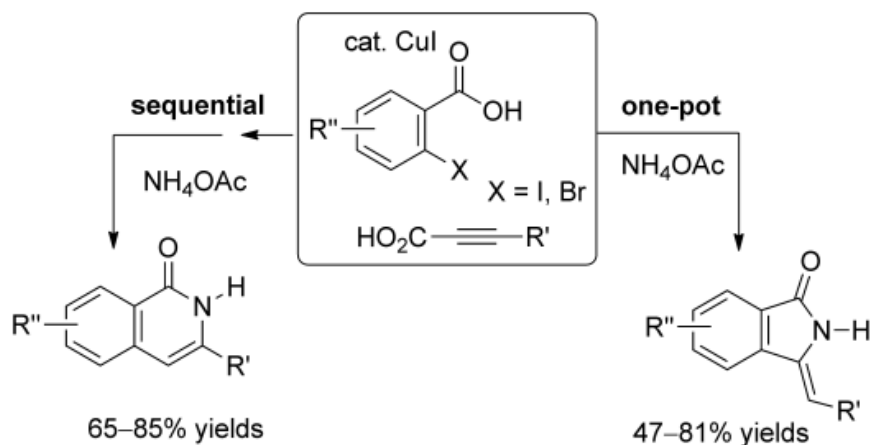


Anupal Googoi, prepared 3-methyleneisoindolin-1-ones using CuI , ligand, base and alkynyl acids [145]. Here alkynyl acid get decarboxylated first and then coupled to 2-halobenzamides followed by cyclization gives 3-methyleneisoindolin-1-ones. For iodo substituted 2-halobenzamides reactions proceeds without ligand.





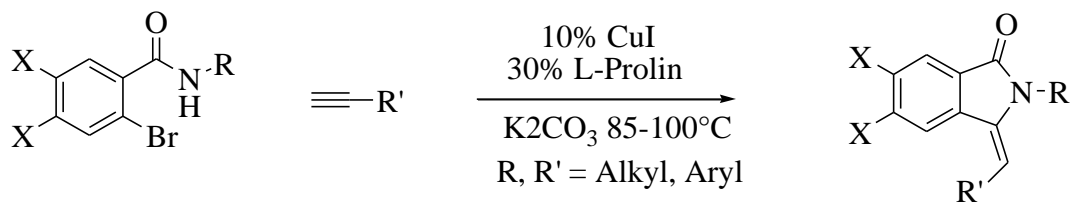
Denis Barbier prepared new chiral isoquinolin by using Grignard reagent and which on reduction with sodium borohydride gives chiral dihydro chiral isoquinolinium which on further debenzylation gives chiral tetra hydro chiral isoquinolin [146].



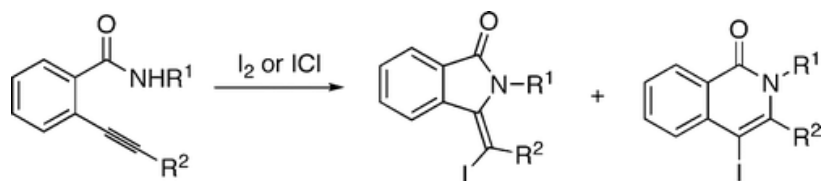
Francis Mariaraj prepared isoindolin and isoquinolin selectively synthesized using 2-halobenzoic acid, ammonium acetate (NH_4OAc), cesium carbonate (Cs_2CO_3) and a copper iodide [147]. When reaction done in one-pot conditions isoindolin-1-ones formation observed. When ammonium acetate was added at 120°C after addition of all reagent isoquinolin-1-ones obtained in good yield.

CuI/L-Proline-Catalyzed Domino Reaction [148] Li Li described the mechanism for Domino reaction and used CuI and L-proline for cyclization of o-alkynylbenzamides in presence of base

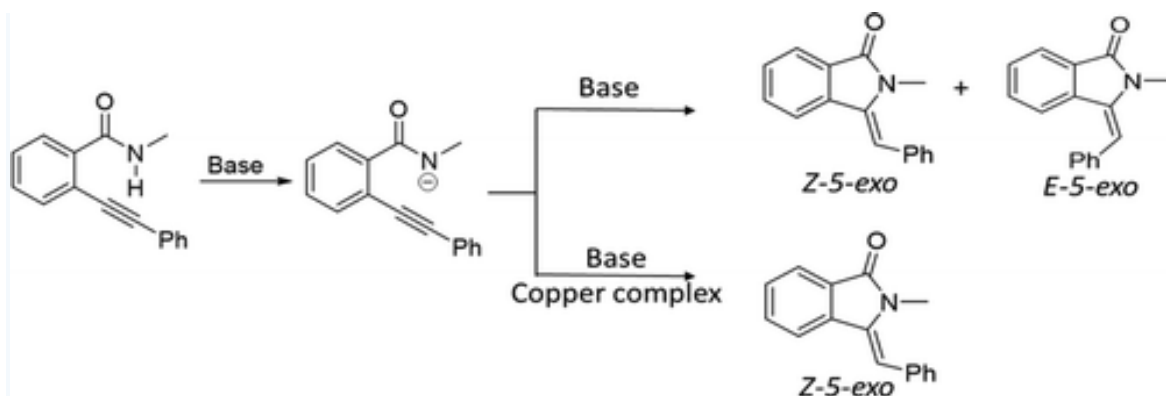
mixture of exo and endo product observed but in presence of copper complex only exo isomer formation observed.



Tuanli Yao prepared Isoindolin-1-ones from o-(1-alkynyl)benzamides using ICl, I₂, and NBS. Some cases substituted isoquinolin-1-ones obtained as major product and prepared cepharanone B. by using this method [149].



Domino Reaction using CuI and l-Proline catalyst and Mechanism for Regioselective Anionic Cyclization [150].



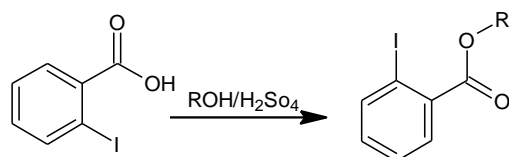
2. EXPERIMENTAL.

All the chemicals used as such purchased without purification from Aldrich, Spectrochem, and Alfa acer. All the solvent used is also used as such without distillation purchased from Qualigens. All the apparatus used is oven dried at 100°C. All the Products were purified over silica column, mesh size 10-200, 230-400 according to requirement using hexane and ethyl acetate as a eluent. All the spectra recorded on Bruker (4000 MHZ) in CDCl₃ Solvent.

A suitable single crystal was collected through the polarising microscope and mounted on the Bruker D8 Venture diffractometer system is equipped with micro focus Cu source, Photon 100 CMOS detector. Crystal is kept at 298K (2) during the data collection with scan width of 0.5mm and distance 40mm from crystal to detector. The structure was solved using the Olex2 with the XT, using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimization.

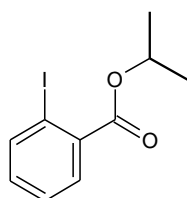
2.1. Preparation of starting materials.

2.1.1. Synthesis of 2-iodobenzoate.



R= Methyl, Ethyl, n-propyl, iso-butyl, sec-butyl.

2.1.1.1 Synthesis of propan-2-yl 2-iodobenzoate

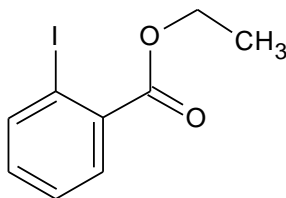


Experimental process

5.0 gm of 2-iodobenzoic acid was charged in 60.0 ml of Isopropanol and charged 5.0 ml of Conc. H₂SO₄. Reaction mass heated to 65°C for 5 hrs, and concentrated completely. Charged 50.0 ml of water and extracted with 25.0 ml ethyl acetate three time, washed ethyl acetate layer with 20.0 ml saturated bicarbonate solution in water, dried over NaHSO₄ and concentrate ethyl

acetate layer completely. Product purified on silica column in 5% ethyl acetate n-Hexane% yield 65%

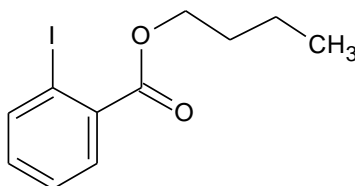
2.1.1.2 Synthesis of ethyl 2-iodobenzoate



Experimental process

5.0 gm of 2-iodobenzoic acid was charged in 60.0 ml of Ethanol and charged 5.0 ml of Conc. H₂SO₄. Reaction mass heated to 65°C for 5 hrs, and concentrated completely. Charged 50.0 ml of water and extracted with 25.0 ml ethyl acetate three time , washed ethyl acetate layer with 20.0 ml saturated bicarbonate solution in water, dried over NaHSO₄ and concentrate ethyl acetate layer completely, % yield 99%

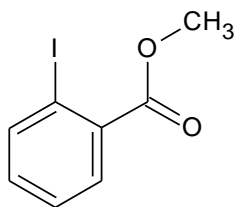
2.1.1.3 Synthesis of butyl 2-iodobenzoate



Experimental process

5.0 gm of 2-iodobenzoic acid was charged in 60.0 ml of n-butanol and charged 5.0 ml of Conc. H₂SO₄. Reaction mass heated to 65°C for 3hrs, and concentrated completely. Charged 50.0 ml of water and extracted with 25.0 ml ethyl acetate three time , washed ethyl acetate layer with 20.0 ml saturated bicarbonate solution in water, dried over NaHSO₄ and concentrate ethyl acetate layer completely, % yield 97%

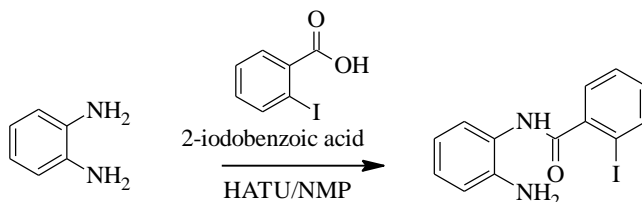
2.1.1.4 Synthesis of methyl 2-iodobenzoate



Experimental process

5.0 gm of 2-iodobenzoic acid was charged in 50.0 ml of Methanol and charged 5.0 ml of Conc. H₂SO₄. Reaction mass heated to 65°C for 3hrs, and concentrated completely. Charged 50.0 ml of water and extracted with 25.0 ml ethyl acetate three time , washed ethyl acetate layer with 20.0 ml saturated bicarbonate solution in water, dried over NaHSO₄ and concentrate ethyl acetate layer completely, % yield 97%

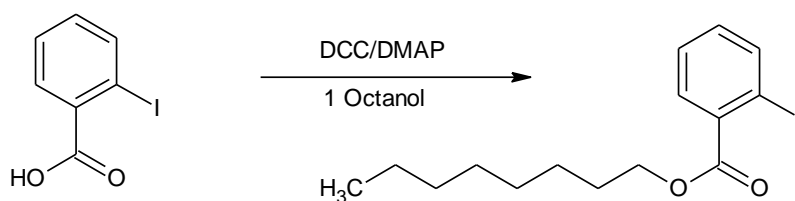
2.1.1.5. Synthesis of N-(2-aminophenyl)-2-iodobenzamide.



Experimental process

2.0 gm of 2-iodobenzoic acid was charged in 10.0 ml of DMF and charged 1.0 gm of benzene - 2,2diamine at 25°C. Charged 3.5 gm of HATU followed by addition of 1.23 ml of NMP. Reaction mass stirred for 30 min. and charged 25 ml of water, Filtered the solid and washed with 20.0 ml water and 10ml ethyl acetate. Dried under vacuum for 6 hrs at 55°C %, yield **90%**

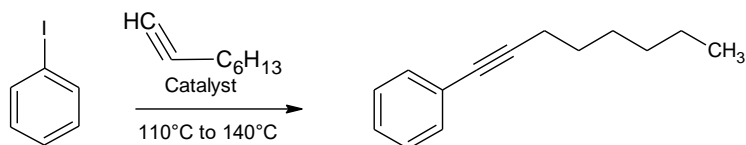
2.1.1.6. Synthesis of Octyl 2-iodobenzoate



2.0 gm 1-Octyne, 2.7 gm of 4-N, N Dimethylaminopyridine, 3.3 gm of Dicyclohexyl Carbodimide and 2.99 of iodobenzoic acid was charged in 30.0 ml of Dichloromethane. Reaction mass stirred for 30 min. and charged 25 ml of water filtered the reaction mass through cillite bead and organic layer washed with 1N 50.0 ml aq. HCl, 50.0 ml saturated NaHCO₃ Solution. Dried over Anhydrous Na₂SO₄ and concentrated completely. %, yield 98%

2.2 Optimization of reaction condition.

2.2.1 Catalyst screening



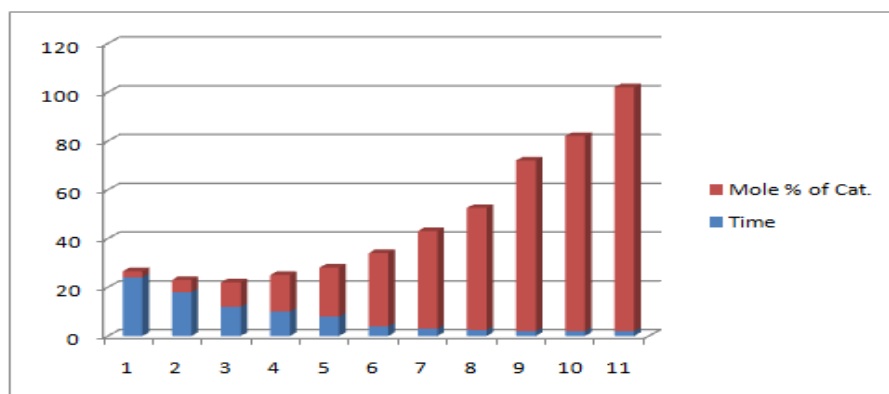
Base	Temp	Solvent	Catalyst	% yield
Cesium carbonate	140°C	DMF	Fe powder	2
Cesium carbonate	140°C	DMF	Cu(OAc) ₂	0
Cesium carbonate	140°C	DMF	MnCl ₂	0
Cesium carbonate	140°C	DMF	CeCl ₂	0
Cesium carbonate	140°C	DMF	MgCO ₃	0
Cesium carbonate	140°C	DMF	Mg metal	Dimmer formation
Cesium carbonate	140°C	DMF	Zn metal	0
Cesium carbonate	140°C	DMF	Zn/Fe	0
Cesium carbonate	140°C	DMF	Mg/Fe	0
Cesium carbonate	140°C	DMF	CuI	55
Cesium carbonate	140°C	DMF	CuBr ₂	22
Cesium carbonate	140°C	DMF	Cu powder	97
Cesium carbonate	140°C	DMF	CuI/orthophenylene diamine	75
Cesium carbonate	140°C	DMF	Copper Carbonate	79
Cesium carbonate	140°C	DMF	CuI binap complex	82
Cesium carbonate	140°C	DMF	Vanillin Cu Complex	85
Cesium carbonate	140°C	DMF	CuI(PPh ₃) ₃	96
Cesium carbonate	140°C	DMF	CuBr ₂ (PPh ₃) ₃	91

During catalytic screening we found that Cu metal and their complexes giving good result

2.2.2. Mole % variation study

Mole % variation study of copper metal on standard protocol shows that reaction with 2.5 mole % of copper metal the time required for completion of reaction is 24 hrs. with

increasing mole % of rate of reaction increases and become constant after 80mole % .copper metal is so chipper that one has to fix the Mole % of catalyst against the time.



2.2.3. Base selection.

Sr. No	Base	Solvent	Hrs.	Cat
1	Cs ₂ CO ₃	--	5 hrs	CuI(pph ₃) ₃
2	K ₂ CO ₃	--	5 hrs	CuI(pph ₃) ₃
3	TEA	--	--	CuI(pph ₃) ₃
4	Na ₂ CO ₃	---	---	CuI(pph ₃) ₃
5	NaOH	---	6 hrs	CuI(pph ₃) ₃
6	NaHCO ₃	---	---	CuI(pph ₃) ₃
7	KOH	DMF		CuI(pph ₃) ₃
8	Cs ₂ CO ₃	DMF	2 hrs	CuI(pph ₃) ₃
9	K ₂ CO ₃	DMF	2 hrs	CuI(pph ₃) ₃
10	TEA	DMF	---	CuI(pph ₃) ₃
11	Na ₂ CO ₃	DMF	---	CuI(pph ₃) ₃
12	NaOH	DMF	4 hrs	CuI(pph ₃) ₃
13	NaHCO ₃	DMF	---	CuI(pph ₃) ₃
14	KOH	DMF	4 hrs	CuI(pph ₃) ₃

Reaction working well in Cesium carbonate, sodium carbonate, NaOH and KOH.

2.2.4. Solvent selection.

Sr.No.	Base	Solvent	Catalyst	Time
1	K ₂ CO ₃	DMSO	CuI(pph ₃) ₃	6 hrs
2	K ₂ CO ₃	ACN	CuI(pph ₃) ₃	12 hrs
3	K ₂ CO ₃	Toluene	CuI(pph ₃) ₃	15 hrs
4	K ₂ CO ₃	MIBK	CuI(pph ₃) ₃	19 hrs
5	K ₂ CO ₃	NMP	CuI(pph ₃) ₃	4 hrs
6	K ₂ CO ₃	Xylene	CuI(pph ₃) ₃	13 hrs
7	K ₂ CO ₃	DMF	CuI(pph ₃) ₃	3 hrs

Reaction working in all solvent with different rate.

3.1. SONOGASHIRA REACTION USING COPPER POWDER.

Keeping in view of these drawbacks, the efforts were made to carry out Sonogashira cross coupling reactions of alkyl-2-iodobenzoates with terminal alkynes using copper powder as a catalyst under solvent, co-catalyst, and base free conditions.

A simple and successful protocol has been developed for Sonogashira coupling reactions. In this protocol, initially we synthesized derivatives of iodobenzoic acid (**I-V**) by the reaction of iodobenzoic acid with different alcohols (methanol, ethanol, *n*-butanol, iso-butanol and *sec*-butanol). Then copper powder instead of palladium has been used as a catalyst in the absence of co-catalyst under mild solvent free conditions for the successful coupling reactions of alkyl-2-iodobenzoates with terminal alkynes (**A-J**)

Scheme 1. Besides, a reasonable mechanism for formation of Sonogashira coupled products is shown in **scheme 2**. The yield of the coupled products (**A-J**) was founded quite good in the range of 84-97%. The analytical and spectroscopic data of the coupled products (**A-J**), supported their proposed structures. The chemical structures of initial and final coupled products are given in **Table 1**. The structures of synthesized compounds (**A-J**) were determined by CHNS, ¹H NMR and ¹³C NMR spectroscopy. The formations of products (**A-J**) were confirmed by the presence of the characteristic ¹H NMR signal of alkyl protons in the range of 0.91-4.41 ppm, while aromatic protons appeared in the range of 7.12-8.37 ppm. In addition to it the coupled products were found fully soluble in ethyl acetate and dichloromethane and partially soluble in *n*-hexane, *n*-heptane. For ready reference, the ¹H NMR of compounds **I** and **J** are shown in **Fig**. The main advantages of our new protocol for the development of sonogashira coupling products are as; high yields of products, nonpoisonous nature of catalyst and mild reaction conditions.

3.1.1 Importance of work

The iodoarenes are higher reactive than chloro, bromo ones for the synthesis of substituted arynes/alkynes. As per the literature, the iodoarenes used in coupling reactions by a palladium catalyst resulted poor yields because of poisonous palladium catalyst. But in this research article, the coupling reactions were performed with iodoarenes by copper catalyst. The copper catalyst is not poisoned by iodoarenes; leading to good yields of substituted arynes/alkynes. In addition to it, our

method is found to be eco-friendly involving no use of ligands, co-catalyst, base and solvent that is the main speciality of our work. Furthermore, the prediction of the activities of the synthesized compounds was carried out by online software (pass prediction). It was observed that the compounds have anti-cizomatics, anti-fobic disorder and inhibition of aspulvinone dimethylallyltransferase properties. Besides, in silico studies also indicated the prepared compounds may act as inhibitor for aspulvinone dimethylallyltransferase enzyme to control Alzheimer's, Schizophrenia etc. diseases.

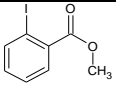
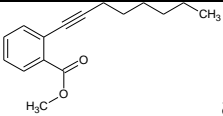
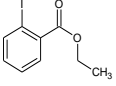
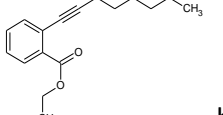
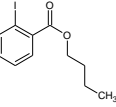
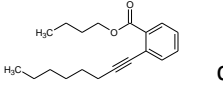
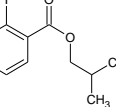
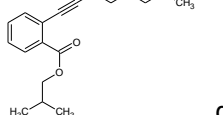
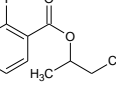
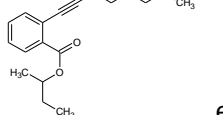
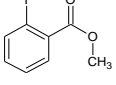
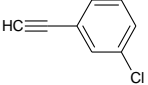
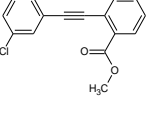
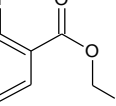
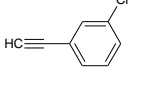
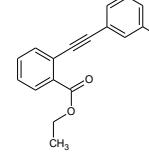
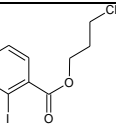
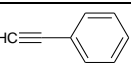
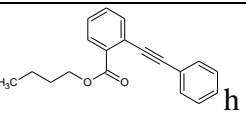
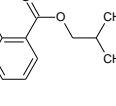
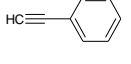
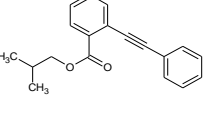
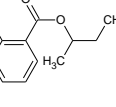
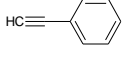
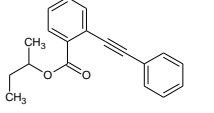
3.1.2 Synthesis of Alkyl 2-Benzoates (I-V).

Iodobenzoic acid (10 g) was added to 60 mL of alcohol derivatives (methanol, ethanol, *n*-butanol, iso-butanol and *sec*-butanol) in 5 mL conc. H₂SO₄, separately. The reaction mixtures were stirred electromagnetically in an oil bath at 65, 78, 100, 105 and 95°C for 24, 5, 2, 4 and 4 hrs, respectively. Then excess alcohol derivatives were removed under vacuum rotary evaporator. Then water and ethyl acetate were added to final residues and organic layer was separated and washed three times with water and with a saturated bicarbonate solution. Finally, the mixtures were dried over Na₂SO₄ and excess solvent was removed by distillation that resulted 97% yield of methyl-2-iodobenzoate, 99% yield of ethyl 2-iodobenzoate, 95% yield of *n*-butyl 2-iodobenzoate, 96% yield of 2-methylpropyl-2-iodobenzoate and 98% yield of butan-2-yl- 2-iodobenzoate, respectively.

3.1.3. Synthesis of Final Coupled Products (A-J)

Reaction mixtures of **1-V** (10 mL, 10 mM) separately, 1-octyne (12 mL, 12 mM), copper powder (7.8mM, 0.5 g) in dichloromethane (DCM) were stirred electromagnetically at 120°C for 12 hrs. Filtration removed the catalyst. The crude products were purified over silica gel column chromatography in 0.25% ethyl acetate with *n*- hexane solvent system and resulted **A-E** products. Reaction mixtures of **1-V** (10 mL, 10 mM) separately, 1-chloro-3-ethynylbenzene, 1-chloro-3-ethynylbenzene, phenylacetylene, phenylacetylene, phenylacetylene (12 mL, 12 mM), respectively, copper powder (0.5 g) in dichloromethane (DCM) were stirred electromagnetically at 120°C for 12 hrs. Filtration removed the catalyst. The crude products were purified over silica gel column chromatography in 0.25% ethyl acetate with *n*- hexane solvent system and resulted **F-J** products (**Scheme 1, Table 3.1**).

Table 3.1: Chemical structures and percentage yields of **I-V** and **A-J**.

Sr. No.	Iodobenzoate	Alkynes	Substituted Alkynes	Yield
I		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{CH}$	 a	97%
II		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{CH}$	 b	95%
III		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{CH}$	 c	93%
IV		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{CH}$	 d	86%
V		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{CH}$	 e	89%
I			 f	90%
II			 g	94%
III			 h	91%
IV			 i	92%
V			 j	84%

3.1.4. In silico studies.

Combinatorial chemistry and virtual screening are well reputed, possibly due to their reduction of the extremely time consuming steps of organic and inorganic synthesis and biological screening. Molecular docking is a very valuable tool for the prediction of the interactions of drugs with various biological macromolecules at a supra molecular level

[151]. In biochemistry, transferase is the general name for the class of enzymes that enact the transfer of specific functional groups (e.g. a methyl or glycosyl group) from one molecule to another [152]. In enzymology, an aspulvinone dimethylallyltransferase enzyme catalyzes the chemical reaction of 2-dimethylallyl diphosphate and aspulvinone E in 2-diphosphate + aspulvinone H. The systematic name of this enzyme class is dimethylallyl-diphosphate: aspulvinone-E dimethylallyltransferase. This enzyme is also called dimethylallyl pyrophosphate: aspulvinone dimethylallyltransferase. These results showed the possible inhibitor for the aspulvinone dimethylallyltransferase enzyme to control various diseases including Alzheimer's, Schizophrenia etc.

The rigid molecular of tRNA dimethylallyltransferase docking of the ligands has been carried out using AutoDock 4.2 to find out the possible sites of the interactions of aspulvinone dimethylallyltransferase with the ligands. The docking studies of ligands were performed with aspulvinone dimethylallyltransferase (PDB ID: 2CRM). The order of binding affinity of the synthesized compounds was **F > G > J > B = C > H > E > I > A = D**. The docked models of **A, B** and **C** are shown in (**Fig. 3.1-10**). It is clear from the docked models that all the compounds interacted with tRNA

dimethylallyltransferase enzyme *via* different sites. The number of H- bonds formed by the compounds **A–J** is given in **Table 3.2**. The number of hydrogen bonds were zero (**F–J**), one (**A, B and E**), two (**D**), three (**C**). The common moieties of ligands involved in hydrogen bonding were carbonyl and ether groups and residues of receptor involved were ALA-215H01, ARG-219H01, ASP-20H01, GLY-17H01, SER-303H01, GLU-229H01, ARG-225H01 and ALA-218H01. In addition to hydrogen bondings, hydrophobic interactions were also observed (**Table 3.2**). In addition, hydrophobic interactions were also observed. The common residues involved Arg282, Ala221, Glu222, Arg225, Ser303, Val215, Leu21, Leu304, Ser303 and Tyr270. The different simulation parameters of the final compounds (**A–J**) are given in **Table 3.2**.

Table 3.2. The different simulation parameters of **A-J** with aspulvinone dimethylallyltransferase.

Compounds	Binding affinity (kcal/mol)	Number of hydrogen bonds	Residues involved in H-bonding (<i>Bond length</i>)	Residues involved in hydrophobic attractions
A	-3.3	1	A: ALA-215H01:: O of carbonyl group (3.4)	Arg282:: C1&C2, Ala218::C10 Ala221:: C1,C7,C9,C12&C14 Glu222::C3,C4,C8&C11 Arg225::C4, C5,C9
B	-3.8	1	A: ARG-219H01:: O of ester group (3.5)	Ser303::C1,C5,C9&C14 Arg219::C4,C7,C10,c16,C17&O2 Val215::C4,C7, Asp20::C2,C9 Leu304::C8,C11&C12
C	-3.8	3	A: ASP-20H01::O of carbonyl group (3.5) B: GLY-17H01:: O of carbonyl group (3.5) C: SER-303H01:: O of ester group (3.2)	Arg219::C1, Leu21::C8 Asp20::C4,C5,C8,C9,C13&C19 Ala16::C11, Leu304::C11 Ser303::C11,C17&C19 Ala304::C12, Ala305::C12,C18
D	-3.3	2	A: GLU-229H01:: O of carbonyl group (3.5)	Tyr270::C2,C3,C5 Glu226::C4&C9, Glu222::C6 Arg225::C5,C6,C10,C13&C14
			B: ARG-225H01:: O of carbonyl group	Glu229::C18,C19,01&O2

			(3.3)	
E	-3.6	1	A: ALA-218H01:: O of carbonyl group (3.4) Glu222	Ser303::C1&C2 Val215::C16 Ala15&Pro210::C1 Ala16::C3,Ala15::C5 ::C4,C6,C8,C9, Ala218::O1Ala219::C5,C10,C10 ,C16C17,O1
F	-4.6	0	-	Ala218::C2,C5,Ala15::C3 Arg219::C5,C6,C10,C11&C14 Ser303::C7,C1,Leu304::C13&C1, Val215::C11,C15&O2
G	-4.4	0	-	Ala16::C1,Ala15::C1 Pro210::C1,C2,Arg219::C5,C11, C16,Ala218::C3,C7 Ala215::C2,C5,C6, Leu304::O1 Ser303::C1,Leu216::C2, Val215::C6,C10,C11C15
H	-3.7	0	-	Arg225::C2,C6,C7,C9C10C13,C 15&C17,Glu229::C2,C3,C15 Glu222::C4,C10,C14 Glu226::C6&C9
I	-3.5	0	-	Arg225::C10,C15,C13,C9,C5& O1,Gln226::C2&C5 Glu222::C14,C17,C9&C5
J	-3.9 0	0 -	-	Ala218::C1&C4, Gln226::C5 Ala221::C10,Arg225::C15,C13, C5&O1 Gln222::C10,C9,C17,C15,C8,

3.1.5. Docked models of A-J

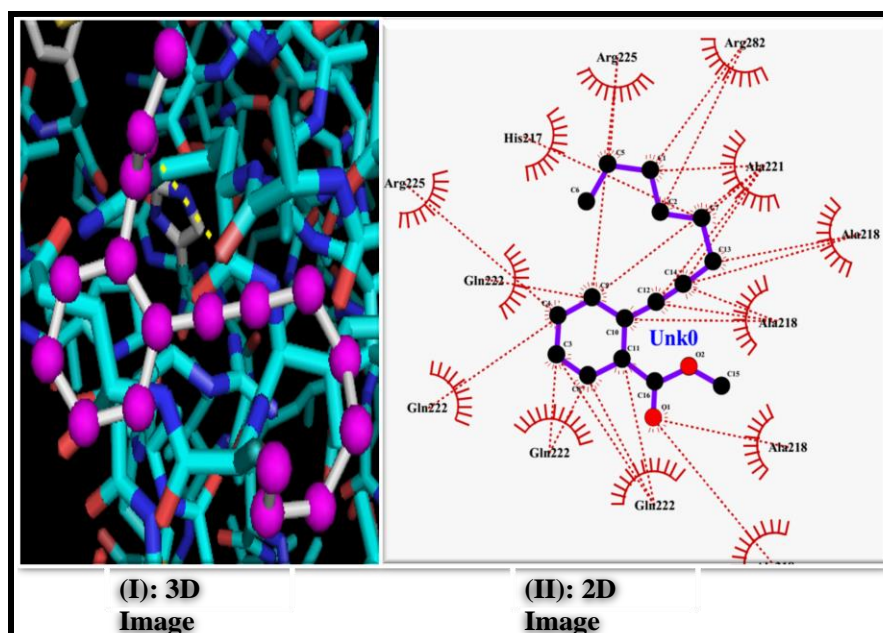


Fig. 3.1: 2D and 3D docking poses of A with aspuvinone dimethylallyltransferase.

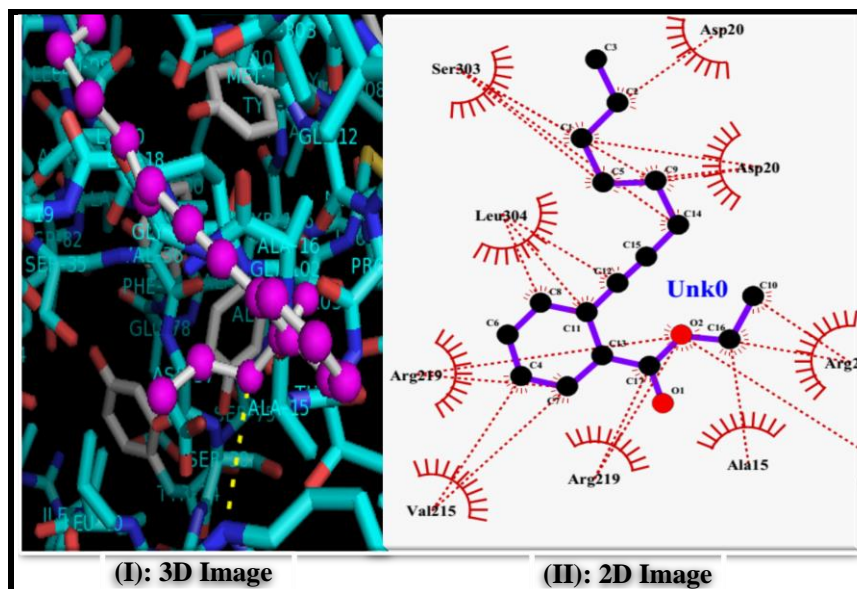


Fig. 3.2: 2D and 3D docking poses of B with aspuvinone dimethylallyltransferase.

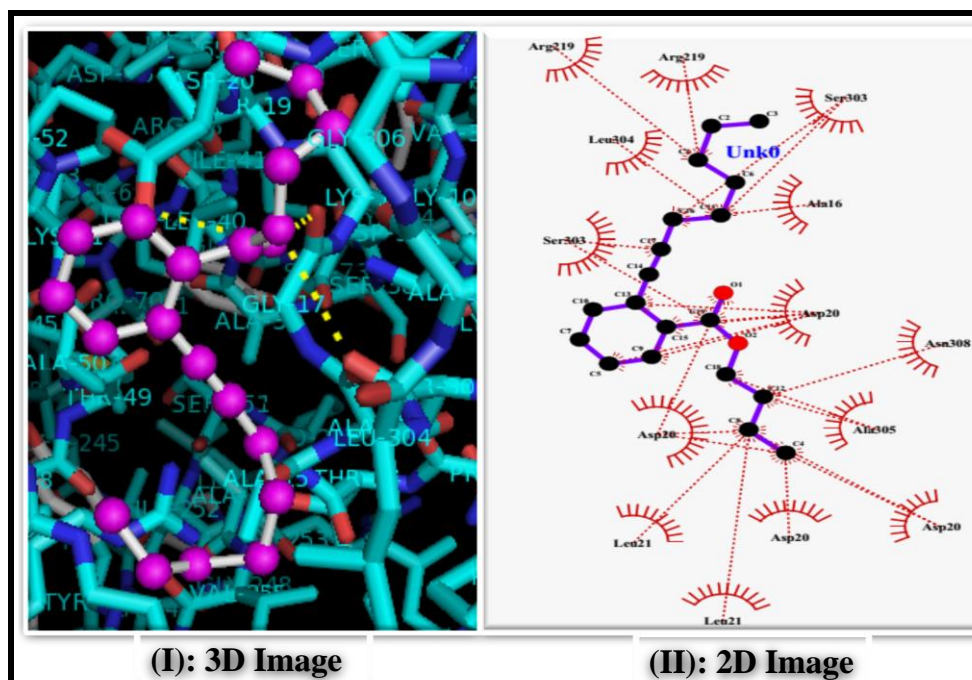


Fig. 3.3: 2D and 3D docking poses of **C** with aspulvinone dimethylallyltransferase.

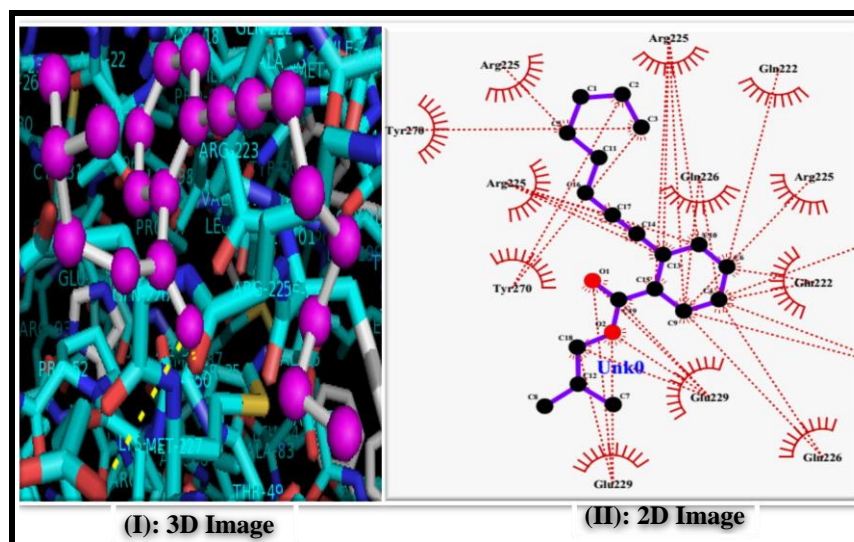


Fig.3.4: 2D and 3D docking poses of **D** with aspulvinone dimethylallyltransferase.

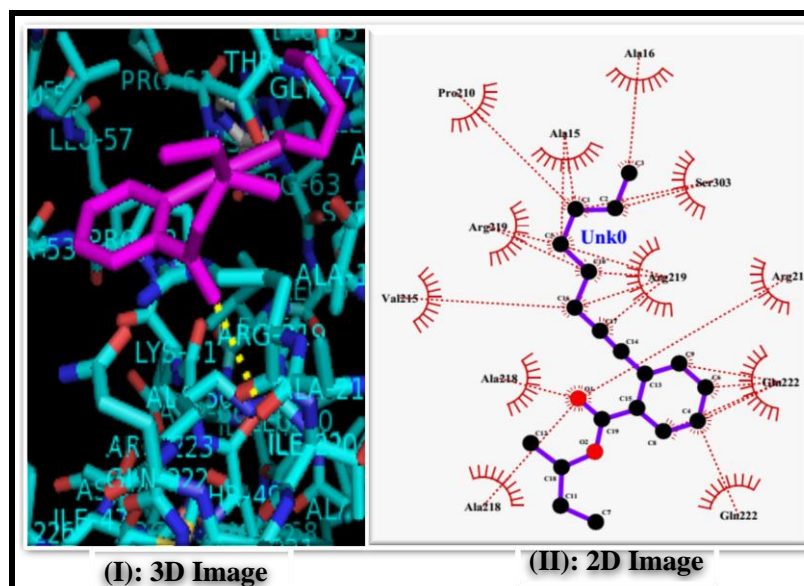


Fig.3.5: 2D and 3D docking poses of **E** with aspulvinone dimethylallyltransferase.

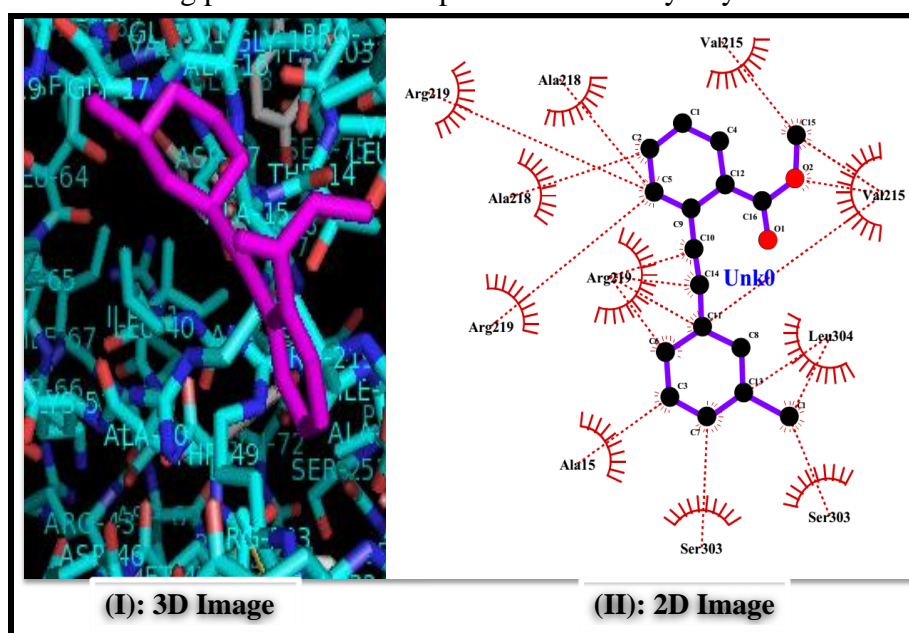


Fig.3.6: 2D and 3D docking poses of **F** with aspulvinone dimethylallyltransferase.

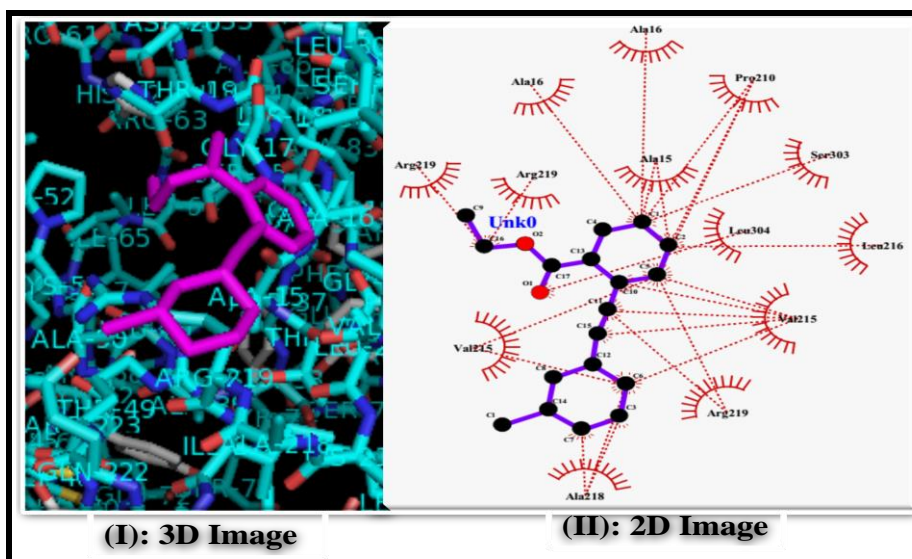


Fig.3.7:2D and 3D docking poses of **G** with aspulvinone dimethylallyltransferase.

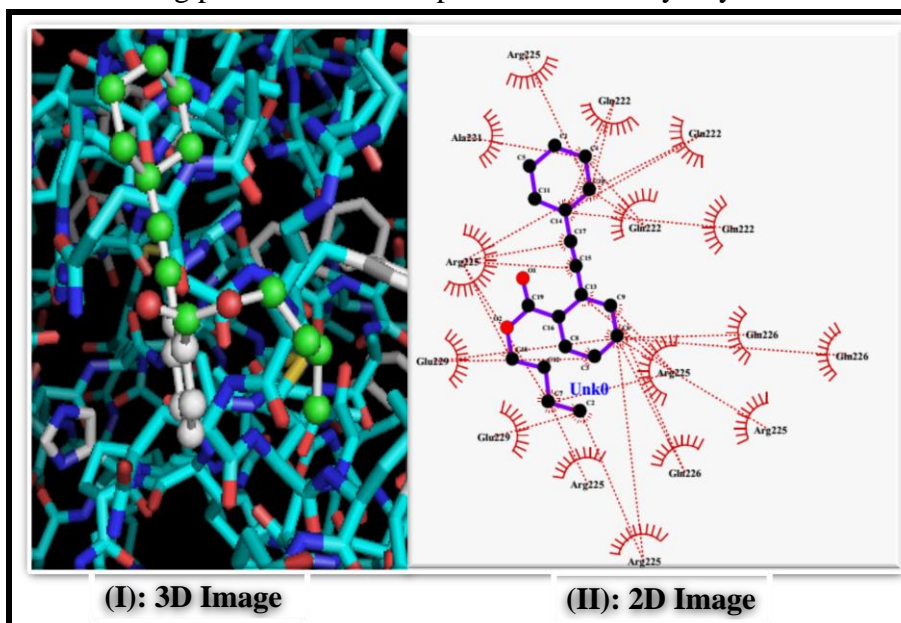


Fig.3.8:2D and 3D docking poses of **H** with aspulvinone dimethylallyltransferase.

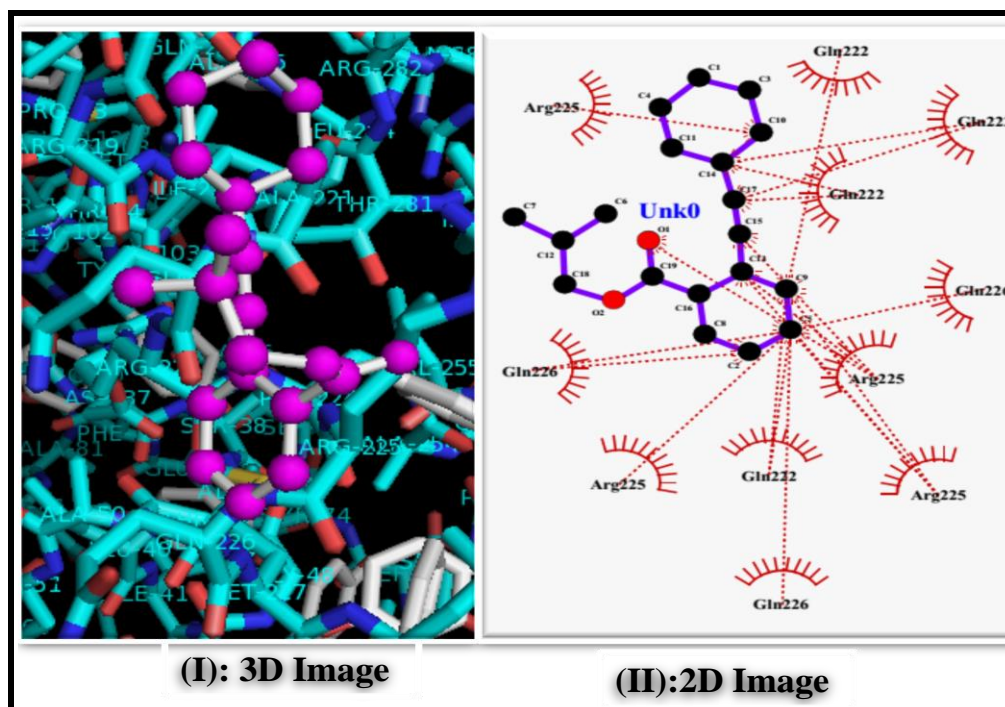


Fig.3.9:2D and 3D docking poses of **I** with aspulvinone dimethylallyltransferase.

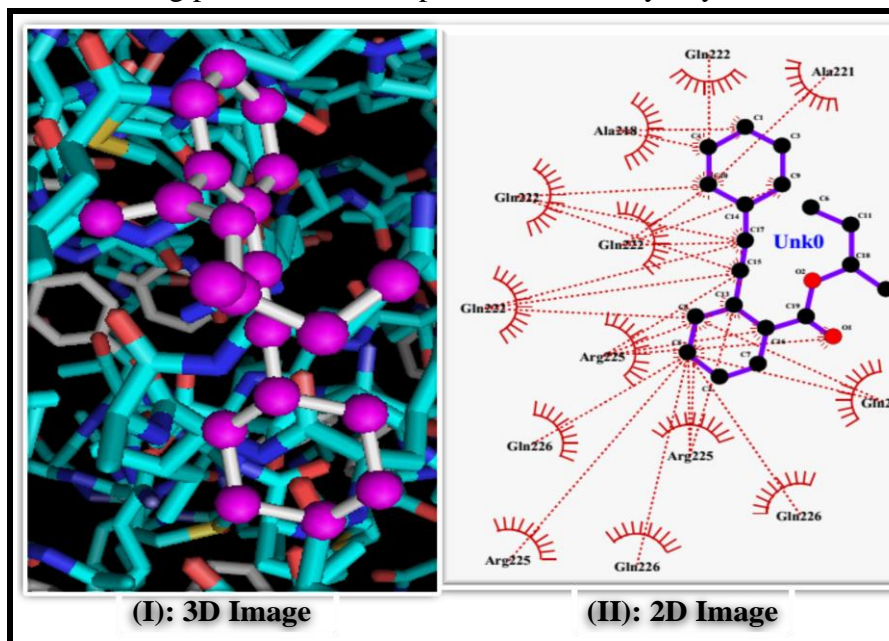
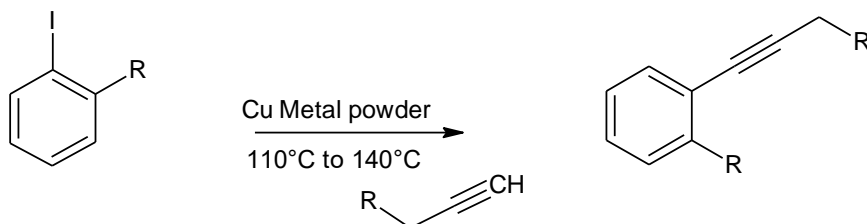


Fig.3.10:2D and 3D docking poses of **J** with aspulvinone dimethylallyltransferase.

Scheme 3.1. Synthesis of Internal Alkyne benzoate.



3.1.4 Spectroscopic data of Compound (A-J)

3.1.4.1. Methyl 2-(oct-1-yn-1-yl)-benzoate (A)

M wt. 244 Da, Anal. Calcd for C₁₆H₂₀O₂ (%): Calcd C (78.65), H (8.25); found C (78.55) H (8.26); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.96 (3H,t),1.53(4H m),1.67(4H m *J*=8),2.51(2H t *J*=4),3.95(3H s), 7.31(1H m *J*=8),7.43(1H q *J*=8),7.55(1H d *J*=8),7.92(1H *J*=8) ¹³C NMR (100 MHz, CDCl₃) 14.09,19.73,22.68,28.00, 29.19,31.63,52.06,79.22,96.09,123.49,127.10, 134.24,131.48,135.17,141.35,167.05.

3.1.4.2. Ethyl 2-(oct-1-yn-1-yl)-benzoate (B)

M wt. 258 Da, Anal. Calcd for C₁₇H₂₂O₂ (%): Calcd C (79.03), H (8.58); found C (79.05) H (8.60); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.33(3H t *J*=8), 1.42(3H t *J*=8),1.47(4H *J*=8),1.62(2H *J*=4),1.67(2H *J*=8), 2.48 (2H t *J*=8),4.41(2H *J*=8),7.31(1H t *J*=8),7.43(1H *J*=8),7.53 (1H d *J*=4),7.88(1H d *J*=4) ¹³C NMR (100 MHz, CDCl₃) 14.06,14.29 ,19.81 ,22.58, 28.68, 31.41, 33.83, 60.14,115.89,127.07,127.85, 131.29,132.45,134.51, 166.61.

3.1.4.3. Butyl 2-(oct-1-yn-1-yl)-benzoate (C)

M wt. 286 Da, Anal. Calcd for C₁₉H₂₆O₂ (%): Calcd C (79.68), H (9.15); found C (79.65) H (9.18); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.93 (3H *J*=4), 1.01(3H *J*=4), 1.35(4H m), 1.48 (4H m), 1.68(2H q *J*=8) 1.78(2H q *J*=8), 2.49(2H t *J*=8), 7.32(1H t *J*=8), 7.42(1H t *J*=4) 7.54(1H t *J*=4), 7.91(1H d *J*=8) ¹³C NMR (100 MHz, CDCl₃) 13.74, 14.11, 19.30, 19.85, 22.58, 28.70,29.71, 30.80, 31.42, 64.96, 79.32, 95.89, 123.42, 127.07, 129.53, 131.28, 134.29, 139.23, 166.68.

3.1.4.4. Methylpropyl 2-(oct-1-yn-1-yl)-benzoate(D)

M wt. 286 Da, Anal. Calcd for C₁₉H₂₆O₂ (%): Calcd C (79.68), H (9.15); found C (79.71) H (9.19); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.89(3H t), 1.01(6H d), 1.32(2H m), 1.45(2H q), 1.62(2H q) 2.1(1H m), 1.98(2H t) 2.44(2H t) ,4.11(2H t), 7.29(1H dd *J*=8.4),7.41(1H t *J*=8), 7.49(1H d *J*=8), 7.99(1H d *J*=8)

3.1.4.5. Butan-2-yl 2-(phenylethynyl)-benzoate(E)

M wt. 286 Da, Anal. Calcd for $C_{19}H_{26}O_2$ (%): Calcd C (79.68), H (9.15); found C (79.61) H (9.11); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.89 (3H t), 0.99(6H m), 1.42(2H m), 1.67(4H m), 1.79(2H m), 2.47 (2H m), 7.29(1H m $J=8$), 7.39(1H m $J=8$), 7.5 (1H t $J=8$), 7.86 (1H d $J=8$)

3.1.4.6. Methyl 2-[(3-chlorophenyl)ethynyl]-benzoate (F)

M wt. 270 Da, Anal. Calcd for $C_{16}H_{11}ClO_2$ (%): Calcd C (70.99), H (4.15); found C (70.71) H (4.19); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.98(3H s), 7.30(1H m), 7.34(1Hm), 7.41(1Hm), 7.48 (1Hm), 7.51 (1H m), 7.59(1Hm), 7.67(1Hm), 8.02(1Hm) ^{13}C NMR (100MHz, $CDCl_3$) 52.25, 89.41, 92.80, 123.28, 125.08, 128.27, 128.77, 129.62, 129.90, 130.57, 131.53, 131.80, 131.89, 134.09, 134.22, 166.46.

3.1.4.7. Ethyl 2-[(3-chlorophenyl)ethynyl]-benzoate (G)

M wt. 284 Da, Anal. Calcd for $C_{17}H_{13}ClO_2$ (%): Calcd C (71.71), H (4.6); found C (71.66) H (4.7); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (3H t), 4.45(2H m), 7.40(3H m), 7.50(1Ht), 7.61(2Hm), 7.69(1Hm), 8.02(1Hm); ^{13}C NMR(100MHz, $CDCl_3$) 14.24, 61.25, 88.31, 94.23, 123.38, 123.59, 127.90, 127.93, 128.38, 128.50, 130.43, 131.57, 130.84, 131.57, 131.70, 134.06, 166.42.

3.1.4.8. Butyl 2-(phenylethynyl)- (H)

M wt. 278Da, Anal. Calcd for $C_{19}H_{18}O_2$ (%): Calcd C (91.99), H (6.5); found C (10.91) H (6.69); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (3H t $J=4$), 1.44(2H m $J=8$), 1.80(2H m $J=4$), 4.38(2H t $J=8$), 7.41(4H m), 7.49(1H m $J=4$), 7.61(2H m $J=4$), 7.69(1H dd $J=8$), 8.01(1H m $J=4$) ^{13}C NMR (100MHz, $CDCl_3$) 14.12, 22.66, 31.82, 65.53, 88.34, 94.25, 123.40, 123.64, 127.91, 128.34, 128.48, 129.55, 130.44, 131.55, 131.71, 132.26, 132.81, 134.11, 166.45.

3.1.4.9. 2-methylpropyl 2-(phenylethynyl)-benzoate (I)

M wt. 278 Da, Anal. Calcd for $C_{19}H_{18}O_2$ (%): Calcd C (81.99), H (6.52); found C (81.88) H (6.66); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.01(6H t), 2.09(1H m), 4.13(2H m), 7.35 (4H m), 7.49(2H t $J=8$), 7.56(1H d, d $J=4$), 7.64(1H d $J=8$), 7.98(d $J=8$). ^{13}C NMR (100MHz, $CDCl_3$) δ 19.4, 27.7, 74.4, 92.9, 122.7, 124.0, 128.4, 128.5, 132.2, 132.3, 132.7, 133.3, 166.0

3.1.4.10. Butan-2-yl-2-(phenylethynyl)-benzoate (J)

M wt. 278 Da, Anal. Calcd for $C_{19}H_{18}O_2$ (%): Calcd C (81.99), H (6.52); found C (81.68) H (6.62); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.97(3H t), 1.34(3H d), 1.66 (1H m), 1.76(1H m), 5.14 (1H m), 7.35(4H m), 7.48(1H t $J=8$), 7.56(1H t $J=4$), 7.63(1H d $J=8$), 7.95(1H d $J=8$). ^{13}C NMR

(100MHz, CDCl₃) δ 9.87, 19.64, 28.97, 73.33, 88.40, 94.13, 123.44, 127.91, 128.35, 128.44, 1130.32, 131.41, 131.66, 132.64, 134.17, 166.05.

3.1.5 ¹H NMR, ¹³CMR, ¹³Dept. Spectra of Internal alkynebenzoate;

Fig-3.11: ¹H NMR of 1-(oct-1-ynyl)benzene

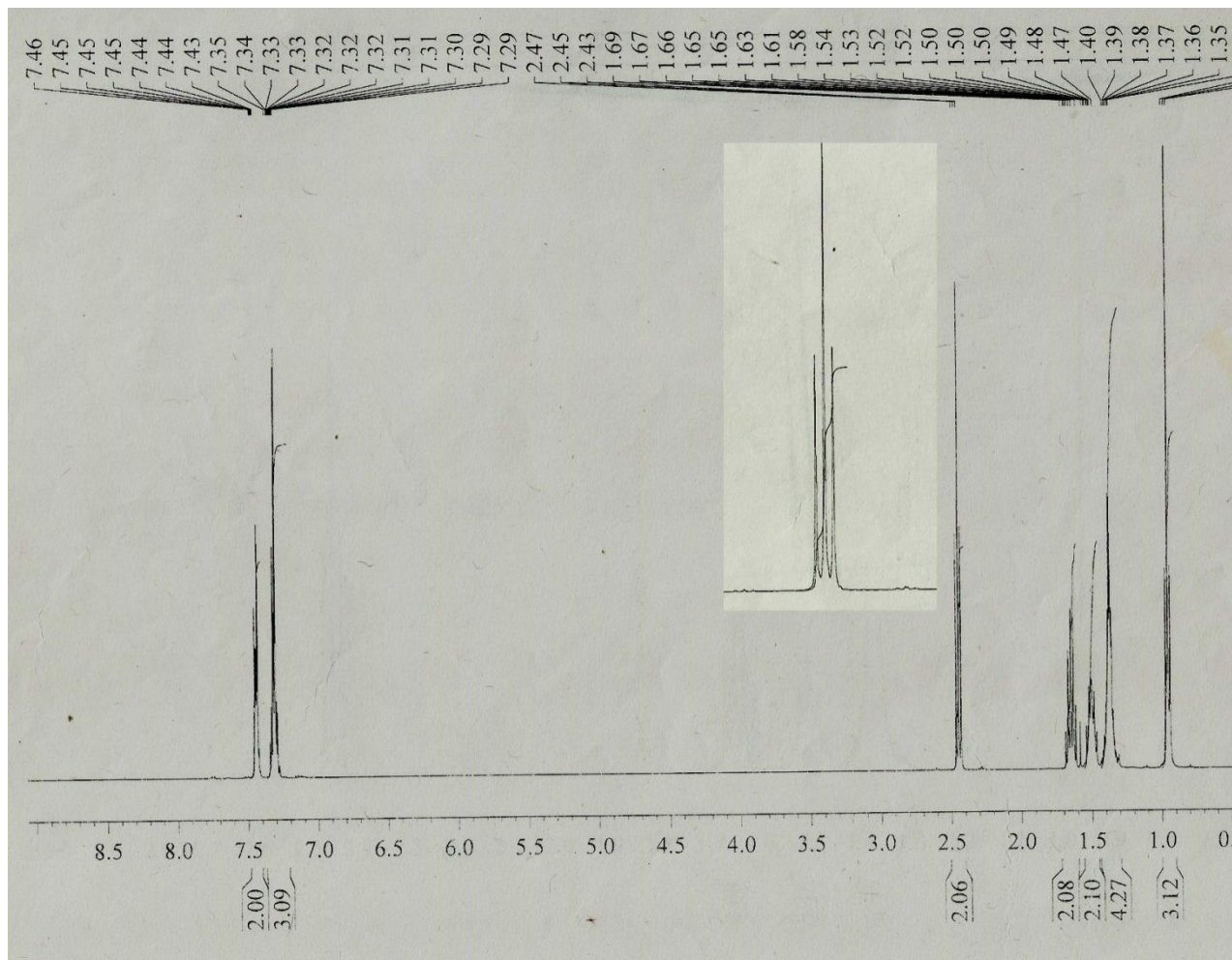


Fig-3.12: ^{13}C NMR of 1-(oct-1-ynyl)benzene

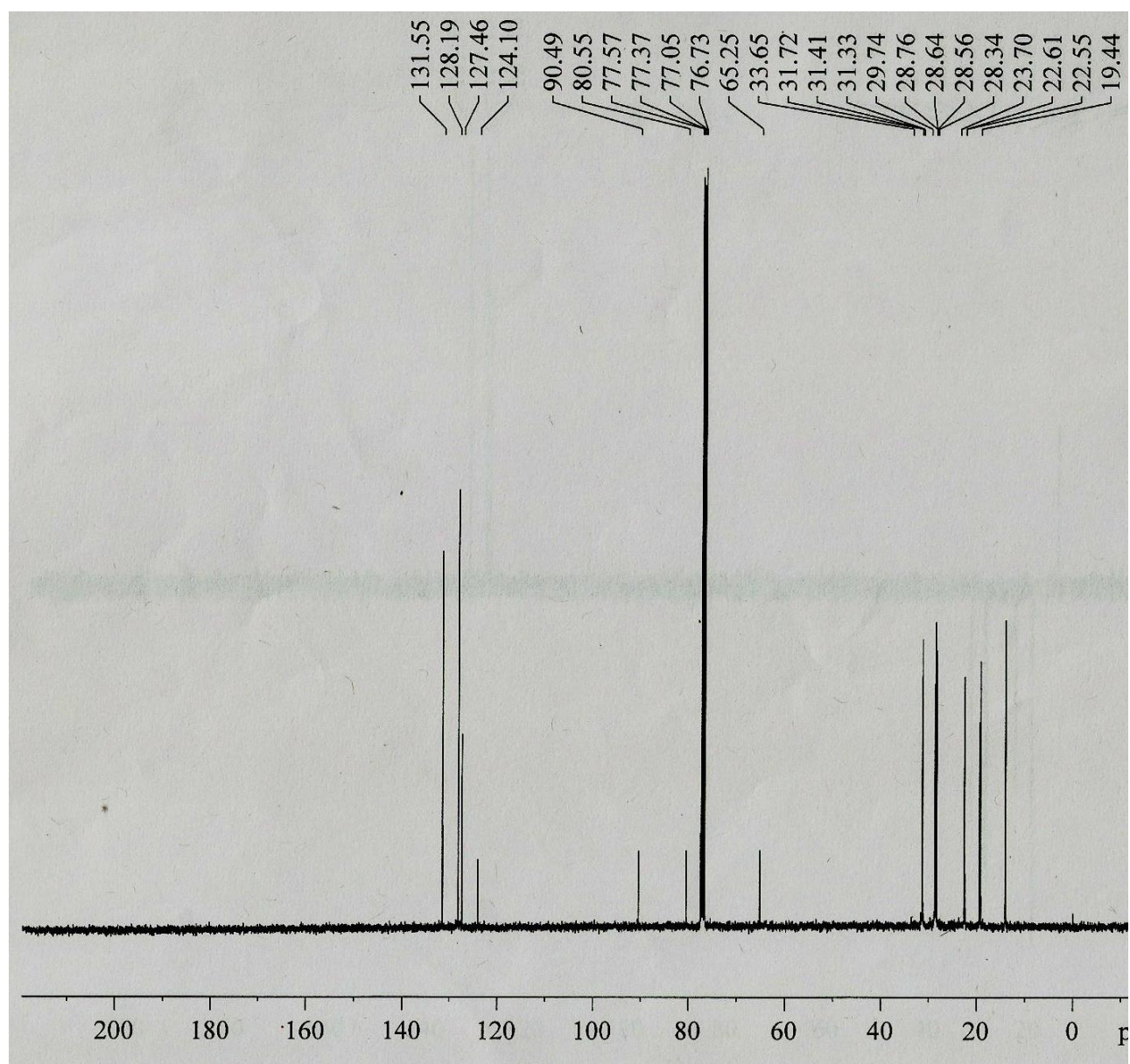


Fig-3.13: ^{13}C Dept of 1-(oct-1-ynyl)benzene.

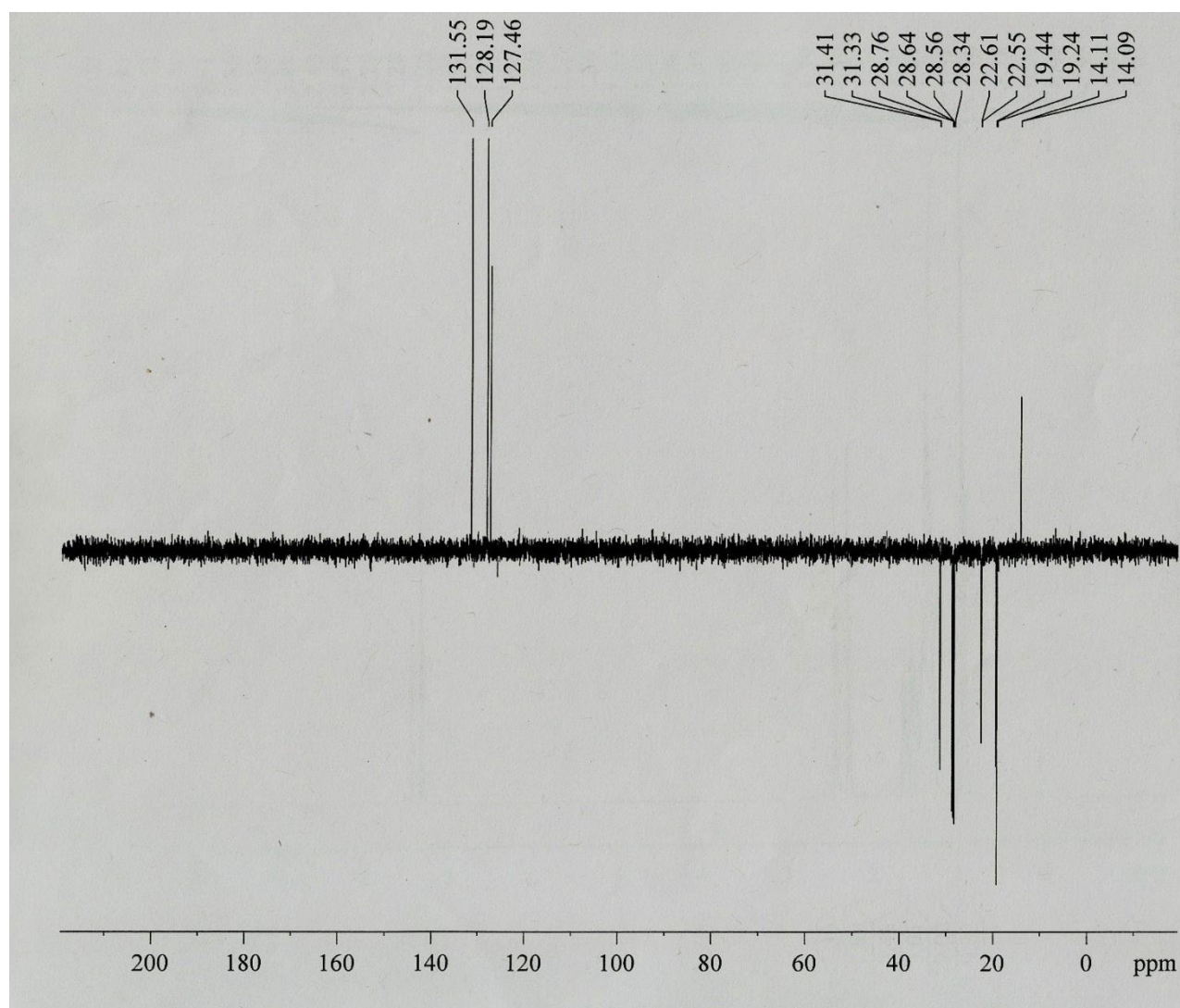


Fig-3.14: ^1H NMR of methyl 2-(oct-1-yn-1-yl)benzoate.

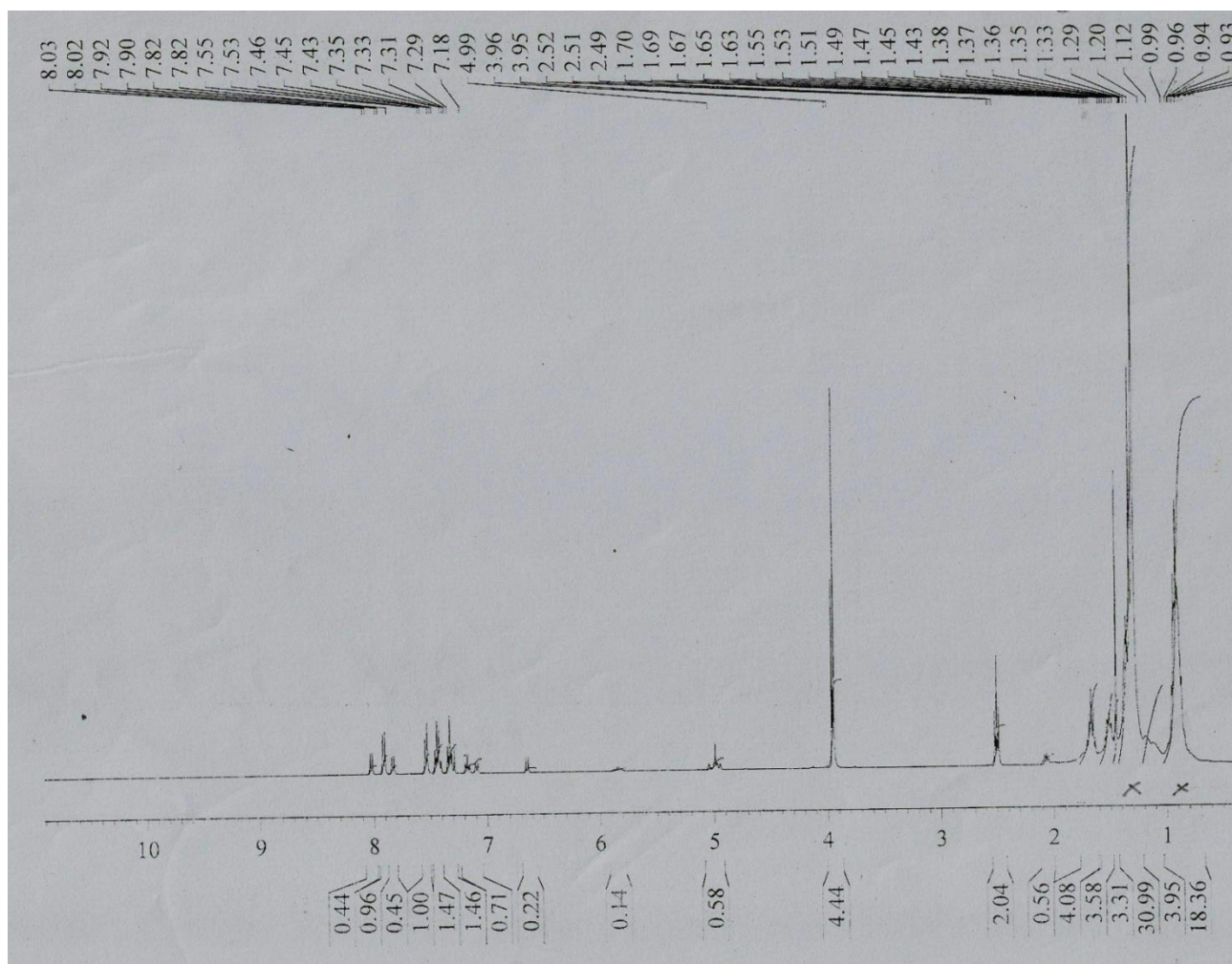


Fig 3.15: ^{13}C NMR of methyl 2-(oct-1-yn-1-yl)benzoate.

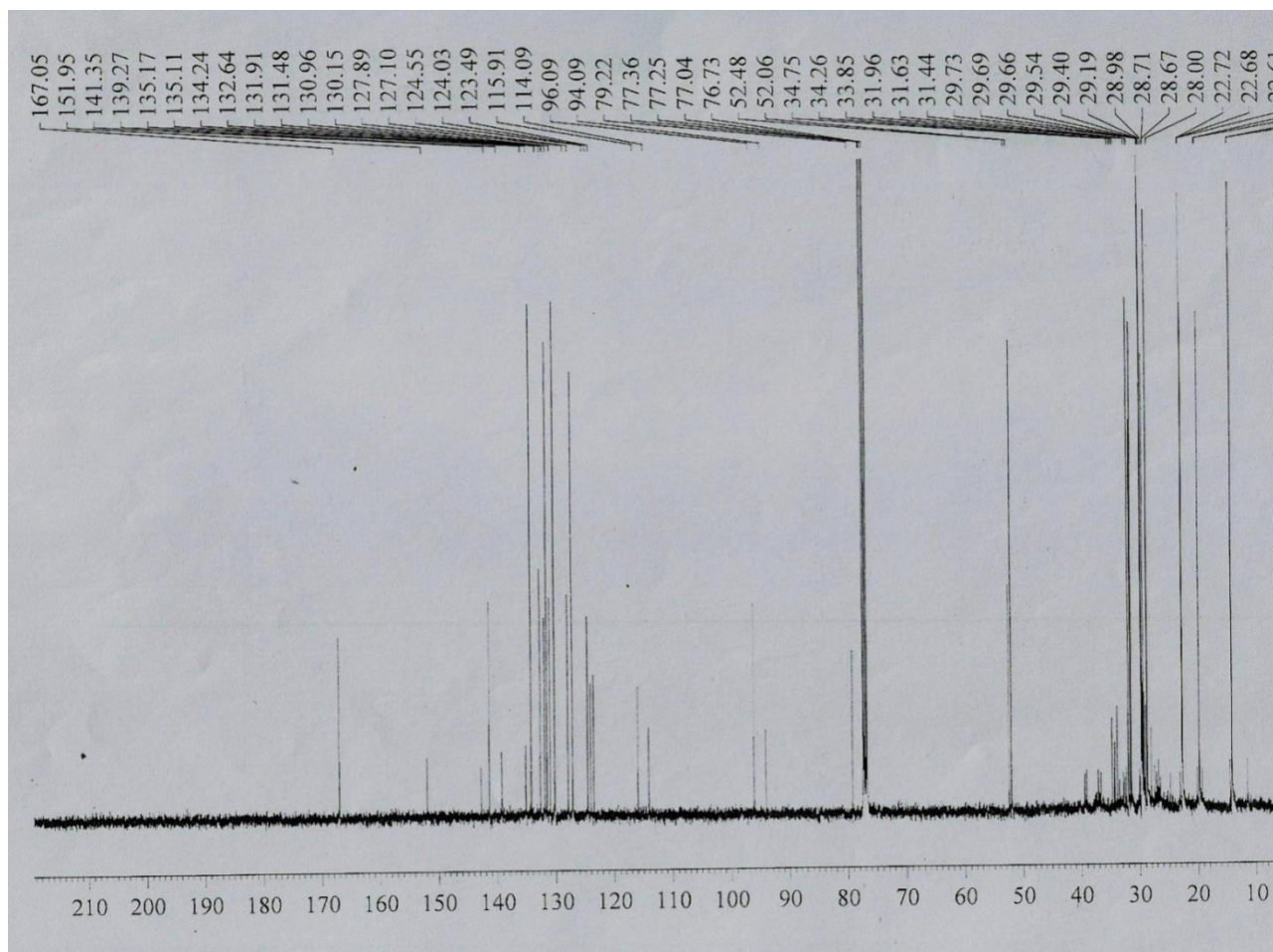


Fig 3.16: ^{13}C Dept. of methyl 2-(oct-1-yn-1-yl)benzoate

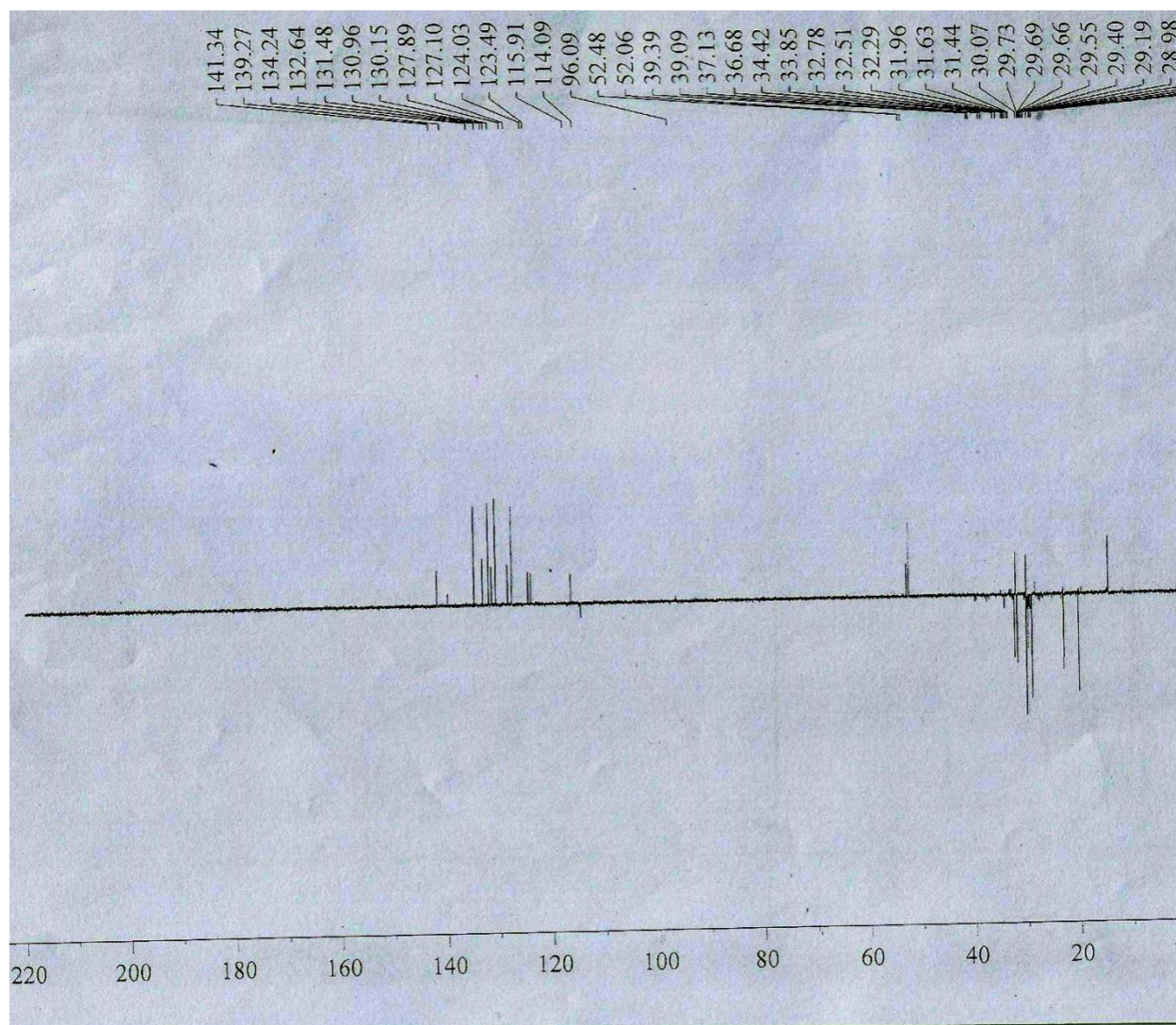


Fig 3.17: ¹H NMR of Methyl 2-(5-chloropent-1-ynyl)benzoate

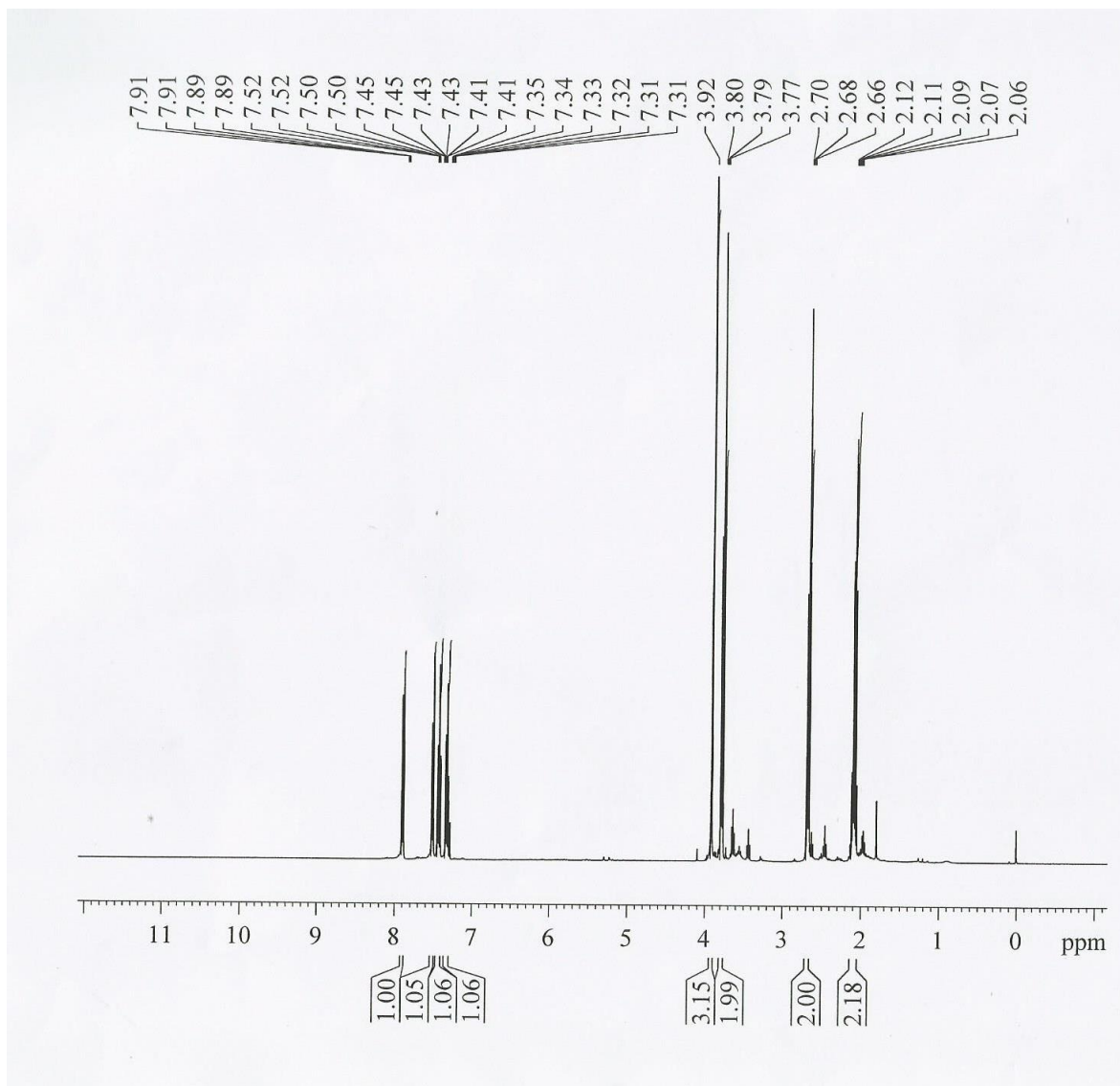


Fig 3.18: ^{13}C NMR of Methyl 2-(5-chloropent-1-ynyl)benzoate

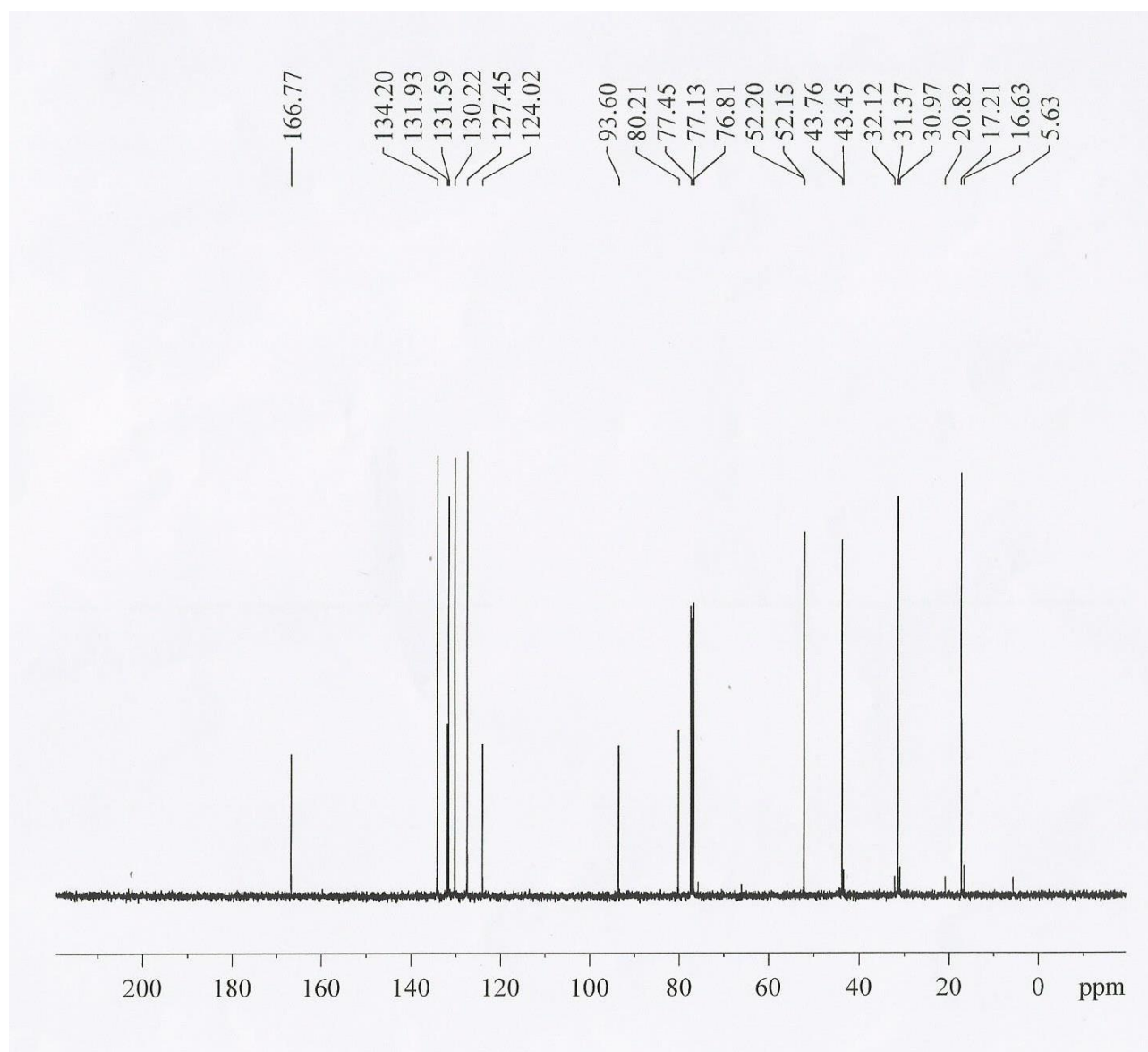


Fig 3.19: ^{13}C Dept. of Methyl 2-(5-chloropent-1-ynyl)benzoate.

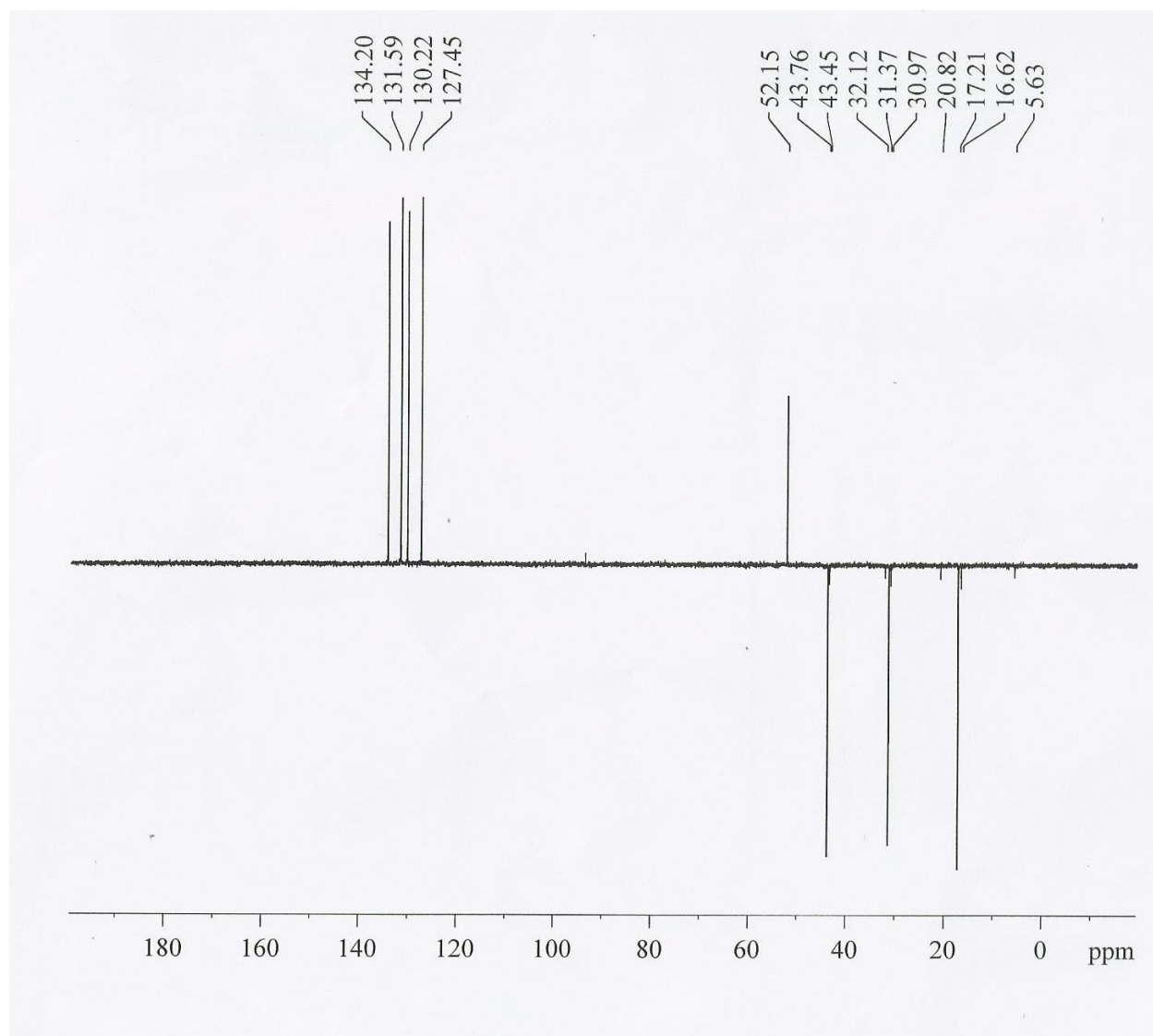


Fig 3.20: ^1H NMR of methyl 5-chloro-2-(2-phenylethyl)benzoate

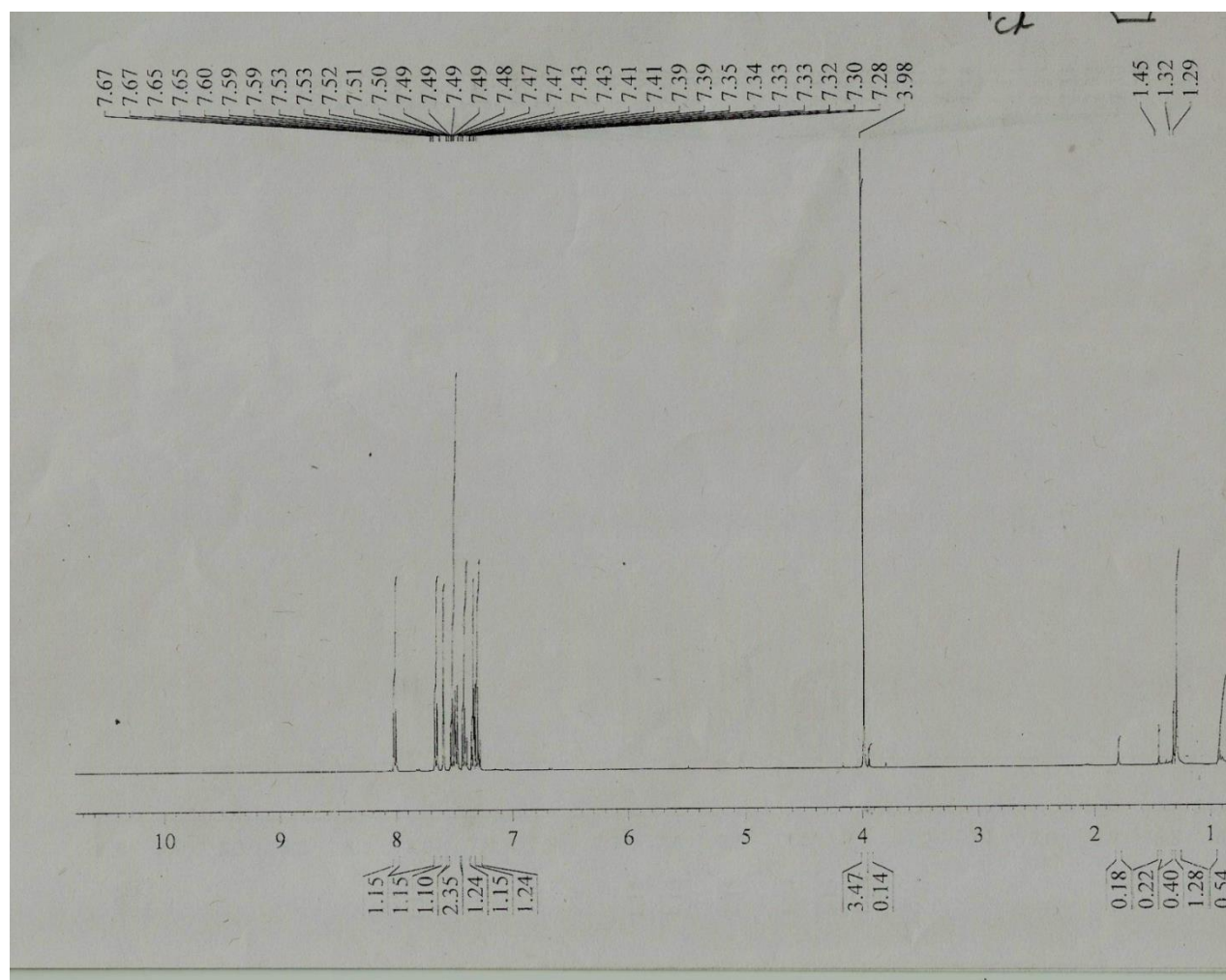


Fig 3.21: ^{13}C NMR of methyl 5-chloro-2-(2-phenylethyl)benzoate

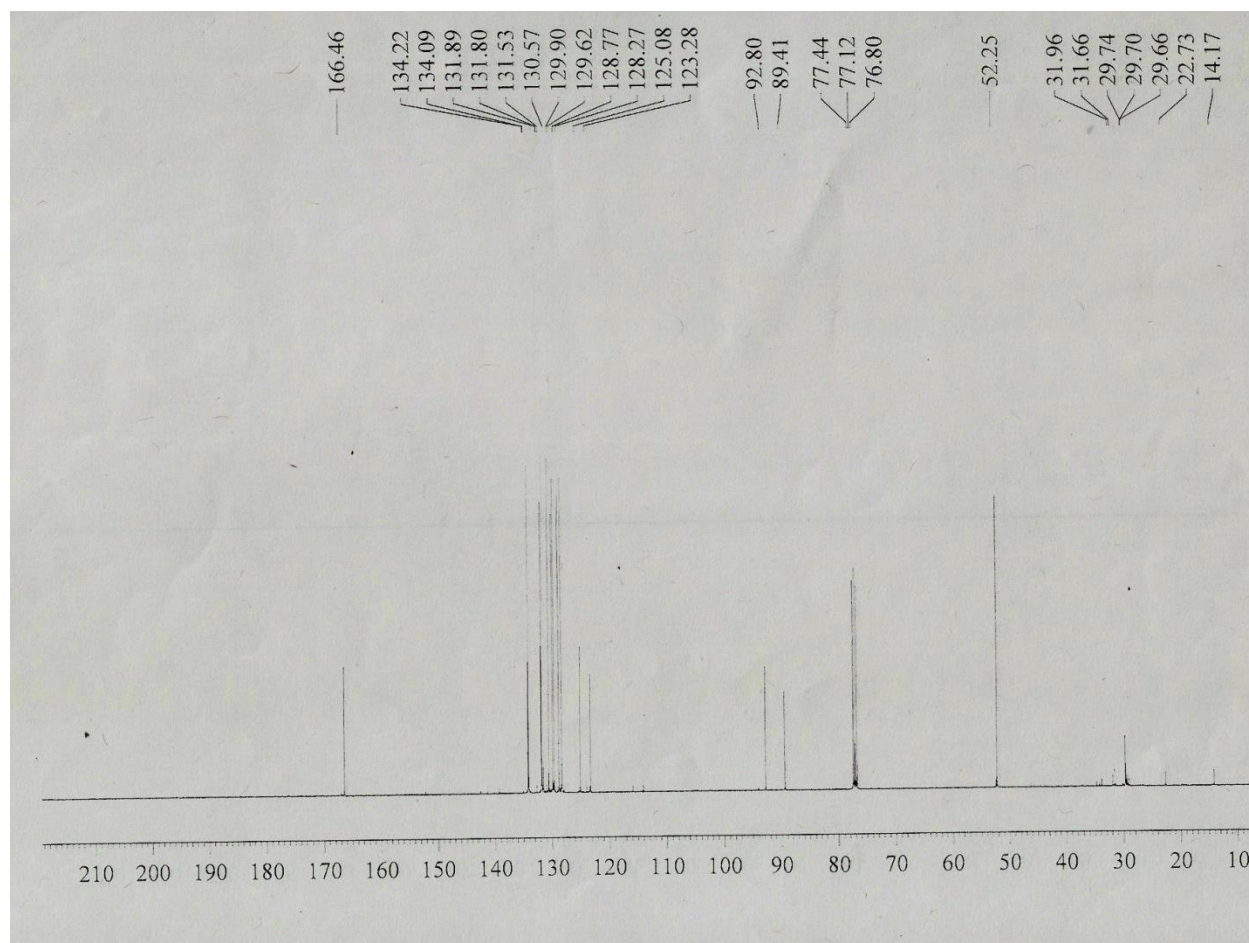


Fig 3.22: ^{13}C Dept. of methyl 5-chloro-2-(2-phenylethyl)benzoate.

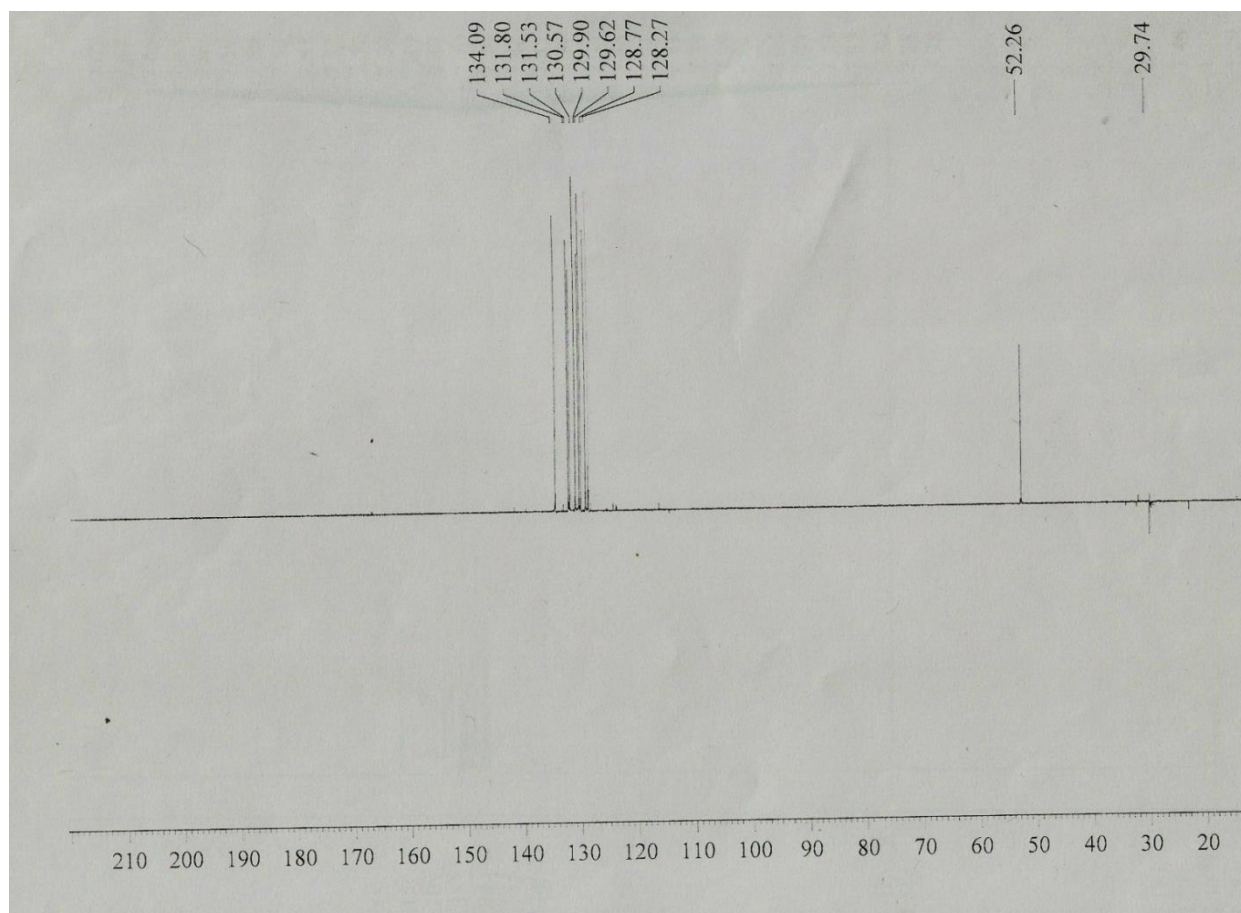


Fig 3.23: ^1H NMR of ethyl 2-(2-(3-chlorophenyl)ethynyl)benzoate

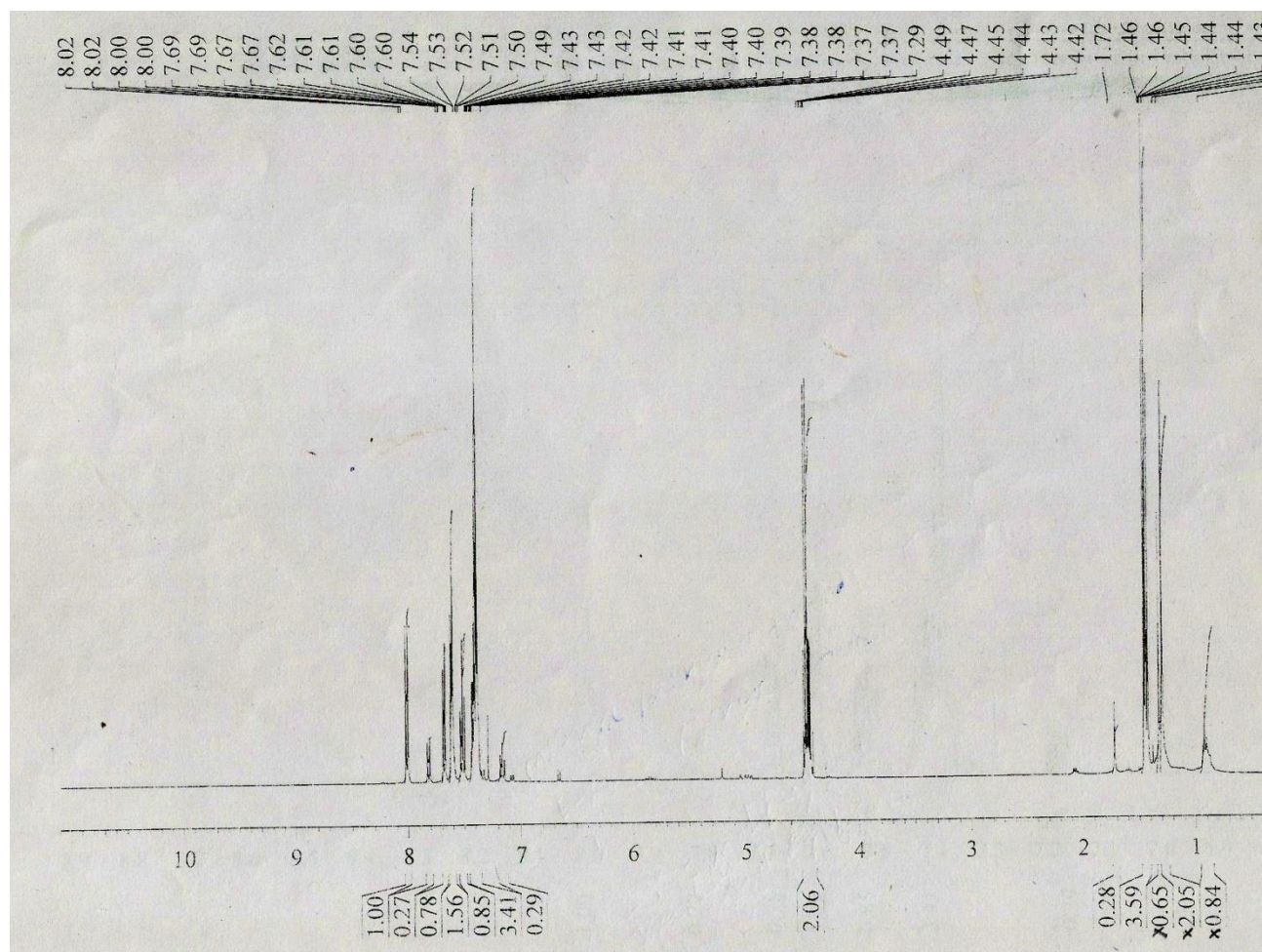


Fig 3.24: ^{13}C NMR of ethyl 2-(2-(3-chlorophenyl)ethynyl)benzoate

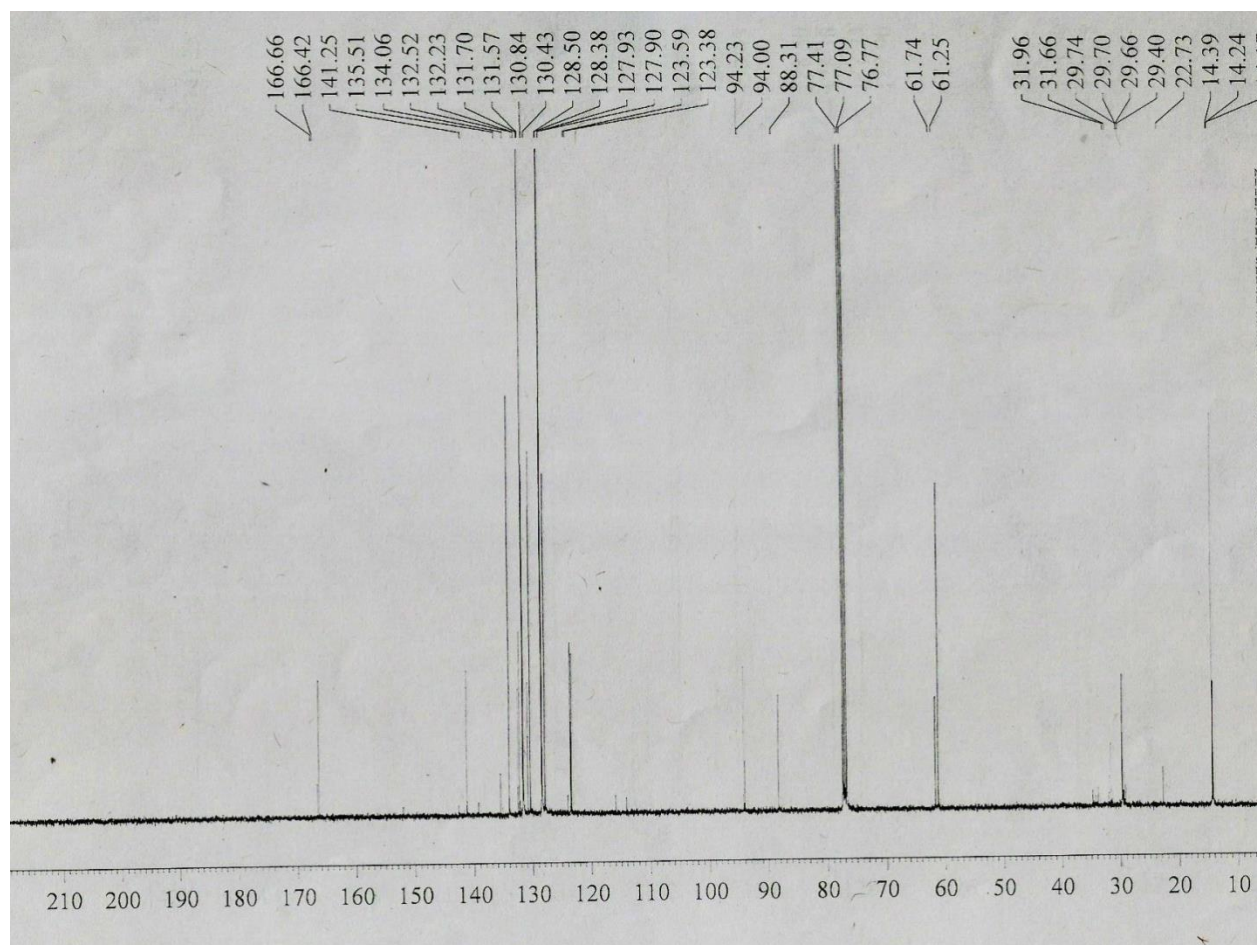


Fig 3.25: ^{13}C Dept of ethyl 2-(2-(3-chlorophenyl)ethynyl)benzoate

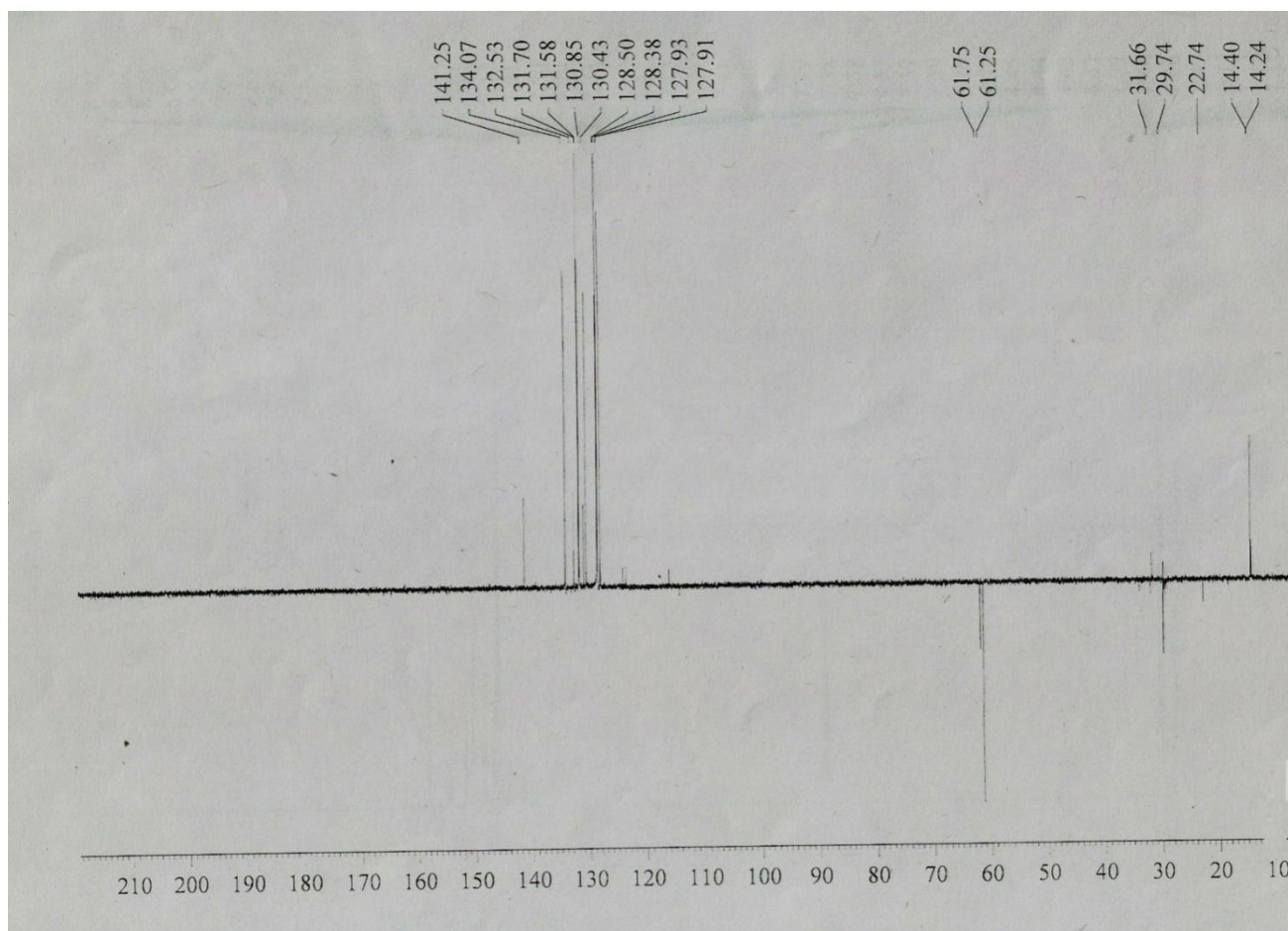


Fig 3.26: ^1H NMR of Butyl 2-(oct-1-yn-1-yl) benzoate

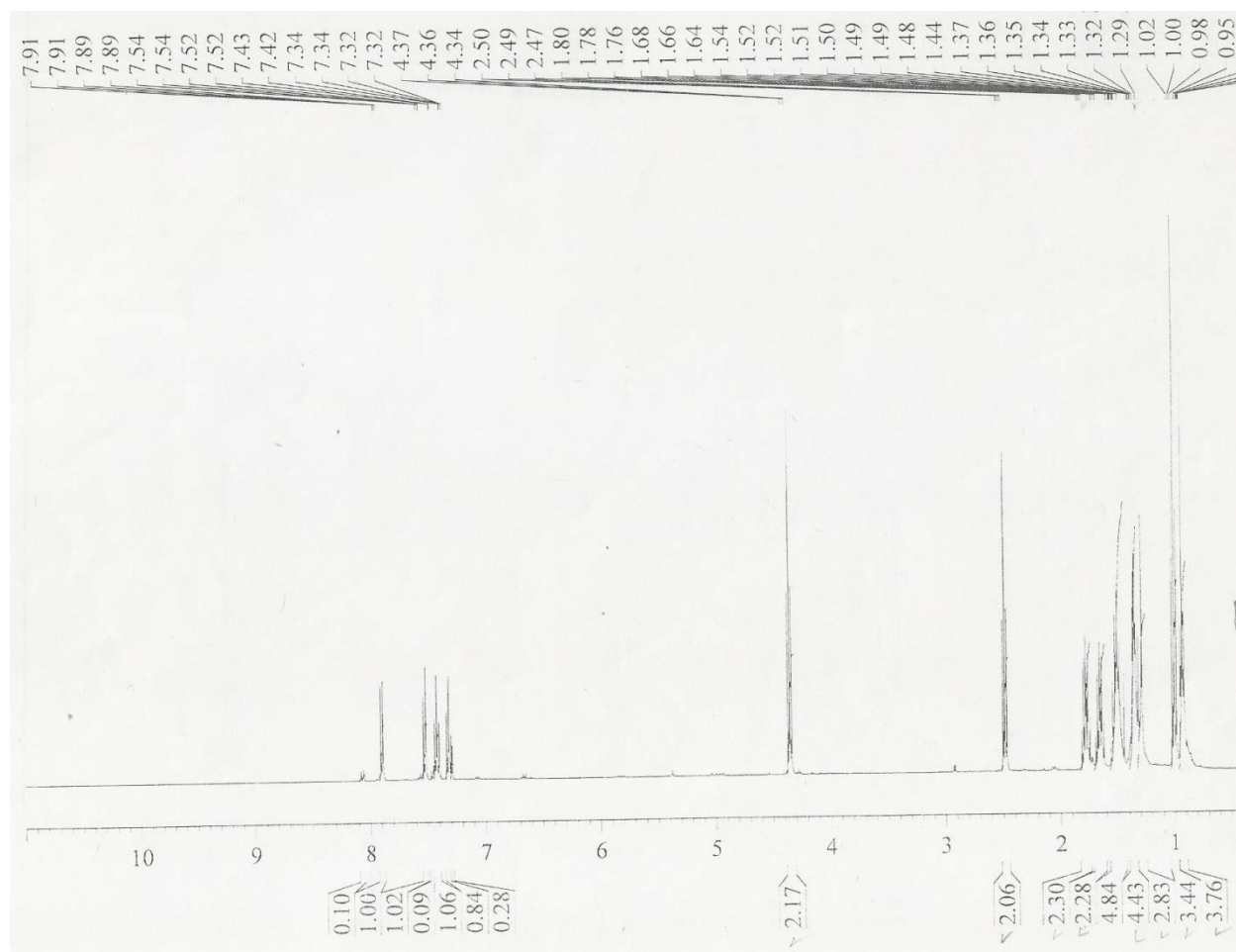


Fig 3.27: ^{13}C NMR of Butyl 2-(oct-1-yn-1-yl) benzoate

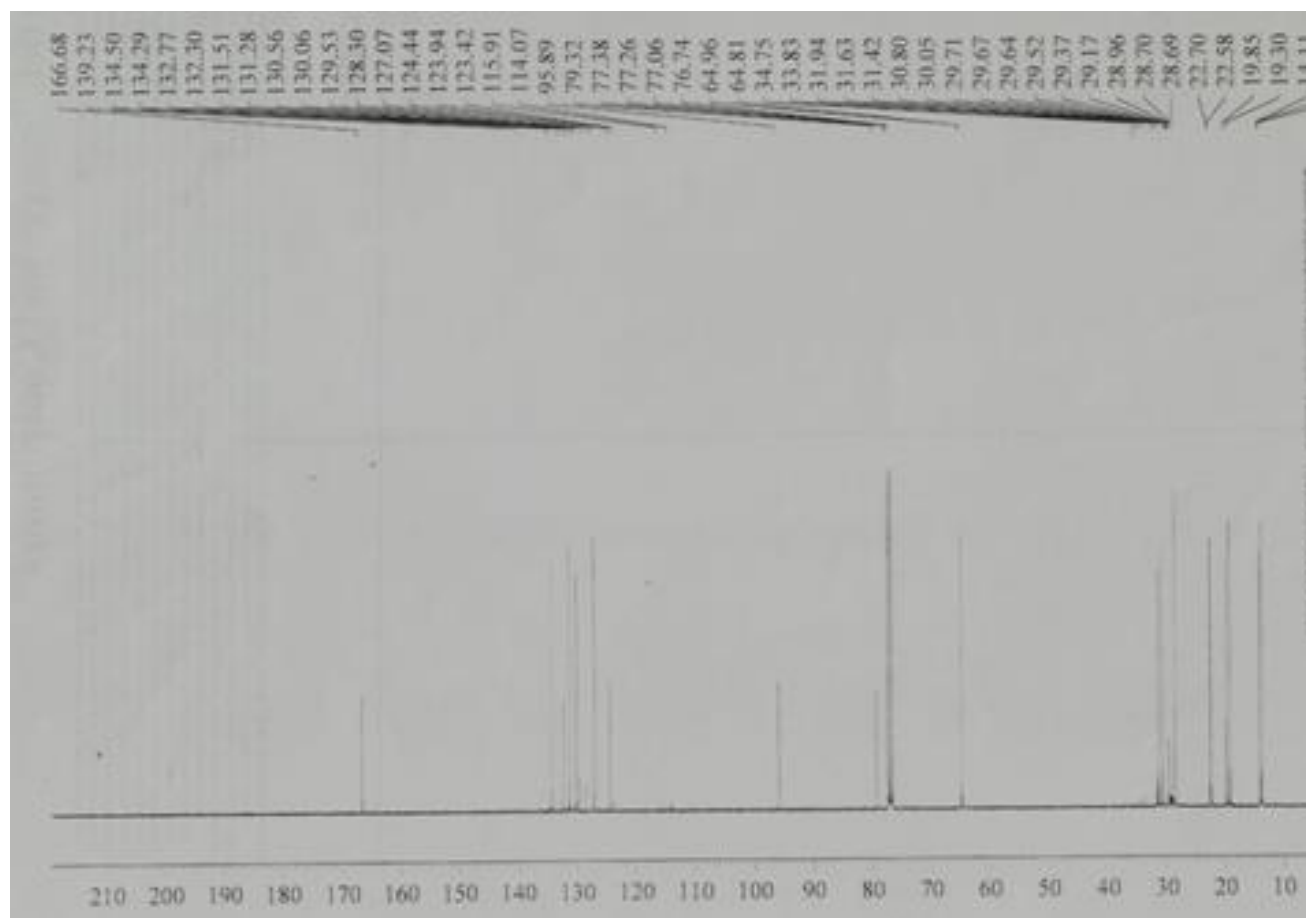


Fig 3.28: ^{13}C Dept of Butyl 2-(oct-1-yn-1-yl) benzoate

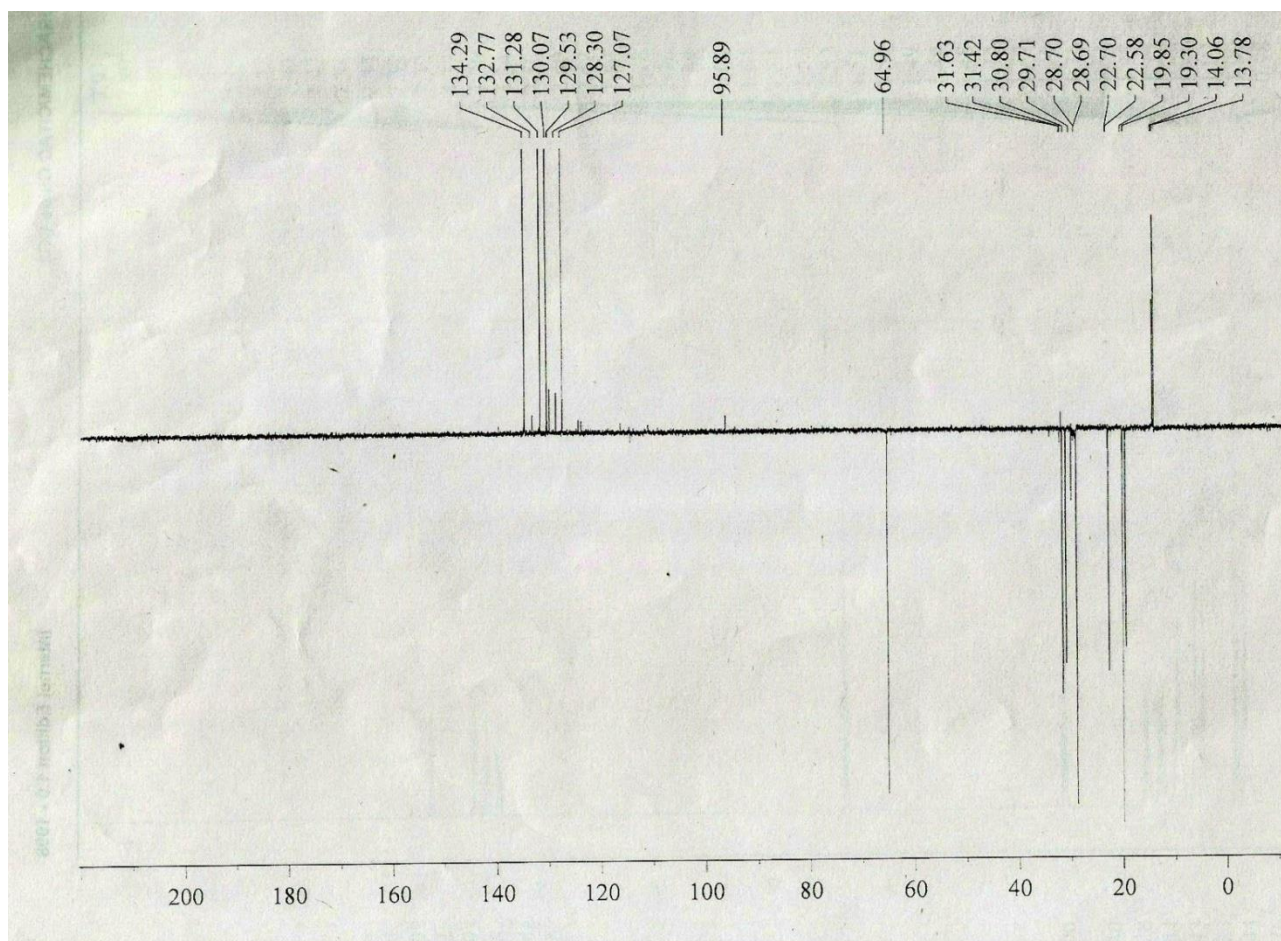


Fig 3.29: ^1H NMR of butyl 2-(2-phenylethynyl) benzoate

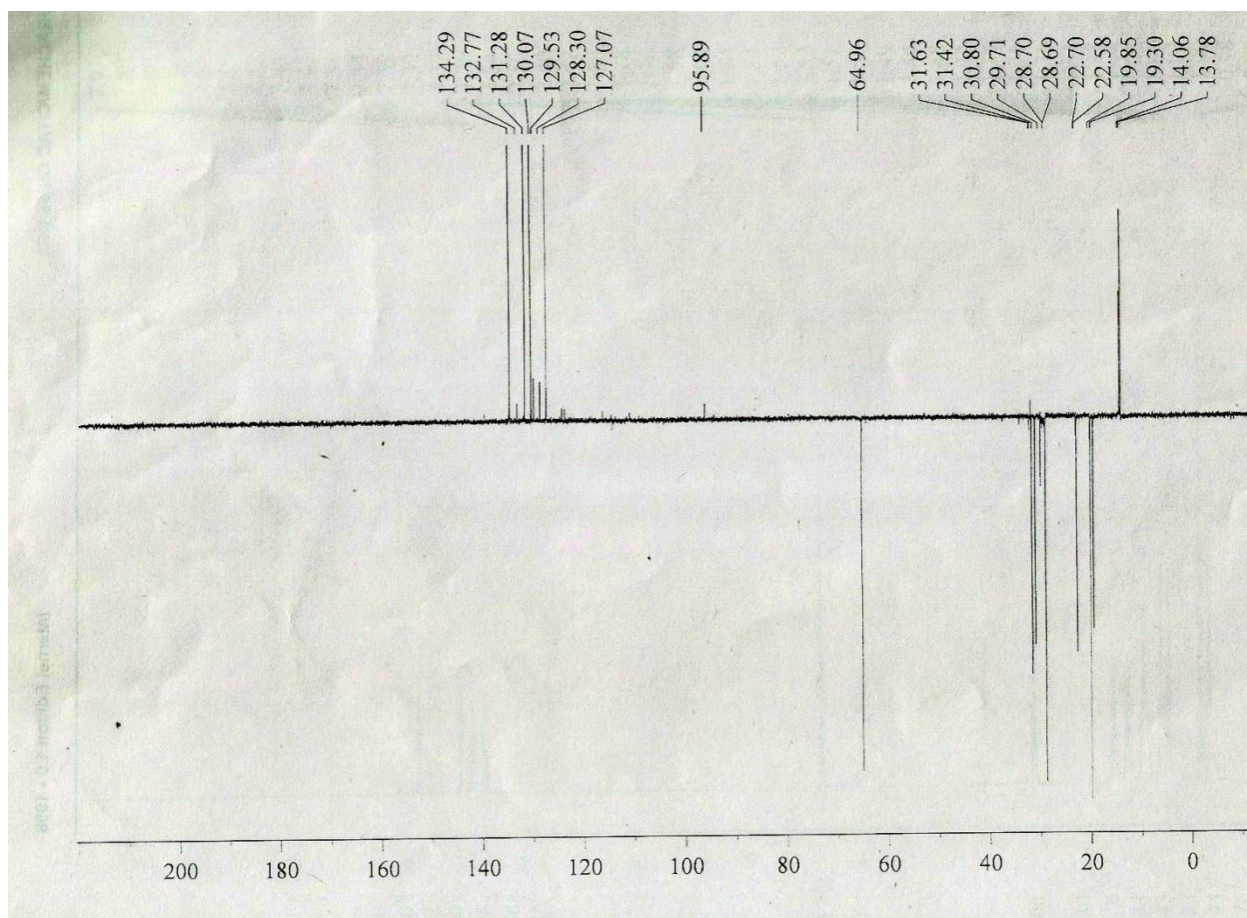


Fig 3.30: ^{13}C NMR of butyl 2-(2-phenylethynyl) benzoate

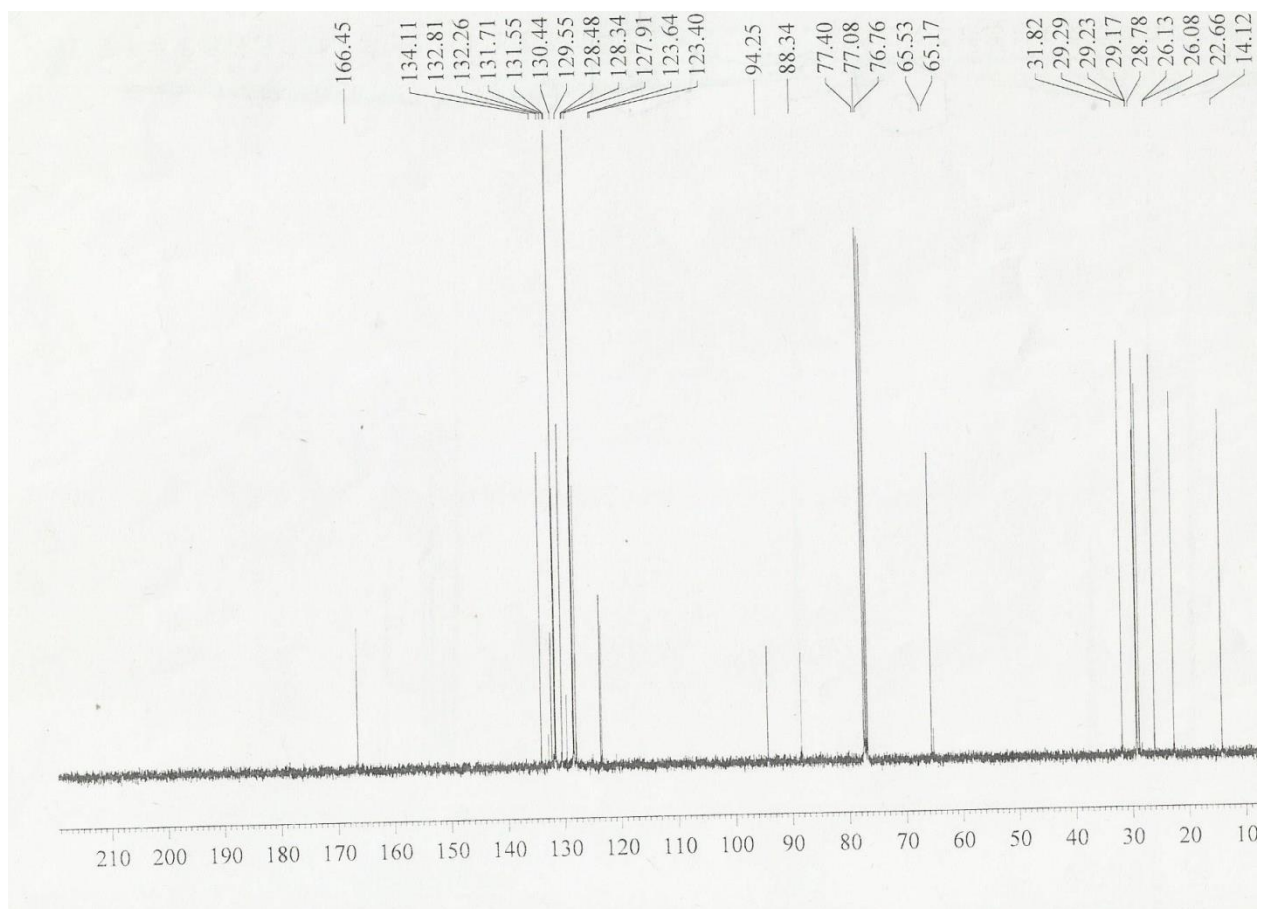


Fig 3.31: ^{13}C Dept of butyl 2-(2-phenylethynyl) benzoate

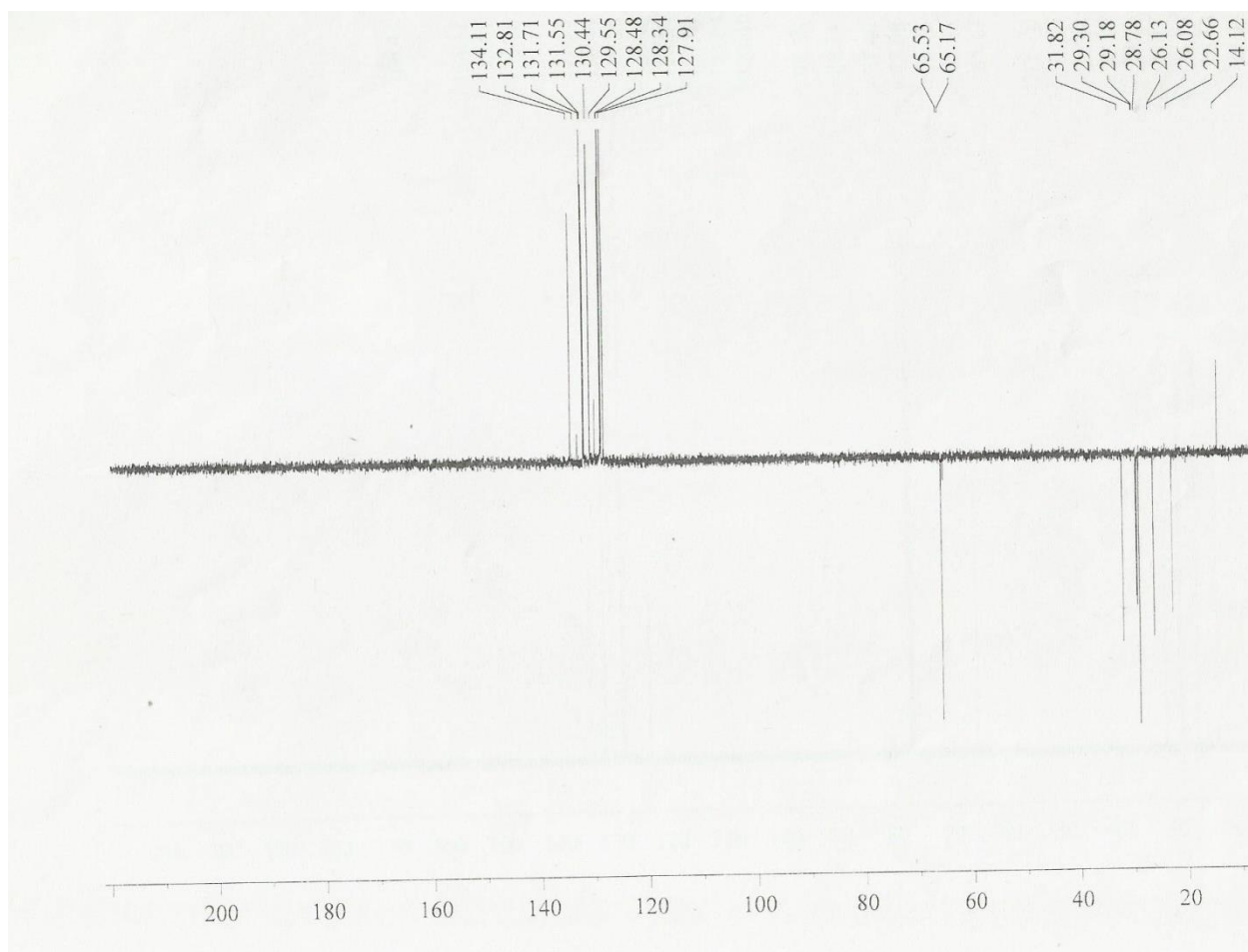


Fig 3.32: ¹H NMR of 1-nitro-4-(oct-1-ynyl) benzene

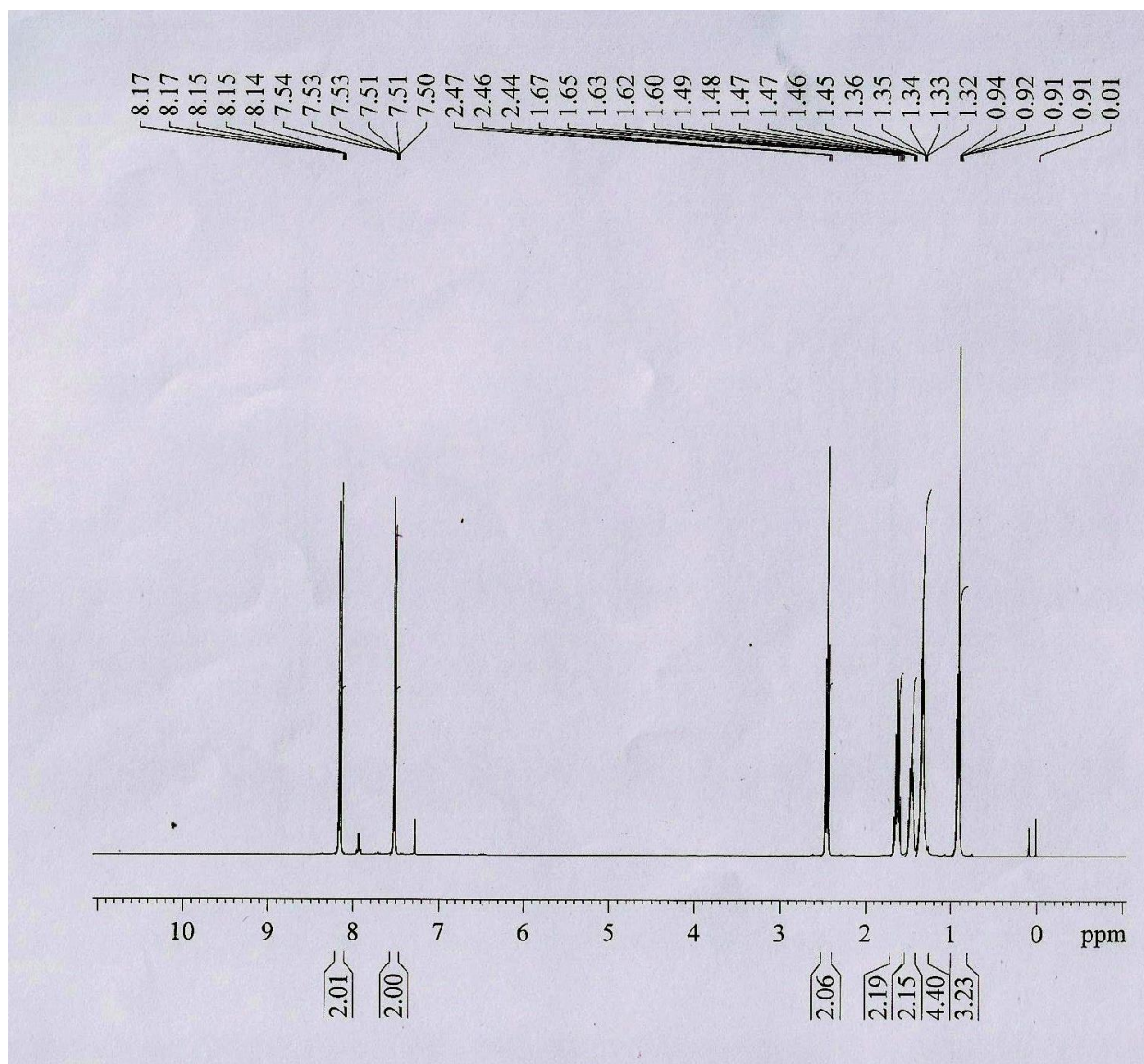


Fig 3.33 ^{13}C NMR of 1-nitro-4-(oct-1-ynyl) benzene

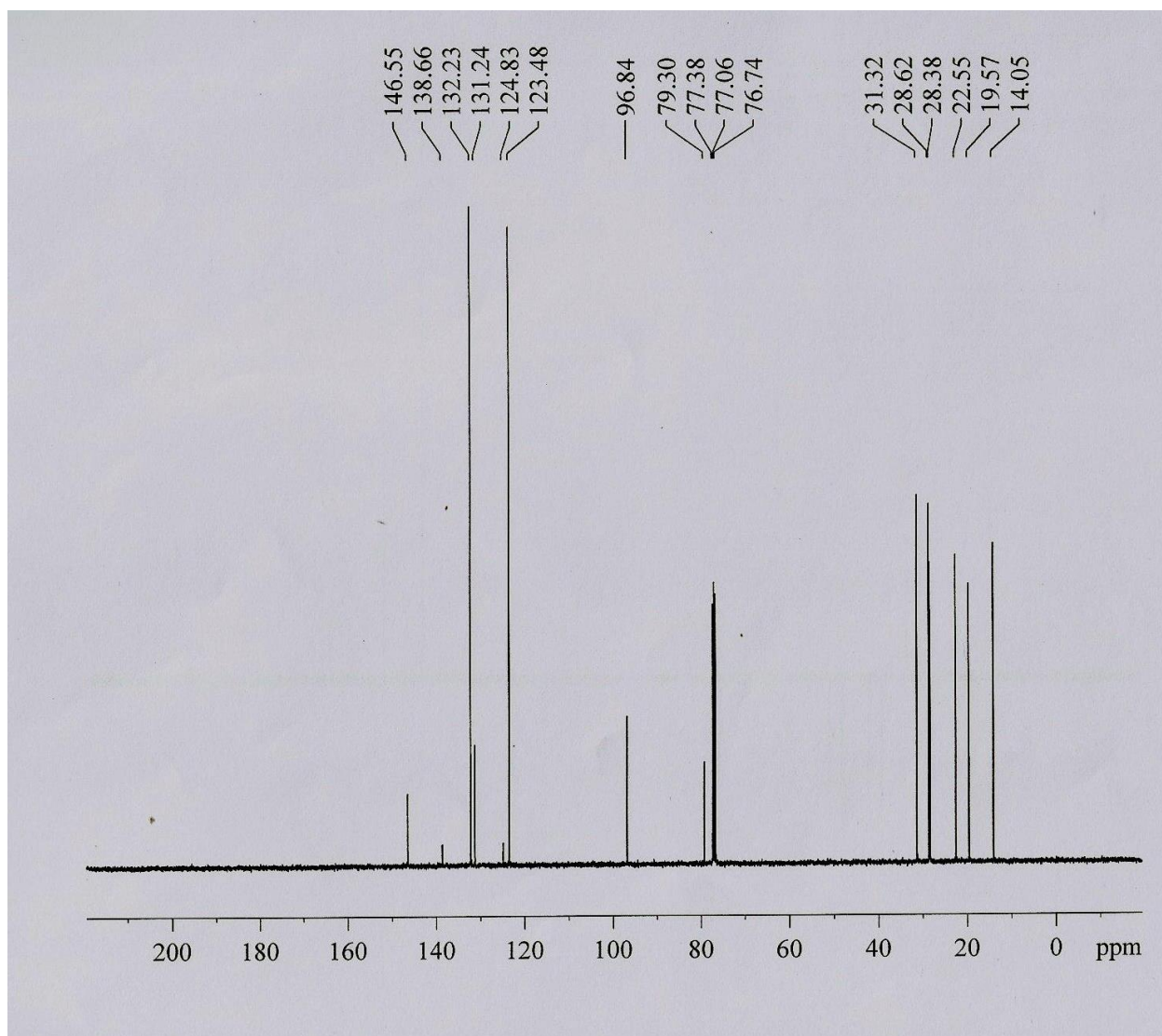


Fig 3.34 ^{13}C Dept of 1-nitro-4-(oct-1-ynyl) benzene.

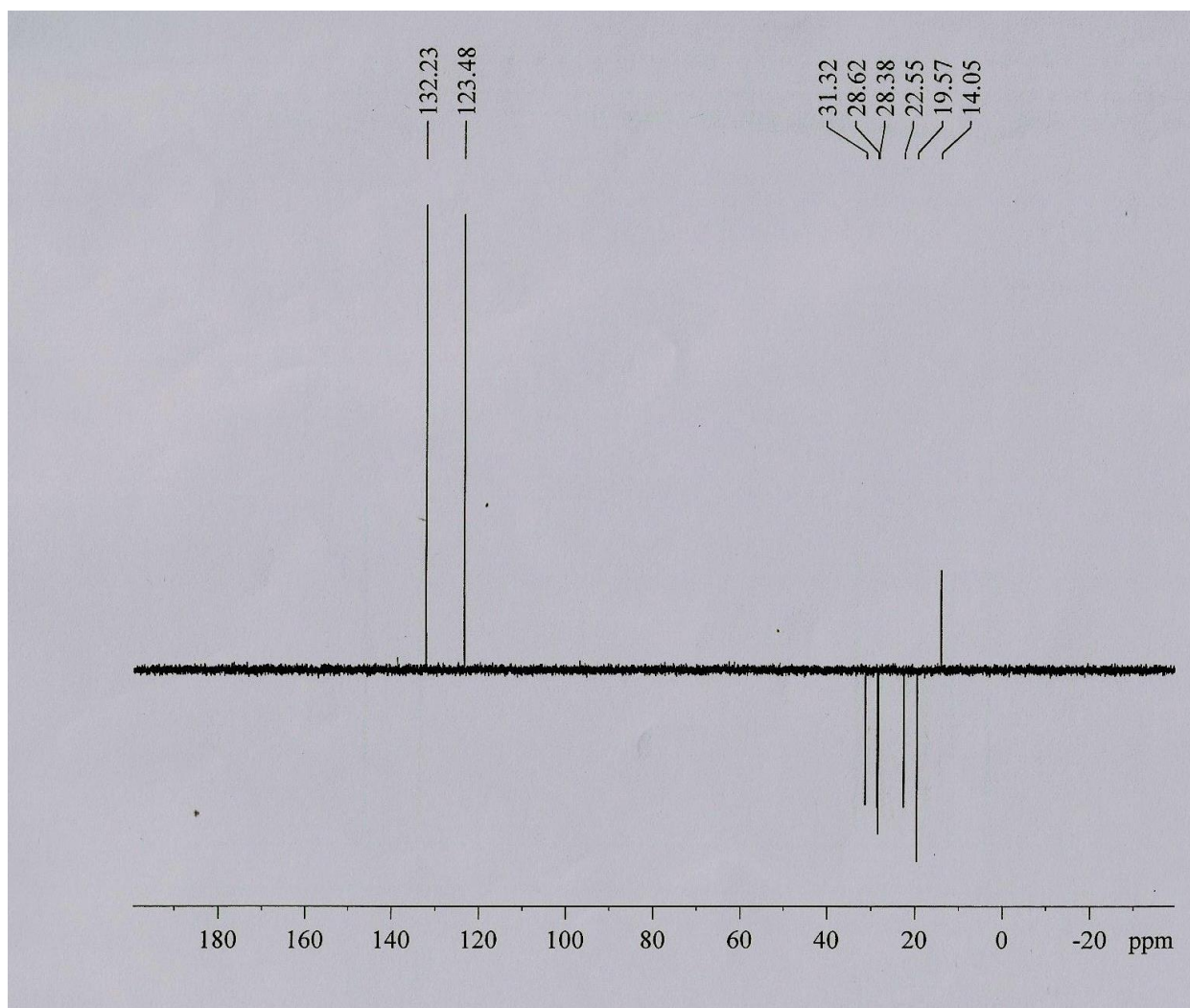


Fig 3.35 ¹H NMR of 2-methylpropyl 2-(oct-1-yn-1-yl)benzoate.

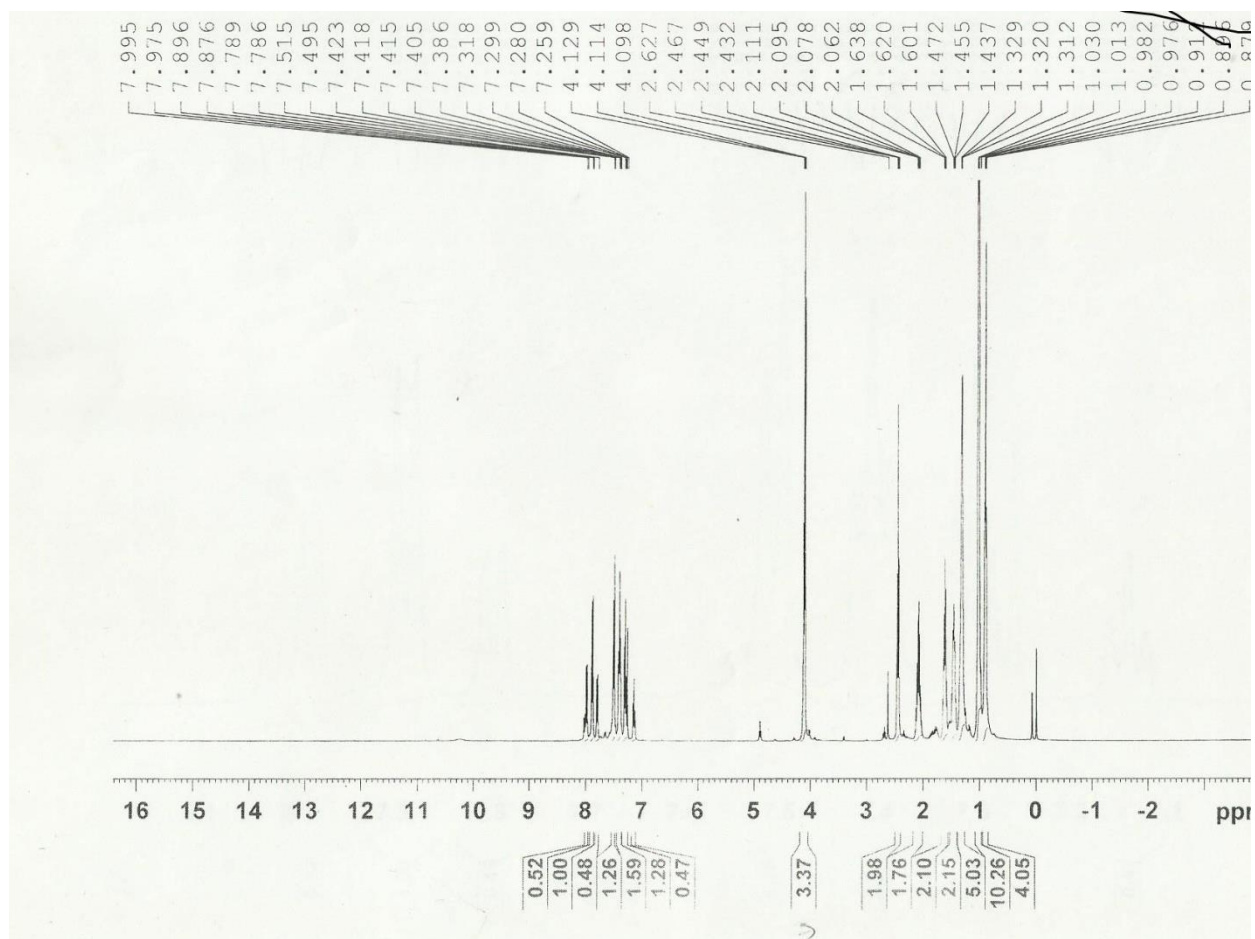


Fig 3.36 ^1H NMR of 2-methylpropyl 2-(phenyl ethynyl)benzoate.

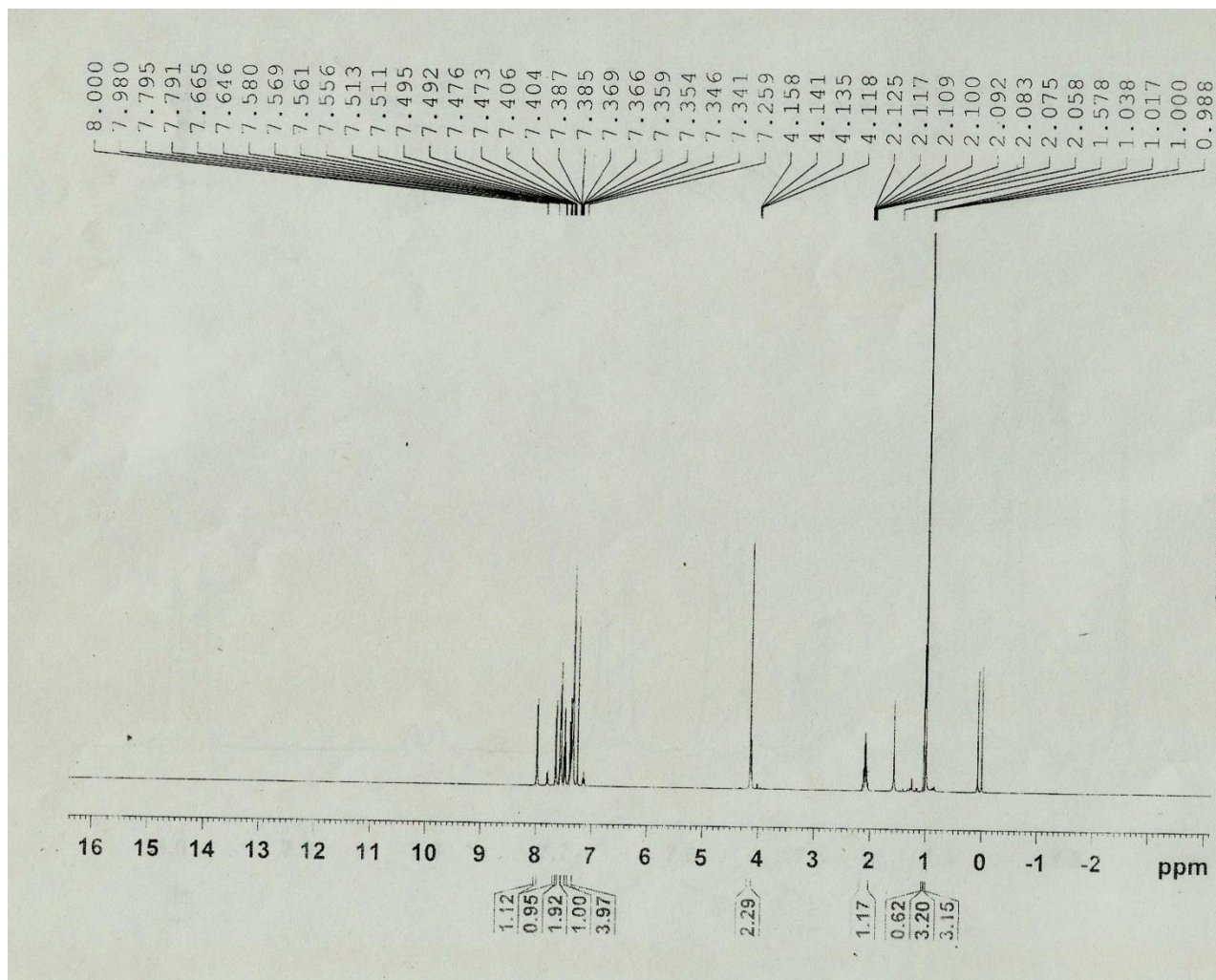


Fig 3.37 ^1H NMR of Butan-2-yl 2-(phenyl ethynyl)benzoate

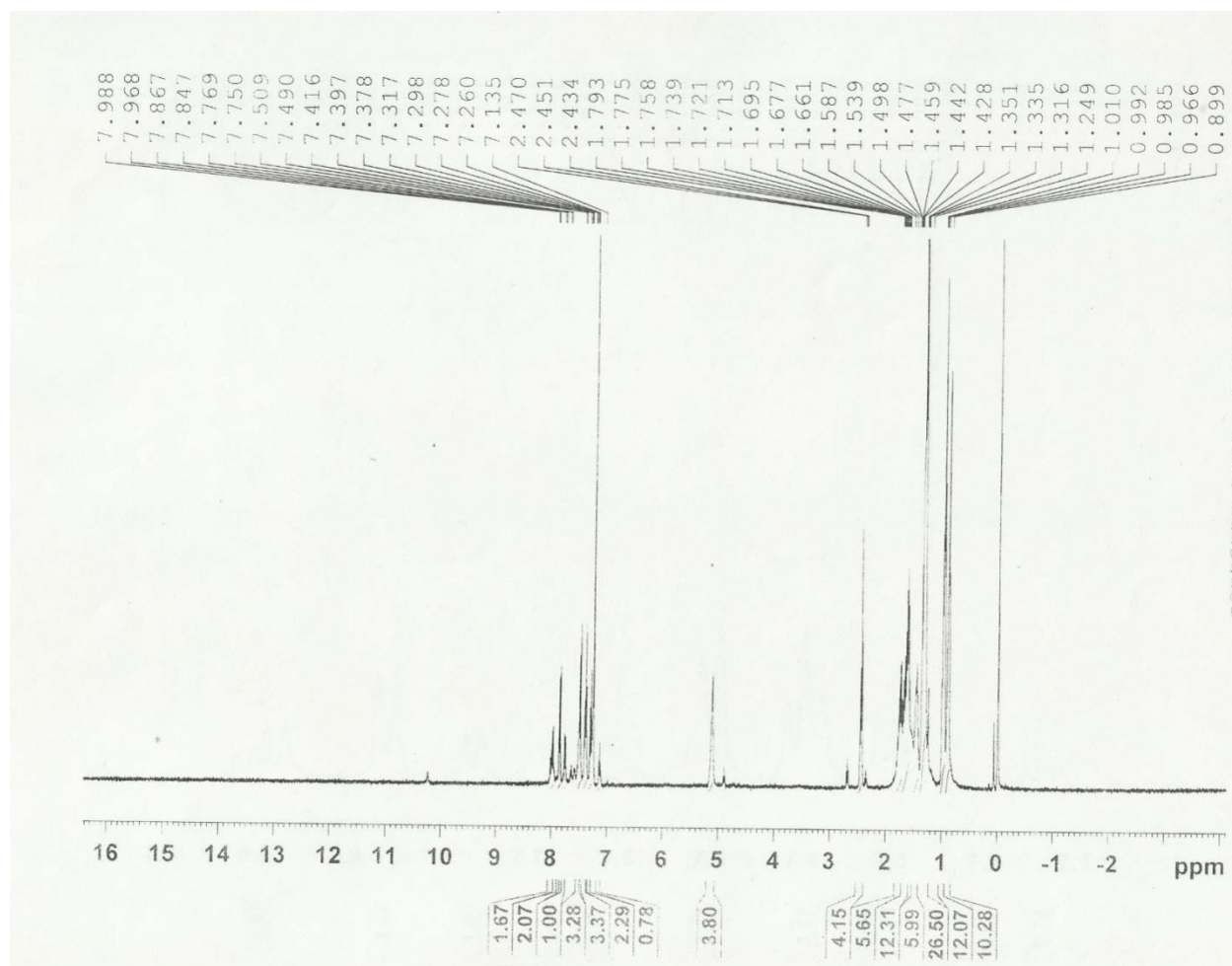


Fig 3.38 ¹H NMR of butan-2-yl 2-(phenyl ethynyl)benzoate

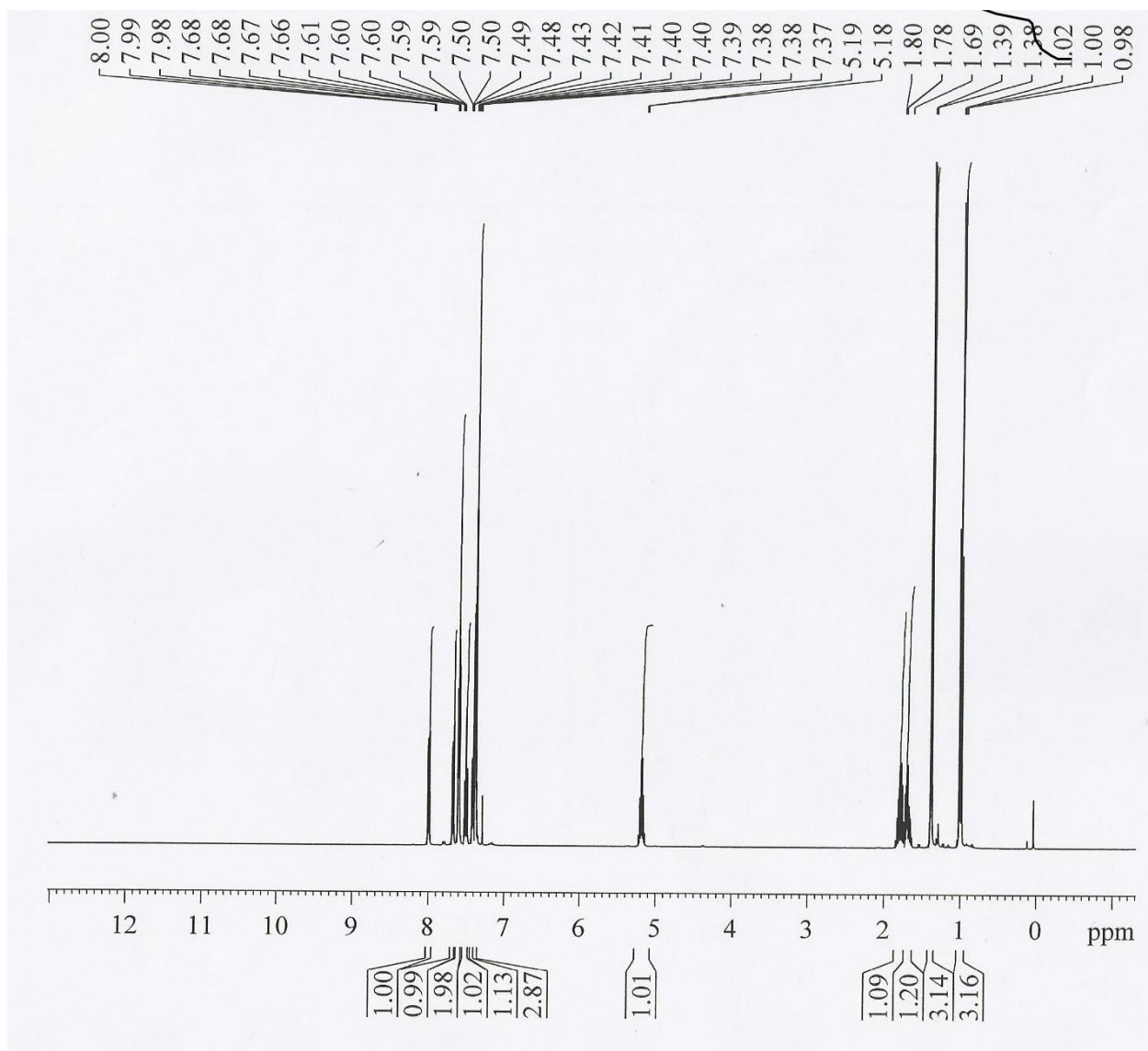


Fig 3.39: ^{13}C NMR of butan-2-yl 2-(phenyl ethynyl)benzoate

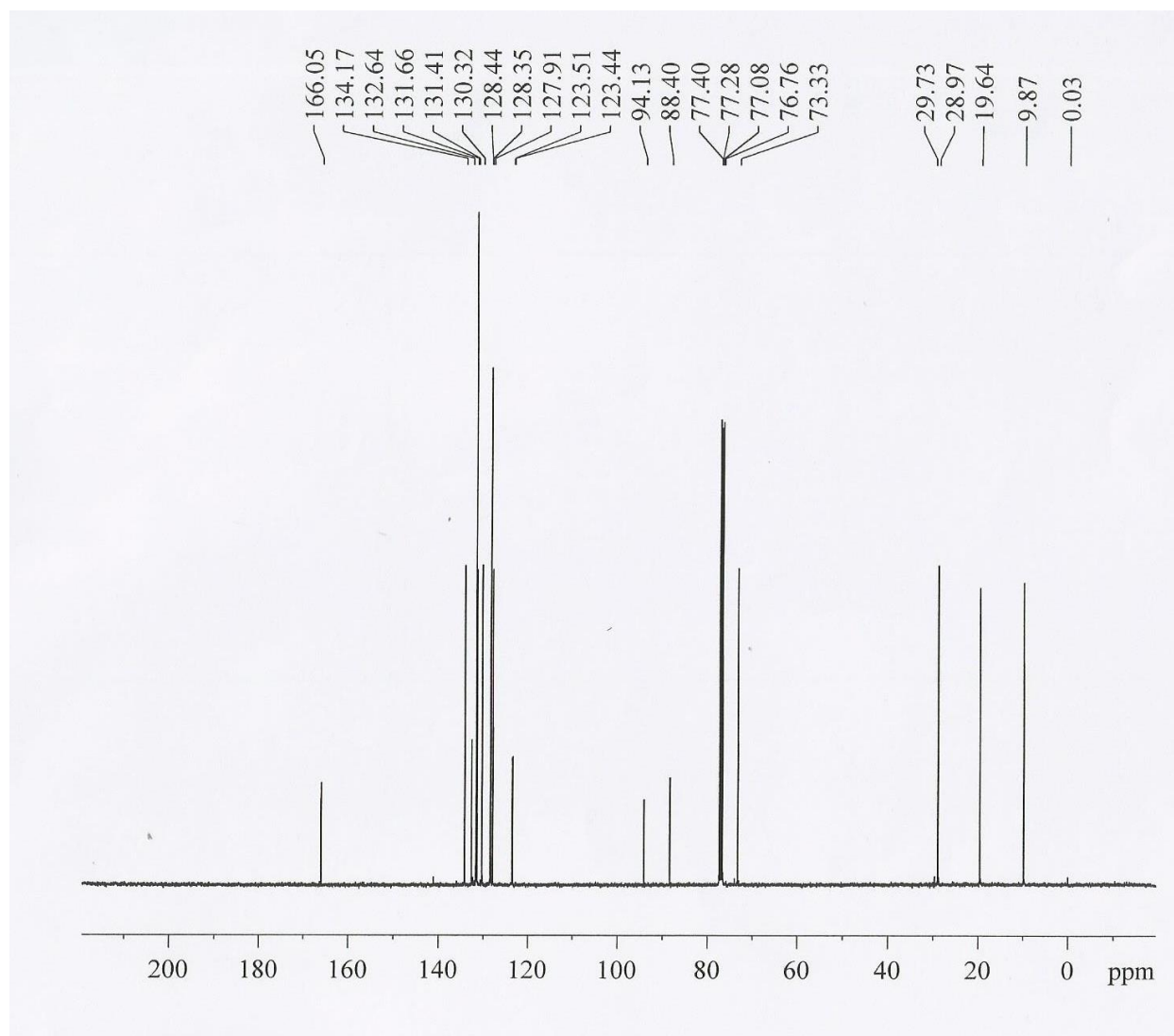
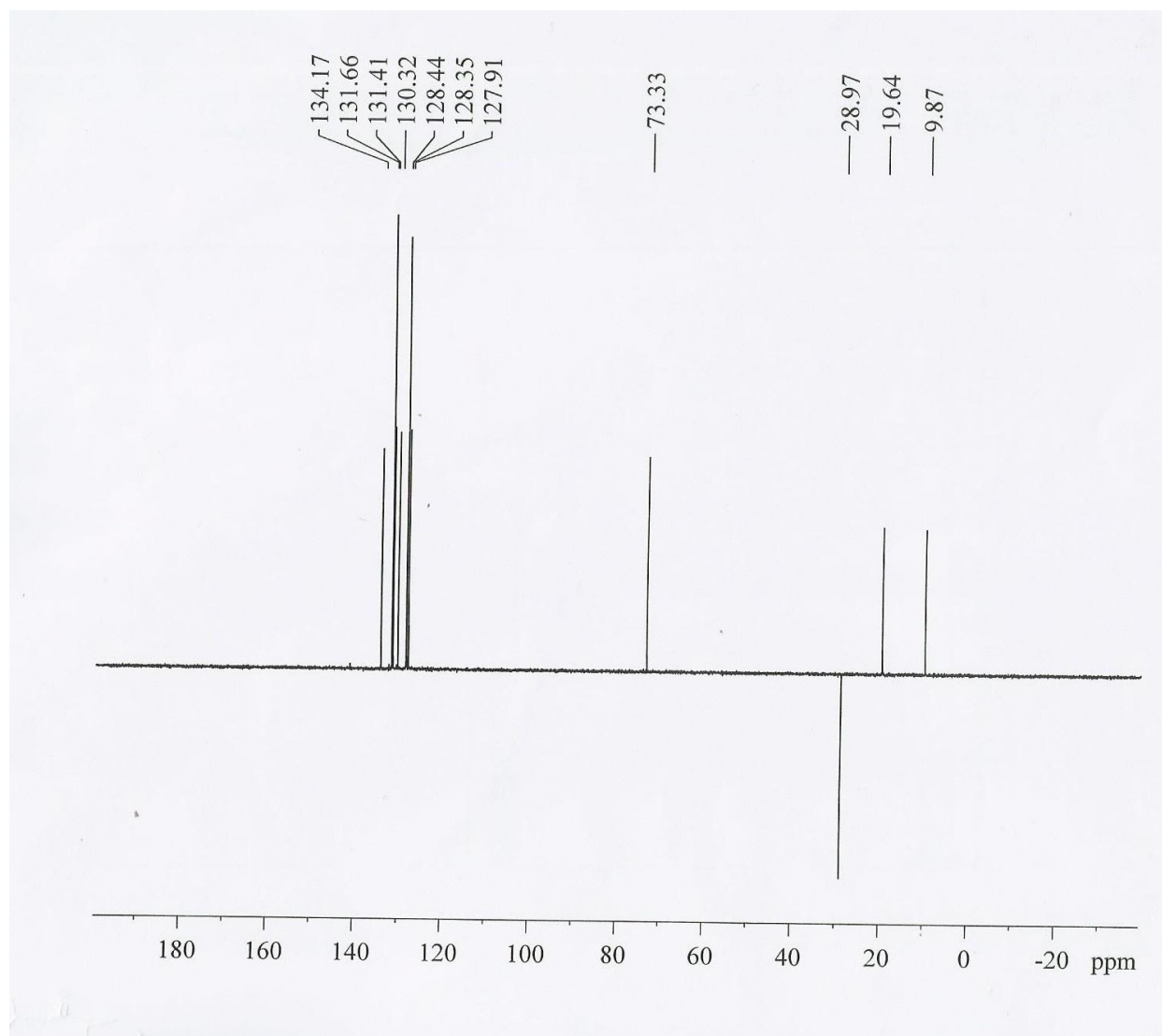


Fig 3.40 ^{13}C Dept. of butan-2-yl 2-(phenyl ethynyl)benzoate



3.2. INDUSTRIAL SCALE PROCESS DEVELOPMENT OF $\text{CuI}(\text{PPh}_3)_3$ AND ITS APPLICATION IN SONOGASHIRA COUPLING REACTION:

A new simplest industrially applicable, inexpensive, ecological process developed for preparation of $\text{CuI}(\text{PPh}_3)_3$ and explored its activity in Sonogashira Coupling reaction of aryl iodides with phenyl and hexyl acetylenes in solvent free condition. This reaction furnished disubstituted alkynes in good yield and tolerated many functional groups. Moreover, it is simple method involving green approach.

To avoid costly, poisonous palladium catalyst, many attempts have been developed by several groups [153-155] but the difficulties in the reaction were the poor solubility of copper salt in organic solvents. Ramaiyer Venkatraman et. al. [156] also prepared the copper catalyst in somewhat good results. Zhenning Yu et. al. [157] reported the catalyst in chloroform which is not industrially useful solvent. In both the above papers the system is neither environmental friendly nor industrially viable. Only 1/26 of acetonitrile have been used for the preparation of $\text{CuI}(\text{PPh}_3)_3$ compare with reported process which support system close to green process.



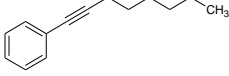
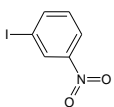

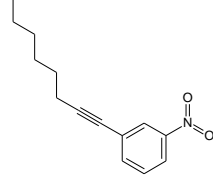
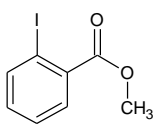

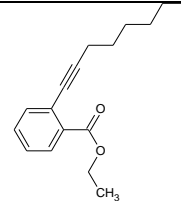
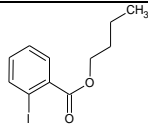

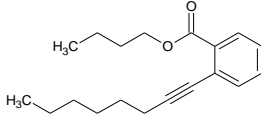
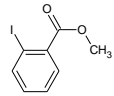
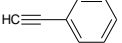
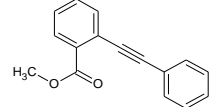


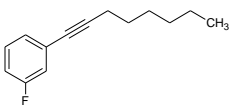
3.2.1 General process for preparation of $\text{CuI}(\text{PPh}_3)_3$

3 mole equivalents of triphenylphospine was dissolved in 5 volume of solvent at 80°C and 1 mole equivalents of copper iodide was added under stirring. Reaction mass was cooled to 25°C and filtered the solid which dried under vacuum at 50°C

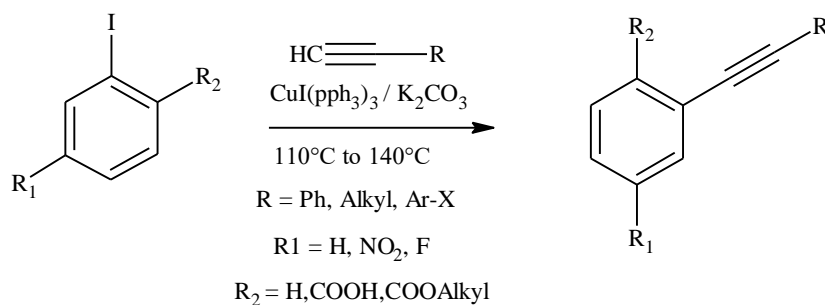
3.2.2 Experimental process for preparation of aryl or alkyl 2-(oct-1-yn-1-yl)benzoate

A mixture of iodoarenes (10 mmol), 1-alkyne or 1-aryne (12 mmol), potassium carbonate (10 mmol), $\text{CuI}(\text{PPh}_3)_3$ 10mole % was stirred on oil bath at 120°C for 6 hrs. The progress of the reaction monitored on TLC. Dichloromethane was added and catalyst and base was removed by filtration and the crude product purified by silica column chromatography.

Table -3.3 Preparation of Substituted internal alkynes using CuI(PPh₃)₃.

Sr. No.	Iodobenzoate	Alkynes	Substituted Alkynes	Yield
1				81%
2				79%
3				93%
4				95%
5				91%
6				67%

Schem-3.2 Preparation of Substituted internal alkynes using CuI(PPh₃)₃



3.2.3 ¹H NMR, ¹³C NMR Alkyl benzoate.

3.2.3.1 Oct-1-yn-1-ylbenzene

¹H NMR (400 MHz, CDCl₃) δ 0.96 (3H, t, J=8), 1.37(4H, m), 1.48(2H, m), 1.66(2H, m), 2.45 (2H, t, J=8), 7.31(3H, m), 7.45(2H, m).

3.2.3.2 1-Nitro-3-(oct-1-yn-1-yl)benzene

¹H NMR (400 MHz, CDCl₃) δ 0.93(3H, t, J=4), 1.36 (4H, m), 1.48(2H, m J=8), 1.63(2H, m, J=8), 2.45(2H, t, J=8), 7.48(1H, dd, J=4), 7.71(1H, J=4), 7.13 (1H, d, J=4), 8.25(1H, J=4), ¹³C NMR (100MHz, CDCl₃) δ 14.07, 19.39, 22.56, 28.45, 31.06, 78.51, 93.67, 122.22, 126.40, 129.13, 130.7, 132.46, 143.48, 148.08.

3.2.3.3 Methyl 2-(oct-1-yn-1-yl)benzoate.

¹H NMR (400 MHz, CDCl₃) δ 0.96(3H,t),1.53(4H m),1.67(4H, m J=8),2.51(2H, t J=4),3.95(3H, s), 7.31(1H m J=8),7.43(1H, q, J=8),7.55(1H, d J=8),7.92(1H, J=8) ¹³C NMR (100 MHz, CDCl₃)δ 14.09, 19.73, 22.68, 28.00, 29.19, 31.63, 52.06, 79.22, 96.09, 123.49, 127.10, 134.24, 131.48, 135.17, 141.35, 167.05.

3.2.3.4 Butyl 2-(oct-1-yn-1-yl)benzoate.

¹H NMR (400 MHz, CDCl₃) δ 0.93 (3H, J=4), 1.01(3H, J=4), 1.35(4H, m), 1.48(4H, m), 1.68(2H, q, J=8) 1.78(2H, q, J=8), 2.49(2H, t, J=8), 7.32(1H, t, J=8), 7.42(1H, t, J=4) 7.54(1H, t, J=4),7.91(1H, d, J=8).¹³C NMR (100MHz,CDCl₃) δ 13.74,14.11,19.30,19.85, 22.58, 28.70, 29.71, 30.80, 31.42, 64.96, 79.32, 95.89, 123.42, 127.07, 129.53, 131.28, 134.29, 139.23, 166.68.

3.2.3.5 Methyl 2-[(3-chlorophenyl)ethynyl]benzoate

¹H NMR (400 MHz, CDCl₃) δ 3.98(3H, s), 7.32(1H, m), 7.41(1H, m), 7.48(1H, m), 7.59(1H, m), 7.67(1H, m), 8.02(1H, m) ¹³C NMR (100MHz, CDCl₃) 52.25, 89.41, 92.80, 123.28, 125.08, 128.27, 128.77, 129.62, 129.90, 130.57, 131.53, 131.80, 131.89, 134.09, 134.22, 166.46.

3.2.3.6 1-Fluoro-3-(oct-1-yn-1-yl)benzene

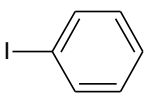
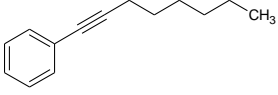
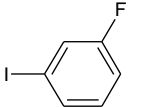
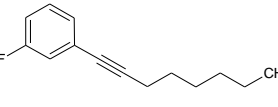
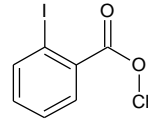
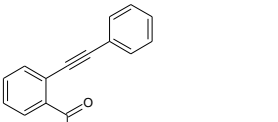
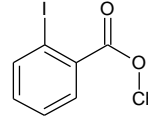
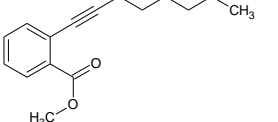
¹H NMR (400 MHz, CDCl₃) δ 0.94(3H, t) 1.43(2H, m), 1.58 (2H, m), 1.65(2H, m), 2.27(2H, t J=8), 2.44(2H, t J=8), 7.00(1H, m), 7.1(1H, m), 7.2(1H, m), 7.3(1H, m), ¹³C NMR (100MHz, CDCl₃) δ 14.07, 19.19, 19.38, 22.58, 28.61, 31.71, 79.84, 91.66, 114.67, 114.88, 118.24, 118.46, 127.42, 131.27.

3.3 PREPARATION OF (Z)-5-((2-MERCAPTOPHENYLIMINO)METHYL)-2-METHOXY PHENOL COPPER COMPLEX AND ITS USE FOR PALLADIUM FREE COUPLING OF ARYL IODIDE AND ALKYNES.

The drawbacks of the Pd catalyst systems, such as high cost and toxicity [158-160] in this way, the use of a cheaper metal instead of Pd provides another attractive route. [161] of these, copper-based alternatives are particularly attractive, due to their orders of magnitude lower cost and harmfulness to the environment than any noble metal. [162-163] although copper catalysts have been used in many cross-coupling transformations, surprisingly; there are only few publications on the use of such reagents for the reactions. [164] Herein we report a simple protocol for the preparation of substituted alkynes using (Z)-5-((2-mercaptophenyl imino)methyl)-2-methoxyphenol. Legad and its copper complex

(Z)-5-((2-mercaptophenylimino)methyl)-2-methoxy phenol legad prepared and characterized using H^1NMR , $^{13}CNMR$ and prepared its copper complex with CuBr. Using this complex palladium free protocol developed for preparation Substituted Alkynes avoiding Poisonous Pd Catalytic System with good yield. Reaction closes to the green approach.

Table 3.4 Reaction of different substituted aryl halide and different alkynes.

Entry	Iodo Arenes	Terminal Alkynes	Product	Yield %
1		$H_3C(CH_2)_6C\equiv CH$		71%
2		$HC\equiv C(CH_2)_6CH_3$		68%
3		$HC\equiv C-C_6H_5$		79 %
4		$H_3C(CH_2)_6C\equiv CH$		81%

5				73%
6				63%
7				83%
8				78%

3.3.1 Preparation of (Z)-5-((2-mercapto phenyl imino)methyl)-2-methoxyphenol legend

Charged 2 gm of vanillin and 1.6 gm 2-amino thiophenol in 50 ml ethanol, cat. amount of acetic acid was added and reaction mass was heated to reflux for 5 hrs. The reaction mass was concentrated to half of the total volume and stirred for 20 min. at 25°C. Filtered the reaction mass and washed the product with 2 ml ethanol. Dried under vacuum at 43°C

3.3.2 Preparation of (Z)-5-((2-mercapto phenylimino)methyl)-2-methoxy phenol Copper complex

Charged (1.00 mmol) of Copper bromide, (2.00 mmol) of Legend in 5 volume of ethanol and heated reaction mass for 2 hrs. Reaction mass cooled to 25°C and filtered the solid.

3.3.3 Typical process for preparation of substituted alkynes.

Charged (1.00 mmol) of Aryl halide, (2.00 mmol) of Alkynes and (0.1 mmol) of Cu Catalyst in a sealed tube and heated reaction mass under stirring at 110-120°C for required time TLC (1:10 Ethyl Acetate, n-Hexane). After completion of reaction product purified on silica column in (0.5:99.5 Ethyl acetate, n-Heptane)

3.3.4 ¹H NMR and ¹³C NMR data of Internal substituted alkynes.

3.3.4.1 Oct-1-yn-1-ylbenzene

¹H NMR (400 MHz, CDCl₃) δ 0.96 (3H, t, J=8), 1.37(4H, m), 1.48(2H, m), 1.66(2H, m), 2.45 (2H, t, J=8), 7.31(3H, m), 7.45(2H, m). ¹³C NMR (CDCl₃) δ 131.55, 128.19, 127.46, 124.10, 90.94, 80.55, 65.25, 31.41, 28.64, 22.61, 19.44, 14.1.

3.3.4.2 1-Fluoro-3-(oct-1-yn-1-yl)benzene.

¹H NMR (400 MHz, CDCl₃) δ 0.94 (3H, t) 1.43(2H, m), 1.58 (2H, m), 1.65(2H, m), 2.27(2H, t J=8), 2.44(2H, t J=8), 7.00(1H, m), 7.1(1H, m), 7.2(1H, m), 7.3(1H, m), ¹³C NMR (100MHz, CDCl₃) δ 14.07, 19.19, 19.38, 22.58, 28.61, 31.71, 79.84, 91.66, 114.67, 114.88, 118.24, 118.46, 127.42, 131.27.

3.3.4.3 Methyl 2-[(3-chlorophenyl)ethynyl] benzoate

¹H NMR (400 MHz, CDCl₃) δ 3.98(3H, s), 7.32(1H, m), 7.41(1H, m), 7.48(1H, m), 7.59(1H, m), 7.67(1H, m), 8.02(1H, m), ¹³C NMR (100MHz, CDCl₃) 52.25, 89.41, 92.80, 123.28, 125.08, 128.27, 128.77, 129.62, 129.90, 130.57, 131.53, 131.80, 131.89, 134.09, 134.22, 166.46.

3.3.4.4 Methyl 2-(oct-1-yn-1-yl)benzoate

¹H NMR (400 MHz, CDCl₃) δ 0.96(3H,t), 1.53(4H m), 1.67(4H, m J=8), 2.51 (2H, t J=4), 3.95(3H, s), 7.31(1H m J=8), 7.43(1H, q, J=8), 7.55(1H, d J=8), 7.92(1H, J=8) ¹³C NMR (100 MHz, CDCl₃) δ 14.09, 19.73, 22.68, 28.00, 29.19, 31.63, 52.06, 79.22, 96.09, 123.49, 127.10, 134.24, 131.48, 135.17, 141.35, 167.05

3.3.4.5 Butyl 2-(oct-1-yn-1-yl)benzoate

¹H NMR (400 MHz, CDCl₃) δ 0.93 (3H, J=4), 1.01(3H, J=4), 1.35(4H, m), 1.48(4H, m), 1.68(2H, q, J=8) 1.78(2H, q, J=8), 2.49(2H, t, J=8), 7.32(1H, t, J=8), 7.42(1H, t, J=4) 7.54(1H, t, J=4), 7.91(1H, d, J=8). ¹³C NMR (100MHz, CDCl₃) δ 13.74, 14.11, 19.30, 19.85, 22.58, 28.70, 29.71, 30.80, 31.42, 64.96, 79.32, 95.89, 123.42, 127.07, 129.53, 131.28, 134.29, 139.23, 166.68.

3.3.4.6 1-Nitro-3-(oct-1-yn-1-yl)benzene

¹H NMR (400 MHz, CDCl₃) δ 0.93(3H, t, J=4), 1.36 (4H, m), 1.48(2H, m J=8), 1.63(2H, m, J=8), 2.45(2H, t, J=8), 7.48(1H, dd, J=4), 7.71(1H, J=4), 7.13 (1H, d, J=4), 8.25(1H, J=4), ¹³C NMR (100MHz, CDCl₃) δ 14.07, 19.39, 22.56, 28.45, 31.06, 78.51, 93.67, 122.22, 126.40, 129.13, 130.7, 132.46, 143.48, 148.08.

Fig 3.4.1 ^1H NMR (Z)-5-((2-mercapto phenyl imino)methyl)-2-methoxyphenol legend

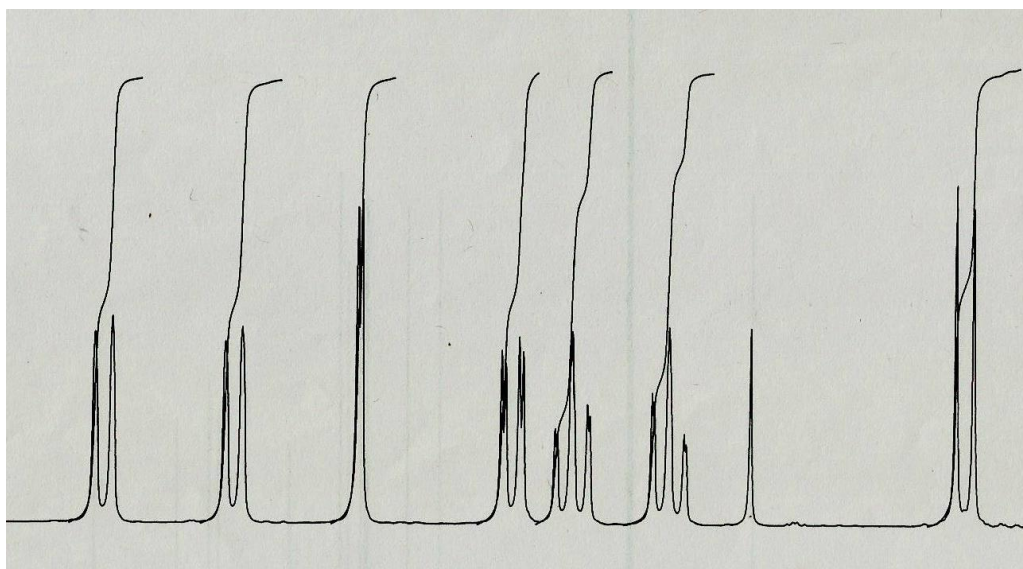
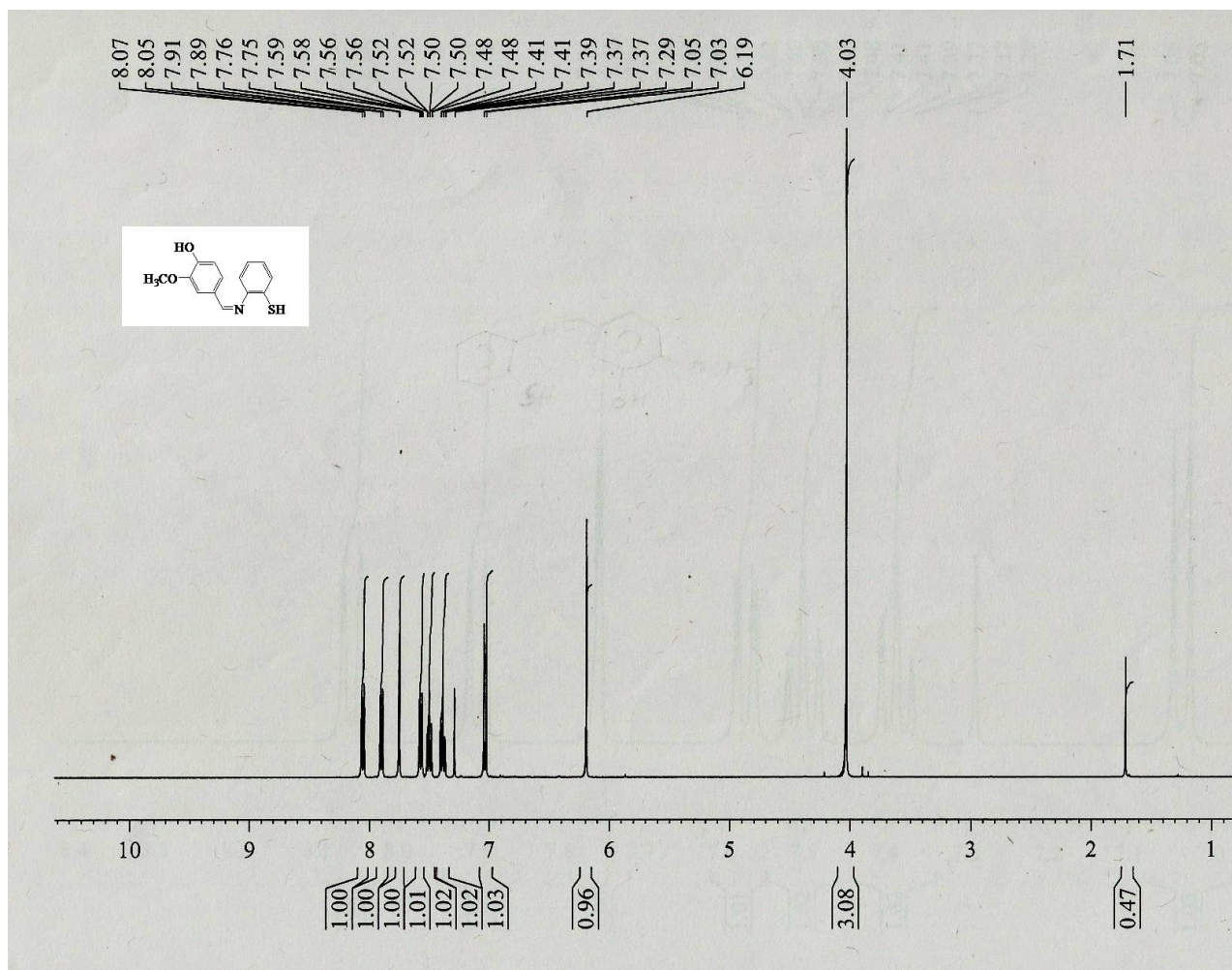
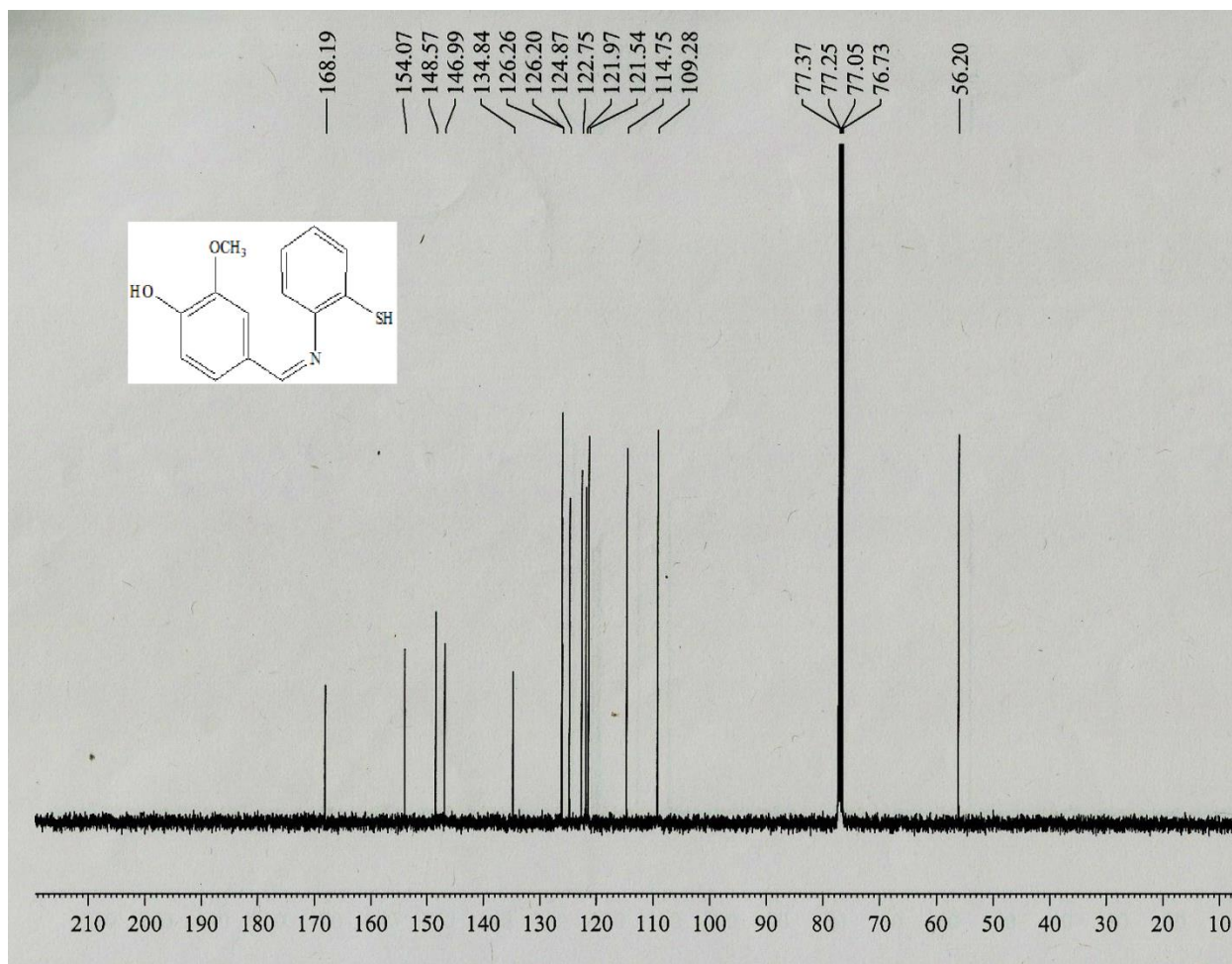
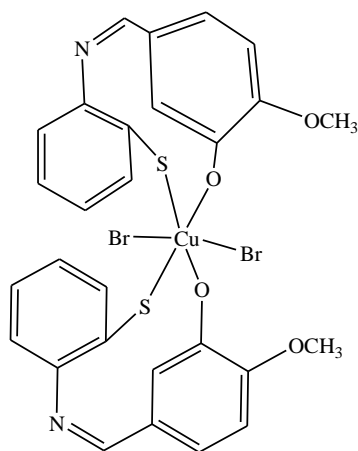


Fig 3.4.2 ^{13}C NMR (Z)-5-((2-mercapto phenyl imino)methyl)-2-methoxyphenol legend



3.3.5 Probable structure of Complex



3.4 SOLVENT FREE AND BASE FREE PROTOCOL FOR SONOGHASHI-RA REACTION USING BROMOTRIS(TRIPHENYLPHOSPHINE)

COPPER(I)

Solvent and base free protocol developed for preparation of a Substituted Alkynes by using Bromotris(Triphenylphosphine) Copper(I) by avoiding Poisonous Pd Catalytic System towards the green approach. A series of copper catalysts and ligands were evaluated. Substituted alkynes prepared by using different Alkynes and Arenes.

Herein we report a simple solvent free and base free protocol for the preparation of substituted alkynes. We have screened different catalyst for this reaction by using iodobenzene as alkyl halide and 1-Octyne as a model reaction and we found that Bromotris(Triphenylphosphine) Copper(I) giving good result as compare to other Catalyst

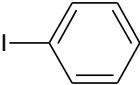
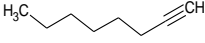
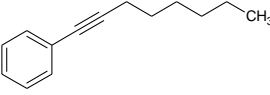
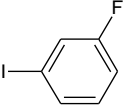
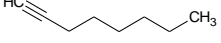
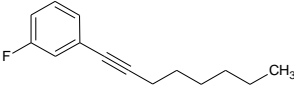
3.4.1 General process for preparation of CuBr(PPh₃)₃

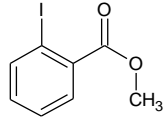
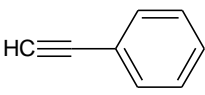
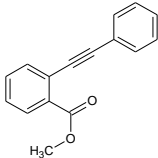
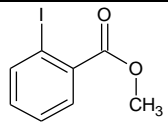
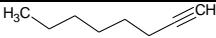
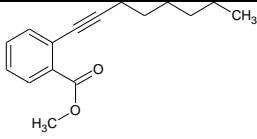
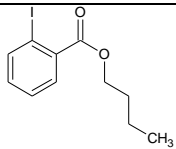

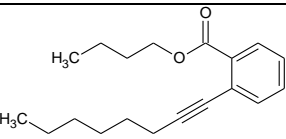
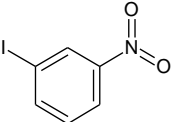
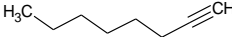
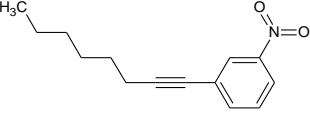
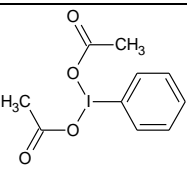
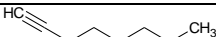
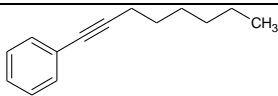
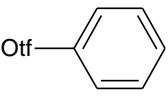
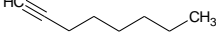
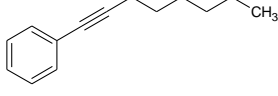
3 mole equivalents of triphenylphosphine was dissolved in 5 volume of solvent at 80°C and 1 mole equivalents of copper iodide was added under stirring. Reaction mass was cooled to 25°C and filtered the solid which dried under vacuum at 50°C

3.4.2 Experimental process for preparation of aryl or alkynebenzoate.

Charged (1.00 mmol) of Aryl halide, (2.00 mmol) of Alkynes and (0.1 mmol) of CuBr(PPh₃)₃ in a sealed tube and heated reaction mass under stirring at 110-120°C for required time TLC (1:10 Ethyl Acetate, n-Hexane). After completion of reaction Product purified on silica column in (0.5:99.5 Ethyl acetate, n-Heptane

Table-3.5: Reaction of different substituted aryl halide and different alkynes.

Entry	Iodo Arenes	Terminal Alkynes	Product	Yield %
1				85%
2				88%

3				78%
4				73%
5				89%
6				91%
7				89 %
8				77%

3.4.3 ¹H NMR and ¹³CNMR data of Internal substituted alkynes.

3.4.3.1 Oct-1-yn-1-ylbenzene.

¹H NMR (400 MHz, CDCl₃) δ 0.96 (3H, t, J=8), 1.37(4H, m), 1.48(2H, m), 1.66(2H, m), 2.45 (2H, t, J=8), 7.31(3H, m), 7.45(2H, m).

3.4.3.2 1-Fluoro-3-(oct-1-yn-1-yl)benzene

¹H NMR (400 MHz, CDCl₃) δ 0.94(3H, t) 1.43(2H, m), 1.58 (2H, m), 1.65(2H, m), 2.27(2H, t J=8), 2.44(2H, t J=8), 7.00(1H, m), 7.1(1H, m), 7.2(1H, m), 7.3(1H, m), ¹³CNMR (100MHz, CDCl₃) δ 14.07, 19.19, 19.38, 22.58, 28.61, 31.71, 79.84, 91.66, 114.67, 114.88, 118.24, 118.46, 127.42, 131.27.

3.4.3.3 Methyl 2-[(3-chlorophenyl)ethynyl] benzoate

¹H NMR (400 MHz, CDCl₃) δ 3.98(3H, s), 7.32(1H, m), 7.41(1H, m), 7.48(1H, m), 7.59(1H, m), 7.67(1H, m), 8.02(1H, m), ¹³C NMR (100MHz, CDCl₃) 52.25, 89.41, 92.80, 123.28, 125.08, 128.27, 128.77, 129.62, 129.90, 130.57, 131.53, 131.80, 131.89, 134.09, 134.22, 166.46.

3.4.3.4 Methyl 2-(oct-1-yn-1-yl)benzoate

¹H NMR (400 MHz, CDCl₃) δ 0.96(3H,t), 1.53(4H m), 1.67(4H, m J=8), 2.51(2H, t J=4),3.95(3H, s), 7.31(1H m J=8),7.43(1H, q, J=8), 7.55(1H, d J=8),7.92(1H, J=8) ¹³C NMR (100 MHz, CDCl₃) δ 14.09,19.73, 22.68, 28.00, 29.19, 31.63, 52.06, 79.22, 96.09, 123.49, 127.10, 134.24, 131.48, 135.17, 141.35,167.05.

3.4.3.5 Butyl 2-(oct-1-yn-1-yl)benzoate

¹H NMR (400 MHz, CDCl₃) δ 0.93 (3H, J=4), 1.01(3H, J=4), 1.35(4H, m), 1.48(4H, m), 1.68(2H, q, J=8) 1.78(2H, q, J=8), 2.49(2H, t, J=8), 7.32(1H, t, J=8), 7.42(1H, t, J=4) 7.54(1H, t, J=4),7.91(1H, d, J=8).¹³C NMR (100MHz,CDCl₃) δ 13.74,14.11,19.30,19.85, 22.58, 28.70, 29.71, 30.80, 31.42, 64.96, 79.32, 95.89, 123.42, 127.07, 129.53, 131.28, 134.29, 139.23, 166.68.

3.4.3.6 1-Nitro-3-(oct-1-yn-1-yl)benzene

¹H NMR (400 MHz, CDCl₃) δ 0.93(3H, t, J=4), 1.36 (4H, m), 1.48(2H, m J=8), 1.63(2H, m, J=8), 2.45(2H, t, J=8), 7.48(1H, dd, J=4), 7.71(1H, J=4), 7.13 (1H, d, J=4), 8.25(1H, J=4), ¹³C NMR (100MHz, CDCl₃) δ 14.07, 19.39, 22.56, 28.45, 31.06, 78.51, 93.67, 122.22, 126.40, 129.13, 130.7, 132.46, 143.48, 148.08.

3.5 GREEN PROTOCOL FOR SP-SP² COUPLING OF ARYL IODIDE AND ALKYNES USING COPPER CARBONATE: FACILE SYNTHESIS OF ARYL ALKYNES.

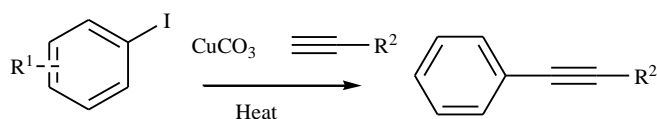
Iodo-arenes coupled with terminal alkynes and arynes in presence of copper carbonate in DMF at 125°C to offered substituted alkynes in good to moderate yield. The reaction features the use of CuCO₃ which act as efficient base as well as catalyst to promote the reaction. The newly developed protocol has been successfully employed for the synthesis of substituted internal alkynes.

Herein we developed protocol for coupling of aryl halide with alkynes using copper carbonate. CuCO₃ itself act as a base as well catalyst.

3.5.1 Experimental process for preparation of aryl or alkynebenzoate using copper carbonate.

Charged 1 gm of Aryle iodide (0.0049 moles), 1.2 gm of Alkynes (0.0059 moles), 0.5 gm of Copper carbonate (0.004 moles) in 5 ml DMF in a sealed tube reaction mass stirred on magnetic stirrer for 20-25 hrs at 125°C. Reaction mass cooled to 25°C and filtered the solid. The oily mass purified on silica column in ethyl acetate-heptane 1% gives Oily product.

3.5.1.1 Preparation of aryl or alkynebenzoate using copper carbonate.



1a-R¹ = H, 2a-R¹=COOMe, 3a-R¹=COOEt, 4a-R¹=COOn-Bu, 5a=Iodobenzenediacetate, 6a=3F,Iodo benzene, 7a-R¹= P-NO₂, 8a=iso but, 9a= Sec.But,10a-R¹= m-NO₂,1b-R²= Octyl, 2b-R²= Phenyl, 3b-R²= 3Chloro Phenyl,4b-R²= 3Chloro Propane

Sr. No.	Aryl Iodide	Alkynes/ Arenes	Substituted Arynes	% Yield
1	1a	1b	1	65%
2	2a	1b	2	61%
3	2a	3b	3	62%
4	2a	4b	4	68%
5	3a	3b	5	64%
6	4a	1b	6	71%
7	4a	2b	7	63%
8	5a	1b	8	75%
9	6a	1b	9	72%
10	7a	1b	10	49%
11	8a	1b	11	53%
12	8a	2b	12	68%
13	9a	1b	13	71%
14	9a	2b	14	64%
15	10a	1b	15	69%

3.5.2. ¹H NMR of Alkynes benzene.

3.5.2.1 ¹H NMR of 1-(oct-1-ynyl)benzene.

(CDCl₃ 400 MHz) δ 7.43(t, *J* = 4Hz, 2H), 7.32(m, 3H), 2.42 (t, *J* = 8Hz 2H), 1.64 (m, 2H), 1.54(m, 2H), 1.35 (m 4H), .94 (t *J* = 4Hz 3H) ¹³C NMR (CDCl₃) δ 131.55, 128.19, 127.46, 124.10, 90.94, 80.55, 65.25, 31.41, 28.64, 22.61, 19.44, 14.1

3.5.2.2 ¹H NMR of methyl 2-(oct-1-yn-1-yl)benzoate

(CDCl₃ 400 MHz,) δ 0.96(t, 3H), 1.53(m, 4H), 1.67(m, 4H, *J*=8), 2.51 (t 2H, *J*=4), 3.95(s, 3H), 7.31(m, 1H *J*=8), 7.43(q, 1H, *J*=8), 7.55(d, 1H, *J*=8), 7.92(1H, *J*=8) ¹³C NMR (100 MHz, CDCl₃) δ 14.09, 19.73, 22.68, 28.00, 29.19, 31.63, 52.06, 79.22, 96.09, 123.49, 127.10, 134.24, 131.48, 135.17, 141.35, 167.05.

3.5.2.3 ¹H NMR of methyl 5-chloro-2-(2-phenylethyl)benzoate

(CDCl₃ 400 MHz) δ 8.02(m, 1H), 7.67(m,1H), 7.59(m, 1H), 7.48(m, 2H), 7.41(m, 1H), 7.35(m 1H), 7.32(m, 1H), 3.98(s, 1H). ¹³C NMR (CDCl₃) δ 166.46, 134.22, 134.09, 131.89, 131.80, 131.53, 130.57, 129.90, 129.62, 128.77, 128.27, 125.08, 123.28, 92.80, 89.41, 52.25.

3.5.2.4 ¹H NMR of Methyl 2-(5-chloropent-1-ynyl)benzoate

(CDCl₃ 400 MHz) δ 2.09(m 2H), 2.68(t 2H *J*=8), 3.79(t 2H *J*=8), 3.93(S 3H), 7.32(m 1H), 7.43(m 1H), 7.50(m 1H), 7.89(m 1H), ¹³C NMR (100MHz, CDCl₃) δ 17.21, 31.37, 43.76, 52.15, 80.21, 79.6, 124.02, 127.45, 130.22, 131.59, 131.93, 134.2, 166.77.

3.5.2.5 ¹H NMR of ethyl 2-(2-(3-chlorophenyl)ethynyl)benzoate

(CDCl₃ 400 MHz) δ 8.02 (d *J* = 8Hz 1H), 7.69(d *J* = 8Hz 1H), 7.6 (m, 2H), 7.51 (t *J* = 4 1H), 7.4 (m 4H), 4.5 (m, 2H), 1.44 (t, 3H) ¹³C NMR (CDCl₃) δ 166.66, 141.25, 135.51, 134.04, 132.53, 131.70, 131.58, 130.85, 130.43, 128.50, 128.38, 127.93, 127.91, 94.23, 88.31, 31.66, 14.24

3.5.2.6 ¹H NMR of Butyl 2-(oct-1-yn-1-yl) benzoate

(400 MHz, CDCl₃) δ 0.93 (3H, *J*=4), 1.01(3H, *J*=4), 1.35(4H, m), 1.48(4H, m), 1.68(2H, q, *J*=8) 1.78(2H, q, *J*=8), 2.49(2H, t, *J*=8), 4.36(t 2H *J*=8), 7.32(1H, t, *J*=8), 7.42(1H, t, *J*=4) 7.54(1H, t, *J*=4),7.91(1H, d, *J*=8).¹³C NMR (400 MHz, CDCl₃) δ 13.74,14.11, 19.30, 19.85, 22.58, 28.70, 29.71, 30.80, 31.42, 64.96, 79.32, 95.89, 123.42, 127.07, 129.53, 131.28, 134.29, 139.23, 166.68

3.5.2.7 ¹H NMR of butyl 2-(2-phenylethynyl) benzoate

(CDCl₃ 400 MHz) δ 8.00(d J = 8 1H), 7.67(d J = 8 1H), 7.6 (m 2H), 7.51(t, 1H), 7.42(d J = 8 1H), 7.40 (m, 3H), 4.38 (t, J = 8 2H), 1.8 (m, 2H), 1.44 (m 2H), 0.92(t, J = 8 3H) ¹³C NMR (CDCl₃) δ 166.66, 134.11, 132.8, 131.71, 131.54, 130.44, 129.55, 128.47, 128.37, 127.9, 123.64, 123.40, 94.24, 88.33, 65.53, 34.87, 29.23, 26.08, 14.12.

3.5.2.8 ¹H NMR of 1-(oct-1-ynyl)benzene.

(CDCl₃ 400 MHz) δ 7.43(t, J = 4Hz, 2H), 7.32(m, 3H), 2.42 (t, J = 8Hz 2H), 1.64 (m, 2H), 1.54(m, 2H), 1.35 (m 4H), .94 (t J = 4Hz 3H) ¹³C NMR (CDCl₃) δ 131.55, 128.19, 127.46, 124.10, 90.94, 80.55, 65.25, 31.41, 28.64, 22.61, 19.44, 14.1

3.5.2.9 ¹H NMR of 1-fluoro-3-(oct-1-ynyl) benzene.

(CDCl₃ 400 MHz) δ 7.24(m, J = 8Hz, 1H), 7.20(d, J = 8Hz, 1H), 7.10 (t, 1H, J = 4Hz), 7.00 (m, 1H), 2.41(t, j = 4Hz 2H), 2.27 (t J 8Hz, 2H), 1.63 (m, 2H), 1.55(m, 2H), 1.47(m, 2H), 0.91(t J = 4Hz, 3H) ¹³C NMR (CDCl₃) δ 163.63, 133.37, 131.27, 125.97, 118.46, 114.67, 92.66, 79.55, 31.71, 29.39, 22.64, 19.38, 14.07.

3.5.2.10 ¹H NMR of 1-nitro-4-(oct-1-ynyl) benzene.

(400 MHz, CDCl₃) δ 8.17(m 2H), 7.51(m 2H), 2.46(t 2H J=8), 1.63(m 2H), 1.47(m 2H), 1.33(m 4H), 0.94(t 3H, J=4), ¹³C NMR (100MHz, CDCl₃) δ 14.05, 19.57, 22.55, 28.38, 28.62, 31.32, 79.3, 96.84, 123.48, 131.24, 132.23, 146.55

3.5.2.11 ¹H NMR of 2-methylpropyl 2-(oct-1-yn-1-yl)benzoate.

(400 MHz, CDCl₃) delta 0.89(3H t), 1.01(6H d), 1.32(2H m), 1.45(2H q), 1.62(2H q) 2.1(1H m), 1.98(2H t) 2.44(2H t) ,4.11(2H t), 7.29(1H dd J=8.4),7.41(1H t J=8), 7.49(1H d J= 8), 7.99(1H d J=8)

3.5.2.12 ¹H NMR of 2-methylpropyl 2-(phenyl ethynyl)benzoate.

(400 MHz, CDCl₃) delta 1.01(6H t) 2.09(1H m), 4.13(2H m), 7.35 (4H m), 7.49(2H t J=8), 7.56(1H d,d J=4), 7.64(1H d, J=8), 7.98(1H, d J=8)

3.5.2.13 ¹H NMR of Butan-2-yl 2-(phenyl ethynyl)benzoate.

(400 MHz, CDCl₃) delta 0.89 (3H t) 0.99(6H m), 1.33(2H) 1.42(2H m), 1.67(4H m), 1.79(2H m), 2.47 (2H m), 5.12(t 1H J=8), 7.29(1H m J=8), 7.39(1H m J=8), 7.5 (1H t J=8), 7.86 (1H d J=8)

3.5.2.14 ¹H NMR of butan-2-yl 2-(phenyl ethynyl)benzoate.

(400 MHz, CDCl₃) δ 0.97(3H t), 1.34(3H d), 1.66 (1H m), 1.76(1H m),5.14 (1H m), 7.35(4H m), 7.48(1H t J=8), 7.56(2H t J=4), 7.63(1H d J=8), 7.95(1H d J=8) ¹³ C NMR δ 9.87, 19.64,

28.97, 73.33, 88.40, 94.13, 123.44, 127.91, 128.35, 128.44, 130.32, 131.41, 131.66, 132.64, 134.17, 166.05.

3.5.2.15 ¹H NMR of 1-Nitro-3-(oct-1-yn-1-yl)benzene.

(400 MHz, CDCl₃) δ 0.93(3H, t, J=4), 1.36 (4H, m), 1.48(2H, m, J=8), 1.63(2H, m, J=8), 2.45(2H, t, J=8), 7.48(1H, dd, J=4), 7.71(1H, J=4), 7.13 (1H, d, J=4), 8.25(1H, J=4), ¹³C NMR (100MHz, CDCl₃) δ 14.07, 19.39, 22.56, 28.45, 31.06, 78.51, 93.67, 122.22, 126.40, 129.13, 130.7, 132.46, 143.48, 148.08.

3.6. COPPER NANOPARTICLE ASSISTED BASE AND LEGEND FREE APPROACH FOR SYNTHESIS OF SUBSTITUTED INTERNAL ALKYNES ESTERS AND STUDY THE EFFECT OF ALKYL GROUP ON RATE OF REACTION.

Now a day the concept of nano particle adapted in several catalytic coupling reactions due to their high surface area and solubility in different solvents and is often used in chemical synthesis to increase the conversion and yield of product. Several people worked on shape, sizes, and physical property of the nanoparticle. Reports show that more than 50% increase in yield and reaction rate due to increase in surface area of the catalyst. But the most important challenge about the nanoparticle is their stability, most of the work done on their stability, simple and easy preparation.

We have prepared copper nanoparticle in aerobic condition with stability for longer period outside the solution. With this simplest and scalable method reported in literature [**Error! Reference source not found.**] we have prepared copper nanoparticle and developed a protocol for the preparation of substituted alkynes. Initially we have screened different Iron metal complexes, Copper metal complexes, magnesium, zinc metal complexes their salts with ligands and their mixtures.

3.6.1 Optimization of reaction condition

We also tried different metal powder and their mixtures in presence or absence of base and legend. Surprisingly we observed the good yield with Copper powder in absence of base and ligand. But the time required for reaction was 12-36 hrs. Then we thought to use nanoparticle

of copper to reduce the time we have studied the reaction of nanoparticale at different condition and with different ligands and base and reduced the time for completion of reaction up to 12 to 4 time than with normal copper powder with higher conversion.

We did a comparative reaction rate study of different esters with different alkynes we observed that reaction of 2 iodo methylbenzoate with Octyne in presence of Copper powder completed in 12hrs(T1) when same reaction carried out at same condition in presence of copper nanoparticle reaction get completed in 1 hrs(T2) (entry-1). Same is the case for 2-iodo ethyl benzoate (entry-2). With 2- iodo n-Buthyl benzoate and Octyne in presence of Copper powder reaction completed 14 hrs. (T2) and with nanoparticle 1hrs in same condition (T2) (entry 3). Likewise reaction of 2 iodo iso Buthyl benzoate, 2 iodo Sec Buthyl benzoate, 2 iodo hexyl benzoate, 2 iodo Octyl benzoate, with 1-Octyne takes 16, 17,20, 28 hrs in presence of copper powder where as with nanoparticale 2,3,4,8 hrs. Entry 4-7). Reaction of 2 iodo methylbenzoate, 2 iodo ethyl benzoate, 2 iodo n Buthyl benzoate, 2 iodo iso Buthyl benzoate, 2 iodo Sec Buthyl benzoate, 2 iodo hexyl benzoate, 2 iodo Octyl benzoate, with Phenylactylene takes 2,2,3,3,3,6,10hrs respectively in presence of copper powder and with nanoparticale in same condition complete in 12, 12, 18, 20, 22, 24, 36hrs. respectively. (Entry-8-14)

Even compound having Bromine , triflete, diacetates, borate groups as a leaving group can be coupled with alkynes and giving good yield with this method. Long chain esters like hexyl 2 iodo benzoate and Octyl 2 iodobenzoate preperd and sucefully coupled with log chain alkynes like octyne and hexyne. We have also coupled these esters with aromatic Alkynes as phenyl acetylene.

Table: 3.6- Reaction rate comparison table between 2-iodobenzoate, Alkynes or arenes in presence of nanopartical (T₁) and under same condition 2-iodobenzoate, Alkynes or arenes in presence of normal copper powder (T₂).

Entry.	Halides	Alkyne	T ₁	T ₂
1	2 iodo methylbenzoate	Octyne	1hrs.	12 hrs
2	2 iodo ethyl benzoate	Octyne	1 hrs.	12 hrs
3	2 iodo n Buthyl benzoate	Octyne	1 hrs.	14 hrs

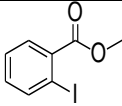
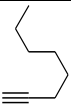
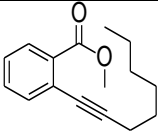
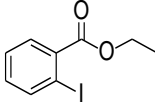
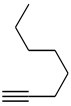
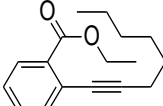
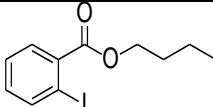
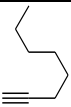
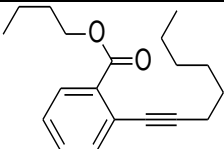
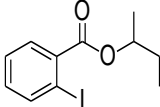
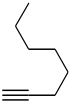
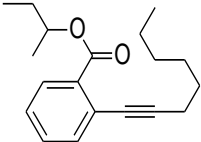
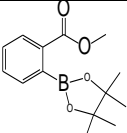
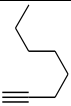
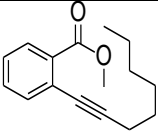
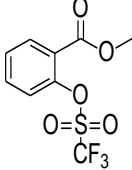
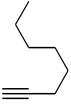
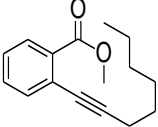
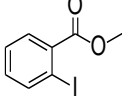
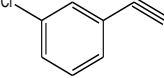
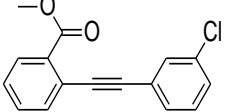
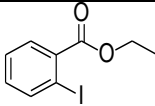
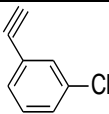
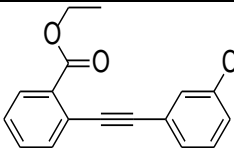
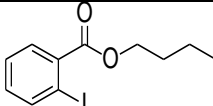
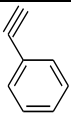
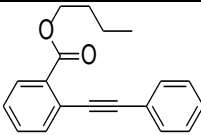
4	2 iodo iso Buthyl benzoate	Octyne	2hrs.	16 hrs
5	2 iodo Sec Buthyl benzoate	Octyne	3 hrs.	17 hrs
6	2 iodo hexyl benzoate	Octyne	4 hrs.	20 hrs
7	2 iodo Octyl benzoate	Octyne	8 hrs.	28 hrs
8	2 iodo methylbenzoate	Phenyl Acetylene	2 hrs	12 hrs
9	2 iodo ethyl benzoate	Phenyl Acetylene	2 hrs	12 hrs
10	2 iodo n Buthyl benzoate	Phenyl Acetylene	3 hrs.	18 hrs.
11	2 iodo iso Buthyl benzoate	Phenyl Acetylene	3 hrs.	20 hrs.
12	2 iodo Sec Buthyl benzoate	Phenyl Acetylene	3hrs.	22 hrs.
13	2 iodo hexyl benzoate	Phenyl Acetylene	6 hrs.	24hrs.
14	2 iodo Octyl benzoate	Phenyl Acetylene	10hrs.	36 hrs.

Reaction done with 1 mole of iodobenzoate 1.5 moles of Alkyne or Arenes, 0.5 mole of copper catalyst at 110°C.

3.6.2 Process for preparation of Substituted internal alkynes or arenes.

Charged 0.5 gm of Alkyl benzoate (1.9 m mole), 0.31 gm (2.8 m mole) of Alkynes or Arenes, 0.085gm (0.95m mole) of Copper nanoparticle in 2ml DMF was heated to 110-120°C in a sealed tube for required time. Reaction monitoring was done on TLC ethyl acetate: n- hexane (1:9) as mobile phase. After completion of reaction 3ml Dichlorometane was added and filtered the solid. 3 ml water was added to filtrate and Dichloromethane layer was separated and evaporated. The crude oil was purified on silica column using ethyl acetate and n-Heptane as solvent.

Table: 3.7- Compounds prepared by using this protocol.

Entry	2-halobenzoate	Alkynes/Arenes	Product	Yield
1				92%
2				95%
3				89%
4				83%
5				81%
6				82%
7				92%
8				90%
9				87%

10				83%
11				81%
12				79%
13				84%
14				76%
15				74%
16				78%
17				89%

Reaction done with 1 mole of iodobenzoate 1.5 moles of Alkyne or Arenes, 0.5 mole of copper catalyst at 110°C.

3.6.3 ¹H NMR and ¹³C NMR of 2-Alkyne benzoate.

3.6.3.1 ¹H NMR and ¹³C NMR of 2-(oct-1-yn-1-yl)benzoate.

¹H NMR (400 MHz, CDCl₃) δ 0.96(3H, t), 1.53(4H m), 1.67(4H, m J=8), 2.51(2H, t, J=4), 3.95(3H, s), 7.31(1H, m, J=8), 7.43(1H, q, J=8), 7.55(1H, d, J=8), 7.92(1H, J=8) ¹³C NMR (100 MHz, CDCl₃) δ 14.09, 19.73, 22.68, 28.00, 29.19, 31.63, 52.06, 79.22, 96.09, 123.49, 127.10, 134.24, 131.48, 135.17, 141.35, 167.05.

3.6.3.2 ¹H NMR and ¹³C NMR of Ethyl 2-(oct-1-yn-1-yl)benzoate.

¹H NMR (400 MHz, CDCl₃) delta 1.33(3H t J=8), 1.42(3H t J=8), 1.47(4H J=8), 1.62(2H J=4), 1.67(2H J=8), 2.48 (2H t J=8), 4.41(2H J=8), 7.31(1H t J=8), 7.43(1H J=8), 7.53 (1H d J=4), 7.88(1H d J=4). ¹³C NMR (100 MHz, CDCl₃) 14.06, 14.29, 19.81, 22.58, 28.68, 31.41, 33.83, 60.14, 115.89, 127.07, 127.85, 131.29, 132.45, 134.51, 166.61.

3.6.3.3 ¹H NMR and ¹³C NMR of Butyl 2-(oct-1-yn-1-yl)benzoate

¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.93 (3H J=4), 1.01(3H J=4), 1.35(4H m), 1.48 (4H m), 1.68(2H q J=8) 1.78(2H q J=8), 2.49(2H t J=8), 4.36(2H t J=8) 7.32(1H t J=8), 7.42(1H t J=4) 7.54(1H t J=4), 7.91(1H d J=8) ¹³C NMR (100 MHz, CDCl₃) 13.74, 14.11, 19.30, 19.85, 22.58, 28.70, 29.71, 30.80, 31.42, 64.96, 79.32, 95.89, 123.42, 127.07, 129.53, 131.28, 134.29, 139.23, 166.68.

3.6.3.4 ¹H NMR and ¹³C NMR of 2-methylpropyl 2-(phenylethynyl)benzoate.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.89 (3H t) 0.99(6H m), 1.42(2H m), 1.67(4H m), 1.79(2H m), 2.47 (2H m), 5.12(1H m) 7.29(1H m J=8), 7.39(1H m J=8), 7.5 (1H t J=8), 7.86 (1H d J=8)

3.6.3.5 ¹H NMR and ¹³C NMR of 2-methylpropyl 2-(oct-1-yn-1-yl)benzoate

¹H NMR (400 MHz, CDCl₃) delta 0.89(3H t), 1.01(6H d), 1.32(2H m), 1.45(2H q), 1.62(2H q) 2.1(1H m), 1.98(2H t), 2.44(2H t), 4.11(2H t), 7.29(1H dd J=8.4), 7.41(1H t J=8), 7.49(1H d J=8), 7.99(1H d J=8).

3.6.3.6 ¹H NMR and ¹³C NMR of Methyl 2-[(3-chlorophenyl)ethynyl] benzoate.

¹H NMR (400 MHz, CDCl₃) delta 3.98(3H s), 7.30(1H m), 7.34(1Hm), 7.41(1Hm), 7.48 (1Hm), 7.51 (1H m) 7.59(1Hm), 7.67(1Hm), 8.02(1Hm) ¹³C NMR(100MHz, CDCl₃) 52.25, 41.92, 80, 123.28, 125.08, 128.27, 128.77, 129.62, 129.90, 130.57, 131.53, 131.80, 131.89, 134.09, 134.22, 166.46,

3.6.3.7 ¹H NMR and ¹³C NMR of Ethyl 2-[(3-chlorophenyl)ethynyl]benzoate

^1H NMR (400 MHz, CDCl_3) δ 0.91 (3H t), 4.45(2H M), 7.40(3H m), 7.50(1H t), 7.61(2H m), 7.69(1H m), 8.02(1H m), ^{13}C NMR (100MHz, CDCl_3) 14.24, 61.25, 88.31, 94.23, 123.38, 123.59, 127.90, 127.93, 128.38, 128.50, 130.43, 131.57, 130.84, 131.57, 131.70, 134.06, 166.42.

3.6.3.8 ^1H NMR and ^{13}C NMR of Butyl 2-(phenylethynyl)benzoate

^1H NMR (400 MHz, CDCl_3) δ 0.91 (3H t $J=4$), 1.44(2H m $J=8$), 1.80(2H m $J=4$), 4.38(2H t $J=8$), 7.41(4H m), 7.49(1H m $J=4$), 7.61(2H m $J=4$), 7.69(1H dd $J=8$), 8.01(1H m $J=4$) ^{13}C NMR (100MHz, CDCl_3) 14.12, 22.66, 31.82, 65.53, 88.34, 94.25, 123.40, 123.64, 127.91, 128.34, 128.48, 129.55, 130.44, 131.55, 131.71, 132.26, 132.81, 134.11, 166.45.

3.6.3.9 ^1H NMR and ^{13}C NMR of Sec-butyl 2-(oct-1-ynyl)benzoate

^1H NMR (400 MHz, CDCl_3) δ (ppm): 0.89 (3H t) 0.99(6H m), 1.42(2H m), 1.67(4H m), 1.79(2H m), 2.47 (2H m), 5.12(1H m) 7.29(1H m $J=8$), 7.39(1H m $J=8$), 7.5 (1H t $J=8$), 7.86 (1H d $J=8$)

3.6.3.10 ^1H NMR and ^{13}C NMR of 2-methylpropyl 2-(phenylethynyl) benzoate

^1H NMR (400 MHz, CDCl_3) δ 1.01(6H t) 2.09(1H m), 4.13(2H m), 7.35 (4H m), 7.49(2H t $J=8$), 7.56(1H d, d $J=4$), 7.64(1H d $J=8$), 7.98(d $J=8$)

3.6.3.11 ^1H NMR and ^{13}C NMR of Butan-2-yl-2-(phenylethynyl)-benzoate

^1H NMR (400 MHz, CDCl_3) δ (ppm): 0.97(3H t), 1.34(3H d), 1.66 (1H m), 1.76(1H m), 5.14 (1H m), 7.35(4H m), 7.48(1H t $J=8$), 7.56(1H t $J=4$), 7.63(1H d $J=8$), 7.95(1H d $J=8$).

3.6.3.12 ^1H NMR and ^{13}C NMR of butyl 2-(2-(3-chlorophenyl)ethynyl)benzoate.

^1H NMR (400 MHz, CDCl_3) δ 0.93 (3H t) 1.49(2H m), 1.8(2H m), 4.38(2H q), 7.39(3H m), 7.52(1H t $J=8,4$), 7.61(2H m) 7.69(1H m) 8.02(1H m), ^{13}C NMR (100MHz, CDCl_3) δ 13.75, 19.33, 30.80, 65.6, 88.32, 94.23, 123.38, 123.63, 127.91, 128.34, 128.47, 130.43, 130.48, 131.55, 131.70, 132.24, 132.50, 134.12, 135.57, 141.27, 166.45.

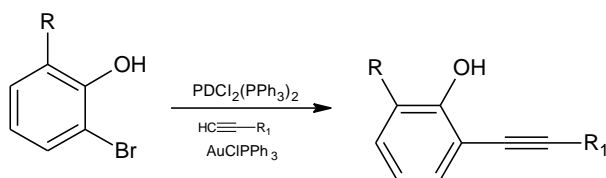
4.1 ALKENEYL PHENOL (2-VINYLPHENOLS)

Alkyne phenols are the phenolic compounds containing reactive double bond at Ortho position to phenolic groups hence they are versatile intermediates for preparation of coumarins, 3,4-dihydro-2H-2,4-methanochromans, lactones, cyclic ketons, Chiral *cis*-disubstituted tetra hydro quinolines

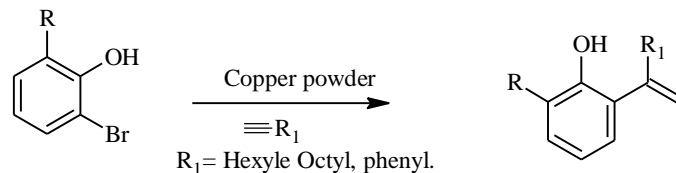
While doing work with Sonogashira reaction using 2 bromo phenols as starting material we observed different product formation as compare to normal product using Sonogashira reaction. After optimizing reaction condition we developed cheap, simple and best protocol as of now reported in the literature.

Generally in Sonogashira the terminal alkyne proton get substituted by alkyl or aryl group . But here we got addition product. Generally in the nucleophilic addition addition takes place according to Markovnikov's rule and nucleophile will attach to less substituted carbon atom but Here in reported protocol substitution takes place according to anti Markovnikov's rule. According to current literature we are reporting first time this type of reaction.

Scheme-1 Normal product formation using reported Sonogashira reaction



Scheme-2 Anti markovnikov's addition according to our protocol.



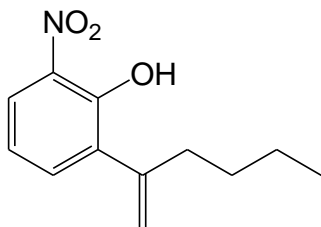
4.1.1 Typical process for preparation of Alkenyl Phenols using Copper powder

Charged 1 m. mole of Bromo phenol, 1.2 m. mole of terminal alkyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 12-15 hrs. Reaction progress was monitored on TLC . After completion of reaction content was cooled to room temp. and diluted with dichloromethane, filtered through centered funnel. Charged 10 ml. water and extracted reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column.

4.1.2.1 Prepration of 2-nitro-6-(Aryl-1-en-2-yl)phenol

4.1.2.1.1 2-nitro-6-(hex-1-en-2-yl)phenol

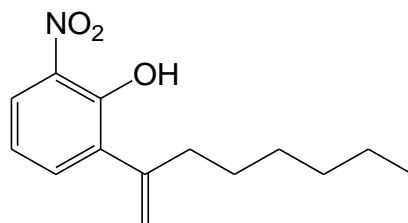
Charged 1 m. mole of Bromo phenol, 1.2 m. mole of 1-Hexyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 12-15 hrs. Reaction progress was monitored on TLC . After completion of reaction content was cooled to room temp. and diluted with dichloromethane, filtered through centered funnel. Charged 10 ml. water and extracted reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column gives yellow oil, 2-nitro-6-(hex-1-en-2-yl)phenol .



^1H NMR (400 MHz, CDCl_3) δ 0.96(t 3H), 1.41(m 2H), 1.61(m 2H), 2.32(t 2H J=8), 4.24(d 1H), 4.53(d 1H), 7.22(s 1H), 8.20(dd 1H J=8,4), 8.51(d J=4). ^{13}C NMR (100MHz, CDCl_3) δ 13.81, 13.86, 18.51, 22.26, 29.72, 32.95, 94.21, 114.88, 118.78, 124.19, 129.47, 146.46, 158.20, 160.98.

4.1.2.1.2 2-nitro-6-(oct-1-en-2-yl)phenol.

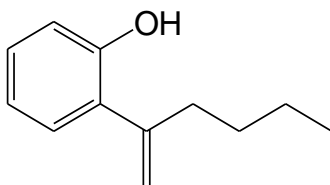
Prepared same as the process of prepration of 2-nitro-6-(hex-1-en-2-yl)phenol using 2 Bromo 6 nitro phenol, 1.2 m. mole of 1-Heptyne, and 20 mole % of copper powder .



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.89(t 3H), 1.37(m 6H), 1.64(m, 2H), 2.131(t 2H J=8), 4.24(s 1H), 4.52(s 1H), 7.22(d 1H), 8.2(d 1H), 8.50(s 1H).

4.1.2.1.3 2-(hex-1-en-2-yl)phenol.

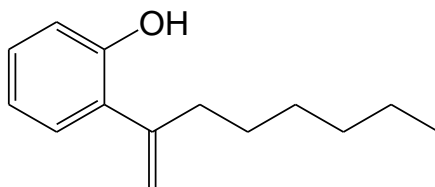
Prepared same as the process of preparation of 2-nitro-6-(hex-1-en-2-yl)phenol using 2 Bromo phenol, 1.2 m. mole of 1-Hexyne, and 20 mole % of copper powder .



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.972(t 3H), 1.47(m 2H), 1.7 (m 4H), 4.34(t 2H J=6.4), 7.37(m 2H), 7.66(m 1H), 7.77(m 1H).

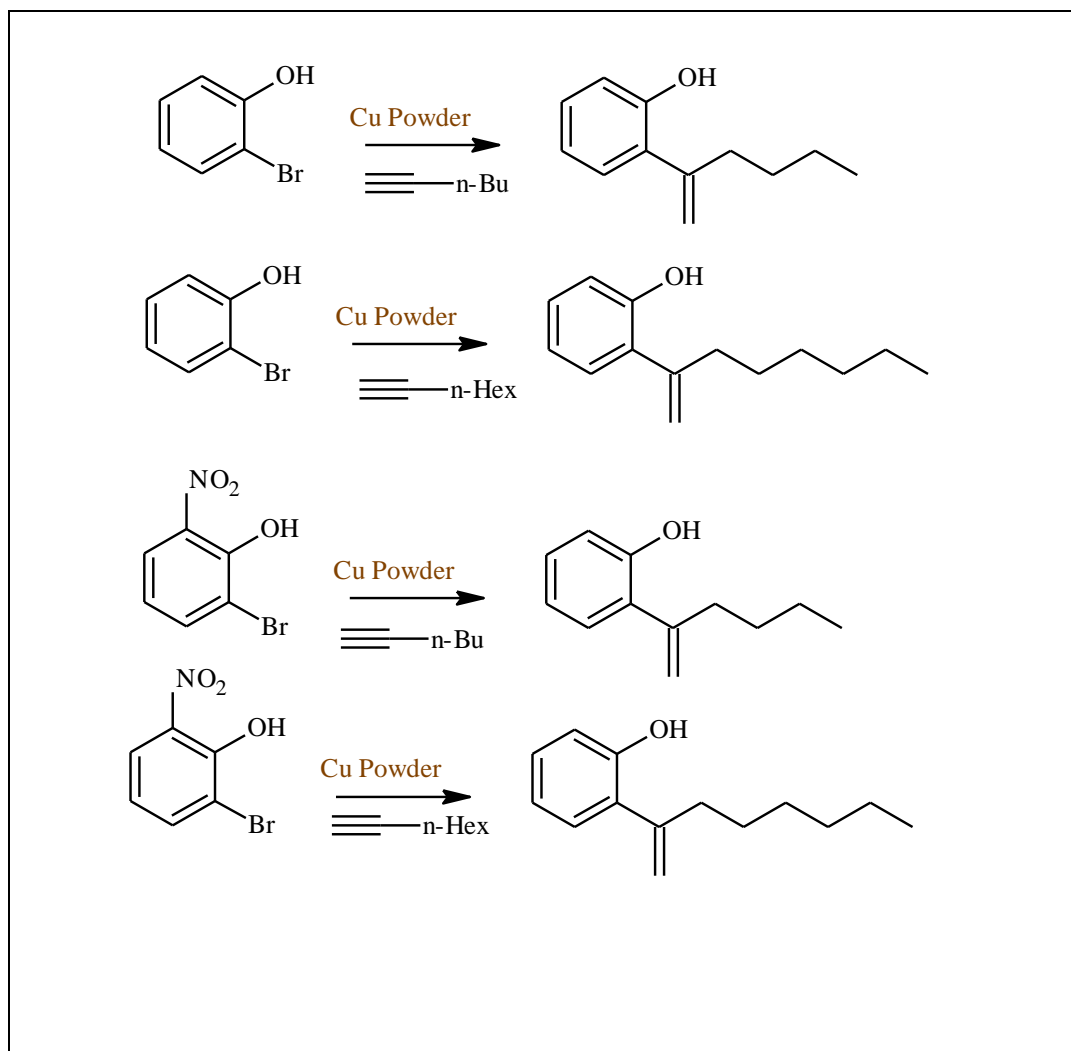
4.1.2.1.4 2-(hept-1-en-2-yl)phenol.

Prepared same as the process of preparation of 2-nitro-6-(hex-1-en-2-yl)phenol using 2 Bromo phenol, 1.2 m. mole of 1-Heptyne, and 20 mole % of copper powder .

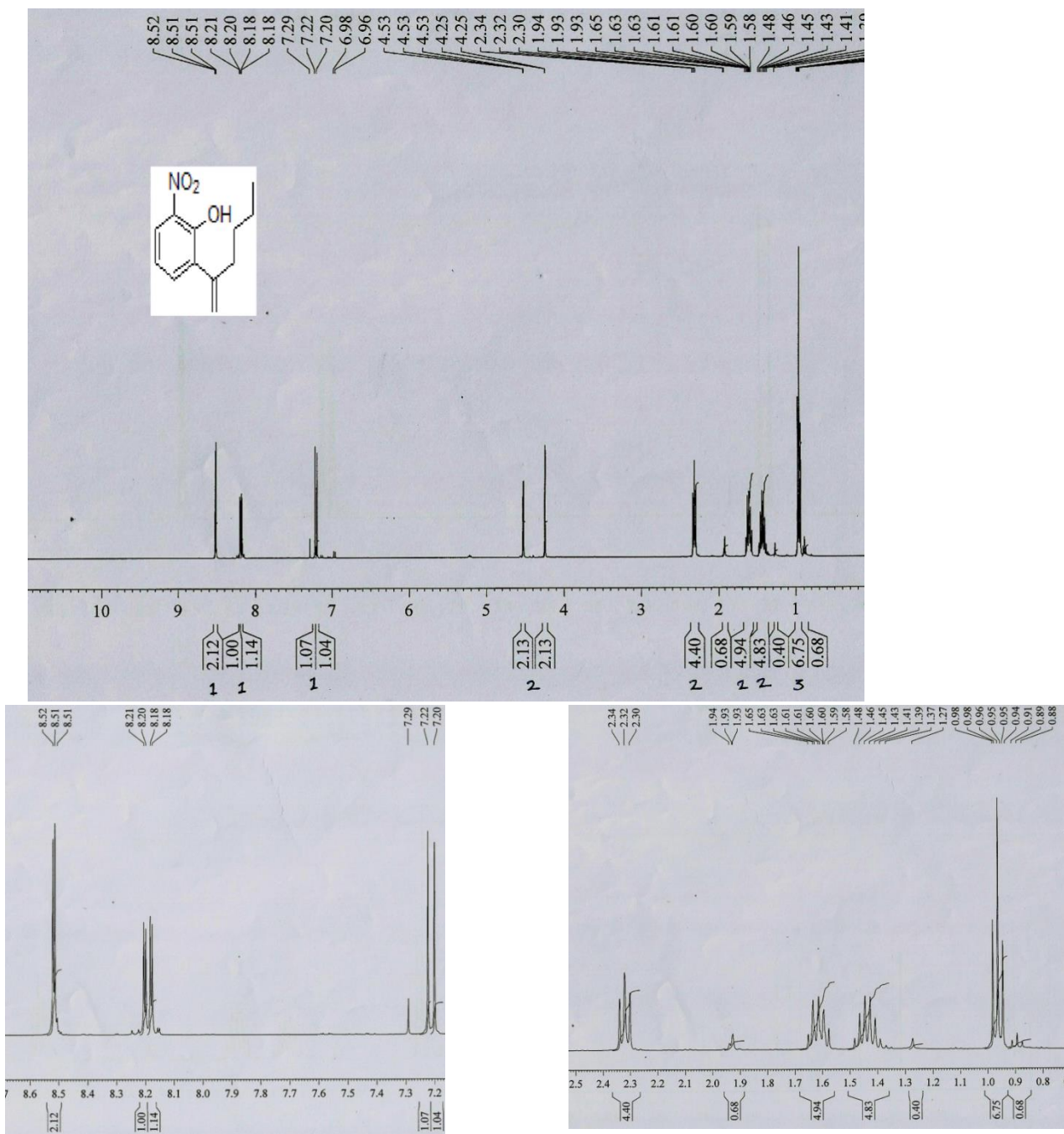


$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.972(t 3H), 1.47(m 2H), 1.7 (m 6H), 4.34(t 2H J=6.4), 7.37(m 2H), 7.66(m 1H), 7.77(m 1H).

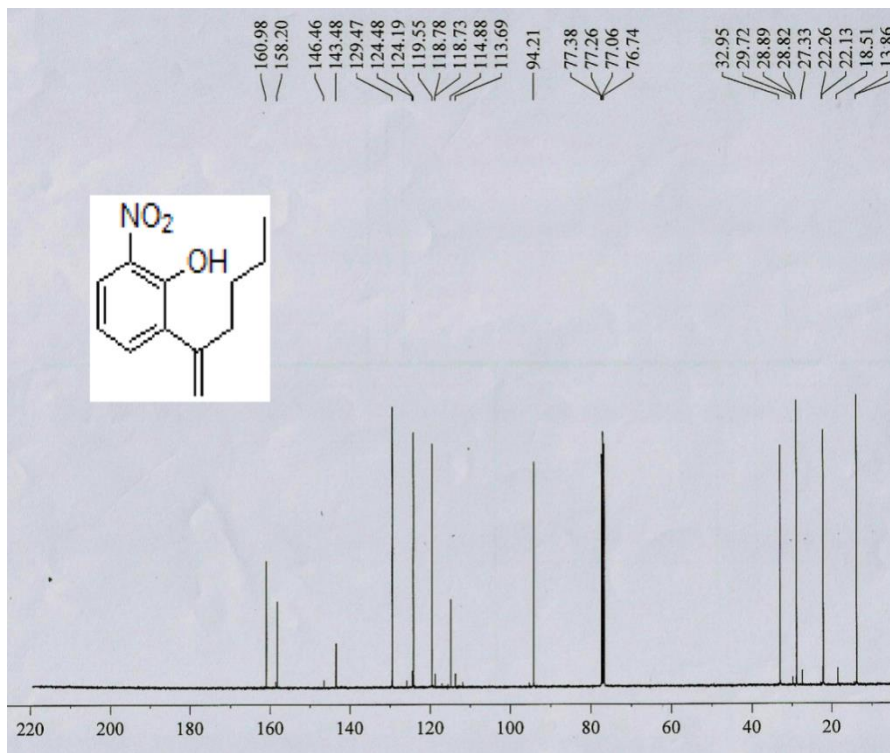
Table-06. Preparation of 2-(Alkyne)-6-nitrophenol.



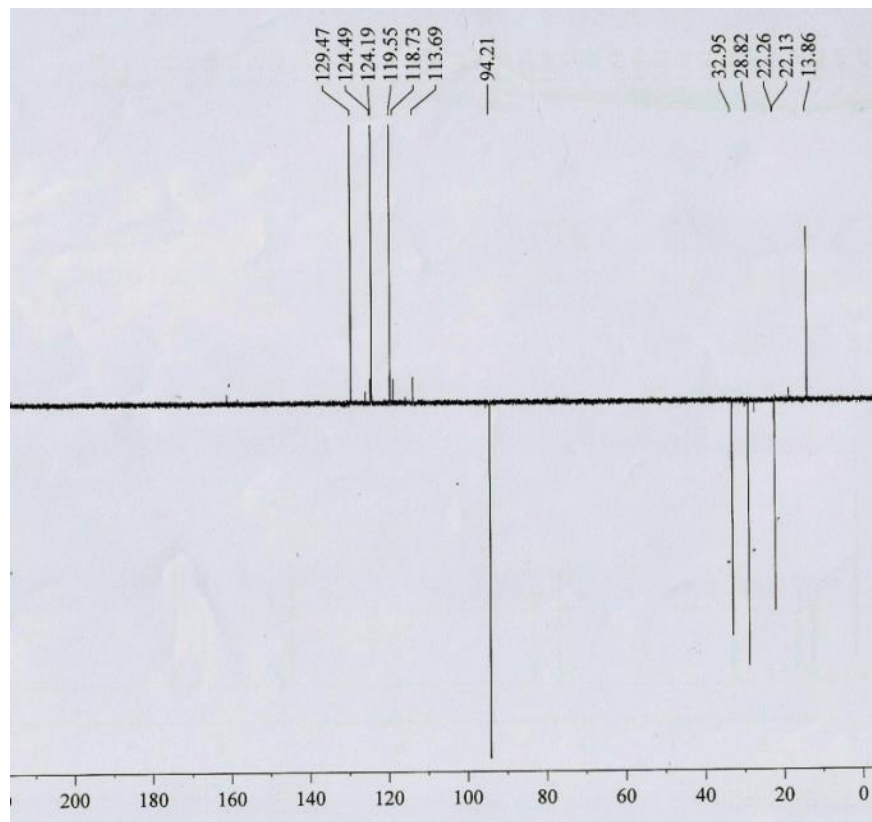
^1H NMR Spectra 2-(hex-1-en-2-yl)phenol.



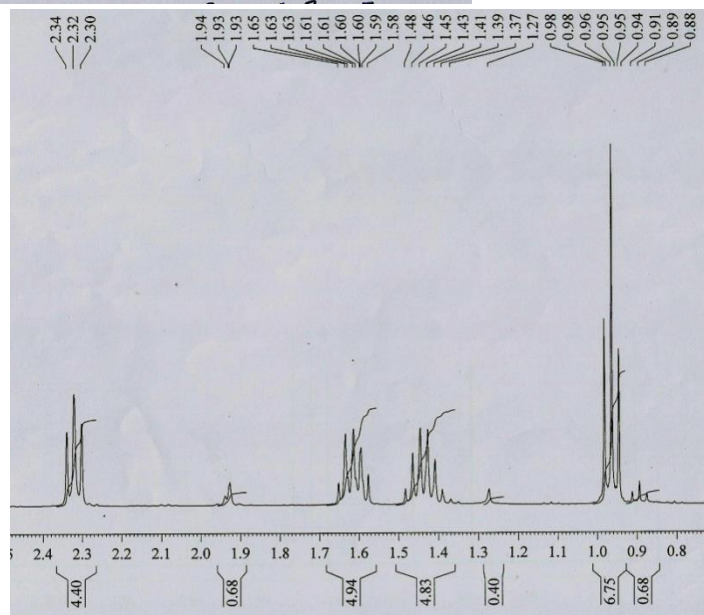
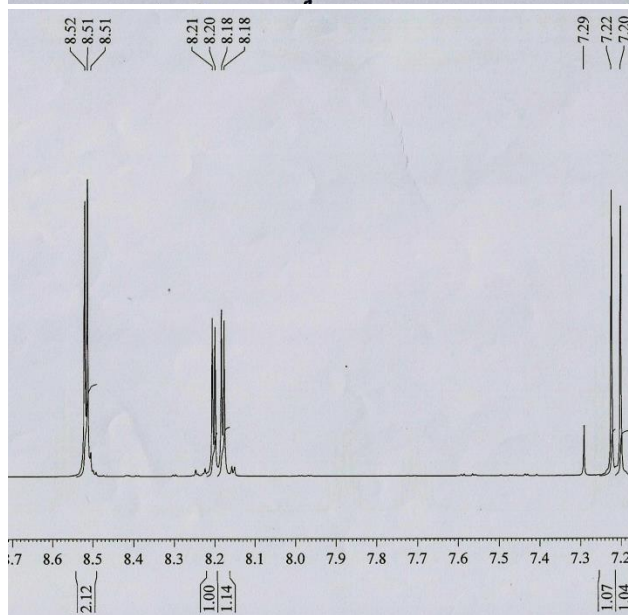
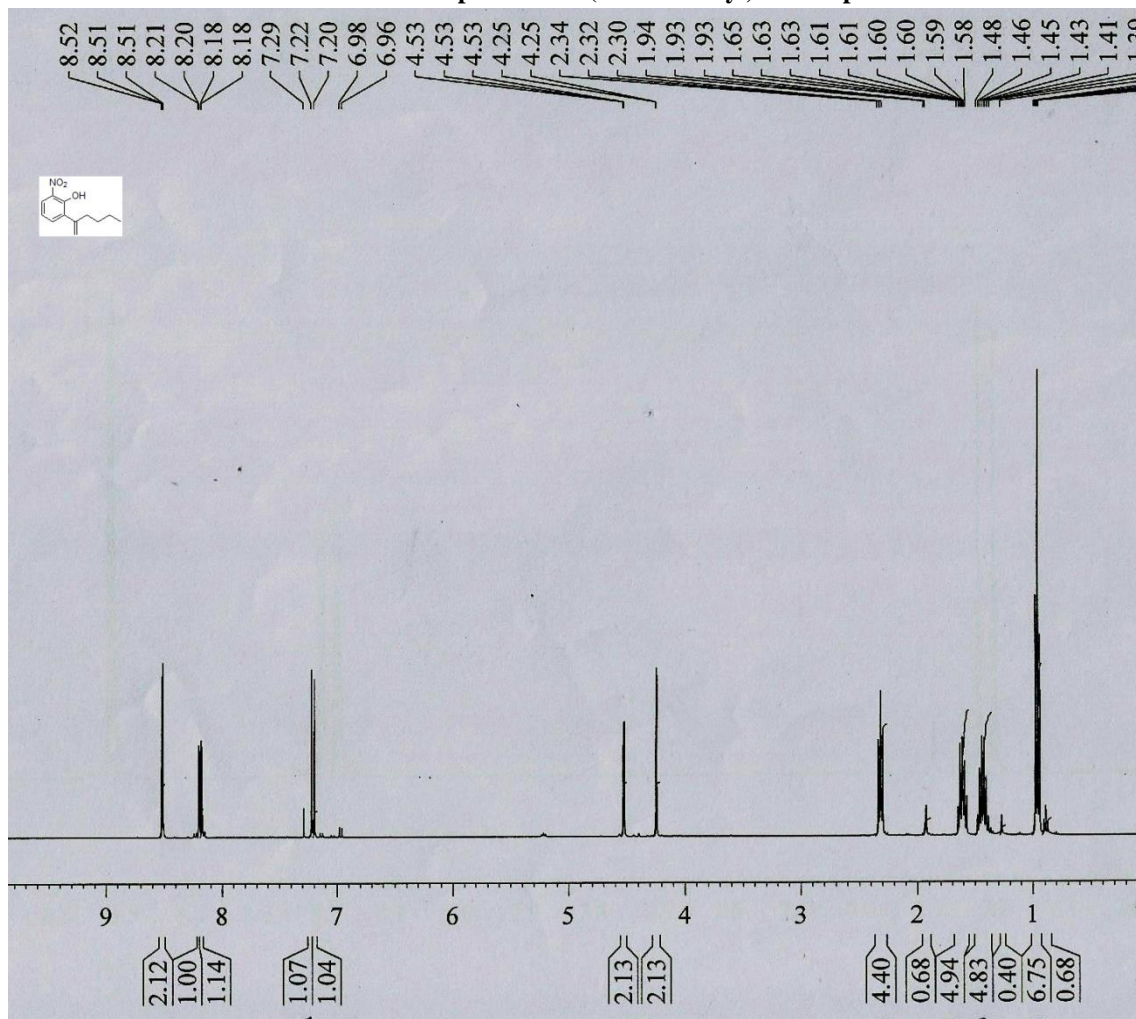
C^{13} NMR Spectra 2-(hex-1-en-2-yl)phenol



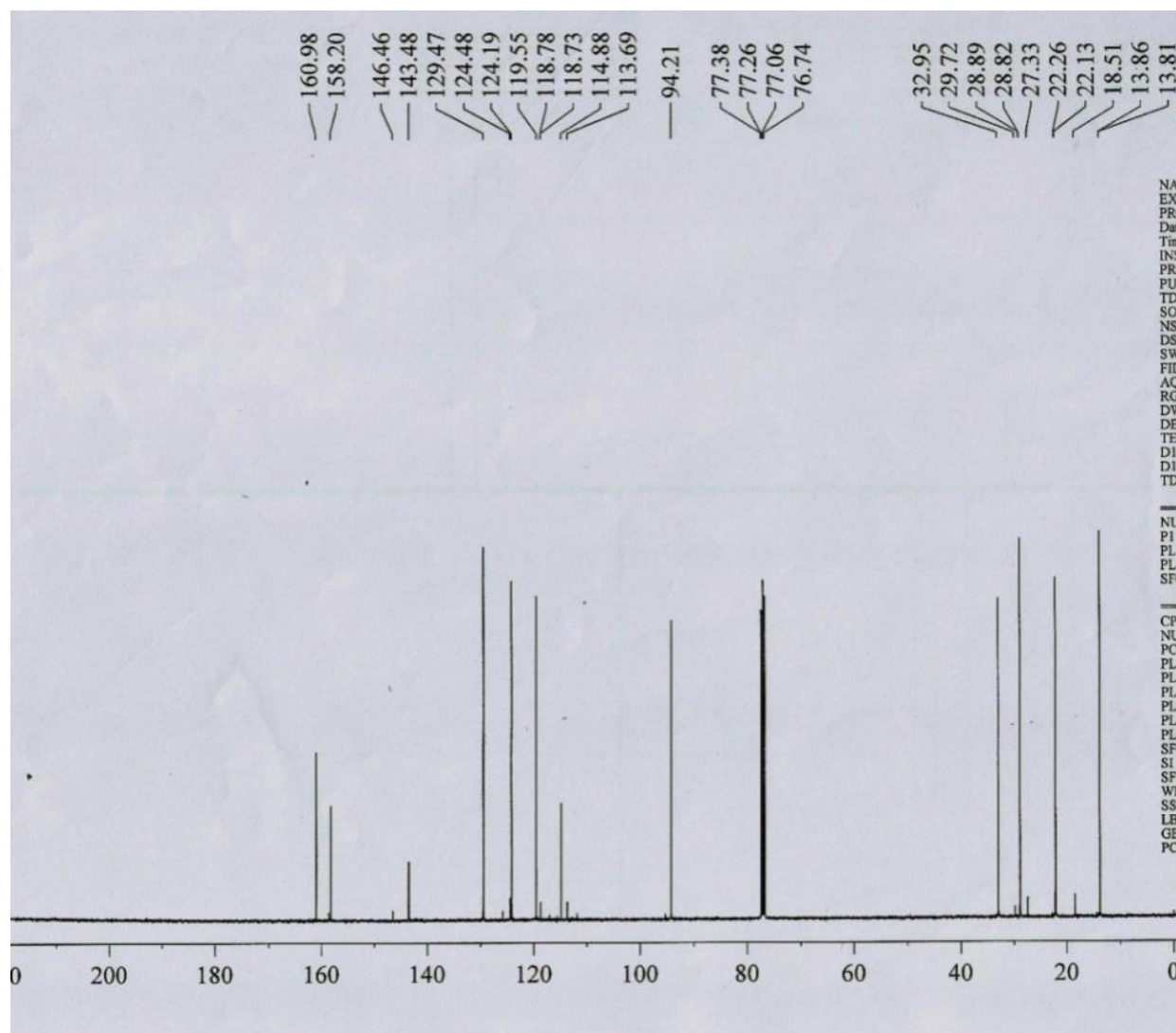
C^{13} Dept Spectra 2-(hex-1-en-2-yl)phenol



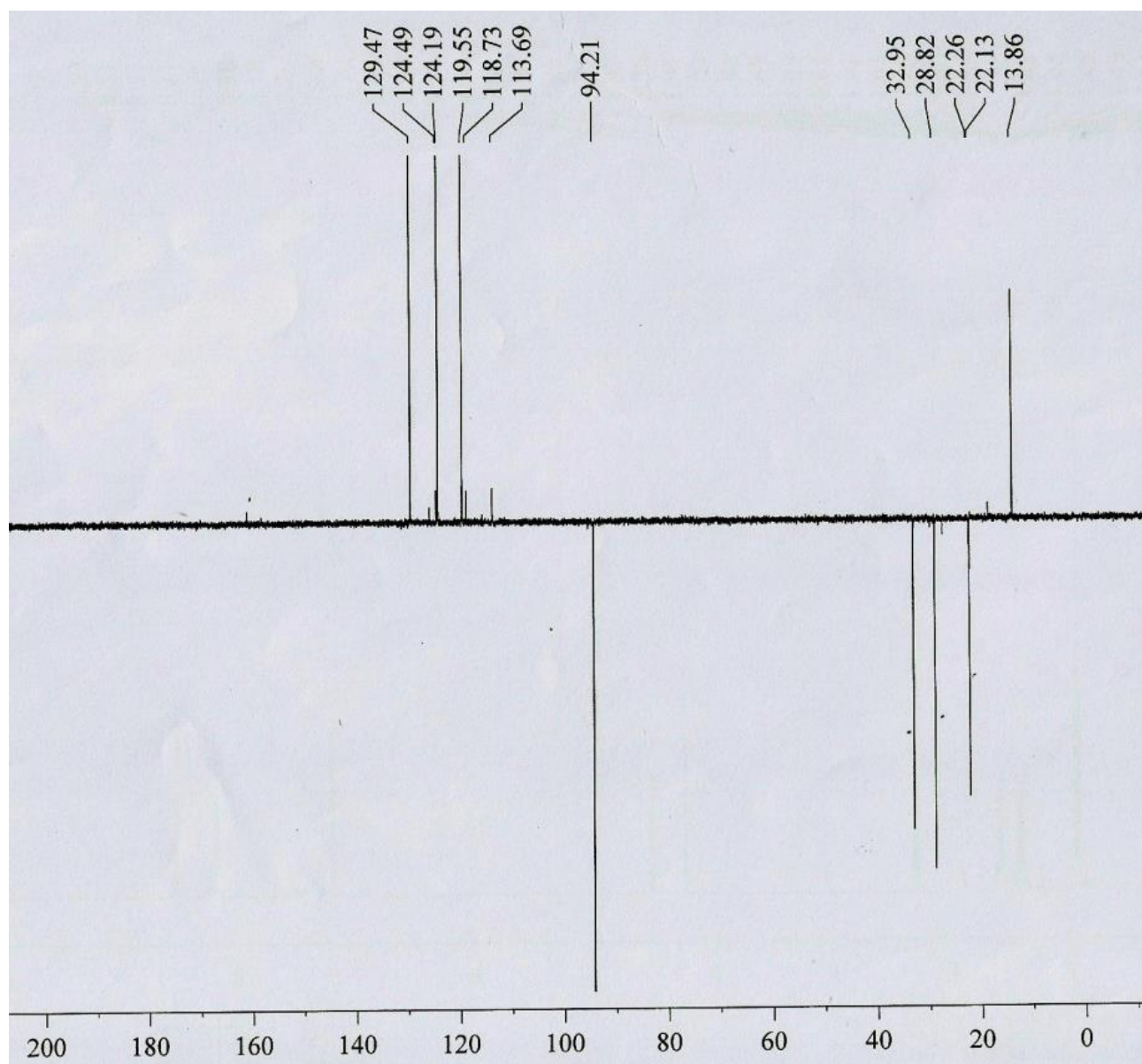
¹H NMR Spectra of 2-(hex-1-en-2-yl)-6-nitrophenol



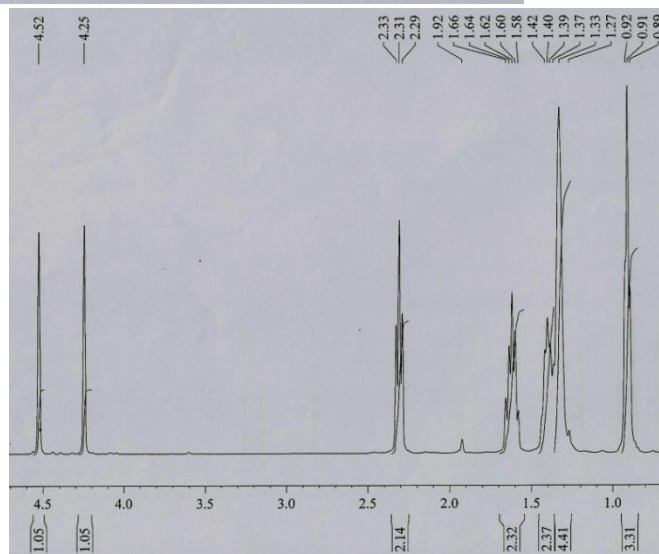
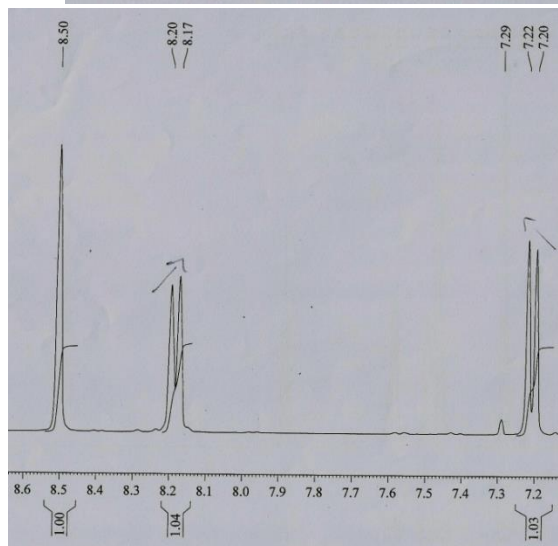
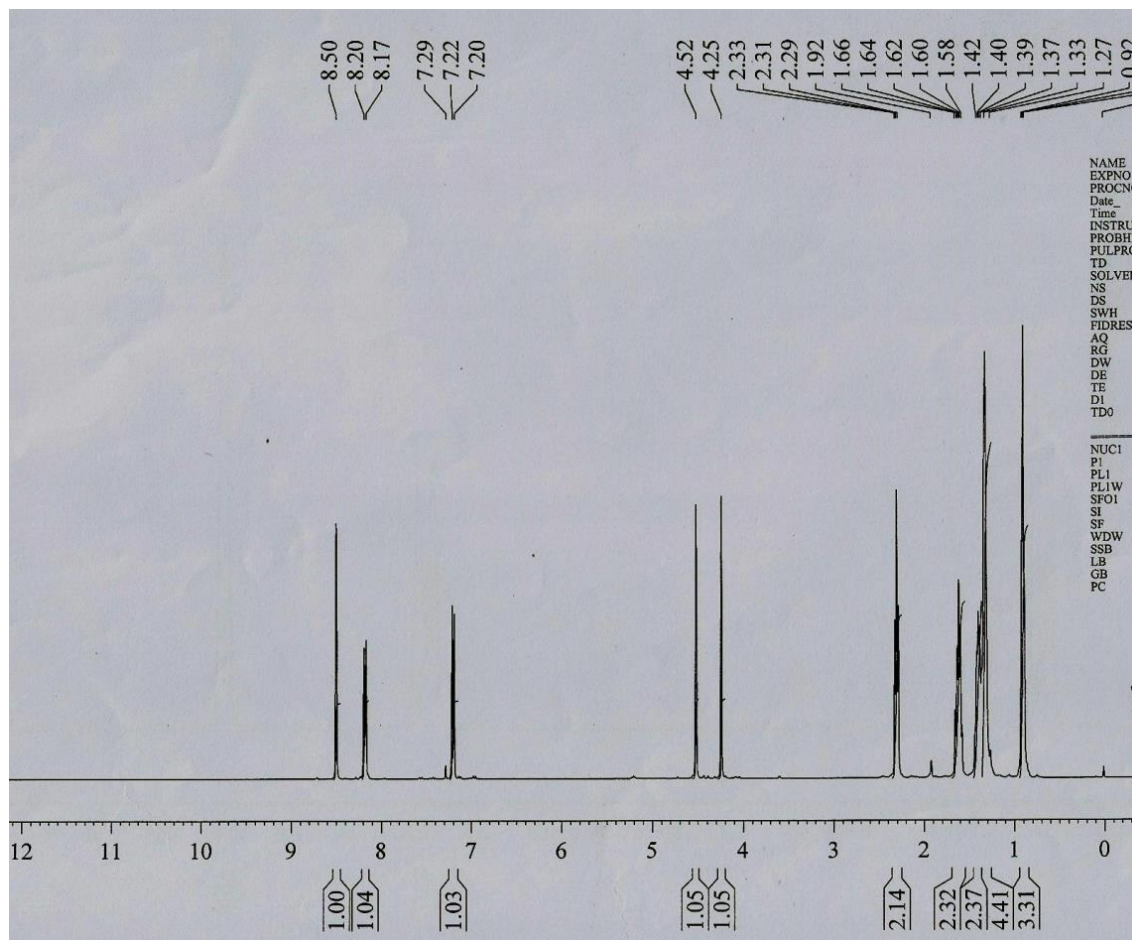
C^{13} NMR Spectra of 2-(hex-1-en-2-yl)-6-nitrophenol.



C^{13} NMR Spectra of 2-(hex-1-en-2-yl)-6-nitrophenol



H¹ NMR Spectra 2-nitro-6-(oct-1-en-2-yl)phenol



4.2 ISOCUMARIN.

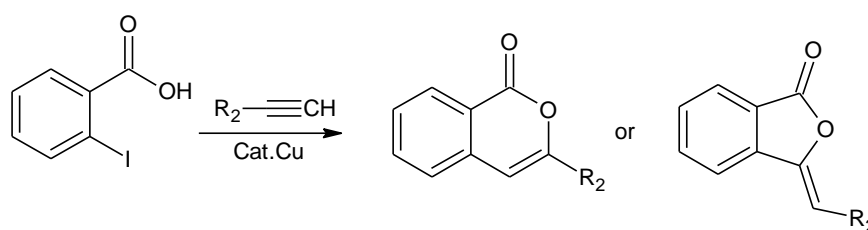
Isocoumarin derivatives are having wide range of biological activity nephrotoxic, antifungal, hepatotoxic, protease inhibitory, antiallergic, cytotoxic, immunomodulatory, antimalarial, mosquito larvicidal activities.[166-168]. These are isomers of coumarin and due to their wide range of application pharmaceutically they are very important compounds. Mohammad thussain and co-worker also synthesis this comp at elevated temp 200°C [169] Tuanli Yao prepared this comp in two step with palladium catalyst [170] Castro prepared this comp from copper acetylides [171] Manivel, P prepared this compound from Grignard reagent [172] Garino prepared from palladium catalyst [173] most of above method uses costly palladium catalyst and hazardous reagent like Grignard or organocuprate.

In present invention we have developed a protocol for preparation of isocoumarin in very simple way and direct copper metal powder is involved in reaction this is the first report in which direct copper metal powder is involved in this type of reaction without use of base and many cases where both the reactants are liquid the solvent free reaction condition also used without workup just by filtering copper powder and purification by column chromatography. This reaction also gives good results with the α Iodo esters in this case reaction occur in three steps in one pot first formation of coupled alkynes secondly hydrolysis of ester at same temperature and lastly cyclization, C-C and C-O bond formation occur simultaneously to form a isocoumarin derivative.

4.2.1 Typical process for preparation of isocoumarin using Copper powder.

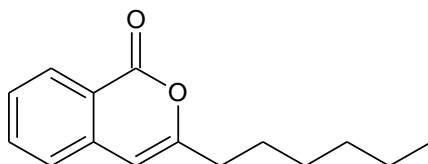
Charged 1 m. mole of iodobenzoic acid, 1.2 m. mole of Terminal alkyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 12-15 hrs. Reaction progress was monitored on TLC. After completion of reaction content was cooled to room temp., diluted with dichloromethane and filtered through cintered funnel. Charged 10 ml water and extracted reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column.

Reaction Scheme: Preparation of isocoumarin using Copper powder.



4.2.1.1 3-hexyl-1H-isochromen-1-one.

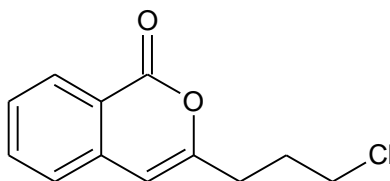
Charged 1 m. mole of iodobenzoic acid, 1.2 m. mole of 1-Heptyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 12-15 hrs. Reaction progress was monitored on TLC. After completion of reaction content was cooled to room temp., diluted with dichloromethane and filtered through cintered funnel. Charged 10 ml water and extracted reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column gives 3-hexyl-1H-isochromen-1-one.



^1H NMR (400 MHz, CDCl_3) δ 0.88 (t 3H), 1.08(m 6H), 1.61(m 2H), 2.40(t 2H), 6.17(S 1H), 7.26(d 1H, J=8), 7.34(t 1H J=8), 7.58(t 1H J=8, J=4), 8.14(d 1H J=8), ^{13}C NMR (100MHz, CDCl_3) δ 14.00, 22.47, 26.81, 28.64, 29.67, 31.46, 33.44, 102.79, 119.97, 125.02, 127.41, 129.27, 134.63, 137.56, 158.18, 162.92.

4.2.1.2 3-(3-chloropropyl)-1H-isochromen-1-one

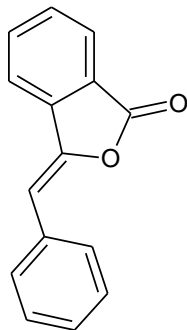
Prepared same as the process of preparation 3-hexyl-1H-isochromen-1-one from iodobenzoic acid, 1.2 m. mole of 5-Chloro1-Pentyne, and 20 mole % of copper powder.



^1H NMR (400 MHz, CDCl_3) δ 8.27(d 1H), 7.7(m 1H j=8), 7.46(m 1H J=8), 7.37(d 1H), 6.34(S 1H), 3.61(t 2H J=4), 2.73(t 2H J=8), 2.20(m 2H J=8).

4.2.1.3 (3Z)-3-benzylidene-2-benzofuran-1(3H)-one.

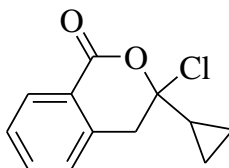
Prepared same as the process of preparation 3-hexyl-1H-isochromen-1-one from iodobenzoic acid, 1.2 m. mole of phenylactylene and 20 mole % of copper powder.



^1H NMR (400 MHz, CDCl_3) δ 7.93(d, 1H J=8), 7.85(d, 2H J=8), 7.73(m, 2H J=8), 7.51(m, 1H), 7.41(t, 1H), 7.29(m, 1H), 6.41(s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.10, 144.57, 140.59, 134.53, 133.11, 130.15, 129.80, 128.85, 128.79, 128.44, 125.53, 125.24, 119.86, 107.10.

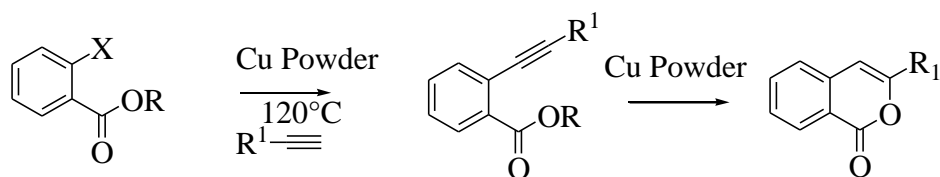
4.2.1.3. 3-chloro-3-cyclopropyl-3,4-dihydroisochromen-1-one

Prepared same as the process of preparation 3-hexyl-1H-isochromen-1-one from iodobenzoic acid, 1.2 m. mole of 5-Chloro-1-Pentyne, and 20 mole % of copper powder.



^1H NMR (400 MHz, CDCl_3) δ 8.15(m, 1H), 7.53(m, 1H), 7.39(m, 1H), 7.25(d, 1H, J=8), 4.30(s, 1H), 2.05(m, 1H), 1.08(m, 2H), 0.92(m, 1H).

4.2.2 Preparation of isocumarins from 2 iodo esters.



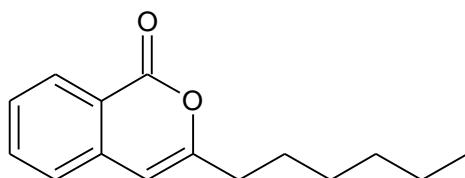
X=I, I(OAc)₂, OTf, Br, R= Octyl, Hexyl, isobutyl. R₁= Octyne, Hexyne, phenyl

Charged 1 m. mole of 2 iodobenzoate, 1.2 m. mole of Terminal alkyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 12-15 hrs. Reaction progress was monitored on TLC. After completion of reaction content was cooled to room temp., diluted with dichloromethane and filtered through cintered funnel. Charged 10 ml water and extracted

reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column as a white solid.

4.2.2.1. 3-hexyl-1H-isochromen-1-one.

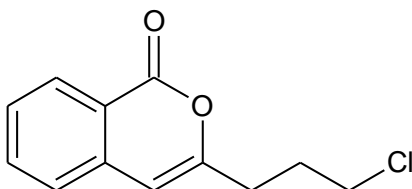
Charged 1 m. mole of 2 iodomethylbenzoate, 1.2 m. mole of 1-Octyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 25-30 hrs. Reaction progress was monitored on TLC. After completion of reaction content was cooled to room temp., diluted with dichloromethane and filtered through cintered funnel. Charged 10 ml water and extracted reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column gives 3-hexyl-1H-isochromen-1-one.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.88 (t 3H), 1.08(m 6H), 1.61(m 2H), 2.40(t 2H), 6.17(S 1H), 7.26(d 1H, $J=8$), 7.34(t 1H $J=8$), 7.58(t 1H $J=8$, $J=4$), 8.14(d 1H $J=8$), $^{13}\text{C NMR}$ (100MHz, CDCl_3) δ 14.00, 22.47, 26.81, 28.64, 29.67, 31.46, 33.44, 102.79, 119.97, 125.02, 127.41, 129.27, 134.63, 137.56, 158.18, 162.92.

4.2.2.2. 3-(3-chloropropyl)-1H-isochromen-1-one.

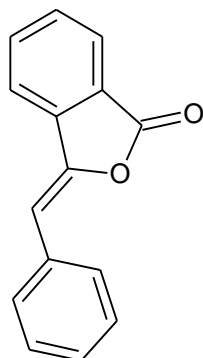
Prepared same as the process of prepration 3-hexyl-1H-isochromen-1-one from iodobenzoic acid, 1.2 m. mole of 5-Chloro1-Pentyne, and 20 mole % of copper powder.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.27(d 1H), 7.7(m 1H $j=8$), 7.46(m 1H $J=8$), 7.37(d 1H), 6.34(S 1H), 3.61(t 2H $J=4$), 2.73(t 2H $J=8$), 2.20(m 2H $J=8$).

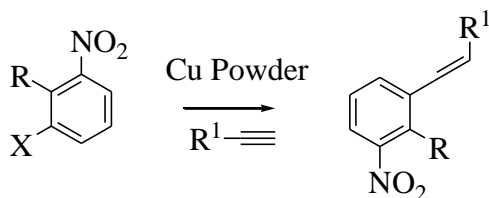
4.2.2.3 (3Z)-3-benzylidene-2-benzofuran-1(3H)-one.

Prepared same as the process of preparation 3-hexyl-1H-isochromen-1-one from iodobenzoic acid, 1.2 m. mole of phenylacetylene and 20 mole % of copper powder.



^1H NMR (400 MHz, CDCl_3) δ 7.93(d, 1H J=8), 7.85(d, 2H J=8), 7.73(m, 2H J=8), 7.51(m, 1H), 7.41(t, 1H), 7.29(m, 1H), 6.41(s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.10, 144.57, 140.59, 134.53, 133.11, 130.15, 129.80, 128.85, 128.79, 128.44, 125.53, 125.24, 119.86, 107.10.

4.2.3. Preparation of Nitro styrene using Copper powder.



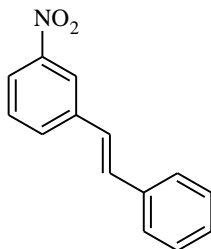
R= H, COOH X=I, I(OAC)₂, OTf, Br, R₁= Octyne, Hexyne, phenyl

Charged 1 m. mole of Nitro iodobenzene, 1.2 m. mole of Terminal alkyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 12-15 hrs. Reaction progress was monitored on TLC. After completion of reaction content was cooled to room temp., diluted with dichloromethane and filtered through cintered funnel. Charged 10 ml water and extracted reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column as a white solid.

4.2.3.1 Process for preparation of (E)-1-(3-nitrostyryl)benzene using Copper powder.

Charged 1 m. mole of 3-Nitro iodobenzene, 1.2 m. mole of Terminal alkyne, and 20 mole % of copper powder in DMF. Reaction mass heated to 120°C for 12-15 hrs. Reaction progress was monitored on TLC. After completion of reaction content was cooled to room temp., diluted with

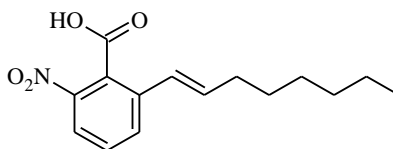
dichloromethane and filtered through cintered funnel. Charged 10 ml water and extracted reaction mass with 20 ml ethyl acetate. Ethyl acetate layer concentrated completely and purified over silica column as a white solid.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.26(m 1H $J=3.2, 8, 8$) 7.37(t 2H $J=9.6, 3.6, 2, \text{)}$, 7.54(m 2H $J=2, 3.2, 4, 3.6, 8$), 7.833(d 1H $J=7.61$), 8.015(d 1H $J=7.61$), 8.190(m 2H $J=0.4, 1.2, 7.6$), 8.37(s 1H), 8.56(d 1H $J=1.2$)

4.2.3.2 Process for preparation of 1-nitro-3-[(E)-2-phenylethenyl]benzene.

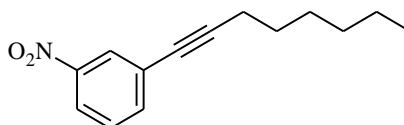
Prepared same as the process of prepration of (E)-1-(3-nitrostyryl)benzene using iodobenzoic acid, 1.2 m. mole of 1-Heptyne, and 20 mole % of copper as a starring materials.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.79(d,1H, $J=8$), 7.69(m, 2H), 7.50(m 1H), 5.66(t, 1H $J=8$), 2.55(m, 2H), 1.57(m 2H), 1.41(m 2H), 0.98(t, 3H), 167.26, 145.64, 139.6, 134.72, 129.49, 127.54, 119.63, 109.76, 102.89, 33.22, 29.71, 28.99, 25.53, 22.39, 13.78.

4.2.3.3. 1-Nitro-3-(oct-1-yn-1-yl)benzene.

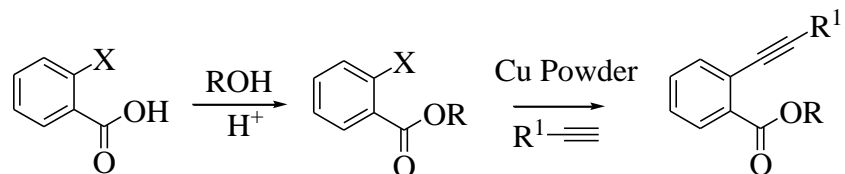
Prepared same as the process of prepration of (E)-1-(3-nitrostyryl)benzene using iodobenzoic acid, 1.2 m. mole of 1-Heptyne, and 20 mole % of copper as a starring materials.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.93(3H, t, $J=4$), 1.36 (4H, m), 1.48(2H, m $J=8$), 1.63(2H, m, $J=8$), 2.45(2H, t, $J=8$), 7.48(1H, dd, $J=4$), 7.71(1H, $J=4$), 7.13 (1H, d, $J=4$), 8.25(1H, $J=4$), ^{13}C

NMR (100MHz, CDCl₃) δ 14.07, 19.39, 22.56, 28.45, 31.06, 78.51, 93.67, 122.22, 126.40, 129.13, 130.7, 132.46, 143.48, 148.08.

4.2.4 Preparation of internal substituted long chain Alkynyl benzoate.

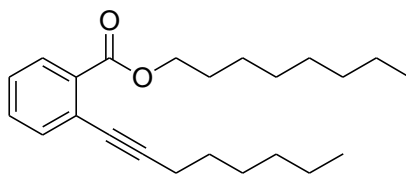


4.2.4.1 Process for preparation of Substituted internal long chain Alkynyl benzoate.

Charged 0.5 gm of Iodo Alkyl benzoate (1.9 m mole), 0.31 gm (2.8 m mole) of Alkynes or Arenes, 0.085gm (0.95m mole) of Copper nanoparticle in 2ml DMF was heated to 110-120°C in a sealed tube for required time. Reaction monitoring was done on TLC ethyl acetate: n- hexane (1:9) as mobile phase. After completion of reaction 3ml Dichlorometane was added and filtered the solid. 3 ml water was added to filtrate and Dichloromethane layer was separated and evaporated. The crude oil was purified on silica column using ethyl acetate and n-Heptane as solvent

4.2.4.2 Octyl 2-(oct-1-ynyl)benzoate.

Charged 0.5 gm of 2 Iodo Octyl benzoate (1.9 m mole), 0.31 gm (2.8 m mole) of Octyne 0.085gm (0.95m mole) of Copper nanoparticle in 2ml DMF was heated to 110-120°C in a sealed tube for required time. Reaction monitoring was done on TLC ethyl acetate: n- hexane (1:9) as mobile phase. After completion of reaction 3ml Dichlorometane was added and filtered the solid. 3 ml water was added to filtrate and Dichloromethane layer was separated and evaporated. The crude oil was purified on silica column using ethyl acetate and n-Heptane as solvent.

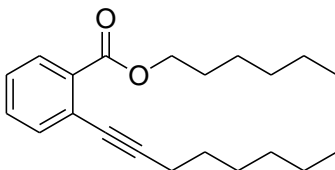


¹H NMR (400 MHz, CDCl₃) δ 7.90(m 1H), 7.53(m 1H), 7.42(m 1H), 7.33(m 1H), 4.34(t 2H), 2.48(t, 2H), 1.78(m, 2H), 1.71(m, 2H), 1.48(m, 4H), 1.35(m, 12H), .92(m 6H). ¹³C NMR (100

MHz, CDCl₃) δ 166.69, 134.29, 132.28, 131.30, 130.07, 127.08, 124.44, 95.90, 65.30, 31.83, 31.64, 31.43, 29.72, 29.34, 29.24, 28.72, 26.10, 22.66, 22.60, 19.86, 14.09.

4.2.4.3. Hexyl 2-(oct-1-ynyl)benzoate.

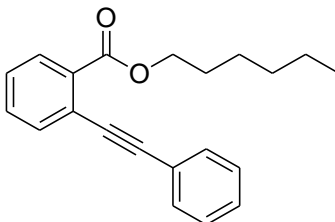
Prepared same as the process of preparation of Octyl 2-(oct-1-ynyl)benzoate using 2 Iodo hexylbenzoate 1.2 m. mole of 1-Octyne, and 20 mole % of copper as a starting materials.



¹H NMR (400 MHz, CDCl₃) δ 7.91(d,d, 1H), 7.54(d,d 1H), 7.41(m, 1H), 7.31 (m, 1H), 4.34(t, 2H), 2.49(t, 2H), 1.83(t, 2H), 1.66(m, 2H), 1.49(m 4H), 1.46(m 10H), 0.93(m, 6H), ¹³C NMR (100 MHz, CDCl₃) δ 166.69,141.26, 135.60, 134.30, 132.47, 132.29, 131.30, 130.83, 130.07, 129.54, 127.88, 127.09, 124.43, 95.91, 79.30, 65.29, 31.45, 28.72, 25.76,22.59, 19.86,14.04.

4.2.4.4. Hexyl 2-(2-phenylethynyl)benzoate.

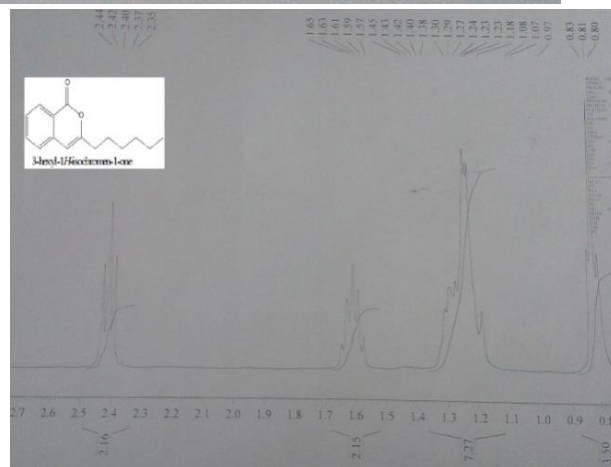
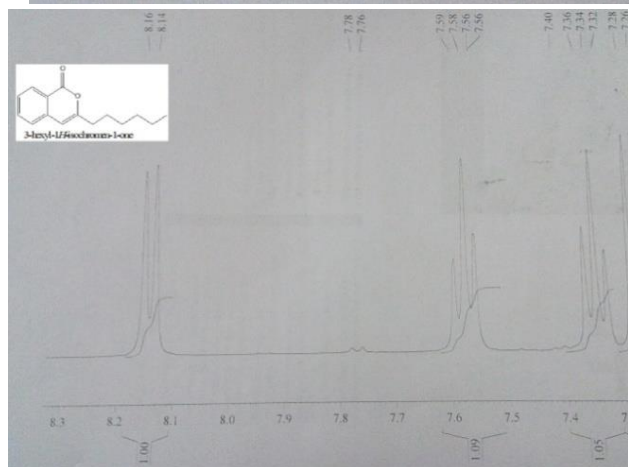
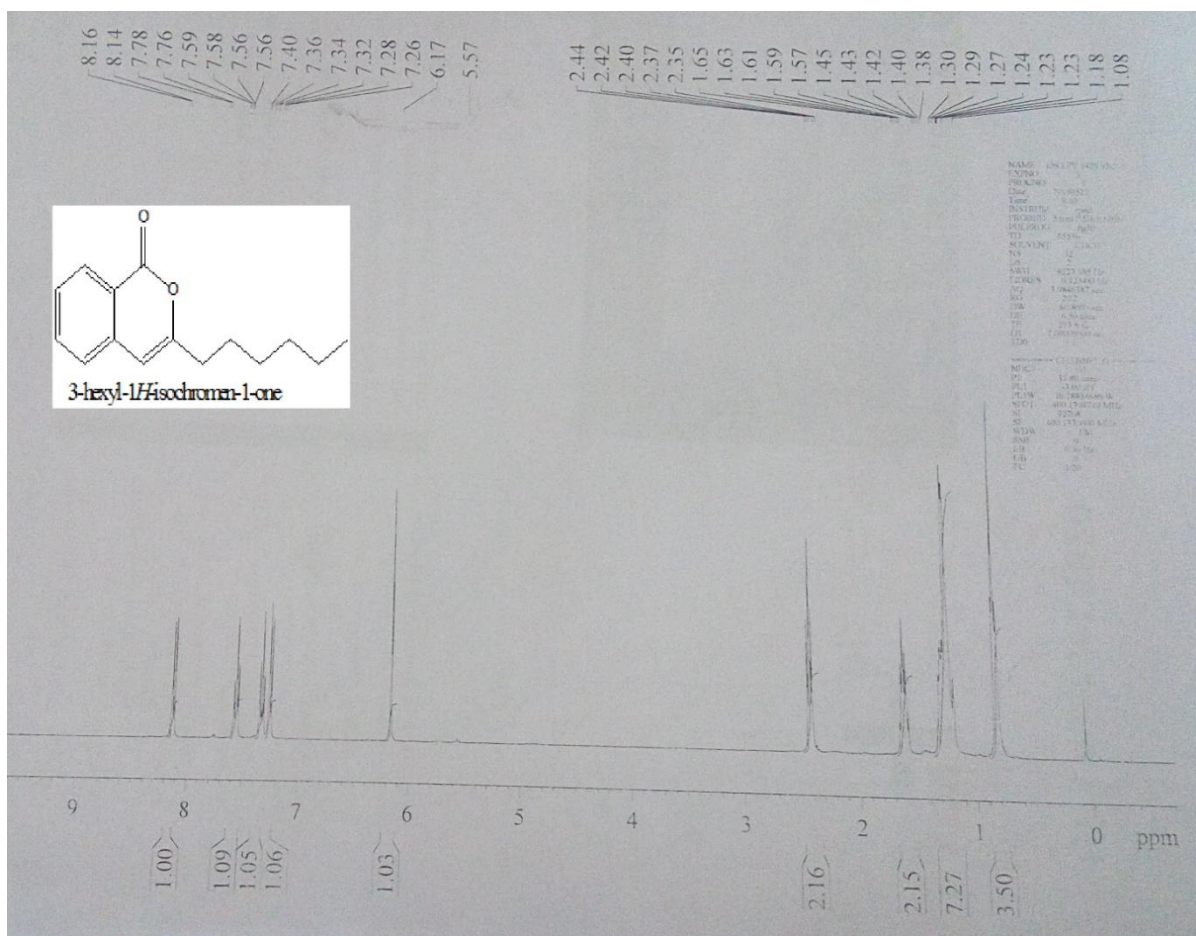
Prepared same as the process of preparation of Octyl 2-(oct-1-ynyl)benzoate using 2 Iodo hexylbenzoate 1.2 m. mole of Phenyl actylene, and 20 mole % of copper as a starting materials.



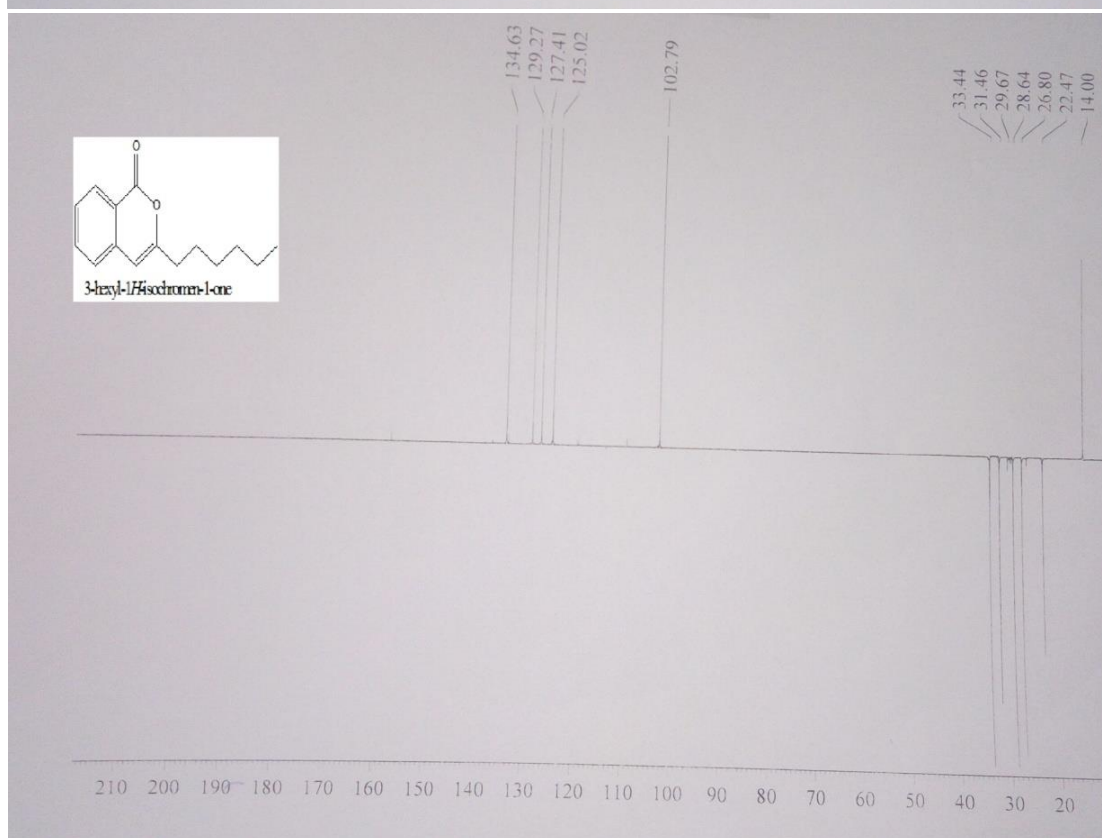
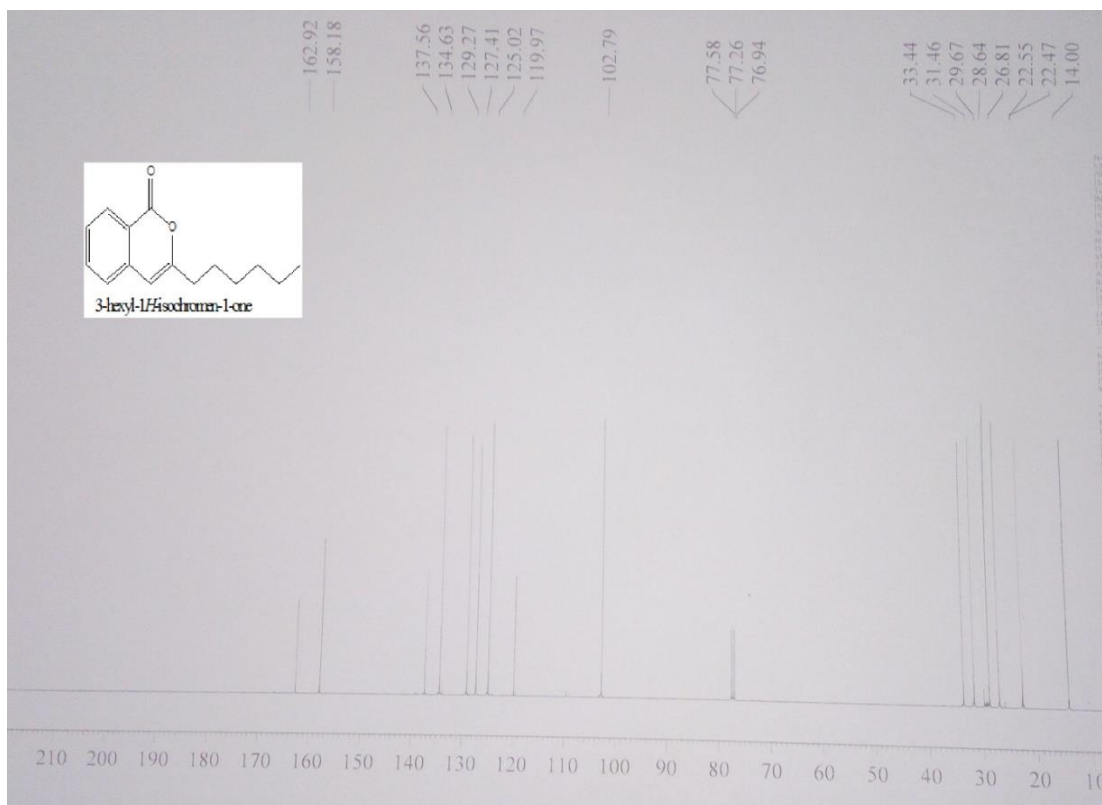
¹H NMR (400 MHz, CDCl₃) δ 7.98(d, 1H), 7.66(d, 1H),7.57(m 1H), 7.49(m,1H), 7.36(m, 4H), 4.34(t, 2H), 1.78(m, 2H), 1.42(m, 2H), 1.26(m, 4H), 0.87(t,3H)

4.2.5. ^1H NMR and ^{13}C NMR Spectras of reported compound.

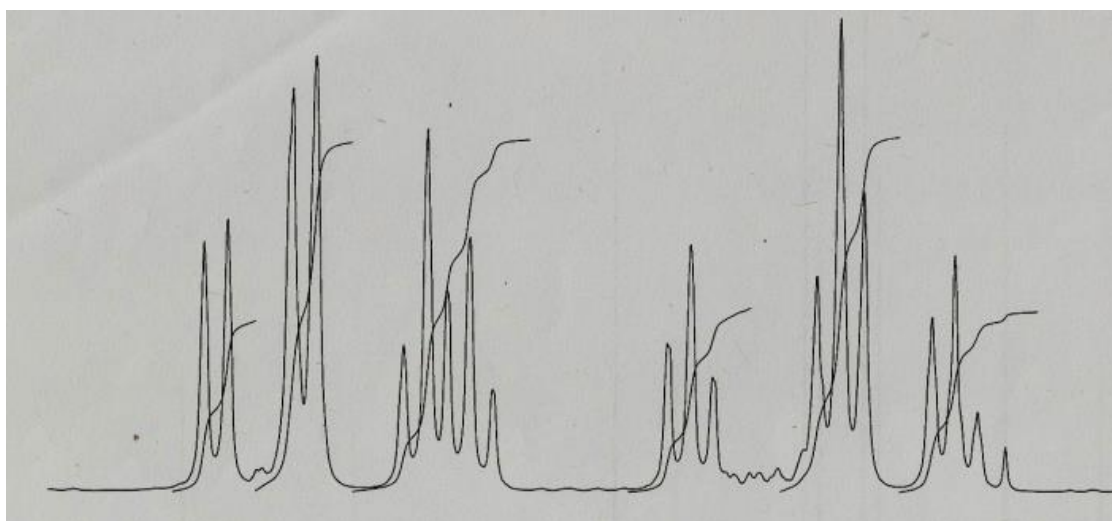
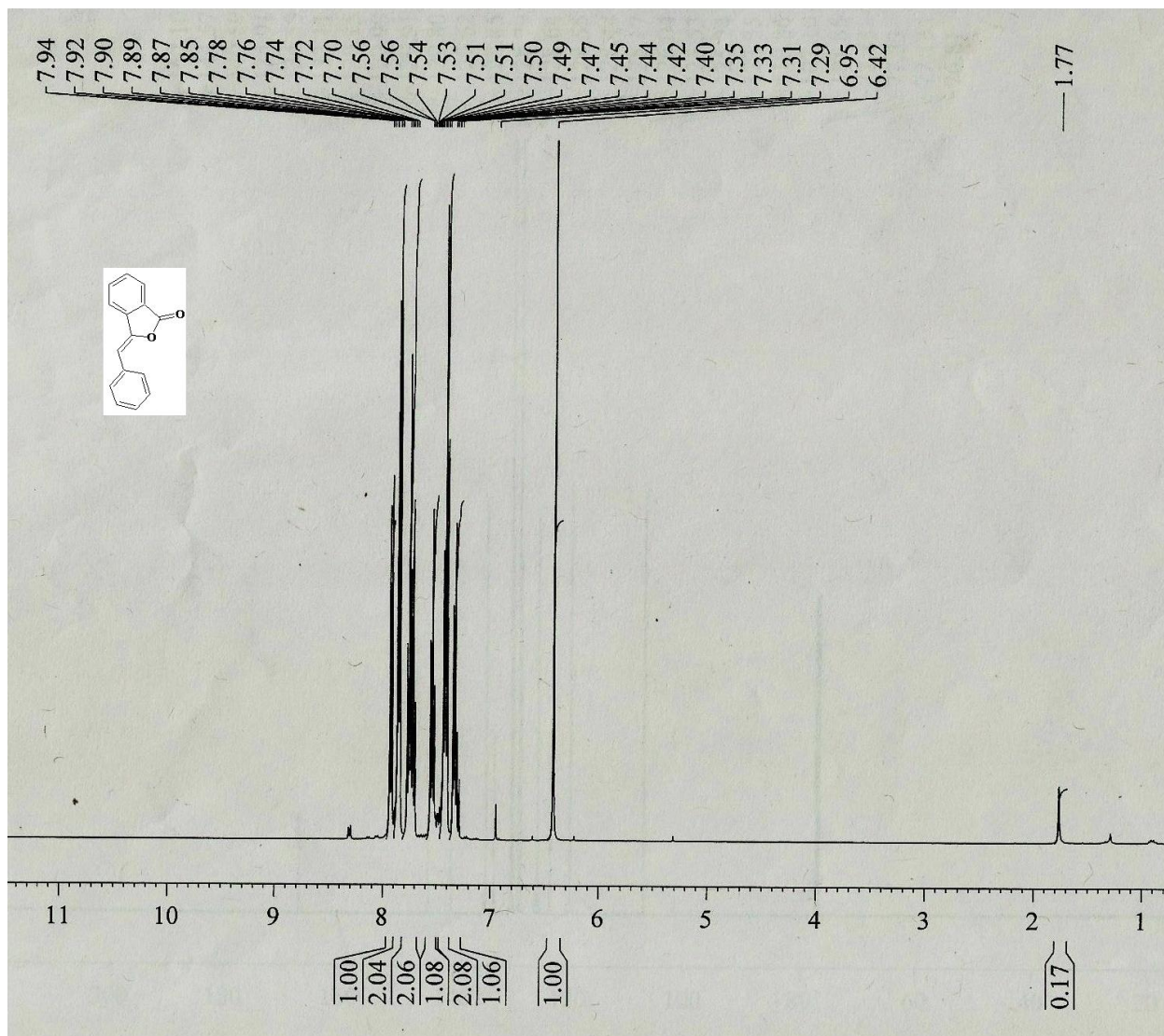
3-hexyl-1H-isochroman-1-one NMR



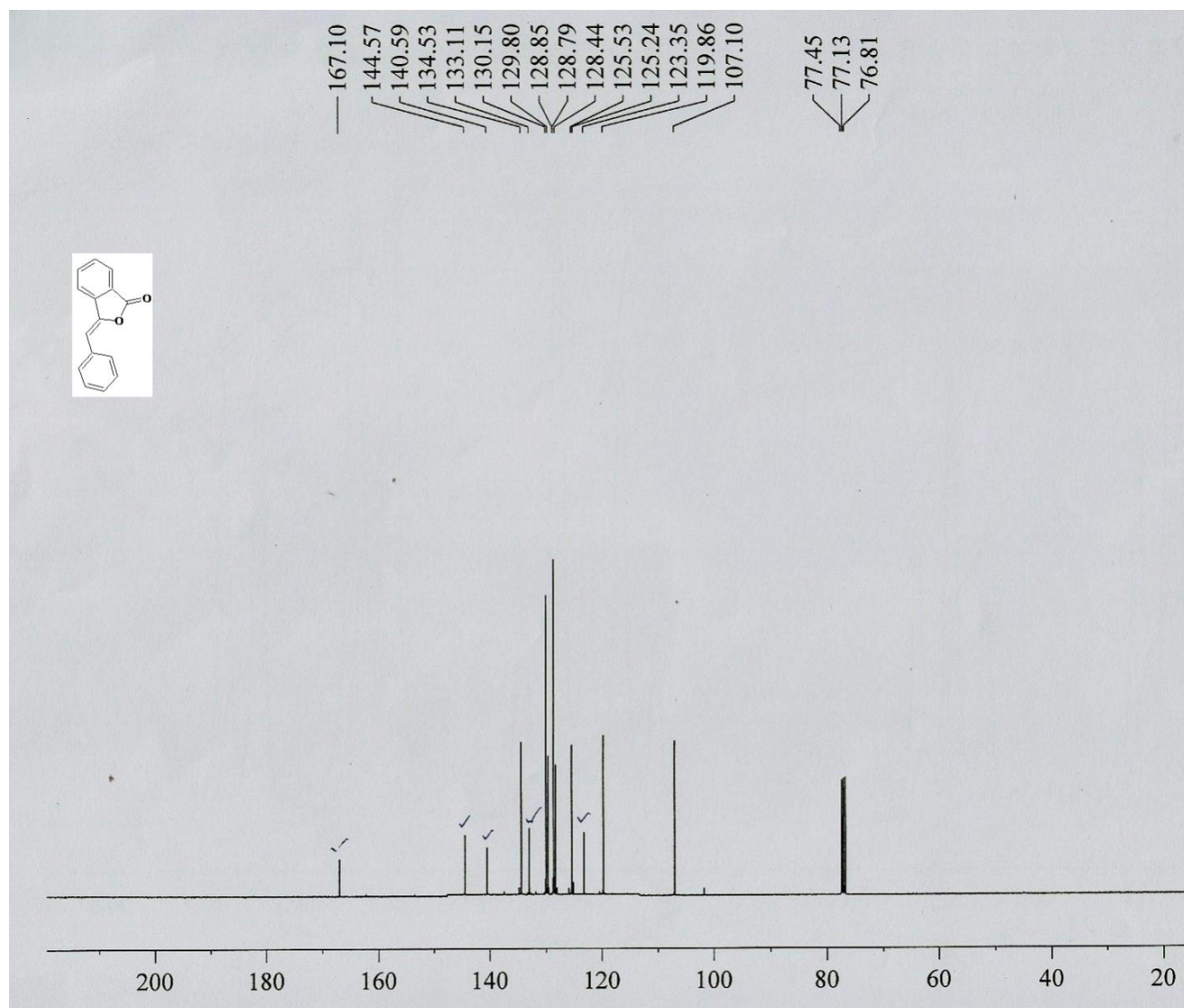
3-hexyl-1H-isochromen-1-one ¹³C NMR



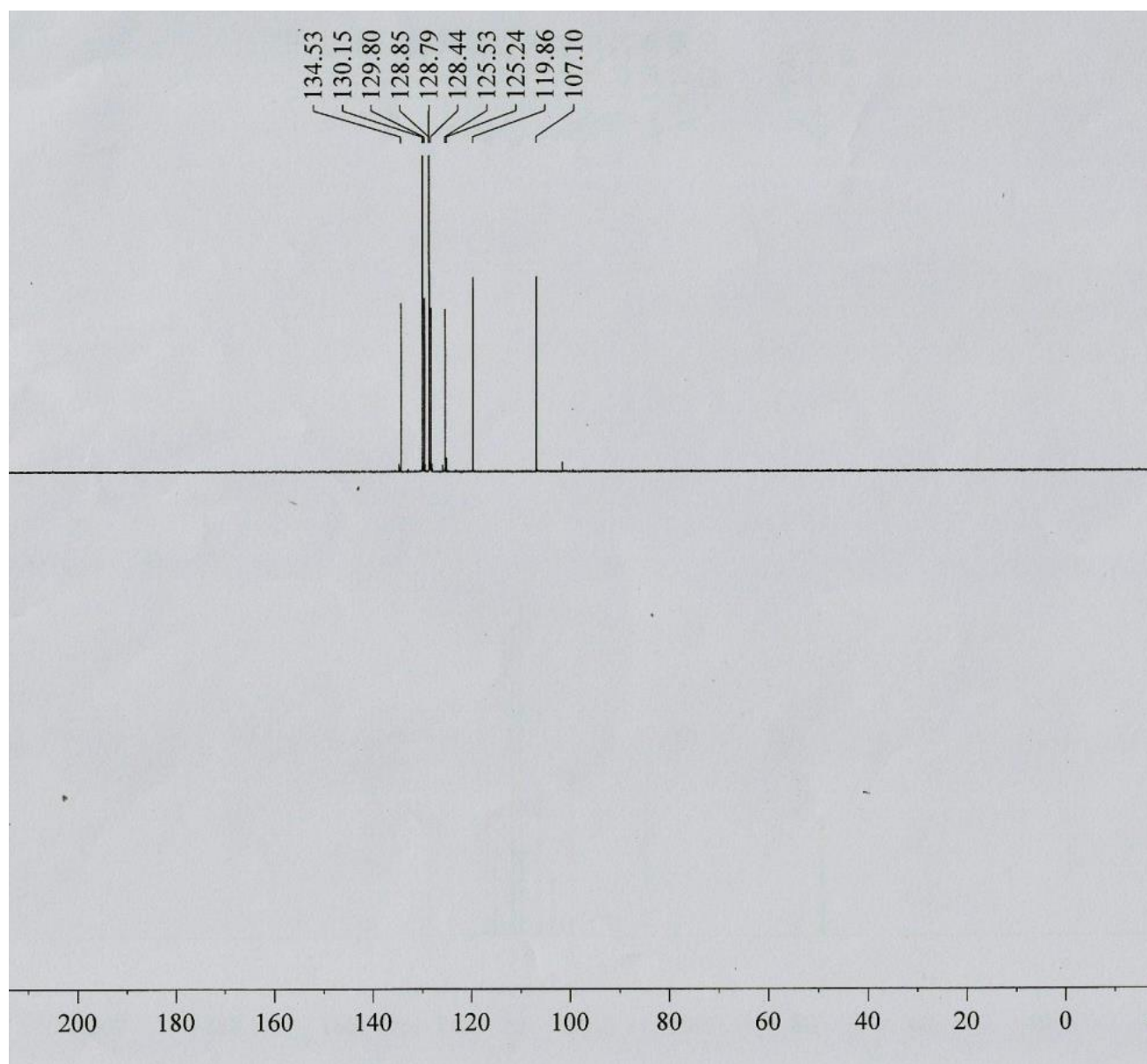
^1H NMR 3-phenyl-1H-isochromen-1-one.



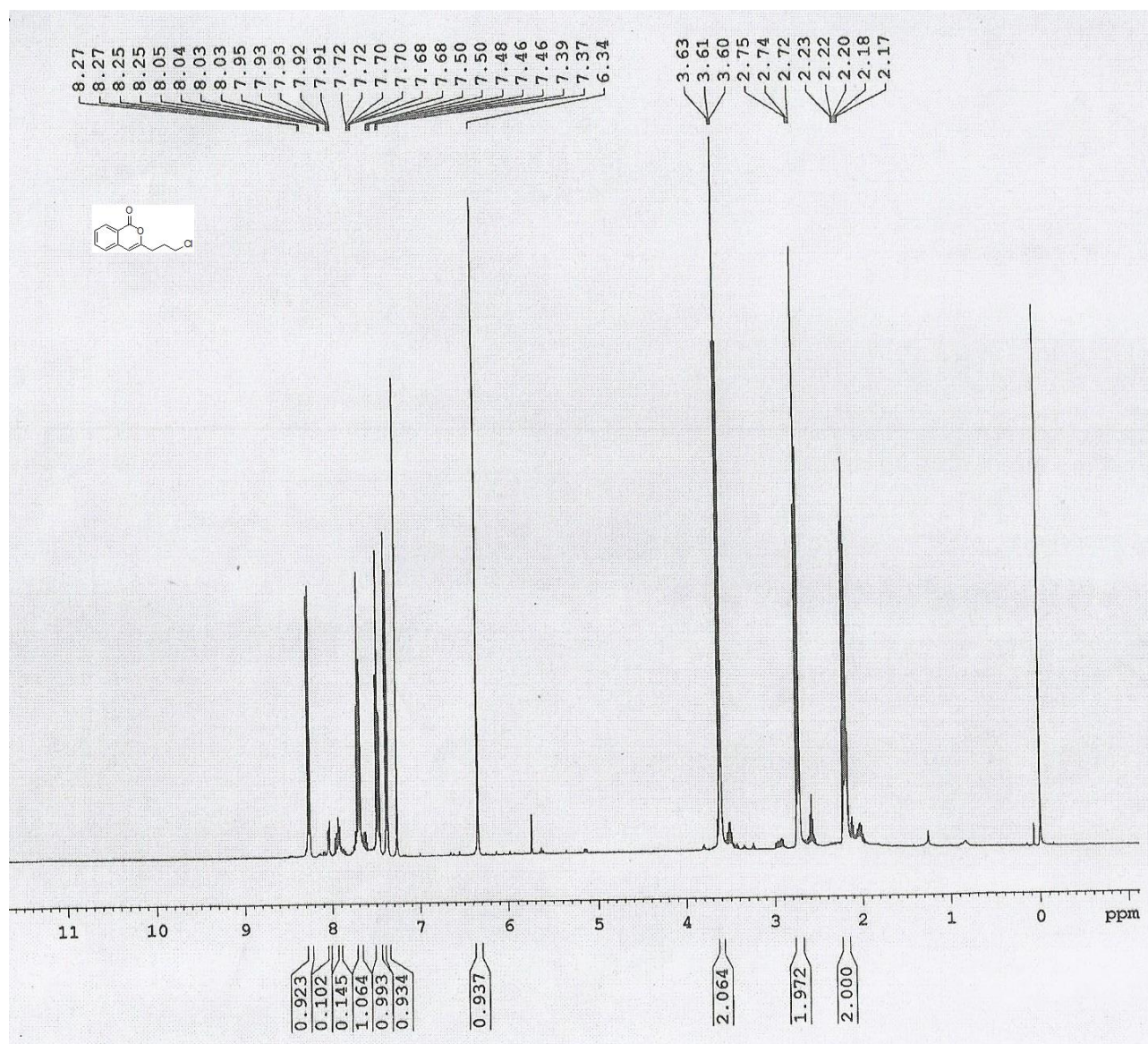
¹³C NMR 3-phenyl-1H-isochromen-1-one



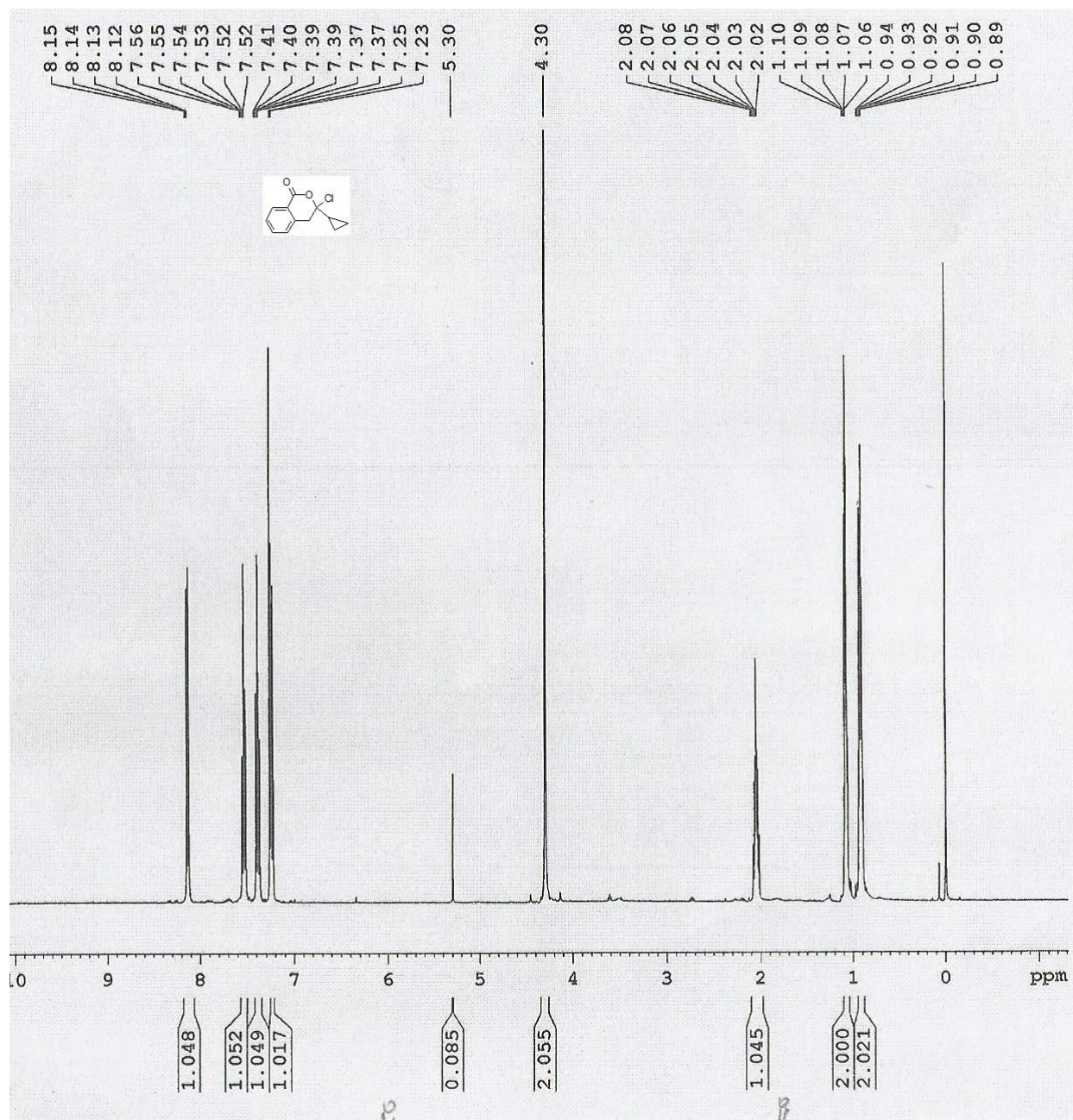
¹³C Dept 3-phenyl-1H-isochromen-1-one



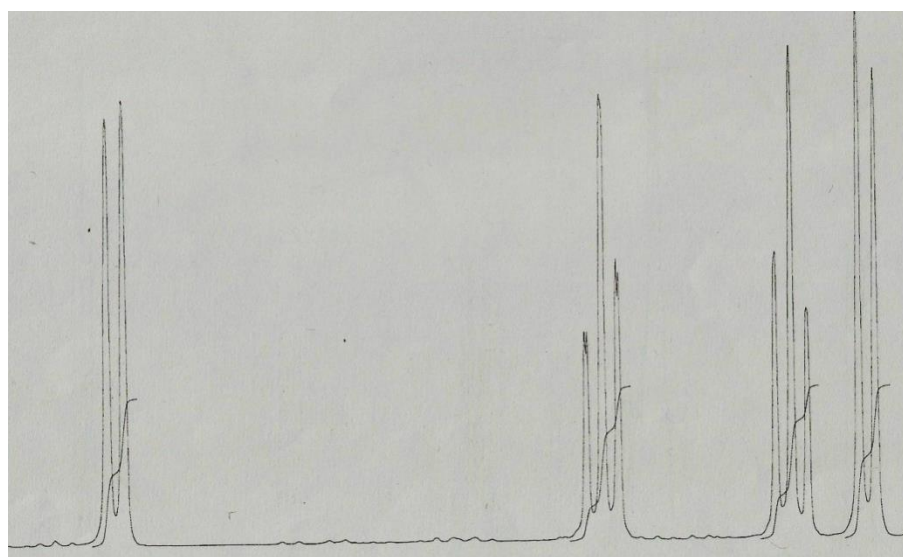
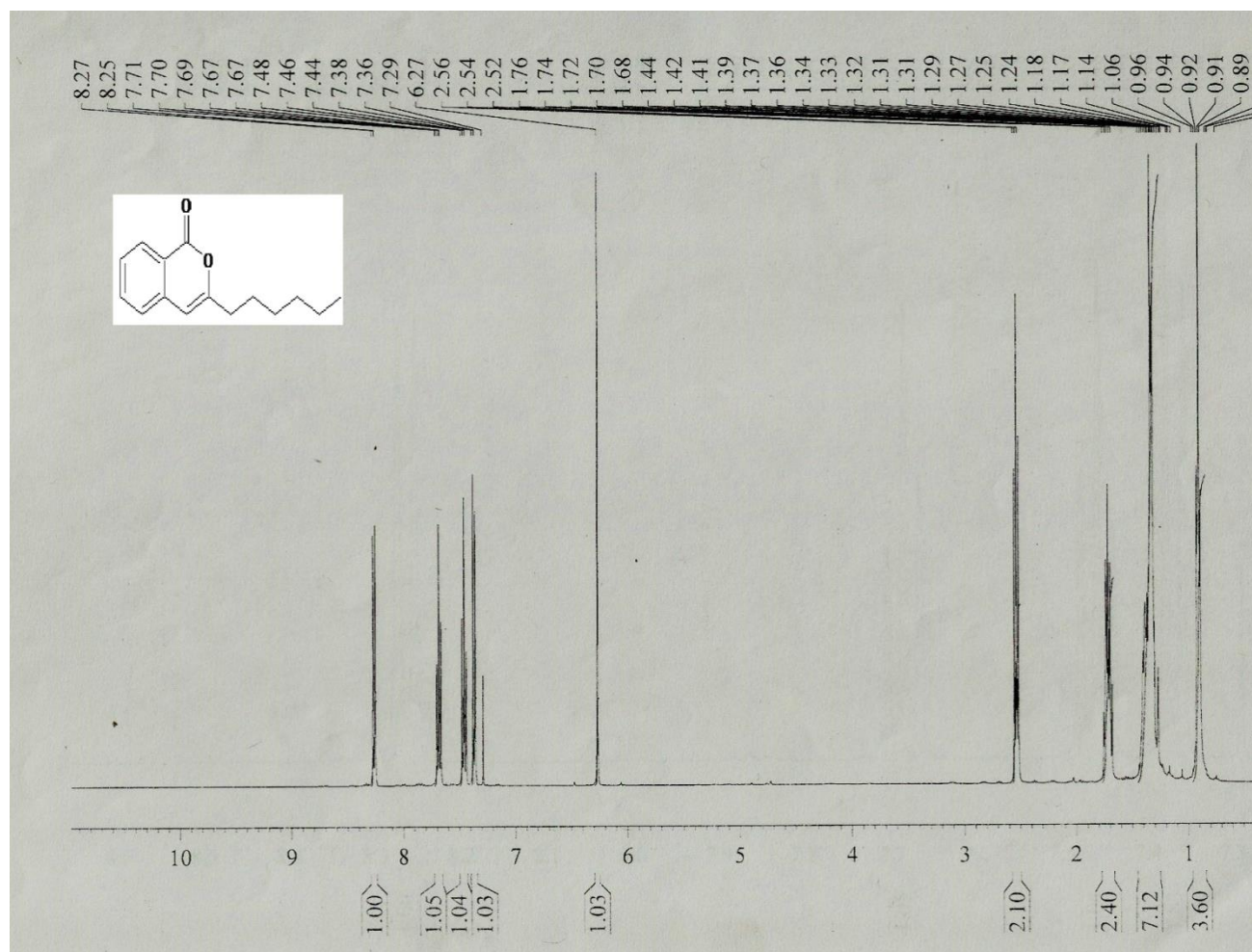
¹H NMR 3-(3-chloropropyl)-1H-isochromen-1-one



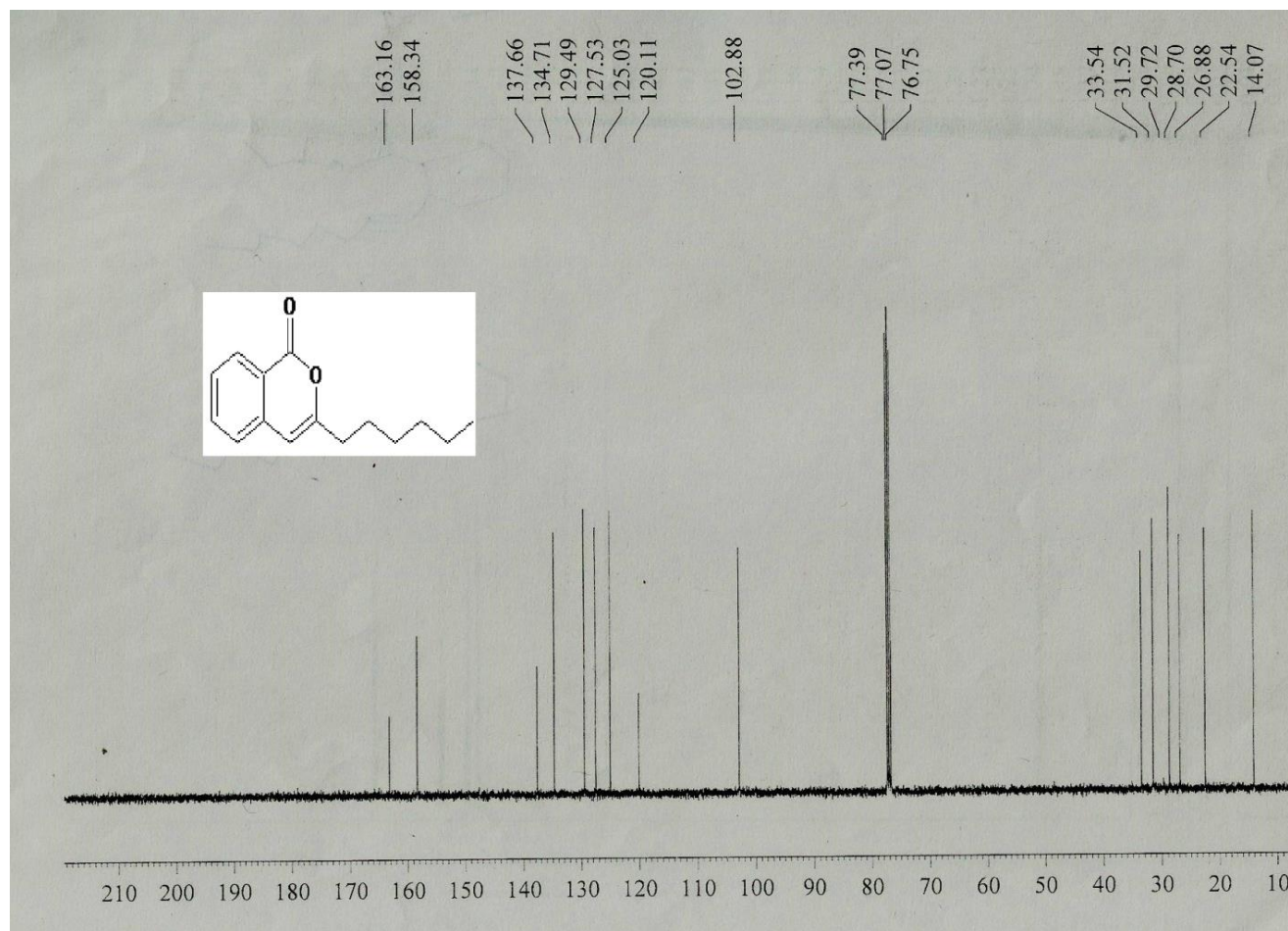
¹H NMR Spectra 3-chloro-3-cyclopropyl-3,4-dihydroisochromen-1-one.



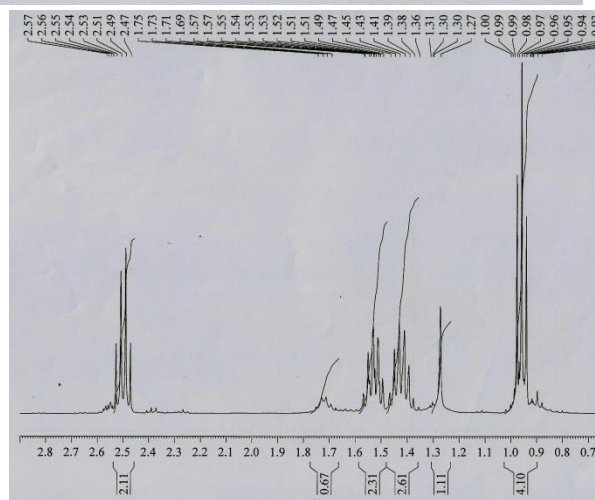
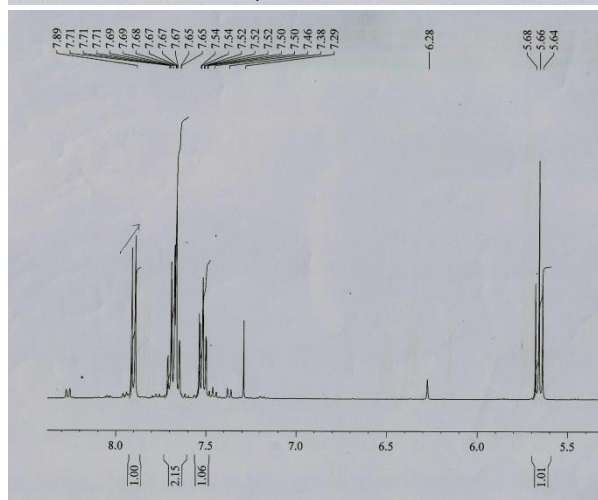
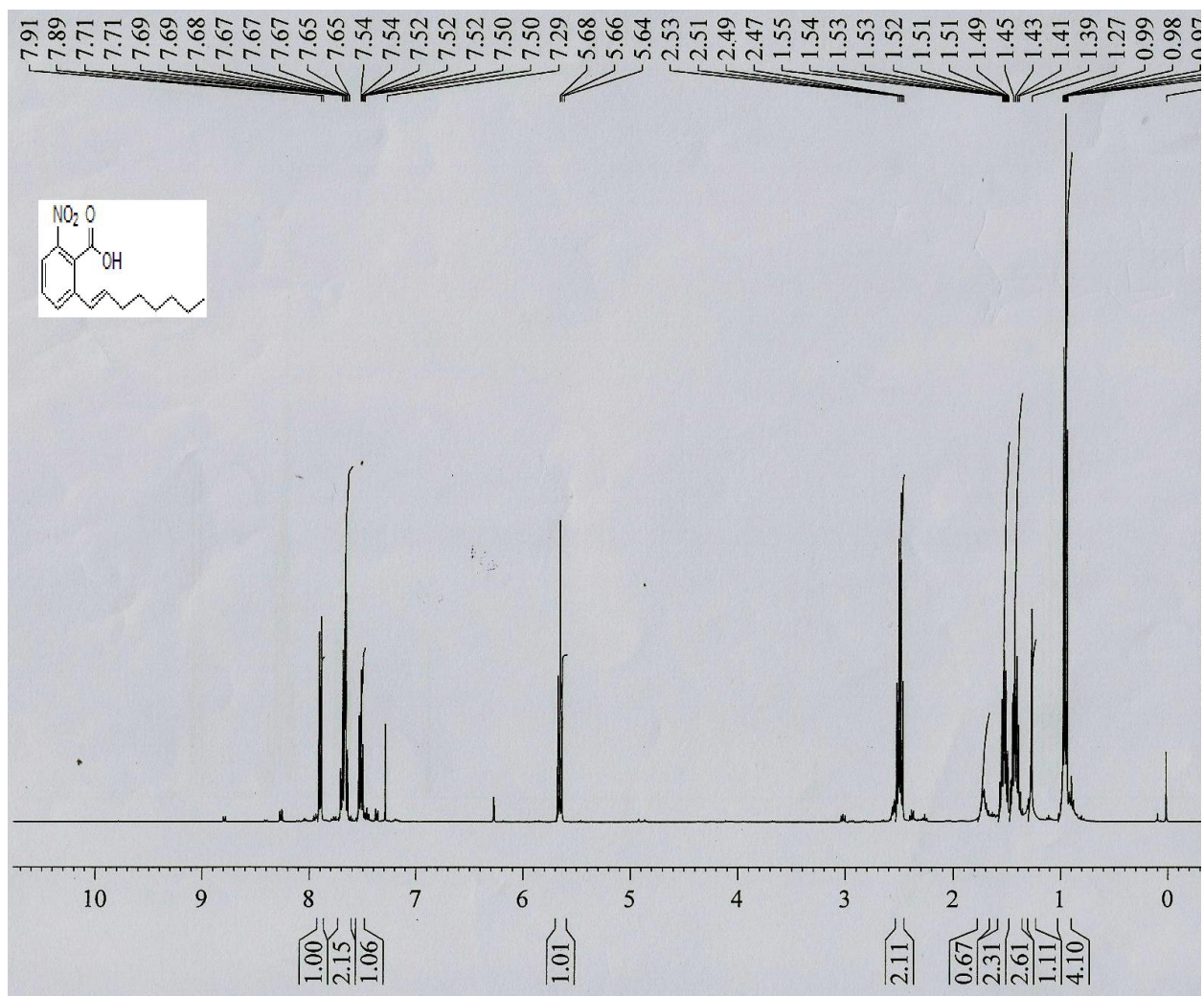
¹H NMR 3-hexyl-1H-isochromen-1-one.



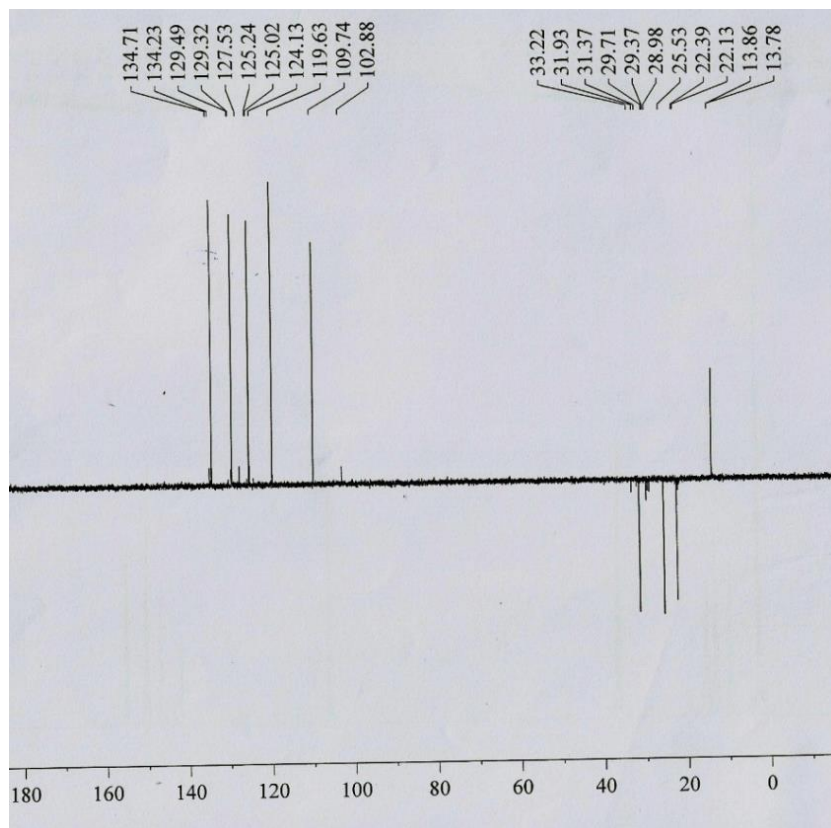
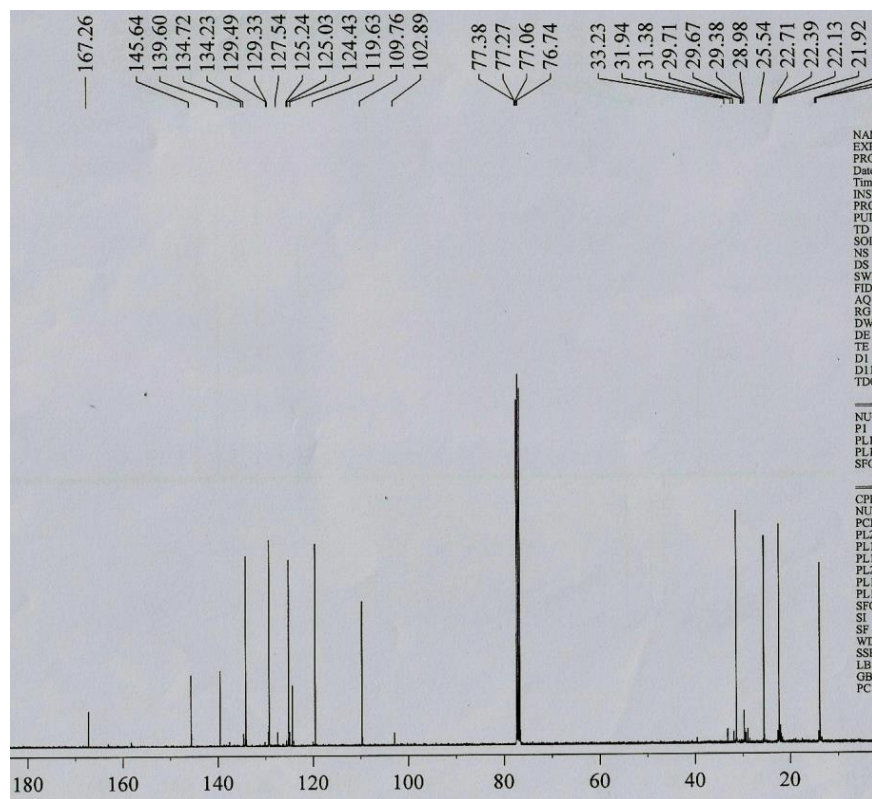
¹³C NMR 3-hexyl-1H-isochromen-1-one.



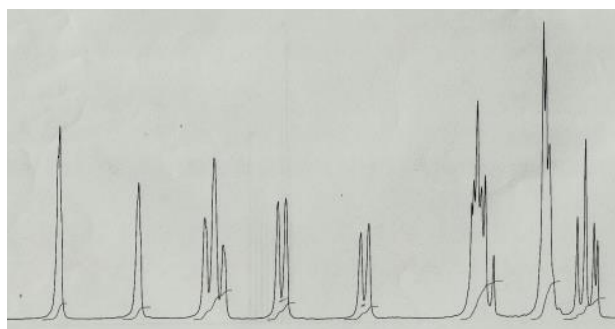
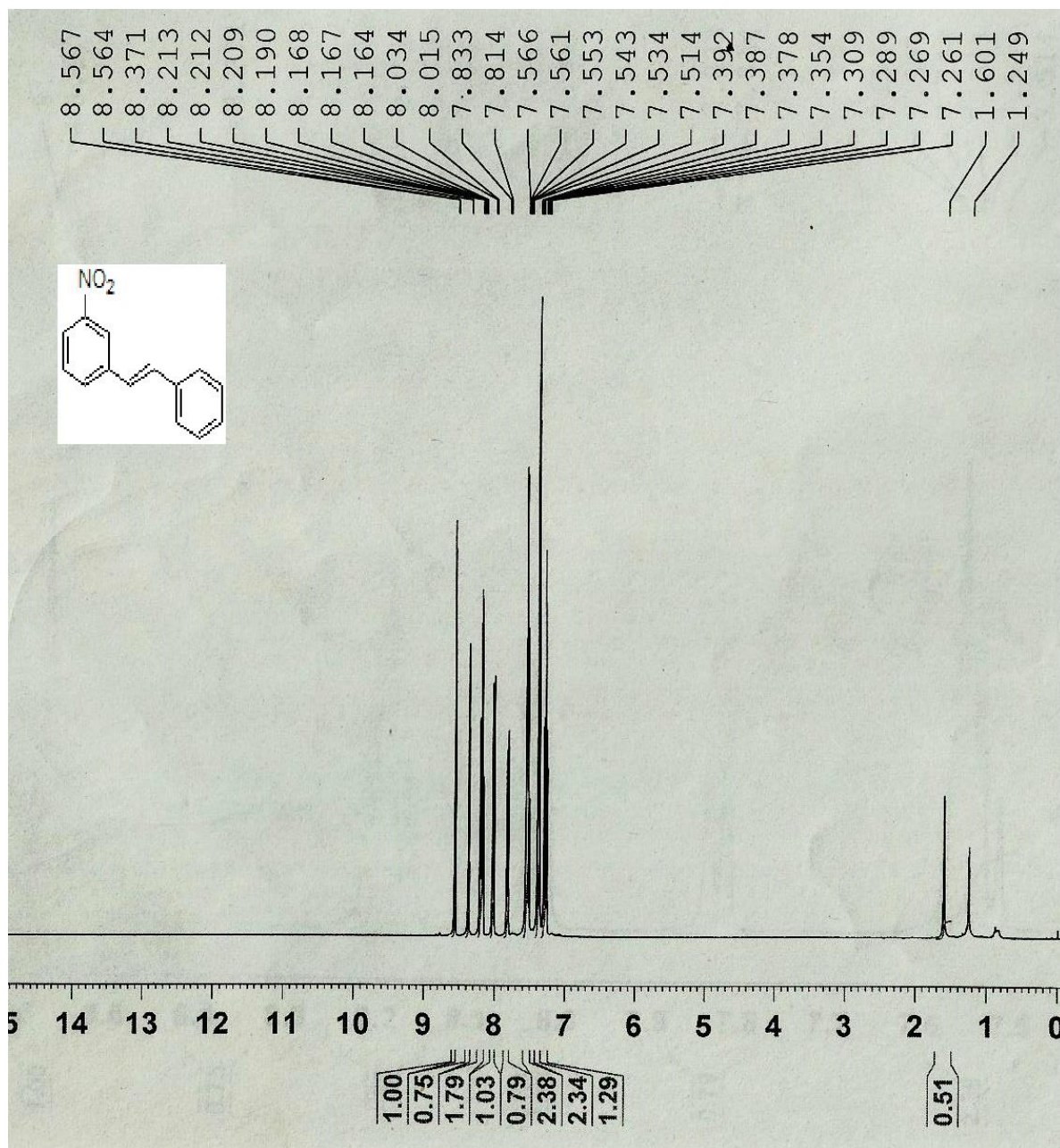
¹H NMR Spectra (E)-2-nitro-6-(oct-1-enyl)benzoic acid



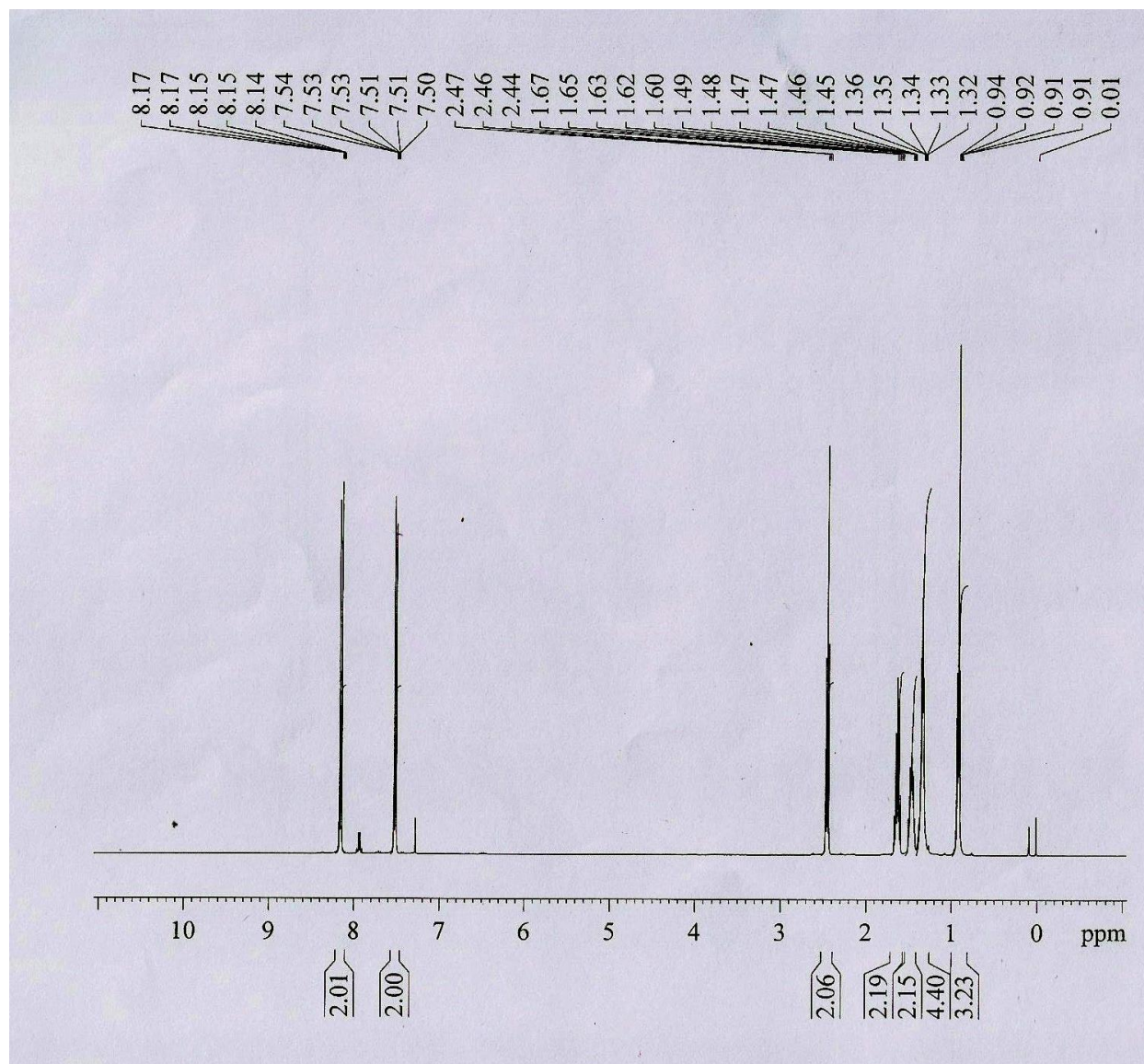
¹³C NMR and ¹³C Dept. Spectra (E)-2-nitro-6-(oct-1-enyl)benzoic acid



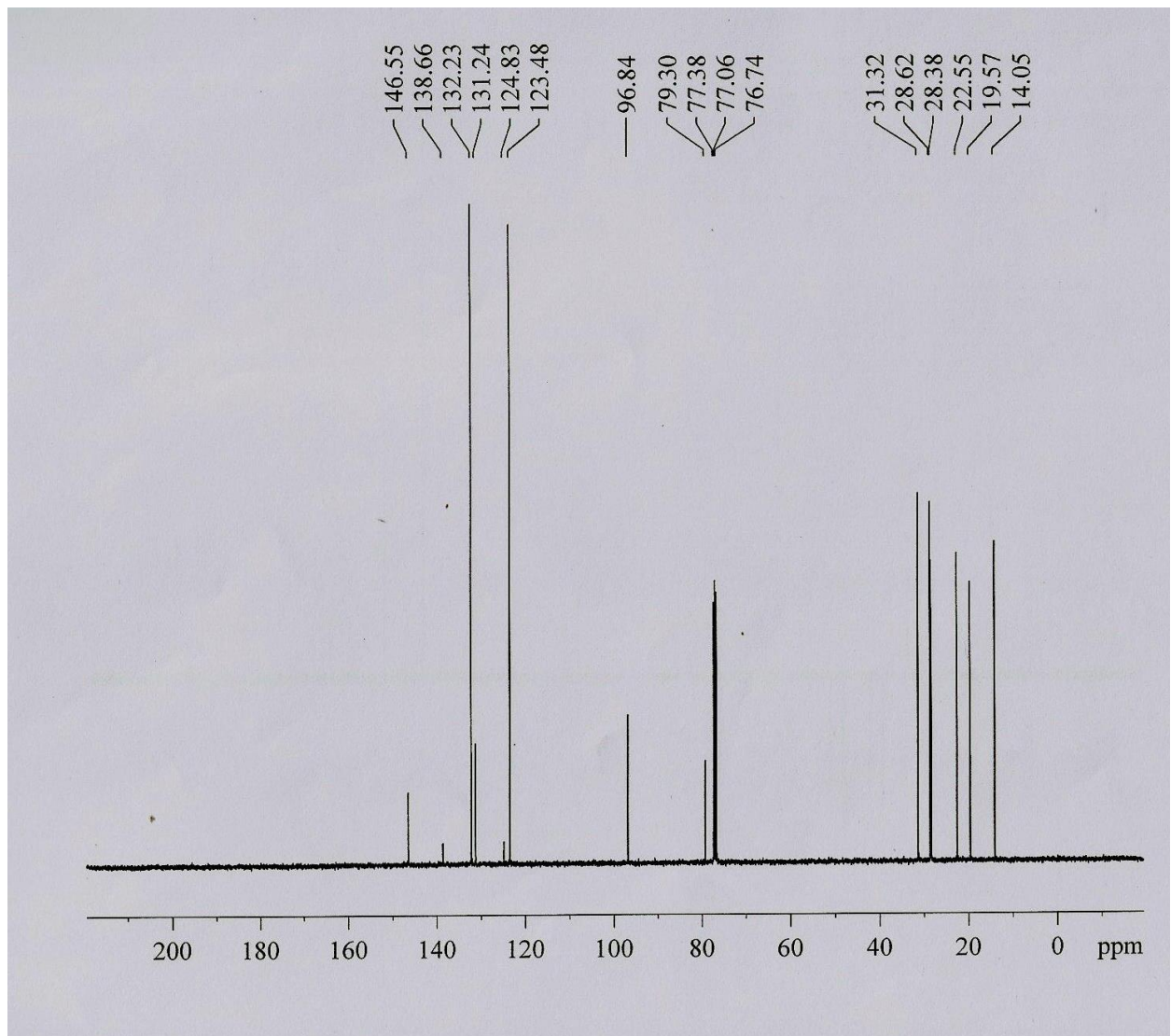
^1H NMR 3-Nitro styrene



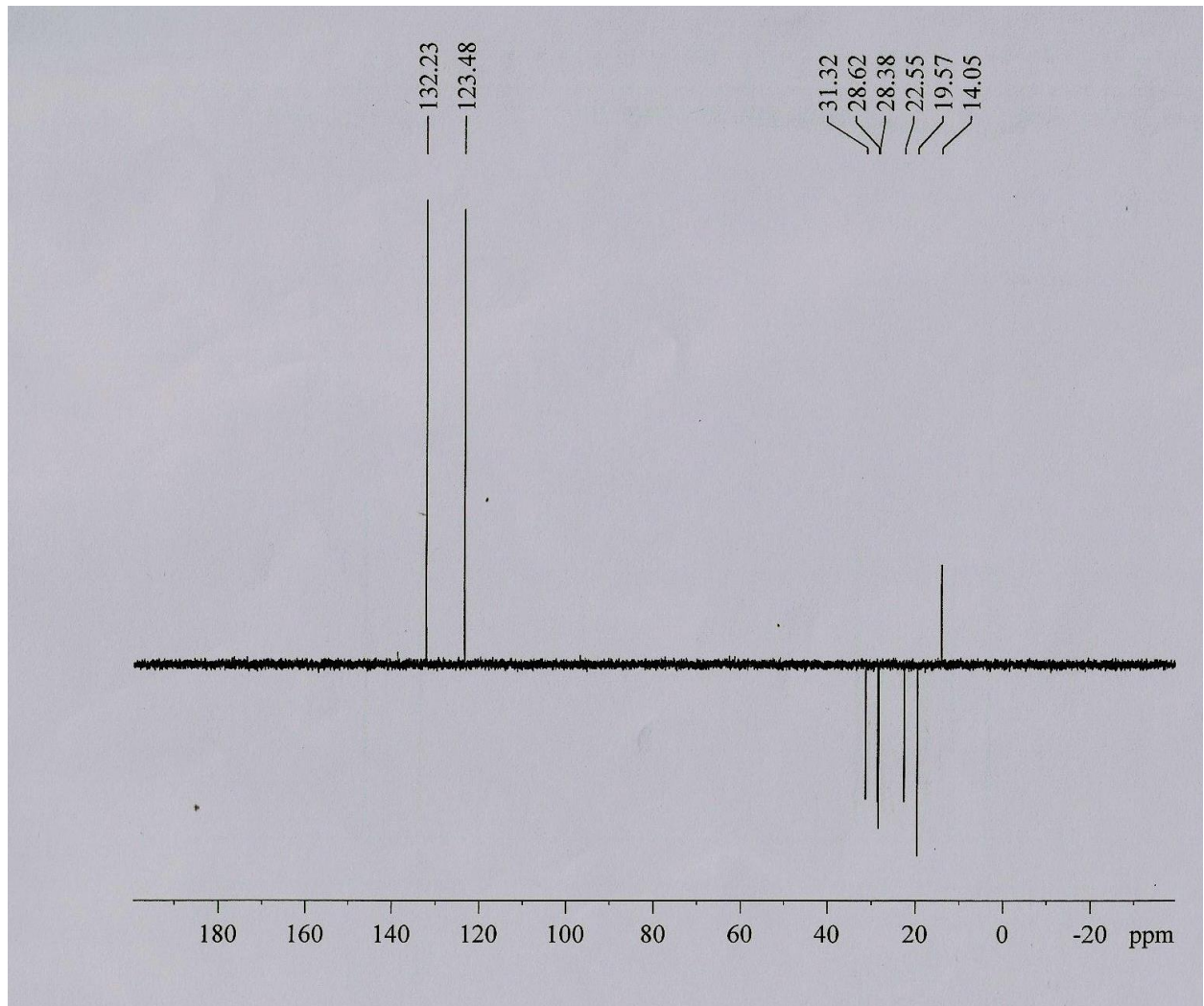
1H NMR of 1-nitro-4-(oct-1-ynyl) benzene



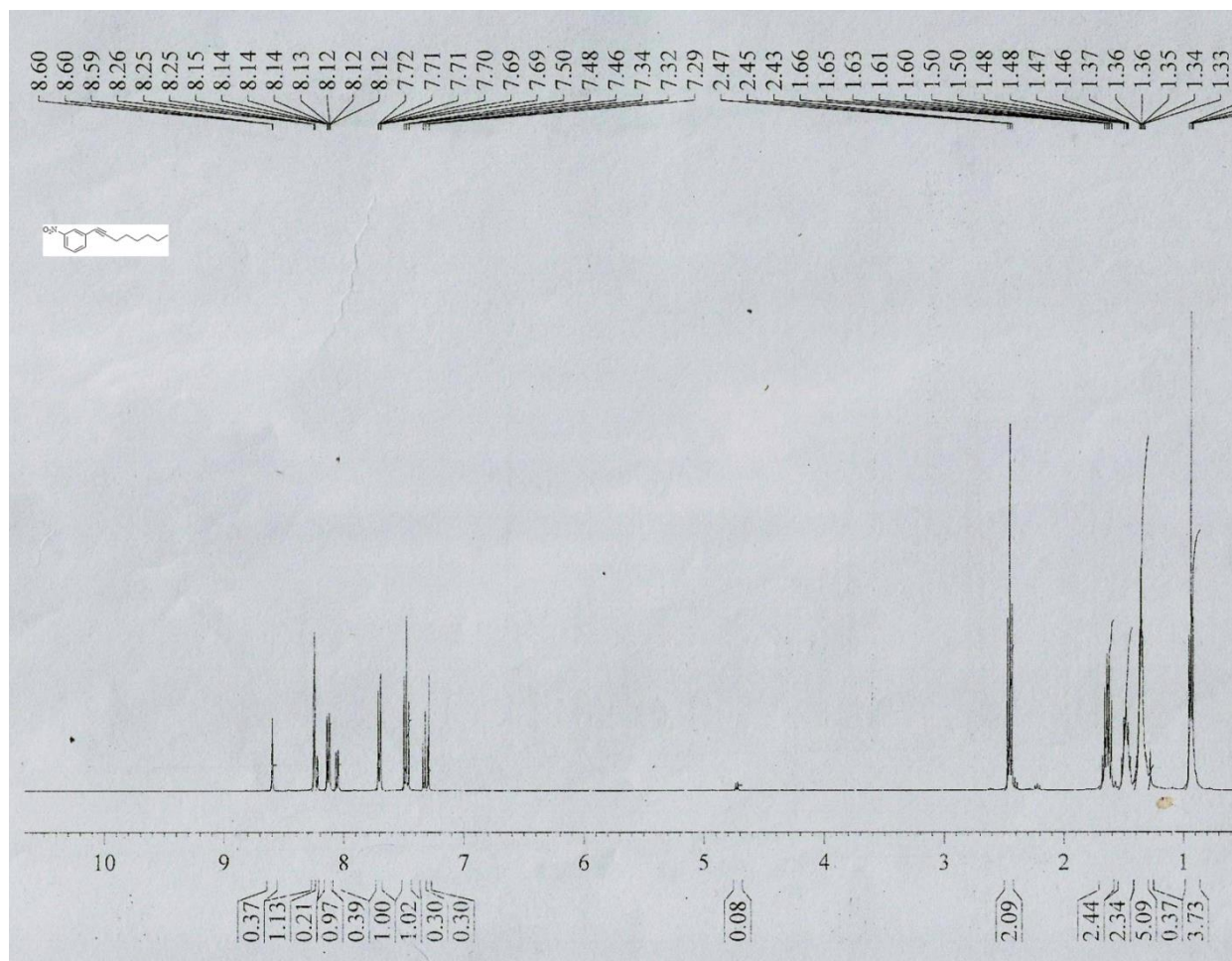
¹³C NMR of 1-nitro-4-(oct-1-ynyl) benzene



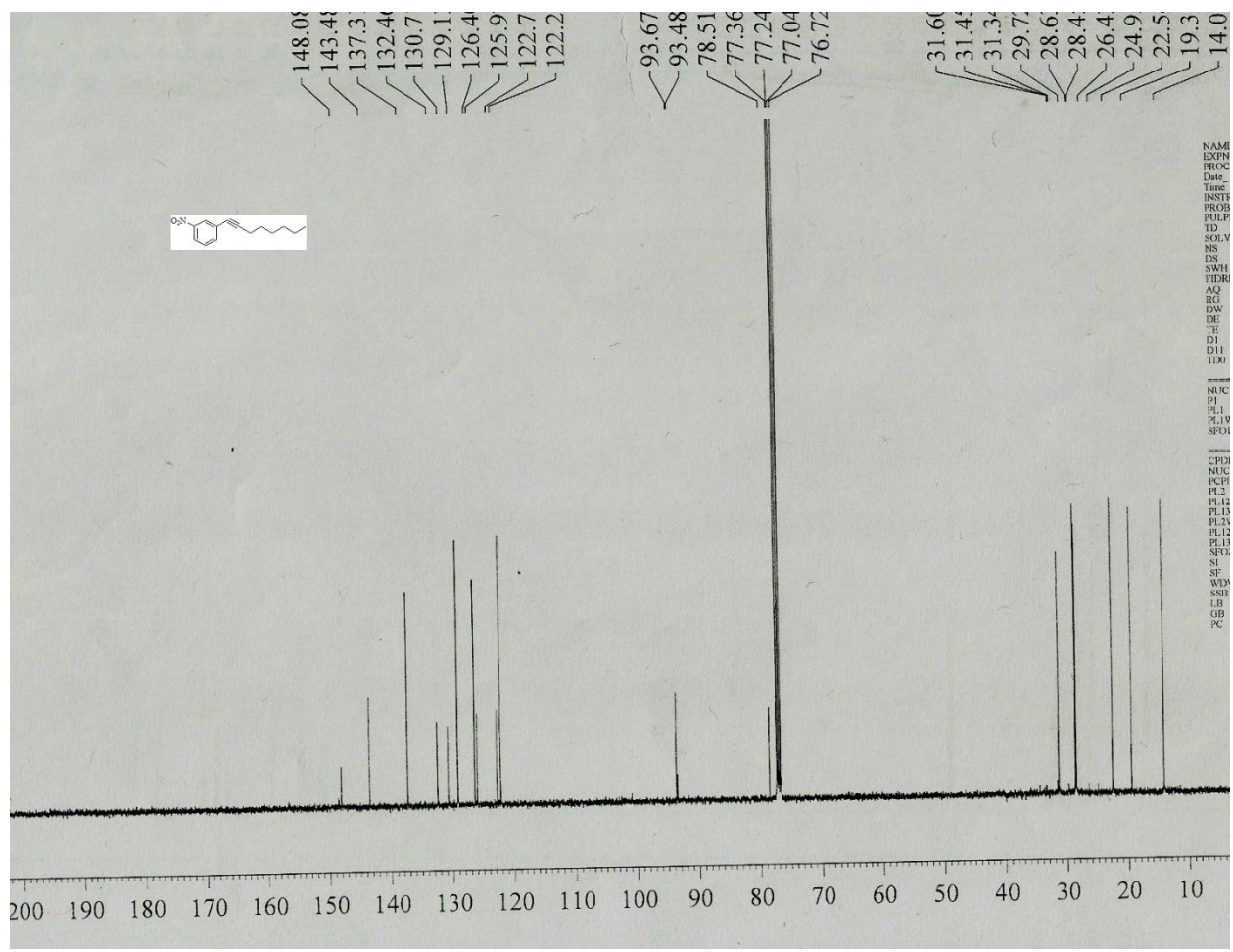
¹³C Dept of 1-nitro-4-(oct-1-ynyl) benzene



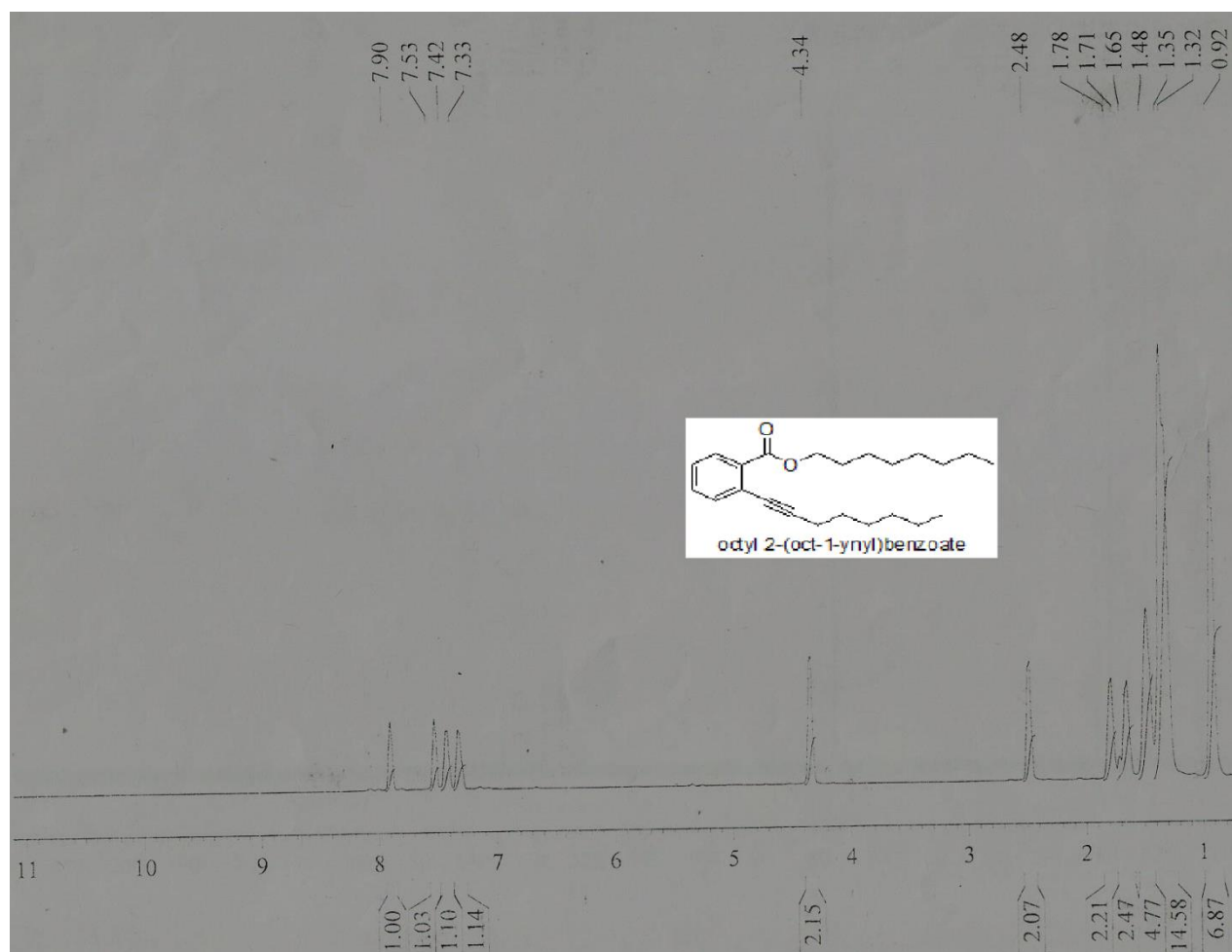
¹H NMR 1-nitro-3-(oct-1-yn-1-yl)benzene



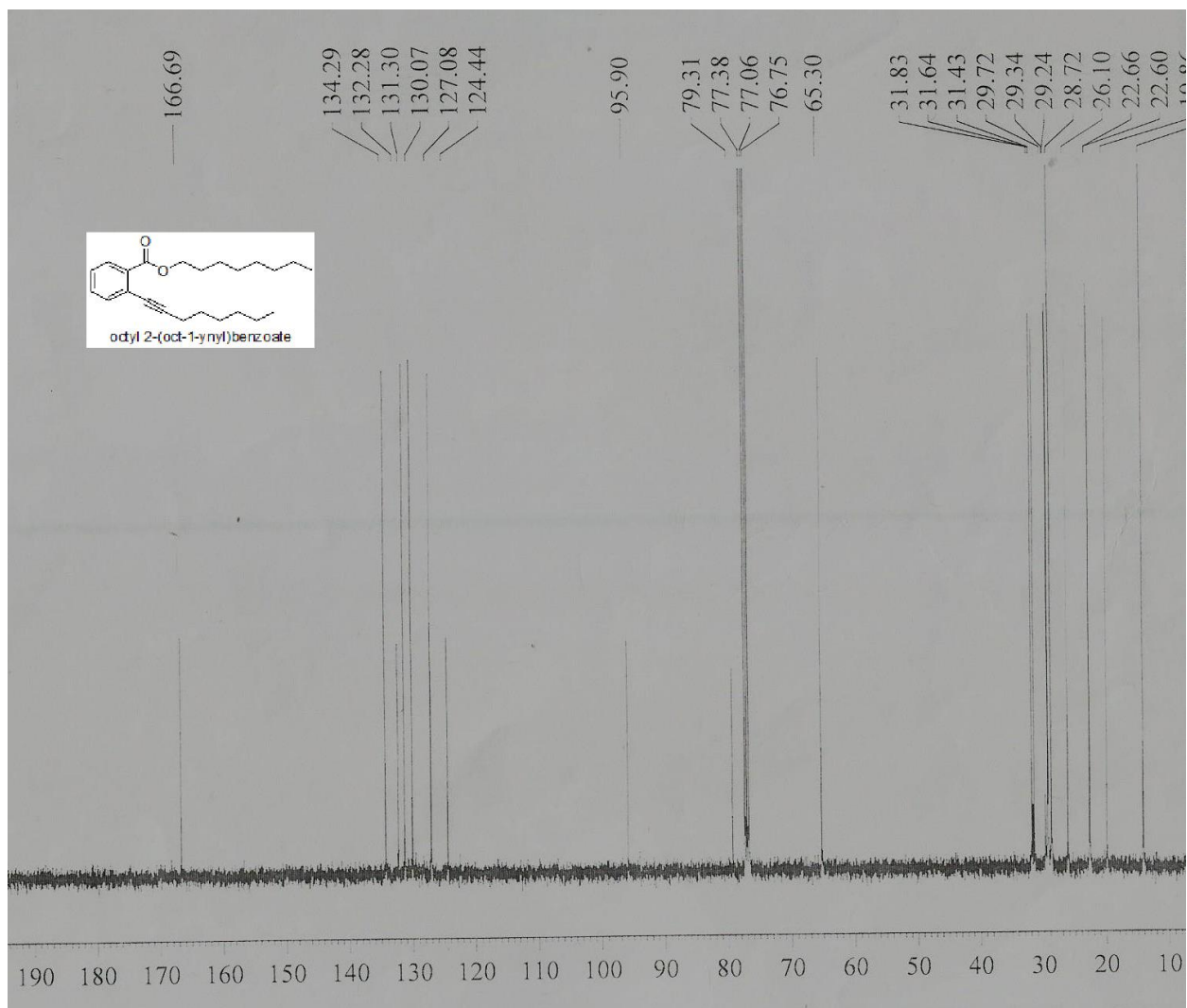
¹³CMR 1-nitro-3-(oct-1-yn-1-yl)benzene



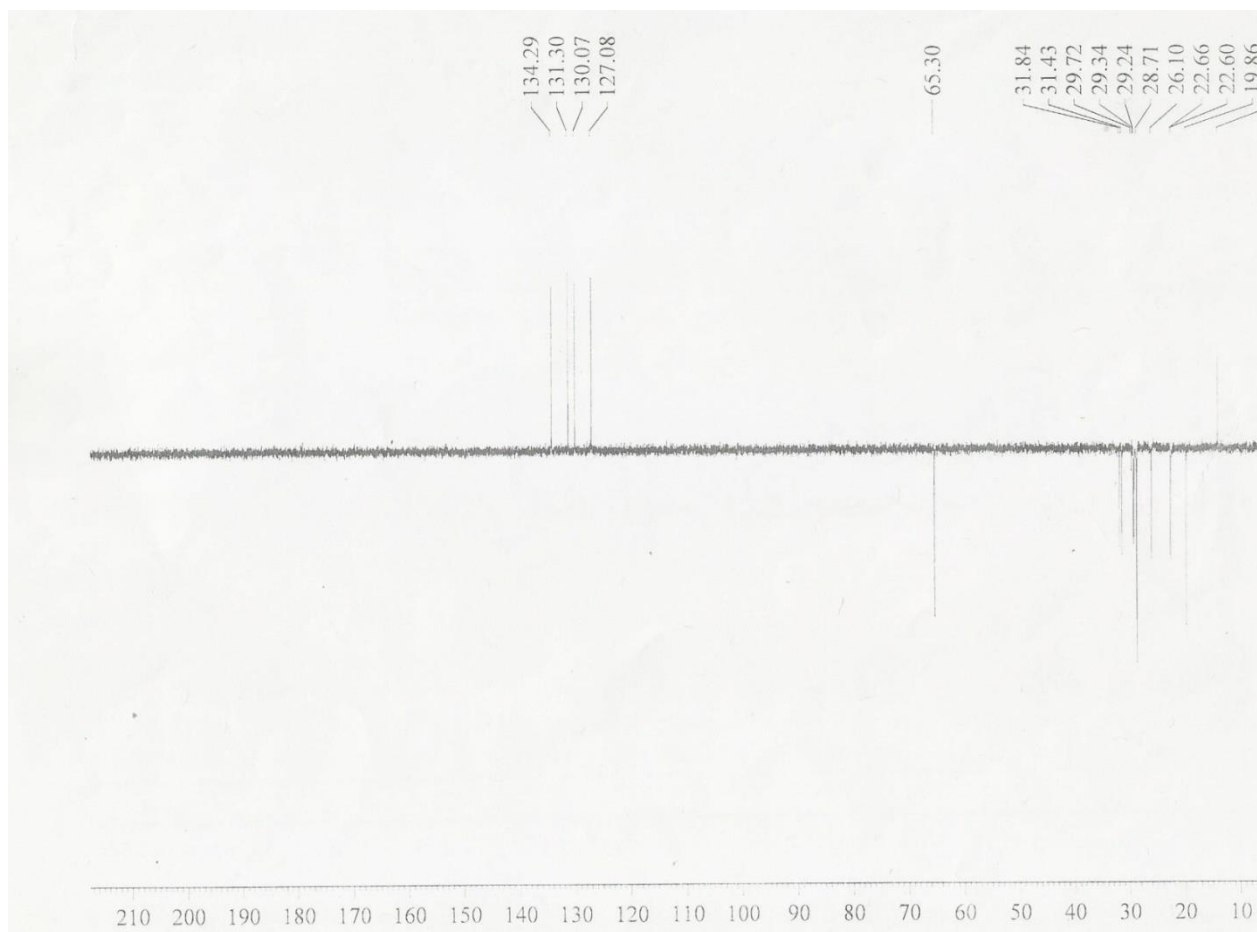
¹H NMR octyl 2-(oct-1-ynyl)benzoate



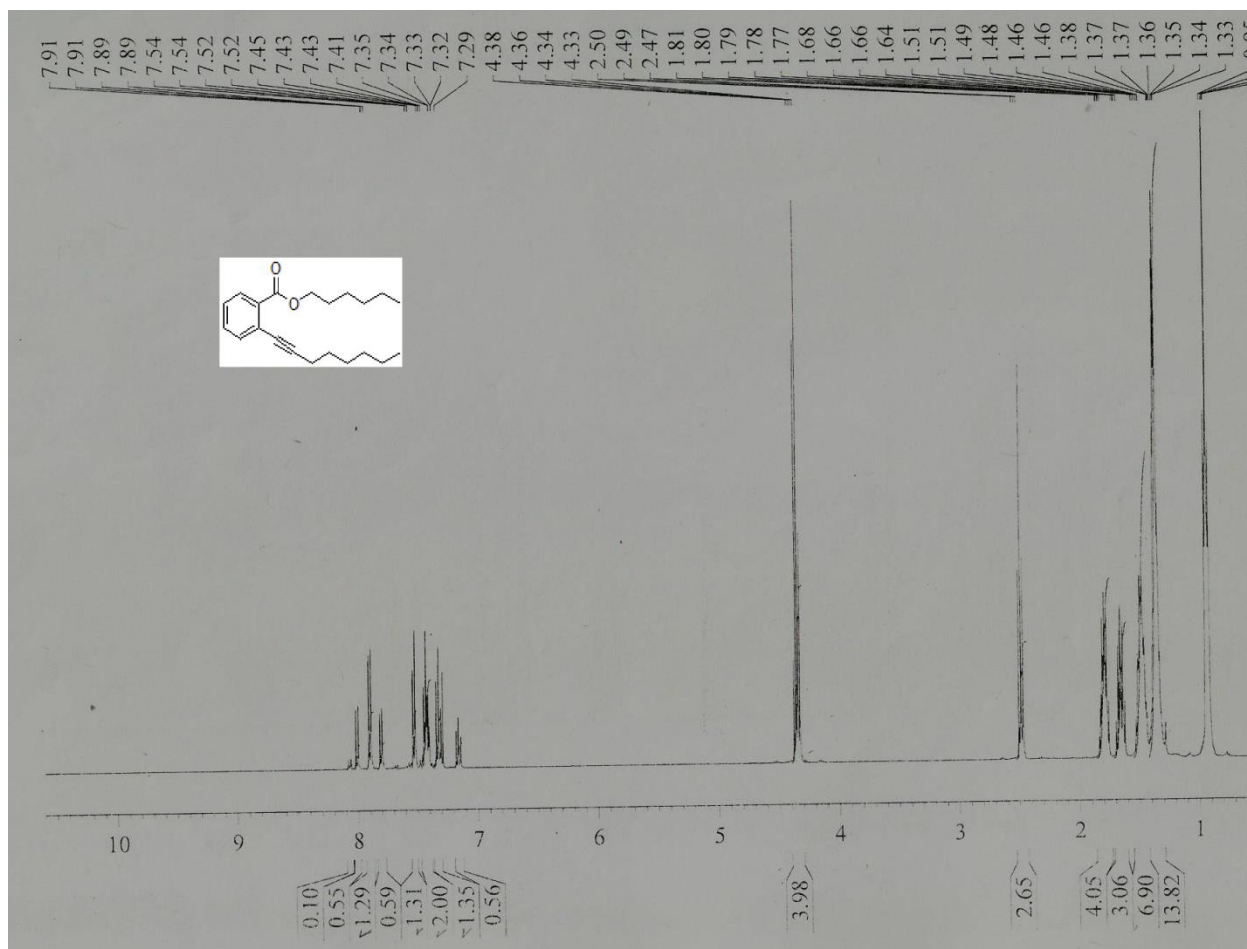
¹³C NMR octyl 2-(oct-1-ynyl)benzoate



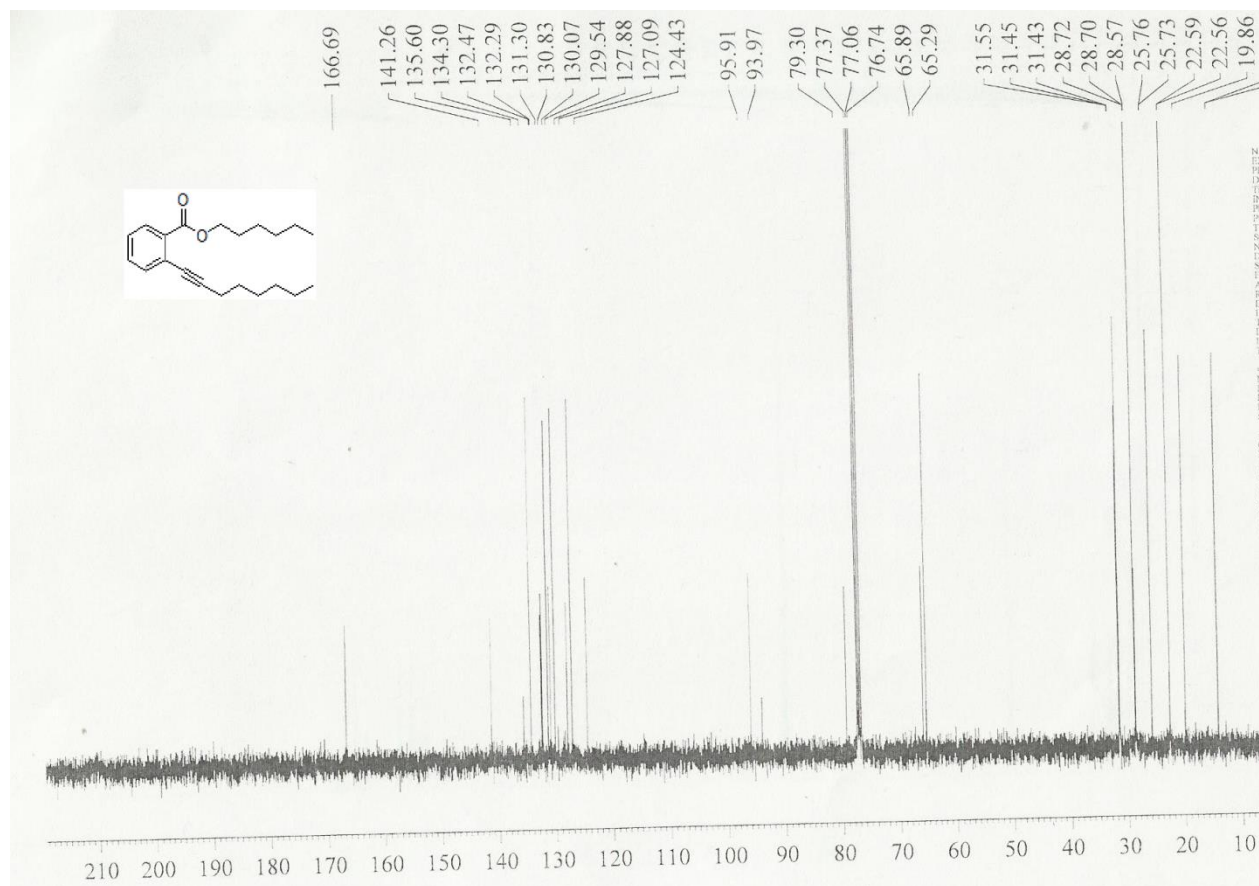
¹³C Dept. octyl 2-(oct-1-ynyl)benzoate.



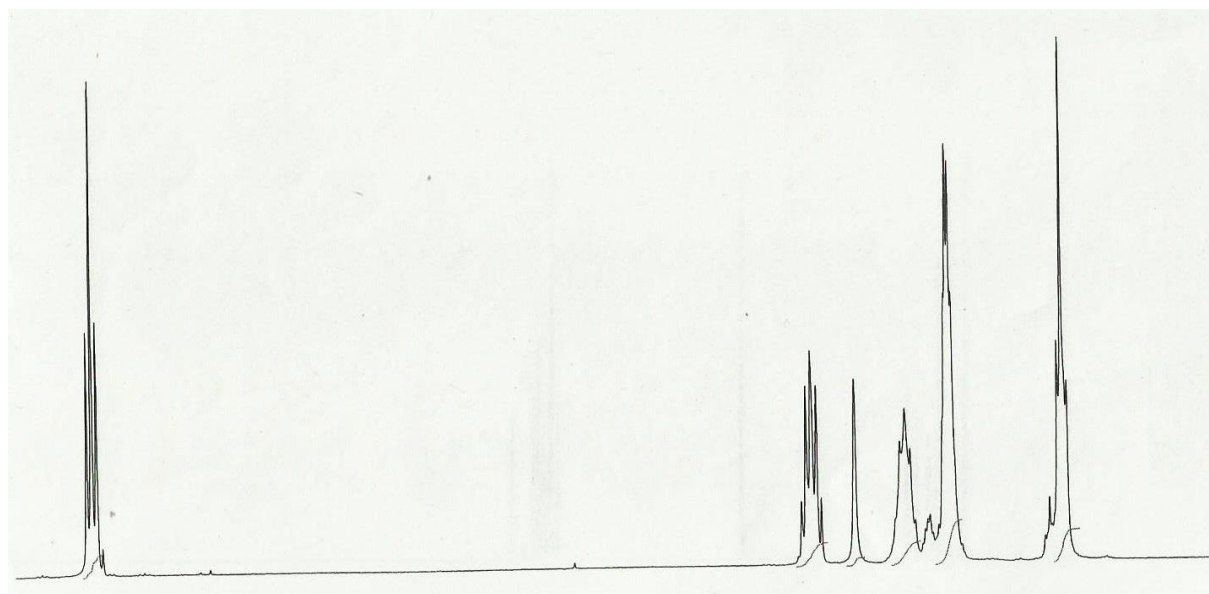
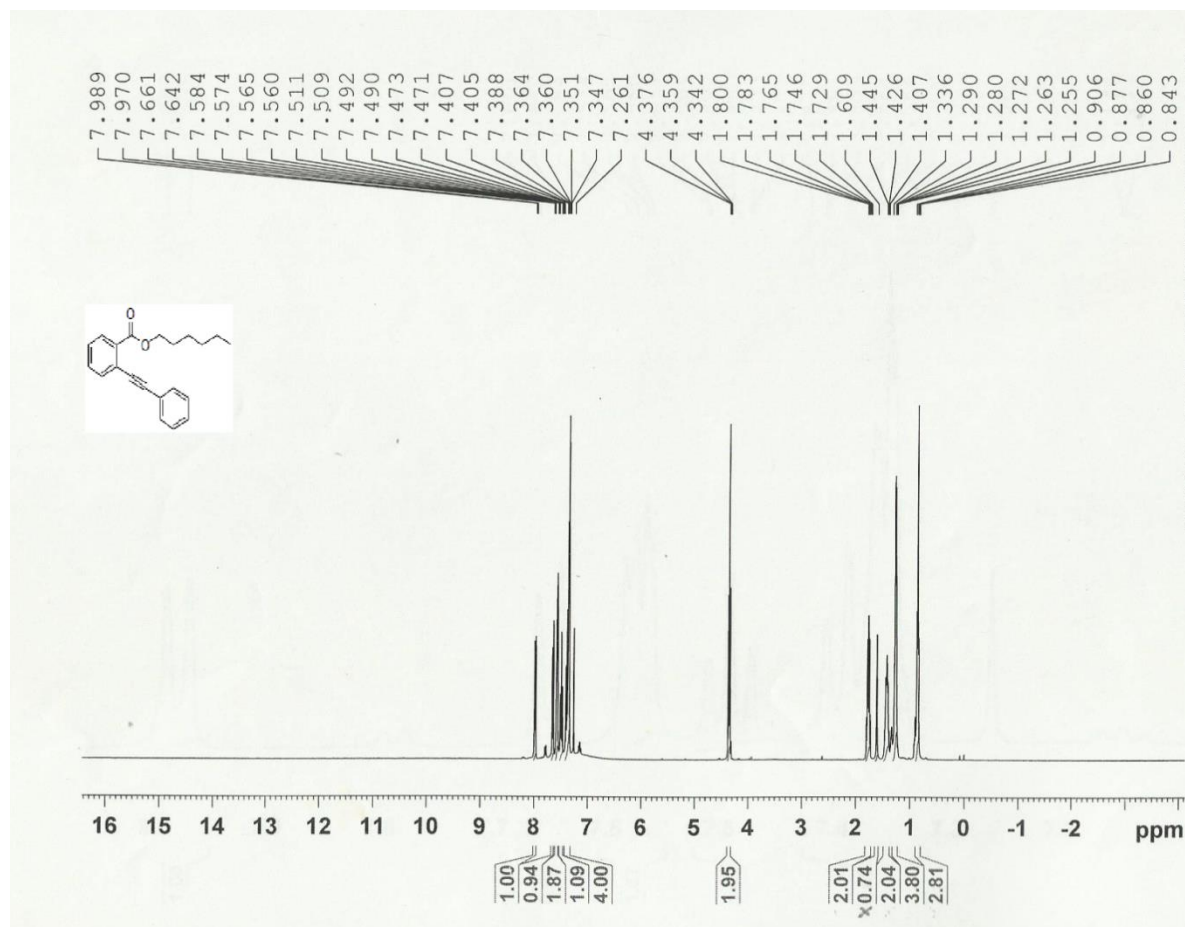
¹H NMR hexyl 2-(oct-1-ynyl)benzoate



¹H NMR hexyl 2-(oct-1-ynyl)benzoate



¹H NMR of octyl 2-(hex-1-ynyl)benzoate



5.1 KETO OXAZOLINE.

5.1.1 Synthesis of new compounds Keto Oxazoline.

When N-(2-hydroxy-1-phenylethyl) benzamide was heated with 20 mol % copper in a polar solvent, such as DMF, ethanol, or acetonitrile, the alkyne group was converted to a ketonic group, and then, the molecule cyclized to produce 1-(2-(4-phenyl-4,5-dihydro oxazol-2-yl)phenyl)-2-one. This is a new rearrangement in which the one of the oxygen from N-acylamino alcohol group is transferred to alkyne group and N-acylamino group cyclized to form oxazoline moiety. Both this transformation occurs through single unstable intermediate.

When compound (V) is treated with copper powder in DMF up to 125°C, no product formation is observed, indicating that the amido alcohol group is involved in the reaction with alkynes (Scheme2). We prepared different types of compounds using this method. We checked the progress of the reaction at various time points, but we could not observe any intermediates, indicating that intermediate (III) was readily converted to the product.

According to the reaction mechanism, there is a possibility of forming intermediate (III), which is immediately converted to the product. To check the role of the triple bond and to gain further insight in to the reaction mechanism, we performed the reaction with compound (V), and no product formation was observed. This supports the formation of intermediate (III). The detail reaction mechanism is shown in scheme-4. There is probability of formation of intermediate (III), (VI), (VII) but only intermediate (III) has possibility of conversion in to product through intermediate (VIII).

Alternatively, when compound (I) was directly heated with a terminal alkyne in the presence of copper powder in DMF at 120°C, the formation of compound (IV) was directly observed with a 46% yield.

5.1.2. Optimization of reaction condition.

During optimization the reaction was carried out at different temperature ranging from 50-110°C. The reaction rate is very slow at 50°C and reaction requires 7-8 hrs at 75°C, 1 hrs at 110° for complete conversion in to product. Reaction working well in polar solvent likes Acetonitrile, Ethanol, DMF and DMSO.

5.1.3 Importance of work.

Method for preparation of the Keto Oxazoline is not available in the literature and we are reporting first time the preparation of Keto Oxazoline in single step. Due to use of mild reagent copper powder side reaction, impurity formation and effect on chiral center in the molecule not observed.

5.1.4 Typical Process for Preparation of Keto Oxazoline (IV)

N-(2-hydroxy-1-phenylethyl)-2-(1-ynyl)benzamide (1 g) in 5 ml of ethanol and 0.2 g of copper powder were charged in to a closed vial and heated for 4-5 h at 80°C. The reaction was monitored by TLC (8:2 n-hexane, ethyl acetate). After the reaction completed, the reaction contents were cooled to 25°C and filtered to afford the solid copper powder. Then, the filtrate was concentrated and purified on a silica column using n-hexane and ethyl acetate.

5.1.5 Process for preparation (R)-N-(2-hydroxy-1-phenylethyl)-2-(ynyl)benzamide (II)

(R)-N-(2-hydroxy-1-phenylethyl)-2-iodobenzamide (5.44 mmol) in 7 ml of DMF, 100 mg of bis(triphenylphosphine)palladium(II) dichloride(0.04 mmol) and Triethylamine (10.88 mmol) were combined under a nitrogen atmosphere and stirred for 30 min. Then, Alkyne (8.15 mmol) was added to the mixture, and the reaction was heated to 80°C for 2 h. After the reaction completed, the product was extracted in 15 ml of ethyl acetate by adding 15 ml of water. The obtained crude oil was purified on a silica column using ethyl acetate and n-hexane, affording (R)-N-(2-hydroxy-1-phenylethyl)-2-(ynyl)benzamide as a white solid (5.44 mmol).

5.1.6 Alternative Process for Preparation of Keto Oxazoline (IV)

(R)-N-(2-hydroxy-1-phenylethyl)-2-iodobenzamide (5.44 mmol) in 7 ml of DMF, 100 mg of Copper powder, Alkyne (8.15 mmol) were added to the mixture, and heated to 110°C for 2 h. After the reaction completed, the product was extracted in 15 ml of ethyl acetate by adding 15 ml of water. The obtained crude oil was purified on a silica column using ethyl acetate and n-hexane, affording Keto Oxazoline as a white solid. (5.44 mmol)

5.1.6.1 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra)

(R)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide (1 g) in 5 ml of ethanol and 0.2 g of copper powder were charged in to a closed vial and heated for 4-5 h at 80°C. The reaction was monitored by TLC (8:2 n-hexane:ethyl acetate). After the reaction completed, the reaction contents were cooled to 25°C and filtered to afford the solid copper powder. Then, the filtrate was concentrated and purified on a silica column using n-hexane and ethyl acetate, providing 0.95 g of (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one (m+1- 250.2). ¹H NMR (400 MHz, CDCl₃) δ 8.05(dd 1H J=8), 7.47(td 1H J=8), 7.39(t 3H J=8), 7.32(m 3H J=4), 7.25 (d 1H J=8), 5.38(t 1H J=8), 4.72(t J=8), 4.26(d 1H J=16), 4.19(d 1H J=12), 4.17(1H J=8), 2.46(m 2H J=8,4), 1.54(m 2H), 1.24(m 6H), 0.88(t 3H J=8). ¹³C NMR (400 MHz, CDCl₃) δ 208.32, 164.14, 142.46, 136.18, 132.33, 131.04, 130.27, 128.71, 127.56, 127.01, 126.73, 126.71, 73.76, 70.72, 49.41, 42.55, 31.65, 28.92, 23.58, 22.53, 14.01.

5.1.6.2 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one.

The experimental process was the same as that for 1a using (R)-2-(hex-1-ynyl)-N-(2-hydroxy-1-phenylethyl)benzamide as a starting material, which gave (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one as a white solid Yield: 0.91 g. ¹H NMR (400 MHz, CDCl₃) δ 8.04(d 1H), 7.47(m 1H J=8), 7.38(t 3H J=8), 7.30(m 3H), 7.25(d 1H), 5.38(t 1H J=16), 4.19(m 2H), 2.45(m 2H), 1.52(m 2H), 1.21(m 1H), 0.83(t 1H). ¹³C NMR (400 MHz, CDCl₃) δ 208.4, 164.13,

142.45, 136.13, 134.18, 132.33, 131.07, 130.27, 128.72, 127.57, 127.04, 126.75, 126.66, 73.77, 70.70, 49.43, 42.25, 25.25, 22.33, 13.91.

5.1.6.3 (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one

The experimental process was the same as that for 1a using (R)-2-(5-chloropent-1-ynyl)-N-(2-hydroxy-1-phenylethyl)benzamide as a starting material, which gave (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one as a white solid Yield: 0.93 g. ¹H NMR (400 MHz, CDCl₃) δ 8.05(d 1H J=8), 7.47(t 1H J=8), 7.38(m, 3H J=8), 7.29(m 4H J=8), 5.38(t 1H J=8), 4.71(t 1H J=8), 4.26(d 1H J=16), 4.18(m 2H J=8,16), 3.42(m 2H J=8,4), 2.62(m 2H J=4,8), 1.93(m 2H J=4,8), ¹³C NMR (100 MHz, CDCl₃) δ 206.65, 163.96, 142.40, 135.91, 132.34, 131.07, 130.28, 128.72, 127.61, 127.12, 126.70, 126.59, 77.33, 77.01, 76.69, 73.68, 70.78, 49.55, 44.51, 39.02, 26.36.

5.1.6.4 (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Sa)

The experimental process was the same as that for 1a using (S)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide which gave 0.95 g of (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one (m+1- 250.2). ¹H NMR (400 MHz, CDCl₃) δ 8.05(dd 1H J=8), 7.47(td 1H J=8), 7.39(t 3H J=8), 7.32(m 3H J=4), 7.25 (d 1H J=8), 5.38(t 1H J=8), 4.72(t J=8), 4.26(d 1H J=16), 4.19(d 1H J=12), 4.17(1H J=8), 2.46(m 2H J=8,4), 1.54(m 2H), 1.24(m 6H), 0.88(t 3H J=8). ¹³C NMR (400 MHz, CDCl₃) δ 208.32, 164.14, 142.46, 136.18, 132.33, 131.04, 130.27, 128.71, 127.56, 127.01, 126.73, 126.71, 73.76, 70.72, 49.41, 42.55, 31.65, 28.92, 23.58, 22.53, 14.01.

5.1.6.5 (R)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide

(R)-N-(2-hydroxy-1-phenylethyl)-2-iodobenzamide (2g, 5.44 mmol) in 7 ml of DMF, 100 mg of bis(triphenylphosphine)palladium(II) dichloride(0.04 mmol) and 1.1 g of triethylamine were

combined under a nitrogen atmosphere and stirred for 30 min. Then, 0.89 g of 1-octyne (8.15 mmol) was added to the mixture, and the reaction was heated to 80°C for 2 h. After the reaction completed, the product was extracted in 15 ml of ethyl acetate by adding 15 ml of water. The obtained crude oil was purified on a silica column using ethyl acetate and n-hexane, affording 1.67 g of (R)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.54(dd 1H), 8.54 (d 1H), 8.12(m 1H), 7.48(m 1H), 7.42(m 6H), 5.31(t 1H), 4.00(m 1H), 3.26(m 1H), 2.23(m 1H), 1.44(m 2H), 1.3(m 6H), 0.92(t 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.97, 138.95, 133.97, 133.87, 130.80, 130.35, 128.96, 128.20, 127.94, 126.94, 120.60, 79.29, 67.15, 57.28, 31.32, 28.71, 28.33, 22.55, 19.47, 14.09.

5.1.6.6 (S)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide

The experimental process was the same as that for (R)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide by using (S)-N-(2-hydroxy-1-phenylethyl)-2-iodobenzamide as a starting material gives 1.67 g of (S)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.54(dd 1H), 8.54 (d 1H), 8.12(m 1H), 7.48(m 1H), 7.42(m 6H), 5.31(t 1H), 4.00(m 1H), 3.26(m 1H), 2.23(m 1H), 1.44(m 2H), 1.3(m 6H), 0.92(t 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.97, 138.95, 133.97, 133.87, 130.80, 130.35, 128.96, 128.20, 127.94, 126.94, 120.60, 79.29, 67.15, 57.28, 31.32, 28.71, 28.33, 22.55, 19.47, 14.09.

5.1.6.7 (R)-2-(5-chloropent-1-ynyl)-N-(2-hydroxy-1-phenylethyl)benzamide

The experimental process was the same as that for (R)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide by using (R)-N-(2-hydroxy-1-phenylethyl)-2-iodobenzamide as a starting material gives 1.67g of (R)-2-(5-chloropent-1-ynyl)-N-(2-hydroxy-1-phenylethyl) benzamide as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, 1H), 8.7(m 1H), 7.49(m 1H), 7.41(6H), 7.32(m 1H), 5.30(m 1H), 4.00(m 2H), 3.64(m 2H), 3.24(t 1H), 2.43(m 2H), 1.91(q 2H). ¹³C

NMR (100 MHz, CDCl₃) δ 166.75, 138.98, 134.47, 133.87, 130.82, 130.82, 130.21, 128.98, 128.51, 127.96, 126.93, 120.12, 96.02, 80.01, 66.87, 56.98, 43.72, 30.91, 16.94.

Fig 5.1 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) H¹ NMR

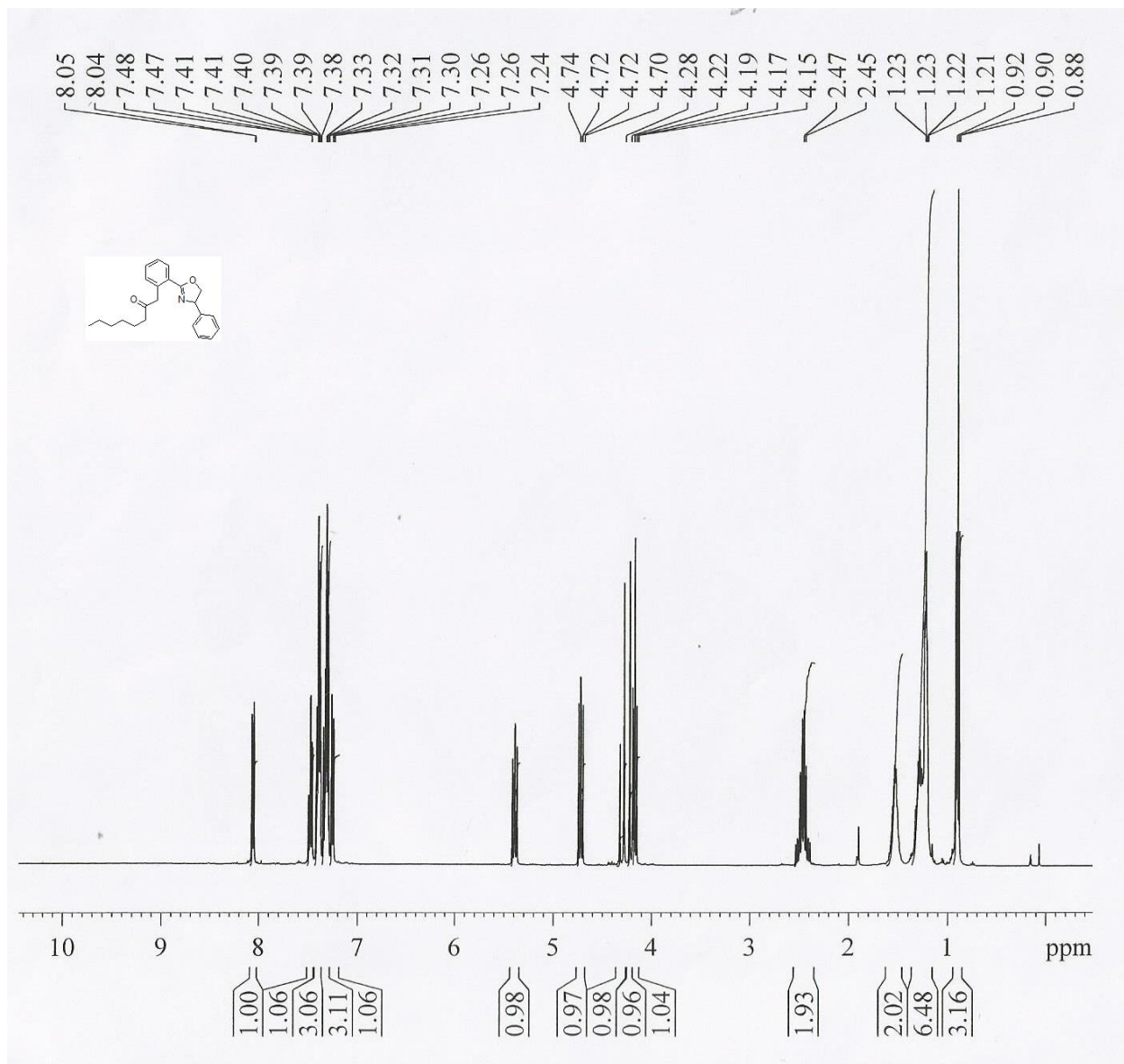


Fig 5.2 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) H¹ NMR Expansion :-

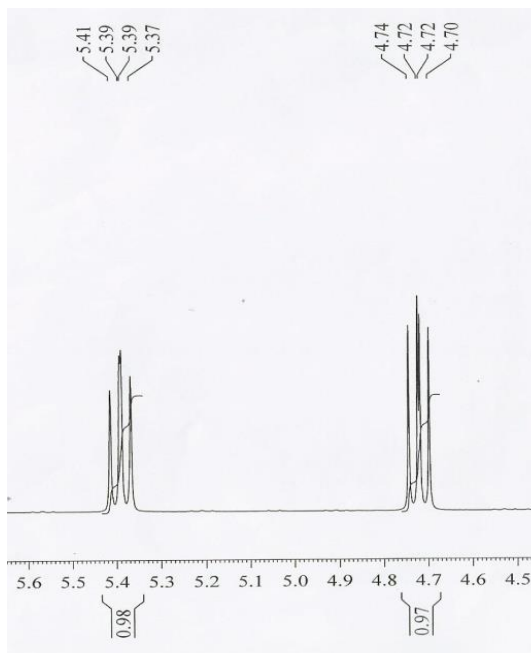
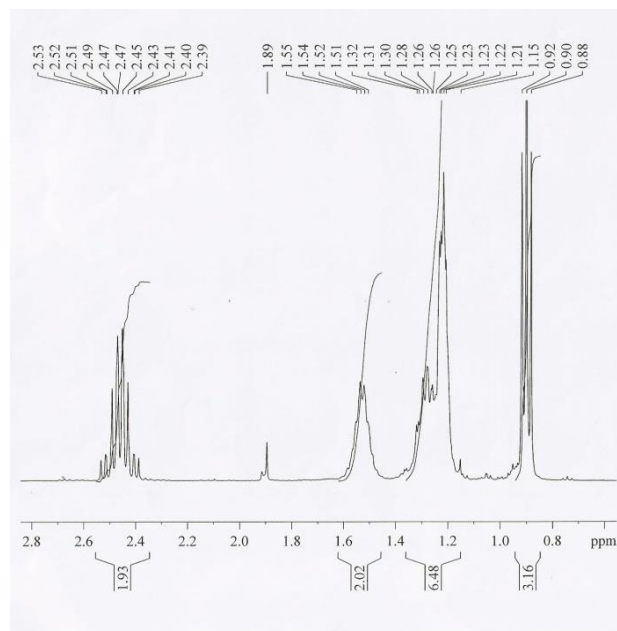
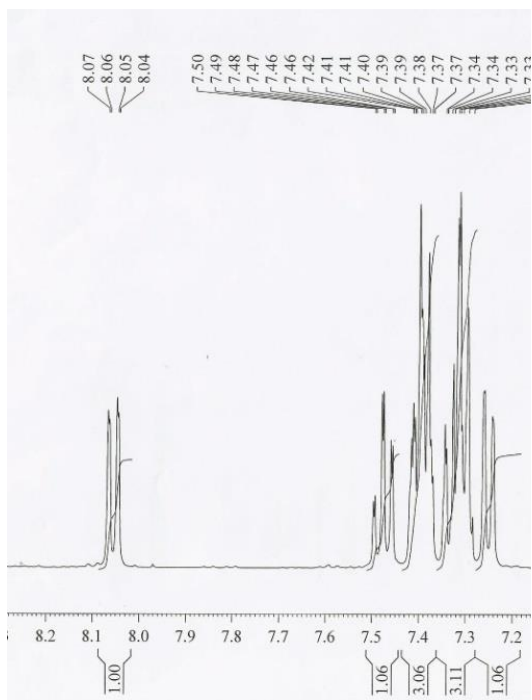


Fig 5.3 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) C¹³ NMR

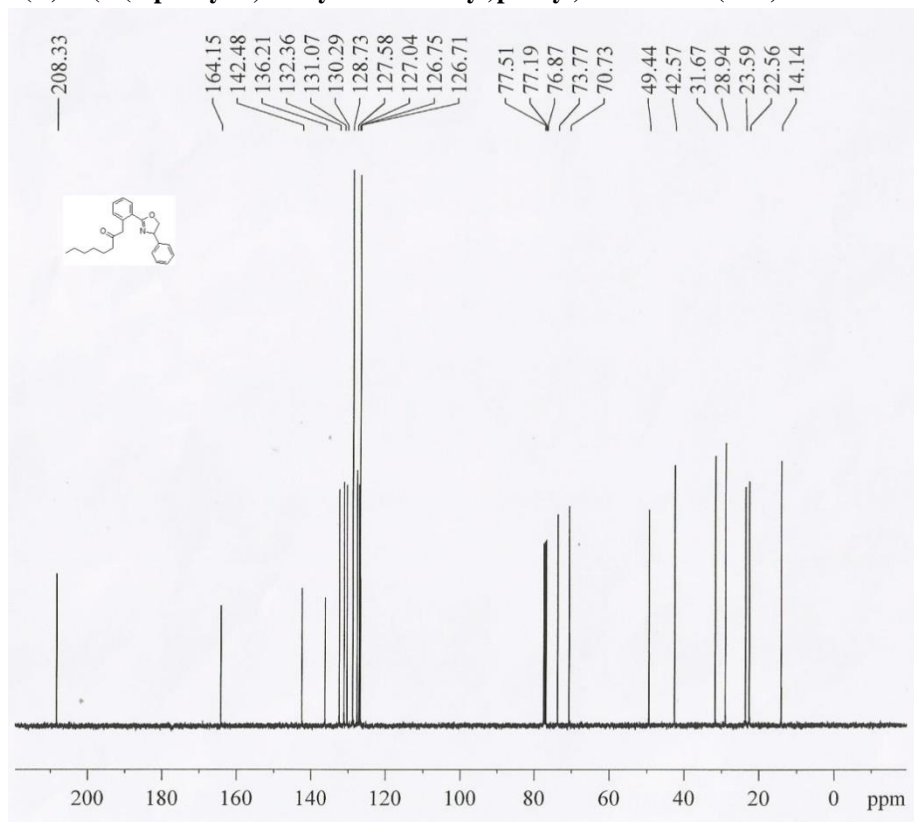


Fig 5.4 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) C¹³ Dept.

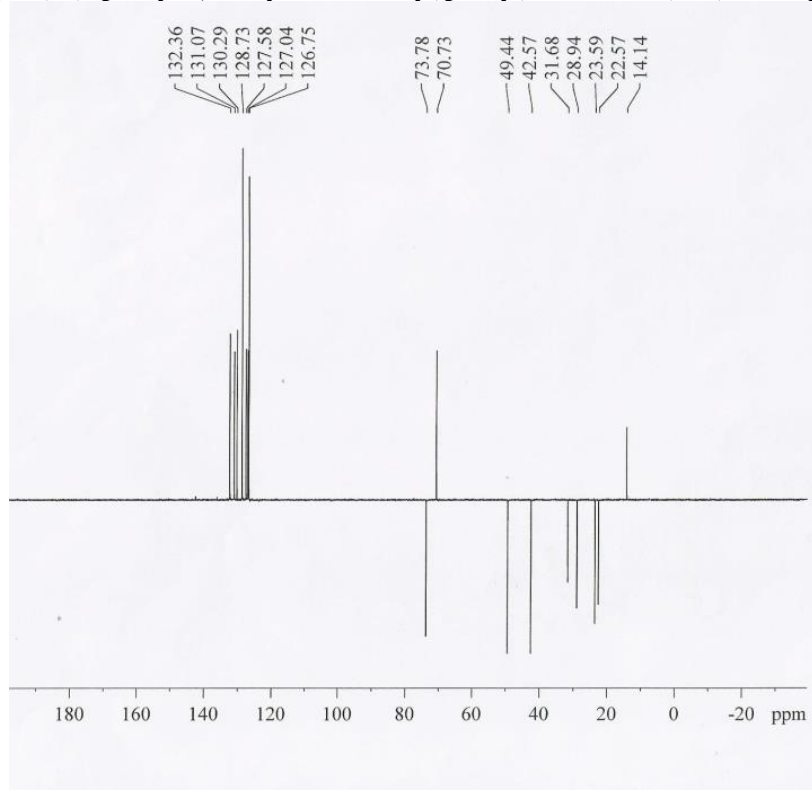


Fig 5.5 (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one H^1 NMR

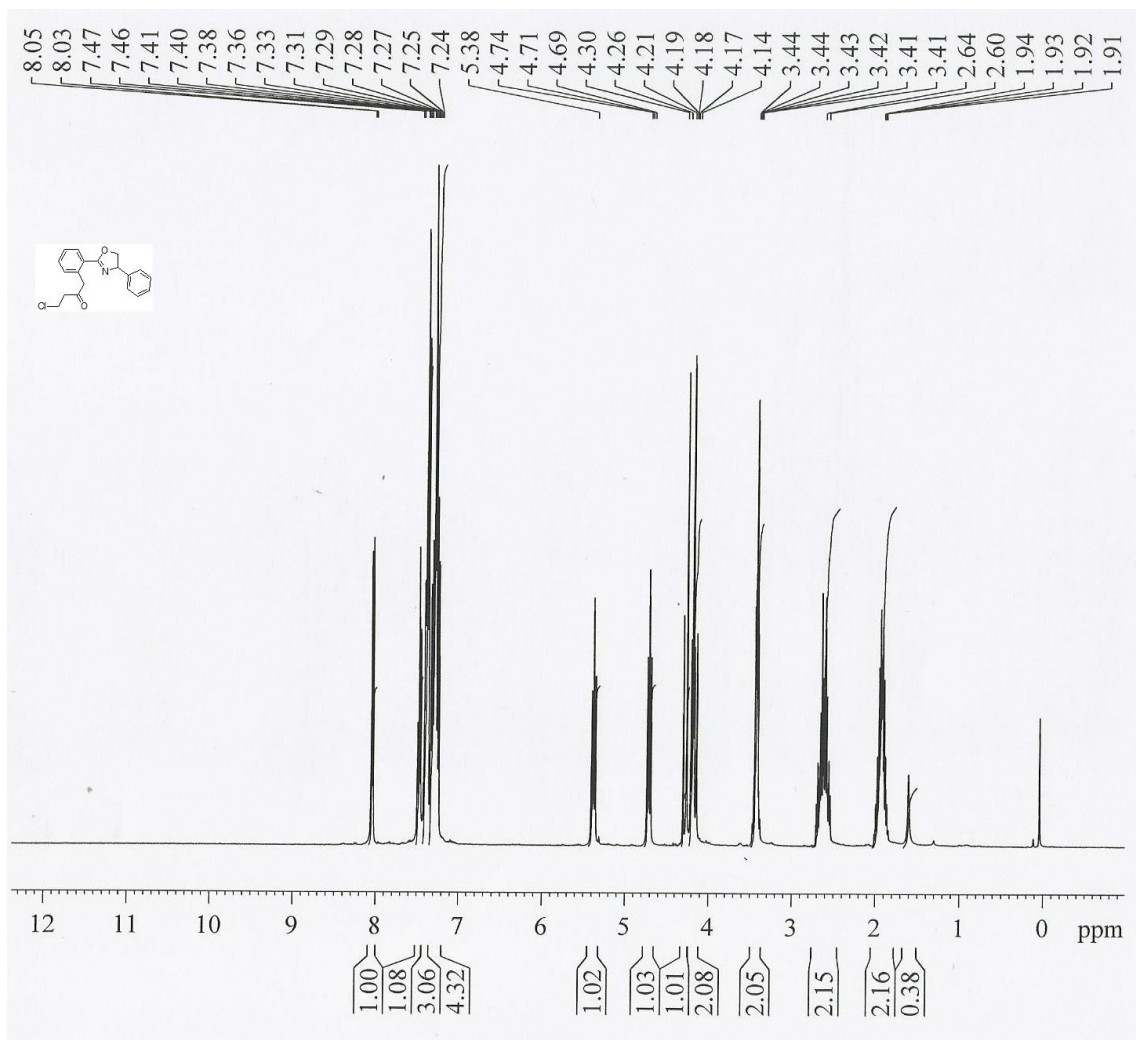


Fig 5.6 (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one H^1 NMR expansion.

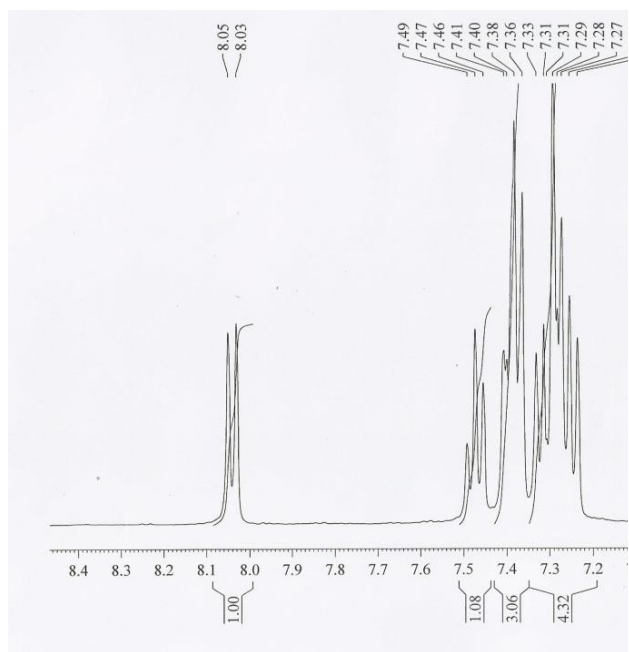
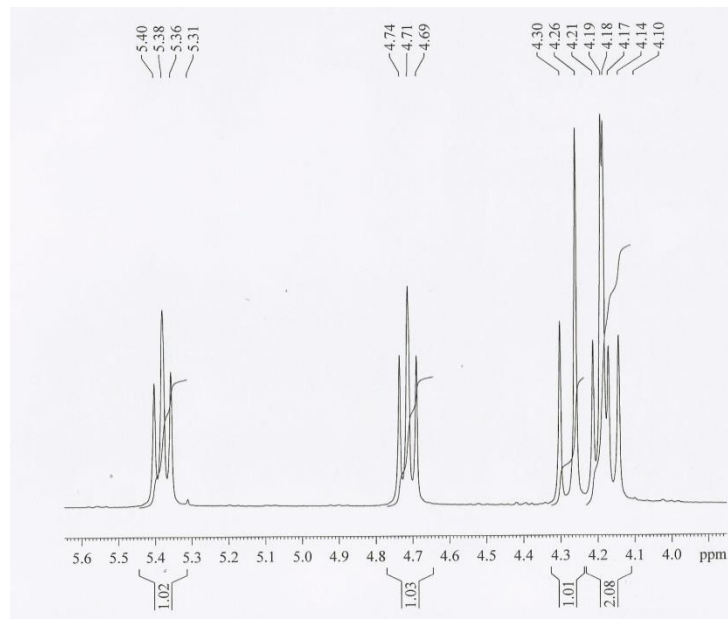
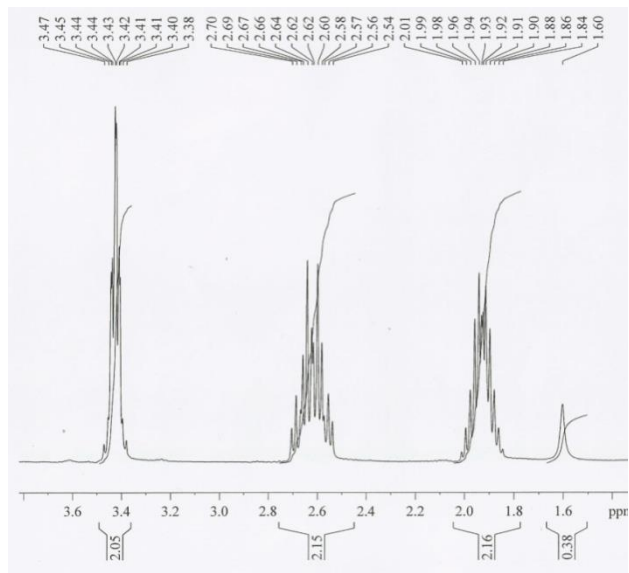


Fig 5.7 (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one C¹³ NMR

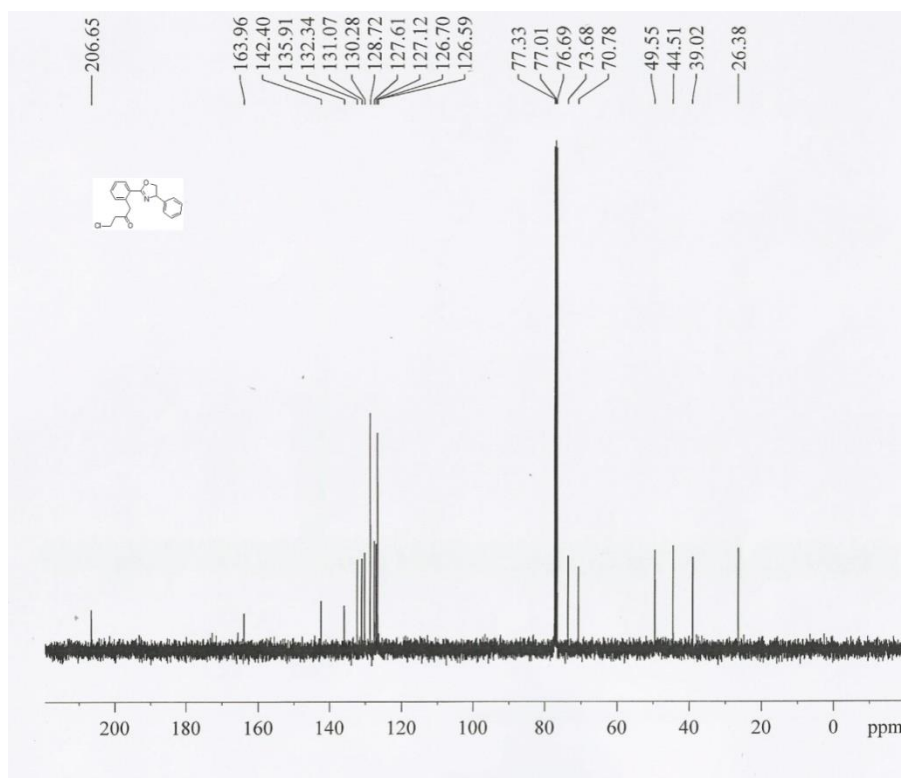


Fig 5.8 (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one C¹³ Dept.

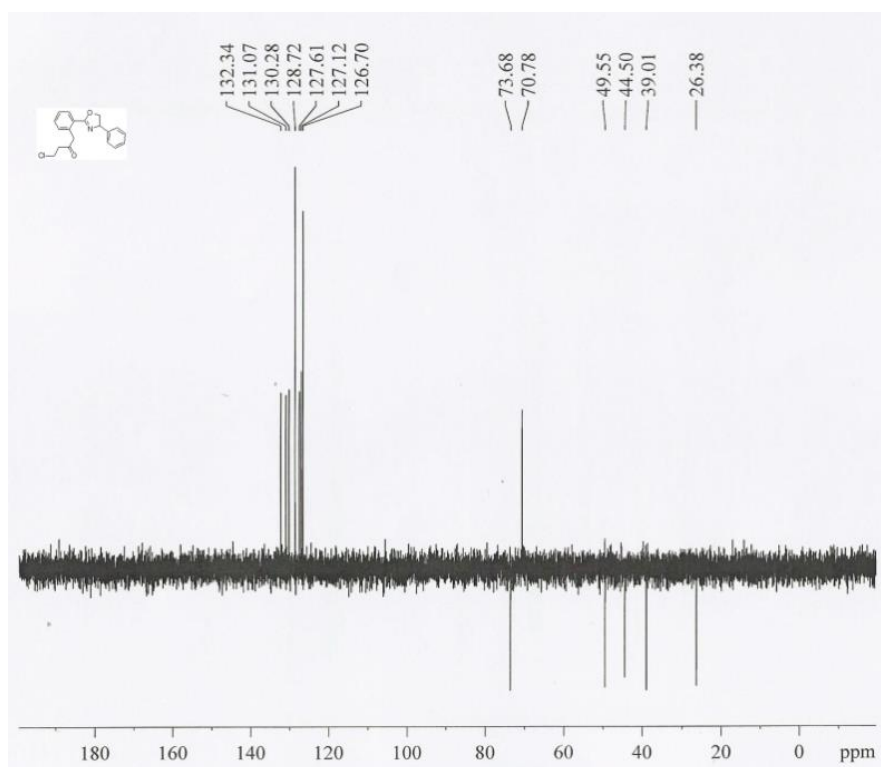


Fig 5.9 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one H^1 NMR

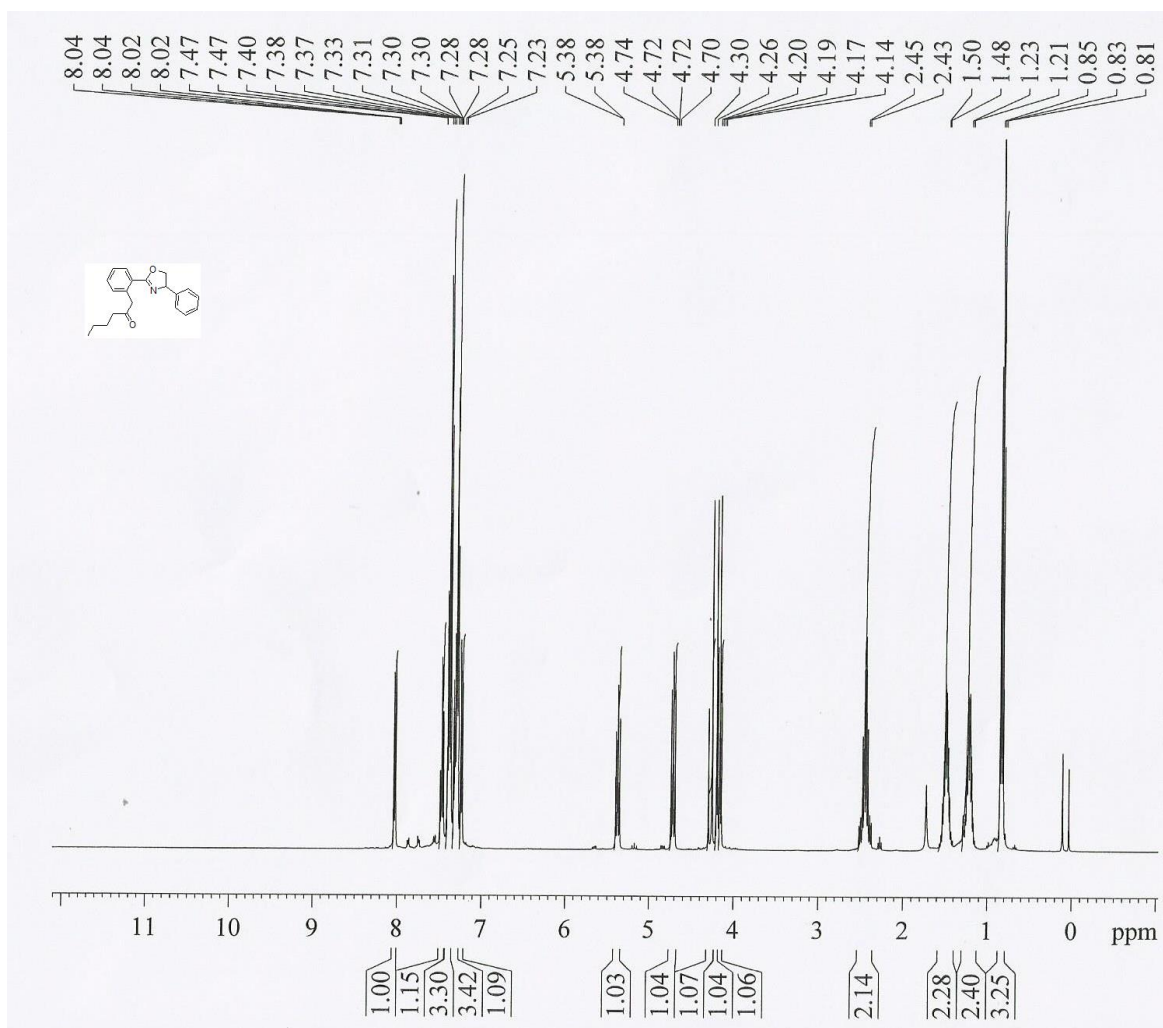


Fig 5.10 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one H^1 NMR expansion.

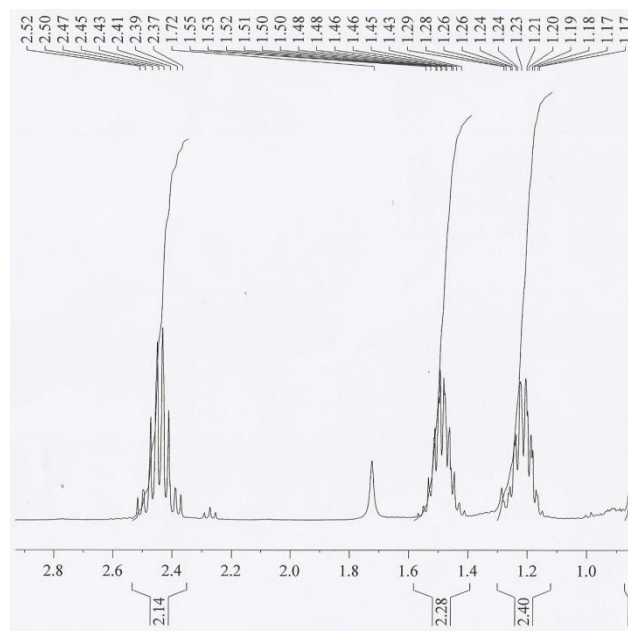
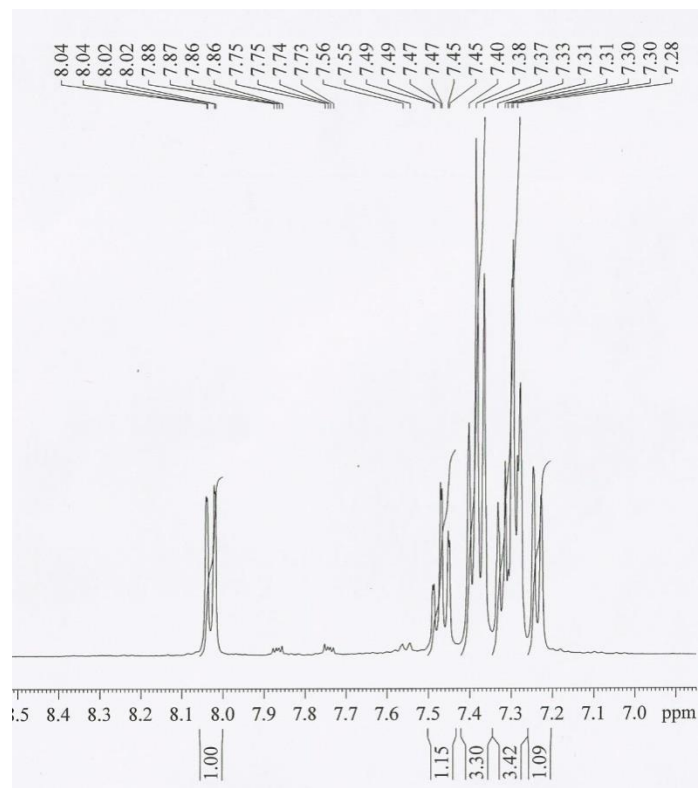
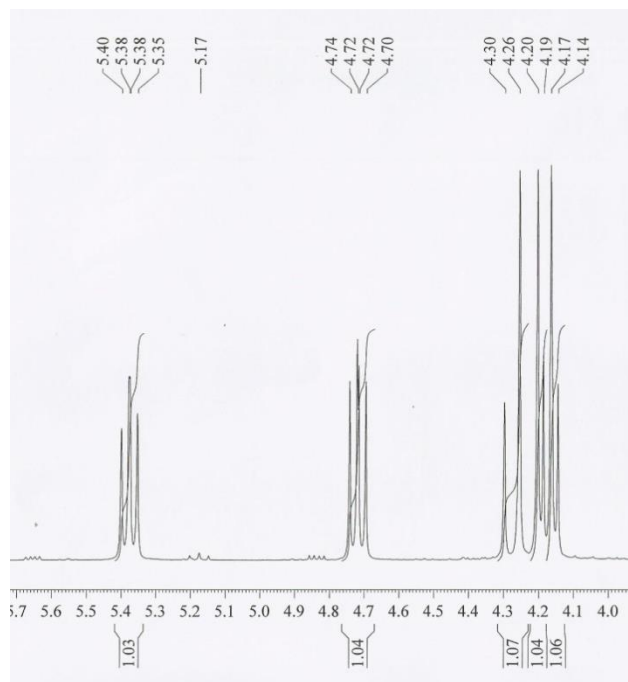


Fig 5.11 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one C^{13} NMR

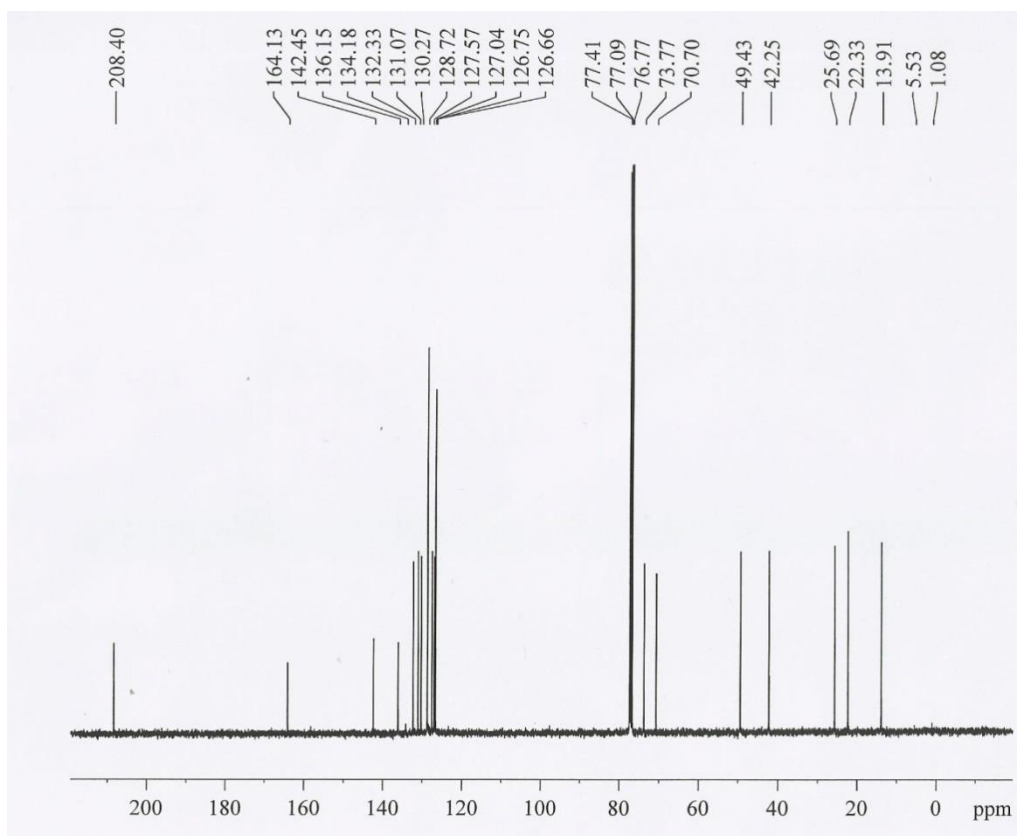


Fig 5.12 (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one C^{13} NMR

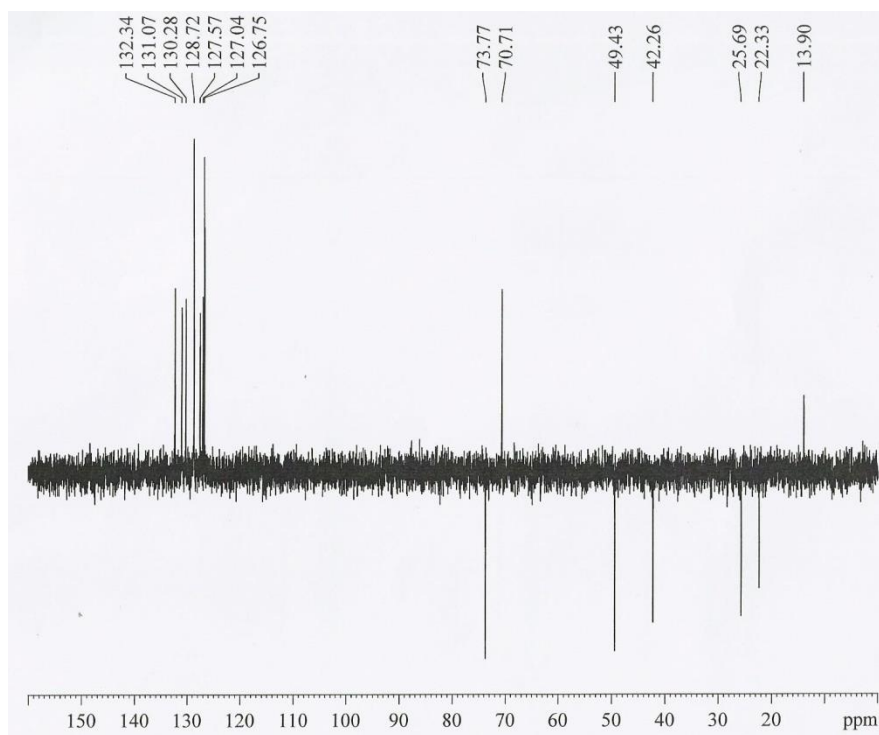


Fig 5.13 (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) H¹ NMR

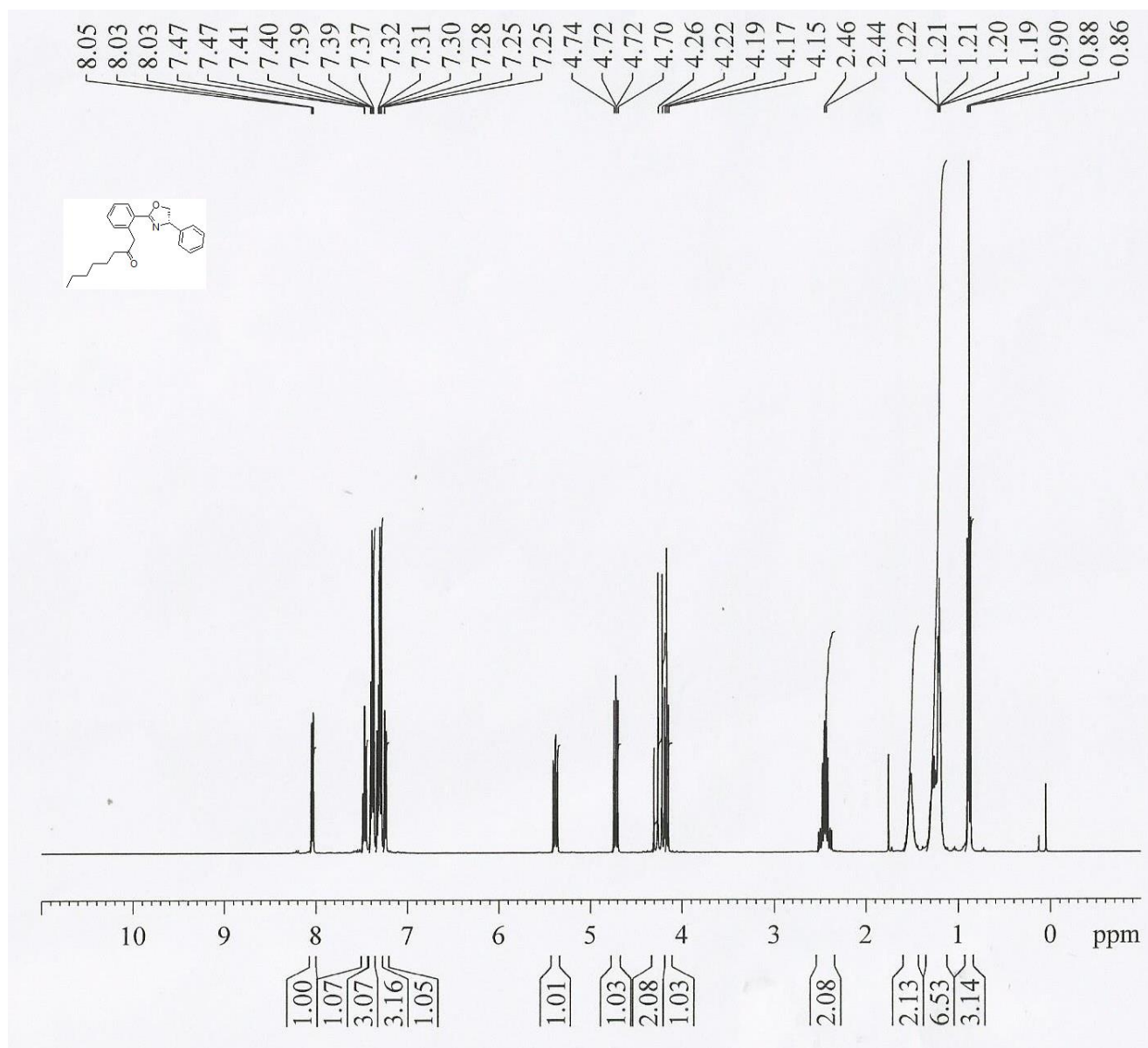


Fig 5.14 (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) H¹ NMR

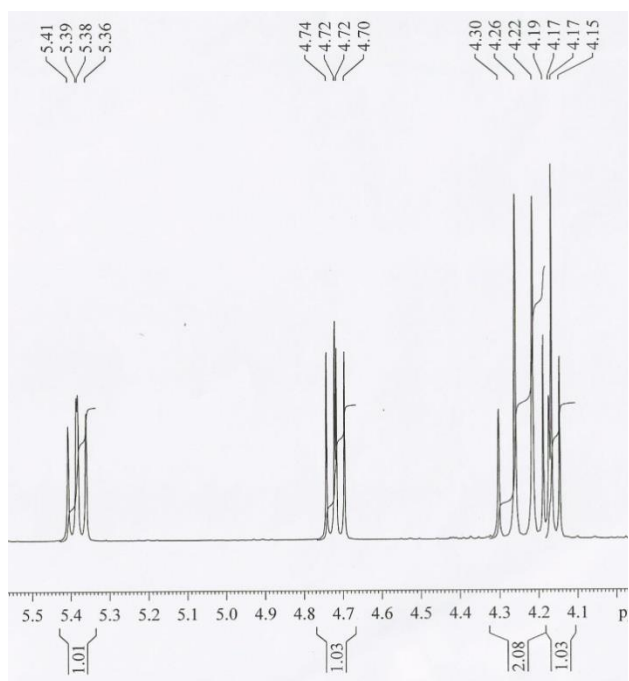
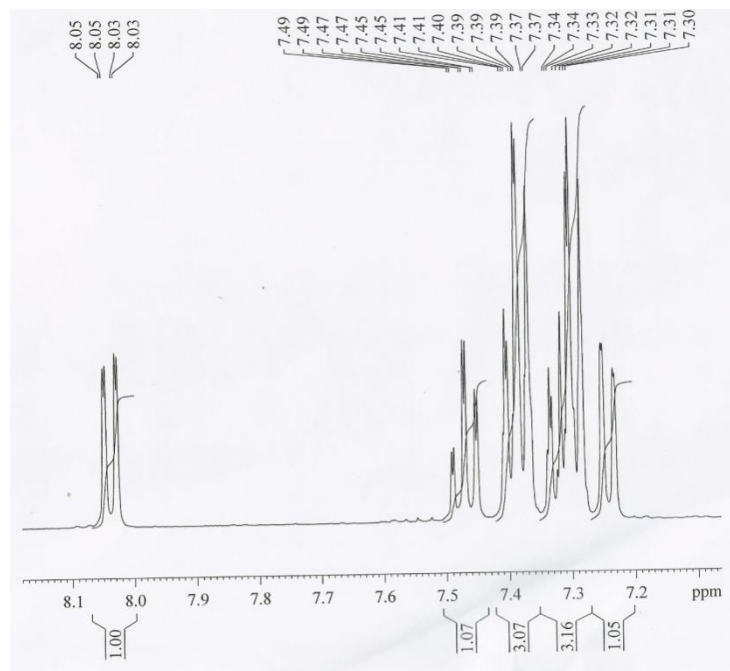
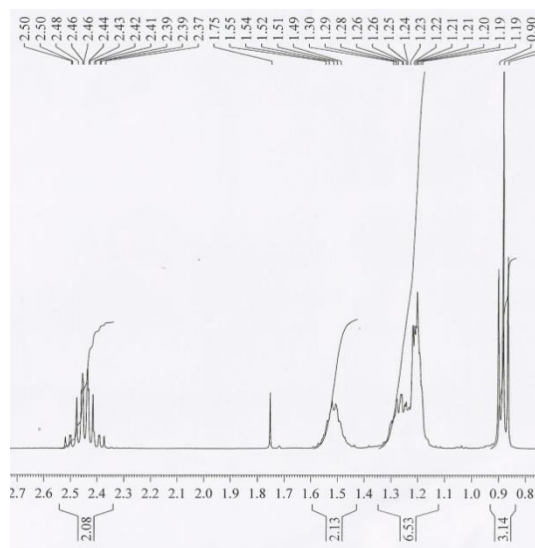


Fig 5.15 (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) c^{13} NMR

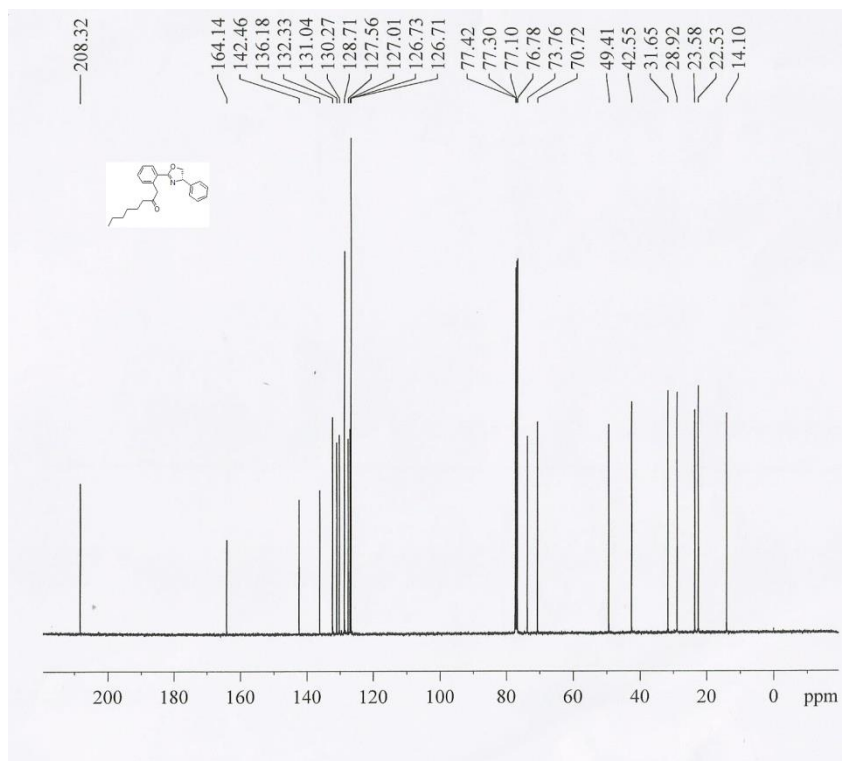
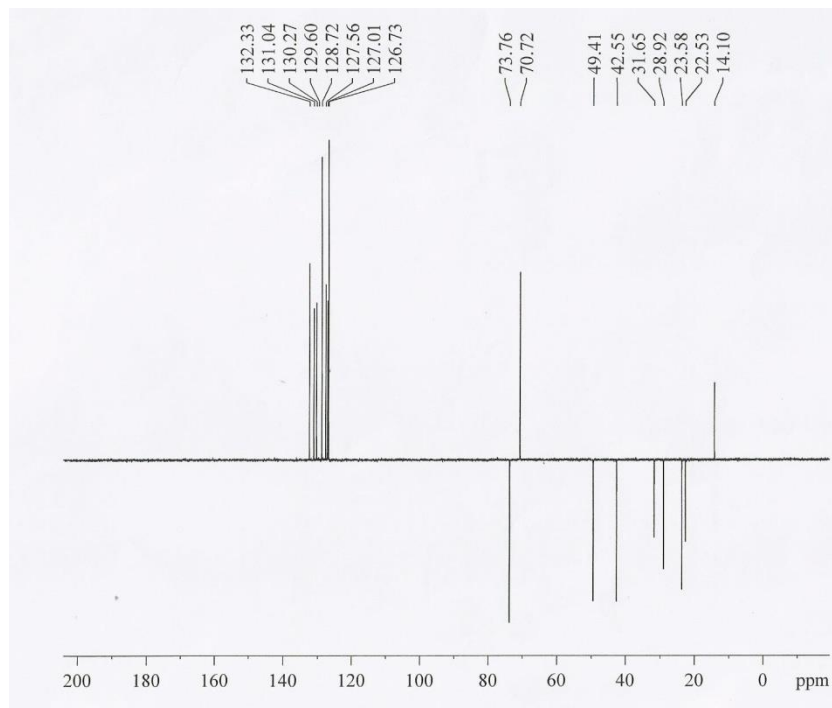
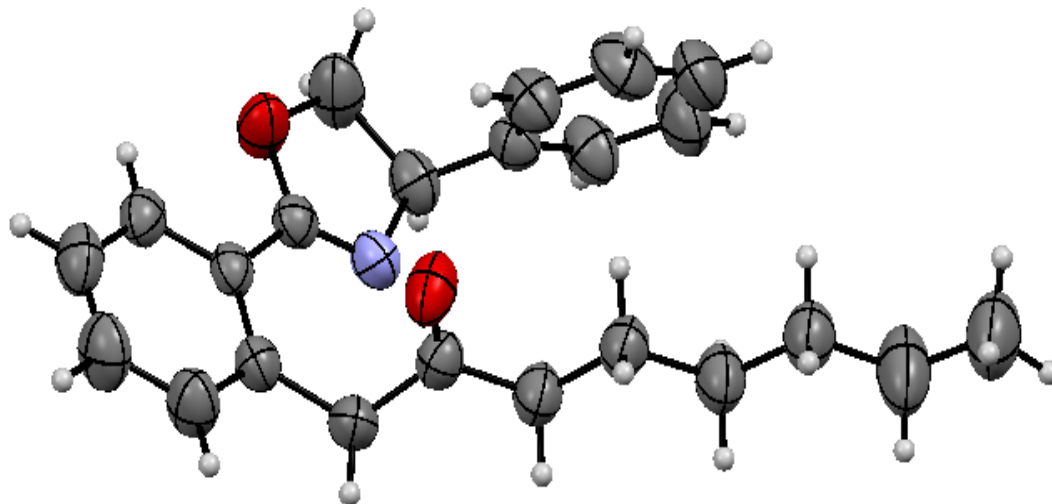


Fig 5.16 (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra) C^{13} Dept



5.1.7. Crystal Structure: (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra)



A suitable single crystal was collected through the polarizing microscope and mounted on the Bruker D8 Venture diffractometer system is equipped with micro focus Cu source, Photon 100 CMOS detector.

Crystal is kept at 298K (2) during the data collection with scan width of 0.5mm and distance 40mm from crystal to detector.

The structure was solved using the Olex2 with the XT, using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimization.

Table 1 Crystal data and structure refinement for (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1Ra)

Identification code	DN_GL_R
Empirical formula	C ₂₃ H ₂₇ NO ₂
Formula weight	349.48
Temperature/K	298(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	8.0247(3)
b/Å	9.1249(4)
c/Å	27.7740(12)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2033.74(15)

Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.1413
μ/mm^{-1}	0.564
F(000)	754.2
Crystal size/ mm^3	$0.24 \times 0.23 \times 0.22$
Radiation	Cu K α ($\lambda = 1.54178$)
2 Θ range for data collection/ $^\circ$	10.2 to 140.4
Index ranges	$-9 \leq h \leq 9, -11 \leq k \leq 11, -33 \leq l \leq 33$
Reflections collected	17143
Independent reflections	3806 [$R_{\text{int}} = 0.0228, R_{\text{sigma}} = 0.0179$]
Data/restraints/parameters	3806/0/235
Goodness-of-fit on F^2	1.055
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0373, wR_2 = 0.1033$
Final R indexes [all data]	$R_1 = 0.0394, wR_2 = 0.1063$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.13/-0.11
Flack parameter	-0.20(18)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for DN_GL_R. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	U(eq)
O2	-404.6 (16)	5527.5 (13)	3633.8 (4)	71.3 (3)
O1	3972.4 (16)	3992.8 (13)	2681.5 (4)	66.7 (3)
N1	3693.3 (18)	4449.6 (14)	3473.1 (4)	57.7 (3)
C10	1668.8 (16)	2850.5 (13)	3070.6 (5)	44.7 (3)
C9	3147.6 (17)	3801.8 (14)	3102.3 (5)	45.9 (3)
C11	1321 (2)	2161.4 (15)	2631.6 (5)	51.9 (3)
C17	454.8 (18)	4981.3 (16)	3940.5 (5)	51.5 (3)
C15	600.4 (18)	2622.7 (14)	3462.9 (5)	49.7 (3)
C4	4920.8 (18)	6913.9 (15)	3448.2 (5)	52.1 (3)
C19	520 (2)	7407.6 (17)	4393.8 (5)	59.9 (4)
C16	835 (2)	3356.0 (16)	3944.5 (5)	55.2 (3)
C5	3502 (2)	7657.5 (19)	3304.3 (6)	65.5 (4)
C7	5163 (2)	5312.1 (16)	3326.8 (6)	58.4 (4)
C12	-19 (2)	1237.5 (18)	2582.0 (6)	66.3 (4)
C18	1174 (2)	5858.4 (17)	4349.4 (5)	60.6 (4)
C3	6097 (2)	7659.4 (18)	3709.6 (6)	67.0 (4)
C14	-757 (2)	1704.6 (19)	3398.4 (6)	69.1 (4)
C8	5330 (3)	4989 (2)	2783.3 (7)	77.1 (5)
C13	-1063 (2)	1011 (2)	2964.5 (7)	75.4 (5)
C6	3272 (3)	9106 (2)	3422.1 (8)	78.6 (5)
C20	1374 (3)	8260.3 (18)	4789.2 (6)	70.7 (5)

C1	4443 (3)	9842.3 (19)	3688.6 (8)	83.5 (6)
C21	738 (3)	9802.0 (19)	4859.9 (6)	72.7 (5)
C2	5839 (3)	9123 (2)	3834.1 (8)	86.5 (6)
C22	1576 (4)	10619 (2)	5260.3 (9)	105.8 (9)
C23	942 (5)	12117 (3)	5359.3 (9)	109.1 (9)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for DN_GL_R. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^*U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
O2	79.2 (8)	69.7 (6)	65.0 (6)	20.8 (6)	-15.9 (6)	-17.1 (5)
O1	68.4 (7)	68.3 (7)	63.5 (6)	-15.6 (6)	19.0 (5)	-13.6 (5)
N1	64.9 (7)	50.4 (6)	57.7 (7)	-14.2 (6)	-0.5 (6)	0.3 (5)
C10	51.1 (7)	33.2 (5)	49.8 (6)	4.8 (5)	-4.2 (5)	-0.9 (5)
C9	49.4 (6)	36.8 (6)	51.6 (7)	4.9 (5)	2.4 (5)	0.2 (5)
C11	59.1 (8)	44.6 (6)	51.8 (7)	8.3 (6)	-2.2 (6)	-4.4 (5)
C17	51.2 (7)	55.6 (8)	47.8 (7)	-0.1 (6)	3.3 (6)	-6.4 (6)
C15	55.7 (7)	39.7 (6)	53.8 (7)	-2.6 (6)	0.9 (6)	-1.7 (5)
C4	50.7 (7)	49.6 (7)	56.1 (7)	-6.1 (6)	1.1 (6)	3.7 (6)
C19	67.2 (9)	59.0 (8)	53.6 (7)	1.6 (7)	-0.6 (7)	-9.5 (6)
C16	65.8 (8)	50.8 (7)	48.9 (7)	-6.8 (7)	3.6 (6)	0.9 (6)
C5	60.2 (9)	61.1 (9)	75.3 (10)	-0.8 (7)	-11.2 (8)	4.8 (8)
C7	51.3 (8)	50.9 (7)	73.0 (9)	-4.6 (6)	-3.3 (7)	-2.6 (6)
C12	72.1 (10)	58.9 (8)	68.0 (9)	0.9 (8)	-16.0 (8)	-16.2 (7)
C18	71.0 (9)	56.6 (8)	54.3 (7)	0.4 (7)	-5.6 (7)	-8.3 (6)
C3	58.6 (9)	57.8 (8)	84.5 (11)	-8.2 (7)	-12.0 (8)	0.4 (8)
C14	66.3 (10)	65.0 (9)	75.9 (10)	-17.8 (8)	10.2 (8)	-11.0 (8)
C8	69.2 (10)	72.7 (11)	89.5 (12)	-18.1 (9)	26.3 (9)	-18.7 (9)
C13	64.9 (10)	71.3 (10)	90.1 (12)	-19.1 (9)	-4.0 (9)	-18.4 (9)
C6	79.6 (12)	60.2 (9)	95.8 (13)	14.9 (9)	0.8 (10)	15.1 (9)
C20	86.3 (12)	57.7 (9)	68.2 (9)	-2.9 (9)	-15.2 (9)	-10.8 (7)
C1	107.1 (16)	49.0 (8)	94.5 (13)	0.2 (10)	7.3 (12)	-1.2 (9)
C21	86.1 (12)	63.4 (9)	68.5 (10)	2.7 (9)	-4.3 (9)	-13.3 (8)
C2	98.9 (15)	60.6 (10)	99.8 (14)	21.2 (11)	16.1 (12)	-9.2 (9)
C22	140 (2)	73.7 (12)	103.9 (15)	11.5 (15)	41.2 (16)	26.7 (12)
C23	150 (3)	80.7 (13)	96.4 (15)	10.3 (16)	12.0 (16)	30.5 (12)

Table 4 Bond Lengths for DN_GL_R.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O2	C17	1.2041 (19)	C4	C7	1.513 (2)
O1	C9	1.3542 (16)	C4	C3	1.371 (2)
O1	C8	1.447 (2)	C19	C18	1.513 (2)
N1	C9	1.2658 (18)	C19	C20	1.510 (2)
N1	C7	1.475 (2)	C5	C6	1.374 (3)
C10	C9	1.4729 (19)	C7	C8	1.544 (2)
C10	C11	1.3998 (18)	C12	C13	1.369 (3)
C10	C15	1.4021 (19)	C3	C2	1.395 (3)
C11	C12	1.373 (2)	C14	C13	1.383 (2)
C17	C16	1.514 (2)	C6	C1	1.372 (3)
C17	C18	1.5044 (19)	C20	C21	1.509 (2)
C15	C16	1.5073 (19)	C1	C2	1.360 (3)
C15	C14	1.385 (2)	C21	C22	1.498 (3)
C4	C5	1.385 (2)	C22	C23	1.484 (3)

Table 5 Bond Angles for DN_GL_R.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C8	O1	C9	106.27 (12)	C20	C19	C18	112.52 (14)
C7	N1	C9	107.56 (12)	C15	C16	C17	113.78 (12)
C11	C10	C9	118.50 (12)	C6	C5	C4	120.87 (17)
C15	C10	C9	122.25 (11)	C4	C7	N1	110.60 (13)
C15	C10	C11	119.24 (13)	C8	C7	N1	103.71 (13)
N1	C9	O1	118.23 (12)	C8	C7	C4	114.42 (14)
C10	C9	O1	114.71 (11)	C13	C12	C11	119.60 (14)
C10	C9	N1	127.05 (12)	C19	C18	C17	115.18 (13)
C12	C11	C10	121.27 (14)	C2	C3	C4	120.26 (18)
C16	C17	O2	121.74 (13)	C13	C14	C15	121.93 (16)
C18	C17	O2	122.24 (13)	C7	C8	O1	104.22 (13)
C18	C17	C16	116.00 (13)	C14	C13	C12	119.90 (16)
C16	C15	C10	123.19 (12)	C1	C6	C5	120.50 (18)
C14	C15	C10	118.02 (13)	C21	C20	C19	114.93 (16)
C14	C15	C16	118.77 (13)	C2	C1	C6	119.23 (17)
C7	C4	C5	120.98 (14)	C22	C21	C20	114.15 (17)
C3	C4	C5	118.42 (14)	C1	C2	C3	120.71 (19)
C3	C4	C7	120.60 (14)	C23	C22	C21	116.3 (2)

Table 6 Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for DN_GL_R.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
H11	2011 (2)	2332.6 (15)	2368.5 (5)	62.2 (4)
H19a	681 (2)	7912.9 (17)	4090.0 (5)	71.9 (4)
H19b	-668 (2)	7374.8 (17)	4458.4 (5)	71.9 (4)
H16a	1979 (2)	3215.5 (16)	4047.9 (5)	66.2 (4)
H16b	118 (2)	2881.6 (16)	4178.5 (5)	66.2 (4)
H5	2693 (2)	7170.1 (19)	3125.6 (6)	78.7 (5)
H7	6150 (2)	4941.6 (16)	3495.2 (6)	70.1 (4)
H12	-216 (2)	768.6 (18)	2290.2 (6)	79.6 (5)
H18a	948 (2)	5344.8 (17)	4648.1 (5)	72.8 (4)
H18b	2374 (2)	5900.3 (17)	4310.1 (5)	72.8 (4)
H3	7071 (2)	7187.4 (18)	3804.1 (6)	80.3 (5)
H14	-1483 (2)	1550.2 (19)	3654.4 (6)	82.9 (5)
H8a	6396 (3)	4537 (2)	2712.1 (7)	92.5 (6)
H8b	5224 (3)	5882 (2)	2595.9 (7)	92.5 (6)
H13	-1977 (2)	392 (2)	2932.8 (7)	90.5 (6)
H6	2315 (3)	9591 (2)	3320.4 (8)	94.3 (6)
H20a	1243 (3)	7728.6 (18)	5089.3 (6)	84.9 (5)
H20b	2556 (3)	8304.7 (18)	4718.3 (6)	84.9 (5)
H1	4284 (3)	10821.8 (19)	3768.8 (8)	100.2 (7)
H21a	893 (3)	10343.4 (19)	4562.6 (6)	87.2 (6)
H21b	-448 (3)	9762.1 (19)	4924.9 (6)	87.2 (6)
H2	6631 (3)	9612 (2)	4018.5 (8)	103.7 (7)
H22a	1470 (4)	10045 (2)	5552.5 (9)	127.0 (11)
H22b	2754 (4)	10690 (2)	5186.2 (9)	127.0 (11)
H23a	1260 (20)	12760 (6)	5102 (4)	163.7 (13)
H23b	-251 (5)	12093 (5)	5384 (8)	163.7 (13)
H23c	1410 (20)	12468 (11)	5656 (5)	163.7 (13)

Experimental

A suitable crystal was selected and on a Bruker APEX-III CMOS diffractometer. The crystal was kept at 298(2) K during data collection. Using Olex2 [174], the structure was solved with the ShelXT [175] structure solution program using Intrinsic Phasing and refined with the olex2.refine [176] refinement package using Gauss-Newton minimization.

Fig 5.17 HRMS of (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1)

Elemental Composition Report

Single Mass Analysis

Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
 Selected filters: None

Monoisotopic Mass, Even Electron Ions

14 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

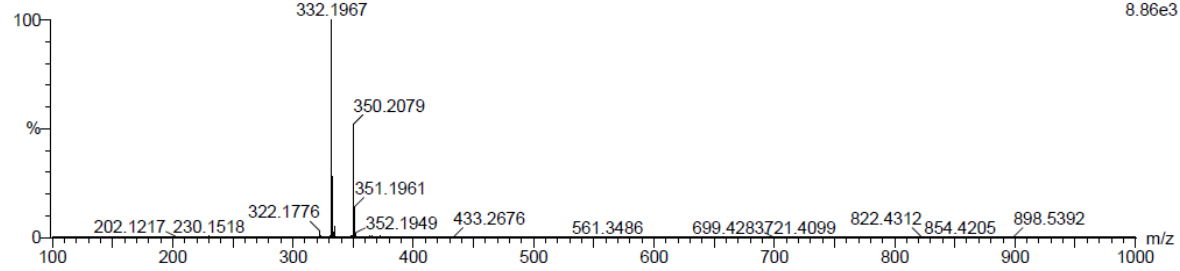
Elements Used:

C: 0-24 H: 0-28 N: 0-2 O: 0-3

Sample Name :RPGOCT

111217-RPGOCT 26 (0.630) AM (Cen,2, 80.00, Ht,5000.0,0.00,1.00); Sm (Mn, 2x3.00); Cm (10:37)

1: TOF MS ES+
8.86e3



Minimum: 5.0 20.0 -1.5
 Maximum: 5.0 20.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
350.2079	350.2120	-4.1	-11.7	10.5	15.3	C23 H28 N O2

Fig 5.18 Mass of (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(1)

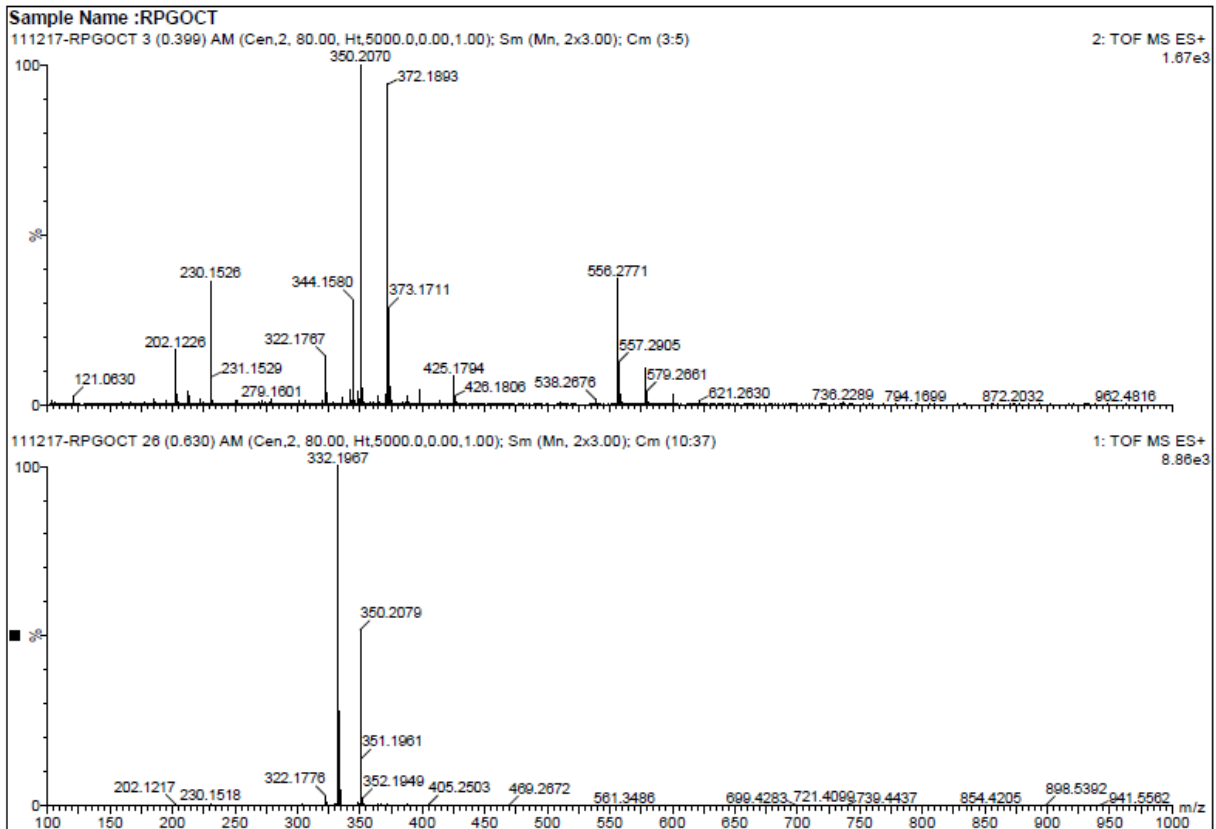


Fig 5.19 HRMS of (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(2)
Elemental Composition Report Page 1

Single Mass Analysis
 Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
 Selected filters: None

Monoisotopic Mass, Even Electron Ions
 14 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

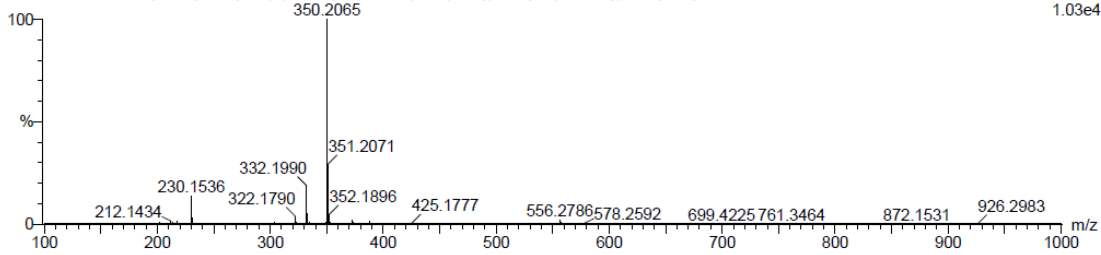
Elements Used:

C: 0-24 H: 0-28 N: 0-2 O: 0-3

Sample Name :SPGOCT

111217-SPGOCT 2 (0.059) AM (Cen,2, 80.00, Ht,5000.0,0.00,1.00); Sm (Mn, 2x3.00); Cm (2:20)

1: TOF MS ES+
1.03e4



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
350.2065	350.2120	-5.5	-15.7	10.5	37.1	C23 H28 N O2

Fig 5.20 Mass of (S)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)octan-2-one(2)

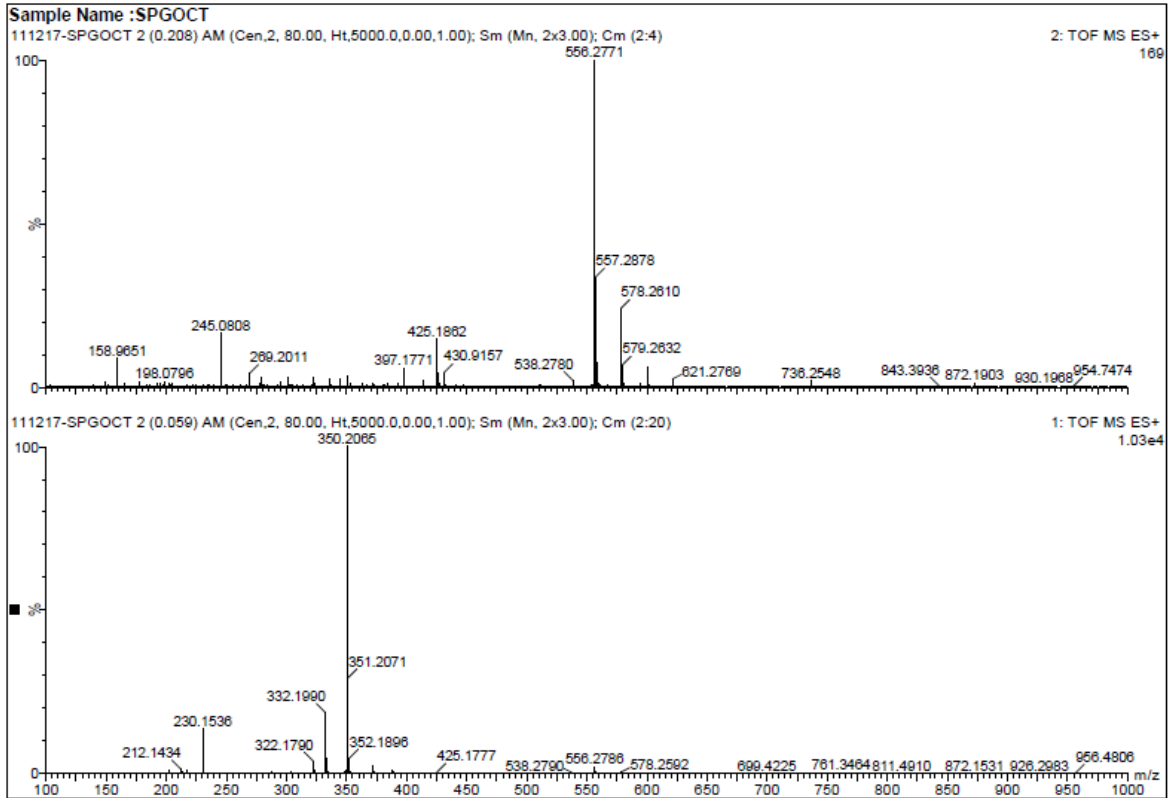


Fig 5.21 HRMS of (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one(3)

Elemental Composition Report

Single Mass Analysis

Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

21 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

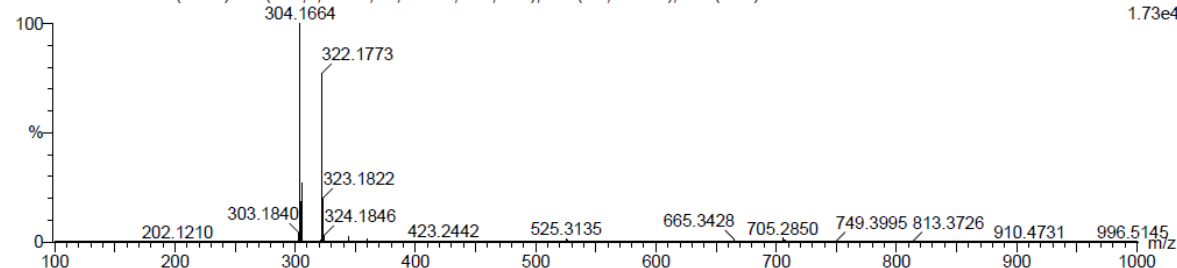
Elements Used:

C: 0-24 H: 0-24 N: 0-2 O: 0-3

Sample Name :RPGHEX

111217-RPGHEX 18 (0.520) AM (Cen,2, 80.00, Ht,5000.0,0.00,1.00); Sm (Mn, 2x3.00); Cm (3:24)

1: TOF MS ES+
1.73e4



Minimum: -1.5
Maximum: 5.0 20.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
322.1773	322.1807	-3.4	-10.6	10.5	16.0	C21 H24 N O2

Fig 5.22 Mass of (R)-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)hexan-2-one(3)

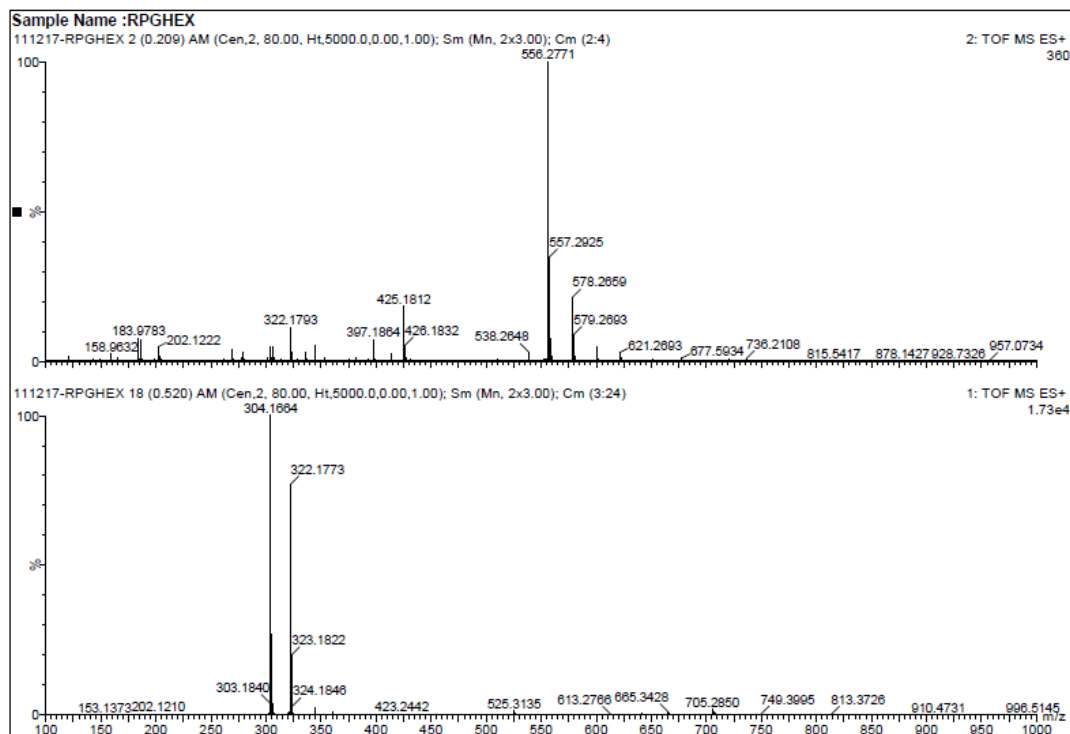


Fig 5.23 MRMS of (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one(4)

Elemental Composition Report

Single Mass Analysis

Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

19 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

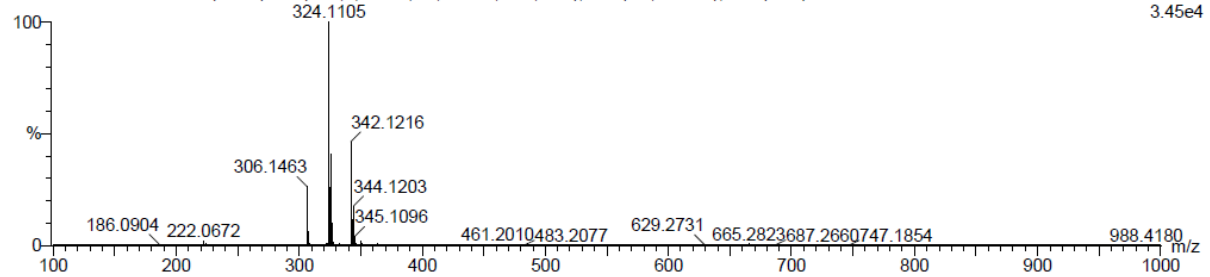
Elements Used:

C: 0-21 H: 0-21 N: 0-2 O: 0-3 Cl: 0-1

Sample Name :RPGCLPENT

111217-RPGCLPENT 17 (0.420) AM (Cen,2, 80.00, Ht,5000.0,0.00,1.00); Sm (Mn, 2x3.00); Cm (6:40)

1: TOF MS ES+
3.45e4



Minimum: -1.5
Maximum: 5.0 20.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
342.1216	342.1261	-4.5	-13.2	10.5	31.9	C20 H21 N O2 Cl

Fig 5.24 Mass of (R)-5-chloro-1-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)pentan-2-one(4)

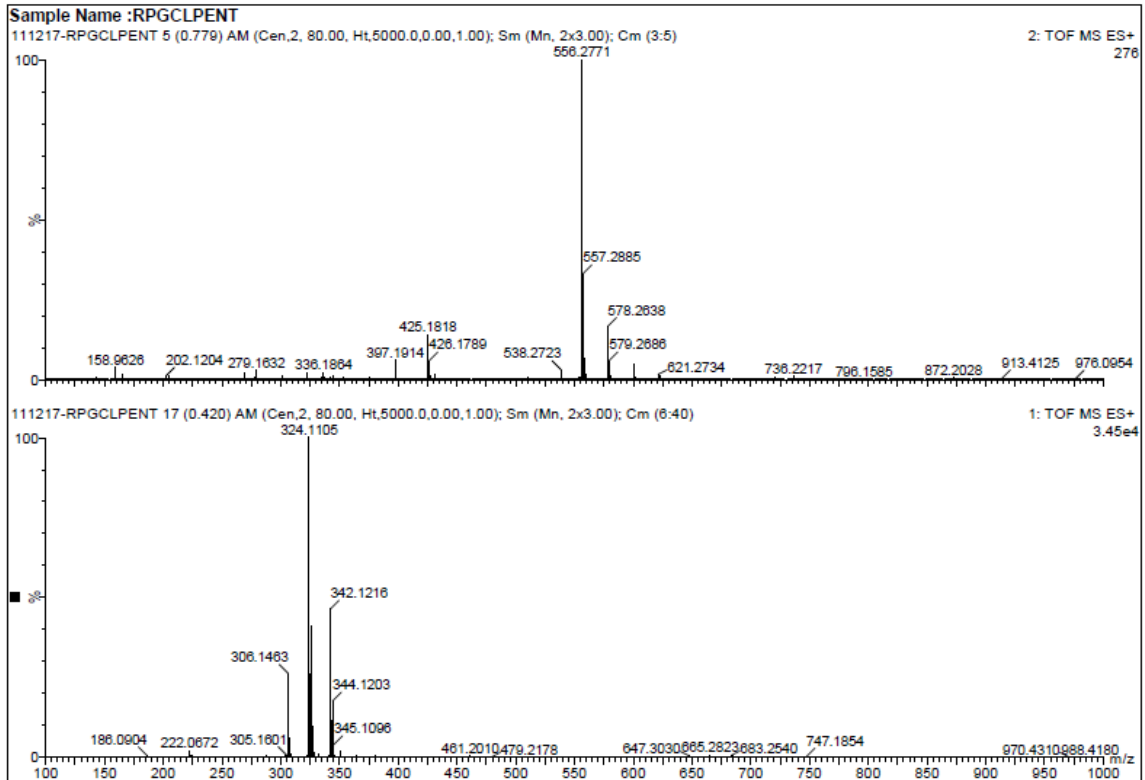


Fig 5.25 HRMS of (R)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide

Elemental Composition Report

Single Mass Analysis

Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

14 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

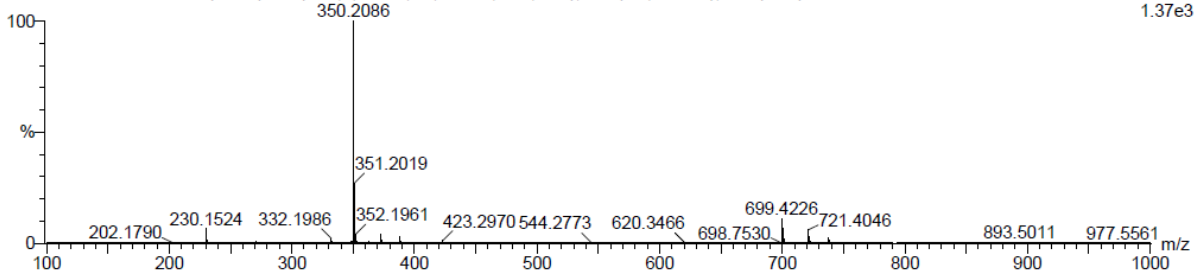
Elements Used:

C: 0-24 H: 0-28 N: 0-2 O: 0-3

Sample Name :RPGOCTBENZ

111217-RPGOCTBENZ 2 (0.059) AM (Cen,2, 80.00, Ht,5000.0,0.00,1.00); Sm (Mn, 2x3.00); Cm (2:24)

1: TOF MS ES+
1.37e3



Minimum: -1.5
Maximum: 5.0 20.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
350.2086	350.2120	-3.4	-9.7	10.5	2.6	C23 H28 N O2

Fig 5.26 Mass of (R)-N-(2-hydroxy-1-phenylethyl)-2-(oct-1-ynyl)benzamide

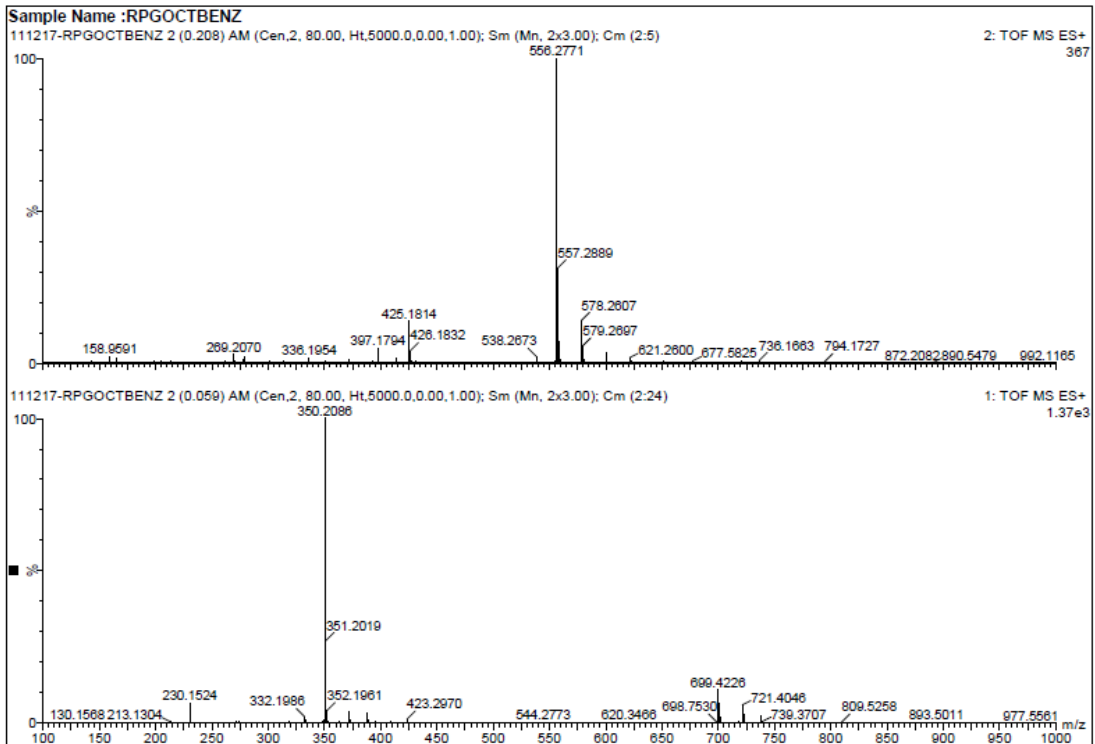


Fig 5.27 MRMS of (S)-N-(2-hydroxy-1-phenylethyl)-2-(hex-1-ynyl)benzamide

Elemental Composition Report

Single Mass Analysis

Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

24 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

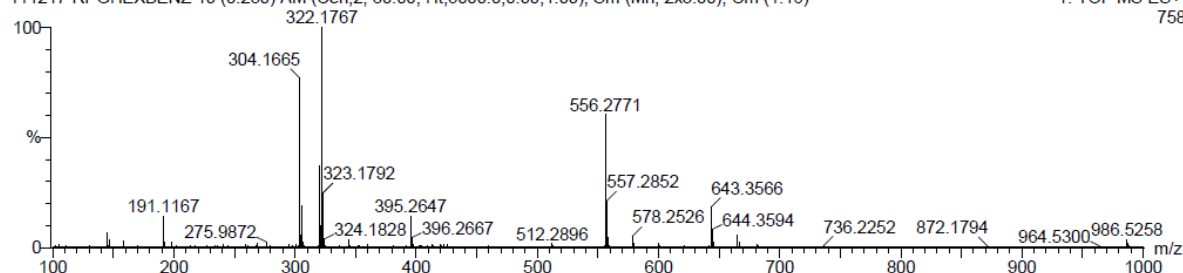
Elements Used:

C: 0-24 H: 0-28 N: 0-2 O: 0-3

Sample Name :RPGHEXBENZ

111217-RPGHEXBENZ 10 (0.250) AM (Cen,2, 80.00, Ht,5000.0,0.00,1.00); Sm (Mn, 2x3.00); Cm (1:16)

1: TOF MS ES+
758



Minimum: -1.5
Maximum: 5.0 20.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
322.1767	322.1807	-4.0	-12.4	10.5	0.8	C21 H24 N O2

Fig 5.28 Mass of (S)-N-(2-hydroxy-1-phenylethyl)-2-(hex-1-ynyl)benzamide

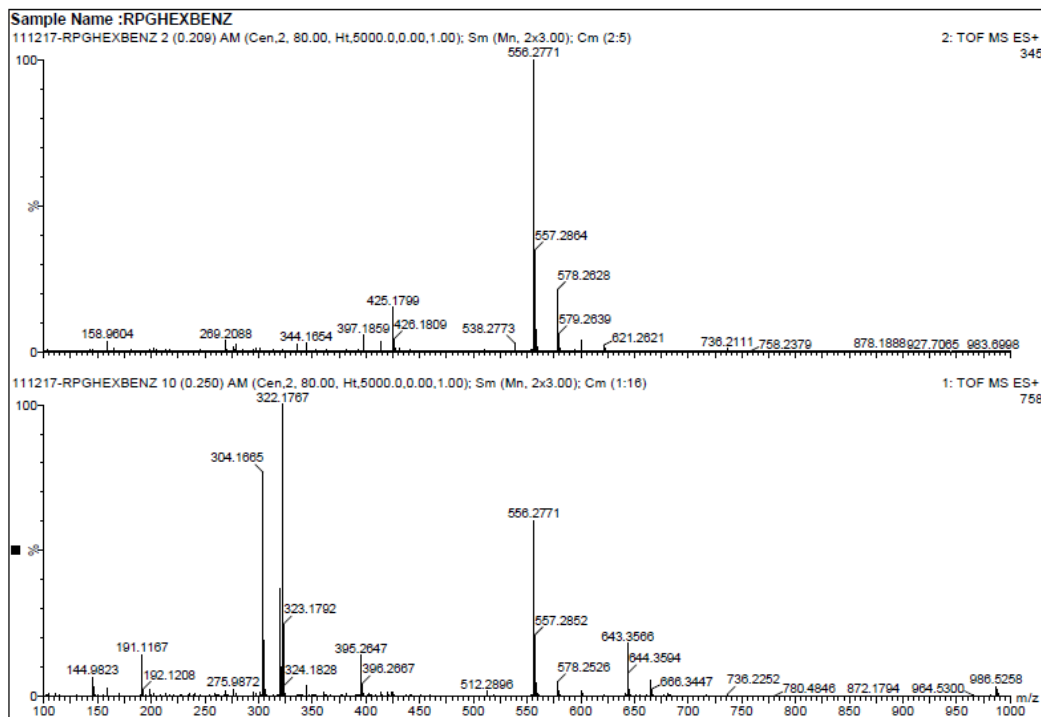
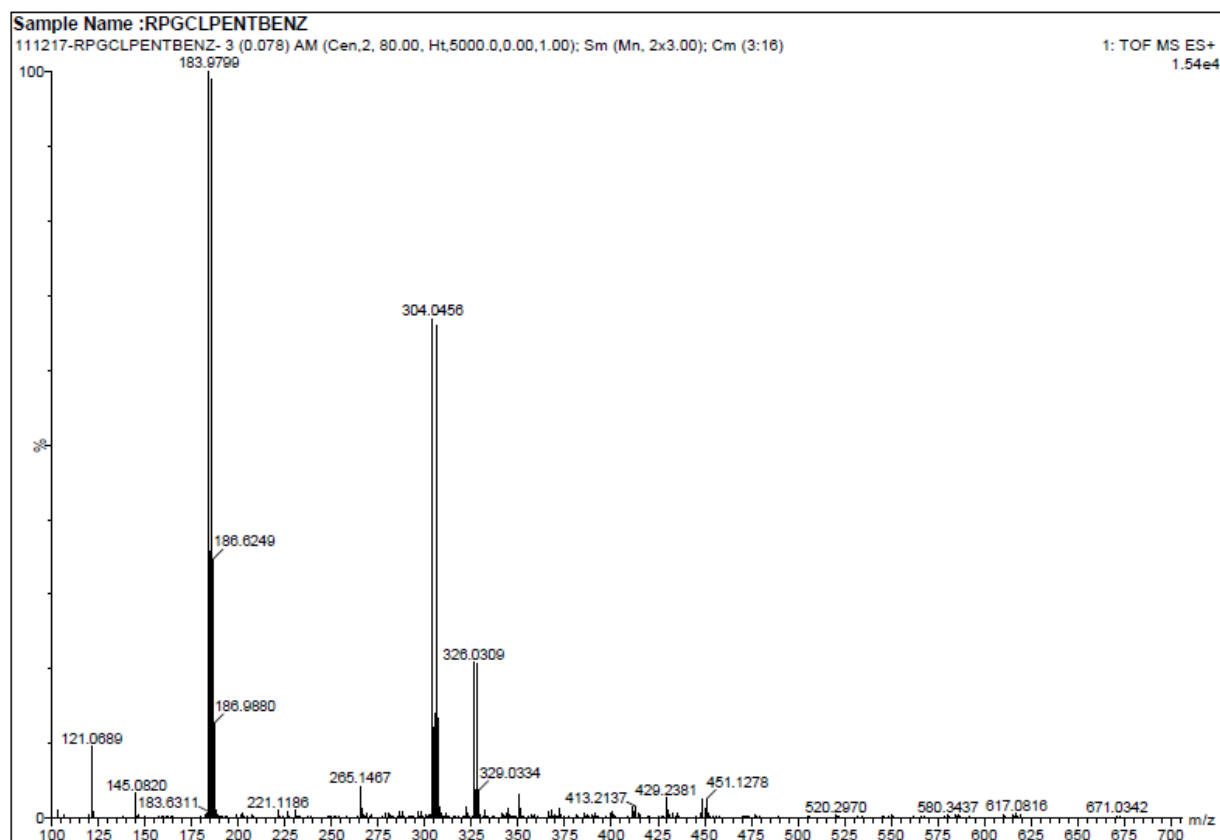


Fig 5.29 Direct infusion (R)-2-(5-chloropent-1-ynyl)-N-(2-hydroxy-1-phenylethyl)benzamide



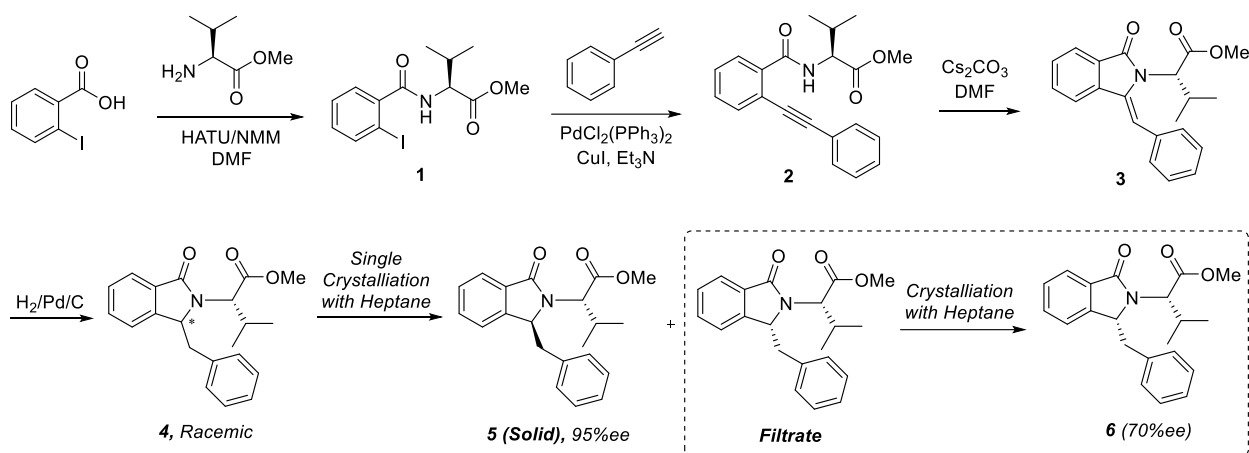
5.2 “CHIRAL INDUCTION (ISOINDOLINONE)”

Isoindolinones have received extensive attention in recent years because isoindolin-1-one (2,3-dihydro-1H-isoindolin-1-one) is a key structural feature found in many pharmaceutically interesting molecules and natural products like pazinaclone is an anxiolytic drug candidate, chlorthalidone is a diuretic and antihypertensive drug [177a,b]. lennoxamine, nuevamine, and chilene are alkaloids isolated from various barberry species [178a,b,c]. Moreover, (R) and (S)-3-methyl-1H-isoindolin-1-ones have been shown to be valuable chiral auxiliaries [179a,b,c]. A variety of methods for the synthesis of iso-indolinones have been developed in literature, phthalimides [180a,b,c,d]. or phthalimidines [181a,b,c,d]. are directly used as starting materials to prepare isoindolinones especially 3-substituted derivatives. The second approach is the construction of the lactam ring through various cyclization reactions of functionalized aromatic compounds. amination reaction of o-halomethyl or o-acylbenzoate derivatives, [182a,b,c,d,e,f] Some new approaches, such as the transition metal-catalyzed carbonylation and C-H

fictionalization, Diels Alder and inverse-electron demand Diels Alder, aza-Wittig and radical cyclization reactions as well as organocatalytic reactions. The o-lithiation/cyclization procedures have also been reported to produce substituted isoindolinones, [183]. In spite of all these achievements, the starting materials were not readily available in many of above-mentioned methods, which were usually obtained by multistep reactions. Consequently, the development of new synthetic routes for isoindolinone derivatives from simple and readily available starting materials is important. However, few methods are available for the asymmetric synthesis of simple 3-alkyl-isoindolin-1-ones in high enantiomeric excess. [184-189]. accordingly, the development of flexible method for the asymmetric synthesis of 3-alkyl-isoindolin-1-ones is highly desirable. Herein, we report a simple, efficient and Chemo selective method for preparation of Isoindolinones.

A simple Chemoselective process has been developed for the preparation of isoindolinone, with 95% ee, using alkynes, substituted 2-iodo amide and copper metal powder in a one pot alkylation, cyclization followed by hydrogenation at room temperature.

In literature there is no straight forward method for preparation of Isoindolinones with readily available starting materials. Hazardous reagent like organolithium used and yield observed was low. We have selected 2-Iodobenzoic acid as cheap starting material and commonly used chiral auxiliary valine methyl ester and prepared **1** with **95%** yield by simple acid amine coupling using HATU. Which on coupling with phenylacetylene gives **2** with 86% yield? With weak base cesium carbonate **2** further converted to isoindolin **3** which on hydrogenation with hydrogen gas in presence of palladium on charcoal was expected to display asymmetric induction but observed both diastereoisomer in 1:1 ratio compound **5** which on single crystallization from n-heptane gives ee 95% **6**. Filtrate on atmospheric evaporation and crystallization from n-Heptane gives another isomer **7** with 80 % ee.



5.2.1. Experimental process for preparation of (R)-methyl 3-methyl-2-(2-(2-phenylethynyl)benzamido)butanoate

Charged 1 gm of (R)-methyl 1-(2-iodobenzamido)-2-methylpropylcarbamate in 5 ml DMF under nitrogen atmosphere. Charged 5 mole % of $\text{PdCl}_2(\text{PPh}_3)_3$ and gm of Triethylamine stirred for 10 min. Charged Phenylacetylene and reaction mass heated to 80°C for 4 hrs. Cooled reaction mass to 25°C and 5 ml water product was extracted with 5 ml ethyl acetate. Dried ethyl acetate layer on sodium sulphate and concentrated to get crude product which was purified on silica column using 30% ethyl acetate in n-hexane. ^1H NMR (400 MHz, CDCl_3) δ 0.95(d 3H), 0.97(d 3H), 2.24(m 1H), 3.72(s 1H), 4.85(t 1H), 7.39(m 3H), 7.45(m 2H), 7.61(m 2H), 7.65(m 1H), 8.00(d 1H $J=8$), 8.11(m 1H). ^{13}C NMR (100MHz, CDCl_3) δ 18.26, 19.03, 31.56, 52.10, 58.23, 87.44, 96.10, 119.95, 122.26, 128.44, 129.06, 130.21, 130.76, 131.80, 134.00, 134.73, 166.02, 172.25.

5.2.2 Experimental process for preparation of (R,E)-methyl 2-(1-benzylidene-3-oxoisindolin-2-yl)-3-methylbutanoate

Charged 1gm of (R)-methyl 3-methyl-2-(2-(2-phenylethynyl)benzamido)butanoate in 5 ml toluene, charged 1gm cesium carbonate and heated to 110°C for 4 hrs. Charged 5 ml water and product extracted in 5 ml ethyl acetate. Concentrate completely and purified on silica column using ethyl acetate n-Hexane as a solvent. ^1H NMR (400 MHz, CDCl_3) δ 0.65(t 3H), 0.75(t 3H),

2.62(m 1H), 3.76(s 3H), 4.19(d 1H), 6.85(s 1H), 7.35(m 5H), 7.52(t 1H J=8), 7.64(t 1H J=8), 7.79(d J=8), 7.97(d J=8).

5.2.3 Experimental process for preparation of (R)-methyl 2-((S)-1-benzyl-3-oxoisindolin-2-yl)-3-methylbutanoate

1 gm of (R,E)-methyl 2-(1-benzylidene-3-oxoisindolin-2-yl)-3-methylbutanoate in 10 ml ethanol was charged 0.1 gm 5% palladium on charcoal 50% wet under nitrogen atmosphere and apply hydrogen gas using hydrogen balloon at 25°C after one hr. filter reaction mass and concentrated completely. (Mix. 1:1 NMR)

Crude product was crystallized from n-Heptane 350 mg crystalline solid was obtained ¹H NMR (400 MHz, CDCl₃) δ 1.02(d 3H), 1.11(d 3H), 2.59(t 1H), 2.65(m 1H), 3.81(s 3H), 3.86(1H m), 4.5(M 1H), 4.81(M1H), 6.49(d 1H J=8), 7.03(m 2H), 7.26(m 5H), 7.85(d 1H). ¹³C NMR (100MHz, CDCl₃) δ 19.16, 20.16, 29.93, 39.76, 52.15, 62.01, 62.76, 123.28, 123.85, 127.14, 128.21, 128.73, 129.68, 131.09, 131.20, 136.97, 145.29, 168.70, 171.03. The solid was characterized using ¹H and ¹³C NMR and identified as (R)-methyl 2-((S)-1-benzyl-3-oxoisindolin-2-yl)-3-methylbutanoate X-Ray crystallography.

5.2.4 Preparation of (R)-methyl 2-((R)-1-benzyl-3-oxoisindolin-2-yl)-3-methylbutanoate

Filtrate on atmospheric evaporation and crystallization from n-Heptane 300mg solid was obtained ¹H NMR (400 MHz, CDCl₃) δ. 0.92(d 3H), 1.17(d 3H), 2.53(m 1H), 2.76(m 1H), 3.61(dd, 1H), 3.75(s 3H), 4.61(d 1H J=12), 4.78(m 1H), 6.53(d 1H), 7.16(d 1H), 7.26(m1H), 7.40(m 1H), 7.78(d1H). ¹³C NMR (100MHz, CDCl₃) δ 19.65, 20.56, 28.7, 39.01, 52.16, 60.60, 123.29, 123.99, 127.10, 128.26, 128.65, 129.65, 131.07, 131.23, 136.59, 145.37, 169.15, 171.63.

5.2.5 ^1H , ^{13}C NMR and ^{13}C Dept. Spectas of Isoindolinone.

Fig 5.30 ^1H NMR methyl [(1R)-2-methyl-1-([2-(phenylethynyl)phenyl]carbonyl)amino)propyl]carbamate

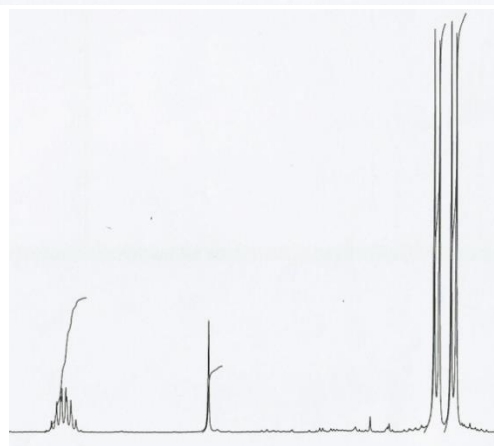
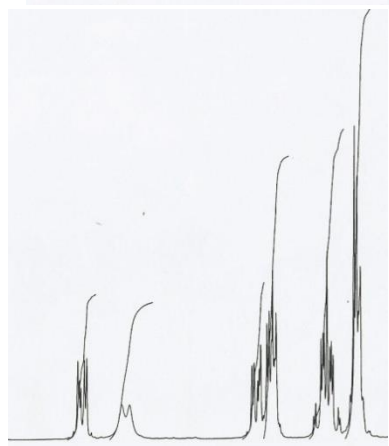
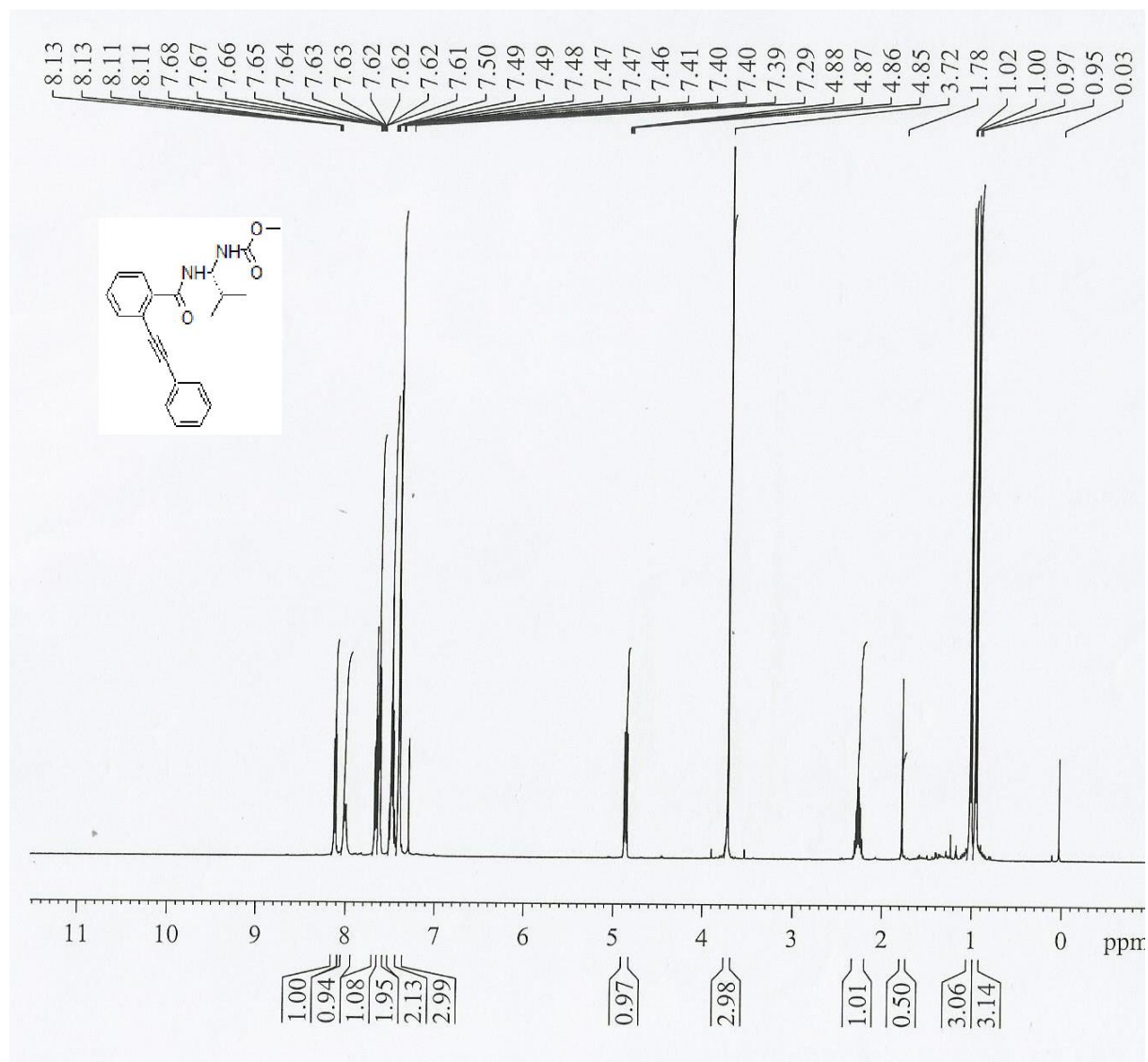


Fig 5.31 C^{13} NMR methyl [(1R)-2-methyl-1-([2-(phenylethynyl)phenyl]carbonyl)amino]propyl]carbamate

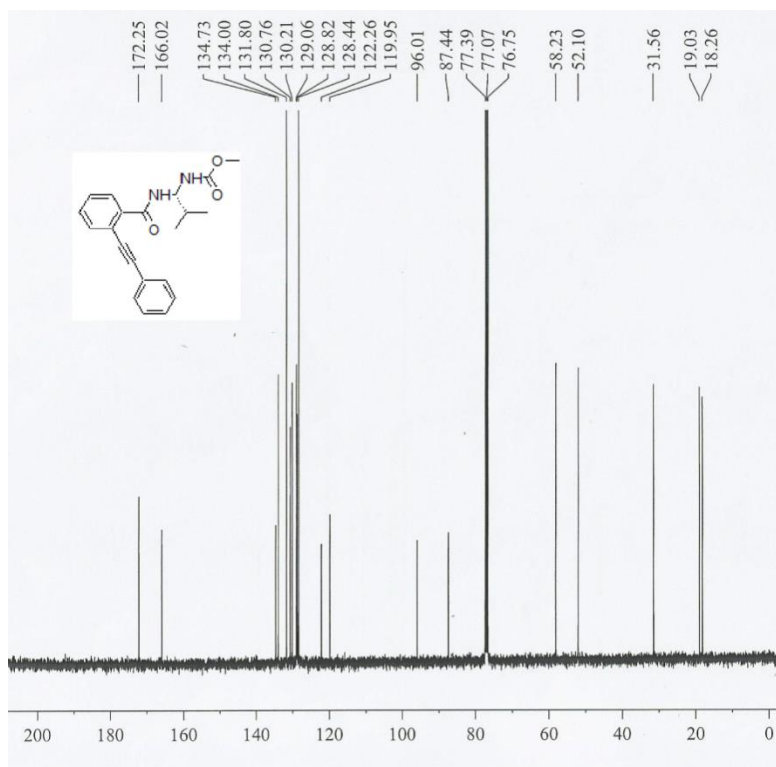


Fig 5.32 C^{13} Dept. methyl [(1R)-2-methyl-1-([2-(phenylethynyl)phenyl]carbonyl)amino]propyl]carbamate

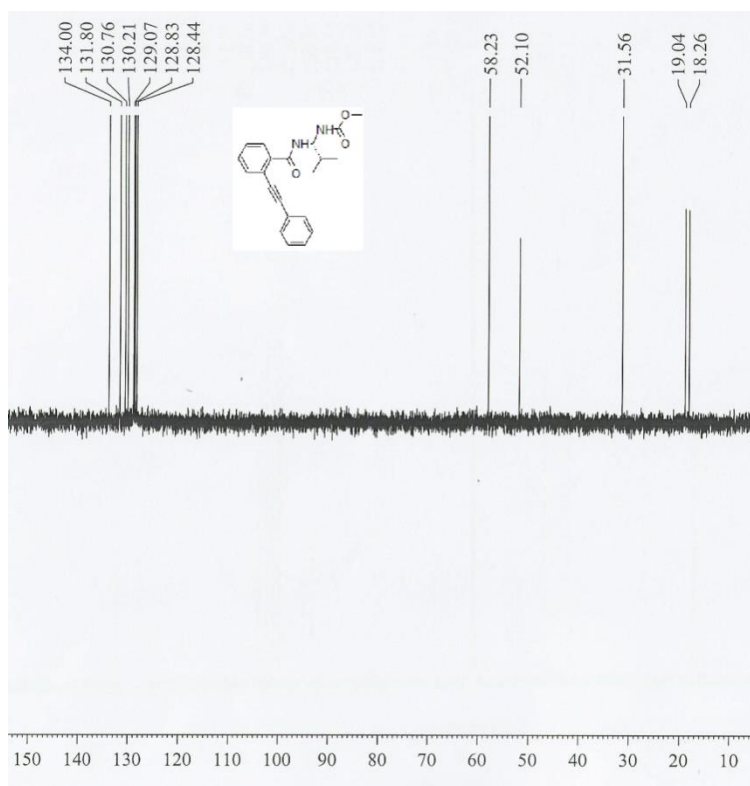


Fig 5.33 ^1H NMR Spectra methyl (2R)-2-[(1E)-1-benzylidene-3-oxo-1,3-dihydro-2H-isoindol-2-yl]-3-methylbutanoate

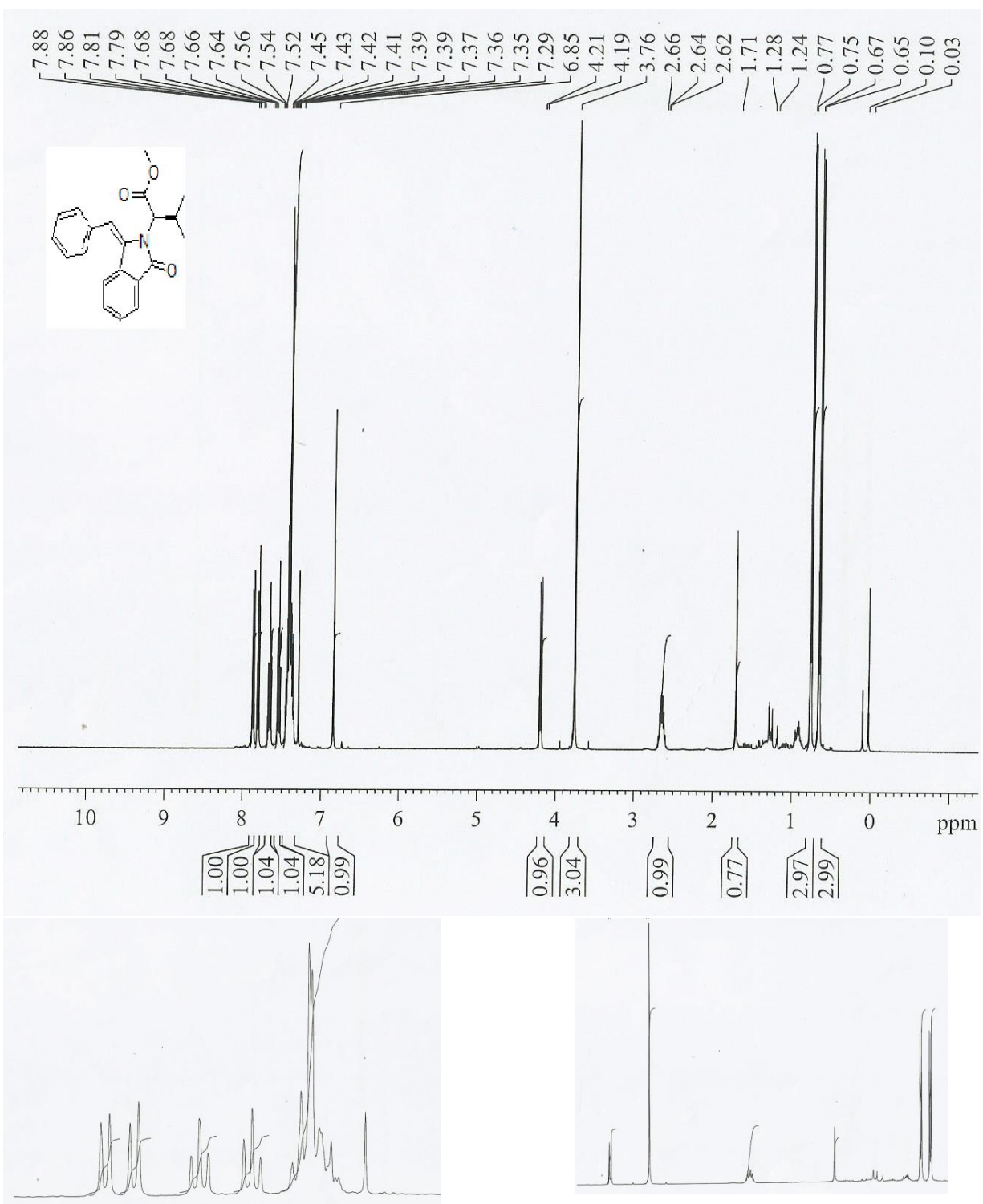


Fig 5.34 ^1H NMR Spectra methyl (2R)-2-(1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl)-3-methylbutanoate (Recimic)

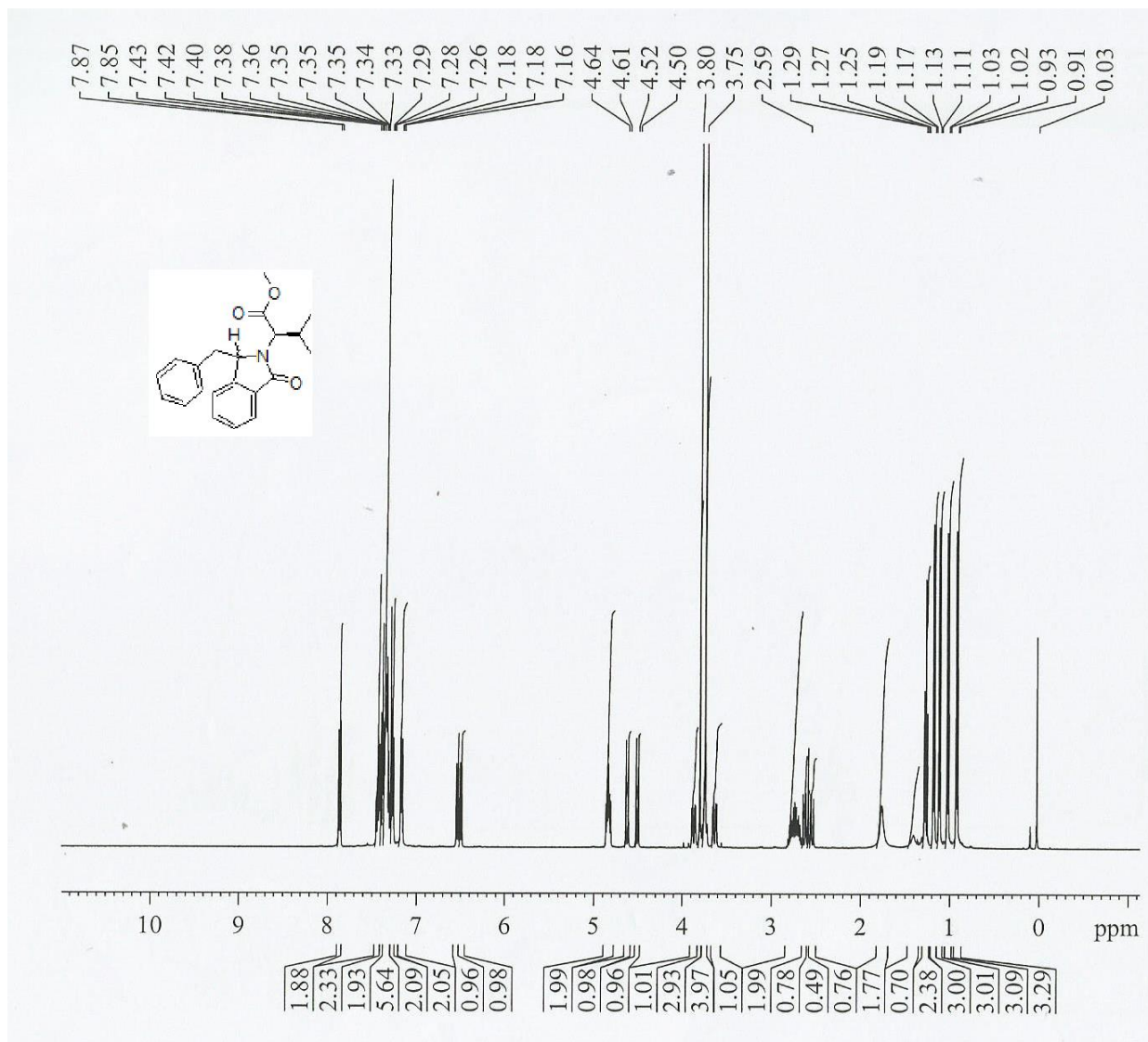


Fig 5.35 ^1H NMR expansion Spectra methyl (2R)-2-(1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl)-3-methylbutanoate

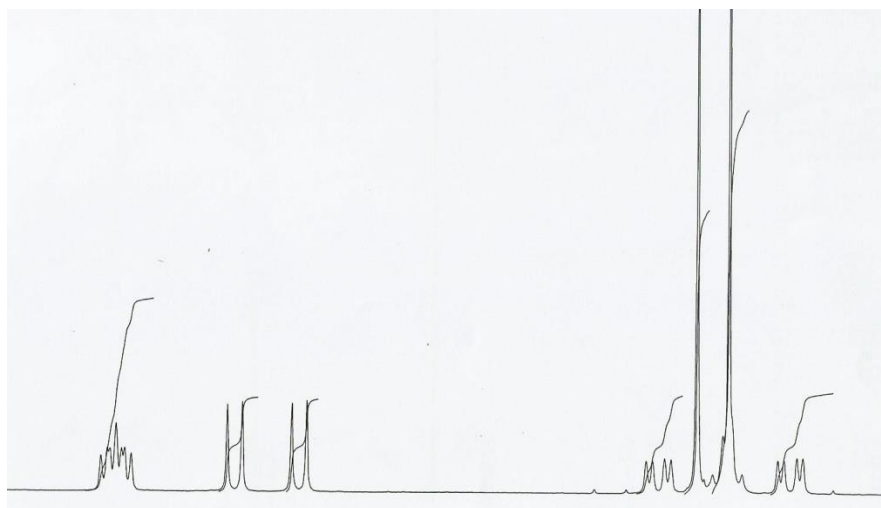
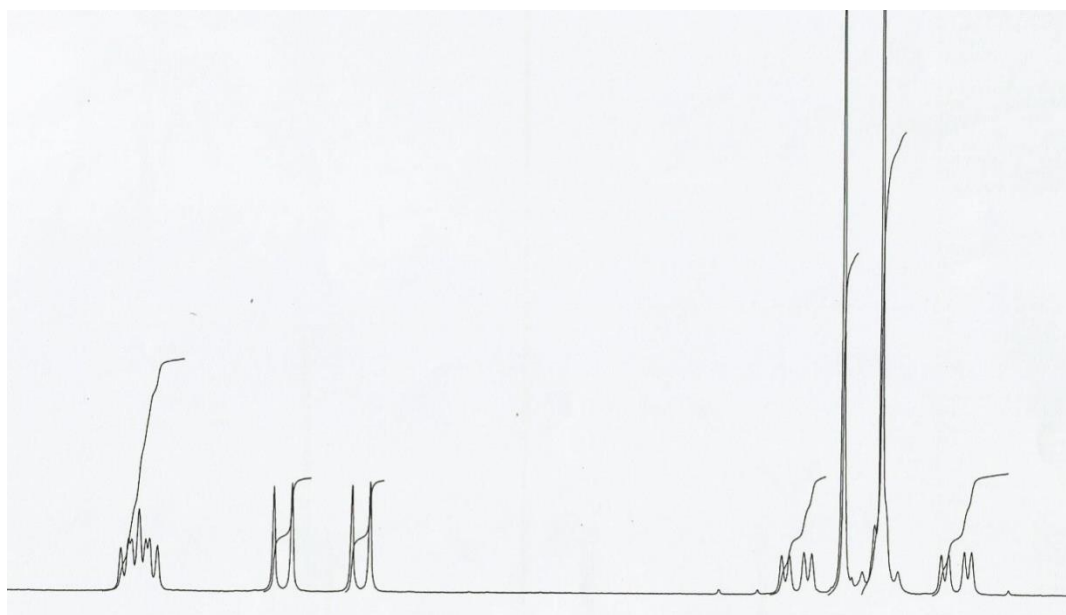
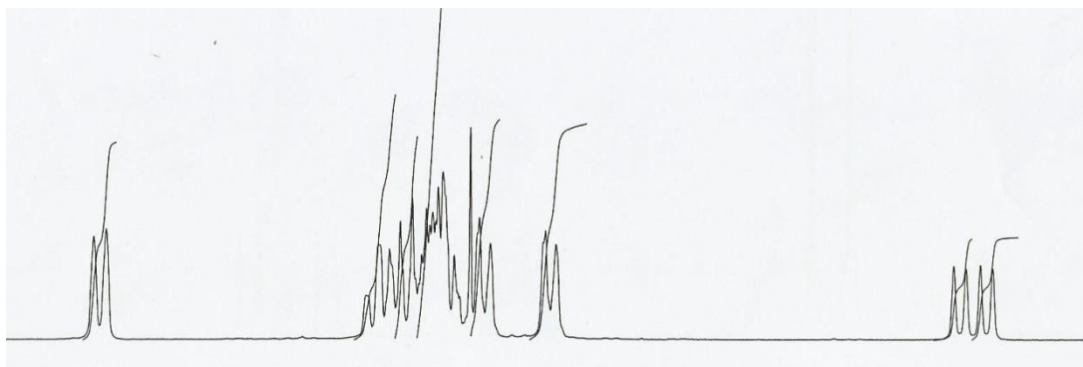


Fig 5.36 C^{13} NMR Spectra methyl (2R)-2-(1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl)-3-methylbutanoate

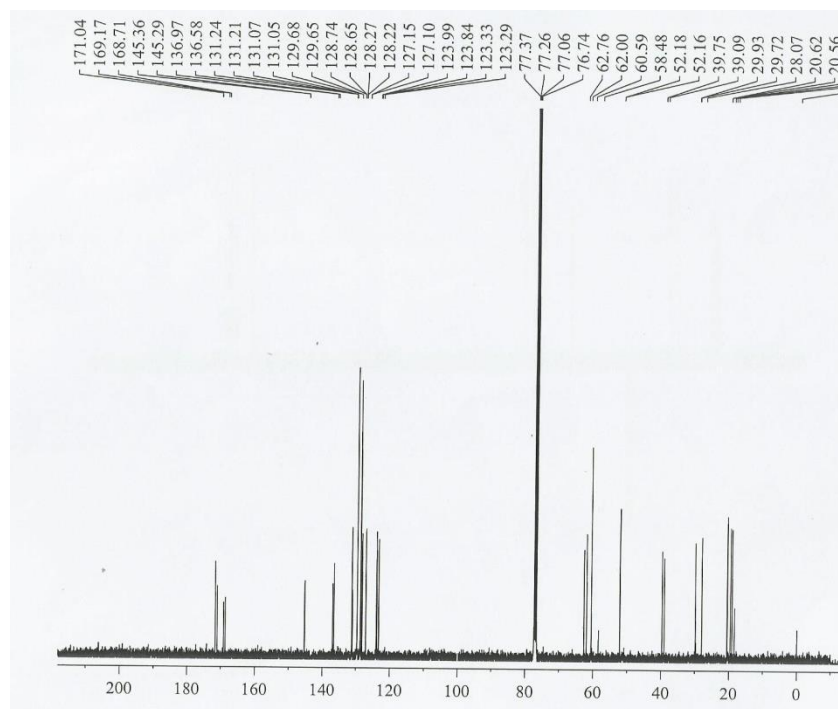


Fig 5.37 C^{13} Dept. Spectra methyl (2R)-2-(1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl)-3-methylbutanoate

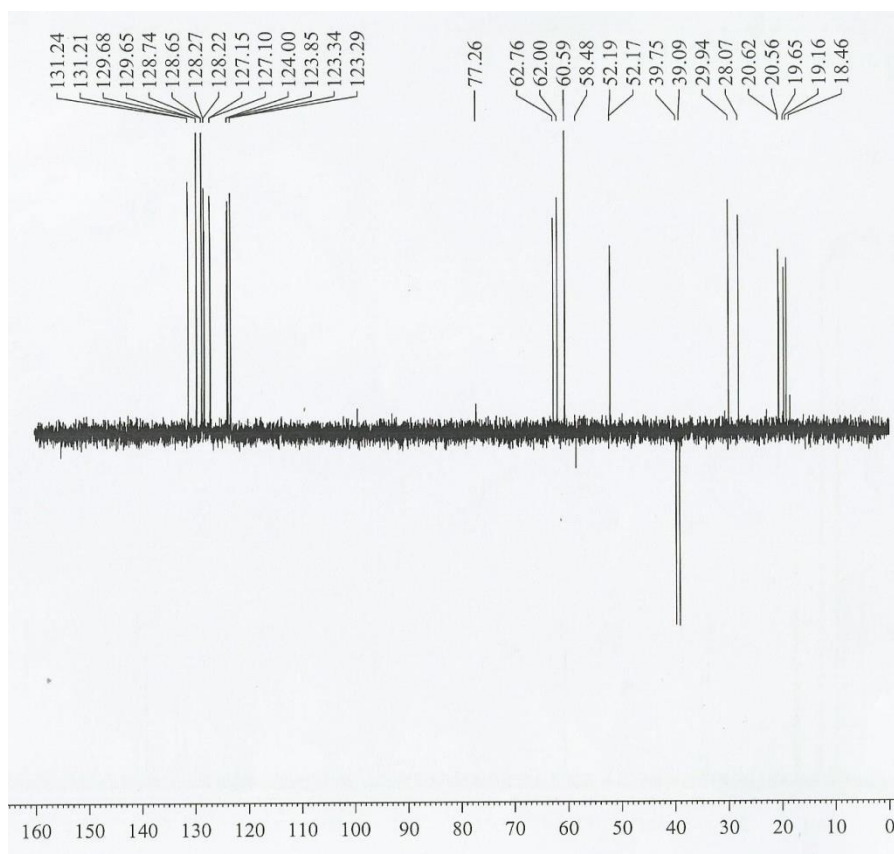


Fig 5.38 ^1H NMR Spectra methyl (2R)-2-[(1R)-1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl]-3-methylbutanoate

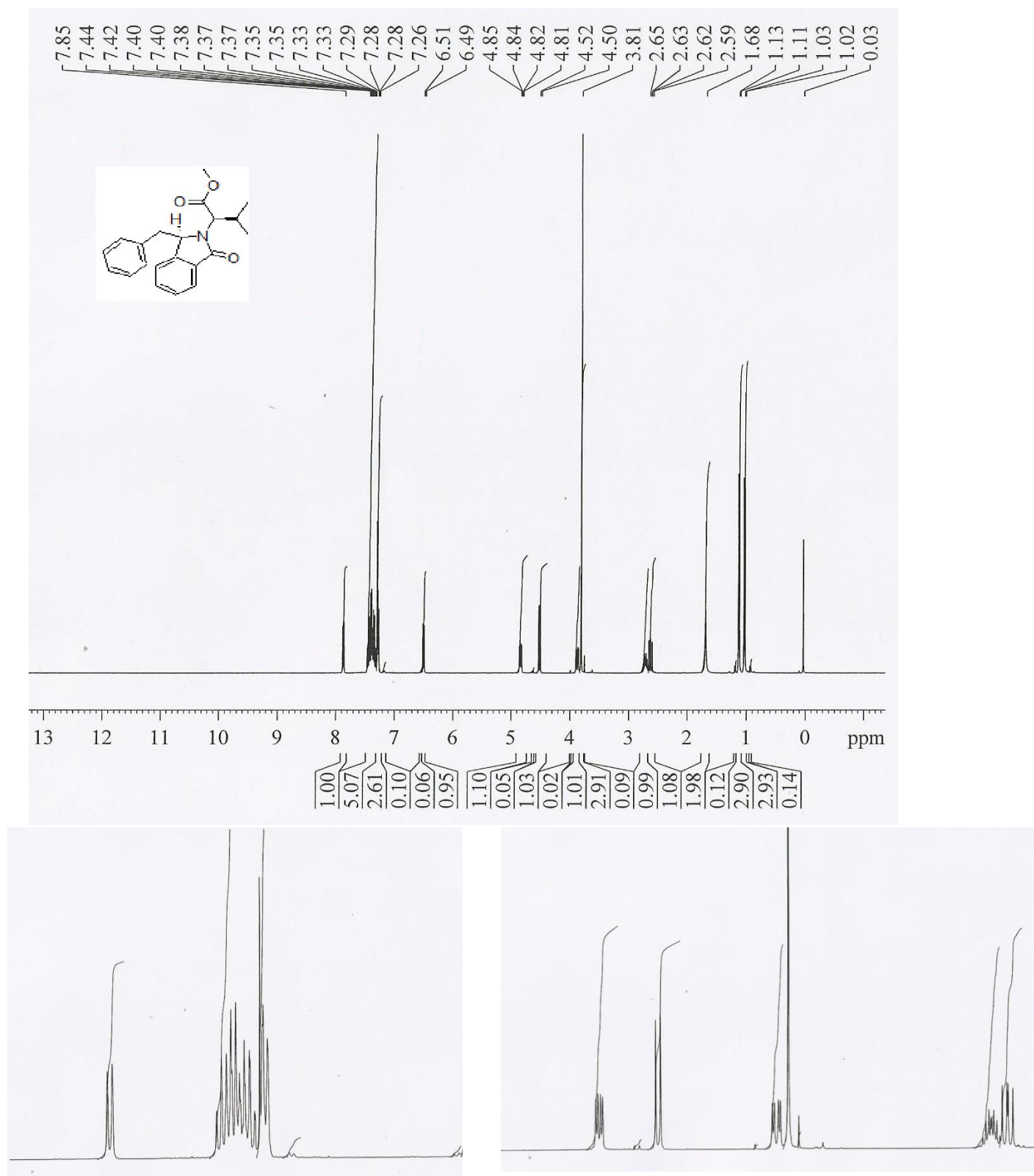


Fig 5.39 C^{13} NMR Spectra methyl (2R)-2-[(1R)-1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl]-3-methylbutanoate

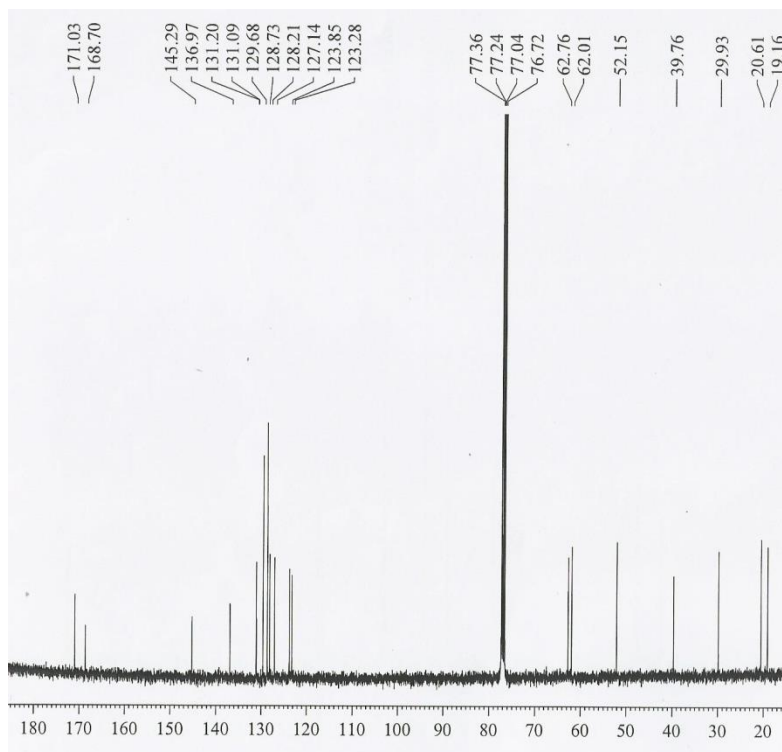


Fig 5.40 C^{13} Dept. Spectra methyl (2R)-2-[(1R)-1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl]-3-methylbutanoate

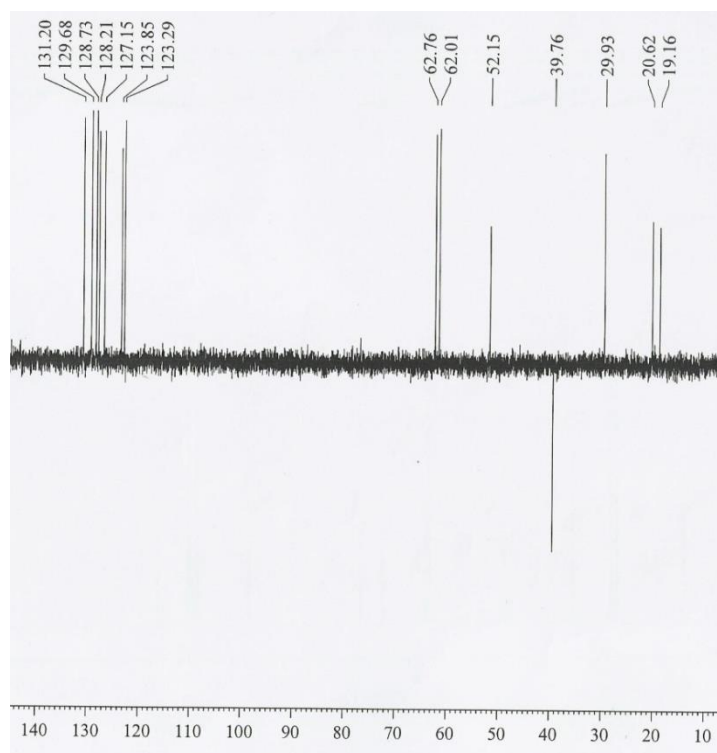
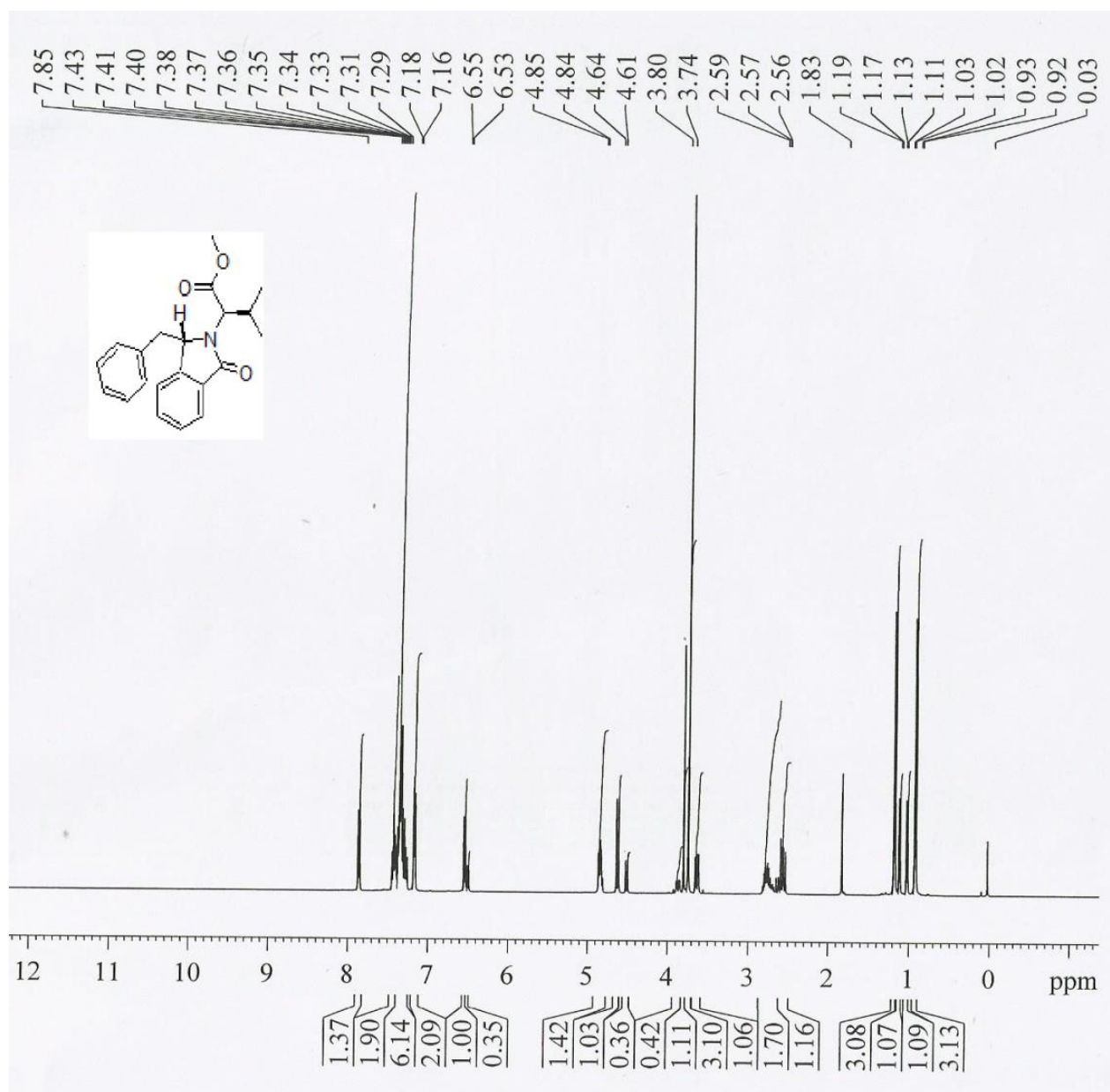
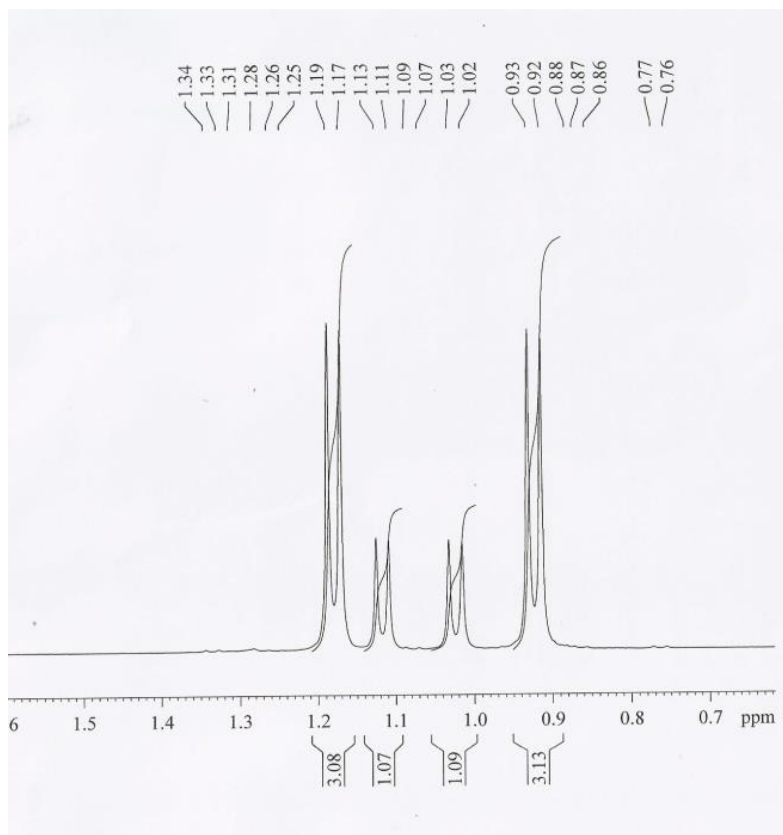
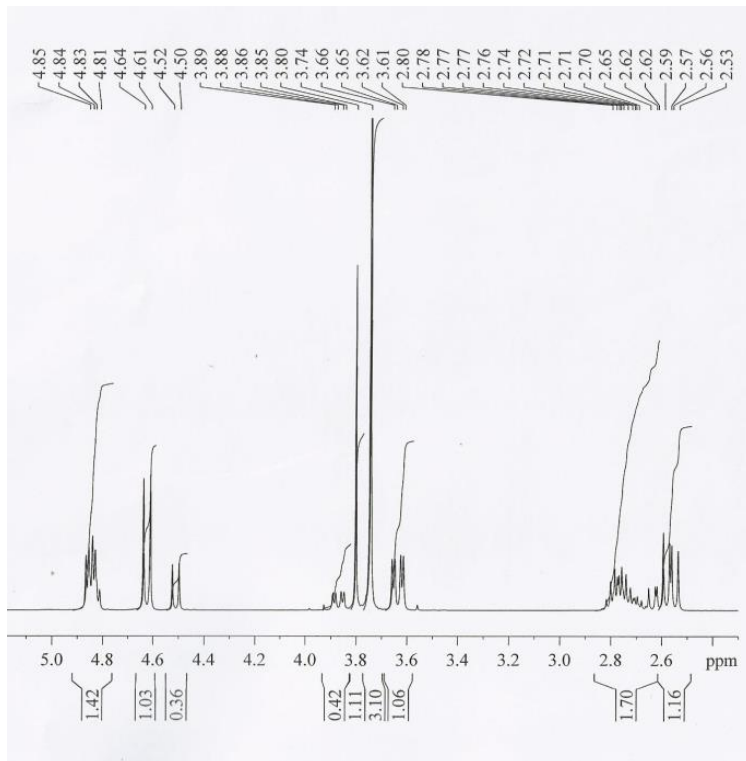
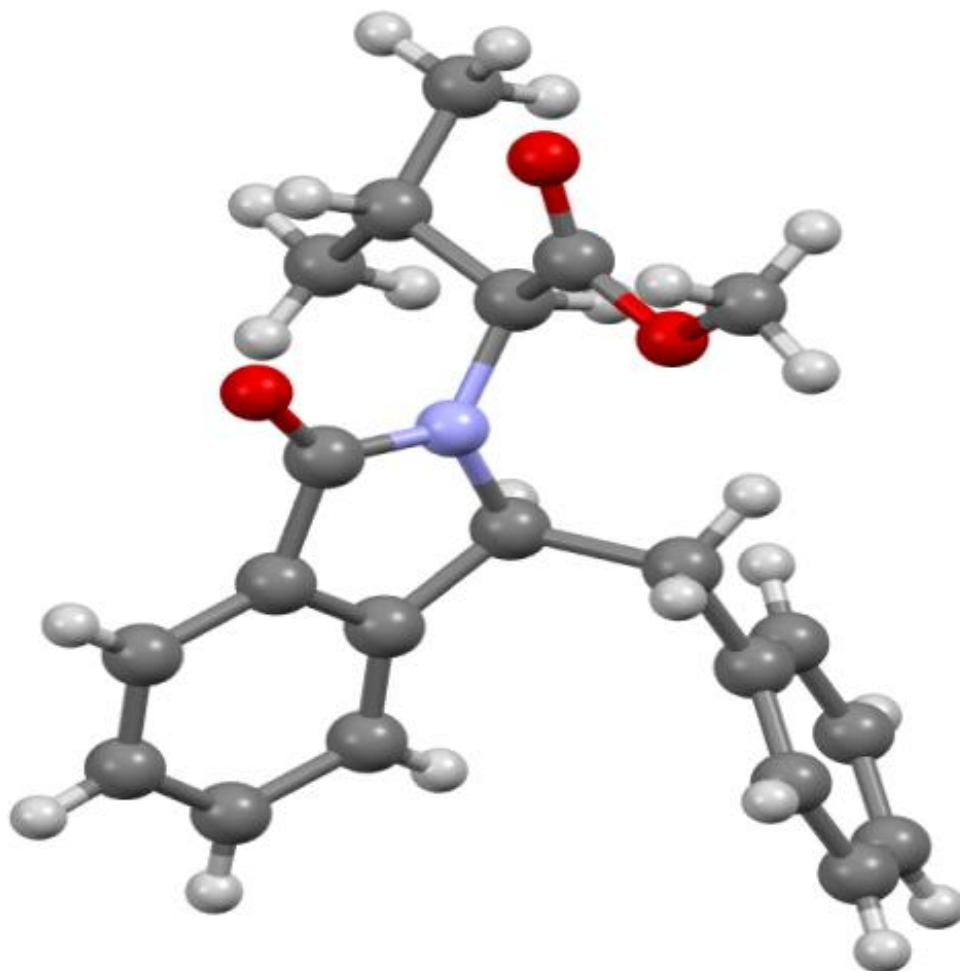


Fig 5.41 ^1H NMR methyl (2R)-2-[(1S)-1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl]-3-methylbutanoate





Crystal Structure: methyl (2R)-2-[(1R)-1-benzyl-3-oxo-1,3-dihydro-2H-isoindol-2-yl]-3-methylbutanoate



A suitable single crystal was collected through the polarizing microscope and mounted on the Bruker D8 Venture diffractometer system is equipped with micro focus Cu source, Photon 100 CMOS detector.

Crystal is kept at 298K (2) during the data collection with scan width of 0.5mm and distance 40mm from crystal to detector.

The structure was solved using the Olex2 with the XT, using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimization.

Crystal Data:

Table 1 Crystal data and structure refinement.

Identification code	DN_VAN_Ph
Empirical formula	$C_{21}H_{11}N_1O_3$
Formula weight	168.70
Temperature/K	298(2)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	7.2422(4)
b/Å	11.4558(7)
c/Å	11.2829(6)
$\alpha/^\circ$	90
$\beta/^\circ$	98.064(4)
$\gamma/^\circ$	90
Volume/Å ³	926.83(9)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.209
μ/mm^{-1}	0.645
F(000)	360.0
Crystal size/mm ³	0.1 × 0.08 × 0.06
Radiation	CuK α ($\lambda = 1.54178$)
2 Θ range for data collection/ $^\circ$	7.914 to 133.002
Index ranges	-8 ≤ h ≤ 8, -13 ≤ k ≤ 13, -12 ≤ l ≤ 13
Reflections collected	8688
Independent reflections	3196 [R _{int} = 0.0683, R _{sigma} = 0.0754]
Data/restraints/parameters	3196/1/230
Goodness-of-fit on F ²	1.042
Final R indexes [I ≥ 2 σ (I)]	R ₁ = 0.0800, wR ₂ = 0.1737
Final R indexes [all data]	R ₁ = 0.1547, wR ₂ = 0.2133
Largest diff. peak/hole / e Å ⁻³	0.23/-0.17
Flack parameter	0.0(3)

Table 2 Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for DN_VAN_Ph. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	U(eq)
C6	1323 (11)	4164 (8)	2323 (6)	63 (2)
C5	-20 (13)	4748 (9)	1563 (8)	88 (3)
C20	4840 (20)	5466 (15)	6566 (10)	152 (7)
C12	4579 (13)	5696 (9)	1220 (7)	83 (3)
N1	5387 (11)	5415 (9)	4485 (6)	109 (3)

O1	6935 (12)	7074 (9)	5126 (8)	160 (4)
C1	1674 (11)	3017 (8)	2066 (7)	72 (2)
C8	4483 (11)	4871 (9)	3364 (6)	81 (3)
C2	739 (13)	2478 (9)	1073 (8)	85 (3)
C7	2358 (12)	4748 (10)	3410 (7)	86 (3)
C14	6219 (15)	7562 (12)	1203 (12)	114 (4)
C9	6178 (17)	6405 (13)	4329 (9)	125 (5)
C11	4956 (11)	5735 (8)	2449 (7)	77 (3)
C13	5248 (15)	6657 (11)	591 (9)	99 (3)
C4	-972 (14)	4190 (13)	566 (8)	104 (3)
C10	5948 (15)	6633 (10)	3030 (9)	97 (3)
C15	6598 (15)	7587 (11)	2410 (11)	110 (4)
C16	5686 (13)	4775 (13)	5631 (7)	126 (5)
C3	-591 (14)	3059 (11)	336 (8)	96 (3)
C17	7750 (15)	4450 (20)	6013 (9)	185 (9)
O2	5635 (17)	5622 (12)	7581 (7)	215 (7)
C19	8528 (17)	3900 (30)	4966 (12)	259 (15)
C18	8014 (17)	3630 (20)	7041 (12)	220 (11)
C21	2160 (20)	6327 (16)	7079 (12)	202 (9)
O3	3138 (16)	5749 (11)	6212 (8)	177 (5)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for DN_VAN_Ph. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C6	67 (5)	69 (6)	51 (4)	0 (4)	2 (4)	-4 (5)
C5	98 (7)	71 (6)	98 (7)	12 (5)	21 (6)	14 (6)
C20	164 (12)	230 (16)	72 (7)	-63 (8)	46 (8)	-141 (13)
C12	84 (6)	99 (7)	69 (5)	-11 (5)	22 (4)	-2 (6)
N1	103 (6)	167 (9)	61 (5)	-39 (5)	26 (4)	-80 (6)
O1	151 (7)	219 (10)	122 (6)	-95 (6)	58 (5)	-116 (7)
C1	72 (5)	68 (6)	70 (5)	11 (4)	-7 (4)	-8 (5)
C8	74 (5)	117 (8)	51 (4)	-25 (5)	8 (4)	-38 (5)
C2	85 (6)	90 (7)	75 (6)	-24 (5)	-6 (5)	-15 (6)
C7	81 (6)	111 (8)	71 (5)	-15 (5)	22 (4)	-36 (6)
C14	101 (9)	113 (10)	138 (11)	4 (9)	54 (8)	-6 (7)
C9	105 (8)	192 (13)	90 (7)	-75 (8)	52 (6)	-77 (9)
C11	70 (6)	101 (7)	65 (5)	-26 (5)	22 (4)	-13 (5)
C13	93 (7)	128 (10)	79 (6)	11 (6)	24 (6)	14 (7)
C4	81 (7)	150 (11)	73 (6)	16 (7)	-16 (5)	16 (8)
C10	96 (7)	110 (8)	96 (7)	-38 (6)	54 (6)	-40 (7)

C15	100 (8)	111 (9)	131 (10)	-30 (7)	58 (7)	-25 (7)
C16	96 (7)	233 (15)	52 (5)	-31 (7)	20 (5)	-83 (9)
C3	84 (7)	126 (10)	73 (6)	-28 (6)	-2 (5)	-17 (7)
C17	74 (7)	410 (30)	69 (6)	4 (12)	3 (5)	-71 (11)
O2	252 (12)	321 (15)	78 (5)	-74 (7)	45 (6)	-188 (12)
C19	82 (8)	580 (50)	113 (10)	37 (18)	20 (7)	48 (16)
C18	101 (9)	450 (30)	103 (9)	60 (15)	-8 (7)	-33 (16)
C21	224 (18)	249 (19)	160 (12)	-125 (14)	121 (12)	-107 (15)
O3	158 (9)	267 (13)	119 (7)	-114 (8)	69 (7)	-96 (9)

Table 4 Bond Lengths for DN_VAN_Ph.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C6	C5	1.376 (11)	C8	C7	1.554 (11)
C6	C1	1.377 (11)	C8	C11	1.504 (12)
C6	C7	1.502 (10)	C2	C3	1.356 (13)
C5	C4	1.389 (13)	C14	C13	1.383 (15)
C20	C16	1.516 (17)	C14	C15	1.352 (14)
C20	O2	1.220 (12)	C9	C10	1.475 (14)
C20	O3	1.283 (19)	C11	C10	1.368 (12)
C12	C11	1.376 (10)	C4	C3	1.358 (15)
C12	C13	1.430 (14)	C10	C15	1.413 (15)
N1	C8	1.479 (10)	C16	C17	1.541 (16)
N1	C9	1.294 (15)	C17	C19	1.52 (2)
N1	C16	1.475 (13)	C17	C18	1.49 (2)
O1	C9	1.248 (12)	C21	O3	1.446 (15)
C1	C2	1.372 (10)			

Table 5 Bond Angles for DN_VAN_Ph.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C5	C6	C1	117.9 (8)	O1	C9	N1	126.7 (11)
C5	C6	C7	121.4 (9)	O1	C9	C10	125.7 (12)
C1	C6	C7	120.7 (8)	C12	C11	C8	129.7 (8)
C6	C5	C4	120.5 (9)	C10	C11	C12	121.6 (9)
O2	C20	C16	123.1 (17)	C10	C11	C8	108.7 (7)
O2	C20	O3	124.1 (14)	C14	C13	C12	120.9 (10)
O3	C20	C16	112.3 (9)	C3	C4	C5	120.2 (10)
C11	C12	C13	116.2 (9)	C11	C10	C9	108.8 (9)
C9	N1	C8	113.8 (9)	C11	C10	C15	122.2 (10)

C9	N1	C16	122.8 (9)	C15	C10	C9	129.0 (10)
C16	N1	C8	122.2 (9)	C14	C15	C10	116.6 (11)
C2	C1	C6	121.1 (9)	C20	C16	C17	113.6 (10)
N1	C8	C7	109.3 (6)	N1	C16	C20	109.0 (12)
N1	C8	C11	101.2 (7)	N1	C16	C17	112.4 (8)
C11	C8	C7	113.8 (8)	C2	C3	C4	119.8 (10)
C3	C2	C1	120.5 (10)	C19	C17	C16	109.5 (8)
C6	C7	C8	113.4 (7)	C18	C17	C16	112.5 (10)
C15	C14	C13	122.4 (11)	C18	C17	C19	108.8 (18)
N1	C9	C10	107.5 (9)	C20	O3	C21	116.5 (11)

Table 6 Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for DN_VAN_Ph.

Atom	x	Y	z	U(eq)
H5	-293	5522	1718	106
H12	3925	5080	821	100
H1	2561	2601	2574	86
H8	5041	4108	3243	97
H2	1019	1709	905	102
H7A	2176	4301	4114	104
H7B	1833	5518	3490	104
H14	6626	8177	768	137
H13	5026	6672	-241	119
H4	-1873	4593	55	124
H15	7253	8200	2813	132
H16	4989	4041	5510	151
H3	-1240	2684	-326	115
H17	8451	5169	6243	222
H19A	7751	3259	4664	388
H19B	9770	3626	5227	388
H19C	8555	4472	4345	388
H18A	7571	3981	7720	330
H18B	9314	3445	7239	330
H18C	7326	2924	6829	330
H21A	937	6549	6705	303
H21B	2838	7010	7376	303
H21C	2051	5804	7731	303

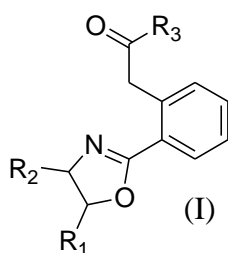
6.1 CONCLUSION.

1. We have reported a mild and efficient method for copper-catalyzed I-substitution of alkyl-2-iodobenzoates with alkynes under solvent free conditions (Sonogashira coupling reactions). The reactions were performed smoothly to generate the desired products (**A-J**) in moderate to excellent yields (**84-97%**). This method offers one of the important motifs for the synthesis of Sonogashira coupled products. Furthermore,
2. **A-J** compounds were soluble in ethyl acetate and dichloromethane. The docking affinities varied from 3.3 to 4.6 kcal/mol, and the compounds formed 1-3 hydrogen bonds with the amino acid residues of aspulvinone dimethylallyltransferase enzyme. The reported compounds may be future anti-cizomatics, anti-fobic disorder and inhibition of aspulvinone dimethylallyltransferase properties to control Alzheimer's, Schizophrenia etc. diseases.
3. We have developed a concise and a convenient new strategy for the synthesis of novel 1-(4-bromobenzyl)-3-methyl-6-(piperidin-1-yl) pyrimidine-2,4(1H,3H)-dione and its derivatives high pure and high yields from 1-bromo-4-(bromomethyl) benzene. This method is highly efficient and convenient for the preparation of title compound and its derivatives. This process has highly economical, environmental friendly and easily scalable process. One pot synthesis has reduced usage of solvents, reagents and chemicals and also reduces the cycle time of reaction, so we can able to increase the productivity.
4. A new simplest industrially applicable, inexpensive, ecological process developed for preparation of $\text{CuI}(\text{PPh}_3)_3$ and explored its activity in Sonogashira Coupling reaction of aryl iodides with phenyl and hexyl acetylenes in solvent free condition. This reaction furnished disubstituted alkynes in good yield and tolerated many functional groups. Moreover, it is simple method involving green approach.
5. We have developed a simple palladium free, green protocol for the Sonogashira reaction. Due to higher cost of the palladium the synthesis of the product is not commercially compatible but due to use of copper catalyst the cost reduces to more than

10 times and become commercially compatible. Here we developed the green approach for coupling of Aryl halide and Alkynes.

6. We have developed a simple palladium free, solvent and base free, green protocol for the Sonogashira reaction. Due to higher cost of the palladium the synthesis of the product is not commercially compatible but due to use of copper catalyst the cost reduces to more than 10 times and become commercially compatible. Here we developed the green approach by avoiding base, solvent. Table-1 summarizes the results of this reaction with different catalyst Entry 5 For $\text{Cu}(\text{PPh}_3)_3$ gives good results, Table 2 gives yield of Different substituted Aryl halide and Alkynes Coupling.
7. We have developed the method for preparation of substituted alkynes using Di- μ -iodidobis[bis(diphenyl phosphanyl)-1,1'-binaphthyl]copper(I) Complex with good yield, with reasonable cost with respect to palladium and Ruthenium.
8. (Z)-5-((2-mercaptophenylimino)methyl)-2-methoxy phenol ligand prepared and characterized using $^1\text{H NMR}$, $^{13}\text{C NMR}$ and prepared its copper complex with CuBr . Using this complex palladium free protocol developed for preparation Substituted Alkynes avoiding Poisonous Pd Catalytic System with good yield. Reaction closes to the green approach.
9. Ligand and base free protocol developed for coupling of 2-iodobenzoate and Alkynes or Arenes in presence of copper nanoparticle. And compared there reactivity with normal copper powder. During this study we observe that Time required for reaction for 2 iodobenzoate with Octyne in presence of Copper nanoparticle and same reactant in same reaction condition in presence of normal copper powder is 12 to 4 time less. With increasing number of carbon atom in ester chain, the rate of reaction is decrease. Long chain 2-iodobenzoate prepared and successfully coupled with Alkynes and Arenes. Bromo, Triflet esters, boronate esters, diactyl esters are also coupled successfully with Alkynes or arenes by using this protocol.
10. We have developed palladium free reaction condition for coupling of aryl halides with alkynes or arynes using copper carbonate. In this reaction copper carbonate act as base as well as catalyst to promote the reaction and prepared internal alkynes with good yield using developed protocol.

11. In all we have developed six protocols for preparation of six different copper catalysts and explored catalytic activity of each catalyst for Sonogashira reaction. Prepared 20-30 examples (Compounds) and characterized each compound by NMR and CMR, and ^{13}C Dept. experiment for each catalyst using developed protocol.
12. Developed process for preparation of keto oxazoline compounds of formula (I).



where oxazoline moieties and ketonic moieties are attached to carbon atom adjacent to each other, keto group is at β position from the benzene ring, R₁ and R₂ are independently hydrogen, optionally alkyl, aryl or optionally substituted poly aryl, optionally substituted lower alkyl, or R₁, R₂ combined together with carbon atom through which they are attached, from an optionally substituted 6-membered fused aromatic, aliphatic or 5-membered aromatic or aliphatic ring provided that R₁ and R₂ are attached to carbon atom adjacent to each other; R₃ is Alkyl, Aryl, substituted alkyl or aryl, Chloro alkyl or Chloro aryl; or an enantiomeric mixture thereof ; Comprising the step containing an alkyne acylamino alcohol using copper reagent, the present invention efficiently converts the alkyne acylamino alcoholic compound in to highly chemo selective Keto oxazoline compounds with remarkable verity of substrate , mild reaction condition with higher conversion.

13. We have developed process for preparation of isoindolinone with less hazardous and easily available raw materials with higher yield than reported in different literatures. Successfully explored the activity of copper metal powder for Sonogashira coupling and ring closer one pot synthesis to form E Isoindol derivative selectively. Developed method of preparation of chiral isoindlin with ee 70-95%.
14. We have developed the method for preparation of substituted isocumarin using copper powder, iodobenzoic acid and alkyne with good yield, with reasonable cost with respect to palladium and Ruthenium catalyst.

15. While doing reaction with nitro halo compounds and terminal alkyne the internal alkene formation observed instead of internal alkyne. Further we studied effect of electron withdrawing and donating group on the reaction and we observed that the alkene formation favors when terminal alkyne used is aromatic or iodo compound contains electron withdrawing group like carboxylate attached at ortho position to Iodine group.
16. We have developed method for preparation of substituted isocoumarin using copper powder, 2 Iodo arylbenzoate and alkyne with good yield, with reasonable cost with respect to palladium and Ruthenium catalyst.
17. We have developed the method for preparation of 2-Vinylphenol using copper powder, 2 bromophenol and Terminal alkynes as simple starting materials with good yield.

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**COUPLING OF HALOARENES WITH TERMINAL ALKYNES BY USING
COPPER, IT'S COMPLEXES THEIR SYNTHESIS AND ITS
APPLICATION IN SYNTHETIC ORGANIC CHEMISTRY**

**A
THESIS
SUBMITTED TO**



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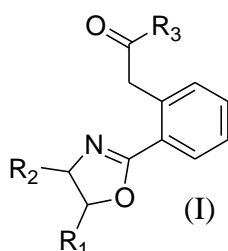
6.1 CONCLUSION.

1. We have reported a mild and efficient method for copper-catalyzed I-substitution of alkyl-2-iodobenzoates with alkynes under solvent free conditions (Sonogashira coupling reactions). The reactions were performed smoothly to generate the desired products (**A-J**) in moderate to excellent yields (**84-97%**). This method offers one of the important motifs for the synthesis of Sonogashira coupled products. Furthermore,
2. **A-J** compounds were soluble in ethyl acetate and dichloromethane. The docking affinities varied from 3.3 to 4.6 kcal/mol, and the compounds formed 1-3 hydrogen bonds with the amino acid residues of aspulvinone dimethylallyltransferase enzyme. The reported compounds may be future anti-cizomatics, anti-fobic disorder and inhibition of aspulvinone dimethylallyltransferase properties to control Alzheimer's, Schizophrenia etc. diseases.
3. We have developed a concise and a convenient new strategy for the synthesis of novel 1-(4-bromobenzyl)-3-methyl-6-(piperidin-1-yl) pyrimidine-2,4(1H,3H)-dione and its derivatives high pure and high yields from 1-bromo-4-(bromomethyl) benzene. This method is highly efficient and convenient for the preparation of title compound and its derivatives. This process has highly economical, environmental friendly and easily scalable process. One pot synthesis has reduced usage of solvents, reagents and chemicals and also reduces the cycle time of reaction, so we can able to increase the productivity.
4. A new simplest industrially applicable, inexpensive, ecological process developed for preparation of $\text{CuI}(\text{PPh}_3)_3$ and explored its activity in Sonogashira Coupling reaction of aryl iodides with phenyl and hexyl acetylenes in solvent free condition. This reaction furnished disubstituted alkynes in good yield and tolerated many functional groups. Moreover, it is simple method involving green approach.
5. We have developed a simple palladium free, green protocol for the Sonogashira reaction. Due to higher cost of the palladium the synthesis of the product is not commercially compatible but due to use of copper catalyst the cost reduces to more than

10 times and become commercially compatible. Here we developed the green approach for coupling of Aryl halide and Alkynes.

6. We have developed a simple palladium free, solvent and base free, green protocol for the Sonogashira reaction. Due to higher cost of the palladium the synthesis of the product is not commercially compatible but due to use of copper catalyst the cost reduces to more than 10 times and become commercially compatible. Here we developed the green approach by avoiding base, solvent. Table-1 summarizes the results of this reaction with different catalyst Entry 5 For $\text{Cu}(\text{PPh}_3)_3$ gives good results, Table 2 gives yield of Different substituted Aryl halide and Alkynes Coupling.
7. We have developed the method for preparation of substituted alkynes using Di- μ -iodidobis[bis(diphenyl phosphanyl)-1,1'-binaphthyl]copper(I) Complex with good yield, with reasonable cost with respect to palladium and Ruthenium.
8. (Z)-5-((2-mercaptophenylimino)methyl)-2-methoxy phenol ligand prepared and characterized using $^1\text{H NMR}$, $^{13}\text{C NMR}$ and prepared its copper complex with CuBr . Using this complex palladium free protocol developed for preparation Substituted Alkynes avoiding Poisonous Pd Catalytic System with good yield. Reaction closes to the green approach.
9. Ligand and base free protocol developed for coupling of 2-iodobenzoate and Alkynes or Arenes in presence of copper nanoparticle. And compared there reactivity with normal copper powder. During this study we observe that Time required for reaction for 2 iodobenzoate with Octyne in presence of Copper nanoparticle and same reactant in same reaction condition in presence of normal copper powder is 12 to 4 time less. With increasing number of carbon atom in ester chain, the rate of reaction is decrease. Long chain 2-iodobenzoate prepared and successfully coupled with Alkynes and Arenes. Bromo, Triflet esters, boronate esters, diacyl esters are also coupled successfully with Alkynes or arenes by using this protocol.
10. We have developed palladium free reaction condition for coupling of aryl halides with alkynes or arynes using copper carbonate. In this reaction copper carbonate act as base as well as catalyst to promote the reaction and prepared internal alkynes with good yield using developed protocol.

11. In all we have developed six protocols for preparation of six different copper catalysts and explored catalytic activity of each catalyst for Sonogashira reaction. Prepared 20-30 examples (Compounds) and characterized each compound by NMR and CMR, and ¹³C Dept. experiment for each catalyst using developed protocol.
12. Developed process for preparation of keto oxazoline compounds of formula (I).



where oxazoline moieties and ketonic moieties are attached to carbon atom adjacent to each other, keto group is at β position from the benzene ring, R₁ and R₂ are independently hydrogen, optionally alkyl, aryl or optionally substituted poly aryl, optionally substituted lower alkyl, or R₁, R₂ combined together with carbon atom through which they are attached, from an optionally substituted 6-membered fused aromatic, aliphatic or 5-membered aromatic or aliphatic ring provided that R₁ and R₂ are attached to carbon atom adjacent to each other; R₃ is Alkyl, Aryl, substituted alkyl or aryl, Chloro alkyl or Chloro aryl; or an enantiomeric mixture thereof ; Comprising the step containing an alkyne acylamino alcohol using copper reagent, the present invention efficiently converts the alkyne acylamino alcoholic compound in to highly chemo selective Keto oxazoline compounds with remarkable verity of substrate , mild reaction condition with higher conversion.

13. We have developed process for preparation of isoindolinone with less hazardous and easily available raw materials with higher yield than reported in different literatures. Successfully explored the activity of copper metal powder for Sonogashira coupling and ring closer one pot synthesis to form E Isoindol derivative selectively. Developed method of preparation of chiral isoindlin with ee 70-95%.
14. We have developed the method for preparation of substituted isocoumarin using copper powder, iodobenzoic acid and alkyne with good yield, with reasonable cost with respect to palladium and Ruthenium catalyst.

15. While doing reaction with nitro halo compounds and terminal alkyne the internal alkene formation observed instead of internal alkyne. Further we studied effect of electron withdrawing and donating group on the reaction and we observed that the alkene formation favors when terminal alkyne used is aromatic or iodo compound contains electron withdrawing group like carboxylate attached at ortho position to Iodine group.
16. We have developed method for preparation of substituted isocoumarin using copper powder, 2 Iodo arylbenzoate and alkyne with good yield, with reasonable cost with respect to palladium and Ruthenium catalyst.
17. We have developed the method for preparation of 2-Vinylphenol using copper powder, 2 bromophenol and Terminal alkynes as simple starting materials with good yield.

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