# Synthetic studies towards Quinagolide, 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one and continuous flow synthesis of Miltefosine

by

**Patil Niteen Baswaraj**
**10CC17J26004**

A thesis submitted to the
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in
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Under the supervision of

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# Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, *"Synthetic studies towards Quinagolide, 3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one and continuous flow synthesis of Miltefosine",* submitted by *Mr. Patil Niteen Baswaraj* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged

Mr. Patil Niteen Baswaraj

Research Student

26/07/2021

Dr. Subhash Prataprao Chavan

Research Supervisor

26/07/2021

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I Mr. Patil Niteen Baswaraj, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC17J26004 hereby undertake that, the thesis entitled "Synthetic studies towards Quinagolide, 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one and continuous flow synthesis of Miltefosine" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)"*.

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Date : 26/07/2021
Place : Pune

*This dissertation is dedicated to all those people who have always given me the love, trust, and support to come to this stage of my life*

*To my beloved parents and teachers*

z

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*prayers, constant struggle and relentless hard work to overcome the odds of life, which has inspired me to pursue life with greater optimism. The warmth and moral value of my parents have stood me in good stead throughout my life and I would always look up to them for strength no matter what I have to go through. This Ph. D. thesis is a result of the extraordinary will, efforts and sacrifices of my parents. My all successes are dedicated to them now and always. I really grateful to our little champ Prathmesh, Abhishek, Punam, Yashshree, Prerana, Aniket, Prajot, Chaitanya, Arush, Pankaj, Adiv, Aaradhya who are full of happiness, joy and curiosity brought everlasting encouragement in my life.*

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*Niteen Baswaraj Patil*

***CSIR-NCL, Pune***

# Contents

## Chapter 3

## Continuous flow synthesis of miltefosine

# Abbreviations

## Units

| | |
|---|---|
| °C | Degree centigrade |
| Mg | Milligram |
| H | Hour |
| Hz | Hertz |
| µg | Microgram |
| mL | Millilitre |
| min | Minutes |
| MHz | Megahertz |
| Mmol | Millimole |
| Ppm | Parts per million |

## Chemical Notations

| | |
|---|---|
| Ac | Acetyl |
| AcOH | Acetic Acid |
| Ar | Aryl |
| $CH_3CN$ | Acetonitrile |
| n-BuLi | n-Butyl Lithium |
| $^tBuOH$ | tert-Butyl alcohol |
| MOMCl | Chloromethyl Methyl Ether |
| $CCl_4$ | Carbon tetrachloride |
| $CDCl_3$ | Deuterated Chloroform |
| $CD_3OD$ | Deuterated Methanol |
| DBAB | Dibenzyl azodicarboxylate |
| DMF | N, N'-Dimethylformamide |
| DMAP | N,N'-Dimethylaminopyridine |
| DIPEA | N, N-Diisopropylethylamine |
| $Et_2O$ | Diethyl Ether |
| $(DHQ)_2PHAL$ | 1,4-bis(Dihydroquinin-9-O-yl)phthalazine |

| | |
|---|---|
| $(DHQD)_2PHAL$ | 1,4-bis(Dihydroquinindin-9-O-yl)phthalazine ii |
| DIAD | Diisopropylazodicarboxylate |
| DCE | 1,2-Dichloroethane |
| DET | Diethyl Tartrate |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DBN | 1,5-Diazabicyclo[4.3.0]non-5-ene |
| DCC | N,N' -Dicyclohexylcarbodiimide |
| EtOH | Ethanol |
| Et | Ethyl |
| EtOAc | Ethyl Acetate |
| IBX | Iodoxybenzoic Acid |
| LAH | Lithium Aluminum Hydride |
| m-CPBAm- | Chloroperbenzoic Acid |
| MeOH | Methanol |
| Me | Methyl |
| MeI | Methyl Iodide |
| Ph | Phenyl |
| PMB | para-Methoxy Benzyl |
| p-TSA | para-Toluenesulfonic Acid |
| NaBH4 | Sodiumborohydride |
| NaH | Sodium Hydride |
| TBAI | Tetra-n-Butylammonium Iodide |
| TBAF | Tetra-n-Butylammonium Fluoride |
| TBDMS | tert-ButyldimethylSilyl |
| TBSCl | tert-ButyldimethylSilyl Chloride |
| TIPSOTf | TriisopropylsilylTrifluoromethanesulfonate |
| TEMPO | 2,2,6,6-Tetramethyl-1-piperidinyloxy |
| Ts | Toluenesulfonyl |
| TMS | Trimethylsilyl |

## Other Notations

| | |
|---|---|
| Calcd | Calculated |
| δ | Chemical shift |
| J | Coupling constant in NMR |
| RCM | Ring Clossing Metathesis |
| DEPT | DistortionlessEnhancement by Polarization Transfer |
| Dr | Diastereomeric excess |
| Ee | Enantiomeric excess |
| Equiv | Equivalents |
| ESI | Electrospray ionization Mass spectrometry |
| HPLC | High Pressure Liquid Chromatography |
| HMBC | Heteronuclear Multiple Bond Correlation |
| COSY | Homonuclear Correlation Spectroscopy |
| HRMS | High Resolution Mass Spectrometry |
| IR | Infra Red |
| m/z | Mass-to-charge ratio |
| M.S | Molecular sieves |
| Mp | Melting Point |
| NMR | Nuclear Magnetic Resonance |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| ORTEP | Oak Ridge Thermal Ellipsoid Plot |
| rt | Room temperature |

## *General remarks*

- Deuterated solvents for NMR spectroscopic analyses were used as received. All $^{1}H$ NMR and $^{13}C$ NMR and 2D NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz or 500 MHz spectrometers. Coupling constants were measured in Hertz. All hemical shifts are quoted in ppm, relative to TMS and $CHCl_3$ in $CDCl_3$, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [($ESI^{+}$+/- 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as m/z. GC-HRMS (EI) was recorded in Agilent 7200 Accurate-mass-Q-TOF.
- Infrared spectra were scanned on Bruker ALPHA spectrometers with sodium chloride optics and are measured in $cm^{-1}$
- Optical rotations were measured with a JASCO P-2000 digital polarimeter.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus and are uncorrected and the temperatures are in centigrade scale.
- All reactions are monitored by Thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde or KMnO4followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 15.1. v

- Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

| | |
|---|---|
| AcSIR | **Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for award of the Degree of Doctor of Philosophy in Chemistry** |
| **Name of the Candidate** | Patil Niteen Baswaraj |
| **Degree Enrollment No. &Date** | Ph. D. in Chemical Sciences (10CC17J26004); January 2017 |
| **Laboratory** | CSIR-National Chemical Laboratory, Pune |
| **Title of the Thesis** | "Synthetic studies towards Quinagolide, 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one and continuous flow synthesis of Miltefosine" |
| **Research Supervisor** | Dr. S. P. Chavan |

## 1) Introduction

Biologically active products and their synthetic derivatives have found the largest contribution to drug discoveries. In that context, challenging structural features and bioactivity of products attracted synthetic chemists for its economic and scalable synthesis through the development of synthetic methodologies. The thesis hereby presents a unique design and state-of-art strategies for the synthesis of D2 receptor agonist quinagolide in racemic fashion, along with the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one and continuous flow synthesis of Miltefosine. The work embodied in this thesis has been divided into three chapters as described below

## 2) Statement of problem and objectives:

The first line therapy for patients with hyperprolactinaemia is pharmacological intervention with a dopamine agonist, currently there are three dopamine agonist available for hyperprolactinaemia therapy: bromocriptine, quinagolide and cabergoline. Bromocriptine has a long history of use however, a range of 5-18% of patients are reported to show bromocriptine resistance, with only partial lowering of plasma prolactin levels and an absence of tumour shrinkage. The clinical use of quinagolide in comparison to other dopamine agonist for hyperprolactinaema therapy is discussed. Quinagolide may improve patient compliance to treatment owing to its reduced side effect profile, simple and rapid

titration over just 7 days, one's daily dosing regimen and easy to use starter pack (available insome countries). Quinagolide offers additional benefits for patients wishing to become pregnant, as it can be used until the point of confirmation of pregnancy. Therefore as a well-tolerated and effective therapy with a simple dosing regimen, quinagolide should be considered as a first line therapy in treatment of hyperprolactinaemia.

Among the sulfonylurea class of anti-diabetic drugs, glimepiride has many distinctive advantages and is by far the most superior blood glucose lowering agent. Its biological activity initiates with binding to the 65 KD protein of the putative receptor. In addition, glimepiride shows a three-fold faster rate of association and a nine-fold faster rate of dissociation than glibenclamide, which permitted its use as a once daily administration drug. Glimepiride prevents post excessive insulin release thereby decreasing the risk of hypoglycemia. Studies on the metabolism of therapeutically active compounds are increasingly being carried out because metabolites provide superior safety and efficacy profi-les, but more importantly offer opportunities to study the metabolic pathways. The metabolism of glimepiride has been observed in animals and humans *via* oxidative pathway

Miltefosine is an alkylated phosphocholine that has *in vitro* and *in vivo* activity against several bacteria, fungi and parasites including several Leishmania species. Miltefosine appears to act by affecting phospholipid membrane integrity and mitochondria function of the microorganism. Miltefosine has been shown to be effective in inducing cures of visceral (kala azar), mucosal and cutaneous leishmaniasis in a high proportion of patients. Miltefosine was approved for use in India in 2002 and in the United States in 2014 and was the first oral therapy of visceral and cutaneous leishmaniasis. It is available as capsules of 50 mg under the commercial name Impavido. The recommended dose is 50 mg twice (body weight 30 to 44 kg) or three times (45 kg or above) daily for 28 days. Miltefosine also has been reported to be effective in other serious bacterial, fungal and parasitic conditions such as amebiasis (primary amoebic meningoencephalitis), trypanosoma cruzii infection (Chagas disease), cryptococcosis and candidiasis, but is not formally approved for these conditions. Miltefosine is generally well tolerated, but side effects can include nausea, vomiting, diarrhea, abdominal discomfort, anorexia, pruritus, headache, dizziness and somnolence. Rare, but potentially severe adverse events include decrease in reproductive capacity, embryo-fetal toxicity, renal dysfunction and hypersensitivity reactions including Stevens

Johnson syndrome. While miltefosine is rarely used in the United States, it is an important medication from a worldwide perspective and has played an essential role in public health efforts to eradicate visceral and cutaneous leishmaniasis.

**3) Results:** Each chapter is summarized briefly.

## Chapter 1
## Attempts towards quinagolide

### Section 1: Introduction and Literature Review

Alkaloids synthesis has always been considered to be one of the more attractive targets and their synthetic derivatives, with their wide spectrum of pharmacodynamics activity,[1] have found use in the treatment of a variety of pathophysiological disturbances. During the last few years, following the successful use of such compounds for the treatment of hyperprolactinemia,[2] acromegaly, and parkinsonism, increasing efforts have been concentrated on the synthesis of new derivatives and partial structures with the aim of dissecting out a specifically dopaminomimetic pharmacophore. Octahydrobenzo[*g*]-quinolines, synthetic analogues of the ergot family structure, are potent dopamine agonists.

The responsible moiety for dopaminomimetic activity of the ergolines had initially been assumed to be a rigid arylethylamine, a phenyl ethylamine,[1] a tryptamine, (aminoethyl) indole **la- ld** (**fig 1**). These hypotheses led to the synthesis of a variety of partial structures, such as benz[*cd*] indolamines, octahydrobenzo[*f*]quinolines, 4 -piperidinyl- and 4-tetrahydropyridinylindoles, 4-(2-aminoethyl)indoles, and 9-oxaergolines. Some of these compounds were certainly potent dopamine agonists.

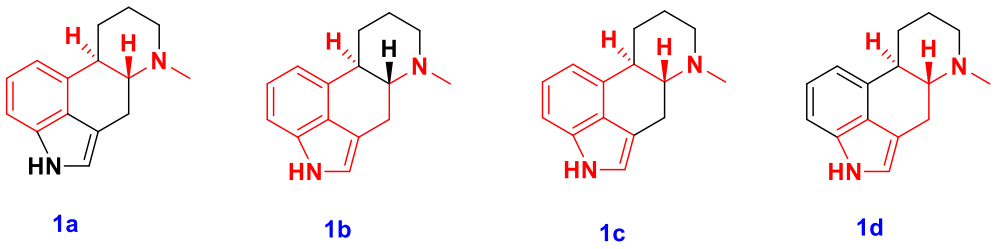



**Fig. 1** Moiety responsible for dopaminomietic activity of the ergolines

**Discovery of quinagolide**

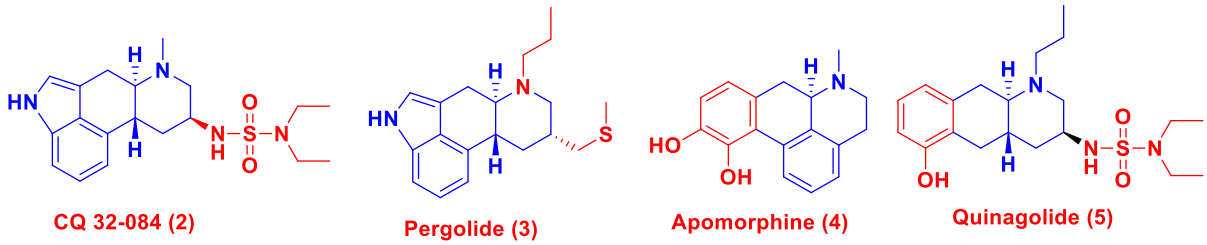



**Fig. 2**

**Fig. 2** Origin of quinagolide through combining structural features of ergot and apomorphine alkaloids

In given framework, a close comparison of well-known dopamine agonists such as ergolines CQ 32-084 (**2**) and pergolide (**3**) and apomorphine (**4)** particularly paying attention to the absolute configuration of both led to the discovery of new dopamine agonist namely quinagolide (**5),** (**Fig 2**). Hence, quinagolide (**5),** as a selective D2 receptor agonist that is used for the treatment of elevated levels of prolactin (called hyperprolactinemia) has the combined structural features of both ergolines and apomorphine (**Figure 2**). Quinagolide hydrochloride is marketed under the trade name Norprolac® by Ferring Pharmaceuticals, Lausanne, Switzerland.

## Literature Review[3-6]

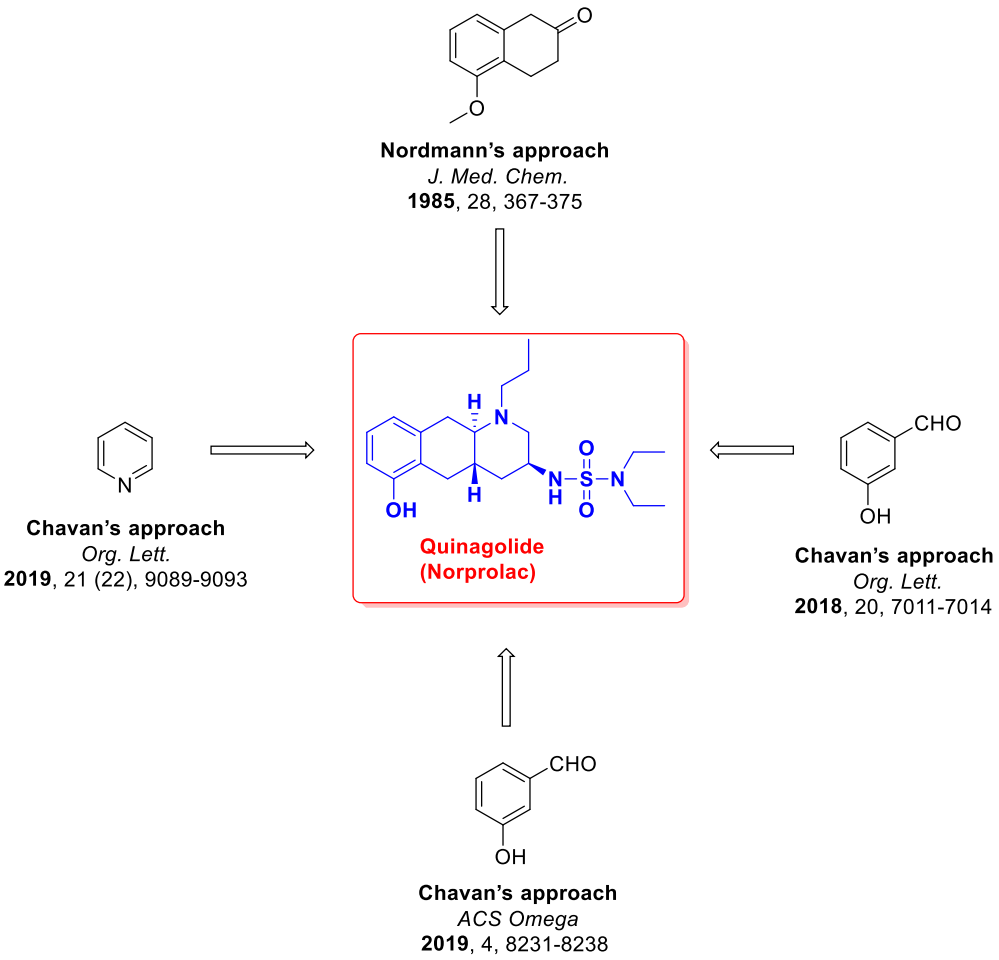
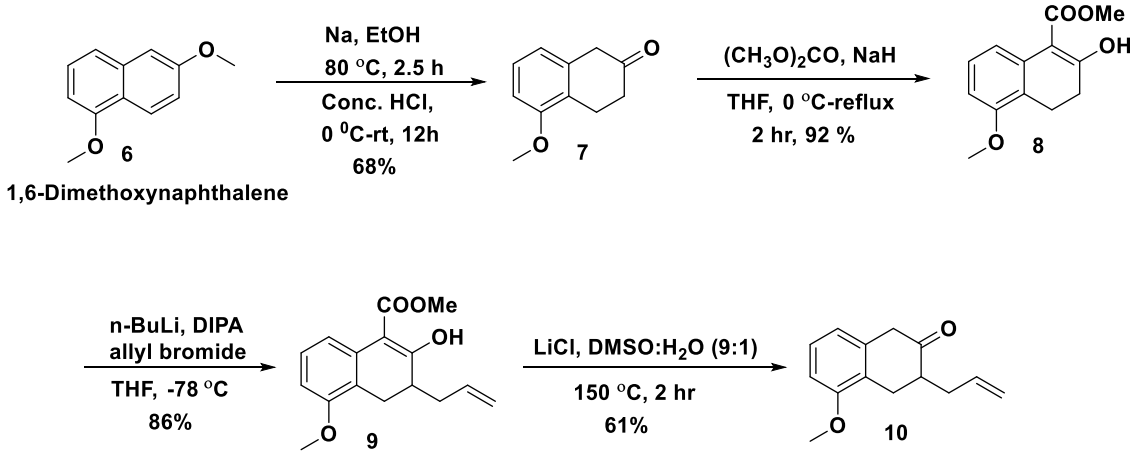



**Fig. 3**

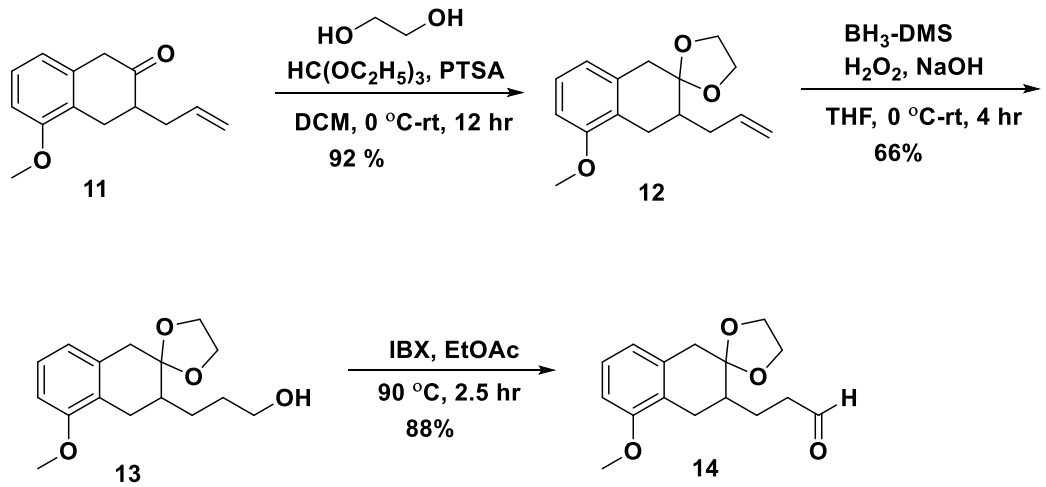
## Section-II : Attempts towards synthesis of advanced intermdiate of quinagolide




**Scheme 1**

Synthesis of quinagolide **5** began with the commercially available 1,6-dimethoxynaphthalene as the starting material. (**Scheme 1**)1,6-dimethoxy naphthalene **6** was treated with sodium in ethanol to obtain β-tetralone **7** In the next step, compound **10** was subjected for introduction of ester functionality by using NaH and dimethyl carbonate in THF to give hydroxyl ester **8** In the next step, the regioselective alkylation of hydroxyl ester **8** was carried out by converting it to its dianion by using LDA and treating with allyl bromide to give alkylated product **9**. Then, the next target was Krapcho decarboxylation of ester **9** the formation of the product **52.** Also, in the $^{13}$C-NMR spectrum, signals appeared at δ 210.96 and 44.21 corresponding to ketone and $CH_2$ carbons respectively. In $^{13}$C DEPT NMR spectrum, the

## Synthesis of aldehyde 14

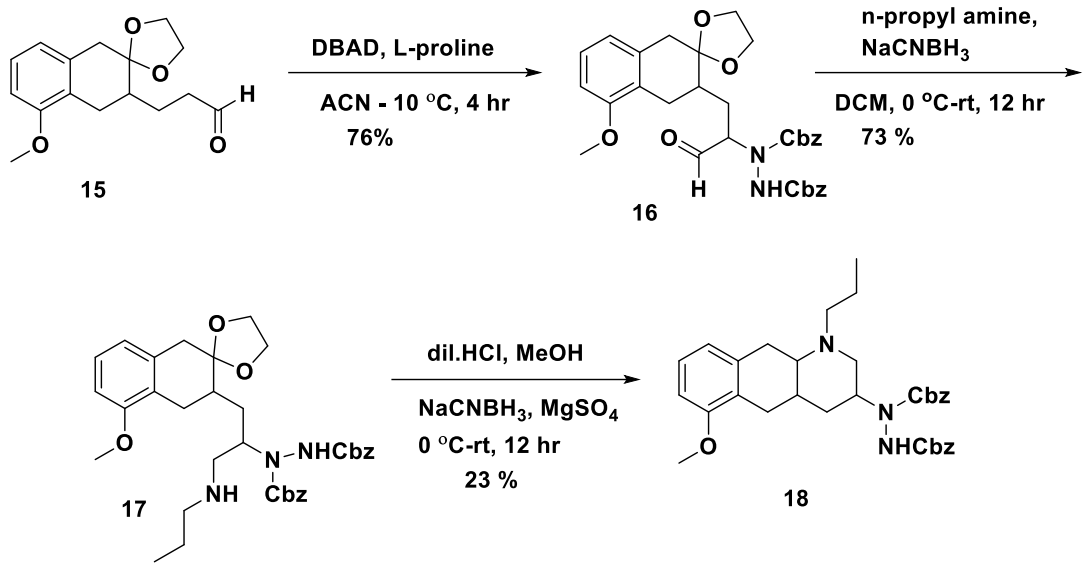



**Scheme 2**

Then, the ketal protection of free ketone **11** was effected by using ethylene glycol, triethyl orthoformate protecting group and catalytic amount of p-toluenesulfonic acid to afford a protected compound **12**. In the next step of hydroboration-oxidation of **12** the olefin **53** was treated with $BH_3$.DMS room temperature and further treated with NaOH and $H_2O_2$ afford the alcohol **13** further oxidation of alcohol 13 using IBX to give aldehyde **14**

### Synthesis of tricyclic core of quinagolide 18

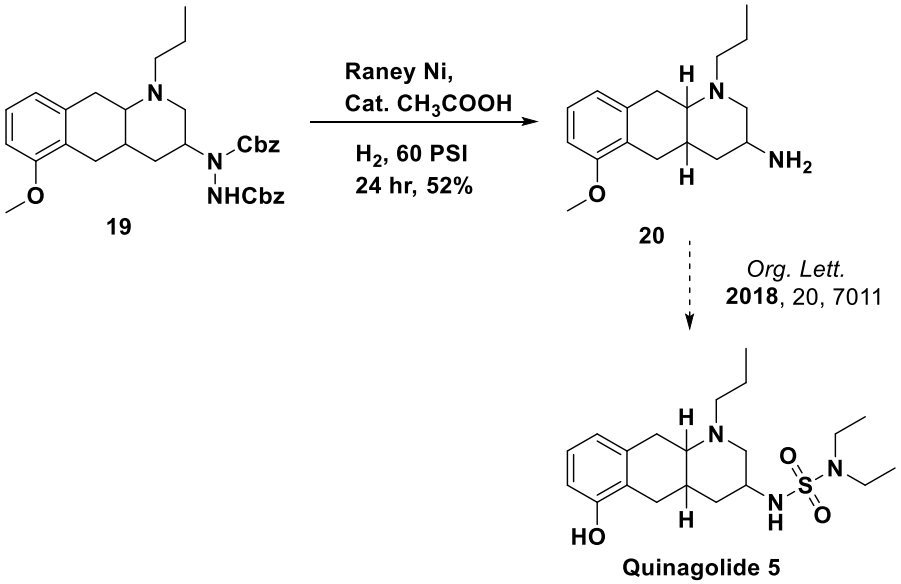
The next aim was to install amine functionality at α position of aldehyde **14.** The aldehyde **14** was subjected to proline catalysed α-amination reaction[5] using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and L-proline as a catalyst to give α-aminated product **16.**




**Scheme 3**

Further with the crucial intermediate in hand, the next aim was the synthesis of the propyl amino side chain. Amino aldehyde **16** was subjected to reductive amination reaction. The aldehyde was treated with n-propyl amine and $NaCNBH_3$ for *in situ* imine formation and reduction of imine to afford the amine **17.** The next aim was to achive tricyclic core of quinagolide, ketal deorotection using catalytic amount of PTSA in methanol and sodium cyanoborohydride afford the tricyclic core of quinagolide **18.**

**Completion of the Synthesis of amine 20**




**Scheme 3**

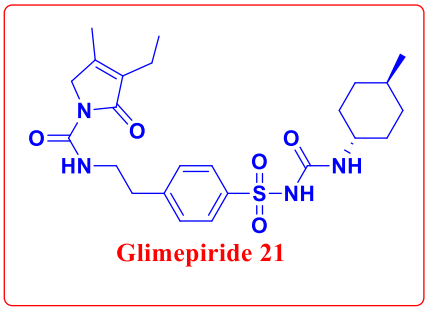
The N-N bond of compound **19** was cleaved under hydrogenation conditions using freshly prepared Raney-Ni, at 60 psi formation of product was observed. This advanced tricycic intermediate would pave way for the synthesis of quinagolide **5**

**Summary:** Synthesis of an advanced tricyclic intermediate of quinagolide was successfully achieved from 1,6-dimethoxynaphthalene as a starting material in 11 purification steps.

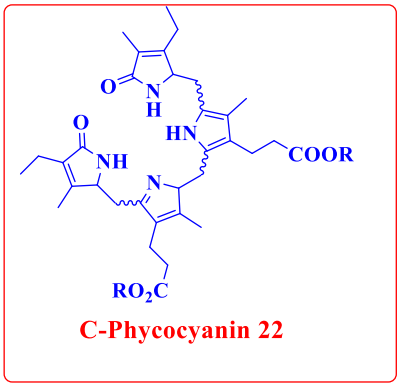
## Chapter 2
## Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one

### Section:I Introduction and literature of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one.

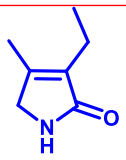
**Intraduction:** Among the sulfonylurea class of anti-diabetic drugs, glimepiride has many distinctive advantages and is by far the most superior blood glucose lowering agent. Its biological activity initiates with binding to the 65 KD protein of the putative receptor. In addition, glimepiride shows a three-fold faster rate of association and a nine-fold faster rate of dissociation than glibenclamide, which permitted its use as a once daily administration drug.




Glimepiride 21




C-Phycocyanin 22




23

3-Ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one

**Fig. 4**

Glimepiride prevents post excessive insulin release thereby decreasing the risk ofhypoglycemia. Studies on the metabolism of therapeutically active compounds are increasingly being carried out because metabolites provide superior safety and efficacy profiles, but more importantly offer opportunities to study the metabolic pathways. The metabolism of glimepiride has been observed in animals and humans *via* oxidative pathway.

- 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one is an important heterocyclic building block of antidiabetic drug glimepiride and its derivatives
- Lactam is present as main precursor in blue protein *C-phycocyanin*, it was isolated from the blue-green algae *Synechococcus sp. 6301*. C-Phycocyanin takes part in photosynthesis
- Five membered α,β-unsaturated lactam bearing substituent at positions 3 and 4, due to its utility in the field of medicinal chemistry and biology, devising an efficient and practical route has attracted the attention of synthetic chemists

**Literature Review:**

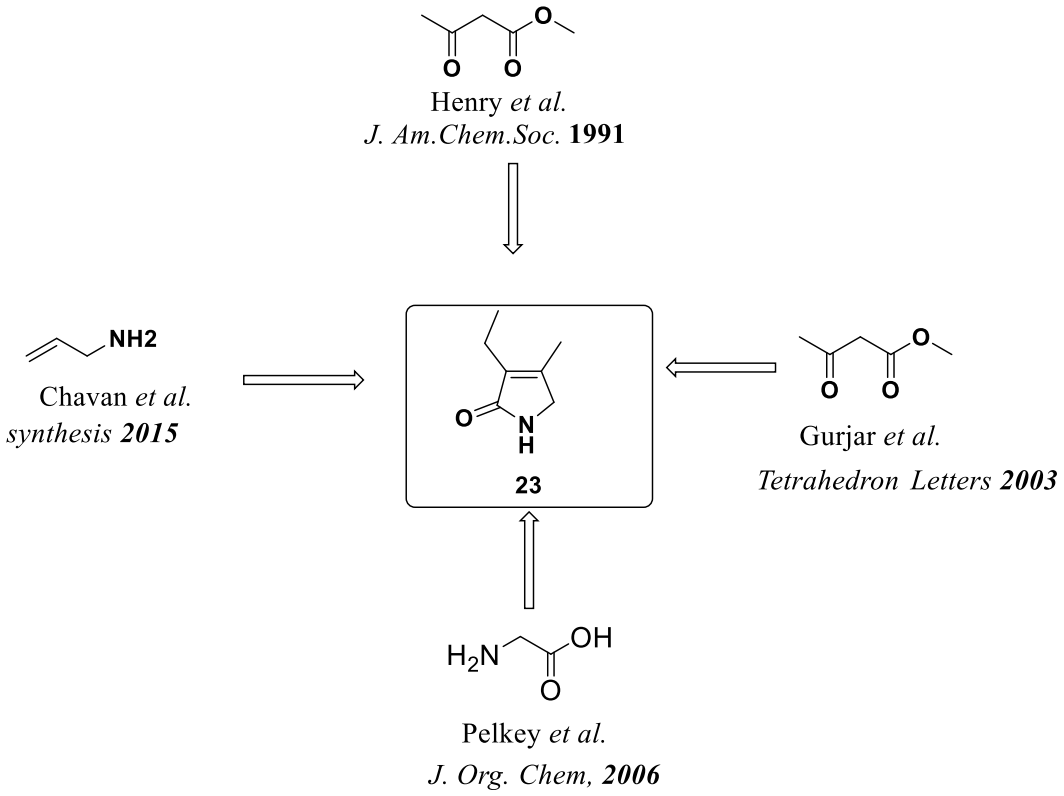


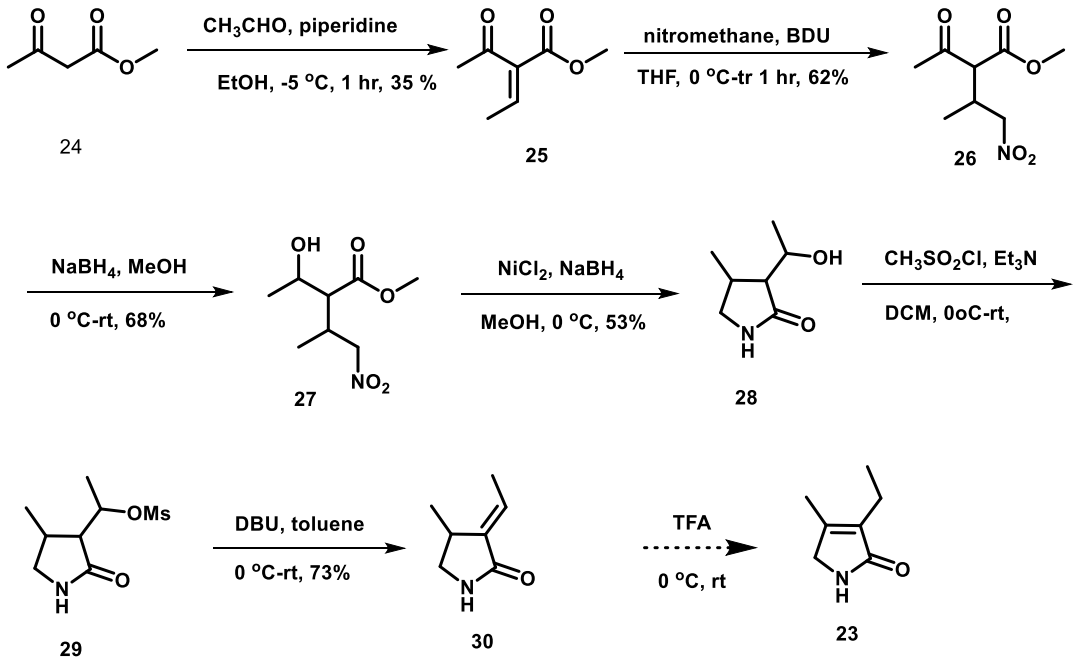

**Fig 5**

Gurjar[7] *et al.* in 2003 reported the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one form commercially avalible methylacetoacetate as a starting material by using cyanohydrin reaction and Ni catalysed hydrogenation reaction. Further the Pelkey[8] *et al*. reported the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one from Boc-glycine using DCC coupling reaction. Then the Chavan[9] *et al*. reported in 2015 the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one is described starting from commercially available allylamine and 4-methoxybenzylamine employing palladium-catalyzed cyclization or ring-closing metathesis as the key steps.

**Section-II**

**Synthesis of 3-ethyl-4 methyl- 1,5- dihydro-2*H* pyrrol-2-one by using methyl acetoacetate**

In the scheme 3-ethyl-4-methy-3-pyrrolin-2-one the synthesis of **23** start from methyl acetoacetate aldol condensation of methyl acetoacetate **24** and acetaldehyde to give this compound **25**. Michael reactions of alkene **25** using nitromethane to form the nitro compound **26.** Further the reduction of ketone using sodium borohydride to give this alcohol **27** further the reduction and cyclisation of the nitroester **27** using $NiCl_2$ and $NaBH_4$, to form the cyclised compound **28** further the protection of alcohol using mesyl chloride give the corresponding mesyl protected compound further the elimination of mesyl group using DBU to give this compound **30** further the migration of double bond of compound **30** .



**Scheme 4**

**Summary:** In summary, the synthesis of synthesis of 3-ethyl-4 methyl- 1,5- dihydro-2*H* pyrrol-2 intermediate by using methyl acetoacetate starting material in 5 purification steps.

## Chapter 3
## Continuous flow synthesis of miltefosine

### Section-I Introduction and literature review of miltefosine

Miltefosine is the first effective oral drug against both visceral and cutaneous forms of leishmaniasis infection[10], preserving its activity against antimonial-resistant parasites. Leishmaniasis is a complex disease, with visceral and cutaneous manifestations, and is caused by over 15 different species of the protozoan parasite genus Leishmania. There are significant differences in the sensitivity of these species both to the standard drugs, for example, pentavalent antimonials and miltefosine, and those on clinical trial, for example, paromomycin. Over 60% of patients with visceral leishmaniasis in Bihar State, India, do not respond to treatment with pentavalent antimonials. This is now considered to be due to acquired resistance. Although this class of drugs has been used for over 60 years for leishmaniasis treatment, it is only in the past 2 years that the mechanisms of action and resistance have been identified, related to drug metabolism, thiol metabolism, and drug efflux. With the introduction of new therapies, including miltefosine in 2002 and paromomycin in 2005-2006, it is essential that there be a strategy to prevent the emergence of resistance to new drugs; combination therapy, monitoring of therapy, and improved diagnostics could play an essential role in this strategy.

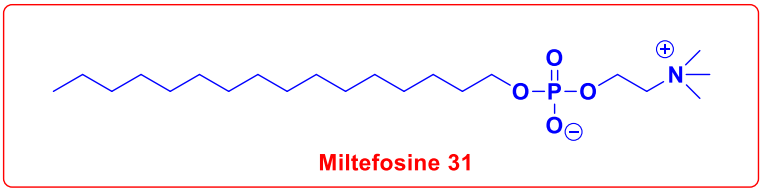



**Fig. 6**

Leishmaniasis and other nglected tropical diseases are often seen in the economically weaker sections of the society in poor, under developed and developing countries. Although the cost of treatment is not much, still the individuals cannot afford them. This not only makes these diseases neglected, but even the need of research on developing efficient methods for

synthesis of drugs for such diseases also does not appear as a priority. Among many of these neglected diseases, Leishmaniasis is one of the top parasitic diseases and it is caused by the bite of infected female phlebotomine sandflies. These sandflies are usually observed in non-hygienic areas. On an average 0.7 to 1 Mi cases occur annually and depending on the type of infection, it can be fatal or can have lifelong scars or serious disability or even in certain cases partial or total destruction of mucous membranes in the oral section. There are number of reported synthesis of miltefosine in batch method all are discussed detailed in chapter 3

**Use of Miltefosine**

- Miltefosine (Impavido) is the first and only oral treatment for visceral, mucosal and cutaneous leishmaniasis approved by the U.S. Food and Drug Administration
- It is on the world health organizations list of essential medicines, the most effective and safe medicines needed in a health system.


**Fig. 7**

**Section II Continuous flow Synthesis of miltefosine**

In recent years, continuous flow synthesis of active pharmaceutical ingredients (API), agrochemicals, petrochemicals, pesticides, fine chemicals, bulk chemicals, and nanomaterials has achieved significant importance in academia and industrial research.[11] The multi-step flow synthesis approach has been used to access complex organic molecules with diverse bioactive natural products. Recently, Rutjes and co-workers have reviewed all the efforts on continuous flow multi-step synthesis of active pharmaceutical ingredients.[12] Flow synthesis has several advantages over traditional batch process, in terms of efficient mixing, heat transfer, interfacial mass transfer, safety, excellent kinetic control of the reaction, reproducibility, productivity and the possibility of distributed production using modular systems. Recently several drug molecules and relatively complex molecules are reported using flow synthesis followed by in-line work-up including the formulations in certain cases.

A few of the most advanced examples include; the flow synthesis of quinolone antibiotic ciprofloxacin, end-to-end manufacturing process for aliskiren hemifumarate solid-supported synthesis of imatinib development of a single dedicated platform for the multiple drug molecules [13] flow synthesis of Rolipram using heterogeneous catalyst four-step continuous flow process for antihistamines from bulk alcohols, seven-step continuous flow synthesis of Linezolid molecule[14] and continuous flow synthesis and purification of Ibuprofen. The development and operation of fully automated pilot plant enables efficient and end-to-end integrated continuous manufacturingof the pharmaceutical product and small drug molecules, including continuous solvent recovery for sustainable manufacturing. Recently, Kappeet *et al*.have developed a real-time analysis platform and fully integrated multistep synthesis of an active pharmaceutical ingredient, mesalazine.

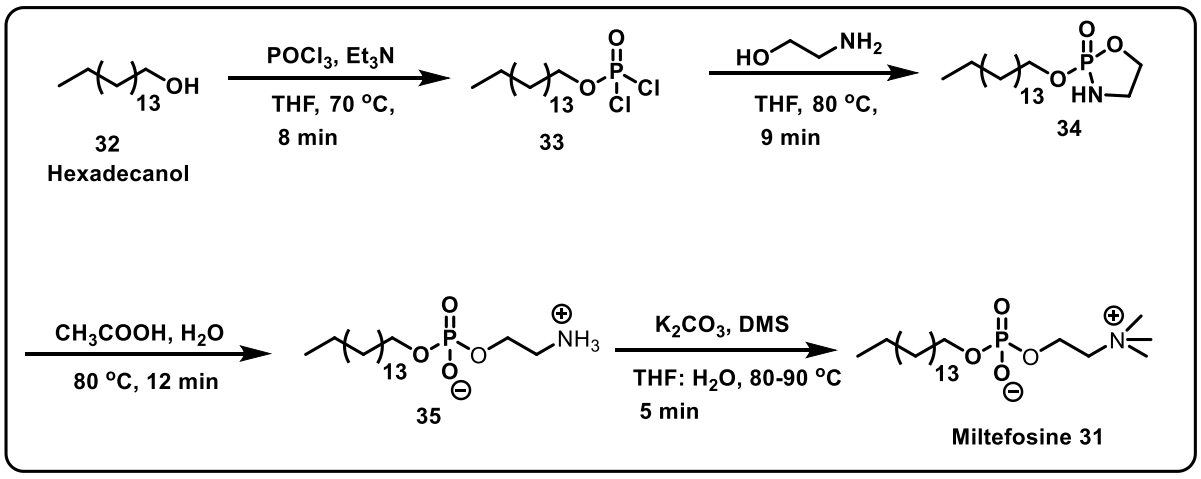



**Fig 8**

The primary investigation into the flow synthesis of miltefosine **31** started with the preparation of hexadecyl phosphorodichloridate **33** by phospho-chlorination using hexadecanol, triethylamine, and tetrahydrofuran $POCl_3$ awas employed as a chlorinating agent in THF and the reaction was allowed to proceed for 8 min residence time at 70 $^0$C temperature. After completion of reaction, the product stream containing reactive hexadecyl phosphorodichloridate **33** intermediate. The dichloro compound **33** was treated with ethanolamine the required residence time was 9 min at 80 $^0$C in THF solvent. Further, compound **34** on treating with a solution of acetic acid and water at 80 $^0$C for 12 min residence time to afforded the ring opeaning compound **35**. The alkylation reaction of **35** in screw reeder reaction it gives final product **31**.

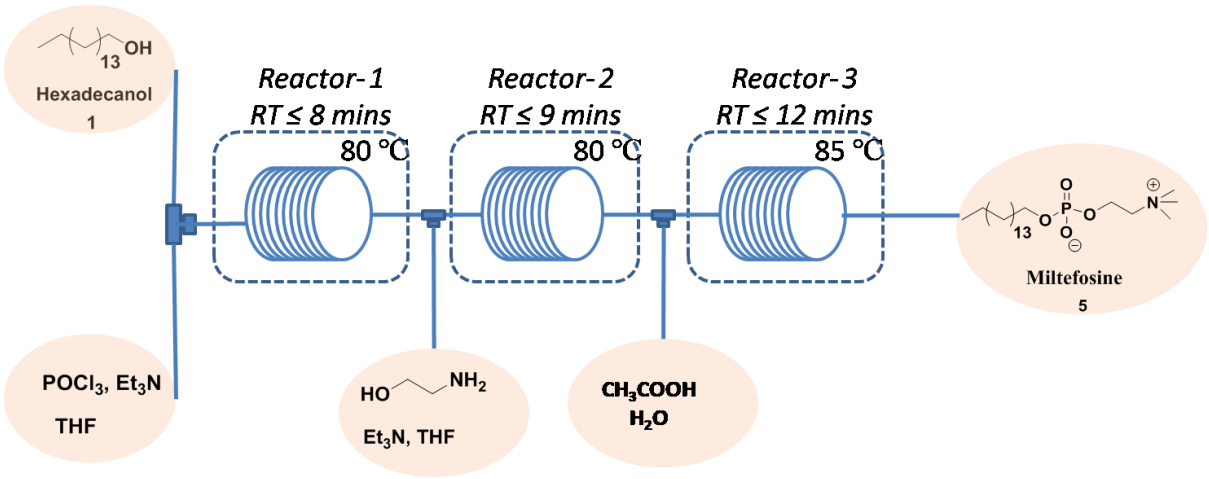



**Fig. 9** Telescopic continuous flow synthesis of miltefosine

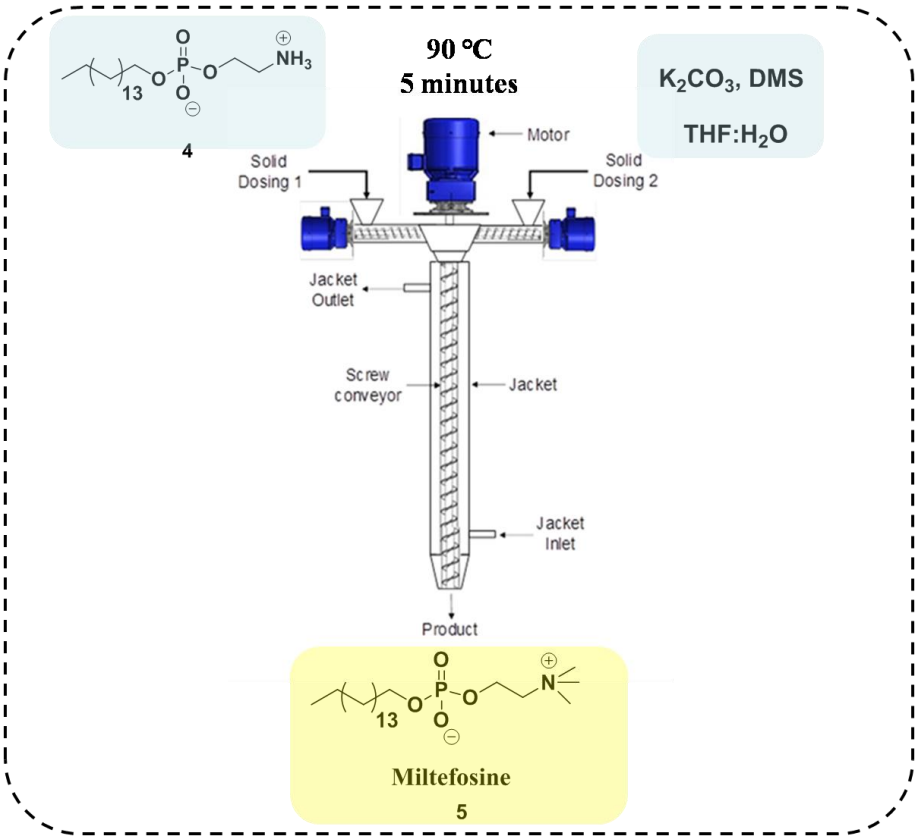



**Fig 10** Screw Feeder Reactor

## 4) Summary

An efficient telescopic continuous flow synthesis protocol for synthesis of miltefosine, reported for the first time.

**5) Summary (Overall):**

In summary, It is believed that the undesired epimer was synthesised by this route, from 1,6-dimethoxynaphthalene as a starting material in 11 purification steps. The key step involved regioselective C-alkylation of β-ketoester followed hydroboration oxidation, proline catalysed α-amination reaction to install amine functionality and one pot ketal deprotection and cyclizatin reaction. In the second chapter the formal synthesis of synthesis of 3-ethyl-4 methyl- 1,5- dihydro-2*H* pyrrol-2 by using methyl acetoacetate starting material in 5 purification steps. In third chapter the first time, an efficient telescopic continuous flow synthesis protocol for miltefosine The total residence time for the four-step sequence is 34 minutes, which is significantly shorter than the reported traditional batch protocol (> 15 hours). The protocol does not need any isolation, and purifications of intermediates until 3$^{rd}$ step which are all performed in a tubular reactor. The fourth step is performed using a screw reactor as the reactants are in the viscous paste form involving large fraction of solids.

**6) Publications**

**List of Publications and Patents**

1) Subhash P. Chavan; Sanket A. Kawale; **Niteen B. Patil**; Dinesh B. Kalbhor; Application of allylic amine formation from aziridine-2-ol under Appel reaction condition: Synthesis of N-(tert-butoxycarbonyl)-D-vinyl glycine methyl ester. *Tetrahedron Letters* **2021,** 73 153-119.

2) Subhash P. Chavan; Ambaji A. Pawar; **Niteen B. Patil**; Appasaheb L. Kadam, Shrikrishna S. Shinde; Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one:An Important Building Block of the Antidiabetic Drug Glimepiride. *Synthesis* **2020**, 52, 3480–3484.

3) Abhijeet N. Purude; Kailash P. Pawar; **Niteen B. Patil**; Uttam R. Kalkote ; Subhash P. Chavan; Total synthesis of (R)-lipoic acid and (S)-lipoic acid *via* an Mn (III)-salen-catalyzed oxidative kinetic resolution. *Tetrahedron: Asymmetry* **2015**, 26, 281–287.

4) Subhash P. Chavan; Kailash P. Pawar; Ch. Praveen; **Niteen B. Patil**; Chirality induction and chiron approaches to enantioselective total synthesis of a-lipoic acid *Tetrahedron* **2015** 71 4213-4218.

5) Process for the Preparation of Glimepiride intermediate. *Chavan, S. P.; Pawar, A. A.; **Patil, N. B**.; Kadam, A. L.; Shinde, S. S. IN Patent App. 201,911,040,874.

6) **Niteen B. Patil**; Ranjit S. Atapalkar ; Subhash. P. Chavan; and Amol A. Kulkarni; Multi-step Synthesis of Miltefosine: Integration of Flow Chemistry with Continuous Mechanochemistry.( Communicated)

**7) References:**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3) Nordmann, R.; Petcher, T. J.; *J. Med. Chem*. **1985**, 28, 367.
4) Chavan, S. P.; Kadam, A. L.; Lasonkar, P. B.; Gonnade, R. G.; *Org. Lett*. **2018**, 20, 7011−7014.
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6) Chavan, S. P.; Kadam, A. L.; Gonnade, R. G.; *Org. Lett*. **2019**, 21, 9089−9093.
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8) Coffin,A. R.; Roussell, M. R.; Tserlin, E.; and Pelkey, E. T.; *J. Org. Chem*. **2006**, 71, 6678-6681.
9) Chavan, S. P.; Pathak, A. B.; Pawar, K. P; *Synthesis* **2015**, 47, A–F.
10) Sunder, S.; Jha, T. K.; Thakur, C. P. ; Engel, J.; Sindermann, H.; Fischer, C.; Junge, K.; A. Bryceson, B.; Berman, J.; *N Engl J Med*. **2002,** *347*, 1739-1746.
11) Baumann, M.; Bexandale, I. R.; *Beilstein J. Org. Chem.* **2015,** *11*, 1194–1219;
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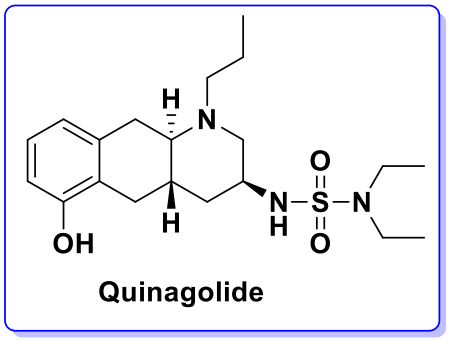
# Chapter 1: Attempts towards quinagolide

## Section-I

## "Introduction and literature review of quinagolide"




Quinagolide

### 1.1.1 Introduction

Alkaloids synthesis has always been considered to be one of the more attractive targets and their synthetic derivatives, with their wide spectrum of pharmacodynamics activity, have found use in the treatment of a variety of pathophysiological disturbances. During the last few years, following the successful use of such compounds for the treatment of hyperprolactinemia, acromegaly, and parkinsonism, increasing efforts have been concentrated on the synthesis of new derivatives and partial structures with the aim of dissecting out a specifically dopaminomimetic pharmacophore. Octahydrobenzo[*g*]-quinolines, synthetic analogues of the ergot family structure, are potent dopamine agonists.

The responsible moiety for dopaminomimetic activity of the ergolines had initially been assumed to be a rigid arylethylamine, a phenyl ethylamine,[1] a tryptamine, (aminoethyl) indole **la- ld** (**fig 1**). These hypotheses led to the synthesis of a variety of partial structures, such as benz[*cd*] indolamines, octahydrobenzo[*f*]quinolines, 4 -piperidinyl- and 4-tetrahydropyridinylindoles, 4-(2-aminoethyl)indoles, and 9-oxaergolines. Some of these compounds are potent dopamine agonists.

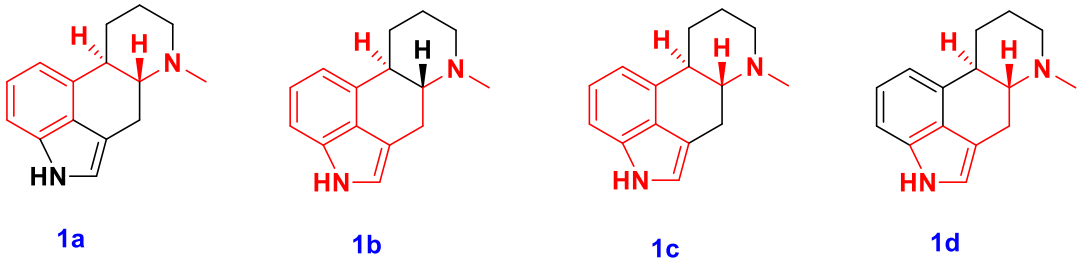



**Fig 1** Moiety responsible for dopaminomimetic activity of the ergolines

### Discovery of quinagolide.

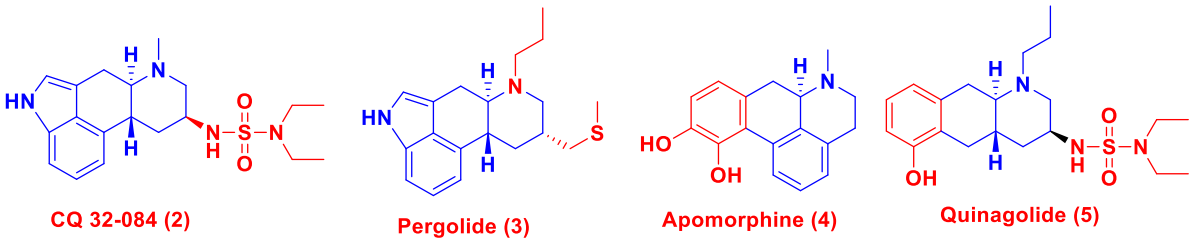



**Fig 2** Origin of quinagolide through combining structural features of ergot and apomorphine alkaloids

In this below given framework, a close comparison of well-known dopamine agonists such as ergolines CQ 32-084 (**2**) and pergolide (**3**) and apomorphine (**4)** particularly paying attention to the absolute configuration of both led to the discovery of new dopamine agonist namely quinagolide (**5)**, (**Figure 2**). Hence, quinagolide (**5),** as a selective D2 receptor agonist that is used for the treatment of elevated levels of prolactin (called hyperprolactinemia) has the combined structural features of both ergolines and apomorphine (**Figure 2**). Quinagolide hydrochloride is marketed under the trade name Norprolac® by Ferring Pharmaceuticals, Lausanne, Switzerland.

## Hyperprolactinemia

The presence of abnormally elevated levels of prolactin in the blood[2] called as hyperprolactinemia. The most general reason for the hyperprolactinemia is tumour on the pituitary gland also names as a prolaction. Pharmacological causes like stress, pregnancy. The symptoms in hyperprolactinemia are infertility and erectile dysfunction in men. There are few drugs for hyperprolactinemia disease such as bromocriptine (**6**), cabergoline (**7**) and quinagolide (**5**) (**Figure 3**) are used as medications[3].

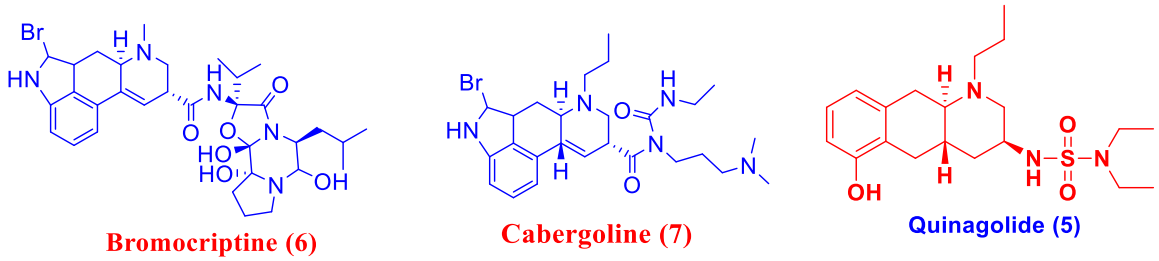



**Fig 3**. Available hyperprolactinemia medications bromocriptine (**6**), cabergoline (**7**) and quinagolide (**5**).

Out of these available medications in the market, bromocriptine (**6**) has serious side effects, whereas quinagolide (**5**), which may improve patient compliance to treatment due to its reduced side effect profile, has distinct advantages over cabergoline (**7**). Owing to being well-tolerated and effective therapy, with a simple dosing regimen, quinagolide (**5**), which is newly introduced by Ferring Pharmaceuticals under the trade name Norprolac, is considered as first-line therapy in the treatment of hyperprolactinemia.

## Enantiomers of Quinagolide 5

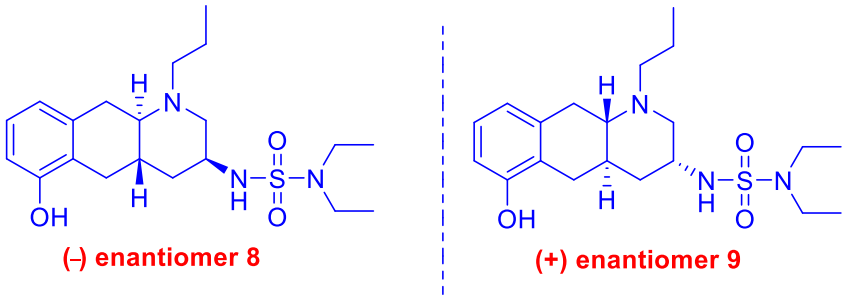


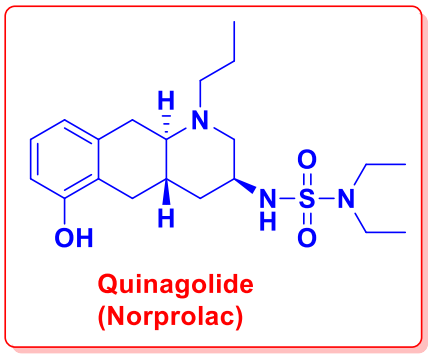

**Figure 4:** Enantiomers of quinagolide **5**

Nordmann *et al.* reported the synthesis of both the enantiomers of quinagolide **5** (**Figure 4**) and checked their dopaminomimetic bioactivity. It was observed that it is the (-) enantiomer of quinagolide **5** which entirely shows dopaminomimetic bioactivity and has the (3*S*, 4a*R*, 10a*R*) absolute configuration. Till date quinagolide **5** is sold in the market in racemic form.

## Quinagolide - a valuable medication choice for hyperprolactinemia

Quinagolide **5** is advertised by Ferring Pharmaceuticals, Lausanne, Switzerland under the brand name Norprolac. Quinagolide **5** acts as a selective $D_2$ receptor agonist. Quinagolide **5** is as effective as bromocriptine **6** for the treatment of hyperprolactinemia. It effectively reduces the elevated level of prolactin and helps in shrinkage of tumour in the majority of patients. Quinagolide **5** is also effective in patients who show resistance or intolerance to bromocriptine medication. Cabergoline **7** is one step ahead to quinagolide **5** in terms of a percentage of patients beneficial to cure hyperprolactinemia disease, however, clinical efficacy was found to be similar. It is observed that some patients who are resistant to one dopamine agonist may be treated effectively with another dopamine agonist. Due to specificity of quinagolide **5**, it shows better tolerability and shows fewer side effects in comparison to bromocriptine **6**. Unlike bromocriptine **6**, quinagolide **5** is found to be safer for women wishing to be pregnant and can be used until the point of affirmation of pregnancy. Hence, quinagolide **5** is a valuable medication choice for hyperprolactinemia.

## Quinagolide (Norprolac)





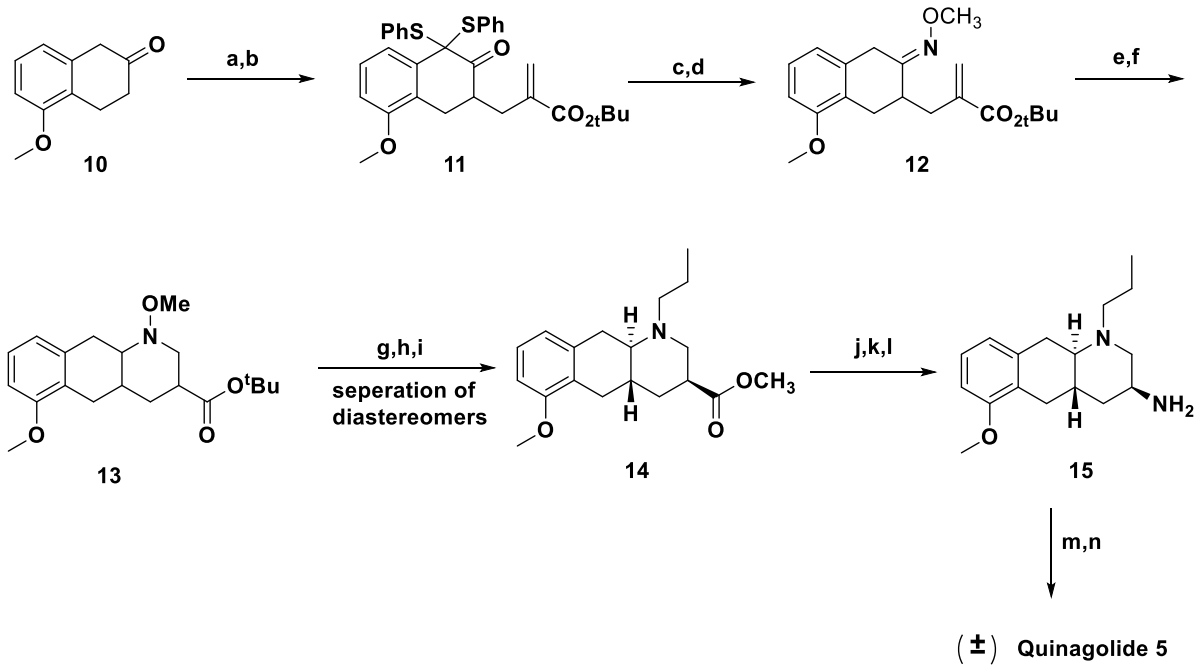
Rane Nordmann and Trevor J. Petcher from Sandoz Ltd. (Switzerland) have discovered quinagolide in 1985. Quinagolide hydrochloride is marketed by Ferring Pharmaceuticals, Lausanne, Switzerland under the brand name Norprolac® in its racemic form. Tablets containing 0.025, 0.050, 0.075, or 0.150 mg quinagolide as the hydrochloride are available in the market.

### 1.1.2. Literature Review

Though quinagolide is sold in its racemic form, and it is a synthetic analog of ergot family alkaloids, till date, there are 7 synthetic routes reported in literature. Here all of these synthetic approaches are discussed in detail.

1) **Nordmann's approach**[2] **(***J. Med. Chem.* **1985**, *28*, 367-375)

Nordmann *et al*. in the year 1985 reported the discovery and total synthesis of new dopamine agonist quinagolide by combining the structural features of ergot and apomorphine alkaloids. Synthesis of quinagolide commenced with β-tetralone **10** as the starting material **(Scheme 1).** For the synthesis of the third piperidine ring, tetralone **10** was converted into ester **11** using regioselective alkylation with *tert*-butyl 2-(bromomethyl)acrylate and LDA as a base.

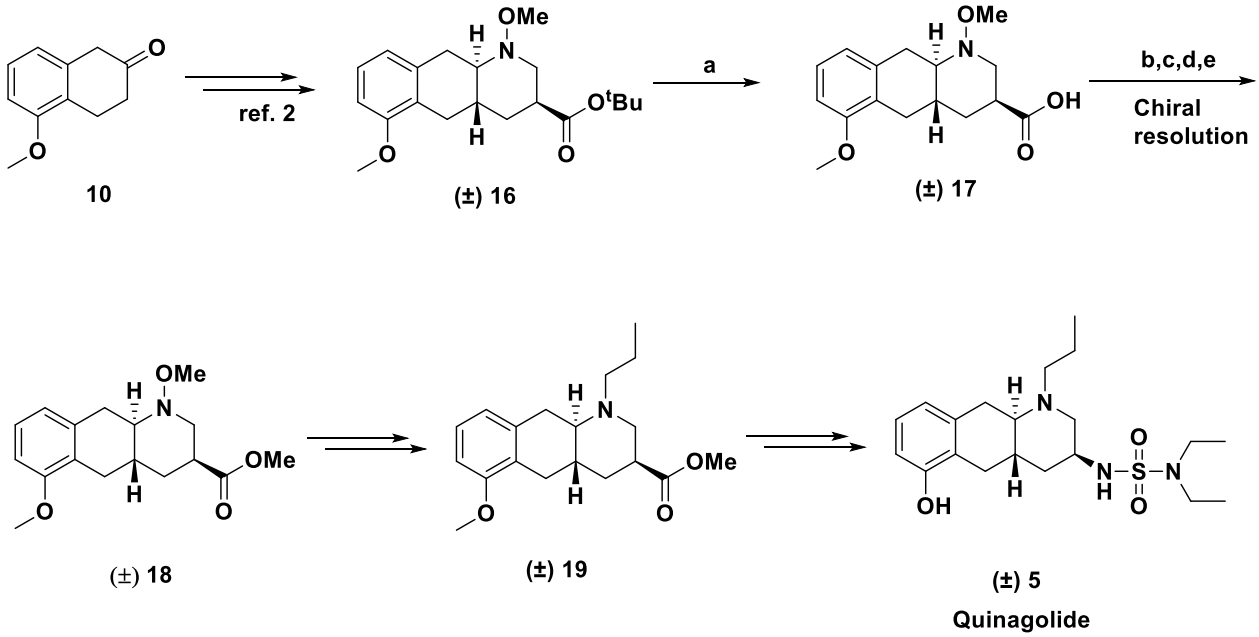



**Scheme 1**

**Scheme 1: Reagents and conditions:** (a) S-phenyl benzenethiosulfonate, NaOAc, MeOH, rt, 82%; (b) LDA, tert-butyl 2-(bromomethyl) acrylate, $Et_2O$-THF-HMPT, –78 °C, 66%; (c) Al(Hg), THF-$H_2O$, 50 °C, 2 h, 71%; (d) $H_2NOCH_3$.HCl, $Na_2HPO_4.2H_2O$, MeOH, rt, 4 h, 72%; (e) $NaCNBH_3$, MeOH, rt, 12 h; (f) MeOH, rt, 72 h; (g) $H_2SO_4$, MeOH, reflux, overnight, 92%; (h) Zn, AcOH, $H_2O$, rt, overnight, 72%; (i) Propanal, $H_2$, 10% Pd/C, PrOH, rt, overnight, 74%; (j) Hydrazine hydrate, MeOH, 50 °C, 20 h, 80%; (k) NOCl, THF, reflux, 1 h; (l) HCl, THF, reflux, 1 h, 61% (over 2 steps); (m) $Et_2NSO_2Cl$, $CHCl_3$, 50 °C, overnight, 87%; (n) $BBr_3$, $CH_2Cl_2$, –10 °C, 4 h, 89%.

Further, compound **12** was then converted to tricyclic ring **13** as a mixture of four diastereomers through reduction and cyclization of oxime **12**. All four diastereomers were separated using silica gel column chromatography. Required diastereomer **13** was converted to the methyl ester **14** by alkylation with propanal under hydrogenation condition. For the construction of side chain, the Curtius rearrangement of the corresponding azide derived from methyl ester **14** was used to obtain 3-amino piperidine **15**. Amine **15** was then converted to the final product **5** by the sulfonation using *N*,*N*-diethyl sulfamoyl chloride and ether cleavage with $BBr_3$.

**2) Med-Chem approach**[3] (*J. Med. Chem*. **1985**, *28*, 1540-1542)



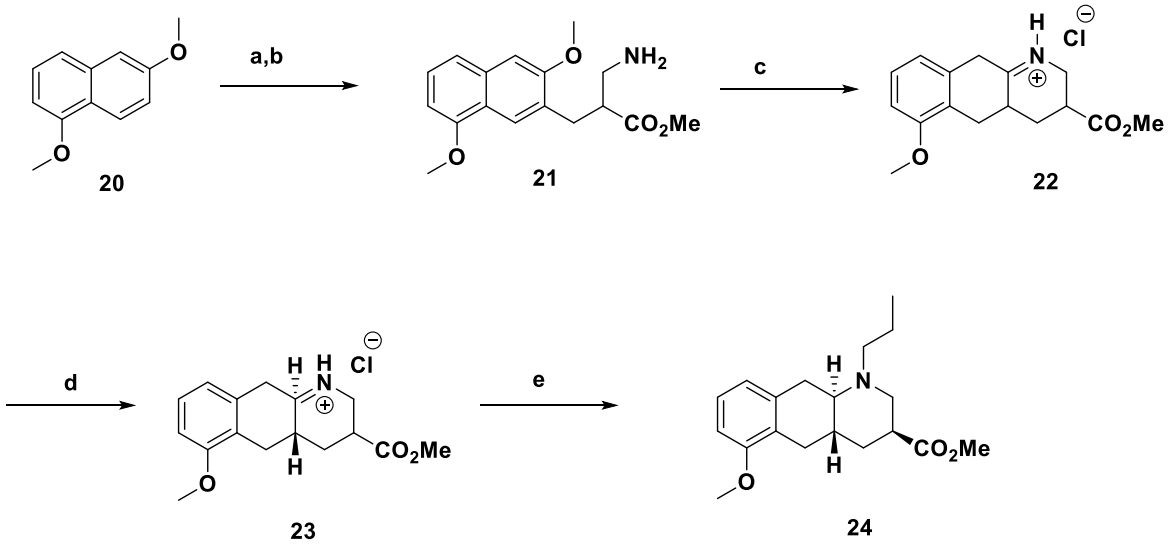

**Scheme 2**

**Scheme 2: Reagents and conditions:** (a) TFA, rt, 45 min, 90%; (b) D-(+)-α methylbenzylamine $CH_2Cl_2$-$Et_2O$, –20 °C, 30%; (c) L-(–)-α-methylbenzylamine, $CH_2Cl_2$-$Et_2O$, –20 °C, 28%; (d) 1 N HCl; (e) $CH_2N_2$, $CH_2Cl_2$, 98%.

In the same year (1985) Nordmann *et al.* reported the absolute configuration and the dopaminomimetic activity of quinagolide through the resolution of racemic intermediate (**Scheme 2**). Firstly, they were unsuccessful to resolve the parent compound **(±) 5**. Then the acid **(±) 17** was resolved with the D-(+)-α- methylbenzylamine and L-(-) - α- methylbenzylamine. The two enantiomers were converted to the methyl esters **(+)-18** and **(–)-18** by esterification of the corresponding acids with diazomethane. Further by using the reaction sequence that was used in case of **(±)-5**, compounds **(+)-18** and **(–)-18** were converted to the enantiomerically pure **(+)-5** and **(–)-5** respectively.

**3) Banziger's approach**[4] (*Org. Process Res. Dev.* **2000**, *4*, 460-466)

Bänziger *et al.* in 2000 developed a large-scale manufacturing route for quinagolide intermediate **24** using 1,6-dimethoxynaphthalene **20** as starting material using 9 purification steps with 13% overall yield ( **Scheme-3).**



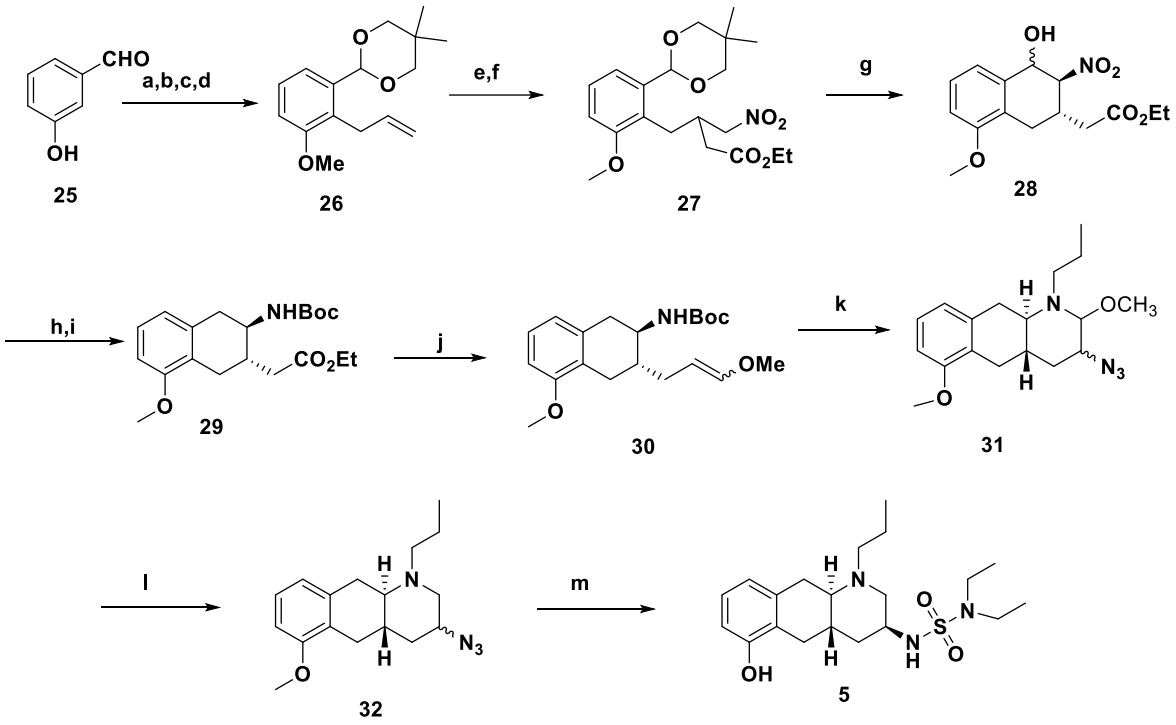

**Scheme 3**

**Scheme 3: Reagents and conditions:** a) hexyllithium, ethoxymethylenecyanoacetate, THF, -70 $^0$C, 55%; (b) Pt/C, $H_2$ (10 bar), $H_2SO_4$, EtOH, 50 $^0$C then LiOH, $H_2O$, 83%; (c) Li/$NH_3$, t-BuOH, THF, -70 $^0$C then conc. HCl, $H_2O$, 0 °C, 97%: (d) $NaBH_4$, EtOH, 70 °C then conc. $H_2SO_4$, MeOH, reflux then basic workup then p-TSA, EtOAc, 70 °C, 78%; (e) n-propyliodide, $K_2CO_3$, DMF, 55 °C then LDA, TMSCl, THF, 40 °C then 15% HCl, 2 h, 85%.

The synthesis started from 1,6-dimethoxynaphthalene **20** which was ortho alkylated at the C-7 position by ethoxy methylene cyanoacetic acid ethyl ester using hexyllithium as a lithiating agent which after hydrogenation and acid hydrolysis gave amino acid **21**. Birch reduction of **21** followed by acid hydrolysis of resulting enol ether using conc. HCl gave compound **22**. Iminium hydrochloride **22** was reduced by $NaBH_4$ followed by reflux in methanol in presence of sulphuric acid and then after basic work-up treated with *p*-TSA to give compound **23**. Compound **23** was alkylated with *n*-propyliodide and finally treated with LDA and TMSCl to give compound **24** as a single diastereomer.

**4) Chavan's approach**[5] (*Org. Lett.* **2018**, *20*, 7011-7014)

Chavan *et al.* in 2018 reported the synthesis of quinagolide by using ceric ammonium nitrate mediated azidoalkoxylation of enol ether to construct 3-aminopiperidone skeleton of quinagolide **5** starting from 3-hydroxybenzaldehyde **25** with 14 purification steps **(Scheme 4).**

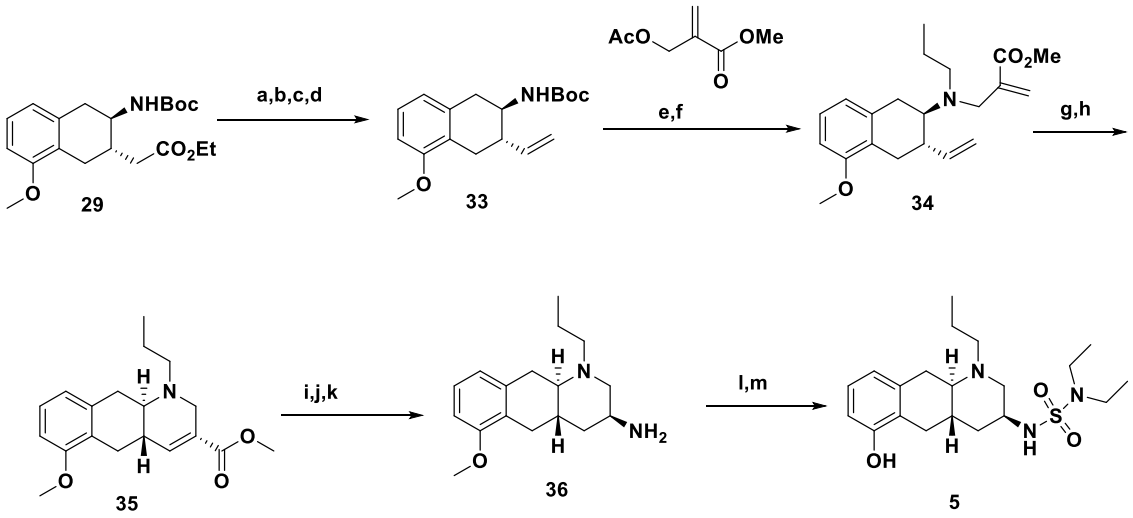



**Scheme-4**

**Scheme 4: Reagents and conditions**: a) allyl bromide, $K_2CO_3$, EtOH, reflux, 97%; (b) microwave, 800 W, 240 $^0$C, 45%; (c) $Me_2SO_4$, $K_2CO_3$, acetone, reflux, 95%; (d) 2,2-dimethyl-1,3-propanediol, $HC(OEt)_3$, *p*-TSA, $CH_2Cl_2$, rt, 95%; (e) i) $OsO_4$, NMO, $CH_3CN$:$H_2O$ (9:1); ii) $NaIO_4$, acetone:$H_2O$ (3:1), rt, $Ph_3PCHCO_2Et$, $CH_2Cl_2$, rt, 72% (over 3 steps); (f) $CH_3NO_2$, DBU, reflux, 83%; ( g) PPTS, acetone:$H_2O$ (4:5), reflux, 82%; (h) $H_2$, Pd/C, $(Boc)_2O$, $Et_3N$, EtOAc, 60 psi, 90%; (i) $Pd(OH)_2$, $H_2$, cat. HCl, MeOH, 60 psi, 83%; (j) i) DIBAL-H, $CH_2Cl_2$, -78 $^0$C ii) $CH_3OCH_2PPh_3Cl$, KO*t*-Bu, THF, 0 $^0$C -rt, *E*/*Z*=80:20, 64% (over 2 steps) ; (k) i) CAN, $NaN_3$, MeOH, $CH_3CN$, 0 $^0$C- rt ii) $NaBH_3CN$, TFA: EtOH (1:9), 0 $^0$C- rt; iii) *n*-propyl iodide, $K_2CO_3$, DMF, 50 $^0$C, 45 % (over 3 steps); (l) $PPh_3$, $H_2O$, THF, reflux, 83%; (m) $Et_2NSO_2Cl$, $Et_3N$, $CHCl_3$, 50 $^0$C, 71%; ( n) $AlCl_3$, EtSH, $CH_2Cl_2$, rt, 66%.

Olefin **26** obtained from 3-hydroxybenzaldehyde **25** was dihydroxylated followed by chopping of diol and two-carbon Wittig olefination to give unsaturated ester which on heating in nitro methane in presence of DBU gave Michael addition adduct **27**. PPTS mediated acetal deprotection and Henry reaction of nitroester **27** occurred in one pot to provide compound **28**. Compound **28** was converted to compound **29** by reduction of the nitro group to amine followed by its Boc protection and benzylic deoxygenation. Further, the ester **29** on reduction and MOM-Wittig reaction afforded **30**. Then the compound **30** was subjected to ceric ammonium nitrate mediated azidoalkoxylation of enol ether followed by reduction with sodium cyanoborohydride to obtain 3-azido piperidine **32**. Finally, the azide **32** was reduced to amine followed by its protection and demethylation to give quinagolide **5**.

**5) Chavan's approach**[6] (*ACS Omega* **2019**, *4*, 8231-8238)



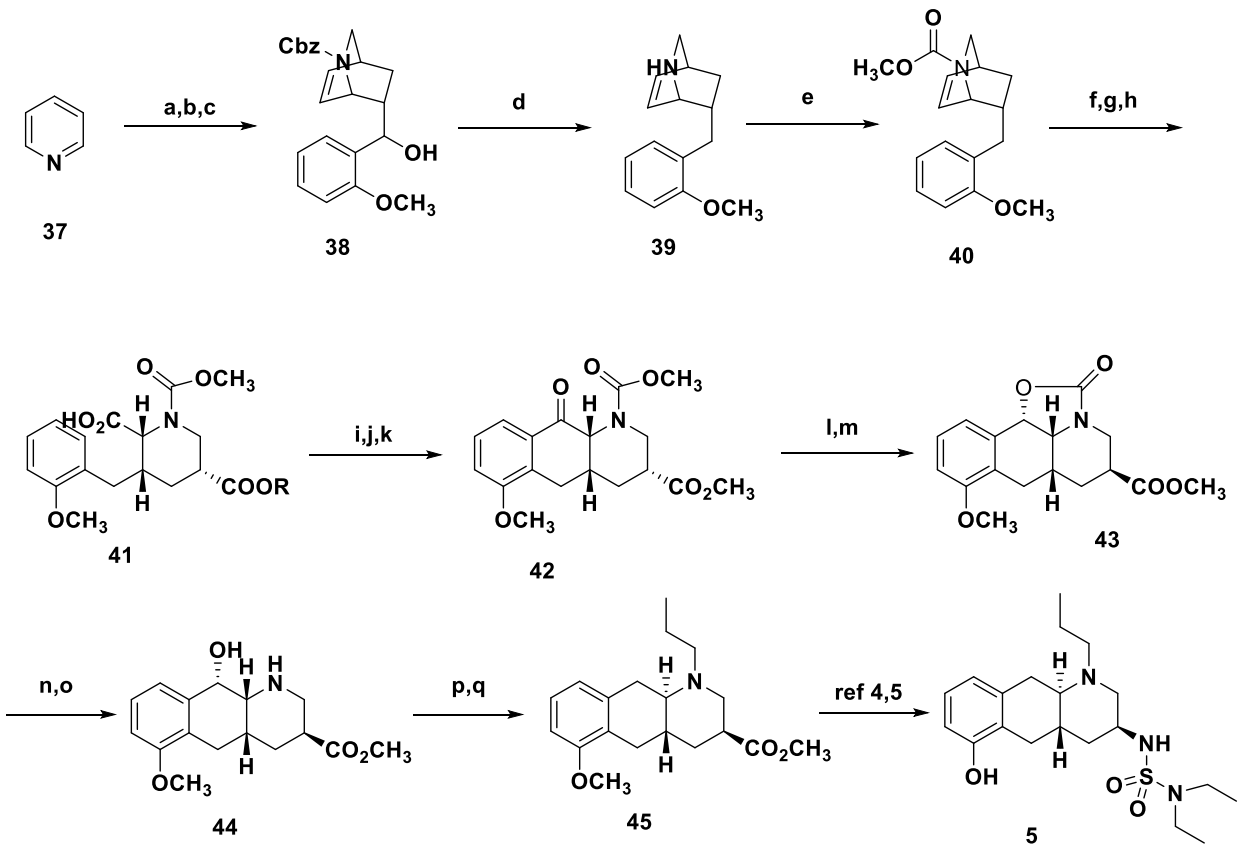

**Scheme-5**

**Scheme 5: Reagents and conditions:** a) $NaBH_4$, LiCl, THF:EtOH, reflux, 16 h, 68%; (b) $(PhS)_2$, $Bu_3P$, THF, rt, 24 h, 95% c) $NaIO_4$, MeOH:$H_2O$, 0 $^0$C- rt, 12 h, 95% ; (d) $NaHCO_3$, xylene, reflux, 15 h, 98%; (e) i) TFA, $CH_2Cl_2$, 0 $^0$C- rt, 5 h, ii) acrylate, $CH_2Cl_2$, rt, 12 h, 80% (over 2 steps) ; (f) *n*-propyl iodide, $K_2CO_3$, $CH_3CN$, reflux, 15 h, 70%; (g) Grubbs' 2$^{nd}$ gen. catalyst, *p*-TSA, toluene, 14 h, 93%; (h) $H_2$, Pd/C, MeOH, 60 psi, 6 h, 87%; (i) LDA, TMSCl, THF, 40 $^0$C, 2 h, then $H_3O^+$, 85%; (j) $CaCl_2$, $NH_3$, MeOH, 80 $^0$C (sealed tube), 24 h, 90%; (k) $PhI(CF_3CO_2)$, $CH_3CN$:$H_2O$, rt, 12 h, 82%; (l) Diethylsulfamoyl chloride, $Et_3N$, $CHCl_3$, 50 $^0$C, 12 h, 71%; (m) $AlCl_3$, EtSH, $CH_2Cl_2$, rt, 12 h, 66%.

The intermediate **29** synthesized as mentioned above was also converted to quinagolide **5** using ring-closing metathesis approach as shown in **Scheme 5**. The aminoester **29** was converted into the diene **34** which was treated with Grubbs' second generation catalyst and PTSA to provide the tricyclic core **35.** FGI afforded amine **36** which was subjected to reaction with diethylsulfamoyl chloride followed by demethylation to give quinagolide **5**.

**6) Chavan's approach**[7] (*Org. Lett.* **2019,** 21 (22), 9089-9093)

Chavan *et al.* in 2019 reported the total synthesis of quinagolide by using pyridine as a starting material (**Scheme 6**).




**Scheme 6**

**Scheme 6: Reagents and conditions:** (a) Cbz-Cl, $NaBH_4$, MeOH, -50 °C-0 °C, 2 h; (b) Acrolein $CH_3CN$-$H_2O$, 0 °C, 24 h; (c) Grignard reagent from 2-bromoanisole, THF, -30 °C to rt, 2 hr 34% (3 steps); (d) Li, liq $NH_3$, THF, - 78 °C, 15 min; (e) $ClCO_2CH_3$, $Na_2CO_3$, $CH_2Cl_2$, 0 °C to rt, 12 h , 64 % (2 steps); (f) $OsO_4$, NMO, THF-$H_2O$, rt, 2 days; (g) Silica supported $NaIO_4$, $CH_2Cl_2$, rt,

1 h; (h) $NaH_2PO_4$, $NaClO_2$, 2-methyl-2-butene, t-BuOH, 12 h, 95% (3 steps); (i) $(COCl)_2$, $CH_2Cl_2$ 0 °C to rt, 1 h; (j) $TiCl_4$, $CH_2Cl_2$, 0 °C, 2 (k) MeOH, -30 °C to rt, 3 h, 62%; (l) $LiBH_4$, THF, 0 °C to rt, 2 h, 68% ; (m) $NaOCH_3$, MeOH, 0°C to rt, 12 h, 70%; (n) NaOH, EtOH, reflux, 1 h; (o) $CH_2N_2$, MeOH-$Et_2O$, 0°C to rt, 1 h, 53 % (2 steps); (p) PTSA, toluene, reflux, 2 h, then $NaBH_3CN$, MeOH; (q) propyl iodide, $K_2CO_3$, DMF, 50 °C, 2.5 h, 61 % (2 steps).

Initially, pyridine **(37)** was treated with Cbz-Cl and $NaBH_4$ in methanol followed by Diles-Alder reaction with acrolein and further subjected to Grignard reaction using 2-bromoanisole to afford the Cbz protected compound **38.** Further, it was subjected for deoxygenation under Birch reduction condition to furnish bicyclic amine **39** which was subjected to protection of amine group using methyl chloroformate to obtain the intermediate **40**. Further dihydroxylation of **40** using $OsO_4$ and diol cleavage and Pinnick oxidation afforded **41.** The acid **41** was converted in to acid chloride followed by $TiCl_4$ mediated Friedel Crafts cyclization to afford tricyclic keto ester **42.** Reduction of ketone using $LiBH_4$ to give tricyclic carbamate **43** and epimerization of ester using NaOMe afforded carbamate ester **43**. The tetracyclic carbamate **43** was opened with ethanolic NaOH and subjected to esterification with diazomethane to get the amino alcohol **44**. Enamine formation with PTSA followed by reduction with $NaBH_3CN$ and N-alkylation of the corresponding amine with propyl iodide afforded ester **45**. The synthesis of quinagolide **5** from the ester **45** is known in literature.

### 1.1.3 Conclusion

Quinagolide contains a *trans*-fused 3-aminopiperidine skeleton and has combined structural features of ergot and apomorphine alkaloids. Though, its *trans*-fused 3-substituted piperidine scaffold challenging to the synthetic chemists. In this context, the synthesis of quinagolide is an attractive target due to its challenging structural features and medicinal importance. Though, quinagolide, a D2 receptor agonist used for the treatment of hyperprolactinemia is currently sold in racemic form and Nordmann *et al*.

### 1.1.4 References

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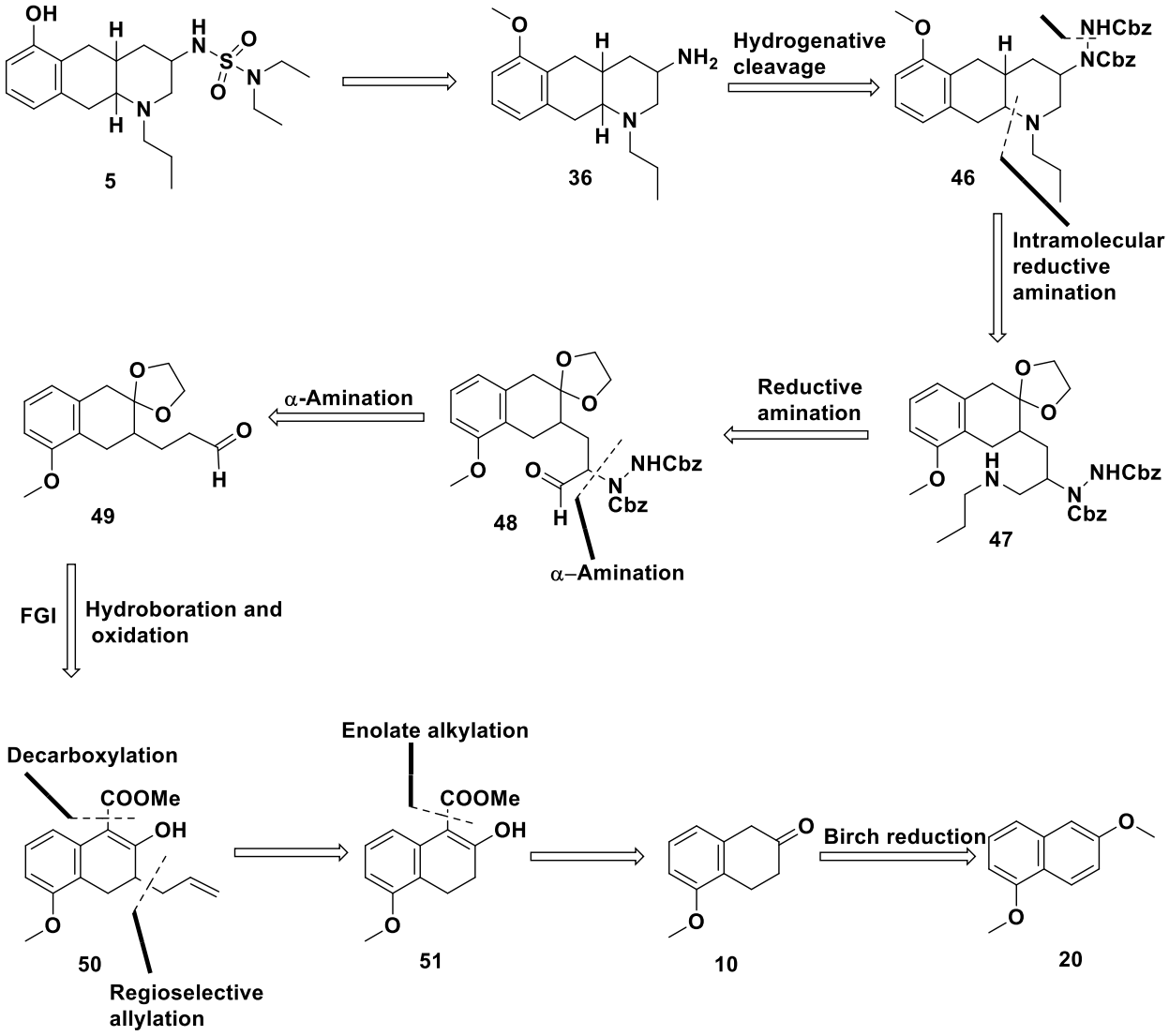
# Chapter 1, Section-II

# Attempts towards synthesis of advanced intermediate of quinagolide

## 1.2.1. Present work

### Retrosynthetic analysis

As per the retrosynthetic plan, (**Scheme-7**), quinagolide **5** could be obtained from tricyclic amine **36** by using diethylsulfamoyl chloride as a protecting group. The tricyclic amine **36** could be obtained by using hydrogenation reaction. Further the tricyclic core of quinagolide **46** can be obtained from acetal amine **47** by using acetal deprotection and imine reduction reaction with the help of dil. HCl and sodium cyanoborohydride. Amine **47** can be obtained from α-amino aldehyde **48** by using intermolecular reductive amination which would play an important role in

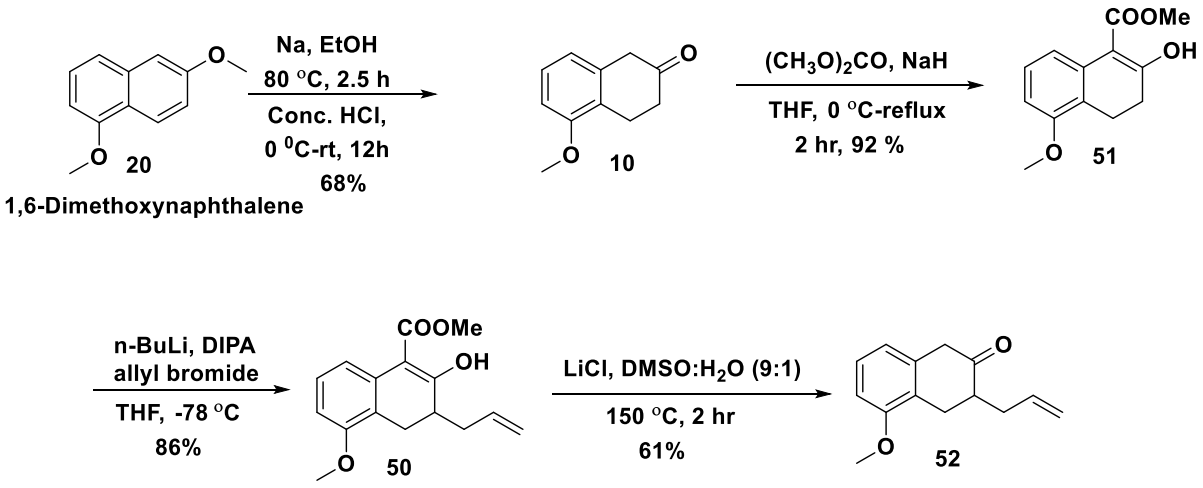



**Scheme-7**

the formation of tricyclic core of quinagolide using propyl amine and sodium cyanoborohydride. The amine functionality in compound **48** can be accessed from corresponding aldehyde **49** *via* a crucial proline catalyzed α-amination reaction. The aldehyde **49** can be readily afforded by functional group interconversion of **50** by using Krapcho decarboxylation, protection, hydroboration and oxidation reaction of alcohol to access aldehyde **49.** Further, alkene **50** could be obtained from keto ester **51** by using regioselective alkylation reaction. The β-keto ester **51** can be obtained from 5-methoxy 2-tetralone **10** and the 5-methoxy 2-tetralone can be accessed from 1,6-dimethoxynaphthalene **20.**

## 1.2.2. Results and discussion

Synthesis of quinagolide **5** began with the commercially available 1,6-dimethoxynaphthalene as the starting material[1] (**Scheme 8**). 1,6-Dimethoxynaphthalene **20** was treated with sodium in ethanol at 80 °C for 3 h. Further, the reaction mixture was cooled at 0°C and acidified very carefully with concentrated hydrochloric acid to pH = 1, heated at 80 °C for 30 min, and stirred at room temperature overnight to obtain β-tetralone **10** with 68 % yield. In $^{1}$H-NMR spectrum of compound **10**, there were 6 protons found in aliphatic region **[**peaks at **δ** 3.61 (s, 2H), 3.13 (t, 2H) and 2.58 (t, 2H)] and this indicated the formation of the product. Also in the $^{13}$C-NMR spectrum, signals appeared at δ 210.96 and 44.66, 37.86 and 20.90 ppm corresponding to carbonyl ketone and aliphatic $CH_2$ carbons respectively. The formation of compound **10** was confirmed by the IR spectrum, in which peak at 1718 cm$^{-1}$ corresponded to the ketone group.




**Scheme 8**

In the next step, compound **10** was subjected for introduction of ester functionality by using NaH and dimethyl carbonate in THF at reflux for 2 h to give hydroxyl ester **51** in 92% yield. In $^{1}$H-NMR spectrum of compound **51,** there were protons found in methyl ester region at δ 3.93 (s, 3H). Also in the $^{13}$C-NMR spectrum, carbonyl ketone peak disappeared. The formation of compound **51** was confirmed by the IR spectrum, in which peak at 3409.86 $cm^{-1}$ corresponded to the hydroxyl group. The peak observed at 234.0965 $[M + H]^+$ in the HRMS spectrum further confirmed the molecular formula $C_{13}H_{16}O_4$ of compound **51.**

In the next step, the regioselective alkylation of hydroxyl ester[2] **51** was carried out by converting it to its dianion by using LDA and treating with allyl bromide at -50 ℃ to give alkylated product **50** in 86 % yield. The formation of product **50** was evident by $^{1}$H NMR spectroscopy. The peaks in alkene region at δ 5.85-5.76 (m, 1H) and δ 5.07-4.99 (m, 2H) indicated the presecnce of terminal alkene. In $^{13}$C NMR spectrum of the compound **50,** there were two peaks observed at δ 134.99 and 117.96 ppm for alkene carbons. Further, the formation of compound **50** was confirmed by its IR spectrum, in which peak at 2935 $cm^{-1}$ corresponded to the alkene group. The structure of **50** was further confirmed by HRMS, which showed a peak at 275.1278 corresponding to the molecular formula $C_{16}H_{22}O_4$ $[M + H]^+$ of the product.

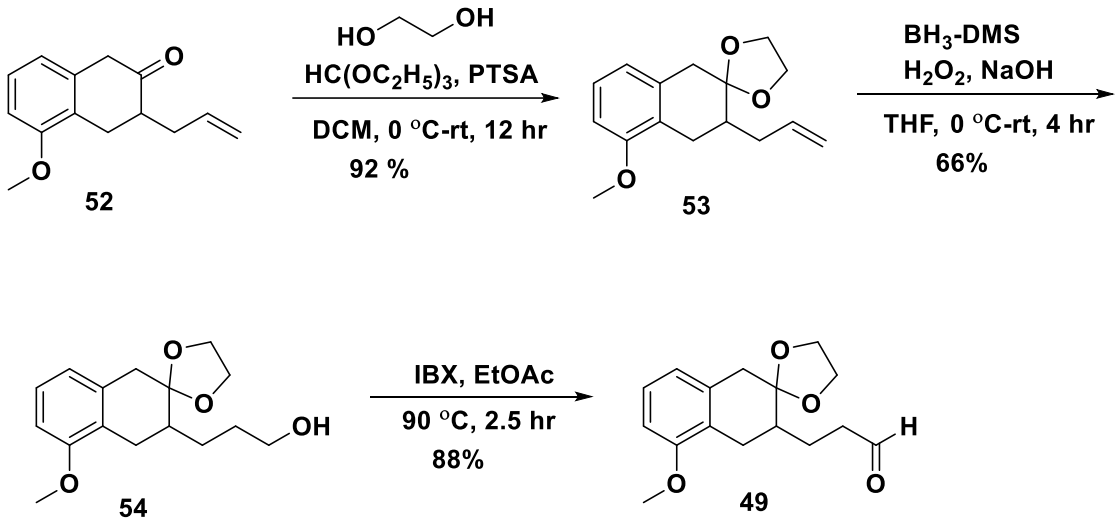
Then, the next target was Krapcho decarboxylation of ester[3] **50** which was achieved by using LiCl in DMSO: $H_2O$ (99:1) at 150 ℃ for 4 h to give the ketone **52** in 61% yield. The $^{1}$H NMR spectrum showed the disappearance of methyl ester peak at δ 3.92 indicating the formation of the product **52. A**lso, in the $^{13}$C-NMR spectrum, signals appeared at δ 210.96 and 44.21 corresponding to ketone and $CH_2$ carbons respectively. In $^{13}$C DEPT NMR spectrum, the peak at 44.21 was seen for the newly formed $CH_2$ which indicated the formation of the product **52**. The formation of ketone **52** was confirmed by IR spectrum where in the peak of ketone group appeared at 1713 $cm^{-1}$. The structure of **52** was further confirmed by HRMS, which showed a peak at 217.1223 corresponding to the molecular formula $C_{14}H_{16}O_2$ $[M + H]^+$ of the product **52**.

## Synthesis of aldehyde 49

Then, the ketal protection of free ketone **52** was effected by using ethylene glycol, triethyl orthoformate and catalytic amount of p-toluenesulfonic acid in $CH_2Cl_2$ for 12 h at room temperature to afford the protected compound **53** in 92% yield. IR spectrum showed the

disappearance of ketone peak that exhibited a band at 1713 $cm^{-1}$ which indicated the protection of ketone functionality. The presence of multiplet at δ 4.02-4.11 (m, 4H) for ketal protons in $^{1}H$ NMR spectrum also indicated the formation of product **53.** In $^{13}C$-NMR spectrum disappearance of ketone peak at δ 210.96 and appearance of peaks at δ 65.08 and 64.72 indicated the presence of ketal $CH_2$ carbons in the product. In DEPT NMR spectrum the presence of peaks at δ 38.31 and 33.26 were seen for ketal carbons which indicated the formation of the product. The structure of **53** was further confirmed by HRMS, which showed a peak at 261.1485 corresponding to the molecular formula $C_{17}H_{22}O_2$ $[M + H]^+$ of the product.

In the next step of hydroboration-oxidation[4] of **53,** the olefin **53** was treated with $BH_3$.DMS at 0 °C to room temperature for 4 h and further treated with NaOH and $H_2O_2$ at 0 °C to room temperature for 4 h to afford the alcohol **54** in 66% yield. The formation of the compound **54** was indicated by IR spectrum wherein the peak of alcohol group appeard at 3452 $cm^{-1}$. The formation of product **54** was also confirmed by $^{1}H$ NMR spectroscopy The disappearance of alkene protons at δ 5.85-5.76 (m, 1H) and δ 5.07-4.99 (m, 2H) and appearance of additional protons in aliphatic region indicate the formation of the product. The structure of **54** was further confirmed by HRMS, which showed a peak at 279.1591 corresponding to the molecular formula $C_{16}H_{23}O_4$ $[M + H]^+$ of the product.

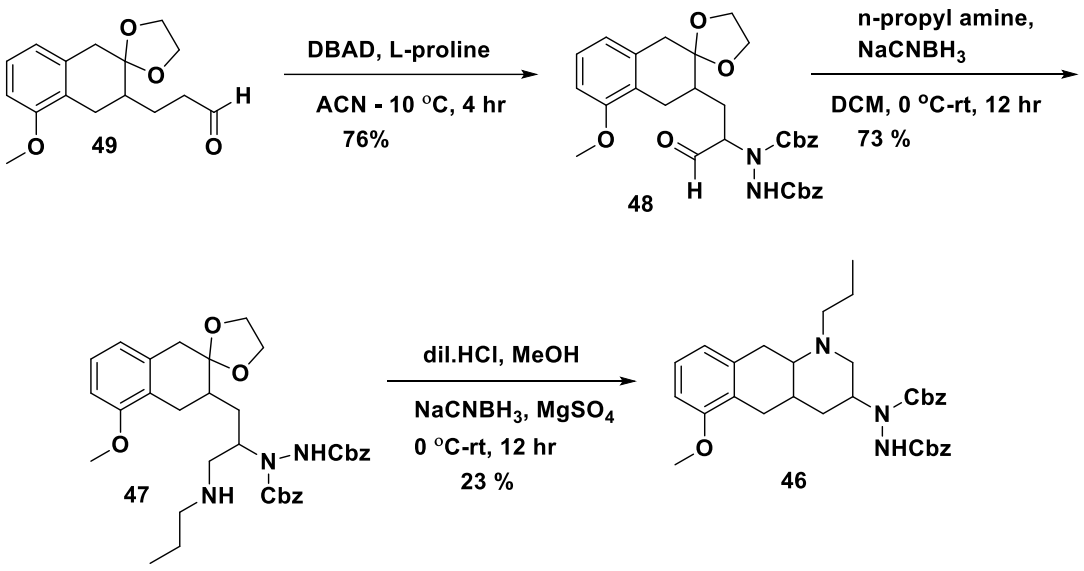



**Scheme: 9**

The next aim was the synthesis of aldehyde **49**. The alcohol **54** was treated with IBX in EtOAc at 90 °C for 4 h to give aldehyde **49** in 88% yield. In $^{1}$H-NMR spectrum of compound **49** peaks at δ 9.80 (s, 1H) corresponded to the presence of aldehyde proton indicating the formation of the product. In $^{13}$C-NMR spectrum, the signal appearing at δ 202.65 ppm corresponded to the aldehyde carbon indicating the formation of the product and it was further supported by the disappearance of alcoholic $CH_2$ carbon that appeared at δ 62.88 in the alcohol **54**. The formation of compound **49** was confirmed by IR spectrum which showed the peak for aldehyde group at 1710.10 $cm^{-1}$. The structure of **49** was further confirmed by HRMS, which showed a peak at 277.1434 corresponding to the molecular formula $C_{16}H_{21}O_4$ $[M + H]^+$ of the product.

**Synthesis of tricyclic core 46 of quinagolide**

The next aim was to install amine functionality at α position of aldehyde **49.** The aldehyde **49** was subjected to proline catalysed α-amination reaction[5] using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and L-proline as a catalyst to give α-aminated product **48** in 76% yield with 7:3 diastereomeric ratio (by NMR).

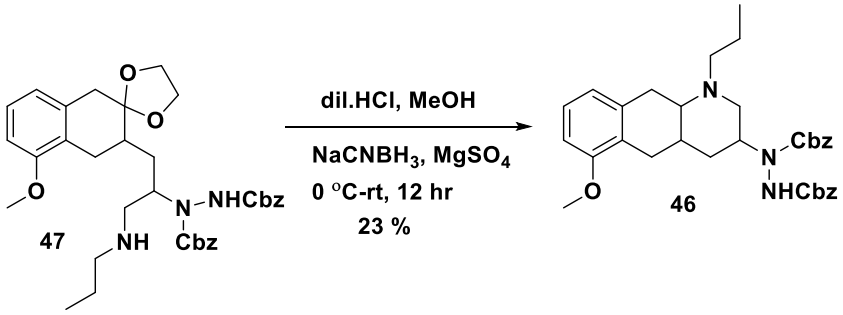



**Scheme: 10**

The structure of compound **48** was supported by $^{1}$H NMR spectrum in which peaks at δ 7.33 (bs, 10H) and δ 5.16 (s, 4H) for phenyl and benzylic $CH_2$ protons respectivelywere seen. In $^{13}$C-NMR spectrum in addition to the peaks at δ 128.50-128.08 for aromatic carbons the benzylic

$CH_2$ carbon was seen at δ 64.99 which indicated the formation of the product. The structure of **48** was further confirmed by HRMS, which showed a peak at 575.2388 corresponding to the molecular formula $C_{32}H_{35}N_2O_8$ $[M + H]^+$ of the product.

After crucial intermediate in hand, the next aim was the synthesis of the propyl amino side chain. The diastereomeric mixture of amino aldehyde **48** was subjected to reductive amination reaction. The compound **48** was treated with n-propyl amine and $NaCNBH_3$ for *in situ* imine formation to afford the amine **47** with 73 % yield. The formation of product was confirmed by $^1H$ NMR spectrum wherein disappearance of aldehyde peak that appeared at δ 9.75 (s, 1H) in **48** and the appearance of peak at δ 0.98 (t, 3H) for the terminal $CH_3$ protons which indicated the formation of the product. Further, the formation of the product was supported by $^{13}C$-spectrum which showed the disappearance of peak corresponding to aldehyde carbon. The formation of compound **47** was confirmed by the IR spectrum, which showed disappearance of peak at 1718 $cm^{-1}$ for the aldehyde functionality



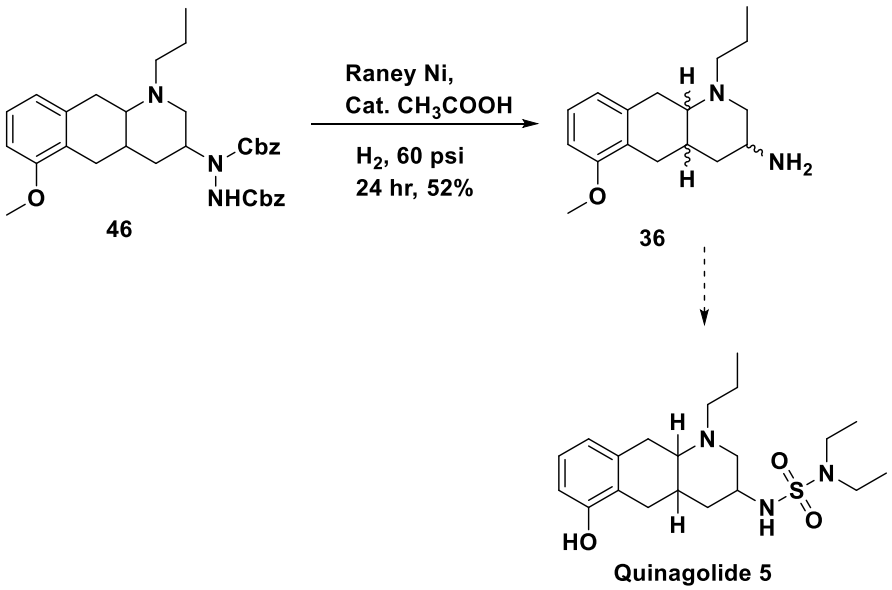

| Entry | Conditions | Formation of Product 46 | Starting Material 47 |
|---|---|---|---|
| 1 | PTSA, MeOH, $NaCNBH_3$, $MgSO_4$, 0 °C to rt, 24h | 12% | 80% |
| 2 | PTSA, toluene, reflux Dean-Stark $NaCNBH_3$, $MgSO_4$, 24 h | 17% | 70% |
| 3 | Dil. HCl, MeOH, $NaCNBH_3$, $MgSO_4$, 0 °C-rt, 24 h | 15% | 78% |
| 4 | Dil. HCl, toluene, reflux Dean Stark, $NaCNBH_3$, $MgSO_4$, 24 h | 23 % | 70% |

**Table-1**

In the next crucial step, when ketal amine **47** was subjected to ketal deorotection using catalytic amount of PTSA in methanol and sodium cyanoborohydride at 0 °C to rt to gave 12 % product.

As the yield was low the reaction was performed in toluene using the same above condition and Dean-Stark apparatus for 24 h but it resulted in only 17% product and 70 % starting material was recovered. Then in the next condition, methanol was used as a solvent and catalytic amount of HCl and $NaCNBH_3$ for 24 h rt which gave cyclic compound **46** in 15% yield. Finally, the compound **47** was treated with catalytic amount of HCl in toluene using Dean-Stark apparatus for 24 h and then the imine formed was reduced with $NaCNBH_3$ to afford the cyclic compound **46** in 23% yield. The formation of product **46** was confirmed by $^1H$ NMR wherein the multiplet for ketal protons disappeared. Further support was provided by $^{13}C$ NMR spectrum of compound **46** which showed the disappearance of peaks observed at δ 134.99 and 117.96. Further, the structure of **46** was confirmed by HRMS, which showed a peak at 558.2923 corresponding to the molecular formula $C_{33}H_{40}N_3O_5$ $[M + H]^+$ of the product.

**Completion of the synthesis of amine 36**




46 36

**Scheme: 11**

The N-N bond of compound **46** was cleaved under hydrogenation conditions using freshly prepared Raney-Ni, at 60 psi of $H_2$ for 24 h to give free amine **36.** The formation of product was confirmed by $^1H$ NMR spectroscopy. The disappearance of Cbz aromatic protons in the range of δ 7.35-7.11 as multiplet and also disappearance of benzylic $CH_2$ that appeared at δ 5.18 (s 4H) indicated the formation of amine product. At the same time, $^{13}C$-NMR spectrum showed

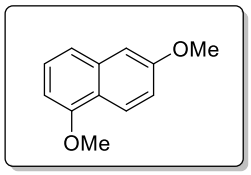
disappearance of benzylic $CH_2$ carbon and aromatic carbons that appear at δ 67.82 and 128.35 respectively in 46 which supported the formation of the product. The structure of **36** was further confirmed by HRMS, which showed a peak at 274.2045 corresponding to the formula $C_{17}H_{27}N_2O$ $[M + H]^+$ of the product. However, the close analysis of spectral data did not match with the one reported for amine **36**.

### 1.2.3 Conclusion

It is believed that the undesired epimer was synthesised by this route. Due to paucity of time due to COVID pandemic and shutdown of lab no further work to attempt the synthesis of desired amine could be carried out.

### 1.2.4 Experimental Section

**Preparation of 1,6-dimethoxynaphthalene-20**




Dimethylsulfate (43.3 ml, 468 mmol) was added to a suspension of potassium carbonate (75.5 g, 548 mmol) and 1,6-dihydroxynaphthalene (25 g, 156 mmol) in acetone (250 mL). The mixture was heated at 70 °C for 3.5 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. The reaction mixture was filtered using filter paper and washed with acetone. The solvent was evaporated under reduced pressure, and the resulting residue was redissolved in ethyl acetate. The solution was washed with a solution of sodium hydroxide (1 M) and brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (1:99) afforded pure product **20** (26.300 gm, 94% yield) as a white solid.

**Rf:** 0.6 (EtOAc–PE =2:98);

**Yield:** 94%;

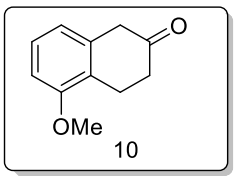
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 8.15 (d, *J* = 9.3 Hz, 1 H), 7.24 (d, *J* = 5.1 Hz, 2 H), 7.09 (dd, *J* = 2.6, 9.2 Hz, 1 H), 6.99 (d, *J* = 2.5 Hz, 1 H), 6.54 - 6.49 (m, 1 H), 3.77 (s, 3 H), 3.71 (s, 3 H);

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 158.0, 155.5, 135.8, 126.5, 123.6, 120.6, 119.1, 117.3, 105.5, 101.8, 55.0, 54.8;

**IR ($CHCl_3$):** $\nu_{max}$ 1473.72, 1345.08, 1172.78 $cm^{-1}$;

**HRMS (ESI):** $[M + H]^+$: 188.0837.

**Preparation of 5-methoxy-3,4-dihydronaphthalen-2(*1H*)-one 10**




Sodium (6.104 gm, 265 mmol, 10 equiv) was added portionwise to a solution of 1,6-dimethoxynaphthalene (5 gm, 265 mmol, 1 equiv) in ethanol (50 mL), and the mixture was then stirred at 80 °C for 2.5 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. Further, the reaction mixture was cooled at 0°C and acidified very carefully with concentrated hydrochloric acid to pH = 1, heated at 80 °C for 30 min, and stirred at room temperature overnight. The solution was diluted with water (230 mL) and extracted with $CH_2Cl_2$ (3X50 ml). The organic phase was washed with brine and dried over sodium sulfate and filtered. Evaporation of the solvent *in vacuo* and purification of the resulting residue by flash column chromatography [EtOAc: pentane = 0:100−10:90, Rf = 0.5 (EtOAc: pentane 1:99)] gave pure product (3.2 g, yield 68%) as a yellow oil.

**Rf:** 0.7 (EtOAc–PE =1:99).

**Yield:** 68%.

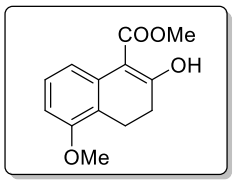
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.22 (t, *J*=7.94 Hz, 1H), 6.77 (d, *J*=7.88 Hz, 1H), 6.82 (d, *J*=8.25 Hz, 1H), 3.89 (s, 3H), 3.61 (s, 2H), 3.13 (t, *J*=6.75 Hz, 2H), 2.56 (t, J=6.75 Hz, 2H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 210.96, 156.38, 134.96, 127.48, 124.97, 120.42, 108.43, 55.43, 44.66, 37.86, 20.90.

**IR ($CHCl_3$):** $\nu_{max}$ 3008.85, 2958.80, 2903.37, 1718.49, 1473.49, 1311.47, 1195.64 $cm^{-1}$

**HRMS (ESI)** m/z calcd for $C_{11}H_{13}O_2$ $[M + H]^+$: 177.0910, found: 177.0907.

**Preparation of methyl 2-hydroxy-5-methoxy-3,4-dihydronaphthalene-1-carboxylate 51**




To a mixture of NaH (7.5 gm, 312 mmol, 5 equiv) in dimethyl carbonate (112.5 mL , 1250 mmol, 20 equiv) was added dropwise β-tetralone **10** (11 gm, 62.5 mmol, 1 equiv) at 0 °C under nitrogen at room temperature. The mixture was refluxed until disappearance of the starting material on TLC. After completion of reaction, the reaction mixture was cooled to 0 °C and quenched with saturated aq $NH_4Cl$. The aqueous layer was extracted with ethyl acetate, the organic phase was

washed with brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (1:99) afforded pure product (13.500 gm, 92% yield).

**Rf:** 0.6 EA:PE (3:97)

**Yield:** 92%.

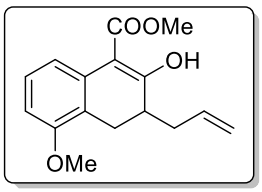
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 13.36 (s, 1 H), 7.39 - 7.34 (m, 1 H), 7.18 (t, *J* = 8.13 Hz, 1 H), 6.76 - 6.71 (d, 1 H), 3.93 (s, 3 H), 3.85 (s, 3 H), 2.88 (t, 2 H), 2.52 (t 2 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 178.6, 172.4, 155.6, 132.6, 126.4, 121.3, 118.7, 107.6, 99.7, 55.4, 51.6, 28.9, 19.2.

**IR ($CHCl_3$):** $\nu_{max}$ 3409.86, 3016.83, 2955.23,1740, 1337.81, 1315.30 $cm^{-1}$.

**HRMS (ESI):** m/z calcd for $C_{13}H_{15}O_4$ $[M + H]^+$: 235.0965, found: 235.0963.

**Preparation of methyl 3-allyl-2-hydroxy-5-methoxy-3,4-dihydronaphthalene-1-carboxylate 50**




A solution of diisopropylamine 4.869 mL (16.4 mmol, 2.1 equiv) in 30 mL of THF at -50 °C was treated with 1.6 M n-butyl lithium (in hexane), 21.601 mL (34.5 mmol, 2.1 equiv) stirred at -50 °C for 15 min and then at 0 °C for 15 min, and then at -50 °C treated dropwise with 4 g (16.4 mmol) of ß-keto ester **51** in 70 mL of THF. The resulting yellow suspension was stirred for 1 h at 0 °C and then treated with allyl bromide 1.422 mL (16.4 mmol, 1 equiv) in 20 mL of THF. The resulting orange solution was stirred for 1 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to 0 °C, quenched with 30 mL of 1 M aqueous hydrochloric acid, and after quenching of reaction; THF was removed on rotavapour and extracted with ethyl acetate. The organic phase was washed with brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (1:99) afforded pure product **50** (4. gm., 87% yield).

**Rf:** 0.6 (EtOAc–PE =2:98).

**Yield:** 87%.

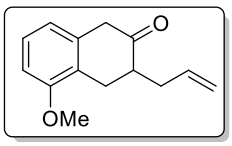
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.34 (d, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 8.1 Hz, 1 H), 6.73 (d, *J* = 8.1 Hz, 1 H), 5.81 (dt, *J* = 7.2, 17.1 Hz, 1 H), 5.09 - 4.93 (m, 2 H), 3.92 (s, 3 H), 3.83 (s, 3 H), 2.95 (dd, *J* = 5.9, 15.9 Hz, 1 H), 2.78 (dd, *J* = 5.9, 15.9 Hz, 1 H), 2.61 - 2.55 (m, 1 H), 2.39 - 2.31 (m, 1 H), 2.13 - 2.03 (m, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 180.5, 172.7, 156.4, 135.6, 132.1, 126.5, 119.9, 118.6, 117.1, 107.9, 99.3, 55.6, 51.7, 38.6, 33.8, 23.9.

**IR ($CHCl_3$):** $\nu_{max}$3410, 3020, 2935, 1473, 1215, 1043, 1739, 1595 $cm^{-1}$.

**HRMS (ESI)** m/z calcd for $C_{16}H_{19}O_4$ $[M + H]^+$: 275.1278, found: 275.1273.

**Preparation of 3-allyl-5-methoxy-3,4-dihydronaphthalen-2(1*H*)-one 52**




A solution of 4 g of ß-keto ester **50** (14.59 mmol) anhydrous lithium chloride (0.612 gm) and 2 ml of water in 38 ml of $Me_2SO$ was heated for 4 h at 150 °C. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool at room temperature. The reaction mixture was extracted with ice cold water and brine, the organic layer was dried ($Na_2SO_4$) and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (2:98) afforded ketone **52** as a pure product (2.33 gm, 74 % yield) as a yellow oil.

**Rf:** 0.6 (EtOAc–PE =2:98).

**Yield:** 74 %.

**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.17 (t, *J* = 7.9 Hz, 1 H), 6.80 - 6.67 (m, 2 H), 5.90 - 5.72 (m, 1 H), 5.16 - 4.99 (m, 2 H), 3.84 (s, 3 H), 3.68 - 3.58 (m, 1 H), 3.58 - 3.49 (m, 1 H), 3.36 (dd, *J* = 5.8, 16.0 Hz, 1 H), 2.67 - 2.56 (m, 2 H), 2.50 (ddd, *J* = 5.4, 7.7, 10.6 Hz, 1 H), 2.27 - 2.13 (m, 1 H).

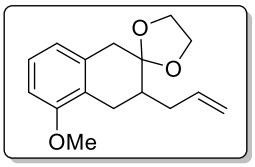
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 211.0, 156.4, 135.5, 134.8, 127.4, 124.2, 120.1, 116.9, 108.2, 55.3, 46.6, 44.2, 33.9, 26.6.

**IR ($CHCl_3$):** $\nu_{max}$ 3078, 3019, 2936, 1713. 1473, 1440, 1215 $cm^{-1}$.

**HRMS (ESI):** m/z calcd for $C_{14}H_{17}O_2$ $[M + H]^+$: 217.1223, found: 217.1222.

**Preparation of 3-allyl-5-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,2'-[1,3]dioxolane] 53**

Triethylorthoformate (16.77 mL, 101 mmol, 4 equiv) was added dropwise to the solution of ketone **52** (5.5 g , 25.4 mmol, 1 equiv) and 50 mL of $CH_2Cl_2$, then p-toluenesulfonic acid monohydrate (148 mg, 101 mmol, 0.1 eq), and ethylene glycol (25.83 mL, 458 mmol, 18 equiv)



were added the reaction mixture was stirred at 25 °C for 22 h. The progress of the reaction was monitored by TLC. After completion of reaction the reaction mixture was extracted with methylene chloride (3X50) mL. The organic layer was washed with brine and dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (2:98) afforded pure product alkene **53**, 6.600 gm as (93 % yield) as a yellow oil.

**Rf:** 0.6. EA:PE (5:95)

**Yield:** 93 %.

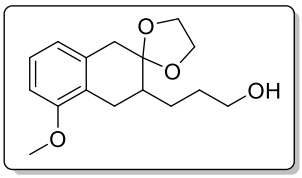
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.13 (t, *J* = 7.9 Hz, 1 H), 6.69 (dd, *J* = 1.8, 7.9 Hz, 2 H), 5.99 - 5.84 (m, 1 H), 5.15 - 5.04 (m, 2 H), 4.14 - 3.94 (m, 4 H), 3.83 (s, 3 H), 3.11 - 2.87 (m, 3 H), 2.69 - 2.53 (m, 2 H), 2.17 - 2.06 (m, 1 H), 2.03 - 1.92 (m, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 157.3, 137.2, 135.6, 126.4, 123.8, 121.0, 115.8, 109.5, 107.3, 65.1, 64.7, 55.1, 40.5, 38.3, 33.3, 27.4.

**IR ($CHCl_3$):** $\nu_{max}$ 3410.60, 2930.28, 2334.95, 1639.781471.51, 1256. 90 $cm^{-1}$

**HRMS (ESI):** m/z calcd for $C_{16}H_{21}O_3$ $[M + H]^+$: 261.1485, found: 261.1479.

**Preparation of 3-(5-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,2'-[1,3]dioxolan]-3-yl)propan-1-ol 54**



Borane dimethylsulfide (BMS 1.70 mL, 19 mmol, 1.1 equiv) was added dropwise at 0 °C to the solution of alkene **53** (4.5 gm, 17.3 mmol, 1 equiv) in 40 mL of THF. The reaction mixture was then stirred at 0 °C for 1 h and then 3N NaOH solution (0.760 gm, 19 mmol, 1.2 equiv) was added, followed by dropwise addition of 30% $H_2O_2$ (2.35 mL, 69 mmol, 4 equiv). The solution was stirred for 12 h at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the THF solvent was removed under reduced pressure and the reaction mixture was diluted with ethyl acetate (3X50 mL), washed with brine and dried over $Na_2SO_4$, and the solvents were evaporated. Purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (25:75) afforded pure product **54** (3.2 gm, 66 %yield).

**Rf:** 0.4**.** EA: PE (30:70)

**Yield:** 66 %.

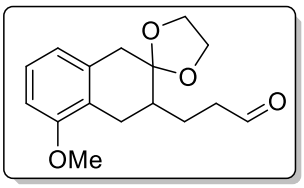
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.10 (t, *J* = 7.9 Hz, 1 H), 6.66 (dd, *J* = 4.6, 7.8 Hz, 2 H), 4.08 - 4.04 (m, 1 H), 4.02 (d, *J* = 1.1 Hz, 1 H), 4.00 - 3.98 (m, 2 H), 3.81 (s, 3 H), 3.64 (t, *J* = 6.3 Hz, 2 H), 3.09 - 2.99 (m, 1 H), 2.97 (s, 2 H), 2.91 (s, 1 H), 2.61 (dd, *J* = 8.4, 17.5 Hz, 1 H), 2.03 - 1.94 (m, 1 H), 1.80 (d, *J* = 8.4 Hz, 2 H), 1.64 - 1.52 (m, 1 H), 1.28 - 1.18 (m, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 157.2, 135.6, 126.4, 123.6, 121.0, 109.8, 107.2, 65.0, 64.6, 62.9, 55.1, 42.5, 40.2, 38.0, 30.5, 27.6, 24.7.

**IR ($CHCl_3$):** $\nu_{max}$ 3410.60, 2930.28, 1473.57, 1114.49 $cm^{-1}$

**HRMS (ESI)** m/z calcd for $C_{16}H_{23}O_4$ $[M + H]^+$: 279.1586, found: 279.159.

**Preparation of 3-(5-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,2'-[1,3]dioxolan]-3-yl)propanal 49**




Aldehyde (2 gm, 0.7.4 mmol, 1 equiv) was dissolved in 20 mL of ethyl acetate and IBX (4.028 gm, 14.49 mmol, 2 equiv) was added. The reaction mixture was then stirred at 90 °C for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered over celite, the filtrate was extracted with ethyl acetate, the organic phase was washed with brine and dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (1:99) afforded pure product aldehyde **49** (1.68 mg, 84% yield) as an orange liquid.

**Rf:** 0.5 (EA: PE) 20:80

**Yield:** 84 %.

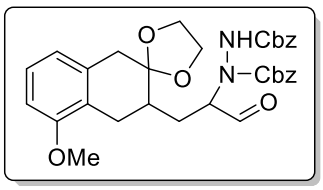
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 9.80 (s, 1 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 6.67 (dd, *J* = 5.0, 8.0 Hz, 2 H), 4.11 - 3.94 (m, 4 H), 3.81 (s, 3 H), 3.08 - 2.94 (m, 2 H), 2.94 - 2.84 (m, 1 H), 2.72 - 2.46 (m, 3 H), 2.16 - 2.06 (m, 1 H), 2.04 - 1.96 (m, 1 H), 1.53 (tdd, *J* = 4.6, 9.3, 13.6 Hz, 1 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 202.6, 157.1, 135.5, 126.6, 123.2, 121.1, 109.5, 107.2, 65.0, 64.7, 55.1, 42.1, 39.9, 38.1, 27.7, 21.2.

**IR ($CHCl_3$):** $\nu_{max}$ 3020, 2935, 1730, 1438 $cm^{-1}$

**HRMS (ESI):** m/z calcd for $C_{16}H_{21}O_4$ $[M + H]^+$: 277.1434, found: 277.1431.

**Dibenzyl 1-(1-(5-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,2'-[1,3]dioxolan]-3-yl)-3-oxopropan-2-yl)hydrazine-1,2-dicarboxylate 48**




To a cooled solution of dibenzyl azodicarboxylate (DBAD) (1.71 gm, 5.75 mmol, 1 equiv) and L-proline (0.066 gm, 0.575 mmole, 0.1 equiv) in $CH_3CN$ (20 mL) at 0 °C was added above aldehyde (1.6 gm, 5.75 mmol, 1 equiv) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C. The progress of the reaction was monitored by TLC. After completion of reaction the ACN solvent was removed under reduced pressure and then reaction mixture was diluted with ethyl acetate and extracted with DCM (53X50 mL), washed with brine and dried over $Na_2SO_4$, filtered and the solvents were evaporated. Purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) afforded diastereomeric mixture of **48** (2.60 gm, 78 % yield) as a white solid.

**Rf:** 0.6. EA: PE (30:70)

**Yield:** 78.

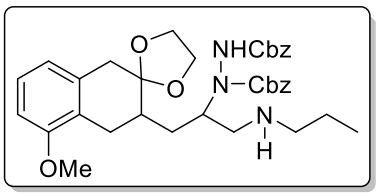
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 9.75 (s, 1 H), 9.69 (s, 1 H), 7.33 (s, 14 H), 7.15 - 7.09 (m, 2 H), 6.70 - 6.63 (m, 3 H), 5.25 (br. s., 1 H), 5.23 - 5.07 (m, 6 H), 4.03 (s., 2 H), 3.94 (s., 3 H), 3.79 (s, 3 H), 3.10 - 2.95 (m, 2 H), 2.95 - 2.81 (m, 2 H), 2.71 - 2.52 (m, 2 H), 2.34 - 2.20 (m, 1 H), 2.12 - 2.01 (m, 1 H), 1.86 - 1.71 (m, 1 H), 1.58 (t, *J* = 10.2 Hz, 1 H).

**$^{13}$C NMR ($CDCl_3$, 101 MHz):** δ 199.94, 157.3, 157.0, 156.4, 156.1, 156.0, 135.5, 135.4, 128.50, 128.47, 128.35, 128.14, 128.0, 127.73, 126.60, 126.60, 122.98, 121.06, 120.98, 109.83, 109.49, 107.32, 64.99, 64.59, 55.11. 37.8, 37.7, 36.3, 29.3, 28.0, 27.8, 26.6, 25. 9, 25. 5, 24. 9, 18. 3.

**IR ($CHCl_3$)**: $\nu_{max}$ 3831, 3719, 3476, 3282, 1719, 1463, 1220. $cm^{-1}$

**HRMS (ESI)** m/z calcd for $C_{32}H_{35}N_2O_8$ $[M + H]^+$: 575.2388, found: 575.2381.

**Dibenzyl 1-(1-(5-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,2'-[1,3]dioxolan]-3-yl)-3-(propylamino)propan-2-yl)hydrazine-1,2-dicarboxylate 47**




Amino aldehyde 48 (1.8 gm, 31.3 mmol, 1 equiv) was dissolved in 20 mL of methanol, then propylamine (0.765 mL, 94 mmol, 3 equiv) was added and the reaction mixture was then stirred at RT and to it was then 5 gm of $MgSO_4$ was added and stirred it for 5 min and then add sodium cyanoborohydride (0.600 gm, 1.5 equiv) was added to the reaction mixture and the reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent methanol was removed on rotavopor and the residue was diluted with ethyl acetate. The organic phase was

washed with brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (40:60) afforded diastereomeric mixture of **48** (1.52 gm, 78 % yield) as a sticky white liquid.

**Rf:** 0.6 EA:PE (40:60)

**Yield:** 78 %.

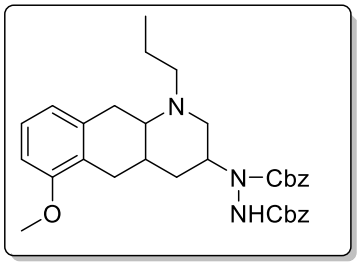
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.38 (s, 10 H), 7.12 (t, *J* = 7.9 Hz, 2 H), 6.72 - 6.56 (m, 3 H), 5.28 - 5.13 (m, 4 H), 4.02 (d, *J* = 18.1 Hz, 3 H), 3.94 (s, 2 H), 3.81 (s, 3 H), 2.91 (s, 6 H), 2.77 - 2.49 (m, 4 H), 1.68 (d, *J* = 7.3 Hz, 4 H), 1.26 (s, 2 H), 0.98 (t, *J* = 6.9 Hz, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 157.2, 156.7, 134.8, 134.6, 128.9, 128.7, 128.6, 128.3, 128.2, 128.0, 126.9, 121.0, 109.5, 109.3, 107.5, 69.4, 65.0, 64.6, 55.2, 37.7, 37.3, 37.0, 36.8, 29.3, 19.7, 10.8.

**IR ($CHCl_3$):** $\nu_{max}$ 3778.01, 3638.41, 3380.69, 1708.9914.61.98

**HRMS (ESI):** m/z calcd for $C_{35}H_{44}N_3O_7$ $[M + H]^+$: 618.3174, found: 618.3162

**Dibenzyl 1-(6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-3-yl)hydrazine-1,2-dicarboxylate 46**




Amine **47** (0.800 gm, 1.29 mmole, 1 equiv) was dissolved in 10 mL of methanol and l the reaction mixture was cooled to 0 ℃ then add a catalytic amount of dil. HCl was added to it followed by sodium cyanoborohydride (0.243 gm, 3.88 mmol, 3 equiv) and stirred it at RT and then $MgSO_4$ (4 gm) of was added and the reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled at 0 ℃ and quenched with saturated $Na_2CO_3$ solution then solvent methanol was removed on rotavopour and the residue was diluted with ethyl acetate and the organic phase was washed with brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* to afford crude cyclic amine. purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded diastereomeric mixture of **46** (0.240 gm, 33 % yield) as a sticky white liquid.

**Rf:** 0.6. EA: PE (30:70)

**Yield:** 33%.

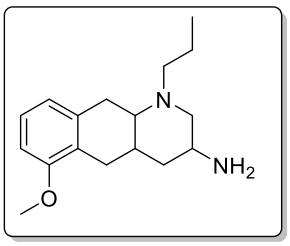
**$^1$H NMR ($CDCl_3$, 500 MHz):** δ 7.35 (s, 10 H), 7.11 (t, *J* = 7.8 Hz, 1 H), 6.74 (d, *J* = 7.6 Hz, 1 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 5.18 ( s, 4 H), 4.36 (s, 1 H), 3.82 (s, 3 H), 3.14 (d, *J* = 15.3 Hz, 1 H), 2.97 (d, *J* = 16.4 Hz, 1 H), 2.80 - 2.70 (m, 1 H), 2.68 - 2.57 (m, 1 H), 2.51 (s, 1 H), 2.30 (t, *J* = 9.9 Hz, 1 H), 2.25 - 2.08 (m, 3 H), 1.74 (s, 1 H), 1.49 ( s, 1 H), 1.39 (q, *J* = 11.7 Hz, 1 H), 0.89 (t, *J* = 6.9 Hz, 3 H).

**$^{13}$C NMR ($CDCl_3$, 126 MHz)** δ 156.8, 156.7, 136.4, 135.8, 135.5, 128.5, 128.5, 128.4, 128.2, 128.0, 126.2, 124.3, 121.2, 106.9, 67.8, 59.9, 55.2, 54.8, 36.5, 35.1, 34.7, 30.7, 17.6, 11.9.

**IR ($CHCl_3$):** $\nu_{max}$ 3666.64, 3481.92, 3275.05, 3198.40, 3116.04, 2930.18, 1714.05. $cm^{-1}$

**HRMS (ESI) HRMS (ESI)** m/z calcd for $C_{33}H_{40}N_3O_5$ $[M + H]^+$ 558.2962, found:558.2953

**6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-3-amine36**




The solution of Dibenzyl 1-(6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-3-yl)hydrazine-1,2-dicarboxylate **46** (0.26 g, 0.377 mmol, 1 equiv) in MeOH (10 mL) and acetic acid (8 drops) was treated with Raney-Nickel (0.6 g, excess), in $H_2$ (60 psi) atmosphere for 12 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered over celite and cooled to 0 °C and quenched with sat. $NaHCO_3$ solution. Methanol was removed on rotavapor under reduced pressure and residue was extracted with $CH_2Cl_2$ and washed with brine. The organic layer was dried over anhydrous $Na_2SO_4$ and filtered and concentrated to give crude amine. Purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc-MeOH (98:2) afforded diastereomeric mixture of **36** in 52 % yields as a yellow liquid.

**Rf:** 0.4. (40:60 MeOH: DCM)

**Yield:** 52.

**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 7.10 (t, *J* = 7.9 Hz, 1 H), 6.71 (d, *J* = 7.6 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 5.06 - 4.96 (m, 2 H), 3.78 (s, 3 H), 3.40 (t, *J* = 10.9 Hz, 2 H), 3.15 (dd, *J* = 4.8, 16.0 Hz, 1 H), 3.01 (dd, *J* = 4.8, 17.4 Hz, 1 H), 2.93 - 2.66 (m, 3 H), 2.49 - 2.38 (m, 2 H), 2.35 - 2.18 (m, 2 H), 1.87 (br s, 1 H), 1.65 - 1.52 (m, 2 H), 1.38 - 1.18 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

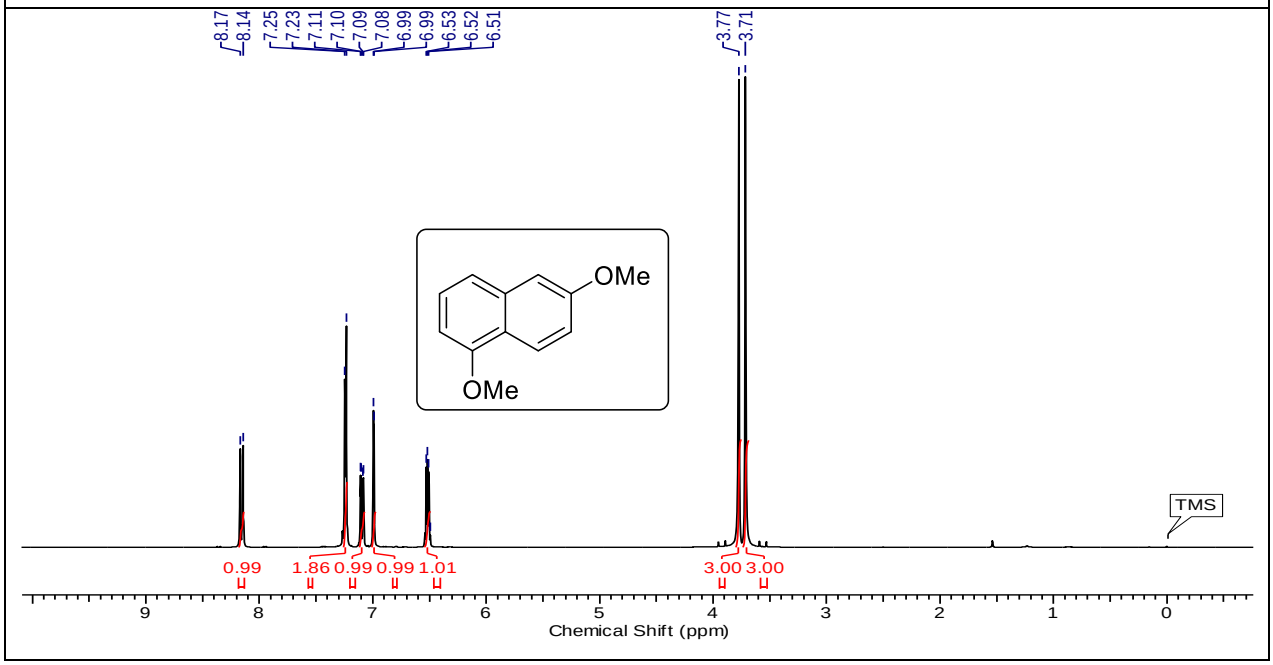
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 156.7, 135.3, 128.8, 128.7, 126.5, 123.8, 121.1, 107.2, 60.3, 55.2, 54.6, 47.1, 35.7, 33.7, 30.4, 17.0, 11.7.

**IR ($CHCl_3$)** $\nu_{max}$ 3558, 3463, 3369, 2949 $cm^{-1}$

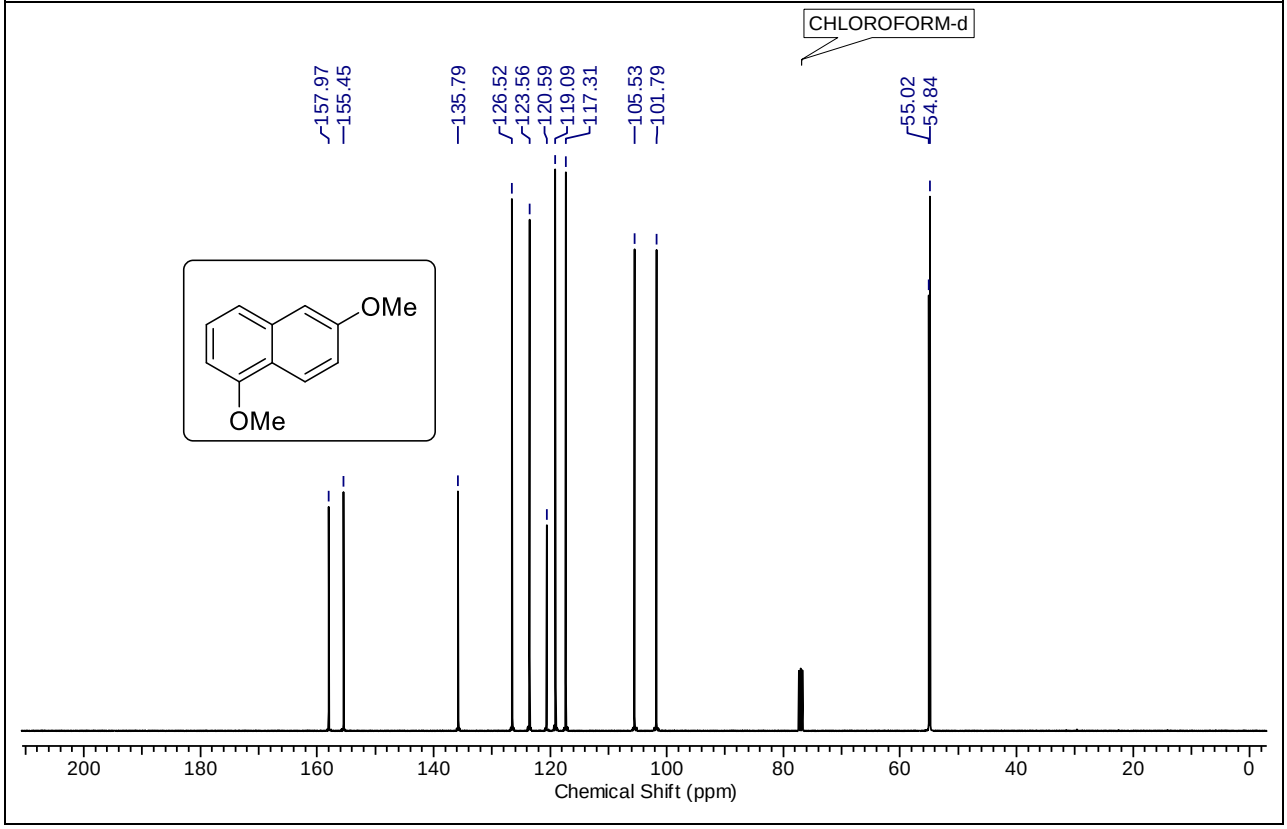
**HRMS (ESI) HRMS (ESI)** m/z calcd for $C_{17}H_{27}N_2O$ $[M + H]^{+\cdot}$, 275. 2045 found: 275.2049

## 1.2.5 Spectral Data

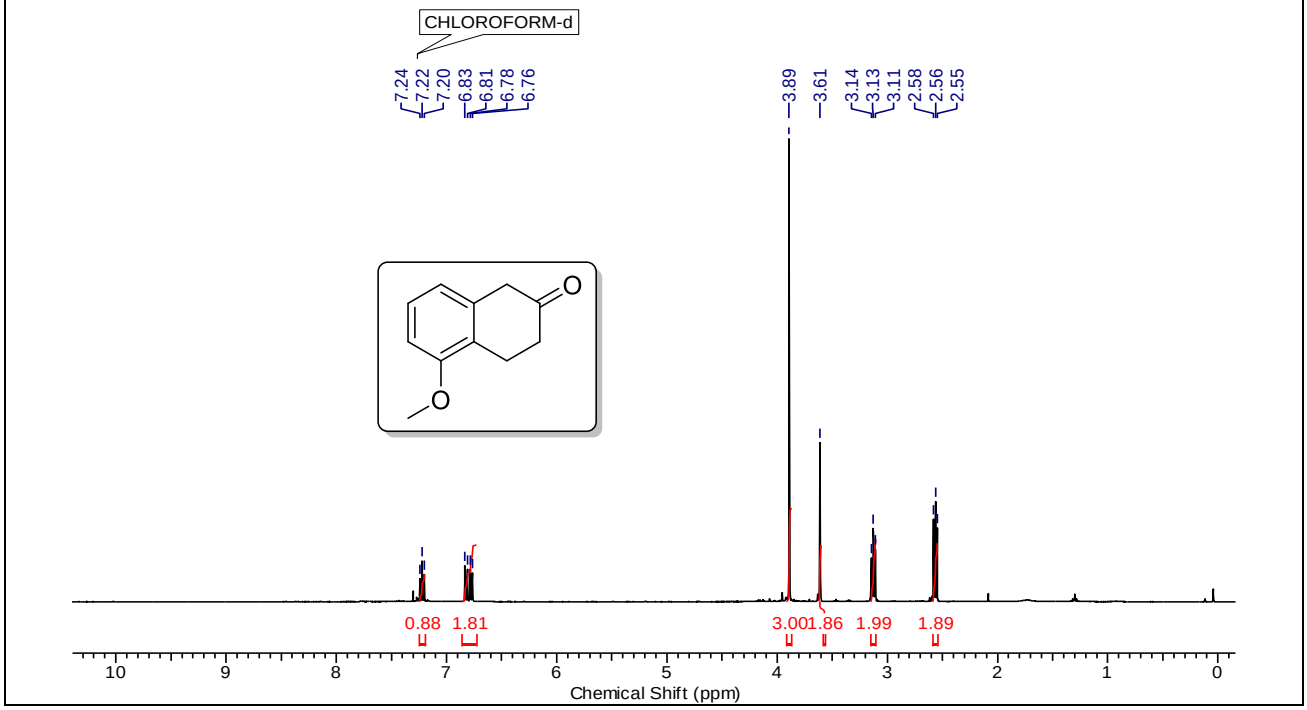
**$^{1}$H-NMR spectrum of compound 20 ($CDCl_3$, 400 MHz)**



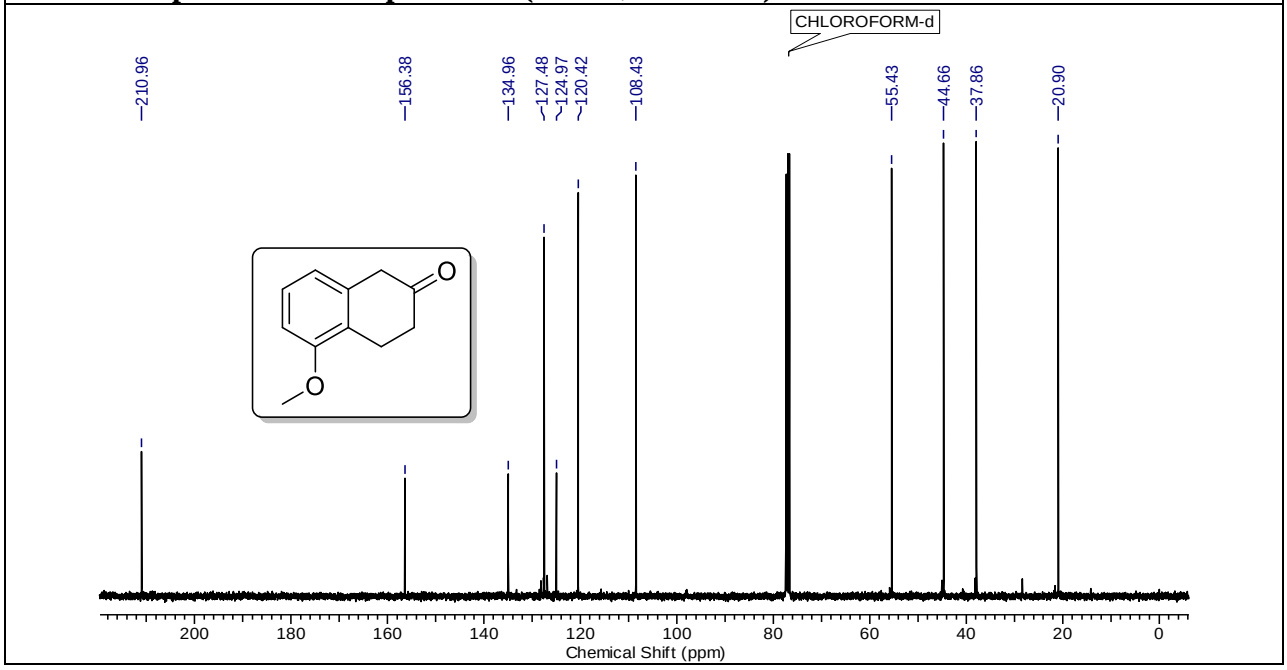

**$^{13}$C-NMR spectrum of compound 20 ($CDCl_3$, 100 MHz)**



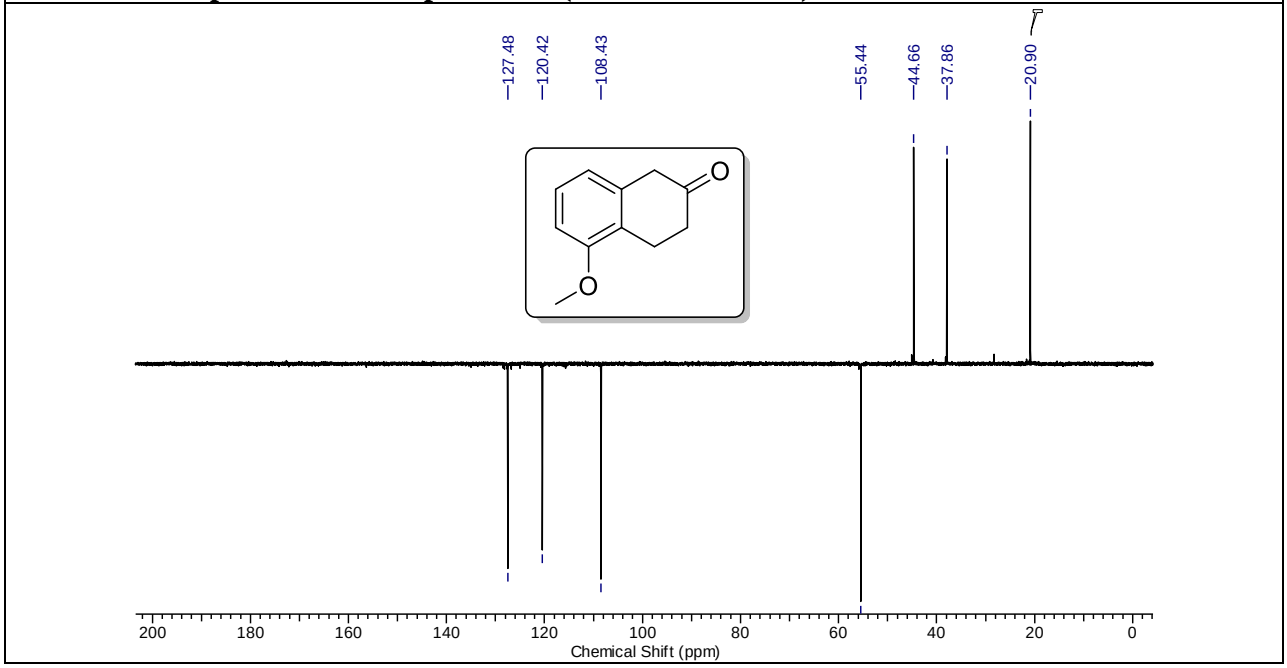
## 1H-NMR spectrum of compound 10 ($CDCl_3$, 400 MHz)



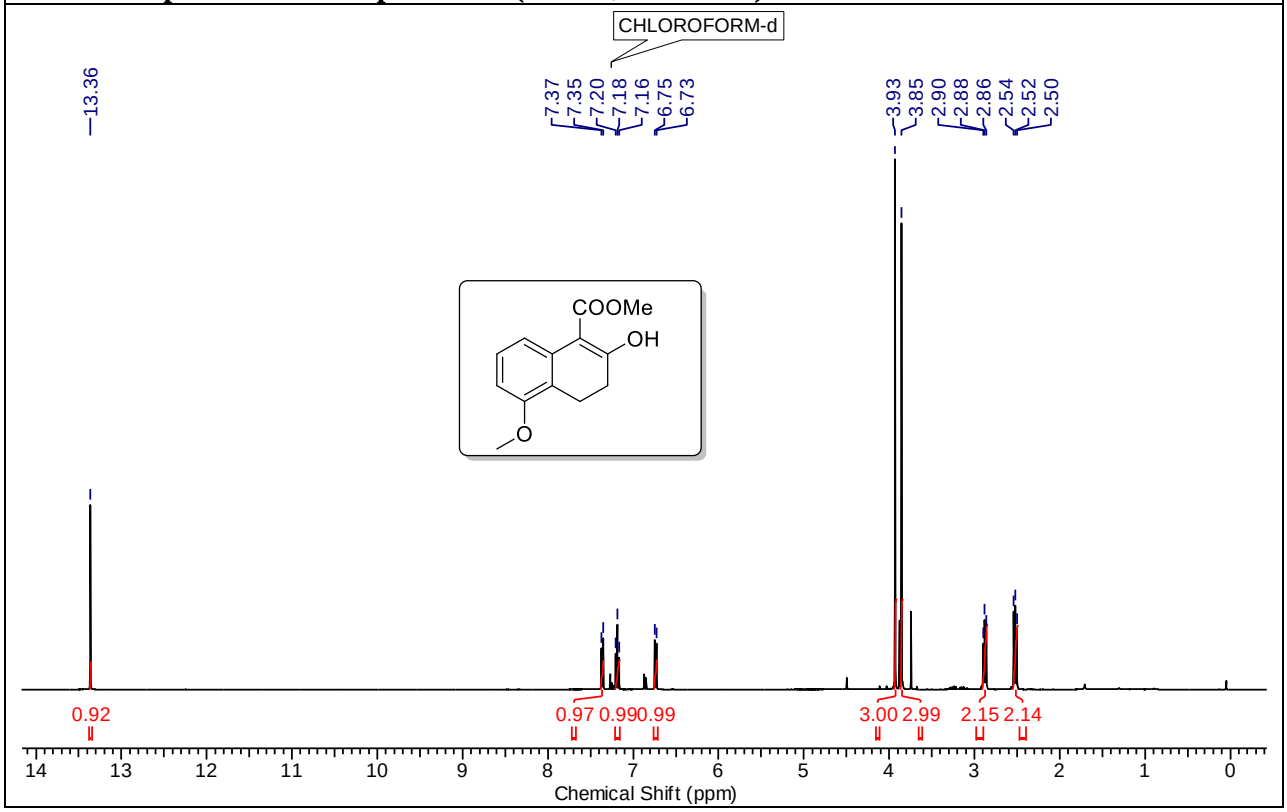

## $^{13}C$-NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



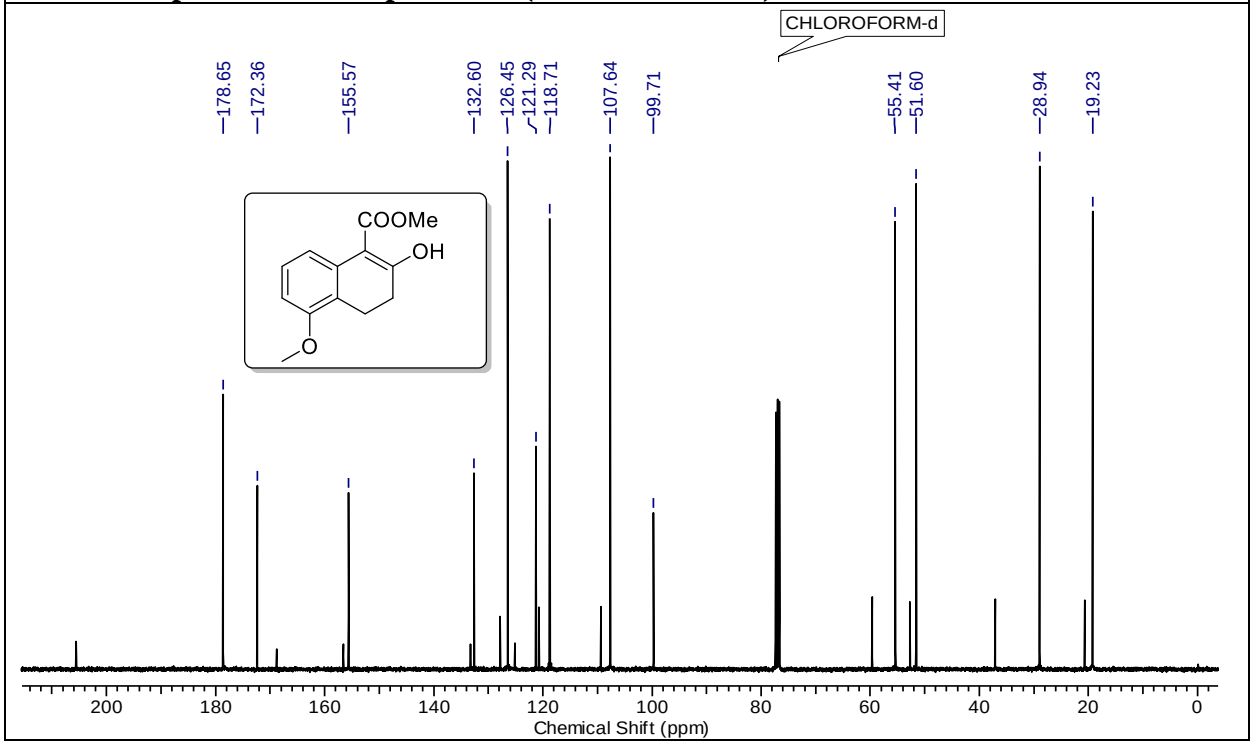
**DEPT NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)**



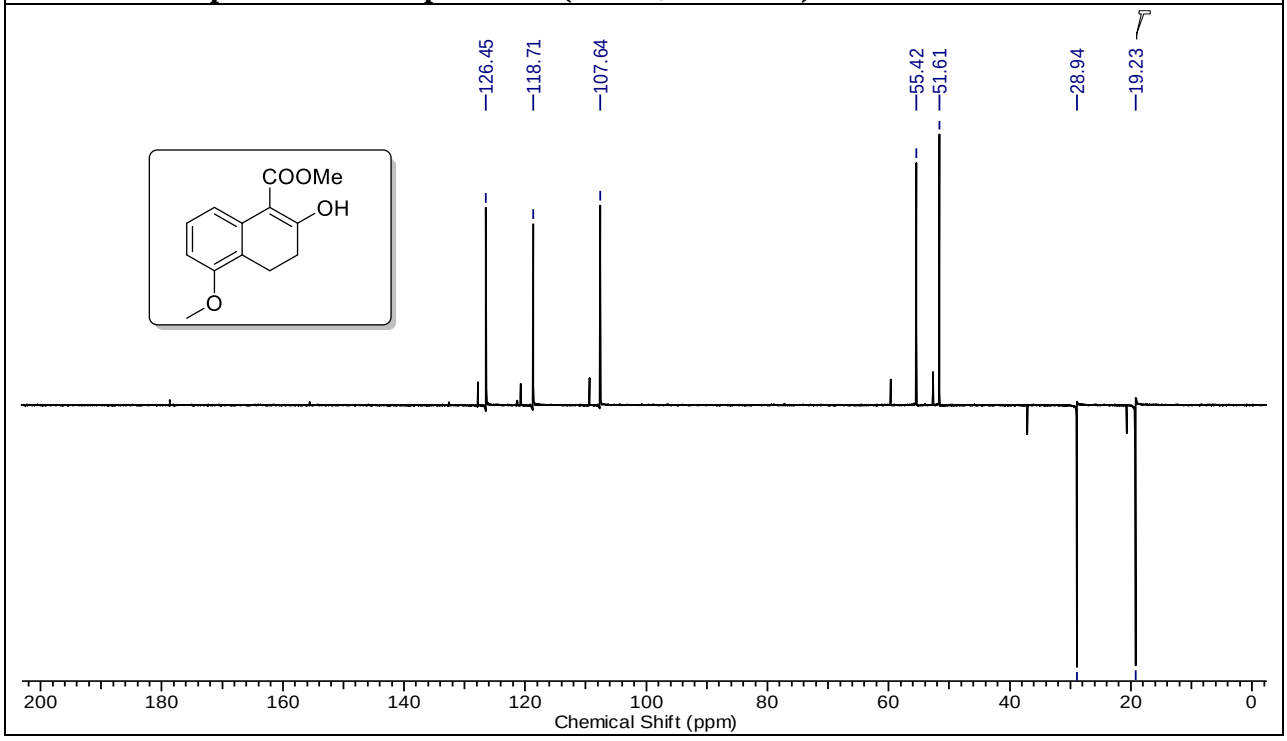

**$^1$H-NMR spectrum of compound 51 ($CDCl_3$, 400 MHz)**



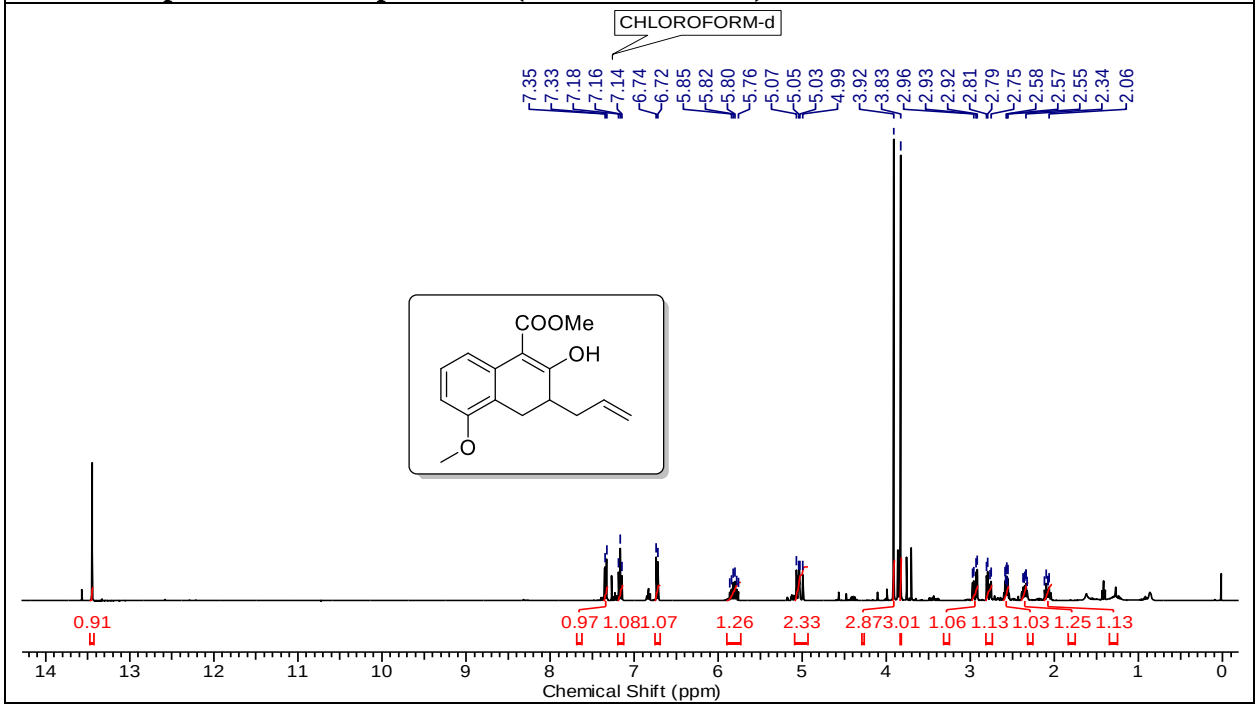
**$^{13}$C-NMR spectrum of compound 51 ($CDCl_3$, 100 MHz)**



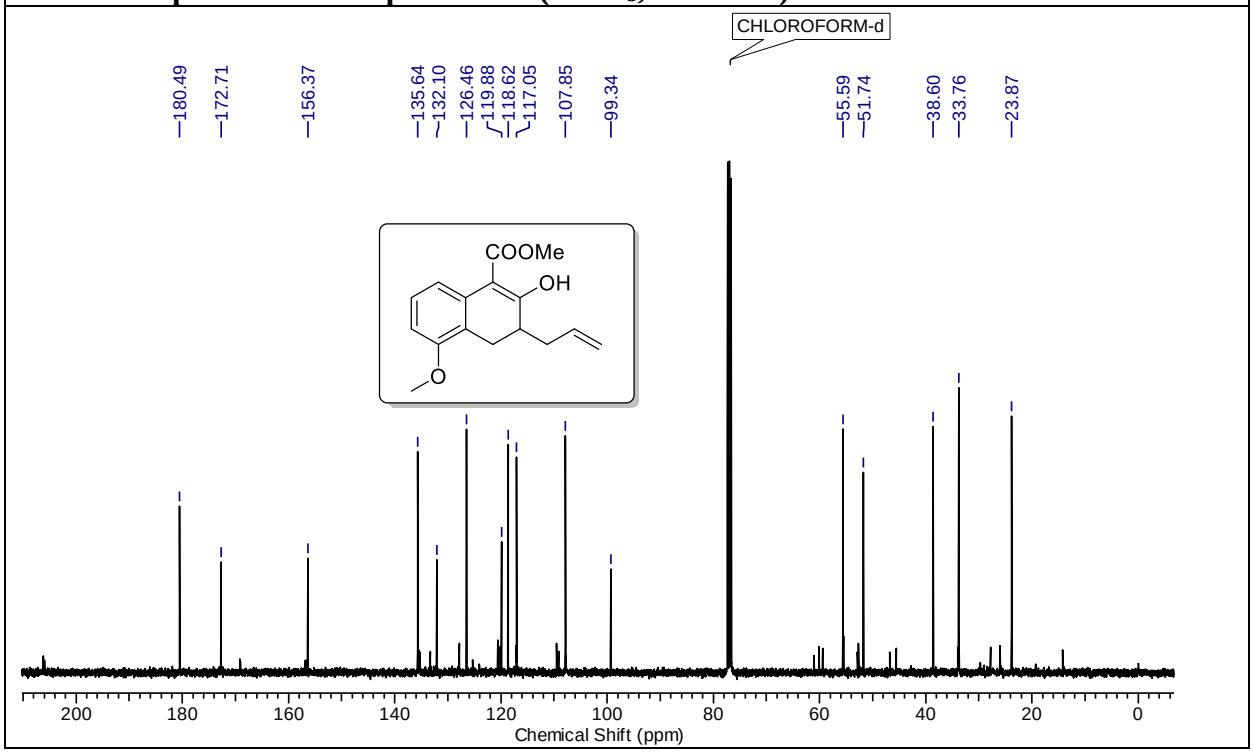

**DEPT NMR spectrum of compound 51 ($CDCl_3$, 100 MHz)**



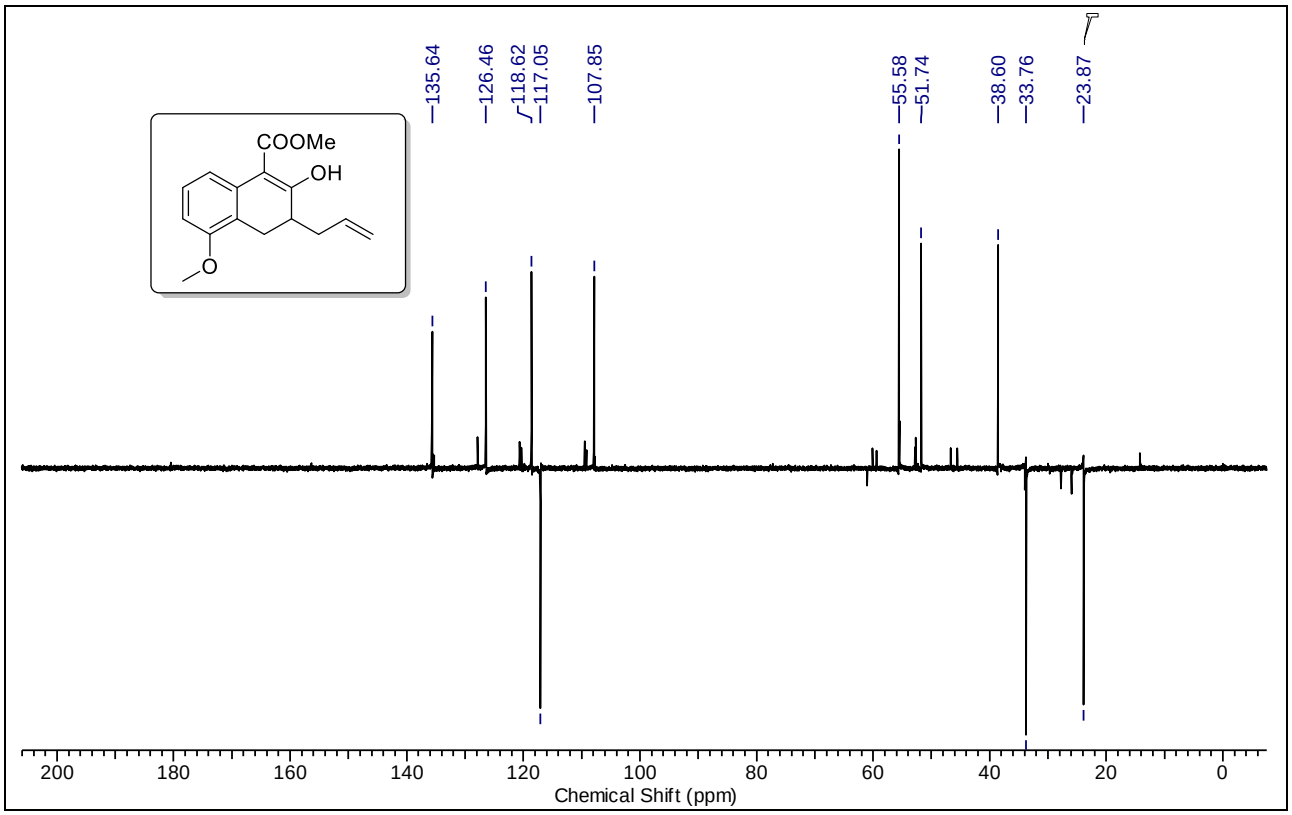
**$^{1}$H-NMR spectrum of compound 50 ($CDCl_3$, 400 MHz)**



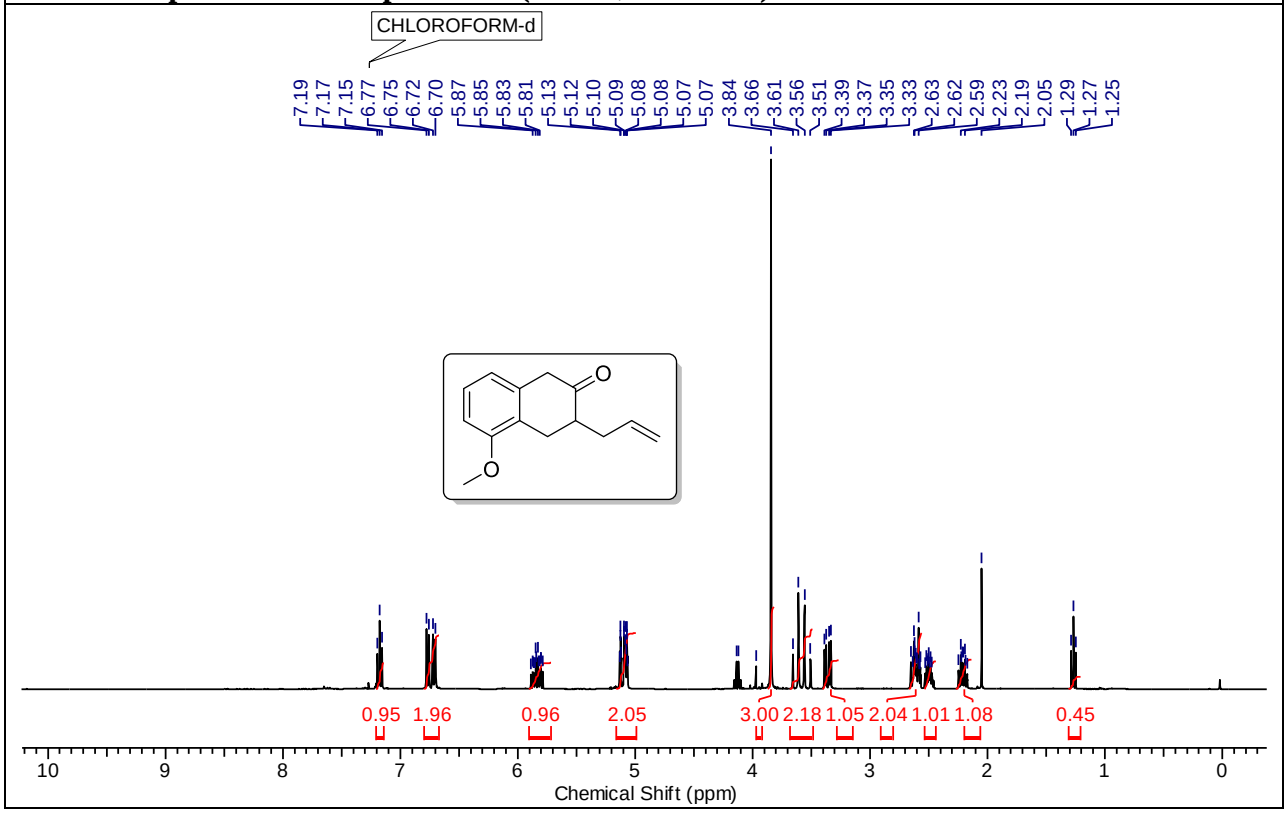

**$^{13}$C-NMR spectrum of compound 50 ($CDCl_3$, 100 MHz)**



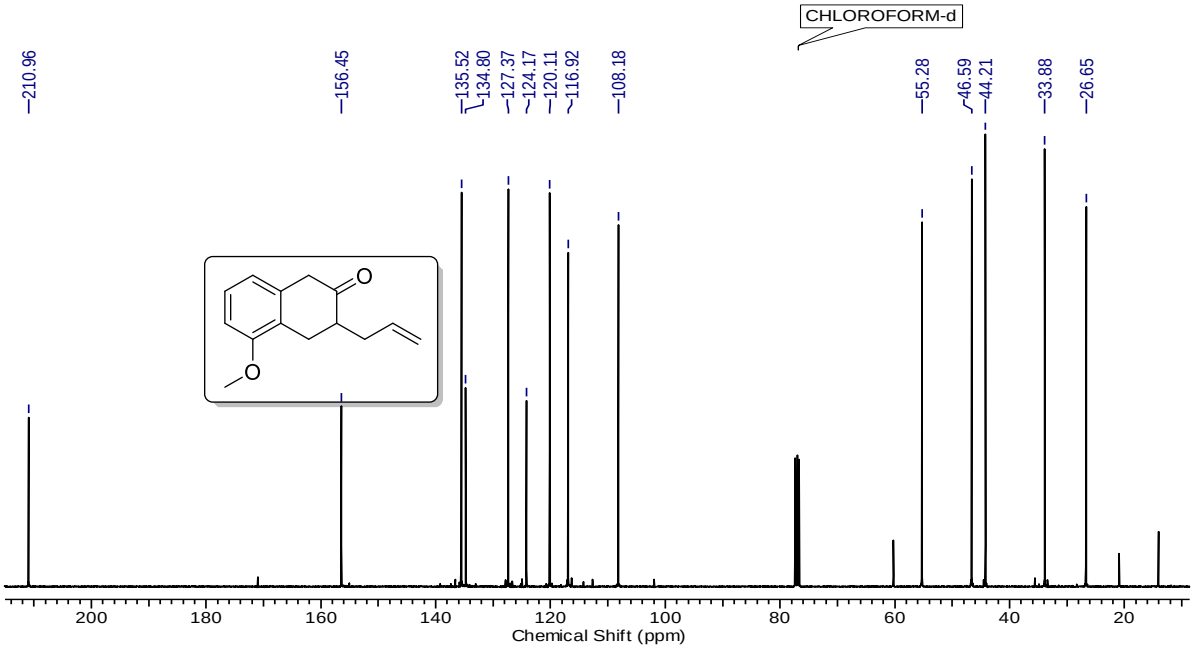

**DEPT NMR spectrum of compound 50 ($CDCl_3$, 100 MHz)**



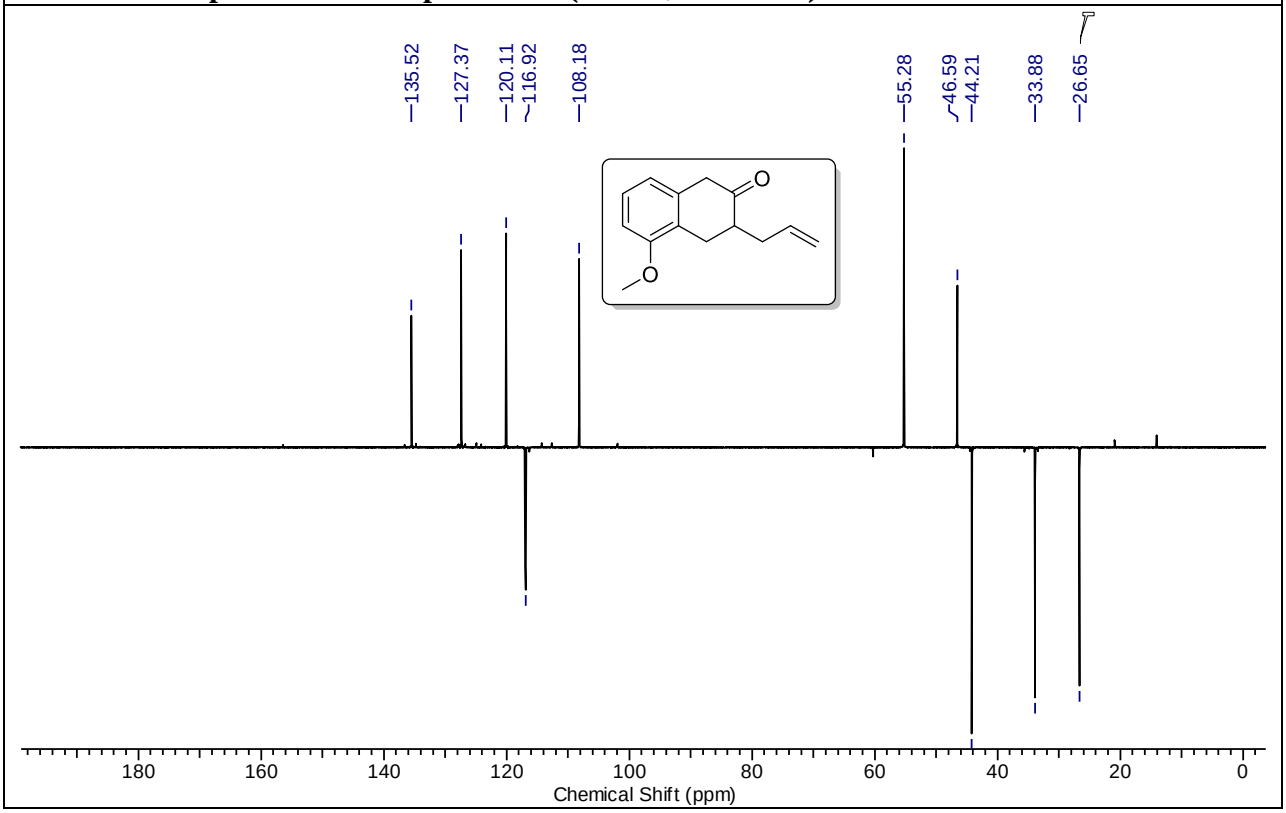

**1H-NMR spectrum of compound 52 ($CDCl_3$, 400 MHz)**



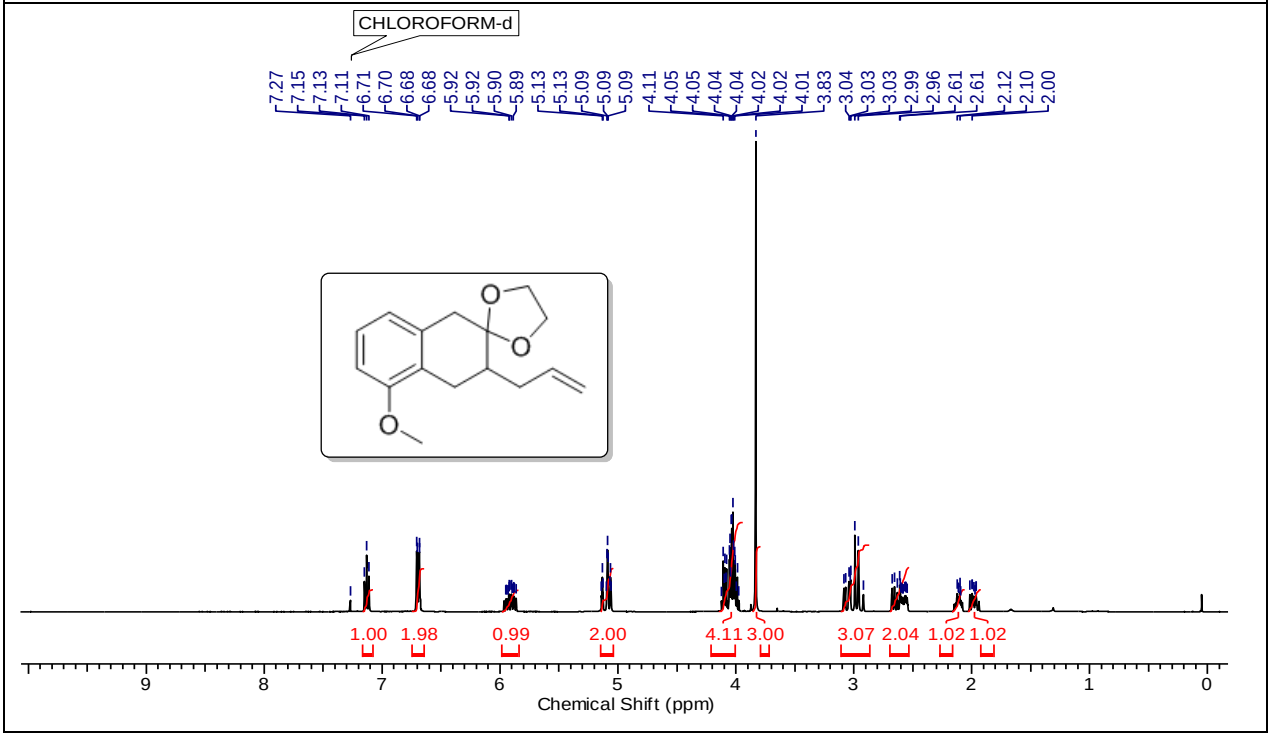
**$^{13}$C-NMR spectrum of compound 52 ($CDCl_3$, 100 MHz)**



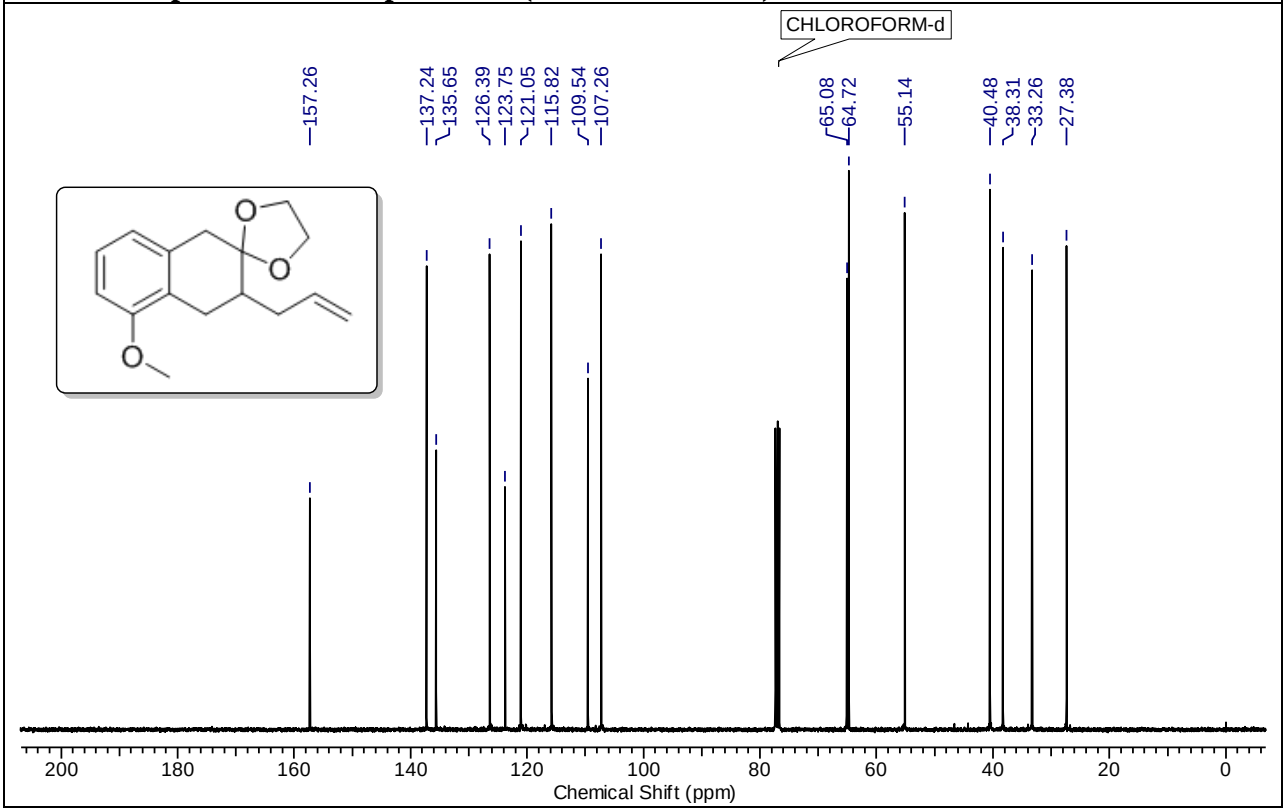

**DEPT NMR spectrum of compound 52 ($CDCl_3$, 100 MHz)**



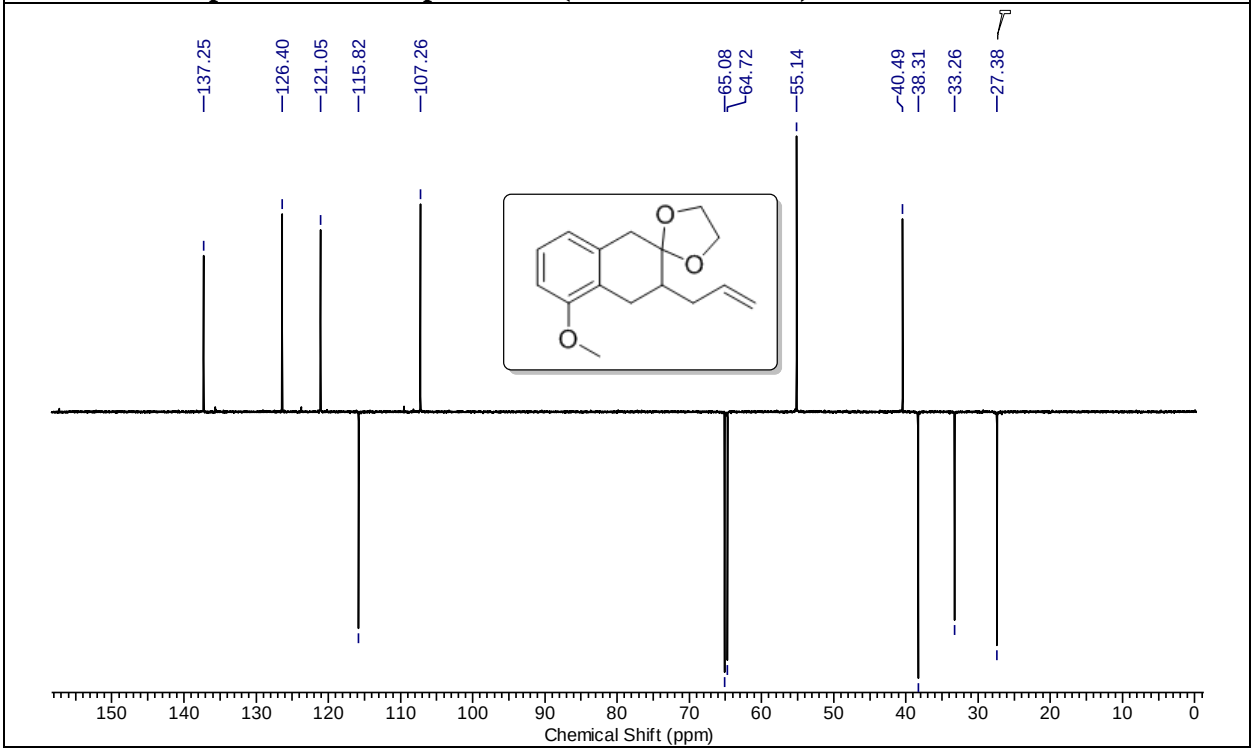
**$^{1}$H-NMR spectrum of compound 53 ($CDCl_3$, 400 MHz)**



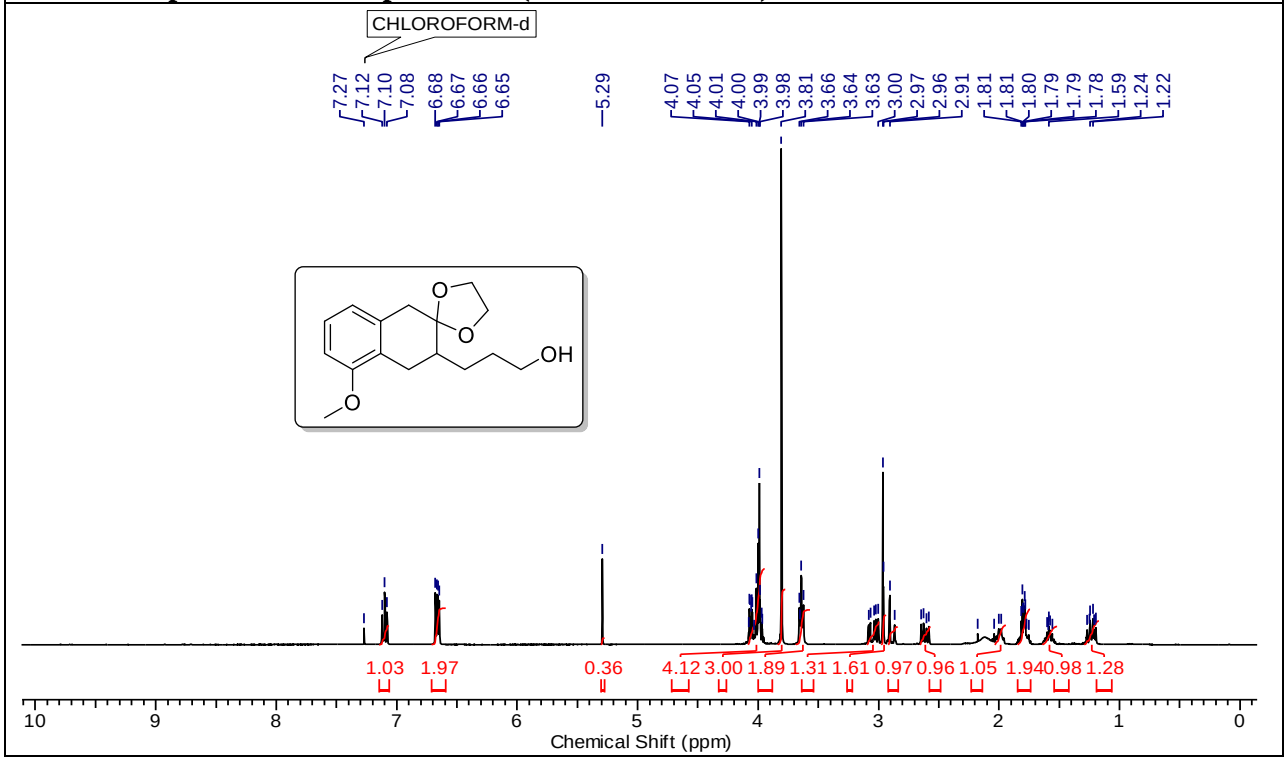

**$^{13}$C-NMR spectrum of compound 53 ($CDCl_3$, 100 MHz)**



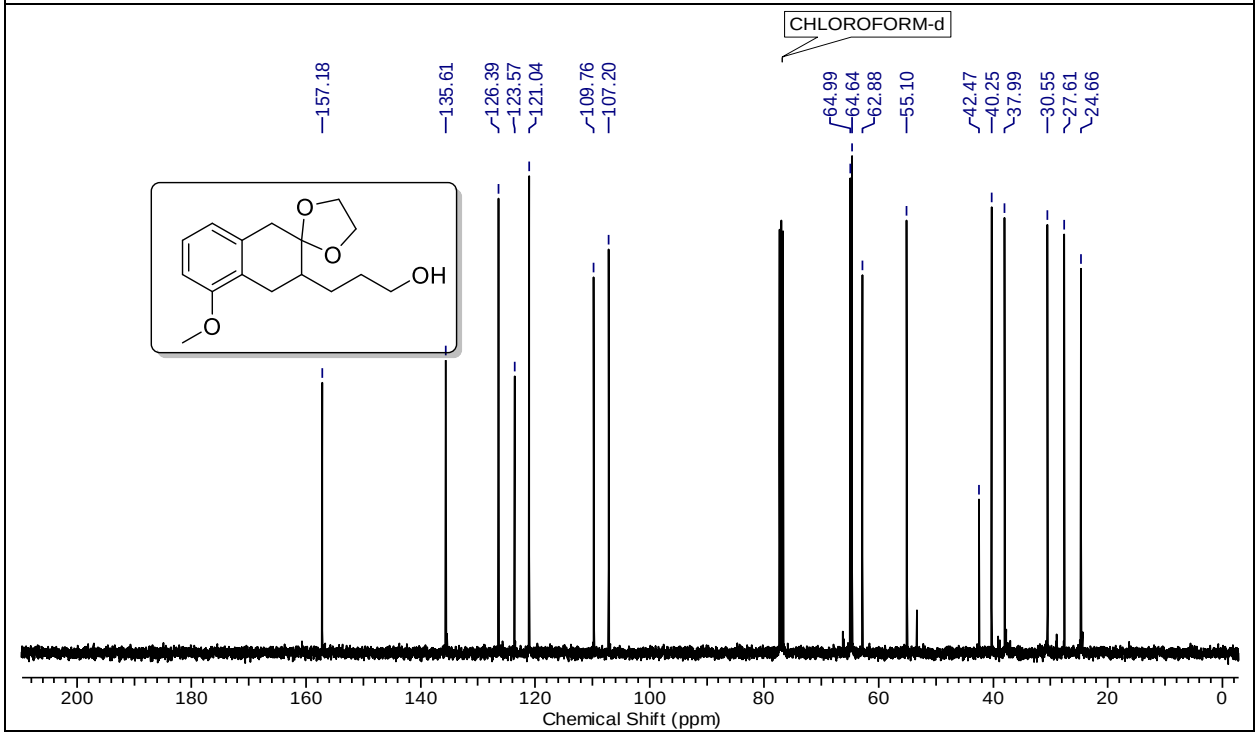
**DEPT NMR spectrum of compound 53 ($CDCl_3$, 100 MHz)**



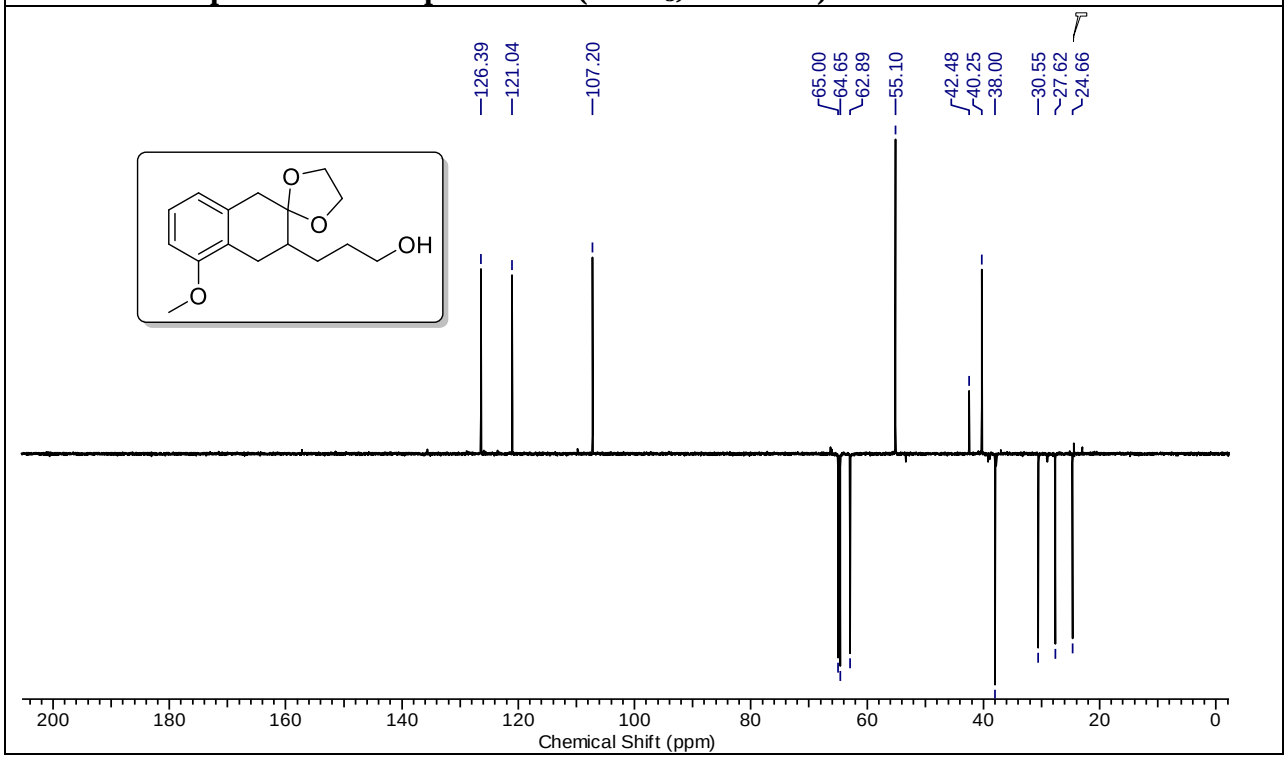

**1H-NMR spectrum of compound 54 ($CDCl_3$, 400 MHz)**



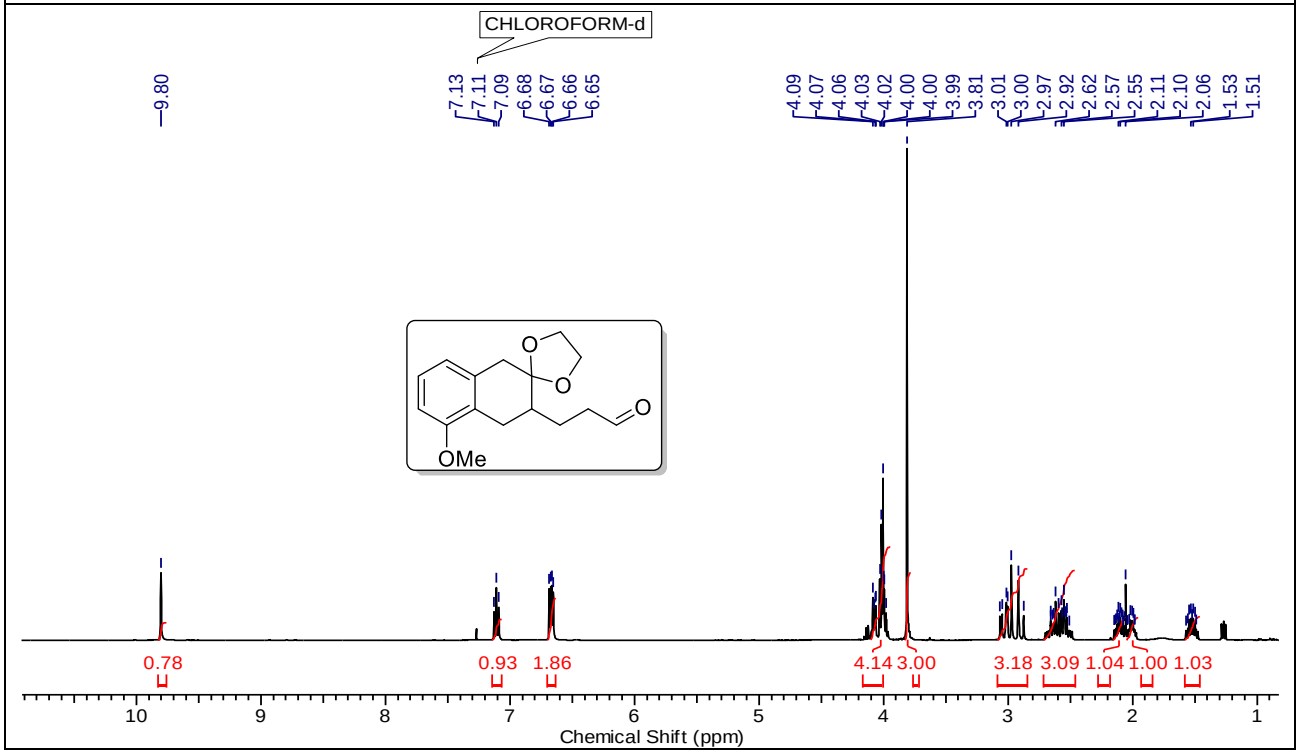
**$^{13}$C-NMR spectrum of compound 54 ($CDCl_3$, 100 MHz)**



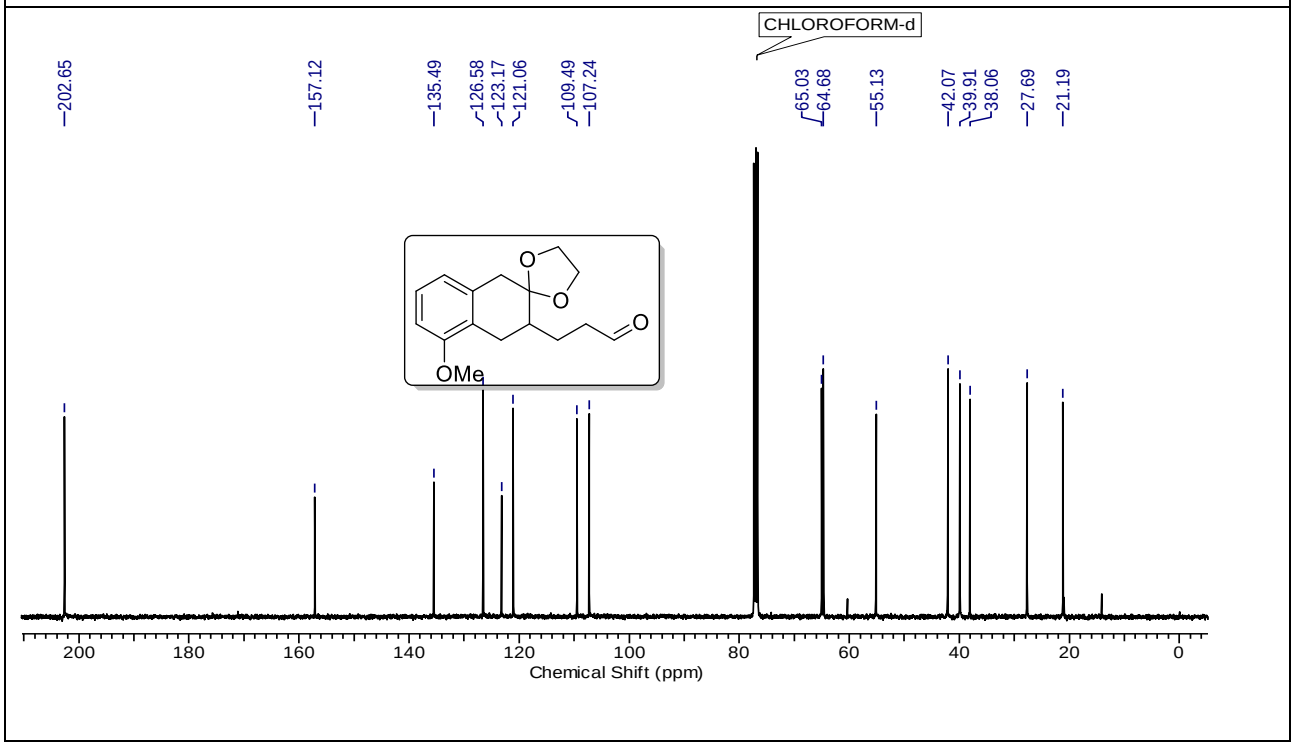

**DEPT NMR spectrum of compound 54 ($CDCl_3$, 100 MHz)**



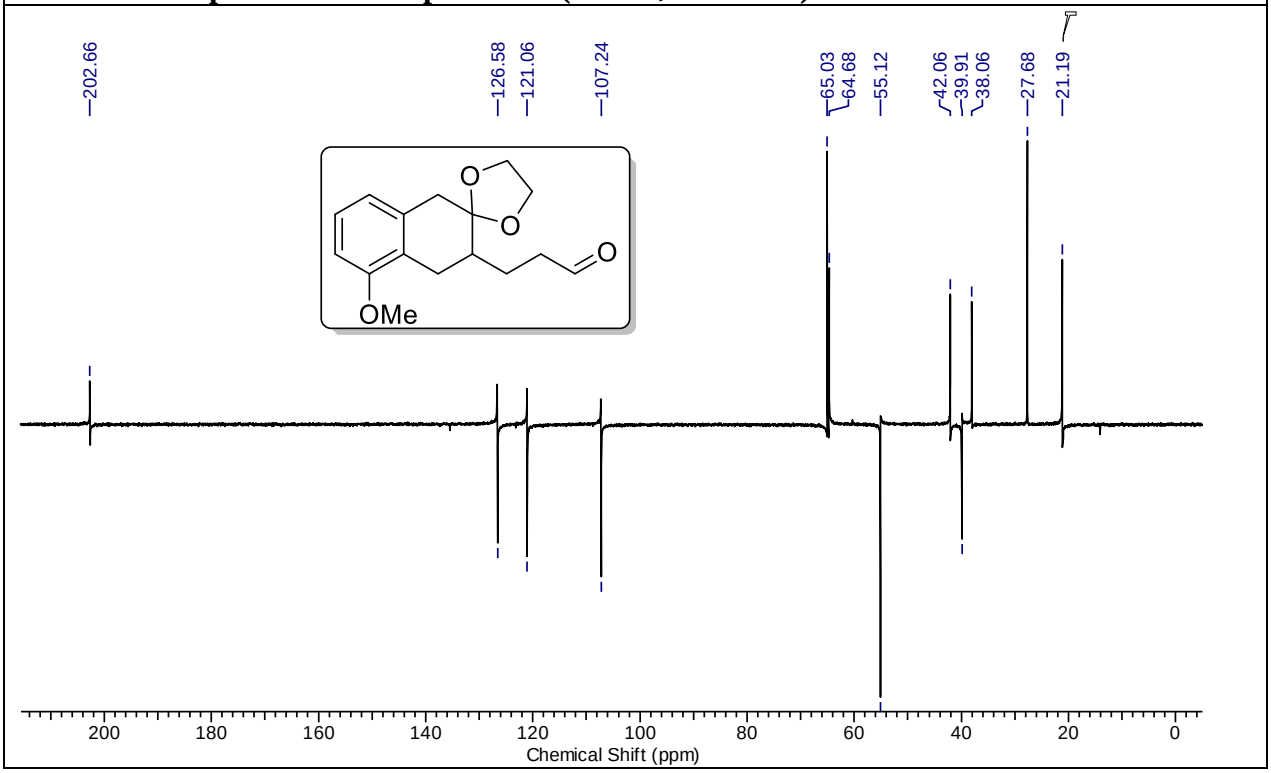
**$^{1}$H-NMR spectrum of compound 49 ($CDCl_3$, 400 MHz)**



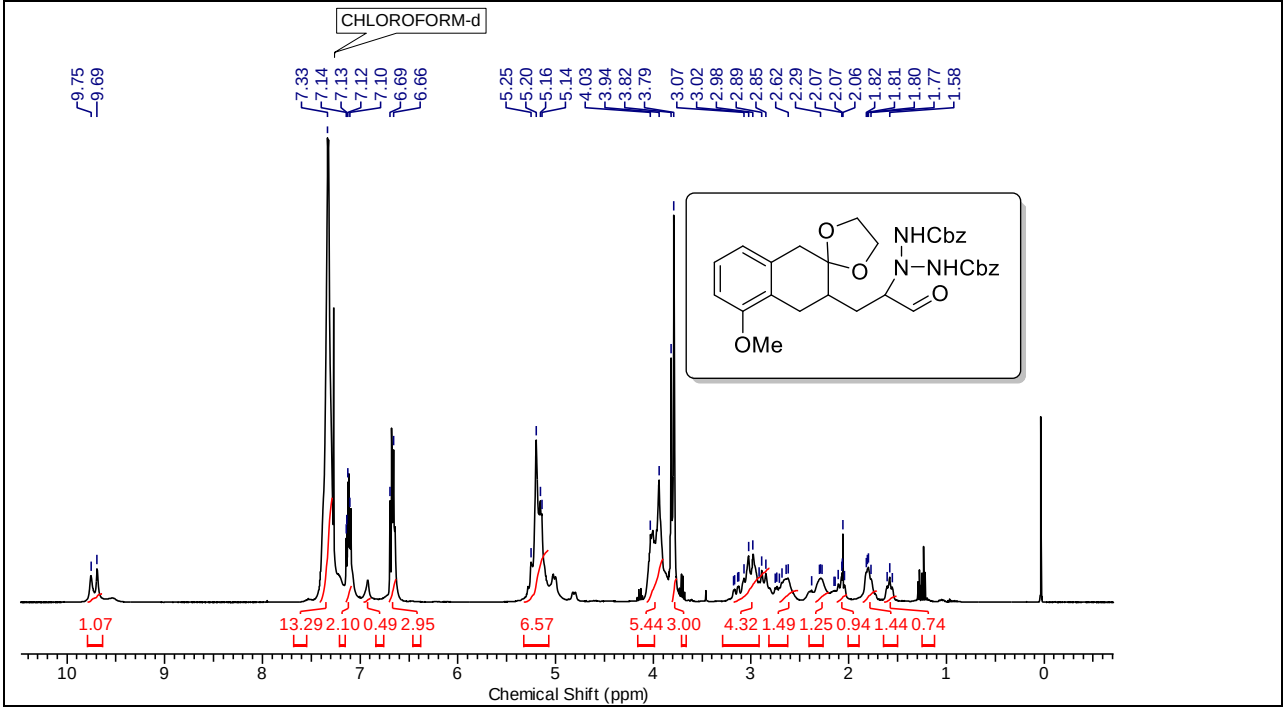

**$^{13}$C-NMR spectrum of compound 49 ($CDCl_3$, 100 MHz)**



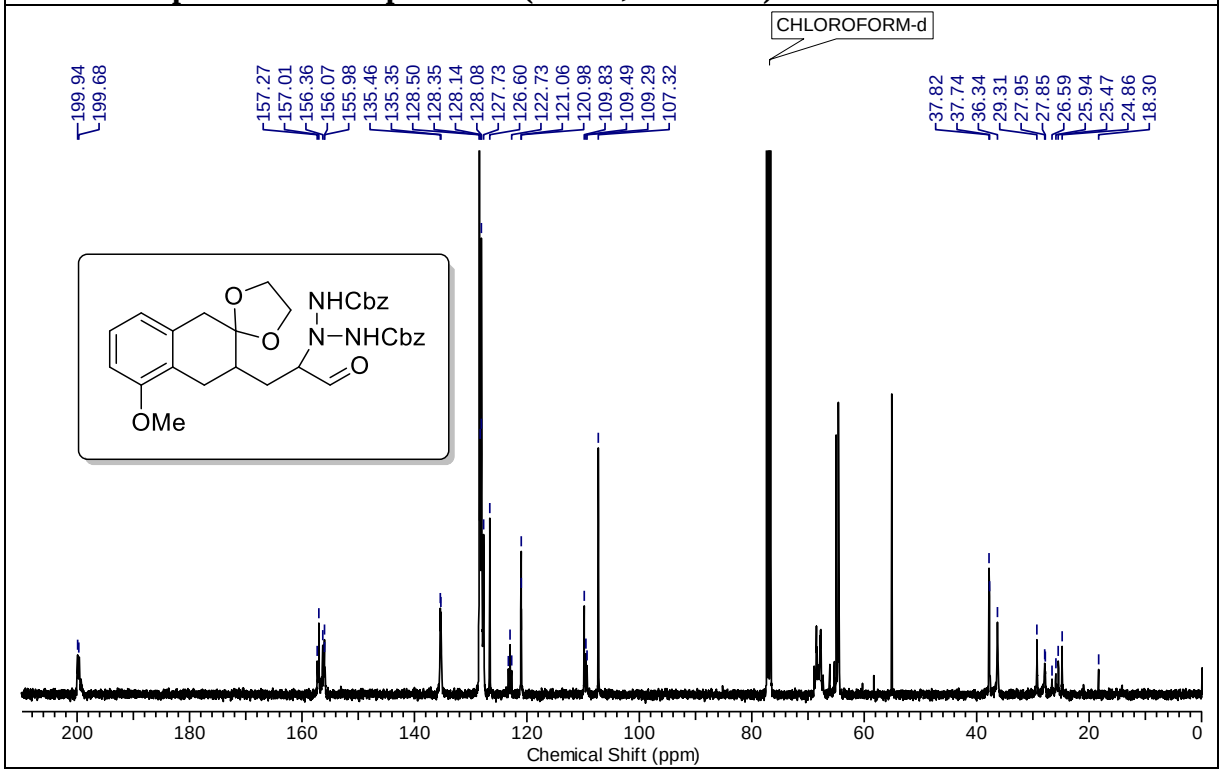
**DEPT NMR spectrum of compound 49 ($CDCl_3$, 100 MHz)**



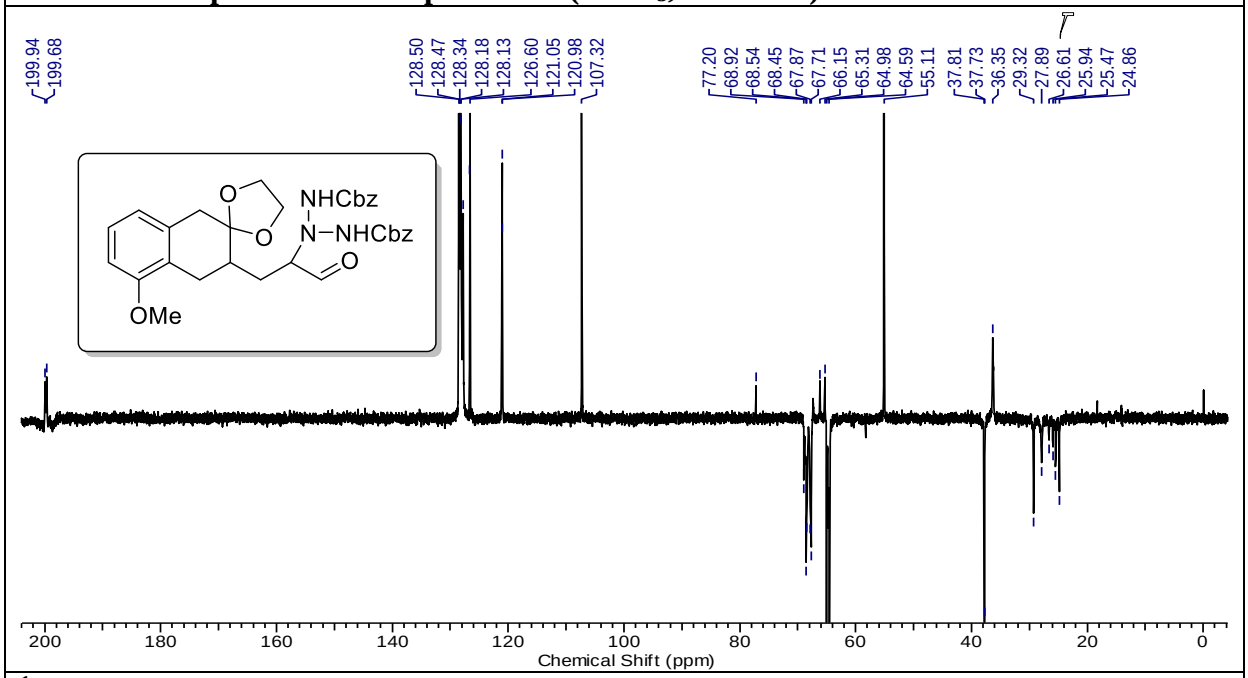

**$^1$H-NMR spectrum of compound 48 ($CDCl_3$, 400 MHz)**



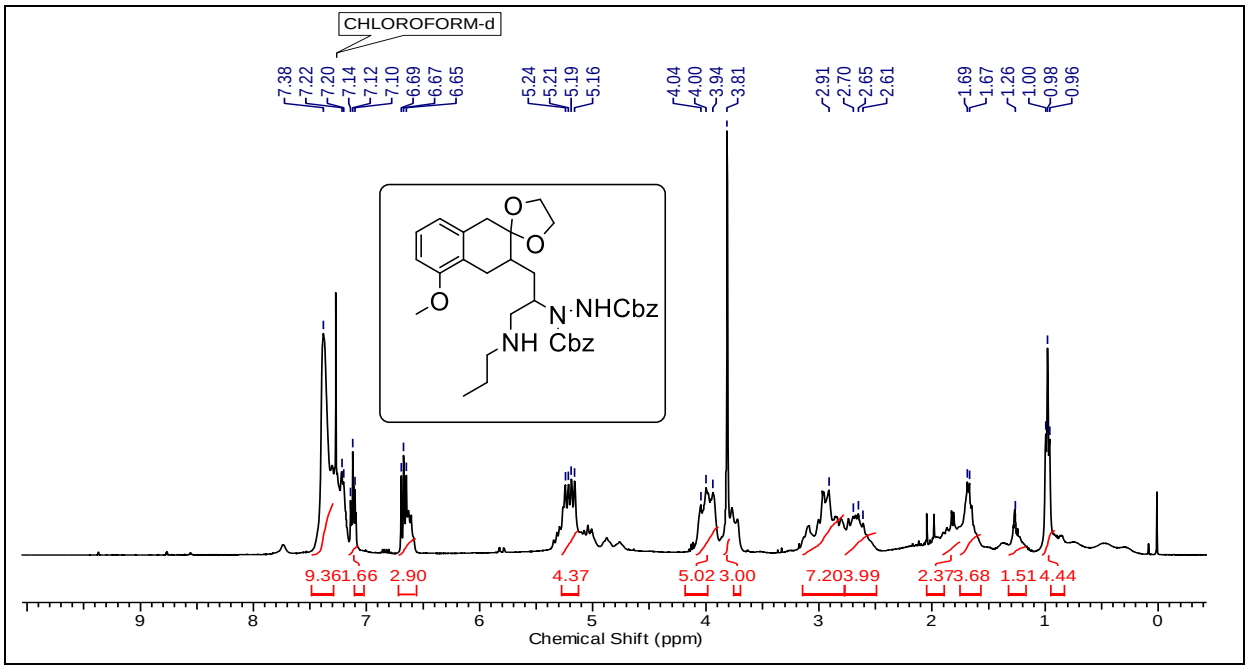
**$^{13}$C-NMR spectrum of compound 48 ($CDCl_3$, 100 MHz)**



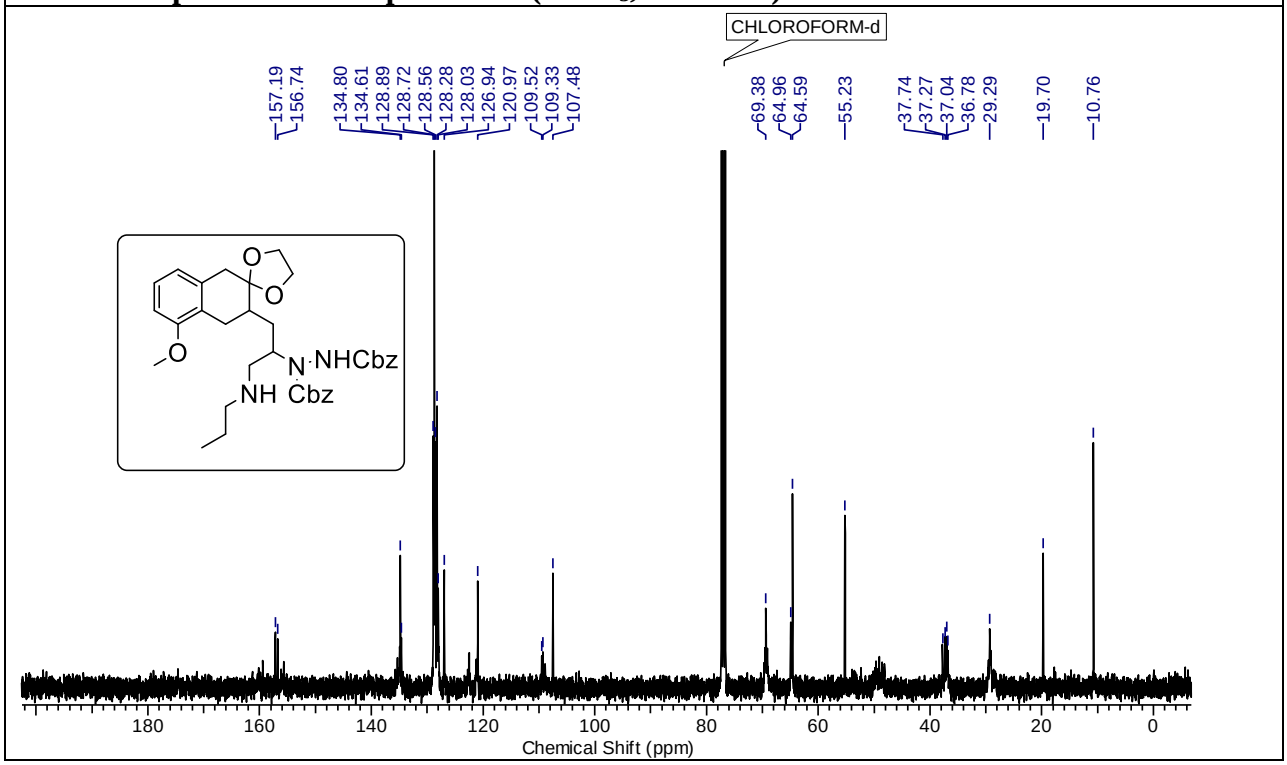

**DEPT NMR spectrum of compound 48 ($CDCl_3$, 125 MHz)**



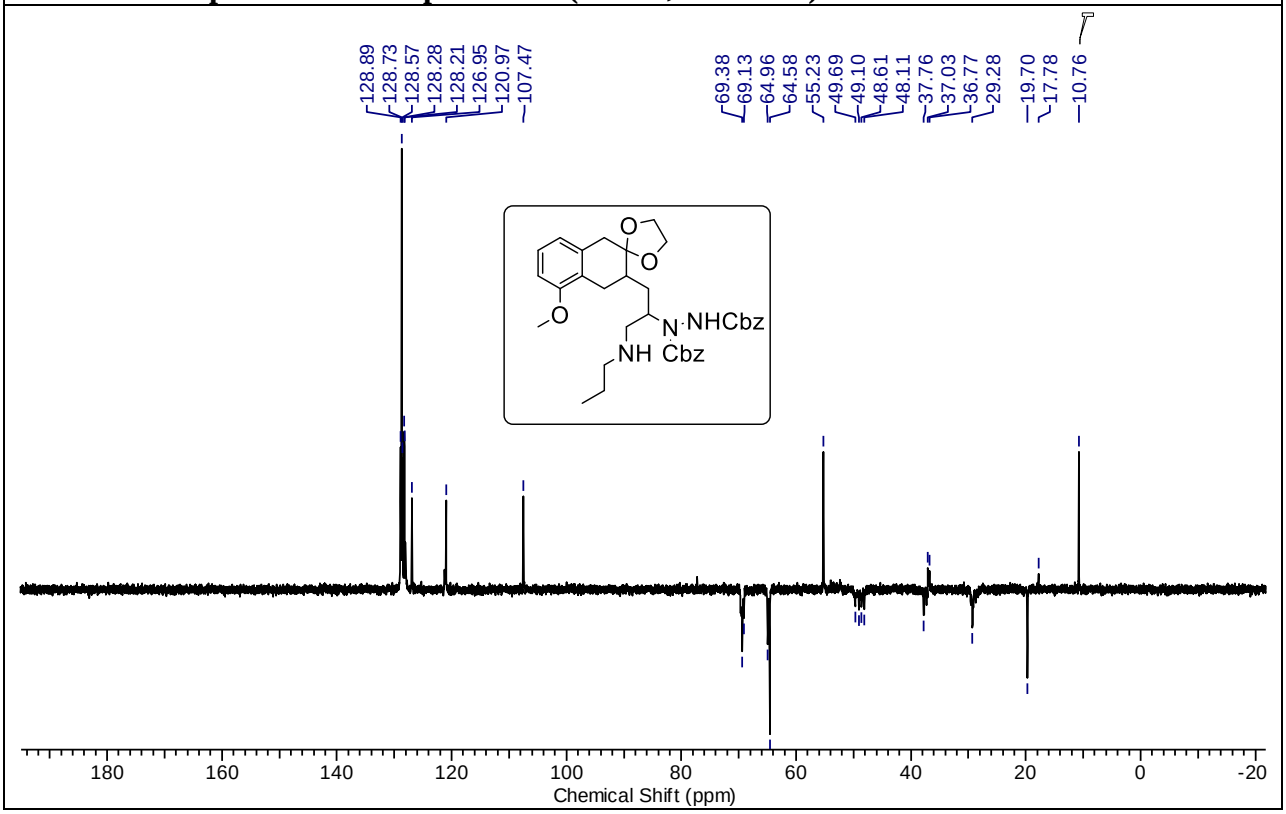

**$^{1}$H-NMR spectrum of compound 47 ($CDCl_3$, 400 MHz)**



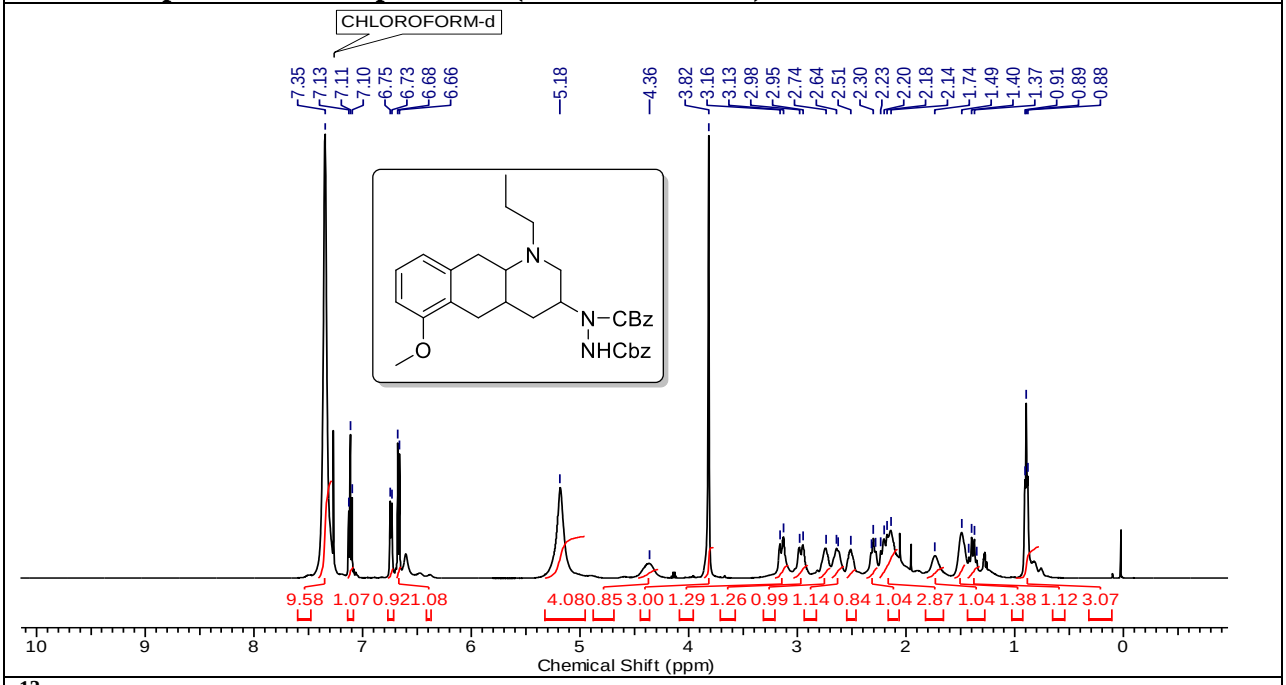

**$^{13}$C-NMR spectrum of compound 47 ($CDCl_3$, 100 MHz)**



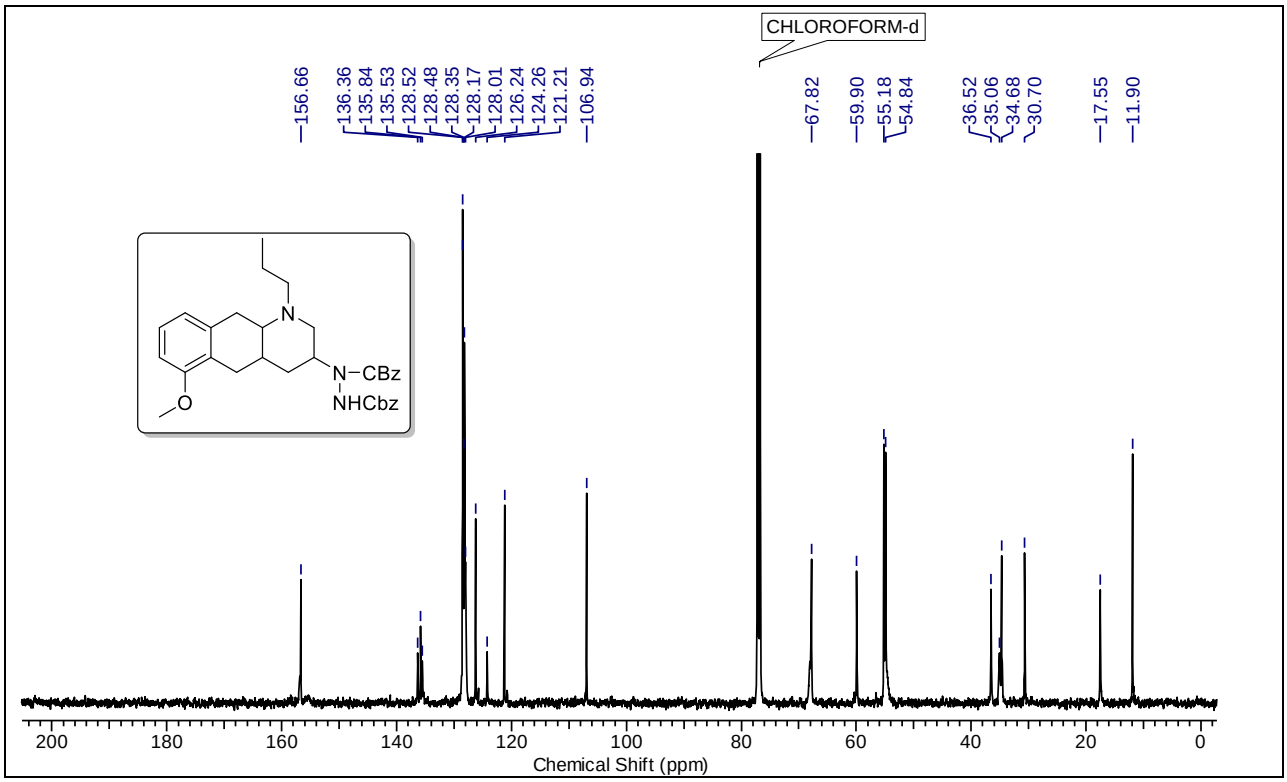
**DEPT NMR spectrum of compound 47 ($CDCl_3$, 100 MHz)**



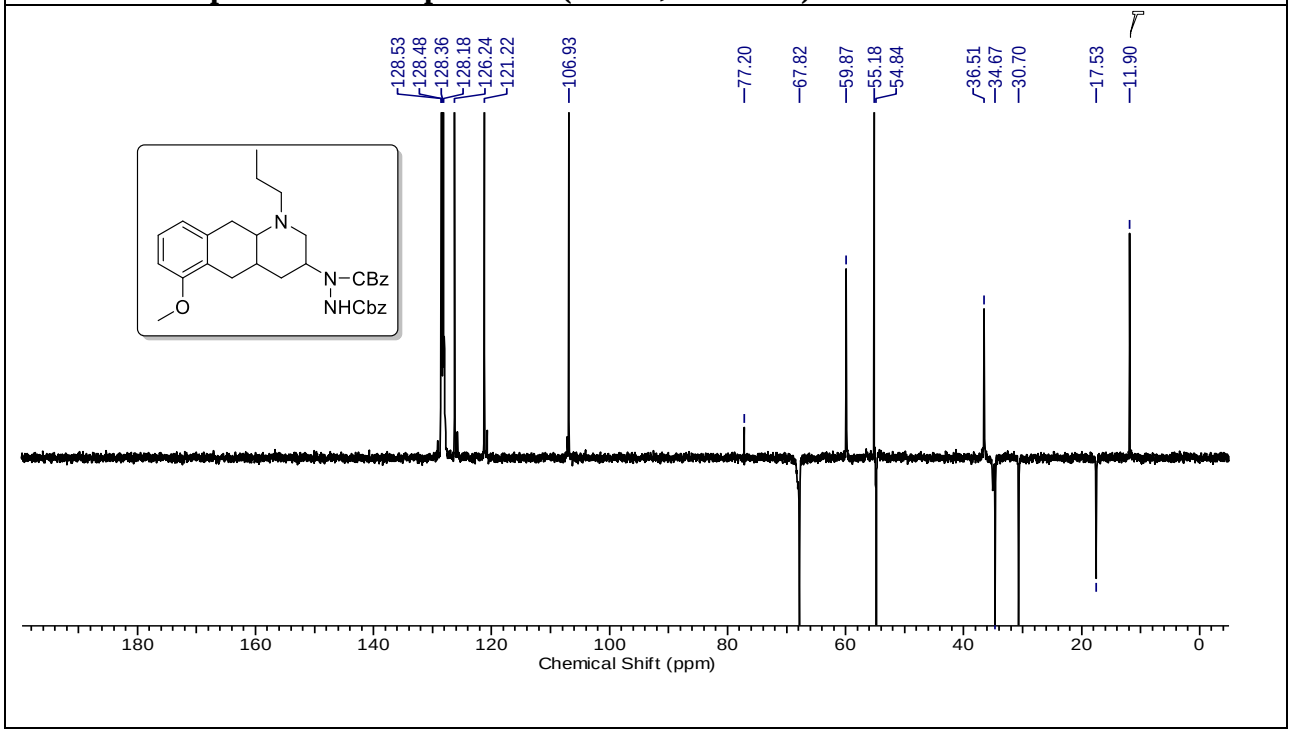

**$^{1}$H-NMR spectrum of compound 46 ($CDCl_3$, 500 MHz)**



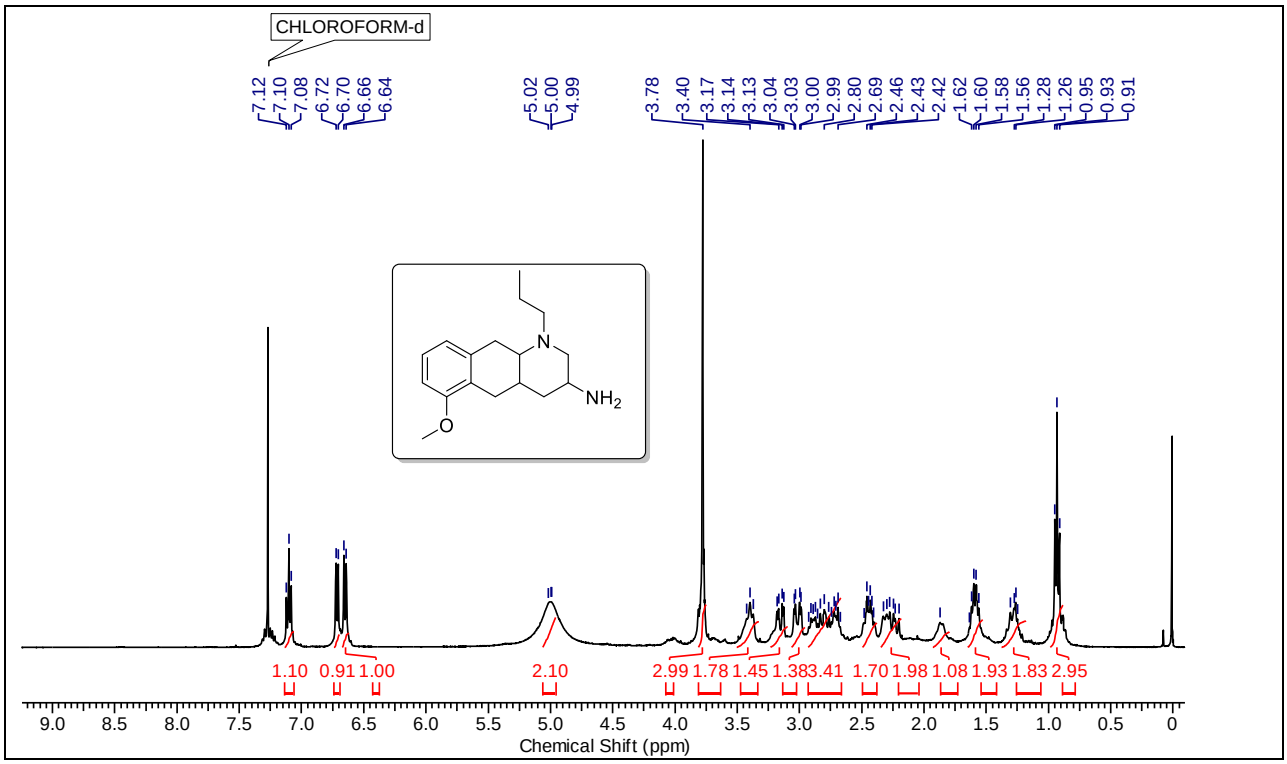

**$^{13}$C-NMR spectrum of compound 46 ($CDCl_3$, 125 MHz)**



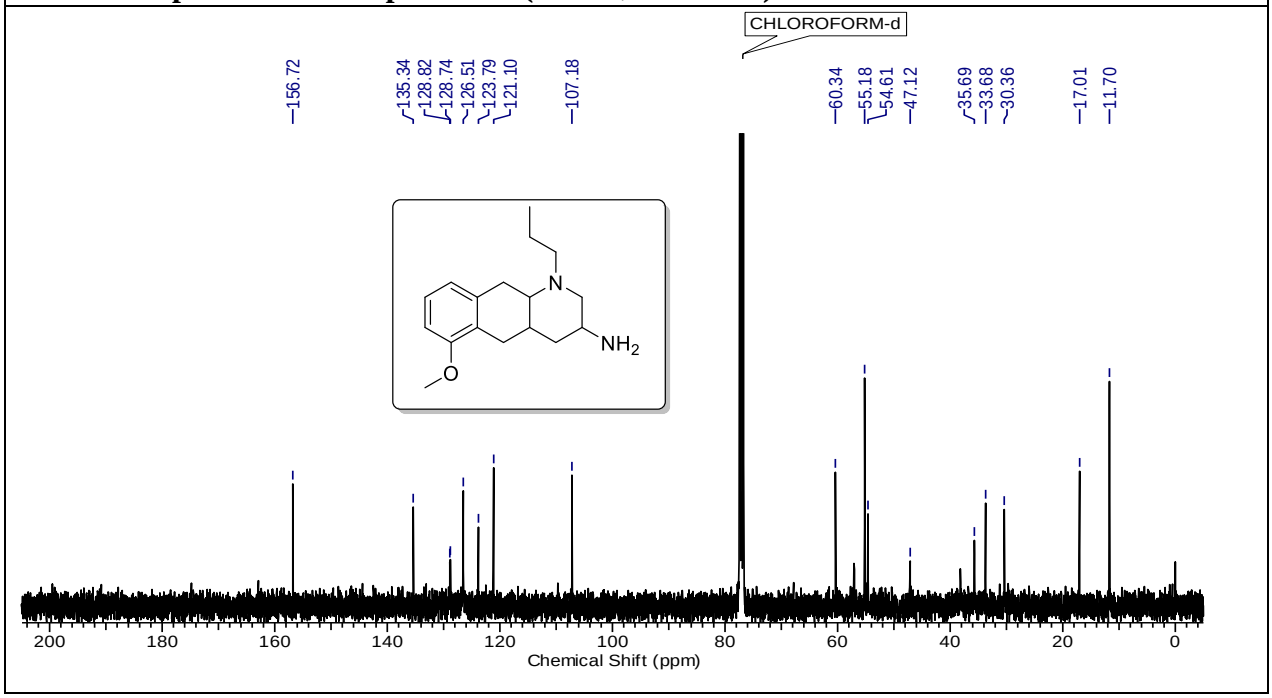

**DEPT NMR spectrum of compound 46 ($CDCl_3$, 125 MHz)**



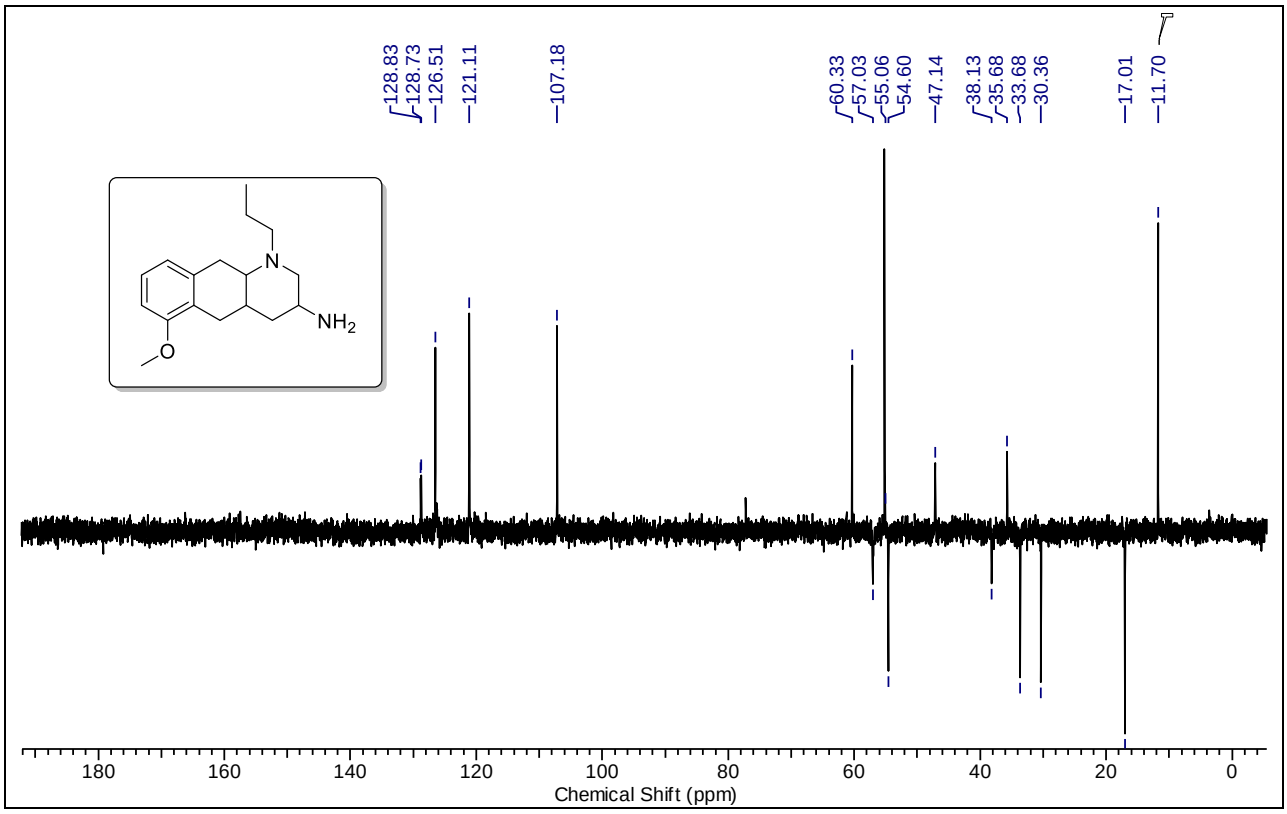

**$^1$H-NMR spectrum of compound 36 ($CDCl_3$, 400 MHz)**




**$^{13}$C-NMR spectrum of compound 36 ($CDCl_3$, 100 MHz)**




**DEPT NMR spectrum of compound 36 ($CDCl_3$, 100 MHz)**



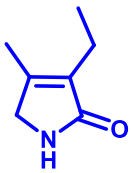

## 1.2.6 References


1) Donthamsetti, P. C.; Winter, N.; Schönberger, M.; Levitz, J.; Stanley, C.; Javitch, J. A.; Isacoff, E. Y.; Trauner, D. *Journal of the American Chemical Society* **2017**, *139*, 18522.
2) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *Journal of the American Chemical Society* **1985**, *107*, 7967.
3) Makai, S.; Falk, E.; Morandi, B. *Journal of the American Chemical Society* **2020**.
4) Tagmatarchis, N.; Thermos, K.; Katerinopoulos, H. E. *Journal of medicinal chemistry* **1998**, *41*, 4165.
5) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *Journal of the American Chemical Society* **2002**, *124*, 6254.

# Chapter 2: Synthesis of 3-ethyl-4 methyl-1, 5- dihydro-2H pyrrol-2-one

## Section I

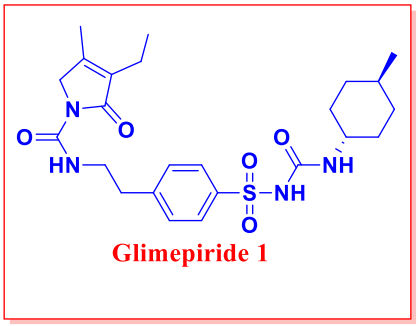
## Introduction and literature survey of 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one



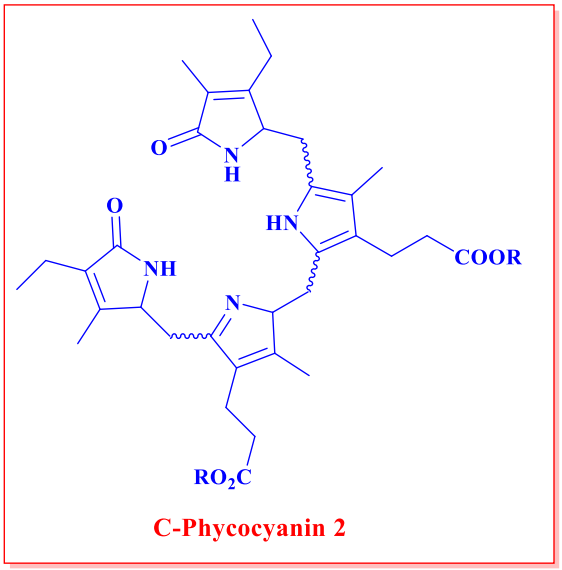

**3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one**

## 2.1.1 Introduction

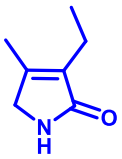
Diabetes is a disease that occurs when the blood glucose, also called blood sugar, is too high. Currently diabetes is increasingly most common, potentially devasting, treatable yet incurable, lifelong disease and becoming a major and serious problem in society. According to the survey in USA, cost of the treatment of diabetes is $ 90 billion dollar annually. It is more than the AIDS, cancer, and heart disease. Now in the India also this disease is increasing at the alarming rate and it is estimated that India will soon become diabetes capital of the world.




Glimepiride 1




C-Phycocyanin 2




3

3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one

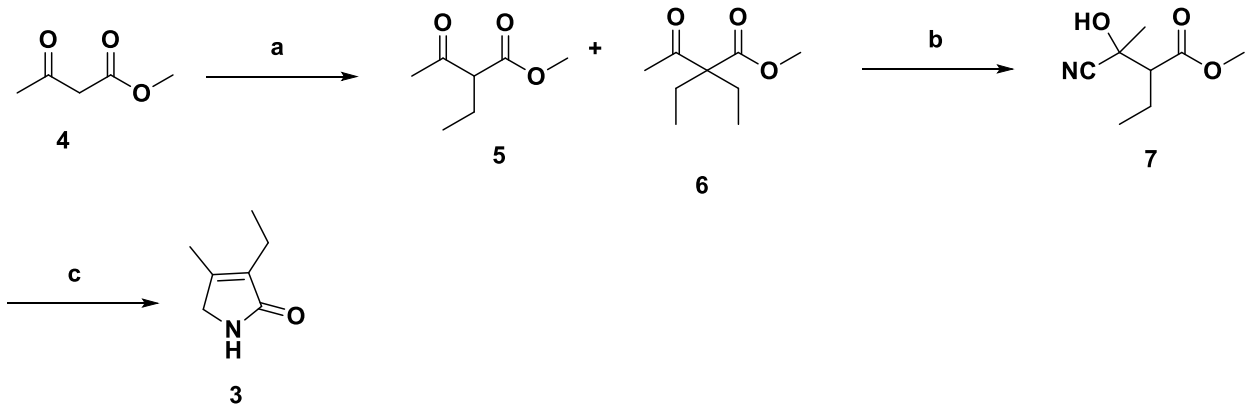
In most of biologically active natural products five and six membered lactones and lactams are widely present in the key building block in many natural products showing promising biological activity. The 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one is an important heterocyclic building block of antidiabetic drug glimepiride (**1**) and its derivatives. Lactam is present as main precursor in blue protein *C-phycocyanin* (**2**) which was isolated from the blue-green algae *Synechococcus sp. 6301*. C-Phycocyanin takes part in photosynthesis. Five membered α, β-

unsaturated lactam bearing substituents at positions 3 and 4, due to its utility in the field of medicinal chemistry and biology, has attracted the attention of synthetic chemists devising an efficient and practical route.

### 2.1.2 Literature survey

**Henry's approach** [1] *(J. Am. Chem. Soc.* **1991**, 113, 8024)

In 1991 Henry and co-workers reported the synthesis of **3** from ethyl acetoacetate **4,** which was alkylated with ethyl iodide using sodium ethoxide in ethanol at reflux temperature to give the mixture of monoalkylated product **5** and dialkylated compound **6.** Monoalkylated compound **5** was subjected to treatment with $Na_2CO_3$ and sodium cyanide to furnish cyanohydrin **7** employing Raney nickel in $H_2$, atmosphere under 60 psi at 33 ℃ and dehydration using sodium carbonate to afford desired **3** in 29%.



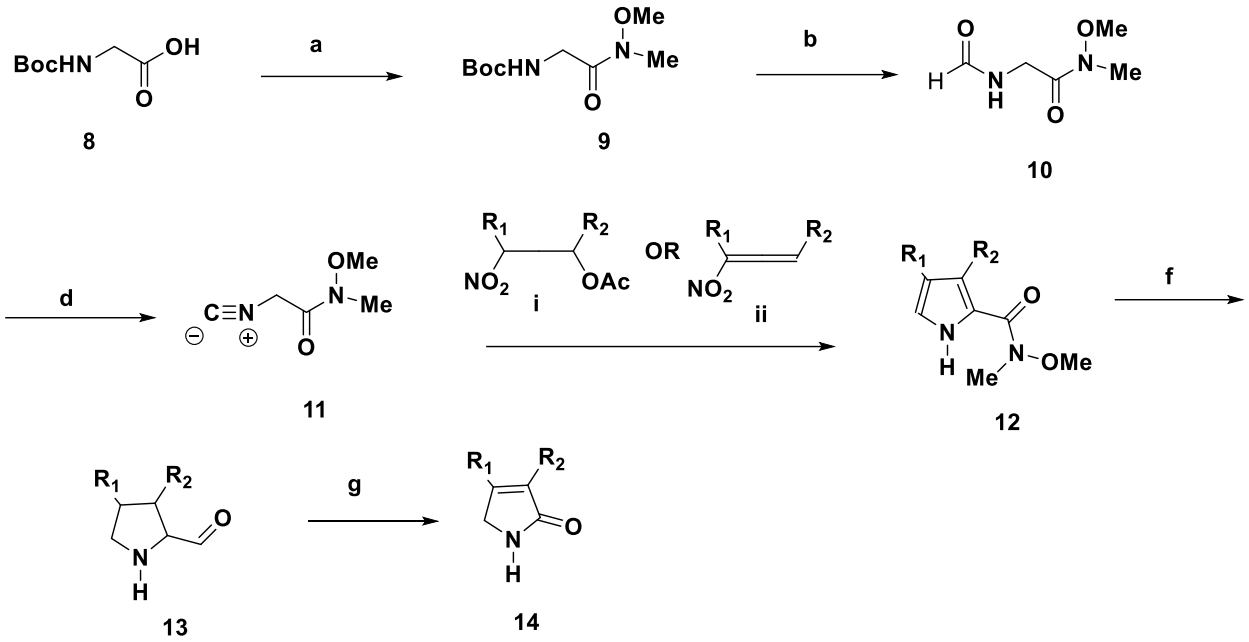

4 5 6 7 3

**Scheme 1**

**Scheme 1** Reagents and conditions: (a) NaOEt, (1.0 equiv), EtI (1.0 equiv), EtOH, 80 ℃, 4 h, 52% (a) $NaHSO_3$, (1.23 equiv), NaCN (1.05 equiv), $H_2O$, 0 ℃, 3 h (c) (ii) $H_2$, T-1 Ra-Ni, $Ac_2O$, 50 psi, 33 ℃, 12 h, reflux, 8 h, $Na_2CO_3$, $H_2O$, reflux, 4 h 29%.

**Pelkey's approach** [2] **(***J. Org. chem.* **2006**, 71, 6678)

Pelkey and co-workers in 2006 reported the synthesis of **14** in seven steps in 14% overall yield as shown in **Scheme 2** Starting the synthesis from Boc-glycine **8**, DCC coupling of **8** with N, O-dimethylhydroxylamine gave **9** in 78% yields.

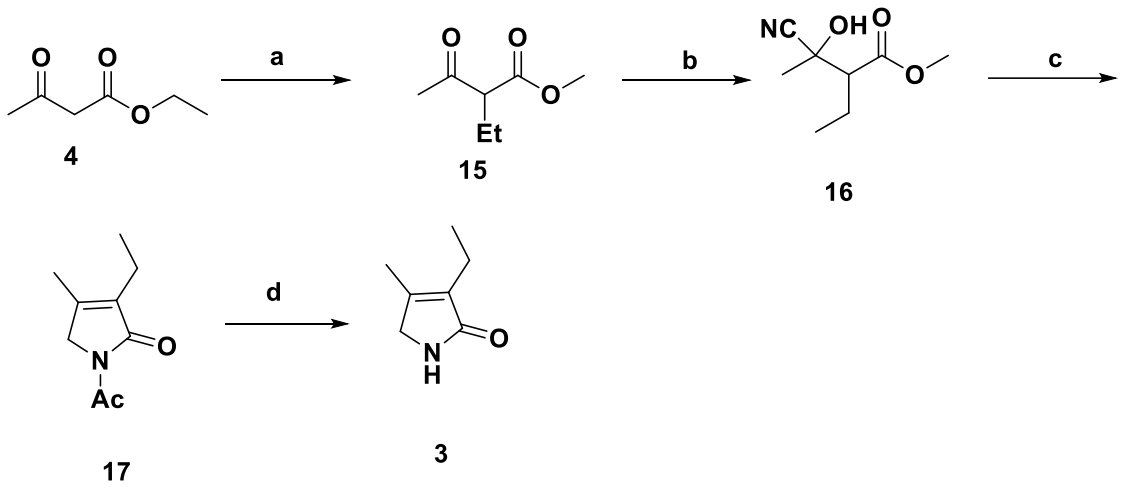



**Scheme 2**

**Scheme 2** Reagents and conditions: (a) MeONHMe, DCC, $CH_2Cl_2$, 0 ℃, rt, 78%; (b) $HCO_2H$, 80 ℃; (c) $HCO_2Et$, $Et_3N$, heat, (65% two steps); (d) $POCl_3$, $Et_3N$, THF, 70% (e) **i** or **ii,** DBU, THF**,** 0 ℃-rt, 90% (f), $LiAlH_4$, THF, 0 ℃, 65%, (g) $H_2O_2$, $NaHCO_3$, MeOH, rt, 67%.

**Gurjar Approach** [3] (*Tetrahedron Letters* **2003** 4853–4855)

Gurjar and co workers in 2003 reported the synthesis of **3** from commercially available ethyl acetoacetate **4** as a starting material which was alkylated by using dimethylamine and diethyl sulphate at 10-15 ℃ to furnish monoalkylated product **15**. Further the compound **15** was treated with sodium cyanide in dimethyl formamide as a solvent to afford the cyanohydrin **16** in 80% yield. The cyanohydrin **16** was reduced and followed by cyclization by using Raney nickel catalyst in presence of hydrogen gas and acetic anhydride to access the lactam **17**. Finally removal of acetate group by using the sodium carbonate in water under reflux condition resulted in the formation of expected lactam **3** in 90% yield.

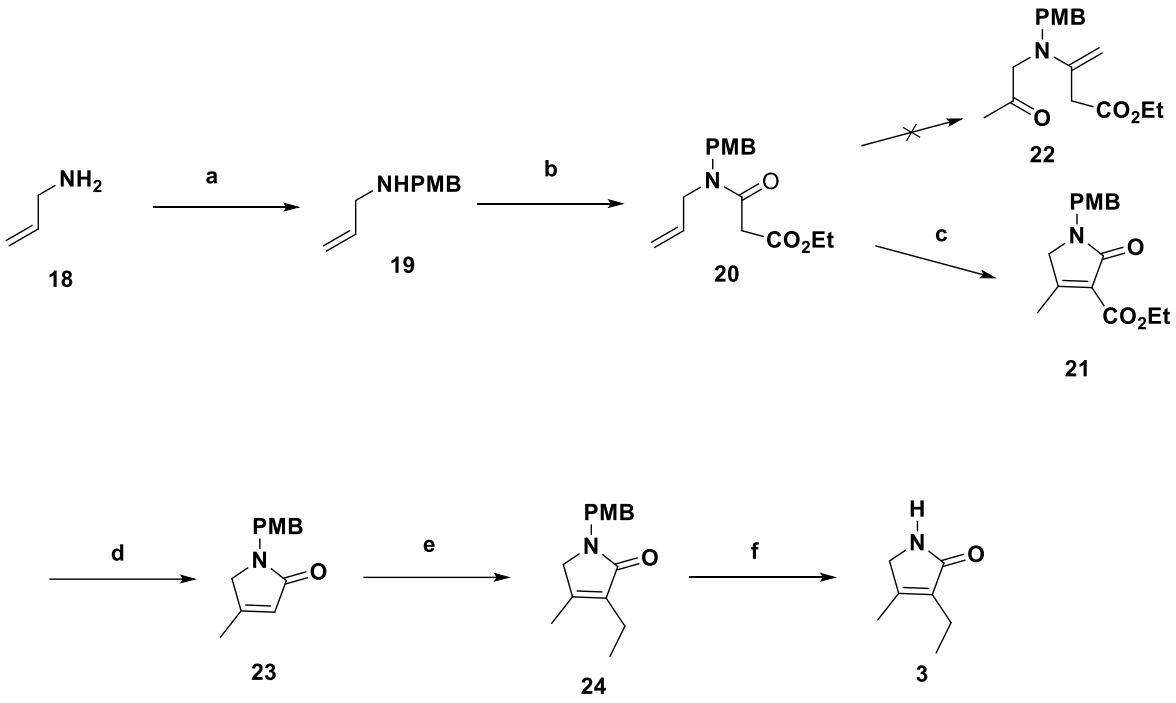



**Scheme 3**

**Scheme 3** : Reagents and conditions: (a) $HNMe_2$, $Et_2SO_4$, 10–15°C (70%); (b) NaCN, DMF, 0–5°C (80%); (c) $H_2$, Ra–Ni, $Ac_2O$, 40°C, 5 Kg/cm2 (15%); (d) $Na_2CO_3$, $H_2O$, reflux (90%).

**Chavan's Approach** [4]

**Method –I** Chavan *et al.* (this group) in 2015 reported the synthesis of **3** by applying novel palladium catalysed cyclization and other method used was the ring closing metathesis reaction. The synthesis was started by using commercially available and cheap allyl amine **18** as a starting material. The amine **18** was converted to PMB protected secondary amine **19** by using *p*-anisaldehyde and further reduction of imine by using sodium borohydride. The imine **19** was converted to amide **20** by using ethylmalonyl chloroacetate in 86% yield. Additionally the amide **20** on treatment with 10 mol% palladium chloride in presence of copper chloride as a co-oxidant in DMF-$H_2O$ system at 95 °C for 6 h afforded the cyclized lactam **21** in 62% yield. However, the desired ketone **22** was not formed. The lactam **21** was then converted to compound **23** by using Krapcho decarboxylation reaction. Finally the regiselective alkylation of **23** by using ethyl iodide and sodium hydride led to formation of the desired product **24**. The CAN mediated PMB deprotection of **24** furnished the expected product **3** in good yield.



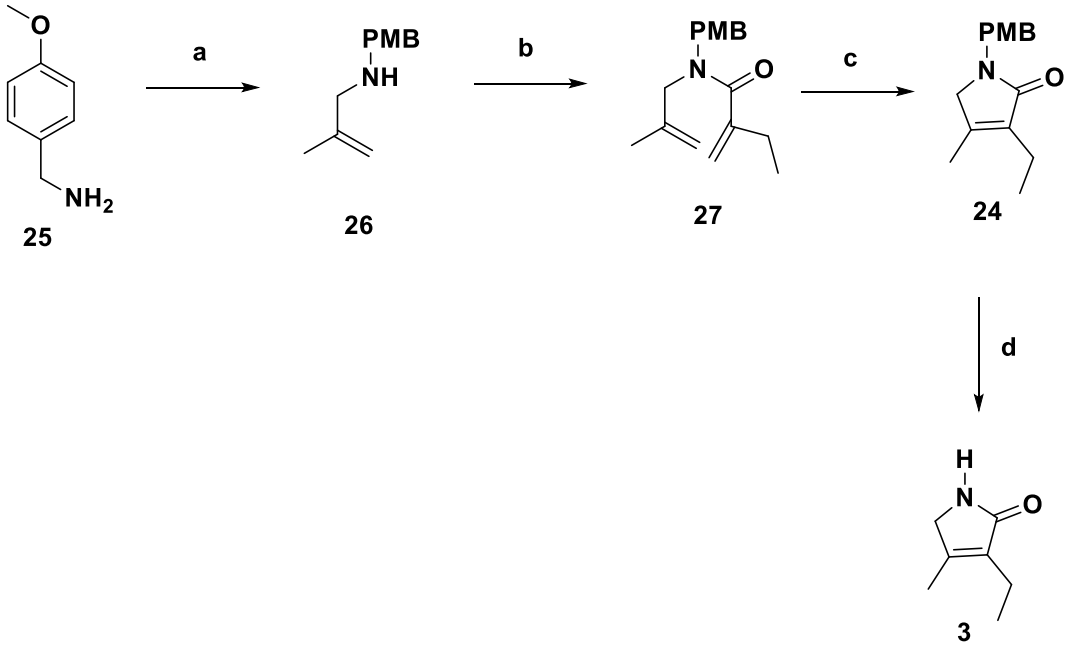

**Scheme 4**

**Scheme 4** : Reagents and conditions: (a) (i) p-Anisaldehyde, (1.1 equiv), MeOH, ℃, 1 h; (ii) $NaBH_4$, (1.01 equiv, MeOH, ℃, 1 h, 97%; (b) $K_2CO_3$ (1.2 equiv), ethyl malonyl chloride (1.2 equiv), $CH_2Cl_2$, 0 ℃, 1 h, 86%; (c) $PdCl_2$, (10 mol%), $CuCl_2$ (2.1 equiv) , DMF-$H_2O$ (3:1), 95 ℃, 6-8 h, 62%; (d) NaCl (4.0 equiv) DMSO-$H_2O$, (3:1), 120-130 ℃, 12 h, 87%; (e) NaH, (1.2 equiv), EtI (1.2 equiv), anhyd THF, 0 ℃, to rt, 3 h, 71%; (f) CAN (2.5 equiv, MeCN-$H_2O$, (5:1), rt, 2 h, 80%.

**Method-II**

In another method Chavan *et al. (this group)* reported the synthesis of compound **3** by using the ring closing metathesis as the key step as shown in scheme **5**. In this method the synthesis was started by using the readily available 4-methoxy benzylamine **25** as a starting material which was subjected for the alkylation by using methallyl chloride, potassium carbonate, and catalytic amount of potassium iodide to give secondary amine **26**. Further, the amine **26** was N-acylated by using ethacryloyl chloride which was synthesized from the butyraldehyde by the reported protocol to furnish the tertiary amine **27** in very good yield. After acheiving the intermediate amide **27** it was then subjected for ring closing metathesis reaction by using 10 mol% of Grubbs' 2 $^{nd}$ generation catalyst in dry toluene at 80 ℃ for 24 h to give lactam **24** in 40% yield.

Finally the lactum **24** was converted to desired product **3** by the known method described in **scheme 4**




**Scheme 5**

**Scheme 5**: Reagents and conditions: (a) Methallyl chloride (0.33 equiv), $K_2CO_3$, (1.2 equiv) KI (cat.), anhyd. $CH_2Cl_2$, 0 ℃, to rt. 12 h, 84%; (b) $K_2CO_3$, (1.2 equiv), ethacryloyl chloride (1.2 equiv), anhyd. $CH_2Cl_2$, 0 ℃, to rt, 3 h, 91%; (c) Grubbs' II catalyst (10 mol %), $Ti(Oi\text{-}Pr)_4$, (2.0 equiv), anhydrous toluene, 80 ℃, 12 h,.

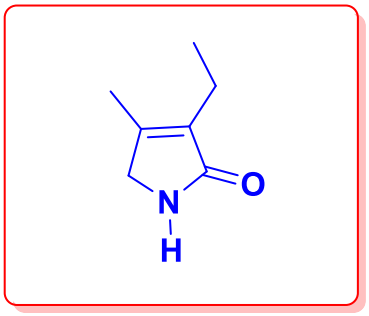
**2.1.3 Conclusion** The above literature survey depits that how different reactions can be used for synthesis of 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one

### 2.1.4 References:


1) Bishop, J. E.; Nagy, J. O.; O'Connell, J. F.; Rapoport, H. *J. Am. Chem. Soc.* **1991**, *113*, 8024.
2) Coffin, A. R.; Roussell, M. A.; Tserlin, E.; Pelkey, E. T. *The Journal of Organic Chemistry* **2006**, *71*, 6678.
3) Gurjar, M. K.; Joshi, R. A.; Chaudhuri, S. R.; Joshi, S. V.; Barde, A. R.; Gediya, L. K.; Ranade, P. V.; Kadam, S. M.; Naik, S. J. *Tetrahedron letters* **2003**, *44*, 4853.
4) Chavan, S. P.; Pathak, A. B.; Pawar, K. P. *Synthesis* **2015**, *47*, 955.

# Chapter 2 Section II

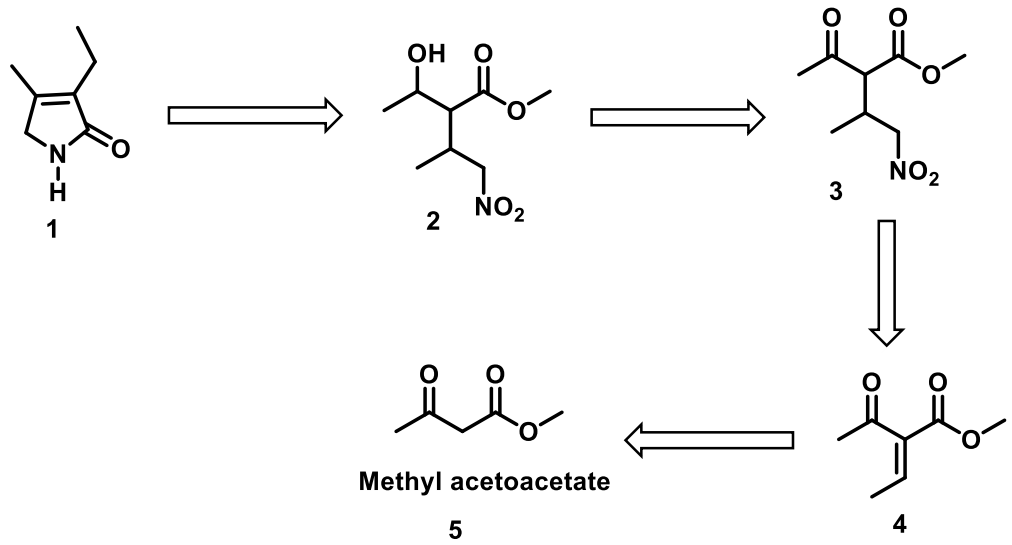
## Study towards the synthesis of 3-ethyl-4-methyl-1, 5-dihydro-2*H* pyrrol-2 –one



## 2.2.1 Result and discussion

### Retrosynthesis

As per the retrosynthetic plan, (**Scheme-1**), 3-ethyl-4-methyl-1, 5-dihydro- 2*H*-pyrrol-2-one **1** could be obtained from nitroester **2** by using reduction and cyclisation of nitroester **3.** Further the alcohol functionality of **2** can be obtained from ketone **3** using reduction reaction. The nitro compound **3** could be obtained from **4** by using Michael reaction of olefin **4** using nitromethane. The olefin compound **4** can be obtained from methyl acetoacetate by using Knoevenagel condensation reaction.

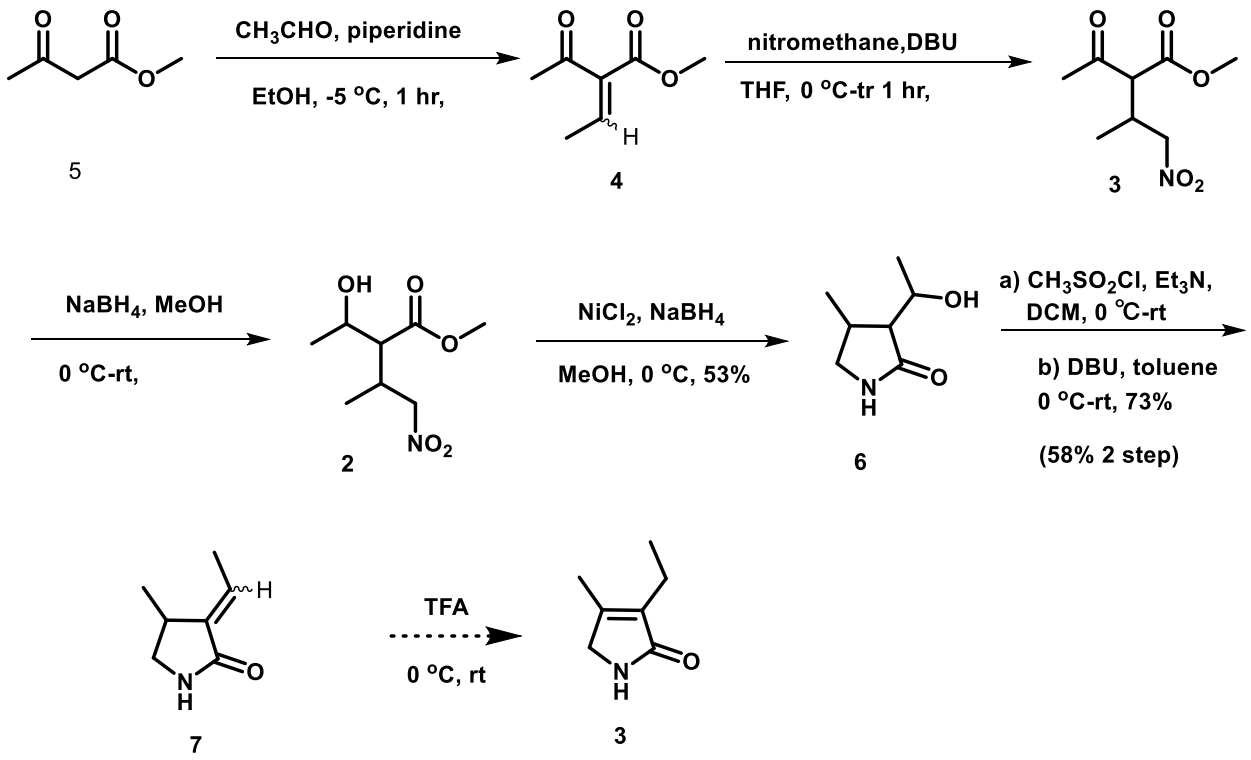



**Scheme 1**

### Synthesis of 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one

Synthesis of 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one **1** started from mthyl acetoacetate as a commercially available starting material. Mthyl acetoacetate was treated with acetaldehyde in the presence of catalytic amount of piperidine in ethanol at -5 to 0 ℃ for 1 hr to give olefin **4**. Due to stability probelms it was not characterized. The crude olefin **4** was treated with nitromethane in presence of catalytic amount of piperidine in THF at 0 ℃ for 1 hr and reaction was monitored by TLC. After completion of reaction, THF was removed and and product was extracted with dichloromethane and organic layer was concentrated on rotavopour to give crude nitro compound **3.** Due to unstable nature the crude nitro compound **3** was subjected for next reaction. The reduction of crude ketone **3** using $NaBH_4$ in methanol at 0 ℃ for 10 min afforded

the nitro alcohol **2.** It was characterized by using $^{1}H$ NMR spectroscopy in which the peaks at δ 4.80 (dd, 1H) and 1.26 (d, 3H) for CH and $CH_3$ protons indicated that the formation of product. Also in $^{13}C$ NMR spectrum the disappearance of carbonyl ketone at δ 202.65 indicated the formation of product. Further it was confirmed by LCMS which showed a peak at 206.21 corresponding to the molecular formula $C_8H_{16}NO_5$ $[M + H]^+$ of the product.




**Scheme: 2**

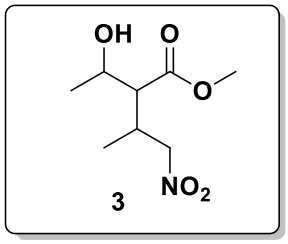
Further one-pot reduction and cyclisation of the nitroester **2** using $NiCl_2$ and $NaBH_4$, at 0 °C in methanol for 12 hr at room temperature afforded the distereomeric mixture of lactam **6** in 53% yield. It was confirmed by using $^{1}H$ NMR spectroscopy in which the peaks appeared at δ 3.47 (dd, 1H) and δ 2.93 (dd, 1H) which showed the CH protons while disappearance of ester peak that appears at δ 3.77. Also in the $^{13}C$-NMR spectrum, signal appeared at δ 180.67 for amide and ester carbon at δ 173.80 disappeared. The structure of **6** was further confirmed by the HRMS spectrum which showed a peak at 144.1019 corresponding to the molecular formula $C_7H_{14}NO_2$ $[M + H]^+$ of the product.

Further the protection of alcohol using mesyl chloride in presence of triethyl amine in DCM for 12 hr furnished O-mesyl protected compound. Further elimination of mesyl group using DBU in toluene at rt for 12 hr led to formation of eliminated compound **7**. It was confirmed by using $^{1}H$ NMR spectroscopy in which the peaks appeared at δ 5.93 (q, 1H) in the olefinic region for CH. Also in the $^{13}C$-NMR spectrum, signals appeared at δ 135.06 and 131.62 in the olefinic region. In DEPT NMR the appearance of quaternary carbon indicated the formation of product.

**2.2.2 Conclusion**: Synthetic effort were made towards of 3-ethyl-4-methyl-1,5-dihydro- 2*H*-pyrrol-2-one from cheap and commercially available methyl acetoacetate as a starting material. It is very close to synthesis of desired 3-ethyl-4-methy-3-pyrrolin-2-one.

### 2.2.3 Experimental Section:

**Preparation of methyl 2-(1-hydroxyethyl)-3-methyl-4-nitrobutanoate 2**



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To a solution of methyl acetoacetate **5** (1 gm, 1 equiv) in ethanol (10 mL) at -5 ℃ were added piperidine (catalytic amount) and acetaldehyde (0.568 gm, 1.5 equiv) and stirred at 0 ℃ for 1 hr. The progress of reaction was monitored by TLC until the substrate disappeared. After completion of reaction, the reaction mixture was diluted with diethyl ether (50 mL) and water (25 mL). The organic layer was separated and washed with water (2x 25 ml) dried over anhydrous sodium sulphate and filtered. Concentration of organic layer *in vacuo* furnished crude residue of olefin **4.**

Crude olefin **4** was treated with nitromethane (2 gm, 1 equiv) in presence of catalytic amount of DBU (0.20 ml, 0.1 equiv) in THF (20 mL) at 0 ℃, the reaction was monitored by TLC until the substrate disappeared. After completion of reaction, the solvent THF was removed on rotavopor and the residue was diluted with ethyl acetate and the organic phase was washed with brine and dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* afforded crude nitro compound **3** as a liquid. The crude nitro compound was further subjected for ketone reduction using $NaBH_4$ (0.450 gm, 1.5 equiv) in methanol at 0 ℃ for 10 min the progress of reaction was monitored by TLC. After completion of reaction, the solvent methanol was removed on rotavopor and the residue was diluted with ethyl acetate, the organic phase was washed with brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered and

concentrated to give crude hydroxy compound which on purification by silica gel (230–400 mesh) column chromatography using EtOAc-PE (20:80)) afforded distereomeric mixture of **2**(0.430 gm) in 44 % yield as a colorless liquid.

**Rf:** 0.3 (EA: PE 30:70).

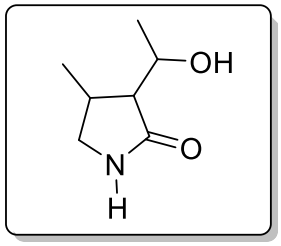
**Yield:** 44%.

**$^{1}$H NMR ($CDCl_3$, 400 MHz):** δ 4.80 (dd, *J* = 4.3, 12.5 Hz, 1 H), 4.38 (dd, *J* = 9.6, 12.6 Hz, 1 H), 3.73 (s, 3 H), 2.99 - 2.89 (m, 1 H), 2.53 (dd, *J* = 4.5, 8.0 Hz, 1 H), 2.00 (br. s, 1 H), 1.65 (br. s, 1 H), 1.26 (d, *J* = 6.1 Hz, 3 H), 1.12 (d, *J* = 6.9 Hz, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 173.9, 173.8, 79.2, 79.2, 66.5, 65.9, 54.8, 54.0, 51.9, 51.9, 32.7, 32.2, 22.3, 21.6, 16.2, 15.1.

**IR ($CHCl_3$)** $\nu_{max}$ 1550, 1724 $cm^{-1}$.

**Preparation of 3-(1-hydroxyethyl)-4-methylpyrrolidin-2-one (6)**




The nitroester **2** (0.400 gm, 1 equiv) was dissolved in methanol (10 mL) under nitrogen atmosphere and $NiCl_2.6H_2O$ (2.300 gm, 2 equiv) was added. The reaction mixture was cooled at 0°C and $NaBH_4$, (0.458 gm, 2 equiv) was added portionwise. The reaction mixture was slowly warmed to room temperature overnight. Afterwards a saturated aqueous $NH_4Cl$ solution (5 mL) was added and the aqueous phase was extracted with dichloromethane (3X10 mL). The combined organic fraction was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc-PE (30:70) to afforded diastereomeric mixture of **6a** and **6b** product in 53 % yield colorless liquid.

**Rf:** 0.4 (EA: PE 40:60).

**Yield:** 53%.

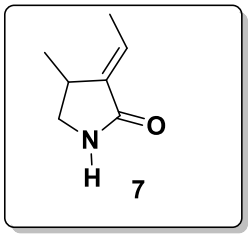
**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.66 (br s., 1 H), 3.86 (qd, *J* = 6.2, 8.8 Hz, 1 H), 3.47 (dt, *J* = 1.1, 9.1 Hz, 1 H), 2.92 (dd, *J* = 8.1, 9.5 Hz, 1 H), 2.28 - 2.14 (m, 1 H), 1.93 (t, *J* = 8.9 Hz, 1 H), 1.26 (d, *J* = 6.3 Hz, 3 H), 1.20 (d, *J* = 6.8 Hz, 3 H).

**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 180.7, 69.3, 53.9, 48.1, 32.4, 21.1, 19.4

**IR ($CHCl_3$):** $\nu_{max}$ 3648. $cm^{-1}$

**HRMS (ESI):** *m/z* calcd for $C_7H_{14}N_2O$ $[M + H]^+$: 144.1019, found: 144.1017.

**Preparation of (*E*)-3-ethylidene-4-methylpyrrolidin-2-one (7)**



7

The alcohol **6** (0.200 gm, 1.0 equiv) was dissolved in dichloromethane (10 mL) cooled to 0 ℃ and then triethylamine (0.240 mL, 1.5 equiv) added followed by methanesulfonyl chloride (0.320 mL, 1.5 equiv) dropwise and stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC. The reaction mixture after completion of reaction was cooled and quenched with sat. $NaHCO_3$ solution and extracted with DCM (3x10 mL). The organic phase was washed with brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* gave crude mesylate. Further, the O-mesylated crude compound (0.300 gm, 1.0 equiv) was treated with DBU (0.230 mL, 1.2 equiv) in dichloromethane (5 mL) for 24 hr at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was washed with water. The organic phase was washed with brine and the organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **7** (0.110 gm, 52% yield).

**Rf:** 0.4 (EA: PE 40:60).

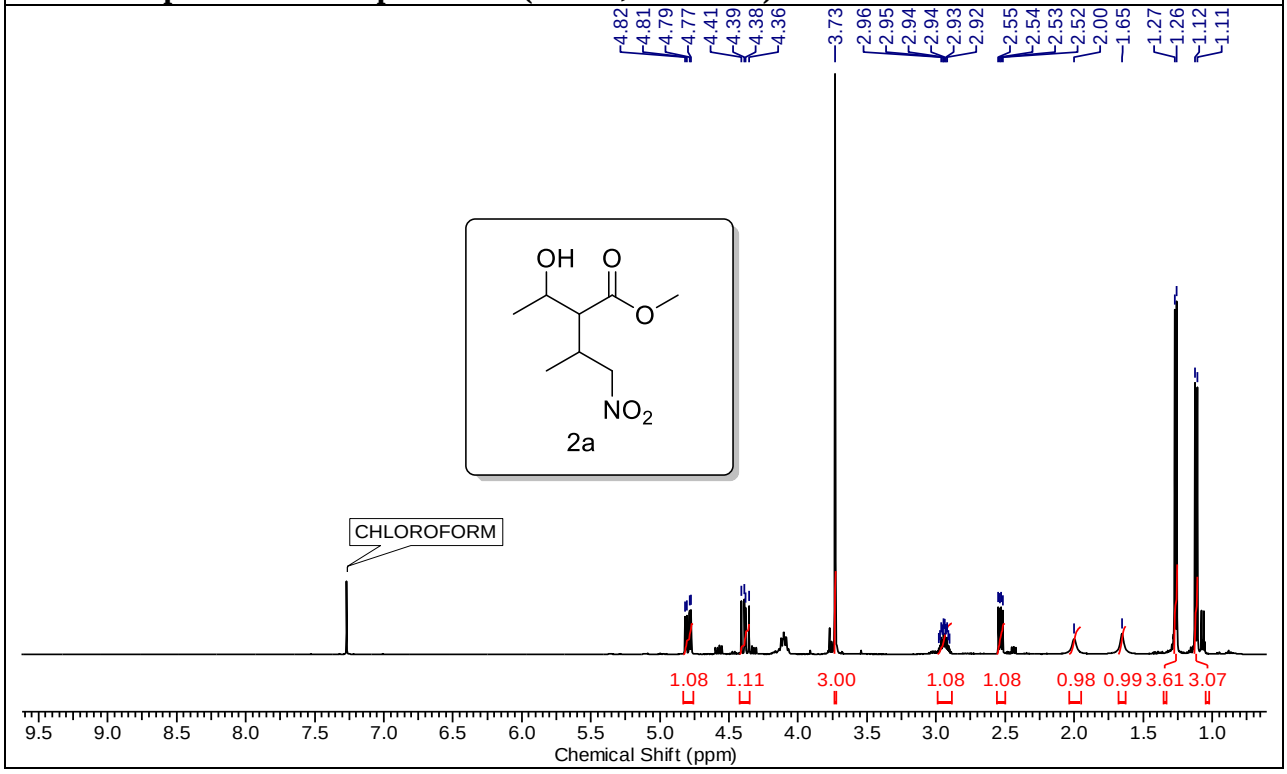
**Yield:** 52%.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 6.66 (br s, 1 H), 5.93 (q, 1H), 3.51 (t, 1H), 2.95 (br,s 1H), 2.91(t, 1H), 2.88 (d, 3H), 1.18 (d, 3H).

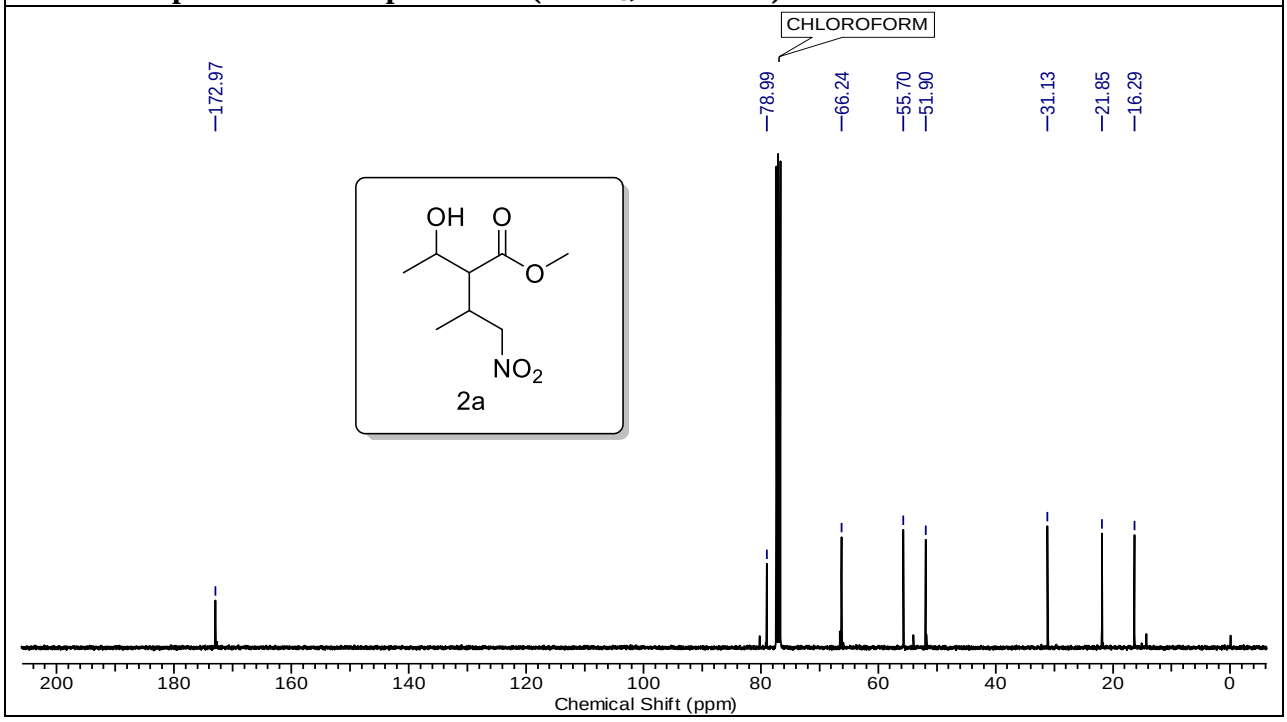
**$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 172.12, 135.06, 131.62, 47.20, 34.49, 19.70, 13.13.

## 2.2.4 Spectral Data

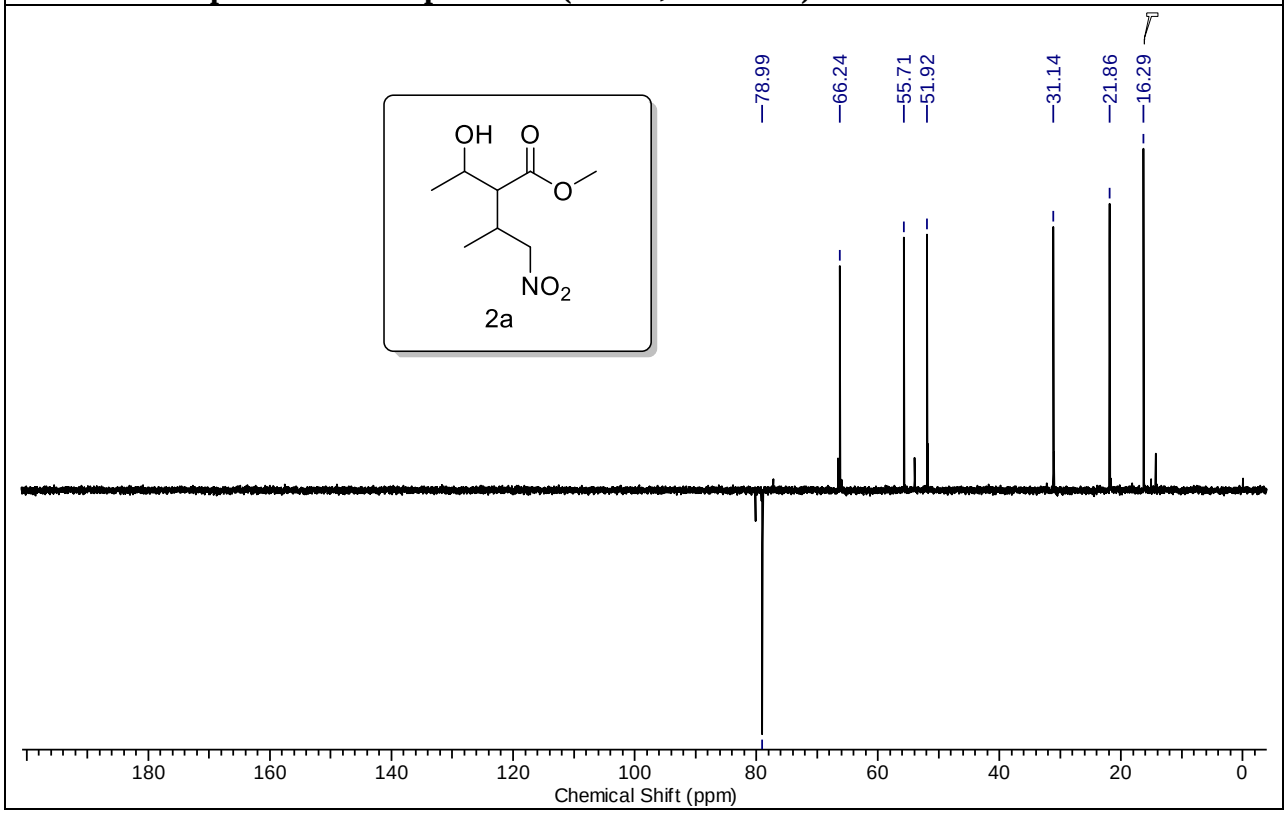
**$^{1}$H-NMR spectrum of compound 2a ($CDCl_3$, 400 MHz)**



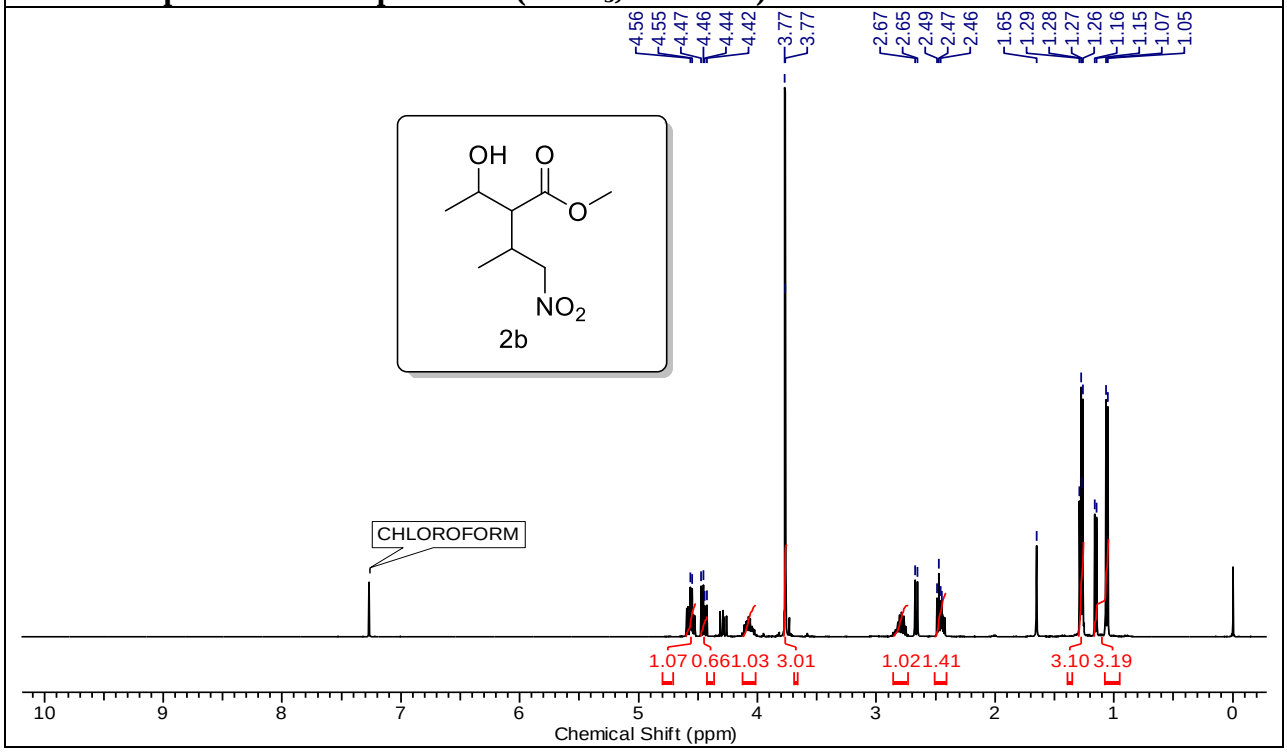

**$^{13}$C-NMR spectrum of compound 2a ($CDCl_3$, 100 MHz)**



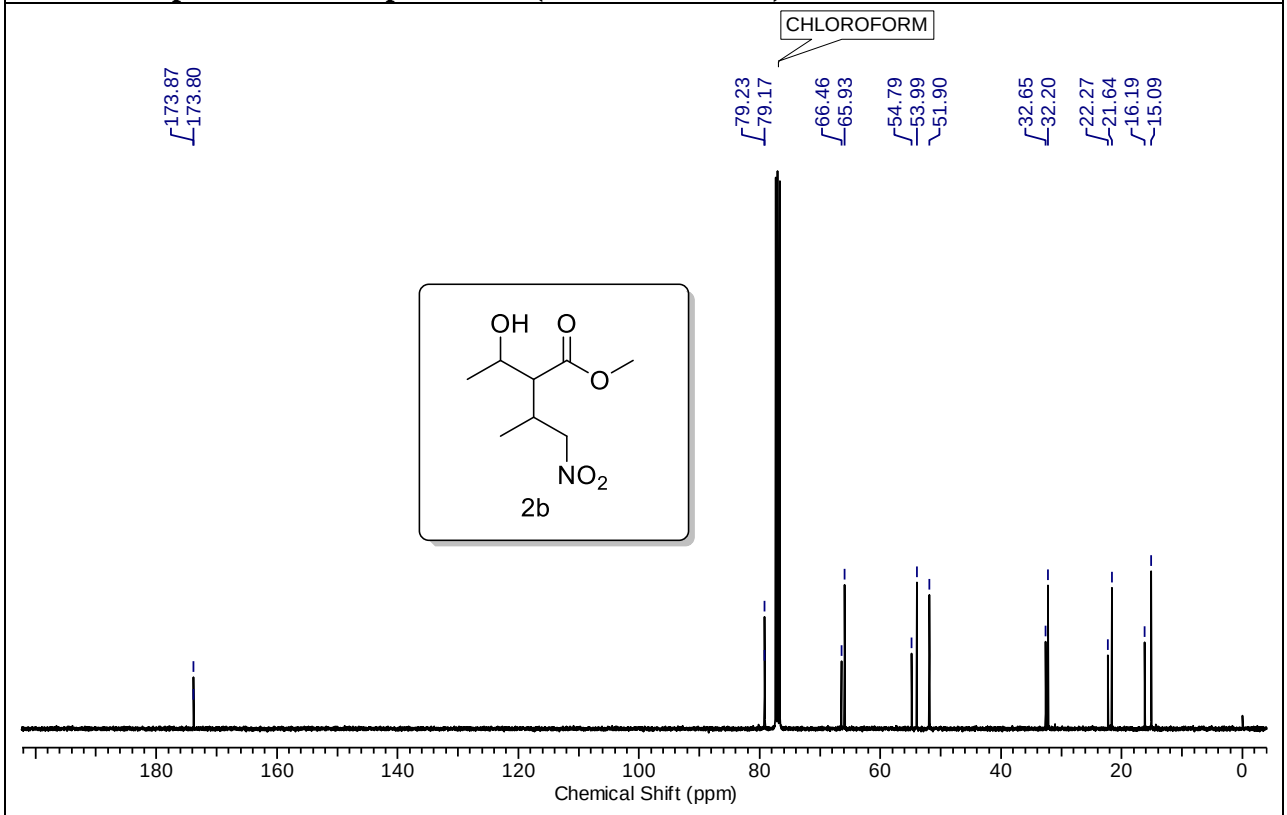
**DEPT NMR spectrum of compound 2a ($CDCl_3$, 100 MHz)**



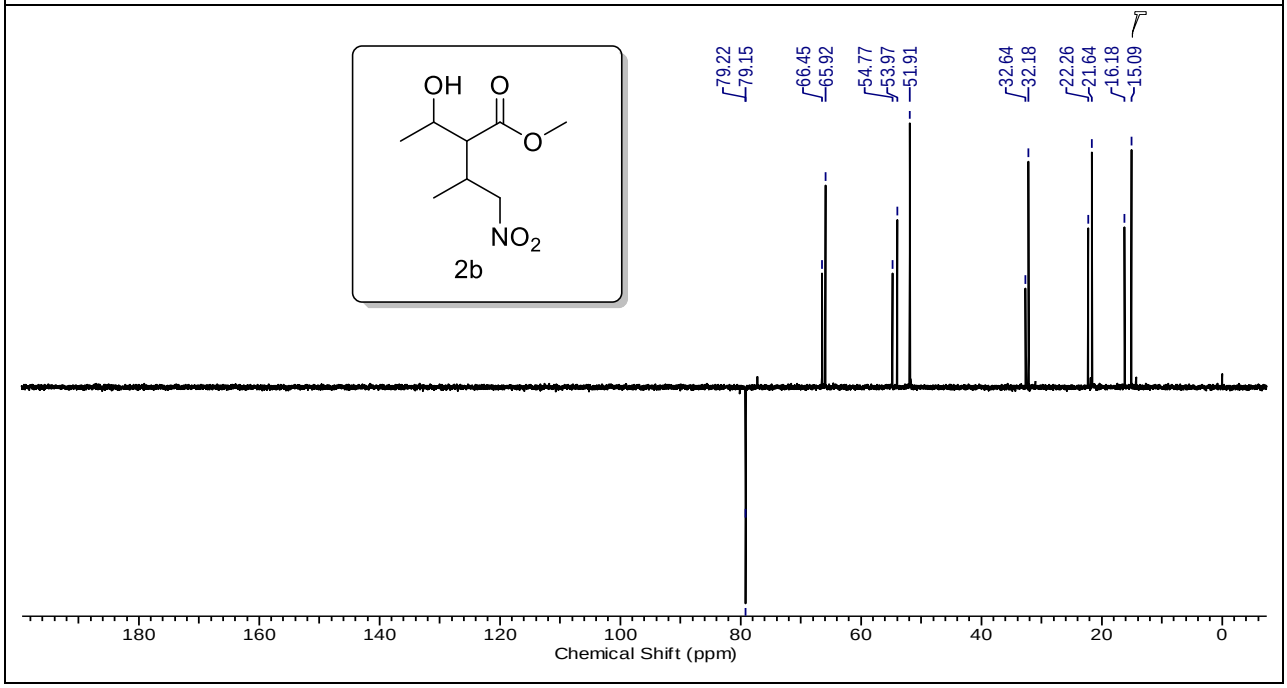

**$^1$H-NMR spectrum of compound 2b ($CDCl_3$, 400 MHz)**



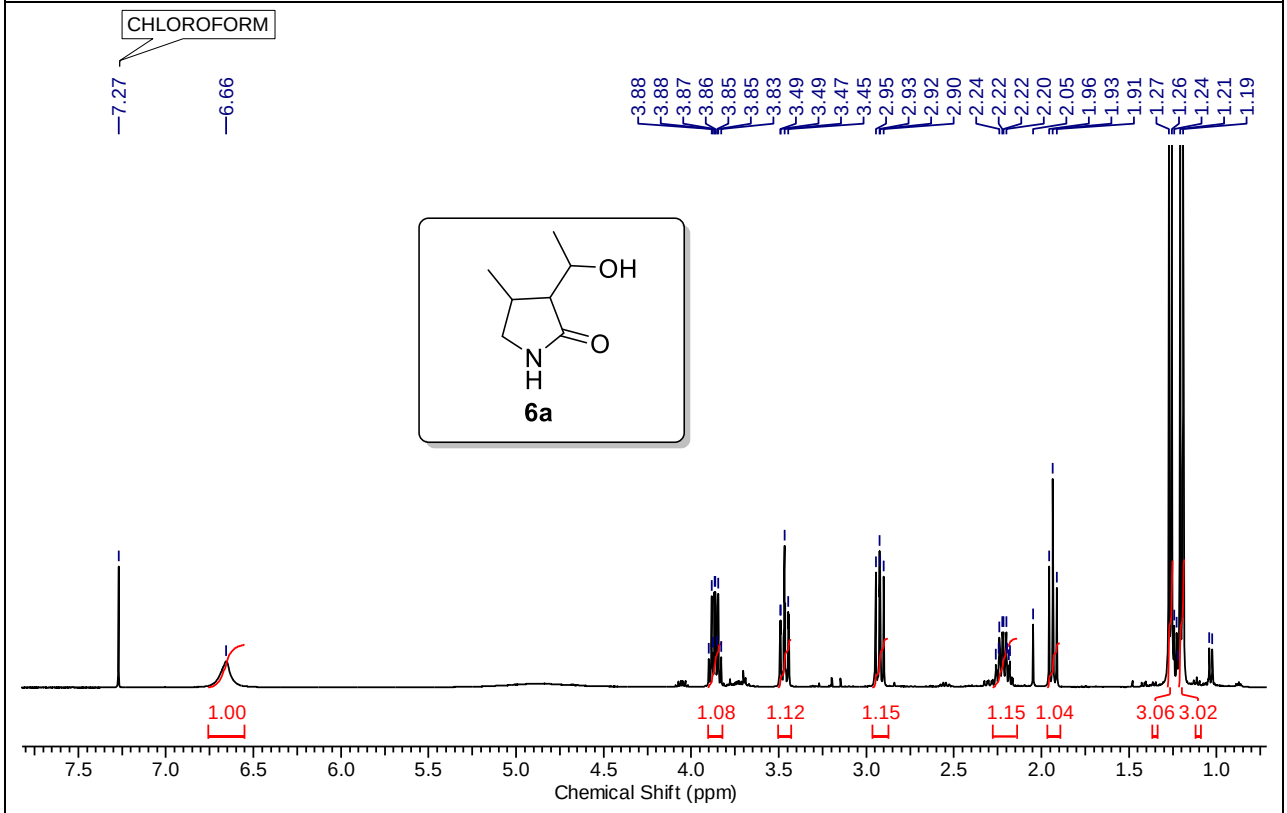
**$^{13}$C-NMR spectrum of compound 2b (CDCl$_3$, 100 MHz)**



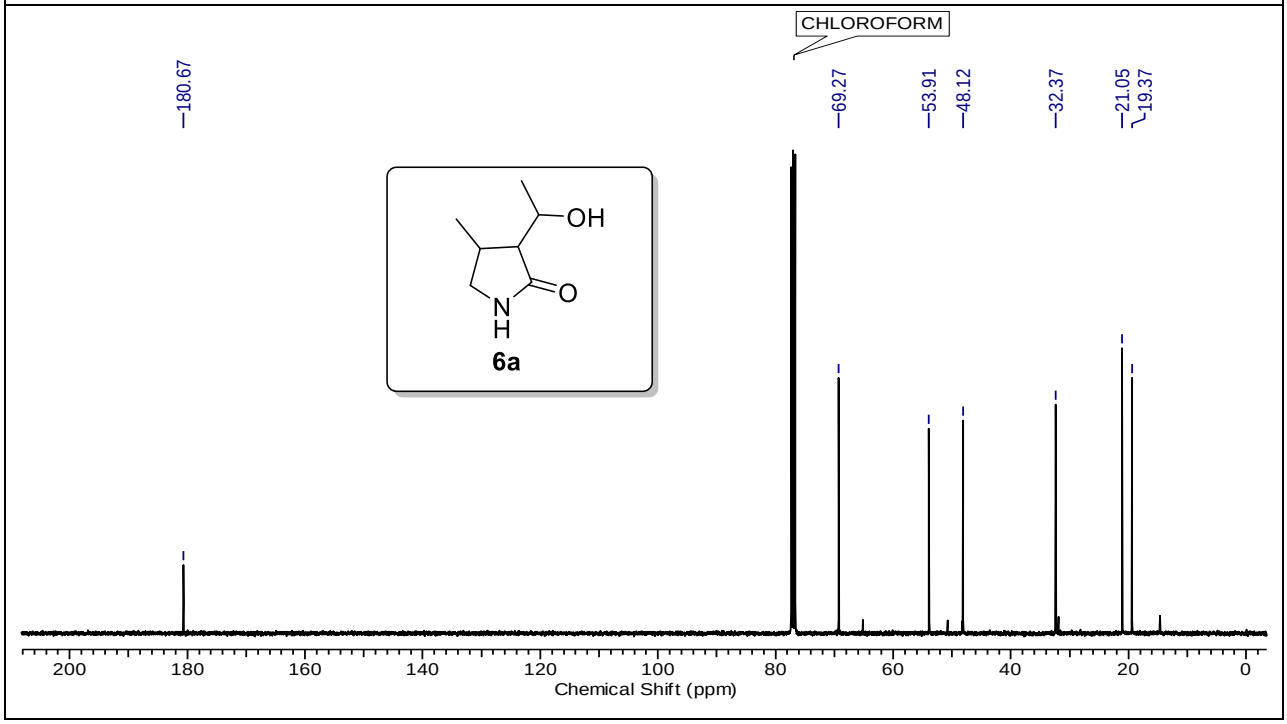

**DEPT NMR spectrum of compound 2b (CDCl$_3$, 100 MHz)**



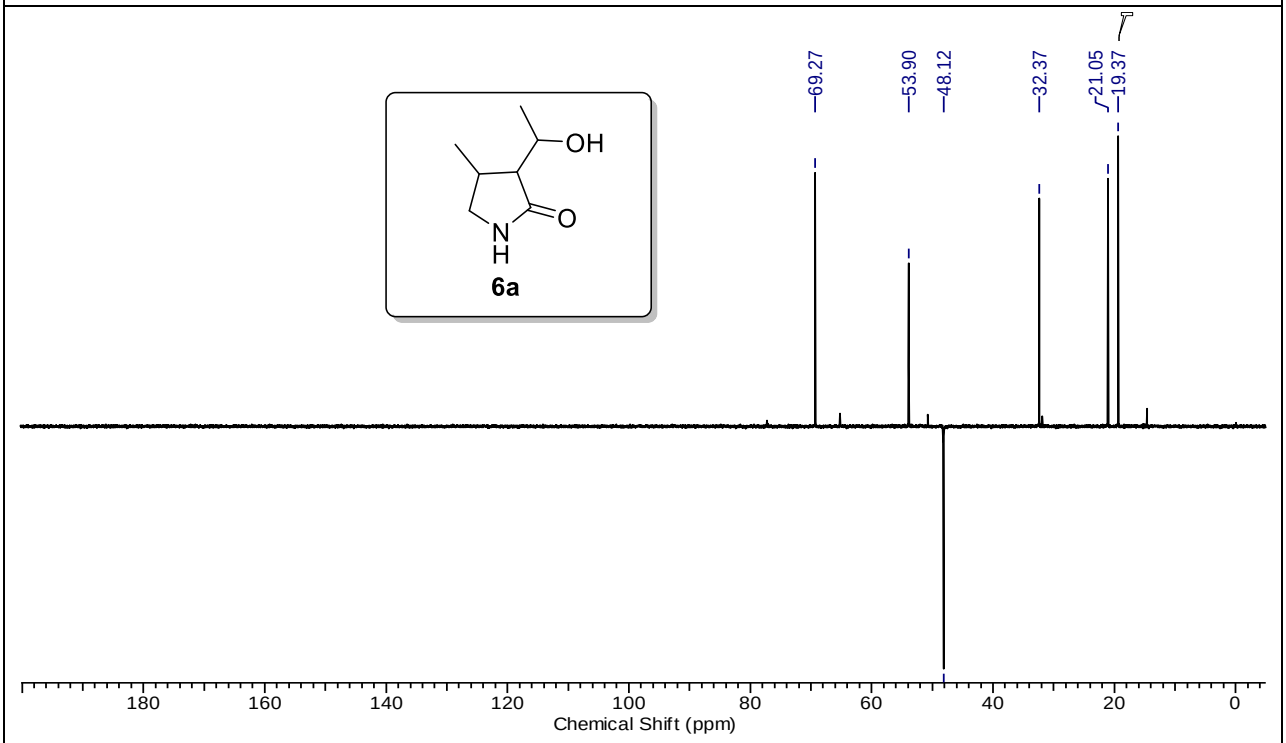
**$^{1}$H-NMR spectrum of compound 6a ($CDCl_3$, 400 MHz)**



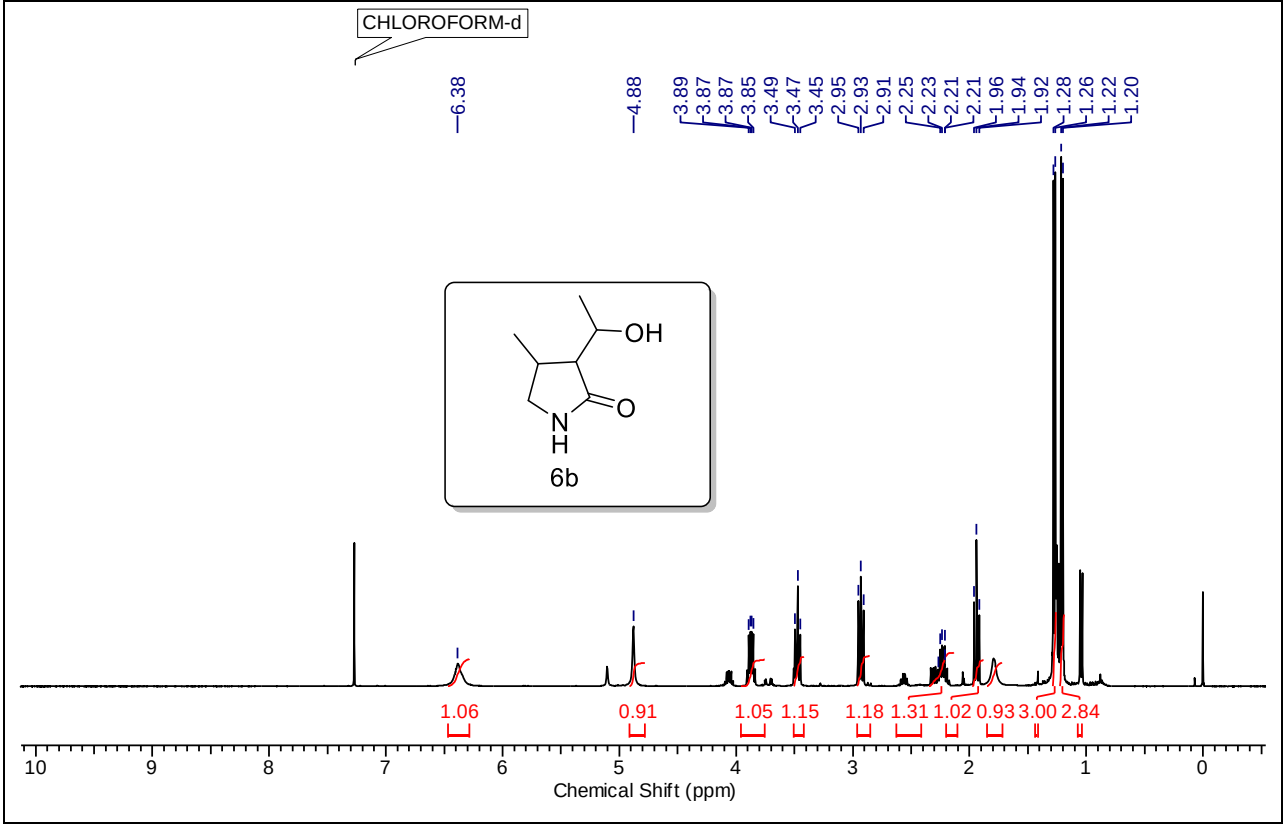

**$^{13}$C-NMR spectrum of compound 6a ($CDCl_3$, 100 MHz)**



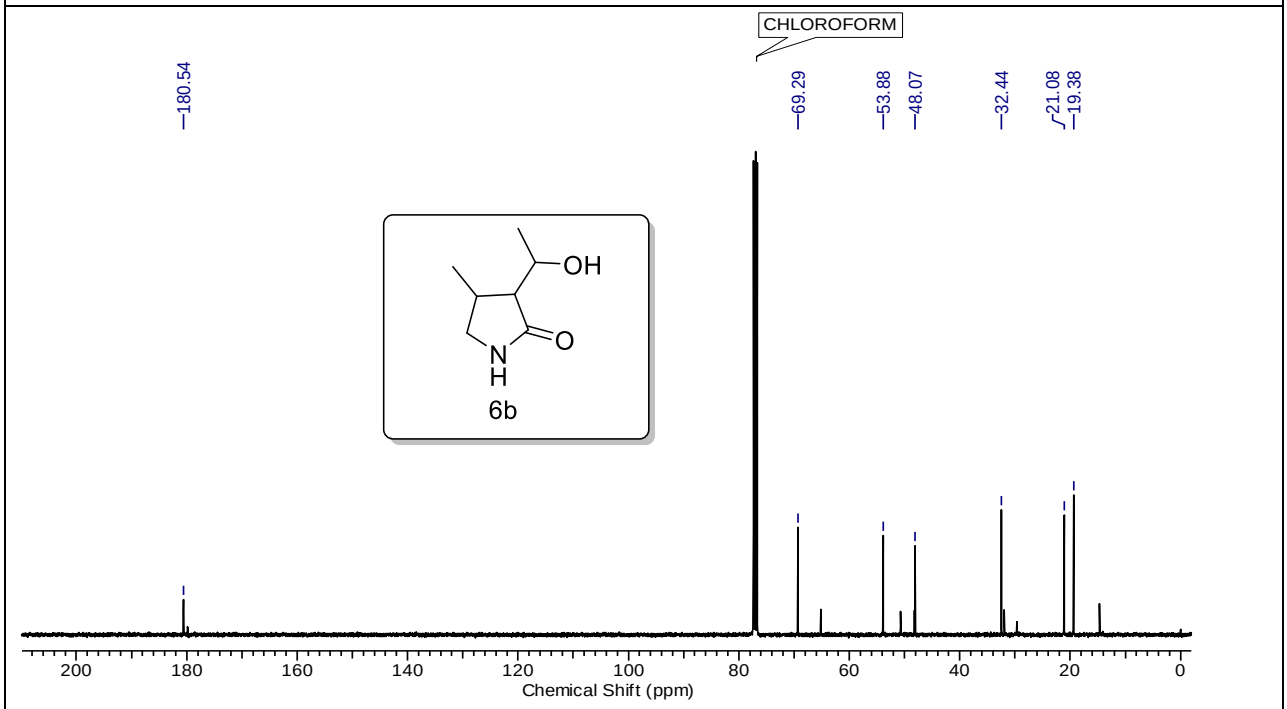
**DEPT NMR spectrum of compound 6a ($CDCl_3$, 100 MHz)**



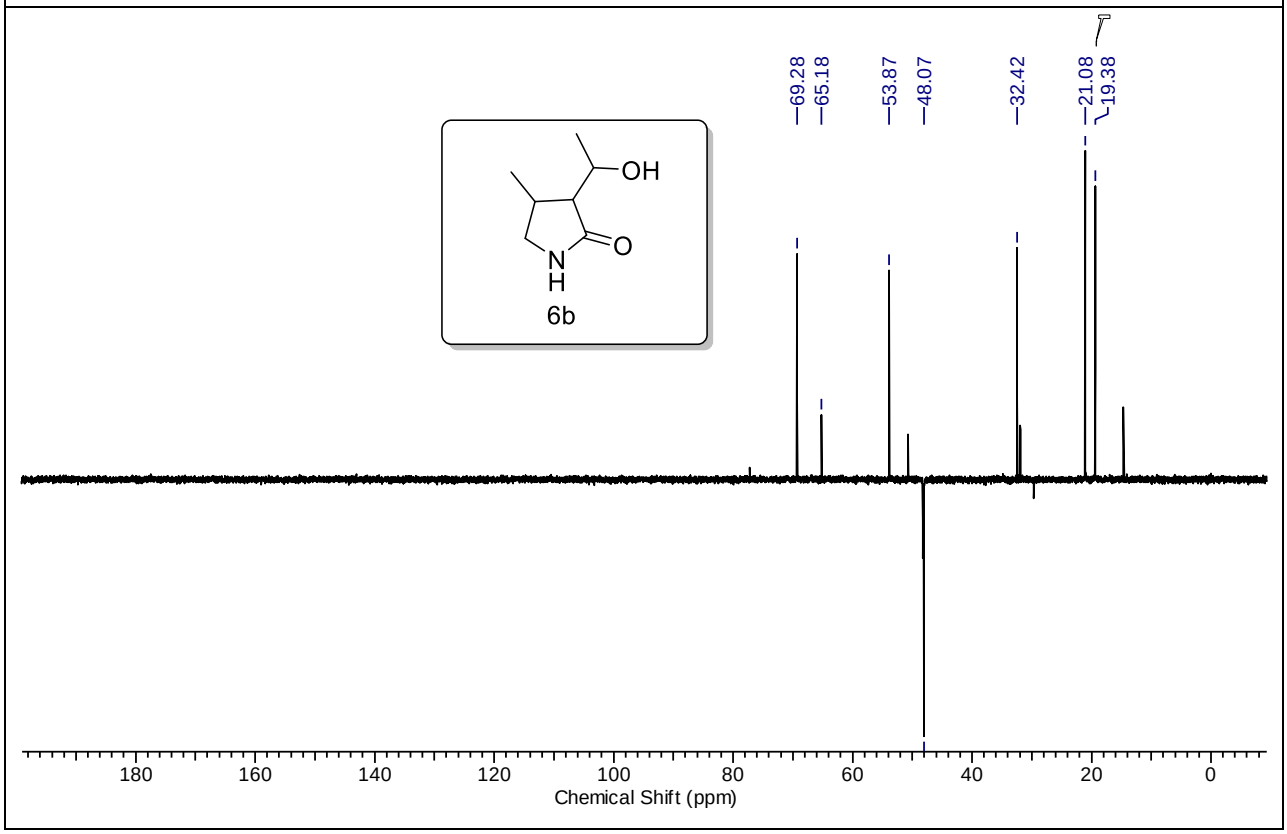

**$^1$H-NMR spectrum of compound 6b ($CDCl_3$, 400 MHz)**



**$^{13}$C-NMR spectrum of compound 6b (CDCl$_3$, 100 MHz)**




**DEPT NMR spectrum of compound 6b (CDCl$_3$, 100 MHz)**



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20180308-125005-42650
Nitin

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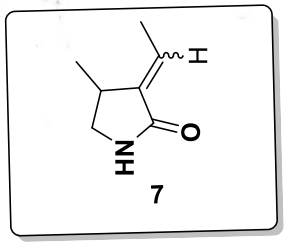


7

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11 Mar 2018
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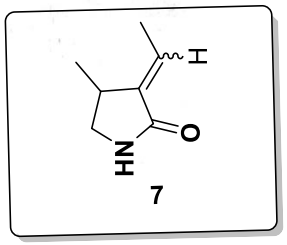


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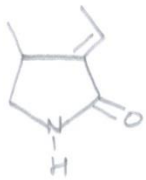

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11 Mar 2018
20180308-125005-42650
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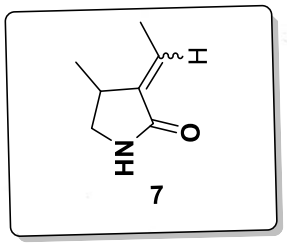


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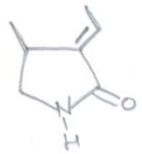
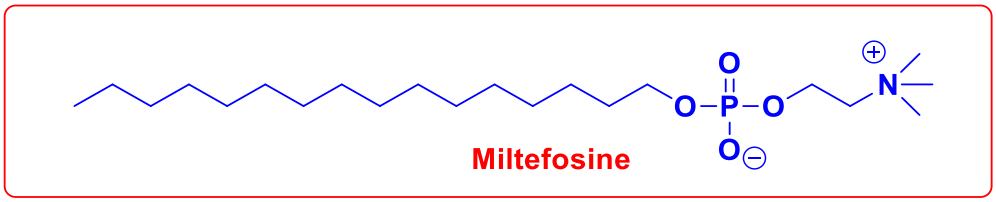


# Chapter 3: Continuous flow synthesis of miltefosine

## Section-I Introduction and literature review of miltefosine



### 3.1.1 Introduction

Miltefosine is an alkylphosphocholine drug with demonstrated activity against various parasite species and cancer cells as well as some pathogenic bacteria and fungi[1]. Initially miltefosine was studied as a cancer medication, due to side effects it was never used for this purpose. Miltefosine is the first effective oral drug against both visceral[2] and cutaneous[3,4] forms of the infection, preserving its activity against antimonial-resistant parasites[5] or on immunodepressed patients without the severe side effects common to most of the first-line leishmanicidal drugs.[6]

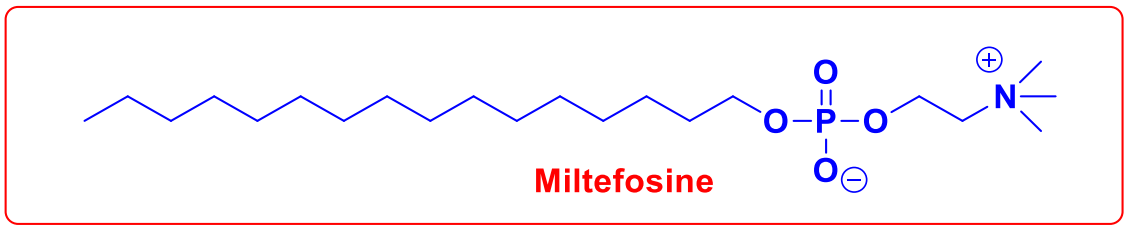



**Figure 1**

It is the first and still the only oral drug that can be used to treat visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL). Visceral leishmaniasis (VL or kala-azar, which means black fever in Hindi), the most severe form of leishmaniasis, is typically caused by the *Leishmania donovani* species complex. It can be caused by about 20 different protozoan species of *Leishmania* species[7] which are transmitted to humans through the bite of female phlebotomine sandflies. During the dimorphic life cycle, the parasites develop in the guts of the sandfly into promastigotes[8]. Once the parasite is transmitted to humans, they grow up within the parasitophorous vacuole of human macrophages into amastigote forms followed by host cell destruction to release *Leishmania* parasites for repeated infection of macrophages.

**Transmission of leishmaniasis**

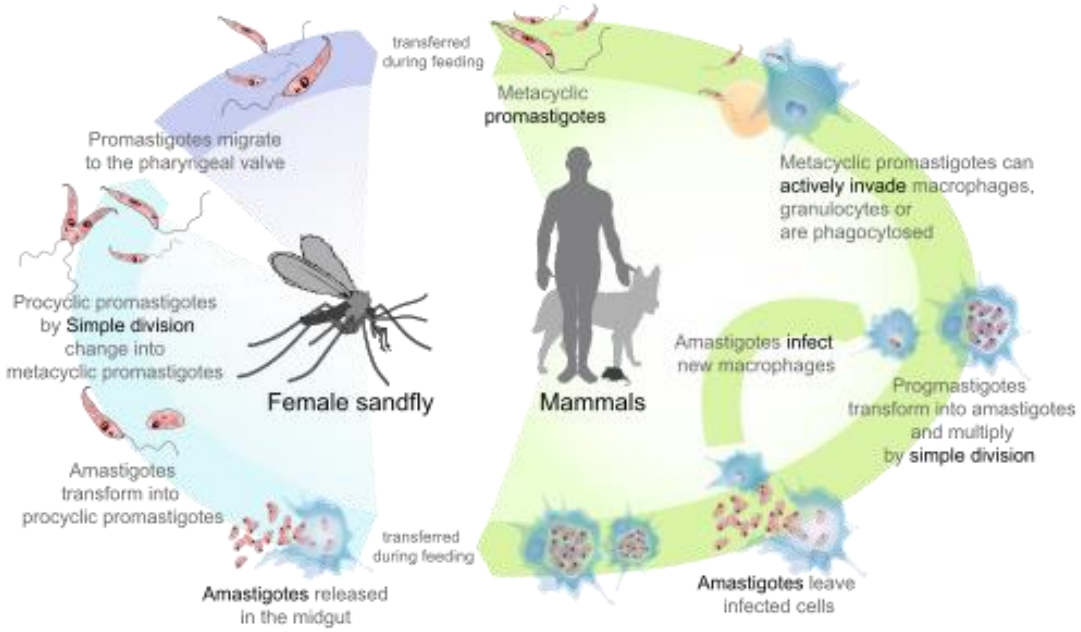



**Figure 2**

**Increasing Devastation of Leishmaniasis**

90 % of visceral leishmaniasis cases are found in 5 countries India, Sudan, Brazil, Eastern Africa and Uganda. Indian subcontinent accounts for about 70% of world's visceral leishmaniasis (VL) burden. India alone contributes~50% and the north eastern state of Bihar accounts for majority of visceral leishmaniasis (VL).

**Status of endemicity of visceral leishmaniasis worldwide 2018**

- 103 countries in tropical temperate regions.
- Most of them are developing or least developed.
- 2 Million cases occur annually.
- More than 350 million people are at risk.
- Prevalence of 12 million.
- Human leishmaniasis is on the increase worldwide.

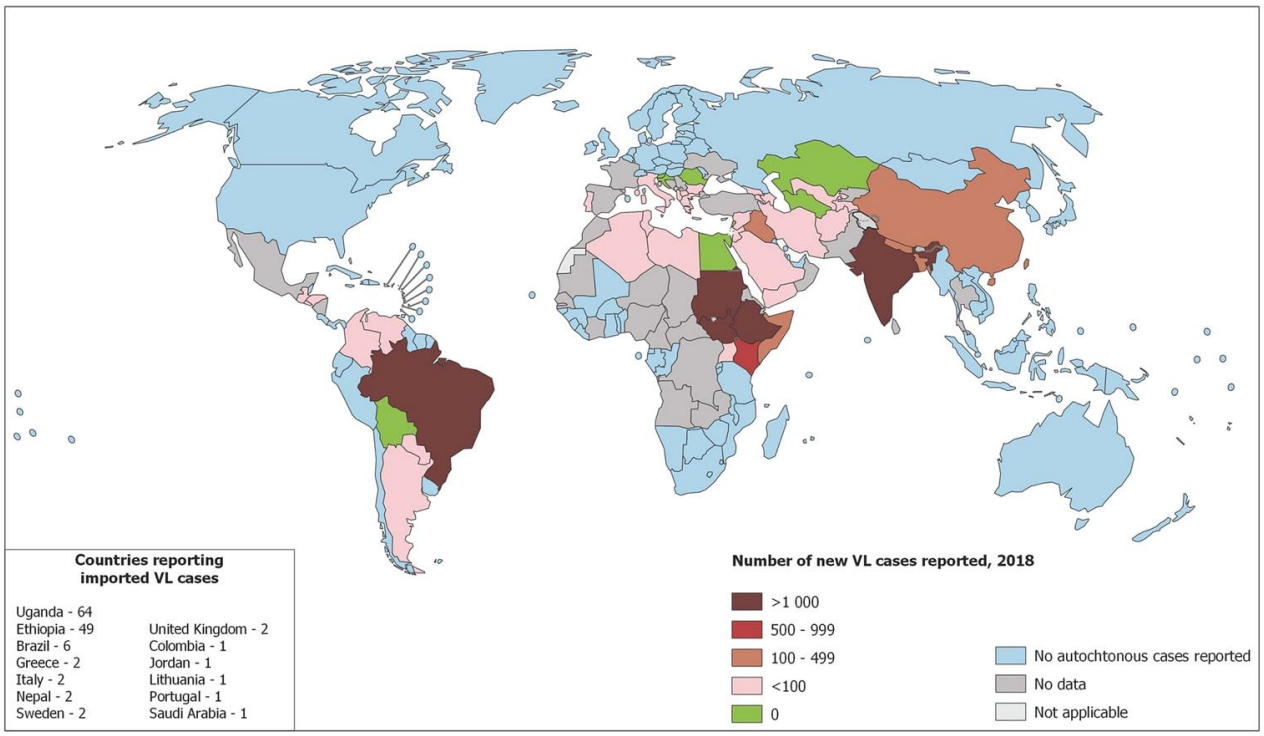



**Figure 3** Status of endemicity of visceral leishmaniasis worldwide 2018

## Miltefosine (Impavido)

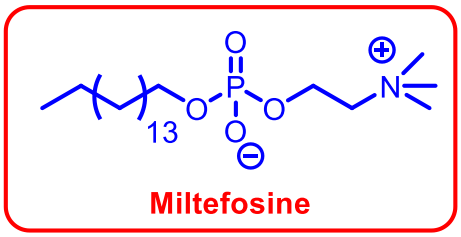




**Figure 5**

Impavido 50 mg Capsule (7 Capsules in 1 strip)

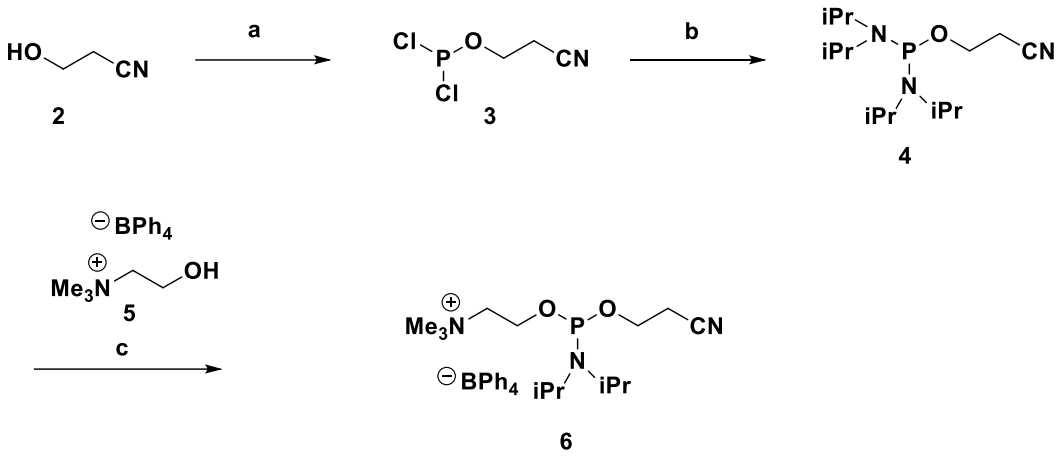
**Manufacturer:** Zydus Cadila

### 3.1.2 Literature review

**1) Steven**[15] ***et al.*** (*Org. Biomol. Chem.,* **2020**, 18, 767)

**a) Synthesis of Phosphoramidite 6**

Recently in 2020 Steven *et al.* reported the synthesis of miltefosine (Scheme **1a**) in one-pot, three-step sequence (phosphitylation, oxidation, and phosphate deprotection). 2-Cyanoethanol **2**, was reacted with phosphorus trichloride to provide phosphorus dichloride **3.** Then on reaction with diisopropylamine, it gives phosphordiamidite **4** which is further treated with choline tetraphenyl borate to give the compound **6.**

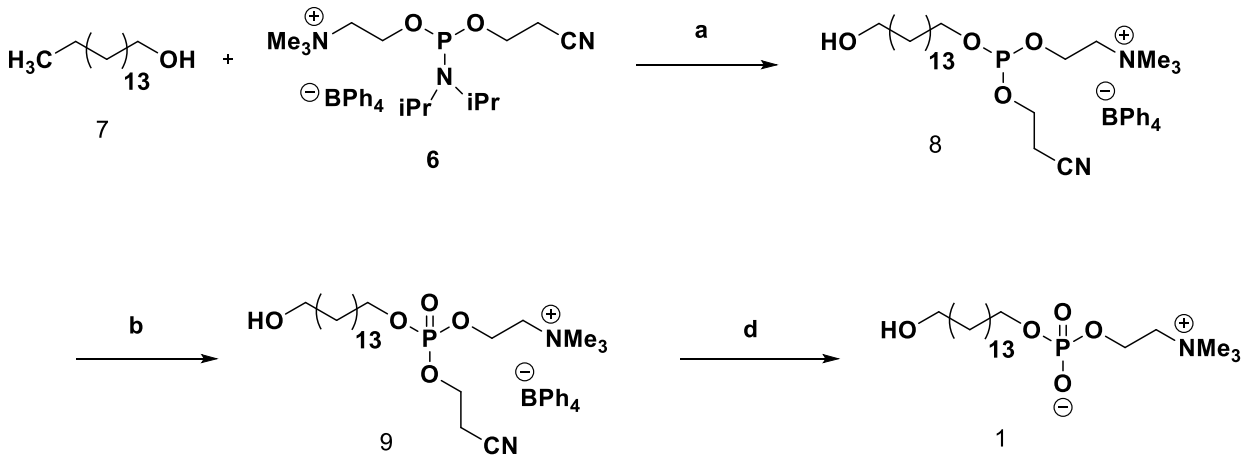



***Scheme 1a*:** Synthesis of Phosphoramidite **6**

***Scheme 1a:*** **Reagents and Conditions:** (a) $PCl_3$, $CH_3CN$, 0 °C, $N_2$, 2 h,; (b) diisopropyl amine, rt, 12 h,; (c) tetraphenyl borate, 1*H*-tetrazole, 0 °C-rt, 12 h.

**b) Synthesis of miltefosine**

Steven *et al.* reported the synthesis of miltefosine by using hexadecanol as a starting material. Hexadecanol was treated with slight excess (1.2 equiv.) of the phosphoramidite **6** and 1*H*-tetrazole to give intermediate **8.** Further, the compound **8** was treated with TBHP to give **9** and then the compound **9** was treated with execess of DBU to gives the miltefosine (**Scheme 1b**).

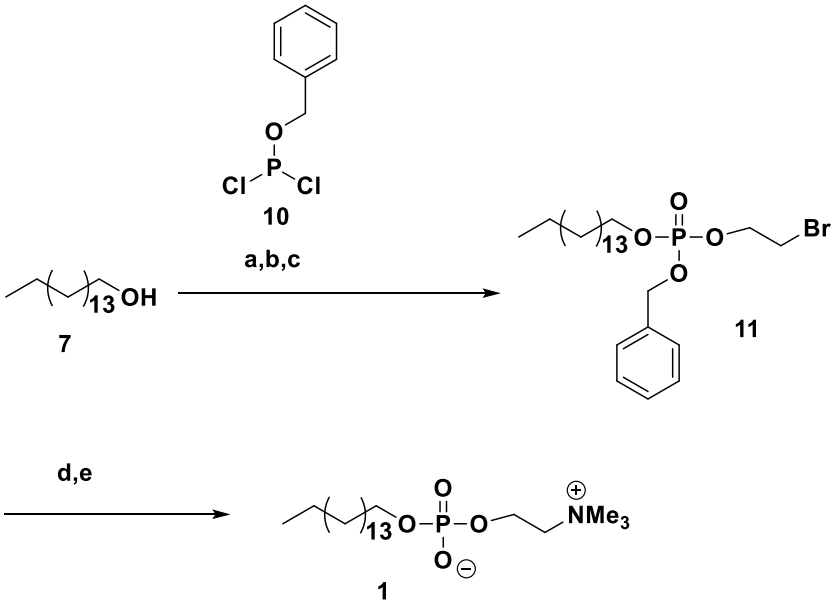


***Scheme 1b***

***Scheme 1b*: Reagents and Conditions: (**a) 1*H*-tetrazole, $CH_3CN$, 25 °C; (b) TBHP, 25 °C, 3 h; (c) DBU, $CH_2Cl_2$ , 25 °C, 12 h.

**2) Zaffalon *et al.*[16] (***Synthesis* **2011**, *2011*, 778)

Zaffalon *et al.* in 2011 reported synthesis of miltefosine **1** by using benzyloxydichlorophosphine (BODP) which has been found to be a convenient reagent for the synthesis of phospholipids. A series of artificial ether and ester phospholipids have been prepared in good to high yields **(Scheme 2).**



***Scheme 2***

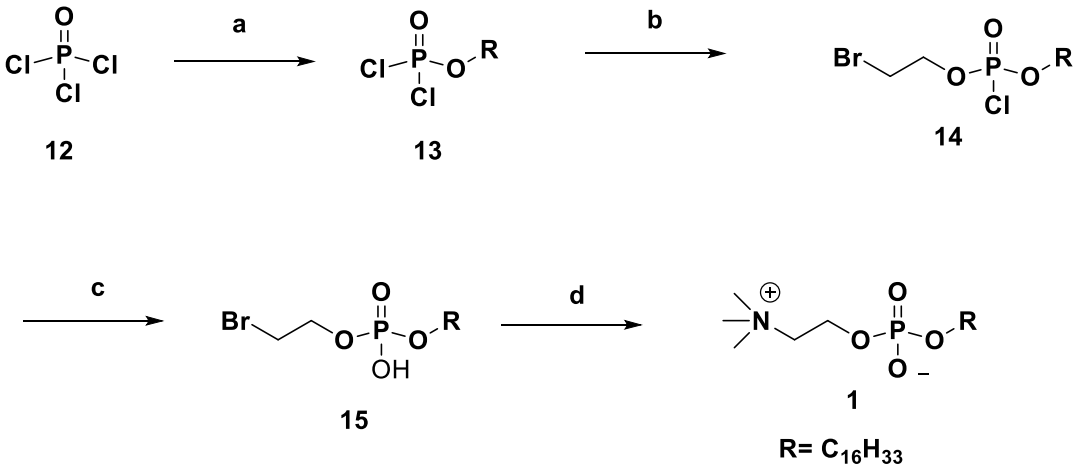
***Scheme2:*** **Reagents and conditions:** (a) BODP, $Et_3N$, THF, 0 °C, 3 hr.; (b) Bromoethanol, 0 °C, 3 hr,; (c) MCPBA, (d) TFA, $CH_2Cl_2$, (e) $Me_3N$, MeCN, $CHCl_3$, i-PrOH, 40%.

The synthesis of miltefosine started from hexadecanol **7** which was reacted with BODP **10** followed by reaction with bromoethanol and oxidation using MCPBA to give the protected phosphate **11** followed by deprotection with trifluoroacetic acid and substitution with trimethylamine led to the final desired product **1** in two steps and 37% overall yield.

**3) North *et al.*** [17] (*Bioorg. Med. Chem.* **2009**, *17*, 3433.)

**Method -I**

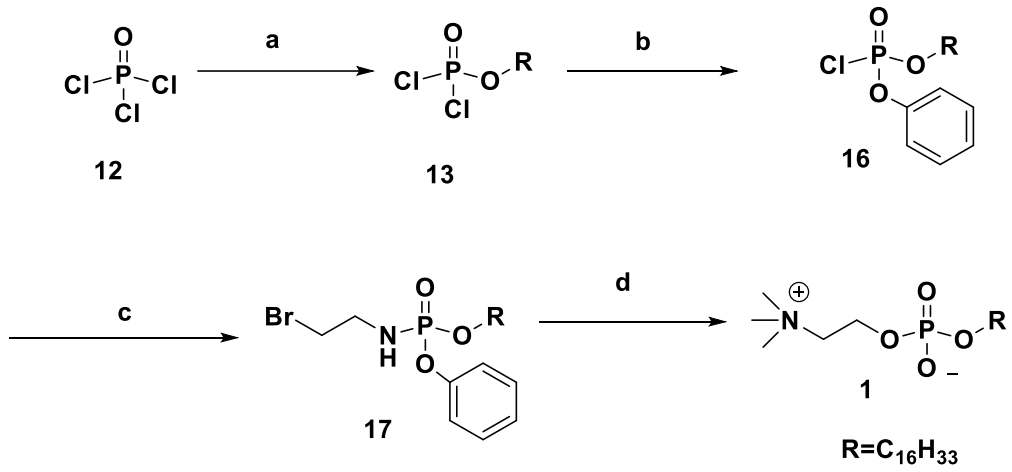
In 2009 North *et al.* reported the synthesis of miltefosine from phosphorus oxychloride. Phosphorus oxychloride **12** was reacted first with a long chain alcohol (hexadecanol), to form the dichloro compound **13.** Compound **13** was treated with 2-bromoethanol to give the bromo compound **14** and then the bromo compound **14** was reacted with water to give the compound **15.** Finally the nucleophilic displacement of bromine in the presence of trimethylamine gave miltefosine **1** in good yields. **(Scheme 3a)**




***Scheme 3a***

***Scheme 3 a)*** **Reagents and Conditions** (a) Hexadecanol, $Et_3N$, THF, 0 °C; (b) Bromoethanol, $Et_3N$, THF, 0 °C; (c) $H_2O$, $Et_3N$, THF, rt; (d) $N(CH_3)_3$, EtOH, MeOH, 50 °C.

**b)** A phosphoramidate modified synthesis by Garrido-Hernandez and co-workers for the phosphonamidate series was also described (Scheme 3b) Phosphorus oxychloride **12** was successively reacted with a long chain alcohol (hexadecanol) in the presence of triethylamine, to form dichloro compound **13.** Further the compound **13** was treated with phenol to give compound **16.** The displacement of chlorine using 2-bromoethylamine hydrobromide to form bromo compound **17** and treatment with trimethylamine using EtOH and MeOH gave final products **1.**

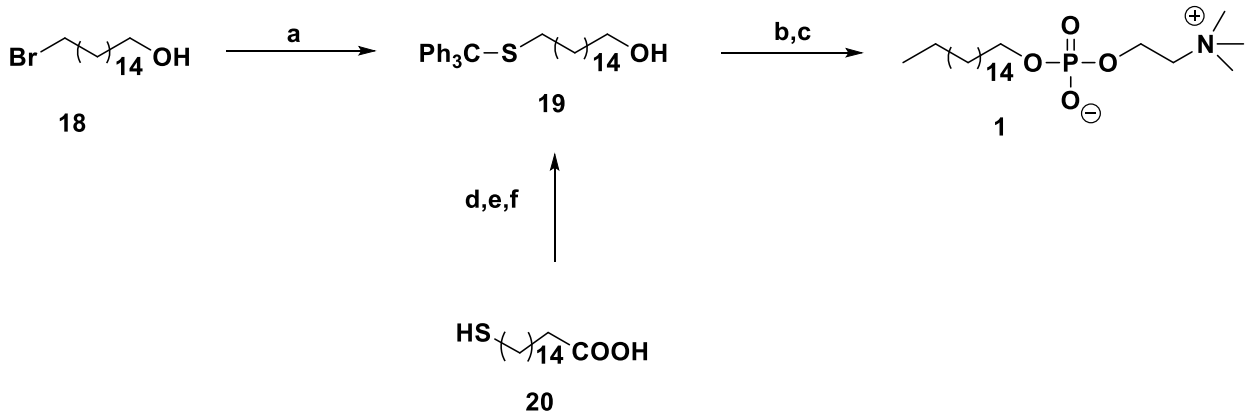



***Scheme 3b***

***Scheme 3b)*** **Reagents and Conditions** (a) Hexadecanol, $Et_3N$, THF, 0 °C,; (b) Phenol, $Et_3N$, THF, 0 °C,; (c) bromoethylamine, $H_2O$, $Et_3N$, THF, DMF, rt.; (d) $N(CH_3)_3$, EtOH, MeOH, 50 °C.

**4) Guerria *et al.*** [18] **(**Bioorg. Med. Chem. Lett. **2006**, 16, 5190–5193)

In 2006 Guerria *et al* .reported the synthesis of miltefosine by using bromoalcohol **18** in three steps (**Scheme 4).** Bromoalcohol **18** was treated with trityl sulfide to give thiol protected alcohol **19**. Further the introduction of phosphocholine group in thiol protected alcohol **19** by using 2-chloro-2-oxo-1,3,2-dioxaphospholane and trimethylamine and further trityl deprotection with triethylsilane/trifluoroacetic acid gave final product. Alternate approach using acid 20 was also described.

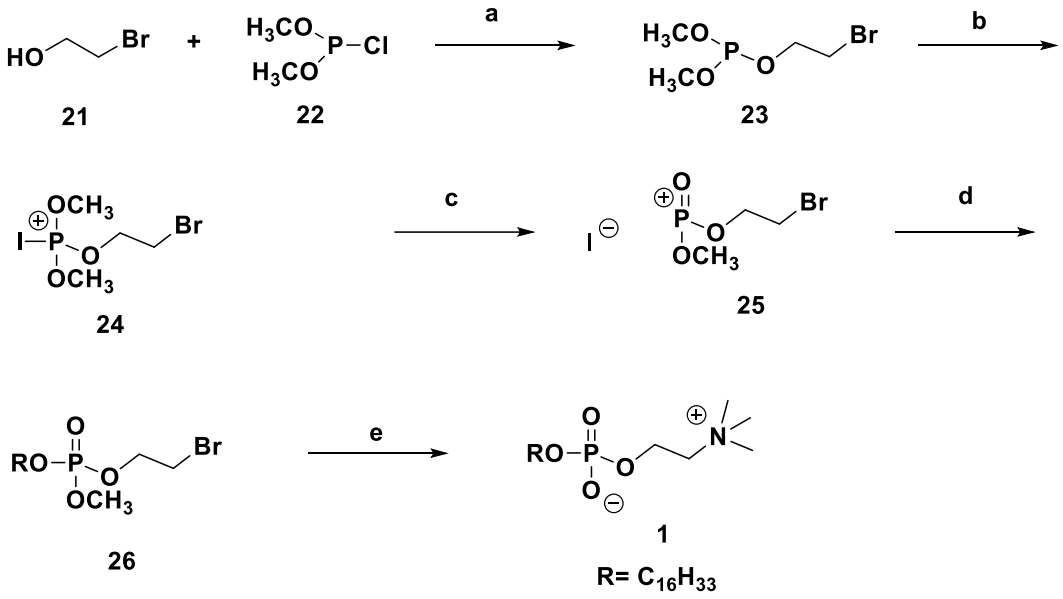



***Scheme 4***

***Scheme 4*** **Reagents and conditions:** (a) $Ph_3CSH$, $K_2CO_3$, MeOH, Ar, 90%; (b) 2-chloro-2-oxo-1,3,2-dioxaphospholane, $Me_3N$, MeCN, Ar, pressure tube, 78 °C, then rt, 2 h, and 70 °C, 4 h, 43%; (c) triethylsilane, TFA/$CH_2Cl_2$ 1:1, Ar, rt, 1 h, 83%; (d) $Ph_3CCl$, DMF, Ar, rt, 48 h, 60%; (e) $Cl_2SO$, MeOH, Ar, 0 °C, then rt, 1 h, 98%; (f) DIBAL-H, MePh, Ar, rt, 1 h, 85%.

**5) Hendrickson *et al.*** [19] (*Chem. Phys. Lipids*, **2001**, *109*, 203)

Hendrickson *et al.* in 2001 reported the synthesis of miltefosine by using bromoethanol as a starting material (**Scheme 5**).



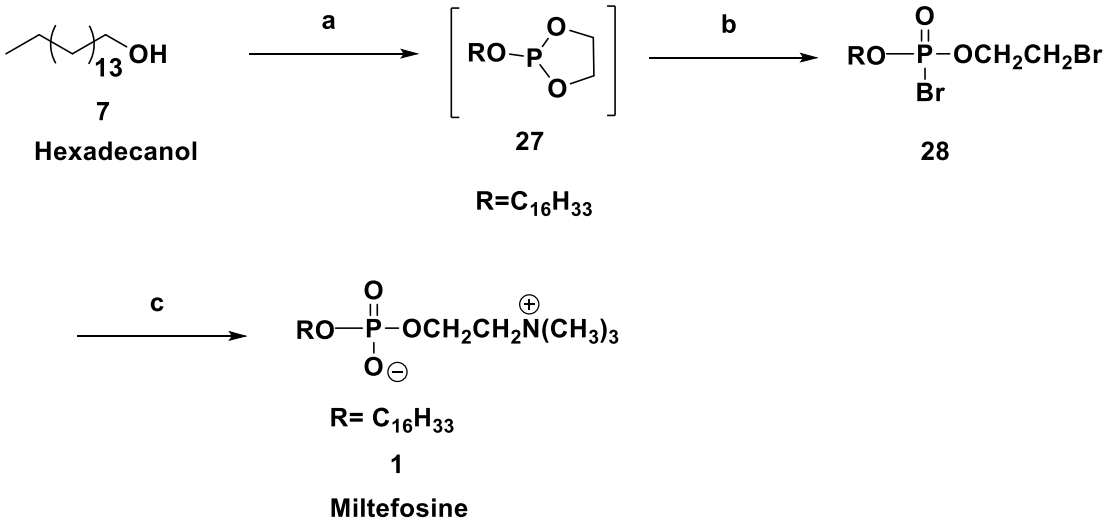

***Scheme 5***

***Scheme 5*: Reagents and Conditions** (a) Pyridine, $CH_2Cl_2$, 0 °C.; (b) $I_2$, $CH_2Cl_2$, 10 min.; (c) $I_2$, dimethylphosphite,; (d) Hexadecanol, pyridine, $CH_2Cl_2$, 0 °C,; (e) 40% aq. trimethylamine, DCM : IPA, 45 min.

2-Bromoethanol **21** was treated with solution of dry pyridine and dimethylchlorophosphite **22** to give bromo compound **23.** Further, the compound **23** was treated with stoichiometric amount of $I_2$ to form iodo compound **24** and the compound **24** was treated with alcohol in presence of pyridine to give bromo compound **25** which was treated with aq. trimethylamine to give final compound miltefosine in good yield.

**6) Bittmann et *al.*** [20] **(***Tetrahedron. Lett.* **1994**, *35*, 5783.)

Bittmann *et al.* in 1994 reported the synthesis of miltefosine using a simple one-pot method for insertion of a phosphocholine moiety into hexadecanol **7** by using easily available ethylene chlorophosphite. (**Scheme 6**)




***Scheme 6***

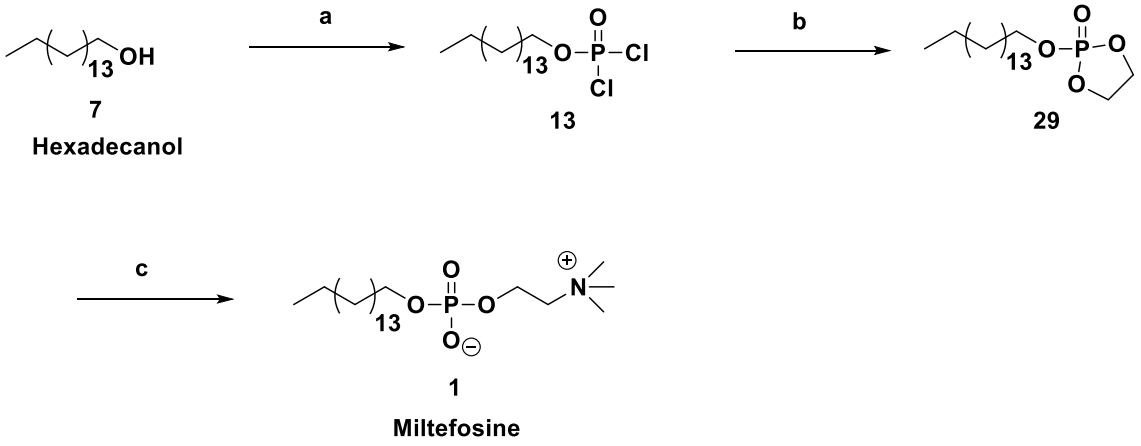
***Scheme 6*: Reagents and Conditions:** (a) ethylene chlorophosphite, EtN(Pr-*i*)$_2$, DCM, -20 °C,; (b) $Br_2$, $CH_2Cl_2$, 0 °C, or -20 °C.; (c) aq. $Me_3N$, *i*-PrOH/$CH_3CN$/$CHCl_3$, sealed tube.

Ethylene chlorophosphite was reacted with hexadecanol **7** to form cyclic phosphate **27.** The cyclic phosphate **27** was further reacted with bromine to give (2-bromoethyl) phosphate ester **28.** In the next step, hydrolysis of the P-Br bond, and quaternization of **28** was carried out by

prolonged heating of with anhydrous trimethylamine (gas) in a pressure tube to obtain miltefosine **1.**

**7) Magold's *et al.*[21] (***Tetrahedron Letters* **1985**, *26*, 1167)

Magold *et al.* in 1985 reported a two-pot, three-steps process for the synthesis of miltefosine. (**Scheme 7**).




**Scheme 7**

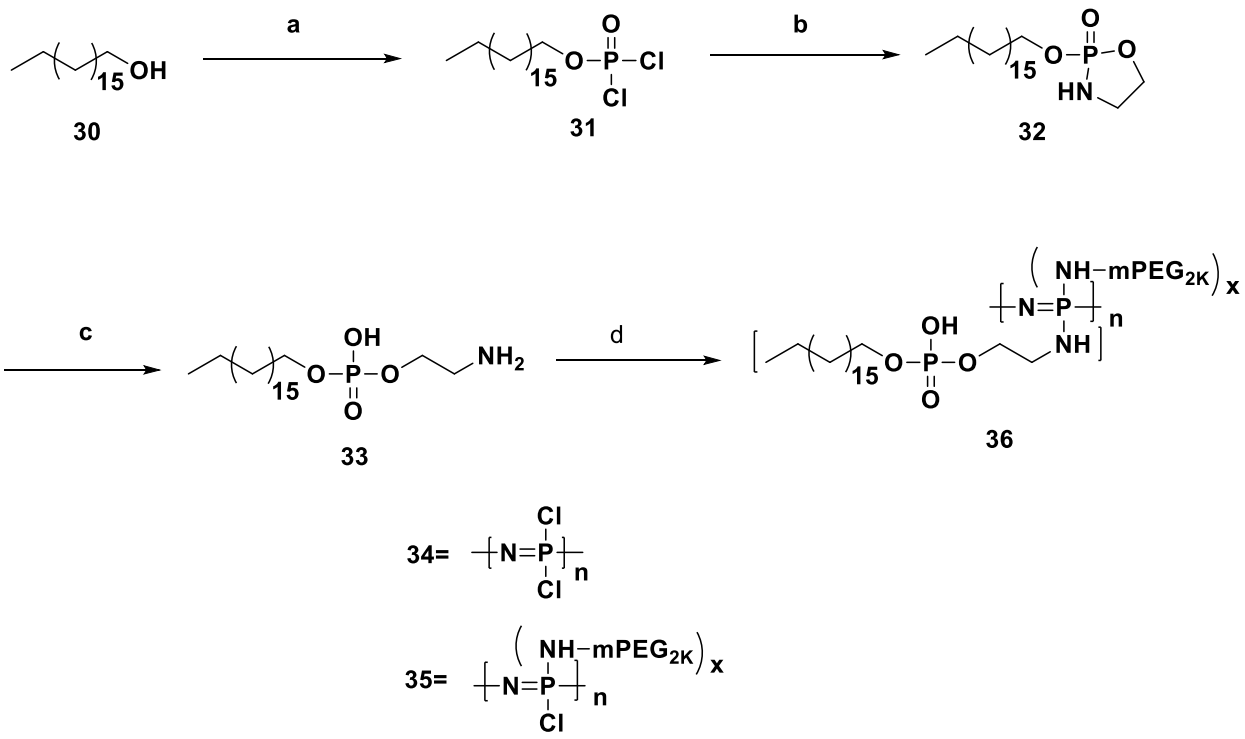
**Scheme 7: Reagents and Conditions:** (a) $POCl_3$, $Et_3N$, $Et_2O$, 0 ℃, 0.5 h; (b) ethylene glycol, $Et_3N$, 0 ℃, 12 h, rt, 65 %,; (c) trimethylamine, sealed tube, 30 h, 75 ℃, 35-50%.

The hexadecanol **7** was treated with $POCl_3$ in presence of triethylamine at 0 ℃ to give dichlorophosphate **13**. Further the dichlorophosphate **13** was treated with ethylene glycol and triethyl amine for 12 h to give the cyclic phosphate **29**. Finally the cyclic phosphate **29** was treated with 3 equiv of trimethylamine in sealed tube for 30 h at 75 ℃ to afford the miltefosine **1** as the final product.

**8) Liyan et al. (***RSC Adv***., 2020**, 10, 7887–7897)

reported the synthesis of Synthesis of poly[methoxy-poly(ethyleneglycol)/ octadecylphosphoethanol-amine]phosphazene (poly[(mPEG)(OPA)phosphazene], PEOP) (Compound **34**) in **Scheme 8**. Synthesis of compound **34** started with octadecanol. The octadecanol 30 was treated with triethylamine in anhydrous THF. Then a solution of $POCl_3$ in

THF was added at 0 ℃ to room temperature for 5 hours. After 5 hours dichloro compound 31 was treated with ethanolamine and triethylamine in THF to give cyclic amine compound **32.** Further the ring opeaning of **32** in acetic acid and water at 70 ℃ for 6 hours to give ring opeaning compound **33** was treated with readily prepared **34** and **35** in presence of triethylamine to obtained desire product **36.**




**Scheme 8**

**3.1.3 Conclusion:** The above literature survey reveals different synthestic routes for the synthesis of miltefosine

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# Chapter 3, Section II

# Continuous flow synthesis of miltefosine

### 3.2.1 Introduction

In the past few years the application of the continuous-flow technologies for the preparation of fine chemicals,[1] such as natural products, medicinal, active pharmaceutical ingredients (APIs), pesticides, bulk chemicals industry, nanomaterials, petrochemicals has gained very significant importance in academia and industrial research.[2] Recently the continuous-flow technology with channel dimensions in the micro- or millimeter region have found widespread application in organic synthesis.[3] The characteristic properties of these reactors are their exceptionally fast heat and mass transfer, less manpower and time saving technique. In the micro structured devices of this type, virtually instantaneous mixing can be achieved for all but the fastest reactions. Similarly, the accumulation of heat, dangers of thermal runaways and formation of hot spots can be prevented. As a result of the small reactor volumes, the overall safety of the process is significantly improved, even when harsh reaction conditions are used.

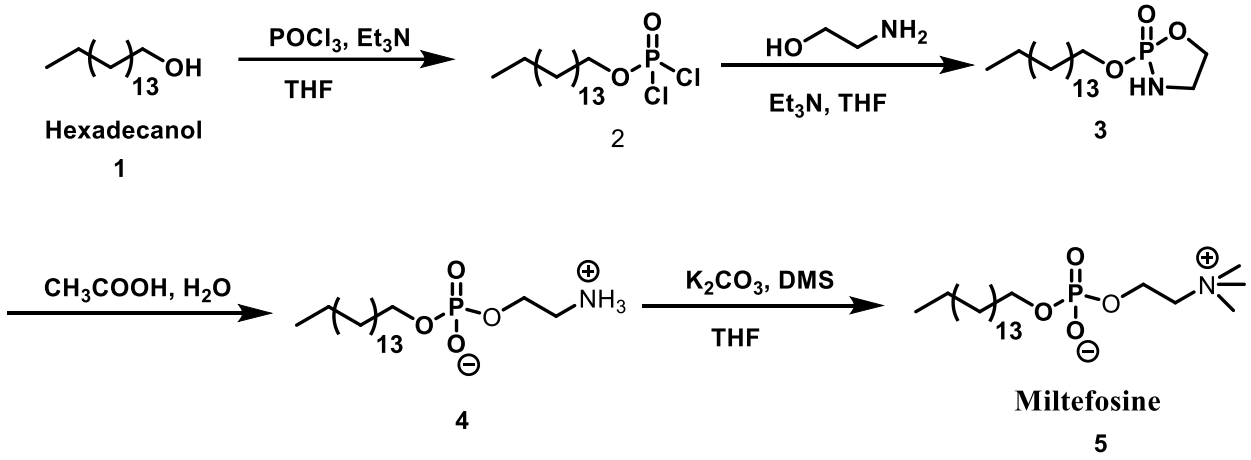
The multi-step flow synthesis approach has been used to access complex organic molecules including diverse bioactive natural products. Recently, Rutjes and co-workers have reviewed all the efforts on continuous flow multi-step synthesis of active pharmaceutical ingredients.[4] Flow synthesis has several advantages over traditional batch process, in terms of efficient mixing, heat transfer, interfacial mass transfer, safety, excellent kinetic control of the reaction, reproducibility, productivity and the possibility of distributed production using modular systems.[5] Recently several drug molecules and relatively complex molecules are reported using flow synthesis followed by in-line work-up including the formulations in certain cases. [6-7]

A few of the most advanced examples include: the flow synthesis of quinolone antibiotic ciprofloxacin,[8] end-to-end manufacturing process for aliskiren hemifumarate,[9] solid-supported synthesis of imatinib.[10] development of a single dedicated platform for the multiple drug molecules,[11] flow synthesis of rolipram using heterogeneous catalyst,[12] four-step continuous flow process for antihistamines from bulk alcohols,[13] seven-step continuous flow synthesis of linezolid molecule[14] and continuous flow synthesis and purification of ibuprofen.[15] The development and operation of fully automated pilot plant enables efficient and end-to-end integrated continuous manufacturing of the pharmaceutical products and small drug molecules,[16-18] including continuous solvent recovery for sustainable manufacturing.[19] Recently, Kappe *et al.*

have developed a real-time analysis platform and fully integrated multistep synthesis of an active pharmaceutical ingredient, mesalazine.

## General batch procedure for synthesis of Miltefosine

Synthesis of miltefosine was initially conducted in a batch process. The synthesis of miltefosine started from nucleophilic displacement of chlorine from $POCl_3$ using commercially available 1-hexadecanol **1** as a starting material. 1-Hexadecanol **1** was reacted with phosphorous oxychloride in presence of triethylamine in THF at 0 $^0$C for 4 hrs to give dichloro compound **2.** Further, dichloride compound **2** was treated with ethanolamine in presence of triethylamine in THF at 0 $^0$C for 3 hrs to afford cyclic compound **3.** The cyclic compound **3** was subjected for ring opening using acetic acid and water at 70 $^0$C for 3 hrs to give the compound **4.** Finally, the compound **4** was subjected for alkylation reaction using dimethyl sulphate as an alkylting agent and potassium carbonate as a base at 70 $^0$C for 5 h to afford miltefosine **5.**




After trying all reactions in batch process, it was observed that there were some limitations in batch process on large scale production.

**Challenges:**

- Solid handling issue
- To decrease the reaction time
- Integration of four reaction steps

## 3.2.2 Results and discussion

### Experimental observations:

**1) General experimental setup for hexadecylphosphorodichloridate**

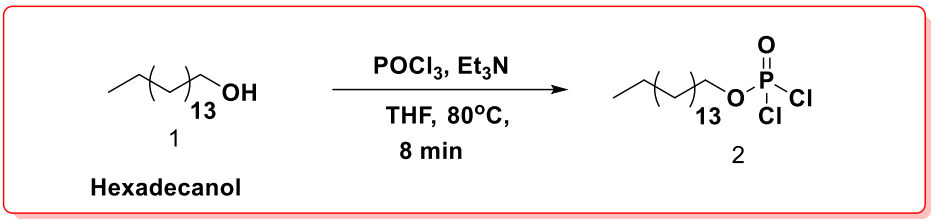



**Figure 2**

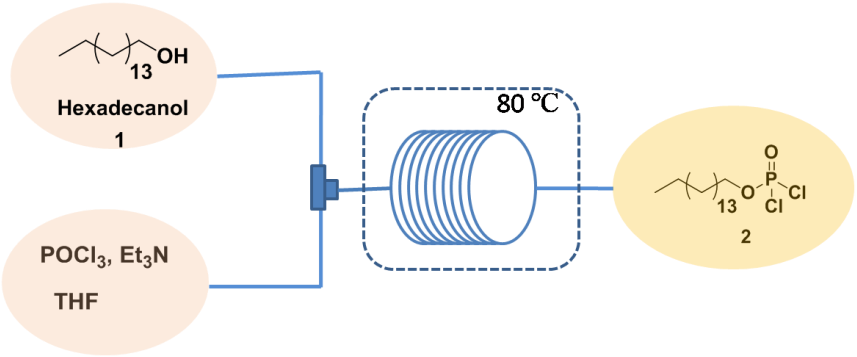



**Figure 3**

**Table 1: Optimization for hexadecyl phosphorodichloridate**

| Sr. No | Solvent (ml) | $POCl_3$: $Et_3N$ (equiv.) | Reactor | Temp ($^0C$) | Res. Time in min | Observation SM= starting material RC= reactor clogged |
|---|---|---|---|---|---|---|
| 1 | THF | 1.2:1 | Teflon tube | RT | 0.5 | No reaction (SM not consumed) |
| 2 | THF | 1.2:1 | Teflon tube | RT | 5 | Small amount of product formation and RC |
| 3 | $CHCl_3$ | 1.2:1 | Teflon tube | 60 | 5 | Solvent evaporated, RC |
| 4 | THF:$CHCl_3$ (1:1)) | 1.5:1.2 | Teflon tube | RT | 10 | No reaction (SM not consumed), RC |
| 5 | THF | 1.2: 0.4 | Teflon tube | 80 | 10 | More than 80 % SM consumed , RC |
| 6 | THF | 1.2: 00 | SS tube rect. | 80 | 10 | complete SM not consumed |
| **7** | **THF** | **1.3 :0.3** | **SS tube react** | **80** | **8** | **Complete SM consumed** |

**Table-1**

The general experimental set up for preparation of dichloro compound is given in **Figure 3**. In this reaction the nucleophilic displacement of chlorine was carried out using commercially available hexadecanol as starting material and triethylamine in THF as a solvent (hexadecanol + triethylamine + THF). Solution in the first syringe was reacted with solution of phosphorus

oxychloride in THF ($POCl_3$+THF) in second syringe at different temperatures and residence time and the results shown in the **Table 1.**

For preparation of dichloride compound **2,** in initial experiments hexadecanol (1 equiv) was treated with $POCl_3$ (1.2 equiv) in presence of triethylamine (1.0 equiv) at room temperature for 0.5 min residence time and it was observed that there was no product formation, starting material remained unreacted. In the next experiment, the residence time was further increased to 5 min. In this experiment, small amount of product formation was observed with clogging of reactor. When the temperature was increased at 60 °C, in chloroform was solvent small amount of product formation was observed but complete starting material was not consumed and chloroform got evaporated due to high temperature and there was clogging of reactor. In the next experiment, a mixture of solvents THF: $CHCl_3$ (50:50) was used at room temperature for 10 min residence time but there was no reaction and clogging of reactor was observed. In these experiments, due to formation of triethylamine hydrochloride salt ($Et_3N.HCl$) clogging of reactor was observed. Then it was decided to reduce the amount of triethylamine (0.4 eq) and to try one experiment without triethylamine with different temperature and residence time maximum starting material was consumed without clogging of reactor. As small amount of starting material remained even after trying a number of experiments it was planned to change the reactor from teflon tube reactor to stainless steel tube reactor. In this SS tube reactor, heat transfer is good so it add help to consume complete starting material. Accordingly a SS-316 coil reactor (15 ml) was used and experiment was conducted but in this case also complete starting material was not consumed. After trying a number of experiments it was observed that 1 eq of hexadecanol, 0.3 eq of triethylamine and 1.3 eq of $POCl_3$, in THF at 80 $^0$C and 8 min residence time complete starting material was consumed and formation of product took place without clogging of reactor.

**2) General experimental setup for (S)-2-(hexadecyloxy)-1, 3, 2- oxazaphospholidine 2-oxide**

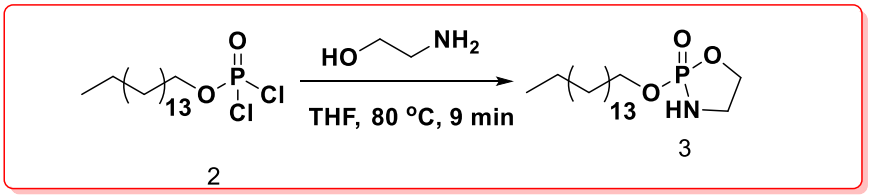



**Figure 4**

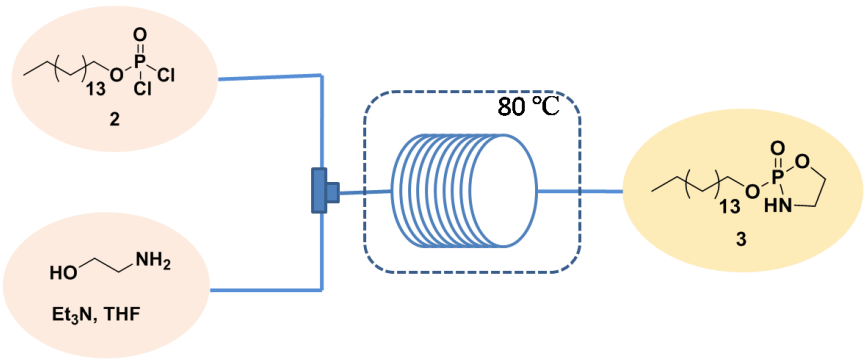



**Figure 5**

**Table 2: Optimization for -2-(hexadecylosy)-1, 3, 2- oxazaphospholidine 2-oxide**

| Sr. No. | Solvent (mL) | $HOCH_2CH_2NH_2$: $Et_3N$ (equiv.) | Reactor | Temp. ($^0$C) | Resi. time min. | Observation SM= starting material RC= reactor clogged |
|---|---|---|---|---|---|---|
| 1 | $CHCl_3$ | 1:1.2 | Teflon tube | RT | 2 | SM not consumed |
| 2 | $CHCl_3$ | 1:1.2 | SS tube react. | RT | 10 | SM Not consumed completely and RC after 22 min |
| 3 | THF | 1.5:1.2 | SS tube react. | RT | 10 | Complete SM not consumed and reactor clogged |
| 4 | THF | 1.2:0.5 | SS tube react. | 80 | 10 | SM consumed and RC after 52 min. |
| 5 | **THF** | **1:5:0** | **SS tube react.** | **80** | **9** | **Complete SM consumed and formation of product** |

**Table 2**

The cyclisation reaction of dichloride compound **2** was carried out using ethanolamine**.** When a solution of dichloride compound **2** in first syringe was treated with solution of ethanolamine (ethanolamine +THF) in second syringe at different temperature and residence time the result obtained are given **Table 2.** Initially all reactions were perfoemed in teflon tube reactor using various conditions and it was observed that clogging of reactor in all the experiments.

After trying the series of experiments, in teflon tube reactor, and observing the clogging of reactor in all conditions occurred. SS-316 micro-reactor was used to carry out a number of experiments given below **Table 2.** Initially when started a reaction in $CHCl_3$ dichloride compound **2** (1 equiv) was reacted with ethanolamine (1.2 eq) at room temperature for 10 min. residence time, some amount of starting material was consumed but reactor clogged. In the next experiment, the volume of ethanolamine was increased to (1.5 equiv.) and increases the residence time 10 min at room temperature but in this reaction also complete starting material was not consumed and reactor clogged.

After trying some reactions it was decided to change the solvent and THF was used instead of $CHCl_3$. When a reaction a was tried THF, with 1.5 eq. ethanolamine and 1.2 eq. triethylamine at room temperature for 10 min. residence time complete starting material was not consumed and clogging of reactor due to formation of triethylaminehydrochloride salt formation was observed. It was therefore decided to reduce the amount of triethylamnine to avoid clogging and used 0.5 eq. of triethylamine was used and fewer amounts of triethylaminehydrochloride salt formation and maximum starting material consumed with clogging of reactor. After trying a series of experiments it was observed that there is no need of triethylamine and use of triethylamine avoided, when the reaction was tried without the use of triethylamine complete starting material was consumed in 1.5 equiv. of ethanolamine at 80 $^0$C for 9 min without clogging of reactor.

### 3) General experimental setup for 2-ammonioethyl hexadecyl phosphate

In the batch process, the cyclic amine was treated with mixture of acetic acid and water at 60 ºC for 8 h. to give the ring opened compound **4**. After completion of reaction, in batch process, the reaction mixture was cooled at 0 ºC for 30 min and product was filtered using a simple filter paper, and washed with cold water and with ice cold acetone to give white solid in the slurry form.

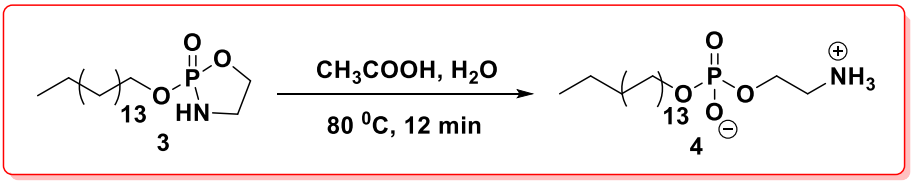



**Figure 6**

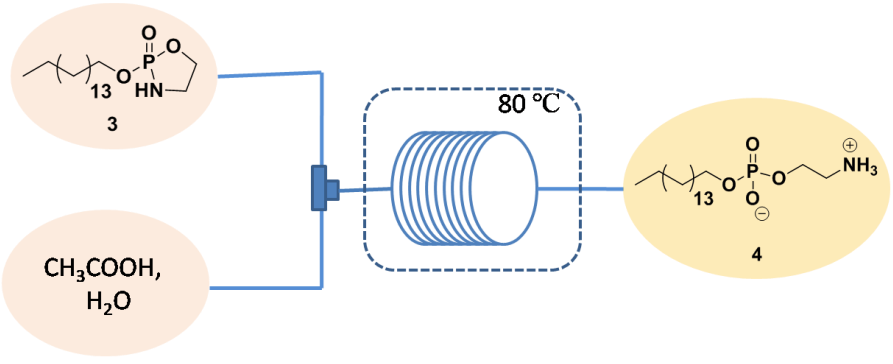



**Figure 7**

**Table 3: Optimization for 2-ammonioethyl hexadecyl phosphate**

| Sr. No. | $H_2O$ equiv. | $CH_3COOH$ equiv | Reactor | Temp. ($^0C$) | Residence time (min) | Observation SM= starting material RC= reactor clogged |
|---|---|---|---|---|---|---|
| 1 | 1 | 1 | Teflon tube react. | RT | 5 | SM remains as it is and RC |
| 2 | 3 | 3 | Teflon tube react. | 70 | 10 | Formation of small amount of product with RC |
| 3 | 4 | 4 | SS tube react. | 80 | 10 | Formation of small amount of product with RC |
| **4** | **5** | **5** | **SS tube react.** | **80** | **12** | **Formation of product without RC** |
| 5 | 6 | 6 | SS tube react. | 80 | 18 | Formation of product with RC |

**Table 3**

On the basis of batch reaction experience, initially reaction was performedin teflon tube reactor was used, the reaction was done at room temperature for 5 min residence time but clogging of reactor was observed. Though in the next experiment the temperature of reaction were changed to 70 $^0$C and 10 min respectively where in small amount of product formation was observed with clogging of reactor and backpressure on syringe pump. After trying a number of experiments in teflon tube reactor and clogging of reactor taking place in all the conditions, it was planned to change the reactor and then SS316 micro-reactor was used. The all expt. are summarised in **Table-3**

In SS316 micro-reactor there is good heat transfer. Initially the reaction was carried out at 80 $^0$C for 10 min. residence time with 3 equivalent of water and 3 equivalent of acetic acid in this experiment small amount of product formation was observed with clogging of the reactor. In the next reaction, the quantity of acetic acid and water was increased (5 equiv. of acetic acid and 5 equiv. of water) at 80 $^0$C for 12 min residence time here the formation of product was observed without clogging of reactor.

**Figure 9: General experimental setup for Miltefosine**

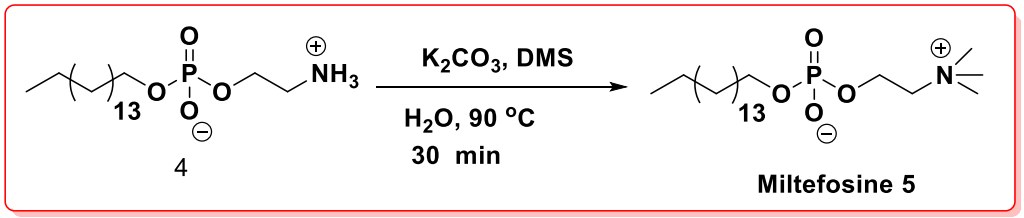



**Figure 8**

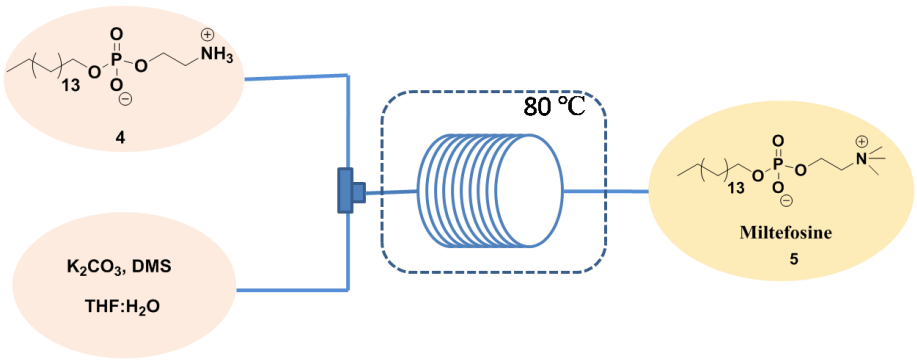



**Figure 9**

**Table 4: Optimization for Miltefosine**

| Sr. No. | Solvent ( ml) | DMS:$K_2CO_3$ (eq.) | Temp. ($^0$C) | Residence time (min) | Observation SM= starting material RC= reactor clogged |
|---|---|---|---|---|---|
| 1 | IPA :DCM:$H_2O$ | 3:3 | RT | 5 | Solubility issue of reagent, RC |
| 2 | $CHCl_3$:$H_2O$:MeOH | 3:3($Et_3N$) | 80 | 20 | Product not formed , RC |
| 3 | THF:$H_2O$ | 3:3 | 95 | 20 | No reaction ( solvent vaporize, RC) |
| 4 | THF:$H_2O$ | 4:4 | 80 | 20 | No reaction (solvent vaporize due to high temp) RC |
| **5** | **THF:$H_2O$** | **6:6** | **80** | **30** | **Small amount of product formation, RC** |

**Table 4**

Alkylation of amine **4** using potassium carbonate as a base and dimethyl sulphate as an alkylating agent was attempted initially in teflon tube T-microreactor wherein clogging of reactor was observed (experiments not added in table). Then SS tube T-microreactor was used and the attempted experiments are given in **Table 4.** Initially the alkylation of amine **4** using DMS:$K_2CO_3$ (3:3 equiv.) in IPA-DCM-$H_2O$ as a solvent at room temperature for 5 min. residence time was attempted and instant clogging of reactor was observed due to the solid reactant ($K_2CO_3$). In the next experiment triethylamine (3 eq) was used as a base at 80 $^0$C for 20 min residence time but product formation was not observed and clogging of reactor took place.

Afterwards the solvent was changed to and used $CHCl_3$: MeOH: $H_2O$ but in this experiment also clogging of reactor was observed. Then THF: $H_2O$ was used as a solvent at different temperature and residence time given in **Table 4** but there was no formation of product observed. The reaction was attempted at high temp i.e. at 95 $^0$C wherein vaporization of solvent took place due to high temperature and instant clogging of reactor was observed. Various

combinations of quantity of reagents, temperature and residence time were attempted but only a small amount of product formation was observed.

### 3.2.3 Synthesis of miltefosine in screw reactor

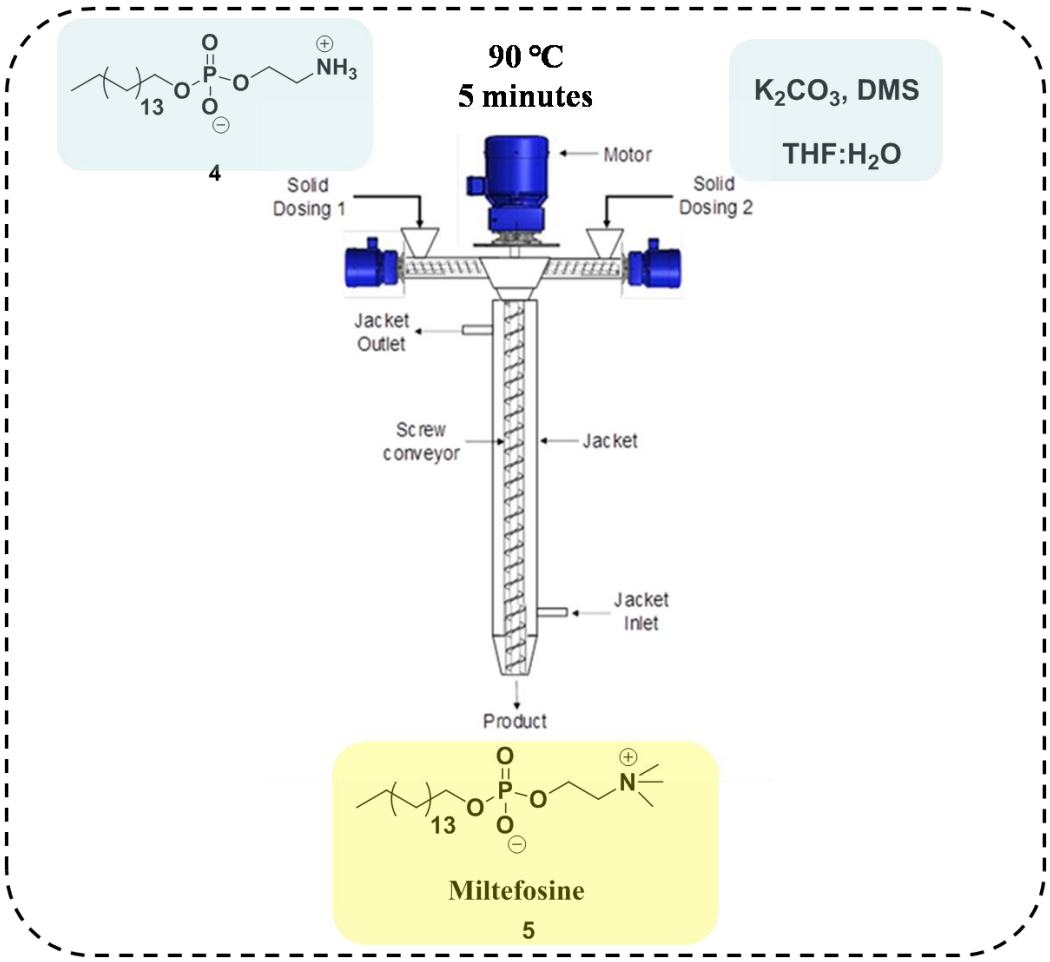



**Figure 10 Screw Feeder Reactor Set-Up**

**Table 5: Optimization for Miltefosine in screw reactor**

| Sr. no | Solvent | DMS: $K_2CO_3$ (equiv) | Temp °C | rpm | Res. time (min) | Observation |
|---|---|---|---|---|---|---|
| 1 | IPA:DCM:$H_2O$ | 3:3 | RT | 400 | 0.5 | Product formation was not observed |
| 2 | $CHCl_3$:MeOH | 3:3 | 50 | 300 | 1 | Product formation was not observed |
| 3 | **THF: $H_2O$** | **3:3** | **90** | **250** | **5** | **Formation of product was observed** |

**Table 5**

The final methylation reaction conditions in batch protocol afforded the product at 60 $^0$C temperature over 4 hours with 65% yield. The stoichiometric quantities of both $K_2CO_3$ and dimethyl sulphate (DMS) in THF and water as solvent, respectively facilitated the reaction to completion We observed rapid clogging of the reactor tubing because at high temperature THF got evaporated resulting in crystallization of $K_2CO_3$. Reactions at room temperature to moderate temperature did not result in complete consumption of the starting material. Even the reaction without water did not proceed due to limited solubility of potassium carbonate in THF. The last step of synthesis of miltefosine from the 2-ammonioethyl hexadecyl phosphate when performed in a tubular reactor, we observed rapid clogging due to almost instantaneous precipitation of the product. This can be avoided using a continuous screw reactor.

The continuous mechano-chemistry is an advanced tool for the synthesis of organic compounds and other complex molecules. The literature reports are available on continuous mechanochemistry. Importantly, salt formation is one of the most common steps in various reactions for the active pharmaceutical ingredients (APIs) and natural bioactive molecules. Recently, Kulkarni and co-workers have reported a solid-solid reaction using a screw reactor for continuous flow solvent-free synthesis for different organic reactions. Yeboue et al. have reported a peptide coupling by reactive extrusion on potential industrial applications of peptide synthesis. In the present work, in the fourth step synthesis of miltefosine, the reactants are in a solid/paste form and continuous mechanochemistry using screw reactor is the only way to make the entire process continuous and efficient. Subsequent to the third step, the outlet stream was given a wash with an ice cold water-acetone mixture to remove the soluble impurities and the solid paste containing the **4** was fed to a jacketed single-screw reactor (Teflon) for continuous flow synthesis of miltefosine (**1**).

The conditions to maximize the yield were obtained by systematically varying temperature, flow rate, mole ratio, residence time and screw rotation speed and all the details are given in in **Table 5.** The solid compound **4** and a paste of $K_2CO_3$ and dimethyl sulphate were fed separately to facilitate the reaction along the screw length. The reaction was monitored by TLC then the final product miltefosine was obtained in 300 s. After completion of the reaction, the product was purified by column chromatography using solvent system (ethyl acetate: pet. ether) and then with 100% methanol that gave 65% yield. When compared with the batch process, where the required

reaction time was three hours for this step, only 300 s were required for a solvent free continuous process in a screw reactor. At the optimal condition in a continuous screw reactor (90 $^{o}$C, screw rotation speed of 250 rpm) the desired product miltefosine was obtained in a short residence time (300 s) with 65% yield.

With all the individual synthesis steps optimized in flow conditions, we further integrated them in a telescopic manner on a single platform. The final reaction conditions and the schematic of the set-up are shown in. Upon integrating all the steps, the final overall yield of the desired product miltefosine was 58% with a total residence time 34 min. The overall synthesis rate of miltefosine using the laboratory scale system was 10 g/hr, which is sufficient to treat 4800 patients per day.

### 3.2.4 Telescopic synthesis of Miltefosine

After trying a number of experiments for every step, we moved in a telescopic continuous flow synthesis of miltefosine. In **Figure 11** demonstrated a telescopic continuous flow set up for miltefosine synthesis shown in **Figure 11.**

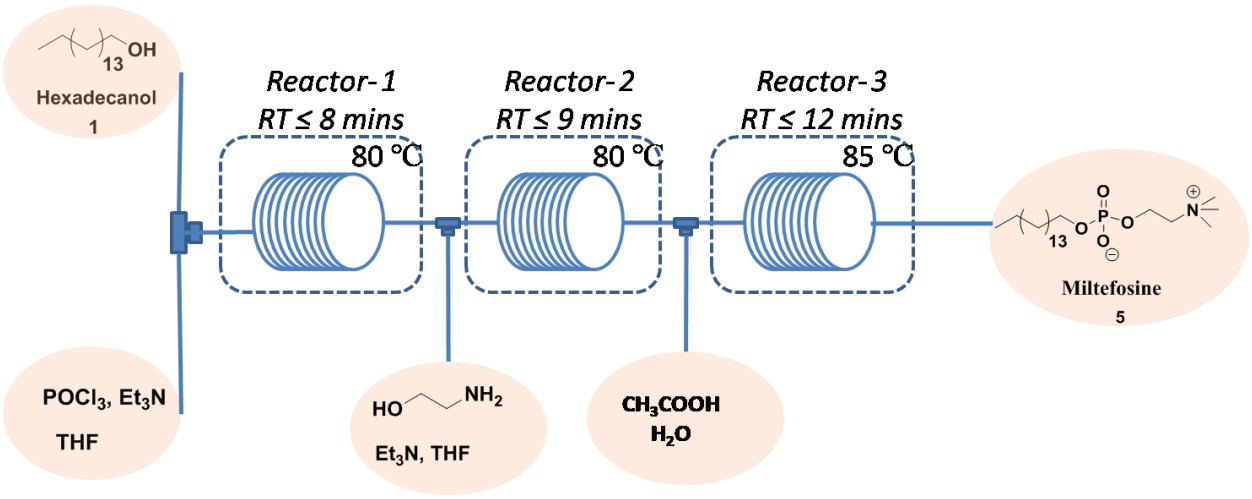



**Figure 11**

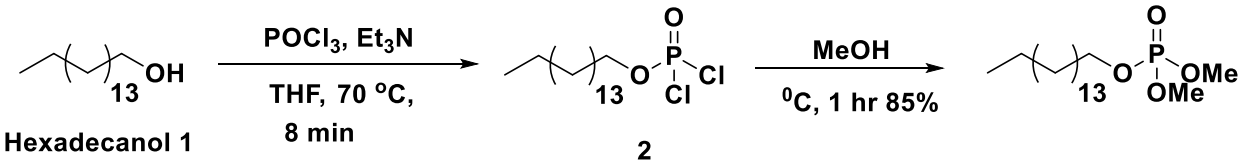
### 3.2.5 Conclusions:

In conclusion, a telescopic continuous flow process for synthesis of miltefosine has been developed. This is the first report for a 4-steps, practical, and easily scalable process for synthesis of miltefosine using continuous flow method. The advantages of this process are scalable synthetic route in very short time with good yield. This method elegantly showcases the handling

of diverse organic reagents. Thus, 3 steps were carried out in stainless steel reactor and last step was optimized by using solid screw reactor. The screw reactor keeping a distance of only 0.25 mm between the screw and the jacket gave precise control of reaction temperature for carrying out the reaction under solvent free conditions or minimum amount of solvent for making a paste or slurry. The separation process of the intermediates of four steps synthesis of Miltefosine was aoided. The approach will be demonstrated for large scale synthesis. Various advantages of continuous flow synthesis of miltefosine include short time, cost effectiveness, minimum amount of solvent used and reduction in the amount of the reagents. Practically it is time saving process for continuous flow synthesis of miltefosine.

### 3.2.5 Experimental Procedure

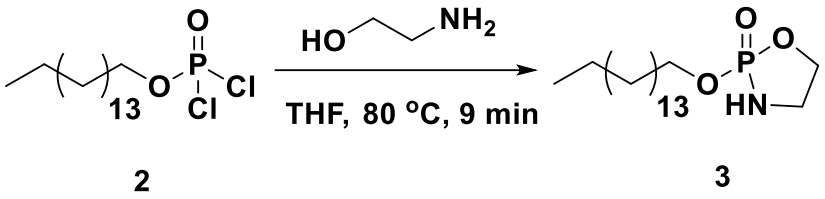
**1) General procedure for the synthesis of hexadecyl diethyl phosphate:**




The mixture of hexadecanol (20.62 mmole, 5.0 g) and triethyl amine (0.41 mmole, 0.57 ml) dissolved in 25 mL THF was treated with $POCl_3$ (20.62 mmole, 2.5 ml) dissolved in 15 mL THF in a SS-316 microreactor, temperature was maintained at $70^0$C. As the reaction progressed, it resulted in the formation of thick white $HCl.Et_3N$ slurry along with hexadecyl phosphorodichloridate in a residence time of 8 min indicating the completion of the reaction monitored by thin layer chromatography. The obtained reaction mixture was quenched with methanol to give the hexadecyl dimethyl phosphate which on concentration under vacuum gave the crude residue. The crude residue was purified by flash column chromatography (petroleum ether: ethyl acetate =9:1) to afford pure hexadecyl dimethyl phosphate (85%, 6.15 g) as a colorless liquid. The product was analysed by NMR spectroscopy.

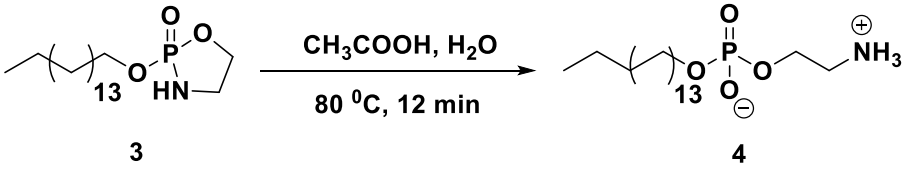
**$^1$H NMR ($CDCl_3$, 400 MHz)**: δ 4.04 (q, *J* = 6.8 Hz, 2 H), 3.77 (s, 2 H), 3.75 (s, 2 H), 1.72 - 1.62-1.71 (m, 2 H), 1.25 (s, 27 H), 0.90 - 0.85 (m, 3 H); **$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 68.1, 68.0, 54.2, 54.1, 31.9, 30.3, 30.2, 29.6, 29.6, 29.6, 29.5, 29.5, 29.3, 29.1, 25.4, 22.6, 14.1; $^{31}$P NMR: ($CDCl_3$162 MHz) : 1.34 ppm.

**2) General procedure for the synthesis of 2-(hexadecyloxy)-1, 3, 2- oxazaphospholidine 2-oxide:**



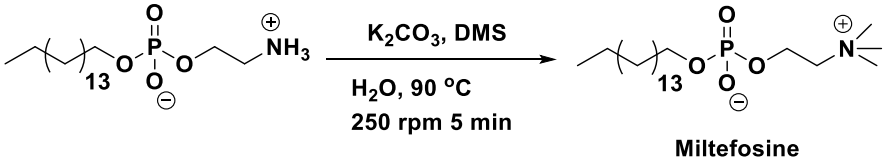

Ethanolamine (27.8 mmole, 1.68 mL) dissolved in 20 ml of THF was reacted with hexadecylphosphorodichloridate (18.5 mmole, 6.64 g) in SS-316 micro-reactor and the temperature was maintained at 80 $^0$C. As the reaction progressed, TLC showed that in the residence time of 9 min. the reaction was completed and formation of -2-(hexadecyloxy)-1, 3, 2-oxazaphospholidine 2-oxide was formed.

**3) General procedure for the synthesis of 2-ammonioethyl hexadecyl phosphate:**




The mixture of acetic acid (83.3 mmole, 5.01 ml) and water (83.3 mmole, 1.50 ml) was treated with -2-(hexadecyloxy)-1, 3, 2- oxazaphospholidine 2-oxide in SS-316 micro-reactor and the temperature was maintained at 80$^0$C, the total residence time required was only 12 min and it resulted in formation of product with light bluish liquid solution. After completion of reaction as monitored by TLC, the solution was cooled at 0 °C for 30 min and formation of solid product was there which was then filtered out using simple filter paper and a white slurry/ paste of desired 2-ammonioethyl hexadecyl phosphate was obtained.

**4) General procedure for the synthesis of miltefosine:**



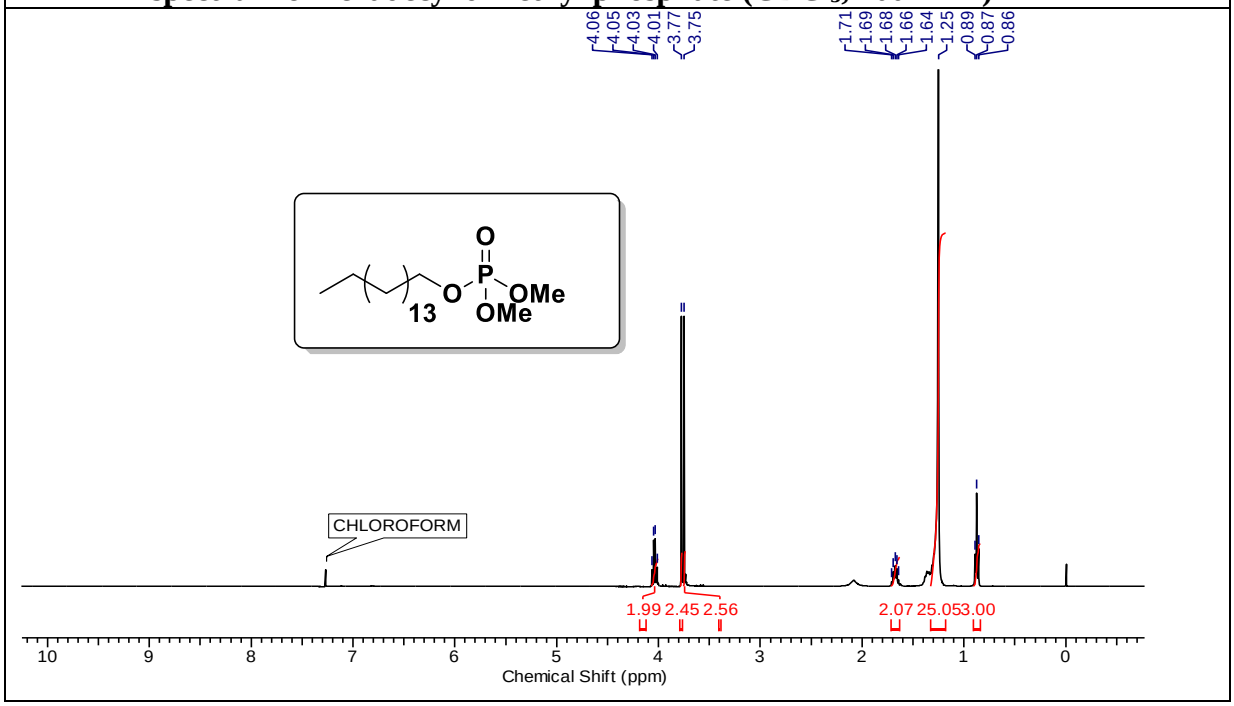
The above generated 2-ammonioethyl hexadecyl phosphate (15.0 mmol, 5.48 g) was fed from solid dosing inlet 1 and the mixture of $K_2CO_3$ (60.01 mmol, 9.45 g) in 10 ml water and dimethyl sulphate ( 60.0 mmol, 9.45 ml) fed from solid dosing inlet 2 in a screw feeder reactor rotating at 250 rpm and temperature was maintained at 90 $^0$C. The total residence time for miltefosine formation was only 5 min. The white miltefosine slurry was collected and then monitored on TLC complete starting material was consumed with the formation of desired miltefosine. The collected sample was dried over anhydrous sodium sulphate and concentrated under vacuum to give the crude miltefosine. The crude miltefosine was purified by flash column chromatography using ethyl acetate and methanol (9:1) to afford white solid miltefosine in 65 % yield. The product was analysed by using NMR spectroscopy.

**$^1$H NMR ($CDCl_3$, 400 MHz):** δ 4.23 (br. s., 2 H), 3.76 (br. s., 4 H), 3.36 (br. s., 9 H), 1.54 (br. s., 2 H), 1.23 (br. s., 26 H), 0.86 (t, *J* = 6.8 Hz, 3 H); **$^{13}$C NMR ($CDCl_3$, 100 MHz):** δ 66.1, 66.1, 66.1, 65.5, 65.5, 59.2, 54.2, 31.9, 31.1, 31.0, 29.7, 29.6, 29.5, 29.3, 25.9, 22.6, 14.0; $^{31}$P NMR: ($CDCl_3$162 MHz) : δ 0.62 ppm.

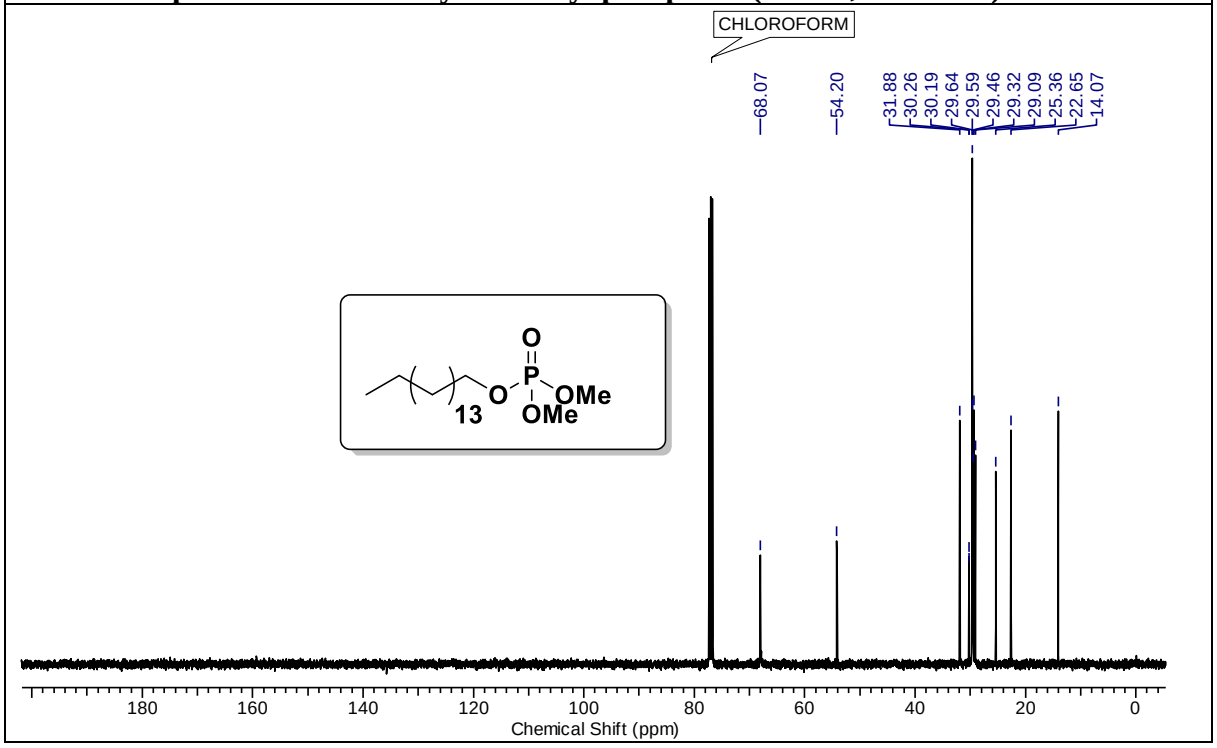
### 3.2.6 Spectral data

#### $^{1}$H-NMR spectrum of hexadecyl dimethyl phosphate:

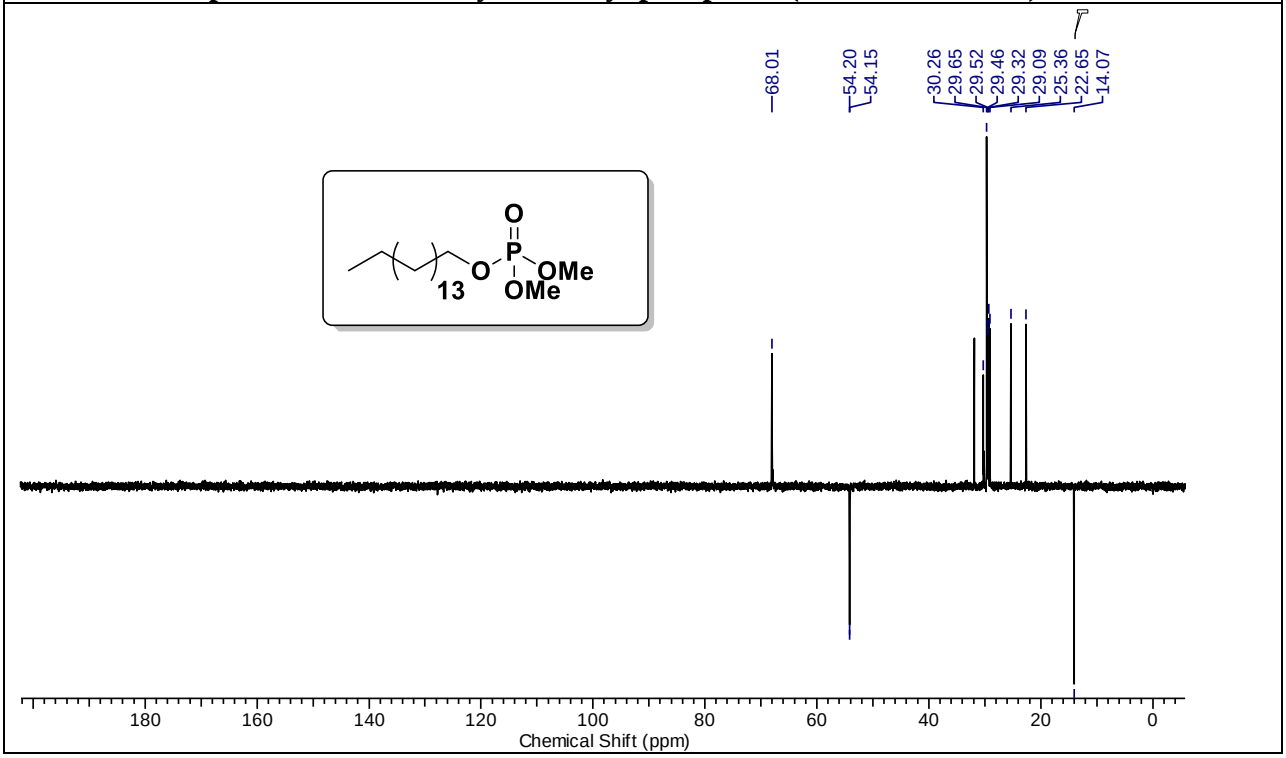
**$^{1}$H-NMR spectrum of hexadecyl dimethyl phosphate ($CDCl_3$, 400 MHz)**



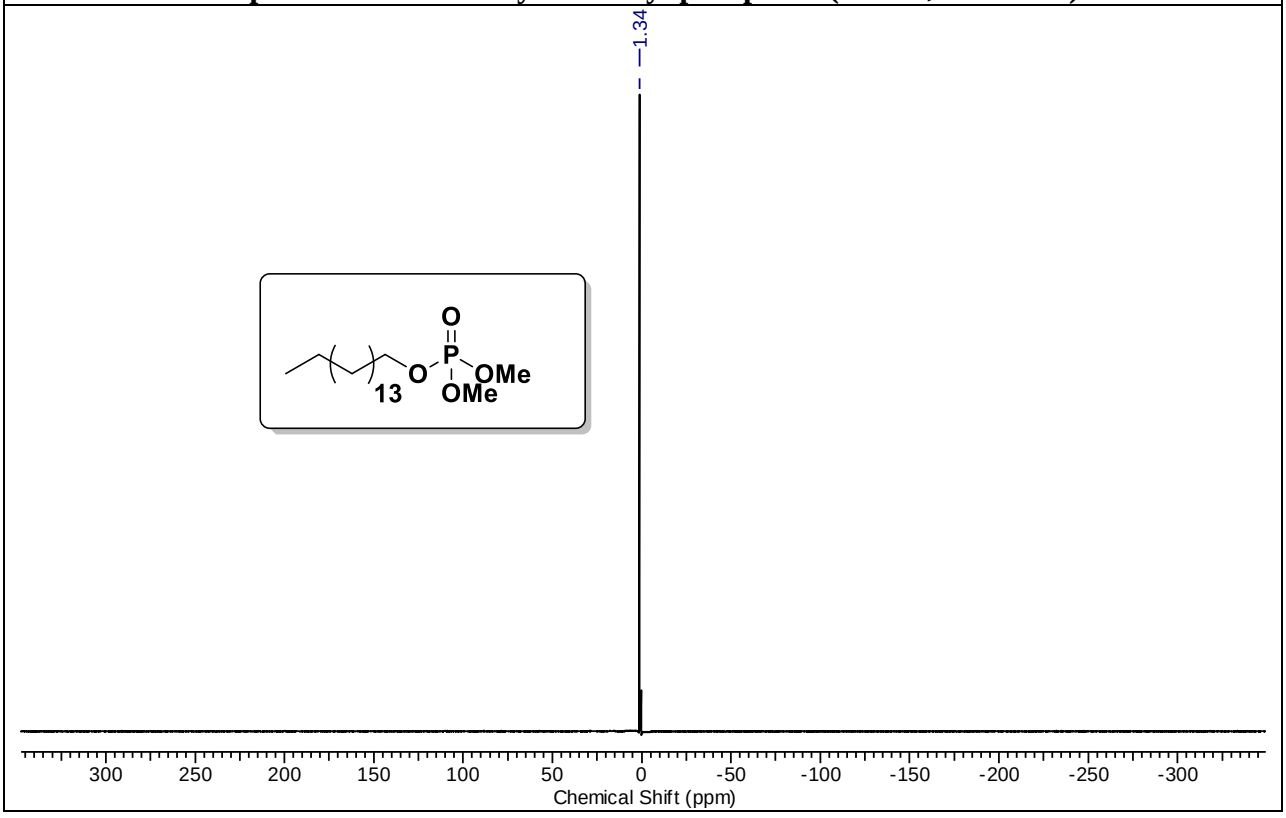

**$^{13}$C-NMR spectrum of hexadecyl dimethyl phosphate ($CDCl_3$, 100 MHz)**



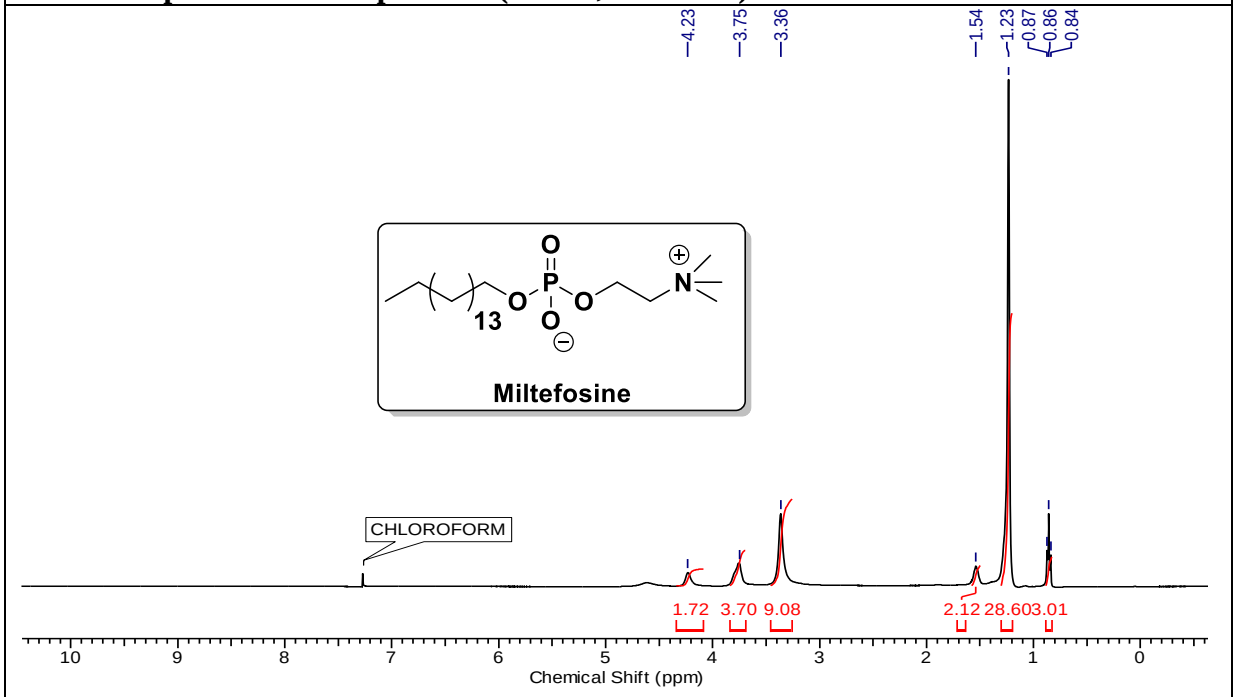
**DEPT NMR spectrum of hexadecyl dimethyl phosphate ($CDCl_3$, 100 MHz)**



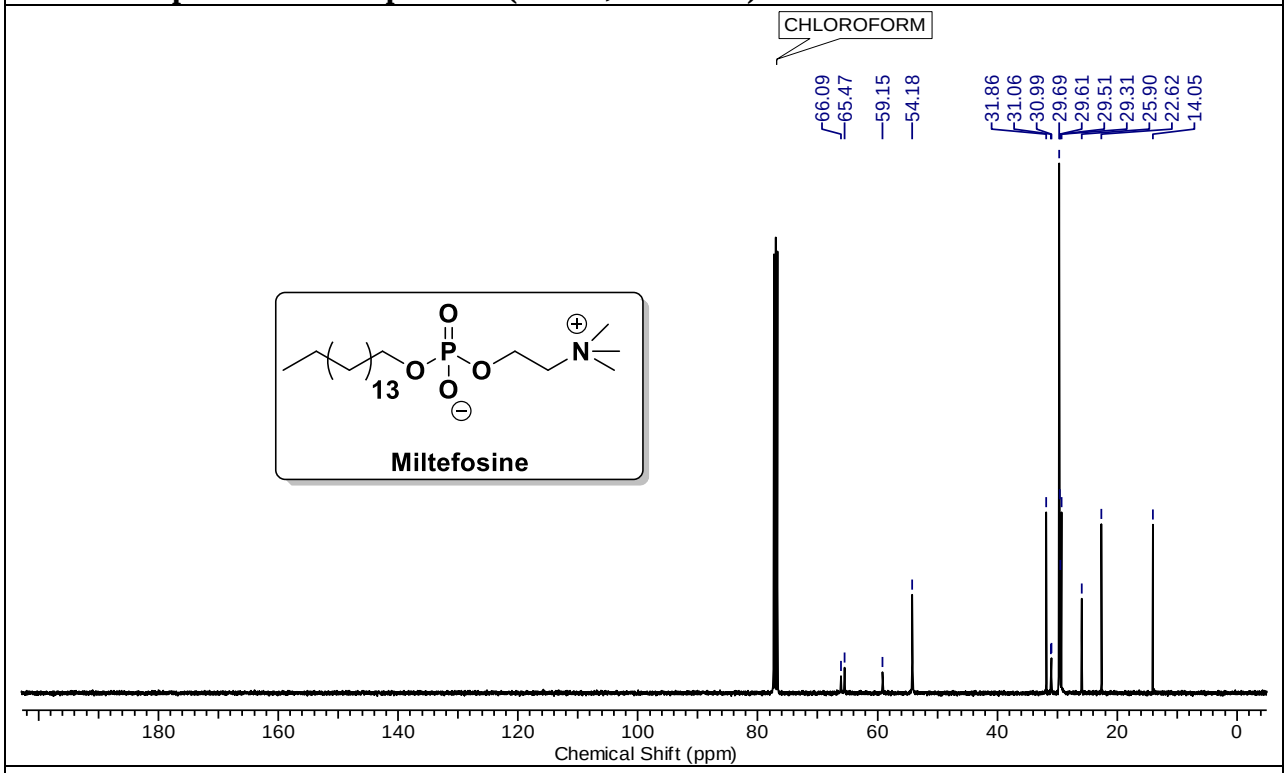

**$^{31}P$ NMR NMR spectrum of hexadecyl dimethyl phosphate ($CDCl_3$, 162 MHz)**



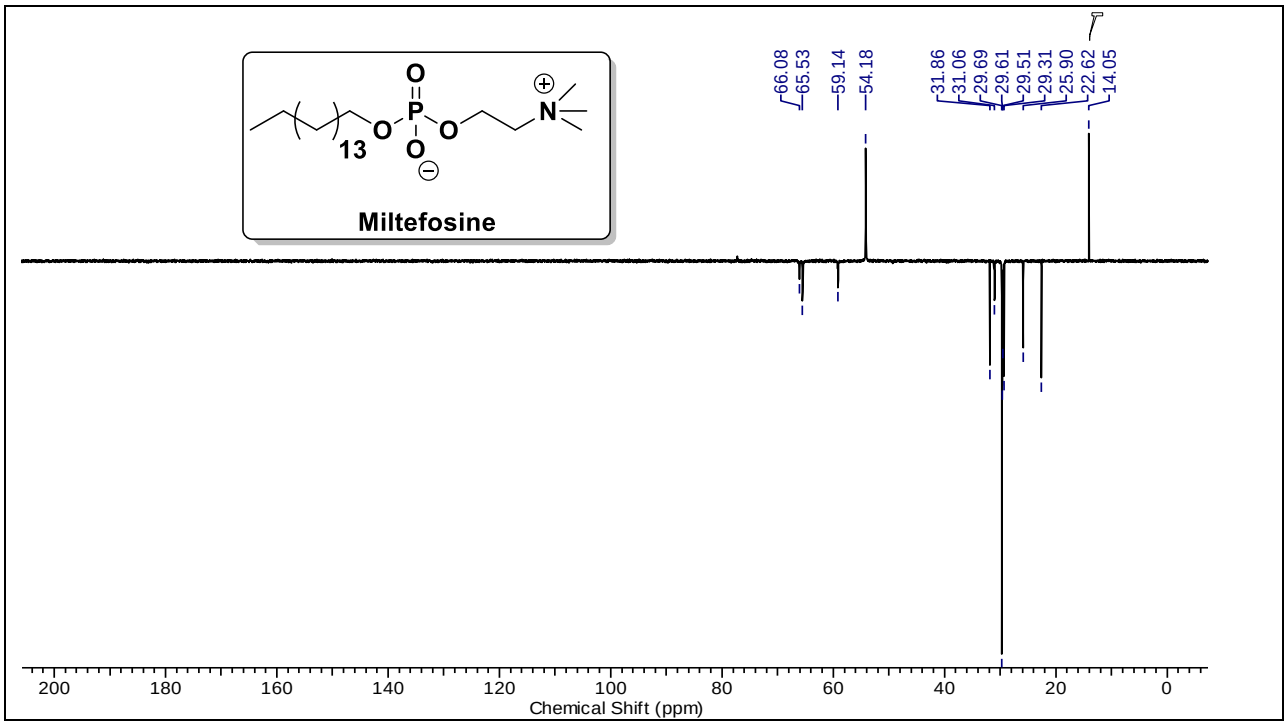
**$^{1}$H-NMR spectrum of compound 5 ($CDCl_3$, 400 MHz)**



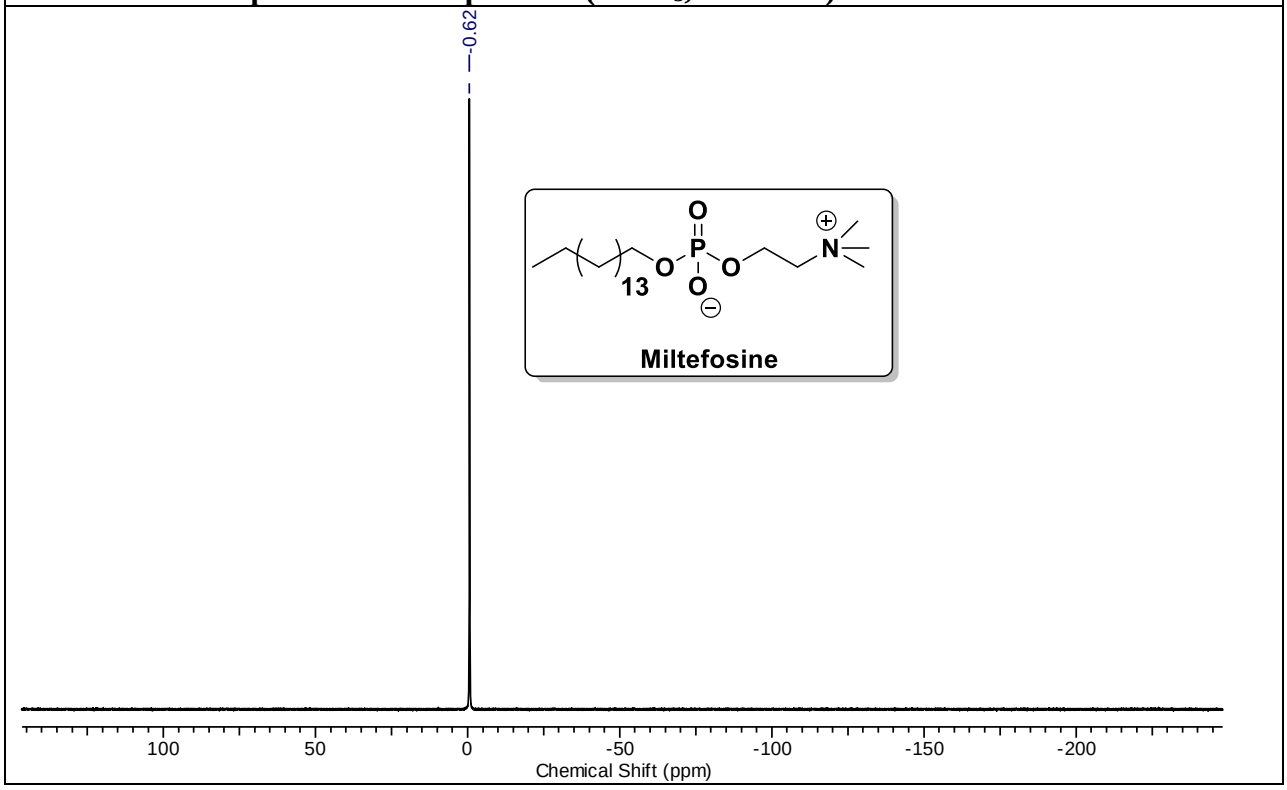

**$^{13}$C-NMR spectrum of compound 5 ($CDCl_3$, 100 MHz)**




**DEPT NMR spectrum of compound 5 ($CDCl_3$, 100 MHz)**




**$^{31}$P NMR NMR spectrum of compound 5 ($CDCl_3$, 162 MHz)**



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# ABSTRACT

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**Name of the Student:** Patil Niteen Baswaraj

**Registration No.:** 10CC17J26004

**Faculty of Study:** Chemical Science

**Year of Submission:** 2021

**AcSIR academic centre/CSIR Lab:**
CSIR-National Chemical Laboratory, Pune

**Name of the Supervisor:** Dr. Subhash Prataprao Chavan

**Title of the thesis:** Synthetic studies towards Quinagolide, 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one and continuous flow synthesis of Miltefosine

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Biologically active products and their synthetic derivatives have found the largest contribution to drug discoveries. In that context, challenging structural features and bioactivity of products attracted synthetic chemists for its economic and scalable synthesis through the development of synthetic methodologies. The thesis hereby presents a unique design and state-of-art strategies for the synthesis of D2 receptor agonist quinagolide in racemic fashion, along with the synthesis 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one is an important heterocyclic building block of antidiabetic drug glimepiride and its derivatives and the continuous flow synthesis of Miltefosine. In recent years, continuous flow synthesis of active pharmaceutical ingredients (API), agrochemicals, petrochemicals, pesticides, fine chemicals, bulk chemicals, and nanomaterials has achieved significant importance in academia and industrial research

## List of Publications Emanating from the Thesis Work

1) Subhash P. Chavan; Ambaji A. Pawar; **Niteen B. Patil**; Appasaheb L. Kadam, Shrikrishna S. Shinde; Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one:An Important Building Block of the Antidiabetic Drug Glimepiride. *Synthesis* **2020**, 52, 3480–3484.

2) **Niteen B. Patil**; Ranjit S. Atapalkar ; Subhash. P. Chavan; and Amol A. Kulkarni; Multi-step Synthesis of Miltefosine: Integration of Flow Chemistry with Continuous Mechanochemistry. (Manuscript submitted).

## List of Publications Non-Emanating from the Thesis Work

3) Subhash P. Chavan; Sanket A. Kawale; Niteen **B. Patil**; Dinesh B. Kalbhor; Application of allylic amine formation from aziridine-2-ol under Appel reaction condition: Synthesis of N-(tert-butoxycarbonyl)-D-vinyl glycine methyl ester. *Tetrahedron Letters* **2021,** 73 153-119.

4) Abhijeet N. Purude; Kailash P. Pawar; **Niteen B. Patil**; Uttam R. Kalkote ; Subhash P. Chavan; Total synthesis of (R)-lipoic acid and (S)-lipoic acid *via* an Mn (III)-salen-catalyzed oxidative kinetic resolution. *Tetrahedron: Asymmetry* 2015, 26, 281–287.

5) Subhash P. Chavan; Kailash P. Pawar; Ch. Praveen; **Niteen B. Patil**; Chirality induction and chiron approaches to enantioselective total synthesis of a-lipoic acid *Tetrahedron* **2015** 71 4213-4218..

## Patents

1) Process for the Preparation of Glimepiride intermediate. *Chavan, S. P.; Pawar, A. A.; **Patil, N. B**.; Kadam, A. L.; Shinde, S. S. IN Patent App. 201,911,040,874.

## List of Posters Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 26-27, **2020**):

   **Title**: Continuous flow Synthesis of Miltefosine

   **Abstract**: Miltefosine is the only oral drug approved for treatment of Leishmaniasis- a parasitic disease transmitted by sandflies. According to the WHO, leishmaniasis is infectious diseases, and in particular neglected tropical diseases in poor developing countries, still play a significant role in a vast number of deaths reported worldwide. The key features of this synthesis are first total synthesis of miltefosine in continuous flow, displacement of chlorine atom by hexadecanol followed by cyclisation of dichloride with ethanolamine, ring opening using water followed by alkylation using dimethyl sulphate in screw feeder reactor. The advantages of this process are scalable synthetic route, short reaction time and high overall yield.

## List of Conference Attended with Details

1) 17th CRSI National Symposium in Chemistry 2015 held in CSIR-NCL Pune, India (February 2015)

Synthesis S. P. Chavan et al. Paper

# Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one: An Important Building Block of the Antidiabetic Drug Glimepiride

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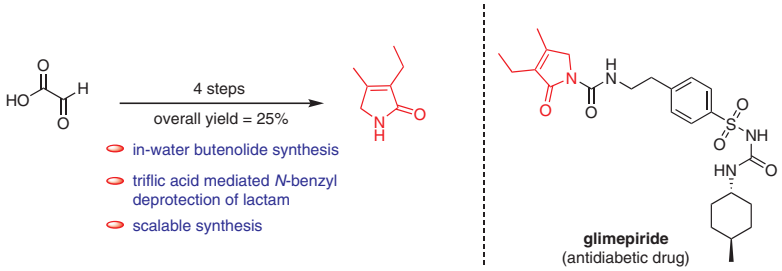


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**Abstract** A four-step, practical, and easily scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one, an important building block of the antidiabetic drug glimepiride, has been accomplished. Key features are the synthesis of 3-methyl-4-hydroxy-2-butenolide in water and triflic acid mediated N-benzyl lactam N-deprotection. The main advantages of this process are the scalable synthetic route and decreased number of reaction steps, which paves the way for the industrial-scale synthesis of 3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one.

**Key words** glimepiride, antidiabetic drug, scalable synthesis, lactams, butenolide

The rapidly rising prevalence of diabetes, especially among the middle- and low-income countries, has caused growing concern among the scientific community. In 2016, diabetes alone was responsible for the deaths of an estimated 1.6 million people. Also, another 2.2 million deaths were attributable to high blood sugar in 2012. Almost half of all deaths due to high blood glucose occur before the age of 70 years. WHO estimates that diabetes was the seventh leading cause of death in 2016.[1]

Currently, many drugs are available in the market for the treatment of diabetes. In that context, in 2003, Gurjar et al. reported the synthesis of *trans*-hydroxyglimepiride, a metabolite of the antidiabetic drug glimepiride (**1**).[2] Glimepiride is a third-generation sulfonylurea approved in 1995 for the treatment of type 2 diabetes mellitus. It is used in medication as a monotherapy or in combination with metformin or insulin, and is currently used in more than 60 countries worldwide. Glimepiride reduces the blood sugar by stimulating the release of insulin by the pancreas and induces increased activity of intracellular insulin receptors.[3] The antidiabetic drug glimepiride (**1**) consists of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) as an essential heterocyclic building block. Pyrrolinone **3** is also present as the main precursor in bile pigments, and is in the blue protein C-phycocyanin[4] (**2**) (Figure 1).

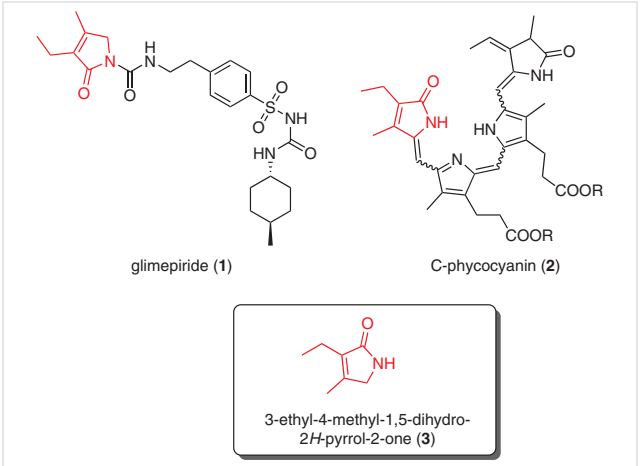



**Figure 1** Glimepiride (**1**) and C-phycocyanin (**2**) consist of the scaffold 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**)

The importance in medicinal chemistry and the challenging structural features of pyrrolinone **3** have attracted synthetic chemists for its short and industrially scalable synthesis.[5,6] The reported synthetic routes involve the use of toxic reagents such as NaCN and $Pb(OAc)_4$, and expensive transition-metal catalysts such as $PdCl_2$ and Grubbs' catalyst (Figure 2). So, there is a long-standing need to develop a short, high yielding, and industrially scalable method using simple and easily accessible reagents. In continuation of our research towards the synthesis of biologically active natural products and medicinally important drug molecules, development of a scalable process for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) was initiated.



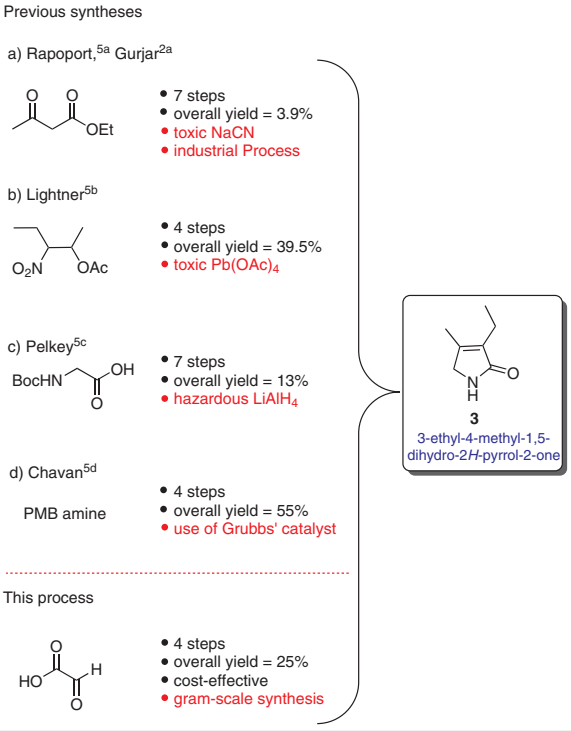
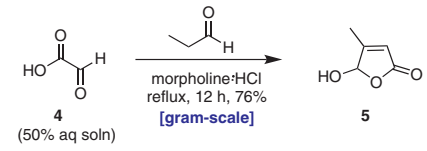



**Figure 2** Synthetic approaches to 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**)

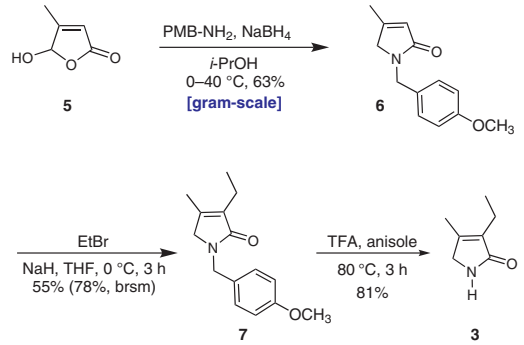
Our synthesis commenced with the preparation of 3-methyl-4-hydroxy-2-butenolide (**5**) using glyoxylic acid (**4**) as starting material (Scheme 1). Synthesis of butenolide **5** from acid **4** and propanal in dioxane as solvent has been reported by Bourguignon and Wermuth.[7] For the large-scale synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**), the cost of the solvent dioxane would contribute significantly to the total cost of compound **3**. So, we decided to develop a process using either water as the solvent, which is considered to be a green solvent, or a solvent-free process. Towards this, when the reaction of glyoxylic acid (50% aqueous solution) with propanal in the presence of morpholine hydrochloride was carried out at reflux temperature, to our delight the formation of 3-methyl-4-hydroxy-2-butenolide (**5**) was observed in 55% yield in 24 hours. After slight optimization of the time, butenolide **5** was isolated in 76% yield in 12 hours. It was observed that longer reaction time (24 h) reduces the yield of the reaction mainly due to decomposition of the product formed. It is noteworthy that morpholine hydrochloride was prepared from morpholine and 35% HCl and used as such without isolation.

Thus, 3-methyl-4-hydroxy-2-butenolide (**5**) was successfully synthesized on a multigram scale using water as solvent, which makes this process green, cost-effective, and industrially applicable.




**Scheme 1** Synthesis of 3-methyl-4-hydroxy-2-butenolide (**5**) in water

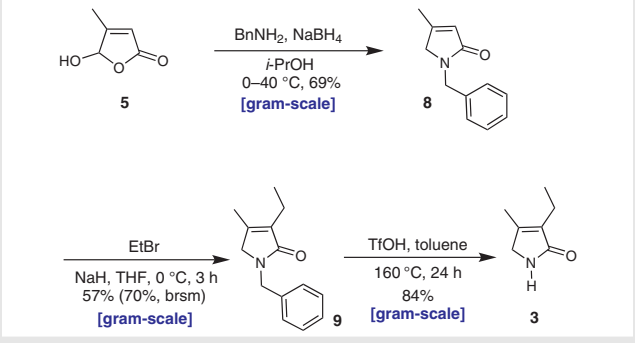
The next crucial step was the synthesis of lactam **6** from butenolide **5**. To this end, when 3-methyl-4-hydroxy-2-butenolide (**5**) was treated with *p*-methoxybenzylamine (PMB amine) in isopropyl alcohol, followed by treatment with $NaBH_4$ under basic conditions, lactam **6** was furnished in 63% yield (Scheme 2). Initially, isolation of hydroxy lactam was attempted, and then it was subjected to reduction using $NaBH_4$, but the yield of lactam was severely reduced to ~20% mainly due to instability of the hydroxy lactam on silica gel purification. For the required substitution on the olefin moiety, lactam **6** was treated with ethyl bromide and NaH at 0 °C to obtain compound **7** in 55% yield (78% brsm).[5d] Here, it was observed that starting material remained even after stirring the reaction mixture for a longer time under a range of temperature conditions. All our efforts to obtain 100% conversion failed in this case. The final step, *N*-PMB deprotection of the lactam, was carried out using CAN, as earlier reported by us.[5d] CAN, a well-known one-electron oxidant, has several disadvantages, one of which is its requirement for excess addition (2 equivalents or more) owing to its high molecular weight. This not only adds to the cost, but also raises disposal and environmental issues. These issues have led to the development of a simple and more convenient method which could be utilized on a large scale. Towards this, *N*-PMB deprotection of lactam **7** was carried out using TFA in anisole at 80 °C under microwave conditions to obtain 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) in 81% yield.[8] The same reaction was reproduced using conventional heating conditions for the synthesis of pyrrolinone **3**.




**Scheme 2** First-generation approach for the synthesis of **3**

Though we achieved a good overall yield for this process (21%) in a decreased number of steps and the process was scalable at large scale, our main goal was to develop a cost-effective and scalable process for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**). It was realized that PMB amine, TFA, and anisole contributed largely to the overall cost of the process. This led us to explore commercially, readily available and inexpensive benzylamine and the development of a cost-effective and practical method for the N-debenzylation of lactam.

Accordingly, following a similar reaction sequence, *N*-benzyl lactam **9** was synthesized from **4** in three steps in 30% yield (Scheme 3). To achieve the last step, the *N*-benzyl deprotection of lactam **9**, known reaction conditions were screened. When *N*-benzyl lactam **9** was treated with TFA in anisole, starting material was recovered after 48 hours and product formation was not observed. But, when *N*-benzyl lactam **9** was subjected to microwave-mediated *N*-benzyl deprotection using triflic acid in toluene, product formation was observed in 86% yield.[9] To avoid the microwave conditions, when the same reaction was carried out using conventional heating with triflic acid in toluene, to our delight the formation of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) was observed in 84% yield, which meets our requirements of a scalable process. The spectroscopic and analytical data of pyrrolinone **3** were in complete agreement with the reported data.[5d]




**Scheme 3** Second-generation approach for the synthesis of **3**

In conclusion, a short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) has been developed. Key features are the synthesis of 3-methyl-4-hydroxy-2-butenolide in water, one-pot opening–reductive cyclization of the butenolide for the synthesis of five-membered lactams, and triflic acid mediated *N*-benzyl deprotection of lactam **9**. As the synthesis of pyrrolinone **3** was achieved in four steps in 25% overall yield, we believe that this short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one, a key building block of the antidiabetic drug glimepiride, paves the way for its industrial-scale synthesis.

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen, unless otherwise mentioned, with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by TLC with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid, *p*-anisaldehyde, 2,4-DNP, $KMnO_4$, or ninhydrin followed by heating with a heat gun for ~15 sec. Melting points are uncorrected. $^1$H NMR spectra were recorded on Bruker AV 200, 400, and 500 MHz NMR spectrometers ($^{13}$C NMR spectra at 50, 100, and 125 MHz, respectively) using solvent residue signal as an internal standard ($CDCl_3$, $^1$H NMR: 7.27 ppm, $^{13}$C NMR: 77.00 ppm). HRMS (ESI) were taken on an Orbitrap (quadrupole plus ion trap) TOF mass analyzer. IR spectra were recorded on a Bruker FT-IR spectrophotometer. Column chromatographic separations were carried out on silica gel (230–400 mesh).

### 5-Hydroxy-4-methylfuran-2(5*H*)-one (5)[7]

To a stirred, ice-cold (0 °C) solution of morpholine (58.2 mL, 675 mmol, 1 equiv), concd HCl (70.4 mL, 675 mmol, 1 equiv) was added dropwise over a 15-min period. The reaction mixture was then stirred for 2 h. To this, glyoxylic acid (100 mL, 50% aqueous solution, 675 mmol, 1 equiv) was added followed by propanal (50.7 mL, 708 mmol, 1.05 equiv), and the reaction mixture was further stirred at rt for 1 h and then refluxed for 12 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and the residue was extracted with EtOAc (3 × 500 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 30:70) afforded pure **5** as a yellow oil; yield: 58.5 g (76%).

$R_f$ = 0.3 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 3407, 1760, 1216, 766 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 1 H), 5.85 (q, *J* = 1.5 Hz, 1 H), 5.41 (br s, 1 H), 2.10 (d, *J* = 1.5 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

### 1-(4-Methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (6)[5d]

To a stirred solution of *p*-methoxybenzylamine (6.52 mL 49.9 mmol, 1.14 equiv) in isopropyl alcohol (40 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at rt. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated to 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by

purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 40:60) afforded pure **6** as a pale yellow solid; yield: 6.0 g (63%).

Mp 121 °C (Lit.[5d] 122 °C); $R_f$ = 0.2 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1222, 760 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.86 (d, *J* = 1.1 Hz, 1 H), 4.52 (s, 2 H), 3.79 (s, 3 H), 3.69 (s, 2 H), 2.00 (d, *J* = 1.1 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

### 3-Ethyl-1-(4-methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (7)[5d]

To a stirred solution of compound **6** (1 g, 4.6 mmol, 1 equiv) in anhydrous THF (25 mL), NaH (0.121 g, 5.06 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (0.41 mL, 5.52 mmol, 1.2 equiv) in anhydrous THF (5 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated $NH_4Cl$ solution and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 20:80) afforded pure **7** as a yellow solid [yield: 0.62 g (55%)] along with recovery of the starting material (0.3 g).

Mp 128 °C (Lit.[5d] 127–131 °C); $R_f$ = 0.6 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1216, 762 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.54 (s, 2 H), 3.79 (s, 3 H), 3.58 (s, 2 H), 2.29 (q, *J* = 7.5 Hz, 2 H), 1.91 (s, 3 H), 1.08 (t, *J* = 7.5 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

### 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (3)[5d]

To a stirred solution of compound **7** (0.2 g, 0.816 mmol, 1 equiv) in anisole (2 mL), TFA (2 mL) was added and the reaction mixture was heated at 80 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (4 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 82 mg (81%).

Mp 103 °C (Lit.[5d] 102 °C); $R_f$ = 0.3 (EtOAc–PE, 70:30).

IR ($CHCl_3$): 3440, 1722, 1216, 765 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, *J* = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, *J* = 7.6 Hz, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

HRMS (ESI): *m*/*z* calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

### 1-Benzyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (8)

To a stirred solution of benzylamine (5.45 mL, 50 mmol, 1.14 equiv) in isopropyl alcohol (45 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at rt. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated to 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **8** as a yellow solid; yield: 5.65 g (69%).

Mp 96–98 °C; $R_f$ = 0.3 (EtOAc–PE, 30:70).

IR ($CHCl_3$): 1674, 1217, 763 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.32–7.09 (m, 5 H), 5.82 (q, *J* = 1.4 Hz, 1 H), 4.53 (s, 2 H), 3.65 (s, 2 H), 1.95 (d, *J* = 1.4 Hz, 3 H).

$^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 171.9, 155.2, 137.3, 128.5 (2 C), 127.8 (C), 127.3, 122.5, 54.9, 45.6, 15.1.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}NO$ $[M + H]^+$: 188.1070; found: 188.1062.

### 1-Benzyl-3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (9)

To a stirred solution of compound **8** (8 g, 42.7 mmol, 1 equiv) in anhydrous THF (200 mL), NaH (1.13 g, 47.0 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (3.83 mL, 51.3 mmol, 1.2 equiv) in anhydrous THF (40 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated $NH_4Cl$ solution and extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 35:65) afforded pure **9** as a sticky yellow solid [yield: 5.25 g (57%)] along with recovery of the starting material (1.5 g).

$R_f$ = 0.26 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1703, 1216, 765 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 5 H), 4.60 (s, 2 H), 3.60 (s, 2 H), 2.31 (q, *J* = 7.5 Hz, 2 H), 1.62 (s, 3 H), 1.09 (t, *J* = 7.6 Hz, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 172.2, 145.4, 137.6, 134.1, 128.6 (2 C), 128.0 (2 C), 127.3, 53.5, 45.9, 17.0, 13.1, 12.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}NO$ $[M + H]^+$: 216.1383; found: 216.1379.

### 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (3) by *N*-Debenzylation of Lactam 9

#### Method A: Microwave Assisted

To a glass vial, equipped with a Teflon cap, compound **9** (0.2 g, 0.93 mmol, 1 equiv) in toluene (2 mL) followed by triflic acid (0.328 mL, 3.72 mmol, 4 equiv) was added. The reaction mixture was kept for 45 min in a microwave reactor (Anton Paar, Monowave 300 microwave synthesis reactor) at 800 W (150 °C). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 0.1 g (86%).

#### Method B: By Heating

To a stirred solution of compound **9** (3 g, 13.9 mmol, 1 equiv) in toluene (30 mL) was added triflic acid (4.94 mL 55.8 mmol, 4 equiv). The reaction mixture was heated at 160 °C for 24 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (20 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 1.47 g (84%).

Mp 103 °C (Lit.[5d] 102 °C); $R_f$ = 0.3 (EtOAc–PE, 70:30).

IR ($CHCl_3$): 3440, 1722, 1216, 765 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, *J* = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, *J* = 7.6 Hz, 3 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

HRMS (ESI): *m*/*z* calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

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## Supporting Information

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