TOTAL SYNTHESIS OF CAMPTOTHECIN & IT'S ANALOGUES AND BIOLOGICALLY ACTIVE COMPOUNDS

RASAPALLI SIVAPPA

National Chemical Laboratory
June 2002

Dedicated to

My

Parents

&
Teachers

TOTAL SYNTHESIS OF CAMPTOTHECIN & IT'S ANALOGUES AND BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS
SUBMITTED TO THE

UNIVERSITY OF PUNE
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
IN

CHEMISTRY

BY

RASAPALLI SIVAPPA

Division of Organic Chemistry : Technology
National Chemical Laboratory
Pune – 411008, INDIA

June 2002

Dr Subhash P. Chavan
Scientist
Division of Organic Chemistry: Technology

Tel: +91-20-5893300 Extn: 2289
Fax: +91-20-5893614
e-mail: spchavan@dalton.ncl.res.in

National Chemical Laboratory
Dr. Homi Bhabha Road
Pune – 411 008, INDIA

CERTIFICATE

Certified that the work incorporated in the thesis entitled *"Total Synthesis Of Camptothecin & It's Analogues And Biologically Active Compounds"* submitted by Rasapalli Sivappa was carried out under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

Dr. Subhash P. Chavan

Research Supervisor

Declaration

I hereby declare that the thesis entitled *"Total Synthesis Of Camptothecin & It's Analogues And Biologically Active Compounds"* submitted for Ph.D degree to the university of Pune has been carried out at NCL under supervision of Dr.Subhash P.Chavan and the work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

Date:
Organic Chemistry: Technology,
Rasapalli Sivappa
National Chemical Laboratory,
Pune-8

CONTENTS

Part - C

Section III :

Synthesis of Nothapodytine B (Mappicine ketone)

CHAPTER – 2

Section – I:

Synthesis of Luotonin A

Section – II:

Synthesis of Pyrroloquinazolonone Alkaloids: Vasicinone & Luotonin A

Section – III:

Synthesis of Pyridoquinazolonone Alkaloids: Rutaecarpine

ACKNOWLEDGEMENTS

It gives me a great pleasure to express my deep sense of gratitude to my mentor Dr. Subhash P. Chavan, who has helped me a lot to learn and think chemistry with his state of the art guidance. I do sincerely acknowledge the freedom rendered to me by him for independent thinking, planning and executing the research. I consider very fortunate for my association with him, which has given a decisive turn and significant boost in my career. I thank him for the patience and forbearance he had shown in my case at times.

I am thankful to Dr. T. Ravindranathan, ex-Deputy Director and Head, Division of Organic Chemistry: Technology, NCL for his inspiration, constant encouragement and, I am equally thankful to Dr. M. K. Gurjar, Deputy Director and Head, OCT Division, for his support and help.

I would like to specially thank Dr. S. K. Kamat, Scientist, for the help he rendered during I through out my research.

I owe my gratitude to Mrs. Latha Sivadasan, Scientist, for her valuable help, suggestions and moral support during ups and downs of the research career. I extend my thanks to Mr. Sivadasan and Smideep for their encouragement and suuport.

Thanks to Director, NCL, for giving me an opportunity to do research at NCL and permitting me to use infrastructure and necessary facilities. Thanks to CSIR, New Delhi for financial support.

I extend my thanks to all the members of Analytical (NMR, IR, Mass and Microanalysis), Library, Administration and technical staff of NCL especially Dr. Raj Mohan, K. D. Desh Pande, Jagtap, V.T. Sathe, Miss. Rupali, Mrs. Phalgune, Mrs. Shantakumari, Sanjay, Dr. Saha, H.B. Singh, Annagiri and Deodhar for their multifarious assistance.

I wholeheartedly thank all my friends at NCL (I am afraid of missing few by trying to name individually) who made the life memorable and pleasant and extended helping hand when in need (especially chemicals and money)..

Thanks are due to all the colleagues and scientists and staff of Organic Chemistry: Technology Division for their interest, encouragement and support during my research work.

I am thankful to Dr. V. H. Deshpande, Dr. R.A. Joshi, Dr (Mrs.). Joshi, Dr. U.R. Kalkote, Dr. H.B. Borate, Dr. Mrs. BhanuChanda, Dr (Mrs.). R.D. Wakhrakar, Dr. G. V. Madhava Sharma, Dr. N. P. Argade, Dr. A. Sarkar, Dr. C.V. Ramana Dr. Lahote, Dr. G.T. Panse, Dr. V. Pal, I. Shiva Kumar, Mrs. Kamalam Balakrishnan , Krishna and Dr. B.S. Rao for their valuable help, suggestions and discussions.

I would like to offer my modest regards to my teachers Prof. Dr. V. Kesavan, Prof. Dr.A.C. Benarjee, Prof. Dr. B. S. Ragahvendra, Prof. Dr. G.T. Bhandage, Prof. Dr. Janardhan, Dr. Seetharamappa, Dr. P.M. Radha Krishna, Dr. Shreemati, Dr. Shinde, Dr. Manjula P.Rao, Dr. M. V. Chalapathi Rao, Dr. Venkat Rao, Dr. Nagabhushanam, Dr. Peddanna, Dr. Saraswathi, Dr. Rachaih, Dr. Savitri, Dr. T. Adinarayana Gupta, Dr. G. KrishnaMurthy, Dr. Obula Reddy, Mariyamma, Divamani, NanjundaRao, Deenakar, Devaraj, Sugunamma, C. Radha, Y. Obula Reddy, Nirmallamma, Vinayakulu, Venkatachalapathi, Venkat Reddy,

Hanumantharao, Baktavaslam, Kesgava Rao and M. P. Nagaiah..I am thankful to A.G. Samuel for having trained me for operating NMR instrument.

I gratefully acknowledge the guidance given to me by my teacher Dr. Sabita Patnaik. I thank her for her care, affection and blessings bequeathed upon me during my stay at RCE, Mysore.

It is a great pleasure for me to thank Mr. Shyam Sunder, Director of ISO and other ISO group members.

On a personal basis I am indebted to Dr. Rajkumar Tejwani, Dr. Prakash Bhosle, Mr. Manmohan Kapoor, Thomas, Mr & Mrs. Nagabhushan Rao, P.N. Rajesh and Mrs. Shantakumari for their help.

It is my pleasure to thank my esteemed seniors Dr. Tripura, Dr. Chitra, Dr. Zubaida, Dr. Shubhada, Dr. Dhondge, Dr. Rani, Dr. R. B. Tejwani, Dr. Sachin, Dr. Etiraj, Dr. Amar Gopal, Dr.Rajendra Kharul, Dr. Anil Sharama and my present labmates Sanjay, Pallavi, Pasupathy, Ramakrishna, Praveen, Ramesh Kale, Mahesh, Sambhaji, Preeti, Swapnanjali, Vikas, Sudhir, Dushyant and Ashok.

My special thanks are due to Dr. M. S. Venkatraman for the initial orientation & training rendered to me. I am thankful to my friend K. Shiva Sankar for inspiring me towards research and introducing me to Dr. S.P. Chavan's group and for his support ever since our M.Sc days.I extend my thanks to Manjit, Mayur, Jain, Purva, Preethi, Rohi, and Abhijeet who made the working as a project assistant easy.

I thank Krishanakanth Reddy, Nitin and SubbaRaO for their help in preparation of this manuscript. Ithank Mandar for his help in the preparation of E version of thesis.It gives me an opportunity to thank my RCE friends - K. M. Jose, Sudharshan, Kanvah, Giriraj, Subbu, Anita, Pavan, Dolly, Ambujavalli, Durga, Bindu, Girija, Chitra, Kala, Varalakshmi, Cheenu, Vijay Kumar, Arjun, Srinivasarao, sriram, vasu, sudhir, Nagaraju, Kirti, Shakkeb, Chakri, Kota, Paapili, supriya, Padmaja, Ashok & Satya; SDGS friends - Syed Ali, Gopal Rao, Kiran, Mahesh, Aswarthu, Reyaz, Shiva, Prasad, Ramakrishna, Kotting & Sriram; Friends from Sadlapalli - Maruthi Reddy, Srinivasa Reddy, T. Praveen Kumar Reddy, Venaktesh, Nabbi, Hanumanthu, Nagaraj, Govardhan , Ramesh , Ananad, Narayana and Balaji . It is my pleasure to thank my best friend Chand for sharing my duties at home front and help my parents in absence. I also take this opportunity to thank Bheemesh, Prasad, M. Sudhakar Reddy, M.Govind Reddy, Abdul Salam, B.C Thimma Reddy, T. Sreenivasa Reddy, Venu Gopal Reddy and K. Narayana Reddy who expressed their interest in my education.

I place on record the help and care of my Grandma, who provided my early education. I am equally indebted to my cousin, Jyothi for her interest in my career and help during our stay with our Grandma.

I am grateful to my Grand father Shri. C. Venkata Reddy, for the interest he showed all through out my education and for his support, encouragement and inspiration.

It is my pleasant duty to thank my aunts Gouramma, Sunanadamma, Jayamma, and Aswarthamma for their love. I wish to thank my cousins T. Sivalinga Reddy, N. Chandrasekhar Reddy, N. Manjunath Reddy, N. Maruthi Reddy, K. Vema Reddy and K. Gopal Reddy for their constant support and encouragement.

Finally, I thank my father, Shri. J. Anjina Reddy and my mother, Smt. Venkata Lakhmamma and my loving sisters -Paru, Kala, and Manju for their unconditional love, care and blessings. It is because of their efforts, sacrifice and encouragement I could afford to study. I thank my Brother- in- laws -Subba Reddy, Govind Reddy and Ravindranth Reddy for their love and assistance. The love, and affection of my nephews and niece [Raja, Gopi, Teja, and Uma, Sneha, Vidya, Susmita], which made the gloomy days shine, is acknowledged finally.

Siva

ABBREVIATIONS

Ac_2O	Acetic anhydride
AIBN	2,2'-Azobisisobutyronitrile
$AlCl_3$	Aluminium chloride
$BF_3.Et_2O$	Borontrifluoride diethyl etherate
Bn	Benzyl
B.P.	Boiling Point
Bu_3SnH	Tributyltinhydride
CAN	Cerium(IV) ammonium nitrate
$CDCl_3$	Deuterated chloroform
$CuSO_4.5H_2O$	Copper(II) sulfate pentahydrate
Cbz	Benzyloxy carbonyl
CPT	Camptothecin
DCC	*N, N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DMAD	Dimethyl actylene dicarboxylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
EtOAc	Ethyl acetate
$FeCl_3$	Iron (III) chloride
g	Gram/s
h	Hour/s
hCPT	Homocamptothecin
H_2O_2	Hydrogen peroxide
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
IR	Infra-red
$KOBu^t$	Potassium tert-butoxide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
M^+	Molecular ion
MnO_2	Manganese(IV) oxide
M.P.	Melting Point
MsCl	Mesyl chloride

Na_2SO_4	Sodium sulfate (anhydrous)
NaOAc	sodium acetate
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
n-BuLi	n-Butyllithium
PBr_3	Phosphorus tribromide
PCC	Pyridinium chlorochromate
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(PPh_3)_4$	Pallaidum tetrakis triphenyl phospine
Pd-C	Palladium on carbon
PDC	Pyridinium dichromate
PCl_3	Phosporous trichloride
PMB	*p*-Methoxy benzyl
$POCl_3$	Phosphorus oxychloride
PPA	Polyphosphoric acid
PTC	Phase transfer catalyst
rt	Room temperature
$SnCl_4$	Tin(IV) chloride
$TBAHSO_4$	Tetrabutylammonium hydrogen sulphate
TOPO-I	Topoisomerase -I
TDC	Topoisomerase dependent cleavage
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TFAA	Trifluoroacetic anhydride
TLC	Thin layer chromatography
TMSCl	Trimethylsilylchloride
TMSI	Trimethyl silyl iodide
*p*TSA	*p*-Toluenesulphonic acid
$ZnCl_2$	Zinc chloride

GENERAL REMARKS

1. All the melting points and boiling points are uncorrected and the temperature is expressed in ^{o}C.

2. All reactions requiring anhydrous conditions were performed under a positive pressure of argon or nitrogen using oven-dried glassware ($120^{o}C$).

3. Progress of the reaction was monitored by TLC and was visualized by UV absorption by fluorescence quenching or I_2 staining or by both.

4. All Solvents used were distilled before use.

5. Solvents for anhydrous reactions were dried by standard procedures.

6. All organic layers obtained after extractions were dried over anhydrous Na_2SO_4. All evaporations were carried out under reduced pressure on Buchi rotary evaporator.

7. In cases where chromatographic purification was done Silica gel has been used as stationary phase and it was 60-120 mesh. Pet. Ether refers to the boiling fraction of 60-$80^{o}C$.

8. IR spectra were recorded on Perkin-Elmer infrared spectrometer model 681or model 1605 FT-IR (ν max is expressed in cm^{-1}).

9. The ^{1}H NMR spectra were recorded using TMS as internal reference on Bruker AC-200 and Bruker MSL-300 instrument using $CDCl_3$or $CDCl_3$ + CCl_4 unless other wise specified in case of other solvents. ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker MSL-300 instrument operating at 50 MHz and 75 MHz respectively. Chemical shifts are recorded in δ.

10. Mass spectra were recorded on Finnigan-Mat 1020C Mass Spectrometer and are obtained at an ionization potential of 70 eV and mass values are expressed as m/z values.

11. Microanalysis was carried out in the microanalytical section of NCL.

12. Scheme numbers and reference numbers given in each section refer to the particular section only.

ABSTRACT

Thesis entitled **"Total synthesis of Camptothecin & it's analogues and Biologically active compounds" is** divided in to two chapters.

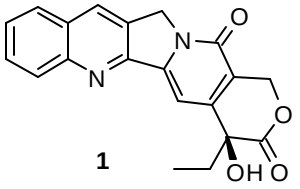
Chapter 1: deals with synthetic approaches towards Camptothecin, which is divided into three sections.

Chapter 2: highlights the synthesis of quinazolinone alkaloids, which is further divided in to three sections

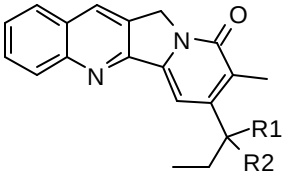
Chapter 1:

The isolation of Camptothecin[i] [**1**], a pyrrole quinoline alkaloid in 1966 by Wall and coworkers from *Camptotheca acuminata*, the elucidation of its structure and above all the finding of high antitumor activity of its various derivatives by an unique mechanism[ii] involving the inhibition of DNA Topoisomerase1 triggered a great deal of interest at the chemical level.

Nothapodytine B [**2**] (Mappicine ketone), isolated recently from *Nothapodytes foetida*[iii] (an oxidized derivative of Mappicine [**3**][iv] and E-ring decarboxylated analogue of Camptothecin) has been identified as antiviral lead with reported selectivities against HSV-1, HSV –2 and HCMV.[v]



1



$R_1=R_2=O$ Nothapodytine B **2**

$R_1=H, R_2=OH$, Mappicine **3**

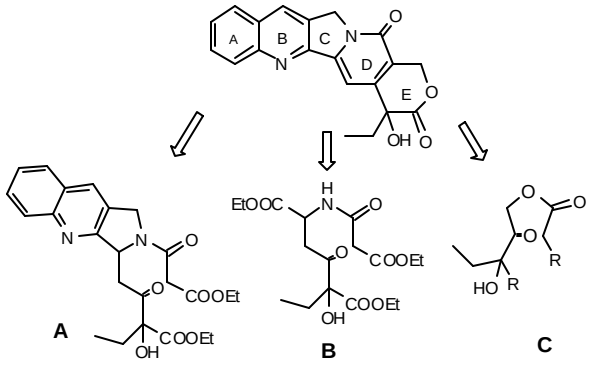
Given with the current continued interest, though many syntheses have been achieved[vi] still there is an evident need for the development of new synthetic routes for Camptothecin and Nothapodytine B amenable to their analogs. This section describes synthetic approaches in this direction.

Section I: Camptothecin Family Alkaloids-A Brief Review

A general introduction to Camptothecin, Mappicine and other naturally occurring analogues along with a concise review on their synthesis emphasizing mainly the synthetic approaches, which have appeared since 1996, is presented in this section.

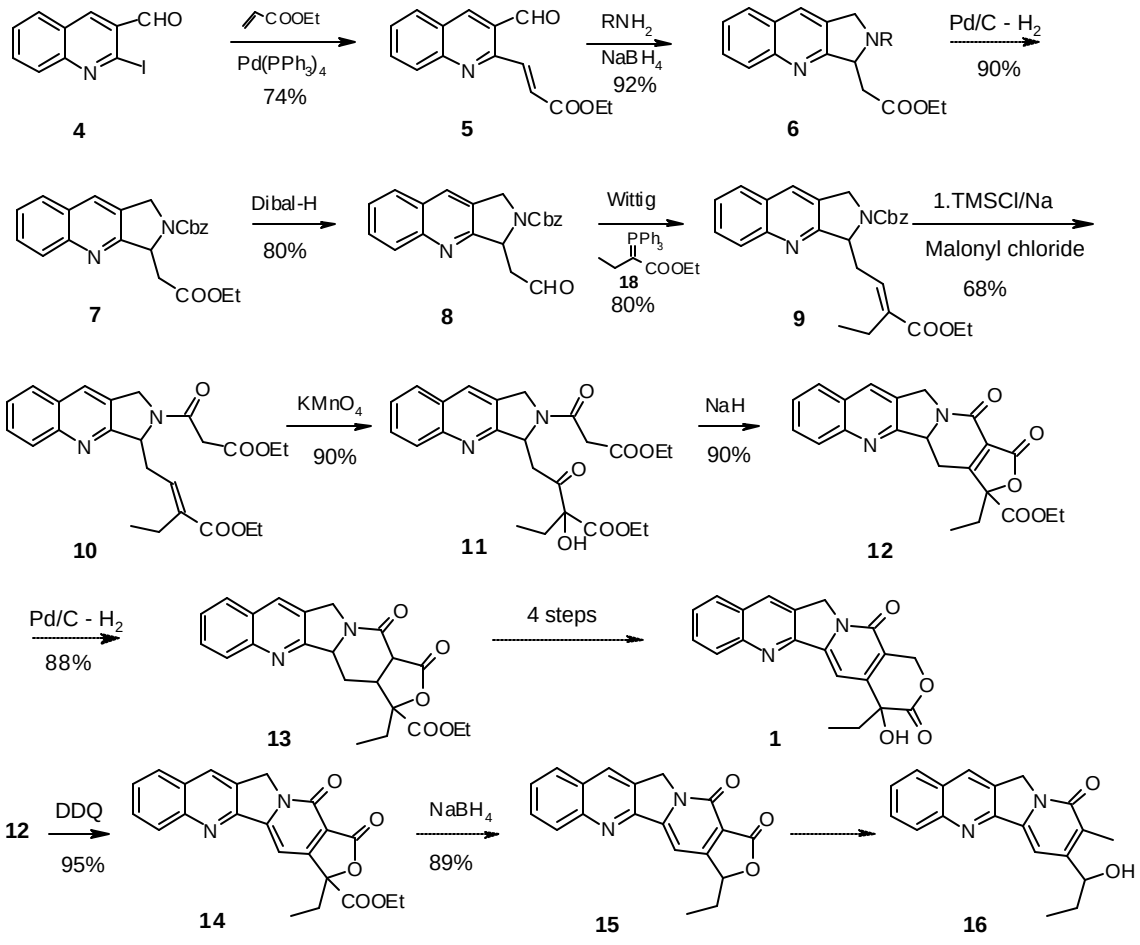
Section II: Synthesis Of Camptothecin

Our retro synthetic analysis of Camptothecin revealed an intramolecular aldol reaction as a key strategy, as depicted in *Scheme 1***,** which could be as well extended to construct the synthetic precursors of the same as discussed in three parts (*Scheme 1*).



Scheme 1

Part A deals with the synthesis of Camptothecin shown in *Scheme 2*.

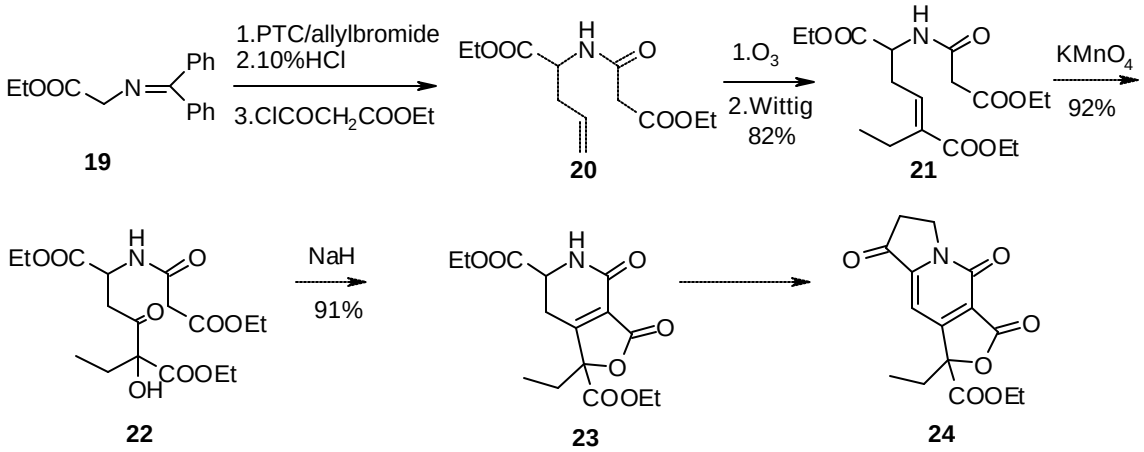


Scheme 2

Our synthesis commences from Meth-Cohn's aldehyde obtained from acetanilide. Thus knowing the reluctance of chloro arenes to participate in Heck olefination, we attempted the same on iodo aldehyde **4** to get the olefin-tethered aldehyde **5** in good yield using classical Heck conditions. Aldehyde **5** was reductively aminated, which suffered an intramolecular Michael addition resulting in tricylic amine **6**. Amine was deprotected and converted to its carbamate **7**. Careful reduction of the ester with Dibal-H resulted in the formation of tricyclic aldehyde **8** which was subjected to Wittig olefination with phosporane **18** to furnish unsaturated ester **9**. The carbamate **9** was deprotected with TMSCl/NaI and condensed with carbethoxy acetyl chloride to yield the amide **10** which on reaction with $KMnO_4$ at acidic pH gave the ketol **11**. Gratifyingly, the effected intramolecular aldol reaction resulted the dihydropyridone **12**. We were delighted with the early introduction of an ethyl and the hydroxy group at Camptothecin C-20 position.The compound **12** was oxidized to pyridone **13** which has got all the necessary atoms in place for Camptothecin and only the simple manipulation of the oxidation states should provide us the title compound. But this seemingly trivial operation seemed extremely difficult and could be effected under no conditions. So we resorted to convert to a known intermediate of Stork's synthesis.[vii] Thus reduction of the dihydropyridone furnished tetrahydropyridone **13**, which was converted to Camptothecin earlier in few steps. Sodium borohydride reduction of the compound **14** resulted in the formation of compound **15** *via* decarbonylative loss of the ester which has the potentiality for the conversion to Mappicine **16** and hence to Nothapodytine B.[2]

Part B deals with the approach towards Camptothecin analogues.

Camptothecin's clinical use has been limited by its insolubility and toxicity,[viii] but extensive structure activity relation studies have identified many analogs with better solubility and with equal or better antitumor activity, which resurged the interest of the chemists as well as oncologists. Synthetic approaches for these analogs have typically involved synthesis of suitably functionalized CDE-rings[ix] or DE-rings[x] or precursors thereof, which was then coupled with suitable counter parts. So we proposed to apply the above methodology at an early stage of the synthesis, which would have the flexibility to obtain the analogues of CPT as shown in *Scheme 3*.

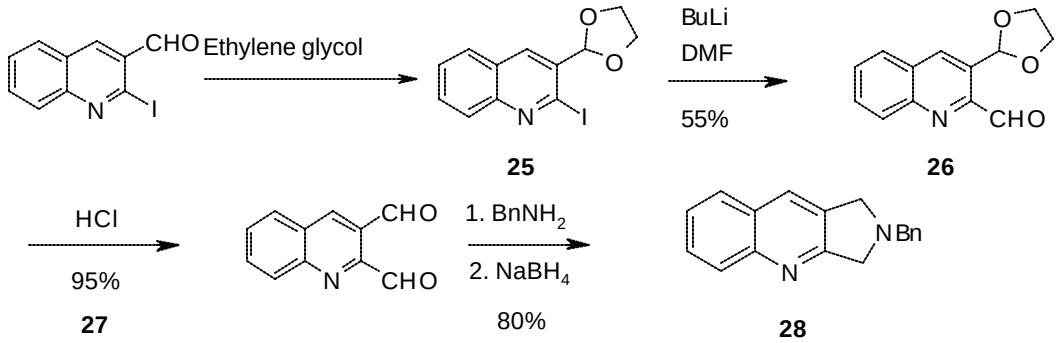


Scheme 3

Thus phase transfer alkylation of Schiff's base **19** followed by hydrolysis resulted in amine, which was then condensed with acid chloride to give olefin **20**. This was subjected for the oxidative cleavage and Wittig olefination. The resulted amide **21** was converted to ketol **22** with $KMnO_4$ in acidic pH. Attempted aldol reaction of ketol with NaH as the base gave us dihydropyridone **23** in excellent yield, which could be converted to CDE intermediate **24,** an established synthon for preparation of CPT analogues

PART C deals with the synthetic approaches towards the synthons of highly convergent approach.

A highly convergent approach,[xi] which involves preformed ABC synthons whose condensation with pseudo acid halide attracted our attention. So we synthesized the same intermediates. Synthesis of the triclic synthon is shown in *Scheme 4***.**

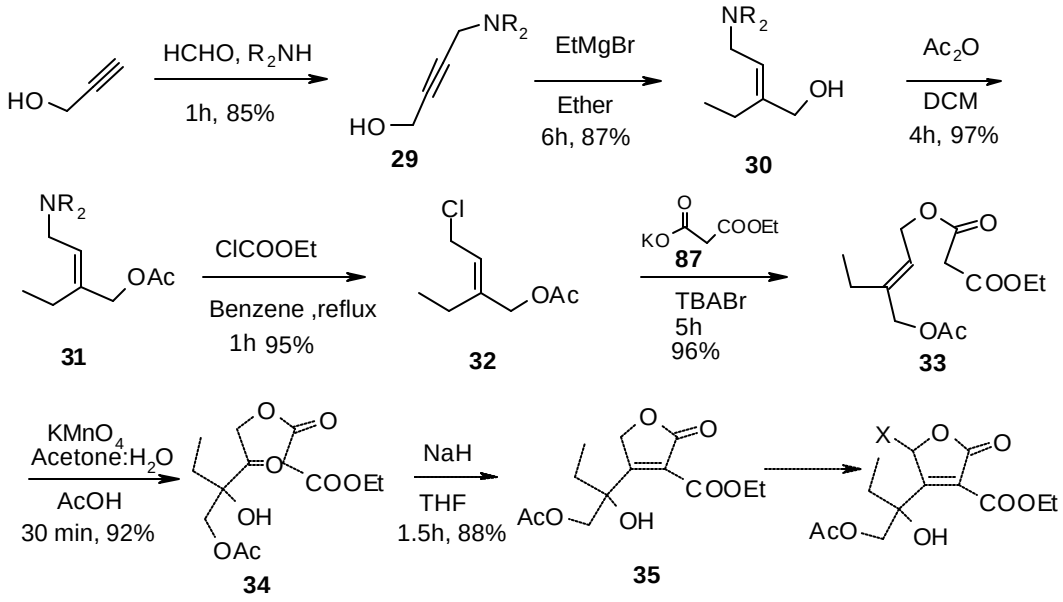


Scheme 4

Accordingly 2-chloro3-formyl quinoline was prepared by Meth-Cohn procedure and converted to 2-iodoaldehyde by Fenklestein reaction. Formyl group of the iodoaldehyde was protected as cyclic acetal **25**. Quenching the lithio derivative with DMF provided 2- formyl

quinoline **26**. The acetal of **26** was deprotected with 20% HCl in ether to get the dialdehyde **27.** It was gratifying to note the formation of tricyclic synthon upon treatment of the dialdehyde with 1 equivalent of benzyl amine in methanol followed by reduction with sodiumborohydride. Thus we achieved an expedious synthetic route for tricyclic amine **28**.

Synthesis of an intermediate for DE synthon has been achieved as shown in *Scheme 5*.



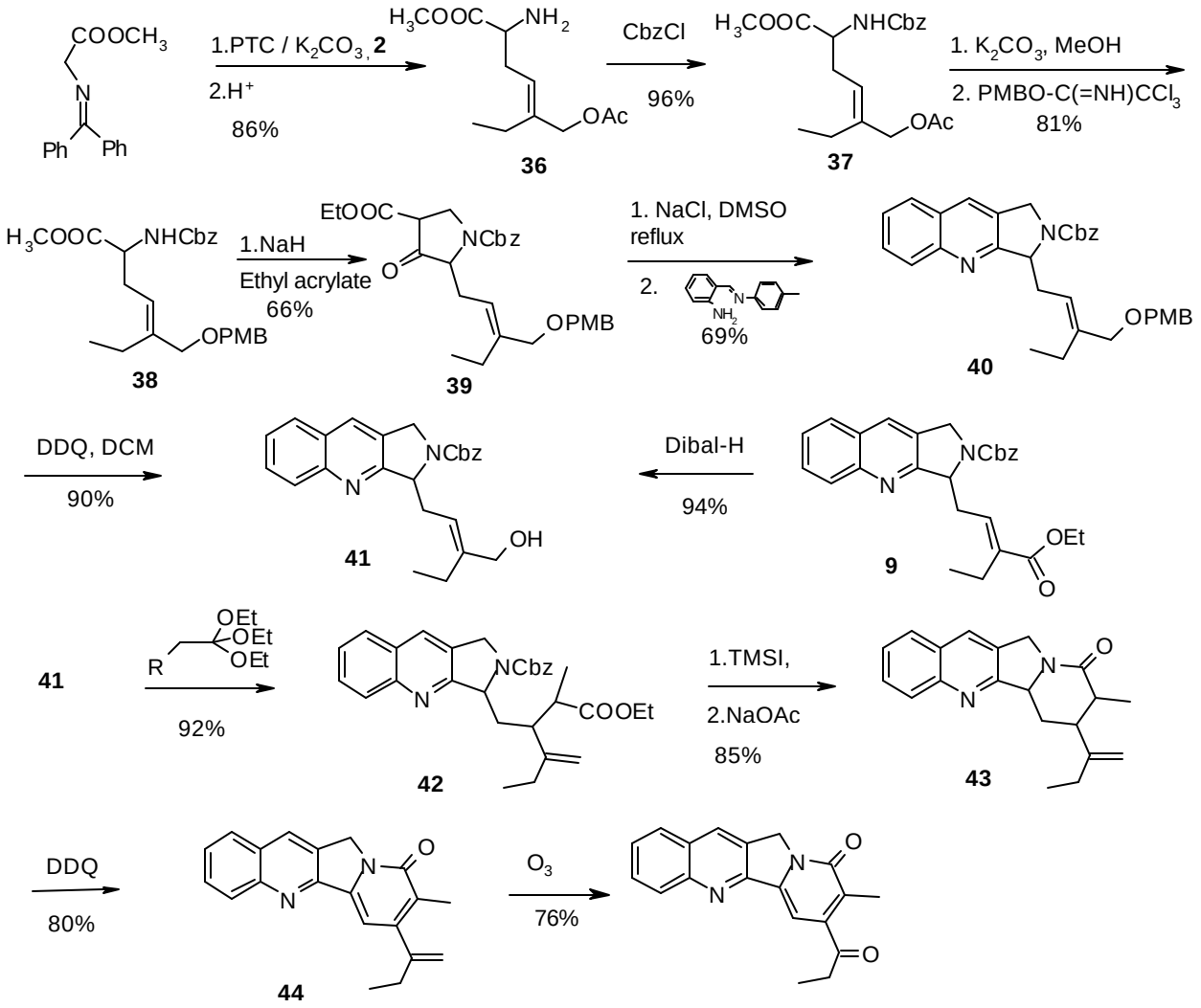
Scheme 5

The Mannich reaction of propargyl alcohol with formaldehyde and dialkyl amine gave the amino alcohol **29**, which on treatment with ethylmagnesiumbromide gave the 2-substituted olefin **30.** Alcohol was protected as acetate **31** and treatment with ethylchloroformate gave the chloro compound **32** in excellent yield. This chloro compound **32** was treated with potassium salt of monoethylmalonate under PTC conditions to get allylic ester **33**. Allylic ester **33** upon treatment with $KMnO_4$ in acidic pH gave ketol **34**. Aldol reaction of the same should lead to the intermediate **35** whose conversion to pseudohalide **36**, followed by coupling with ABC synthon would give the access to CPT and it's analogues.

Section III: Synthesis of Nothapodytine B & Mappicine employing Claisen orthoester rearrangement.

We envisaged a Claisen ortho-ester rearrangement to form the crucial C-C bond required for the D-ring while placing the suitable functionalities for further elaboration as shown in

Scheme 6. Thus alkylation of Schiff's base with the chloro compound **32** under PTC conditions and hydrolysis of the same resulted in amine **36.** Amine was protected as its benzyl carbamate **37** and simple manipulation of hydroxy protecting group from acetate to PMBether gave the compound **38.**



Scheme 6

Michael addition -Dieckmann condensation sequence with ethylacrylate furnished β-ketoester **39**, which was decarboxylated to pyrrolidone which was subjected for Friedlander condensation with the Schiff's base of aminobenzaldehyde followed by deprotection of PMB ether gave allylic alcohol **41,** which was also obtained from Dibal-H reduction of α, β-unsaturated ester **9.**

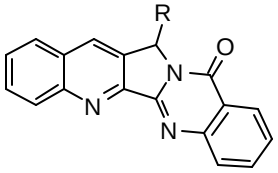
Treatment of **41** with triethyl orthopropionate in the presence of acid catalyst furnished γ, δ-unsaturated ester **42**. The carbamate was deprotected with TMSI to provide amine, which upon treatment with NaOAc in ethanol underwent lactamization resulting in tetrahydropyridone

43 in good yield. DDQ oxidation of the tetrahydro pyridone gave pyridone **43a.** Synthesis of Nothapodytine B was realized by the controlled ozonolysis of the exocyclic methylene.

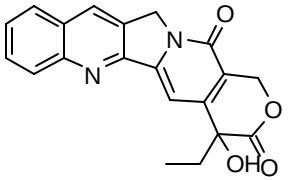
Chapter II: Synthesis of Quinazolinone alkaloids.

Section I: S**ynthesis of Luotonins.**

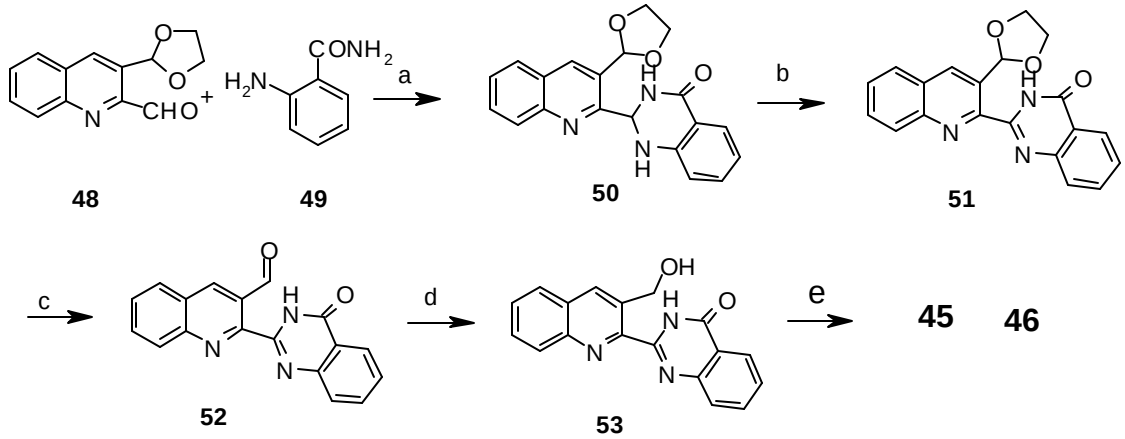
Luotonin A, B and E (**45-47)** are, structurally unique family of pyrrolo quinazolino quinoline alkaloids, isolated from the aerial parts of the Chinese medicinal plant *Peganum nigellastrum* which has been traditionally used for the treatment of rheumatism, inflammation, abscesses and other maladies.[xii] Its structure has been confirmed by earlier syntheses.[xiii] Luotonin's striking reminiscence to Camptothecin **1**, in its cytotoxic activity against mouse leukemia P-388 cells and structure coupled with our interest in the latter led us to develop a general synthetic route for Luotonin A and its analogs.



R=H **45** LUOTONIN A
R=OH **46** LUOTONIN B
R=OMe **47** LUOTONIN E



The *Scheme 7* outlines our synthesis to Luotonins.



Scheme 7

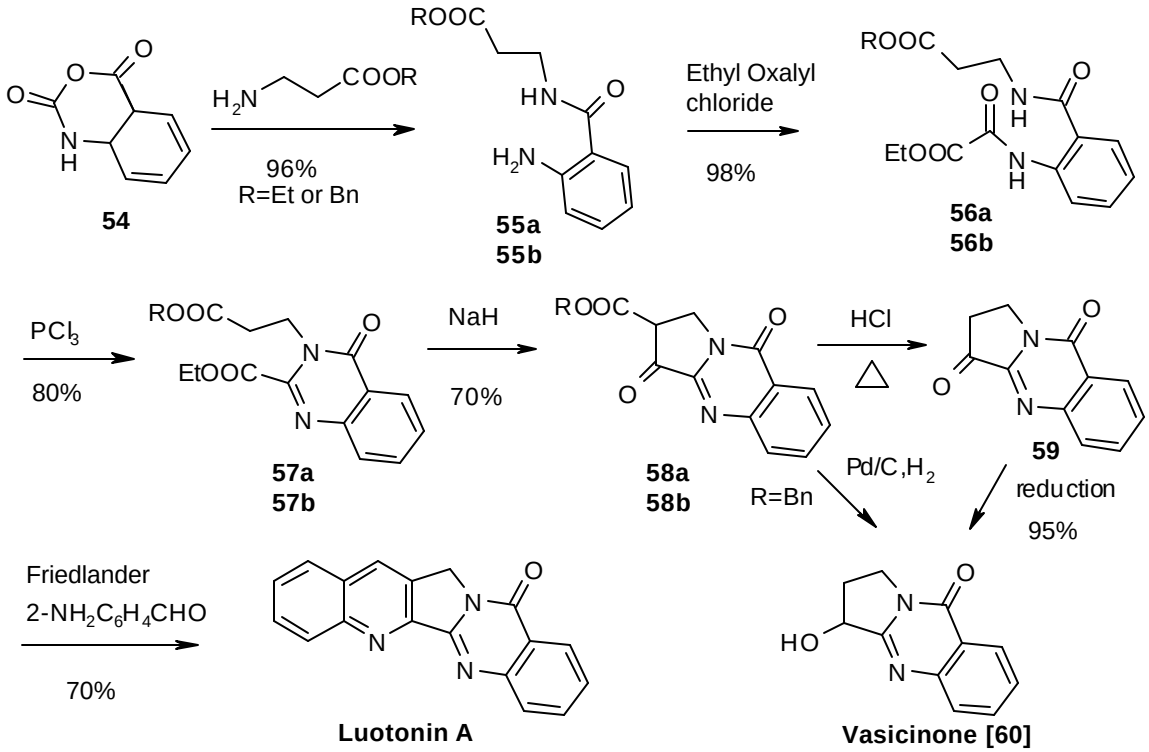
Conditions: a). Ethanol, 15% NaOH, reflux, 5h, 93%; **b**) KMnO4, Acetone, reflux.; **c**) THF, 10% HCl, 30 min., 98%; **d**). $NaBH_4$, CH_3OH, 30 min., 95%; **e**). 60% Ethanolic H_2SO_4, 3h, 73%.

Thus the aldehyde **48** was readily accessed from acetanilide according to Meth-Cohn's procedure. Refluxing of 1:1 mixture of aldehyde **48** and anthranilamide **49** in ethanol with 15% NaOH solution (1.6 ml for 0.025 mole) furnished the dihydroquinazolinone **50**. A point worthy

of note is that the quinazolinone **51** was directly obtained instead of the anticipated dihydro quinazolinone when 20% KOH is employed. Oxidation of 50 with $KMnO_4$ gvae the quinazolinone **51**. Deprotection of the acetal **51** under the acidic conditions furnished aldehyde **52** whose reduction with sodium borohydride gave the alcohol **53** in excellent yields. The final construction of the C-ring was realized by the treatment of the alcohol **53** with 60% ethanolic H_2SO_4 solution to form the Luotonin A in 73% yield by cyclodehydration. Luotonin B was obtained by performing the cyclodehydration in presence of $FeCl_3$. Luotonin B and E were obtained from acetal **51** by acid mediated reactions.

Section II: A general synthetic approach to Pyrroloquinazolonone alkaloids - Vasicinone and Luotonin A.

Vasicinone **60**, a pyrroloquinazoline alkaloid, is isolated from the aerial parts of *Adhatoda vasica*, an evergreen bush used in indigenous medicine for cold, cough, bronchitis, and asthma. These alkaloids are known to possess a broad spectrum of pharmacological activity particularly bronchodialatory activity.[xiv] We have developed an expeditious entry for the same through a common approach, which also constitutes a formal synthesis of Luotonin A *(Scheme 8).*



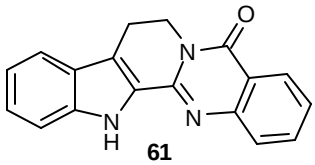
Scheme 8

Accordingly Isatoic anhydride **54** was condensed with β-alanates (R=Et, Bz) to give the anthranilamides **55a & b** which were acylated with ethyloxalyl chloride to give the peptides **56a & b** which were subjected for the cyclodehydration to obtain the quinazalinones **57a & b**. Dieckmann condensation of peptide employing NaH as base furnished β-Keto ester **58a & b**.

Decarboxylation of **58a** with HCl at 100°C gave the desired pyrrolo quinazolinone **52.** $NaBH_4$ reduction of the ketone **59** gave vasicinone **60.** Alternatively the hydrogenation of corresponding Bz ester of the **58b** with Pd/C (10**%**)MeOH: EtOAc directly resulted in the formation of vasicinone. This involves a tandem sequence of debenzylation, decarboxylation, & reduction of the carbonyl to hydroxyl group. The ketone **59** and **60** are the putative intermediates of the earlier syntheses of Luotonin A. Thus an efficient & novel synthesis of Vasicinone as well as Luotonin A has been achieved.

Section 3: Synthesis of Rutaecarpine, an indolopyridoquinazolinone alkaloid.

Rutaecarpine has been isolated from the fruits of *Evoida rutaecarpa* and its naturally occurring derivatives are known to possess cardiotonic and analgesic properties and have been used for the treatment of gastrointestinal disorders and blood pressure.[xv]

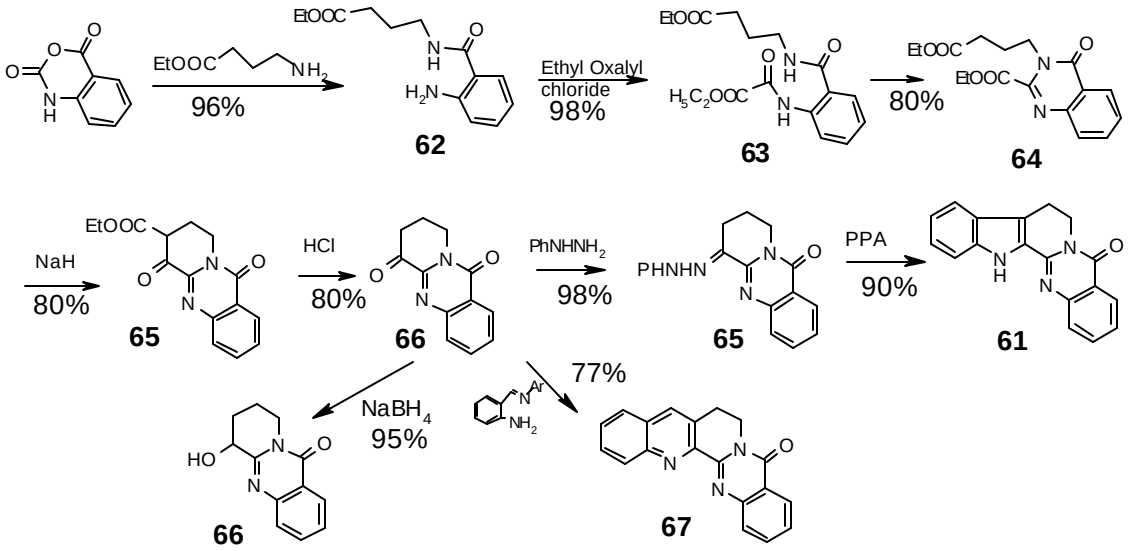


61

Since the above tenet has proven to be efficient for pyrroloquinazolinone alkaloids it was extended to the synthesis of pyridoquinazolinone skeleton and thus to the synthesis of Rutaecarpine.

Accordingly treatment of isatoic anhydride with ethyl 4-aminobutyrate gave amine **62,** which was condensed with Ethyl oxalyl chloride to obtain the peptide **63**. Peptide **63** was cyclodehydrated to quinazolinone diester **64** using PCl_3 in xylene under reflux conditions. This diester was subjected for Dieckmann condensation to get the β-keto ester **65** in much better yield than the 5-membered case This underwent decarboxylation more readily and cleanly to give the pyrido quinazolinone **65**. $NaBH_4$ reduction of the same gave the homovasicinone **66**. Hydrazone **67** was obtained with phenyl hydrazine, which confirmed the structure of the ketone has been

converted to Rutaecarpine **61** by Fischer indolisation. An all together a new hybrid alkaloid comprising the structural features of Luotonin and Rutaecarpine *i.e.* quinolo (2, -b) Pyrido quinazolinone **67** was synthesized by the Friedlander condensation of **65** with the Schiff's base obtained from *o*-amino benzaldehyde



References

[i]. Wall, M.E.; Wani, M.C.; Cook, C. E.; Palmer, K.H.; McPhail, A.T.; Sim, G.A.; *J. Am. Chem. Soc.,* **1966**, *88*, 3888.

[ii]. Fan, Y.; Weinstein, J.N.; Kohn, K.N.; Shi, L.M.; and Pommier, Y.; *J. Med.Chem,*, 1998, *41*, 2216 and references cited there in.

[iii]. Wu, T.S.; Chan, Y.Y.; Leu, Y L.; Chen, C.F.; *Phytochemistry*, **1996**,*42*, 907.

[iv]. Govindachari, T. R.; Ravindranath, K.R.; Viswanathan, N.; *J. Chem. Soc. Perkin.Trans.* **1974**,1215.

[v]. a) Pendark, I.; Barney, S.; Wittrock, R.; Lambert, D.M.; Kingsbury, W.D.; *J. Org. Chem.* **1994,** *59*, 2623. b) Pendark, I.; Barney, S.; Wittrock, R.; Lambert, D.M.; Kingsbury, W.D.; *J. Org. Chem.* **1995, 60**, 2912.

[vi]. Bennasar, L, M.; Juan, C.; Bosch, J.; *Chem.Comm*. **2000,** 2459, and references cited there in.

[vii]. Stork, G.; Schultz, A. G.; *J. Am. Chem. Soc.* **1971**, *93*, 4074.

[viii]. Potmosil, M. and Piendo, H.*Camptothecins: New anticancer agents.***1998** CRC press

[ix]. Henegar, K.E.; Ashford, S.; *J. Org. Chem.*, **1997**, *62*, 658

[x]. Comins, D.L.; Saha, J.A.; *Tetrahedron Lett* ., **1995**, *36*,7995.

[xi]. RamaRao, A.V.; Yadav, J.S.; Valluri, M.; *Tetrahedron Lett* ., **1994**, *35*, 3613

[xii]. a) Ma, Z.Z; Hano, Y; Nomura, T; Chen, Y.J. *Heterocycles*, **1997,** *46*, 541.

b) Ma, Z.Z; Hano, Y; Nomura, T.; Chen, Y.J. *Heterocycles*, 1999**,** *51*, 1883

[xiii]. Molina. P.; Tarraga, A. Tejero, A.G.; Synthesis **2000,** *11*, 1523

[xiv]. Amin, A.H.; Mehta, D.R.; *Nature*, **1959**, *183*, 1317.

[xv]. Patcher, *J. Am. Chem. Soc.* **1960**, *82*, 5187.

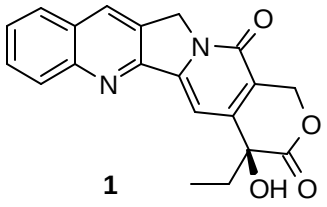
CHAPTER 1

SECTION I

Camptothecin Family Alkaloids-A Brief Review

1.1.1 Introduction

The isolation and characterization of the Camptothecin (**1,CPT**) as the active component contained in extracts from the Chinese tree *Camptotheca acuminata* by Wani and Wall had offered hope in 1966[1] of an antitumor therapeutic agent and triggered great deal of interest among oncologists and synthetic chemists.[2]



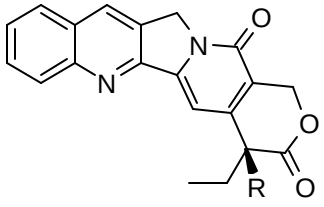
1

Activity of **1** has been demonstrated *in vivo* against leukemia, colon, mammary and ovarian tumor models.[2b] Unfortunately phase1 clinical evaluations of CPT revealed dose-limiting toxicities myelosupression, severe and unpredictable hemorrhagic cystitis and diarrhea, halting the clinical development.[3] Later studies pointed to the insolubility of CPT, which required the drug be formulated as the ring opened seco acid salt, as a key aspect in its clinical failure.

Only after the topoisomerase I being identified by Liu *et al* [4] as the cellular target of CPT, its derivatives resurfaced during the last decade as some of the most promising agents for the treatment of solid tumors by chemotherapy.

1.1.2 Structural Elucidation and properties

The compound was a high melting substance, with molecular weight of 348.11 corresponding to the formula $C_{20}H_{16}N_2O_4$ and was optically active $[\alpha]_D^{25}$ 31.3°. Based on the spectral and chemical properties, structure of Camptothecin was deduced to be (**1**). Formation of monoacetate **1a** and chloroCPT **1b** on treatment with acetic anhydride and thionylchloride /pyridine respectively, suggested the presence of hydroxyl group. Rapid saponification to give sodium salt and regeneration on acidification and lactol formation with $NaBH_4$ confirms the presence of lactone moiety in the molecule.

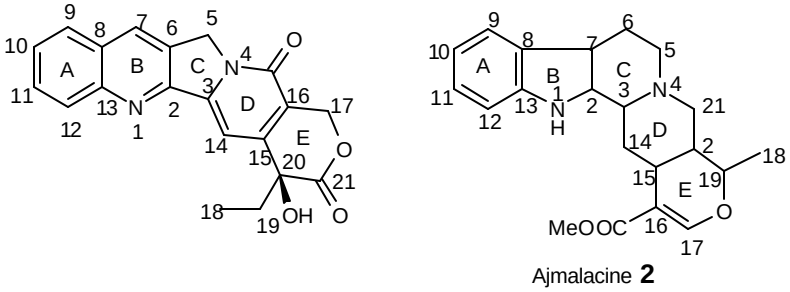


1a R =OAc
1b R =Cl
1c R =$OCOCH_2I$

The X-ray crystallography of iodoacetate **1c**, obtained from chloroacetate by treatment with NaI in acetone and crystallized in orthorhombic crystals unequivocally confirmed the structure to be *S*-4-ethyl-4-hydroxy-1*H* pyrano [3', 4'; 6,7] indolizino [1,2-*b*] quinoline-3, 14 (4*H*, 12*H*)-dione and revealed that the rings ABCD and substituents are coplanar. The ring-E exists in a boat form and the C-20 and lactone oxygen deviate from the planarity. The absolute configuration was determined by Bijvoet's method.

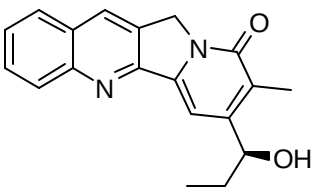
No crystalline salts are formed with variety of mineral acids unlike other alkaloids and it could not be methylated with diazomethane or dimethyl sulphate, which indicates the neutral nature of the molecule. The hydroxyl group imparts electrophilic character to the lactone carbonyl, thus making it highly reactive towards nucleophilic attack by amines, aq alkali, $NaBH_4$.

The Le Men-Taylor numbering system,[5] suggested by Shamma based on the probable biogenetic relation with ajmalacine, had been adapted for Camptothecin.

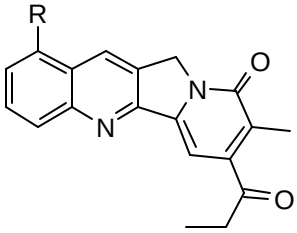


Ajmalacine **2**

Camptothecin undergoes thermal degradation upon heating to give decarboxylated analogues, which were known as Mappicine ketone **4**, much before to their isolation.



Mappicine **5**



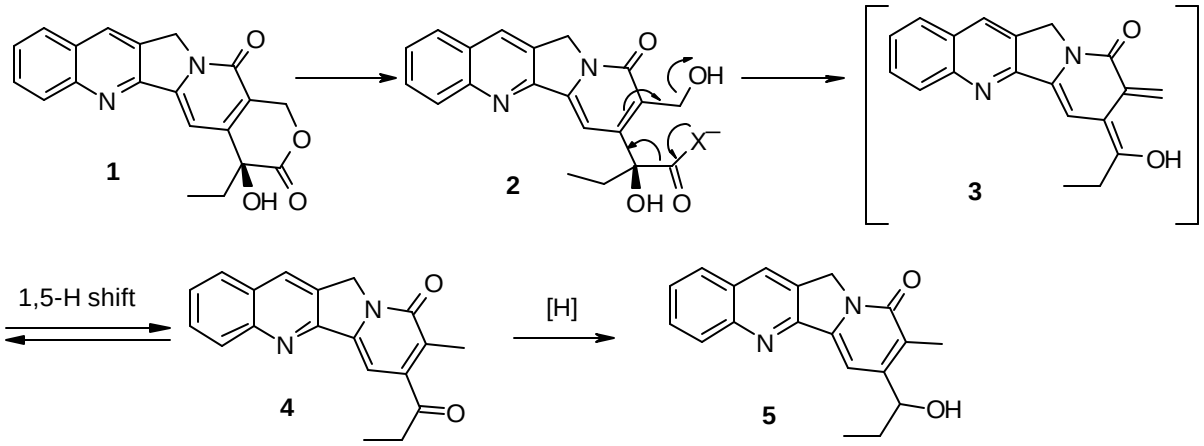
R = H, Nothapodytine B **4a** (Mappicine Ketone)

R = OMe,Nothapodytine A **4b** (Methoxymappicine Ketone)

Later these biologically important alkaloids have been isolated from *Nothapodytis foetida*[6] and cooccurance of CPT, Mappicine,[7] Nothapodytine B (Mappicine ketone) and, Nothapodytine A in *Nothapodytis foetida* suggests that these alkaloids have a common biosynthetic precursor or it is quite possible that **1** is the precursor of **4 & 5** as shown in the

following mechanism, which is observed in the fragmentation of the molecular ions produced from **1** in the electron impact mass spectrometer.

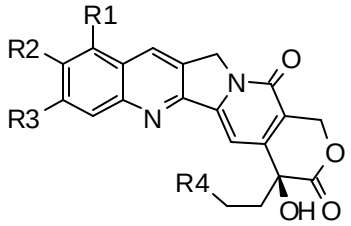
Scheme 1:



Recently Nothapodytine B **4a** has been identified as an antiviral lead compound with selective activity against HSV-1, HSV-2 and human cyto megalo virus (HCMV) with PR_{50} of 2.9, 0.5, 13.2 µM respectively.[8] The antiviral mechanism of Nothapodytine B is distinct from that of acyclovir (ACV) as demonstrated by the observation that ACV-resistant HSV-1 and HSV-2 are inhibited by MPK and that MPK resistant mutants remain sensitive to ACV, which permits them to be used in a complimentary fashion to each other.

1.1.3 Naturally occurring Camptothecins

Several analogues of Camptothecin, collectively called as 'Camptothecins'[9] have been isolated from various botanical species. Some of them possess potent antitumor and anti HIV-properties, often more active than the parent molecule which indicates the combinatorial approach adapted by the nature for lead optimization, and in view of the on going active analogue development programme of CPT it is apt to mention about some of them.



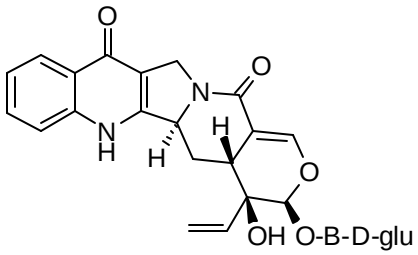
R1=R2=R3=R4=H	Camptothecin (**1**)	*C. acuminatadecene*,[9a] *N.foetida*[9b]*'Ophiorizamungos*[9c] *,Ervatimiaheyneana*[9d], *Merrillidendronmegacarpum*[9e] *Mostucabrunonis*[9f] *Ophiorizapumila*[9g]
R1=R3=R4==H, R2=OH	10-HydroxyCamptothecin (**1b**)	*Camptotheca acuminata decene* [9h] *Nothapodytes foetida*
R1=R3=R4=R5=H, R2=OMe	10-MethoxyCamptothecin (**1c)**	*Camptotheca acuminata* [9h] *Ophioriza mungos* [9c]
R1=OMe, R2=R3=R4=H,	9-MethoxyCamptothecin (**1d**)	*Camptotheca acuminata* [9h] *Nothapodytes foetida* *Ervatimia heyneana* [9h]
R1=R2=R4=H, R3=OH	11-HydroxylCamptothecin (**1e**)	*Camptotheca acuminata* [9l]
R1=R3=H, R2=OMe, R4=$(COCH_2)_4$Me	20-Hexanoyl10-methoxy Camptothecin **(1f**)	*Camptotheca acuminata* [9g]
R1=R2=R3=H, R4=OH,	18-HydroxyCamptothecin(**1g**)	*Camptotheca acuminata* [9j]
R1=OMe,R2=ß-D-gl, R3=R4=H,	Chaboside **(1h**)	*Ophioriza pumila champ* [9g]
R1=ß D-Glu, R2=R3=R4=R5=H	9-ß-GlucosylCamptothecin (**1i**)	*Ophioriza pumila* [9f]

Pumiloside (**6**):[9h] Pumiloside was postulated as the poststrictosamide intermediate of Camptothecin biosynthesis.

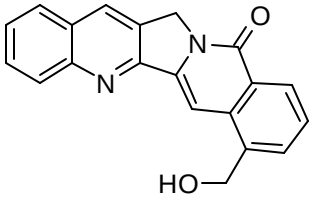
22-Hydroxycuminatine (**7**): [9i] It is a biogenetically novel alkaloid as A-D rings are similar to those of Camptothecin while the E-ring is of Yohimbine type. It showed cytotoxic activity against P388 and KB test systems *in vitro* with Ed50 values of 1.32 and 0.61µg /ml respectively.

Deoxy Camptothecin (**8**): [9j] Showed insignificant activity, presumably due to the lack of hydroxy group.

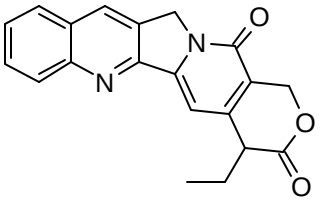
Foetidin I (**9**): [9j] It has A, B, C, D rings in common with Camptothecin and differs in its E-ring having a side chain through a phenolic ester bond. It showed anti tumor activity against ovarian cells A2780 WT (IC_{50}=3.4x10^{-7}) and anti viral activity against HIV viruses (IC_{50}=0.6 µg cm3).



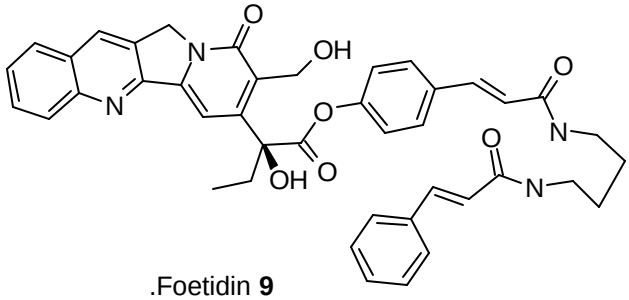
Pumiloside **6**



22-Hydroxycuminatine **7**



Deoxy camptothecin **8**



.Foetidin **9**

Some of the naturally occuring pyrrolo (3,4-b) quinoline alkaloids

1.1.4 Biogenesis

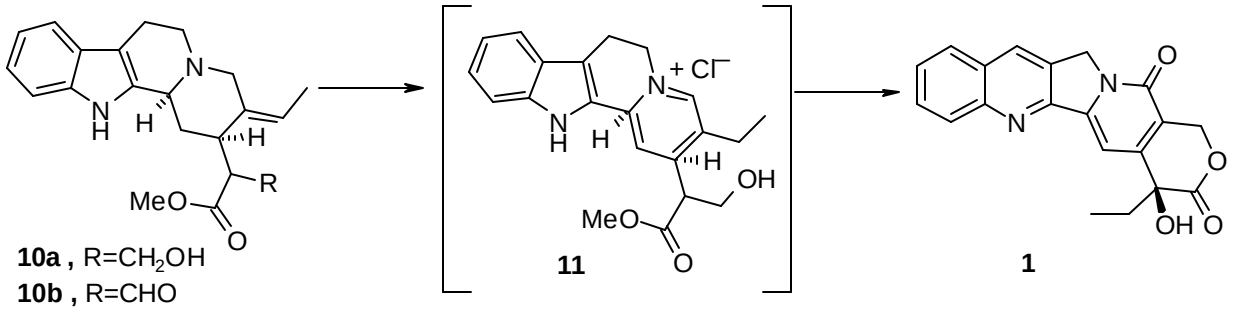
The discussion on biogenesis has its relevance in the present context in view of the recent synthetic developments based on biogenetically patterned disconnections**.**

1.1.4.1 Biogenetic speculations:

Wenkert *et al*[10] speculated Camptothecin to be a monoterpinoid alkaloid, a masked indole alkaloid of Corynantheidine type. The plausible chemical sequences from isositstrikine **10a** to

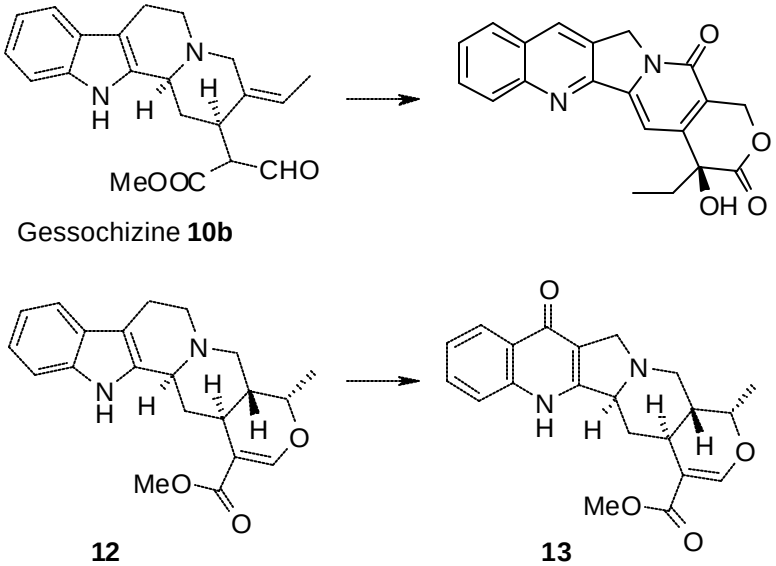
CPT would include oxidation to **11**, D-ring unraveling, reclosing and adjustment in the final oxidation states of the carbons as depicted in *Scheme 2*.

Scheme 2:



Winterfield *et al*[11] proposed gessiochizine **10b** as a more likely intermediate based on his findings of indole alkaloid **12** oxidation to quinoline **13 (***Scheme 3).*

Scheme 3:

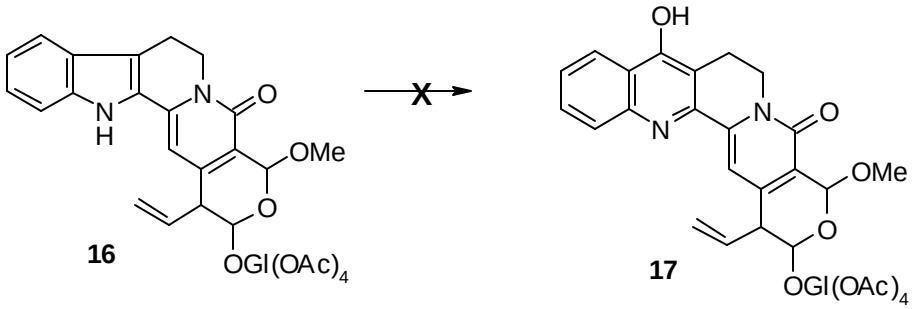


Hutchinson *et al*[12] ruled out the above two hypotheses as there was insignificant incorporation of radioactivity into **1** using [aryl ^{3}H]-**10b** in the feeding experiments and proposed that strictosidine **14a** or Vincoside **14b** could have given rise to Camptothecin **1** (*Scheme 6*). Cordell *et al*[13] have also proposed the same hypothesis for the biogenesis of CPT alkaloids. Experimental results of the feeding of labeled precursors carried out by Heckendorf *et al* [14] proved strictosidine **14a** as the specific penultimate biosynthetic precursor and ruled out epimeric vincoside **14b.**

1.1.4.2 Bio synthetic events from Strictosidine to CPT:

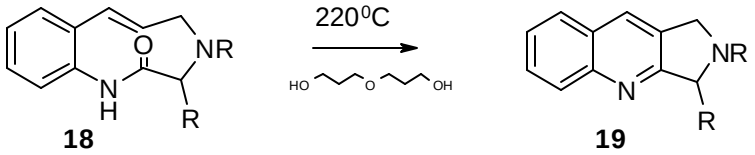
The exact sequence of biosynthetic transformations from strictosidine **14a**, would involve the removal of glucose as the step following the formation of strictosamide **15**, by analogy with the biosynthetic fate of strictosidine **14a** in other higher plants.[15] The D-ring oxidation to pyridone was presumed to be the step subsequent to ABC rearrangement based on the finding that pyridone **16** could not be transformed to quinoline **17** under standard laboratory conditions which are known to convert tetrahydro β-carbolines to quinolines (*Scheme 4*).

Scheme 4:



The thermal cyclization of **18** to the corresponding analogue of **19** supports the later biogenetic concept[16] (*Scheme 5*)

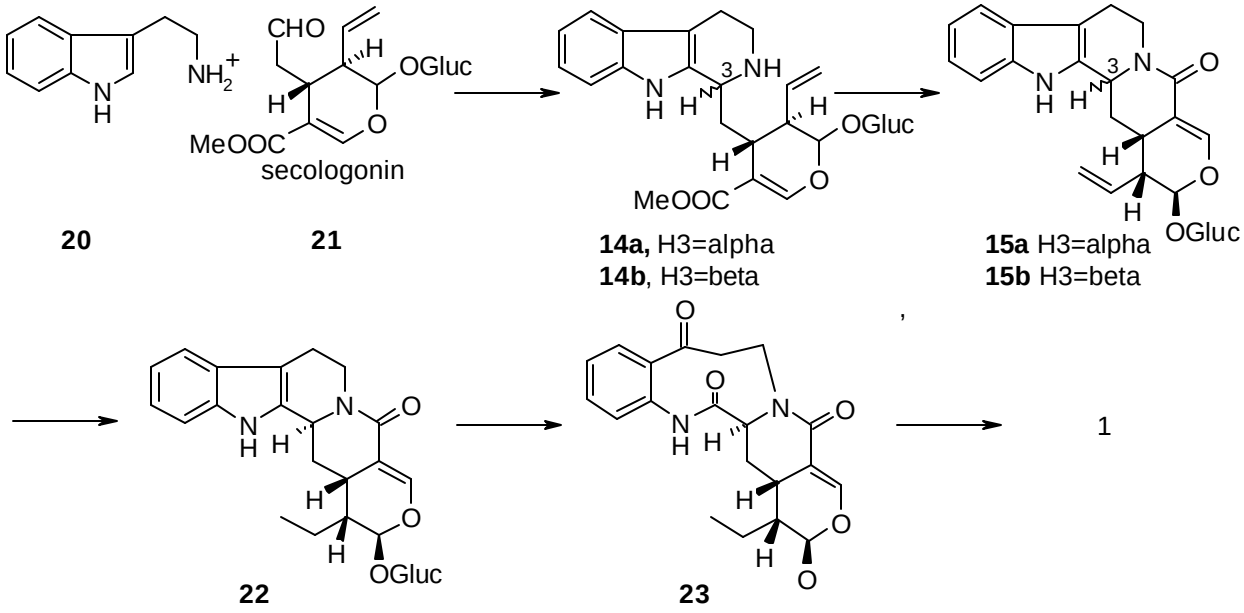
Scheme 5:



By tracer feeding experiments with *C. acuminata* carried out by Sheirha & Rapport[17] and Hutchinson *et al*[18] proved that Camptothecin is derived from tryptamine **20** and secologonin **21,** the established biosynthetic precursors of monoterpine alkaloids found in several other higher plants (*Scheme 6*).

Thus mevalonate is converted by the way of geraniol and loganin into secologanin **21**, which combines with tryptamine **20** to form strictosidine **14a**, isovincoside **14b** which would lactamize to the strictosamide **15**. Reduction to the corresponding 18,19-dihydro derivatives and oxidative cleavage by molecular oxygen or H_2O_2 would lead to the keto lactam **23**. The intramolecular cyclization of **23** produces pyrroloquinoline derivative, which in turn through a sequence of oxidation – reduction steps is transformed into Camptothecin **1**.

Scheme 6:



1.1.5 Pharmacology

Camptothecin (CPT) topoisomerase I (top I) inhibitors are proving useful against a range of refractory tumors, most prominently against some colon and ovarian cancers.[19] Two of the CPTs, Topotecan and CPT-11, have received Food and Drug Administration approval, and several others are in clinical trials. Camptothecin is active against MDRI-tumors, hence its broad spectrum of anti tumor activity.[20] Camptothecin inhibits replication of both SV40 virus[21] and adenoviruses.[22] Camptothecin inhibits retroviruses such as the HIV and the equine infectious anaemia virus.[23] The anti-HIV activity is due to the inhibition of TaT-mediated transcription from the viral promoter.

Camptothecin and its analogues also have significant activity against *Trypanosoma brucei*, the causative parasite of African trypanosomiasis.[24] Camptothecin possesses activity against the malaria parasite as well.[25] Leishmaniasis, a spectrum of disease caused by the Leishmania parasite, is treated by antimony-based drugs which are normally considered to operate by topo-I inhibition which led to the hope that CPT would be better lead to be tested as antileishmenial agents and trials are on in this direction. Camptothecin is also used in China for the treatment of psoriasis, a skin disease.

1.1.6 Mode Of Action

Identification of the molecular target of Camptothecin: Topoisomerase I

The impressive activity of CPT has led to intensive investigation in to its mode of action. Camptothecin was shown to inhibit both DNA and RNA syntheses.[26] Inhibition of DNA synthesis appears to be irreversible while inhibition of RNA synthesis is highly reversible.[27] All the cellular events remained unexplained until the identification of topoisomerase I as the molecular target of Camptothecin.[28] There is good evidence that topo I is the major cellular target of Camptothecin; (1) The potency of Camptothecin derivatives against purified topo I is correlated with their antitumor activity,[29](2) Camptothecin induced DNA breaks produced in cells exhibit the characteristics of topo-I linked DNA breaks;[30] (3) Camptothecin – resistant cells fail to produce topo-I-linked DNA breaks and contain either Camptothecin – resistant topo-I or reduced topo-I levels; (4) Yeast mutants lacking the endogenous topo-I gene are Camptothecin resistant and can be made drug sensitive by transfecting the human topo gene.[31]Cells transferred with human topo-I gene are hypersensitive to Camptothecin.[32] Now CPT and its derivatives are widely recognized as topoisomerase-I poisons. Topoisomerase I, the target enzyme of these new agents, exists in both normal and tumor cells and appears to take advantage of the growth rate difference between them. Researchers are not sure why, but there are two possible explanations. Topoisomerase I is most vulnerable in cells at a stage of the cell cycle known as the "S" phase. In this phase, cells copy their DNA while preparing to divide; therefore, the target enzyme is present more frequently and at a higher concentration. Since rapidly-proliferating tumors have a greater percent of cells in "S" phase, compared to normal, slow-growing cells, tumors are more susceptible to the action of topotecan. A second explanation might be that rapid metabolic processes of tumor cells enable greater influx of the drug.

Mechanism of action:

Topoisomerase I catalyses DNA relaxation by a mechanism that involves enzyme-linked single strand breaks.[33] The topoisomerase I reaction can be conceptually divided in to two steps. This reaction is initiated by a nucleophilic attack on the phosphate of the phospodiester linkage by the tyrosine hydroxyl, resulting in an enzyme-linked single strand-break in which the enzyme is covalently linked to the 3'-phosporyl end of the broken DNA strand. In this stage, the phospo diester linkage opposite to the transient break can presumably swivel. Following swiveling, the rejoining reaction is initiated by a nucleophilic attack on the tyrosyl phosphate by the 5'

hydroxyl to release the tyrosine from the phosphate. The intermediate in topo I-linked DNA breakage is referred to as a "cleavable complex" because it is readily reversible to a noncovalent enzyme-DNA complex before or after topoisomerization of the DNA. Camptothecin presumably interferes with this reaction (relegation) by blocking the rejoining step.[34] Such a blockage results in the accumulation of a reversible "Topo I enzyme-CPT-DNA ternary complex" that stabilizes the trans esterification intermediate.

Prolonged exposure of cancer cells to compounds in the Camptothecin class results in irreversible DNA damage and cell death. The structure of the cleavable complex is not yet clear. CPT appears to be a prototypical topo I Poison that exhibits little or no binding to either DNA or topo I alone.[35] However cross-linking studies suggested that CPT binds to the Topoisomerase I – DNA-Complex at or near the site of DNA cleavage and have prompted the proposal of two models, base flipping model and intercalative model, to explain the structural nature of the ternary CPT-DNA-topo I cleavable complex.

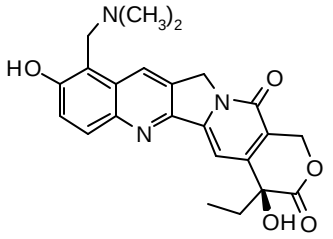
The base flipping model proposed by Hol *et al*[36] postulates that the +1 base flips out of the DNA helix and stacks with the drug. The intercalative model proposed by Pommer *et al*[37] involves the insertion of the drug in between –1 and +1 base pairs while it interacts favorably with both the DNA and the enzyme. According to this model CPT interacts with DNA and topo1 near its catalytic tyrosine. Although the exact structure of complex is still a subject of investigation, the mechanism accounts for the good correlation found between the number of stabilized cleavable complexes and the cytotoxicity of various analogues.

1.1.7. Structure -Activity Relation of CPT

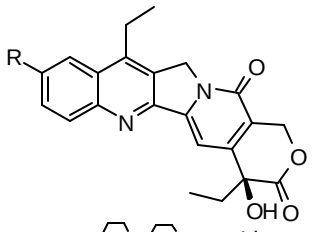
Subsequent to the identification of cellular target as Topoisomerase I and mechanism of action Camptothecin became a valuable lead for cancer treatment and recent structure activity studies conducted for the elucidation of the structural requirements for efficacious CPT analogues and extensive exploration of the possible modifications have led to the identification of many compounds with improved solubility and better antitumor activity and a reasonably well-understood picture of the SAR of CPT is now available based on which the following generalizations are drawn.

- In general substitution on rings A&B especially at C7, C9, C10 and to some extent C11 showed good biological activity with improved physical and pharmacological properties

and analogues with substituents at position 12 were completely inactive.[38] It is conceivable that CPT may bind to an enzyme or enzyme-DNA complex on the face proximal to the C11 and particularly to the C12 region. Hence groups substituted at this position may cause unfavorable steric and stereo electronic interaction. Substitutents at position C9 and C10 are more distant from this region and hence substitution at this location is not detrimental. As a result of these studies derivatives such as Topotecan (**24**) and Irinotecan (**25**) have passed through clinical trials and are now being used for the treatment of solid tumors after the approval of FDA. Several other analogues substituted on A, B rings, which are shown in Scheme, are in various stages of clinical development.



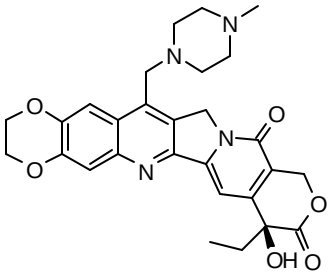
Topotecan **24**



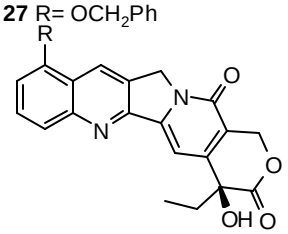
25 R= Irinotecan

26 R= OH SN-38

27 R= OCH_2Ph

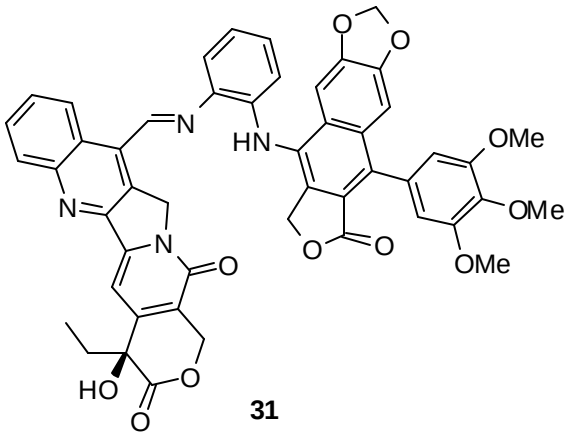


Lurotecan **28**



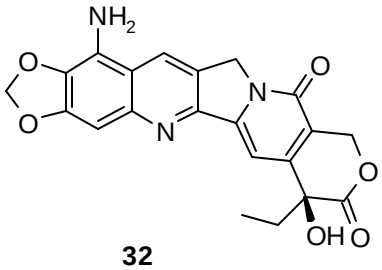
29 R=NH_2 9-AminoCamptothecin

30 R=NO_2 9-NitroCamptothecin



31

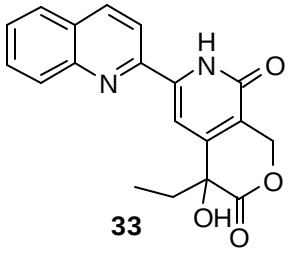
NSC 6835558



32

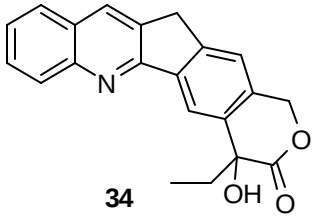
NSC 672552

- Activity is retained when a methoxy group is added at either position 10 or 11, addition of a methylene dioxy group to form a 5-membered ring across positions10 and 11 enhances potency, while simultaneous substitutions with two methoxy groups at 10 and 11(10,1,DMO CPT) inactivates completely confirming the requirement of the planarity for the molecule to be active. (Simultaneous substitution deviates from the planarity)
- Modifications at 7-position leads to compounds with variable activity. Thus *dl*-7-chloroCamptothecin was active than CPT while 7-methoxy Camptothecin was inactive. This can be explained by invoking the alkylation of DNA with the chloro-substituted analogs.
- Alteration of the core sequence has not shown much success. The inactivity exhibited by des-C-ring analogues,[39] for e.g. G-nor- 4, 6-secoCamptothecin **33**, is possibly due to the lack of planarity.

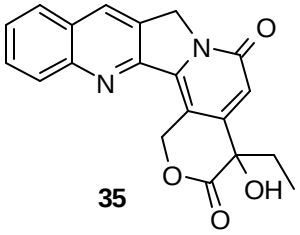


33

- Analogues of CPT in which there was sequential truncating of rings were devoid of activity (tetra cyclic B-E ring, tricyclic CDE- ring, bicyclic DE- rings and monocyclic E-rings) suggesting the importance of all the rings for the activity.[40]
- The importance of pyridine ring for the activity is evident as the compound **34** having same spatial identity was 40 to 60 fold less active while **35** was completely inactive.[41]
  IsoCamptothecin is inactive.[42]

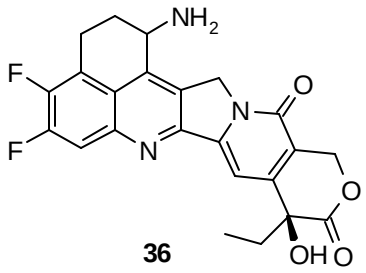


34



35

- Hexa cyclic CPT analogues like **36** exhibited anti tumor activity superior to those of penta cyclic ring system, probably due to the increased planarity exerted by an additional ring.[43]



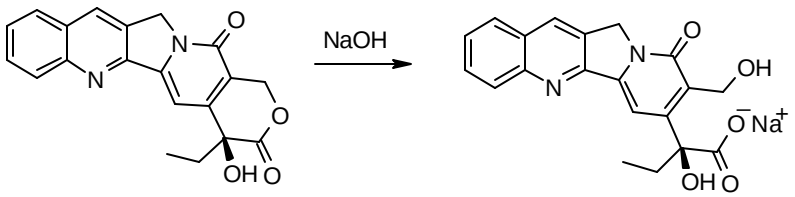
36
DX-8951f

- The natural 20(*S*) configuration is essential for the activity and (R)-Camptothecin is completely inactive in the *in vivo* L1210 leukemia assay and *in vitro* assays. Thus not only is the C20-a- hydroxyl moiety required, but correct specific stereochemistry at C20 is also an absolute necessity for *in vivo* cytotoxicity.[44]
- Hydroxy lactone ring, considered to be *"achellies-heel"* of CPT is generally accepted to be an absolute requirement for high topisomerase I mediated cytotoxycity[45] as many E-ring modifications like CPT-lactol, [46a] CPT-lactam, [46b] a ring opened hydroxy amide, [46c, 46d] an α-halo lactone, [46e] an α–azidolactone, [46e] an α-aminolactone[46e-g] and an α-exo-methylenelactone[46h] were either inactive or showed significantly decreased activity in cell assays relative to parent CPT, due perhaps to a reversible covalent interaction between CPT and the enzyme-DNA complex.

Early efforts were aimed at improving water solubility and potency, while more recent studies have focused on compounds with improved plasma stability [46] resulting in the identification of HomoCamptothecin.

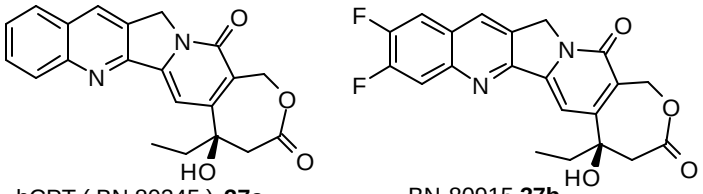
- **HOMO CAMPTOTHECIN**

  Most of the CPT derivatives share the pentacyclic skeleton and all included the highly electrophilic six-membered a-hydroxy lactone.The intrinsic instability of the CPT analogues arises from the rapid hydrolysis of this ring in basic or neutral media to give the opened carboxylate form, which is essentially inactive and lactone form exists only at acidic pH (*Scheme 7*). Pharmacodynamic studies have shown that this pH dependent hydrolytic equilibrium to be shifted toward the carboxylate form in plasma.



Carboxylate (CS)

This explains the diminished activity of various CPT analogues in the clinic compared to the overwhelming results obtained with xenograft models. In an important break through Lavergne and his coworkers found that HomoCamptothecin,[47] a Camptothecin analog with an expanded seven membered lactone obtained by the increase of a methylene group between the alcohol and carbonyl group of CPT has improved stability in plasma due to the reduced electrophilicity of its seven membered ß-hydroxy lactone. Most importantly it proves to be much more cytotoxic than the parent molecule. With its modified lactone hCPT represented an interesting template for the generation of novel analogues and thus paved the way for fluorinated hCPTs[48] and silatecans,[49] which are more powerful than the hCPT itself.



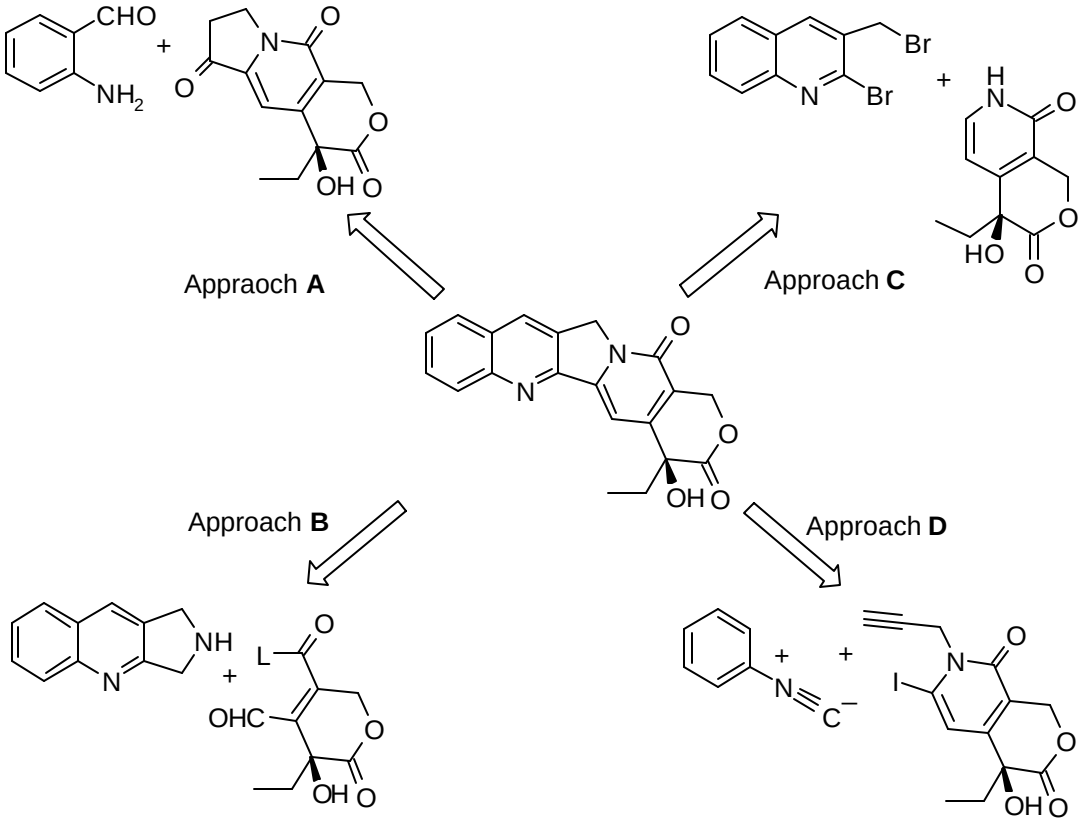
hCPT (BN 80245) **37a** BN 80915 **37b**

Thus research of Camptothecins exemplifies drug development, which with in a few years progressed from a laboratory curiosity to clinical application. Despite enormous efforts in this area, however, many aspects of the cytotoxycity and antitumor activity of Camptothecins remain unclear and warrant further continuation of the quest for the identification of the better lead.

1.1.8 Synthesis of Camptothecin: A Literature Survey

A variety of total syntheses involving creative adaptations of classical reactions as well as new chemistry inspired by the Camptothecin target were accomplished[50,51] and based on their strategic similarities, they are categorized under four groups as shown in the S*cheme 8* (Retro synthetic direction.).

Scheme 8:



Of these, approaches A and B emerged during the "classical era of Camptothecin" Approaches C & D are contemporary and reflect recent advances in synthetic technology.

Since already a detailed discussion of the syntheses published till 1996 is available,[52] only those syntheses of Camptothecin which appeared after 1996 will be discussed in the present section along with that of Mappicine, naturally occurring decarboxylated analogue of CPT & an antiviral lead since we aimed at synthesis of Camptothecin and its analogues.

Murata's approach[53] (Scheme 9, 1997)

The formal total synthesis of the Camptothecin has been achieved *via* two types of lithiation reactions of pyridine derivatives and a Pd catalyzed carbonylation of pyridyl methylsulphonates.

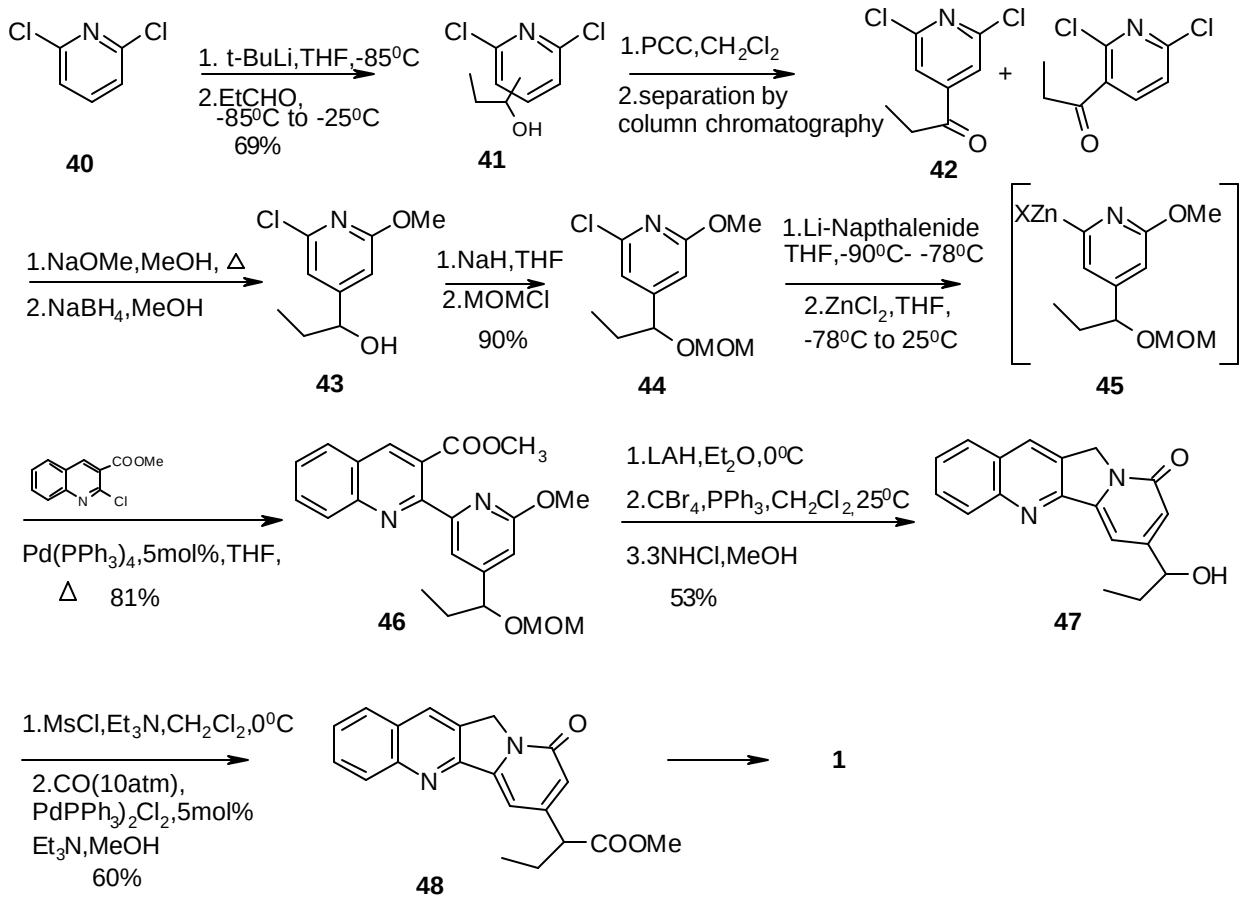
Treatment of THF solution of **40** with t-BuLi at –85°C followed by propanal afforded **41** as a mixture of regioisomers, which were separated after oxidation to ketone by column chromatography. The ketone was transformed into **44** through 3 step conversions.

1) Substitution of the chloride on pyridine ring with methoxide

2) Reduction of the ketone moiety

3) Protection of the resulting hydroxyl group as MOM.

Scheme 9: Murata *et al***,** *Syn Lett.,* 1997,298



The lithioderivtive of the **44**, resulted by the treatment with Li-napthalenilide complex in THF was transmetallated to the Zn derivative **45** and subjected to the Pd catalyzed cross coupling reaction with methyl 2-chloro-3-quinolinecarboxylate to afford **46** in 81% overall yield.

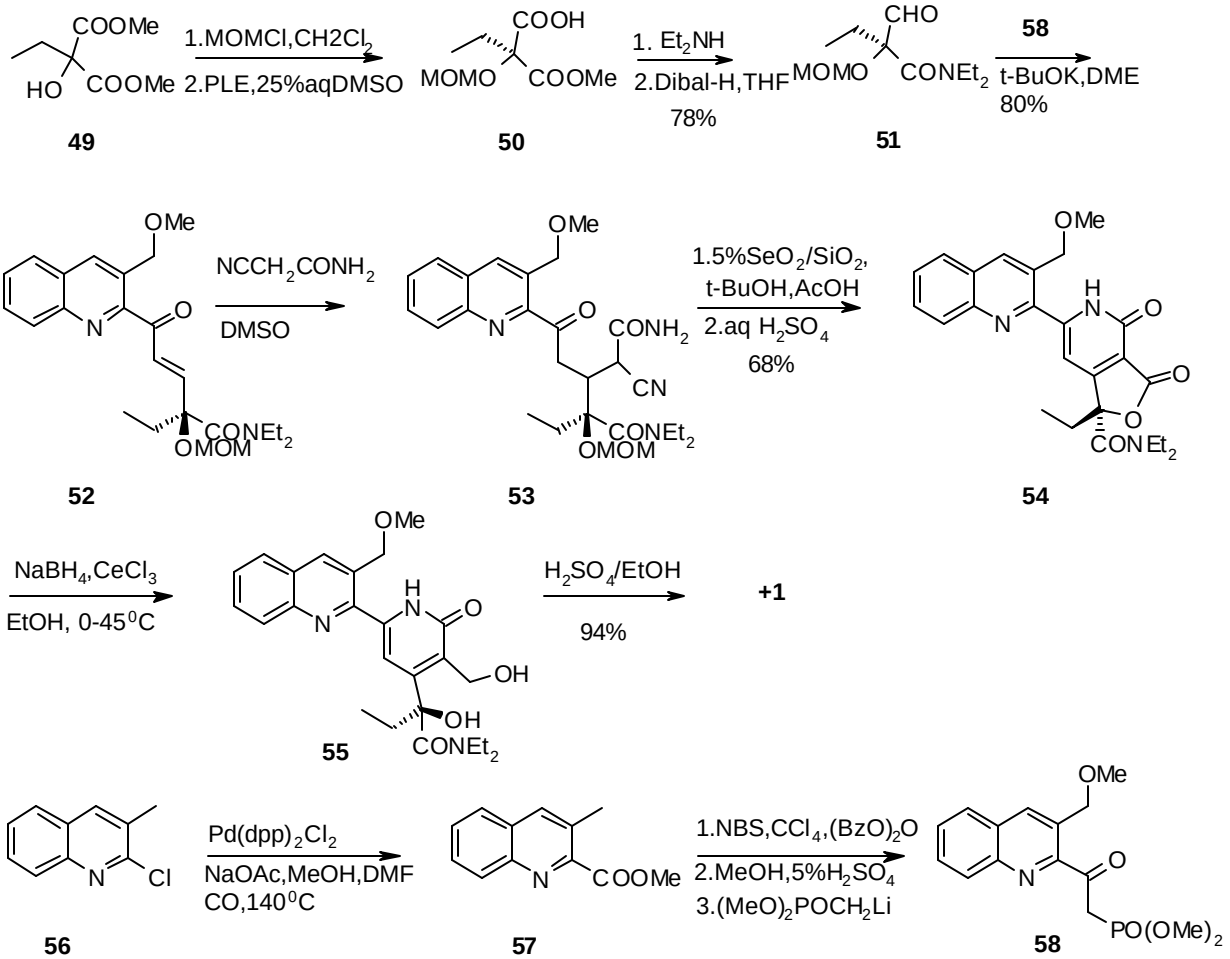
The coupling product was further transformed into **47** *via* the reduction of ester moiety, followed by bromination, hydrolysis and cyclization. Introduction of one carbon unit was effected by Pd-catalyzed carbonylation of the corresponding mesyl derivative of **47** with 10 atm of CO and Pd $(PPh_3)_2Cl_2$ to obtain **48,** which had already been converted to Camptothecin earlier by Danishfesky. The regiomers formation in first lithiation and their separation through oxidation followed by column chromatography (addition of 2 steps) makes the synthetic value diminish of the otherwise an attractive synthesis.

Ciufolini's approach[54] (Scheme 10, 1997)

Ciufolini has employed an intramolecular alkylation, a novel approach to ring C formation .The key C-20 stereo center was established by enzymatic desymmetrization of a malonate ester. Hydroxy malonate **49** was protected as MOM ether. Enantioselective hydrolysis using PL-esterase gave **50**, in above 98% ee with 90% yield. The acid was converted to amide and the ester was selectively reduced to aldehyde **51** using DIBAL-H**.** The quinoline synthon was prepared from 2-chloro-3-methylquinoline **56** *via* a 4-step sequence employing Pd-catalyzed carbonylation to ester **57**, followed by benzylic bromination with NBS and displacement of the bromo with methoxide and condensation with lithio phosponate resulted in the formation of **58**. HWE reaction of **56** with **58** furnished enone **52.** Michael addition of cyanoacetamide to enone followed by cyclization and oxidation afforded pyridone **54**. Borohydride reduction of the lactone under modified Luche's procedure *i.e.* with $CeCl_3$ and $NaBH_4$ gave diol **55** which was treated with 60% ethanolic H_2SO_4 to obtain Camptothecin with concomitant lactonization and G-ring annulation.

Scheme 10: Ciufolini *et al***,** *Tetrahedron.*, **1997**, *53*, 11049

[*Angew. Chem. Int. Eng. Ed.*, **1996**, *24*, 1692]



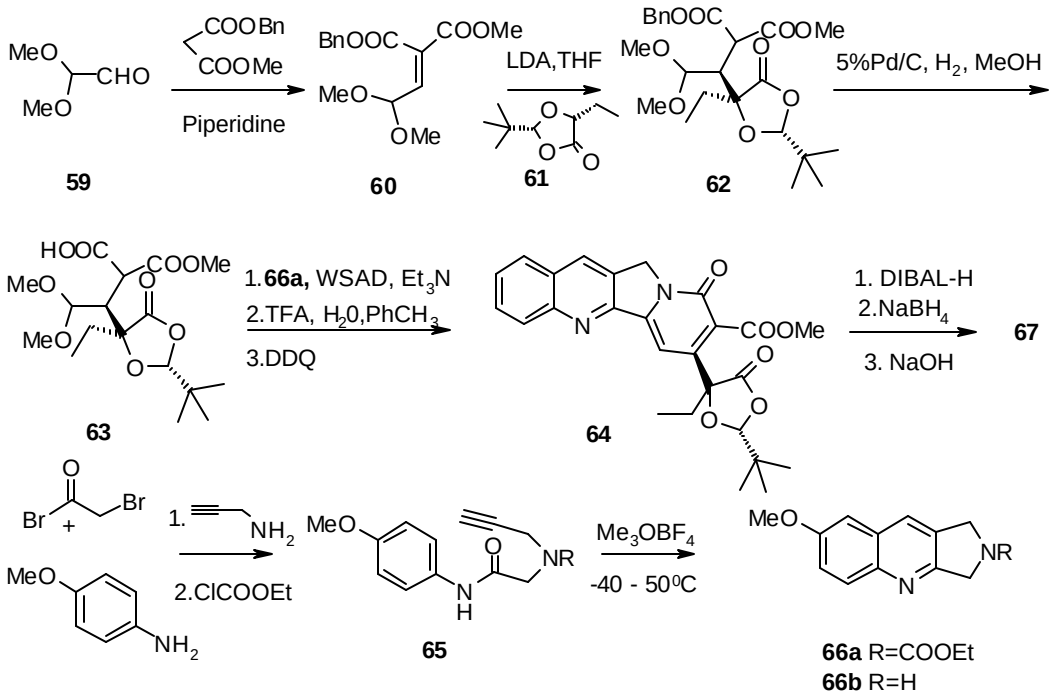
This synthesis requiring linear sequence of 10 steps produces Camptothecin in a 30% overall yield and therefore is the most efficient one. Authors have developed a new reducing reagent system to address the problems encountered in earlier syntheses during conversion of 5-memebered E-ring lactone to Camptothecin.

Fortunak's Approach[55] (Scheme 11, 1996)

Fortunak's convergent strategy relies on the coupling of preformed tricyclic ABC-synthon with the chiral acid **63.** Tricyclic amine **66** was prepared by adapting novel 4+2 cycloaddition of the amide **65**, (obtained from the α-bromo acetyl bromide in a 3 step sequence. *i.e*. condensation with anisidine and alkylation of thus formed amide with propargyl bromide which was protected as carbamate **66a**.

Glyoxal-dimethylacetal **59** on Knoevenagal condensation with benzyl methylmalonate furnished α, β-unsaturated diester **60**. Michael addition of chiral dioxalan-4-one **61** employing LDA as base furnished di ester **62**, which was converted to monoacid **63** by hydrogenation. Condensation of the acid **63** and tricyclic amine **66b** resulted in the formation of acetal which cyclized upon deprotection. The intermediate tetrahydropyridone was oxidized to pyridone **64**. Reduction of conjugated ester to aldehyde was achieved with Dibal-H and further reduction with $NaBH_4$ gave an alcohol which lactonized upon base treatment to give 10-ethoxy Camptothecin **67.**

Scheme 11: Fortunak *et al***,** *Tetrahedron Lett***, 1996,** 5683.

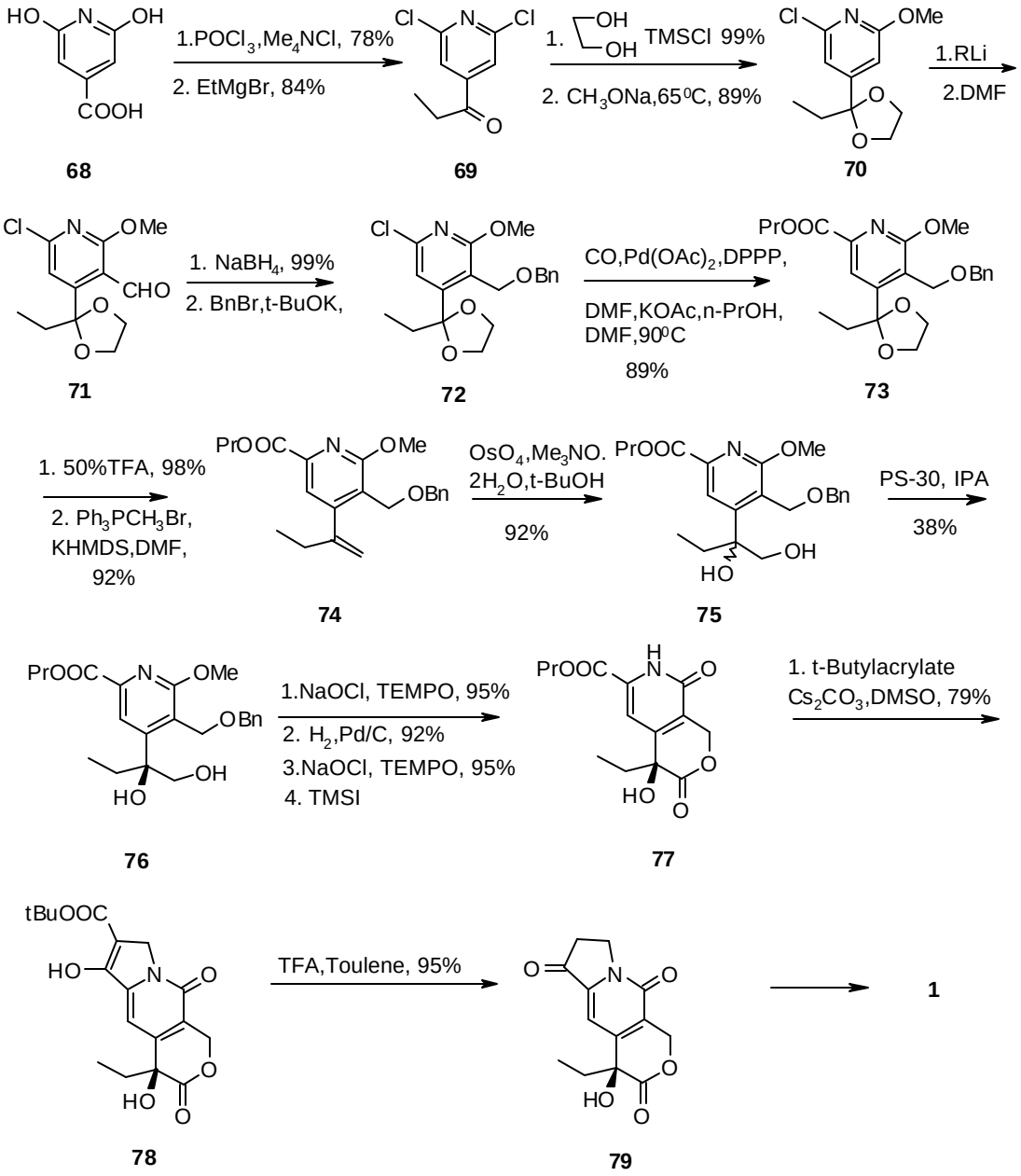


The fact that substituted analogue has been synthesized attests to its amenability to access the various AB-ring substituted analogues by changing the anilines and propargyl bromides in the synthesis.

Henegar's Approach[56] **(Scheme 12, 1997)**

Development of a practical synthesis of Camptothecin *via* tricyclic synthon starts from readily available citrazinic acid, which has been wisely converted to the required pyridone moiety of the parent molecule *via* series of transformations listed below.

Scheme 12: Henegar *et al***,** *J.Org. Chem.*, **1997**, *62*, 6588.



a) Conversion of citrazinic acid **68** to dichlorocitrazinic acid by treatment with $POCl_3$, which was in turn reacted with ethyl magnesium bromide to obtain ethylketone **69.** b) protection of **69** with ethylene glycol, followed by dissymetrization of the ketal to **70** with NaOMe, c) ortholithiation of **70** with *n*BuLi/DMF to get **71**, f) reduction of **71** with $NaBH_4$ and the protection of thus formed alcohol as benzyl ether **72**, g) carbonylation of **72** to **73** with Pd $(OAc)_2$ as the catalyst. Compound **73** was deprotected to ketone and olefinated with phosporane to get **74.** Dihydroxylation of olefin **74** gave racemic diol **75** which was resolved by acetylation with

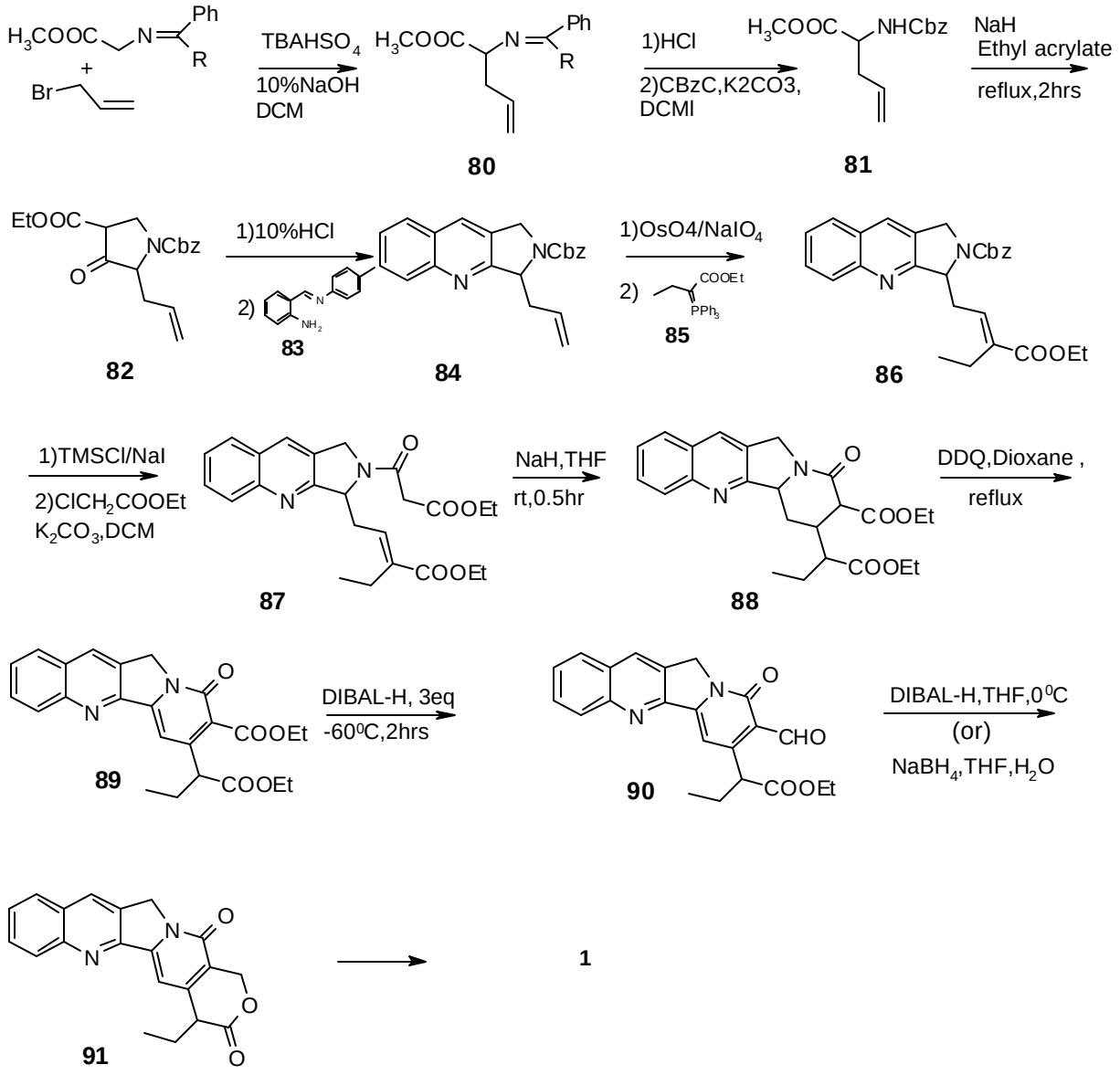
isopropenyl acetate / Amino PS-309 lipase immobilized on celite. S-diol **76** thus obtained in 99% *ee* was converted to compound **77** in 4 high yielding steps. 1) Oxidation of 1^0OH to aldehyde with NaOCl/TEMPO, 2) hydrogenolysis of benzyl ether to lactol with Pd/C, 3) TEMPO oxidation of lactol to lactone 4) Deprotection of *O*-methoxy group of methoxy lactone with TMSI.Annulation of **77** with t-butylacrylate and decarboxylation of thus formed β-ketoester **78** with TFA afforded **79**, tricyclic synthon in 99.6% *ee* (18 steps from **60** and 6.4% overall Yield.), which earlier had been used in synthesis of rac **1**, (-) **1**, and analogues.

This synthesis has been performed on large scale which attests the assert of the authors and the only draw back being the linearity & length of the synthesis.

Chavan's Approach [57] **(Scheme 13,1999)**

Chavan *et al* employed an intramolecular Michael addition, a new pyridone approach to construct a suitably functionalized ABCD-intermediate. Michael acceptor was prepared from readily available starting material, glycine. Thus Glycine Schiff's base was alkylated with allylbromide under PTC conditions employing 10 mol% $TBAHSO_4$ to obtain the allylglycine Schiff's base **80**. Hydrolysis of the Schiff's base with 10%HCl and protection of the amine as benzyloxy carbamate with benzyl chloroformate resulted in the formation of urethane **81.** A tandem Michael-Dieckmann condensation with ethylacrylate/NaH conditions furnished ß-ketoester **82**, which was decarboxylated, and subjected to Friedlander condensation with the Schiff's base **83** to obtain allyl quinoline **84.** Oxidative cleavage of allylquinoline with $OsO_4/NaIO_4$ furnished aldehyde, which was subjected to Wittig olefination with phosporane **85** to get the a, ß-unsaturated ester **86.** Carbamate of **86** was deprotected with TMSCl/NaI and condensed with carbethoxy acetyl chloride to obtain the key intermediate **87**. Treatment of **87** with NaH effected the Michael addition to furnish the tetrahydropyridone **88**, which was oxidized to pyridone **89** with DDQ. The selective reduction of aromatic ester in presence of the aliphatic one with DIBAL-H gave an aldehyde **90**, which was further reduced to alcohol with either $NaBH_4$ or DIBAL-H to obtain deoxy Camptothecin **91.** Following the Winterfields's protocol, *i.e* bubbling oxygen in presence of CuI/Et_3N they completed the synthesis of Camptothecin. Authors did away with the diethylation problem, encountered in earlier syntheses, by introducing the ethyl in the early stage and the need for differently protecting the esters to reduce selectively.

Scheme 13: Chavan *et al*, *Tetrahedron Lett*.**, 1999**, 40, 3847.



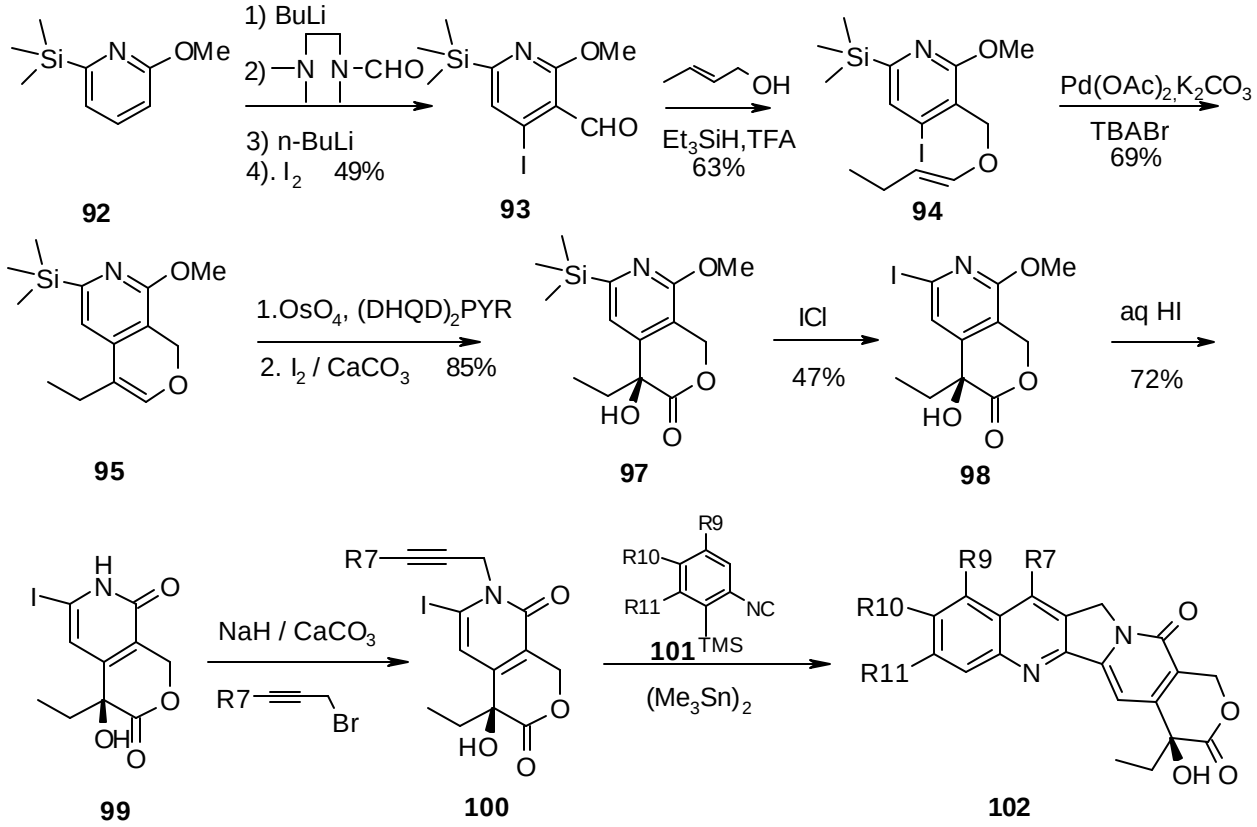
This synthesis is potentially industrially feasible as it involves the use of readily available starting materials and reagents.

Curran's Approach[58] (Scheme 14, 1998)

These authors have employed, in their earlier generation syntheses, a unique (4+1) radical annulation as its key step to form the quinoline part of the molecule. Among the more important new developments is the expansion of the chemistry to encompass new substituents. The regiochemical outcome of the radical cyclization with meta-substituted arylisonitriles was controlled by utilizing strategy that relies on introduction of a TMS group on the aryl iso nitrile.

This substituent acts as a directing group, which was removed after the cascade sequence. A key common intermediate containing the pyridone and lactone (DE) rings of Camptothecin and most derivatives was constructed from 2-trimethylsilyl-6-methoxypyridine by a series of metallation reactions and a Heck cyclization to provide an achiral bicyclic enol ether **95**. Sharpless asymmetric dihydroxylation followed by lactol oxidation and iododesilylation produced the key intermediate **99** in 94% enantiomeric excess.

Scheme 14: Curran *et al*, *Chemistry - A European Journal*, **1998,** *4*, 67-83

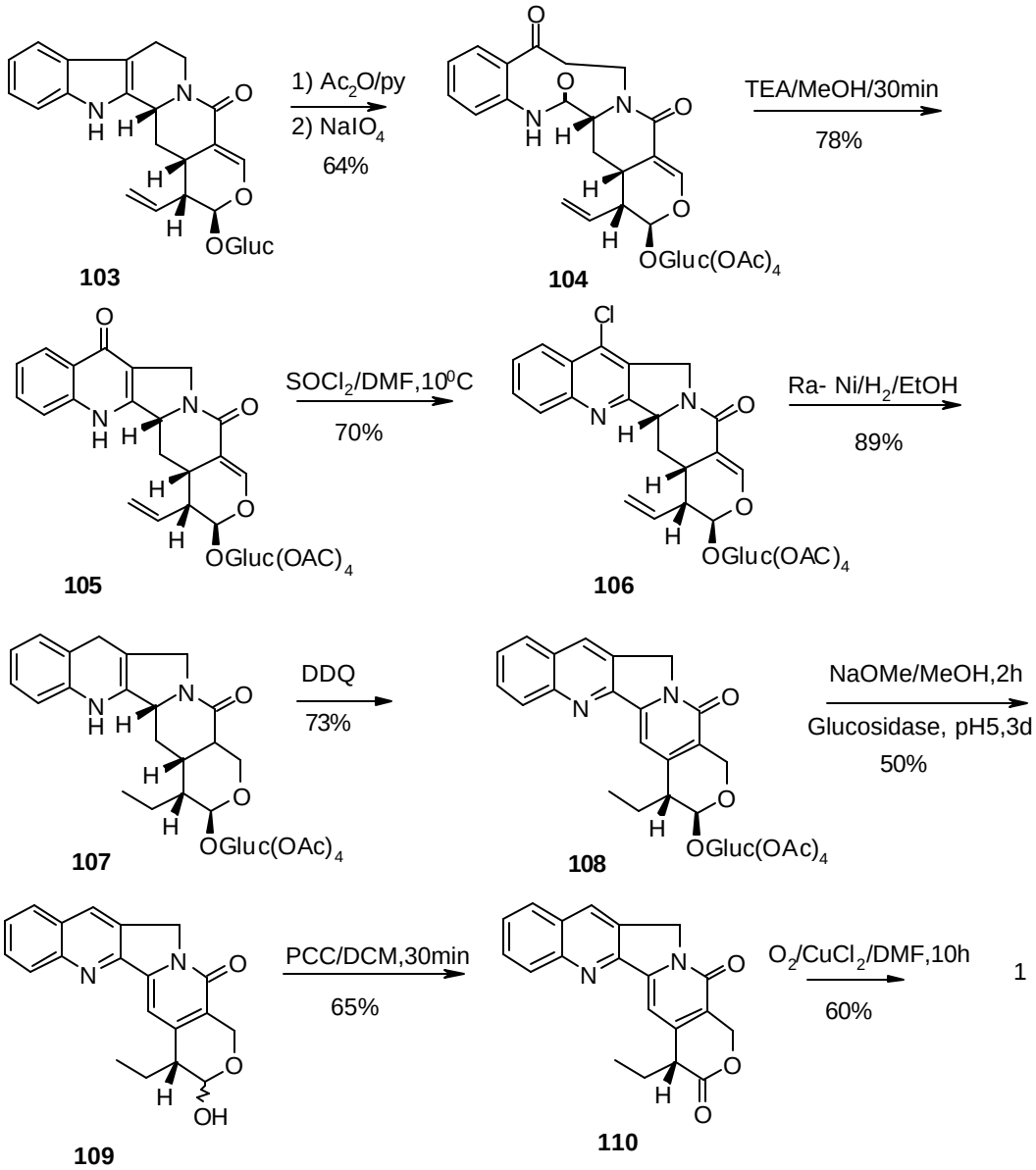


By changing the propargylating agent and the iso nitrile the authors made about 20 other penta- and hexacyclic analogs of Camptothecin with differing single or multiple substituents at C7, C9, C10, C11, and/or C12. Included among these are several drug candidates. This is a very elegant protocol which gives access to a host of Camptothecin derivatives

Brown's Approach[59] **(Scheme 15, 2000)**

This biogenetically patterned synthesis involves conversion of Vincoside and Strictosidine **103** to Camptothecin, which is a net oxidative process.

Scheme 15: Brown *et al***,** *Tetrahedron Lett.*, **2000,** *41*, 859-862



Thus the 3 : 2 mixture of vincoside and strictosidine obtained by the condensation of tryptamine with secologanin was converted to a mixture of the corresponding lactams **103** by heating with Na_2CO_3. Treatment with $NaIO_4$ in refluxing methanol resulted in cleavage of indole 2,7-bond to furnish a keto lactam **104.**

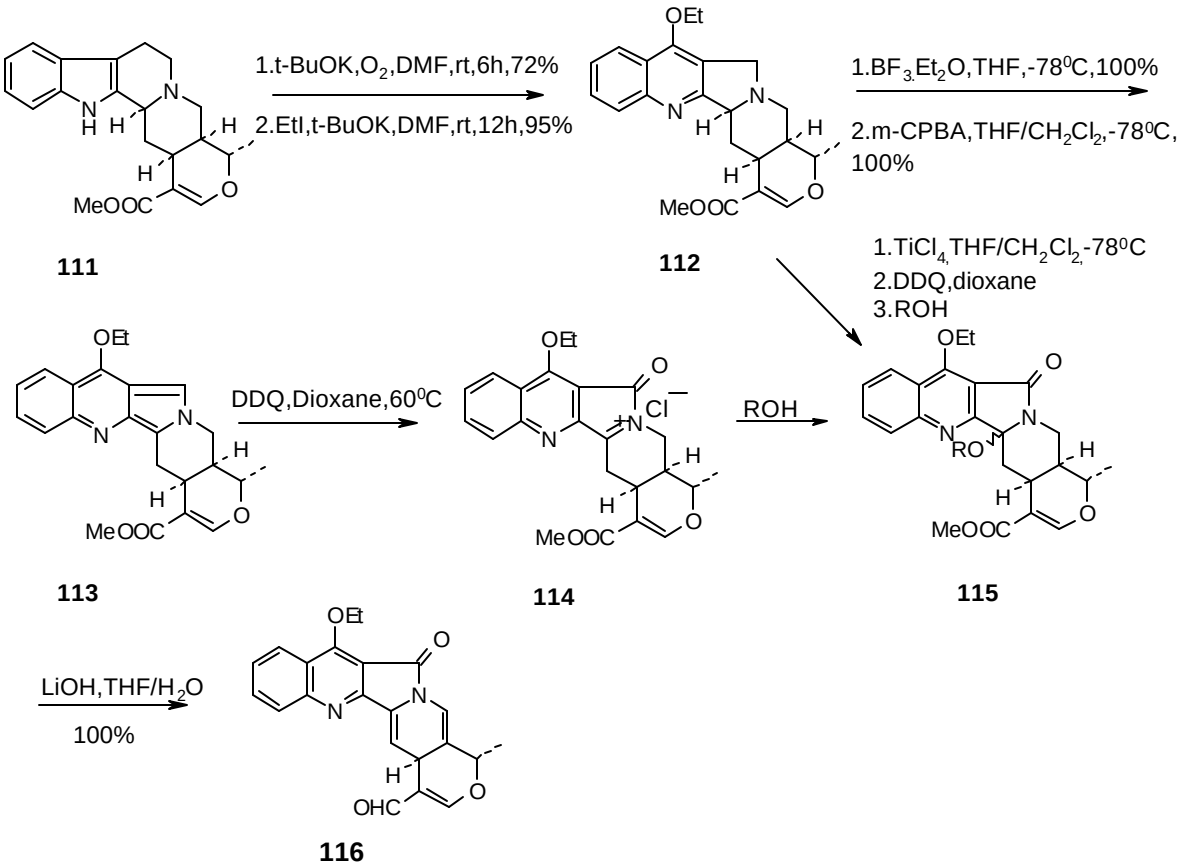
Aldol condensation between C-2 and C-6 effected with Et_3N / MeOH resulted in the formation of the pyrroloquinoline **105,** which was treated with $SOCl_2$ in DMF to give 7-Chloroquinoline **106**. Catalytic hydrogenation of **106** with Raney nickel afforded dihydroquinoline **107**. Subsequent aromatisation with DDQ in dioxane gave conjugated quinolineopyridone **108**. After

Zemplen deacetylation, the glucose was removed with ß-glucosidase in pH5 buffer to yield lactol **109**. Oxidation of lactol **109** with PCC /CH_2Cl_2 gave lactone **110**. Finally H-20 was oxidized to a hydroxyl group by $O_2/CuCl_2$ but with consequent loss of chirality yielding rac-CPT. The authors have achieved biogenetically patterned synthetic route to the monoterpenoid quinoline alkaloids 20-deoxyCamptothecin and (±)-Camptothecin (I) (R = H, OH) from secologanin and tryptamine *via* vincoside/strictosidine lactams. This synthetic sequence afforded likely biosynthetic intermediates for testing *in vivo*. This synthesis can be applied to the synthesis of intermediates with labels for *in vivo* experiments. How ever the chirality present in the molecule 103 is completely destroyed to obtain rac Camptothecin

Dumas's Approach[60] **(Scheme 16, 2001)**

Quinoline–lactone **116** related to CPT has been synthesized from tetrahydroalstonine, which supports biogenesis of CPT. Thus treatment of quinoline **112**, obtained from **111** by Winterfield's oxidation and the alkylation with EtI, with, *m*-CPBA, afforded the pyrrole **113.**

Scheme 16: Dumas *et al*, *Tetrahedron Lett***, 2001**, *42*, 8973-8975.

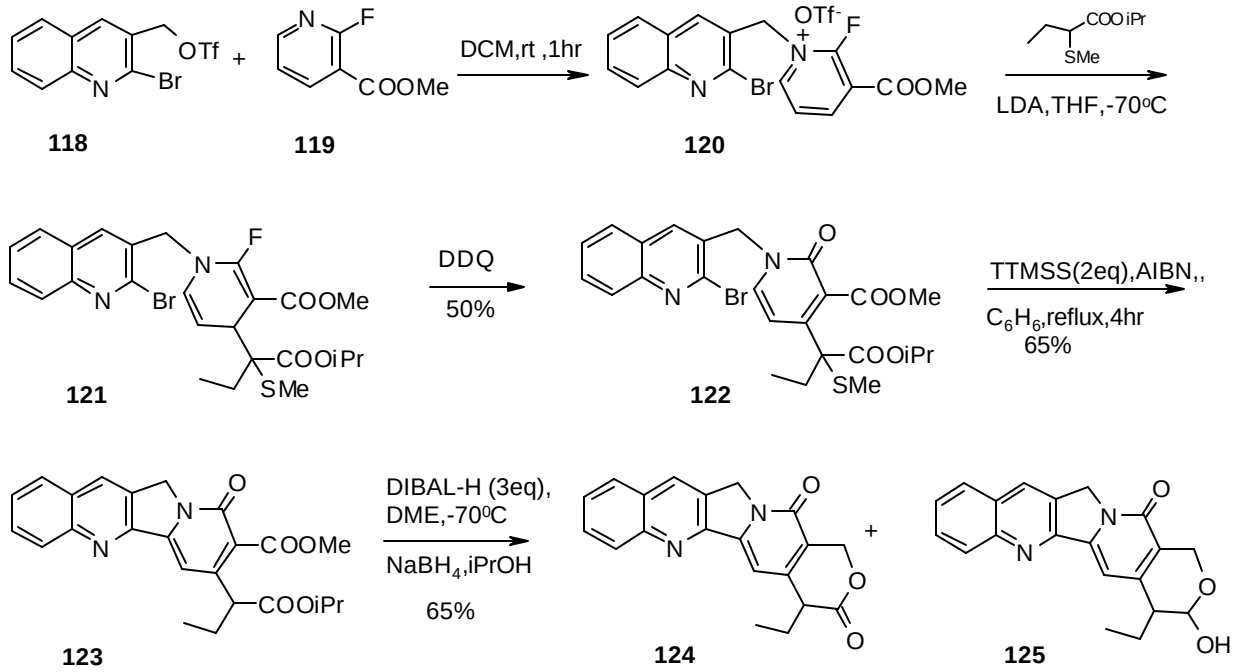


Compound **113** was treated with $TiCl_4$ to form a complex and DDQ oxidation of the latter furnished **114**, which was trapped with alcohol to give alkoxy dihydropyrimidine **115**. (It can be made in one pot process.) Compound **115** rearranges to **116** in basic medium. This key compound represents an important breakthrough, according to authors for the development of new analogues of CPT from indole alkaloids from readily available natural compound tetrahydroalstonine.

Bennasar's Approach [61] **(Scheme 17, 2000)**

Bennasar's approach involves the convergent construction of suitably substituted ABCD ring intermediate and the closure of lactone E-ring at the final stage. Addition of the enolate derived from isopropyl a- (methyl sulfanyl) butyrate to *N*- (quinoloylmethyl)-2-flouropyridinium triflate **120**, obtained by the alkylation of 2-fluoropyridine **119** with triflate **118** furnished the compound **121,** oxidation of which with DDQ yielded pyridone **122**. Treatment of pyridone **122** with tris (trimethylsilyl) silane -AIBN brought about the radical arylation and desulfurization to give the tetracycle **123**. The construction the lactone E ring of CPT required the chemo selective reduction of the conjugated ester in presence of aliphatic one of **123**, and this was achieved by differentiating the two esters (as in pioneering Winterfield synthesis[62]). Treatment of **123** with DIBAL-H in DME at -70ºC and then with $NaBH_4$ in propanol afforded 1:1 mixture of the target lactone **124** and lactol **125**. Lactol **125** was converted to lactone. Taking into account that intermediate **124** has been earlier converted to racemic and chiral CPT by hydroxylation at C-20 the above synthesis constitutes a formal synthesis.

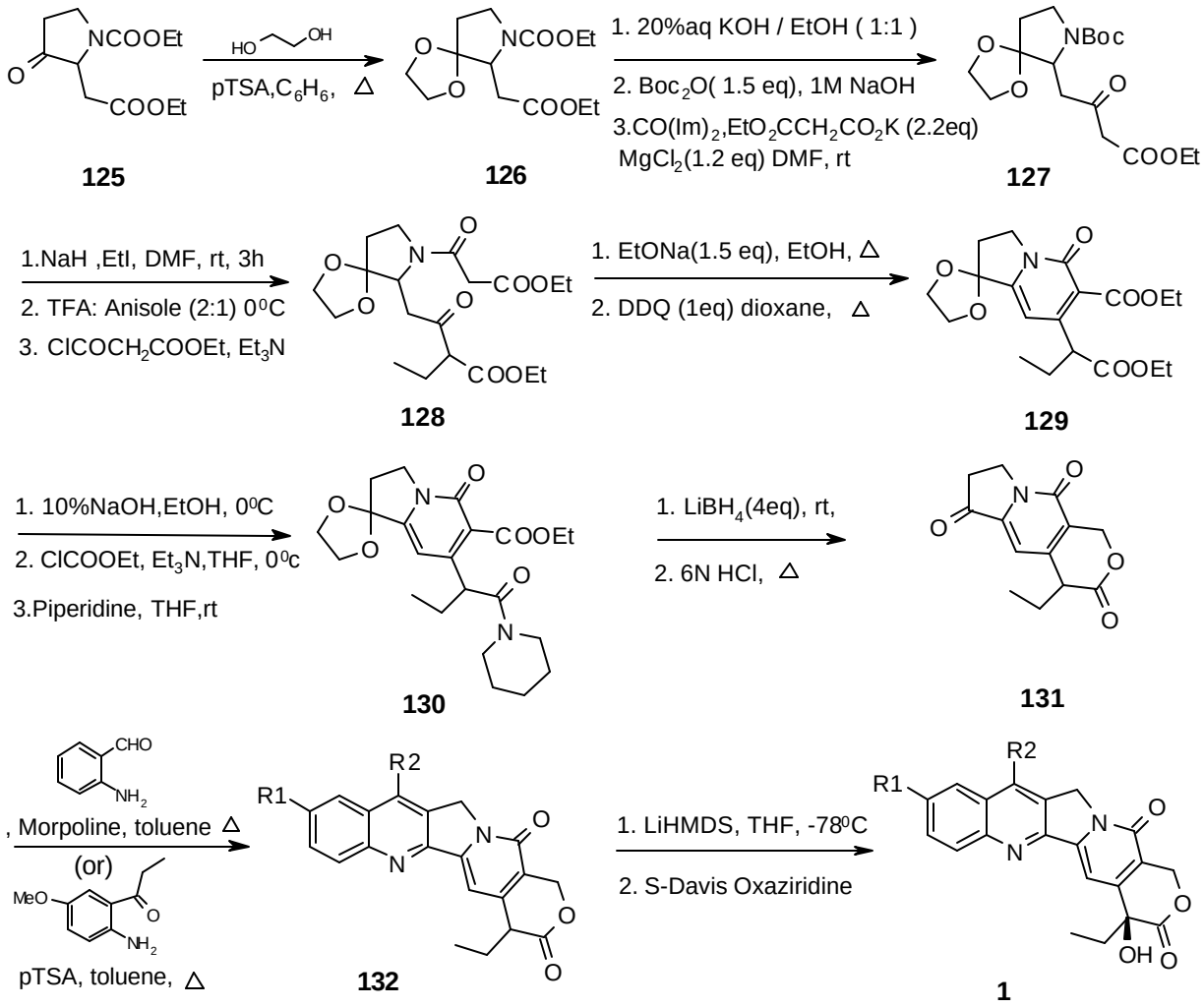
Scheme 17: Bennasar's *et al***,** *Chem Comm.***, 2000,** *2459-2460*



Nagao's approach[63] **(Scheme 18**, **2000)**

Total syntheses of (+)-Camptothecin and (+)-7-ethyl-10-methoxy Camptothecin from racemic ethyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-yl acetate **125** were accomplished *via* asymmetric hydroxylation onto C-20 of racemic 20-deoxyCamptothecin derivative employing a chiral Davis reagent, (2R, 8aS)-(+)-(camphorylsulfonyl) oxaziridine. This synthesis commences from the known pyrrolidone **125.** Ketalization of **125** with ethylene glycol under the conventional conditions gave dioxolane **126**, which was subjected to basic hydrolysis, followed by *N*-Boc protection of the pyrrolidine amine group, and subjection to Masaumne reagent system afforded ß-ketoester **127**. After ethylation of **127** with NaH in DMF, the resulting compound was subjected to the deprotection of the *N*-Boc group and then treated with ethyl malonyl chloride in the presence of Et_3N-DMAP to obtain amide **128.** Dieckmann-type condensation of **128** furnished dihydro pyridine, which was oxidized to pyridone **129**. Selective deprotection of the aliphatic ester in the presence of aromatic one gave monocarboxylic acid, which was converted to amide **130** *via* mixed anhydride. Reduction of ester with $LiBH_4$ to alcohol and the treatment with 6N HCl resulted in the formation of lactone **131**. Friedlander condensation of **131** with aminobenzaldehyde gave deoxy Camptothecin while condensation with 2-amino5-methoxy propiophenone furnished deoxy 7-ethyl –10- methoxy Camptothecin.

Scheme 18: Nagao *et al*, Heterocycles., **2000,** 771

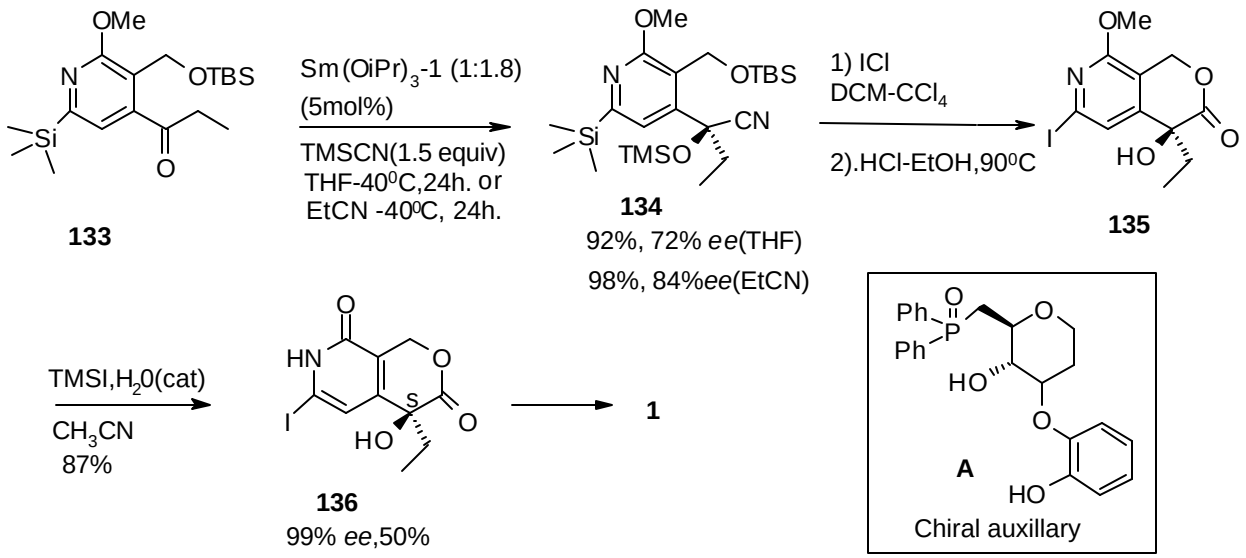


These deoxy compounds, after enolization of with LiHMDS in THF were treated with (2*R*, 8a*S*)-(+) camphor sulfonyl oxaziridine to furnish the Camptothecin and, (+) 7-ethyl-10-methoxy Camptothecin. The *ee* obtained by following Davis's protocol were moderate.

Shibasaki's approach[64] **(Scheme 19, 2001)**

Shibasaki *et al* developed a novel chiral ligand **1** derived from D-glucose and found that the Ti-**A** complex catalyzes a highly enantioselective cyanosilylation of ketones. Curran's (one of the authors) earlier approaches involve a hydroxy lactone as key synthon **136** for the syntheses of Camptothecin family alkaloids.

Scheme 19: Shibasaki's *et al*, J. *Am. Chem. Soc.*, 2001, *123*, 9908

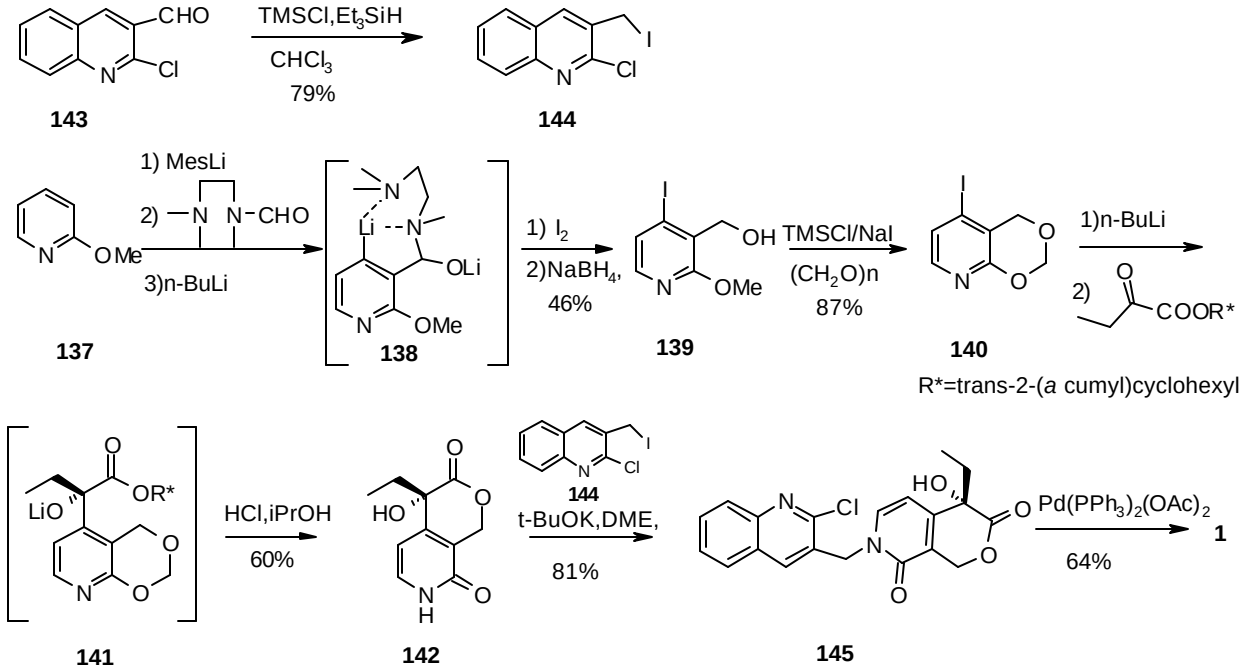


Subjecting **133** to the above conditions catalyzed by Ti-**A** complex (20%) resulted in the formation of **134** was obtained in 34% yield after 6 days with *R*-configuration. The screening of the lanthanide complexes showed much higher activity. Thus, the reaction proceeded at -40^0C in the presence of 5 mol% of catalyst prepared from **A** and Sm $(O^iPr)_3$ in 1:1.8 ratio giving **134** in 92% yield and 72% *ee*. Functional group transformations resulted in the formation of **136,** and thus completing the formal total synthesis of Camptothecin. The notable feature of this approach, *i.e* catalytic asymmetric cyanohydration of ketone to obtain key intermediate of CPT synthesis in an enantioselective way attracts the attention as it is industrially feasible.

Comins Approach:[65] **(Scheme 20, 2001)**

A practical six – step synthesis of (*S*)-Camptothecin was achieved by Comins *et al* which involves a single step preparation of AB ring precursor **144** and 3 step preparation of DE ring fragment **142**. Thus commercially available 2-methoxy pyridine **137** was lithiated at C-3 with mesityllithium and treated with *N*-formyl-*N*,*N*,*N*-trimethylethylenediamine to give a a-amino alkoxide.

Scheme 20: Comins *et al*, *Org Lett*, **2001**, *3*, 4255-4257.



Addition of n-BuLi effected a-amino alkoxide directed lithiation at C-4 to give the dianion **138** which was treated with iodine and worked up with $NaBH_4$ / $CeCl_3$ to obtain alcohol **139** in one pot process. Alcohol **139** was converted directly to dioxane **140** on treatment with NaI/TMSCl/paraformaldehyde, which upon successive treatment with *n*-BuLi followed by the addition of ketoester gave alkoxide **141** *in situ*. Addition of HCl /i-PrOH effected protonation, acetal hydrolysis, and lactonization to afford the desired DE ring intermediate **142**. Commercially available 2-chloroquinoline carboxaldehyde **143** was converted to iodide **144,** AB ring intermediate by treating with Et_3SiH and TMSI in $CHCl_3$ .The two fragments were joined on treatment with t-BuOK in DME to provide compound **145** and the final C-ring was closed using modified Heck reaction conditions to address the decreased reactivity of the quinoline C-2 halogen (Cl *vs* Br) *i.e*. $Pd(PPh_3)_2(OAc)_2$ (15%), and KOAc.

Authors have achieved the shortest asymmetric synthesis of Camptothecin to date, involving commercially available heterocycles which makes it a practical, and amenable to the large-scale synthesis.

1.1.9 Synthesis of Mappicine Ketone and Mappicine-A Literature Survey

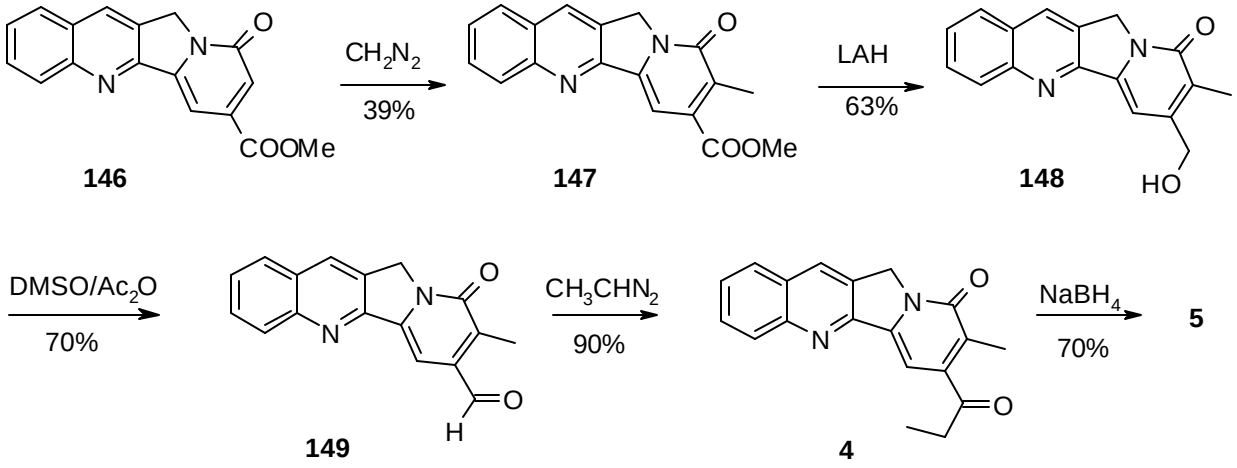
Mappicine ketone **4** and Mappicine **5** have been identified as leads in the search of selective anti viral compounds. General synthetic methods are required to make the analogues of

the same for the Structure – Activity relation studies there by lead optimization. Since these are nor-lactone derivatives of CPT, the chemistry developed for the parent molecule has been directly extended to achieve their synthesis.

Kametani's approach[66] **(Scheme 21, 1975)**

The ester **146**, made in connection with synthesis of Camptothecin was methylated on pyridone-ring by treating with diazomethane to get the methyl derivative **147**, which was reduced to alcohol **148** with LAH. Alcohol was oxidized to aldehyde **149** and treated with diazoethane to introduce ethyl of Mappicine ketone. Ketone was reduced to Mappicine with $NaBH_4$. Formation of **147** in low yields alongwith the cyclopropylated by product reduces the synthetic utility of the synthesis.

Scheme 21: Kametani *et al, J. Chem. Soc. Perkin. Trans 1.,* **1975**,1825



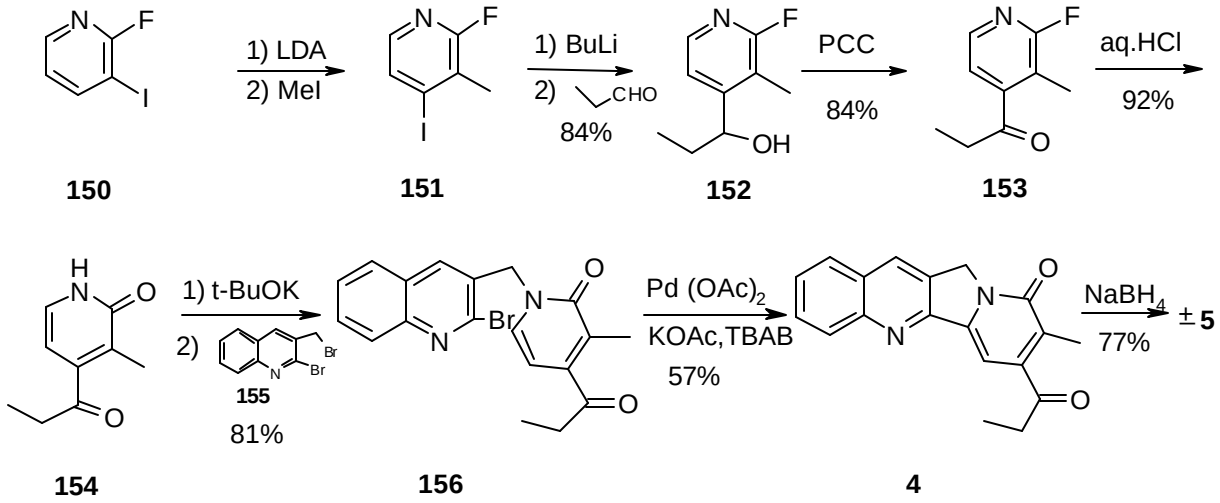
This was apparently the first synthesis of Mappicine and Mappicine ketone (much before their isolation).

Comins'approach[67] **(Scheme 22, 1996)**

A short and convergent route to Mappicine ketone and Mappicine has been developed based on their work on Camptothecin.[68]

Thus treatment of 2-flouro-3-iodopyridine with LDA and methyliodide provided **151** *via* halogen-dance reaction. Lithium-iodine exchange and addition of propionaldehyde gave alcohol **152**, which was oxidized to ketone **153** with PCC.

Scheme 22: Comins *et al*, *J. Org. Chem*., **1996**,*61*,9623.



Hydrolysis of **153** with aq HCl provided ketopyridone **154** whose *N*-alkylation with **155** gave intermediate **156**.The Heck reaction was employed to obtain Mappicine ketone which was reduced to Mappicine according to the Kametani's procedure.

Curran's Approach[69]**(Scheme 23, 1997)**

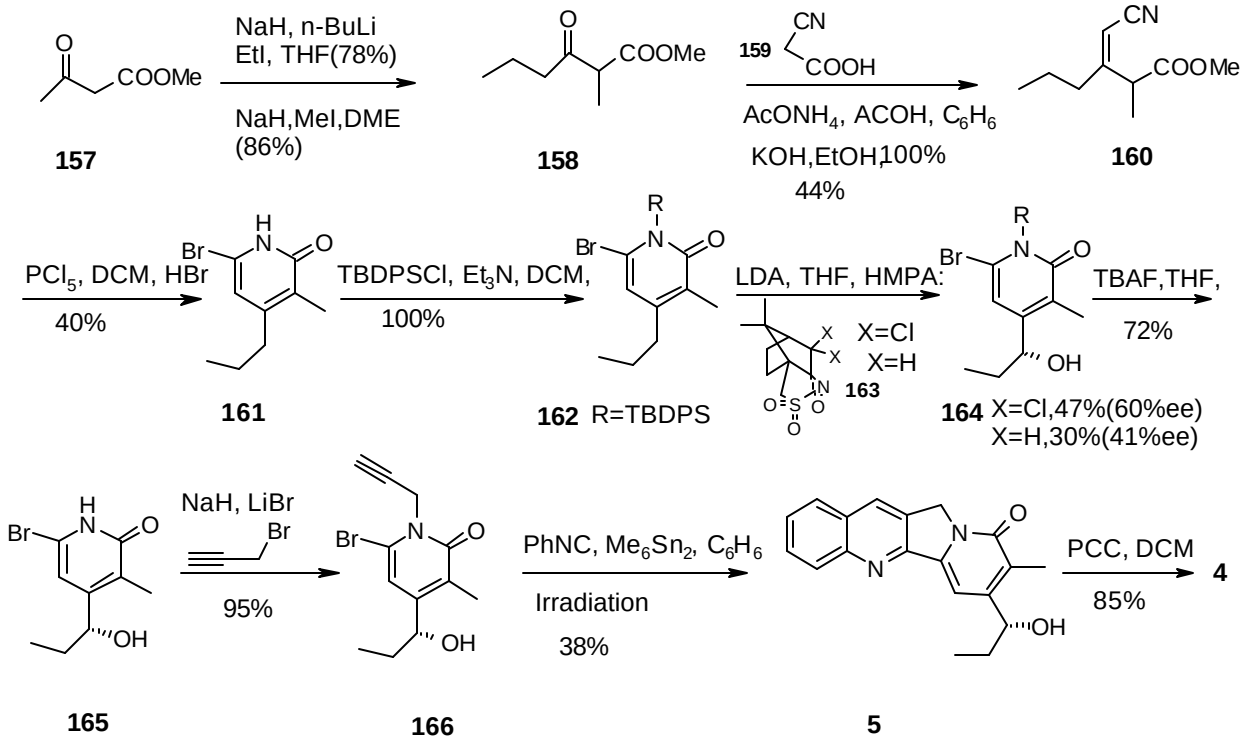
This synthesis features in its key step a BC-ring assembly starting with bromo pyridone **166** and phenyl isonitrile *via* a (4+1) radical cascade reaction originally developed for the synthesis of racemic CPT,[70] and analogues.[71] Successive alkylation of **157** with ethyliodide and methyliodide provided the ketoester **158** which upon standard Doebner condensation with cyanoaceticacid **159** followed by hydrolysis with KOH in ethanol gave the acid **160**. Acid was converted to bromopyridone **161** by treating with PCl_5 followed by saturated HBr solution in 40% yield. Introduction of the hydroxy of mappicine was achieved with Davis's oxaziridine with the TBDPS protected derivative **162**. Amide **165** was deprotected and selectively *N*-propargylated to afford the radical precursor **166**.The radical cascade was effected by irradiating a benzene solution of phenylisonitrile and hexamethyltin to complete the synthesis of Mappicine **5**.

Enantiomerically enriched Mappicine directly formed was isolated in 38% yield and 60%*ee* after flash chromatography. Oxidation of **5** with PCC provided Mappicine ketone.

This synthesis is amenable to prepare a wide assortment of MPK derivative on A/B-ring. Since the radical cascade reaction is tolerant to a wide variety of functionalization, just by varying the propargyl halide and isonitrile components in the last two reactions its potential has

been demonstrated by the combinatorial library preparation[72] of MPK's in solution phase by the authors.

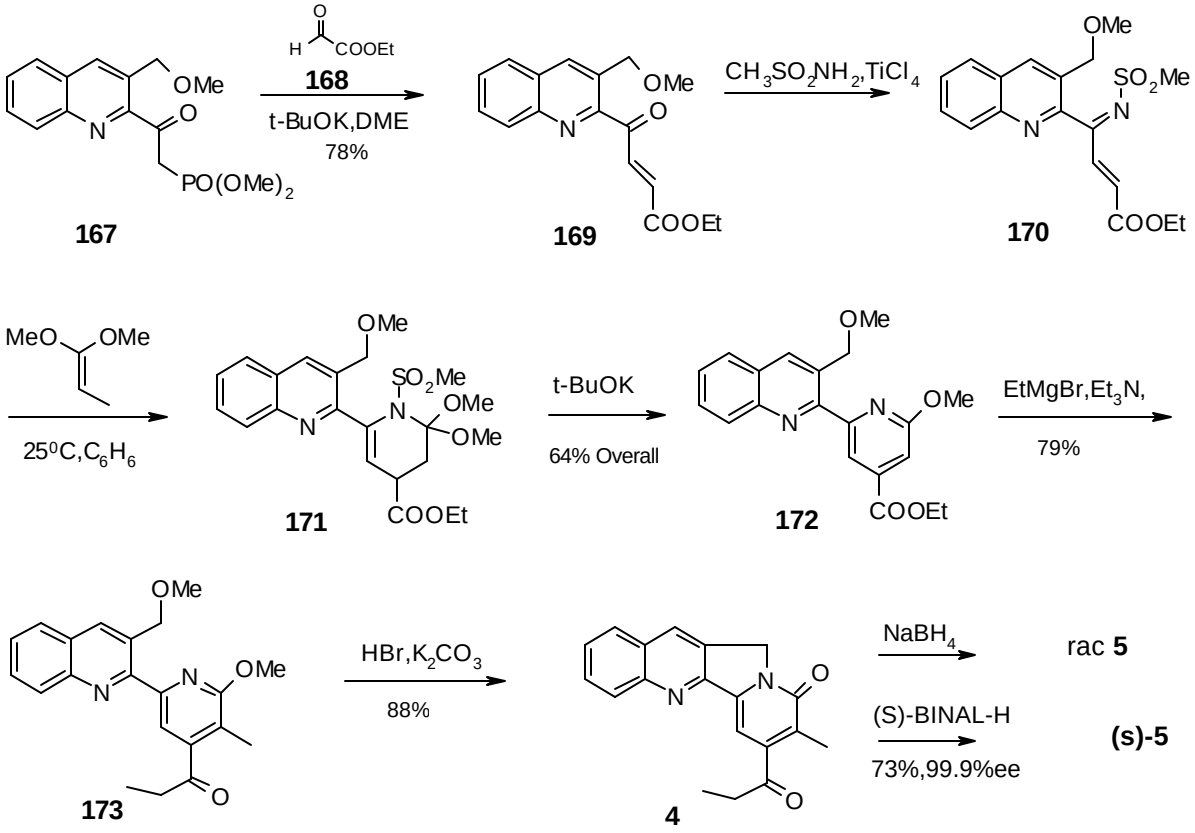
Scheme 24: Curran *et al, Tetrahedron., 1997, 53,* 8881.



Boger's Approach[73] (**Scheme 25, 1998)**

Central to their synthesis is the implementation of room temperature inverse electron demand Diels-Alder reaction of the *N*-sulfonyl1-aza-1,3-butadiene for the introduction of pyridone D-ring with assemblage of the full carbon skeleton of MPK. Wadsworth-Horner-Emmons reaction of ß-ketophosponate **167** (prepared with slight modification of Ciufolini's Method) with **168** provided a, ß- unsaturated ester **169**. The direct $TiCl_4$ –promoted (1.5 eq) condensation of **169** with methanesulfonamide provided **170**, which was directly employed in DA with out purification. Treatment of **170** with 1,1-dimethoxy-1-propene at room temperature led to the formation of the 4+2 cycloadduct **171**. Notably incorporation of the no complimentary C4-EWG resulted in a DA cycloaddition that proceeded at 25^0C presumably by lowering the diene LUMO without altering the inherent cycloaddition regioselectivity. This adduct was aromatized with t-BuOK to provide **172** without intermediate isolation. Addition of EtMgBr to **172** in the presence of a 3^o-amine proceeded cleanly to give the corresponding ethyl ketone **173** without competitive 3^o alcohol formation.

Scheme 25: Boger *et al***,** *J. Am. Che. Soc*., **1998**,*120*,1218.



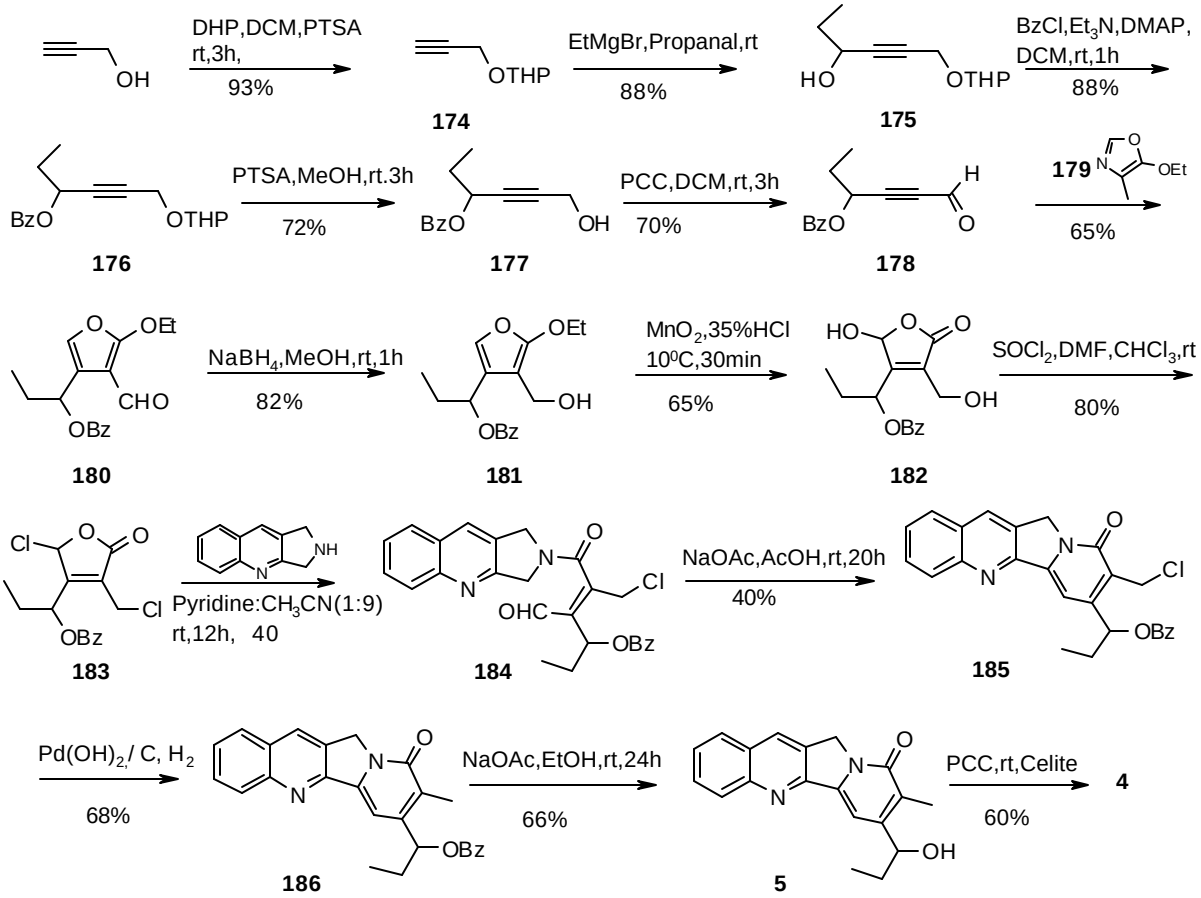
Benzylic and pyridone methylic ethers of **173** were deprotected with saturated solution of HBr in trifluoroethanol and resulted bromide was treated with K_2CO_3 to give the Mappicine ketone. Reduction of the **4** with $NaBH_4$ afforded Mappicine and reduction with (*S*)-BINAL-H afforded (*S*)-Mappicine. This concise and efficient synthesis, which demonstrated the wise implementation of hetero DA with overall yield 35% (from **167**) is extendable to the synthesis of the other analogues of the parent family and the best synthesis for Mappicine and Mappicine ketone devised yet.

Yadav's approach[74] **(Scheme 26, 1999)**

Yadav *et al* condensed pseudo acid chloride with tricyclic amine, a strategy originally developed for the synthesis of CPT earlier,[75] to get the key retron, which had been converted, to MPK. Thus, pyranyl ether of propargyl alcohol **174** was alkylated with propanal to provide compound **175**, Protection of 2^o hydroxy as benzoate and deprotection of the pyranyl ether provided compound **177,** which upon PCC oxidation furnished aldehyde **178.** Diels-Alder reaction of **178** , key reaction to form the furan, with oxazole **179** gave the periselective adduct

180. This adduct was reduced to alcohol **181** with $NaBH_4$ and converted to butenolide unit **182** using MnO_2 and 35% HCl in THF. Compound **182** was then treated with thionylchloride to get the pseudoacid chloride **183** whose coupling with tricyclic amine provided **184** that cyclized to form the key retron **185**.

Scheme 26: Yadav *et al, Tetrahedron.,* 1999, *55*, 5449

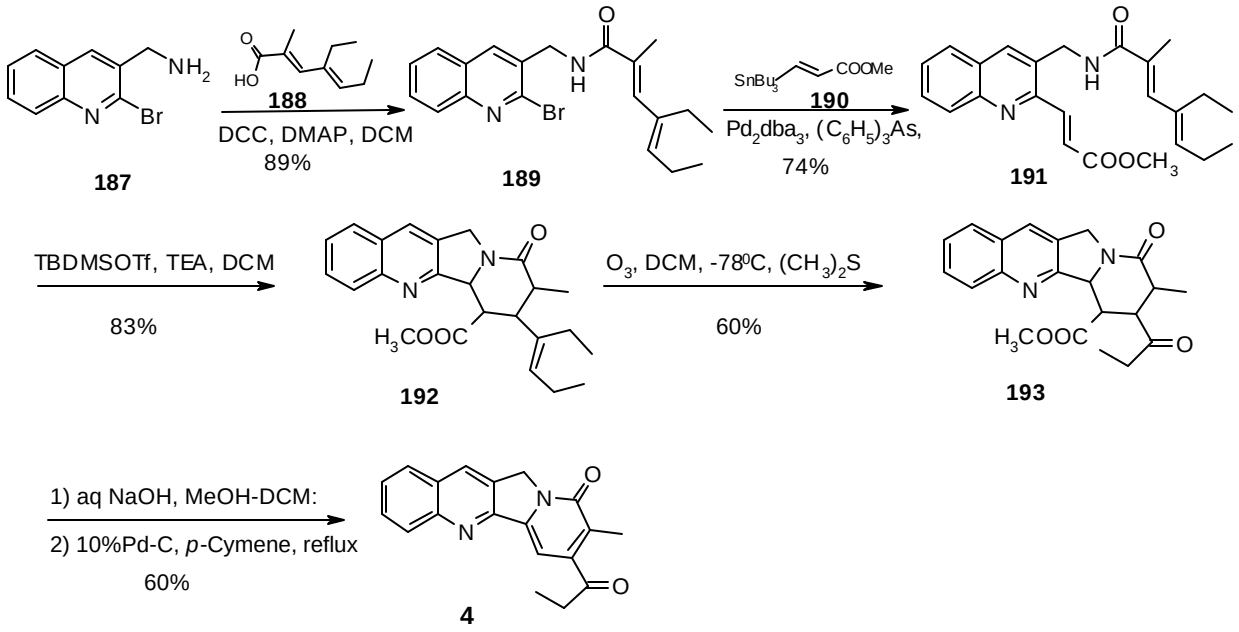


Reductive dechlorination of **185** under catalytic hydrogenation conditions provided the benzoate derivative of Mappicine **186**. Removal of benzoate with sodium methoxide furnished Mappicine **5**, which was oxidized to Mappicine ketone **4** with PCC. This convergent synthesis demonstrated the generality of the original strategy to the naturally occurring analogues of Camptothecin. This simple and efficient synthesis involves readily available starting materials and is amenable to the preparation of AB ring substituted analogues as it involves preformed ABC synthon by Friedlander condensation.

Greene's Approach[76] **(Scheme 27,2000)**

Greene *et al* employed a double Michael reaction to assemble the indolizino quinoline ring system from 2,3-disubstituted quinoline and pyridone formation from piperidone with concomitant loss of EWG group. Amine **187** obtained from Meth-Cohn quinoline carboxaldehyde *via* the known bromide and azide route, was acylated with **188** to give amide **189.** Stille coupling of **189** with stannane **190** provided the olefin **191**, which underwent efficient double Michael addition in the presence of TBDMSOTf to give the **192** as a mixture of epimers. Ozonolysis of **192** provided the keto-ester **193** that was hydrolyzed to acid and dehydrogenated in the presence Pd/C in refluxing cymene to afford Mappicine ketone **4**. This synthesis highlights a new pyridone approach that combined intramolecular double Michael addition, and oxidation–decarboxylation sequence and yields Mappicine ketone **4** in 20% yield and 6 steps from the readily available starting material.

Scheme 27: Greene *et al*, *J. Org . Chem*., **2000,** *65,* 5212

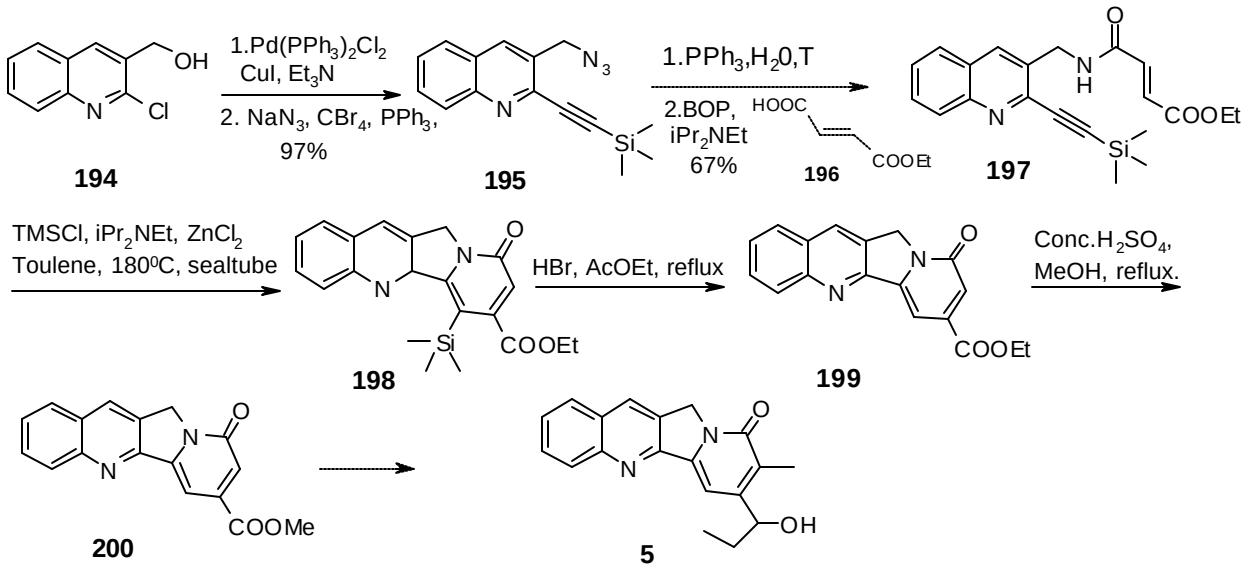


Ihara's approach[77] **(Scheme 28, 2000)**

The highlight of the six-step formal synthesis of Mappicine is an intramolecular hetero Diels-Alder reaction to construct the CD-ring system. The readily available 2-chloroquinoline **194** under Sonogashira coupling conditions *i.e* 5% $Pd(PPh_3)_4$/CuI produced (trimethylsilyl) acetylene derivative **195,** after treatment with sodium azide, CBr_4 and triphenyl phosphine. Azide **195** was subjected to reduction with triphenylphosphine followed by condensation with fumaric

acid monomethylester **196** in the presence of BOP to give rise to the amide **197**.Intramolecular hetero Diels-Alder reaction of **197** led to the cycloadduct **198**, which was treated with aq HBr to provide the ester **199**. The EWG did not impede the cycloaddition rather it promoted the auto oxidation of the cycloadduct. Finally compound **199** was transesterified to obtain methyl ester **200** of Kametani's synthesis to complete the formal synthesis of MPK and Mappicine.

Scheme 28: Ihara *et al*, J. *Org. chem.,* 2000**,** *65,* 7110



Synthesis of Mappicine ketone by degradation of Camptothecin

Although Camptothecin is available in quantity from the biomass of both *Camptotheca acuminata* and *Nothapodytes foetida,* Mappicine ketone **4** and Mappicine **5** are present only in *N. foetida extracts,* and their low abundance prohibits isolation of meaningful amounts. Degradation of CPT to Mappicine ketone and Mappicine makes available multigram quantities of compounds, related to **4** and **5**, which are of interest in medicinal and pharmacological research. Efforts towards degradation of Camptothecin to Mappicine are shown in *Scheme 29.*

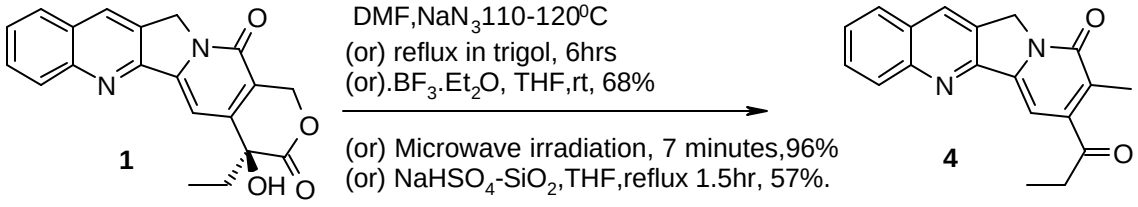
Kingsbury's Method[78] (*Tetrahedron Lett*., **1994**, *35*, 6847)

Kingsbury *et al* effected the rearrangement of Camptothecin to Mappicine by chemical means *i.e* treating the former with sodium azide in hot DMF solution. Sodiumborohydride reduction of the ketone gave Mappicine. Apparently this was the first chemical rearrangement of the Camptothecin to Mappicine ketone.

Fortunak's Method[79] (*Tetrahedron Lett.*, **1994**, *35*, 5763-5764)

Camptothecin was smoothly converted to Mappicine by refluxing in DMF for 4days or in tryglyme for 6hrs. This method is superior to the Kingsbury's method, as it does not require any chemical reagent, thus environmentally benign.

Scheme 29: Synthesis of Mappicine by degradation of Camptothecin



Das's Method-1[80] (*Tetrahedron Lett.*, **1998**, *39*, 431)

Camptothecin was treated with borontriflouride etherate in tetrahydrofuran to give Mappicine ketone in 65% yield. Alternatively Camptothecin was irradiated with out any solvent under microwave irradiation for 7 minutes to form the ketone in 96% yield.

Das's Method-2[81] (*Syn. Comm.*, **2000**, *30*, 3321)

Camptothecin was refluxed in dry THF in presence of $NaHSO_4$-SiO_2 catalyst for 2.5 hrs to afford Mappicine. Inexpensive, non-hazardous catalyst, operational simplicity and high yields of the product makes this method an alternative and attractive to the existing methods.

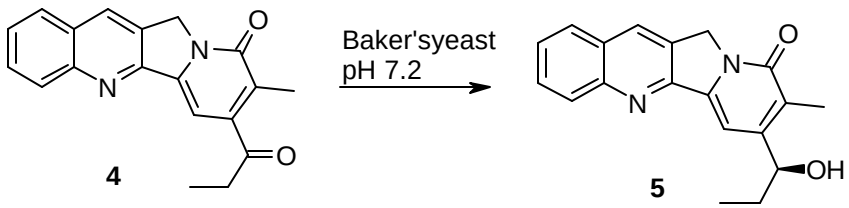
Conversion of Mappicine ketone to (R) or (S) Mappicine

Efforts have been addressed to synthesize Mappicine in optically pure form from the Mappicine ketone by employing biocatalysts.

Das's Approach[82] (Scheme 30, 1998)

Camptothecin has been converted to *S*-mappicine *via* Mappicine ketone by Baker's yeast reduction of Mappicine ketone yielded (*S*)-mappicine in phosphate buffer solution of pH 7.2 in 74% yield and 86% *ee*.

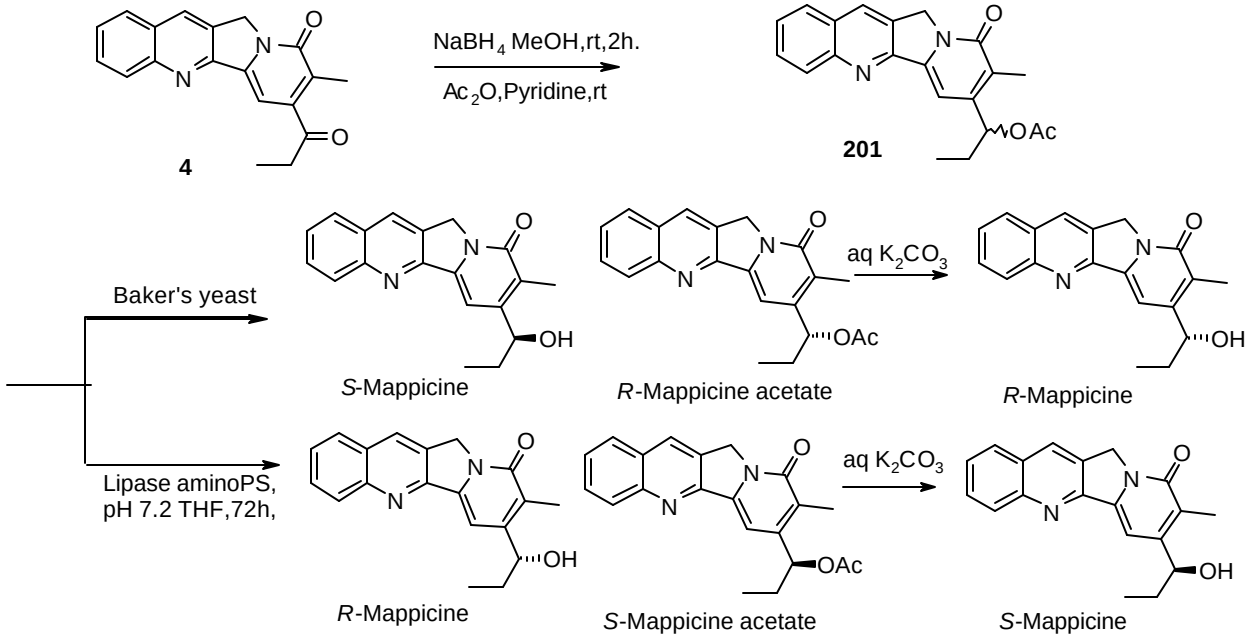
Scheme 30: Das *et al*, *Bio. Org. Med. Chem. Lett.*, **1998**, 1403



Das 's approach[83] **(Scheme 31, 1999**)

This Chemoenzymatic enatntioselective synthesis of (*R*)-and (*S*)- Mappicine involves hydrolysis of racemic Mappicine acetate in an enantioselecive way racemic Mappicine acetate, was prepared by treating rac Mappicine with acetic anhydride and pyridine. Thus hydrolysis of rac **201** with baker's yeast afforded (*S*)- Mappicine in 48% yield and 97% *ee*. Lipase Amino-PS hydrolyzed (*R*)-Mappicine acetate in 47% yield and 92% *ee* .The unchanged acetates in both the cases were hydrolyzed chemically by refluxing with 10% aq K_2CO_3 solution to (*R*) Mappicine and (*S*) Mappicine respectively.

Scheme 31: Das *et al***,** *Tetrahedron*., **1999**, 55, 7875

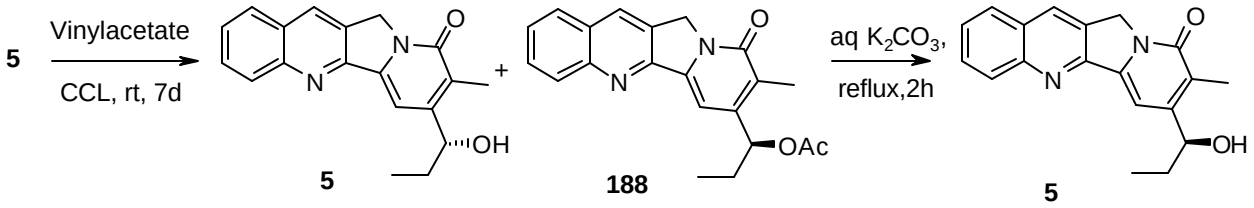


Thus authors have identified two bioactive catalysts, complimentary to each other for the conversion of rac-Mappicine to either of the enantiomers in an optically pure form.

Das' approach[84] **(Scheme 32, 2000)**

In this approach enantioselective acetylation of the rac-alcohol was employed. Mappicine was subjected to acetylation in the presence of *Candida cylindrical lipase* with vinyl acetate to form (*S*)-Mappicine acetate leaving the (*R*)-Mappicine unchanged (97% *ee*). (*S*)-Mappicine acetate was chemically hydrolyzed with aq K_2CO_3 solution under refluxing conditions to produce (*S*)-mappicine with (97% *ee*).

Scheme 32: *J. Chem. Res.*, **2000,** 476.



5 **188** **5**

This efficient chemo enzymatic synthesis of (*R*)- and (*S*)- enantiomers of Mappicine is attractive in the terms of *ee* obtained.

CHAPTER 1

SECTION II

Synthesis of Camptothecin

PART A

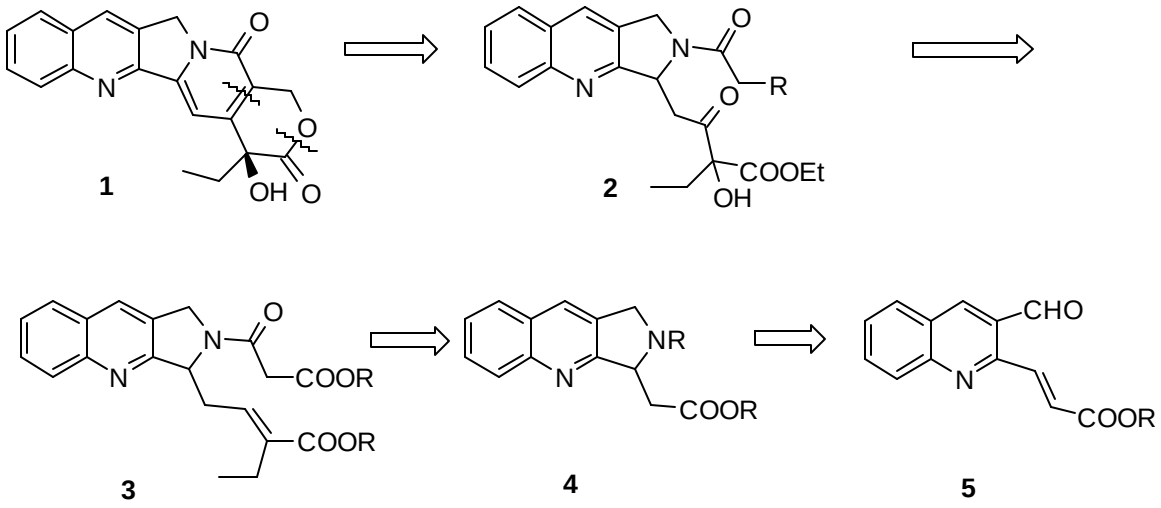
1.2.1.1 Introduction

In light of the impressive biological activity and intriguing mode of action reported for **1**, we decided to develop a synthetic route for Camptothecin amenable to its natural and synthetic analogues.

1.2.1.2 Present work

Our retrosynthetic analysis of Camptothecin, shown in *Scheme1*, revealed an intramolecular aldol condensation[85] of the α-hydroxy β-ketoester **2** (called ketol hereafter) to construct the pyridone ring while placing the necessary functionalities for the E-ring elaboration.

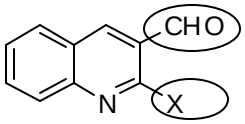
Scheme 1: Retrosynthetic analysis



Ketol **2** was thought to be obtained from olefin **3**, which in turn could be made from tricyclic synthon **4.** We envisaged a reductive amination-Michael addition sequence of a a, ß-unsaturated ester aldehyde **5** to construct the tricyclic synthon **4** since the latter being conceptually one of the simplest methods for the construction of β-amino esters.[86]

1.2.1.3 Results and Discussions

We chose the Meth-Cohn's aldehyde **6**[87] as the AB ring synthon for two reasons .1) It has the amply and appropriately placed handles (halo, formyl) for the further elaboration

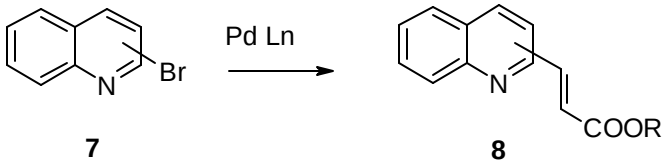


6

2) Meth-Cohn's quinoline synthesis has got the inherent flexibility to obtain the substituted analogues in a relatively simple manner[88] and obviates the need for the expensive and unstable *o*-aminobenzaldehyde.

Aryl halides have been olefinated by Heck reaction conditions.[89] In fact haloquinolines have been converted to olefins under Heck reaction conditions.[90]

Scheme 2:

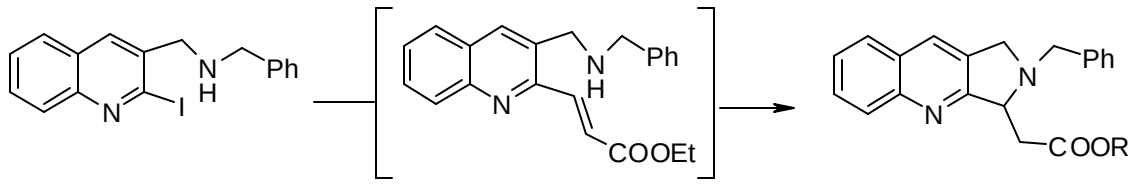


7 **8**

Functional group tolerance and the ready availability and low cost of simple olefins, compared to the vinyl metal compounds that are employed in the corresponding Suzuki, Stille, Kumada, and other cross-coupling reactions, contribute to the exceptional utility of the Heck arylation. So we preferred Heck olefination to other reactions for placing the a, ß-unsaturated ester. While our work was in progress two research groups published the synthesis of Camptothecin analogues, which employed the same substrate and Pd-chemistry.[91] Knowing the reluctance of chloroquinoline aldehyde to participate in Heck olefination,[92] we reasoned and planned to try the same on iodo analogue. Most notable strategies for the construction of pyrrolidines are intramolecular *N*-alkylations,[93] 3+2 cycloadditions,[94] and Li-, Pd- or lanthanoid-catalyzed cyclizations.[95] Among the different methodologies found in the literature for the preparation of ß-amino esters, one of the most widely used is the conjugate addition on to Michael acceptors.[96] Suitably designed aryl halides are known to give the cyclic amines *via* cascade palladium-mediated cyclizations.[97, 98] Among the latter one, the intramolecular tandem aminations of olefins formed in olefination attracts the attention owing to their ability to form the heterocycles in relatively short synthetic sequence.

Thus with the hope of getting the tricyclic amine formation in a single pot we planned to attempt the Pd - mediated olefination on the amine **9** as shown in *Scheme 3*.

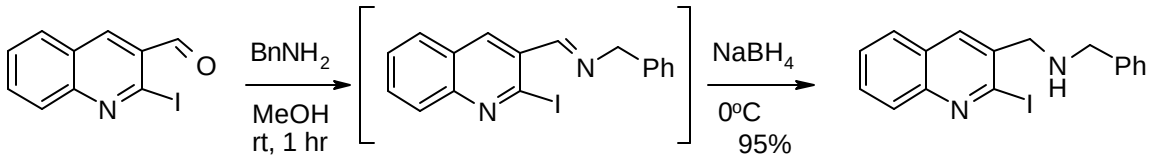
Scheme 3:



9 **10** **4**

Condensation of iodoaldehyde **6,** obtained by the Finklestein reaction[99] from the chloro aldehyde according to reported procedure with benzyl amine *i.e* Schiff's base formation was examined in different solvents and methanol was found be the suitable solvent. Thus equimolar mixture of aldehyde and benzylamine was stirred in methanol at 0°C to form the Schiff's base in quantitative yield. Reduction of this aldimine was carried out directly in methanol at 0°C in the same pot with sodium borohydride to give the corresponding secondary amine in high yield and in very short reaction time. Thus, this stepwise one-pot procedure involving imine formation in methanol followed by *in situ* reduction with sodium borohydride appealed as a potentially very efficient and convenient alternative for conducting reductive aminations, obviating the need for the $NaCNBH_3$ an expensive and hazardous agent.

Scheme 4:

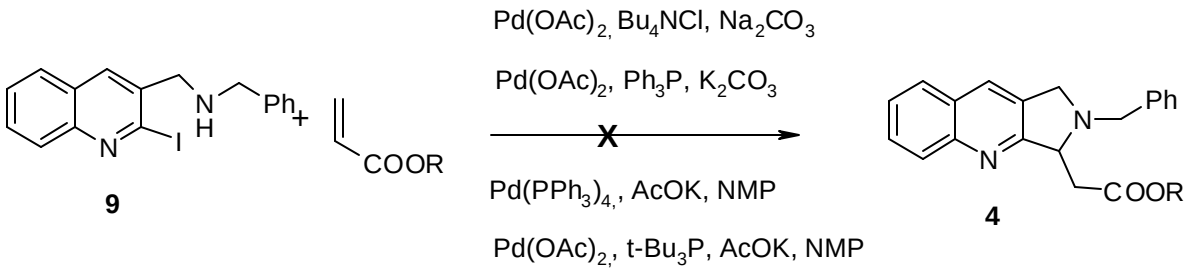


6 **12** **9**

^{1}H NMR spectrum of **9** showed along with the quinoline protons, a multiplet at δ 7.42 (5H) and singlets at δ 3.75 and δ 3.73 and the absence of aldehydic proton at δ 10.3 suggesting the secondary amine formation. ^{13}C spectrum showed two secondary carbons at δ 55.96 and δ 53.40 assigned to the two benzylic methylenes. Mass spectrum further confirmed the same by revealing m/z peak at 374.

Unfortunately the attempted Heck reaction under various conditions resulted in intractable mixture of compounds.

Scheme 5:

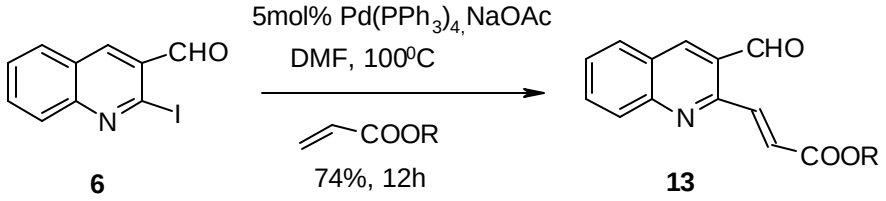


Though we failed to realize the above transformation, we were contented at this stage with successful conversion of the formyl to amine functionality.

Then the stepwise and reversal of the above sequence was in order.

Among various conditions tried, aldehyde **6** under went olefination with ethylacrylate with 5 mol% Pd $(PPh_3)_4$/NaOAc /DMF/100^oC conditions to give olefin **13** in 74% yield along with some reduced product. (The success of the reaction depends mainly on the reaction temperature and the amount of the catalyst. No attempts have been made to optimize the reaction)

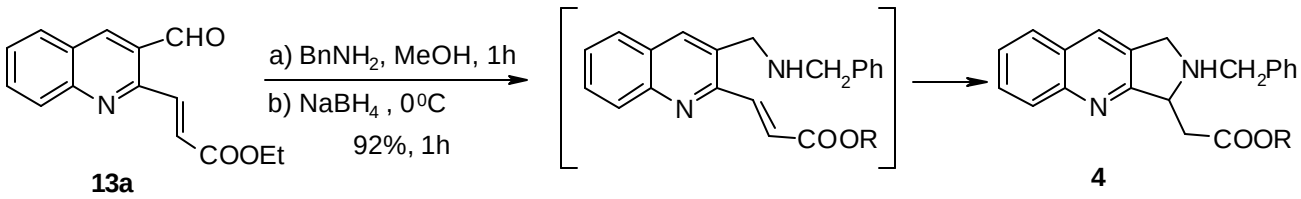
Scheme 6:



IR spectrum of **13** showed the absorptions at 1710 cm^{-1} characteristic of a, ß-unsaturated ester. ^1H NMR spectrum showed along with the quinoline protons, two doublets at d 7.25 (1H) and 8.2 (1H) (merged with one of the quinoline ^1H suggesting the incorporation of the acryl ate moiety -CH=CH-COOEt, along with a singlet at δ 10.35 for –CHO. Mass spectrum showed m/z peak at 255.

Having obtained olefin-tethered aldehyde, we next focused on converting the aldehyde functional group to amine, by employing the conditions that have been optimized in earlier case *i.e* in the preparation of compound 9. Thus equimolar mixture of aldehyde **13a** and benzylamine was stirred in methanol at 0^oC to form the Schiff's base in quantitative yield.

Scheme 7:



The reduction of this aldimine was carried out directly in methanol at 0^oC in the same pot with sodium borohydride to give the corresponding secondary amine. The amine suffered an intramolecular Michael addition upon allowing it to reach the room temperature to form the tricyclic amine **4,** thus avoiding the separation at secondary amine stage and the need for separate transformation for Michael addition (*Scheme 4*).

^{1}H NMR spectrum of **4** showed, apart from quinoline and ester protons, a multiplet at d 7.3 (5H) and singlet at d 4.27(2H) assigned to –*N*-C$\underline{H_2}$C$_6\underline{H_5}$, a triplet at d 4.62, two dd at δ3.79 and 3.34 (1H each) assigned for -C$\underline{H}$-C$\underline{H_2}$-COOEt combinely suggesting the formation of tricyclic compound formation. Mass spectrum further substantiated the structure by revealing the m/z at 346. ^{13}C NMR spectrum showed the pattern of *N*-benzyl pyrrolidone.

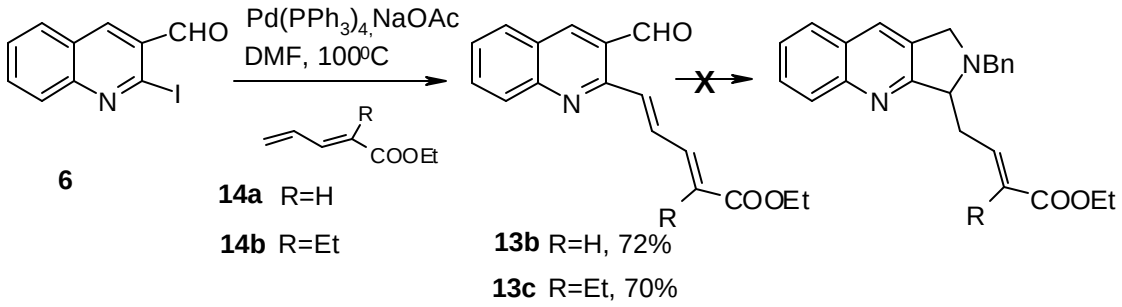
Similar tandem transformation has been reported by Akio Baba *et al*[100] on α, β-unsaturated enones, (while this study was in progress) by employing tributyl tinhydride as the reducing agent to have selectivity for imine over carbonyl enone and he has extended the same to the preparation of piperidones and other *N*-heterocycles.

At this stage, encouraged by the success of Heck reaction with simple acrylic esters and the tandem reductive amination-Michael addition, we reasoned that introduction of the functionalities for the D-ring formation during Heck olefination would reduce the number of steps and there by increase the convergence of the synthesis. Literature survey revealed indeed such a methodological precedent[101] wherein it was shown that dienoate gives the δ-adduct with $BnNH_2$, and β-adduct with the copper reagent and a mixture of both with lithium reagents.

Having been aware of the literature precedents of arylation of dienes under Heck conditions[102] and the 1, 6 addition of the amines to 2,4-dienoates combinely led us to consider

the introduction of 2,4-dienoic ester on to quinoline as Michael acceptor. Thus the required diene **14a** was prepared by condensing acrolein with ethyl malonate in presence of pyridine while **14b** was made by the Wittig reaction of acrolein with phosporane.[103] Arylation of these dienes under the above conditions yielded **13b & 13c** *(Scheme 8)*. ^{1}H NMR spectrum of **13b** showed, apart from ester and quinoline protons, a doublet at d 6.27 (1H), 7.6(1H), 7.88 (1H) and 8.6 (1H) assigned to the olefinic protons (δ, α, β, ? -merged with the quinoline protons) and aldehydic proton at d 10.35. Mass spectrum of **13b** showed m/z peak at 281.

Scheme 8:



^{1}H NMR spectrum of **13c** showed, apart from olefinic, ester, quinoline and aldehydic protons, a triplet at d 1.4 (3H) and quartet at d 2.6 (2H) assigned to the ethyl functionality. Mass spectrum showed molecular ion peak at 304.

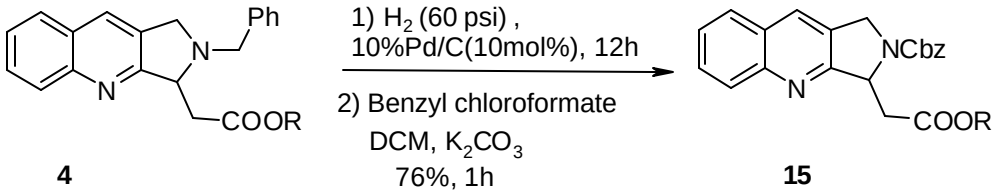
With the suitable diene tethered aldehydes **13b** and **13c** in hand, we next focused on the formation of skeleton tricyclic under the above set conditions. To our disappointment, the attempted cyclization under above set reductive conditions led to the formation of intractable mixture of compounds and under reported conditions also the reaction failed to give the expected product.

Having been successful in the preparation tricyclic core **13a** in a short sequence, we decided to go stepwise about incorporation of the functionalities for the construction of the other two rings. *N*-protecting group of **4** needed to be changed to carbamate keeping the further chemistry and the deprotection at the later stage in view. Among the myriad of protecting groups for nitrogen, the Cbz moiety is regarded as one of the most useful in synthesis. Installation of this protecting group follows from a standard protocol involving treatment of an amine with Cbz-Cl or the equivalent. The value of this blocking group lies in its susceptibility to deprotect under conditions that are orthogonal to other functional groups in the molecule. At a later stage it

would demand the selective deprotection of carbamate in presence of a, ß- unsaturated ester, for the reason, which we chose the benzyloxy carbamate.

Thus under standard hydrogenation conditions *N*-benzyl amine underwent hydrogenolysis to provide 2^{o}-amine which was protected as benzyloxy carbamate **15** by condensing with benzylchloroformate in presence of K_2CO_3 (*Scheme 9*).

Scheme 9:

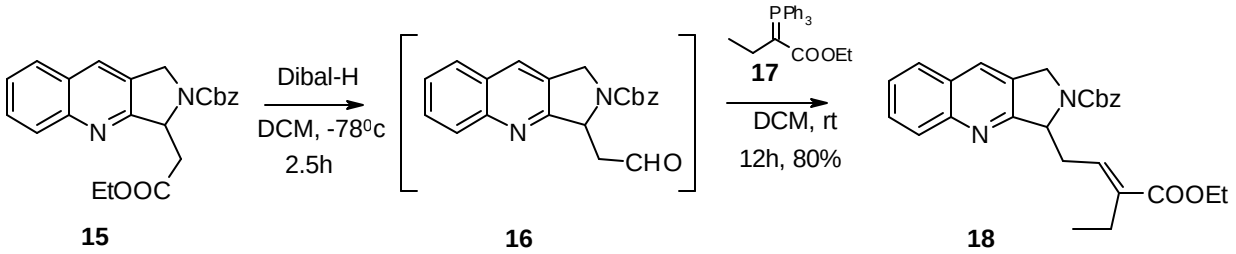


4 **15**

We resorted to Wittig reaction to place the olefin. Wittig reaction of aldehyde with a phosphorus ylide is one of the most commonly used protocols for forming substituted olefins. When stabilized ylides (a-EWG) are employed for the preparation of α, β-unsaturated carboxylic acid derivatives**,** the products are generally obtained with very high levels of *E*-selectivity.

Careful reduction of **15** with Dibal-H furnished aldehyde **16**. The ^{1}H spectrum of **16** showed the aldehyde proton at δ 9.8 and the absence of ester protons. Mass spectrum showed m/z peak at 346. Owing to its instability, the aldehyde with out purification was subjected to the Wittig olefination with phosporane **17** to furnish a, ß- unsaturated ester **18** in good yield (*Scheme 16*).

Scheme 10:



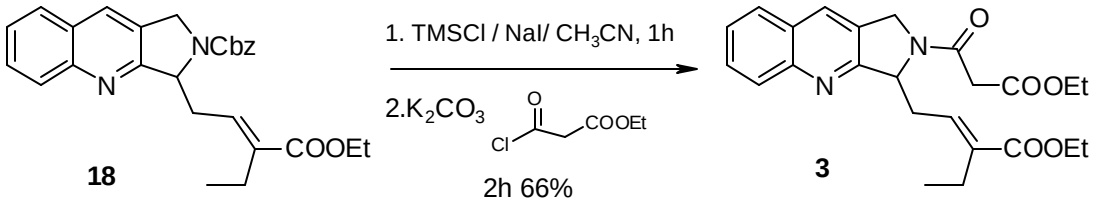
15 **16** **18**

IR spectrum of **18** showed the absorption at 1715cm^{-1} confirming the a, ß- unsaturated ester. ^{1}H NMR spectrum showed, apart from quinoline and benzyl protons, a triplet at d 0.85 (3H) & a multiplet at d 2.20 assigned for ethyl substituent while appearance of a triplet at d 6.45 (1H) was assigned to the olefinic proton ($CH_2C\underline{H}$=C-). Mass spectrum showed molecular ion peak at 444.

It was decided to deprotecet the Cbz with TMSI owing to the presence of highly reactive olefin, which would interfere with other means of deprotection. Iodotrimethylsilane (Me_3SiI) is a commercially available reagent and, as an inexpensive *in situ* alternative, can be easily prepared without any solvents or under mild conditions by treatment of chlorotrimethylsilane (Me_3SiCl) with sodium (or lithium) iodide in acetonitrile (as an Me_3SiI equivalent). It is used extensively in the deprotection of methyl and benzyl esters, ethers, carbamates, and in the deoxygenation of sulphoxides. These chemical properties of Me_3SiI are due to the weak Si-I bond and an intrinsic high affinity of the silicon atom for the oxygen atom.

Selective deprotection of Cbz carbamate of **18** with TMSCl / NaI reagent gave secondary amine, whose instability necessitated with out purification immediate condensation with carbethoxy acetyl chloride to furnish amide **3** in 68% yield.

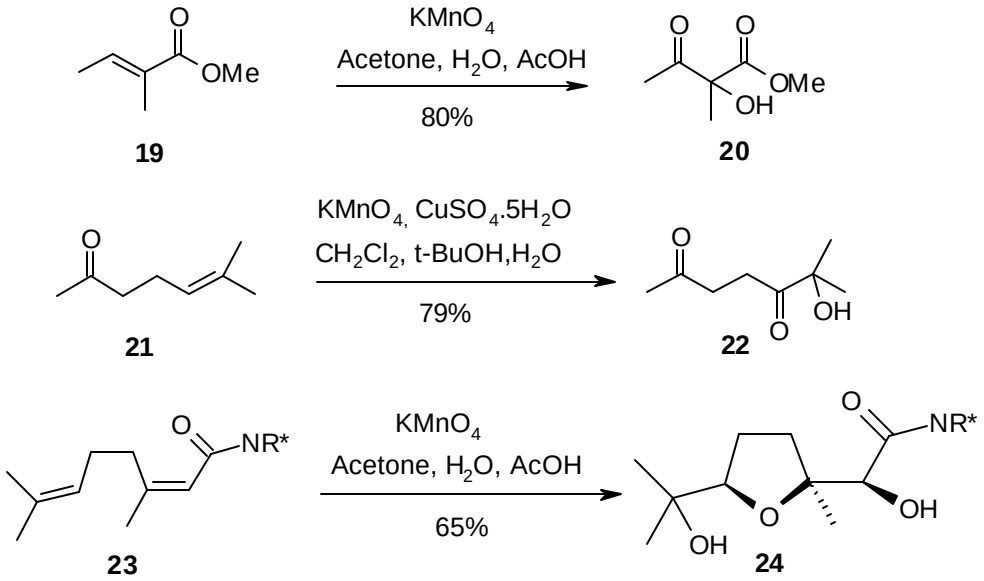
Scheme 11:



The prochiral double bond has been strategically placed to introduce the hydroxy group, (C20-OH) of the target molecule. The stepwise oxidation of olefin *i.e*. Sharpless asymmetric dihydroxylation (ADH), and the oxidation of the 2^o -OH would assemble the required functionality in an enatntioselective manner.

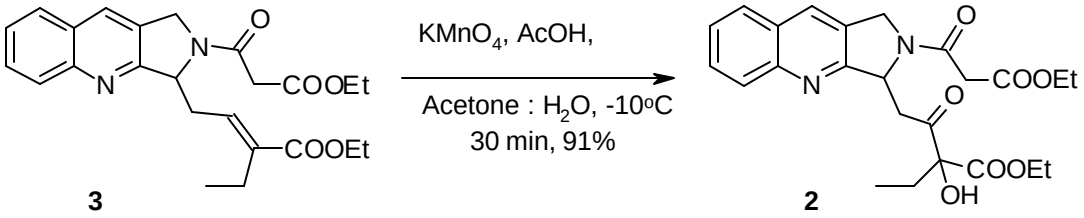
It has been shown in literature[104] that $KMnO_4$ oxidizes the olefins, especially trisubstituted ones, to the corresponding hydroxy ketones involving $4e^-$ oxidation (*Scheme 12*).

Scheme 12:



Indeed $KMnO_4$ is known to do the hydroxylation of the auxiliary tethered substrate **23** in stereoselective manner.[105] Intrigued by the possibility of obtaining the a-hydroxy ß-ketoester in a single pot by $KMnO_4$ and with the idea of standardizing the chemistry with achiral substrates, we subjected the ester **3** for $KMnO_4$ oxidation in presence of acetic acid (acidic pH). As anticipated the smooth reaction ensued to furnish ketol **2** in 90% yield (*Scheme 13*).

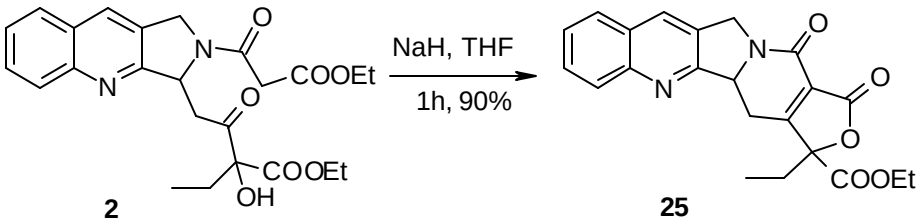
Scheme 13:



IR spectrum of **2** showed absorption at 3485cm^{-1} and 1744cm^{-1} typical of the hydroxy ketone functionality.^{1}H NMR spectrum showed the absence of olefinic protons and appearance of multiplets at d 1.98 (2H), 0.75 (3H) for –C$\underline{H_2}$C$\underline{H_3}$ (the increased multiplicity of these indicates the adjacent quaternary center of the diastereomers) and at δ 3.7 (m, 2H) is assigned to methylene adjacent to keto group (-C$\underline{H_2}$CO-). ^{13}C NMR spectrum confirmed the presence of ketone carbonyl peak at d 204.8 and the newly formed quaternary carbon at δ 84.16, thus indicating the formation of ketol **2**. Mass spectrum showed m/z peak at 456 corresponding to the formula $C_{24}H_{28}O_7N_2$.

Having made the substrate with the necessary functionalities, the stage was set to ascertain the proposed strategy. Pleasingly, treatment of **2** with NaH in tetrahydrofuran at room temperature resulted in the formation of dihydro pyridone **25.**

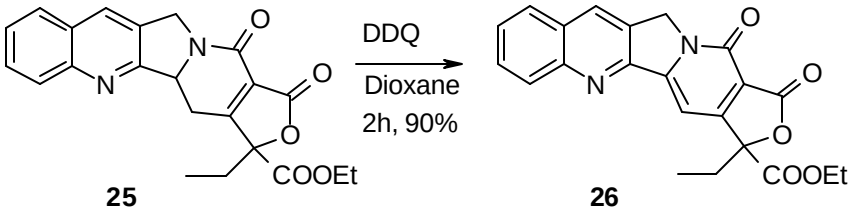
Scheme 14:



IR spectrum of **25** showed the absorption at 1765cm^{-1} and 1679cm^{-1}. The product was identified as diastereomeric mixture of **25** from its ^{1}H NMR spectrum, which showed the absence of active methylene & ethyl ester protons of the malonate ester and the appearance of increased multiplicity of ethyl protons in the region d 2.0- 2.5, the pyridone protons at d 3-3.5 and. the ester protons at d 4.25 & d 1.5 confirm the formation lactone as diastereomeric mixture. ^{13}C NMR spectrum showed the absence of carbonyl carbon of the ketone and the active methylene confirming intramolecular condensation. Mass spectrum revealed m/z peak at 392.

Compound **25** was found to undergo oxidation to pyridone **26** upon long exposure to air, which indicates its high reduction potential. Chemically, the oxidation of dihydropyridone **25** to pyridone was effected with DDQ in refluxing dioxane in good yield.

Scheme 15:

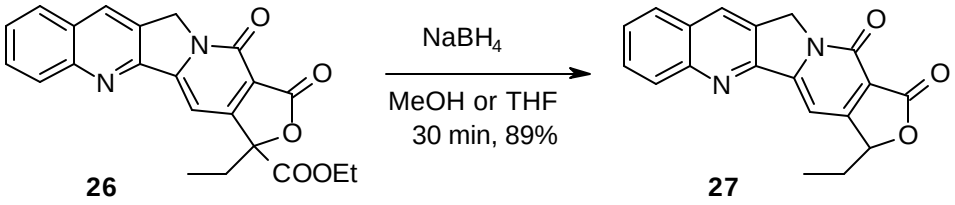


^{1}H NMR spectrum of **26** showed apart from the 5-quinoline and ester protons, the presence of a singlet at d7.52 (1H), assigned to the pyridone proton, two distinctive multiplets at δ 2.1 & 2.5 (1 each) and the triplet at d 1.02 (3H) assigned to C$\underline{H_2}$C$\underline{H_3}$. ^{13}C NMR spectrum showed a CH at δ 94.51 assigned for the pyridone carbon. Mass spectroscopy showed the m/z 390.

Pyridone **26** had all the atoms placed in the proper positions for the elaboration to lactone E-ring and just the adjustment of the oxidation states of carbons should complete the synthesis of Camptothecin.

Towards this end, attempted reduction with $NaBH_4$ resulted in the decarbonylative loss of the ester resulting in the formation of butyrolactone **27** (*Scheme 16*).

Scheme 16:

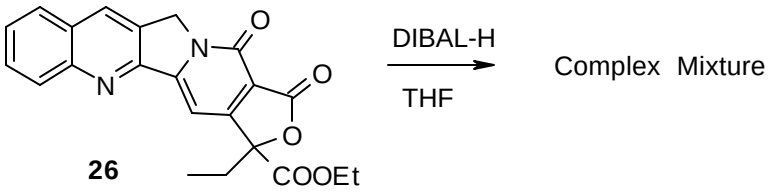


^{1}H NMR spectrum of **27** showed the presence of a singlet (2H) merged with triplet (1H) at d 5.37 (appearing as singlet) and the disappearance of ester protons (quartet and triplet) suggested the structure to be **27**. ^{13}C NMR spectrum of **27** confirmed the absence of the carbonyl of ester. Further evidence comes from the Mass spectrum, which showed molecular ion peak at 318 corresponding to the C_{19} H_{14} N_2O_3 *i.e* loss of ester group COOEt.

Further it was confirmed by chemical means i.e Dibal-H reduction of the **27** gave the diol which confirms the decarboxylated lactone.

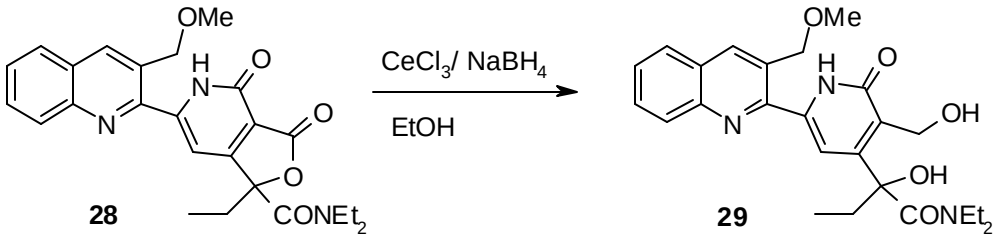
Chavan *et al* [106] had employed Dibal-H reduction for the selective reduction of aromatic ester in presence of aliphatic one. Since the pyridone **26** has the similar grouping, *i.e* one carbonyl being the conjugated, it was subjected for the reported conditions with the hope of achieving the selective reduction. Unfortunately it resulted in the complex mixture, which could not be purified.

Scheme 17:



Ciufolini *et al* in their synthesis[107] addressed the perils associated in similar transformations and they have successfully reduced the amide **28** to diol **29** with modified Luche's procedure.

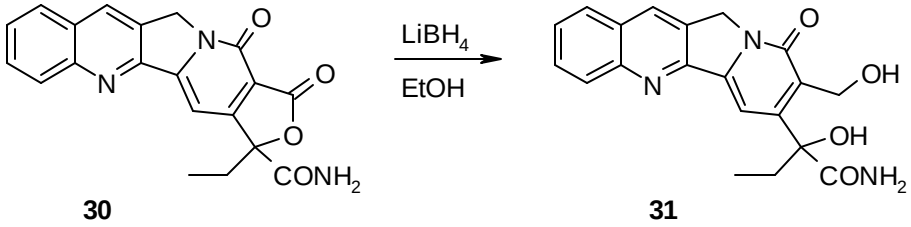
Scheme 18:



The attempted Ciufolini's procedure ($CeCl_3.7H_2O$ / $NaBH_4$) on **26** also resulted only in the decarboxylated compound **27**.

It has been demonstrated[108] that the lactone carbonyl can be selectively reduced to alcohol in presence of amide carbonyl using lithium borohydride.

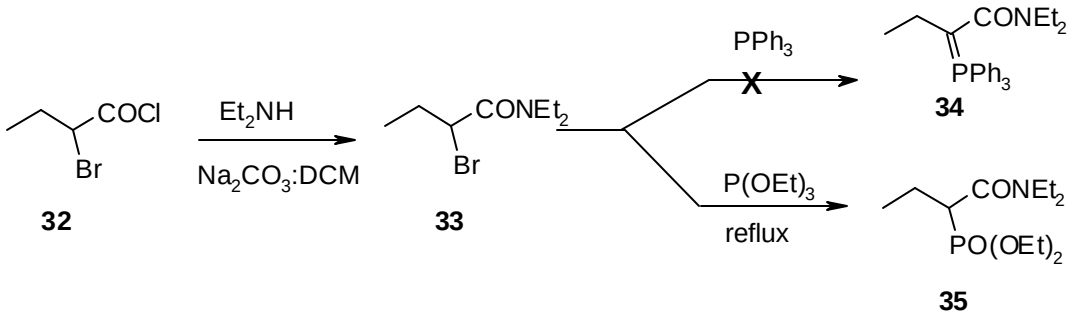
Scheme 19:



Hence we thought of preparing the amide **30** by replacing the ester functionality right in the early stage where it was installed *i.e*. Wittig stage and repeat the synthetic sequence with a, ß-unsaturated amide.

The attempted Wittig salt formation from the bromo amide **33** obtained from acid chloride **32** under Schotten – Baumann conditions failed to give the phosporane **34**. Literature search shows that a, ß- unsaturated amides are often been made *via* Horner-Wadsworth-Emmons (HWE) reaction rather than Wittig reaction of the aldehydes with corresponding phosphonoamides. Hence we prepared phosphonoamide **35** through Arbuzov method *i.e.* by refluxing $POEt_3$ with bromo amide **33.**

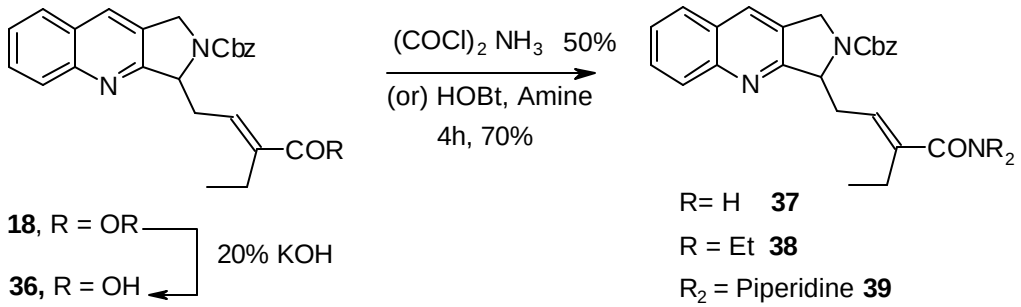
Scheme 20:



Attempted HWE reaction of the aldehyde gave a complex mixture, which could not be characterized. This failure of the olefination left us with the only one option of making the amide by coupling the acid and the amine since the direct amination of the ester couldn't be tried due to the presence of a, ß-unsaturated Michael system.

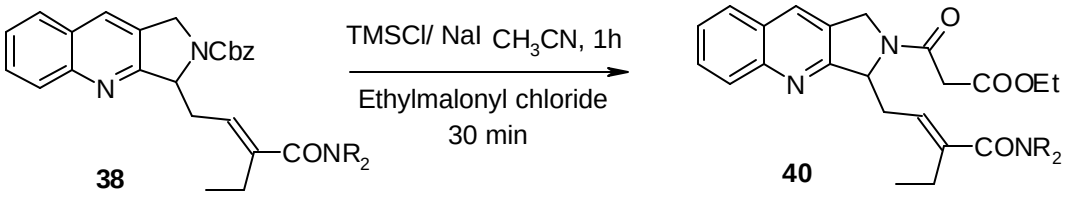
Thus hydrolysis of the ester **18** with ethanolic KOH at 10^{o}C resulted in the formation of the acid **36**. Treatment of the acid with oxaloyl chloride resulted in the formation of the acid chloride, which was bubbled with NH_3 gas to furnish amide **37**. But the lower yields obtained forced us to use the peptide coupling reagents to activate the acid and condense with amine. Thus treatment of the acid in presence of HOBT and DCC with diethyl amine or piperidine gave the amides **38** & **39** respectively.

Scheme 21:



Carbamate protection was smoothly removed with TMSI and condensed with malonyl chloride to obtain the malonamide **40.**

Scheme 22:

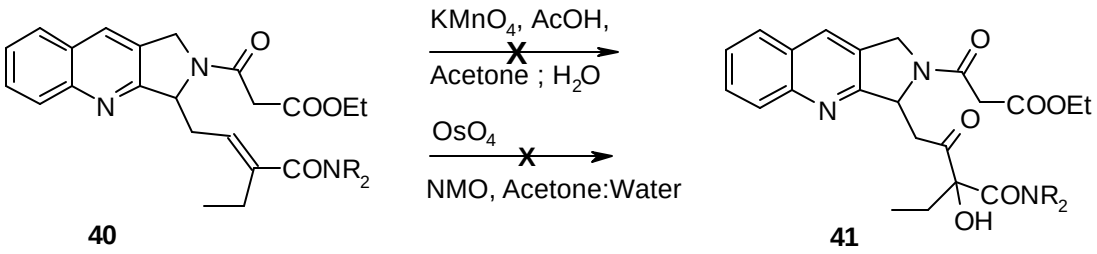


Having been able to obtain amide **40**, we believed that mere repetition of the above sequence should complete synthesis of target molecule. Unfortunately the attempted $KMnO_4$ oxidation failed to provide the ketol of the amide **40.**

Failure to install the hydroxy keto amide in a single step, led us to consider stepwise process for the same *i.e* hydroxylation and oxidation of 2^{o}-OH to keto group.

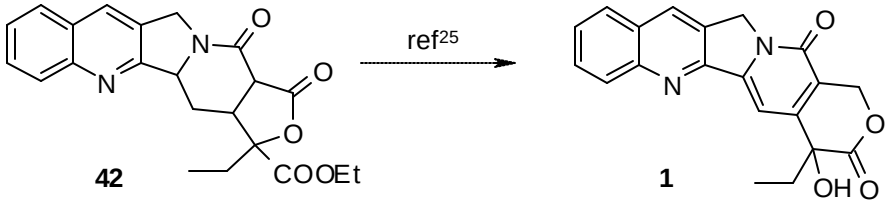
To our dismay, amide **40** showed reluctance to undergo the dihydroxylation even with OsO_4.

Scheme 23:



Literature survey reveals that Stork *et al* have converted the corresponding tetrahydro derivative **42** to Camptothecin.[109]

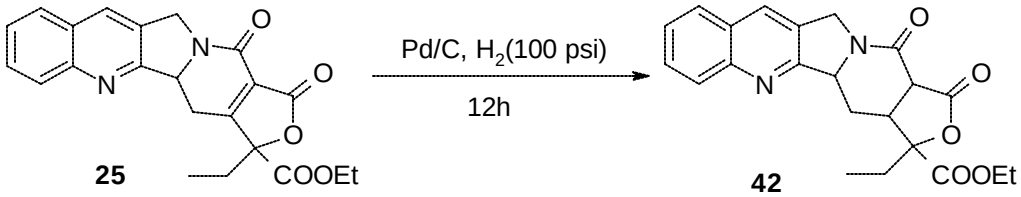
Scheme 24:



Finally we were compelled to resort to the Gilbert Stork intermediate *i.e* a step backward in the synthesis from dihydro to tetrahydro pyridone.

Thus careful reduction of **25** with 10% Pd/C, H_2 provided **42** and since **42** (Stork's intermediate) has already been converted to Camptothecin this completes the formal synthesis of Camptothecin.

Scheme 25:



^{1}H NMR spectrum of **42** showed the presence of multiplet at δ 3.19 and 2.81 assigned to the protons at ring junction, formed by the addition of hydrogen. Mass spectrum confirmed the addition of 2 units by revealing a peak at m/z 394.

It is pertaining to mention that the high loading of the catalyst and the forcing conditions results in the formation of octahydro derivative.

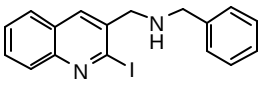
1.2.1.4 Conclusion:

We have successfully demonstrated the Heck olefination of Meth-Cohn quinoline iodo aldehyde and developed a facile synthesis of tricyclic intermediate, which is a key synthon in many earlier synthesis of Camptothecin by a tandem reductive amination – Michael addition sequence. A new pyridone approach with the concomitant placement of the E-ring functionalities has been devised for the synthesis of Camptothecin, which has the potential inherent flexibility for the asymmetric version.

.

1. 2. 1. 5 Experimental

1. Benzyl- (2-iodo-quinolin-3-ylmethyl) amine [9]



9

Quinoline aldehyde **6** (2.85 g, 10 mmol) and benzyl amine (0.75 g, 10.6 mmol) were mixed in MeOH (20 mL) at rt under a N_2 atmosphere. The mixture was stirred at rt for 1h, until the aldimine formation was completed (monitored by TLC). The aldimine in MeOH was cooled to 0^oC and carefully treated with $NaBH_4$ (0.6 g, 1.6 mmol) and stirred for 10 min. and then brought to room temperature and allowed to stir for 1hr after which methanol was removed under reduced pressure, added water and extracted with $CHCl_3$ (3×20 mL). The combined organic extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), concentrated and purified by column chromatography over silica gel using ethyl acetate-pet ether (3:7) as eluent to obtain amine **9.**

Molecular Formula : $C_{17}H_{15}IN_2$, 374.2

Yield : 3.55 g, 95%

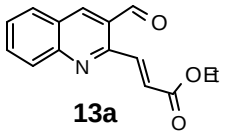
IR ($CHCl_3$) : 3340,1614, 1360cm^{-1};

^{1}H NMR (200MHz) : δ: 7.93 (d, 8.27 Hz, 1H), 7.81 (s, 1H), 7.6 (d, 1H), 7.52 (d, 1H), 7.42 (d, 1H), 7.42-7.2 (m, 5H), 3.75 (s, 2H), 3.73 (d, 2H).

^{13}C NMR (50MHz) : δ: 148.66 (C), 139.79 (C), 135.69 (C), 135.29 (CH), 129.93 (CH), 128.66 (C), 128.57 (2C), 128.36 (CH), 128.29(CH), 128.08(CH), 127.67 (CH), 127.15 (CH), 127.06 (CH), 125.29 (C), 55.96 (CH_2), 53.40 (CH_2).

Mass m/z (%) : 374, 372, 283, 268, 230, 217, 191, 142, 128, 115, 91, 77, 65.

2. 3-(3-Formyl-quinolin-2-yl)-acrylic acid ethyl ester [13a]



13a

To a stirred solution of the aldehyde **6** (1.42 g, 5 mmol) in anhydrous DMF (15.0 mL) were added $Pd(PPh_3)_4$ (0.285g), NaOAc (1.23g, 15 mmol) and ethylacrylate (0.65 mL, 6 mmol) at room temperature, and the mixture was heated to 100^oC for 12h. The reaction mixture was

filtered through Celite, the filtrate was concentrated and purified by column chromatography (siO_2). Elution with 8:2 mixture of hexanes-EtOAc afforded the olefin **13a** as a yellow solid.

Molecular Formula : $C_{15}H_{13}NO_3$, 255.3

Yield : 0.946 g, 74%

M.P. : 119^{o}C.

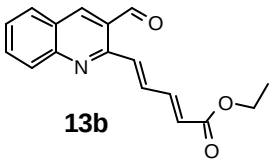
IR : 3020, 1707, 1640, 1371, 1297, 1273 cm^{-1}:

^{1}H NMR (200MHz) : δ: 10.45 (s, 1H), 8.72 (d, *J* = 15.14Hz, 1H), 8.67 (s, 1H), 8.18 (d, *J*=8.3Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.94 (t, *J* = 7.32 Hz, 1H), 7.67 (t, *J*=8.3Hz, 1H), 7.34 (d, *J* = 15.14Hz, 1H), 4.39 (q, *J* =7.32, 1H), 1.36 (t, *J* = 7.34, 3H).

^{13}C NMR (50MHz) : δ: 190.03(C), 166.33 (C), 151.53 (C), 149.24 (C), 142.74 (CH), 138.92 (CH), 130.03 CH), 129.86 (CH), 128.91 (CH), 128.18 (CH), 127.42 (C), 127.02 (C), 126.78 (CH), 60.78 (CH_2), 14.25 (CH_3).

Mass, *m*/*z*, (%) : 255 (6, M^+), 229 (10), 212 (15), 198 (16), 182 (100), 156 (50), 128 (50), 101 (30), 77 (29).

5-(3-Formyl-quinolin-2-yl)-penta-2, 4-dienoic acid ethyl ester [13b]



13b

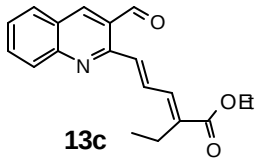
Molecular Formula : $C_{17}H_{15}NO_3$, 281

Yield : 72%.

IR ($CHCl_3$) : 3020, 1707, 1640, 1371, 1297, 1273 cm^{-1}.

^{1}H NMR (200MHz) : δ 10.37 (s, 1H), 8.60 (s, 1H), 8.13 (d, *J* = 8.3Hz, 1H), 8.06 (d, *J* = 15.04Hz, 1H), 7.88 (m, 3H), 7.64 (m, 2H), 6.27 (d, *J* =15.14Hz, 1H), 4.29 (q, *J* =7.32, 2H), 1.36 (t, *J* = 7.34, 3H)

2-Ethyl-5- (3-formyl-quinolin-2-yl)-penta-2, 4-dienoic acid ethyl ester [13c]



13c

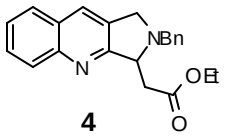
Molecular Formula : $C_{19}H_{19}NO_3$, 304.37

Yield : 70%

IR : 3020, 1707, 1640, 1371, 1297, 1273 cm^{-1}.

^{1}H NMR (200MHz) : δ: 10.39 (s, 1H), 8.60 (s, 1H), 8.20 (d, *J* = 15.14Hz, 1H) 8.08 (d, *J* = 8.3Hz, 1H), 8.03 (s, 1H), 7.96 (m, 2H), 7.65 (m, 1H), 7.4 (m, 1H), 4.33 (q, *J* =7.32, 2H), 2.70 (q, 2H), 1.39 (t, *J* = 7.34, 3H), 1.19 (t, J =7.34, 3H).

3. (2-Benzyl-2, 3-dihydro-1*H*-pyrrolo [3,4-*b*] quinoline-3-yl)-acetic acid ethyl ester [4]



4

Quinoline aldehyde **13a** (1.27 g, 5 mmol) and benzylamine (0.375 g, 6 mmol) were mixed in MeOH (40 mL) at rt and stirred for 1h. The aldimine in MeOH was cooled 0°C, treated with solid $NaBH_4$ (0.6 g, 16 mmol) .The reaction mixture was stirred for 10 min and it was brought to room temperature and allowed to stir for 1h after which methanol was removed under reduced pressure and added water and extracted with $CHCl_3$ (2×30 mL). The combined organic extract was washed with saturated aqueous NaCl and dried (Na_2SO_4). The solvent was evaporated to give the crude product, which was purified by column chromatography (SiO_2) using ethylacetate: pet ether [1:4] as eluent to furnish pure amine **4**.

Molecular Formula : $C_{22}H_{22}N_2O_2$, 346.43

Yield : 1.66g, 92%.

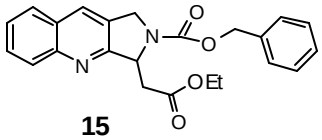
IR ($CHCl_3$) : 3225, 2140, 1770 cm^{-1}.

^{1}H NMR (200MHz) : 8.08 (d, *J* = 8.3 Hz, 1H), 7.85 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.66 (t, *J* = 6.83 Hz, 1H), 7.53-7.26 (m, 6H), 4.62 (t, *J* = 5.37,1H), 4.37-4.12 (4H), 3.79 (d, *J* = 13.79Hz, 2H), 3.34 (dd, *J* = 4.88Hz, 15.63Hz, 1H) 2.99 (dd, J = 4.86Hz, 15.63Hz, 1H), 1.22 (t, *J* = 6.84, 3H)

^{13}C NMR (200MHz) : δ: 171.43 (C), 163.75 (C), 147.35 (C), 138.28 (C), 130.59 (C), 128.57 (CH), 128.31 (CH), 128.09 (2CH), 127.95 (2CH), 127.25 (CH), 126.73 (CH), 125.45 (CH), 64.72 (CH), 59.80 (CH_2), 58.07 (CH_2), 55.02 (CH_2), 38.43 (CH_2), 13.74 (CH_3)

Mass m/z, (%) : 346 (12, M^+), 287 (5), 259 (80), 255 (70), 209 (30), 181 (25), 142 (20), 91 (100).

4. 3-Ethoxycarbonylmethyl-1, 3-dihydro-pyrrolo [3,4-*b*] quinoline-2-carboxylic acid benzyl ester [15]



15

A solution of compound **4** (0.346g, 1mmol) in ethanol was added to the flask containing the Pd / C (10%) in ethanol that was degassed and purged with the hydrogen gas. The reaction mixture was left on parr shaker over night at 60 psi. Examination of the mixture by TLC (silica gel, EtOAc-hexane, 30/70) indicated the disappearance of starting material. The catalyst was filtered from the medium and washed with EtOH (5×10 mL). The solvent was removed under reduced pressure and the residue was taken in dry DCM to which powdered K_2CO_3 was added. The solution was cooled to 0^{o}C and benzyl chloroformate was added dropwise and stirred for an hour at rt. After the completion of the carbamate formation, K_2CO_3 was filtered and washed with 5% HCl and the organic phase was dried (Na_2SO_4), concentrated to give the carbamate **15** which was purified by column chromatography using 30% ethyl acetate: pet ether as eluent.

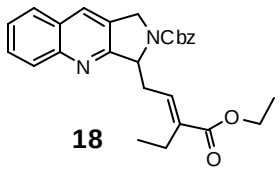
Molecular Formula : $C_{22}H_{22}N_2O_2$, 346.43

Yield : 1.66g, 92%.

IR ($CHCl_3$) : 3225, 2140, 1770 cm^{-1}.

^{1}H NMR (200MHz) : δ: 8.18 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.66 (t, *J* = 6.83 Hz, 1H), 7.51 (t, 6.83Hz, 1H), 7.53-7.26 (m, 5H), 5.5 (t, 1H), 5.3-4.12 (AB q, 2H), 4.89 (m,2H), 4.37 (q, *J*=6.84, 2H), 3.34 -99 (m, 2H), 1.22 (t, *J* = 6.84, 3H)

5. 3-(3-Ethoxycarbonyl-pent-2-enyl)-1,3-dihydro-pyrrolo [3,4-b] quinoline-2-carboxylic acid benzyl ester [18]



18

To 25 mL flame-dried, two-neck flask equipped with an N_2 inlet was added a solution of the starting ester **15** (1.73g, 5 mmol) in 25 mL of dry CH_2Cl_2. After the mixture was cooled to -78 ^oC, DIBAL-H (2.0 M in toluene, 2.75 mL, 5.5 mmol, 1.1 equiv) was added drop wise. After being stirred for 2h. The reaction was quenched by adding MeOH (2.75 mL) followed by 2.75mL of water. And the mixture was warmed to 0^oC. The reaction mixture was stirred for 30 min, allowed to warm to room temperature, and then filtered through Celite bed and extracted with CH_2Cl_2 (3×25mL). The combined CH_2Cl_2 extracts were washed with brine, dried (Na2SO4) and concentrated to afford aldehyde **16**, which was subjected for Wittig olefination (with out purification). The mixture of aldehyde **16** (1.5g) and Wittig reagent **19** (2.25g, 6 mmol, 1.2 equiv) in dry dichloromethane (20 mL) was stirred for 12h. The solution was concentrated to about 4 mL and loaded to a silica gel column. Elution with ethylacetate -petroleum ether gave the pure product **18.**

Molecular Formula : $C_{27}H_{28}N_2O_4$, 444

Yield : 1.42 g, 80%.

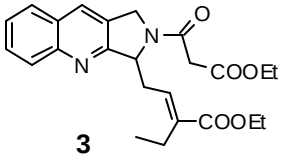
IR (KBr) : 3400, 2900, 1705,1680, 1500 cm^{-1}.

^{1}H NMR (200MHz) : δ: 8.20 (m, 2H), 7.85 (d, 1H), 7.75 (t, *J* = 8.3 Hz, 1H), 7.60(t, *J* = 6.83 Hz, 1H), 7.53-7.26 (m, 5H), 6.45(t, 1H), 5.5-5.25 (m, 2H), 5.2-4.7 (m, 3H), 4.15 (q, 2H), 3.1-3.4 (m, 2H), 2.22 (m, 2H), 1.22 (t, *J*=6.84, 3H), 0.8 (m, 3H)

^{13}C NMR (50MHz) : δ: (for major isomer) 167.3 (C), 161.4 (C), 154.8 (C), 148.0 (C), 141.4 (C), 136.9 (C), 136.4 (C), 136.2 (C), 135.0 (CH), 134.8 (CH), 129.6 (CH), 128.4 (CH), 128.2 (CH), 128 (CH), 127.3 (CH), 127.1 (CH), 126.7 (CH), 126.4 (CH), 67.3 (CH_2), 64.6 (CH_2), 62.4 (CH), 61.9 (CH), 59.12 (CH_2), 50.16 (CH_2), 31.8 (CH_2), 19.93 (CH_2), 13.55 (CH_3)

Mass, *m/z*, (%) : 444 (5, M^+), 399 (25), 325 (15), 303 (30), 325 (15), 169 (12), 91 (100).

6. 4-[2-(2-Ethoxycarbonyl-acetyl)-2,3-dihydro-1*H*-pyrrolo [3,4-*b*] quinoline-3-yl]-2-ethyl-but-2-enoic acid ethyl ester [3]



3

To a stirred solution of NaI (5.02 g, 33mol) and urethane **18** (1.5g, 3.37mmol) **in** dry acetonitrile (25 mL) was added TMSCl (3.67g, 33 mmol) dropwise under nitrogen atmosphere and stirred for 1h, quenched with thiosulphate solution (20%) and the aqueous phase was extracted with ethylacetate (3×50mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to furnish crude amine which was treated with carbethoxy acetyl chloride (0.602 g) in DCM (10mL) in the presence of K_2CO_3 (1.04g, 8.0mmol). The mixture was stirred for an additional 2h at the end of which the K_2CO_3 was filtered and washed with DCM. The combined organic phase was washed with 10% HCl and 10% $NaHCO_3$ solutions, dried ($Na_{2S}O_4$), concentrated and purified by column chromatography over silica gel using 60% ethylacetate -pet ether as eluent to furnish amide **3** as a colourless oil.

Molecular formula : $C_{24}H_{28}N_2O_5$

Yield : 0.943 g, 66%.

IR (Neat) : 1710, 1640,1400, 1030 cm^{-1};

^{1}H NMR (200MHz) : δ: 8.18 (d, *J* = 8.2 Hz, 1H), 8.00 (s, 1H), 7.8 (d, 8.2Hz 1H), 7.75 (t, 1H), 7.55 (t, 1H), 6.65 (t, 1H), 5.6 (m, 1H), 5.3 - 4.75 (m, 3H), 4.25 (q, 2H), 4.11(q, 2H), 3.55 (s, 2H), 3.4 (m, 1H), 3.2 (m, 1H), 2.2 (m, 2H), 1.3 (t, 3H), 1.2 (t, 3H), 0.8 (t, 3H);

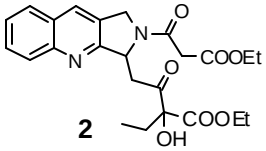
^{13}C NMR (50MHz) : δ: 167.5 (C), 167.1 (C), 165.4 (C), 165.2 (C), 160.9 (C), 148.6 (C), 138.1 (C), 137.3 (C), 134.8 (CH), 133.1 (CH), 129.7 (CH), 129.1 (CH), 127.7 (C), 127.5 (C), 126.7 (CH), 62.6 (CH), 60.2 (CH2), 51.2 (CH_2), 50.1 (CH_2), 42.4 (CH_2), 34.6 (CH_2), 20.0 (CH_2), 14.1 (CH_3), 13 (CH_3);

MS *m/z* (%) : 424 (4), 379 (5), 309 (5), 283 (20), 265 (5), 169 (100), 140 (20), 115 (20),

Anal. : Calcd for $C_{24}H_{28}N_2O_3$: C, 67.6; H, 6.6; N, 6.59;

Found : C, 67.39; H, 6.5; N, 6.47;

7. 4-[2-(2-Ethoxycarbonyl-acetyl}-2,3-dihydro-1*H*-pyrrolo [3,4-*b*] quinoline-3-yl]-2-ethyl-2-hydroxy-3-oxo-butyric acid ethyl ester [2]



2

To a stirred solution of olefin **3** (0.848 g 2mmol) and AcOH (0.7mL) in 10mL of aqueous acetone (1:9 of H_2O: Acetone) maintained at –10°C using an ice-salt bath was added $KMnO_4$ (0.555g, 3.4 mmol) in portions such that the reaction temperature remains below -10°C. After stirring for 1/2 h at 10°C, the black ppt of MnO_2 is filtered off through celite pad and filtrate was evaporated at reduced pressure to remove acetone and extracted with CH_2Cl_2 (3×50mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to furnish crude ketol **2**. Purification by column chromatography over silica gel using 60% ethylacetate – pet ether as eluent to furnish ketol **2** as colourless oil.

Molecular Formula : $C_{24}H_{28}N_2O_7$, 456.43

Yield : 0.828 g, 90%.

IR($CHCl_3$) : 3485, 2140, 1744 cm^{-1}

^{1}H NMR (200MHz, $CDCl_3$) : δ: 8.08 (m, 2H), 7.78 (d, 7.56Hz, 1H), 7.67 (t, *J* = 8.3 Hz, 1H), 7.56 (t, *J* = 6.83 Hz, 1H), 5.5 (m, 1H), 5.12 (AB, *J* = 12Hz, 2H), 4.25-3.9 (m, 6H), 3.7-3.5 (m, 1H), 3.5 (s, 2H), 2.1-1.9 (m, 2H), 1.4 (m, 6H), 0.82 (m, 3H).

^{13}C NMR (50MHz, $CDCl_3$) : δ: 204.80 (C), 170.21 (C), 166.79 C), 165.06 (C), 160.65 (C), 147.64 (C), 129.11 (2 CH), 128.34 (2C), 127.61 (C), 127.24 (CH),

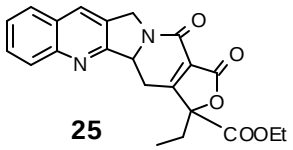
126.21 (CH), 84.16 (C), 62.15 (CH_2), 61.18 (CH_2), 59.20 (CH), 51.09 (CH_2), 41.85 (CH_2), 39.31 (CH_2), 28.06 (CH_2), 13.71 (CH_3), 13.44 (CH_3), 6.93 (CH_3)

Mass, *m*/*z*, (%) : 456 (4, M^+), 411 (6), 325 (23), 283 (70), 209 (20), 183 (21), 169 (100), 115 (18).

Anal. : Calcd for $C_{24}H_{28}N_2O_3$: C, 63.15; H, 6.18; N, 6.14;

Found : C, 63.01; H, 6.05; N, 5.98;

8. Dihydro pyridone [25]



25

To a precooled solution of NaH (0.288g, 50% suspension in mineral oil, 6 mmol) (pre washed with pet ether, 2 x 5mL) in THF (15 mL) was added ketol **2** (1.368g, 3mmol) in THF through syringe, with out allowing the temperature to rise beyond 10°C. The reaction mixture was allowed to rise to room temperature and stirred for 1h., quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3×25mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography over silica gel using 60% ethylacetate–pet ether as eluent furnished dihydropyridone **25** as a yellow solid.

Molecular Formula : $C_{22}H_{20}N_2O_5$, 392.43

Yield : 1.074g, 90%,

M. P. : 220°C.

IR ($CHCl_3$) : 2856, 1785, 1680,1650, 1410, 1460, 1377 cm^{-1}:

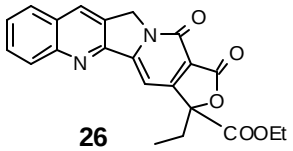
^{1}H NMR (200MHz) : δ: 8.35 (s, 1H), 8.28 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.6Hz 1H), 7.67 (t, *J* = 7 Hz, 1H), 7.56 (t, *J* = 6.9 Hz, 1H), 5.5 (m, 1H), 5.22 (dd, 2H), 4.45 (q, 2H), 3.7-3.5 (m, 1H), 3.0-2.75 (m, 1H), 2.6-2.1 (m, 2H), 1.4 (m, 3H), 0.82 (m, 3H).

^{13}C NMR (200MHz) : δ: 172.84 (C), 167.07 (C), 165.52 (C), 158.1(C), 153.28 (C), 150.86 (C), 148.69 (C), 131.30 (CH), 130.57 (C), 128.91 (CH+1C), 128.36 (CH),

128.03 (CH), 127.90 (CH), 93.60 (CH), 86.20 (C), 62.60 (CH_2), 50.12 (CH_2), 29.23 (CH_2), 20.53 (CH_2), 13.55 (CH_3), 7.08 (CH_3)

Mass, *m*/*z*, (%) : 392 (8, M^+), 317 (100), 261 (10), 235 (30), 205 (34), 168 (60), 151 (24), 140 (25), 115 (8).

9. Pyridone [26].



26

To a solution of dihydropyridone **25** (0.396 g, 1 mmol) in 1,4-dioxan (15mL) was added DDQ (0.25g 1.1mmol) and the resultant mixture was refluxed under nitrogen for 1h, was diluted with ethylacetate and treated with $NaHCO_3$ solution. The organic layer was separated and aqueous phase was extracted with ethylacetate (3×25 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography over silica gel using 80% ethyl acetate – pet ether as eluent furnished pyridone **26** as a pale yellow solid.

Molecular Formula : $C_{22}H_{18}N_2O_5$, 390

Yield : 0.371 g, 95%

M. P. : 234^{o}C.

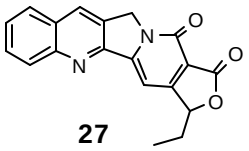
IR (Nujol) : 2856, 1788, 1681, 1446, 1215 cm^{-1}.

^{1}H NMR (200MHz) : δ: 8.49 (s, 1H), 8.28 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.4Hz 1H), 7.86 (t, *J* = 7.2Hz, 1H), 7.53 (t, *J* = 8.3 Hz, 1H), 7.44 (s, 1H) 5.38 (s, 2H), 4.25 (q, 2H), 2.5 (m, 1H), 2.25 (m, 1H), 1.4 (m, 3H), 1.02 (m, 3H)

^{13}C NMR (200MHz) : δ: 167.95 (C), 166.37 (C), 156.1 (C) 153.77 (C), 151.63 (C), 149.54 (C), 131.71 (CH + 1C), 131.20 (C), 130.31 (CH), 129.03 (CH+C), 128.55 (CH), 112.96 (CH), 94.51 (CH), 86.87 (C), 63.19 (CH_2), 50.84(CH_2), 29.97 (CH_2), 14.31 (CH_3), 7.80 (CH_3)

Mass, *m*/*z*, (%) : 390 (12, M^+), 333 (12), 317 (100), 261 (4), 205 (14), 140 (6)

10. **Decarboxylated product [27]**



27

To a solution of pyridone **26** (0.196g, 0.5 mmol) in methanol (5 mL) was added $NaBH_4$ (1.5 mmol) at 0^oC and stirred for 1 hr at room temperature. Then methanol was removed under the reduced pressure and the residue quenched with water (2 mL) and the solution was stirred for 5 min. Water (15 mL) and DCM (25 mL) were then added. The layers were separated, and the aqueous layer was extracted with DCM (2×15 mL). The combined organic extracts were washed with brine and then dried (Na_2SO_4). Evaporation of the solvent at reduced pressure and column chromatography over silica gel using 80% ethylacetate - pet ether as eluent yielded the product.

Reduction of 26 mediated by Cerium trichloride: $NaBH_4$ (0.1mmol) was added in portions to a cold solution of **26** (0.1 mmol) and $CeCl_3.7\ H_2O$ (0.24 mmol) in EtOH (50 mL). The mixture was allowed to warm to room temperature, where upon it was allowed to stir for 30 minutes and heated to 45^oC for 30 min., cooled, poured to in to sat $NaHCO_3$ – NaCl solution, and extracted with CH_2Cl_2 (3×30mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give **27.**

Molecular Formula : $C_{19}H_{14}N_2O_3$, 318.43

Yield : 89% in method A, 70% in method B

IR ($CHCl_3$) : 2856, 1754, 1661,1594, 1551 cm^{-1}:

^{1}H NMR (200MHz) : δ: 8.47 (s, 1H), 8.23 (d, 1H), 7.97 (d, 1H), 7.87 (t, *J* = 8.3 Hz, 1H), 7.72 (t, *J* = 6.83 Hz, 1H), 7.26 (s, 1H), 5.39 (s, 3H), 2.25 (m, 1H), 1.95 (m, 1H), 1.04 (t, 3H)

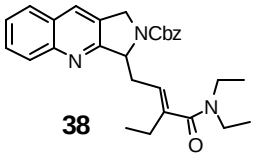
^{13}C NMR (200MHz) : δ: 166.37 (C), 153.77 (C), 151.63 (C), 149.54 (C), 131.71 (CH), 131.20 (C), 130.31 (CH), 129.036 (CH), 128.55 (CH), 112.96 (C), 94.51 (CH), 86.87 (CH_2), 63.19 (CH_2), 50.84 (CH_2), 29.97 (CH_2), 14.31 (CH_3), 7.80 (CH_3)

Mass, *m*/*z*, (%) : 318 (40, M^+), 302 (20), 289 (100), 261 (14), 233 (20) 205 (40), 177 (20), 140 (16).

Anal. : Calcd for $C_{24}H_{28}N_2O_3$: C, 71.69; H, 4.43; N, 8.80;

Found : C, 71.39; H, 4.21; N, 8.57;

11. 3-(3-Diethylcarbamoyl-pent-2-enyl)-1,3-dihydro-pyrrolo [3,4-*b*] quinoline-2-carboxylic acid benzyl ester [38]



38

The compound **18** (0.444 g, 0.1mmol) was added to 1:1 solution of 10% KOH: MeOH solution (15mL), stirred at room temperature for 2h. After the hydrolysis was completed, MeOH was removed under reduced pressure and the residue was cooled to 0^oC, neutralized with $NaHSO_4$ and was extracted with CH_2Cl_2 (3 ×25mL), dried (Na_2SO_4), filtered, and concentrated. The residue was taken in dry DCM (25mL) was added DCC (0.13mmol) and HOBT (0.1mmol) and stirred for 15 minutes to which diethyl amine was added dropwise and stirred at rt for 4 hrs. The reaction mixture was treated with 10% Na_2CO_3 solution and extracted with DCM (3×30 mL) and the combined organic layer was dried and concentrated to give thick liquid which was purified by column chromatography over silica gel using 70% ethyl acetate: pet ether as eluent to obtain the amide **38** as a thick liquid which solidified upon storage.

Molecular Formula : $C_{29}H_{33}N_3O_3$, 471.60

Yield : 0.303g, 70%

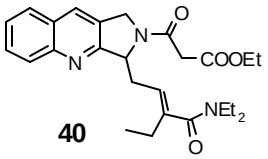
IR ($CHCl_3$) : 3225, 2140, 1650 cm^{-1}

^{1}H NMR (200MHz) : δ: 8.15 (m, 2H), 7.72 (d, 1H), 7.69 (t, *J* = 8.3 Hz, 1H), 7.53(t, *J* = 6.83 Hz, 1H), 7.48-7.29 (m, 5H) 5.45-4.56 (m, 6H), 3.5-3.25 (m, 4H), 3.0(m, 2H), 2.19 (m, 2H), 1.34 (m, 6H), 0.82 (m, 3H)

^{13}C NMR (200MHz) : δ172.19 (C), 164.99 (C), 162.01 (C), 160.65 (C), 148.67 (C), 141.83 (C), 136.76 (C), 129.63 (CH), 129.30 (CH), 128.74 (2 CH), 128.30 (C+CH), 127.90 (CH), 127.3 (CH), 127.72 (C), 126.69 (CH), 122.09 (CH), 67.52 (CH_2), 61.18 (CH), 50.67 (CH_2), 42.44 (CH_2), 37.35 (CH_2), 22.25 (CH_2) 14.10 (CH_3), 13.36 (CH_3), 12.66 (CH_3).

Mass, *m/z*, (%) : 471 (4, M^+), 303 (30), 259 (90), 168 (51), 140 (48), 100 (50).

13. 3-[3-(3-Diethylcarbamoyl-pent-2-enyl)-1,3-dihydro-pyrrolo [3,4-*b*] quinoline-2-yl]-3-oxo-propionic acid ethyl ester [40]



40

Compound **40** was made by following the same procedure employed for ester counter compound **4** *i.e* deprotection by TMSCl/ NaI and converting thus formed amino compound to amide by treating with carbethoxy acetyl chloride**.**

Molecular Formula : $C_{26}H_{33}N_3O_4$, 451.43

Yield : 60%.

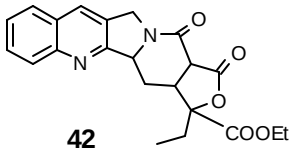
IR : 3225, 2140 , 1740 cm^{-1}

^{1}H NMR (200MHz) : δ: 8.05 (m, 2H), 7.71 (d, *J* = 8.1Hz, 1H), 7.67 (t, *J* = 8.3 Hz, 1H), 7.53(t, *J* = 6.83 Hz, 1H), 5.54 (m, 1H), 5.48-4.56 (m, 3H), 4.25 (q, 2H), 3.7-3.55 (s, 2H), 3.4-2.65 (m, 6H), 2.19 (m, 2H), 1.4 (m, 3H), 0.82 (m, 9H)

^{13}C NMR (200MHz) : δ: 172.19 (C), 168.99 (C), 164.09 (C), 162.01 (C), 65 (C), 148.60 (C), 141.82 (C), 129.63 (CH), 129.30 (CH), 128.74 (CH), 128.30 (CH), 127.90 (CH), 127.72 (C), 126.69 (CH), 122.09 (CH), 121.68 (CH), 61.25 (CH), 61.18 (CH_2), 50.46 (CH_2), 41.69 (CH_2), 31.26 (CH_2), 22.87 (2 CH_2), 14.10 (CH_3), 13.36 (CH_3), 12.66 (CH_3).

Mass, *m*/*z*, (%) : 451 (4, M^+), 411 (6), 325 (23), 283 (70), 209 (20), 183 (21), 169 (100), 115 (18)

14. Tetrahydropyridone, Gillbert Stork's intermediate [42]



42

A solution of compound **25** (0.039g) in ethanol was added to the flask containing the Pd/C (10mol%) in ethanol that was degassed and purged with the hydrogen gas. The reaction mixture was left on parr shaker over night at 100 psi. Examination of the mixture by TLC

indicated the disappearance of starting material and the appearance of a new component. The catalyst was filtered from the medium and washed with EtOH (5×10 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel using ethylacetate as eluent to give the tetrahydro pyridone derivative.

Molecular Formula : $C_{22}H_{22}N_2O_5$, 394.

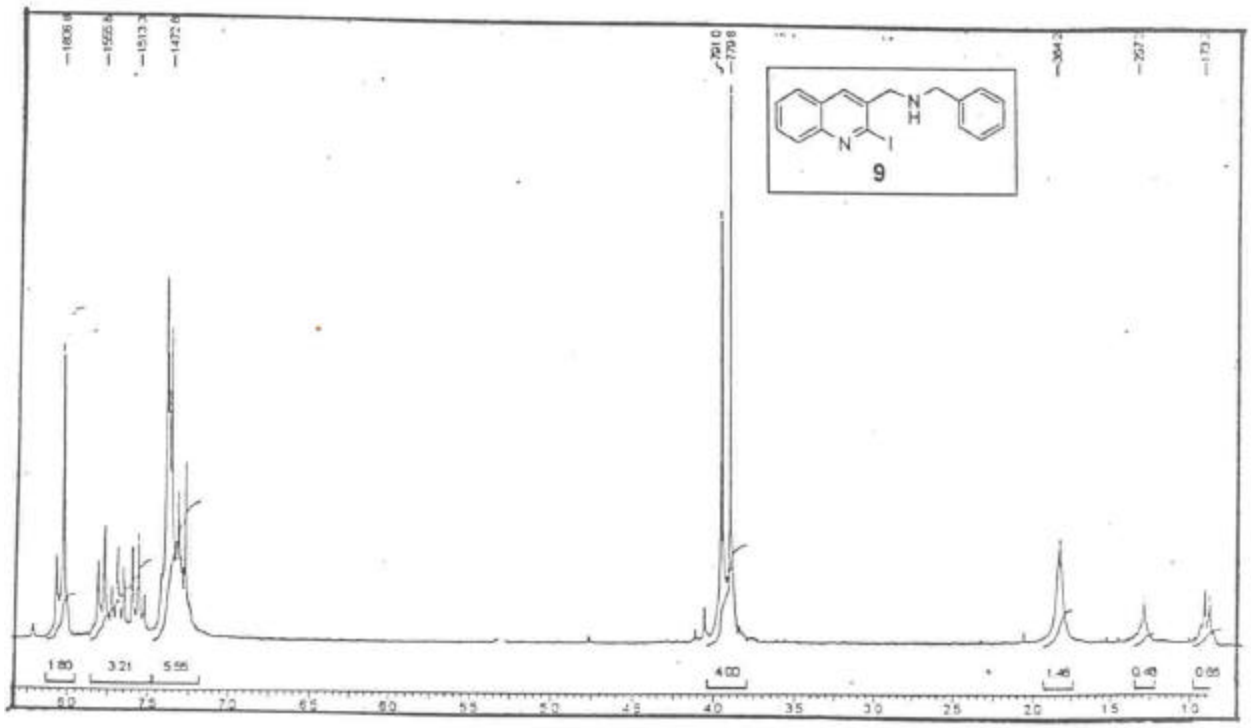
Yield : 0.031g, 80%.

IR ($CHCl_3$) : 2856, 1785, 1680,1460, 1377 cm^{-1}

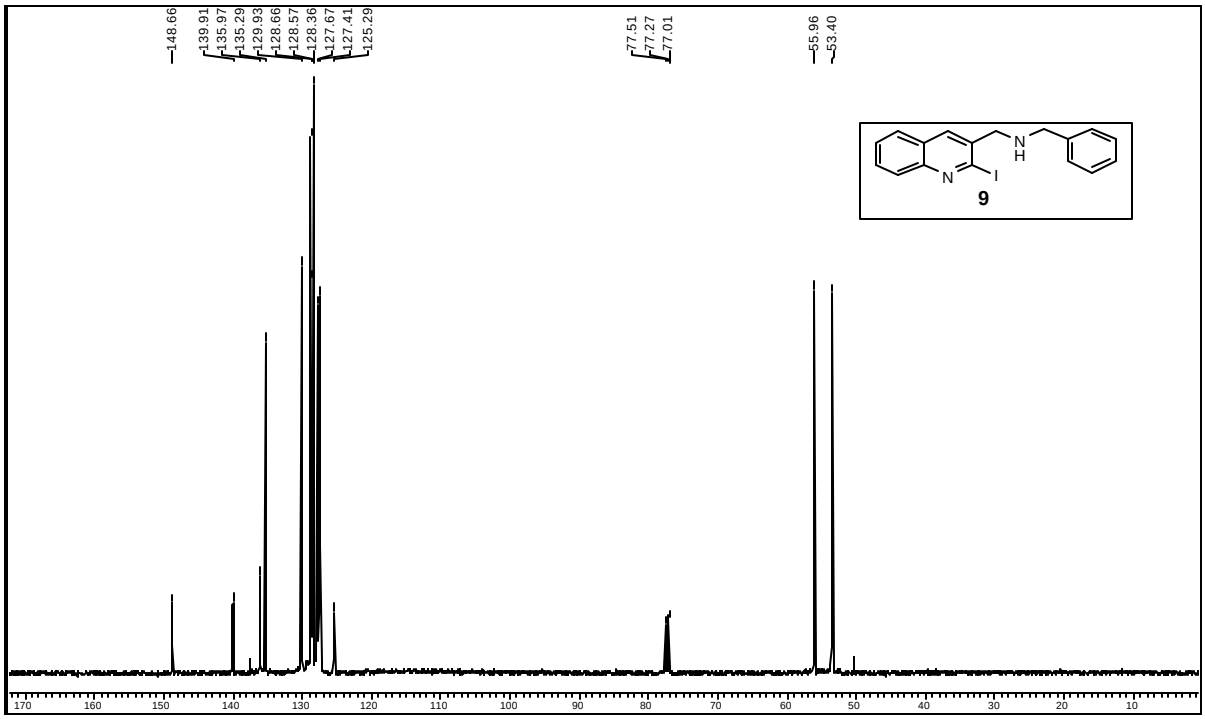
^{1}H NMR (200MHz) : δ: 8.10 (s, 1H), 8.05 (d, 1H), 7.78 (d, 1H), 7.71 (t, *J* = 8.3 Hz, 1H), 7.63 (t, *J* = 6.83 Hz, 1H), 5.35 (d, 1H), 4.95 (dd, 2H), 4.35 (q, 2H), 3.81 (d, 1H), 3.19 (m, 2H), 2.81 (m, 1H), 2.25 (m, 1H), 1.95 (m, 1H) 1.4 (m, 3H), 1.08 (m, 3H)

^{13}C NMR (200MHz) : δ: 173.81 (C), 169.63 (C), 165.81 (C), 161.54 (C), 148.1. (C), 130.10 (CH), 129.3 (C), 129.04 (CH), 128.96 (CH), 127.73 (CH), 127.6(CH), 126.5 (C), 77.09 (CH) , 61.4 (CH_2), 59.03(CH), 52.02(CH), 48.2(CH_2), 35.6(CH), 28.73 (CH_2), 21.3(CH_2), 14.12 (CH_3), 7.08 (CH_3)

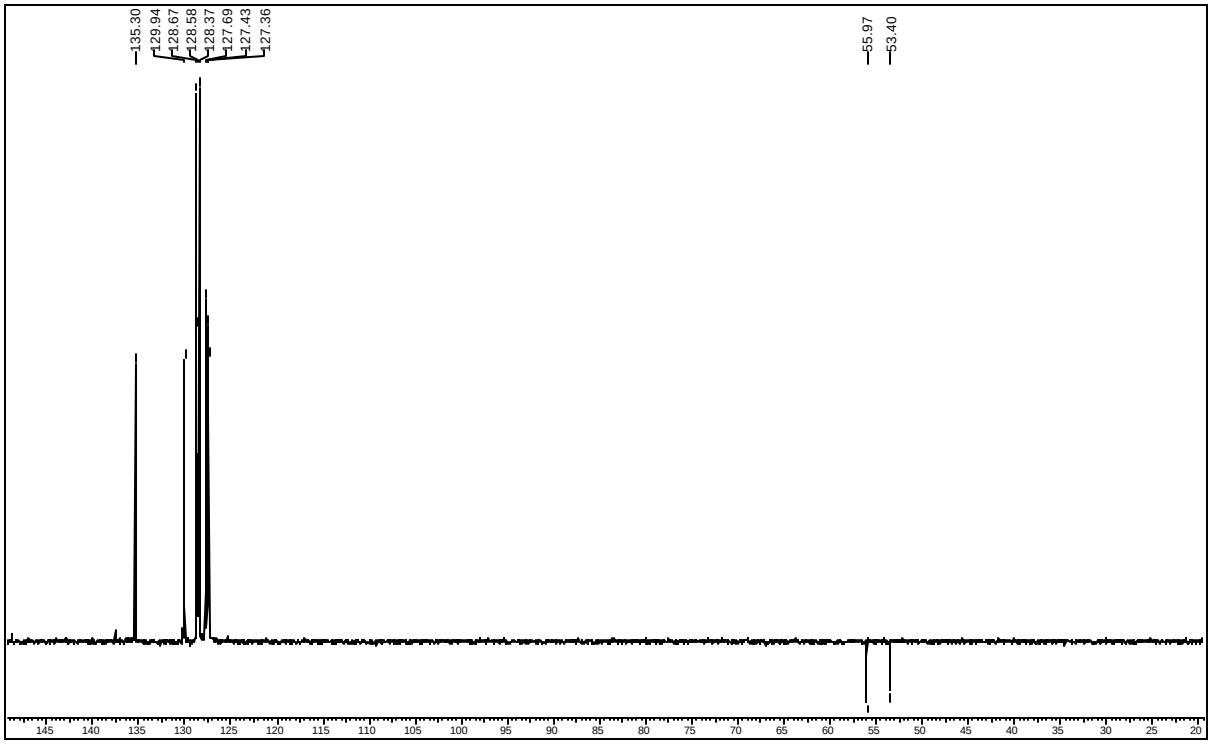
Mass, *m*/*z*, (%) : 394 (8, M^+), 321 (10), 235 (15), 235 (30), 205 (14), 168 (30), 144 (25), 111 (18), 69 (60)

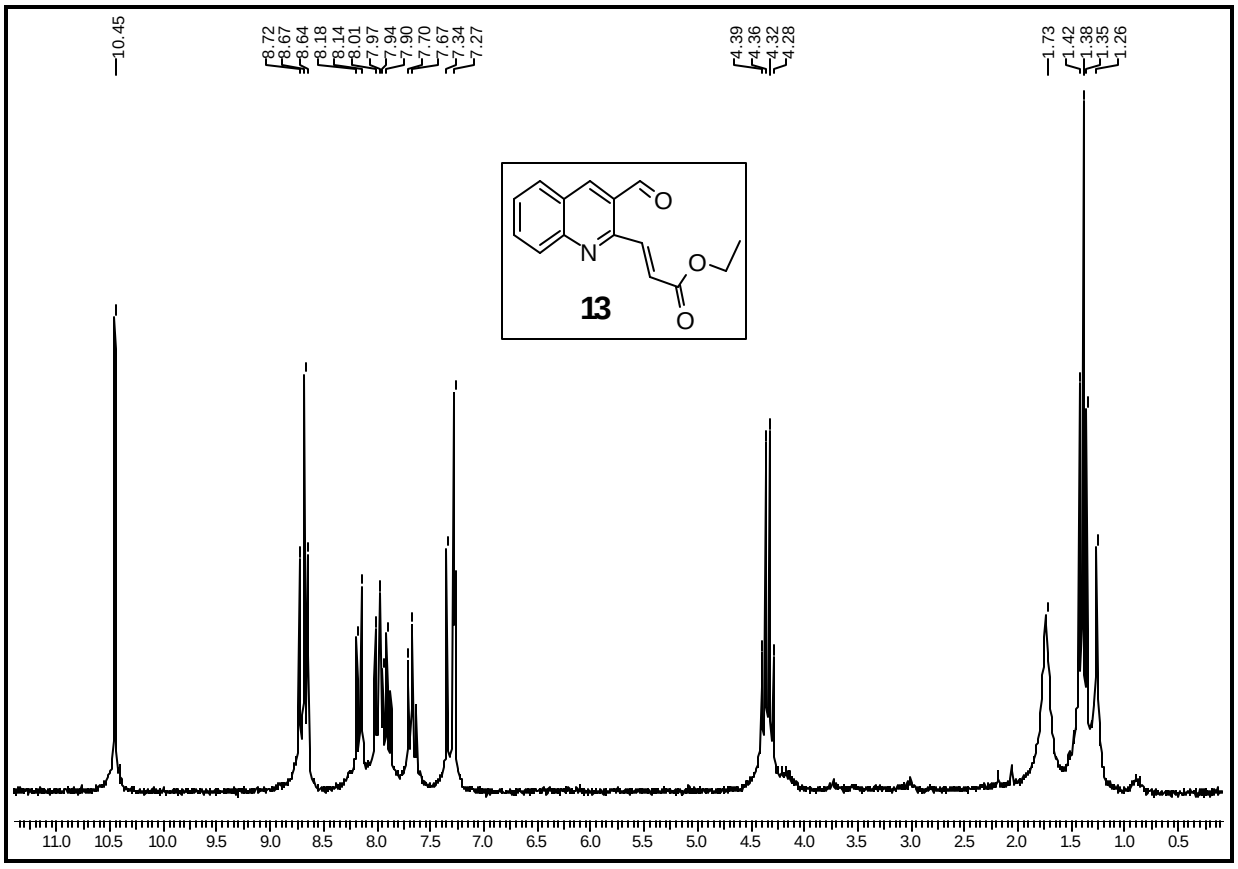


^{1}H-NMR spectrum of compound [9]. ($CDCl_3$, 200 MHz)

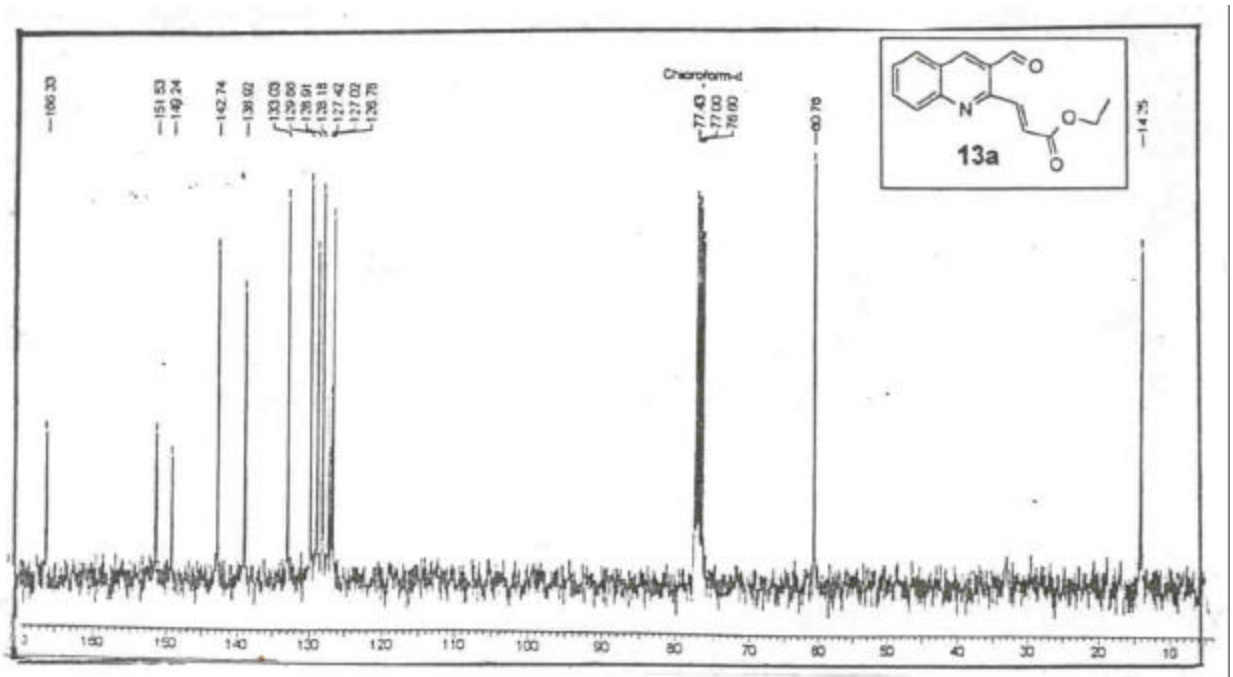


^{13}C & DEPT NMR spectra of compound [9] (50MHz, $CDCl_3$)

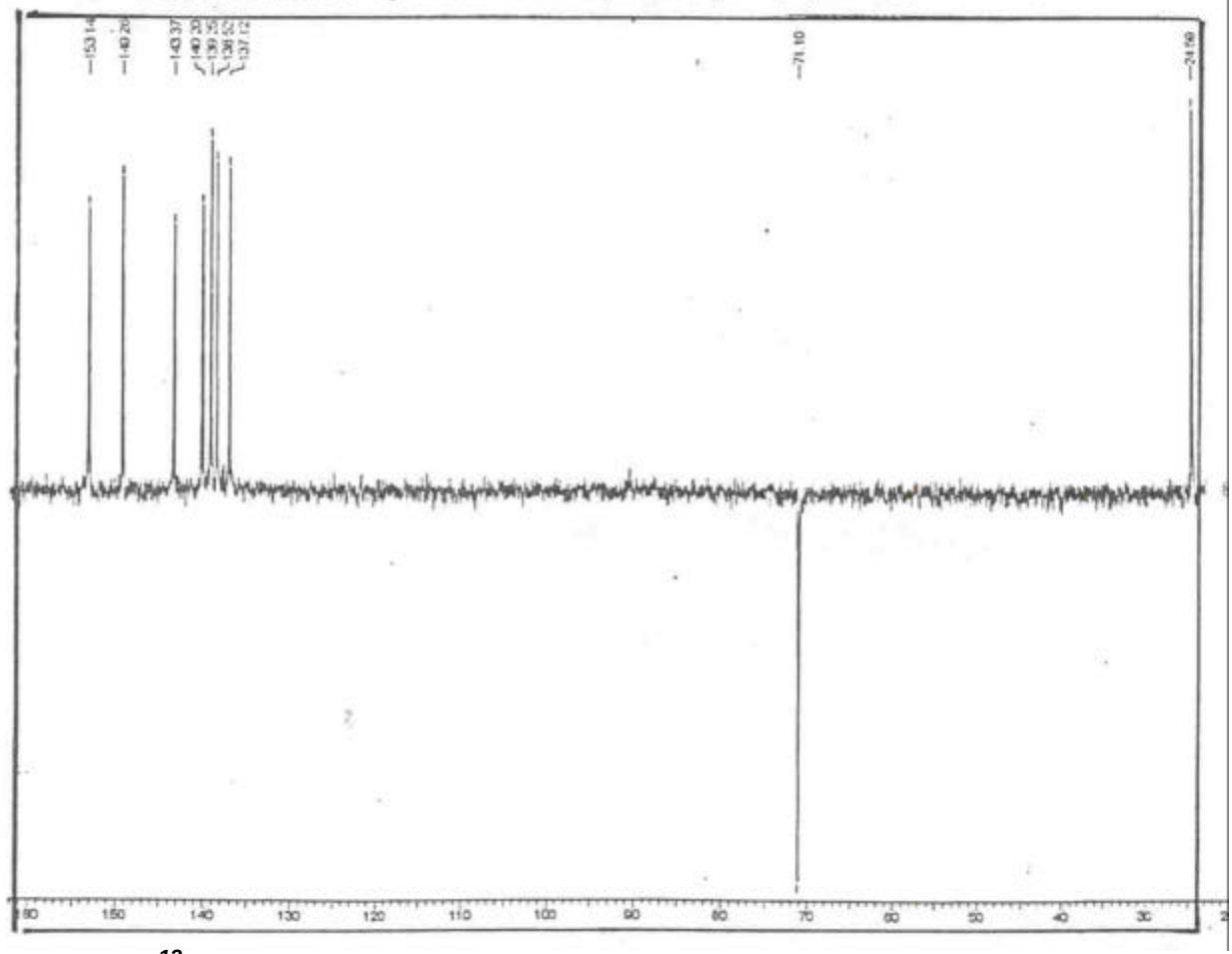




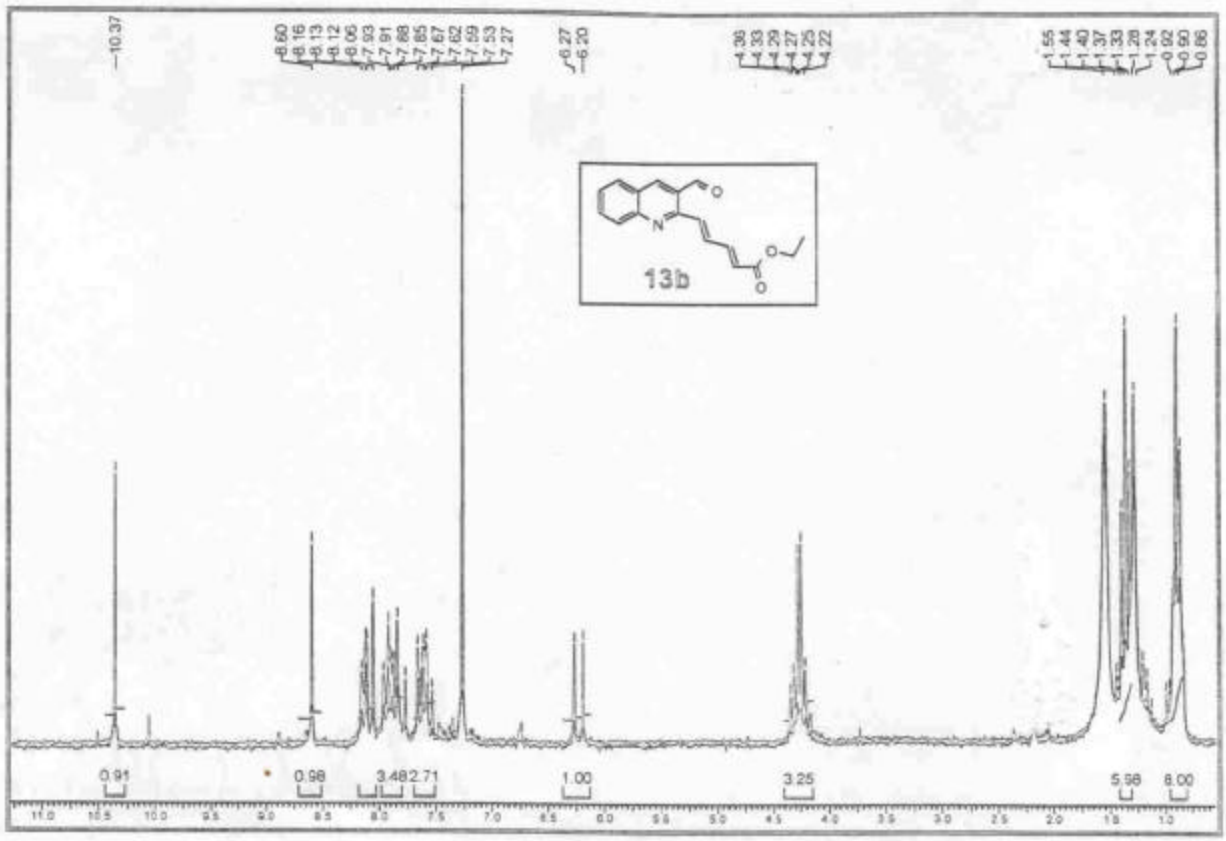
^{1}H NMR spectrum of compound [13a] (200MHz, $CDCl_3$)



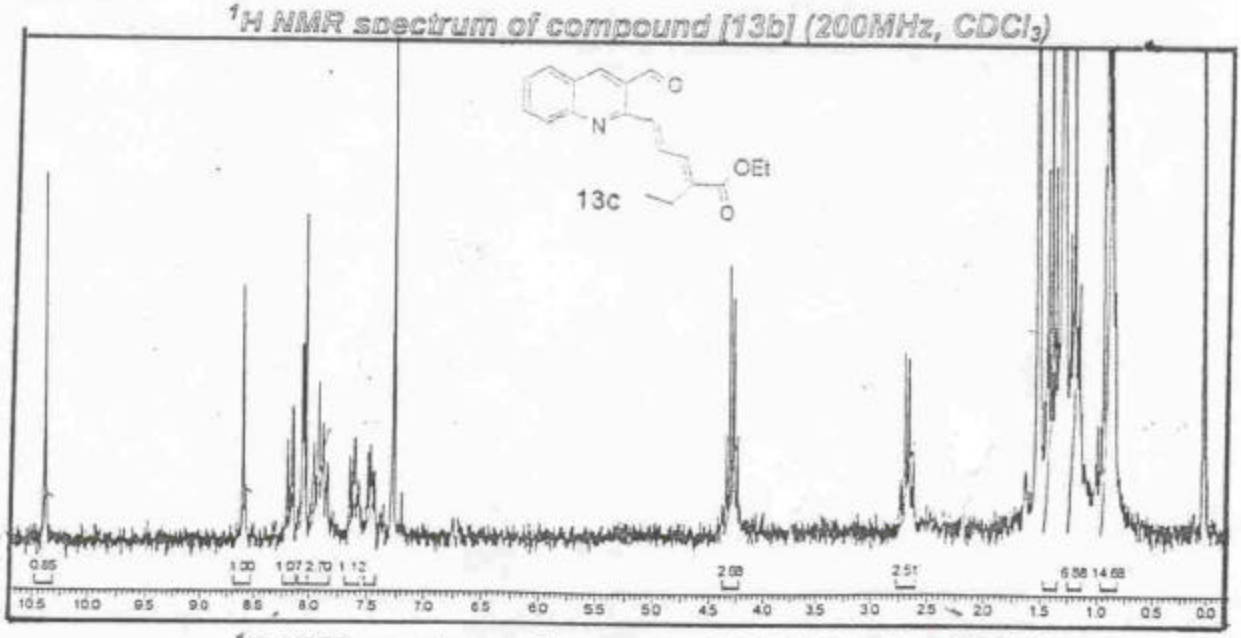
^{13}C-NMR & DEPT spectra of compound **[13a]. ($CDCl_3$, 50 MHz)**



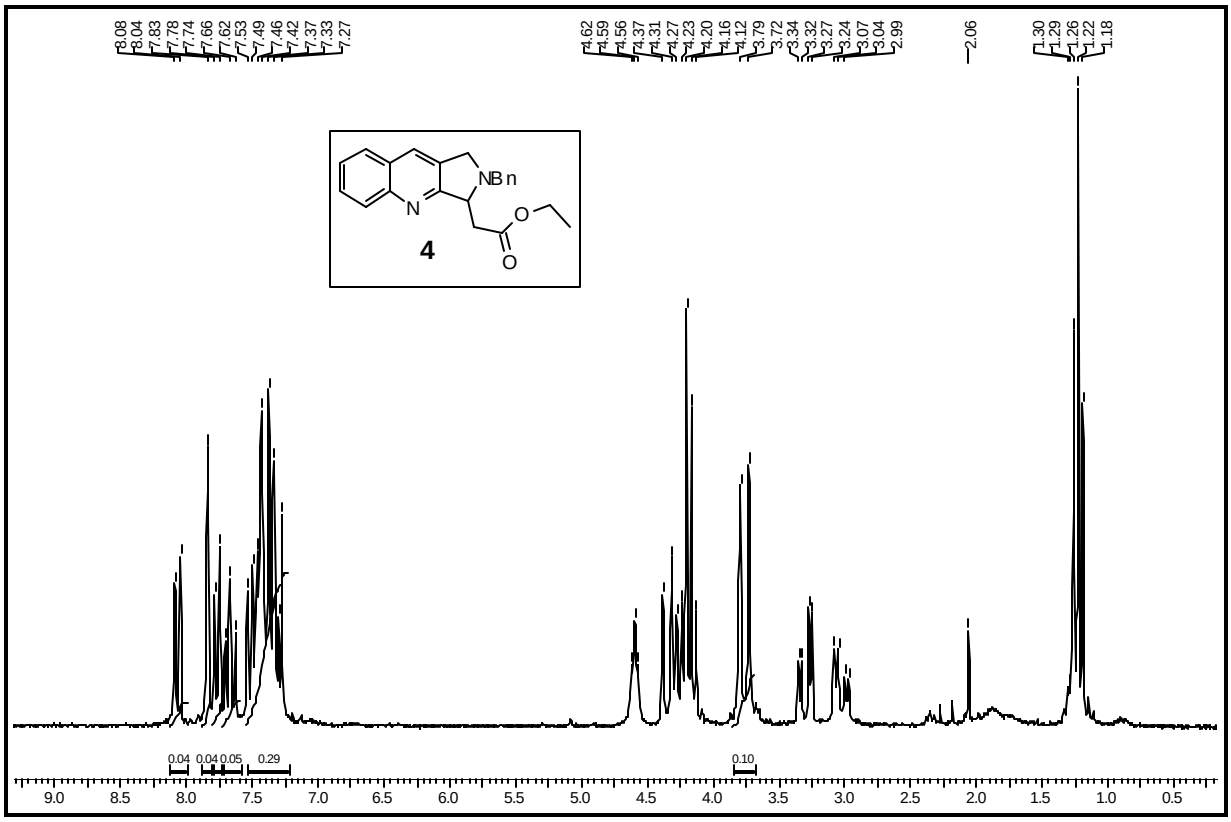
^{13}C & DEPT NMR spectra of compound [13a] **(50MHz, $CDCl_3$)**



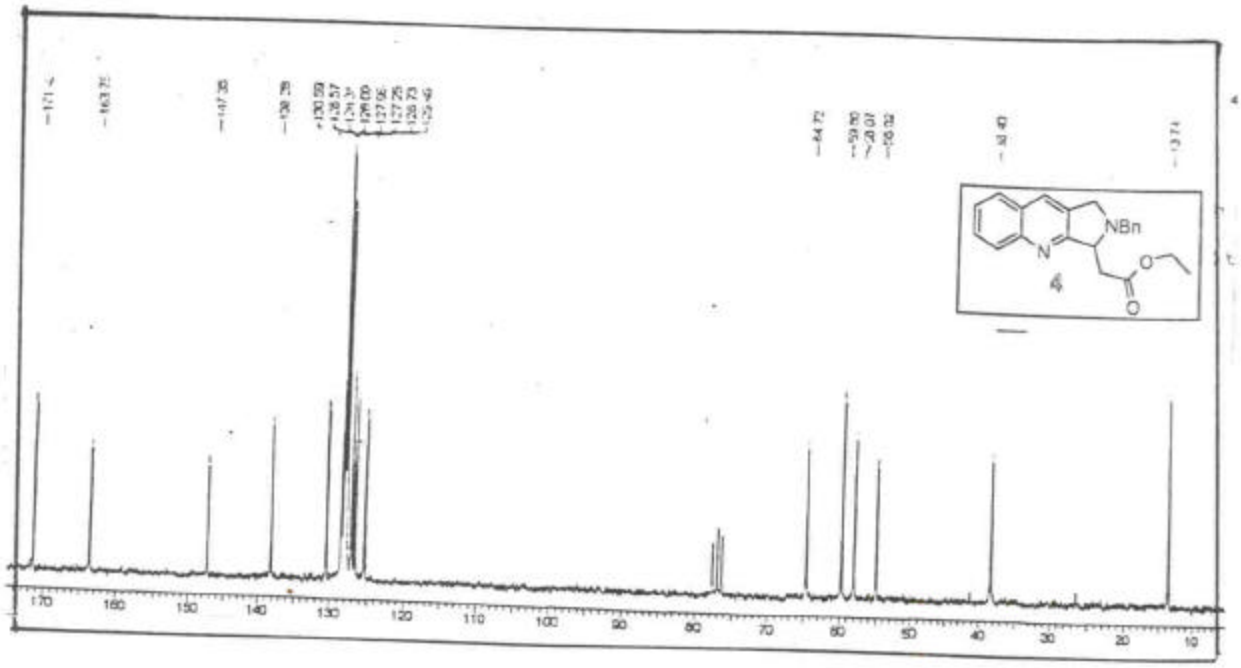
^1H NMR spectrum of compound [13b] (200MHz, $CDCl_3$)



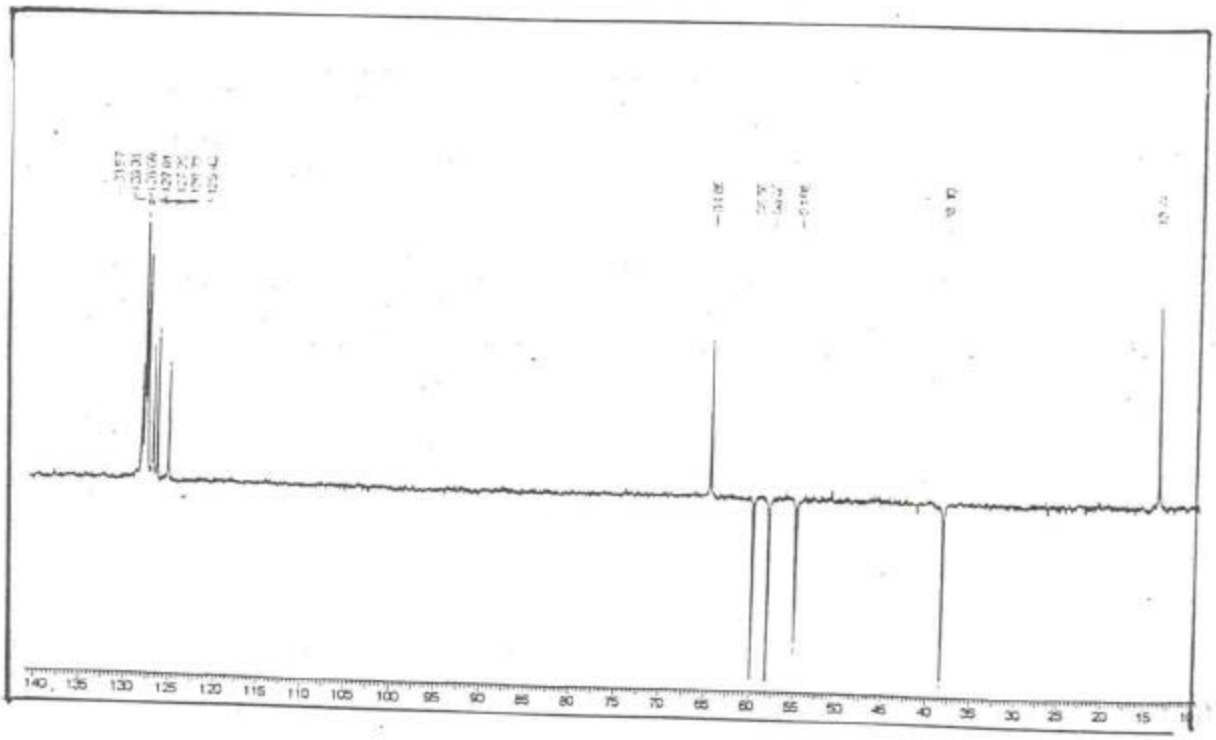
^1H NMR spectrum of compound [13c] (200MHz, $CDCl_3$)

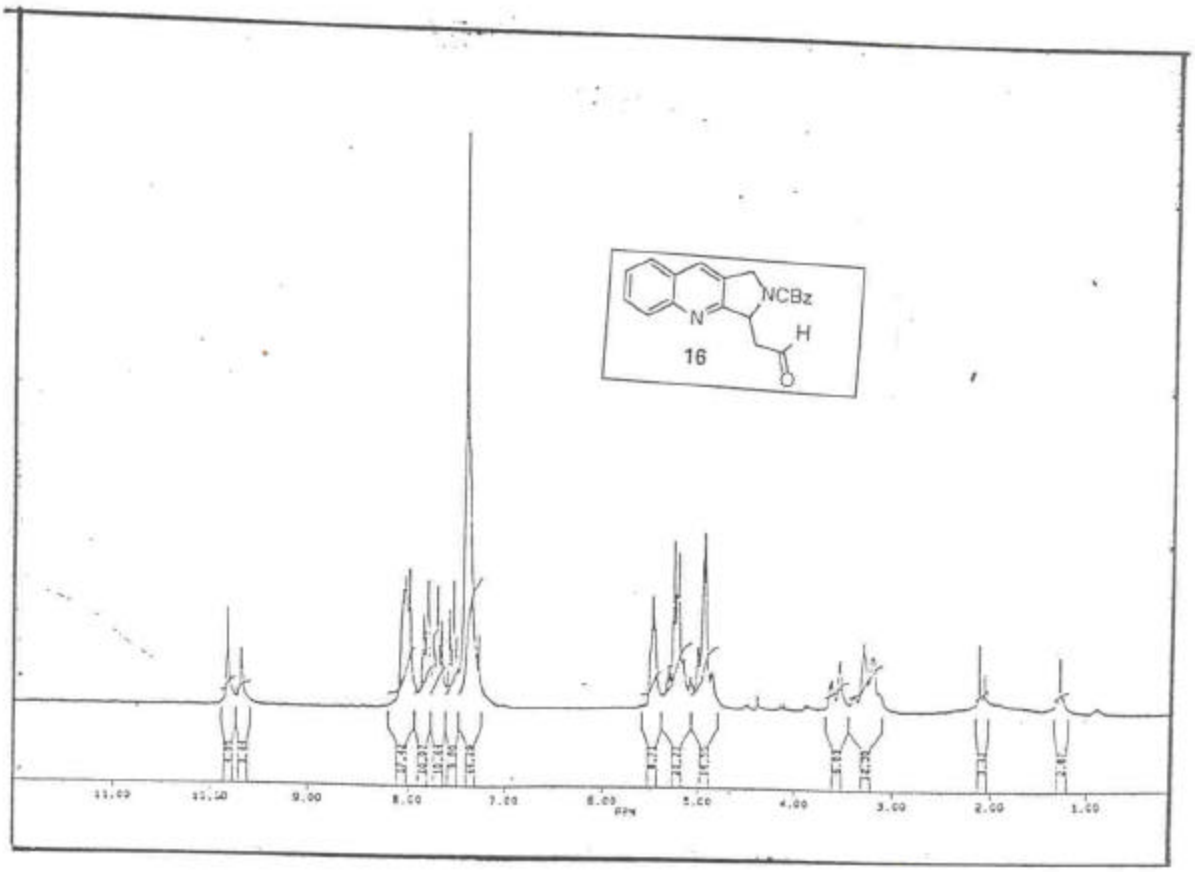


^{1}H NMR spectrum of compound [4] **(200MHz, $CDCl_3$)**

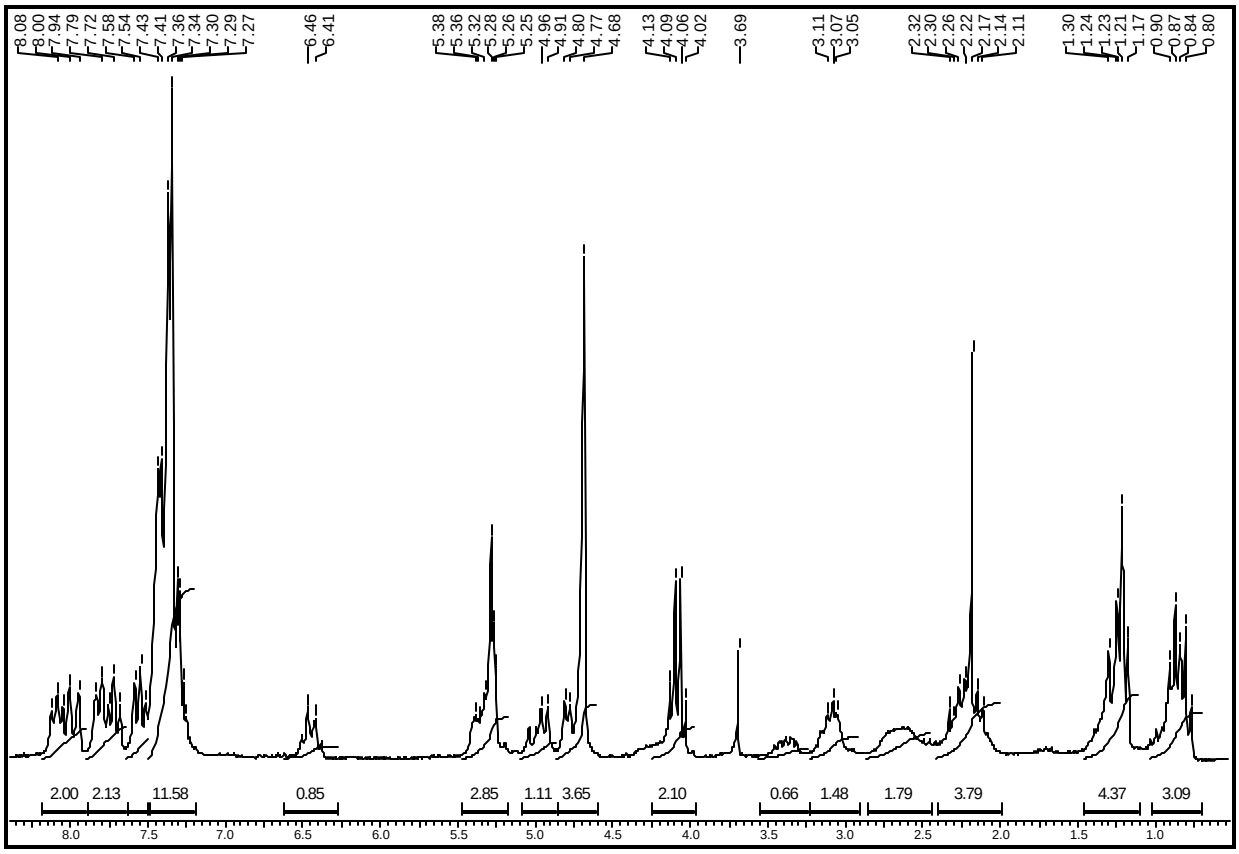


^{13}C & DEPT NMR spectra of compound [4] (50MHz, $CDCl_3$)

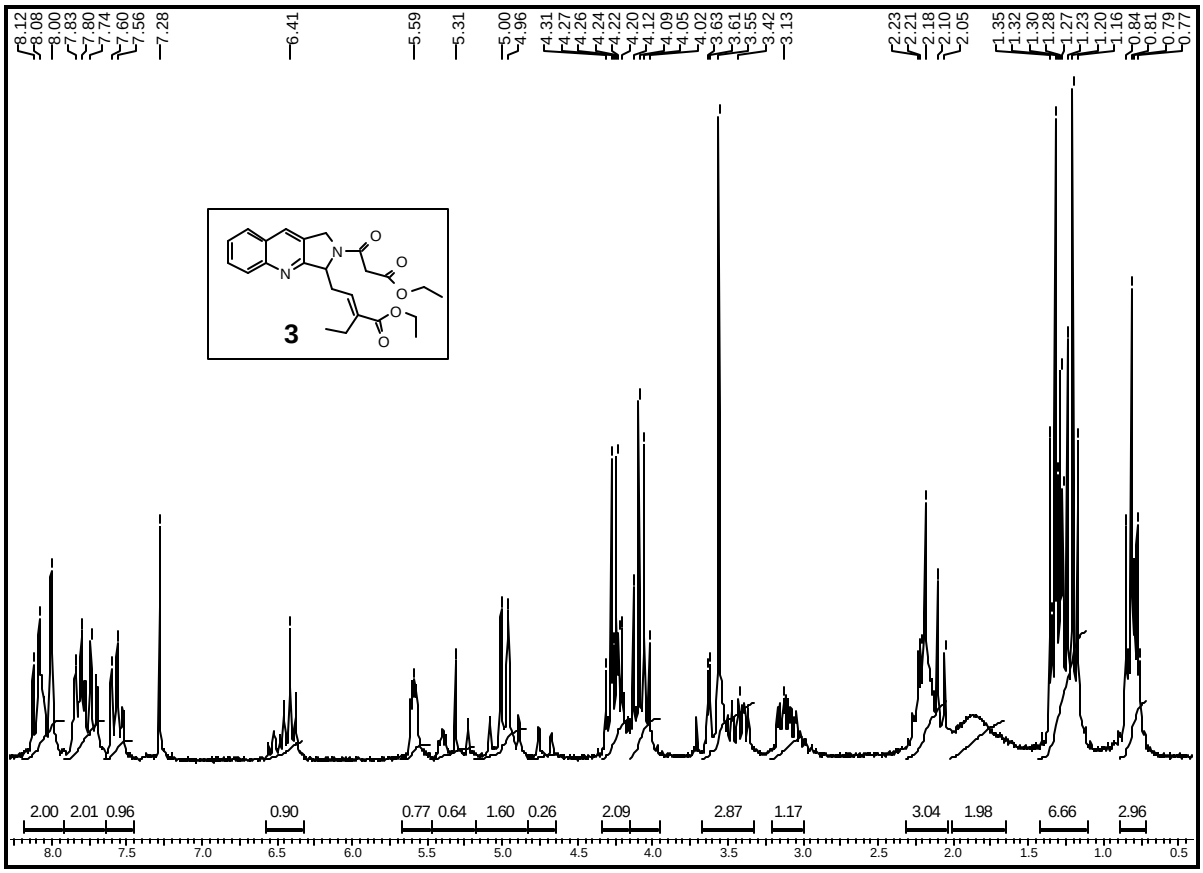




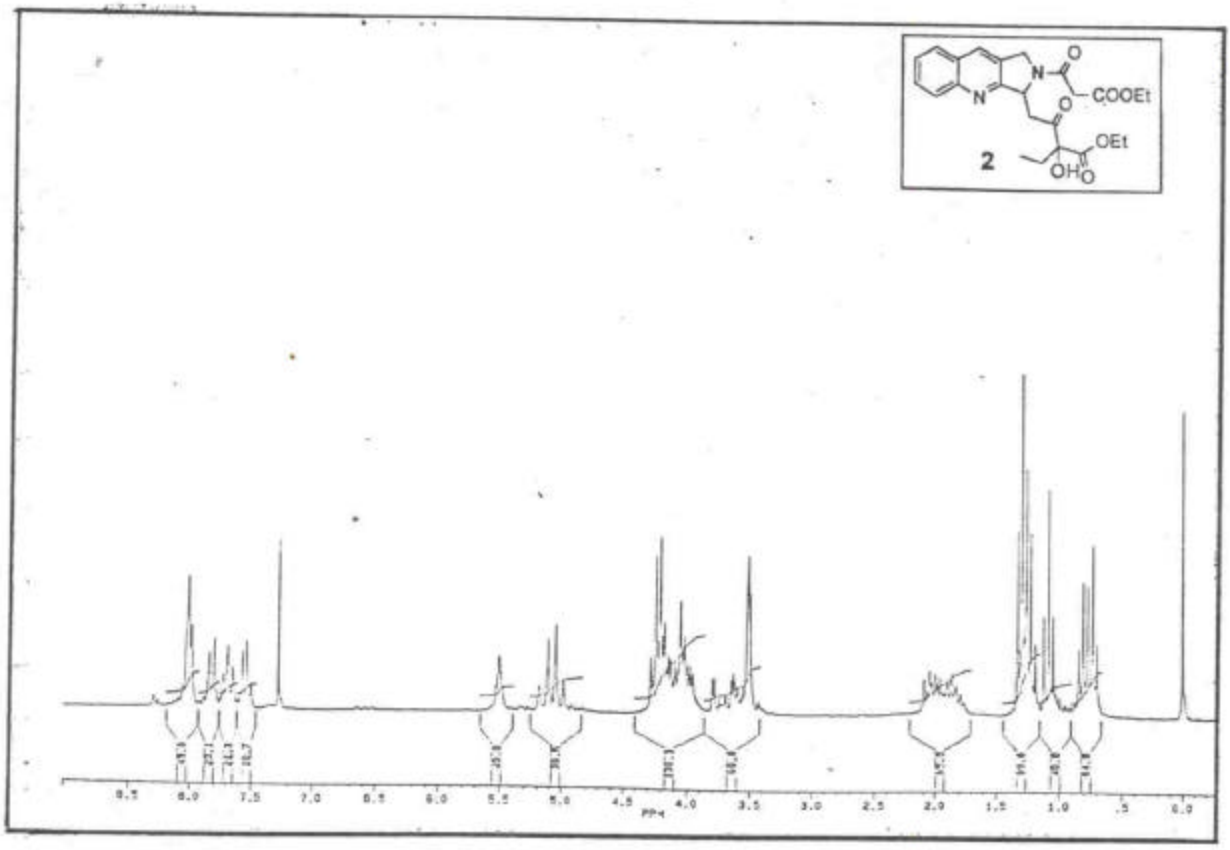
^1H NMR spectrum of compound 16 : (200MHz, $CDCl_3$)



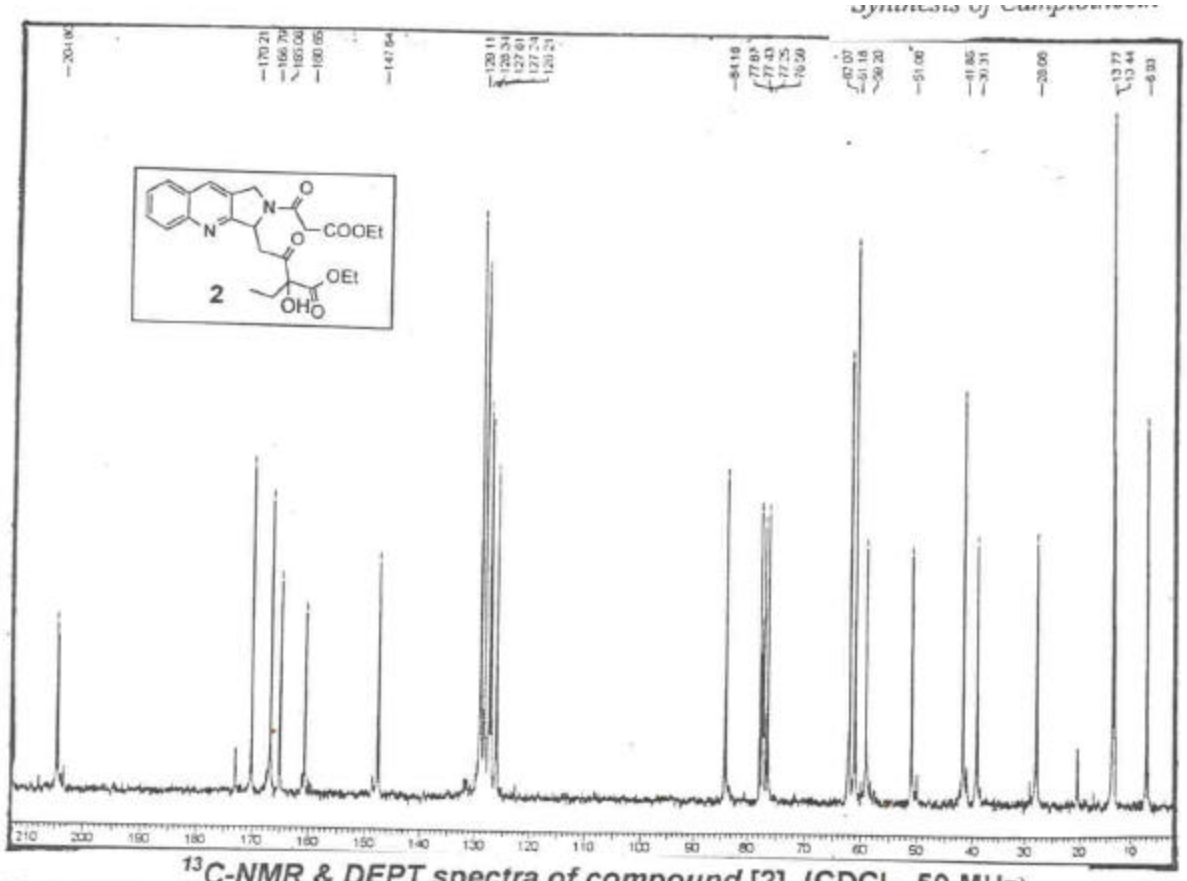
^{1}H NMR spectrum of compound [18] **(200MHz, $CDCl_3$)**



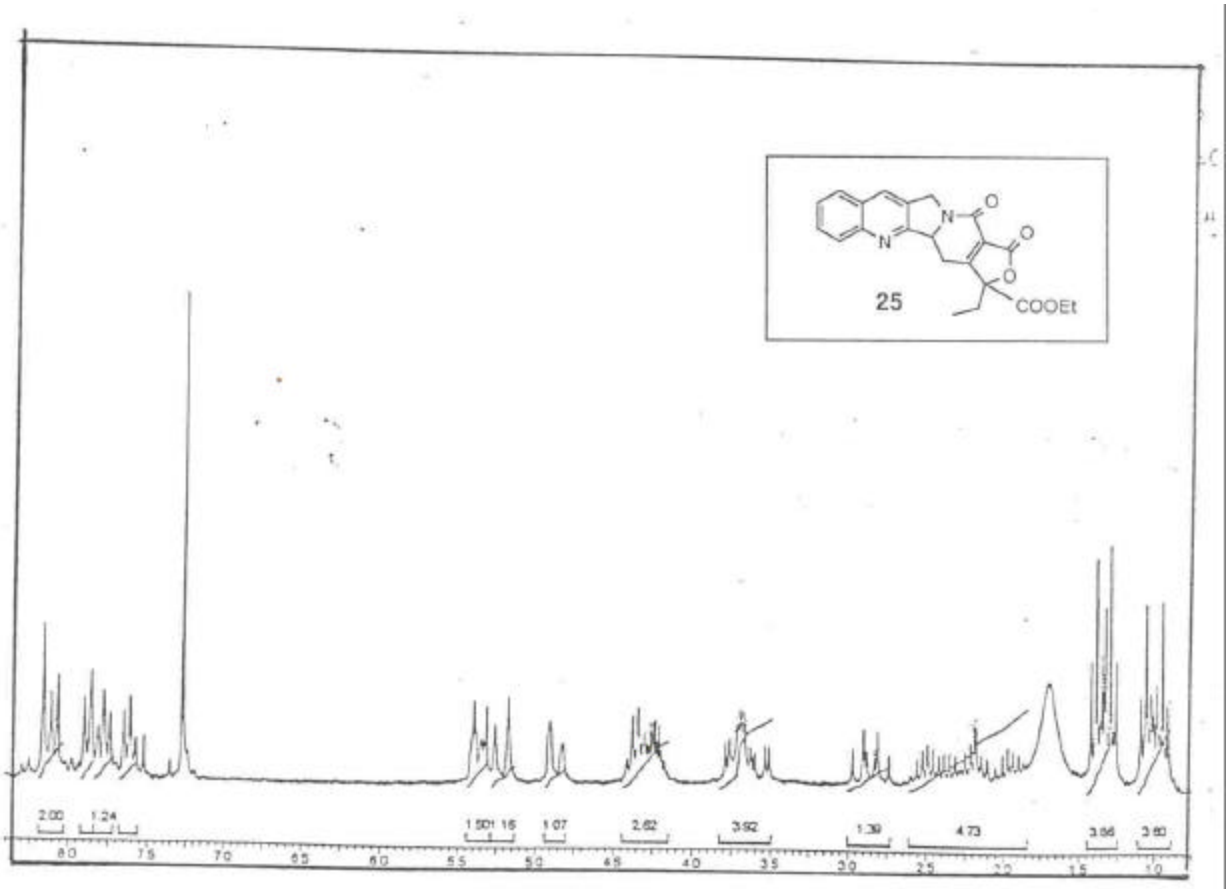
^{1}H NMR spectrum of compound [3] **(200MHz, $CDCl_3$)**



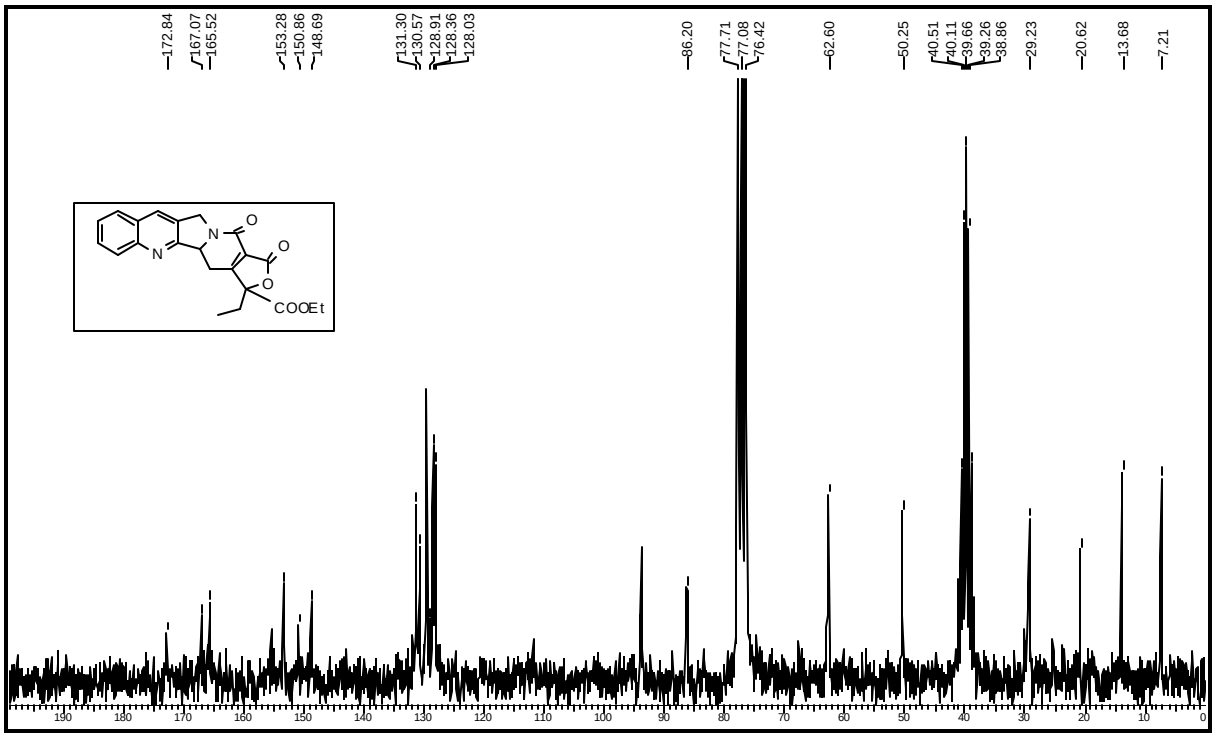
^{1}H-NMR spectrum of compound [2]. ($CDCl_3$, 200 MHz)



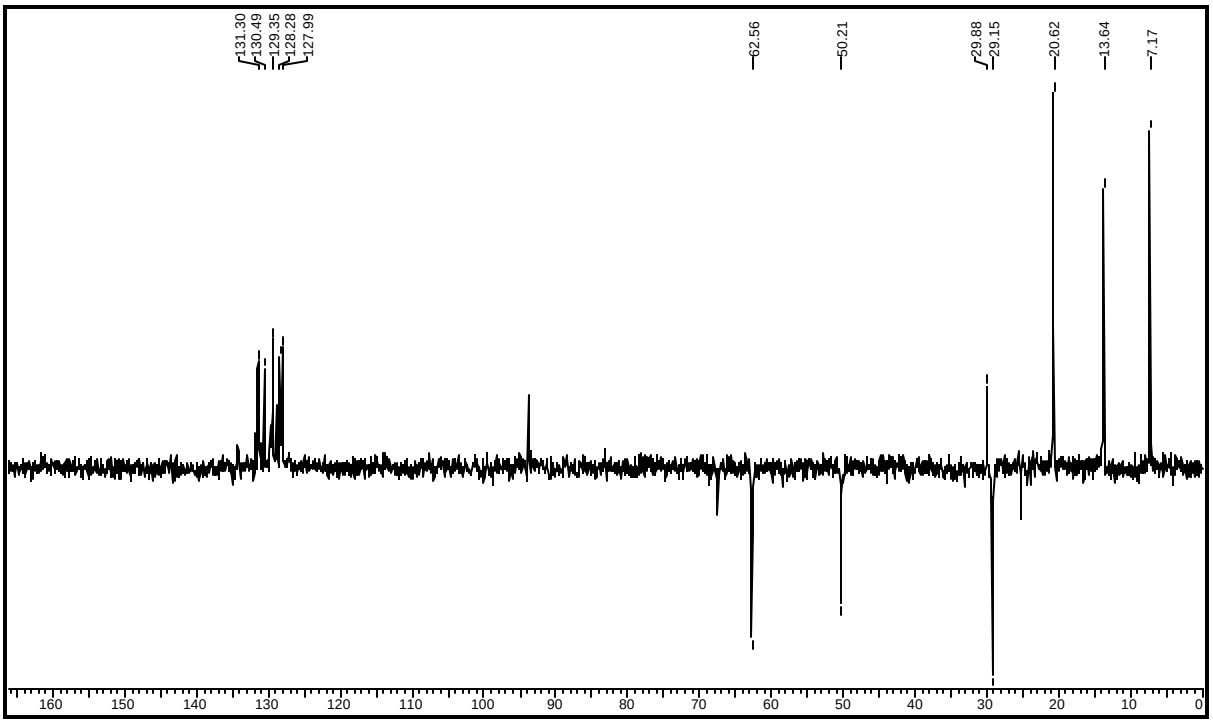
^{13}C-NMR & DEPT spectra of compound [2]. ($CDCl_3$, 50 MHz)

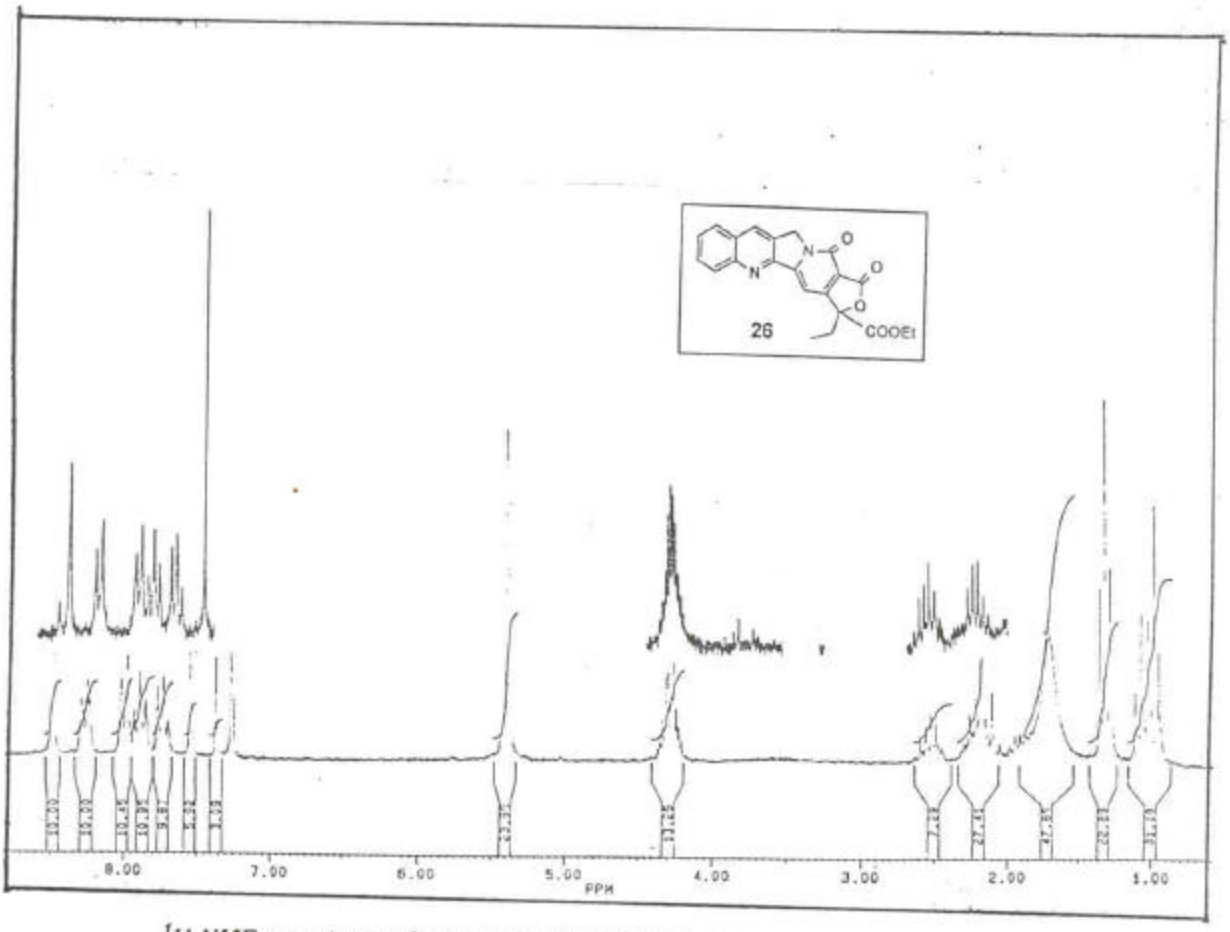


^{1}H NMR spectrum of compound [25] (200MHz, $CDCl_3$)

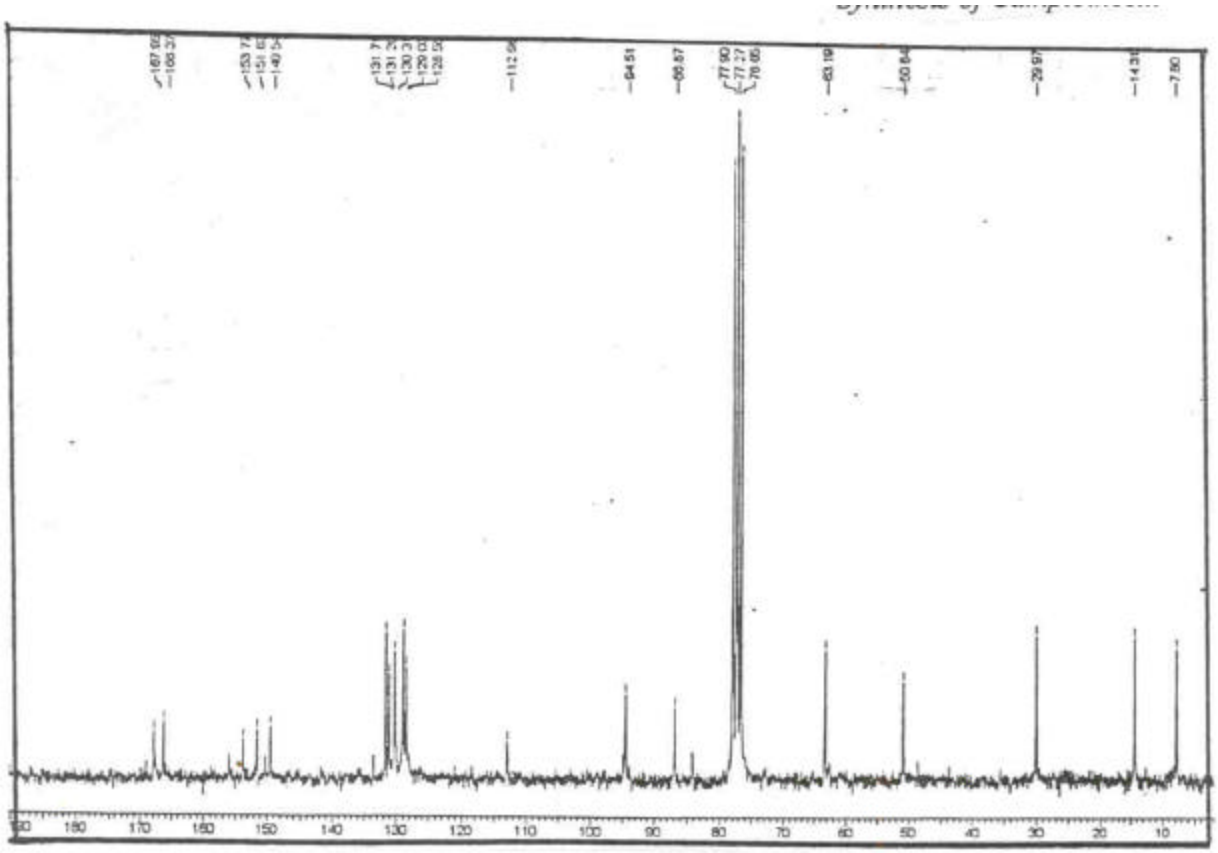


^{13}C & DEPT NMR spectra of compound [25] **(50MHz, $CDCl_3$)**

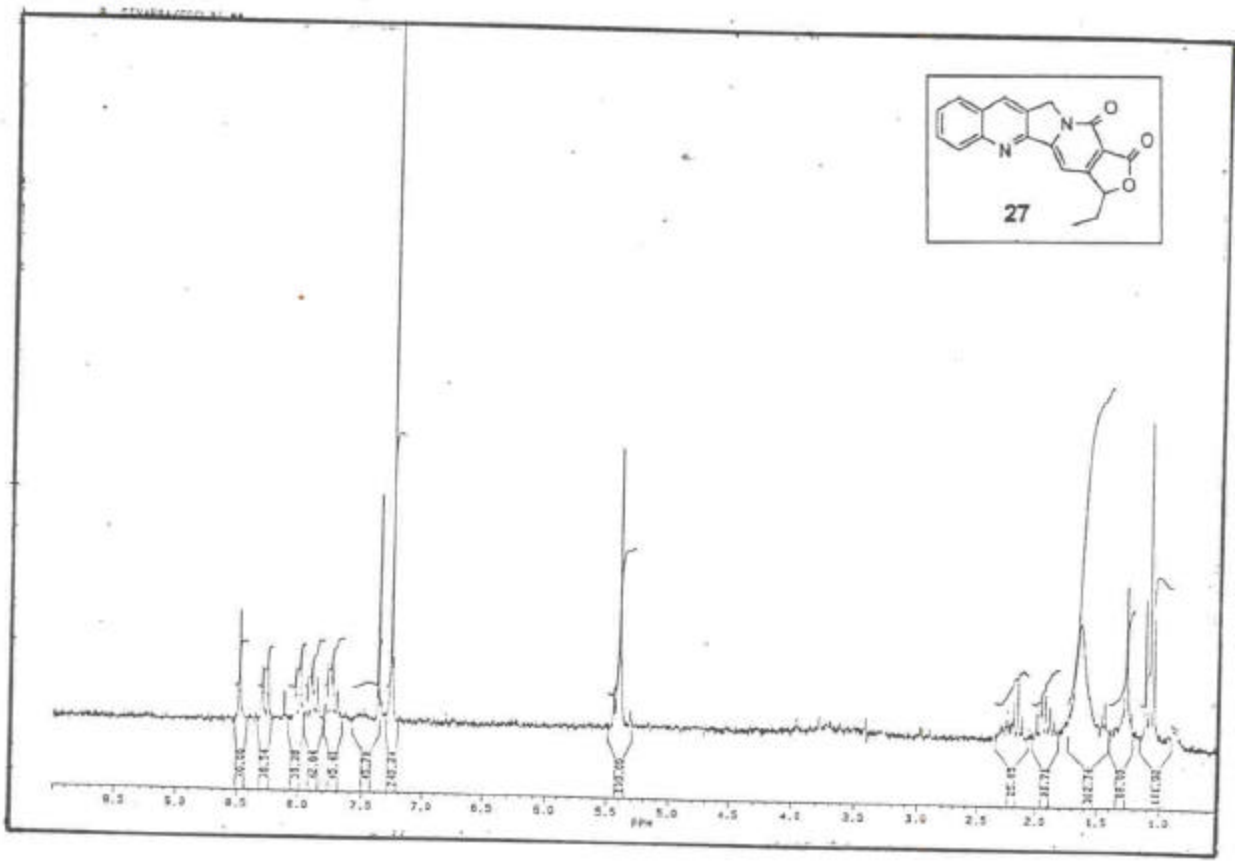




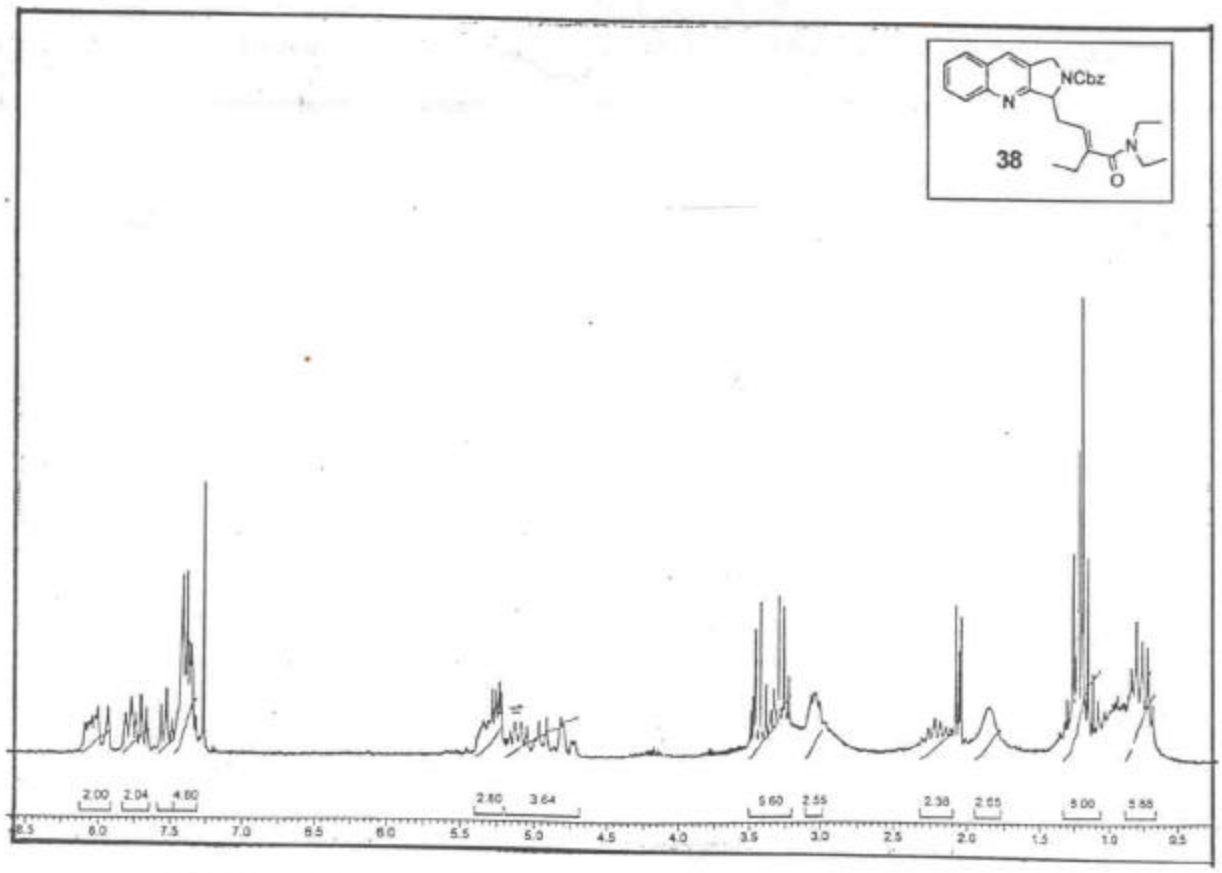
^{1}H-NMR spectrum of compound [26]. ($CDCl_3$, 200 MHz)



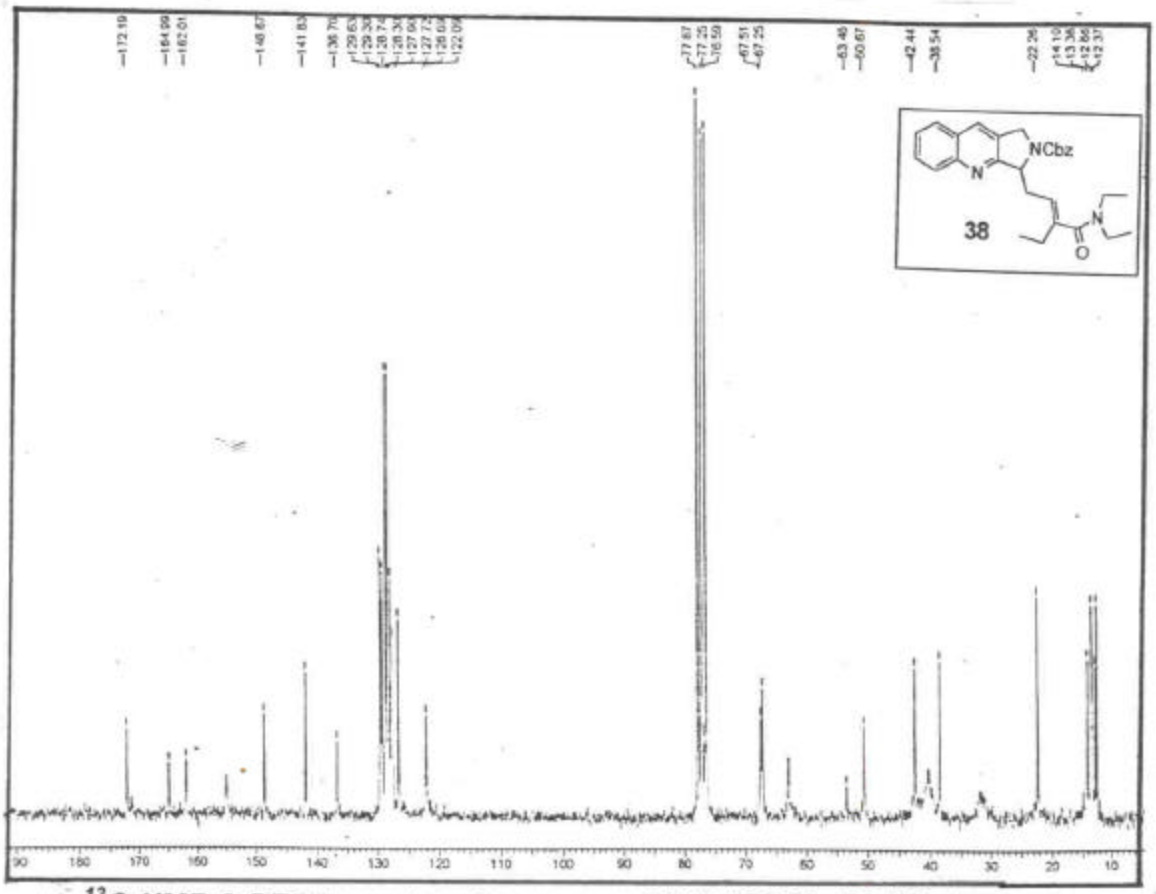
^{13}C-NMR & DEPT spectra of compound **[26]. ($CDCl_3$, 50 MHz)**



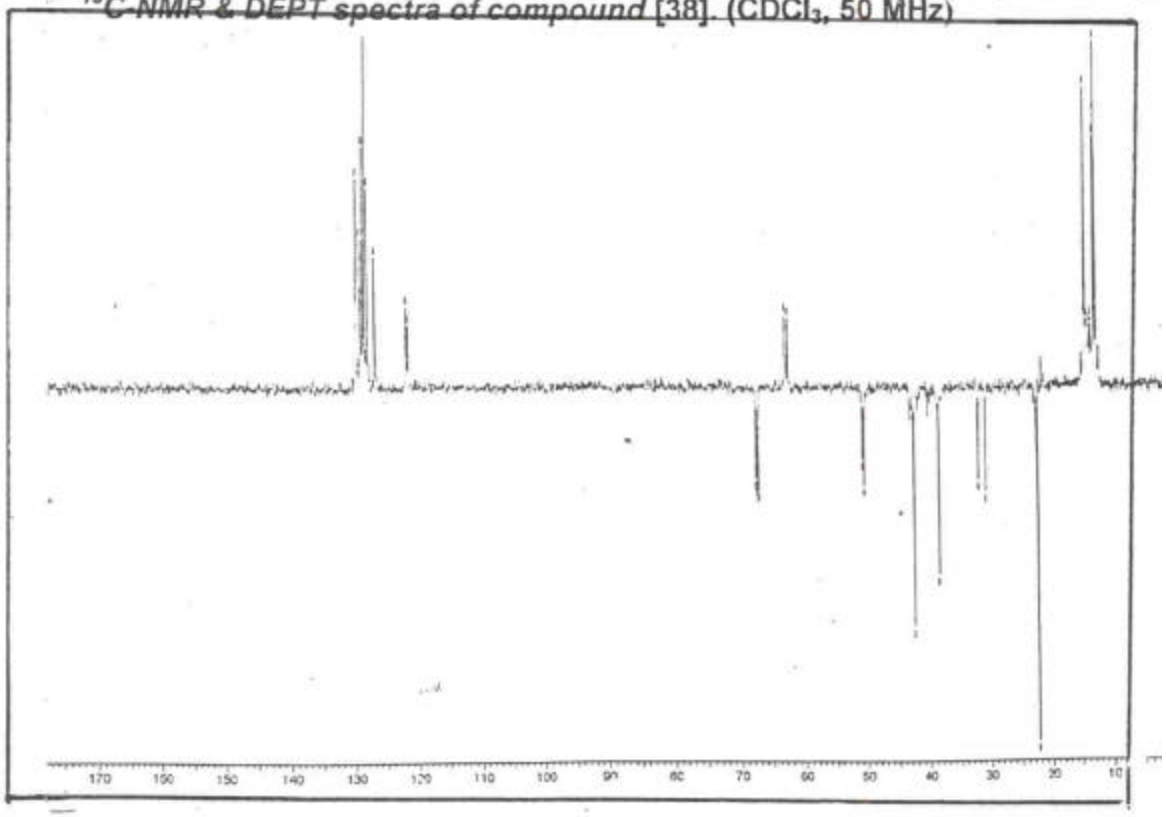
^{1}H-NMR spectrum of compound [27]. ($CDCl_3$, 200 MHz)

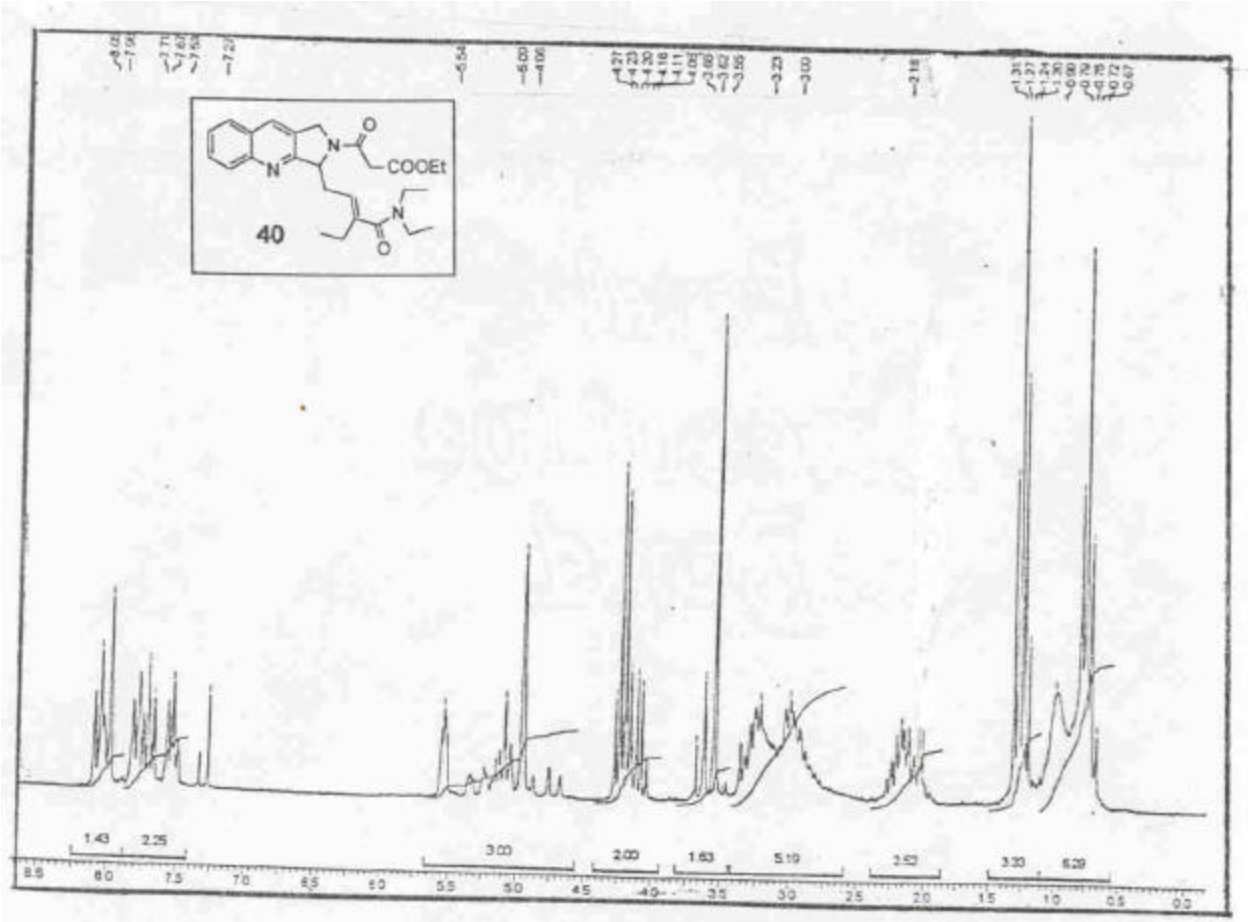


^{1}H-NMR spectrum of compound [38]. ($CDCl_3$, 200 MHz)

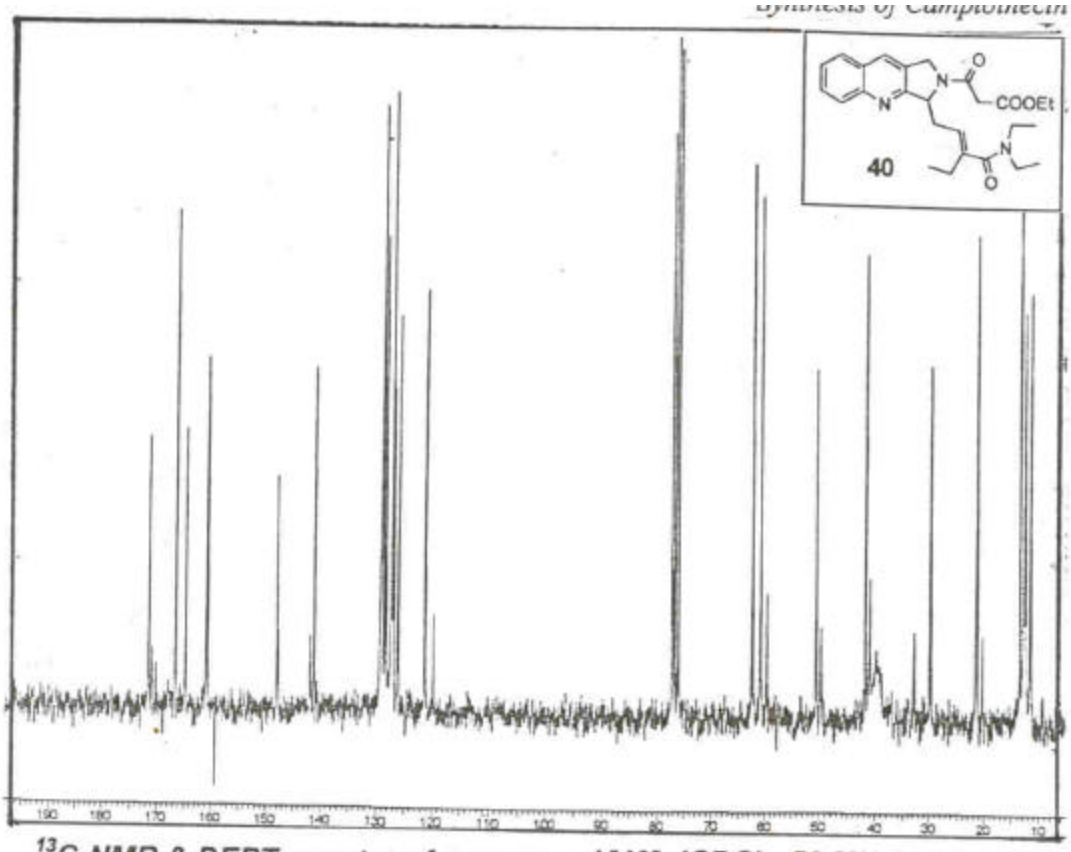


^{13}C-NMR & DEPT spectra of compound [38]. ($CDCl_3$, 50 MHz)

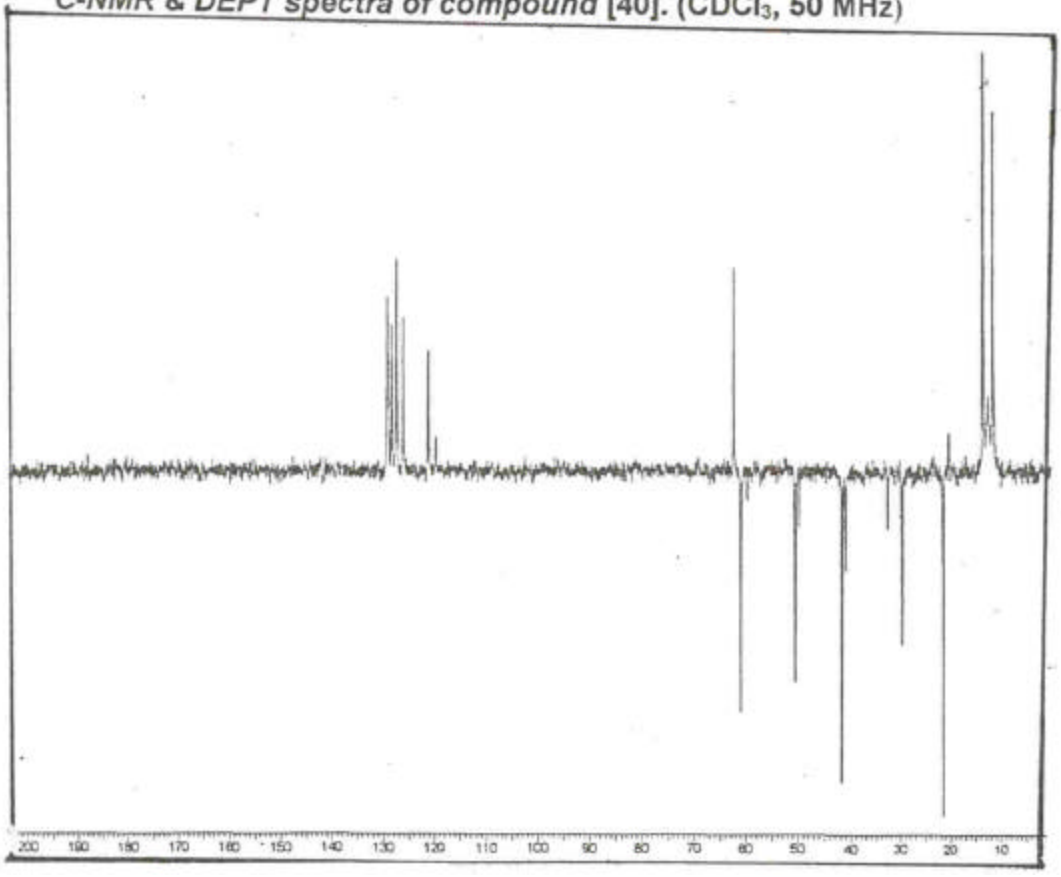


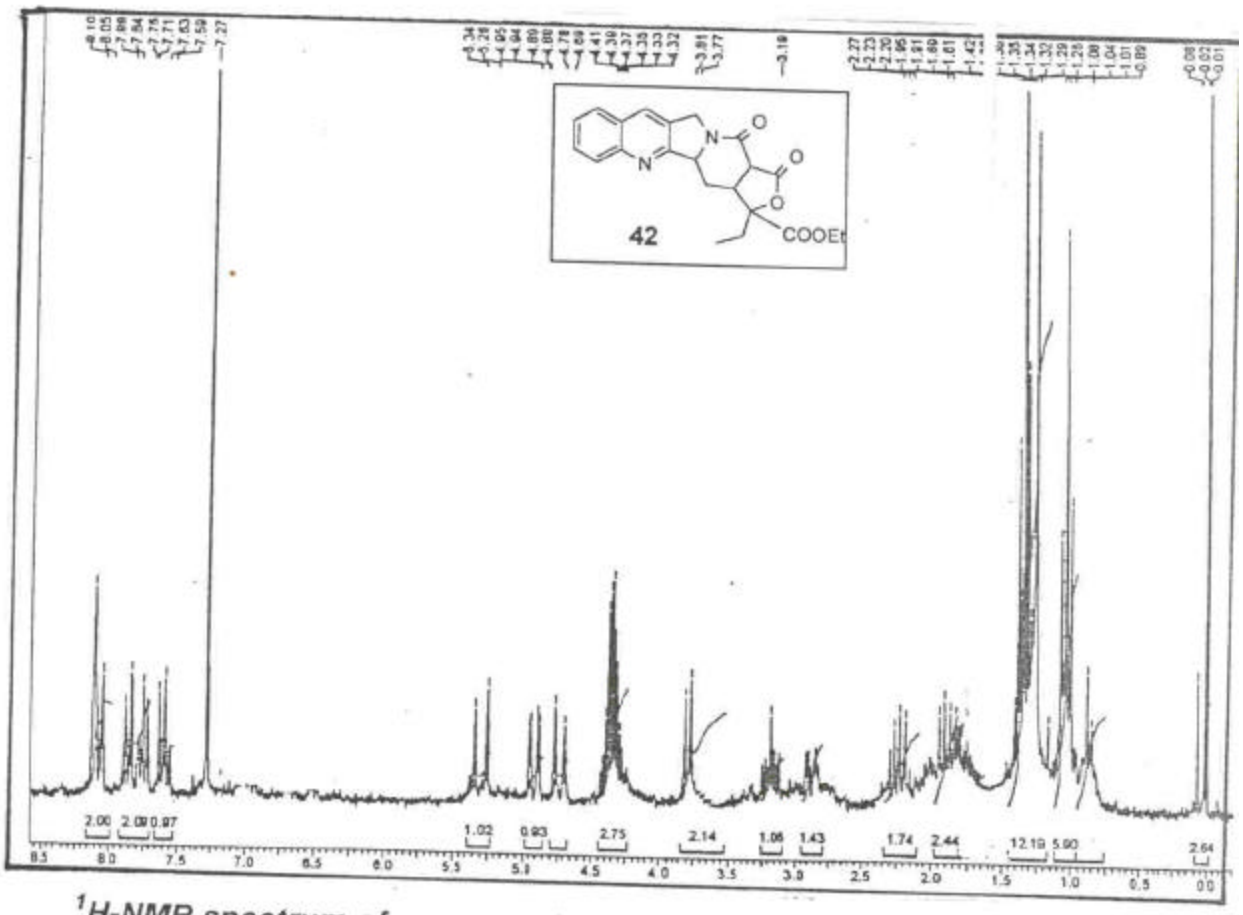


^{1}H-NMR spectrum of compound **[40]. ($CDCl_3$, 200 MHz)**

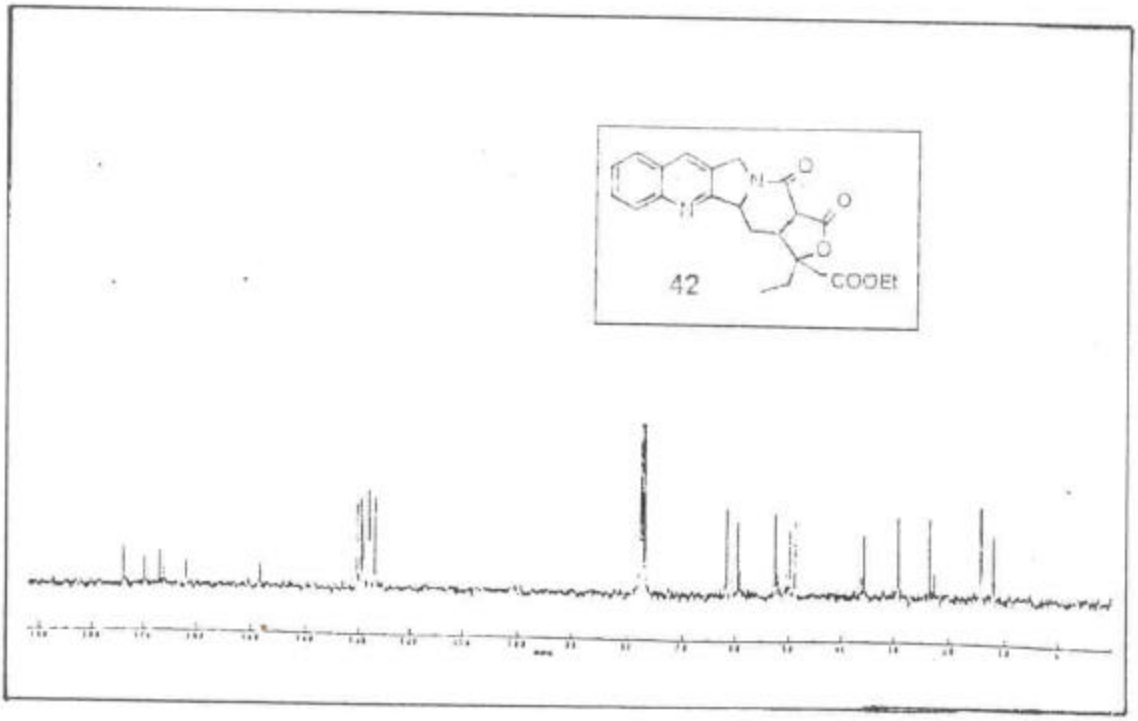


^{13}C-NMR & DEPT spectra of compound [40]. ($CDCl_3$, 50 MHz)

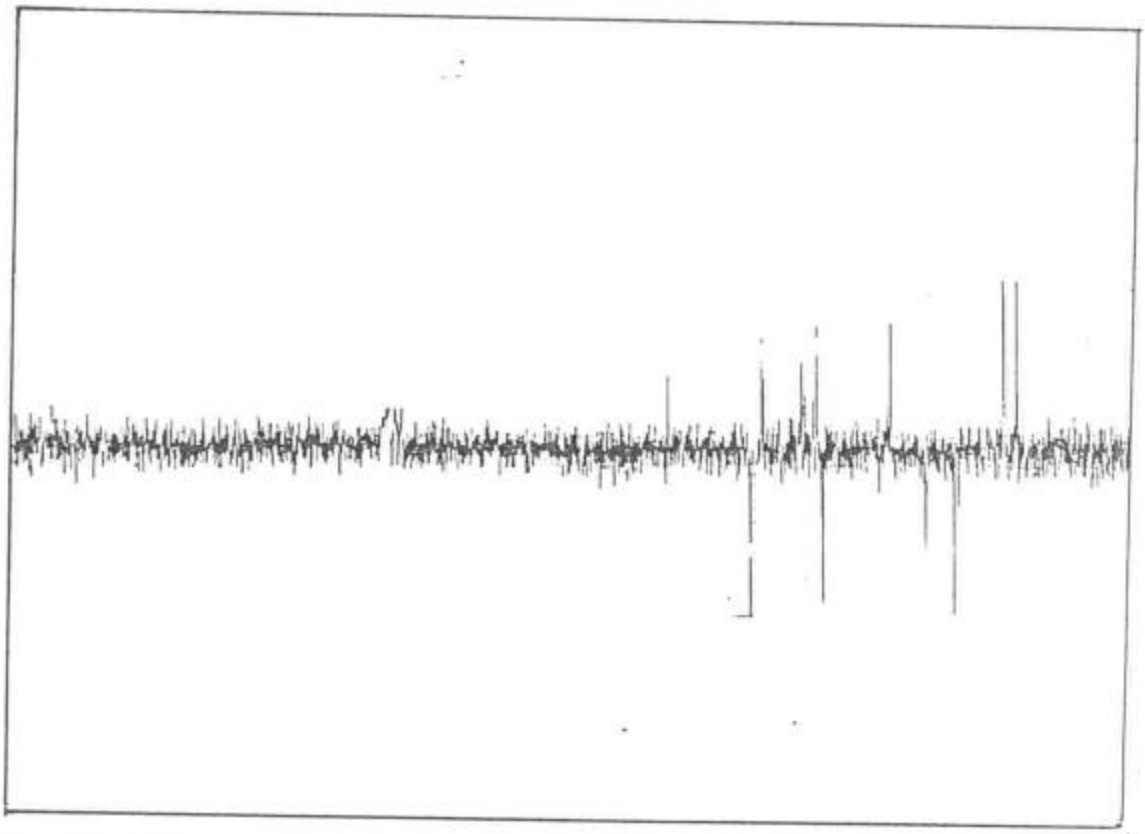




^{1}H-NMR spectrum of compound [42]. ($CDCl_3$, 200 MHz)



^{13}C & DEPT NMR spectra of compound [42] (50MHz, $CDCl_3$)



CHAPTER 1

SECTION II

Synthesis of Camptothecin

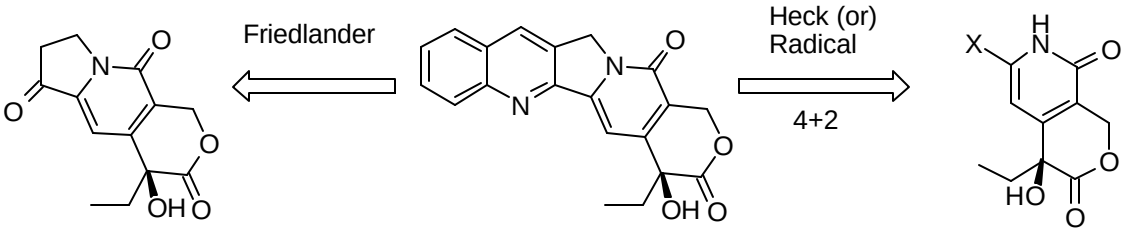
PART B

1.2.2.1 Introduction

Camptothecin **1** was developed more than 30 years ago, but it's clinical use has been limited by its insolubility and toxicity.[110] Extensive structure activity relation studies have identified many analogues with better solubility and with equal or better antitumor activity, which resurged the interest of the chemists as well as oncologists result of which is the launching of the Topotecan (Hycamtin) and Irinotecan in to the market for refractory ovarian and colorectal cancers respectively.[111] But not all the analogues can be accessed from Camptothecin in a semi synthetic way. Synthetic approaches for these analogs have typically involved synthesis of suitably functionalized CDE-rings[112] or DE-rings[113] or precursors thereof,[114] which were then coupled with suitable counter parts.

Among these, the strategy that involved the Friedlander condensation of CDE synthon or radical (or Heck) cyclization of DE intermediate has been adapted quite frequently in the synthesis of analogues.

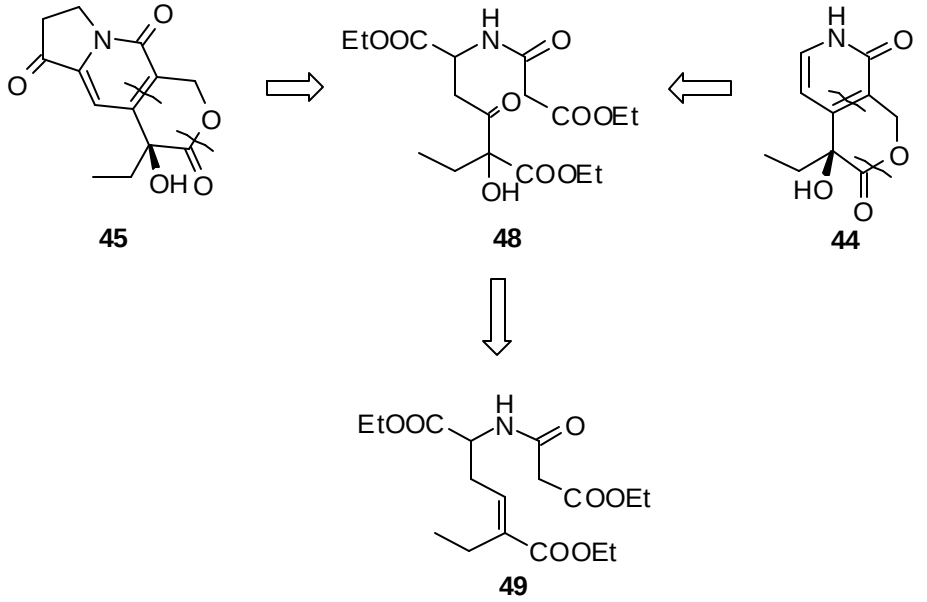
Scheme 1:



1.2.2.2 Present Work

We reasoned that our approach discussed in **Sec-1a** has the inherent flexibility to access the CDE ring intermediate, hence analogues just by delaying the AB-ring construction (changing the sequence of the reactions) to the late stage *i.e* Friedlander condensation by employing suitable counterpart of the ketone or aldehyde, and advancing the intramolecular aldol condensation in the synthetic sequence as shown in retrosynthetic direction (*Scheme 2)*.

Scheme 2:

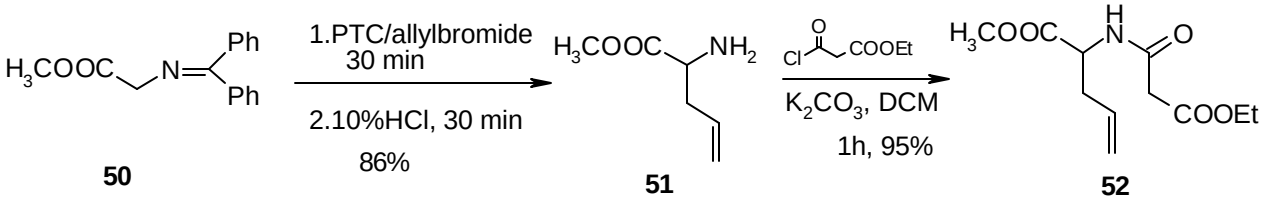


1.2.2.3 Results and discussion

Thus preparation of ketol **48**, substrate for the intramolecular condensation started from glycine, a readily available starting material. Alkylation of Schiff's base **50**[115] with allylbromide under phase transfer conditions followed by hydrolysis furnished allylglycine **51**. ^{1}H NMR showed multiplet at δ 2.6, doublet at δ 5.1 and multiplet at δ 5.7 for the incorporation of $–CH_2=CHCH_2$ group along with multiplet at δ 4.3 for 1H and singlet at δ 3.75 (3H).

Condensation of **51** with carbethoxyacetyl chloride in DCM employing K_2CO_3 as base provided amide **52** (*Scheme 3*)

Scheme 3:

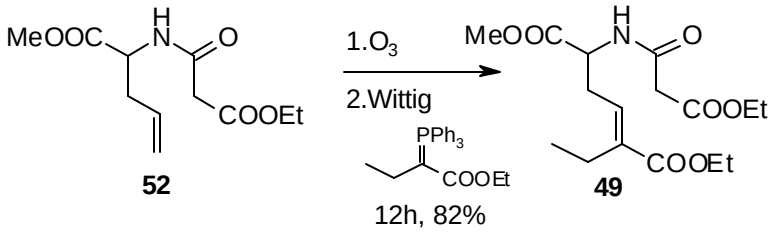


^{1}H NMR spectrum of **52** showed a singlet at δ 3.25 (2H), a triplet at δ 1.25 (3H) and a quartet at δ 4.25 confirming the presence of malonate ($–\underline{CH_2}$-COO$\underline{C_2H_5}$). ^{13}C spectrum

confirmed the presence of three carbonyls δ 171.57, 168.37 and 165.13. Mass spectrum showed m/z peak 243

Oxidative removal of the methylene group of the latent aldehyde in **52** with Leumix-Johnson oxidation ($OsO_4/NaIO_4$) furnished aldehyde in good yield on small scale. But it posed some problems in scale up (multigram scale). Hence the alternative route, ozonolysis was sought for this transformation. Accordingly careful ozonolysis of olefin **52** in DCM at -78^oC resulted in the formation of aldehyde, which was subjected for Wittig olefination with phosporane **17**, without purification owing to its instability, to obtain the a, ß-unsaturated ester **49** (*Scheme 4*).

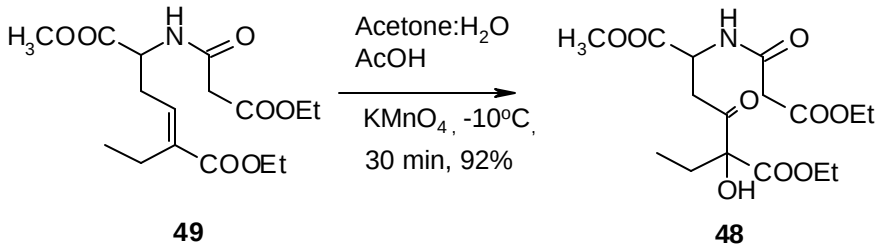
Scheme 4 :



^{1}H NMR spectrum of **49** showed apart from the ester protons, a triplet at δ 0.99 (3H) and multiplet at d 2.32 (2H) indicating the presence of ethyl functionality. A triplet at d 6.3 (1H) was assigned for olefin proton CH_2-CH=C. Mass spectrum showed molecular ion peak at 343. IR spectrum showed the absorption at 1710 cm^{-1} suggesting the presence of a, ß-unsaturated ester.

α, β-Unsaturated ester **49** was converted to ketol **48** with $KMnO_4$ in acidic pH in good yields (*Scheme 5*).

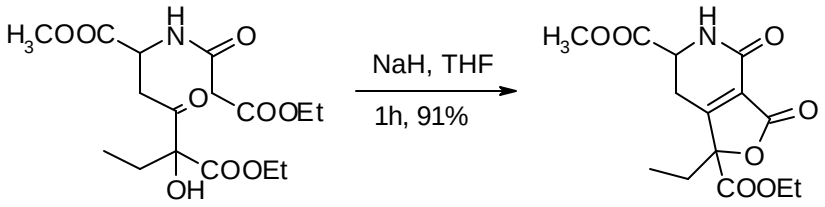
Scheme 5:



^{1}H NMR spectrum of **48** showed a triplet at d 0.75 (3H) & multiplet at d 1.98(2H) indicating the presence of ethyl group adjacent to quaternary carbon (evident by its multiplicity due to the geminal coupling and the diastreomers), multiplet at d 3.2 (2H) for allylic –CH_2-CO- and singlet at δ 3.3 (2H) for –active methylene-CH_2COOEt. IR spectrum showed absorption at 3475cm^{-1} and 1738 cm^{-1} indicative of hydroxy ketone.

Aldol condensation of ketol **48** with NaH as the base provided dihydropyridone **53** in excellent yields.

Scheme 6:

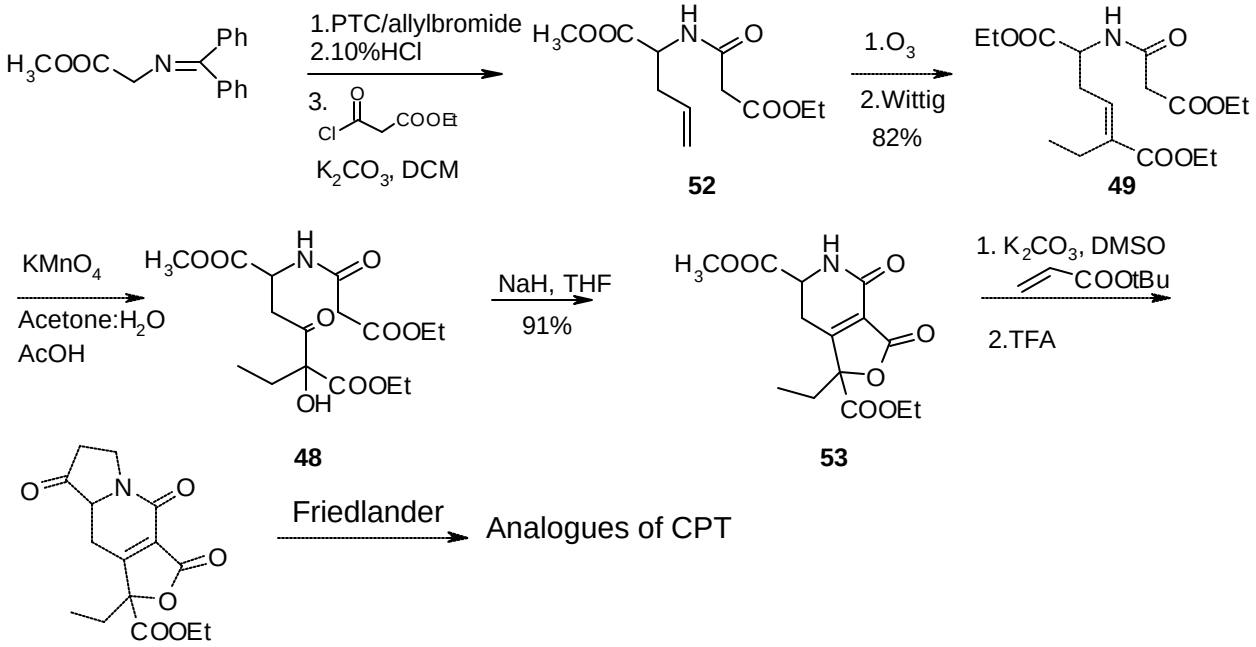


48 **53**

^{1}H NMR spectrum of **53** showed the absence of ester protons and active methylene protons and appearance of two distinct multiplets for $CH_3\underline{CH_2}$- of ethyl group revealing the 5-membered lactone formation. IR spectrum showed the absorption at 1760 cm^{-1}.

Annulation of the C-ring is planned to be effected via tandem Michael addition-Dieckmann condensation and decarboxylation while the formation of AB-ring by Friedlander condensation. In concise the *Scheme 7* delineates the synthetic efforts towards the direction of obtaining the analogues.

Scheme 7

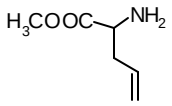


Conclusion

In summary we have demonstrated the feasibility of our intramolecular aldol condensation approach to the construction of the pyridone and have developed a potentially efficient synthetic approach amenable to access the analogues of Camptothecin.

1.2.2.4. Experimental:

1. 2-Amino-pent-4-enoic acid methyl ester [51]



51

To a biphasic solution of DCM and 10% NaOH solution containing Glycine Schiff's base **50** (17.7g 0.1mol) and tetra-*n*-butylammonium hydrogen sulphate (3.2g, 10 mmol) was added allylbromide (13.2g, 0.11 mol) and the reaction mixture was stirred at room temperature for 30 minutes. The organic layer was separated, evaporated and the residue was suspended in a 10% solution of hydrogen chloride (100mL) and stirred for 30 min. The reaction mixture was extracted with DCM and the aqueous phase was treated with a saturated solution of NH_3 (50mL) and extracted with DCM (3×25 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated affording pure amine **51** as pale yellow oil.

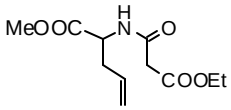
Molecular formula : $C_6H_{11}NO_2$.

Yield : 11. 08g, 86%

IR (Neat) : 3430,1735, 1627 cm^{-1}.

^{1}H NMR (200 MHz) : δ: 5.4 (m, 2H), 5.1 (d, 1 H), 4.36 (q, 1 H), 3.45 (s, 3H) 2.65 (t, 2H), 1.90 (br s, 2 H, NH_2)

2. 2-(2-Ethoxycarbonyl-acetylamino)-pent-4-enoic acid methyl ester [52]



52

To a precooled solution of amine **51** (1.29 g, 10 mmol) in DCM (25 mL) in presence of K_2CO_3 was added a solution of carbethoxy acetyl chloride (14.7 mmol) in DCM (10mL). The resulting solution, which turned from colourless to brown within *ca*. 15 min, was stirred under argon at temperature for 1hr, and again cooled to 0°C. A solution of 1 M HCl (25 mL) was then

added. The resulting solution was stirred for 5 min at room temperature and rapidly extracted with CH_2Cl_2 (3×50 mL), washed with $NaHCO_3$ solution (50 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* at 30°C to give crude amine **52**, which was pure enough for further step.

Molecular formula : $C_{11}H_{17}NO_5$

Yield : 2.308g, 95%

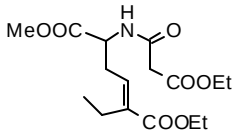
IR (Neat) : 3307, 1735, 1640, 1500 cm^{-1}.

^{1}H NMR (200 MHz) : δ: 7.6 (d, 1H), 5.7 (m, 1H), 5.2 (m, 2H), 4.6 (q, 1H) 4.21(q, *J* =7.3Hz, 2H), 3.71 (t, 3 H), 3.31 (s, 2H), 2.6 (m, 2 H,), 1.3 (t, *J* =7.3 Hz, 3H)

^{13}C NMR (50 MHz) : δ: 171.57 (C), 168.37 (C), 145.13 (C), 132.13 (CH), 118.75 (CH_2), 61.22 (CH_2), 51.88 (CH_3), 51.77 (CH), 41.37 (CH_2), 35.93, (CH_2), 13.73 (CH_3).

Mass *m/z* (%) : 243 (9, M^+), 202 (20), 184 (24), 128 (15), 115 (13), 88 (100), 70 (65)

3. **5-(2-Ethoxycarbonyl-acetylamino)-2-ethyl-hex-2-enedioic acid di ester [49]**



49

Method A: A round-bottom flask (50 mL) was charged with olefin **52** (486 mg, 2.0 mmol) in 1,4-dioxane and water (3:1) and cooled to 0°C .To the above mixture was added a solution of OsO_4 (cat). To the black-colored mixture $NaIO_4$ (1.275, 6 mmol) was added portion wise (ca 10 minutes) to the chilled solution and the resulted mixture was stirred for 4 h. An aqueous solution of $NaHSO_3$ (0.6 g dissolved in 3 mL of H_2O) was then added, and the slurry was stirred at room temperature for 2h. The mixture was diluted with CH_2Cl_2 (50 mL), the aqueous layer was separated and then extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure and the residue was subjected for Wittig olefination with out purification.

Method B: On large scale the above reaction was plagued with multiple compounds formation. So ozonolysis was carried out in dichloromethane at –78°C using excess of ozone. Thus precooled solution of **52** (1.215 g, 5.00 mmol) in 30 mL of DCM was treated with excess of ozone. After the observation of persistent blue color it was admixed with dimethyl sulphide

(1.15 g, 4.40 mmol) and left standing overnight. Residual ozone was flushed out with nitrogen. The solvent was evaporated at reduced pressure to give the residue, which was subjected for Wittig olefination without further purification. A mixture of aldehyde and Wittig reagent (2.256 g, 6 mmol, 1.2 equiv) in dry dichloromethane (40 mL) was stirred for 12h and monitored by TLC until the starting material was no longer detectable. The solution was concentrated to about 3 mL and loaded on to a silica gel column. Elution with ethylacetate /petroleum ether (1/4) gave the pure product.

Molecular formula : $C_{16}H_{25}NO_7$

Yield : 1.43g, 82%

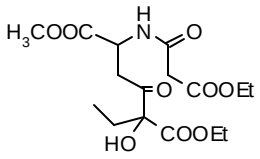
IR (Neat) : 3345, 1739, 1710, 1678, 1532 cm^{-1}.

^{1}H NMR (200 MHz) : δ: 7.74 (d, 1H), 6.62 (t, 1H), 4.73 (q, 1H), 4.20 (m, 4H), 3.77 (s, 3 H), d 3.35 (s, 2H), 2.81 (m, 2 H,), 2.32(q, 2H),1.26 (t, 6H), 1.02 (t, 3H)

^{13}C NMR (50 MHz) : δ: 171.15 (C), 168.10 (C), 166.74 (C), 164.98 (C), 137.11 (C), 134.10 (CH**),** 61.03 (CH_2), 60.07 (CH_2), 51.95 (CH_3), 51.54 (CH_3), 41.40 (CH_2), 30.53 (CH_2), 19.78 (CH_2), 13.94 (CH_3), 13.75 (CH_3), 13.76 (CH_3).

Mass, *m/z* (%) : 343 (M^+, 7)) 262 (10), 238 (11), 184 (17), 153 (20), 139 (40), 124 (70), 114 (20), 88 (100), 84 (50).

4. 5-(2-Ethoxycarbonyl-acetylamino)-2-ethyl-2-hydroxy-3-oxo-hexanedioicacid 1-ethyl ester 6-methyl ester [48]



48

To a stirred solution of α, β-unsaturated ester **49** (0.686g 2mmol) and AcOH (0.7mL) in 10 mL of aqueous acetone (1:9 of H_2O: Acetone) maintained at –10°C was added $KMnO_4$ (0.555g, 3.4 mmol) in portions such that the reaction temperature remains below 10°C. After stirring for 1/2 h at 10°C, the black ppt of MnO_2 is filtered off through celite pad and filtrate was evaporated at reduced pressure to remove acetone and extracted with CH_2Cl_2 (3×50mL) .The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure to furnish crude ketol **48.** Purification by column chromatography over silica gel using 3:2 ethylacetate – pet ether as eluent furnished ketol **48** as a colourless oil.

Molecular formula : $C_{16}H_{25}NO_2$

Yield : 0.674g, 90%

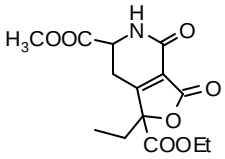
IR (Neat) : 3475, 1728, 1738, 1676 cm^{-1}.

^{1}H NMR (200 MHz) : δ: 7.82 (m, 1H), 4.91(m, 1H), 4.20 (m, 4H), 3.74 (s, 3 H), 3.6-3.2 (m, 4H), 2.07 (m, 2 H), 1.36 (t, 6H), 1.02 (t, 3H)

^{13}C NMR (50 MHz) : δ: 205.26 (C), 170.86 (C), 170.86 (C), 170.53 (C), 168.18 (C), 166.12 (C), 84.22 (C), 62.53 (CH_2), 61.32 (CH_2), 52.35 (CH_3), 48.15 (CH_3), 39.38 (CH_2), 28.31 (CH_2), 13.87 ($2CH_3$), 7.03 (CH_3).

Mass, *m/z* (%) : 376 (M^++1, 8), 277 (50), 244 (23), 216 (65), 184 (20), 158 (18), 113 (57), 102 (100), 88 (30), 57 (22)

5. 1-Ethyl-3, 4-dioxo-1, 3,4,5,6,7-hexahydro-furo [3,4-*c*] pyridine-1, 6-dicarboxylic acid 1-ethylester 6-methyl ester [53]



53

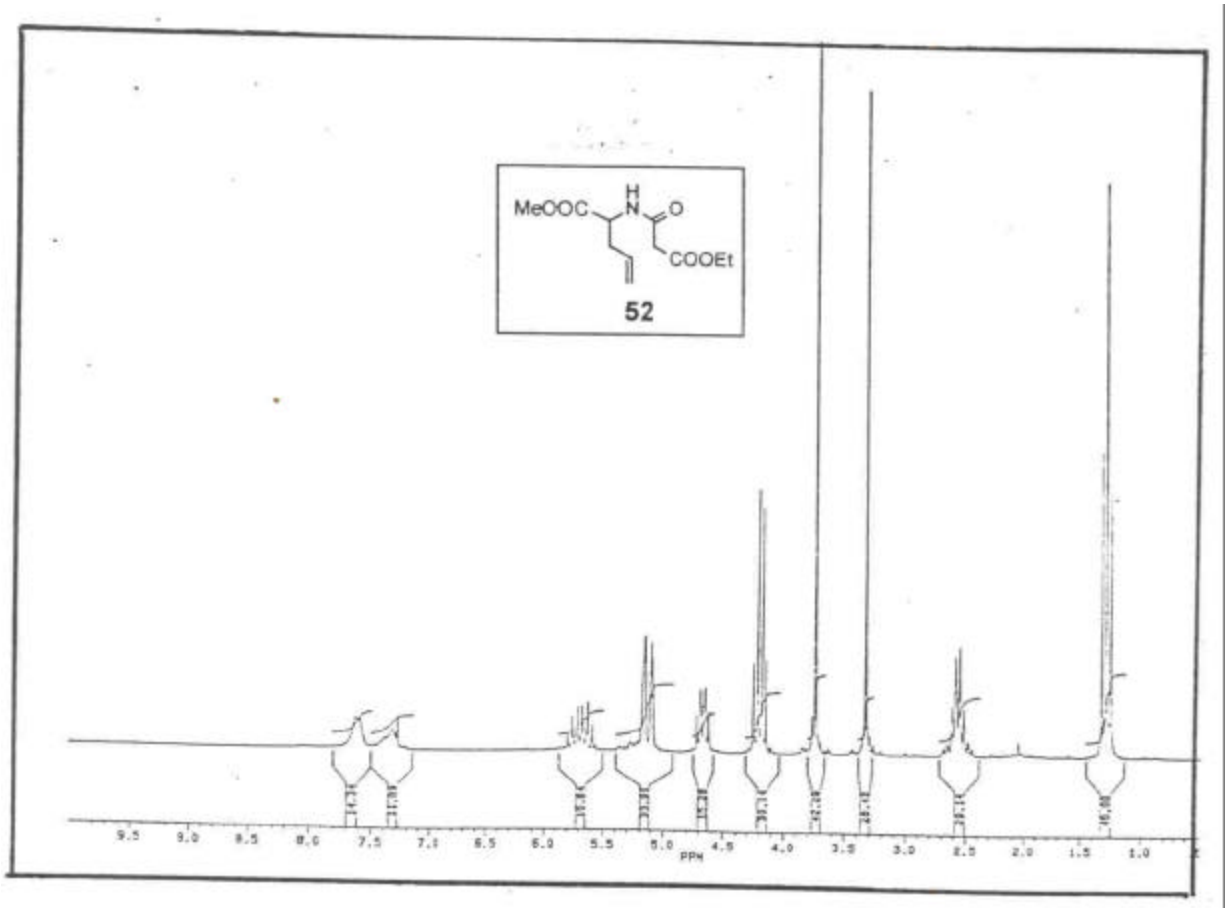
To a precooled solution of NaH (0.288 g, 50% suspension in mineral oil, 6mmol) (pre washed with Pet ether, 2x5mL) in THF (15 mL) was added a solution of diester **48** (1.127g, 3mmol) in THF, with out allowing the temperature to rise beyond 10^{o}C. The reaction mixture was allowed to rise to room temperature and stirred at that temperature for 1h, quenched with 5% HCl solution, and extracted with CH_2Cl_2 (3×20mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography over silica gel using (7:3) ethylacetate – Pet ether as eluent furnished dihydropyridone **53** as colourless oil.

Molecular formula : $C_{14}H_{17}NO_7$

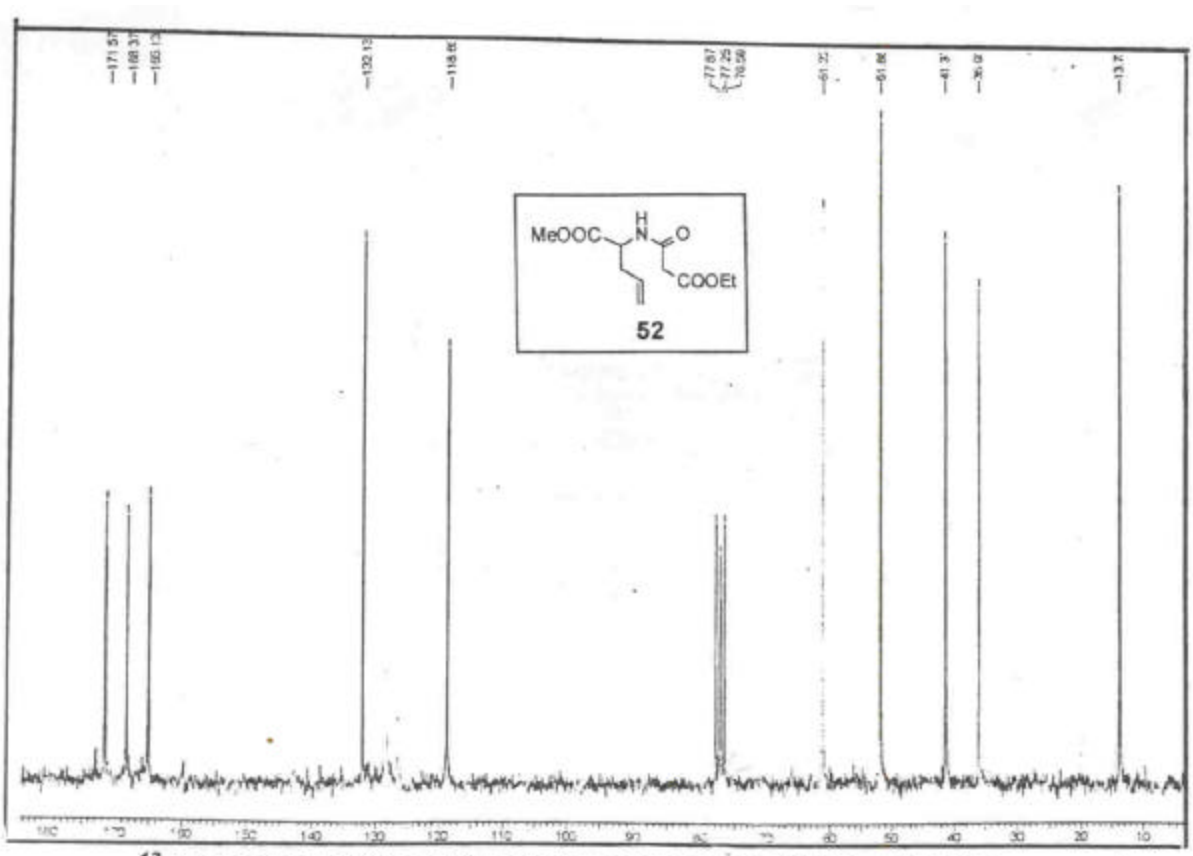
Yield : 0.943 (66% yield).

IR ($CHCl_3$) : 1770, 1660 cm^{-1}.

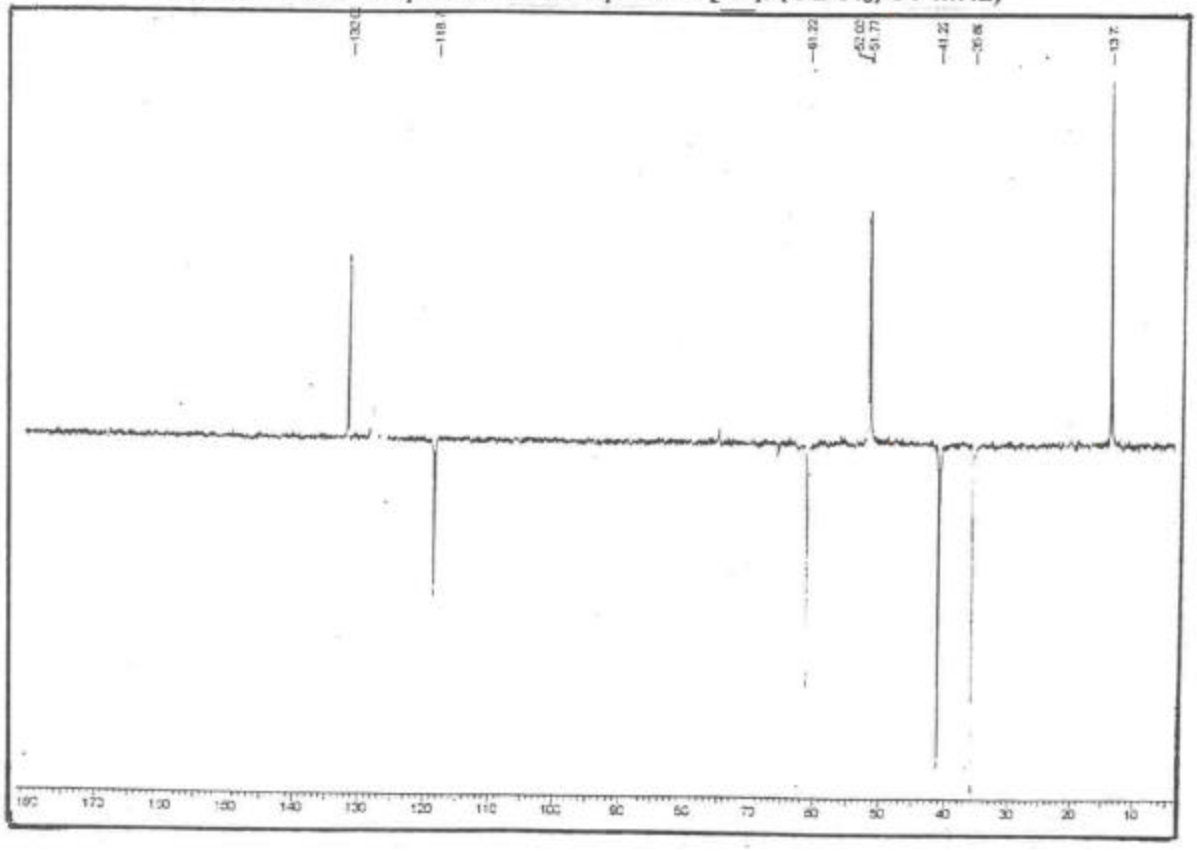
^{1}H NMR (200 MHz) : δ: 4.5 (m, 1H), 4.20 (q, 2H), 3.75 (s, 3 H), 3.3-3.0 (m, 2H), 2.35 (m, 1 H) 1.95 (m, 1 H), 1.36 (m, 3H), 1.02 (m, 3H)

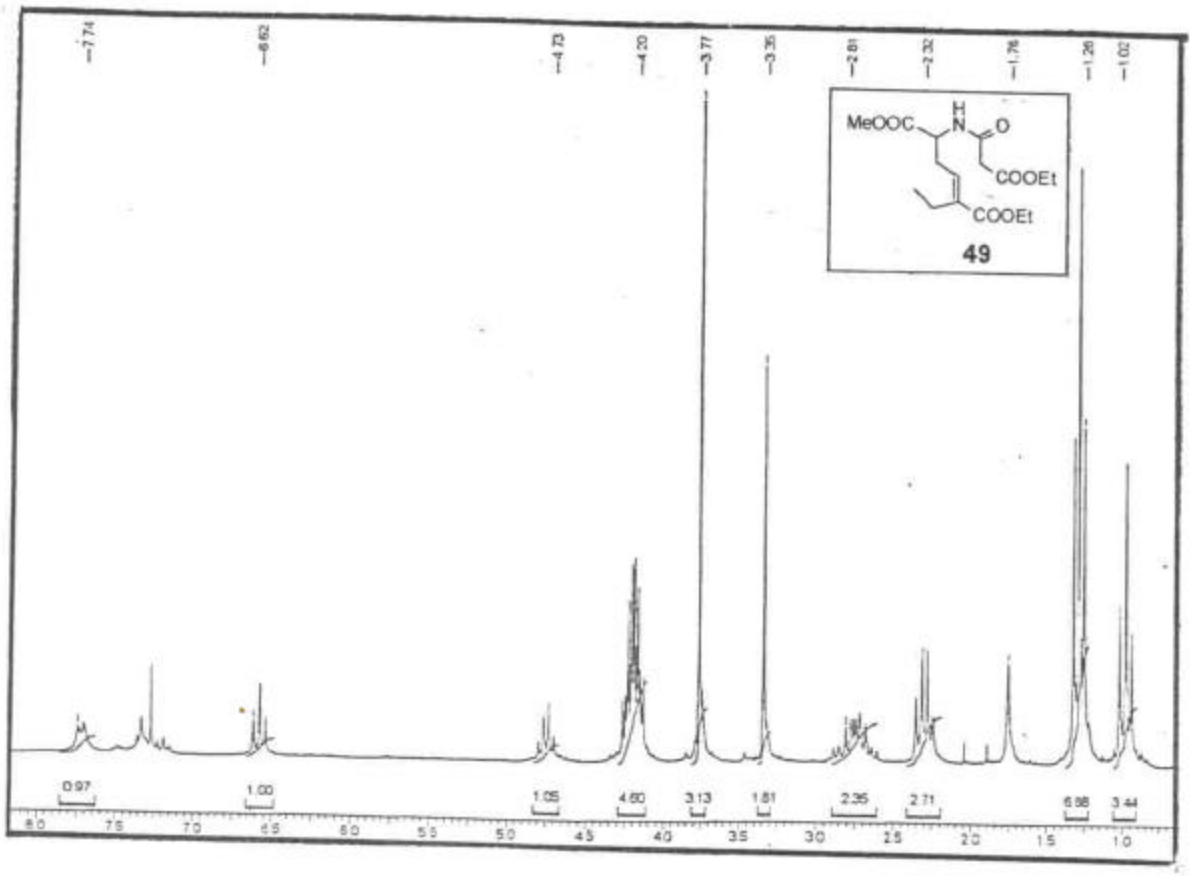


^{1}H NMR spectrum of compound **[52]** **($CDCl_3$, 200 MHz)**

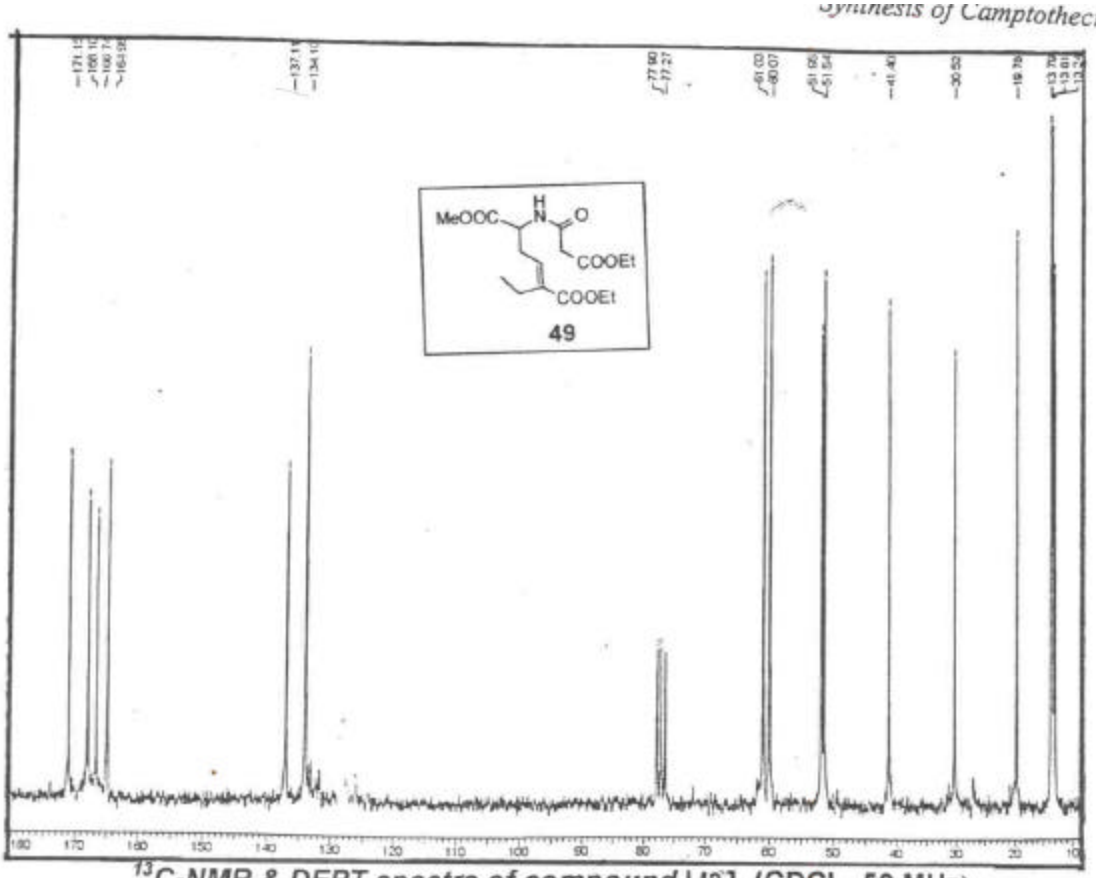


^{13}C-NMR & DEPT spectra of compound [52]. ($CDCl_3$, 50 MHz)

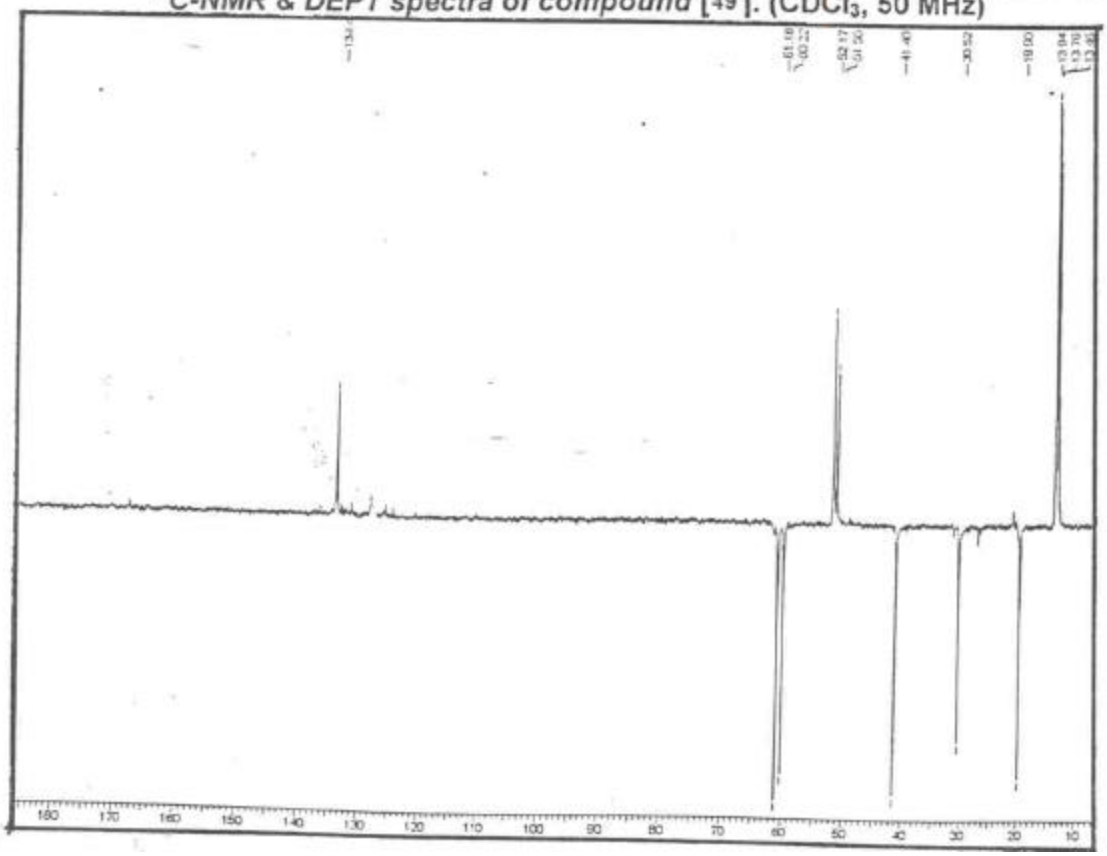


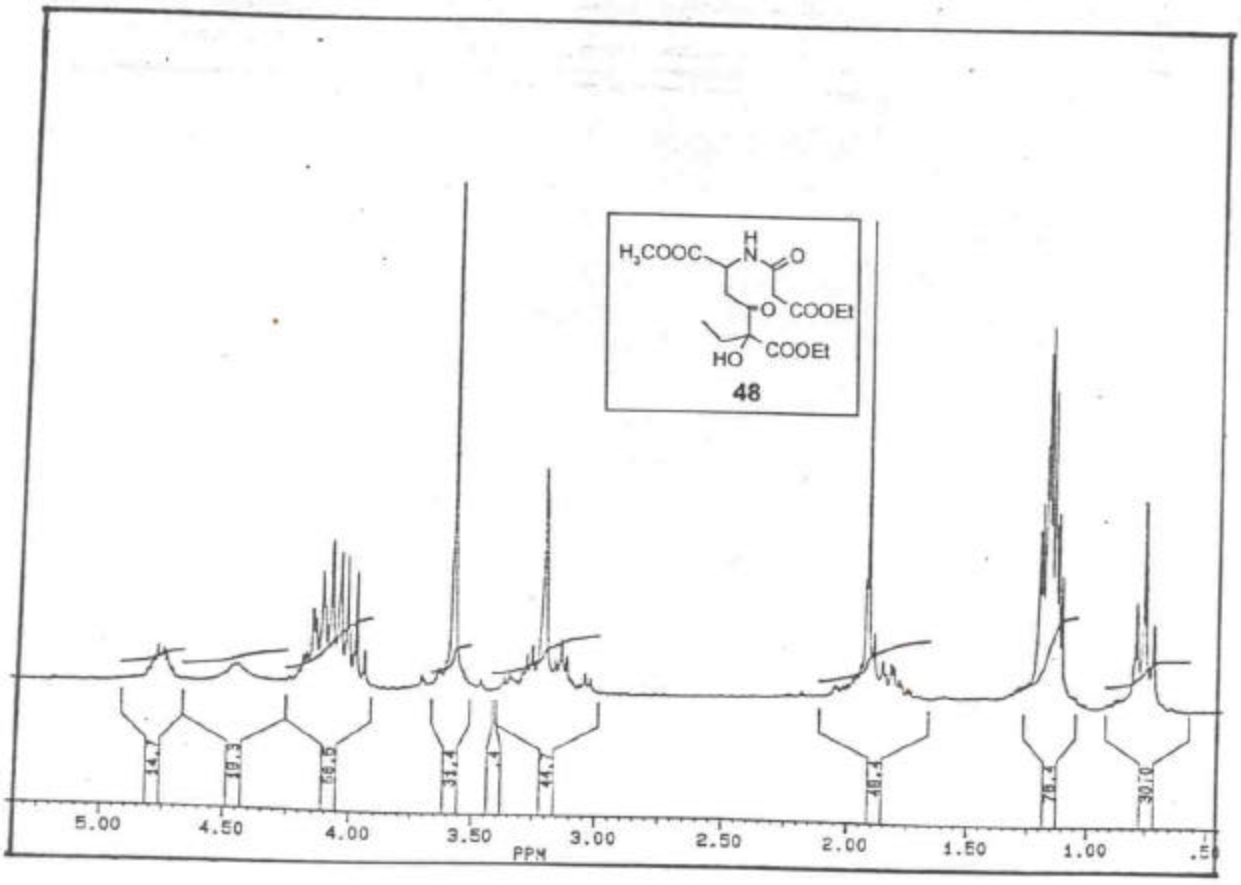


^{1}H-NMR spectrum of compound **[49]. ($CDCl_3$, 200 MHz)**

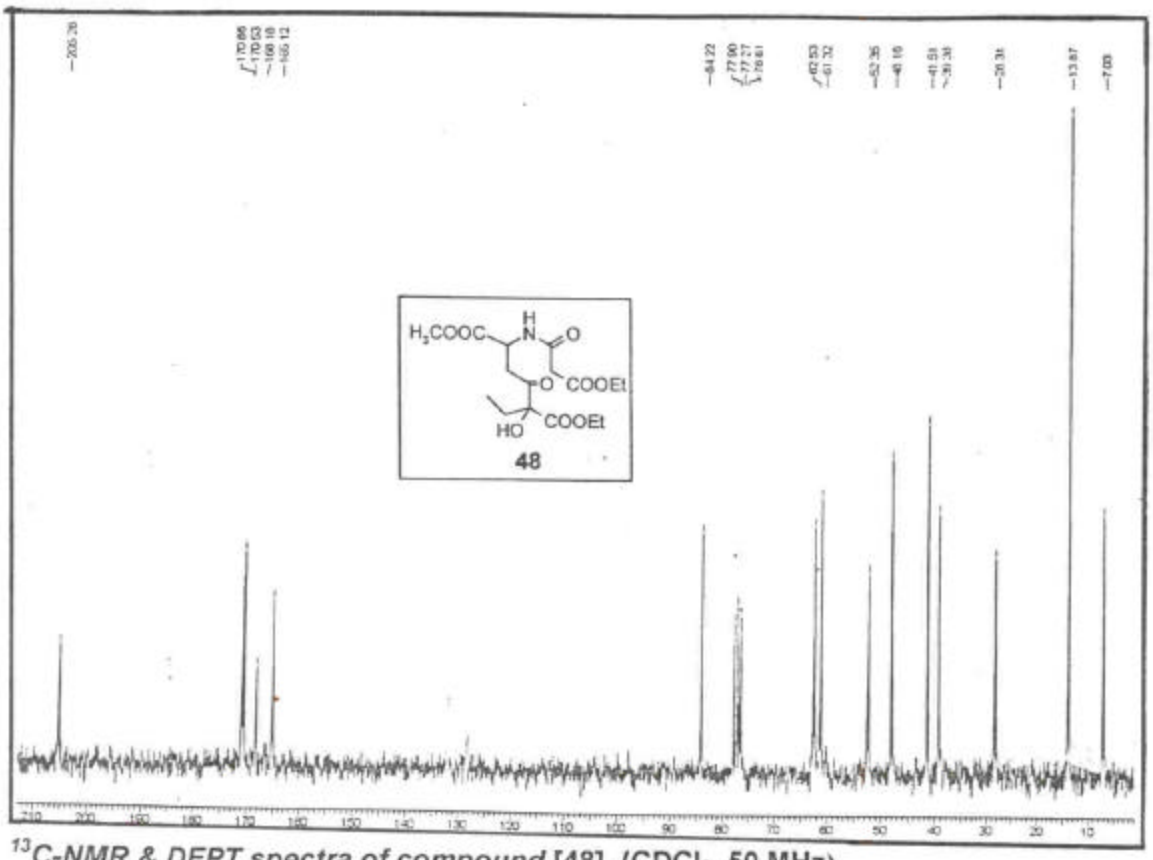


^{13}C-NMR & DEPT spectra of compound [49]. ($CDCl_3$, 50 MHz)

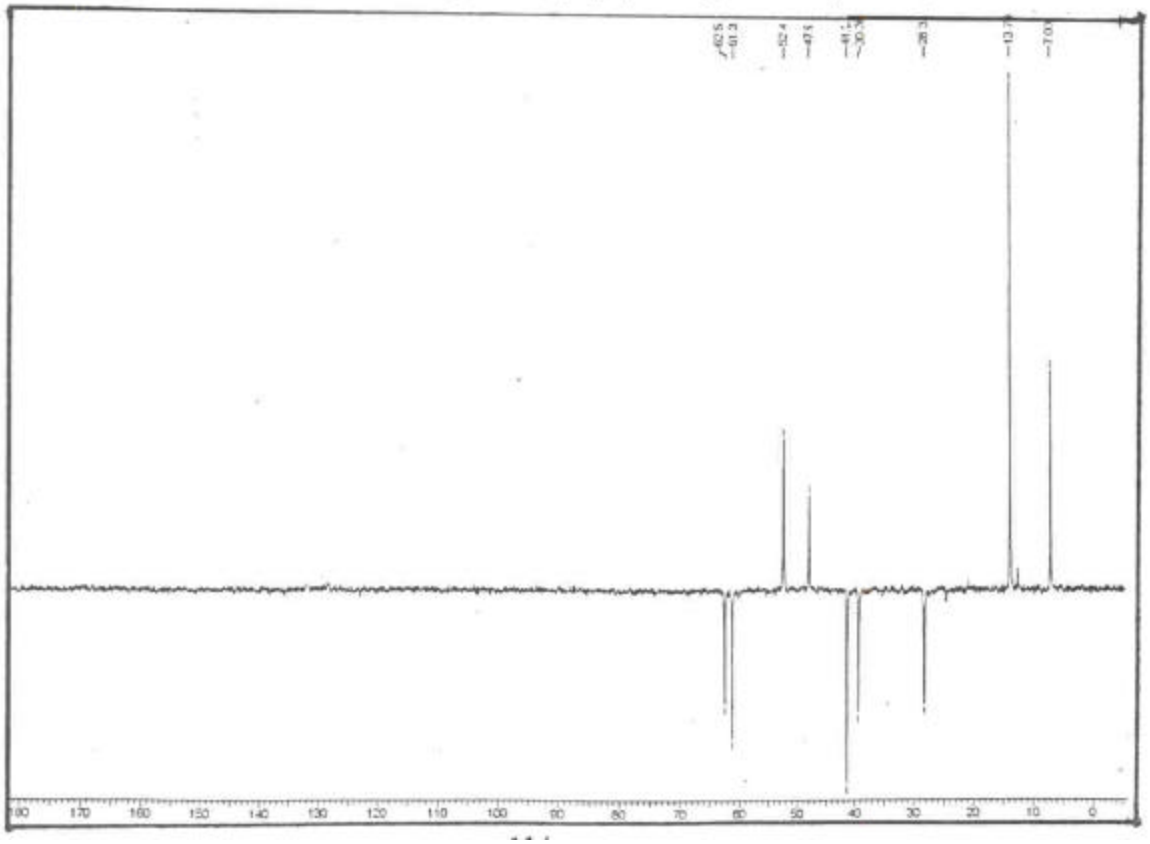


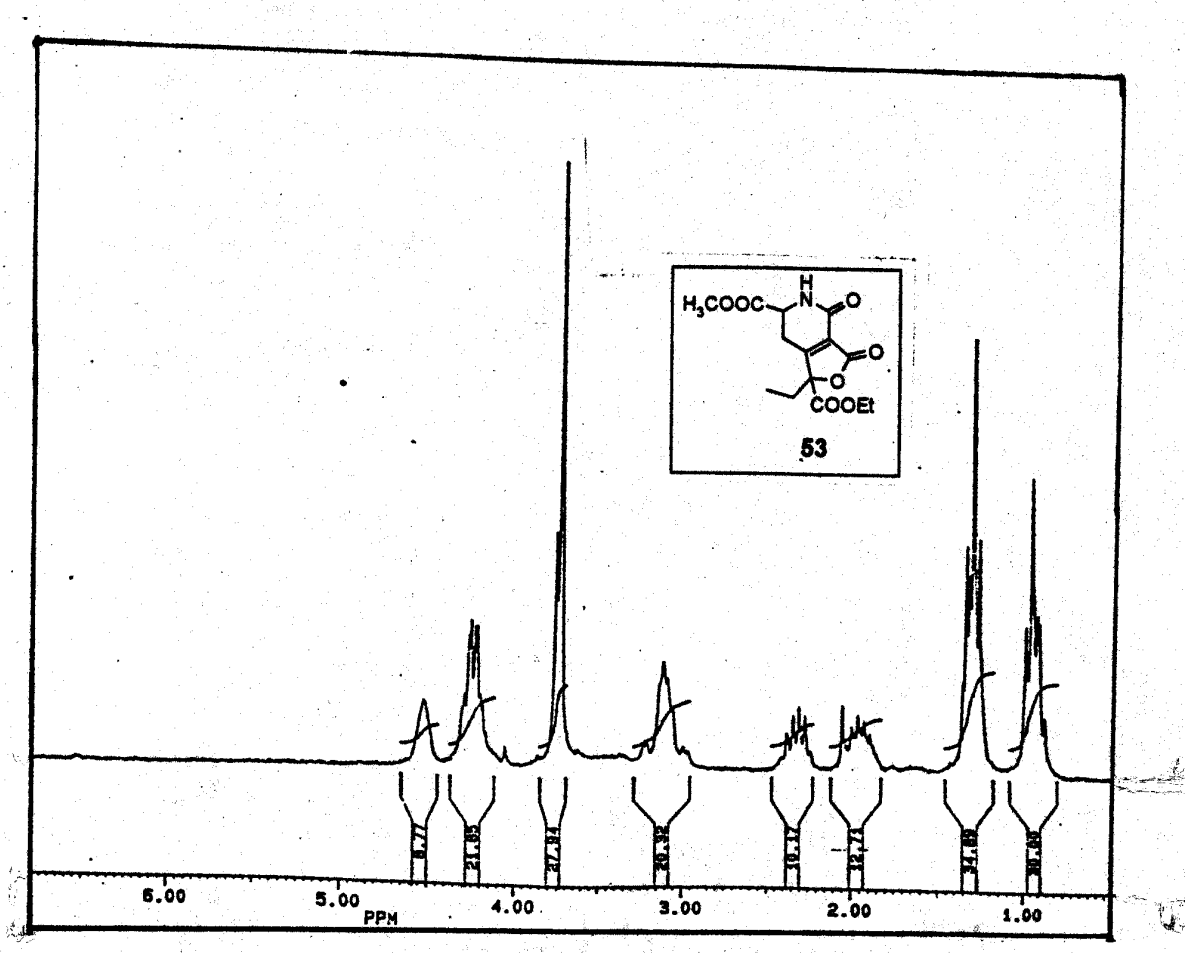


^{1}H-NMR spectrum of compound [48]. ($CDCl_3$, 200 MHz)



^{13}C-NMR & DEPT spectra of compound **[48]. ($CDCl_3$, 50 MHz)**





***^{1}H-NMR spectrum of compound* [53]. ($CDCl_3$, 200 MHz)**

CHAPTER 1

SECTION II

Synthesis of Camptothecin

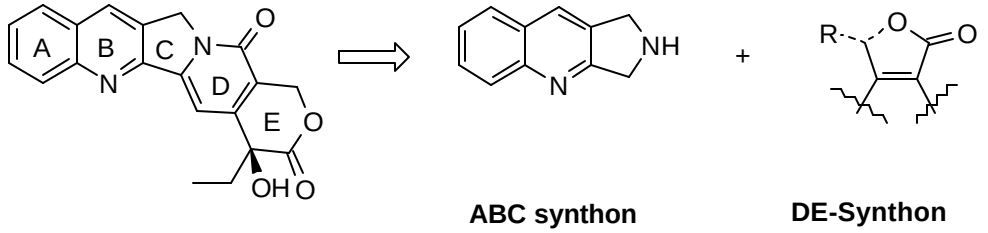
PART C

1.2.3.1 Introduction

The strategy shown in *Scheme 1*, originally formulated by Corey *et al*[116] for the first asymmetric synthesis of Camptothecin and a proven tenet for the assemblage of the skeleton of

Camptothecin, has been employed by many groups in developing their synthetic routes for the title compound with modifications and improvements.

Scheme 1:



1 **54** **55**

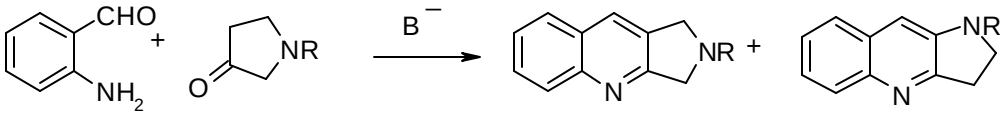
Developing a synthetic route based on this highly convergent approach would involve preparation of ABC synthon and a suitable DE-synthon with necessary functional groups for the coupling with the former. Brief discussion of the reported methods for the preparation of these synthons is given before proceeding to the discussion of actual work.

1.2.3.2 Synthesis of ABC synthon: A Literature Survey

Wall's approach[117] (Scheme 2, 1970).

Wall *et al* relied on the Friedlander condensation of **56** with 2-amino benzaldehyde to obtain the ABC intermediate. Formation of the mixture of regiomers is the limiting factor.

Scheme 2: Wall *et al Chem. Comm*., **1970**, 404

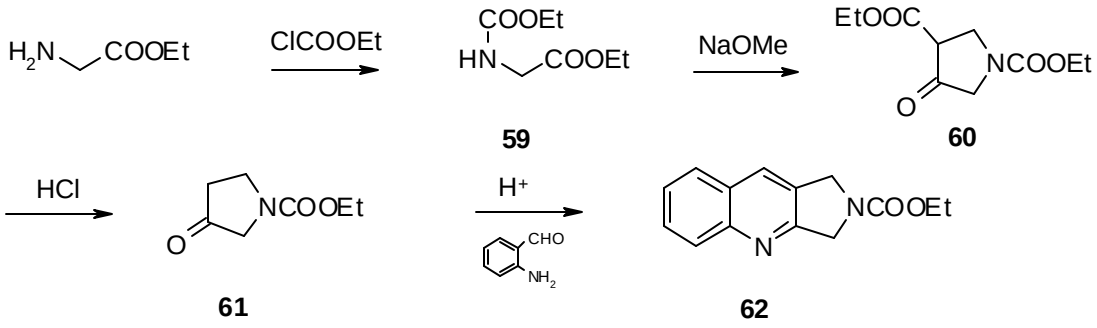


56 **57** **58**

Zalkow's method[118] (**Scheme 3, 1971)**

Glycine carbamate **59** upon Michael addition induced ring closure with ethylacrylate in presence of base provided ß-keto ester **60**, which was decarboxylated to give pyrrolidone **61**. Friedlander condensation of **61** with aminobenzaldehyde resulted in the formation of tricyclic amine ethylcarbamate **62**.

Scheme 3: Jalkow *et.al*, *J. Chem. Soc (C).*, **1971**, 3551

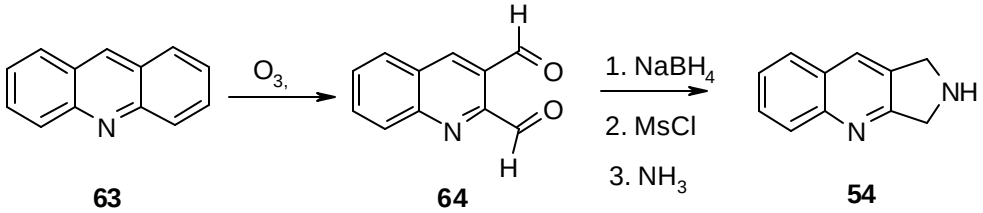


Use of aminobenzaldehyde, and the formation of regioisomers in the final condensation are the drawbacks of this method.

Corey's Method[1] (Scheme 4, 1975)

Quinoline dialdehyde **64** obtained by ozonolysis of acridine was reduced to diol and protected as dimesylate. The cyclization of dimesylate with methanolic ammonia gave the tricyclic amine **54** in 19% yield.

Scheme 4: Corey *et al, J.Org. Chem.* **1975**, *40*, 2140

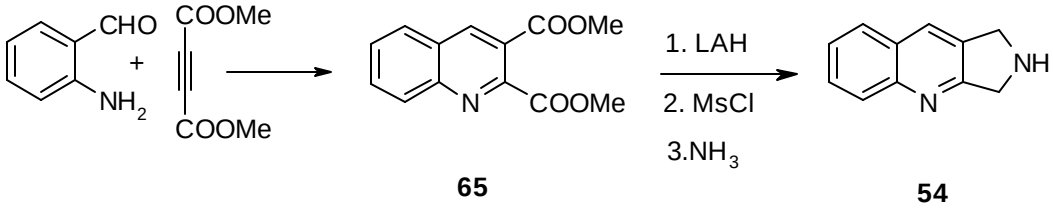


Use of acridine limits the synthetic utility of the approach.

Rama Rao's method[119] (Scheme 5, 1994)

Michael addition of aminobenzaldehyde with DMAD followed by sulfuric acid mediated cyclization afforded the diester **65**, which was reduced to diol and protected as dimesylate. Treatment with methanol ammonia resulted in the formation of tricyclic amine.

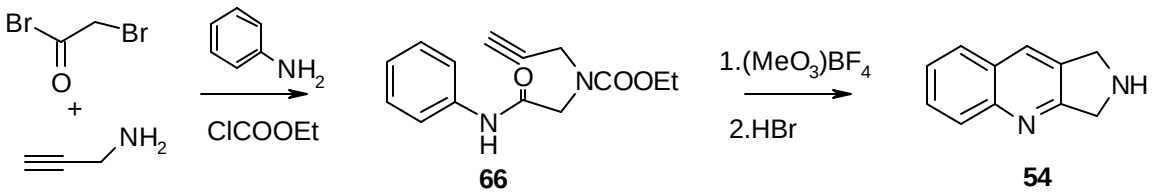
Scheme 5: Rama Rao *et al, Tetrahedron Lett*., **1994**, *35*, 3613



Fortunak's method[120] (Scheme 6, 1996)

The propargylamine was alkylated with bromide, obtained by the condensation of A-bromoacetylbromide to give amide with aniline, which underwent cyclization to give ABC synthon.

Scheme 6: Fortunak *et al, Tetrahedron Lett*., **1996**, *37*, 5683



66 **54**

1. 2. 3. 3 DE-Precursors:

Listed below (chart 1) are some of the synthons employed as DE-precursors that have been condensed with the tricyclic amine **54** for the D-ring formation along with E-ring in some cases or with the suitably placed functional groups for the same.

A careful analysis of these intermediates reveals an underlying common structural requirement *i.e* an acid equivalent for amide formation (normally β-keto ester whose amidation is faster and facile[121] compared to the normal ester) and an aldehyde equivalent (either masked as acetal, or alcohol which is oxidized to aldehyde) for the aldol condensation (C-C bond) with the benzylic position of the tricyclic amine.

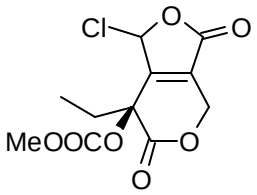
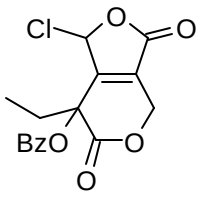
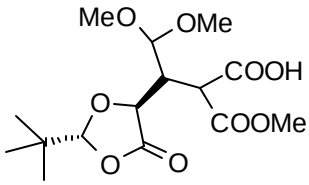
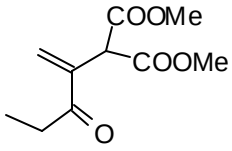
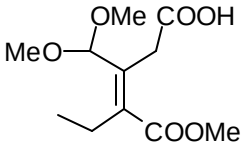
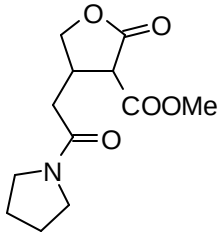
Corey's approach: He employed furan 3, 4-dicarboxylic acid as the starting material. It involved the resolution of the lactones using quinine, which along with the formation of regiomers at later stage limits the synthetic utility.

Rama Rao's approach: He aimed at obtaining the pseudo acid chloride in regio specific manner and overcome the problem of mixture of pseudoacid chlorides encountered by Corey by judiciously employing a tandem Diels-Alder, retro Diels-Alder cycloaddition methods

Fortunak's approach: He employed an asymmetric Michael addition of chiral dioxalonone to the adduct formed by the condensation of the glyoxaldimethyl acetal with benzyl methyl malonate to give the intermediate **69** after hydrogenolysis.

Rest of the synthetic efforts by Wall's[2], Pandit's [6] and Buchi's [7] approaches for DE-synthon are aimed at racemic **1** and vary in the functional groups manipulation while retaining the key structural features discussed above.

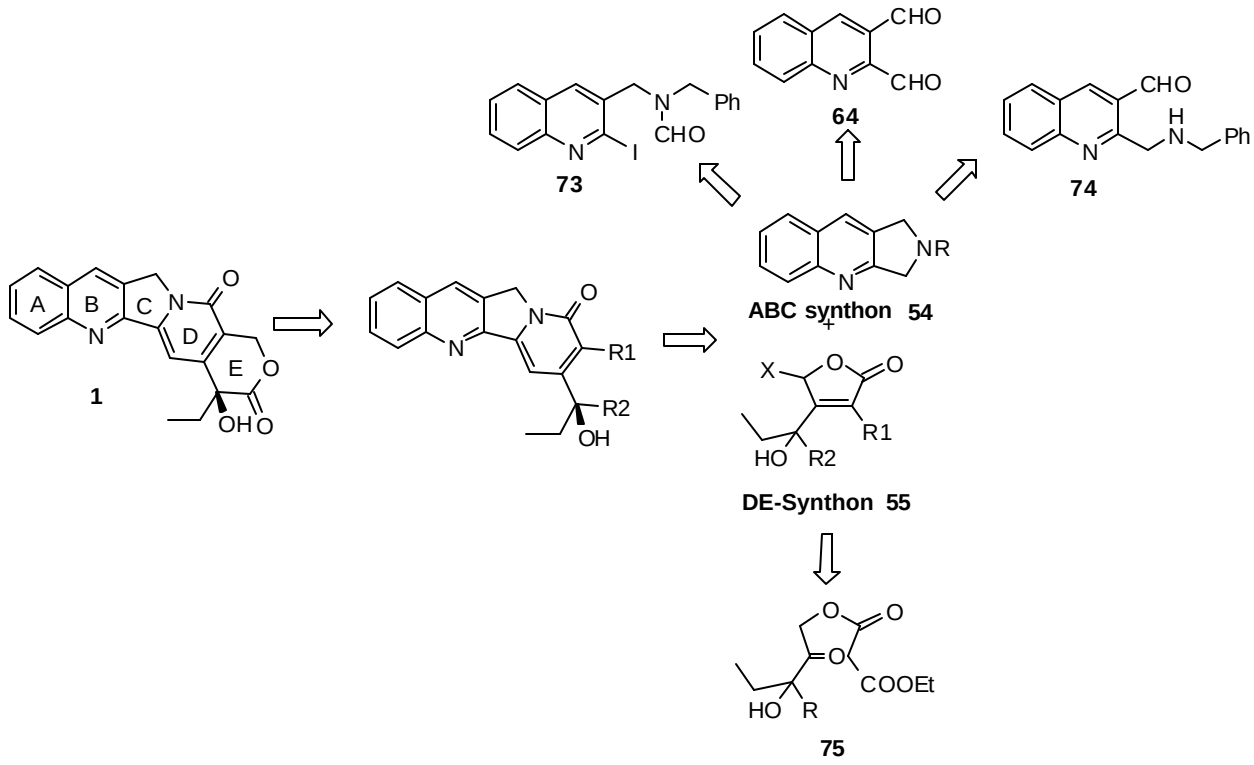
Chart 1

Corey's intermediate[1]  **67**	RamaRao's intermediate[4]  **68**
Fortunak's intermediate[5]  **69**	Wall's Intermediate[2]  **70**
Buchi's intermediate[122]  **71**	Pandit's intermediate[123]  **72**

1.2.3.4 Present Work

We were intrigued by the possibility of straightforward extension of aforementioned methodologies in our synthetic endeavor namely reductive amination of aldehydes and aldol condensation (Section 1.2.1) to synthesize ABC synthon **54** and DE-synthon **55** respectively as will be clear from their retro synthetic analyses (*Scheme 7)*.

Scheme 7: Retroanalysis



1.2.3.5 Results and Discussion

a) **ABC synthon:** Meth-Cohn's quinoline aldehyde **6** with a formyl group at 3-position and the handle at 2-psition for the functionalisation *i.e* C-C bond formation, given the flexibility and simplicity for the analogues preparation appeals to be suitable starting point to do away with the shortcomings of the earlier approaches *i.e* a) usage of 2-aminobenzaldehyde & regiochemistry problems encountered in Friedlander condensation. b) the usage of expensive starting materials like acridine and DMAD.

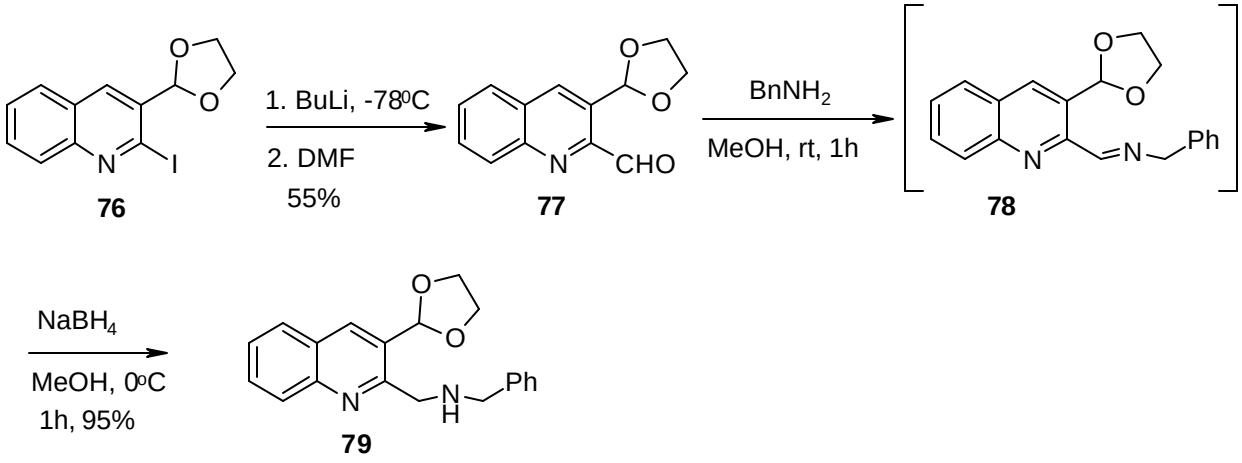
Thus formyl group of the iodoaldehyde **6** was protected as cyclic acetal **76** by treating with ethylene glycol in presence of *p-T*SA (cat) with azeotropic removal of water according to literature procedure. ^{1}H NMR of **76** showed a multiplet at δ 4.18 (4H) and singlet at δ 6.03 (1H) along with the quinoline protons assigned presence of acetal group.

Quenching the litho derivative of **76** with DMF provided 3-oxolyl-2--formyl quinoline **77** in 56% yield after column purification.

^{1}H NMR spectrum of **77** showed a singlet at δ 10.5 (1H) of aldehyde, along with a singlet at δ 6.7 (1H) and multiplet at δ 4.2 (4H) of acetal and quinoline protons in the aromatic region. ^{13}C NMR spectrum showed peak at δ 193.7 confirming the presence of –C=O of aldehyde.

Aldehyde **77** was condensed with benzyl amine in methanol to give Schiff's base **78** whose ^{1}H NMR spectrum showed imine proton at δ 8.60 at the expense of aldehydic proton δ 10.38. Reduction of the Schiff's base **78** with sodium borohydride in methanol furnished amine **79** in quantitative yield.

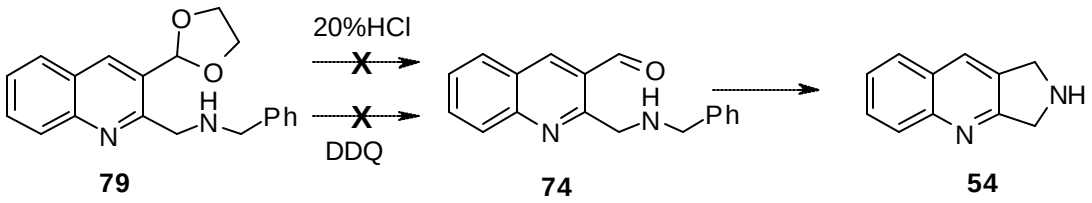
Scheme 8:



^{1}H NMR spectrum of **79** showed apart from quinoline pattern, a multiplet at δ 7.43 (5H) was assigned to phenyl group, two singlets at δ 4.20 and δ 3.94 (2H each) were assigned to the two benzylic -CH_2- groups of the amine.

Attempted deprotection with 20% HCl, failed to give the aminal whose reduction was expected to give the tricyclic amine. In cases where classical deprotection methods fail, DDQ is known to serve the purpose. Unfortunately, even the attempted deprotection of acetal of **79** with DDQ failed to furnish the aldehyde (*Scheme 9*).

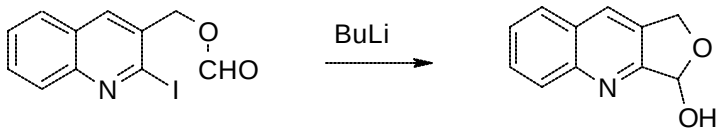
Scheme 9:



79 **74** **54**

Narasimhan *et al* [124] have reported the formation of hemiacetal **81**, which involved the lithiation of *O*-formyl derivative of the quinoline alcohol.

Scheme 10



80 **81**

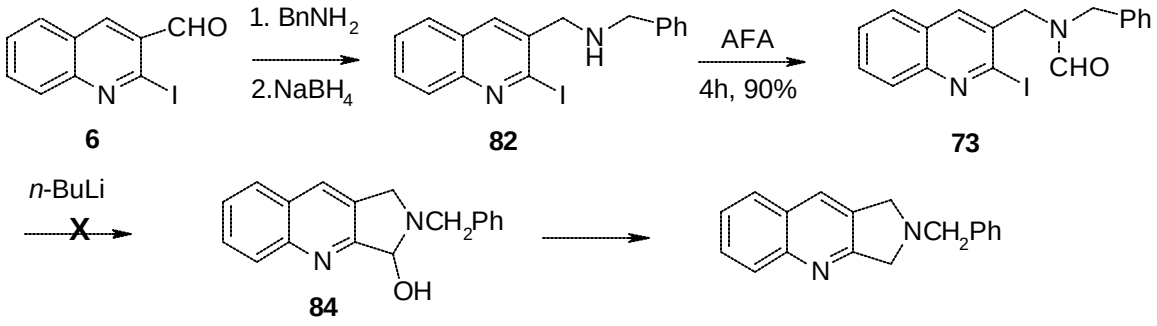
We planned to extend the same principle with *N*-formyl derivative with the idea of converting thus formed aminal **84** to tricyclic synthon **54** by simple reduction. Thus the reductive amination of iodoaldehyde **6** with benzyl amine resulted in the formation of amine **82** in quantitative yield (made in connection with Section 2a).

Treatment of **82** with formylating mixture AFM[125] furnished *N*-formamide **73**.

^{1}H NMR spectrum of **73** showed the singlet at δ 8.59 (1H) assigned to the formyl group, and multiplet at δ 4.5 (4H) assigned for benzylic methylenes.

But the attempts to form the aminal by lithiation followed by the addition of the lithio derivative onto the intramolecular formyl group did not meet with success suggesting the difference in the reactivity of *O*-formate and *N*-formamide.

Scheme 11



6 **82** **73**

84

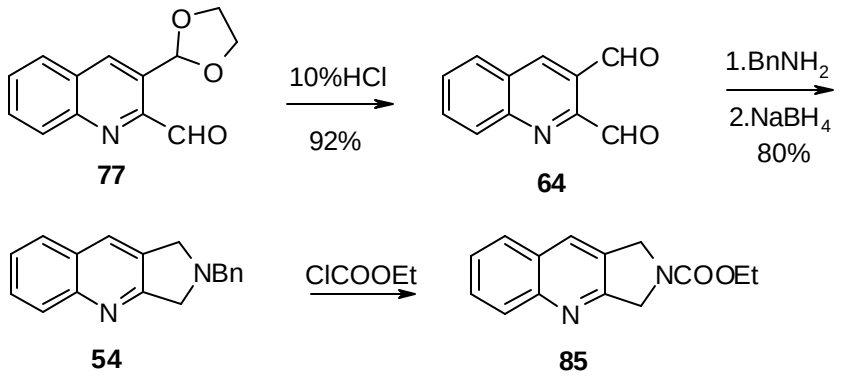
Having failed to effect the C-N bond formation *i.e* deprotection of the acetal protection in the first case and the C-C bond formation in the latter attempt led us consider another alternative *i.e* reductive amination of dialdehyde, which would circumvent these problems.

In this direction, treatment of acteal **77** with 20% HCl in ether furnished dialdehyde **64.** ^{1}H NMR spectrum of **64** showed singlets at δ 11.02 and δ 10.32 (1H each) confirming the 2-formyl groups in the molecule. IR spectrum showed the absorbance at 1705 cm^{-1} and 1680 cm^{-1}

Gratifyingly, the treatment of dialdehyde **64** with 0.6 equivalent of benzyl amine in methanol followed by reduction with sodiumborohydride at 0^{o}C resulted in the formation of tricyclic amine **54** after usual work up and column chromatography. ^{1}H NMR spectrum of **54** showed three distinct singlets at δ 4.13, δ 4.05, δ 4.00 (2H each) assigned to 3 benzylic methylenes of tricyclic amine along with multiplet at 7.2- 7.6 (5H) assigned for -*N*-CH_2-C_6H_5. Further confirmation of the structure was obtained by Mass spectrum, which showed the m/z peak at 260.

Spectral data of the amine **54** thus obtained matched with the spectral data of the sample obtained by a different route and it has been shown that it could be converted to its carbamate **85** by refluxing with ethylchloroformate whose deprotection to tricyclic secondary amine was well established.

Scheme 12:

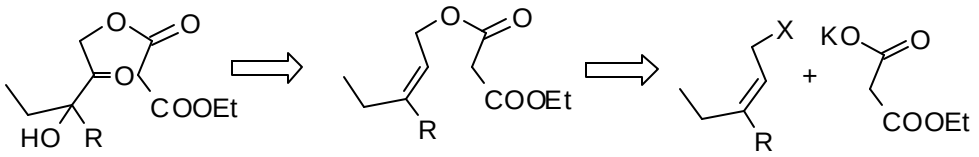


Having been successful in the construction ABC synthon, we turned our attention to the preparation of DE-precursor.

DE-Synthon:

As shown in our retro approach, we envisioned an intramolecular aldol reaction of ketol **75** to construct the basic part with proper functional groups (*Scheme 7)*. The substrate **75** can be traced back to the simple synthons allyl halo compound **86** and potassium salt of malonate **87** (*Scheme 13*).

Scheme 13:

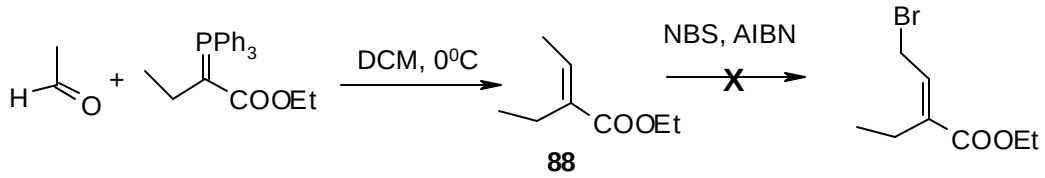


75 **76** **86** **87**

The substrate **86** (R = COOEt) was thought to be obtained by the allylic bromination of the 2-Ethyl but-2-enoic acid ethyl ester which could inturn be obtained from the Wittig reaction of acetaldehyde.

Thus Wittig reaction of acetaldehyde with phosporane gave the ester **88**, but the attempted bromination with NBS resulted in the formation of multiple products, which could not be separated thus warranting an alternative route (Scheme 14).

Scheme 14:



88

A closer look, after simple FGI, suggests an alcohol **86** (R=CH_2OH) to be a suitable substrate which can be advantageous in the final stages of synthesis *i.e* reduction of the ester thus avoiding the decarbonylative loss of ester encountered in the final stages of the synthesis since the oxidation states of the C-17 and C-20 carbonyl would be different (section 1.2.1)

Literature search revealed that such a substrate **86** could be prepared from propargyl alcohol.[126] Thus Mannich reaction of propargyl alcohol[127] with formaldehyde and dialkylamine gave the amino alcohol **89.** ^{1}H NMR spectrum of **89** showed the presence of two singlets at δ 4.24 (2H) and δ 3.39 (2H) were assigned for two propargylic methylenes.

Treatment of compound **89** with ethylmagnesiumbromide[128] gave the 2-ethyl substituted olefin **90.** ^{1}H NMR spectrum of **90** showed a triplet at δ 5.51 (1H) assigned to olefinic proton, doublet at δ 3.41 (2H) for allylic -$\underline{CH_2}$- and quartet δ 2.10 and triplet at δ 0.97 (3H) for ethyl group.

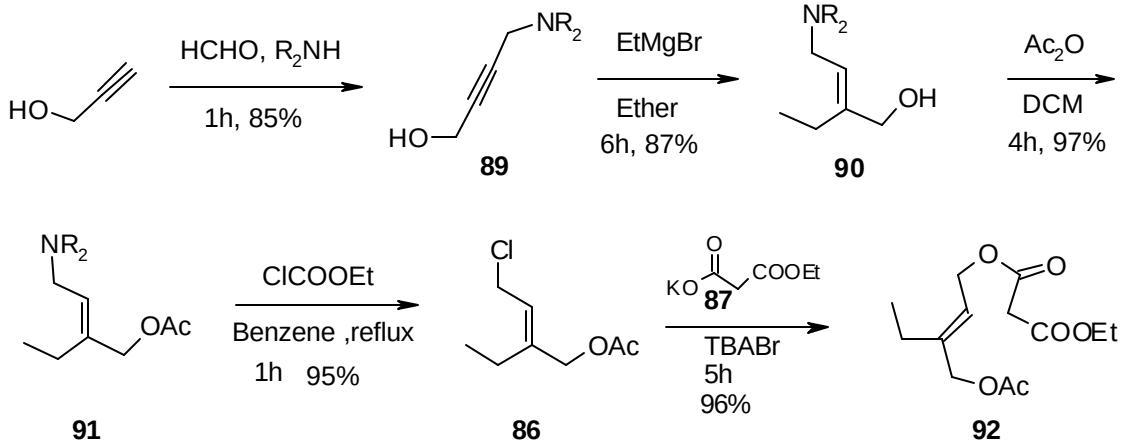
Alcohol was protected as acetate **91** by treating with Ac_2O in DCM followed by neutralization with $NaHCO_3$ solution.

N, *N*-dialkyl group was removed as carbamate by modified Von-Braun reaction[129] *i.e.* by refluxing with ethylchloroformate to obtain the chloro compound **86** in excellent yield. ^{1}H NMR spectrum of **86** showed the absence of alkyl protons and there was a shift in the positions of the allylic -$\underline{CH_2}$- to δ 4.51 (m, 4H) thus confirming the presence of electronegative chloro atom adjacent to it. The acetyl protection was intact.

This chloro compound **86** was treated with potassium salt of monoethylmalonate **87** under PTC conditions to get allylic ester **92** (Scheme 15).

^{1}H NMR spectrum of **92** showed a triplet δ 1.04 (3H) and quartet at δ 2.11 (2H) indicating the presence of ethyl group attached to olefinic-carbon, singlet at δ 2.1 assigned for -OCO$\underline{CH_3}$, singlet at δ3.36 (2H) for active –$\underline{CH_2}$ group, a quartet at δ 4.25 (2H) and triplet (3H) at δ 1.29 for COO$\underline{CH_2}\underline{CH_3}$, singlet at δ 4.34 (2H) for the - $\underline{CH_2}$- OAc, and doublet at δ 4.69(2H) for *O*-$\underline{CH_2}$-CH. IR spectrum showed the absorbance at 1714 cm^{-1}. Mass spectral analysis showed the m/z at 272.

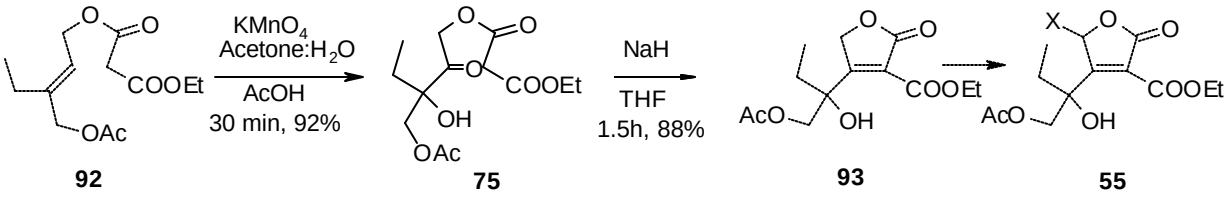
Scheme 15



Treatment of ester **92** in aq acetone with $KMnO_4$ under acidic pH conditions resulted in the formation of ketol **75.** ^{1}H NMR spectrum of **75** showed the absence of olefinic protons, and up field shifted singlet at δ 5.04 (2H) indicating the presence of -O$\underline{CH_2}$CO-, and multiplet at δ 4.25 for –$\underline{CH_2}$-OAc (merged with the quartet of-COOEt) and the multiplet at δ 1.71 (2H) for -$\underline{CH_2}$-CH_3 (due to the adjacent quarternary center causing the multiplicity), singlets at δ 2.09 (3H) and δ 3.49 (2H) were ascribed to for acetyl and active methylene groups respectively. IR spectrum showed absorbance at 3486 cm^{-1} and 1744 cm^{-1} indicating the presence of a-hydroxy β-keto ester functional groups. Mass spectrum showed the m/z peak at 304.

Ketol **75** upon treatment with NaH / THF underwent Aldol condensation to furnish intermediate **93** (*Scheme 16*). ^{1}H NMR spectrum of **93** indicated the absence of singlet of active methylene (–$\underline{CH_2}$-COOEt) and the appearance of quartet at δ 4.8 (2H) due to the lactone formation causing the vicinal coupling (AB pattern), and a singlet at δ 2.1 (3H) and quartet at δ 4.4 (2+2H) and triplet at δ 1.4 (3H) confirming the presence of -$COOC_2H_5$ and acetyl group respectively. IR spectrum showed the absorbance at 1765 cm^{-1} and 1745 cm^{-1}.

Scheme 16



92 **75** **93** **55**

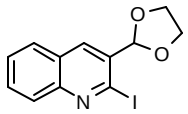
Allylic halogenation of **93** would result in the formation of pseudoacid halide **55** whose coupling with tricyclicamine **54** would in turn provide an advanced intermediate for the Camptothecin synthesis after simple functional group manipulations. Work is in progress.

Conclusion

We have demonstrated the potentiality of our methodologies i.e reductive amination and intramolecular condensation for the synthesis of synthons involved in the convergent approach to Camptothecin.

1.2.3.6. Experimental:

1. 3-[1,3] Dioxaolan-2-yl-2-iodo-quinoline [76]



76

A solution of 2-chloro-3-formyl quinoline (28.3, 0.1mol) in benzene (300mL) containing ethylene glycol (0.3 mol) and catalytic amount of *p*-TSA was heated under reflux for 5h with azeotropic removal of water. The cooled solution was treated with sat. $NaHCO_3$ solution (300 mL) was added and dried and evaporated to give **76** as white solid, which was pure enough for further use.

Molecular Formula : $C_{12}H_{10}INO_2$, 379

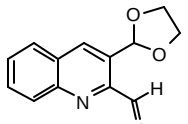
Yield : 34.1g, 90%

IR (Nujol) : 1625, 1555, 1310, 1175 cm^{-1}

^{1}H NMR (200MHz) : δ: 8.18 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.81 (dd, *J* = 8.2Hz, 1.4hz, 1H), 7.61 (t, 1H), 7.57 (t, 1H), 6.03 (s, 1H), 4.18 (m, 4H)

Mass, m/z (%) : 327 (M^+, 5), 235 (80), 204 (10), 200 (30), 190 (50), 163 (100), 148 (75), 127 (50), 101 (30)

2. 3-[1,3] Dioxolan-2-yl-quinoline-2-carbaldehyde [77]



77

3-[1,3] dioxolan-2yl-2-iodo-quinoline **76** (0.654g, 2mmol) in dry ether at -70°C under N_2 atmosphere was treated with *n*-BuLi (1.1 mL, 2M sol in toluene, 2.1mmol) with stirring and after few minutes dry DMF was added. After reaching ambient temp the solution was treated with water and extracted with $CHCl_3$ (3×20mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude aldehyde, which was purified by column chromatography over silica gel using ethylacetate-pet ether (3:7) as eluent to give pure **77**.

Molecular Formula : $C_{13}H_{11}NO_3$, 229

M.P. **:** 145^{o}C

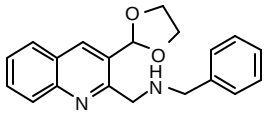
Yield **:** 0.251g, 55%

IR ($CHCl_3$) : 1685, 1617, 1560, 1145, 910cm^{-1}

^{1}H NMR (200MHz): δ: 10.37(s, 1H), 8.6 (s, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.3Hz, 1H), 7.61 (t, 1H), 7.57 (t, 1H), 6.73 (s, 1H), 4.18 (m, 4H)

^{13}C NMR (50Mhz) : δ: 193.79 (C), 149.79 (C), 146.92 (C), 134.65 (CH), 130.31 (CH), 129.57 (C), 129.52(CH), 129.02 (C), 128.21(C), 127.86 (CH), 98.59 (CH), 64.99 (CH_2)

3. (3-[1,3]Dioxolan-2-yl-quinolin-2-ylmethyl)-phenyl-amine [79]



79

Quinoline aldehyde **77** (1.135 g, 5 mmol) and benzylamine (0.648 g, 6 mmol) were mixed in MeOH (40 mL) at rt under N_2 atmosphere and the mixture was stirred at rt for 3h, until the aldimine **78** formation was completed (determined by TLC). The aldimine in MeOH was carefully treated at 0^{o}C with solid $NaBH_4$ (0.6 g, 16 mmol). The reaction mixture was stirred for 10 min at 0^{o}C and it was brought to room temperature and allowed to stir for 1h after which methanol was removed under reduced pressure and water was added and extracted with $CHCl_3$ (2×30 ml) .The combined organic extract was washed with saturated aqueous NaCl and dried (Na_2SO_4). The solvent was evaporated to give the product **79**, which was subjected for formylation directly with out any purification.

Molecular Formula : $C_{20}H_{20}N_2O_2$, 320

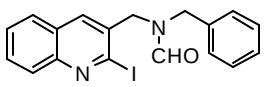
M.P. : 111^{o}C

Yield : 1.45g, , 95%.

IR ($CHCl_3$) : 3425, 1625, 1150cm^{-1}

^{1}H NMR (200MHz) : δ: 8.30 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 8.3Hz 1H), 7.71(m, 1H), 7.52 (m, 1H), 7.43 –7.2 (m, 5H), 6.12 (s, 1H), 4.20 (s, 2H), 4.18 (m, 4H), 3.94 (2H).

4. *N*-Benzyl-*N*- (2-iodo-quinolin-3-ylmethyl)-formamide [73]



73

To the solution of acetic formic anhydride (obtained by Krimen's procedure by 1:1 mixture of sodium formate and acetyl chloride in dry THF) was added amine **82** (0.750g, 2mmol) at 0^oC and was slowly brought to rt at which it was stirred for 4hrs. It was quenched with Na_2CO_3 solution and extracted with ethylacetate (3×50mL). The organic phase was dried and evaporated to give crude *N*-formamide, which was purified by silica gel column chromatography using 50% ethyl acetate and petether as eluent.

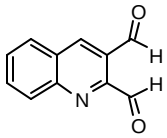
Molecular .Formula : $C_{18}H_{15}IN_2O$, 402.24

Yield : 0.723g, 90%

IR ($CHCl_3$) : 34001, 1750cm^{-1}

^{1}H NMR (200MHz) : δ 8.59 (s, 1H), 8.03 (, 1H), 7.60-7.0 (m, 7H), 4.5 (dd , 4H),.

5. Quinoline-2, 3-dialdehyde [64]



64

The quinoline acetal **77** (0.460g, 2mmol) was suspended in a 1:2 mixture of aq HCl solution (2M) and ether for 1h. Ether layer was removed and the aqueous phase was basified and evaporated with $CHCl_3$ (2×75 mL) and the extracts were dried and evaporated under reduced pressure to give dialdehyde **64** as a yellow solid.

Molecular Formula : $C_{11}H_7NO_2$, 185

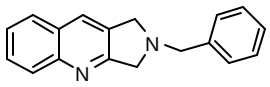
M.P. : 137^oC

Yield : 0.340g, 92%

IR ($CHCl_3$) : 1705, 1680, 1620, 1575cm^{-1}

^{1}H NMR (200MHz) : δ: 11.02 (s, 1H), 10.38 (s, 1H), 8.86 (s, 1H), 8.31 (d, *J* = 8.2Hz, 1H), 8.06 (d, 1H), 7.98 (t, 1H), 7.8 (t, 1H)

6. 2-Benzyl-2, 3-dihydro-1H-pyrrolo [3,4-b] quinoline [54]



54

Quinoline dialdehyde **64** (1.85 g, 10 mmol) and benzylamine (0.645g, 0.6eq) were mixed in MeOH (20 mL) at rt under a N_2 atmosphere and the mixture was stirred at rt for 1h, until the aldimine formation was completed (monitored by TLC). The aldimine in MeOH at $0^oC$was carefully treated with solid $NaBH_4$ (0.6 g, 1.6 mmol) and stirred for 10 min. The reaction mixture was brought to room temperature and allowed to stir for 1hr after which methanol was removed under reduced pressure and added water, extracted with $CHCl_3$ (2×30 ml) .The combined organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was evaporated to give the crude product 54**.** Analytically pure sample was obtained by column chromatography (silica gel, 30% Ethylacetate-petether)

Molecular Formula : $C_{18}H_{16}N_2$, 260

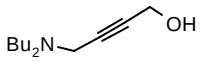
Yield : 210 g, 80%

IR ($CHCl_3$) : 3340, 1540, 1260cm^{-1}

^{1}**HNMR**(200MHz) : δ: 8.05 (d, 1H), 7.86 (s 1H), 7.73 (d, 1H), 7.76 (dt, 1H), 7.5-7.23 (m, 6H), 4.13 (s, 2H), 4.05 (s, 2H), 4.00 (s, 2H)

Mass m/z (%) : 260, 259, 183, 140, 114, 91

7. 4-Dibutylamino-but-2-yn-1-ol [89]



89

Dibutylamine (145g, 1.2moles) was dissolved in water (80mL) and the solution was brought to pH 9 by the addition of a solution of 50% sulfuric acid. Formaldehyde (35% solution in water,1.6 moles) solution was added to the mixture followed by propargyl alcohol (56g, 1mmol). A solution of 5g of $CuSO_4$ in water (50mL)f was admixed with the contents of the reaction vessel and the pH was adjusted to 8.4 by the addition of excess of dibutylamine solution. The reaction was heated at 80^oC under reflux with stirring with the greenish ppt, which gradually turned yellow, indicating the formation of copper propargylate and deposition of metallic copper (1h). The mixture was cooled and poured into 300 mL of the ice-cold con. NH_3. The combined

aqueous solutions were then extracted with DCM (3×200mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was distilled *in vacuo* to yield the amino alcohol **89**.

Molecular. Formula : $C_{12}H_{23}NO$

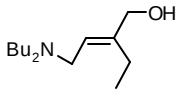
B.P. : 125^oC, 100mm of Hg

Yield : 121 g, 81%.

IR (Neat) : 3600, 780cm^{-1}

^{1}**HNMR**(200MHz) : δ 4.24 (s, 2H), 3.39 (s, 2H), 2.75 (br s, 1H), 2.43 (t, 4H), 1.36 (m, 8H), 0.97 (6H)

8. 4-Butylamino-2-ethyl-but-2-en-1-ol [90]



90

Mg powder (24.3 g, 1 mol) in ether (400 mL) was treated with ethyl bromide (108g, 1 mol) and the mixture stirred for 1h. To this Grignard reagent (1mol) in ether was added dropwise a solution of **89** (65g, 0.33 mol) in ether (260 mL) *dropwise* at room temperature under a N_2 atmosphere and the resulting mixture was stirred for 1h, and under refluxed for 4h. It was treated with a large excess of NH_4Cl solution and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The pure aminoallylic alcohol **90** was obtained by distillation under reduced pressure.

Molecular. Formula : $C_{14}H_{29}NO$, 227

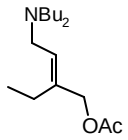
B.P. : 130 ^oC, 10mm

Yield : 60.13g, 87%

IR (Neat) : 3350, 1419 cm^{-1}

^{1}**HNMR**(200MH) : δ: 5.51 (t, 1H), 4.06 (s, 2H), 3.41 (d, 2H), 2.41 (t, 4H +1H of -OH), 2.10 (m, 2H), 1.5-1.26 (m, 8H), 0.97 (m, 9H)

9. Acetic acid 4-dibutylamino-2-ethyl-but-2-enyl ester [91]



91

A solution of 90 (22.5 g, 0.1 mmol) in dry dichloromethane (30 mL) was treated with acetic anhydride (13.85g, 0.13mol). The reaction was quenched after 4h with $NaHCO_3$ solution and evaporated *in vacuo*. The oily residue was distilled under vacuum to obtain the pure acetate **91.**

Molecular. Formula : $C_{16}H_{31}NO_2$, 269

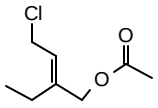
B.P. : 115^oC at 10 mm of Hg

Yield : 25.9 g, 97%

IR (Neat**)** : 3450, 1738cm^{-1},

^{1}**HNMR**(200MHz) : δ: 5.53 (t, 1H), 4.51 (s, 2H), 3.09 (d, 2H), 2.39 (t, 4H), 2.10 (q, 2H), 2.08 (s, 3H), 1.5-1.26 (m, 8H), 0.97 (m, 9H)

10. 4-Chloro-2-ethyl-but-2-enyl acetate [86]



86

To a refluxing solution of amine **91** (13.5g, 0.05mol) in benzene (70mL) was rapidly added a solution of ClCOOEt (1.5 mmol, 7.5 g) in benzene (20mL), and refluxing was continued for 1h. After the appearance of single carbamate, the reaction mixture was cooled and washed with dil. HCl, water and dried (Na_2SO_4) After the evaporation of the solvent under reduced pressure, chloro acetate was obtained by fractional distillation from the carbamate by product.

Molecular Formula : $C_8H_{13}ClO_2$, 176

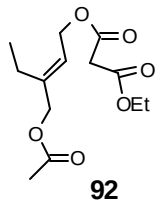
B.P. : 98^oC at 760mm of Hg

Yield : 10.36, 95%.

IR (Neat) : 3448, 1738, 770 cm^{-1}

^{1}**H NMR** (200MHz) : δ 5.63 (t, 1H), 4.51 (m, 4H), 2.20 (q, 2H), 2.08 (s, 3H) 1.06 (t, 3H),

11. Malonic acid 3-acetoxymethyl-pent-2-enyl ester ethyl ester [92]



92

To a suspension of ethyl potassium malonate **87** (2.4g, 14mmol) in CH_2Cl_2 (30mL) in the presence of tetrabutylammonium bromide (0.450g, 10% molar) was added quickly the allyl chloroacetate **86** (1.76g, 10mmol). The reaction mixture was stirred at rt for 5h. After evaporation of CH_2Cl_2 the residue was diluted with ether (40 mL) and then washed with water before drying over Na_2SO_4 .The dried extracts were concentrated on rotaevaporator to yield the allylic malonate **92** as colourless oil.

Molecular Formula : $C_{13}H_{20}O_6$, 272

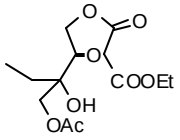
Yield : 2.611 g, 96%

IR (Neat) : 1773, 1740, 1501cm^{-1}

^{1}**HNMR**(200MHz) : δ: 5.58 (t, 1H), 4.69 (d, *J* = 7.2Hz, 2H), 4.54 (s, 2H), 4.23 (q, 2H), 3.36 (s, 2H), 2.12 (q, 2H), 2.11 (s, 3H), 1.26 (t, 3H), 1.0.4 (t, 3H).

Mass m/z (%) : 272 (4), 212 (5), 167 (7), 14 0(20), 115 (38), 98 (100), 80 (48), 69 (20).

12. Malonic acid 3-acetoxymethyl-3-hydroxy-2-oxo-pentyl ester ethyl ester [75]



75

To a stirred solution of olefin **92** (0.574 g 2mmol) and AcOH (0.7ml) in 10ml of aqueous acetone (1: 9 of H_2O: Acetone) maintained at -10^oC, was added $KMnO_4$ (0.555g, 3.4 mmol) in portions such that the reaction temperature remains below -10^oC. After stirring for 1/2 h at 10^oC, the black ppt of MnO_2 is filtered off through Celite pad and filtrate was evaporated at reduced pressure to remove acetone and extracted with CH_2Cl_2 (3×50 mL) .The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to furnish crude ketol **75** Purification by column chromatography over silica gel using 60% ethylacetate -petether as eluent furnished ketol **75** as a colourless oil.

Molecular Formula : $C_{13}H_{20}O_8$, 304.30

Yield : 0.559 g, 92%

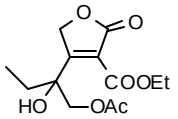
IR : 3486, 3000, 2557.25, 1744, 1436, 1012, 900 cm^{-1}

^{1}HNMR(200MHz) : δ: 5.04 (s, 2H), 4.21 (m, 4H), 3.49 (s, 2H), 2.09 (s, 3H), 1.75 (m, 2H), 1.3 (t, 3H), 0.94 (t, 3H)

^{13}C NMR (50MHz) : δ: 206 (C), 166 (C), 165.1 (C), 165 (C), 82 (CH), 68 (CH_2), 67 (CH_2), 62 (CH_2), 42 (CH_2), 27 (CH_2), 21 (CH_3), 13.5 (CH_3), 12.1 (CH_3),

Mass m/z (%) : 305 (6), 287 (10), 259 (9), 241 (50), 217 (17) 203 (12), 199 (31), 173 (29), 146 (40), 131 (100), 115 (90), 9 (67), 71 (78), 57 (40)

13. 4-(1-Acetoxymethyl-1-hydroxy-propyl)-2-oxo-2, 5-dihydro-furan-3-carboxylic acid ethyl ester [93]



93

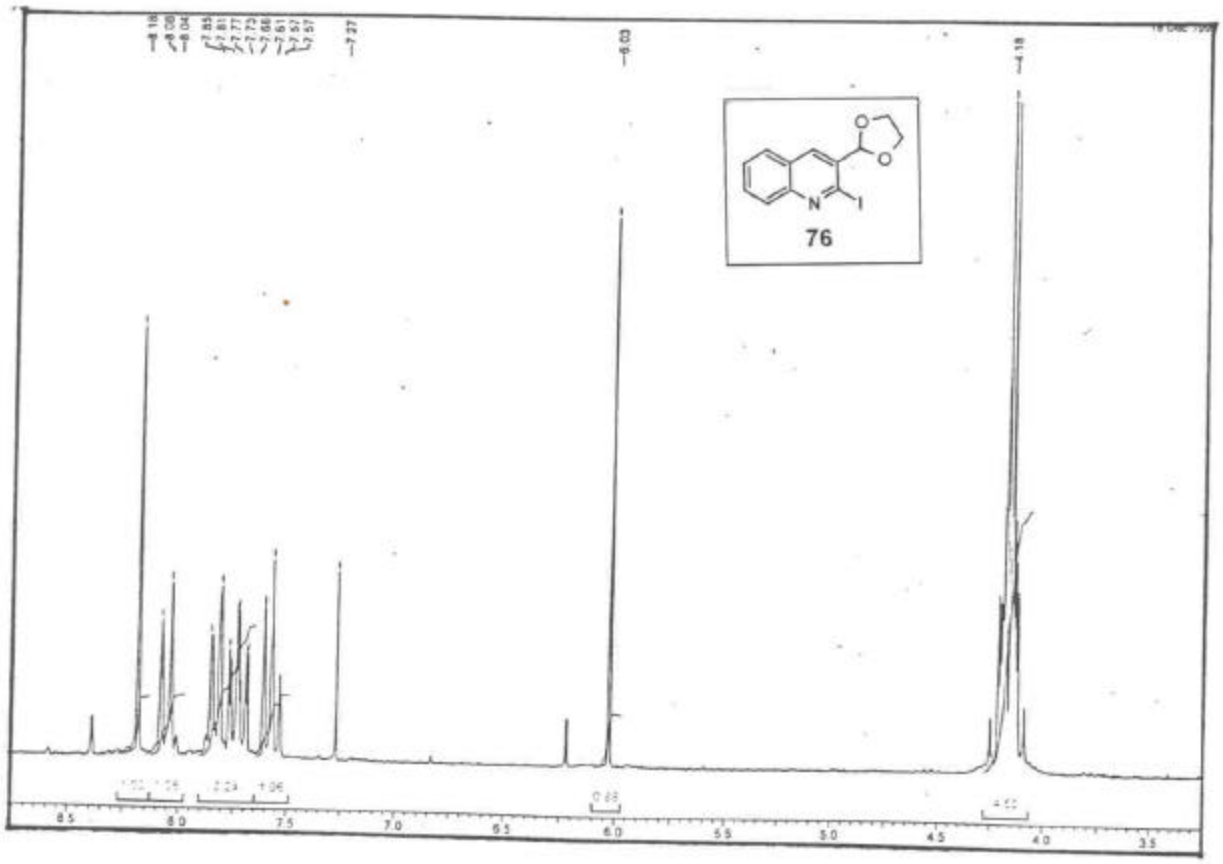
To a precooled solution of NaH (0.134 g, 50% suspension in mineral oil, 0.284 mmol) (pre washed with petether, 2×5ml) in THF (15 mL) was added diester **75** (0.3g) in THF, without allowing the temperature to rise beyond 10^{o}C. The reaction mixture was allowed to rise to room temperature and stirred for 1h, quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 (3×20mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography over silica gel using 60% ethylacetate – pet ether as eluent furnished **93** as a colourless oil

Molecular Formula : $C_{13}H_{18}O_6$

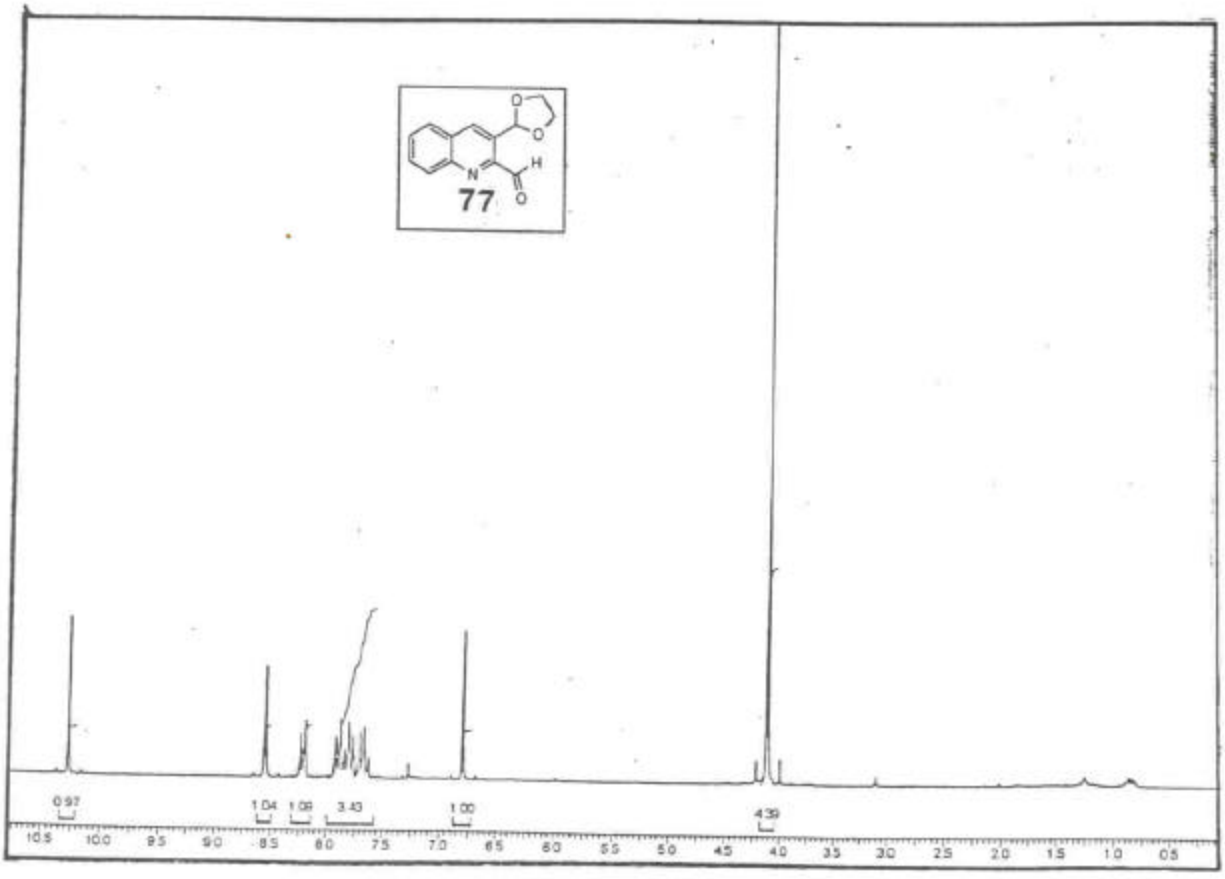
Yield : 0.253 g, 88%

IR : 3516, 3379, 3134, 2980, 1765, 1745, 1461, 1443, 1097 cm^{-1}

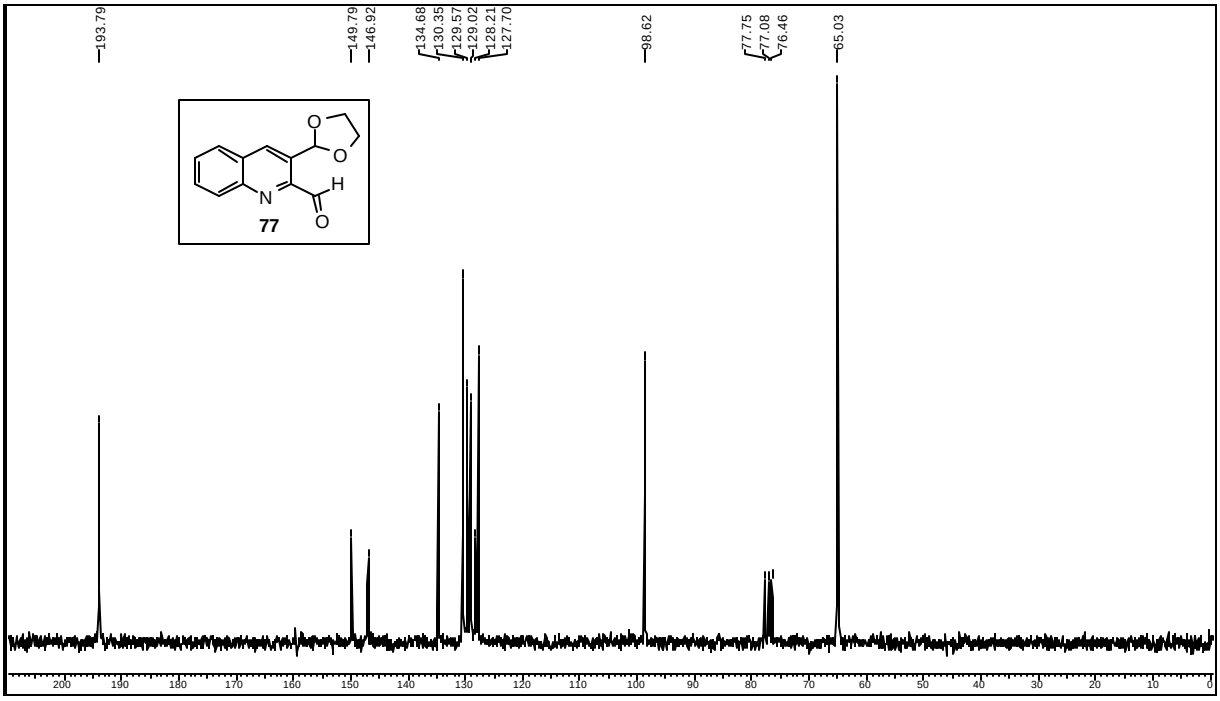
^{1}H NMR (200MHz) : δ: 4.9 (d, *J* = 4.2Hz, 2H), 4.41 (m, 4H), 2.1 (s, 3H), 1.7-1.9 (m, 2H), 1.30 (t, 3H), 0.9 (t, 3H)



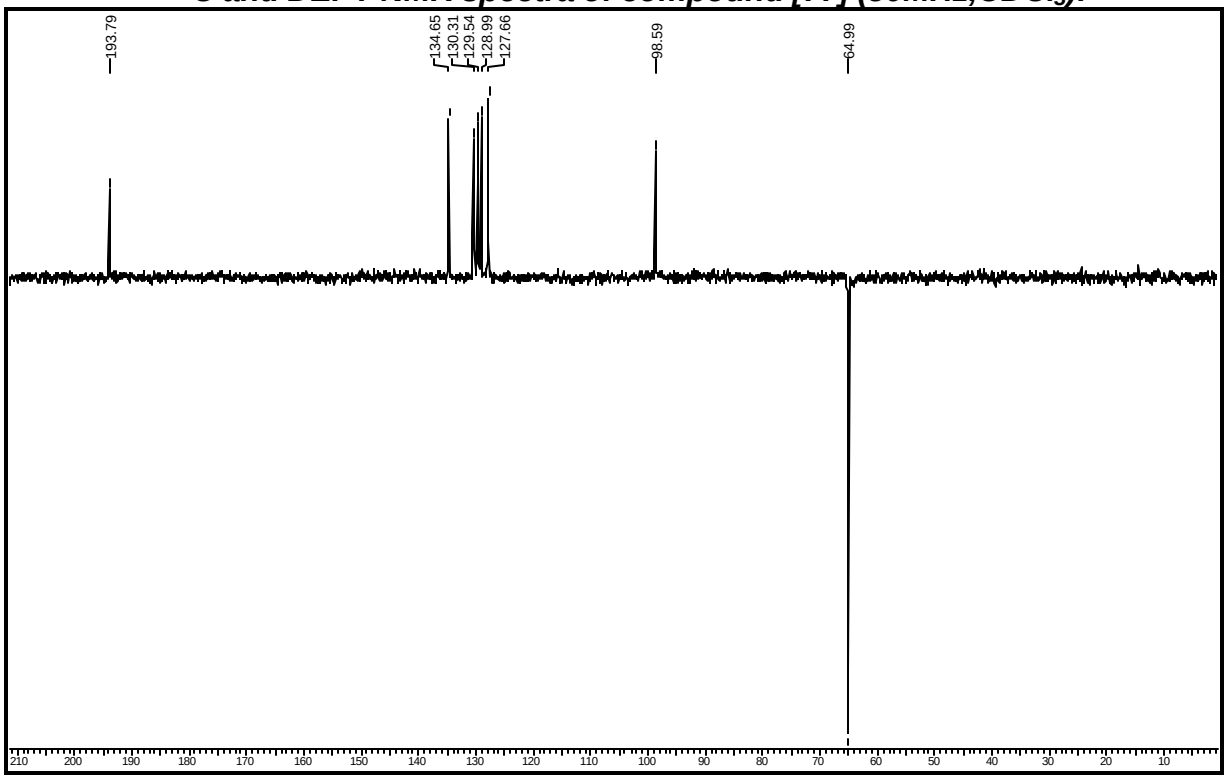
^{1}H-NMR spectrum of compound [76]. ($CDCl_3$, 200 MHz)

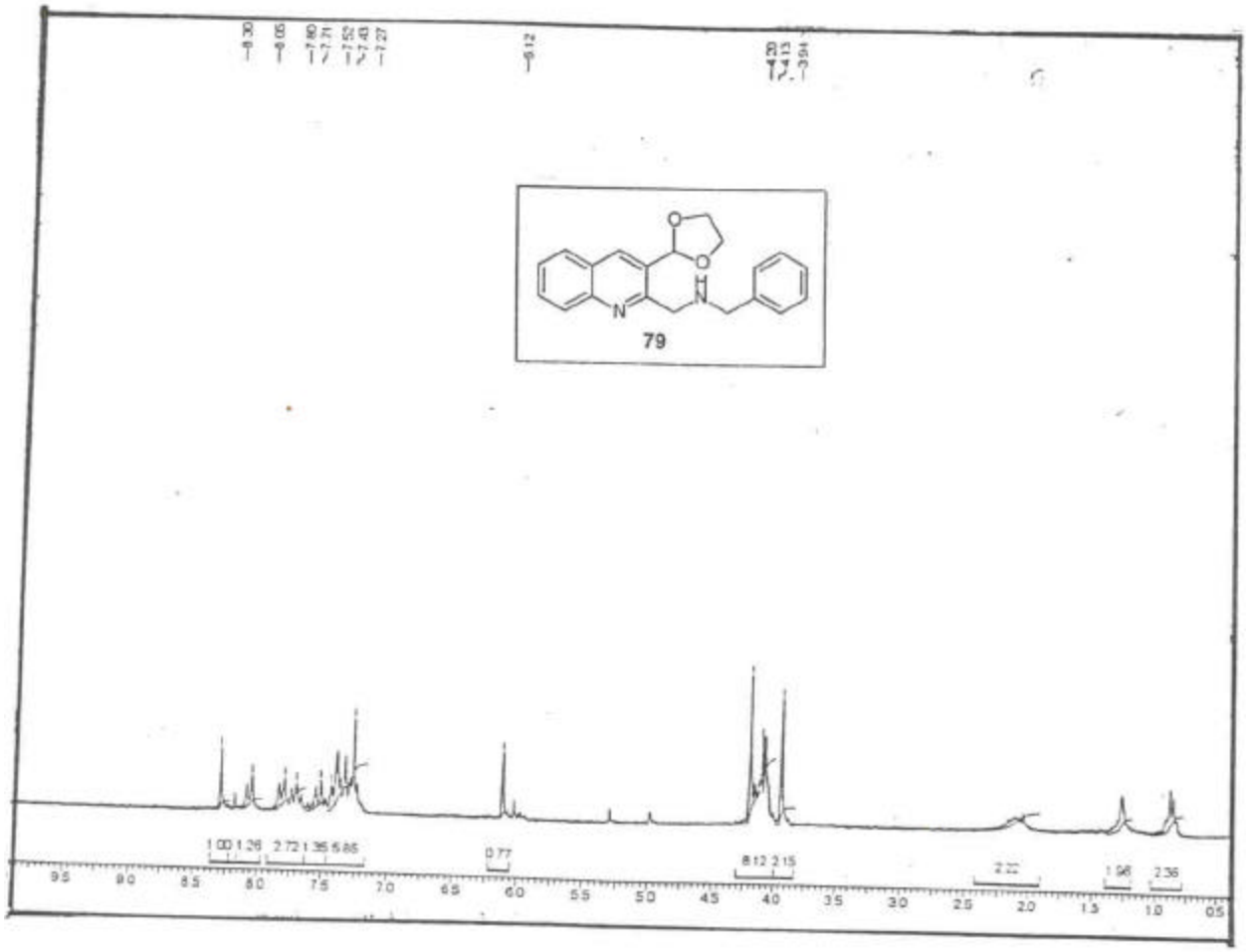


^{1}H-NMR spectrum of compound [77]. ($CDCl_3$, 200 MHz)

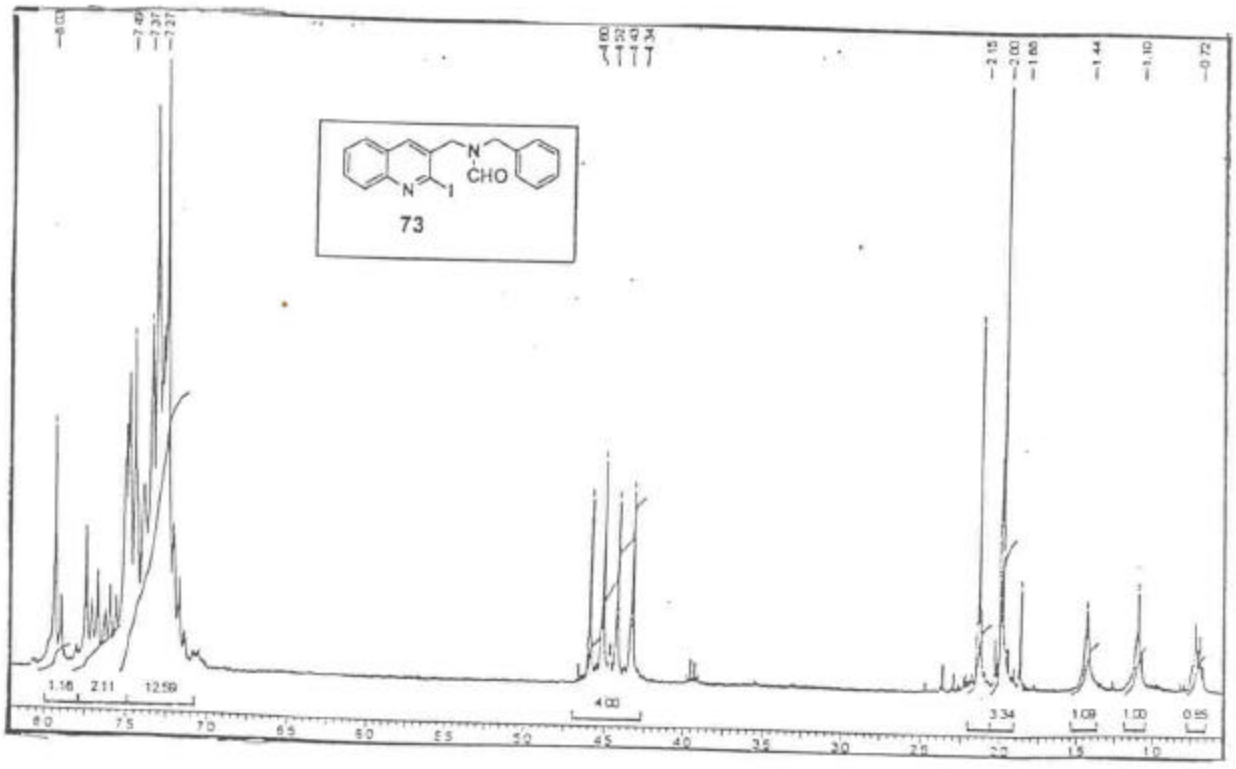


^{13}C and DEPT NMR spectra of compound [77] (50MHz,$CDCl_3$).

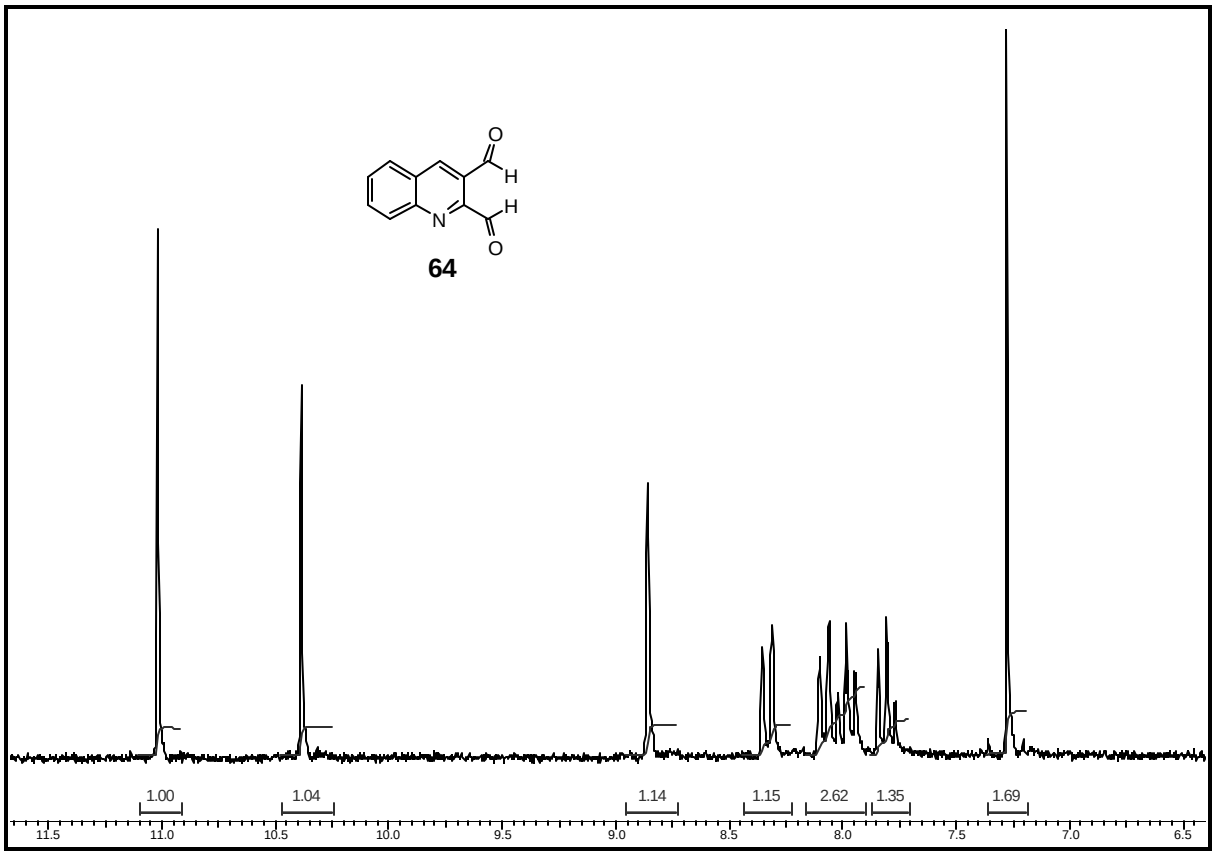




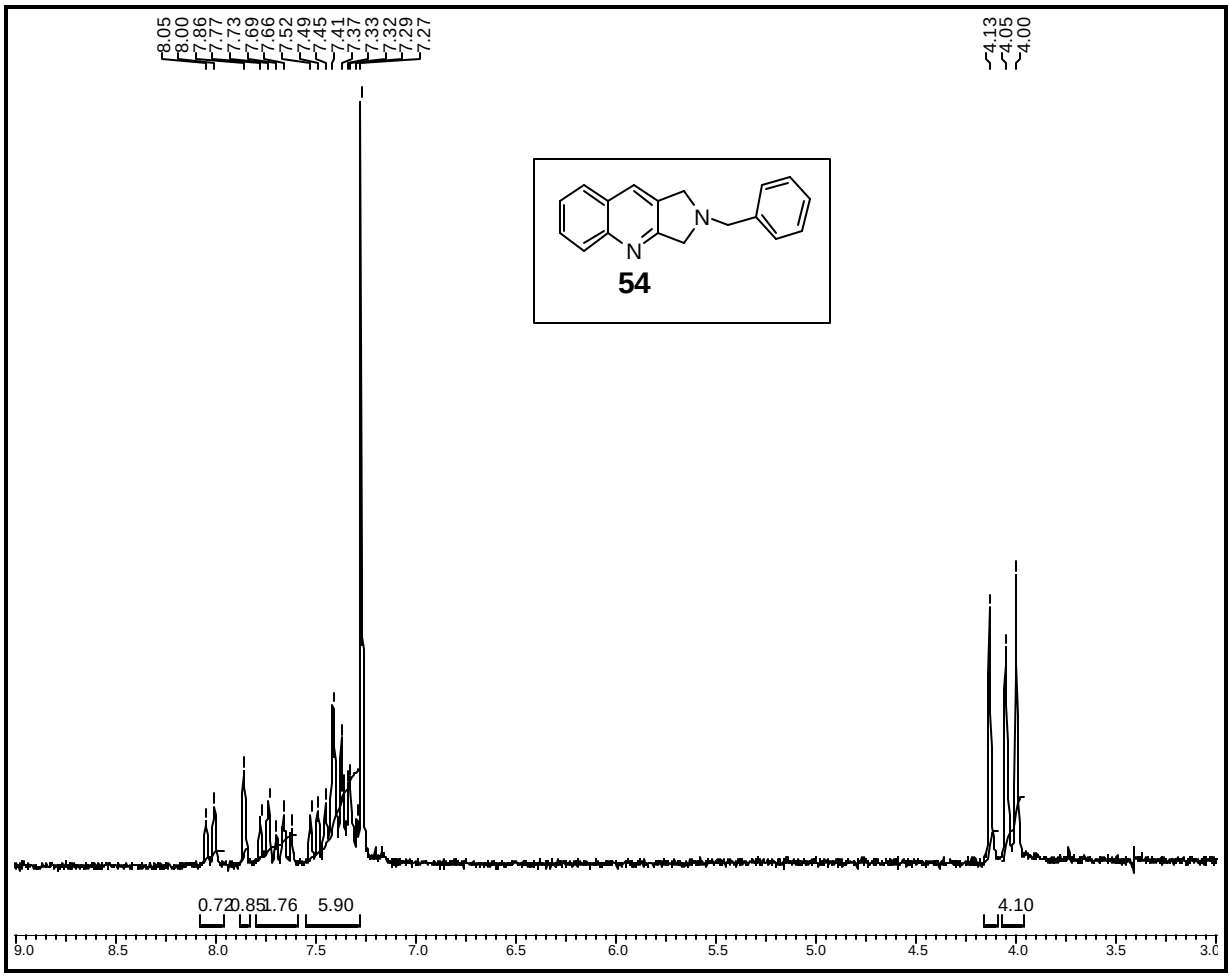
^{1}H-NMR spectrum of compound **[79]**. ($CDCl_3$, 200 MHz)



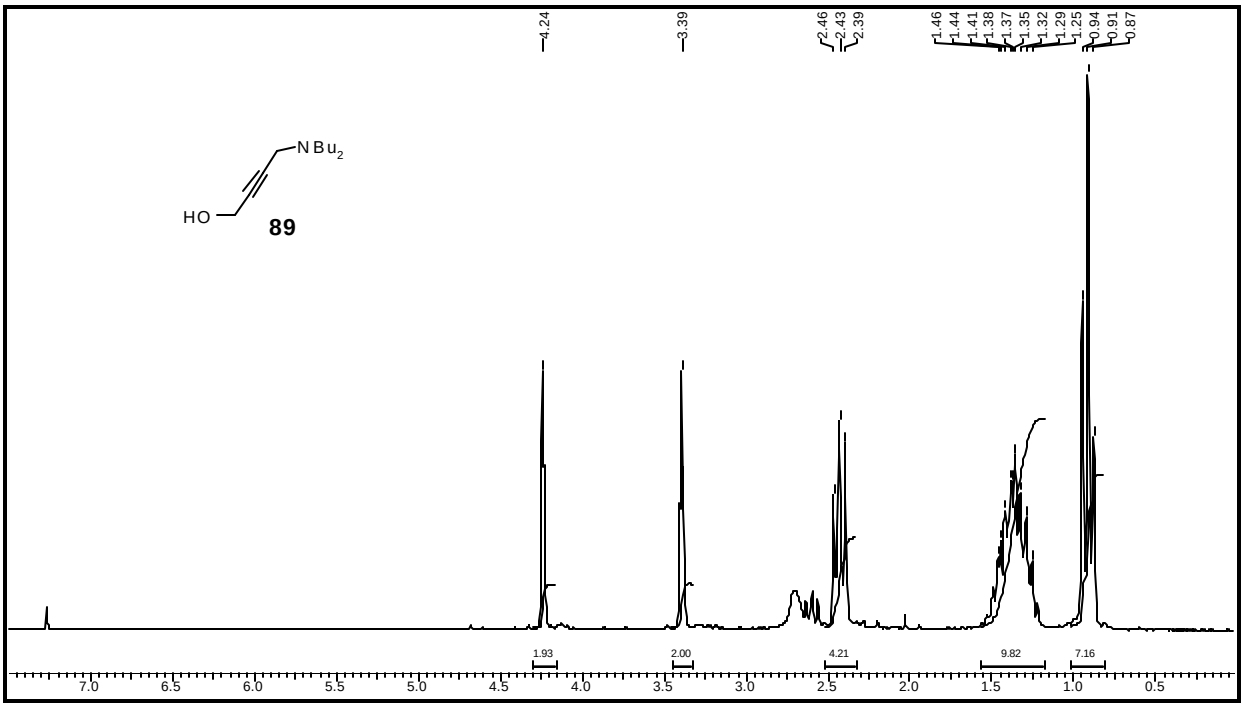
^{1}H-NMR spectrum of compound **[73]** **($CDCl_3$, 200 MHz)**



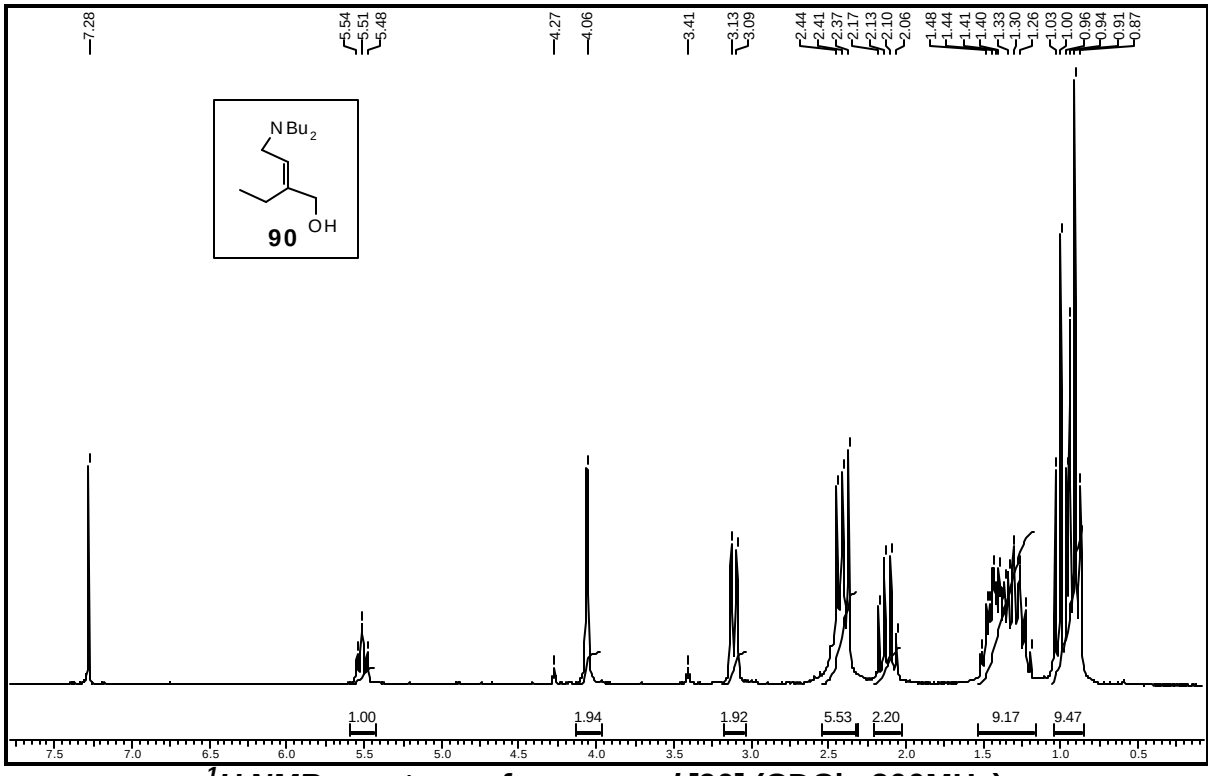
^{1}H NMR spectrum of compound [64]. **($CDCl_3$, 200MHz)**



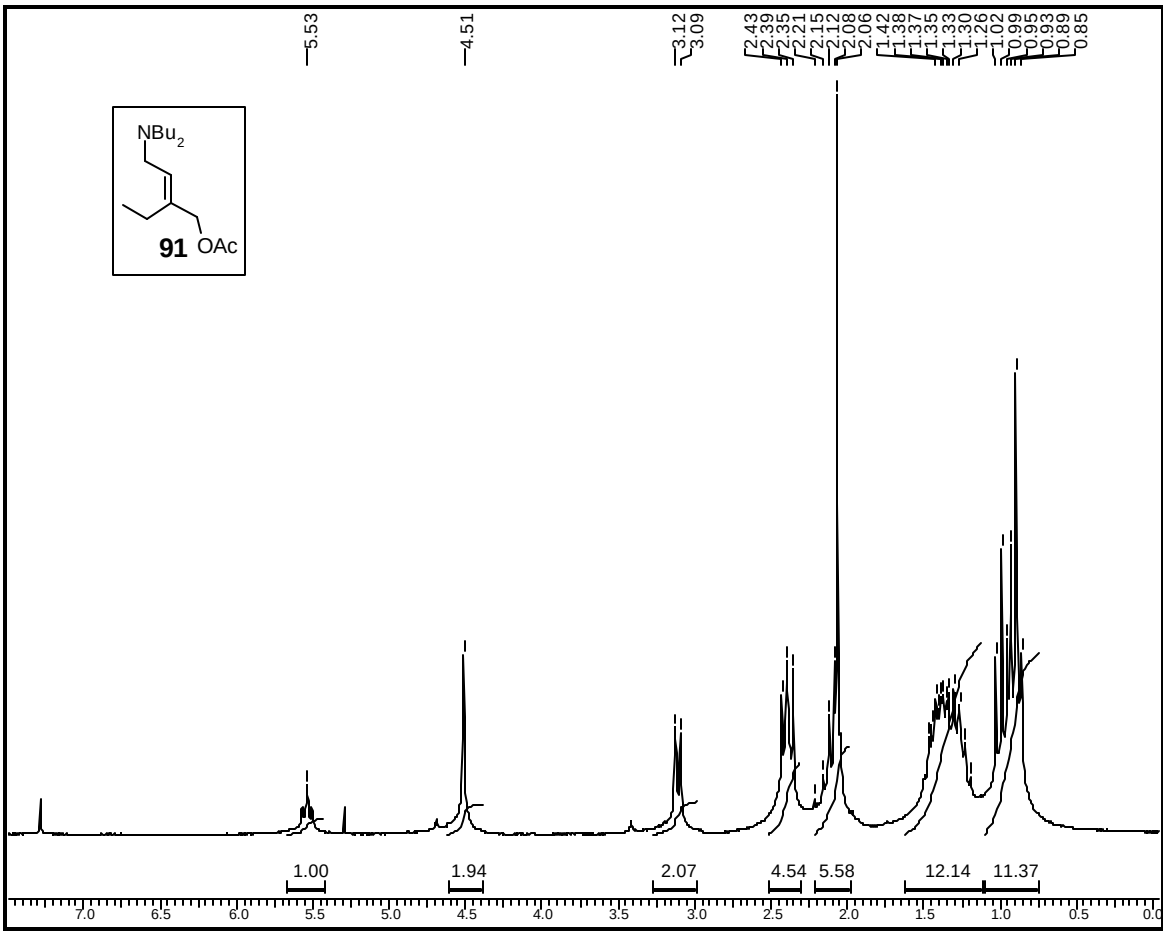
***^{1}H-NMR spectrum of compound* [54]. ($CDCl_3$, 200MHz)**



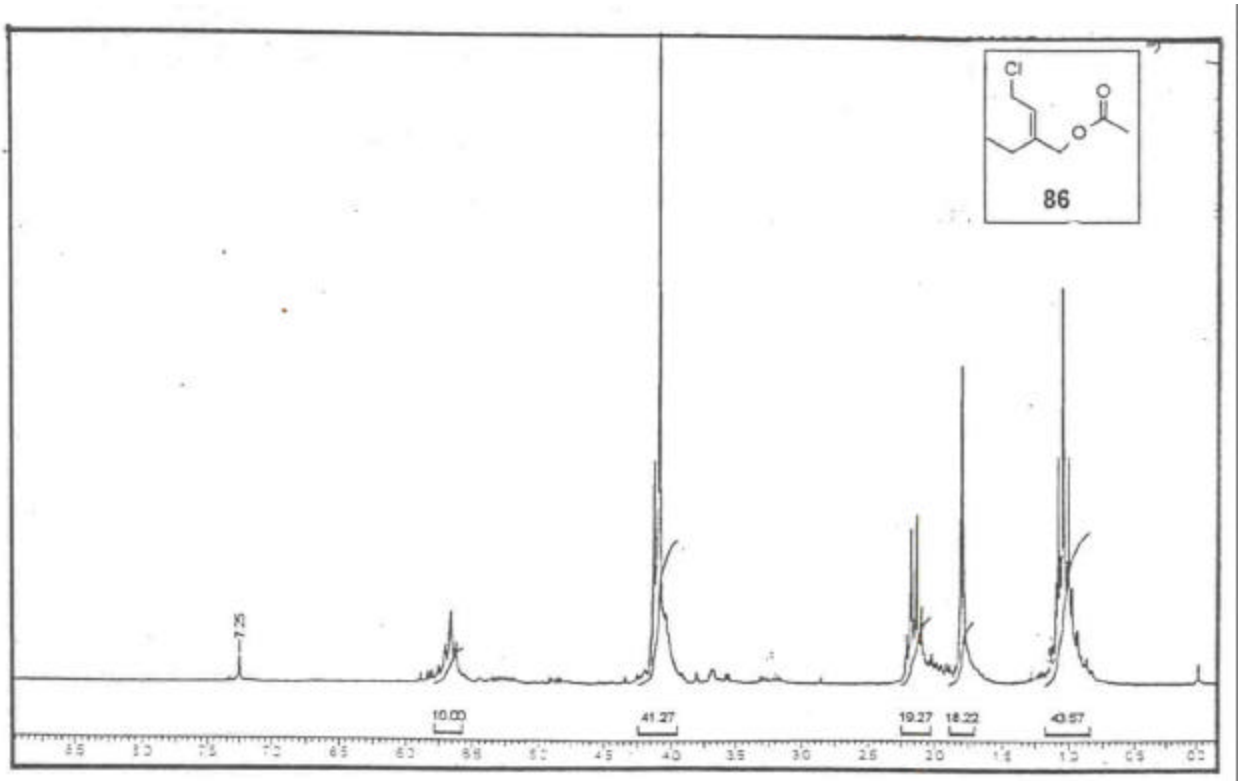
***^{1}H NMR spectrum of compound* [89] ($CDCl_3$, 200MHz)**



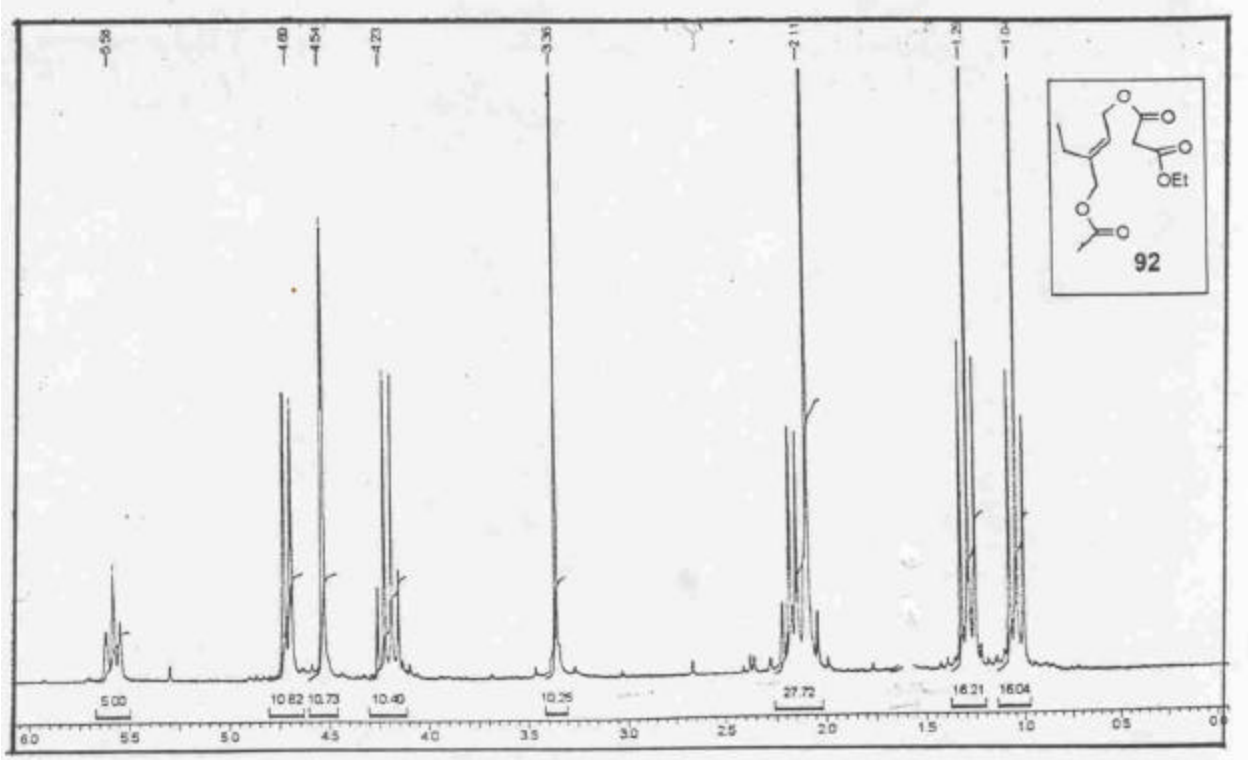
***^{1}H NMR spectrum of compound* [90] ($CDCl_3$, 200MHz).**



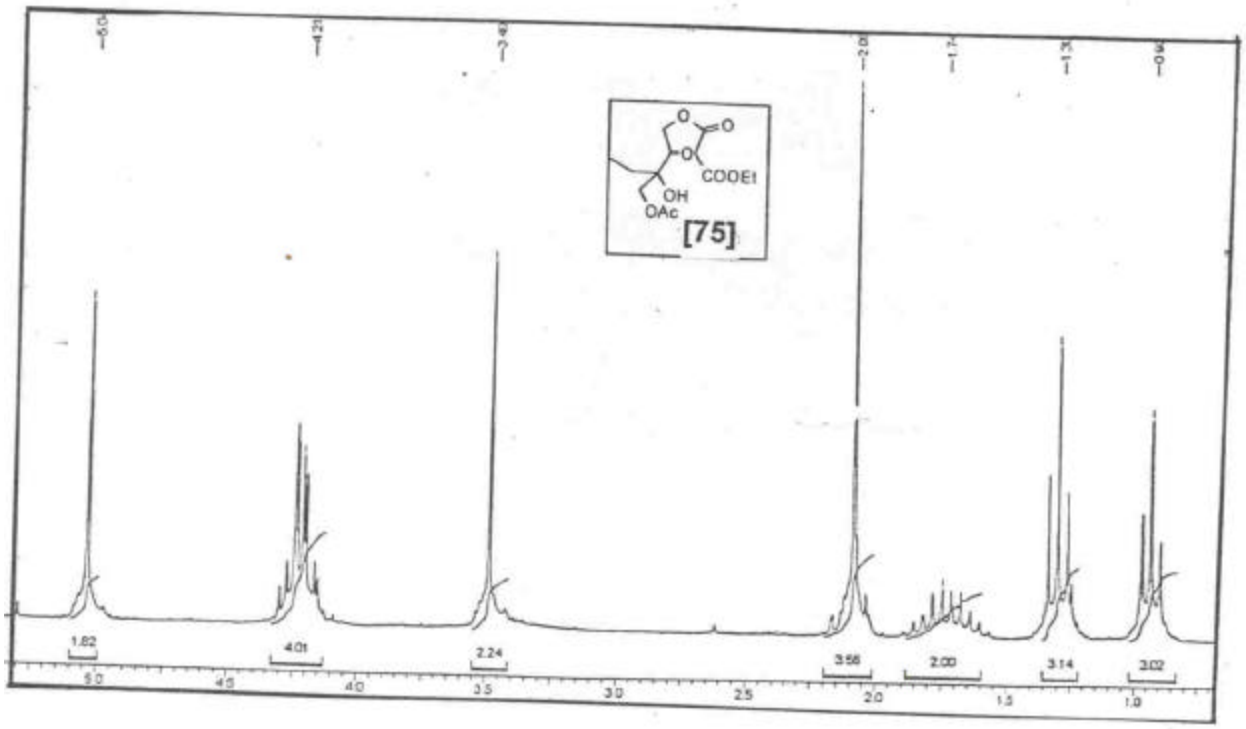
***[1]H-NMR spectrum of compound* [91]. ($CDCl_3$, 200MHz)**



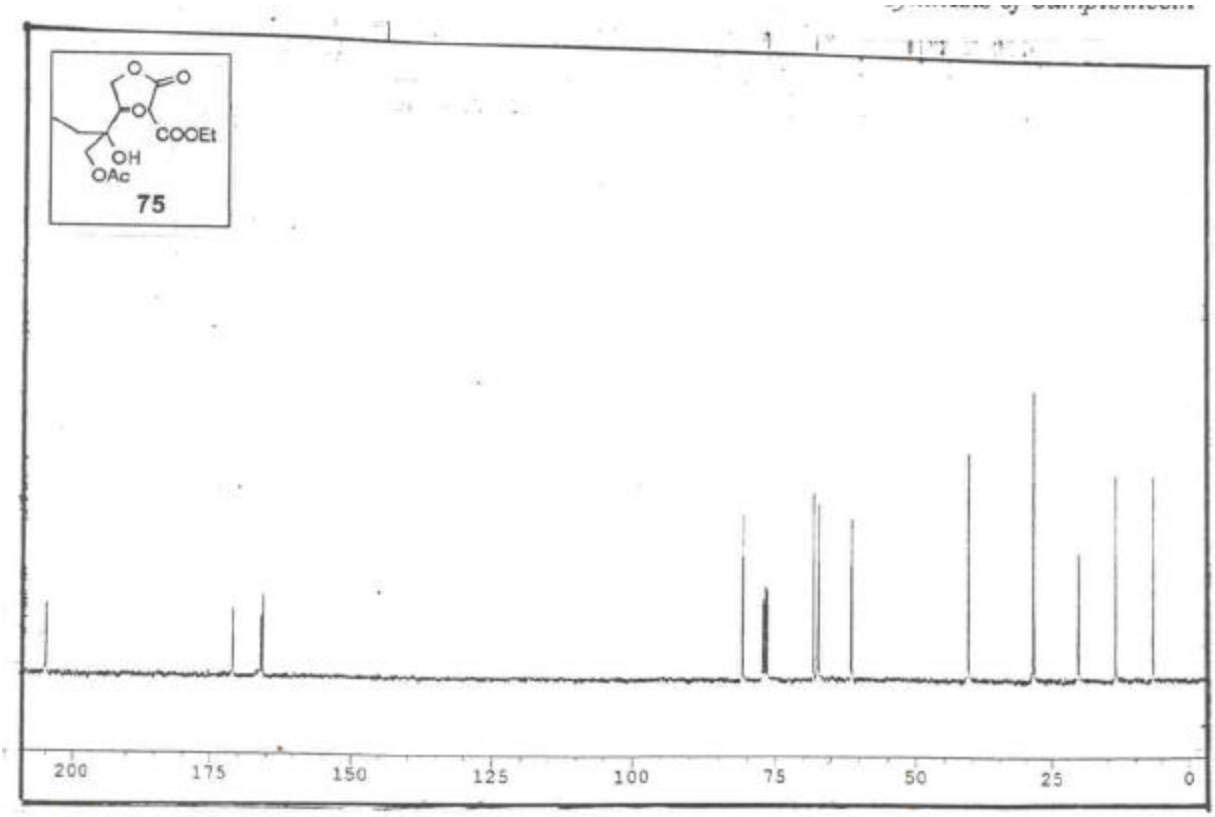
^{1}H-NMR spectrum of compound [86]. ($CDCl_3$, 200 MHz)



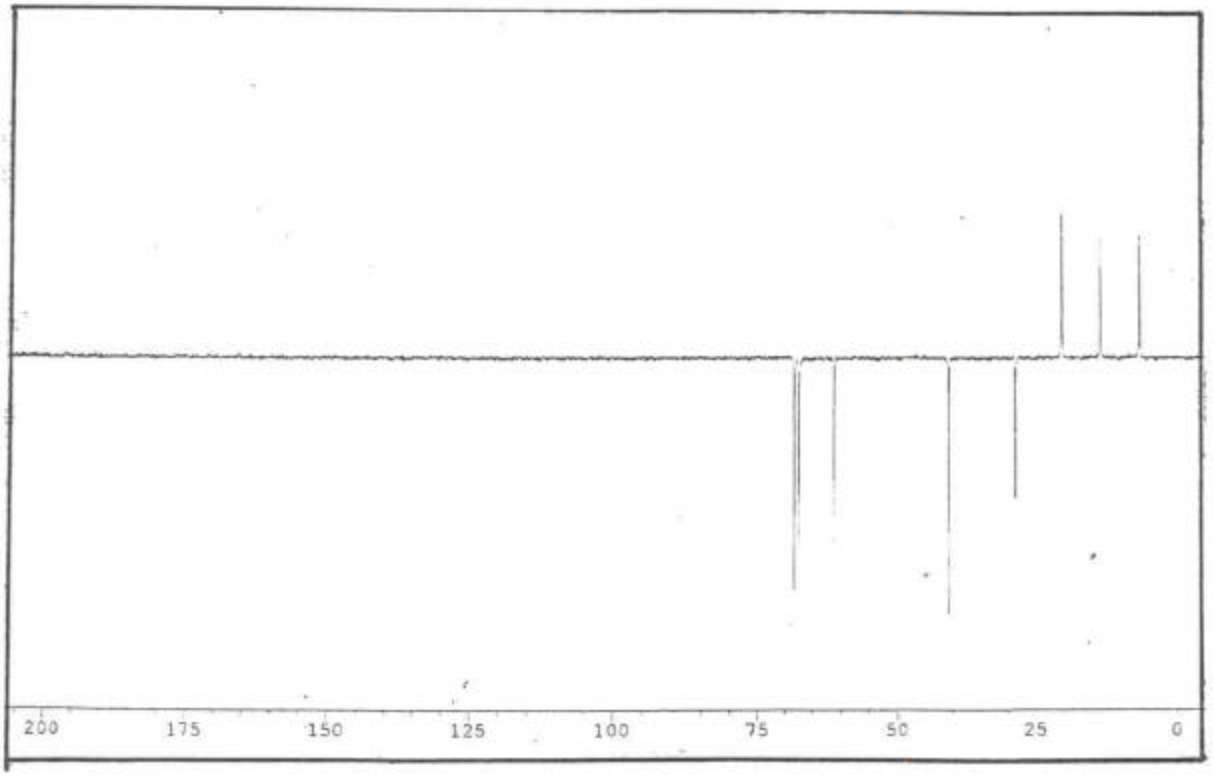
^{1}H-NMR spectrum of compound [92]. ($CDCl_3$, 200 MHz)

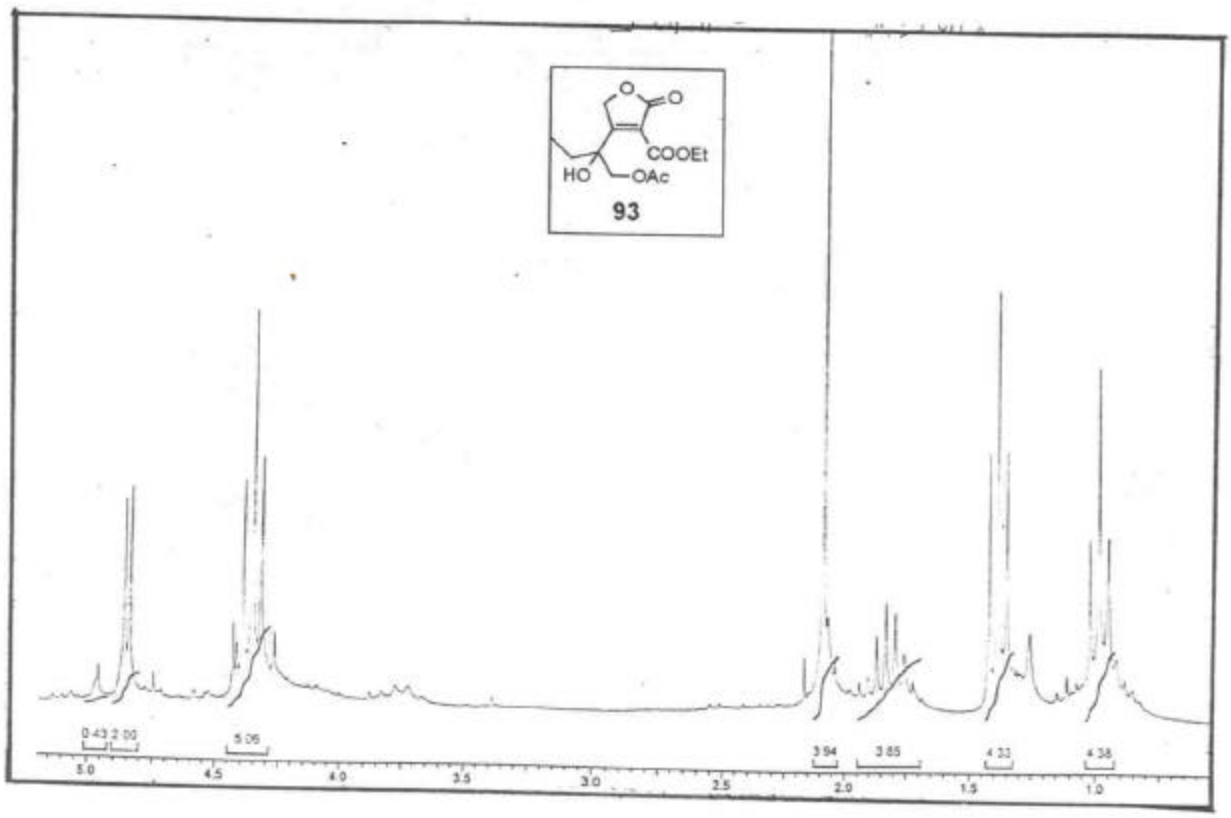


^{1}H-NMR spectrum of compound **[75]. ($CDCl_3$, 200MHz)**



^{13}C-NMR spectrum of compound [75] (200MHz, $CDCl_3$)





^{1}H NMR spectrum of compound **[93]** **($CDCl_3$, 200 MHz)**

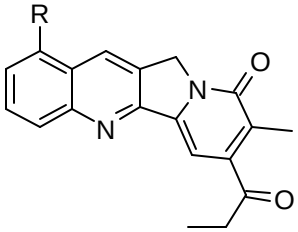
CHAPTER 1

SECTION III

Synthesis of Nothapodytine B (Mappicine ketone)

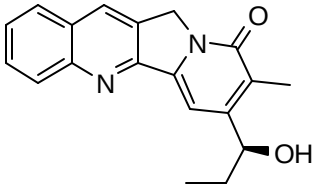
1.3.1 Introduction

The combination of the outstanding antiviral activity of Nothapodytine B coupled with its low abundance (extreme scarcity) and the need for the analogues to develop the structure - activity relations have led to wide interest in the synthetic community. As a result few syntheses have been successfully completed either by adapting the same chemistry by those groups involved in the Camptothecin syntheses[130] or new chemistry as is evident by recent reports[131] discussion of which has been dealt in depth in the **section 1.1.9**.

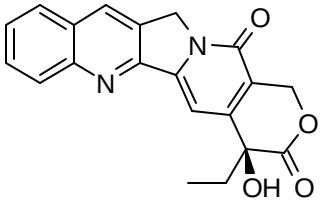


R=OMe,Nothapodytine A (**1**)
(Methoxymappicine ketone)

R= H, NothapodytineB (**2**)
(Mappicine Ketone)



Mappicine (**3**)



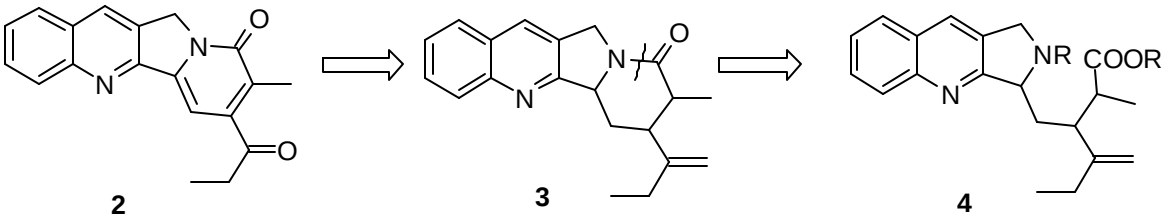
Camptothecin (**4**)

1.3.2 Present Work

These considerations coupled with our interest in the parent molecule of this family led us to devise a synthetic approach for the title compound.

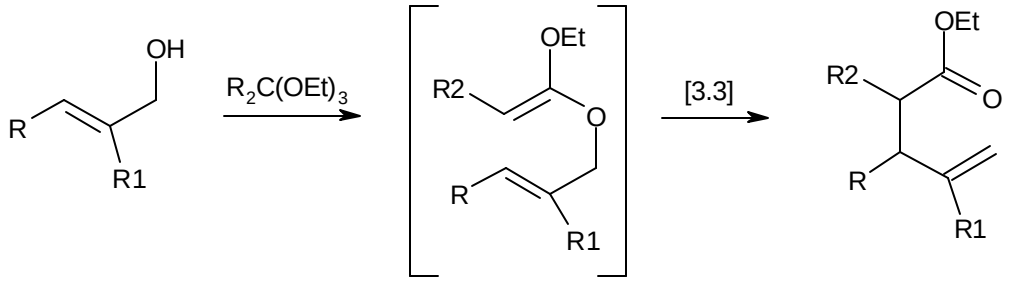
Retro synthetic analysis of Nothapodytine B (Mappicine ketone) reveals a conceptually new approach for the pyridone construction *via N-C* bond formation of an advanced intermediate **4** *i.e.* ? - amino unsaturated ester by lactamization. The D-ring of **2** would be obtained by the oxidation followed by unmasking the latent ketone (*Scheme1*).

Scheme 1: ***Retrosynthetic analysis***



2 **3** **4**

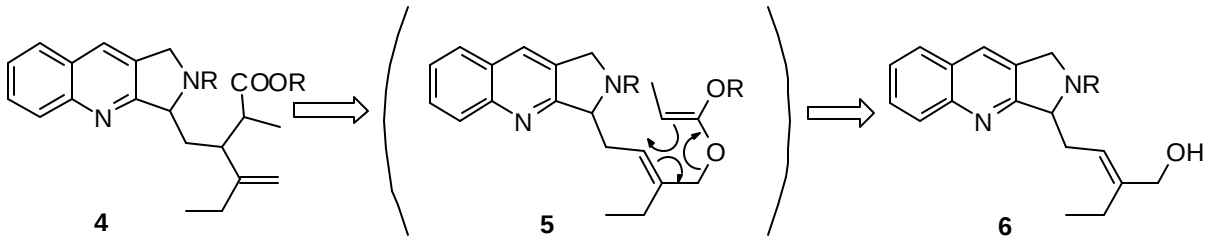
Among the various protocols considered for placing this side chain, aliphatic Claisen rearrangement of allylic vinyl ethers attracted our attention. It belongs to a class of synthetic transformations, namely the sigmatropic shifts, capable of producing a consistent structural modification of the molecular framework with concomitant creation of a new carbonyl function. The widespread application of this synthetic procedure is also due to the outstanding degree of stereo selectivity, arising from the highly ordered transition states, observed in the newly formed carbon-carbon bonds. Of various modified protocols for this [3,3] rearrangement, the Johnson orthoester variant has attained considerable importance since, starting from allylic alcohols, it ultimately results in the synthesis of γ, δ-unsaturated esters involving readily available orthoesters, as shown in the following equation.



From what began as a casual introduction to a paper 76 years ago has blossomed as a reaction of considerable significance. The Claisen rearrangement has stimulated the interest of several generations of chemists. Physical organic chemists have been provided with a mechanistic challenge, the synthetic organic community has had the opportunity to expand the scope of the reaction and apply it to complex syntheses, and bioorganic chemists have solved a formidable challenge in the chemistry of enzymes.

Among various variants of the same Johnson Ortho-ester rearrangement[132] of allylic alcohol **6** appealed as a suitable to place the requisite functional groups and appendages on to tricyclic synthon for further elaboration to pyridone ring as shown in *Scheme 2*.

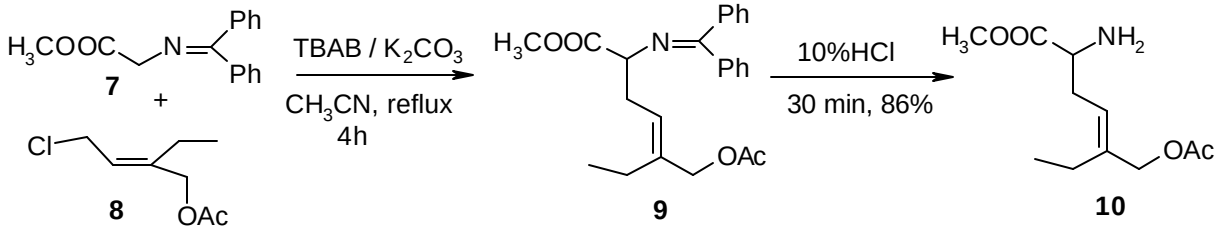
Scheme 2



1.3.3 Results and discussion

Synthesis commences from the glycine, a readily available starting material as shown in *scheme 3*. Allylation of O'Donnell's Schiff's base 7 **with chloro compound** 8**, (prepared from propargyl alcohol according to the Sec. 1.2.3.5) under solid phase transfer conditions in the presence of TBABr afforded the allylated Schiff's base** 9**.**

Scheme 3



^{1}H NMR spectrum of **9** showed apart from a multiplet at d 7- 8 for (10H) of diphenyl group, a triplet at d 5.34 (1H) assigned to olefinic proton and a triplet at δ 2.7 (1H) assigned -CH-COOMe confirming the allylation of the glycinate. The triplet at δ 0.8 (3H) and quartet at 2.4 were assigned to ethyl group (CH_3CH_2 –C), and singlet at δ 2.0 for acetyl (-OCCH_3). Rests of the protons were in consonance with the assigned structure.

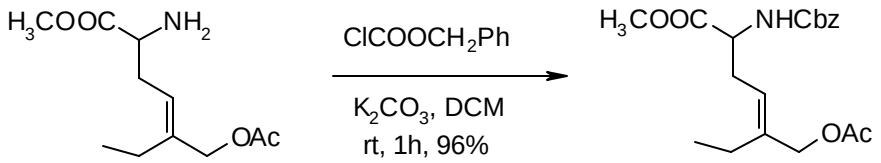
This feat introduces the necessary functionalities that would be required for the Claisen rearrangement in single step and there by avoiding the Wittig reaction employed in our earlier strategy (Sec. 2).

Treatment of Schiff's base **9** with 10% HCl furnished allyl glycine **10** in 86% yield (*Scheme 3*).

^{1}H NMR spectrum of **10** showed the absence of aromatic protons, and the appearance of a singlet at d 2.58 (2H) assigned for H_2N- thus confirming the hydrolysis of Schiff's base. Appearance of a singlet at δ 2.0 (2H) showed that acetate is intact and other protons appeared at their expected chemical shifts.^{13}C NMR spectrum showed two peaks at δ 175.23 and 170.12 assigned to two carbonyls.

Amine was protected as its benzyloxy carbamate **11** by employing potassium carbonate as the base in dry dichloromethane as the solvent (*Scheme 4*).

Scheme 4



10 **11**

^{1}H NMR spectrum of **11** showed the presence of singlet at d 5.07 and a multiplet at d 7.3 (5H) combinely assigned to the -$\underline{CH_2C_6H_5}$ and a doublet at d 5.9 (1H) for -$\underline{NH}$-Cbz confirming the carbamate formation.^{13}C NMR spectrum showed the presence of carbamate carbonyl at δ 155.53 apart from those of esters at d 171.85 and at d 170.12.

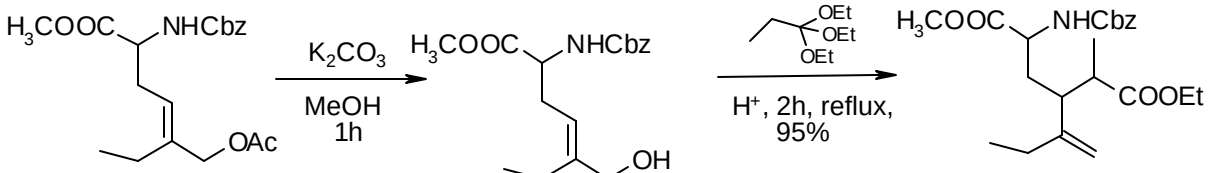
Having obtained the carbamate **11** with necessary functional groups we turned our attention to construct the other rings one by one. In our earlier synthetic approach[133] we annulated C-ring followed by AB and DE and hence we decided to follow the same order.

The attempted tandem Michael-Dieckmann condensation employing ethyl acrylate as Michael acceptor in presence of NaH, originally employed for the pyrrolidone construction[134] failed to afford ß-ketoester.

We recognized that the acetate functionality's incompatibility with the conditions used in reactions of pyrrolidone installation, and that this protecting would have to be carefully chosen in the synthetic sequence. As a result, we decided to convert the acetate to PMB ether, which is preferred in the light of its deprotection conditions orthogonally with the Cbz carbamate.

Towards this direction, the hydrolysis of acetate in presence of K_2CO_3 in methanol produced allylic alcohol **12**.

Scheme 5:



11 **12** **13**

^{1}H NMR spectrum of **12** showed a singlet at δ 4.1 (upfileld shift of allylic protons) confirming the presence of --$\underline{CH_2}$OH. ^{13}C NMR spectrum showed the presence of only one ester carbonyl at δ 172.25 apart from carbamate carbonyl at δ 155.78.

At this stage we recognized the functional group similarities of the substrate **12's**. side chain with that of the quinoline allylic alcohol **6** - proposed substrate for Claisen rearrangement, hence we reasoned that the efficacy of the Claisen rearrangement can be assessed at this stage and such a strategy would impart the flexibility to the synthesis by allowing the construction of DE rings before hand thus making the analogues preparation possible by constructing the AB rings at late stage in the synthesis. Pleasingly, allylic alcohol **12** underwent facile Claisen rearrangement upon treatment with triethylorthopropinate to furnish the ?, d- unsaturated ester **13** in near quantitative yield (*Scheme5*).

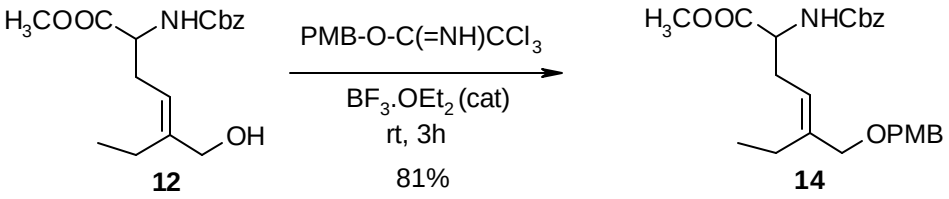
^{1}H NMR spectrum of **13** is in accordance with the assigned structure of ?, d unsaturated ester and the lack of triplet at δ 5 of internal olefin. The ^{13}C NMR spectrum showed the olefin carbon to be a sp^2 carbon at δ 100 and the presence of newly formed carbonyl at δ 174.90.

Encouraged by this result we intensified the efforts to construct the quinoline allylic alcohol while the efforts to siphon this intermediate in to Camptothecin [which would be much the similar to Henagar's route] was postponed and planned to attempt the proposed formation of pyridone by N-C bond formation on ABC synthon **6,** for it would provide the rigidity to the molecule.

Thus treatment of allylic alcohol **13** with PMB chloride in presence of NaH in THF gave multiple compounds. We felt that the presence of amide NH is the cause for the problem in selective protection of alcohol under these conditions. In literature it has been documented that employing the trichloroacetimidate such problems have been circumvented.[135] Hence we resorted to the same protocol.

As anticipated allylic alcohol **12** upon treatment with the p-methoxy benzyl 2,2,2-trichloroacetimidate in the presence of boron triflouride etherate furnished carbamate **14** (*Scheme 6*).

Scheme 6:



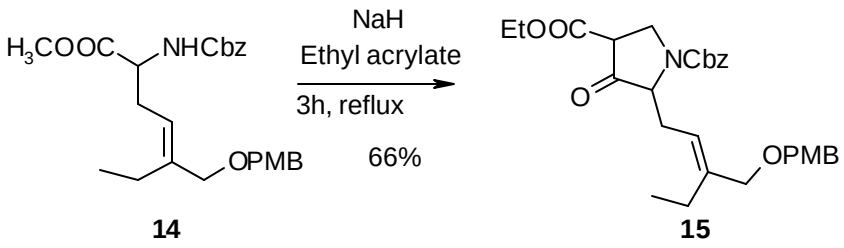
IR spectrum of **14** showed the absorptions at 1732, 1510 cm^{-1}. ^{1}H NMR spectrum revealed the characteristic peaks of PMB ether *i.e.* doublets at δ 7.2 (2H) and δ 6.8 (2H) and the singlet at δ 3.7 (3H) apart from other protons .^{13}C NMR spectrum showed the presence of 5 methylenes in the molecule apart from the aromatic part.

With the desired carbamate **14** in hand we proceeded to construct the pyrrolidone.

Thus the tandem Michael-Dieckmann condensation employing ethyl acrylate as Michael acceptor in presence of NaH, protocol originally employed for the pyrrolidone construction afforded ß-ketoester **15** in 65%.

^{1}H NMR spectrum of **15** showed the absence of methyl ester peaks and the appearance of a multiplet at δ 4.0-4.5 (2H) assigned to pyrrolidone protons, and a quartet at d 4.3 and triplet at δ 1.3 (3H) combinely assigned to ethyl ester peaks.

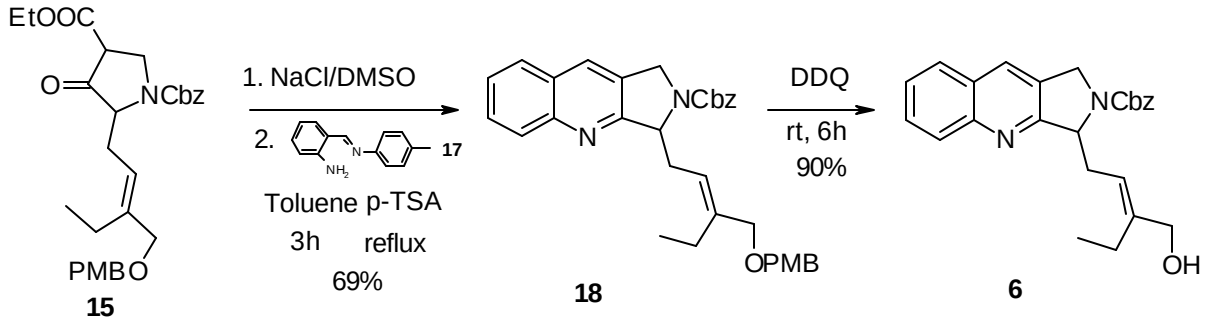
Scheme 7:



14 **15**

ß-ketoester **15** was decarboxylated by refluxing in DMSO in presence of NaCl, *i.e*. Krapcho's conditions to obtain pyrrolidone **16** *(Scheme 7)* which was subjected without purification for Friedlander condensation with Schiff's base **17**, (prepared from *o*-nitrobenzaldehyde and *p*-toludine by a two step procedure[136]) in toluene employing cat *p*-TSA to provide quinoline compound **18.**

Scheme 8:

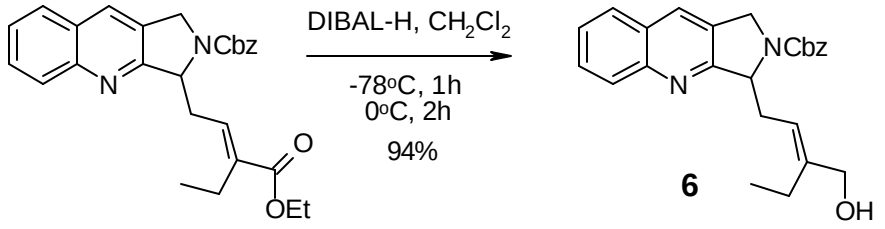


15 **18** **6**

^{1}H NMR spectrum of **18** showed apart from the aliphatic protons the presence of quinoline pattern comprising of triplet at δ 8.2, doublet at δ 7.8, doublet at δ 7.75, triplet at δ7.56 and triplet at δ7.43 (1H each).

The deprotection of PMB ether of quinoline compound with DDQ[137] furnished quinoline allylic alcohol **6** (*Scheme 8*).

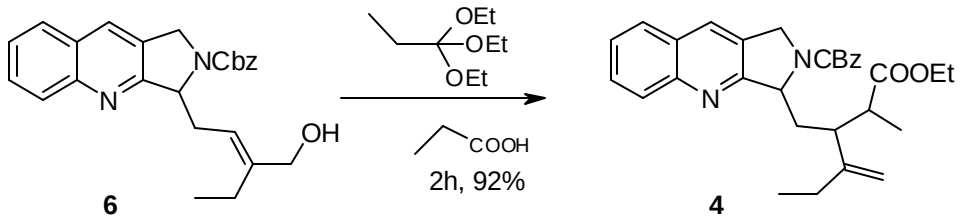
IR spectrum of **6** confirmed the presence of -OH by showing the absorption at 3500cm^{-1}. The ^{1}H NMR spectrum showed the absence of the protons of PMB group and shift in the allylic CH_2 to δ 4.05. The ^{13}C NMR spectrum revealed the presence of only five methylenes apart from other carbons. Mass spectrum showed the m/z peak at 402. The alcohol **6** was also obtained by the DIBAL-H reduction of the a, ß-unsaturated ester (that we have devised in the synthesis of CPT sec 2).



Having obtained the alcohol **6** with the required functionalities and the ABC-part, we just extrapolated the conditions standardized earlier on a norquinoline allylic alcohol **12** for the Claisen rearrangement.

To our delight, allylic alcohol **6** underwent facile rearrangement with triethylorthopropionate in presence of (cat) propionic acid at 140^{o}C to furnish the ?, d – unsaturated ester **4** (*Scheme 9*).

Scheme 9:



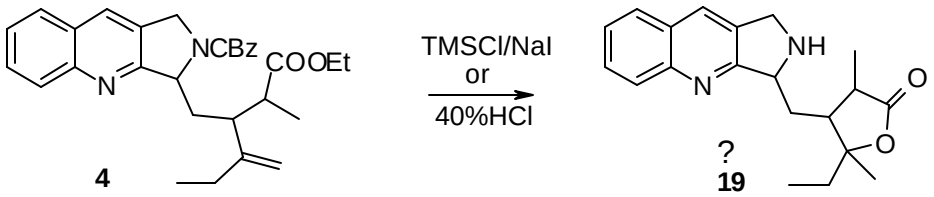
^{1}H NMR spectrum of **4** showed the product to be mixture of diastereomers .The presence of multiplets at δ 5.0, 3.89 and 1.1 were combinely attributed to the γ, δ unsaturated ester. ^{13}C NMR spectrum showed the olefinic carbon to be a *sp*^{2} hybridized one at δ110.9 and the newly formed ester carbonyl was seen at δ 175. Mass spectrum showed the m/z peak at 486 confirming the orthoester-rearranged product. No effort was made to purify this diastereomeric mixture as all the chiral centers were to be destroyed to generate pyridone at the later stages of the synthesis.

Having successfully installed the butylidene and methyl and ester side chain on to the tricyclic carbamate all that needed to construct the D-ring of the title compound was *N-C* bond formation *i.e*. acylation of amine This requires the selective deprotection of carbamate in presence of ?, d-unsaturated ester.

TMSCl / NaI reagent system was employed to selectively deprotect the benzyloxy carbamate of α, β-unsaturated ester in our synthesis of Camptothecin. Treatment of the carbamate ester **4** with TMSCl / NaI resulted in clean deprotection of the carbamate (*N*-Cbz) group to secondary amine. But the ^{1}H NMR spectrum of the product did not show the olefinic and ester protons. ^{13}C NMR revealed the intactness of the carbonyl along with a sp-hybridized carbon at δ 80 at the expense of the olefinic carbon. Mass spectrum showed the molecular ion peak at 324. This compound was basic (amine) in nature *i.e.* formed the hydrochloride salt readily and dissolves in acids.

Carbamates are known to be deprotected with the hydrogen halides, but the undesired propensity of addition of HX to olefins is the factor, which had to be borne in the mind. Compared to other hydrogen halides, HCl does not add readily to the olefins. It appeared worth while to try the deprotection with HCl. Accordingly attempts to deprotect carbamate **4** with 40% HCl under refluxing conditions gave the amine product, but unfortunately with the similar spectral properties as that of the product obtained in the earlier attempt, which suggested the addition of hydrogen halide to the olefin as a side reaction. In the earlier case it would be HI, which invariably is the contaminant with the *in situ* generation of TMSI.

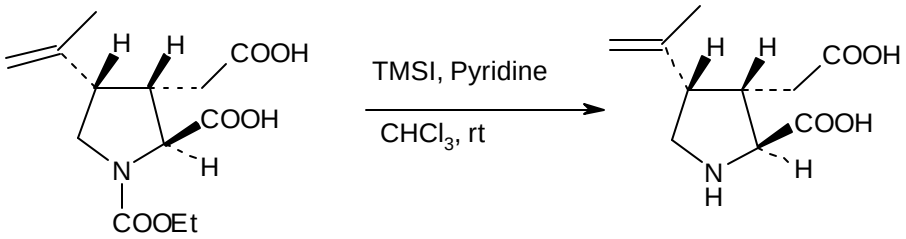
Scheme 10:



4 **19**

While unsure of the exact mechanism of the formation of the saturated product, but based on the spectral properties we proposed the concomitant lactone formation of the addition product of HX to the olefin (in Markonikoff way) and hence structure **19** (tentative assignment). At this stage we became aware of the synthesis of Kianic acid of Gallagher[138] where in deprotection of the carbamate **20** has been achieved by employing the TMSI in the presence of pyridine as a scavenger of HI, confirming our suspection it to be a culprit.

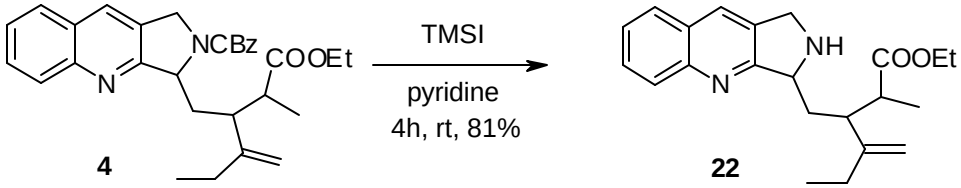
Scheme 11:



21

Iodotrimethylsilane (Me_3SiI) is a commercially available reagent and, can be easily prepared without any solvents.[139] Thus hexamethyldisilane and iodine mixture was refluxed under argon atmosphere for an hour to which the carbamate was added along with the pyridine after cooling. To our delight, carbamate **4** was cleanly deprotected under these conditions to yield secondary amine **22**, which was taken further without purification owing to its instability (

Scheme 12

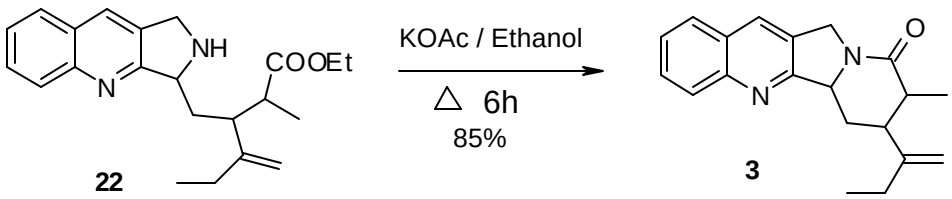


4 **22**

The ^1H NMR spectrum of amine **22** (obtained from acid-base treatment) showed the presence of multiplets at δ 5.03 (2H), 4.14 (2H) and 1.23 (3H) assigned for olefin and ester protons respectively, and the absence of benzylic and multiplet in the aromatic region confirming the selective debenzylation. Mass spectrum showed molecular ion peak at 352 confirming the loss of Cbz from Claisen product **4.**

Generally, the lactam skeleton is constructed through formation of the N-C bond of the amino esters[140] in the presence of base or by heating in a high boiling solvent (some times combination of both). Amine **22** underwent lactamization readily in refluxing ethanol in presence of KOAc to give the tetrahydro pyridone. (*Scheme 13*)

Scheme 13:

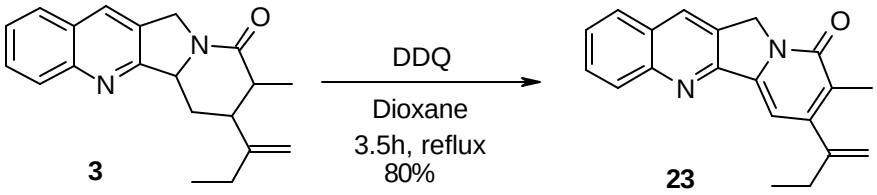


22 **3**

^{1}H NMR spectrum of **3** showed the absence of the ester protons and the product was still a mixture of diastereomers. Multiplet at d 0.9-1.1 (6H) was assigned for the -$\underline{CH_3}$ a-to lactam and -$\underline{CH_3}$ of ethyl group while the multiplet at δ 2.05 (2H) was assigned for -$\underline{CH_2}CH_3$. Mass spectrum further confirmed the cylized product by revealing the m/z peak at 306

Oxidation of the tetra hydro pyridone **3** with DDQ afforded pyridone **23** (*Scheme 14*)**.**

Scheme 14:



3 **23**

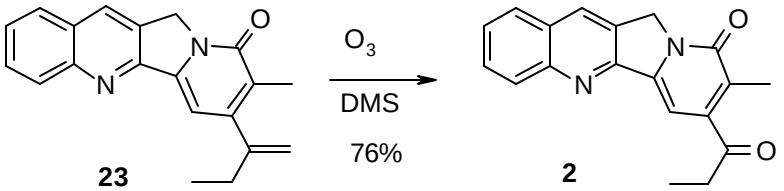
^{1}H NMR spectrum of **23** showed the presence singlet at d 7.18 (1H) assigned to pyridone proton along with the other quinoline protons which appeared as a triplet at d 7.62 and doublet at d 7.8, a doublet at d 7.93 doublet at d 8.22 and a singlet at d 8.3 each integrating for one proton. The presence of quartet at d 2.45 (2H) and triplet at d 1.14 (3H) were assigned to -C_2H_5 and the singlet at δ 2.2 (3H) was assigned for the methyl group on aromatic ring while the two singlets at δ 5.27and 4.90 combinely integrating for 4H were assigned to benzylic and olefinic protons.

^{13}C NMR spectrum showed the presence of amide carbonyl at δ 161.87 alongwith the presence of sp^2 carbons at δ 102.36 and δ 113.50 assigned to pyridone and olefin (CH_2) carbons respectively. Mass spectrum showed the m/z peak at 302 (loss of 2 mass units by dehydrogenation process)

With the key butylidine intermediate **23** in hand, all that left to complete the synthesis is

Of the title compound is the unmasking the latent carbonyl by oxidative removal of the methylene protection. Thus the conversion into the desired ketone was accomplished by a controlled ozonolysis of the olefin to complete the synthesis of Nothapodytine B **2**.

Scheme 16:



23 **2**

The spectral data **2** was in complete agreement with the reported data. [141]

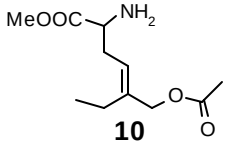
Conclusion

We have achieved the novel synthesis of Nothapodytine B by a conceptually new approach for pyridone formation by employing the Claisen rearrangement in an efficient way, and hence the synthesis of Mappicine.

This protocol would also be suitable to access Camptothecin and HomoCamptothecin by employing the suitable ortho ester in the Johnson ortho ester rearrangement.

1.3.4 Experimental:

1. 5-Acetoxymethyl-2-amino-hept-4-enoic acid methyl ester [10]



10

A suspension of diphenyl Schiff's base (2.539 g, 10 mmol), tetra-*n*-butylammonium bromide (0.322g, 0.1 mmol), potassium carbonate (0.415g, 3 mmol) and the chloro compound (1.5 mmol) in acetonitrile (50 mL) was refluxed for 4h. The solvent was evaporated and the residue was suspended in a 2 M solution of hydrogen chloride (20mL), stirred for 30min and extracted with DCM and the organic phase was discarded and the aqueous phase was treated with a saturated solution of NH_3 (50 mL) and extracted with DCM (3×40 mL), dried (Na_2SO_4) and concentrated affording pure amine **10** as pale yellow oil.

Molecular Formula : $C_{11}H_{19}NO_4$, 229

Yield : 1.97 g, 86%

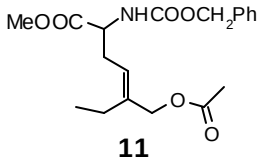
IR (Neat) : 3450, 1740 cm^{-1}

^{1}H NMR (200 MHz) : δ: 5.13 (t, *J* = 7.32 Hz, 1H), 4.20 (s, 2H), 3.41 (s, 3H), 3.22 (t, 1H), 2.11 (m, 2H), 1.75 (q, *J* = 7.33 Hz , 2H), 1.82 (s, 3H), 1.50 (s, 2H), 0.73 (t, *J* =

7.33 Hz, 3H).

^{13}C NMR (50 MHz) : δ: 175.23 (C), 170.12 (C), 138.81 (C), 123.37 (CH), 67.20 (CH_2), 53.62 (CH_3), 51.36 (CH_3), 32.35 (CH_2), 20.37 (CH_2), 20.41 (CH_3), 12.47 (CH_3).

2. 5-Acetoxymethyl-2-benzyloxycarbonylamino-het-4-enoic acid methyl ester [11]



11

To a precooled solution of amine **10** (2.29 g, 10 mmol) in DCM (40 mL) in presence of K_2CO_3 was added a toluene solution of $ClCOOCH_2C_6H_5$ (1.87g, 11 mmol). The resulting solution was stirred under argon at room temperature for 1h, and cooled again to 0°C. A solution of 1 M HCl (225 mL) was then added. The resulting solution was stirred for 5min at room temperature and rapidly extracted with CH_2Cl_2 (3×20 mL) and then washed with $NaHCO_3$ solution (25 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* at 30 °C, to give of crude neutral residue.

Molecular Formula : $C_{19}H_{25}NO_6$, 363

Yield : 0.348 g, 96%.

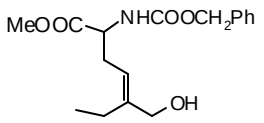
IR (film) : 3425, 1745, 1670cm^{-1}.

^{1}H NMR(200 MHz) : δ: 7.16 (m, 5H), 5.91 (d, 2H), 5.25 (t, *J* = 7.3 Hz, 1H), 4.95 (s, 2H), 4.33 (s, 3H), 3.54 (t, 1H), 2.39 (m, 2H), 1.95 (q, 2H), 1.86 (s, 3H), 0.83 (t, 3H).

^{13}C NMR (50 MHz) : δ: 171.85 (C), 170.12 (C), 155.53 (C), 139.43 (C), 136.16 (C), 128.03 (2, CH) 127.59 (2, CH), 121.97 (CH), 66.98 (CH_2), 66.35 (CH_2), 53.30 (CH_3), 51.76 (CH_3), 29.85 (CH_2), 20.92 (CH_2), 20.24 (CH_3), 12.39 (CH_3).

Mass *m/z* (%) : 363 (2, M^+), 303 (3), 244 (15), 168 (15), 108 (8), 91 (100), 81 (15)

3. 2-Benzyloxycarbonylamino-5-hydroxymethyl-hept-4-enoic acid methyl ester [12]



12

Compound **11** (0.720 g, 2 mmol) and dry powdered K_2CO_3 (0.275g, 2 mmol) were suspended in MeOH (16 mL) and stirred for 1h. MeOH was removed; the residue was treated with water and extracted with DCM (3×60mL). Organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give allylic alcohol. Compound **12** was obtained as colorless syrup with enough purity for the next step.

Molecular Formula : $C_{17}H_{23}NO_5$, 321.78

Yield : 0. 690g, 95%.

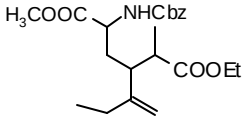
IR (Neat) : 3550, 1723 cm^{-1}

^{1}H NMR (200 MHz) : : 7.35 (m, 5 H), 5.5 (d, 1H), 5.35 (t, *J* = 7.4 Hz, 2 H), 5.2 (s, 2 H), 4.0 (s, 2 H), 3.76 (s, 3H) 2.7-2.6 (m, 2 H), 2.10 (m, 4H), 1.0 (t, 3H)

^{13}C NMR (50 MHz) : δ: 172.25 (C), 155.78 (C), 144.79 (C), 136.04 (C), 128.03 (2,CH) 127.59 2,CH), 117.59 (CH), 66.53 (CH_2), 65.25 (CH_2), 53.49 (CH_3), 51.94 (CH_3), 29.74 (CH_2), 20.73 (CH_2), 13.75 (CH_3), 12.72 (CH_3)

Mass: *m/z* (%) : 321($M^{+,}$ 1), 303 (4), 262 (10), 244 (10), 200 (15), 168 (20), 108(23), 91 (100).

4. 5-Benzyloxycarbonylamino-3- (1-ethyl-vinyl)-2-methyl-hexanedioic acid 1-ethyl ester 6-methyl ester [13]



13

A solution of allylic alcohol **12** (0.322g, 1 mmol) and propionic acid (3 drops) in triethyl orthoacetate (5 mL) was heated under reflux while propionic acid (3 drops) was added every hour and the low boiling fraction was removed occasionally. After two hours, the excess triethyl orthopropionate was distilled off under reduced pressure and the residue was purified by column chromatography using 70% ethyl acetate - pet ether as eluent afforded the unsaturated ester

Molecular Formula : $C_{21}H_{31}NO_6$, 405.78

Yield : 0. 385g, 95%

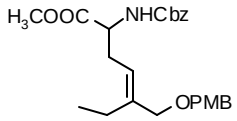
IR ($CHCl_3$) : 3440, 1730 cm^{-1}

^{1}H NMR (200 MHz) : δ: 7.24 (m, 5 H), 5.7 (m, 1H), 5.01 (s, 2 H), 4.79 (m, 4 H), 4.0 (m, 2 H), 3.61 (s, 3H), 1.94 (m, 4 H), 1.19-0.86 (m, 9H)

^{13}C NMR (50 MHz) : (mixture of diastereomers) δ: 174.90 (C), 172.95(C), 155.82(C), 149.17 (C), 136.14 (C), 127.99 (2, CH) 127.63 (2,CH), 110.97 (CH), 66.31 (CH_2), 60.76 (CH_2), 52.42 (CH_3), 51.72 (CH_2), 50.03 (CH), 44.85 (CH), 42.13 (CH), 31.94 (CH_2), 26.13 (CH_2), 20.95(CH_3), 13.75 (CH_3), 12.98 (CH_3) , 11.43 (CH_3).

Mass: *m/z* (%) : 405 (11,M^+) 390 (8), 346 ((11), 330 (11), 316 (12), 304 (13), 302 (25), 270 (30), 168 (50), 121 (80), 108 (25), 91 (100)

5. 2-Benzyloxycarbonylamino-5-(4-methoxy-benzyloxymethyl)-hept-4-enoic acid methyl ester [14]



14

A solution of PMB-OH (5.2g, 37.6mmol) in 35 ml of ether was added to a suspension of 60% NaH (0.15g, 3.88mmol) in 40 mL of ether at rt. The resulting mixture was stirred at rt for 30 minutes and cooled to 0^{o}C. Trichloroacetonitrile (3.8mL, 37.66mmol) was added and the reaction mixture was allowed to warm slowly to room temperature during 4hr.The solution was concentrated to orange syrup. The crude imitate was dissolved in cyclohexane (60mL) and a solution of **12** (8g, 25mmol) in 300 mL of DCM was added. The resulting solution was cooled to 0^{o}C and treated with $BF_3.OEt_2$ (25µl). The reaction mixture was warmed to room temperature and stirred for 6hrs, slowly developing a white ppt. The solution was filtered through Celite and the solids were washed with CH_2Cl_2-cyclohexane mixture. The filtrate was washed with Na_2CO_3, dried (Na_2SO_4) and concentrated and purified by column chromatography over silica gel using ethyl acetate and pet ether mixture as eluent to give PMB ether **13.**

Molecular Formula : $C_{25}H_{31}NO_6$, 441.78

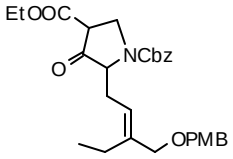
Yield : 8.93g, 81%.

IR : 2848, 1735cm^{-1}

^{1}H NMR (200 MHz) : δ: 7.35 (m, 5 H), 7.23 (d, 2H), 6.89(d, 2H), 5.5 (d, 1H), 5.35 (t, 1 H), 5.2 (s, 2 H), 4.45 (m, 1H), 4.27 (s, 2H), 4.0 (s, 2 H), 3.76 (s, 3H), 3.75 (s, 3H), 2.7-2.7 (m, 2 H), 2.10 (m, 2H), 1.0 (t, 3H)

^{13}C NMR (50 MHz) : δ: 172.14 (C), 163.47 (C), 158.91 (C), 155.64 (C), 141.96 (C), 136.04 (C), 136.04 (C), 130.16 (C), 129.43 (CH) 129.06 (2,CH), 128.21 (CH) 127.74 (CH), 120.31(CH), 113.51 (2CH), 72.78 (CH_2), 70.95 (CH_2), 66.64 (CH_2), 64.25 (CH_2), 54.88 (CH_3), 53.49 (CH), 52.02 (CH_3), 29.96 (CH_2), 20.82 (CH_2), 20.57 (CH_3), 12.57 (CH_3)

6. 5-[3-(4-methoxy-benzyloxymethyl)-pent-2-enyl-4-oxo-pyrrolidine-3-carboxylic acid ethyl ester [15]



15

A solution of Cbz carbamate **14** (2.225, 5.0 mmol) in benzene (25 mL) was added dropwise at 0°C to a suspension of sodium hydride (0.288g, 50% in dispersion in mineral oil, 6mmol) in dry benzene (25 mL). The addition was accompanied by formation of hydrogen and anion of the ester. After stirring the resultant reaction mixture for 30min at room temperature, ethylacrylate (0.62mL, 6.0 mmol) in benzene (14 mL) was added dropwise very slowly to the mixture with stirring. The reaction mixture was, then stirred for 30 min at rt and then refluxed for 2hr. After the completion of the reaction, it was quenched with NH_4Cl solution and organic layer was separated and the aqueous phase was further extracted with ethylacetate

(2×50 mL). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The product was subjected for the decarboxylation without purification.

Molecular Formula : $C_{28}H_{33}NO_6$

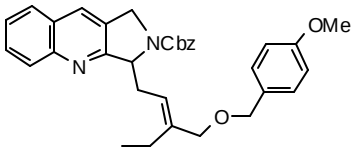
Yield : 1.170 g, 65%.

IR ($CHCl_3$) : 2850, 1740cm^{-1}

^{1}H NMR (200 MHz) : δ: 7.37 (m, 5 H), 7.27 (m, 2H), 6.89 (d, 2H), 5.10 (m, 3H), 4.5-4.18 (m, 4H), 4.0-3.7 (m, 8H), 3.6 (1H), 2.5 (m, 2H), 1.26 (t, 3H), 0.90 (3H).

^{13}C NMR (50 MHz) : δ: 169.2 (C), 167.47 (C), 166.91 (C), 155.64 (C), 154.3(C), 136.8 (C), 136.4 (C), 129.43 (2CH) 128.06 (2CH), 128.03 (CH), 120.31(2CH), 113.51 (2CH), 72.78 (CH_2), 66.64 (CH_2), 64.25 (CH_2), 54.88 (CH_3), 53.49 (CH), 52.02 (CH_3), 45.3 (CH_2), 29.96 (CH_2), 20.82 (CH_2), 20.57 (CH_3), 14.3(CH_3), 12.57 (CH_3)

7. 3-[3-(4-methoxy-benzyloxymethyl)-pent-2-enyl]-1,3-dihydr-1*H*-pyrrolo [3,4-*b*] quinoline-2-carboxylic acid benzyl ester [18]



18

A solution of β-keto carboxylic ester (1.527g, 3.00 mmol) in aq DMSO in presence of NaCl (10 mL) was refluxed for 4 h. After the completion of the reaction it was extracted with DCM (2×90mL). The organic phase was separated, washed with dilute aqueous sodium bicarbonate, and dried. After evaporation of the solvent the residue was subjected for Friedlander condensation. To the crude pyrrolidinone in dry toluene (20mL) was added *N*-(*o*-aminobenzilidine)*p*-toludine (3mmol) and the mixture refluxed for 30 min with azeotropic removal of water after which 0.075g of *p*-TSA was added and the mixture refluxed further 3h. The reaction was quenched with Na_2CO_3 and the organic phase was separated and the aqueous phase was further extracted with ethyl acetate (3×25mL). The combined organic phase was dried (Na_2SO_4), concentrated and purified by chromatography over silica gel using 30% ethylacetate-pet ether as eluent furnished quinoline **15.**

Molecular Formula : $C_{33}H_{34}N_2O_4$, 522

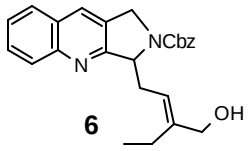
Yield : 1.070g, 70%.

IR ($CHCl_3$) : 2845, 1690, 1420 cm^{-1}

^{1}H NMR (200 MHz) : δ: 7.35 (m, 5 H), 5.5 (d, 1H), 5.35 (t, 2 H), 5.2 (s, 2 H), 4.0 (s, 2 H), 3.76 (s, 3H), 2.7-2.7 (m, 2 H), 2.10 (m, 4H), 1.0 (t, 3H).

^{13}C NMR (50 MHz) : δ: 172.14 (C), 163.47 (C), 158.91 (C), 155.64 (C), 141.96 (C), 136.04 (C), 136.04 (C), 130.16 (C), 129.43 (2, CH) 129.06(2,CH), 128.21 (CH) 127.74 (CH), 120.31 (CH), 113.51 (CH), 72.78 (CH_2), 70.95 (CH_2), 66.64 (CH_2), 64.25 (CH_2), 60.07 (CH_2), 54.88 (CH_3), 53.49 (CH_3), 52.02 (CH_3) 29.96 (CH_2), 20.82 (CH_2) , 20.57 (CH_3), 13.86 (CH_3), 12.57 (CH_3).

8. 3-[3-Hydroxymethyl-pent-2-enyl]-1,3-dihydr-1*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylic acid benzyl ester [6]



6

Method A : To the solution of **15** (0.522g ,1mmol) (in aqueous DCM (1:18) was added DDQ (0.227g, 1mmol) and stirred for 1h. The reaction mixture was treated with $NaHCO_3$ solution , dried (Na_2SO_4) , concentrated and purified by silica gel column chromatography to give the allylic alcohol **6.**

Method B :

Diisobutylaluminium hydride (DIBAL-H) (2M in toluene, 3 equiv, 6mmol, 3 mL) was added at -78 °C to a solution of unsaturated ester (0.894 g, 2 mmol) in dry DCM (14 mL). The temperature was increased to 0°C over 1h and stirred for 2hr at that temperature. It was quenched with 3mL of methanol and 3 mL of water and stirred for an additional 10 minutes and extracted with DCM (3×25mL). The combined organic layers were dried (Na_2SO_4), and concentrated to afford a viscous, colourless liquid. Column chromatography over silica gel employing 50% ethyl acetate/petroleum ether resulted in the isolation of alcohol **6** as a thick liquid, which solidified to white solid upon storage.

Molecular Formula : $C_{25}H_{26}N_2O_3$, 402.5

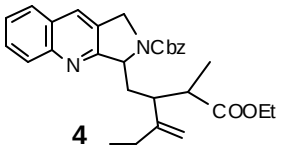
Yield : 0.720g, 90% (Method A 83%)

IR ($CHCl_3$) : 3607-3400, 1677, 1460, 1374cm^{-1}

^{1}H NMR (200 MHz) : : 8.06 (m, 1H), 7.95 (d, *J* = 11.24 Hz, 1H), 7.75 (d, *J* = 8.3, 1H), 7.37 (t, *J* = 8.3Hz, 1 H), 7.3 (t, *J* = 8.3 Hz, 1H), 7.34-7.25 (m, 5H), 5.53-5.22 (m, 4H), 4.75 (dd, J = 15.3Hz, 5.2Hz, 2 H), 3.9 (m, 2H), 3.83 (m, 3H), 2.03 (m, 2 H), 0.86 (m, 3H)

^{13}C NMR (50 MHz) : δ162.09 (C), 153.91 (C), 148.02 (2 C), 144.30 (2 C), 136.51 (C), 129.38 (CH), 129.20 (CH), 128.42 (2 CH), 127.96 (2, CH), 127.62 (CH), 126.9(C), 126.22 (CH), 118.94 (CH), 67.11 (CH_2), 66.90 (CH_2), 62.81 (CH), 50.17 (CH_2), ,31.86 (CH_2), 20.87 (CH_2), 12.64 (CH_3)

9. 3-[2-(1-Ethoxycarbonyl-ethyl)-3-methylene-pentyl]-1, 3-dihydro-pyrrolo[3,4-*b* quinoline 2-carboxylic acid benzyl ester [4].



4

A solution of allylic alcohol (0.522g, 1.3 mmol) and propionic acid (3 drops) in triethyl orthoacetate (5 mL) was heated under reflux (Dean-Stark) while propionic acid (3 drops) was added every hour and the low boiling fraction was removed occasionally. After two hrs, the excess triethyl orthopropionate was distilled off under reduced pressure and the residue was purified by column chromatography afforded the unsaturated ester [hexane/ethyl acetate (7:3)].

Molecular Formula : $C_{30}H_{34}N_2O_4$, 486

Yield : 0.577g, 92%.

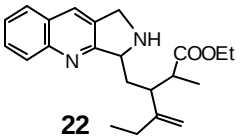
IR : 1736, 1615cm^{-1}

^{1}H NMR (200 MHz) : 8.09 (m, 2H), 7.95-7.75 (m, 3H), 7.37 (t, 8.3Hz, 1 H), 7.43 (t, 7.34 (m, 6H), 5.29-5.25 (m, 3H), 4.95-4.27 (m, 3Hz, 3H), 3.89 (q, 2H), 2.5-0.5 (m,

^{13}C NMR (50 MHz) δ: 175.07 (C), 173.08 (C), 161.91 (C), 154.63 (C), 149.78 (C), 148.16 (CH), 147.8 (C), 136.51 (C), 136.17 (C), 128.97 (2 CH), 128.72 CH), 128.28 (2 CH), 127.87 (CH), 127.47 (CH), 127.32(CH), 110.62 (CH_2), 67.86 (CH_2), 59.97 (CH), 59.61 (CH_2), 50.31 (CH_2), 44.39 (CH), 42.74 (CH), 32.78 (CH_2), 27.08 (CH_2), 13.99 (CH_3), 11.98 (CH_3), 8.70 (CH_3)

Mass: *m/z* (%) : 486 (M^+,5), 424 (5), 385 (5), 351 (10), 306 (18), 277 (8) ,249 (23), 224 (16), 197 (8), 169 (95), 91 (100) , 67 (10)

10. 3-(2,3-Dihydro-1*H*-pyrrolo[3,4-*b*]quinoline-3-yl-methyl}-4-ethyl-2-methyl-pent-4-enoic acid ethyl ester [22]



22

A mixture of hexamethyldisilane (0.3g, 2mmol) and Iodine (0.5g, 2mmol) is heated at about 65^{o}C in 20mL flask fitted with a reflux condenser; an exothermic reaction took place and a homogeneous solution was formed. Then the mixture was heated under reflux for 1h during which the colorless solution of TMSI has been formed. The reaction mixture was cooled and substrate **4** (0.486g, 1mmol) was added in dry $CHCl_3$ (10mL) along with dry pyridine (0.15mL, a

trap for the HI liberated invariably under these conditions). The reaction mixture was further stirred for 4h at rt. The reaction mixture was diluted with $CHCl_3$ and washed with saturated aq $NaHCO_3$ and dilute aq $Na_2S_2O_7$ solutions successively, then dried and evaporated to leave the amine **22** as dark paste which was subjected for lactamisatuion.

Molecular Formula : $C_{22}H_{28}N_2O_2$, 352.48

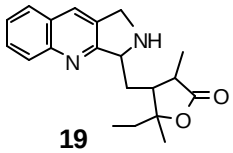
Yield :0.388g, 81%

IR ($CHCl_3$) : 2450, 1735, 1612 cm^{-1}

^{1}H NMR (200 MHz) : δ: 8.09 (m, 1H), 7.89 (m, 1H), 7.75 (m, 1H), 7.67 (m, 1 H), 7.43 (m, 1H), 5.03 - 4.25 (m, 2H), 4.33 (m, 3H), 4.89 (m, 2H), 3.02-2.5 (m, 2H), 2.30 (m, 3H), 1.79 (m, 2H), 1.3-1.01 (9H)

Mass: *m/z* (%) : 352 (M^+, 7), 322 (5), 306 (40), 277 (10), 249 (70), 224 (40), 182 (50), 169 (100), 140 (29), 128 (11),115 (15), 95 (13), 67(30).

*11***.** *Amine by product [19]*



19

Method a) ***To a stirred solution of NaI (0.502 g, 3.3mol) and ester*** *4* ***(0.150g, 0.337mmol) in dry acetonitrile (25 mL) was added TMSCl (0.367g, 3.3 mmol) dropwise under nitrogen atmosphere. The reaction mixture was stirred for 1 h, quenched with thiosulphate solution (20%) and the aqueous phase was extracted with ethylacetate (3x50mL). After acid(HCl)-base(NH_3) treatment, organic layer was dried, concentrated to provide amine*** *19***.**

Method b) A solution of ester **4** (0.486g, 1 mmol) was suspended in 1:1 40% HCl: dioxane solution (15mL) and refluxed for 2h. The reaction mixture was extracted with DCM (15mL). The aqueous phase was basified and extracted with DCM (3×30mL), dried, concentrated to give the amine **19**.

Molecular Formula : $C_{20}H_{24}N_2O_2$, 324

Yield : 70% in method A; 79% in method B.

IR ($CHCl_3$) : 3340, 1770, 1600 cm^{-1}

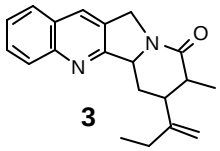
^{1}H NMR (200 MHz) : δ: 8.10 (d, *J* = 8.3Hz, 1H), 7.93 (s, 1H), 7.83 (d, *J* =7.3Hz, 1H), 7.7 (t, 8.3Hz, 1 H), 7.53 (t, 7.3 Hz, 1H), 4.53 (m, 1H), 4.39 (s, 2H), 2.75-2.25 (m, 2H), 1.95-1.53 (m, 2H), 1.5-1.2 (m, 8H), 1.0 (m, 3H)

^{13}C NMR (50 MHz) : δ: 178.41 (C), 168.58 (C), 148.02 (C), 132.61 (C), 129.09 (CH), 129.0 (CH), 127.69 (CH), 127.43 (C), 125.96 (CH), 86.78 (C), 61.01 (CH_3),

48.99 (CH_2), 47.08 (CH), 41.09 (CH), 37.5(CH), 32.93 (CH_2), 27.07 (CH), 20.50 (CH_3), 15.90 (CH_3), 7.71 (CH_3)

Mass:*m/z* (%) : 324 (M^+, 5), 295, 277 (4), 249 (10), 207 (10), 181 (5), 169 (100), 140 (29),115 (15), 84 (3)

12. 8-Methyl-7-(1-methylene-propyl)-5b,7,8,11-tetrahydro-6*H*-indolizino[1,2-*b*] quinoline-9-one [3]



3

A mixture of **13a** (0.321 g, 1 mmol) and anhydrous sodium acetate (0.0826 g, 1 mmol) in ethanol was refluxed for 6h. The pH of the solution was adjusted to 8 by addition of 1 N NaOH. ethanol was removed, and the solution was extracted with chloroform (3×15 mL). The chloroform layer was dried and evaporated to give a gummy solid, which was purified by column chromatography (pet ether/ ethylacetate, 2/3) to give tetrahydropyridone (0.13 g, 80%) as a yellow solid.

Molecular Formula : $C_{20}H_{22}N_2O$, 306.78

Yield : 170 mg,

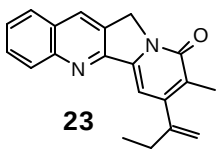
IR ($CHCl_3$) : 1673, 1625 cm^{-1}

^{1}H NMR (200 MHz) : δ: 8.24-8.14 (m, 2H), 7.87 (d, 8.3Hz, 1 H), 7.53 (t, 5.8 Hz, 1H), 7.63 (t, 8.3 Hz, 1H), 5.5-4.5 (m, 5H), 2.90-2.5 (m, 2H), 2.47 (m, 1H), 2.25-1.83 (m, 3H), 1.3-1.0 (m, 6H)

^{13}C NMR (50 MHz) : δ: 178.41 (C), 168.63 (C), 148.52 (C), 132.91 (C), 129.09 (CH), 127.69 (CH), 127.43 (C), 125.96 (CH), 101.78 (CH_2), 58.01 (CH), 49.1 (CH_2), 47.28 (CH), 41.2 (CH), 32.93 (CH_2), 27.08 (CH), 13.98 (CH_3) 12.17 (CH_3)

Mass: *m/z* (%) : 306 (M^+,5), 289 (15), 277 (4), 249 (50), 224 (74), 196 (25), 182 (65), 169 (100), 140 (60), 128 (30), 115 (35), 81 (40), 67 (60)

13. 8-Methyl-7-(1-methylene-propyl)-11*H*-indolizino[1,2-*b*]quinoline-9-one [23]



23

A solution of tetrahydropyridone **3** (0.306g, 1 mmol) was heated at reflux in dioxane in the presence of DDQ (0.478g, 2.1 mmol) with stirring under argon for 3.5h. After being allowed to cool to ambient temperature, the reaction mixture was washed with $NaHCO_3$ and extracted with ethylacetate (4×25mL), dried and concentrated. The residue was subjected to silica gel column chromatography using 80% ethylacetate-pet ether to furnish of compound **23**.

Molecular Formula : $C_{20}H_{18}N_2O$, 302

Yield : 240 mg, 80%

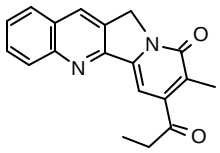
IR : 3057, 1658, 1604 cm^{-1};

^{1}H NMR (200 MHz) : δ: 8.31 (s, 1H), 8.17 (d, 8.3Hz, 1 H), 7.89 (d, 8.3 Hz, 1H), 7.81 (t, 7.3 Hz, 1H), 7.59 (t, 7.3Hz, 1H), 7.18 (s, 1H), 5.28 (s, 1H), 5.27 (s, 2H), 4.98 (s, 1H), 2.44 (q, 2H), 2.24 (s, 3H), 1.1 (t, 3H)

^{13}C NMR (50 MHz) : δ: 161.87 (C), 153.42 (C), 152.61 (C), 149.45 (C), 148.82 (C), 141.88 (C), 130.70 (CH), 130.15 (CH), 129.59 (CH), 128.79 (CH), 128.02 (C), 127.32 (CH), 127.02(C), 126.40 (C), 113.50 (CH_2) 102.62 (CH), 50.01 (CH_2), 29.62 (CH_2), 14.03 (CH_3), 12.23 (CH_3).

Mass: *m/z* (%) : 302 (M^+, 50), 287 (100), 273 (14), 243 (25), 218 (24), 128 (25), 77 (35).

14. 8-Methyl-7-propionyl-11*H*-indolizino [1,2-*b*] quinoline-9-one



A stirred solution of 105 mg (0.35 mmol) of the above olefin in 14 mL of dichloromethane-methanol (6:1) at –78°C was carefully treated with ozone until complete consumption of the starting material (TLC). After the excess ozone was removed with a stream of oxygen, 2 mL of dimethyl sulfide was added to the reaction mixture, and allowed overnight at rt. The solvents were then removed under reduced pressure, and the residue was processed with dichloromethane in the usual way to give the crude reaction product. Purification of this material by column chromatography over silica gel with 15% MeOH in dichloromethane yielded Mappicine ketone **2**.

Molecular Formula : $C_{19}H_{12}N_2O_2$, 304

Yield : 240 mg, 80%

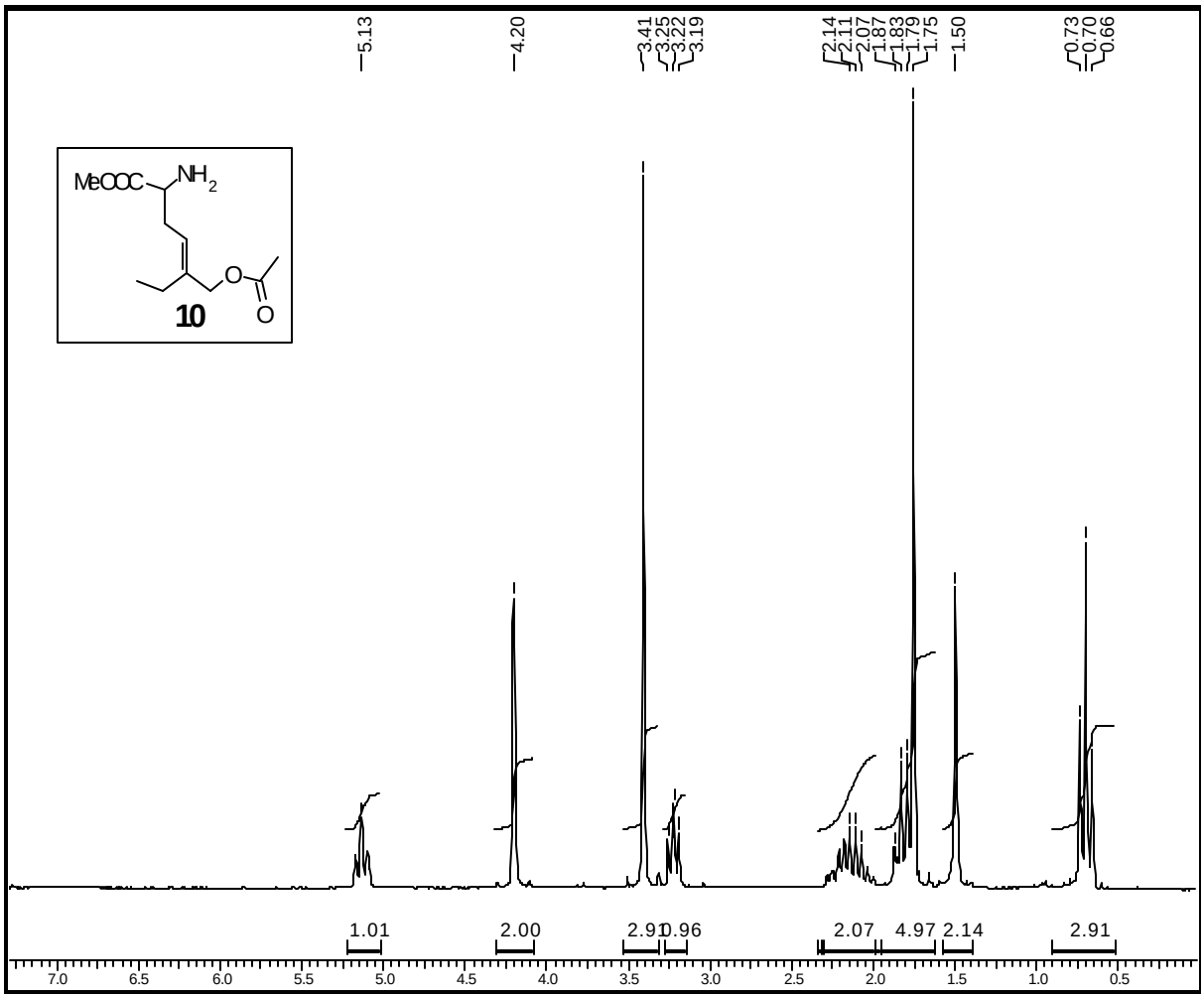
M.P. : 236-237°C (lit. 237-238°C

IR ($CHCl_3$) : 3090, 1704, 1651, 1600 cm^{-1}

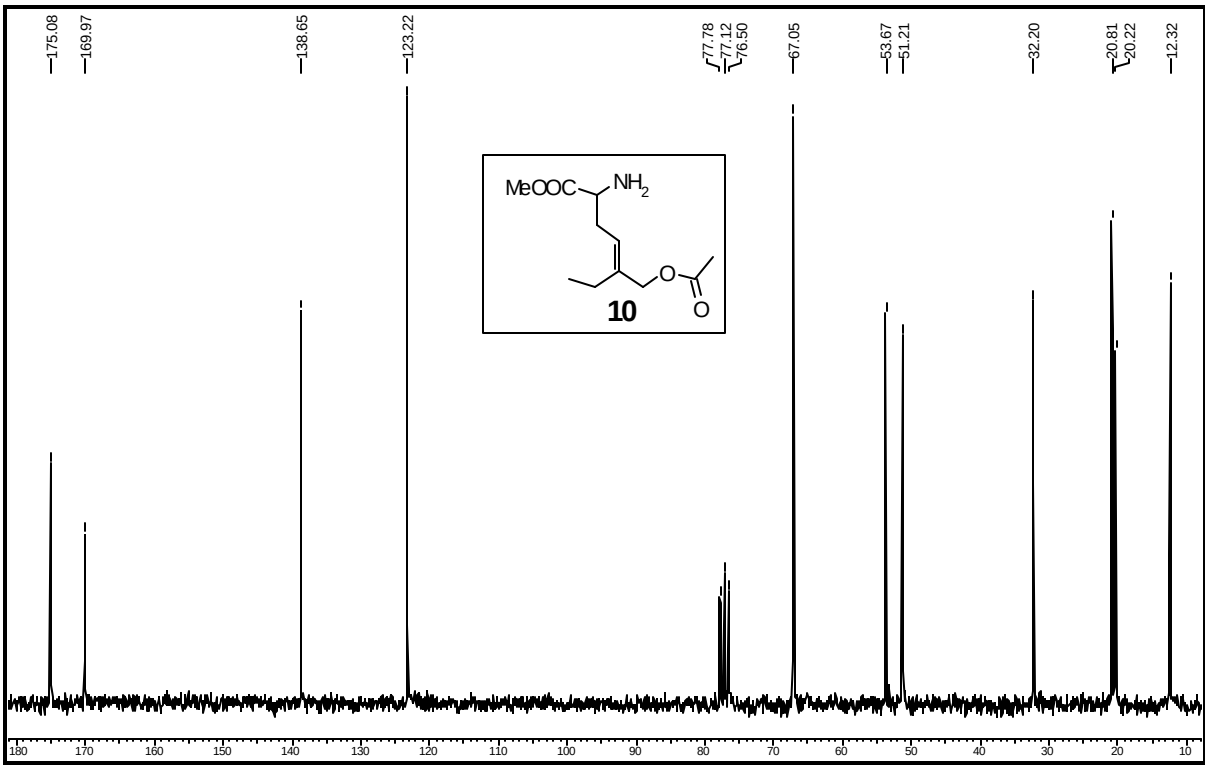
^{1}H NMR (200 MHz) : 8.34 (s, 1 H), 8.17 (d, *J* = 8.6 Hz, 1 H), 7.90 (d, *J* = 7.9 Hz, 1 H), 7.79 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1 H), 7.62 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 7.23 (s, 1 H), 5.27 (2 s, 2 H), 2.89 (q, *J* = 7.2 Hz, 2 H), 2.28 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H);

^{13}C NMR (50 MHz) : 205.5, 161.7, 152.8, 148.8, 148.1, 143.3, 131.0, 130.4, 129.5, 128.5, 128.1, 128.0, 127.7, 127.0, 97.8, 50.2, 36.0, 13.6, and 7.7;

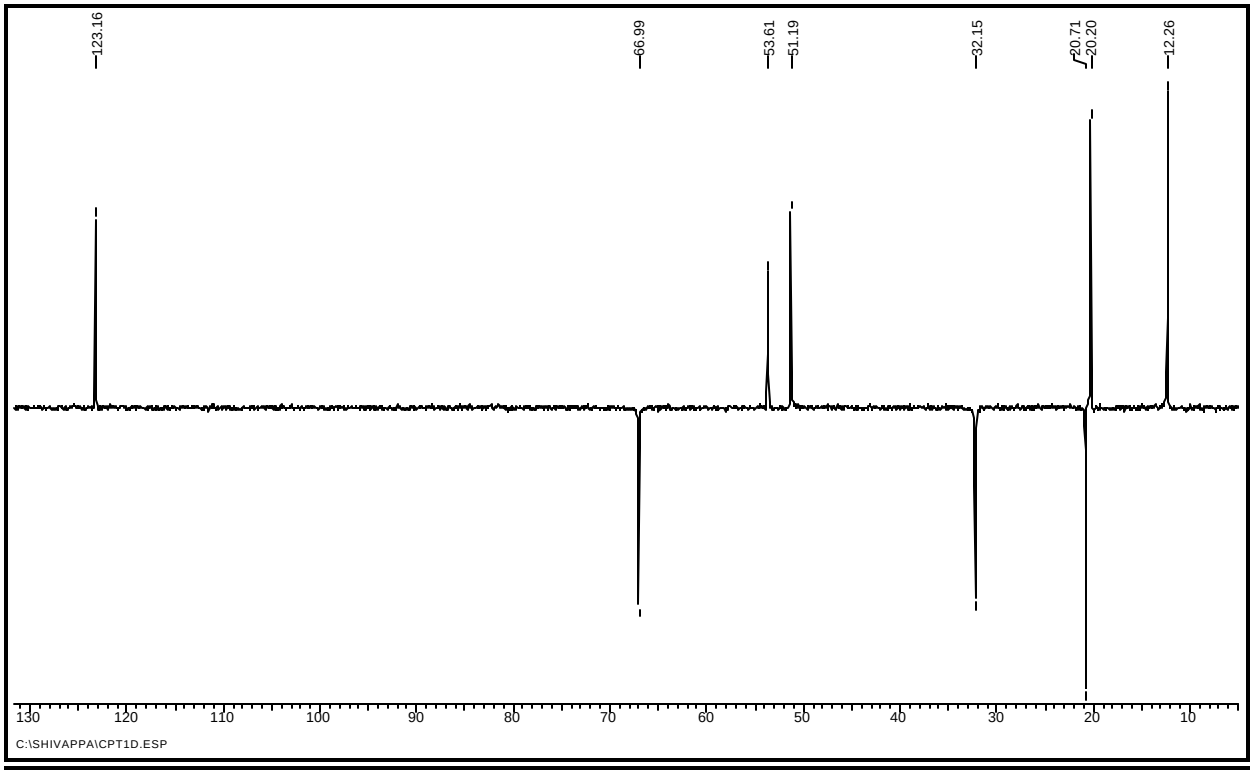
Mass: *m/z* (%) : 304 (M^+, 30), 289 (27), 248 (40), 219 (35), 191 (25), 167 (15), 137(25).

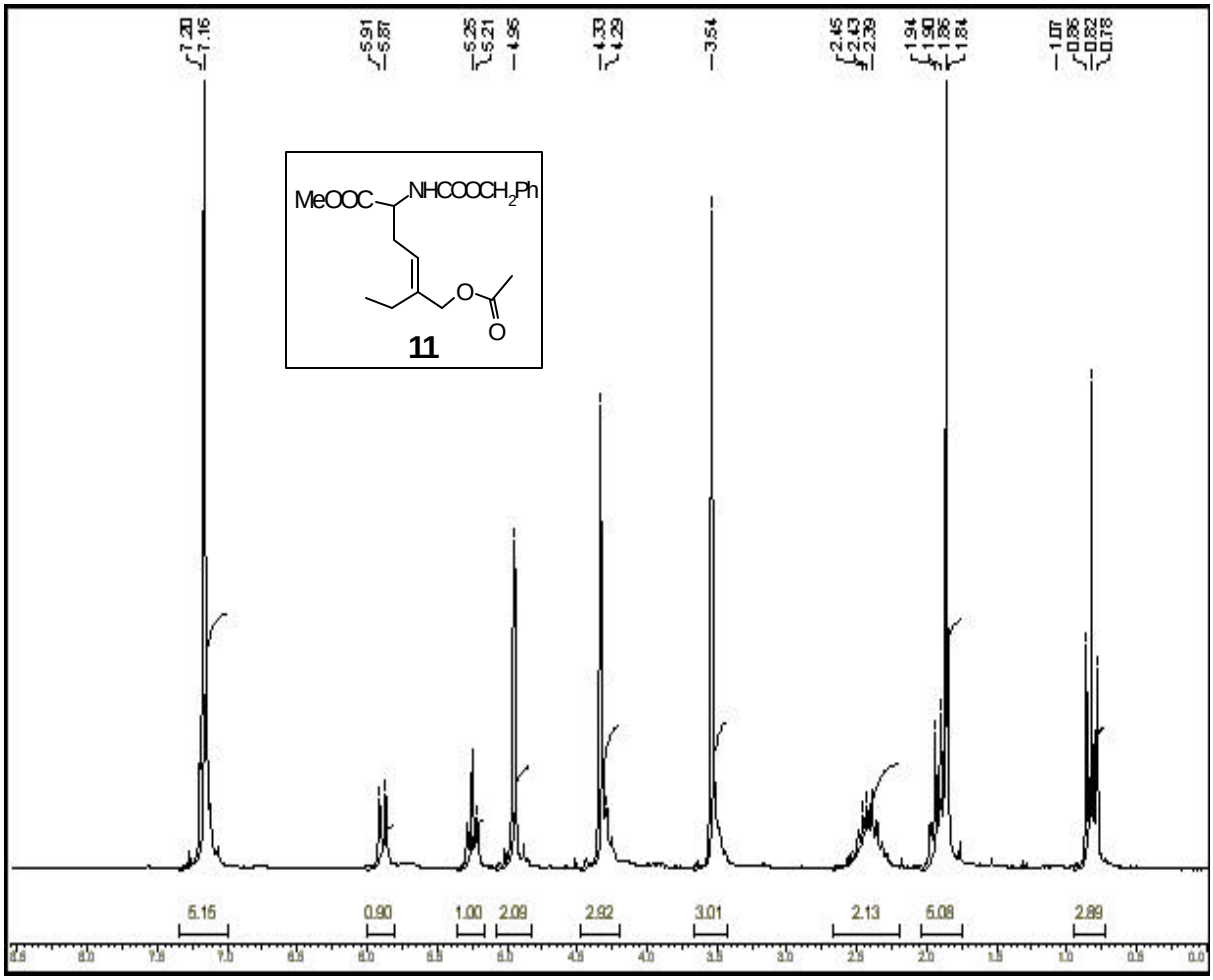


[1]H-NMR spectrum (CDCl3, 200MHz) of compound 10

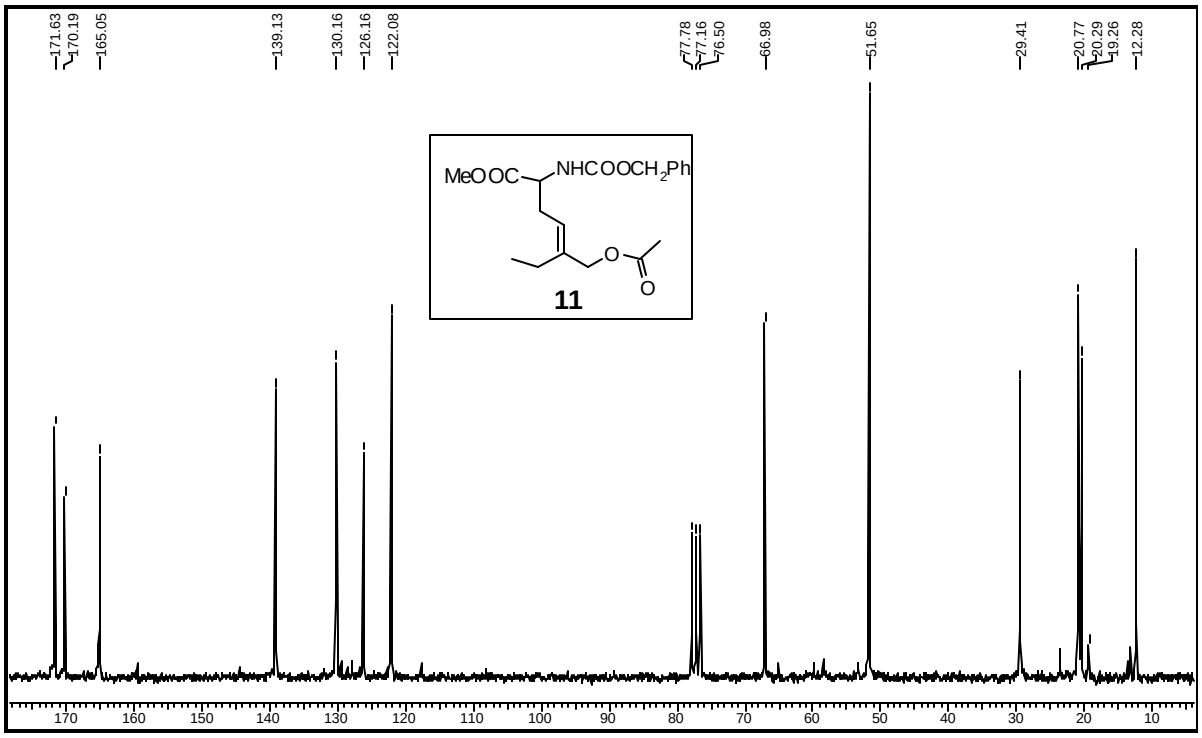


^{13}C and DEPT NMR spectra of compound 10 (50MHz, $CDCl_3$)

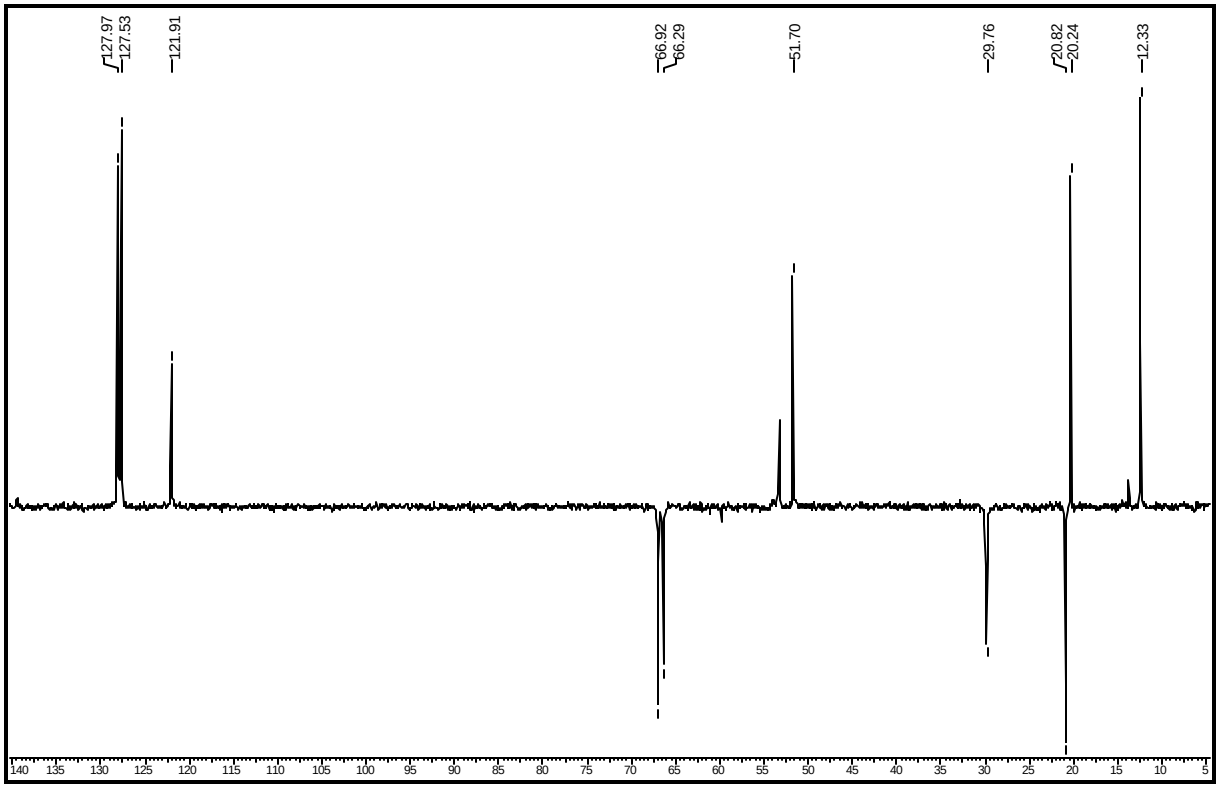


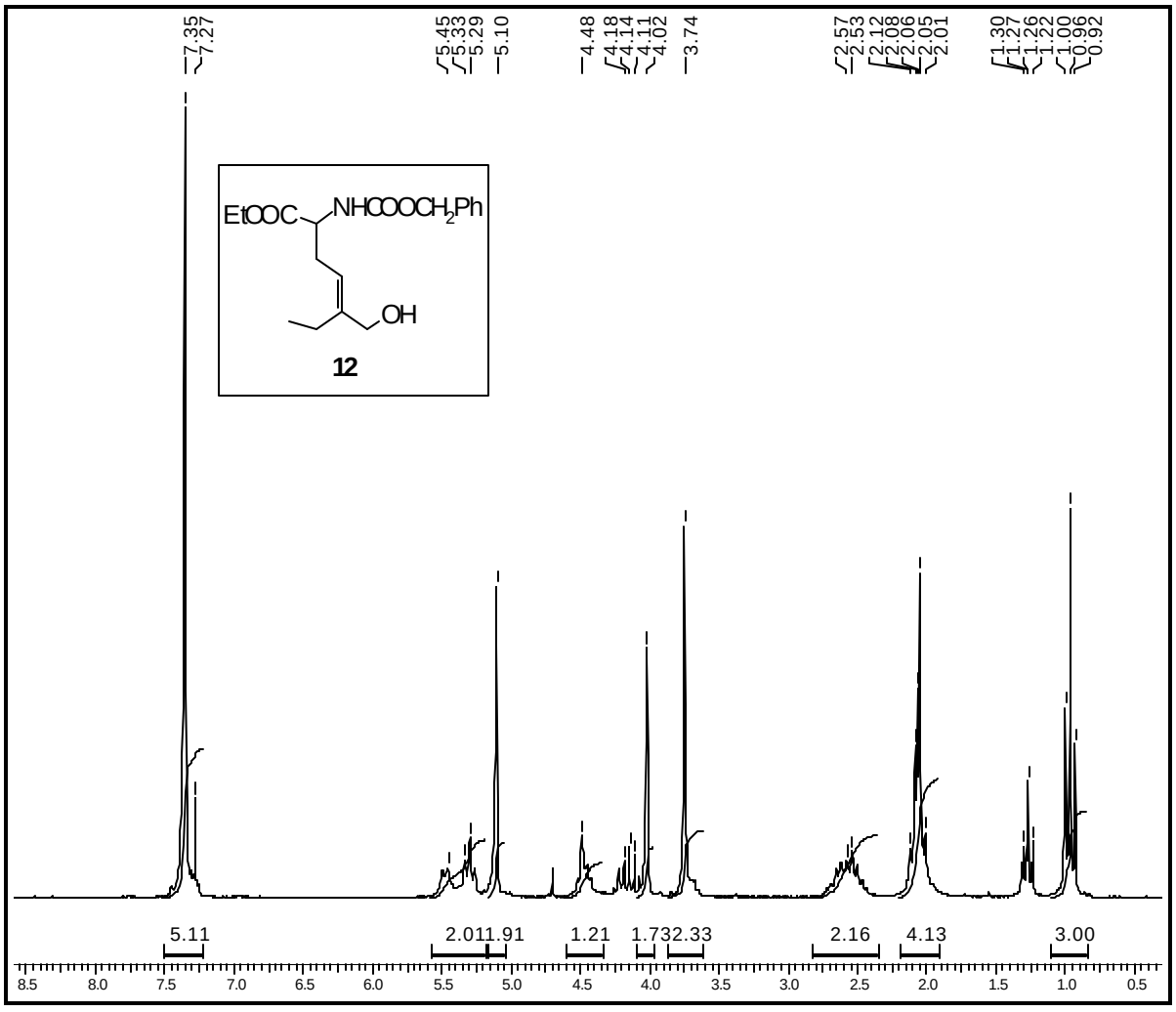


^{1}H-NMR spectrum of compound 11(200MHz, $CDCl_3$)

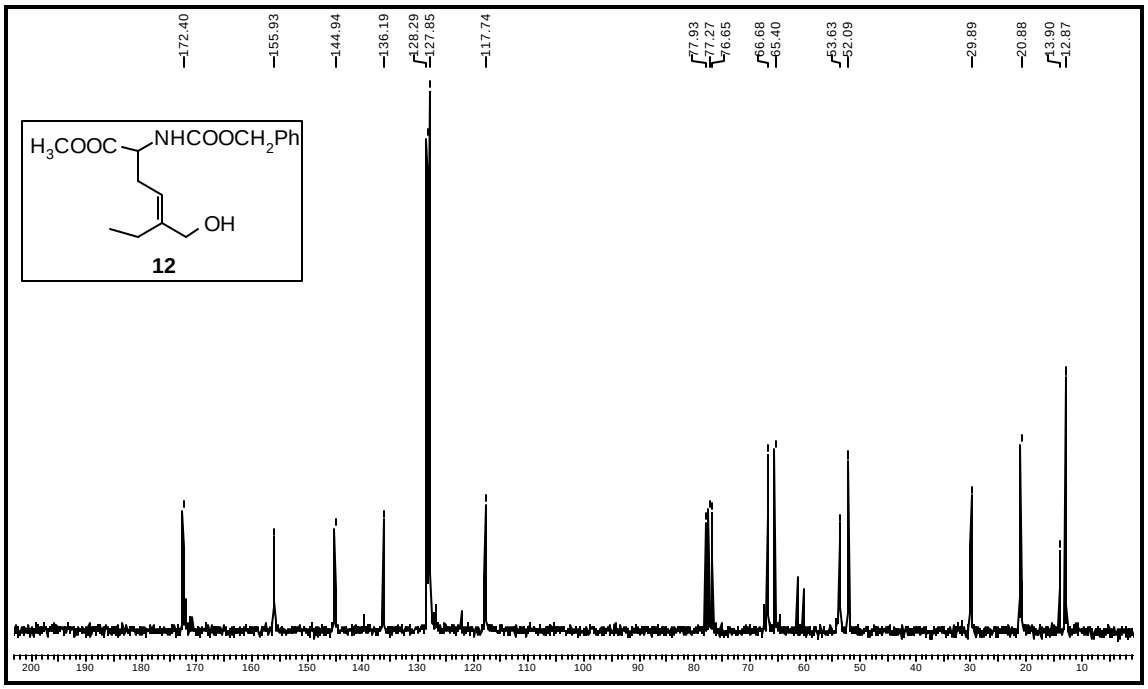


^{13}C & DEPT- NMR spectra of compound [11](50MHz, $CDCl_3$)

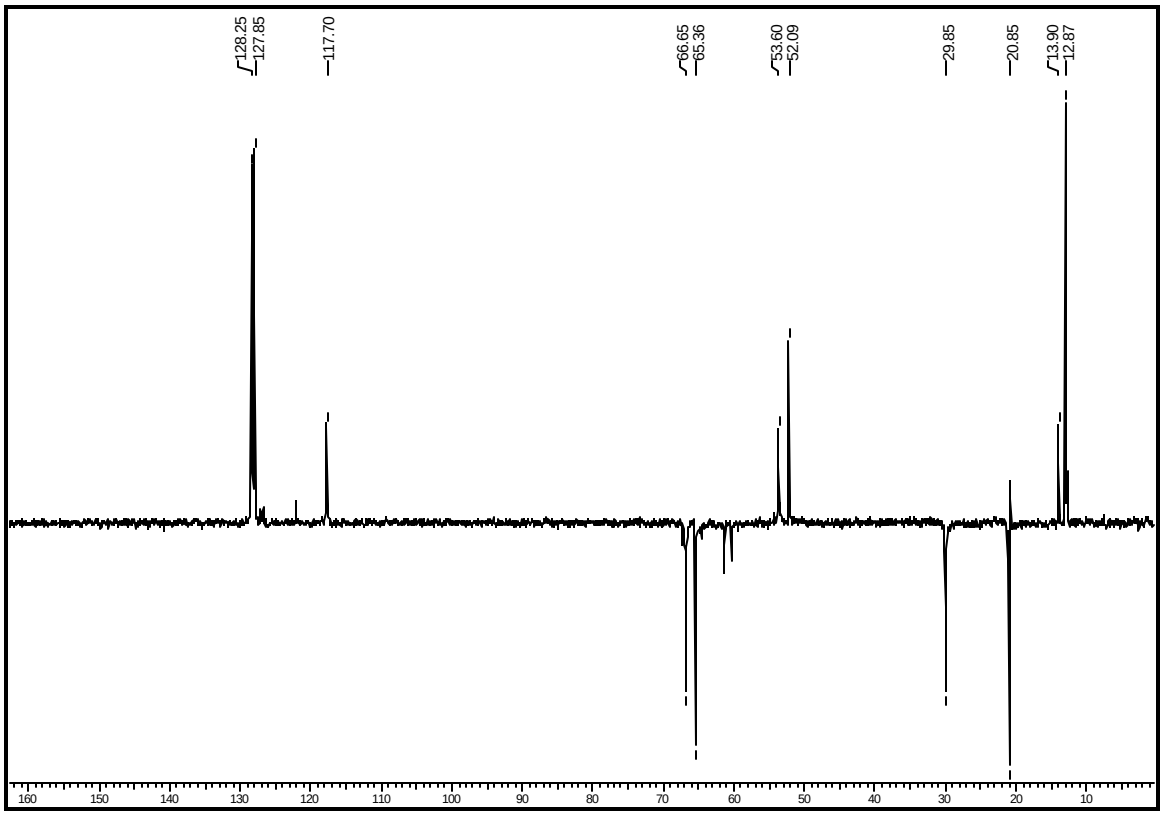


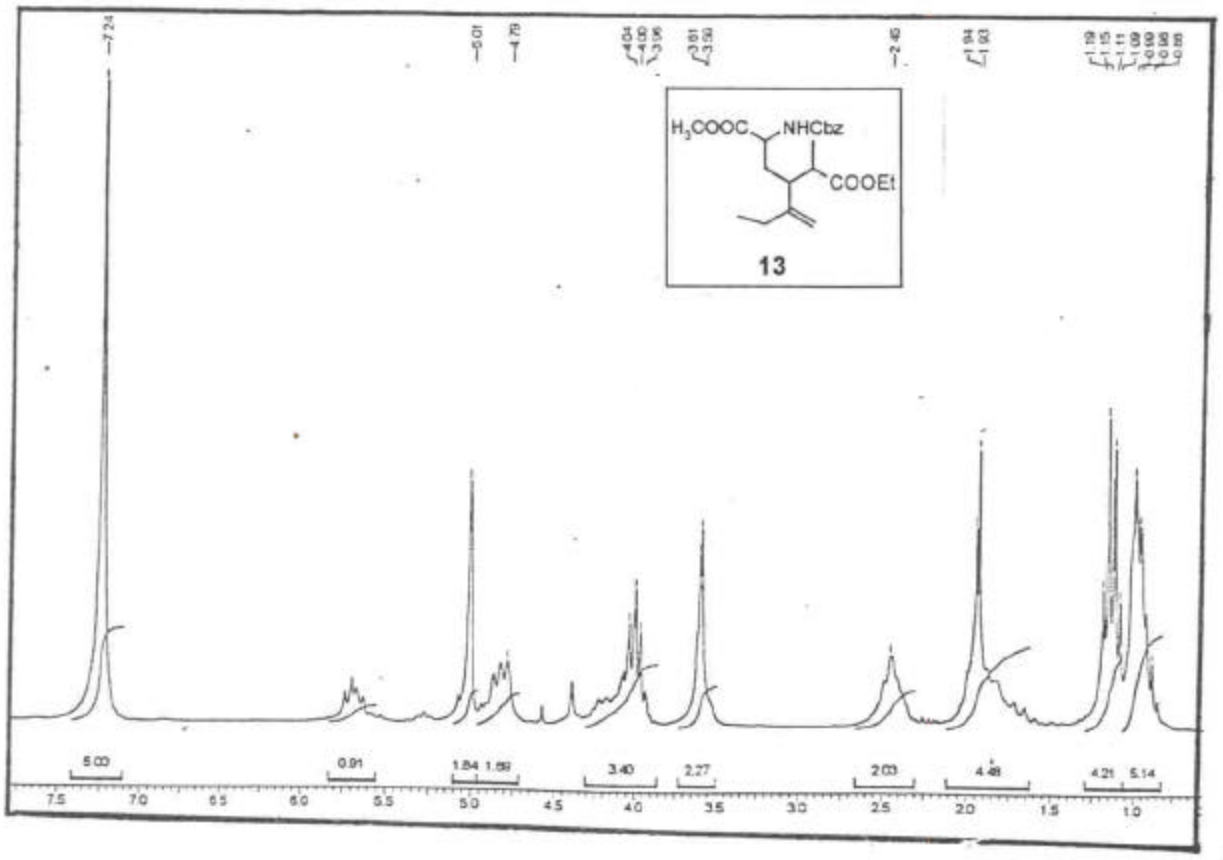


^{1}H-NMR spectrum of compound 12 (200MHz, $CDCl_3$)

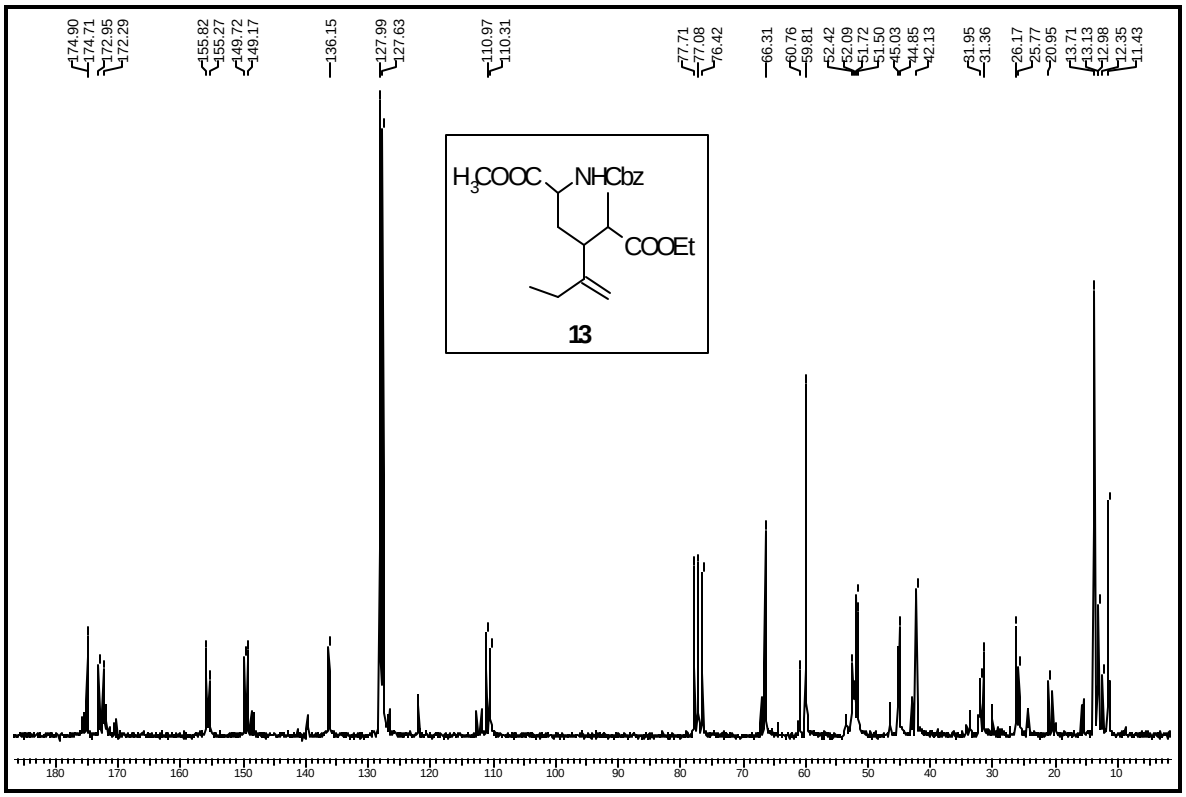


^{13}C & DEPT- NMR spectra of compound [12] (50MHz, $CDCl_3$)

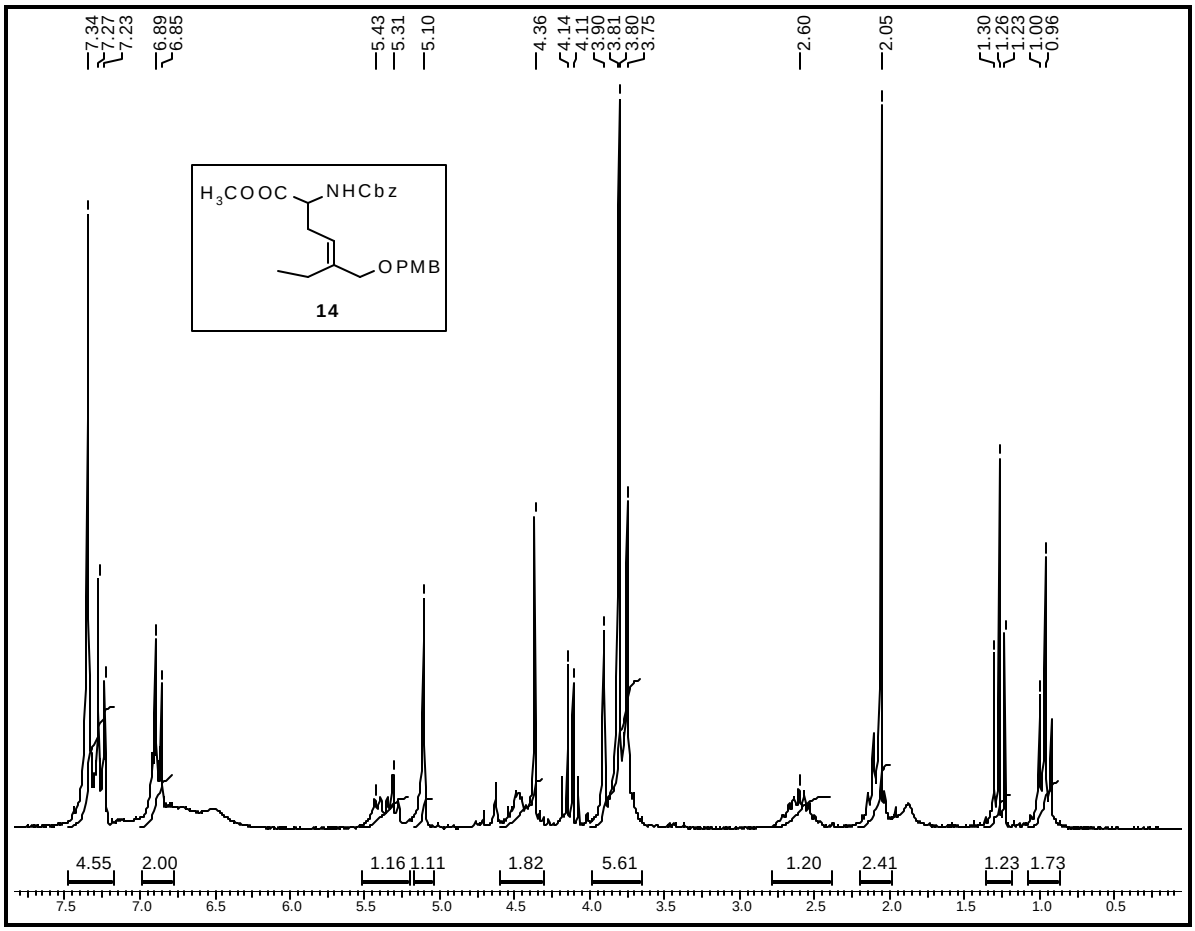




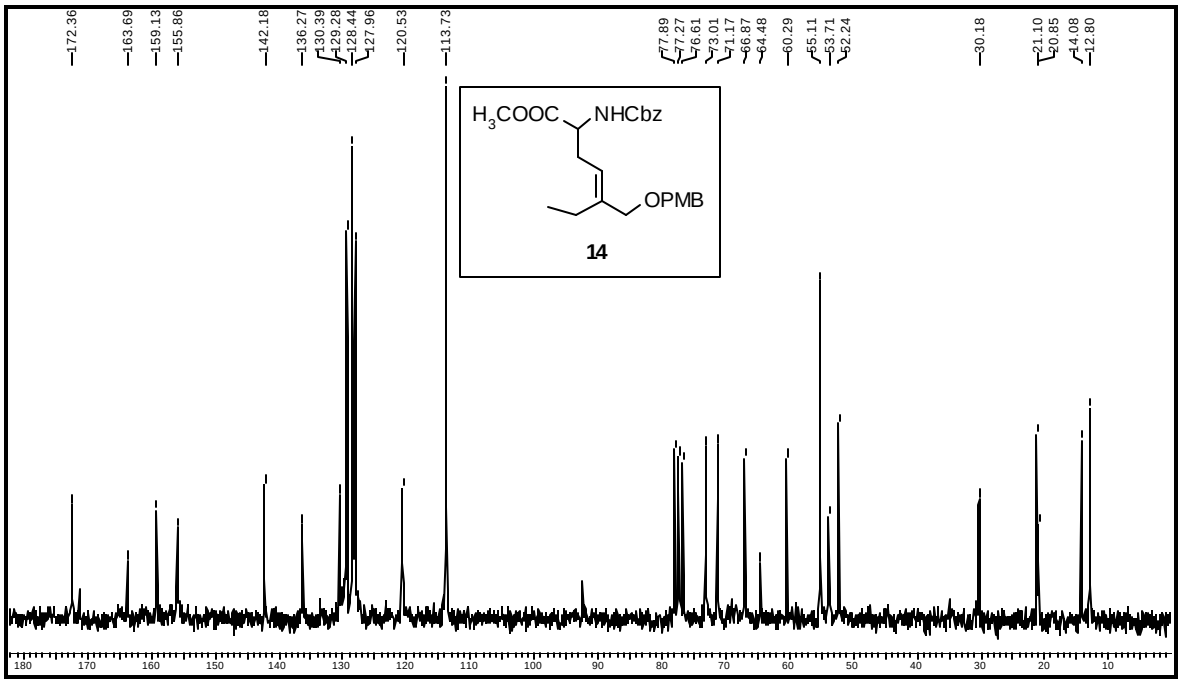
^{1}H-NMR spectrum of compound 13 (200MHz, $CDCl_3$)



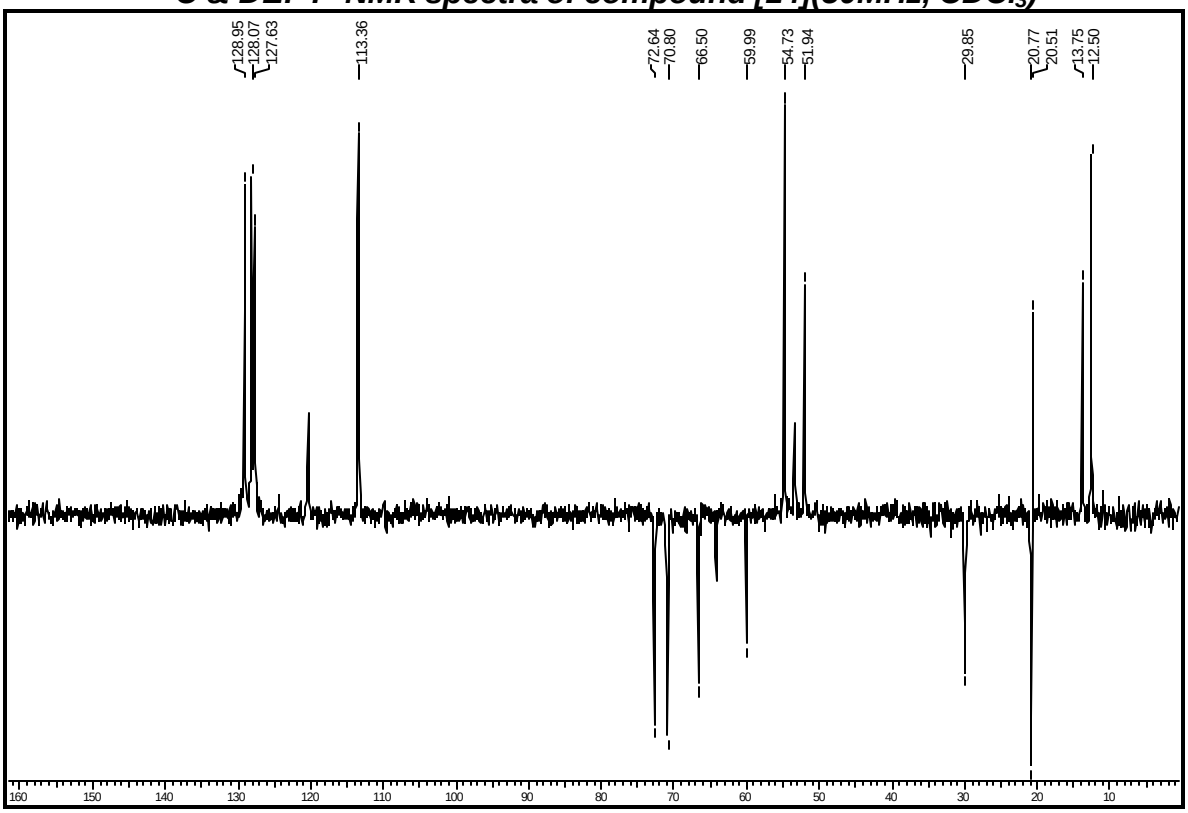
^{13}C & DEPT- NMR spectra of compound [11](50MHz, $CDCl_3$)

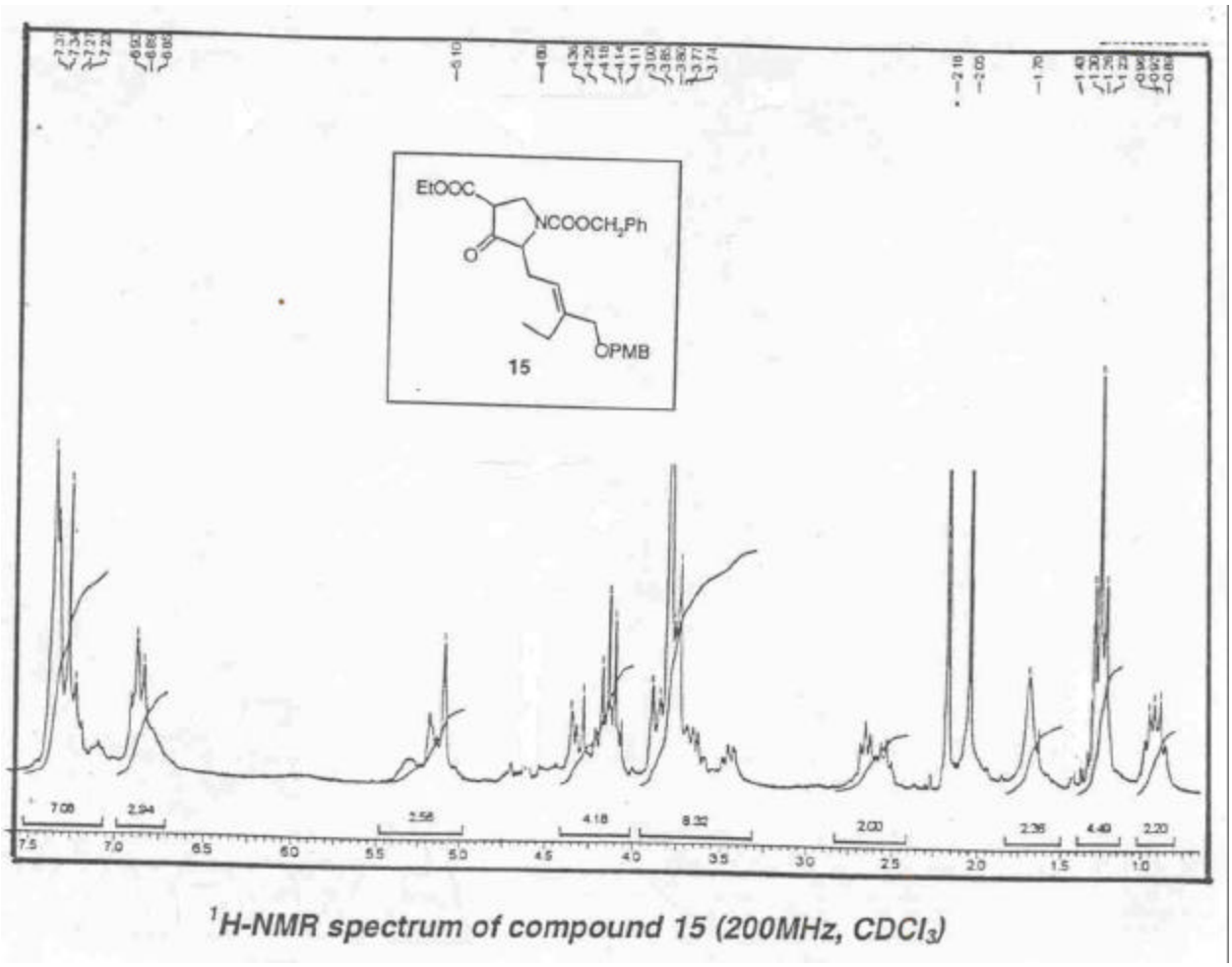


^{1}H-NMR spectrum of compound 14 (200MHz, $CDCl_3$)

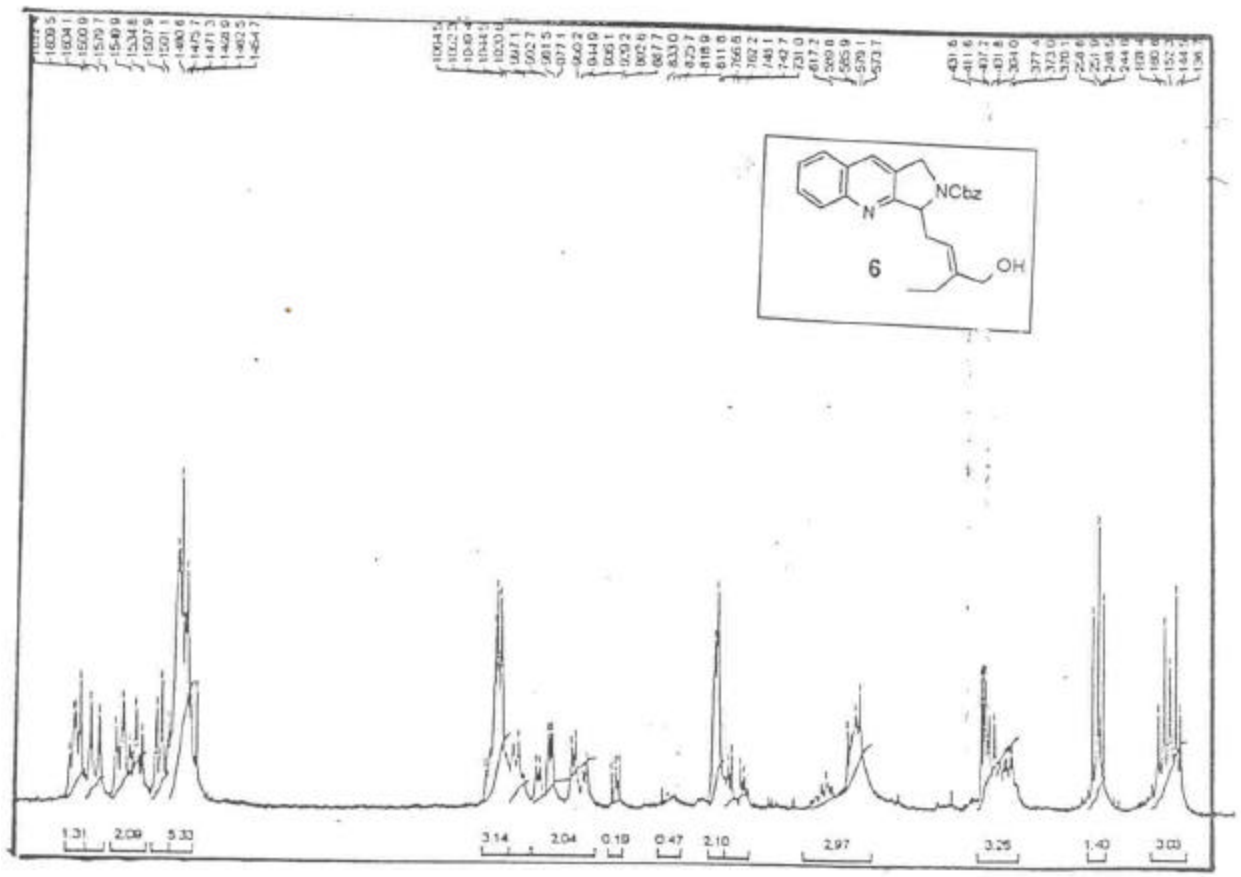


^{13}C & DEPT- NMR spectra of compound [14](50MHz, $CDCl_3$)

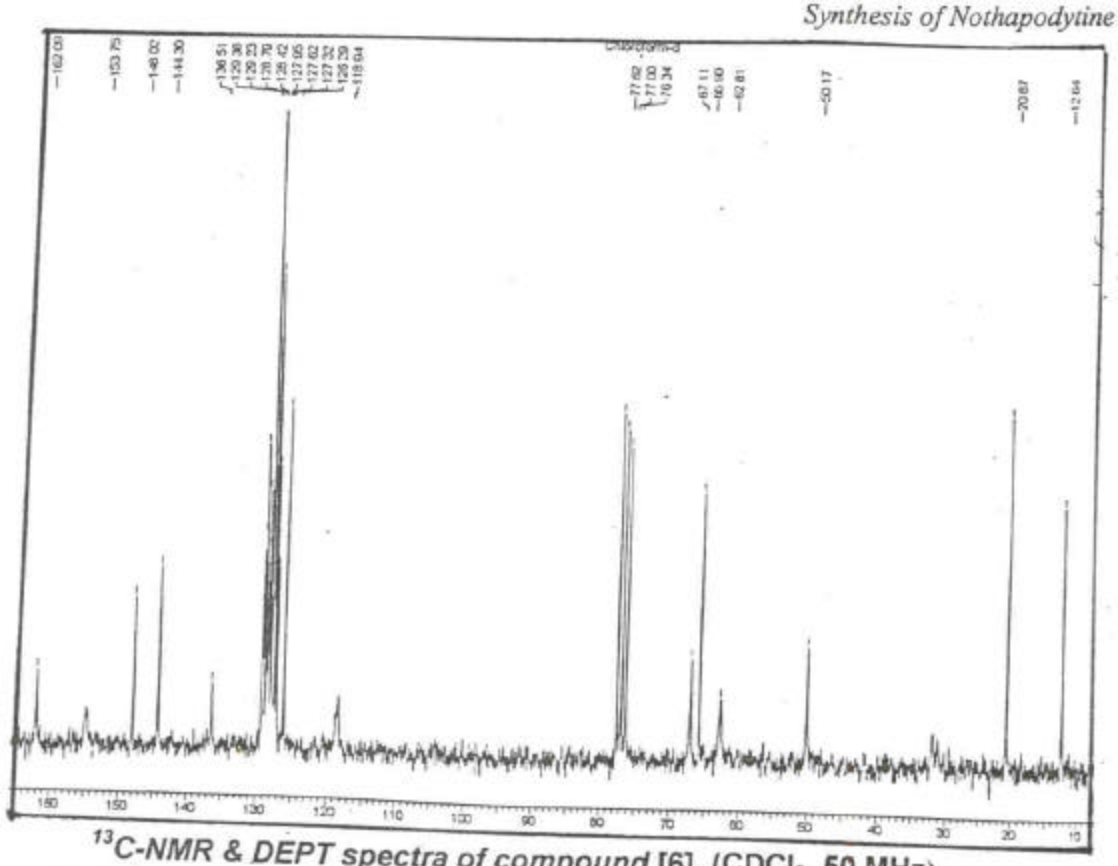




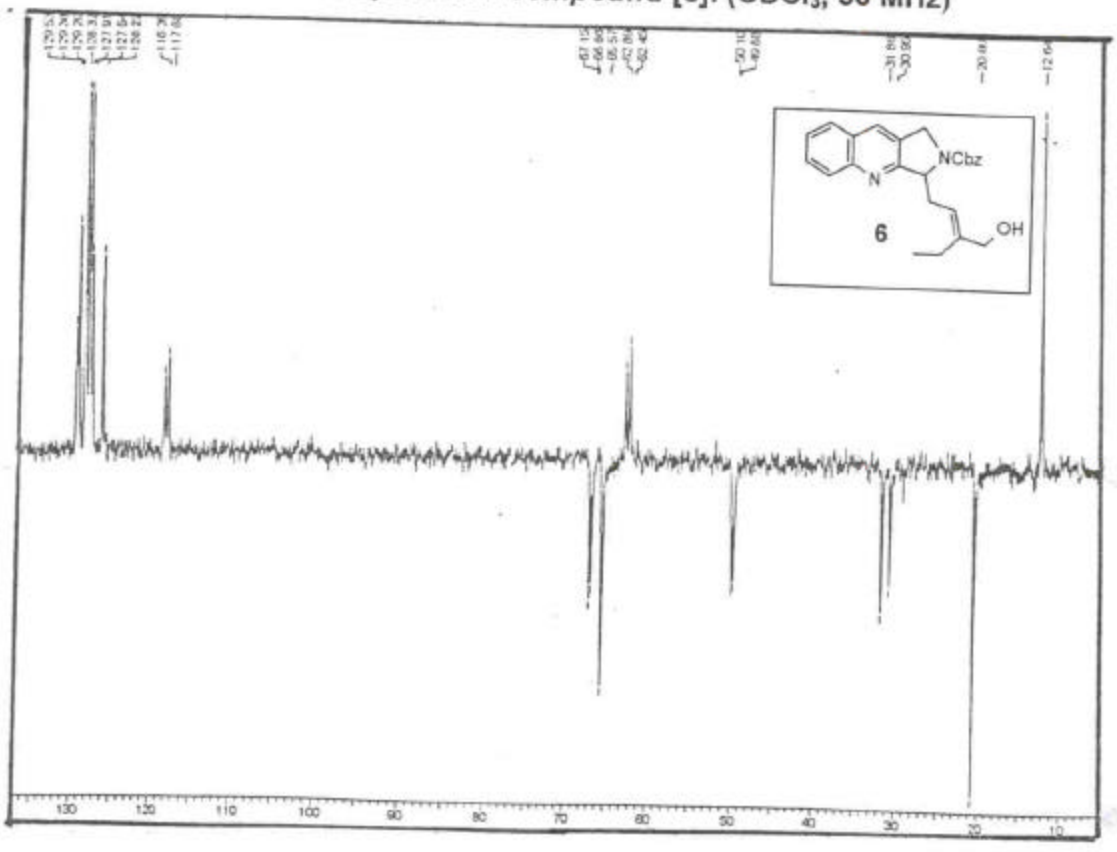
^{1}H-NMR spectrum of compound 15 (200MHz, $CDCl_3$)

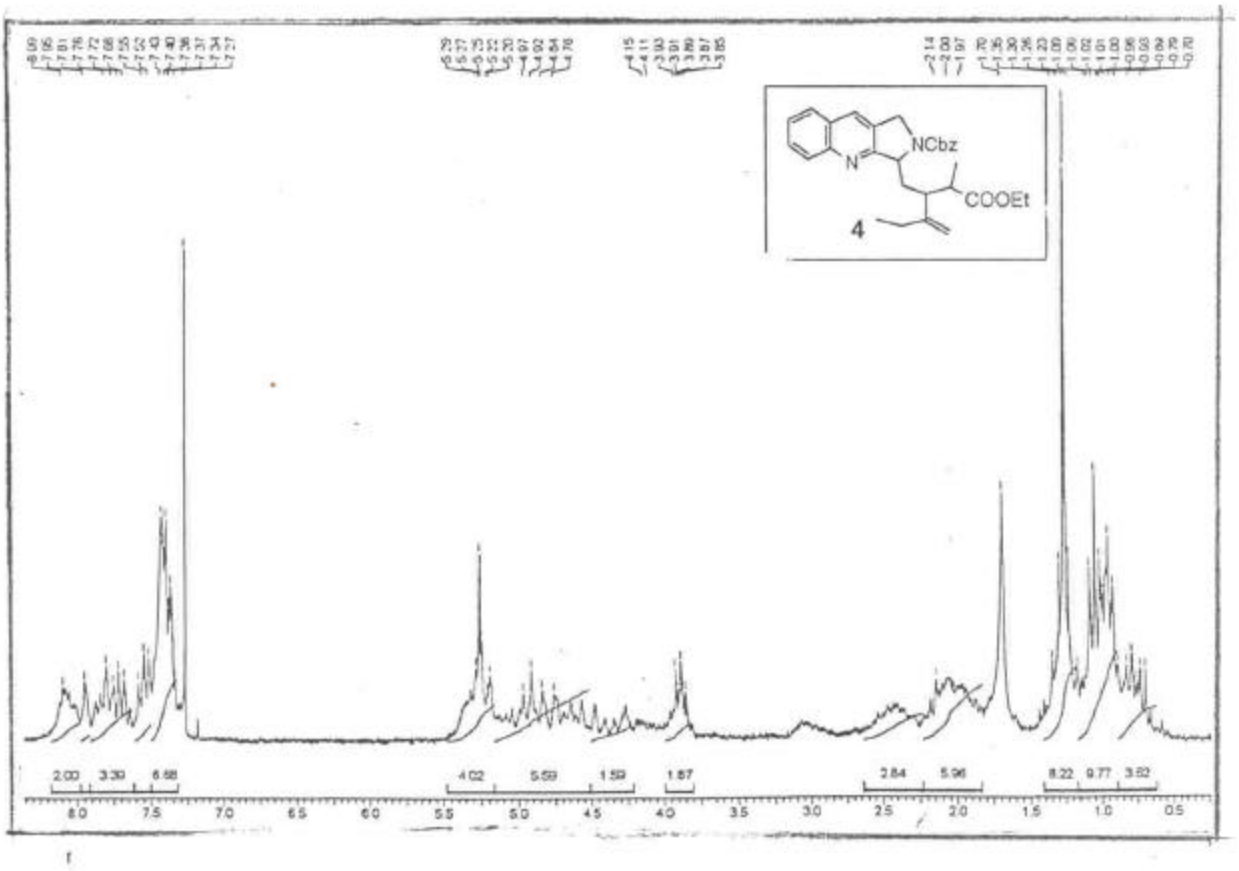


^{1}H-NMR spectrum of compound **[6]**. ($CDCl_3$, 200 MHz)

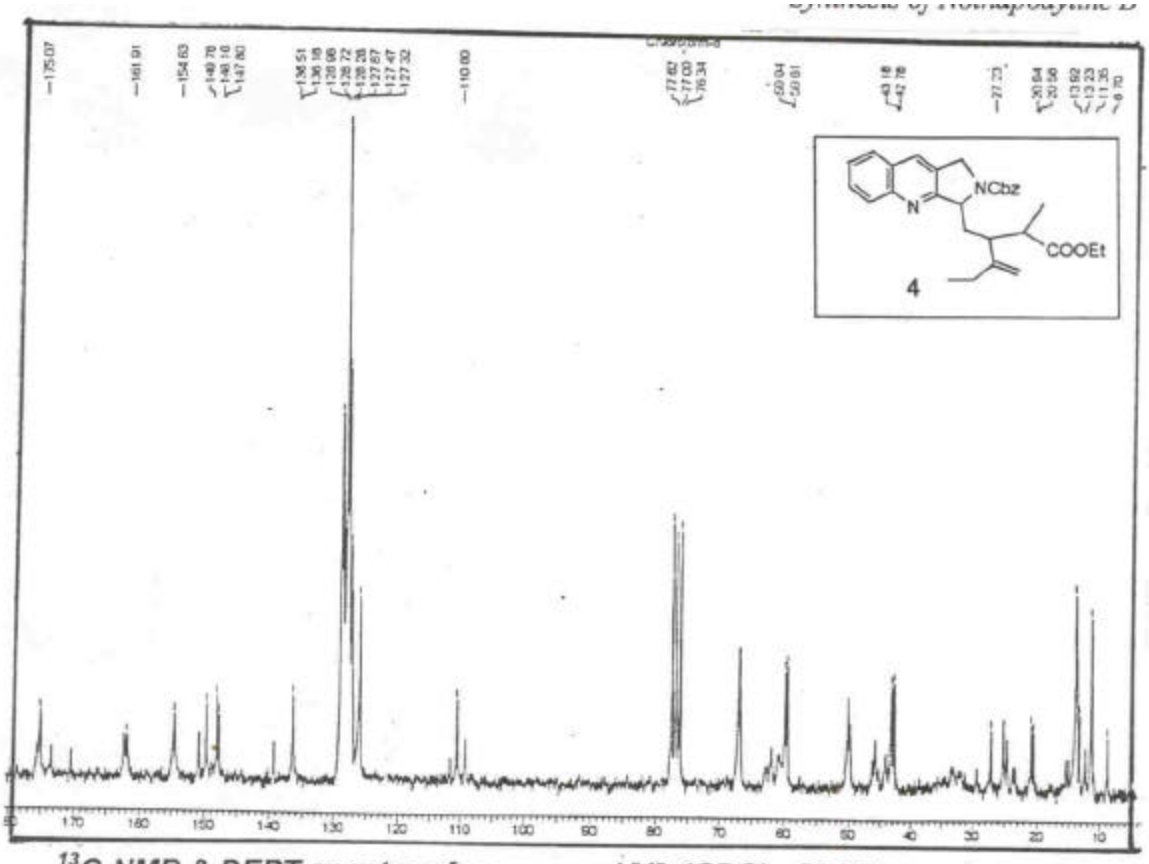


^{13}C-NMR & DEPT spectra of compound [6]. ($CDCl_3$, 50 MHz)

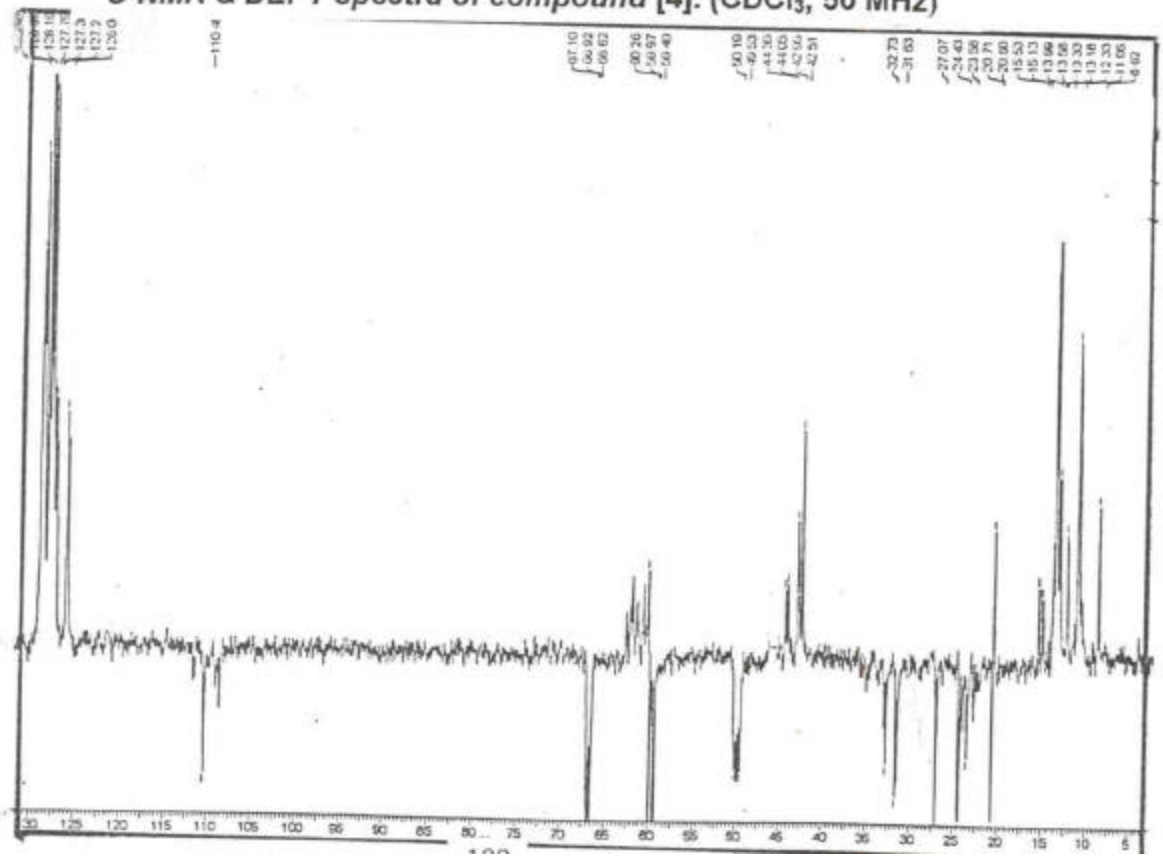


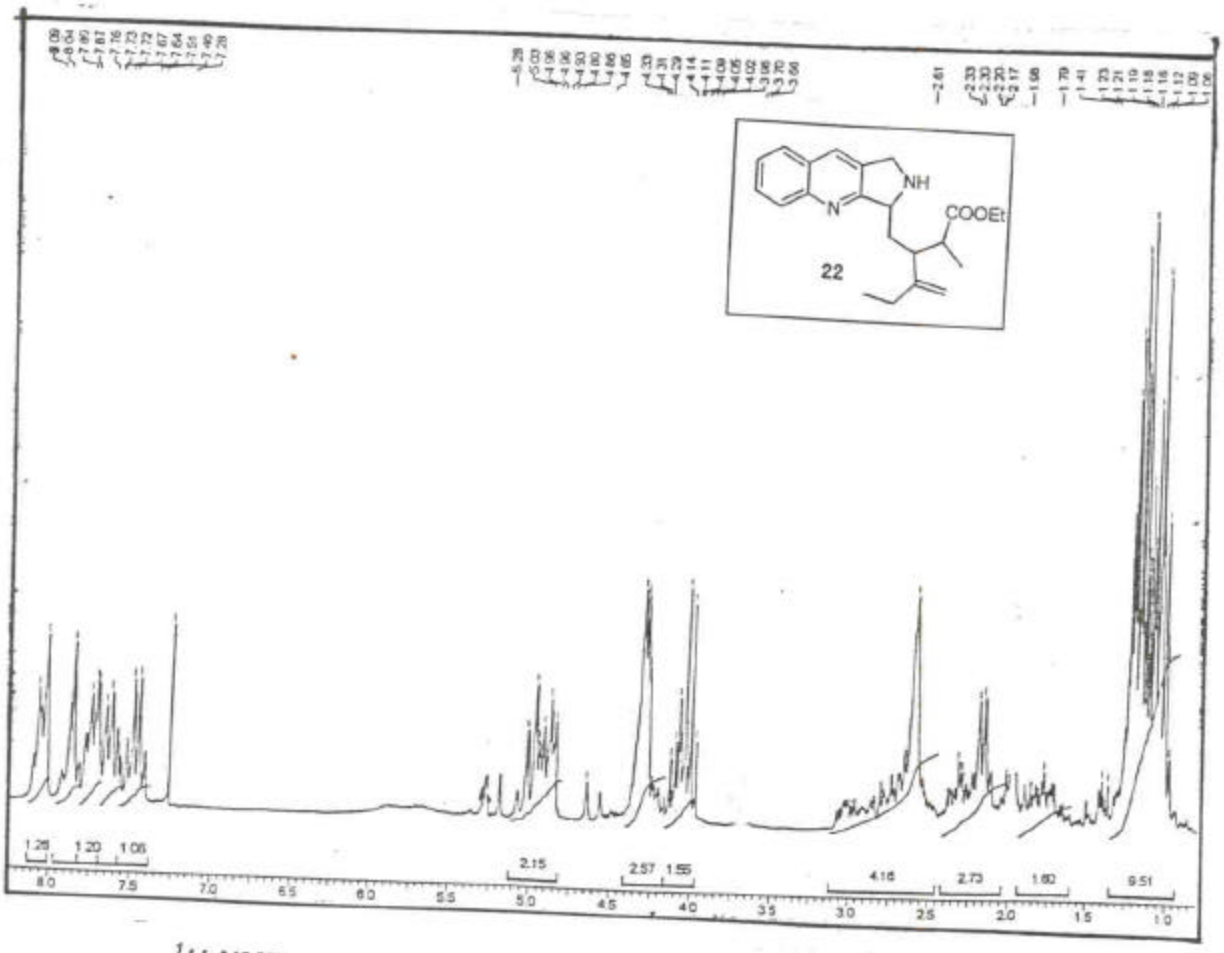


^{1}H-NMR spectrum of compound [4] (200MHz, $CDCl_3$)

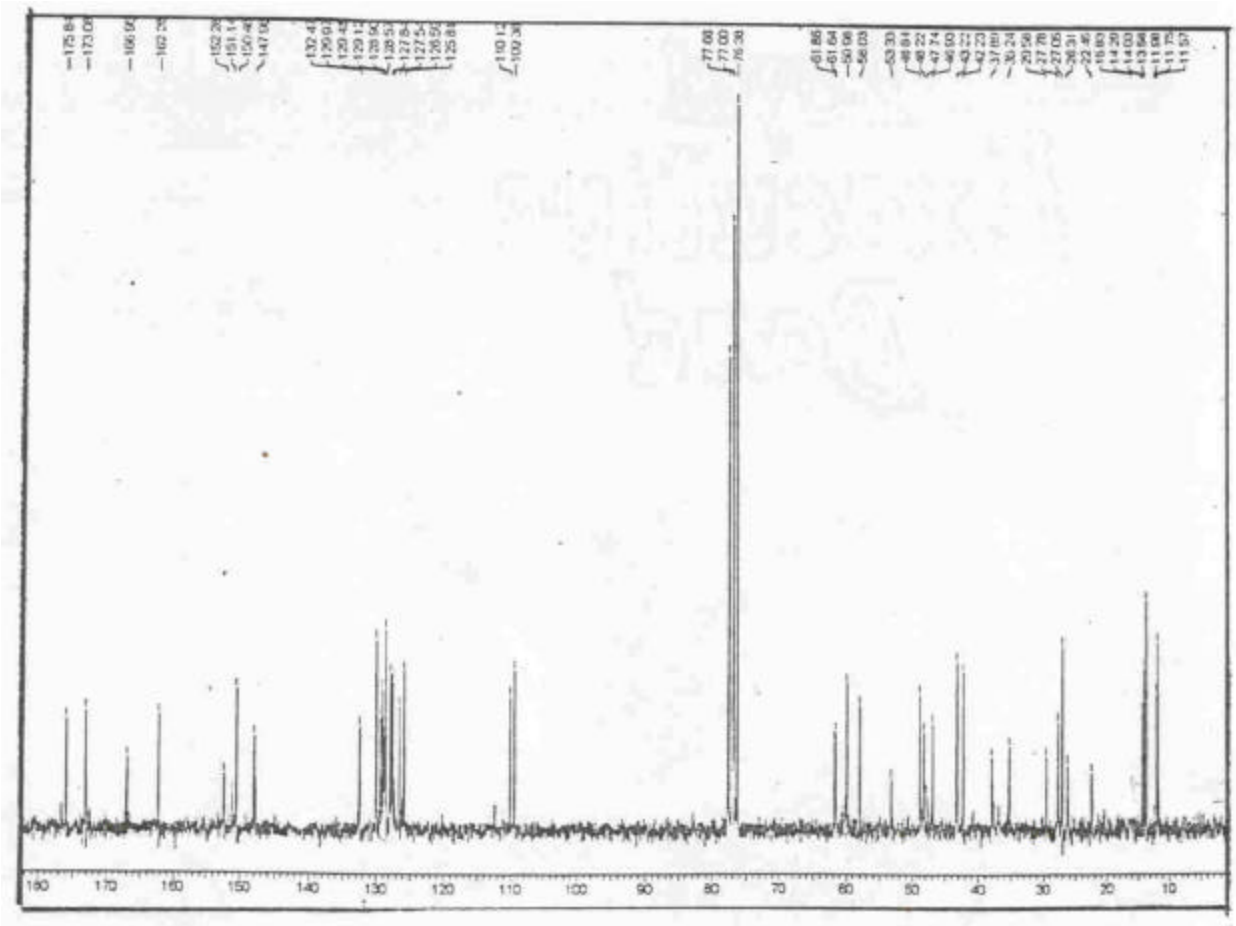


^{13}C-NMR & DEPT spectra of compound [4]. ($CDCl_3$, 50 MHz)

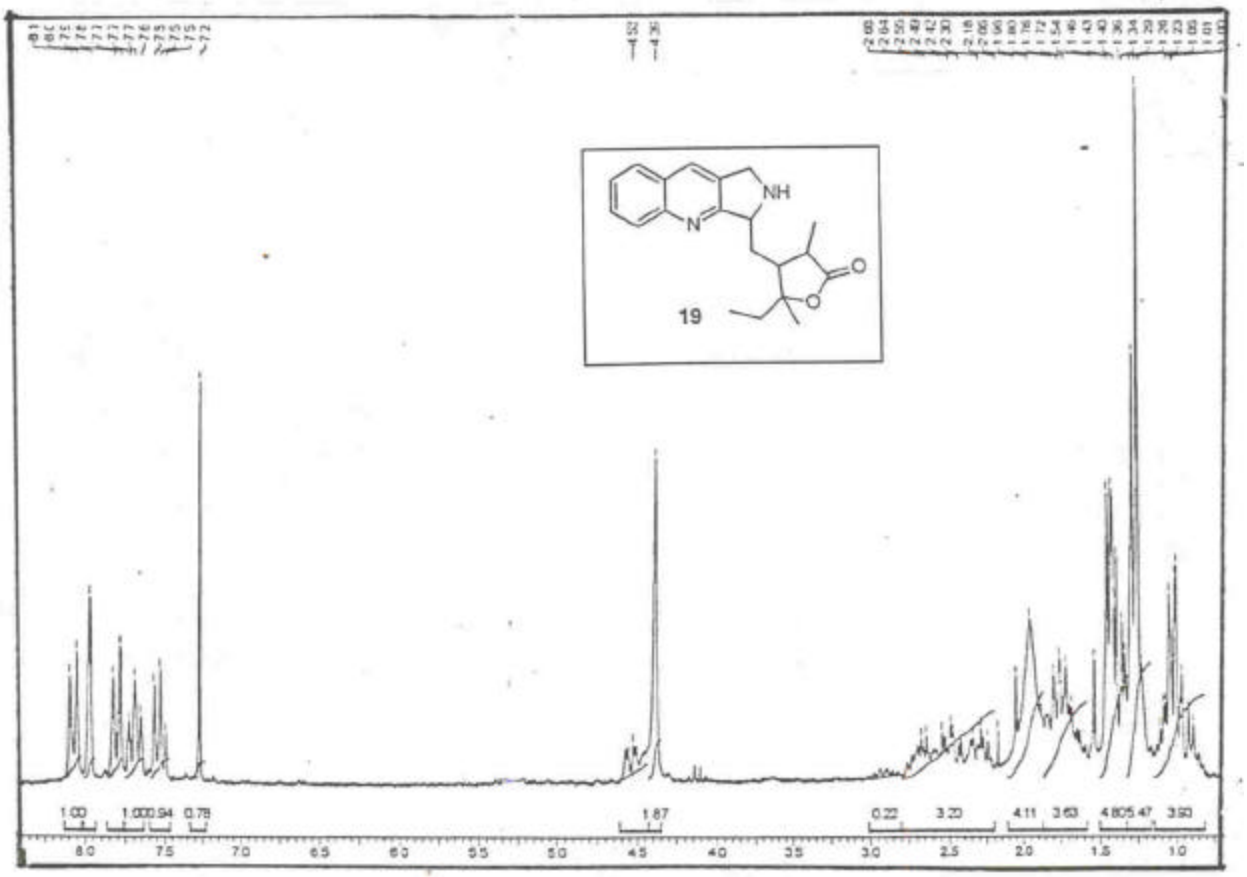




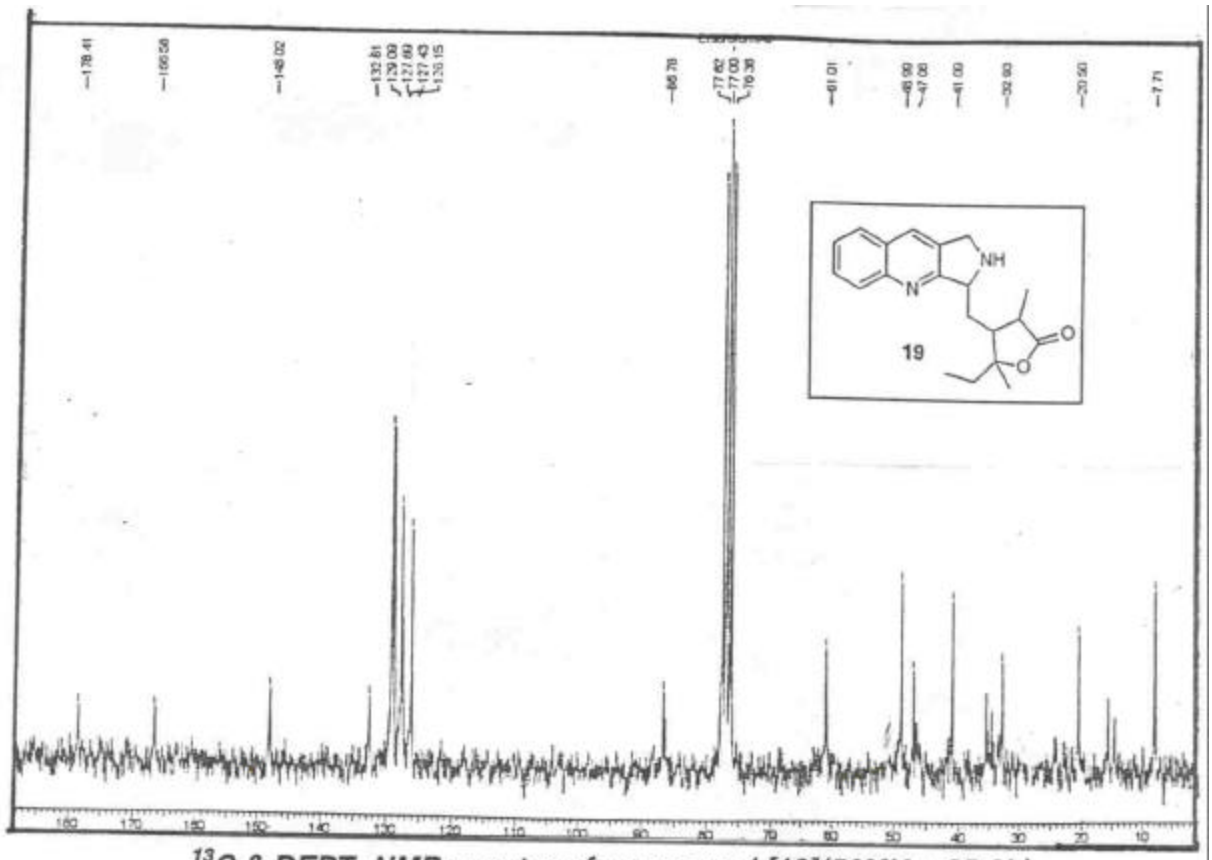
^{1}H-NMR spectrum of compound [22] (200MHz, $CDCl_3$)



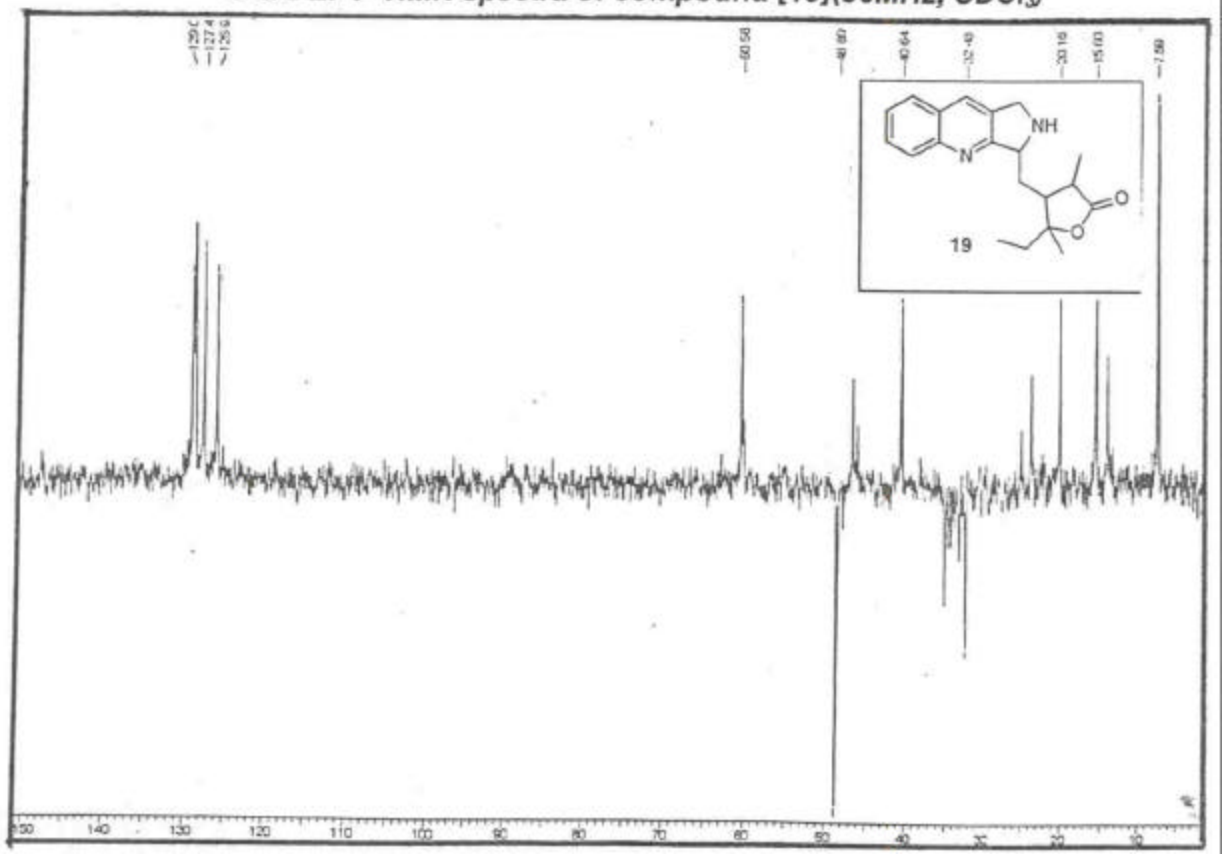
^{13}C - NMR spectrum of compound [22](50MHz, $CDCl_3$)

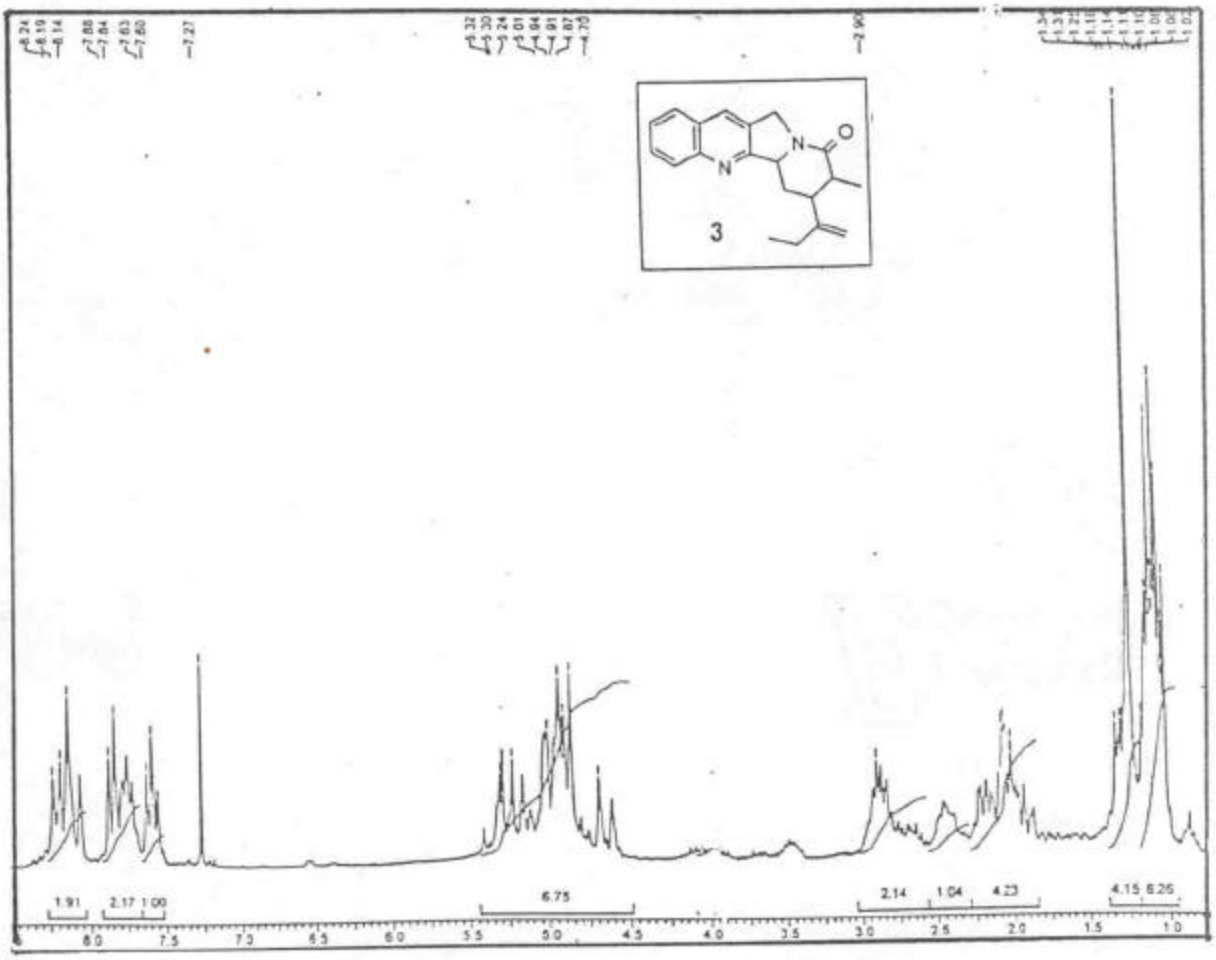


^{1}H-NMR spectrum of compound [19] (200MHz, $CDCl_3$)



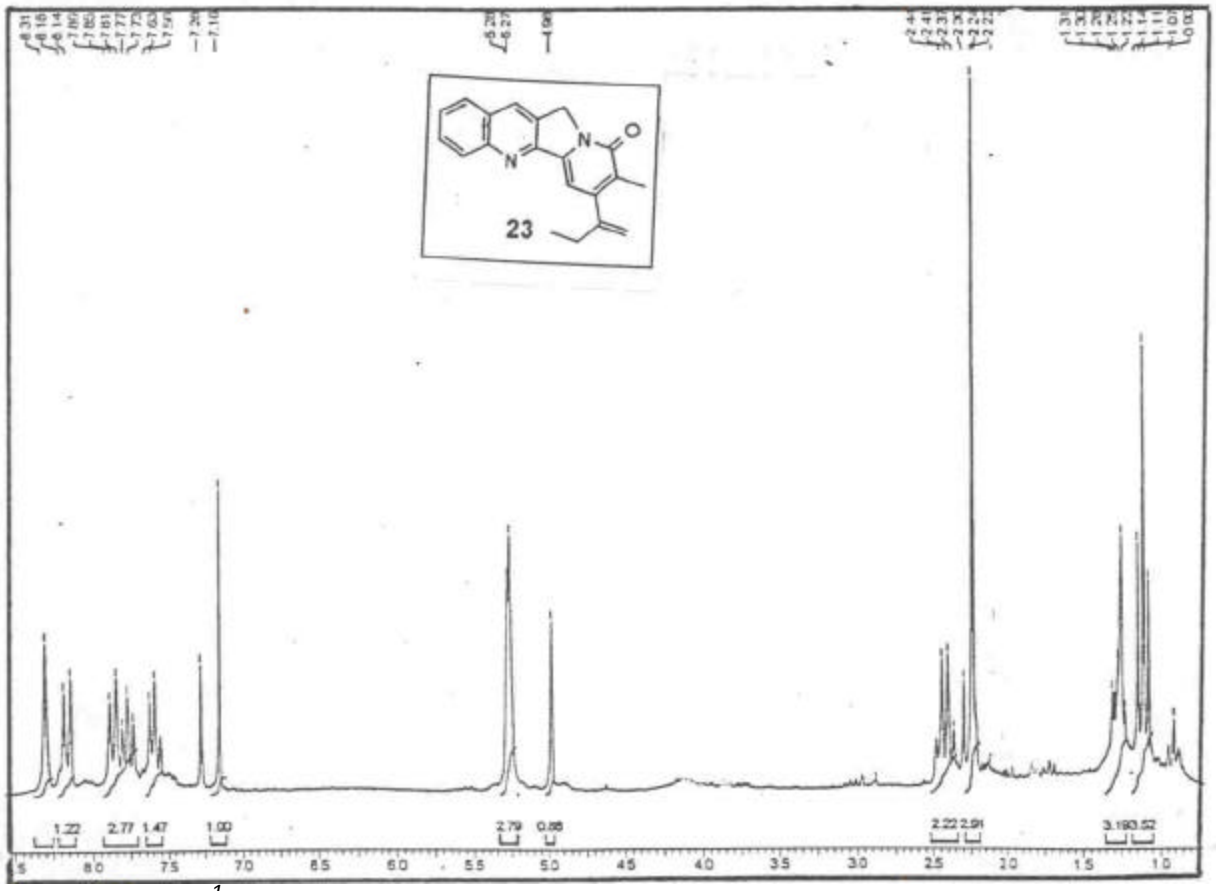
^{13}C & DEPT- NMR spectra of compound [19](50MHz, $CDCl_3$)



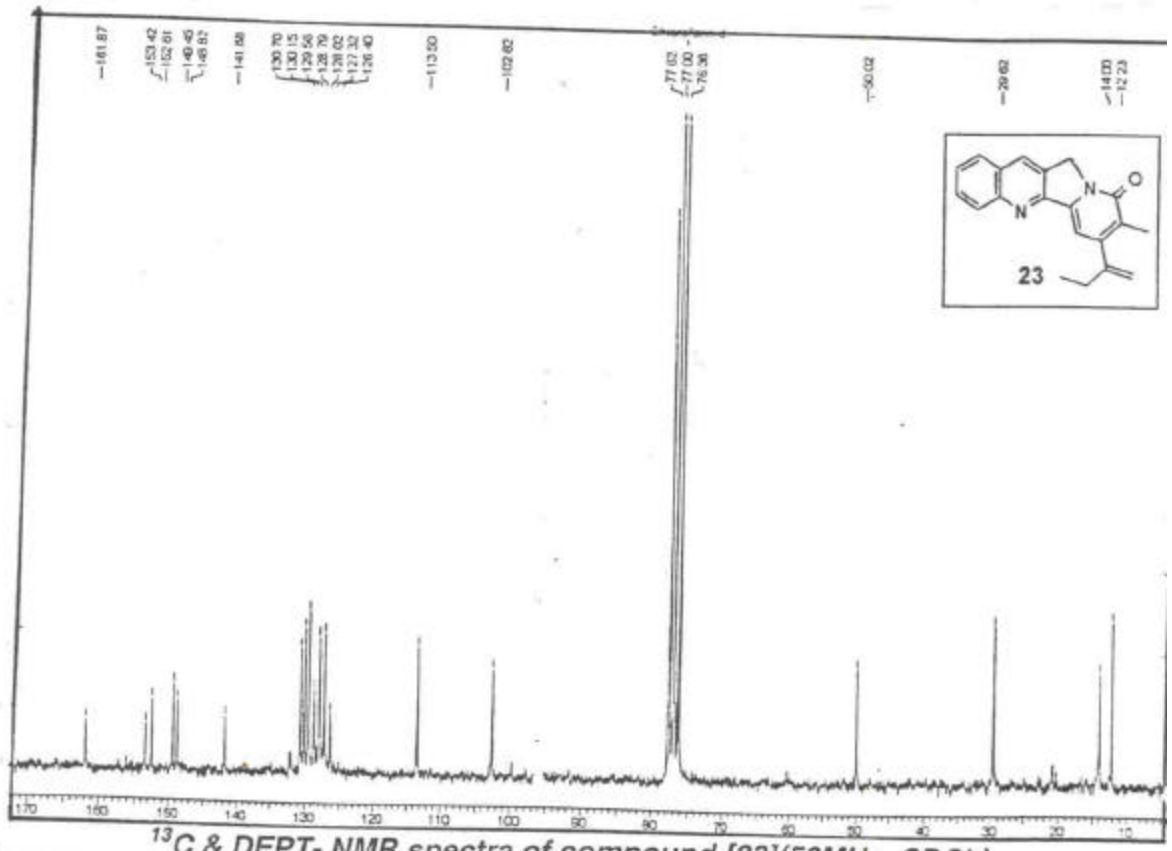


^{1}H-NMR spectrum of compound [3]. ($CDCl_3$, 200 MHz)

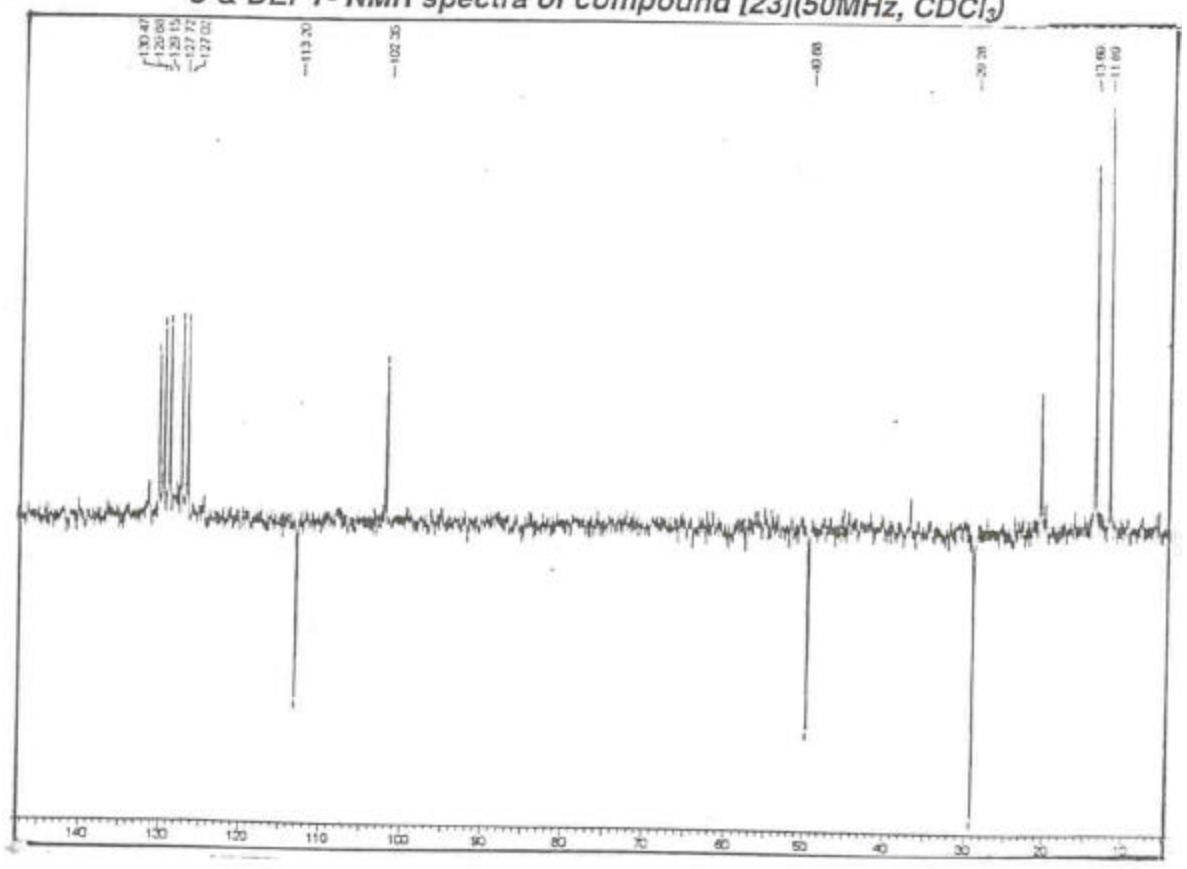
^{1}H-NMR spectrum of compound [3] (200MHz, $CDCl_3$)



^{1}H-NMR spectrum of compound [23] (200MHz, $CDCl_3$)



^{13}C & DEPT- NMR spectra of compound [23](50MHz, $CDCl_3$)



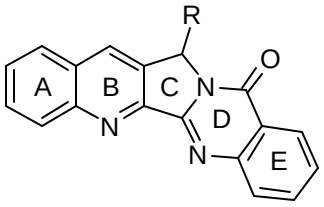
CHAPTER 2

SECTION I

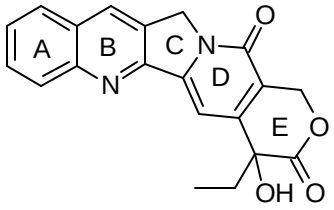
Synthesis of Luotonin

2.1.1 Introduction

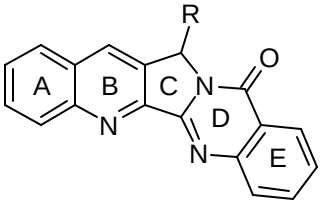
Recently new class of alkaloids -Luotonin A (**1**), [1] B (**2**), [1] C,[142] D, [2] E (**3**)[143] and (F) [3] were isolated from the aerial parts of *Peganum nigellastrum* Bunze, a Chinese medicinal plant used for the treatment of rheumatism, inflammation, abscesses and other maladies. *Peganam nigellastrum* is a rich source of alkaloids and it has been reported that the basic fraction exhibited antitumor activity.[144] Luotonins A, B, and E possess a unique pyrroloquinazoline hetero aromatic skeleton. Their structures have been determined to be **1**, **2**, and **3** based on the spectral properties and analogy with that of Camptothecin **4.** Among these Luotonin A showed remarkable cytotoxic activity against mouse leukemia-P388 cells even at low concentrations (IC_{50} 1.8µg/ml). Luotonin A is a reminiscent of Camptothecin **4** [145] in its pentacyclic structure as well as cytotoxic activity and can be regarded as a DE-ring modified analog of Camptothecin.



R = H, Luotonin A (**1**)
R = OH, Luotonin B (**2**)
R = OMe, Luotonin E (**3**)



Camptothecin (**4**)

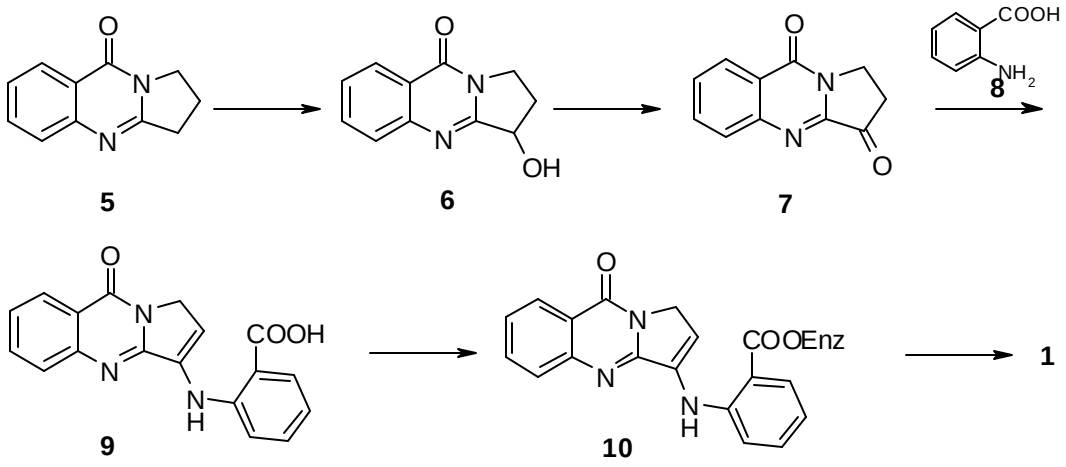


2.1.2 Biogenesis

Quinazoline alkaloids including vasicine have been found to be biosynthesized from anthranilic acid as a key intermediate[146]. Co existence of Luotonins with Vasicine, deoxyvasicine, vasicinone, deoxyvasicinone, besides their having vasicine structure in them,

suggests that the plausible biosynthesis from Vasicinone and anthranilic acid as shown in *Scheme 1.*

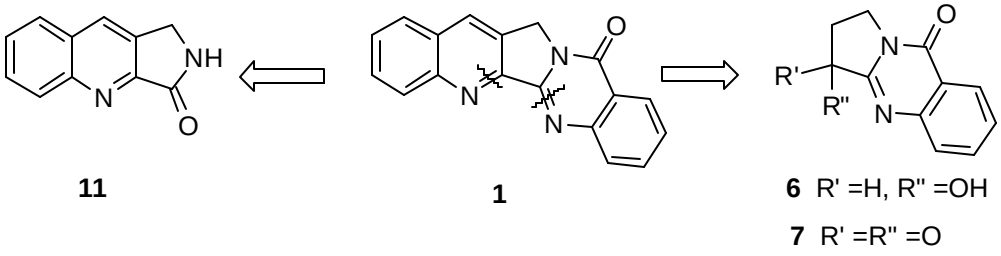
Scheme1:



2.1.3 Synthesis of Luotonins: A Literature Survey

The impressive biological activity of Luotonin A and novel heterocyclic skeleton raises the possibility of obtaining the better analogs by preparation of substituted analogs of AB& E-ring and hence considerable attention has been focused on its synthesis. As a result four syntheses have been reported till date. These synthetic approaches mainly revolve around the connections shown in the *scheme 2.*

Scheme 2: Retrosynthetic analysis

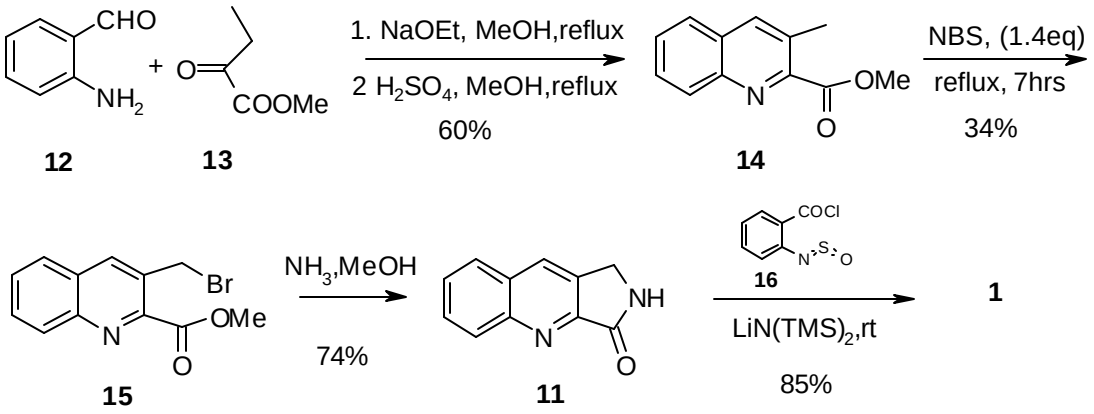


Ganesan's approach[147] (Scheme 3, 1998)

This synthesis relies on Kametani's iminoketene-amide condensation protocol. Thus 3-oxopyroloquinazoline **11** upon condensation with sulfanylaminobenzoyl chloride **16** in presence of LiN (TMS) $_2$ afforded Luotonin A.

3-oxopyrroloquinoline **11** was prepared in 4 steps from 2-aminobenzaldehyde **12** by slight modification of Danishefsky's procedure. This route is adaptable for the preparation of E-analogs as a wide variety of synthetic anthranilic acids are available.

Scheme 3: Ganesan *et al*, *Tetrahedron Lett*., **1998**, *39,* 9097

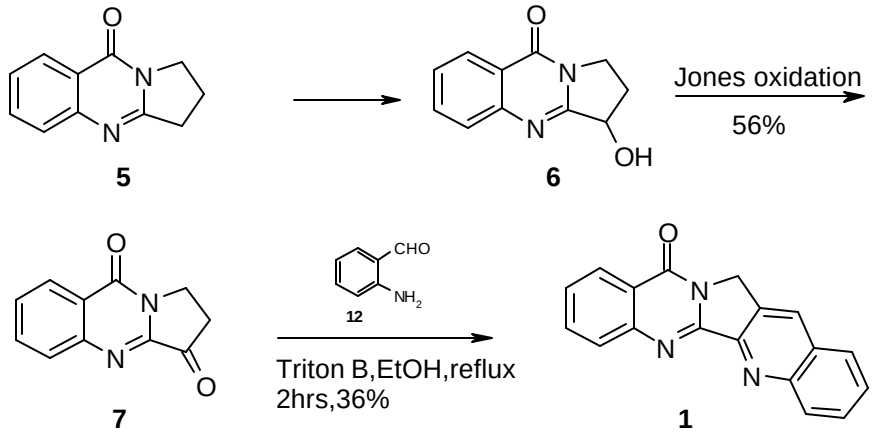


Kelly's approach [148] *(Scheme 4, 1999)*

Kelly in his biosynthetically patterned synthesis employed Friedlander condensation of dione **7** with 2-amiobenzaldehyde **12** to construct the ABC part of the molecule**.**

Dione **7** was prepared from Vasicinone **6**, which inturn was prepared in 5 steps and 22% yield from anthranilic acid and 2-pyrrolidinone by a slightly modified procedure, using Jones oxidation. Friedlander condensation of dione **7** with 2-aminobenzaldehyde gave Luotonin A (1**)** in 36% yield. This synthesis of Luotonin A supports its proposed biosynthesis and provides convenient access to its analogs.

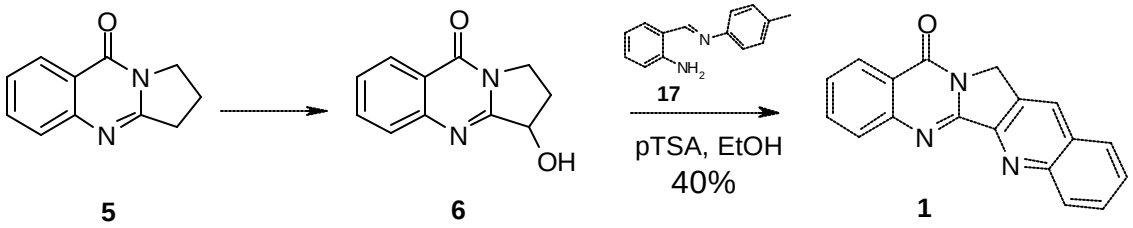
Scheme 4: Kelly *et al*, *Tetrahedron Lett*., **1999**, 40, 2723



Nomura's Approach [149] (Scheme 5, 1999)

Nomura *et al* in their approach employed Friedlander condensation of the Vasicinone **6** for the construction of AB-Rings. This obviates in the need for the oxidation of Vasicinone to dione **7,** which was employed in Kelly's synthesis. The starting material, Vasicinone was made according to the literature procedure.[150]

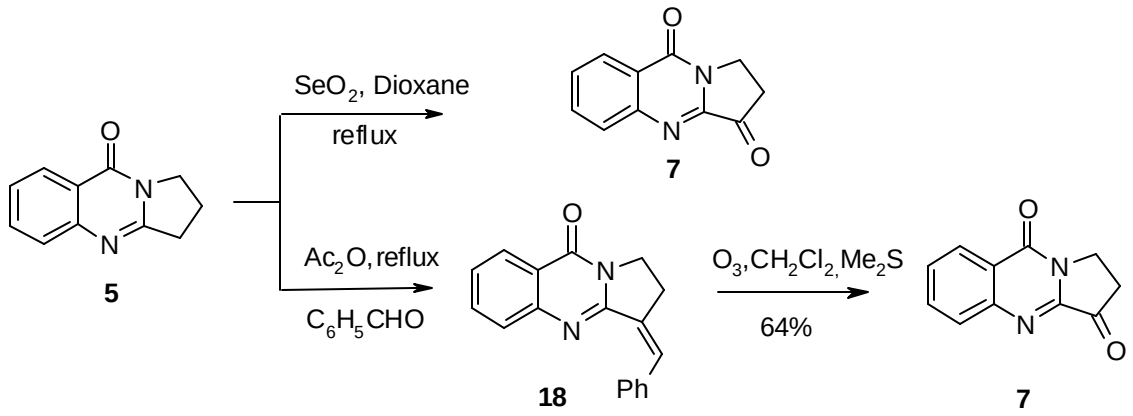
Scheme 5: Nomura *et al*, *Heterocycles*, **1999,** *51*,1593



Molina's approach[151] (Scheme 6, 2000)

Molina's approach aims at the synthesis of the key intermediate of the earlier synthesis *i.e.* dione **7.** Thus selective oxidation of deoxyvasicinone by SeO_2 furnished dione directly. Alternatively it has also been obtained by condensation of deoxyvasicinone with benzaldehyde followed by ozonolysis of the intermediate **18** in 64%yield.

Scheme 6: Molina *et al*, *Synthesis*, **2000**, *11*,1523

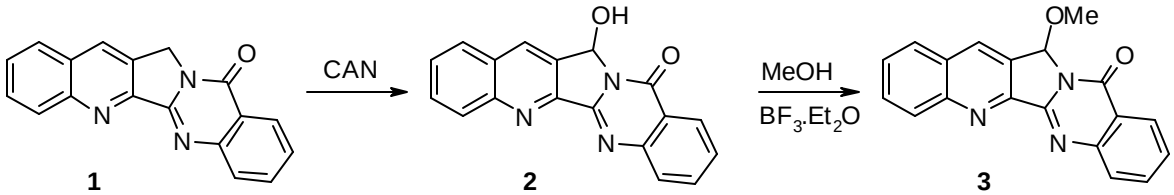


5 7 18 7

This constitutes a formal total synthesis of Luotonin A since the putative intermediate **7**, now available by a shorter route and higher overall yield (31%) than the earlier synthesis, was already converted in to Luotonin A in a straightforward way by Kelly. Luotonin B has been obtained by oxidation of Luotonin A with CAN.

Luotonin E has been synthesized by etherification of Luotonin B (*Scheme 7*).

Scheme 7:



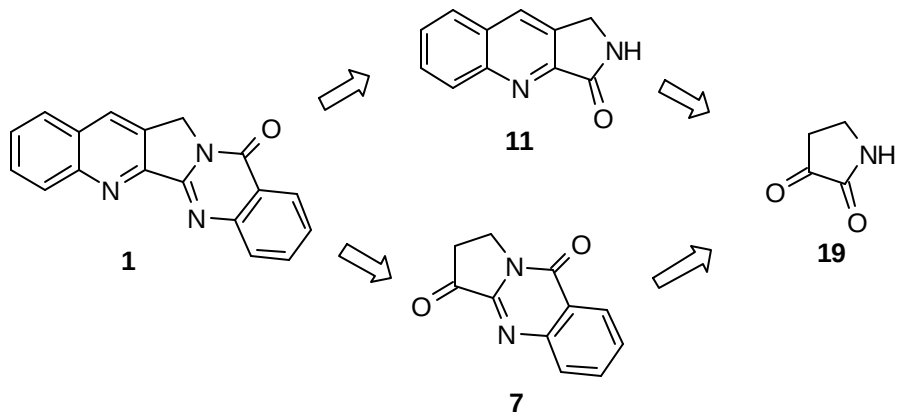
1 2 3

2.1.4 Present work

Impressive biological activity of these unique heterocyclic alkaloids coupled with our interest on quinoline alkaloids led us to develop a synthetic route for the Luotonins.

As is evident from the above discussion, the syntheses of Luotonin involve the annulation of either intermediate **7** or **11**. We envisioned highly convergent synthesis of either of these intermediates from a common precursor **19** as shown *scheme 8*. (while our work was in progress Ganesan *et al* published their synthesis based on this strategy).

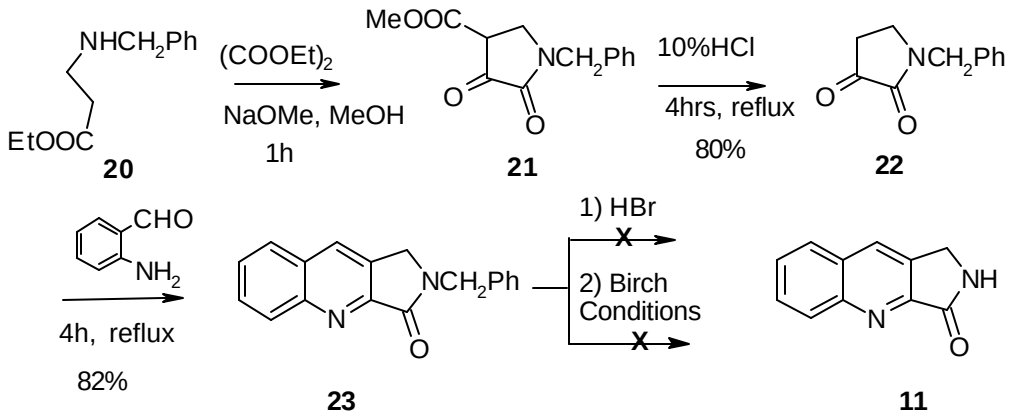
Scheme 8: Retrosynthetic analysis



2.1.5 Results and Discussion

Amine **20**, prepared from benzylamine and ethyl acrylate in methanol at room temperature, on condensation with ethyloxalate using NaOMe as base in refluxing MeOH furnished ketoester **21**. Hydrolytic decarboxylation under acidic conditions gave ketoamide **22**[152] (*Scheme 9*).

Scheme 9:

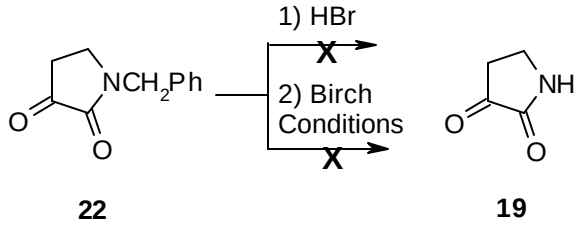


Friedlander condensation with *o*-aminobenzaldehyde in refluxing ethanol gave quinoline amide **23**.

^{1}H NMR spectrum of **23** revealed a multiplet between δ 7.35 and 8.4 integrating for 5 protons was assigned to the five quinoline protons, along with multiplet at δ 7.5 integrating 5 protons of phenyl of benzyl group. Two singlets at δ 4.4 and 5 integrating for 2 protons each were assigned to the benzylic protons. Having obtained the trycyclic synthon we focused efforts on debenzylation. But we were unsuccessful in debenzylation with HBr or Birch reduction conditions.

We thought to effect the debenzylation at an early stage which would have the flexibility to construct the either AB or CD rings at will, and may circumvent the problems encountered in deprotection under Birch reduction conditions. However the attempted deprotection of the dione **22** did not meet with success.

Scheme 10:



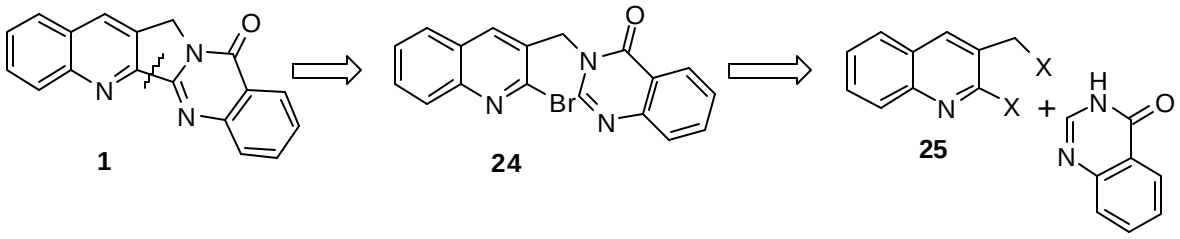
22 **19**

Failure met in adapting the retroanalysis [of the established routes] led us consider alternative novel retro analysis. It is obvious from above discussion of the various synthetic approaches that there have been no efforts to develop a general synthetic route amenable to the synthesis of all three pyrroloquinoline quinazolinone *i.e.* Luotonin A, B, and E.

We reasoned that the delay of C-ring construction to the late stage possible would have the flexibility not only to access substituted [A, B & E ring] analogues, but also for the naturally occurring ones, a strategy that had not been attempted so far.

Retro synthetic analysis based on these lines revealed the AB -DE precursor **24** as a key intermediate as shown in S*cheme11*.

Scheme 11:

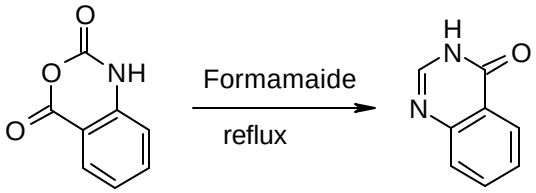


1 **24** **25** **26**

Thus we focused on synthesis of precursor **24** while the C-C bond was thought to be achieved either by Heck cyclization or radical cyclization.

Thus 3*H*-quinazolin-4-one **26** was obtained by condensing isatoic anhydride **27** upon with formamide, according literature method.[153]

Scheme 12:



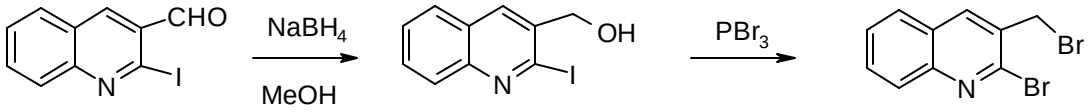
27 **26**

^{1}H NMR spectrum of the compound **26** showed, apart from the 4 aromatic protons, a singlet at δ 7.56 (1H) and a broad singlet at δ 12 (1H) assigned to H-2 and amide NH.

Quinoline synthon **25** was obtained from Meth-Cohn's iodo quinoline aldehyde **28** according to the reported procedure.[154] Thus $NaBH_4$ reduction of aldehyde gave alcohol **29**. The presence of a singlet integrating for two protons at δ 5.5 confirms the -C<u>H$_2$</u> of the alcohol. IR spectrum showed broad absorption at 3300 cm^{-1} confirming the presence of - OH.

Treatment of alcohol **29** with PBr_3 furnished dibromo compound **25**. ^{1}HNMR spectrum showed apart from quinoline protons a singlet at 4.5 as assigned to -<u>CH$_2$</u>- Br.

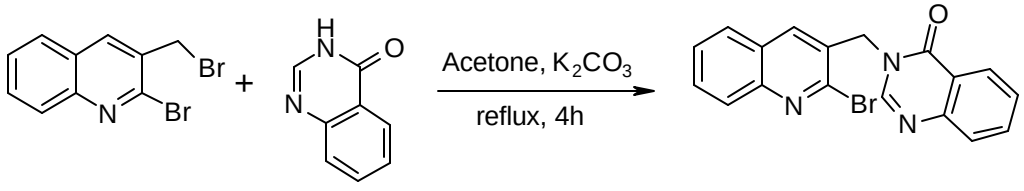
Scheme 13:



28 **29** **25**

Having obtained both the synthons **25** and **26** from readily available starting materials by the route amenable to substituted ones, we proceeded to couple both of them. Thus *N*-alkylation of quinazolinone **26** with bromo compound **25** in presence of K_2CO_3 in acetone under refluxing conditions furnished the intermediate **24.**

Scheme 14:



25 **26** **24**

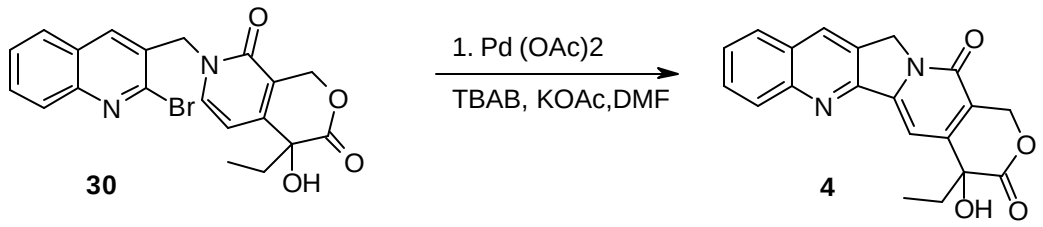
^{1}HNMR spectrum of **24** showed the absence of –NH- broad singlet at δ12 and presence of singlet at δ 5.42 (2H) assigned for the benzylic -C<u>H$_2$,</u> and quinazolino quinoline pattern (10 H)

in aromatic region. IR spectrum showed the carbonyl absorption at 1677 cm^{-1} due to amide carbonyl thus confirming the *N*-alkylation unequivocally.

Having been successfully assembled the AB-DE part of the molecule we considered the ring closure. After weighing the cons and pros of both the options i.e. Heck and radical cyclization we thought to effect the final ring closure with intramolecular Heck cyclization, which has the wide functional group tolerance.

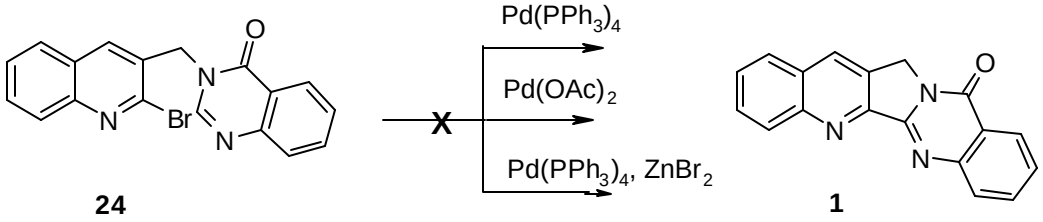
There is a literature precedent[155] in a related pyrroloquinoline alkaloid, which successfully employed Heck cyclization.

Scheme 15:



The attempted reaction on intermediate **24** under these Jeffry conditions failed to give Luotonin A. Various modifications have been reported [156] for the Heck olefination. Unfortunately the cyclization could not be effected under any of these conditions (*Scheme 16*)

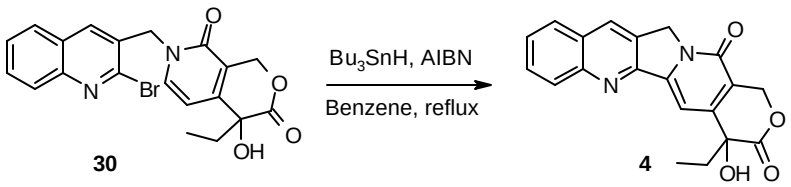
Scheme 16:



This failure led us to consider the radical cyclization for the same. Strategies involving radical reactions[157] have become powerful tools in organic synthesis, in particular; free radical-mediated cyclization has developed as a prominent method for preparing diverse cyclic compounds *via* carbon-carbon bond-forming processes. Intramolecular radical cyclization reactions have drawn the attention of synthetic chemists in recent years because of the wide range of synthetic utilities available through this methodology.

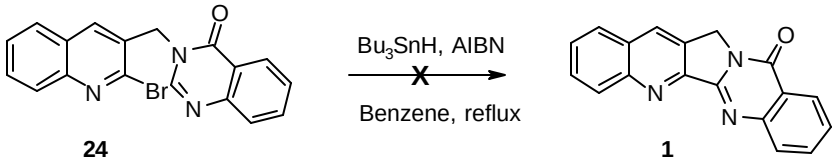
It has been shown by Comins *et al* that pyrroloquinoline alkaloids can be synthesized by radical cyclization.[158]

Scheme 17:



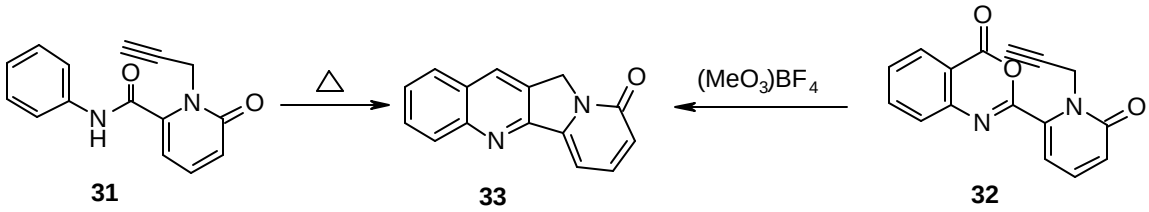
Thus treatment of **24** with tributyl tin hydride under high dilution conditions resulted in a mixture of fluorescence compounds, which couldn't be purified.

Scheme 18:



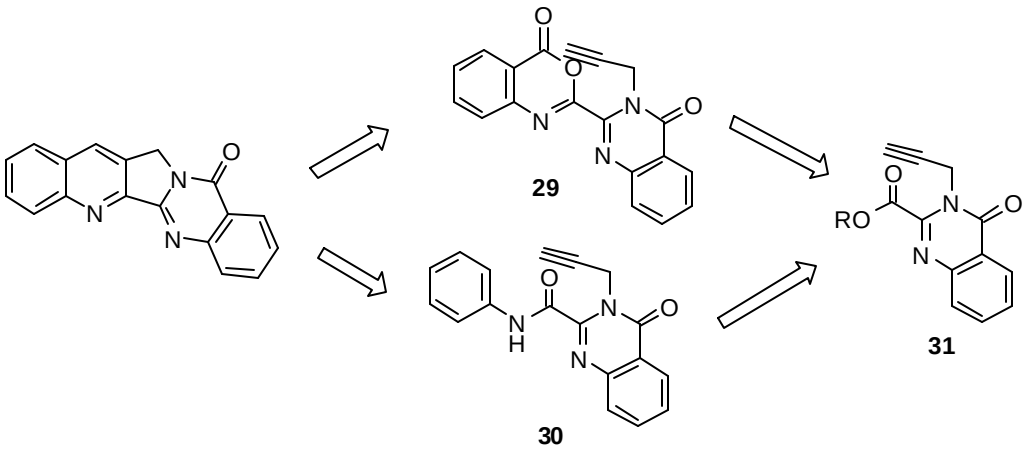
Failure of this approach led us to shift to an alternative strategy for C- ring annulation *i.e.* form the C-C bond under consideration in above attempts before hand and then try the ABC - ring annulation. Recently Fortunak *et al* reported[159] that the ABC skeleton of Camptothecin could be assembled *via* intramolecular 4+2 cycloaddition of anthranilamide **31** or benzoxazine **32** as shown in the *Scheme 19*.

Scheme 19:



Based on these lines we reasoned that, such a strategy if effected on preformed quinazolinone unit should provide Luotonin A as shown in retro synthetic analysis (*Scheme 20*.)

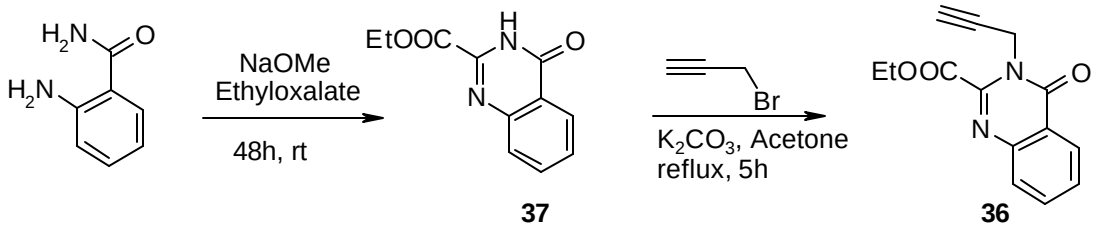
Scheme 20:



Having identified the suitable strategy, we planned to synthesize the intermediate for the same from 2-carbethoxy quinazolinone **37** by alkylation followed by the amide formation.

Thus 2-carbethoxy quinazolinone **37** was prepared according to reported[160] method by reacting the anthranilamide with diethyl oxalate in quantitative yield. .

Scheme 21:



^{1}H NMR spectrum of **37** showed apart from typical quinazolinone protons, [two doublets at δ 8.36(1H), 7.94 (1H) and two triplets at δ 7.61 (1H), 7.88 (1H)], a quartet at δ 4.58 (2H) and triplet at δ 1.48 (1H) assigned to $COO\underline{C_2H_5}$ and a broad singlet at δ 10.5 assigned for quinazolinone NH. IR spectrum showed the absorptions at 1727cm^{-1} and 1682 cm^{-1}.

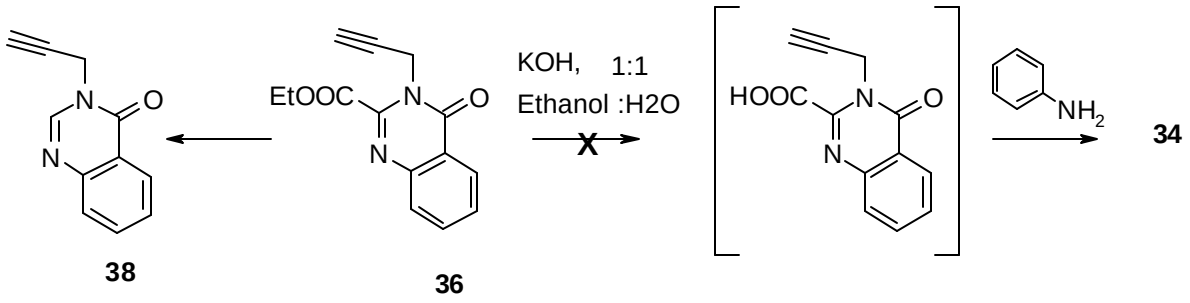
Treatment of **37** with propargyl bromide in presence of K_2CO_3 in refluxing acetone provided the *N*-alkylated quinazolinone **36** in 83% yield. ^{1}H NMR spectrum of **36** showed the absence of amide NH and the presence of a doublet at δ 5.15 (2H) and triplet at δ 2.62 (1H) assigned to propargyl protons apart from the 4aromatic quinazolinone and ester protons. ^{13}C further confirms the *N*-alkylation by revealing two –C=O peaks at δ 160 and δ 161. Mass spectrum showed m/z at 256.

The amide formation was thought to be realized by the usual coupling of amine and acid. In this direction, treatment of **36** with aq KOH in ethanol resulted in the smooth hydrolysis of the

ester (evident by the salt formation in TLC), but the resulted acid upon neutralization underwent spontaneous decarboxylation at room temperature to give

N-propargylated quinazolinone. ^{1}H NMR spectrum of **38** showed the absence ethyl protons and the appearance of extra proton in the aromatic region at δ 8.3 and lack of acid (COOH) proton confirmed the decarboxylation. The absence of carbonyl peak in ^{13}C further confirms the decarboxylation. Attempts involving neutralization of the salt formed at lower temperatures also did not provide acid.

Scheme 22:

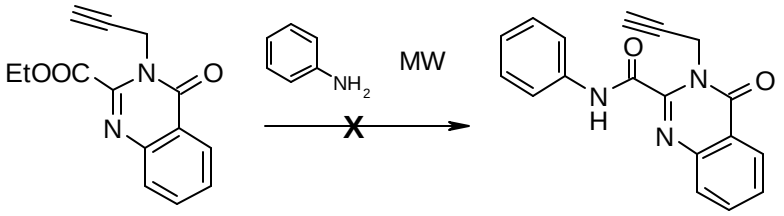


And later we became aware of such behaviour of 2-carboxy quinazolinones which warranted us to consider an alternative way of making amides.

Recently R.S.Varma *et al* [161] reported the microwave-assisted preparation of amides of non-enolizable esters in presence of t-BuOK. Since our substrate met the requirements of this protocol we subjected the same under the reported conditions with the hope of obtaining amide directly.

Unfortunately the reaction of the propargyl quinazolinone with aniline under microwave condition did not proceed to give the desired amide (*Scheme 23*).

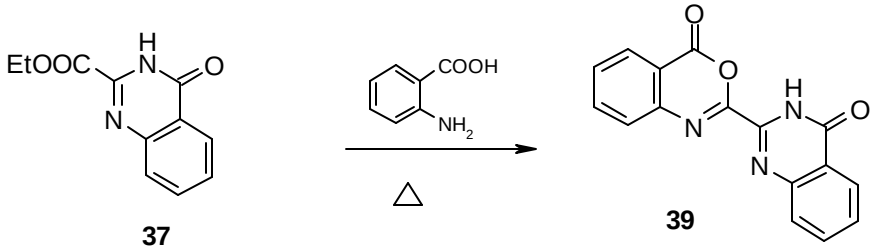
Scheme 23:



36 **35**

Recent report[162] showed that 2-carbethoxy quinazolinones are converted to benzaoxazines by heating the neat mixture with anthranilic acid at elevated temperature (180^{o}C).

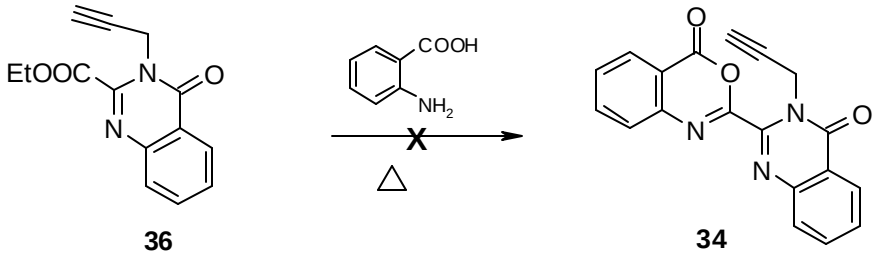
Scheme 24:



37 **39**

It was argued that since the benzaoxazines are better dienes for the proposed cycloaddition and as compound **34** has the dienophile**,** should undergo the tandem sequence of oxazine formation and cycloaddition. Thus premixed anthranilic acid and the propargyl compound was heated at 190^{0}C *i.e.* exactly similar conditions. But **36** did not undergo the desired condensation reaction and resulted only in recovery of the starting materials.

Scheme 25:



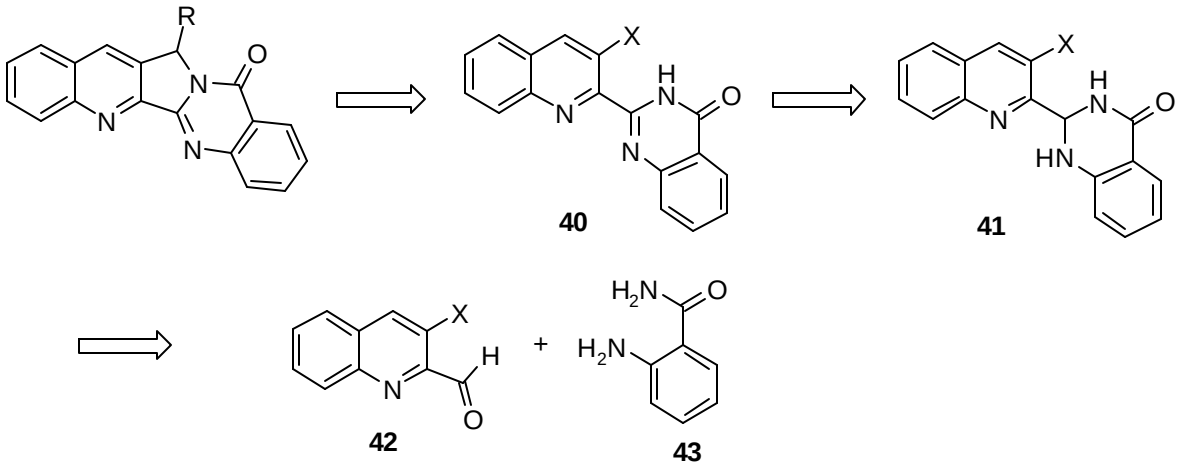
36 **34**

Failure to obtain the designed substrate for the proposed strategy under various conditions led us to abandon the route.

In pursuit of an alternative strategy, close look at the target skeleton revealed the possibility of assembling the AB and DE rings through a C-C bond and C-ring closure through a C-N bond formation as shown in our retro synthetic analysis *(Scheme 26*). This strategy was

deemed more attractive than the earlier, not only by virtue of it being more concise but also because it would involve establishing the entire framework needed for all the Luotonins.

Scheme 26:



We envisioned Meth-Cohn's quinoline synthesis for the construction of the AB rings with an aldehyde functionality at 2-position for quinazoline formation while masking other functional group at the 3-position which would later be unmasked and utilized for the C-ring annulation on to quinazolinone. Retro synthetic analysis on these lines reveals **42** and anthranilamide **43** as the suitable precursors. The wide availability of various substituted anthranilamides and the easy access to the substituted quinolines attests our assert of developing a synthetic route amenable to AB and E substituted analogs of the title compounds. Condensation of anthranilamide to aldehyde to quinazolinone can be effected either by acid or base catalysis[163].

Having identified the suitable strategies for the construction of quinazolinone the problem at hand reduced to the mere coupling of the aldehyde **42** (X= dioxolonyl), which had already been prepared in connection with our work on Camptothecin (Sec 1.2.2) with anthranilamide.

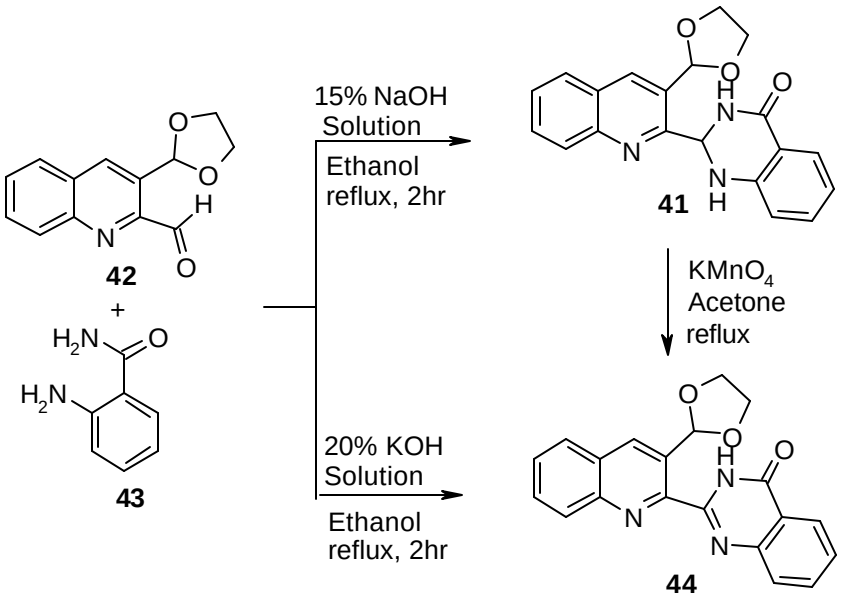
The attempted condensation of **42** with anthranilamide **43** in presence of acids (*p*TSA, AcOH and CSA) gave highly intractable and insoluble mass presumably due to the presence of acetal functionality.

So we turned our attention to the base mediated condensation. The equimolar mixture of aldehyde **42** and anthranilamide **43** in ethanol was treated with 15% NaOH solution and refluxed for 2 hr to afford the dihydroquinazolinone **41**(X=CHO) in quantitative yield.

^{1}H NMR spectrum of **41** showed apart from quinoline protons, dihydroquinazolinone protons-a triplet at δ 6.25, a doublet at δ 6.53, a triplet at δ 6.96 and a doublet at δ 7.75 apart from the acetal protons at δ3.83 (4H) and 5.87 (1H). Additionally ^{13}C NMR spectrum confirmed the assigned structure.

The point worthy of mention is the dependence of reaction outcome on the strength of the base employed. Thus when 20% KOH was employed quinazolinone **44** was obtained, but comparatively in low yields and 25% NaOH resulted in the formation of the mixture of dihydro quinazolinone and quinazolinone.

Scheme 27:



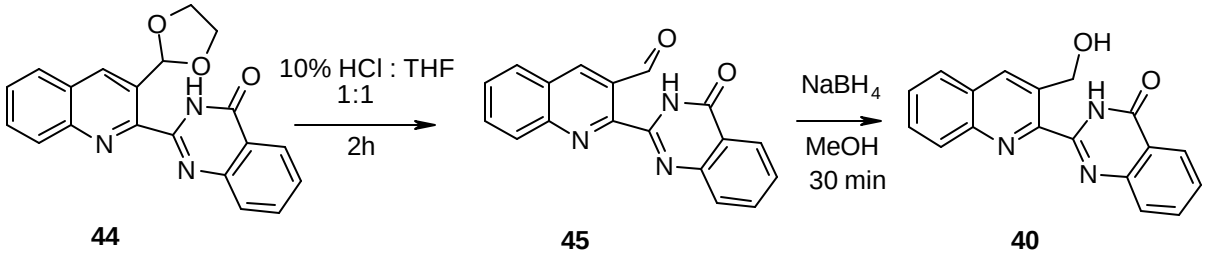
Refluxing the dihydroquinazolinone in acetone with $KMnO_4$ effected oxidation of **41** to quinazolinone **44.**

^{1}H NMR spectrum of **44** showed the quinazolinone quinoline pattern comprising of 9 H in aromatic region and a singlet at δ 4.04 (4H) and δ 7.69 (1H) combinely assigned to the acetal functionality. The broad singlet appearing at δ 11.13 was assigned to the aromatic amide NH. ^{13}C NMR spectrum showed carbonyl at δ 161.51 characteristic of quinazolinone carbonyl, apart from other carbons. Mass spectrum further confirmed the quinazolinone formation by giving the m/z at 345.

Having been successful in construction of the intermediate **44** with AB and DE rings and amply placed handle for the further C-ring annulation all that left was to identify and realize the

synthetic transformations for the different Luotonins which vary in the substitution at the 5-position *i.e.* on C-ring.

Scheme 28:



44 **45** **40**

Towards this end the acetal moiety of **44** was removed under standard conditions *i.e*10% HCl: THF to release the aldehyde **45.**

^{1}H NMR spectrum of **45** showed the absence of acetal protons at δ 4.25 and δ 7,69 and the presence of singlet at δ 8.04 was assigned to the aldehyde proton, along with other aromatic protons. NH proton was still seen at δ 11.3. Mass spectrum showed the m/e peak at 341.

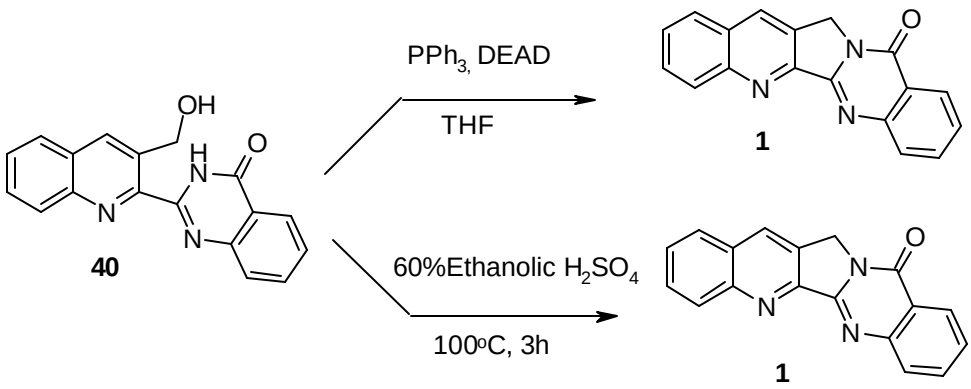
Longer reaction times and the increased strength of the acid gave mixture of compounds suggesting the formation of some other compound.

Reduction of **45** with $NaBH_4$ in MeOH resulted in the formation of alcohol **40** (X=CH_2OH) in quantitative yield.

^{1}H NMR spectrum of **40** showed the absence of singlet at δ 8.04 of aldehyde and the presence of doublet at δ 5.11 (2H) and triplet at δ 6.40 (1H) due to –CH_2OH. Amide NH proton was seen at δ 11.49. IR spectrum showed the absorption at 3370cm^{-1} confirming the presence of -OH group. Mass spectrum showed molecular ion peak at 303.

The C-N bond formation can be realized by either cyclodehydration in one step or nucleophillic displacement of suitable derivative of hydroxy group, which would involve two steps. So we preferred to realize the same by single step cyclodehydration under Mitsunobu conditions which actually involve the activation of the -OH and there by convert it to a good leaving group. Thus treatment of the alcohol with triphenylphospine and DEAD in THF resulted in the consumption of starting material and in the formation of the Luotonin A. But the separation of compound from triphenylphospineoxide involved a laborious column chromatography.

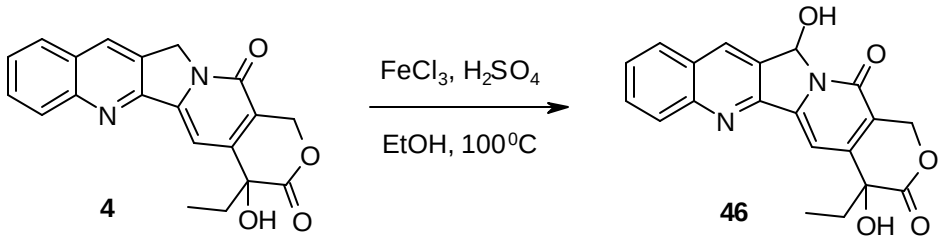
Scheme 29:



Alternatively we realized the formation of Luotonin A by simply treating the alcohol **40** in 60% ethanolic H_2SO_4. This is akin to Williamson oxacycle synthesis.

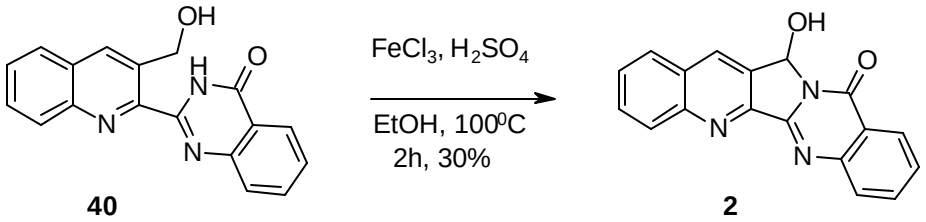
It has been shown[164] that C-ring of pyrroloquinoline system in Camptothecin can be oxidized with H_2SO_4/ $FeCl_3$ recipe to 5-hydroxy Camptothecin **46.**

Scheme 30:



Since our dehydration conditions included H_2SO_4 and EtOH *i.e.* matching partly with the above conditions, we intended to check the out come of the dehydration in presence of the above reagent $FeCl_3$. Thus alcohol **40** was treated with 60% ethanolic H_2SO_4 in the presence of ferric chloride. Interestingly Luotonin B was obtained after work up *albeit* in low yield (30%) and there was unidentified major side product.

Scheme 31:

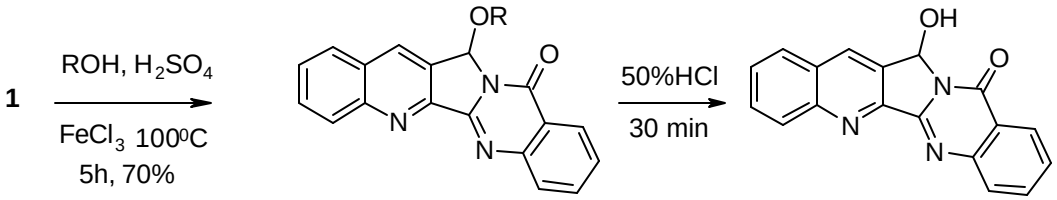


Encouraged by these result, we became interested in testing whether Luotonin A can be transformed in to Luotonin B in much the similar way as the CPT to hydroxy CPT and this would constitute a method for inter conversion of these three alkaloids.

Accordingly Luotonin A was mixed with EtOH / H_2SO_4/ $FeCl_3$ refluxed for 4 hrs to furnish **3** (R= OEt) in 70 % yield. Ethoxy Luotonin was hydrolyzed to Luotonin B with 50% HCl. Spectral data of **2** thus obtained was in agreement with the reported values for the natural one.

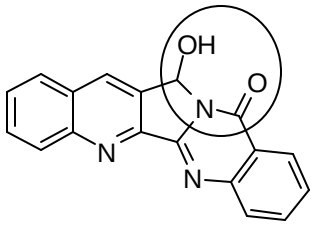
Thus we achieved the semi synthesis of Luotonin B from the Luotonin A and established a method for inter conversion of Luotonin A to B.

Scheme 32:

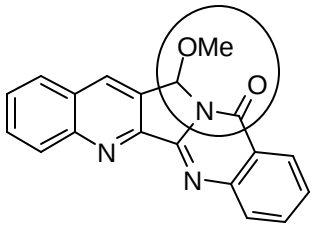


R = C_2H_3 **3** **2**

Basically Luotonin B and E can be regarded as the a- hydroxy amide and a- alkoxy amide respectively.



Luotonin B

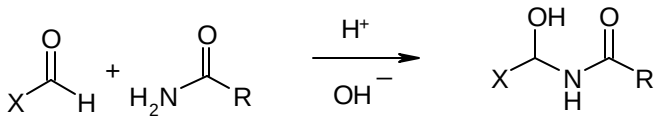


Luotonin E

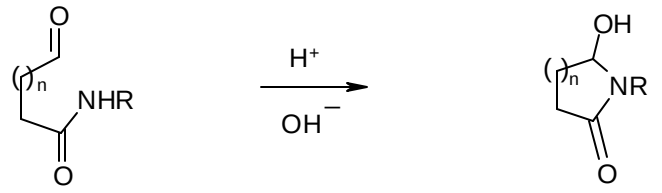
Literature survey reveals that the most straightforward way of preparation of hydroxyamides includes the addition of aldehydes to secondary amides, an equilibrium process in which formation of the adduct is usually disfavored except for two special cases.

First being the case with the activated aldehydes like formaldehyde, trichloroacetaldehyde and Oxoacetic acid or its esters (*Scheme 33*).

Scheme 33:



[x = H, CCl_3, COOH, COOR]



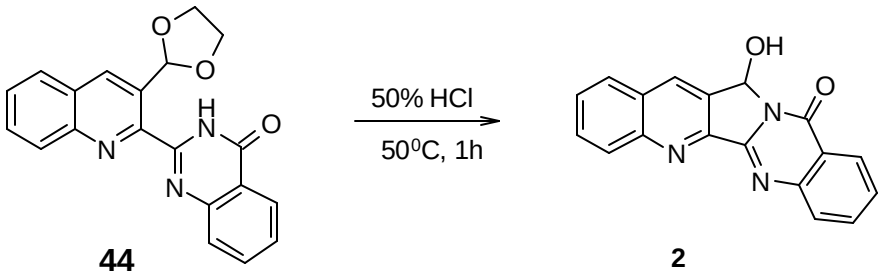
Second special case involves the intramolecular reaction of oxoamides when it is possible to form a 5 or 6 membered rings.

Acids as well as bases as in any other nucleophylic addition of carbonyl catalyze this nucleophilic addition of amides to carbonyl.[165] (In the case of primary amides these intermediates form bisamides by further condensation)

Since we have a substrate with masked aldehyde in the form of acetal that could be deprotected under acidic conditions we reasoned that the treatment with strong acid should give us Luotonin B with the involvement of simultaneous deprotection and the nucleophilic addition of amide on to thus formed aldehyde.

Satisfyingly our logic deemed correct when the treatment of the acetal **44** with 50% HCl in THF resulted in the formation of Luotonin B.

Scheme 34:

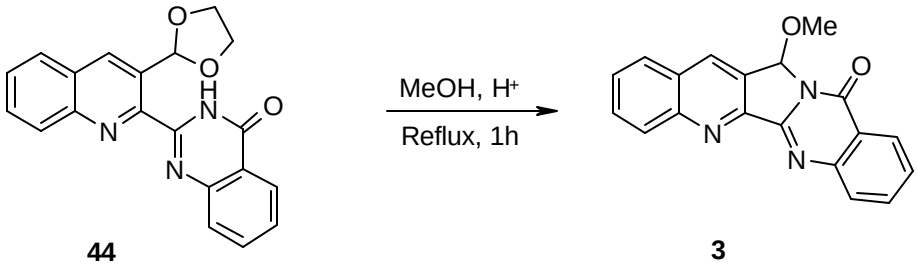


44 **2**

α-Alkoxy amides or α-alkyl amidol are formed when the alcohol is employed as solvent in the presence of strong acid.[22]

Thus acetal **44** upon treatment with 1:1 mixture of methanol and con HCl at reflux temperature for 1h resulted in the formation of Luotonin E.

Scheme 35:



44 **3**

Spectral data of Luotonin A, B and E was in agreement with the reported. Synthetic sample of Luotonin A matched with the authentic sample obtained from Ganesan.[166]

Conclusions:

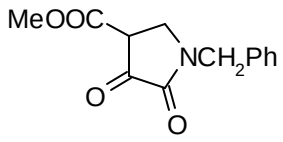
In conclusion a short, highly practical, and efficient synthesis of Luotonin A, B and E, which is amenable to the synthesis of substituted analogues, has been developed. This synthesis obviates the need for the costly and unstable aminobenzaldehyde employed in previous syntheses.

Repertoire of Meth-Cohn aldehydes annulation has been elaborated to the quinazoline heterocycles.

An efficient semi synthetic method (inter conversions) for Luotonin B from Luotonin A. has been devised.

2.1.6 Experimental:

1. Methyl- (1-benzyl)-4,5-dioxo-3-pyrrolidione carboxylate [21]



21

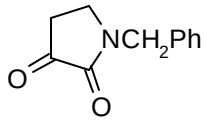
To a solution of NaOMe [obtained from 0.331g (14mmol) of sodium in 15 ml methanol] were added a solution of benzyl amine **20** (3g, 14 mmol) in methanol (5mL) and diethyloxalate (2.105g, 14.4 mmol) and refluxed for 1h. After 1h, the methanol was removed under reduced pressure and the residue partitioned between ethylacetate and water. The organic phase was removed and the aqueous phase was neutralized with dil HCl. The aqueous phase was further extracted with ethylacetate (2×25mL). The combined organic phase was dried (Na_2SO_4), filtered, concentrated and purified by column chromatography over silica gel using 15% ethyl acetate- pet ether to afford **21** as a White solid.

Molecular Formula : $C_{13}H_{13}NO_4$

Yield : 0.113 g, 65%

^{1}H NMR (200MHz) : δ: 7.46 (m, 5H), 5.2 (s, 1H), 4.68 (s, 2H), 3.87 (s, 2H), 3.82 (s, 3H).

2. *N*-Benzylpyrrolidine-2, 3-dione [22]



22

To compound **21** (.001 g, 4.29 mmol) was added 15ml of 10% HCl solution and the reaction mixture was refluxed for 5h. Then cooled to rt, extracted with CH_2Cl_2 (3×25ML), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel to give keto amide **22** as a brown solid.

Molecular Formula : $C_{11}H_{11}NO_2$

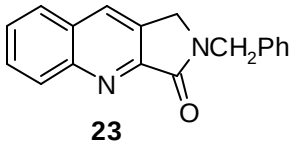
Yield : 0.621 g, 80%

M.P. : 241^{o}C

IR ($CHCl_3$) : 1719, 1692, 1642 cm^{-1};

^{1}H NMR (200MHz_3) : δ: 7.4-7.2 (m, 5H), 4.66 (s, 2H), 4.55 (t, 2H), 2.66 (t, 2H).

3. *N*-Benzyl-3-aminomethyl-2-quinolinecarboxylic acid lactam [23]



23

A solution of ketoamide **22** (0.542 g, 0.284 mmol) and 2-amino benzaldehyde (0.0311g, 0.284mmol) in EtOH (15 mL) was refluxed for 4 h. The white solid that precipitated was filtered and washed with cold ethanol, and recrystallization from ethanol gave quinoline amide **23** as a white solid.

Molecular Formula : $C_{18}H_{14}N_{24}O$

Yield : 0.644 g, 82%

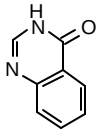
M.P. : 240-242^{o}C;

IR ($CHCl_3$) : 1660, 1442 cm^{-1}

^{1}H NMR (200MHz) : δ: 7.51- 8.45 (m, 5H), 7.30 (s, 5H), 5.0 (s, 2H), 4.45 (s, 2H,).

Mass (m/z) : 274 (100), 245 (10), 218 (10), 183 (12), 169 (12), 141 (80), 115 (15), 91 (37), 73 (25), 65 (20)

4. **3*H*-Quinazolin-4-one [26]**



26

A mixture of anthranilic acid and formamide (4.00 g, 32.0 mmol), was heated under reflux for 30 min with stirring after which reaction mixture was cooled to room temperature and the solid was filtered and recrysatllized from ethanol to give **26** as white crystalline solid.

Molecular Formula : $C_8H_6N_2O$

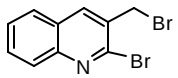
Yield **: 90%**

M.P. : 156^{o}C;

^{1}H NMR (200MHz,) : δ: 11.94 (br s, 1H), 8.33 (d, 1H), 8.15 (s, 1H), 7.84 (m, 2H), 7.55 (m,

1H)

5. 2-Bromo-3-bromomethyl-quinoline [25]



25

To a solution of 2-Iodo 3- formyl quinoline (4.245g, 15 mmol) in methanol (20 mL) was added $NaBH_4$ (1.14g, 32 mmol) at 0^oC. The resulting solution was stirred for 1h at room temperature. Then methanol was removed under the reduced pressure, the residue quenched with dil HCl (2 mL), and the solution was stirred for 5 min. Water (15 mL) and DCM (50 mL) were then added. The layers were separated, and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and column chromatography over silica gel yielded the alcohol as fluffy white solid. This was taken in dry DCM and cooled 0^oC and added PBr_3 drop wise for 15 minutes. The reaction mixture was brought to room temperature and stirred for 1h, quenched with MeOH and extracted with DCM (3×50 ml). The combined organic layers were dried and concentrated to give dibromo compound **25** as solid.

Molecular Formula : $C_{10}H_7Br_2N$

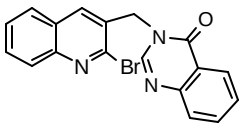
Yield : 3.69g, 80%

M.P. : 134^oC

^{1}H NMR (200MHz) : δ: 8.25 (s, 1H), 8.05 (d, 1H), 7.8-7.57 (m, 2H), 7.78 (m, 1H), 7.50 (m, 1H), 5.42 (s, 2H)

Mass, m/z (%) : 299(M^+), 301(M^+2), 303, 257,255,22,220,177,175, 88,57

6. 3-(2-Bromo-quinolin-3-ylmethyl)-3*H*-quinazolin-4-one [24]



24

A solution of compound **26** (1.46 g, 10 mmol) and **25** (3.6g, 1.2 mmol) in dry acetone (30 mL) in presence of powdered K_2CO_3 (2.76g, 20mmol) was refluxed. After 4h, K_2CO_3 was filtered off, acetone was removed on rotaevaporator and residue was partitioned between water and DCM and the organic layer was separated. The aqueous phase was further extracted with CH_2Cl_2 (3×25mL), the combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the residue thus obtained was purified by column chromatography to give **24** as a white solid.

Molecular Formula : $C_{18}H_{12}BrN_2O$

Yield : 2.562g, 70%

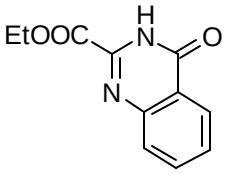
M.P. : 186^oC

^{1}H NMR (200MHz) : δ: 8.34 (s, 1H), 8.30 (d, 1H), 8.21 (s, 1H), 7.99 (d, 1H), 7.78 (m, 4H), 7.50 (m, 2H), 5.42 (s, 2H)

IR ($CHCl_3$) : 1677, 1611, 1469, 1358, 1323, 1215, 1165 cm^{-1}

Mass **(m/z)** **: 286 (M^+, 100) 1 76 (20), 158 (23), 148 (30)**

7. Ethyl-3, 4-dihydro-4-oxo quinazoline-2-carboxylate [37]



37

A solution of anthranilamide (3.4g, 25 mmol) diethyl oxalate (7.3g 50mmol) and NaOEt (0.60g) of in EtOH (120mL) was stirred at 25^oC for 48 h under N_2.The reaction mixture was acidified with 15ml of glacial AcOH and the resulting solid was collected by filtration, washed with ethanol and dried to give **37**.

Molecular Formula : $C_{11}H_{10}N_2O_3$

Yield : 5.4 g, 98%

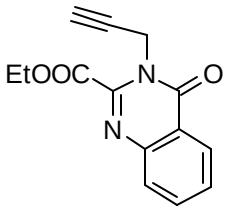
M.P. : 199-200^oC

IR : 3180, 3075, 1730, 1680cm^{-1}

^{1}H NMR (200MHz) : δ: 8.25-7.4 (m, 4H), 4.61(q, *J* = 7.12, 2H), 1.45(t, *J* = 7.1 Hz, 3H).

Mass m/z(%) : 218 (m$^+$, 60), 174, 146, 119, 90

8. 4-Oxo-3-prop-2-ynyl-3, 4-dihydro-quinazoline-2-carboxylic acid ethyl ester [36]



36

To a solution of compound **37** (2.18 g, 10 mmol) in dry acetone (30 mL) in presence of powdered K_2CO_3 was added propargylbromide (1.58g, 1.18mL, 13. 4 mmol). The mixture was refluxed under nitrogen for 4 h. Then K_2CO_3 was filtered off, acetone was removed on rotaevaporator and residue was partitioned between water and DCM and the organic layer was separated .The aqueous phase was further extracted with CH_2Cl_2 (3×50mL), the combined organic phase was dried (Na_2SO_4), filtered, and concentrated to give **36** as a white solid which was pure enough for further use. Analytically pure sample was obtained by column chromatography over silica gel using 30% ethylacetate: Pet ether as eluent.

Molecular Formula : $C_{14}H_{12}N_2O_3$

Yield : 2.12g, 83%

IR ($CHCl_3$) : 1727, 1682, 1601,1457,1374 cm^{-1};

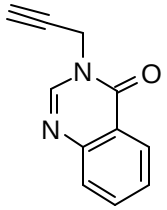
^{1}H NMR (200MHz) : δ: 8.3 (d, *J* =7.7 Hz, 1H), 7.78 (d, *J* =3.3 Hz, 2H), 7.55(m, 1H), 5.14 (d, *J* = 2.56Hz, 2H), 4.52 (q, *J* = 7.32, 2H), 2.29 (t, *J* = 2.56Hz, 1H,), 1.48 (t, *J* = 6.9Hz, 3H,);

^{13}C NMR (50MHz) : δ: 161.39 (C), 160.50 (C), 146.3 (C), 145.65 (C), 135.03 (CH), 128.93 (CH), 127.38 (CH), 126.91 (CH), 121.94 (C), 77.87 (C), 73.39 (CH), 63.65 (CH_2), 33.28 (CH_2), 14.13 (CH_3)

Mass (m/*z*) : δ: 256 (M^+, 91), 227 (100), 211 (28), 184 (88), 155 (74), 145 (50), 129 (97), 119 (65), 102 (80), 90 (60)

Anal. : Calcd for $C_{37}H_{34}N_4O_6$: C, 65.62; H, 4.72; N, 10.93.
Found: C, 65.19; H, 4.46; N, 10.84

9. 3-Prop-2-ynyl-3*H*-quinazolin-4-one



A solution of 36 (0.256 g, 0.1mmol) in a 1:1 mixture of 10% KOH: MeOH (15mL) was stirred at room temperature for 2 h. After the hydrolysis was completed, MeOH was removed under reduced pressure and the residue was cooled to 0^{o}C, neutralized with $NaHSO_4$ and was extracted with CH_2Cl_2 (3×15mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **38** as thick syrup.

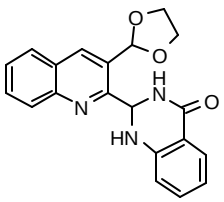
Molecular Formula : $C_{11}H_8N_2O$, 118

IR($CHCl_3$) : 1682, 1601,1457,1374 cm^{-1}

^{1}H NMR (200MHz) : δ: 8.37 (m, *J* = 7.7Hz, 2H), 7.8 (m, 2H), 7.59 (m, 1H), 5.98 (d, *J* = 2.56Hz, 2H), 2.56 (t, *J* = 2.56Hz, 1H);

Mass, m/z (%) : 118 (M^+), 192 (60), 90 (100)

10. 2-(3-[1,3] Dioxalon-2-yl-quinolin-2-yl)-2,3-dihydro-1H-quinazoli-4-one [41]



41

To a solution of anthranilamide (3.40g, 25mmol) and quinoline aldehyde **42** (5.75g, 25mmol) in 100ml of 95% ethanol was added 1.6 ml of 20% aq NaOH solution. The mixture was heated under reflux for 1h and the precipitated solid was filtered and air-dried to give dihydroquinazolinone **41** as a white solid. .

Molecular Formula : $C_{20}H_{17}N_3O_3$

Yield : 8g, 93%

M.P. **: 240°C**

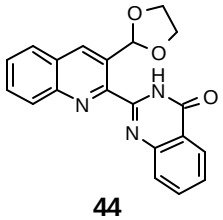
IR (Nujol) : 1644, 1617, 1509, 1462, 1377cm^{-1}

^{1}H NMR (200MHz) : δ: 8.9 (bs, 1H), 8.34 (s, 1H), 8.21 (d, *J* = 8.3Hz, 1H,), 7.80 (d, *J* =7.52Hz, 1H,), 7.72 (t, *J* = 6.85Hz, 1H), 7.51 (d, 6.85Hz, 1H), 7.4(m, 1H), 7.30 (t, *J* = 8.79Hz, 1H), 6.94 (d, *J* = 8.3Hz, 1H), 6.65 (t, *J* = 7.32Hz, 1H), 6.21 (s, 1H), 4.82 (2H), 4.21 (m, 4H)

^{13}C NMR (50MHz) : δ: 171.84 (C), 155.96 (C), 149.24 (C), 146.67 (C), 134.42 (CH), 132.92 (CH), 130.57 (CH), 129.39 (CH), 129.17 (C), 128.54 (CH), 127.04 (CH), 126.63 (C), 115.20 (C), 114.50 (CH), 111.89 (CH), 100.57 (CH), 65.21 (2 CH_2),

Mass (m/z) : 347(m^+), 304 (40), 288 (70), 273 (51), 251 (39), 231 (60), 204 (20), 158 (36), 132 (55), 119 (40), 77 (70)

11. 2-(3-[1,3] Dioxolan-2-yl-quinolin-2-yl)-1H-quinazolin-4-one [44]



44

To a solution of **41** (3.47g, 10mmol) in acetone (100mL) was added $KMnO_4$ (1.00g) and the mixture was refluxed on a steam bath. Slowly the pink color of $KMnO_4$ disappeared. $KMnO_4$ was added in portions of 0.050g each time and refluxing was continued until the pink color persisted. The hot acetone solution was filtered, excess of acetone was distilled off and excess of $KMnO_4$ in the filtrate was destroyed with sodiumsulphite. The resulting solution was extracted with $CHCl_3$ (5×50mL) and solvent was removed from the dried extracts (Na_2SO_4) to furnish the pure quinazolinone **44** as white solid.

Molecular Formula : $C_{20}H_{15}N_3O_3$, 345

Yield : 3.10g, 90%

M.P. : 212^oC

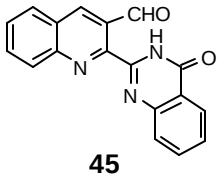
IR ($CHCl_3$) cm^{-1} : 1678,1509,1460,1215cm^{-1}

^{1}HNMR(200MHz) : δ: 11.12 (bs, 1H), 8.60 (s, 1H), 8.27 (d, *J* = 8.15Hz, 1H), 8.07 (d, J = 8.15Hz, 1H), 7.82 (d, *J* = 8 Hz, 1H), 7.6-7.74 (m, 3H), 7.53 (s, 1H), 7.54 (t, *J* = 8.46Hz, 1H), 7.42 (t, *J* = 8.46Hz, 1H), 4.06 (m, 4H)

^{13}C NMR (50 MHz) :δ: 161.51 (C), 149.2 (C), 148.69 (C), 146.07 (C), 145.85 (C), 136.36 (CH), 134.35 (CH), 131.57 (C), 130.90 (CH), 129.66 (CH), 128.55 (CH), 128.47 (C), 128.27 (C), 127.97 (CH), 127.63 (CH), 126.5 (CH), 122.35 (C), 99.86 (CH), 65.28 (2 CH_2)

Mass (m/z) : 345(M^+, 5), 301 (20), 285 (10), 273 (100), 245 (30), 119 (50)

12. 2-(4-oxo-3, 4-dihydro-quinazolin-2-yl)-quinoline-3-carbaldehyde [45]



45

A solution of 44 (0.345 g, 0.1mmol) in a 1:1 mixture of 10% HCl: THF (15mL) was stirred for 2h. After the reaction was completed (TLC), the reaction mixture was extracted with CH_2Cl_2 (3×20mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography to give **45** as a white solid.

Molecular Formula : $C_{18}H_{11}N_3O_2$, 301

Yield : 0.285 g, 95%

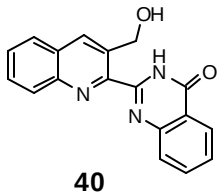
M.P. : 199-200^oC

IR (Nujol) cm^{-1} : 1682, 1464, 1377 cm^{-1};

^{1}H NMR (200MHz) : δ: 11.3 (br s, 1H), 8.82 (s, 1H), 8.54 (m, 2H), 8.24-8.17 (m, 2H), 8-8.1 (m, 2H), 8.04 (s, 1H), 7.94 (t, *J* = 6.89Hz, 1H), 7.77 (t, *J* =6.89Hz 1H),

Mass (m/z) : 301 (M^+, 32), 284 (20), 273 (65), 245 (42), 128 (40), 119 (100), 101 (19), 91 (15).

12. 2-(3-Hydroxymethyl-quinolin-2-yl)-3H-quinazolin-4-one [40]



40

To a solution of crude aldehyde **45** (0.451g, 1.5 mmol) in methanol (20 mL) was added $NaBH_4$ (114g, 3.2 mmol) at 0^oC and the resulting solution was stirred for 1 h at room temperature. Methanol was removed under the reduced pressure and the residue quenched with dil HCl (2 mL), and the solution was stirred for 5 min. Water (15 mL) and DCM (25 mL) were then added. The layers were separated, and the aqueous layer was extracted with DCM (3×15 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). Evaporation and column chromatography yielded the product as a white solid.

Molecular Formula : $C_{18}H_{13}N_3O_2$, 303

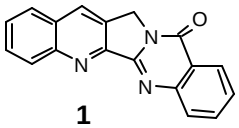
Yield : 98%

IR ($CHCl_3$) : 3373, 1681, 1518, 1461, 1377 cm^{-1}

^{1}H NMR (200MHz) : δ: 1.49 (br s, 1H), 8.43 (d, *J* =7.81Hz, 1H), 8.31 (s, 1H), 8.20 (d, *J* = 8.31Hz, 1H), 7.93-7.78 (m, 4H), 7.72-7.57 (m, 2H), 6.4 (t, 1H,), 5.09 (d, 2H).

Mass (m/z) : 303 ($M^{+,}$ 70), 285 (95), 274 (20), 257 (18), 246 (40), 229 (15), 155 (28), 143 (35), 128 (100), 119 (38), 101 (30), 92 (35)

13. Luotonin A :



1

A solution of alcohol **40** (0.303g, 1mmol) in 60% ethanolic H_2SO_4 (20mL) was heated to 115^oC for 3h.The cooled reaction mixture was added to sat. aq. $NaHCO_3$ solution carefully and extracted with dichloromethane (4×25mL). The extracts were dried (Na_2SO_4), concentrated and the residue was column chromatographed using 90% ethyl acetate as eluent to give Luotonin A as a white solid.

Molecular Formula : $C_{18}H_{11}N_3O$, 285

Yield : 0.208g, 73%

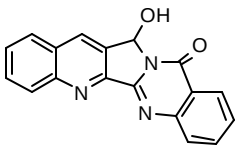
IR : 2854, 1678, 1629, 1606, 1466cm^{-1}

^{1}H NMR **(200MHz) : d : 8.46 (dd, *J* = 1.5, 8.5Hz, 1H), 8.45 (s,1H), 8.42 (dt, *J* = 1.5, 8.0Hz, 1H), 8.11 (dd, *J* = 1.5, 8.0Hz, 1H), 7.93 (dd, *J* = 1.5, 8.0Hz, 1H) 7.86 (dt, *J* = 1.5, 8.0Hz, 1H), 7.864 (dt, *J* = 1.5, 8.0Hz, 1H), 7.67 (dt, *J* = 1.5, 8.0Hz, 1H) 5.4 (s, 2H)**

^{13}C NMR **(50 MHz) : d : 160.66 (C), 152.58 (C), 151.17 (C), 149.37 (C), 149.29 (C), 134.60 (CH), 131.55 (CH), 130.69 (CH), 128.77 (CH+C), 128.53 (C), 127.95 (CH), 127.46 (CH), 126.45 (CH), 121.32(C), 47.31 (CH_2)**

Mass ,m/z (%) : 285 (M^+, 100)**,** 273 (80), 245 (30), 229 (20), 173 (30), 119 (35), 90 (20)

15. Luotonin B



2

Method A: To a solution of crude acetal **44** (0.301g, 1mmol) in THF (20 mL) was added slowly [with out allowing the temperature to raise beyond the rt] HCl (50%) at 0^oC. The resulting solution was stirred for 1 hr at room temperature and refluxed for 1h. Water (15 mL) and DCM (25 mL) were then added. The layers were separated, and the aqueous layer was extracted with DCM (3×25 mL). The combined organic layers were washed with brine and then dried

(Na_2SO_4). Evaporation and column chromatography over silica gel employing ethylacetate as eluent yielded Luotonin B **2** as a white solid.

Method B: To a mixture of Luotonin A (0.070g, 0.25mmol) and $FeCl_3$ (0.100g) dissolved in ethanol (5 mL) ethanol was added H_2SO_4 (0.7mL) dropwise and heated at 70^oC for 5h. Ethanol was removed under reduced pressure and contents were neutralized by adding $NaHCO_3$ solution and extracted with DCM (3×15mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in mixture of 1:1 mixture of ethanol: 50% HCl (5mL) and the reaction mixture was heated to reflux for 30 min. Ethanol was removed under reduced pressure, neutralized the contents by careful addition of $NaHCO_3$, and extracted with DCM (3×8mL),

dried (Na_2SO_4) and concentrated the residue was purified by column chromatography over silica gel using ethyl acetate as an eluent to afford Luotonin B as a yellow solid.

Molecular Formula : $C_{18}H_{11}N_3O_2$, 301

Yield : 0.036g, 70%

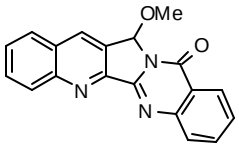
IR : 2925, 2854, 1678, 1630cm^{-1}

^{1}H NMR **(200MHz)** **:** d **: 8.58 (s,1H), 8.49 (dd, *J* = 1.5, 8.0Hz, 1H), 8.44 (dd, *J* = 1.5, 8.0Hz, 1H), 8.11 (dd, *J* = 1.5, 8.0Hz, 1H), 8.01 (dd, *J* = 1.5, 8.0Hz 1H) 7.87 (dt, *J* = 1.5, 8.0Hz, 1H), 7.60 (dt, *J* = 1.5, 8.0Hz, 1H) 7.89 (dt, *J* = 1.5, 8.0Hz, 1H), 7.14 (s, 1H)**

^{13}C NMR (50 MHz) : δ 161.6 (CH), 150.9(C), 150.4 (C), 150.3 (C), 149.6 (C), 135.1 (CH), 133.7 (CH), 131.3 (C), 130.9 (CH), 129.2 (CH), 128.9 (C), 126.5 (CH), 127.9 (CH), 121.9 (C), 80.9 (CH).

Mass (m/z) : 301 (75, M^+), 284 (100), 273 (80), 245 (30), 229 (20), 173 (30), 119 (35), 90 (20)

16. Luotonin E [3]



3

To a solution of crude acetal **44** (0.301g, 1mmol) in methanol (20 mL) was added slowly [with out allowing the temperature to raise beyond the rt] con H_2SO_4 at 0^oC. The resulting solution was stirred for 1 hr at room temperature and refluxed for 1hr. Water (15 mL) was added, carefully neutralized the contents by adding solid $NaHCO_3$, and extracted with DCM (3 × 25

mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). Evaporation and column chromatography yielded the product **3** as a white solid.

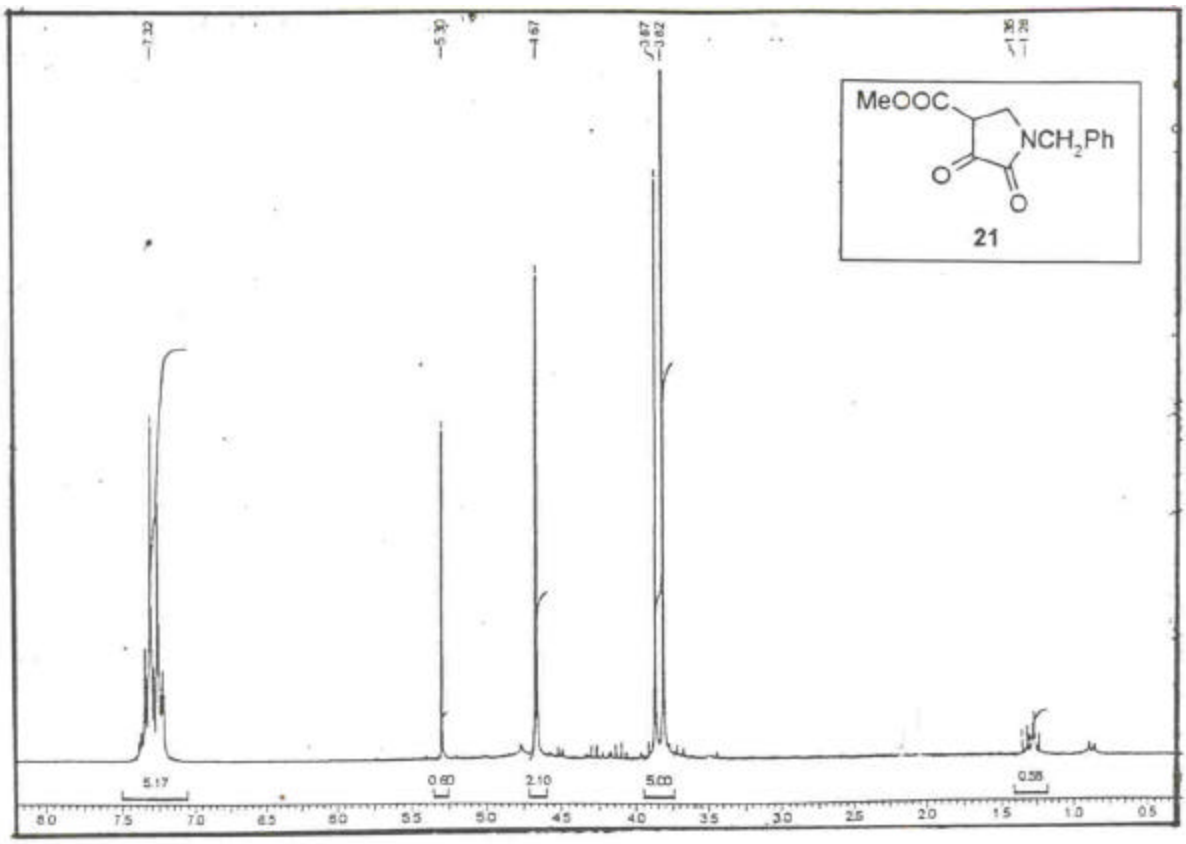
Molecular Formula : $C_{19}H_{13}N_3O_2$, 315

Yield : 0.220g, 72%

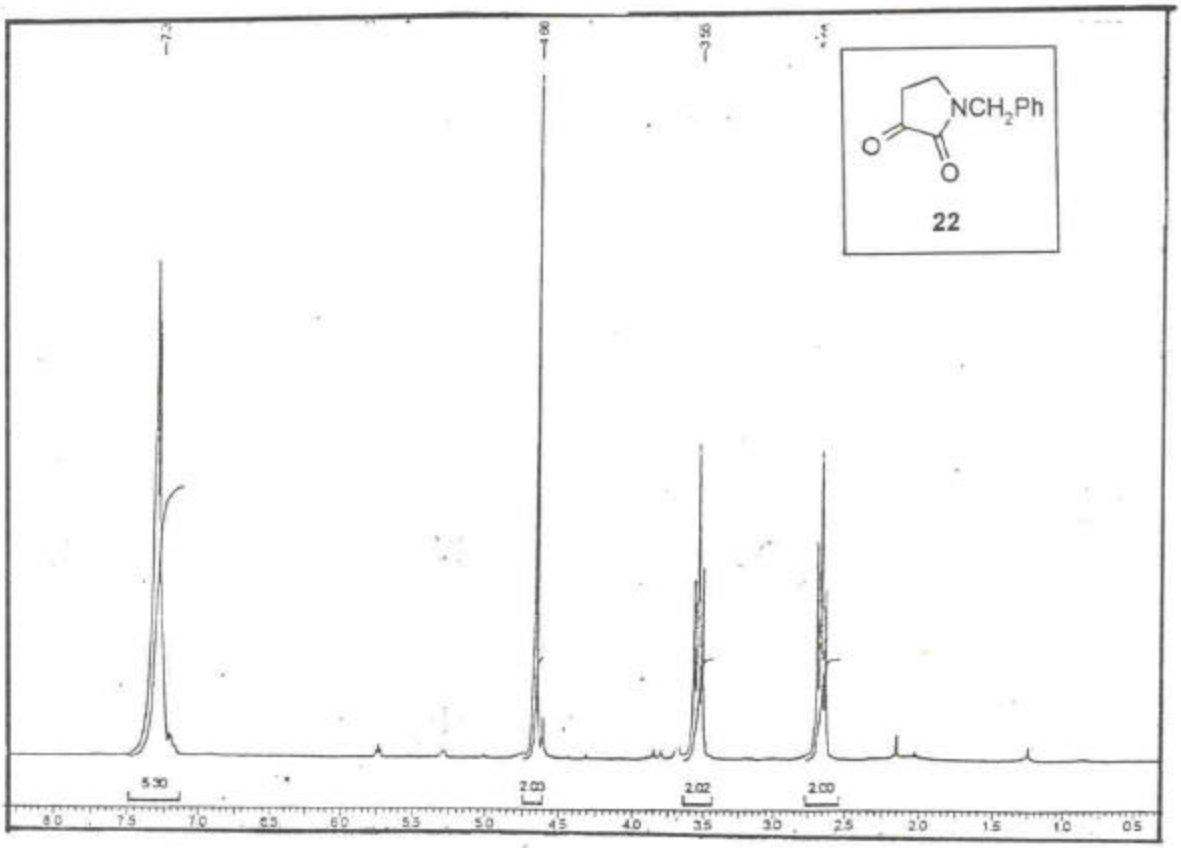
IR : 1680, 1635, 1605, 1405cm^{-1}

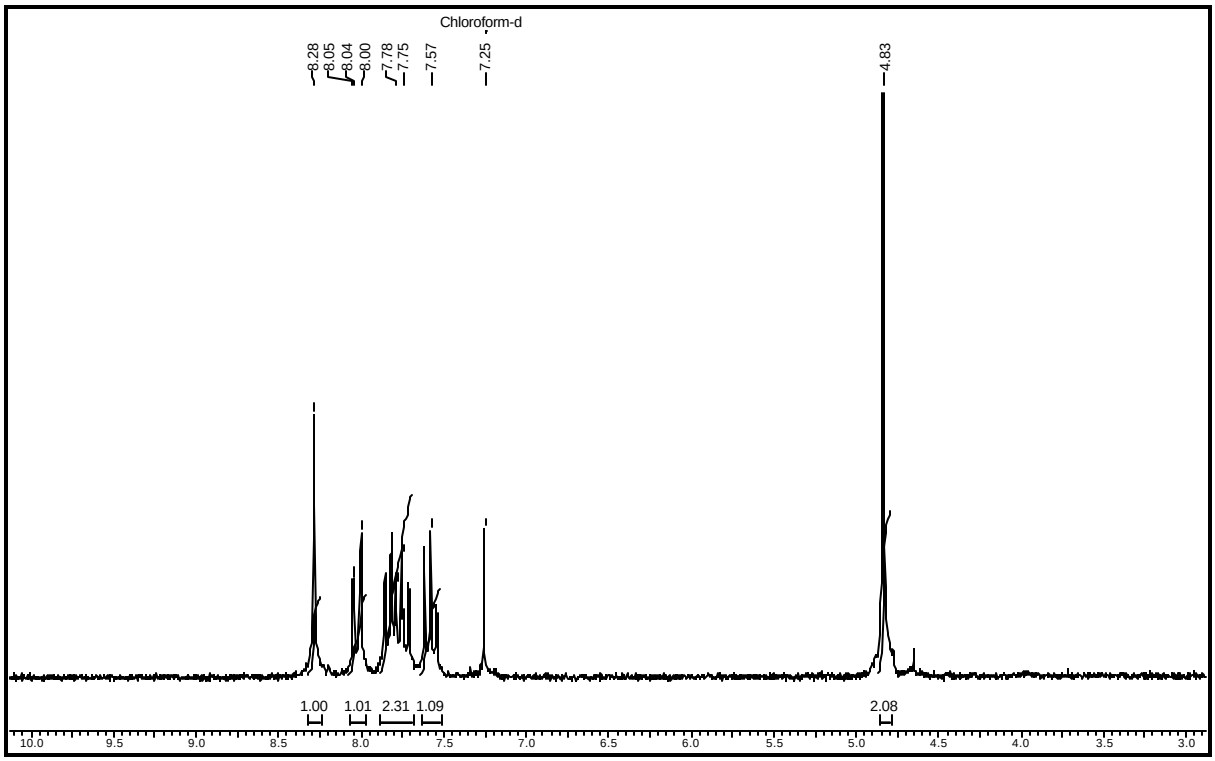
^{1}H NMR **(200MHz) : d : 8.52 (s,1H), 8.43 (dd, *J* = 1.5, 8.0Hz, 1H), 1H), 8.09 (dd, *J* = 1.5, 8.0Hz, 1H), 8.00 (dd, *J* = 1.5, 8.0Hz 1H) 7.88 (dt, *J* = 1.5, 8.0Hz, 1H), 7.72 (dt, *J* = 1.5, 8.0Hz, 1H) 7.85 (dt, *J* = 1.5, 8.0Hz, 1H), 7.59 (dd, *J* = 1.5, 8.0Hz), 6.94 (s, 1H), 3.60 s (3H)**

Mass (m/z) : 315 ($M^{+\cdot}$, 10), 273 (100), 245 (25), 229 (30), 173 (30), 119 (35), 90 (20)

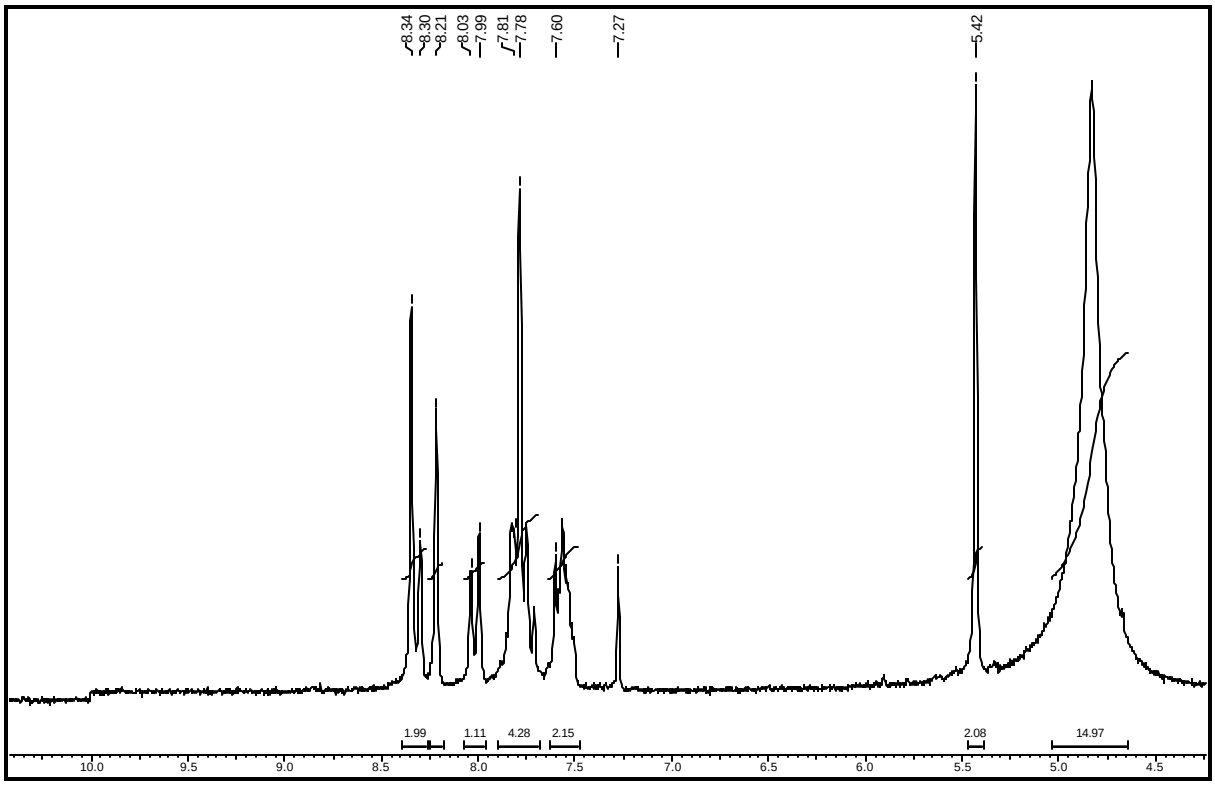


^{1}H NMR spectrum of compound [21] (200 MHz, $CDCl_3$)

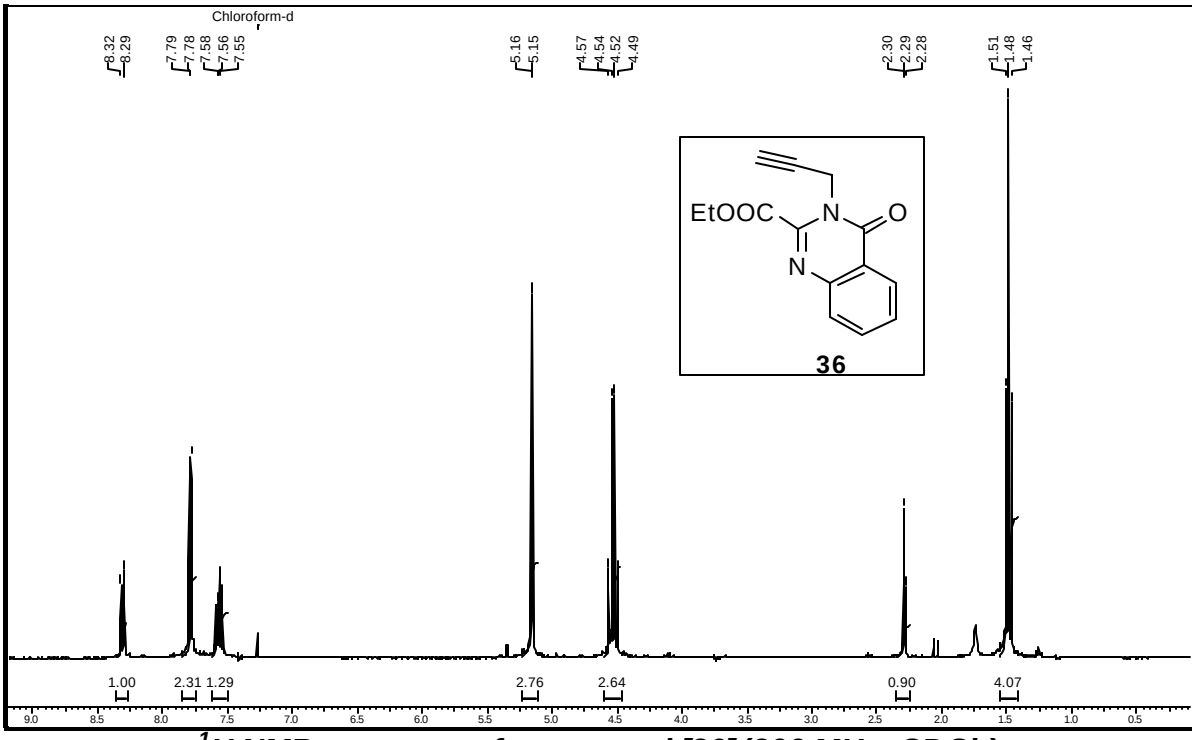




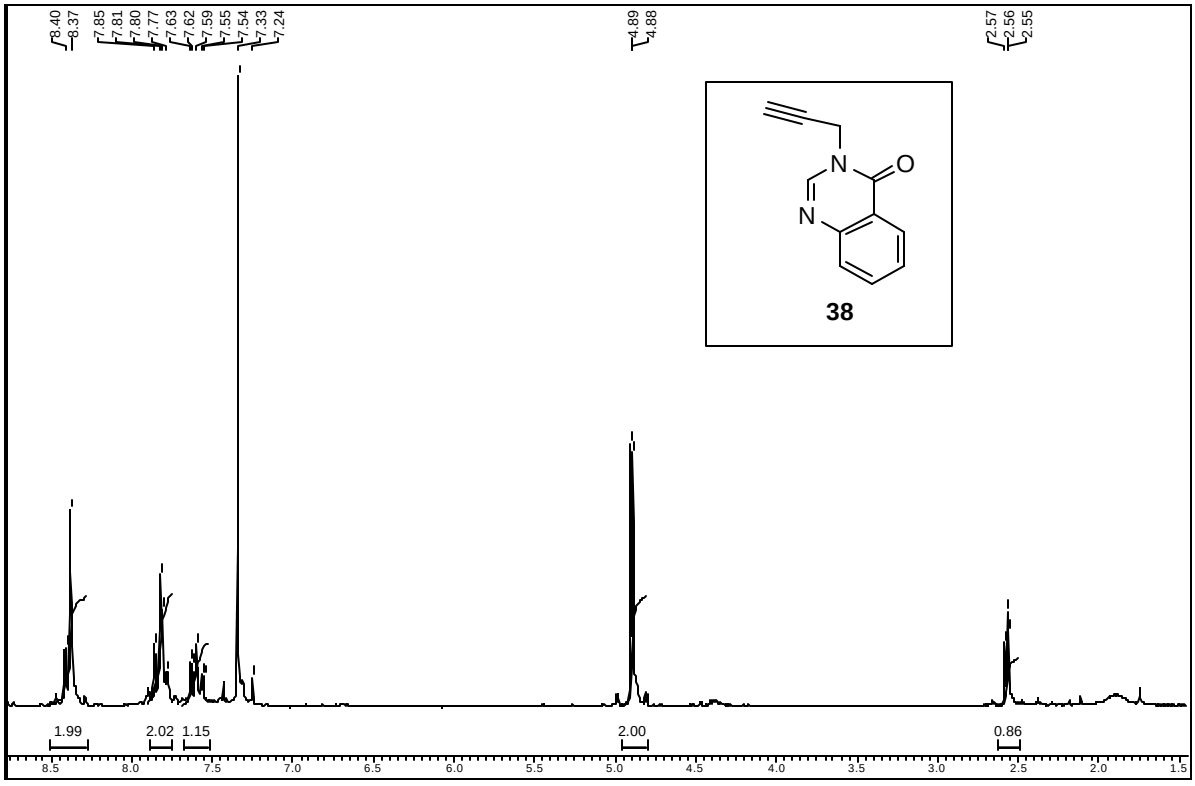
^{1}H NMR spectrum of compound [25] **(200MHz, $CDCl_3$)**



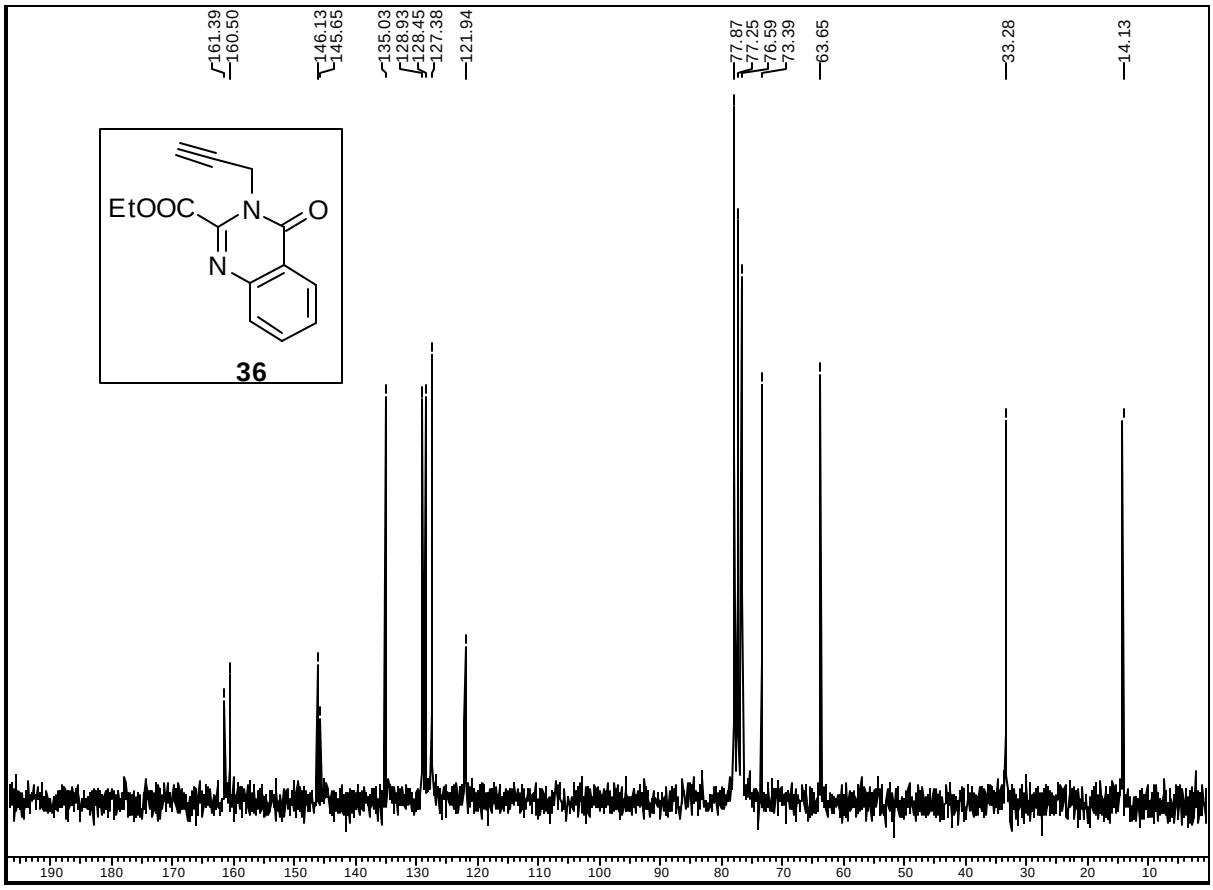
^{1}H NMR spectrum of compound [26] **(200MHz, $CDCl_3$)**



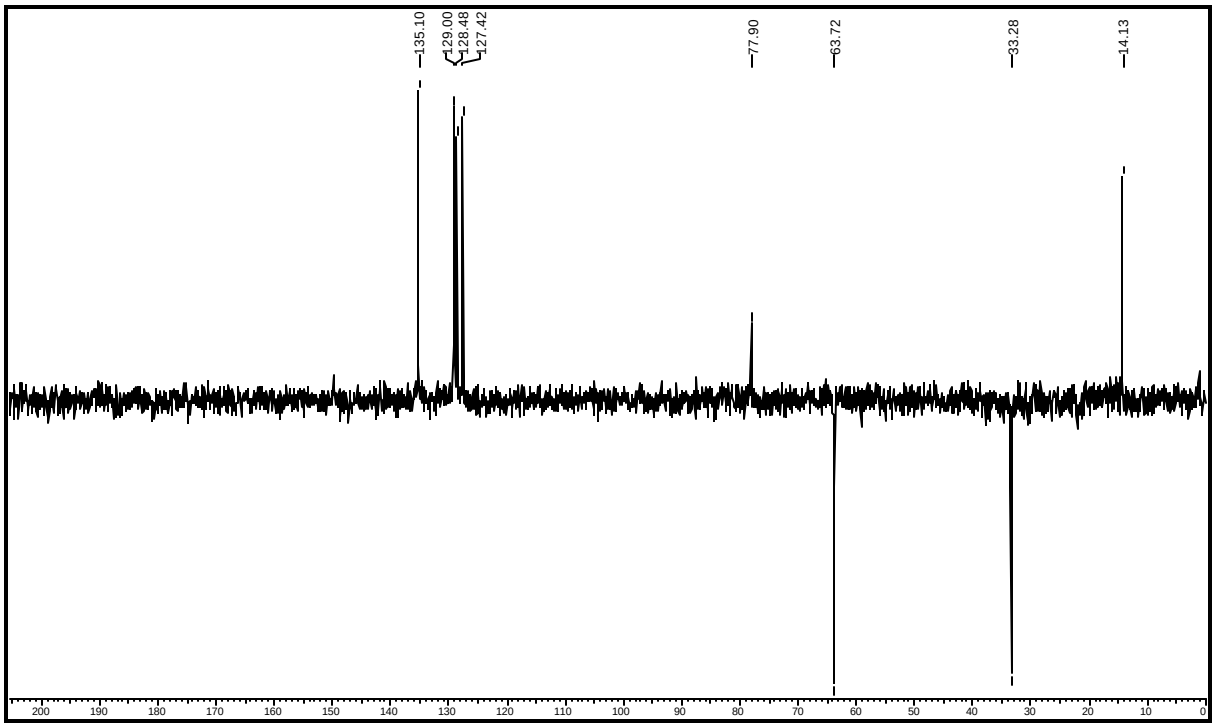
***[1]H NMR spectrum of compound [36]* (200 MHz, $CDCl_3$)**

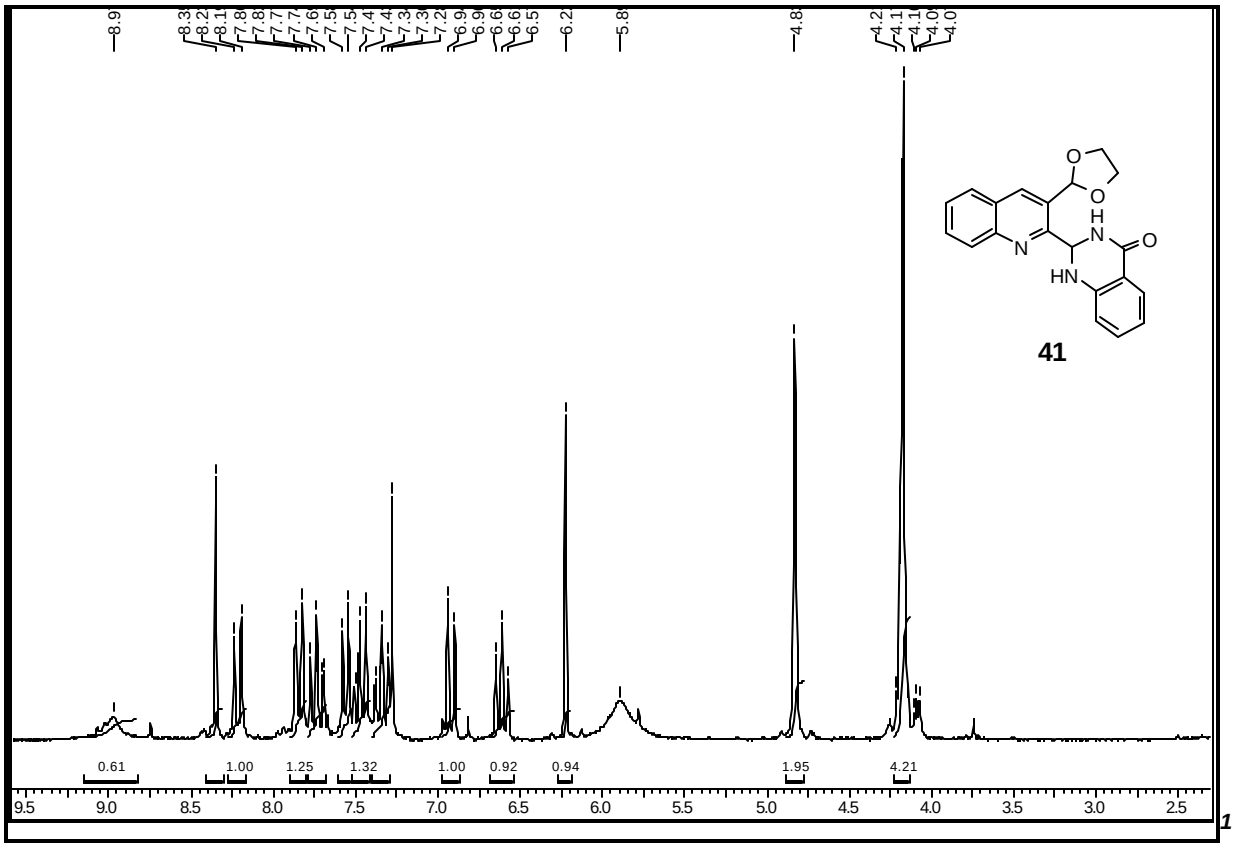


^{1}H NMR spectrum of compound [38] **(200MHz, $CDCl_3$)**

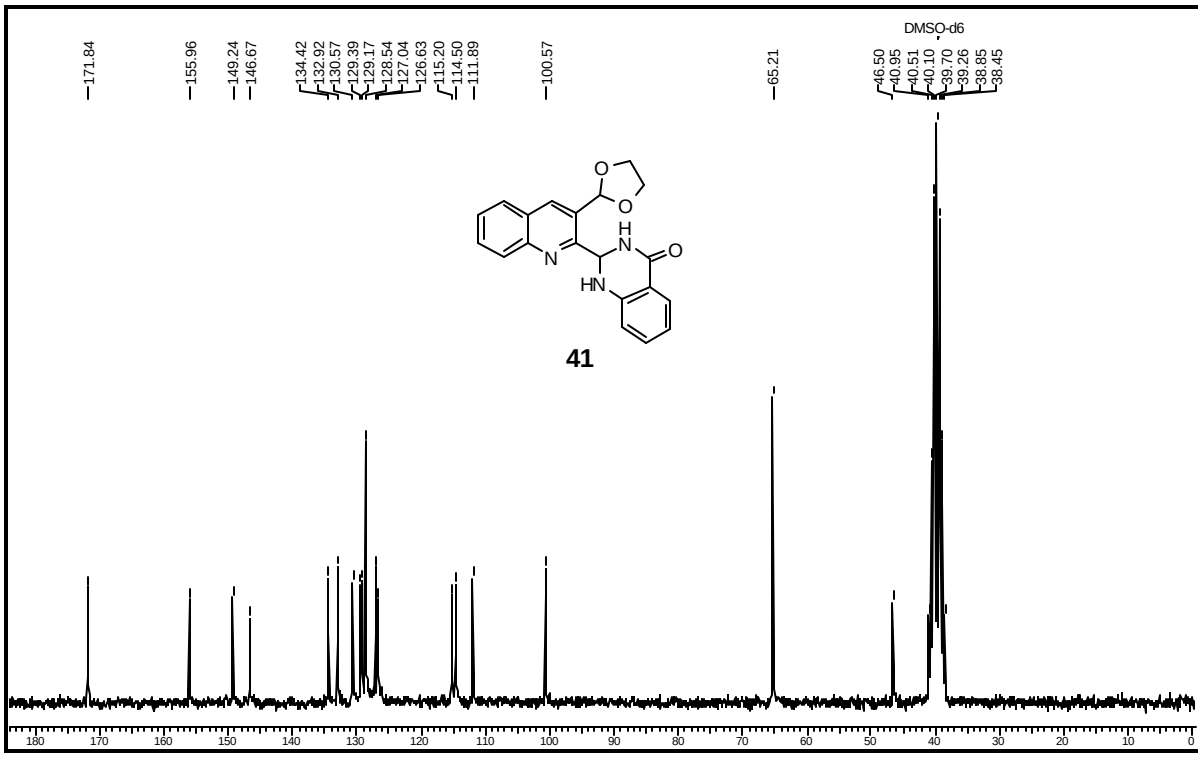


^{13}C & DEPT NMR spectra of compound [36] **(50 MHz, $CDCl_3$)**

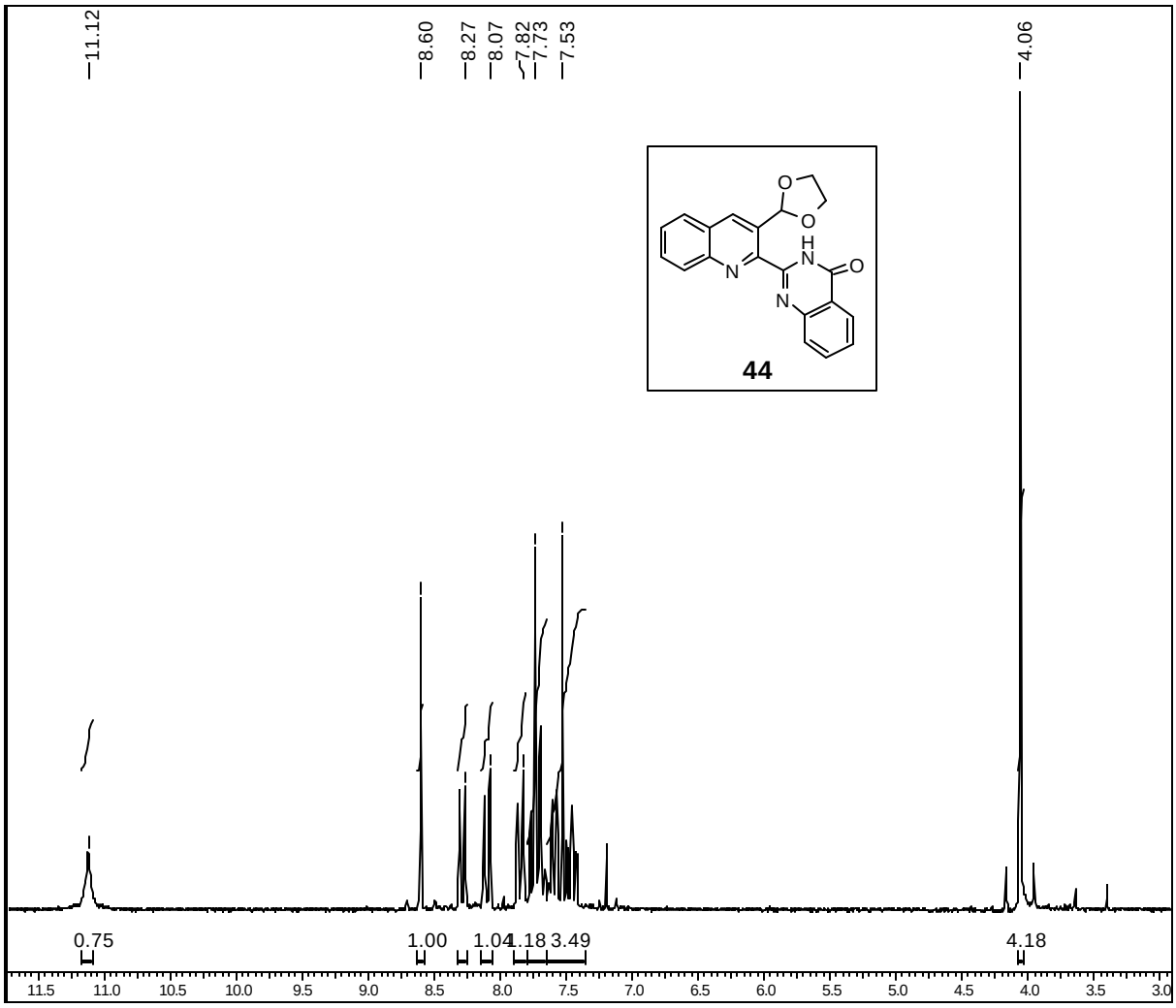

135.10
129.00
128.48
127.42
77.90
63.72
33.28
14.13
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



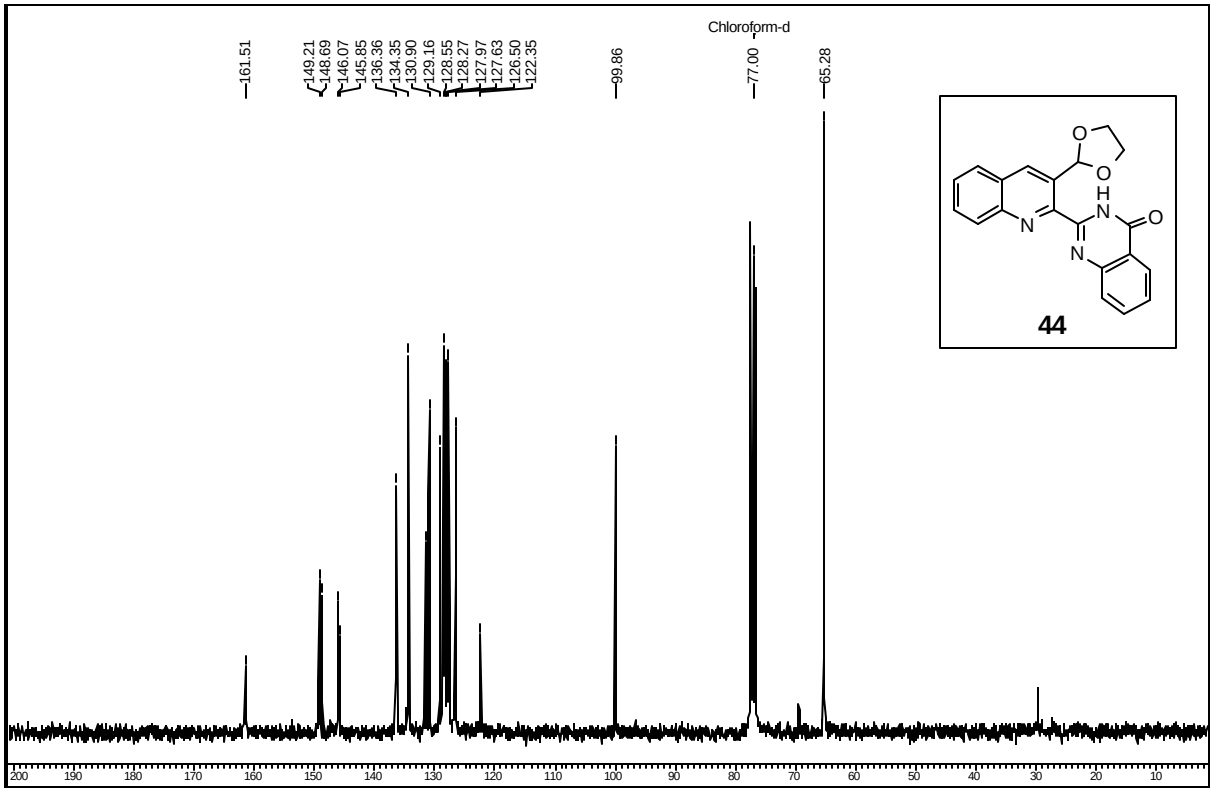
H NMR spectrum of compound [41] **(200MHz, $CDCl_3$)**



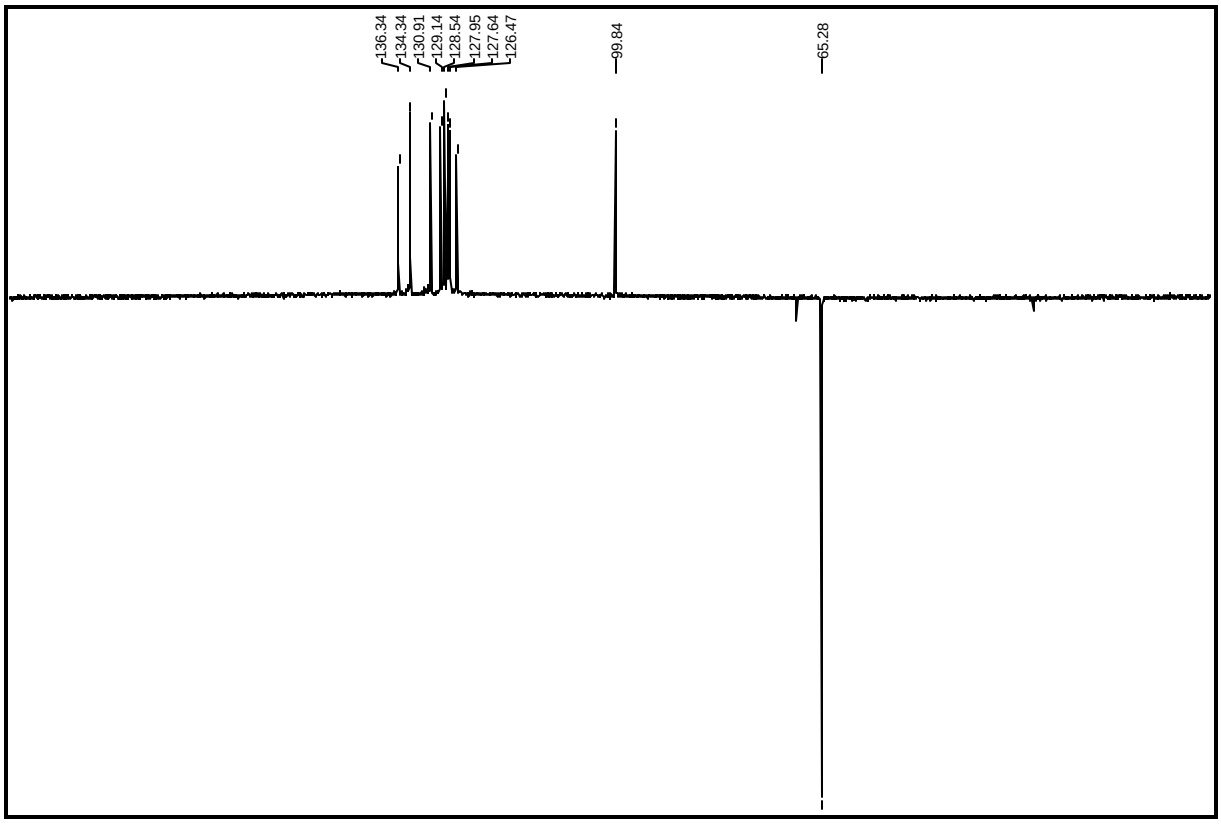
^{13}C NMR spectrum of compound [41] **(50 MHz, $CDCl_3$)**

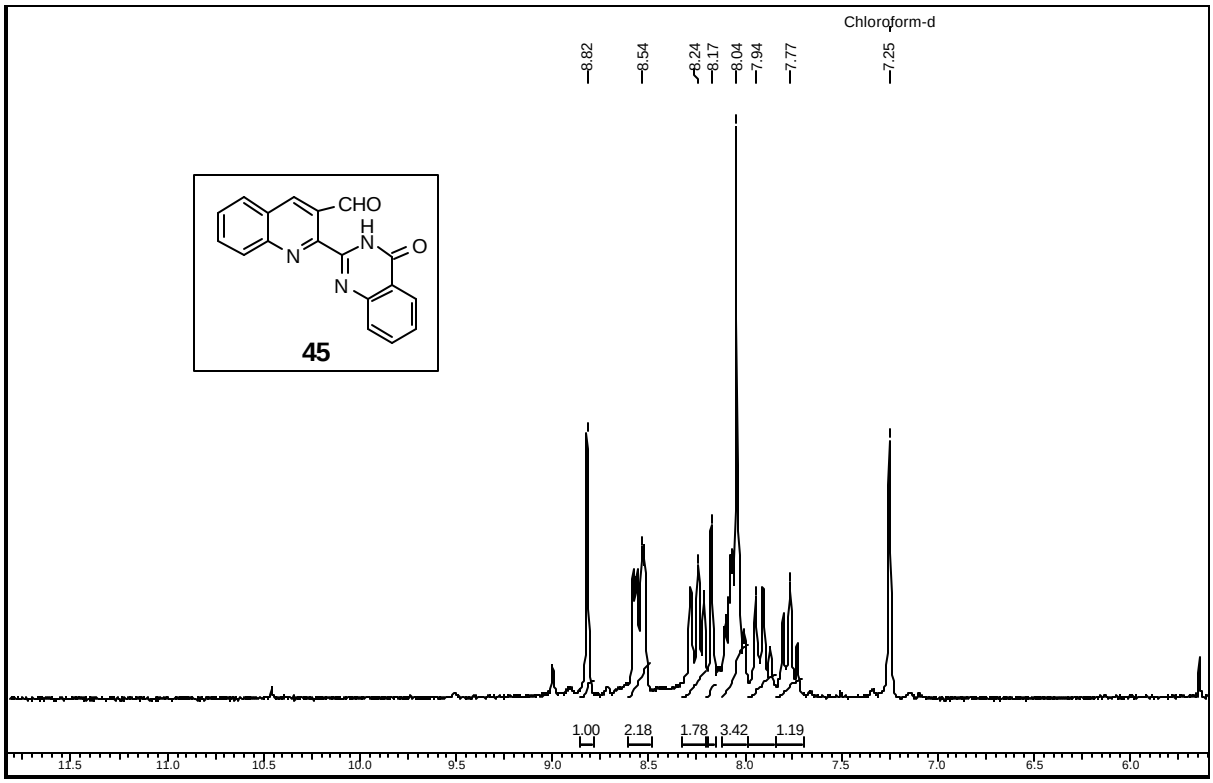


^{1}H NMR spectrum of compound [44] **(200MHz, $CDCl_3$)**

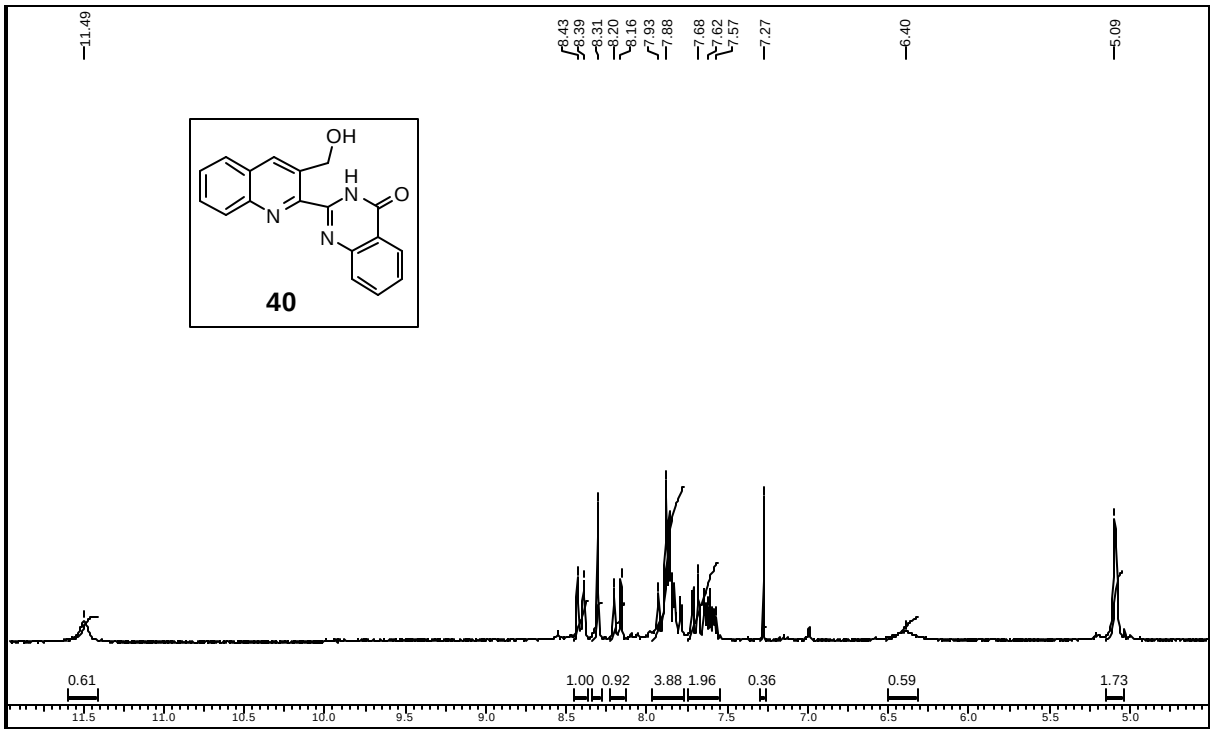


^{13}C & DEPT NMR spectra of compound [44] **(50 MHz, $CDCl_3$)**

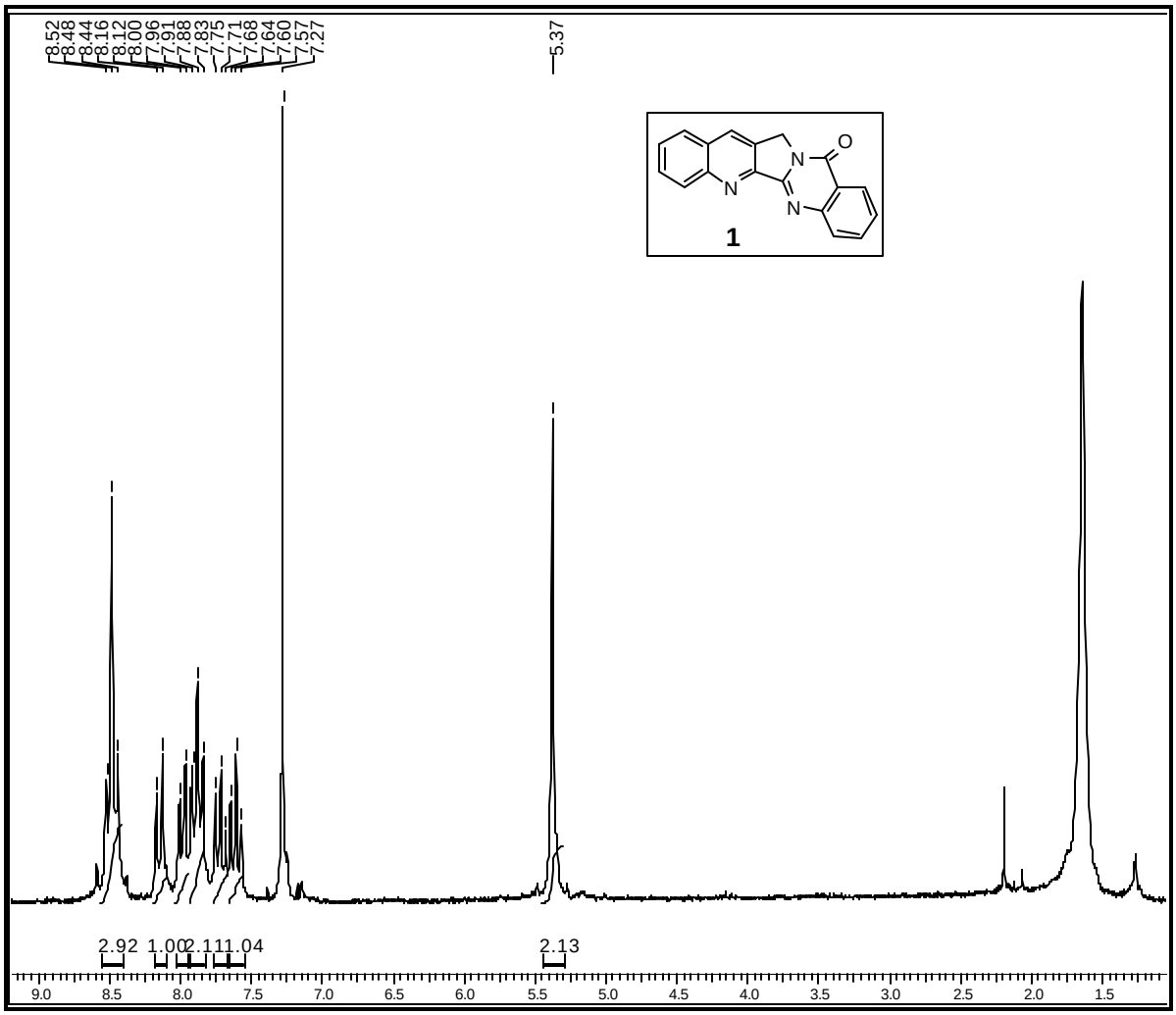




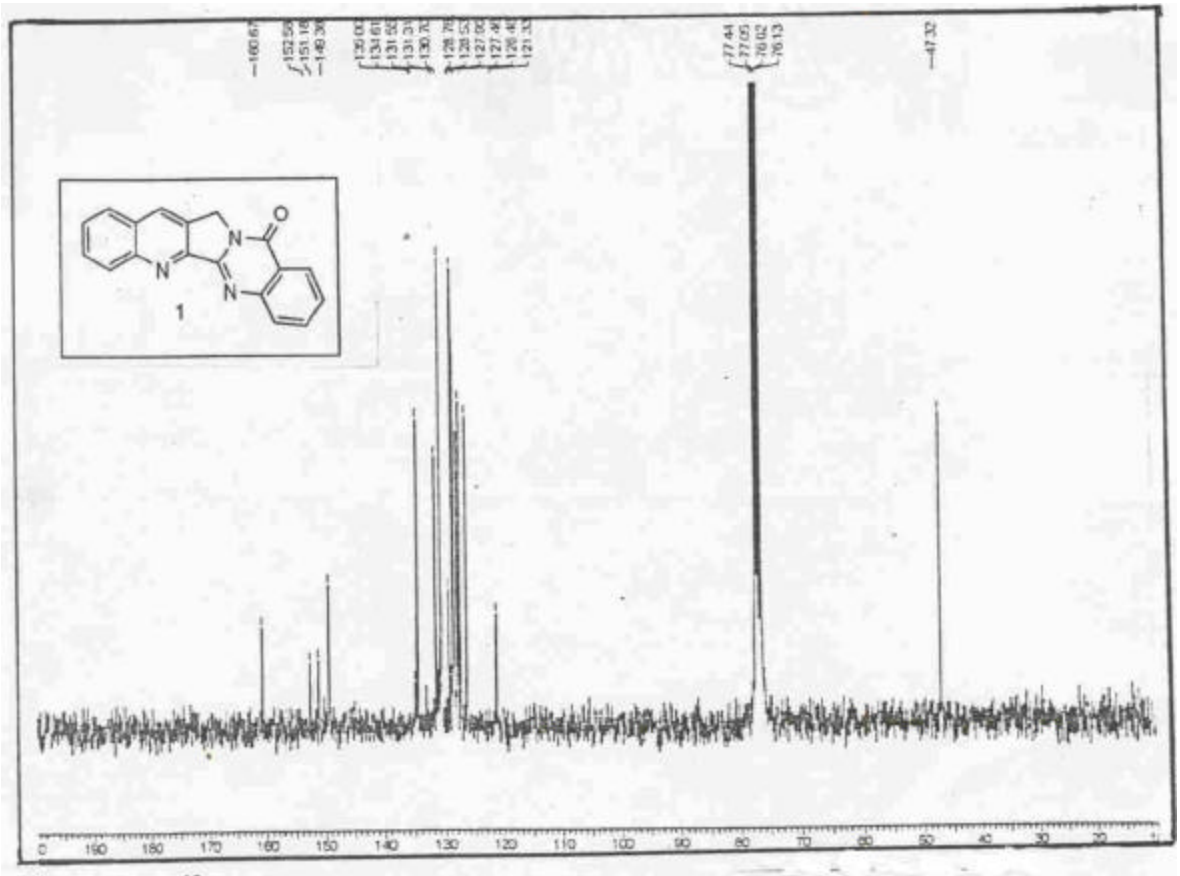
***^{1}H NMR spectrum of compound [45]* (200 MHz, $CDCl_3$)**



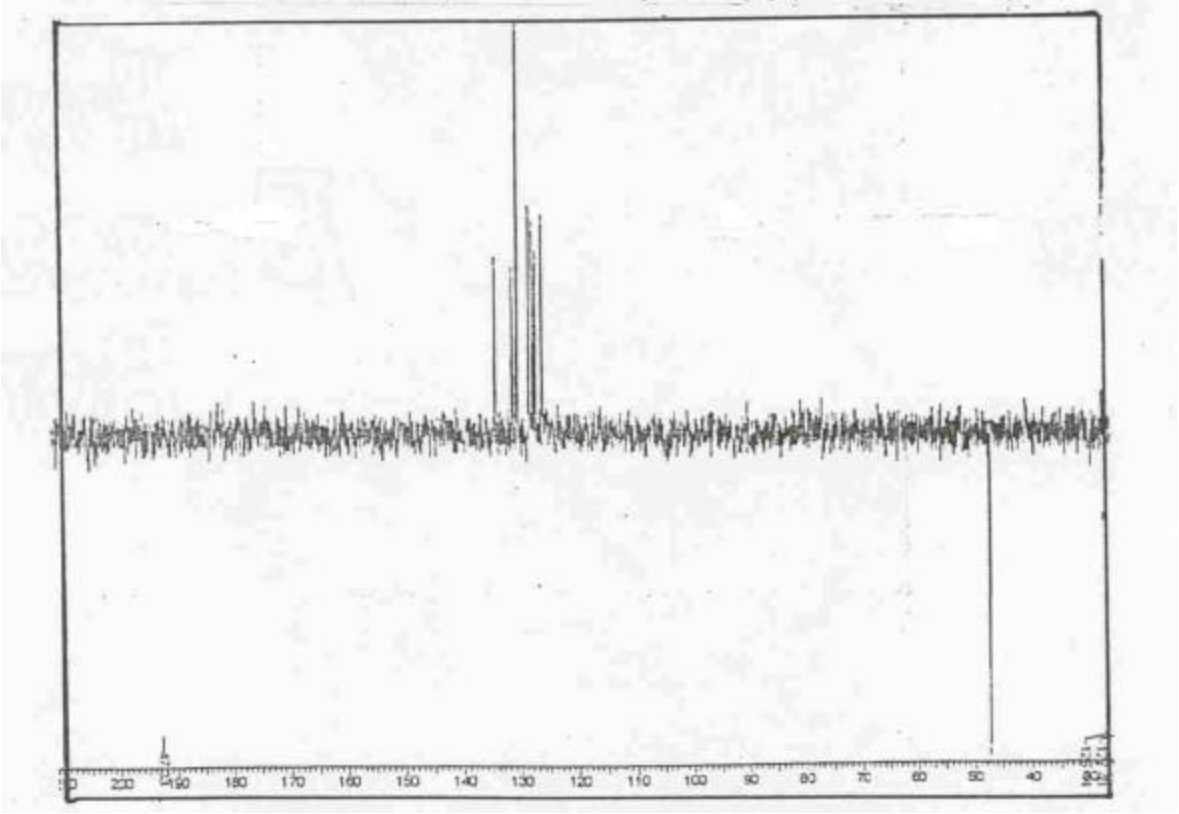
^{1}H NMR spectrum of compound [40] **(200 MHz, $CDCl_3$)**

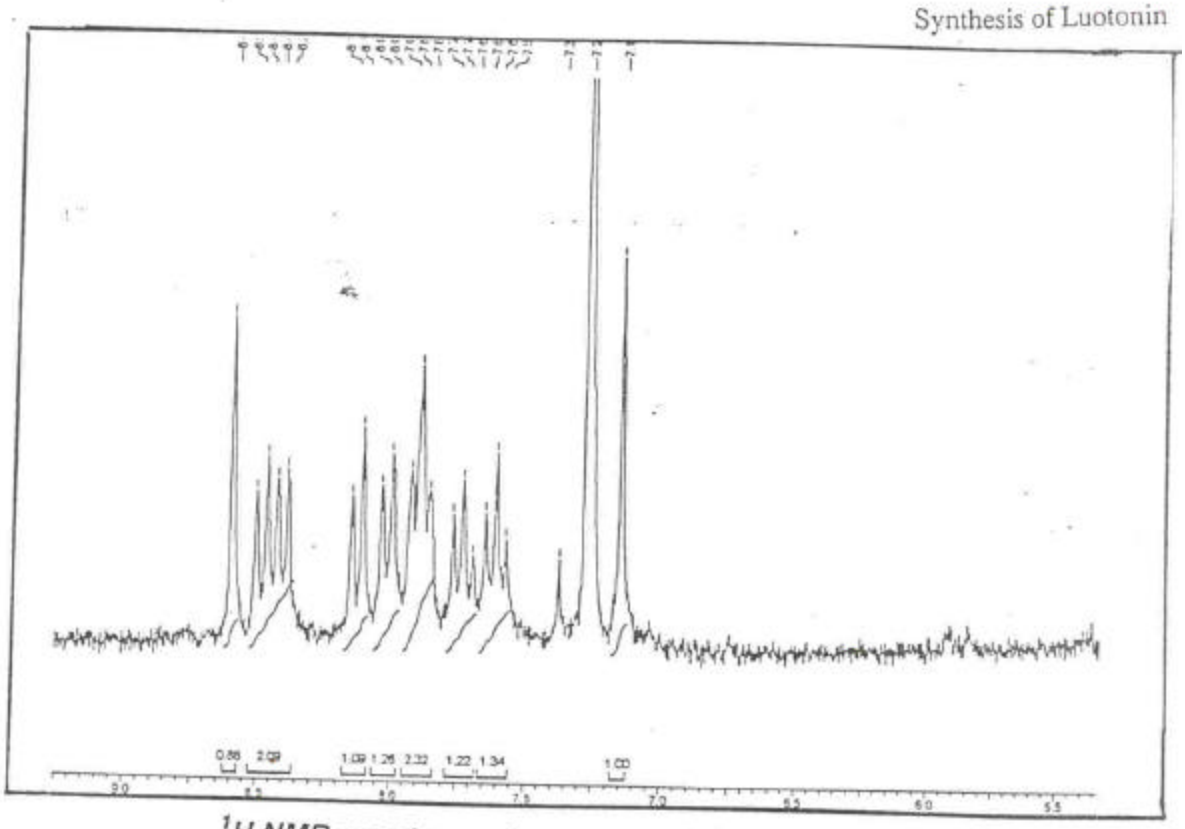


^{1}H NMR spectrum of compound [1] **(200MHz, $CDCl_3$)**

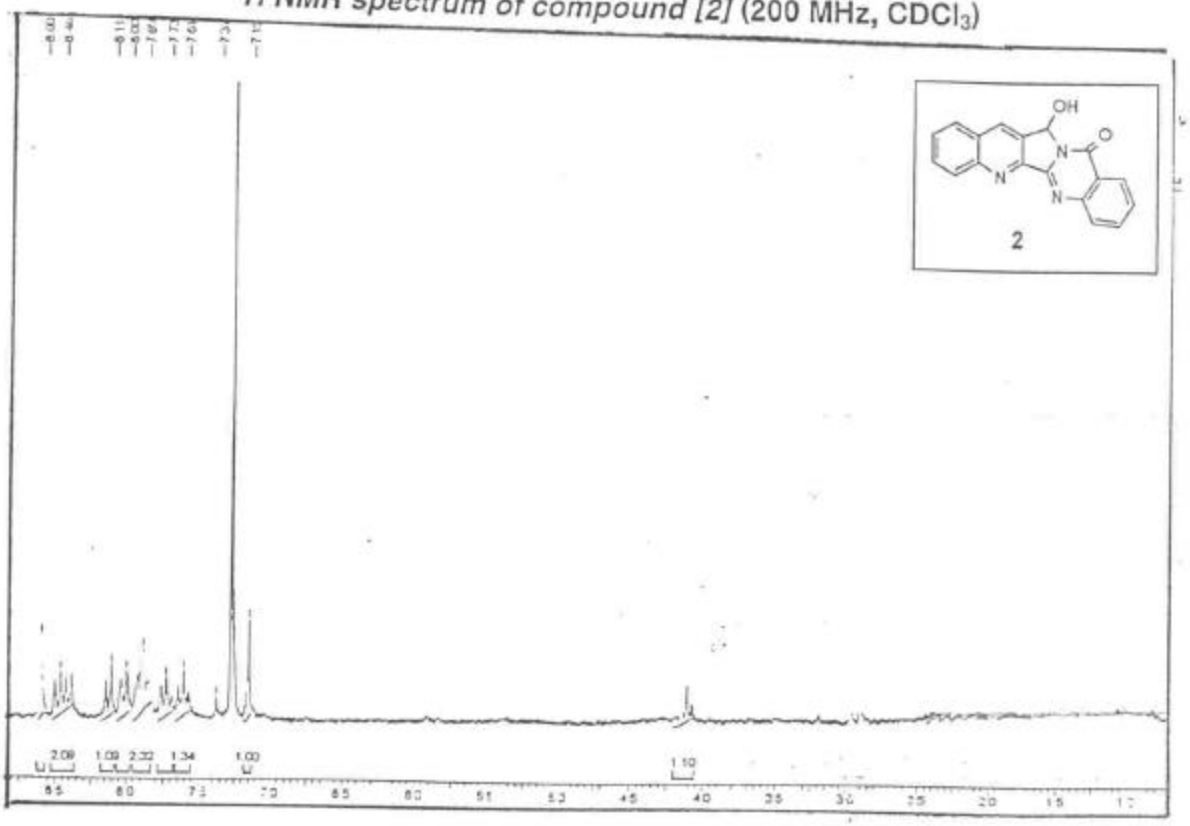


^{13}C & DEPT NMR spectra of compound [1] (50 MHz, $CDCl_3$)





^1H NMR spectrum of compound [2] (200 MHz, $CDCl_3$)



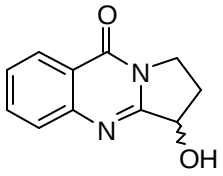
CHAPTER 2

Section II

Synthesis of Pyrroquinazolonone Alkaloids - Vasicinone & Luotonin A

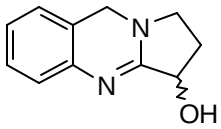
2.2.1 Introduction

Vasicinone **1** is a pyrrolo (2,1-*b*) quinazoline alkaloid isolated from the leaves and infloroscence of *Adhatoda vasica*[167,168] an evergreen subherbascious bush used extensively in indigenous medicine as a remedy for cold, bronchitis, asthma[169] *etc*. The related alkaloids namely Vasicine **2**, Vasicinoline **3** and deoxy Vasicinone **4** have also been isolated from the same plants.[170]

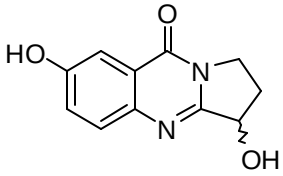


1

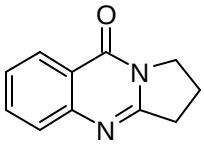
Vasicinone **(1)**



Vasicine **(2)**



Vasicinolone **(3)**



Deoxyvasicinone **(4)**

Vasicinone coexists the Luotonins in *P.nigellastrum*[171] which led to consider it as the biogenetic precursor based on the similarity in their skeleton too. Previously assigned 3-(*R*) configuration of natural Vasicinone has been corrected to be the 3-(*S*) configuration on the basis of X-ray crystallography of Vasicinone hydrochloride derivative of Vasicinone[172a] and by Mosher ester analysis.[6b]

2.2.2 Pharmacology

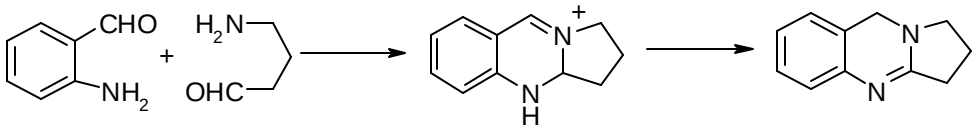
Most of these quinazoline alkaloids are known to possess a broad spectrum of pharmacological activity particularly bronchodilatory activity. Very recently a series of analogues of Vasicinone have been synthesized and evaluated for their bronchodilatory activity.[173] (-) Vasicinone exhibits antitumor,[174] bronchodilating,[3] hypotensive,[175] anthelmintic[176] antianaphylactic[177] activities and antihistaminic effects.[178, 3, 4] Uterine stimulant activity and moderate of the alkaloids has been reported. Thrombopoeitic activity of vasicine has also been observed.[179] Intraamniotic injection of vasicine hydrochloride was effective in inducing mid-trimester abortions at dose of 60mg.[180] It is also prescribed commonly for bleeding due to

idiopathic thrombocytopenic purpura, local bleeding due to peptic ulcer, piles, menorrhagia etc. Its local use gives relief in pyorrhoea and in bleeding gums.[181]

2.2.3 Biogenesis

Speculation on the biogenesis of this group of compounds began when Robinson suggested[182] that vasicine might be derived from anthranilic acid and proline or closely related metabolites. This possibility was strengthened when Schopf and Oechler[183] synthesized deoxy vasicine under "physiological" conditions as shown in *Scheme 1*.

Scheme 1:



5 **6** **7** **9**

Thus the condensation of *o*-aminobenzaldehyde **5** with γ-amino butyraldehyde **6** at pH 5 yielded a quaternary salt **7** that underwent double-bond migration under reducing conditions to form deoxyvasicine **9.**

Tracer studies[184] with *in vivo* systems have been reported. In feeding experiments conducted on *P. harmala* with carboxyl ^{14}C anthranilic acid, labelled Vasicine was obtained. Similar experiments with *Adathoda vasica* also yielded labelled vasicine whose chemical degradation showed a specific incorporation since all the activity was localized at C-8 of the alkaloid.[185] In addition, administration of ^{14}C labeled proline, putrescine and γ-hydroxy glutamic acid to *A. vasica* has led to the isolation of radioactive vasicine in each case. Anthranilic acid is incorporated into vasicine in *Adhatoda vasica*. The rest of the molecule may be attributable to aspartic acid.

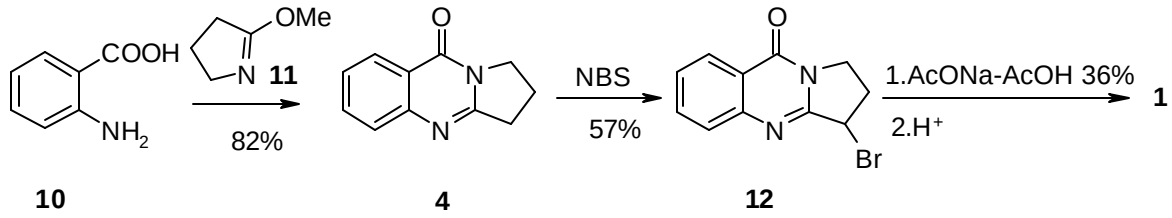
2.2.4 Synthesis of Vasicinone: A Literature survey

In the view of the medicinal properties of this alkaloid many syntheses have been achieved. Many of these syntheses involve deoxyVasicinone **4** as a precursor for the synthesis of Vasicinone.

Onaka's approach[186] (Scheme 2, 1971)

Condensation of *O*-methyl butyrolactim **11** with anthranilic acid **10** gave deoxy Vasicinone **4** that was brominated with NBS to obtain bromo compound **12** along with minor amount of dibromo compound. Compound was acylated with NaOAc–AcOH to acetyl Vasicinone, which was hydrolyzed to Vasicinone **1**. Use of lactam ether limits the synthetic utility of the approach.

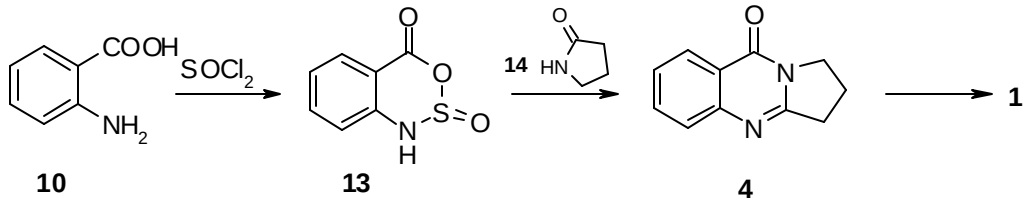
Scheme 2: Onaka *et al*, *Tetrahedron Lett*, **1971**, *12*, 4387



Kametani's approach[187] (Scheme 3, 1976)

Kametani *et al* employed thier methodology-cycloaddition of iminosulfinamide anhydride as key step. Imino sulfinamide anhydride **13** prepared from anthranilic acid and thionylchloride was treated with 2-pyrrolidone **14** in dry benzene to give deoxy Vasicinone **4** in quantitative yield which was converted to Vasicinone **1** by Onaka's method. The fact that the reaction of the lactam proceeded in higher yield than that of the lactim ethers indicates that this new synthesis of quinazolinones is an effective method.

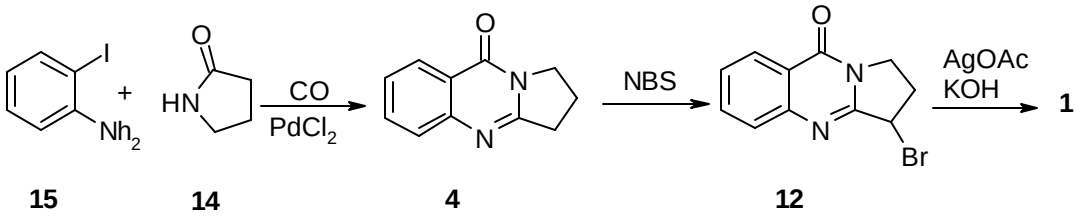
Scheme 3: Kametani *et al*, *J. Am. Chem. Soc*, **1976**, *98*, 6186



Mori's approach[188] (Scheme 4, 1985)

This synthesis features Pd catalyzed carbonylation as key step. Pd catalyzed carbonylation of iodoaniline **15** with 2-pyrrolidinone **14** and CO (5atm) gave the pyrroloquinazoline **4** in 52% yield which was converted to Vasicinone by modification of Onaka's method. Thus treatment of the bromo **12**, obtained by bromination of **4** with NBS, with silver acetate furnishes acetate, which was hydrolyzed to Vasicinone **1.**

Scheme 4: Mori *et al*, *Heterocycles*, **1985**, *23*, 2803

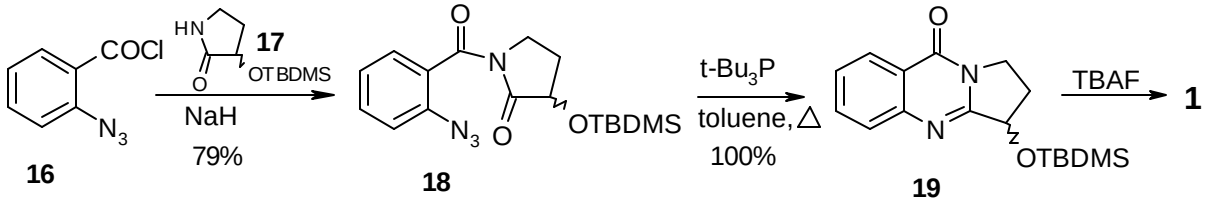


15 **14** **4** **12**

Eguchi's approach[189] (Schemes 5 & 6 1996)

Both optical isomers of Vasicinone were synthesized by two different methods. The racemic synthesis involved condensation of the synthon **17** (which was prepared by TBDMS protection of 3-hydroxy γ-lactam) with *o*-azido benzoyl chloride **16** using NaH to obtain the precursor **18** for the aza Wittig reaction. The addition of *t*-Bu_3P initiated the tandem Staudinger/intramolecular azawittig reaction to give the *O*-TBDMS Vasicinone **19**. The deprotection of silyl protecting group by TBAF in THF gave the *dl*-Vasicinone**1**. (S)-Vasicinone was obtained by employing the (3*S*)-3-hydroxy γ-lactam **17** as a chiral synthon in the above sequence in 97% *ee*.

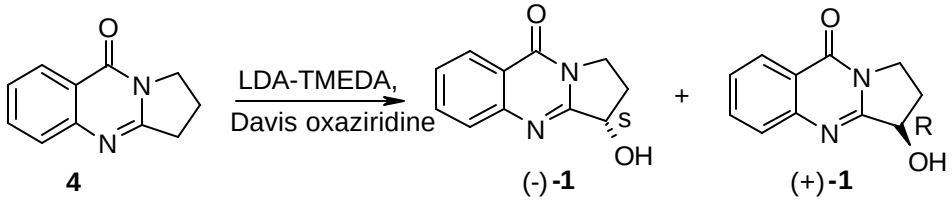
Scheme 5: Eguchi *et al, J. Org. Chem.*, **1996**, *61*, 7316-7319



16 **18** **19**

The second method involved oxygenation of deoxyVasicinone with (1*S*) or (1*R*)-(10-Camphorsulfonyl) oxaziridine respectively. Thus the aza-enolate anion of deoxy Vasicinone was treated with (*S*)-(+) reagent to afford *R*- (+) Vasicinone in 71% *ee*, while the reaction with (*R*)-(-) reagent gave (*S*)- (-) Vasicinone in 62% *ee*.

Scheme 6: Eguchi *et al, J. Org. Chem.*, **1996**, *61*, 7316-7319



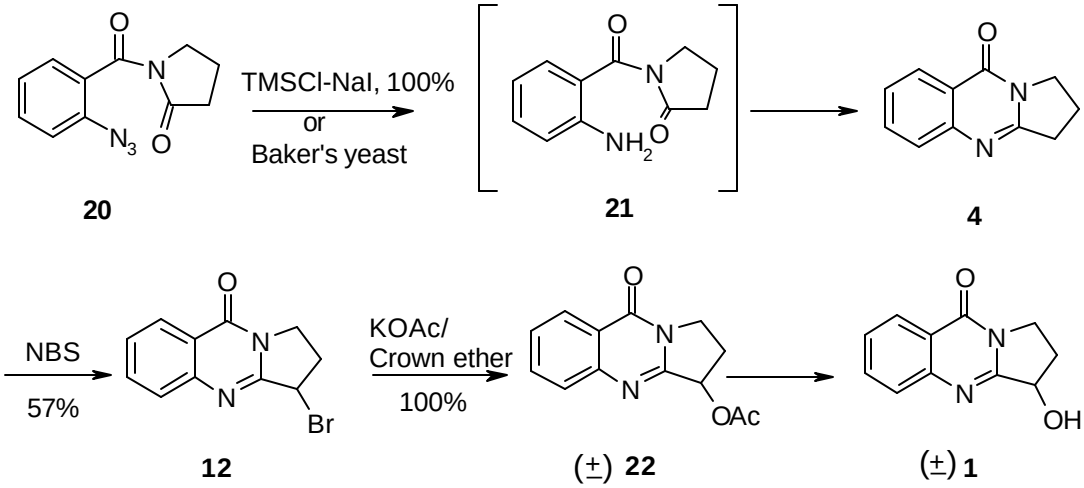
4 (-)**-1** (+)**-1**

l-Vasicinone **d-Vasicinone**

Kamal's approach[190] (Schemes 7 & 8, 2001)

Kamal *et al* employed azidoreductive cyclization strategy in their elegant synthesis of Vasicinone. The appropriate precursor 2-azidobenzoyl lactam **20** was prepared by coupling of 2-azidobenzoic acid with lactam **14**. The reductive cyclization with TMSCl-NaI provided deoxyVasicinone **4** in quantitative yields. The reaction timings were of the order of few minutes unlike with TPP or Bu_3P.The same transformation was effected with presonicated baker's yeast *albeit* in low yields.

Scheme 7: Kamal *et al., J. Org. Chem.*, **2001**, *66*, 997

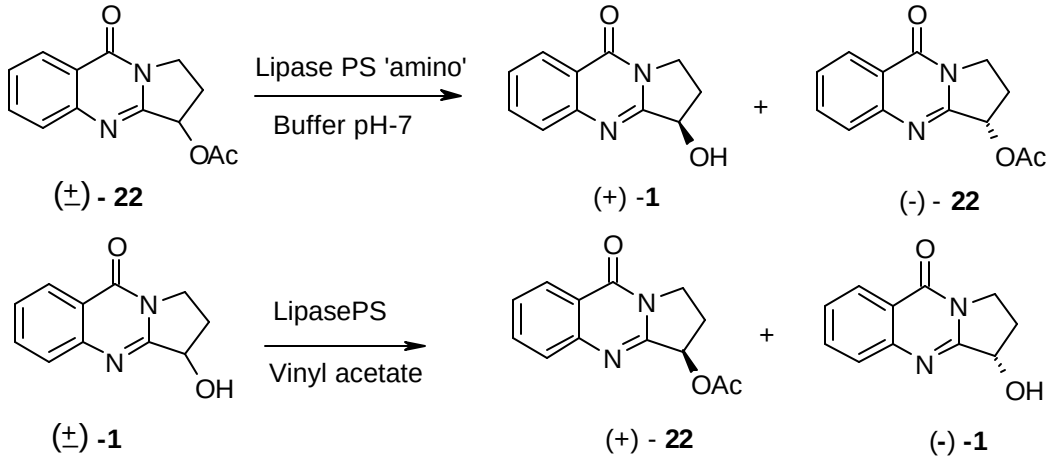


Racemic Vasicinone was prepared from deoxyVasicinone by its bromination, acetylation with KOAc in presence of crown ethers and the hydrolysis of the acetate. Acetyl Vasicinone thus obtained was subjected to enzymatic hydrolysis with different lipases in different solvents. Lipase PS provided (*R*) -Vasicinone and (*S*)- acetate in 98% *ee*.

Alternatively racemic Vasicinone was resolved by transesterification using different lipases employing vinyl acetate as acetyl source and this job was best done by Lipase PS.

The authors have realized resolution of Vasicinone and acetyl Vasicinone by biocatalysts for the first time.

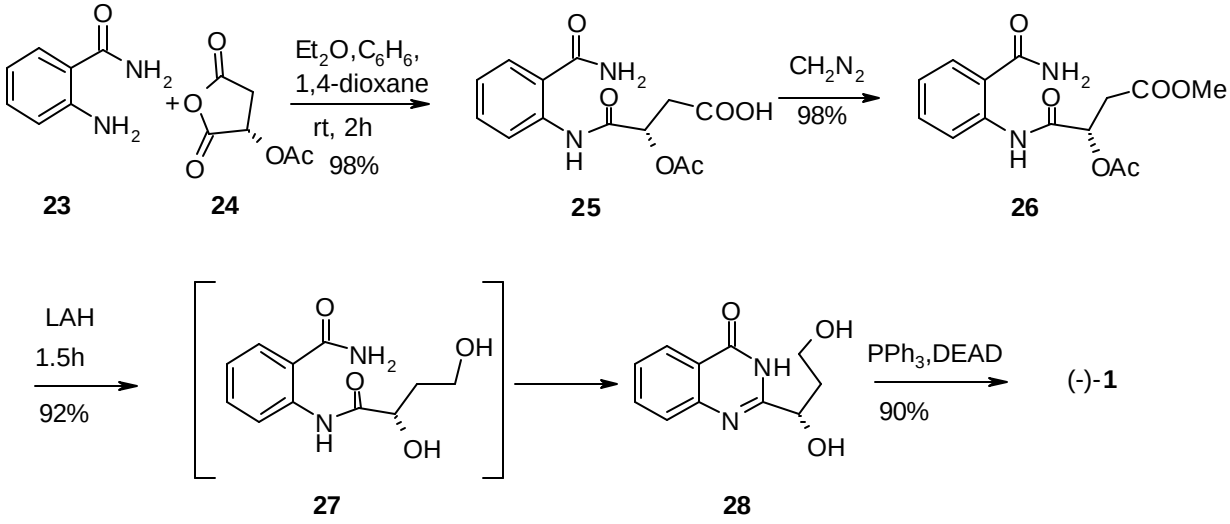
Scheme 8: Kamal *et al*, *J.Org.Chem.*, **2001**, *66*, 997



Argade's Approach [191] (Scheme 9, 2001)

Central to their approach is the 100% regioselective opening of optically pure cyclic anhydride **24** with anthranilamide **23**, which resulted in the formation of amide **25**. Reduction of corresponding ester **26** with LAH resulted in the alcohol **27** which underwent concomitant quinazolinone formation. Mitsunobu cyclization of the intermediate **28** completes the synthesis of (-) Vasicinone.

Scheme 9: Argade *et al*, *J. Org. Chem.*, **2001**, *66*, 9038-9040.



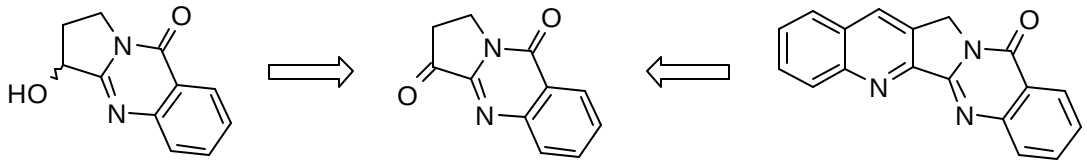
2.2.5 Present Work

Vasicinone attracted our attention not only due to its impressive biologically activity but also as a precursor of Luotonin A. (From the discussion of synthesis of Luotonin A (sec-1) it is evident that except Ganesan's approach[192] which involves annulation of DE-rings on to preformed ABC –unit, rest other three syntheses aim at the annulation of AB-rings on to either Vasicinone **1**[193] or dione **29**, [194] oxidized derivative of the Vasicinone, which have been obtained from deoxyVasicinone by adapting multistep sequences. The classical oxidation of Vasicinone failed to give the dione **29** and hence attempts were aimed at dione **29** from the deoxyVasicinone.

It is also clear from the above discussion that there is no synthetic strategy developed which involves the installation of the hydroxy group of Vasicinone *via* ketone functionality.

A prochiral ketone functional group placed on the pyrroloquinazolinone would act as a handle for *rac*-Vasicinone synthesis by simple reduction, (-) or (+) Vasicinone by chiral reduction as well as to Luotonin A by Friedlander condensation with amino benzaldehyde as shown in our retrosynthetic analysis (*Scheme 10*) and thus developing a synthetic strategy for the dione would be a convergent synthesis of these two alkaloids.

Scheme 10: Retrosynthetic analysis

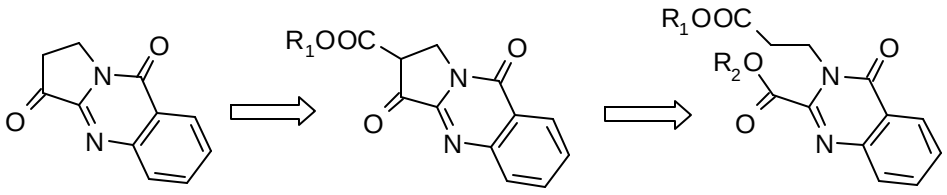


Vasicinone (**1**) **29** Luotonin A

2.2.6 Results and Discussion

We envisioned β-ketoester **30** as a key intermediate, which could be obtained by the Dieckmann condensation of the diester **31**, to furnish dione **29** upon decarboxylation as shown in *Scheme 11*.

Scheme 11:

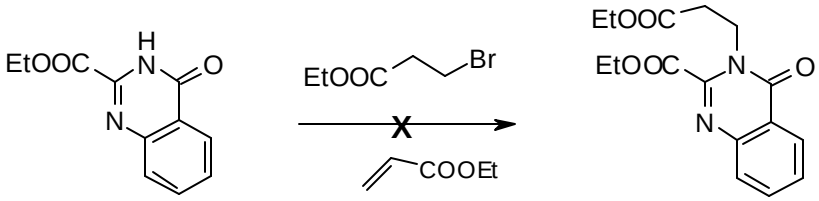


29 **30** **31**

Diester was planned to be obtained by the alkylation of the 2-carbethoxy quinazolinone with the bromopropionate despite of knowing the reluctance of **32** to undergo the same[195] only for the reason that alkylation of **32** was achieved with propargyl bromide. (See section I)

Various bases K_2CO_3 / Acetone, K_2CO_3 / DMF, NaH / THF, NaOMe / Methanol, t-BuOK / THF were tried unsuccessfully. Even Michael addition to ethyl acrylate failed to give the desired compound.

Scheme 12:



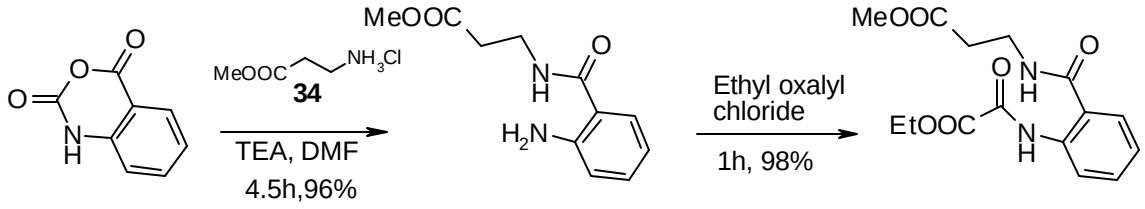
32 **31**

We had to differ in our plan, in the sense form the N-C bond before hand and then form the quinazolinone ring.

Thus we resorted to make the amide by using isatoic anhydride chemistry.[196] Among its many versatile applications in organic synthesis isatoic anhydride has been used a source of the amino benzoyl moiety in the preparation of anthranilamide analogues by being susceptible to nucleophillic attack by amines, normally at the acid carbonyl.

Thus the treatment of isatoic anhydride[197] **33** with methyl β-alanate hydrochloride in DMF in presence DMAP (cat)/ Et_3N furnished amine **35** in 96% yield. ^{1}H NMR spectrum of **35** showed the presence of a quartet at δ 3.68 (2H) a triplet at δ 2.04 (2H) and singlet at δ 3.7 (3H) confirming the NH$\underline{CH_2}\underline{CH_2}COO\underline{CH_3}$ grouping in the molecule apart from the aromatic protons.

Scheme 13:



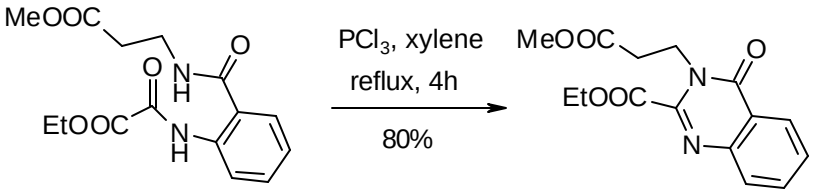
33 **35** **36**

Amine **35** was condensed with ethyl oxalyl chloride to obtain the peptide **36** in almost quantitative yield.

^{1}H NMR spectrum of **36** showed a quartet at δ 4.25 and triplet at δ 1.46 indicative of the incorporation of COO$\underline{CH_2CH_3}$ apart from the other protons. A broad singlet at δ 12.77 was assigned to the oxalylamide NH .^{13}C NMR spectrum of **36** showed the presence of four carbonyls at δ 172.95 (C), 168.39 (C), 160.56 (C), & 154.76 (C)) confirming the peptide formation. Mass spectrum showed the m/z peak at 322.

Having obtained the desired peptide we turned our attention to form the quinazolinone ring. Literature survey revealed that such dehydration of anthranilamide to quinazolinone could be achieved with dehydrating agents.[198] Thus the cyclodehydration of the peptide **36** was efficiently achieved with PCl_3 in refluxing xylene (*Scheme 14*).

Scheme 14:



36 **31**

^{1}H NMR spectrum of **31** showed characteristic quinazolinone periproton at δ 8.25 as a doublet, others as multiplets at δ 7.52 (2H) and 7.48 (1H). The amide NH proton was absent. ^{13}C spectrum showed three carbonyls at δ171.3(C), 161.48(C), 161.13(C)) and quinazolinone quartenary carbon at δ 134 formed at the expense of amide carbonyl. The mass spectrum showed the molecular ion peak at 304, thus indicating the loss of water *i.e* cyclodehydration.

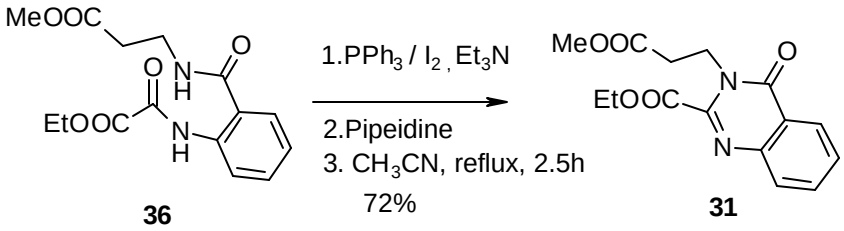
Since the first two steps involve peptide couplings, the reaction for which solid-phase synthesis was first developed[199] and which proceeds in almost quantitative yield for a variety of amino acids we reasoned if we can effect the quinazolinone formation under these mild conditions our route would be amenable to solid phase synthesis as the Dieckmann condensation

of diesters has already been reported on solid phase[200] with added advantage of cyclo release upon grafting the oxalyl ester part on to resin.

At this stage we became aware of the methodology developed Ganesan *et al* for the quinazolinone formation, which was directly, adapted on solid phase synthesis of the quinazolinone alkaloids.[201]

Thus treatment of peptide **36** with triphenyl phosphine / iodine / Et_3N followed by treatment with piperidine and heating thus formed amidine in acetonitrile furnished quinazolinone diester **31** which attests to the feasibility of the same on solidphsae.

Scheme 15:

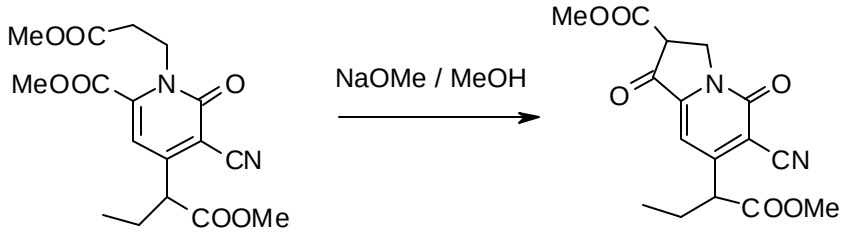


36 **31**

With the suitable diester **31** in hand, stage was reached to ascertain the proposed strategy *i.e* Dieckmann condensation for the construction of β-keto ester.

Quick *et al*. employed NaOMe as a base in Dieckmann condensation of diester of pyridone.[202]

Scheme 16:

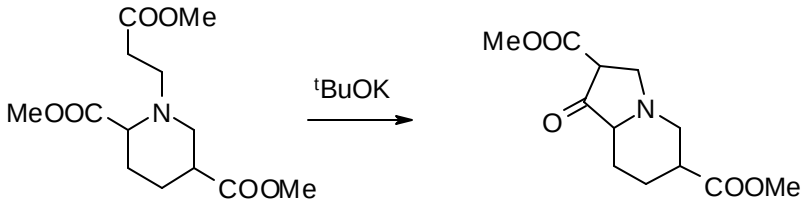


37 **38**

Surprisingly the treatment of the diester under above conditions did not result in the formation of expected compound, but the intractable mass.

In yet another report[203] ^tBuOK has been employed for the Dieckmann condensation of the piperidone diester.

Scheme 17:

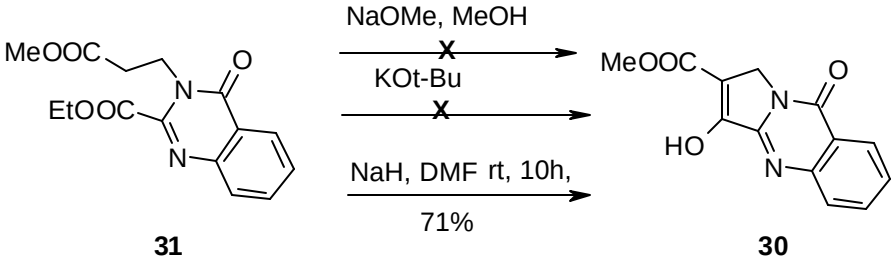


39 **40**

The attempted condensation of **31** with ^{t}BuOK did not proceed to give the cyclized compound.

After extensive experimentation with the combinations of various solvents and bases, NaH/DMF was found be the suitable choice and it afforded β-keto ester **30** in 71% yield.

Scheme 18:

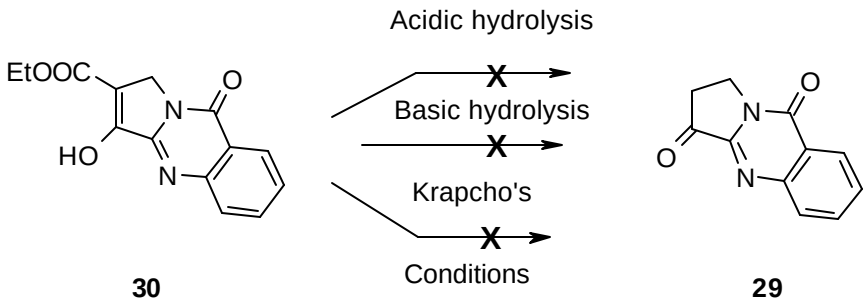


31 **30**

^{1}H NMR spectrum showed that the product **30** exists mainly as the enol form. ^{13}C NMR spectrum showed one methylene at δ 32.73 and confirms the presence of the enol form. Mass spectrum showed the molecular ion peak at 272 confirming the assigned structure.

Initial efforts of effecting decarboxylation of β-keto ester **30** under milder conditions were frustrating. The attempted hydrolysis of the ester either with mild acid or mild basic conditions resulted only in the recovery of the ester. Even the Krapcho's[204] conditions employed various salts NaCl; $MgCl_2$ & LiCl in combinations with either DMF or DMSO did not effect the decarboxylation (*Scheme19*).

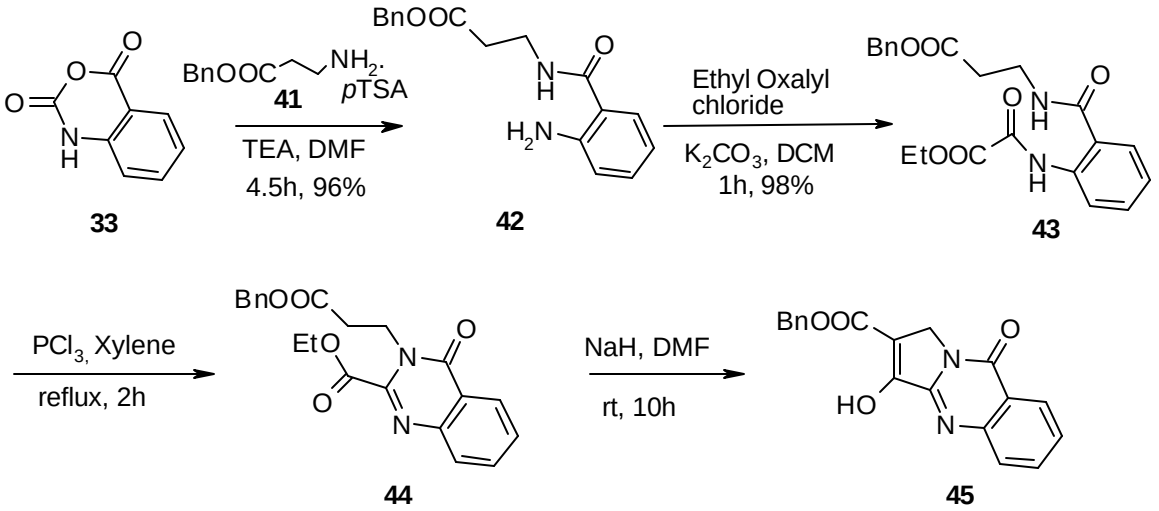
Scheme 19:



30 **29**

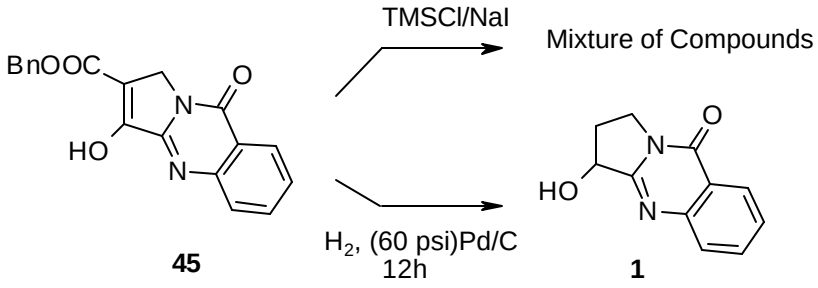
At this stage we reconsidered to change the ester functionality's nature from ethyl to benzyl, which could be removed either with TMSI or hydrogenation conditions. Thus starting with benzyl β-alanate **41** and repeating the whole sequence under essentially same conditions furnished benzyl-β-ketoester **45,** notably with better yields in Dieckmann condensation than its methyl counter part (*Scheme 20*).

Scheme 20:



Treatment of ester **45** with TMSCl / NaI did not effect the debenzylation as anticipated. Hydrogenation with 10% Pd/C under hydrogen atmosphere (60 psi) resulted in the smooth debenzylation (*Scheme 21*).

Scheme 21:

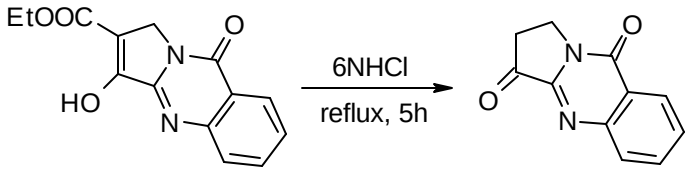


The ^{1}H NMR spectrum of the product did not show peaks corresponding to expected dione, but the pattern of Vasicinone .We reasoned that product obtained was the result of the tandem sequence of debenzylation of the ester, decarboxylation and reduction of the thus obtained ketone to Vasicinone.

Though we achieved synthesis of Vasicinone, the objective behind initiation of the work *i.e* dione **29** formation was to be addressed yet.

After having tried all the possible ways we were forced to attempt the decarboxylation under harsh conditions. Gratifyingly refluxing the β-ketoester **30** with 6N HCl solution resulted in the formation of dione **29** effectively.

Scheme 22:

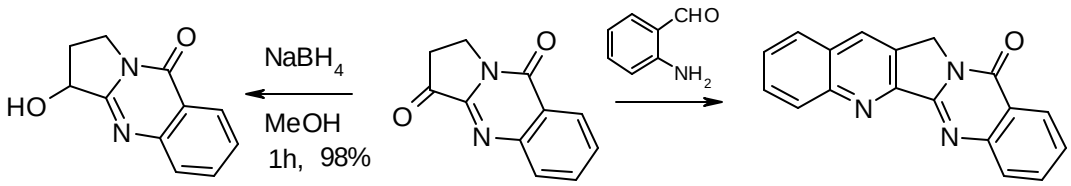


30 **29**

^{1}H NMR spectrum of **29** showed the presence of two triplets at δ 4.41 and 3.05 integrating for two protons each and were assigned to the pyrrolidone methylenes. Other protons were in accordance with the reported values. And the ^{13}C NMR spectrum showed the presence of carbonyl at δ198 along with that of amide carbonyl appearing at δ 160 and the two methylene carbons at δ 79.2 and 32.7. IR spectrum showed absorption at 1746 cm^{-1} and 1658 cm^{-1}. Further evidence of the structure came from Mass spectroscopy, which showed m/z peak at 200.

$NaBH_4$ reduction of dione afforded Vasicinone (**1**) in quantitative yield. The spectral properties were in complete agreement with the reported. Friedlander condensation of dione **29** with the aminobenzaldehyde afforded Luotonin A (*Scheme 22*).

Scheme 23:



Vasicinone **29** Luotonin A

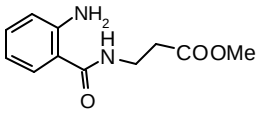
Conclusions:

In summary, a novel and efficient entry to pyrroloquinazolinone alkaloids *via* dione, which would be amenable to access the analogues, has been developed. The synthetic strategy has intrinsic flexibility and the robustness for the solid phase synthesis of the title compounds.

Prochiral ketone reduction would lead to chiral Vasicinone, with vast array of reagents available. Asymmetric reduction of ketone with chiral reducing agent is general method for the preparation of optically active secondary alcohols. Known industrial methods involve reduction by chiral hydride reagents such as Corey's oxazaborolidine, Yamaguchi-Mosher reagent, $LiAlH_4$ coordinated by BINAL-H or Chirald, Mukaiyama's reduction of ketones by $NaBH_4$ in the presence of chiral Co (II) complexes, or Brown's chiral boranes such as Alpine-Borane. Recently, asymmetric hydrogenation of ketones has been developed using ruthenium catalysts coordinated by chiral diamines or chiral amino alcohols, which shows the possibility of obtaining the Vasicinone from the benzyl ester in the tandem sequence by employing this system in place of Pd/C in hydrogenation.

2.2.7 Experimental:

1. 3-(2-Amino-benzylamino)-propionic acid methyl ester [35]



35

To a mixture of β-alanine methyl ester hydrochloride **34** (1.38 g, 10 mmol) and TEA (2.99 g, 15.6 mmol) in DMF (70 mL) and catalytic amount of DMAP was added isatoic anhydride **33** (1.82 g, 13.2 mmol) in 10 portions over 15 min at room temperature with stirring. After being stirred for an additional 4h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 / aqueous Na_2CO_3, extracted with CH_2Cl_2 (3×50mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was pure enough and taken as such for the next step.

Molecular Formula : $C_{11}H_{14}N_2O_3$, 222

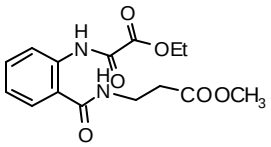
Yield : 2.13 g, 96%

IR ($CHCl_3$) : 1747, 1645, 1611, 1582 cm^{-1}

^{1}H NMR (200MHz) : δ: 7.33 (d, *J* = 7.82 Hz, 1H), 7.20 (t, *J* = 8.3Hz, 1H), 6.79 (br s, 1H) 6.69-6.64 (m, 2H), 5.54 (br s, 1H), 3.70 (s, 3H), 3.65 (t, *J* = 5.86 Hz, 2H), 2.64 (t, *J* = 5.86Hz, 2H);

^{13}C NMR (50MHz) : δ: 172.91 (C), 169.31 (C), 148.73 (C), 132.11 (CH), 127.37 (CH), 117.04 (CH), 116.27 (CH), 115.72 (C), 51.61(CH_3), 35 (CH_2), 33.75 (CH_2),

2. 3-[2-(Ethoxyalyl-amino)-benzoylamino]-propionic acid methyl ester [36]



36

A solution of compound **35** (2.22 g, 10 mmol) in dry CH_2Cl_2 (30 mL) was added Ethyl oxalyl chloride (1.762 g, 13 mmol). The mixture was stirred for 5 min, followed by addition of aqueous Na_2CO_3 (1 M, 20 mL, 20 mmol). After being stirred for a total of 1 h, the mixture was extracted with CH_2Cl_2 (3×25mL). The combined organic extract was treated with $NaHCO_3$ and

dried (Na_2SO_4), filtered, and concentrated to give **36** as a white solid which was pure enough for further use.

Molecular formula : $C_{15}H_{18}N_2O_6$, 322

Yield : 3.191 g, 98%

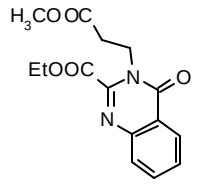
IR ($CHCl_3$) : 3364, 1724, 1642, 1588 cm^{-1}

^{1}H NMR (200MHz) : δ: 12.77 (br s, 1H), 8.55 (d, *J* = 8.8 Hz, 1H), 7.53 (m, 2H), 7.14 (m, 2H), 4.37 (q, *J* = 7.32 Hz, 2H,), 3.72 (t, *J* = 5.46 Hz, 2H), 3.70 (s, 3H), 2.66 (t, *J*=5.46 Hz, 2H), 1.44 (t, *J* = 7.32, 3H);

^{13}C NMR (200MHz) : δ: 172.95 (C), 168.39 (C), 160.56 (C), 154.76 (C), 138.07 (C), 132.66 (CH), 127.19 (CH), 124.19 (CH), 124.17 (CH), 121.09 (CH), 63.41 (CH_2), 51.41 (CH_3), 35.38 (CH_2), 33.49 (CH_2), 13.97 (CH_3);

Mass (*m/z)* : 322 (M^+, 10), 291(15), 249(40), 217 (22), 146 (100), 120 (22), 90 (19)

3. 3-(2-Ethoxycarbonyl-ethyl)-4-oxo-3, 4-dihydro-quinazoline-2-carboxylicacid methyl ester [31]



31

Method A: To a pre cooled (0-5^{o}C) solution of compound **36** (1.61 g, 5 mmol) in dry xylene (30 mL) was added PCl_3 (1.35g, 10mmol) dropwise through a dropping funnel over a period of 30 minutes The reaction mixture was stirred at rt for 1h and then refluxed for 2h. After the reaction was completed (TLC) the solvent was distilled off under reduced pressure and the residue was dissolved in dichloromethane and washed with aqueous $NaHCO_3$ (2×50mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **31** as a white solid. The residue was pure enough for further use.

Method B: To a solution of compound **36** (0.091g, 0.284 mmol) in CH_2Cl_2 (15 mL) were added Ph_3P (0.370 g, 1.41 mmol), I_2 (0.352 g, 1.39 mmol), and Et_3N (0.50 mL, 2.87 mmol). The reaction mixture was stirred at room temperature for 2.5 h, quenched with aqueous Na_2CO_3, and extracted with CH_2Cl_2 (3x15mL), dried (Na_2SO_4), filtered, and concentrated. Residue was treated with CH_2Cl_2 (4.0 mL) and piperidine (1.0 mL) in DCM (4mL) at room temperature for 15

min, followed by solvent evaporation. The vacuum-dried crude residue was dissolved in MeCN (10 mL) and refluxed for 2 h. The reaction mixture was purified by column chromatography to afford **31**.

Molecular formula : $C_{15}H_{16}N_2O_5$, 314

Yield : 1.23g, 80%; 72% (Method B)

M.P. : 182^oC

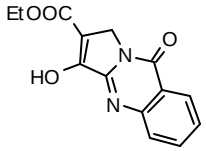
IR ($CHCl_3$) : 1737, 1687, 1590, 1474 cm^{-1}

^{1}H NMR (200 MHz) : δ: 8.23 (d, *J* = 7.8 Hz, 1H), 7.71 (m, 2H), 7.56-7.4 (m, 1H), 4.53(q, *J* = 7.32 Hz, 2H), 4.34 (t, *J* = 7.36 Hz, 2H), 3.63 (s, 3H), 2.88 (t, *J* =7.36 Hz, 2H), 1.42 (t, *J* = 7.32 Hz, 3H);

^{13}C NMR (50MHz) : δ: 171.3 (C), 161.48 (C), 161.13 (C), 146.83 (C), 146.24 (C), 134.70 (CH), 128.49 (CH), 128.12 (CH), 126.80 (CH), 121.83 (C), 63.46 (CH_2), 51.88 (CH_3), 41.74 (CH_2), 32.73 (CH_2), 13.99 (CH_3);

Mass (*m*/*z*) : 314 (M^+, 15), 258 (65), 227 (30), 199 (100), 170 (31), 130 (15), 90 (18)

4. 3,9-Dioxo-1, 2,3,9-tetrahydro-pyrrolo [2,1-b] quinazoline-2-carboxylicacid ethyl ester [30]



30

:

To a solution of NaH (0.288g 50% suspension in mineral oil, 6 mmol, pre washed with pet ether, 2×5mL) in DMF (5 mL) was added diester **31** (1.59g, 5mmol) in DMF (10 mL through syringe, with out allowing the temperature to rise beyond RT. The reaction mixture was stirred at room temperature for 4h. It was quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3×20mL), dried (Na_2SO_4), filtered, and concentrated. The residue was pure enough for the next step.

Molecular formula : $C_{14}H_{12}N_2O_4$, 272

Yield : 0.952g, 70%

M.P. : 199-200^oC;

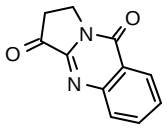
IR ($CHCl_3$) : 1719, 1692, 1642 cm^{-1}.

^{1}H NMR (200MHz) : δ: 8.40 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.3Hz, 1H), 7.82 (t, *J*=8.6Hz, 1H) 7.56 (t, *J* = 8.3Hz, 1H), 4.75 (s, 2H), 4.44 (q, *J* = 7.32, 2H), 1.45 (t, *J*=7.32Hz, 3H)

^{13}C NMR (50MHz)($CDCl_3$+DMSO-d_6): δ: 161.32 (C), 157.38 (C), 152.56 (C), 150.90 (C), 47.18 (C), 132.62 (CH), 125.95 (CH), 125.40 (CH), 124.83 (C), 124.49 (CH), 106.53 (C), 58.80 (CH_2), 44.82 (CH_2), 12.63 (CH_3)

Mass (m/z) : 272 ($M^{+)}$, 226, 199 (100), 170, 145, 130, 119, 102, 89, 75

5. 1,2-Dihydro-pyrrolo [2,1-b] quinazolinone-3, 9-dione [29]



29

A solution of 30 (0.272 g, 1 mmol) was added in 6N HCl (10mL) and the reaction mixture was refluxed for 5 h, after the decarboxylation was completed it was cooled and extracted with CH_2Cl_2 (3×15mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give **29** as a brown solid

Molecular formula : $C_{11}H_8N_2$, 200

Yield : 0.148g**,** 74%

M.P. : 169^{o}C

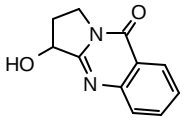
IR ($CHCl_3$) : 1740,1652, 1468, 1386, 1100 cm^{-1}

^{1}H NMR (200 MHz) : δ: 8.37 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J*=8.3Hz, 1H), 7.85 (t, *J*=7.8Hz, 1H), 7.63 (t, *J*=7.8Hz, 1H), 4.41 (t, *J* = 6.6 Hz, 2H), 3.05 (t, *J* = 6.6Hz, 2H)

^{13}C NMR (50MHz) (DMSO-D_6): δ: 197.0 (C), 160.1 (C), 148 (C), 134.5 (CH), 128.7 (C), 128.2 (CH), 125.6 (CH), 121.7 (CH), 79.2 (CH_2), 32.7 (CH_2)

Mass (m/z) : 200(M^+),

6. 3-Hydroxy-2, 3-dihydro-1H-pyrrolo [2,1-b] quinazolin-9-one [1]



1

Method A:

A solution of compound **45** (0.334g, 1mmol) in ethanol was added to the flask containing the Pd/C (10%) in ethanol that was degassed and purged with the hydrogen gas. The reaction mixture was left on parr shaker over night at 60 psi. Then catalyst was filtered from the medium and washed with EtOH (5×10 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography to give **1** as white solid.

Method B:

To a solution of dione **29** (0.300g, 1.5 mmol) in methanol (20 mL) was added $NaBH_4$ (0.114g, 3.2 mmol,) at 0^oC and stirred for 1h at room temperature. After the reaction was completed, methanol was removed under the reduced pressure and the residue quenched with water (2 mL) and the solution was stirred for 5 min. Water (15 mL) and DCM (25 mL) were then added. The layers were separated, and the aqueous layer was extracted with DCM (2×15 mL). The combined organic extracts were washed with brine and then dried (Na_2SO_4). Evaporation and silica gel column chromatography yielded the product **1** as a white solid.

Molecular formula : $C_{11}H_{10}N_2O_2$, 202.

Yield : 0.296g, 98%

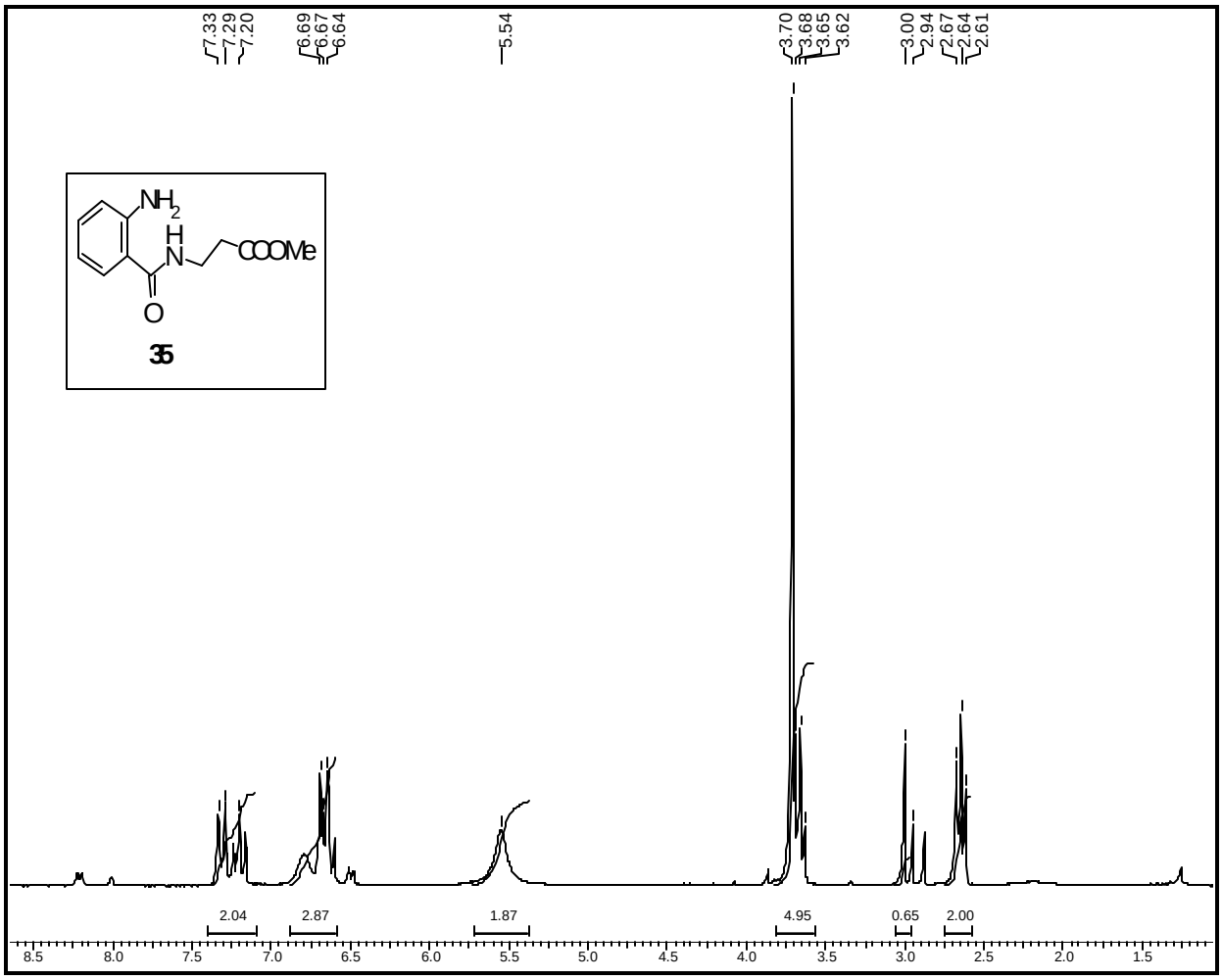
M.P. : 203-204^oC;

IR : 3132, 1688, 1644, 1463 cm^{-1}

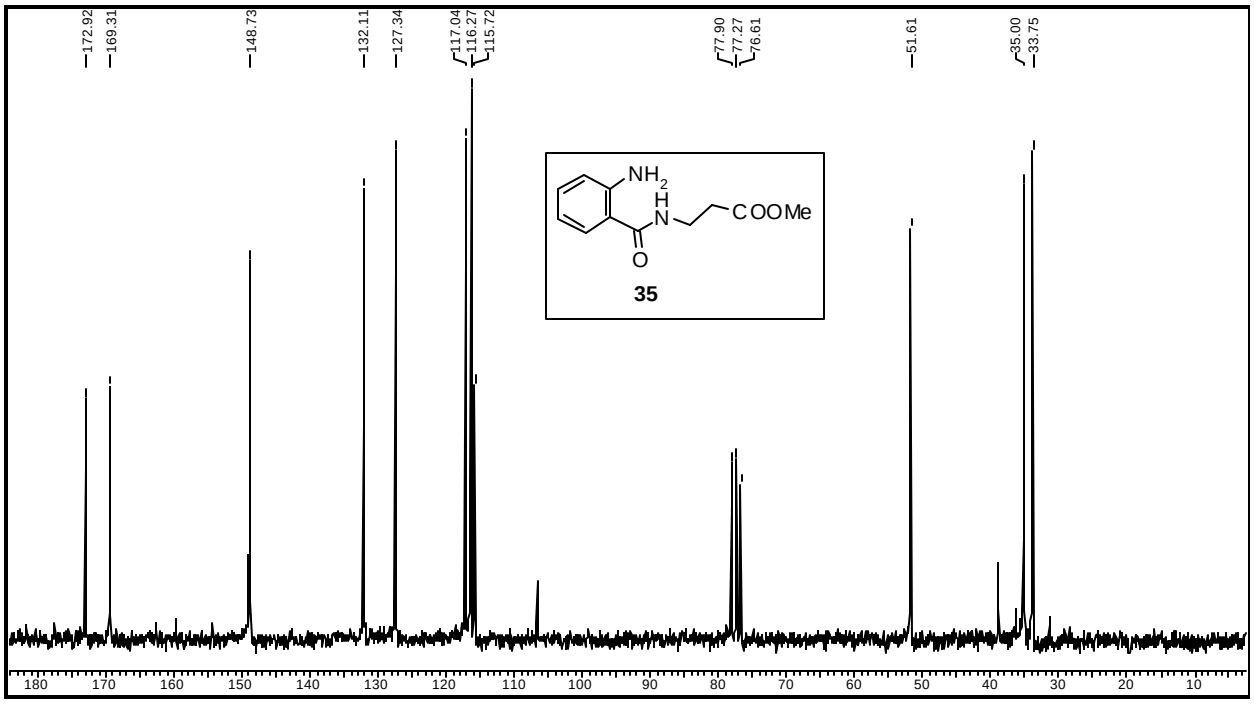
^{1}H NMR (200 MHz) : δ: 8.33 (d, *J* = 8.1 Hz, 1H) 7.76-7.54 (m, 2H), 7.5-7.46 (m, 1H), 5.27 (t, *J* = 6.1 Hz, 1H), 4.3-4.5 (m, 1H), 4.0-4.2 (m, 1H), 2.6-2.72 (m, 1H), 2.27-2.38 (m, 1H);

^{13}C NMR (50 MHz) : δ: 160.6 (C), 160.2 (C), 148. 6(CH), 134.4 (CH), 126.8 (CH), 126.7 (C), 121.1 (CH), 72.01 (CH), 43.5(CH_2), 29.4 (CH_2)

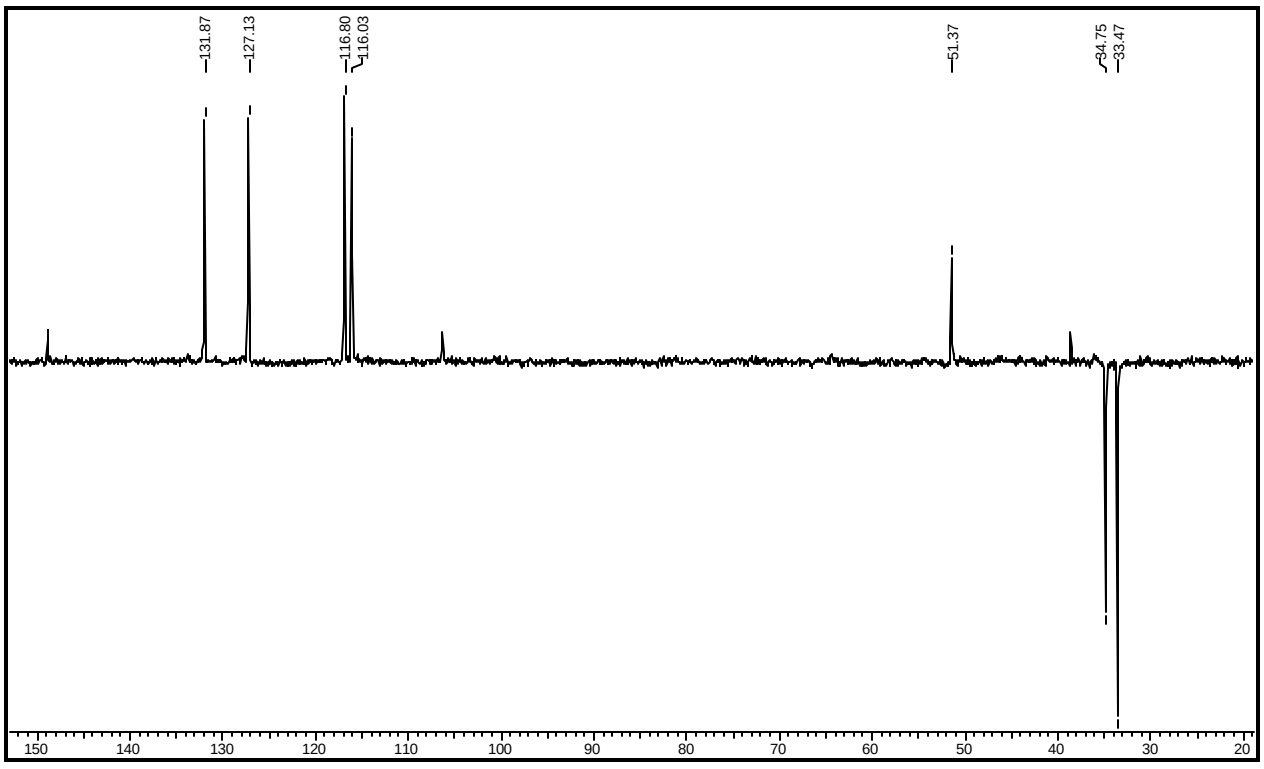
Mass (*m*/*z*): : 202 (M^+), 185,174, 146, 130, 119, 102, 90, 76, 63, 55.

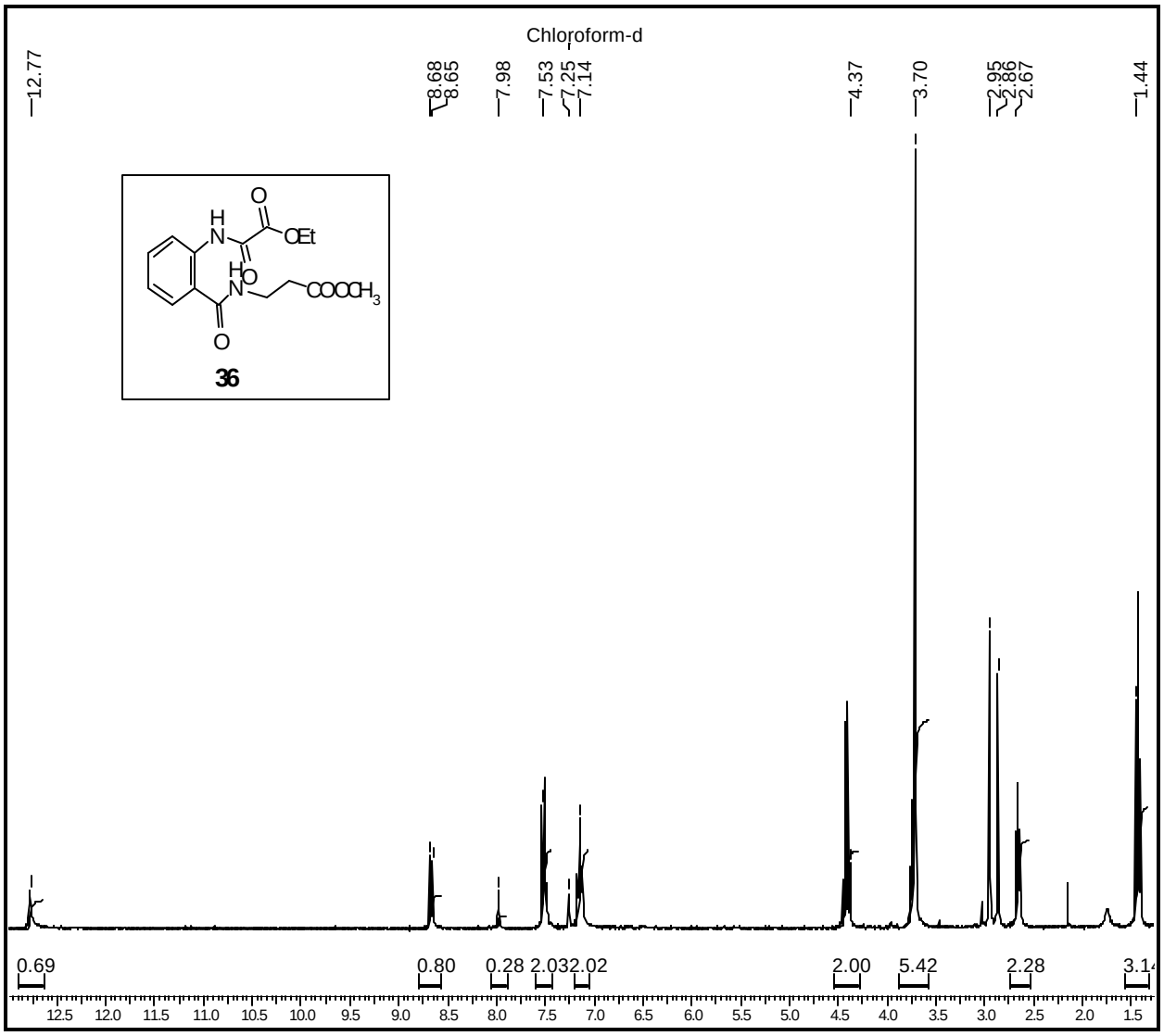


^{1}H NMR spectrum of compound [35] **(200 MHz, $CDCl_3$)**

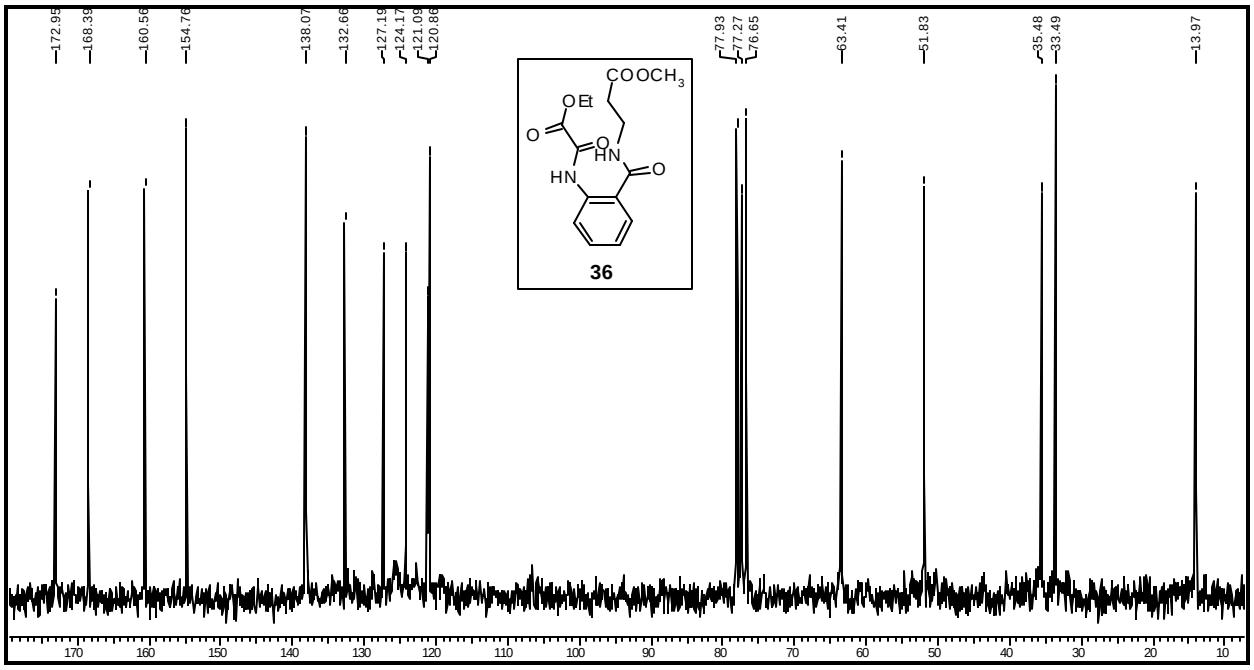


***13 C & NMR spectra of compound* [35] (50 MHz, $CDCl_3$)**

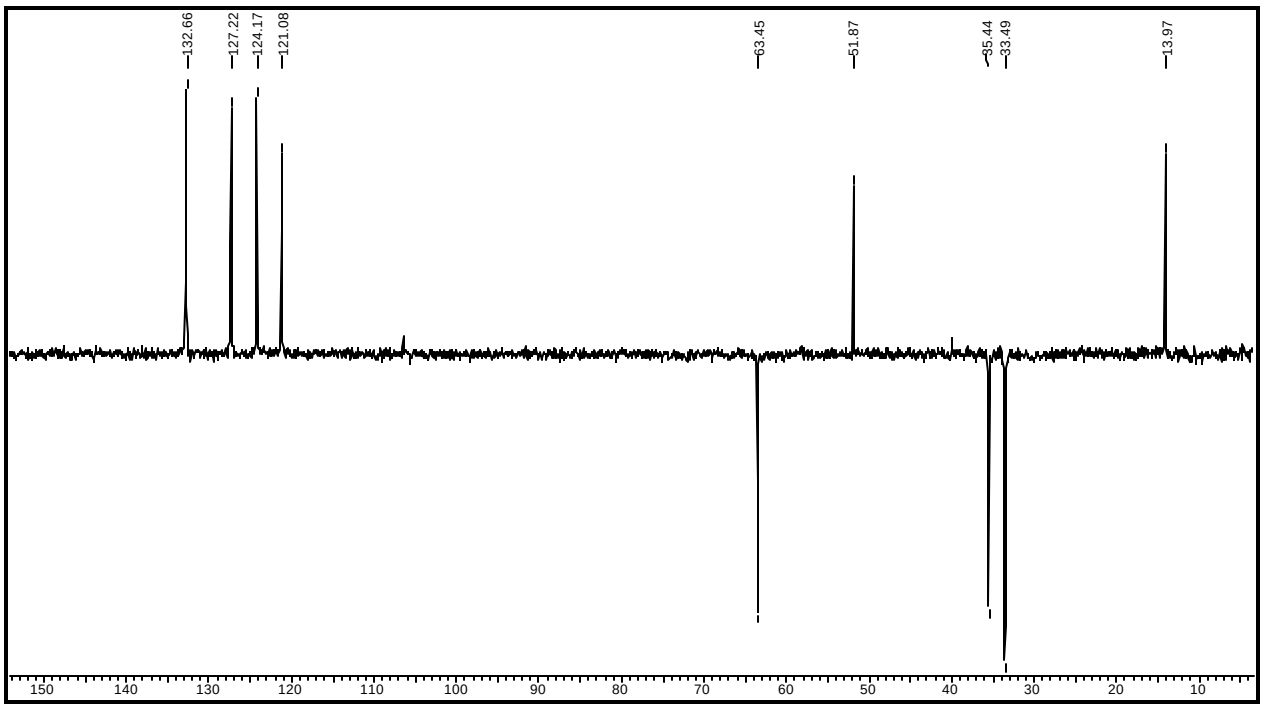


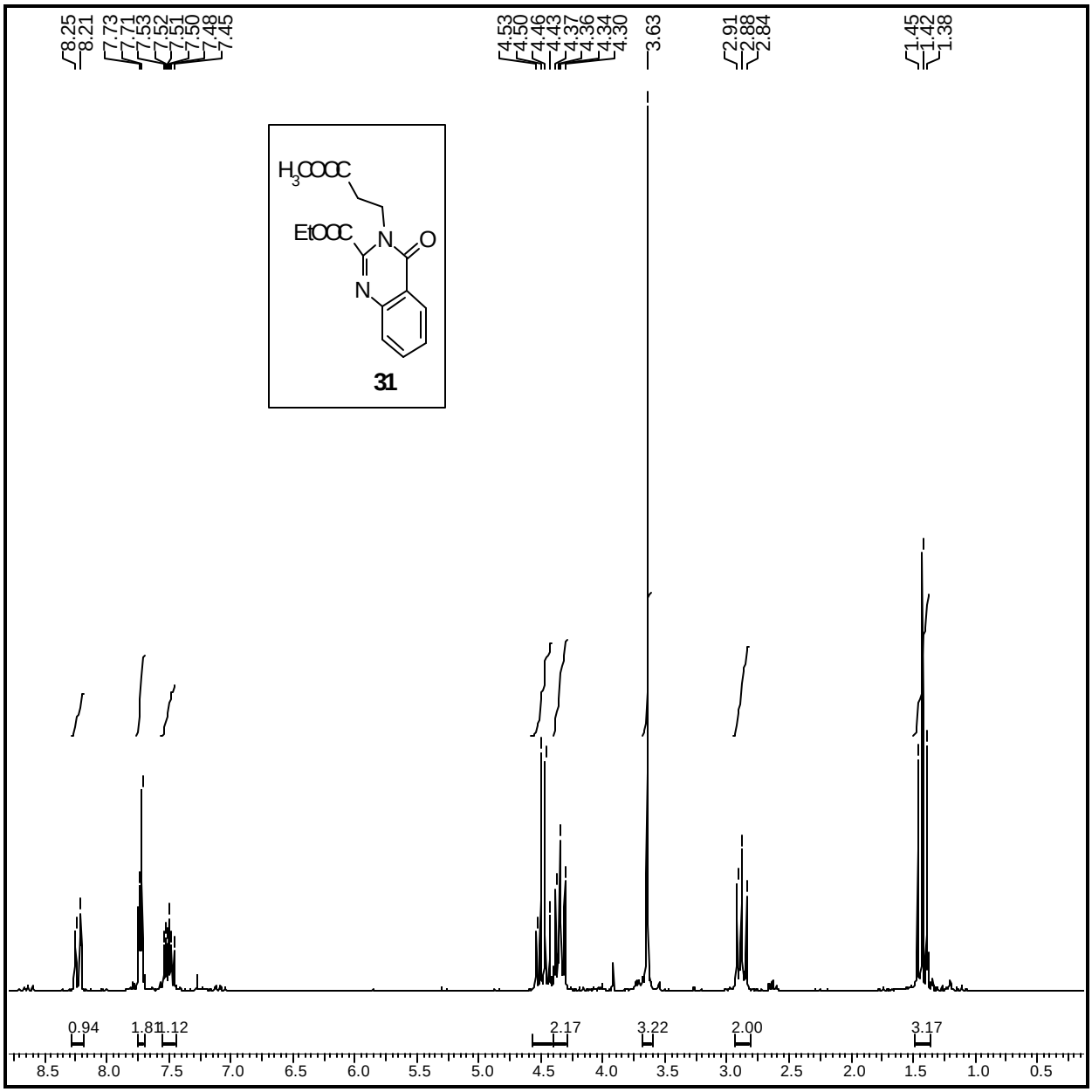


***^{1}H NMR spectrum of compound* [36] (200 MHz, $CDCl_3$)**

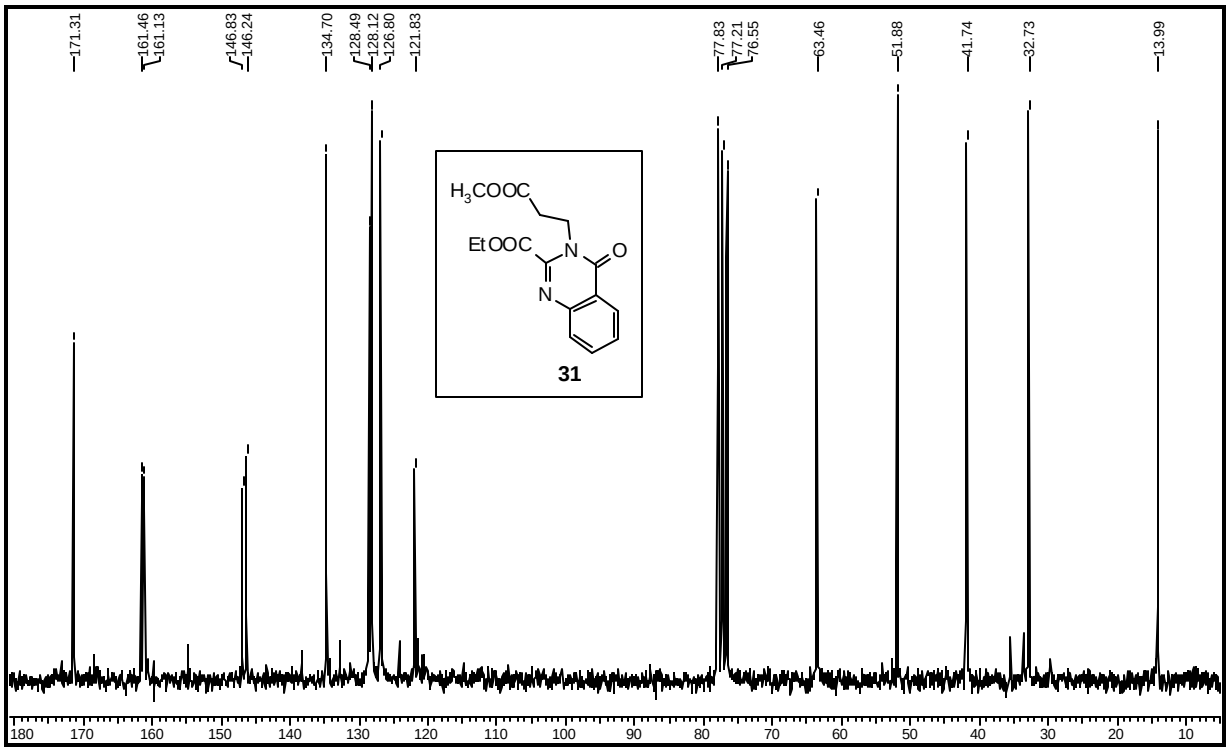


***13 C & DEPT NMR spectra of compound* [36] (50MHz, $CDCl_3$)**

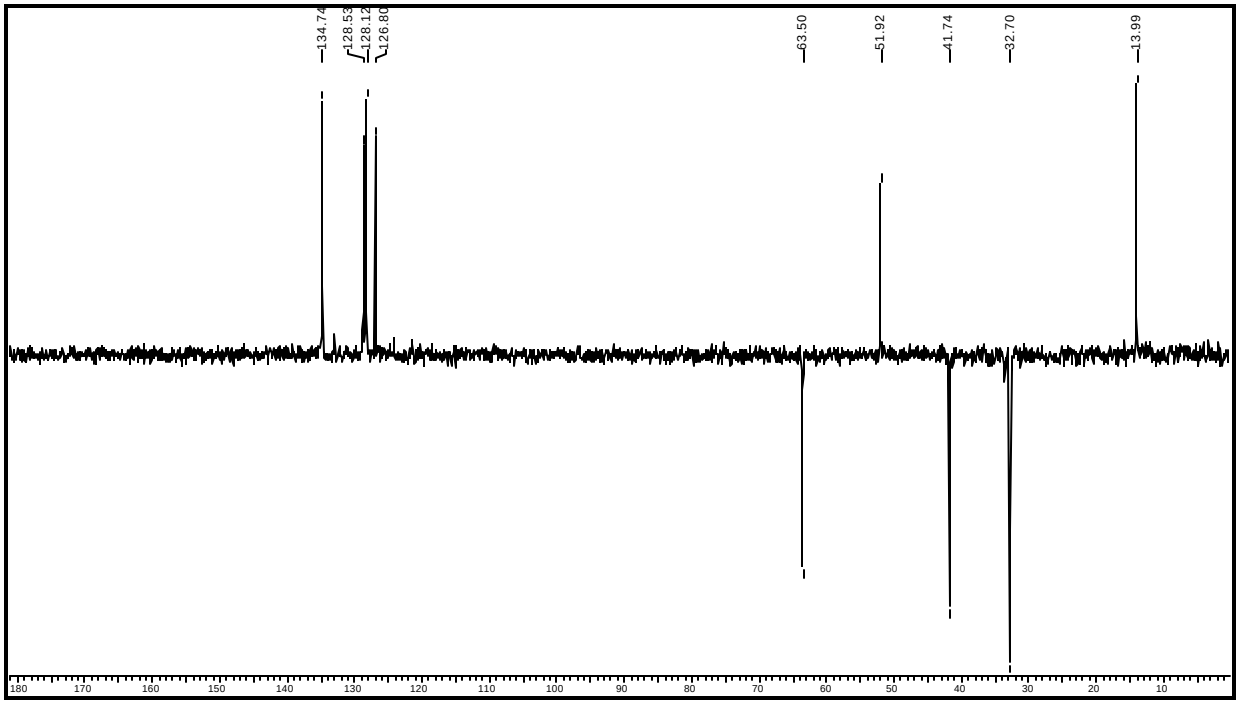


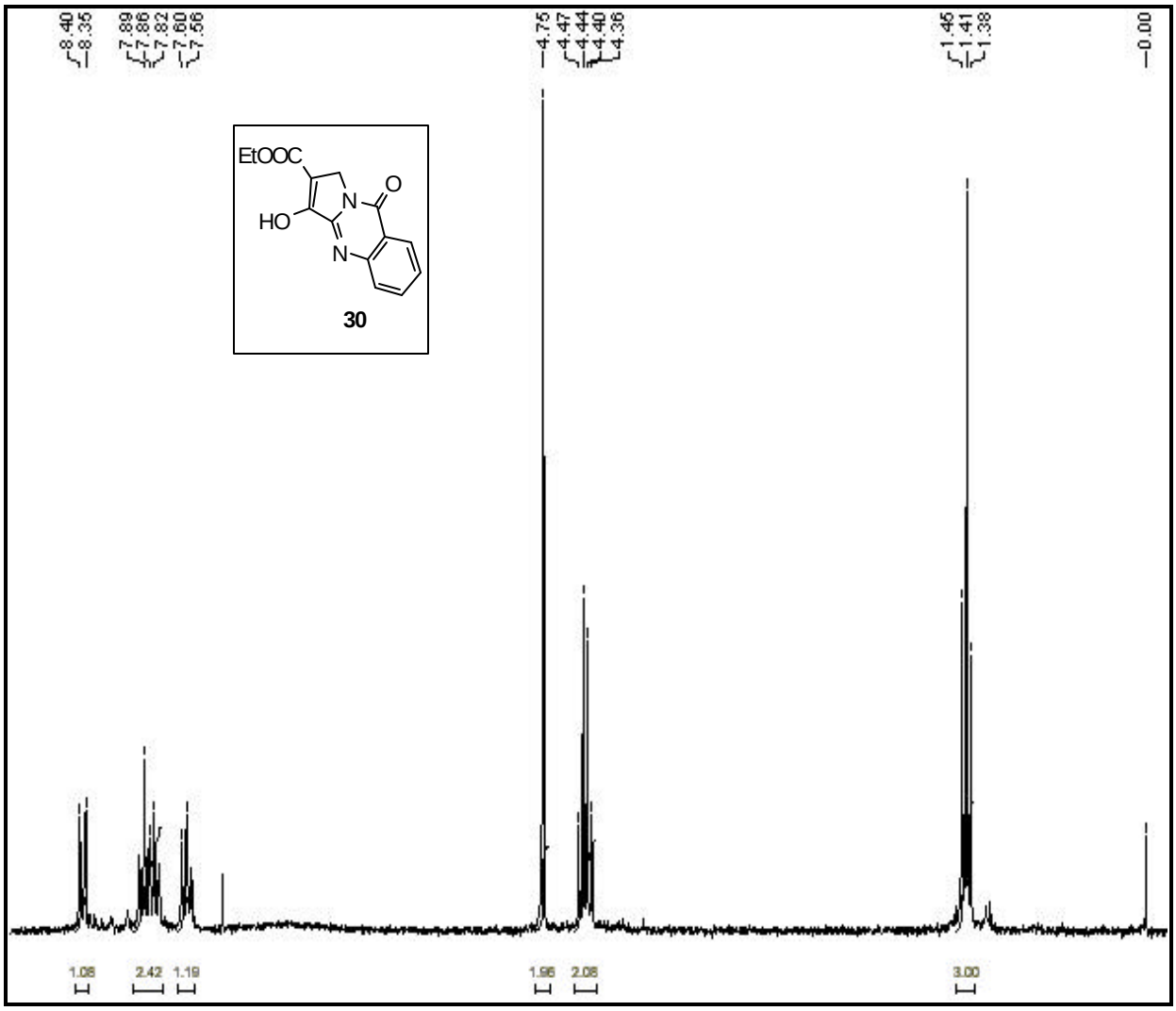


***^{1}H NMR spectrum of compound* [31] (200 MHz, $CDCl_3$)**

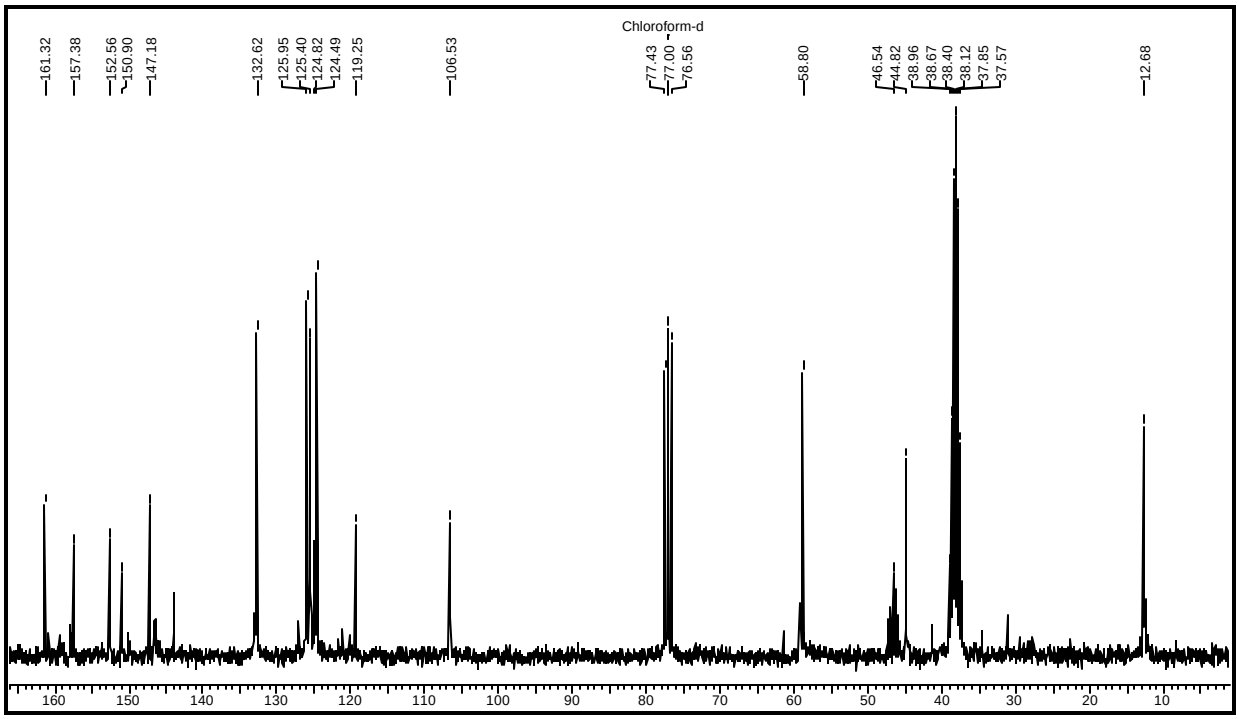


***^{13}C & DEPT NMR spectra of compound* [31] (50MHz, $CDCl_3$)**

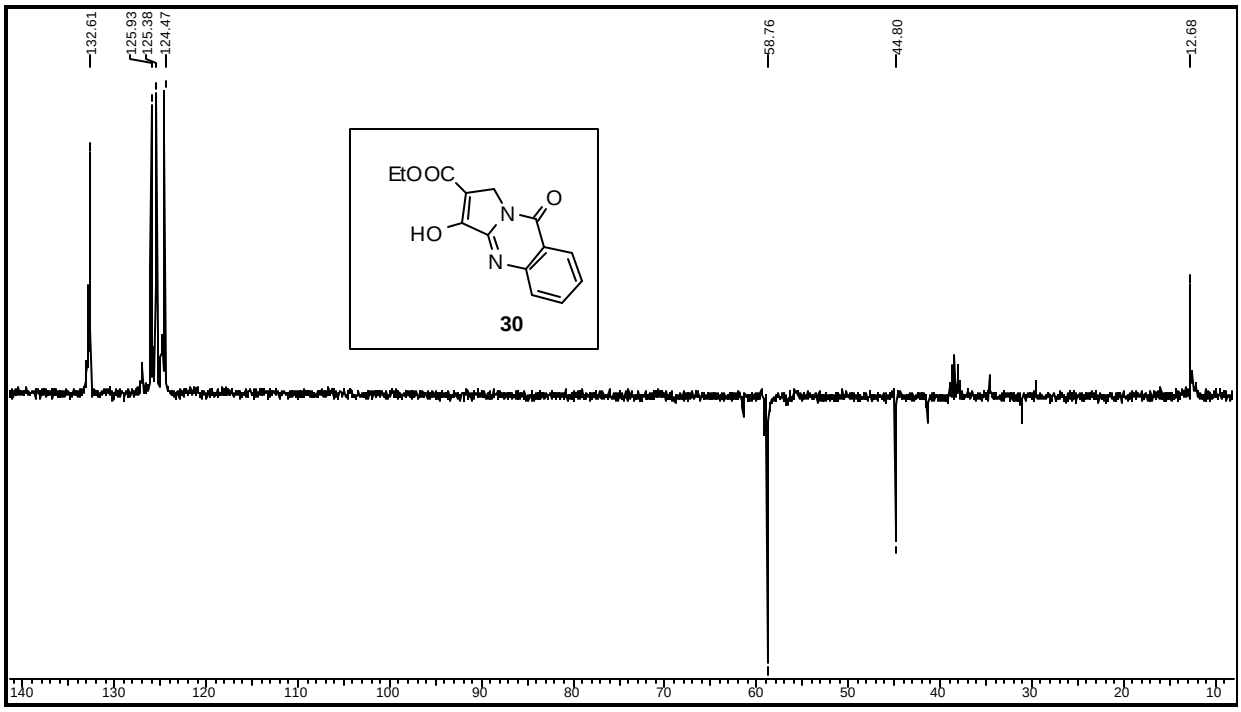


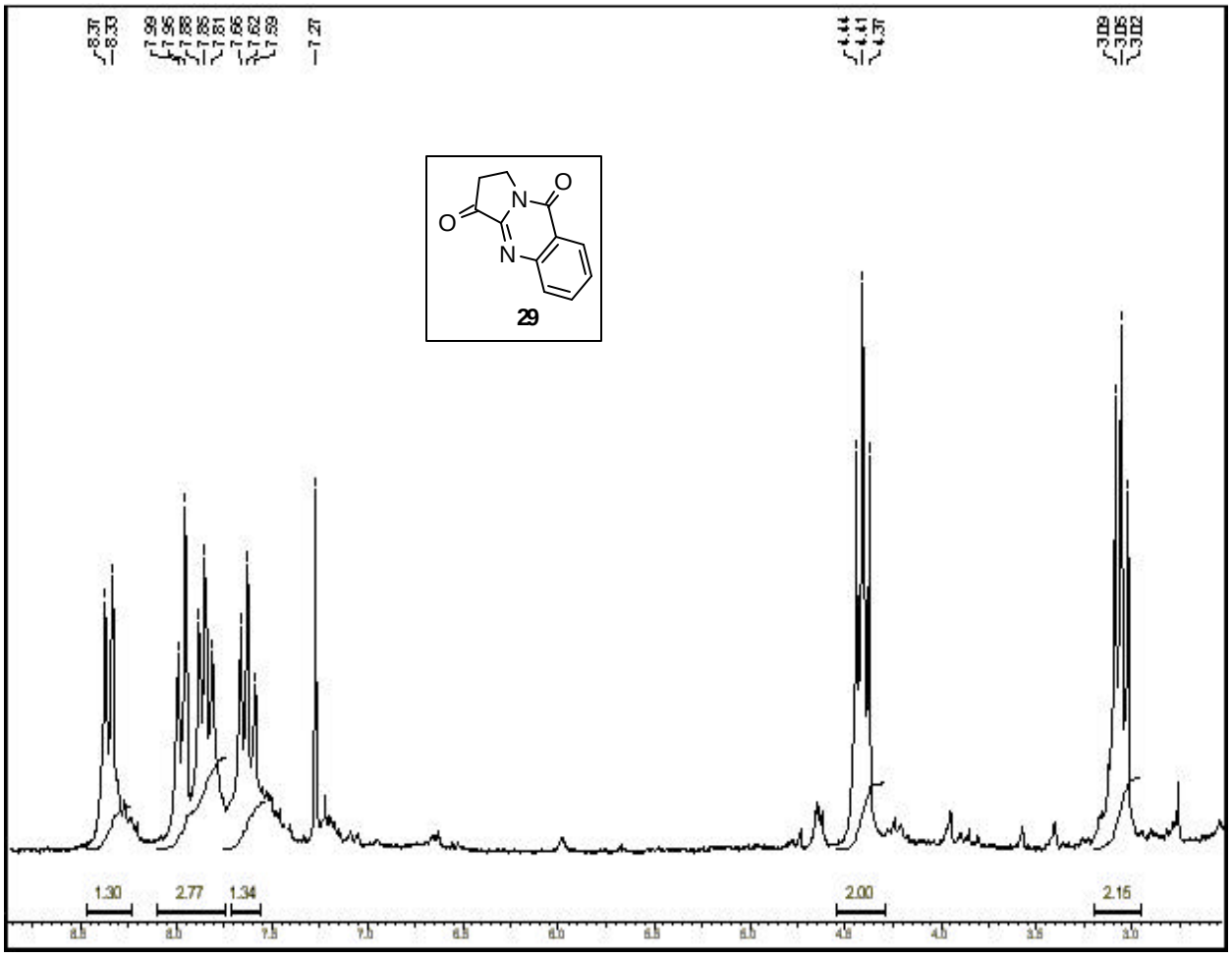


***^{1}H NMR spectrum of compound* [30] (200 MHz, $CDCl_3$)**

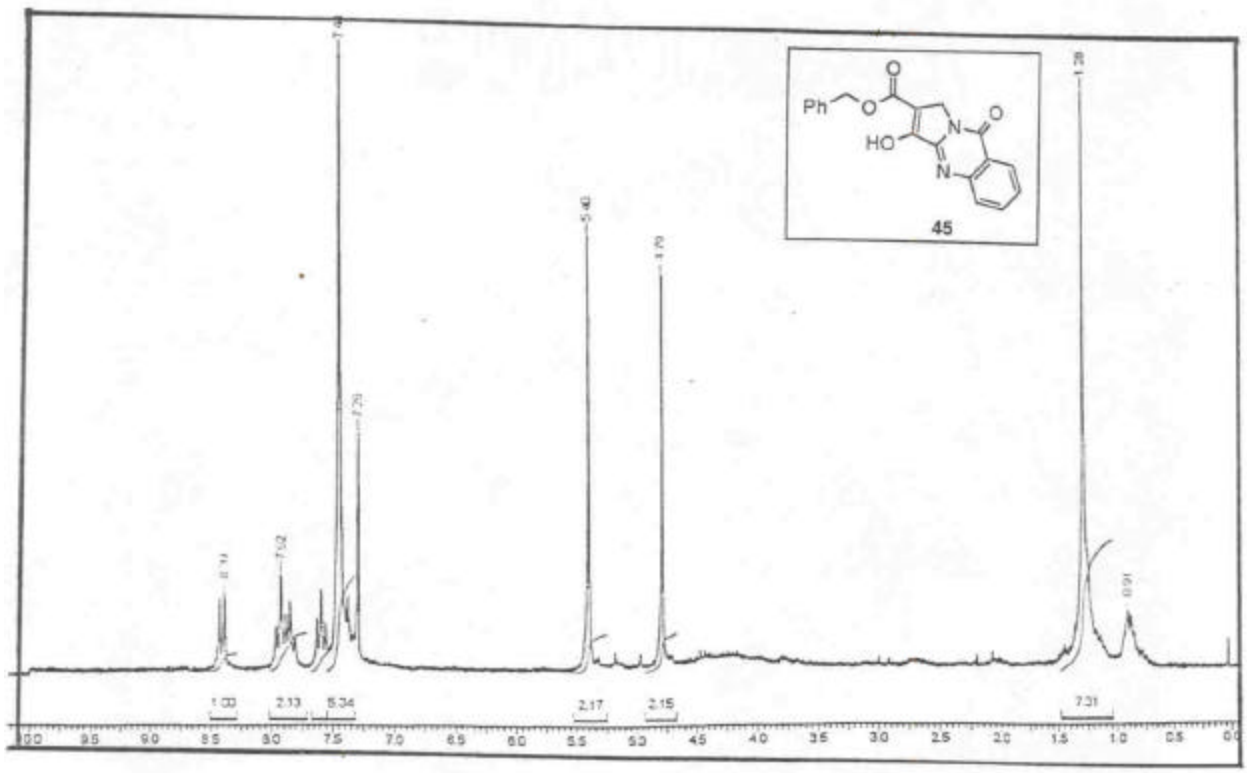


***^{13}C NMR spectrum of compound* [30] (50MHz, $CDCl_3$)**

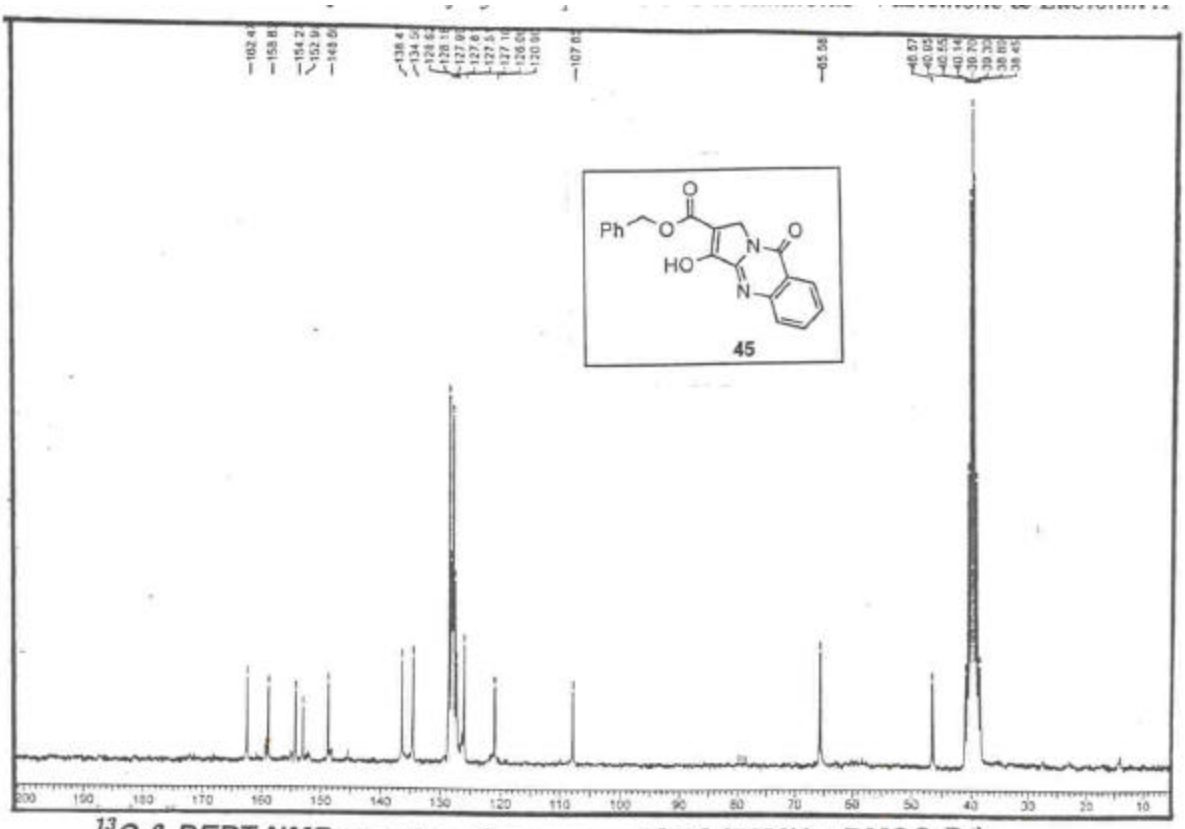




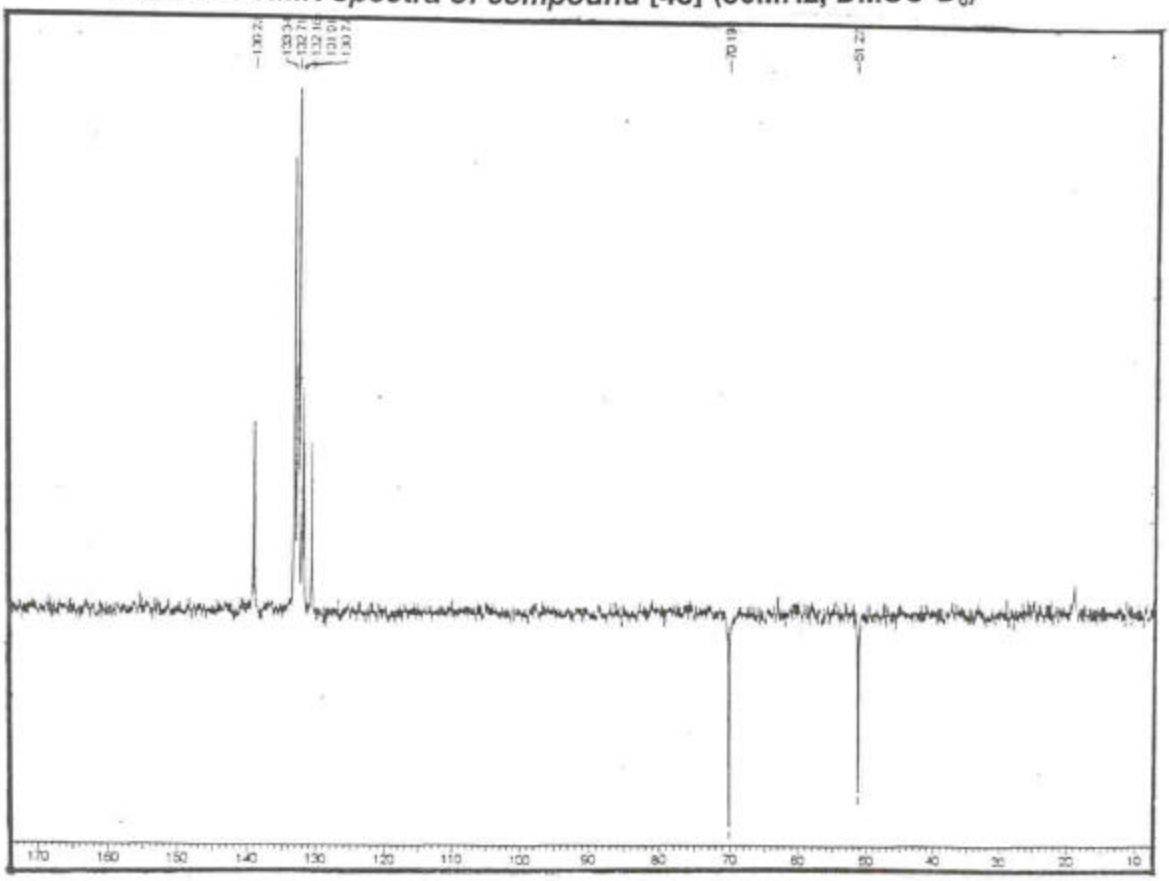
***^{1}H NMR spectrum of compound* [29] (200MHz, $CDCl_3$)**

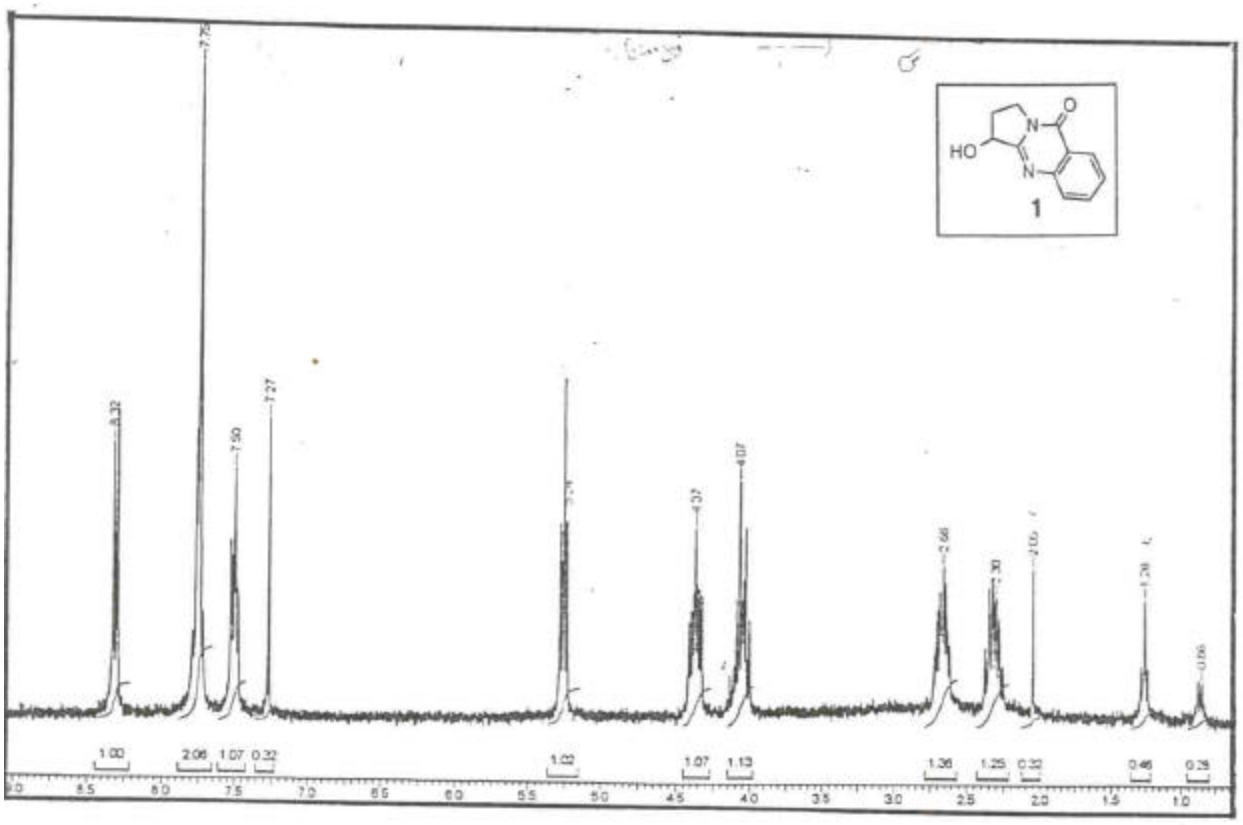


^1H NMR spectrum of compound **[45] (200MHz, $CDCl_3$)**

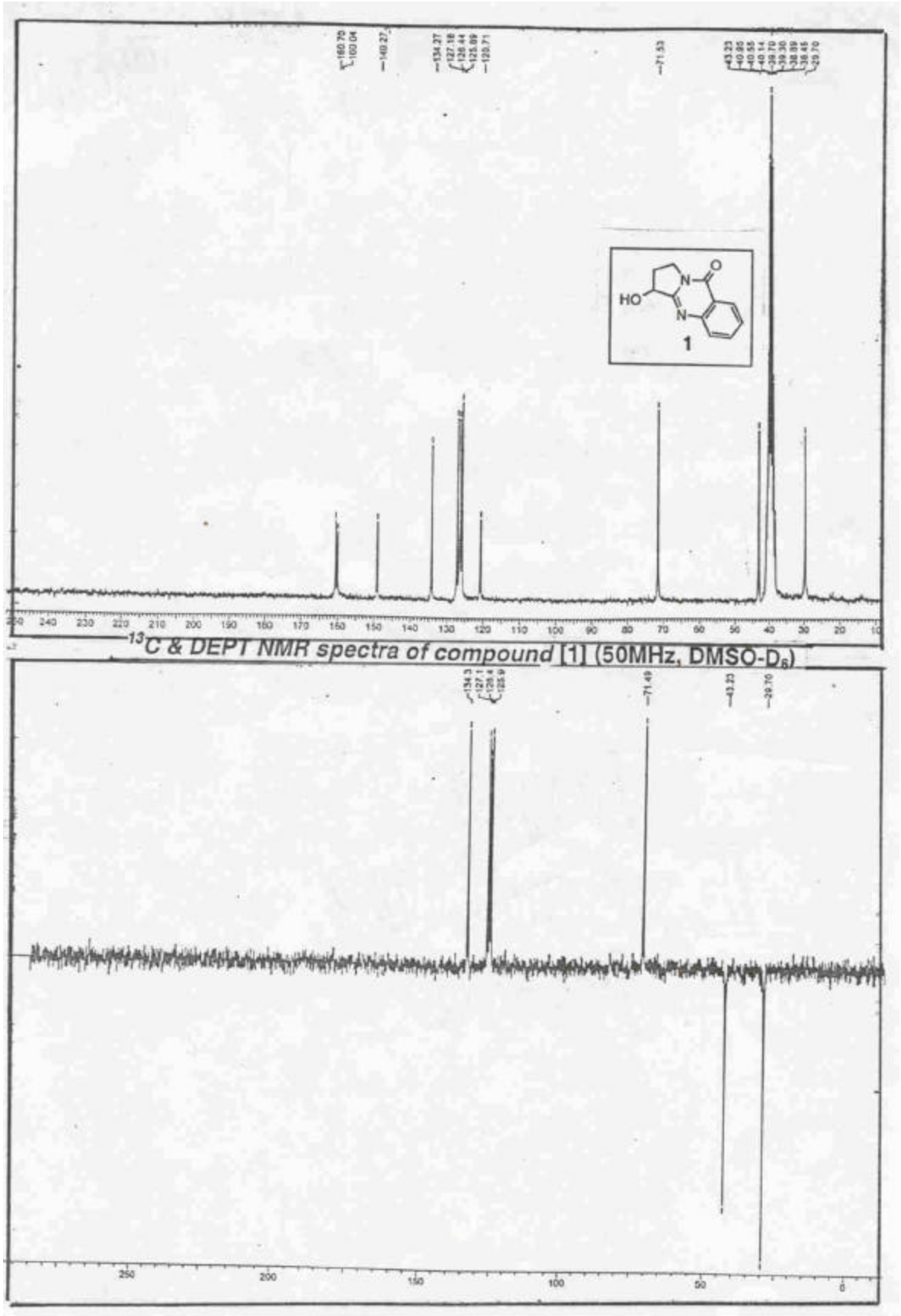


^{13}C & DEPT NMR spectra of compound [45] (50MHz, DMSO-D_6)





***^{1}H NMR spectrum of compound* [1] (200 MHz, $CDCl_3$)**



^{13}C & DEPT NMR spectra of compound [1] (50MHz, DMSO-D_6)

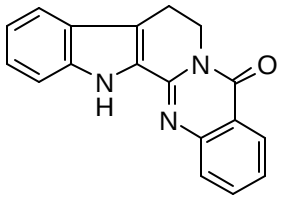
CHAPTER 2

SECTION III

Synthesis of Pyridoquinazolinone Alkaloid - Rutaecarpine

2.3.1 Introduction

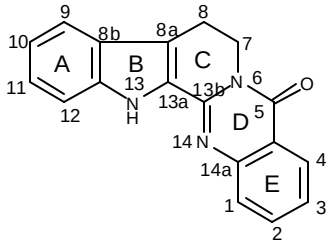
Rutaecarpine **1**, (7,8-dihydro indolo (2', 3': 3,4) pyrido (2,1-*b*) quinazolin-5-one, is an alkaloid of *Evodia rutaecarpa*[205] and is known as one of the constituents involved in Chinese drugs *Wou-chou -yu*[206] and *Shih-hu.*[207] It has also been isolated from the genera *Hortia, Zanthoxalum, Euxylophora* and *Phellodendron*, all members of rutaceae.[208]



Rutaecarpine **(1)**

2.3.2 Structure and Chemical properties

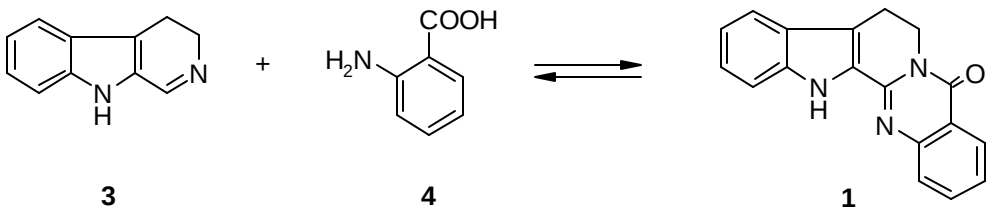
The first suggested structure **was** based on the erroneous identification of one of the products of its fission with alkali.[209] The fission fragment ultimately proved to be tryptamine and this finding led to the correct structure as **1**, since the second fragment had already been recognized as anthranilic acid. Most authors currently use the following numbering system



2.3.3 Biogenesis

The synthesis reported by Schopf and Steur[210] under the physiological condition by the condensation of anthranilic acid with **3**, which was prepared from tryptamine and formic acid, suggests a biogenesis of this alkaloid involving tryptamine, anthranilic acid and a one carbon unit.

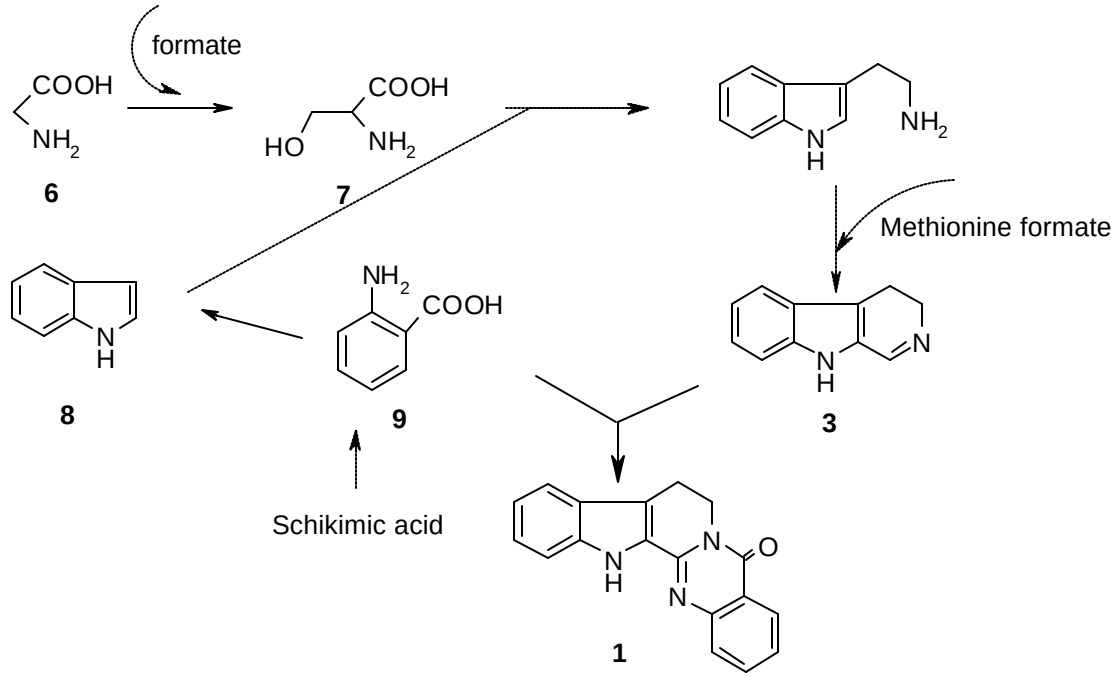
Scheme 1:



3 **4** **1**

The feeding experiments conducted by Yamazaki *et al* around 1966[211] revealed the incorporation of labels into Rutaecarpine as well as Evodiamine. The degradation of these radioactive compounds showed the incorporation of one-carbon unit into the biosynthesis of the indole alkaloids. From the fruits of *E. rutaecarpa* fed with methionine $^{14}CH_3$ or sodium formate-^{14}C, radioactive Evodiamine and Rutaecarpine were isolated and systematic degradation studies showed that C1-unit from methionine or formate was introduced to the 13b-position of both the alkaloids. On the feeding of sodium ^{14}C formate, which would be reasonably accepted by the fact that C1-unit from formic acid or formaldehyde is directly incorporated to the serine by hydroxymethylation of glycine and hence in to tryptophan, synthesized biogenetically from indole and serine. It should be noted that there is no evidence for the involvement of β-carboline.

Scheme 2:



2.3.4 Naturally occurring analogues of Rutaecarpine

More than 20 analogues of natural Rutaecarpine analogues have been isolated from the various sources. Some of the important ones are shown in **Chart1.**

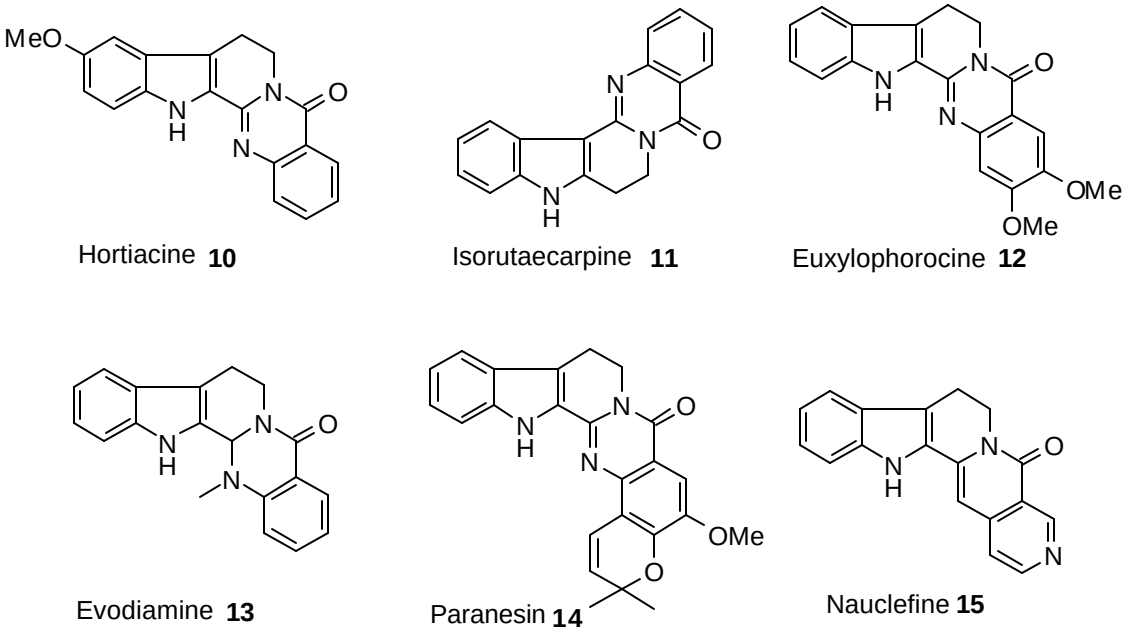


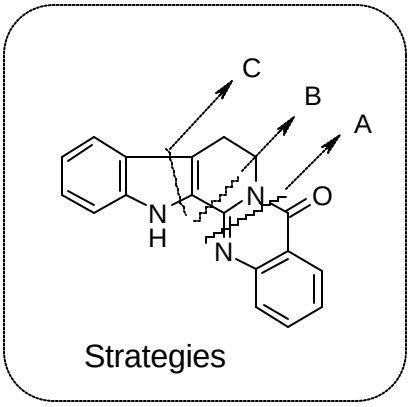
Chart 1

2.3.5 Medicinal chemistry

Rutaecarpine and its substituted derivatives are constituents of traditional Chinese folk medicines *Wou-chou –yu*[2] and *Shih-hu*[3] that have been used for the treatment of abdominal pain, gastrointestinal disorders, headache, dysentery, and amenorrhoea. The Chinese crude drug the bark of *Phellodendron amurense* Rupr has been used as a stomachic for intestinal function control and antibacterial, anti-inflammatory agent.[212] Rutaecarpine is known to possess cardiatonic[213] and analgesic properties.[214] Rutaecarpine, its 11-methoxy and 10,11-methylene dioxy analogues are shown to have better antitumor activity especially selective cytotoxicity against ovarian cancer cells.[215] Rutaecarpine and its derivatives containing pharmacologically important quinazolinone skeleton[216] demand interest as hypertensive, diuretic and uterotonic, positive inotropic and platelet aggregation inhibitory agents. The hypotensive, antiarrhythmic, anti-anoxic and vasorelaxant effects have been investigated more intensively and synthetic and pharmacological development in this field is expected to lead to therapeutic applications. Kong *et al* reported the uterotonic activity of Rutaecarpine.[217] Recently it has been shown that the derivatives of Rutaecarpine exhibit cycloxygenase (COX-2) inhibitory activity.[218]

2.3.6 Synthesis of Rutaecarpine: A Literature Survey

Because of its interesting structure with pharmacologically important units indole and quinazolinone, it has attracted a large amount of synthetic interest, which has culminated in several total syntheses after its first synthesis being achieved a decade later to its isolation by Asahina, Manske and Robinson.[219] The synthetic efforts have been reviewed.[220] Few analogues have also been prepared and tested for their inhibition of tumor growth with contradictory results.[221]



Theses syntheses will be discussed under 3 categories based on respective unique retro synthetic analyses shown below.

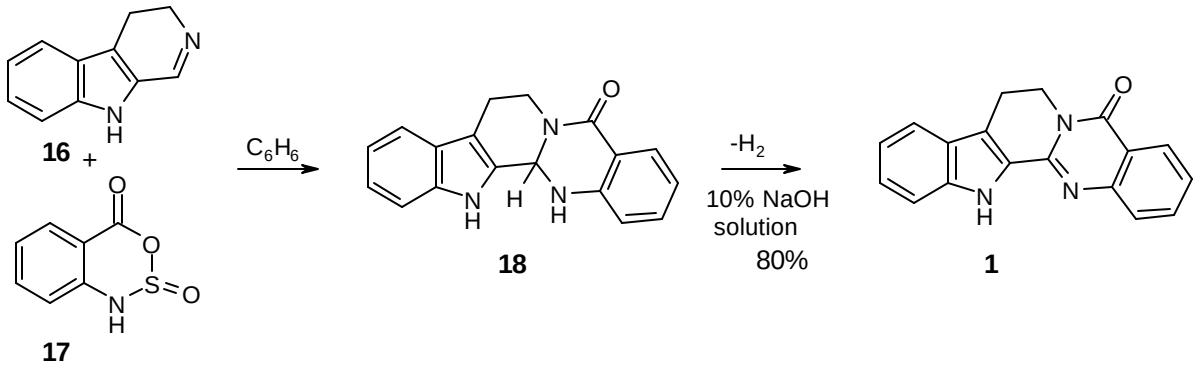
I. Retrosynthetic approach A.

Among these routes, approach A provides obviously the most straight forward synthesis of Rutaecarpine by annulation of ABC- or AB – rings *via* iminoketene cycloadditions and isatoic anhydride condensation methods as demonstrated by Kametani *et al* and by aza Wittig reaction by Egouchi *et al*.

Kametani's Approach[222] (Scheme 3, 1976)

Kametani *et al* achieved a novel regiospecific synthesis of the quinazolinone system by cycloaddition of imine with iminoketene derived from anthranilic acid and thionyl chloride, the retro mass spectrometric approach. Thus 3,4-dihydro B-carboline **16** was condensed with sulphinamide anhydride **17** to form **18,** which during workup with 10% NaOH gave the Rutaecarpine, after spontaneous dehydrogenation in 80% yield. However isatoic anhydride **19** was found to be not suitable precursor for the condensation with imine such as **16.**

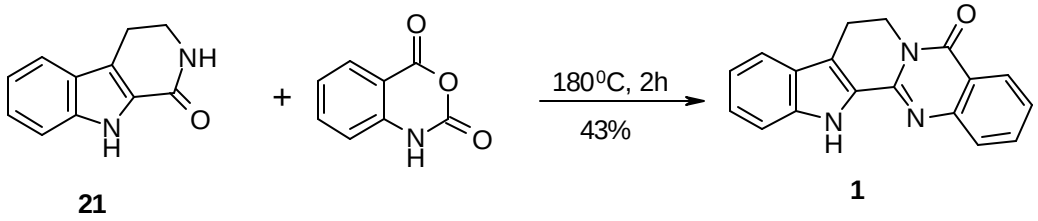
Scheme 3: Kametani *et al, J. Am. Chem. Soc.*, **1976,** *98***,** 6186.



Kametani's Approach[223] (**Scheme 4, 1978**]

Having identified that the isatoic anhydride **19** does not react with imine, they employed the lactam **21** and the condensation resulted Rutaecarpine in 43% yield.

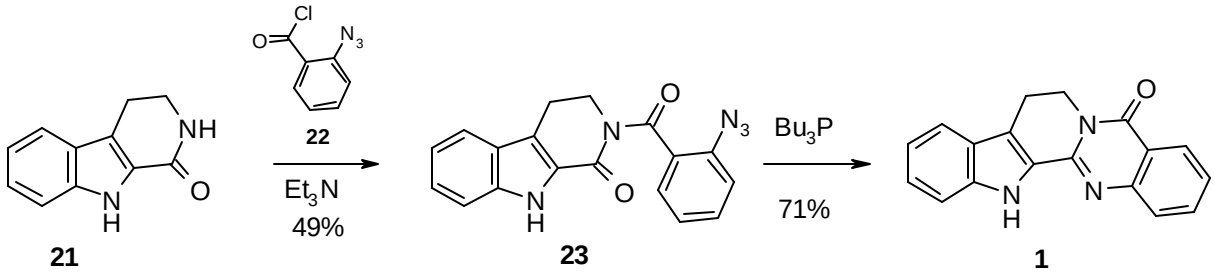
Scheme 4: Kametani *et al*, *Chem. Pharm. Bull.*, **1978,** *28*, 1972.



Eguchi's approach[224] **(Scheme 5, 1992)**

Eguchi *et al* have extended their aza Wttig reaction to the synthesis of quinazolinone part of **1.** Thus the carboline **21** was *o*-azidobenzylated with acid chloride **22** to afford the imide **23** as a pale yellow solid, which was treated with tributylphosphine to give Rutaecarpine.

Scheme 5: Eguchi *et al***,** *Heterocycles.*, **1992**, *33*, 153.



Thus this elegant methodology paved a simple entry to Rutaecarpine **1** under mild conditions and is attractive from synthetic point of view as it involves lactams in place of lactam ethers.

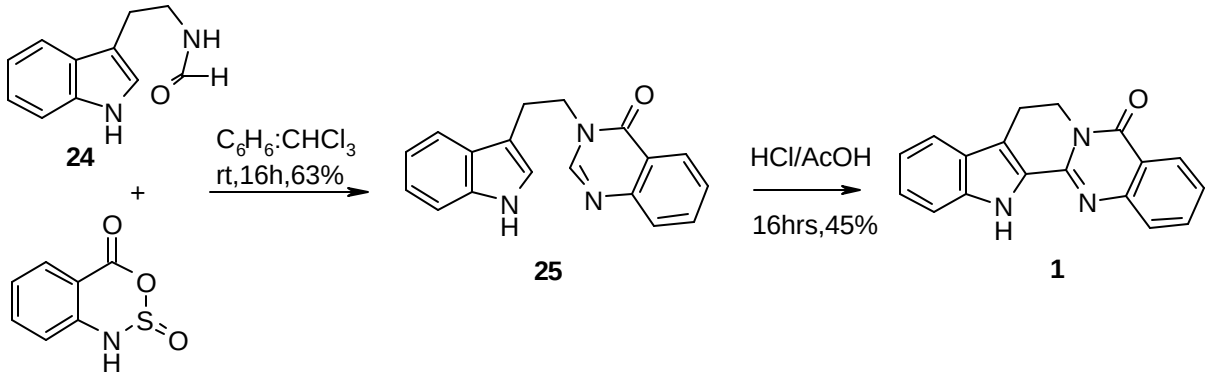
II. Retrosynthetic approach B

In this approach C-ring formation, as the last step of the synthesis, executed on preformed AB-DE intermediate.

Kametani's approach[225] (Scheme 6, 1977)

AB-DE intermediate **25** was prepared by condensation of *N*-formyl tryptamine **24** with the sulphinamide anhydride **18**. The final cyclization was realized with con HCl in acetic acid to afford Rutaecarpine.

Scheme 6: Kametani *et al*, *J. Am. Chem. Soc.*, **1977**, *99*, 2306.

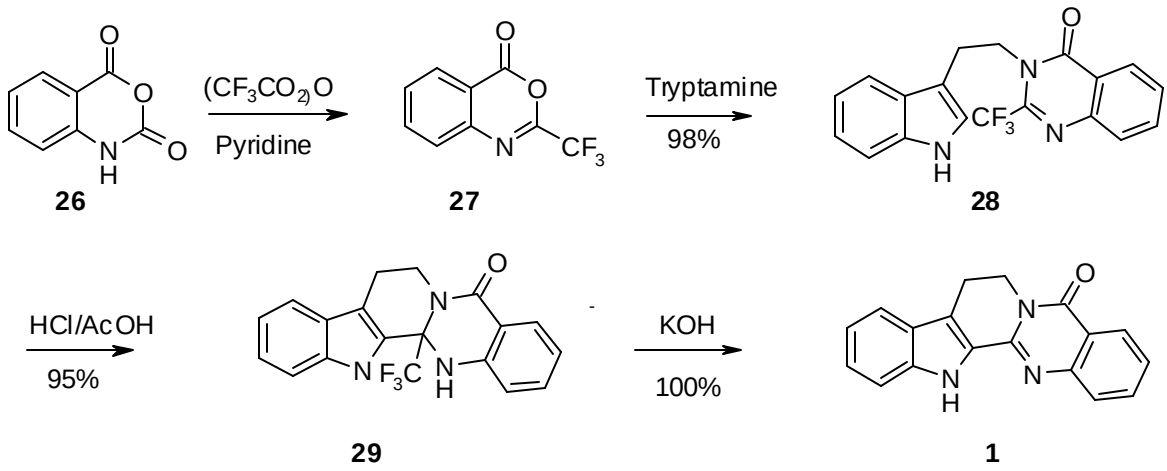


Some of the problems involved in Kametani's imino-ketene cycloadditions are the low yields, long reaction times coupled with the necessary column chromatography of multi component reaction mixture makes this more of an academic interest approach.

Bergman's approach[226] (Scheme 7, 1985)

Bergman *et al* improved on Kametani's approach by introducing a group to assist the C-ring annulation. Thus protonation of 4(3*H*)-quinazolinone moiety **28**, obtained by the condensation of trypatmine with triflouroisatoic anhydride **27**, followed by electrophilic attack on the indole ring leads to **29**, a compound with angular CF_3 group in the 13b position. Compound **29** was converted to Rutaecarpine by base treatment. This synthesis is amenable to prepare other quinazolino carboline alkaloids related to Rutaecarpine such as Horticine and Euxylophorocine and superior to Kametani's approach in both yield and reaction timings which are due to the presence of CF_3 –group at the 2-position of the quinazoline ring which not only facilitates the ring closure of the intermediate but also acts as a good leaving group in the final step.

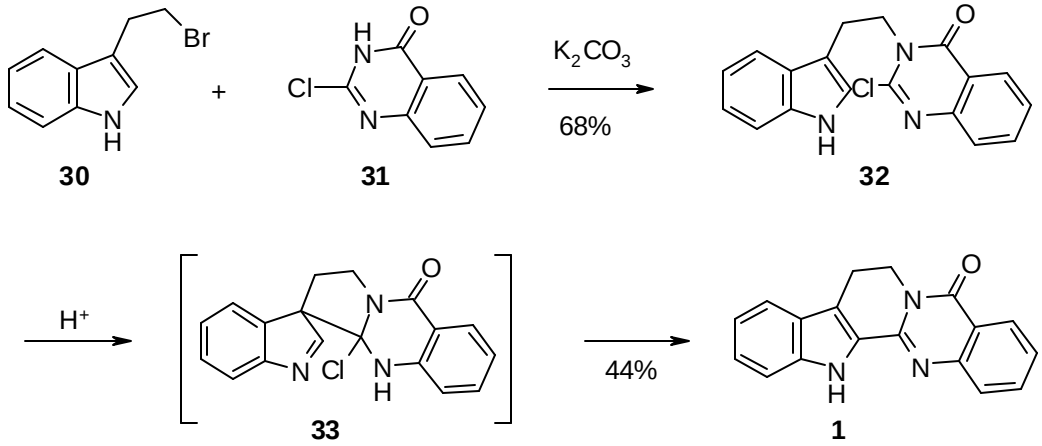
Scheme 7: Bergman *et al*, *Heterocycles*, **1981**, *16*, 347; *J. Org. Chem.*, **1985,** *50*, 1246



Kaneko 's Approach[227] (Scheme 8, 1985)

Kaneko *et al* used chloro as leaving group in final cyclization. Reaction of tryptyl bromide **30** with 2-chloro -4-quinazolinone **31** in acetone in the presence of K_2CO_3 afforded **32**, which was subjected to acid catalyzed cyclization reaction under $CHCl_3$/HCl condition to give Rutaecarpine **1**. This approach uses chloro as a leaving group, which retains the advantages of Bergman's approach to some extent.

Scheme 8: Kaneko *et al*, *Heterocycles*, **1985**, *23*,1385.

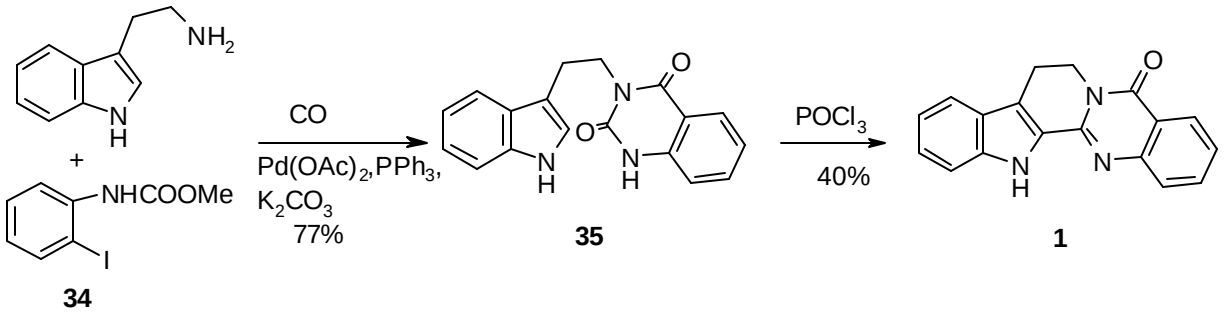


Mori's Approach[228] (Scheme 9, 1985)

Central to his approach is Bischler- Napieralski reaction to form the carboline part of the molecule. *N*-carbethoxy *o*-iodoaniline **34** and tryptamine were allowed to react with CO (5 atm)

at 120^0C in presence of Pd catalyst to furnish **35.** Bischeler Napieralski reaction of **35** gave Rutaecarpine.

Scheme 9: Mori *et al*, *Heterocycles***, 1985**, *23*, 2803.



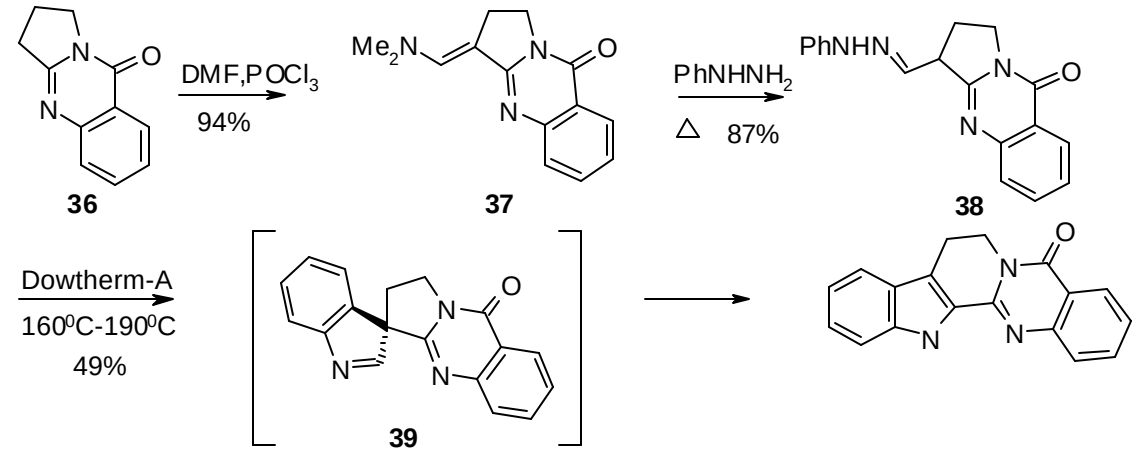
III. Retrosynthetic approach C

The earlier syntheses involved tryptamine or tryptamine derivatives as starting materials and then connect the other rings. This approach connects the BC rings in crucial Fischer indolization step. The fact that phenyl hydrazines rather than tryptamines are required as starting materials makes this route attractive for the synthesis of Rutaecarpine derivatives substituted in the A-ring.

Kokosi's Approach [229] (Scheme 10, 1981)

Deoxy vasicinone **36** was treated with Vilsmeier-Haack formylation agent *i.e*. dimethyl formamide and $POCl_3$ to give the adduct **37** which was converted to phenyl hydrazone **38** by refluxing with excess phenyl hydrazine. Hydarzone **38** was converted to spiro intermediate **39** by heating with Dowtherm-A at 160°C-190°C which rearranges to Rutaecarpine **1**.

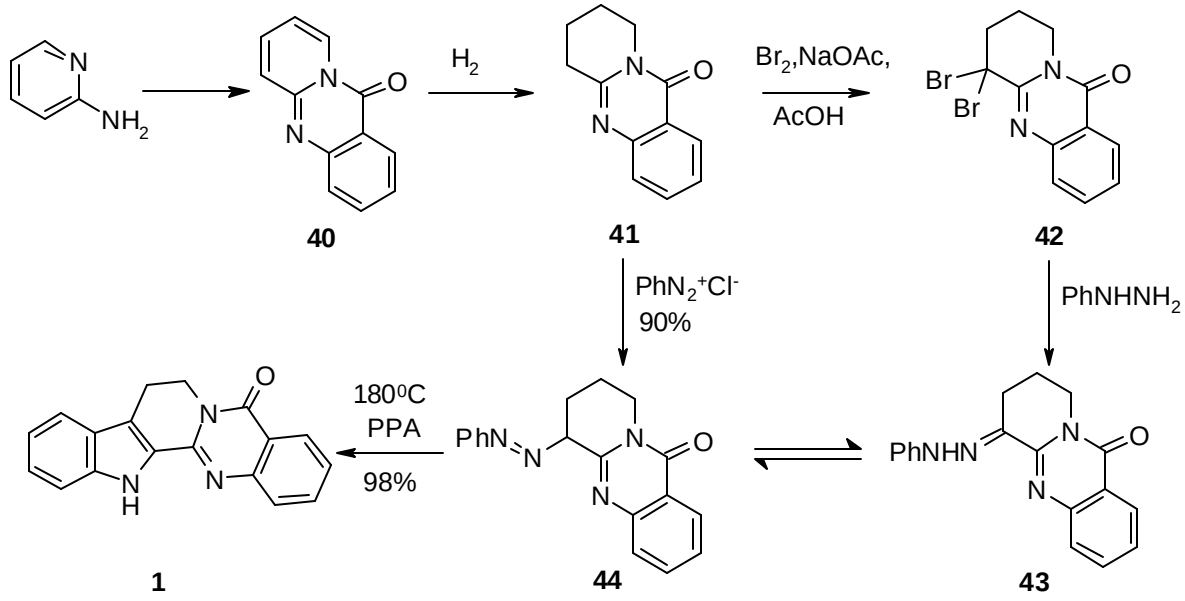
Scheme 10: Kokosi *et al*, *Tetrahedron Lett*., **1981**, *22*, 4861.



Kokosi's II-approach[25b] (Scheme 11, 1988)

Hydrazone was prepared from tetrahydropyrido quinazolinone (obtained from the reduction of pyridoquinazoline) by bromination followed by reaction with phenyl hydrazine or by diazotisation with benzene diazonium chloride. Fisher indole cyclization of **43** with PPA at 180^{o}C afforded Rutaecarpine in quantitative yield.

Scheme 11: Kokosi *et al*, *Tetrahedron Lett.*, **1988**, *22*, 4861.



The generalization of this synthesis provided facile access for the preparation of Rutaecarpine analogues, for example, substituted derivatives on A & E ring,[230a] their 1,2,3,4 tetrahydroderivatives,[230b] its-ring homologues,[230c] its C-ring opened homologues,[230d] E-ring debenzoderivatives and thus makes SAR studies of these alkaloids easy and possible.

2.3.7 Present Work

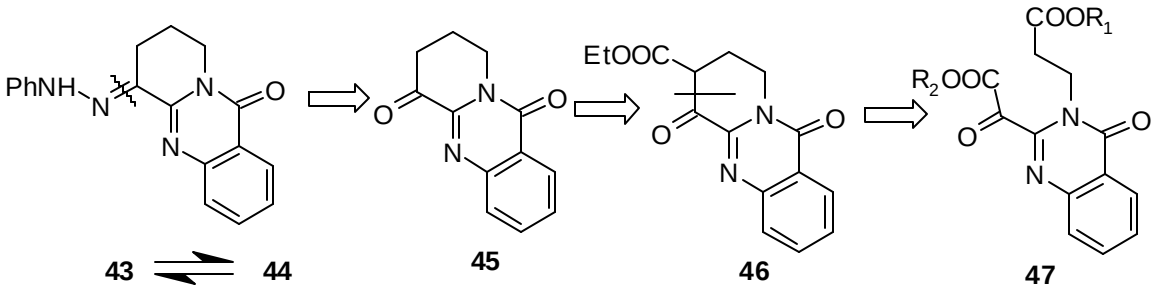
The indole nucleus is an important element in many pharmacologically active compounds.[231] Of the many methods developed for indole synthesis, the oldest and most widely used is the Fischer indole synthesis,[232] in which an *N*-aryl hydrazone undergoes acid-catalyzed or thermal sigmatropic rearrangement to generate, after elimination of ammonia, the indole skeleton. Although a number of methods exist for the preparation of *N*-aryl hydrazones,[233] the most common is the condensation of an aldehyde or ketone with an *N*-aryl hydrazine. The *N*-aryl

hydrazine, in turn, is typically prepared *via* reduction of the corresponding aryl diazonium species obtained from the anilines.

Among the various approaches reported, Kokosi's approach, involves the construction of AB rings *via* Fischer-indole synthesis of phenyl hydrazones, and proved to be generalized and amenable to access the various analogues of the Rutaecarpine. Obtaining the phenyl hydrazones from tetrahydropyrido quinazolinones is the limiting factor of this otherwise an excellent synthesis to obtain the derivatives of Rutaecarpine. They have been made *via* prior functionalization of the 6,7,8,9-tetrahydro-11H-pyrido [2,1-*b*] quinazolinone.

We found, however, that a more convenient means to access the desired *N*-aryl hydrazones was *via* the intermediacy of the ketone carbonyl, hitherto not reported for the synthesis of Rutaecarpine, with phenyl hydrazine in a straightforward way as shown in our retrosynthetic analysis (*Scheme 12*). So the problem of devising the synthetic route to Rutaecarpine reduced to the preparation of the 8,9-dihydro-7H-pyrido [2,1-*b*] quinazoline-6, 11-dione **45.**

Scheme 12: Retrosynthetic analysis



We envisioned a Dieckmann condensation-decarboxylation sequence of quinazolinone diester to place ketone, which has been adapted for the pyrroloquinazolinone alkaloids (Sec2).

2.3.8 Results and discussion

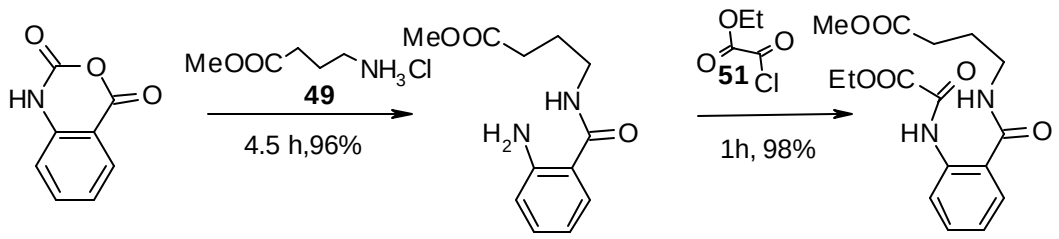
The chemistry that has been developed for the synthesis of Vasicinone has been directly adapted for the synthesis of the dione **45**.

Thus the treatment of isatoic anhydride **48** with methyl γ-amino butyrate hydrochloride **49** in DMF in presence of Et_3N/DMAP furnished amine **50** in 96% yield.(*Scheme 13*)

^{1}H NMR spectrum of **50** showed apart from aromatic protons a quintet at δ 1.66 (2H), a triplet at δ 2.37 (2H) and a quartet at δ 3.65 (2H), a singlet at δ 3.61 (3H) suggesting the incorporation of butyrate part as anthranilamide.

Condensation of amine **50** with ethyl oxalyl chloride in dry DCM in presence of K_2CO_3 resulted in the formation of peptide **52.**

Scheme 13:



48 **50** **52**

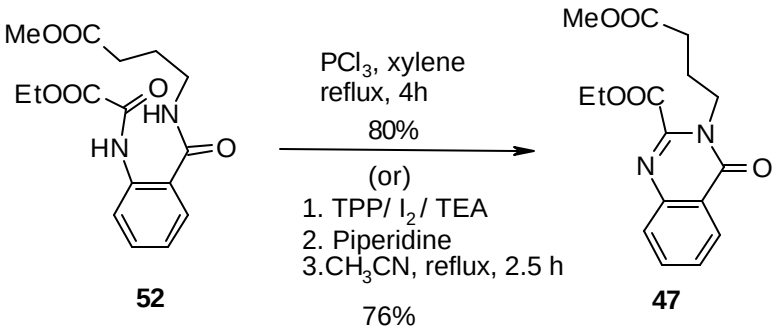
^{1}H NMR spectrum of **52** showed the presence of a quartet at δ 4.42 and a triplet at δ 1.42 and a broad singlet at δ 12.82 (1H) suggesting the formation of oxalyl amide of the amine **50**. ^{13}C NMR spectrum showed peaks at δ 174.02 (C), 168.47 (C), 160.53 (C), 154.94 (C) confirming the presence of four carbonyl carbons and hence the assigned structure.

Quinazolinone construction *via* cyclodehydration of the peptide was achieved with PCl_3 in refluxing xylene (*Scheme 14*). ^{1}H NMR spectrum of **47** showed the absence of –CONH- proton and the appearance of quinazolinone characteristic peri proton at δ 8.29 along with other aromatic protons and aliphatic protons. ^{13}C NMR spectrum confirmed the formation of **47** by showing three carbonyls at δ173.69, 161.41 and 160.36 respectively and the newly formed quinazolinone quaternary carbon appeared at δ 147 (at the expense of amide carbonyl). Mass spectrum showed m/z at 318 confirming the loss of water from the peptide.

The quinazolinone formation was attempted under the conditions (PPh_3/I_2/ Et_3N) amenable to solid phase synthesis of the same with the idea of rendering flexibility to the synthesis for obtaining the analogues in combinatorial fashion since the other steps involved are well-established on solid phase.

Thus treatment of peptide **52** with PPh_3/I_2/ Et_3N followed by the refluxing of amidine formed with piperidine in acetonitrile furnished quinazolinone diester **47** in 70% yield after column purification which attests to the feasibility of the same on solid phase.

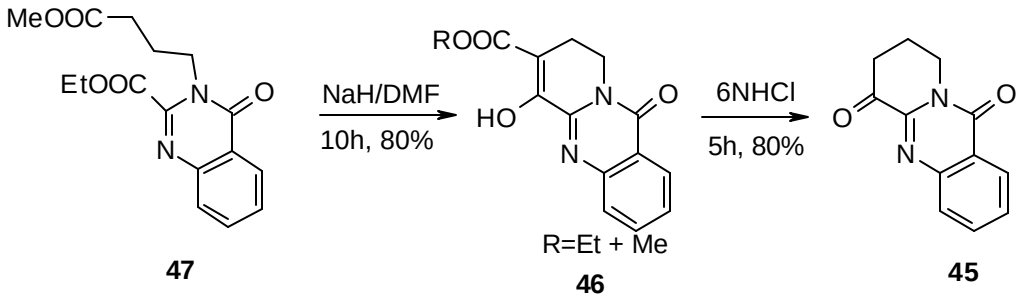
Scheme 14:



With the suitable diester **47** in hand, we proceeded to ascertain the proposed strategy i.e Dieckmann condensation for the construction of β-keto ester (*scheme 15*). Treatment of the diester **47** with NaH/DMF afforded β-keto ester **46** in 80% yield, notably in better yield that in the case of its lower analogue.

^{1}H NMR spectrum showed that this compound **46** exists exclusively in the enol form as mixture of the ethyl and methyl esters, formed by the trans esterification and the appearance of triplet at δ 2.27 (2H) and triplet at δ 4.31(2H) confirms the structure of **46.** The quinazolinone pattern was seen by the presence of a doublet at δ 8.32 (1H), doublet at δ 7.9 (1H), triplet at δ 7.88 (1H), and a triplet at δ 7.58 (1H). ^{13}C NMR spectrum confirmed the enolic structure by the absence of ketone carbonyl and by appearance of a new peak corresponding to the olefinic carbon at δ 104.19. Mass spectrum showed the molecular ion peak at 272 for **46** (R = Me) and 286 (R = Et).

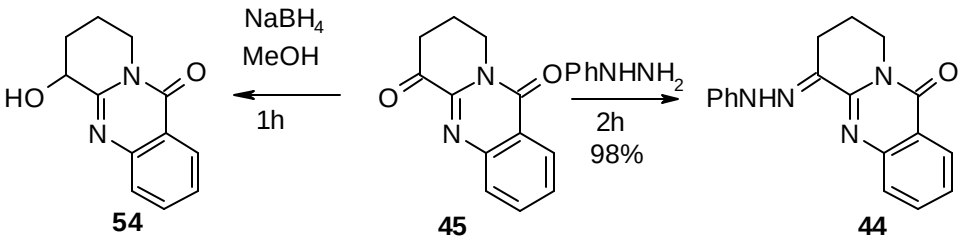
Scheme 15:



β-keto ester **46** was decarboxylated to afford dione **45** under refluxing conditions with 6N HCl solution. ^{1}H NMR spectrum of **45** showed that it exists as keto-enol tautomers (the appearance of triplet at δ 5.77 was assigned to enolic olefin proton and the absence of ester peaks confirmed the decarboxylation). ^{13}C NMR spectrum confirmed the presence of ketone at δ

189.89. Mass spectrum of **45** confirmed the structure by presence of the molecular ion peak at 218. It was further confirmed by sodium borohydride reduction to alcohol i.e homovasicinone **54**.

Scheme 16:

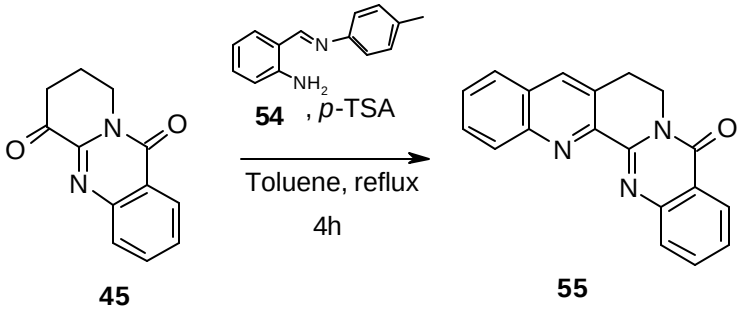


The dione **45** was treated with phenylhydrazine under acidic conditions to form hydrazone **44** in quantitative yield (*Scheme 16*).

Hydrazone **44** was subjected to reported[9b] conditions of Fischer indole synthesis i.e performing the reaction in the presence of PPA at 180°C to obtain Rutaecarpine **1** in 95% yield. The spectral data of **1** synthesized were identical with those reported for the natural product.

Having made the Luotonin and Rutaecarpine a hybrid of the two alkaloids was planned. Thus Friedlander condensation of dione **45** with *o*-aminobenzaldehyde Schiff's base **54** resulted an altogether new non-natural alkaloid *i.e* quinolopyrido quinazolinone **55 (***Scheme17***).**

Scheme 17:



^{1}H NMR spectrum of **55** exhibited the quinolo quinazolinone pattern apart from the two triplets δ 4.52 and 3.31 integrating for 2H each were assigned to the two methylenes of the pyridone part.

Conclusions

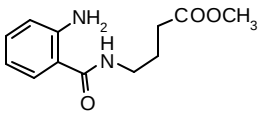
This robust chemistry coupled with the potential flexibility of the synthesis for the solidphase, should make this an attractive route for the development of analogues on solid phase as well as in solution phase too in a combinatorial fashion.

We have prepared homovasicinone a new alkaloid homologue of Vasicinone, which could be tested to study the pharmacological properties of the same in comparison with Vasicinone, a naturally occurring alkaloid.

We developed a non-natural alkaloid, molecular hybrid comprising the structural features of Luotonin A and Rutaecarpine. Thus we devised a novel entry to pyrido quinazolinone alkaloids.

2.3.9 Experimental

1. 4-(2-Amino-benzoylamino)-butyric acid methyl ester [50]



50

To a mixture of γ-amino butyric acid ethyl ester hydrochloride (1.68 g, 10 mmol) and TEA (2.99 g, 15.6 mmol) in DMF (70 mL) and catalytic amount of DMAP was added isatoic anhydride (1.82 g, 13.2 mmol) in 10 portions over 15 min at room temperature with stirring. After being stirred for an additional 4h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 / aqueous Na_2CO_3, extracted with CH_2Cl_2 (3×30mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give amide **50** which was pure enough and was taken as such for the next step.

Molecular Formula :$C_{12}H_{16}N_2O_3$, 236

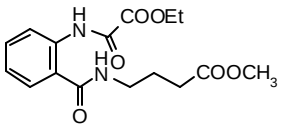
Yield : 2.17 g, 93%

IR ($CHCl_3$) : 3425, 3320, 1727, 1645, 1611, 1582 cm^{-1};

^{1}H NMR (200MHz) : δ: 7.33 (d, *J* = 7.82Hz, 2H), 7.7 (t, *J* = 8.3Hz, 1H), 6.69 (br s, 1H), 6.63-6.62 (m, 2H), 5.39 (br s, 1H), 3.61 (s, 3H), 3.65 (q, *J* = 5.86Hz, 2H), 2.37 (t, 5.86Hz, 2H,), 1.66 (m, 2H)

^{13}C NMR (50MHz) : δ: 174.09 (C), 169.5 (C), 148.59 (C), 132.01 (CH), 127.34 (CH), 117.16 (CH), 116.42 (CH), 116.32 (C), 51.47(CH), 39.34 (CH_2), 33.86(CH_2), 29.2.7(CH_2).

2. 4-[2-(Ethoxyoxalyl-amino)-benzylamino]-butyricacid methylester [52]



52

To a solution of compound **50** (2.360 g, 10 mmol) in dry CH_2Cl_2 (30 mL) was added ethyl oxalyl chloride (1.76 g, 13 mmol). The mixture was stirred for 5 min, followed by addition of aqueous Na_2CO_3 (1 M, 20 mL, 20 mmol). After being stirred for a total of 1 h, the mixture

was extracted with CH_2Cl_2 (3×20mL), treated with $NaHCO_3$ and dried (Na_2SO_4), filtered, and concentrated to give **52** as a white solid which was pure enough for further use.

Molecular Formula : $C_{16}H_{20}N_2O_6$, FW = 336.

Yield : 3.22 g, 96%

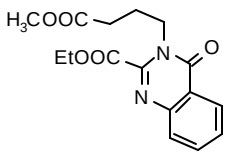
M.P. : 178-180^oC

IR ($CHCl_3$) : 3417, 3340, 1726, 1692, 1588 cm^{-1};

^{1}H NMR (200MHz) : δ: 12.82 (br s, 1H), 8.61 (d, *J* = 8.31Hz, 1H), 7.6 (d, *J* = 7.8, 1H), 7.31-7.46 (m, 2H), 7.07 (t, *J* = 8.31Hz, 1H), 4.37 (q, *J* = 7.32Hz, 2H), 3.61 (s, 3H), 3.47(q, *J* = 6.3Hz, 2H), 2.8 (t, *J*=6.3Hz, 2H), 1.95 (m, 2H) 1.38 (t, J = 7.32, 3H);

^{13}C NMR (50MHz) : δ: 174.02 (C), 168.47 (C), 160.53 (C), 154.79 (C), 137.00 (C), 132.33 (CH), 127.26 (CH), 124.03 (CH), 121.63 (CH), 121.12 (C), 63.34 (CH_2), 51.47 (CH_3), 39.74 (CH_2), 33.82 (CH_2), 29.01 (CH_2), 14.05 (CH_3);

3. 3-(3-Ethoxycarbonyl-propyl)-4-oxo-3, 4-dihydro-quinazoline-2-carboxylicacid ethyl ester [47]



47

To a pre cooled solution of compound **52** (1.68 g, 5 mmol) in dry xylene (30 mL) was added PCl_3 (1.350 g, 10 mmol) through a dropping funnel over 30 minutes. The mixture was stirred for 2h at reflux temperature. After the reaction was completed (TLC) the solvent was distilled off under reduced pressure. The residue was dissolved in dichloromethane and washed with aqueous $NaHCO_3$ (2×50mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give **47** as a solid, which was pure enough for further use.

Molecular Formula : $C_{16}H_{18}N_2O_5$, 318

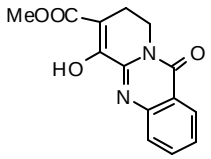
Yield : 1.272g, 80%

IR ($CHCl_3$) : 3477, 3432, 1726, 1692, 1642, 1588 cm^{-1};

^{1}H NMR (200MHz) :δ: 8.29 (d, *J* = 7.8Hz, 1H), 7.76 (m, 2H), 7.56-7.4 (m, 1H), 4.55 (q, *J* = 7.32Hz, 2H), 4.15 (t, *J* = 7.36Hz, 2H), 3.66 (s, 3H), 2.42 (t, *J* = 7.6Hz, 2H), 2.10 (m, 2H), 1.43 (t, *J* = 7.32, 3H);

^{13}C NMR (50MHz) : δ: 173.69 (C), 161.41 (C), 160.36 (C), 147.11 (C), 145.30 (C), 134.47 (CH), 128.14 (CH), 127.74 (CH), 126.14 (CH), 121.82 (C), 63.19 (CH_2), 51.36 (CH_3), 45.74 (CH_2), 33.64 (CH_2), 28.61 (CH_2), 13.99 (CH_3);

4. 6-Hydroxy-11-oxo-8, 11-dihydro-9H-pyrido [2,1-b] quinazoline-7-carboxylic acid methyl ester [46]



46

To a solution of NaH (0.288 g 50% dispersion in mineral oil, 6 mmol, 1.2 eq) pre washed with petether, 2×5mL) in DMF (15 mL) was added diester **47** (1.59g, 5mmol) in DMF through syringe, with out allowing the temperature to rise beyond rt. The reaction mixture was stirred at room temperature for 4h. The reaction was quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3×30mL), dried (Na_2SO_4), filtered, and concentrated to give **46** as a pale yellow solid. The residue was pure enough for the next step. .

Molecular Formula : $C_{14}H_{12}N_2O_4$, 272

Yield : 1.07 g, 79%:

M.P. : 199-200 C;

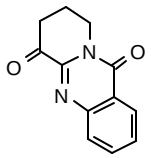
IR ($CHCl_3$) : 1719, 1692, 1642 cm^{-1};

^{1}H NMR:(200MHz) : δ: (mixture of esters due to transesterification) 12,01 (br s, 1H), 11.88 (br s, 1H) 8.32 (d, *J* =7.8 Hz, 1H), 7.92 (d, J =8.3, 1H), 7.82 (t, J=7.8Hz, 1H) 7.58 (t, J = 8.3Hz, 1H), 4.38, 4.38 (q) 4.24 (t, *J* = 6.83Hz, 2H), 3.91(s), 2.77 (t, *J* = 6.83, 2H) 1.45 (t, *J*=7.32Hz, 3H),

^{13}C NMR (50MHz) : δ: (mixture of esters due to transesterification) δ170.79 (C), 170.51 (C), 160.50 (C), 156.20 (C), 146.46 (C), 144.72 (C), 134.29 (CH), 128.39 (CH), 127.97 (CH), 126.66 (CH), 121.50 (C), 104.19 (C), 103.98 (C), 61.68 (CH_2), 52.37 (CH_3), .38.48 (CH_2), 19.96 (CH_2), 13.98 (CH_3)

Mass (m/z) :272 (M^+, 60, {286, 10}), 241 (26), 212 (100), 185 (58), 145 (25), 130 (52), 102 (51), 90 (48), 76 (50)

5. 8, 9-Dihydro-7H-pyrido [2,1-b] quinazoline-6, 11-dione [45]



45

To β-ketoester **46** (0.280 g, 1 mmol) was added l0 mL of 6N HCl solution and the reaction mixture was refluxed for 5 h, after the decarboxylation was completed it was cooled and extracted with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography to give **45** as a brown solid.

Molecular Formula : $C_{12}H_{10}N_2O_2$, 214

Yield : 0.175 g, 81%

M.P. : 228^oC

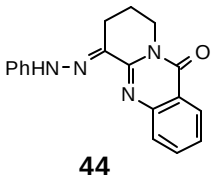
IR : 3550, 1692, 1642, 1200 cm^{-1};

^{1}H NMR (200MHz) : δ: [keto-enol tautomers (6:4)] 8.22 (m, 1H), 7.47-7.91 (m, 3H), 5.77 (t, *J* = 4.8Hz), 4.16-4.31 (m, 2H,), 4.50-4.35 (m, 3H), 2.68 (m), 2.3-2.6(m);

^{13}C NMR (50MHz) : δ: [Keto-enol tautomers (6:4)] 189.89 (C), 160.78 (C), 145.81 (C), 144.13 (C), 141.92 (C), 104.69 (CH) 134.28 (C), 133.99, 129.13, 128.69, 126.63, 126.23, 121.56 (C), 104.69 (CH), 41.91 (CH_2), 38.86 (CH_2), 37.17 (CH_2), 20.18 (CH_2);

Mass (m/z) : 214 (M^+, 75), 186 (100), 160 (8), 145 (23), 102 (25), 90 (24), 76 (71), 63 (70), 55 (72).

6. 6-(phenyl-hydrazono)-6, 7, 8, 9-tetrahydro-pyrido [2, 1-b] quinazolin-11-one [44]



44

To a solution of dione **45** (0.214g, 1 mmol) in CH_2Cl_2 (6 mL) at 25^o C was added phenyl hydrazine (0.30 mL, 3.95 mmol). After 5 min, a catalytic amount of concentrated HCl (aq) (1 drop) was added. After being stirred for 2 h, the cloudy suspension was filtered, dried in *vacuo* to give the hydrazone **44** as a yellow brownish solid.

Molecular Formula : $C_{18}H_{16}N_4O$, 304

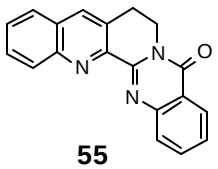
M.P. : 146-8^oC.

Yield : 0.288g, 95%

IR ($CHCl_3$) : 3515, 1640cm^{-1}

^{1}H NMR (200MHz,) : δ: 14.65 (br s, 1H), 8.27(d, *J* =7.82 Hz, 1H) 7.73 (t, *J* = 8.3Hz, 1H) 7.63-(d, *J* =7.82 Hz, 1H), 7.47 (t, *J* = 8.3, 1H), 7.34-6.93 (m, 5H), 4.11 (t, 5.86Hz, 2H), 2.87 (t, 5.86Hz, 2H), 2.14 (m, 2H)

7. 6,7-Dihydro-5a, 13,14-triaza-pentaphen-5-one [55]



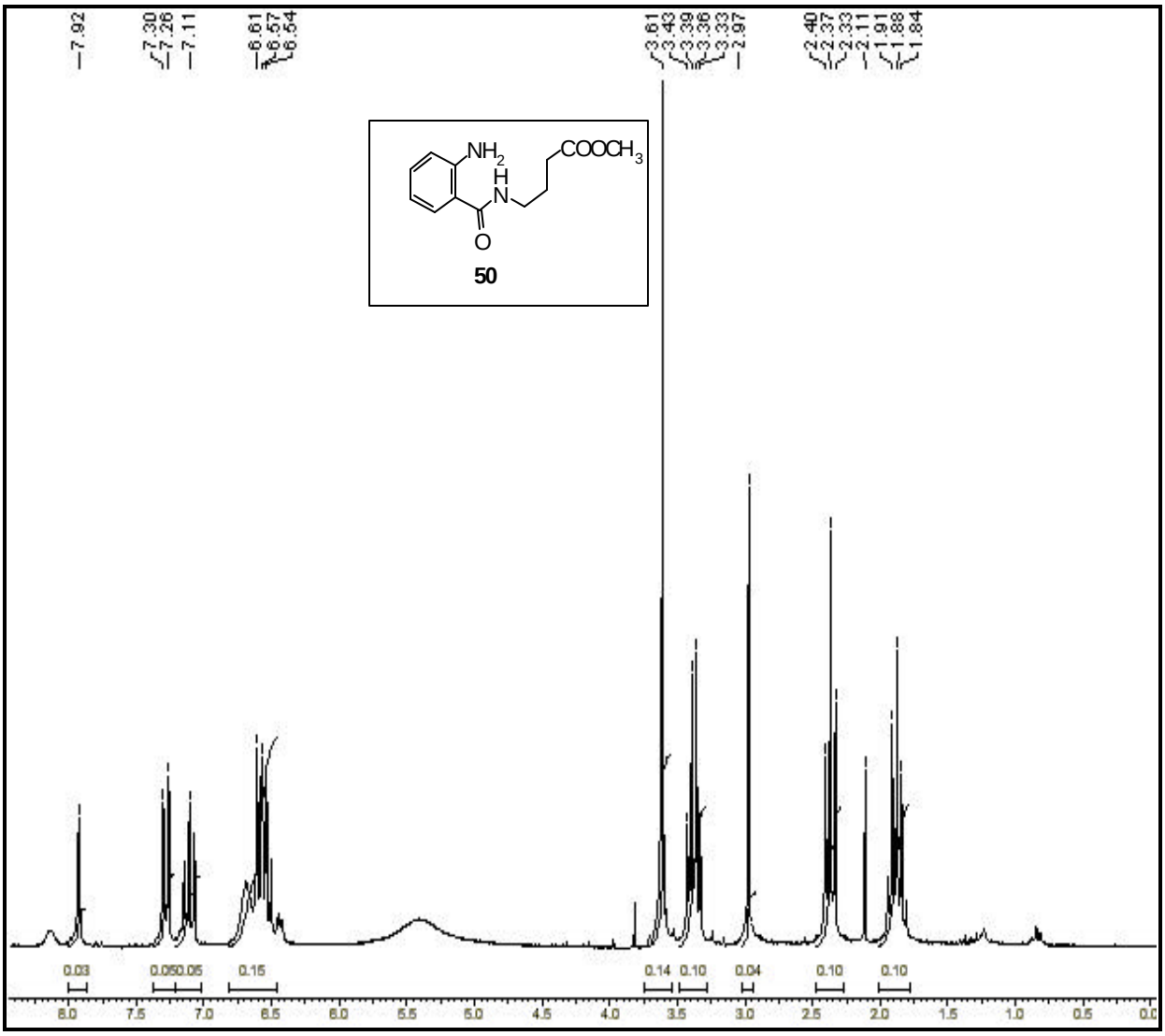
55

To the crude dione **45** (0.215g, 1mmol) in dry toluene (20mL) was added N- (o-aminobenzilidine) p-toluidine (3mmol) and the mixture refluxed for 30 min with azeotropic removal of water. 0.050g of *p*-TSA was added and the mixture refluxed further 3h. The reaction was quenched with Na_2CO_3 and the organic phase was separated and the aqueous phase was further extracted with ethyl acetate (3×25mL). The combined organic phase was dried (Na_2SO_4), concentrated and purified by chromatography over silica gel using 30% ethylacetate-pet ether as eluent furnished quinoline compound **55**.

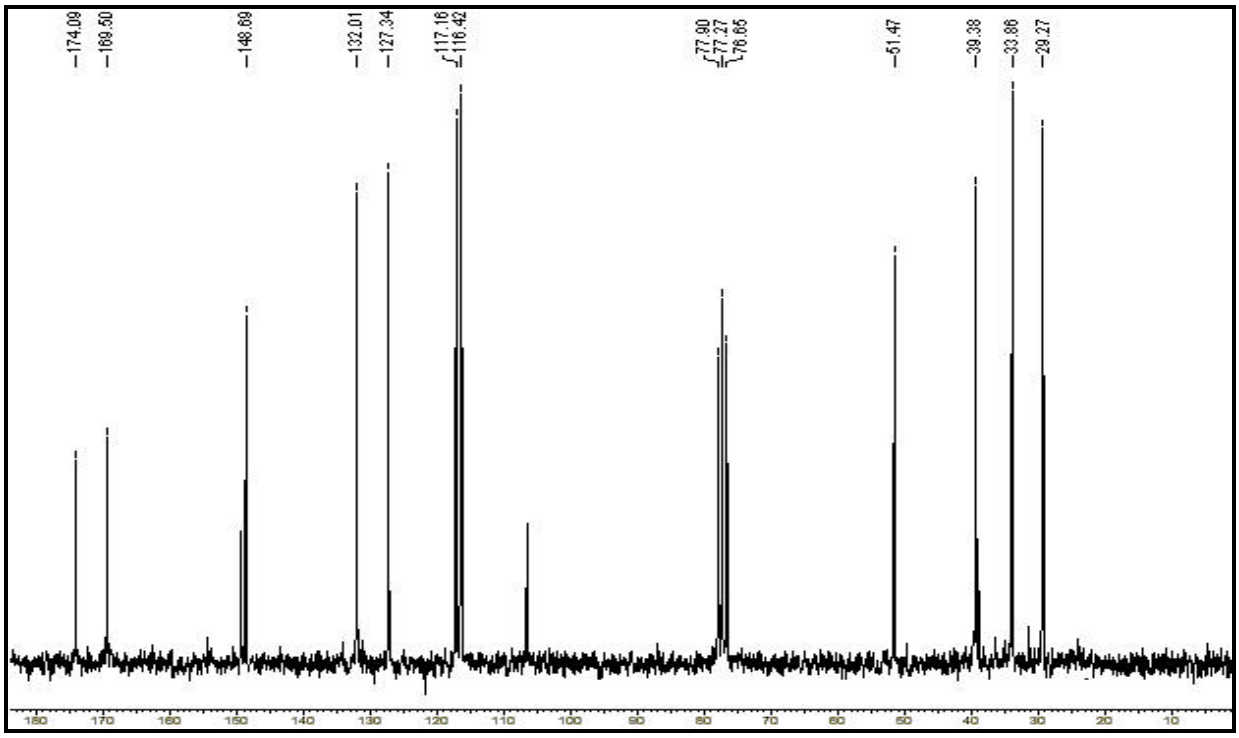
Molecular Formula : $C_{19}H_{13}N_3O$, 299.33

Yield : 220, 75%

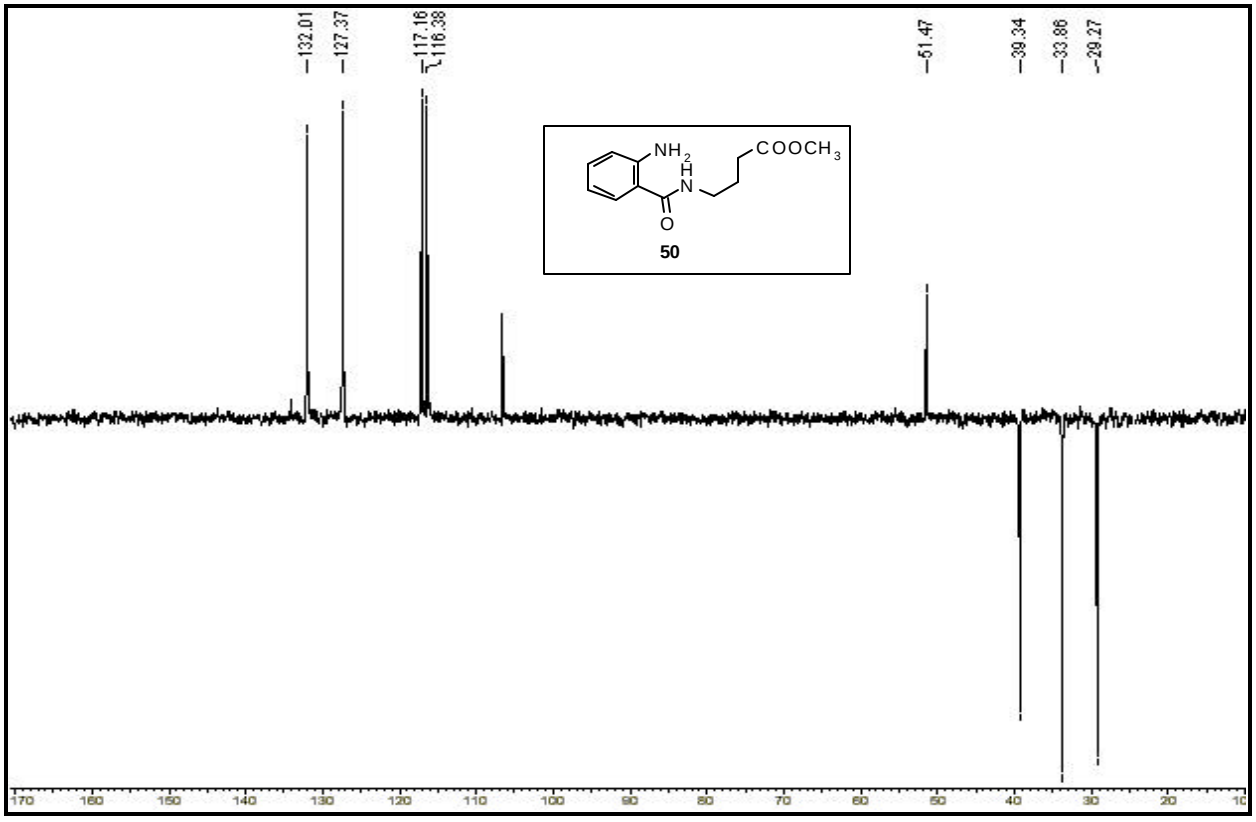
^{1}H NMR ($CDCl_3$): δ: 8.43-8.3 (m, 2H), 8.07 (m, 2H), 7.82-7.75 (m, 3H), 7.63-7.51 (m, 2H), 4.52 (t, *J* = 6.35Hz, 2H), 3.31 (t, *J* = 6.35Hz, 2H);

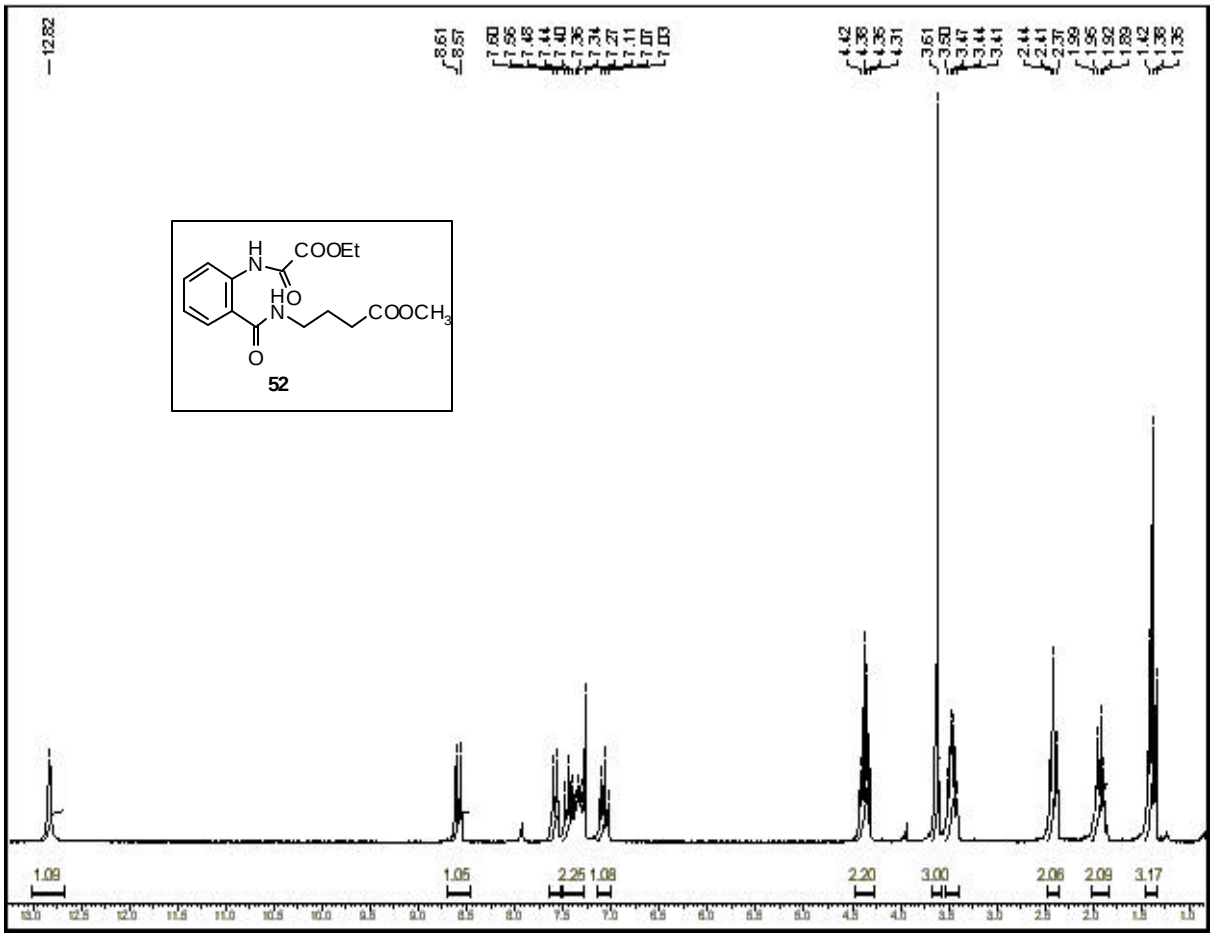


^{1}H NMR spectrum of compound [50] **(200 MHz, $CDCl_3$)**

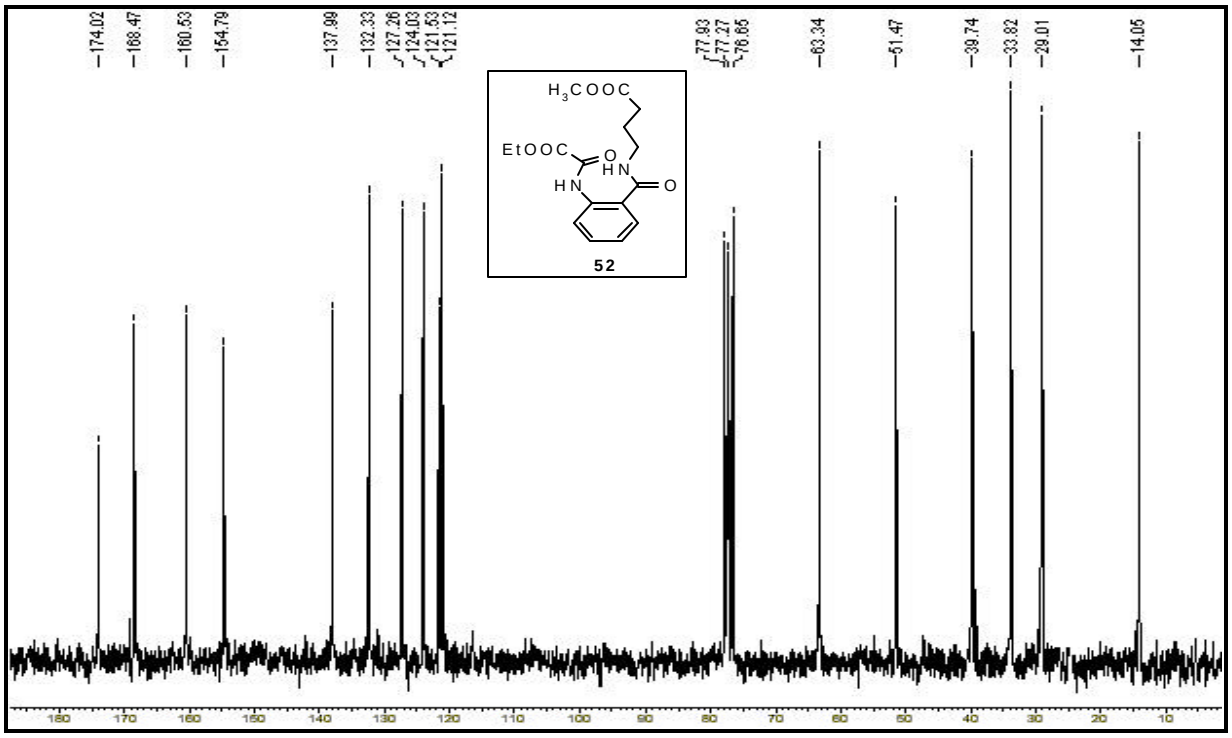


^{13}C & DEPT NMR spectra of Compound 50 **(50MHz, $CDCl_3$)**

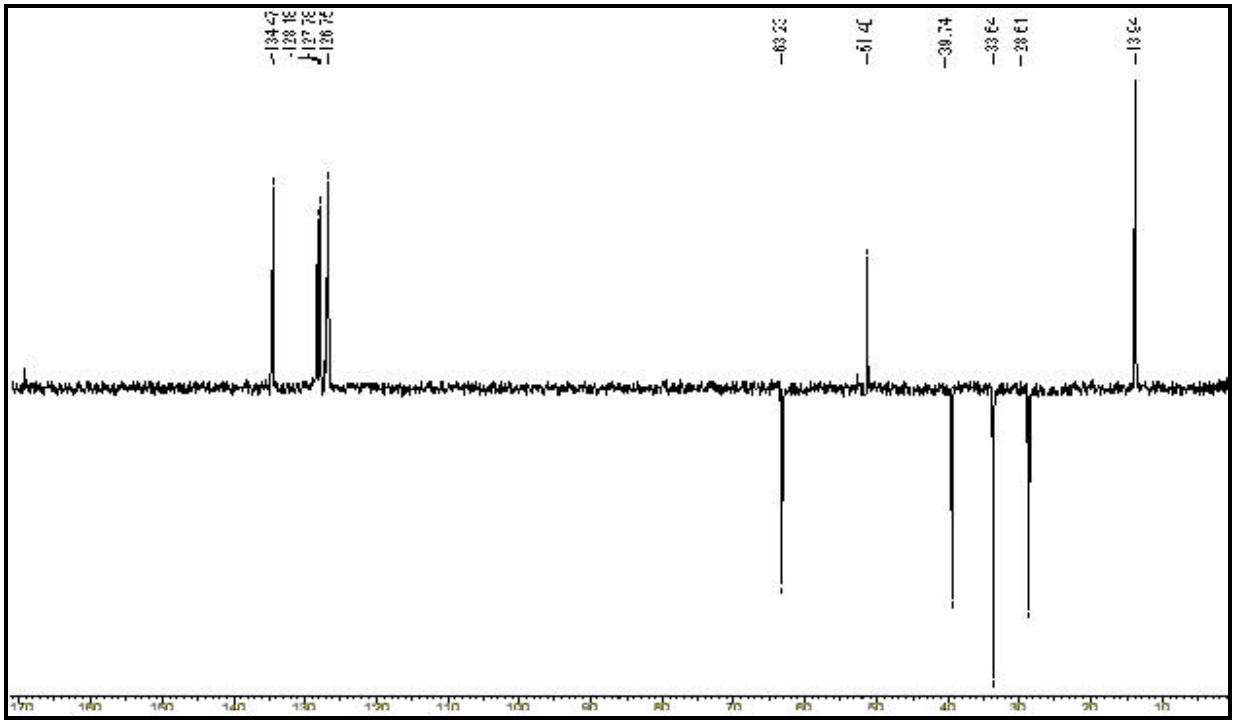


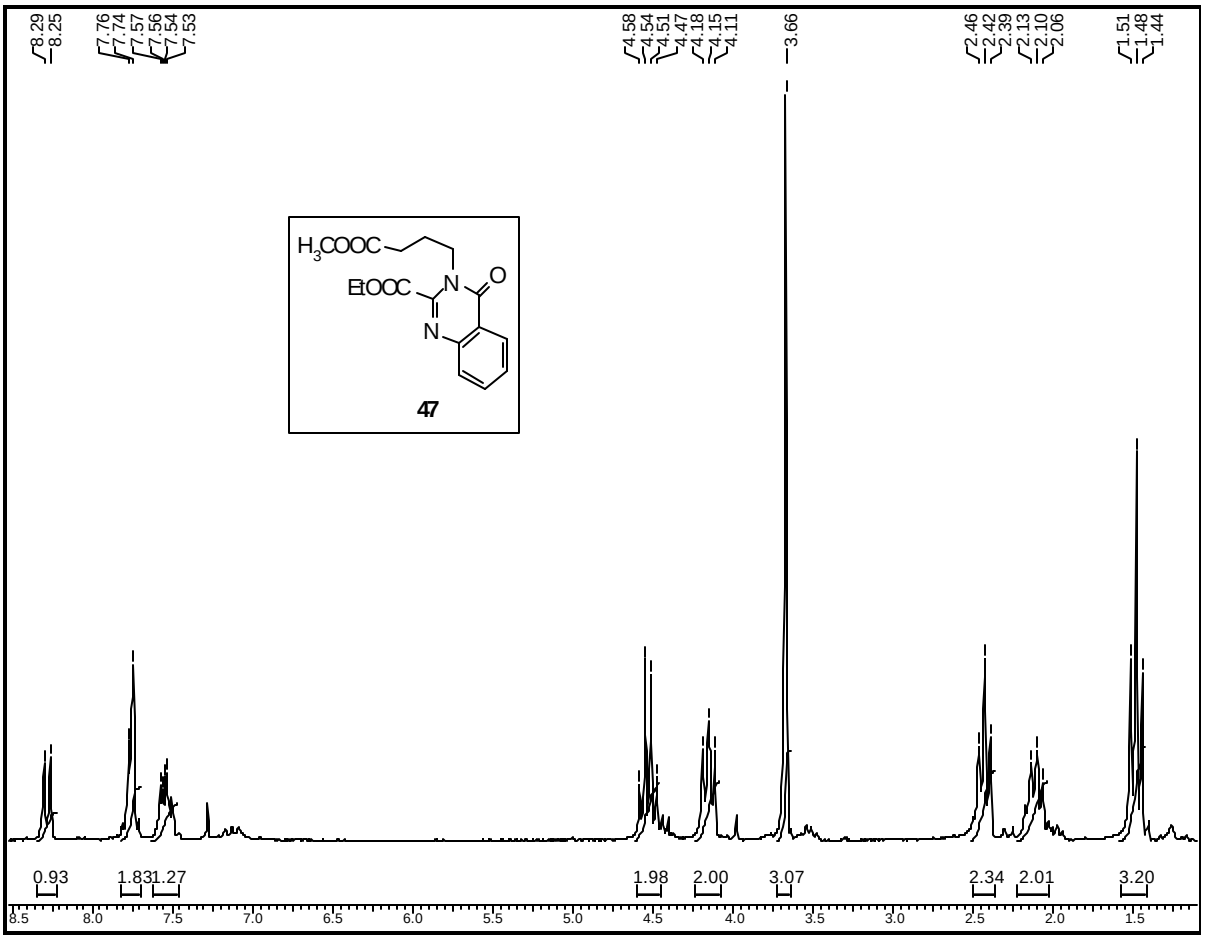


^{1}H NMR spectrum of compound 52 **(200MHz, $CDCl_3$)**

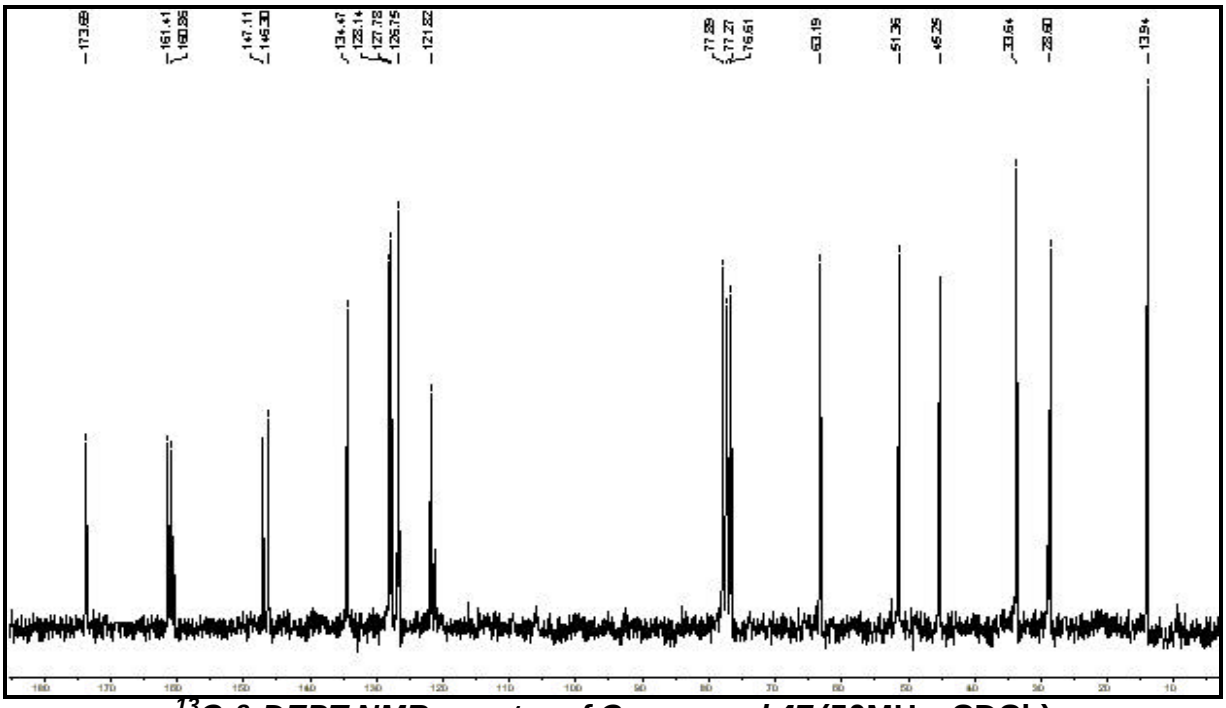


***^{13}C & DEPT NMR spectra of Compound 52* (50MHz, $CDCl_3$)**

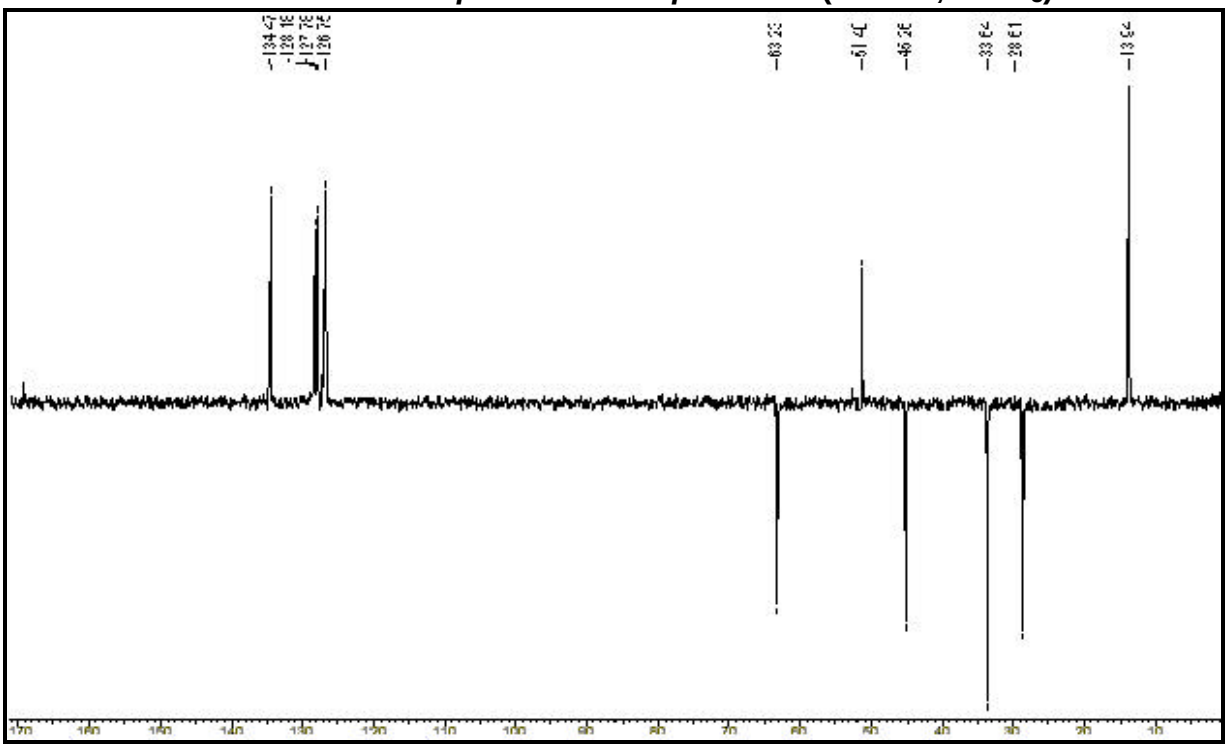


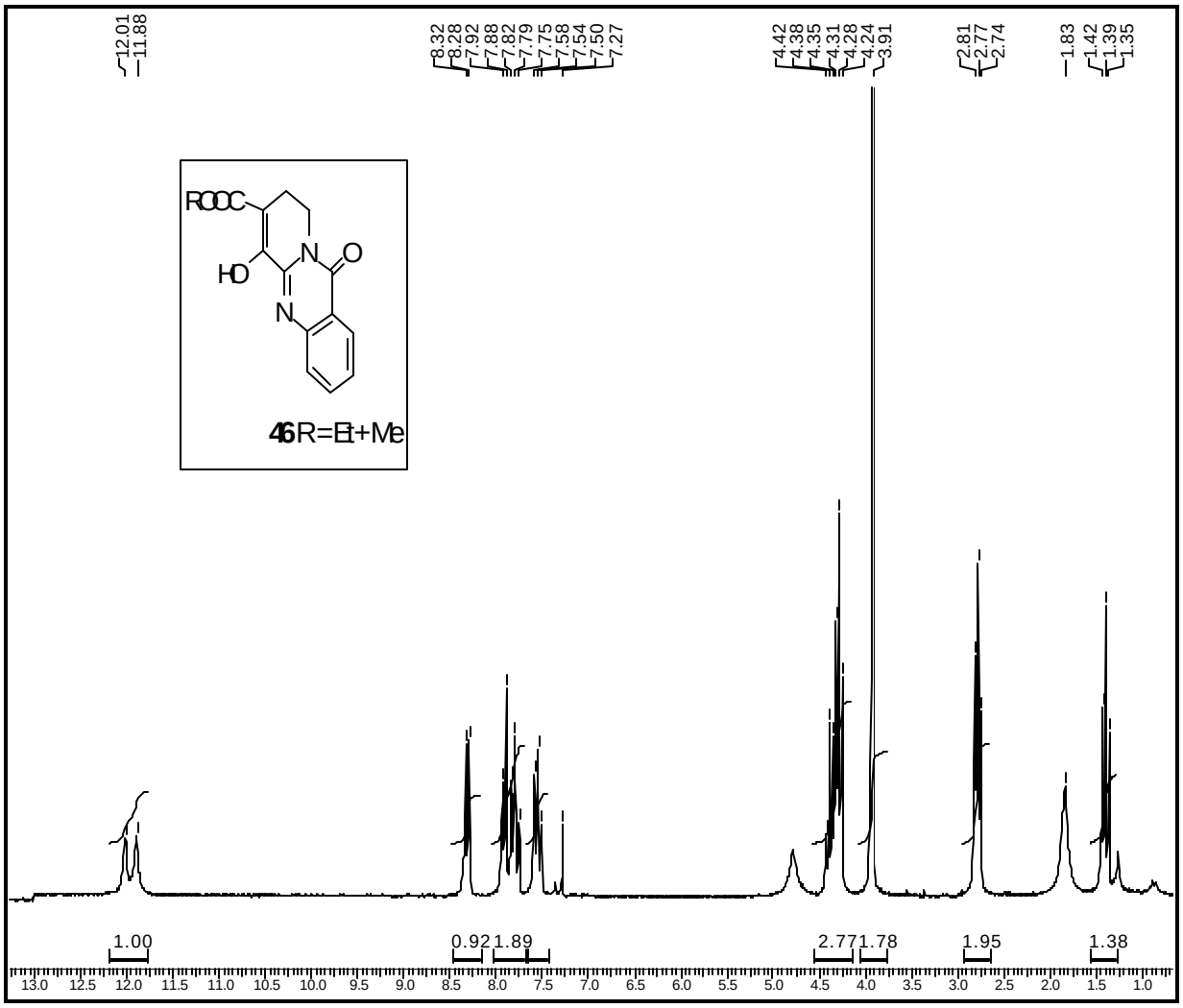


^{1}H NMR spectrum of compound 47 (200MHz, $CDCl_3$)

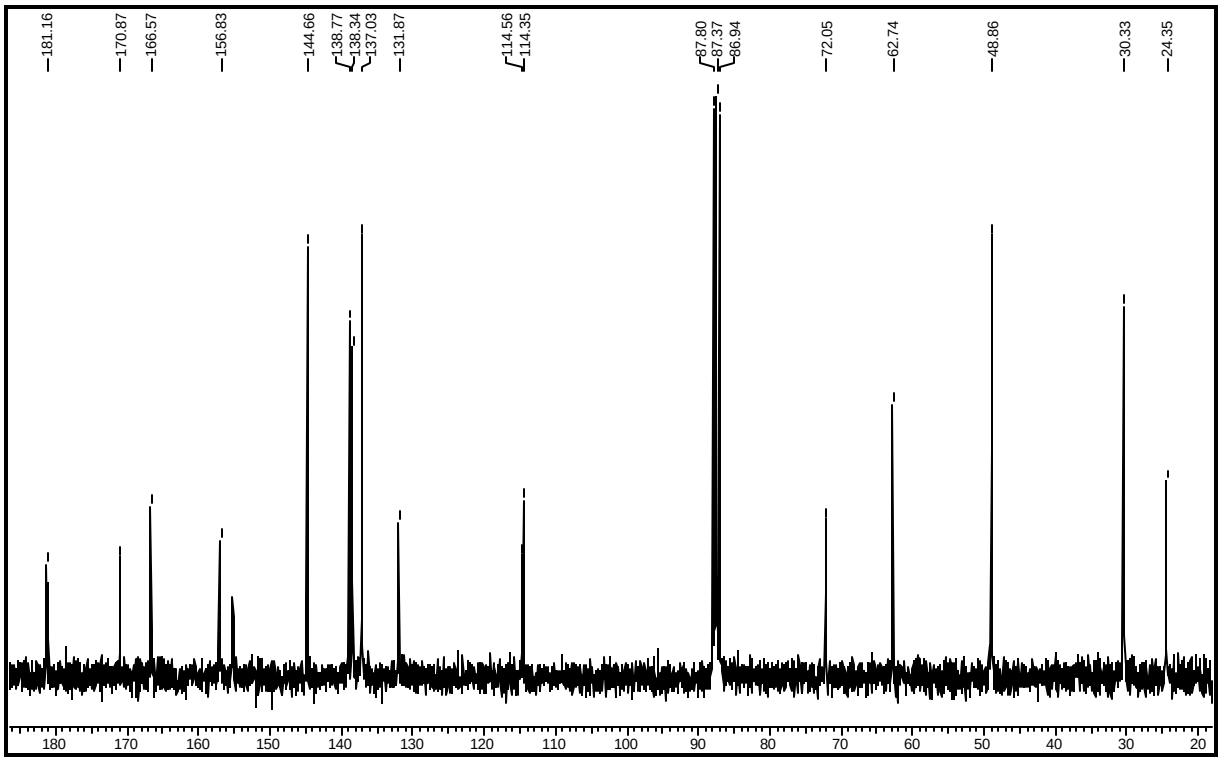


^{13}C & DEPT NMR spectra of Compound 47 **(50MHz, $CDCl_3$)**

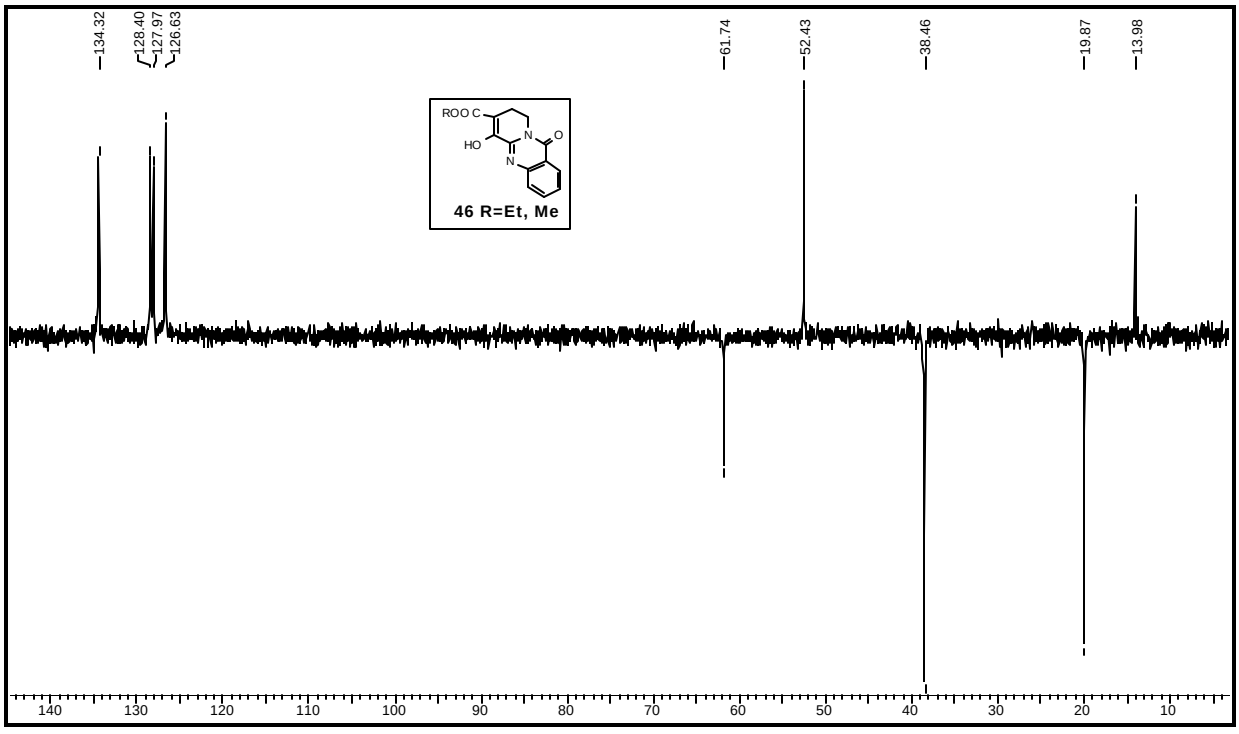


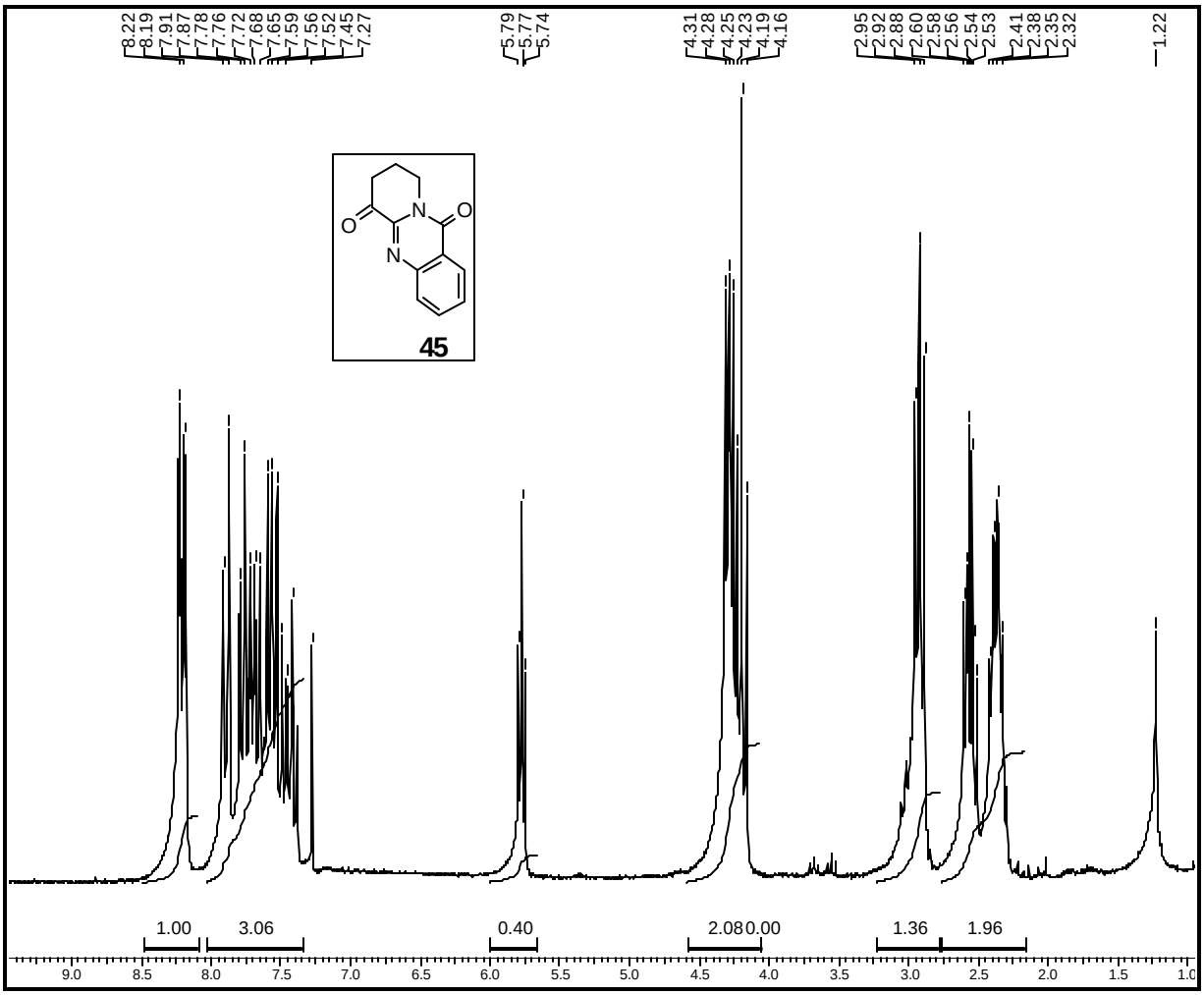


^{1}H NMR spectrum of compound 46 **(200 MHz, $CDCl_3$)**

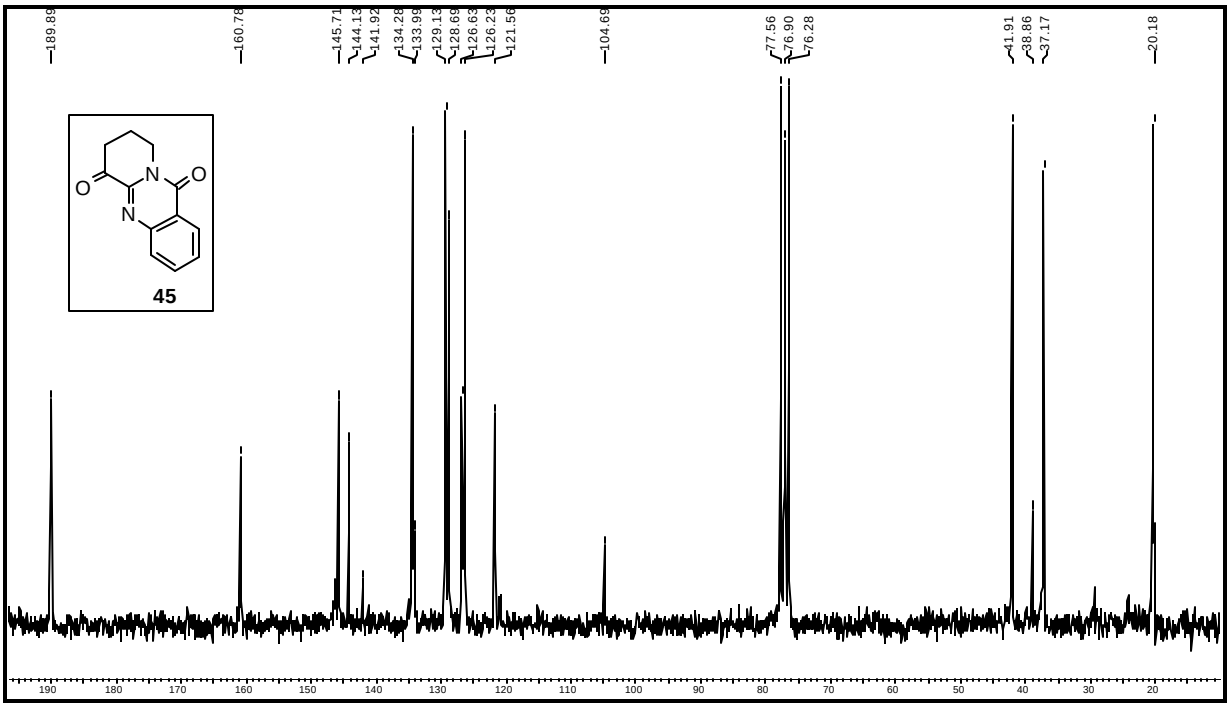


^{13}C & DEPT NMR spectra of Compound 46 **(50MHz, $CDCl_3$)**

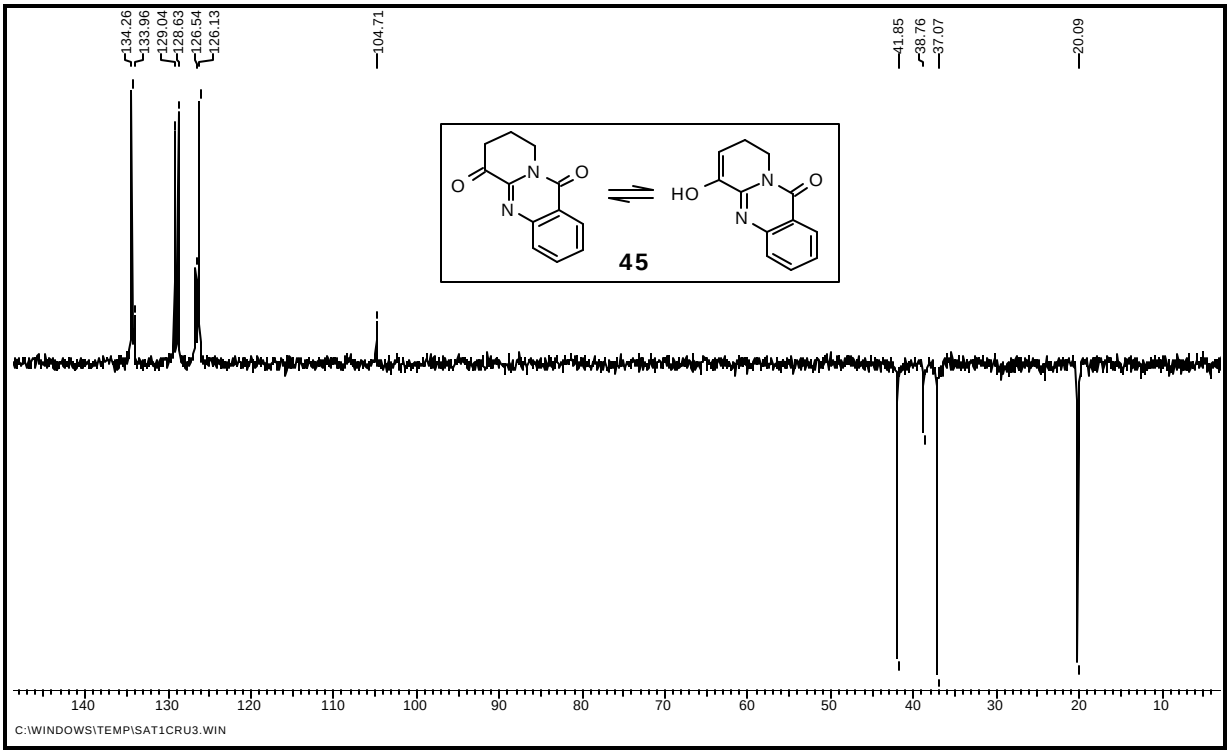


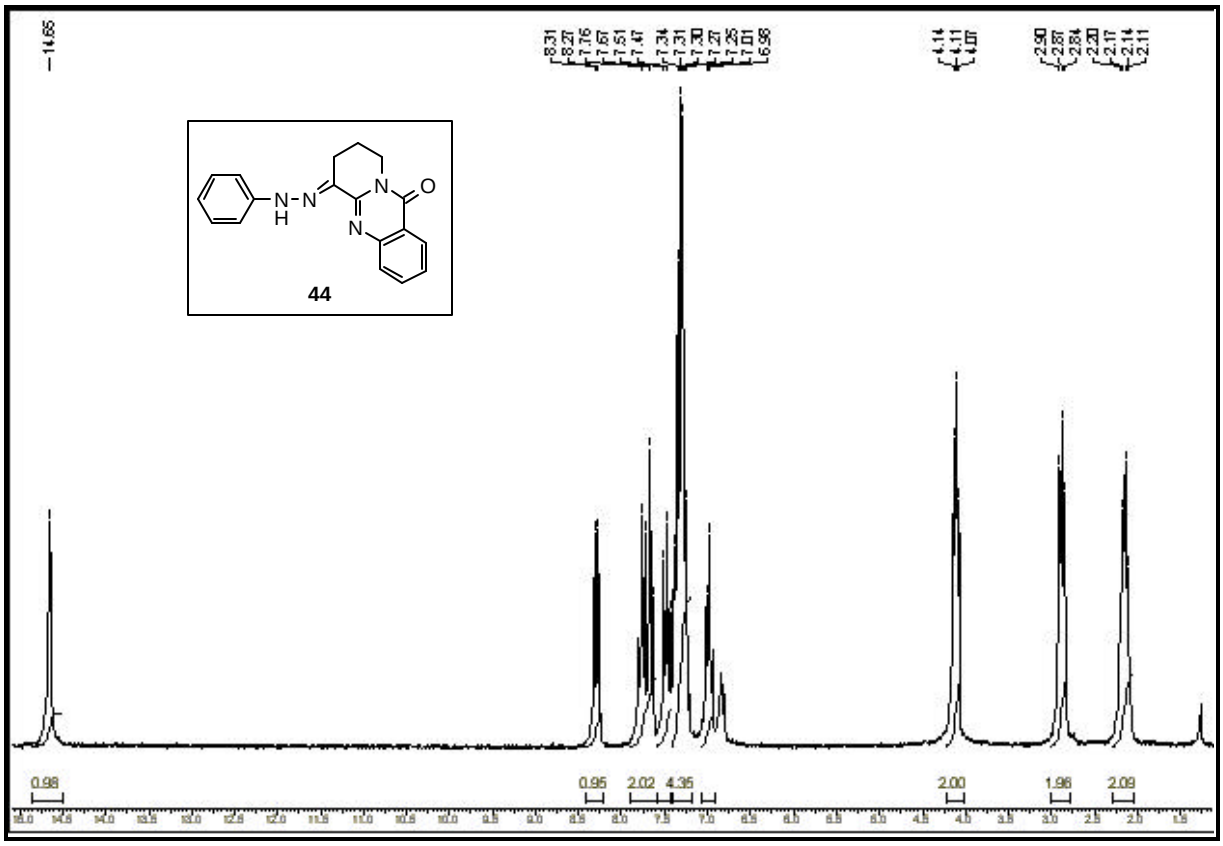


^{1}H NMR spectrum of compound 45 **(200MHz, $CDCl_3$)**

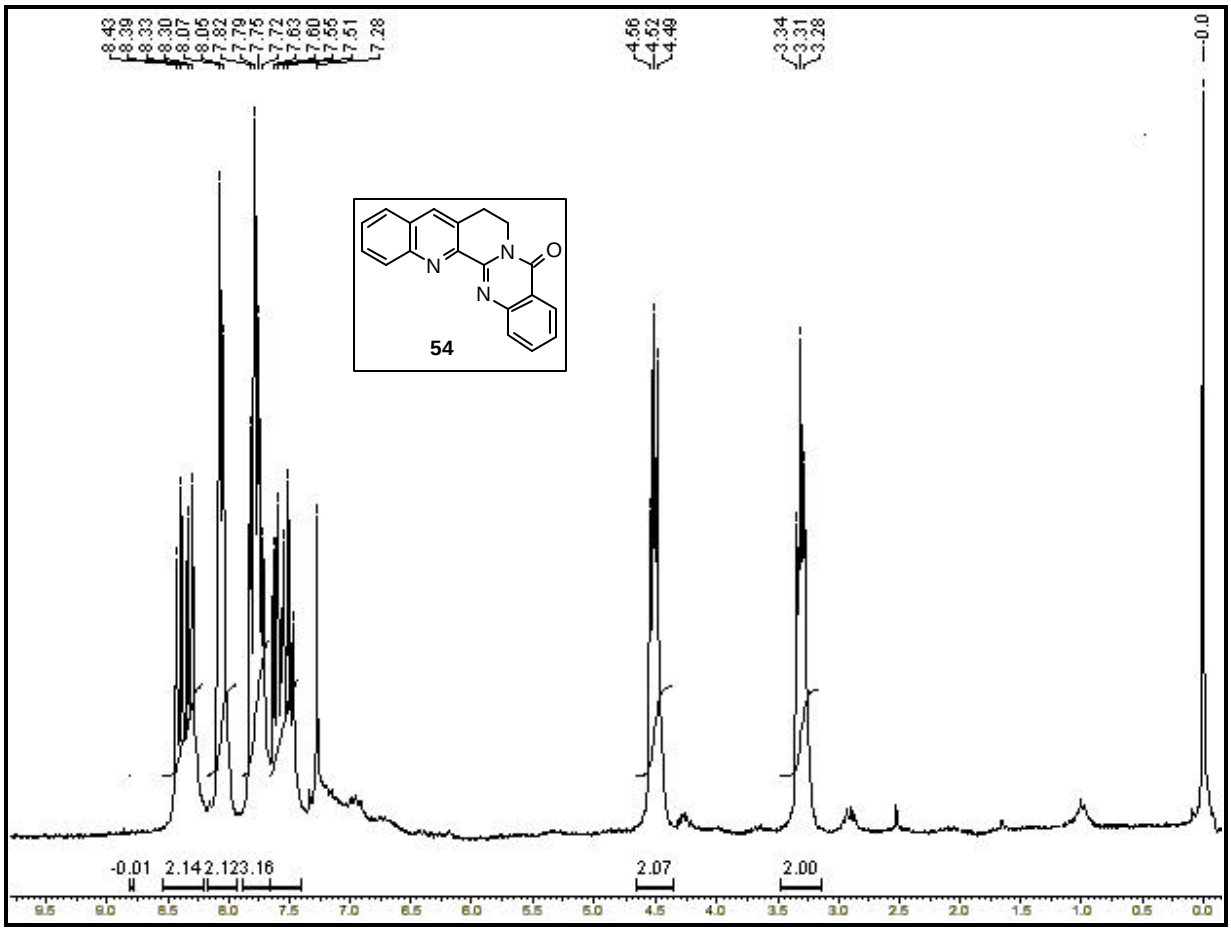


^{13}C & DEPT NMR spectra of Compound 45 **(50MHz, $CDCl_3$)**





***^{1}H NMR spectrum of compound 44* (200MHz, $CDCl_3$)**



***[1]H NMR spectrum of compound 54* (200MHz, $CDCl_3$)**

References

1. Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc*., **1966**, *88*, 3888.

2. a) Camptothecin*s: New Anticancer Agents*; Potmesil, M., Pinedo, H. M., Eds. CRC Press: Boca Raton, FL, 1995; b) Schultz, A.G.; *Chem. Rev*., *73*, 1973, 385. c) Wani, M.C.; Wall, M.E. *J. Org. Chem*, **1969**, *34*, 1364.

3. a) Muggia, F. M., In Camptothecin*s: New Anticancer Agents*; Potmesil, M., Pinedo, H. M., Eds.; CRC Press: Boca Raton, FL, **1995**; pp 43-50. b) Burris, H. A.; Fields, S. M.; Kuhn, J. G.; Von Hoff, D. D. in Camptothecin*s: New Anticancer Agents* , Potmesil, M., Pinedo, H. M., Eds.; CRC Press: Boca Raton, FL, **1995,** 113.

4. Hsiang, Y. H.; Hertzberg, R.; Hecht, S.; Liu, L. F. *J. Biol. Chem.*, **1985**, *260*, 14873-878.

5. LeMen, J.; Taylor, W.I. *Experientia.*, **1965,** *21*, 508.

6. Wu, T.S.; Chan, Y.; Leu, Y. l.; Chen, C.Y.; Chen, C.F. *Phytochemistry.*, **1996**, *42*, 907.

7. Govindachari, T.R.; Viswanathan, N. *J. Chem. Soc. Perkin Tran1*., **1974**, 1215

8. a) Pendark, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem*., 1994, *59*, 2623. b) Pendrak, I.;Wittrock, R.; Kingsbury, W. D. *J. Org. Chem.*, **1995**, *60*, 2912.

9. Das, B. Madhusudhan, P. *Ind. J. Chem*., **2001**, *40b* ,453. b) Govindachari, T. R.; Viswanathan.N.; *Phytochemistry*., **1972**, *11*, 3529. c) Tafur, S. Nelson, J. D.; Delong, D.C.; Svoboda, C.H. *Lloyda*, **1976**, *39*, 761. d) Gunasekhara, S.P.; Badani, M.M.; Cordell, G. A.; Fransworth, N.R.; Chitnis, M. *J. Nat. Prod*., **1979**, *42*, 475. e) Ariswa, M. *Plant Med*., **1981**, 43, 404. f) Dai, R. Hallock, Y.F, Cordellina, I.M.; Boyl, M.A. *J. Nat. Prod*, **1999**, *62*, 1427. g) Kitizawa, M.; Nakamura, M.; Takayama, H.; Suito, K.; Stockight, J. *Tetrahedron Lett*, **1997**, *38*, 8997. h) Aiara, R. Nagai, H.; Nakata,K.; Shinowara, C.; Sawada, S.; *Phytochemistry*, **1988**, *27*, 3663. i) Carte, B.K.; Debrose, C. Westley, J.W. *Tetrahedron*, **1990**, *46*, 2747.j) Brillo, A.; Verolta, L.; Gariberdi,P.; Torregiana, E.;Bomarddhi,E. *J. Chem. Soc. PerkinTrans1* **1995**, 583.

10. Wenkert, E.; Dave, K.G.; Lewis, R.G.; Sprague, P.W. *J. Am. Chem. Soc*., **1967,** *89*, 6741.

11. Winterfield, E. *Leibigs. Ann.Chem*., **1971**, *32*, 745.

12. Hutchinson, C.R.; Heckendorf, A.H.; Straughn, J.L.; Doddana, P.E.; Cane, D.E. *J. Am. Chem. Soc.*, **1974**, *56*, 996.

13. Cordell, G.A. *Lloydia.*, **1974**, *219*, 37.

14. Heckendorf, A.H.; Hutcinson, C.R. *Tetrahedron Lett*, **1972**, 4153.

15. a) Stockigt, J.; Zenk, M.H. *J. Chem, Soc., Chem. Comm*.**1977**, 646. b) Scott, A.I.; Lee Capita, S.C.; Culner, M.G.; Hutchinson, C.R. *Heterocycles* **1977**, *7*, 979.

16. Hutchinson, C.R.; Straughn, J.L Unpublished results

17. Shriera, GM.; Rapport, H. *Phytochemistry*., **1976,** *15*, 505

18. Hutchinson, C. R.; Heckendorf, A. H.; Straughn, J. L.; Doddana, P. E.; Cane, D. E. *J. Am. Chem. Soc*, **1979,** *101*, 3358.

19. Takimoto, C. H.; Wright, J.; Arbuck, S. G *Biochim. Biophys. Acta* **1998**, *140*, 107-119

20. Ginovanella, B.C., Hinz, H.R., Kozielski, A.J., Stehlin, J. S. J., Silber, R. and Potmesil, M. *Cancer Res.*, **1991**, 51, 3052–3055. b) Wani, M.C., Nicholas, A.W., Manikumar, G. and Wall, M.E., *J. Med. Chem*. **1987,** *30*, 1774–1779. c) Wani, M.C., Nicholas, A.W., Manikumar, G. and Wall, M. E. *J. Med. Chem*., **1987,** *30*, 2317-2319.

21. Hortwitz, M. S.; Hortwitz, S.B. *Biochem. Biophy. Res. Comm*., **1971,** *45*, 723-727.

22. Hortwitz, S.B.; Chang, C.-K.; Grollman,A.P. *Antimicro.Agents and Chemo.*, 2: 395-401.

23. Priel, E.; Showalter, S.D.; Blair, D.G. *AIDS Res. Hum. Retroviruses.*, **1991**, *7*, 65

24. a) Bodley, A.; Wani, M.; Wall, M.; Shapiro, T. *Biochem. Pharmacol.*, **1995,** *50*, 937.
b) Lucumi, A.; Robledo, S.; Gama, V.; Saravia, N. *Anti-microb. Agents Chemother*., **1998,** *42*, 1990. c). Wani, M. E; Nicholas, A.; Wall, M. C. *J. Med. Chem*., **1986**, *29*, 2358.

25. Bodley, A.; Cumming, J.; Shapiro, T. *Biochem. Pharmacol.*,**1998,** *55*, 709

26. Boseman, H. B., Coli. E *Biochem. Biophys. Res. Comm.*, **1970,** *41*,1412-1420,

27. Kessel, D.; Boseman, H. B., ; Lohr, K., *Biochem. Biophys. Acta*., **1972**, *269*, 210.

28. Hsiang, Y.H., Lihou, M.G., Liu, L.F., *Cancer Res*. **1989,** *49*, 5077,

29. Jaxel, C.; Kohn, K.W.; Wani, M. C.; Wall, M.E .; Pommier, Y. *Cancer Res.*, **1989**, *49*, 1465.

30. Covey, J.M.; Jaxel, C.; Kohn, K.W.; Pommier, Y. *Cancer Res.*, **1989,** *49*, 5016. b) Hsiang, Y.H. Liu, L. F. *Cancer Res.*, **1988,** *48*, 1722.

31. a) Nitiss, J.; Wang, J.C. *Proc. Nat. Acad. Sci. USA*. **1988,** *85*, 7501. b) Bjornisti, M-A.; Beneditti, P.; Viglianti, G.A.; Wang, J.C. *Cancer Res* ., **1989,** *49*, 6318. c) Eng, W.K.; Faucette, L.; Johnson, R.K.; Strenglanz, R. *Mol. Pharmacol.*, **1988,** *34*, 755.

32. Madden, K.R., Champoux, J. *J. Cancer Res.,* **1992,** *52*, 525.

33. a) Hsiang, Y. H.; Hertzberg, R.; Hecht, S.; Liu, L. F . *J. Biol. Chem*. **1985**, *260*, 14873.
b) Jaxel, C.; Kohn, K.W.; Pommier, Y. *Nuclic. Acids Res*., **1988,** *16*,11157. c) Jaxel, C.; Caprianico ,G.; Kerrigan, D.; Kohn, K.W.; Pommier, Y. *J. Biol. Chem* **1991.** *266*, 20418.

34. Portet, S.E.; Champoux, J.J. *Nucliec Acid Res.*, **1989 ,** *17*, 8521.

35. Hertzberg, R.; Carafa, M.J.; Hecht, S.; Liu, L. F . *Bio. Chem.* **1989**, *28*,4629.

36. Redinb, M.R.; Stewart, L.; Kuhn, P.; Champoux, J.J.; Hoi, W. G. *Science.,279*, 1504.

37. Fan, Y.; Kohn, K.W.; Shi, L.M.; Pommier, Y. *J. Med.Chem*, **1998**, *41*, 2216.

38. a) Pommier, Y.; Jaxel, C.; Heise, C. R.; Kerrigan, D.; Kohn, K. W. *Structure- activity relationship by* Camptothecin *derivatives: evidence for the existence of a ternary cleavable complex*; Oxford University Press: New York, **1991.** b) Jaxel, C.; Kohn, K. W.; Wani, M. C.; Wall, M. E.; Pommier, Y. *Cancer Res*., **1989**, *49*, 1465. c) Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, R. P. *J. Med. Chem.*, **1991**, *34*, 98. 107. d) Sawada, S.; Nokata, K.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem. Pharm.*

Bull., **1991**, *39*, 2574. d) Emerson, D. L.; Besterman, J. M.; Brown, H. R.; Evans, M. G.; Leitner, P. P.; Luzzio, M. J.; Shaffer, J. E.; Sternbach, D. D.;Uehling, D.; Vuong, A. *Cancer Res.*, **1995**, *55*, 603.

39. Kurihara, T. Tanno, H. Takemura, S¸ Harusawa, S.; Yoneda, Y. *J. Heterocycl. Chem.,* **1993,** *30*, 643.

40. Lackey, K.; Besterman, J.M.; Fletcher, W.; Leitener, P.; Morton,B.; Sternboch, D.D. *J. Med. Chem*, **1995,** *38*, 906.

41. Nicholas, A.W.; Wani, M. C.; Manikumar, G. Wani, M.E. Kohn, . K. W.; Pommier, Y. *J. Med. Chem.*, **1990,** *33*, 972.

42. Danishfesky, S.;Volkmann, R.; Horwitz, S. B. *Tetrahedron Lett* **1973,** 2521.

43. a) Mitsui, I.; Kuranazawa.; Hirota,Y.; Aonuma.; Sugimori, M.; Ohsuki, S.; Uoto,K.; Ejima, A.Teresawas, H. Sato, K. *Jpn. J. Chem. Res* **1996,** *55*, 776. b). Kim, D.A., Ryu, D.H.; Lee, J.Y,Lee, N,; Kim, Y.W.; Kim, J.S.; Chang, K.; Im, K.G.; Kim, T.K.; Choi. V.C. *J. Med. Chem.*, **2001,** *44*, 1594-1602.

44. a) Wall, M.E.; Wani, M.C. *Economic and Medicinal plant Research* vol 5, **1991**, Cha 5.
b) Wang, X.; Zhou, X.; Hecht, S. M. *Biochemistry*; **1999,** *38*, 4374.

45. a) Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc. Perkin Trans 1*., **1974**, 1215. b) Hertzberg, R. P.; Caranfa, M. J.; Holden, K. G.; Jakas, D. R.; Gallagher, G.; Mattern, M. R.; Mong, S.-M.; Bartus, J. O.; Johnson, R. K.; Kingsbury, W. D. *J. Med. Chem*. ,**1989**, *32*, 715. c) Adamovics, J. A.; Hutchinson, C. R. *J. Med. Chem*.**1979,** *22*, 310. d) Sawada, S.; Yaegashi, T.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem. Pharm. Bull*. **1993**, *41*, 310. e) Nicholas, A. W.; Wani, M. C.; Manikumar, G.; Wall, M. E.; Kohn, K. W.; Pommier, Y. *J. Med. Chem*., **1990**, 33,972. f) Ejima, A.; Terasawa, H.; Sugimori, M.; Ohsuki, S.; Matsumoto, K.; Kawato, Y.; Yasuoka, M.; Tagawa, H. *Chem. Pharm. Bull*., **1992,** *41*, 683. g) Ejima, A.; Terasawa, H.; Sugimori, M.; Ohsuki, S.; Matsumoto, K.; Kawato, Y.; Tagawa, H. *Chem. Pharm. Bull*., **1989**, *37*, 2253. h) Snyder, L.; Shen, W.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem*., **1994**, *59*, 7033.

46. Cao, Z.; Harris, N.; Kozielski, A.; Vardeman, D.; Stehlin, D.S.; Giovanella**,** B ., *J.Med. Chem*., **1998**, *41*, 31

47. a) Lavergne, O.; Lesueur-Ginot, L.; Rodas, F. P.; Bigg,D. C. H. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 2235. b) Lavergne, O.; Lesueur-Ginot, L.; Rodas, F. P.; Kasprzyk, P. G.; Pommier, J.; Demarquay, D.; Prevost , G.; Ulibarri, G.;Rolland, A.; Schiano-Liberatore, A.-M.; Harnett.; Pons, D.;Camara, J.; Bigg, D. C. H. *J. Med. Chem*. **1998,** *41*, 5410. c)Lavergne, O.; Harnett, J.; Rolland, A.; Lanco, C.; Lesueur-Ginot, L.; Demarquay, D.; Huchet, M.; Coulomb, H.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 2599. d) Bailly,C.; Lansiaux, A.; Dassonneville, L.; Demarquay, D.; Coulomb,H.; Huchet, M.; Lavergne, O.; Bigg, D. C. H. *Biochemsitry.*, **1999**, *38*, 15556. e) Lesueur-Ginot, L.; Demarquay, D.; Kiss, R.; Kasprzyk, P. G.; Dassonneville, L.; Bailly, C.; Camara, J.; Lavergne, O.; Bigg, D. C. H. *Cancer Res*., **1999**, *59*, 2939. f) Philippart, P.; Harper, L.; Chaboteaux, C.; Decaestecker,C.; Bronckart, K.; Gordover, L.; Lesueur-Ginot, L.;

Malonne, H.; Lavergne, O.; Bigg, D. C. H.; da Costa, P. M.;Kiss, R. *Clinical Cancer Res.* **2000**, *6*, 1557. g) Lavergne, O.; Demarquay, D.; Bailly, C.; Lanco, C.; Rolland, A.; Huchet, M.; Coulomb, H.; Muller, N.; Baroggi, N.; Camara, J.; Breton, C. L.; Manginot, E.; Cazaux, J.-B.; Bigg, D. C. H. *J. Med. Chem*., **2000**, *43*, 2285.

48. Larsen, A K; Gilbert, C; Chyzak, G; Plisov, S Y; Naguibneva, I; Lavergne, O; Lesueur- Ginot, L; Bigg, D C., *Cancer Research.*, **2001**, *61*, 2961-2967.

49. Bom, D.; Curran, D. P.; Chavan, A. J.; Kruszewski, S.; Zimmer, S. G.; Fraley, K. A.; Burke, T. G. *J. Med. Chem*., **1999**, *42*, 3018.

50. For reviews on the synthetic efforts in this field see: a) Shultz, A. G. *Chem. Rev*., **1973**, *73*, 385. b) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047.c) Hutchinson, C. R. in *The alkaloids*, Brossi,.**1983**, *21*,101 d) Curran, D.P.; Sisko, J.; Yeske, P.E., *Pure .Appl. Chem.*, **1993**, *65*, 1153.

51. a) Stork, G.; Schultz, A.G. *J. Am. Chem. Soc*., **1971**, *93*, 4074. b) Volkmann, R.; Danishefsky, S.; Eggler, J.; Solomon, D.M.; *J. Am. Chem. Soc*., **1971**, *93*, 5576. c) Sugasawa.T, Toyoda, T.; Sasakura, K. *Tetrahedron Lett*., **1972**, 5109. d) Shamma, M.; Georgiv.; *J. Pharm. Sci*, **1974**, *63*, 163. e) Corey, E. J; Crouse, D. N.; Anderson, J. E.; *J. Org. Chem.*, **1975**, *40*, 2140.f) Fang, C. F. S.; Morrow, C. J.; Rapoport. H. *J. Am. Chem. Soc*., **1975**, *97*, 159. g) Hutchinson, C. R.; *Tetrahedron.*, **1981**, *37*, 1047. h) Wani, M.C.; Ronman, P. E.; Lindley, J.T.; wall, M.E., *J. Med. Chem*., **1980**, *23*, 554. i) Ihara, M.: Noguchi, K.; Ohsawa, T.; Fukumoto, K.; *J. Org. chem.*,**1983**, *48*, 3150. j) Ejima, A.; Teresawa, H.; Sugimori, M.; Tagawa, H. *J. Chem. Soc. Perkin Trans I*, **1990**, *27*. k) Ejima, A.; Teresawa, H.; Sugimori, M.; Ohsuki, S.; Matsumoto, K.; Kawato, Y.; Tagawa, H.; *Chem. Pharm. Bull*., **1989**, *37*, 2253. l) Sawada, S; Okajima, R.; Aiyama, K.; Nokata, T.; Furuta, T.; Yokokura, Sugino, E.; Yamaguchi, K.; Miyasaka, T.; *Chem. Pharm. Bull*., **1991**, *39*, 1446. m) Kingsbury, W.D.; Boehm, J. C.; Jakas, D.R.; Holden, G.; Hecht, S.M.; Gallagher, G.; Caranafa, W. J.; McCabe, F.L.; Faucette, L. F.; Johnson, R. K; Hertzberg, R.P.; *J. Med. Chem*., **1991**, *34*, 98. n) Shen, W.; Coburn, C. A.; Bornamann, W. G.; Danishfesky, S. J. *J. Org. chem.*, **1993**, *58*, 611. o) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett*., **1994**, *35*, 5331.p) Jew, S-S.; Ok, K,-D.; Kim, H-J.; Kim, J. M.; Hah, J. M.; Cho, S. *Tetrahedron. Asymmetry.*, **1995**, *6*, 1245.

52. Thesis of Dr. M.S Venkatraman submitted University of Pune

53. Murata, N; Sugihara, T; Kondo, Y; Sakamoto, T., *Syn Lett.*, **1997**, 298

54. Ciufolini, M.A.; Roschangar, F.; *Tetrahedron*, **1997,** *53, 11049.*
b) Ciufolini, M.A.,Roschangar, F. *Angew. Chem. Int. Eng. Ed*., **1996**, *24*, 1692.

55. Fortunak, J.M.D.; Kitteringham, J.; Mastrocola, A.R.; Mellinger, M.; J. Sisti, N.J.; Wood J . L. and Ping, Z.Z. *Tetrahedron Letters*, **1996**, *37*, 5683.

56. Henegar, K.E.; Ashford,S.; Baughman, T.A.; Sih, J.C.; Gu, R-L. *J. Org. Chem*.**, 1997,** *62*, 6588.

57. Chavan, S.P.; Venkatraman, M.S. *Terahedron Lett.,***1998**, *40*, 3847.

58. Josien, H.; Ko, S. B.; Bom, D.; Curran, D. P *Chemistry - A European Journal*, **1998**, *4*, 67.

59. Brown, R.T.; Jianli, L.; Santos, C.A. M *Tetrahedron Lett.*, **2000,** *41, 859-862.*

60. Dumas, C.; Royer J.; Husson, H. P.; *Tetrahedron Lett.*, **2001**, *42*, 8973.

Dumas, C.; Royer J.; Husson, H.-P *Eur J. Org Chem.*, **2000,** 3601-3606.

61. Bennasar, M.-L.; Juan, C.; Bosch, J. *Chem Comm*., **2000,** *2459-2460*

62. Krohn, K.; Winterfield, E. *Chem Ber.*, **1975**, *108*, 2126.

63. Keiko, T.; Norio, N.; Shigeki,S.; Yoshimitsu. *Heterocycles*, **2000**, *53*, 771-776 .

64. Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, H.; Kanai, M.; Du, W.; Curran, D. P.; Masakatsu.; *J. Am. Chem. Soc.*, **2001,** *123*, 9908.

65. Comins, D. L.; Nolan J. M. *Org. Lett.*, **2001,** *3*, 4255-4257.

66. Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *J. Chem .Soc. Perkin Trans 1***1975**, 1825.

67. Comins, D.L.; Saha, J. K. *J.Org. Chem*., **1996**, *61*, 9623.

68. Comins, D.L.; Saha, J. K. *J.Org. Chem*., **1994**, *59*, 5120.

69. Curran, D.P.; Josien, H. *Tetrahedron*., **1997**, *53*, 8881.

70. Curran, D.P.; Hui, L. *J. Am. Chem. Soc.*, **1992**, *114*, 5863.

71. Curran, D.P.; Ko, S-B. Josien, H. *Angew. Chem. Int. Ed. Eng*., **1995**, *34*,2683.

72. Frutos, O.D.; Curran, D. P. *J. Comb. Chem*., **2000**, *2*, 639-649.

73. Boger, D. L.; Hong. *J. Am Chem. Soc.*, **1998**, *120*,1218-1222.

74. Yadav, J. S.; Sarkar, S.; Chandrasekhar, S. *Tetrahedron.*, **1999**, *55*, 5449-5456

75. RamaRao, A, V.; Yadav, J. S.; Valluri, M. *Tetrahedron Lett*, **1994,** *35*, 3613

76. Mekouar, K.; Génisson, Y.; Leue, S.; Greene A.E. *J Org Chem*., **2000,** *65*, 5212.

77. Toyota, M. Komori, C.; Ihara, M. *J. Org. Chem*., **2000,** *65*, 7110-7113

78. Kingsbury, W.D. *Tetrahedron Lett*, **1994**, *35*, 6847

79. Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Wood, J.L. *Tetrahedron Lett.*, **1994,** *35*, 5763-5764.

80. Das, B.; Madhusudhan P.; Kasinatham. *Tetrahedron lett*.,**1998**, *39*, 431.

81. Das.B, Madhusudhan, P. *Syn. Comm*., **2000**, *30*, 3321.

82. Das, B.; Madhusudhan, P.; Kashinatham, A. *Bio & Med. Chem Lett.*, **1998**, 1403-1406.

83. Das, B.; Madhusudhan, P. *Tetrahedron* .,**1999**, *55*, 7875.

84. Das, B.; Madhusudhan, P. *J. Chem. Res.*, **2000,** 476.

85. Though this condensation is not aldol condensation in its true sense, the term has been used for the sake of convenience.

86. a) Kwaiatkowski, S.: Jeganathan, A.; Tobin, T, Watt, D.S. *Synthesis*, **1989**, 946

b) Yamamoto, Y.; Asao, N.; Uyehara, T.; *J. Am. Chem. Soc*, **1992**, *114*, 5427.

c) Dumas, F.; Mezrhab, B.; d'Angelo, J.; Riche, C; Chiaroni, A. *J. Org. Chem*., **1996,** 61, 2293.

c) For quinazolinone heterocycles : Saito, T; Tsuda, K. *Tetrahedron Lett., 37,* **1996,** 9071.

87. a) Meth-Cohn, O.; Narine, B; Tarnowiski, B. *J.Chem.Perkin Trans 1*. **1981,**1537.

b) Meth-Cohn, O.; Narine, B; Tarnowiski, B. *J. Chem. Perkin Trans1*. **1981,** 2509.

88. Ali, M. M.; Tasneem; Rajanna, K. C.; Prakash, P. K. Sai., *Synlett*, **2001,** (*2*), 251-253

89. Jiro Tsuji in " *Palladium reagents in organic synthesis*" John Wiley& Sons, **1995**

90. a) Janine. C.; Christophe, P.; Pardo, G; Domingo Tetrahedron Lett., **1998**, *39*, 2965-2968.

b) Comins, D L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc*., **1992**, *114* , 10971-2.

91. a) Mekouar, K.; Génisson, Y.; Leue, S.; Greene A.E.; *J Org Chem*., **2000**, *65*, 5212-5215

b) Toyota, M. Komori, C.; and Ihara, M.*; J.Org. Chem*., **2000**, *65*, 7110-7113

92. Ciufolini, M.A.; Roschangar, F.; *Tetrahedron*, **1997,** *53, 11049*

Ciufolini, M.A.; Mitchell, J.W.; Roschangar, F.; *Tetrahedron Lett,* **1996,** *37* , 8281

93. a) Nadin, A.; *J. Chem. Soc. Perkin Trans. 1* **1998**, 3493-3513. b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927-964.

94. a)Gothelf, K. V.; Jorgensen, K. A.; *Chem. Rev*. **1998**, *98*, 863-909. b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*,2475-2486.

95. a) Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett*. **1992**, *33*, 6359-6362. b) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev*.**1999**, *28*, 199-207.

c) Tamaru, Y.; Kimura, M. *Synlett* **1997**,749-757.

d) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J.; *J. Am. Chem. Soc*. **1999**, *121*, 3633-3639

96. For some reviews, see: (a) Cardillo, G.; Tomasini, C. Chem. Soc. Rev. **1996**, 117. b) Cole, D. C.*Tetrahedron* **1994**, *50*, 9517. c) Enantioselective Synthesis of -Amino Acids; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

97. a) Yang, B.H.; Buchwal, S.L; *Org. Lett*., **1999**,*1*, 35.

b) Wolfe, J. P.; Wagaw, S.; Marcoux, J. -F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805.

c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem*. **1999**, *576*, 121.

d) Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2090

e) Hartwig, J. F. *Synlett* . **1997**, 329.

f) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

g) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

98. a) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellow, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 1900.

b) Larock, R. C.; Tu, C; Pace, P. *J. Org. Chem*., **1998**, 63, 6859.

c) Larock, R. C.; Berrois-pena, N. G.; Fried, C. A.; Yum, F.C.; Tu. C.; Leong, W. *J. Org. Chem*., **1993**, 58, 4509

99. Finklestein, H.; *Chem.Ber.*, **1910,** *43*, 1528

100. Suwa, T. Shibata, I.; Nishino, K.; Baba, A.; *Org. Lett.*, **1999,** *1*, 1579 -1581,.

101. Ojea, V.; Conde, S.; Ruiz, M.; Fernandez, M.; Quintela, J. M. *Tetrahedron Lett*., **1997**, *38*, 4311.

102. a) Stackem, Heck, R.F. *J. Org. Chem*., **1980**, *45*, 3584. b) Jeffery , T. *Tetrahedron Lett*., **1992**, 33, 1989.

103. Kuchar, M.; Kakac, B.; Newark, O.; Kraus, E.; Holubek, J. *Collect. Czech. Chem. Com*, **1973**, *38*, 447.

104. a) Baskaran, S.; Das, J.; Chandrasekhran, S.; *J. Org. Chem*., **1992**, *57*, 1928.

b) Baskaran, S.; das, J.; Chandrasekhran, S.; *J. Org. Chem*, **1989**, *54*, 5128.

c) Sreenivasan, N.S.; Lee, D. G.; *synthesis*, **1979**,520.

d) Crout, D. H.G.; Rathdone, D. L.; *synthesis*, **1989**, 40.

105. Walla, D.M.; Pryzybyla, C. A.; Walker, Jr. C. B. *J. Am. Chem. Soc*., **1990**, *112*, 5624.

106. Chavan, S. P.; Venkatraman, M. S. *Tetrahedron lett.***, 1998**, 40, 3847.

107. Ciufolini, M. A.; Roschangar, F.; *Tetrahedron*, **1997,** *53, 11049*. b) Ciufolini, M. A.; Roschangar, F.; *Angew. Chem. Int. Eng. Ed*., **1996**, *24*, 1692.

108. Wall, M. E.; Campbell, H. F.; Wani, M. C.; Levine, G. S.; *J. Am. Chem. Soc*., **1972**, *94*, 3631

109. Stork, G.; Schultz, A. G. *J. Am. Chem. Soc*., **1971**, *93*, 4074.

110. Wall ME, Wani MC: Camptothecin and taxol: discovery to clinic--Thirteenth Bruce F. Cain Memorial Award Lecture. *Cancer Res.*, **1995**, *55*, 753-760.

111. On April 19 of **1996**, FDA's Oncologic Drugs Advisory Committee unanimously recommended approval of Topotecan as second line therapy to treat advanced ovarian cancer. Topotecan is marketed by SmithKline Beecham of Philadelphia, Pa.

Hycamtin (Topotecan hydrochloride) for injection, by SmithKline Beecham Pharmaceuticals received additional approval on November 30, **1998**.

b) Irinotecan (Camptosar) received full approval from the FDA in **1998** as a second-line treatment for metastatic colorectal cancer to Pharmacia & Upjohn Company.

112. Henegar, K.E.; Ashford, S.; Baughman, T.A.; Sih, J. C.; Gu, R-L. *J. Org. Chem.*, **1997,** *62*, 6588 and references cited there in.

113. a) Curran, D.P.; Josien, H. *Tetrahedron*., **1997**, *53*, 8881

b) Comins D.L.; Nolan J.M. *Org Lett*; **2001,** *3,* 4255-4257 and references cited there in.

114 a) Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org.Chem*. **1975**, 40, 2140.

b) RamaRao, A, V.; Yadav, J.S.; Valluri, M. *Tetrahedron Lett*, **1994,** *35*, 3613.

115 O'Donell, M.J.; Polt, R.L. *J. Org. Chem*., 1982, 47, 2603

116. Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem*. **1975**, *40*, 2140.

117. Wall, M. E.; Wani, M. C.; Kalper, J. A.; Thompson, J. B.; Levine, G. S.; *Chem. Comm*., **1970**, 404.

118. Zalkow, L. H.; Nators, J. B.; French, K.; Bisarya, S.O. *J. Chem. Soc (C)*, **1971**, 3551

119. Rama Rao, A.V.; Yadav, J. S.; Valluri, M.; *Tetrahedron Letters*, **1994**, *35*, 3613

120. Fortunak, J. M. D.; Kitteringham, J.; Mastrocola, A. R.; Mellinger, M.; J. Sisti, N. J.; Wood J.L.; Ping, Z. Z., *Tetrahedron Lett*, **1996**, *37*, 5683

121. Labelle; Gravel, *J. Chem. Soc. Chem. Commun*, **1985**, 105

122. Bradely, J. C.; Buchi, G. *J. Org. Chem.*, **1976**, *41*, 699

123. Walraven, H. G. M.; Pandit, U. K.; *Tetrahedron*, **1980**, *36*, 321.

124. Narasimhan, N. S.; Sunder, N M.; Ammanamanchi, R.; Bonde, B, D. *J. Am. Chem. Soc.*, **1990.** *112*, 4431,

125.. Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081

126. Mornet, R.; Gouin, L.*Tetrahedron Lett.*, **1977**, *18*, 167

127. Salvador, R. L.; Simon, D., *Can. J. Chem.*, **1966**, *44*, 2570

128. Mornet, R.; Gouin, L. *Bull. Chem. Soc. France*., **1977**, 737

129. Kcmetani, T.; Shiotani ,S.; Mitsuhashi, H. *Chem. Pharm. Bull*., 1976, *24*, 342

130. a) Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc. Perkin. Trans 1*, **1975**, 1825.

b) Comins, D.L.; Saha, J. K. *J. Org. Chem*., **1996**, *61*, 9623.

c) Comins, D.L.; Saha, J. K. *J. Org. Chem*., **1994**, *59*, 5120.

d) Curran, D.P.; Josien, H. *Tetrahedron*., **1997**, *53*, 8881.

e) Curran, D. P.; Hui, L. *J. Am. Chem. Soc.*, **1992**, *114*, 5863.

f) Curran, D. P.; Ko, S-B. Josien, H. *Angew. Chem. Int. Ed. Eng*., **1995**, *34*, 2683.

g) Frutos, O.D.; Curran, D. P. *J. Comb. Chem*., **2000**, *2*, 639.

h) Yadav J. S.; Sarkar, S.; Chandrasekhar, S. *Tetrahedron.*, **1999**, *55*, 5449.

131. Boger, D. L.; Hong. *J. Am. Chem. Soc.*, **1998**, *120*, 1218.

Mekouar, K.; Génisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem*., **2000,** *65*, 5212.

Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem*., **2000**, *65*, 7110.

132. For reviews on the Claisen rearrangement: a) Wipf, P. In *Comprehensive Organic Synthesis*; rost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., **1991**; Vol. 5, Chapter 7.2, p 827.

For some recent elegant studies on stereoselective Claisen rearrangement, see:

a) Hiersemann, M.; Abraham, L. *Org. Lett.* **2001**, *3*, 49.

b) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911.

c) He, S.; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 190.

d) Yoon, T. P.; Dong, V. M. MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.

133. Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.*, **1998**, *40*, 3847.

134. Hayshi, T.; Kanihera, K.; Hagihara, T.; Kumuda, M. *J. Org. Chem.*, **1988**, *53*, 113.

135. Johansson, R.; Samuelsson, B. *J. Chem. Soc. Perkin Trans I*, **1984**, 2371.

136. Tang, C.; Rapport, H. *J. Am. Che. Soc.*, **1972**, 8615.

137. a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 885.

138. Cooper, J.; Knight, D.W.; Gallagher, P.T. *J. Chem. Soc., Perkin Trans.1*, 1992, 553.

139. Lissel, M.; Drechsler, K. *Synthesis,* **1983**, 459.

140. a) Patil, N.T.; Tilekar, N.J; Dhavale, D.D. *J. Org. Chem.* **2001**, *66*, 1066.

b) Curran, D. P. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., **1991**; Vol. 4, p 779.

141. Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K,. Heterocycles 1975,3,167

142. Ma, Z-Z; Hano, Y; Nomura, T; Chen, Y-J *Phytochemistry*, **2000**, *53*, 1075.

143. Ma, Z-Z; Hano, Y; Nomura, T.; Chen, Y. J. *Heterocycles,* **1999**, *51*, 1883.

144. Xiao, X. H.; Qoh, G-L, Wang, H-L.; Lui, L. S.; Zheng, Y. L. Jia, J.; Dens, J. B. *Chinese J. Pharmacol. Toxicol,* **1988**, *2*, 232

145. a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G.A., *J. Am. Chem. Soc*., 1966, *88*, 3888. b) *Camptothecins: New AnticancerAgents*; Potmesil, M., Pinedo, H. M., Eds.; CRC Press., Boca Raton, FL, 1995;

146. Ma, Z-Z; Hano, Y; Nomura, T; Chen, Y-J *Phytochemistry*, **2000**, *53*, 1075

147. Wang, H.; Ganesan, A. *Tetrahedron Lett*. **1998**.9097, *39*,

148. Kelly, T. R.; Chamberland, S; Silva, R. A. *Tetrahedron Lett*., **1999,**40,2723

149. Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y.J. *Heterocycle*s, **1999,** 51,1593

150. Onaka, T. *Tetrahedron Lett*., **1971**, *12*, 4387.

151. Molina. P.; Tarraga, A. Tejero, A.G. *Synthesis* 1523, *11*, **2000**

152. Southwick, P.L.; Previc, E.P.;Cassanova, J.; Carlson, E. *J. Org. Chem*., **1956**, 1087. Shamma, M.; Novak, Z. *Collect. Czech. Chem. Comm*., **1970**, *35*, 3280.

153. Dighe, V. S.; Somasekhara, S.; Bagavant, G.; Mukherjee, S. L. *Current Sci. (India)* **1964**, *33*, 78.

154. Ph.D Thesis of Dr. Neelam Ghokale submitted to university of Pune.

155. Comins, D.L.; Baevsky, M.F.; Hao, H., *J. Am. Chem. Soc*, **1992**, *114*, 10971

156. Tsuji. J., " *Palladium reagents in organic synthesis*" John Wiley& Sons, **1995**

157. Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thomas, G.; Kulicke, K.J.; Trach, F. Org.React., 48, 1996

158. Comins, D.L.; Saha, J.A., *Tetrahedron Lett*, **1995**, *36*, 7995

159. Fortunak, J.M.D.; Kitteringham, J.; Mastrocola, A.R.; Mellinger, M.; J. Sisti, N.J.; Wood J. L. and Ping, Z.Z. *Tetrahedron Letters*, **1996**, *37*, 5683 and preceding paper.

160 a) Susse, M. V.; Alder, F.; Johne, S., *Helv. Chem. Acta*, **1986**, 1017. b) Nakanishi, S, Masett, S.S, *Org. Prep. Proc*, 1980, 220

161. Varma, R.S.; Naicker, K.P.; Tetrahedron Letters, **1999**, *40*, 6177-6180

162. Amine, M.S.; Hashash, M. A.; Attia, J., *Ind. J. Chem. Soc*. **1993**, 577.

163. a) Lalezari, I.; Stein, C. A. *J. Heterocycl. Chem*. **1984**, *21*, 5. b) Kornet, M. J.; Varia, T.; Beaven, W. *J. Heterocycl. Chem*. **1984**, *21*, 1533. c) Maillard, J.; Vincent, M.; Benard, M.; Jolly, R.; Morin, R.; Menillet, C. *Chim. Ther*. **1968**, Mar-Apr, 100. d) Papadopoulos, E. P.; Torres, C. D. *J. Heterocycl. Chem*. **1982**, *19*, 269 e) Dean, W. D.; Papadopoulos, E. P. *J. Heterocycl. Chem*. **1982**, *19*, 1117 f) Mayoral, J.; Melendez, E.; Merchan, F.; Sanchez, J. *Synthesis* **1981**, 962. g) Couture, A.; Cornet, H.; Grandclaudon, P. *Synthesis* **1991**, 1009 .h) Paster, G.; Blanchard, C.; Montginoul, C.; Torreilles, E.; Giral, L. *Bull. Soc. Chim. Fr*. **1974**, 1331. i) Herlinger, H. *Angew. Chem., Int. Ed. Engl*. **1964**,

3, 378. j) Garin, J.; Melendez, E.; Merchan, F. L.; Tejero, T.; Villarroya, E. *Synthesis* **1963**, 406. k) Taylor, E. C.; Shvo, Y. *J. Org. Chem.* **1968**, *33*, 1719. l) Papadopoulos, E. P. *J. Heterocycl. Chem.* **1981**, *18*, 515. m) Papadopoulos, E. P. *J. Heterocycl. Chem.* **1980**, *17*, 1553. k)Minami, T.; Ogata, M.; Hirao, I. *Synthesis* **1982**, 231. n) Canonne, P.; Aksssira, M.; Dahdouh, A.; Kasmi, H.; Boumzebra, M. *Heterocycles* **1993**, *36*, 1305. o) Al-Talib, M.; Jochims, J. C.; Hamed, A.; Wang, Q.; Ismail, A. E. *Synthesis* **1992**, 697. p) Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12. q) Doleschall, G.; Lempert, K. *J. Monatsh. Chem.* **1964**, *95*, 1068. r) Gouilleux, L.; Fehrentz, J.-A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7031. s) Buckman, B. O.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439. t) Villalgordo, J. M.; Obrecht, D.; Chucholowsky A. *Synlett* **1998**, 1405-1407

164. Subrahmanyam, D.; Sarma, V.M.; Venkateswarulu, A.; Sastry, V.R.S.T.; Srinivas, S.S.V.A., Krishna, C.V.; Deevi, D.S.; Kumar, A.S.; Babu, M. J.; Damodaran, N.K.; *Bioorg. Med. Chem. Lett*., **2000**, *10*, 369

165. a) Zagg; Martin. *Org. React.,* **1965**, *14*, pp 52-69. b) Gilbert, *synthesis*, **1972**, 80. c) Challis in *'The chemistry of Amides'*, pp 754-759

166. The spectral data matched with that of the data provided by Wang, H. and Ganesan, A. We thank them for the same.

167. Amin, A.H.; Mehta, D. R. *Nature,* **1959**, *183*, 1317

168. Mehta, D. R.; Naravane, J. S.; Desai, R. M. *J. Org. Chem*., **1963**, *28*, 445.

169. Choudary, M. K. *Naturwissenschaften.* **1979**, *66*, 205.

170. a) Ghosal, S.; Chauhan, P. S. R. B.; Mehta, R. *Phytochemistry.* **1975**, *14*, 830. b) Chatterjee, A.; Ganguly, M. *Phytochemistry.* **1968**, *7*, 307.

171. Ma, Z.Z; Hano, Y; Nomura, T; Chen, Y.J. *Heterocycles.* **1997**, *46*. 541.

172. a) Joshi, B. S. Newton, M. G.; Lee, D. W.; Barber, A. D.; Pelletier, S. W., *Tetrahedron: Asymmetry*, **1996**, *7*, 25. b). Joshi, B. S.; Pelletier, S. W. *Heterocycles*, **1999,** *51*, 183

173 a) Hermcz, I.; Vasavari-debreczy, I.; Hervath, A.; Balogh, M.; Kokosi, J; Devos, C.; Rodriguez, L. *J. Med. Chem*., **1987**, *30*, 1543. b) Dunn, A.D.; Kinnear, K.I.; Norrie, R.; Ringan, N.; Martin, D. *J. Heterocycl. Chem.*, **1987**, *24*, 175.

174. a) Duan, J.; Zhou, R.; Zhao, S.; Wang, M.; Che, C. *Zhongguo Yaoke Daxue Xuebao* **1998**, *29*, 21. b) Fan, Z.; Yao, X.; Gu. L.; Wang, J.; He, A.; Zhang, B.; Wang, X.; Wang,

H., ShenyangYaoxueyuan Xuebao. **1993**, *10*, 136.

175. Rahman, A. U.; Sultana, N.; Akhter, F.; Nighat, F.; Choudhary, M. I., *Nat. Prod. Lett.* **1997**, *10*, 249.

176. D'Cruz, J. L.; Nimbkar, A. Y.; Kokate, C. K. *Indian Drugs*, **1980**, *17*, 99.

177. Bhide, M. B.; Mahajani, S. S. *Bull. Haffkine Inst.* **1975**, *3*, 128.

178. a) Atal, C. K.*Chemistry and Pharmacology of vasicine - A new oxytocic and abortifacient,* P.58. New Delhi (**1980**).

b) Chopra, R. N.: *Indigenous Drugs of India*, Academic Publishers, Calcutta (**1982**).

179. Atal, C. K. et al., *Ind. J. Exp. Biol.*, **1982**, *20*, 704.

180. *J. Obstet, Gynaecol. India* **1979**, *29*, 939.

181. Doshi, J. J. *Int. J. Crude Drug Res*., **1983**, 21, 173.

182. Robinson, R. *The Structural Relations Of Natural Products* Carlendon press, Oxford, **1995.**

183. Schopf, C. and Oechler, F. *Ann. chem*., **1936,** *523*, 1.

184. Groger, D.; Mothes K. *Arch. Pharm,* **1960,** *293*, 1049.

185. Groger, D.; Mothes, K. *Expermentia*, **1965,** *21*,13,

186. Onaka, T. *Tetrahedron Lett*., **1971**, *12*, 4387.

187. Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc*., **1977**, *99*, 2306.

188. Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles*, **1985**, *23*, 2803.

189. Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem*. **1996**, *61*, 7316.

190. Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem*. **2001**, *66*, 997.

191. Mhaske, S, B Argade, N.P. *J. Org. Chem*, **2001,** *66*, 9038-9040.

192. Wang, H.; Ganesan, A. *Tetrahedron Lett*. **1998**, *39*, 9097.

193. Kelly, T. R.; Chamberland, S; Silva, R. A. *Tetrahedron Lett*., **1999**, *40*, 2723.

194. a) Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y.J. *Heterocycles*, **1991**, *51*, 593.

b) Molina. P.; Tarraga, A. Tejero, A.G. *Synthesis*, **2000,** *11*, 1523.

195. Susse, M. V.; Alder, F.; Johne, S., *Helv. Chem. Acta*, **1986**, 1017.

196. Coppala, G. M., *Synthesis*, **1980**, 505.

197. Venuti, M.C., S*ynthesis*, **1982**, 266.

198. a) Buchi, G.; Deshong, P. R.; Katsumura, S.; Sugimura, Y., *J. Am. Chem. Soc*., **1979**, *101*, 5084.

b) Ohnuma, T.; Kimura, Y.; Bany, *Tetrahedron Lett*., **1981**, *22*, 4969.

c) Nakagawa, M.; Tanigenchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc*., **1983**, 105, 3709.

199. Merrifield, R. B. *J. Am. Chem. Soc.*, **1963**, *85*, 2149.

200. a) Crowley, J. I.; Rapoport, H. *J. Am. Chem. Soc.*, **1970**, *92*, 6363.

b) Crowley, J. I.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 3215.

201. Wang, H.; Ganesan, A; *J. Org. Chem.*, **2000,** *65*, 1022.

202. Quick, J., *Tetrahedron Lett*, **1977**, *18*, 327.

203. Tang, C.; Rapoport, H. *J. Am. Chem. Soc.*, **1972**, *94*, 8615.

204. Krapcho, P. A.; Weimaster, J. F.; Elderidge, T. M.; Jahngen, Jr., E. G. E., Lovey, A. J.; Stephens, W. P., *J. Org. Chem*., **1978**, *43*, 138.

205. Asahina, Y.; Kashiwaki, K. *J. Pharm. Soc. Jpn.*, **1915**, *35*,1293

206. Chu, J. H.: *Chem. Abstract*, **1952**, *46*, 11589

207. Hing-tao, Li and Houng, Ho-I. *Chem. Abstract*, **1966**, *65*, 3922c

208. a) Bergman, J. *The Alakloids*; Brossi, A.R., Ed.; Academic Press: NewYork **1983**, *21*, 29

b) Ikuta, A.; Urabe, H.: Nakamura .J. *J. Nat. Prod*, **1998**, *61*,1012

209. Asahina, Y; Mayeda, S. *Chem. Abstract*, **1917,** *11*, 332.

210. Scnopf, C.; Steuer, H. *Ann*, **1947**, *558*, 124.

211. a) M.Yamazaki and A.Ikuta, *Tetrahedron Letters*, 1**966,** 5221.

b) Yamazaki, M.; Ikuta, A.; Mori, T.; Kawana, T. *Tetrahedron Lett*, **1967,** *8*, 3317

212. Tomita, M.; Kunimoto, J. *Yakugaku Zasshi*, **1960**, *80*, 1300.

213. a) Shoji, N.; Umeyama, A.; Takemoto, T.; Kajiwara, A.; Ohizumi, Y. *J.Pharm.Sci*, **1986**, *75*, 612.

b) Kong, Y, C, *Adv. pharm. Ther*., **1982**, *6*, 239.

214. Kong, Y.C.; Hu, S, Y.; Lau, F.K.; Che, C.T.; Yeung, H.W.; Cheung, S.; Hwang, C.C. *Am. J. Chin. Med*., **1976**, *4*, 105.

215. a) Yang, L.M.; Lin, S-J; Lin, L-C, Kuo, Y-H. *Chin. Pharm. J.* **1999**, *51*, 219.

b) Yang, L.M.; Chen, C-F.; Kuo, H-L. *Bio. Org. Med. Lett*, **1995**,*5*,465

216. Larksap, C.; Alper, H., *J. Org. Chem.* **2000**, *65*, 2776

217. King, C, L.; Kong. Y.C.; Wong, N.S.; Fong, H.H.; Sankaran, V. *J. Nat. Pro,* **1980,** *51*, 245

218. Illibino, S.; Choshi, T. *Nat. Prod. Rep*. **2001**,*18*,66.

219. Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc*.**1927**, 1708

220. Bergman, J. *In The Alkaloids:* Brossi, A.R.Ed. Academic Press: New York, 1983, *21*, 29-54.

221. Li-Ming Yang, Chieh-Fu Chen and Kuo-Hsiung Lee.

Bioorg & Med. Chem. Lett., **1995,** *5,* 465-468

222. Kametani, T.La, C.V.; Hige, T.; Koizumi, M.; Ihara, M.; Fukumato, K.

J. Am. Che. Soc. **1976,** *98***,** 6186,

223. Kametani, T.; Oshawa, T.; Ihara, M.; Fukumato, K. *Chem. Pharm. Bull*., **1978**, *28*,1972

224. Eguchi, S.; Takeuchi, H.; Matsushita, Y. *Heterocycles*, **1992**, 33, 153

225. Kametani, T.La, C.V,: Hige, T.; Koizumi, M.; Ihara, M.; Fukumato, K.

J. Am. Che. Soc., 1977, *99*, 2306

226. a) Bergman, J.: Bergman, S. *Heterocycles* **1981**, 2347

b) Bergman, J.: Bergman, S. *J.Org. Chem*. **1985,** *50*, 1246

227. Kaneko, C.; Chiba, T; Kasaki, K. and Miwa, C. *Heterocycles*, **1985,** *23*,1385

228. Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles*, **1985**, *23*, 2803.

229. Kokosi, J.; Hermecz, I.; Szasz, G.; Meszaros, Z. *Tetrahedron.Lett***.**, **1981**, *22*, 4861.

230. a) Kokosi, J.; Hermecz, I.; Podanyi, B; Szasz, G.; Meszaros, Z.

J. Heterocycl. Chem., **1985**, *22*,1373

b) Hermecz, I.; Kokosi, J.; Horvath, A.; Vasavari, D. I.; Podanyi, B; Szasz, G.;

Meszaros, Z. *J. Heterocycl. Chem*., **1987**, *24*, 1045.

c) Hermecz, I.; Kokosi, J.; Vasavari, D.I; Horvath, A.; Podanyi, B; Szasz, G.;

Meszaros, Z. *Chem. Abstact.,* 1989, *110*, 231939

d) Hermecz, I.; Kokosi, J.; Vasavari, D. I.; Podanyi, B; Szasz, G. Heterocycles, **1994,** *37***,**

903.

231. For a description of the biological activity of indoles, see: Sundberg, R. J. *Indoles*;

Academic Press: London, **1996**, and references therein.

232. For a review on the Fischer indole synthesis, see: Hughes, D. L.

Org. Prep. Proced. Int. **1993**, *25*, 607.

233. For preparative routes to *N*-aryl hydrazones, see: (a) Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: Chichester, **1982**; pp 48-59. (b) Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N-N Bonds*, 2nd ed.; The Benjamin/Cummings Publishing Company: Reading, MA, **1983**; Chapter 2.