"DESIGN AND SYNTHESIS OF β-SUBSTITUTED-γ-METHYLENEFURANONES, RELATED LIGNAN ANALOGUES AND SYNTHETIC STUDIES TOWARDS SAINTOPIN"

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BY

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DEDICATED

TO

MY BELOVED GRANDMOTHER

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"DESIGN AND SYNTHESIS OF β-SUBSTITUTED-γ-METHYLENEFURANONES, RELATED LIGNAN ANALOGUES AND SYNTHETIC STUDIES TOWARDS SAINTOPIN"** submitted by Mr. Vishal Ashok Mahajan was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such material as obtained from other sources has been duly acknowledged in the thesis.

Dr. (Mrs.) R. D. WAKHARKAR **October 2005**

Research Supervisor

DECLARATION

I hereby declare that the work presented in the thesis entitled **"DESIGN AND SYNTHESIS OF β-SUBSTITUTED-γ-METHYLENEFURANONES, RELATED LIGNAN ANALOGUES AND SYNTHETIC STUDIES TOWARDS SAINTOPIN"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, Pune, India under the supervision of **Dr. (Mrs.) R. D. WAKHARKAR.** 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.

VISHAL A. MAHAJAN

Date: October 2005.

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Vishal A. Mahajan

ABREVATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
$AlCl_3$	Aluminium chloride
Bp	Boiling point
brs	Broad singlet
CAN	Cerric ammonium nitrate
$CDCl_3$	Deuterated chloroform
d	doublet
DCM	Dichloromethane
DMF	Dimethylformamide
DMS	Dimethylsulphate
DMSO	Dimethyl sulfoxide
DMP	Dess-Martin periodinane
EDC	Ethylene dichloride
g	Grams
h	Hours
IR	Infra red
m	Multiplet
Me	Methyl
Mp	Melting point
M^+	Molecular ion
mg	Milligrams
min	Minutes
ml	Milliliters
mmol	Millimole
n-BuLi	n-Butyllithium
Na_2SO_4	Sodium Sulphate
NBS	N-Bromosuccinamide
NMR	Nuclear Magnetic Resonance
$Pd(PPh_3)_4$	tetrakis (triphenylphosphine) Palladium (0)
PCC	Pyridiniumchlorochromate
q	Quartet
rt	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TMSCl	Trimethylsilylchloride
$ZnCl_2$	Zinc chloride

GENERAL REMARKS

1 All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on the Celsius scale (^{0}C).

2 IR spectra were recorded in chloroform, on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FT-IR and ATI Mattson, UK, Model-RS-1 FT-IR, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).

3 Proton NMR spectra were recorded using tetramethylsilane as internal reference on DRX 500, Bruker MSL-300 and Bruker AC-200. Chemical shifts were recorded in parts per million (δ). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, brs = broad singlet, br = broad peak, dt=doublet of triplet and m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.

4 ^{13}C NMR spectra were recorded on DRX 500, Bruker MSL-300 and Bruker AC-200 instrument operating at 125 MHz, 75.2 MHz and 50.3 MHz respectively.

5 Mass spectra were recorded at ionization energy 70 eV on Finnigan MAT-1020; automated LC/MS instrument and mass values are expressed as *m/z*.

6 Elemental analyses (C, H, N) were obtained on a Carlo-Erba 1100 automatic analyzer at NCL and the values are reported in %.

7 The reactions were monitored with thin layer chromatography plates, precoated with silica gel GF 254 (Merck). Column chromatography was carried out with silica gel as a stationary phase.

8 Pet-ether refers to the fraction boiling between 60-80 °C.

9 Organic layers were dried over anhydrous sodium sulphate (Na_2SO_4)

10 All the compounds screened for biological activity were analyzed by HPLC (Shimatzu) using C- 18 column and the purity of compound was in the range of 90-97%.

Thesis Abstract

Thesis Title: "Design and Synthesis of β-Substituted-γ-Methylenefuranones, Related Lignan Analogues and Synthetic Studies Towards Saintopin"

Thesis is divided into three chapters

CHAPTER-1: Design, Synthesis and Cytotoxicity Study of β-Substituted γ-Methylenefuranones, Related Lignan Analogues and Concise Synthesis of Solafuranone

CHAPTER-2: Synthetic Studies Towards Saintopin

CHAPTER-3: Synthesis of 2-Arylidenetetralones and Iodoetherification

CHAPTER-1: Design, Synthesis and Cytotoxicity Study of β-Substituted-γ-Methylenefuranones, Related Lignan Analogues and Concise Synthesis of Solafuranone

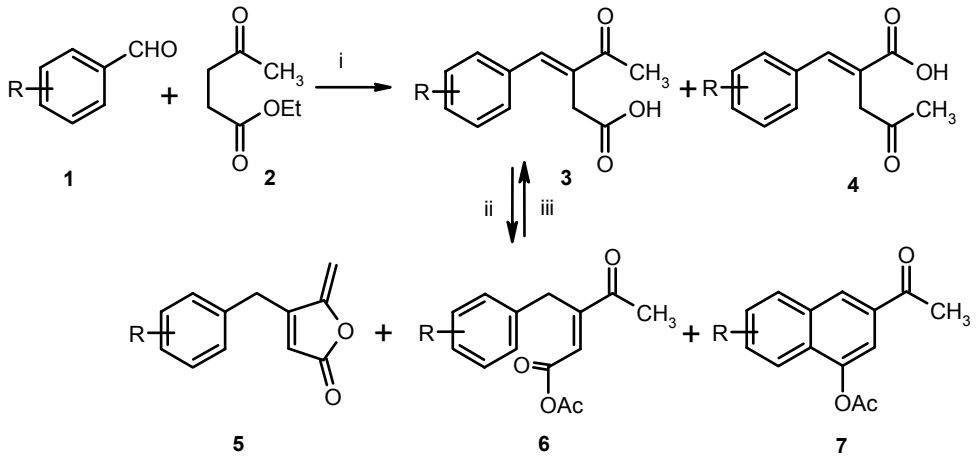
This chapter is divided into four sections. These sections summarize the synthesis of β-substituted-γ-methylenefuranone derivatives, exploration of these derivatives towards the synthesis of 1,4-dihydronaphthalene lignan analogues and study of cytotoxicity of these derived novel chemical entities. This chapter also includes synthesis of naturally occurring solafuranone.

SECTION-1: Synthesis of β-Substituted-γ-methylenefuranones

The γ-methylenefuranone moiety is present in a number of natural products and is found to be an important platform for the total synthesis of various natural products as well as for the development of new asymmetric methodologies[1]. Synthesis of novel β-substituted-γ-methylenefuranones disclosed herein represent a shortest elegant method using bench chemicals. Due to the advantage of structural and method novelty, reaction conditions were standardized and generalized which are discussed in this section.

The synthetic method involved Stobbe condensation of variety of aldehydes with ethyl levulinate to give the key intermediate **3**, followed by treatment with anhydrous sodium acetate and acetic anhydride to afford β-substituted-γ-methylenefuranones **5**. (Scheme 1)[2]

Scheme 1.



Reagents and conditions: (i) Aq. NaOH, ethanol, -10 °C, 4 -5 h, (**3**, 43-82 %); (ii) Anhydr. NaOAc, Ac_2O, 80 °C, 3 h, (**5**, 48-72%); (iii) Aq. NaOH, ethanol, rt, 2-3 h.

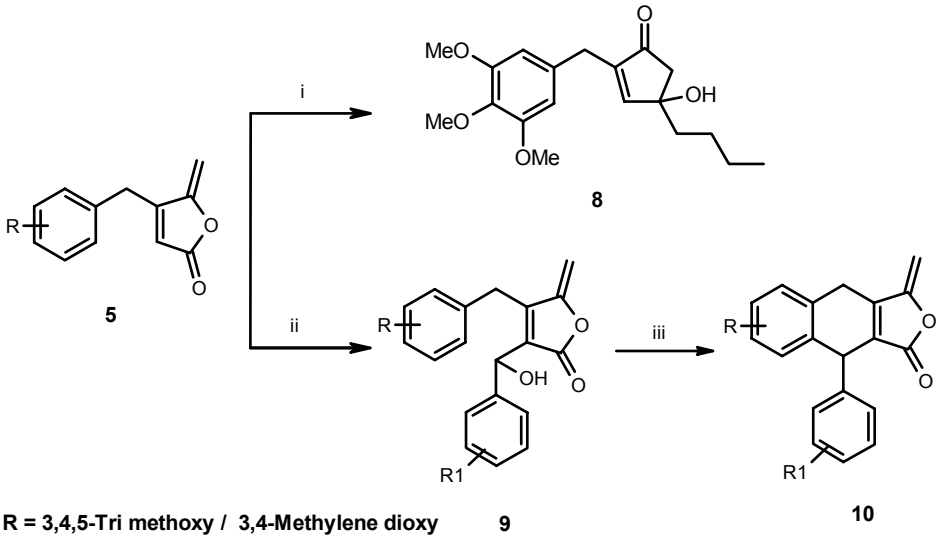
The formation of furanone **5** from the corresponding acid **3** involved consecutive sequence of reactions in one pot. The furanones **5** were characterized by spectroscopic methods and the structure of the furanone was established beyond doubt by COSY and NOESY experiments and X-ray spectroscopic technique. A library of 22 structurally novel β-substituted-γ-methylenefuranone [or 4-benzyl-(substituted)-5-methylene-2-(5*H*)-furanones **5**] derivatives was prepared.

SECTION 2:
Part A: Design and Synthesis of 1,4-Dihydronaphthalene Lignan Analogues

Owing to the structural feature of γ-methylenefuranone **5**, its derivatization was undertaken in order to synthesize the analogues of natural products bearing five membered lactone rings such as lignans. The literature survey revealed that various naturally occurring lignan lactones possess wide range of biological activity and to enhance their pharmaceutical value, various structural modifications have been fruitful.[3]
To synthesize acyclic lignan, LDA was found to be the best choice as a base instead of n-BuLi, which could generate vinylic carbanion of γ-methylenefuranone regiospecifically.
γ-Methylenefuranone **5** was treated with various substituted benzaldehydes in the presence of LDA in dry THF at -78 °C to give acyclic hydroxy lignans **9** (Scheme 2),

which were further subjected for cyclization to give unnatural 1,4-dihydronaphthalene lignans **10** as depicted in Scheme 2.

Scheme 2.



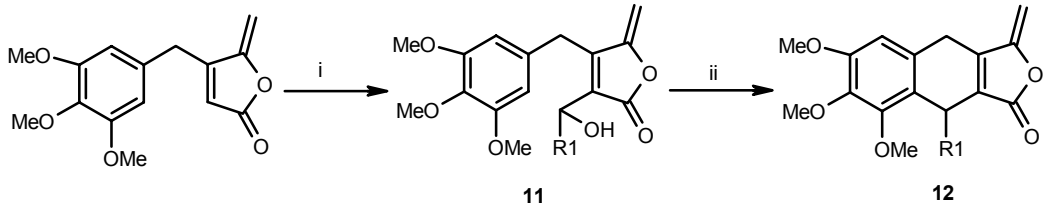
Reagents and conditions: (i) n-BuLi, THF, -78 ºC, (ii) LDA, substituted aromatic aldehydes, THF, -78°C, 1 h; (iv) Trifluoroacetic acid, dry DCM, rt, 1-2 h.

Generalizing this protocol, different analogues including dehydrodeoxypodophyllotoxin and 1,4-dihydrotaiwanin[4] were synthesized.

Synthesis of Naphthalene Analogues of Lignans

We have been able to synthesize naphthalene and heterocyclic lignan analogues, starting from furanone **5** and their respective aldehydes as shown in Scheme 3.

Scheme 3.

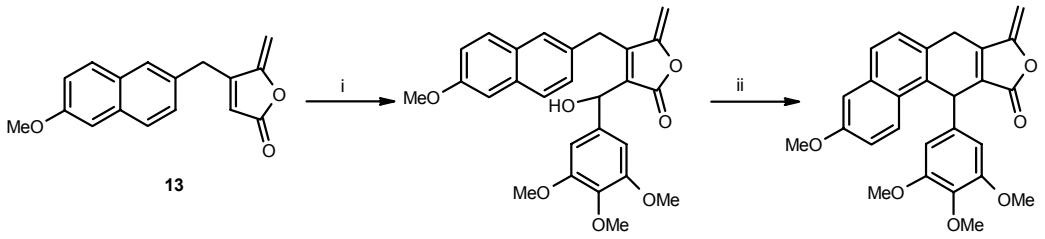


Reagents and conditions: (i) LDA, aldehyde, THF, -78°C, 1h; (ii) Trifluoroacetic acid, dry DCM, rt, 1-2 h.

Part B: Angular Naphthalene Lignan Analogue

Due to the structural novelty and for evaluation of the biological activity, we have designed and synthesized angular naphthalene lignan analogue (Scheme 4). Furanone **13** on treatment with 3,4,5-trimethoxybenzaldehyde in the presence of LDA gave hydroxy lignan derivative **14**, which on cyclization gave the angular naphthalene analogue **15**.

Scheme 4.



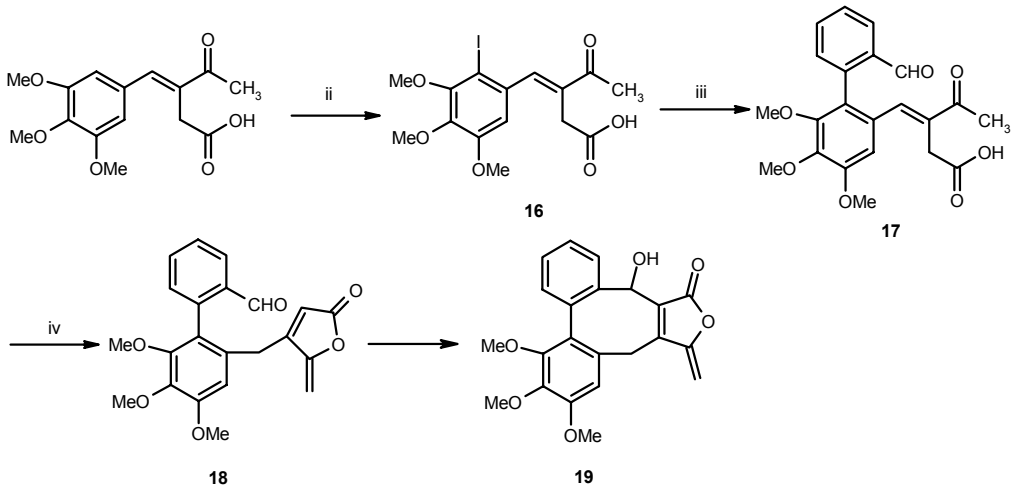
Reagents and conditions: (i) LDA, 3,4,5-trimethoxy benzaldehyde, THF, -78°C, 1h, 45%; (ii) Trifluoroacetic acid, dry DCM, rt, 1-2 h, 83%.

Part C: Synthetic Attempts Towards Dibenzocyclooctene Lignan Lactone

Dibenzocyclooctene is another important class of lignan; steganone, steganacin and steganane are the main bioactive molecules of this class, having inhibitory activity of tubulin polymerization both *in vitro* and *in vivo*.[5]

It was envisaged that dibenzocyclooctene lignan could be synthesized from γ-methylenefuranone **5**. Therefore acid **16** was subjected to intermolecular biaryl coupling with 2-carboxybenzyl boronic acids by Suzuki-Mayura coupling method in the presence of palladium tetrakis triphenylphosphine to afford substituted levulinic acid **17**, which was subjected to lactone formation by treating with anhydrous sodium acetate and acetic anhydride at 80°C for 3 h, which afforded the lactone **18**. Intramolecular cyclization by neucleophilic attack on the aldehyde group was expected to result in the dibenzocyclooctene lignan **19** (Scheme 5).

Scheme 5.



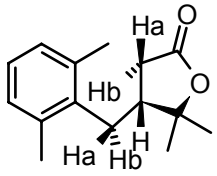
Reagents and conditions: (i) CF_3COOAg, I_2, chloroform, 1h, 43%; (iii) 2-Carboxyaryl boronic acid, aq. Na_2CO_3, Pd $(PPh_3)_4$, dimethoxyethane, 24h, 45.2%; (iv) Anhydr. NaOAc, Ac_2O, 80°C, 3h, 13%.

SECTION 3: Biological and SAR Study of β-Substituted-γ-methylenefuranone and Related Lignan Derivatives

5-Methylene-4-benzyl-(substituted) and 3, 4–dibenzyl (substituted)-2(5*H*)-furanones and deoxydehydropodophyllotoxin analogues were designed and synthesized in 2-4 steps starting from the corresponding aromatic aldehydes and ethyl levulinate as described in section 1 and 2. Some of the novel entites were screened for their cytotoxicity and anti-fungal activity.

These derivatives were screened for *in vitro* cytotoxicity against human cancer cell lines viz. PTC (Colon), SW620, MOLT-4 (Leukemia), 293 (Kidney), DU145 (Prostate), KB (Oral Squamous cell), L132, MIA PaCa, Hep2 (Larynx), PA1 (Ovary), U87MG, ECV (Endothelial) and MCF7 (Breast) cell lines. Most of the new compounds have shown significant cytotoxicity. Structure-Activity Relationships have been discussed with respect to the new chemical entities studied in this section.

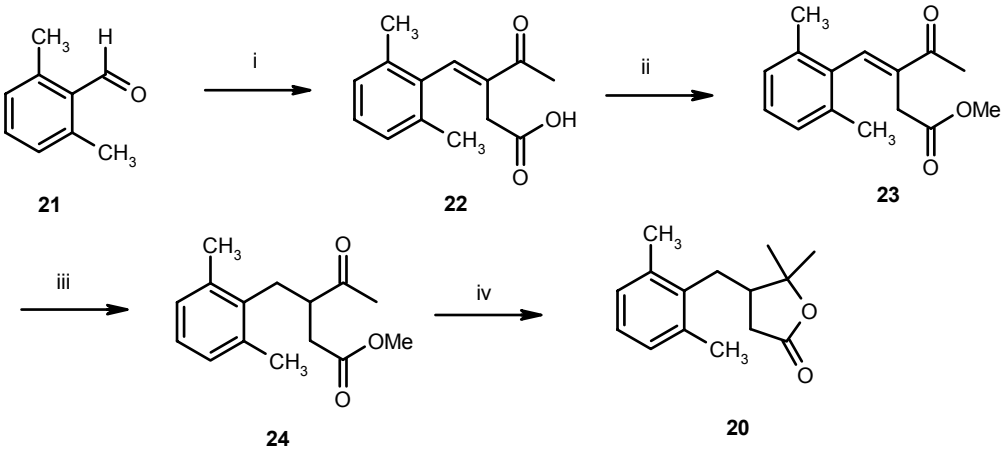
SECTION 4: An Efficient Synthesis of Solafuranone



20

Solafuranone[6] **20**, was isolated from *Solanum indicum* and it has been widely used in folk medicine as an analgesic for toothache, rhinitis and breast cancer.Structure of solafuranone contains a 2,6-dimethylbenzyl moiety, which occurs rarely in nature.

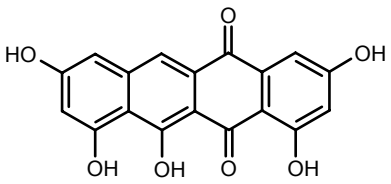
Scheme 6.



Reagents and conditions: (i) Aq. NaOH, methanol, -10 °C, 4-5 h, 78%; (ii) CH_2N_2, methanol, rt, 88.4%; (iii) H_2, Pd /C, methanol, rt, 83%; (iv) CH_3MgI, $CeCl_3$, ether, -78 °C, 5 h, 48%.

Since there were no reports in the literature for the synthesis of this molecule and also due to the structural relevance with the research covered in this chapter (Section-1), the synthesis of solafuranone was undertaken. Stobbe condensation of 2,6-dimethyl benzaldehyde **21** with ethyl levulinate gave acid **22** regioselectively. Esterification was carried out with diazomethane to give ester **23**, which was hydrogenated using Pd on carbon, to give ester **24**. This ester **24** was further subjected to Grignard reaction using methyl magnesium iodide in the presence of anhydrous $CeCl_3$ followed by acidic workup to give racemic solafuranone **20**.

CHAPTER 2: Synthetic Studies Towards Saintopin



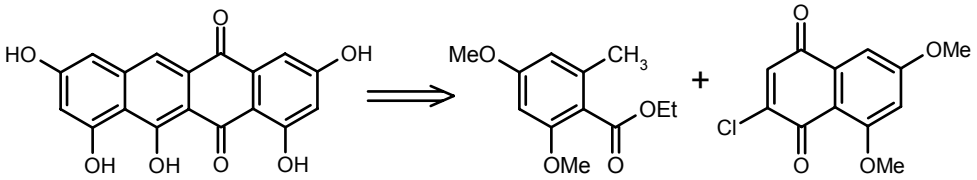
25

Saintopin **25**,[7] a natural antitumor antibiotic was isolated from *paecilomyces* species. Saintopin is a dual inducer of topoisomerase I and topisomerase II mediated DNA cleavage. It is equipotent to *m*-AMSA and VP16 and camptothecin derivative and it showed cytotoxic activity against a human cancer cell, HeLaS3 and antitumor activity against murine leukemia cell P388 *in vivo*.[8] For the synthesis of Saintopin different approaches were applied such as (i) Diels-Alder reaction approach (ii) Stobbe condensation reaction (iii) Michael addition-Dickmann condensation approach which are briefly discussed as follows

SECTION 1: Diels-Alder Reaction Approach

The Diels-Alder reaction approach involved cycloaddition of dienophile 2-chloro-6, 8-dimethoxy- [1,4] naphthoquinone **27** and diene generated in situ from orthotoluic acid **26** (Scheme -7).

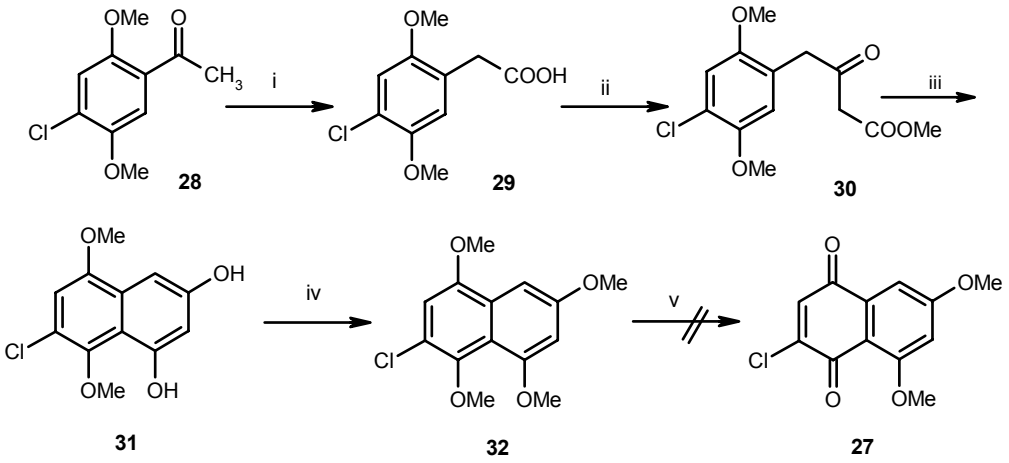
Scheme 7. Retrosynthetic analysis of saintopin



25 26 27

Attempts towards the perparation of 2-chlorojuglone **27** involved sequence of reactions as depicted in Scheme 8. Substituted acetophenone **28** was subjected to one carbon homologation using well-known Willgerodt reaction to give acid **29**. It was treated with Meldrum's acid followed by acidic treatment in dry methanol to give β-ketoester **30**, which on cyclization and methylation gave substituted naphthalene derivative **32** in good yield. Various attempts for oxidation of compound **32** were unsuccessful to achieve 2-chloro-6, 8-dimethoxy-[1,4] naphthoquinone (**27**) as depicted in Scheme 8.

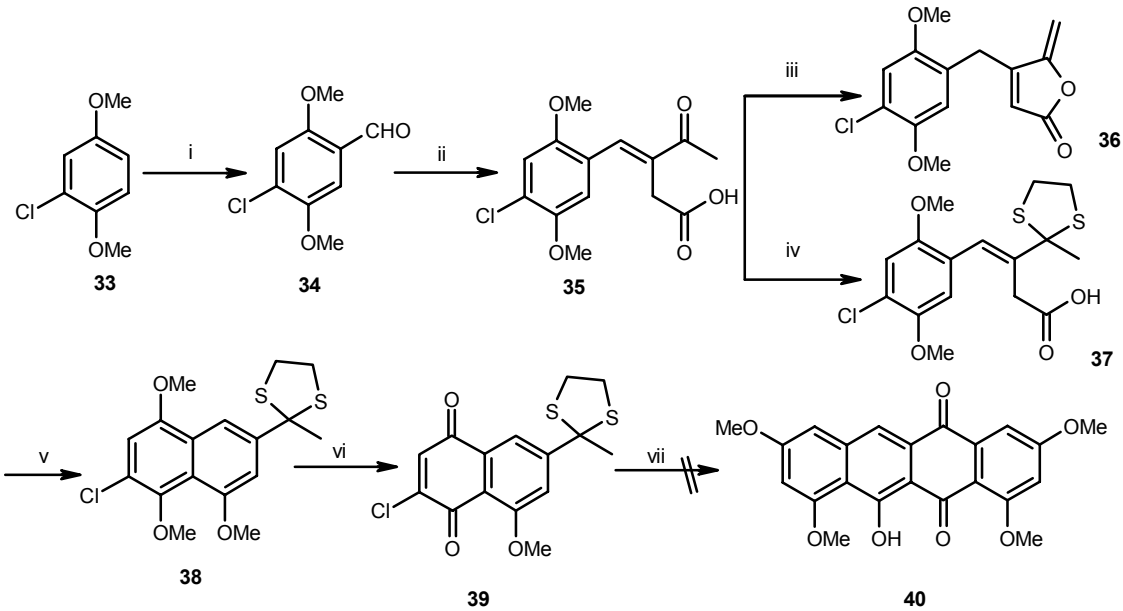
Scheme 8.



Reagents and conditions: (i) (a) S, morpholin, reflux, 5h; (b) 10% Aq. NaOH solution, ethanol, reflux-rt, 56 %, 12h; (ii) (a) $SOCl_2$, toluene; (b) Meldrums acid, Et_3N, then reflux in methanol 12h, 55.2%; (iii) C H_2SO_4, 0ºC, 76.6%; (iv) Dimethyl sulphate, K_2CO_3, acetone, reflux, 4h, 90%; (v) CAN, aq. CH_3CN, rt.

Alternatively study the Diels-Alder reaction approach 2-chloronaphthoquinone derivative was synthesized as depicted in Scheme 9.

Scheme 9.



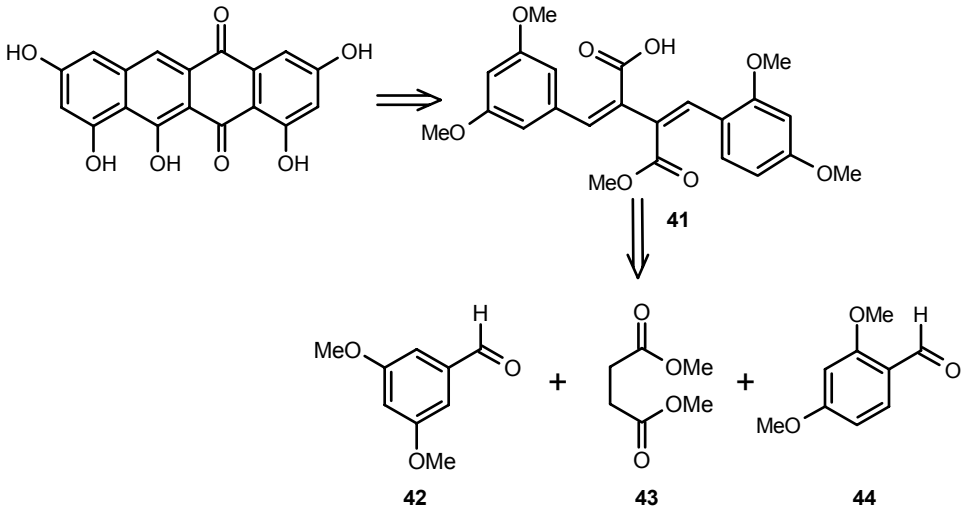
Reagents and conditions: (i) HMTA, TFA, DCM, reflux, 12h, 78%; (ii) Aq. NaOH soln, ethylevulinate, ethanol, -10ºC, 4-5h; (iii) Anhydr. NaOAc, Ac_2O, 120 ºC, 45% (iv) Ethane dithiol, I_2, $CHCl_3$, 92% (v) (a) Anhydr. NaOAc, Ac_2O, 120 ºC, 74.4%; (b) Aq. NaOH, ethanol, rt, 85.5 %; (c) Dimethyl sulphate, K_2CO_3, acetone, 4-5h, 94.2%; (vi) CAN, aq. CH_3CN, rt, 89.6%. (vii) Ethyl 2,4-dimethoxy-6-methylbenzoate, LDA, THF, -78ºC, then TMSCl

The synthesis of quinone derivative commences from 2-chloro-1, 4-dimethoxy benzene **33**. It was subjected to formylation using trifluoroacetic acid and hexamethylene tetramine to give aldehyde **34**, which was condensed with ethyl levulinate to afford acid **35**. Thereafter compound **35** was treated with acetic anhydride in the presence of sodium acetate when furanone **36** was obtained instead of the corresponding substituted naphthalene derivative.

Therefore cyclization was carried out after masking of carbonyl function. The cyclized product **38** was oxidized to 2-chloro-8-methoxy-6-(2-methyl-[1,3]dithiolan-2-yl)-[1,4]naphthoquinone (**39**) in the presence of CAN. Further it was treated with ortho tolic ester in the presence of LDA, on the basis that in situ generated diene of the corresponding ester could react with naphthaquinone **39** to afford the desired naphthacene dione **40** but this reaction did not work under different conditions.

SECTION 2: Stobbe Condensation Approach

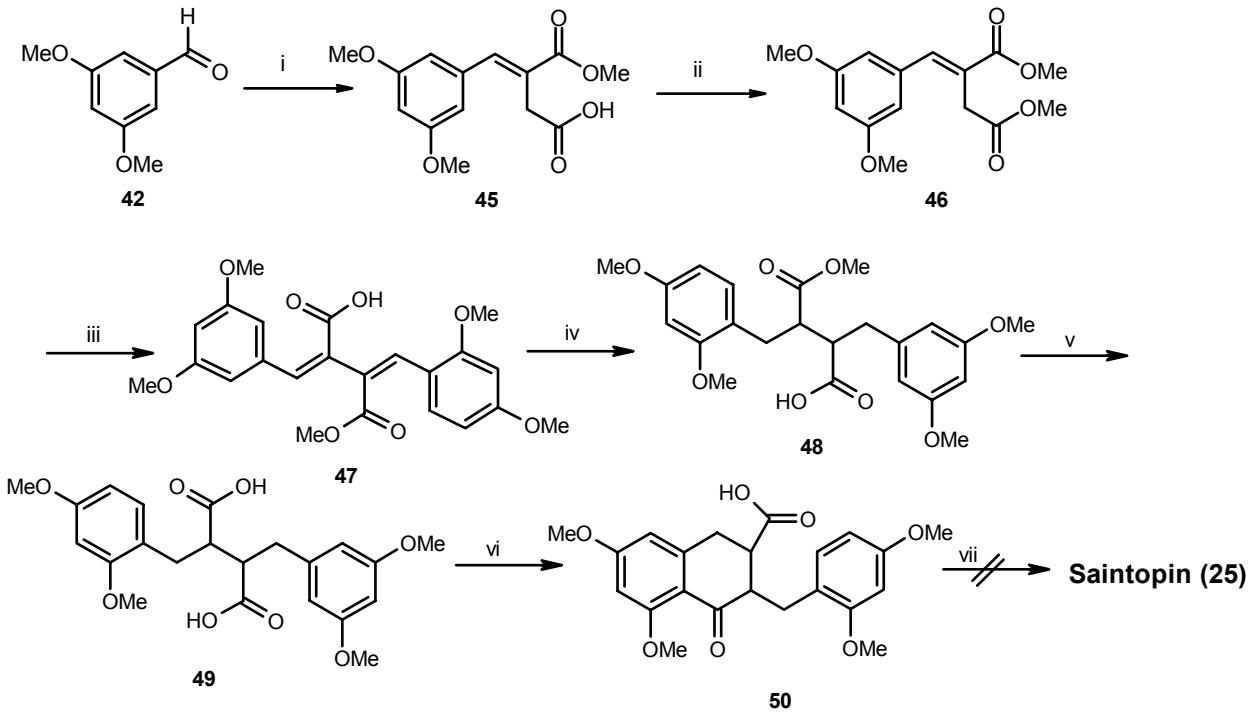
Scheme 10. Retrosynthetic analysis of Saintopin



Stobbe condensation approach commenced from the condensation of 3, 5-dimethoxy benzaldehyde **42** with dimethylsuccinate (**43**) followed by esterification with diazomethane to collect the ester **46**. Ester **46** was further condensed with 2, 4-dimethoxy benzaldehyde to afford the acid **47** in good yield. It was hydrogenated and hydrolyzed to obtain the diacid **49** as shown in Scheme 11. The acid **49** was treated with trifluoroacetic

acid in dichloromethane at room temperature to give cyclized product **50,** which was further subjected for aromatization in the presence of DDQ, however under different reaction conditions the desired product was not obtained (Scheme 11).

Scheme 11.

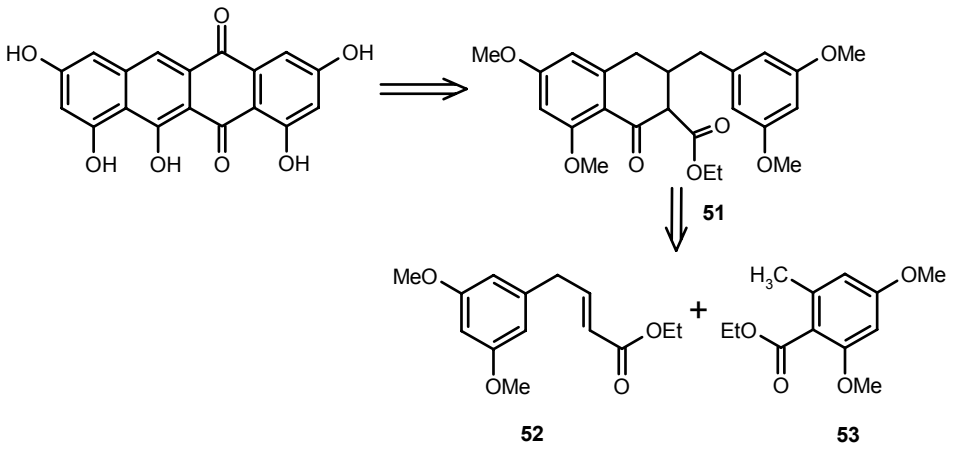


Reagents and conditions: (i) Dimethyl succinate, NaOMe, MeOH, 0ºC to rt, 80%; (ii) CH_2N_2, ether, methanol, 82.8%; (iii) 2,4-Dimethoxy-benzaldehyde, NaOMe, MeOH, 0ºC, 1h, then rt 4h, 34%; (iv) Pd/C, H_2 gas, MeOH, 81%; (v) Aq. NaOH, MeOH, 82%, (vi) TFA, TFAA, DCM, 0ºC then rt, 31.1%; (vii) DDQ, toluene, 80ºC.

SECTION 3: Tandem Michael Addition-Dickmann Condensation Approach Towards the Synthesis of Saintopin

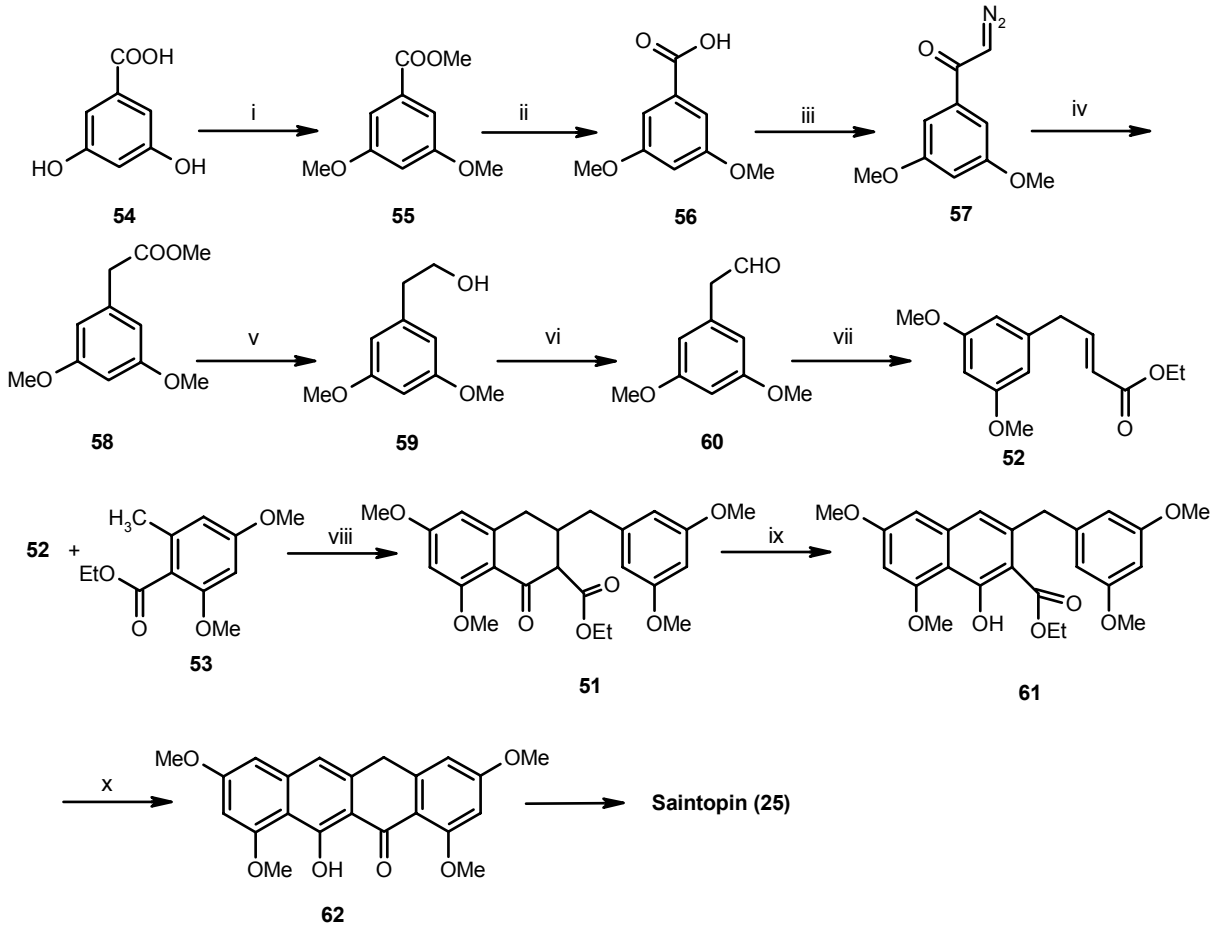
Tandem Michael Addition-Dickmann condensation approach is an alternative approach studied for the synthesis of saintopin.

Scheme 12. Retrosynthetic analysis of saintopin



The desired intermediate 52, as per the retrosynthestic analysis was obtained from 3,5-Dimethoxybenzoic acid **56**, which was subjected for Wolf rearrangement for one carbon homologation using diazomethane and silver oxide to afford rearranged product **58**. This ester **58** was reduced to alcohol **59** with DIBAL-H and oxidized to aldehyde **60** using DMP in dry dichloromethane. Aldehyde **60** was subjected for Wittig reaction to get the α, β-unsaturated ester **52**. The intermediate **52** thus obatained was treated with ethyl 2,4-dimethoxy-6-methylbenzoate **53** in the presence of LDA at –78 °C and then at 0 °C. The reaction involved Michael addition followed by Dickmann condensation leading to the key intermediate **51**. It was then aromatized to obtain compound **61** in the presence of DDQ in toluene at 80 ºC. Aromatized product **61** was cyclized in the presence of conc. H_2SO_4 to afford tetracyclic framework **62**. Further transformations (oxidation and demethylation) are incomplete due to the time constraint. (Scheme 13)

Scheme 13.



Reagents and conditions: (i) Dimethyl sulphate, K_2CO_3, acetone, 95%; (ii) Aq. NaOH, ethanol, rt, 4-5h, 86%; (iii) (a) $SOCl_2$, toluene, reflux, 4h; (b) CH_2N_2, ether, 30 min, 55%; (iv) Ag_2O, methanol, reflux, 1h, 80%; (v) DIBAL-H, THF, rt, 4h, 73%; (vi) DMP, dichloromethane, rt, 56%; (vii) PPh_3= CH-COOEt, benzene, reflux, 1h, 66%; (viii) LDA, THF, -78 °C, 4h, 50.7%; (ix) DDQ, toluene, 80 ºC 4h, 38%; (x) Conc. H_2SO_4, 0ºC then 50 ºC, 20 min, 27%.

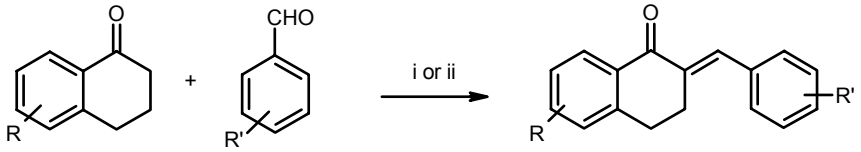
CHAPTER 3: Synthesis of 2-Benzylidene-tetralones and Iodoetherification

Section 1: Design, Synthesis and Cytotoxic Activity of Substituted 2-benzylidene-1-tetralones

A number of chalcones have demonstrated cytotoxic and anti-cancer properties.[9] Substituted tetralones were condensed with a variety of arylaldehydes to give 2-arylidenetetralones using aqueous sodium hydroxide as represented in Scheme **14** and

tested for their cytotoxicity. We screened 24 compounds of this category for their potential as cytotoxic agents. All the spectral data and biological activity data is discussed.

Scheme 14.



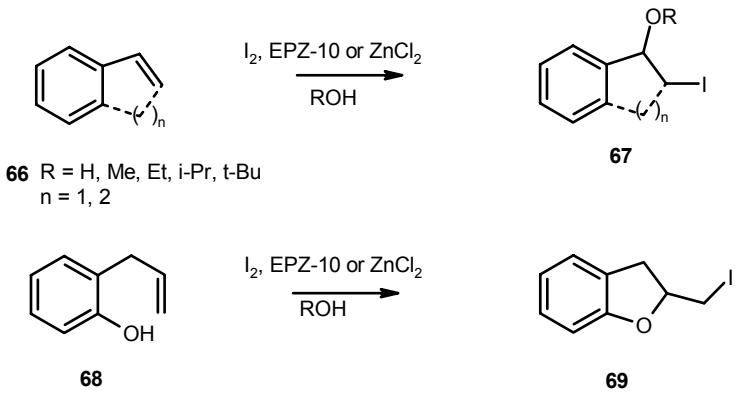
64 **65**

Reagents and conditions: (i) 40 % Aq. NaOH, ethanol, (ii) 50 % HCl.

Section 2: EPZ-10 Catalyzed Regioselective Transformation of Alkenes into β-Iodoethers

β-Iodoethers are useful intermediates for stereoselective radical reaction and for synthesis of *E* or *Z* alkenes with good to moderate distereoselectivity. Considerably growing interest in the catalysis of organic reactions by inorganic reagents supported on high surface area inorganic material led to a new family of supported reagents *viz* Envirocat®, which is a breakthrough in environmentally friendly chemistry. EPZ-10® is commercially available from Envirocat contract chemicals.[10]

Scheme 15.



We studied the EPZ-10® mediated convenient protocol for the regioselective synthesis of β-iodo alkyl ethers from olefins and direct conversion of *o*-allylphenols into the

corresponding 2-iodomethyl-2,3-dihydrobenzofurans in a single step as depicted in Scheme 15.[11] The efficasy of the heterogeneous catalyst EPZ10 (conataining Zn) has been supported by the comparative results using $ZnCl_2$ (as homogeneous catalyst) for all the examples.

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1.0.1. Cancer: General Introduction

Cancer is considered as a disease of our modern age, but people throughout history recognized the uniqueness of some tumors and sought to find treatments for them. The oldest description of human cancer was found in an Egyptian papyri written between 3000-1500 BC, it referred to tumors of the breast. The oldest specimen of a human cancer was found in the remains of a female skull dating back to the Bronze Age (1900-1600 BC). The mummified skeletal remains of Peruvian Incas, dating back 2400 years ago (BC), contained lesions suggestive of malignant melanoma. Therefore cancer is not a disease of our modern industrialized age, as some may have believed at one time.[1]

One of the earliest human cancers found in the remains of mummies was a bone cancer suggestive of osteosarcoma. Louis Leakey found the oldest possible hominid malignant tumor in 1932 from the remains of either a Homo erectus or an Australopithecus. This tumor was suggestive of a Burkitt's lymphoma (although that nomenclature was certainly not in use then). Diseases that we know to be rare cancers today have had a long history.[2, 3] Hippocrates (Greek physician) is credited with being the first to recognize the difference between benign and malignant tumors; his writings describe cancers of many body sites. The swollen blood vessels around the malignant tumors so reminded him of crab claws, he called the disease karkinos (the Greek name for crab). In English this term translates to carcinos or carcinoma.[4]

The English surgeon, Stephen Paget[5] devised a theory on cancer growth referred to as the "seed and soil theory". He theorized that metastasis tumor cells are like seeds, evenly distributed throughout the body through the bloodstream, but grow only in the organ ('soil') they find compatible. In 1896, a German Physics Professor Wilhelm Conrad Roentgen used 'X-ray' for the diagnosis of cancer. He received the first Nobel Prize in Physics for his contribution.[6]

John Hill first recognized[7] an environmental cause from the dangers of tobacco use in 1761 and published a book "Cautions Against the Immoderate Use of Snuff". Percivall Pott of London in 1775 described an occupational cancer of the scrotum caused by soot from chimney sweeps. This led to identification of a number of occupational

carcinogenic exposures and public health measures to reduce cancer risk. This was the beginning of understanding that there may be an environmental cause to certain cancers.

Therapies to cure cancer

In the 1880s and 1890s, William Stewart Halsted devised an extensive operation for breast cancer that entailed removal of the breast and underlying muscles, and lymph nodes under the arm. He eventually achieved an unprecedented 72 percent five-year cure rate for patients whose disease had not spread to adjoining glands. Wilhelm Conrad Roentgen's discovery of X-ray technology in 1896 led to the use of X-ray, in the form of radiation, for cancer treatment by 1899.

The first drug used for cancer chemotherapy was not initially developed for that use. Mustard gas was used as a chemical warfare agent during World War I and was studied further during World War II. During a military operation in World War II, a large number of military personnel were accidentally exposed to mustard gas and were later found to have abnormally low white blood cell counts. It was reasoned that an agent that damaged the rapidly growing white blood cells might have a similar effect on cancer. Therefore, in the 1940s, several patients with advanced lymphomas were given the drug (by vein, rather than by breathing the irritating gas). It proved to be effective, temporarily; but it did initiate research into other substances used for cancer treatment.

There after combat against the malignant cancer was started in different branches of science. Many studies regarding its physiology and treatments were documented with positive and negative results. The outcome of the vast research is the three main approaches to treating established cancer: surgical excision, irradiation and chemotherapy. The role of each of these depends on type of tumors and the stage of its development. Chemotherapy is the treatment of cancer with drugs and it is often used in combination with other types of therapies such as surgery, radiation or immunotherapy. After a long fight with cancer, it is still a worldwide problem of human health and leading disease-related cause of death of the human population and chemotherapy still has a wide scope in this field.

Cancer chemotherapy[9]

Chemotherapy is a biochemical process occurring in smallest flasks called as cells. From the birth of new cell to its cell division, it has to undergo different phases, i.e. different chemical transformations and the application of chemotherapy is based on these intracellular chemical transformations.

Chemotherapy is the treatment of cancer with drugs that can damage cancer cell by inhibiting biochemical reactions in cell cycle. The use of chemical agents to destroy cancer cells is a mainstay in the treatment of malignancies. The discovery of anticancer agents to treat the cancer was stated in early 1900's during World War II and it is still continued. A major advantage of chemotherapy is its ability to treat widespread or metastatic cancer, whereas surgery and radiation therapies are limited to treating cancers that are confined to specific areas.

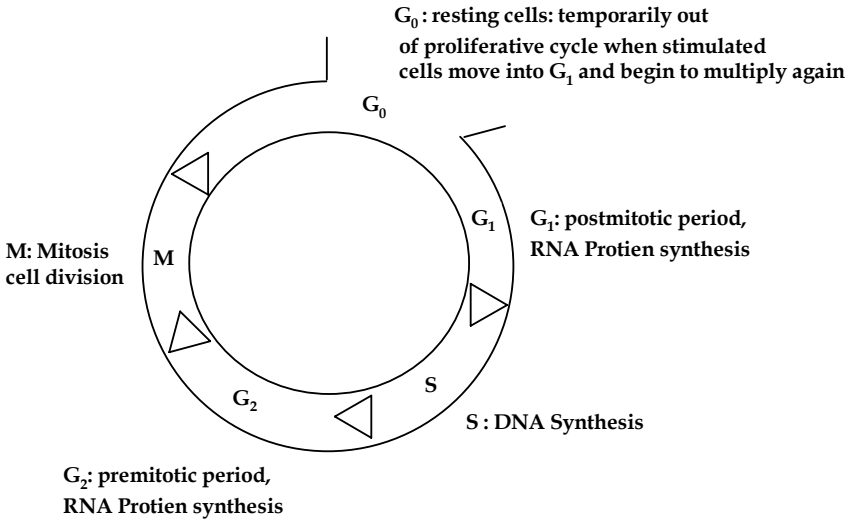


Figure 1. Proliferative cell cycle of normal cell

The main object of chemotherapeutic drugs is to destroy cancer cell without harming the healthy normal cell, therefore it is necessary to understand the life cycle of cell. Normal cells divide and replicate in controlled manner (Figure 1), while cancerous cells divide and replicate in uncontrolled manner. Therefore targeting some aspect of the cell growth cycle seems to be reasonable. Fast growing cells would be affected the most and slow growing cells would be least disturbed, is the basis for many chemotherapeutics.

Figure 2 represents exercise of anticancer agents, according to biochemical transformations that occur during phase cycle of the cells. Thus by understanding the biochemical process of phase cycle of normal and cancer cell, type of actual treatment of cancer is manifested.

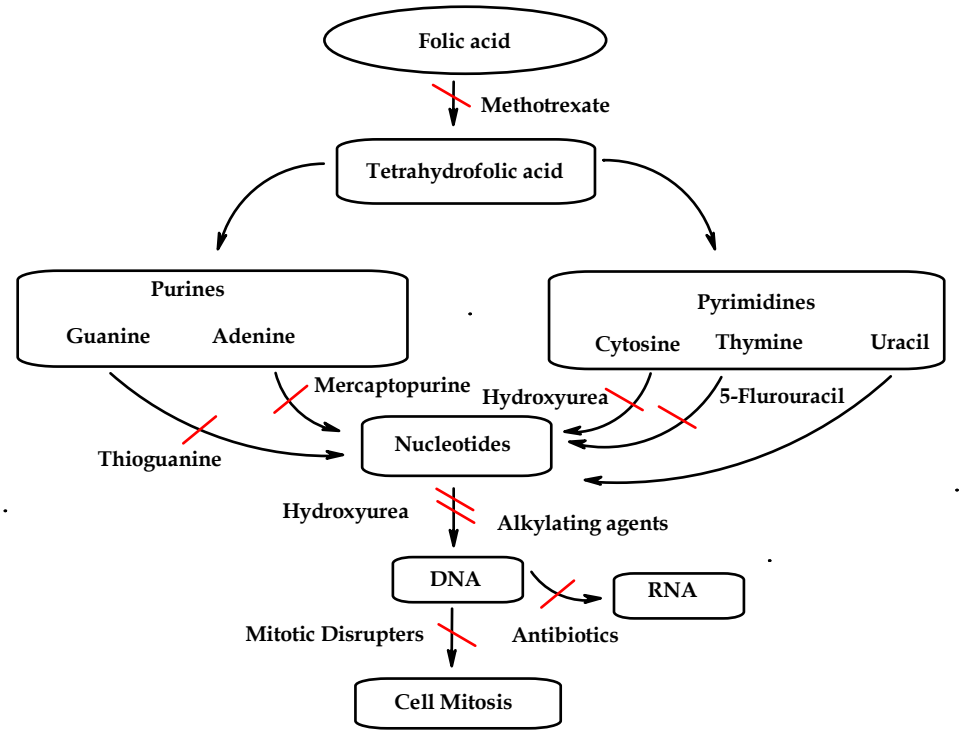


Figure 2. Mechanism of chemotherapy according to cell cycle

Chemotherapy varies with type of cancer and stage of its development and mode of action of anticancer agents. Reactions between DNA enzymes and anticancer agents are irreversible and shut down the functioning of the enzymes, leading to ultimate death of cell.

The anticancer agents are divided into different main categories according to their mode of action. The main categories of anticancer agents are (1) anti-metabolites, (2) alkylating agents, (3) anti-mitotic agents, (4) topoisomerase inhibitors, (5) anti-hormonal agents, and (6) enzyme inhibitors.[10]

1. Antimetabolites[11]

Antimetabolites are structural analogs of naturally occurring compounds and they interfere with the production of nucleic acids. Antimetabolites inhibit the growth of the most rapidly proliferating cells in the body (e.g. bone marrow, G.I. tract, etc.). All drugs in this category affect the cell during the "S" phase of the cell cycle.

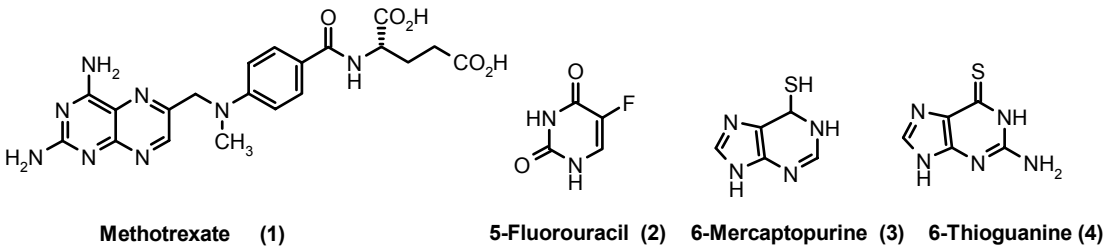


Figure 3.

Antimetabolites may be used in the treatment of acute and chronic leukemias, choriocarcinoma, and some tumors of the gastrointestinal tract, breast and ovary. There are three categories of antimetabolites: antifolates, purine analogs and pyrimidine antimetabolites. Examples of commonly used antimetabolites are 5-fluorouracil (**2**) and 6-mercaptopurine (**3**).

Antifolates

Folic acid is an essential growth factor and it must be reduced in two successive steps by dihydrofolate reductase (DHFR) before it can function as a coenzyme. Methotrexate (**1**) is a strong inhibitor of DHFR and it acts as an antineoplastic, an antirheumatic, a nucleic acid anti-metabolite and a folic acid antagonist. It has a high affinity for the tumor cell enzyme blocking DHFR and formation of tetrahydrofolate needed for thymidylate and purine synthesis.

Purine antimetabolites

The antipurines can both inhibit nucleotide and nucleic acid synthesis. Among these compounds are not only anticancer drugs but also immunosuppressives (azathioprine) and antiviral compounds (acyclovir, ganciclovir etc.). The two major anticancer drugs in

this category are 6-mercaptopurine (**3**) and 6-thioguanine (**4**). These drugs are analogs of hypoxanthine and guanine, respectively.

Pyrimidine antimetabolites

Members of this group are direct inhibitors of thymidylate synthetase, the key enzyme in thymidylate synthesis and indirect inhibitor of dihydrofolate reductase. Pyrimidine analogs have also been used in the treatment of diseases as diverse as cancer, psoriasis, fungal infections and viral infections. 5-Fluorouracil (**2**), 5-fluorodeoxyuridine and fluoropyrimidines are the most important members of this group.

2. Alkylating agents[12]

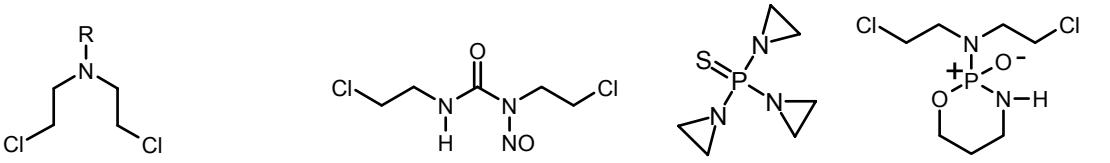


Figure 4.

Alkylating agents are the oldest class of anticancer drugs. Nitrogen mustard gas is the first example of anticancer agents; it was originally developed for military use. All of the alkylating agents form strong electrophiles through the formation of cabonium ion intermediate. Some common examples (Figure 4) of alkylating agents are mechlorethamine (**5**), chlorambucil (**6**), melphalan (**7**), nitrosourea (**8**), thiotepta (**9**) and cyclophosphamide (**10**). This class of anticancer drugs is very powerful and is used in almost every type of cancer both solid tumors and leukemias.

3. Antimitotic agents [13]

Microtubules are protein polymers that are responsible for various aspects of cellular shape and movement. The major component of microtubules is the polymer tubulin, a protein containing two nonidentical subunits (alpha and beta). The antimitotic agents act

by affecting the equilibrium between free tubulin dimers and assembled polymers. Microtubule interactive agents (MIAS) act by affecting the equilibrium between free tubulin and assembled polymers, which inhibit polymerization in cells undergoing mitosis, leading to arrest at metaphase and consequently result into death of cell.

The two major classes of natural products and derived antimitotic agents that act through inhibition of tubulin polymerization are those that bind to β- tubulin at colchicine site and those that bind to vinca-domain. Combretastatin A-4 (**11**), colchicine (**12**), podophyllotoxin (**13**) and stegnacin (**14**), inhibit the polymerization due to binding to β-tubulin at colchicine binding site.

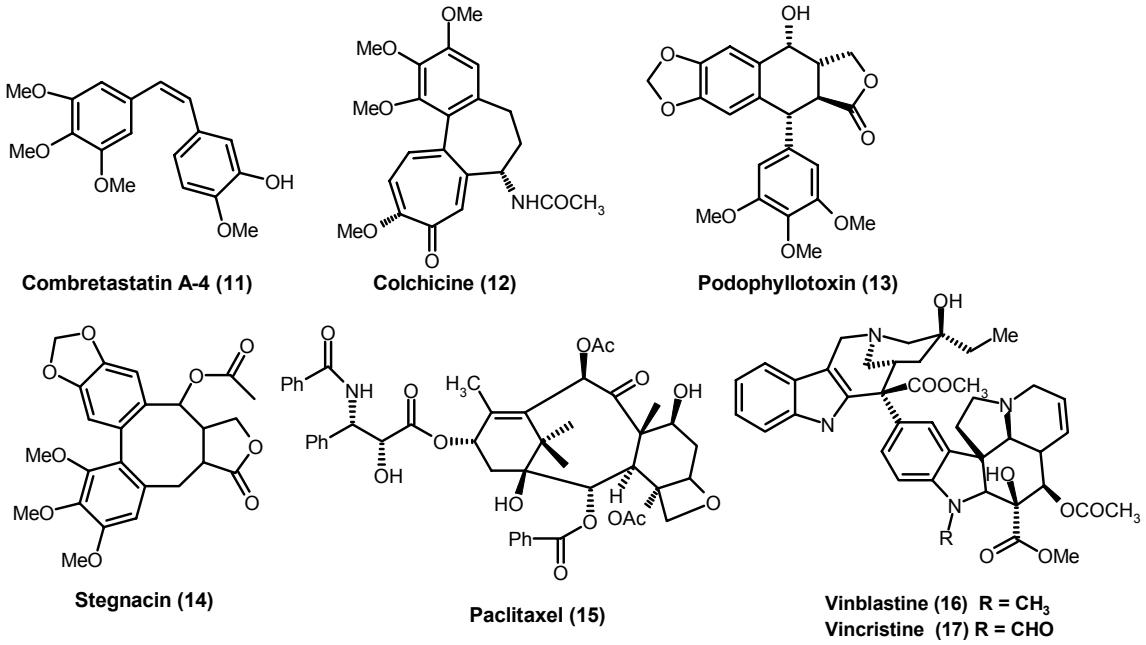


Figure 5.

One of the interesting agent of this type is combretastatin A-4 (CA-4). A large number of mimics are being developed of this molecule out of which three are in clinical trials, while 13 are in preclinical development. This chemical class has served as a model for the synthesis of most of the analogues containing the essential trimethoxyaryl moiety linked to substituted aromatic moieties through a variety of two or three atom bridges including heterocyclic rings and sulfonamides. This impressive display of the power of a relatively simple natural product structure to spawn a prolific output of medicinal and combinatorial chemistry has been blistering topic of chemotherapy.

The vinca alkaloids are cell specific agents and block cells in mitosis. Their biological activity is explained by their specific binding to tubulin. Upon binding to vinca alkaloids, tubulin dimers are unable to aggregate to form microtubules. Vinblastine (**16**), and vincristine (**17**) are the today's leading drugs of this type.

Taxane (Paclitaxel **15**) is another example of this type, which was first isolated from the bark of the Pacific Yew (*Taxus brevifolia*). Docetaxel is a more potent analog that is produced semisynthetically. In contrast to other microtubule antagonists, taxol disrupts the equilibrium between free tubulin and microtubules by shifting it in the direction of assembly, rather than disassembly. As a result, taxol treatment causes both the stabilization of microtubules and the formation of abnormal bundles of microtubules.

4. Antibiotics (Topoisomerase inhibitors) [14]

DNA topoisomerases are a class of enzymes involved in the regulation of DNA super coiling. Type I topoisomerases change the degree of super coiling of DNA by causing single-strand breaks and re-ligation, whereas type II topoisomerases (such as bacterial gyrase) cause double-strand breaks. The different roles of DNA topoisomerase I and II may indicate an opposing pair of roles in the regulation of DNA super coiling. Both activities are especially crucial during DNA transcription and replication, when the DNA helix must be unwound to allow proper function of large enzymatic machinery, and topoisomerases have indeed been shown to maintain both transcription and replication. Topoisomerase I-directed agents currently in regular clinical use are the semisynthetic derivatives of podophyllotoxin such as tenoposide (**18**) and etoposide (**19**) and compounds derived from camptothecin (**20**) such as topotecan (**21**) and irinotecan (**22**). Although camptothecin itself was originally isolated as a cytotoxin and the topoisomerase I activity was not discovered until later, these semisynthetic derivatives were synthesized in efforts to overcome the instability of the lactone ring and the innate insolubility of the parent compound, while maintaining topoisomerase I inhibitory activity. Saintopin (**23**), doxorubicin (**24**), daunomycin (**25**) are the examples of naphthacenedione and anthracyclines respectively; which exert their cytotoxic effects through interaction with topoisomerase enzymes.

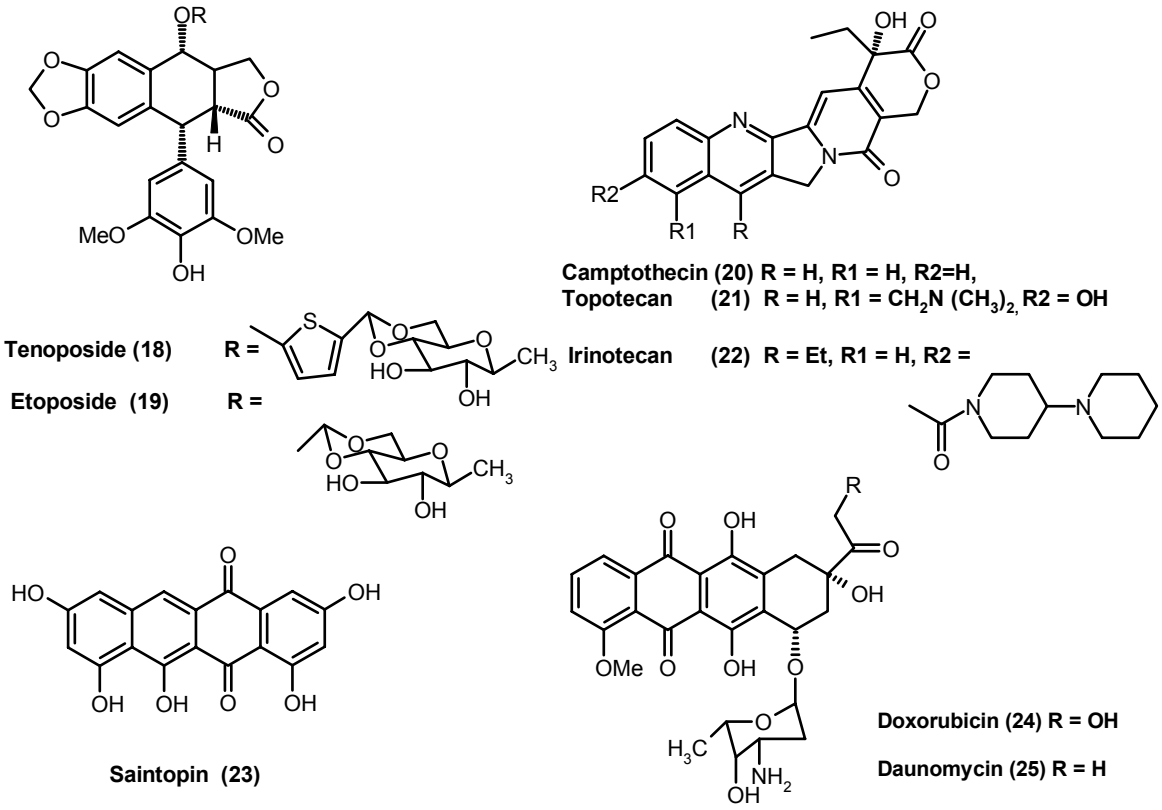
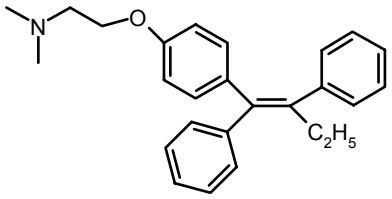


Figure 6.

Along with the topoisomerase inhibitory activity, anthracyclines/anthraquinones also work by the formation of free oxygen radicals. These radicals result in DNA strand breaks and subsequent inhibition of DNA synthesis and function.

5. Antiestrogens[15]

Tamoxifen (Figure 7) is a competitive inhibitor of estradiol binding to the estrogen receptor. It is used in the treatment of metastatic breast cancer. It is used alone for palliation of advanced breast cancer in women with estrogen receptor -positive tumors, and it is used for adjuvant therapy in certain types of early stage disease depending on the patient's age, receptor status of the tumor and degree of nodal involvement.



Tamoxifen (26)

Figure 7.

6. Enzyme inhibitors[16]

Enzyme ribonucleotide reductase is closely related to proliferative status in cancer cells. Specifically, it inhibits ribonucleotide reductase to block deoxyribonucleotide formation and DNA synthesis. Hydroxyurea is S phase specific drug; it inhibits DNA synthesis by reacting with enzyme ribonulcleotide reductase.

Recent study of *exo*-methylene butyrolactones and butenolides from sesquiterpenes family and from individual plant extracts and their synthetic derivatives shows that they have enzyme-inactivating properties. Due to the conjugated enone system, GST isoenzymes undergo Michael type of addition with SH or NH nucleophile present in certain enzymes such as glutathione S-transferase, S-adenosyl L-homocysteine hydrolase etc. Formation of Michael adduct with those over expressed enzymes and consequently cell division (Figure 8).

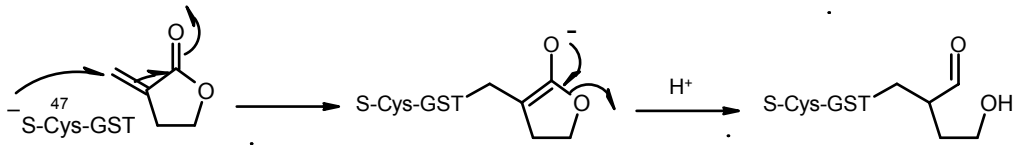
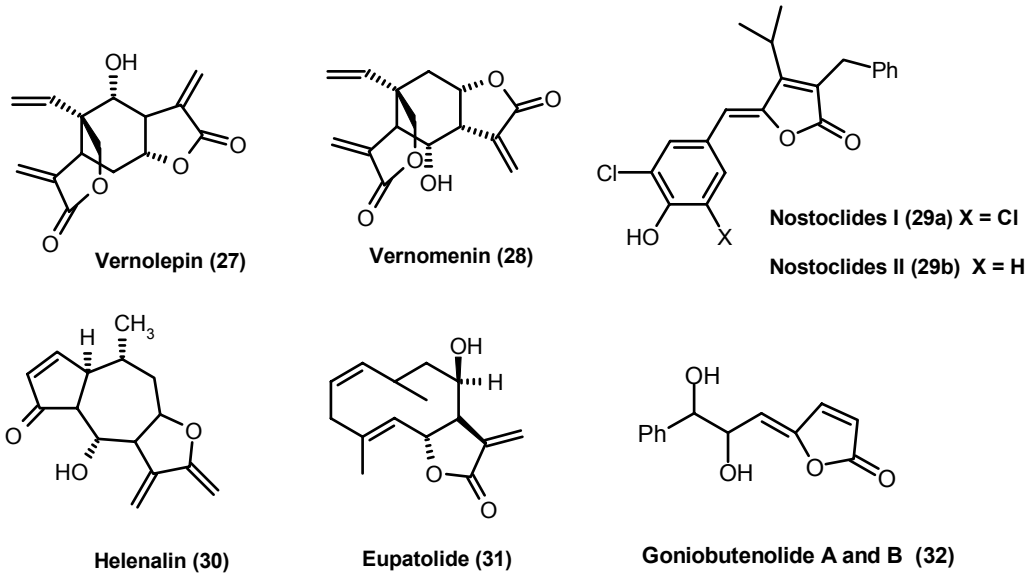


Figure 8. Inhibitory effect of α, β-unsaturated enones on GST-π enzymes

Some of the examples (Figure 9) of sesquiterpenes are vernolepin (**27**), vernomenin (**28**), helanin (**30**) and *exo*-alkylidene butenolides goniobutenolide (**32**), and nostocilides (**29a** and **29b**).


OH
O
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Vernolepin (27)
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OH
O
Vernomenin (28)
Ph
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O
Cl
HO
X
Nostoclides I (29a) X = Cl
Nostoclides II (29b) X = H
H
CH3
O
O
HO
Helenalin (30)
OH
H
O
O
Eupatolide (31)
OH
Ph
OH
O
O
Goniobutenolide A and B (32)

Figure 9.

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1.1.1. INTRODUCTION

Functionalized furanones are important subunits present in a large variety of natural products and biologically active compounds such as alkaloids,[1] lignan lactones[2] and sex attractant insect pheromones.[3] Many of these compounds exhibit a variety of properties including anti-cancer and antifungal, insecticidal, antibacterial, phytotoxic, or anti-inflammatory activities; some of them are antibiotics, cyclooxygenase or phospholipase A2 inhibitors.

From the introductory remarks, it is apparent that γ-methylene/ alkylidene furanones are of interest from both synthetic as well as from medicinal point of view. *Exo*-alkylidene furanone is an important subclass of furanone family with very attractive structural and biological properties. Among these, γ-alkylidenefuranones is an interesting class with unique structural features and wide range of biological activities, due to which it has attracted extensive attention of organic chemists.[4]

γ-Alkylidenefuranones have been isolated from natural sources and many of them have shown a wide range of biological activity such as nostoclides I and II (**29a, 29b**), [5] goniobutenolide (**32**) [6] and pentadienolide (**44**)[6b] are cytotoxic, xerulin (**37**)[7] and its derivatives *i.e.* xerulinic acid (**38**)[8] and dihydroxerulin (**39**)[9] act as cholesterol biosynthesis inhibitors, while protoanemonin (**33**), [10] rubrolide (**41**),[11] tetrenolin (**42**),[12] and tetrodecamycin (**45**) [12b] and teronomycin (**46**) [12c] possess anitibiotic activity. Bovolide (**34**),[12d] thiophenbutenolide (**35**),[12e] ligustilide (**36**),[12f] eremolactone (**40**)[12g] and peridinin (**43**)[12h] are some of the distinguished examples of naturally occurring γ-alkylidenefuranones (**Figure 1**).

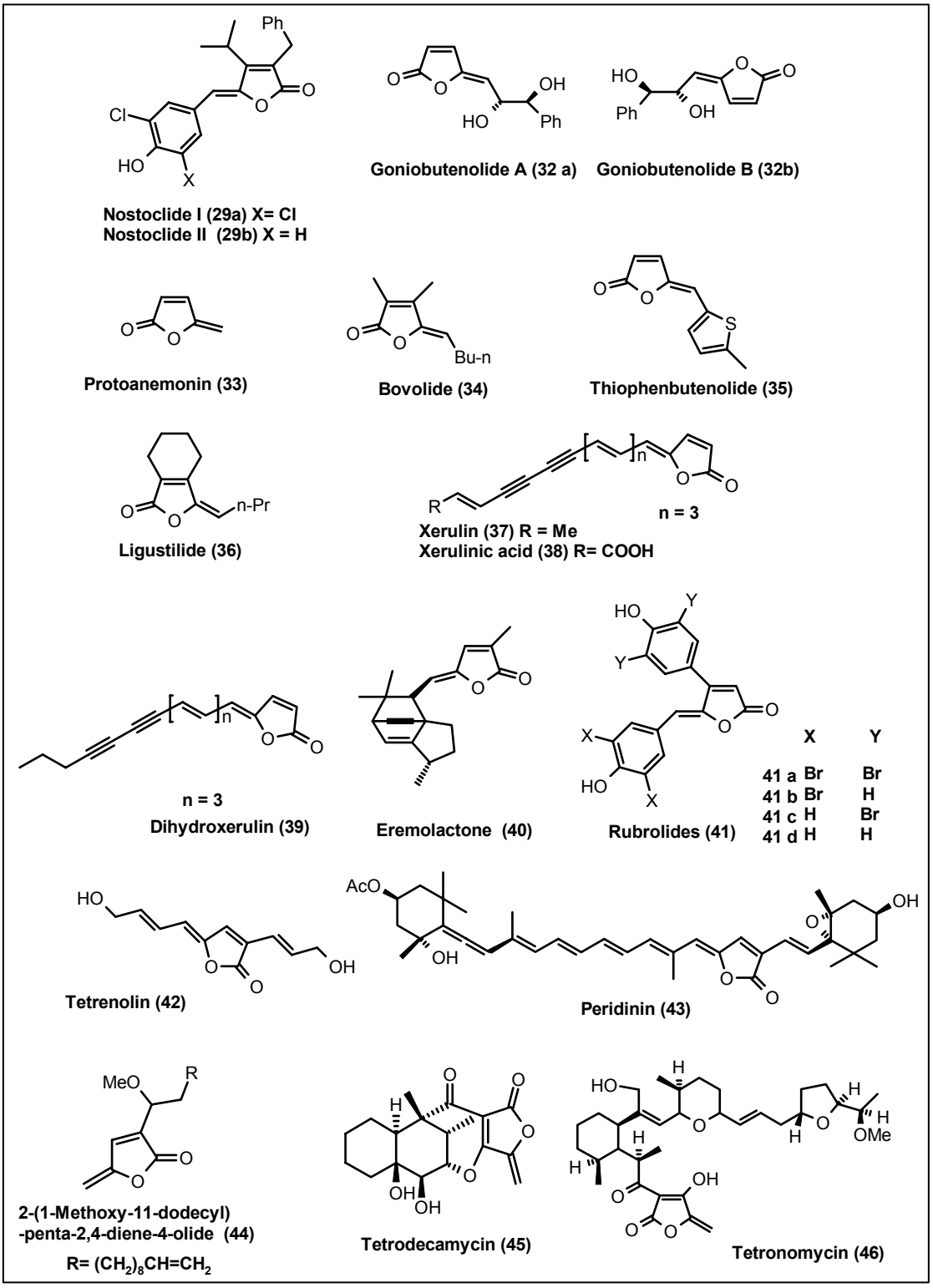


Figure 1. Naturally occurring γ-alkylidenefuranones

Since the foregoing discussion in this chapter concerns with the development of a strategy for the γ-methylenefuranone, it is pertinent to mention briefly the important methodologies reported in literature to put this study in total perspective.

Review of the literature on synthesis of γ-alkylidenefuranones

For the synthesis of compounds having exocyclic double bond, different methods are documented in literature that are summarized below. These methods are classified according to the type of substrates and reagents used for their synthesis.

1. Synthesis of γ-alkylidenefuranones from

1.1 γ-Keto acids

1.2 γ-Hydroxy acids

1.3 Alkylidenation of five membered heterocycles

1.4 Bis-silyl enolethers

2. Synthesis of γ-alkylidenefuranones using catalytic methods

2.1 Cobalt carbonyl catalyzed lactonization

2.2 Chromium carbonyl catalyzed lactonization

2.3 Ag and Hg-catalyzed lactonization of 4-alkynoic acids

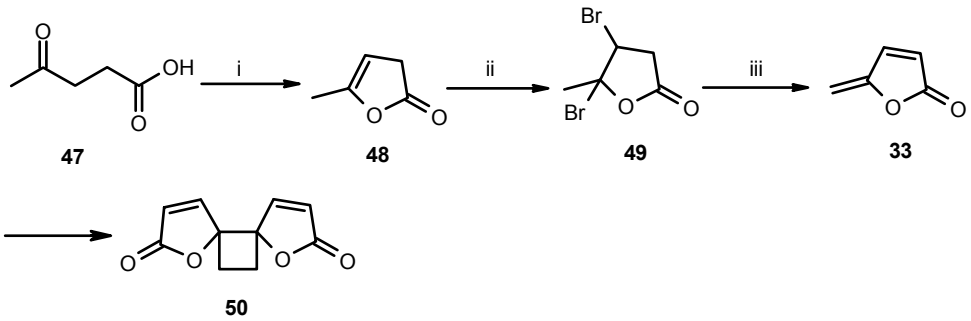
2.4 Pd or Rh-catalyzed lactonization of 4-alkynoic acids

1. Synthesis of γ-alkylidenefuranones

1.1. Synthesis of γ-alkylidenefuranones from γ-keto acids

Lactonization of γ-keto acids is one of the oldest route for the synthesis of γ-alkylidenefuranones. Synthesis of protoanemonin (**33**),[13] an antibiotic isolated from *rannulaceae* and synthesized from levulinic acid (**47**), is the simplest example of lactonization of γ-ketoacids (Scheme 1).

Scheme 1. Synthesis of protoanemonin *J. Am. Chem. Soc.* **1955**, *77,* 2332-2235.

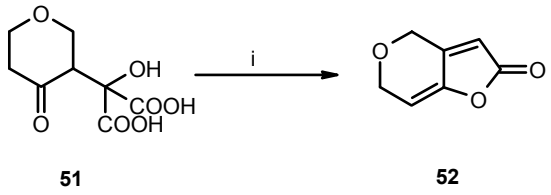


Reagents and conditions: (i) Ac_2O, H_2SO_4; (ii) Br_2, CS_2, -20 ºC; (iii) NEt_3.

Lactonization of levulinic acid (**47**) gave α-angelica lactone (**48**) followed by its bromination and dehydrobromination to form protoanemonin (**33**) with 30% yield. It is very unstable and easily dimerizes through (2+2) head to head cycloaddition to give bioinactive crystalline anemonin (**50**) as depicted in Scheme 1.

Similarly synthesis of deoxy-patulin (**52**)[14] involved treatment of γ-keto acid **51** with warm acetic anhydride and sulphuric acid in acetic acid as shown in Scheme 2.

Scheme 2. Synthesis of deoxypatulin *J. Am. Chem. Soc.* **1949,** *71*, 758.

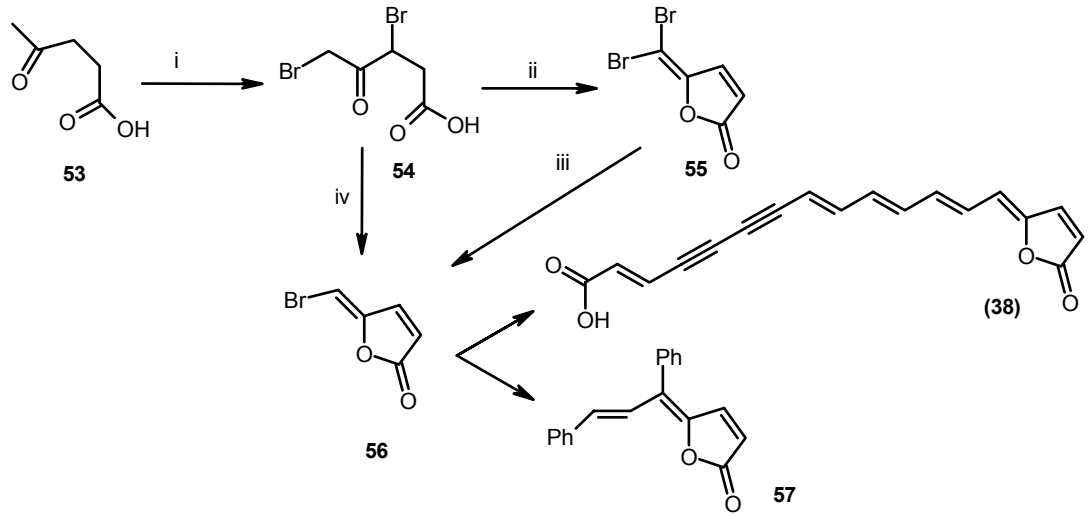


Reagents and conditions: (i) Sulphuric acid, acetic anhydride, acetic acid.

R. Bruckner and coworker's reported[15] access to γ-alkylidenefuranones starting from dibromolevulinic acid **54**, which was prepared from levulinic acid **53**. Dibromolevulinic acid **54** was subjected to lactonization using oleum/conc. H_2SO_4 (2:1) followed by treatment with tributyltin hydride in the presence of $Pd(PPh_3)_4$ to afford the intermediate

bromobutenolide **56**. In another sequence using P_4O_{10} followed by treatment with Et_3N, which induced β-elimination of HBr to gave four times better yield of **56** was obtained. Bromobutenolide **56** was further utilized for the Stille coupling and for the synthesis of xerulinic acid (**38**).

Scheme 3. Synthesis of xerulinic acid *Angew.Chem. Int. Ed* **2004,** *43,* 4523-4526.

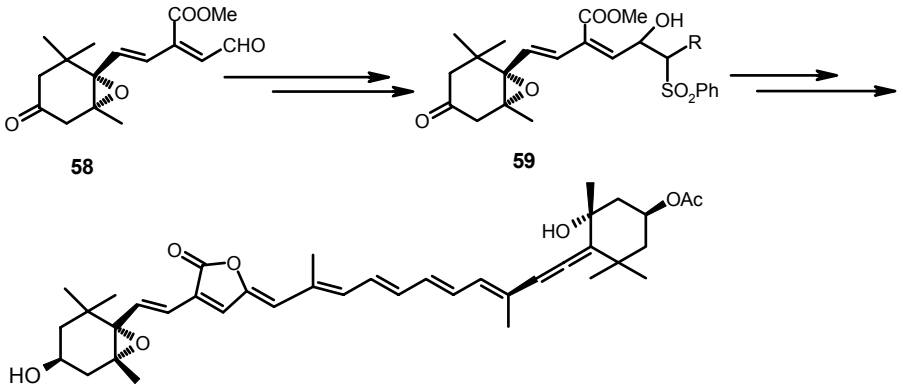


Reagents and conditions: (i) Br_2, DCM, 0 ºC, 2h; (ii) Conc. H_2SO_4, 6 min; (iii) $HSnBu_3$, [Pd $(PPh_3)_4$], THF, 65 ºC, 3h; (iv) P_4O_{10}, then Et_3N; 0 ºC, 1h.

1.2. Synthesis from γ-hydroxyacids

It is well known that γ-hydroxyacids readily cyclize to give γ-lactones. This strategy has been used for the synthesis of γ-alkylidenefuranones. Various natural products were synthesized from γ-hydroxyacids. In this case the functional group adjacent to γ-hydroxyl group such as allyl, alkenyl, halogen, oxygen and sulphur are appropriate for elimination reaction and lead to an *exo*-alkylidenene bond as demonstrated by the synthesis of peridinin (**43**) [16] from substituted γ-hydroxyacid **59**.

Scheme 4. Synthesis of peridinin *J. Chem. Soc., Perkin Trans.* 1, **1990,** 197.



Peridinin (43)

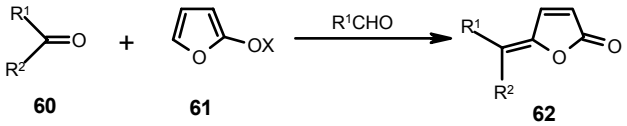
1.3. Alkylidenation of five membered heterocycles

This method involved the synthesis of γ-alkylidenefuranones from 2-oxyfurans,[17] γ-lactones[18] or maleic anhydride derivatives.[19] Synthesis of γ-alkylidenefuranones by this method is nonstereoselective but due to the steric and electronic reasons, formation of *Z*-isomer is dominated as it is thermodynamically preferred.

1.3.1. Synthesis from 2- oxyfurans

Synthesis of γ-alkylidenefuranones **62** involved alkylidenation of five membered oxygen heterocycles such as 2-oxyfurans **61** which act as nucleophiles. Many natural and unnatural congeners were synthesized from substituted 2-oxyfurans involving β-elimination pathway to obtain γ-alkylidenefuranones as depicted in scheme 5.

Scheme 5.



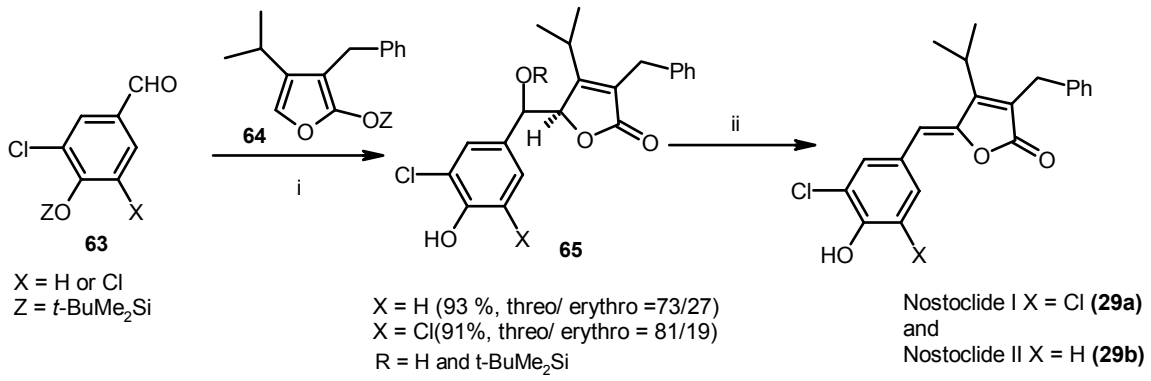
60 **61** **62**

X = OMe, *t*- Bu, $SiMe_3$, $SiMe_2Bu$-t

Due to steric and electronic factors of substituted functional group, the formation of *Z*-isomer is favoured. Nostoclide II (**29b**) [20] was synthesized in two steps (82% overall yield) from substituted furan **64** and aldehyde **63** by TBDMSOTf induced aldolisation

and subsequent β-elimination of the resulting mixture of diastereoisomers **65**. Exclusive formation of *Z*-isomer occurred due to the presence of isopropyl group in the β-position as shown in Scheme 6.

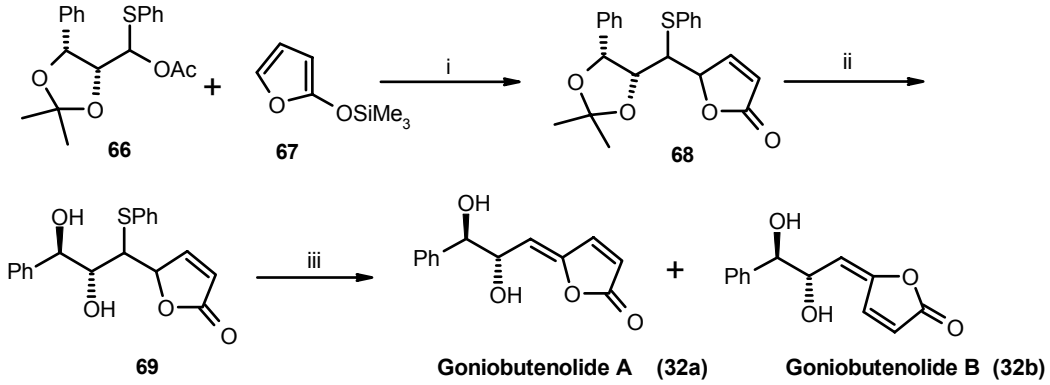
Scheme 6. Synthesis of nostoclide *Tetrahedron Lett.* **1994**, *35*, 7897-7901.



Reagents and conditions: (i) TBDMSOTf (0.5 equiv), CH_2CI_2, -78 °C, 2 h, (ii) DBU (4 equiv), $CHCl_3$, reflux, 18-24 h; I = 96%, II = 90%.

Ko and coworkers synthesized goniobutenolides (**32**) stereoselectively (Scheme 7).[21] Goniobutenolides A (**32a**) and B (**32b**) were isolated from the ethanolic extract of stem bark of G*oniothalums giganteus* having cytotoxic activity against human tumor cell lines.

Scheme 7. Synthesis of goniobutenolides A and B *Tetrahedron Lett.* **1995,** *36,* 2101-2104.

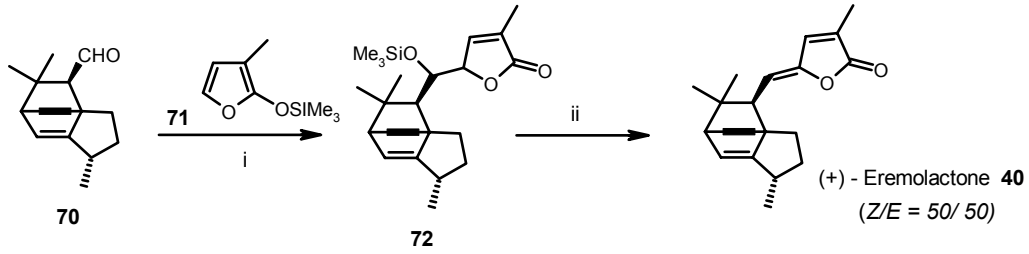


Reagents and conditions: (i) $SnCl_4$, DCM, -78°C; (ii) 90% aq. TFA, (iii) AgF, pyridine, 68%

Goniobutenolides were synthesized from 2-trimethylsilyloxyfuran **67** *via* Mukaiyama coupling with acetals in presence of Lewis acid followed by β-elimination of thiophenol using AgF/pyridine. Chromatographic purification afforded mixture of goniobutenolides A and B (**32 a** and **32 b**; 68 % combined yield), which were separated by flash column chromatography.

Eremolactone (**40**)[22] is another example of *exo*-alkylidene furanone which was isolated from *Eremophila fraseri and E. freelingii.* It was synthesized from substituted 2-trimethylsilyloxyfuran **71** by treating it with aldehyde in presence of $SnCl_2$ followed by β-elimination (Scheme 8).

Scheme 8. Synthesis of eremolactone *Tetrahedron Letters*, **1983**, *24,* 4487-4490.

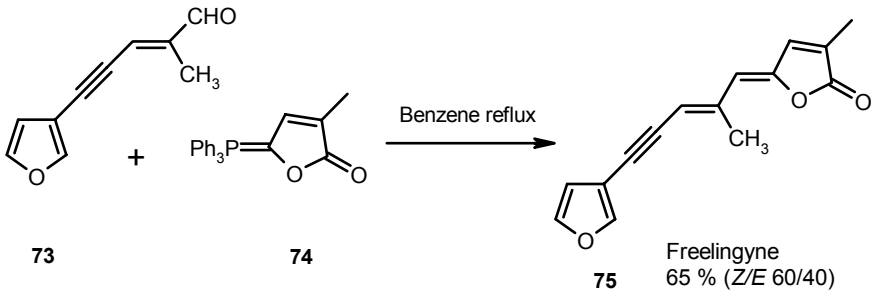


Reagents and conditions: (i) $SnCl_4$, DCM, -78 °C; (ii) NEt_3, TFA, rt or DBU, CH_3CN, rt, 1h.

1.3.2. Synthesis of γ-alkylidenefuranones from γ-lactones

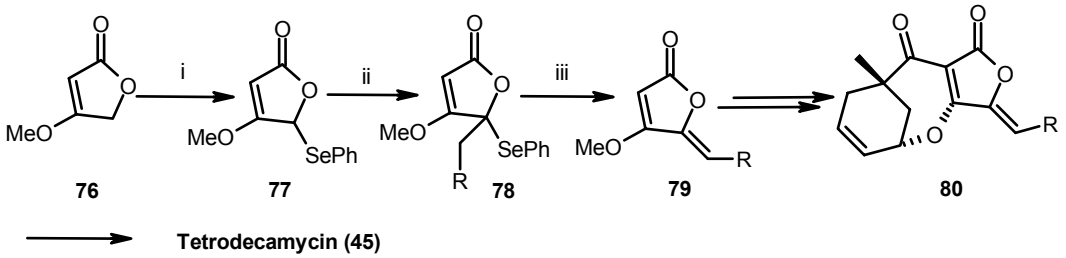
γ-Lactones could be converted to γ-alkylidenefuranones by Wittig olefination reaction; for e.g. sesquiterpene freelingyne (**75**) [23] isolated from *Eremophila freelngyne* was synthesized by the application of Wittig reaction of 3-methyl-5-triphenyl phosphoranylidene-(5*H*)-furan-2-one (**74**) with 5-furan-3-yl-2-methyl-pent-2-en-4-yanal (**73**) depicted in Scheme 9.

Scheme 9. Synthesis of freelingyne *J.Chem. Soc. Perkin Trans 1* **1975**, 641-643.



Paintner and coworkers reported formal synthesis of tetrodecamycin (**45**), having unique ring skeleton bearing *exo*-methylene moiety (**79a**).[24]

Scheme 10. Synthesis of tetrodecamycin *Tetrahedron Lett.* **2000**, *41*, 9977-9980.

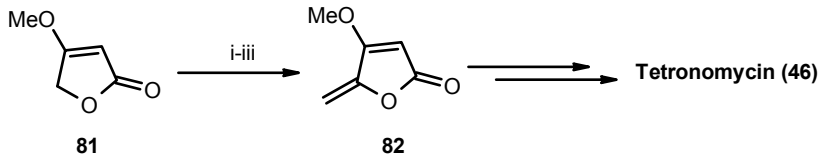


Reagents and conditions: (i) (a) *n*-BuLi, THF, -78°C; (b) PhSeCl, -78°C (90%); (ii) (a) *tert*-BuLi, THF, -78°C; (b) RCH_2X, -78°C to rt [**78a**: (R = H, X=I) 82%; **78b**: (R=Me, X=I) 65%; **78c**: (R=Ph, X=Br) 76%]; (iii) MCPBA, CH_2Cl_2, 0°C [**79a**: 92%; **79b**: 95%; **79c**: 91%]

4-Methoxy-5-phenylseleno-2(*5H*)-furanone prepared by selenation of commercially available 4-methoxy-2(*5H*)-furanone (**76**) was alkylated followed by oxidative elimination of phenyl selenium group using MCPBA to afford the γ-alkylidene derivative **80** (Scheme 10) which is an intermediate for the synthesis of tetrodecamycin (**45**).

Yoshi *et al.* reported synthesis of tetronomycin (**46**),[25] an antibiotic active against gram-positive bacteria and *mycoplasma* and *neisseria* species.

Scheme 11. Synthesis of Tetronomycin *J. Org. Chem.* **1992,** 57, 2888-2992.



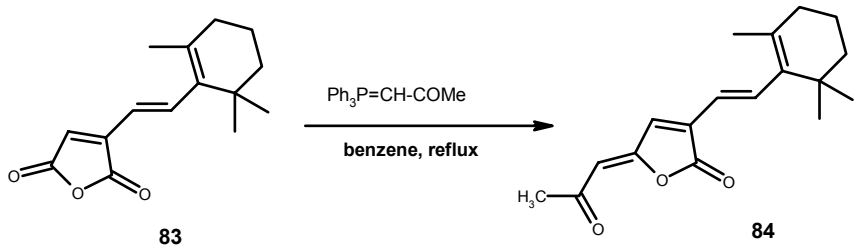
Reagents and conditions: (i) (Me_2N) CHOMe; (ii) Na (CN) BH_3; (iii) MeI, $NaHCO_3$

Tetronomycin (**46)** a complex molecule featured with exomethylene moiety was synthesized from 4-methoxy-5-methylene-(5*H*)-furan-2-one **82**, which was prepared in three steps as shown in Scheme 11. Dimethylamino-methylation at C5 using $CH(NMe_2)OMe$, reduction with sodium cyanoborohydride followed by treatment with methyl iodide and aqueous $NaHCO_3$ afforded the required exomethylene furanone **82**.

1.3.3 Synthesis of γ-alkylidenefuranones from maleic anhydride derivatives[19]

Maleic anhydride derivatives **83** were transformed into γ-alkylidenefuranones **84** by Wittig olefination in one step as shown in Scheme 12.

Scheme 12. *Heterocycles* **1982**, *19,* 1385-1387.

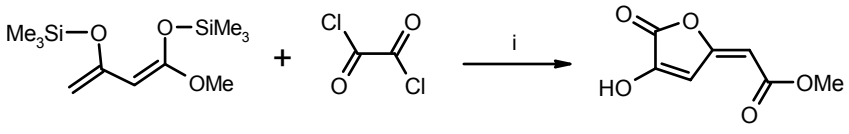


83 **84**

1.4. Synthesis of substituted γ-alkylidenefuranones from 1, 3 bis-silyl enol ethers

Langer P. reported[26] simple and efficient method for the synthesis of γ-alkylidene furanone **87** involving Me_3SiOTf-catalyzed cyclization of 1,3- bis(trimethylsilyloxy)-1,3-butadiene **85** with oxalyl chloride **86**. Lewis acid Me_3SiOTf (trimethylsilyl trifluoromethane-sulfonate) was used to obtain most favorable results as depicted in Scheme 13.

Scheme 13. S*ynthesis* **2002**, 441-444



85 **86** **87**

Reagents and conditions: (i) 0.3 eq., Me_3SiOTf, CH_2Cl_2, -78 °C.

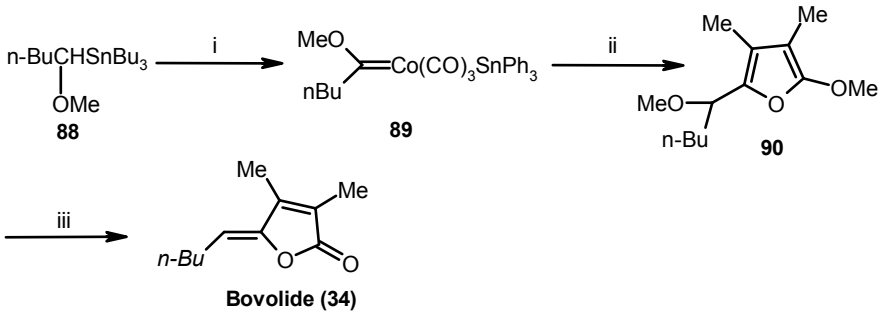
2. Synthesis of γ-alkylidenefuranones using catalytic methods

Alkylidene derivatives were synthesized by using different types of metal complexes. These methods either involved metal catalyzed carbonylation or intermolecular or intramolecular reactions of alkyenes, alkenes or organic halides using Co, Cr, Ag, Hg, and Pd complexes. Transition metals like Co[27] and Cr[28] also have been used for the synthesis of γ-alkylidenefuranones.

2.1. Cobalt carbonyl catalyzed lactonization

Synthesis of bovolide **34** has been carried out using cobalt complex as shown in Scheme 14. The α-methoxy-n-pentylcobalt carbonyl complex **89** was prepared from α-stannyl ether **88** and triphenyltincobalttetracarbonyl, which was heated with 3 equivalents of 2-butyne in benzene under inert atmosphere. The crude reaction mixture was then treated with 3 equivalents of trimethylsilyl iodide to give bovolide (**34**) in 48 % yield.

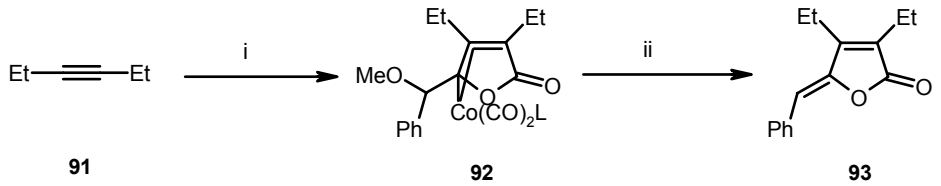
Scheme 14. Synthesis of bovolide *J. Am. Chem. Soc.* **1986**, *108,* 520.



Reagents and conditions: (i) n-BuLi, $Ph_3SnCo(CO)_4$, $Me_3O^+BF_4$, 45%; (ii) 2-Butyne, 50 ºC, 4 days, (iii) Me_3SiI (3 equiv), 48%.

Acyl cobalt carbonyl compounds, substituted in the α-position with a leaving group react with internal alkyne to give rise to substituted furanones (5-methylene-2(*5H*)-furanones) in good yields.[29] The reaction of a 1,2-disubstituted alkyene with an acyl cobalt carbonyl, which contains a leaving group such as acetate in α-position yielded conjugated butenolides after regioselective elimination (Scheme 15).

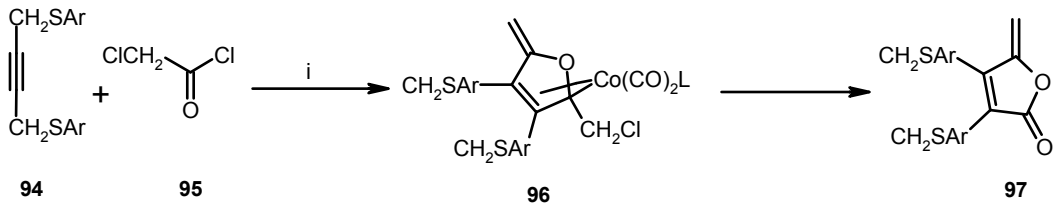
Scheme 15. *Synlett* **1991**, 865-866.



Reagents and conditions: (i) PhCH(OAc)COCl, (ii) $NaCo(CO)_4$, 0 ºC, 6 h.

Similarly 1,4-(bis-4-ethylphenylthio)-2-butyne (**94**) on treatment with chloroacetyl chloride in presence of sodium cobalt carbonyl complex [$NaCo(CO)_4$] provided furanone **97** in 49-85 % yield (Scheme 16).

Scheme 16. *Synlett* **1991**, 865-866.

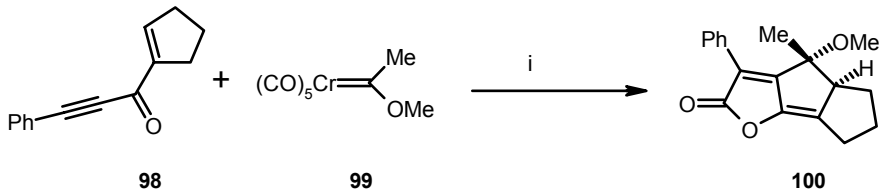


Reagents and conditions: (i) $NaCo(CO)_4$, 0 ºC, 6 h.

2.2. Chromium carbonyl catalyzed lactonization

Alkylchromium carbene complex **99** and ketoalkyne **98** when heated in dry THF at 70 °C afforded lactone as demonstrated for the synthesis of tricyclic lactone **100** with γ-alkylidene moiety[30] as depicted in Scheme 17.

Scheme 17. *J. Am. Chem. Soc.* **1991**, *113,* 5459-5461.

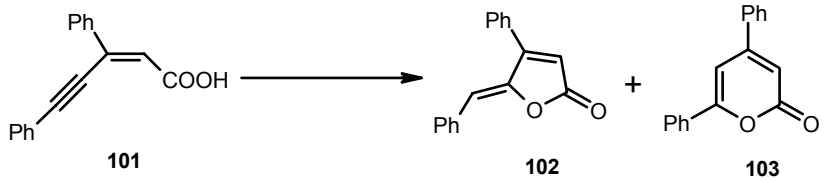


Reagents and conditions: (i) THF, 70 ºC, 60 h.

2.3. Ag and Hg-catalyzed lactonization of 4-alkynoic acids

Silver catalysed lactonization [31] was found to be very fast and cleaner as compared to other methods reported in early 1958. Various silver reagents eg. $AgNO_3$, $AgClO_4$, $AgCO_3$, AgO, Ag were used for lactonization of 4-alkynoic acid. These reactions proceeded cleanly in ethanol/water at room temperature to provide γ-alkylidenefuranone **102** with *Z*-geometry (Scheme 18).

Scheme 18. *J. Chem. Soc. Perkin Trans. 1,* **1981***,* 582.



Mercury reagents[32] such as HgO, $Hg(OAc)_2$, $Hg(OCOCF_3)$ gave desired γ-alkylidenefuranones **102** with poor yield, and pyrone derivatives **103** as exclusive side product.

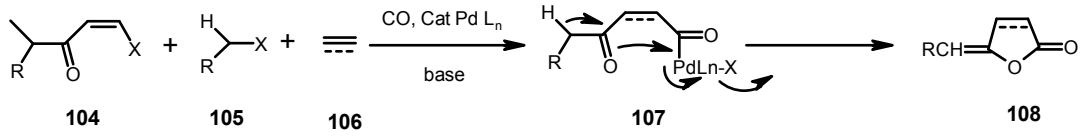
2.4. Pd-catalyzed lactonization of 4-alkynoic acids

Palladium catalyzed carbonylation is most widely used for the synthesis of γ-alkylidene-furanones. Stereoselectivity of this method is better than other methods but it varies with substitution pattern of the substituents.

This method involved synthesis of γ-alkylidenefuranones *via* γ-ketoacyl palladium derivatives, which could be generated by palladium-catalysed carbonylation of (Z)- β-halo-α,β-unsaturated ketones, alkynes or alkenes. Oxidative addition with Pd complex of

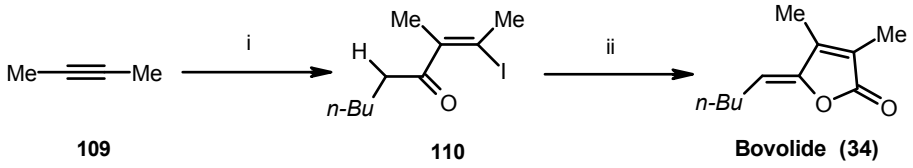
alkenyl, allyl, benzyl and acyl halides in presence of suitable base afforded γ-alkylidene furanones **108** as shown in Scheme 19.

Scheme 19.



Negishi and coworkers synthesized bovolide[33] using Pd catalyzed carbonylation method. β-Iodoenone **110** containing α-hydrogen atoms give γ-alkylidene furanones under 40 atmosphere pressure of carbon monoxide in presence of 5 mol % of $Cl_2Pd(PPh_3)_2$ and 2 equivalents of triethylamine as shown in Scheme 20.

Scheme 20. Synthesis of bovolide *J. Am. Chem. soc.* **1995**, *117,* 3422.

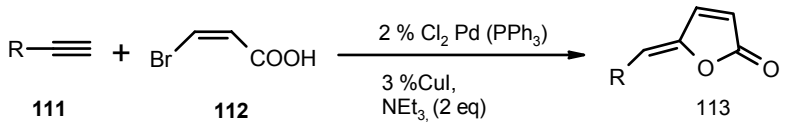


Reagents and conditions: (i) (a) Et_2ZrCp_2, n-Pent-CN, 62% (b) I_2, H_3O^+; (ii) CO (40 atm), $Cl_2Pd(PPh_3)_2$ 5%, NEt_3, DMF, 100 ºC, 10 h, 82%.

Palladium catalysed stereoselective synthesis of γ-alkylidenefuranones:

Consecutive cross coupling-lactonization is highly efficient and selective method for the synthesis of a variety of γ-alkylidenefuranones **113**,[34] with *Z*-stereochemistry. This process involves two-step mechanism i) Sonogashira type cross coupling, ii) HPdL*n*-induced anti lactonization and reductive elimination (Scheme 21).

Scheme 21.



111 **112** 113

R	yield	*Z/E*
Ph	80	97/3
n-Pent	60	91/ 9
Ph- CH-(OH)	56	97/3
$THPOCH_2$	62	93/7
Me_2C (OH)	86	94/6

A large number of methods developed for the synthesis of γ-alkylidenefuranones demonstrate the importance of these molecules in organic and biochemistry.

1.1.2. PRESENT WORK

Reactions are the tool kit for chemist to create new chemical entities with novel properties. They are the basis of today's organic chemistry and art of assembling complex molecules with predefined properties. Novel methods for the synthesis of complex molecules are still a challenging part of organic chemistry. The utility of new reactions can be defined as giving a target molecule in optimal yield while using a shorter synthesis. Getting an important novel product with few side products is the concept of divergences and convergences in organic synthesis.

Literature survey revealed that the numerous methods have been reported for the synthesis of β-substituted-γ-methylenefuranones. The present section describes the method for the synthesis of novel 4-(substituted)-benzyl-5-methylene-2(5*H*)-furanones (β-substitutes-γ-methylenefuranones or γ-methylenefuranones). This method for the preparation of γ-methylenefuranone is the outcome of serendipitous results obtained during the synthesis of saintopin, which is discussed in second chapter.

1.1.3. RESULTS AND DISCUSSION

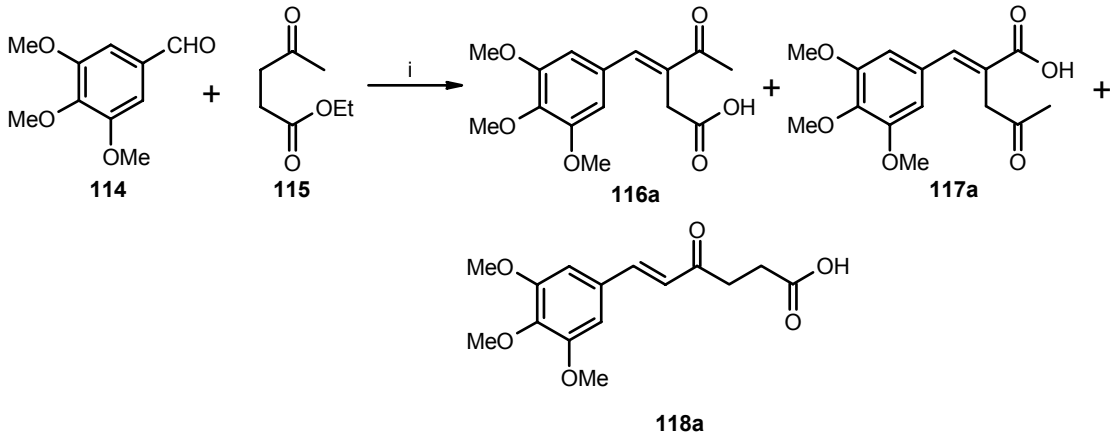
The present method involved Stobbe condensation of ethyl levulinate with substituted aromatic and aliphatic aldehydes in the presence of aqueous sodium hydroxide to afford the acid intermediate which on treatment with anhydrous sodium acetate and acetic anhydride afforded γ-methylenefuranones. In order to elaborately study the scope and limitations of the above mentioned two reactions, several aldehydes were subjected to the sequence.

Ethyl levulinate is γ-ketoester and peculiar compound in the sense that each of its three-methylene groups are situated next to carbonyl group providing three active sites to generate carbanion. To utilize ethyl levulinate as substrate for condensation reaction, it is necessary to select suitable base and to standardize reaction conditions to achieve desired selectivity in the product.

We employed different bases for the condensation of ethyl levulinate with substituted aromatic aldehydes. B. Swaminathan, in 1976[35] reported condensation reaction of substituted benzaldehyde and ethyl levulinate in presence of freshly prepared potassium *tert*-butoxide in *tert*-butanol at room temperature but using this method mixture of acid

was obtained therefore in the present study various bases were attempted under different reaction conditions. Initially we studied condensation of 3,4,5-trimethoxy benzaldehyde with ethyl levulinate in the presence of bases such as KO*t*Bu, NaOMe, NaH, Na_2CO_3, NaOH and KOH for the optimization of conditions and to achieve selectivity in the formation of regioisomers of condensation product as shown in Scheme 22.

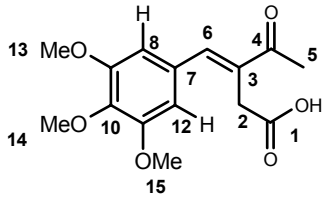
Scheme 22.



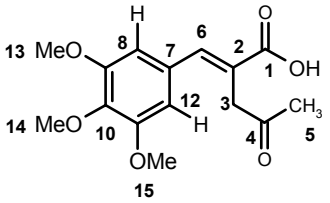
Reagents and conditions: (i) Aq. NaOH, ethanol, -10˚C then at rt, 4-5 h.

It was noted that the use of aqueous sodium hydroxide in ethanol at -10°C gave desired acid intermediate **116a** as a major product, but the formation of its regioisomer **117a** could not be completely avoided (Scheme 22). In the presence of sodium hydride as a base formation of compound **118a** was predominant.

We extended our study to achieve regioselective condensation product **116a** by employing bases such as Et_3N, diisopropyl amine, diisopropyl ethylamine, pyridine and DBU under different reaction conditions. Using DBU the reaction proceeded to provide acid **117a** as a major product while **116a** and **118a** are not detected. The acids **116a** and **117a** and were characterized by spectral techniques. IR spectrum of acid intermediate **116a** showed peaks at 1709 cm^{-1} and at 1655 cm^{-1} corresponding to carboxylic acid and ketone carbonyl respectively.



116 a



117 a

Figure 2. Acids 116a and 117a

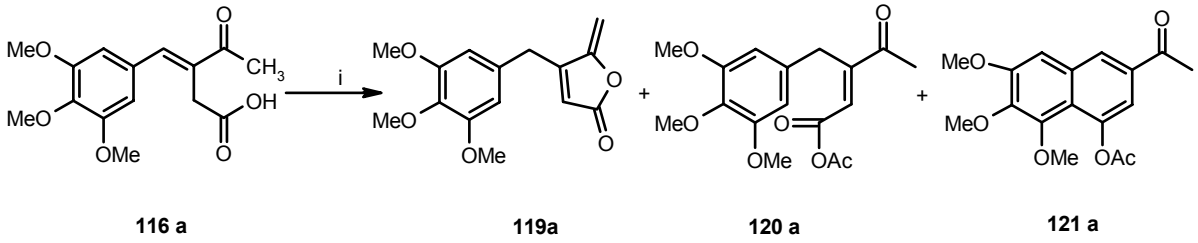
^{1}H NMR spectrum of acid **116a** exhibited various peaks in accordance with the assigned structure. A sharp singlet at δ 2.50 integrating for three protons was attributed to acyl methyl group (CO-C<u>H</u>$_3$), while other singlet at δ 3.55 integrating for two protons was assigned to methylene protons adjacent to carboxylic acid (C<u>H</u>$_2$-COOH). A sharp singlet at δ 3.86 appeared for 9 protons corresponding to three OCH_3 groups, two aromatic protons on C8 and C12 appeared as a singlet at δ 6.68, while the singlet at δ 7.67 was assigned to olefinic proton at C6. The structure assigned was further supported by the ^{13}C NMR spectrum of acid **116a**, which showed 15 signals. Acyl carbon C5 appeared at δ 25.17 and methyl C2 appeared at δ 32.8. Acid carbonyl carbon C1 appeared at δ 176.1 while ketone carbonyl C4 appeared at δ 199.4. Mass spectrum showed molecular ion (M^+) peak at 294 corresponding to acid **116a**.

^{1}H NMR spectrum of the acid **117a** showed a sharp singlet at δ 2.06 integrating for three protons that was assigned to acyl methyl group (CO-C<u>H</u>$_3$) while other singlet for methylene proton adjacent to carboxylic acid (C<u>H</u>$_2$-COOH) appeared at δ 3.47. These protons appeared upfield as compared to acid **116a**. The two aromatic protons on C8 and C12 appeared as a singlet at δ 6.39 and the singlet at δ 6.89 was assigned to olefinic proton at C6. Thus the characteristic splitting pattern of ^{1}H NMR spectrum revealed the structure of acid **117a**. It was observed that protons of acid **116a** appeared downfield as compared to the protons of conjugated acid **117a**.

Initially the acids **116a** and **117a** were independently treated with anhydrous sodium acetate in presence of 10 equivalent of acetic anhydride at 120 ºC (as mentioned in Chapter 2 Section 1). Acid **116a** under these conditions afforded mixture of three products, γ-methylenefuranone **119a**, mixed anhydride **120a** and aromatized naphthalene

derivative **121a** as depicted in Scheme 23. It was found that the temperature of reaction and molar ratio of acetic anhydride controlled the nature of product. To improve the yield of furanone derivatives it was felt necessary to standardize the reaction conditions. Accordingly the reaction was performed at different temperatures from room temperature to ~120 °C.

Scheme 23.



116 a **119a** **120 a** **121 a**

Reagents and conditions: (i) Anhydr. NaOAc, AC_2O, 80-90 ˚C, 3h.

At room temperature the formation of mixed anhydride was detected but the conversion rate was very low and the starting material remained unreacted. The higher temperature i.e. at 50-70 °C, favored the formation of mixed anhydride with traces of furanone derivative **119a**. At 80-90°C, the yield of desired γ-methylenefuranone **119a** could be improved with minimizing the formation of other side products **120a** and **121a.** At temperature higher than 90 °C naphthalene derivative **121a** was found to be the major product of the reaction. In order to optimize the molar ratio of acetic anhydride reactions were conducted at different mole ratio i.e. using catalytic to 10 equivalents of acetic anhydride. Five equivalents of acetic anhydride was found to be the best proportion to achieve furanone **119a** in good yield.

A conceivable mechanism for the formation of the *exo*-methylene furanone **119** from acid **116** involved the formation of mixed anhydride from the acid **116,** there after isomerization of double bond from aryl conjugation to carbonyl conjugation, followed by enolization and lactonization to afford furanone **119** (Figure 3). We believe that the double bond isomerization proceeds to give a mixture of *cis* and *trans* products and the *cis* isomer of compound **120** favors the formation of furanone **119**, while its *trans* isomer remains unreacted at 80-90°C. On the other hand higher temperature (110-120°C) favors

the formation of more stable *trans* isomer which readily cyclizes to the naphthalene derivatives **121**.

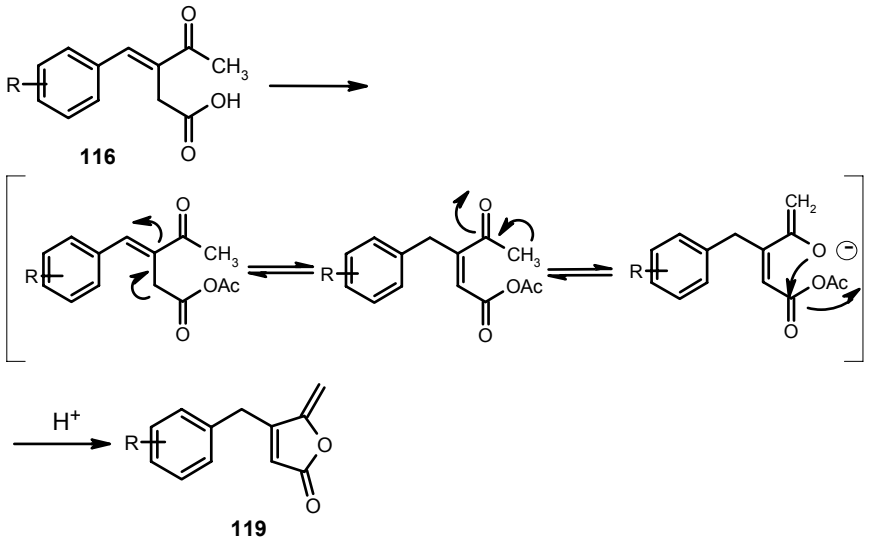
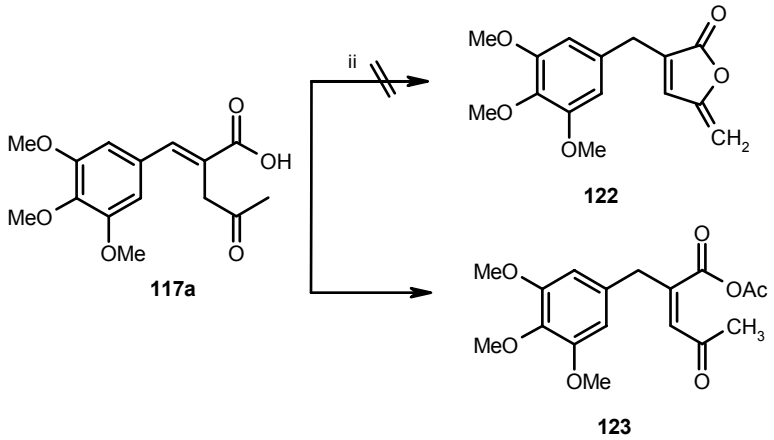


Figure 3. Proposed mechanistic pathway for the synthesis of γ-methylenefuranone 119a

The acid **117a** was treated with sodium acetate and acetic anhydride in an attempt to get the furanone **122** but the formation of corresponding mixed anhydride **123** was observed and desired furanone **122** was not detected.

Scheme 24.

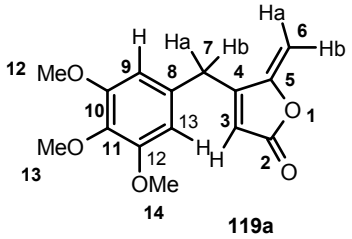


Reagents and conditions: (i) Anhydr. NaOAc, Ac_2O, 80-90 ˚C, 3h.

Furanone **119a** prepared from acid intermediate **116a** was characterized by all spectral means. IR spectrum of γ-methylenefuranone **119a** showed splitting of carbonyl peak. This characteristic carbonyl absorption is exhibited by the presence of conjugated and

strained small ring compounds. Such type of splitting pattern is reported for the protoanemonin derivatives and maleic anhydride derivatives.[36] IR spectrum of furanone **119a** showed carbonyl absorption at 1787, 1764 cm^{-1} indicating the presence of carbonyl function and other absorptions at 3016, 1500, 1217, 749 cm^{-1}.

Figure 4. Furanone 119a



119a

^{1}H NMR of furanone **119a** indicated the presence of benzylic protons at C7, which appeared as a singlet at δ 3.71 integrating for two protons. The nine protons corresponding to three OCH_3, appeared at δ 3.79 (3H) and 3.81 (6H) as a sharp singlets. Proton Ha at C6 appeared as a doublet (J = 4Hz) centered at δ 4.93 and proton Hb at C6 appeared at δ 5.15 as a doublet of doublet (J = 4 Hz and 1.8 Hz). Broad singlet at δ 5.81 for one proton was assigned for olefinic protons at C3, while aromatic protons at C9 and C13 appeared as a singlet at δ 6.36 integrating for two protons (Figure 5).

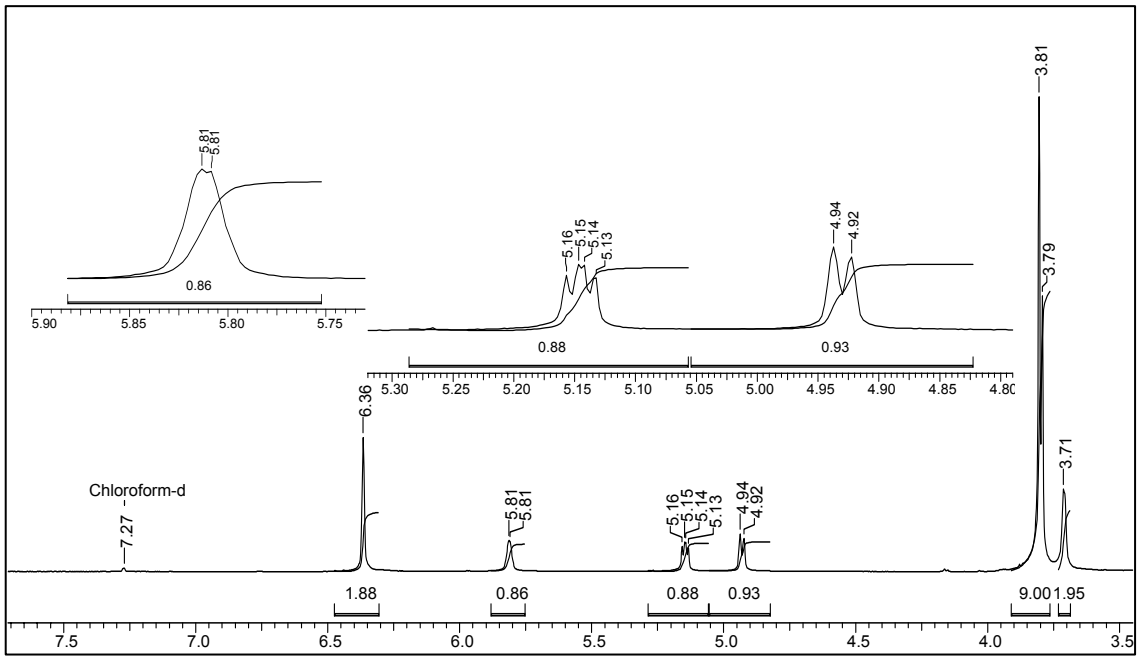


Figure 5. ^{1}H NMR spectrum of furanone 119a

The peak assignment was done on the basis of ^{1}H-^{1}H COSY experiments. The splitting pattern observed in ^{1}H NMR for H6b was due to its long range coupling with olefinic proton at C3 through five bonds and geminal coupling with proton H6a. The benzylic protons (Ha and Hb) at C7 exhibiting the connectivity with olefinic proton at C3 through four bonds (Figure 6).

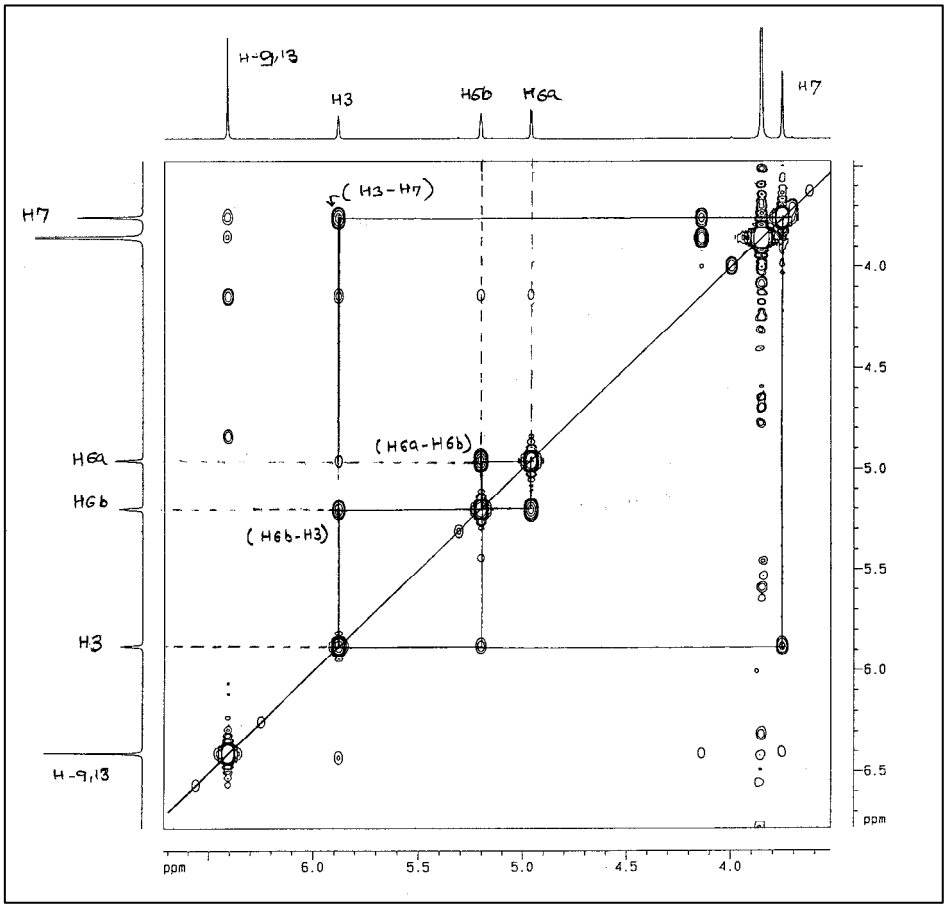


Figure 6. COSY Spectrum of furanone 119a

Important COSY correlations:

H7 δ3.71 with H 3 δ5.81 (J = 0.98 Hz)

H3 δ5.81 with H6b δ5.14 (J = 1.96 Hz)

H 6a δ4.93 with H 6b δ5.14 (J = 2.93 Hz)

H 6b δ 5.14 with H 6a δ4.93 and H 3 δ5.81 (J = 2.93 and 1.96 Hz)

^{13}C NMR spectrum fully supported the structure of furanone **119a**; it displayed 12 signals for 15 carbons, the upfield signal at δ 33.0 was assigned for benzylic methyl C7 carbon. Signal at δ 94.6 was assigned for γ-methylene carbon C6 and carbonyl carbon C2 of the lactone ring appeared at δ 168.4 while other peaks were at their expected chemical shifts. Mass spectrum showed molecular ion peak at *m/z* 276 (M^+).

Since the product was obtained in a single step from the corresponding acid **116** conjunctively involving three bond formation steps the structure was further confirmed by X-ray crystallography, for which we selected furanone synthesized from 4-chloro-2, 5-dimethoxybenzaldehyde (**119i,** Table 1, Entry 9). Furanone **119i** was crystallized from petroleum ether-ethyl acetate by slow crystallization method. The Crystal data of **119i**: $C_{14}H_{13}O_4Cl$, M.W. 280.51, crystal system: triclinic, space group P-1, Unit cell dimensions: a = 6.4265(10) A α = 102.614(3) deg.; b = 10.024 (2) A, β = 98.763 (3) deg.; c = 10.606(2) A, γ = 95.190(3) deg. Å, β = 103.419 (8)°, V= 653.5(2) A^3, Z (calculated density) = 1, 5.777 Mg/m^3, and other characteristic spectral information confirmed the structure of furanone which is presented in experimental section and elucidated structure is presented in figure 7.

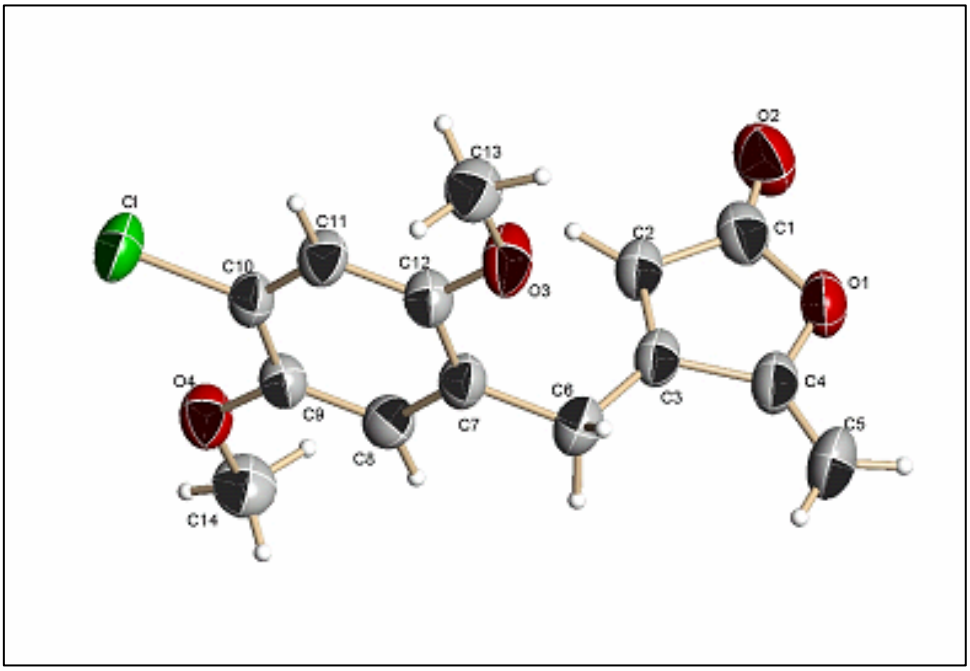
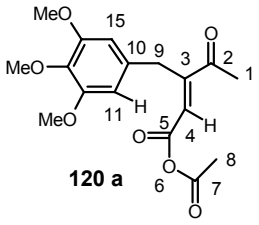


Figure 7. ORTEP diagram of γ-methylenefuranone 119i (Table 1, Entry 9)

Mixed anhydride **120a** was obtained as side product in this reaction; we assumed that *trans* isomer remained unreacted during lactonization. It was important to confirm its geometry by spectral techniques. NOESY spectrum showed very weak connectivity between vinylic proton H4 and aromatic proton H11, which indicated that they are away from each other as expected with *trans* geometry (Figure 8).



120 a

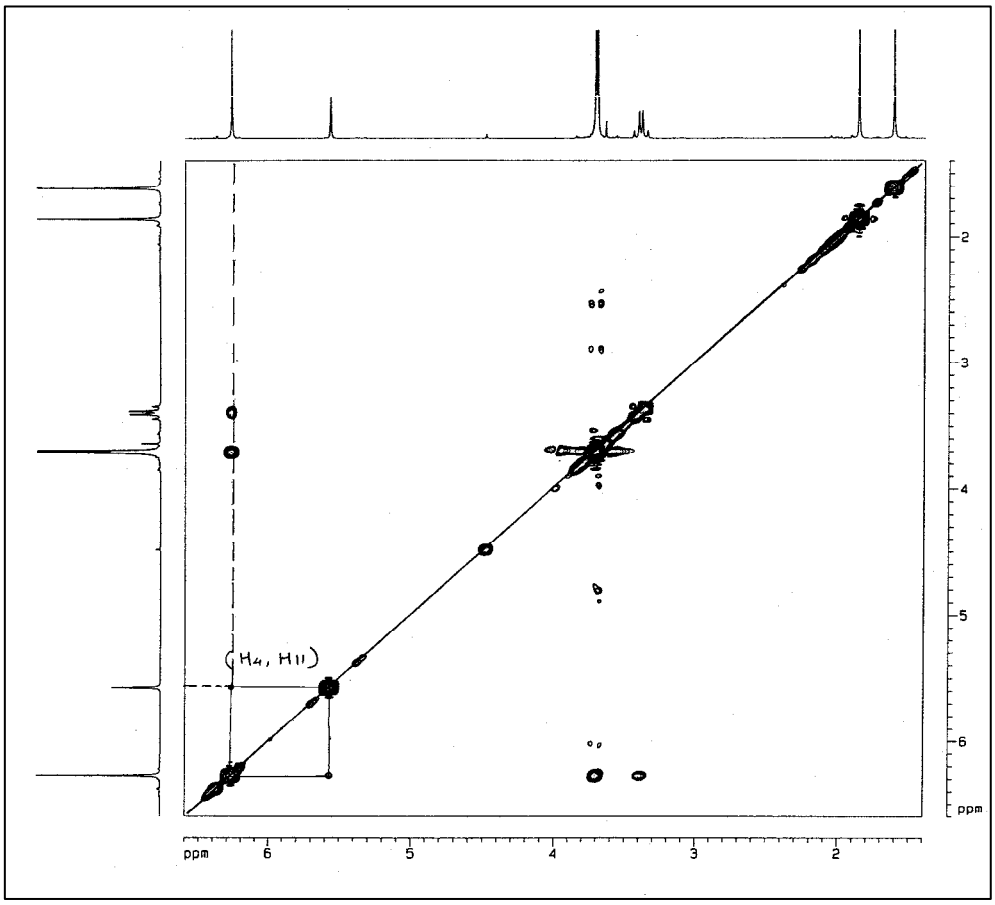
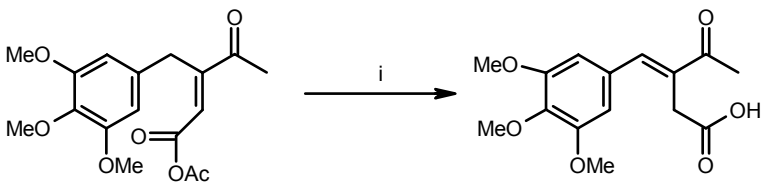


Figure 8. NOESY Correlation spectrum of mixed anhydride 120a

The *trans* mixed anhydride **120a** was hydrolyzed with aqueous sodium hydroxide solution in ethanol. It was found that during hydrolysis the double bond isomerizes from carbonyl conjugation to aryl conjugation and regained its original position to afford the

acid **116a** in good yields. The *trans* geometry of the mixed anhydride **120a** also explains the feasible formation of naphthalene derivatives at elevated temperature (**121a**, Scheme 23).

Scheme 25.

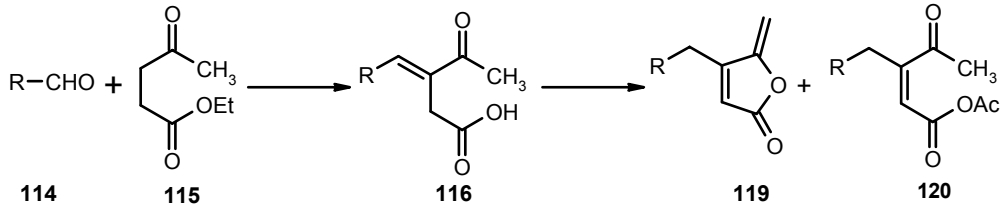


120 **116**

Reagents and conditions: (i) Aq. NaOH, ethanol, 0˚C then at rt, 4-5 h, 65%.

Employing the optimized two-step protocol for the synthesis of γ-methylenefuranone starting from the various aldehydes and ethyl levulinate a library of 22 furanones was generated. Table 1 exhibits the intermediate carboxylic acids furanones and corresponding mixed anhydried synthesized. The scope of the reaction sequence was confirmed by aliphatic aldehyde viz. dodecyl aldehyde which also provided the corresponding acid and γ-methylenefuranone satisfactorily (Table 1, Entry 22). All the compounds were characterized by spectroscopic methods and showed satisfactory spectral data.

Table 1.



114 115 116 119 120

Entry	Code	Aldehyde 114 R	116 %	119 %	120 %
1	**a**	3, 4, 5-Trimethoxyphenyl	75	72	17
2	**b**	4-Methoxyphenyl	60	52	27
3	**c**	3-Methoxyphenyl	55	50	32
4	**d**	2, 4-Dimethoxyphenyl	62	64	18
5	**e**	3,4-Dimethoxyphenyl	77	67	24
6	**f**	4-Methylsulfanylphenyl	72	63	22
7	**g**	3,4-Methylenedioxyphenyl	74	56	21
8	**h**	7-Methoxy-benzo [1,3] dioxol-5-yl	57	55	12
9	**i**	4-Chloro-2, 5-dimethoxyphenyl	52	75	10
10	**j**	2-Iodo-3, 4, 5-trimethoxyphenyl	43	57	33
11	**k**	4-Biphenyl	64	60	23
12	**l**	4-Allyloxy-3-methoxyphenyl	60	48	20
13	**m**	3-Allyloxy-4-methoxyphenyl	68	57	-
14	**n**	3-Methoxy-4-oxiranyl-methoxyphenyl	65	57	34
15	**o**	Naphthalen-1-yl	58	67	15
16	**p**	4-Methoxynaphthalen-1-yl	72	62	18
17	**q**	2-Methoxynaphthalen-1-yl	45	61	20
18	**r**	4,8-Dimethoxynaphthalen-1-yl	58	52	29
19	**s**	2,7-Dimethoxynaphthalen-1-yl	46	58	32
20	**t**	6-Methoxynaphthalen-2-yl	67	57	12
21	**u**	1,4-Dimethoxynaphthalen-2-yl	55	64	17
22	**v**	Undecyl	82	51	24

The some of the γ-methylenefuranone analogues were tested for their cytotoxicity and for antifungal activity. The results of biological studies and the structure activity relationship are summarized in section three of this chapter.

1.1.4. CONCLUSION

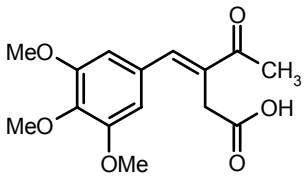
We have developed an efficient and conceptually novel strategy for the synthesis of 4-(substituted)-benzyl/naphthylmethylene-5-methylene-2-(5*H*)-furanones (β-substituted-γ-methylenefuranones) (**119a-v**). The important feature of the present synthetic strategy involves consecutive three steps in one pot to afford the target compound. The described method has the advantages of simplicity to obtain novel furanone derivatives in good yields from commercially available starting materials. Atom economy was also checked by recovering the acid intermediate from the hydrolysis of its mixed anhydride. In order to study the structure activity relationship we have synthesized 22 furanone analogues; including one aliphatic example substituted at 4-position of γ-methylene furanone and all compounds were characterized by spectral and analytical methods.

1.1.5. EXPERIMENTAL

Typical procedure for the synthesis of acid 116a

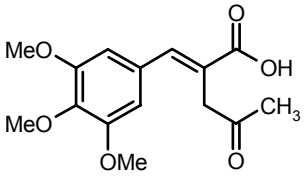
To a well stirred mixture of substituted benzaldehyde (0.127 mol) and ethyl levulinate (0.317 mol) in methanol (250 ml), aqueous sodium hydroxide solution (0.317 mol) was added dropwise at -10˚C. After complete addition, reaction mixture was stirred at same temperature for 4-5 h and the reaction was monitored by thin layer chromatography. After completion of reaction, methanol was removed under vacuum, reaction mixture was diluted with water and washed with ethyl acetate and aqueous layer was acidified with conc HCl (Till confirm acidic pH). The yellow oil separated was extracted with ethyl acetate (3x 100 ml) , and it was repeatedly washed with water to remove traces of levulinic acid, followed by brine, dried over sodium sulphate and evaporated to yield acid **116** (yield ranges from 43-77%).

3-Acetyl-4-(3,4,5-trimethoxy-phenyl)-but-3-enoic acid (116a)



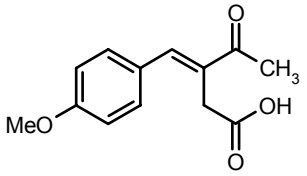
Nature: Yellow solid; **Yield**: 2.80 g, 75%; **Mp**: 118-120 ºC; **IR** (Chloroform): *v* 3016, 1709, 1655, 1581, 1239, 1129, 755 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.55 (s, 3H), 3.55 (s, 2H), 3.86 (s, 9H), 6.68 (s, 2H), 7.67 (s, 1H), 8.80 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 25.1, 32.8, 55.9, 60.6 (2C), 106.3 (2C), 129.8, 133.8, 138.8, 143.4, 153.0 (2C), 176.1, 199.4; **MS** (ES): *m/z* 295 (M^++1), 313 (M^++H_2O); **Anal Calcd for** $C_{15}H_{18}O_6$: C, 61.22; H, 6.12; **Found:** C, 61.10; H, 6.27.

2-(2-Oxo-propyl)-3-(3,4,5-trimethoxy-phenyl)-acrylic acid (117)



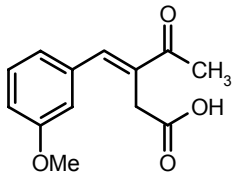
Nature: Semisolid; **Yield**: 2.39 g, 64%; **IR** (Chloroform): *v* 3016, 1712, 1665, 1212, 755 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.06 (s, 3H), 3.47 (s, 2H), 3.80 (s, 6H), 3.83 (s, 3H), 6.39 (s, 2H), 6.89 (s, 1H); **MS** (ES): *m/z* 295 (M^++1), 312 (M^++H_2O); **Anal Calcd for** $C_{15}H_{18}O_6$: C, 61.22; H, 6.12; **Found:** C, 61.30; H, 6.34.

3-Acetyl-4-(4-methoxy-phenyl)-but-3-enoic acid (116b)



Nature: Yellow solid; **Yield**: 1.78 g, 60%; **Mp**: 105-107 ºC; **IR** (Chloroform): *v* 3020, 1716, 1663, 1217, 757 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.44 (s, 3H), 3.52 (s, 2H), 3.80 (s, 3H), 6.92 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 7.66 (s, 1H), 9.46 (bs, 1H). **MS** (ES): *m/z* 234 (M^+), 257 (M^++Na); **Anal. Calcd for** $C_{13}H_{14}O_4$: C, 66.66; H, 5.98; **Found**: C, 66.80; H, 5.73.

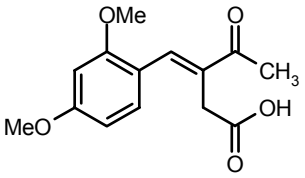
3-Acetyl-4-(3-methoxy-phenyl)-but-3-enoic acid (116c)



Nature: Yellow semisolid; **Yield**: 1.63 g, 55%; **IR** (Chloroform): ν 3020, 1713, 1667, 1554, 1212 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.51 (s, 3H), 3.54 (s, 2H), 3.83 (s, 3H), 6.65-6.71 (m, 3H), 7.20-7.48 (m, 1H),

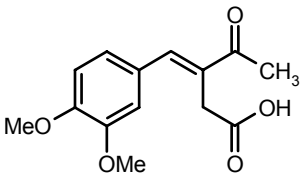
7.28 (s, 1H), 7.80 (bs, 1H). **MS** (ES): *m/z* 234 (M^+), 252 (M^++H_2O); **Anal**. **Calcd for** $C_{13}H_{14}O_4$: C, 66.66; H, 5.98; **Found**: C, 66.59; H, 5.83.

3-Acetyl-4-(3,4-dimethoxy-phenyl)-but-3-enoic acid (116d)



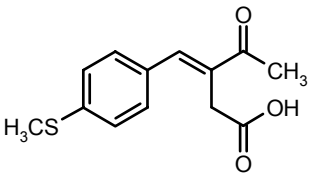
Nature: White solid; **Yield:** 2.07 g, 62%; **Mp:** 114 ºC; **IR (Chloroform):** ***v*** 3022, 1715, 1630, 1506, 1430, 1216, 756 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.42 (s, 3H), 3.43 (s, 2H), 3.76 (s, 6H), 6.48 (dd, *J* = 8, 2 Hz, 2H), 7.23 (d, *J* = 8 Hz, 1H), 7.82 (s, 1H), 9.55 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 25.3, 33.26, 55.4 (2C), 98.3, 104.6, 116.3, 130.9, 132.6, 139.5, 158.8, 162.4, 176.8, 200.2. **MS (ES)**: *m/z* 265 (M^++1), 283 (M^{+1}+ H_2O); **Anal. Calcd for** $C_{14}H_{16}O_5$: C, 63.63; H, 6.06; **Found: C,** 66.69; H, 6.18.

3-Acetyl-4-(2,4-dimethoxy-phenyl)-but-3-enoic acid (116e)



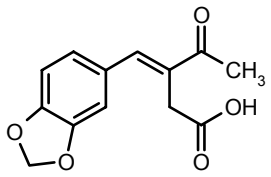
Nature: Yellow thick oil; **Yield**: 2.58 g, 77%; **IR** (Chloroform): *v* 2922, 1698, 1654, 1504, 1281, 1209 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.42 (s, 3H), 3.50 (s, 2H), 3.76 (s, 6H), 6.85 (dd, *J* = 8, 2 Hz, 2H), 7.31(d, *J* = 8 Hz, 1H) 7.63 (s, 1H), 9.55 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 30.6, 33.4, 55.1 (2C), 106.6, 107.3, 125.9, 127.0, 135.9, 136.4, 142.1, 160.5, 174.2, 208.2.; **MS (ES):** *m/z* 265 (M^++1), 283 (M^{+1}+ H_2O); **Anal Calcd for** $C_{14}H_{16}O_5$: C, 63.63; H, 6.06; **Found**: C, 66.48; H, 5.90.

3-Acetyl-4-(4-methylsulfanyl-phenyl)-but-3-enoic acid (116f)



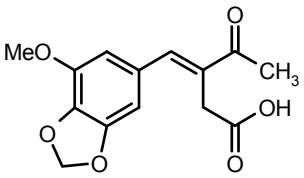
Nature: Yellow solid; **Yield**: 2.28 g, 72%; **Mp**: 121-124ºC; **IR:** (Chloroform) *v* 3021, 1786, 1653, 1593, 1419, 1217, 978, 756 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.03 (s, 3H), 2.56 (s, 3H), 3.50 (s, 2H), 7.12 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.65 (s, 1H), 10.49 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 14.8, 25.1, 32.5, 125.6, 126.2, 129.5, 130.7, 133.7, 134.1, 140.9, 142.7, 176.1, 199.4; **MS** (ES): *m/z* 251 (M^++1); **Anal Calcd for** $C_{13}H_{14}O_3S$: C, 62.40; H, 5.60; S, 12.80; **Found:** C, 62.38; H, 5.82; S, 12.64.

3-Acetyl-4-benzo [1,3] dioxol-5-yl-but-3-enoic acid (116g)



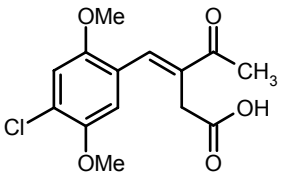
Nature: Pink solid; **Yield**: 2.33 g, 74%; **Mp**: 87-89 ºC; IR: (Chloroform) *v* 3010, 1732, 1680, 1486, 1236, 1038, 933, 697 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.29 (s, 3H), 3.30 (s, 2H), 5.85 (s, 2H), 6.51 (d, *J* = 2Hz, 1H), 6.62 (d, *J* = 8, 2Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 7.44 (s, 1H); **^{13}C NMR** (50 MHz): δ 25.0, 32.1, 100.9, 108.0, 108.6, 119.5, 123.7, 128.4, 133.8, 141.6, 147.4, 172.7, 198.5; **MS** (ESI): *m/z* 249 (M^++1); 266 (M^++H_2O); **Anal Calcd for** $C_{13}H_{12}O_5$: C, 62.90; H, 4.83; **Found**: C, 63.11; H, 4.98.

3-Acetyl-4-(7-methoxy-benzo[1,3]dioxol-5-yl)-but-3-enoic acid (116h)



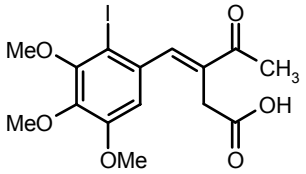
Nature: Brown solid; **Yield:** 2.01 g, 57%; **Mp:** 113-115 ºC; **IR:** (chloroform) *v* 2998, 1710, 1682, 1510, 1221 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.48 (s, 3H), 3.54 (s, 2H), 3.90 (s, 3H), 6.02 (s, 2H), 6.59 (bs, 1H), 6.66 (bs, 1H), 7.61 (s, 1H), 8.96 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 23.7, 30.9, 53.6, 100.2, 105.2, 107.0, 119.1, 122.9, 127.5, 132.5, 140.8, 146.5, 171.4, 197.7; **MS:** *m/z* 278; 233, 263, 247, 233, 203, 189, 161, 103, 77. **Anal. Calcd for** $C_{14}H_{14}O_6$: C, 60.43; H, 5.03; **Found:** C, 60.24; H, 5.23.

3-Acetyl-4-(4-chloro-2,5-dimethoxy-phenyl)-but-3-enoic acid (116i)



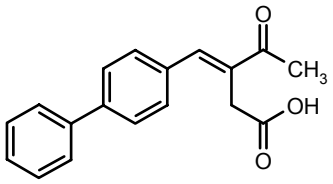
Nature: Yellow solid; **Yield**: 3.22 g, 85%; **Mp**: 127-130ºC; **IR**: (chloroform) *v* 3020, 1712, 1670, 1495, 1215, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.52 (s, 3H), 3.53 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 6.67 (s, 1H), 6.69 (s, 1H), 7.81 (s, 1H); **MS**: *m/z* 298.0, 268, 196, 152, 89; **Anal. Calcd for** $C_{14}H_{15}O_5Cl$: C, 56.37; H, 5.03; **Found**: C, 56.39; H, 5.28.

3-Acetyl-4-(2-iodo-3,4,5-trimethoxy-phenyl)-but-3-enoic acid (116j)



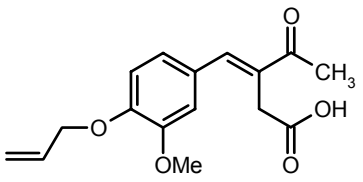
Nature: Brown solid; **Yield**: 3.62 g, 68%; **Mp**: 120-122 ºC; **IR**: (Chloroform) *v* 3013, 1710, 1672, 1477, 1382, 1201, 1104, 755 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.52 (s, 3H), 3.36 (s, 2H), 3.80 (s, 3H), 3.88 (s, 6H), 6.85 (s, 1H), 7.62 (s, 1H), 10.20 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 26.3, 32.6, 56.0, 60.6, 60.8, 108.9, 133.6, 134.5, 142.1, 146.6, 153.1, 153.6, 158.5, 176.3, 199.2; **MS**: *m/z* 420 (M^+), 438 (M^++H_2O); **Anal. Calcd for** $C_{15}H_{17}O_6I$: C, 42.85; H, 4.04; **Found**: C, 42.90; H, 4.27.

4-(1,1'-Biphenyl-4-ylmethyl)-5-methylenefuran-2 (5*H*)-one (116k)



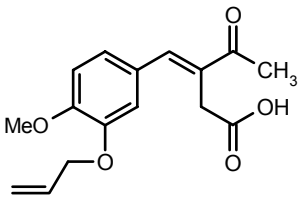
Nature: White solid; **Yield**: 1.62g, 57%; **Mp**: 103-105 ºC; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz) δ 2.51 (s, 3H), 3.53 (s, 2H), 7.20-7.58 (m, 10H).

3-Acetyl-4-(4-allyloxy-3-methoxy phenyl)-but-3-enoic acid (116l)



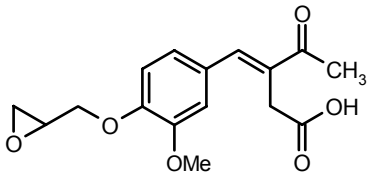
Nature: Semisolid; **Yield**: 2.20g, 60%; **IR** (Chloroform): *v* 3029, 1716, 1680, 1210, 756 cm^{-1}; **^{1}H NMR**: ($CDCl_3$+CCl_4, 200 MHz) δ 2.50 (s, 3H), 3.59 (s, 2H), 3.85 (s, 3H), 4.60 - 4.68 (m, 2H), 5.28-5.46 (m, 2H), 6.01-6.15 (m, 1H), 6.72-7.03 (m, 3H), 7.70 (s, 1H), 8.20 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 24.8, 32.3, 55.4, 69.1, 112.2, 112.4, 117.8, 122.5, 127.1, 132.3, 132.5, 143.2, 148.6, 148.7, 175.2, 199.6; **MS**: *m/z* 290, 249, 175, 151, 116, 91; **Anal. Calcd for** $C_{16}H_{18}O_5$: C, 66.20; H, 6.20; **Found**: C, 66.32; H, 5.16.

3-Acetyl-4-(3-allyloxy-4-methoxy-phenyl)-but-3-enoic acid (116m)



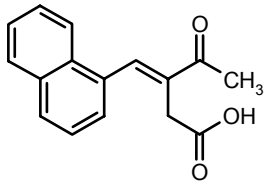
Nature: Thick liquid; **Yield:** 2.50g, 68%; **IR** (Chloroform): *v* 3029, 1718, 1686, 1212, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz) δ 2.49 (s, 3H), 3.56 (s, 2H), 3.91 (s, 3H), 4.62-4.68 (m, 2H), 5.24-5.45 (m, 2H), 5.97-6.15 (m, 1H), 6.90-7.08 (m, 3H), 7.67 (s, 1H), 9.48 (bs, 1H); **MS** (ES): *m/z* 291 (M^++1), 308 (M+H_2O); **Anal Calcd for** $C_{16}H_{18}O_5$: C, 66.20; H, 6.20; **Found**: C, 66.13; H, 6.18.

3-Acetyl-4-(3-methoxy-4-oxiranylmethoxy-phenyl)-but-3-enoic acid (116n)



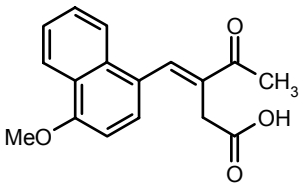
Nature: Semisolid; **Yield:** 2.52g, 65%; **IR** (Chloroform): *v* 3030, 1721, 1676, 1220, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.45 (s, 3H), 3.43 (s, 2H), 3.85 (s, 3H), 3.90-4.02 (m, 3H), 4.18-4.38 (m, 2H), 6.77 (m, 2H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.20 (bs, 1H), 7.63 (s, 1H); **^{13}C NMR** (50 MHz): δ 25.3, 32.6, 37.8, 55.8, 63.4, 70.2, 111.5, 120.8, 127.5, 130.3, 133.07, 144.5, 147.8, 150.1, 174.4, 200.0; **MS** (ES): *m/z* 307 (M^++1); **Anal Calcd for** $C_{16}H_{18}O_6$: C, 62.74; H, 5.88; **Found:** C, 52.23; H, 6.06.

3-Acetyl-4-naphthalen-1-yl-but-3-enoic acid (116o)



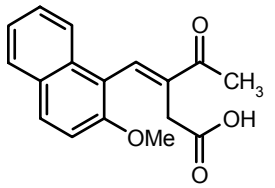
Nature: Yellow solid; **Yield:** 1.87g, 58%; Mp: 118-120 ºC; **IR** (Chloroform): *v* 3020, 1719, 1680, 1488, 1183, 1041, 757, 668 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.62 (s, 3H), 3.43 (s, 2H), 7.28- 7.60 (m, 4H), 7.82- 7.92 (m, 3H) 8.24 (s, 1H); **^{13}C NMR** (50 MHz): δ 28.9, 37.1, 102.1, 102.8, 103.1, 109.3, 123.5, 128.4, 133.0, 136.2, 137.1, 143.0, 148.5, 148.7, 176.3, 207.9; **MS** (ES): *m/z* 255 (M^++1), 272 (M^++H_2O); **Anal Calcd for** $C_{16}H_{14}O_3$: C, 75.59; H, 5.51; **Found**: C, 75.62; H, 5.60.

3-Acetyl-4-(4-methoxy-naphthalen-1-yl)-but-3-enoic acid (116p)



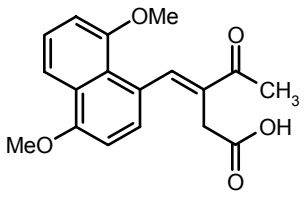
Nature: Greenish yellow solid; **Yield**: 2.59g, 72%; **Mp**: 131-133 ºC; **IR** (Chloroform): *v* 3029, 1719, 1690, 1503, 1216, 757 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.88 (s, 3H), 3.28 (s, 2H), 3.61 (s, 3H), 6.84 (d, *J* = 8 Hz, 1H), 7.43- 7.58 (m, 3H), 7.52-60 (m, 3H); **MS** (ES): *m/z* 284 (M^+), 307 (M^++Na); **Anal Calcd for** $C_{17}H_{16}O_4$: C, 71.83; H, 5.63; **Found**: C, 71.72; H, 5.56.

3-Acetyl-4-(2-methoxy-naphthalen-1-yl)-but-3-enoic acid (116q)



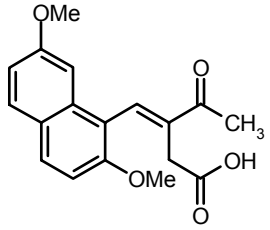
Nature: Yellow solid; **Yield**: 1.62g, 45%; **Mp**: 148-151 ºC; **IR** (Chloroform): *v* 3030, 1722, 1667, 1512, 1212, 755 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.17(s, 3H), 3.49 (s, 2H), 3.80 (s, 3H), 6.82 (d, *J* = 8 Hz, 1H), 7.40- 7.58 (m, 3H), 7.82 (dd, *J* = 8, 2 Hz, 1H), 8.21 (s, 1H); **MS** (ES): *m/z* 284 (M^+), 307 (M^++Na); **Anal Calcd for** $C_{17}H_{16}O_4$: C, 71.83; H, 5.63; **Found**: C, 71.60; H, 5.69.

3-Acetyl-4-(4,8-dimethoxy-naphthalen-1-yl)-but-3-enoic acid (116r)



Nature: Brownish yellow solid; **Yield**: 2.31g, 58%; **Mp**: 153-155ºC; **IR** (Chloroform): *v* 3029, 1720, 1680, 1513, 755 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.16 (s, 3H), 3.48 (s, 2H), 3.88 (s, 3H), 3.96 (s, 3H), 6.70 (d, *J* = 8 Hz, 1H), 6.92 (t, *J* = 8, 2 Hz, 2H), 7.39 (t, *J* = 8, 2 Hz, 1H), 7.86 (m, 2H), 9.75 (bs, 1H); **MS** (ES): *m/z* 314 (M^+), **Anal Calcd for** $C_{18}H_{18}O_5$: C, 68.78; H, 5.73; **Found:** C, 68.69; H, 5.75.

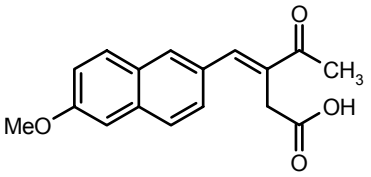
3-Acetyl-4-(2,7-dimethoxy-naphthalen-1-yl)-but-3-enoic acid (116s)



Nature: Brownish yellow solid; **Yield**: 1.83g, 46%; **Mp**: 98-100 ºC; **IR**: (Chloroform) *v* 3019, 1714, 1670, 1215 757 cm^{-1}; **^{1}H NMR**: ($CDCl_3$+CCl_4, 200 MHz) δ 2.63 (s, 3H), 3.57 (s, 2H), 3.82 (s, 3H), 3.93 (s, 3H), 6.85-7.12 (m, 3 H), 7.71 (m, 3H); **MS** (ES):

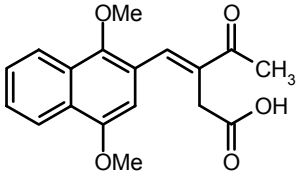
m/z 315 (M^++1), 332 (M^++H_2O); **Anal Calcd for** $C_{18}H_{18}O_5$: C, 68.78; H, 5.73; **Found**: C, 68.83; H, 5.61.

3-Acetyl-4-(6-methoxy-naphthalen-2-yl)-but-3-enoic acid (116t)



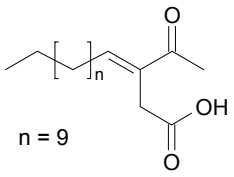
Nature: Yellow solid; **Yield**: 2.41g, 67%; **Mp**: 122-123ºC; **IR**: (Chloroform) *v* 3019, 1718, 1686, 1530, 1216, 757 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.52 (s, 3H), 3.63 (s, 2H), 3.93 (s, 3 H), 7.11-7.20 (m, 2H), 7.46 (d, *J* = 8 Hz, 1H), 7.73-7.86 (m, 4H), 10.14 (bs, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 25.3, 32.1, 55.2, 105.5, 119.5, 123.2, 125.2, 126.7, 127.1, 128.4, 129.2, 130.0, 134.7, 143.5, 158.6, 202.1; **MS** (ES): *m/z* 285 (M^++1), 302 (M^++H_2O); **Anal Calcd for** $C_{17}H_{16}O_4$: C, 71.83; H, 5.63; **Found**: C, 71.89; H, 5.58.

3-Acetyl-4-(1,4-dimethoxy-naphthalen-2-yl)-but-3-enoic acid (116u)



Nature: Brownish yellow solid; **Yield**: 2.19g, 55%; **Mp**: 117-120 ºC; ^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz): δ 2.16 (s, 3H), 3.57 (s, 2H), 3.80 (s, 3H), 3.92 (s, 3H), 6.47 (s, 1H), 7.11(s, 1H), 7.50-7.53 (m, 2H), 8.12 (dd, *J* = 8, 2 Hz, 2H), 10.23 (bs, 1H); **MS** (ES): *m/z* 314 (M^+), 332 (M^++H_2O); **Anal Calcd for** $C_{18}H_{18}O_5$: C, 68.78; H, 5.73; **Found**: C, 68.82; H, 5.65.

3-Acetyl-pentadec-3-enoic acid (116v)

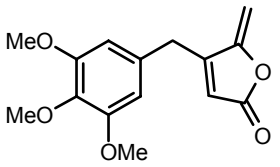


Nature: Thick oil, **Yield**: 2.25g, 63 %; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 0.88 (t, 3H), 1.20-1.30 (m, 20 H), 2.35 (s, 3H), 3.35 (s, 2H), 6.82 (s, 1H), 7.75 (bs, 1H).

Typical procedure for the synthesis of 5-methylene-4-benzyl (substituted)-2(5H)-furanones (119).

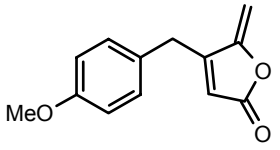
The carboxylic acid **117** (10.2 mmol) was mixed with anhydrous sodium acetate (20.4 mmol) and acetic anhydride (51.0 mol) allowed to stirr at 85˚C, under nitrogen atmosphere for 3 h. The mixture was allowed to cool to room temperature when crystals of sodium acetate were thrown out. The reaction mixture was poured over ice, stirred vigorously for 30 min and extracted with ethyl acetate. The organic layer was washed repeatedly with fresh portions of water, followed by dilute sodium bicarbonate solution, to remove all traces of acetic anhydride and acetic acid. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Purification of residue by column chromatography provided desired furanones **119** (Yields 48-75%).

5-Methylene-4- (3, 4, 5-trimethoxybenzyl)- 2(5*H*)-furanone (119a)



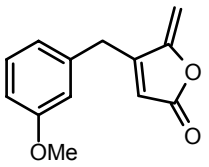
Nature: White solid; **Yield**: 2.02 g, 72%; **Mp**: 115-117°C; **IR**: (Chloroform): ν 3016, 1787, 1764, 1500, 1217, 1037, 749 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.71 (s, 2H), 3.81 (s, 9H), 4.93 (d, *J* = 2.9 Hz, 1H), 5.14 (J = 2.9 Hz, 1.96 Hz, 1H), 5.85 (bs, 1H); 6.39 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 33.0, 56.2 (2C), 60.8, 94.6, 106.2 (2C), 118.6, 131.5, 137.6, 153.8 (2C), 155.7, 157.8, 168.4; **MS** (FAB): *m/z* 276 (M^+), 261, 245, 217, 181, 166; **Anal. Calcd for** $C_{15}H_{16}O_5$: C, 65.21; H, 5.79; **Found**: C, 65.45; H, 5.58.

4-(4-Methoxybenzyl)-5-methylene-2(5*H*)-furanone (119b)



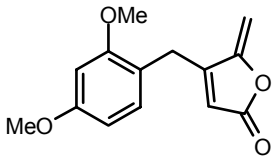
Nature: Viscous oil; **Yield**: 1.14 g, 52%; IR (Chloroform): ν 3020, 1764, 1513, 1249 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.72 (s, 2H), 3.81 (s, 3H), 4.94 (d, *J* = 2.7 Hz, 1H), 5.15-5.19 (m, 1H), 5.81 (bs, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 31.3, 54.8, 94.5, 113.9 (2C), 117.7, 127.5, 129.5 (2C), 155.1 (2C), 158.4, 168.3; **MS**: *m/z* 216, 201, 145, 121, 77; **Anal. Calcd for** C_{13} $H_{12}O_3$: C, 72.22; H, 5.55 **Found** C, 72.29; H, 5.37.

4-(3-Methoxybenzyl)-5-methylenefuran-2- (5*H*)-one (119c)



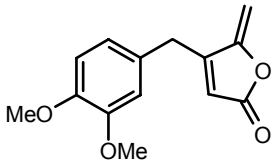
Nature: Viscous oil; **Yield**: 0.66 g, 30.6%; **IR** (Chloroform): *v* 3018, 1768, 1652, 1214 cm^{-1}; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.76 (s, 2H), 3.81 (s, 3H), 4.95 (d, *J* = 2.9 Hz, 1H), 5.14-5.19 (m, 1H), 5.86 (bs, 1H), 6.71-6.89 (m, 3H), 7.27 (t, *J* = 8 Hz, 1H); **MS** (ES): *m/z* 216 $(MH)^+$.

4-(2,4-Dimethoxybenzyl)-5-methylene-2(5*H*)-furanone (119d)



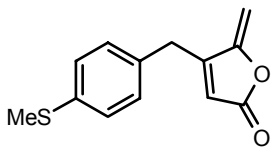
Nature: Viscous oil; **Yield**: 1.6 g, 64%; **IR** (Chloroform): *v* 3021, 1764, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.71 (s, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 5.01 (d, *J* = 2.7 Hz, 1H), 5.13-5.17 (m, 1H), 5.75 (bs, 1H), 6.44-6.53 (m, 2H), 7.02 (d, *J* = 8 Hz, 1H); **^{13}C NMR**: (50 MHz, $CDCl_3$ + CCl_4) δ 25.9, 54.7 (2C), 93.9, 98.1, 104.0, 107.9, 116.2, 116.9, 130.1, 155.1, 157.5, 158.3, 168.4; **MS** (ESI): *m/z* 247 $(MH)^+$; **Anal**. **Calcd for** $C_{14}H_{14}O_4$: C, 68.29, H, 5.69; **Found** C, 68.16, H, 5.74.

4-(3,4-Dimethoxybenzyl)-5-methylene-2(5*H*)-furanone (119e)



Nature: Viscous oil; **Yield**: 1.68 g, 67%; **IR** (Chloroform): *v* 3020, 1778, 1760, 1709, 1502, 1237 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.71(bs, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.91(d, *J* = 2.7 Hz, 1H), 5.11-5.14(m, 1H), 5.79 (bs, 1H), 6.66 (dd, *J* = 7.8, 2 Hz, 1H), 6.73 (dd *J* = 7.8, 2 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.0, 55.6 (2C), 94.7, 111.3, 111.6, 117.9, 120.7, 128.0, 148.0, 149.0, 155.2, 158.2, 168.5; **MS** (ESI): *m/z* 246 (M^+); **Anal. Calcd for** $C_{14}H_{14}O_4$: C, 68.29; H, 5.69; **Found** C, 68.35; H, 5.66.

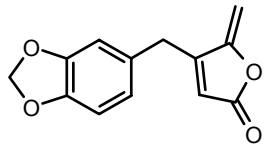
5-Methylene 4-(4-thiomethyl) benzyl-2(5*H*)-furanone (119f)



Nature: Yellow solid; **Yield**: 1.49 g, 63%; **Mp**: 55-57°C; **IR** (Chloroform): *v* 3021, 1788, 1765, 1652, 1212 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.42 (s, 3H), 3.72 (s, 2H), 4.91 (d, *J* = 3.1Hz, 1H), 5.08-5.13 (m, 1H), 5.76 (bs, 1H), 7.07 (d, *J* = 8 Hz, 2H), 7.17 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 15.3, 31.6, 94.6, 118.0, 126.5 (2C), 129.0 (2C),

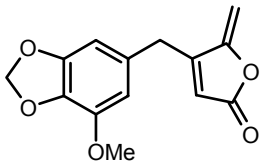
132.3, 137.2, 155.1, 157.6, 168.2; **MS** (ESI): *m/z* 232 $(MH)^+$; **Anal**. **Calcd for** $C_{13}H_{12}O_2S$: C, 67.24; H, 5.17; S, 13.79; **Found** C, 67.13; H, 4.95; S, 13.68.

4-(1,3-Benzodioxol-5-ylmethyl)-5-methylene-2(5*H*)-furanone (119g)



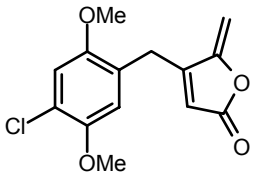
Nature: Viscous oil; **Yield**: 1.31 g, 56%; **IR** (Chloroform): *v* 3018, 1787, 1764, 1217 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$ +CCl_4): δ 3.71 (s, 2H), 4.93 (d, *J* = 2.3 Hz, 1H), 5.13-5.17 (m, 1H), 5.84 (bs, 1H), 5.95 (s, 2H), 6.60- 6.69 (m, 2H), 6.75 (d, *J* = 8.5, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 31.8, 94.5, 100.8, 108.1 (2C), 108.7, 117.8, 121.5, 129.2, 147.6, 155.0, 157.9, 168.2; **MS** (ESI): *m/z* 231 $(MH)^+$; **Anal. Calcd for** $C_{13}H_{10}O_4$: C, 67.82; H, 4.31; **Found** C, 67.61; H, 4.26.

4-[(7-Methoxy-1, 3-benzodioxol-5-yl)-methyl]-5-methylene-2(5*H*)-furanone (119h)



Nature: Brownish yellow solid; **Yield**: 1.45 g, 55%; **Mp**: 150°C; **IR** (Chloroform): *v* 3020, 1788, 1766, 1512, 1215 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.69 (unresolved doublet, 2H), 3.86 (s, 3H), 4.93 (d, *J* = 2.7 Hz, 1H), 5.12-5.18 (m, 1H), 5.83 (bs, 1H), 5.94 (s, 2H), 6.34 (unresolved doublet, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): *δ* 32.7, 56.5, 94.8, 101.4, 102.7, 108.2, 108.3, 118.2, 130.0, 143.6, 149.1, 155.2, 157.8, 169.2; **MS** (ESI): *m/z* 261 $(MH)^+$; **Anal**. **Calcd for** $C_{14}H_{12}O_5$: C, 64.61; H, 4.61; **Found** 64.53; H, 4.49.

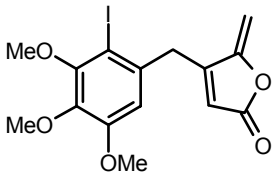
4-(4-Chloro-2, 5-dimethoxybenzyl)-5-methylene-2(5*H*)-furanone (119i)



Nature: Pale yellow solid; **Yield**: 2.14 g, 75%; **Mp**: 115-117 °C; **IR** (Chloroform): *v* 3019, 1788, 1763, 1499, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): *δ* 3.73 (s, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.98 (d, *J* = 2.9 Hz, 1H), 5.13-5.18 (m, 1H), 5.74 (bs, 1H), 6.73 (s, 1H), 6.92 (s, 1H); **^{13}C**

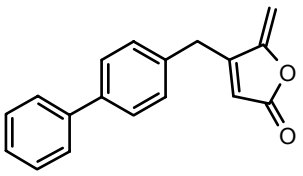
NMR (50 MHz, $CDCl_3$ + CCl_4): δ 26.9, 56.0, 57.0, 94.4, 113.5, 115.1, 118.0, 122.1, 123.7, 149.3, 151.3, 155.5, 157.3, 168.6; **MS** (ESI): *m/z* 282 (M^++2), 280, 244, 221, 185, 158, 89; **Anal. Calcd for** $C_{14}H_{13}O_4Cl$: C, 59.89; H, 4.64; **Found** C, 60.12; H, 4. 70.

4-(2-Iodo-3, 4, 5-trimethoxybenzyl)-5-methylene-2(5*H*)-furanone (119j)



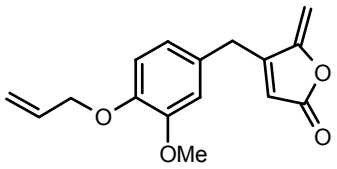
Molecular formula: $C_{15}H_{15}O_5I$; **Nature**: Pinkish brown solid; **Yield**: 2.33 g, 57%; **Mp**: 109°C; **IR** (Chloroform): ν 3016, 1788, 1764, 1562, 1228 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.80 (s, 2H), 3.81 (s, 6H), 3.84 (s, 3H), 4.99 (d, *J* = 3.1 Hz, 1H), 5.12-5.15 (m, 1H), 5.65 (bs, 1H), 6.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 37.8, 55.9, 60.5, 60.7, 94.5, 109.2, 118.2, 134.4, 141.0, 153.3, 153.7 (2C), 155.0, 156.6, 168.2; **MS** (ESI): *m/z* 403 $(MH)^+$, 420 (M+ H_2O); **Anal. Calcd for** $C_{15}H_{15}O_5I$: C, 44.77; H, 3.73; **Found** C, 44.52; H, 3.64.

4-(1,1'-Biphenyl-4-ylmethyl)-5-methylenefuran-2 (5*H*)-one (119k)



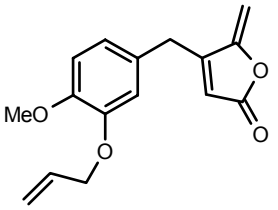
Nature: White solid; **Yield**: 1.60 g, 60%; **Mp**: 108-110°C; **IR** (Chloroform): *v* 3019, 1788, 1605, 1530, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 2H), 4.98 (d, *J* = 2.7 Hz, 1H), 5.17-5.26 (m, 1H), 5.90 (bs, 1H), 7.20-7.68 (m, 9H); **MS**: (ES) *m/z* 262 (M^+).

4-[4-(Allyloxy)-3-methoxybenzyl]-5-methylene-2(5*H*)-furanone (119l)



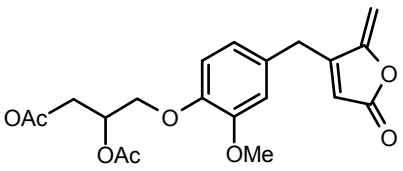
Nature: Viscous oil; **Yield**: 1.33 g, 48%; **IR** (Chloroform): ν 3015, 1788, 1765, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.71 (bs, 2H), 3.83 (s, 3H), 4.54 - 4.59 (m, 2H), 4.91 (d, *J* = 2.9 Hz, 1H), 5.12-5.16 (m, 1H), 5.21-5.42 (m, 2H), 5.79 (bs, 1H), 5.95 - 6.14 (m, 1H), 6.61-6.75 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 31.8, 55.6, 69.5, 94.2, 112.1, 113.6, 117.5, 117.9, 120.5, 128.3, 132.9, 147.0, 149.5, 155.2, 157.8, 168.2; **MS**: *m/z* 272 (M^+), 231, 203, 137, 77; **Anal. Calcd for** $C_{16}H_{16}O_4$: C, 70.58; H, 5.88; **Found** C, 70.63; H, 5.77.

4-[3-(Allyloxy)-4-methoxybenzyl]-5-methylene-2 (5*H*)-furanone (119m)



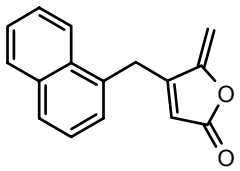
Nature: Thick pale yellow gum; **Yield**: 1.58 g, 57%; **IR** (Chloroform): *v* 3015, 1788, 1765, 1215 cm^{-1}; **^{1}H NMR**: (200 MHz, $CDCl_3$+CCl_4) δ 3.74 (bs, 2H), 3.88 (s, 3H), 4.61 (d, *J* = 6 Hz, 2H), 4.95 (d, *J* = 2.5 Hz, 1H), 5.20 (d, *J* = 2.5 Hz, 1H), 5.28-5.42 (m, 2H), 5.83 (s, 1H), 5.88-6.18 (m, 1H), 6.70-6.88 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 32.0, 55.9, 70.0, 94.4, 112.4, 114.7, 117.6, 118.2, 121.4, 128.2, 133.2, 148.3, 149.0, 155.5, 158.0, 168.4; **MS** (ESI): *m/z* 273 (M^++1), 291 (M+H_2O); **Anal. Calcd for** $C_{16}H_{16}O_4$: C, 70.58; H, 5.88; **Found** C, 70.61; H, 5.97.

2-(Acetyloxy)-1-({2-methoxy-5-[(2-methylene-5-oxo-2,5-dihydrofuran-3-yl)methyl]phenoxy}methyl)ethyl acetate (119n)



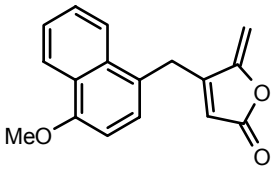
Nature: Thick oil; **Yield**: 2.26 g, 57%; **IR** (Chloroform): *v* 3016, 1765, 1738, 1650, 1562, 1487, 1220 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.07 (s, 3H), 3.71 (s, 2H), 3.81 (s, 3H), 4.11 (d, *J* = 4Hz, 2H), 4.20 - 4.32 (m, 1H); 4.38 - 4.50 (m, 1H), 4.91 (d, *J* = 2.4 Hz, 1H), 5.12-5.17 (m, 1H), 5.25 -5.45 (m, 1H), 5.82 (bs, 1H); 6.73 - 6.82 (m, 3H).

5-Methylene- 4 - (1-naphthylmethyl)- 2(5*H*)-furanone (1l9o)



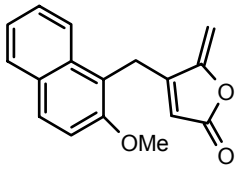
Nature: Pinkish white solid; **Yield**: 1.61 g, 67%; **Mp**: 115°C; IR (Chloroform): *v* 2926, 1768, 1719, 1220 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 4.24 (s, 2H), 5.13 (d, *J* = 2.7 Hz, 1H), 5.25-5.30 (m, 1H), 5.57 (bs, 1H), 7.30-7.56 (m, 4H), 7.80-7.95 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 29.9, 94.5, 118.5, 123.2, 125.3, 125.8, 126.4, 127.2, 128.2, 128.8, 131.2, 131.7, 133.7, 155.2, 157.6, 168.4; **MS** (ESI): *m/z* 236 (M^+), 254 (M^++ H_2O); **Anal. Calcd for** $C_{16}H_{12}O_2$: C, 81.35; H, 5.08; **Found** C, 81.47; H, 5.10.

4-[(4-Methoxy-1-naphthyl) methyl]-5-methylene-2(5*H*)-furanone (119p)



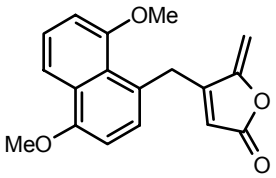
Nature: Pale yellow solid; **Yield**: 1.68 g, 62%; **Mp**: 82°C; **IR** (Chloroform): ν 3019, 1787, 1765, 1653, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 4.00 (s, 3H), 4.09 (s, 2H), 5.07 (d, J = 2.7 Hz, 1H), 5.21-5.23 (m, 1H), 5.55 (bs, 1H), 6.76 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H); 7.46 -7.55 (m, 2H), 7.64-7.73 (m, 1H), 8.31- 8.38 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 29.3, 55.2, 94.2, 103.0, 118.2, 122.6, 123.0, 123.5, 125.0, 125.8, 126.7, 127.2, 131.9, 155.0, 155.2, 158.1, 168.3; **MS** (ESI): *m/z* 266 $(M)^+$; **Anal. Calcd for** $C_{17}H_{14}O_3$: C, 63.90; H. 5.26; **Found** C, 64.13; H, 5.32.

4-[(2-Methoxy-1-naphthyl) methyl]-5-methylene-2(5*H*)-furanone (119q)



Nature: Pale yellow solid; **Yield**: 1.65 g, 61%; **Mp**: 135°C; **IR** (Chloroform): ν 3020, 1770, 1768, 1530, 1212 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.97 (s, 3H), 4.24 (s, 2H), 5.22 (d, J = 2.9 Hz, 1H), 5.24-5.28 (m, 1H), 5.46 (bs, 1H), 7.30-7.53 (m, 3H), 7.68 (d, J = 8 Hz, 1H), 7.79-7.91 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 21.9, 56.1, 94.0, 112.6, 116.5, 117.6, 122.2, 123.4, 126.8, 128.5, 128.9, 129.2, 132.4, 154.4, 155.6, 158.0, 168.8; **MS**: *m/z* 266 $(M)^+$, 251, 236, 221, 171, 77; **Anal. Calcd for** $C_{17}H_{14}O_3$: C, 63.90; H, 5.26; **Found** C, 63.93; H, 5.27.

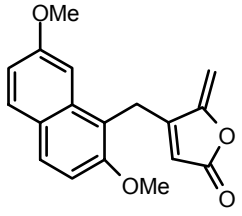
4-(4,8-Dimethoxy-naphthalen-1-ylmethyl)-5-methylene-2 (5*H*)-furanone (119r)



Nature: Pale yellow solid; **Yield**: 1.57 g, 52%; **Mp**: 129°C; IR (Chloroform): ν 2926, 1765, 1744, 1500, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.76 (s, 3H), 4.01 (s, 3H), 4.28 (s, 2H), 5.09 (d, J = 2.5 Hz, 1H), 5.23-5.26 (m, 1H), 5.34 (bs, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.5, 54.9, 55.3, 93.3, 103.7, 106.4, 114.9, 116.0,

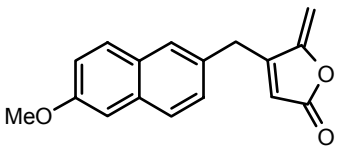
123.3, 124.3, 125.3, 128.0, 129.0 (2C), 154.7, 156.0, 161.4, 169.2; **MS** (ESI): *m/z* 297 $(MH)^+$; **Anal. Calcd for** $C_{18}H_{16}O_4$: C, 72.97; H, 5.40; **Found** C, 73.18; H, 5.29.

4-[(2,7-Dimethoxy-1-naphthyl) methyl]-5-methylene-2(5*H*)-furanone (119s)



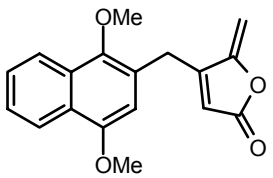
Nature: Pale yellow solid; **Yield**: 1.75 g, 58%; **Mp**: 85°C; **IR**: (Chloroform): ν 3019, 1768, 1605, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.85 (s, 3H), 3.93 (s, 3H), 4.16 (unresolved doublet, 2H), 5.19-5.27(m, 2H), 5.53 (bs, 1H), 6.88 (d, J = 2 Hz, 1H), 7.03 (dd, J = 8, 2 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.74 (t, J = 8, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.1, 55.0, 56.0, 94.1, 101.3, 110.0, 115.5, 115.7, 117.6, 124.4, 129.0, 130.1, 133.8, 155.0, 155.7, 158.1, 158.5, 168.8; **MS**: *m/z* 296, 268, 253, 237, 216, 201, 185, 165, 105, 77; **Anal. Calcd for** $C_{18}H_{16}O_4$: C, 72.97; H, 5.40; Found C, 72.83; H, 5.51.

4-[(6-Methoxy-2-naphthyl) methyl]-5-methylene-2(5*H*)-furanone (119t)



Nature: Pale yellow solid; **Yield**: 1.54 g, 57%; **Mp**: 122°C; **IR**: (Chloroform): ν 3019, 1778, 1765, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + acetone-d_6): δ 3.92 (bs, 5H), 4.96 (d, J = 2.9 Hz, 1H), 5.15-5.21 (m, 1H), 5.85 (bs, 1H), 7.10-7.28 (m, 3H), 7.57 (bs, 1H), 7.69 (t, J = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 31.8, 54.5, 93.9, 105.1, 117.7, 118.6, 126.6 (2), 126.7, 128.4 (2C), 130.6, 133.1, 155.0, 157.2, 157.6, 167.6; **MS**: *m/z* 266 $(M)^+$, 251, 177, 91; **Anal. Calcd for** $C_{17}H_{14}O_3$: C, 63.90; H. 5.26; **Found** C, 63.76, H, 5.13.

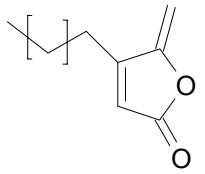
4-[(1,4-Dimethoxy-2-naphthyl) methyl]-5-methylene-2(5*H*)-furanone (119u)



Nature: Pale yellow solid; Yield: 1.93 g, 64%; **Mp**: 87 °C; **IR**: (Chloroform): *v* 2920, 1768, 1717, 1672, 1221 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.96 (s, 3H), 4.01 (bs, 2H), 5.12 (d, J = 2.9 Hz, 1H), 5.20-5.25 (m, 1H), 5.88 (bs, 1H), 7.49-7.65 (m, 3H), 8.04 (dd, J = 8,

2 Hz, 1H), 8.26 (dd, *J* = 8, 2 Hz, 1H); **MS** (ESI): *m/z* 296 $(M)^+$; **Anal. Calcd for** $C_{18}H_{16}O_4$: C, 72.97; H, 5.40; **Found** C, 72.93; H, 5.38.

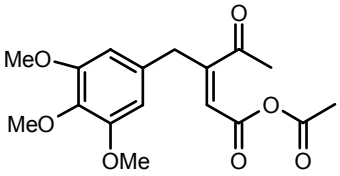
4-Dodecyl-5-methylene-5*H*-furan-2-one (119v)



Nature: Oil; **Yield**: 45%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 0.89 (t, *J* = 6 Hz, 3H), 1.20-1.45 (m, 20 H), 1.70-1.77 (m, 2H), 4.90 (d, *J* = 2.3 Hz, 1H), 5.12-5.18 (m, 1H), 5.87 (t, *J* = 1.97 Hz, 1H).

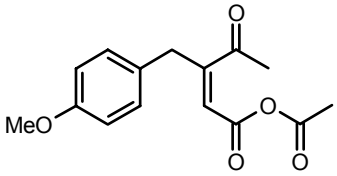
Spectral data for mixed anhydride 120

Mixed anhydride 120a



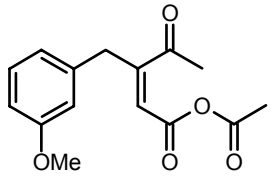
Nature: Pale brown solid; **Yield**: 0.582 g, 17%; **Mp**: 65-67 °C, IR (Chloroform): *v* 3019, 1778, 1717, 1662, 1515, 1263, 1216, 757 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.73 (s, 3H), 1.98 (s, 3H), 3.50 (q, *J* = 4 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 6H), 5.69 (s, 1H), 6.38 (s, 2H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 21.10, 23.42, 33.4, 55.90 (2C), 60.48, 105.5, 106.15, 118.4, 130.14, 131.2, 137.2, 153.2 (2C), 167.66, 168.5, 199.0; **MS** (ESI): *m/z* 354 $(M^+ + H_2O)^+$, 337 $(MH)^+$; **Anal Calcd for** $C_{17}H_{20}O_7$: C, 60.71; H, 5.99; **Found**: C, 60.61; H, 6.07.

Mixed anhydride 120b



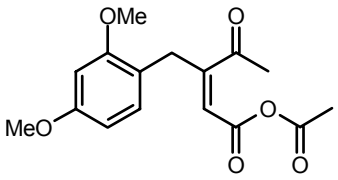
Nature: Semisolid; **Yield**: 0.760 g, 27%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.89 (s, 3H), 2.11 (s, 3H), 3.57 (s, 2H), 3.81 (s, 3H), 5.33 (bs, 1H), 6.87 (d, *J* = 8Hz, 2H), 7.11 (d, *J* = 8Hz, 2H). **Anal Calcd for** $C_{15}H_{16}O_5$ C, 65.21; H, 5.84; Found: C, 65.16; H, 5.94;

Mixed Anhydride 120c



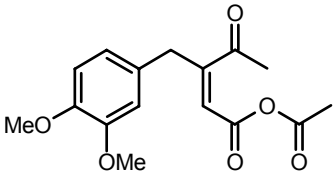
Nature: Thick oil; **Yield**: 0.908 g, 32%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.86 (s, 3H), 2.10 (s, 3H), 3.58 (s, 2H), 3.89 (s, 3H), 5.62 (bs, 1H), 6.75-6.82 (m, 3H), 7.30 (d, *J* = 2Hz, 1H).

Mixed anhydride 120d



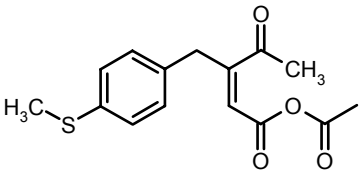
Nature: Semisolid; **Yield**: 0.591 g, 18 %; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.65 (s, 3H), 2.10 (s, 3H), 3.54 (s, 2H), 3.82 (s, 6H), 5.32 (bs, 1H), 6.40-6.48 (m, 2H), 7.03 (d, J = 8Hz, 1H); **MS** (ES): *m/z* 307 (M^++1)

Mixed anhydride 120e



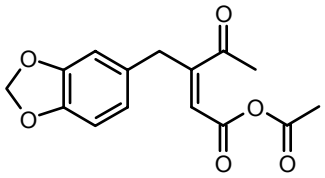
Nature: Thick oil; **Yield**: 0.788 g, 24%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.72 (s, 3H), 2.00 (s, 3H), 3.51(s, 2H), 3.80(s, 3H), 3.82 (s, 3H), 5.32 (t, J = 2Hz, 1H), 6.68 (m, 2H), 6.80 (d, J = 8 Hz, 1H).

Mixed anhydride 120f



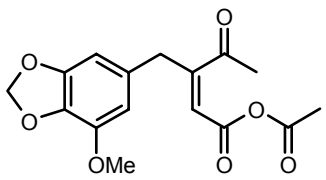
Nature: Thick yellow oil; **Yield**: 0.583 g, 22%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.73 (s, 3H), 2.00 (s, 3H), 2.48 (s, 3H), 3.52 (s, 2H), 5.63 (s, 1H), 7.10 (dd, J = 8, 2Hz, 2H), 7.25 (dd, J = 8, 2Hz, 2H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 15.3, 21.1, 23.3, 32.4, 105.5, 118.2, 126.5 (2C), 129.4 (2C), 131.3, 137.3, 167.7, 168.4, 168.9; **Anal Calcd for** $C_{15}H_{16}O_4S$: C, 61.64; H, 5.47; S, 10.95; **Found**: C, 61.44; H, 5.52; S, 11.10.

Mixed anhydride 120g



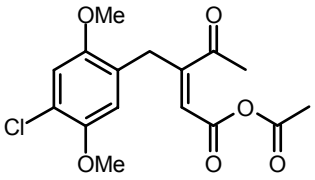
Nature: Thick oil; **Yield**: 0.621 g, 21 %; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.78(s, 3H), 2.10 (s, 3H), 3.58 (s, 2H), 5.37 (bs, 1H), 5.85 (s, 2H), 6.64-6.70 (m, 2H), 6.78 (d, J = 8 Hz, 1H).

Mixed anhydride 120h



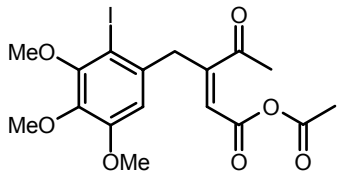
Nature: Semisolid; **Yield**: 0.391 g, 12%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.80 (s, 3H), 2.13 (s, 3H), 3.54 (s, 2H), 3.81 (s, 3H), 5.35 (bs, 1H), 5.88 (s, 2H), 6.55 (s, 2H).

Mixed anhydride 120i



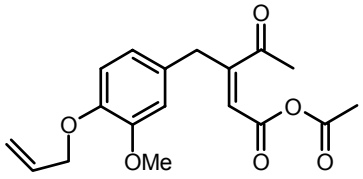
Nature: Semisolid; **Yield**: 0.346 g, 10%; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.86 (s, 3H), 2.11 (s, 3H), 3.52 (s, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 5.35 (bs, 1H), 6.70 (s, 1H), 6.85 (s, 1H).

Mixed anhydride 120j



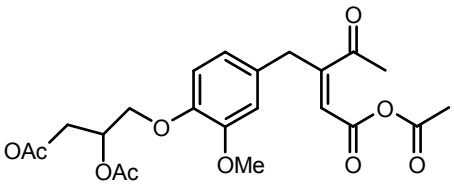
Nature: Thick gum; **Yield**: 0.155 g, 33 %; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.87 (s, 3H), 2.03 (s, 3H), 3.58 (s, 2H), 3.89 (s, 9H), 5.40 (bs, 1H), 6.65 (s, 1H).

Mixed anhydride 120l



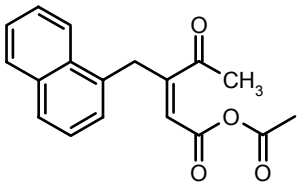
Nature: Thick gum; **Yield**: 0.677 g, 20%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.75 (s, 3H), 1.98 (s, 3H), 3.53 (s, 2H), 3.84 (s, 3H), 4.54-4.59 (m, 2H), 5.41 (bs, 1H), 5.28-5.42 (m, 1H), 5.95-6.08 (m, 2H), 6.69-6.71 (m, 2H), 6.80 (d, J = 8, 2Hz, 1H).

Mixed anhydride 120n



Nature: Thick gum; **Yield**: 1.56 g, 34%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.07 (s, 6H), 2.10 (s, 6H), 3.80 (s, 3H), 3.49 (s, 2H), 4.10-4.50 (m, 5H), 5.32 (t, J = 2Hz, 1H), 6.70-6.75 (m, 3H).

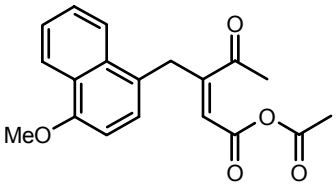
Mixed anhydride 120 o



Nature: Semisolid; **Yield**: 0.452 g, 15 %; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.89 (s, 3H), 2.06 (s, 3H), 4.00 (s, 2H), 5.39 (s, 1H), 7.30-7.50 (m, 5H), 7.78-7.89 (m, 2H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 21.4, 23.3, 26.3, 30.62, 105.7, 118.4, 123.3, 125.2, 125.7,

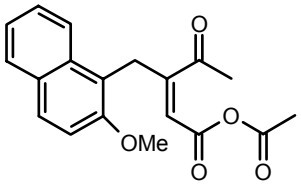
126.3, 127.6, 128.6 (2C), 131.1, 133.6, 167.8, and 168.8; **MS**: 296, 278, 238, 221, 208, 165; **Anal Calcd for** $C_{18}H_{16}O_4$: C, 72.97; H, 5.40; **Found**: C, 73.12; H, 5.32.

Mixed anhydride 120p



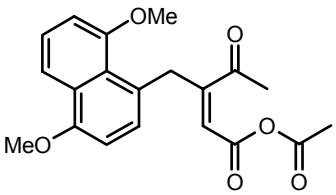
Nature: Semisolid; **Yield**: 0.598g, 18%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.85 (s, 3H), 2.10 (s, 3H), 3.56 (s, 2H), 3.80 (s, 3H), 5.36 (bs, 1H), 6.76 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 7.53-7.57 (m, 2H), 7.70 (t, J = 8 Hz, 2Hz, 1H), 8.35 (t, J = 8 Hz, 2Hz, 1H).

Mixed anhydride 120q



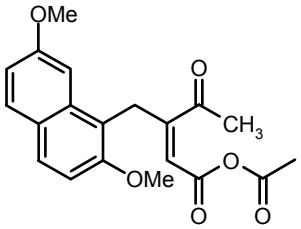
Nature: Semisolid; **Yield**: 0.665g, 20%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.87 (s, 3H), 2.00 (s, 3H), 3.60 (s, 2H), 3.91 (s, 3H), 5.39 (bs, 1H), 7.30-7.47 (m, 3H), 7.68 (d, J = 8 Hz, 1H), 7.87 (t, J = 8 Hz, 2Hz, 2H).

Mixed anhydride 120r



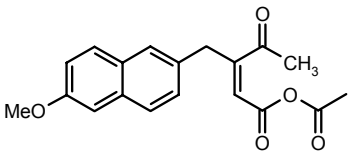
Nature: Semisolid; **Yield**: 1.05 g, 29%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.95 (s, 3H), 2.03 (s, 3H), 3.53 (s, 2H), 4.09 (s, 3H), 3.85 (s, 3H), 5.45 (bs, 1H), 6.77 (m, 3H), 7.94 (m, 2H).

Mixed anhydride 120s



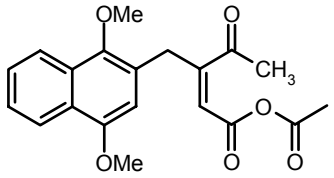
Nature: Semisolid; **Yield**: 1.16 g, 32%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.88 (s, 3H), 2.05 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.13 (q, J = 12 Hz, 2H); 5.37 (t, J = 2Hz, 1H); 6.95-7.20 (m, 3H), 7.69 (d, J = 8Hz, 1H), 7.75 (d, J = 8Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 23.0, 23.6, 54.9, 56.0, 101.2, 105.6, 109.8, 114.8, 116.2, 117.7, 124.2, 128.8, 129.7, 134.02, 134.02, 154.9, 158.5, 167.6, 168.5, 168.7. **Anal Calcd for** $C_{20}H_{20}O_6$: C, 67.41; H, 5.61; **Found**: C, 67.52; H, 5.53.

Mixed anhydride 120t



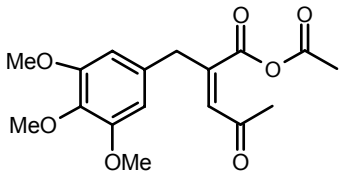
Nature: Semisolid; **Yield**: 0.399g, 12%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.78 (s, 3H), 1.98 (s, 3H), 3.72 (s, 2H), 3.94 (s, 3H), 5.66 (t, J = 2 Hz, 1H), 7.13-7.26 (m, 3 H), 7.59-7.56 (m, 3H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 21.2, 23.4, 33.1, 54.9, 105.5 (2C), 105.67, 118.4, 119.06, 127.2 (2C), 127.3,128.7, 129.7, 133.4, 157.6, 167.7, 168.5, 169.02; **MS**: *m/z* 326, 266, 251, 223, 195, 152; **Anal. Calcd for** $C_{19}H_{18}O_5$: C, 69.99; H, 5.52; **Found:** C, 70.17; H, 5.42.

Mixed anhydride 120 u



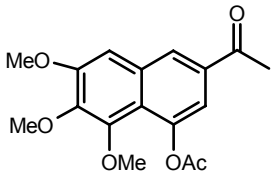
Nature: Semisolid; **Yield**: 0.617g, 17%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.82 (s, 3H), 1.97 (s, 3H), 3.75 (s, 2H), 3.85 (s, 3H), 3.96 (s, 3H), 5.69 (bs, 1H), 6.50 (s, 1H), 7.40-7.55 (m, 2H), 7.82 (d, J= 8Hz, 1H), 8.23 (d, J = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 21.3, 23.6, 27.6, 55.5, 62.2, 104.9, 118.5, 121.7, 122.7, 122.8, 125.5, 125.7, 126.2, 126.8, 129.4, 147.4, 152.1, 167.9, 168.6, 169.1; **Anal Calcd for** $C_{20}H_{20}O_6$: C, 67.41; H, 5.61; **Found**: C, 67.37; H, 5.57

Mixed anhydride 123



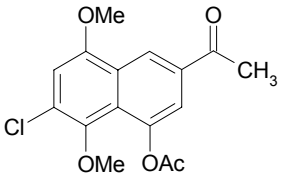
Nature: Semisolid; **Yield**: 0.582 g, 17%; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.73 (s, 3H), 2.02 (s, 3H), 3.50 (s, 2H), 3.85 (s, 9H), 5.70 (s, 1H), 6.87 (s, 1H), 6.99 (s, 1H).

Acetic acid 3-acetyl-6, 7, 8-trimethoxy-naphthalen-1-yl ester (121a)



Nature: Brown solid; **Yield**: 0.291 g, 9%; **Mp**: 116-117 °C, **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.75 (s, 3H), 2.15 (s, 3H), 3.85 (s, 6H), 3.88 (s, 3H), 5.89 (s, 1H), 6.85 (d, J = 2.5, 1H), 6.89 (d, J = 2.5, 1H); MS: (ESI): *m/z* 318 (M^+)

Acetic acid 3-acetyl-7-chloro-5,8-dimethoxy-naphthalen-1-yl ester (121i)



Nature: White solid; **Yield**: 0.492 g, 15%; **Mp**: 138-140 °C; **IR**: (chloroform): *v* 3029, 1723, 1712, 1215, 765 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.49 (s, 3H), 2.53 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 6.65 (s, 1H), 6.68 (d, J = 2 Hz, 1H), 6.73 (d, J = 2 Hz, 1H); **MS**: *m/z* 322, 308, 264, 235, 199.2, 79.

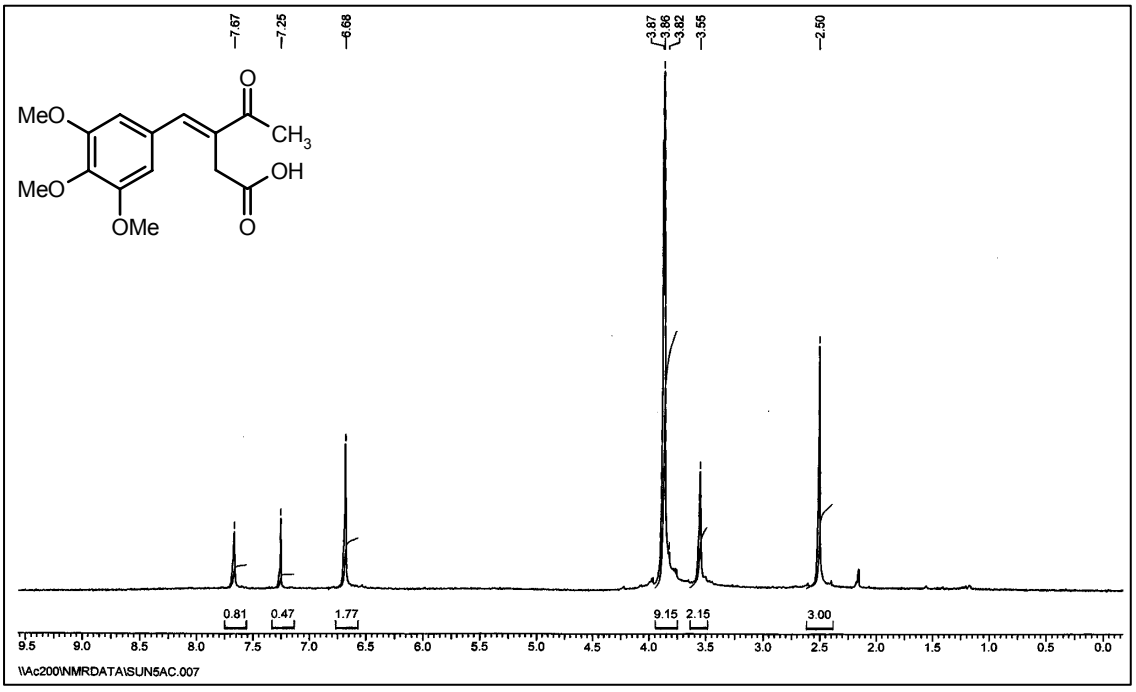
Table 2. Crystal data and structure refinement for the furanone 119 i.

Empirical formula	$C1_{40}\ H_{52}\ C_{l8}\ O_{16}$
Formula weight	2273.42
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 6.4265(10) A α = 102.614(3) deg. b = 10.024(2) A β = 98.763(3) deg. c = 10.606(2) A γ = 95.190(3) deg.
Volume	653.5(2) A^3
Z, Calculated density	1, 5.777 Mg/m^3
Absorption coefficient	1.161 mm^{-1}
F(000)	1156
Theta range for data collection	2.00 to 25.00 deg.
Reflections collected / unique	6333 / 2302 [R(int) = 0.0335]
Completeness to theta = 25.00	99.8 %
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0408, wR2 = 0.1091
R indices (all data)	R1 = 0.0467, wR2 = 0.1141
Largest diff. peak and hole	0.223 and -0.201 $e.A^{-3}$

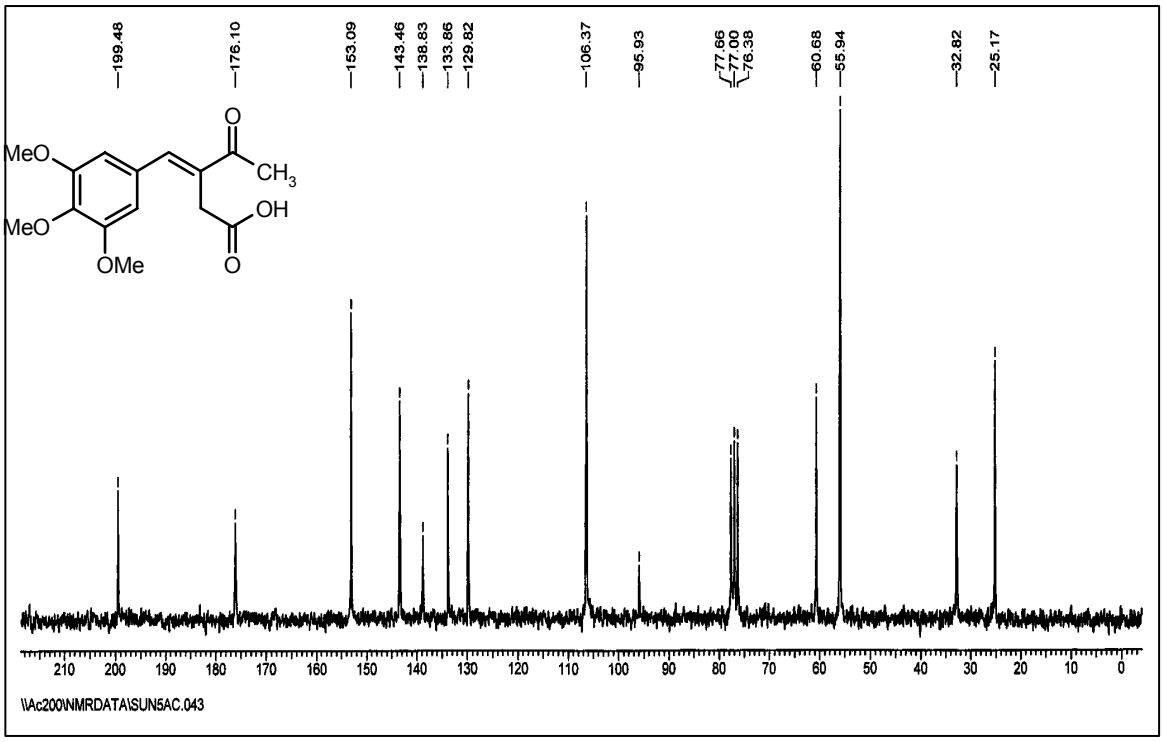
Table 3. Bond lengths [A] and angles [deg] for S143.

Bond lengths [A]		**Bond angles [deg]**	
Cl-C(10)	1.7330(18)	C(1)-O(1)-C(4)	108.05(15)
O(1)-C(1)	1.379(3)	C(12)-O(3)-C(13)	118.07(16)
O(1)-C(4)	1.389(3)	C(9)-O(4)-C(14)	116.67(17)
O(2)-C(1)	1.194(3)	O(2)-C(1)-O(1)	120.40(19)
O(3)-C(12)	1.376(2)	O(2)-C(1)-C(2)	132.2(2)
O(3)-C(13)	1.405(3)	O(1)-C(1)-C(2)	107.39(18)
O(4)-C(9)	1.364(2)	C(3)-C(2)-C(1)	109.13(18)
O(4)-C(14)	1.423(3)	C(2)-C(3)-C(4)	107.54(17)
C(1)-C(2)	1.456(3)	C(2)-C(3)-C(6)	129.52(17)
C(2)-C(3)	1.323(3)	C(4)-C(3)-C(6)	122.94(17)
C(3)-C(4)	1.460(2)	C(5)-C(4)-O(1)	121.4(2)
C(3)-C(6)	1.493(3)	C(5)-C(4)-C(3)	130.7(2)
C(4)-C(5)	1.306(3)	O(1)-C(4)-C(3)	107.85(17)
C(6)-C(7)	1.505(3)	C(3)-C(6)-C(7)	112.78(17)
C(7)-C(8)	1.383(3)	C(8)-C(7)-C(12)	118.87(17)
C(7)-C(12)	1.390(3)	C(8)-C(7)-C(6)	120.43(17)
C(8)-C(9)	1.379(3)	C(12)-C(7)-C(6)	120.69(18)
C(9)-C(10)	1.384(3)	C(9)-C(8)-C(7)	121.84(17)
C(10)-C(11)	1.380(3)	O(4)-C(9)-C(8)	124.98(16)
C(11)-C(12)	1.377(3)	O(4)-C(9)-C(10)	117.12(16)
		C(8)-C(9)-C(10)	117.89(17)
		C(11)-C(10)-C(9)	121.65(16)
		C(11)-C(10)-Cl	119.34(14)
		C(9)-C(10)-Cl	119.01(14)
		C(12)-C(11)-C(10)	119.39(17)
		O(3)-C(12)-C(11)	124.05(16)
		O(3)-C(12)-C(7)	115.60(16)
		C(11)-C(12)-C(7)	120.34(17)

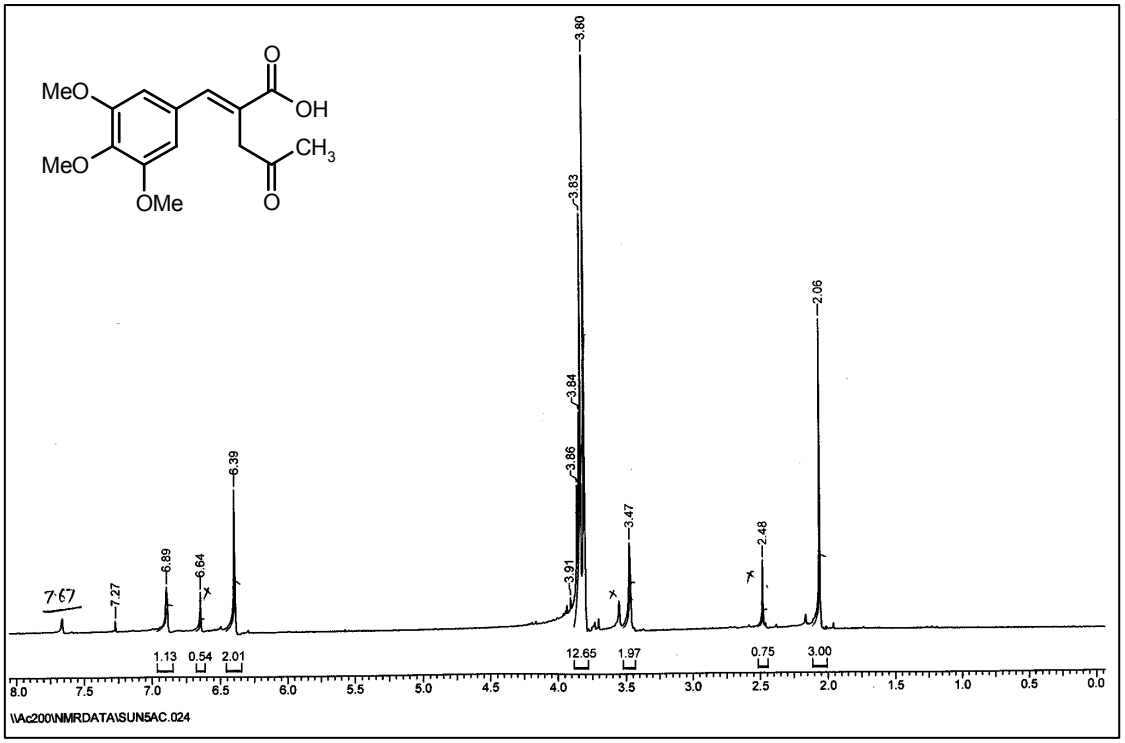
^{1}H NMR of compound 116a ($CDCl_3$+CCl_4, 200 MHz)



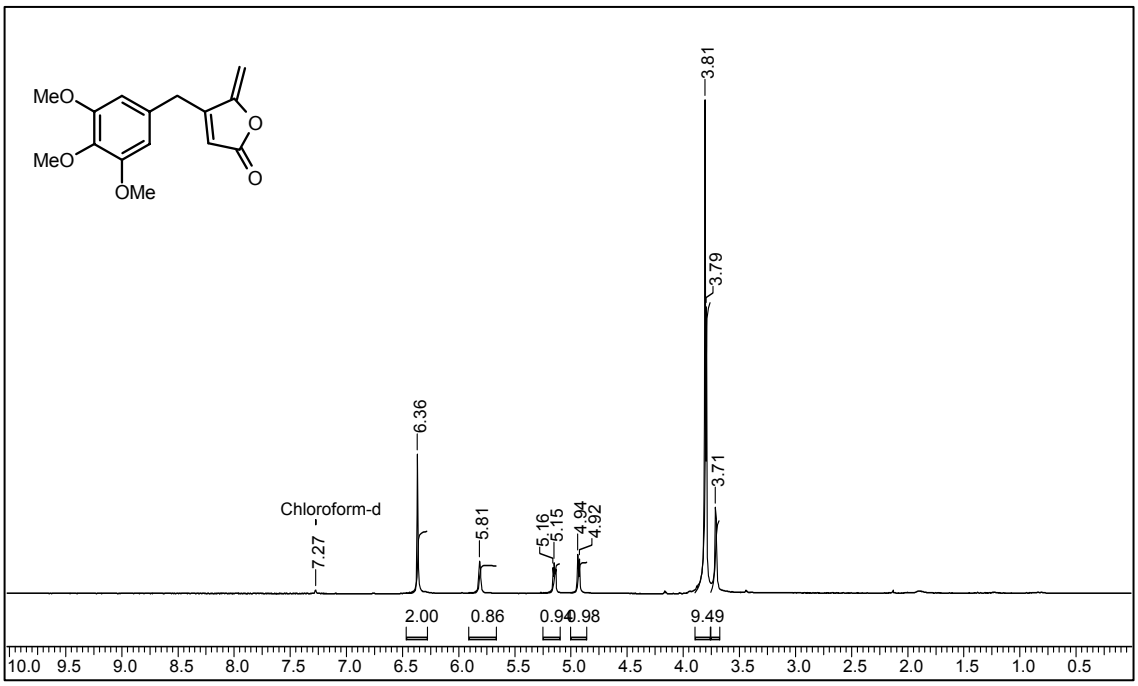
^{13} C NMR of compound 116a ($CDCl_3$+CCl_4, 50 MHz)



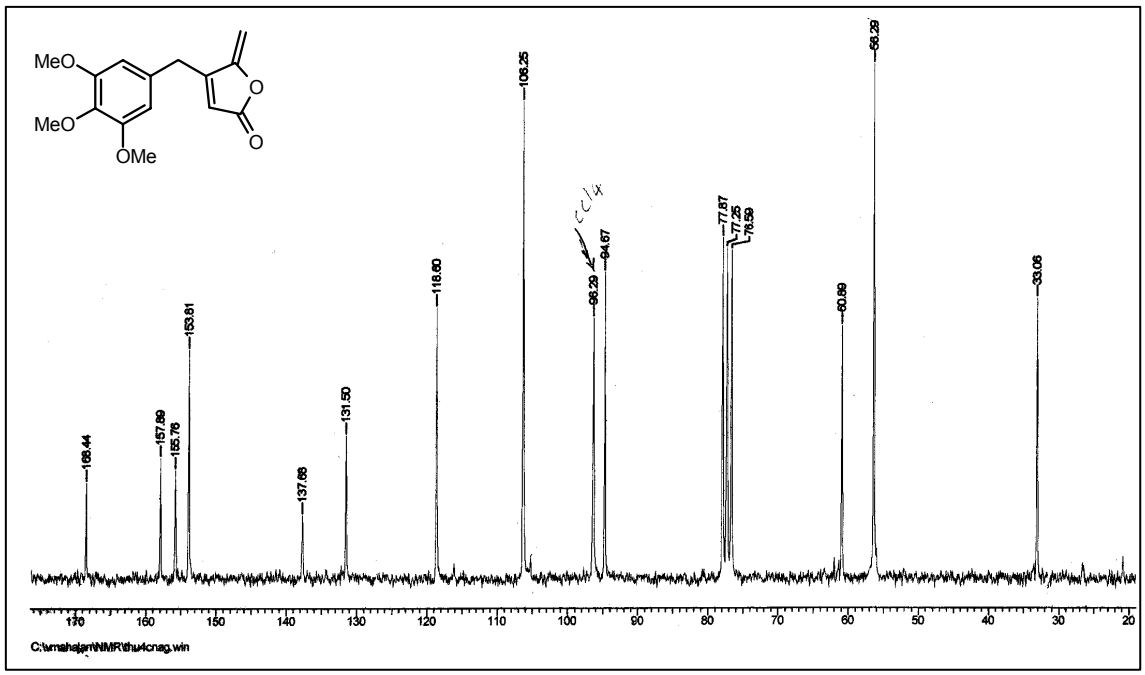
^{1}H NMR of compound 117a ($CDCl_3$+CCl_4, 200 MHz)

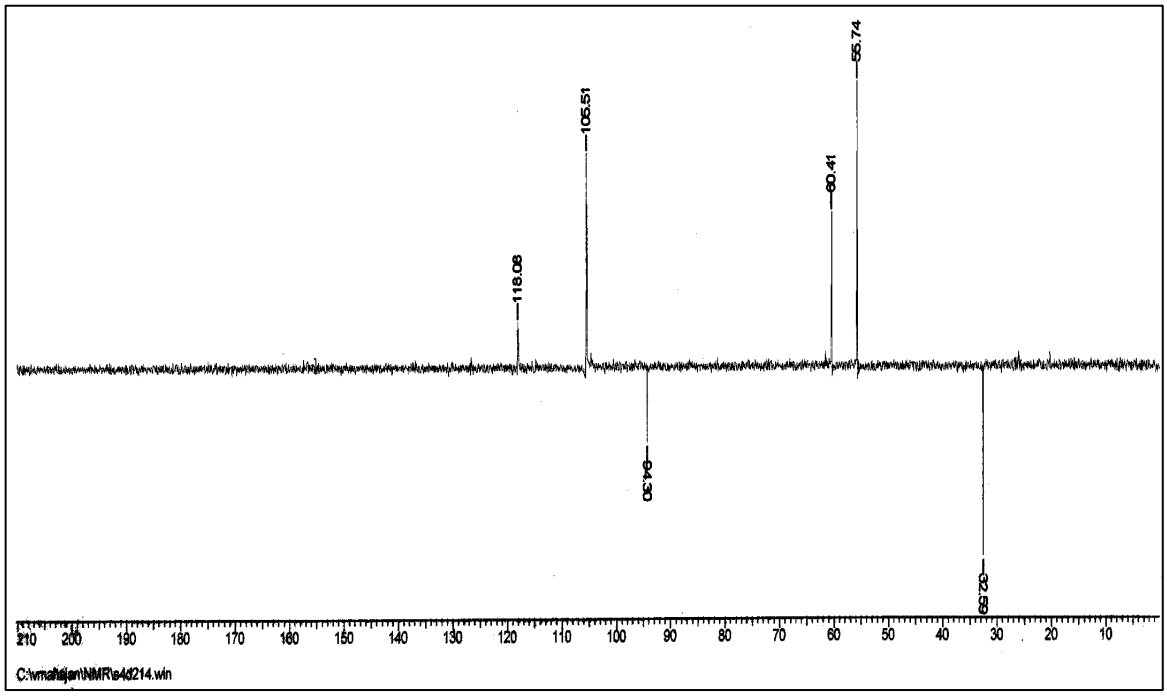


^{1}H NMR of compound 119a ($CDCl_3$, 200 MHz)

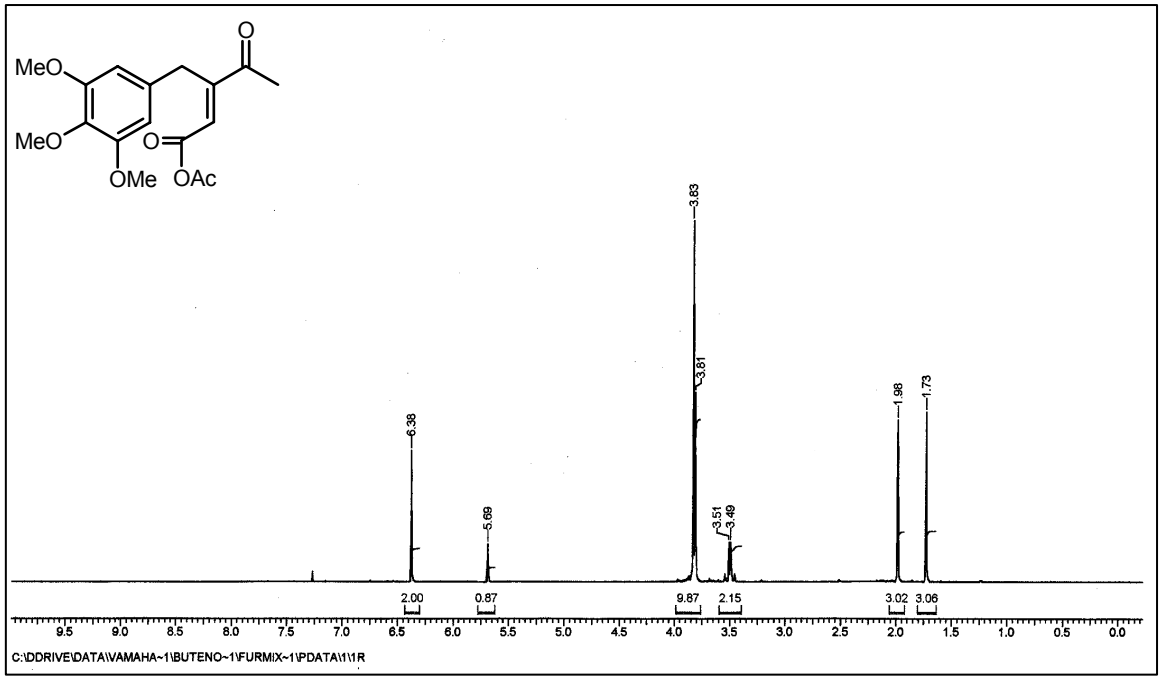


^{13}C NMR and DEPT of compound 119a ($CDCl_3$ +CCl_4, 50 MHz)

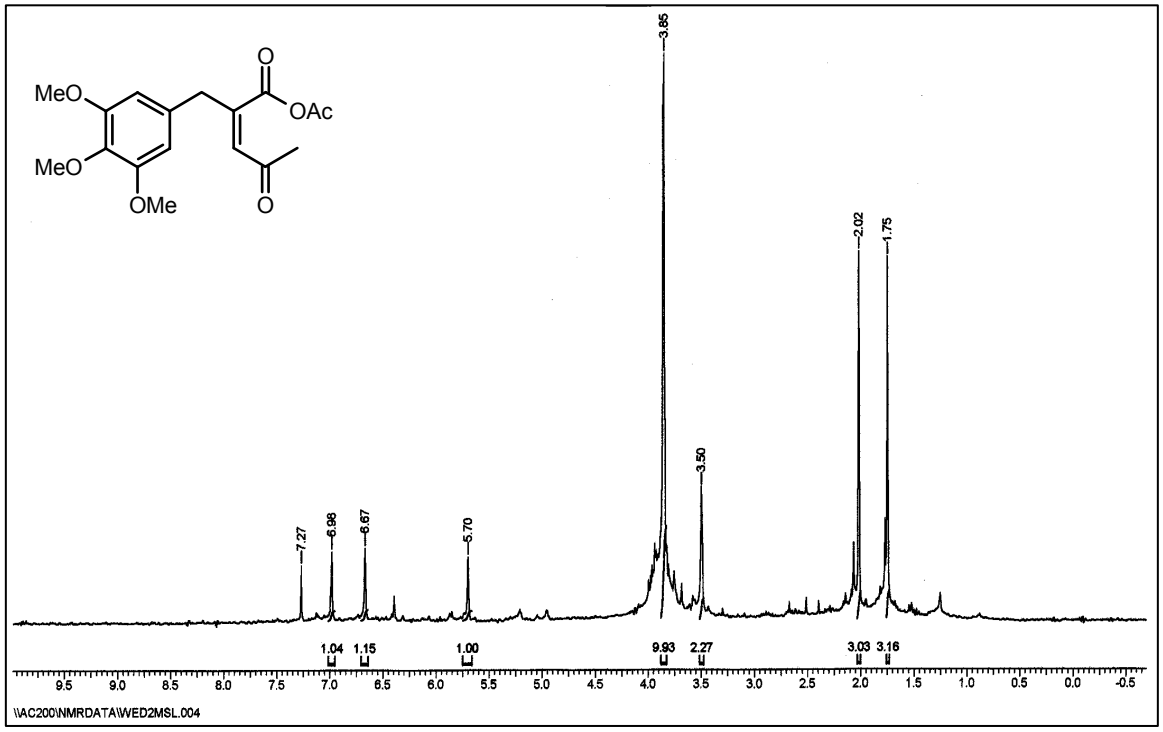




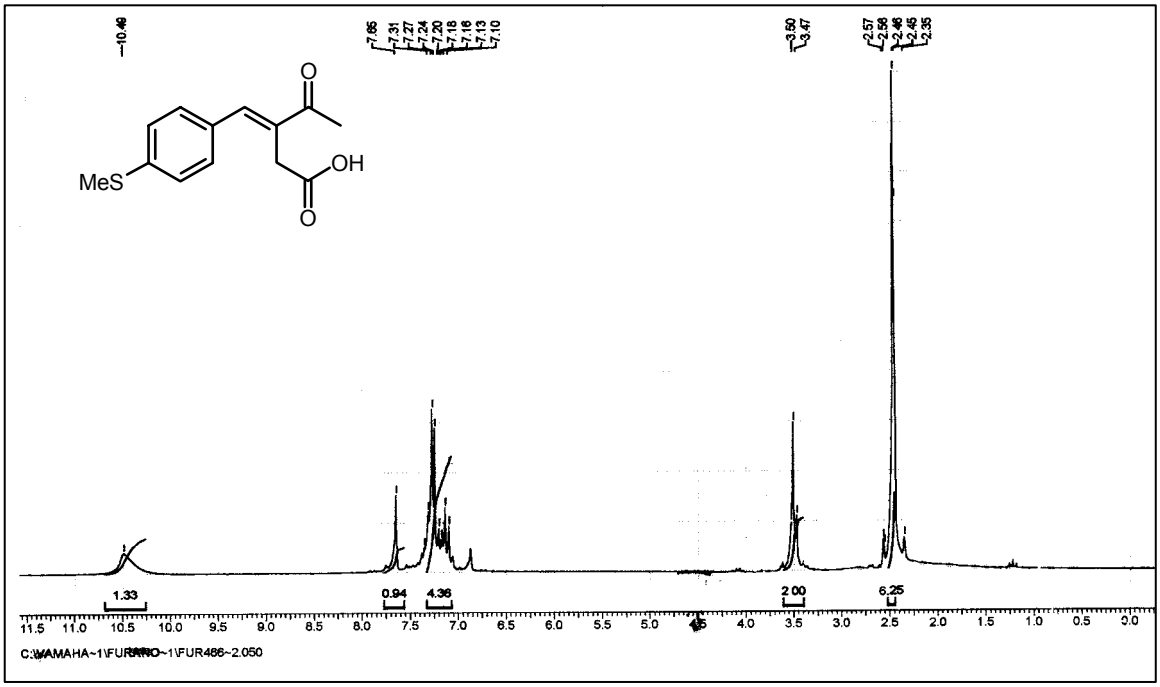
^{1}H NMR spectrum of compound 120a ($CDCl_3$, 200 MHz)



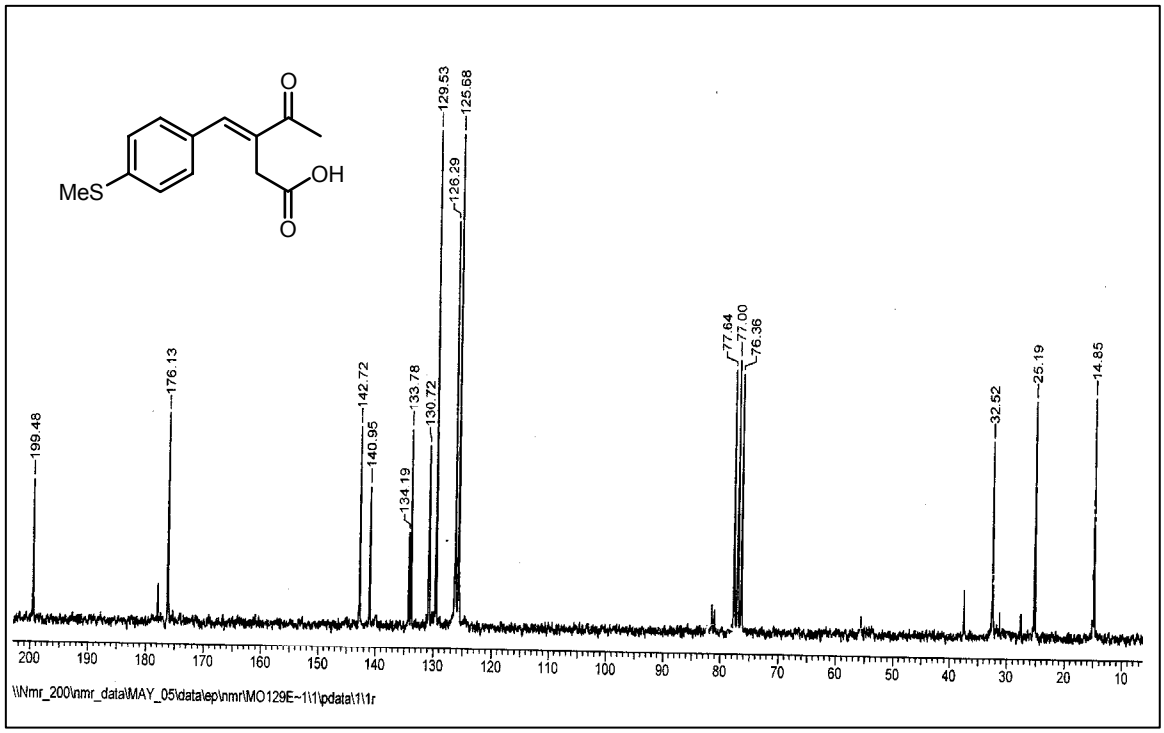
^{1}H NMR of compound 123 ($CDCl_3$, 200 MHz)



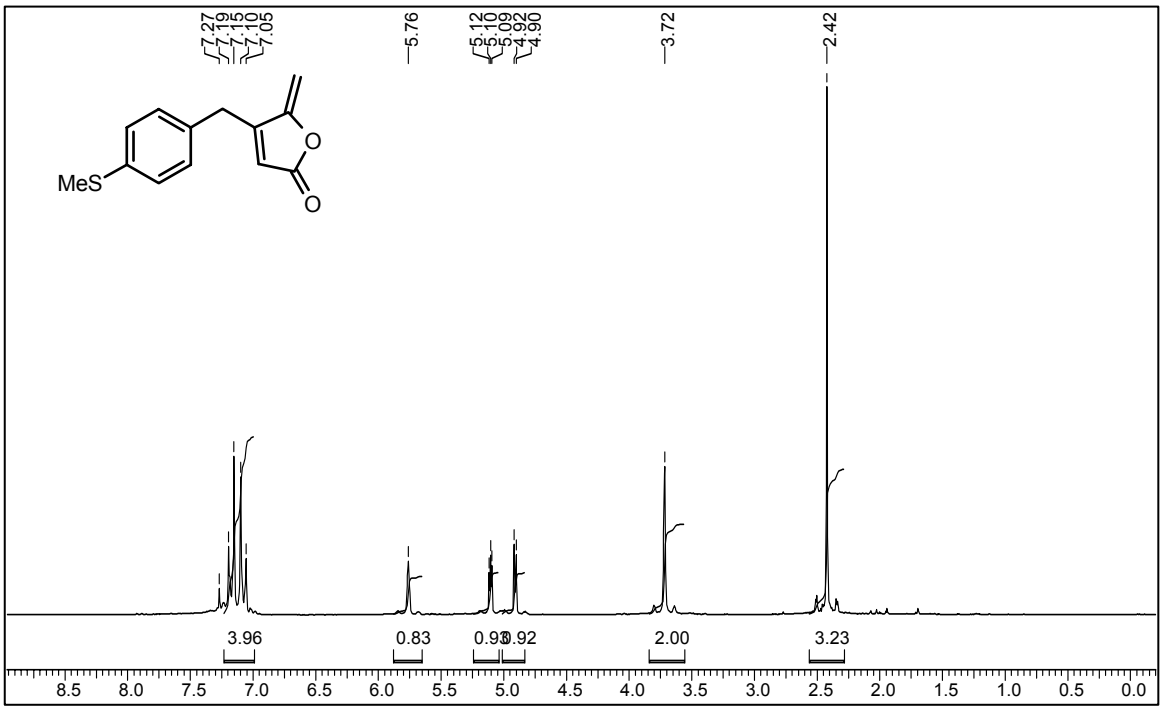
^{1}H NMR spectrum of compound 116f ($CDCl_3$, 200 MHz)



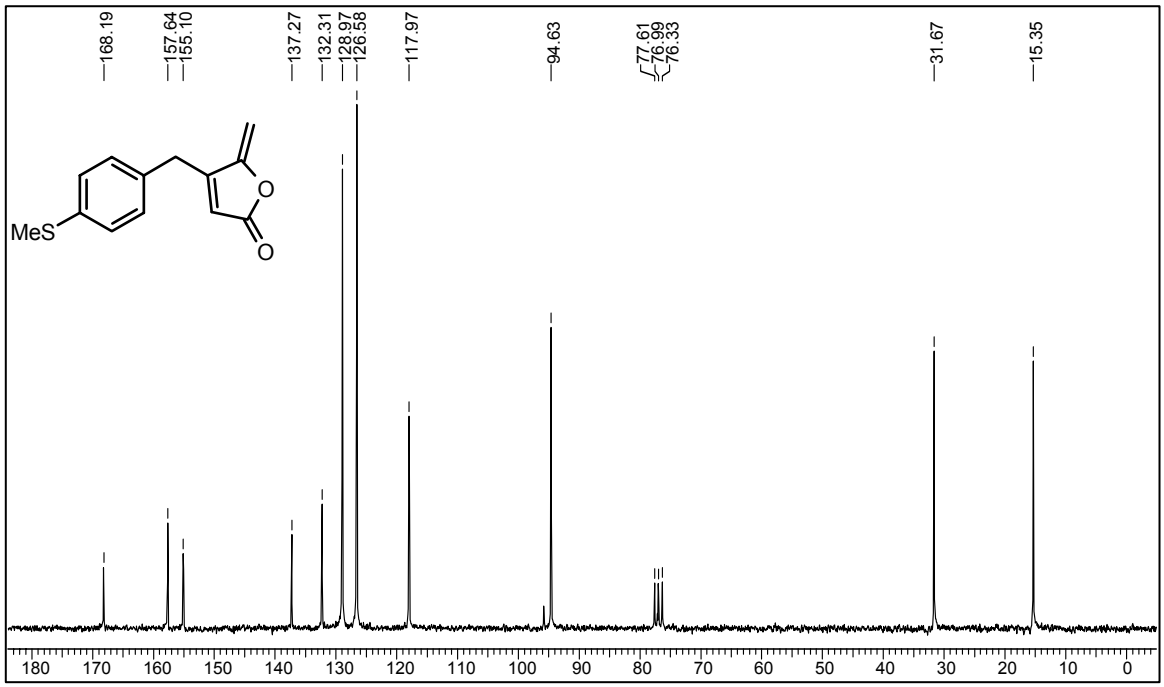
^{13}C NMR of compound 116f (50 MHz, $CDCl_3$ +CCl_4)

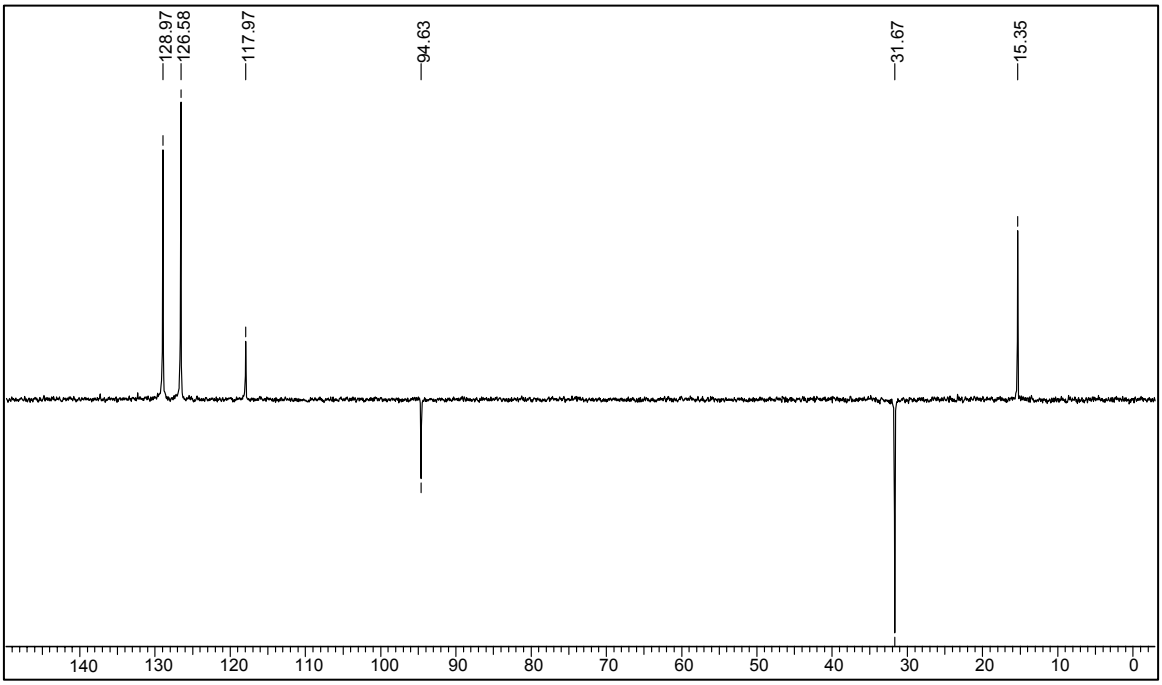


^{1}H NMR of compound 119f ($CDCl_3$, 200 MHz)

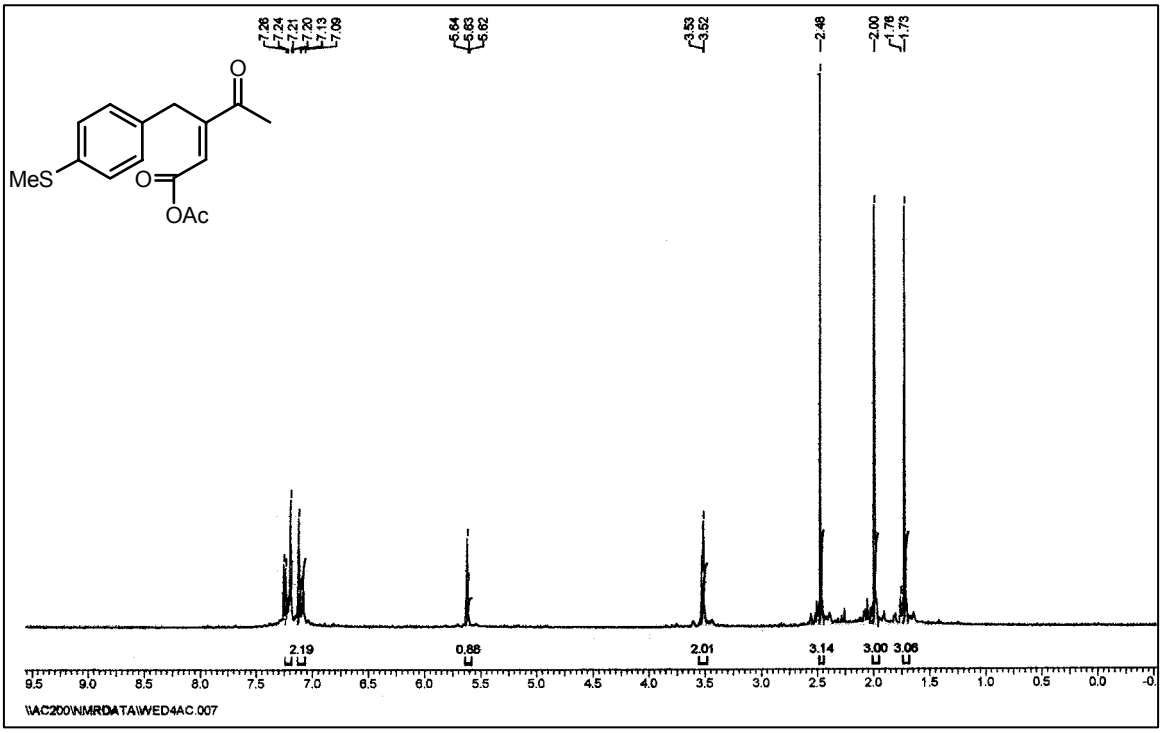


^{13}C NMR and DEPT of compound 119f ($CDCl_3$ +CCl_4, 50 MHz)

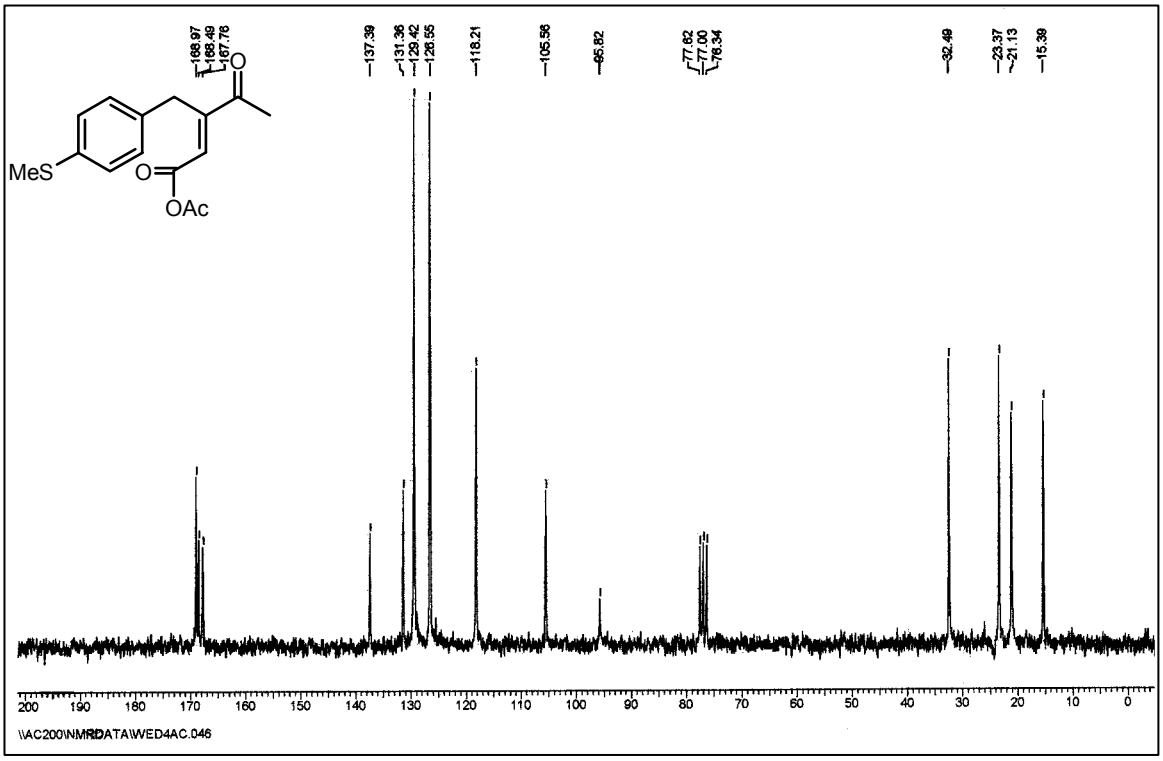




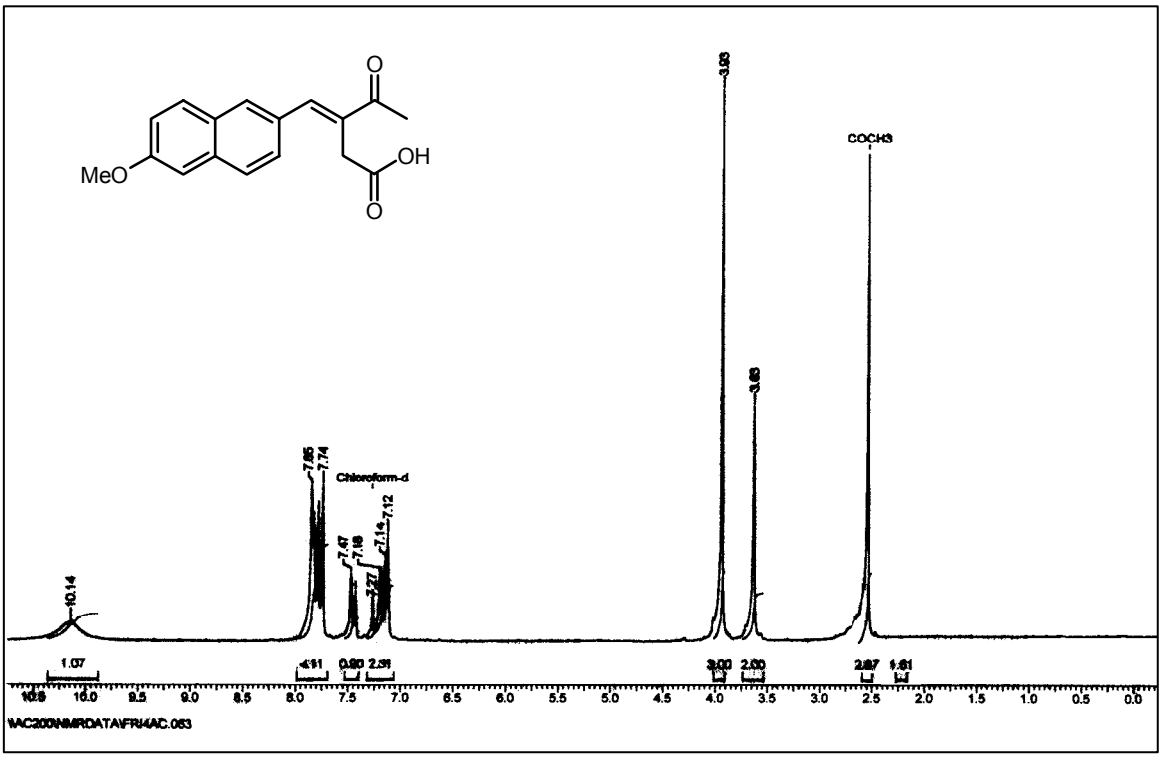
^{1}H NMR spectrum of compound 120f ($CDCl_3$, 200 MHz)



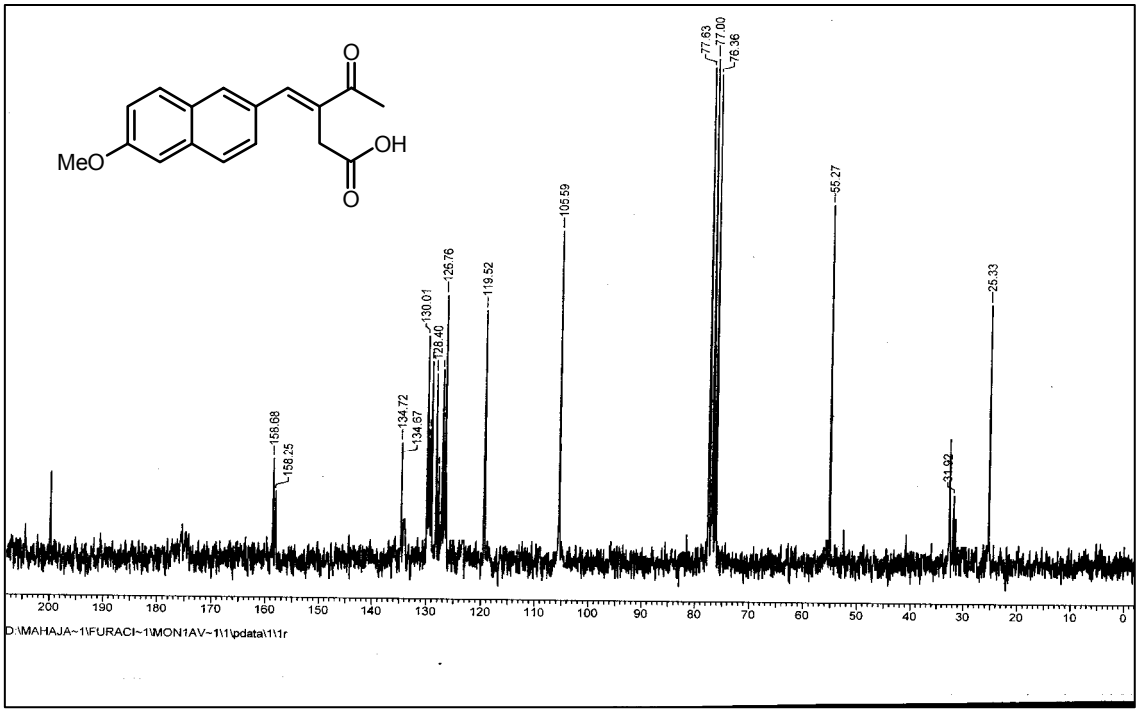
^{13}C NMR spectrum of compound 120f ($CDCl_3$, 50 MHz)



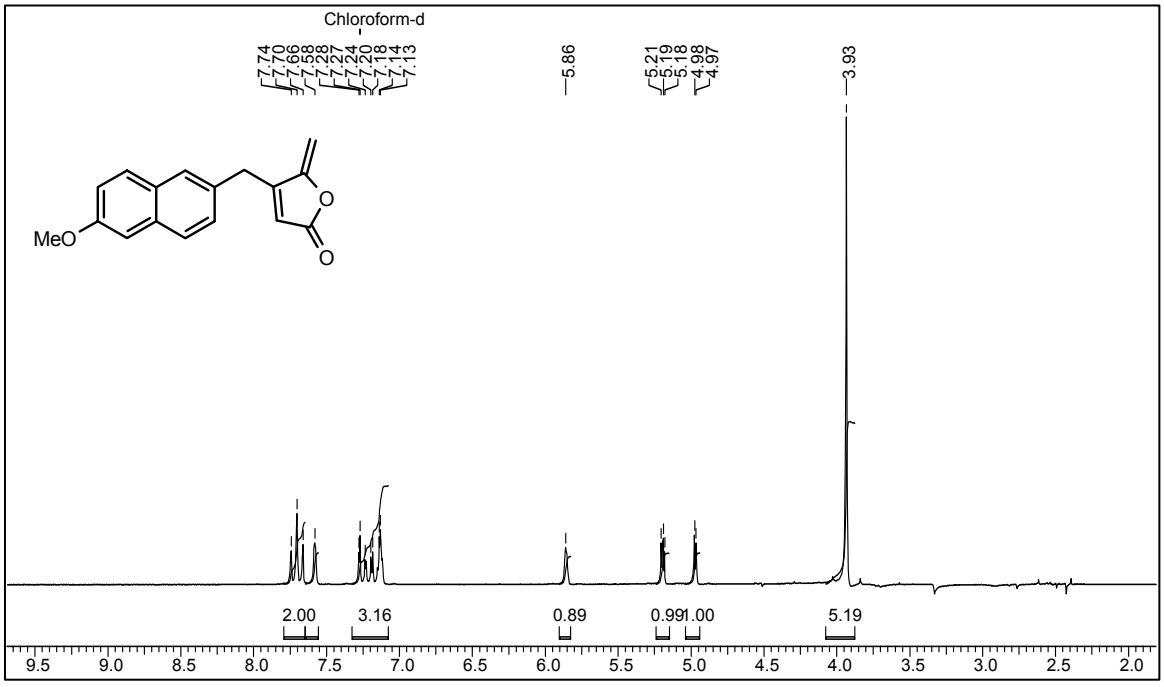
^{1}H NMR of compound 116t ($CDCl_3$, 200 MHz)



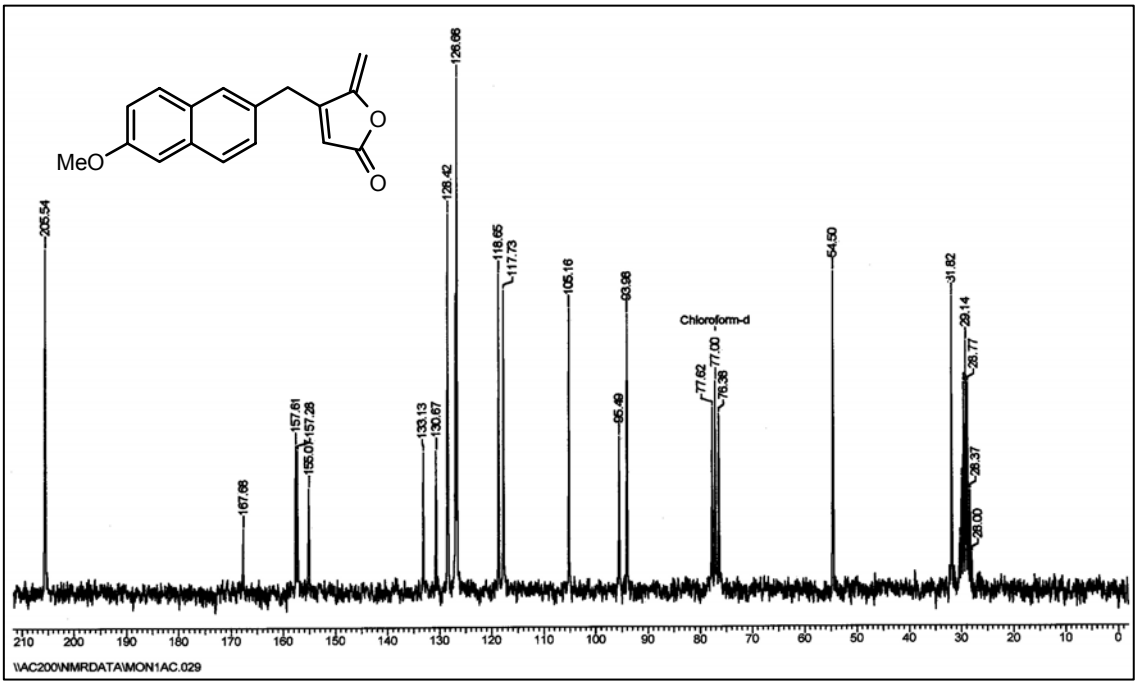
^{13}C NMR of compound 116t ($CDCl_3$, 50 MHz)

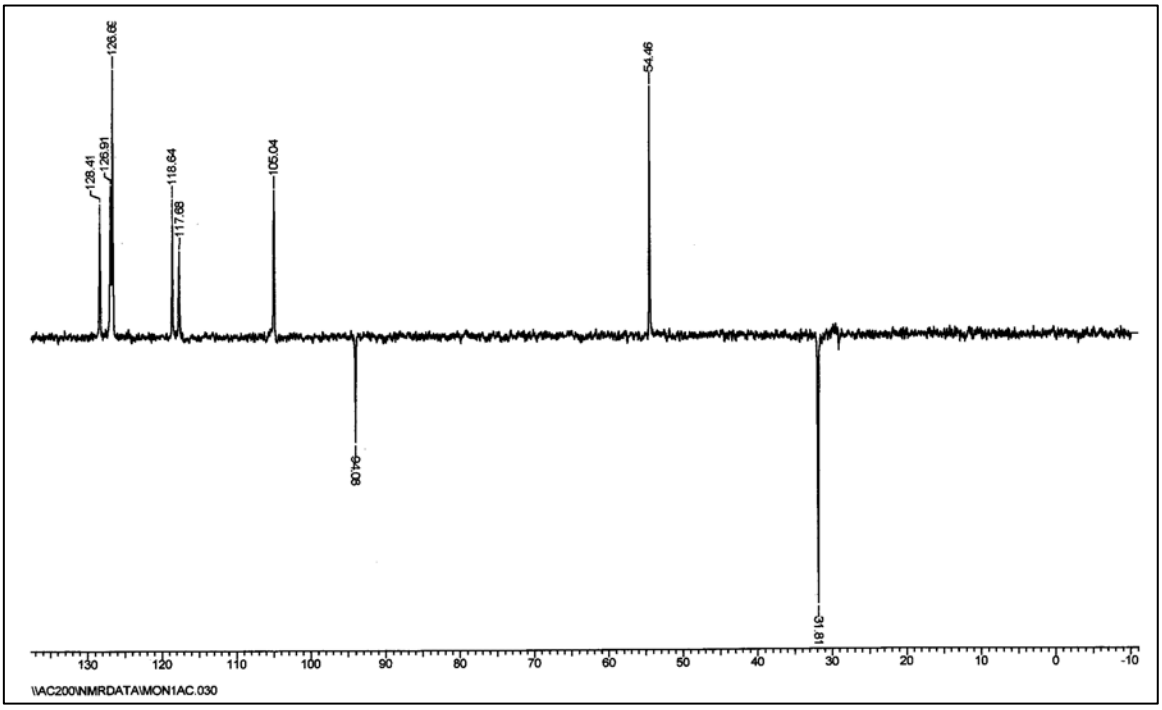


^{1}H NMR of compound 119t ($CDCl_3$, 200 MHz)

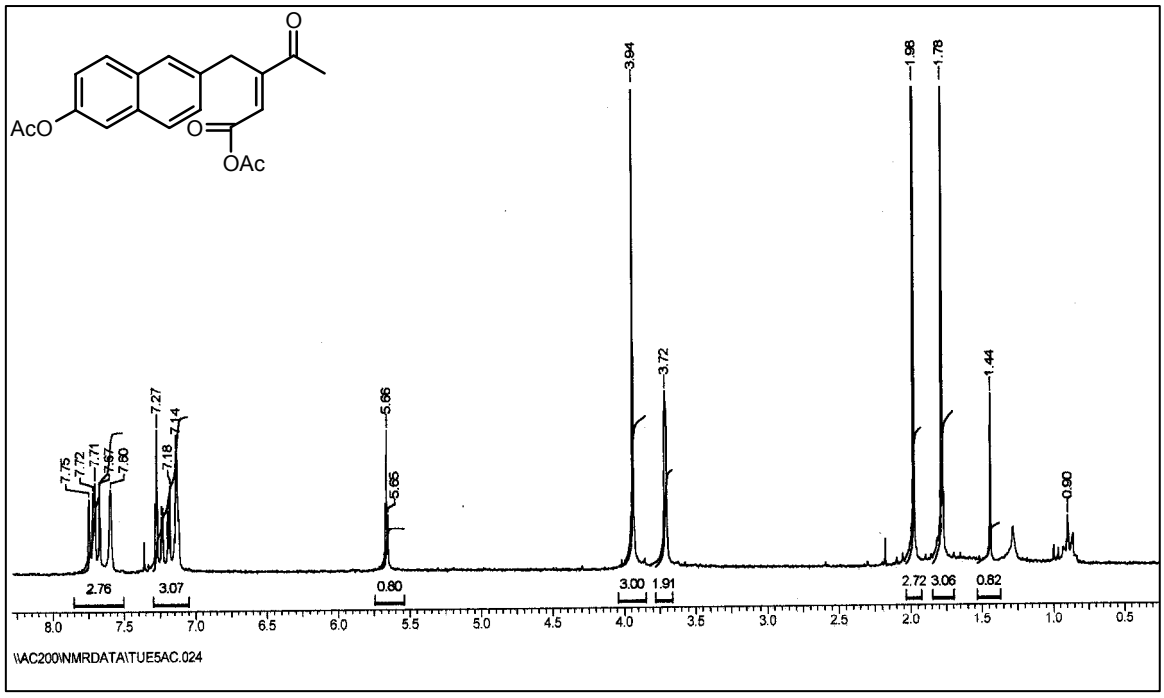


^{13}C NMR and DEPT of compound 119t ($CDCl_3$ +CCl_4, 50 MHz)

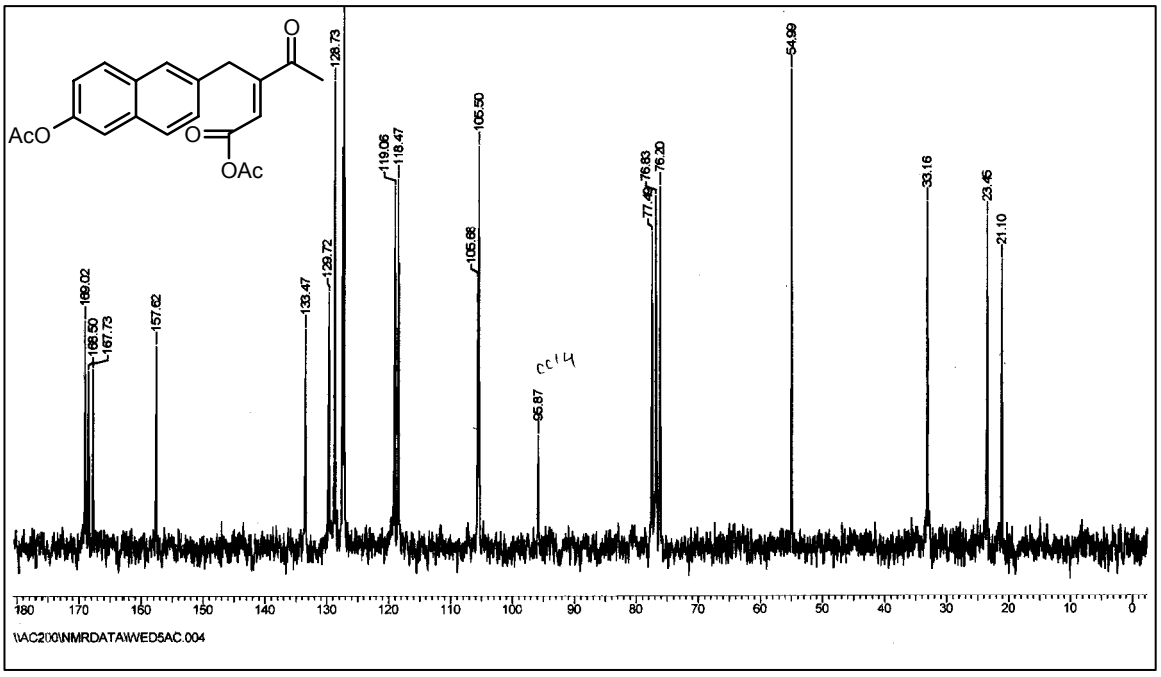




^{1}H NMR spectrum of compound 120t ($CDCl_3$+CCl_4, 200MHz)



^{13}C NMR spectrum of compound 120t ($CDCl_3$, 50 MHz)



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1.2.1. INTRODUCTION

Lignans form a well-known family of natural products characterized by two phenyl propane units bonded through C8-C8' bond. It is an important class that has retained interest of synthetic as well as medicinal chemists over 50 years.[1] Due to structural diversity lignans are classified according to presence of additional C-C bond other than C8-C8' bond; the bonding of phenyl propane unit other than C8-C8' is known as neolignan.[1a] They are classified as acyclic lignans, aryl naphthalene lignan derivatives and dibenzocyclooctene derivatives.

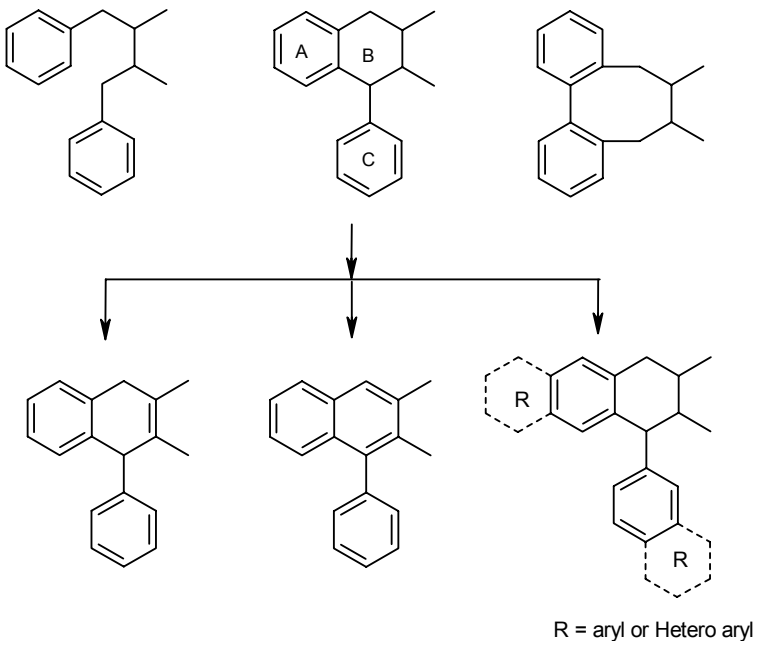


Figure 1. Classification of basic skeleton of lignan

The presented classification is according to variation in B ring and heterocyclic ring instead of phenyl ring unit. This classification does not fully cover all the types of derivatives but further extension is beyond the scope of present work.

Lignans are fairly widespread throughout the plant kingdom and have been documented in species belonging up to seventy-plant families. They have been identified in

pterydophytes, gymnosperms and angiosperms.[2] Their functions and ubiquitous distribution evidences their role in plant evolution, as the structure of lignans increases in complexity with the evolution of gymnosperms and angiosperms. They have been considered one of the earliest forms of defense to evolve in vascular plants as a *in planta*. Lignans occur in all parts of plants such as heartwood, roots, leaves, flowers, fruits and even seeds as well as secreted products. They are the secondary plant metabolites biosynthetically derived from the shikimate pathway. They play an important part in the defense mechanism of many plant species against pathogens and predators. Another significant role of lignans in certain species is in heartwood formation, since they affect color, durability and texture of the resulting wood.

Lignans display an important physiological role in human nutrition and medicine giving their extensive health protective and curative properties. Various roles in chemical defense such as fungicidal, bactericidal and insecticidal have been demonstrated for these secondary metabolites.[3] Biological activity of lignans have been studied in detail and a vast variety of lignans possessing antitumor, anti-HIV, antiviral, ability to influence nucleic acid metabolism, inhibition of enzyme, cathartic, allergenicity, piscicidal, toxicity to mammals, antimicrobial, fungistatic and germination inhibitory activity have been discovered.[4]

Among the lignan family; it is found that terahydronaphthalene lignans is an important class of compounds; podophyllotoxin is the exceptional example of this class. Podophyllotoxin is highly cytotoxic, acts as potent tubulin binding agent and is used in the treatment of genital warts while its semisynthetic analogue etoposide acts as topoisomerase II inhibitor. Accordingly many synthetic modifications have been reported in order to study the structure activity relationship in comparison with the natural compound (Figure 2).[5]

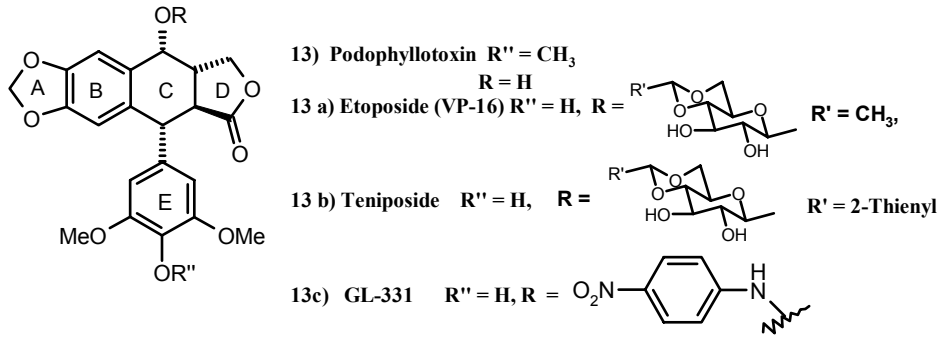
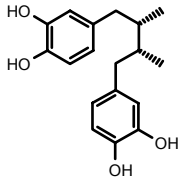
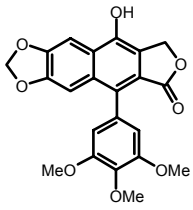
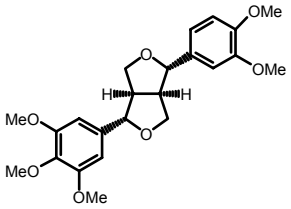
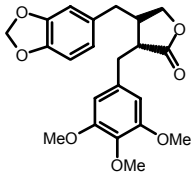
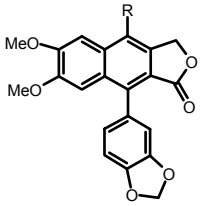
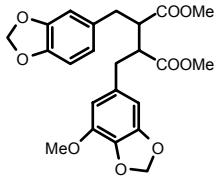


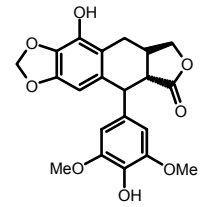
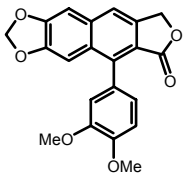
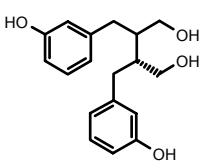
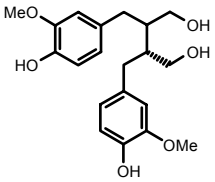
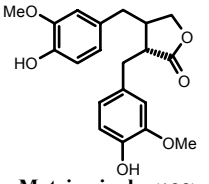
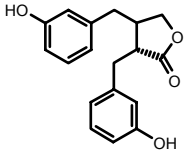
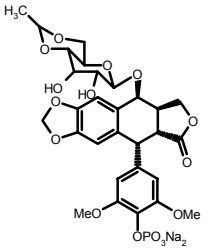
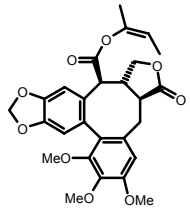
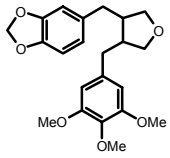
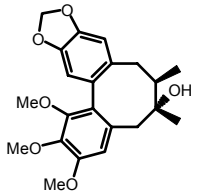
Figure 2. Podophyllotoxin and its synthetic analogues

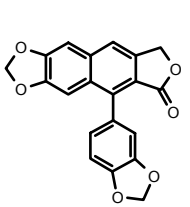
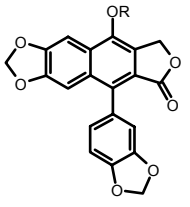
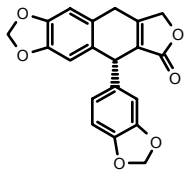
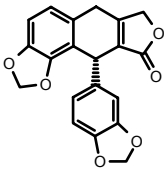
Consequently, lactone ring D modifications have been reported in literature to avoid the undesired *trans* to *cis* C/D ring fusion epimerization and to enhance the stability of D-ring. Transformation of the podophyllotoxin lactone D-ring into *trans*-fused cyclopententane,[6] tetrahydrofuran, tetrahydrothiophene or *δ*-lactone gave stable compounds, in some cases the biological activity was lost whereas several modifications have become fruitful.[7]

1-Aryl naphthalene lignans and 1,4-dihydronaphthalene lignans (*β*-apolignan) form another important class of lignan family. Most of these naturally occurring lignans possess lactone moiety in their structure.[8] The plant genus *Justicia* (*acanthaceae*) consist of about six hundred species and are reach source of lignans. The plants are used as folk medicine for the treatment of fever; pain, cough and some are used for pulmonary infections.[9] Isolated lignan derivatives from these plant sources exhibit wide range of biological activities[10] such as cytotoxic,[10a] piscidal,[10b] antiviral,[10c] antiplatelet,[10d] leukotriene biosynthesis inhibitory[10e] and phospodiesterase inhibitiory activities (anti asthmatic activity).[10f] Therefore this class of compound has received wide attention for their construction. Some of them are enlisted in Table 1.

Table 1. Lignans and their bioactivity[4]

Entry	Naturally occurring Lignans	Source	Activity
1	 **Nonhydroguaiaric acid (122)**	*Larrea tridentate*	Used as antioxidant in foodstuff. Used to enhance functioning of kidney.
2	 **Dehydropodophyllotoxin (123)**	*Podophyllum hexandrum*	Fungicidal activity against: i) *Epidermatophyton floccosum*, ii) *Curularia lunata*, iii) *Nigrospora oryzae, Microsporium canis*.
3	 **(+)- Epimagnolin (124)**	*Magnolia fargesii*	Insecticidal activity: *D. melanogaster larvae*
4	 **Burseherinin (125)**	*Brusera microphylla*	Antinematodes: Inhibits hatching of potato cyst nematodes *Globodera pallida*
5	 **R = OMe Justicidin A (126)** **R = H Justicidin B (127)**	*Justicia hayatai ver. De cumbens*	Antidefendant / Toxic: Flour beetles and granary weevil; Used as a fish poison
6	 **Rhinacanthin F (128)**	*Rhinacanthaceae*	Antiviral: influenza type A virus

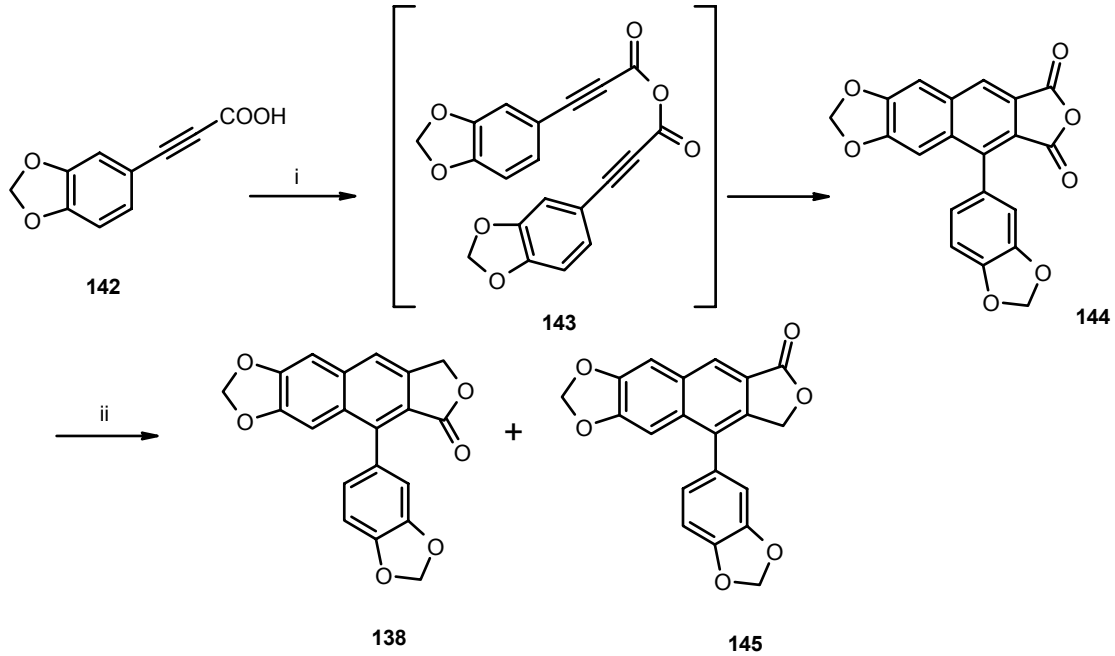
7	 **(-)α-Peltatin (129)**  **Retrojusticidin B (130) and Podophyllotoxin (13)**	*Juscticia*	Anti viral: Anti HIV 1 activity
8	 **Enterdiol (131)**  **(-) Secoisolariciresinol (132)**  **Matairesinol (133)**  **Enterolactone (134)**	*Juscticia hyssopifolia*	Health protection and anti breast and prostate cancer: Protecting against the inhibition of various sexharmone-iduced cancers. They bind with 50% of circulating testosterone in men and 80% of oestrogen in women.
9	 **Etoposide phosphate (135)**  **(-) Steganangin (14)**  **Burseran (136)**	14: *Steganotaenia araliacea* 136: *Brusera microphylla*	Antitumor activity: Ability to form stable tertiary complex with topoisomerase II and breaking of DNA strand in G2 phase as well as microtubule inhibitor.
10	 **Gomsin A (137)**	*Schizandra chinesis* Fruit	Protects liver from hepatotoxic compound such as CCl_4, galctosam lipopolysaccharides, useful in liver regenaration, prevents muscular damage due to excessive exercise

Entry	Naturally occurring Lignan	Sourse	Activity
11	 **Justicidin E (138)**  **R = H, Taiwanin E (139) R = Me, Taiwanin E methyl ether (140)**  **1,4-Dihydrotaiwanin C (140a)**  **Jusneesiin (141)**	*Justicia nessi*	Miscellaneous bioactivity: Phoshodiestrase ester, Anti inflamentry, antiasthmatic, antidepressant

Various methods have been developed for the synthesis of the aryl naphthalene lignan skeleton. These are classified by the key reaction of strategy, intramolecular or intermolecular Diels-Alder reactions, biaryl-coupling reactions; conjugate addition reaction and benzannulation reaction. These approaches are briefly described as follows.

The first approach involving intramolecular Diels-Alder reaction of an acetylenic acid anhydride **143** derived from acetylenic acid [11] is illustrated by the synthesis of justicidin E (**138**) and taiwanin C (**145**) as depicted in Scheme 1.

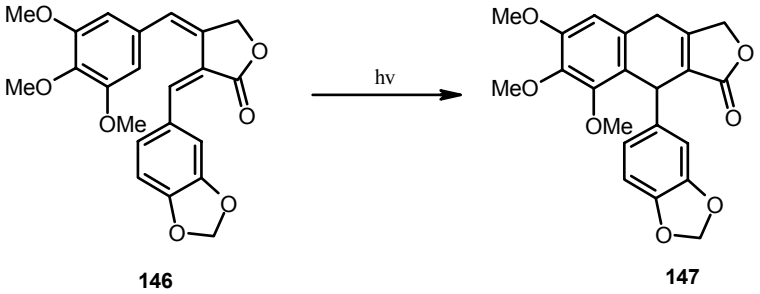
Scheme 1. *J. Org. Chem.* **1971**, *36*, 3450-3452.



Reagents and conditions: (i) Ac_2O, refulx, 4h; (ii) LAH, THF, reflux, 12h, Ag_2CO_3-celite, benzene, reflux, 5h.

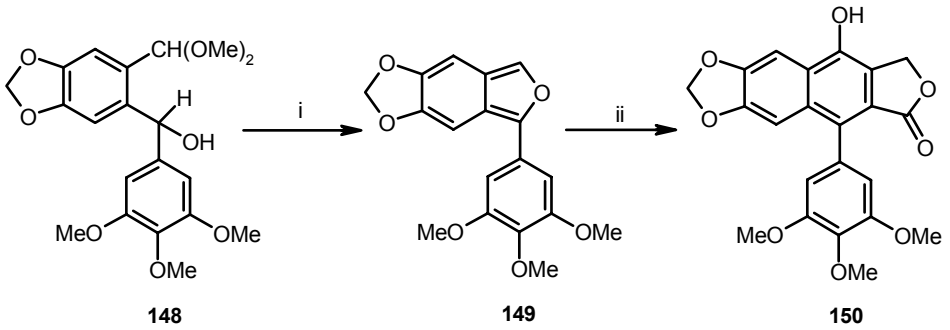
Cyclization of the (*E,E*)-α,β-bisbenzylidene-γ-lactones **146** (Scheme 2) and corresponding lactones has been achieved photochemically to afford 1, 4-dihydronaphthalene lignan derivatives **147**.[12]

Scheme 2. *J. Chem. Soc. Chem. Commn.* **1976**, 50-52.



Another elegant application, of Diels-Alder reaction for the synthesis of naphthalene lignan involved the generation of an isobenzofuran **149** and its reaction with dimethyl acetylene dicarboxylate (DMAD) affording dehydropodophyllotoxin **150**[13] as shown in Scheme 3.

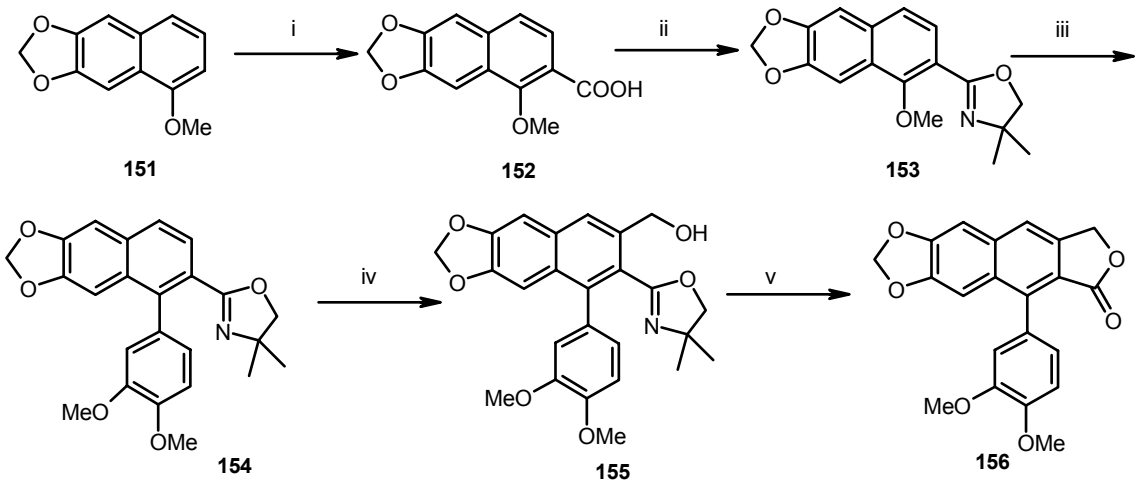
Scheme 3. *J. Chem. Soc. Chem. Commn* **1980**, 354-357.



Reagents and conditions: (i) H^+, (ii) (a) DEMAD, TsOH; (b) BH_3, Me_2S.

Meyers and Avila reported[14] applications of aryloxazoline derivatives to the synthesis of lignan lactones as depicted in Scheme 4. Oxazoline derivative of *ortho*-methoxy benzoic acid **153** reacted readily with nucleophile displacing the methoxy group leading to form ortho substituted biaryl oxazoline derivative **154**, which on functional group transformation led to lignan lactone **156**.

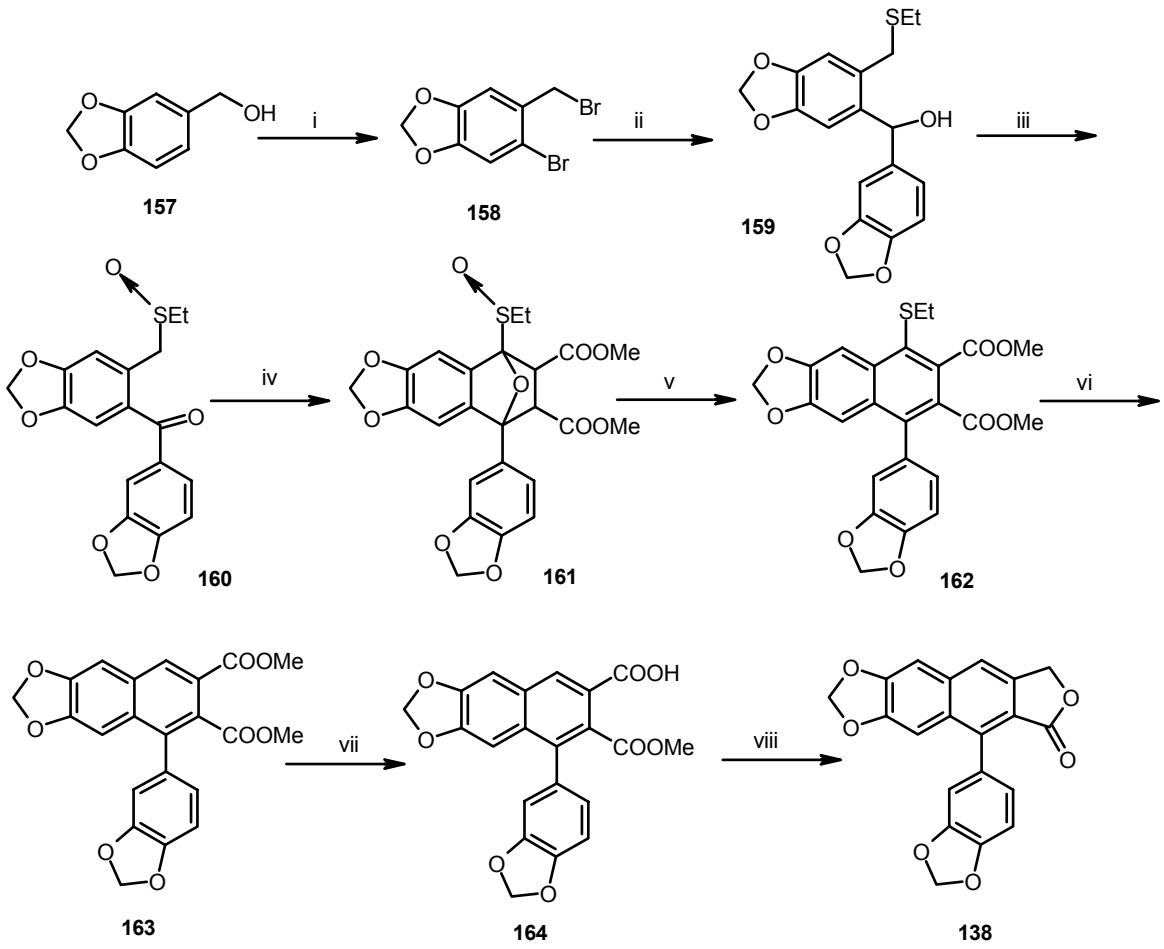
Scheme 4. *J. Org. Chem.* **1981**, *46*, 3881-3886



Reagents and conditions: (i) *n*-BuLi, CO_2, -78 °C; (ii) (a) $SOCl_2$, reflux; (b) 2-Amino-2-methyl propanol, DCM, 74 %; (iii) 4-Bromo-veratrole, *n*-BuLi, THF, -78 ° C, 4h, 90 %; (iv) *s*-BuLi, DMF, $NaBH_4$, 94.4 %; (v) 6N, HCl, rt, 6h, 93%.

Albert Padawa and co workers reported[15] synthesis of justicidin E (**138**) and several 1-aryl naphthalene lignans based on tandem Pummerer-Diels-Alder reaction sequences as depicted in Scheme 5.

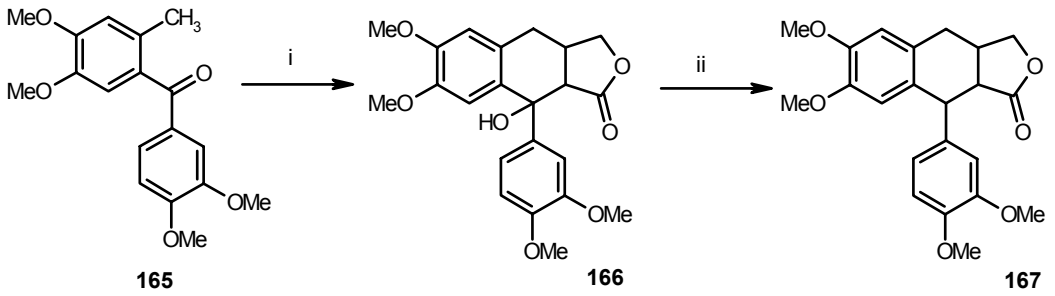
Scheme 5. *J. Org. Chem.* **1995**, *60*, 3938-3939.



Reagents and conditions: (i) Br_2, HOAc; (ii) (a) EtSH; (b) *t*-BuLi, Pipernaldehyde; (iii) MnO_2, $NaIO_4$, (iv) Ac_2O, dimethyl maleate (v) H^+; (vi) Ra (Ni); (vii) $KOSiMe_3$; (viii) $LiEt_3BH$.

Kobayashi and coworkers reported conjugate addition reaction[16] of o-aroylbenzyllithiums with furan-2-(*5H*)-one to afford cyclized product which on dehydration and aromatization afforded 1-aryl naphthalene lignans **167** as shown in Scheme 6.

Scheme 6. *J. Chem. Soc. Perkin Trans. 1* **1995**, 3013-3016.

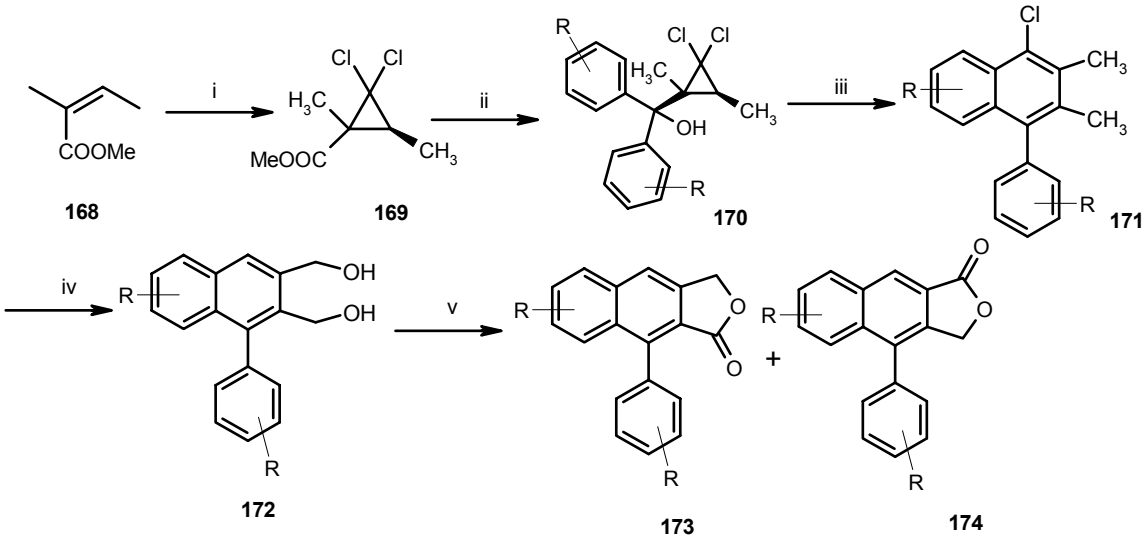


165 **166** **167**

Reagents and conditions: (i) (a), LDA, - 78 ˚C. THF; (b) furan-2-(5*H*)-one; (ii) (a) $SOCl_2$, pyridine, $CHCl_3$, room temp; (b) 10%, Pd-C, p-cymene, reflux.

Benzannulation approach[17] involved construction of the 4-aryl-1-chloro-2,3-dimethylnaphthalene skeleton **171** as the key step (Scheme 7). Dichlorocarbene addition with methyl-angelate **168** gave the gem-dichlorocyclopropyl ester **169**, which on further transformations gave mixture of lignans **173** and **174**.

Scheme 7. *J.Chem. Soc. Perkin Trans. I*, **1996**, 2157-2165.



168 **169** **170** **171**

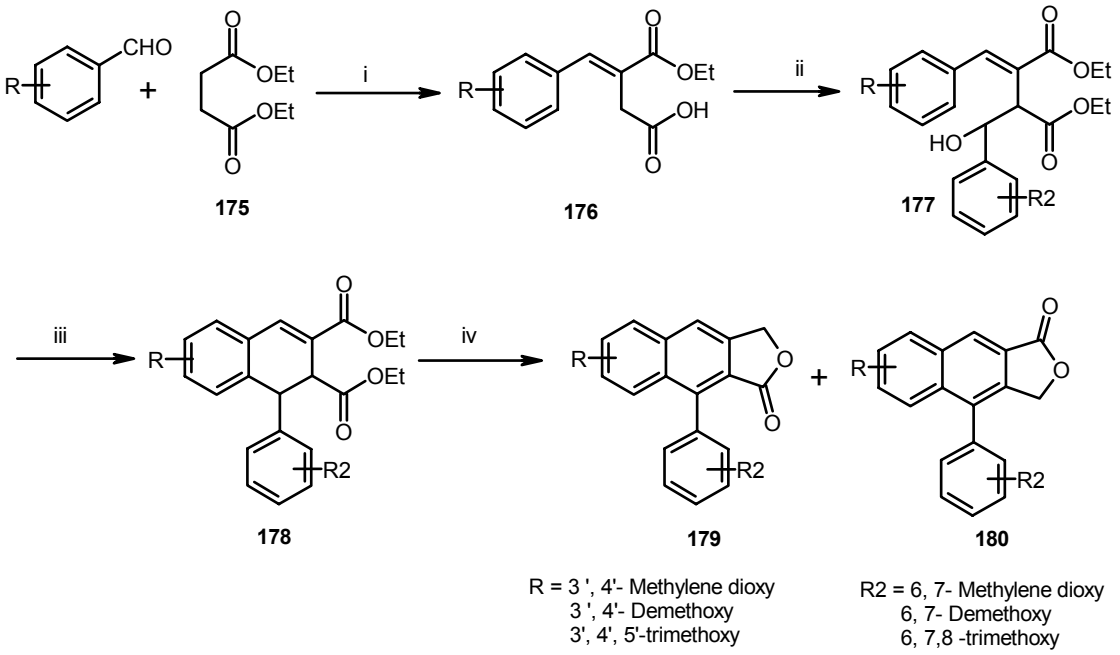
172 **173** **174**

Reagents and conditions: (i) $CHCl_3$, 50% aq. NaOH, cat. $PhCH_2\ N^+\text{-}Et_3Cl^-$; (ii) 3,4-(-$OCH_2O$-)$C_6H_3$,Li; (iii) $SnCl_4$, (0.1 equiv.), MS 4 Aº; (iv) $LiAlH_4$,-$TiCI_4$; v) 2 NBS; (vi) $AgNO_3$, aq. NaOH; (vii) Fetizon's reagent.

Recently Cow and coworkers reported[18] synthesis of aryl dihydronaphthalene lignans. It involved classic Stobbe condensation of diethyl succinate **175** with substituted aryl

aldehydes. The crude monoacid **176** was esterified to diethyl ester followed by treatment with benzaldehyde in the presence of LDA to give hydroxy derivative which on cyclization, aromatization and reduction afforded mixture of naturally occurring lignans **179** and **180** as shown in Scheme 8.

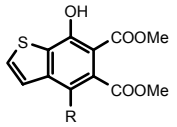
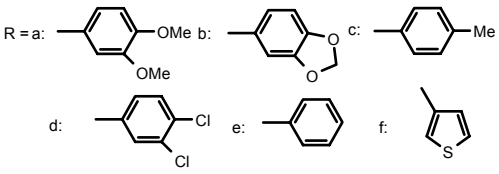
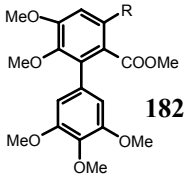
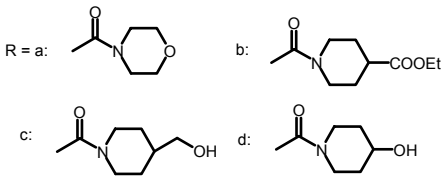
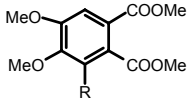
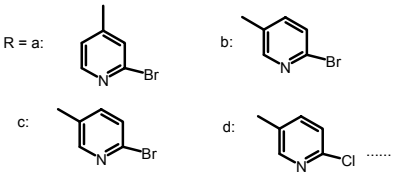
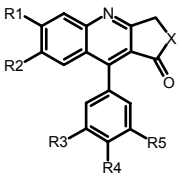
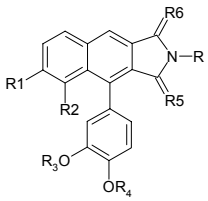
Scheme 8. *Can. J. Chem.* **2000**, *78*, 554-561.



Reagents and conditions: (i) *t*-BuOK, t-BuOH; (ii) (a) Conc. H_2SO_4, EtOH; (b) LDA, Ar-CHO (iii) Trifluoroacetic acid, DCM, rt; (iv) DDQ, toluene, reflux, 2-5 h; (v) LiCl, $NaBH_4$, MeOH.

Due to the structural simplicity and attractive wide range of biological activity, aryl naphthalene lignan class became field of choice for organic as well as medicinal chemists for their synthetic studies and structure activity relationship studies. **Table 2** comprises selected examples of synthetic lignan analogues and their biological acitivity.

Table 2. Lignan analogues and their biological activity

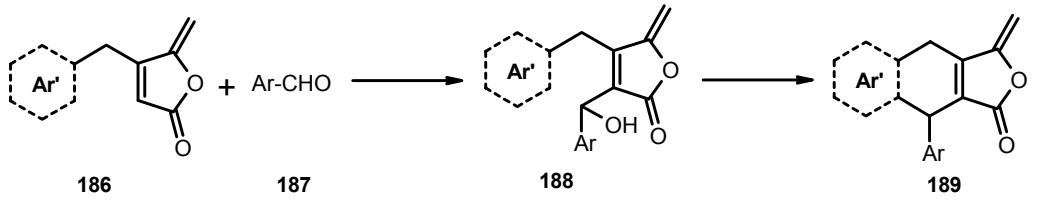
Entry	Synthetic lignan analogues (Text number)	Selected functional groups (R)	Screened bioactivity	Ref.
1	 **181**		Antihyper-lipidimic	19
2	 **182**		Phoshodiest erase Inhibitor	20
3	 **183**		Phospho-diesterase Inhibitor	21
4	 **184**	R1, R2= OCH_2O R3 = OMe, R4= OMe, R5 = OMe R3 = OMe, R4= H, R5 = H R3 = OMe, R4= OMe, R5 = H X = O, CH_2	Antihyper-lipidimic	22
5	 **185**	R = H, CH_3, (CH_2) OBn, (CH_2) OH R1,R2= OCH_2O R3 = R4= CH_2, CH_3 R5 = CO / CH_2 R6 = CO / CH_2	Antiviral activity	23

1.2.2. PRESENT WORK

Literature survey revealed the importance of lignans and their derivatives from medicinal as well as synthetic point of view. Huge amount of derivatization has been reported in case of podophyllotoxin and other lignan derivatives, however derivatization of naphthalene lignans have attracted relatively less attention in view of their structure activity relationship studies. It was observed that lignans with antitumor activity exhibit the following common features: (i) five memebered lactone ring (ii) a 3,4,5-trimethoxy phenyl group and (iii) two substituted phenyl groups separated by a four carbon chain.

From the preceding synthetic endeavor of γ-methylenefuranone synthesis described in Section 1; it was envisaged that γ-methylenefuranone could be utilized for the synthesis of novel lignan derivatives. Accordingly we proposed synthetic strategy for the synthesis of lignan analogues commencing from the γ-methylenefuranone as depicted in Scheme 9.

Scheme 9. Proposed synthetic plan for 1,4-dihydronaphthalene lignan analogues



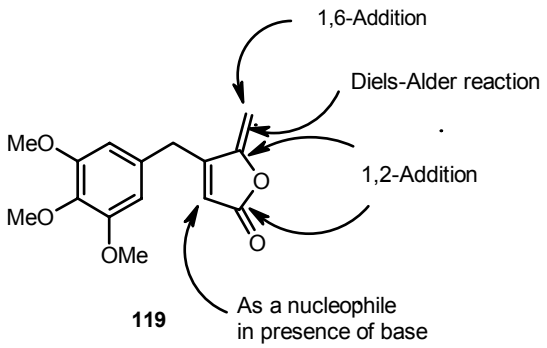
Ar'= substituted phenyl and naphthyl groups

Ar-CHO = substituted benzaldehydes, α-naphthaldehydes, β-naphthaldehydes

It was assumed that the generation of α-vinylic carbanion on the lactone followed by the reaction with various aldehydes should result in the formation of carbinol **188** (hydroxy lignans). Cyclization of these hydroxy lignans **188** under either acidic or basic condition for C-C bond formation should lead to the cyclic lignan lactones **189** to generate a library of wide variety of novel lignan derivatives. Before commencing with derivatization of furanone we considered its active sites for further synthetic application. γ-Methylenefuranone has four active sites for different reactions as shown in Figure 7. Generation of a vinylic carbanion on α-carbon of furanone ring should be possible by selection of a base. It was expected that basic conditions could disturb the framework of γ-methylenefuranone by opening lactone ring during reaction and workup conditions.

Therefore it was quite important to select a base, which could generate α-vinylic carbanion without affecting skeleton of furanone under reaction conditions and also in workup conditions.

Figure 7. Active sites of γ-methylenefuranone



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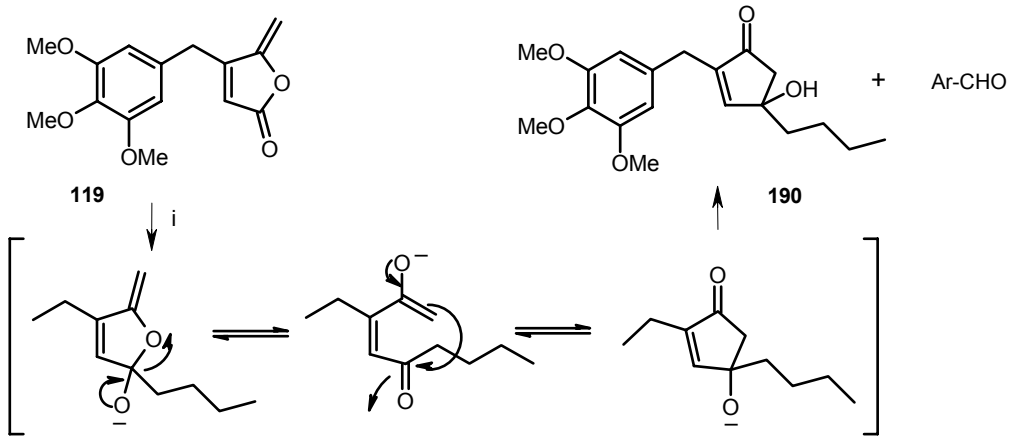
1.2.3. RESULTS AND DISCUSSION

Part A: Analogues of 1,4-dihydronaphthalene lignans

We selected furanone derivative synthesized from 3,4,5-trimethoxy benzaldehyde **114a**, i.e. 5-methylene-4-(3,4,5-trimethoxybenzyl)-2(5*H*)furanone (**119a**) since 3,4,5-trimethoxy phenyl moiety is most common in naturally occurring biologically active compounds.

In order to select an appropriate base we initially treated furanone **119a** with n-butyl lithium followed by addition of benzaldehyde. It was observed that benzaldehyde remained unreacted while the furanone got converted into new product. This product was identified as the compound **190,** indicating that 1,2-addition of butyl group on the lactone carbonyl group followed by ring opening and ring closing reactions to give 4-hydroxy-4-butyl cyclopentenone derivative **190** (45%) in one step as depicted in Scheme 10. Structure of cyclopentenone derivative was fully confirmed by spectroscopic techniques. This reaction was repeated in absence of 3,4,5-trimethoxybenzaldehyde to confirm the formation of product **190**.

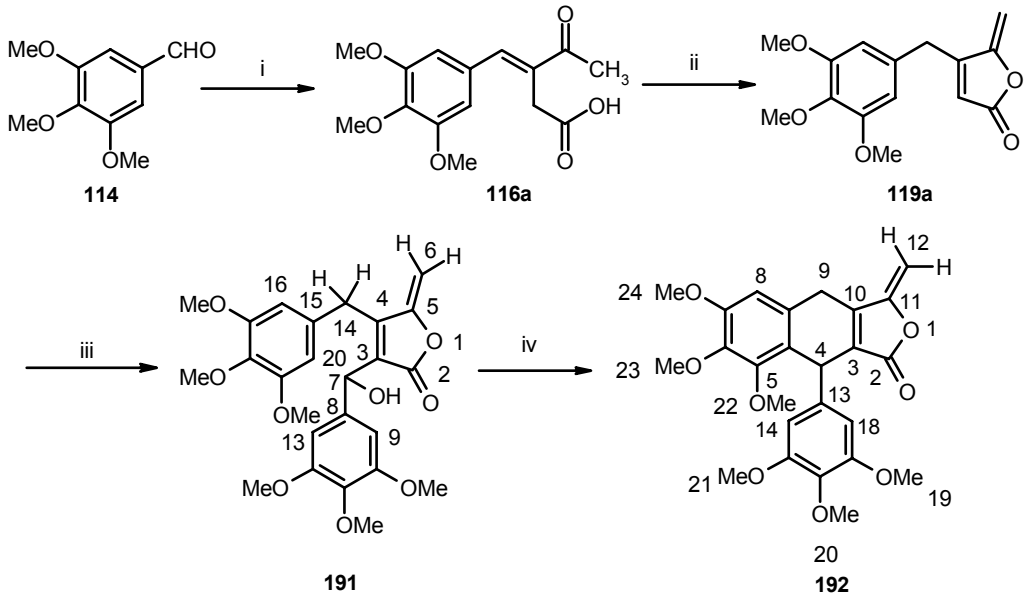
Scheme 10.



Reagents and conditions: (i) (a) n-BuLi, THF, -78°C; (b) Ar-CHO, THF, -78°C, 1h.

LDA[24] was found to be the best choice to generate α-vinylic carbanion selectively of furanone **119a**; which reacted with 3,4,5-trimethoxy-benzaldehyde **114a**; at -78°C in presence of LDA to form carbinol **191.** The product was characterized as acyclic hydroxy lignan derivative (**191**, Scheme 11). It was characterized as all spectroscopic methods.

Scheme 11.



Reagents and conditions: (i) Ethyl levulinate, aq. NaOH, ethanol, -10˚C, 4-5 h, (ii) Anhydr. sodium acetate, acetic anhydride, 80-90 ˚C; (iii) LDA, 3,4,5-Trimethoxybenzaldehyde, -78 °C, 45%; (iv) TFA, dichloromethane, 1.5h rt, 83%.

IR spectrum of compound **191** showed absorption at 3515 cm^{-1} indicating the presence of hydroxy group, while absorption at 1766 cm^{-1} confirmed the presence of carbonyl function of lactone ring.

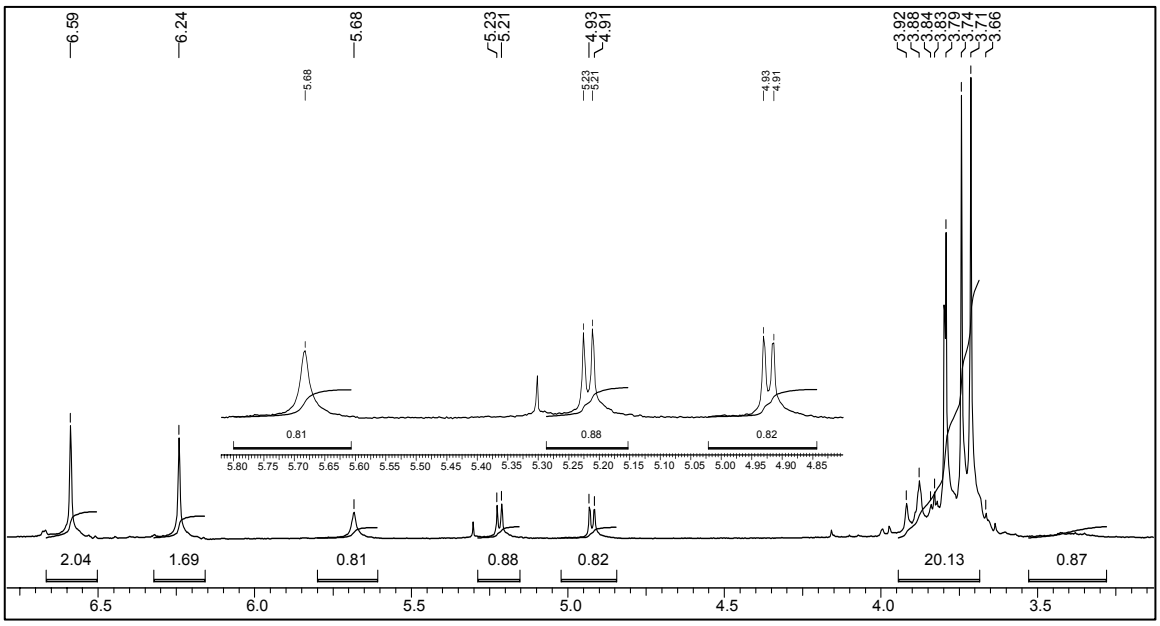


Figure 8. ^{1}H NMR of hydroxy lignan 191

^{1}H NMR of **191** showed the presence of 6 methoxy groups, which appeared as singlets at δ 3.71, 3.74 and 3.79 integrating for six protons each. Multiplet for two protons between δ 3.80-3.92 was assigned for benzylic proton at C14. Doublet centered at δ 4.92 (J = 2.3 Hz) and another doublet centered at δ 5.22 (J = 2.3 Hz) integrating for one proton each indicated the presence of *exo*-methylene moiety. Broad singlet at δ 5.68 integrating for one proton was assigned for methine proton at C7 indicating the formation of carbinol. Singlets at δ 6.24 and 6.59 integrating for two protons each were assigned for aromatic protons on (C16 and C 20) and (C9, C13) respectively. The ESI mass gave molecular ion peak at 472 (M^{+}).

Carbinol **191** was initially treated with PTSA in refluxing toluene to afford cyclized product **192** however the reaction proceeded with very slow rate and poor yield. Subsequently cyclization was carried out using mesyl chloride in the presence of NEt_3 at 0 °C in dry dichloromethane to afford the cyclized product **192**.

Same conversion was achieved with better yield in the presence of trifluoroacetic acid in dry dichloromethane at room temperature. 1,4-Dihydronaphthalene lignan **192** was characterized by all spectroscopic techniques. IR spectrum of cyclized lignan **192** showed carbonyl stretching at 1768cm^{-1} indicating the presence of lactone carbonyl. ^{1}H NMR showed benzylic proton on C9 as a multiplet in the region of δ 3.77-3.91 and disappearance of singlet at δ 5.68 and appearance of broad triplet centered at δ 5.21 integrating for one proton confirmed the formation of cyclized product.

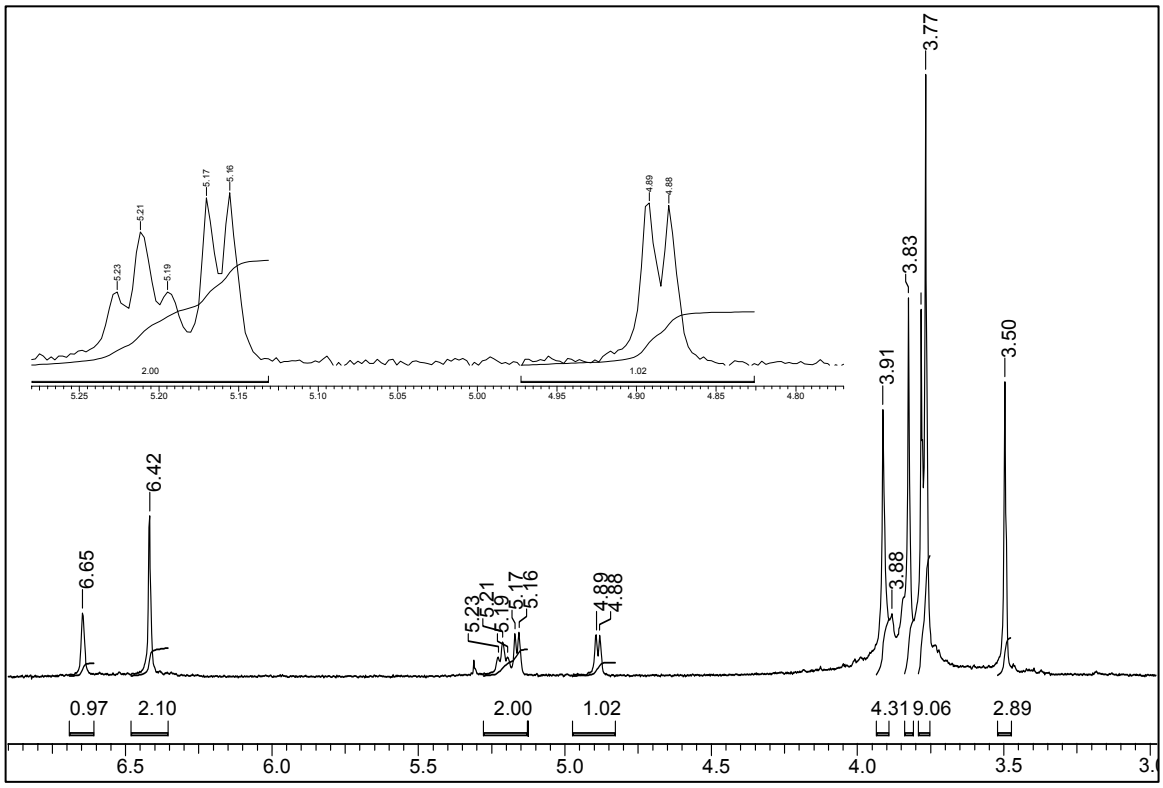


Figure 9. ^{1}H NMR of cyclic lignan 192

In addition, the connectivity of proton was identified with the help of COSY and NOESY experiments. A COSY correlation spectrum showed connectivity between protons H4 with benzylic protons H9 through five bonds (Figure 10).

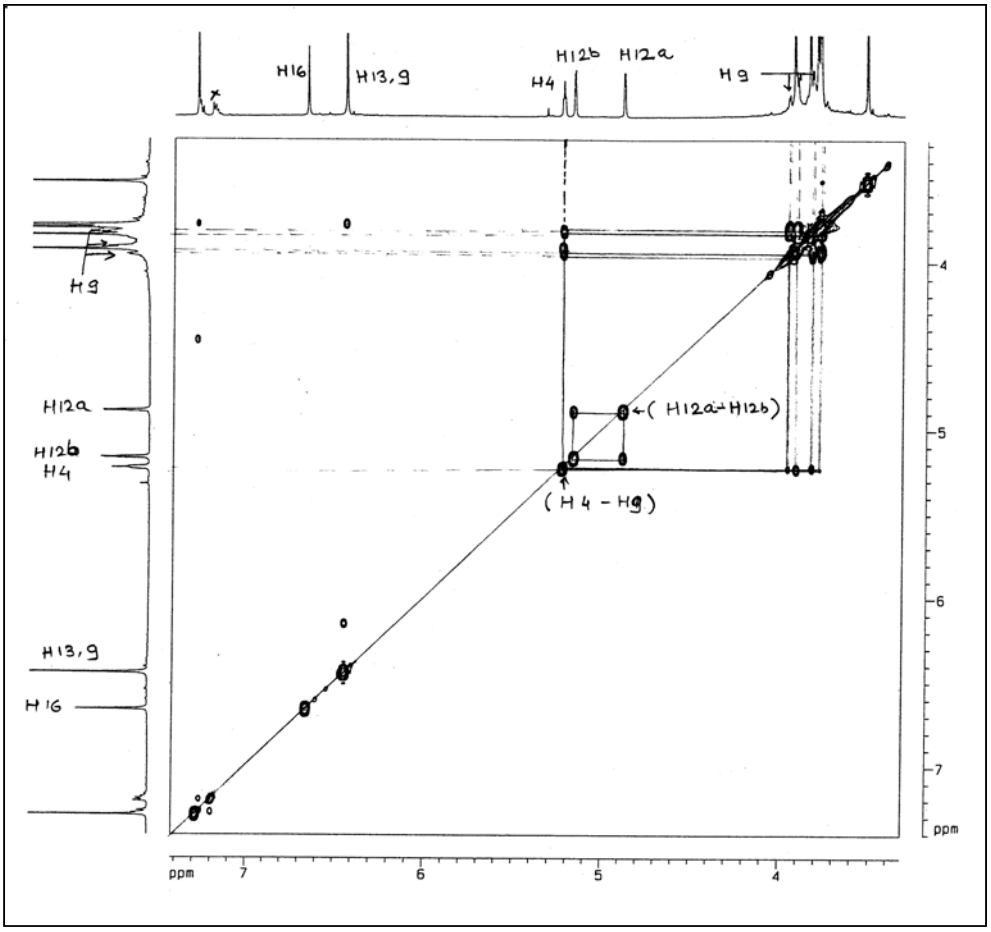
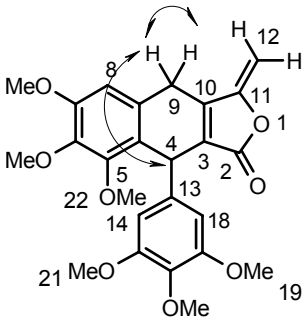
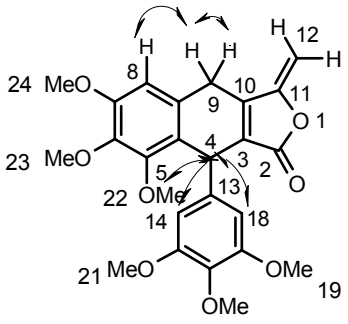


Figure 10. COSY Spectrum of 192



COSY correlations



NOESY correlations

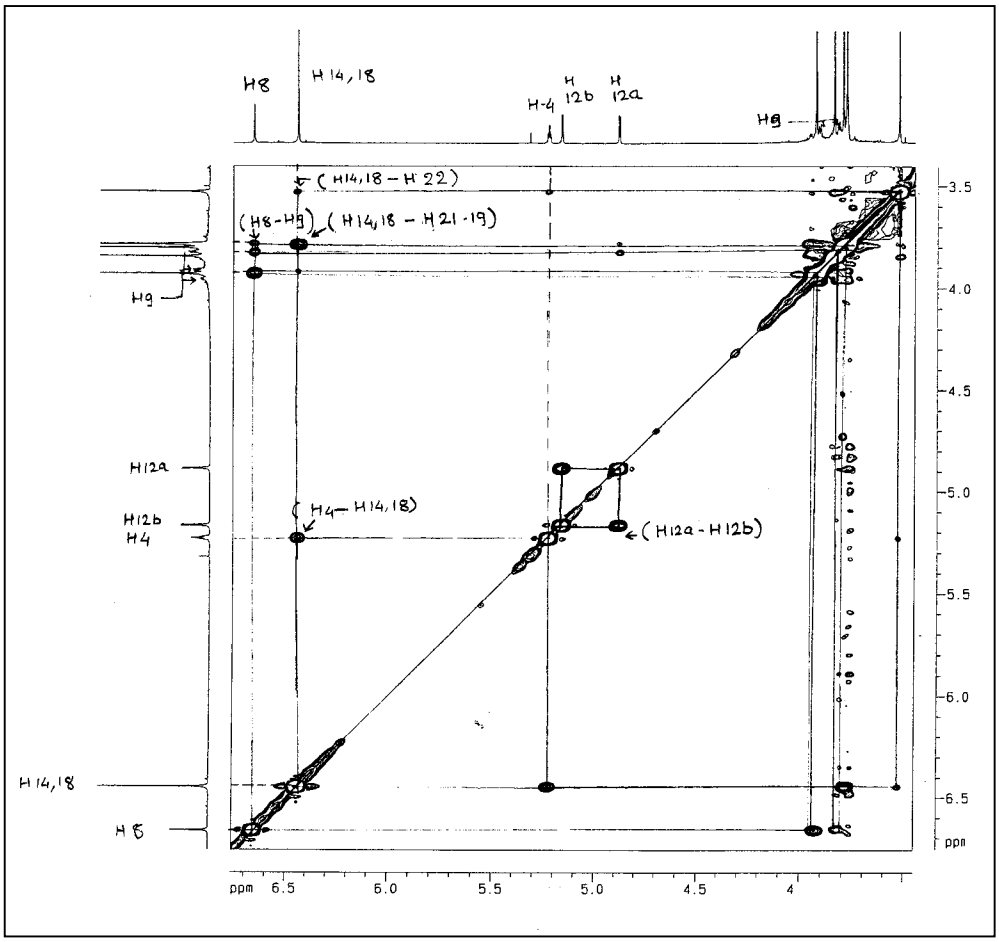
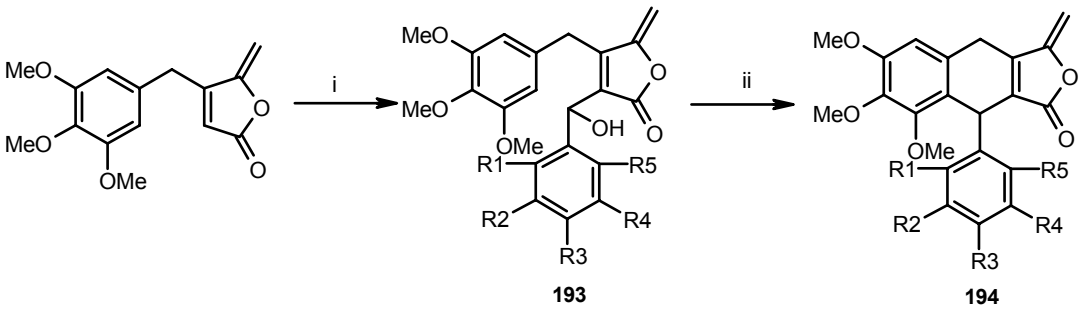


Figure 10. NOESY spectrum of 192

NOESY correlation spectrum showed through space correlation between aromatic proton H8 and benzyllic protons H9, and two aromatic protons H14 and H18 couple with proton H4 i.e. they are in the close vicinity. These results confirmed the structure of cyclized product. Utilizing this synthetic strategy other acyclic hydroxy and 1,4-dihydronaphthalene lignan derivatives were synthesized as shown in Scheme 12. All derivatives were characterized by spectroscopic methods. The various acyclic and cyclic lignans synthesized by this strategy have been presented in Table 3.

Scheme 12.



Reagents and conditions: (i) Substituted benzaldehydes, LDA, -78 °C; (ii) TFA, dichloromethane, rt.

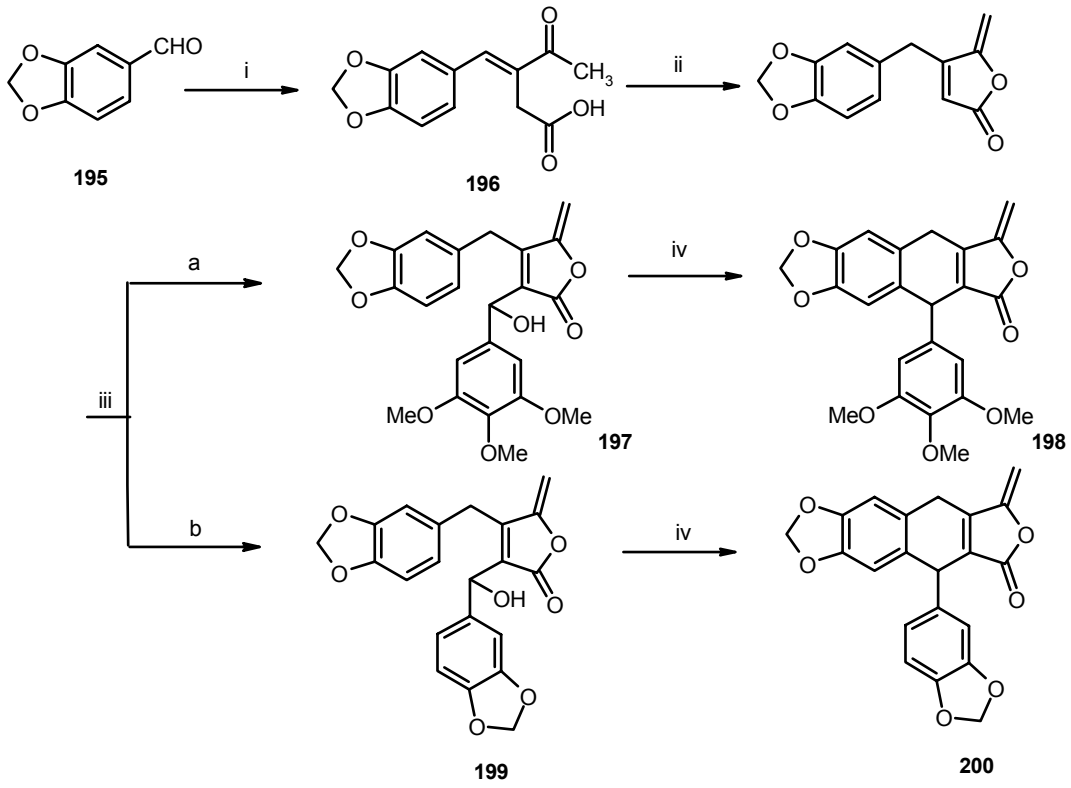
Table 3. Acyclic and cyclic lignan analogues

Entry	R1	R2	R3	R4	R5	Acyclic Comp. No.	Cyclic Comp. No.
1	H	OH	OCH_3	H	H	**193 a**	**194 a**
2	H	OCH_2O		H	H	**193 b**	**194 b**
3	H	OCH_2O		OCH_3	H	**193 c**	**-**
4	H	NO_2	OCH_3	H	H	**193 d**	**-**

Synthesis of deoxydehydropodophyllotoxin and 1,4-dihydrotaiwanin C analogues

To study the versatility of our synthetic strategy we planned synthesis of deoxydihydropodophyllotoxin and 1,4-dihydrotaiwanin C analogues. At the inception of the synthesis, furanone **119 g** (Section 1, Table 1, Entry 7), synthesized from piperonaldehyde and ethyl levulinate, was treated with 3,4,5-trimethoxy benzaldehyde in presence of LDA to give hydroxy lignan derivative. The product **197** on cyclization in the presence of trifluoroacetic acid afforded deoxydehydropodophyllotoxin **198** in good yield as depicted in Scheme 13. Similarly 1,4-dihydrotaiwanin C analogue **200** was achieved by employing 3,4-methylenedioxy benzaldehyde in the above two step sequence from **119g** as showed in Scheme 13. The ^{1}H NMR spectrum of 1,4-dihydrotaiwanin analogue **200** clearly showed the long range coupling between the proton at ring junction C4 and benzylic proton at C9.

Scheme 13.

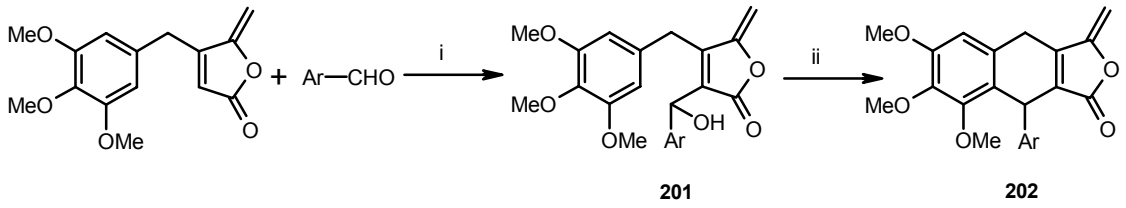


Reagents and conditions: (i) Ethyl levulinate, aq. NaOH, ethanol, -10˚C, 4-5 h, (ii) Anhydrous sodium acetate, acetic anhydride, 80-90 ˚C, 3h; (iii) (a) 3,4,5-Trimethoxybenzaldehyde, LDA, -78 °C, 1.5h, 55%; (b) 3,4-Methylenedioxy benzaldehydes, LDA, -78 °C, 1.h 52%; (iv) TFA, dichloromethane, rt, 2h, **198** (85%), **200** (82%)

Part B: Naphthalene analogues of 1,4-dihydronaphthalene lignan

A large number of variations have been introduced in 8-8'*bis*-phenyl propane unit, but very little attention has been directed towards the replacement of phenyl ring unit by naphthalene unit. Owing to the promising cytotoxicity for the naphthalene furanone derivatives it was felt necessary to replace phenyl ring unit with naphthalene to achieve naphthalene analogue of lignans with *exo*-methylene furanone moiety. Some naphthalene analogues were synthesized by using naphthaldehydes instead of benzaldehydes. Scheme 14 and the Table 3 depict the naphthalene analogues prepared for SAR studies starting from the furanone **119a** and corresponding naphthaldehydes.

Scheme 14.



Reagents and conditions: (i) LDA, Substituted naphthaldehydes, -78 °C; (ii) TFA, dichloromethane, rt.

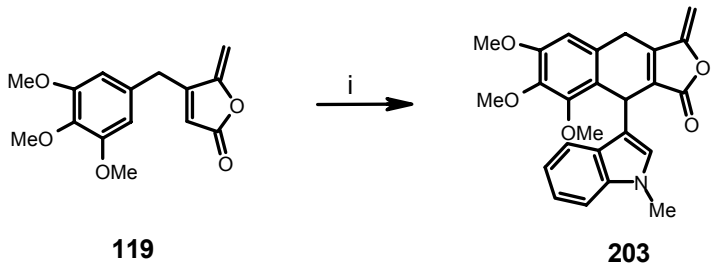
Table 3.

Entry	Naphthaldehydes	Acyclic lignan 201	Cyclic lignan 202
1	4-Methoxy-1-naphthaldehyde	**201 a**	**202 a**
2	2-Methoxy-1-naphthaldehyde	**201 b**	**202 b**
3	4,8-Dimethoxy-1-naphthaldehyde	**201 c**	**202 c**
4	6,7-Dimethoxy-1-naphthaldehyde	**201 d**	**-**
5	6-Methoxy-2-naphthaldehyde	**201 e**	**202 d**

In order to study an example of heterocyclic lignan analogues we have synthesized 1,4-dyhydronaphthalene lignan derivative with n-methyl indole at C9. Thus the furanone **119a** was treated with LDA at -78ºC followed by N-methylindole-3-carboxaldehyde.

It was noteworthy to find that the reaction of N-methyl-indole-3-carboxaldehyde with furanone in the presence of LDA and acidic work up afforded the cyclic lignan **203** directly and the intermediate hydroxylignan was not detected. This represents a convergent three-step synthesis of highly functionalized heterocyclic lignan, starting from trimethoxybenzaldehyde as shown in Scheme 15 (only third step shown).

Scheme 15.

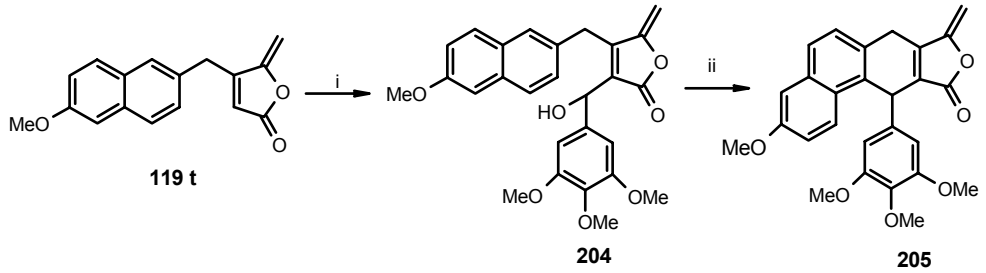


119 **203**

Reagents and conditions: (i) (a) N-methylindole-3-carboxaldhyde, LDA, -78 °C; (b) Dil. acetic acid, 64%.

To annex the versatility of lignan derivatives angular 1,4-dihydronaphthalene lignan analogue derived from the corresponding 4-(6'-methoxynaphthalen-2-yl) methyl-5-methylene-2(5*H*)-furanone **119t** was obtained as depicted in Scheme-16.

Scheme 16.



119 t **204** **205**

Reagents and conditions: (i) LDA, -78 °C, 3,4,5-trimethoxybenzaldehyde 53%; (ii) TFA, dichloromethane, rt, 2h 86%.

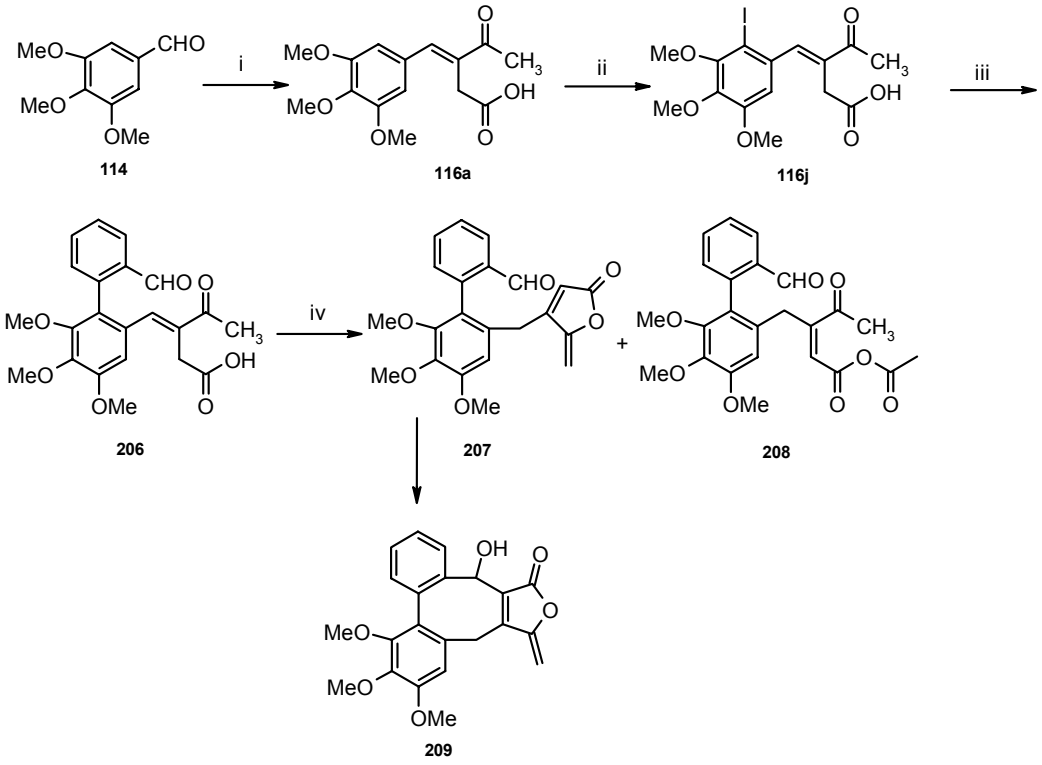
PART: C

Synthetic attempts towards dibenzocyclooctene lignan lactone

Dibenzocyclooctene is another important class of lignans[25]; steganone, steganancin and steganane[26] are the main bioactive molecules of this class, having inhibitory activity of tubulin polymerization both *in vitro* and *in vivo,* similar to that of colchicines and podophyllotoxin. They are also reported to possess potent antileukemic activity.[27] Several C_{18} dibenzocyclooctadiene lignans have been isolated from plants of the *Schizandraceae* and these have exhibited pharmacological effects such as anti-oxidant, anti-hepatitis, anti-hepatotoxic and anti lipid peroxidative.[28] (+)-Gomisin K3, gomisin B and gomisin G showed antihepatatic activity[29] in addition to strongest cyctotoxicity. This class of lignans represents a popular target for organic chemist because of dibenzocyclooctene unit and anticancer activity and many structural modifications have been studied to improve the cytotoxicity exhibited by the parent molecule. Some Structure Activity Relationship in stignancin series have been described in literature by studying the functional variation at C5 and C 8 of the skeleton of the stegnancin.[30]

As a consequence of our studies directed towards design and synthesis of γ-methylene furanone derivatives, we exploited the γ-methylenefuranone for the synthesis of 1,4-dihydronaphthalene lignan derivatives. In present work we decided to apply the synthetic methodology of 4-substituted-5-methylene-2(*5H*)-furanone for the synthesis of dibenzocyclooctene analogues.

Scheme 17.



Reagents and conditions: (i) Ethyl levulinate, ethanol, aq. NaOH, -10 ºC, 75%; (ii) CF_3COOAg, I_2, chloroform, rt, 43%; (iii) 2-Carboxyaryl boronic acid, dimethoxy ethane, aq. Na_2CO_3, $Pd(PPh_3)_4$, reflux 12h, 45.2%; (iv) Anhydr. NaOAc, Ac_2O, 80°C, 3h, 13%.

3,4,5-Trimethoxy benzaldehyde (**114**) was subjected for condensation with ethyl levulinate, by using aqueous sodium hydroxide solution in ethanol at -10°C, to give the carboxylic acid **116 a** (Scheme 17). Regioselective aromatic iodination of this acid was effected by using silver trifluroacetate and iodine in dry chloroform to get acid **116 j** which was subjected to intermolecular biaryl coupling with 2-carboxybenzyl boronic acids by Suzuki-Mayura coupling method using palladium tetrakistriphenylphosphine and sodium bicarbonate as a base in dimethoxy ethane and water as solvent to give biaryl acid **206**. Substituted levulinic acid **206** was subjected to lactone formation by treating with anhydrous sodium acetate and acetic anhydride at 80°C for 3 h, which afforded a mixture of traces of furanone **207**, mixed anhydride **208** as major product. The desired

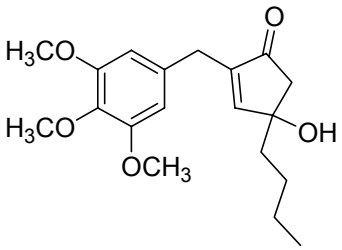
furanone **207** was a minor product in this reaction and the yield could not be improved to collect sufficient quantity for further transformation to the target molecule **209**.

1.2.4. CONCLUSION

We have successfully utilized furanone derivatives for synthesis of highly substituted acyclic and 1,4-dihydronaphthalene lignan derivatives involving regioselective alkylation of γ--methylene furanones using LDA without affecting their basic framework followed by cyclization. Representative examples of heterocyclic and angular analogues have been synthesized. Present studies have potential to contribute novel 1,4-dihydronaphthalene lignan derivatives to unnatural lignan family.

1.2.5. EXPERIMENTAL

4-Butyl-4-hydroxy-2-(3,4,5-trimethoxy-benzyl)-cyclopent-2-enone (190)



A solution of furanone **119a** (0.20 gm, 0.72 mmol) in dry tetrahydrofuran (2 ml) was added drop wise into a solution of n-butyl lithium (0.90 mmol) in dry tetrahydrofuran (15 ml) at -78˚C over 30 min. the brick red colored reaction mixture and the reaction was allowed to stirr at 0ºC for 1h. It was then quenched with saturated ammonium chloride. The reaction mixture was extracted with ethyl acetate, organic layer was washed with water followed by brine and dried over sodium sulphate. After evaporation, the residue was chromatographed over silica gel with petroleum ether-ethyl acetate as an eluent to afford the title compound.

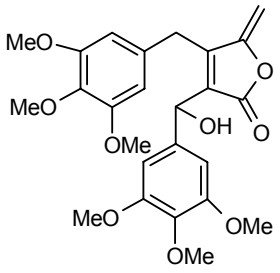
Nature: Pale yellow thick oil; **Yield**: 0.108 g, 45%; **IR** (Chlorofrom): ν 3500, 2940, 1720, 1580, 1220 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.86 (t, J = 6 Hz, 3H), 1.18-1.30 (m, 2H), 1.50-1.80 (m, 2H), 2.50 (q, J = 18 Hz, 2H), 3.35 (s, 2H), 3.78 (s, 3H), 3.80 (s, 6 H), 6.36 (s, 2H), 6.87 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 13.8, 22.8, 26.4, 31.1, 40.2, 49.3, 56.0 (2C), 60.8, 106.0 (2C), 128.5, 133.7, 136.2, 145.22, 153.2 (2), 160.15, 205.8; **MS**: (ESI) *m/z* 335 $(MH)^+$, 352 $(M^+ + H_2O)$; **Anal. Calcd for** $C_{19}H_{26}O_5$: C, 68.26; H, 7.78; Found C, 68.31; H, 7.34

Typical procedure for the synthesis of 5-methylene-3, 4-dibenzyl (substituted)-2(5*H*)-furanones (B)

A solution of γ-methylenefuranone (0.200 gm, 0.72 mmol) in dry tetrahydrofuran (2 ml) was added dropwise into a solution of lithium diisopropyl amide (0.90 mmol) in dry tetrahydrofuran (7 ml) at -78˚C over 10 min. and stirred further for 20 min. Aldehyde (0.411, 0.72 mmol) in dry tetrahydrofuran was added dropwise to brick red colored reaction mixture, reaction was allowed to stirr at same temperature for 1 h, and then it was quenched with saturated ammonium chloride containing acetic acid (Till confirmed acidic pH). The reaction mixture was extracted with ethyl acetate, organic layer was washed with water, dilute sodium bicarbonate solution followed by brine and dried over

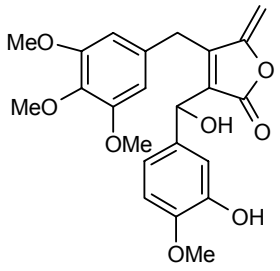
sodium sulphate. After evaporation, the residue was chromatographed on silica gel with petroleum ether-acetone (8:2) as an eluent to collect the title compounds.

3-[Hydroxy-(3,4,5-trimethoxy-phenyl)-methyl]-5-methylene-4-(3,4,5-trimethoxy-benzyl)-5*H*-furan-2-one (191)



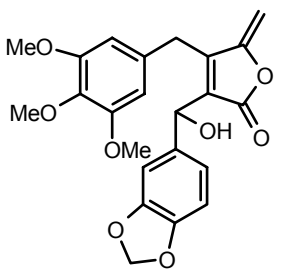
Nature: Pale yellow gum; **Yield:** 0.163 g, 48 %; **IR** (Chloroform): ν 3515, 1766, 1713, 1655, 1223 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.71 (s, 6H), 3.74 (s, 6H), 3.75-3.95 (m including s at 3.79, 8H), 4.92 (d, J = 2.9 Hz, 1H), 5.22 (d, J = 2.9 Hz, 1H), 5.68 (bs, 1H), 6.24 (s, 2H), 6.59 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 30.5, 55.9 (4C), 60.6 (2C), 68.6, 96.0, 102.9 (2C), 105.3 (2C), 131.3, 132.1, 136.5, 136.9, 148.6, 153.3 (4C), 154.7 (2C), 169.0; **MS** (ESI): *m/z* 472 (M^+); **Anal. Calcd for** $C_{25}H_{28}O_9$: C; 63.55; H, 5.93; **Found** C, 63.47; H, 6.05.

3-[Hydroxy-(3-hydroxy-4-methoxy-phenyl)-methyl]-5-methylene-4-(3,4,5-trimethoxy-benzyl)-5*H*-furan-2-one (193a)



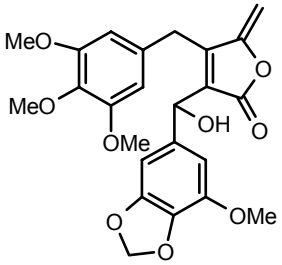
Nature: Thick yellow gum; **Yield:** 0.170 g, 55%; **IR** (Chloroform): ν 3540, 3019. 1765, 1592, 1508, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.73 (s, 6H), 3.80 (s, 3H), 3.86 (s, 3H), 3.89 (s, 2H), 4.91 (d, J = 2.9 Hz, 1H), 5.19 (d, J = 2.9 Hz, 1H), 5.65 (bs, 1H), 5.74 (bs, 1H), 6.27 (s, 2H), 6.76 (d, J = 8 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 6.89 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 30.7, 55.9, 56.0, 56.2, 60.7, 68.5, 96.1, 105.7, 107.1, 110.7, 112.5, 117.8, 129.6, 131.3, 132.1, 134.3, 143.9,145.9, 148.7, 153.5 (2C), 154.8, 169.0; **MS** (ESI): *m/z* 428 $(MH)^+$; **Anal. Calcd for** $C_{23}H_{24}O_8$: C, 64.48; H, 5.60; **Found** C, 64.54; H, 5.62.

3-(Benzo[1,3]dioxol-5-yl-hydroxy-methyl)-5-methylene-4-(3,4,5-trimethoxy-benzyl)-5*H*-furan-2-one (193b)



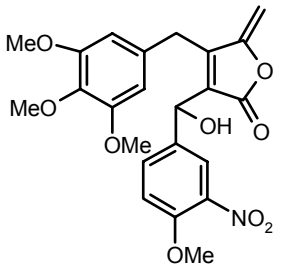
Nature: Thick pale yellow gum; **Yield:** 0.184 g, 60%; **IR** (Chloroform): ν 3498, 3018, 1763, 1592, 1505, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.74 (s, 6H), 3.80 (s, 3H), 3.90 (s, 2H), 4.93 (d, J = 2.9 Hz, 1H), 5.21 (d, J = 2.9 Hz, 1H), 5.65 (bs, 1H), 5.93 (s, 2H), 6.27 (s, 2H), 6.72 (d, J = 8 Hz, 1H), 6.76 –6.89 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 26.8, 56.0 (2C), 60.8, 68.7, 96.3, 101.1, 105.4 (2C), 106.0, 108.2, 119.6, 131.1 (2C), 132.0, 134.9, 147.4, 148.0, 153.4(2C), 154.7(2C), 169.0; **MS** (ESI): *m/z* 426 (M^+), 443 ($M+H_2O$); **Anal. Calcd for** $C_{23}H_{22}O_8$: C, 64.78; H, 5.16; **Found** C, 64.70; H, 5.23.

3-[Hydroxy-(7-methoxy-benzo[1,3]dioxol-5-yl)-methyl]-5-methylene-4-(3,4,5 trimethoxy-benzyl)-5*H*-furan-2-one (193c)



Nature: Thick yellow gum; **Yield:** 0.171 g, 52%; IR (Chloroform): ν 3438, 1763, 1637, 1508, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.75 (s, 6H), 3.81 (s, 3H), 3.82 (s, 3H), 3.90 (bs, 2H), 4.94 (d, J = 2.9 Hz, 1H), 5.22 (d, J = 2.9 Hz, 1H), 5.64 (s, 1H), 5.94 (s, 2H), 6.27 (s, 2H), 6.50 (bs, 1H), 6.59 (bs, 1H); **MS** (ESI): *m/z* 456 (M^+), 475 ($M+NH_3$), **Anal. Calcd for** $C_{22}H_{24}O_9$: C, 61.11; H. 5.55; **Found** C, 61.28; H, 5.67.

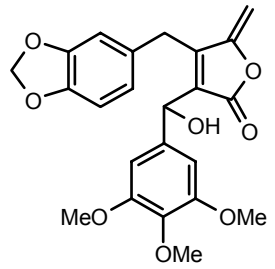
3-[Hydroxy-(4-methoxy-3-nitro-phenyl)-methyl]-5-methylene-4-(3,4,5-trimethoxy-benzyl)-5*H*-furan-2-one (193d)



Nature: Thick tan gum; **Yield:** 0.161 g, 49%; **IR** (Chloroform) ν 3515, 3015, 1766, 1713, 1655, 1592, 1492, 1223 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4) δ 3.75 (s, 6H), 3.80 (s, 3H), 3.85 (S, 2H), 3.93 (s, 3H), 5.02 (d, J = 2.9 Hz, 1H), 5.29 (d, J = 2.9 Hz, 1H), 5.71 (bs, 1H), 6.28 (s, 2H), 6.98 (d, J = 8 Hz, 1H), 7.48 (dd, J = 8, 2 Hz, 1H), 7.76 (d, J = 2 Hz, 1H,) **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.7, 56.2(2C), 56.6, 60.8, 67.4, 96.8, 105.7 (2C), 113.7, 123.2, 130.2, 131.5, 131.7, 133.3,

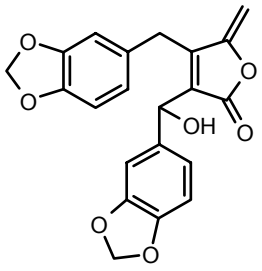
137.6, 149.6, 152.6, 153.7 (2C), 154.9, 159.7, 168.7; **MS** (ESI): *m/z* 457 $(M)^+$, 475 $(M+H_2O)$; **Anal. Calcd for** $C_{23}H_{23}NO_9$: C 60.39; H, 5.32; N, 3.06; **Found** C, 60.41; H, 5.38; N, 3.13.

3-(Benzo[1,3]dioxol-5-yl-hydroxy-methyl)-4-benzo[1,3]dioxol-5-ylmethyl-5-methylene-5H-furan-2-one (197)



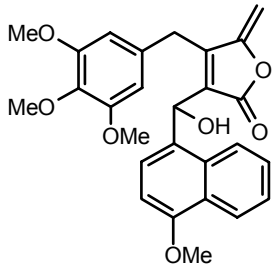
Nature: Thick pale yellow gum; **Yield**: 0.169 g, 55%; **IR** (Chloroform): ν 3446, 3018, 1755, 1708, 1217, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.74 (s, 3H), 3.79 (s, 3H) 3.81 (m, 2H), 3.84 (s, 3H), 4.88 (d, J = 2 Hz, 1H), 5.18 (d, J = 2 Hz, 1H), 5.68 (bs, 1H), 5.92 (s, 2H), 6.52-6.69 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 29.7, 55.6 (2C), 60.4, 68.5, 96.2, 100.8, 102.6, 103.4, 108.0, 108.3, 115.7, 120.9, 130.3, 130.7, 136.2, 146.6, 146.7, 148.8, 153.0 (2C), 154.4, 168.92; **MS** (ESI): *m/z* 426 (M^+), 443 $(M+H_2O)$; **Anal. Calcd for** $C_{23}H_{22}O_8$: C, 64.78; H, 5.16; **Found** C, 64.83; H, 5.21.

3-(Benzo[1,3]dioxol-5-yl-hydroxy-methyl)-4-benzo[1,3]dioxol-5-ylmethyl-5-methylene-5*H*-furan-2-one (199)



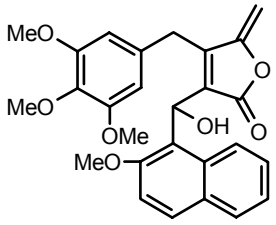
Nature: Thick gum; **Yield**: 0.142 g, 52%; **IR** (Chloroform): ν 3446, 2935, 1743, 1593,1240, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.86 (q, J = 20 Hz, 2H), 4.92 (d, J = 2Hz, 1H), 5.22 (d, J = 2 Hz, 1H), 5.65 (s, 1H), 5.95 (bs, 2H), 6.56 (d, J = 8 Hz, 2H), 6.72-6.83 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 67.26, 94.75, 100.2 (2C), 105.9, 107.1, 107.3, 108.17, 115.08 (2C), 118.65, 120.78, 131.8, 136.3, 147.8, 149.2 (2C), 154.1, 172.2; **MS** (ESI): *m/z* 381 $(MH)^+$, 399 (M+18); **Anal. Calcd for** $C_{21}H_{16}O_7$: C, 55.26; H, 4.21; **Found** C, 55.31; H, 4.23.

3-[Hydroxy-(4-methoxy-naphthalen-1-yl)-methyl]-5-methylene-4-(3,4,5-trimethoxy-benzyl)-5*H*-furan-2-one (201a)



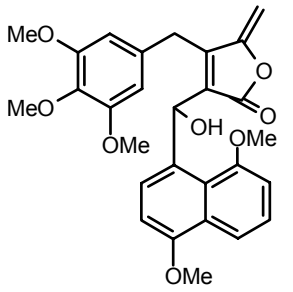
Nature: Brownish yellow gum; **Yield**: 0.250 g, 75 %; IR (Chloroform): ν 3426, 3015, 2939, 1764, 1594, 1592, 1239 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.54 (s, 6H), 3.66 (bs, 2H), 3.72 (s, 3H), 3.97 (s, 3H), 4.94 (d, J = 2.9 Hz, 1H), 5.25 (d, J = 2.9 Hz, 1H), 6.03 (s, 2H), 6.37 (s, 1H), 6.67 (d, J = 8, 1H), 7.30-7.60 (m, 3H), 8.00 (dd, 1H, J = 8, 2 Hz, 1H), 8.28 (dd, J = 8, 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 30.6, 55.3 (2C), 55.6, 60.6, 65.2, 96.3, 102.4, 105.0 (2C), 122.6, 123.0, 124.0, 125.1, 127.0 (2C), 127.6, 130.8, 131.3, 131.7, 136.4, 150.0, 153.0 (2C), 154.7, 155.7, 169.7; **MS** (ESI): *m/z* 463 $(MH)^+$, 480 (M + H_2O); **Anal. Calcd for** $C_{27}H_{26}O_7$: C, 70.12; H, 5.62; **Found**: C, 69.93; H, 5.49.

3-[Hydroxy-(2-methoxy-naphthalen-1-yl)-methyl]-5-methylene-4-(3,4,5-trimetho-xybenzyl)-5*H*-furan-2-one (201b)



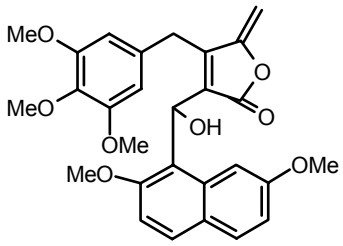
Nature: Thick pale yellow gum; **Yield:** 0.173 g, 52 %; **IR** (Chloroform): ν 3421, 3019, 1760, 1595, 1508, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.33-3.65 (m, 2H), 3.61 (s, 6H), 3.76 (s, 3H), 3.87 (s, 3H), 4.84 (d, J = 2.9 Hz, 1H), 5.18 (d, J = 2.9 Hz, 1H), 5.88 (s, 2H), 6.68 (s, 1H), 7.15 (d, J = 9.2 Hz, 1H), 7.30 -7.52 (m, 2H), 7.77 (dd, J = 9.2, 2.4 Hz, 2H), 8.06 (d, J = 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 30.1, 56.0 (2C), 56.4, 60.6, 63.8, 96.1, 105.3 (2C), 109.2, 113.3, 123.0, 123.7 (2C), 127.1, 128.7, 129.4, 130.8 (2C), 131.7, 137.1, 146.9, 150.0, 153.2, 154.9, 158.5, 169.2; **MS** (ESI): *m/z* 462 $(M)^+$, 444 (M^+-H_2O); **Anal. Calcd for** $C_{27}H_{26}O_7$: C, 70.12; H, 5.62; **Found** C, 70.27; H, 5.72.

3-[(4,8-Dimethoxy-naphthalen-1-yl)-hydroxy-methyl]-5-methylene-4-(3, 4, 5-trimethoxy-benzyl)-5*H*-furan-2-one. (201c)



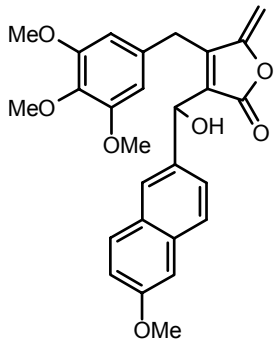
Nature: Yellow solid; **Yield:** 0.195 g, 55 %; Mp: 197°C, IR (Chloroform): ν 3400, 3018, 2938, 1772, 1599, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.41 (q, J = 14 Hz, 2H), 3.67 (s, 6H), 3.78 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 4.82 (d, J = 2.9 Hz, 1H), 5.12 (d, J = 2.9 Hz, 1H), 6.23 (s, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.75-6.92 (m, 2H), 7.36 (t, J = 8 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 36.8, 56.0 (2C), 60.7, 69.2, 96.2, 105.6 (2C), 119.9 (2C), 123.8, 124.8, 125.0, 126.8, 126.9, 131.3, 132.0, 139.4, 140.9, 141.8, 143.3 (2C), 143.8, 148.7, 153.5 (2C), 154.8, 169.1; **MS** (ESI): *m/z* 492 $(M)^+$, 474 $(M\text{-}H_2O)^+$; **Anal. Calcd for** $C_{28}H_{28}O_8$: C, 68.29; H, 5.69; **Found:** C, 68.30; H, 5.74.

3-[(2,7-Dimethoxy-naphthalen-1-yl)-hydroxy-methyl]-5-methylene-4-(3,4,5-trimethoxy-benzyl)-5*H*-furan-2-one (201d)



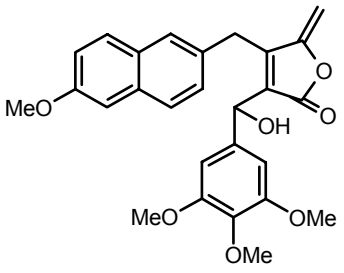
Nature: Pale yellow gum; **Yield:** 0.202 g, 57%; **IR** (Chloroform): ν 3418, 3015, 2900, 1778, 1615, 1212 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.57 (s, 6H), 3.74 (s, 2H), 3.84 (s, 9H), 4.81 (d, J = 2.9 Hz, 1H), 4.89 (bs, 1H), 5.16 (d, J = 2.9 Hz, 1H), 5.84 (s, 2H), 6.67 (bs, 1H), 6.95 (dd, J = 2, 6.6 Hz, 2H), 7.40 (d, J = 2 Hz, 1H), 7.65 (t, J = 7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 30.0, 55.2, 55.7 (2C), 56.1, 60.6, 63.8, 95.6, 101.6, 104.4 (2C), 110.2, 116.4, 119.5, 124.7, 130.1, 130.4, 131.4, 131.7, 133.2, 136.2, 147.3, 152.9 (2C), 154.5, 155.2, 158.6, 169.7; **MS** (ESI): *m/z* 492 $(M)^+$; **Anal. Calcd for** $C_{28}H_{28}O_8$: C, 68.29; H, 5.69; **Found**: C, 68.08; H, 5.81.

3-[Hydroxy-(6-methoxy-naphthalen-2-yl)-methyl]-5-methylene-4-(3,4,5-trimethoxy-benzyl)-5H-furan-2-one (201e)



Nature: pale yellow solid; **Yield**: 0.190 g, 57%; **Mp**: 82°C; **IR** (Chloroform): ν 3435, 3018, 1764, 1594, 1506, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.55 (s, 6H), 3.75 (s, 3H), 3.82 (d, 2H), 3.90 (s, 3H), 4.90 (d, J = 2.9 Hz, 1H), 5.19 (d, J = 2.9 Hz, 1H), 5.88 (s, 1H), 6.18 (s, 2H), 7.04-7.15 (m, 2H), 7.43 (d, J = 8, 2 Hz, 1H), 7.64 (dd, J = 8, 2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 30.8, 55.2, 55.8 (2C), 60.7, 68.9, 96.1, 105.4, 105.5, 119.2, 124.4, 124.7, 127.4, 128.6, 129.4, 131.2, 132.0, 134.2, 136.0, 137.0, 148.9, 153.3(2C), 154.7, 158.0, 159.6, 169.1; **MS** (ESI): *m/z* 462 $(MH)^+$**; Anal. Calcd for** $C_{27}H_{26}O_7$: C, 70.12; H, 5.67; **Found**: C, 70.23; H, 5.55.

3-[Hydroxy-(3,4,5-trimethoxy-phenyl)-methyl]-4-(6-methoxy-naphthalen-2-ylmethyl)-5-methyl-5*H*-furan-2-one (204)

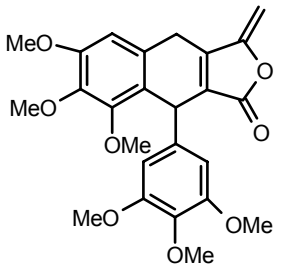


Nature: Thick yellow foam; **Yield**: 0.176 g, 53%; IR (Chloroform): ν 3401, 3019, 1773, 1653, 1507, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.58 (s, 6H), 3.77 (s, 3H), 3.85 (s, 3H), 4.11 (q, J = 15.6 Hz, 2H), 4.92 (d, J = 2.9 Hz, 1H), 5.19 (d, J = 2.9 Hz, 1H), 5.70 (bs, 1H), 6.53 (s, 2H), 6.55 (d, J = 8 Hz, 1H), 7.05-7.18 (m, 2H), 7.38 (bs, 1H), 7.56 (d, J = 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 30.3, 55.2, 55.9, 56.0, 60.6, 69.1, 96.1, 103.4, 104.1, 105.7, 119.2, 126.5, 126.7, 127.3, 128.9, 131.3, 131.7, 133.4, 136.4, 136.6, 137.6, 148.8, 153.3 (2C), 155.0, 157.8, 169.0; **MS** (ESI): *m/z* 462 $(M)^+$, 480 $(M+H_2O)$; **Anal. Calcd for** $C_{27}H_{26}O_7$: C, 70.12; H, 5.67; **Found**: C, 70.19; H, 5.64.

Typical procedure for the synthesis of cyclic naphthalene lignans

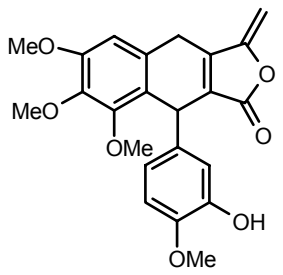
Hydroxy lignans (2 mmol) were taken in dry dichloromethane under nitrogen atmosphere and cooled to 0˚C. Trifluoroacetic acid (1.5 eq.) was added dropwise within 5 min. The reaction mixture became dark blue in color. It was allowed to stirr at room temperature and the reaction was monitored by thin layer chromatography. After completion of reaction (1 to 4 h), the mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with dilute bicarbonate solution followed by water and brine and dried over anhydrous sodium sulphate. After removal of solvent the residue was chromatographed on silica gel with petroleum ether – acetone (8:2) as an eluent to collect the cyclized products (yield ranges from 60-90%).

6,7,8-Trimethoxy-3-methylene-9-(3,4,5-trimethoxy-phenyl)-4,9-dihydro-3*H*-naphtho [2,3-c] furan-1-one (192)



Nature: Yellow brownish solid; **Yield**: 0.708 g, 78%; **Mp**: 56 °C; IR (Chloroform): ν 2920, 1768, 1717, 1450, 1221, 1150 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.50 (s, 3H), 3.65-4.50 (m including s at 3.77, 3.82 and 3.91, 17H), 4.87 (d, J = 2.4, 1H), 5.15 (d, J = 2.4 Hz, 1H), 5.20 (bs, J = 2.9 Hz, 1H), 6.41 (s, 2H), 6.63 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ +CCl_4): δ 32.6, 55.6 (4C), 60.3 (2C), 72.8, 96.2, 104.9 (2C), 105.3, 123.5 (2C), 128.7, 130.9, 134.1, 137.1, 152.7 (4C), 153.0 (2C), 169.0; **MS** (ESI): *m/z* 455 $(MH)^+$; **Anal. Calcd for** C_{25} $H_{26}O_8$: C, 66.07; H, 5.72; **Found**: C, 66.32; H, 5.79.

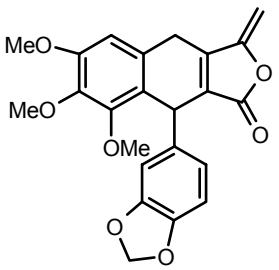
9-(3-Hydroxy-4-methoxy-phenyl)-6,7,8-trimethoxy-3-methylene-4,9-dihydro-3*H*-naphtho [2,3-c] furan-1-one (194a)



Nature: Yellow brownish solid; **Mp**: 87°C; **Yield:** 0.607 g, 74 %; **IR** (Chloroform): ν 3408, 3019, 1766, 1653, 1423, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.47 (s, 3H), 3.69-4.05 (m including s at 3.81,

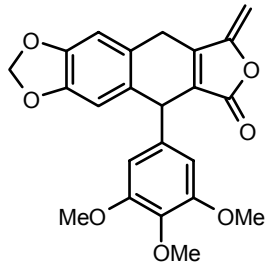
3.84 and 3.90, 11H), 4.86 (d, J = 2.4 Hz, 1H), 5.14 (bs, 2H), 5.55 (bs, 1H), 6.52 (d, J = 2 Hz, 1H), 6.61 (s, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.92 (dd, J = 8.3, 2 Hz, 1H); MS (ESI): *m/z* 411 $(MH)^+$; **Anal. Calcd for** $C_{23}H_{22}O_7$: C, 56.09; H, 5.36; **Found** C, 57.21; H, 5.30.

9-Benzo[1,3]-dioxol-5-yl-6,7,8-trimethoxy-3-methylene-4,9-dihydro-3*H*-naphtho[2,3-c]furan-1-one (194b)



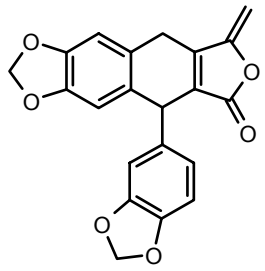
Nature: Yellow gum; **Yield:** 0.742 g, 91%; **IR** (Chloroform): ν 3018, 1762, 1592, 1216, 758 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$ + CCl_4): δ 3.40 (s, 3H), 3.64-3.87 (m including s at 3.72 and 3.80, 8H), 4.77 (bs, 1H), 5.04 (bs, 2H), 5.79 (bs, 2H), 6.53 (bs, 2H), 6.56-6.64 (dd, J = 8, 2 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$ + CCl_4): δ 26.6, 37.6, 55.9, 60.2, 60.6, 92.9, 100.8, 106.8, 108.0, 108.6, 121.5, 123.2, 126.6, 131.0, 136.4, 141.5, 146.2, 146.7, 147.5, 151.7, 153.0, 153.6, 167.7; **MS** (ESI): *m/z* 409 $(MH)^+$; **Anal. Calcd for** $C_{23}H_{20}O_7$: C, 67.64; H, 4.90; **Found** C, 67.78; H, 5.12.

8-Methylene-5-(3,4,5-trimethoxy-phenyl)-5,9-dihydro-8*H*-furo[3',4':6,7] naphtha [2,3-d] [1,3]dioxol-6-one (198)



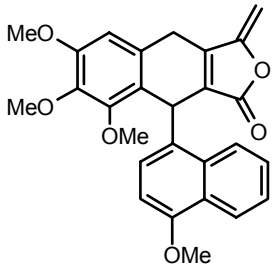
Nature: Off-white crystalline solid; **Yield**: 0.694 g, 85%; **Mp**: 102-104 °C; **IR** (Chloroform): ν 3019, 1788, 1763, 1607, 1490, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.79 (s, 9H), 3.82-3.88 (m, 2H), 4.88 (t, J = 4 Hz, 1H), 4.91 (d, J = 4 Hz, 1H), 5.18 (d, J = 4 Hz, 1H), 5.96 (bs, 2H), 6.35 (s, 2H), 6.63 (s, 1H), 6.75 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 26.5, 42.5, 55.7 (2C), 60.4, 93.2, 101.0, 105.1(2C) 105.3, 107.5, 107.6, 108.9, 115.7, 123.2, 128.7 (2C) 131.2, 138.3, 146.9, 153.2 (2C), 168.6; **MS** (ESI): *m/z* 409 $(MH)^+$; **Anal. calcd for** $C_{23}H_{20}O_7$: C, 67.64; H, 4.94; Found: 67.83, H, 5.23.

5-Benzo[1,3]dioxol-5-yl-8-methylene-5,9-dihydro-8*H*-furo[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6-one (200)



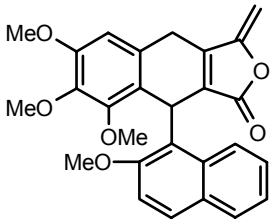
Nature: Off-white crystalline solid; **Yield**: 82%; Mp: 117-119 °C; **IR** (Chloroform): ν 2898, 1786, 1764, 1652, 1490 cm^{-1}; **^{1}H NMR** ($CDCl_3 + CCl_4$): δ 3.82 (dq, J = 18, 6 Hz, 2H), 4.84 (t, J = 6 Hz, 1H), 4.90 (d, J = 2.5 Hz, 1H), 5.18 (d, J = 2.5 Hz, 1H), 5.89 (s, 2H), 5.92 (d, J = 10 Hz, 2H), 6.08 (d, J = 2.8 Hz, 1H), 6.51 (s, 1H), 6.59 (s, 1H), 6.72 (bs, 3H); **MS** (ESI): *m/z* 363 (M+1); **Anal. Calcd for** $C_{21}H_{14}O_6$: C, 69.61; H, 3.85; **Found**: C, 69.41; H, 3.93.

3-(4-Methoxynaphthalen-1-yl)-methyl]-5-methylene-4-(3,4,5-trimethoxybenzyl)-5*H*-furan-2-one (202a)



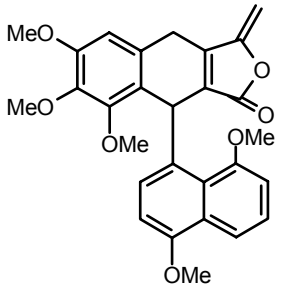
Nature: Pale yellow crystalline solid; **Yield**: 0.719 g, 81%; **Mp**: 113-115 °C; **IR** (Chloroform): ν 3018, 1780, 1594, 1507, 1216 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$ + CCl_4): δ 2.89 (s, 3H), 3.77 (s, 3H), 3.90-3.95 (m including s at 3.92 and 3.93, 7H), 4.13 (dd, J = 18, 2.3 Hz, 1 H) 4.88 (d, J = 2.9 Hz, 1H), 5.11 (d, J = 2.9 Hz, 1H), 5.94 (bt, J = 1.9 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 6.67 (s, 1H), 6.87 (d, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 1H), 7.68 (t, J = 8, 2 Hz, 1H), 8.30 (d, J = 8 Hz, 1H), 8.61-8.64 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 26.8, 32.8, 55.3, 56.0, 59.4, 60.5, 92.3, 103.4 (2C), 106.8, 122.1, 124.2 (2C), 125.5(2C), 125.8, 126.5, 131.9, 132.4, 141.8, 146.1, 151.8, 152.9, 154.0 (2C), 154.1, 167.5; **MS** (ESI): *m/z* 445 $(MH)^+$; **Anal. Calcd for** $C_{27}H_{24}O_6$: C, 72.97; H, 5.40; **Found**: C, 72.91; H, 5.57.

6,7,8-Trimethoxy-9-(2-methoxy-naphthalen-1-yl)-3-methylene-4,9-dihydro-3*H*-naphtho[2,3-c]furan-1-one (202b)



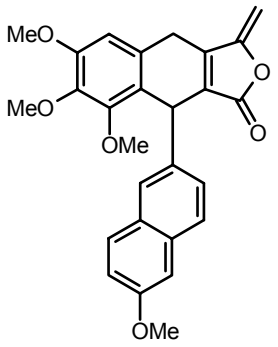
Nature: Pale yellow crystalline solid; **Yield**: 0.542 g, 61%; Mp: 219°C; **IR** (Chloroform): ν 3019, 1775, 1600, 1515, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 2.67 (bs, 3H), 3.46 (bs, 3H), 3.71 (s, 3H), 3.86 (s, 5H), 4.84 (bs, 1H), 5.08 (bs, 1H), 5.99 (bs, 1H), 6.58 (s, 1H), 7.07 (d, J = 8 Hz, 1H), 7.37-7.42 (m, 1H), 7.66-7.74 (m, 3H); 8.63 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 26.8, 30.0, 55.5, 56.7, 59.0, 60.3, 93.0, 106.1, 111.4, 114.3, 116.5, 123.1, 123.4, 123.7, 126.4, 128.0, 129.0 (2C), 132.9, 148.3, 151.2, 151.7, 153.7, 155.2, 157.8, 158.7, 168.7; **MS** (ESI): *m/z* 463 $(M + H_2O)^+$; **Anal. Calcd for** $C_{27}H_{24}O_6$: C, 72.97; H, 5.40; **Found**: C, 72.68; H, 5.35.

9-(4,8-Dimethoxy-naphthalen-1-yl)-6,7,8-trimethoxy-3-methylene-4,9-dihydro-3*H*-naphtho[2,3-c]furan-1-one (202c)



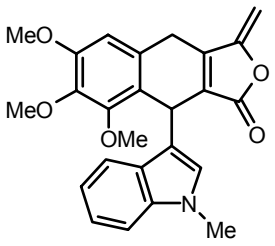
Nature: Yellow crystalline solid; **Yield**: 0.597 g, 63%; Mp: 119°C; **IR** (Chloroform): ν 2925, 1772, 1635, 1460, 1220 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3 + CCl_4$): δ 3.00 (s, 3H), 3.76 (s, 3H), 3.84 (dd, J = 18, 3 Hz, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 4.05 (dd, J = 18, 3 Hz, 1H), 4.10 (s, 3H), 4.81 (d, J = 2.9 Hz, 1H), 5.07 (d, J = 2.9 Hz, 1H), 6.57 (d, J = 8 Hz, 1H), 6.62 (s, 1H), 6.70 (d, J = 8 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 7.35 (t, J = 2.9 Hz, 1H), 7.39 (t, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 26.4, 34.4, 55.3, 55.8, 56.2, 59.6, 60.5, 91.4, 103.7, 106.3, 108.0, 114.8, 124.9 (2C), 125.4, 125.8, 126.7, 127.6, 132.7, 133.0, 141.5, 144.5, 151.8, 152.5, 153.8, 154.0, 158.5, 167.3; **MS** (ESI): *m/z* 475 $(MH)^+$; **Anal. Calcd for** $C_{28}H_{26}O_7$: C, 70.88; H, 5.48; **Found**: C, 70.86; H, 5.52.

6,7,8-Trimethoxy-9-(6-methoxy-naphthalen-2-yl)-3-methylene-4,9-dihydro-3*H*-naphtho[2,3-c]furan-1-one (202d)



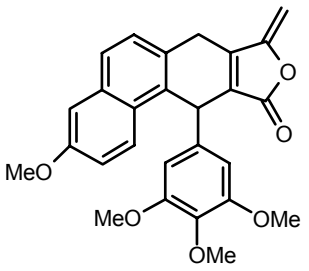
Nature: Yellow crystalline solid; **Yield**: 0.790 g, 89%; Mp 118°C; **IR** (Chloroform): ν 3019, 1772, 1605, 1465, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ 3.33 (s, 3H), 3.75- 4.12 (m including s at 3.80, 3.87 and 3.91, 11 H), 4.87 (d, J = 2.7 Hz, 1H), 5.12 (d, J = 2.7 Hz, 1H), 5.35 (t, J = 3.92 Hz, 1H), 6.67 (s, 1H), 7.08 (dd, J = 8, 2 Hz, 2H), 7.31 (dd, J = 8.6, 1.9 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H); 7.63 (dd, J = 8.6, 2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 26.8, 38.1, 55.2, 56.0, 60.2, 60.6, 92.7, 105.6, 106.8, 118.7 (2C), 123.5, 126.7, 126.9, 127.1, 128.9, 129.3, 131.3, 133.5, 137.8, 141.6, 146.6, 152.0, 153.1, 153.9, 157.6, 167.6; **MS** (ESI): *m/z* 445 $(MH)^+$; **Anal. Calcd for** $C_{27}H_{24}O_6$: C, 72.97; H, 5.40; **Found**: C, 72.89; H, 5.60.

6,7,8-Trimethoxy-9-(1-methyl-2,3-dihydro-1*H*-indol-3-yl)-3-methylene-4,9-dihydro-3H-naphtho[2,3-c]furan-1-one (203)



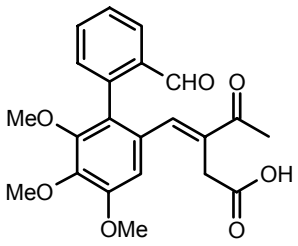
Nature: White crystalline solid; **Yield**: 0.534 g, 64 %; Mp 128-130°C; **IR** (Chloroform): ν 3019, 1767, 1658, 1537, 1215 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3 + CCl_4$): δ 3.40 (s, 3H), 3.63-4.19 (m including s at 3.72, 3.80 and 3.92, 11 H), 4.83 (d, J = 2.9 Hz, 1H), 5.09 (d, J = 2.9 Hz, 1H), 5.50 (t, J = 2.9 Hz, 1H), 6.66 (s, 1H), 6.96 (t, J = 8 Hz, 1H), 6.98 (s, 1H), 7.12 (t, J = 8 Hz, 1H), 7.17-7.23 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3 + CCl_4$): δ 26.8, 32.5, 56.0, 60.2, 60.6, 92.3, 106.9, 109.1(2C), 115.1, 118.9, 119.3, 121.2, 121.3, 123.6, 126.6, 127.7, 131.2, 136.9, 141.6, 146.3, 152.2, 152.8, 153.7, 167.9; **MS** (ESI): *m/z* 416 $(M-1)^+$; **Anal. Calcd for** $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36; **Found**: C, 72.10; H; 5.51; N, 3.43.

3-Methoxy-8-methylene-11-(3,4,5-trimethoxy-phenyl)-8,11-dihydro-7H-9-oxa-cyclopenta[b]phenanthren-10-one (205)



Nature: Pale yellow crystalline solid; **Yield**: 0.764 g, 86%; **Mp**: 135°C; **IR** (Chloroform): ν 3019, 1764, 1589, 1215, 757 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$ + CCl_4): δ 3.72 (s, 6H), 3.78 (s, 3H), 3.93 (s, 3H), 3.98 (dd, J = 18 Hz, 1H), 4.04 (dd, J = 2, 18 Hz, 1H), 4.96 (d, J = 2.9 Hz, 1H), 5.21 (d, J = 2.9 Hz, 1H), 5.69 (t, J = 2 Hz, 1H), 6.47 (s, 2H), 7.13 (dd, J = 8, 2 Hz, 1H), 7.17 (d, J = 2 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.77 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H); **MS** (ESI): *m/z* 445 $(MH)^+$; **Anal**. **Calcd for** $C_{27}H_{24}O_6$: C, 72.97; H, 5.40; **Found**: C, 73.12; H, 5.26.

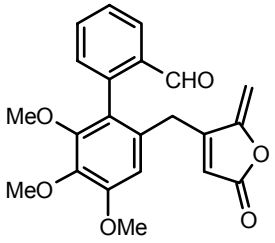
3-Acetyl-4-(2'-formyl-4,5,6-trimethoxy-biphenyl-2-yl)-but-3-enoic acid (206)



To a stirred solution of acid **116j** (0.28 g, 0.66 mmol) **in** dimethoxy ethane (15 ml), 2-carboxy-aryl-boronic acid (0.100 gm, 0.66 mmol) was added and to this solution Na_2CO_3 (0.212, 2.01 mmol), ethanol (1 ml) and water (0.5 ml) were added. The reaction mixture was degassed, to this mixture Pd (PPh_3) (0.02 mg) was added at once. Reaction mixture was allowed to reflux for 12 h. after which reaction mixture was filtered through Whatman filter paper, and acidified with 10 N HCl and extracted with chloroform. The organic layer was washed with water and brine and dried over sodium sulphate. Solvent was evaporated under reduced pressure, residue was purified by column chromatography using petroleum ether and ethyl acetate as an eluent (8:2), to afford pure acid 0.120 g, 45.2%.

Nature: brown solid; **Yield**: 45.2%; **Mp**: 120 ºC; IR ($CHCl_3$) υ 3394, 3019, 1754, 1696, 1670, 1597, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.97 (s, 3H), 3.40 (d, J =2.5 Hz, 2H), 3.47 (s, 3H), 3.80 (s, 3H), 3.85(s, 3H), 6.84 (s, 1H), 7.13 (dd, J = 8, 2 Hz, 1H), 7.36 (t, J = 8, 2 Hz, 1H), 7.54 (t, J = 8, 2 Hz, 1H), 7.92 (dd, J = 8, 2 Hz, 1H), 9.63 (s, 1H).

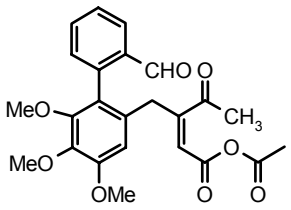
2',3',4'-Trimethoxy-6'-(2-methylene-5-oxo-2,5-dihydro-furan-3-ylmethyl)-biphenyl-2-carbaldehyde (207)



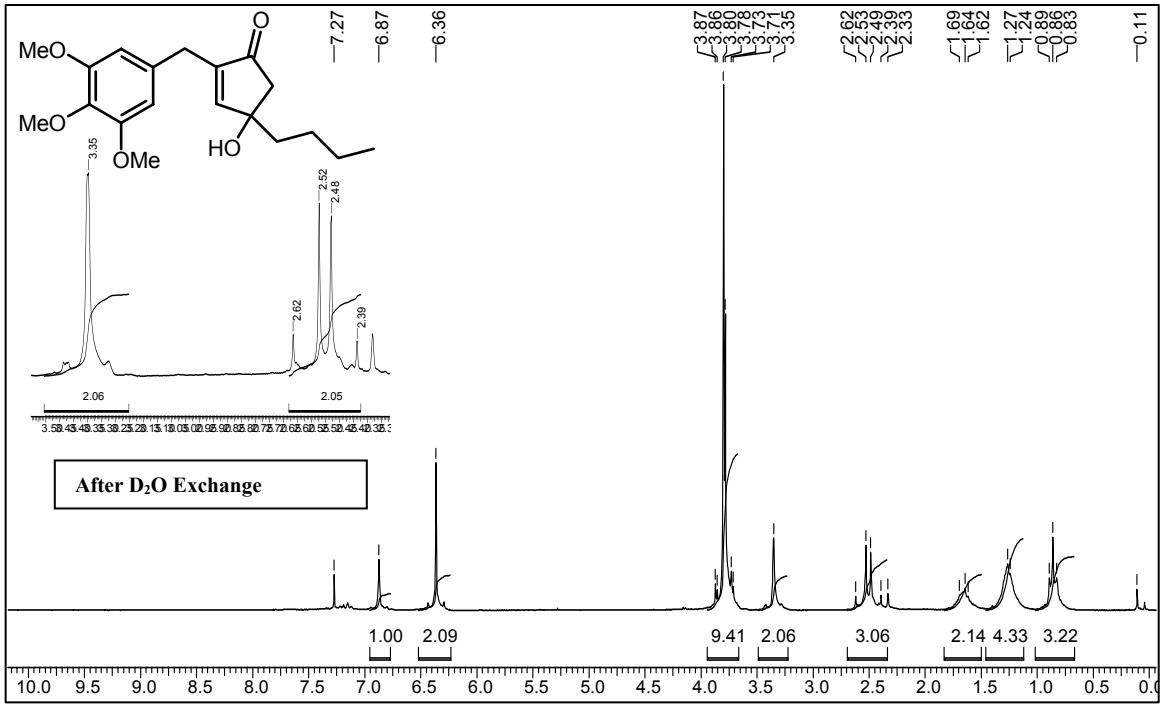
Acid **206** (0.112g, 0.294 mmol) was taken in dry two neck round bottom flask to this anhydrous NaOAc (0.048g, 0.585 mmol) was added followed by addition of acetic anhydride (0.148g, 0.137 ml, 1.47 mmol). Reaction mixture was stir under nitrogen atmosphere at 80 ºC, for 3h, after which it was quenched with crushed ice mixture was extracted with ethyl acetate (3 x15ml). Organic layer was washed with water (3 x 20 ml) followed by brine solution (2 x 5 ml) and dried over sodium sulphate. Residue was purified by column chromatography using petroleum ether and ethyl acetate (90:10) to afford furanone **207** (0.014g, 13%).

207:Nature: brown solid; **Yield**: 13% **Mp**: 108ºC; IR ($CHCl_3$) υ 3019, 1773, 1598, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.48 (d, J = 2.5 Hz, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 3.84(s, 3H), 6.84 (s, 1H), 7.13 (dd, J = 8, 2 Hz, 1H), 7.36 (t, J = 8, 2 Hz, 1H), 7.54 (t, J = 8, 2 Hz, 1H), 7.92 (dd, J = 8, 2 Hz, 1H), 9.63 (s, 1H).

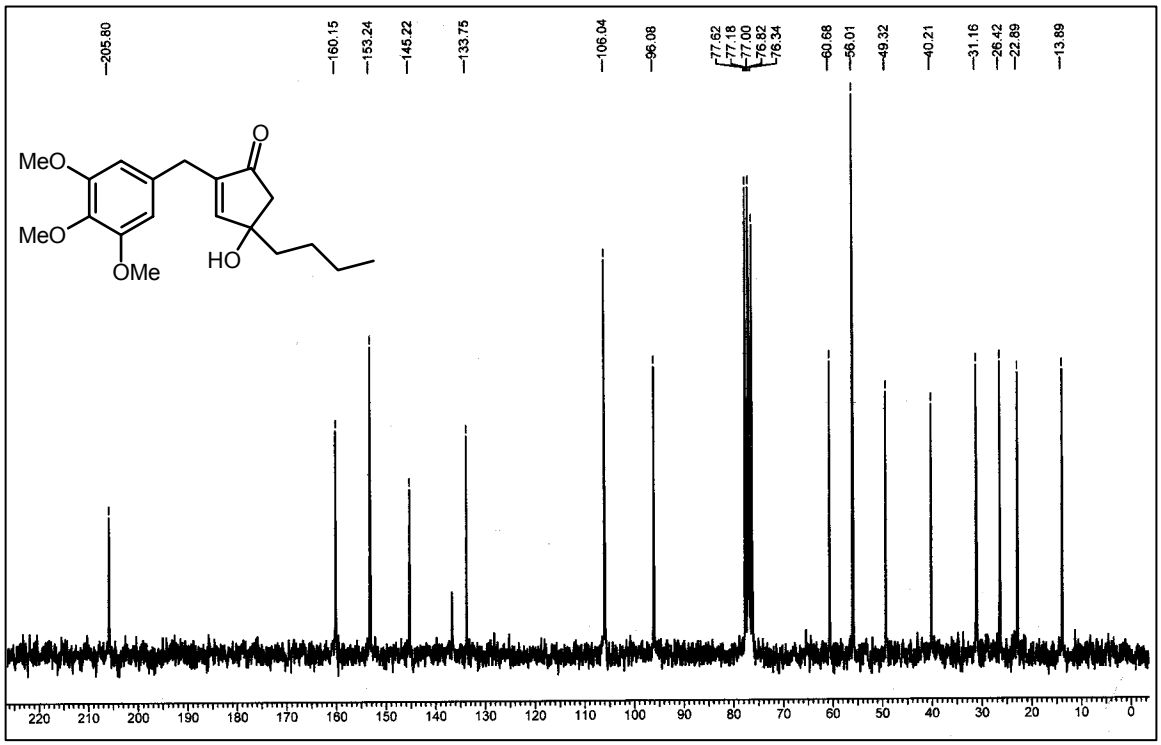
208:Nature: Thick gum; **^{1}H NMR:** ($CDCl_3$, 300 MHz) δ 1.93 (s, 3H), 2.11 (s, 3H), 3.98 (s, 5H), 4.00 (s, 3H), 4.08 (s, 3H), 6.46 (s, 1H), 7.28 (S, 1H), 7.63 (dd, J = 8, 2 Hz, 2H), 7.72 (dd, J = 8, 2 Hz, 1H), 7.86 (dd, J = 8, 2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 21.2, 21.6, 55.9, 56.2, 109.0, 109.2, 120.5, 127.4, 128.02, 129.3,, 129.8, 130.6, 132.7, 133.4, 137.7, 143.1, 151.1, 152.8, 153.09, 154.3, 167.6, 170.7, 191.4.

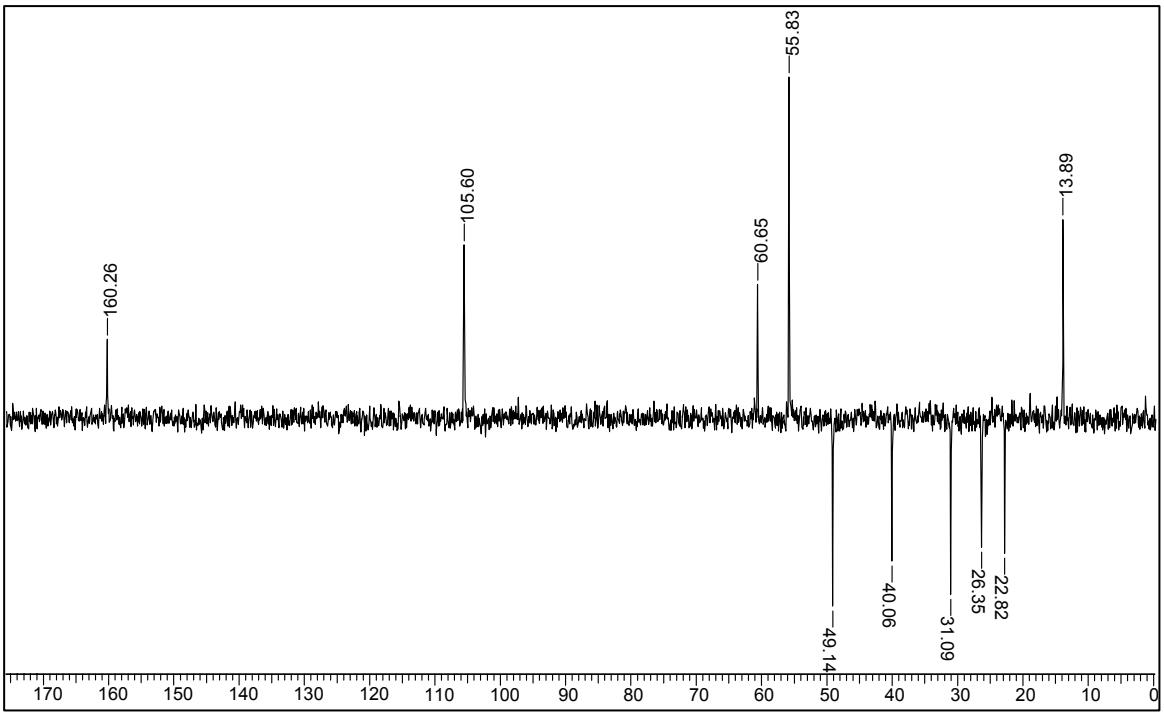


^{1}H NMR of compound 190 ($CDCl_3$+CCl_4, 200MHz)

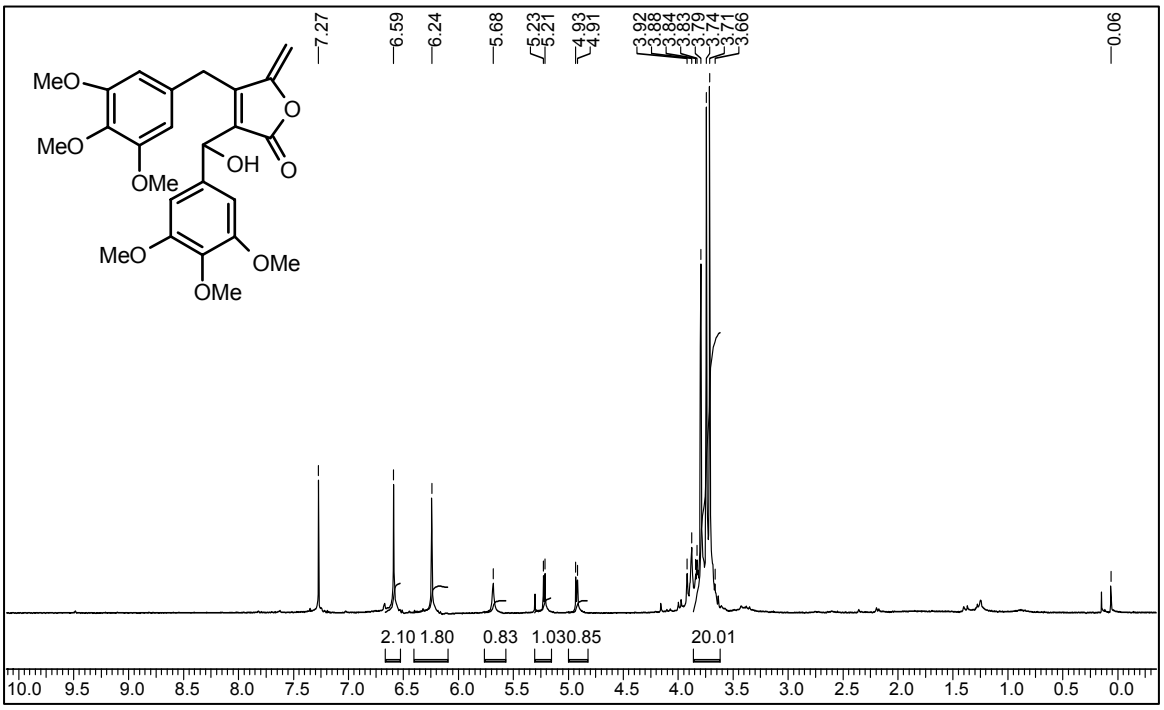


^{13}C NMR and DEPT of compound 190 ($CDCl_3$+CCl_4, 50 MHz)

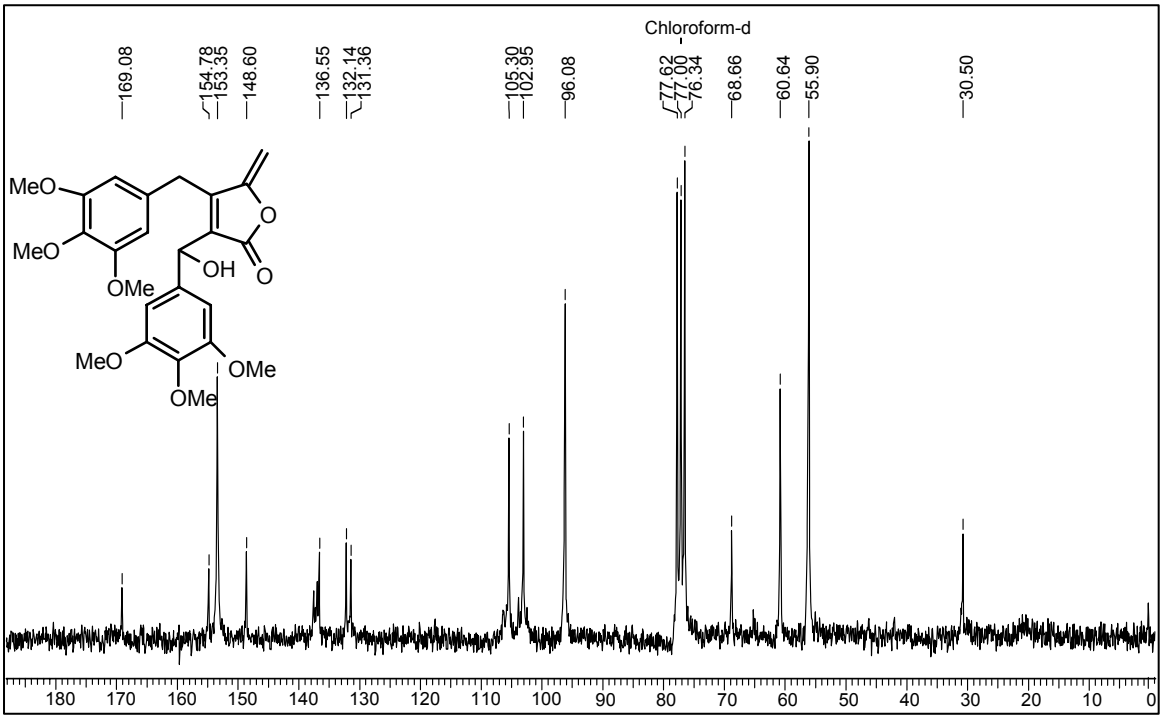


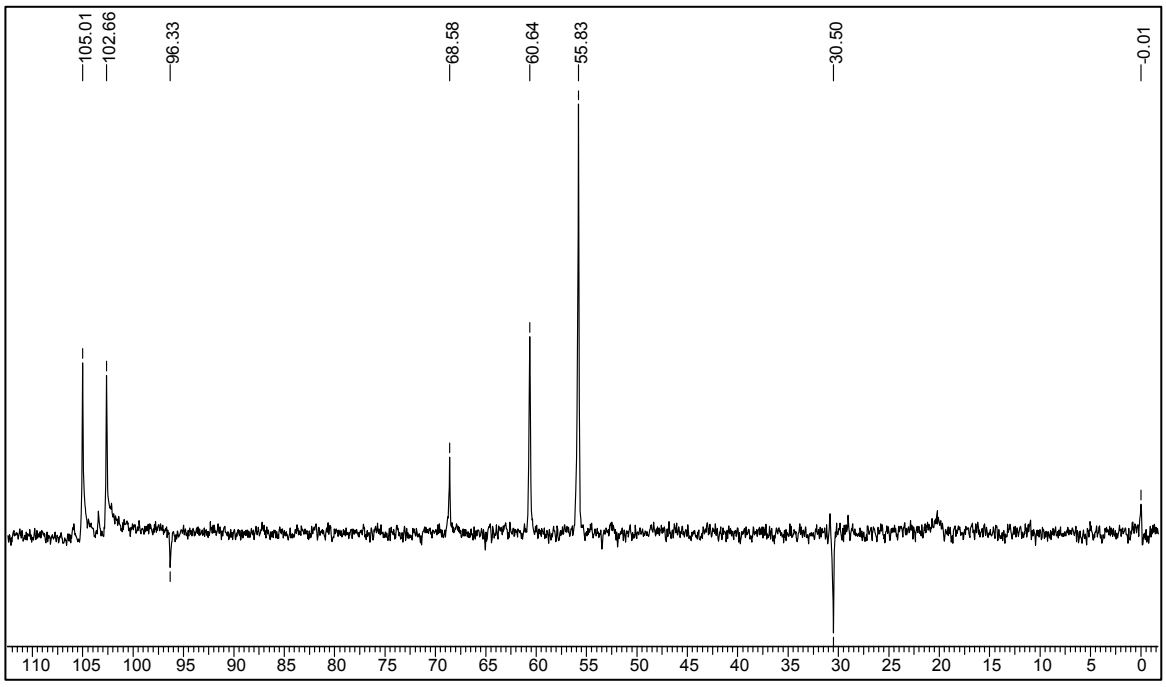


^{1}H NMR of compound 191 ($CDCl_3$+CCl_4, 200 MHz)

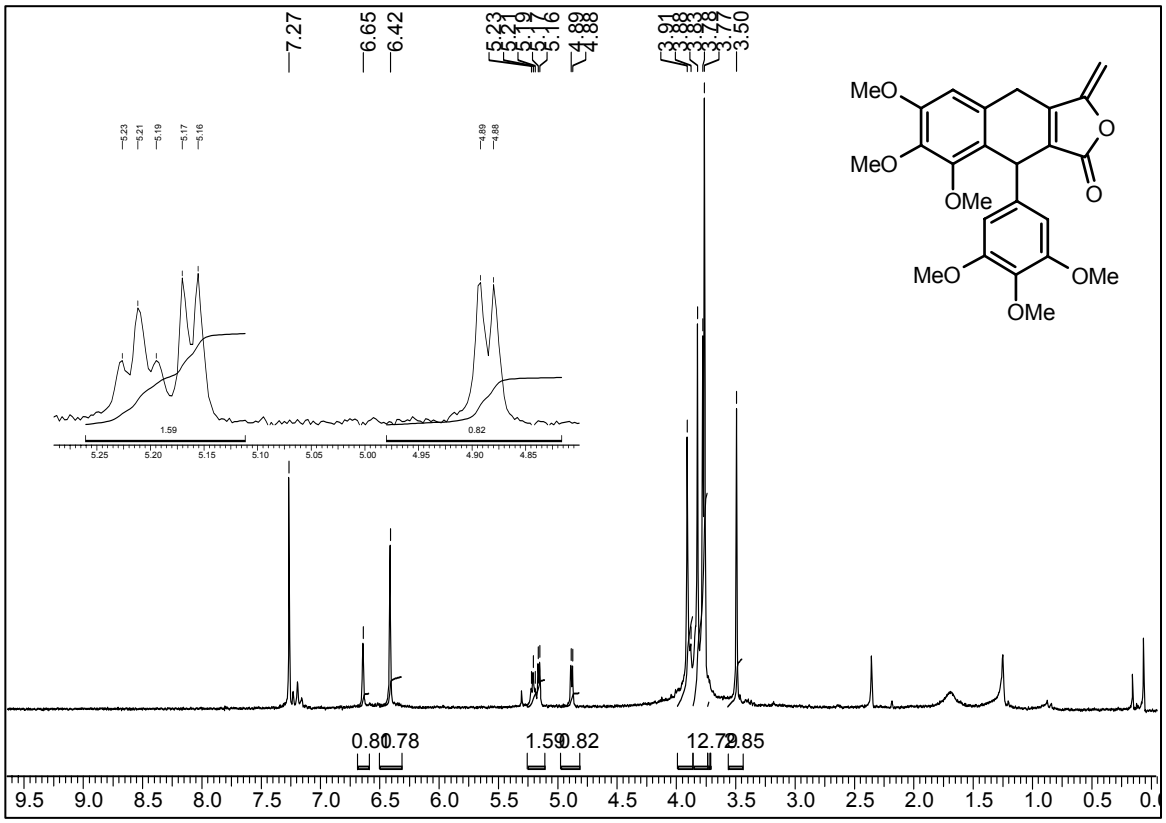


^{13}C NMR and DEPT of compound 191 ($CDCl_3$+CCl_4, 50 MHz)

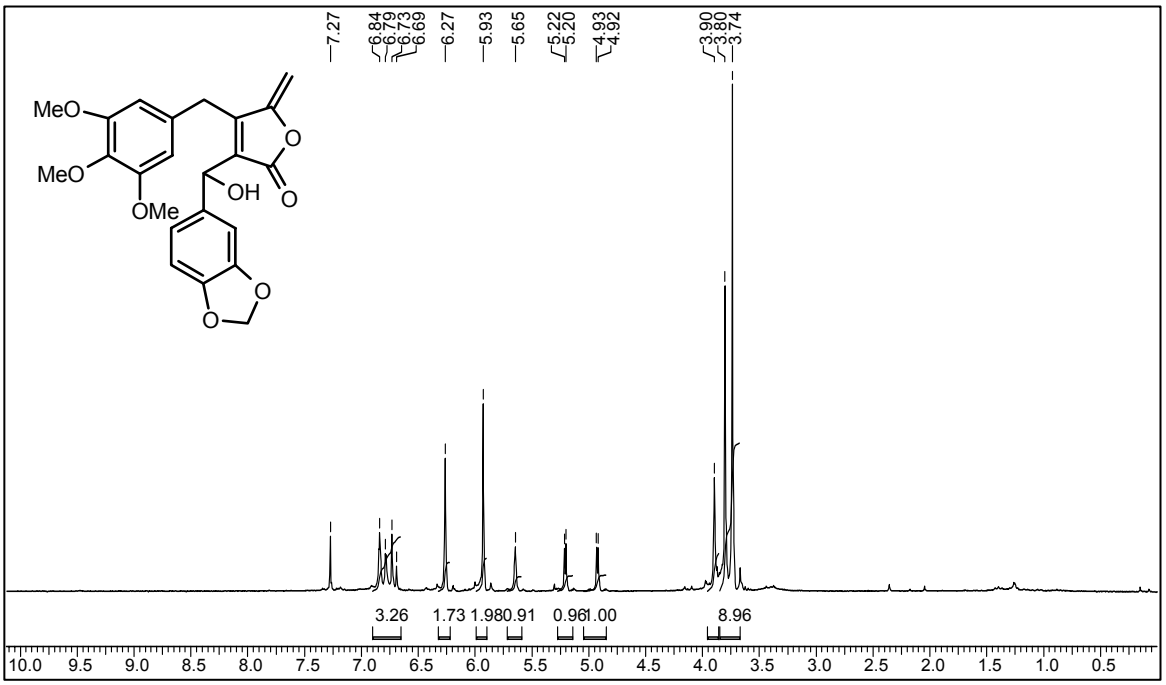




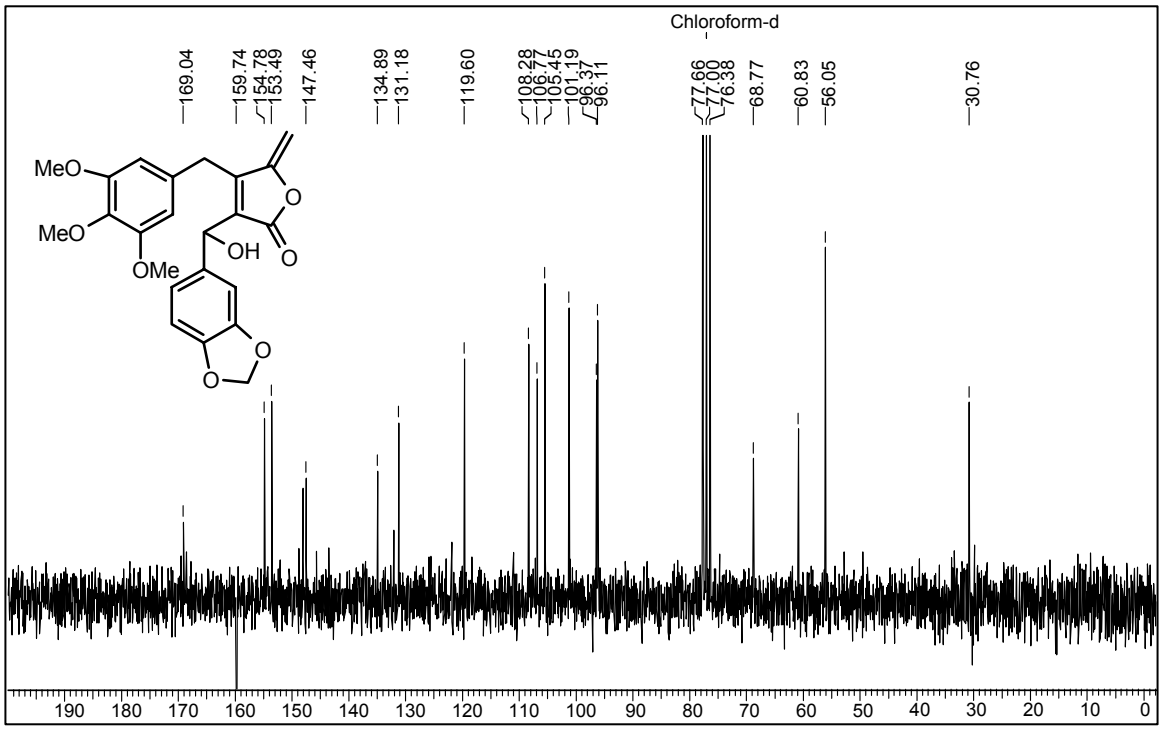
^{1}H NMR of compound 192 ($CDCl_3$+CCl_4, 200 MHz)



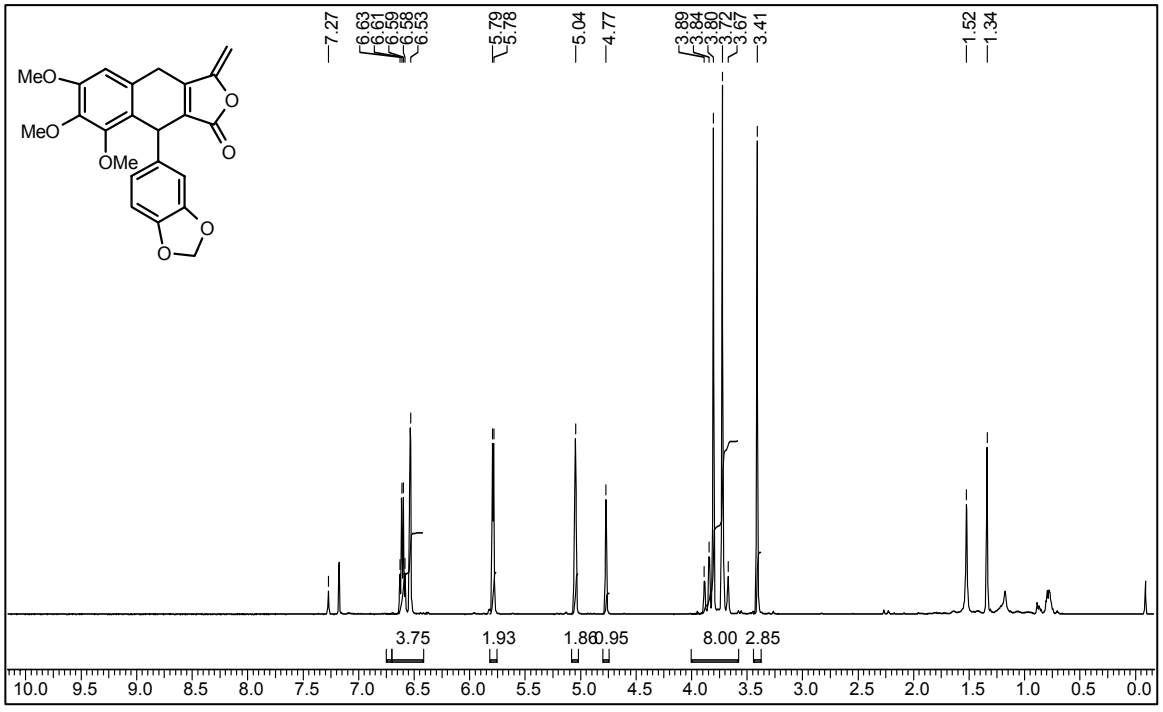
^{1}H NMR of compound 193b ($CDCl_3$+CCl_4, 200 MHz)



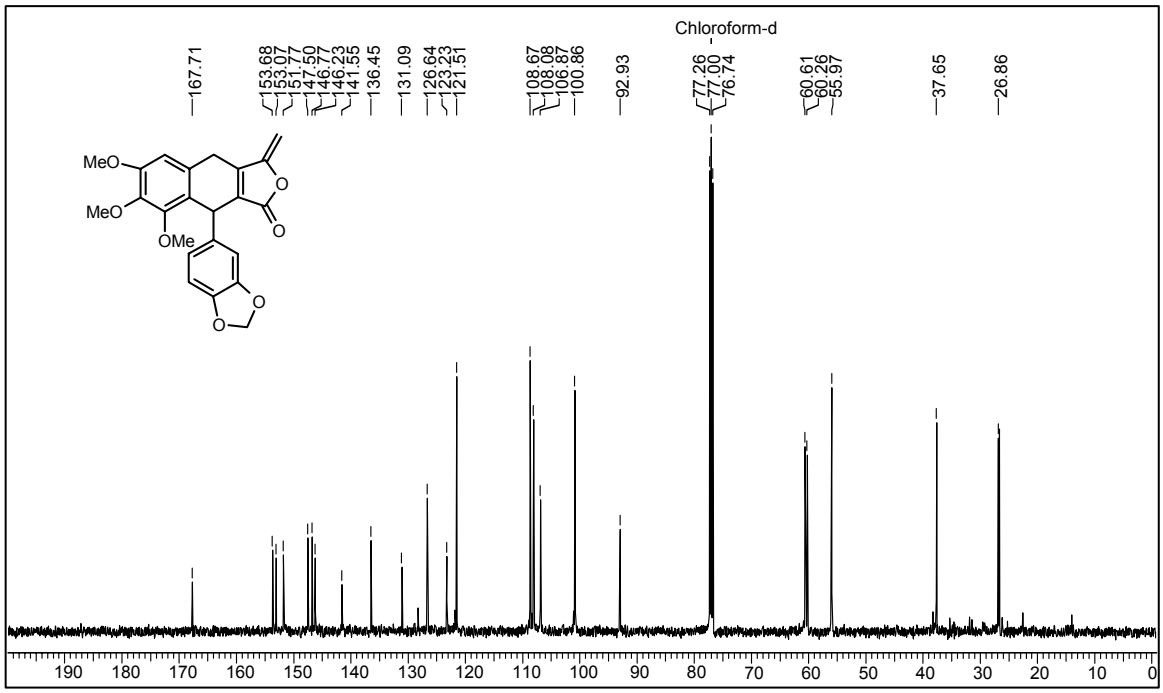
^{13}C NMR of compound 193b ($CDCl_3$+CCl_4, 50 MHz)

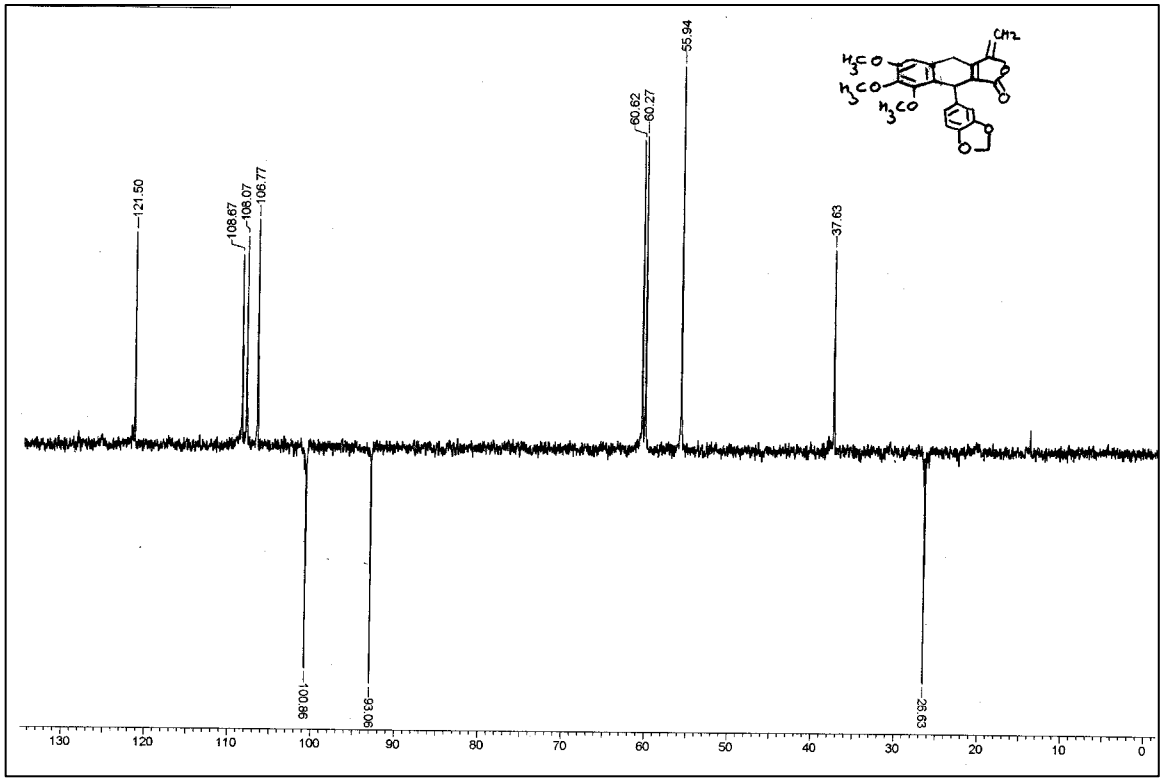


^{1}H NMR of compound 194b ($CDCl_3$+CCl_4, 200 MHz)

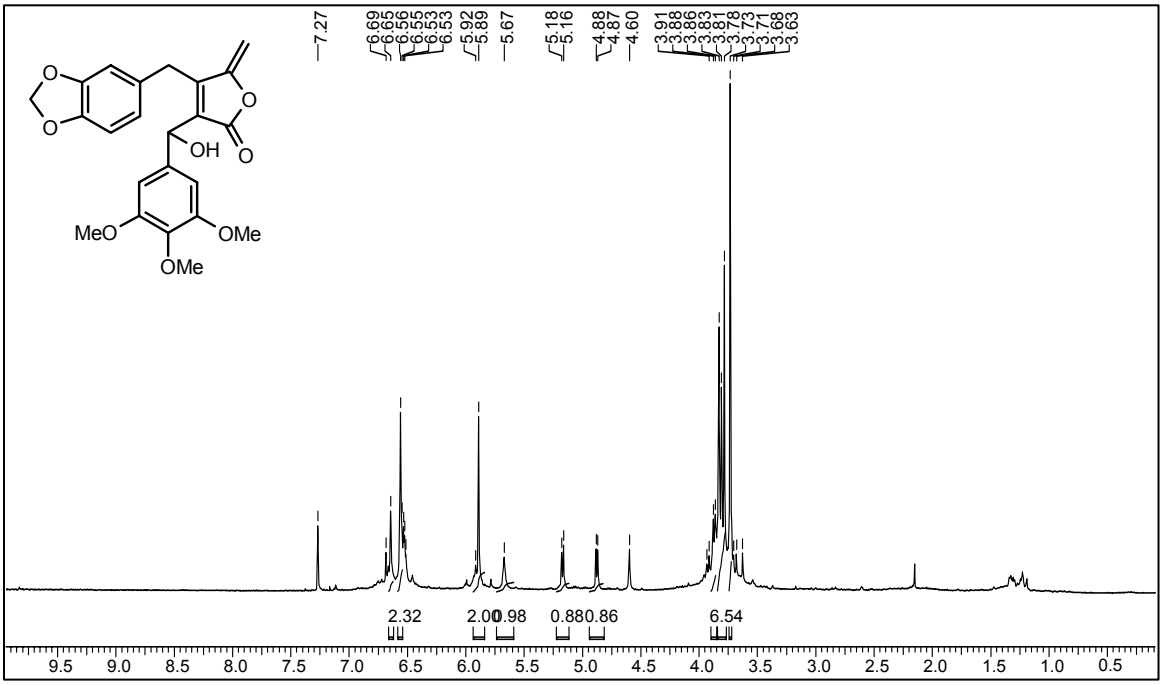


^{13}C NMR and DEPT of compound 194b ($CDCl_3$+CCl_4, 50 MHz)

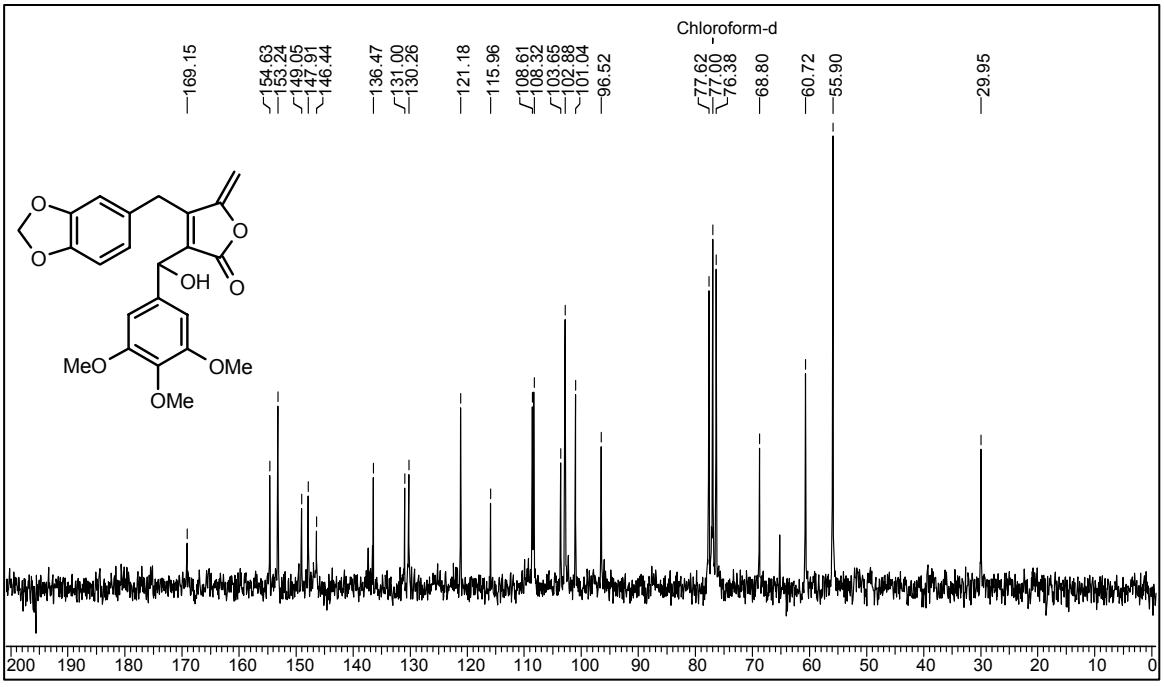


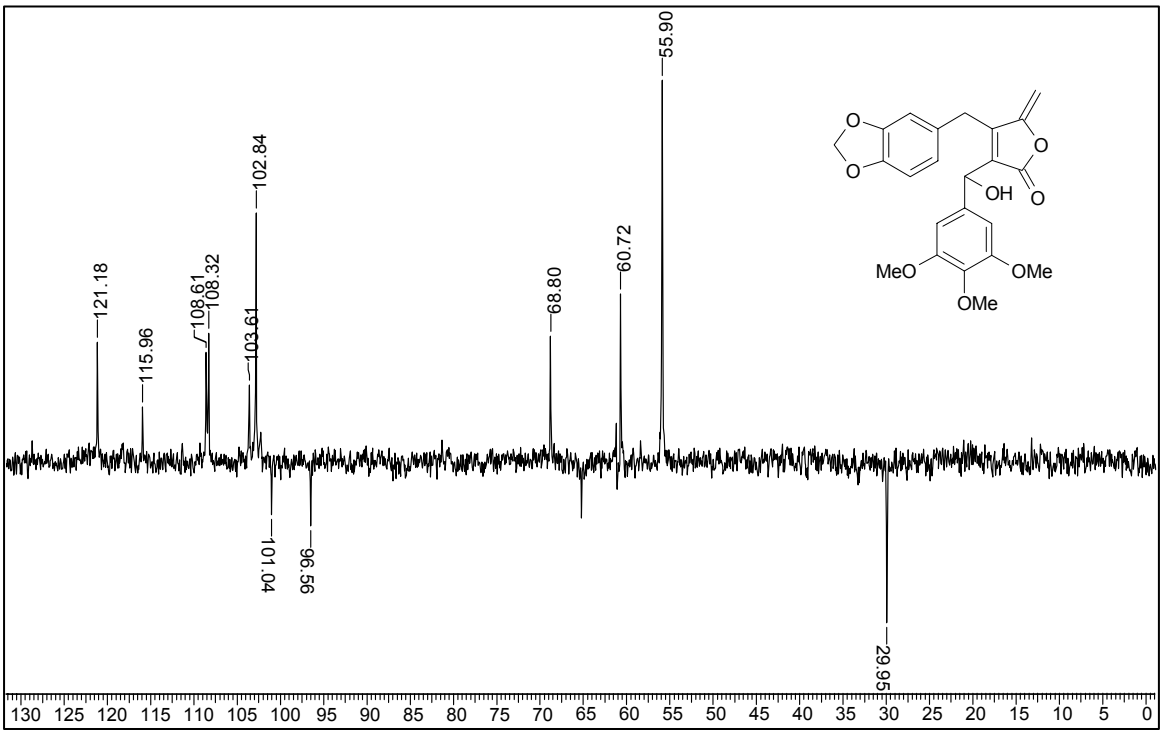


^{1}H NMR of compound 197 ($CDCl_3$+CCl_4, 200 MHz)

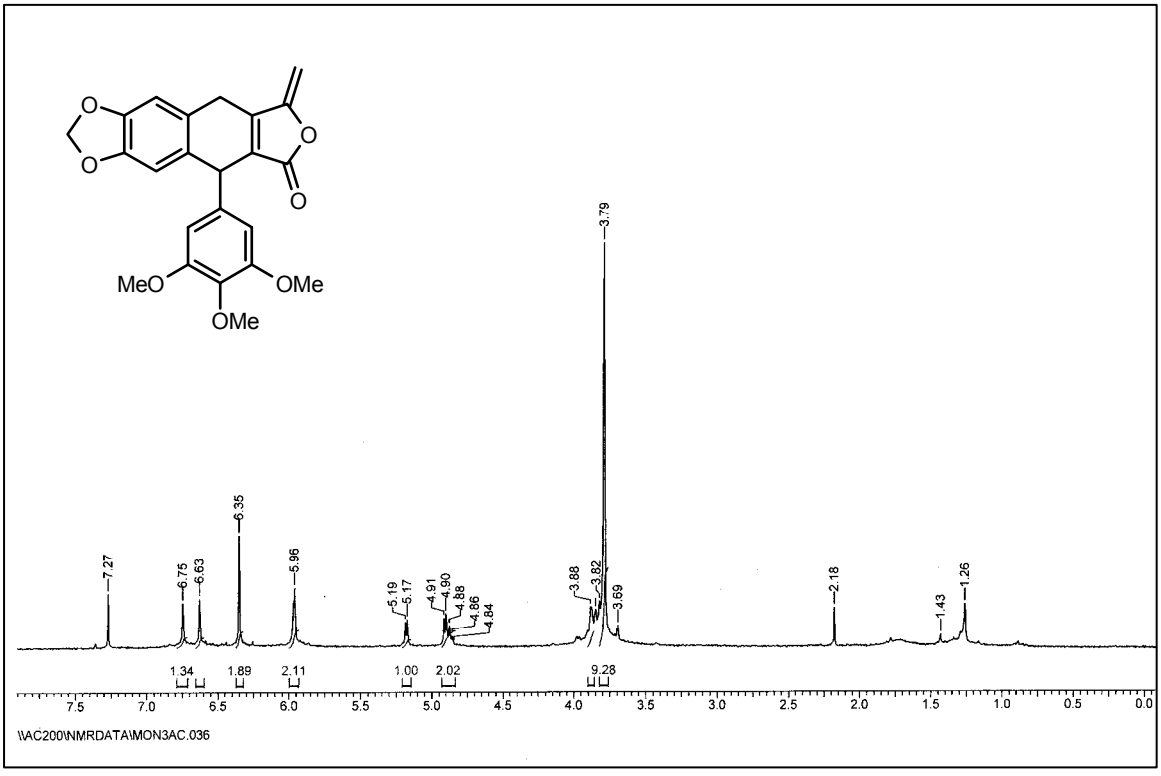


^{13}C NMR and DEPT of compound 197 ($CDCl_3$+CCl_4, 50 MHz)

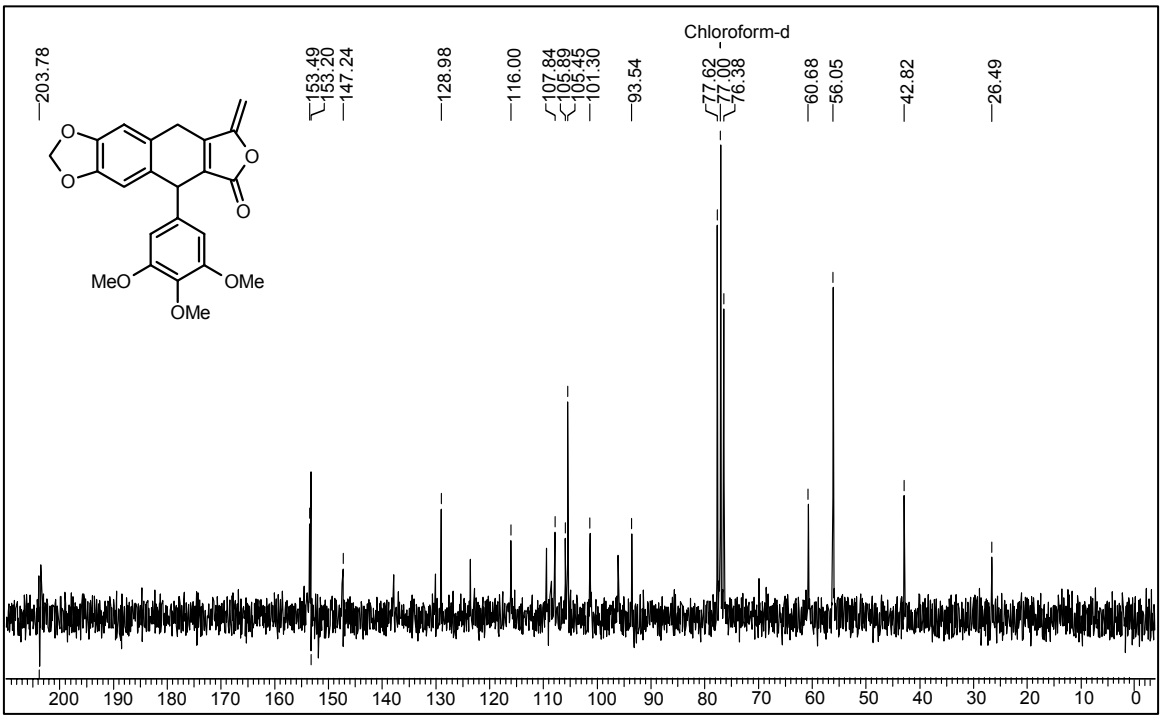




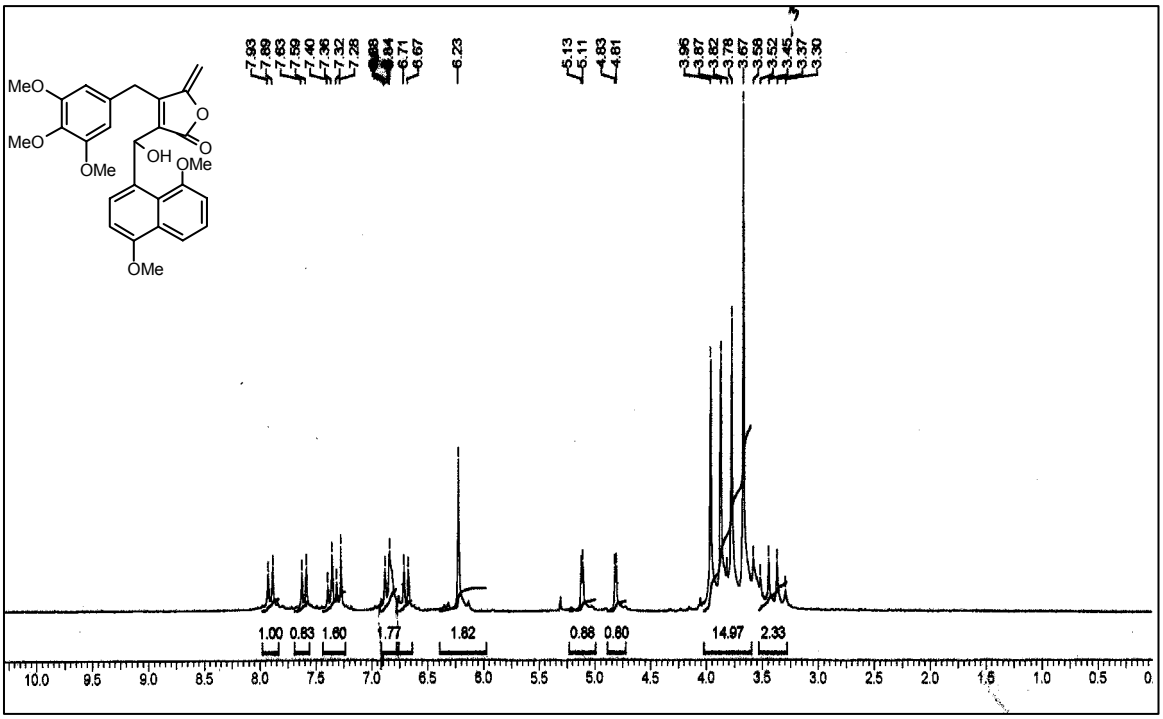
^{1}H NMR of compound 198 ($CDCl_3$+CCl_4, 200 MHz)



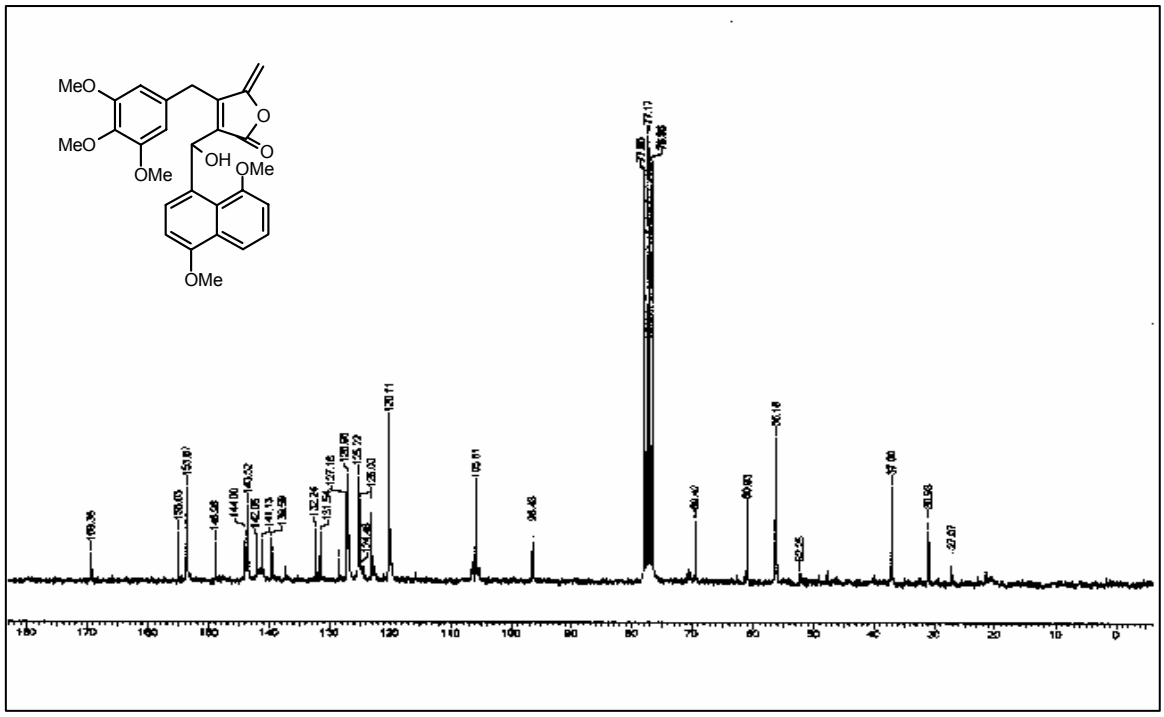
^{13}C NMR of compound 198 ($CDCl_3$+CCl_4, 50 MHz)



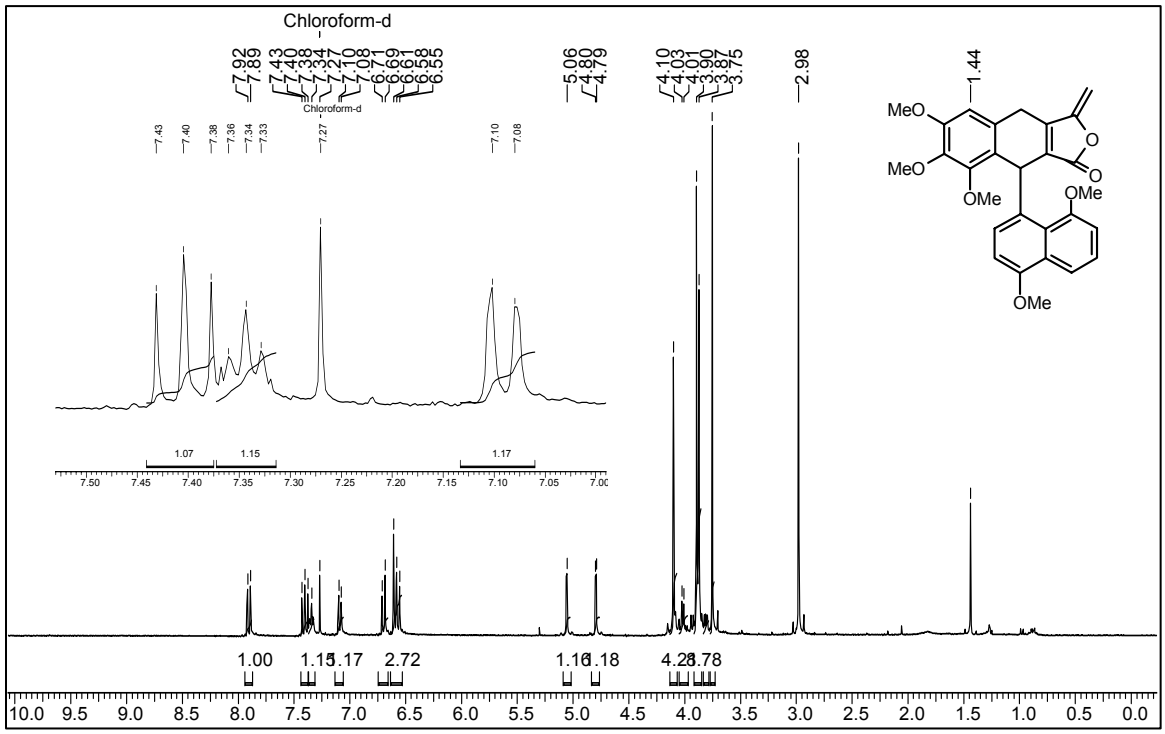
^{1}H NMR of compound 201c ($CDCl_3$+CCl_4, 200 MHz)



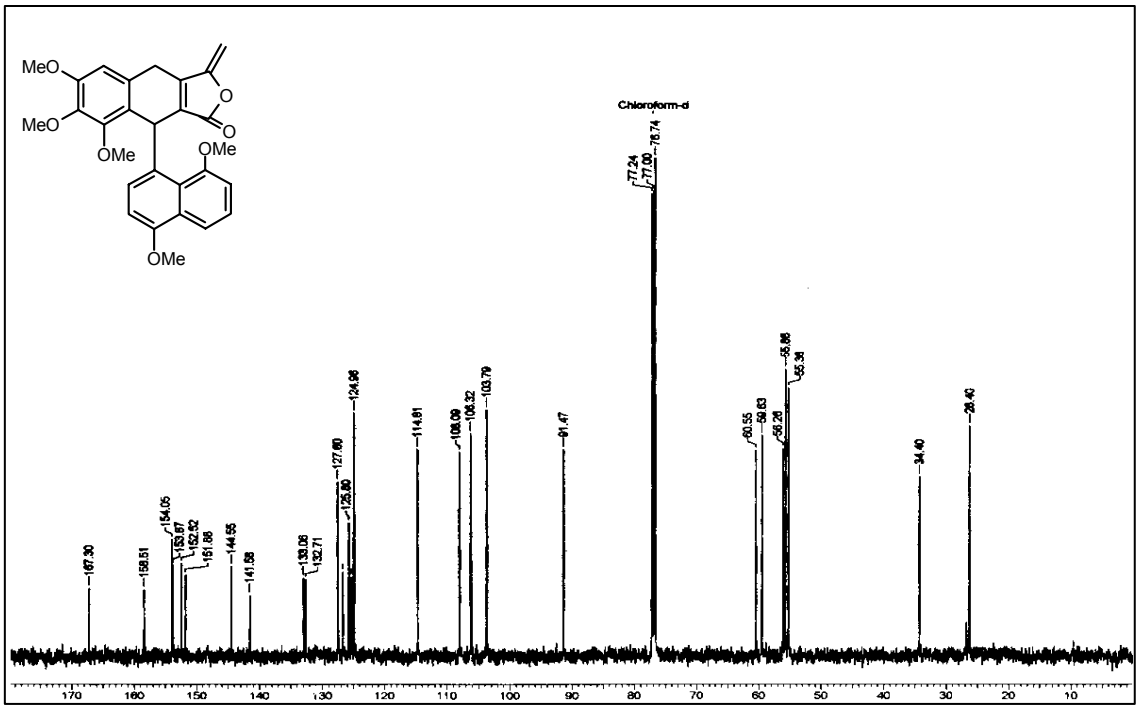
^{13}C NMR of compound 201c ($CDCl_3$+CCl_4, 50 MHz)



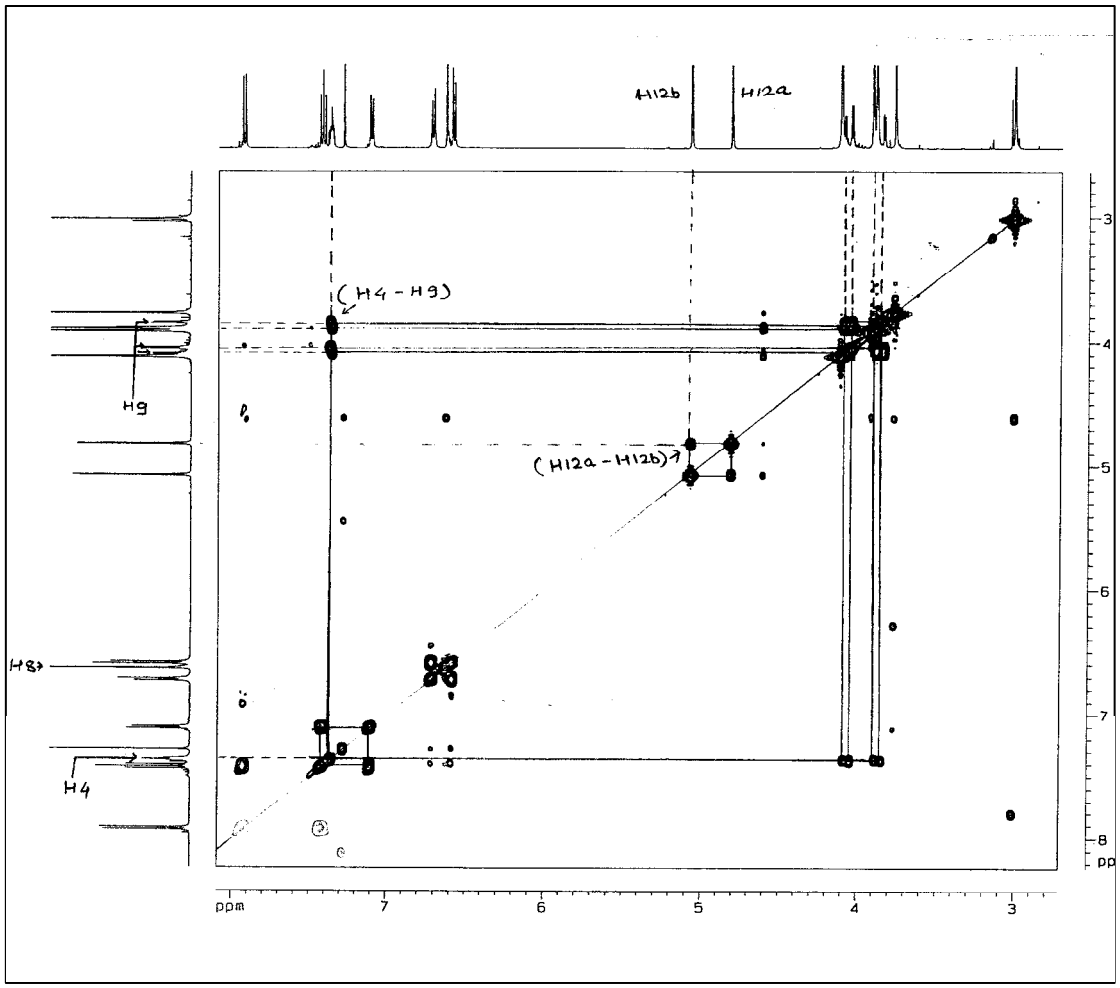
^{1}H NMR of compound 202c ($CDCl_3$+CCl_4, 200 MHz)



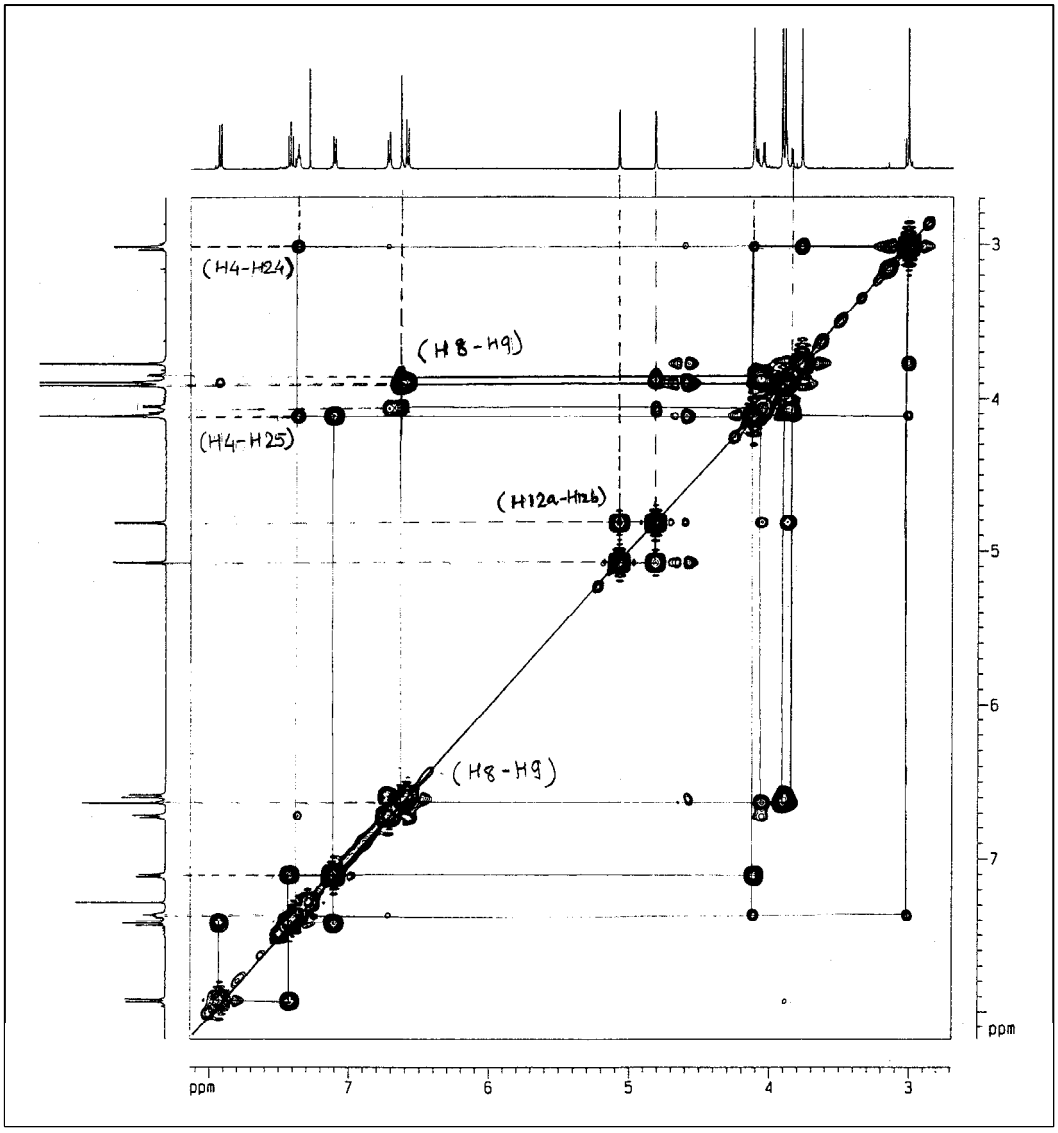
^{13}C NMR of compound 202c ($CDCl_3$+CCl_4, 50MHz)



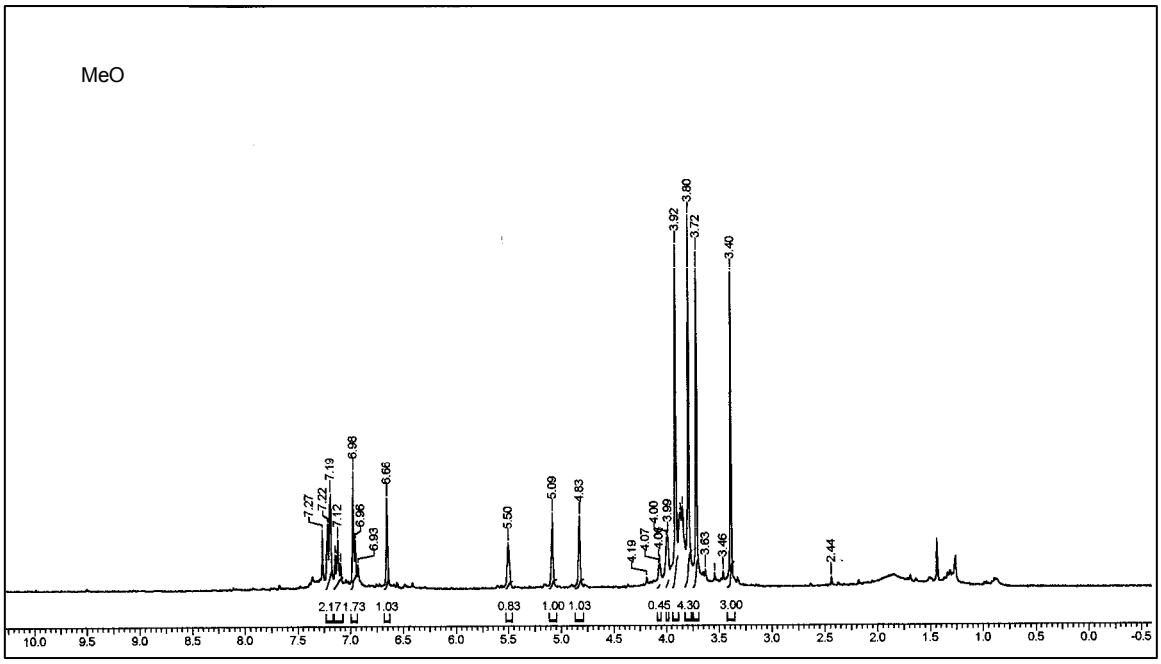
COSY spectrum of compound 202c



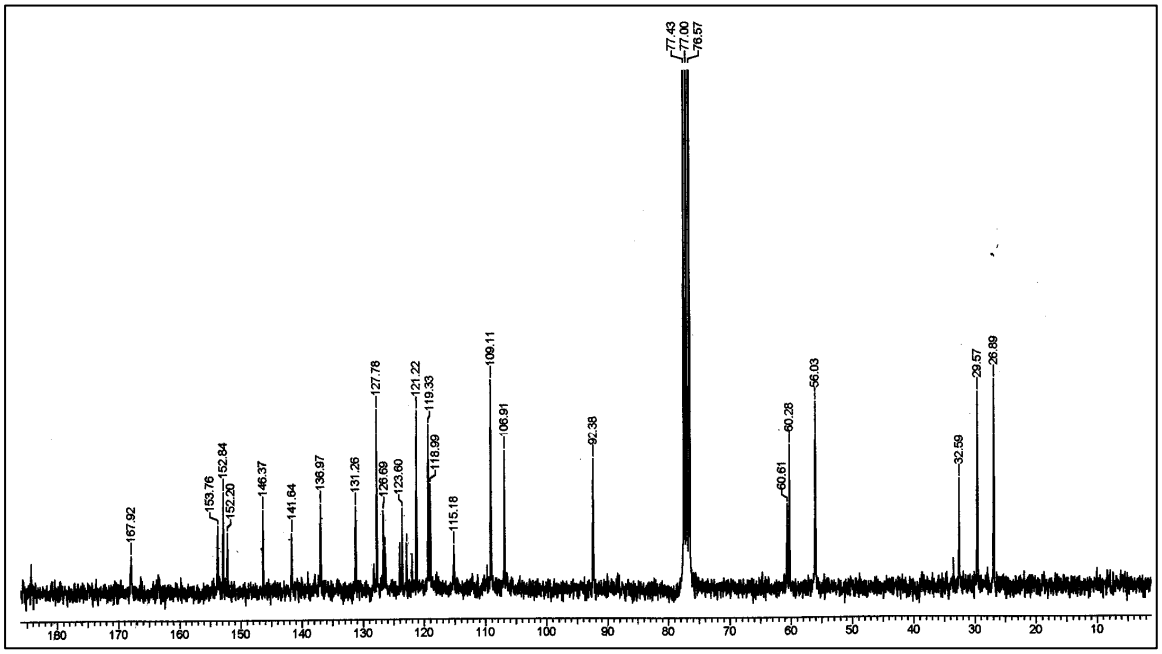
NOESY spectrum of compound 202c



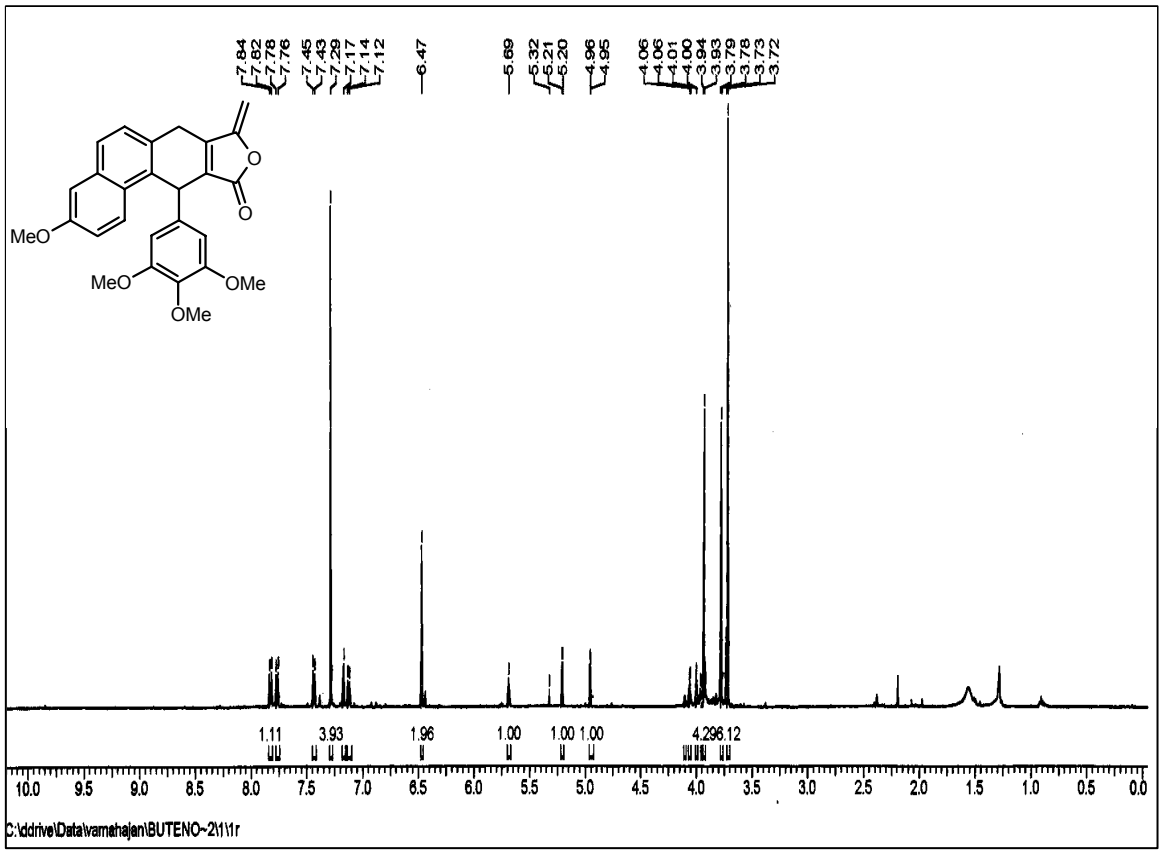
^{1}H NMR of compound 203 ($CDCl_3$+CCl_4, 200 MHz)



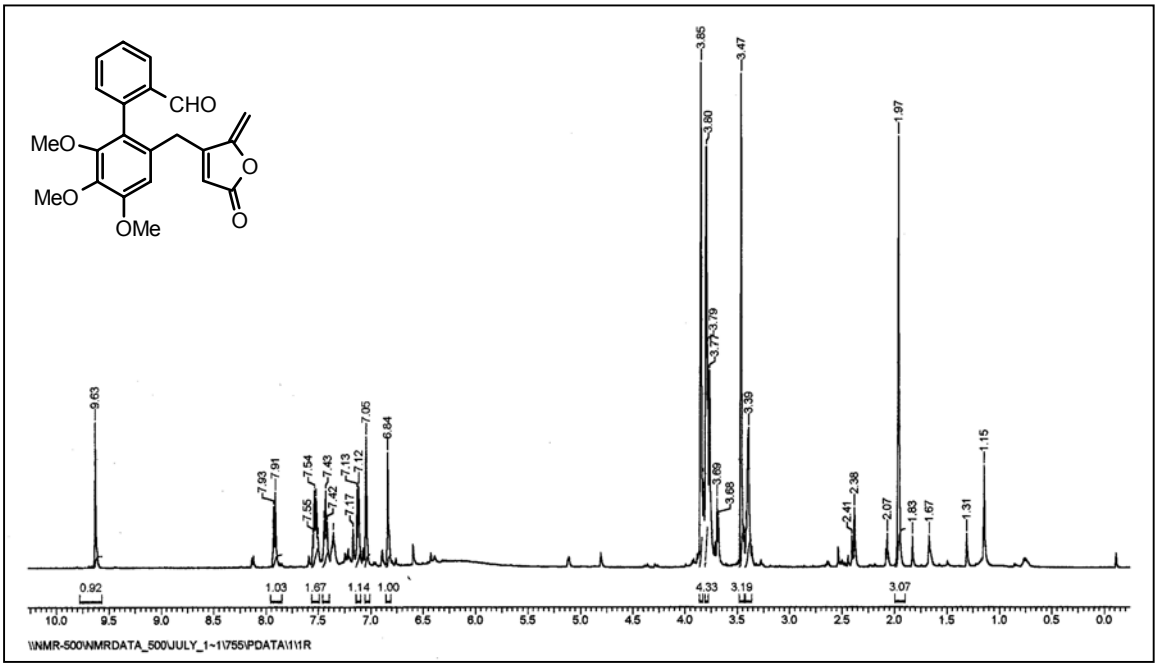
^{13}C NMR of compound 203 ($CDCl_3$+CCl_4, 50 MHz)



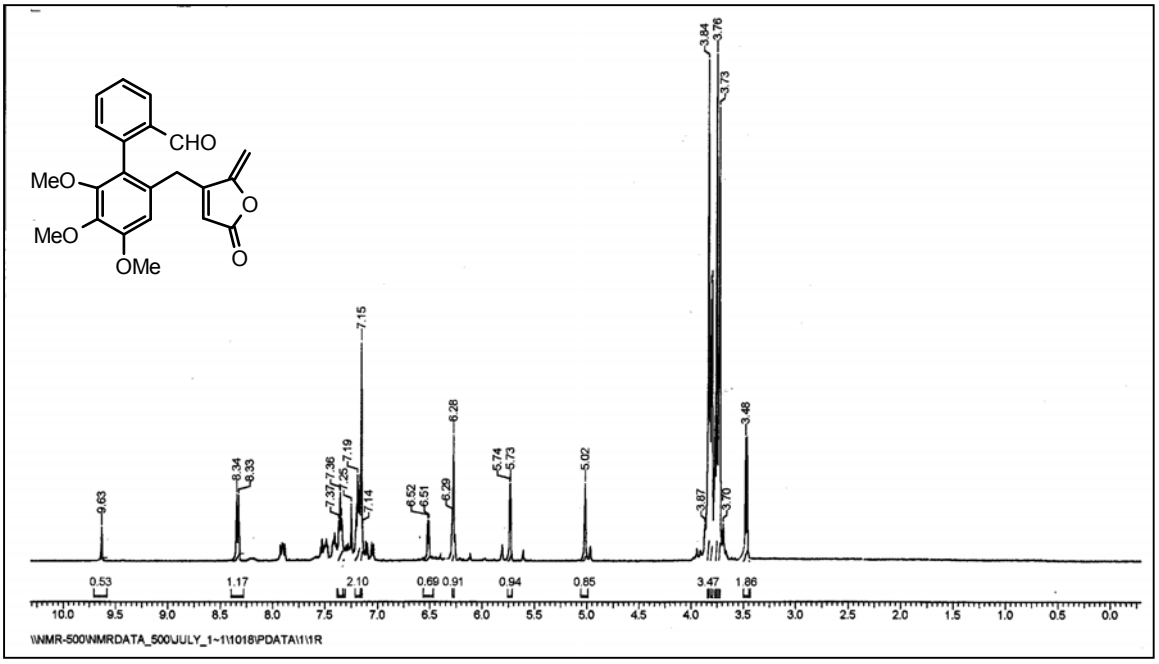
^{1}H NMR spectrum of compound 205 ($CDCl_3$+CCl_4, 500 MHz)



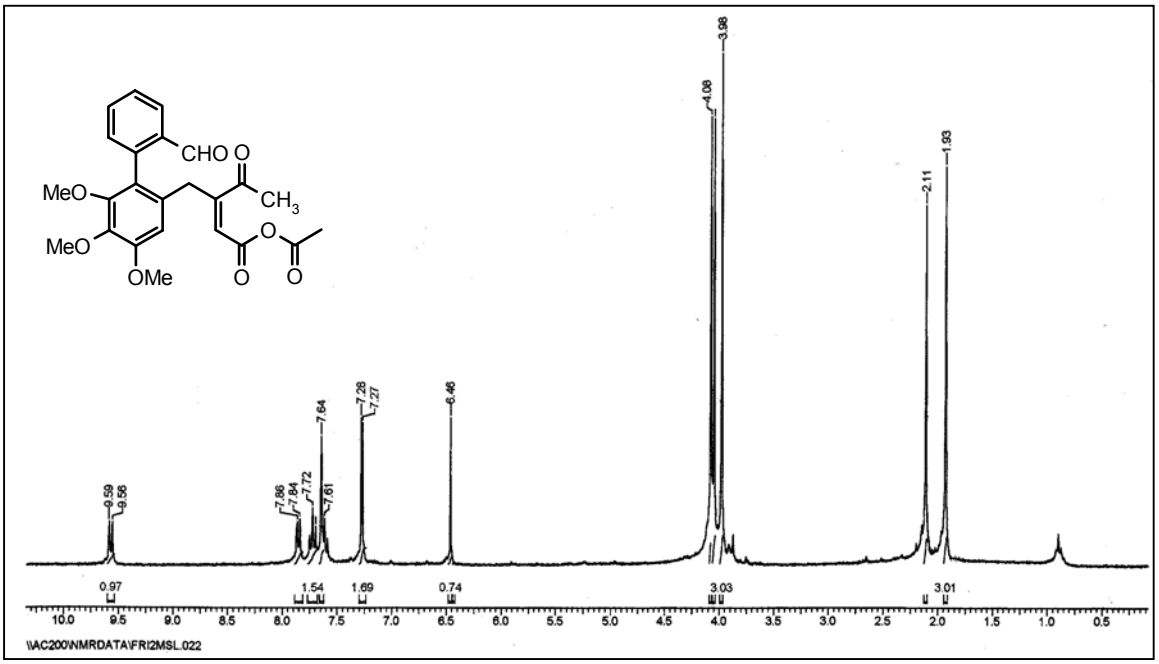
^{1}H NMR of compound 206 ($CDCl_3$+ CCl_4, 500 MHz)



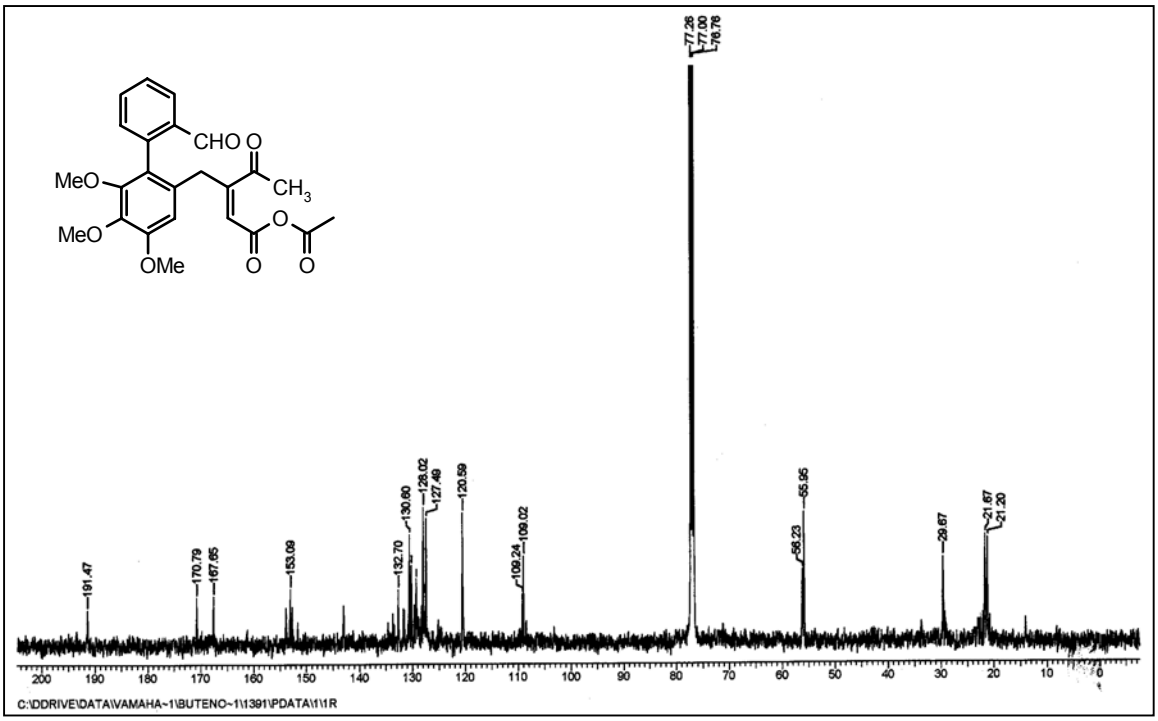
^{1}H NMR of compound 207 ($CDCl_3$+CCl_4, 500 MHz)



^{1}H NMR of compound 208 ($CDCl_3$+CCl_4, 300 MHz)



^{13}C NMR of compound 208 ($CDCl_3$+CCl_4, 125 MHz)



1.2.5. REFERENCES

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1.3.1. INTRODUCTION

Cancer is a multi-step process in which multiple genetic alterations must occur, usually over a span of years, to have a cumulative effect on the control of cell differentiation, cell division and growth. The efficacy of clinical cancer chemotherapy is largely encountered by two major problems which are yet to be overcome: the lack of cell selectivity of anticancer agents and the occurrence of intrinsic or acquired resistances leading to significant side effects and sometimes failures of treatment. The search for new drugs with higher therapeutic index and lower capacity to induced resistance still remains an active field of investigation in medicinal chemistry.

As discussed in introductory part of this chapter chemotherapy is having exceptional importance in the treatment of cancer. Till date different types of natural and unnatural congeners were in the treatment and many of them are under different stages of clinical trials. In addition, huge amount of research has been devoted in the search of new hit-lead molecules to fight against the cruel disease 'cancer'.

Chemotherapy faces different problems in the treatment of cancer due to poor efficacy of the anticancer compounds and their side effects during ongoing treatments. Therefore search of such anticancer compound that could cure cancer without side effects or with minor side effects continues.

In cancer chemotherapy,[1] cell is considered as smallest flask of the reactions, in which many chemical transformations occur. These transformations are in controlled manner in normal cells and are unrestrained in cancerous cells. Therefore in the modern era search of new anticancer compounds is based on chemical transformations occurring during the cell replication, recombination and transcription. But chemical constituents of these reactions are near about similar in both of these cells so the main challenge of cancer chemotherapy is to distinguish the cancer cells from normal cell and abort the life cycle of cancerous cells selectively. This cell selectivity could reduce the side effects of the cancer treatment. The chemotherapeutic agents based on the phase of cell cycle have been discussed in the introduction of this chapter. In past years different natural products were isolated and screened for their cyctoxicity and this research has brought up with number of well-known anticancer natural products such as podophyllotoxin (**13**), vinblastine (**16**), vincristine (**17**), paclitaxel (**15**), camptothecin (**20**), stignancin (**14**) and

many more. But certain synthetic modifications of these naturally occurring compounds became valuable gift for the cancer chemotherapy. There after thrust of medicinal research has been diverted towards design and synthesis of novel chemical entities and their quantitative structure activity relationship (QSAR) based on the bioactive natural products. This is because the conventional "isolation-purification-testing of natural products" will not be able to cope up with this increasing demand of bioactive molecules in time and thus will not be able to cater to the exponentially increasing need of futuristic drug industries.

Aim and objectives of present work

Alkylating agents were one of the first cancer chemotherapeutic agents employed and are most widely and successfully used antitumor agents in clinical use till date, but number of alkylating agents used in cancer chemotherapy are deactivated by over expression of enzyme, glutathione *S*-transferase.[2] It is an enzyme formed in cell, which is over expressed in cancerous cells in the form of GST isoenzymes (α, μ, π). These enzymes play an important role in deactivation of antineoplastic agents such as melphalan, chlorambucil (nitrogen mustard) and cyclophosphamide. Due to such over expression of enzymes and deactivation of anticancer agents tumor cells become drug resistant as reported in carcinoma of colon, lung, kidney, ovary, pancreas, esophagus, stomach and breast.

It is well known that MSK (methyl styryl ketone), conjugated enone system and butenolides from sesquiterpeniods showed cytotoxic activity by inhibiting the cellular enzymes such as glutathione *S*-transferase, *S*-aldenosyl *C*-homocystine hydrolase etc. These over expressed enzymes in cancerous cells react with conjugated enone sysytem and consequently it abort the cell division.[3]

1.3.2. PRESENT WORK

Our research aim is to come up with the synthesis of novel chemical entities by short synthetic pathways and which were featured with wide range of biological activity to contribute global drug discovery program. With this target we have standardized reaction conditions for the synthesis of γ-methylenefuranones. We have synthesized different analogues of the furanone derivatives, which were further explored for the synthesis of hydroxy, and cyclic lignan derivatives as described in section 1 and 2 of this chapter. Some of these analogues were screened for their cytotoxicity and antifungal activity. Cytotoxic activity was studied at Dabur Reseach Foundation (DRF) Gaziabad. The present section describes structure activity relationship of furanone and lignan analogues.

1.3.3. RESULTS AND DISCUSSION

Cytotoxic assay

The cytotoxicity of furanone and derivatives was tested by performing a 72-hour MTT cytotoxicity assay, which is based on the principle of uptake of MTT [3- (4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide], a tetrazolium salt, by the metabolically active cells where it is metabolized by active mitochondria into a blue-colored formazan product, which can be read spectrophotometrically.[21] To prepare the MTT stock solution needed for the one-day MTT cytotoxic assay, MTT (Sigma catalogue number M 2128) was dissolved in phosphate buffered saline with a pH of 7.4 to obtain an MTT concentration of 5 mg/ml, the resulting mixture was filtered through a 0.22 μ filter to sterilize and remove a small amount of insoluble residue and the filtered mixture was used as the MTT stock solution (20 μl / 200 μl of medium). Briefly, for each type of tumor cell, approximately 10,000-50,000 cells were seeded in a 96-well culture plate and incubated with each of the furanone derivatives in a CO_2 incubator for 72 hours. The concentrations of the furanone derivatives were in the range of 1 – 100 μg/ml. Controls, which were not treated with the furanone derivatives, were similarly incubated. The assay was terminated after 72 hours by adding 100 μg /(20 μl) of MTT to each well, then incubating for approximately one additional hour, and finally adding 50 μl of 10% SDS-0.01 N HCl to each well to lyse the cells and dissolve the formazan. After incubating for one hour at 37^{o}C, the plate was read spectrophotometrically at 540 nm and the

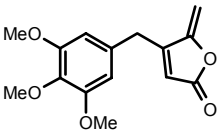
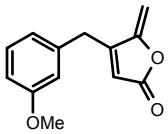
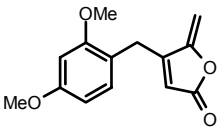
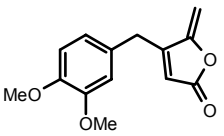
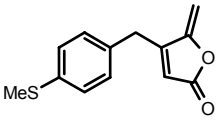
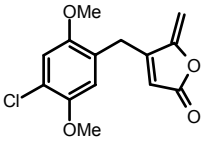
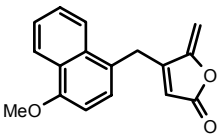
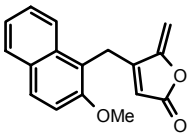
cytotoxicity percentage (i.e., the killing percentage or the inhibition percentage) was calculated using the following formula:

Cytotoxicity percentage = 100 x [1-(X/R_1)].

X= (Absorbance of the treated sample at 540 nm)-(Absorbance of a blank at 540 nm),
R_1 = (Absorbance of the untreated control at 540 nm)-(Absorbance of a blank at 540 nm).

Thus, in each of the MTT cytotoxicity assays reported herein, the cytotoxicity percentage was calculated according to the above formula and was based on the proliferation of the untreated controls, the value of which was taken as 100%. A dose response curve was prepared and IC_{50} values determined graphically. Tables 1, 2 and 3 show the mean IC_{50} values with standard deviation.

Table 1. Cytotoxic activity of furanone derivatives

			ED 50 µg/ml								
Entry	**Comp**	**Structure**	**SW**	**MOL T4**	**293**	**DU 145**	**L 132**	**Mia Paca**	**Hep 2**	**PA1**	**ECV**
1	**119a**		**8**	**<1**	ND	**4**	**<1**	**10**	**4**	**4**	**5**
2	**119c**		50	ND	32	55	100	60	40	ND	9
3	**119d**		20	ND	29	45	20	40	15	ND	8
4	**119e**		>100	ND	>100	>100	>100	>100	>100	ND	36
5	**119f**		15	ND	27	30	70	60	40	ND	10
6	**119i**		**2.5**	**8.4**	**4**	**2**	**2**	**5**	**8**	**4**	**10**
7	**119p**		**<1**	**<1**	ND	**4**	**<1**	**>100**	**3**	**<1**	**4**
8	**119q**		**<1**	**<1**	ND	**5**	**5**	**6**	**3**	**7**	**5**

ND = Not Done

Table 2. Cytotoxic activity of hydroxy lignan derivatives

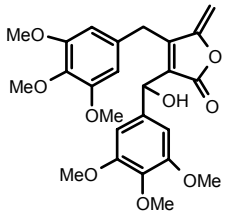
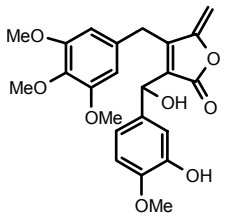
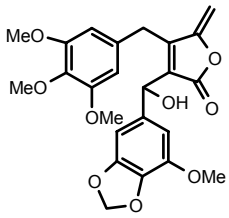
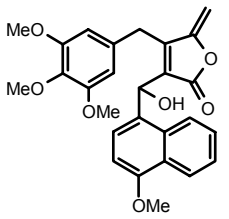
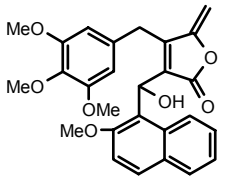
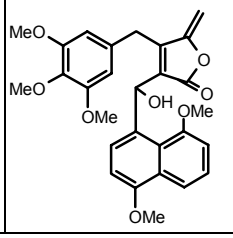
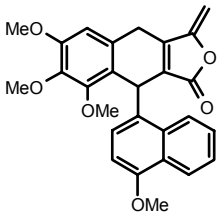
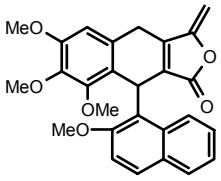
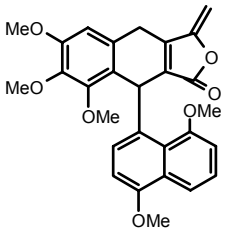
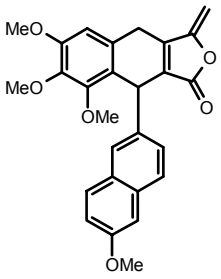
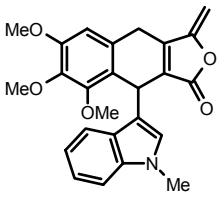
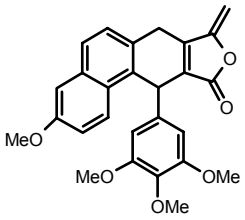
			ED 50 µg/ml							
Entry	**Comp**	**Acyclic Lignans**	**PTC**	**DU 145**	**KB**	**L 132**	**Mia Paca**	**PA1**	**U87 MG**	**MCF 7**
1	**191**		16	**9.5**	**6**	**8**	**9**	24	**10**	**10**
2	**193a**		36	16	13	18	23.5	31	26	26
3	**193c**		6	17.5	7.5	25	23	27	7	31
4	**201a**		6	**8**	**7**	**5**	**6**	**8.5**	**6**	**6**
5	**201b**		9	**4**	**<1**	**4.5**	**8**	**8.5**	**6**	**8**
6	**201c**		7	**8**	**4**	**9**	**8**	**7**	**6**	>100

Table 3. Cytotoxic activity of cyclic lignan derivatives

ED 50 µg/ml						
Entry	**Comp**	**Cyclic Lignans**	**PA1**	**U87MG**	**DU145**	**MiaPaca**
1	**202a**		9.5	>100	23	26
2	**202b**		>100	>100	>100	>100
3	**202c**		74	>100	>100	53
4	**202d**		**6**	**8**	**4**	**4.5**
5	**203**		**4**	**4**	**7**	**3**
6	**205**		**7**	**27**	**16**	**22**

Some of the γ-methylene furanone analogues were screened for their cytotoxicity against nine tumor cell lines such as SW (ovary), MOLT 4, (leukemia), 293 (kidney), DU 145 (prostate), L132 (lung), MiaPaca (pancreas), Hep (larynx), PA-1 (ovary), ECV (endothelial), U87 and MCF7 (breast).

Furanone **119i** derived from 2-chlorobenzaldehyde was initially screened for cytotoxicty against these cell lines and it showed potential cytotoxicity but also showed toxicity against normal cell lines.

It was postulated that presence of chloro in the molecules might be toxic to the normal cells. Therefore we designed the furanone derivative starting from benzaldehydes and naphthaldehydes where in there are no halogens. Furanone **119** bearing 3,4,5-trimethoxy substituents on aromatic ring showed excellent cytotoxicity against MOLT4 (leukemia) and L132 (lung) cancer cell lines and potential cytotoxicity against other cell lines (table 1, entry 1).

Furanones **119c**, **119d**, **119e** derived from 3-methoxy, 2,4-dimethoxy, and 3,4-dimethoxy benzaldehydes showed moderate to poor cytotoxicity, it may be due to the stability problem of these analogues.

Furanone **119f** also showed poor cytotoxicity due to its stability problem. But the furanone derivatives **119p** and **119q** derived from 4-methoxy and 2-methoxy naphthaldehydes showed promising and encouraging cytotoxicity.

Further hydroxy lignan analogues were screened for their cytotoxicity against available cancer cell lines as mentioned in Table 2.

For the synthesis of lignan derivatives we had selected furanone derivatives furanone derivative **119a**, which was derived from 3,4,5-trimethoxy benzaldehyde. The selected furanone **119a** was having good stability and prominent cytotoxicity and also because the 3,4,5-trimethoxy functionality is widely observed in case of well-known cytotoxic agents such as podophyllotoxin and combretastatin.

Hydroxy lignan **191** derived from condensation of furanone **119a** and 3,4,5-trimethoxybenzaldehyde has retained cytotoxicity and shown considerable cytotoxicity against DU145, KB, L132 and MiaPaca cell lines. (Table 2, Entry 1).

Derived naphthalene hydroxy lignans showed moderate cytotoxicity. It was interesting to note that hydroxy lignan derivatives derived from 4-methoxy, 2-methoxy or 4, 8-

dimethoxy naphtaldehydes showed potential cytotoxicity (Table 2, Entry 201 a, 201b, 201c).

These results encouraged us to study the cytotoxicity of cyclic lignan analogues, therefore some cyclized lignan analogues (Table 3, Entry 1-6) were screened for their cytotoxicity against available four cell lines such as PA1, U87, DU-145 and Mia Paca showed promising cytoxicity. Finally heterocyclic **203** and angular lignan **205** anlogues also showed good cytotoxicity.

Mode of action of γ-methylenefuranones

From the literature survey it was envisaged that the γ-methylene furanone could show cytotoxicity due to its conjugated *exo*-methylene moiety. Proposed schematic representation of biochemical reaction is shown in figure 1.

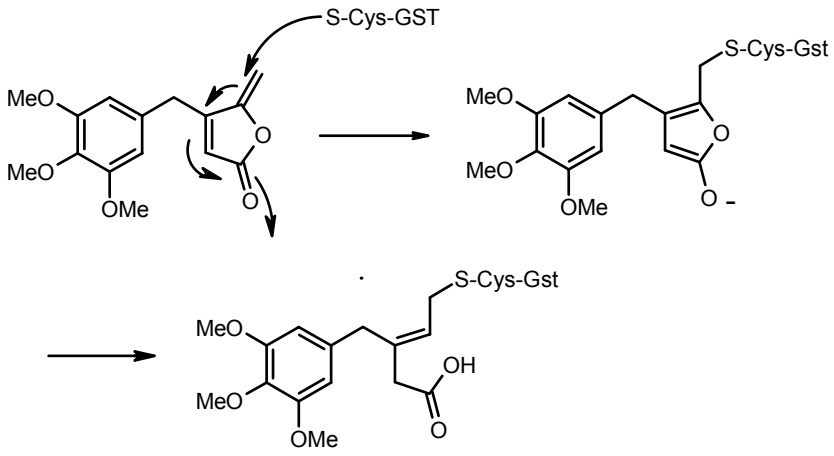


Figure 1. Plausible Inhibitory effect of γ-methylenefuranone on GST-π enzymes

Anti-fungal activity of γ-methylene furanone analogues

Two selected NCEs viz. furanones **119a** and furanone derived from 6-methoxy-1-naphthaldehyde (**119t**) were screened for antifungal activity at FDC Ltd. Mumbai. Three slandered ATCC strains of fungal cultures were used for the testing; *Candida ablicans* ATCC 24433, *Aspergillus niger* ATCC 16404 and *Fusarium proliferatum* ATCC 10052. The activity screenig was performed by macrobrotu dilution method optimized by using amphotericin B and fluconazole as the standards.

Table 4. Anti-fungal Activity Data

Entry	NCE	C. ablicans ATCC 24433	A. niger ATCC 16404	F. proliferatum ATCC 10052
1	**Amphotericin-B (AMB)**	0.25	1	2
2	**FLU (Fluconazole)**	1	128	NI at 128
3	**119a**	NI at 128	**16**	**32**
4	**119t**	NI at 4	**1**	NI at 4

NI: No Inhibition

The activity data is depicted in Table 4 which indicated that both the compounds showed selectivity against *A. niger*. The napathalene analogue **119t** showed comparable activity for *A. niger* with that of Amhoptericin B and was found to be better than fluconazole.

1.3.4. CONCLUSION

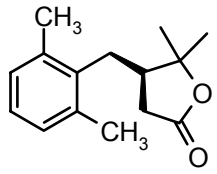
The presented biological data revealed that, the designed γ-methylenefuranone derivatives showed promising cytotoxicity as well as some furanone derivatives showed considerable Antifungal activity. The designed and derived hydroxy and cyclic lignan analogues retained their cytotoxicity after derivatization. These results contribute a novel class of compounds with potential activity to the global drug discovery program.

1.2.5. REFERENCES

1. *Cancer and chemotherapy*, (Academic press) **1981**, vol. 3, chap. 1-11, pp 1-293.
2. (a) Suar, J. M.; Smith R. L.; Bao, J.; Kattnig, M. J.; Kuster, R. K.; Mcclure, T. D. Mayersohn, M; Sipes, J.; Glenn, I. *Drug Metabolism* **1997**, *25*, 732. (b) Spencer, S. R.; Xue, L.; Klenz, S.; Talahay, P. *Biochem*. *J*. **1991**, *273*, 711-717.
3. Wang, W.; Ballatori, N. Pharmacological Reviews **1998**, *50*, 335-345.

1.4.1. INTRODUCTION

Solafuranone (**210**) is a natural product isolated[1] from the plant *Solanum indicum* (Solanaceae), widely grown in Taiwan. It is a folk medicine used as an analgesic for toothache, rhinitis and breast cancer.[2]



210

Solafuaranone

The biological study of solafuranone indicated cytotoxicity on ovarian cancer OVCAR-3. It is considered that solvateione (**211**) is precursor for solafuranone.[3] It is isolated from the same extract of *Solanum indicum* with antibacterial and cytotoxic activity for OVCAR-3 with IC_{50} 0.1 nm. It is hypothetical that solvateione may be biologically converted to solafuranone as shown in figure 1.[1]

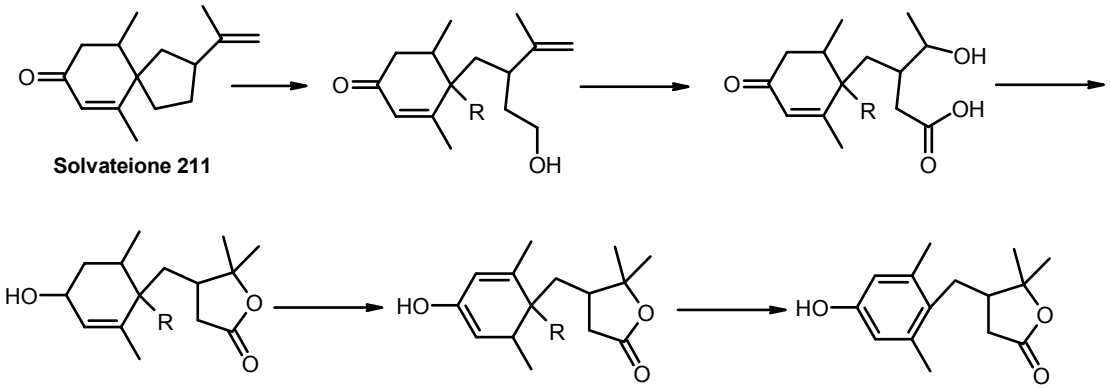


Figure 1. Biochemical pathway of solafuranone synthesis from Solvateione[1]

Solafuranone (**210**) obtained as colorless plates from ethyl acetate/hexane, melting point 132-133 ºC, is optically active with $[\alpha]_D$ of +14.0º and absolute configuration (R). Solafuranone consists of 2,6-dimethyl benzyl moiety, which occurs rarely in nature and represents one of the smallest molecules exhibiting biological activity of importance.

Since there are no reports in the literature for the synthesis of solafuranone and also due to the structural relevance with the research covered in this chapter (Section-1), the synthesis of solafuranone was undertaken.

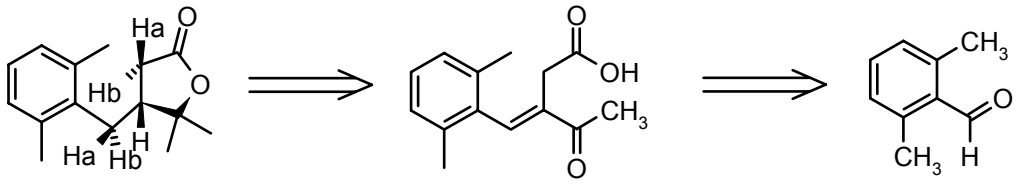
1.4.2. PRESENT WORK

The present section primarily concerns with synthesis of solafuranone, possessing five membered lactone moiety, having cytotoxic activity. It was thought worthwhile to attempt the synthesis of solafuranone because of its structural novelty, including one chiral center at C-4 and our keen interest in the synthesis of five membered lactone derivatives.

Solafuranone is featured with γ-dimethyl function as well as 2,6-benzyl moiety. In view that synthesis of solafuranone could represent application of our synthetic strategy described in section-1 of this chapter, the retrosynthesis was planned as shown in Scheme-1.

The acid intermediate **212** could be obtained by the Stobbe condensation of ethyl levulinate with 2,6-dimethyl benzaldehyde **213**, which could be used as starting material for the synthesis of naturally occurring solafuranone **211**. As briefed in Scheme 1 acid **212** could be converted to its saturated ester; followed by its treatment with methyl magnesium bromide and lactonization to afford the target molecule.

Scheme 1. Retrosynthetic analysis of solafuranone

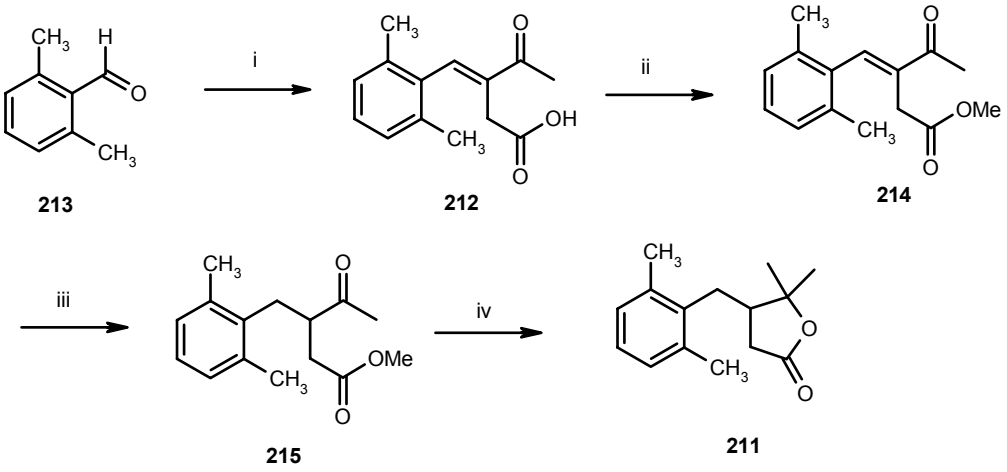


211 **212** **213**

1.4.3. RESULTS AND DISCUSSION

The synthetic journey began with Stobbe condensation of 2,6-dimethyl benzaldehyde (**213**) with ethyl levulinate in the presence of aqueous sodium hydroxide solution. Condensation reaction led to give an acid **212** IR spectrum of which showed unsaturated ketone carbonyl absorption at 1670 cm^{-1} and acid carbonyl absorption at 1712 cm^{-1}. ^1H NMR spectrum showed acyl CH_3 at δ 1.72 and characteristic methylene ($-CH_2COOH$) at δ 3.50, integrating for two protons whereas ^{13}C NMR showed a peak at δ 177.2 signifying ester carbonyl and a peak at δ 201.5 for ketone carbonyl while the ESI mass exhibited molecular ion peak at M^+ 222. Acid **212** on esterification with diazomethane in diethyl ether formed an ester **214** in 88% yield. IR spectrum of ester showed carbonyl stretching at 1763 cm^{-1} while ^1H NMR spectrum showed additional singlet at δ 3.36 integrating for 3 protons revealing presence of ester **214**. In ^{13}C NMR spectrum, the ester carbonyl carbon appeared at δ 171.9.

Scheme 3.



213 212 214 215 211

Reagents and conditions: (i) Aq. NaOH, methanol, -10 °C, 4-5 h, 78%; (ii) CH_2N_2, methanol, rt, 88.4%; (iii) H_2, Pd /C, methanol, rt, 83%; (iv) CH_3MgI, $CeCl_3$, ether, -78 °C, 5 h, 48%.

The unsaturated ester **214** was hydrogenated using Pd/C to afford saturated ester in excellent yield. ^1H NMR demonstrated surge in integration values in the aliphatic region with multiplets between δ 2.67-2.98 integrating for four protons and at δ 3.28-3.50

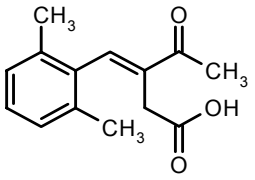
integrating for one proton. Lack of olefinic proton in aromatic region confirmed the presence of hydrogenated product **215**. Ester **215** on Grignard reaction with methyl magnesium iodide in the presence of anhydrous $CeCl_3$ [anhydrous $CeCl_3$ was prepared from $CeCl_3.7H_2O$ by heating at 140 ºC at 10 torr for 3 h to collect white powder] in dry THF at –78 ºC. Cerium chloride was used to increase the nucleophilicity of Grignard reagent.[4] Acidic workup furnished the racemic natural product solafuranone directly. The product was identical in all respects viz. Mp, IR, ^{1}H NMR, ^{13}C NMR, and EI with that of naturally occurring solafuranone (**210**).[1]

1.4.4. CONCLUSION

Thus we have described a total synthesis of solafuranone in 4-steps from 2,6-dimethylbenzaldehyde. Asymmetric hydrogenation of the intermediate **214** followed by the Grignard reaction in the presence of anhydr. $CeCl_3$ should provide the optically active natural product R-solafuranone. A simple protocol for the synthesis of racemic solafuranone is represented.

1.4.5. EXPERIMENTAL

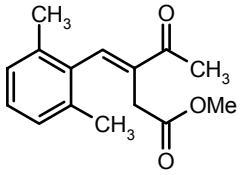
3-Acetyl-4-(2,6-dimethylphenyl)-but-3-enoic acid (212)



To a well-stirred mixture of 2,6-dimethyl benzaldehyde **213** (1.00 g, 7.42 mmol) and ethyl levulinate (3.22 g, 22.2 mmol) in methanol (250 ml), aqueous sodium hydroxide solution (0.317g, 22.2 mmol in 5 ml water) was added drop wise at -10˚C. After complete addition, reaction mixture was stirred at same temperature for 4-5 h and the reaction was monitored by thin layer chromatography. After completion of reaction, methanol was removed under vacuum, reaction mixture was diluted with water and washed with ethyl acetate and aqueous layer was acidified with conc. HCl. The yellow oil separated was extracted with ethyl acetate (3 × 20 ml) and it was repeatedly washed with water to remove traces of levulinic acid, followed by brine, dried over sodium sulphate and evaporated to yield acid **212** (1.34 gm, 78%) as an oil which crystallized on standing.

Nature: White crystalline solid; **Yield**: 78%; **Mp**: 97 ºC; **IR** (Chloroform): *v* 3020, 1712, 1670, 1466, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.21 (s, 6H), 3.50 (s, 2H), 7.05-7.15 (m, 4H), 7.97 (bs, 1H); **^{13}C NMR** (50 MHz): δ 20.1 (2C), 28.9, 39.5, 127.5 (2C), 127.9, 135.0, 135.1 (2C), 136.5, 139.5, 177.2, 201.4; MS: 232 $(M)^+$; **Anal Calcd for** $C_{14}H_{16}O_3$: C, 72.41; H, 6.89; **Found**: C, 72.52; H, 6.91.

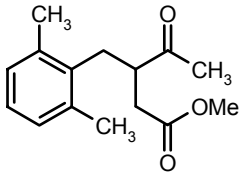
3-Acetyl-4- (2,6-dimethylphenyl)-but-3-enoic acid methyl ester (214)



Acid **212** (0.80 gm, 3.44 mmol) was dissolved in distilled methanol (15 ml) and the solution was cooled to 0 ºC. A solution of diazomethane in ether (50 ml) prepared from NMU (1.77 gm, 17.2 mmol) was added slowly with constant stirring. After being stirred for 1h, solvent was evaporated under vacuum and the crude ester was purified by column chromatography using 10% acetone in petroleum ether as an eluent to afford pure ester **214** (0.750 gm, 88.4%).

Nature: Yellow oil; **Yield**: 88 %; **IR** (Chloroform): *v* 3019, 1775, 1715, 1466, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.88 (s, 6H), 3.13 (s, 2H), 3.36 (s, 3H), 6.67-6.78 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.3 (2C), 29.1, 39.6, 51.9, 127.7 (2C), 128.0, 135.2, 135.8 (2C), 137.3, 139.0, 171.9, 201.2; **MS** (ESI): *m/z* 246 $(MH)^+$; **Anal Calcd for** $C_{15}H_{18}O_3$: C, 72.58; H, 7.25; **Found**: C, 72.60; H, 7.19.

3-(2,6-Dimethylbenzyl)-4-oxo-pentanoic acid methyl ester (215)

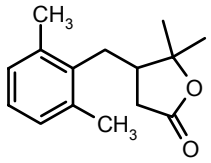


Ester **214** (0.720 gm, 2.92 mmol) was dissolved in distilled methanol in two-necked round bottom flask, purged with nitrogen gas and charged with 10% Pd/C (10 mg). Then the reaction was flushed with hydrogen gas and stirred for 1 h under H_2 gas (balloon). Reaction mixture was then filtered

through Whatman filter paper, filtrate was evaporated to dryness and the residue was purified by column chromatography using 5 % acetone in pet ether as an eluent to afford pure ester **215** (0.600 gm, 83%).

Nature: Yellow oil; **Yield**: 83%; **IR** ($CHCl_3$): *v* 3022, 1771, 1714, 1585, 756 cm $^{-1}$; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.17 (s, 3H), 2.32 (s, 6H), 2.67-2.98 (m, 4H), 3.28-3-50 (m, 1H), 3.59 (s, 3H), 7.02 (bs, 3H); **MS** (ESI): *m/z* 249 (M+1); **Anal**. **Calcd for** $C_{15}H_{20}O_3$: C, 72.58; H, 8.06; **Found**: C, 72.67; H, 8.17.

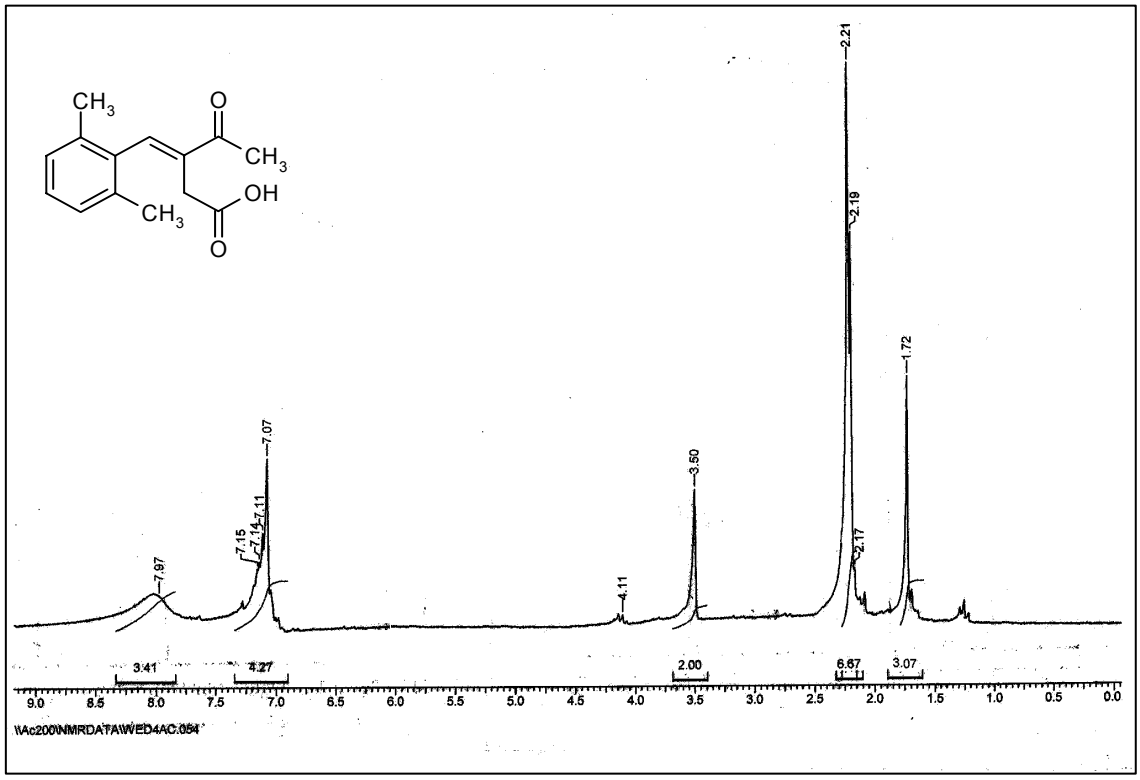
4-(2,6-Dimethylbenzyl)-5,5-dimethyl-dihydro-2(3*H*)-furanone (210)



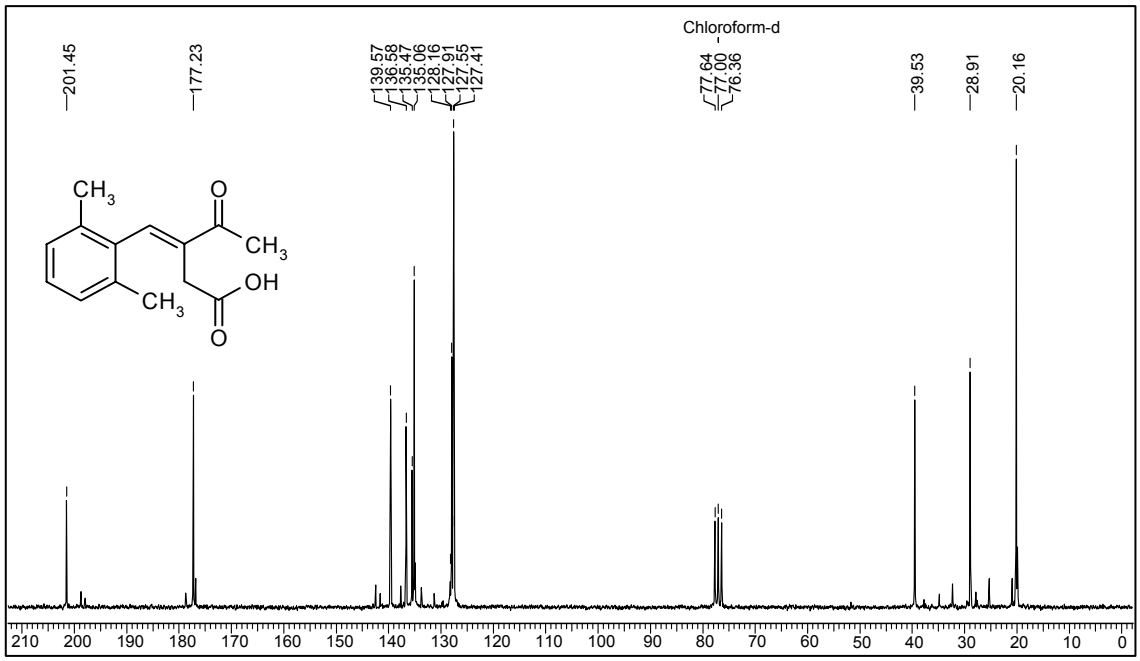
To a suspension of activated magnesium metal (0.019 gm, 0.79 mmol) in dry THF (5 ml) was added iodomethane (0.137 gm, 0.097 mmol) drop wise over 10 min at room temperature. To the resultant solution of methyl magnesium iodide, suspension of $CeCl_3$ (0.247 g, 1.01 mmol) in dry THF (2 ml) was added followed by ester **215** (0. 200 gm, 0.8 mmol) in dry THF (1 ml) over a period of 10 min. at 0 ºC. The reaction mixture was stirred at same temperature for 4 h after which it was quenched with dilute HCl (50 %, 2 ml). The resulting suspension was stirred for another 10 min and then extracted with ethyl acetate. Organic layer was washed with water, brine and dried over sodium sulphate. Evaporation of the solvent gave crude lactone, which was purified on silica gel column using 10% acetone in pet ether as an eluent to afford the pure lactone **211** (0.090 gm, 48.0%).

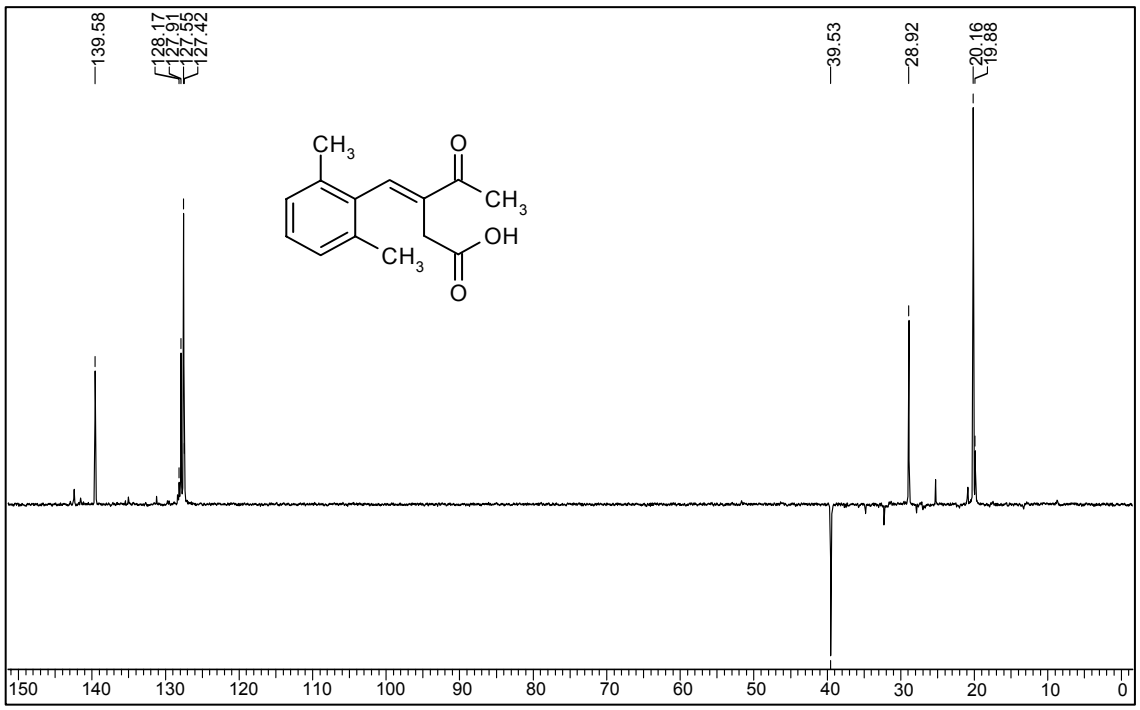
Nature: White crystalline solid; **Yield**: 48%; **Mp**: 132-133 ºC; **IR** (Chloroform): *v* 3019, 2978, 1761, 1522, 1474, 1215, 1121, 929, 669 cm $^{-1}$; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (s, 3H), 1.58 (s, 3H), 2.34 (s, 6H), 2.40-2.50 (m, 3H), 2.76 (dd, *J* = 8, 3 Hz, 2H), 7.04 (bs, 3H); **^{13}C NMR** (50.5 MHz, $CDCl_3$): δ 20.2 (2C), 21.6, 26.9, 28.5, 34.4, 45.8, 86.5, 126.4, 128.7 (2C), 135.6, 135.9 (2C), 175.3; **MS**: *m/z* 233 $(MH)^+$; **Anal Calcd for** $C_{15}H_{20}O_2$: C, 77.58; H, 8.62; **Found**: C, 77.49; H, 8.92.

^{1}H NMR of compound 212 ($CDCl_3$, 200 MHz)

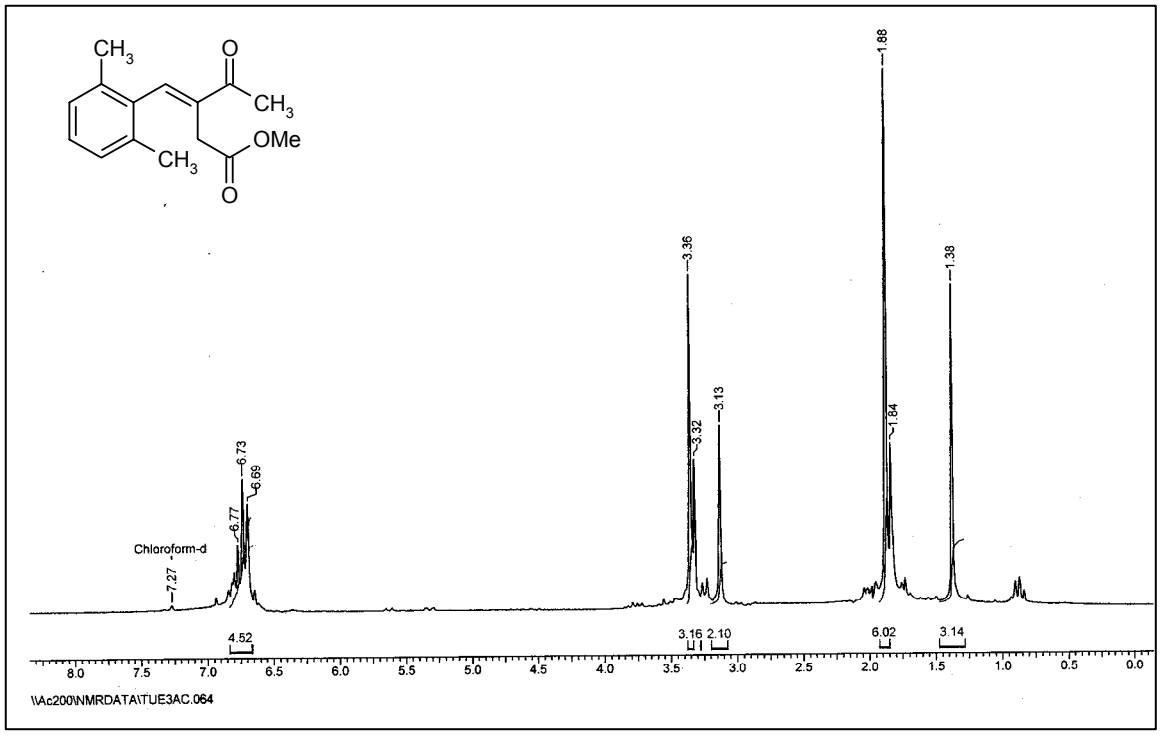


^{13}C NMR and DEPT of compound 212 ($CDCl_3$, 50 MHz)

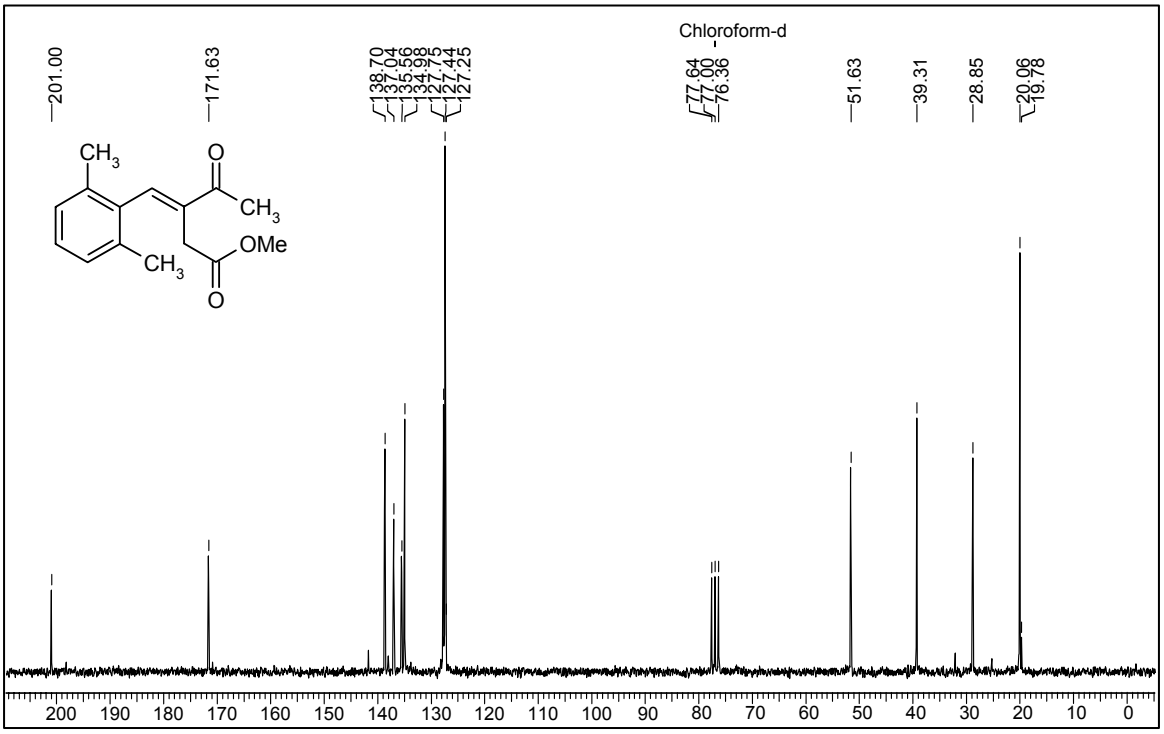


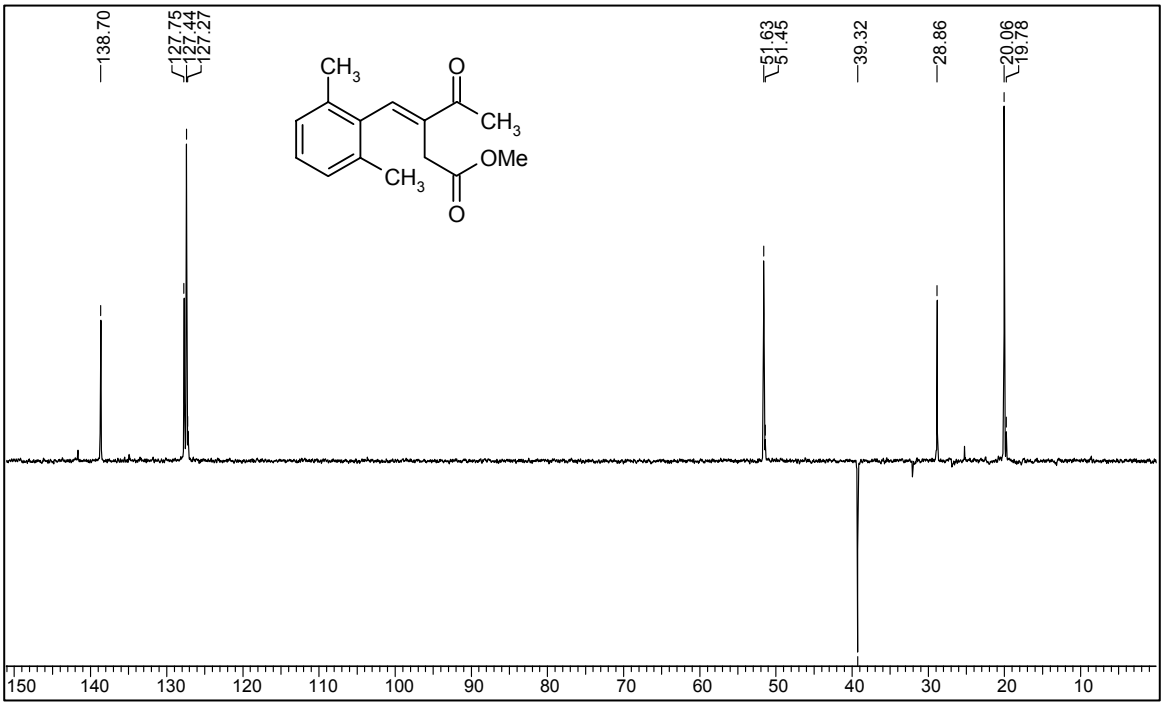


^{1}H NMR of compound 214 ($CDCl_3$, 200 MHz)

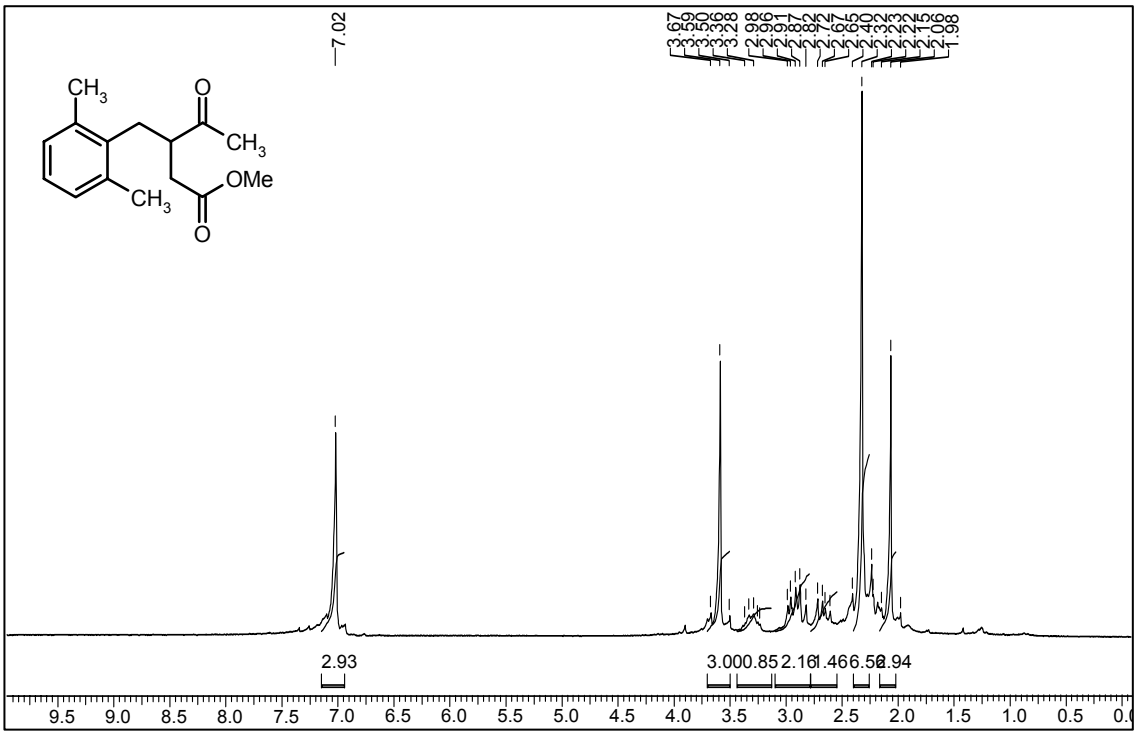


^{13}C NMR and DEPT of compound 214 ($CDCl_3$, 50 MHz)

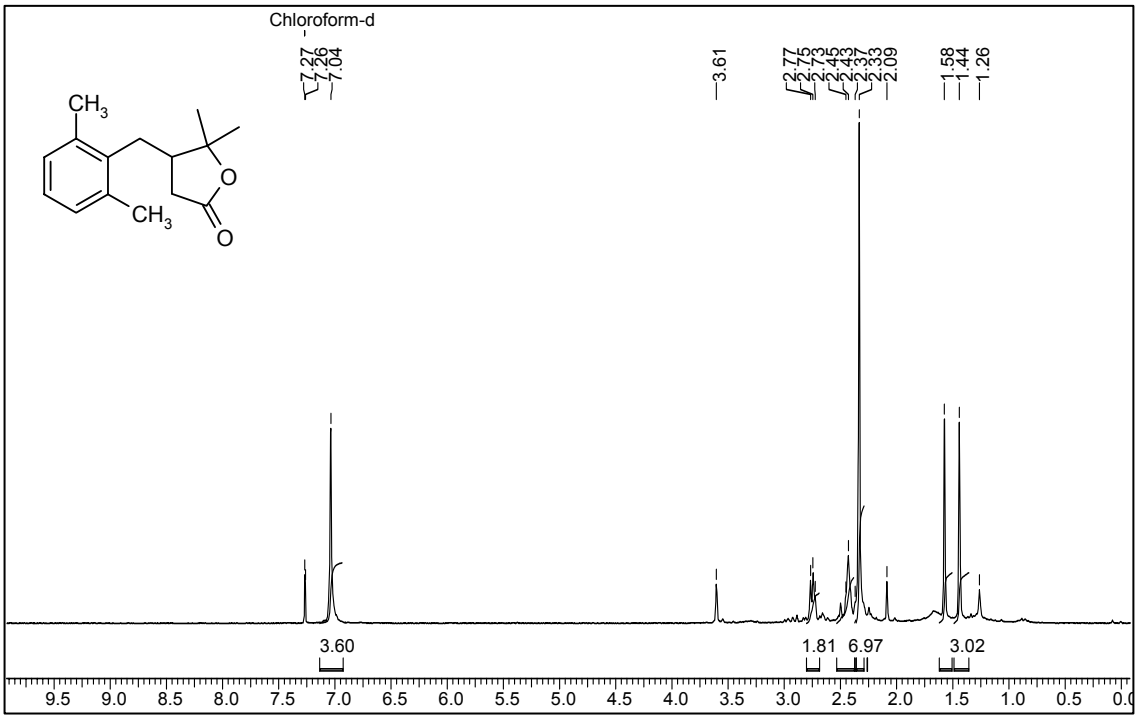




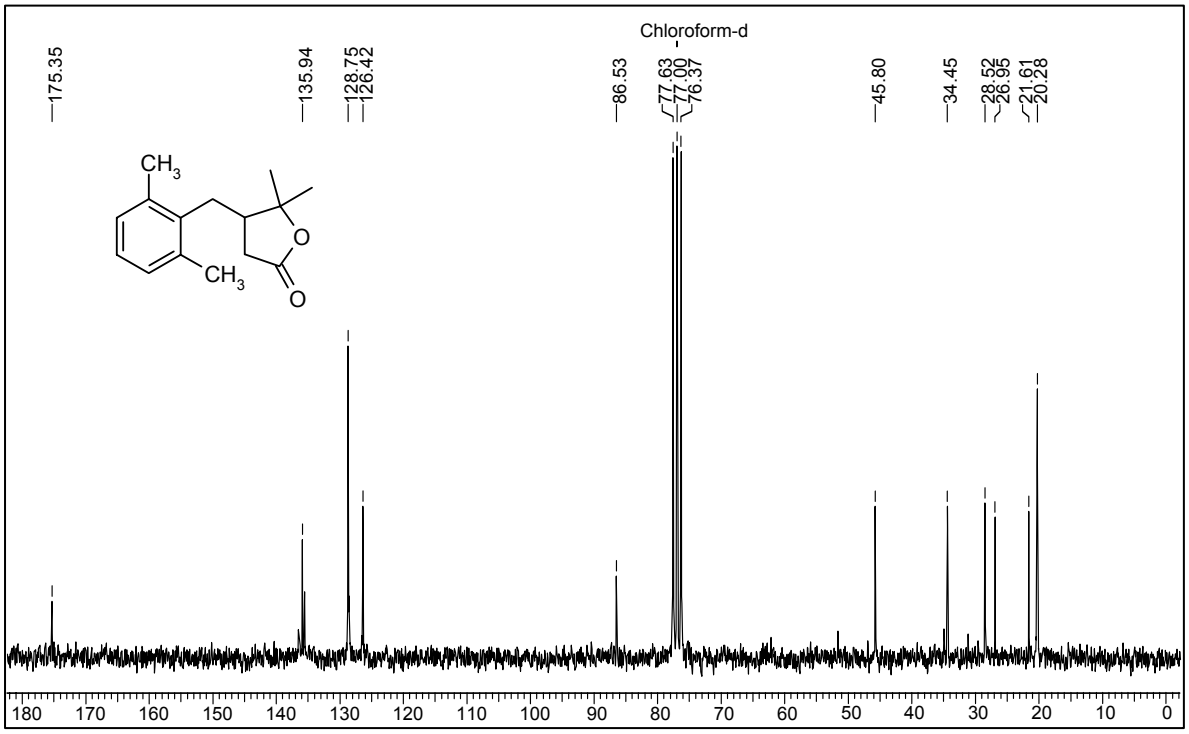
^{1}H NMR of compound 215 ($CDCl_3$, 200 MHz)

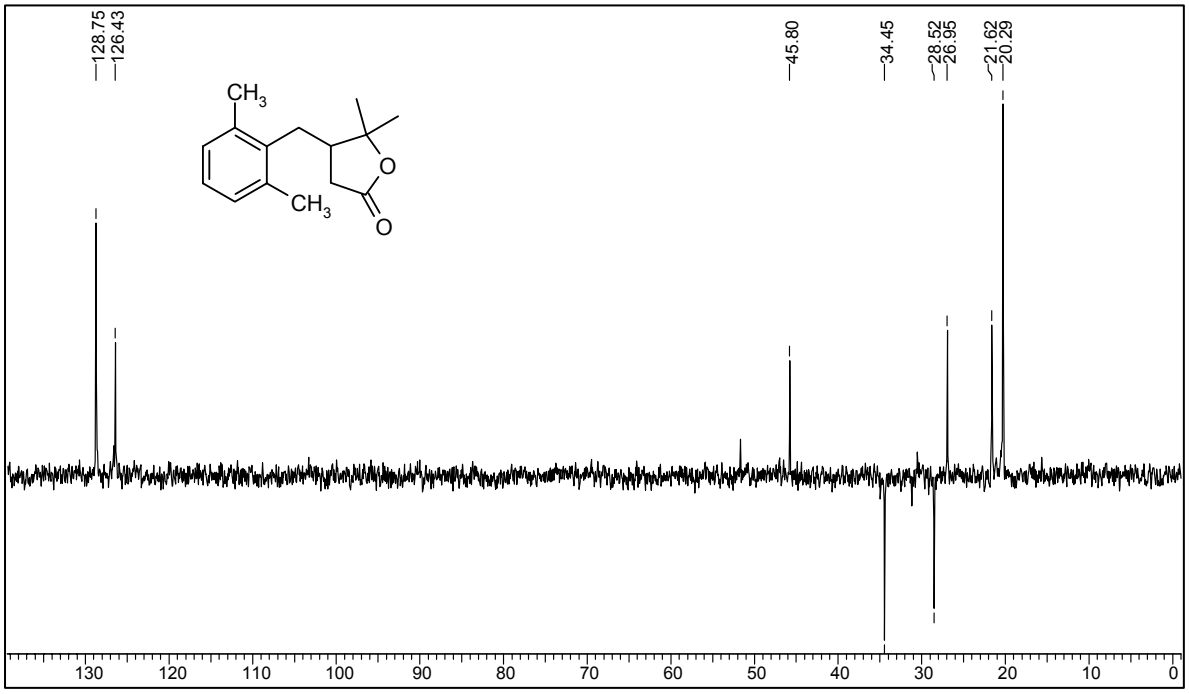


^{1}H NMR spectrum of Solafuranone 210 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of Solafuranone 210 ($CDCl_3$, 200 MHz)



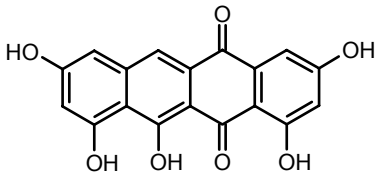


1.4.6. REFERENCES

1. Syu, W.; Don, M.; Lee, G.; Sun, C. *J. Nat. Prod.* **2001**, *64,* 1232-1233.
2. Kao, M. T.; Popular Herbal Remedies of Taiwan (2); Southern materials center, inc. Taipei 1988, P139.
3. Hwu, J. R.; Wetzcl, J. M. *J. Org. Chem.* **1992**, *57*, 922-928.
4. (a) Bartoli, G.; Marcantoni, E; Petrini, M.; Sambari, L. *Tetrahedron Lett*. **1994**, *35*, 8453-8456. (b) Bartoli, G.; Marcantoni, E; Petrini, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1061-1062.

2.1.1. INTRODUCTION

Saintopin (**1**) is an anti-tumor antibiotic isolated from the culture broth of *Pacilomyces sp* in 1990 by Yamashita and coworkers.[1] Saintopin induces both topoisomerase I and II mediated DNA cleavage. Saintopin induced topoisomerase I mediated DNA cleavage is equipotent to that of camptothecin and topoisomerase II mediated DNA cleavage is comparable to those of *m*-AMSA and VP-16. In addition, it showed weak or partial intercalation with DNA proved by surface-enhanced Raman scattering spectroscopy (SERS).



Saintopin (1)

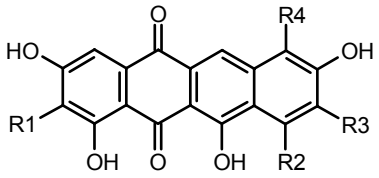
Saintopin showed cytotoxic activity against human tumor cell line HeLaS3 (IC_{50} 0.35 ug/ml) *in vitro* and further more it showed antitumor activity against murine leukemia P388, *in vivo*, exhibiting a statistically significant increase in life span (IL 30%) at a dose of 25 mg/Kg. It also exhibited a weak microbial activity against gram-positive bacteria.[2]

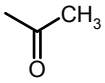
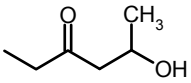
Mode of Action

Topological problem is probably defined as a twisting of daughter DNA; it may arise in the course of cellular processes such as DNA replication, transcription, recombination, repair, chromosome segregation, and maintenance of chromosome structure. During these events, torsional strain of double-strand DNA leads to super coiling, which inevitably interferes with biological process.[3]

DNA topoisomerases are the enzymes that resolve such problems by catalyzing the concerted breakage and rejoining of DNA strands. Two major topoisomerases, topoisomerase I and topoisomerase II, have been identified in all eukaryotic cells; the

former type catalyzes the passage of the DNA strand through a transient single-strand break, whereas the latter catalyzes the passage of DNA double strands through a transient double-strand break. Thus, both topoisomerases now appear to be important targets for the development of new cancer chemotherapeutic drugs.[4]



Compounds	R1	R2	R3	R4
SAINTOPIN E (**2**)	H	-OH		H
UCE 1022 (**3**)	H	-O-SO_3H	H	H
UCE 6 (**4**)	CH_3		H	H
BM 2419-1(**5**)	H	OH	H	OH
BM 2419-2 (**6**)	H	OH	H	CH_3

Saintopin (**1**), saintopin E (**2**),[5] UCE1022 (**3**),[6] and UCE6 (**4**),[7] are isolated from *Actinomycetes* fermentation broth. BM2419-1 (**5**) and 2 (**6**) were also isolated from the culture broth of a fungus *Pacilomyces sp.* BM2419.[8] Among these compounds, only saintopin has been identified as the dual inducer of the cleavable complex with both topoisomerase I and topoisomerase II.

Other Topoisomerases I and II Inhibitors

There is good evidence that topoisomerases are the principal intracellular targets for a number of clinically important antitumor drugs. These drugs, referred to as topoisomerase poisons, include synthetic intercalators e.g., *m*-AMSA, mitoxantrone,[9] antibiotics from microbes e.g., anthracyclines, actinomycin D,[10] and derivatives of plant metabolites e.g., camptothecin (**9**) and its derivatives such as CPT-11[11] (**9a**) and

topotecan (**10**)[12] and epipodophyllotoxin derivatives such as VP-16 (etoposide) (**7**) and VM-26 (teniposide) (**8**)[13] These drugs interfere with the breakage-rejoining reaction of topoisomerases by stabilizing key reaction intermediates of topoisomerases (cleavable complex). These congeners either act as topoisomerases I or topoisomerases II inhibitors. It was noticeable that saintopin showed inhibitory activity for both the topoisomerases, which is equipotent to that of camptothecin (**9**), *m*-AMSA (**14**) and VP-16 (**8**). [14]

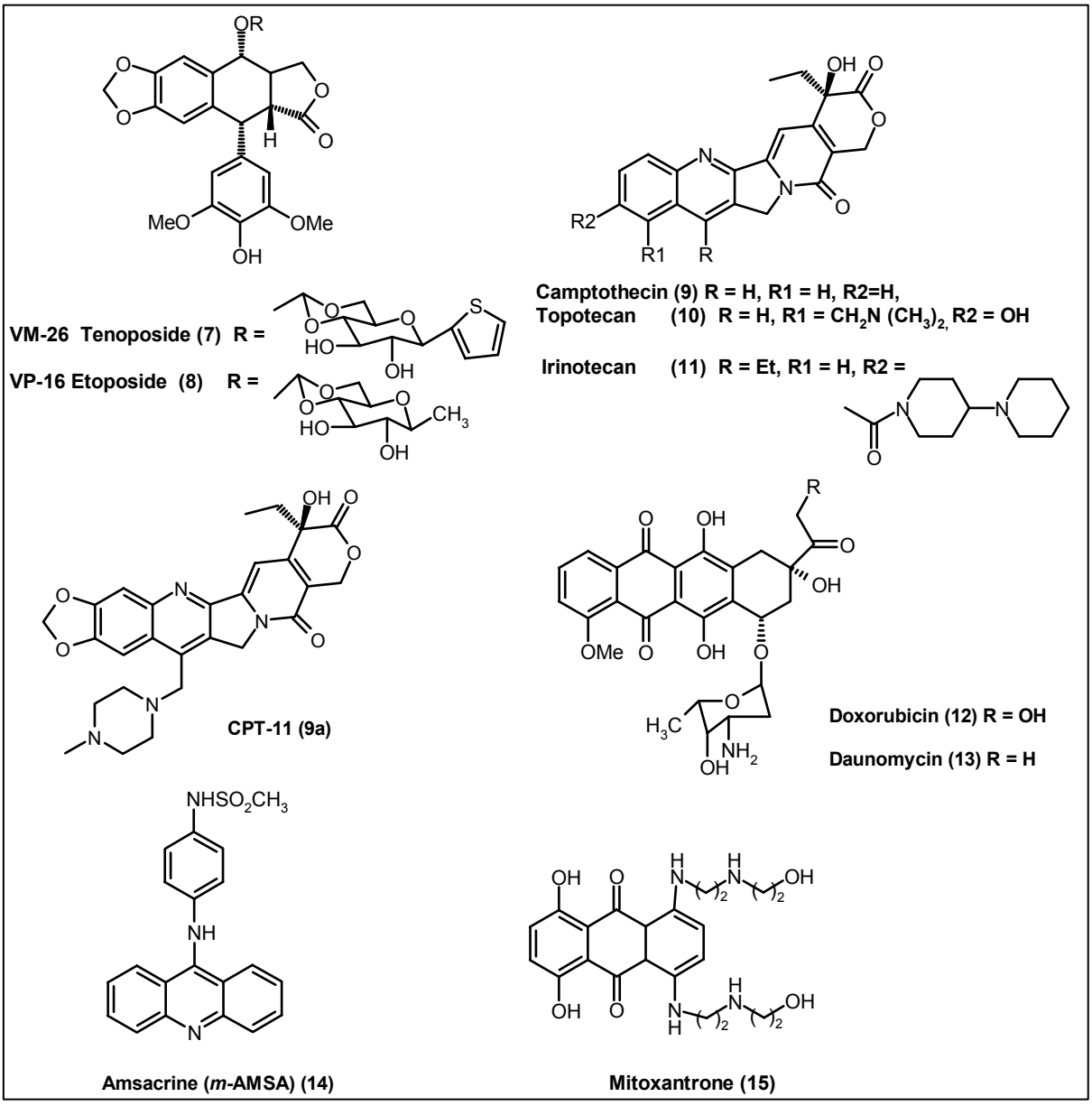


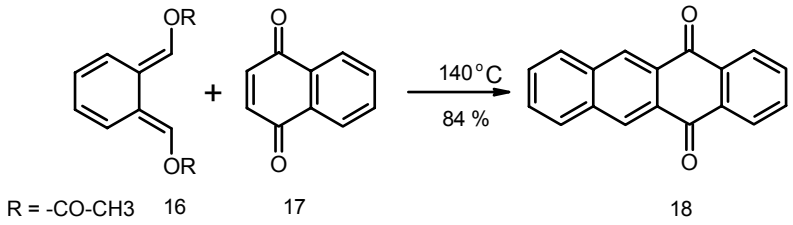
Figure 1.

Synthetic approaches: **Synthesis of orthoquinodimethane and naphthacenedione**

Saintopin belongs to the family of naphthacenediones for which different synthetic approaches have been comprehensively studied. Cycloaddition reaction is most commonly used for their synthesis to generate tetracyclic framework. Different types of ortho-quinodimethide intermediates have been extensively used for the synthesis of anthraquinones and naphthacenediones. Selected methods are summarized here on the following pages.

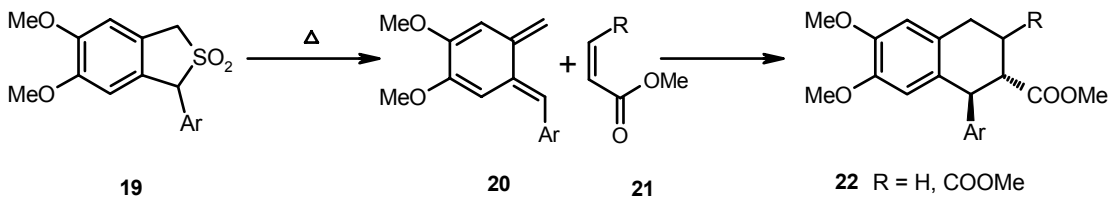
Arnold and coworkers[15] reported thermal treatment of the hydroxy-*o*-quinone dimethide **16** with dienophile such as 1,4-naphthaquinone **17,** via Diels-Alder reaction approach resulting in the naphthacenedione **18** in good yield followed by *in situ* elimination of diacetate as depicted in Scheme 1.

Scheme 1. *J. C. S. Perkin trans I,* **1974**, 415-418



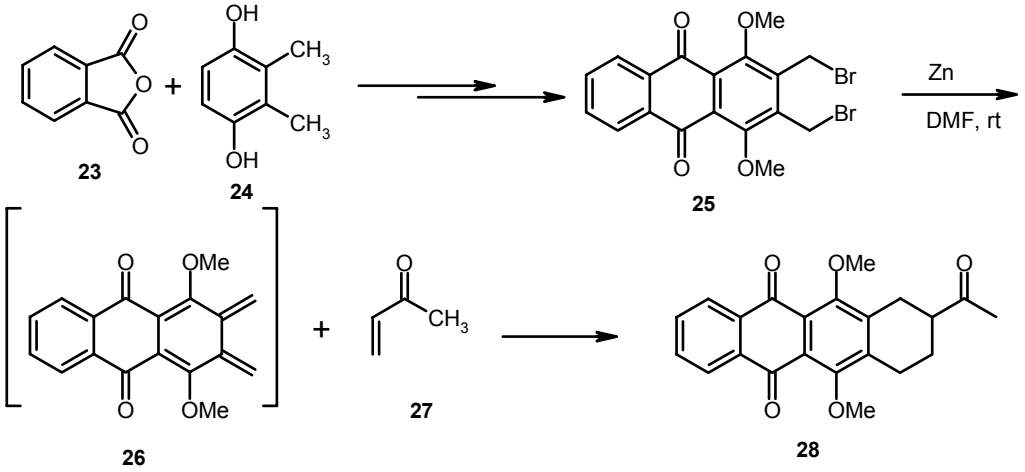
Charloton and coworker[16] have shown that the α-phenyl sulphone **19** generates an orthoquinodimethane **20** that adds to methyl acrylate or dimethyl maleate to afford tetralin derivatives **22** (Scheme 2).

Scheme 2. *J. Org. Chem.***1985**, *50*, 4829-4833.



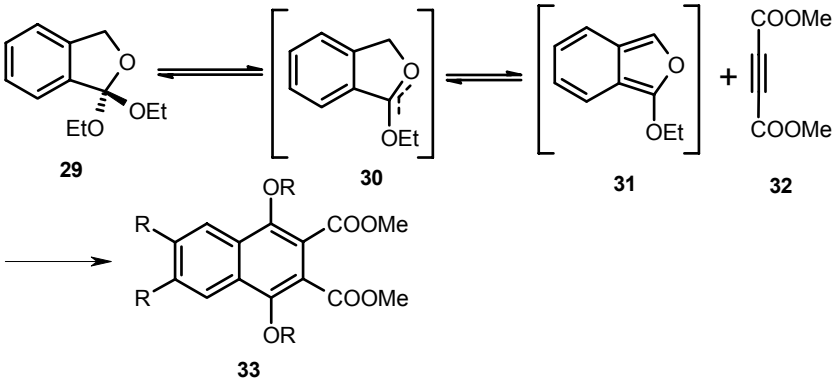
Cava and coworkers[17] reported, synthesis of (±)-4-demethoxy daunomycinone **28** (Scheme 3) via Diels-Alder addition of reactive *o*-quinone dimethane intermediate **26** with the olefinic proton of α, β-unsaturated ketone **27**.

Scheme 3. *J. Am. Chem. Soc.***1978**, *78*, 3615-3616.



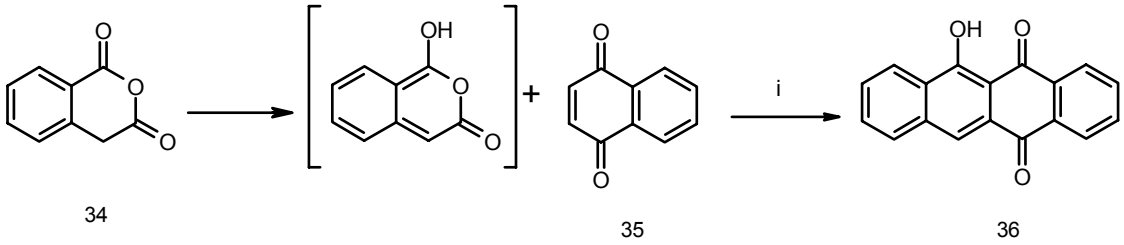
Maclean and coworkers[18] reported cycloaddition of isobenzofurans intermediate **31** with dimethyl acetylene dicarboxylate **32** to afford poly-substituted naphthalene derivatives **33** as depicted in Scheme 4.

Scheme 4. *Tetrahedron Lett*. **1978**, *44*, 4237-4240.



Tamura and coworkers reported[19] cycloaddition of homophthalic anhydride **34** with naphthaquinone to give linearly condensed naphthacenedione **36** at 200ºC in dichlorobenzene as shown in Scheme 5.

Scheme 5. *Tetrahedron Lett*. **1981**, *22*, 4283-4286.

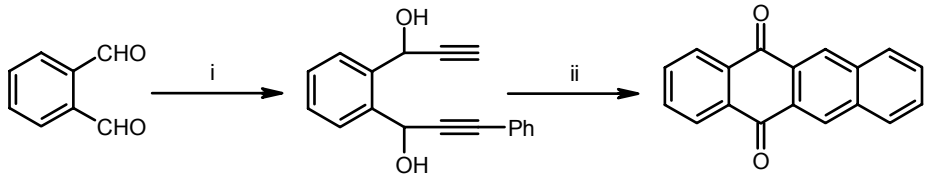


34 35 36

Reagent and conditions: (i) Dichlorobenzene, 200 °C, 7-15h

Recently Saa and coworkers[20] reported, intramolecular dihydro Diels-Alder reaction approach involving heating of asymmetric diol in sealed tube which afforded naphthacenedione **39** with 23 % yield (Scheme 6).

Scheme 6. *Org. Lett.* **2003**, *5*, 3119-3121.

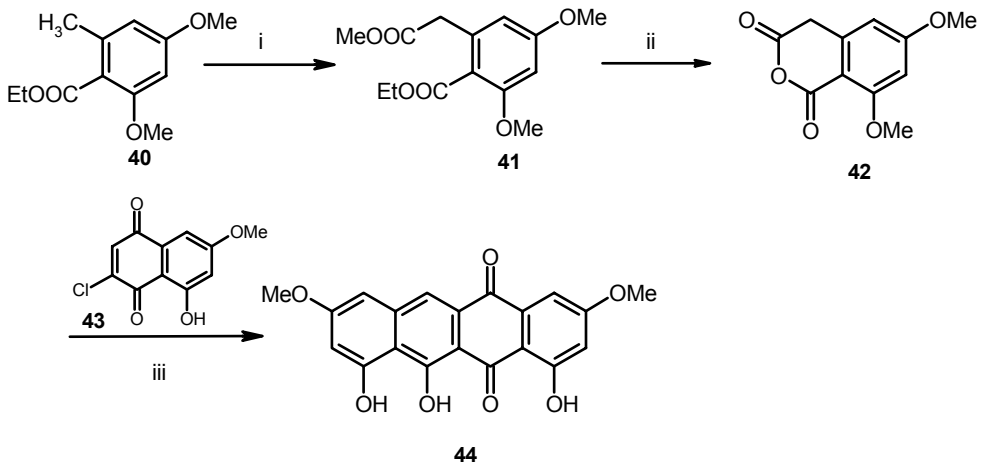


37 **38** **39**

Reagents and conditions: (i) (a) Phenylacetylene, n-BuLi, THF, -78 °C, 15 min; (b) trimethylsilylacetylene, n-BuLi, THF, -78 °C to rt, 1 h; (ii) (a) KOH, MeOH, rt, 95% (3 steps). (b) *o*-Xylene/Et_3N, sealed tube, 205 °C, 23%

Gesson and coworkers reported[21] first formal synthesis of saintopin (**1**) wherein the strategy based on cycloaddition of the homophthalic anhydride **42** and 2-chlorojuglone **43** was utilized as depicted in Scheme 7.

Scheme 7. *Bioorg. Med. Chem*. **2002**, *10*, 253-260**.**



Reagents and conditions: (i) LDA, THF-hexane, $(EtO)_2CO$; -78ºC; (ii) (a) NaOH, ethanol-water; (b) AcCl, acetone, 20ºC, (iii) NaH, THF, 0 ºC to rt.

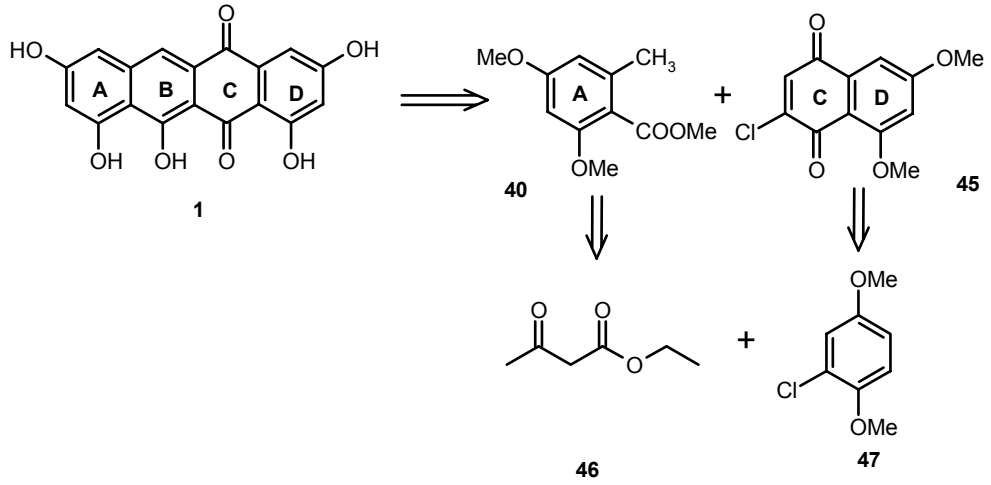
2.1.2. PRESENT WORK

Saintopin was found to be the first natural product having both topoisomerase I and II inhibitory activity with a typical structure of naphthacenedione featured with 1, 3, 8, 10, 11-pentahydroxy substitutions. The biological activity and substitution pattern of hydroxy function was found to be the synthetic challenge and also its low natural content and low abundance of the species required a good synthetic strategy for its production.

Our interest in the synthesis of natural products promoted us to undertake the synthesis of saintopin. Our approaches toward the synthesis of saintopin stemmed from three different routes simultaneously, utilizing 1) cycloaddition reaction involving *in situ* generated orthoquinodimethane intermediate, 2) Stobbe condensation and 3) tandem Michael addition-Dickmann condensation. These attempts have been described in this chapter. Although synthesis of naphthacenediones was studied earlier to some extent as summarized in the preceding introduction, synthesis of saintopin was not reported when we undertook it. During the simultaneous research Gesson and coworkers[21] reported the first formal synthesis of saintopin dimethyl ether by the route schematically represented in the Scheme 7.

Cyloaddition via *o*-quinodimethane approach

As stated in retrosynthetic analysis (Scheme 8) we assumed that preparation of functionalized A ring synthon and its cycloaddition with C, D-ring synthon would give the desired tetracyclic framework. The most important C, D ring synthon has been widely used in the synthesis of anthracyclines.[22]

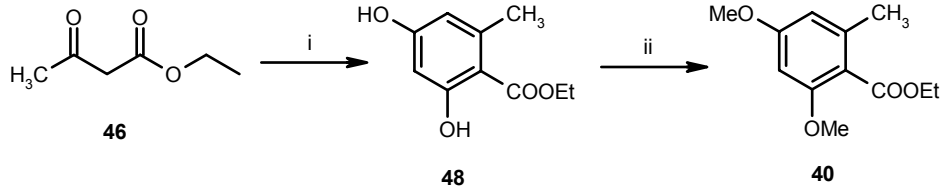


Scheme 8. Retrosynthetic analysis

2.1.3. RESULTS AND DISCUSSION

The most appropriate A ring synthon **40**, was prepared from ethyl acetoacetate **46**, by reported method[23] as shown in Scheme 9.

Scheme 9.



Reagents and conditions: (i) NaH, n-BuLi, THF, -78ºC, then at rt, 12h, 43%; (ii) Dimethyl sulphate, K_2CO_3, acetone, refulx, 4h, 95%.

Ethyl acetoacetate (**46**) was treated with sodium hydride and consecutively with n-BuLi in dry THF to collect 3,5-dihydroxy orthotoluic acid ethyl ester (**48**), which on treatment

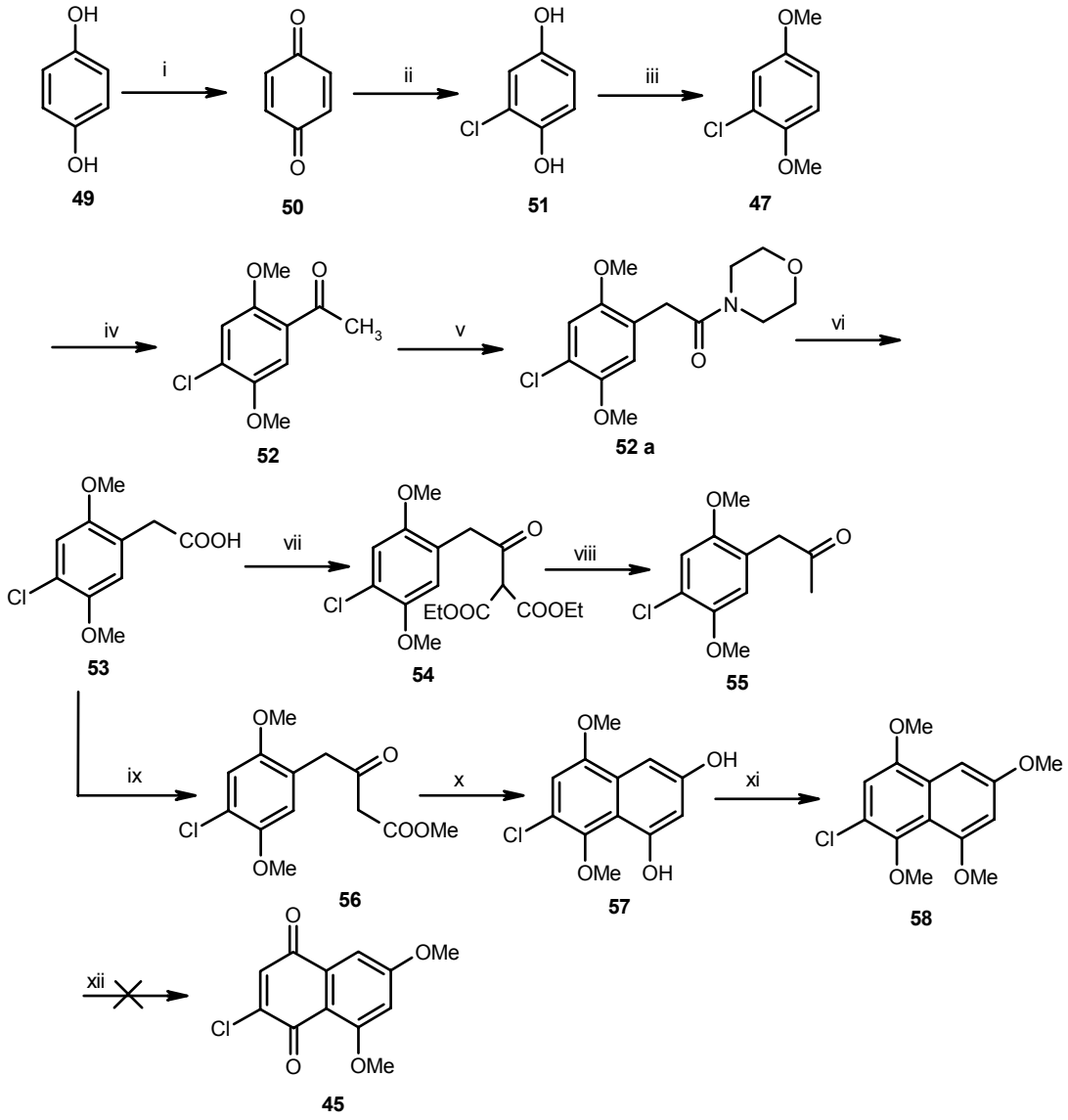
with dimethyl sulphate and potassium carbonate gave 3,5-dimethoxy-orthotoluic acid ethyl ester (**40**).

After synthesizing A-ring synthon, efforts were directed towards the synthesis of CD ring synthon i.e. 2-chlorojuglone **45**. It is the most well known synthon for the synthesis of anthracyclines.The most popular method for synthesis of 2-chlorojuglone involves Diels-Alder reaction of silylated dienes with halogenated benzoquinones[22] and for its preparation meticulous reaction conditions are required; hence preparation of this halo-juglone was achieved by an alternative procedure.

The synthesis of 2-chlorojuglone began from easily available 1,4-hydroquinone **49**. It was converted into 4-chloro-2, 5-dimethoxyacetopheneone (**52**) in four steps involving oxidation of 1,4-hydroquinone **49** to benzoquinone **50** in the presence of sodium dichromate. Benzoquinone **50** was monochlorinated with dry HCl gas in dry ether to afford 2-chloro-hydroquinone **51** in quantitative yield,[24] it was further protected to afford 2-chloro-1, 4-dimethoxy-benzene (**46**)[25] which was treated with acetyl chloride in the presence of aluminium chloride by Friedel-Crafts acylation reaction to afford acetophenone **52**.[26]

The IR spectrum of acetophenone **52** showed intense carbonyl stretching at 1710 cm^{-1}. In ^{1}H NMR spectrum a sharp singlet integrating for three protons at δ 2.61 was assigned for acetyl group (CO-C$\underline{H_3}$); singlets at δ 7.03 and δ 7.40 integrating for one proton each indicated that acylation occurred at *para*-position of chlorine group which confirmed formation of 4-chloro-2, 5-dimethoxyacetophenone (**52**). According to the retrosynthetic plan; it was envisaged that to achieve 2-choro-6, 8-dimethoxy naphthaquinone **45** from acetophenone **52** it was essential to achieve one carbon homologation. Consequently acetophenone **52** was subjected for one carbon homologation in the presence of sulphur and morpholine by Willgerodt reaction[27] to afford thiomorpholide **52a.**

Scheme 10.



Reagents and conditions: (i) $Na_2Cr_2O_7$, H_2SO_4, 0ºC; (ii) Dry HCl, ether, 0ºC; (iii) Dimethyl sulphate, K_2CO_3, acetone, reflux, 4 h; (iv) AcCl, DCM, 0ºC, 1.5 h, 91%; (v) S, morpholine, reflux, 5 h; (vi) 10% Aq. NaOH solution, ethanol, reflux, 12 h, 56 %; (vii) (a) $SOCl_2$, toluene; (b) Mg, ethanol, diethyl malonate, rt; (viii) NaCl, DMSO, H_2O, 80 ºC, 30 min; (ix) (a) $SOCl_2$, toluene; (b) Meldrums acid, Et_3N, then reflux in methanol 12 h, 55.2%; (x) Conc. H_2SO_4, 0ºC, 76.6%; (xi) Dimethyl sulphate, K_2CO_3, acetone, reflux, 4 h, 90%; (xii) CAN, aq. CH_3CN, rt.

Thiomorpholide **52a** was hydrolyzed with 10% sodium hydroxide solution in refluxing methanol to afford carboxylic acid **53** with 56% yield. IR spectrum of **53** showed

carbonyl stretching at 1670 cm^{-1}. Its ^1H NMR showed a sharp singlet at δ 3.64 integrating for two protons which was assigned to benzylic protons ($C\underline{H}_2$-COOH) and mass spectrum showed molecular ion (M^+) peak at *m/z* 230. These spectral characteristics confirmed the structure of acid **53**.

The next step of was to prepare β-ketoester **56**; therefore the carboxylic acid **53** was converted to corresponding acid chloride with thionyl chloride and subsequently treated with the complex of diethylmalonate and magnesium methoxide[28] to afford the diester **54** which was characterized by IR, ^1H NMR, ^{13}C NMR and mass spectral techniques. IR spectrum showed carbonyl stretching frequency at 1731 cm^{-1} (broad peak). ^1H NMR showed triplet at δ 1.25 integrating for six protons with J = 6Hz; and quartet for four protons at δ 4.19 indicating the presence of diester group. A singlet appeared at δ 4.54 integrating for one proton flanked between two carbonyl groups (–CO-C<u>H</u>- $(COOEt)_2$) and MS spectrum showed molecular ion peak at *m/z* 372 which supported the structure of the diester **54.**

In order to synthesize the corresponding β-ketoester the diester **54** was treated with a mixture of sodium chloride and DMSO at 80ºC when the product obtained was the decarboxylated product **55**. To avoid this problem the reaction was performed using meldrums acid in the presence of triethyl amine and the crude product obtained was decarboxylated in refluxing methanol to afford the β-ketoester **56** in 55% yield. Its structure was confirmed by spectral analysis. IR spectrum showed carbonyl stretching at 1763 cm^{-1} for ester and 1713 cm^{-1} for ketone carbonyl; proton NMR spectrum showed additional singlet of active methylene group (CO-$C\underline{H}_2$- COOMe) at δ 3.72 integrating for two protons while the mass spectrum confirmed the structure by showing molecular ion peak at *m/z* 286 (M^+).

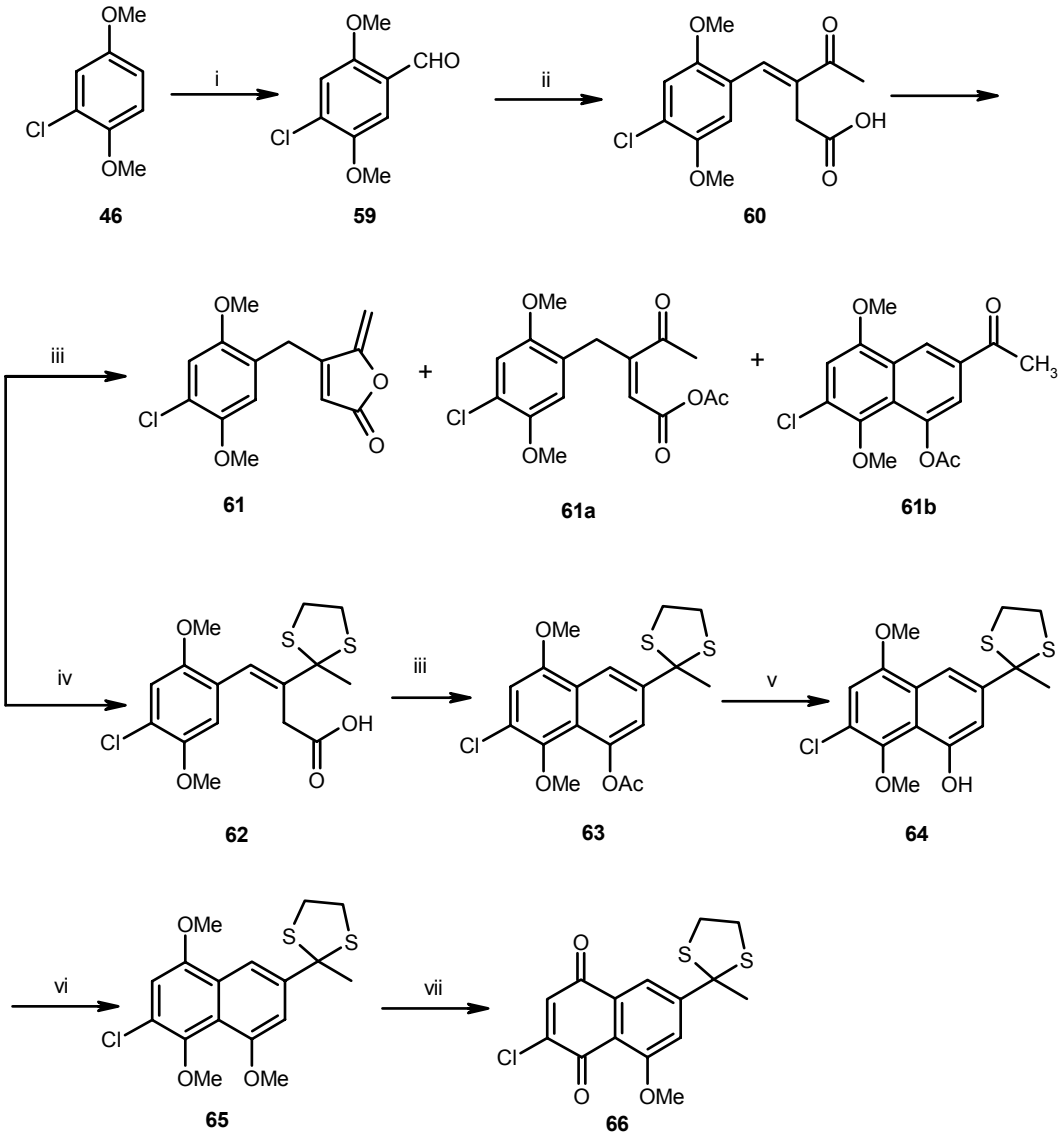
β-Ketoester **56** was cyclized to naphthol **57** in the presence of concentrated sulphuric acid. It showed disappearance of carbonyl stretching frequency and the presence of intense hydroxyl absorption at 3450 cm^{-1} in IR spectrum. Proton NMR spectrum showed the absence of benzylic methylene and active methylene protons and the presence of additional meta coupled doublets at δ 6.62 and δ 7.03 indicating the formation of aromatized product. Molecular ion peak at *m/z* 254 authenticated the structure of naphthol **57**.

Naphthol **57** was methylated with dimethyl sulphate in the presence of anhydrous potassium carbonate in dry acetone to afford tetramethoxy naphthalene derivative **58**. It was subjected to oxidation in the presence of cerric ammonium nitrate in aqueous acetonitrile solution however it failed to give the regioselective product **45**. Oxidation was attempted under various reaction conditions but the desired 2-chlorojuglone **45** could not be obtained.

Due to the failure in oxidation reaction we decided to synthesize the derivative of 2-chlorojuglone **45** in order to study the model reaction and also for derivatization of saintopin. Accordingly another route for 2-chlorojuglone derivative was instigated from 2-chloro-1, 4-dimethoxy benzene **46**. It was treated with hexamethyl tetramine in refluxing trifluroacetic acid to give 4-chloro-2, 5-dimethoxy benzaldehyde **59** with 78% yield. The aldehyde **59** was subjected for Stobbe condensation with ethyl levulinate in the presence of aq. Sodium hydroxide solution to give acid **60**, which was further subjected for cyclization in the presence of anhydrous sodium acetate in acetic anhydride at 110 ºC. The reaction product was found to be a mixture of furanone **61,** mixed anhydride **61a** and required cyclized naphthalene derivative **61b**. This reaction was studied extensively by means of synthetic and spectroscopic point of view and the results have been presented in chapter 1.

Our target was to achieve 2-chlorojuglone derivative; therefore ketone carbonyl of the compound **60** was protected with ethane dithiol in the presence of iodine to afford carboxylic acid **62**. This protected carboxylic acid **62** was cyclized cleanly under similar conditions to afford naphthalene derivative **63**. The cyclized naphthol acetate **63** was hydrolyzed to **64** in the presence of aqueous sodium hydroxide solution followed by methylation with dimethyl sulphate and potassium carbonate to afford naphthalene **65**.

Scheme 11.



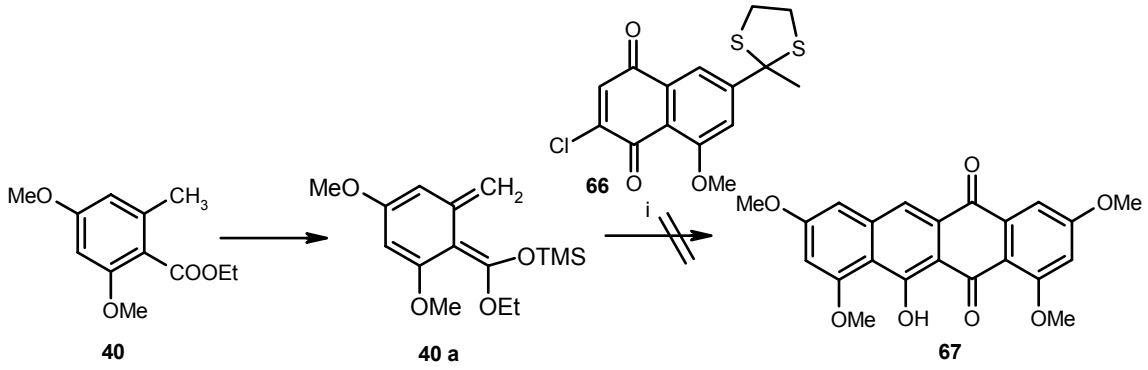
Reagents and conditions: (i) HMTA, TFA, DCM, reflux, 12 h, 78%; (ii) Aq. NaOH soln, ethyl levulinate, ethanol, -10ºC, 4-5 h; (iii) Anhydr. NaOAc, Ac_2O, 120 ºC, (**61b**: 15%) (iv) Ethane dithiol, I_2, $CHCl_3$, 92% (v) (a) Anhydr. NaOAc, Ac_2O, 120 ºC, 74.4%; (b) Aq. NaOH, ethanol, rt, 85.5 %; (c) Dimethyl sulphate, K_2CO_3, acetone, 4-5h, 94.2%; (vi) CAN, aq. CH_3CN, rt, 89.6%.

The naphthalene derivative **65** was oxidized in the presence of aqueous ceric ammonium nitrate[29] to afford 1,4-naphthaquinone **66** regioselectively. In the IR spectrum it showed carbonyl absorption at 1679 cm^{-1}. ^1H NMR spectrum of **66** showed the presence of only

one methoxy group at δ 4.6 integrating for three protons and molecular ion peak at *m/z* 340 in mass spectrum cofirmed the structure of 1,4-naphthaquinone **66**.

Finally to study the Diels-Alder reaction orthotoluic ester **40** was treated with LDA, followed by treatment with TMSCl at -78ºC and the resulting reaction mixture was further treated with quinone derivative **66**, when most of the starting material remained unreacted. The reaction was studied at different temperature conditions but desired cycloaddition adduct **67** was not detected.

Scheme 12.

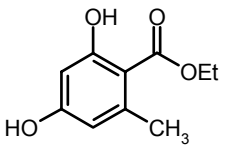


Reagents and conditions: (i) LDA, THF, -78ºC, then TMSCl.

It was assumed that the stability of *in situ* generated diene **40a** was not enough to pursue the reaction in order to afford the naphthacenediones **66** therefore this route was abandoned.

2. 1. 5. EXPERIMENTAL

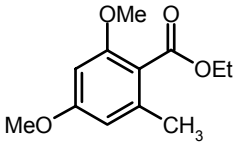
2,4-Dihydroxy-6-methyl-benzoic acid ethyl ester (48)



Ethyl acetoacetate (10 gm, 9.79 ml, 76.9 mmol) in 75 ml THF was added dropwise to a stirred suspension of sodium hydride [(2.76 g, 115 mmol) 50% dispersion washed with hexane (3×20 ml)] and 100 ml of dry THF at 0°C under argon atmosphere. The solution was then cooled to -78°C and 2.6 M solution of *n*-butyl lithium (38.43 ml, 2 M in *n*-hexane, 76.9 mmol) was added. The solution was warmed to room temperature and stirred overnight. Reaction was quenched with dil. HCl and the mixture was extracted with ethyl acetate (2×100 ml) and dried over sodium sulphate. Evaporation of the solvent left a residue of orthotoluic ester, which was purified by column chromatography using ethyl acetate in petrolium ether (80:20) as an eluting system to afford *ortho*- toluic ester **48** as a white solid (6.5 g, with 43.3 %).

Nature: White crystalline solid; **Yield:** 43.3%; **Mp**: 89-91ºC; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.34 (t, J = 8 Hz, 3H), 2.49 (s, 3H), 4.42 (q, J = 8 Hz, 2H), 5.12 (bs, 1H), 6.23 (s, 1H), 6.28 (s, 1H), 11.7 (s, 1H).

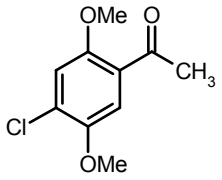
2,4-Dimethoxy-6-methyl-benzoic acid ethyl ester (40)



Dihydroxy-orthotoluic ester **48** (3.5g, 17.8 mmol) was dissolved in dry acetone (100 ml) in two-necked round bottom flask equipped with reflux condenser and two-way stopcock. Solution was charged with anhydrous K_2CO_3 (6.14 g, 44.5 mmol) followed by dimethyl sulphate (5.62 g, 4.22 ml, 44.5 mmol) and the reaction was allowed to reflux for 4-5 h. After complete conversion reaction mixture was filtered through sintered funnel to remove solid K_2CO_3, filtrate was concentrated; residue was washed thoroughly with water and extracted with ethyl acetate (2 × 150 ml). Organic layer was dried over sodium sulphate and solvent was evaporated under reduced pressure. Crude orthotoluic ester **40** was purified by column chromatography using pet ether and ethyl acetate as an eluent (90:10) to achieve pure orthotoluic ester as white crystals (3.8 g, with 95 %).

Nature: White crystals; **Yield**: 95%; **Mp**: 65-67°C; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.39 (t, J = 8 Hz, 3H), 2.32 (s, 3H), 3.82 (s, 6H), 4.40 (q, J = 8 Hz, 2H), 6.33 (s, 2H); **MS**: *m/z* 224,196, 150, 122 and 94.

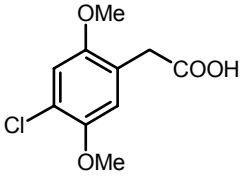
1-(4-Chloro-2, 5-dimethoxy-phenyl)-ethanone (52)



2-Chloro-1,4-dimethoxy benzene (27 g, 156.97 mmol), was dissolved in dry dichloromethane (100 ml) in double neck round bottom flask fitted with calcium chloride guard tube and mixture was cooled to 0°C using ice bath. To this solution anhydrous $AlCl_3$ (20.74 g, 156.97 mmol) was added in portions with the help of solid addition funnel and the reaction mixture was stirred for 10-15 min. after which acetyl chloride (15.35 g, 13.87 ml, 156.97 mmol) was added drop wise with constant stirring. Reaction was allowed to stir at room temperature for 1.5 h. After complete conversion, mixture was poured over crushed ice (approx 500 g), the mass stirred for 30 min. and subsequently extracted with ethyl acetate. Organic layer was washed with water (5×250 ml), followed by brine 50 ml and it is dried over sodium sulphate. Purification by column chromatography using petroleum ether and ethyl acetate (90:10) afforded pure acetopheneone **52** (30.5 g with 91%).

Nature: Pale yellow solid; **Yield**: 91%; **Mp**: 122°C; **IR** (Chloroform): v 3019, 1671, 1492, 1215, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.61 (s, 3H), 3.89 (s, 6H), 7.03 (s, 1H), 7.40 (s, 1H); **MS** (FAB): *m/z* 214, 199, 165, 141, 113, 97, 77.

(4-Chloro-2, 5-dimethoxy-phenyl) acetic acid (53)

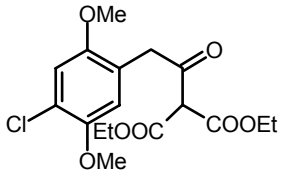


A mixture of acetophenone **52** (20 g, 93 mmol), sulfur (3.57 g, 111.5 mmol) and morpholine (12.19 g, 12.11 ml, 111.5 mmol) was refluxed for 5 h after which pour the reaction mixture slowly in to ice cold water allowing the first addition to crystallized before the bulk of the mixture is added. The yellow solid obtained was filtered of with constant washing with water (5× 100 ml) and dried in air. The thiomorpholide **52a** obtained was hydrolyzed by refluxing with 10%

NaOH, in ethanol (42 ml) for overnight. The maximum amount of ethanol was then distilled off, mixture was acidified using concentrated hydrochloric acid (25 ml) and extracted twice with dichloromethane (2 × 250 ml), dried over sodium sulphate and concentrated Crude residue was purified by crystallization using petroleum ether and ethyl acetate (85:15) to afford acid **53** (12 gm, 56 %).

Nature: Pale yellow crystals; **Yield**: 56%; **Mp**: 123-125 °C; **IR** (chloroform): *v* 3019, 1670, 1555, 756 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.64 (s, 2H), 3.79 (s, 3H), 3.86 (s, 3H), 6.81 (s, 1H), 6.92 (s, 1H), 7.89 (bs, 1H); **MS**: *m/z* 230 (M^+), 185, 171, 155, 122, 105; **Anal. Calcd for** $C_{10}H_{11}ClO_4$: C, 52.17; H, 4.78; **Found**: C, 52.22; H, 4.84.

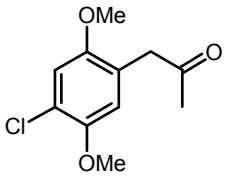
2-[2-(4-Chloro-2, 5-dimethoxy-phenyl)-acetyl]-malonic acid diethyl ester (54)



Magnesium (0.900 g, 37.5 mmol) was covered with dry toluene (50 ml) containing absolute ethanol (2 ml) in three necked flask equipped with reflux condenser. After the addition of crystal iodine a small portion of solution of diethyl malonate (3.08 g, 2.98 ml, 13 mmol), in dry toluene (50 ml) containing 0.5 ml of ethanol was added and the mixture was heated if necessary, until a vigorous reaction set in. The remaining solution was added at convenient rate and the mixture refluxed until dissolution of magnesium was complete. At this stage, the reflux condenser was replaced by fractionating column. Mixture was distilled until most of ethanol had been removed by azieotrop with toluene. The requisite acid chloride (1.0 g, 4.69 mmol) (prepared from 1.2 g of phenyl acetic acid (**53**) and 1.8 ml of $SOCl_2$) in dry toluene was added with stirring and external cooling to the solution of ethoxy magensiomalonic ester during 30 min and reaction was allowed to reflux for 1h. The reaction was then quenched with dil. H_2SO_4 (10%, 15 ml) and organic layer was thoroughly shaken with excess of dil H_2SO_4 followed by water. Organic layer was dried over sodium sulphate, toluene was removed by distillation and excess of malonic ester was recovered by vacuum distillation. The residue obtained was purified by column chromatography over silica gel to afford diester **54** as a pink crystalline solid (0.650 gm, 41.1%).

Nature: Pink crystalline solid; **Yield**: 41.1%; **Mp**: 93-95 ˚C; **IR** (Chloroform) *v* 3020, 1715 (broad), 1504, 1215, 1038, 755 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.25 (t, J = 6 Hz, 6H), 3.76 (s, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.21 (q, J = 6 Hz, 4H), 4.54 (s, 1H), 6.73 (s, 1H), 6.89 (s, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 13.6 (2C), 43.1, 49.0, 55.3, 56.7, 61.2, 61.7, 112.8, 115.4, 115.4, 121.0, 148.8, 151.0, 164.2, 168.1, 196.1; **MS**: *m/z* 372, 326, 212, 185, 155; **Anal Calcd for** $C_{17}H_{21}ClO_7$: C, 54.83; H, 5.64; **Found**: C, 54.75; H, 5.73.

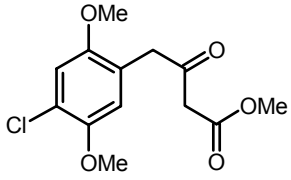
1-(4-Chloro-2, 5-dimethoxy-phenyl)-propan-2-one (55)



A mixture of diester **54** (0.100 g, 0.296 mmol), water (0.10 ml), sodium chloride (0.17 gm, 0.296 mmol), and DMSO (1 ml) was heated at 110-120ºC for 2.5 h, and is then poured into ice water. It was then extracted with ethyl acetate; organic layer was washed with water and dried over sodium sulphate. Solvent was removed under reduced pressure and the residue was purified by column chromatography to yield the ketone **55** (0.043 g, with 70.4%).

Nature: Thick oil; **Yield**: 70.4%; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.13 (s, 3H), 3.61 (s, 2H), 3.75 (s, 3H), 3.81 (s, 3H), 6.70 (s, 1H), 6.87 (s, 1H).

(4-Chloro-2, 5-dimethoxy-phenyl)-3-oxo-butyric acid methyl ester (56)

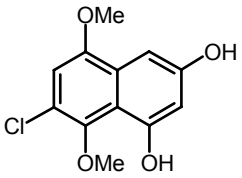


To a solution of meldrums acid (2.12 g, 14.72 mmol) in 15 ml of anhydrous dichloromethane, anhydrous pyridine (2.90 g, 2.96 ml, 36.70 mmol) was added with stirring under argon atmosphere over a period of 10 min. To the resulting colorless solution, a solution of phenyl acetyl chloride (prepared from acid **53**, 3.66 g, 14.7 mmol) in 20 ml anhydrous dichloromethane was added over a period of 1h, at 0ºC. After the additional 1 h at room temperature, the reaction was diluted to 25 ml with dichloromethane and then poured in to 20ml of 2N HCl containing crushed ice. The organic phase was extracted twice with 25 ml portions of 2N hydrochloric acid and 30 ml of saturated sodium chloride solution and dried over sodium sulphate. The solvent was evaporated to yield the acyl meldrums acid as a pale yellow

solid. The solid acyl medrums acid without further purification was refluxed in 150-ml of anhydrous methanol for 2.5 h. Methanol was removed with rotary evaporator and residual oil was purified by column chromatography to give pure ester **56** (2.33 g, 55.2 %).

Nature: Pinkish white crystals; **Yield**: 55.2 %; **Mp**: 76-78 °C; **IR**: (chloroform): ν 3020, 1712, 1520, 1212 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.48 (s, 2H), 3.72 (s, 3H), 3.77 (s, 5H), 3.85 (s, 3H), 6.76 (s, 1H), 6.92 (s, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 44.0, 47.8, 51.9, 55.7, 56.4, 112.8, 115.4, 121.3, 121.6, 148.5, 151.1, 167.3, and 200.0; **MS**: *m/z* 286, 228, 185, 155, 77; **Anal Calcd for** $C_{13}H_{15}ClO_5$: C, 54.54; H, 5.24; **Found**: C, 54.62; H, 5.80.

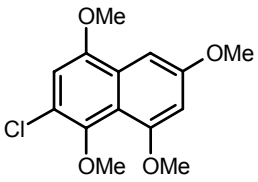
7-Chloro-5, 8-dimethoxy-naphthalene-1, 3-diol (57)



To an ice-cold solution of β-ketoester **56** (1.2 g, 4.78 mmol), 2 ml of conc. H_2SO_4 was added and the resulting mixture was stirred for 20-30 min. (reaction mixture became dark violet in color). It was then poured over crushed ice, and emulsion formed was filtered through celite pad. The filtrate was extracted with ethyl acetate, organic layer was washed with water followed by brine and dried over sodium sulphate. Solvent was evaporated and residue obtained was chromatographed over silica gel using petroleum ether and ethyl acetate (60:40) as an eluent to afford pure naphthol **57** (0.930 g, 76.6 %).

Nature: Violet crystals; **Yield**: 76.6%; **Mp**: 118-120 °C; **IR**: (chloroform): *v* 3352, 1603, 1501, 1215 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.93 (s, 3H), 4.04 (s, 3H), 6.62 (d, J = 2.2 Hz, 1H), 6.64 (s, 1H), 7.03 (d, J = 2.2 Hz, 1H); **MS**: *m/z* 254, 239, 211, 196, 161, 91; **Anal Calcd for** $C_{12}H_{11}ClO_4$: C, 56.69; H, 4.33; **Found**: C, 56.58 H, 4.27.

2-Chloro-1, 4, 6, 8-tetramethoxy-naphthalene (58)

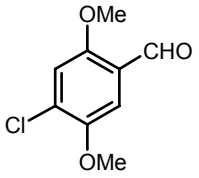


1,3-Naphthalenediol **57** (1.5 g, 5.90 mmol) was dissolved in dry 25 ml acetone in two neck round bottom flask equipped with reflux condenser and two-way stopcock. Solution was charged with anhydrous K_2CO_3 (2.036 g, 14.76 mmol)

followed by dimethyl sulphate (1.86 g, 1.39 ml, 14.76 mmol) and the reaction was allowed to reflux for 4-5 h, after which it was filtered through sintered funnel to remove solid K_2CO_3. Filtrate was concentrated; residue was washed thoroughly with water and extracted with ethyl acetate. Organic layer was dried over sodium sulphate and solvent was evaporated under reduced pressure. Crude naphthalene derivative was purified by column chromatography using pet ether and ethyl acetate as an eluent (90:10) to obtain pure naphthalene derivative **58** (1.52 g, 90 %).

Nature: White crystals; **Yield**: 90%; **Mp**: 166-167 °C; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.92 (s, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.59 (d, J = 2.2 Hz, 1H), 6.78 (s, 1H), 7.11 (d, J = 2.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 54.9, 55.5, 55.9, 61.2, 100.2, 106.6, 116.7, 121.4, 127.9, 145.3, 150.3, 156.6, 157.8 (2C); **MS**: *m/z* 282, 267, 231, 189, 159, 141, 115; **Anal Calcd for** $C_{14}H_{15}ClO_4$: C, 59.57; H, 5.31; **Found**: C, 59.61 H, 5.10.

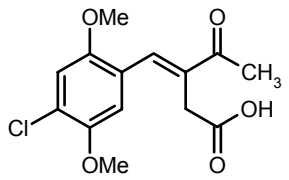
4-Chloro-2,5-dimethoxy-benzaldehyde (59)



Trifluoroacetic acid (28.4 ml, 249.12 mmol) was added to a mixture of 1-chloro-2, 5-dimethoxybenezene (3.19 gm, 18.5 mmol) and hexamethyltetramine (2.59 g, 18.5 mmol). The solution was immediately placed in preheated oil bath (90-95 °C) and refluxed for 12 h. The hot solution was then poured on crushed ice and the resultant dark orange mixture was rapidly stirred for 30 min after the ice had melted. The solution was made basic with excess of sodium bicarbonate until yellow precipitate formed. It was then extracted with ethyl acetate (3×50 ml); organic layer was washed with excess of water followed by brine and dried over sodium sulphate. Ethyl acetate was removed under vacuum to afford yellow mass, which was recrystallized form petroleum ether to afford pure fluorescent aldehyde (2.9 g, 78 %).

Nature: Yellow crystalline solid; **Yield**: 78%; Mp: 106 °C; **IR** (chloroform): ν 2966, 2943, 1675, 1501, 1276 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.83 (s, 6H), 6.99 (s, 1H), 7.30 (s, 1H), 10.32 (s, 1H); **MS** (ESI): *m/z* 200 (M^+), 202 (M+2).

3-Acetyl-4-(4-chloro-2,5-dimethoxy-phenyl)-but-3-enoic acid (60)

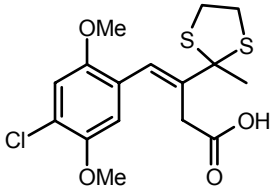


To a well-stirred mixture of substituted benzaldehyde **59** (2.50 g, 12.5 mmol) and ethyl levulinate (5.4 g, 5.31 ml, 37.5 mmol) in methanol (50 ml), aqueous sodium hydroxide solution (1.5 g, 37.5 mmol; in 15 ml H_2O) was added dropwise at -10˚C. After complete addition, reaction mixture was stirred at same temperature for 4-5 h and the reaction was monitored by thin layer chromatography. After completion of reaction, methanol was removed under vacuum, reaction mixture was diluted with water and washed with ethyl acetate (3×20 ml) and aqueous layer was acidified with conc HCl. The yellow oil separated was extracted with ethyl acetate (3×25 ml), and it was repeatedly washed with water to remove traces of levulinic acid, followed by brine, dried over sodium sulphate and evaporated to yield acid **60** (3.20 g, 86 %) as an oil which crystallized on standing.

Nature: Yellow solid; **Mp**: 127-130ºC; **IR**: (chloroform) *v* 3020, 1712, 1670, 1495, 1215, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.52 (s, 3H), 3.53 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 6.67 (s, 1H), 6.69 (s, 1H), 7.81 (s, 1H); **MS**: *m/z* 298.0, 268, 196, 152, 89; **Anal. Calcd for** $C_{14}H_{15}O_5Cl$: C, 56.37; H, 5.03; **Found**: C, 56.39; H, 5.28.

* The spectral data of **61, 61a, 61b** is presented in chapter 1 sec.1. Number of particular compound is **119i, 120i, and 121i.**

4-(4-Chloro-2,5-dimethoxy-phenyl)-3-(2-methyl-[1,3]dithiolan-2-yl)-but-3-enoic acid (62)

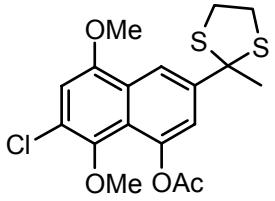


The solution of acid **60** (2.43g, 8.15 mmol) in dry chloroform was added ethane dithiol (0.766 g, 0.685 ml, 8.15 mmol) with help of syringe, followed by addition of catalytic amount of iodine (0.002 g). Reaction was stirred at room temperature for 45 min. The reaction mixture was extracted with chloroform (2 x 25 ml) and combined organic layer was washed with sodium thiosulphate solution (10 ml) followed by water

(10 ml) and brine (5 ml). Concentration of organic layer under reduced pressure and purification of residue by column chromatography furnished pure protected acid **60** (2.80 g, 92%).

Nature: White crystalline solid; **Yield**: 92%; **Mp**: 110-112 ºC; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.79 (s, 3H), 2.20-2.28 (m, 2H), 2.60-2.70 (m, 2H), 3.47 (s, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 6.86 (s, 1H), 7.03 (s, 1H), 7.17 (s, 1H). **Anal Calcd for** $C_{16}H_{19}ClO_4S_2$: C, 51.34; H, 5.08; S, 17.11; **Found**: C, 51.45 H, 4.98; S, 17.14.

Acetic acid 7-chloro-5, 8-dimethoxy-3-(2-methyl-[1,3]dithiolan-2-yl)-naphthalen-1-yl ester (63)

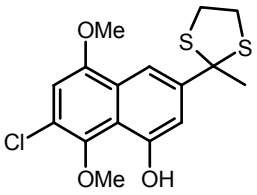


The carboxylic acid **62** (2.5 g, 6.68 mmol) was mixed with anhydrous sodium acetate (1.09 gm, 13.36 mmol) and acetic anhydride (3.40 g, 3.14 ml, 13.36 mmol) and allowed to stir at 120 ºC under nitrogen atmosphere for 3 h. The mixture was allowed to cool to room temperature when crystals of sodium acetate were thrown out. The reaction mixture was poured over ice (approx 100 g), stirred vigorously for 30 min and extracted with ethyl acetate (3×30 ml). The organic layer was washed repeatedly with fresh portions of water (4×50 ml) followed by dilute sodium bicarbonate solution (2×10 ml) to remove traces of acetic anhydride and acetic acid. The organic layer was washed with brine (10 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure. Purification of residue by column chromatography (80:20 pet ether: ethyl acetate) provided desired naphthalene derivative **63** as a white crystalline solid (1.98 g, 74.4%).

Nature: White crystalline solid; **Yield**: 74.4%; **Mp**: 122-124 ºC; **IR**: (chloroform): ν 3017, 1770, 1591, 1458, 1215 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.23 (s, 3H), 2.40 (s, 3H), 3.30-3.55 (m, 4H), 3.85 (s, 3H), 3.90 (s, 3H), 6.79 (s, 1H), 7.60 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 2.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 20.7, 33.1, 40.6 (2), 65.9, 61.6, 68.0, 106.8, 117.7, 121.4, 121.6, 125.4, 126.4, 143.6, 143.9, 145.1, 152.3, 169.3; **MS**: *m/z*

398, 356, 341, 311, 296, 281; **Anal Calcd for** $C_{18}H_{19}ClO_4S_2$: C, 54.27; H, 4.77; S, 16.08; **Found**: C, 54.43 H, 4.82; S, 17.94

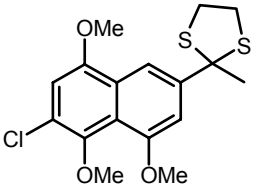
7-Chloro-5, 8-dimethoxy-3-(2-methyl-[1,3]dithiolan-2-yl)-naphthalen-1-ol (64)



Acetate **63** (1.90 g, 4.77 mmol) was dissolved in distilled ethanol and solution was cooled to 0 °C. A solution of sodium hydroxide (0.250 g, in 5 ml H_2O) was added. And the reaction mixture was allowed to stirred at room temperature for 4 h. After complete hydrolysis ethanol was removed under vaccum. Residue was diluted with water (15 ml) and washed with ethyl acetate, aqueous layer was acidified with dilute HCl and precipitate was extracted with ethyl acetate (3×15 ml). Organic layer was washed with water followed by brine solution (10 ml) and finally dried over sodium sulphate. Residue was purified by column chromatography using petroleum ether and ethyl acetate (65:35) as an eluent to afford brown needles of naphthol derivative **64** as brown needles with 1.45 g, 85.5% yield.

Nature: Brown needles; **Yield**: 85.5%; **Mp**: 131-132 ºC; **IR** (chloroform): *v* 3372, 3018, 2932, 1597, 1264 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.22 (s, 3H), 3.38-3.53 (m, 4H), 3.97 (s, 3H), 4.02 (s, 3H), 6.70 (s, 1H), 7.39 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H); **MS**: *m/z* 356 (M^+), 374 ($M+H_2O$); **Anal Calcd for** $C_{16}H_{19}ClO_3S_2$: C, 53.93; H, 4.77; S, 17.97; **Found**: C, 54.04 H, 4.75; S, 18.07.

2-(6-Chloro-4, 5, 8-trimethoxy-naphthalen-2-yl)-2-methyl-[1,3]dithiolane (65)

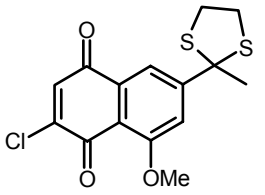


Naphthol **64** (2.0 g, 5.61 mmol) was taken in dry acetone 50 ml in two-necked round bottom flask fitted with reflux condenser. Anhydrous K_2CO_3 (0.969 g, 7.02 mmol) was added at once, followed by addition of distilled dimethyl sulphate (0.884 g, 0.66 ml, 7.02 mmol). Reaction mixture was refluxed for 5 h, after which it was filtered through celite pad and washed with acetone. Filtrate was concentrated under vacuum; crude residue obtained was washed thoroughly with water and extracted with ethyl acetate (2× 50 ml). Organic layer was

dried on sodium sulphate and crude product was purified by column chromatography (pet ether-ethyl acetate, 90:10) to afford naphthalene derivative **65** (1.95 g) with 94.2% yield.

Nature: Pale yellow solid; **Yield**: 94%; **Mp**: 143-145 ºC; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.24 (s, 3H), 3.28-3.60 (m, 4H), 3.85 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 6.68 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 8.11 (d, J = 2.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 33.3, 40.3 (2), 55.7, 56.4, 61.4, 68.8, 106.2, 106.8, 108.2, 112.1, 120.1, 124.8, 126.6, 143.3, 151.8, 155.4; **Anal Calcd for** $C_{17}H_{19}ClO_3S_2$: C, 55.13; H, 5.13; S, 17.29; **Found**: C, 55.25 H, 5.20; S, 17.40.

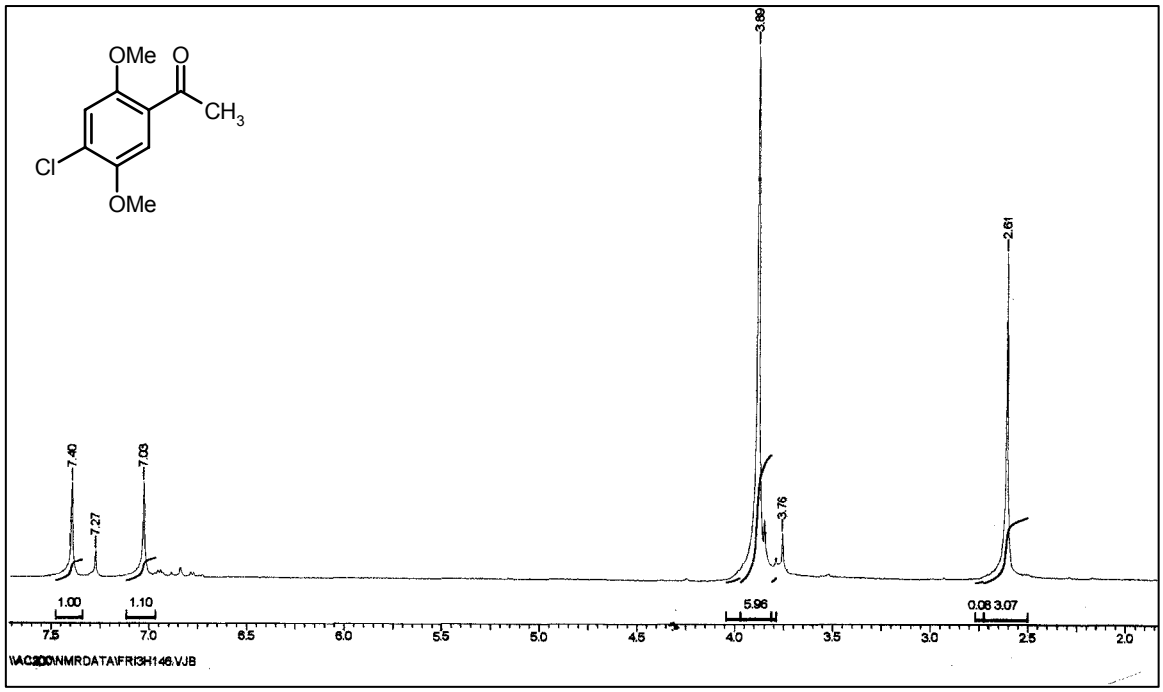
2-Chloro-8-methoxy-6-(2-methyl-[1,3]dithiolan-2-yl)-[1,4]naphthaquinone (66)



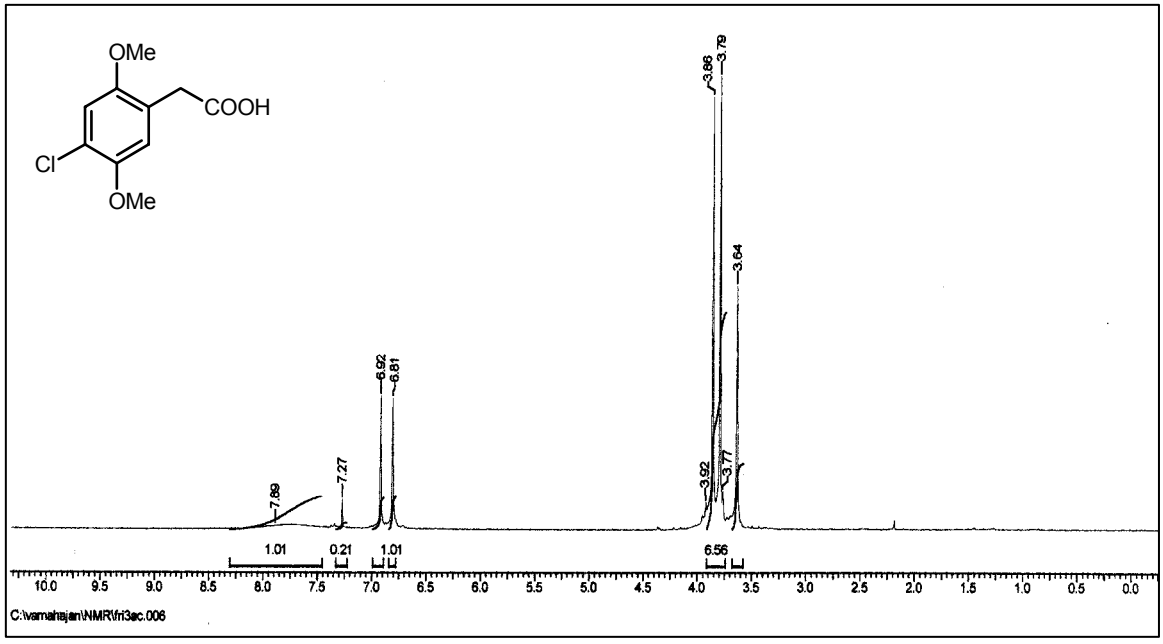
A solution of naphthalene derivative **65** (1.80 g, 4.86 mmol) dissolved in distilled acetonitrile (20 ml) was cooled to 0 °C and a solution of cerric ammonium nitrate (5.33 g, 9.73 mmol in 10 ml water) was added dropwise. The reaction was allowed to stirr at room temperature for 30 min after which acetonitrile was removed under vacuum and the residue was extracted with ethyl acetate (2×25 ml). Organic layer was washed with water followed by brine, dried over sodium sulphate and concentrated. Residue was purified by column chromatography using petroleum ether and ethyl acetate (90:10) as an eluent to afford pure napthaquinone derivative **66** (1.48 g, 89.6 %).

Nature: Brownish yellow crystal; **Yield**: 89.6%; **Mp**: 123 ºC; **IR**: (chloroform): ν 3020, 1670, 1591, 1215, 756 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.16 (s, 3H), 3.30-3.57 (m, 4H), 4.05 (s, 3H), 7.13 (s, 1H), 7.80 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 1.8 Hz, 1H); **MS**: *m/z* 340, 325, 281, 221, 119 and 59; **Anal Calcd for** $C_{15}H_{13}ClO_3S_2$: C, 52.94; H, 3.82; S, 18.82; **Found**: C, 53.14 H, 3.75; S, 18.94.

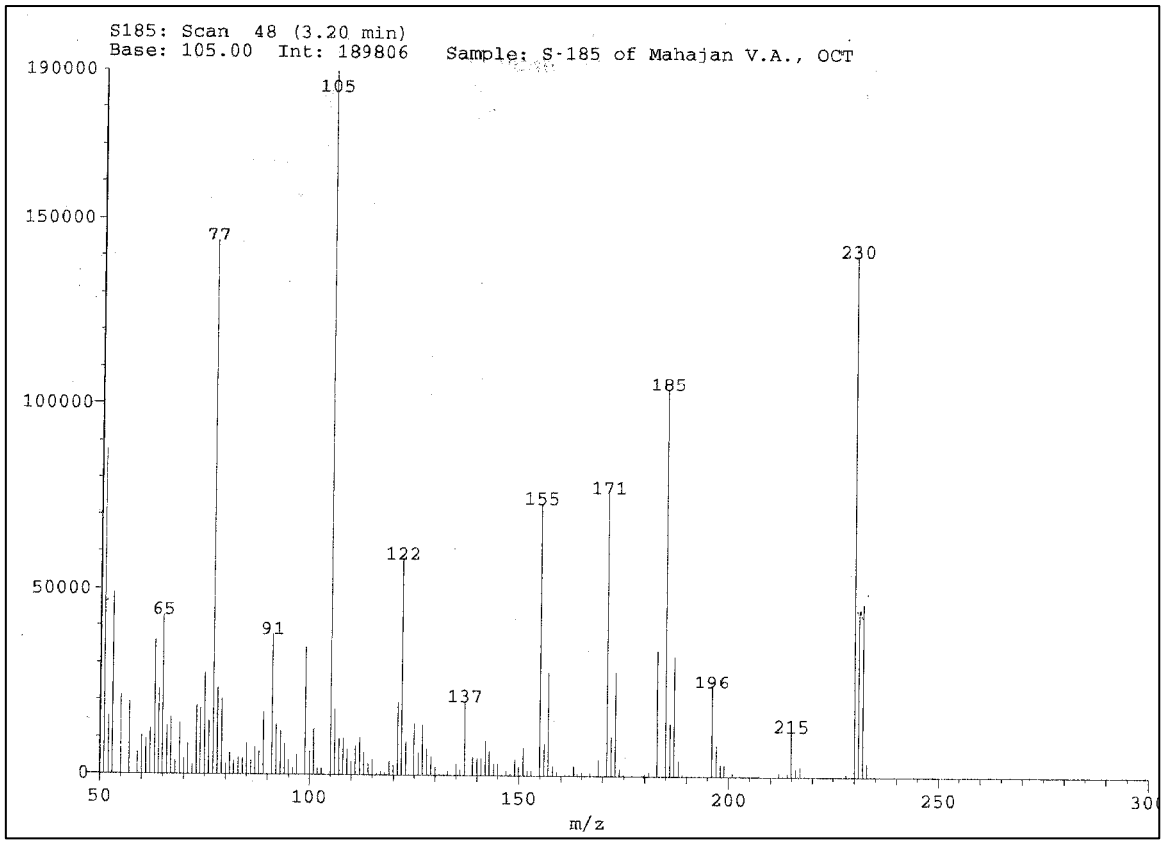
^{1}H NMR spectrum of compound 52 ($CDCl_3$, 200 MHz)



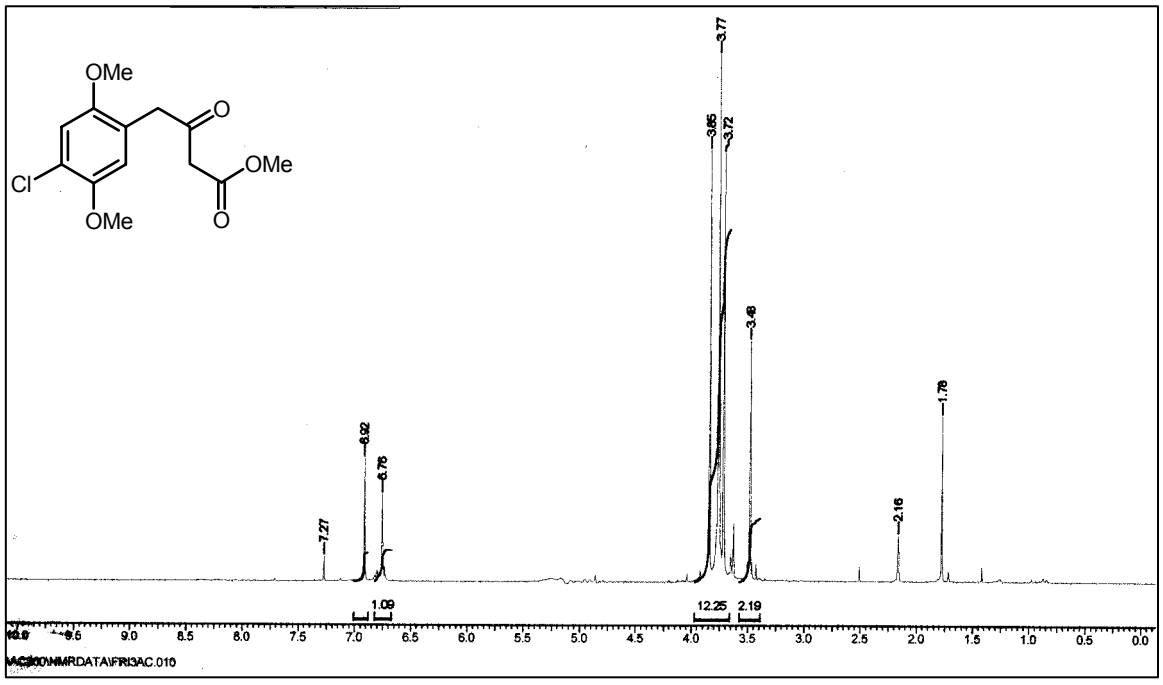
^{1}H NMR spectrum of compound 53 ($CDCl_3$, 200 MHz)



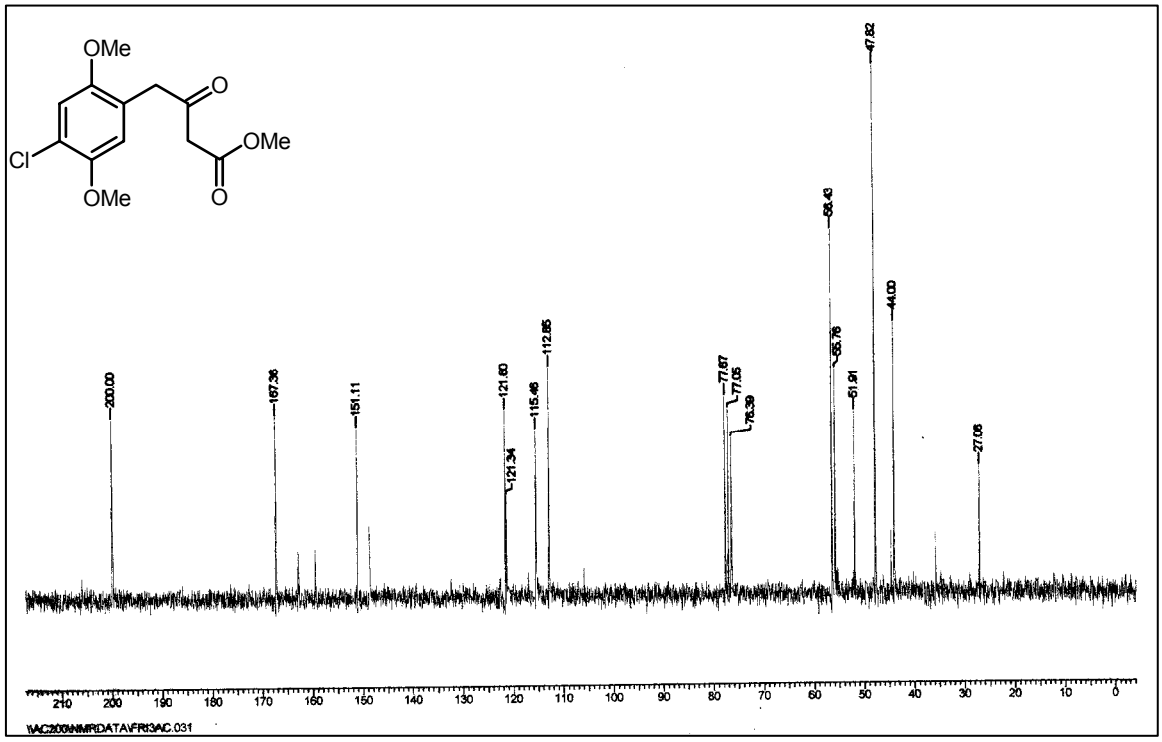
Mass spectrum of compound 53

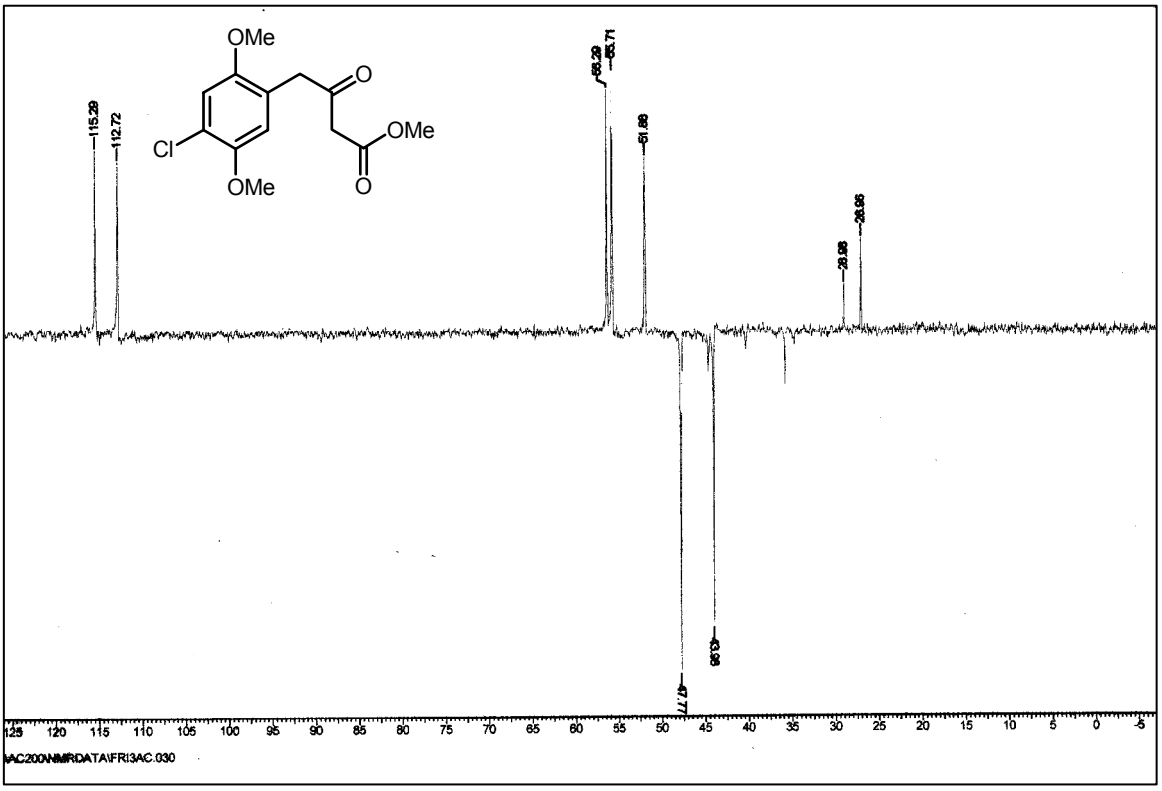


^{1}H NMR spectrum of compound 56 ($CDCl_3$, 200 MHz)

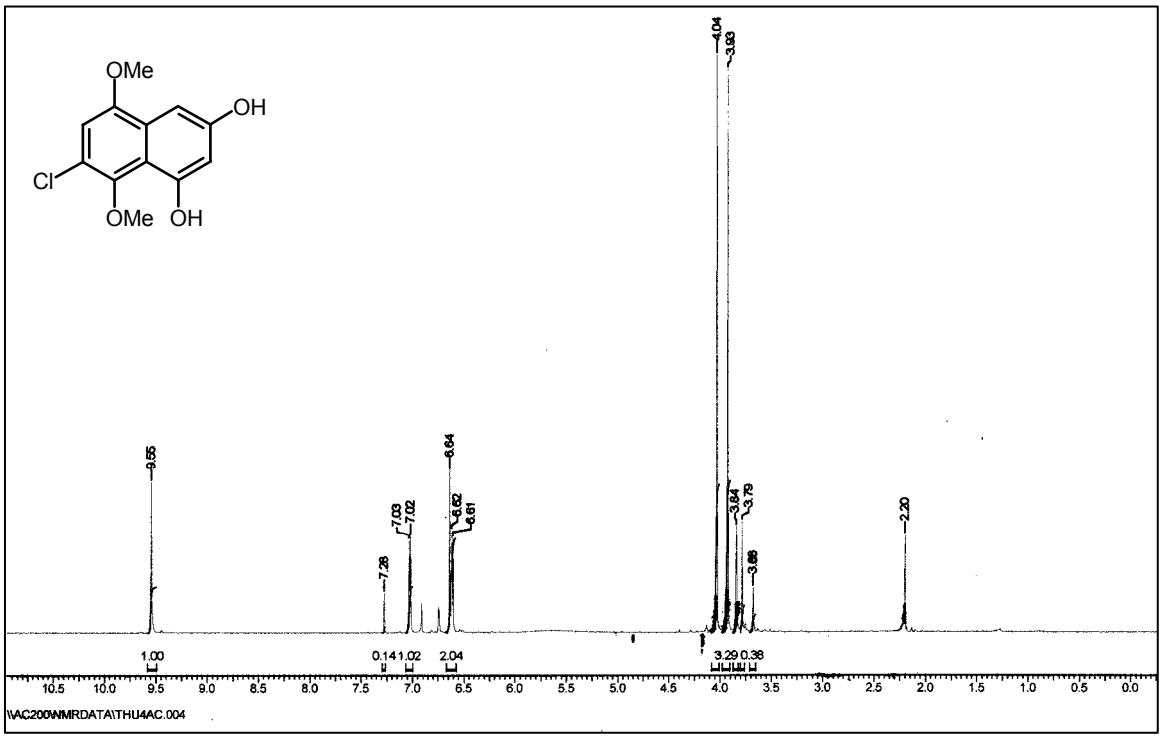


^{13}C NMR and DEPT spectrum of compound 56 ($CDCl_3$, 50 MHz)

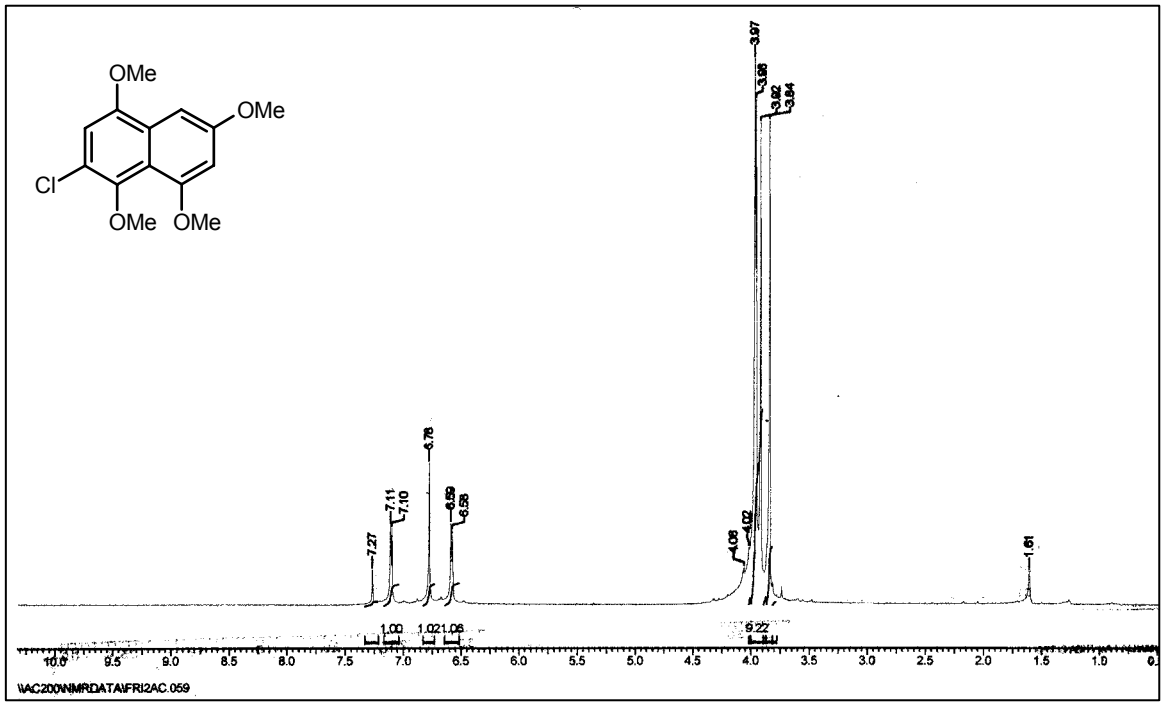




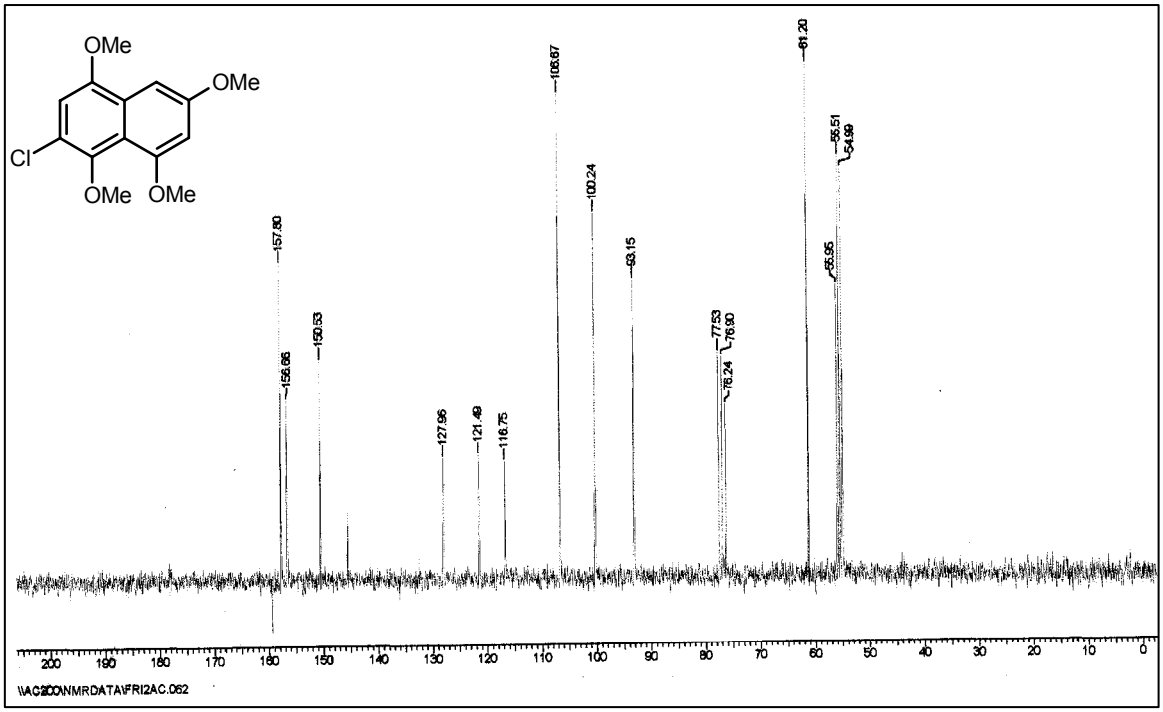
^{1}H NMR spectrum of compound 57 ($CDCl_3$, 200 MHz)



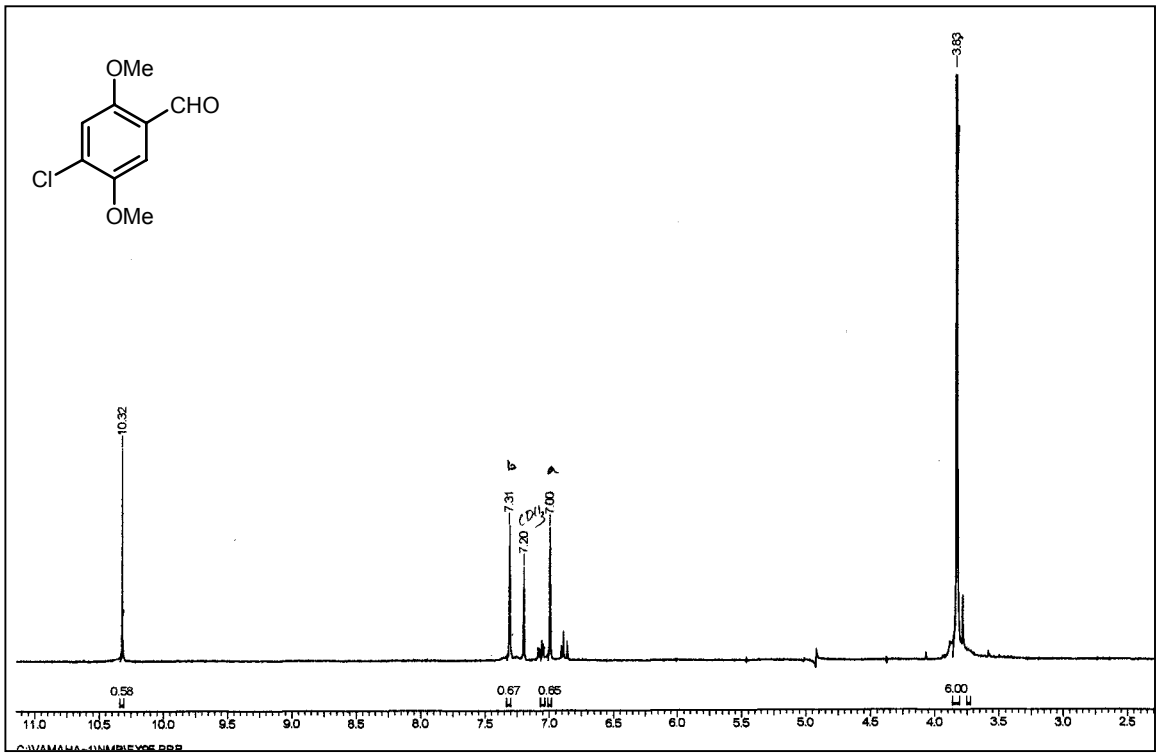
^{1}H NMR spectrum of compound 58 ($CDCl_3$, 200 MHz)



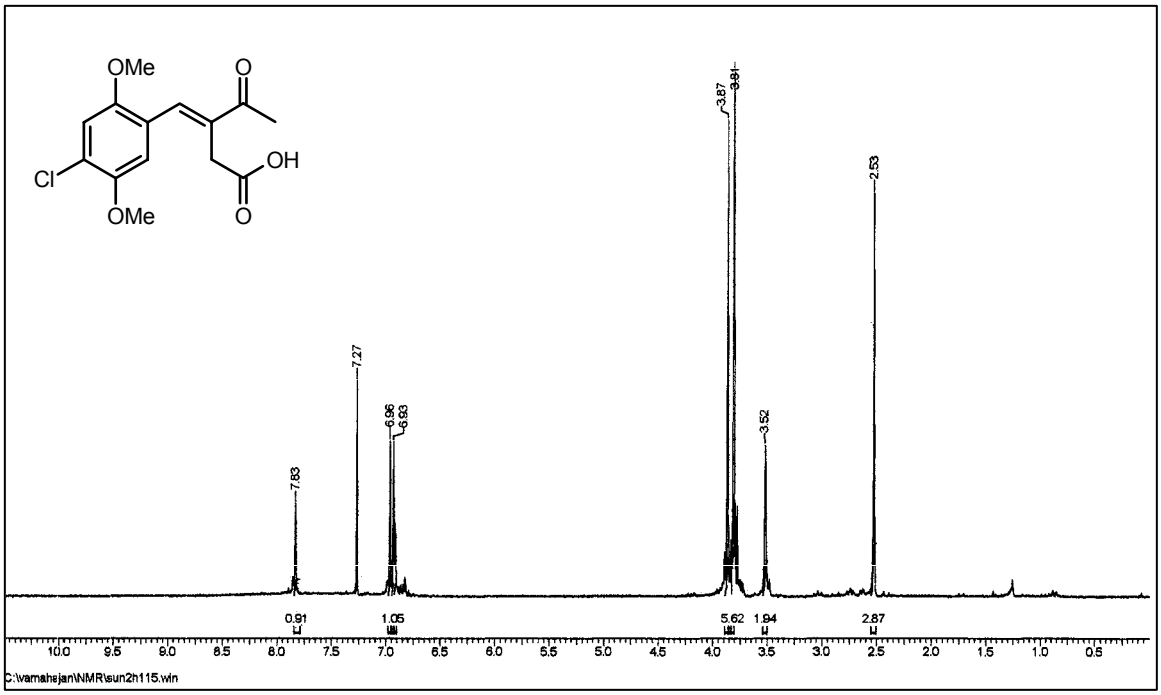
^{13}C NMR spectrum of compound 58 ($CDCl_3$, 50 MHz)



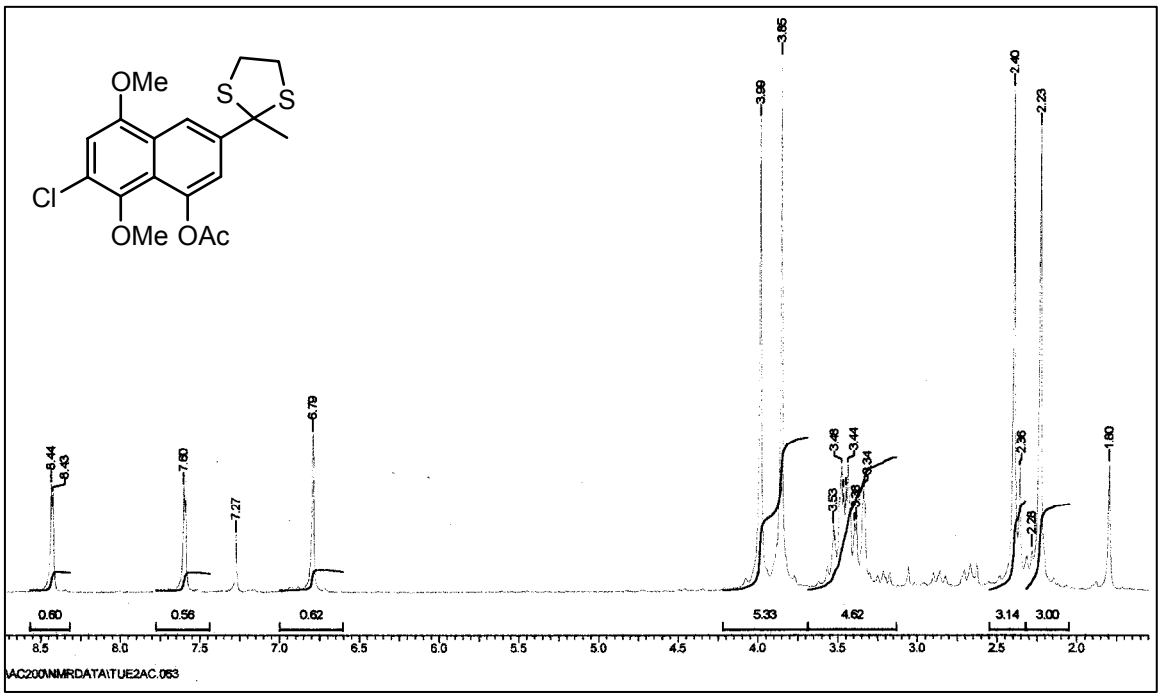
^{1}H NMR spectrum of compound 59 ($CDCl_3$, 200 MHz)



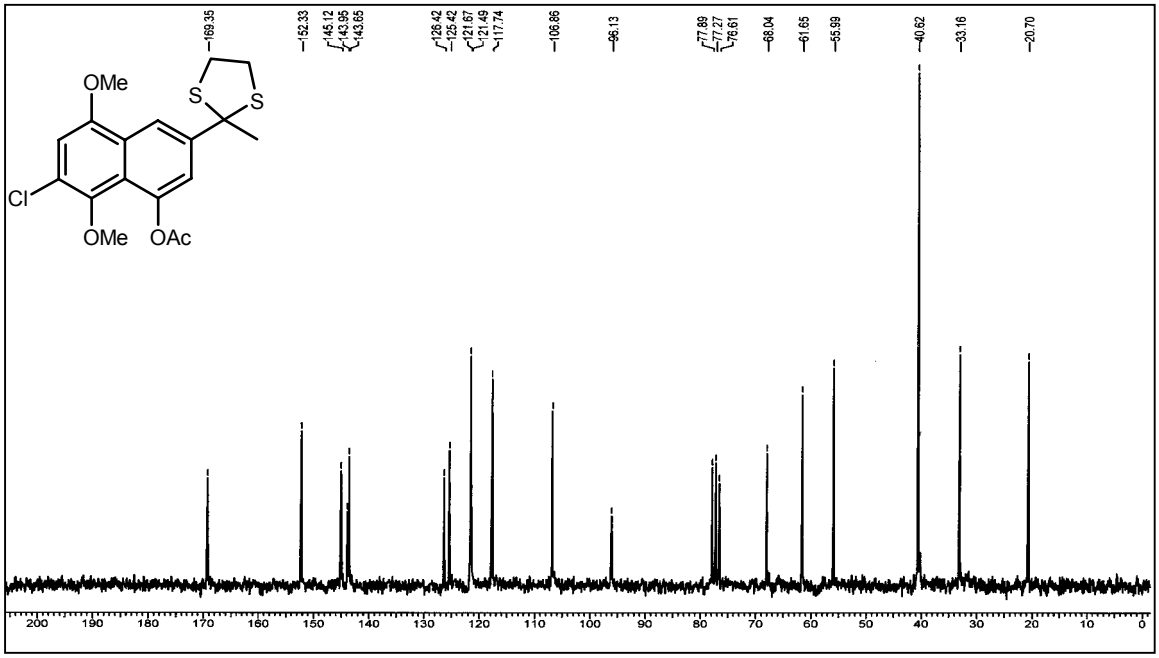
^{1}H NMR of compound 60 ($CDCl_3$, 200 MHz)



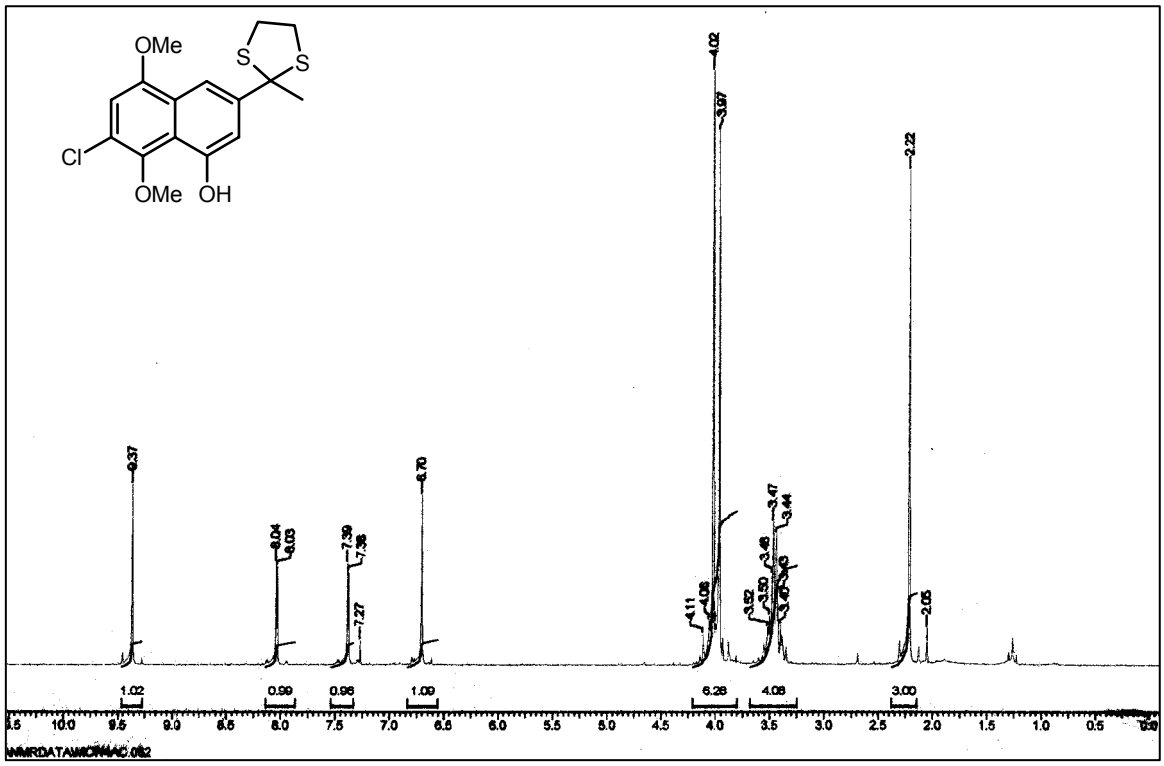
^{1}H NMR spectrum of compound 63 ($CDCl_3$, 200 MHz)



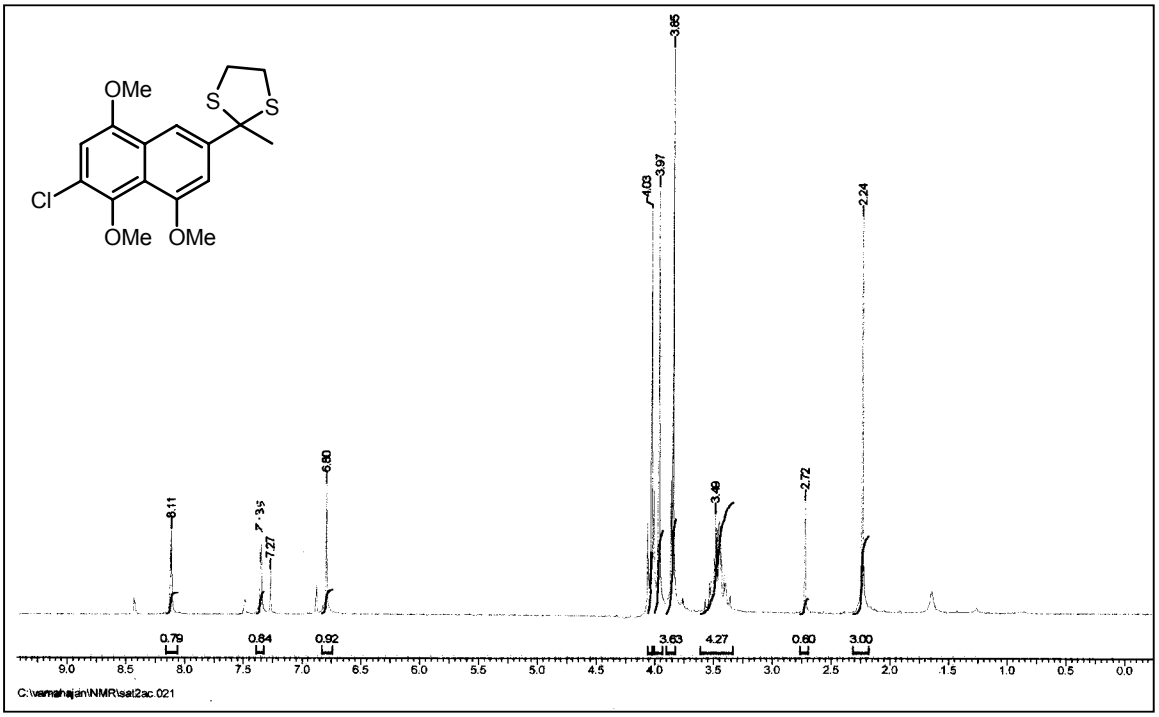
^{13}C NMR spectrum of compound 63



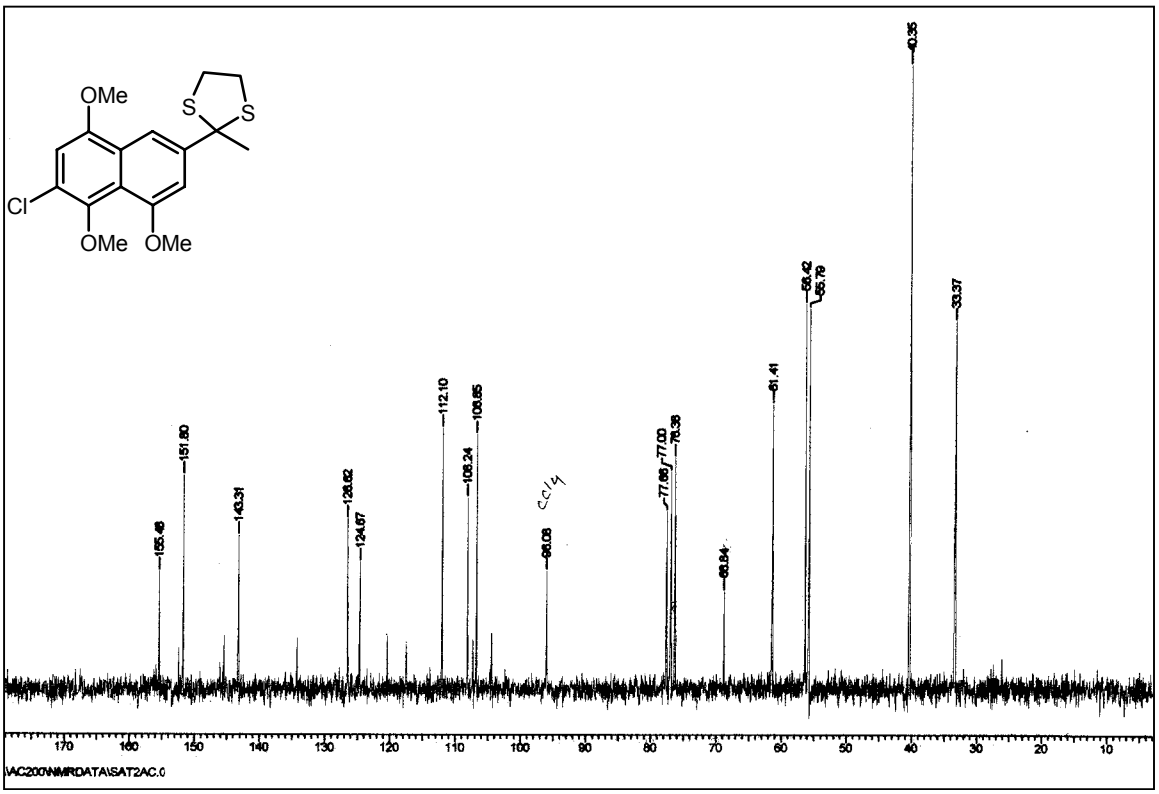
^{1}H NMR spectrum of compound 64 ($CDCl_3$, 200 MHz)



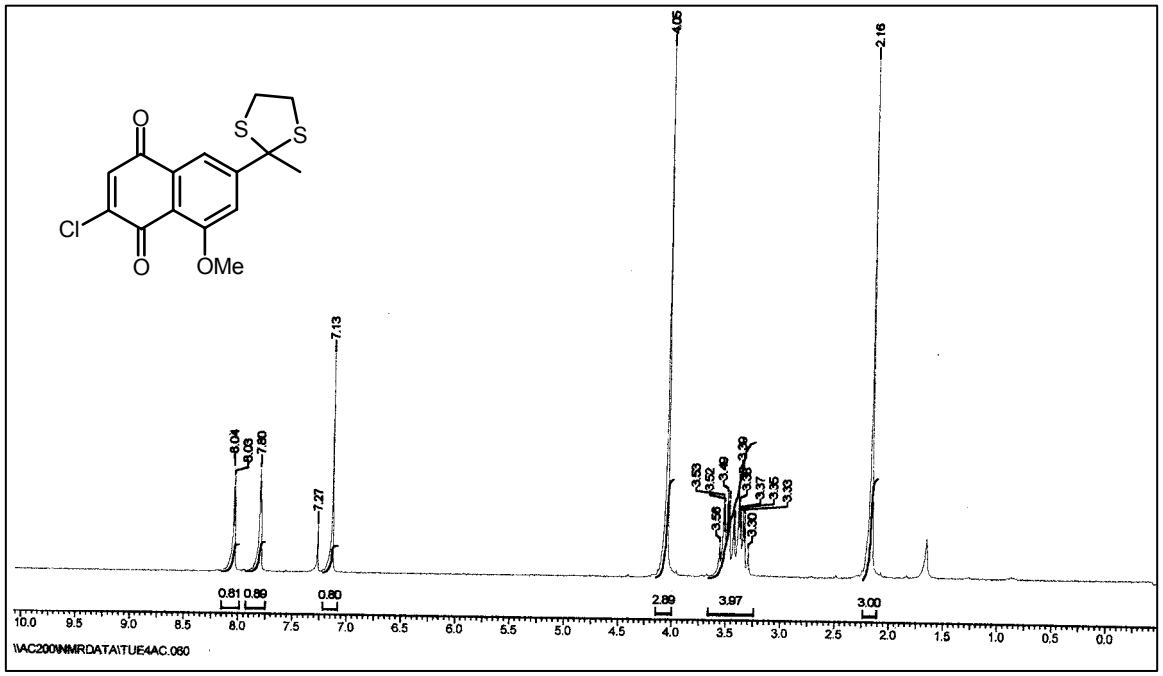
^{1}H NMR spectrum of compound 65 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 65 ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of compound 66



2.1.6. REFERENCES

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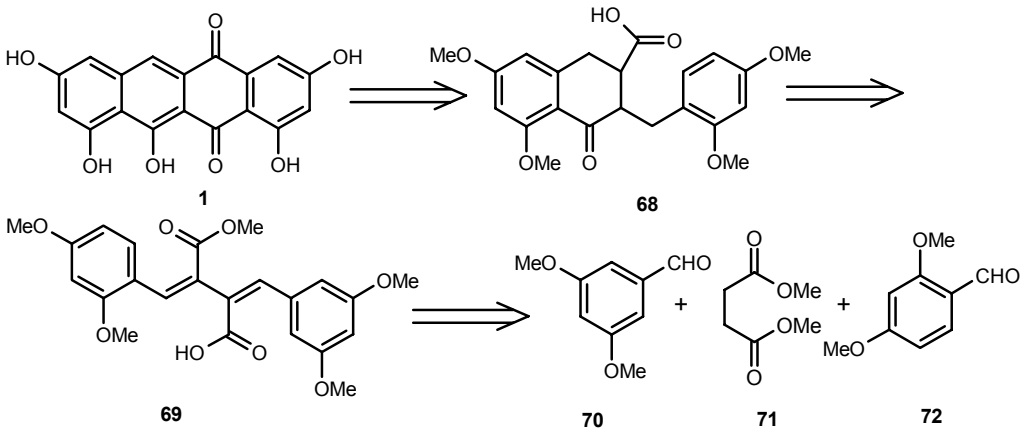
2.2.1. INTRODUCTION

In an effort to synthesize saintopin we attempted Stobbe condensation approach. Literature survey revealed that this approach has not been attempted for the synthesis of naphthacenedione. This well-known name reaction commences between an aldehyde and an active methylene in the presence of base.[1]

2.2.2. PRESENT WORK

The present section describes our attempt towards the synthesis of saintopin via Stobbe condensation of appropriately substituted benzaldehydes and dimethyl succinate. The retrosynthetic plan (Scheme1) indicated that 3,5-dimethoxybenzaldehyde and 2,4-dimethoxybenzaldehyde could serve as the desired building blocks to generate tetracyclic framework of the target molecule. These two benzaldehydes should react with dimethyl succinate sequentially to provide the key intermediate **69**. Further stepwise cyclization and chemical transformations by manipulation of sequence should complete the synthesis of saintopin in much shorter route. Our contribution, efforts and the problems faced during this approach are discussed.

Scheme 1. Retrosynthetic plan



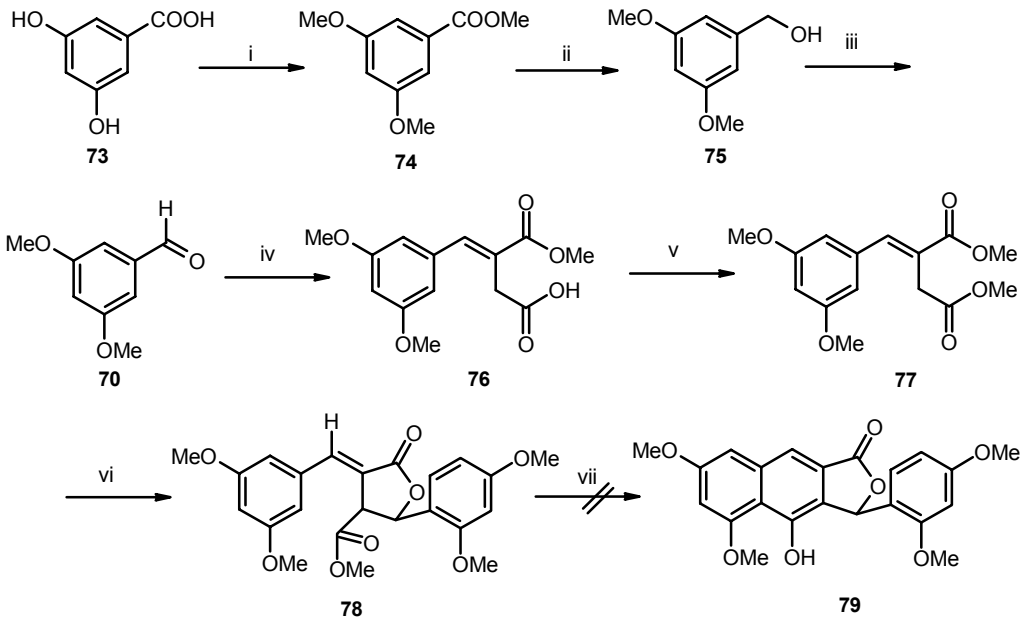
2.2.3. RESULTS AND DISCUSSION

The synthesis initiated with the preparation of the desired intermediate from their commercially available starting materials. Thus 3, 5-dihydroxybenzoic acid **73** was treated with dimethyl sulphate in the presence of potassium carbonate in refluxing acetone to afford methyl 3, 5-dimethoxybenzoate (**74**). Ester **74** was reduced with lithium aluminum hydride in THF at 0ºC to get 3, 5-dimethoxy benzyl alcohol **75**. IR spectrum of alcohol showed characteristic peak for hydroxy function at 3440 cm^{-1} and absence of carbonyl absorption.

3,5-Dimethoxybenzyl alcohol **75** was oxidized to 3, 5-dimethoxy-benzaldehyde **70** in the presence of pyridinium chlorochromate in dry DCM. Formation of aldehyde **70** was confirmed by IR spectrum, which showed carbonyl stretching at 1720 cm^{-1}. 3,5-Dimethoxybenzaldehyde was further subjected for condensation reaction with dimethyl succinate in the presence of freshly prepared sodium methoxide, in dry methanol to afford monoacid derivative **76**. The IR spectrum of compound **76** showed carbonyl absorption at 1712 cm^{-1}. ^1H NMR spectrum showed singlet for methylene group ($C\underline{H}_2$-COOH) at δ 3.60 and a singlet appearing at δ 7.85 integrating for one proton was assigned for olefinic proton (-C<u>H</u>=C-); mass spectrum showed (M^++1) peak at *m/z* 281 as confirming the structure.

Monoester **76** on esterification with of diazomethane in dry diethyl ether afforded diester **77**. The second Stobbe condensation on the diester **77** was performed with 2,4-dimethoxy benzaldehyde **72**, in the presence of LDA at –78 ºC. The product obtained was found to be the lactone **78** and was characterized by means of spectral analysis. The IR spectrum showed two carbonyl absorptions at 1729 cm^{-1} and 1667 cm^{-1} indicating the presence of ester carbonyl and unsaturated lactone carbonyl respectively. ^1H NMR spectrum showed doublet of doublet at δ 4.59 and at δ 5.87 with J = 8 Hz indicating that these protons belong to lactone ring. Mass spectrum showed (M^++1) peak at *m/z* 429 and its adduct with water molecule (M^++18) at *m/z* 446 which confirmed the presence of lactone **78**.

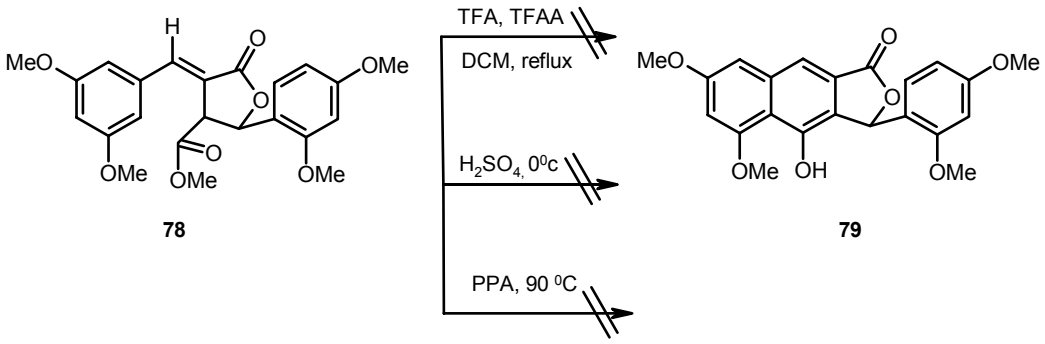
Scheme 2.



Reagents and conditions: (i) DMS, K_2CO_3, acetone, reflux, 4-5 h, 97%; (ii) LAH, THF, 0ºC then reflux; 84%; (iii) PCC, DCM, rt, 1h, 88%; (iv) Dimethyl succinate (**70**), NaOMe, MeOH, 80%; (v) CH_2N_2, ether, methanol, 82.8%; (vi) 2,4-Dimethoxy-benzaldehyde (**72**), LDA, -78ºC, 1h, 64.7 %; (vii) TFA, TFAA, DCM, 0ºC then rt.

The absence of the expected diene dicarboxylate **69** was evident from the above spectral data. The product obtained showed the presence of only one methoxy group from ester functionality (as against two methoxy groups for the diester) and one olefinic proton in the NMR spectrum. The spectral data was in full agreement with the lactone structure **78.** The lactone intermediate **78** was eventually subjected for cyclization in the presence of trifluoroacetic acid and acetic anhydride to afford the cyclized product as depicted in Scheme 2. However this reaction did not proceed to give the desired product **79**. The starting material **78** got completely converted to the product, spectral data of which did not match with the desired compound **79**. The cyclization was also attempted in the presence of sulfuric acid when similar complex product formation was observed.

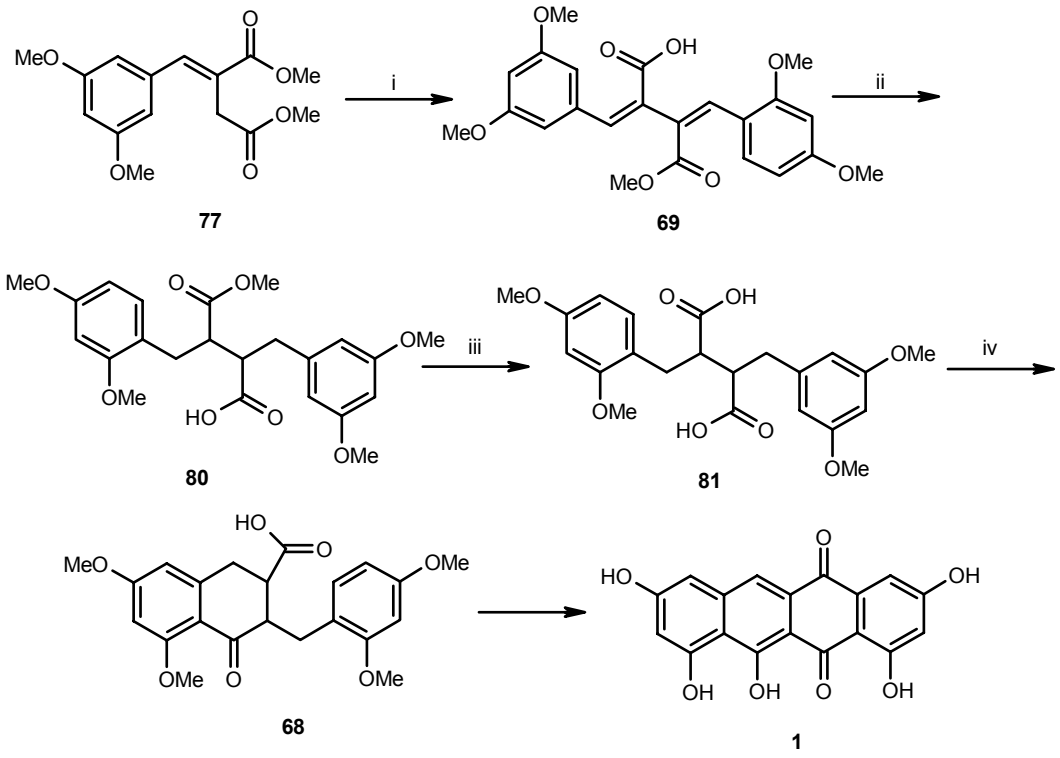
Scheme 3.



Ester **77** (Scheme 4) was condensed with 2,4-dimethoxy-benzaldehyde (**72**) in the presence of sodium methoxide in dry methanol, which after acidic workup gave the monoester **69**. In the IR spectrum the product obtained showed ester carbonyl stretching at 1728 cm^{-1} while acid carbonyl stretching at 1708 cm^{-1}. ^{1}H NMR spectrum showed additional two singlets integrating for two protons each at δ 7.80 and at δ 8.19 which were assigned for olefinic protons; ^{13}C NMR spectrum showed acid carbonyl at δ 172.3 while ester carbonyl at δ 167.5.

Monoacid **69** thus obtained was hydrogenated in the presence of Pd/C to afford saturated monoester derivative **80** and its the structure was confirmed by means of ^{1}H NMR spectrum which indicated surge in the integration in aliphatic region between δ 2.52-3.42 with multiplet for six protons and disappearance of olefinic protons in aromatic region. Monoacid **80** was hydrolyzed to diacid **81** with aqueous sodium hydroxide. IR spectrum of diacid **81** showed strong carbonyl stretching at 1708 $cm^{-1}$with disappearance of the absorption at 1728 cm^{-1} corresponding to the ester carbonyl. Diacid **81** was subjected to cyclization with trifluoroacetic acid and trifluoroacetic anhydride, which afforded tetralone derivative **68** as depicted in Scheme 4.

Scheme 4.

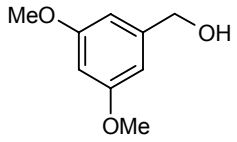


Reagents and condition: (i) 2,4-Dimetoxy-benzaldehyde (**72**), NaOMe, MeOH, 0ºC, 1h then rt 4h, 34%; (ii) Pd/C, H_2 gas, MeOH, 81%; (iii) Aq. NaOH, MeOH, 82%, (iv) TFA, TFAA, DCM, 0ºC then rt., 31.1%.

Compound **68** was characterized by the spectral techniques. It was expected that under these conditions diacid **81** could lead to linear cyclized product, but desired tranformation could not be achieved. Cyclized tetralone derivative **68** was subjected for aromatization in presence of DDQ however various attempts met with failure to provide the aromatized product.

2.2.4. EXPERIMAENTAL

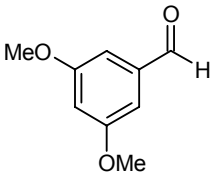
(3,5-Dimethoxy-phenyl)-methanol (75)



A 250 ml two necked round bottom flask equipped with reflux condenser and two-way stopcock, was charged with lithium aluminum hydride (4.90 g, 128.9 mmol) under nitrogen atmosphere. Dry tetrahydrofuran (150 ml) was added at –10˚C with constant stirring. To this suspension 3,5-dimethoxy-methyl benzoate (25 g, 128.3 mmol) in dry tetrahydrofuran 100 ml was added slowly. After addition, reaction mixture was stirred at same temperature for 30 min. and at room temperature for 30 min. It was then refluxed for 5 h. After complete conversion, the reaction mixture was poured slowly over the crushed ice (approx. 100gm). The mixture was stirred for 30 min, acidified using concentrated HCl, extracted with ethyl acetates the organic layer was washed with water (3×250 ml) followed by brine (25 ml) and dried over sodium sulphate. Crude product obtained after solvent evaporation was purified by column chromatography using pet ether and ethyl acetate (70:30) to afford the alcohol **75**. (18 g, 84.03%).

Nature: Pale yellow crystals; **Yield**: 84.03 %; **Mp:** 56 ºC; **IR** (chloroform): ν 2929, 3450, 1511 cm $^{-1}$; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.75 (s, 6H), 4.58 (s, 2H), 6.35 (t, J = 2 Hz, 1H), 6.48 (d, J = 2Hz, 2H).

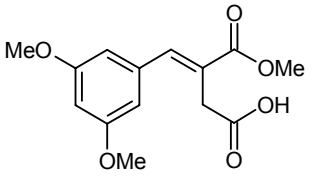
3,5-Dimethoxy benzaldehyde (70)



Alcohol **75** (11gm, 65.4 mmol) was dissolved in dry DCM (110 ml), the solution was cooled to 0 ºC, and charged with freshly activated molecular sieves (5 g). To the mixture, PCC (17.5 g, 81.3 mmol) was added in portions and reaction mixture was allowed to stirr at room temperature. After complete conversion, reaction mixture was filtered through celite pad, DCM was evaporated under vaccum and residue was purified by column chromatography using pet ether and ethyl acetate (95:5) as an eluent to afford the pure aldehyde **70** (9.5 g, 87.7%).

Nature: Pale yellow crystals; **Yield**: 87.7%; **Mp**: 45-48 ºC; **IR** (chloroform): *v* 3019, 1720, 1516, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.78 (s, 6H), 6.42 (t, *J* = 2 Hz, 2H), 7.23 (d, *J* = 2 Hz, 1H), 9.49 (s, 1H).

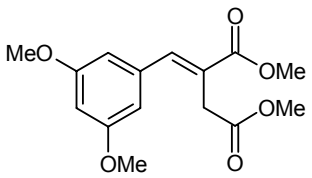
2-(3,5-Dimethoxy-benzylidene)-succinic acid 1-methyl ester (76)



To a solution of sodium methoxide in dry methanol (150 ml, prepared from 1.55 g of sodium metal) a mixture of dimethyl succinate (9.89 g, 67.73 mmol) and 3,5-dimethoxybenzaldehyde (7.5 g, 45.1 mmol) in dry methanol (20 ml) was added drop wise at 0˚C. The mixture was stirred at room temperature for 3-4 h. The reaction mixture was cooled to 0ºC and quenched with dil HCl (30ml). Methanol was removed under vacuum and the residue was extracted with ethyl acetate. Organic layer was washed with water followed by brine and dried over sodium sulphate. Crude product was purified by column chromatography (pet ether and ethyl acetate, 70:30) to obtain the acid **76** (12,65 g, 80.6%).

Nature: Pale yellow crystals; **Yield**: 80.6%; **Mp**: 87-91 ºC; **IR** (chloroform): *v* 3020, 1712, 1598, 1215, 1156, 759 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.60 (s, 2H), 3.78 (s, 6H), 3.82 (s, 3H), 6.45 (t, *J* = 2.5 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 2H), 7.85 (s, 1H), 10.72 (bs, 1H); **MS**: *m/z* 280.09 $(M)^+$; **Anal Calcd for** $C_{14}H_{16}O_6$: C, 60.00; H, 5.71; **Found**: C, 60.17 H, 5.82.

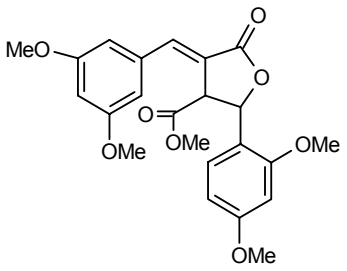
2-(3,5-Dimethoxy-benzylidene)-succinic acid dimethyl ester (77)



Acid **76** (10 g, 35.7 mmol) was dissolved in dry methanol and ether (200 ml, 1:1) and cooled to 0 ˚C, A solution of diazomethane in dry ether (prepared from 5.35 gm of NMU) was added drop wise. Brisk effervescence was observed during addition. Mixture was stirred for 1h at room temperature and ether was removed under vacuum. Column chromatography of the crude residue (80:20 petroleum ether/ethyl acetate) afforded diester **77** (8.7 g, 82.85 %).

Nature: Thick oil; **Yield**: 82.85 %; **IR** (chloroform): *v* 3019, 1731, 1598, 1216, 757 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.51 (s, 2H), 3.68 (s, 3H), 3.73 (s, 3H), 3.78 (s, 6H), 6.38 (t, *J* = 2.5 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 2H), 7.78 (s, 1H); **MS** (ESI): *m/z* 294 $(M)^+$, 312 $(M^+ + H_2O)$;

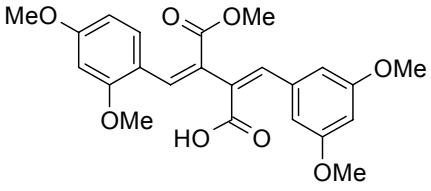
4-(3,5-Dimethoxy-benzylidene)-2-(2,4-dimethoxy-phenyl)-5-oxo-tetrahydro-furan-3-carboxylic acid methyl ester (78)



To a stirred solution of LDA (prepared from diisopropyl amine (0.284 g, 0.396 ml, 2.82 mmol) and n-butyl lithium (1.87 ml, 1.5 M) in dry THF at –78 ºC, diester **77** (0.552 g, 1.88 mmol) in dry THF (ml) was added dropwise during 30 min. To this solution 2,4-dimethoxybenzaldehyde (0.311 g, 1.88 mmol) in dry THF (5 ml) was added dropwise and reaction was allowed to stirr for 1h, and then quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3×20 ml). The organic layer was washed with water followed by brine and dried over sodium sulphate and purified by column chromatography using pet ether and ethyl acetate (70:30) to afford lactone **78** (0.520g, 64.75%).

Nature: Thick gum; **Yield**: 64.7%, **IR** (Chloroform): *v* 3019, 1729, 1667, 1502, 1215, 757 cm^{-1}, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.23 (s, 3H), 3.69 (s, 9 H), 3.86 (s, 3H), 4.52 (d, *J* = 8 Hz, 1H), 5.82 (d, *J* = 8 Hz, 1H), 6.38-6.48 (m, 3H), 6.58 (dd, *J* = 8, 2Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 2Hz, 1H), 7.57 (s, 1H). **MS** (ESI): *m/z* 429 $(M^+ + 1)$, 446 $(M^+ + 18)$; **Anal Calcd for** $C_{23}H_{24}O_8$: C, 64.48; H, 5.60; **Found**: C, 64.51 H, 5.65.

2-(3,5-Dimethoxy-benzylidene)-3-(2,4-dimethoxy-benzylidene)-succinicacid 4-methyl ester (69)

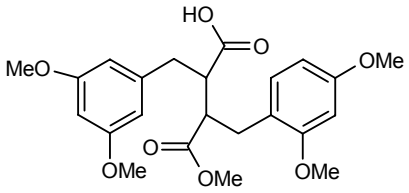


To a solution of sodium methoxide (0.551 g, 10.20 mmol) in methanol (25 ml), mixture of diester (2 g, 6.8 mmol) and 2,4-dimethoxy

benzaldehyde (1.12g, 6.8 mmol) in dry methanol (15 ml) was added drop wise under N_2 atmosphere at 0˚C. Reaction mixture was stirred for 1 h, and then allowed to stirr at room temperature for 4-5 h. It was then quenched with dilute HCl, methanol was removed under vacuum and the residue was extracted with ethyl acetate (3 ×50 ml). Organic layer was washed with water (3×100 ml), followed by brine and dried over sodium sulphate. Crude residue was purified by column chromatography to obtain monoacid **69** (1.0g, 34 %).

Nature: Thick gum; **Yield**: 34%; **IR** (Chloroform): ν 3019, 1728, 1215, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.69 (s, 6H), 3.77 (s, 3H), 3.81 (s, 6H), 6.33-6.40 (m, 3H), 6.59 (d, J = 2.5, 1H), 7.36 (dd, J = 8, 2.5 Hz, 1H), 7.80 (s, 1H), 8.19 (s, 1H); **^{13}C NMR** (50 MHz): δ 52.15, 55.06, 102.4, 104.7, 107.2, 116.4, 123.6, 127.3, 129.8, 136.07, 137.9, 143.6, 159.2, 160.3, 162.2, 167.5, 172.3; **MS** (ESI): *m/z* 428 $(M)^+$; **Anal Calcd for** $C_{23}H_{24}O_8$: C, 64.48; H, 5.60; **Found**: C, 64.53; H, 5.56.

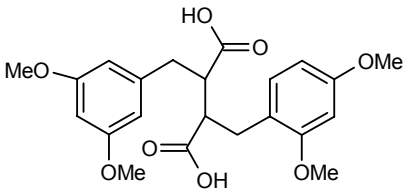
2-(2,4-Dimethoxy-benzyl)-3-(3,5-dimethoxy-benzyl)-succinic acid 1-methyl ester (80)



Monoester **69** (1g, 1.8mmol) was dissolved in dry methanol (15 ml), in double neck round bottom flask equipped with two way stopcock and 10% Pd/ C (0.003g) was added, under argon atmosphere. Reaction mixture was flushed with hydrogen gas and stirred under hydrogen atmosphere for 3-4 h. After complete conversion Pd/C was removed by filtration, methanol was removed under vacuum and the crude product was purified by column chromatography to afford pure hydrogenated product **80** (0.808 g, 81.2%).

Nature: Semisolid; **Yield**: 81.2%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.50-3.20 (m, 6H), 3.73 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 6.05 (d, J = 2Hz, 1H), 6.28-6.43 (m, 4H), 6.86 (d, J = 8 Hz, 1H); **Anal Calcd for** $C_{23}H_{28}O_8$: C, 63.88; H, 6.48; **Found**: C, 63.91 H, 6.52.

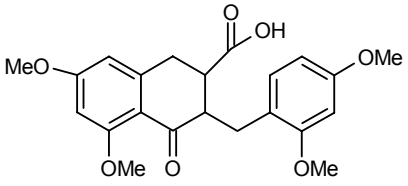
2-(3,5-Dimethoxy-benzyl)-3-(2,4-dimethoxy-benzyl)-succinic acid (81)



Monoester **80** (0.800g, 1.85 mmol) was dissolved in distilled methanol (7 ml), aq. sodium hydroxide solution (40%, 2 ml) was added to it at once and reaction mixture was refluxed. After complete hydrolysis, methanol was removed under vacuum, residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified with dil. HCl and extracted with ethyl acetate. organic layer was washed with water (2×50 ml), brine and dried over sodium sulphate. Diacid obtained was purified by column chromatography using petroleum ether and ethyl acetate to afford pure diacid **81** (0.635g, 82.04%).

Molecular formula: $C_{22}H_{26}O_8$; **Nature**: White solid, **Yield**: 82.0%; **Mp**: 87-89 ºC; **IR** (Chloroform): *v* 3018, 1708, 1596, 1215, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.60-3.20 (m, 6H), 3.69 (s, 3H), 3.72 (s, 6H), 3.77 (s, 3H), 6.15-6.42 (m, 5H), 6.98 (d, J = 8 Hz, 1H), 9.81 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 30.1, 36.0, 45.0, 46.7, 52.1, 54.8, 55.4 (3C), 103.8, 107.0 (3C), 118.8 (2), 141.1, 158.6, 159.1, 160 (2C), 179.7, 180.5; **Anal Calcd for** $C_{22}H_{26}O_8$: C, 63.15; H, 6.20; **Found**: C, 63.22 H, 6.02.

3-(2,4-Dimethoxy-benzyl)-5,7-dimethoxy-4-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (68)

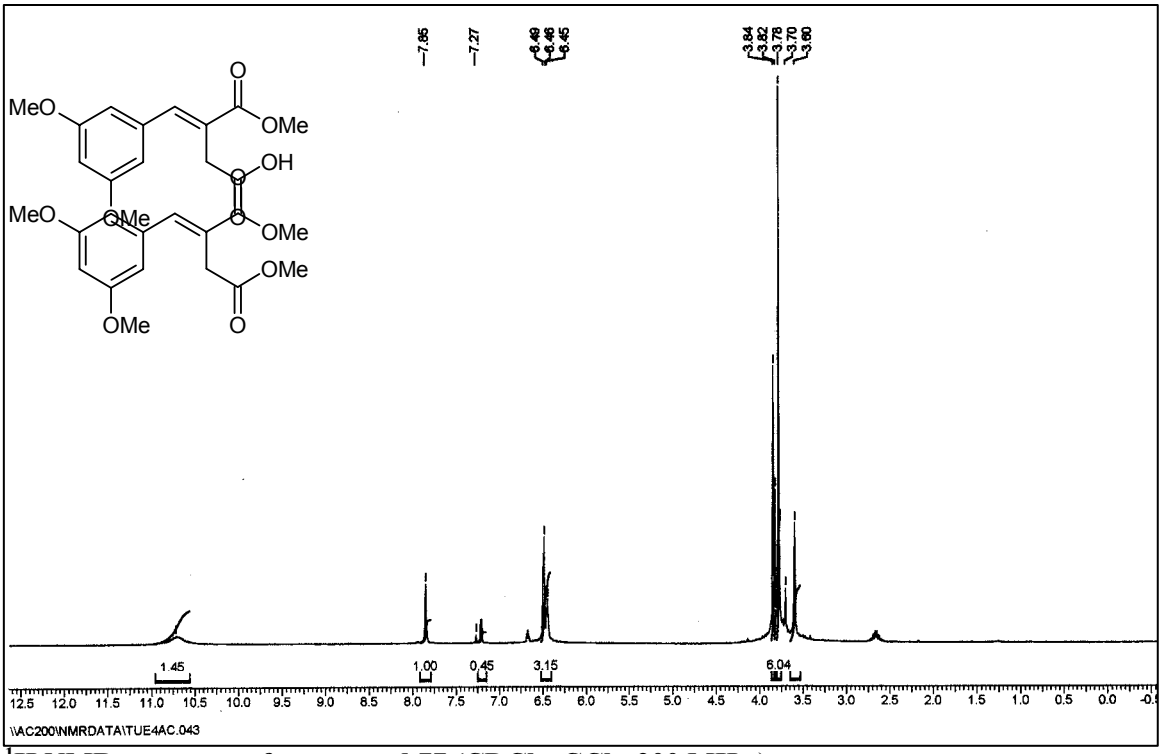


Diacid **81** (0.200 g, 4.7 mmol) was dissolved in dry DCM; solution was cooled to 0 ºC under nitrogen atmosphere. To this stirring solution trifluroacetic acid (1 ml) and trifluraoacetic anhydride (0.5 ml) was added. The reaction was allowed stir at 0 ºC for 30 min then at room temperature. The reaction was monitored by TLC and after complete conversion of the starting material, reaction was quenched with ice-cold water (10 ml) and this mixture was extracted with DCM and washed with water followed by brine and dried over sodium

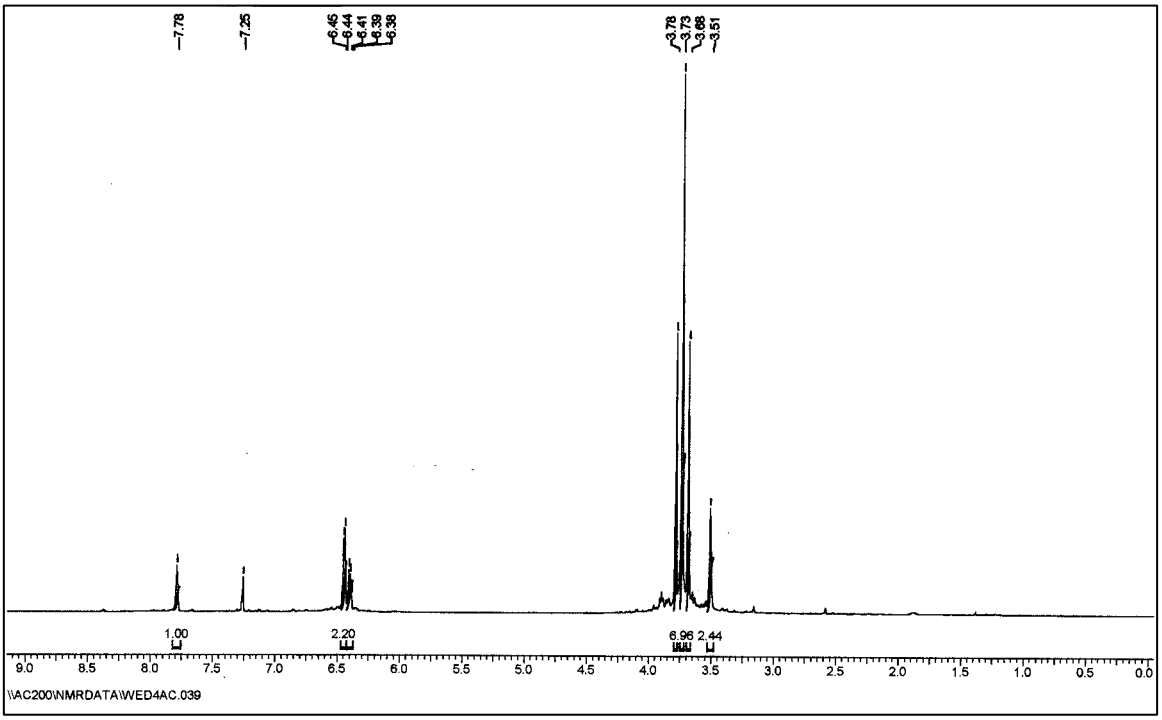
sulphate and purified by column chromatography using ethyl acetate to afford cyclized product as a white foam (0.060 g, with 31.4 %).

Molecular formula: $C_{22}H_{24}O_7$; **Nature**: White foam; **Yield**: 31.4%; **IR** (Chloroform): ν 3020, 1731, 1666, 1598, 754 cm $^{-1}$; **^{1}H NMR**: (200 MHz, $CDCl_3$): δ 2.80-3.18 (m, 5H), 3.74 (s, 6H), 3.77 (s, 3H), 3.81 (s, 3H), 6.05 (d, J = 2Hz, 1H), 6.30-6.45 (m, 3H), 6.88 (d, J = 8 Hz, 1H); **^{13}C NMR**: (50 MHz, $CDCl_3$): δ 30.3, 35.2, 43.7, 46.1, 54.8 (2C), 55.6 (2C), 98.4, 98.91, 104.2, 107.2, 116.5, 131.4, 138.0, 158.1 (2C), 160.3, 160.3, 160.9, 172.2, 189.2; **Anal Calcd for** $C_{22}H_{24}O_7$: C, 66.00; H, 6.00; **Found**: C, 66.24 H, 6.16.

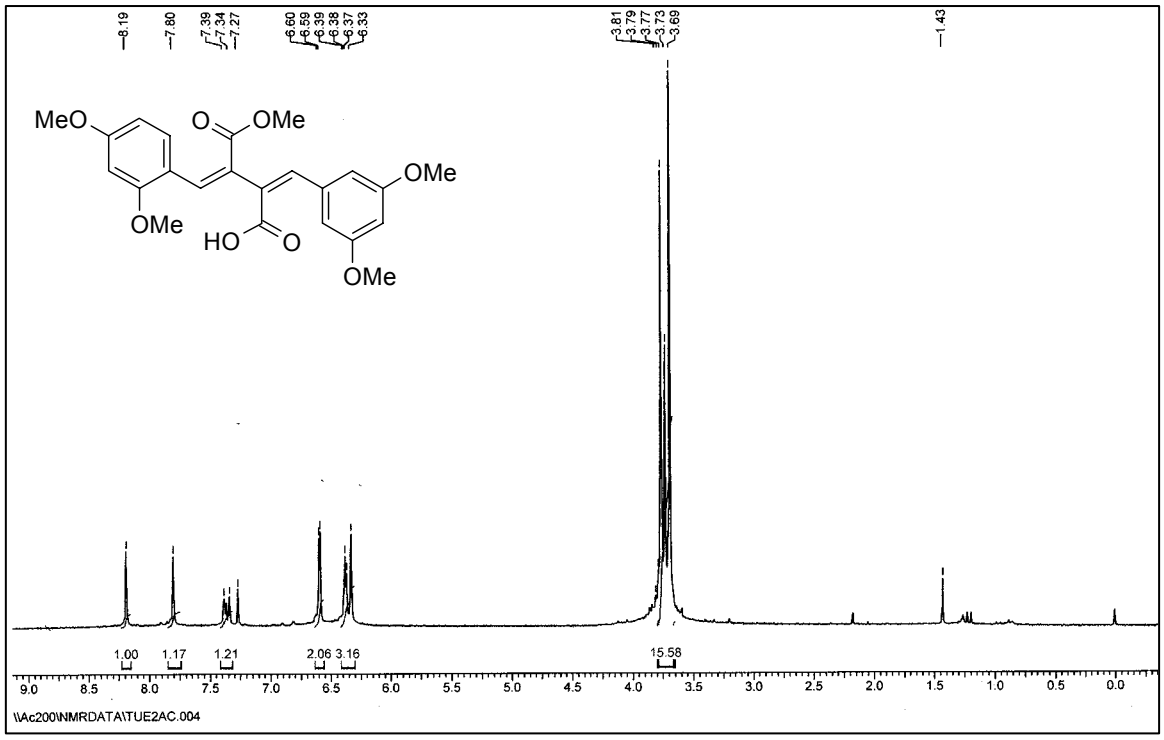
^{1}H NMR spectrum of compound 76 ($CDCl_3$+CCl_4, 200 MHz)



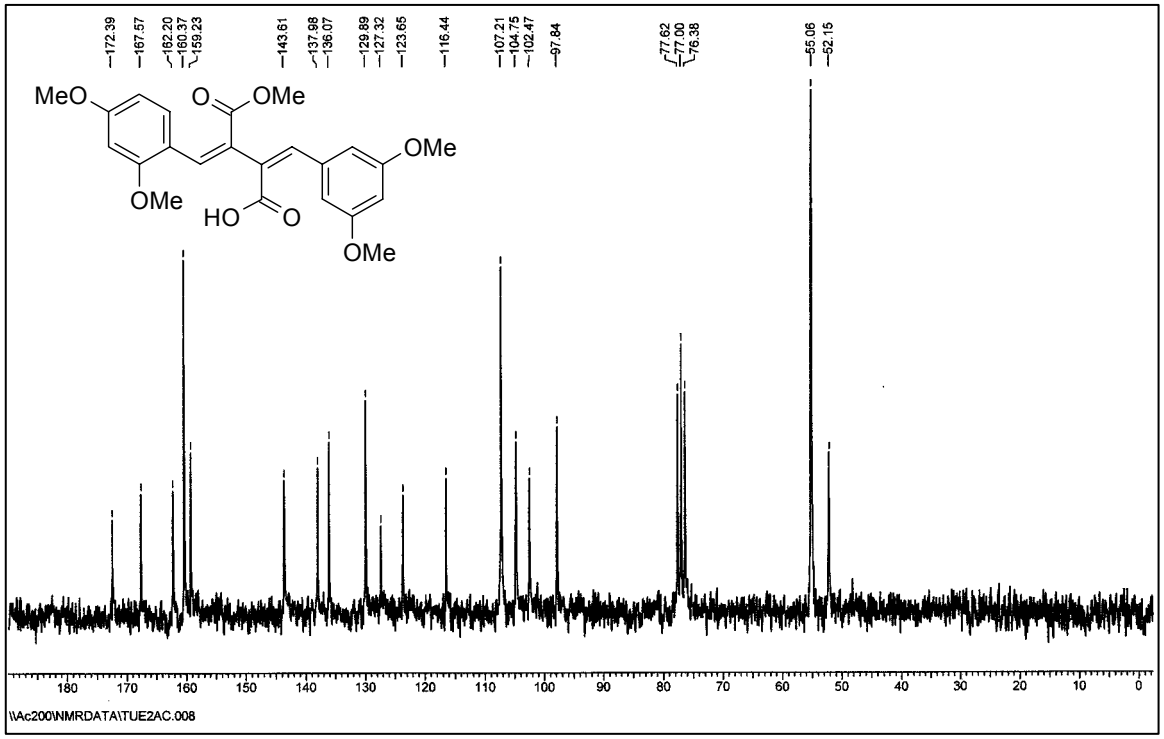
^{1}H NMR spectrum of compound 77 ($CDCl_3$+CCl_4, 200 MHz)



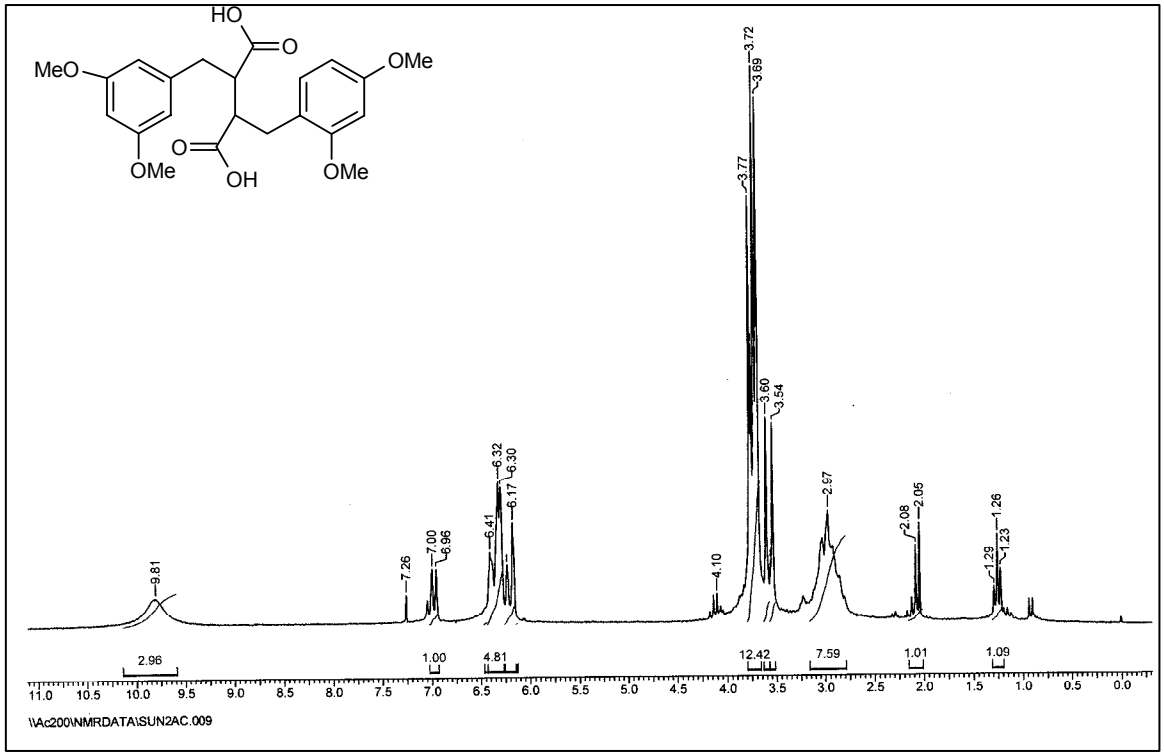
^{1}H NMR spectrum of compound 69 ($CDCl_3$+CCl_4, 200 MHz)



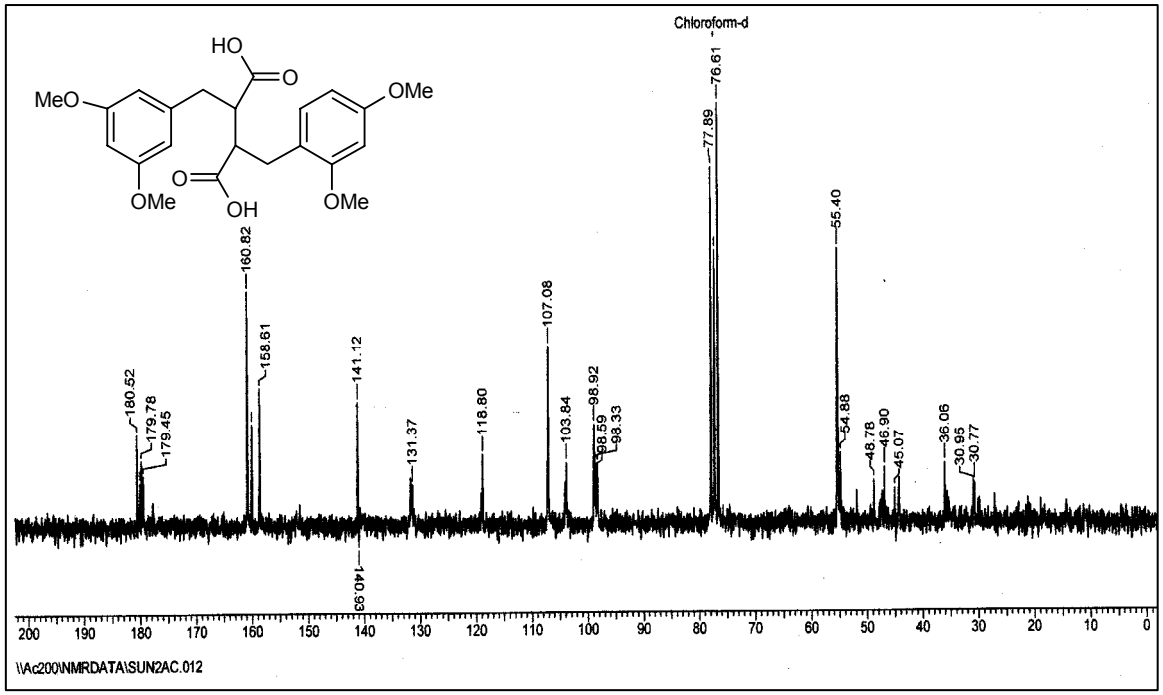
^{13}C NMR spectrum of compound 69 ($CDCl_3$+CCl_4, 50 MHz)



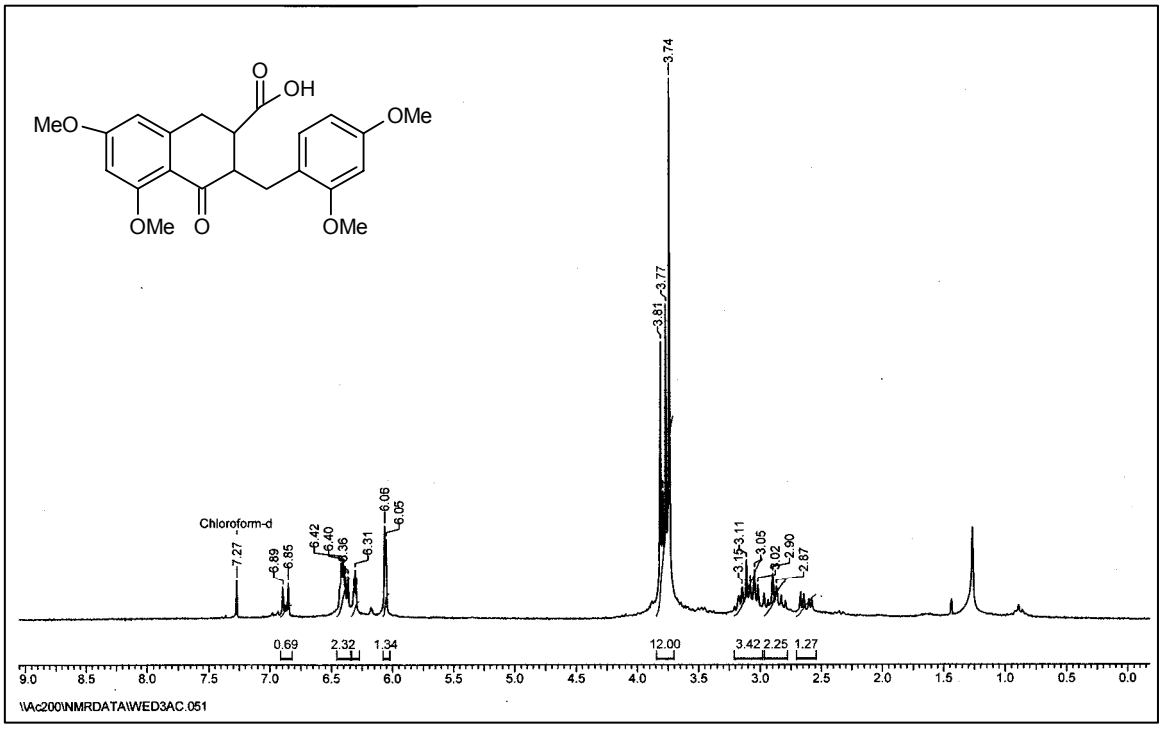
^{1}H NMR spectrum of compound 81 ($CDCl_3$+CCl_4, 200 MHz)



^{13}C NMR spectrum of compound 81 ($CDCl_3$+CCl_4, 50 MHz)



^{1}H NMR spectrum of compound 68 ($CDCl_3$+CCl_4, 200 MHz)

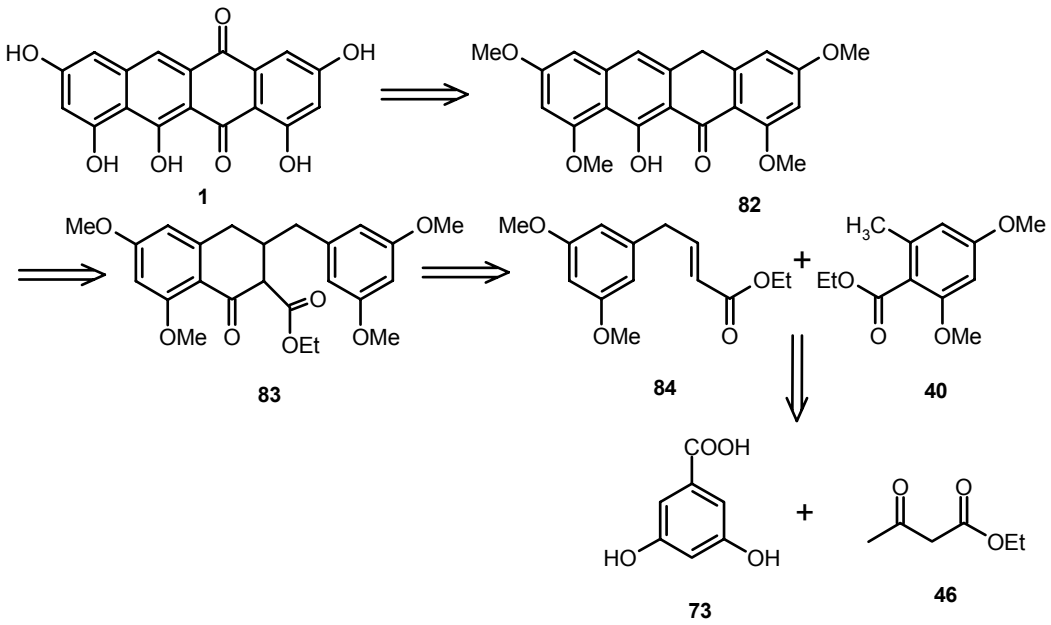


2. 2. 5. REFERENCE

1. Johnson, W. S.; Daub, G. H.; *Org. Reactions* **1951**, *6*, 1.
2. Gor daliza, M.; Del corral, J. M. M.; Castro, M. A.; Salinero, M. A. San Feliciano, A; Drado; J. M. Valle, F. *Synlett* **1996**, 1201-1202.

2.3.1.PRESENT WORK

In previous sections we have described our attempts towards the synthesis of saintopin by Diels-Alder approach and Stobbe condensation approach. It was readily envisaged that regioselective synthesis of saintopin could be possible by the application of tandem Michael addition-Dickmann condensation approach[1] as exhibited in the schematic representaion in retrosynthetic route (Scheme 1).



Scheme 1. Retrosynthetic analysis

The present section describes the study towards the synthesis of Saintopin via Michael addition-Dickmann condensation reaction as the key step of reaction sequence. It is well known that methyl acrylate and its derivatives act as Michael acceptors[2] while Hauser and Staunton observed that anion generated on orthotoluic ester was sufficiently stable in solution and it could be used for further reactions.[3] The application of this anion as the Michael donar could be used for the synthesis of Saintopin. Accordingly we proposed retrosynthetic analysis based on Michael addition-Dickmann condensation approach as depicted in scheme 1 above.

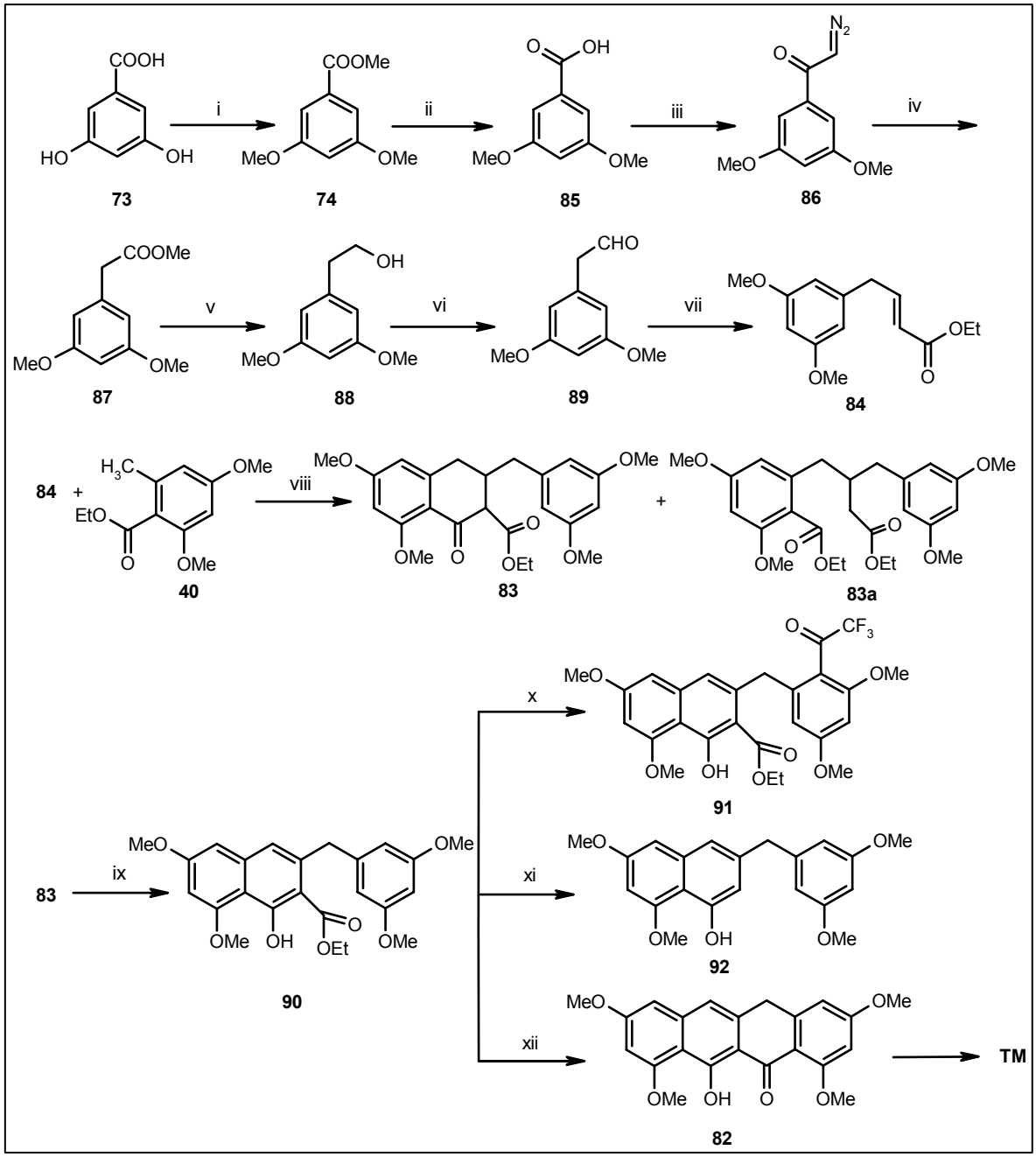
2.3.2. RESULTS AND DISCUSSION

As per retrosynthetic plan ethyl-2,4-Dimethoxy-6-methyl benzoate **40** and 4-(3,5-Dimethoxy-phenyl)-but-2-enoic acid ethyl ester (**84**) are the desired synthons. Orthotoluic ester **40** was prepared by reported method as discussed in section 1 of this chapter.

Preparation of the ester synthon **84** involved few steps of reactions, including Arndt-Eistert synthesis[4] for one carbon homologation, reduction-oxidation and wittig olefination. Arndt-Eistert synthesis is the procedure for converting a carboxylic acid to its higher homologous acid or as ester and amide. It involves the formation of a α-diazomethyl ketone, which is converted into derivatives of carboxylic acid in the presence of solid silver oxide or silver benzoate in solution as a catalyst, the last step is known as Wolf rearrangement.

For one carbon homologation of 3, 5-dihydroxybenzoic acid (**73**), it was converted to 3,5-dimethoxy benzoic acid (**85**) by methylation followed by hydrolysis of ester **74**. 3,5-Dimethoxy benzoic acid (**85**) was treated with thionyl chloride to afford 3,5-dimethoxy benzoyl chloride, which was treated with diazomethane in the presence of triethyl amine at 0°C to afford diazoketone **86** in 55% yield. The diazoketone was characterized by IR, ^{1}H and ^{13}C NMR spectral analysis. IR spectrum of diazoketone showed characteristic C=N stretching at 2103 cm^{-1} and carbonyl stretching at 1697 cm^{-1}. ^{1}H NMR spectrum of diazoketone **86** showed singlet for six protons at δ 3.80, which was assigned for two methoxy groups and singlet at δ 5.81 integrating for one proton was assigned for acyl proton (CO-C<u>H</u>=N_2). In aromatic region; triplet integrating for one proton and doublet integrating for two protons at δ 6.57 and δ 6.84 with coupling constant J = 2 Hz confirmed the meta-substitution pattern of the functional groups on aromatic ring.

Scheme 3.



Reagents and conditions: (i) Dimethyl sulphate, K_2CO_3, acetone, 95%; (ii) Aq. NaOH, ethanol, rt, 4-5h, 86%; (iii) (a) $SOCl_2$, toluene, reflux, 4h; (b) CH_2N_2, ether, 30 min, 55%; (iv) Ag_2O, methanol, reflux, 1h, 80%; (v) DIBAL-H, THF, rt, 4h, 73%; (vi) DMP, dichloromethane, rt, 56%; (vii) PPh_3= CH-COOEt, benzene, reflux, 1h, 66%; (viii) LDA, THF, -78 °C, 4h, 50.7%; (ix) DDQ, toluene, 80 ºC 4h, 38%; (x) TFA, TFAA, DCM, 0ºC then rt, 4h, 64 %; (xi) Aq. NaOH, EtOH, reflux, 1h, 68.2%; (xii) Conc. H_2SO_4, 0ºC then 50 ºC, 20 min, 27%.

Diazoketone **86** was further subjected for Wolf rearrangement in the presence of silver oxide in refluxing methanol to get 3,5-dimethoxyphenylacetic acid ester (**87**) with 80.7% yield. The ester **87** thus obtained synthesis was characterized by spectral analysis: it showed characteristic carbonyl stretching at 1739 cm^{-1} in IR spectrum. ^{1}H NMR showed singlet for benzylic methylene ($C\underline{H_2}$-COOMe) at δ 3.57 integrating for two protons and singlet at δ 3.70 integrating for three protons indicating presence of phenyl acetic methyl ester group ($C\underline{H_2}$-COO$C\underline{H_3}$). ^{13}C NMR spectrum showed benzylic carbon at δ 41.03 and signal at δ 171.4 for ester carbonyl, which supported the structure of ester **87**.

Our next target was to synthesize phenyl acetaldehyde from ester **87** therefore it was treated with one equivalent of DIBAL-H at –78 ºC but reaction gave low yield of required aldehyde **89** with mixture of unreacted starting material and alcohol **88.** Therefore attempts were made for complete reduction of ester with two equivalents of DIBAL-H to provide the corresponding alcohol **88** in 73%. IR spectrum of alcohol showed characteristic absorption at 3411 cm^{-1} and ^{1}H NMR showed triplets for two protons each at δ 3.67 and at δ 4.71, which confirmed complete reduction to alcohol **87**.

Subsequently, alcohol **87** was oxidized to afford aldehyde **89** in the presence of PCC in dry DCM with poor yield of requisite aldehyde. Hence oxidation was performed in the presence of Dess–Martin periodinate in dry DCM at ambient temperature which furnished 56% yield of aldehyde **89**. The structure of aldehyde unambiguously corroborated from the combined spectral data from IR, ^{1}H NMR, ^{13}C NMR and MS. IR spectrum showed disappearance of absorption of alcohol at 3411 cm^{-1} and exhibited aldehyde carbonyl stretching at 1722 cm^{-1}, ^{1}H NMR showed characteristic singlet at δ 9.89 integrating for one proton indicating presence of aldehyde **89** and, ^{13}C NMR showed carbonyl carbon at δ 191.9.

Next step of aldehyde olefination was conveniently achieved by Wittig reaction using ylide synthesized from ethyl bromoacetate and triphenyl phosphine; as per Witting reaction procedure to afford the 3,5-dimethoxy-phenyl-butanoic acid-ethyl ester (**84**). It was authenticated by spectral techniques; IR spectrum showed characteristic unsaturated ester carbonyl stretching frequency at 1717 cm^{-1}, ^{1}H NMR showed presence of *trans* olefin confirmed by coupling constant of olefinic protons; which appeared as doublet at δ 6.40 (dd) and at δ 7.57 integrating for one proton each with coupling constant J = 14 Hz.

^{13}C NMR showed ester carbonyl at δ 166.0. Thus required synthons were made available for the key step of synthesis, which comprised tandem Michael addition-Stobbe condensation.

An anion of ethyl 2,4-dimethoxy-6-methylbenzoate (**40**) was generated using LDA at –78 ºC and consequently treated with ester **84** to furnish the tetralone derivative **83**, which was adequately substantiated by spectral studies. In IR spectrum it showed two carbonyl stretching frequencies one at 1732 cm^{-1} for ester carbonyl and other for ketone carbonyl at 1666 cm^{-1}. ^{1}H NMR spectrum showed the absence of olefinic protons and indicated the presence of multiplet due to the benzylic protons located between δ 2.17–2.66 (2H) and another multiplet between δ 2.76- 2.93 (3H) was assigned for protons at Cβ and benzylic protons (CH_2) of tetralone ring; while proton at Cα of tetralone ring appeared as doublet at 3.38 (J =10 Hz). ^{13}C NMR and DEPT experiments supported the structure by representing ester carbonyl signal at δ 170 and ketone carbonyl signal at δ 190.2 and rest of carbons were located at their expected regions. EIMS showed molecular ion peak at *m/z* 429.6 (M^++1).

Thus the spectral data was in full agreement with the structure of tetralone derivative **83**. During this one pot Michael addition followed by Dickmann cyclization reaction we also isolated a minor product in addition to the compound **83**. This minor product was identified by spectroscopic methods as the Michael addition product **83a**. The formation of this intermediate **83** also revealed the sequence of this one pot reaction. The spectral data is given in experimental section.

It was decided to advance with aromatization of tetralone derivative **83**, which was treated with DDQ to afford aromatized naphthol derivative **90**. Evidences from IR, 1H NMR, and MS spectral data confirmed the formation of **90**. IR spectrum showed hydroxy absorption at 3450 cm^{-1} and intense carbonyl absorption at 1760 cm^{-1}; ^{1}H NMR validated the structure of naphthol **90** by showing absence of multiplicity in upfield region, and showing singlet at δ 7.16 integrating for one proton and chelated hydroxyl singlet at δ 10.22 integrating for one proton and the rest of the protons were located as expected. Mass spectrum showed molecular ion peak at *m/z* 427 (M^++1) confirming the structure of aromatized product **90**.

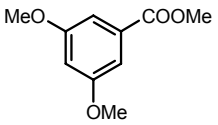
The next target was to cyclize the naphthol derivative **90** for the construction of C ring and to achieve linear tetracyclic structure. Consequently naphthol **90** was treated with trifluoroacetic anhydride and trifluoroacetic acid in dry DCM initially at 0ºC when the reaction gave unexpected acylated product **91** instead of the cyclized product. It was found that trifluoroacetic anhydride acted as source of electrophile to afford the acylated product with $COCF_3$ functionality. ^{1}H NMR spectrum showed signals due to ethyl group of ester (OCH_2CH_3) appearing at δ 0.96 as triplet (J = 7.1 Hz) and the methylene at δ 4.37 ppm (J = 7.1 Hz) as a quartet. In downfield region two meta-coupled doublets integrating for two protons each at δ 6.65 and δ 6.94 were observed due to acylation in D-ring. This observation was further supported by mass spectral fragmentation e.g. *m/z* 522 (M^+), 540 (M^++18), 444 (M^++18-$COCF_3$). In order to facilitate the cyclization reaction, it was planned to hydrolyze the ester **90** to its acid. The hydrolysis was carried out at room temperature when the reaction did not proceed and at reflux temperature of ethanol, decarboxylated product **92** was obtained instead of the desired carboxylic acid. We continued our attempts for cyclization of ester **90**; using concentrated sulphuric acid at 0ºC and then at 50 ºC to afford desired tetracyclic framework **82.** IR, ^{1}H NMR, and Mass spectral analyasis unambiguously confirmed the product obtained. IR spectrum indicated the presence of ketone carbonyl stretching at 1712 cm^{-1}. ^{1}H NMR spectra showed benzylic proton at δ 3.74 integrating for two protons and methoxy protons appeared at δ 3.93, 3.95, 3.98 and 4.01 integrating for three protons each, while in aromatic region four meta coupled doublets at δ 6.34, 6.49 6.73 and 6.82 integrating for one proton each and singlet at δ 7.26 and chelated hydroxy proton appeared at δ 12.94. Mass spectrum showed molecular ion peak (M^+) at 380. Corresponding to the cyclized product **82**. The oxidation of naphthacene derivative to naphthacenedione is a well-known transformation in the anthraquinone chemistry. Thus the product **82** on oxidation followed by demethylation should complete the total synthesis of saintopin.

2.3.4. CONCLUSION:

The total synthesis of Saintopin was attempted by three different approaches viz. (1) cycloaddition reaction involving in situ generated orthoquinodimethane intermediate as diene (2) stobbe condensation and (3) tandem Michael addition-Dickmann condansation. The first two approach faced problems at last steps. The third approach involving the tandem Michael addition–Dickmann condensation pathway successfully afforded the tetracyclic framework of Saintopin. Further conversions including oxidation and demethylation reactions should afford the target molecule.

2.3.5. EXPERIMENTAL

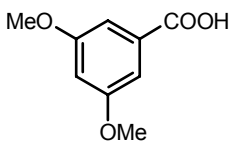
3, 5-Dimethoxy-benzoic acid methyl ester (74)



3,5-Dihydroxy benzoic acid **73** (10 g, 64.93 mmol) was dissolved in dry acetone (200 ml) under nitrogen atmosphere, dry potassium carbonate (31.3 g, 227.2 mmol) was added and stirred the mixture was stirred for 10-15 min at room temperature, after which freshly distilled dimethyl sulphate (28.63 g, 21.53 ml, 227.2 mmol) was added to the mixture with constant stirring. Mixture was allowed to stir at same temperature for 10 –15 min then it was refluxed for 4-5 h. After complete conversion reaction mixture was filtered through sintered funnel, solvent was evaporated and crude product was extracted with ethyl acetate (3x100ml). The organic layer was washed with water thoroughly then with brine and dried over sodium sulphate and concentrated under reduced pressure to afford ester **74** as a white solid (12g, 95 %).

Nature: White crystalline solid; **Yield**: 95%; **Mp**: 42-43 ºC; **^{1}H NMR**: ($CDCl_3$, 200 MHz) δ 3.84 (s, 3H), 3.92 (s, 6H), 6.66 (t, J = 2 Hz, 1 H), 7.19 (d, J = 2 Hz, 2H).

3, 5-Dimethoxy-benzoic acid (85)

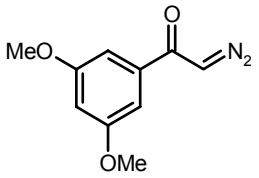


In a single necked round bottom flask, 3,5-dimethoxy-methyl benzoate **73** (12 g, 61.22 mmol) was placed and 1.5 equivalent of sodium hydroxide (3.06 g, 76.53 mmol) in 50 ml of water was added. The mixture was stirred at room temperature for 2h

and then at 70-80 ºC for 5 h. After complete conversion of the starting material reaction, the mixture was diluted using water and extracted with ethyl acetate. The aqueous layer was separated and acidified using 5N HCl. White precipitate obtained was filtered through sintered funnel and washed thoroughly with water and dried under vacuum to get acid **85** (9.8 g, 87.9 %).

Nature: White solid; **Yield:** 88%; **Mp**-181-182ºC; **IR** (chloroform): *v* 3435, 3019, 1688, 1598, 1215, 759 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.82 (s, 6 H), 6.82 (t, J = 2 Hz, 1 H), 7.25 (t, J = 2 Hz, 2 H); **MS**: (ESI) 182, 220 ($M+H_2O$).

2-(3, 5-Dimethoxy-phenyl)-2-oxo-ethanediazonium (86)

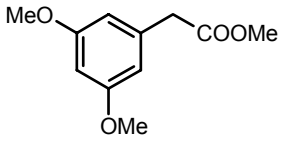


To the acid **85** (11 g, 60.43 mmol) dissolved in dry toluene was placed in two necked round bottom flask equipped with reflux condenser and guard tube, thionyl chloride (10.6 g, 6.94 ml, 90.65 mmol) was added slowly using dropping funnel over the period of 20 min. at 0 ºC. The reaction mixture was allowed to warm to room temperature and then refluxed for 4-5 h. After complete conversion, unreacted thionyl chloride was removed by vacuum distillation. The crude acid chloride was dried under vacuum (9.8 g, 49.00 mmol) dissolved in dry toluene and this solution was added dropwise to a solution of diazomethane (Prepared from 24.73 g of NMU, 240.05 mmol) in ether containing triethylamine (24.2 g, 33.28 ml, 240.05 mmol) at –10 ºC, the mixture was stirred for 1h. After complete conversion, reaction was quenched by ice-cold water, extracted using ether (3×200 ml) and organic layer was washed with water (3×100 ml) and saturated bicarbonate solution (2×50 ml) followed by brine. The organic layer was dried over sodium sulphate and evaporated on rotavapor. Crude product was purified by column chromatography (80:20 pet ether ethyl acetate), to get bright yellow crystalline diazoketone **86** (5.50 g, 55.4%).

Nature: Yellow crystalline solid; **Yield**: 54.4%; **Mp**: 103 ºC dec; IR: (chloroform): *v* 3078, 2103, 1697, 1582, 1202 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.80 (s, 6H), 5.81 (s,

1H), 6.57 (t, *J* = 2Hz, 1H), 6.84 (d, *J* = 2Hz, 2H); **^{13}C NMR** (50 MHz): δ 54.1, 55.1, 104.2 (3C), 138.2, 160.5 (3C), 185.7.

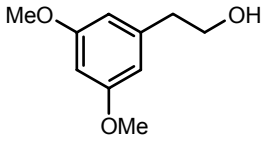
(3,5-Dimethoxy-phenyl)-acetic acid methyl ester (87)



To a suspension of silver oxide (6.16 g, 26.5 mmol) in dry methanol (150 ml), a solution of diazoketone **86** (5.50 g, 26.5 mmol) from the previous experiment in dry methanol (30 ml) was added under nitrogen atmosphere. Reaction mixture was refluxed for 1h (during the reaction continuous evolution of nitrogen gas was observed). After completion of the reaction, the reaction mixture was filtered through celite pad and organic layer was concentrated under vaccum and purified by column chromatography on silica gel. (90:10 pet ether ethyl acetate) to collect, pale yellow liquid (4.50 g, 80.7 %).

Nature: Pale Yellow oil; **Yield**: 80.7%; **IR** (Chloroform): ν 2952, 1739, 1597, 1206 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.57 (s, 2H), 3.70 (s, 3H), 3.78 (s, 6H), 6.38 (t, *J* = 2 Hz, 1H), 6.45 (d, *J* = 2 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 41.0, 51.6, 54.9 (2C), 98.8, 107.0 (2C), 135.8, 160.5 (2C), 171.4; **MS** (ESI): 210 $(M)^+$; **Anal Calcd for** $C_{11}H_{14}O_4$: C, 62.85; H, 6.66; **Found**: C, 62.87 H, 6.71.

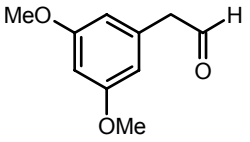
2-(3,5-Dimethoxy-phenyl)-ethanol (88)



Ester **87** (4 g, 19.04 mmol) was taken in dry toluene in two-necked round bottom flask under argon atmosphere and cooled to 0 ˚C, DIBAL-H (5.40 g, 38 mmol; 15.86 ml of 2.4 M solution) was then added dropwise with constant stirring. Reaction was allowed to stir at same temperature for 30 min then stirred at room temperature for 2h. After complete conversion reaction was quenched with saturated ammonium chloride solution and reaction mass was filtered through sintered funnel. Filtrate was extracted with ethyl acetate; organic layer was washed with water followed by brine dried over sodium sulphate, solvent was evaporated and residue was purified by column chromatography to give 2.5 g, 73% alcohol.

Nature: Yellow oil; **Yield**: 73%; **IR** (chloroform): *v* 3411, 2941, 1597, 1205, 1066 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.81 (t, *J* = 6 Hz, 2H), 3.79 (s, 6H), 3.87 (t, *J* = 6 Hz, 1H), 6.30 (t, *J* = 6 Hz, 2H), 6.37 (d, *J* = 2 Hz, 2H); **^{13}C NMR** (50 MHz): δ 39.1, 54.9 (2 C), 63.0, 98.0, 106.7 (2C), 140.7, 160.5 (2C).

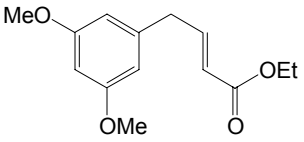
(3,5-Dimethoxy-phenyl)-acetaldehyde (89)



Alcohol **88** (4.6 g, 25.2 mmol) was dissolved in dry chloroform, under nitrogen atmosphere and the solution was cooled to 0˚C. DMP (15.9 g, 37 mmol) was added in portions to the stirring solution. Reaction mixture was stirred for 2 h after which it was filtered through pad of celite. Chloroform was removed under reduced pressure and the residue was purified by column chromatography using petroleum ether and ethyl acetate as an eluent to afford pure aldehyde **89** (2.5 g, 56 %).

Nature: Yellow oil; **Yield**: 56%; **IR** (chloroform): *v* 2940, 1722, 1596, 1206 cm^{-1}; **^{1}H NMR**: (200 MHz, $CDCl_3$) δ 3.60 (s, 2 H), 3.84 (s, 6H), 6.34 (t, *J* = 2 Hz, 1H), 6.99 (d, *J* = 2 Hz, 2H), 9.89 (s, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 50.5, 55.1, 55.4, 99.2, 107.3, 107.5, 160.7, 161.1 (2C), 191.7.

4-(3,5-Dimethoxy-phenyl)-but-2-enoic acid ethyl ester (84)

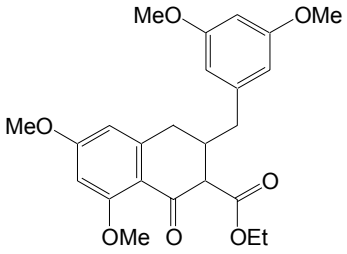


Aldehyde **89** (2.5 g, 13.8 mmol) was dissolved in dry toluene ylide of 2-bromoethylacetate (6.04 g, 17.35 mmol) was added at once and the reaction mixture was heated to 80 ˚C for 1 h. After complete conversion, toluene was removed under vacuum. Residue was purified over silica gel by column chromatography to give pure ester (2.3 g, 66.2 %) as yellow oil.

Nature: Yellow oil; **Yield**: 66.2 %; **IR** (chloroform): *v* 2939, 1717, 1596, 1206 cm^{-1}; **^{1}H NMR**: ($CDCl_3$, 200 MHz,) δ 1.34 (t, *J* = 8 Hz, 3 H), 3.78 (s, 3 H), 3.81 (s, 5 H), 4.18 (q, *J* = 8 Hz, 2H), 6.41 (d, *J* = 16 Hz, 1 H), 6.49 (t, *J* = 2 Hz, 1H), 6.66 (d, *J* = 2 Hz, 2 H), 7.61

(d, J = 16 Hz, 1 H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 13.9, 38.3, 54.8 (2C), 59.9, 105.6, 106.5 (2C), 122.5, 139.7, 146.6, 160.7 (2C), 166.0; **Anal Calcd for** $C_{14}H_{18}O_4$: C, 67.20; H, 7.20; **Found**: C, 67.36 H, 7.11.

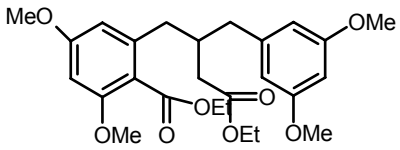
3-(3,5-Dimethoxy-benzyl)-6,8-dimethoxy-1-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl ester (83)



To double necked round bottom flask dry THF (15 ml), was added with the help of syringe. Dry diisopropyl amine (0.333 g, 0.464 ml, 33.00 mmol) was added at once and solution was cooled to –10 ˚C. 1.6 M, n-butyl lithium (0.211 g, 1.43 ml, of 2.3M solution, 33.0 mmol); was added slowly with constant stirring and the solution was allowed to stirr at same temperature for 30 min. It was then cooled to –78 ˚C and ortho-toluic ester **40** (0.825 g, 33.00 mmol) in dry THF was added dropwise with constant stirring at -78˚C. The reaction mixture was stirred for 15 min. To this solution ester **84** (0.500 g, 22.0 mmol) was added slowly and mixture was stirred for 30 min at -78 ˚C, and stirred at room temperature for 4 h. The reaction was quenched with saturated ammonium chloride and extracted using ethyl acetate (3×15 ml), crude product was purified by column chromatography using petroleum ether and ethyl acetate (70:30) to collect cyclized product **83** (0.485 g, 50.78%) and the diester **83a**.

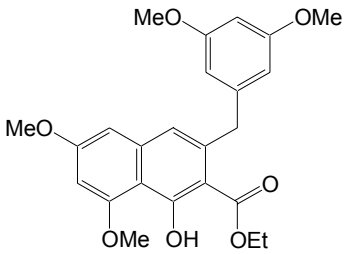
Nature: Yellow gum; **Yield**: 50.78 %; **IR**: (chloroform) ν 3013, 1732, 1666, 1599, 1204 cm^{-1}; **^{1}H NMR**: ($CDCl_3$, 200 MHz) δ 1.12 (t, J = 6 Hz, 3 H), 2.17-2.70 (m, 2H), 2.77-2.87 (m, 3H), 3.39 (d, J = 10 Hz, 1 H), 3.78 (s, 3H), 3.79 (s, 6H), 3.86 (s, 3 H), 4.27 (q, J = 6 Hz, 2 H), 6.20- 6.45 (m, 5H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 14.0, 34.3, 38.3, 40.38, 55.0 (3C), 55.7, 60.8, 62.0, 97.3, 98.4, 104.6, 107.2 (2C), 140.6, 147.0, 160.6 (3C), 162.1, 164.3, 170.1, 190.2; **MS**: (LCMS) 429 (M^++1), 451 (M^++Na), 467 (M^++K); **Anal Calcd for** $C_{24}H_{28}O_7$: C, 67.27; H, 6.54; **Found**: C, 67.52 H, 5.57.

2-[3-(3,5-Dimethoxy-benzyl)-2-ethoxycarbonylmethyl-propyl]-4,6-dimethoxy-benzoic acid ethyl ester (83a)



Nature: Pale yellow foam; **Yield**: 11.9 %, **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.12 (t, J = 6 Hz, 3 H), 2.10-2.40 (m, 2H), 2.60-3.00 (m, 5H), 3.70-3.92 (m, including singlets at 3.73, 3.77, 3.86, 3.92, 18H), 6.32 (d, J = 2 Hz, 1H), 6.26-6.40 (m, 4H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 13.3, 34.1, 34.7, 35.0, 39.8, 55.0, 55.1, 55.8, 56.7, 60.7 (2C), 97.2, 97.9, 98.6, 103.4, 106.4, 107.1, 119.8, 137.3, 141.4, 143.2, 160.0, 160.5 (2C), 163.9, 172.01.

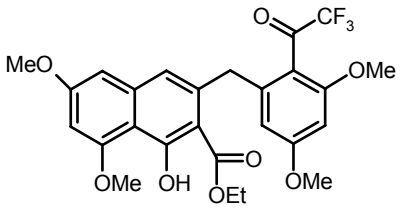
3-(3,5-Dimethoxy-benzyl)-1-hydroxy-6, 8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (90)



The compound **83** (0.158 g; 0.369 mmol) was dissolved in dry toluene (15 ml), then dichlorodicyanoquinone (DDQ) (0.83 g, 0.369 mmol) was added and the mixture was heated at reflux for 6 h. The reaction mixture was cooled to room temperature and quenched by addition of saturated ammonium chloride solution. The product was extracted in 25 ml of ethyl acetate and washed with dilute sodium bicarbonate solution, then with water and followed with brine solution. The organic layer was dried over anhydrous sodium sulphate. Aromatized product **89** was purified by column chromatography to afford orange crystals (0.060 g, with 38%).

Nature: Orange crystals; **Yield**: 38%; **Mp**. 146-147 ºC; **IR** (Chloroform): υ 3450, 1760, 1530, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.04 (t, J = 7 Hz, 3H), 3.74 (s, 2H), 3.81(s, 6H), 3.90 (s, 3H), 4.04 (s, 3H), 4.15 (q, J = 7 Hz, 2H), 6.46 (t, J = 2 Hz, 1H), 6.50 (d, J = 2 Hz, 1H), 6.60 (d, J = 2 Hz, 2H), 6.70(d, J = 2 Hz, 1H), 7.16 (s, 1H), 10.21 (s, 1H); **MS** (LCMS): 426 (M^+), 449 (M^++ Na); **Anal Calcd for** $C_{24}H_{26}O_7$: C, 67.60; H, 6.10; **Found**: C, 67.52 H, 5.94.

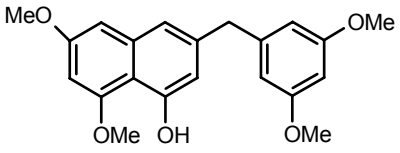
3-[3,5-Dimethoxy-2-(2,2,2-trifluoro-acetyl)-benzyl]-1-hydroxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (91)



Naphthol **90** (0.50 g, 0.117 mmol) was dissolved in dry dichloromethane, TFA (1 ml) and TFAA (0.5 ml) were added at 0ºC, reaction mixture was then allowed to stirr at room temperature for 4 h, after which it was concentrated and the crude product was purified by coloumn chromatography to afford acylated product **91**, as white solid (0.039 g, 63.9 %).

Nature: White solid; **Yield**: 63.9 %; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.96 (t, J = 8 Hz, 3H), 3.79 (s, 8H), 4.04 (s, 3H), 4.15 (s, 5H), 6.65 (d, J = 2 Hz, 2H), 6.94 (d, J = 2 Hz, 2H), 7.11 (s, 1H); 12.91 (s, 1H) **MS** (LCMS): *m/z* 522 (M^+) 540 (M^++18), 444 (M^++18-$COCF_3$); **Anal Calcd for** $C_{26}H_{25}F_3O_8$: C, 59.77; H, 4.78; **Found**: C, 59.83 H, 4.74.

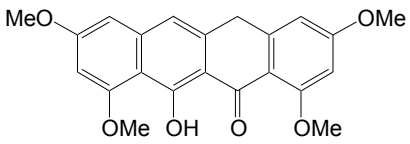
3-(3,5-Dimethoxy-benzyl)-6,8-dimethoxy-naphthalen-1-ol (92)



Naphthol **90** (0.050 g, 0.117 mmol) was dissolved in ethanol, aqueous solution of sodium hydroxide (0.010 g, in 1ml water), was added and reaction mixture was stirred at rt, after which it was refluxed for 4 h. The reaction mixture was then acidified at 0ºC and extracted with ethyl acetate, organic layer was washed with water and brine and dried over sodium sulphate. Residue was purified by column chromatography to afford decarboxylated product **92** as a brown solid (0.28g, 68.2%).

Nature: Brown solid, **Yield**: 68.2%; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.87 (s, 8H), 3.92 (s, 3H), 4.06 (s, 3H), 6.47 (d, J = 2 Hz, 1H), 6.50 (d, J = 2 Hz, 1H), 6.79 (d, J = 2 Hz, 1H), 6.85 (d, J = 2 Hz, 2H), 7.01 (d, J = 2 Hz, 1H), 7.41 (d, J = 2 Hz, 1H), 9.16 (s, 1H); **Anal Calcd for** $C_{21}H_{22}O_5$: C, 71.18; H, 6.21; **Found**: C, 71.26 H, 6.38.

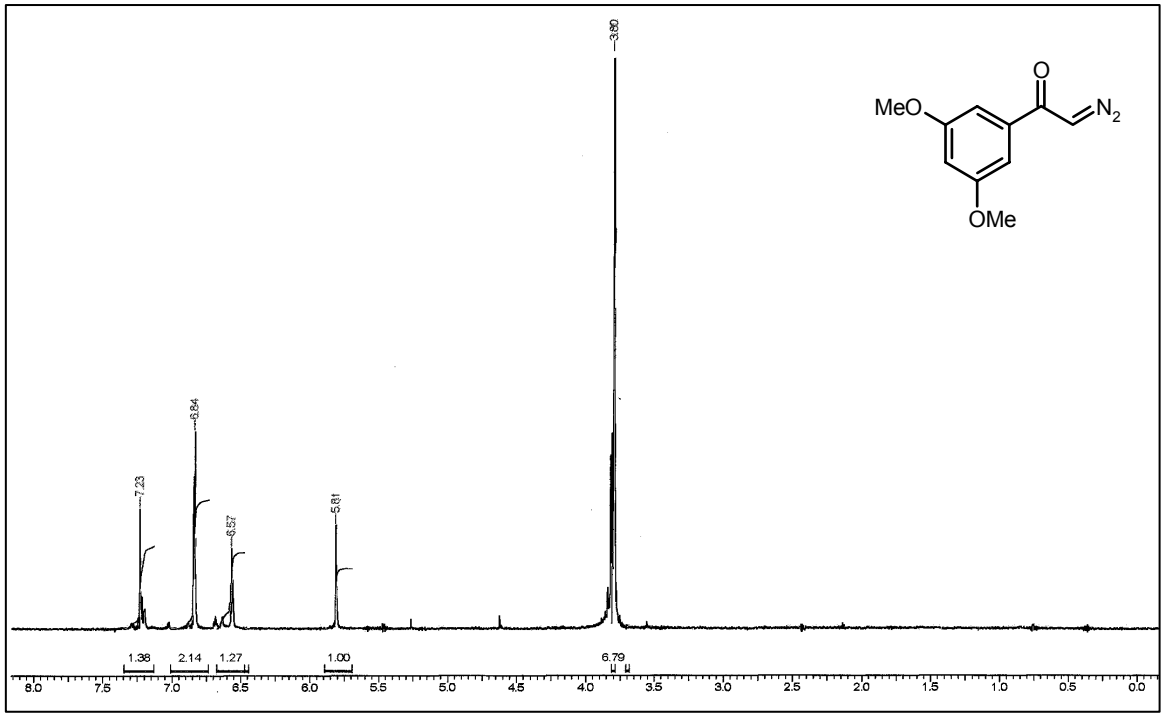
6-Hydroxy-2, 4, 7, 9-tetramethoxy-12H-naphthacen-5-one (82)



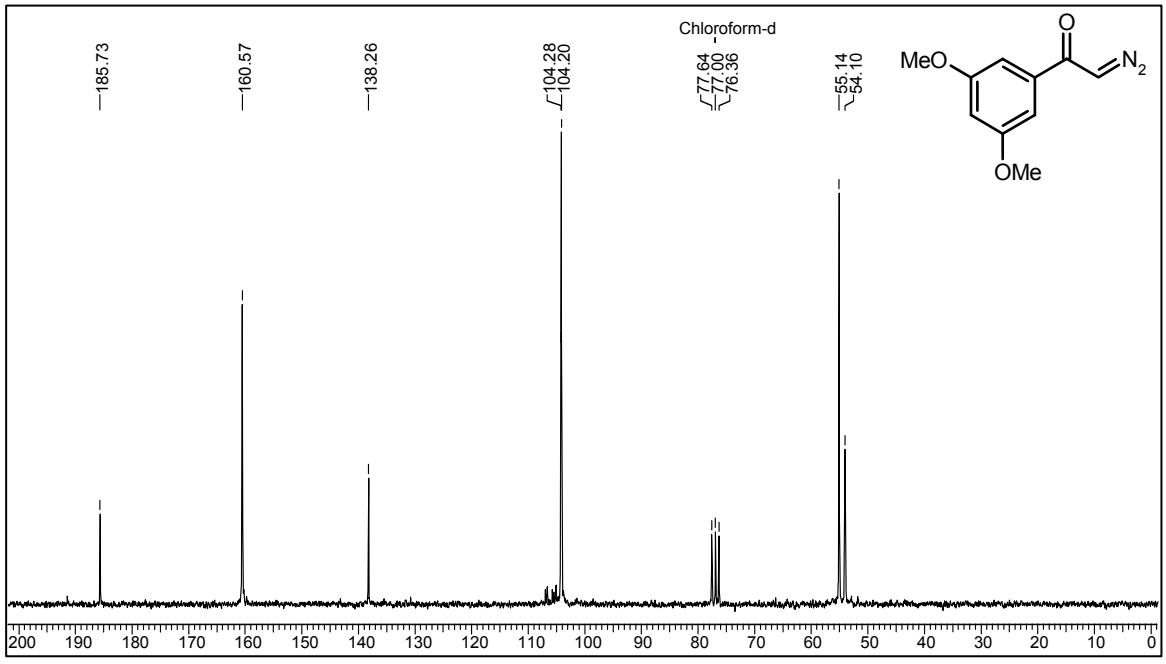
Aromatized product **90** (0.025 g, 0.058 mmol) was cooled to 0˚C, and then 0.5ml of concentrated sulphuric acid was added to it, the mixture was allowed to stirr for 15 min. The mixture was warmed to 60˚C for 30 minutes, poured over crushed ice and extracted with ethyl acetate. Organic layer was washed with water followed by brine and dried over sodium sulphate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to collect cyclized product **82** as brown crystals 0.006 g, with 27% yield.

Nature: Brown-crystals; **Yield**: 27%; **Mp**: 195-197 ºC; **IR** (Chloroform): *v* 3020, 1712, 1530, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.74 (s, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 6.35 (d, J = 2.2 Hz, 1H), 6.48 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 2.2, 1H), 6.82 (d, J = 2.2 Hz, 1H), 7.25 (s, 1H), 10.51(s, OH); **MS** (LCMS): *m/z* 380 (M^+); **Anal Calcd for** $C_{22}H_{20}O_6$: C, 69.47; H, 5.26; **Found**: C, 69.58 H, 5.29.

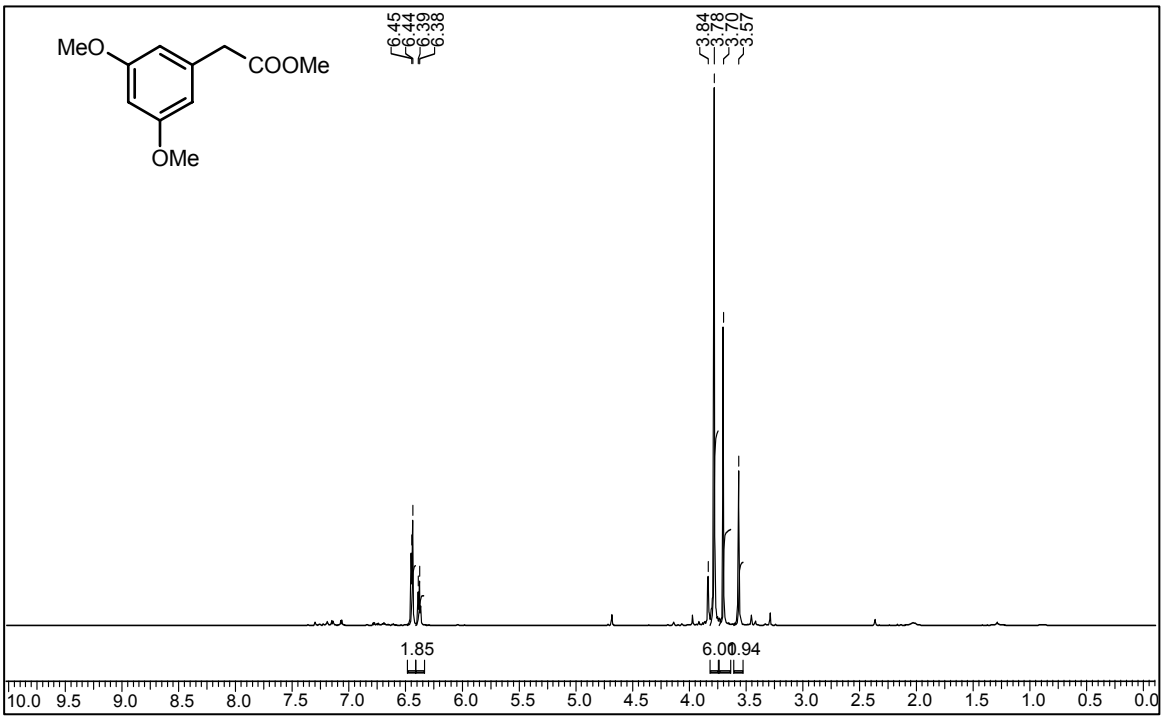
^{1}H NMR spectrum of compound 86 ($CDCl_3$+ CCl_4, 200 MHz)



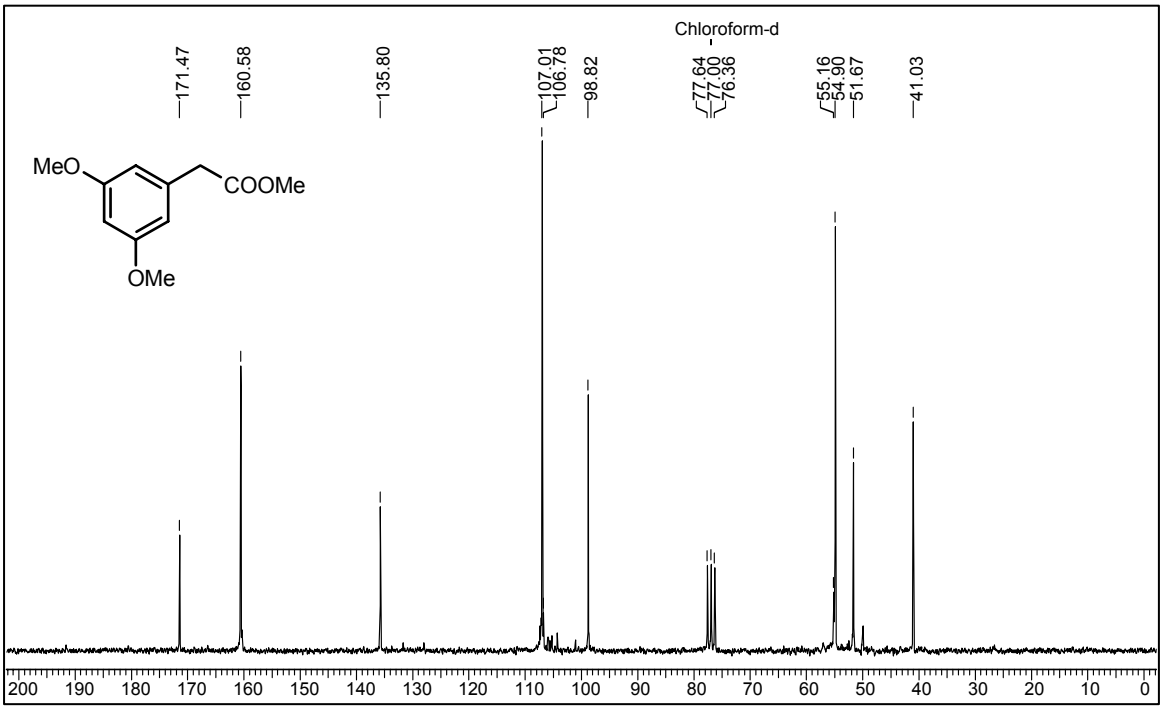
^{13}C NMR of compound 86 ($CDCl_3$, 200 MHz)

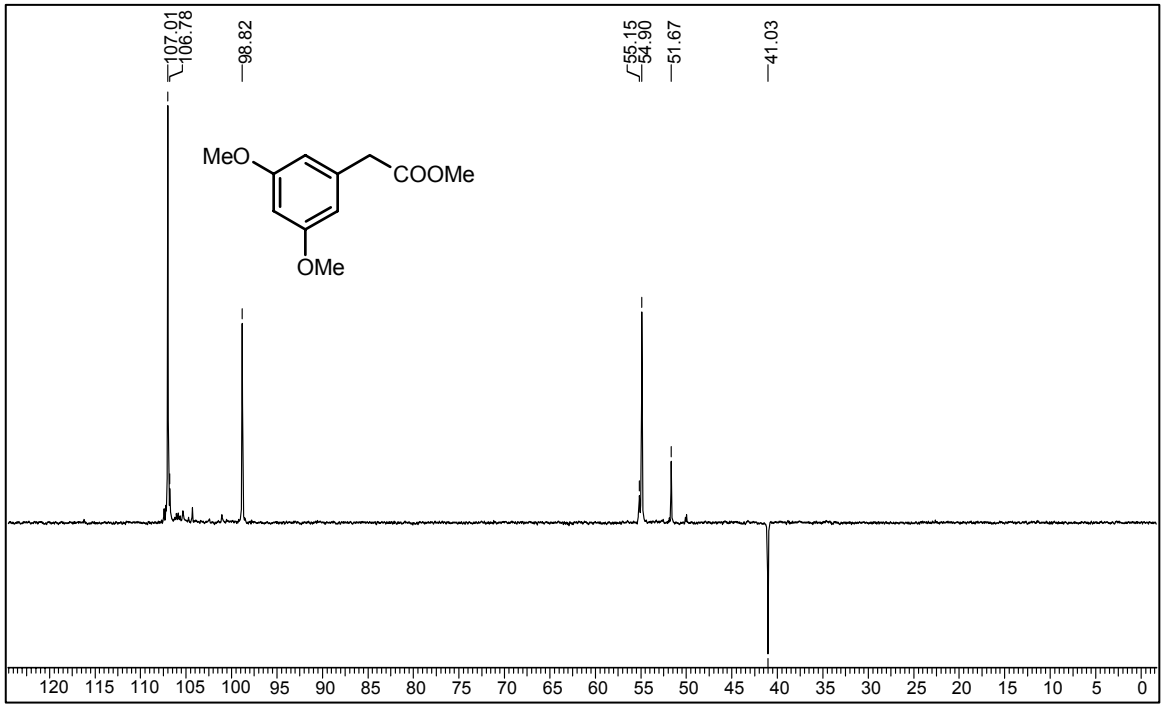


^{1}H NMR spectrum of compound 87 ($CDCl_3$+ CCl_4, 200 MHz)

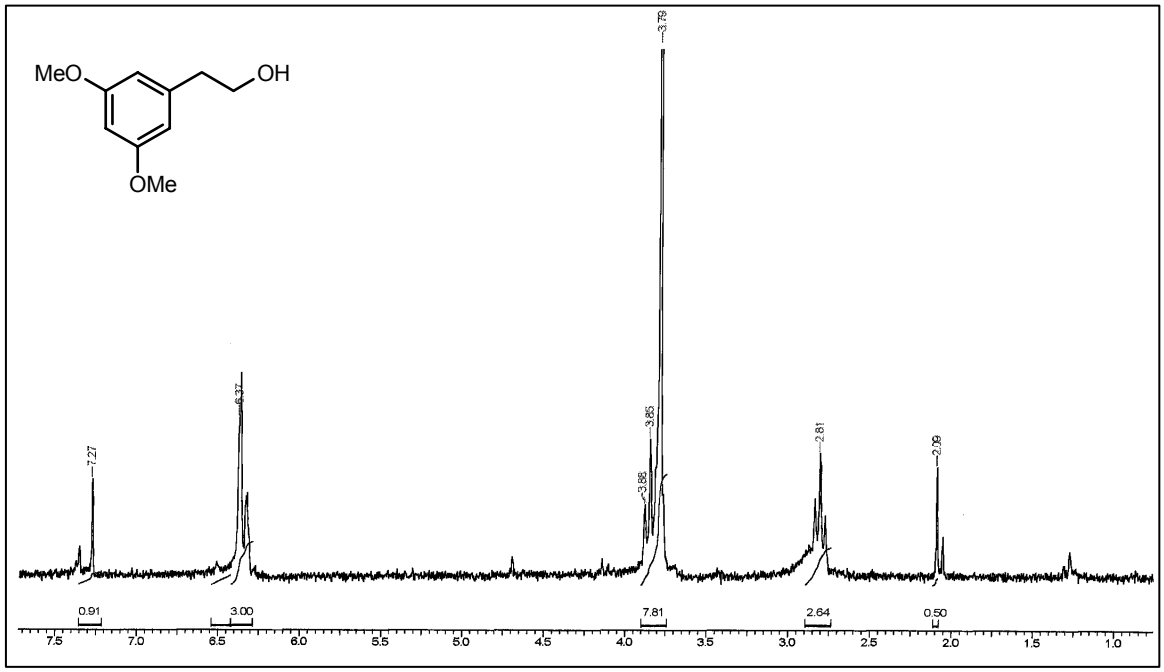


^{13}C NMR and DEPT of compound 87 ($CDCl_3$+CCl_4, 50 MHz)

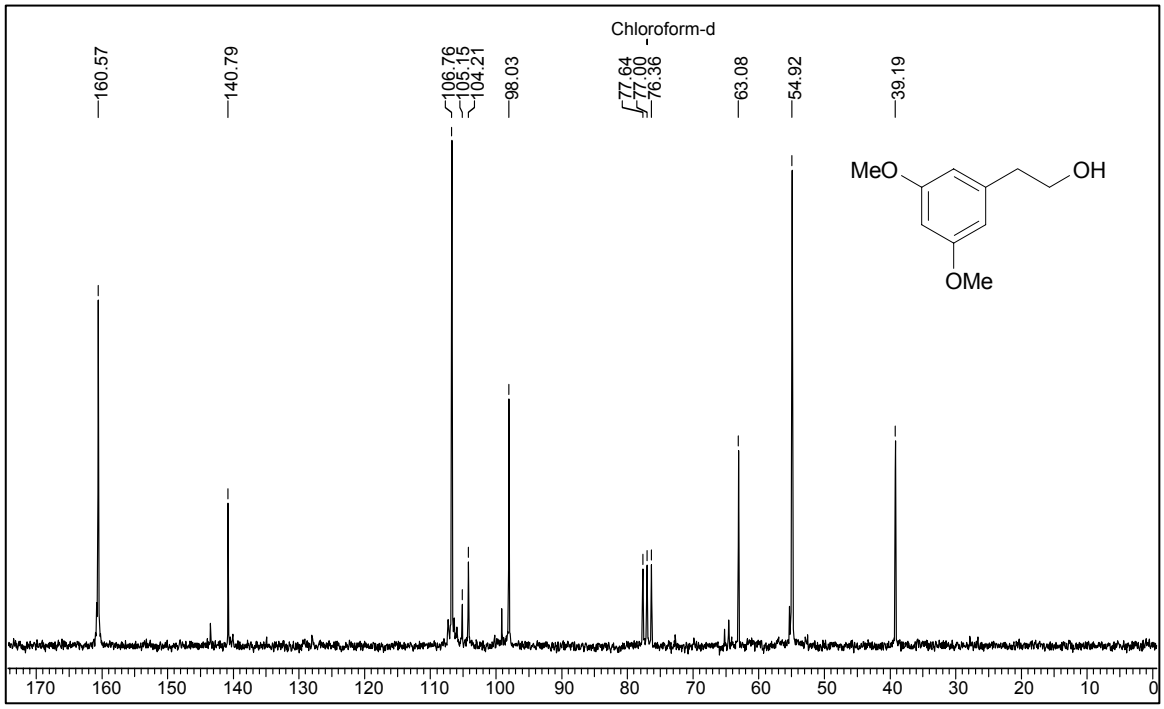


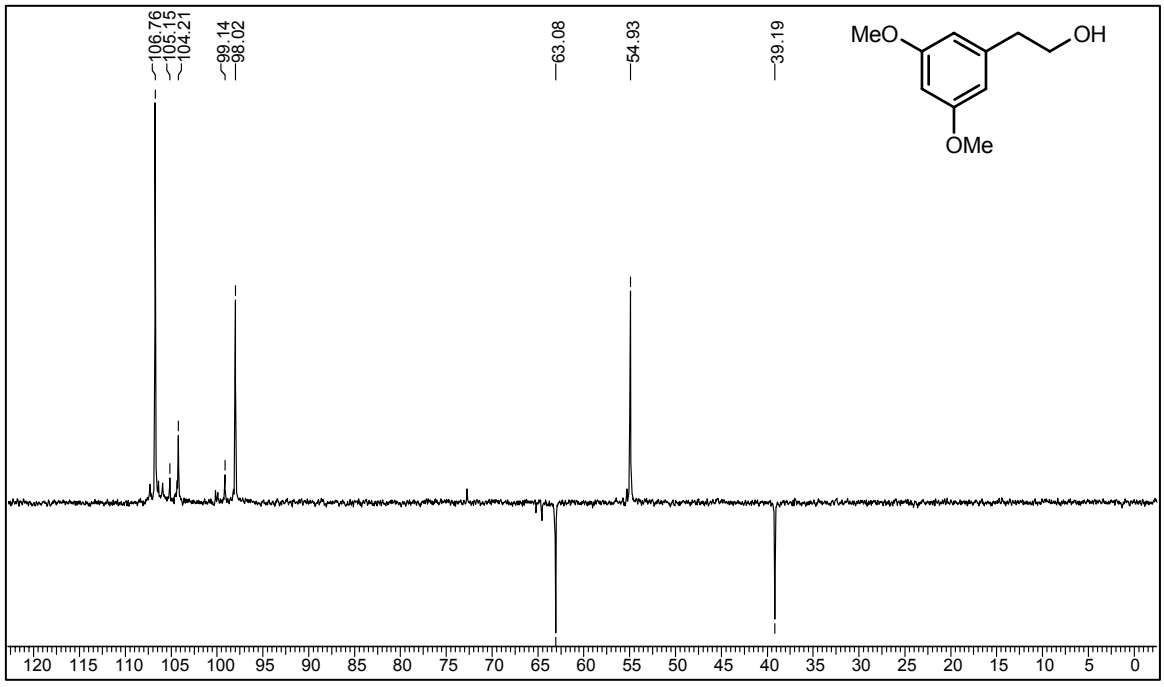


^{1}H NMR spectrum of compound 88 ($CDCl_3$+ CCl_4, 200 MHz)

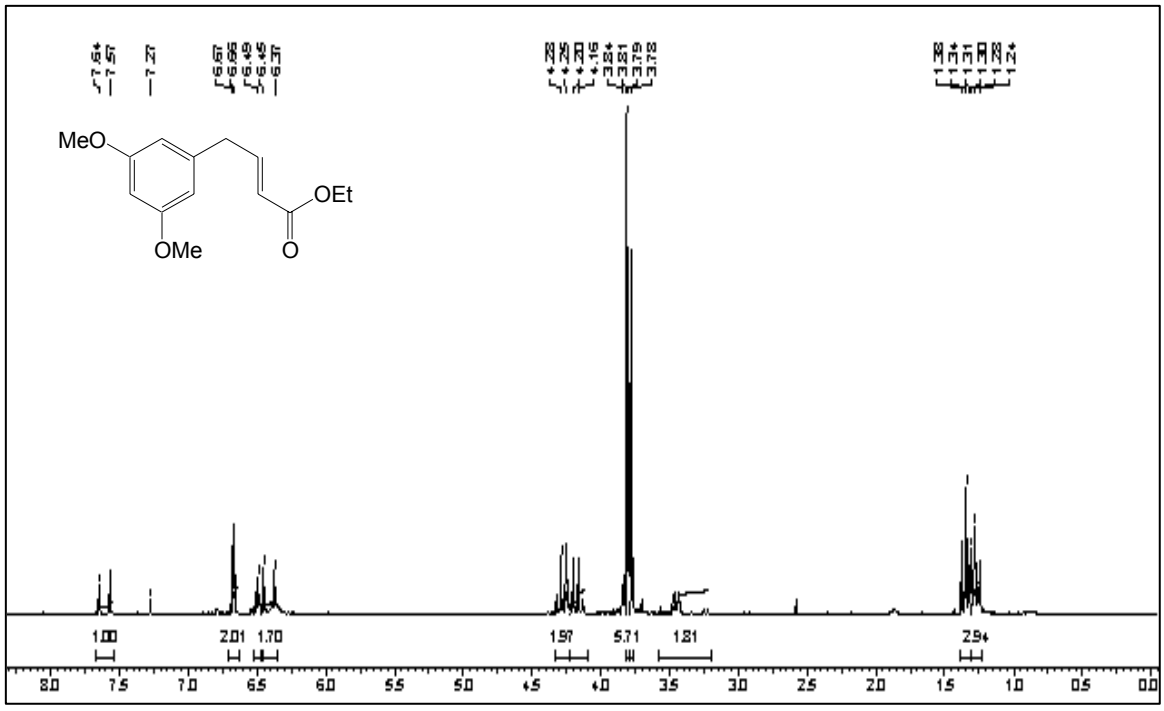


^{13}C NMR and DEPT of compound 88 ($CDCl_3$+CCl_4, 50 MHz)

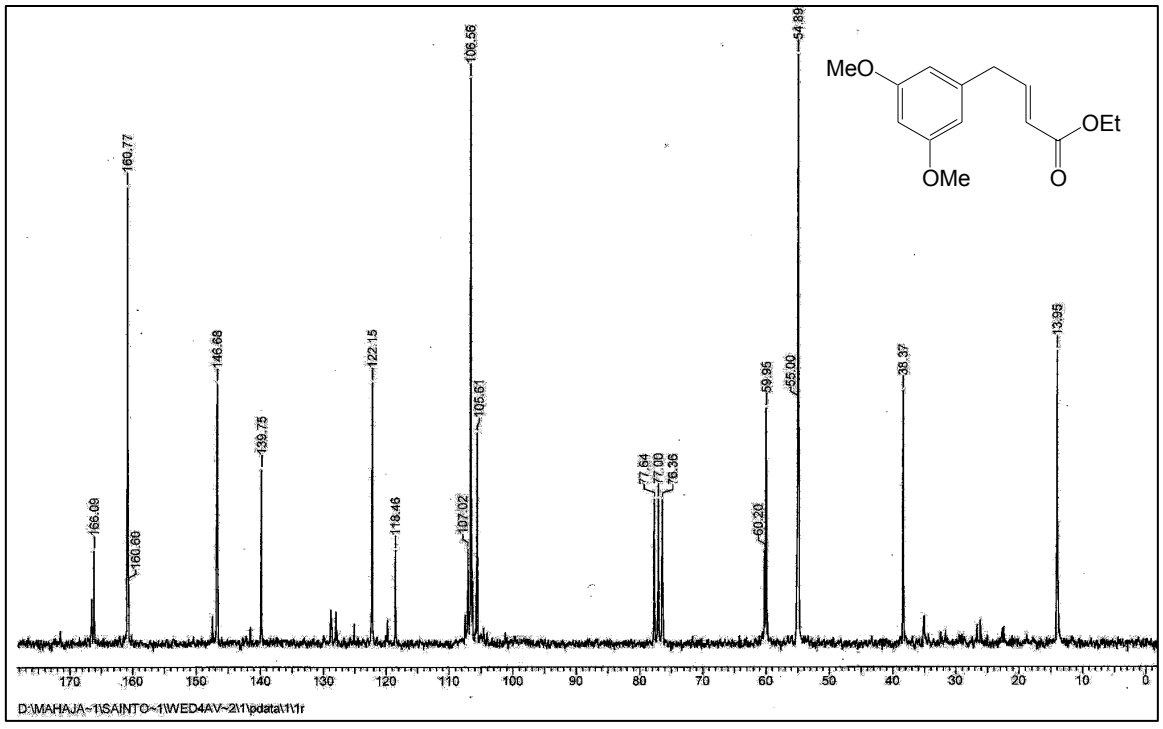


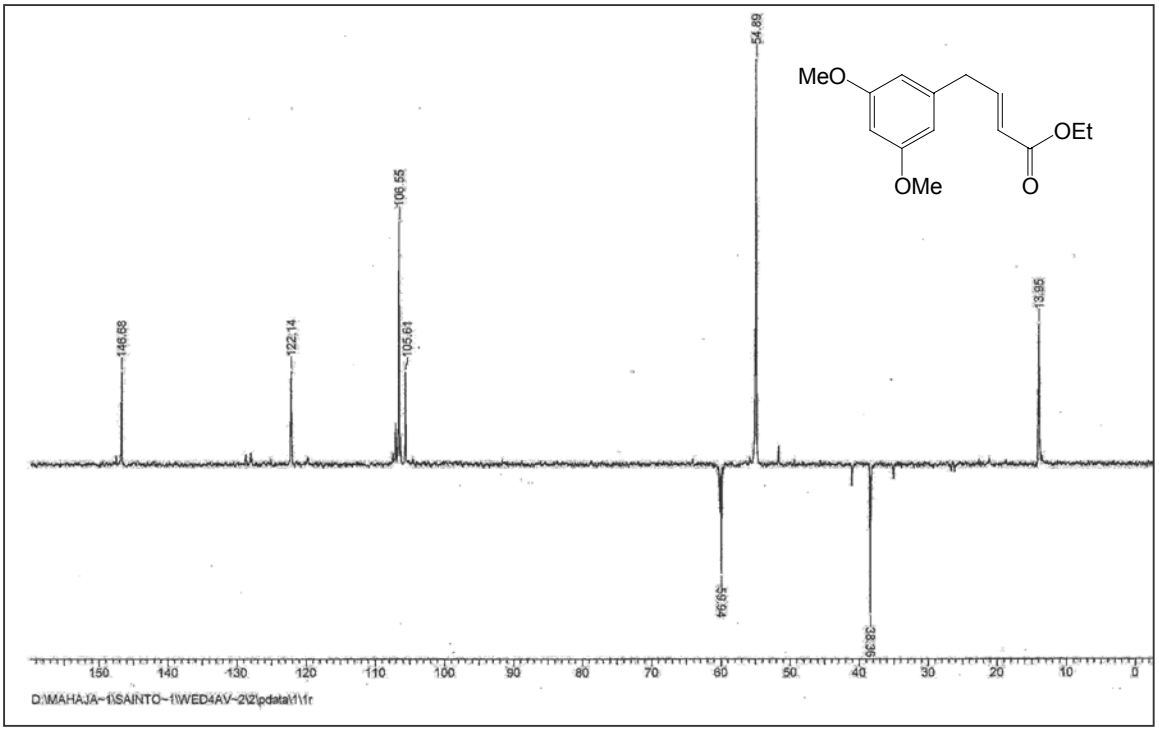


^{1}H NMR spectrum of compound 84 ($CDCl_3$+ CCl_4, 200 MHz)

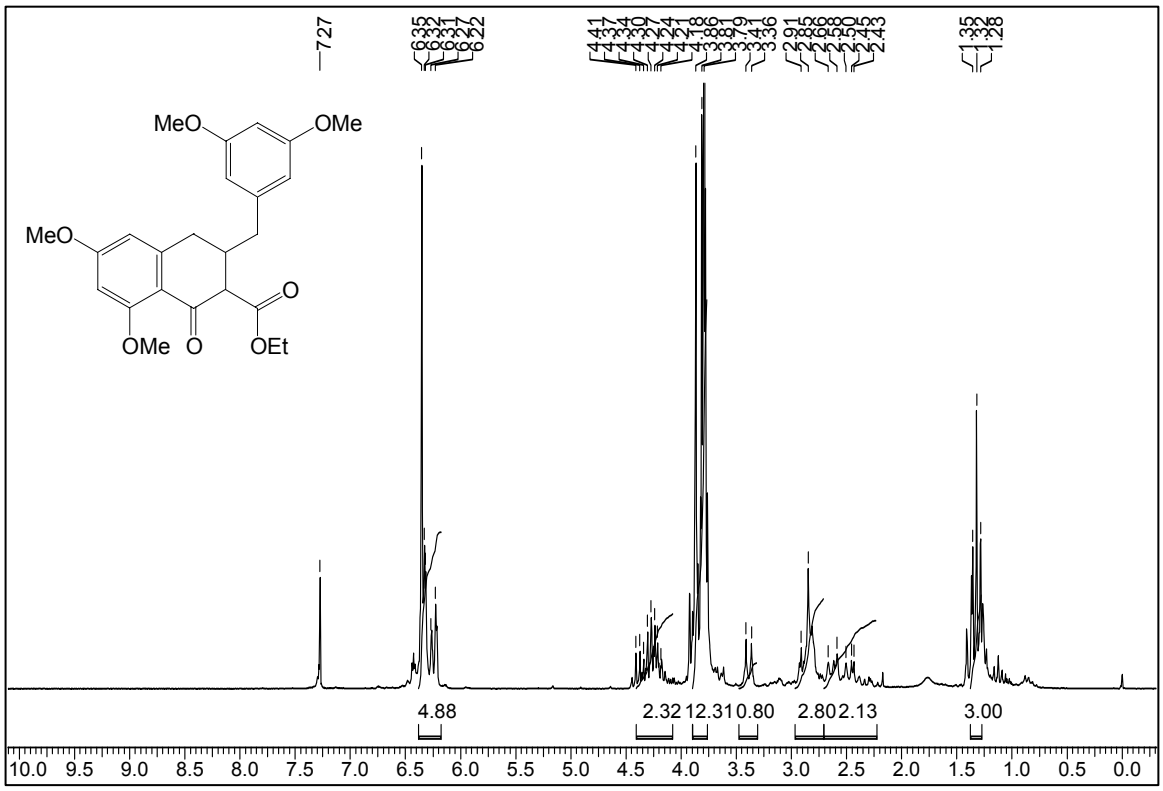


^{13}C NMR and DEPT of compound 84 ($CDCl_3$+CCl_4, 50 MHz

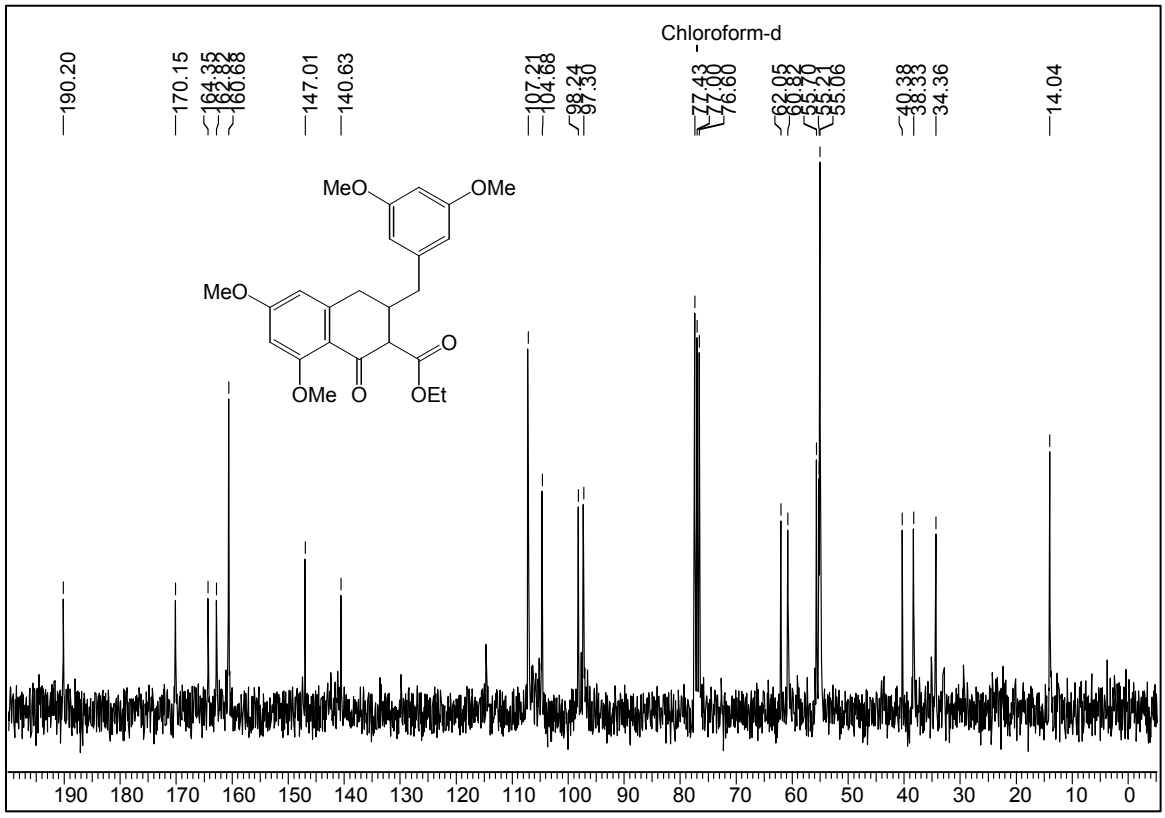


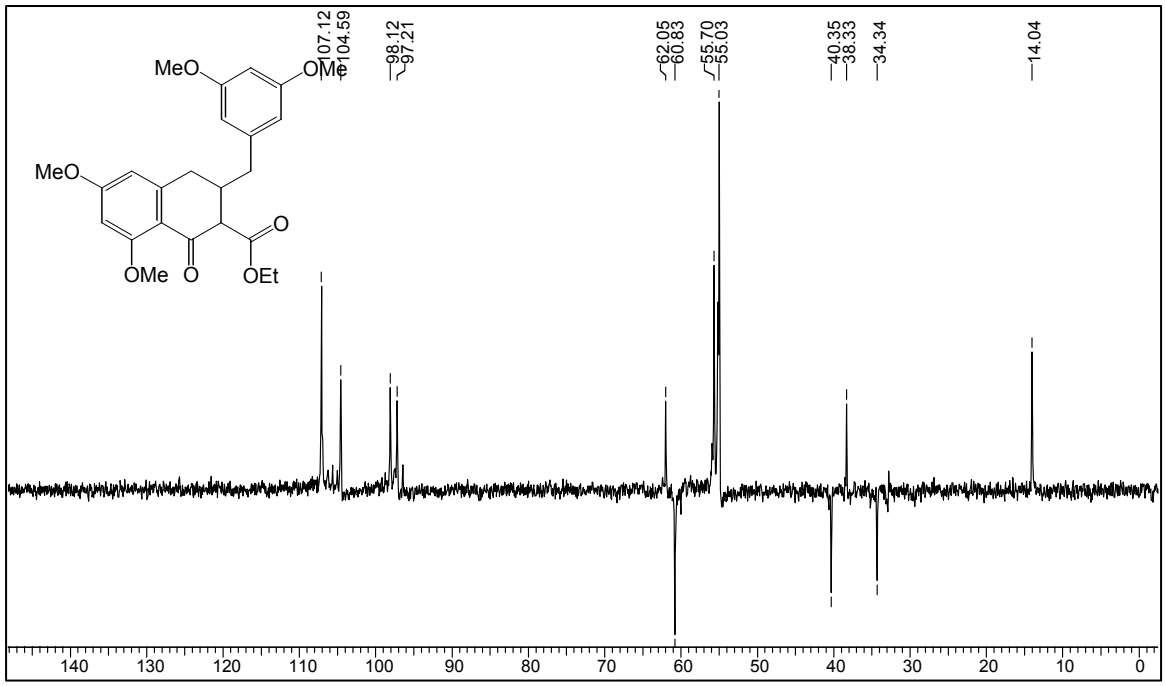


^{1}H NMR spectrum of compound 83 ($CDCl_3$+ CCl_4, 200 MHz)

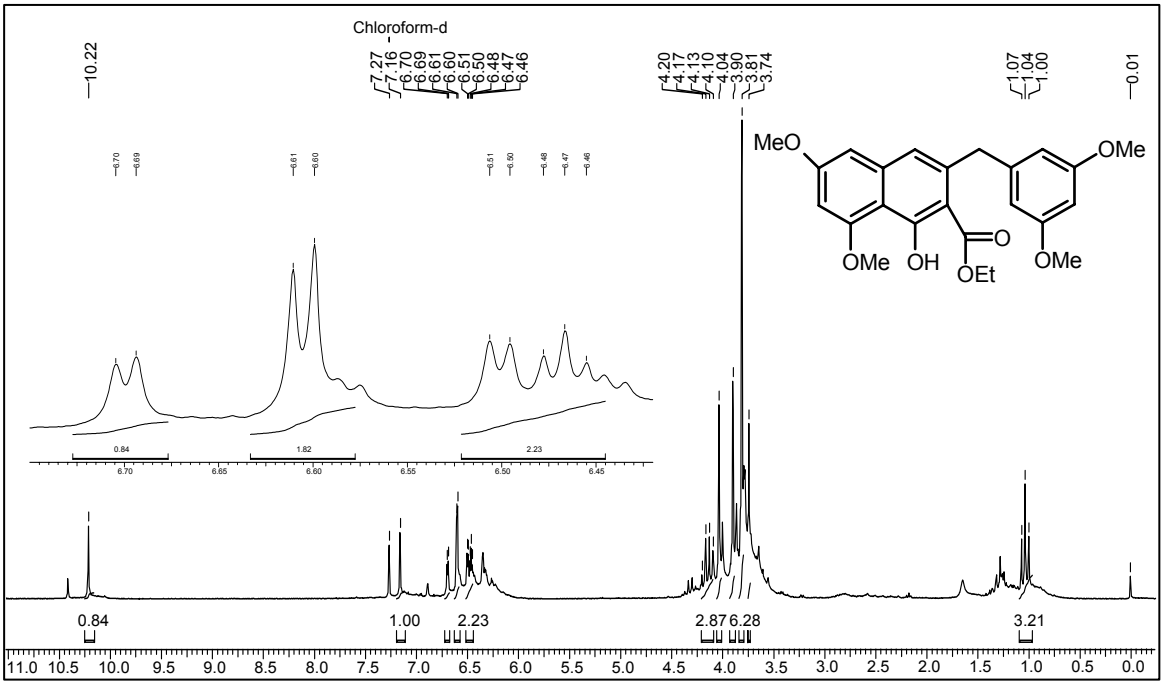


^{13}C NMR and DEPT of compound 83 ($CDCl_3$+CCl_4, 50 MHz)

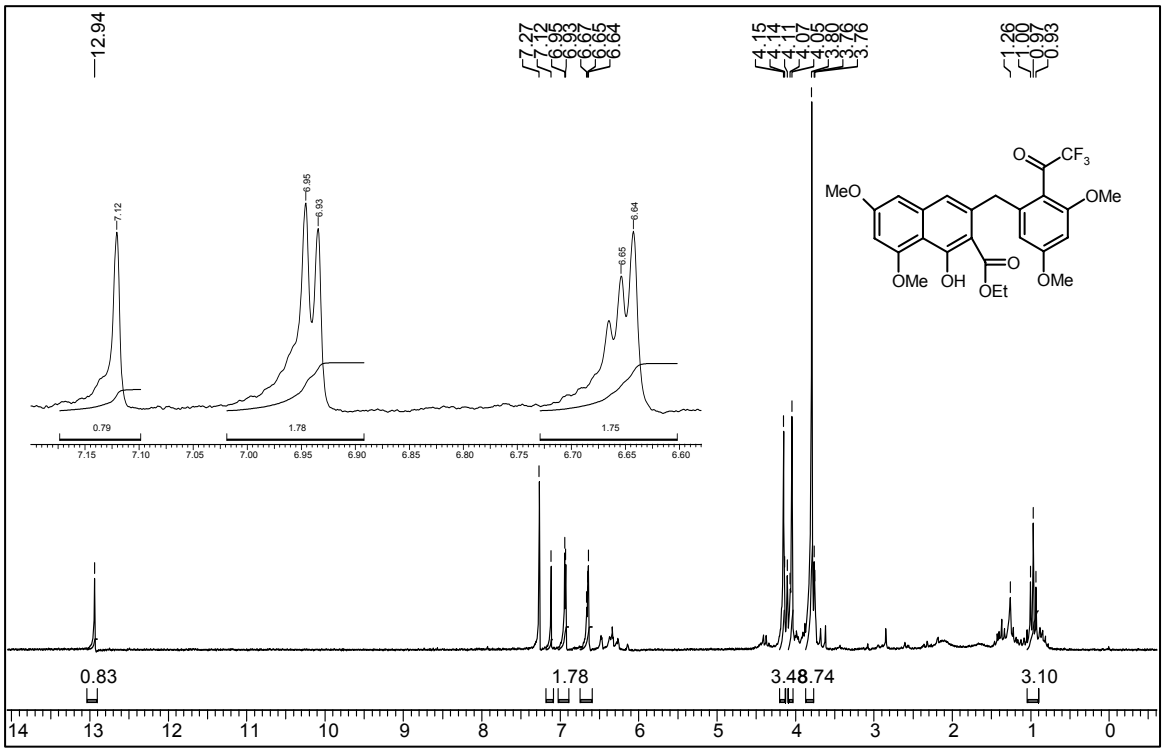




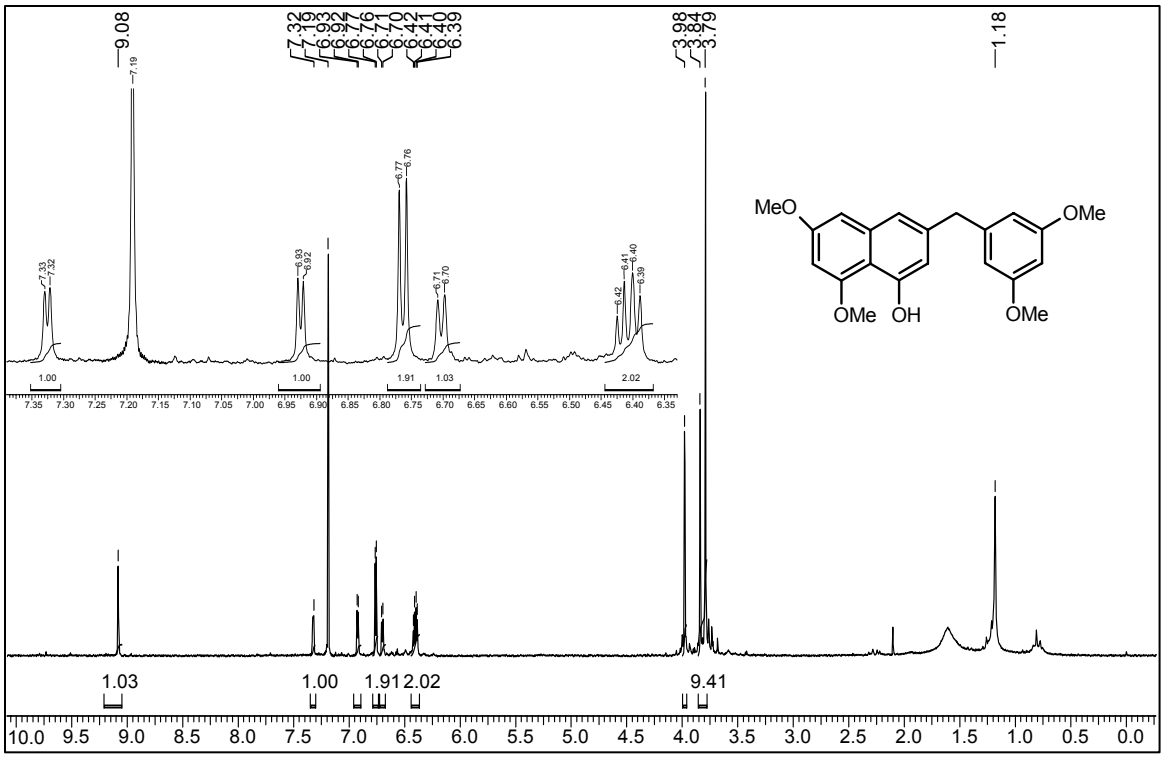
^{1}H NMR spectrum of compound 90 ($CDCl_3$+ CCl_4, 200 MHz)



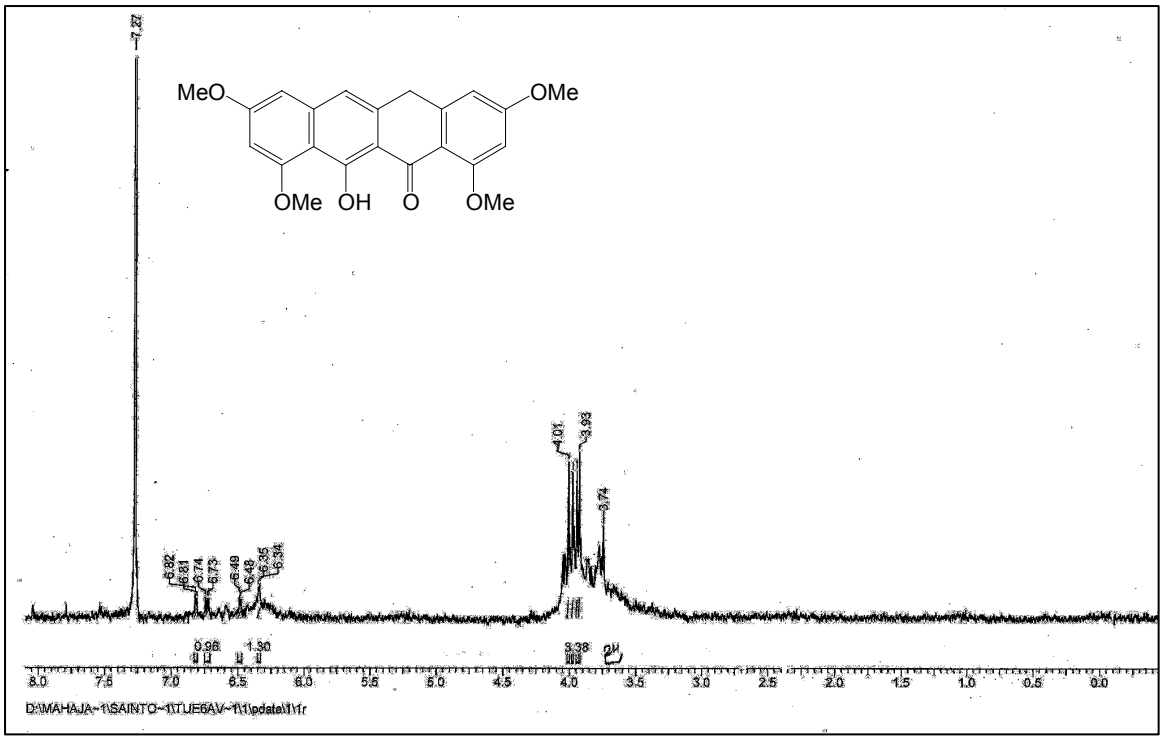
^{1}H NMR spectrum of compound 91 ($CDCl_3$+ CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 92 ($CDCl_3$+ CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 82 ($CDCl_3$+ CCl_4, 200 MHz)



2.3.6. REFERENCE

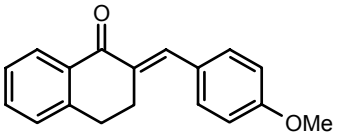
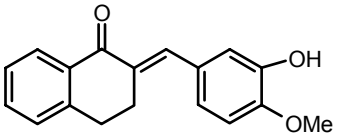
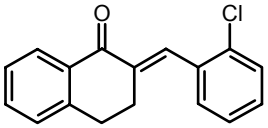
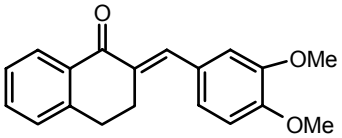
1. Paul, K. A. *Synthesis* **1982**, 805.
2. Tarnchompoo, B., Thebtaranonth, C.; Thebtaranonth, Y. Synthesis 1986, 785-786.
3. Hauser, F. M.; Rhee, R. P.; Prasanna, S. *Synthesis* **1980**, 72.
4. (a) Arndt F.; Eistert, B.; Partale, W. Ber. Dtch. Chem. Ges. **1927**, *60*, 1364-1370. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94,* 1091-1160. (c) Gill, C. B. Comp. Org. Synthesis 1991, 3, 887.

3.1.1. INTRODUCTION

Trans-methyl styryl ketone (MSK) has wide range of industrial and commercial uses.[1] It is a reactive carbonyl compound, an example of simple α, β-unsaturated ketones used in organic synthesis, as well as serves as a pharmaceutical intermediate. MSK has been shown to be positive in several in *vitro* mutagenic assays and does not seem to be toxic. It is relatively non-toxic in animal models.[1a] It is an electrophilic substrate and Michael acceptor that causes the induction of glutathiones *S*-transferase and quinone reductase in human and animals.[1b] It represents potential mechanism for the precipitation of toxic or neoplastic events.[1c] Since it is structurally similar to several well characterized chemical compounds and metabolites, its mechanism of metabolism has been studied. Many studies were directed towards structure activity relationship and aqueous solubility of the designed enone derivatives.[1d]

It is pertinent to study the literature reports regarding the SAR of α, β-unsaturated enone systems. Benzylidene tetralone derivatives represent a class of compounds with α, β-unsaturated moiety and literature survey revealed that several such derivatives have been synthesized and studied for various biological activities like antifungal, [2] anticoagulant, [3] platelet-antiaggregant[4] etc (Table 1).

Table 1.

Entry	2-Arylidene-1-tetralone derivatives	Activity studied
1		Antifungal
2		Antifungal
3		Anticoagulant
4		Antiaggregant and antifungal

The α, β-unsaturated ketone moiety in this class of compounds showed potential cytotoxicity due to the preferential reactivity towards cellular thiols particularly with glutathione *S*-tranferase by forming irreversible complex with these enzymes as shown in figure 1.[1e]

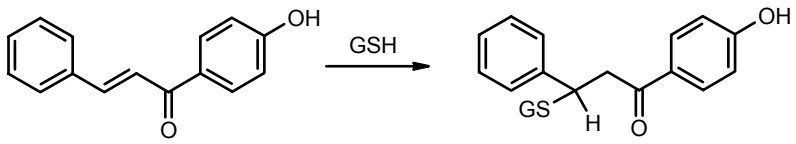


Figure 1. Alkylation reaction of α, β-unsaturated ketones with glutathione (GSH)

The currently available antineoplastics that act by alkylation of cellular nucleophiles suffer from a number of significant disadvantages, many of which are related to their interactions with nucleic acids. In contrast, various α,β-unsaturated ketones react preferentially or exclusively with thiols but not with amino or hydroxy groups.[5] Hence, since thiols are not the part of the nucleic acid structures, conjugated enones may be significantly less mutagenic and carcinogenic than conventional drug strategies using alkylating agents.[6]

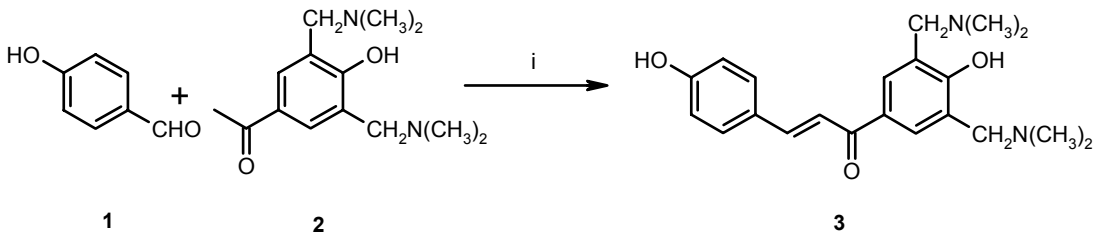
It has been reported observed that Mannich bases of conjugated styryl ketones showed potential cytotoxicity against two cell lines (P388, L1210) which are resistant to Melphaln.[7] Cytotoxicity exhibited by the enones towards cancer cell lines equivalent to that of established alkylating agents can be explained by similar mode of action.Thus the preparation of a number of prototype enones and related compounds as cytotoxic and anticancer agents was considered a profitable avenue to pursue.

A number of years ago, the cytotoxicity of *E*-2-benzylidenecyclohexanone towards an epidermoid carcinoma of the nasopharynx (KB screen) was described in which this enone had an ED_{50} of 1.34 mM.[8] There after many studies were undertaken in the search of synthetic congener to achieve hit-lead to explore the biodiversity.

Dimmock and coworkers reported[1e] cytotoxic activities of Mannich bases of chalcones and related compound against different cancer cell lines such as P388, L1210, MOLT4,

and CEM cells. The synthetic strategy used for the synthesis of these compounds is shown in Scheme 1.

Scheme 1. *J. Med. Chem.* **1998**, *41*, 1014-1026.

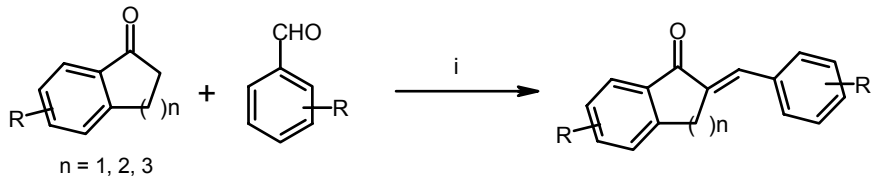


1 2 3

Reagents and conditions: (i) Hydrochloric acid; 50 ºC.

In 1999, Dimmock and coworkers[9] screened 2-arylidene-1-tetralone and indanone derivatives (Scheme 2) for cancer cell lines, which showed good to prominent cytotoxicity for cell lines such as P388, L1210, MOLT4, and CEM cells (Scheme 2).

Scheme 2. *J. Med. Chem.* **1999**, 42, 1358-1366

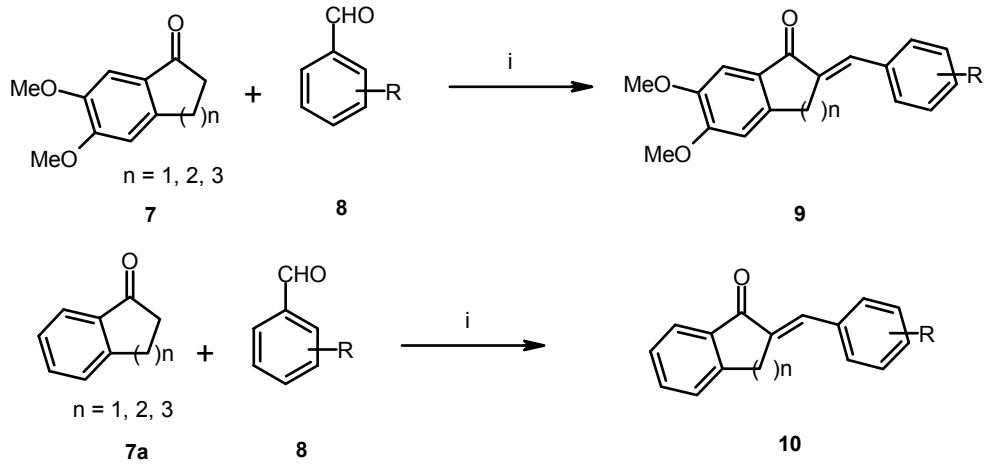


4 5 6

Reagents and conditions: (i) Hydrochloric acid, 50 ºC.

Shih and coworkers[10] reported SAR study of 6, 7-dimethoxy-1-tetralone and 6, 7-dimethoxy-1–indanone derivatives as shown in Scheme 3. The derived analogues were screened for different cell lines viz. CEM, L-1210, B-16, MOLT-4, WIL-2, WI38, K562, HL-60, H-596, H-292, MCF-7, A-549 and NIH-T3; most of the analogues showed poor cytotoxicity and were found to be cytotoxic against only Jurkat cell line.

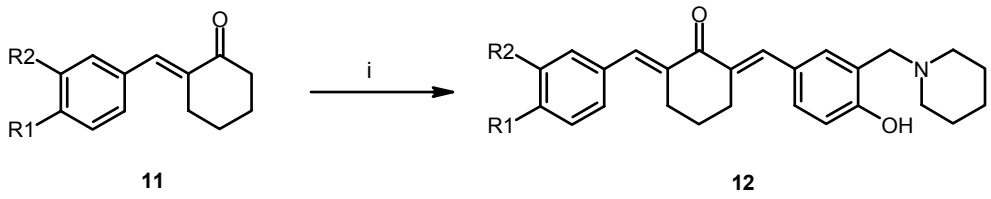
Scheme 3. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 487- 490.



Reagents and conditions: (i) Basic or acidic condition.

Dimmock and coworkers[11] screened 2-arylidene cyclohexanones, 2,6-bis(arylidene) cyclohexanones and related Mannich bases (Scheme 4) for their cytotoxicity against P388, L1210, MOLT-4 and T-lymphocytes.

Scheme 4. *Eur. J. Med. Chem.* **2000**, *35,* 967-976.



Reagents and conditions: (i) (a) 4-Hydroxybenzaldehyde, hydrochloric acid; (b) dipiperidinomethane.

3.1.2. PRESENT WORK

Literature survey revealed that 2-aryllidene-1-tetralones have been screened for various biological activities like antifungal, anticoagulant, platelet-antiaggregant etc (Table 1). This group of compounds has attracted the attention of chemists, biologists and medicinal practitioners all over the world in recent years as these compounds were found to exhibit promising biological activity. It was then observed that this structurally simple class of compounds was not explored for the cytotoxic activity; therefore we planned to synthesize number of arylidene tetralones and screened them for their potential cytoxcity against different types of cancer lines. However, simultaneously a few reports appeared on the anticancer activity. The structure-activity relationship of these compounds as well as benzylidene indanones, benzylidenebezosuberones etc has been studied.

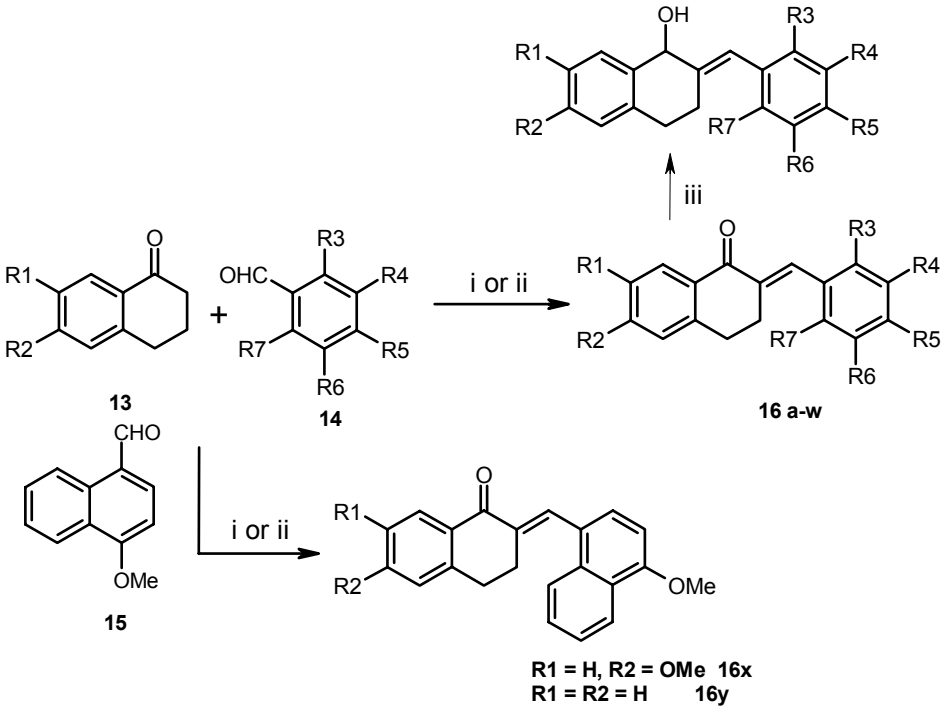
However these reports include only unsubstituted or 6,7-dimethoxy tetralones. This prompted us to synthesize various benzylidene and naphthalidenetetralones with different substituents on tetralone moiety as well as on aryl ring and subject them to screening for cytotoxic activity; the results were presented in this section.

Our aim was to synthesize 2-aryldiene-1-tetralone derivatives with wide range of substituents on this basic skeleton and evaluate these compounds against human cancer cell lines viz. MOLT-4, SW620, DU145, KB, L132, Mia Paca, Hep2, PA1, HuTu80, and ECV. Present section describes the synthesis of 2-arylidene-1-tetralone derivatives by Claisen-Schmidt condensation reaction. A library of 23 compounds was generated and studied for cytotoxicity.

3.1.3. RESULTS AND DISCUSSION

The various chemical entities studied in the present work were prepared by the synthetic sequences shown in Scheme-5. The arylidenetetralones 1-26 were synthesized by Claisen-Schmidt condensation of substituted-1-tetralones with substituted benzaldehydes (Table 1) while the naphthalidene tetralones were obtained by Claisen-Schmidt condensation of 1-tetralones with 4-methoxy naphthaldehyde.

Scheme 5.



Reagents and conditions: (i) Aq. NaOH, ethanol, 0ºC then at rt, or (ii) Dil. HCl, ethanol, 50 ºC; iii) $NaBH_4$, MeOH, rt.

The 2-arylidene-1-tetralone derivatives have been synthesized by Claisen-Schmidt condensation using substituted 1-tetralones and arylaldehydes with groups different in hydrophobicity and steric and electronic parameters to elucidate structural requirement for biological activity. Claisen-Schmidt condensation was carried out under either acidic or basic condition and the products obtained were characterized by all spectroscopic means.

^{1}H NMR spectrum showed that the compounds were isomerically pure and the olefinic protons were located at δ 7.3 – 7.8 indicating the presence of trans double bond in the derived 2-arylidene-1-tetraolne derivatives. This was further confirmed by X-ray crystallography and supported by the literature. There was no evidence for the formation of *Z*- isomer in all the examples studied.

3.1. Cytotoxicity studies

The cytotoxicity of 2-arylidene-1-tetralone derivatives was tested by performing a 72-hour MTT cytotoxicity assay, based on the principle of uptake of MTT [3- (4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide], a tetrazolium salt, by the metabolically active cells where it is metabolized by active mitochondria into a blue-colored formazan product which can be read spectrophotometrically.

To prepare the MTT stock solution needed for the one-day MTT cytotoxicity assay, MTT (Sigma catalogue number M 2128) was dissolved in phosphate buffered saline with a pH of 7.4 to obtain an MTT concentration of 5 mg/ml, the resulting mixture was filtered through a 0.22 μ filter to sterilize and remove a small amount of insoluble residue and the filtered mixture was the MTT stock solution (20 μl / 200 μl of medium). Briefly, for each type of tumor cell, approximately 10,000-50,000 cells were seeded in a 96-well culture plate and incubated with each of the furanone derivatives in a CO_2 incubator for 72 hours. The concentrations of the 2-arylidene-1-tetralone derivatives were in the range of 1 – 100 μg/ml. Controls, which were not treated with the 2-arylidene-1-tetralone derivatives, were similarly incubated. The assay was terminated after 72 hours by adding 100 μg /(20 μl) of MTT to each well, then incubating for approximately one additional hour, and finally adding 50 μl of 10% SDS-0.01 N HCl to each well to lyse the cells and dissolve the formazan. After incubating for one hour at 37^{o}C, the plate was read spectrophotometrically at 540 nm and the cytotoxicity percentage (i.e. the killing percentage or the inhibition percentage) was calculated using the following formula:

Cytotoxicity percentage=100. [1-(X/R_1)],

X=(absorbance of the treated sample at 540 nm)-(absorbance of a blank at 540 nm),

R_1 =(absorbance of the untreated control at 540 nm)-(absorbance of a blank at 540 nm).

Thus, in each of the MTT cytotoxicity assays reported herein, the cytotoxicity percentage was calculated according to the above formula and was based on the proliferation of the untreated controls, the value of which was taken as 100%. A dose response curve was prepared and IC_{50} values determined graphically. Table 2 shows the mean IC_{50} values with standard deviation.

3.2. Cytotoxicity: Results and discussions

23 compounds were screened for their *in vitro* cytotoxicty against 10 different human cancer cell lines and the results are summarized in Table 2. The cell lines were MOLT4 (leukemia), SW620 (colon), DU145 (prostate), KB (oral), L132 (lung), MIAPaCa-2 (Pancreas), Hep2 (larynx), PA1 (ovary), HuTu 80 (duodenum), ECV (endothelial) and MCF7 (Breast). Some of these compounds showed prominent cyctotoxicity. Due to the wide substitution pattern it was worthwhile to undertake the comparative study of structure activity relationship of these analogues.

Among the 6-Methoxy-2-benzylidene-1-tetralone, the most potent compounds were **16b**, **16f**, **and 16 j**. It was found that OCH_3 substitution at R-4 position was helpful to improve the cytotoxicity. Substitution of OCH_3 at R-4 position helps to elicit cytotoxicity (Table 2) against cancer cell lines except KB cell line, while groups other than OCH_3 such as NO_2 and NHAc failed to improve cytotoxicity, that may be due to lack of hydrogen bonding, while compounds **16b**, **16f** and **16p** with R-4 = alkoxy substituent, maintained their cytotoxicity. Compounds **16m** and **16n** with -OH and -Cl respectively at R-3 with minimum steric crowding exhibited potential cytotoxicity.

In comparartive study, compounds **16c** and **16j** exhibited the surprising variation in cytotoxicity. **16j** is found to be more cytotoxic than **16c**, where there was only change in position of substituents. It is interesting to note that 3'-hydroxy-4-methoxy phenyl derivative **16o** and 2'hydroxyphenyl derivative **16m** exhibited cytotoxicity against a number of cell lines. Upon interchanging the substituents in compound **16o** (compound **16 p**), activity decreased though this compound was still potent on MOLT4 and PA1 cell lines. Upon removal of hydroxy in **16p** (compound **16q**), activity was lost. Upon introduction of one methoxy group at 5'-position in **16 p** (compound **16s**), activity vanished. It indicated that the most active compound in unsubstituted tetralone series was the one with trimethoxyl (16l) group. Compounds synthesized from amino and chloro tetralones exhibited marginal cytotoxicities (except for PA 1 cell line). Urea derivative of 2-arylidine-1-tetralone **16w** failed to retain the cytotoxicity. α, β-Saturated tetralone derivatives prepared by hydrogenation lost their activity; which confirmed that the conjugation is essential for the anticancer activity.

Table 2.The cytotoxicity data (IC 50 (*μg*/ml)) of 2-arylidene-1-tetralone derivatives

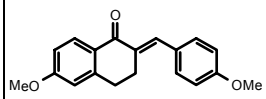
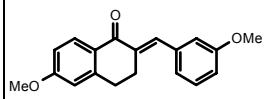
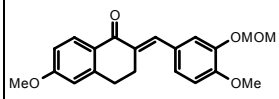
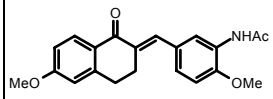
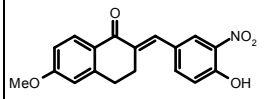
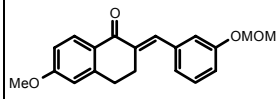
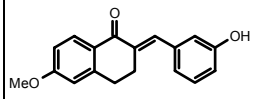
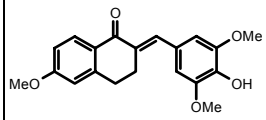
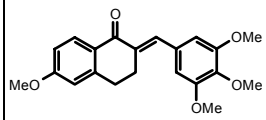
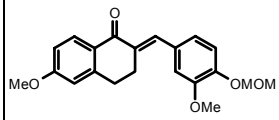
S. N.	2-Arylidene-1-tetralones	Y %	MOLT-4	SW 620	DU 145	KB	L 132	Mia	Hep 2	PA1	Hu Tu80	ECV
16a		**85**	35	>100	>100	40	>100	>100	30	>100	>100	89
16b		**88**	**4**	**7**	**4**	**>100**	**8**	**10**	**10**	**8**	**13**	**17**
16c		**70**	40	>100	>100	>100	>100	>100	38	50	80	>100
16d		**74**	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
16e		**68**	31	>100	>100	>100	>100	>100	68	>100	>100	>100
16f		**72**	**5**	**4**	**15**	**14**	**4**	**15**	**10**	**9**	**10**	**13**
16g		**67**	**3**	95	>100	>100	>100	>100	>100	18	>100	35
16h		**71**	ND	ND	41	65	45	55	60	43	ND	62
16 i		**92**	6	ND	>100	ND	>100	ND	20	ND	ND	>100
16j		**88**	**4**	**8**	**10**	**>100**	**8**	**10**	**10**	**13**	**13**	**17**

Table 2. Continued …

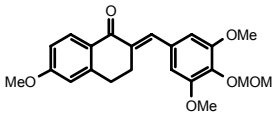
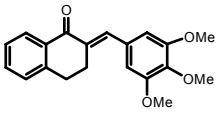
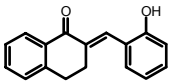
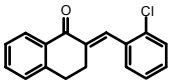
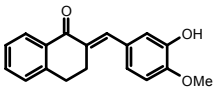
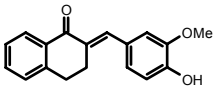
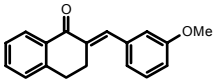
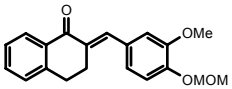
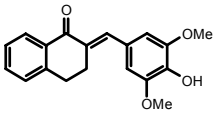
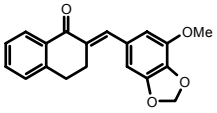
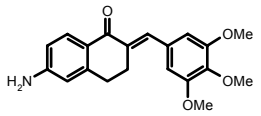
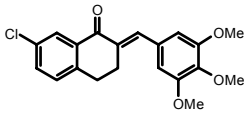
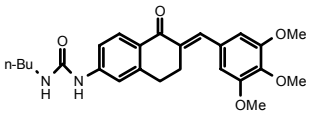
S. N.	2-Arylidene-1-tetralones	Y %	MOLT-4	SW 620	DU 145	KB	L 132	Mia	Hep 2	PA 1	Hu Tu80	ECV
16k		**78**	ND	ND	>100	78	>100	87	>100	16	ND	>100
16l		**97**	**3.6**	**1**	**10**	**10**	**10**	**2**	**14**	**9**	18.5	12
16 m		**72**	**3**	**5**	**1.5**	**5**	**10**	**2**	**15**	**8**	ND	ND
16n		**70**	33	20	15	15	15	**2**	44	40	ND	ND
16 o		**67**	4.6	**1**	**15**	**5**	**10**	**5**	**6**	**<1**	**87**	20
16 p		**73**	**3**	72	82	70	80	33	35	**9**	24	22
16q		**93**	**3**	>100	>100	>100	>100	23.3	21	**8**	18	14
16r		**85**	ND	ND	86	67	81	74	37	21	ND	23
19s		**68**	ND	ND	>100	>100	>100	>100	>100	>100	>100	>100
20 t		**91**	ND	ND	35	22	40	>100	41	15	ND	24

Table 2. Continued …

S. N.	2-Arylidene-1-tetralones	Y %	MOLT-4	SW 620	DU 145	KB	L 132	Mia	Hep 2	PA1	HuTU 80	ECV
16u		**96**	17	>100	ND	70	50	>100	21	17	32	>100
16 v		**66**	ND	ND	49	44	>100	>100	>100	**7**	ND	32
16w		**90**	ND	ND	>100	58	>100	80	>100	25	ND	>100

ND: **Not Done**

It is hypothetical that α, β- unsaturated enones are found to be cytotoxic because during biochemical process they undergo addition or alkylation reaction.

3.1.4. CONCLUSION

A number of chalcones have demonstrated cytotoxic and anti-cancer properties[1]. Substituted tetralones were condensed with a variety of aldehydes to give 2-arylidene tetralones using aqueous sodium hydroxide as represented in scheme **5**. These derivatives were screened for their cytotoxicities against panel of ten cancer cell lines such as *In vitro* cytotoxic potency of these derivatives towards human cancer cell lines viz. MOLT-4, SW620, DU145, KB, L132, Mia Paca, Hep2, PA1, HuTu80, ECV etc. has been described. Most of the new compounds have shown significant cytotoxicity and the most potent compounds were **16b, 16f, 16j, 16l, 16m, 16n, 16o,** and **16q**. Structure – activity relationships have been discussed with respect to the studied new chemical entities. This investigation is helpful to improve the design and development of more potent anticancer agents together with superior efficacy and shortest chemical sequences.

3.1.5. EXPERIMENTAL

General procedure for synthesis of 2-arylidene 1-tetralone

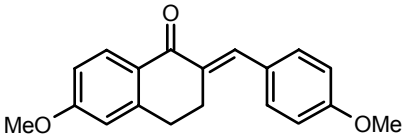
Condensation under basic condition:

A mixture of α-tetralone (1 mmol) and substituted benzaldehyde (1.2 mmol) in distilled ethanol was cooled to 0 ºC, aqueous solution of sodium hydroxide (3 mmol) was added drop wise and the mixture was stirred at same temp for 30 minute. It was then allowed to stir at room temperature and the reaction was monitered by TLC. After complete conversion ethanol was removed under vacuum (in case of free phenolic compound reaction mixture was acidified using dilute HCl) and the residue was then extracted with ethyl acetate. Organic layer was washed with brine and dried over sodium sulphate. Crude derivatives were purified by column chromatography and characterized by spectral techniques. (HPLC purity 90-97% using C-18 Column)

Condensation under acidic condition

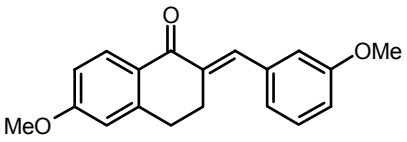
To the mixture of α-tetralone (1 mmol) and substituted benzaldehyde (1.2 mmol) in distilled ethanol (15ml) 50% HCl (5ml) was added and the mixture, was sirred at 50 ºC for 3-4 h, after which reaction mixture was extracted with ethyl acetate organic layer was washed with brine and dried over sodium sulphate. Crude derivatives were purified by column chromatography.

6-Methoxy-2- (4-methoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16a)



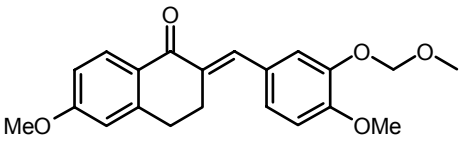
Nature: Pale yellow solid; **Yield:** 0.249g, 85%; **Mp**: 139ºC; **IR** (Chloroform): *v* 3015, 1665, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.92 (t, *J* = 8 Hz, 2H), 3.11 (t, *J* = 8 Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 6.72 (d, *J* = 8 Hz, 1H), 6.82 (d, *J* = 8 Hz, 2H), 7.15 (dd, *J* = 8 Hz, 1H), 7.78 (s, 1H), 8.12 (dd, *J* = 8, 2 Hz, 2H)

6-Methoxy-2- (3-methoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16b)



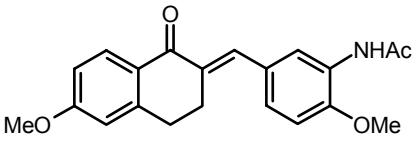
Nature: Semisolid; **Yield:** 0.258g, 88%; **IR** (Chloroform): *ν* 3016, 1670, 1494, 1252 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): *δ* 2.92 (t, *J* = 8 Hz, 2H), 3.11 (t, *J* = 8 Hz, 2H), 3.85 (s, 6H), 6.80 -7.05 (m, 4H), 7.32 (t, *J* = 8 Hz, 1H), 7.79 (s, 1H), 8.01(d, *J* = 8 Hz, 1H), 8.09 (d, *J* = 8 Hz, 1H).

6-Methoxy-2-(4-methoxy-3-methoxymethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16c)



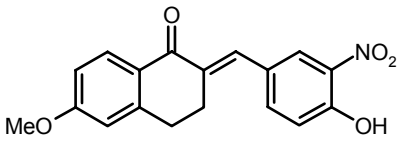
Nature: Pale yellow solid; **Yield:** 0.247g, 70%; **Mp**: 129ºC; **IR** (Chloroform): *ν* 3018, 1658, 1512, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): *δ* 2.90 (t, *J* = 6 Hz, 2H), 3.12 (t, *J* = 6 Hz, 2H), 3.53 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 5.23 (s, 2H), 6.68 (d, *J* = 2Hz, 1H), 6.85- 6.93 (m, 3H), 7.08 (dd, *J* = 8, 2Hz, 1H), 7.76 (S, 1H), 8.08 (d, *J* = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): *δ* 25.8, 27.7, 54.1, 54.5, 54.8, 94.2, 110.9, 112.1, 117.4,121.0, 123.6, 127.1, 127.3, 129.0, 132.7, 144.2, 144.8, 144.9, 149.1, 162.1, 184.62.

N-[2-Methoxy-5-(6-methoxy-1-oxo-3,4-dihydro-*1H*-naphthalen-2-ylidenemethyl)-phenyl]-acetamide (16d)



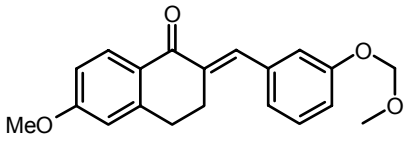
Nature: White solid; **Yield:** 0.259g, 74%; **Mp**: 174ºC **IR** (Chloroform): *ν* 2910, 1660, 1521, 1210 cm^{-1}; **^{1}H NMR**: 2.23 (s, 3H), 2.92 (t, *J* = 6 Hz, 2H), 3.18 (t, *J* = 6 Hz, 2H), 3.87 (s, 3 H), 3.92 (s, 3H), 6.69 (d, *J* = 2 Hz, 1H), 6.80-6.92 (m, 2H), 7.13 (dd, *J* = 8, 2 Hz, 1 H), 7.77 (bs, 2H), 8.08 (d, *J* = 8 Hz, 1H), 8.58 (s, 1H).

2-(4-Hydroxy-3-nitro-benzylidene)-6-methoxy-3,4-dihydro-*2H*-naphthalen-1-one (16e)



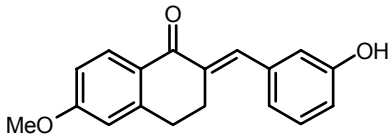
Nature: Yellow solid; **Yield:** 0.221g, 68%; **Mp**: 170ºC; **IR** (Chloroform): *v* 2967, 1662, 1510, 1209 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.95 (t, *J* = 6 Hz, 2H), 3.10 (t, *J* = 6 Hz, 2H), 3.89 (s, 3H), 6.71 (d, *J* = 2 Hz, 1H), 6.91 (dd, *J* = 8, 2 Hz, 1H), 7.21 (d, *J* = 8 Hz, 1H), 7.64 -7.72 (dd, *J* = 8 Hz, 2 Hz, 2H), 8.09 (d, *J* = 8 Hz, 1H), 8.15 (d, *J* = 8 Hz, 1H), 10.69 (s, 1H); **MS**: *m/z* 325, 297, 178, 91, 77.

6-Methoxy-2-(3-methoxymethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16f)



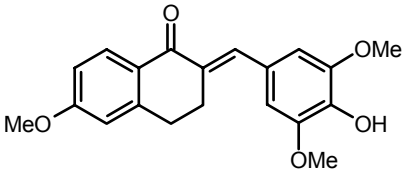
Nature: Semisolid; **Yield:** 0.233g, 72%; **IR** (Chloroform): *v* 3010, 1667, 1520, 1212 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.91 (t, *J* = 6 Hz, 2H), 3.12 (t, *J* = 6 Hz, 2H), 3.50 (s, 3H), 3.87 (s, 3H), 5.19 (s, 2 H), 6.69 (d, *J* = 2 Hz, 1H), 6.86 (dd, *J* = 8, 2 Hz, 1H), 6.96 -7.09 (m, 3H), 7.28 (d, *J* = 8 Hz, 1H), 7.77 (s, 1H), 8.09 (d, *J* = 8 Hz, 1H); **MS**: *m/z* 324, 293, 279, 263, 251, 91.

2-(3-Hydroxy benzylidene)-6-methoxy-3, 4-dihydro-*2H*-naphthalen-1-one (16g)



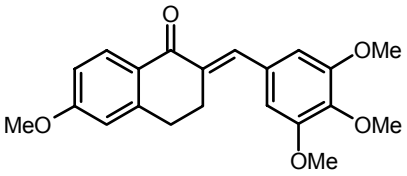
Nature: Pale yellow solid; **Yield:** 0.280g, 67%; **Mp**: 164 ºC; **IR** (Chloroform): *v* 3228, 2924, 2854, 1647, 1591, 1458 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.92 (t, *J* = 6.3 Hz, 2H), 3.12 (t, *J* = 6.3 Hz, 2H), 3.88 (s, 3H), 6.75 (d, *J* = 2.3 Hz, 1 H), 6.80-6.92 (m, 4H), 7.20 (d, *J* = 8 Hz, 1H), 7.69 (s, 1H), 8.03 (d, *J* = 8 Hz, 1H); **MS**: *m/z* 279, 263, 189, 115, 77.

6-Methoxy-2-(4-Hydroxy-3,5-dimethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16h)



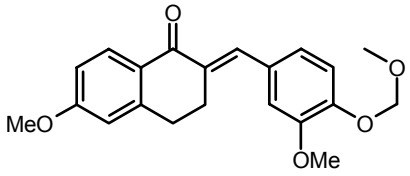
Nature: Yellow solid; **Yield:** 0.241g, 71%; **Mp**: 180 ºC; **IR** (Chloroform): *v* 3410, 3012, 1660, 1593, 1218 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.8 (t, *J* = 6.4 Hz, 2H), 3.10 (t, *J* = 6.4 Hz, 2H), 3.50 (s, 3H), 3.82 (s, 6H), 6.70 (s, 2H), 6.87 (dd, *J* = 8, 2 Hz, 2H), 7.75 (s, 1H), 8.10 (d, *J* = 2 Hz, 2H).

6-Methoxy-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16i)



Nature: Yellow solid; **Yield:** 0.325g, 92%; **Mp**: 109 ºC; **IR** (Chloroform): ν 2940, 1660, 1593, 1256 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.90 (t, *J* = 6 Hz, 2H), 3.08 (t, *J* = 6 Hz, 2H), 3.59 (s, 3H), 3.82 (s, 6H), 3.87 (s, 3H), 6.65 (s, 2H), 6.81 (dd, *J* = 8, 2 Hz, 2 H), 6.95 (dd, *J* = 8, 2 Hz, 1H), 7.72 (s, 1H).

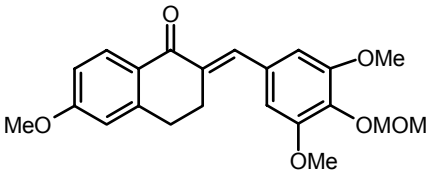
6-Methoxy-2-(3-methoxy-4-methoxymethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16j)



Nature: Pale yellow solid; **Yield:** 0.311g, 88%; **Mp**: 74ºC; **IR** (Chloroform): *v* 2940, 1660, 1593, 1256 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.86 (t, *J* = 6.4 Hz, 2H), 3.08 (t, *J* = 6.4 Hz, 2H), 3.49 (s, 3H), 3.82 (s, 3H), 3.87 (s,

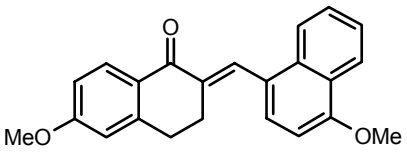
3H), 5.22 (s, 2H), 6.65 (d, *J* = 2 Hz, 1H), 6.81 (dd, *J* = 8, 2 Hz, 1H), 6.95 (dd, *J* = 8, 2 Hz, 2H), 7.12 (d, *J* = 8 Hz, 1H), 7.73 (s, 1H), 8.05 (d, *J* = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 26.9, 28.8, 55.0, 55.7, 55.8, 94.9, 111.9, 112.9, 113.4, 115.6, 122.5, 126.8, 130.0, 130.3, 134.0, 135.6, 145.1, 146.5, 149.1, 163.1, 185.9; **MS**: *m/z* 354, 323, 311, 279, 181, 153, 120, and 77.

2-(3,5-Dimethoxy-4-methoxymethoxy-benzylidene)-6-methoxy-3,4-dihydro-*2H*-naphthalen-1-one (16k)



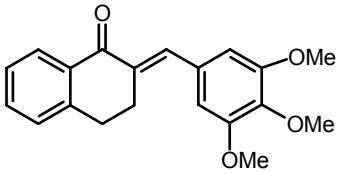
Nature: Yellow solid; **Yield:** 0.299g, 78%; **Mp**: 127ºC; **IR** (Chloroform): *v* 3017, 1660, 1593, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.90 (t, *J* = 7 Hz, 2H), 3.12 (t, *J* = 7 Hz, 2H), 3.60 (s, 3H), 3.86 (s, 9H), 5.14 (s, 2H), 6.64 (s, 2H), 6.75 (d, *J* = 2 Hz, 1H), 6.85 (dd, *J* = 8, 2 Hz, 1H), 7.73 (s, 1H), 8.08 (d, *J* = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 27.1, 29.0, 55.2, 55.9 (2C), 56.9, 98.0, 106.9, 112.09, 113.1, 126.8, 130.5 (2C), 131.7, 134.7, 134.9, 135.9, 145.3, 153.0 (2C), 163.3, 186.2.

6-Methoxy-2-(4-methoxy-naphthalen-1-ylmethylene)-3,4-dihydro-2H-naphthalen-1-one (16y)



Nature: Yellow solid; **Yield:** 0.314g, 97%; **Mp**: 140ºC; **IR** (Chloroform): ν 2924, 1655, 1580, 1264, 778; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.88 (t, *J* = 8 Hz, 2H), 3.03 (t, *J* = 8 Hz, 2H), 3.88 (s, 3H), 4.05 (s, 3H), 6.70 (bs, 1H), 6.82 -6.95 (m, 2H), 7.38 (d, *J* = 8 Hz, 1H), 7.50-7.60 (m, 2H), 7.96 –8.05 (m, 1H), 8.20 (d, *J* = 8 Hz, 1H), 8.30-8.37 (m, 2H).

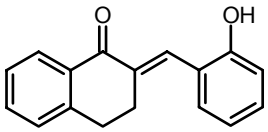
2-(3,4,5-Trimethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16l)



Nature: Yellow solid; **Yield:** 0.341g, 97%; **Mp**: 102ºC; **IR** (Chloroform): *v* 3018, 1690, 1591, 1505, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.97

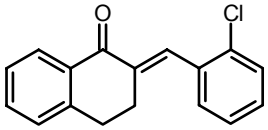
(t, *J* = 6 Hz, 2H), 3.17 (t, *J* = 6 Hz, 2H), 3.89 (s, 9 H), 6.67 (s, 2 H), 7.11-7.60 (m, 3H), 7.80 (s, 1H), 8.12 (d, *J* = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 26.9, 28.3, 55.7 (2C), 60.3, 106.9 (2C), 126.5, 127.7 (2C), 130.8, 132.7, 133.0, 134.3, 136.3, 138.3, 142.3, 152.6 (2C), 186.8.

2-(2-Hydroxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16m)



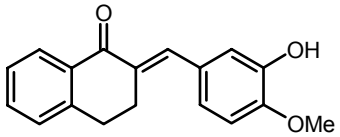
Nature: Semisolid; **Yield:** 0.180g, 72%; **IR** (Chloroform): *v* 3420, 3015, 1644, 1549, 1208 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.86 (t, *J* = 6 Hz, 2H), 2.96 (t, *J* = 6 Hz, 2H), 6.67 - 6.85 (m, 2H), 7.01-7.45 (m, 5H), 7.82 (s, 1 H), 7.92 (d, *J* = 8 Hz, 1H), 9.32 (bs, OH); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 25.3, 26.6, 114.0, 116.9, 120.7, 124.9, 125.6, 126.5, 128.0, 130.7, 131.2, 131.4, 135.5, 141.4, 154.9, 185.0; **MS**: *m/z* 250, 233, 202, 178, 144, 91 and 77.

2-(2-Chloro-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16n)



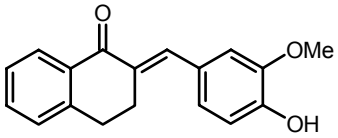
Nature: Semisolid; **Yield:** 0.187g, 70%; **IR** (Chloroform): *v* 3115, 1642, 1520 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.97 (bs, 4H), 7.10 -7.68 (m, 6H), 7.92 (s, 1H), 8.18 (s, 1 H), 8.18 (d, *J* = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 27.2, 28.8, 127.2, 128.1, 128.4 (2C), 129.6, 129.7, 129.7, 133.4, 133.6, 134.6, 134.9, 137.6, 137.7, 143.3, 187.0; **MS**: *m/z* 268, 233, 202, 115, 89.

2-(3-Hydroxy-4-methoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16o)



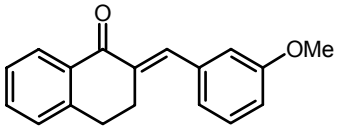
Nature: Pale yellow solid; **Yield:** 0.188g, 67%; **Mp**: 72ºC; **IR** (Chloroform): *v* 3544, 3019, 1687, 1605, 1509, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.93 (t, *J* = 6 Hz, 2H), 3.15 (t, *J* = 6 Hz, 2H), 3.93 (s, 3H), 6.85-6.99 (m, 3 H), 7.40-7.50 (m, 3H), 7.81 (s, 1H), 8.18 (s, 1 H), 8.10 (dd, *J* = 8, 2 Hz, 1H).

2-(4-Hydroxy-3-methoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16p)



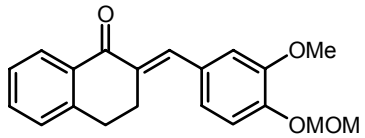
Nature: Yellow solid; **Yield:** 0.204g, 73%; **Mp**: 123ºC; **IR** (Chloroform): *v* 3450, 3016, 1648, 1580, 1210 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.95 (t, *J* = 6 Hz, 2H), 3.18 (t, *J* = 6 Hz, 2H), 3.94 (s, 3H), 5.79 (bs, OH), 6.90 -7.10 (m, 3 H), 7.20 -7.50 (m, 3H), 7.61 (s, 1H), 7.82 (d, *J* = 8 Hz, 1H); **MS**: *m/z* 280, 265, 249, 137, 91.

2-(3-Methoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16q)



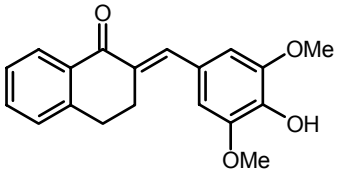
Nature: Pale yellow solid; **Yield:** 0.245g, 93%; **Mp**: 73-74 ºC; **IR** (Chloroform): ν 3108, 1640, 1550, 1208 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.95 (t, *J* = 6 Hz, 2H), 3.14 (t, *J* = 6 Hz, 2H), 3.84 (s, 3H), 6.87 - 7.08 (m, 3 H), 7.23 -7.56 (m, 4H), 7.85 (s, 1H), 8.14 (d, *J* = 8 Hz, 1H); **MS**: *m/z* 264, 233, 115, 90, 77.

2-(3-Methoxy-4-methoxymethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16r)



Nature: Semisolid; **Yield:** 0.275g, 85%; **IR** (Chloroform): ν 3019, 1689, 1514, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.45 (t, *J* = 6 Hz, 2H), 2.86 (t, *J* = 6 Hz, 2H), 3.40 (s, 3H), 3.88 (s, 3 H), 5.23 (s, 2H), 6.88 (m, 2H), 7.11-7.47 (m, 4H), 7.51 (s, 1H), 8.10 (d, *J* = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 23.8, 25.6, 54.4, 61.9, 94.3, 109.7, 112.7 (2C), 114.1, 119.4, 122.6, 125.3, 125.5, 127.2, 128.8, 132.6, 141.9, 145.8, 151.9, 189.1.

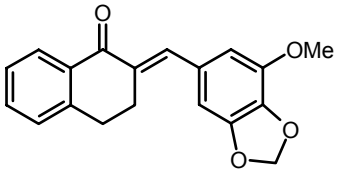
2-(4-Hydroxy-3, 5-dimethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16s)



Nature: Pale yellow solid; **Yield:** 0.210g, 68%; **Mp**: 88ºC; **IR** (Chloroform): *v* 3412, 1639, 1529, 1208 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.01 (t, *J* = 6 Hz, 2H), 3.19 (t, *J* = 6 Hz, 2H), 3.94 (s, 6H), 5.70 (bs, 1H, OH), 6.72 (s, 2H), 7.10-7.60 (m, 3H), 7.81 (s, 1H), 8.14 (d, *J* = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 27.0, 28.4, 56.1 (2C), 107.3

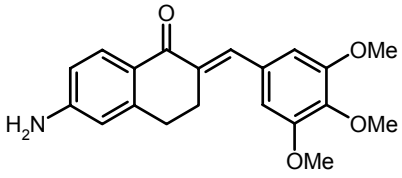
(2C), 126.6 (2C), 127.8, 132.8 (2C), 132.8, 132.9, 135.9 (2C), 137.06, 142.6, 146.8, 187.2.

2-(7-Methoxy-benzo [1,3] dioxol-5-ylmethylene)-3,4-dihydro-*2H*-naphthalen-1-one (16t)



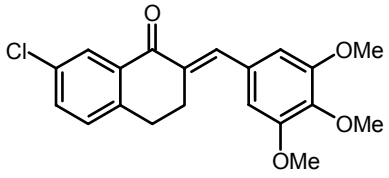
Nature: Pale yellow solid; **Yield:** 0.280g, 91%; **Mp**: 95 °C; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.98 (t, J = 6 Hz, 2H), 3.13 (t, J = 6 Hz, 2H), 3.92 (s, 3H), 6.03 (s, 2H), 6.67 (d, J = 2 Hz, 2H), 7.22-7.52 (m, 3H), 7.78 (s, 1H), 8.10 (d, J = 8 Hz, 1H).

6-Amino-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16u)



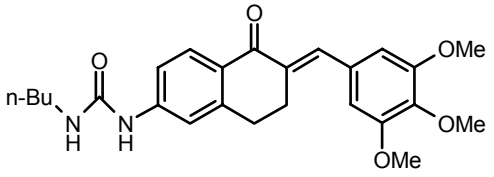
Nature: Brown solid; **Yield:** 0.325g, 96%; **Mp**: 147ºC; **IR** (Chloroform): v 3430, 1666, 1522, 1210 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.83 (t, J = 6 Hz, 2H), 3.09 (t, J = 6 Hz, 2H), 3.88 (s, 9H), 4.16 (bs, 2H), 6.40 (s, 1H), 6.50-6.65 (m, 3H), 7.72 (s, 1H), 7.97 (d, J = 8 Hz, 1H); **MS** (ESI): *m/z* 339 (M^+), 324, 309, 252, 181.

7-Chloro-2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-*2H*-naphthalen-1-one (16v)



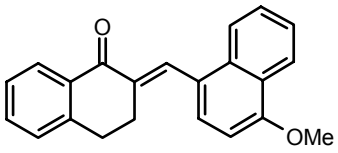
Nature: Yellow solid; **Yield:** 0.207g, 66%; **Mp**: 118ºC; **IR** (Chloroform): v 3455, 1643, 1530, 1208 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.92 (t, J = 6 Hz, 2H), 3.12 (t, J = 6 Hz, 2H), 3.86 (s, 6H), 3.90 (s, 3H), 6.62 (s, 2H), 7.17 (d, J = 6 Hz, 1H), 7.38 (dd, J = 8, 2 Hz, 1H), 7.74 (s, J = 8 Hz, 1H), 8.01 (d, J = 2 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 27.2, 28.4, 56.3 (2C), 61.0, 106.9, 107.6 (2C), 128.0, 129.8, 131.1, 133.1, 134.0, 134.2, 137.8, 141.2, 153.3 (2C), 159.9, 190.8.

1-[5-Oxo-6-(3,4,5-trimethoxy-benzylidene)-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-butyl-urea (16w)



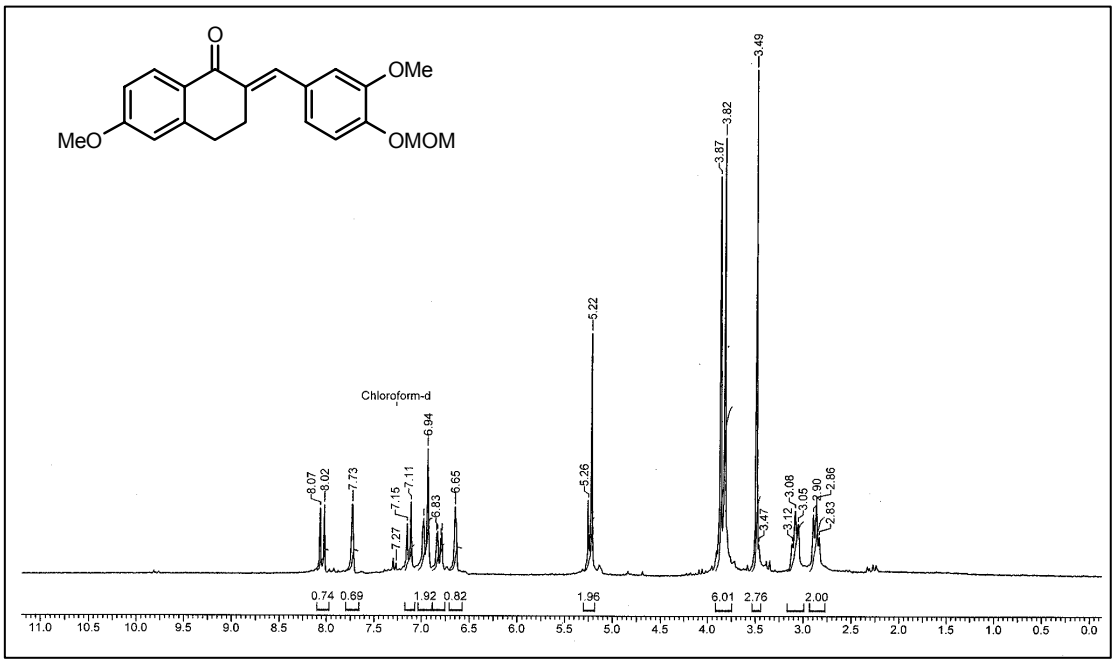
Nature: Yellow solid; **Yield:** 0.354g, 90%; **Mp**: 129ºC; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.87 (t, J = 6 Hz, 3H), 1.15-1.50 (m, 4H), 2.80 (t, J = 6 Hz, 2H), 3.04 (t, J = 6 Hz, 2H), 3.25 (m, 2H), 3.85 (s, 6H), 3.87 (s, 3H), 6.12 (t, 1H), 6.60 (s, 2H), 7.02 (dd, J = 8, 2 Hz 1H), 7.56 (d, J = 2 Hz, 1H), 7.69 (d, J = 2 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 8.35 (bs, 1H). **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 13.7, 20.0, 27.2, 29.1, 32.1, 39.8, 56.8, 60.8, 103.6, 107.2 (2C), 116.4, 116.8, 127.2, 129.4, 131.3, 135.1, 136.4, 138.4, 144.8, 145.2, 153.0, 155.6, 186.9.

2-(4-Methoxy-naphthalen-1-ylmethylene)-3,4-dihydro-2H-naphthalen-1-one (16z)

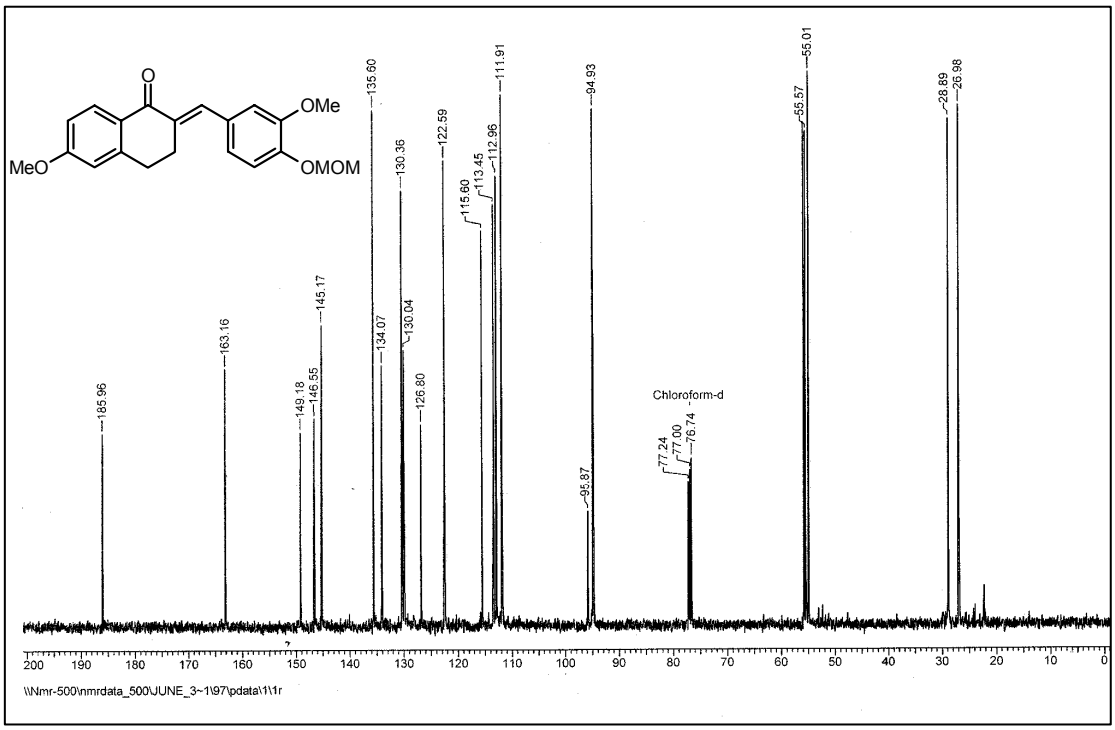


Nature: Yellow solid; **Yield:** 0.251g, 80%; **Mp**: 131ºC; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.92 (t, J = 8 Hz, 2H), 3.07 (t, J = 8 Hz, 2H), 4.06 (s, 3H), 6.83 (d, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 1H); 7.36 -7.61 (m, 5H), 7.95 –8.03 (m, 1H), 8.20 (d, J = 8 Hz, 1H), 8.30 –8.39 (m, 2H).

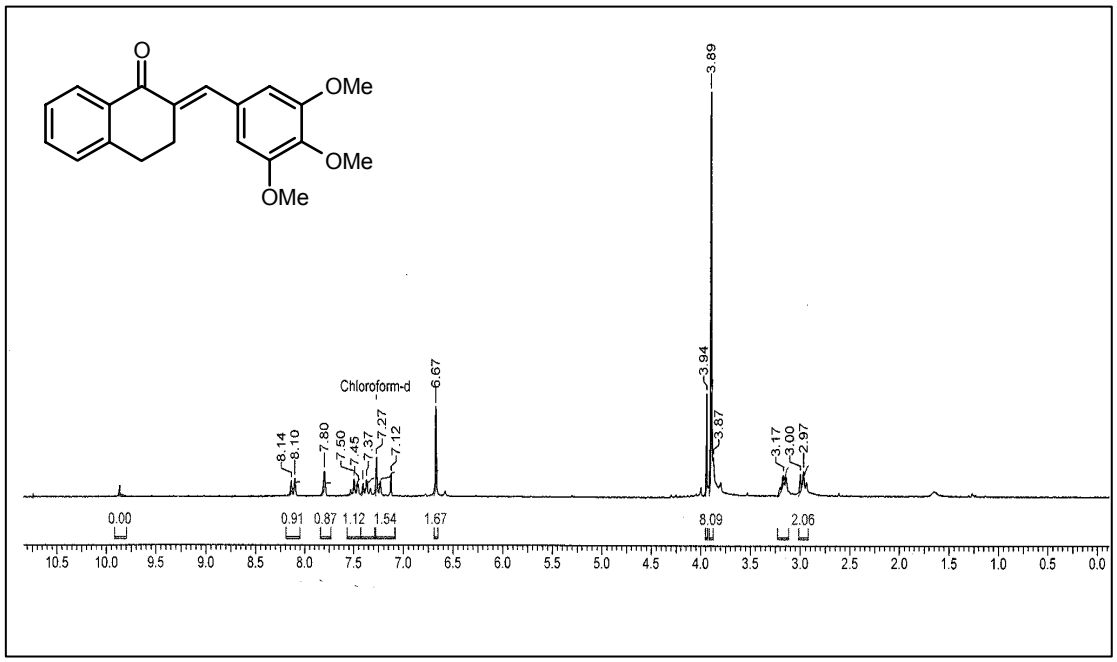
^{1}H NMR spectrum of 16j ($CDCl_3$, 200 MHz)



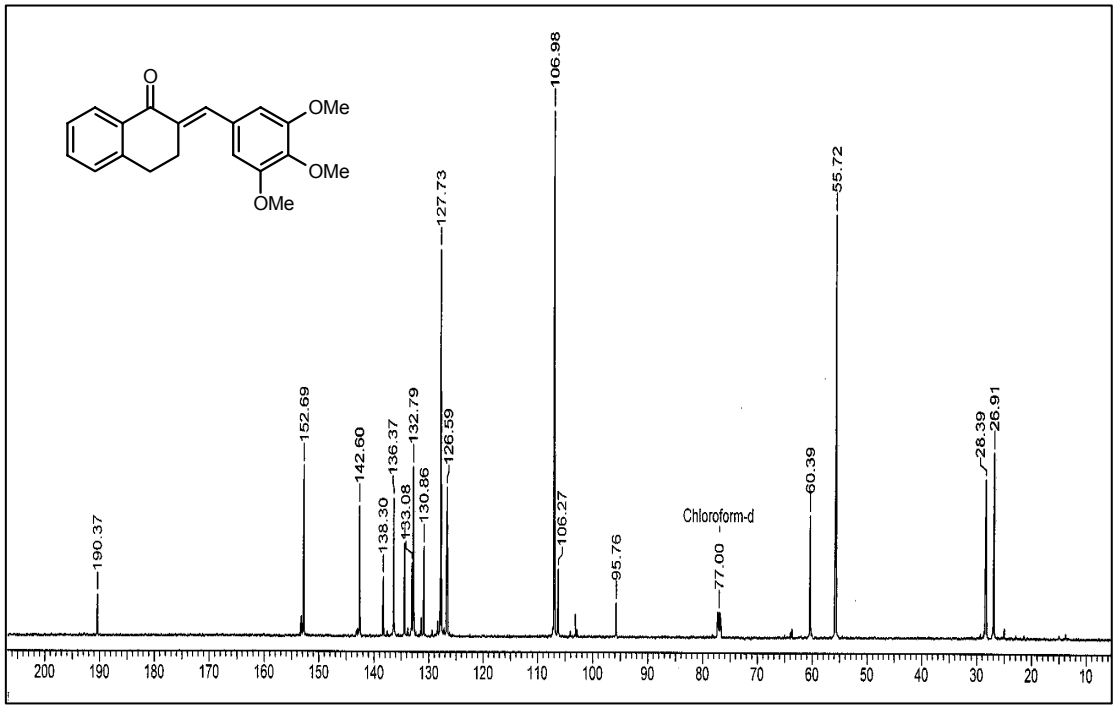
^{13}C NMR spectrum of 16j ($CDCl_3$, 50 MHz)



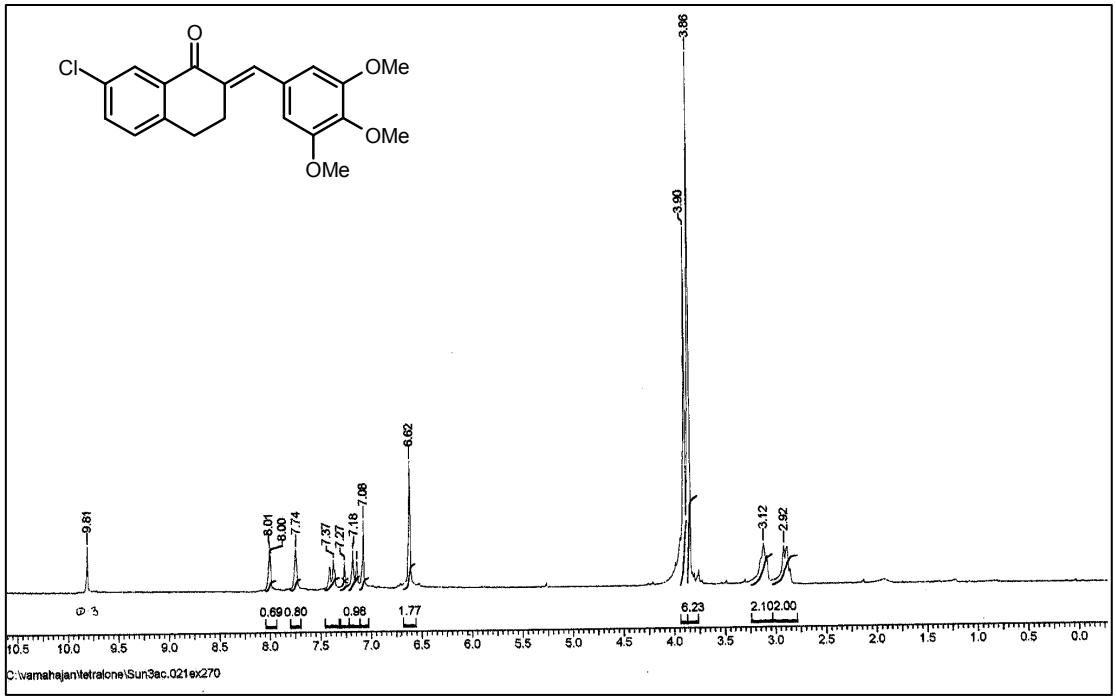
^{1}H NMR spectrum of 16l ($CDCl_3$, 200 MHz)



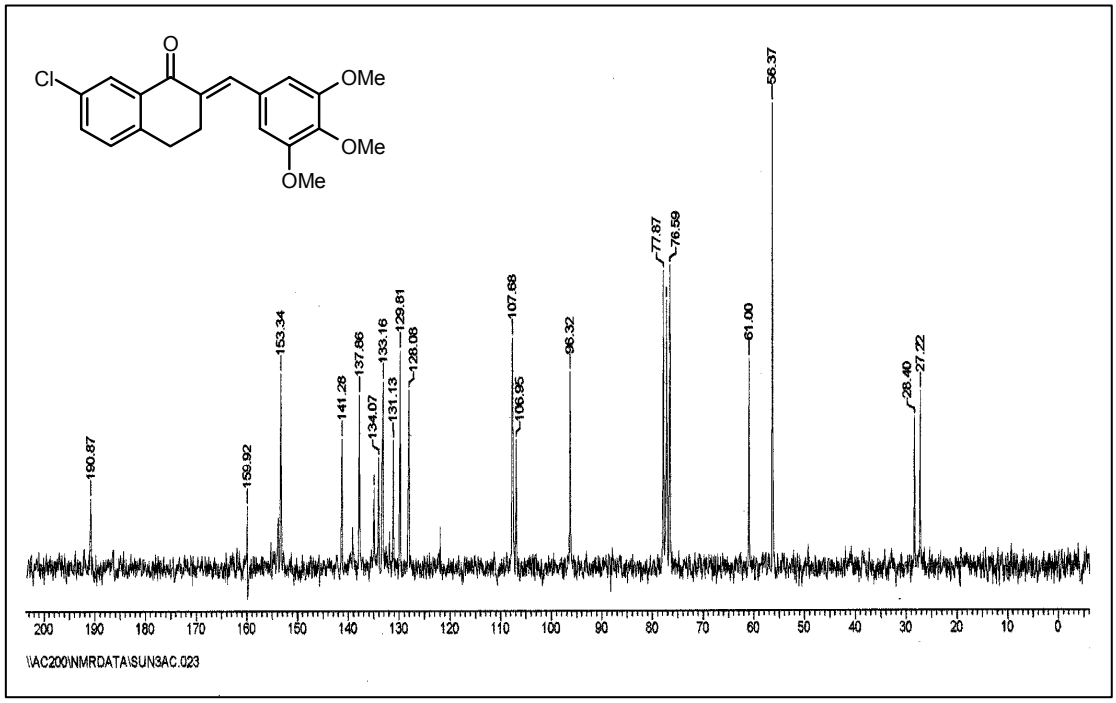
^{13}C NMR spectrum of 16l ($CDCl_3$, 50 MHz)



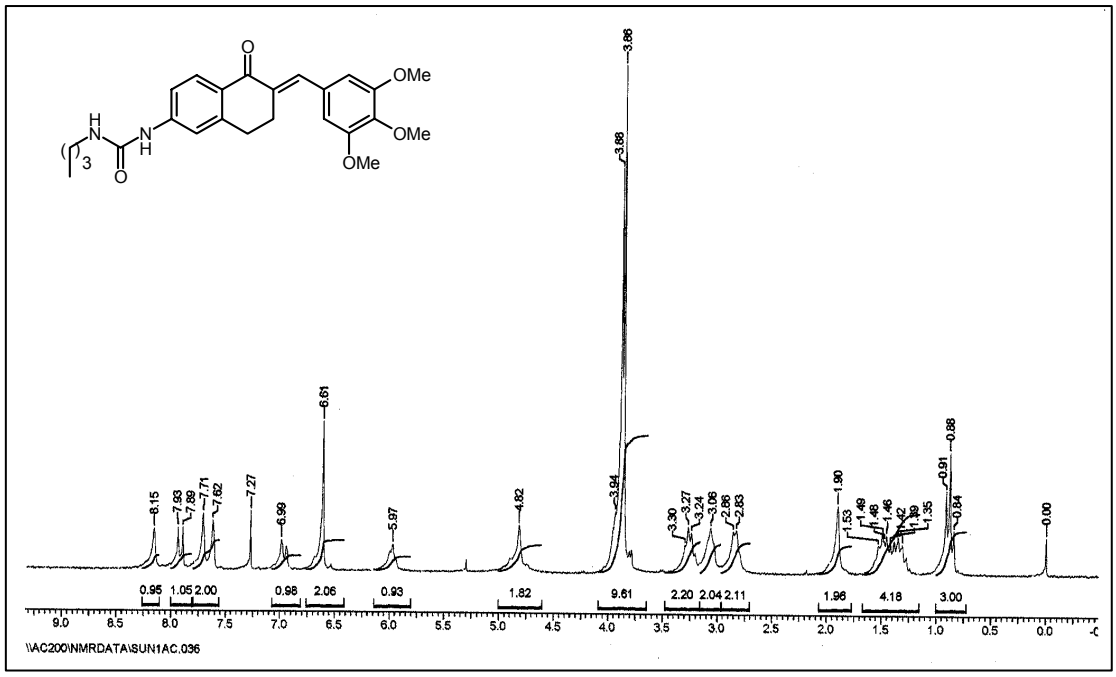
^{1}H NMR spectrum of 16v ($CDCl_3$, 200 MHz)



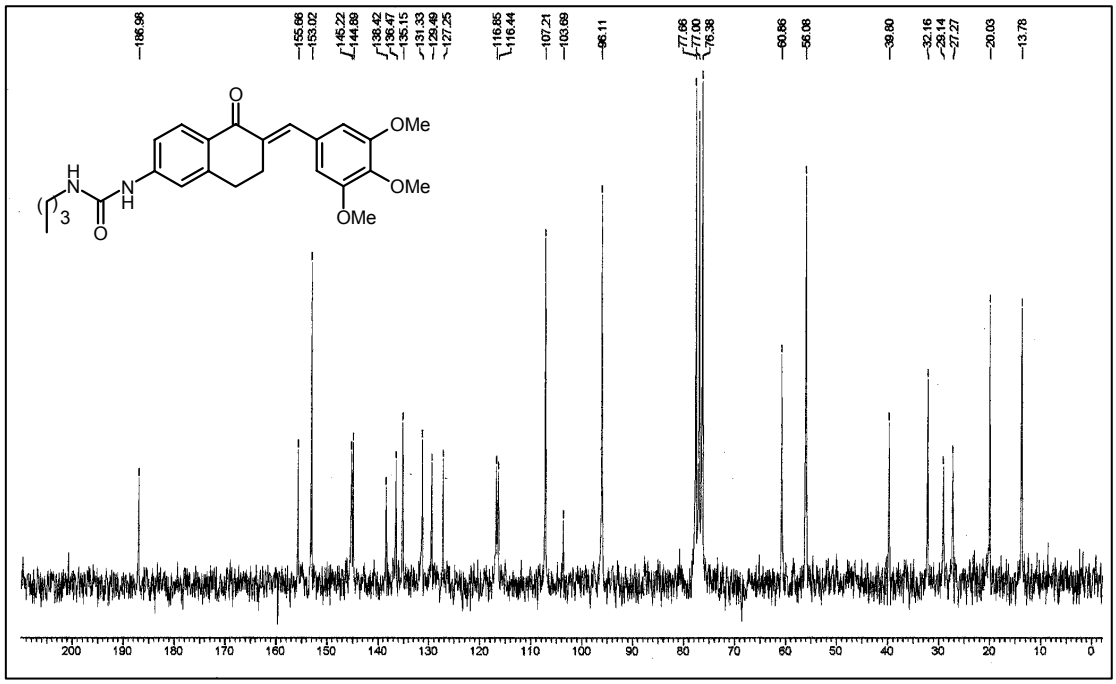
^{13}C NMR spectrum of 16v ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of 16w ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of 16w ($CDCl_3$, 50 MHz)



3.1.6. REFERENCES

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11. Dimmock, J. R.; Kumar, P.; Nazarali, A. J.; Motaganahalli, N. L.; Kowalchuk, T. P.; Beazely, M. A.; Quail, J. W.; Oloo, E. O.; Allen, T. M.; Szydlowski, J.; DeClercq, E.; Balzarini, J. *Eur. J. Med. Chem*. **2000**, *35*, 967-976.

3.2.1. INTRODUCTION

The regio and stereo controlled functionalisation of carbon–carbon double bonds abide enormous potential in organic synthesis. This area of research has been extensively studied and reviewed, as alkenes are amongst the most important starting materials accessible in much diversity and in large quantities. Iodine electrophiles for the functionalisation of alkenes have been known for a long time. A wide range of nucleophiles can be successfully used to generate a variety of different products making the activation of double bonds by iodine a reliable transformation in synthesis.[1]

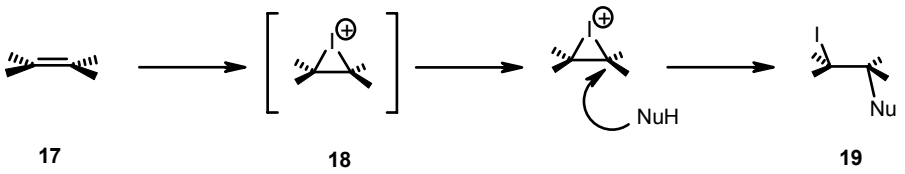
The interaction of iodine electrophiles with double bonds leads to their activation and the addition of a nucleophile in either intermolecular or intramolecular fashion results in *trans*-addition products. The regiochemistry of simple electrophilic additions is controlled by electronic factors (Markovnikov rule) and by steric factors. The factors controlling the stereochemistry will, furthermore, be dependent on whether the addition of the electrophile or the nucleophilic addition (or cyclisation) is the rate-limiting step. Most of the double bond functionalisations with iodine electrophiles result in stereospecific *anti* additions across the double bond.[2]

There are numerous ways to efficiently perform iodination of alkenes or iodocyclisations. The traditional reaction conditions, a basic solution of elemental iodine and potassium iodide are still in practice, but have also occasionally been replaced by other, more reactive sources of I^+. Oxygen is probably the nucleophile used most frequently in such reactions, but nitrogen, sulfur and carbon nucleophiles can be used as well and give admittance to a range of differentially substituted compounds.[3]

Treatment of alkenes with iodine in presence of certain nucleophilic species leads to the formation of 2-functionalised iodo-compounds such as 1,2-iodoisocyanates,[4] 1,2-halohydrins[5] and 1,2-haloacetoxy[6] compounds. The *trans*-2-functionalised iodo compounds are useful intermediates for the synthesis of epoxides,[7] *cis*-diols,[8] episulfides,[9] aziridines[10] *etc.* Vicinal iodo alkoxy alkanes in particular have been prepared by reaction of alkene with iodine and the corresponding alcohol in the presence of sulfolane.[11] Applications of these compounds are well documented in the literature.[12–15]

Iodoetherifications, where the nucleophile is an alcohol, ether or carbonyl oxygen atom, are also common and have been extensively studied and applied to a number of interesting syntheses e.g. of prostacyclin.

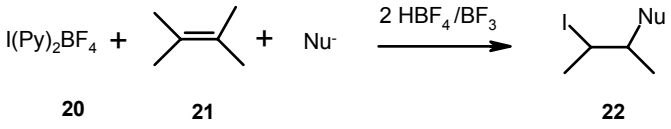
Figure 1. Iodonium ion alkene insertion



Various reagents have been applied for the title reaction and also reaction was generously applied for the synthesis of natural products and large ring skeletons. The survey of reagent and catalyst used for iodoetherification and application of the reaction has been described on the following pages.

Barluenga and coworkers reported[18] new reagent bis-(pyridine)-iodine-tetrafluroborate (**20**) [$I(Py)_2$ BF_4] for 1,2-iodofunctionalization of olefins in the presence of tetrafluoroboric acid or boron trifluoride. The versatility of protocol has been illustrated using olefins and nucleophiles as depicted in scheme 1.

Scheme 1. *Angew. Chem. Int. Ed. Engl.* **1985***, 24*, 319-320.

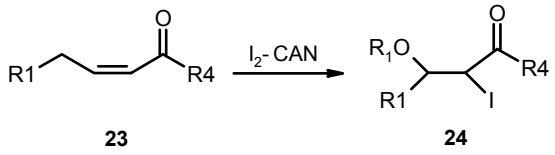


21 = Ethylene, cyclohexene, styrene

Nu^- = F, Cl, NO_2, OCN, H_2O, CH_3OH, CH_3COOH, CH_3CN, benezene, Et_3SiH

Horiuchi and coworkers reported[19] reaction of α,β-unsaturated ketones and electron deficient unsaturated ester **23** with iodine-ceric (IV) ammonium nitrate in alcohol under 50ºC and/or reflux conditions which gave the corresponding β-hydroxy-α-iodoketones **24** and esters in good yields (Scheme 2).

Scheme 2. *Chem. Lett.* **1994**, 185-188

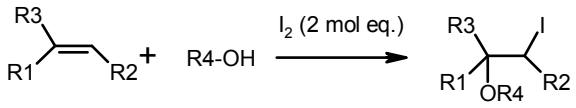


23 **24**

Solvent : MeOH, EtOH, n-PrOH, CH_3CN, H_2O

Mattos and sanverino reported[20] iododetherification of alkenes **25** using 2 mol of I_2, in alcohols (EtOH, i-PrOH, t-BuOH) or water as shown in Scheme 3.

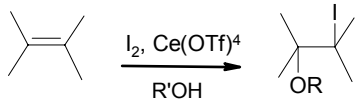
Scheme 3. *Synthesis* **1998**, 1584-1586.



25 **26**

Iranpoor and Shekarriz reported[21] regioselective 1,2-alkoxy, hydroxy and acetoxy iodination of alkenes **27** with I_2 (0.75 mol) catalyzed by cerium triflate $Ce(SO_3CF_3)_4$ (0.25 mol) at room temperature as depicted in Scheme 4.

Scheme 4. *Tetrahedron* **2000**, *56*, 5209-5211

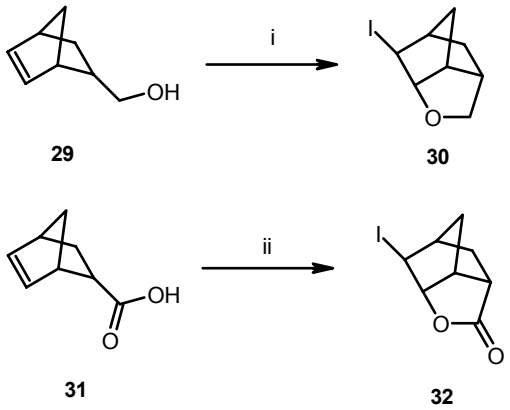


Olefins **27** **28**

Olefins = Styrene, Indene, Cyclohexene, 1-methyl cyclohexene
R' = Me, Et, *i*-Pr, Ac, H

S. P. Chavan and Sharma had developed[22] a new approach to generate the intermediate iodonium ion using NaI with $FeCl_3$ (two equivalents of each) as the reagent and the application is depicted in Scheme 5.

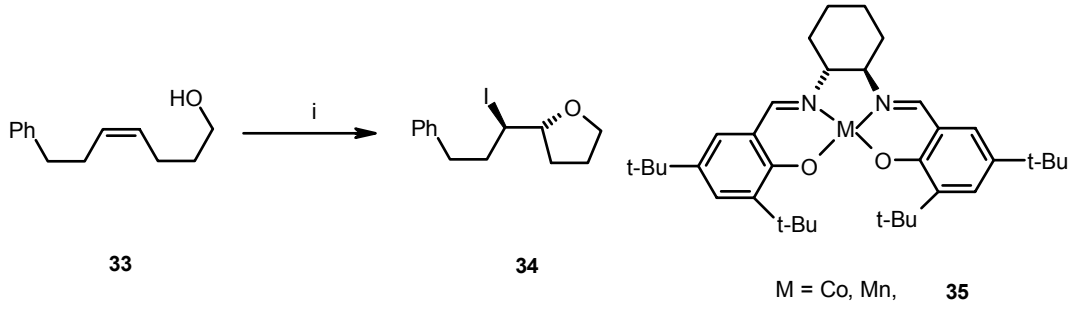
Scheme 5. *Tetrahedron Letters* **2001,** *42*, 4923–4924.



Reagents and conditions: (i) $FeCl_3$, NaI, CH_3CN, reflux, 4-6 h

Chiral salen–cobalt complexes **35**[23] were used in the enantioselective intramolecular iodoetherification of γ-hydroxy-(*Z*)-alkenes **33** to yield 2-substituted tetrahydrofurans **34**. It was found that the addition of *N*-chlorosuccinimide further increased selectivities. The choice of solvent seems to play a crucial role and reactions in toluene gave products with up to 90% *ee* as shown in Scheme 6.

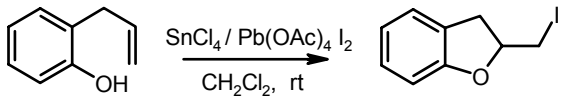
Scheme 6. *J. Am. Chem. Soc.* **2003,** 125, 15748-15749.



Reagents and conditions: (i) I_2 (1.2 eq), 35, NCS (0.75 eq), toluene, -78ºC, 20 h, 73%.

Orito and coworkers reported[24] Tin (IV) Chloride assisted iodo cyclization of 2-allyl phenol (**36**) which gave 2-iodomethyl-2,3-dihdrobenzofuran as depicted in Scheme 7.

Scheme 7. *Synthesis* **1997**, 23-25.



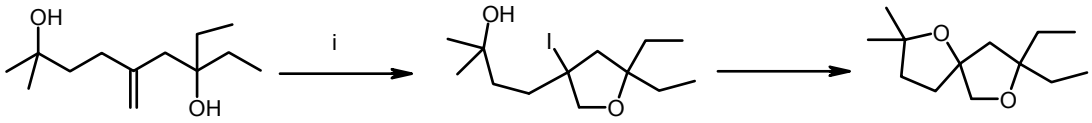
36 **37**

Applications of iodoetherification reaction

Iodoetherification reaction is widely applicable for the synthesis of natural products and unique ring skeletons. Selected representative applications are described below.

Methylidenic diol **38** in the presence of iodine and silver (I) oxide in dioxane–water, underwent double intramolecular iodoetherification[25] to give the corresponding 1,7-dioxaspiro [4.4] nonanes (**40**).

Scheme 8. *Tetrahedron Letters* **2004,** *45,* 1717–1720

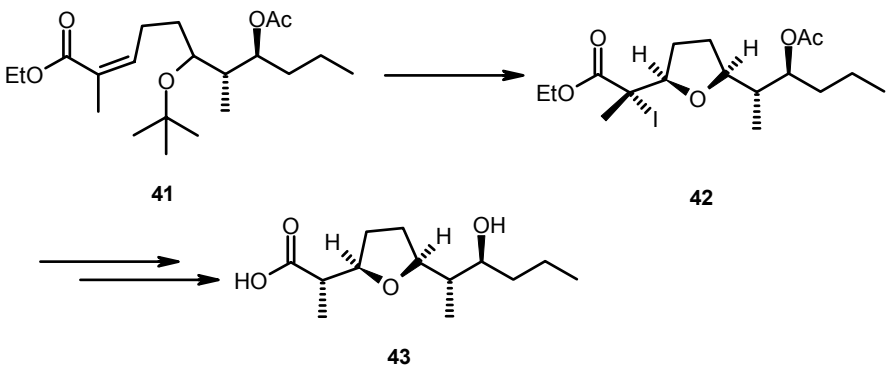


38 **39** **40**

Reagents and conditions: (i) I_2, Ag_2O, dioxane–H_2O (7:1), 20 ºC, overnight; 98%

The synthesis of the fragment of pamamycin-635A (**43**) was achieved[26] *via* a *cis*-selective iodoetherification and a stereospecific deiodination as the key steps as shown in Scheme 9.

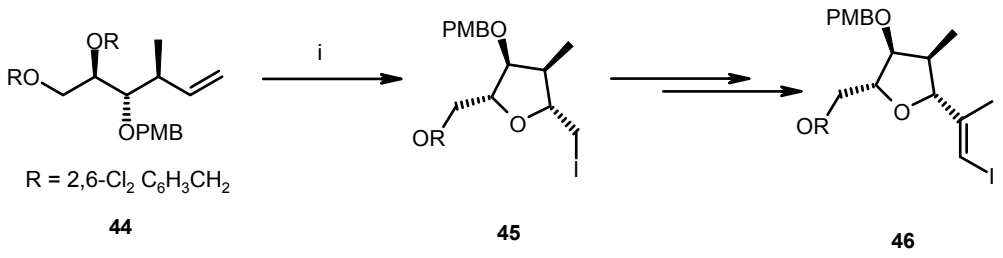
Scheme 9. *Tetrahedron* **2005**, *61*, 1061–1067.



Reagents and conditions: (i) ICl, $NaHCO_3$, CH_3CN, 20 ℃

A bis-(2,6-dichlorobenzyl) ether **44** was shown to undergo efficient and highly stereoselective intramolecular iodoetherification to yield a *cis*-2,5-disubstituted tetrahydrofuran **46** and it was transformed into a subunit suitable for incorporation into the shellfish toxin gymnodimine[27] as depicted in Scheme 10.

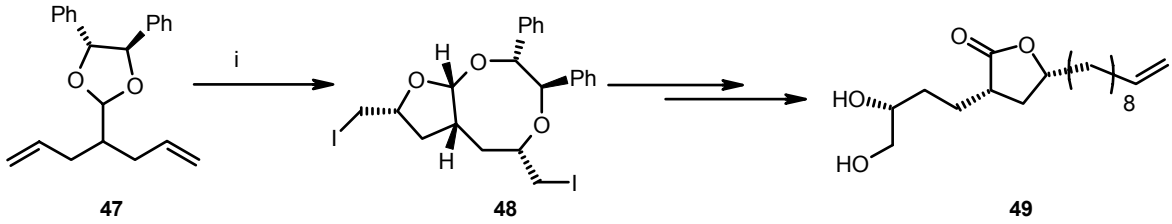
Scheme 10. *Org. Lett.* **2003,** *5*, 4109-4112.



Reagents and conditions: (i) I_2, CH_3CN, -20ºC;

Kita and coworkers reported[28] double iodoetherification of σ-symmetric diene acetals **47** (Scheme 11) in the presence of n-iodosuccinimide to afford subsequent five and eight memebered bicyclic framework **48**, which on further functional group transformations, gave naturally occurring rubenolide (**49**).

Scheme 11. *Angew. Chem. Int. Ed*. **2005**, *44*, 734 –737.



Reagents and condition: (i) NIS (2.5 eq), H_2O, CH_3CN, - 40 ºC ~ 0ºC

From the literature survey it was apparent that none of the iodoetherification was reported by heterogeneous catalytic method. Increasing demand of a new environmental legislation recommended clean technology from the chemical industries for the manufacture of fine chemicals and for their sequential chemical process.[29]

In view of cleaner processes, chemical research of catalysis has developed heterogeneous catalysts with supported inorganic reagents. These catalysts are virtually in the application of manufacture of fine chemicals and chemical intermediates. The use of such heterogeneous solid supported catalysts replaces traditional lengthy processes and ultimately reduces the pollution problems. Due to advantages of cleaner process and environmental safety, considerable growth in the research and application of heterogeneous catalysis has been reported.[30]

The heterogeneous catalysts mostly include clay, montmorillonite K10, alumina and zeolites. These materials are doped with variety of inorganic reagents by simple process to afford heterogeneous catalyst with characteristic chemical properties. These reagents are developed for the manufacture of fine chemicals and their intermediates with the aim of truly catalytic methods. Different solid supported catalysts are characterized according to their applications e. g.[31]

1. Supported fluorides
2. Supported cyanides
3. Supported oxidants
4. Supported acids

1. Supported fluorides

KF-Alumina is the well-known example of this class, which is basic in nature. It includes differents species such as AlF_4^-, AlF_6^{3-}, OH^-, O_2^-, CO_3^{2-}. These types of catalysts were used for the Aldol condensation, alkylation and Michael addition reaction.

2. Supported cyanides

The most active supported reagent for the cyanation of aromatic halide is the KCN-supported alumina; it is more reactive than KCN-Crown ether complex. CuCN doped alumina is another example of this class used for the cyanation of aliphatic and aromatic halides.

3. Solid supported oxidants

Solid supported oxidants include $KMnO_4$-silica or $K_2Cr_2O_7$ on silica. They are efficient for selective oxidization of alkyl aromatics at atmospheric pressure using air as the source of oxygen; further more reaction can be run in the absence of solvent when the substrate is liquid.

4. Supported acids

Zeolites are well known examples of this class for excellent catalytic activity, shape selectivity and ease of handling. They are widely used in vapor phase process but slow diffusion in liquid phase makes them poor catalysts. Friedel-Crafts reactions including aryl acylation, benzoylation, and sulphonation are the acid catalyzed reactions and traditional methods involve the use of $AlCl_3$, H_2SO_4, and HF as reagents, which face certain drawbacks.

Clay based material was used for such type of reactions but has certain limitations such as longer time of process and yield of the products. The 'Clayzic' overcame these difficulties; Clayzic is the catalyst prepared by doping the inorganic reagents such as $CuCl_2$, $NiCl_2$, $ZnCl_2$ montmorillonite clay and K10; these clayzics are having lewis acids properties. Among these Mont. K10-$ZnCl_2$ clayzic has been found to be remarkable catalyst for Friedel Crafts alkylation reactions.

Structure and properties of Clayzic (EPZ-10) [32]

Envirocat contract chemical introduced K10-$ZnCl_2$-Clayzic by the trade name EPZ10 prepared from Mont K10 and $ZnCl_2$. Mont K10 is the member of the bentonite family of clays. The original structure is a typical sheet structure consisting of three layers, the outer layers being SiO_4 tetrahedra, the inner AlO_6 octahedra as evident from the study done on the basis of XRD.

The preparation of EPZ-10 involves acid treatment of Mont-K10, which causes loss of sheet structure due to the progressive exchange of Al-ions for the protons. After acid treatment and doping of $ZnCl_2$ Mont-K10 loses lamellar parent structure and obtains porous structure. Exact details of acid treatment and doping of $ZnCl_2$ are not published. It was demonstrated that Mont–K10 is having Bronsted sites but no Lewis acid sites. It was found that EPZ-10 having both Bronsted- Lewis acid sites, Bronsted sites are from K10 and Zn ions behave like Lewis acid centers.

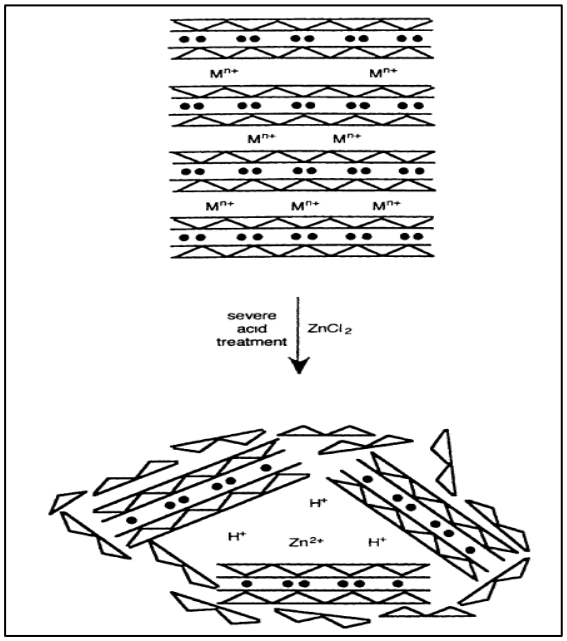


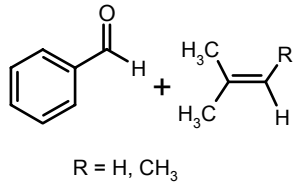
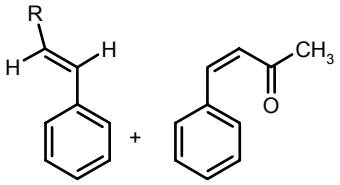
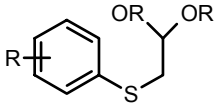
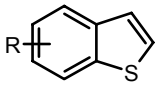
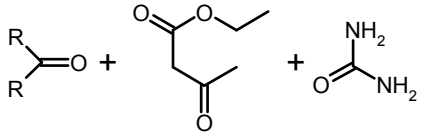
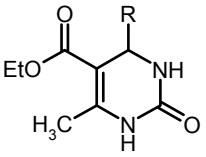
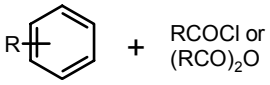
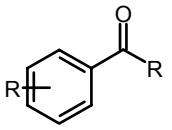
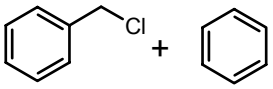
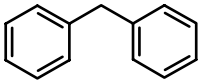
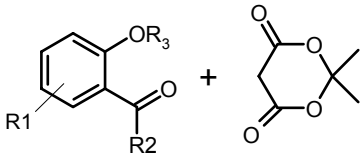
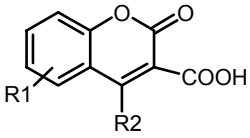
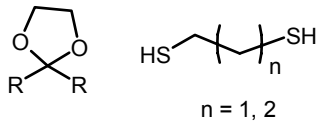
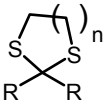
Figure 2. Schematic diagram of EPZ10 preparation

Application of EPZ-10

Catalysis of organic reaction by inorganic solid supported reagents is an important new dimension of preparative organic chemistry. These reactions are effected by the reagents immobilized on porous solid supports and have advantages over the conventional

solution phase reactions. EPZ-10 is one of the Envirocats[R] having non-toxic and reusable characteristics, due to which it represents eco-friendly green catalyst for organic transformations. EPZ-10 is a polar mesoporous catalyst featured with both Bronsted and Lewis acid sites and therefore has been exploited by research chemists as well as in industries. Some of the important applications of EPZ-10 are discussed in Table 1.

Table 1. EPZ10 catalyzed reactions

Entry	Substrates	Conditions	Product	Ref
1	 R = H, CH_3	$MeNO_2$ rt, 44h		33
2		PhCl, 132ºC		34
3		Toluene, reflux, 6 h		35
4	 RCOCl or $(RCO)_2O$	MW, 10-100 sec		36
5		rt, 15 min.		32
6	 R1=H, Cl, OMe; R2=R3= H, Me	MW, 1-7 min		37
7	 n = 1, 2	CH_2Cl_2, Reflux, 4h		38

3.2.2. PRESENT WORK

Functionalization of alkenes finds applications in the synthesis of complex natural products and in various important organic transformations. Several reagents have been used for vicinal iodo functionalization of alkenes as discussed earlier. Development of newer and environmentally preferred synthetic methodologies has gained attention from the reseach community in recent years and a lot of work is being reported in this field.

An efficient method for the regioselective synthesis of β-iodo ethers and iodohydrines from styrene, indene and dihydronaphthalene in presence of EPZ-10® has been demonstrated in the present section. Similarly, *o*-allylphenols are converted to 2-iodomethyl-2,3-dihydrobenzofurans.

3.2.3. RESULTS AND DISCUSSION

Initially we studied β-iodoetherification of styrene, wherein it was treated with 0.5 equivalent of iodine in the presence of $ZnCl_2$ in anhydrous methanol to afford the (1-Methoxy-2-iodo-ethyl)-benzene (**53a**). Simillar experiment was performed under heterogeneous reaction condition i.e. in the presence of EPZ10 in place of $ZnCl_2$, which lead to the same product. The yield of product in presence of EPZ-10 (20% w/w) was well comparable to that of product obtained in the presence of $ZnCl_2$ (0.5 eq.).

We belive that the first mechanistic step of reaction described here is the interaction between electrophile and π-system of alkyene in the presence of $ZnCl_2$ or EPZ-10 (20% w/w). In second step it was considered that iodorinium complex could be opened by the attack of nucleophile. Therefore to study the mechanistic part and to generalize the reaction conditions, reaction was performed using different solvent systems such as methanol, ethanol, isopropanol, *tert*-butanol and water, wherein these solvents could be a source of nuclophile.

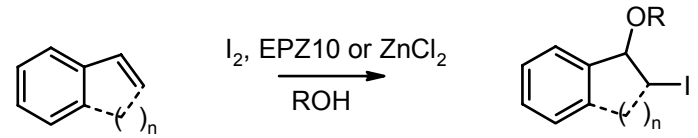
The regiochemistry of simple elctrophilic addition is controlled by Markonikov rule. The products of the reactions and their yields are mentioned in Table 2, Entry 1-5.

Consequently reactions were carried out with indene (**51**) and 1,2-dihydronaphthalene (**52**) to study the versatility of the protocol. Reactions in presence of $ZnCl_2$ or EPZ-10 gave expected products as mentioned in Table 2, Entry 6-13.

The products obtained showed satisfactory spectral data for all compounds synthesized in the presence of $ZnCl_2$ or EPZ-10.

When the reaction was carried out in dioxane with water olefins *viz*. styrene, indene and 1,2-dihydronaphthalene gave the corresponding iodohydrins (Table 2, entries 5, 9 and 13) in excellent yield. These representative examples clearly showed the efficacy of EPZ-10, which was comparable with that of $ZnCl_2$. The Markonikov addition of iodine to the olefin is probably *via* the stepwise formation of iodonium ion that is opened by regioselective nucleophilic attack (ROH or H_2O) leading to the β-iodo ethers and iodohydrins, respectively.

Scheme 12.



R = H, Me, Et, *i*-Pr, *t*-Bu
Styrene (50) n = 0
Indene (51) n = 1
1,2-Dihydronaphthalene (52) n = 2

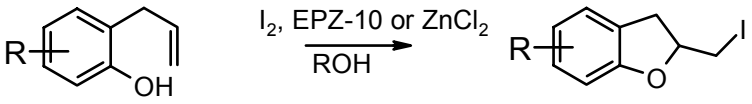
n = 0 53
n = 1 54
n = 2 55

The atom economy (of iodine) exhibited in this reaction can be explained by oxidative regeneration of iodine and hydrogen due to the dissociation of the hydriodic acid formed during the addition reaction. The study of the addition of alkoxide ions on the iodonium ion revealed that the rate of reaction is faster if conducted in methanol and ethanol than in 2-propanol. Therefore the time required for complete conversion is mentioned in Table 2 and it could briefly summarized as MeOH < EtOH < *i*-PrOH < *t*-BuOH. In order to explore the scope of this reaction we selected *o*-allylphenols to perform this reaction.

Iodo-cyclization of 2-allylphenol **56** or 2-allylcyclohexanol is reported in literature in the presence of $SnCl_4$ or $Pb(OAc)_4$ and NaI, respectively as mentioned in scheme 7.

When *o*-allylphenol (Table 2, Entry 14) was treated with iodine (0.5 equiv. in methanol) in presence of EPZ-10, 2-iodomethyl-2, 3-dihydrobenzofuran was obtained exclusively in high yield arising from intramolecular nucleophilic attack on the iodonium intermediate (Scheme 13). The generality of this transformation was substantiated by the reaction on substituted phenols and a naphthol derivative Scheme 13 (Table 2, entries 14–17).

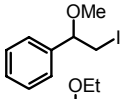
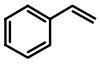
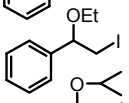
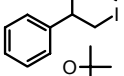
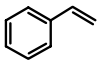
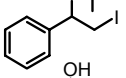
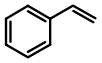
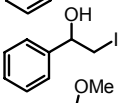
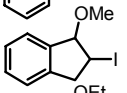
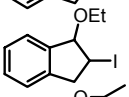
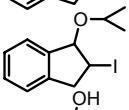
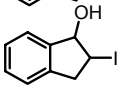
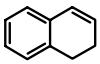
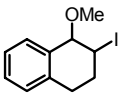
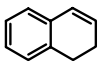
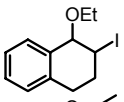
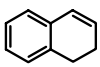
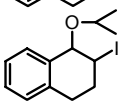
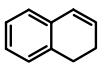
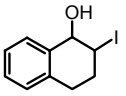
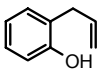
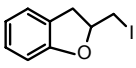
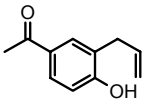
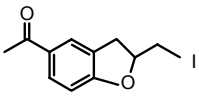
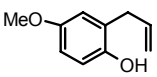
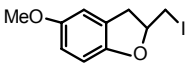
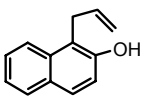
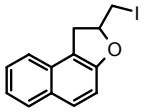
Scheme 13.



56 **57**

The same procedure was followed for the preparation of all 1,2-iodo ethers and 2-iodomethyl-2, 3-dihydrobenzofuran using EPZ-10®/ $ZnCl_2$ as listed in Table 2.

Table 2. Iodoetherification using $ZnCl_2$/ EPZ-10®

Entry No.	Substrate	Alcohol	Comp. No	Product	Time (min.)	Yield[a] %	
						$ZnCl_2$	EPZ-10
1		MeOH	**53a**		30	98	97
2		EtOH	**53b**		40	98	98
3			**53c**		50	92	95
4			**53d**		60	93	96
5		H_2O	**53e**		45	90	93
6		MeOH	**54a**		30	98	98
7		EtOH	**54 b**		40	95	97
8			**54c**		55	93	95
9		H_2O	**54 d**		45	98	97
10		MeOH	**55a**		30	98	97
11		EtOH	**55b**		30	92	94
12			**55c**		55	87	91
13		H_2O	**55d**		45	95	94
14		MeOH	**57a**		35	80	85
15		MeOH	**57b**		30	85	86
16		MeOH	**57c**		30	75	84
17		MeOH	**57d**		30	70	80

3.2.4. CONCLUSION

In conclusion, we have found that EPZ-10® serves as an efficient catalyst for preparation of β-iodoethers and iodohydrins formation in excellent yields. The potential for intramolecular nucleophilic attack leading to formation of 2-iodomethyl-2,3-dihydrobenzofuran derivatives demonstrated herein is noteworthy. The conversion is fast and the advantages of heterogeneous catalyst in terms of easy work up procedures coupled with simple operation and recyclability (7–8 times after reactivation) of the catalyst are obvious. Although the rate of reaction was more-or less the same using EPZ-10 and $ZnCl_2$ the quantity of EPZ-10 required (20% w/w) is much less than that of $ZnCl_2$ (0.5 equiv.). Moreover, since iodine is completely consumed the reaction represents an example of atom economy, which is of current interest to 'Green Chemistry'.

3.2.5. EXPERIMENTAL

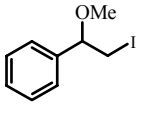
Typical procedure for the preparation of 2-iodo-1-methoxy- 2,3-dihydro-1*H*-indene 54a using EPZ-10

A mixture of EPZ-10 (20% w/w) and indene (0.5 g) was stirred in anhydrous methanol (10 ml). This was heated to reflux under an argon atmosphere for 10 min, cooled to room temperature and iodine (0.547 g, 0.5 equiv.) was added. The reaction mixture was further refluxed for 30 min. The solution was allowed to cool to room temperature, the catalyst EPZ-10 was filtered off and solvent was removed under reduced pressure. Chromatographic purification of the crude product over silica gel gave 2-iodo- 1-methoxy-2,3-dihydro-1*H*-indene as a colorless liquid (97%).

Typical procedure for the preparation of 2-iodo-1-methoxy-2,3-dihydro-1*H*-indene 54a using $ZnCl_2$

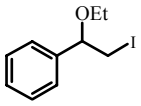
A mixture of anhydrous $ZnCl_2$ (0.293 g, 0.5 equiv.) and indene (0.5 g) was stirred in anhydrous methanol (10 ml). This was heated to reflux under an argon atmosphere for 10 min, cooled to room temperature and iodine (0.547 g, 0.5 equiv.) was added. The reaction mixture was further refluxed for 30 min. The solution was allowed to cool to room temperature and poured into ice-cold water and extracted with diethyl ether. The organic layer was separated and washed twice with water and dried over $MgSO_4$. Solvent was removed under reduced pressure and chromatographic purification over silica gel gave 2-iodo-1-methoxy- 2,3-dihydro-1*H*-indene as a colorless liquid (98%).

(1-Methoxy-2-iodo-ethyl)-benzene (53a)



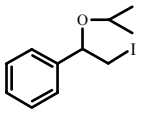
Nature: Pale yellow oil; **IR** (chloroform): *v* 3055, 2968, 1558, 1490, 1376, 1170, 1070, 762, 698 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 3.30 (s, 3H), 3.35 (d, J = 8 Hz, 2H), 4.30 (t, J = 8 Hz, 1H), 7.20-7.40 (m, 5 H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 10.2, 56.7, 83.4, 126.2 (2C), 128.4 (2C), 128.6, and 139.5; **MS**: *m/z* 262 $(M)^+$.

(1-Ethoxy-2-iodo-ethyl)-benzene (53b)



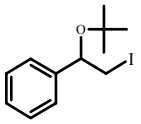
Nature: Pale yellow oil; **IR** (chloroform): *v* 2950, 2750, 1480, 1420, 1160, 1060, 900, 750, 690 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.20 (t, *J* = 8 Hz, 3H); 3.24-3.60 (m, 4H), 4.40 (d, *J* = 8 Hz, 1H), 7.20 –7.45 (m, 5 H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 11.03, 15.2, 65.0, 81.8, 126.5 (2C), 128.2, 128.6, 140.6 (2C); **MS**: *m/z* 276, 254, 231, 171, 149, 141, 135.

(2-Iodo-1-isopropoxy-ethyl)-benzene (53c)



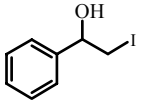
Nature: Pale yellow oil; **IR** (chloroform): *v* 3060, 2966, 2879, 1171, 1118, 1091, 1064, 763, 699 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.10 (d, *J* = 6 Hz, 3H); 1.25 (d, *J* = 6 Hz, 3H) 3.25 (d, *J* = 8 Hz, 2H), 3.50-3.55 (m, 1H), 4.50 (t, *J* = 8 Hz, 1H), 7.20 –7.45 (m, 5 H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 11.7, 21.5, 23.3, 70.5, 79.7, 126.6 (2C), 128.2, 128.7 (2C), 141.5; **MS**: *m/z* 290, 231, 171, 149, 107, 91, 77, 57.

(1-tert-Butoxy-2-iodo-ethyl)-benzene (53d)



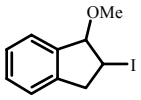
Nature: Pale yellow oil; **IR** (chloroform): *v* 2973, 1556, 1337, 1188, 1127, 1068, 699, 667 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.08 (s, 9H); 3.27 (d, *J* = 8 Hz, 2H), 4.65 (t, 1H), 7.20 –7.45 (m, 5 H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 13.5 (2C), 28.5, 31.4, 74.9, 75.7, 125.9 (2C), 127.2, 128.2 (2C), 142.3; **MS**: *m/z* 304, 107, 91, 77, 57.

2-Iodo-1-phenyl-ethanol (53e)



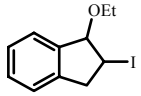
Nature: Pale yellow oil; **IR** (chloroform) *v* 2973, 1556, 1337, 1188, 1127, 1068, 699, 667 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.43 (bs, 1H), 3.27-3.45 (m, 2H), 4.65- 4.85 (m, 1H), 7.22 –7.44 (m, 5 H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 28.5, 74.9, 125.9 (2C), 127.2, 128.2 (2C), 142.3; **MS**: *m/z* 248, 231, 217, 204, 193, 141, 127; 121, 107, 91, 77.

2-Iodo-1-methoxy-indan (54a)



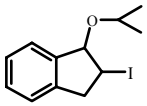
Nature: Pale yellow oil; **IR** (chloroform): *v* 2975, 1550, 1347, 1160, 1068, 699, 665 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 3.25 (dd, *J* = 16, 8 Hz, 1H), 3.50 (dd, *J* = 16, 8 Hz, 1H), 3.60(s, 3H), 4.50 (m, 1H), 5.10 (d, *J* = 8 Hz, 1H), 7.25 (m, 3H), 7.50 (m, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 25.6, 43.5, 57.5, 93.3, 124.7, 125.1, 127.1, 129.0, 140.2, 141.3; **MS**: *m/z* 274, 147, 217, 204, 193, 141, 127; 121, 107, 91, 77.

1-Ethoxy-2-iodo-indan (54b)



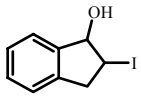
Nature: Pale yellow oil; **IR** (chloroform): *v* 2920, 2820, 1630, 1430, 1300, 1200, 1150, 880, 850 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.45 (t, *J* = 8 Hz, 3H), 3.30 (dd, *J* = 16, 8 Hz, 1H), 3.40(dd, *J* = 16, 8 Hz, 1H), 3.50-4.00 (m, 2H), 4.20-4.30 (m, 1H), 5.25 (d, *J* = 8 Hz, 1H), 7.20-7.40 (m, 3H), 7.50-7.60 (m, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 15.7, 26.5, 43.4, 65.6, 91.8, 124.5, 124.8, 127.0, 128.8, 140.7, 141.2; **MS**: *m/z* 288.

2-Iodo-1-isopropoxy-indan (54c)



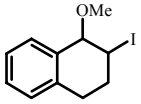
Nature: Pale yellow oil; **IR** (chloroform): *v* 2920, 2820, 1630, 1430, 1300, 1200, 1150, 880, 850 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.25 (d, *J* = 6 Hz, 6H), 3.30 (dd, *J* = 16, 8 Hz, 1H), 3.70 (dd, *J* = 16, 8 Hz, 1H), 4.00-4.20 (m, 1H), 4.30-4.45 (m, 1H), 5.25 (d, *J* = 6 Hz, 1H), 7.15- 7.45 (m, 4H); **MS**: *m/z* 302, 259, 243, 191, 175, 149, 133, 91, 77.

2-Iodo-indan-1-ol (54d)



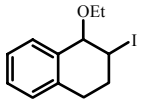
Nature: Pale yellow oil; **IR** (chloroform): *v* 3408, 3012, 2820, 1632, 1430, 680, 630 cm^{-1}; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.00 (bs, 1H), 3.35 (dd, *J* = 16, 6 Hz, 1H), 3.65 (dd, *J* = 16, 8 Hz, 1H), 4.25 (q, *J* = 8 Hz, 1H), 5.40 (d, *J* = 8 Hz, 1H), 7.25-7.40 (m, 2H), 7.41-7.55 (m, 2H); **^{13}C NMR** (50 MHz): δ 30.0, 42.3, 84.9, 96.1, 123.8, 124.2, 127.4, 128.7, 142.1.

2-Iodo-1-methoxy-1,2,3,4-tetrahydro-naphthalene (55a)



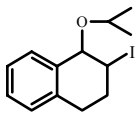
Nature: Pale yellow oil; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.62-2.20 (m, 2H), 2.45-2.72 (m, 2H), 3.80 (s, 3H), 4.10-4.15 (m, 1H), 5.05 (d, J = 8 Hz, 1H), 7.20-7.55 (m, 4H).

1-Ethoxy-2-iodo-1, 2, 3, 4-tetrahydro-naphthalene (55b)



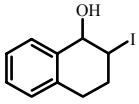
Nature: Pale yellow oil; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.25 (t, J = 6 Hz, 3H), 1.60-2.40 (m, 2H), 2.67-2.80 (m, 2H), 3.70 (q, J = 6 Hz, 2H), 4.20-4.25 (m, 1H), 4.95 (d, J = 8 Hz 1H), 6.80-7.34 (m, 4H). **MS**: *m/z* 302 (M^+), 200, 165, 129, 115, 102, 91, 77.

2-Iodo-1-isopropoxy-1, 2,3,4-tetrahydro-naphthalene (55c)



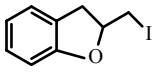
Nature: Pale yellow oil, **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.45 (d, J = 6Hz, 6H), 1.60-1.85 (m, 2H), 2.75-2.90 (m, 3H), 3.90- 3.95 (m, 1H), 4.50 (d, J = 8Hz, 1H), 6.80-7.50 (m, 4H).

2-Iodo-1,2,3,4-tetrahydro-naphthalen-1-ol (55d)



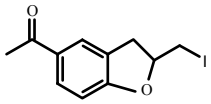
Nature: Pale yellow oil, **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 1.65-1.80 (m, 2H), 2.48-2.63 (m, 2H), 4.20-4.25 (m, 1H), 5.20 (d, J = 8 Hz, 1H), 6.78-7.35 (m, 4H).

2-Iodomethyl-2, 3-dihydro-benzofuran (57a)



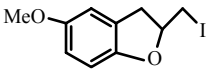
Nature: Thick oil; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 3.04 (dd, J = 16, 6.6 Hz, 1H), 3.25-3.60 (m, 3H), 4.75-5.10 (m, 1H), 6.78-7.10 (m, 2H), 7.12-7.18 (m, 2H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz): δ 8.4, 35.9, 81.4, 109.4, 120.6, 124.8, 125.0, 128.0, 159.1; **MS**: *m/z* 260, 141, 133, 105, 91, and 77.

1-(2-Iodomethyl-2, 3-dihydro-benzofuran-5-yl)-ethanone (57b)



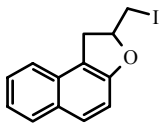
Nature: Thick oil; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.52 (s, 3H), 2.50-2.90 (m, 1H), 3.08-3.15 (m, 1H), 3.30-3.60 (m, 2H), 4.90-5.20 (m, 1H), 6.78 (d, J = 8 Hz, 1H), 7.80-7.88 (m, 2H); **MS**: *m/z* 302, 287, 176, 161, 133, 103, 91, 77.

2-Iodomethyl-5-methoxy-2,3-dihydro-benzofuran (57c)



Nature: Thick oil; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 2.80 (dd, J = 16, 8 Hz, 1H), 3.20-3.45 (m, 2H), 3.75 (s, 3H), 4.80-4.98 (m, 1H), 6.63-6.70 (m, 3H). **MS**: *m/z* 290, 260, 133, 119, 107, 91.

2-Iodomethyl-1,2-dihydro-naphtho[2,1-b]furan (57d)



Nature: Thick oil; **^{1}H NMR** ($CDCl_3$+CCl_4, 200 MHz): δ 3.14-3.60 (m, 4H), 5.00-5.20 (m, 1H), 7.20-7.50 (m, 4H), 7.78 (d, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 1H); **MS**: *m/z* 310, 210, 195, 184, 165, 155, 141, 128, 115, 105, 91, 77.

3.2.6. REFERENCES

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