NEW 2-ARYLIDENE TETRALONE, 5-HYDROXY CYCLOPENTENONE DERIVATIVES WITH POTENTIAL ANTICANCER ACTIVITY; FURANONE AND AZOLE DERIVATIVES AS ANTIFUNGAL AGENTS AND SOME ORGANIC TRANSFORMATIONS

A THESIS
SUBMITTED TO THE
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FOR THE DEGREE OF
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BY
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PUNE 411 008, INDIA

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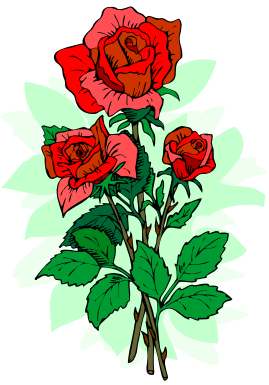
DEDICATED

TO

MY PARENTS



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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"NEW 2-ARYLIDENE TETRALONE, 5-HYDROXY CYCLOPENTENONE DERIVATIVES WITH POTENTIAL ANTICANCER ACTIVITY; FURANONE AND AZOLE DERIVATIVES AS ANTIFUNGAL AGENTS AND SOME ORGANIC TRANSFORMATIONS"** submitted by Mr. Vinod Hanmantrao Jadhav was carried out 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 November 2007

Research Supervisor

DECLARATION

I hereby declare that the work presented in the thesis entitled **"NEW 2-ARYLIDENE TETRALONE, 5-HYDROXY CYCLOPENTENONE DERIVATIVES WITH POTENTIAL ANTICANCER ACTIVITY; FURANONE AND AZOLE DERIVATIVES AS ANTIFUNGAL AGENTS AND SOME ORGANIC TRANSFORMATIONS"** 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.

Vinod H. Jadhav

Date: November 2007

Division of Organic Chemistry

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Vinod H. Jadhav

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Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
$AlCl_3$	Aluminium chloride
AIBN	2,2'-Azobisisobutyronitrile
B. P.	Boiling point
$BF_3.OEt_2$	Borontrifluoride diethyl etherate
b	Broad (signal)
Boc	*tert* – butyloxycarbonyl
COSY	2D-Correlation spectroscopy
$CDCl_3$	Deuterated chloroform
d	Doublet
DIBAL	Diisobutyl aluminium hydride
DMAP	*N, N*'-Dimethylaminopyridine
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-D_6	Duterated dimethyl sulfoxide
EDC	Ethylene dichloride
ee	Enantiomeric excess
g	Grams
GC	Gas chromatography
h	Hours
HMPA	Hexamethyl phosphoric triamide
IR	Infra red
LDA	Lithium diisopropylamide
m	Multiplet
M. p.	Melting point
M^+	Molecular ion
mg	Milligrams
min	Minutes
ml	Millilitre
mmol	Millimole
n-BuLi	*n*-Butyllithium
Na_2SO_4	Sodium sulfate
NBS	*N*-Bromosuccinimide
NOESY	Two dimensional nuclear overhauser spectroscopy
NMR	Nuclear Magnetic Resonance
$Pd(dba)_2$	Palladium di-benzylidine acetone
PPTS	Pyridinium *p*-toluenesulfonate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
q	Quartet
r. t.	Room temperature
s	Singlet
t	Triplet
TBAF	Tetrabutylammonium fluoride

THF	Tetrahydrofuran
$TiCl_4$	Titanium (IV) chloride
TBDMS	*tert*-Butyldimethyl silyl
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
$ZnCl_2$	Zinc chloride

General remarks

1. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware.
2. Progress of the reaction was monitored by TLC and was visualized by UV absorption by florescence quenching or I_2 staining or by both.
3. Solvents for anhydrous reactions were dried by standard procedures. All organic layers obtained after extractions were dried over anhydrous Na_2SO_4. All evaporations were carried out under reduced pressure on Buchi or Heidolph rotary evaporator. Silica gel for column chromatography was 60-120 mesh.
4. Optical measurements were recorded on a JASCO digital polarimeter.
5. All the temperatures are in ^{0}C. All the melting points and boiling points are in ^{0}C and are uncorrected. Melting points were recorded on Buchi B-540 melting point apparatus.
6. IR spectra were recorded on a Perkin-Elmer infra-red spectrometer model 599-B and model 1620 FT-IR (ν-max in cm^{-1}).
7. Unless otherwise stated, ^{1}H-NMR spectra were recorded using TMS as internal reference on Bruker AC-200, MSL-300 and 500 instruments using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million downfield from TMS. The coupling constants (J values) are reported in Hertz.
8. ^{13}C-NMR spectra were recorded on Bruker AC-200, MSL-300 or 500 instruments operating at 50 MHz, 75 MHz and 125 MHz respectively.
9. Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.
10. GC analysis was carried out on Hewlett Packard 5890; unless otherwise stated.
11. Microanalysis was carried out in the microanalytical section of NCL.
12. The compound numbers, scheme numbers and references given in each chapter refer to that particular chapter only.

Thesis Abstract

Thesis Title

"New 2-Arylidene Tetralone, 5-Hydroxy Cyclopentenone Derivatives with Potential Anticancer Activity; Furanone and Azole Derivatives as Antifungal Agents and Some Organic Transformations"

Thesis is divided into three chapters

CHAPTER-1: New 2-Arylidene Tetralone and 5-Hydroxy Cyclopentenone Derivatives With Potential Anticancer Activity.
CHAPTER-2: Synthesis of Furanone and Azole Derivatives as Antifungal Agents.
CHAPTER-3: Some Useful Organic Transformations.

CHAPTER-1: New 2-Arylidene Tetralone and 5-Hydroxy Cyclopentenone Derivatives With Potential Anticancer Activity.

Modern combinatorial chemistry[1] allows the synthesis of millions of new compounds in a relatively short time. These libraries can be evaluated for their biological activity using high-throughput screening (HTS) techniques.[2] However, the success of such purely random approaches has been not very pronounced, which may especially be due to the lack of new chemical entities (NCEs) with high diversity. Bearing this in mind the next logical step seems to be to profit from Nature's structural diversity by combining two or more natural products to form a hybrid[3]. Nature employs such a strategy; for example, in the case of vitamin E, the terpenoid phytyl chain interacts with the cell membrane and the phenol moiety derived from shikimic acid forms a radical trap. Artificial natural product hybrids have not yet been used as drugs, as this idea is quite new, but several novel compounds of this type developed in the recent years show promising biological activity.
This chapter, further divided in to three sections, summarizes the synthesis of new chemical entities, which were designed as hybrids of two parent molecules exhibiting good cytotoxicity. The parent molecules used here for designing the NCEs are the

combretastatin A-4 and 2-arylidene tetralones. We developed two synthetic approaches for the synthesis of NCEs (fig. 1) as described in first section of this chapter. We have also synthesized some new analogues of CA-4 using the QSAR study as a continuation of previous research work in our group.[4] The chiral separation of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one using chromatographic technique was successfully completed and described in second section of this chapter.

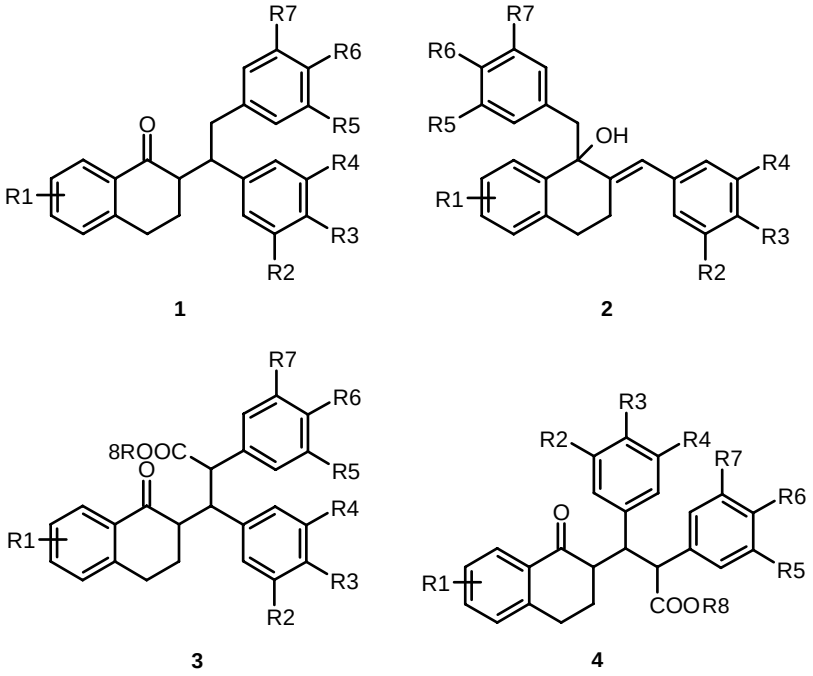


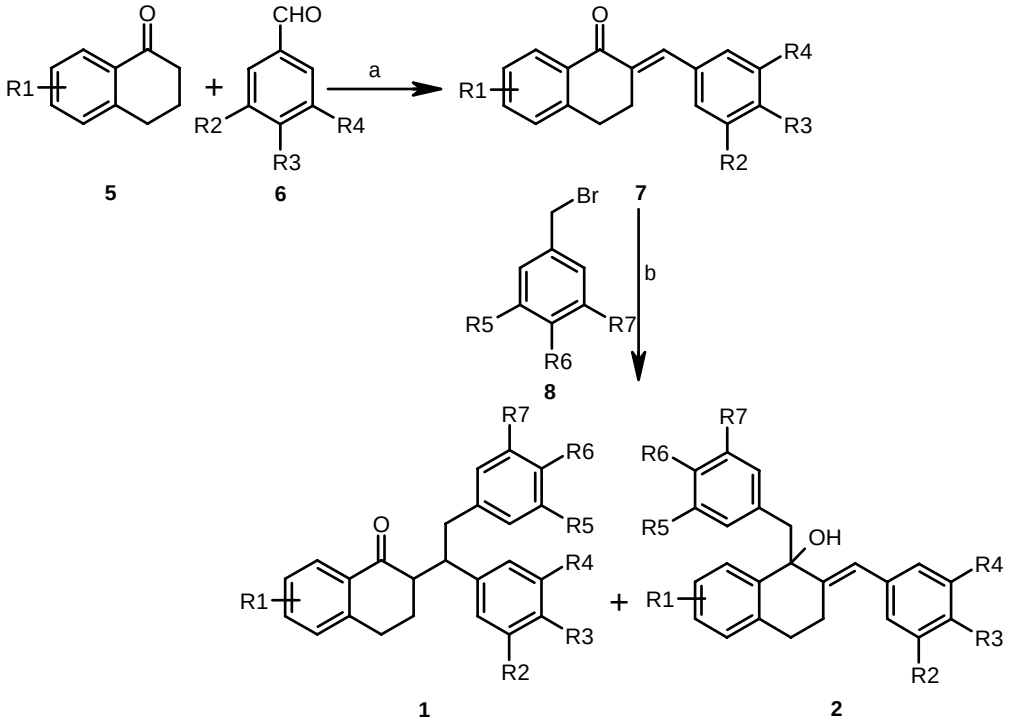
Fig. 1 New Chemical Entities

SECTION-I: New 2-Arylidene Tetralone Derivatives

PART-A: Mg Mediated 1,2 and 1,4-Addition Products

Synthesis of hybrid molecules to generate biologically active new chemical entities has been one of the well-adapted techniques under new drug discovery research programmes[1]. Structural hybrid compounds are usually designed by selecting at least two biologically active small molecules. We have synthesized the new chemical entities

from substituted 2-arylidene tetralones (**7**) and substituted benzyl bromides (**8**) as starting materials. The 2-arylidene tetralone was treated with substituted benzyl bromides in presence of magnesium metal in dry tetrahydrofuran and the resultant products were identified as 1, 2 and 1, 4-addition products. In order to elaborately study the scope and limitations of the above mentioned reactions, several aldehydes and benzyl bromides were subjected to the sequence as shown in scheme-1. In this approach we obtained the 1, 4-addition product as the major and 1, 2-addition product as the minor component. Consequently, a library of 32 NCEs was generated.

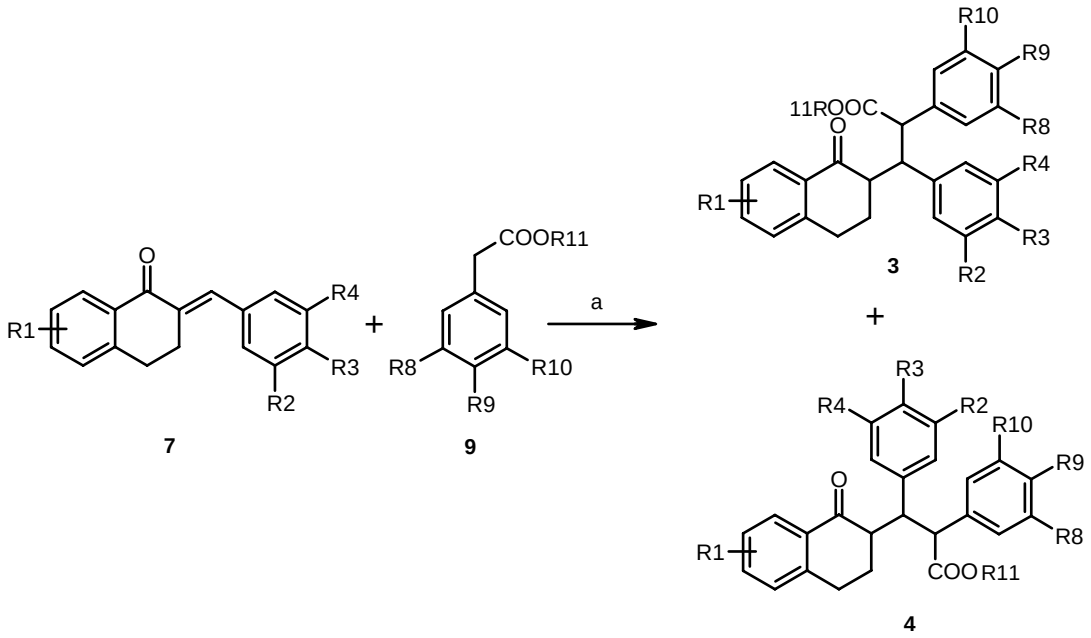


Reagents and Conditions: a) NaOH, EtOH, r t, 12 h b) Mg, THF, r t, 3 h

Scheme - 1

PART-B: Selective 1,4-Addition Products:

In first part of this section we synthesized some new hybrid molecules for screening as cytotoxic agents. In continuation, we synthesized some NCEs using LDA instead of Mg when benzyl halides were replaced by esters of substituted phenyl acetic acid **9**, as discussed in the part-I. Schematic presentation in scheme-2 highlights the mixture of diastereoisomers and regeoisomers (**3** and **4**) obtained by this route.



Reagents and Conditions: a = LDA, THF, HMPA, -78 ^{0}C, 4h.

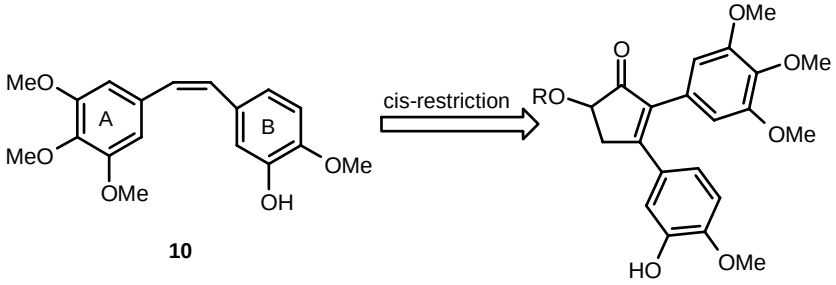
Scheme - 2

The anion generated by LDA in the active methylene of the phenylacetic acid ester (**9**) prefers to produce 1, 4-addition products rather than the 1, 2-addition products when treated with arylidene tetralones (**7**). This reaction consistently yielded a mixture of two compounds which were charcterised by spectroscopic methods and supported by X-ray crystallography. The results of the biological activity of both the isomers obtained in these reactions have been described in the third section of this chapter.

SECTION-II: New 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one derivatives with potential anticancer activity:

PART-A: New 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one derivatives:

Considering the structure activity relationship study of CA-4 (**10**) 3, 4, 5-trimethoxy substitutent on A- ring and 4-OMe group on B-ring of CA-4 are essential for cytotoxic activity.[5,6] We introduced 5-hydroxycyclopentenone ring in place of olefinic double bond between two aryl rings, keeping 3, 4, 5-trimethoxy substituents on A ring to obtain compounds with pharmaceutically acceptable properties and improved antitumor activity. We have attached the aminoacid chain to the 5-hydroxy group in cyclopentenone ring (**11**).

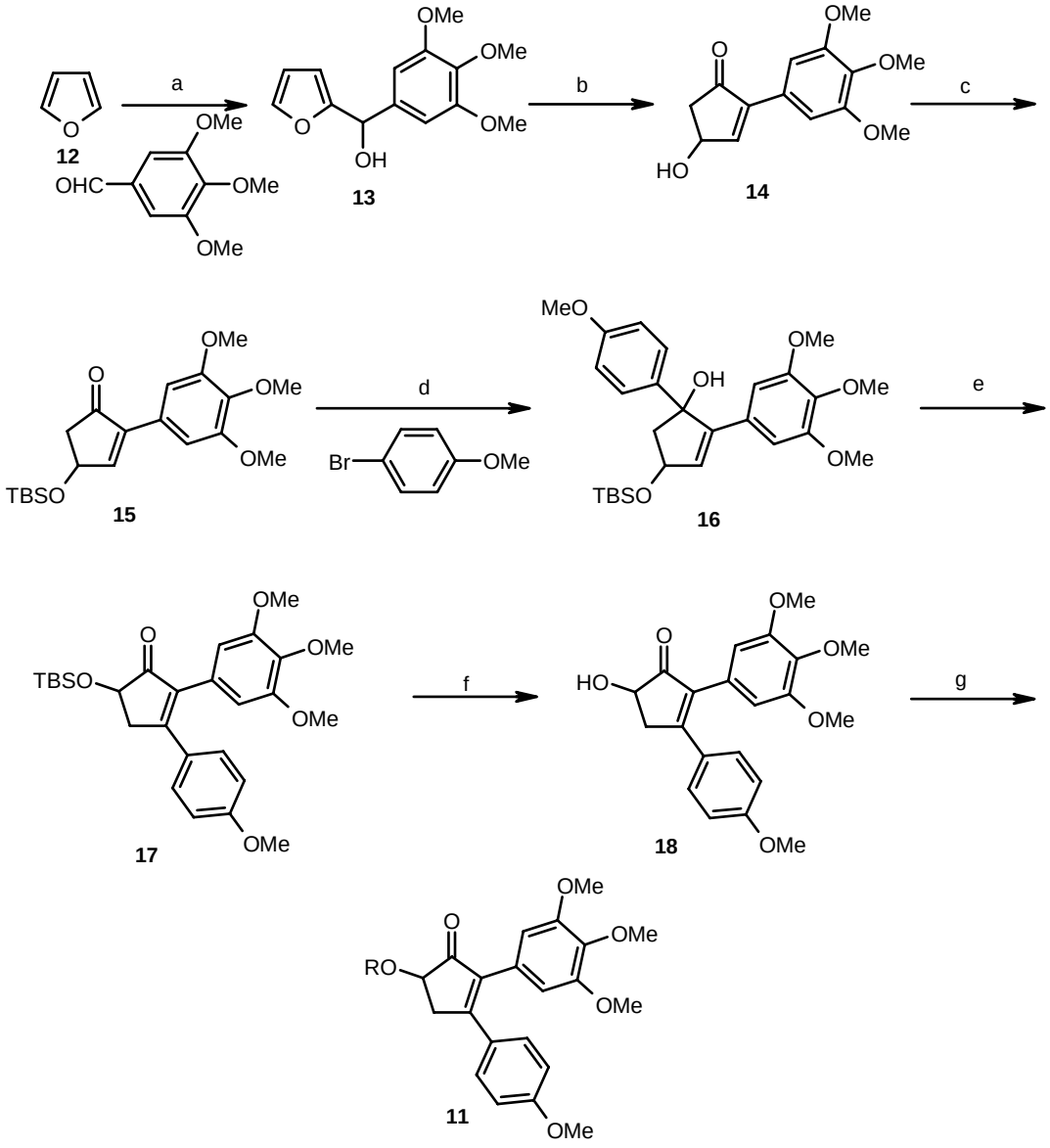


10

R = amino acids

11

We have synthesized 2,3-diaryl -5-hydroxycyclopenten-2-en-1-one analogues keeping 3,4,5-trimethoxy substituent on A ring and methoxy group on B-ring. We have synthesized the intermediate 2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one (**18**) which was important intermediate for the synthesis of various analogues of CA-4. The intermediate **18** was prepared from 3,4,5-trimethoxy benzaldehyde as shown in scheme-3. Reaction of furyl magnesium bromide with 3,4,5-trimethoxybenzaldehyde gave the 2-furyl (3,4,5-trimethoxy) phenyl methanol (**13**) which on rearrangement with $ZnCl_2$ in dioxane/water gave the intermediate **14** in excellent yield. The hydroxyl group was protected as *tert*-butyldimethylsilyl ether to give the intermediate **15**.



Reagents and conditions: a) i) n-BuLi, THF ii) $MgBr_2$, THF, -30 ^{0}C, 4 h, 93 % b) $ZnCl_2$, dioxan/water, reflux, 24 h, 90 % c) TBDMS-Cl, DMAP, DCM, Et_3N, 3 h, 74 % d) Mg, THF, 0 ^{0}C-rt, 2 h, 72 % e) PDC (2 eq.), DCM, r t, 12 h, 46 % f) CH_3COOH-THF-H_2O (3:1:1), 50 ^{0}C, 20 h, 84 % g) amino acids, EDCI, DCM, 0 0C - rt, 7 h.

Scheme - 3

The addition of Grignard reagent or organolithium reagents in tetrahydrofuran prepared from 4-methoxy bromobenzene to intermediate **15** afforded the corresponding 1,2-addition product **16** in good to excellent yields. Further treatment of cyclopentenol **16** with pyridinium dichromate (2-3 equivalents) in dichloromethane at 0 ^{0}C to room temperature afforded the corresponding intermediate **17.** The deprotection of TBS group in intermediate **17** gave the alcohol **18** in good yield, which was further treated with different amino acids to achieve the final products **11**, thus providing 10 NCEs of this class of compounds

PART-B: Resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) - cyclopent-2-en-1-one and its derivative:

The importance of obtaining optically pure materials hardly requires restatement. Manufacture of chemical products applied either for the promotion of human health or to combat pests that otherwise adversely impact on the human food supply is now increasingly concerned with the enantiopurity. A large proportion of such products contain at least one chiral center. To show importance of single-enantiomer drugs, Sujan Ba, Director of Chiral Chemistry Consulting Services at the consulting firm Technology Catalyst International (TCI) measured their appearance among the top-selling drugs. Of the top 100 drugs world wide, 50 are single enantiomers.

The alcohol **18** from the part - A of this section was selected for resolution using chiral HPLC method. We have developed a method of resolution of alcohol **18** by using analytical chiral HPLC method, in which we have separated both the *R*-enantiomer and *S*-enantiomer. The analytical method was developed for alcohol **18** on CHIRALCEL OD-RH column. The enantiomer eluted first (RT 10.4 min) showed rotation $[\alpha]^{25}_D$ + 21.33^0 (c 0.55, $CHCl_3$) while the one, which eluted later (RT 11.1 min), had rotation $[\alpha]^{25}_D$ - 21.26^0 (c 0.55, $CHCl_3$). On the basis of optical rotation observed, the two enantiomers were identified as **18a** and **18b** (fig. 2) respectively by direct comparison with the reported values.[7]

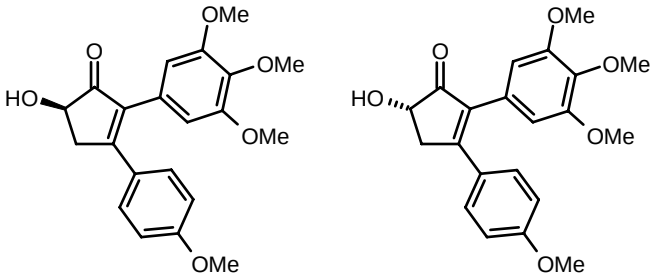
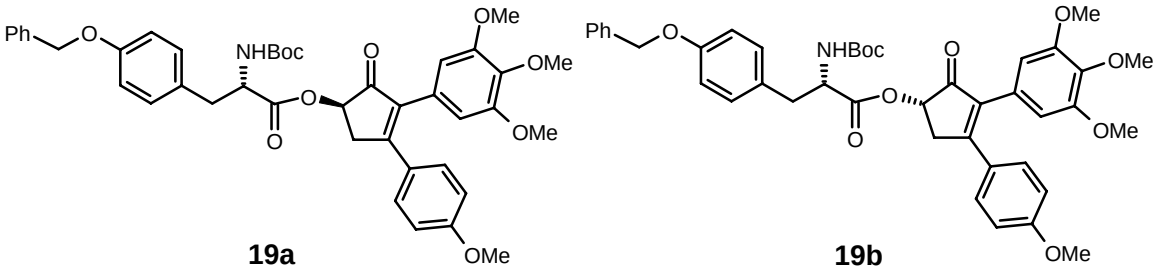


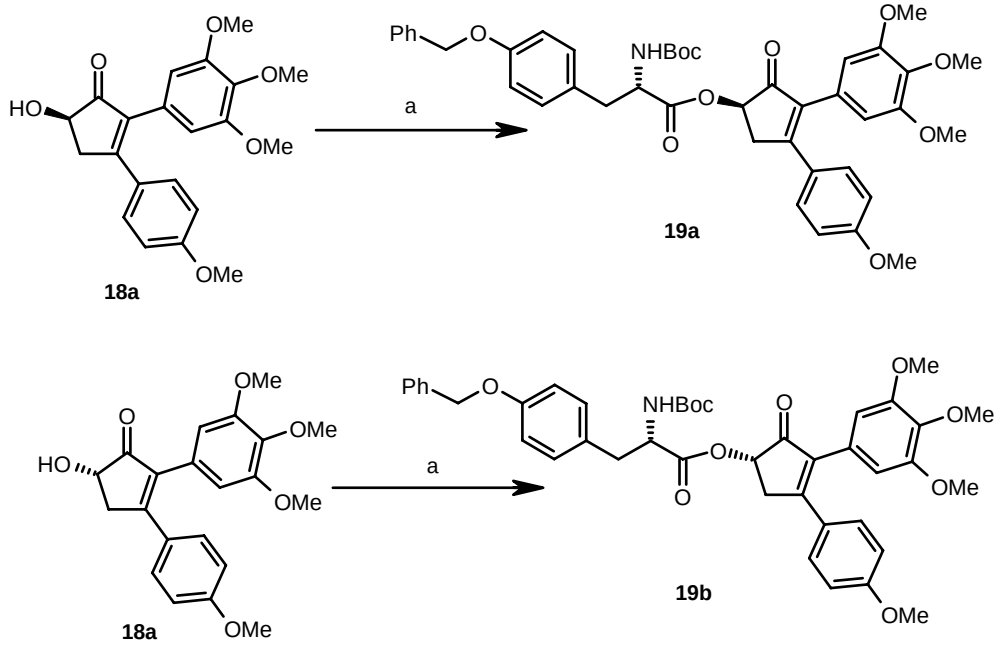
Fig. 2

We also developed a novel resolution method for the alcohol **18** by using the Boc protected-O-benzyl tyrosine. We synthesized the ester of alcohol **18** by treatment with Boc-O-benzyl protected tyrosine in presence of EDCI in dry DCM. The mixture of diastereoisomers of **19** (scheme - 4) was separated by column chromatography on silica gel using petroleum ether and ethyl acetate as an eluent, to collect the *R*-isomer **19a** and *S*-isomers **19b**.



Scheme - 4

The diastereoisomers **19a** and **19b** were identified by direct comparison with the ester formed by using the enantiomers **18a** and **18b**. The HPLC technique fully supported our conclusion.



Reagents and Conditions: a) Boc protected-O-benzyl tyrosine, dry DCM, EDCI, 0 ^{0}C-rt, 7 h.

Scheme - 5

SECTION-III: Biological Activity of Designed NCE's as Anticancer Agents

The synthesized new chemical entities (NCEs) from section - I and II were tested for cytotoxicity against cancer cell lines. Out of 56 NCEs submitted for screening 34 NCEs were actually tested for cytotoxicity by plate assay method. A three day MTT cytotoxicity assay was performed and some of the NCEs synthesized as described in section I and II displayed cytotoxic activity comparable with combretastatin A-4.

The biological activity study of amino acid esters of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (described in section - II, Part - A) indicated that these derivatives retained the potential anticancer activity of the selected lead molecule **18**. Some of the derivatives showed enhanced activity probably due to higher solubility and biocompatibility.

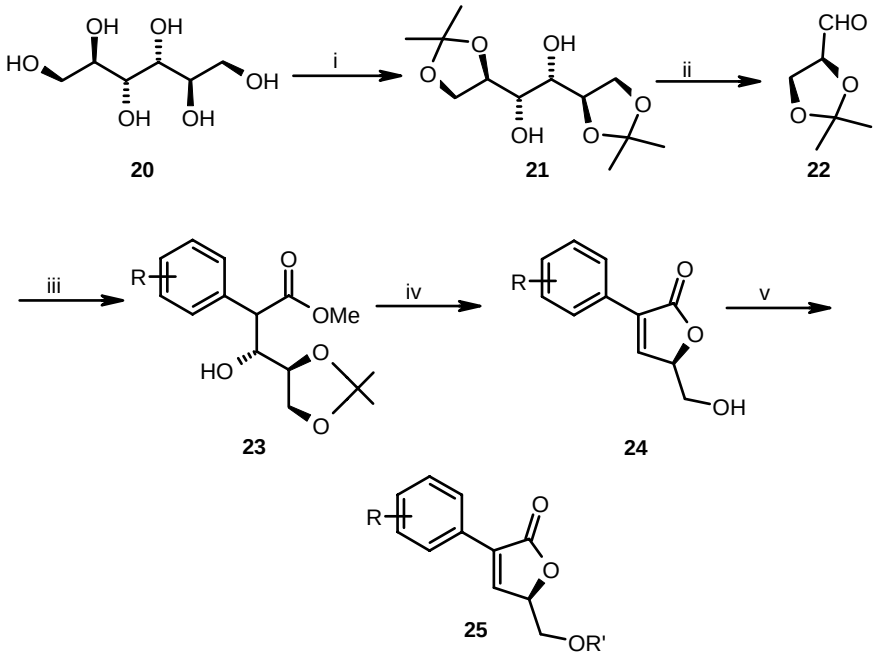
CHAPTER-2: Synthesis of Furanone and Azole Derivatives as Antifungal Agents

Fungal infections in human range from the superficial and common, such as dermatophytoses and oncomycoses, to deeply invasive and disseminated, such as candidiasis and aspergillosis. In the past 20 years the frequency of systemic fungal infections have increased dramatically along with the number of invasive, mostly opportunistic species. The main factor for the increase is the proliferation of severely immunocompromised patients either with AIDS, undergoing cancer chemotherapy or immunosuppressive therapy for organ transplantation. The higher incidence of several fungal infections that was noted in the late 1940's with an advent of anti-bacterial agents first and steroid therapy later, continue to increase throughout ensuing decades. We have synthesized some furanone derivatives and azole derivatives as new antifungal agents. This chapter summarizes the synthesis of furanone and azole derivatives and their antifungal activity.

SECTION-I: Design and synthesis of furanone derivatives as antifungal agents

Furanones are important constituents of natural products[8] and useful synthetic intermediates[9] which have recently received much attention as synthetic targets[10]. Functionalized furanones are important subunits present in a large variety of natural products and biologically active compounds such as alkaloids,[11] lignan lactones[12] and sex attractant insect pheromones.[13] Many of these compounds exhibit a variety of properties including antifungal and anticancer, insecticidal, antibacterial, phytotoxic, or anti-inflammatory activities; some of them are antibiotics, cyclooxygenase or phospholipase A2 inhibitors.

In our approach for the synthesis of furanone derivatives we have used the commercially available mannitol (**20**) as starting material which on diacetonide protection gave the intermediate **21**. The acetonide of Garners aldehyde (**22**) obtained from intermediate **21** was treated with methyl phenylacetates in presence of LDA to get the intermediate **23** which was converted to the furanones **24** in a single step as shown in scheme-6. Further esterification of **24** with different carboxylic acids produced 27 NCEs as this class of compound (scheme-6). The synthesized derivatives were screened for antifungal activity which has been discussed in the third part of this chapter.



Reagents and Conditions: i) 2, 2-Dimethoxy propane, *p*-TSA, dry DMSO, rt, 48 h ii) $NaIO_4$, MeOH, H_2O, rt, 2 h iii) Ester of substituted phenyl acetic acid, LDA, THF, HMPA, -78 ^{0}C, 4 h iv) *p*-TSA, MeOH, 45 ^{0}C, 48 h v) depending upon the R'COCl, base.

Scheme - 6

SECTION-II: Synthesis of azole derivatives as antifungal agents

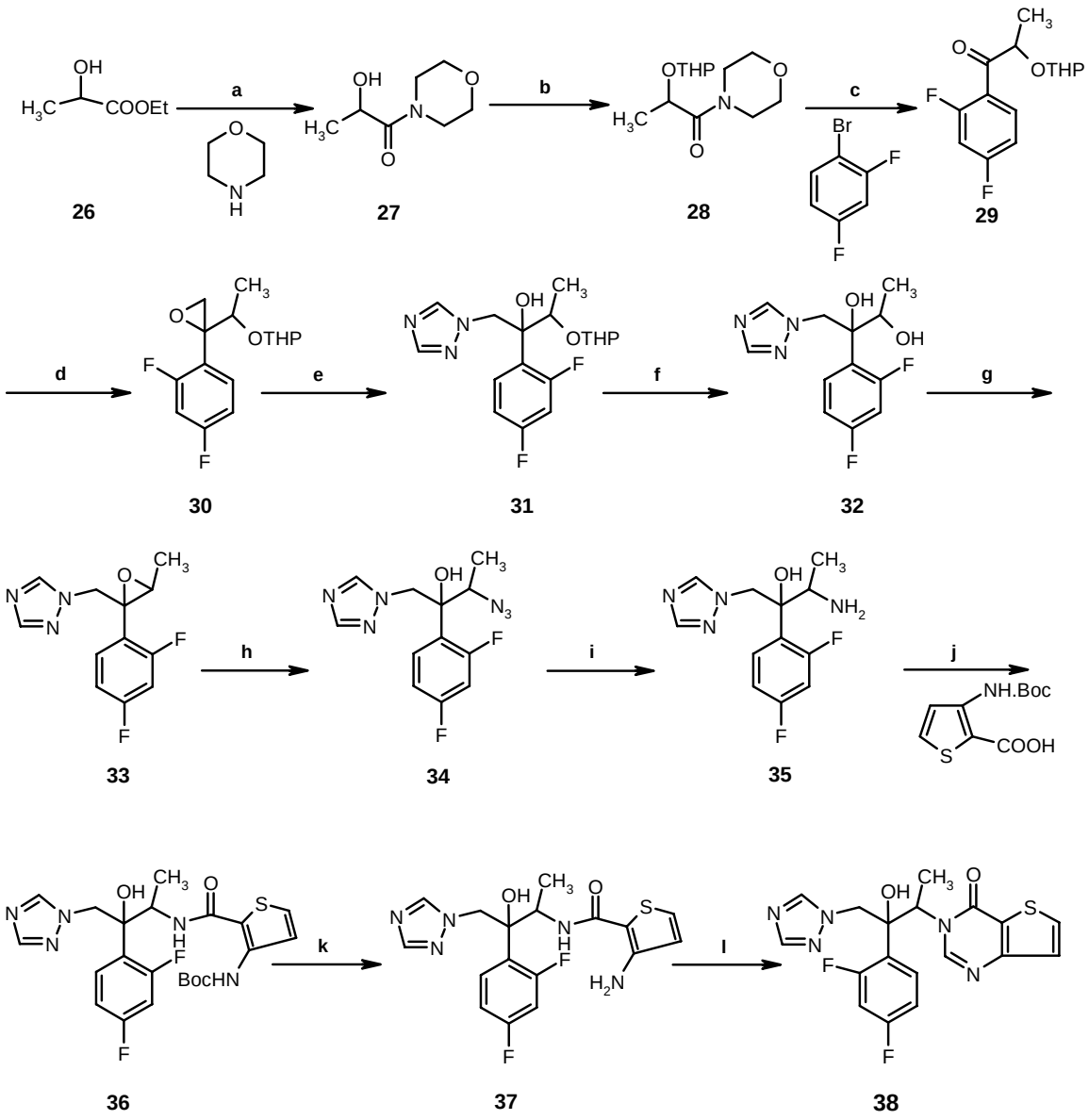
The azole antifungals, discovered in the late 1960s are totally synthetic and are most rapidly expanding group of antifungal agents.[14,15] They are classified as imidazoles or triazoles on the basis of whether they have two or three nitrogen atoms in the 5-

membered azole ring. Systemic azoles have fungistatic, broad spectrum activity that includes most yeasts and filamentous fungi and some emerging pathogens such as Trichosporon species. Due to the immunity developed by the pathogens towards the azoles, development of newer analogues is a continued search for scientists working in this field.[16,17]

Voriconazole is one of the recently introduced drug for antifungal treatment. We synthesized variconazole and fluconazole derivatives wherein the pyrimidine ring was replaced by thienopyrimidone moiety. Two synthetic approaches were used for the synthesis of NCEs of this category. The first synthetic approach used was as shown in scheme-7.

Ethyl lactate (**26**) was used as the starting material which was treated with morpholine at 80 ^{0}C for 60 h to get intermediate **27**. This intermediate was protected by THP group by treating it with dihydropyran. Ether **28** was treated with difluorobromobenzene and Mg in tetrahydrofuran to get ketone intermediate **29**. This ketone intermediate **29** on epoxidation by the use of trimethylsulphoxonium iodide furnished the epoxide **30**, which was further reacted with triazole in presence of sodium hydride as a base and dimethyl formamide as a solvent to give the alcohol **31**. Further this alcohol **31** on deprotection of THP ether by PPTS gave the diol **32**, which on selective mesylation by mesyl chloride and triethyl amine, followed by treatment with sodium methoxide gave the intermediate epoxide **33**.

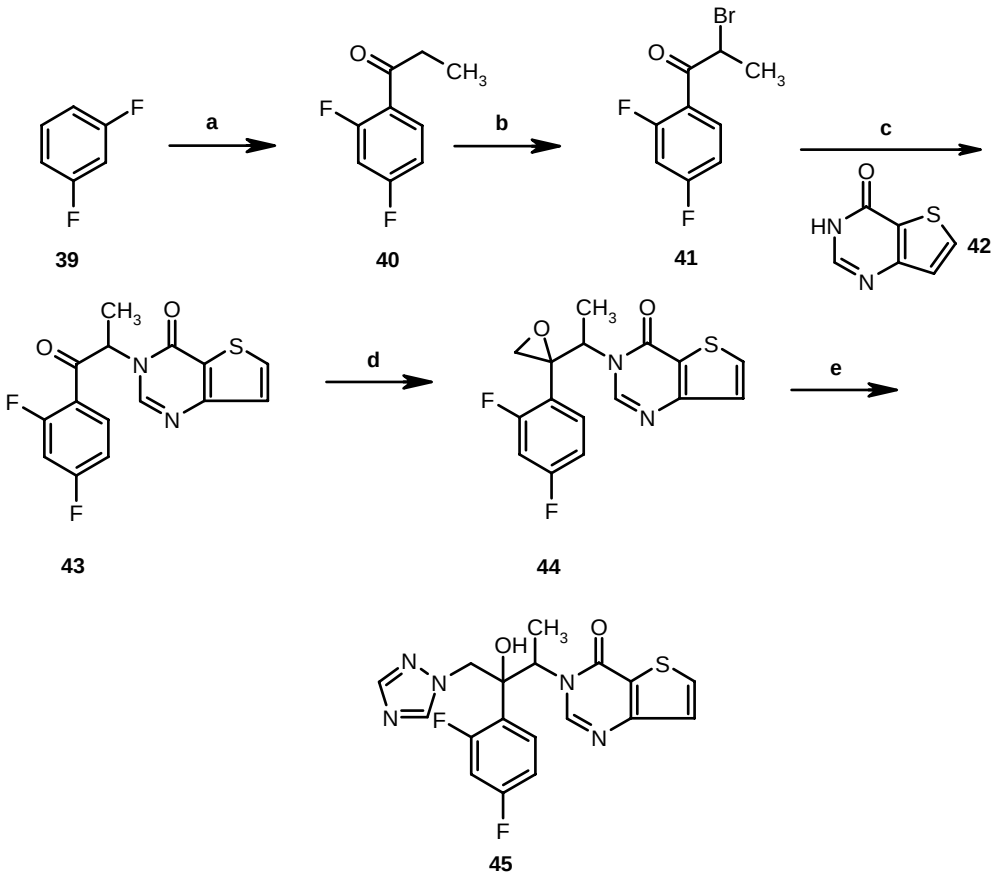
The epoxide **33** was further treated with sodium azide to achieve the intermediate azide **34**. The intermediate azide **34** was reduced by hydrogenation to get amine **35** which was further condensed with Boc protected 3-amino-thiophene-2-carboxylic acid to get the condensed intermediate **36**. The deprotection of Boc-derivative **36** by trifluoroacetic acid (TFA) gave the amine **37** which on cyclization by using formamidine acetate and NMP gave the final azole derivatives **38** in good yield.



Reagents and Conditions: a) 85 ^{0}C, 60 h, 70 % b) DHP, *p*-TSA, DCM, 0 ^{0}C, 30 min, 83 % c) Mg, THF, rt, 4 h, 85 % d) Trimethylsulfoxonium iodide, NaH, DMSO, rt, 4 h, 80 % e) 1*H*-1,2,4-Triazole, NaH, DMF, 0 ^{0}C-rt, 1 h, 55 % f) PPTS, EtOH, 55 ^{0}C, 4 h, 42 % g) i) Methanesulfonyl chloride, ethyl acetate, 0 ^{0}C-rt, 45 min, ii) NaOMe, MeOH, 0 ^{0}C, 15 min, h) NaN_3, ammonium chloride, DMF, 110 ^{0}C, 2.5 h i) Pd/C, H_2, MeOH, rt, 4 h j) Boc-protected 3-amino-thiophene-2-carboxylic acid, 1-hydroxybenzotriazole, DMF, DCC, rt, 18 h, 56 % k) TFA, THF, rt, 2 h, 85 % l) Formamidine acetate, NMP, 130 ^{0}C, 24 h, 60 %.

Scheme - 7

The second method was developed by a very short route starting from commercially available 2, 4-difluorobenzene (**39**), which on acylation gave acylated intermediate **40**. Further this intermediate **40** on bromination by NBS gave bromo compound **41**, which was condensed with thienopyrimidinone to give intermediate **43**. Methylene insertion to get epoxide **44** and epoxide opening with triazole under basic conditions yielded the desired analogue **45** as shown in scheme-8.



Reagents and Conditions: a) Propionyl chloride, $AlCl_3$, dry DCM, rt, 24 h b) NBS, AIBN, CCl_4, UV light, 8 h c) Thienopyrimidinone, K_2CO_3, TBAB, dry ethyl acetate, reflux, half h d) Trimethyl sulphoxonium iodide, cetrimide, DCM, reflux, overnight e) NaOMe, *tert*-butanol, 1,2,4-triazole, reflux, overnight.

Scheme - 8

SECTION - III: Biological activity of designed NCEs as antifungal agents:

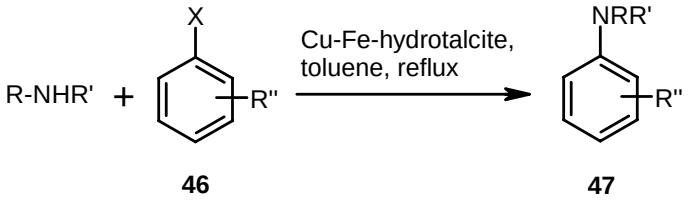
The synthesized new chemical entities (NCEs) from section I and II of this chapter were tested for antifungal activity. All the synthesized new chemical entities were submitted for screening against *C. albicans, F. Proliferatum* and *A. niger*. Some NCEs have shown antifungal activity, comparable to voriconazole. Antifungal activity data of 36 NCEs synthesized in section - I and section - II of this chapter have been discussed in this section.

CHAPTER 3: Some Useful Organic Transformations

Section I: Effcient *N*-arylation of amines catalyzed by Cu-Fe- hydrotalcite

N-arylation of various amines and amides has continued to attract synthetic chemists as the *N*-arylated products constitute the subunits of many biologically active molecules.[18] The different methods reported[19] for *N*-arylation include coupling of amines or isocyanates with aryl boronic acids, aryl halides, aryl triflates, etc. using copper, cuprous iodide, cupric acetate, copper-diamine complexes, palladium, cobalt, or nickel catalyst. Cu-catalyzed Ullmann coupling protocols and Ullmann type processes for C-N bond formation have been reported.

We have developed an efficient useful method for *N*-arylation of amines by reaction of different amines with aryl halides in presence of Cu-Fe-hydrotalcite.[20] The reaction conditions are mild and various functional groups are tolerated (scheme-9). In comparison with reported protocols this method avoids the use of expensive catalysts and ligands, excess of amines or use of base and instead employs a heterogeneous catalyst that is easily removed from the product and can be recycled and reused. No hazardous chemicals are used and the reaction is performed in environmentally friendly solvent (toluene) and products are obtained simply by filtration and concentration of the filtrate. Selective *N*-arylation of primary amines is possible in case of amino benzaldehyde without formation of Schiffs base.



46 **47**

R-NHR' = Substituted aniline, indole, cyclohexyl amine, benzyl amine

X = Br, I

R'' = H, OMe, NO_2, Cl, CHO

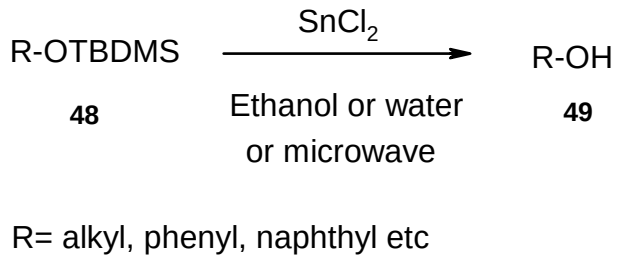
Scheme - 9

Section II: A simple method for deprotection of *tert*-butyldimethylsily ethers by using stannous chloride under microwave irradiation

The scientific community uses a large number of protecting groups for various functionalities routinely as the protection-deprotection strategies are the inevitable steps in synthetic organic chemistry. *tert*-Butyldimethylsilylation of alcohols and phenols is a versatile method because these silyl ethers are stable under a variety of conditions like Wittig reaction, Grignard reaction, reductions with diisobutylaluminium hydride etc. The enormous work in the silylation chemistry has resulted in the development of various methods for silylation and desilylation[21] and every year newer methods are being added for these transformations. Recently $BiCl_3$-NaI and cesium carbonate have been reported to effect the deprotection of *tert*-butyldimethylsilyl ethers.

Stannous chloride is an easily available, stable and cheap reagent widely used in the food industry as a preservative, colour retention agent and a component in food packaging materials as well as it is used for various organic conversions including reduction, dehalogenation, protection-deprotection of various functional groups etc. We considered that environmentally benign method for deprotection of *tert*-butyldimethylsilyl ethers could be developed using stannous chloride. In the present section deprotection of a number of *tert*-butyldimethylsilyl ethers in presence of stannous chloride under

microwave irradiation and solvent free conditions as well as in ecofriendly solvents such as ethanol and water has been described[22] as shown in scheme 10.

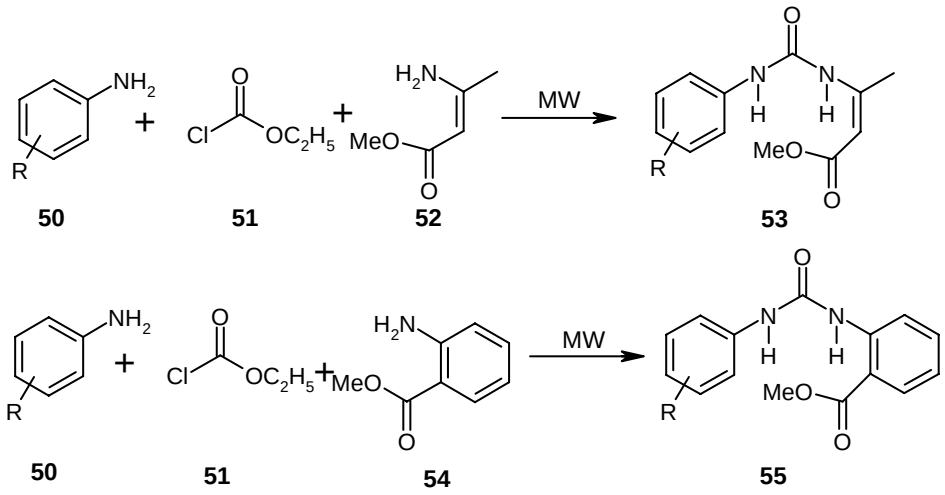


Scheme - 10

Section - III: Microwave promoted solvent-free one-pot synthesis of *N, N'*-disubstituted urea derivatives

Symmetrical and unsymmetrical *N*, *N*'-disubstituted aryl/alkyl urea derivatives are well known for their biological activities such as herbicidal,[23-26] COX-2 inhibition,[27] fat metabolism inhibition,[28] *etc*. Symmetrical disubstituted aromatic ureas are useful as agrochemicals and their intermediates, stabilizers for smokeless gun powder, propellants and solid rocket fuels.

The one - pot multi-component reaction protocol has attracted considerable attention in organic synthesis as one of the tools for environmentally benign synthetic procedures. Initially, we treated aniline, methyl 3-amino-2-butenoate and ethyl chloroformate in equal ratio under microwave solvent-free conditions for 5 min at 130 °C and found that the product was a mixture of the corresponding carbamates and urea derivatives.[29] Sequential addition of ethyl chloroformate followed by 3-amino-2-butenoate or methyl anthranylate gave the corresponding *N*, *N*'-disubstituted urea derivatives in good yield as shown in scheme-11.



Scheme - 11

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CHAPTER - I

NEW 2-ARYLIDENE TETRALONE AND 5-HYDROXY CYCLOPENTENONE DERIVATIVES WITH POTENTIAL ANTICANCER ACTIVITY

1.0.1: CYTOTOXIC STUDY: GENERAL INTRODUCTION:

Cancer a most dreaded disease, is the foremost killer disease in western countries and India. Cancer, the growth of abnormal body tissues, is actually referred to more than hundred forms of the disease. Tumor is a general term indicating any normal mass or growth of tissues that is not necessarily life threating. A "cancerous tumor" is malignant neoplasm of potential danger. Cancer can arise in any organ of the body even though some sites are more prone than others. The most dangerous property of cancer cells which normal cells lack, is their ability to enter other body organs through blood and lymph vessels. This disease has attracted worldwide attention and search for reliable methods to cure it is continuously going on.[1]

The main curative therapies for cancer can be divided into four types: surgery, radiation, chemotherapy and combined modality therapy, out of which surgery and radiation are generally successful only if the cancer is found at an early localized stage. But once the disease has progressed to local advanced cancer or metastatic cancer, these therapies are less successful. Then the only tool in oncologist's hand to fight against cancer, to save the patient is chemotherapy alone or in combination with radiation and surgery.

In early 1940 chemotherapeutic drugs were developed. Physicians found that "combination of drugs" may cure leukemias, lymphomas and testicular cancers. Unfortunately, the majority of the most common cancers like breast, lung, colorectal and prostate cancers are not yet curable with chemotherapy alone.

Combined modility therapy requires the efforts of wide assortment of specialists, oncologists, surgeons, pathologists and radiologists. Most approaches to cancer chemotherapy have centered around the idea that cytotoxic drugs can be used to eradicate proliferating neoplastic cells. Chemotherapy has curative potential in patients with various haematologic malignancies, testicular cancer and germ cell tumors. Despite improvements in the treatment of most metastatic solid tumors, these remain largely incurable. Reasons for this are insufficient tumor selectivity of anti-cancer agents and poor penetration within the tumor mass.[2,3] The main disadvantage of cancer chemotherapy is the toxicity of the drugs used.

A large number of anticancer drugs, possessing diverse molecular structures, are being used presently. Further, many are undergoing clinical trials. Some of the antineoplastic agents although efficient are not specifically cytotoxic to tumor cells as they also kill normal cells. Most of the anticancer agents in use affect the function or the synthesis of DNA and are therefore more active in rapidly proliferating cell population.

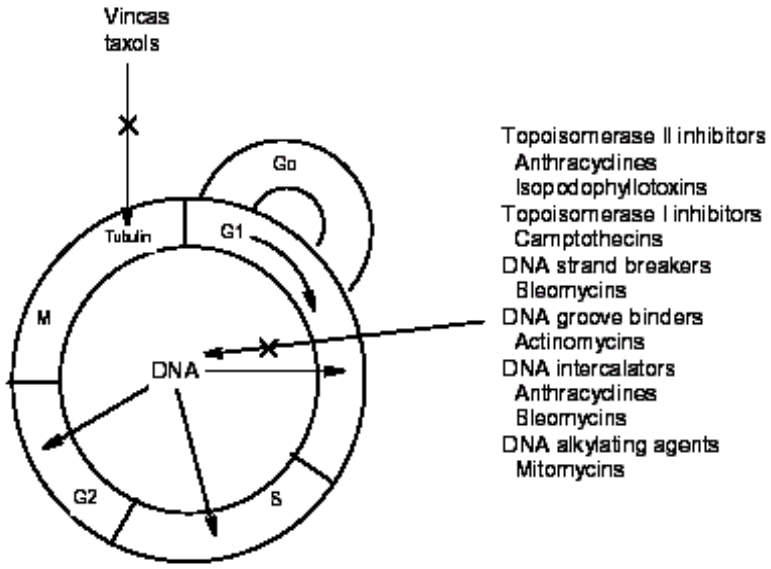


Fig. 1: Synopsis of molecular modes of action of various prominent antitumor natural products.

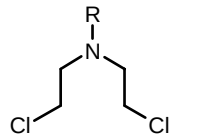
Fig. 1 illustrates the various points of attack of prominent natural antitumor agents on growing cells. From the figure 1 it is clear that DNA or tubulin in one way or another (either by direct attack or by interference with enzymes processing these important cellular macromolecules) is the primary target of all these agents and that most phases of the cell cycle are involved.

All the antineoplastic agents can be classified into six categories namely

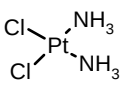
1) Alkylating agents
2) Antimetabolites
3) Anthracycline antibiotics
4) Natural products
5) Mitotic inhibitors
6) Miscellaneous agents

1) Alkylating agents:

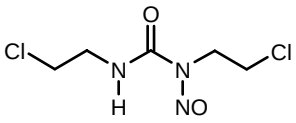
The compounds that alkylate DNA have long been of interest as anticancer drugs. Alkylating agents behave as electrophiles that can replace a hydrogen atom by alkyl group under physiological conditions. The various alkylating agents are mustards [mechlorethamine (**1**), chlorambucil (**2**), melphalan (**3**), cyclophosphamide, ifosamide], platinum complexes (cisplatin, carboplatin, tetraplatin etc.) cyclopropylindoles (adozelesin, carzelesin), nitrosoureas (CCNU, BCNU, stroptozotocin) and triazenes (dacarbazine, mitozolomide. temozolomide).



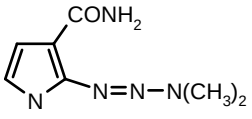
(**1**) R = CH_3
(**2**) R = $(CH_2)_3CO2H$
(**3**) R = $CH(NH_2)CO_2H$



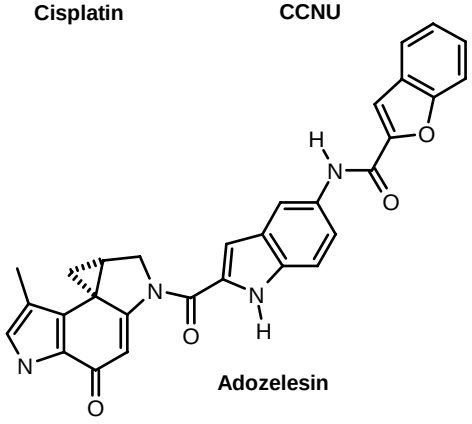
Cisplatin



CCNU



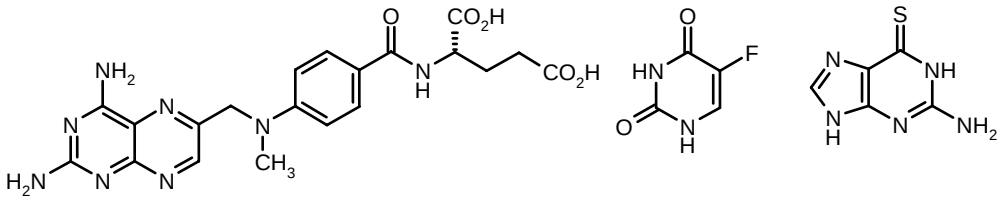
Dacarbazine



Adozelesin

2) Antimetabolites:

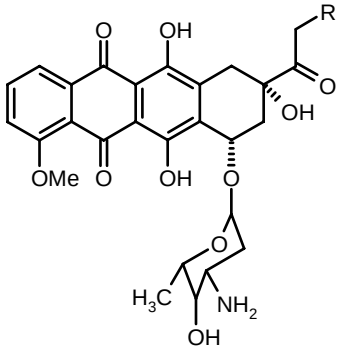
The compounds which interfere in varying ways with the synthesis of DNA are known as antimetabolites. Various antimetabolites used in cancer chemotherapy are folic acid analogues (methotrexate, edatrexate, raltitrexed etc.), pyrimidine analogous (5-fluorouracil, cytosine arabinoside, gemcitabine), purine analogues (6- mercaptopurine, 6-thioguanine, fludarabine etc.)



Methotrexate **5-Fluorouracil** **6-Mercaptopurine**

3) Anthracyclines:

The anthracyclines are a group of structurally related antitumor antibiotics. The two prototype anthracyclines are adriamycin (**4**) and daunomycin (**5**) produced from steptomyces species.[4] Their potent activity was discovered in 1963 when adriamycin and daunomycin[5] first isolated by Di Marco *et al*., were found to be effective as antileukemic agents. The tumor cell growth inhibiting property of the anthracyclines has generally been attributed to the interaction of these drugs with DNA. Adriamycin has shown promising results in solid tumors also.

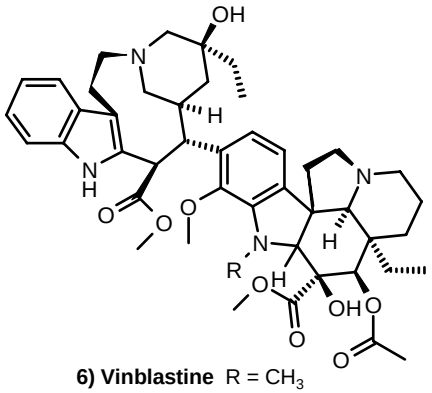


(4) Adriamycin R = OH
(5) Daunomycin R = H

4) Natural products: Drugs derived from plant sources

A wide array of complex terrestrial and marine natural products possess antitumor activity.[6-10] To acquire new anticancer agents a variety of sources have been explored including synthetic compounds, microbial and plant extracts etc. The most important development in the investigation of plant products as potential anticancer agents is the

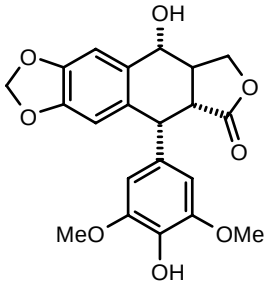
discovery of the dimeric alkaloids, *Vinca rosea L.*[11] Two of the alkaloids, vinblastine (**6**) and vincristine (**7**) (VCR), have demonstrated remarkable antitumor activity. They have been the first examples of antitumor agents isolated from plant sources.



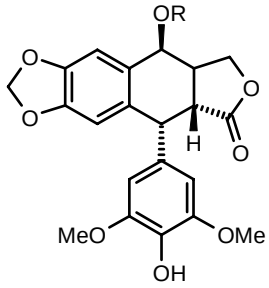
6) Vinblastine R = CH_3
7) Vincristine R = CHO

Isopodophyllotoxins:

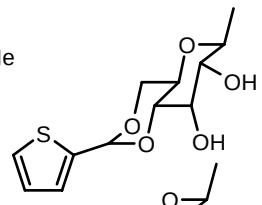
The lignan podophyllotoxin (**8**) is an ancient folk remedy found in the May apple, *Podophyllum peltatum.*[12,13] The isopodophyllotoxins are semisynthetic analogues of podophyllotoxin resulting from acid catalyzed reaction with suitably protected sugars followed by additional transformations. Teniposide (**9**) and etoposide (**10**) are the most prominent analogues so produced and these are available in the market as antitumor agents.



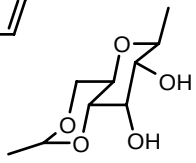
Podophyllotoxin (8)



Teniposide (9) R =



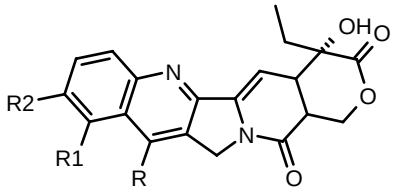
Etoposide (10) R =

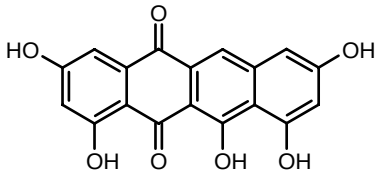


Camptothecin:

Camptothecin (**11**) a pentacyclic alkaloid was isolated by Wall *et al.*[14] in 1966 from the stem wood of the tree *Camptotheca acuminata* Decne (Nyssaceae), a tree distributed widely and abundantly in the Southern part of China. Despite its early promise in laboratory and rodent studies, it was disappointing in clinical studies because of the severe toxicity and so it has not found clinical use as itself. Topotecan (**12**) and Irinotecan (**13**) are two analogues of campotothecin. Irinotecan (**13**) is an analogue hydroxylated in the quinoline ring and further converted to amine- bearing prodrug linker. Topotecan is used for ovarian[15,16] and small-cell lung cancers.[17,18] Camptothecins are inhibitors of the action of mammalian topoisomerase I.

The recent interest in topoisomerase inhibitiors has been in agents which are capable of simultaneous inhibition of both enzymes topoisomerase I and topoisomerae II. The anthraquinone Saintopin (**14**) is a potent poision of both topoisomerase I and topoisomerase II [19] but has not been developed as a drug.



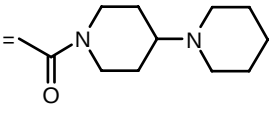


Camtothecin (11) R= H, R^1= H, R^2 = H

Saintopin (14)

Topotecan (12) R = H, R^1 = $CH_2N(CH_3)_2$, R^2 = OH

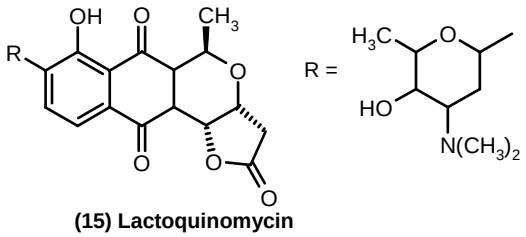
Irinotecan (13) R = Et, R^1 = H, R^2 =



5) Miscellaneous agents:

Miscellaneous agents are the compounds isolated from various sources like bacteria, fungi etc. and their mode of action is not known. During the course of screening programme for new antitumor antibiotics Tanaka *et al.*[20] found that a *Streptomyces* strain IM 8442 T produces a novel antibiotic which inhibits antibiotic resistant cell sublines of

L 5178 Y murine lymphoma more markedly than the parent cells. The new agent was named as lactoquinomycin (**15**).



(15) Lactoquinomycin

6) Mitotic inhibitors:

The cell division cycle regulating chromosome replication/ segregation and cell division is of fundamental importance for any living organism and in diseases such as cancer. Limitless replicative potential, self-sufficieny in growth signals and insensitivity to antigrowth signals are acquired capabilities of malignant cancer cells, leading to the uncontrolled cell cycling.[21]

The M-phase or mitosis is the most important part of the cell division cycle and includes condensation of nuclear chromatin and disruption of the nuclear envelope, organization of a mitotic spindle, and chromosome segregation. The key player within cell cycle, namely cyclindependent kinase (cdks), cdk inhibitors, microtubules and microtubule associated proteins (MAPs), have been selected as targets for the discovery of new antimitotic cancer drugs.

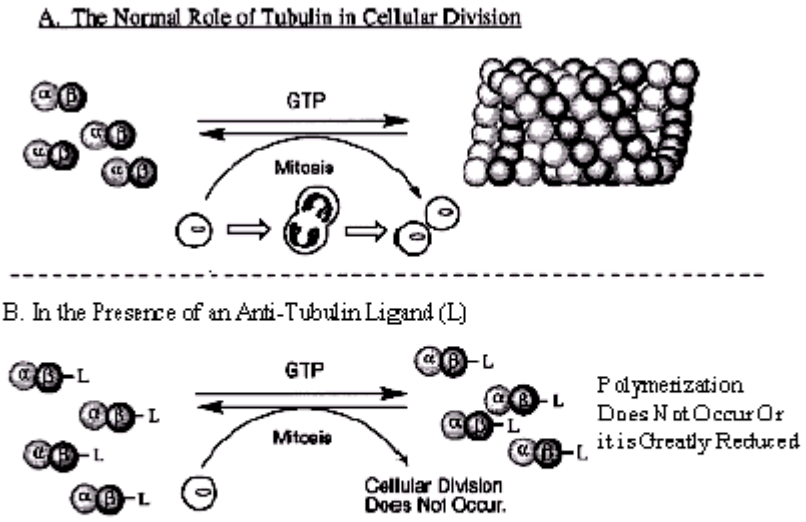


Fig 2: A) Normal tubulin polymerization dynamics in cell division. B) Disruption of dynamic polymerization in the presence of an anti-tubulin ligand (L).

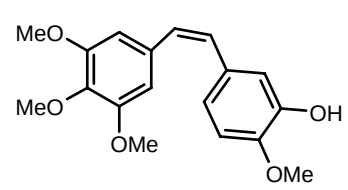
The microtubule system of eukaryotic cell is an important target for the development of anticancer agents; chemicals which attack microtubules through tubulin disrupt cellular microtubule structure and function resulting in mitotic arrest. The tubulin-binding agents generally exert their effects by microtubule depolymerization or stabilization.

Tubulin is a heterodimeric protein consisting of α and β subunits, each approximately 50 k Da in size.[22,23] The α and β subunits have a high degree of homology (40-50%) to each other.[24] Upon binding of GTP, tubulin polymerizes into microtubule which are helical arrays of alternating α and β subunits. The polymerization and subsequent depolymerization of microtubules is responsible for ciliar and flagellar movement, vesicle movement in secretion, transport of organelles down the axons in nerve cells, chromosome separation during cell division (mitosis) and the generation and maintenance of cell shape.[22-25]

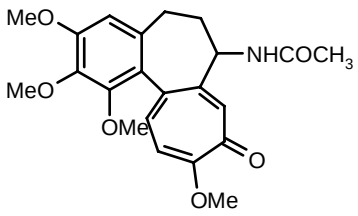
During cellular division, the interphase microtubule array largely disassembles, and the α, β- tubulin repolymerizes to form the microtubule framework of the mitotic spindle, which is essential for chromosome separation and formation of two daughter cells. When ligands that interact with α, β-tubulin or with microtubules are present, a reduction in cellular division is observed. Due to the key role played by tubulin during cell division,

ligands that interrupt the dynamic instability inherent to this system have been developed as antimitotic, anticancer drugs.

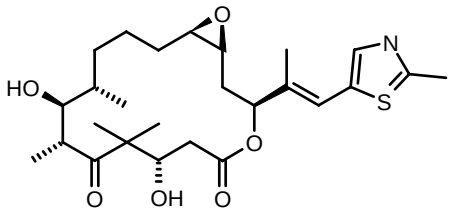
A large number of naturally occurring ligands that inhibit tubulin polymerization have been reported (Fig. 3) in the literature for many years, and there has been a continuing discovery of new agents with pronounced structural diversity.[26]



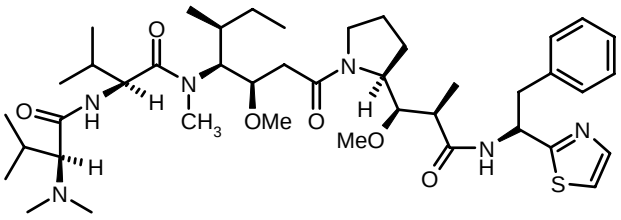
Combretastatin A-4 (16)



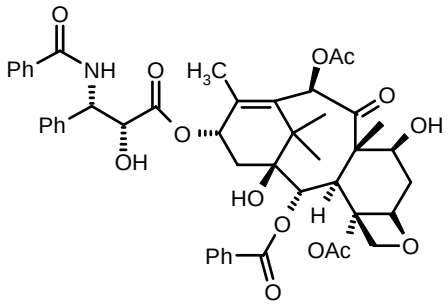
Colchicine (17)



Epothilone A (18)



Dolastatin 10 (19)



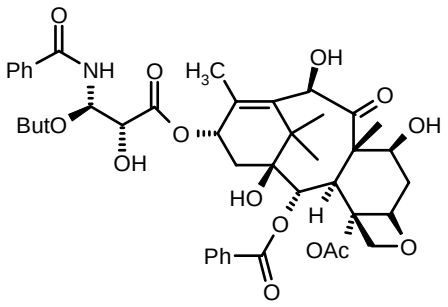
Paclitaxel (20)

Fig.3: Representative antimitotic compounds which interact with tubulin.

There are a variety of synthetic compounds that also demonstrate efficient inhibition of tubulin polymerization.

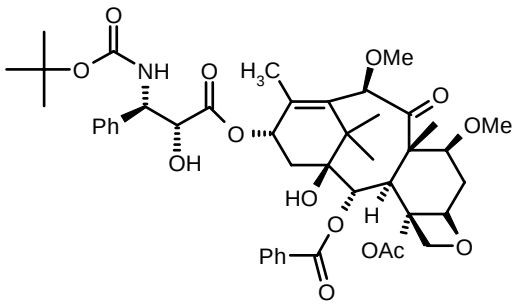
Some of the semisynthetic and synthetic microtubule inhibitors:

There are a number of semisynthetic or synthetic compounds which inhibit microtubule assembly. Paclitaxel (**21**) is one of the ligand, which inhibits microtubule system. Paclitaxel was isolated from the bark of pacific yew *Taxus brevifolia*.[27]

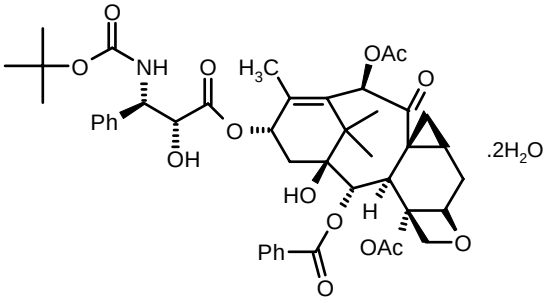


Docetaxel (21)

The docetaxel (**21**) a semisynthetic analogue of paclitaxel, vinblastine (**6**) and vincristine (**7**) are standard agents in cancer therapy. The clinical use of paclitaxel (**20**) and docetaxel (**21**) is restricted mainly by oral bioavailability, although they are highly potent and effective cancer drugs, drug resistance and toxicity are related to the mechanism of action. Numerous new semisynthetic analogues of paclitaxel are under clinical study. Bristol-Myers-Squibb, the company which developed paclitaxel, have reported two paclitaxel analogues BMS-184476 and BMS-188797,[28] which are in phase – I and II clinical trials and they displayed similar or superior efficacy in nude mice xenograft models.



TXD-258 (22)



RPR-109881A (23)

Two taxane analogues in clinical development by Aventis Pharma, i. e. TXD-258 (**22**) and RPR-109881A (**23**),[29,30] have been reported to be effective against various human tumor xenografts, including MDR- positive and taxane-resistant models.

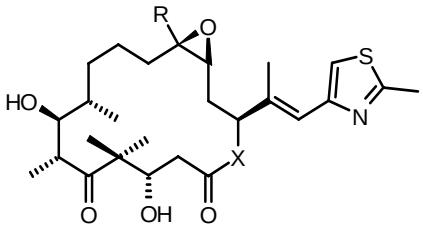
Natural compounds of diverse structures:

Many tubulin-binding compounds from various natural sources and semisynthetic analogues have been described within the last two decades. Natural compounds like combretastatin A-4 (**16**), cryptophycin 52 (**28**), dolastatin 10 (**19**) and dolastatin 15 destabilize tubulin, whereas epothilones, laulimalide, peloruside A, eleutherobine and (+)-discodermolide, stabilize microtubules similar to paclitaxel. The various tubulin-binding natural and semisynthetic compounds are shown in table 1.

Table 1:

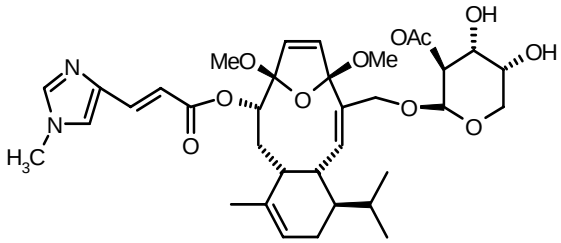
Compound	**Source**	**Toxicity**
Epothilone B (**24**) [31]	Novartis	0.2-0.8 µM
BMS-247550 (**25**) [32]	Bristol-Myers Squibb	3.9 nM (mean)
Eleutherobin (**26**) [33]	Bristol-Myers Squibb	10-60 nM
(+)-Discodermolide (**27**) [34]	Novartis	8-36 nM
Vinflunine [35]	Pierre Fabre	18 nM
Cryptophycin 52 (**28**) [36]	Eli Lilly	13-232 pM
Combretastatin A-4 (**16**) [37, 38]	Oxigene	---
ZD-6126 (**29**) [39, 40]	AstraZeneca	n. p.
Dolastatin 10 (**19**) [41, 42]	NCI	0.5 nM (L1210 model)

n. p. = not published.

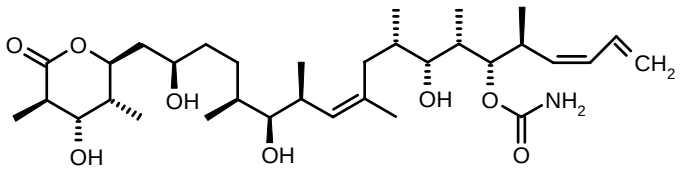


Epothilone B (24) X = O, R = CH_3

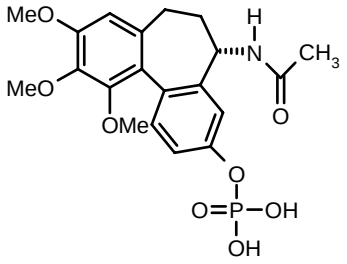
BMS - 247550 (25) X =NH, R = CH_3



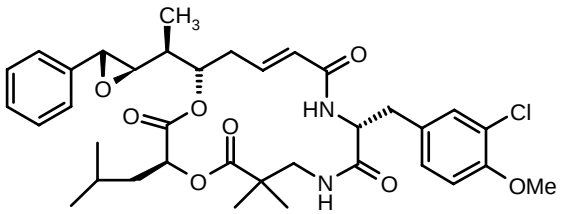
Eleutherobin (26)



Discodermolide (27)



ZD-6126 (29)



Cryptophycin 52 (28)

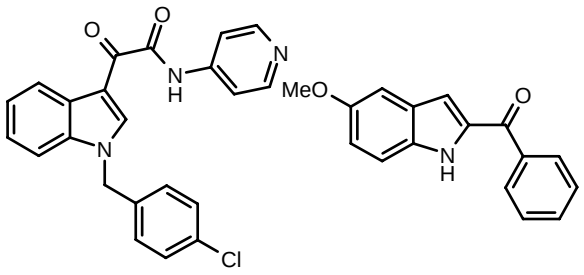
Synthetic low molecular-weight compounds:

From the synthetic point of view, compounds with low molecular weight (small molecules) are very attractive as a drug format. Recently, various synthetic small-molecules have been described as tubulin inhibitors. Most but not all, compete with colchicines for binding to β-tubulin, thereby acting as destabilizing agents. These compounds have been grouped into heterocombretastatins, sulfonamides, phenstatins, indols and quinones.

Table 2: Synthetic small molecule tubulin inhibitors

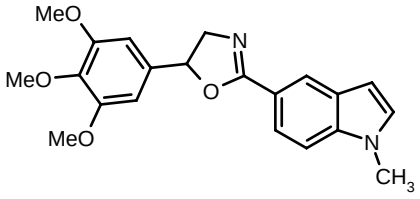
Compound	**Toxicity *in vitro* (IC_{50})**
D-24851 (**30**)[43]	36-285 nM
D-64131 (**31**)[44,45]	24-144 nM
A-289099 (**32**)[46]	7 nM
Indanocine (**33**)[47,48]	< 20 nM (mean)
E-7010 **(34)**[49,50]	0.2-40 ng/ml
Cl-980 (**35**)[51,52]	11-165 nM

Further, there are a number of quinolones and related structures which also represent a promising group of compounds affecting tubulin. The synthetic 2-phenyl-4-quinolones which are structurally related to naturally occurring and antimitotic flavonoids, displayed promising activity and impressive differential cytotoxicity against human tumor cell lines, comparable to that of colchicines.[53,54-56] The structurally related 2-phenyl-1,8-naphthyridin-4-ones containing additional nitrogen in position 8 of the aromatic system also exhibited potent cytotoxicity.

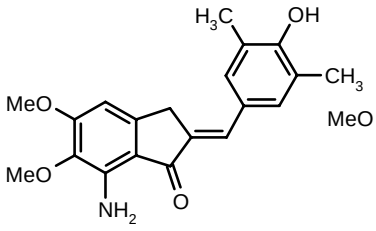


D -24851 (30)

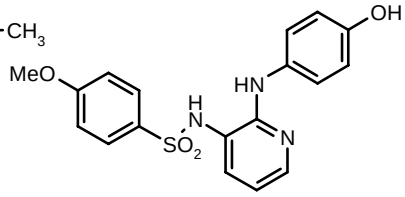
D - 64131 (31)



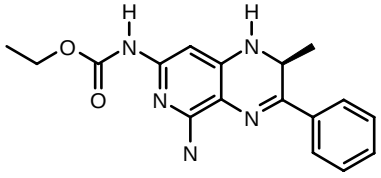
A - 289099 (32)



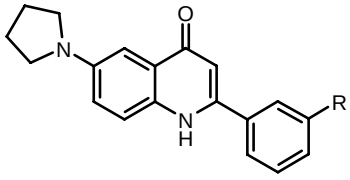
Indanocine
NSC-698666



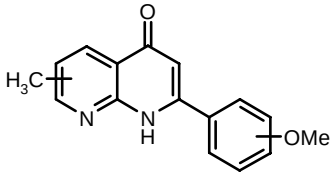
E- 7010



Carbamate, CI-980

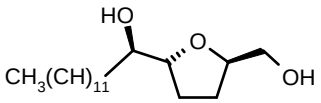


2-Phenyl-quinolones
R = OCH_3 or Cl

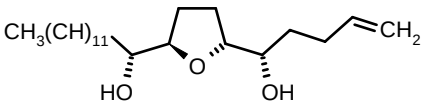


2-Phenyl-1,8-naphthyridin-4-one

Recently, Jan *et al.*[57] reported COBRA-0 (WHI-261) (**36**) and COBRA-1 (**37**), the compounds containing monotetrahydrofuran moiety attached to a C_{12} aliphatic chain, which were found to bind to α-tubulin and exhibited cytotoxicity at concentrations of 100 μM or higher.



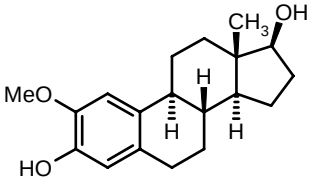
WHI-261 (36)



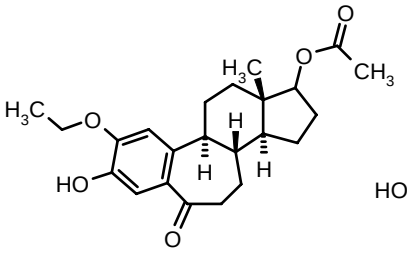
COBRA 1 (37)

Synthetic steroids with colchicines-type substructure:

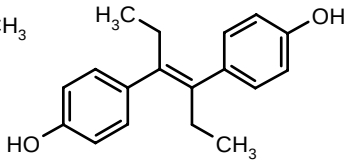
2-Methoxyestradiol (NSC-659853) (**38**), a cytotoxic human metabolite developed by Entremed Ind., binds to the colchicines site of tubulin with reasonable affinity (IC_{50} = 4.7 μM). It was shown to have antiproliferative effects on hormone-dependent and harmone-independent breast cancer cells as well as antiangiogenic activity.[58] Further, B ring expanded 2-ethoxyestradiol analogue (**39**) was synthesized by Wang *et al.*[59] in which B-ring of the steroid was replaced by the B-ring of colchicine. The resulting analogues showed significant affinity to the colchicine binding site consistent with the proposed structural resemblance.



(38)
2-Methoxyyestradiol (NSC-659853)



(39)
Ring expanded homologue of NSC-659853



(40)
Diethylstilbestrol

Chaudoreille *et al.*[60] reported another tubulin binding agent diethylstilbestrol (**40**) which was originally developed as an synthetic estrogen. The antineoplastic effect of the diethylstilbestrol was due to the depolymerization of microtubules. Tamoxifen, a stilbene derivative is already in use for the treatment of cancer.

A REVIEW ON HYBRID COMPOUNDS:

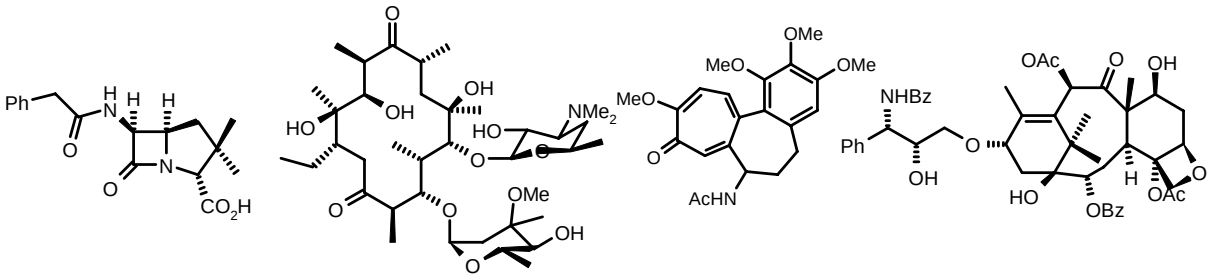
When modern synthetic chemistry came into being in the middle of the 19th century, Nature had already been generating a plethora of substances for millions of years. Many of those producing organisms are equipped with an evolutionary advantage to survive in a more or less hostile environment. Therefore the percentage of biologically active substances in Nature is relatively high as compared to substances from artificial sources. In fact, man has always taken advantage of Nature as a pharmacy, approximately 40 % of the drugs that have been approved in last five years are either natural products or derivatives and analogues thereof.[61] Among anticancer and antiinfective agents, the percentage is even estimated to exceed 60 % including such well-known examples as penicillin G (**41**) and erythromycin A (**42**), as well as colchicine (**17**), vinblastine (**6**), vincristine (**7**), and paclitaxel (taxol, **20**). Organ transplantation would not have been possible without immunosuppressive natural products such as cyclosporin A (**43**), FK506 (**44**), or rapamycin (**45**). Natural products and their analogues have been put to use not only in pharmacology but also in modern crop protection.[62] They play an important role as highly potent insecticides, for example, pyrethrin (**46**), spinosyne A (**47 a**), and spinosyne D (**47 b**), or as fungicides such as the derivatives of strobilurin A (**48**).

Modern combinatorial chemistry[63] allows the synthesis of millions of new compounds in a relatively short time. These libraries can be evaluated for their biological activity using high-throughput screening (HTS) techniques.[64] However, the success of such purely random approaches has not been very pronounced, which may especially be due to the lack of new chemical entities (NCEs) with high diversity. Bearing this in mind the next logical step seems to be to profit from Nature's structural diversity by combining two or more natural products to form a hybrid.

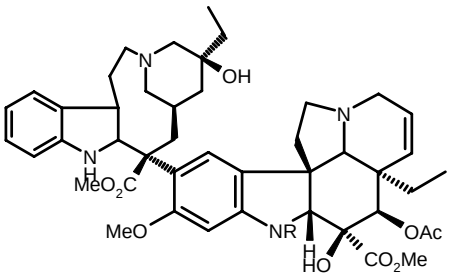
Naturally, the question arises as to whether such an approach is of any use for the development of new biologically active therapeutic compounds with novel properties, or if there are any examples that demonstrate the potential of the methodology. Actually, from a general standpoint, the approach is not quite new, since even Nature employs such a strategy; for example, in the case of vitamin E the terpenoid phytyl chain interacts with the cell membrane and the phenol moiety derived from shikimic acid forms a radical trap.

Another naturally occourring hybrid compoud, the indole alkaloid vincristine (**7)** mentioned above, has completely changed the fate of young children afflicted with lymphatic leukemia. Previously, this disease was fatal, but vincristine is now used in its treatment with success rate of over 60 %. The compound is a dimeric indole alkaloid consisting of vindoline-an alkaloid of the *Aspidosperma* subgroup and catharanthine a member of the *Iboga* subgroup of indole alkaloid. It is of special interest that both monomeric alkaloids do not express any pronounced or useful biological activity. Artificial natural product hybrids have not yet been used as drugs, as this idea is quite new, but several novel compounds of this type developed in the last years show promising biological activity, which will be discussed below.

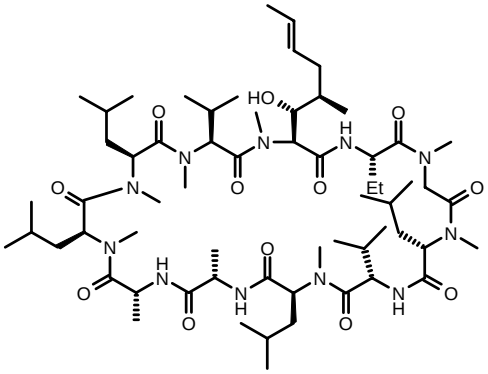
Such hybrids can be synthesized either by classical organic methods or by hybridization of the corresponding biosynthetic devices, namely by a transfer of gene clusters into a new host, which will then produce new "non-natural" natural products. This area has been applied mainly to the synthesis of polyketides and is often referred to as "combinatorial biosynthesis".[65, 66] We wish to present here some new chemical entities as hybrid molecules in which both the parent molecules show promising anticancer activity. As there already are excellent literature surveys that cover combinatorial biosynthesis and the production of hybrid molecules by employing genetically engineered organisms, this field was not been covered, in this review.



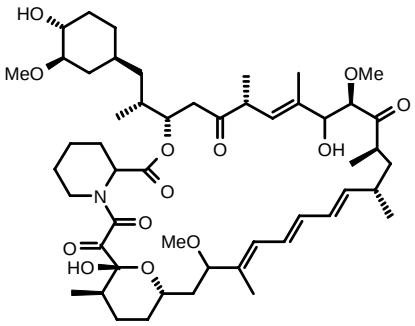
41 : Penicillin G **42 :Erythromycin A** **17 : Colchicine** **20 : Paclitaxel**



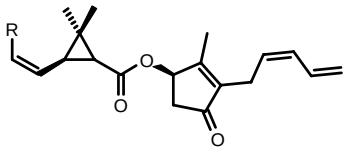
6 : Vinblastine R=Me
7 : Vincristine R=CHo



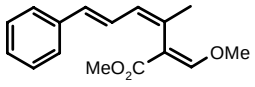
43 : Cyclosporin A



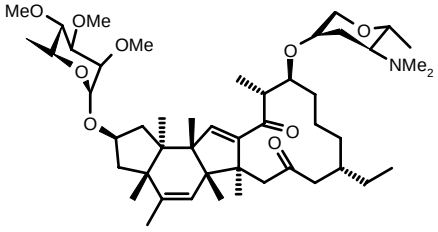
45 : (-)- Rapamycin



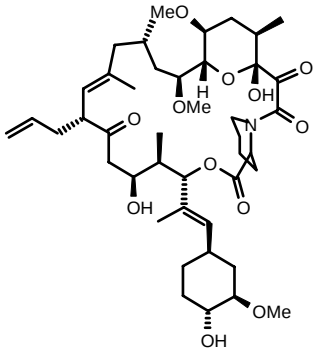
46a : Pyrethrin I R = Me
46b : Pyrethrin II R = CO_2Me



48 : Strobilurin A



47 a: (-) Spinosyn A R= H
47 b: (-) Spinosyn D R= Me



44 : (-)-FK-506 (Tacrolimus)

We have divided hybrid molecules depending upon their occurrence and nature as fallows:

A) Naturally Occurring Hybrid Molecules

1) Naturally occurring hybrids of natural products or their analogues.
2) Naturally occurring hybrids of partial structures of natural products or their analogues.

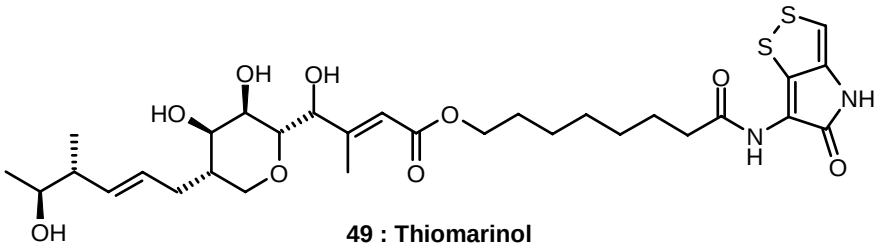
B) Synthetic Hybrid Molecules

1) Synthetic hybrids of natural products or their analogues.
3) Synthetic hybrids of partial structures of natural products or their analogues.

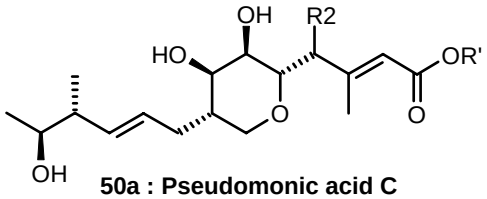
A) Naturally Occurring Hybrid Molecules:

1) Naturally occurring hybrids of natural products or their analogues.

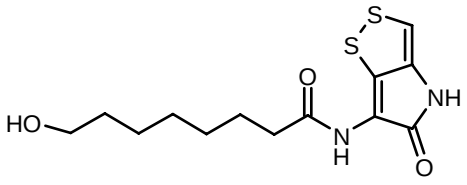
An interesting example of this class of natural hybrids is the antimicrobial antibiotic thiomarinol (**49**), which was isolated from a culture broth of the marine bacterium *Alteromonas rava* sp. Nov. SANK 73390 and was shown to be a hybrid of the pseudomonic acid C analogue **50b** and holothin (**51**).[67] Importantly, the antimicrobial spectrum of **49** shows characteristics of both parent compounds, it is active against Gram-positive and Gram-negative bacteria (e.g. multiresistant *Staphylococcus aurea* strains), and its effects are more pronounced than those of either parent compound.



49 : Thiomarinol



50a : Pseudomonic acid C
$R^1 = (CH_2)_8CO_2H$, R^2 = H
50b : R^1 = H, R^2 = OH



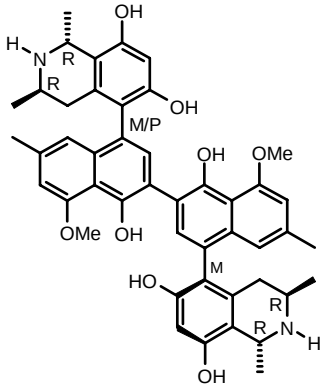
51 : Holothin

The formation of dimers of natural products is a common feature in nature. The new hybrids usually exhibit a different biological activity to that of the monomer. Some of the best known examples are the dimeric indole alkaloids vinblastine (**6**) and vincristine (**7**), which are both used clinically. Other examples are the bisbenzylisoquinoline alkaloids such as tubocurarine, which has been used for a long time in surgery as a muscle relaxant.

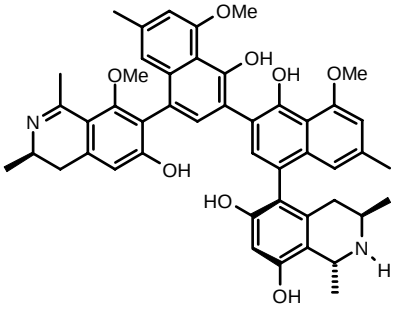
It has now been replaced by amino steroid derivatives such as vecuronium bromide and rocuronium bromide.

Some new examples of dimeric natural product hybrids found in nature are the dimeric naphthylisoquinoline alkaloids michellamine A (**52a**), michellamine B (**52b**), korundamine A (**53**)[68] and michellamine A (**54**) in all respects, whereas michellamine B (**52b**) has the same constitution, but a different configuration at one of the two stereogenic axes. In contrast, korundamine A (**53**) is a heterodimer of korupensamine A (**54**) and yaoundamine A (**55**).

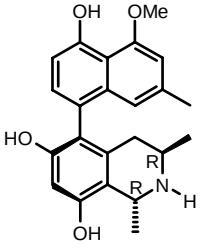
Whereas the monomeric naphthylisoquinoline alkaloids exist abundantly in the plant families *Ancistrocladaceae* and *Diocophyllaceae*, the dimeric compounds have so far only been found in a single species, *Ancistrocladus korupensis*. Michellamine B (**52b**) and korundamine A (**53**) show strong anti-HIV activity (EC_{50} = 2 μM). In addition, korundamine A (**53**) is a potent antimalarial compound with an in vitro IC_{50} value of 1.1 μg mL^{-1} against *plasmodium falciparum.*



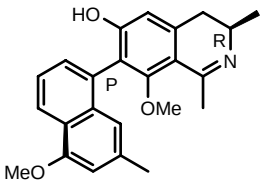
52a : (-) - Michellamine A (P, P)
52b : (-) - Michellamine B (M, P)



53 : Korundamine A

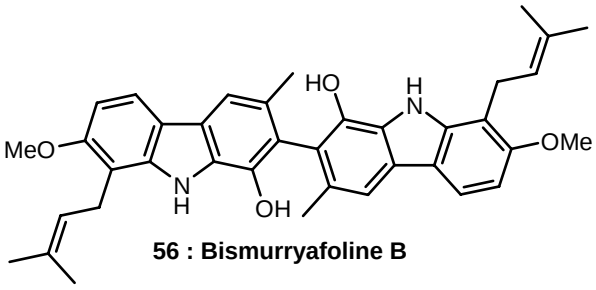


54 : Korupensamine A

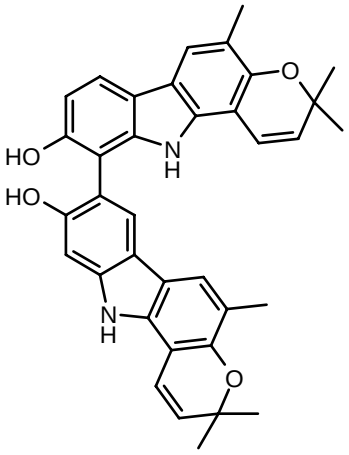


55 : Yaoundamine A

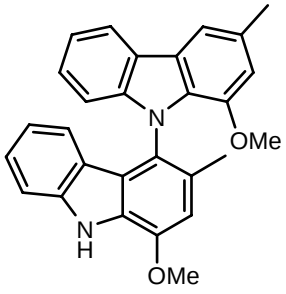
Another interesting class of dimeric compounds are the biaryl-biscarbazole alkaloids such as **56** and **57**. Only 14 are currently known, all isolated from plants of two genera of the family *Rutaceae, Clausena and Murraya S.*[69] The unique feature of these alkaloids again is a stereogenic axis. However, dimeric compounds coupled through a C-N bond (e.g. **58**) are also found in these plants. The biological activity of the biaryl biscarbazole alkaloids is not as pronounced as that of the dimeric naphthylisoquinoline alkaloids. However, some of the compounds are active against *Leischmania donovani*, the pathogenic agent of leishmaniasis, and exhibit a moderate fungicidal activity.



56 : Bismurryafoline B



57 : Bis-7-hydroxy-girinimbine-B



58: Murrastifoline-F

2) Naturally Occurring Hybrids of Partial Structures of Natural Products or Analogues:

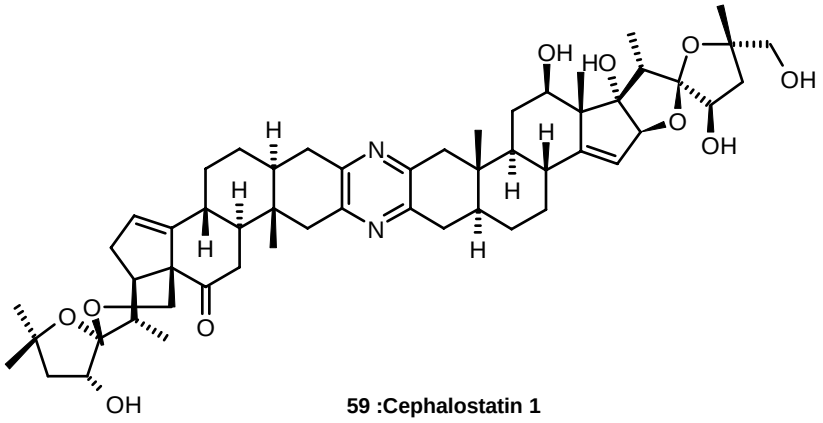
In this section we discuss a few natural product hybrids in which a part of at least one of the component molecules has been lost, for example, a hydroxyl group or a carbon center. An example are the fissistigmatins A-D (**60-63**), which were isolated from *Fissistigma bracteolatum* Chatt. (Annonaceae), a creeper grown in North Vietnam, and characterized as hybrid composed of a falvonoid and a sesquiterpene moiety.[73] In South

East Asia, the extract of this plant is used in traditional medicine, especially to stop wound bleeding and also as an antiinfective.[74] The biosynthesis has not been determined yet, but it has been proposed that a mixed biosynthetic pathway is involved in the combination of a chalcone unit **64** with either a germacrene- **65** or a bicyclogermacrene-type unit **66**.

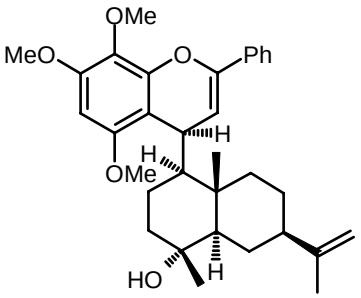
There are thousands of *O*- and *N*- glycosidic natural products. Such as the saponines, flavones, ribonucleosides, and anthracyclic glycosides, which contain a carbohydrate and another natural compound (the aglycone) and may therefore also be considered as natural product hybrids. These substances are not covered in this review but we have included some C-glycosides. Several C-glycosidic antitumor antibiotics are hybrids of carbohydrates and tetracyclines. These compounds generally fall under the anthracycline class of natural products, which is amply covered in the literature. [75]

The cephalostatins and ritterazines are dimeric natural product hybrids with especially high biological activity; however, they exhibit completely different properties to their monomers. Both types of compounds contain pyrazine unit, which is connected to a highly oxygenated steroid moiety on each side. Cephalostatin 1 (**59**), the most potent compound of this type, was isolated from the marine worm *Cephalodiscus gilchristi*.[70] In an in vitro screening against a National Cancer Institute (NCI) panel of 60 human cancer cell lines, **59** was shown to have a GI_{50} value of about 2.20 nM.

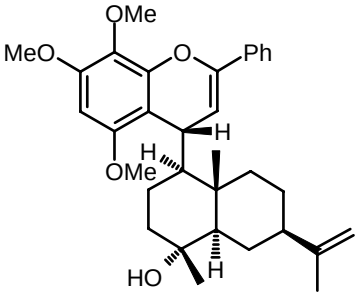
Many other examples of the combination of natural products are known, for example, the cebetins,[71] some anthraquinones-xanthone conjugates, and the secalonic acids[72] in which two xanthone units are bound to each other.



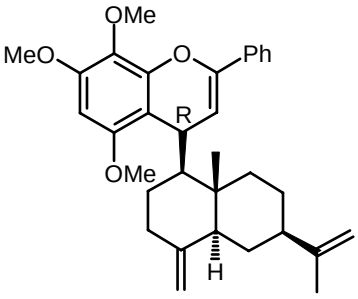
59 :Cephalostatin 1



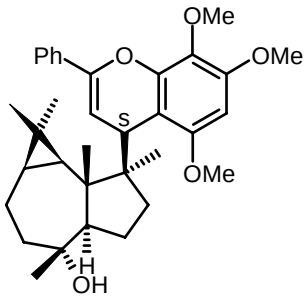
60 : Fissistigmatin A



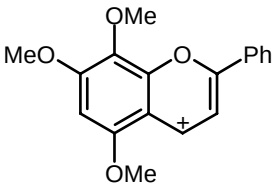
61 : Fissistigmatin B



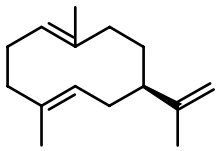
62 : Fissistigmatin C



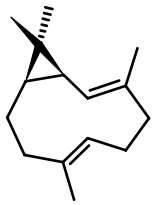
63 : Fissistigmatin D



64

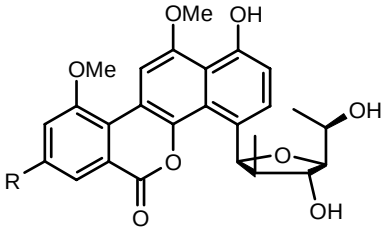


65

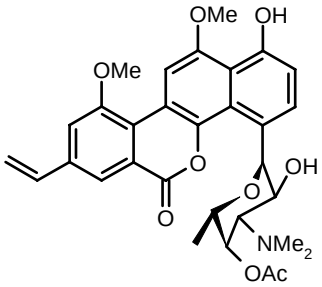


66

Gilvocarcin (**67**) and ravidomycin (**68**) represent a new class of aryl C-glycoside antitumor antibiotics that have a benzonaphthopyrone tetracycle in common and differ in the carbohydrate at C4 (a fucose unit in gilvocarcin and an amino sugar in ravidomycin).[76] It has been shown that the amino sugar congener is biologically more potent.



67a : (-)- Gilvocarcin M
R = Me
67b : Gilvocarcin V
R = CH =CH_2

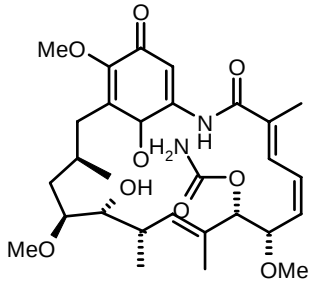


68 : Ravidomycin

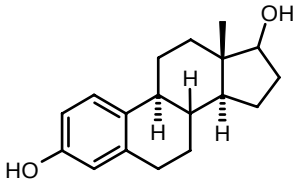
B) Synthetic Hybrid Molecules:

1) Synthetic hybrids of natural products or their analogues:

Geldanamycin (**69**), an ansamycin antibiotic first isolated from *Streptomyces hygroscopicus,* binds to the Hsp90 chaperone protein and causes the degradation of several important signaling proteins. Therefore, it was hoped that an appropriately fashioned hybrid drug of **69** and estradiol (**70**) would offer the ability to induce a selective degradation of estrogen receptor (ER).[77]

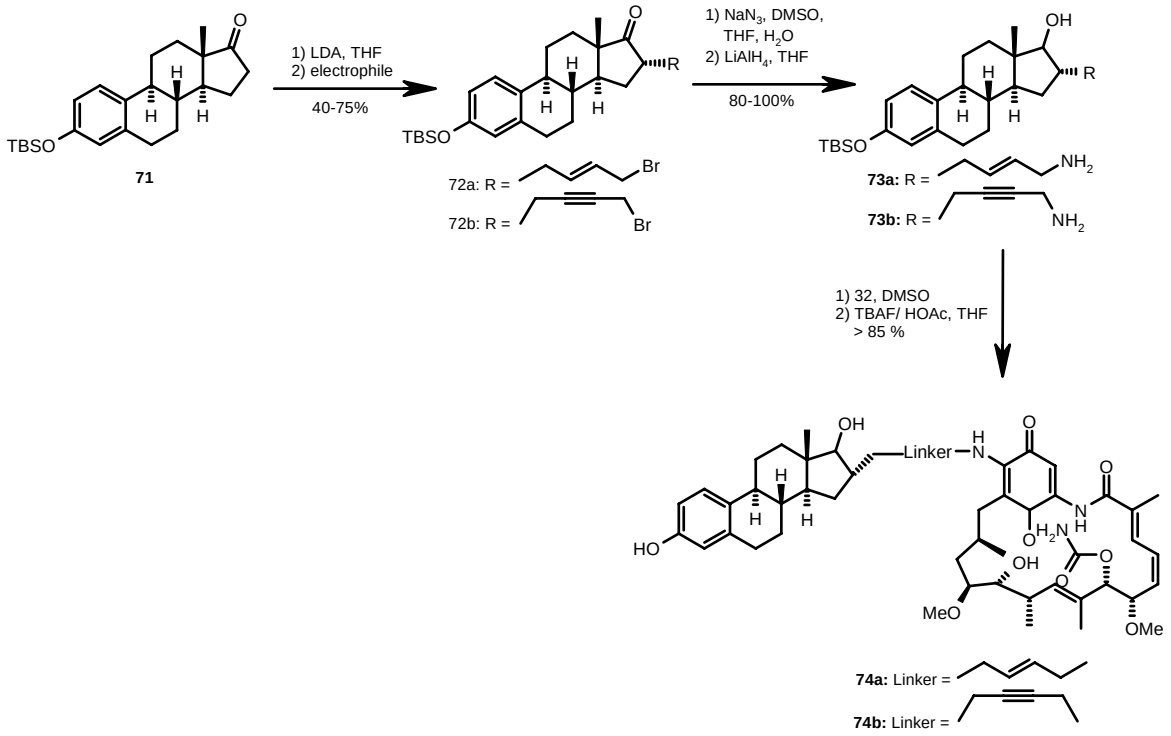


69 : Geldanamycin



70 : Estradiol

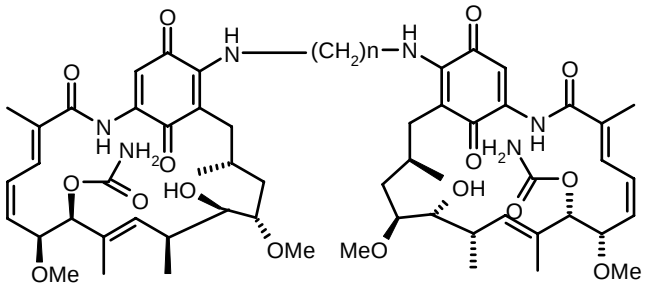
A linker was attached to the protected estrone derivative through α-alkylation of the enolate with a 1,4-dihalide as the electrophile (Scheme 1). The required amino function was introduced by nucleophilic substitution with an azide followed by reduction with $LiAlH_4$.



Scheme 1: Synthesis of hybrids of geldanamycin (69) and esteradiol (70) connected through a linker

The coupling to geldanamycin (GDM, **69**) relied on its Michael acceptor character at C17. Cleavage of the phenolic TBS ether afforded the final estradiol –GDM hybrid **74**, which was subjected to biological tests. The concentrations necessary to reduce the expression of different tumor-relevant proteins in MCF-7 breast cancer cells (HER2, ER, and Raf-1) is summarized in Table 1. A second assay on these proteins and IGFIR revealed that hybrid **74a** is more selective than geldanamycin (**69**) and estradiol (**70**) towards the degradation of HER2 and ER.

As HER-kinases, which are inhibited very effectively by geldanamycin, undergo dimerization on activation, it was speculated that both units of the HER-kinase dimer interact with Hsp90.[78] Accordingly it seemed reasonable that a geldanamycin dimer might be able to interact with both subunits of the HER-kinase dimers, which led to the synthesis of the homohybrids **75a-d**. The two monomers were connected by a diamino alkyl linker of variable length attached to the respective C17 atoms, since this is the only atom not buried in the binding pocket, as revealed by crystal-structure analysis. The selectivity was found to decrease with increasing chain length of the linker. The best selectivity was exhibited by dimer **75a** with butyl linker. It was especially active against SKBR-3, a cell line in which the *HER*2 gene is highly overexpressed. As the GMD-4c dimer has a less pronounced effect on other key signaling proteins, it is likely to be less toxic than geldanamycin itself.



75 a: GMD-4c n = 4
75 b: GMD-7c n = 7
75 c: GMD-9c n = 9
75 d: GMD-12c n = 12

2) Synthetic hybrids of partial structures of natural products or analogues:

This class is again divided in to different types depending upon the parent molecules present in the hybrid molecules, which are as follows

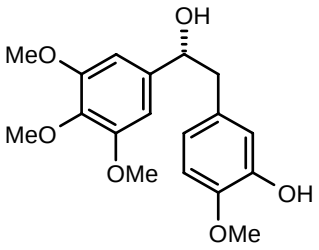
1) Hybrids with a steroid substructure, e. g. hydrocortisone and oleanolic acid[79]
2) Hybrids with a DNA-binding lexitropsin substructure, e. g. synthesis of seco Cl-lexitropsin hybrids.[80]
3) Hybrids with an enediyne substructure, e. g. synthesis of the paclitaxel-esperamicin hybrid taxamicin[81]

4) Hybrid with a peptide substructure, e. g. hybrid of cecropin A and melittin[82, 83, 84]
5) Hybrid with a carbohydrate substructure, e. g. hybrid of calicheamicin-daunorubicin.[85, 86]
6) Hybrids with a microtubule-stabilizing substructure. e. g. hybrid of taxol and epothilone A.[87]
7) Hybrid with a porphyrin substructure, e. g. hybrid of the discodermolide dictyostatin-1.[88, 89]
8) Miscellaneous hybrid molecules, e. g. hybrid of the mucocin-ubiquinone[90]

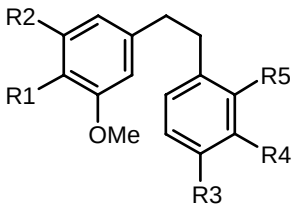
In the present study combretastatin A-4 and benzylidenetetralone moieties were selected for hybridization technique of designing new chemical entities. Therefore SAR studies reported for these parent molecules were surveyed and some relevant reports have been summarized on the following pages.

1. Combretastatin A-4:

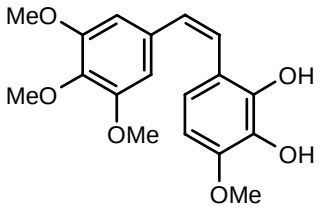
Among the various small molecules, the naturally occurring combretastatins have attracted attention of synthetic organic chemists as well as biologists due to their structural simplicity, biological activity and capacity to bind the colchicines binding sites. Combretastatins are antimitotic agents isolated from the South African tree *Combretum caffrum* Kuntze (Combretaceae). Pettit *et al*.[91] in 1982 isolated and characterized the new cell growth inhibitory substance combretastatin (**76**) which showed marginal cytotoxic activity against the murine P388 leukemia as well as the 9ASK system.



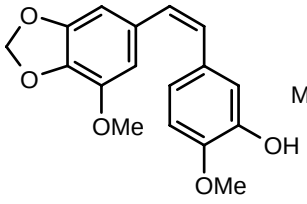
Combretastatin (76)



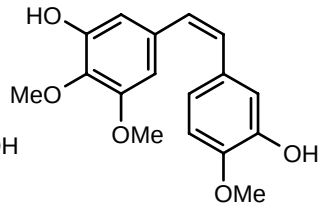
Combretastatin B -1 R1, R2, R3 = OMe; R4, R5 = OH
Combretastatin B -2 R1, R2 = OMe; R3, R4 = OH; R5 = H
Combretastatin B -3 R1, R2 = OMe; R3, R4 = OH; R5 = H
Combretastatin B -4 R1, R5 = H; R2 = OMe; R3, R4 = OH



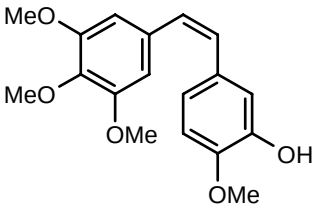
Combretastatin A-1 (77)



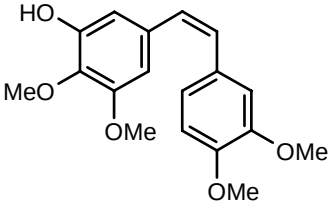
Combretastatin A-2 (78)



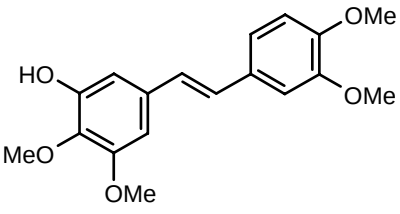
Combretastatin A-3 (79)



Combretastatin A-4 (16)

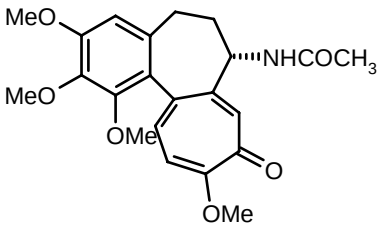


Combretastatin A-5 (80)

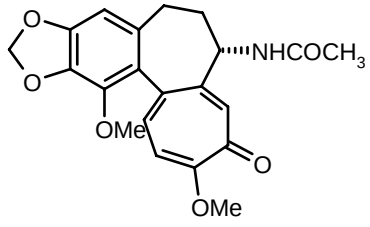


Combretastatin A-6 (81)

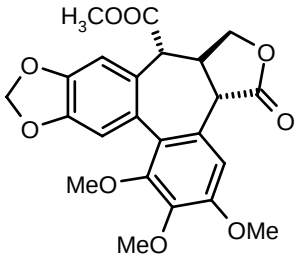
They further isolated series of structurally related compounds [92, 93] combretastatin A-1 (**77**) and B-1 and found that combretastatin A-1 is potent inhibitor of tubulin polymerization (IC_{50} 20 μM). Combretastatin A-2 (**78**), A-3 (**79**), A-5 (**80**), A-6 (**81**), B-2, B-3 and B-4 were also having P388 cell growth inhibitory activities. Combretastatin A-2 and A-3 were also found to markedly inhibit tubulin polymerization.



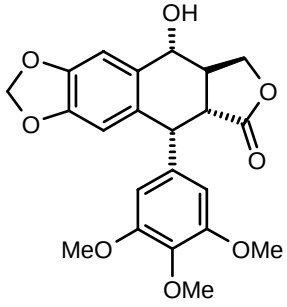
Colchicine (17)



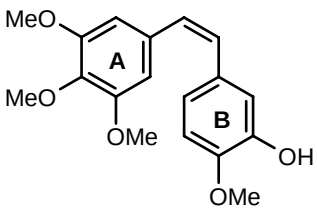
Cornigerine (82)



Steganacin (83)



Podophyllotoxin (8)

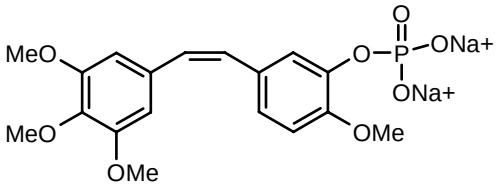


Combretastatin A-4 (16)

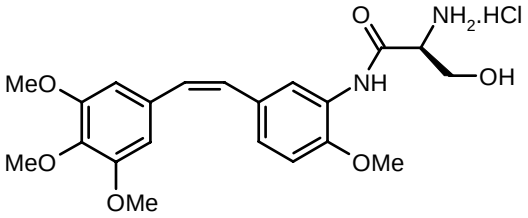
Pettit *et al*.[94] in 1989 isolated combretastatin A-4 (**16)**, a potent inhibitor of microtubule assembly from the South African tree *Combretum caffrum,* showing IC_{50} 2-3 μM. CA-4 binds to tubulin on the colchicine binding site. Many natural products, such as cornigerine (**82**),[95] podophyllotoxin (**8**),[96] steganacin (**83**)[97] and combretastatin A-4 (**16**)[98, 99] bind to the colchicine (**17**) site.

Among the various antimitotic agents inhibiting tubulin polymerization by interaction with the colchicine site, combretastatin derivatives constitute one of the most extensively investigated groups since the discovery of combretastatin A-4.

Numerous studies on structure-activity relationship of combretastatin A-4 have established that 3,4,5-trimethoxy substituents in the A ring and *cis*-orientation between ring A and B are essential for strong cytotoxicity. However, during storage and administration *cis* combretastatin analogues are prone to conversion into *trans* forms. The *trans* forms of these compounds show dramatic reduction in both antitubulin activity and cytotoxicity. Also the low aqueous-solubility of CA-4 was considered and enhanced by making the disodium salt of CA-4 phosphate (**84**)[100,101] and AC -7700 (**85**) reported by Ohsumi *et al*.[104] These compounds show marked tumor growth suppression against the colon 26 murine tumor model and also exert potent antitumor activity.

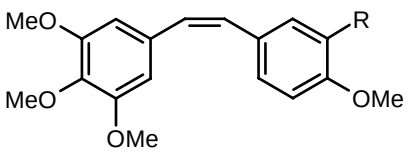


84

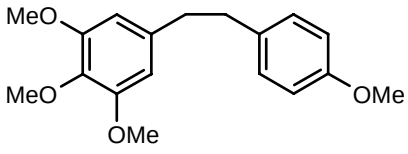


AC - 7700 (85)

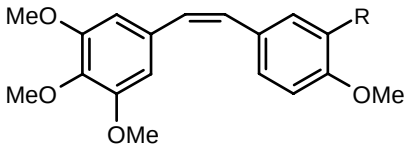
Cushaman *et al*.[102] found that the (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethane (**86**) acts as a cytotoxic tubulin polymerization inhibitor with potency comparable to that of combretastatin A-4. They also found that dihydro derivative **87** works as a potent cytotoxic tubulin polymerization inhibitor. So they prepared the structural congeners of **86** and **87** in an effort to probe the structural features associated with their antitubulin and anticancer activities and synthesized a conformationally restricted analogues[103] of **87**.



R = H (86)
R =OH (CA-4)



87



88

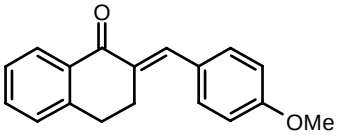
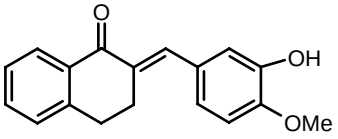
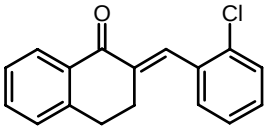
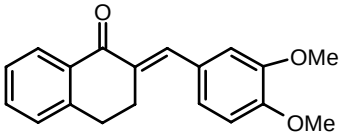
They replaced 4-OMe group on B-ring of **86** and **87** with variety of substituents like OEt, On-Pr, SMe, Me, Et, i-Pr, t-Bu groups. These studies indicated that substitution with large group like t-Bu resulted in the reduction of cytotoxicity and replacement of 4-OMe of B-ring with –SMe group resulted in the compound which was as cytotoxic as the parent compound **86**. From above studies they noticed that increase in steric bulk at this position results in a decrease in activity. The only compound more effective than the parent compound as an inhibitor of tubulin ploymrization was **88**, in which methyl group replaced the 4-methoxy group of CA-4. The potency of this agent as a tubulin polymerization inhibitor was equivalent to combretastatin A-4 (**16**) the natural product, even though it was lacking the adjacent hydroxyl group in the B-ring.

2. Arylidene Tetralone:

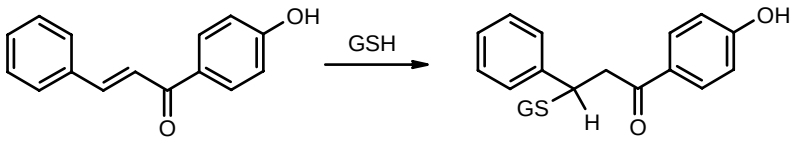
Trans-methyl styryl ketone (MSK) has wide range of industrial and commercial uses.[105] It is a reactive carbonyl compound, an example of simple α, β-unsaturated ketones used in organic synthesis, as well as serves as a pharmaceutical intermediate. MSK has been shown to be positive in several *in vitro* mutagenic assays and does not seem to be toxic. It is relatively non-toxic in animal models.[105a] It is an electrophilic substrate and Michael acceptor that causes the induction of glutathiones *S*-transferase and quinone reductase in human and animals.[105b] It represents potential mechanism for the precipitation of toxic or neoplastic events.[105c] 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.[105d]

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,[106] anticoagulant, [107] platelet-antiaggregant[108] etc (Table 3).

Table 3.

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 3.[105e]



89 **90**

Fig. 3 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.[109] 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.[110]

It has been reported that Mannich bases of conjugated styryl ketones showed potential cytotoxicity against two cell lines (P388, L1210) which are resistant to Melphaln.[111] 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.[112] There after many studies were undertaken in the search of synthetic congener to achieve hit-lead to explore the biodiversity.

Dimmock and coworkers reported[113] cytotoxic activities of Mannich bases of chalcones and related compounds against different cancer cell lines such as P388, L1210, MOLT4 and CEM cells.

Considering the strong background of parent compounds against cytotoxic activity we planned to synthesize the hybrid of combretastatin A-4 and arylidene tetralones which were showed comparable cytotoxic activity to parent molecules the results were described in this chapter.

CHAPTER - I

SECTION - I

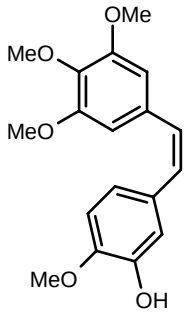
NEW 2-ARYLIDENE TETRALONE DERIVATIVES

PART - A

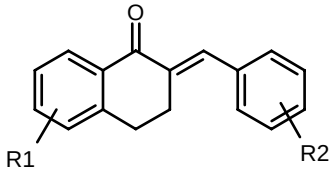
Mg MEDIATED 1,2 AND 1,4-ADDITION PRODUCTS

1.1.1: INTRODUCTION:

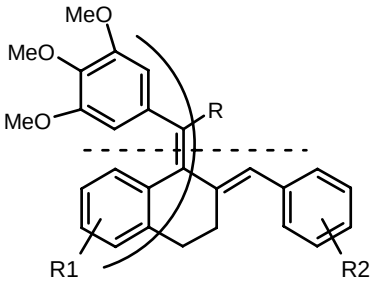
Synthesis of hybrid molecules to generate biologically active new chemical entities has been one of the well-adapted techniques under new drug discovery research programmes.[113] Structural hybrid compounds are usually designed by selecting at least two biologically active small molecules. We have been lately working on the synthetic analogues[114] of combretastatin A-4 (**16)**. One of the designed hybrid molecules **92** was expected to show enhanced cytotoxic activity by inhibition of tubulin polymerization since it encompassed combretastatin A-4 (**16)** and 2-benzylidene-1-tetralones (**91)** as shown in Fig. 1 which are independently known for this activity.



16: Combretastatin A-4



91: Benzylidene-1-tetralone



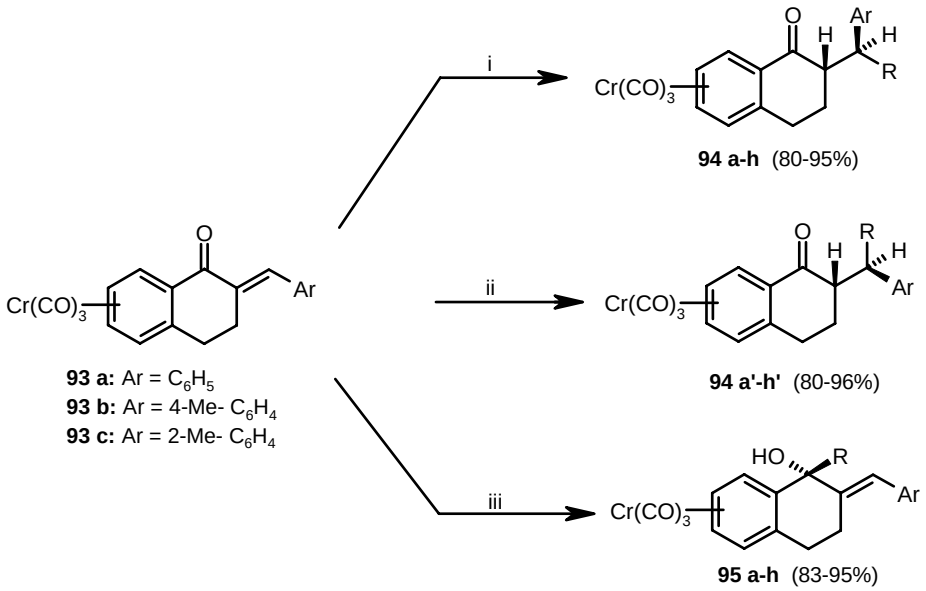
92: Designed hybrid

Fig. - 1

Synthesis of 2-benzylidene-1-tetralones (**91)** and their biological activity screening was the first step in this research work. The designed molecules **92** could be synthesized from the enones **87** by 1, 2-addition of benzyl bromides followed by elimination. Literature survey revealed scattered reports on the Grignard reaction on 2-benzylidene-1-tetralones.

BRIEF REVIEW OF LITERATURE:

Literature survey revealed only one report on synthesis of similar compounds by 1,4-addition on 2-benzylidene-1-tetralone. Sarkar A. *et al*. reported[115] that metal complexation to one face of an aromatic ring in arene tricarbonylchromium complexes permits excellent stereocontrol in reaction at aromatic, benzylic as well as homobenzylic positions, where the reagent approaches preferentially from the face opposite to the metal (anti-addition). In suitably designed substrates and reactions, such steric bias can be transmitted to reaction centers even three carbons away from the complexed arene ring thereby extending the scope of stereoselective synthesis on such metal templates. A lone exception to this general trend is a syn-selective cyclopropanation of a 2-arylidene-1-tetralone-$Cr(CO)_3$ complex by dimethylsulfoxonium methylide. Otherwise, a syn-addition is observed only if the reagent is delivered from the metal. With the availability of optically pure starting complexes and methods for obtaining them, enantioselective synthesis of various target molecules has now been achieved. One can now conceptually integrate such methodologies into tailored approaches to multi-functionalised aliphatic or alicyclic structures as depicted in Scheme-1.



Reagents and Conditions : i: $TiCl_4$ -90 ^{0}C 15 min ; RLi or RMgX, -90 ^{0}C, 15 min; **ii :** $R_2Cu(CN)Li_2$, -78 ^{0}C, 1h
iii : RLi, -90 ^{0}C, 30 min

Scheme - 1

1.1.2: PRESENT WORK:

Reactions are the tool kit for chemists 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 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 and getting an important novel product with few side products is the concept of divergences and convergences in organic synthesis.

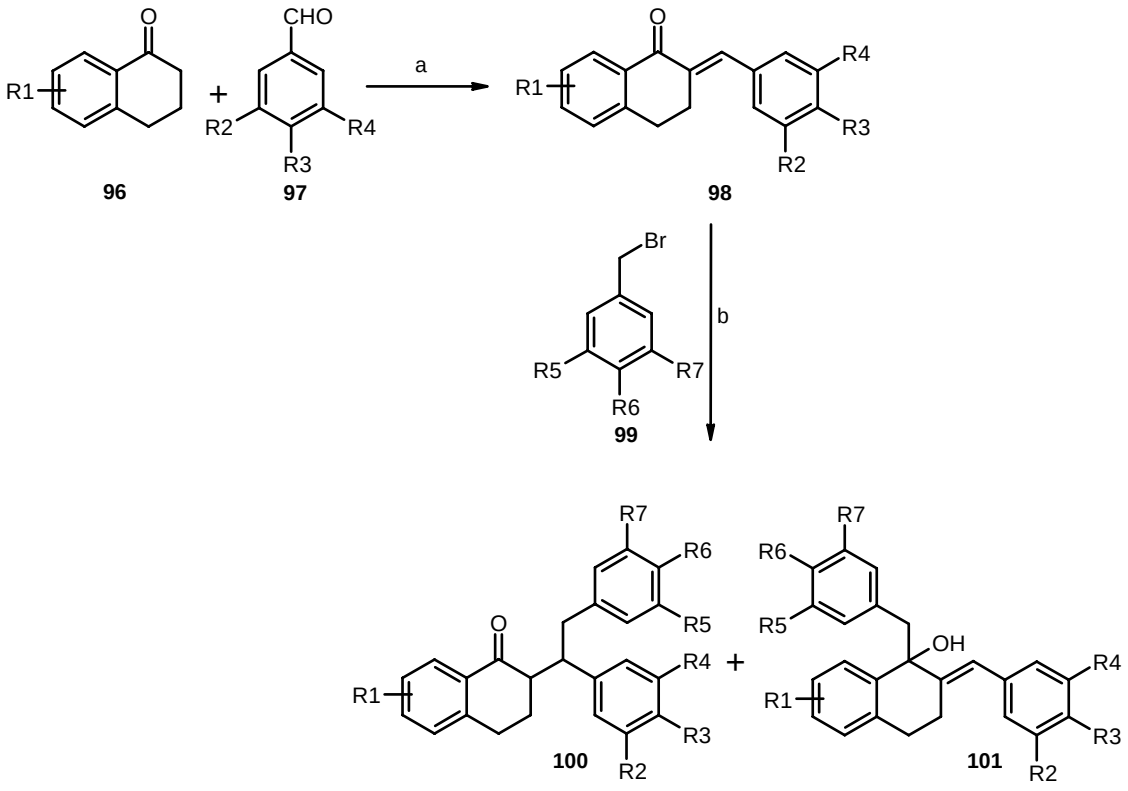
Literature survey revealed that the number of hybrid molecules are showing promising cytotoxic activity as compared to their parent molecules. Structural hybrid compounds are usually designed by selecting at least two biologically active small molecules. We have been lately working on the synthetic analogues of combretastatin A-4 (**16**). The designed hybrid molecules **92** were synthesized in the present work and studied for anticancer activity and the results are discussed in this section. The compounds **16** and **91** are independently known for anticancer activity.

1.1.3: RESULTS AND DISCUSSION:

Literature survey revealed that 2-arylidene-1-tetralones have been screened for various biological activities like antifungal, anticoagulant, platelet-antiaggregant etc. The various new chemical entities studied in the present work were prepared by the synthetic sequences shown in scheme-2. The 2-arylidene-1-tetralone derivatives have been synthesized by Claisen-Schmidt condensation using substituted 1-tetralones and arylaldehydes with substitutents 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 spectra of compound **98** showed that the compounds **98** 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-tetralone derivatives.

We employed Grignard reaction for the synthesis of designed new chemical entities **100** and **101**. The intermediates **98** were subjected for Grignard reaction with substituted benzyl bromides **99** to furnish the NCEs **100** and **101**. The conventional method of Grignard reagent formation from benzyl bromide provided self coupled product quantitatively as expected. However, this self-coupling could be avoided by addition of arylidene-1-tetralone and benzyl bromide to magnesium in tetrahydrofuran simultaneously. The product obtained was a mixture of two compounds which were expected to be 1, 2- and 1, 4- addition products. To our surprise the major product from most of the examples was identified as 1, 4-addition product along with the 1, 2-addition product as the minor component.



Reagents and Conditions: a) NaOH, EtOH, rt, 12 h b) Substituted benzyl bromides, Mg, THF, rt, 3 h

Scheme - 2

In a typical example α – tetralone was treated with benzaldehyde in ethanol by using aqueous sodium hydroxide at room temperature to furnish the 2-benzylidene-3, 4 –

dihydro-2*H*-naphthalen-1-one (**98a**). This 2-benzylidene-3, 4-dihydro-2*H*-naphthalen-1-one (**98a**) was further treated with benzyl bromide (**99** wherein R5 = R6 = R7 = H) in the presence of magnesium metal in dry tetrahydrofuran at room temperature. The product after usual work-up gave mixture of two components. The major and minor components in PMR and CMR exhibited various peaks in accordance with the 1, 4- addition product **100a**, while the minor product was assigned as a 1, 2-addition product **101a**. The assignments of the structures were done as described below.

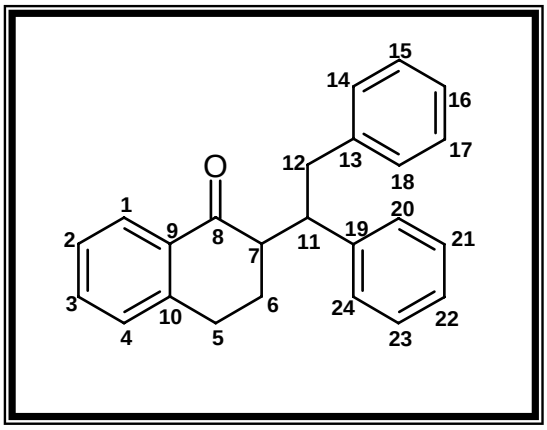


Table 1, Compound (100a)

^{1}H NMR spectrum of compound **100a** exhibited various peaks in accordance with assigned structure as 1, 4-addition product. A multiplet at δ 1.90 - 2.00 for two protons was seen for the methylene –CH_2 present at C-6, while the multiplet at δ 2.57 - 2.74 for three protons and a multiplet at δ 2.81 - 3.10 for three protons were assigned for the protons from C-5, 7, 11 and 12 respectively. The multiplets at δ 6.44 - 6.55 and 6.83 - 7.28 were due to the aromatic protons including the protons at C - 3 and C - 4. A triplet at δ 7.44 was assigned for the proton present on C - 2 (J = 8 Hz) and a doublet at δ 7.94 was due to proton at C - 1.

^{13}C NMR spectrum fully supported the structure of 1, 4 - addition product **100a**. It displayed 19 signals for 24 carbons, the upfield signal at δ 25.65 was assigned for benzylic methyl C - 12, while the signals at δ 34.13 and 37.29 were due to presence of two methylene groups from tetralone moiety at C - 5 and 6. Signal at δ 50.97 was assigned for the C - 11 and 12. The carbonyl carbon C - 8 of the tetralone ring appeared at δ 202.35 while other peaks from aromatic region were at their expected chemical

shifts. From the ^{1}H NMR and ^{13}C NMR spectral evaluation the structure was assigned for compound **100a** and was further confirmed from other characteristic spectral information presented in experimental section.

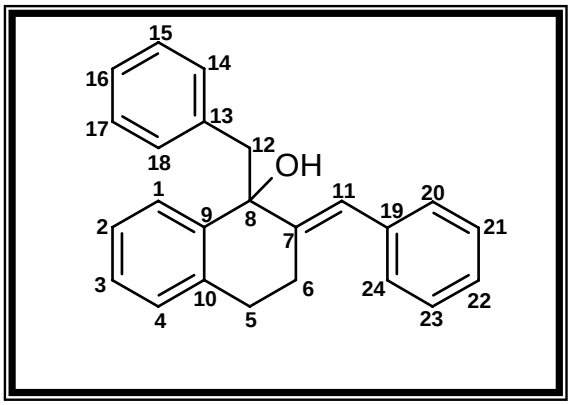
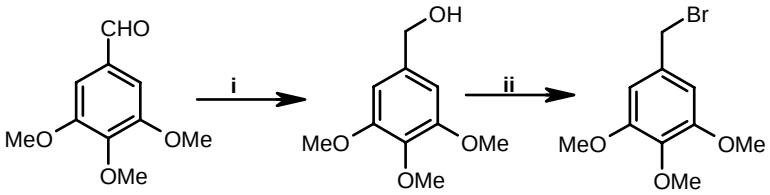


Table 1, Compound (101a)

The minor compound **101a** was characterized as 1, 2 - addition product from ^{1}H NMR as well as ^{13}C NMR spectrum and other analytical. ^{1}H NMR spectrum of compound **101a** exhibited various peaks in the spectrum which could be assigned and were in full agreement with the 1, 2-addition product. A multiplet at δ 2.60 - 2.90 was assigned for two protons from tetralone ring on C - 6, a multiplet at δ 3.20 - 3.50 (4H) was due to the presence of benzylic protons at C - 5 and C - 12, while a broad singlet at δ 4.06 was assigned for the alcoholic –OH present on C - 8. The other aromatic protons from C - 14 to C - 18, C - 20 to C - 24 and C - 3, 4 appeared as a set of multiplets from δ 6.93 - 7.42. The olefinic singlet of C - 11 was found to be merged in aromatic multiplets. A triplet at δ 7.58 (J = 6 Hz) was assigned for the proton on C - 2, while the doublet at δ 7.75 (J = 6 Hz) was assigned for the proton on C - 1. The absence of carbonyl functional group in the structure was confirmed by IR spectrum, which showed the absence of carbonyl functional group in the IR spectrum.

The structure of minor compound **101a** was further confirmed by ^{13}C NMR spectrum. It exhibited 18 signals for 24 carbon atoms including the upfield signal at δ 26.17 which was assigned for benzylic methylene at C - 12, while the signals at δ 32.56 and 34.98 were due to the presence of two methylene groups from tetralone moiety at C - 5 and 6. The characterstic difference in the structure of **100a** and **101a** is the presence of carbonyl

functional group in 1, 4-addition product **100a** and absence of it in 1, 2-addition product **101a**. The signal at δ 77.97 was assigned for the C - 8 while this carbon showed a signal at δ 202.35 in 1, 4–addition product. The absence of carbonyl functional group was also confirmed by IR spectrum. All other peaks from the assigned structure **101a** were at their expected chemical shifts which are listed in experimental section.



102 **103** **104**

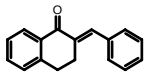
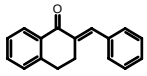
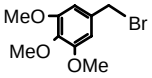
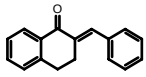
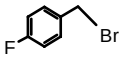
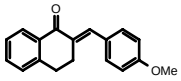
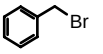
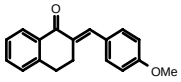
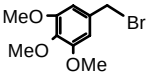
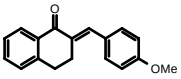
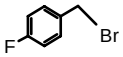
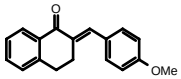
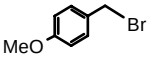
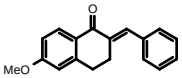
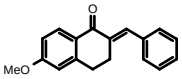
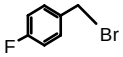
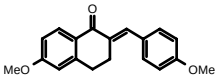
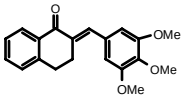
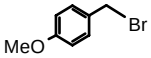
Reagents and Conditions: i = $NaBH_4$, MeOH, R T, 4 h **ii**= PBr_3, CCl_4, R T, 7 h

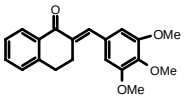
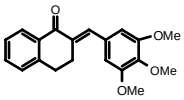
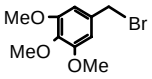
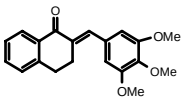
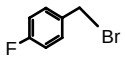
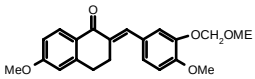
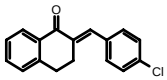
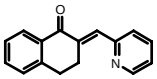
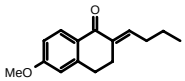
Scheme – 3

The required benzyl bromides were synthesized from the commercially available substituted aromatic aldehyeds as shown in scheme-3. 3,4,5-Trimethoxy benzaldehyde (**102**) was subjected to reduction with sodium borohydride in dry methanol at room temperature for 7 h to furnish corresponding 3,4,5-trimethoxybenzyl alcohol (**103**). Further this 3,4,5-trimethoxybenzyl alcohol (**103**) was brominated with PBr_3 in carbon tetrachloride under nitrogen atomosphere at room temperature and the resulting 3,4,5 – trimethoxybenzyl bromide (**104**) was used for the synthesis of compounds **100b** and **101b** in presence of magnesium and tetrahydropyran using Grignard reaction conditions.

Table-1 depicts the compounds (**100a-100r** to **101a-101r**) synthesized by the above described magnesium mediated reaction using variably substituted arylidene tetralones as starting materials. The reaction was selective for 2-arylidene-1-tetralone as indicated by the results depicted in table-1 entries a to q. The 2-alkylidene-1-tetralone (entry r) did not react under these conditions. The ratio of product formation was almost consistant in the examples **100a-q** to **101a-q**.

Table-1: NCEs by Grignard Reaction:

Entry	Enone	Benzyl Bromides	1, 4-Add. Product (100) Yield (%)	1, 2-Add. Product (101) Yield %)	Time in hr
a	 **(98a)**		**70**	**23**	**3**
b	 **(98a)**		**70**	**20**	**3**
c	 **(98a)**		**75**	**20**	**3**
d	 **(98b)**		**65**	**20**	**3**
e	 **(98b)**		**72**	**20**	**3**
f	 **(98b)**		**75**	**18**	**3.5**
g	 **(98b)**		**75**	**18**	**4**
h	 **(98c)**		**73**	**18**	**3**
i	 **(98c)**		**75**	**20**	**3**
j	 **(98d)**		**70**	**19**	**3.5**
k	 **(98e)**		**75**	**20**	**3**

l	 **(98e)**		**70**	**22**	**3**
m	 **(98e)**		**70**	**19**	**4**
n	 **(98e)**		**76**	**20**	**3**
o	 **(98f)**		**65**	**25**	**3**
p	 **(98g)**		**72**	**21**	**3**
q	 **(98h)**		**85**	**--**	**3**
r	 **(98i)**		**NIL**	**NIL**	**24**

Some of the analogues obtained by condensation of substituted benzylhalides and arylidene-1-tetralone were tested for their cytotoxicity activity. The results of biological studies and the structure activity relationship are summarized in section three of this chapter.

1.1.4: CONCLUSION:

We synthesized the new chemical entities as hybrid molecules of combretastatin A-4 and arylidene tetralones. We have used the Grignard reaction approach to generate library of 36 new chemical entities. These compounds were screened for their potential cytotoxicity.

1.1.5: EXPERIMENTAL:

General procedure for synthesis of 2-arylidene 1-tetralone (98):

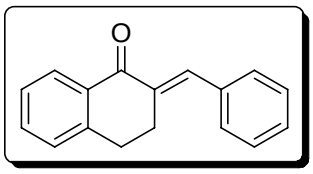
Condensation under basic condition:

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 reaction was monitored 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 (15 ml) 50 % HCl (5ml) was added and the mixture, was stirred 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.

2-Benzylidene-3,4-dihydro-2H-naphthalen-1-one (98 a):

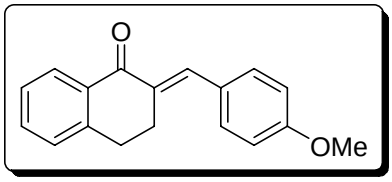


Nature: Pale yellow solid; **Yield:** 88 %; **M. p.** 128 ºC; **IR** (Chloroform)**:** ν_{max} 3014, 1668, 1210 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.95 (t, J = 8 Hz, 2H), 3.14 (t, J = 8 Hz, 2H), 7.23 - 7.52 (m, 8H), 7.88 (s, 1H), 8.15 (d, J = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz)**:** δ 26.9, 28.5, 126.7 (2C), 127.9 (2C), 128.2 (2C), 129.6

(2C), 132.9 (2C), 134.0, 134.1, 136.2, 142.8, 187.2; **Anal. Calcd. for** $C_{17}H_{14}O$**:** C, 87.15; H, 6.02 %. **Found:** C, 87.02; H, 5.93 %.

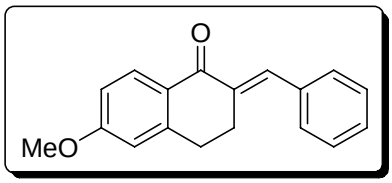
2-(4-Methoxy-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (98 b):

Nature: Pale yellow solid; **Yield:** 84 %; **M. p.** 86 ºC; **IR** (Chloroform)**:** ν_{max} 3012, 1668, 1210 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.32 (t, J = 8 Hz, 2H), 2.65 (t, J = 8 Hz, 2H), 3.80 (s, 3H), 6.72 (d, J = 8 Hz, 2H), 6.82 (d, J = 8 Hz, 2H), 7.10 - 7.70 (m, 5H), 8.12 (d, J = 8, 1H); **Anal. Calcd. for** $C_{18}H_{16}O_2$**:** C, 81.79; H, 6.10 %. **Found:** C, 81.63; H, 6.05 %.



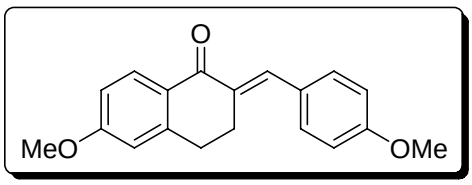
2-Benzylidene-6-methoxy-3,4-dihydro-2H-naphthalen-1-one (98 c):

Nature: Pale yellow solid; **Yield:** 91 %; **M. p.** 79 ºC; **IR** (Chloroform)**:** ν_{max} 3010, 1667, 1217 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.94 (t, J = 8 Hz, 2H), 3.10 (t, J = 8 Hz, 2H), 3.73 (s, 3H), 6.72 (d, J = 8 Hz, 1H), 6.82 (s, 1H), 7.12 - 7.32 (m, 5H), 7.62 (s, 1H), 7.85 (dd, J = 8 and 2 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz)**:** δ 25.9, 29.4, 56.0, 111.8, 114.0, 126.2 (2C), 127.7, 128.4 (2C), 129.1, 134.6, 134.9, 142.4, 167.7, 187.1; **Anal. Calcd. for** $C_{18}H_{16}O_2$**:** C, 81.79; H, 6.10 %. **Found:** C, 81.52; H, 6.00 %.



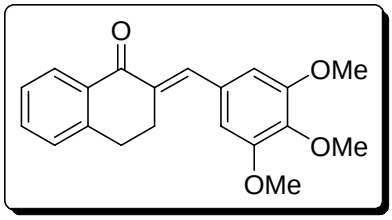
6-Methoxy-2-(4-methoxy-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (98 d):

Nature: Pale yellow solid; **Yield:** 85 %; **M. p.** 139 ºC; **IR** (Chloroform)**:** ν_{max} 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 and 2 Hz, 2H), 7.78 (s, 1H), 8.12 (dd, J = 8 and 2 Hz, 2H); **Anal. Calcd. for** $C_{19}H_{18}O_3$**:** C, 77.53; H, 6.16 %. **Found:** C, 77.39; H, 6.03 %.



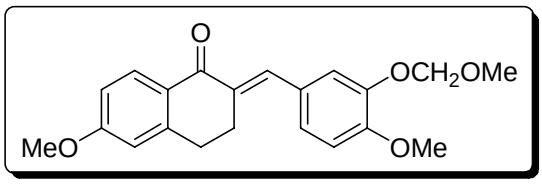
2-(3,4,5-trimethoxy-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (98 e):

Nature: Yellow solid; **Yield:** 97 %; **M. p.** 102 ºC; **IR** (Chloroform)**:** ν_{max} 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, 9H), 6.67 (s, 2H), 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; **Anal. Calcd. for** $C_{20}H_{20}O_4$**:** C, 74.06; H, 6.21 %. **Found:** C, 73.92; H, 6.07 %.



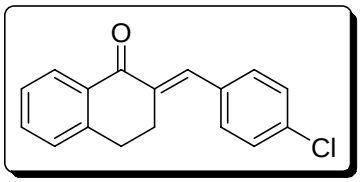
6-methoxy-2-(4-methoxy-3-methoxymethoxy-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (98 f):

Nature: Pale yellow semisolid; **Yield:** 72 %; **IR** (Chloroform)**:** ν_{max} 3010, 1670, 1605, 1506, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.91 (t, J = 6 Hz, 2H), 2.75 (t, J = 6 Hz, 2H), 3.26 (s, 3H), 3.76 (s, 6H), 5.40 (s, 2H), 6.55 - 6.90 (m, 5H), 7.62 (s, 1H), 7.80 (d, J = 8, Hz, 1H); **Anal. Calcd. for** $C_{21}H_{22}O_5$**:** C, 71.17; H, 6.26 %. **Found:** C, 71.10; H, 6.15 %.



2-(3-chloro-benzylidene)-3,4-dihydro-2H-naphthalen-1-one (98 g):

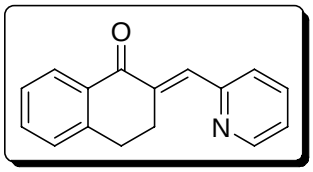
Nature: Pale yellow semisolid; **Yield:** 89 %; **IR** (Chloroform)**:** ν_{max} 3019, 1668, 1606, 1490, 1457, 1435 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.91 (t, J = 8 Hz, 2H), 3.03 (t, J = 6 Hz, 2H), 7.10 - 7.24 (m, 2H), 7.25 - 7.40 (m, 3H), 7.41 - 7.50 (m, 2H) 7.73 (s, 1H), 8.06 (d, J = 8, Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4, 50 MHz)**:** δ 27.1, 28.6, 127.0, 128.1, 128.2, 128.6 (2C), 131.0 (2C), 133.2,



134.0, 134.1, 135.1, 135.8, 142.9, 187.2; **Anal. Calcd. for** $C_{17}H_{13}OCl$**:** C, 75.98; H, 4.88; Cl, 13.19 %. **Found:** C, 75.79; H, 4.73; Cl, 13.02 %.

2-Pyridin-2-ylmethylene-3,4-dihydro-2H-naphthalen-1-one (98 h):

Nature: Pale yellow semisolid; **Yield:** 91 %; **IR** (Chloroform)**:** ν_{max} 3019, 1669, 1595, 1516, 1473, 1457 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.93 (t, J = 6 Hz, 2H), 3.51 (t, J = 6 Hz, 2H), 7.10 - 7.50 (m, 5 H), 7.56 - 7.74 (m, 2H), 8.05 (d, J = 8 Hz, 1H), 8.63 (d, J = 4, Hz, 1H); **Anal. Calcd. for** $C_{16}H_{13}NO$**:** C, 81.68; H, 5.57; N, 5.95 %. **Found:** C, 81.52; H, 5.73; N, 5.79 %.

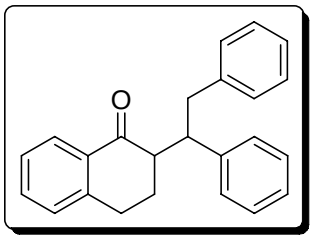


Typical Procedure for Grignard reaction: (Table-1, entry a)

Magnesium turnings (51 mg, 2.13 mmol, activated) were taken in a dry 50 ml two-necked round bottom flask, the flask was evacuated and flushed with nitrogen. Freshly distilled dry THF (2 ml) was added in it. In another 25 ml round bottom flask 2-benzylidene-3,4-dihydro-2*H*-naphthalen-1-one (500 mg, 2.13 mmol) was flushed under nitrogen and dissolved in dry THF (5 ml). Benzyl bromide (366 mg, 2.13 mmol) was added followed by immediate addition of 2-benzylidene-3,4-dihydro-2*H*-naphthalen-1-one in THF at room temperature. After 20 min, the colour of reaction mixture became dark red. Complete disappearance of starting material was observed after 3 h (reaction was monitored by TLC). The reaction mixture was then cooled in ice, quenched with dil HCl (1N, 2 ml) and extract with ethyl acetate (3 x 100 ml), dried over sodium sulphate. It was then concentrated on rotary evaporator and purified on column chromatography yielded pure products.

***3,4-dihydro-2-(1,2-diphenylethyl)naphthalen-1(2H)-one (100 a)*:**

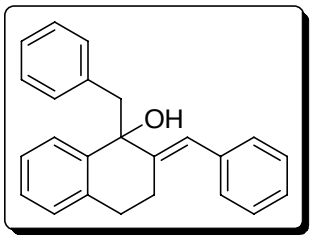
Nature: Brick red semisolid; **Yield:** 70 %; **IR** (chloroform)**:** ν_{max} 3019, 1678, 1602, 1492, 1453 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.90 - 2.05 (m, 2H), 2.55 - 2.80 (m, 3H), 2.82 - 3.05 (m, 3H), 6.35 - 6.55 (m, 2H), 6.81 - 6.90 (m, 2H), 7.02 - 7.32 (m, 8H), 7.44 (t,



J = 8 Hz, 1H), 7.94 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.6, 34.1, 37.3, 51.0 (2C), 125.6, 125.8, 126.9, 126.9, 127.0, 127.7 (2C), 128.0 (2C), 128.9 (2C), 129.6 (2C), 130.4, 134.0, 139.3, 140.0, 143.3, 202.3; **Anal. Calcd. for** $C_{24}H_{22}O$**:** C, 88.31; H, 06.79 %. **Found:** C, 88.12; H, 06.52 %.

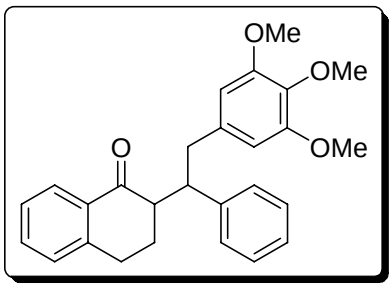
***1-Benzyl-2-benzylidene-1,2,3,4-tetrahydro-naphthalen-1-ol (101 a)*:**

Nature: Brick red semisolid; **Yield:** 23 %; **IR** (chloroform)**:** ν_{max} 3412, 1606, 1502, 1456 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.60 - 2.95 (m, 2H), 3.22 - 3.50 (m, 4H), 4.06 (s, 1H), 6.91 - 6.99 (m, 2H), 7.06 - 7.20 (m, 6H), 7.25 - 7.45 (m, 5H), 7.58 (t, *J* = 6 Hz, 1H) 7.75 (d, *J* = 6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 26.2, 32.6, 35.0, 77.97, 125.7, 125.8, 126.9 (2C), 127.7 (2C), 128.0 (2C), 128.6, 128.8 (2C), 128.9 (2C), 129 (2C), 131.2, 133.5, 138.4, 140.1, 142.3; **Anal. Calcd. for** $C_{24}H_{22}O$**:** C, 88.31; H, 06.79 %. **Found:** C, 88.05; H, 06.60 %.



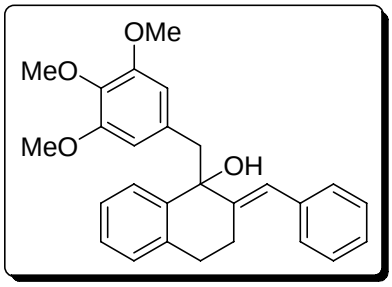
3,4-Dihydro-2-(2-(3,4,5-trimethoxyphenyl)-1-phenylethyl)naphthalen-1(2H)-one (100 b):

Nature: Dark brown semisolid; **Yield:** 70 %; **IR** (chloroform)**:** ν_{max} 3016, 1680, 1591, 1508, 1456 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.89 - 2.01 (m, 2H), 2.14 - 2.27 (m, 1H), 2.58 - 3.02 (m, 5H), 3.40 (s, 6H), 3.61 (s, 3H), 5.61 (s, 2H), 7.10 - 7.25 (m, 5H), 7.26 - 7.35 (m, 1H), 7.46 (t, *J* = 6 Hz, 1H), 7.91 (d, *J* = 6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.6, 34.1, 37.7, 51.0, 55.6 (2C), 60.6, 78.0, 105.9 (2C), 126.9 (2C), 127.5, 128.2 (2C), 128.9, 129.1, 129.8 (2C), 130.4, 134.0, 135.5, 135.7, 140.5, 143.3, 152.4, 202.3; **Anal. Calcd. for** $C_{27}H_{28}O_4$**:** C, 77.88; H, 06.73 %. **Found:** C, 77.50; H, 06.50 %.



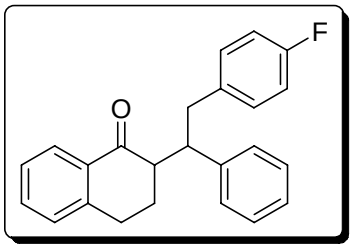
***2-Benzyl-1-(3,4,5-trimethoxy-benzyl)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 b)*:**

Nature: Dark brown semisolid; **Yield:** 20 %; **IR** (chloroform)**:** ν_{max} 3410, 1600, 1510, 1454, 1402 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.06 - 2.40 (m, 2H), 2.74 - 3.10 (m, 4H), 3.63 (s, 6H), 3.71 (s, 3H), 6.11 (s, 2H), 7.09 - 7.31 (m, 8H), 7.33 - 7.41 (m, 1H), 7.97 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{27}H_{28}O_4$**:** C, 77.88; H, 06.73 %. **Found:** C, 77.65; H, 06.62 %.



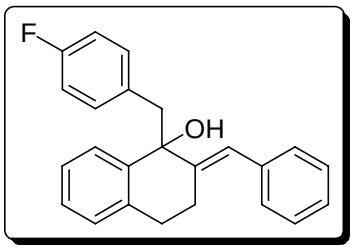
2-(2-(4-Fluorophenyl)-1-phenylethyl)-3,4-dihydronaphthalen-1(2H)-one (100 c):

Nature: Brown semisolid; **Yield:** 75 %; **IR** (chloroform)**:** ν_{max} 3019, 1679, 1602, 1509, 1454, 1435 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.02 - 2.14 (m, 2H), 2.40 - 2.55 (m, 1H), 2.77 - 3.11 (m, 6H), 6.51 - 6.71 (m, 3H), 7.17 - 7.61 (m, 9H), 8.08 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.0, 33.5, 35.8, 48.1, 50.5, 77.3, 113.7, 114.1, 126.4 (2C), 127.0, 127.5 (2C), 128.1, 129.0, 129.6, 129.8, 133.5, 134.7, 139.2, 142.7 (2C), 158.0, 201.6; **Anal. Calcd. for** $C_{24}H_{21}FO$**:** C, 83.72; H, 06.10; F, 5.52 %. **Found:** C, 83.55; H, 06.05; F, 5.38 %.



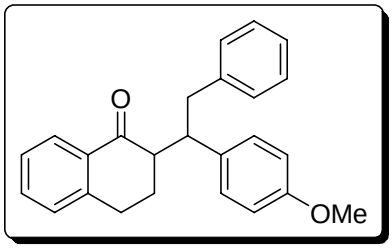
***2-Benzylidene-1-(4-fluoro-benzyl)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 c)*:**

Nature: Brown semisolid; **Yield:** 20 %; **IR** (chloroform)**:** ν_{max} 3402, 1600, 1506, 1456, 1423 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.12 - 2.34 (m, 3H), 2.62 - 3.15 (m, 4H), 6.50 - 6.76 (m, 4H), 7.20 - 7.76 (m, 10H); **Anal. Calcd. for** $C_{24}H_{21}FO$**:** C, 83.72; H, 6.10; F, 05.52 %. **Found:** C, 83.65; H, 06.00; F, 05.45 %.



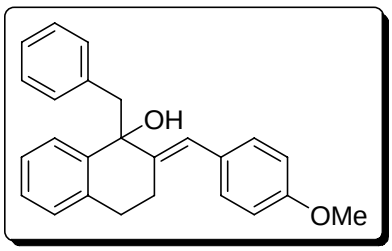
3,4-Dihydro-2-(1-(4-methoxyphenyl)-2-phenylethyl) naphthalen-1(2H)-one (100 d):

Nature: Dark red semisolid; **Yield:** 65 %; **IR** (chloroform)**:** ν_{max} 3026, 1680, 1603, 1509, 1454, 1375, 1286, 1249 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.73 - 0.87 (m, 2H), 1.84 - 1.95 (m, 1H), 2.49 - 3.02 (m, 5H), 3.60 (s, 3H), 6.59 - 6.68 (m, 2H), 6.78 - 6.87 (m, 2H), 6.97 - 7.29 (m, 5H), 7.37 (t, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{25}H_{24}O_2$**:** C, 84.26; H, 06.74 %. **Found:** C, 84.10; H, 06.72 %.



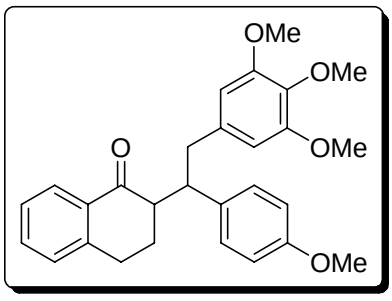
***1-Benzyl-2-(4-methoxy-benzylidene)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 d)*:**

Nature: Dark red semisolid; **Yield:** 20 %; **IR** (chloroform)**:** ν_{max} 3402, 1600, 1502, 1456, 1380, 1280 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.03 - 2.32 (m, 3H), 2.56 - 3.02 (m, 4H), 3.66 (s, 3H), 6.68 - 6.96 (m, 3H), 6.98 - 7.38 (m, 10H), 7.52 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{25}H_{24}O_2$**:** C, 84.26; H, 6.74 %. **Found:** C, 84.16; H, 6.68 %.



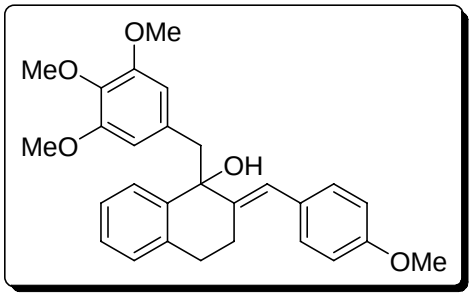
3,4-Dihydro-2-(2-(3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)ethyl)naphthalen-1(2H)-one (100 e):

Nature: Brick red semisolid; **Yield:** 72 %; **IR** (chloroform)**:** ν_{max} 3002, 1680, 1606, 1510, 1450, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.02 - 2.25 (m, 1H), 2.30 - 2.40 (m, 1H), 2.60 - 3.10 (m, 5H), 3.51 (s, 3H), 3.69 (s, 6H), 3.81 (s, 3H), 6.20 (s, 2H), 6.70 - 6.90 (m, 2H), 7.10 - 7.45 (m, 5H), 8.23 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{28}H_{30}O_5$**:** C, 75.34; H, 06.73 %. **Found:** C, 75.10; H, 06.68 %.



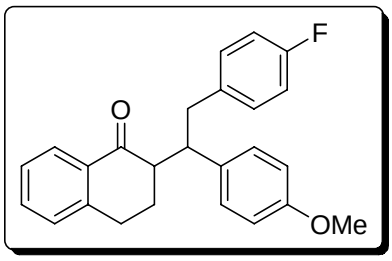
2-(4-Methoxy-benzylidene)-1-(3,4,5-trimethoxy-benzyl)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 e):

Nature: Brick red semisolid; **Yield:** 20 %; **IR** (chloroform)**:** v_{max} 3402, 1600, 1512, 1456 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.10 - 2.42 (m, 3H), 2.50 - 3.14 (m, 4H), 3.60 (s, 3H), 3.70 (s, 6H), 3.82 (s, 3H), 6.25 (s, 2H), 6.70 - 6.95 (m, 3H), 7.10 - 7.42 (m, 5H), 7.54 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{28}H_{30}O_5$**:** C, 75.34; H, 06.73 %. **Found:** C, 75.21; H, 06.57 %.



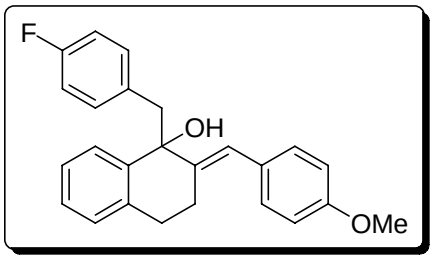
2-[2-(4-Fluorophenyl)-1-(4-methoxyphenyl)ethyl)-3,4-dihydronaphthalen-1(2H)-one (100 f):

Nature: Brownish semisolid; **Yield:** 75 %; **IR** (chloroform)**:** v_{max} 3017, 1678, 1600, 1504, 1450, 1434 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.90 - 2.10 (m, 2H), 2.15 - 2.35 (m, 1H), 2.50 - 3.10 (m, 5H), 3.70 (s, 3H), 6.44 - 6.78 (m, 5H), 6.90 - 7.17 (m, 4H), 7.25 - 7.49 (m, 2H), 7.95 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.6, 34.1, 36.5, 50.3, 54.9, 78.1, 113.5 (4C), 114.1, 114.7, 127.0, 128.1, 129.0, 129.5, 130.2, 130.4, 130.5, 131.5, 134.1, 135.5, 143.3, 158.5, 202.4. **Anal. Calcd. for** $C_{25}H_{23}FO_2$**:** C, 80.21; H, 06.15; F, 5.07 %. **Found:** C, 80.00; H, 06.10; F, 4.96 %.



***1-(4-Fluoro-benzyl)-2-(4-methoxy-benzylidene)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 f)*:**

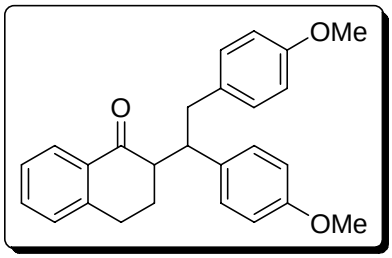
Nature: Brownish semisolid; **Yield:** 18 %; **IR** (chloroform)**:** v_{max} 3402, 1602, 1495, 1452, 1430 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.08 - 2.40 (m, 3H), 2.56 - 3.04 (m, 4H), 3.72 (s, 3H), 6.42 - 6.75 (m, 6H), 6.88 - 7.12 (m, 4H), 7.23 - 7.34 (m, 2H), 7.52 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{25}H_{23}FO_2$**:** C, 80.21; H, 06.15; F, 5.07 %.



Found: C, 80.11; H, 06.07; F, 4.93 %.

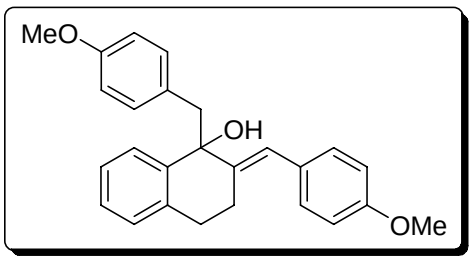
2-(1,2-Bis(4-methoxyphenyl)ethyl)-3,4-dihydronaphthalen-1(2H)-one (100g):

Nature: Brown semisolid; **Yield:** 75 %; **IR** (Chloroform)**:** ν $_{max}$ 3008, 2933, 1681, 1610, 1511, 1455, 1301, 1247 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.50 - 1.85 (m, 1H), 1.95 - 2.45 (m, 2H), 2.55 - 3.15 (m, 5H), 3.73 (s, 3H), 3.76 (s, 3H), 6.65 - 6.87 (m, 4H), 6.95 (d, *J* = 8 Hz, 1H), 7.05 - 7.35 (m, 5H), 7.38 - 7.55 (m, 1H), 8.01 (d, *J* = 8 Hz 1H); **^{13}C NMR** (50 MHz, CDCl3+CCl_4)**:** δ 25.0, 28.0, 39.0, 44.4, 51.3, 55.0 (2C), 113.4 (2C), 113.5 (2C), 126.5, 127.5, 128.5, 129.7, 129.8 (2C), 130.0 (2C), 132.8, 133.0, 133.8, 143.4, 157.8, 158.0, 199.3; **MS:** (ES) m/z: 409 $(MNa)^+$; **Anal. Calcd. for** $C_{26}H_{26}O_3$**:** C, 80.82; H, 06.73 %. **Found:** C, 80.79; H, 06.75 %.



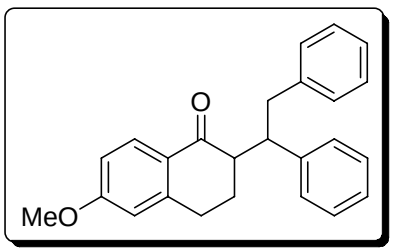
1-(4-Methoxy-benzyl)-2-(4-methoxy-benzylidene)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 g):

Nature: Brown semisolid; **Yield:** 18 %; **IR** (Chloroform)**:** ν $_{max}$ 3410, 3019, 1607, 1510, 1423, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.35 - 2.55 (m, 1H), 2.60 - 2.95 (m, 3H), 3.06 (s, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 6.69 - 6.85 (m, 4H), 6.89 - 7.14 (m, 5H), 7.19 - 7.25 (m, 3H), 7.62 (d, *J* = 8 Hz, 1H); **MS:** (ES) m/z: 409 $(MNa)^+$; **Anal. Calcd. for** $C_{26}H_{26}O_3$**:** C, 80.82; H, 06.73 %. **Found:** C, 80.81; H, 06.72 %.



3,4-Dihydro-6-methoxy-2-(1,2-diphenylethyl)naphthalene-1(2H)-one (100 h):

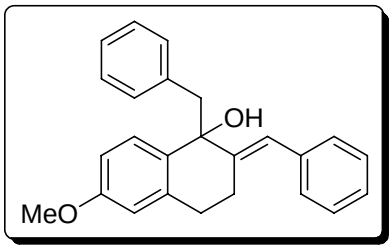
Nature: Brick red semisolid; **Yield:** 73 %; **IR** (chloroform)**:** *v* $_{max}$ 3020, 1669, 1600, 1495, 1453, 1351 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** *δ* 1.20 - 1.30 (m, 1H), 1.93 - 2.05 (m, 2H), 2.30 - 3.10 (m, 5H), 3.84 (s, 3H), 6.45 - 6.70 (m, 3H), 6.80 - 7.00 (m, 4H), 7.10 - 7.35 (m, 5H), 7.99 (d, *J* = 8 Hz, 1H); **^{13}C NMR:** (50 MHz, $CDCl_3$+CCl_4)**:** *δ* 26.5, 34.5, 37.7, 51.8, 52.1, 55.8, 78.1, 113.2, 114.2, 124.2, 126.0, 127.2, 128.1 (2C),



129.4 (2C), 129.9 (2C), 130.2 (2C), 130.9, 140.5, 140.8, 146.3, 164.7, 201.2; **Anal. Calcd. for** $C_{25}H_{24}O_2$**:** C, 84.27; H, 06.74 %. **Found:** C, 84.20; H, 06.75 %.

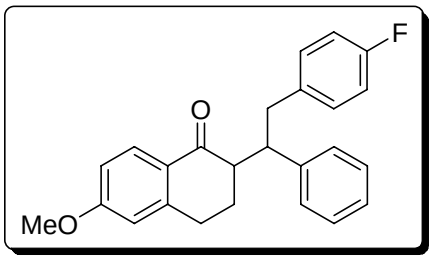
***1-Benzyl-2-benzylidene-6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ol (101 h)*:**

Nature: Brick red semisolid; **Yield:** 18 %; **IR** (chloroform)**:** ν_{max} 3412, 1608, 1450, 1390 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.06 - 2.32 (m, 3H), 2.53 - 2.86 (m, 4H), 3.81 (s, 3H), 6.52 - 6.76 (m, 3H), 6.82 - 7.04 (m, 5H), 7.06 - 7.35 (m, 5H), 7.51 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{25}H_{24}O_2$**:** C, 84.27; H, 06.74 %. **Found:** C, 84.12; H, 06.52 %.



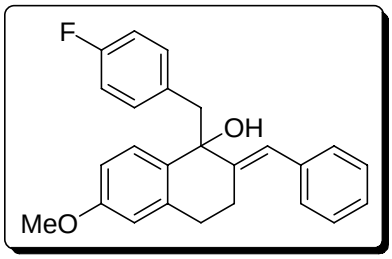
2-(2-(4-Fluorophenyl)-1-phenylethyl]-3,4-dihydro-6-methoxynaphthalen-1(2H)-one (100 i):

Nature: Dark brown semisolid; **Yield:** 75 %; **IR** (chloroform)**:** ν_{max} 3021, 1678, 1600, 1560, 1501, 1440, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.95 - 2.05 (m, 2H), 2.07 - 2.17 (m, 1H), 2.60 - 3.20 (m, 5H), 3.86 (s, 3H), 6.46 - 6.67 (m, 3H), 6.90 (d, J = 8 Hz, 1H), 7.10 - 7.60 (m, 7H), 8.12 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{25}H_{23}FO_2$**:** C, 80.21; H, 06.15; F, 05.07 %. **Found:** C, 80.10; H, 06.08; F, 04.97 %.



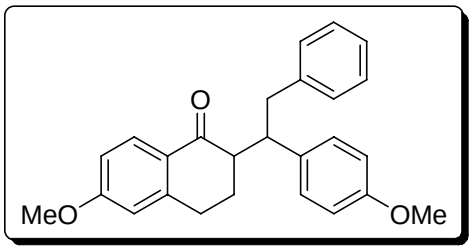
***2-Benzylidene-1-(4-fluoro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ol (101 i)*:**

Nature: Dark brown semisolid; **Yield:** 20 %; **IR** (chloroform)**:** ν_{max} 3410, 1600, 1552, 1500, 1442, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.05 - 2.28 (m, 3H), 2.62 - 3.22 (m, 4H), 3.84 (s, 3H), 6.56 - 6.78 (m, 4H), 6.91 (d, J = 8 Hz, 1H), 6.96 - 7.16 (m, 7H), 7.50 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{25}H_{23}FO_2$**:** C, 80.21; H, 6.15; F, 05.07 %. **Found:** C, 80.10; H, 6.08; F, 05.01 %.



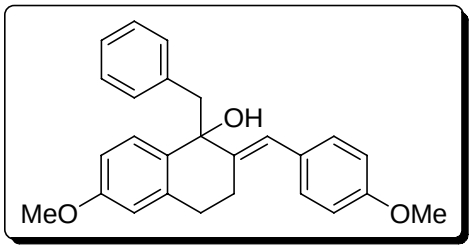
3,4-Dihydro-6-methoxy-2-(1-(4-methoxyphenyl)-2-phenylethyl]naphthalen-1(2H)-one (100 j):

Nature: Reddish brown semisolid; **Yield:** 70 %; **IR** (Nujol)**:** ν_{max} 3019, 1731, 1601, 1512, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.05 - 2.26 (m, 1H), 2.63 - 2.81 (m, 2H), 2.94 - 3.40 (m, 5H), 3.73 (s, 3H), 3.88 (s, 3H), 6.61 - 6.77 (m, 3H), 6.79 - 6.89 (m, 3H), 6.94 - 7.25 (m, 5H), 7.69 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 27.1, 33.1, 35.8, 49.3, 55.2, 55.7, 78.2, 113.1, 113.6 (2C), 114.1, 125.2, 126.1, 128.4 (2C), 129.3 (2C), 130.4 (2C), 130.7, 131.1, 141.0, 145.3, 158.8, 164.2, 199.4. **Anal. Calcd for** $C_{26}H_{26}O_3$**:** C, 80.82; H, 06.73 %. **Found:** C, 80.72; H, 06.68 %.



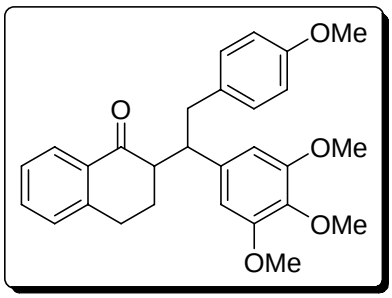
***1-Benzyl-6-methoxy-2-(4-methoxy-benzylidene)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 j)*:**

Nature: Reddish brown semisolid; **Yield:** 19 %; **IR** (Nujol)**:** ν_{max} 3404, 1600, 1512, 1430 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.10 - 2.36 (m, 3H), 2.73 - 3.10 (m, 4H), 3.71 (s, 3H), 3.86 (s, 3H), 6.63 - 6.79 (m, 4H), 6.82 - 6.97 (m, 3H), 7.00 - 7.29 (m, 5H), 7.53 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{26}H_{26}O_3$**:** C, 80.82; H, 06.73 %. **Found:** C, 80.55; H, 06.58 %.



***3,4-Dihydro-2-(1-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)ethyl)naphthalen-1(2H)-one (100 k)*:**

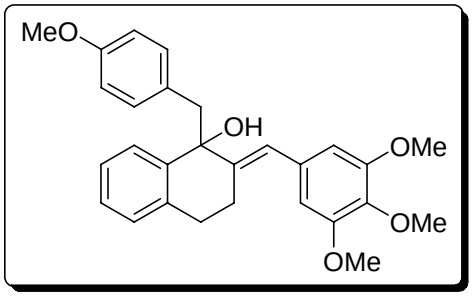
Nature: Reddish semisolid; **Yield:** 75 %; **IR** (chloroform)**:** ν_{max} 3014, 1680, 1588, 1511, 1458, 1421 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.87 - 2.26 (m, 3H), 2.48 - 3.02 (m, 5H), 3.55 (s, 3H), 3.66 (s, 6H), 3.73 (s, 3H), 6.29 - 6.45 (m, 5H), 7.08 - 7.23 (m, 2H), 7.24 - 7.33 (t, J = 8 Hz, 1H), 7.37 - 7.52 (t, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 26.0, 34.3, 36.5, 51.3, 55.0, 56.2 (2C), 60.6, 78.1, 107.3, 113.2 (2C), 114.1, 125.4, 126.9 (2C), 128.9 (2C), 129.8 (2C),



131.8, 133.9, 135.9, 143.2, 152.7 (2C), 152.7, 202.2. **Anal. Calcd. for** $C_{28}H_{30}O_5$**:** C, 75.33; H, 06.72 %. **Found:** C, 75.20; H, 06.65 %.

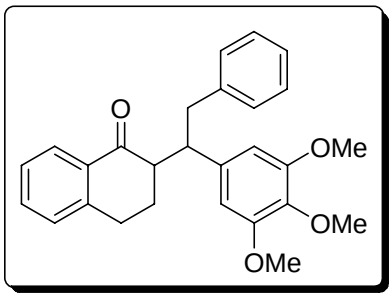
***1-(4-Methoxy-benzyl)-2-(3,4,5-trimethoxy-benzylidene)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 k)*:**

Nature: Reddish semisolid; **Yield:** 20 %; **IR** (chloroform)**:** ν_{max} 3412, 1610, 1511, 1458, 1421 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.20 - 2.36 (m, 3H), 2.48 - 3.06 (m, 4H), 3.60 (s, 3H), 3.67 (s, 6H), 3.76 (s, 3H), 6.52 (s, 2H), 6.80 - 7.02 (m, 2H), 7.14 - 7.43 (m, 6H), 7.63 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{28}H_{30}O_5$**:** C, 75.31; H, 06.77 %. **Found:** C, 75.12; H, 06.62 %.



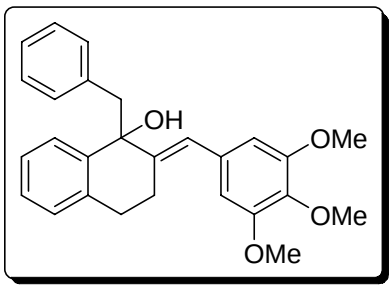
3,4-Dihydro-2-(1-(3,4,5-trimethoxy-phenyl)-ethyl]-3,4-dihydro-2H-naphthalen-1-one (100 l):

Nature: Reddish brown semisolid; **Yield:** 70 %; **IR** (chloroform)**:** ν_{max} 2936, 1690, 1590, 1507, 1454, 1421, 1328 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.49 - 3.35 (m, 8H), 3.67 (s, 6H), 3.73 (s, 3H), 6.20 (s, 2H), 6.95 (d, J = 8 Hz, 1H), 7.00 - 7.23 (m, 6H), 7.25 - 7.37 (t, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{27}H_{28}O_4$**:** C, 77.88; H, 06.73 %. **Found:** C, 77.67; H, 06.70 %.



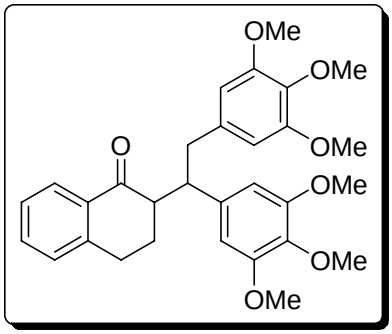
***2-(3,4,5-Trimethoxybenzylidene)-1-benzyl-1,2,3,4-tetrahydronaphthalen-1-ol (101l)*:**

Nature: Reddish brown semisolid; **Yield:** 22 %; **IR** (chloroform)**:** ν_{max} 3406, 1600, 1560, 1456, 1410 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.09 - 2.45 (m, 3H), 2.60-3.10 (m, 4H), 3.68 (s, 6H), 3.72 (s, 3H), 6.26 (s, 2H), 6.96 (d, J = 8 Hz, 1H), 7.02 - 7.30 (m, 7H), 7.54 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{27}H_{28}O_4$**:** C, 77.88; H, 06.73 %. **Found:** C, 77.70; H, 06.68 %.



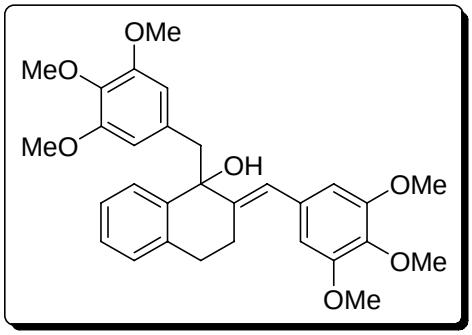
2-[1,2-bis-(3,4,5-Trimethoxyphenyl)ethyl]-3,4-dihydronaphthalen-1(2H)-one (100 m):

Nature: Brown semisolid; **Yield:** 70 %; **IR** (chloroform)**:** ν_{max} 3018, 1676, 1580, 1508, 1450, 1418 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.10 - 2.30 (m, 2H), 2.65 - 2.80 (m, 1H), 3.10 - 3.25 (m, 5H), 3.66 (s, 6H), 3.70 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 6.10 (s, 2H), 6.16 (s, 2H), 6.29 - 6.54 (m, 2H), 7.48 - 7.58 (m, 1H), 7.70 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{30}H_{34}O_7$**:** C, 71.14; H, 06.71 %. **Found:** C, 71.00; H, 06.65 %.



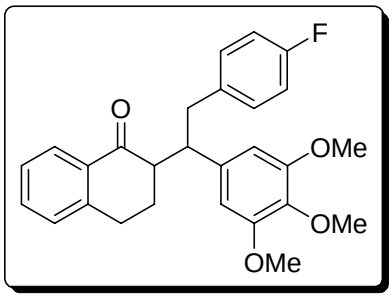
1-(3,4,5-Trimethoxy-benzyl)-2-(3,4,5-trimethoxy-benzylidene)-1,2,3,4-tetrahydro-naphthalen-1-ol (101 m):

Nature: Brown semisolid; **Yield:** 19 %; **IR** (chloroform)**:** ν_{max} 3410, 1600, 1512, 1456, 1416 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.04 - 2.25 (m, 3H), 2.50 - 2.75 (m, 4H), 3.67 (s, 6H), 3.71 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 6.20 (s, 2H), 6.35 (s, 2H), 6.30 - 6.63 (m, 3H), 7.40 - 7.52 (m, 1H), 7.58 (d, J = 8 Hz, 1H); **Anal. Calcd for** $C_{30}H_{34}O_7$**:** C, 71.14; H, 06.71 %. **Found:** C, 71.05; H, 6.58 %.



***2-(2-(4-Fluorophenyl)-1-(3,4,5-trimethoxyphenyl)ethyl)-3,4-dihydronaphthalen-1(2H)-one (100 n)*:**

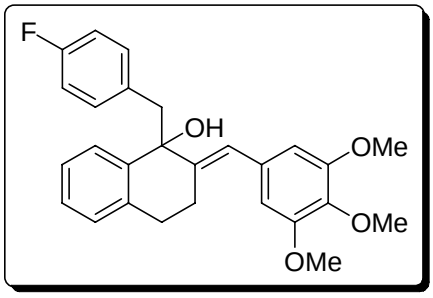
Nature: Dark red semisolid; **Yield:** 76 %; **IR** (chloroform)**:** ν_{max} 3019, 1680, 1601, 1501, 1454, 1428 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.00 - 2.15 (m, 2H), 2.19 - 2.27 (m, 1H), 2.72 - 3.10 (m, 5H), 3.77 (s, 6H), 3.85 (s, 3H), 6.38 - 6.72 (m, 4H), 6.75 - 7.20 (m, 2H), 7.25 - 7.60 (m, 3H), 8.03 (d, J = 4 Hz, 1H); **^{13}C NMR:** (50 MHz, $CDCl_3$+CCl_4): δ 26.0, 34.4, 36.8, 51.4 (2C), 56.2 (2C), 60.8, 78.1 (2C), 107.2 (2C), 114.4, 114.7 (2C), 127.0, 128.0, 128.9, 130.4 (2C), 134.1,



135.6, 143.3, 152.9 (2C), 202.2. **Anal. Calcd. for** $C_{27}H_{27}FO_4$**:** C, 74.65; H, 06.22; F, 4.37 %. **Found:** C, 74.60; H, 06.18; F, 4.22 %.

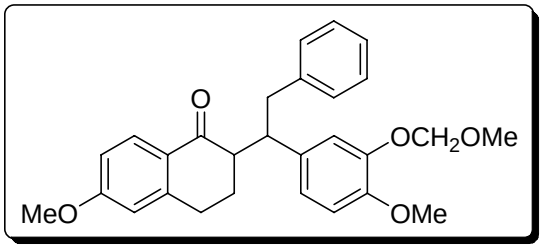
***2-(3,4,5-Trimethoxybenzylidene)-1-(4-fluorobenzyl)-1,2,3,4-tetrahydronaphthalen-1-ol (101 n)*:**

Nature: Dark red semisolid; **Yield:** 20 %; **IR** (chloroform)**:** ν_{max} 3409, 1600, 1510, 1452, 1424 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.02 - 2.32 (m, 3H), 2.45 - 2.95 (m, 4H), 3.76 (s, 6H), 3.86 (s, 3H), 6.38 - 6.78 (m, 5H), 6.86 - 7.35 (m, 2H), 7.45 - 7.67 (m, 4H); **Anal. Calcd. for** $C_{27}H_{27}FO_4$**:** C, 74.65; H, 6.22; F, 4.37 %. **Found:** C, 74.58; H, 6.10; F, 4.20 %.



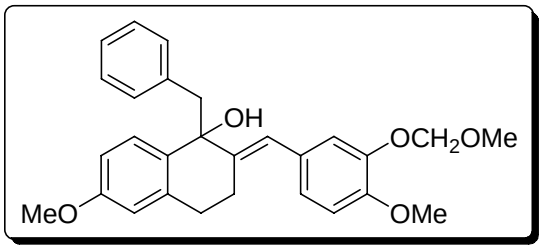
3,4-Dihydro-6-methoxy-2-(1-(4-methoxy-3-methoxymethoxy)phenyl)-2-phenylethyl)naphthalene-1(2H)-one (100 o):

Nature: Reddish semisolid; **Yield:** 65 %; **IR** (chloroform)**:** ν_{max} 3019, 1668, 1600, 1513, 1465, 1454, 1421 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.20 - 1.45 (m, 1H), 1.93 - 2.35 (m, 2H), 2.65 - 3.00 (m, 5H), 3.52 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 5.20 (s, 2H), 6.53 - 6.70 (m, 3H), 6.88 - 7.05 (m, 5H), 7.23 - 7.39 (m, 2H), 8.02 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{28}H_{30}O_5$**:** C, 75.33; H, 06.72 %. **Found:** C, 75.00; H, 06.65 %.



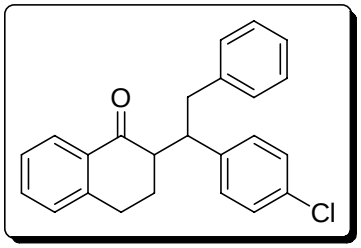
***2-(4-Methoxy-3-(methoxymethoxy)benzylidene)-1-benzyl-1,2,3,4-tetrahydro-6-methoxynaphthalen-1-ol (101 o)*:**

Nature: Reddish semisolid; **Yield:** 25 %; **IR** (chloroform)**:** ν_{max} 3412, 1610, 1520, 1460, 1452, 1418 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.04 - 2.29 (m, 3H), 2.54 - 2.79 (m, 4H), 3.54 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 5.15 (s, 2H), 6.50 - 6.75 (m, 4H), 6.92 - 7.10 (m, 5H), 7.20 - 7.40 (m, 2H), 7.52 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{28}H_{30}O_5$**:** C, 75.33; H, 6.72 %. **Found:** C, 75.10; H, 6.60 %.



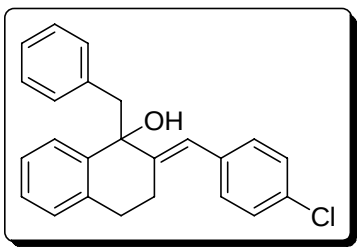
2-(1-(4-Chlorophenyl)-2-phenylethyl)-3,4-dihydronaphthalen-1(2H)-one (100 p):

Nature: thick paste; **Yield:** 73 %; **IR** (chloroform)**:** ν_{max} 3019, 1686, 1603, 1493, 1455, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.90 - 2.05 (m, 2H), 2.60 - 2.80 (m, 3H), 2.82 - 3.05 (m, 2H), 6.40 - 6.52 (m, 2H), 6.86 - 6.95 (m, 3H), 7.07 - 7.22 (m, 7H), 7.47 (t, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 26.3, 32.7, 35.0, 48.9 (2C), 126.0, 127.1, 128.0 (2C), 128.2 (2C), 128.9 (2C), 130.3 (2C), 131.1, 132.5, 133.8, 133.9, 137.0, 140.0, 142.4, 127.9, 200.3; **Anal. Calcd. for** $C_{24}H_{21}ClO_4$**:** C, 79.88; H, 05.87; Cl, 09.82 %; **Found:** C, 79.75; H, 05.78; Cl, 09.76 %.



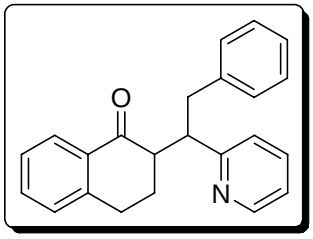
2-(4-Chlorobenzylidene)-1-benzyl-1,2,3,4-tetrahydronaphthalen-1-ol (101 p):

Nature: Brown semisolid; **Yield:** 19 %; **IR** (chloroform)**:** ν_{max} 3404, 1604, 1500, 1454, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.62 - 2.78 (m, 2H), 3.06 - 3.35 (m, 4H), 6.75 (d, J = 8 Hz, 2H), 6.86 - 6.96 (m, 2H), 6.98 - 7.09 (m, 4H), 7.13 - 7.32 (m, 4H), 7.50 (t, J = 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{24}H_{21}ClO_4$**:** C, 79.88; H, 05.87; Cl, 09.82 %. **Found:** C, 79.73; H, 05.68; Cl, 09.74 %.

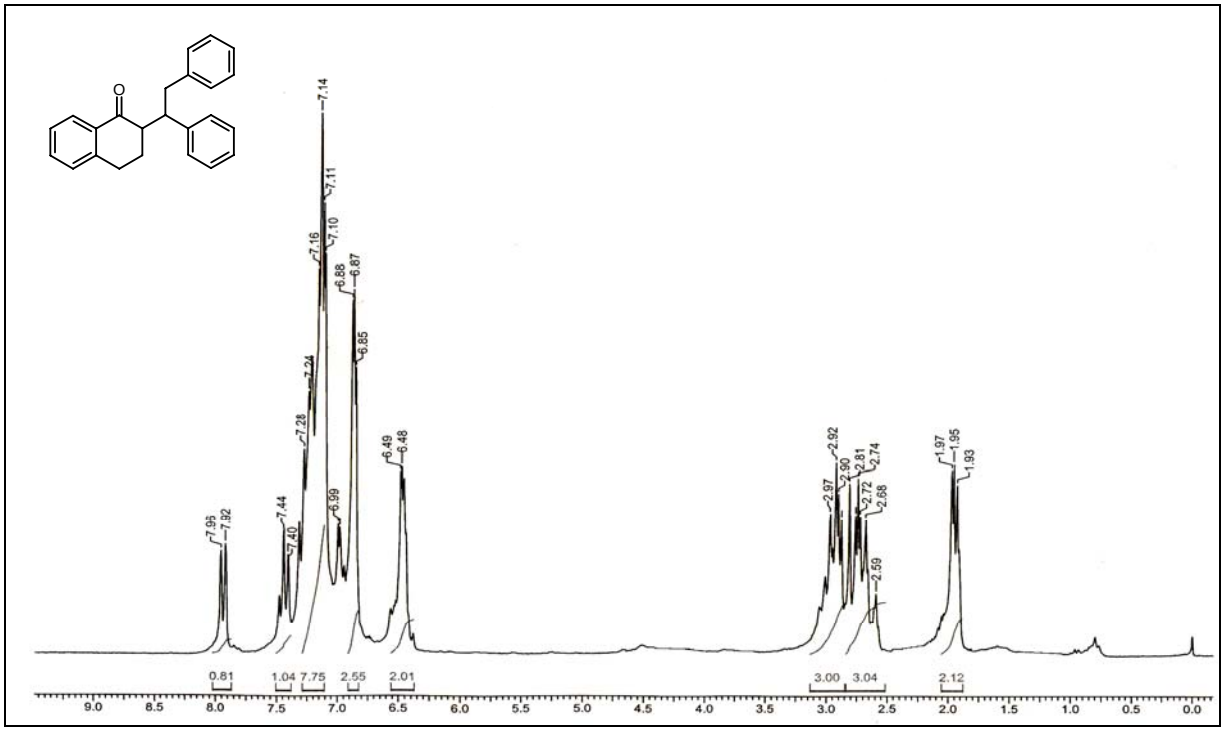


3,4-Dihydro-2-(2-phenyl-1-(pyridin-2-yl)ethyl)naphthalen-1(2H)-one (100 q):

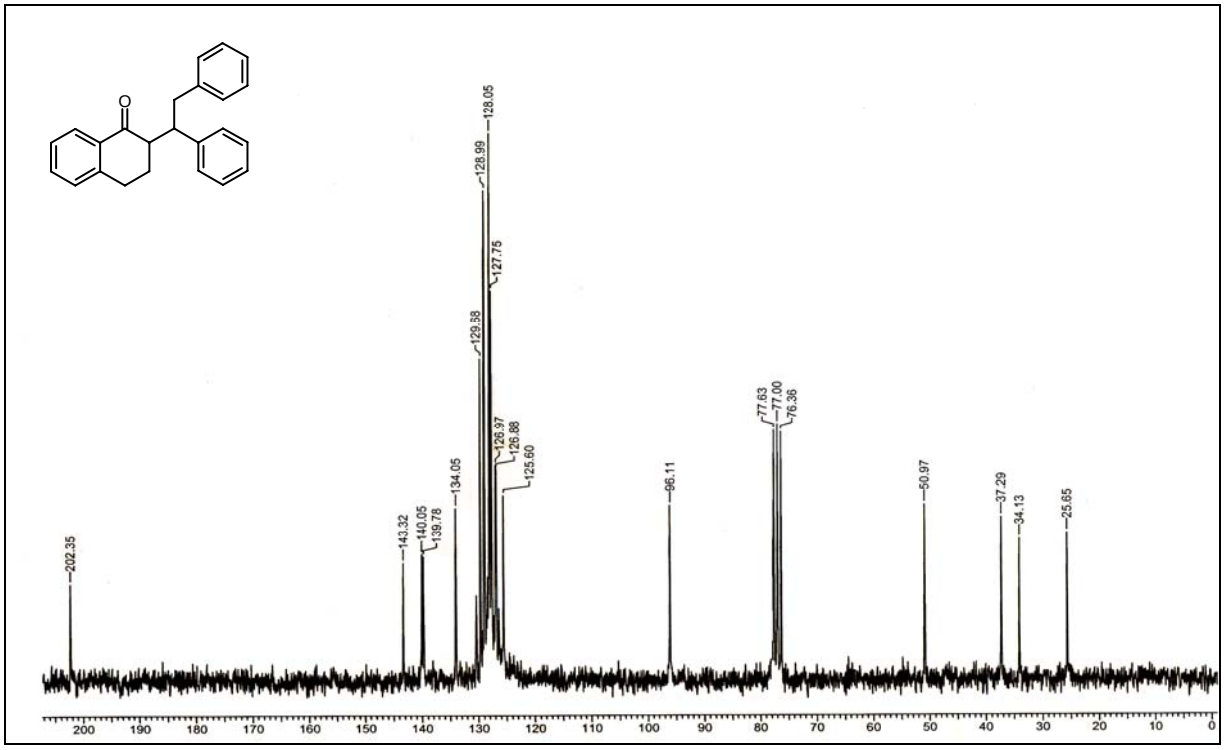
Nature: Brown semisolid; **Yield:** 87 %; **IR** (chloroform)**:** ν_{max} 3016, 1676, 1600, 1454, 1434, 1401 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.50 - 1.70 (m, 1H), 2.02 - 2.25 (m, 2H), 2.82 - 2.93 (m, 3H), 3.06 - 3.25 (m, 1H), 3.81 - 4.02 (m, 1H) 6.80 - 7.15 (m, 6H), 7.20 - 7.50 (m, 5H), 7.89 - 8.04 (m, 1H), 8.49 (d, J = 4 Hz, 1H); **^{13}C NMR:** (50 MHz, $CDCl_3$+CCl_4): δ 25.6, 36.0, 38.8, 48.0, 51.5, 121.4, 125.3, 125.9, 126.5, 127.5, 128.0, 128.2 (2C), 129.0 (2C), 133.0, 135.9, 136.2, 140.4, 143.7, 148.7, 161.5, 199.2; **Anal. Calcd. for** $C_{23}H_{21}NO$**:** C, 73.80; H, 05.61; N, 04.28 %. **Found:** C, 73.42; H, 05.60; N, 04.20 %.



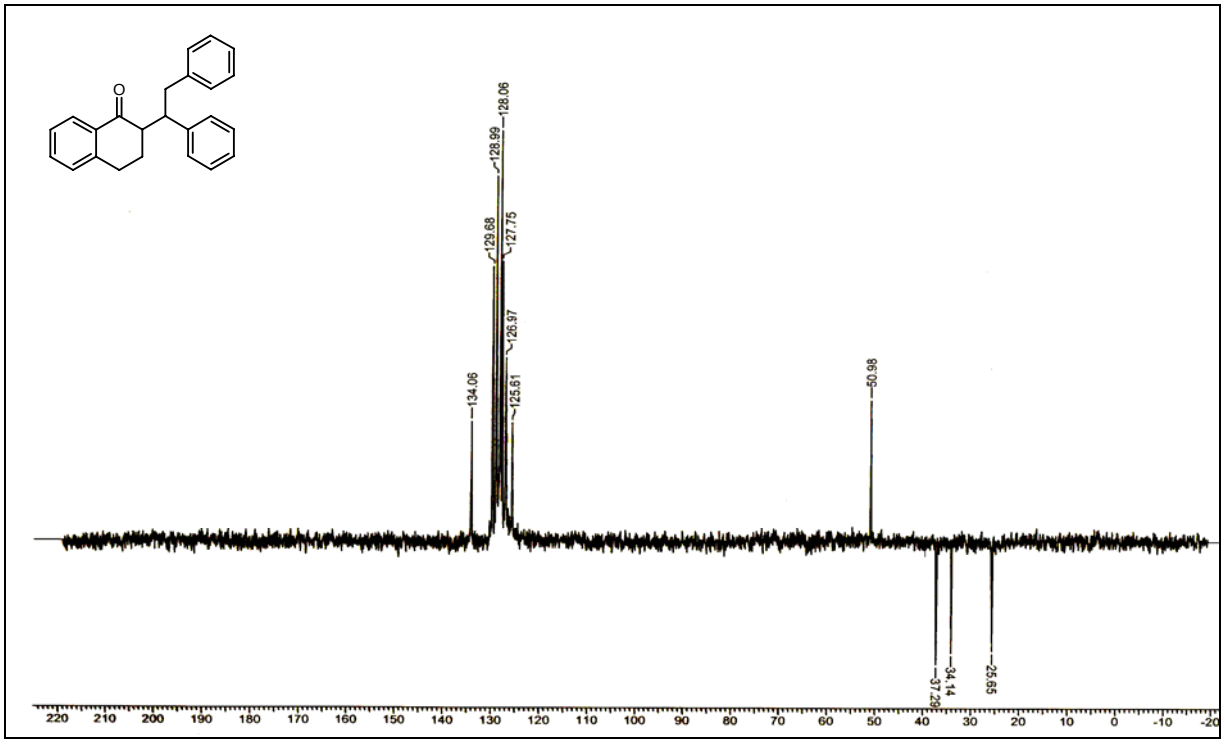
^{1}H NMR spectrum of Compound 100 a ($CDCl_3$+CCl_4, 200 MHz)



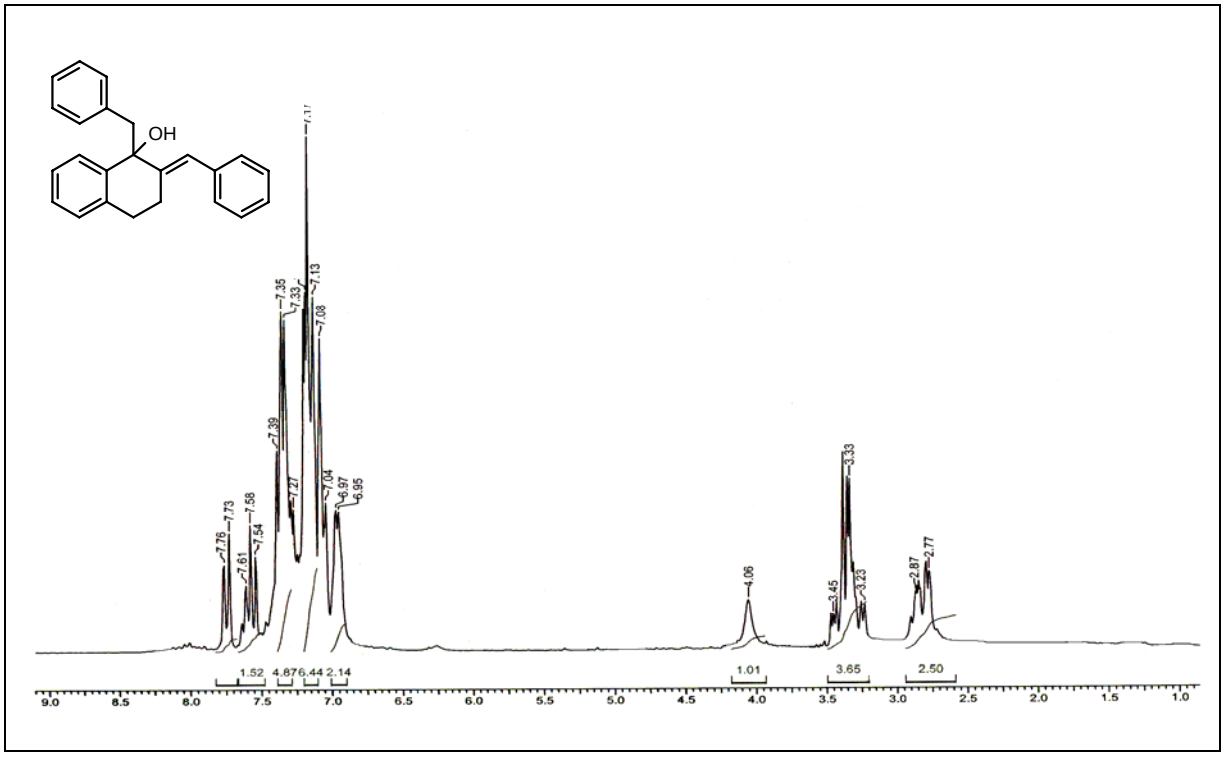
^{13}C NMR Spectrum of Compound 100 a ($CDCl_3$+CCl_4, 50 MHz)



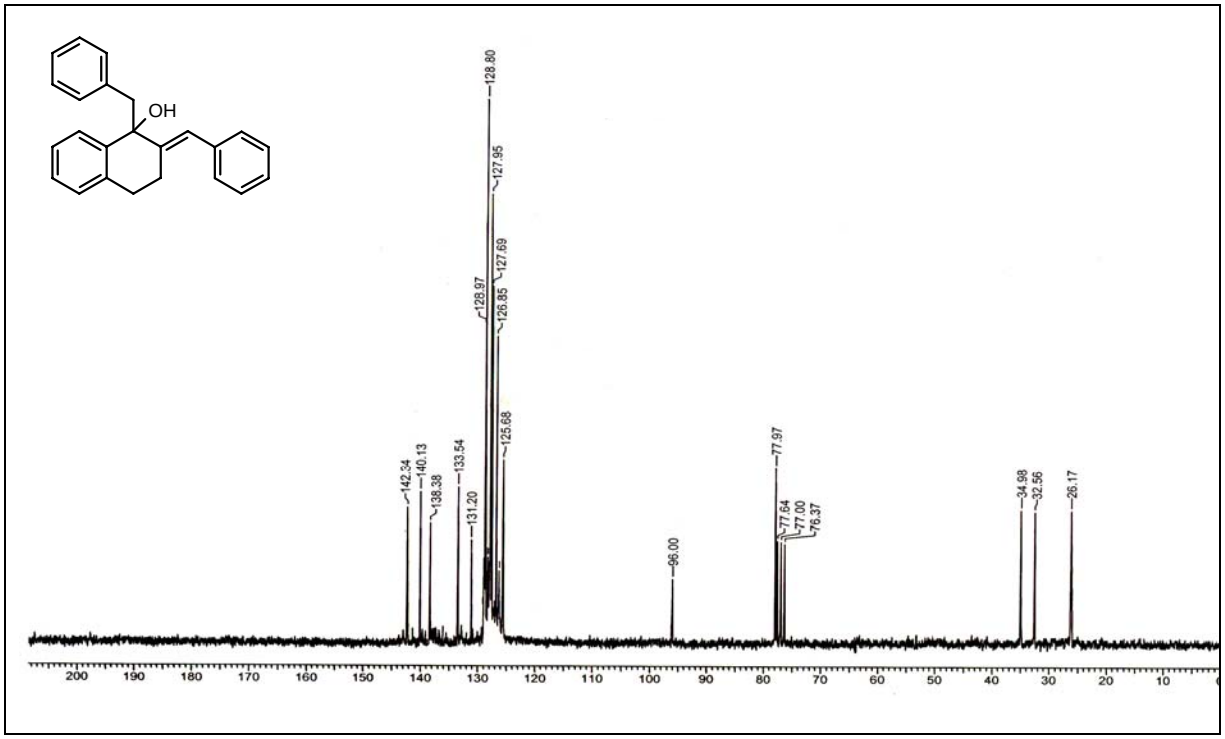
DEPT spectrum of Compound 100 a ($CDCl_3$+CCl_4, 50 MHz)



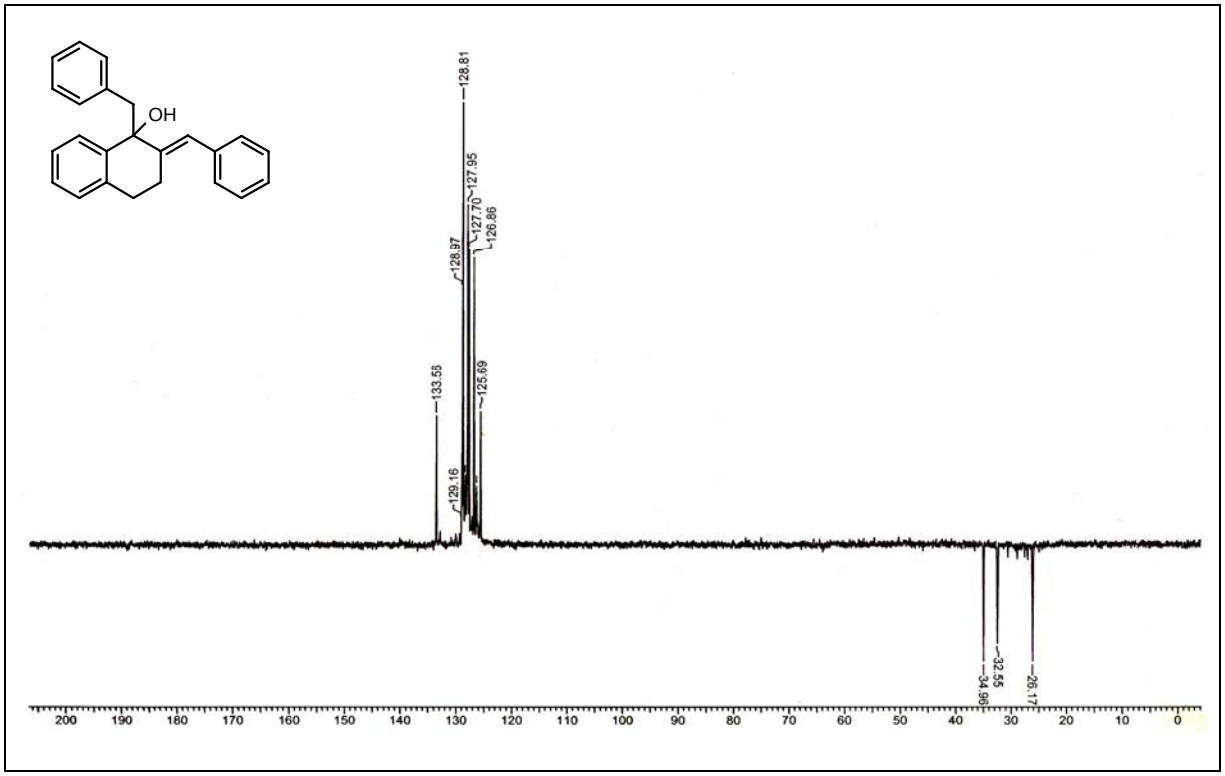
^{1}H NMR Spectrum of Compound 101 a ($CDCl_3$+CCl_4, 200 MHz)



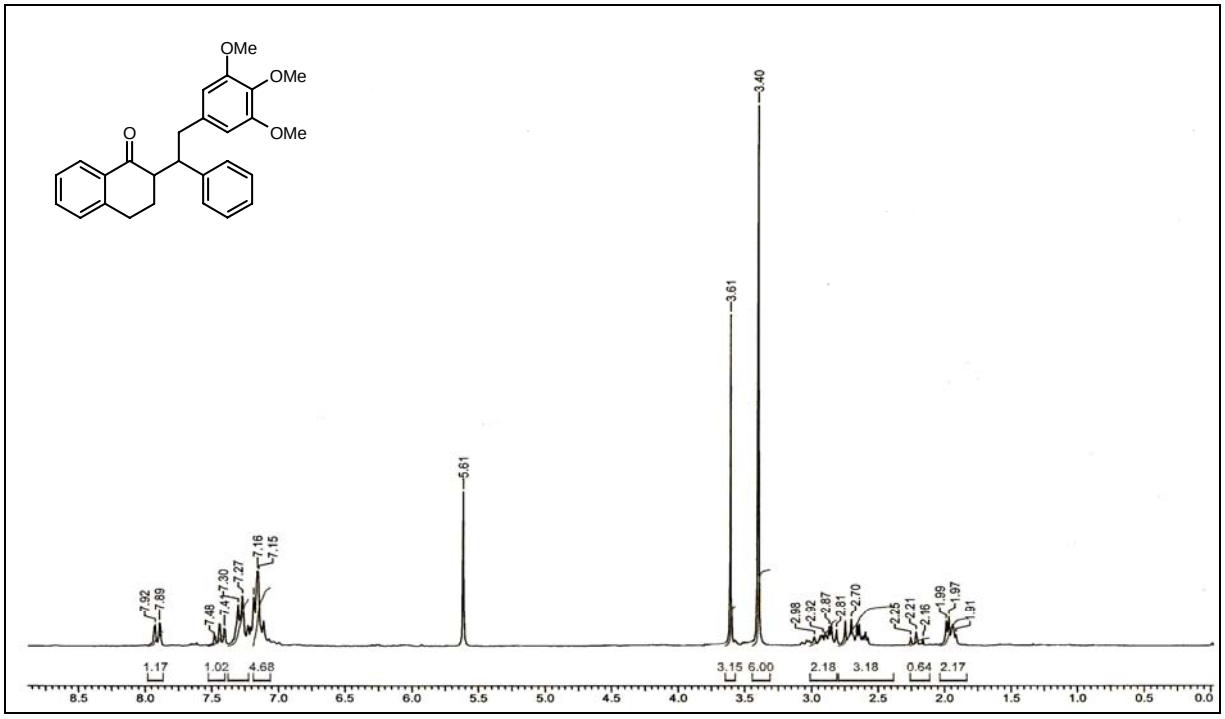
^{13}C NMR spectrum of Compound 101 a ($CDCl_3$+CCl_4, 50 MHz)



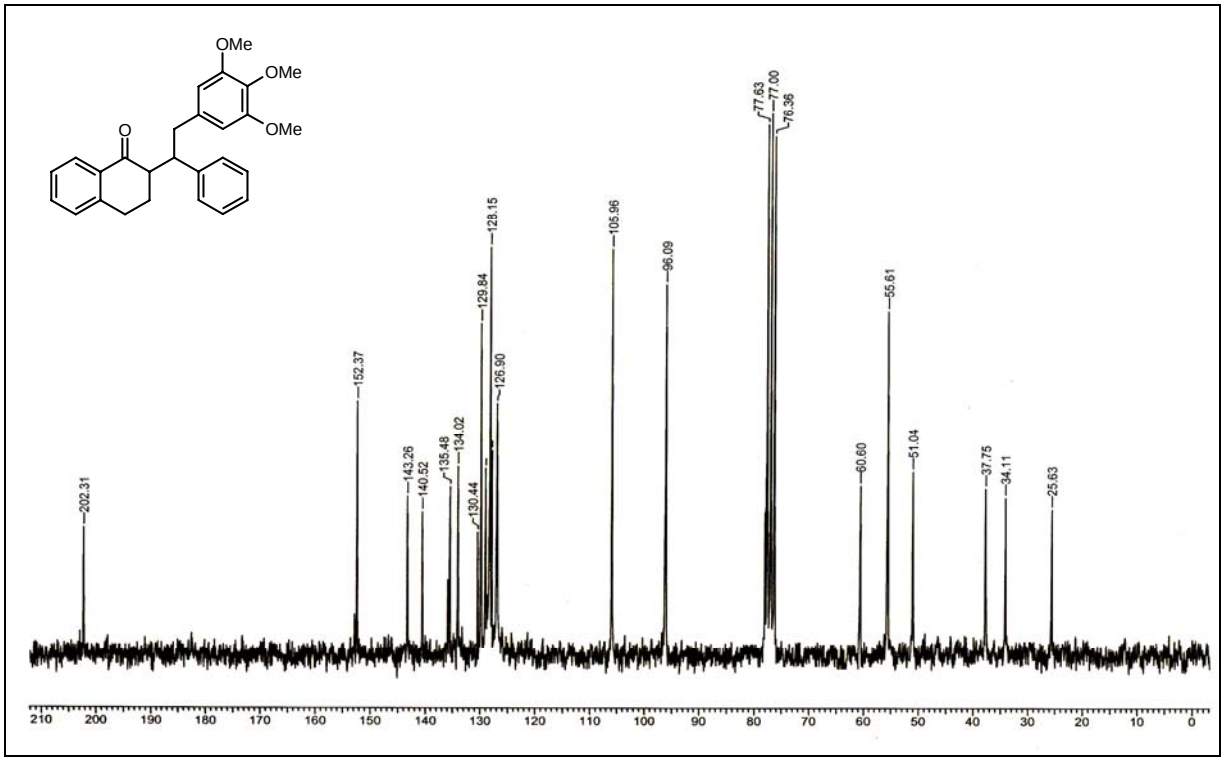
DEPT Spectrum of Compound 101 a ($CDCl_3$+CCl_4, 50 MHz)



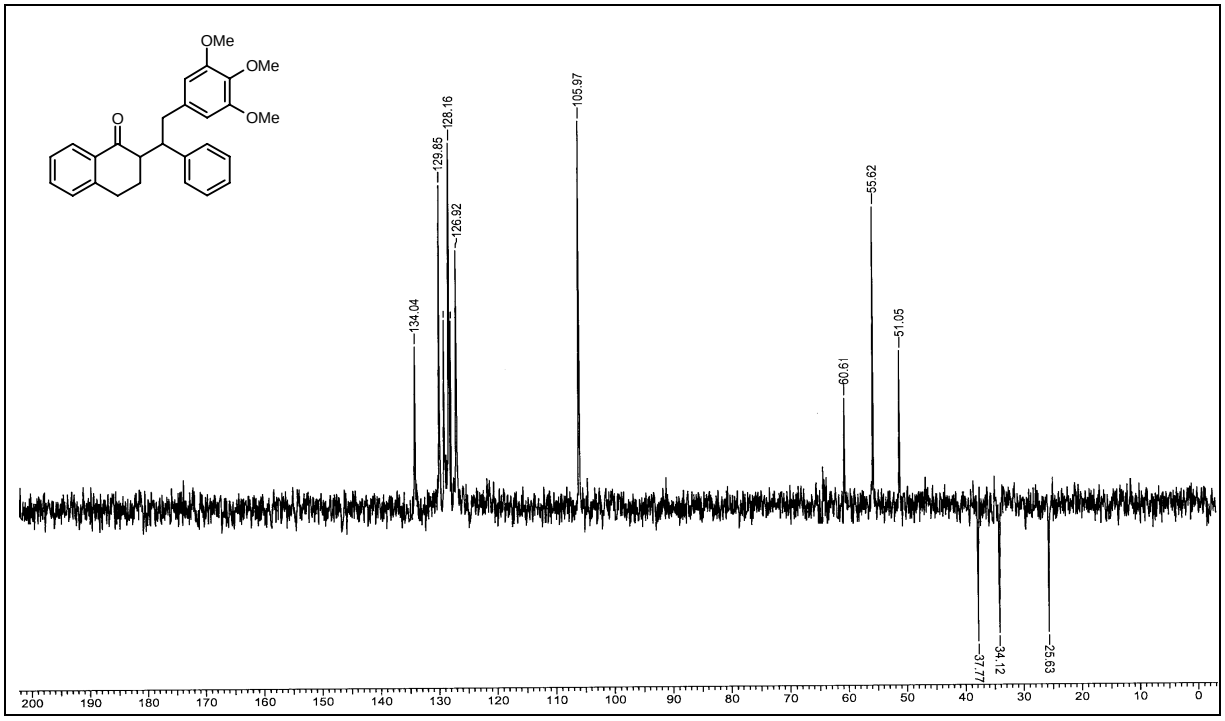
^{1}H NMR Spectrum of Compound 100 b ($CDCl_3$+CCl_4, 200 MHz)



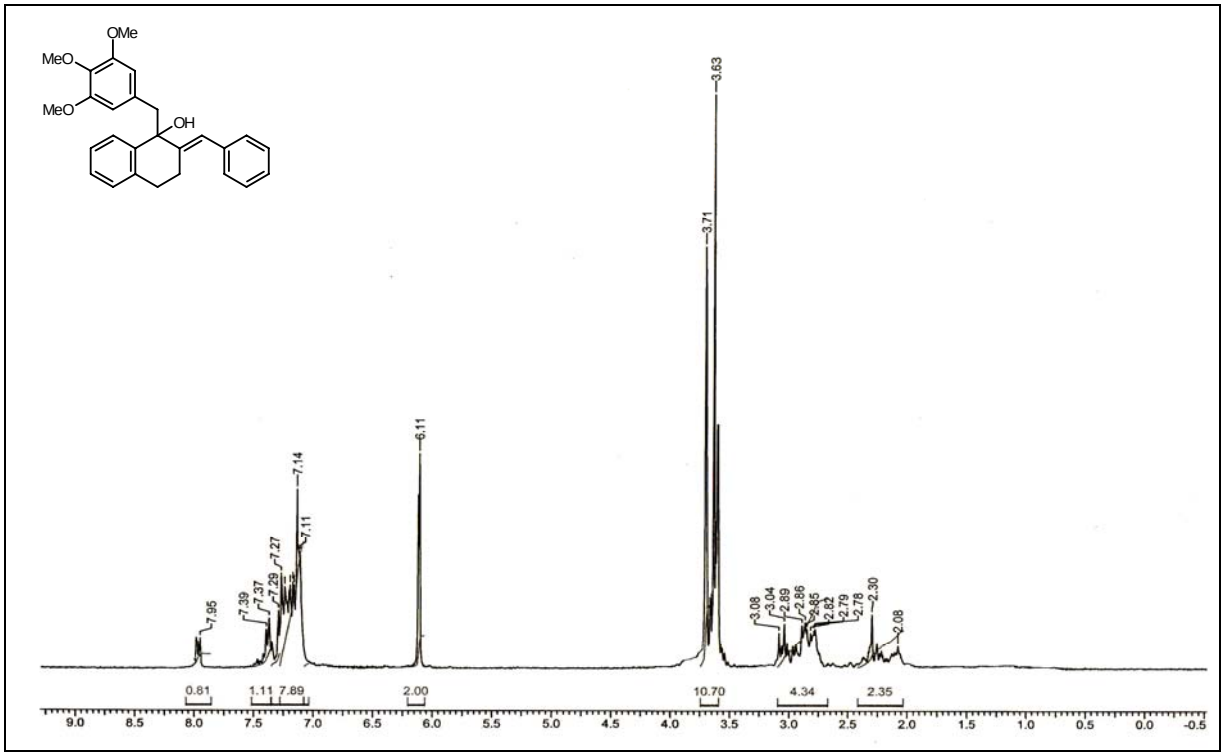
^{13}C NMR spectrum of Compound 100 b ($CDCl_3$+CCl_4, 50 MHz)



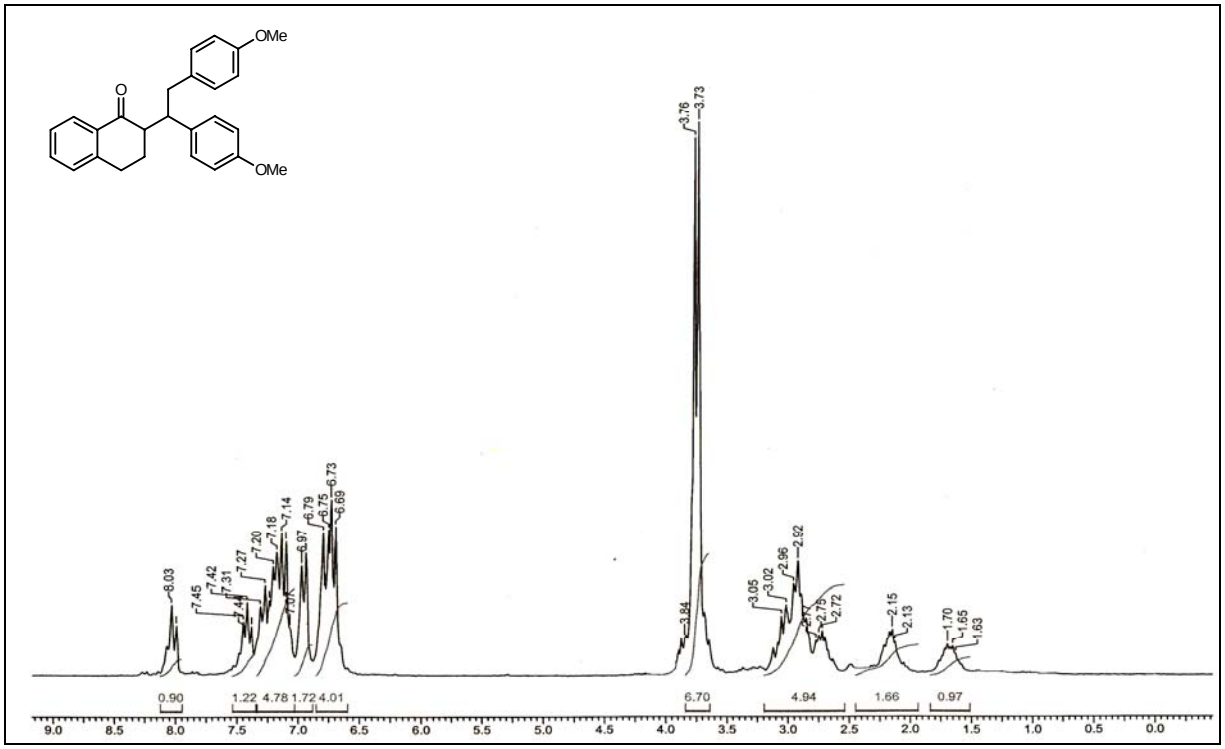
DEPT spectrum of Compound 100 b ($CDCl_3$+CCl_4, 50 MHz)



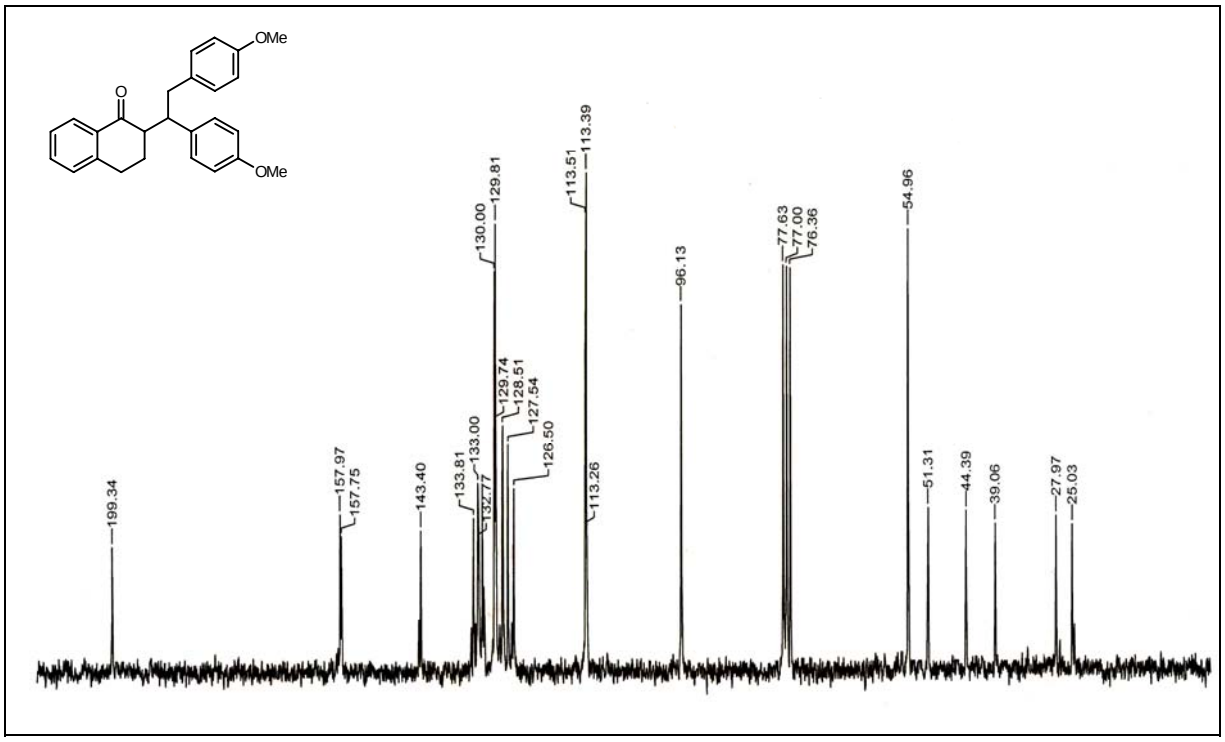
^{1}H NMR Spectrum of Compound 101 b ($CDCl_3$+CCl_4, 200 MHz)



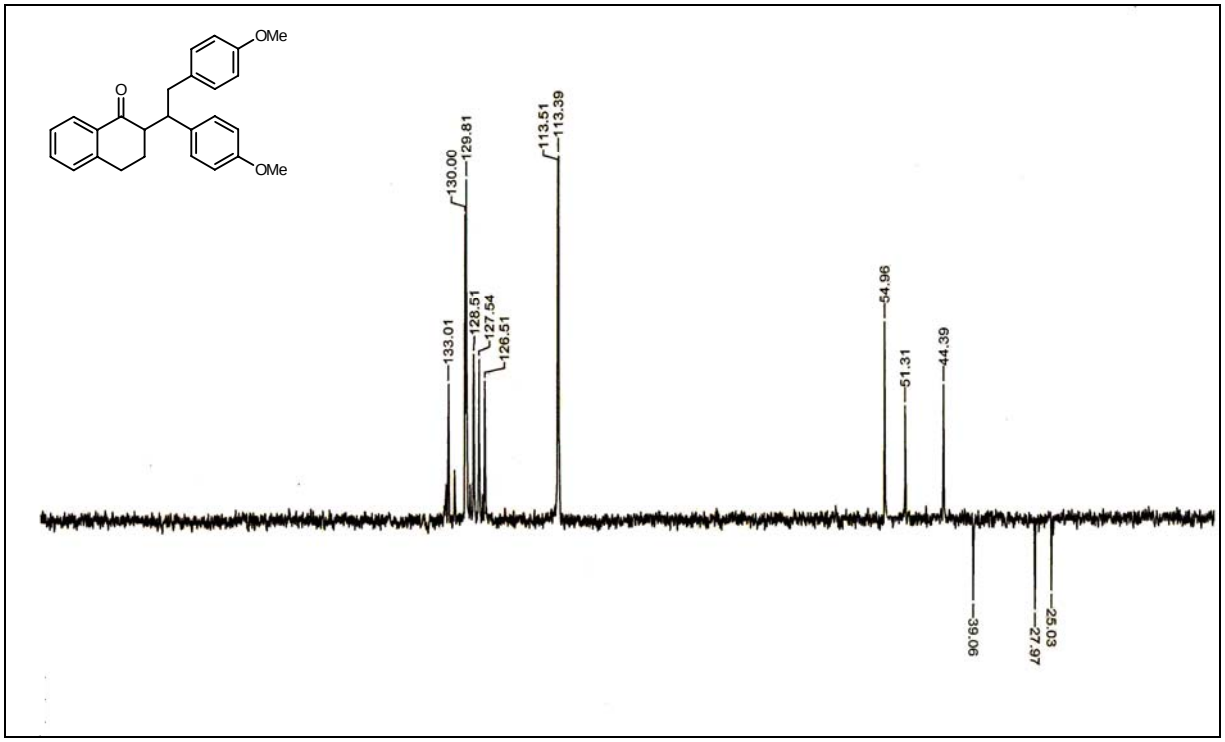
^{1}H NMR spectrum of Compound 100 g ($CDCl_3$+CCl_4, 200 MHz)



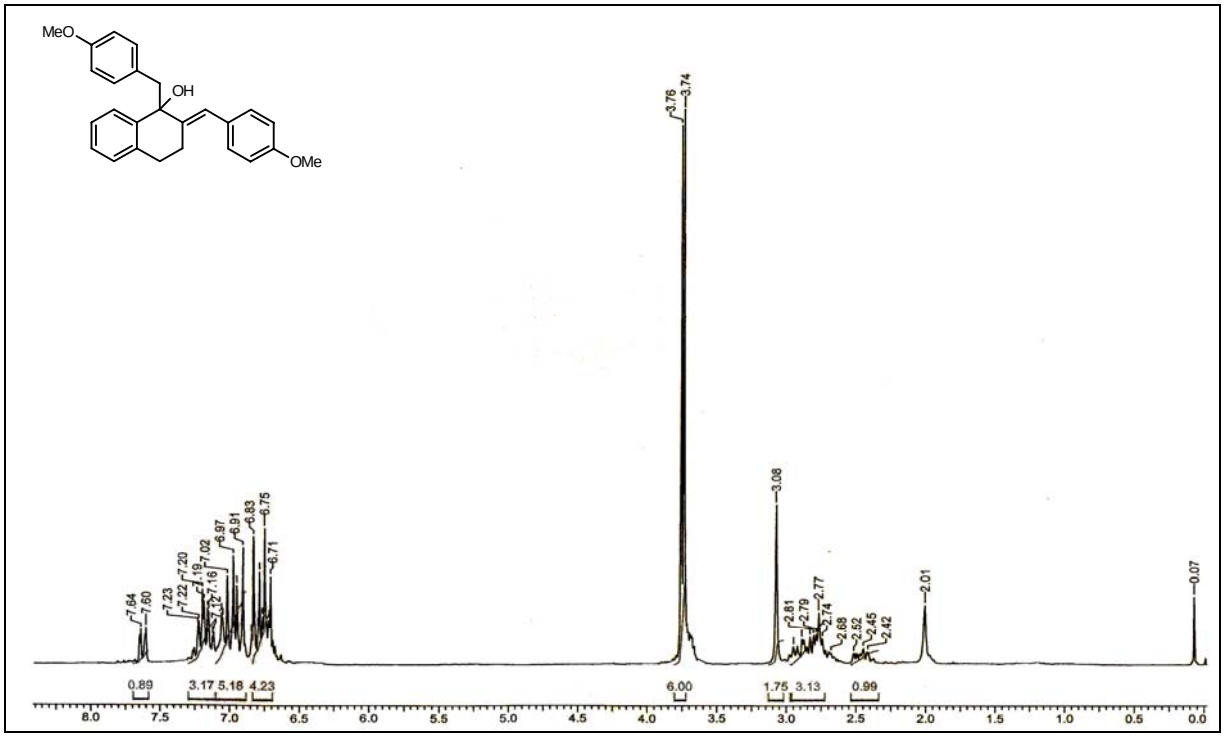
^{13}C NMR Spectrum of Compound 100 g ($CDCl_3$+CCl_4, 50 MHz)



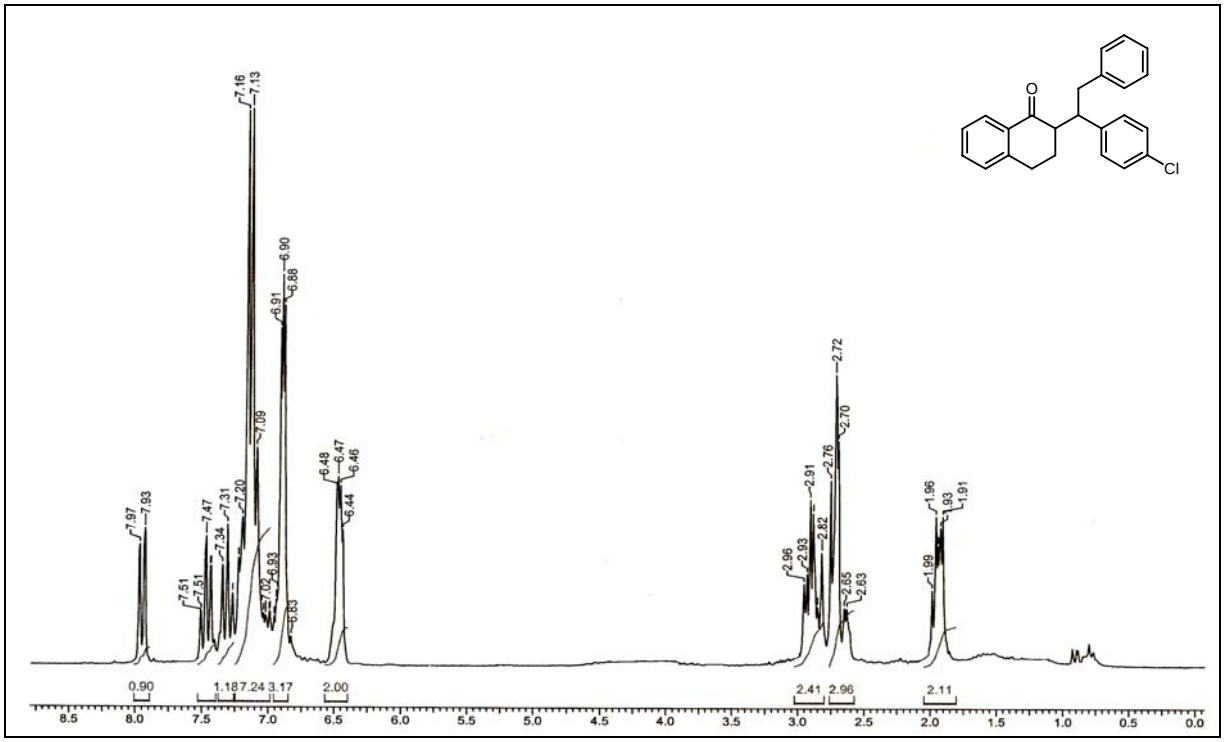
DEPT spectrum of Compound 100 g ($CDCl_3$+CCl_4, 50 MHz)



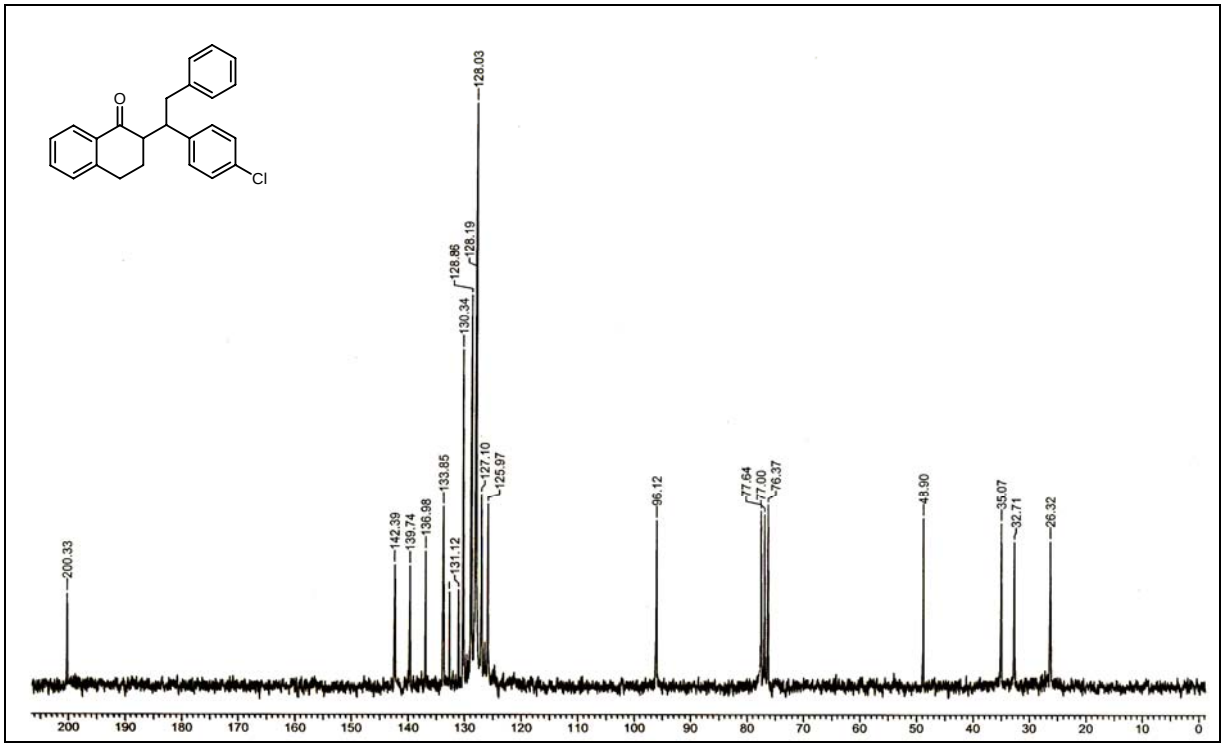
^{1}H NMR Spectrum of Compound 101 g ($CDCl_3$+CCl_4, 200 MHz)



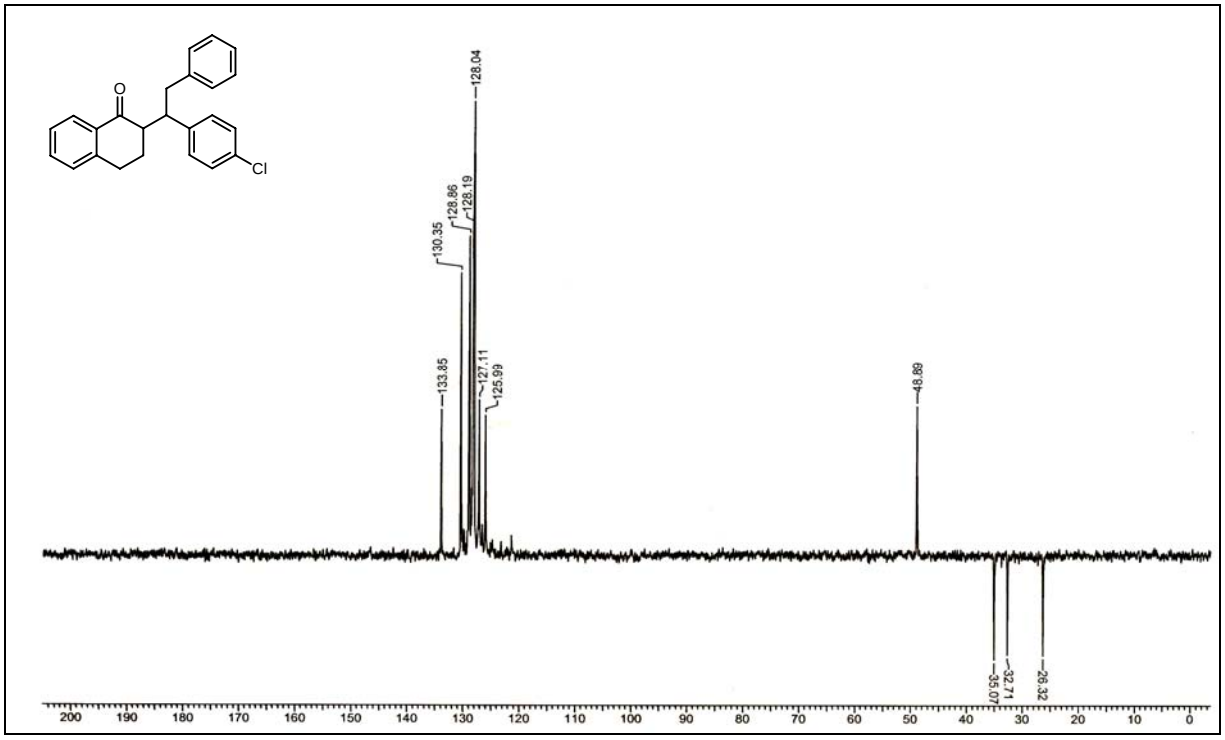
^{1}H NMR spectrum of Compound 100 p ($CDCl_3$+CCl_4, 200 MHz)



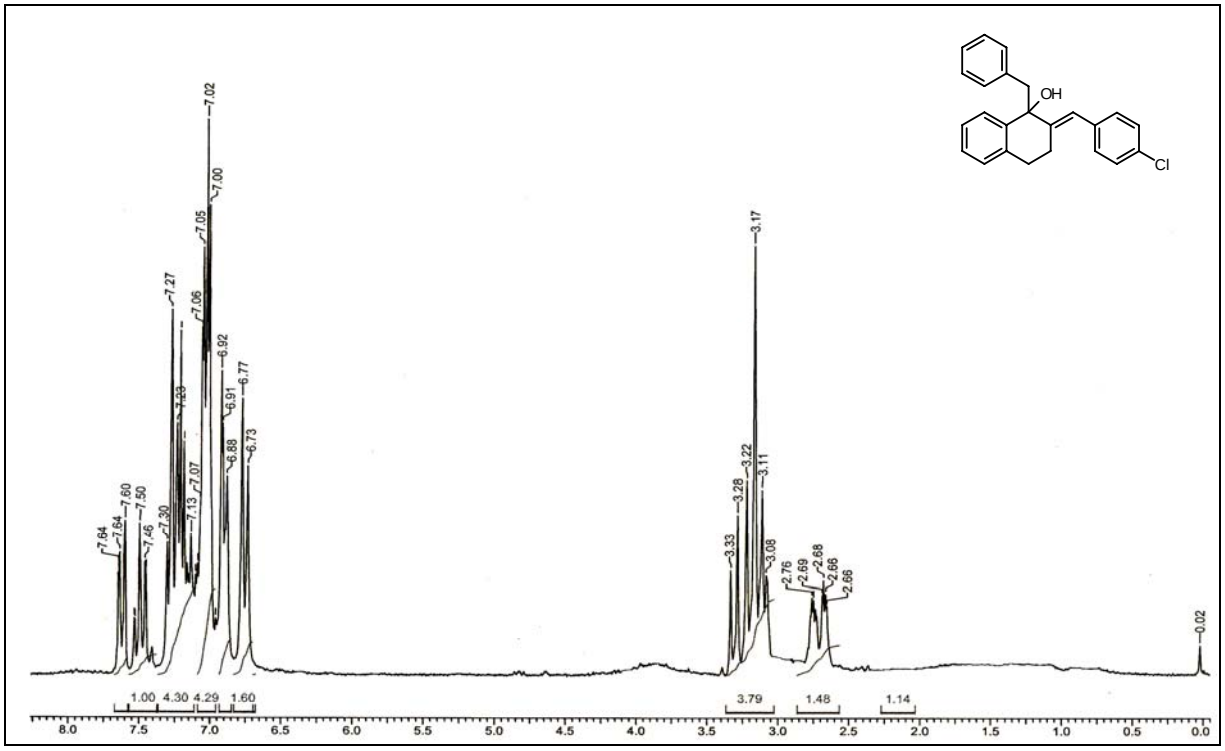
^{13}C NMR Spectrum of Compound 100 p ($CDCl_3$+CCl_4, 50 MHz)



DEPT spectrum of Compound 100 p ($CDCl_3$+CCl_4, 50 MHz)



18) ^{1}H NMR Spectrum of Compound 101 p ($CDCl_3$+CCl_4, 50 MHz)



CHAPTER - I

SECTION - I

NEW 2-ARYLIDENE TETRALONE DERIVATIVES

PART - B

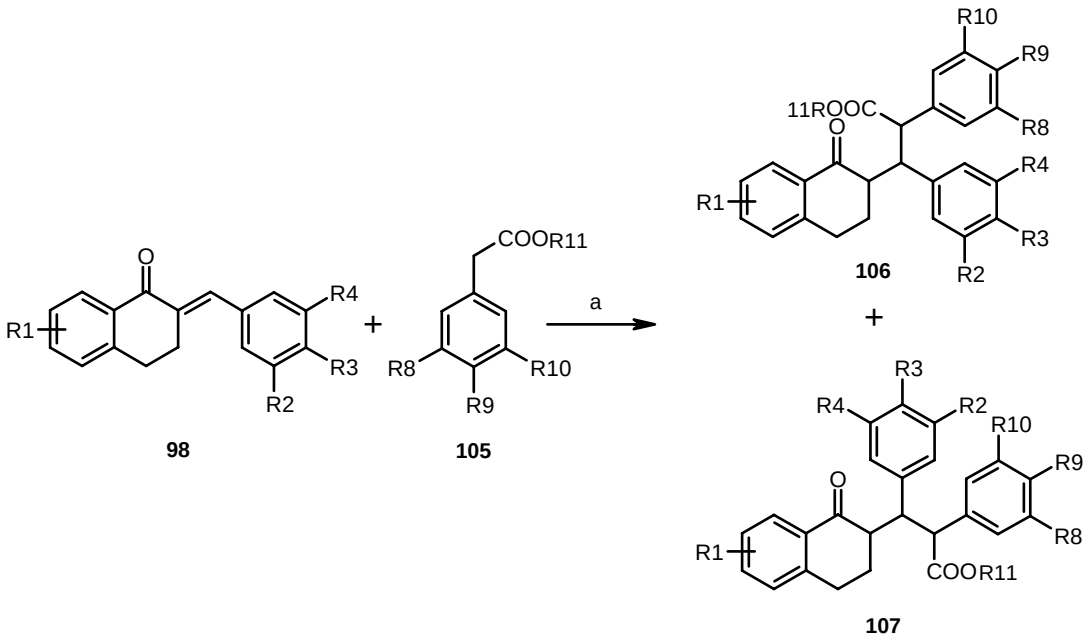
SELECTIVE 1,4-ADDITION PRODUCTS

1.2.1: PRESENT WORK:

It has been observed that hybrids show better biological activity as compared to their parent molecules. Considering this point of view and to produce a library of NCEs it is necessary to derivatize the new hybrids which are showing some good cytotoxic activity. In first part of this section we have synthesized some new hybrid molecules which showed good cytotoxicity, in continuation with that and to increase the number of NCEs for SAR studies we synthesized some new chemical entities using LDA as a base. In this part we have used the esters of substituted phenyl acetic acids instead of substituted benzyl bromides as discussed in part-A as the Michael donars and 2-arylidene tetralones as the Michael acceptors.

1.2.2: RESULTS AND DICUSSION:

The substituted 2-arylidene-1-tetralones (**98a-i**) were treated with substituted methyl or ethyl esters of phenyl acetic acids (**105a-d**). The various esters of substituted phenyl acetic acids (**105a-d**) were used from commercial source or synthesized from commercially available starting materials. Esters of substituted phenyl acetic acids (**105a-d**) were treated with lithium diisopropyl amide (LDA) in tetrahydrofuran as a solvent at -78 ^{0}C and the anion formed was stabilized by using HMPA as a stabilizer. The substituted 2-arylidene-1-tetralone (**98a-i**) dissolved in tetrahydrofuran was added to the reaction mixture at -78 ^{0}C and stirred at same temperature for 3 - 4 h. After the complete disappearance of both the starting materials as monitored by TLC, the reaction mixture was worked up (scheme-1). The crude product was a mixture of two compounds **106** and **107** which were separated and purified by column chromatography. The two compounds were fully characterized by PMR, CMR, IR, spectroscopy and supported by HETCOR, COESY, NOESY spectroscopic methods. The X-ray crystallography confirmed the structures as **106** and **107** assigned to the compounds obtained as the products of the above reaction.



Reagents and Conditions: a = LDA, THF, HMPA, -78 ^{0}C,

Scheme - 1

In a typical experiment 2-arylidene-1-tetrlone (**98a,** wherein R1 = R2 = R3 = R4 = H) was treated with methyl-4-methoxyphenyl acetate (**105c**, R8 = R10 = H, R9 = OMe, R11 = Me) in the presence of lithium diisopropyl amide (LDA) in tetrahydrofuran at -78 ^{0}C to collect a mixture of two diastereomers **106a** and **107a** (Table-1). The two isomers could be separated in pure forms by column chromatography using silica gel (60 - 120 mesh) and pet ether:ethyl acetate as eluent. Unlike the magnesium mediated reaction (discussed in part-I) we obtained only 1, 4-addition products. Formation of 1, 2-addition product was not observed in any of the experiments. The spectral evaluation of the isomers **106a** and **107a** is described in detail as follows.

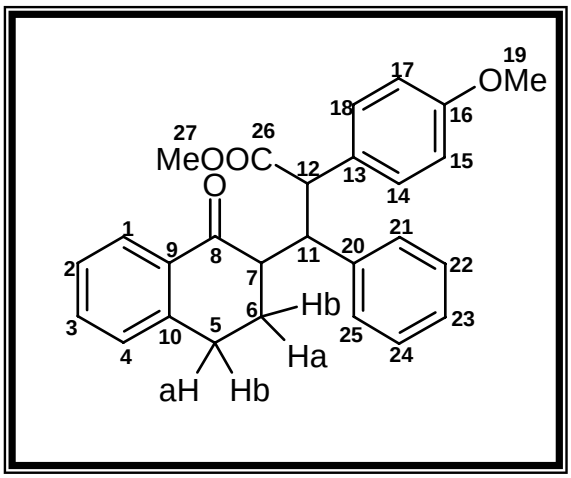


Table - 1; Comp. 106a

The PMR spectrum of isomer **106a** exhibited various peaks in accordance with the assigned structure. The upfield multiplets at δ 1.76 - 1.91 and 2.09 - 2.23 were assigned to the protons on C - 6 which showed two separate multiplets for each proton, the protons at C - 5 also showed two separate multiplets for each proton at δ 2.78 - 2.90 and 2.95 - 3.07. A multiplet at δ 3.08 - 3.30 was assigned for the proton on C - 7, while the multiplet at δ 3.58 - 3.66 was assigned for C - 11. The proton which appeared as a doublet at δ 5.08 (J = 12 Hz) was assigned to C - 12 in isomer **106a.** The two sharp singlets at δ 3.67 and 3.72 were assigned for two methoxy groups, while the doublet at δ 8.07 (J = 8 Hz) was assigned for the aromatic proton on C - 1.

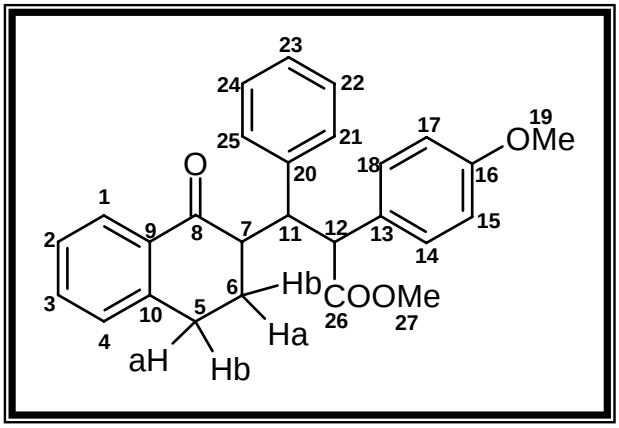


Table -1; Comp. 107a

The PMR spectrum of other isomer **107a** exhibited the peaks in accordance with the assigned structure. Multiplets at δ 1.62 - 1.72 and 2.16 - 2.29 were assigned to two protons at C - 5. A multiplet at δ 2.67 - 3.04 was due to three protons at C - 6 and C - 7. The two methoxy groups were observed at δ 3.56 and 3.59 as singlets (C -19 and C - 27). The proton at C - 12 showed a doublet at δ 4.10 (J = 12 Hz), proton at C - 11 showed doublet of doublet at δ 4.46 (J = 12 and 4 Hz). The proton at C - 1 showed a doublet at δ 7.91 (J = 8 Hz) which is due to the carbonyl group present at C - 8, the other aromatic protons showed the peaks at their expected chemical shifts described in experimental part of this section.

It was evident from the PMR data of **106a** and **107a** that the PMR spectra of these two compounds differ only for protons at C - 7, C - 11 and C - 12. The IR and mass spectra of **106a** and **107a** were identical.

In the IR spectroscopy the absorbance at ν_{max}1722 and 1677 cm^{-1} confirmed the presence of cyclic ketone and ester groups in the compound **106a,** while in compound **107a** these groups showed absorbance at ν_{max}1729 and 1679 cm^{-1}.

The assigned structures of isomers **106a** and **107a** were further supported by ^{13}C NMR spectroscopy. The ^{13}C spectrum of isomer **106a** displayed 22 signals for 27 carbon atoms, the upfield signals at δ 28.69 and 29.52 were assigned to methylenes present at C - 5 and C - 6. Signal at δ 49.84 was assigned for C - 7, while the signals at δ 52.00 and 53.00 were assigned the C - 11 and C - 12. The carbonyl group from ester at C - 26 showed a signal at δ 174.88 and carbonyl group from tetralone ring at C - 8 showed a signal at δ 199.45. The two methoxy C -19 and C - 27 showed the signals at δ 53.44 and 54.89 respectively.

^{13}C NMR spectrum of isomer **107a** displayed 21 signals for 27 carbon atoms, the upfield signals at δ 25.26 and 28.37 were assigned for two methlyene carbons at C - 5 and C - 6. A signal at δ 45.48 was assigned to C - 11. Signals at δ 51.68 and 54.94 were assigned to C - 7 and C - 12, two methoxy carbons appeared at δ 53.28 and 54.94. The downfield signal at δ 197.89 is a characteristic signal for carbonyl carbon present in a molecule at C - 8. The presence of ester group was confirmed by appearance of signal at δ 173.84 and the other carbon atoms resonated at their expected chemical shifts described in experimental part of this section.

The HETCOR studies provide the connectivity of protons to the specific carbon. Therefore the HETCOR spectra were recorded on Brucker 500 MHz NMR instrument in pure $CDCl_3$ for **106a** and **107a**. Figure 1 shows the correlation between the protons with the corresponding carbon atoms in the compound **106a**. Similarly fig. 2 shows the correlation of protons with carbon atoms in the compound **107a,** which was further confirmed by COESY and NOESY spectroscopic studies.

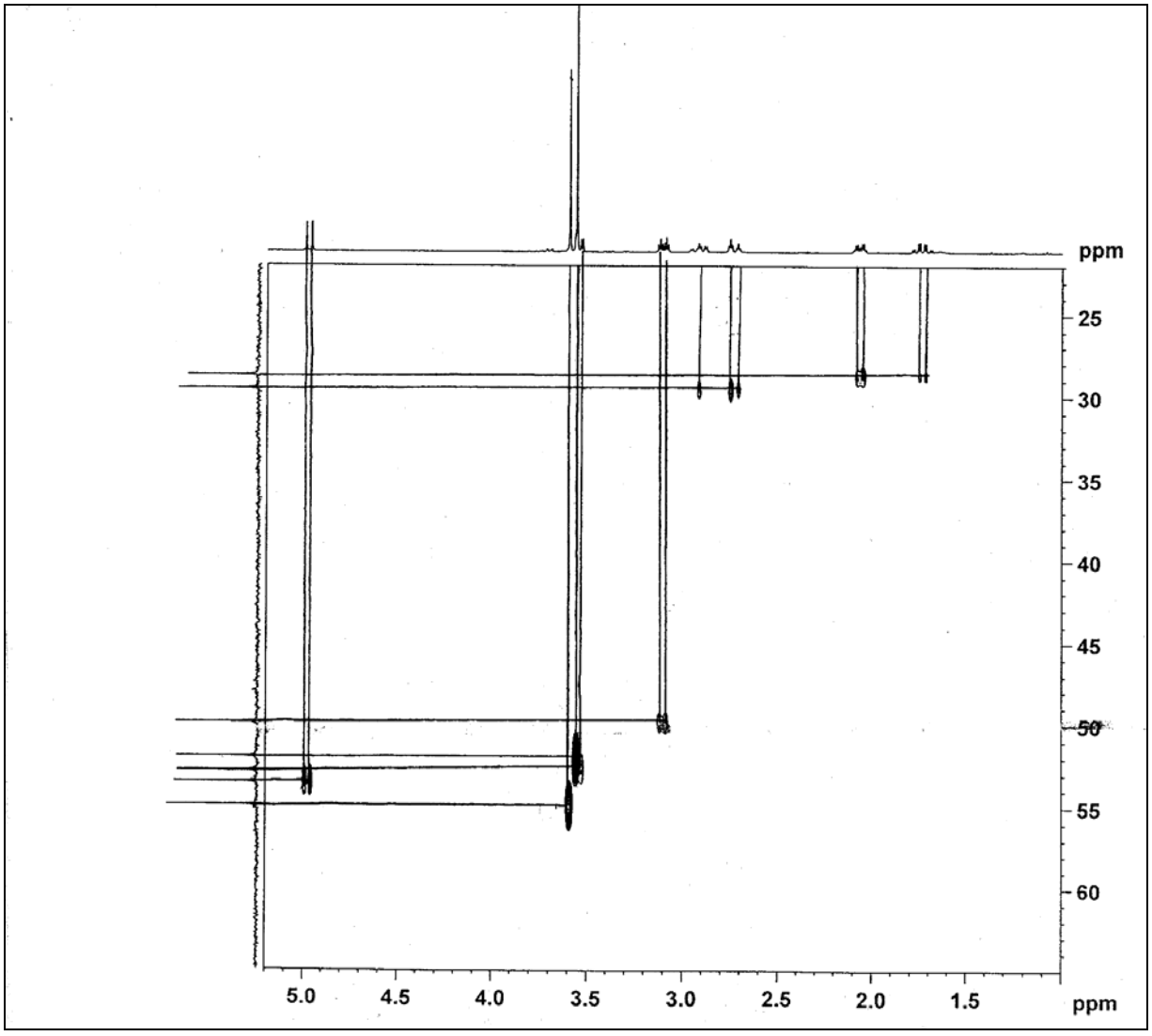


Fig. 1: HETCOR spectrum of compound 106a

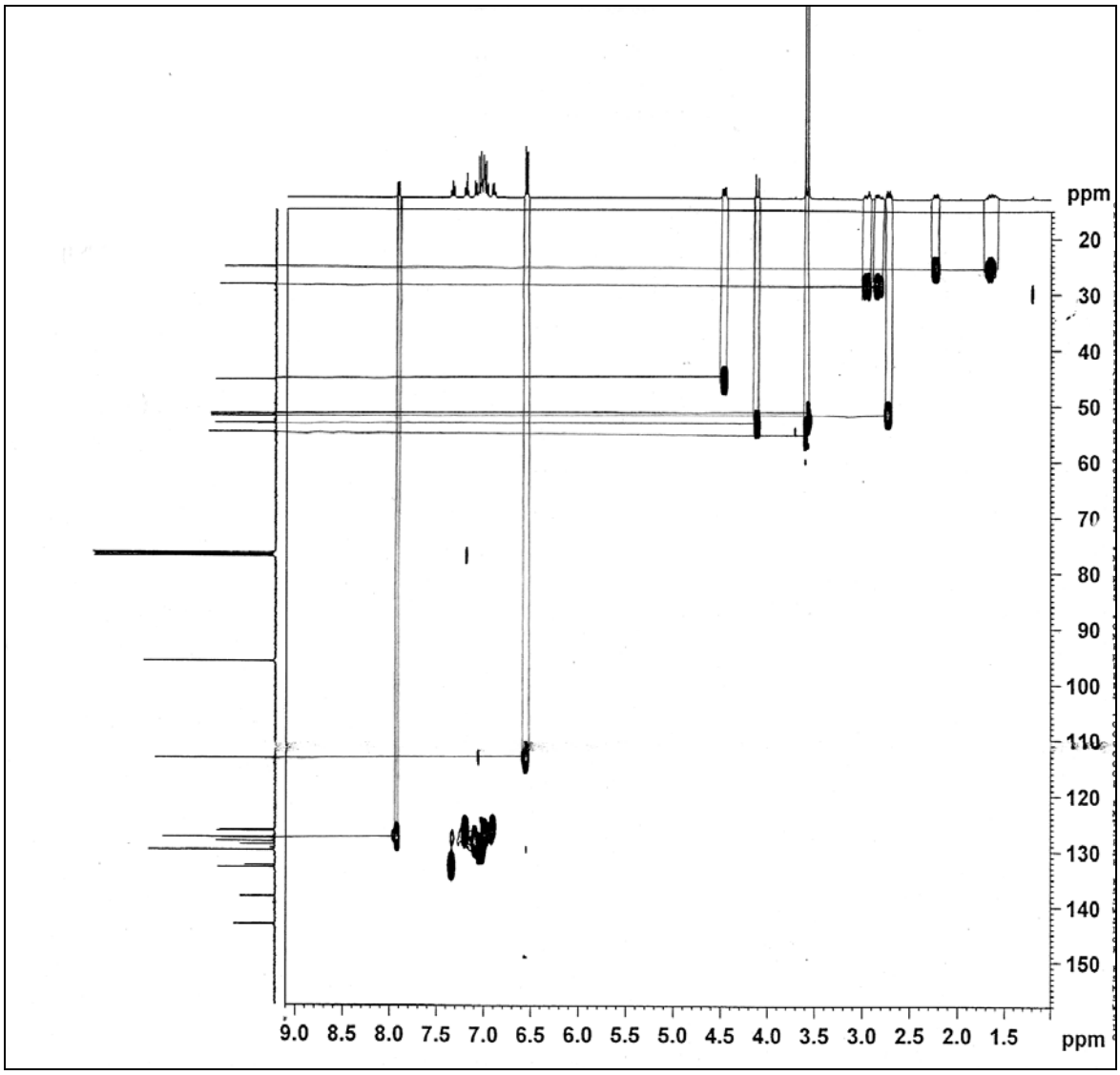


Fig. 2: HETCOR spectrum of compound 107a

The peak assignment of isomer **106a** was done on the basis of ^{1}H-^{1}H COESY experiments. In COESY spectrum the splitting patteren of protons on C - 5 and C - 6 showed multiplets due to the self coupling of benzylic (-CH_2) protons on C - 5 as well as with the protons at C - 6 showing a weak band in COESY spectrum. Similarly the protons from C - 6 showed the connectivity with the protons on C - 5, due to which the protons at C - 5 and C - 6 showed four different multiplets in ^{1}H NMR spectrum which was confirmed from COESY spectrum (Fig. 3).

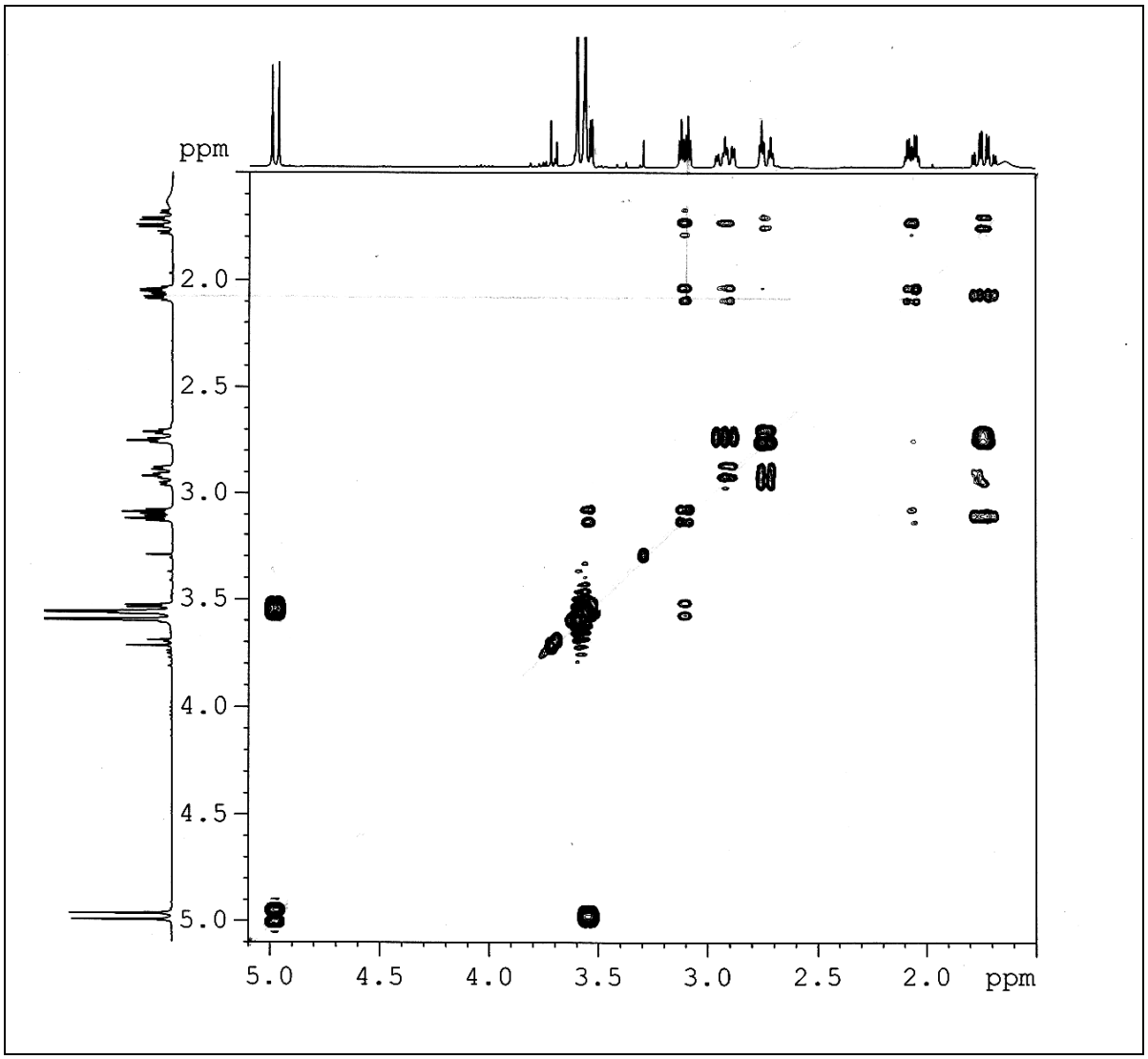


Fig. 3: COESY spectrum of compound 106a

The peak assignment of compound **107a** was also done on the basis of ^{1}H-^{1}H COESY experiments. The splitting pattern observed in ^{1}H NMR spectrum for protons at C - 5 and C - 6 is due to the long range coupling of protons at C - 5 with a proton on C - 6. Both the ($-CH_2$) protons showed a multiplet for each proton in ^{1}H NMR spectra which is supported by COESY experiments. In ^{1}H spectrum it was seen that the proton at C - 7 was *cis* to the proton at C - 11 and the proton at C - 11 was *trans* with respect to the proton at C - 12

which was proved from their *J* values. In support of this COESY spectrum showed the same pattern (Fig. 4)

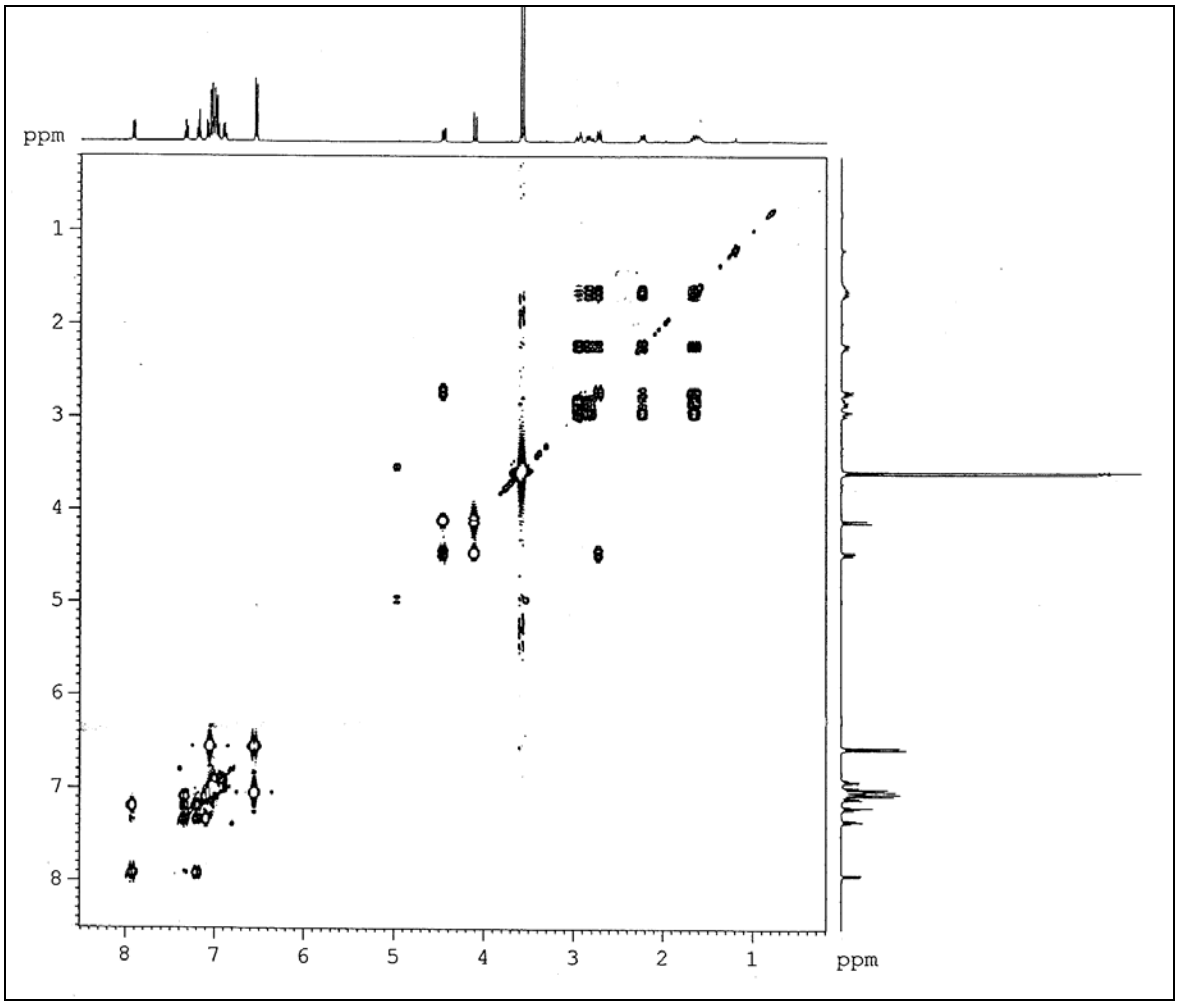


Fig. 4: COESY spectrum of compound 107a

To confirm the geometry of protons on C - 7, C - 11 and C - 12 it was necessary to take the NOESY spectrum of the isomers **106a** and **107a**. In NOESY experiment of compound **106a** the proton at C - 7 showed strong band correlation with the proton at C - 11 which clearly indicated that these two protons are on the same side and *cis* to each other while the proton at C - 11 showed weak band correlation with C - 12 which indicated that these two protons are *trans* to each other which was also supported by *J* values in ^{1}H NMR spectrum (Fig. 5).

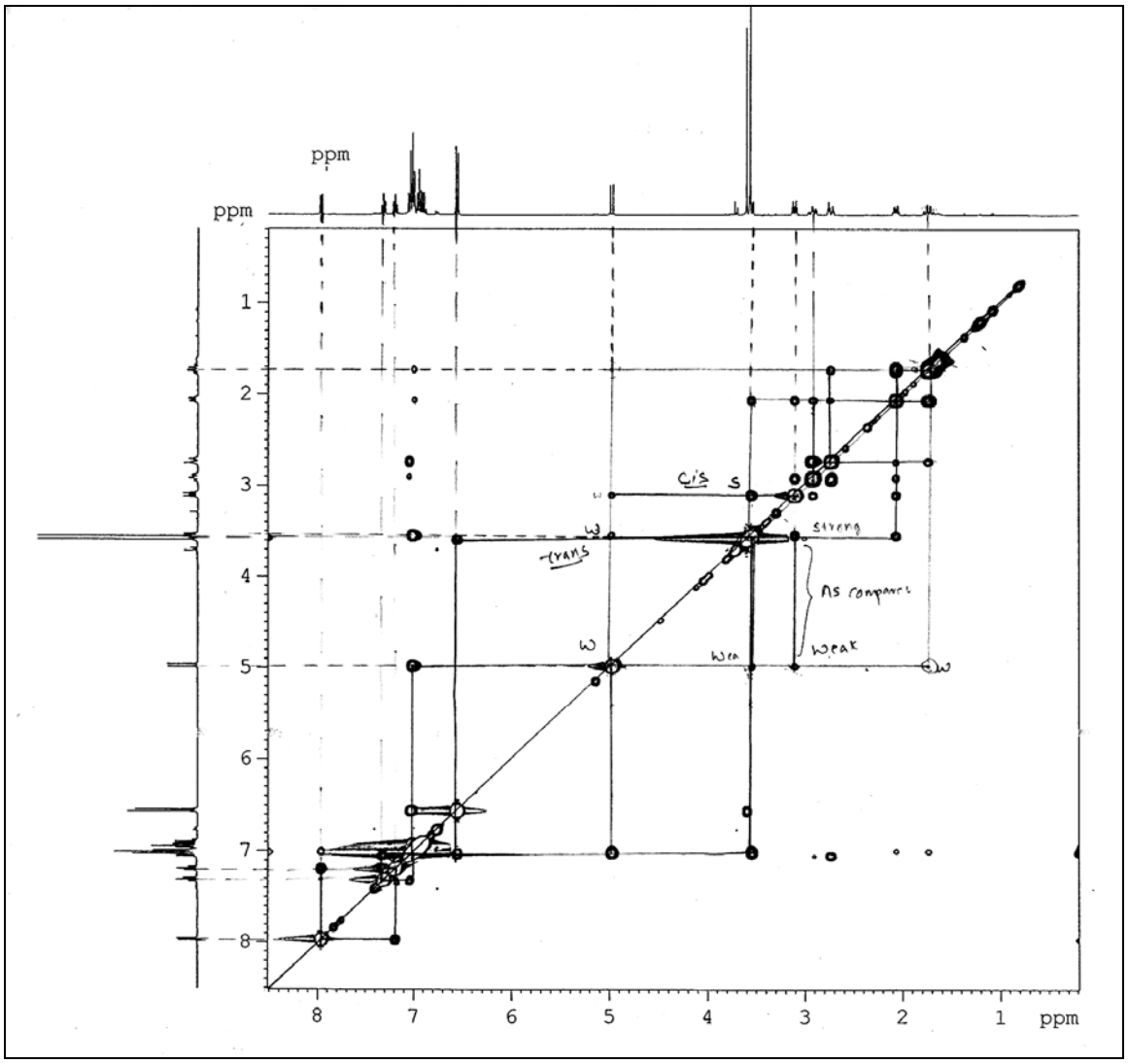


Fig. 5: NOESY spectrum of compound 106a

Similarly in the NOESY spectrum of compound **107a** the proton at C - 7 showed the strong band with the proton at C - 11 which clearly indicated that these protons are *cis* to each other, while C - 11 showed weak band with C - 12 which indicated the *trans* pattern which was also supported by *J* values in PMR of the compound (Fig. 6).

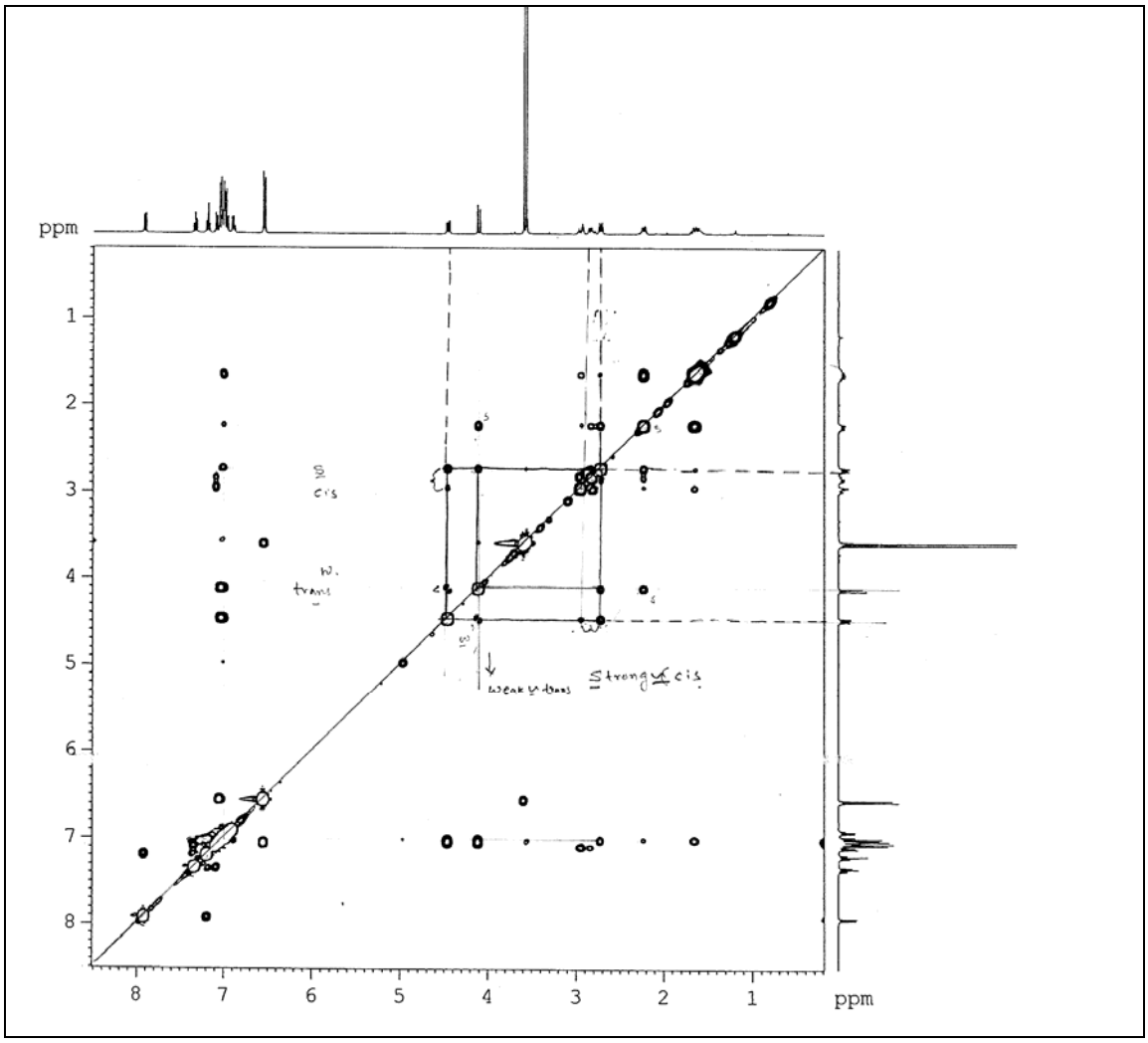


Fig. 6: NOESY spectrum of compound 107a

The structures of isomers **106a and 107a** were confirmed by all above spectroscopic methods, to support thes structures we used X-ray crystallography method which confirmed structures assigned from the ^{1}H NMR, ^{13}C NMR, HETCOR, COESY and NOESY spectroscopic data. The isomer **106a,** synthesized from 2-arylidene-1-tetralone and a methyl ester of *p*-methoxy phenylacetic acid, was crystallized from petroleum ether-ethyl acetate by slow crystallization method. Colourless rectangular crystal of approximate size 0.25 x 0.20 x 0.03 mm, was used for data collection on *Bruker SMART*

APEX CCD diffractometer using Mo K_α radiation with fine focus tube with 50 kV and 30 mA. The crystal data of isomer - **106a:** M.F. $C_{27}H_{26}O_4$, M.W. 414.48 crystal system: monoclinic, space group P-21/c, unit cell dimensions: a = 21.6485 (10) A; b = 11.5249 (13) A; c = 8.895, β = 92.020 (5); (2) A. V = 2218.0 (7) A^3, Z (calculated density) = 4, 1.242 mg/m^3, all the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in the tables 2 and 3. Characteristic spectral information confirmed the structure of isomer **106a** which is presented in experimental section and elucidated structure is presented in ORTEP diagram (Fig. 7)

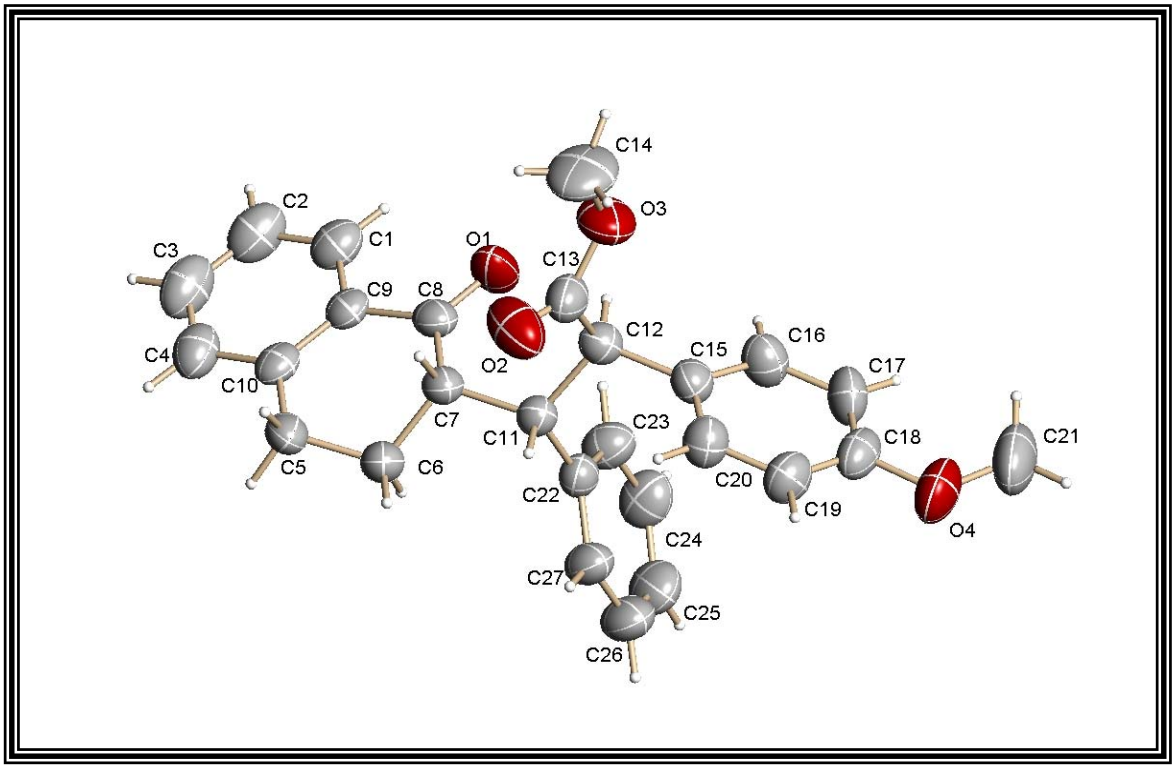


Fig. 7: ORTEP diagram of compound 106a

Similarly the isomer **107a** was crystallized from petroleum ether-ethyl acetate by slow crystallization method. Colourless rectangular crystal of approximate size 0.33 x 0.16 x 0.14 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50 kV and 30 mA. The crystal data of isomer - **107a:** M.F. $C_{27}H_{26}O_4$, M.W. 414.48 crystal system: monoclinic, space group P-21, unit cell dimensions: a = 6.6799 (4) A; b = 18.3749 (12) A; c = 8.7475 (6) A, β = 94.1400 (10); V = 1070.89 (12) A^3, Z (calculated density) = 2, 1.285 mg/m^3, all the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in the tables 4 and 5. Characteristic spectral information confirmed the structure of isomer **107a** which is presented in experimental section and elucidated structure is presented in ORTEP diagram (Fig. 8)

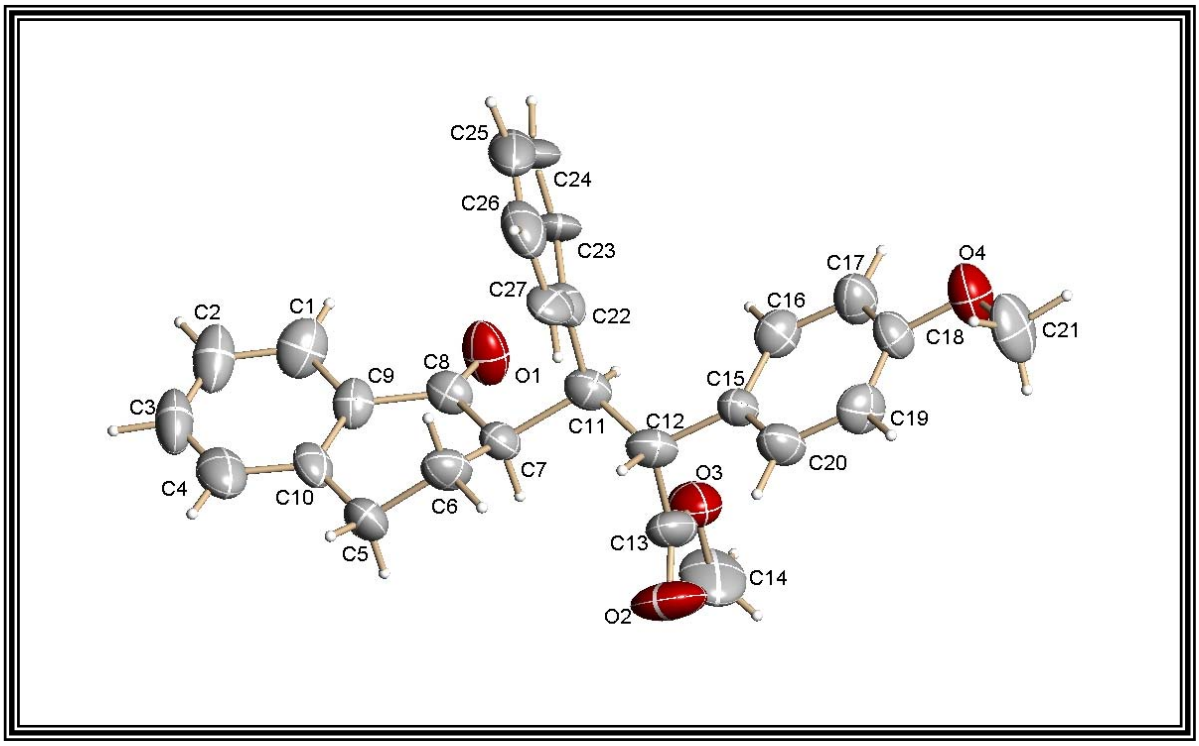
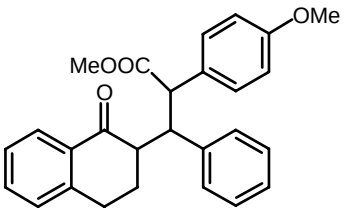
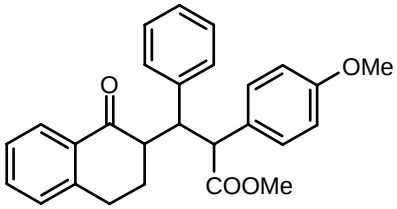
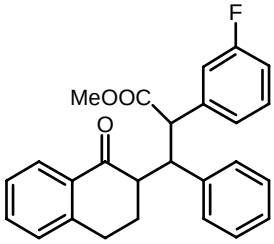
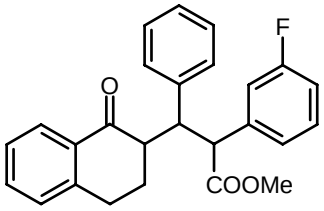
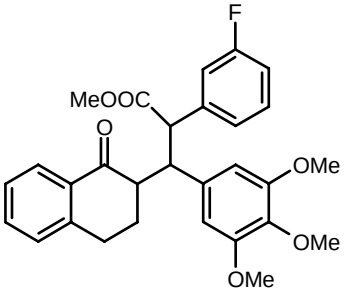
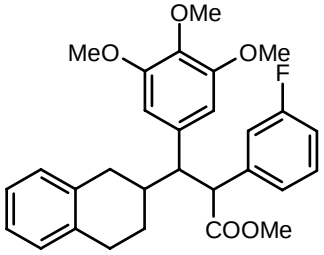
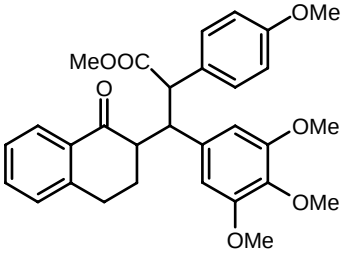
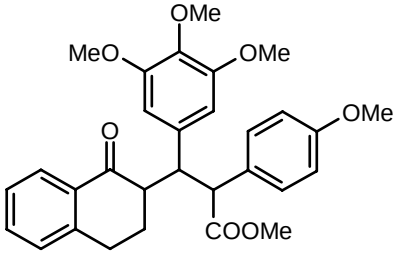


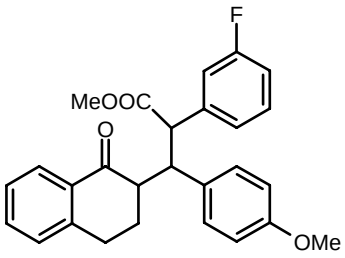
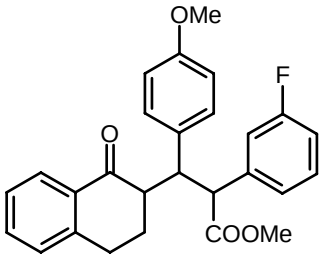
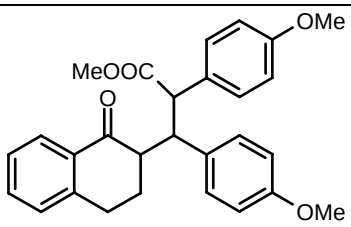
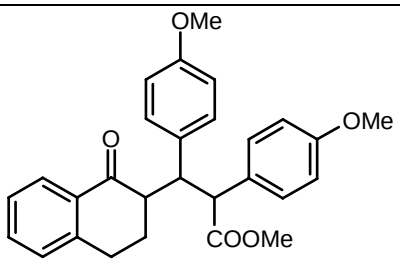
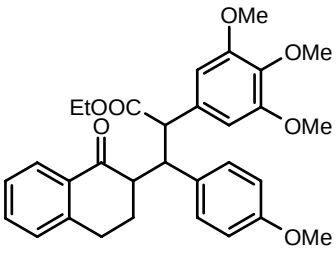
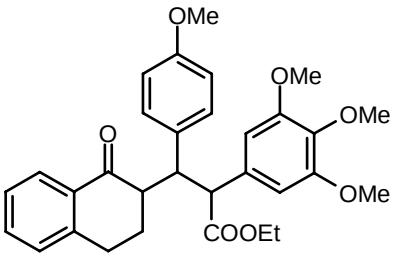
Fig. 8: ORTEP diagram of compound 107a

Both the products are formed in equimolar quantity in all reactions of this series.

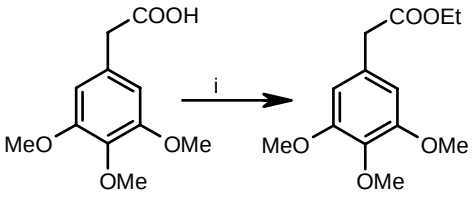
Employing the optimized protocol the compounds **106** and **107** were synthesized using the starting materials as substituted arylidene tetralones and esters of substituted phenyl acetic acids (Table - 1). An equimolar mixture of compounds **106** and **107** was obtained from all the reactions in this series. All the compounds were characterized by spectroscopic methods and showed satisfactory spectral data described in experimental part of this section.

Table 1: NCEs from LDA reaction

S. No.	Structure	S. No.	Structure
106a		**107a**	
106b		**107b**	
106c		**107c**	
106d		**107d**	

106e		**107e**	
106f		**107f**	
107g		**107g**	

The intermediate esters of substituted phenyl acetic acid **105** were prepared from commercially available substituted phenyl acetic acids. 3,4,5-Trimethoxy phenyl acetic acid was treated with methanol or ethanol in presence of sulfuric acid in catalytic amount under reflux condition overnight, (Scheme - 2) which furnished the ethyl ester of 3,4,5-trimethoxy phenyl acetic acid (**105a**).



108 **105a**

Reagents and Conditions: i = EtOH, H_2SO_4, reflux overnight.

Scheme - 3

Some of the NCEs were tested for their cytotoxicity on some important cell lines. The results of biological studies and the structure activity relationship are summarized in section three of this chapter.

1.2.3: CONCLUSION:

A number of NCEs synthesized have demonstrated antifungal, cytotoxic and anticancer properties. In this part we have synthesized substituted arylidene tetralone derivatives selectively at 1,4-addition, instead of 1,2-addition in part-Ist of this section. Synthesized NCEs in this part were screened for their cytotoxicities against a panel of cell lines. Most of the new compounds have shown significant cytotoxicity both the isomers show comparable activity. This investigation is helpful to improve the design and development of more potent anticancer agents together with superior efficacy and shortes chemical sequences.

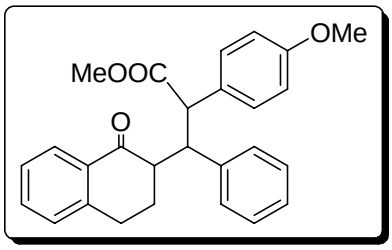
1.2.4: EXPERIMENTAL:

Typical procedure for the methyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2-(4-methoxyphenyl)-3-phenylpropanoate (106a and 107a):

In a dry 250 ml two-necked round bottom flask evacuated and flushed with nitrogen, freshly distilled dry tetrahydrofuran (50 ml) was added and cooled in ice salt mixture, n-BuLi (1.6 M, 2.9 ml, 7.264 mmol) was added dropwise followed by diisopropyl amine (0.545 ml, 7.264 mmol). The reaction mixture was stirred for 50 min at same temperature and then for additional 20 min at -78 ^{0}C. Methyl 2-(4-methoxyphenyl)acetate (1.153 g, 6.410 mmol) dissolved in dry tetrahydrofuran (10 ml) was added in the reaction mixture slowly, after 5 min. HMPA (0.5 ml) was added in it and stirred for 40 min at same temperature. Then 2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (1 g, 4.273 mmol) dissolved in dry tetrahydrofuran (15 ml) was added in the reaction mixture slowly and the reaction mixture was stirred for 3 h at -78 ^{0}C. Reaction was monitored by TLC, which showed completion of reaction after 3 h. Reaction mixture was quenched with ammonium chloride and extracted with ethyl acetate (3 x 50 ml). The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure on rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: ethyl acetate as eluent) to yield two isomers in (44:40 % proportion).

Methyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2-(4-methoxyphenyl)-3-phenylpropanoate (106 a):

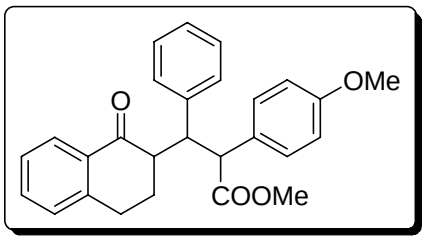
Nature: White solid; **Yield:** 44 %; **IR** (chloroform)**:** ν_{max} 3020, 1722, 1677, 1600, 1511, 1454, 1436 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.76 - 1.91 (m, 1H), 2.09 - 2.23 (m, 1H), 2.78 - 2.90 (m, 1H), 2.95 - 3.07 (m, 1H), 3.08 - 3.30 (m, 1H), 3.58 - 3.66 (m, 1H), 3.67 (s, 3H), 3.72 (s, 3H), 5.09 (d, J = 12 Hz, 1H), 6.67 (d, J = 8 Hz, 2H), 7.03 - 7.19 (m, 7H),



7.28 - 7.50 (m, 3H), 8.07 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.6, 29.5, 49.8, 52.0, 53.0, 53.4, 54.8, 113.5 (2C), 126.5, 127.3, 127.8 (2C), 128.0, 129.4 (2C), 129.8 (2C), 130.0, 133.1 (2C), 133.5, 139.4, 143.6, 158.3, 174.8, 199.4; **Anal. Calcd. for** $C_{27}H_{26}O_4$**:** C, 78.26; H, 6.28 %. **Found:** C, 78.20; H, 6.25 %.

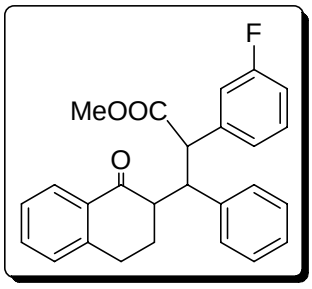
Methyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2-(4-methoxyphenyl)-3-phenylpropanoate (107 a):

Nature: White solid; **Yield:** 40 %; **IR** (chloroform)**:** ν_{max} 3019, 1729, 1679, 1610, 1600, 1512, 1454 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.64 - 1.73 (m, 1H), 2.16 - 2.29 (m, 1H), 2.67 - 3.04 (m, 3H), 3.56 (s, 3H), 3.59 (s, 3H), 4.10 (d, J = 12 Hz, 1H), 4.46 (dd, J = 12 and 4 Hz, 1H), 6.55 (d, J = 8 Hz, 2H), 6.91 - 7.37 (m, 10H), 7.91 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.2, 28.3, 45.4, 51.6, 52.1, 53.2, 54.9, 113.5 (2C), 126.3, 126.5, 127.6 (2C), 128.1, 128.2, 129.9 (4C), 132.6, 133.1 (2C), 138.3, 143.3, 158.4, 173.8, 197.8; **Anal. Calcd. for** $C_{27}H_{26}O_4$**:** C, 78.26; H, 6.28 %. **Found:** C, 78.15; H, 6.20 %.



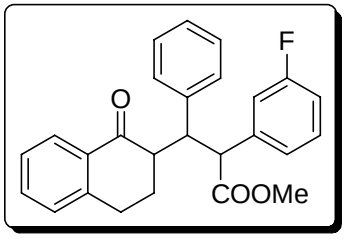
Methyl-2-(3-fluorophenyl)-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-3-phenylpropanoate (106 b):

Nature: Light pink solid; **Yield:** 44 %; **IR** (chloroform)**:** ν_{max} 3020, 1725, 1676, 1614, 1598, 1487, 1453 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.60 - 1.82 (m, 1H), 1.95 - 2.15 (m, 1H), 2.65 - 2.85 (m, 1H), 2.86 -3.00 (m, 1H), 3.02 - 3.22 (m, 1H), 3.55 (dd, J = 12 and 4 Hz, 1H), 3.60 (s, 3H), 5.03 (d, J = 12 Hz, 1H), 6.69 (t, J = 10 Hz, 1H), 6.80 - 7.15 (m, 9H), 7.18 - 7.40 (m, 2H), 7.98 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.7, 29.5, 49.7, 52.1, 52.8, 54.1, 114.1, 115.0, 124.5, 126.5, 127.8, 128.0 (2C), 128.5, 129.5, 129.7 (2C), 129.9, 133.2, 133.4, 138.9, 140.6, 140.7, 143.6, 174.1, 199.3; **Mass:** M^{+Na}; 397; **Anal. Calcd. for** $C_{26}H_{23}O_3F$; C, 77.59; H, 5.62; F, 4.72 %. **Found:** C, 77.46; H, 5.50; F, 4.59 %.



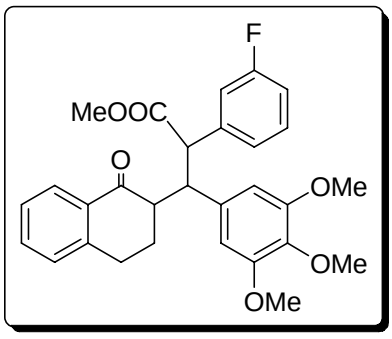
Methyl-2-(3-fluorophenyl)-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-3-phenylpropanoate (107 b):

Nature: Light pink solid; **Yield:** 41 %; **IR** (chloroform)**:** ν_{max} 3019, 1729, 1676, 1610, 1512, 1456, 1430 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.75 - 2.05 (m, 1H), 2.32 - 2.65 (m, 1H), 3.16 - 3.30 (m, 1H), 3.45 - 3.56 (m, 1H), 3.62 (s, 3H), 4.15 (d, J = 10 Hz, 1H), 4.38 (dd, J = 18 and 4 Hz, 1H), 6.65 (t, J = 10 Hz, 1H), 6.68 - 7.18 (m, 9H), 7.20 - 7.45 (m, 2H), 8.00 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{26}H_{23}O_3F$**:** C, 77.59; H, 5.62; F, 4.72 %. **Found:** C, 77.43; H, 50.45; 4.63 %.



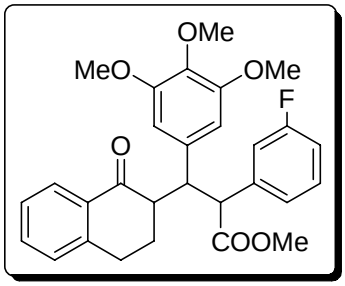
Methyl-2-(3-fluorophenyl)-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl-3-(3,4,5-trimethoxyphenyl)propanoate (106 c):

Nature: White solid; **Yield:** 42 %; **IR** (chloroform)**:** ν_{max} 3019, 1725, 1674, 1592, 1509, 1487 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.70 - 1.95 (m, 1H), 2.05 - 2.20 (m, 1H), 2.70 - 2.90 (m, 1H), 2.92 - 3.10 (m, 1H), 3.12 - 3.30 (m, 1H), 3.43 (dd, J = 16 and 4 Hz, 1H), 3.63 (s, 3H), 3.69 (s, 3H), 5.03 (d, J = 12 Hz, 1H), 6.23 (s, 2H), 6.75 - 7.00 (m, 3H), 7.02 - 7.23 (m, 2H), 7.25 - 7.50 (m, 2H), 8.06 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.7, 29.3, 49.3, 52.2, 53.7, 54.6, 55.8 (2C), 60.6, 106.8 (2C), 114.2, 115.3, 124.4, 126.6, 127.2, 128.5, 129.4, 133.3, 133.6, 134.6, 136.6, 140.5, 140.8, 143.8, 152.5 (2C), 174.0, 200.0; **Anal. Calcd. for** $C_{29}H_{29}O_6$**:** C, 70.73; H, 5.89; F, 3.86 %. **Found:** C, 70.50; H, 5.95; F, 3.69 %.



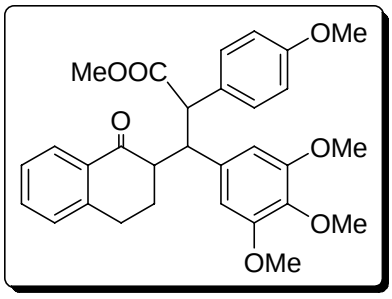
Methyl-2-(3-fluorophenyl)-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl-3-(3,4,5-trimethoxyphenyl)propanoate (107 c):

Nature: White solid; **Yield:** 39 %; **IR** (chloroform)**:** ν_{max} 3018, 1726, 1675, 1600, 1512, 1466, 1446 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.20 - 2.45 (m, 1H), 2.72 - 2.95 (m, 1H), 2.96 - 3.08 (m, 1H), 3.10 - 3.14 (m, 1H), 3.66 (s, 3H), 3.71 (s, 3H), 3.73 (s, 6H), 4.18 (d, J = 10 Hz, 1H), 4.44 (dd, J = 18 and 4 Hz, 1H), 6.28 (s, 2H), 6.80 - 7.18 (m, 3H), 7.25 - 7.55 (m, 5H), 8.02 (d, J = 8 Hz, 1H); **Anal. Calcd. for** $C_{29}H_{29}O_6F$**:** C, 70.73; H, 5.89; F, 3.86 %. **Found:** C, 70.65; H, 5.80; F, 3.72 %.



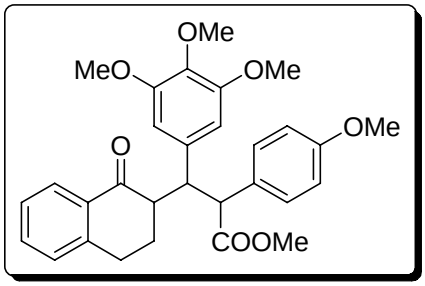
Methyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-3-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)propanoate (106 d):

Nature: White solid; **Yield:** 47 %; **IR** (chloroform)**:** ν_{max} 3017, 1725, 1671, 1591, 1511, 1456, 1423 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.90 - 2.09 (m, 1H), 2.10 - 2.22 (m, 1H), 2.75 - 2.96 (m, 1H), 2.98 - 3.04 (m, 1H), 3.16 - 3.26 (m, 1H), 3.48 (dd, J = 12 and 4 Hz, 1H), 3.66 (s, 6H), 3.68 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 4.95 (d, J = 12 Hz, 1H), 6.26 (s, 2H), 6.68 (d, J = 10 Hz, 2H), 7.05 - 7.55 (m, 5H), 8.07 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.6, 29.2, 49.4, 51.9, 53.6, 53.9, 54.9, 55.8 (2C), 60.5, 106.8 (2C), 113.5 (2C), 126.5, 127.1, 128.4, 129.3 (2C), 130.1, 133.2, 133.6, 135.2, 136.3, 143.8, 152.3 (2C), 158.4, 174.6, 200.0; **Anal. Calcd. for** $C_{30}H_{32}O_7$**:** C, 71.42; H, 6.34; %. **Found:** C, 71.40; H, 6.25 %.



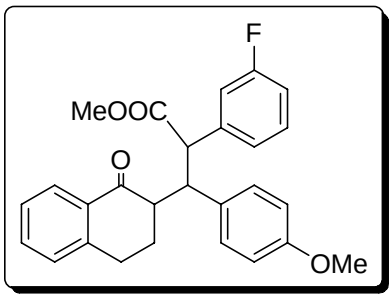
Methyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-3-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)propanoate (107 d):

Nature: White solid; **Yield:** 45 %; **IR** (chloroform)**:** ν_{max} 3019, 1729, 1677, 1692, 1511, 1464 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.93 - 2.10 (m, 1H), 2.20 - 2.45 (m, 1H), 2.70 - 3.15 (m, 3H), 3.64 (s, 3H), 3.71 (s, 6H), 3.80 (s, 3H), 3.84 (s, 3H), 4.13 (d, J = 12 Hz, 1H), 4.46 (dd, J = 16 and 4 Hz, 1H), 6.28 (s, 2H), 6.67 (d, J = 8 Hz, 2H), 6.86 (t, J = 8 Hz, 1H), 7.05 - 7.50 (m, 4H), 8.01 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.3, 28.2, 45.5, 51.5, 52.1, 53.2, 54.9, 56.0 (2C), 60.6, 107.3 (2C), 113.5 (2C), 126.6, 127.7, 128.5, 128.9, 129.5, 129.9 (2C), 133.2, 133.94, 133.99, 143.3, 152.2, 152.5, 158.5, 173.6, 198.1; **Anal. Calcd. for** $C_{30}H_{32}O_7$**:** C, 71.42; H, 6.34 %. **Found:** C, 71.35; H, 6.30 %.



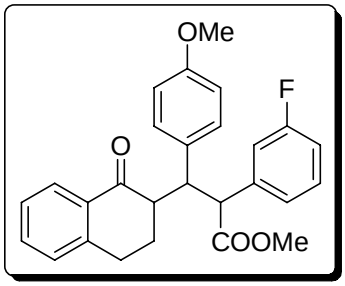
Methyl-2-(3-fluorophenyl)-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-3-(4-methoxyphenyl)propanoate (106 e):

Nature: White solid; **Yield:** 46 %; **IR** (chloroform)**:** ν_{max} 3020, 1725, 1676, 1613, 1592, 1531 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.70 - 1.95 (m, 1H), 2.03 - 2.20 (m, 1H), 2.72 - 3.08 (m, 2H), 3.10 - 3.25 (m, 1H), 3.55 (dd, J = 12 Hz and 4 Hz, 1H) 3.65 (s, 3H), 3.66 (s, 3H), 5.13 (d, J = 12 Hz, 1H), 6.57 (d, J = 10 Hz, 2H), 6.75 (t, J = 10 Hz, 1H), 6.90 - 7.22 (m, 5H), 7.25 - 7.50 (m, 3H), 8.04 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 28.5, 29.2, 49.6 (2C), 51.8, 54.10, 54.4, 113.0 (2C), 113.6, 115.3, 124.3, 126.2, 127.0, 128.1, 129.2, 130.5 (2C), 132.94, 133.2, 140.6, 143.4, 157.8, 159.8, 164.7, 173.9, 199.1; **Anal. Calcd. for** $C_{27}H_{25}O_4F$**:** C, 75.00; H, 5.78; F, 4.39 %. **Found:** C, 74.80; H, 5.75; F, 4.26 %.



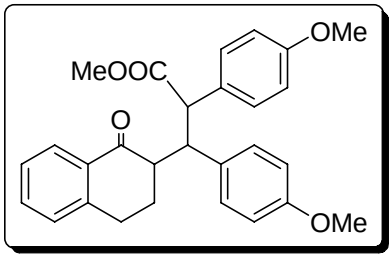
Methyl-2-(3-fluorophenyl)-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-3-(4-methoxyphenyl)propanoate (107 e):

Nature: White solid; **Yield:** 43 %; **IR** (chloroform)**:** ν_{max} 3020, 1732, 1677, 1592, 1513, 1488, 1410 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.50 - 2.05 (m, 1H), 2.10 - 2.30 (m, 1H), 2.35 - 3.05 (m, 3H), 3.53 (s, 3H), 3.55 (s, 3H), 4.12 (d, J = 12 Hz, 1H), 4.42 (dd, J = 12 and 4 Hz, 1H), 6.51 (d, J = 8 Hz, 2H), 6.65 (t, J = 8 Hz, 1H), 6.84 - 7.02 (m, 5H), 7.04 - 7.40 (m, 3H), 7.90 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 25.0, 28.2, 44.7, 51.5, 52.1, 54.1, 54.6, 113.0 (2C), 114.3, 116.0, 124.7, 126.4, 127.6, 128.4, 129.2, 130.6 (2C), 132.9, 133.0, 139.5, 143.2, 157.8, 159.9, 164.8, 173.0, 197.5; **Anal. Calcd. for** $C_{27}H_{25}O_4F$**:** C, 75.00; H, 5.78; F, 4.39 %. **Found:** C, 74.92; H, 5.60; F, 4.21 %.



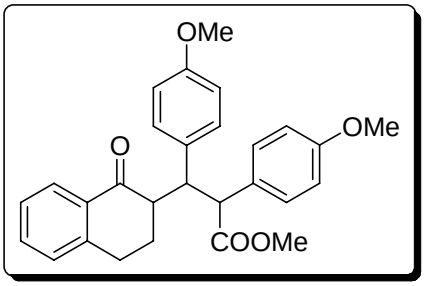
Methyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2,3-bis(4-methoxyphenyl)propanate (106 f):

Nature: White solid; **Yield:** 45 %; **IR** (chloroform)**:** ν_{max} 3019, 1721, 1670, 1612, 1512, 1409 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.60 - 1.70 (m, 1H), 1.95 - 2.14 (m, 1H), 2.65 - 2.95 (m, 2H), 2.97 - 3.15 (m, 1H), 3.45 (dd, J = 12 and 4 Hz, 1H), 3.56 (s, 3H), 3.57 (s, 3H), 3.62 (s, 3H), 4.95 (d, J = 12 Hz, 1H), 6.48 (d, J = 8 Hz, 2H), 6.57 (d, J = 8 Hz, 2H), 6.91 (d, J = 10 Hz, 2H), 7.01 - 7.08 (m, 3H), 7.19 - 7.33 (m, 2H), 7.95 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.8, 29.5, 49.9, 51.9, 52.0, 53.6, 54.7, 54.8, 113.2 (2C), 113.5 (2C), 126.4, 127.3, 128.5, 129.5 (2C), 130.5, 130.8 (2C), 131.1, 133.0, 133.6, 143.7, 157.9, 158.3, 174.9, 199.5; **Anal. Calcd. for** $C_{28}H_{28}O_5$: C, 75.65; H, 06.35 %. **Found:** C, 75.48; H, 6.23 %.



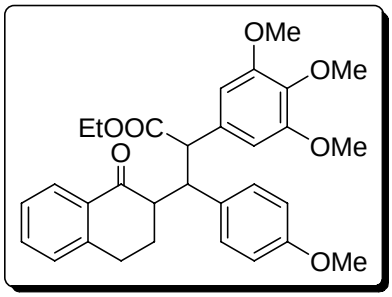
Methyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2,3-bis(4-methoxyphenyl)propanate (107 f):

Nature: White solid; **Yield:** 43 %; **IR** (chloroform)**:** ν_{max} 3018, 1724, 1676, 1692, 1510, 1452, 1435 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.63 - 1.72 (m, 1H), 2.18 - 2.28 (m, 1H), 2.65 - 2.95 (m, 3H), 3.56 (s, 6H), 3.60 (s, 3H), 4.07 (d, J = 12 Hz, 1H), 4.44 (dd, J = 12 and 6 Hz, 1H), 6.49 - 6.59 (m, 4H), 6.93 (d, J = 8 Hz, 2H), 7.00 - 7.15 (m, 3H), 7.20 - 7.45 (m, 2H) 7.92 (d, J = 10 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.1, 28.4, 44.6, 51.7, 52.0, 53.2, 54.8, 54.9, 113.0 (2C), 113.5 (2C), 126.5, 127.7, 128.0, 129.0, 130.0 (2C), 130.8 (2C), 133.0, 133.07, 143.3 (2C), 157.7, 158.4, 173.8, 197.8; **Anal. Calcd. for** $C_{28}H_{28}O_5$**:** C, 75.65; H, 6.35 %. **Found:** C, 75.52; H, 6.19 %.



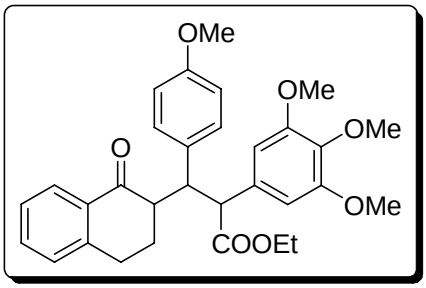
Ethyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)-3-(4-methoxyphenyl)propanoate (106 g):

Nature: White solid; **Yield:** 46 %; **IR** (chloroform)**:** ν_{max} 3019, 1716, 1677, 1594, 1512, 1464, 1424 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.20 (t, J = 8 Hz, 3H), 1.70 - 1.90 (m, 1H), 2.05 - 2.20 (m, 1H), 2.75 - 3.25 (m, 3H), 3.47 (dd, J = 12 and 4 Hz, 1H), 3.66 (s, 3H), 3.73, (s, 6H), 3.74 (s, 3H), 4.05 - 4.20 (m, 2H), 4.97 (d, J = 12 Hz, 1H), 6.37 (s, 2H), 6.57 (d, J = 10 Hz, 2H), 6.92 - 7.05 (m, 2H), 7.12 - 7.42 (m, 3H), 8.03 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 14.0, 28.9, 29.5, 49.8, 52.3, 54.8 (2C), 55.9 (2C), 60.6 (2C), 105.8 (2C), 113.2 (2C), 126.5, 127.3, 128.3, 130.7 (2C), 131.1, 132.9, 133.6, 133.9, 136.7, 143.6, 152.6 (2C), 158.0, 174.1, 199.5; **Anal. Calcd. for** $C_{31}H_{34}O_7$**:** C, 71.81; H, 6.56 %. **Found:** C, 71.75; H, 6.50 %.



Ethyl-3-(1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)-3-(4-methoxyphenyl)propanoate (107 g):

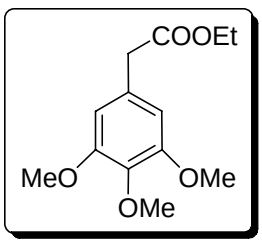
Nature: White solid; **Yield:** 44 %; **IR** (chloroform)**:** ν_{max} 3019, 1719, 1676, 1594, 1594, 1509, 1459, 1424 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.24 (t, J = 8 Hz, 3H), 1.70 - 1.85 (m, 1H), 2.25 - 2.40 (m, 1H), 2.70 - 3.05 (m, 3H), 3.68 (s, 3H), 3.74 (s, 9H), 4.00 - 4.25 (m, 3H), 4.40 (dd, J = 12 and 6 Hz, 1H), 6.41 (s, 2H), 6.61 (d, J = 10 Hz, 2H), 7.02 (d, J = 10 Hz, 2H), 7.18 - 7.47 (m, 3H), 8.00 (d, J = 6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 14.2, 25.2, 28.2, 44.9, 51.4, 54.2, 54.8, 55.9 (2C), 60.5, 60.8, 106.4 (2C), 113.0 (2C), 126.5, 127.6, 128.4, 129.9, 130.8 (2C), 132.0, 132.1, 133.1, 136.9, 143.3, 152.6 (2C), 157.9, 172.9, 197.9; **Anal. Calcd. for** $C_{31}H_{34}O_7$**:** C, 71.81; H, 6.56 %. **Found:** C, 71.60; H, 6.55 %.



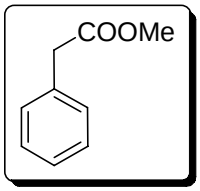
Typical procedure for the preparation of ethyl 3,4,5-trimethoxy phenylacetate (105 a):

In a 250 ml round bottom flask 3, 4, 5- trimethoxyphenyl acetic acid (2 gm, 8.849 mmol) was taken, in it ethanol (or methanol, 25 ml) was added followed by catalytic amount of H_2SO_4 (2-3 drops) the reflux reaction mixture was refluxed for overnight. Ethanol (or methanol) was removed under vacuum on rotary evaporator. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 25 ml). The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure on rotary evaporator. Purification of crude product on column chromatography (pet ether: ethyl acetate as eluent) yielded pure product.

Nature: Pale Yellow Semisolid; **Yield:** 89 %; **IR** (chloroform)**:** ν_{max} 3020, 1725, 1676, 1613, 1592, 1531 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.20 (t, J = 8 Hz, 3H), 3.45 (s, 2H), 3.74 (s, 3H), 3.77 (s, 6H), 4.08 (q, J 8 Hz, 2H), 6.43 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 13.52, 40.75, 55.27, 59.88, 60.03, 105.79 (2C), 129.06, 136.55, 152.57, 170.60; **Anal. Calcd. for** $C_{13}H_{18}O_5$**:** C, 61.40; H, 7.14 %. **Found:** C, 61.27; H, 7.05 %.

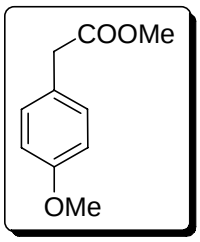


Methyl phenylacetate (105 b):



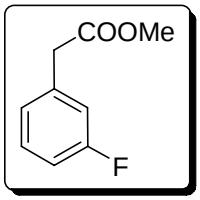
Nature: Pale Yellow Liquid; **Yield:** 91 %; **IR** (chloroform)**:** ν_{max} 3021, 1735, 1603, 1496, 1455 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.53 (s, 2H), 3.60 (s, 3H), 7.12 - 7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 40.93, 51.66, 126.88, 128.35 (2C), 129.04 (2C), 133.82, 171.58; **Anal. Calcd. for** $C_9H_{10}O_2$**:** C, 71.98; H, 6.71 %. **Found:** C, 71.82; H, 6.65 %.

Methyl 4-methoxyphenylacetate (105 c):



Nature: Pale Yellow Liquid; **Yield:** 90 %; **IR** (chloroform)**:** ν_{max} 3018, 1735, 1613, 1585, 1513, 1464, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.61 (s, 2H), 3.73 (s, 3H), 3.83 (s, 3H), 6.90 (d, J = 10 Hz, 2H), 7.24 (d, J = 10 Hz, 2H); **^{13}C NMR**: (50 MHz, $CDCl_3$+CCl_4)**:** δ 39.91, 51.59, 54.78, 113.73 (2C), 125.76, 129.99 (2C), 158.46, 172.08; **Anal. Calcd. for** $C_{10}H_{12}O_3$**:** C, 66.65; H, 6.71 %. **Found:** C, 66.52; H, 6.68 %.

Methyl 3-fluorophenylacetate (105 d):



Nature: Colourless Liquid; **IR** (chloroform)**:** ν_{max} 3023, 1735, 1616, 1592, 1489, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.66 (s, 2H), 3.75 (s, 3H), 6.95 - 7.13 (m, 3H), 7.25 - 7.40 (m, 1H); **Anal. Calcd. for** $C_9H_9FO_2$**:** C, 64.28; H, 5.39; F, 11.30 %. **Found:** C, 64.15; H, 5.19; F, 11.17 %.

Table 2: Crystal data and structure refinement for the isomer **106a**:

Empirical formula	$C_{27}\ H_{26}\ O_4$
Formula weight	414.48
Temperature	293 (2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P-21/c
Unit cell dimensions	a = 21.6485 (10) A b = 11.5249 (13) A; β = 92.020 (5) deg. c = 8.895 (2) A
Volume	2218.0 (7) A^3
Z, Calculated density	4, 1.241 Mg/m^3
Crystal size	0.25 x 0.20 x 0.03 mm
Theta range for data collection	2.58 to 25.00 deg.
Reflections collected / unique	10836 / 2920
Completeness to theta = 25	99.8 %
Goodness-of-fit on F^2	1.005
Final R indices [I>2sigma(I)]	R1 = 0.0600, wR2 = 0.1313
R indices (all data)	R1 = 0.1401, wR2 = 0.1610

Table 3: Bond lengths [A] and angles [deg] for isomer **106a** [$C_{27}H_{26}O_4$]

O(1)-C(8)	1.216(3)
O(2)-C(13)	1.195(4)
O(3)-C(13)	1.339(4)
O(3)-C(14)	1.463(4)
O(4)-C(18)	1.374(4)
O(4)-C(21)	1.415(4)
C(1)-C(2)	1.374(4)
C(1)-C(9)	1.382(4)
C(1)-H(1)	0.9300
C(2)-C(3)	1.378(5)
C(2)-H(2)	0.9300
C(3)-C(4)	1.365(5)
C(3)-H(3)	0.9300
C(4)-C(10)	1.402(4)
C(4)-H(4)	0.9300
C(5)-C(10)	1.490(4)
C(5)-C(6)	1.525(4)
C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700
C(6)-C(7)	1.508(4)
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-C(8)	1.513(4)
C(7)-C(11)	1.550(4)
C(7)-H(7)	0.9800
C(8)-C(9)	1.503(4)
C(9)-C(10)	1.392(4)
C(11)-C(22)	1.531(4)
C(11)-C(12)	1.546(4)
C(11)-H(11)	0.9800
C(12)-C(13)	1.511(4)
C(12)-C(15)	1.529(4)
C(12)-H(12)	0.9800
C(14)-H(14A)	0.9600
C(14)-H(14B)	0.9600
C(14)-H(14C)	0.9600
C(15)-C(16)	1.387(4)
C(15)-C(20)	1.397(4)
C(16)-C(17)	1.389(4)
C(16)-H(16)	0.9300
C(17)-C(18)	1.372(4)
C(17)-H(17)	0.9300
C(18)-C(19)	1.369(4)
C(19)-C(20)	1.379(4)
C(19)-H(19)	0.9300
C(20)-H(20)	0.9300
C(21)-H(21A)	0.9600
C(21)-H(21B)	0.9600
C(21)-H(21C)	0.9600
C(22)-C(23)	1.377(4)
C(22)-C(27)	1.380(4)
C(23)-C(24)	1.349(4)

C(23)-H(23)	0.9300
C(24)-C(25)	1.383(5)
C(24)-H(24)	0.9300
C(25)-C(26)	1.368(4)
C(25)-H(25)	0.9300
C(26)-C(27)	1.378(4)
C(26)-H(26)	0.9300
C(27)-H(27)	0.9300
C(13)-O(3)-C(14)	115.6(3)
C(18)-O(4)-C(21)	117.8(3)
C(2)-C(1)-C(9)	120.4(3)
C(2)-C(1)-H(1)	119.8
C(9)-C(1)-H(1)	119.8
C(1)-C(2)-C(3)	119.4(3)
C(1)-C(2)-H(2)	120.3
C(3)-C(2)-H(2)	120.3
C(4)-C(3)-C(2)	121.0(3)
C(4)-C(3)-H(3)	119.5
C(2)-C(3)-H(3)	119.5
C(3)-C(4)-C(10)	120.5(3)
C(3)-C(4)-H(4)	119.8
C(10)-C(4)-H(4)	119.8
C(10)-C(5)-C(6)	111.6(2)
C(10)-C(5)-H(5A)	109.3
C(6)-C(5)-H(5A)	109.3
C(10)-C(5)-H(5B)	109.3
C(6)-C(5)-H(5B)	109.3
H(5A)-C(5)-H(5B)	108.0
C(7)-C(6)-C(5)	112.0(2)
C(7)-C(6)-H(6A)	109.2
C(5)-C(6)-H(6A)	109.2
C(7)-C(6)-H(6B)	109.2
C(5)-C(6)-H(6B)	109.2
H(6A)-C(6)-H(6B)	107.9
C(6)-C(7)-C(8)	110.7(2)
C(6)-C(7)-C(11)	111.4(2)
C(8)-C(7)-C(11)	117.3(2)
C(6)-C(7)-H(7)	105.5
C(8)-C(7)-H(7)	105.5
C(11)-C(7)-H(7)	105.5
O(1)-C(8)-C(9)	119.0(3)
O(1)-C(8)-C(7)	123.2(3)
C(9)-C(8)-C(7)	117.7(2)
C(1)-C(9)-C(10)	120.6(3)
C(1)-C(9)-C(8)	118.9(3)
C(10)-C(9)-C(8)	120.5(3)
C(9)-C(10)-C(4)	118.1(3)
C(9)-C(10)-C(5)	121.7(3)
C(4)-C(10)-C(5)	120.2(3)
C(22)-C(11)-C(12)	112.0(2)
C(22)-C(11)-C(7)	113.0(2)
C(12)-C(11)-C(7)	115.8(2)
C(22)-C(11)-H(11)	104.9
C(12)-C(11)-H(11)	104.9
C(7)-C(11)-H(11)	104.9
C(13)-C(12)-C(15)	108.9(2)
C(13)-C(12)-C(11)	111.3(2)

C(15)-C(12)-C(11)	110.6(2)
C(13)-C(12)-H(12)	108.7
C(15)-C(12)-H(12)	108.7
C(11)-C(12)-H(12)	108.7
O(2)-C(13)-O(3)	122.9(3)
O(2)-C(13)-C(12)	126.5(3)
O(3)-C(13)-C(12)	110.5(3)
O(3)-C(14)-H(14A)	109.5
O(3)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(3)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(16)-C(15)-C(20)	116.6(3)
C(16)-C(15)-C(12)	121.8(3)
C(20)-C(15)-C(12)	121.6(3)
C(15)-C(16)-C(17)	121.9(3)
C(15)-C(16)-H(16)	119.1
C(17)-C(16)-H(16)	119.1
C(18)-C(17)-C(16)	119.6(3)
C(18)-C(17)-H(17)	120.2
C(16)-C(17)-H(17)	120.2
C(19)-C(18)-C(17)	120.2(3)
C(19)-C(18)-O(4)	115.8(3)
C(17)-C(18)-O(4)	124.1(3)
C(18)-C(19)-C(20)	120.0(3)
C(18)-C(19)-H(19)	120.0
C(20)-C(19)-H(19)	120.0
C(19)-C(20)-C(15)	121.8(3)
C(19)-C(20)-H(20)	119.1
C(15)-C(20)-H(20)	119.1
O(4)-C(21)-H(21A)	109.5
O(4)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(4)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(23)-C(22)-C(27)	116.8(3)
C(23)-C(22)-C(11)	123.2(3)
C(27)-C(22)-C(11)	120.0(3)
C(24)-C(23)-C(22)	122.4(3)
C(24)-C(23)-H(23)	118.8
C(22)-C(23)-H(23)	118.8
C(23)-C(24)-C(25)	120.8(3)
C(23)-C(24)-H(24)	119.6
C(25)-C(24)-H(24)	119.6
C(26)-C(25)-C(24)	117.8(3)
C(26)-C(25)-H(25)	121.1
C(24)-C(25)-H(25)	121.1
C(25)-C(26)-C(27)	121.0(3)
C(25)-C(26)-H(26)	119.5
C(27)-C(26)-H(26)	119.5
C(26)-C(27)-C(22)	121.1(3)
C(26)-C(27)-H(27)	119.4
C(22)-C(27)-H(27)	119.4

Table 4: Crystal data and structure refinement for the isomer **107a**:

Empirical formula	$C_{27}\ H_{26}\ O_4$
Formula weight	414.48
Temperature	293 (2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P-21
Unit cell dimensions	a = 6.6799 (4) A b = 18.3749 (12) A; β = 94.1400 (10) deg. c = 8.7475 (6) A
Volume	1070.89 (12) A^3
Z, Calculated density	2, 1.285 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F (000)	440
Crystal size	0.33 x 0.16 x 0.14 mm
Theta range for data collection	2.22 to 22.50 deg.
Reflections collected / unique	8234 / 2768 [R(int) = 0.0335]
Completeness to theta = 22.50	99.0 %
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0831, wR2 = 0.2006
R indices (all data)	R1 = 0.1309, wR2 = 0.2371
Largest diff. peak and hole	0.247 and -0.228 $e.A^{-3}$

Table 5: Bond lengths [A] and angles [deg] for **107a** [$C_{27}H_{26}O_4$]

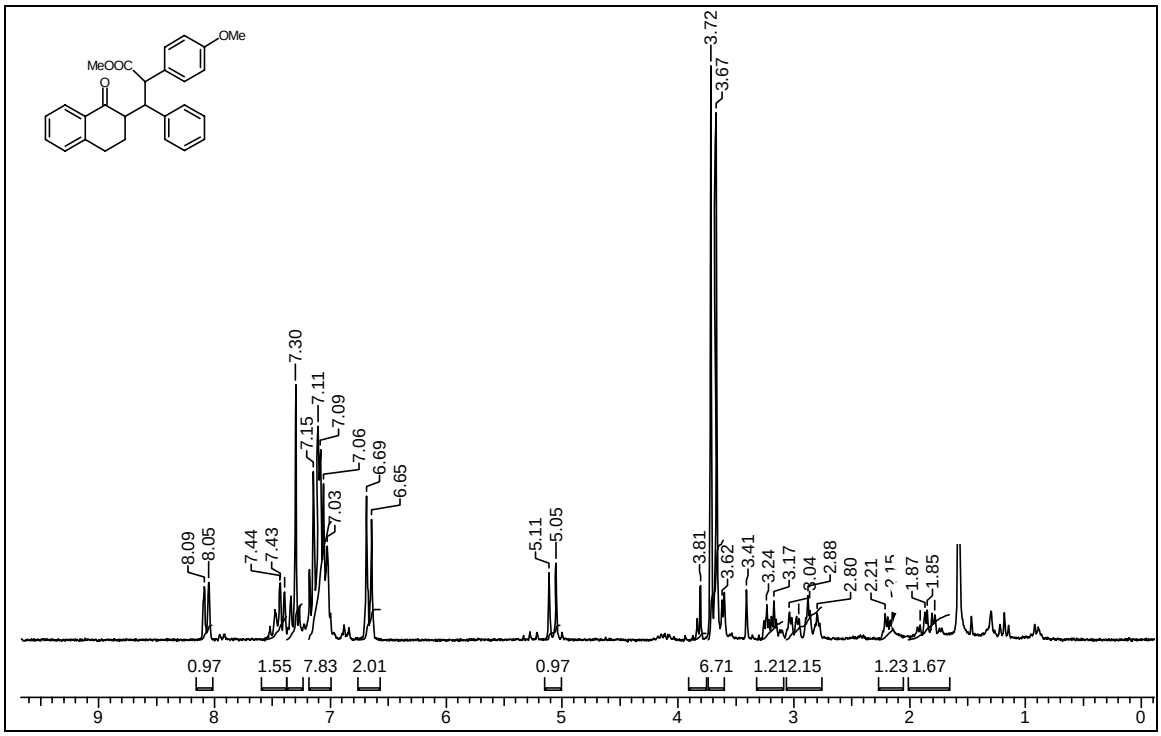
C(7)-C(6)	1.462(10)
C(7)-C(8)	1.479(10)
C(7)-C(11)	1.580(9)
C(7)-H(7)	0.9800
O(4)-C(18)	1.377(9)
O(4)-C(21)	1.447(9)
C(4)-C(3)	1.362(14)
C(4)-C(10)	1.386(12)
C(4)-H(4)	0.9300
C(8)-O(1)	1.203(8)
C(8)-C(9)	1.459(10)
C(10)-C(9)	1.377(10)
C(10)-C(5)	1.456(11)
C(9)-C(1)	1.392(10)
C(27)-C(22)	1.355(11)
C(27)-C(26)	1.361(14)
C(27)-H(27)	0.9300
C(22)-C(23)	1.351(10)
C(22)-C(11)	1.518(11)
C(18)-C(17)	1.325(11)
C(18)-C(19)	1.358(10)
C(15)-C(20)	1.369(9)
C(15)-C(16)	1.388(10)
C(15)-C(12)	1.510(10)
C(11)-C(12)	1.479(10)
C(11)-H(11)	0.9800
C(12)-C(13)	1.530(13)
C(12)-H(12)	0.9800
C(5)-C(6)	1.500(11)
C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700
C(20)-C(19)	1.400(11)
C(20)-H(20)	0.9300
C(17)-C(16)	1.363(11)
C(17)-H(17)	0.9300
C(23)-C(24)	1.306(15)
C(23)-H(23)	0.9300
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(16)-H(16)	0.9300
C(19)-H(19)	0.9300
C(3)-C(2)	1.343(14)
C(3)-H(3)	0.9300
C(1)-C(2)	1.341(13)
C(1)-H(1)	0.9300
C(25)-C(26)	1.347(14)
C(25)-C(24)	1.399(15)
C(25)-H(25)	0.9300
C(2)-H(2)	0.9300
C(26)-H(26)	0.9300
C(24)-H(24)	0.9300
C(21)-H(21A)	0.9600

C(21)-H(21B)	0.9600
C(21)-H(21C)	0.9600
O(3)-C(13)	1.309(11)
O(3)-C(14)	1.459(11)
O(2)-C(13)	1.148(9)
C(14)-H(14A)	0.9600
C(14)-H(14B)	0.9600
C(14)-H(14C)	0.9600

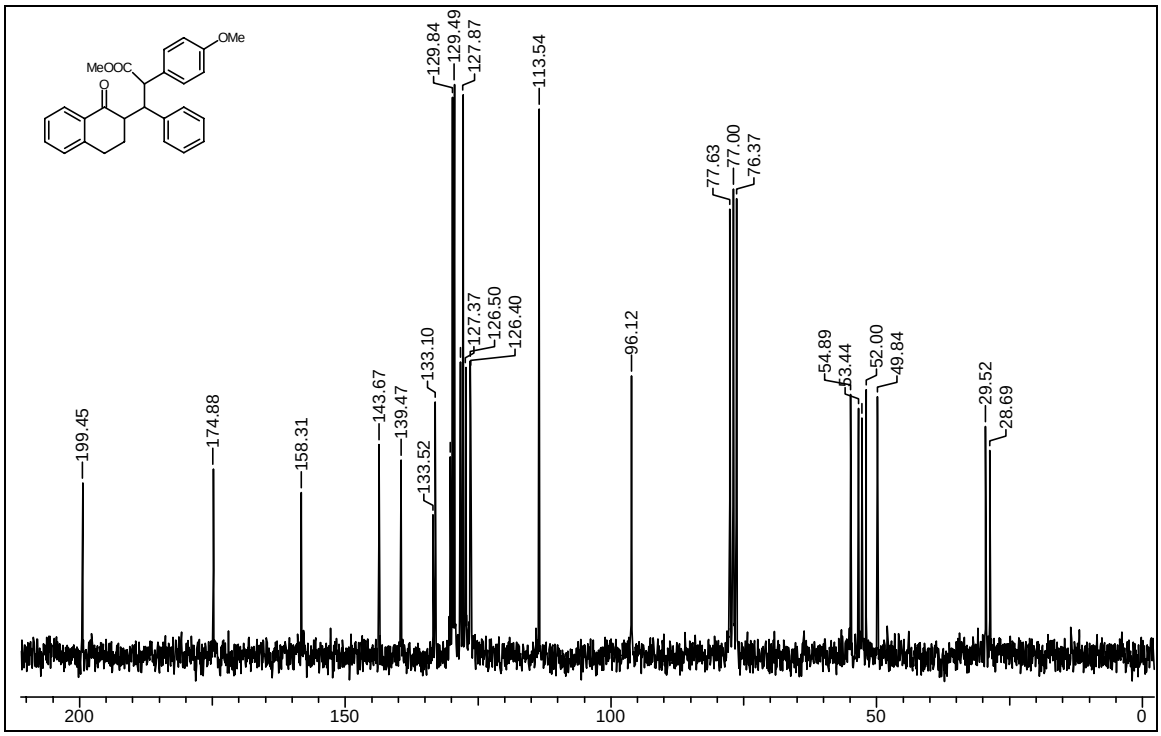
C(6)-C(7)-C(8)	114.0(6)
C(6)-C(7)-C(11)	115.4(6)
C(8)-C(7)-C(11)	110.3(5)
C(6)-C(7)-H(7)	105.3
C(8)-C(7)-H(7)	105.3
C(11)-C(7)-H(7)	105.3
C(18)-O(4)-C(21)	118.0(7)
C(3)-C(4)-C(10)	120.7(10)
C(3)-C(4)-H(4)	119.7
C(10)-C(4)-H(4)	119.7
O(1)-C(8)-C(9)	120.3(7)
O(1)-C(8)-C(7)	122.0(7)
C(9)-C(8)-C(7)	117.3(6)
C(9)-C(10)-C(4)	117.4(8)
C(9)-C(10)-C(5)	120.2(7)
C(4)-C(10)-C(5)	122.4(9)
C(10)-C(9)-C(1)	120.1(8)
C(10)-C(9)-C(8)	120.8(7)
C(1)-C(9)-C(8)	119.1(8)
C(22)-C(27)-C(26)	119.8(9)
C(22)-C(27)-H(27)	120.1
C(26)-C(27)-H(27)	120.1
C(23)-C(22)-C(27)	118.0(8)
C(23)-C(22)-C(11)	120.5(8)
C(27)-C(22)-C(11)	121.4(7)
C(17)-C(18)-C(19)	122.3(7)
C(17)-C(18)-O(4)	115.3(7)
C(19)-C(18)-O(4)	122.3(7)
C(20)-C(15)-C(16)	116.7(7)
C(20)-C(15)-C(12)	118.2(6)
C(16)-C(15)-C(12)	125.1(6)
C(12)-C(11)-C(22)	115.0(6)
C(12)-C(11)-C(7)	110.6(6)
C(22)-C(11)-C(7)	109.9(7)
C(12)-C(11)-H(11)	106.9
C(22)-C(11)-H(11)	106.9
C(7)-C(11)-H(11)	106.9
C(11)-C(12)-C(15)	116.8(6)
C(11)-C(12)-C(13)	110.0(7)
C(15)-C(12)-C(13)	109.0(7)
C(11)-C(12)-H(12)	106.8
C(15)-C(12)-H(12)	106.8
C(13)-C(12)-H(12)	106.8
C(10)-C(5)-C(6)	110.9(6)
C(10)-C(5)-H(5A)	109.5
C(6)-C(5)-H(5A)	109.5
C(10)-C(5)-H(5B)	109.5
C(6)-C(5)-H(5B)	109.5

H(5A)-C(5)-H(5B)	108.1
C(15)-C(20)-C(19)	120.8(7)
C(15)-C(20)-H(20)	119.6
C(19)-C(20)-H(20)	119.6
C(18)-C(17)-C(16)	118.8(8)
C(18)-C(17)-H(17)	120.6
C(16)-C(17)-H(17)	120.6
C(24)-C(23)-C(22)	122.9(11)
C(24)-C(23)-H(23)	118.5
C(22)-C(23)-H(23)	118.5
C(7)-C(6)-C(5)	110.6(7)
C(7)-C(6)-H(6A)	109.5
C(5)-C(6)-H(6A)	109.5
C(7)-C(6)-H(6B)	109.5
C(5)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	108.1
C(17)-C(16)-C(15)	122.7(7)
C(17)-C(16)-H(16)	118.7
C(15)-C(16)-H(16)	118.7
C(18)-C(19)-C(20)	118.5(6)
C(18)-C(19)-H(19)	120.7
C(20)-C(19)-H(19)	120.7
C(2)-C(3)-C(4)	121.2(10)
C(2)-C(3)-H(3)	119.4
C(4)-C(3)-H(3)	119.4
C(2)-C(1)-C(9)	120.7(10)
C(2)-C(1)-H(1)	119.7
C(9)-C(1)-H(1)	119.7
C(26)-C(25)-C(24)	116.7(10)
C(26)-C(25)-H(25)	121.6
C(24)-C(25)-H(25)	121.6
C(1)-C(2)-C(3)	119.7(11)
C(1)-C(2)-H(2)	120.2
C(3)-C(2)-H(2)	120.2
C(25)-C(26)-C(27)	122.0(11)
C(25)-C(26)-H(26)	119.0
C(27)-C(26)-H(26)	119.0
C(23)-C(24)-C(25)	120.3(9)
C(23)-C(24)-H(24)	119.9
C(25)-C(24)-H(24)	119.9
O(4)-C(21)-H(21A)	109.5
O(4)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(4)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(13)-O(3)-C(14)	114.5(8)
O(2)-C(13)-O(3)	125.2(10)
O(2)-C(13)-C(12)	124.1(11)
O(3)-C(13)-C(12)	110.7(7)
O(3)-C(14)-H(14A)	109.5
O(3)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(3)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5

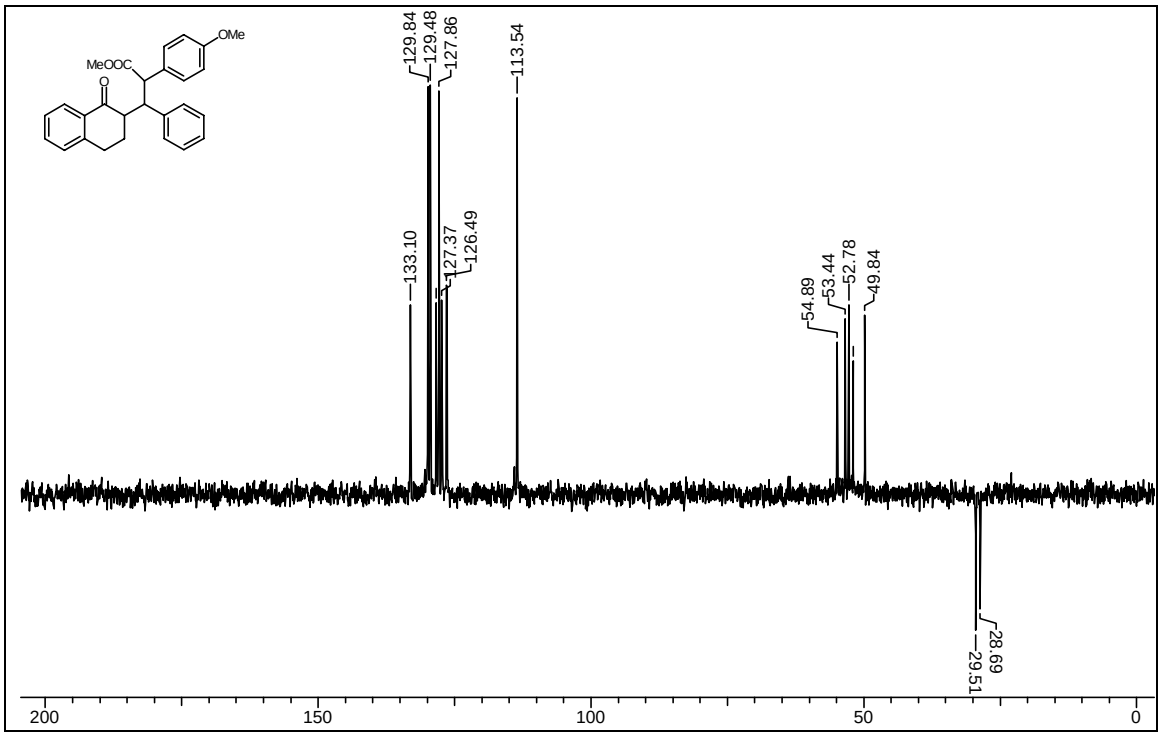
^{1}H NMR spectrum of Compound 106 a ($CDCl_3$+CCl_4, 200 MHz)



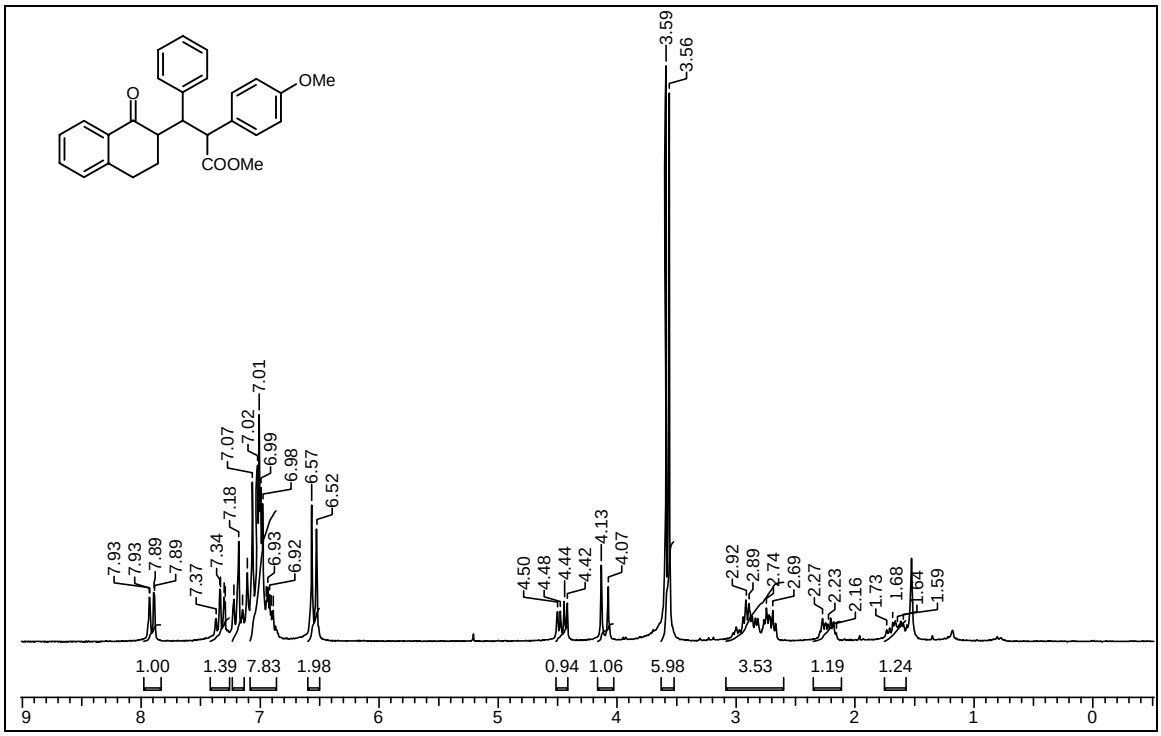
^{13}C NMR Spectrum of Compound 106 a ($CDCl_3$+CCl_4, 50 MHz)



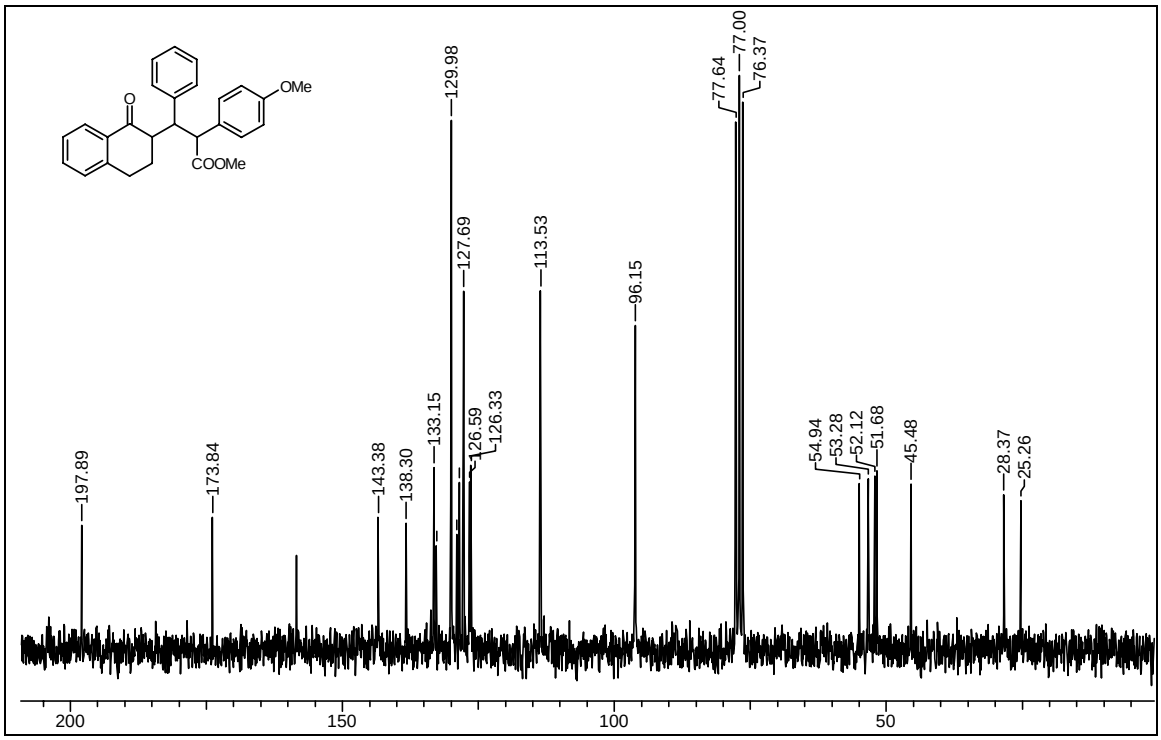
Dept spectrum of Compound 106 a ($CDCl_3$+CCl_4, 50 MHz)



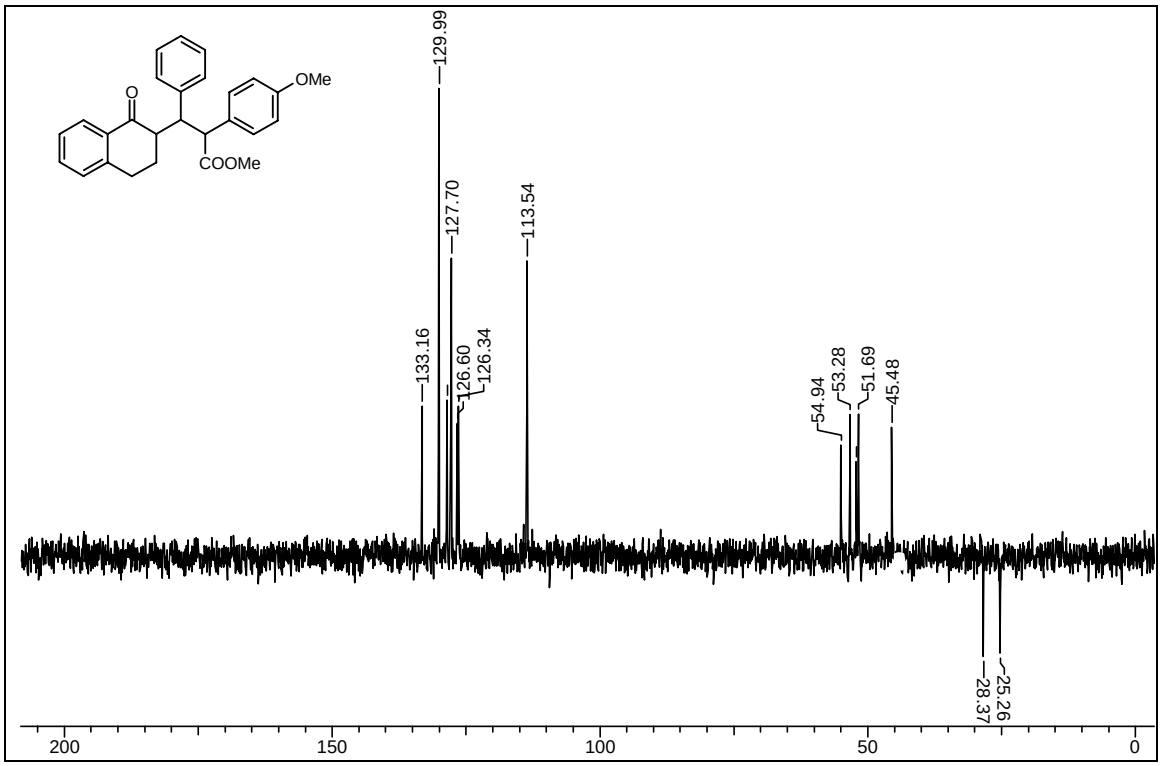
^{1}H NMR spectrum of Compound 107 a ($CDCl_3$+CCl_4, 200 MHz)



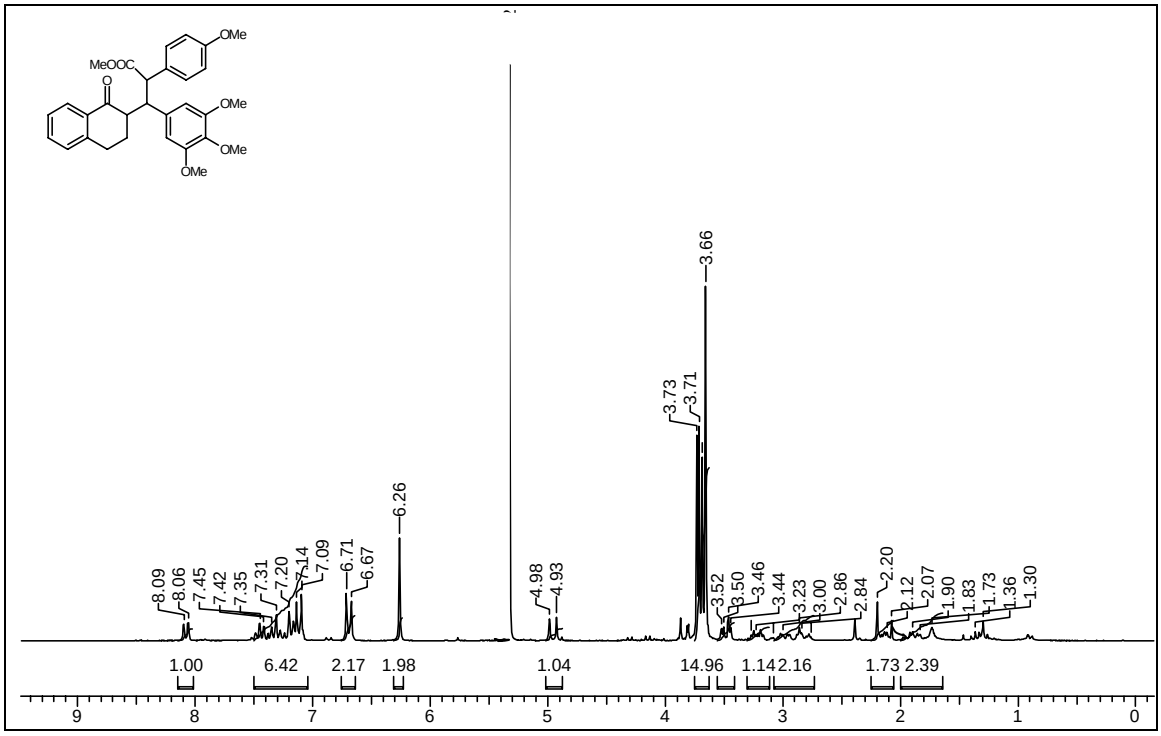
^{13}C NMR Spectrum of Compound 107 a ($CDCl_3$+CCl_4, 50 MHz)



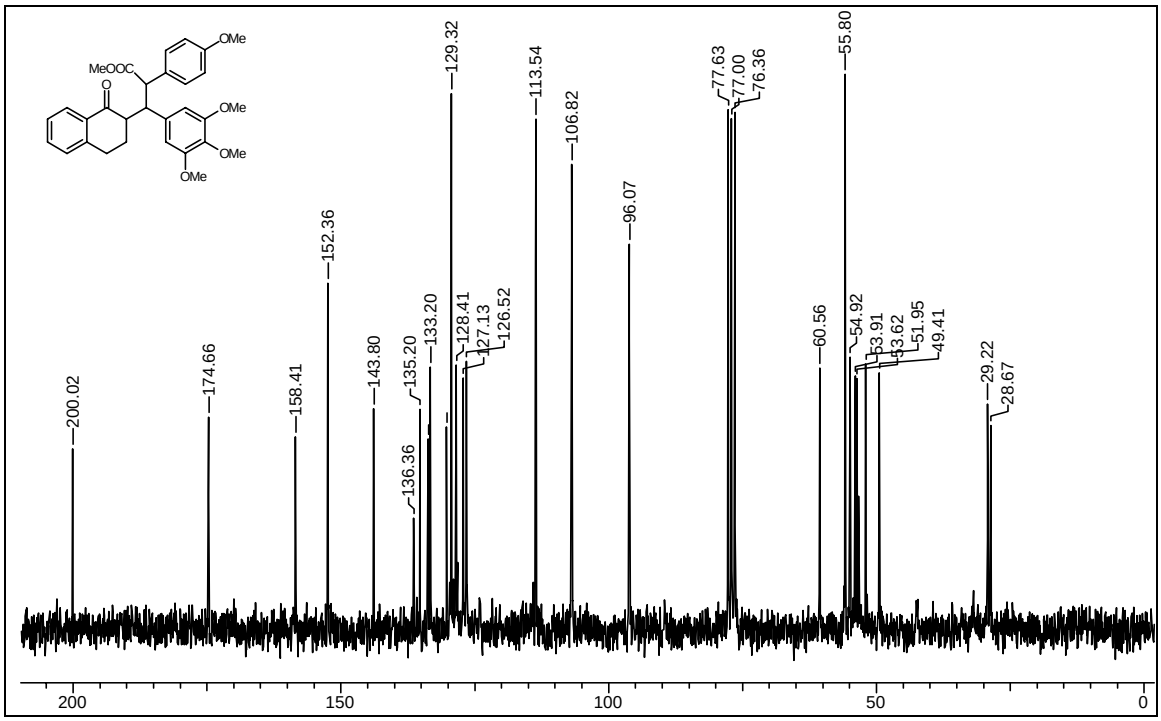
Dept spectrum of Compound 107 a ($CDCl_3$+CCl_4, 50 MHz)



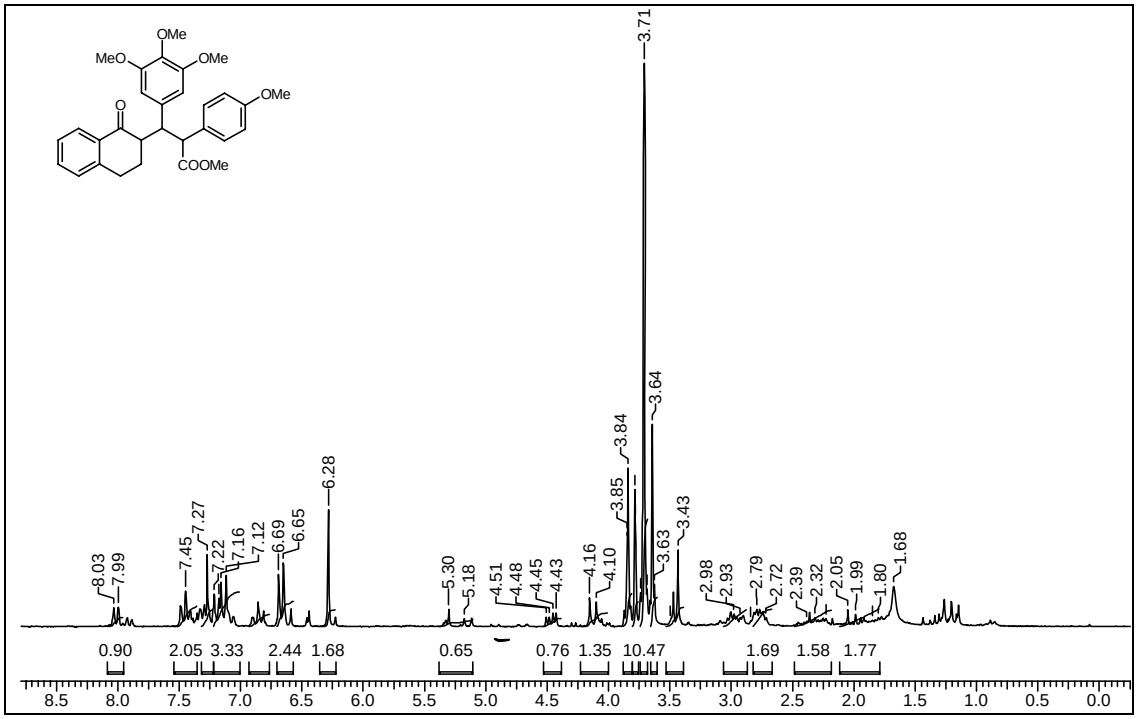
^{1}H NMR spectrum of Compound 106 d ($CDCl_3$+CCl_4, 200 MHz)



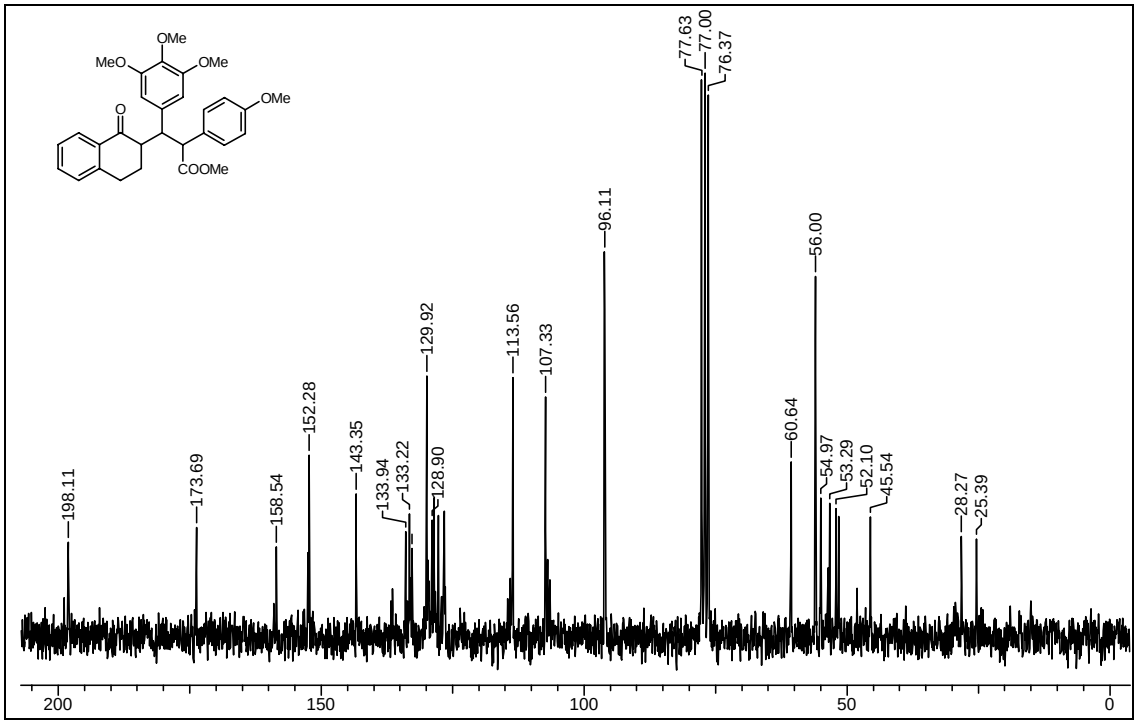
^{13}C NMR spectrum of Compound 106 d ($CDCl_3$+CCl_4, 50 MHz)



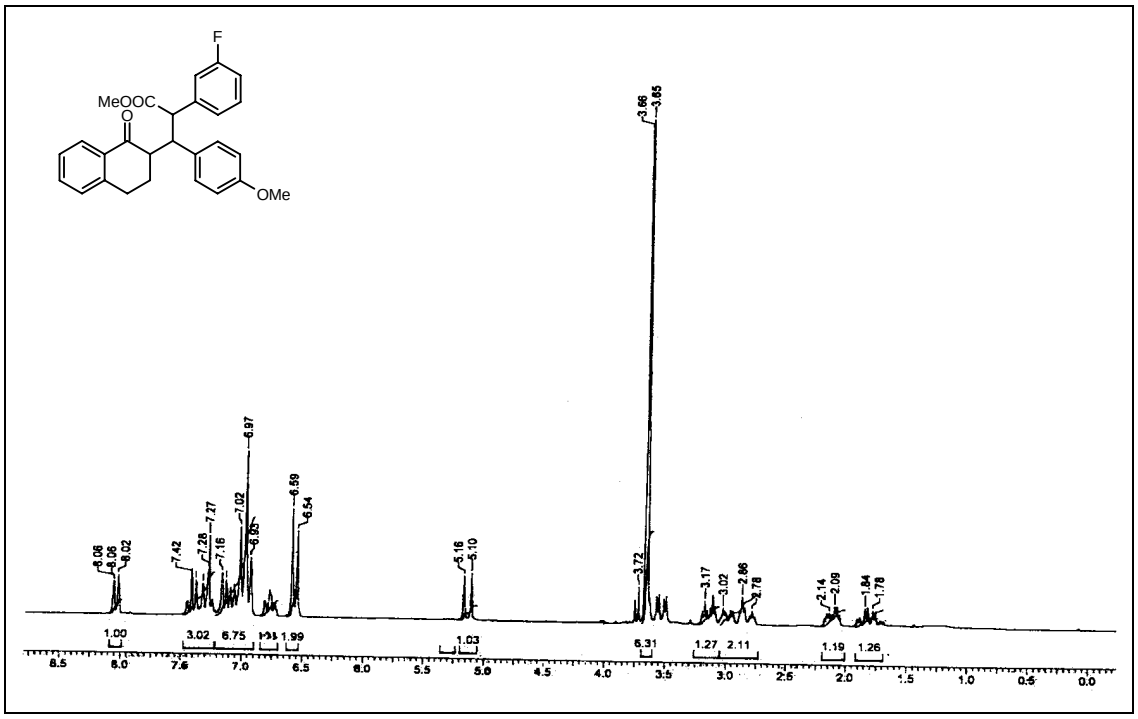
^{1}H NMR spectrum of Compound 107 d ($CDCl_3$+CCl_4, 200 MHz)



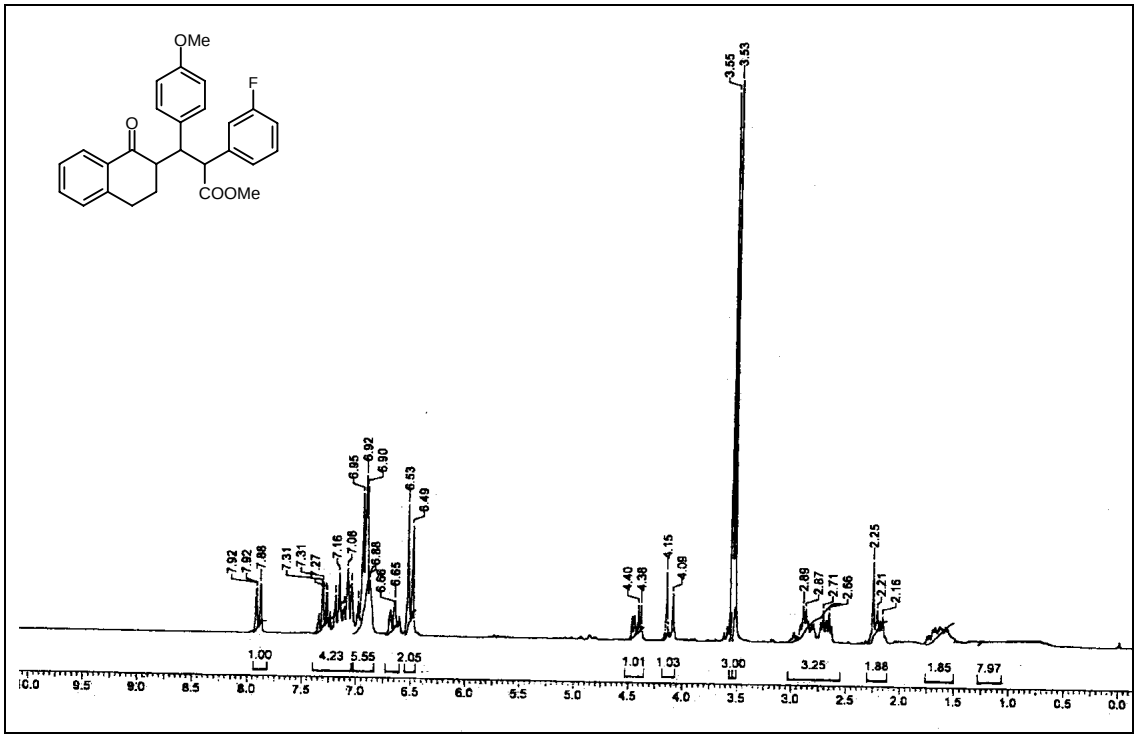
^{13}C NMR spectrum of Compound 107 d ($CDCl_3$+CCl_4, 50 MHz)



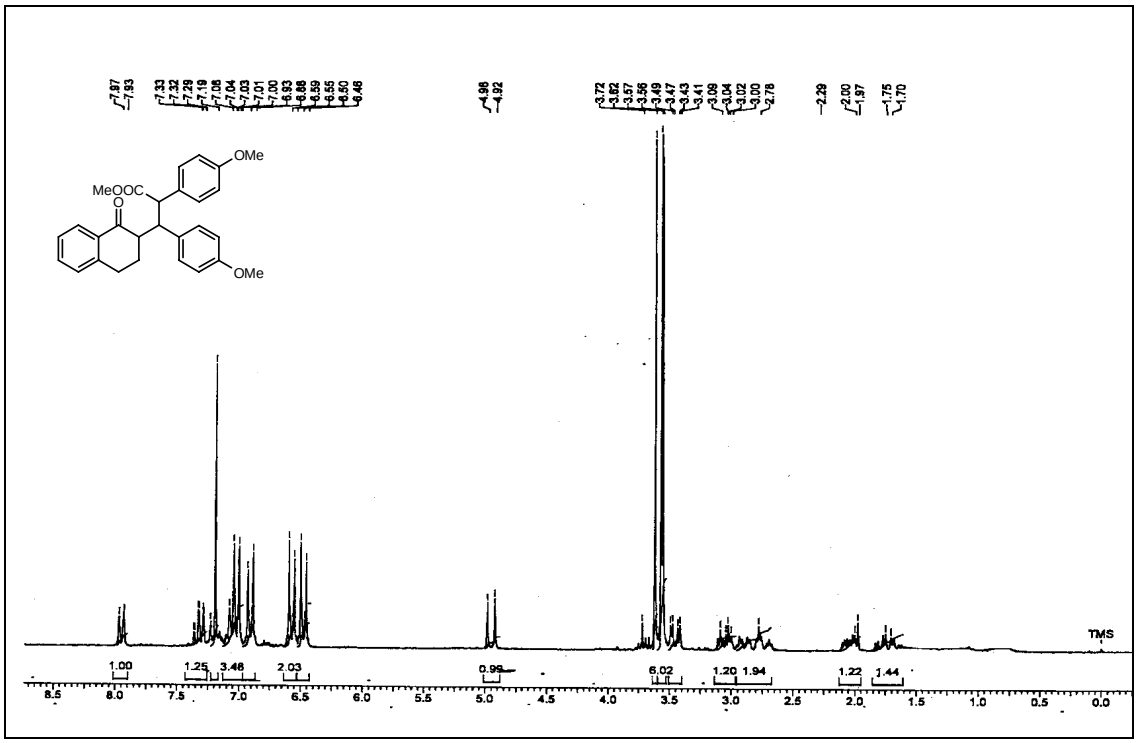
^{1}H NMR spectrum of Compound 106 e ($CDCl_3$+CCl_4, 200 MHz)



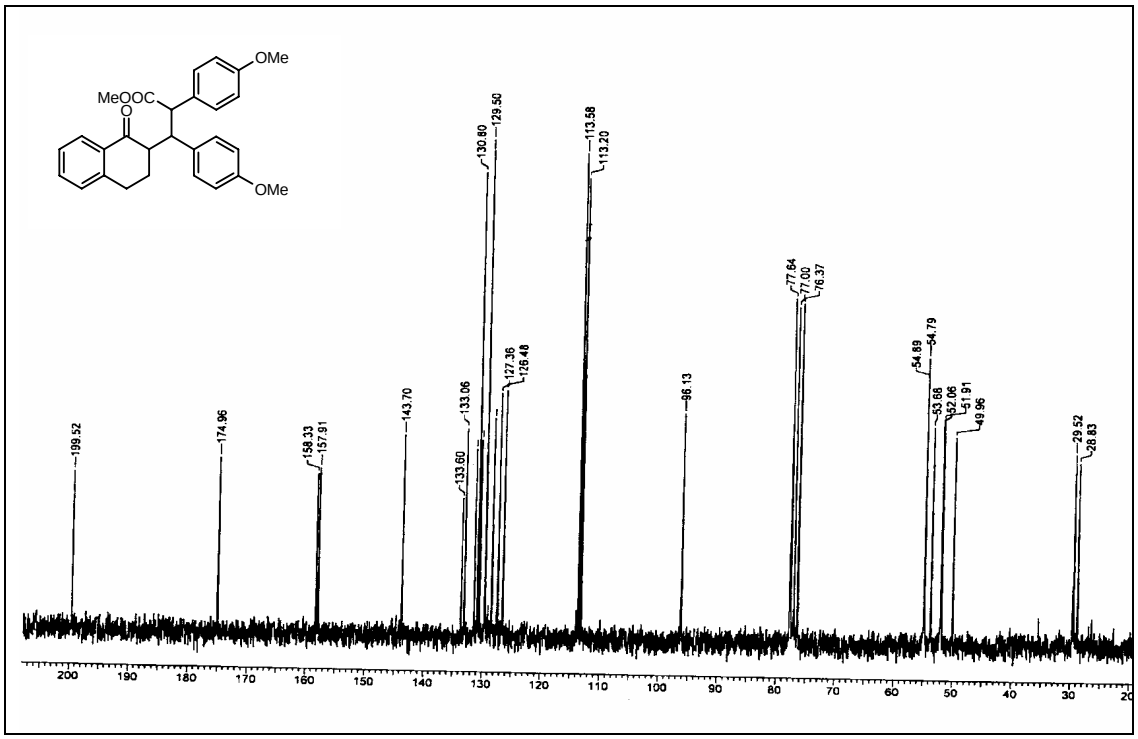
^{1}H NMR spectrum of Compound 107 e ($CDCl_3$+CCl_4, 200 MHz)



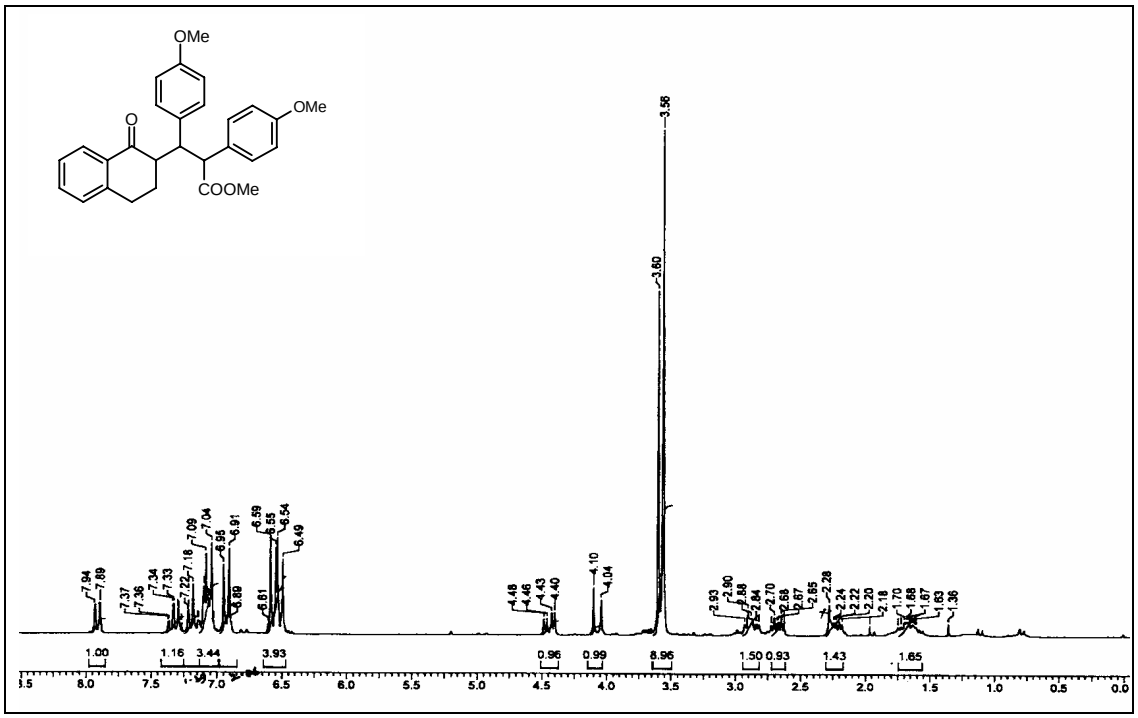
^{1}H NMR spectrum of Compound 106 f ($CDCl_3$+CCl_4, 200 MHz)



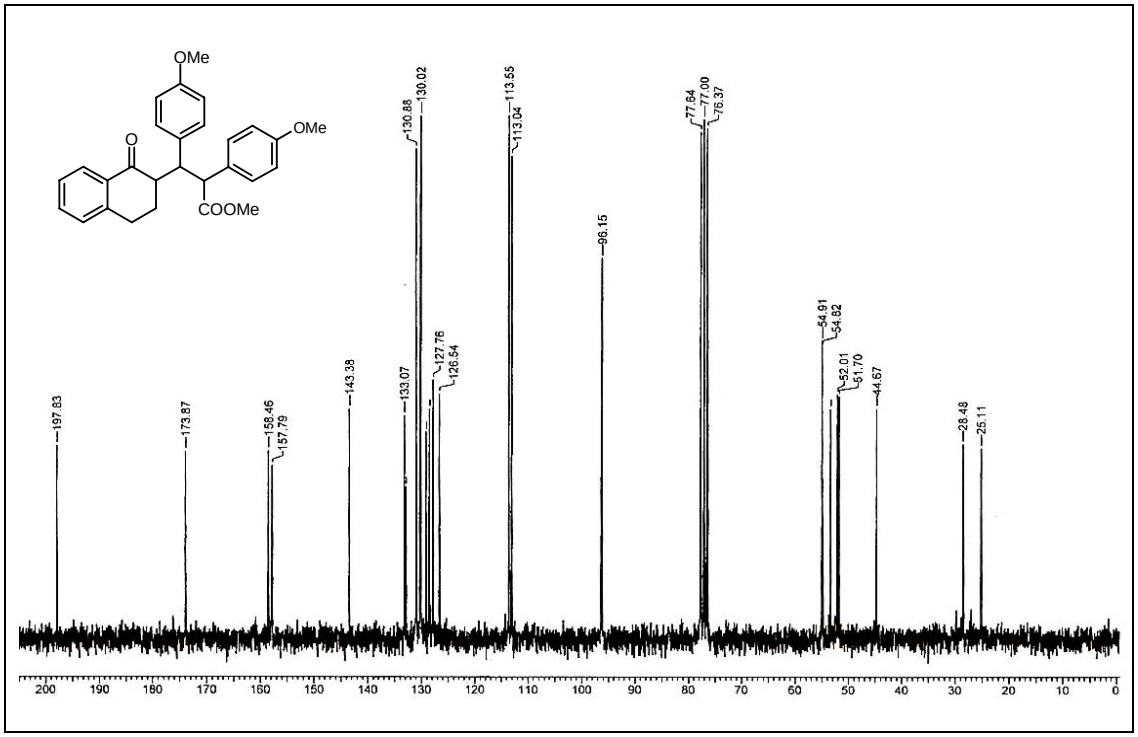
^{13}C NMR spectrum of Compound 106 f ($CDCl_3$+CCl_4, 50 MHz)



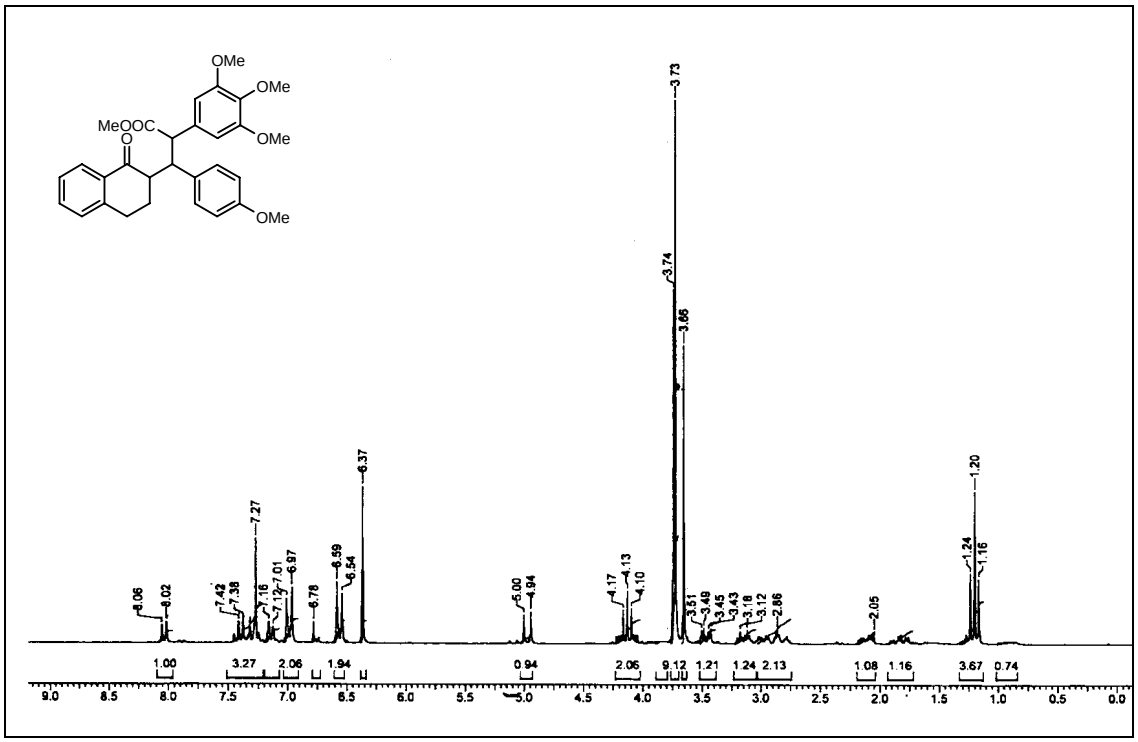
^{1}H NMR spectrum of Compound 107 f ($CDCl_3$+CCl_4, 200 MHz)



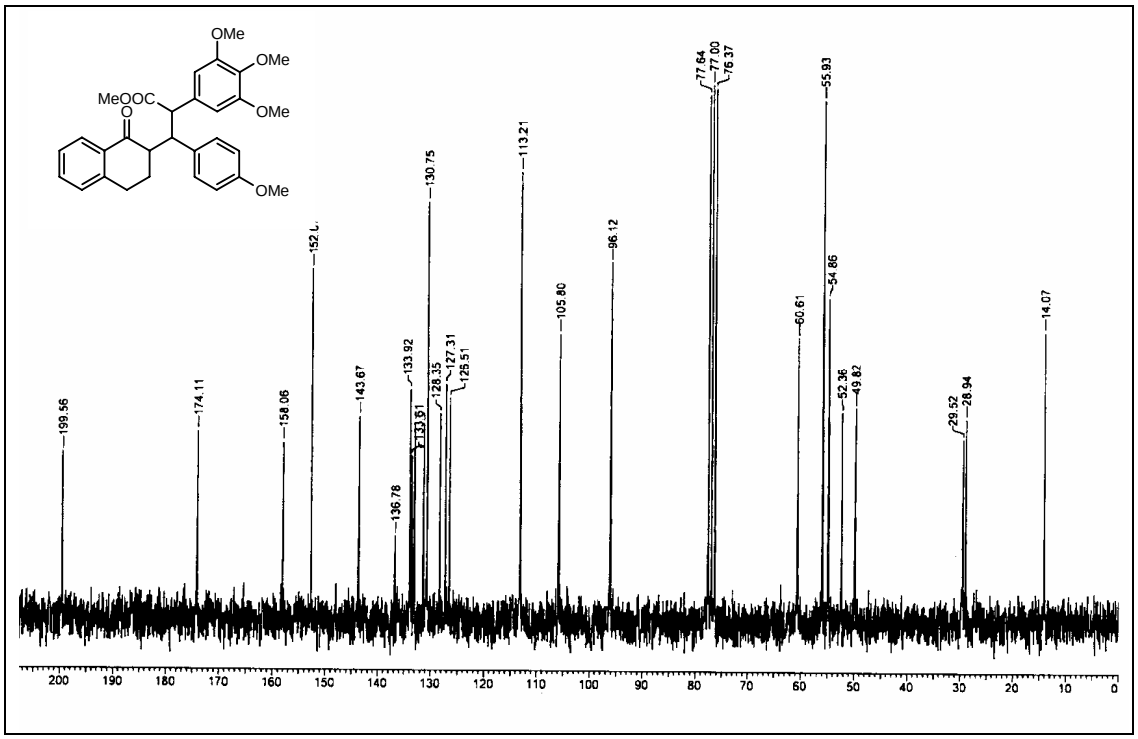
^{13}HC NMR spectrum of Compound 107 f ($CDCl_3$+CCl_4, 50 MHz)



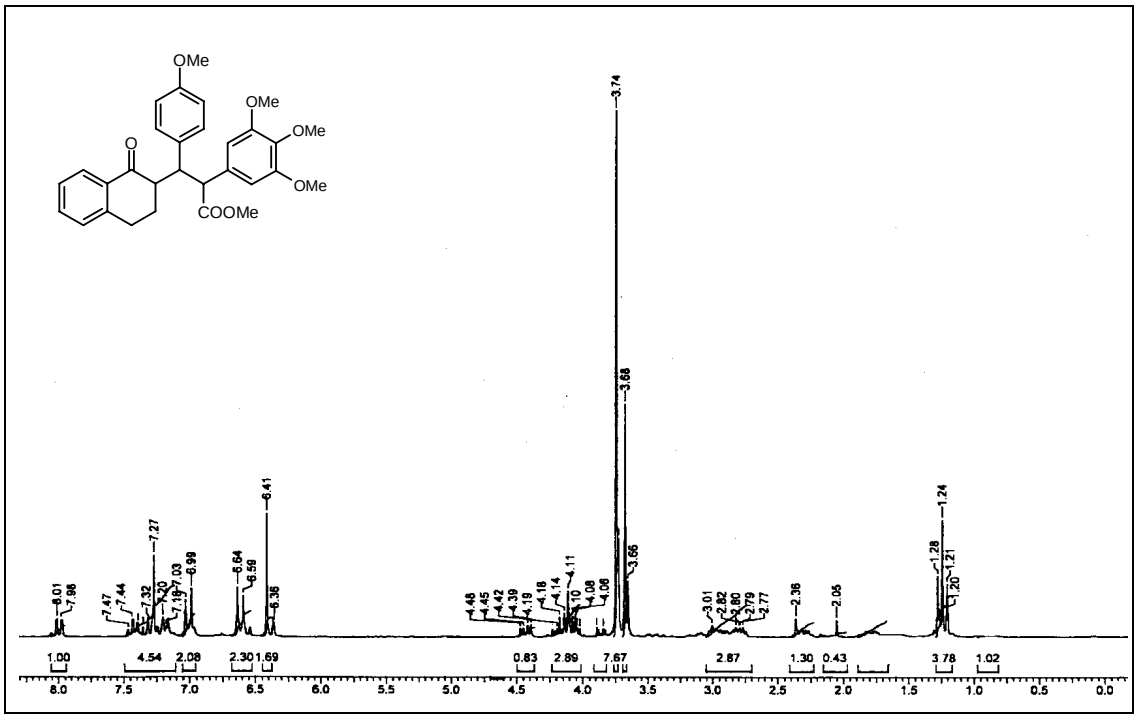
^{1}H NMR spectrum of Compound 106 g ($CDCl_3$+CCl_4, 200 MHz)



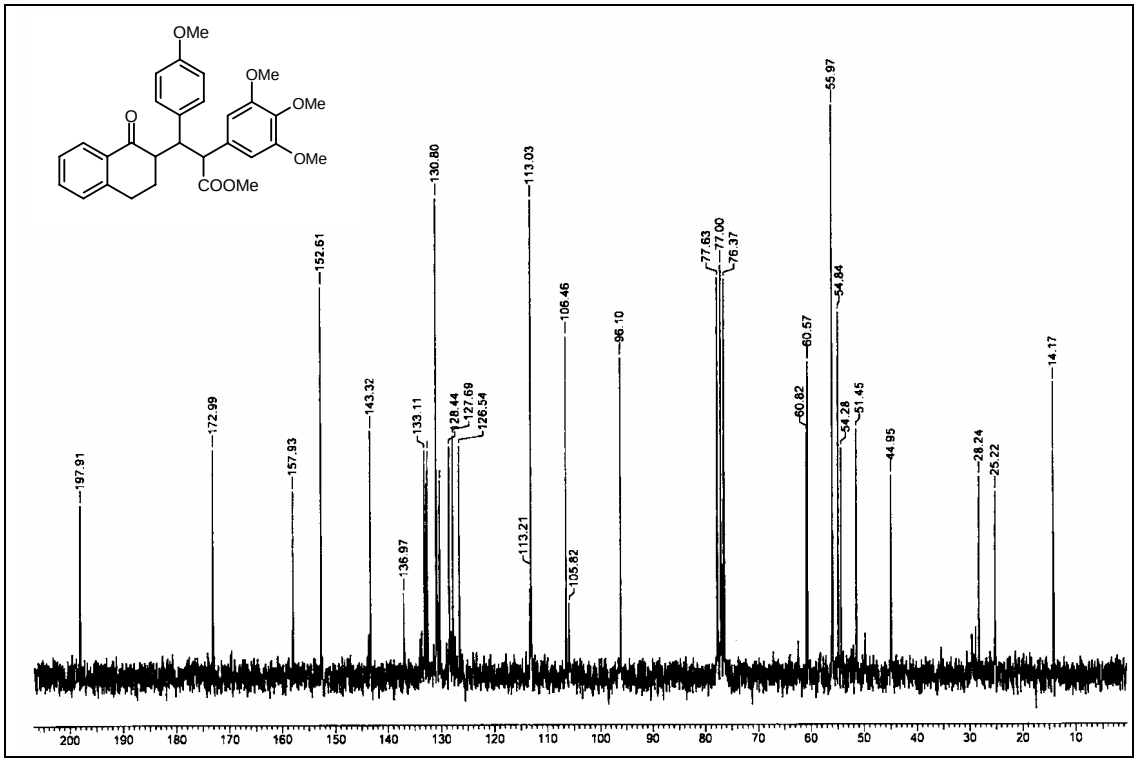
^{13}C NMR spectrum of Compound 106 g ($CDCl_3$+CCl_4, 50 MHz)



^{1}H NMR spectrum of Compound 107 g ($CDCl_3$+CCl_4, 200 MHz)



^{13}HC NMR spectrum of Compound 107 g ($CDCl_3$+CCl_4, 50 MHz)



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CHAPTER - I

SECTION - II

NEW 5- HYDROXY-3-(4-METHOXYPHENYL) 2-(3,4,5-TRIMETHOXYPHENYL)CYCLOPENT-2-EN-1-ONE DERIVATIVES WITH POTENTIAL ANTICANCER ACTIVITY

PART - A

SYNTHESIS OF 5- HYDROXY-3-(4- METHOXYPHENYL)2-(3,4,5-TRIMETHOXYPHENYL)CYCLOPENT-2-EN-1-ONE DERIVATIVES

1.3.1: INTRODUCTION:

Modern drug discovery often involves screening small molecules for their ability to bind to a preselected protein target. Target-oriented synthesis of small molecules, individually or as collections can be planned effectively with retrosynthetic analysis and such target oriented syntheses used in drug discovery efforts involve preselected protein targets and their small molecule regulators. Our efforts in drug discovery research were focused on combretastatin A-4 as the lead molecule. Combretastatin A-4 is believed to bind at the same site as that of colchicines which is tubulin-binding agent. The designed *cis* - restricted combretastatin A-4 analogues were assumed to be tubulin binding which was further confirmed by the biological activity studies conducted at Dabur Research Foundation, Ghaziabad, Delhi.

Our interest in the field of design and synthesis of biologically active compounds prompted us to undertake the synthesis of *cis* restricted analogues of combretastatin A-4 [cis-1-(3,4,5-trimethoxyphenyl)-2-(3' hydroxyl-4'-methoxyphenyl) ethylene].

A number of studies have been reported on structure activity relationship of combretastatin A-4 (**16**). These studies showed that the *cis* orientation of the two benzene rings is essential and 3,4,5-trimethoxy substituents on the A-ring of combretastatin A-4 are indispensable for potent cytotoxicity. CA-4 (*cis)* analogues are prone to isomerization to *trans* forms during storage and administration and *trans* forms of these compounds show dramatic reduction in antitubulin and antitumor activity. CA-4 is in phase-II clinical trials. Cushman *et al*.[1] reported that the active conformation of the combretastatin A-4 is not planar. Considering the structure activity relationship study of CA-4, the 3,4,5-trimethoxy substituents on A-ring and 4-methoxy group on B-ring of CA-4 are essential for cytotoxic activity.

Continuing our ongoing research work in this field we have earlier demonstrated that replacement of the *cis* double bond in combretastatin A-4 by a hydroxy-cyclopentenone moiety proved to be advantageous in the preliminary biological studies using human cancer cell lines. Under this programme, our group synthesized 4-hydroxy and 5-

hydroxy-cyclopentenone analogues of general structure shown in fig. 1, which were screened for cytotoxicity.[2]

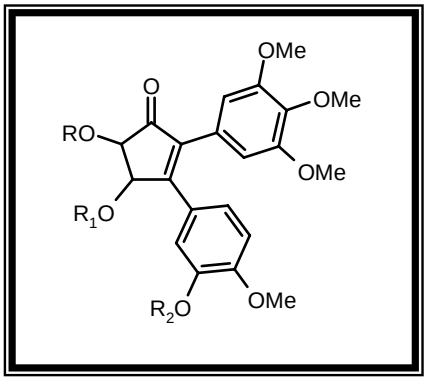


Fig. 1

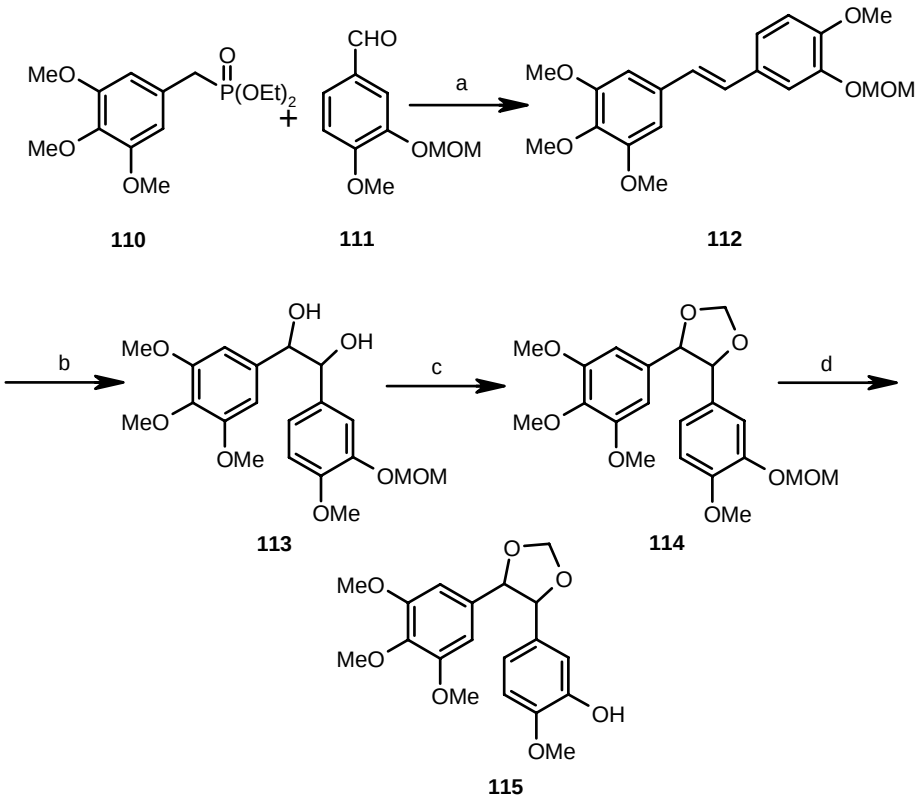
The HIT molecules selected from this class of compounds were subjected to further biological studies, and some of them faced the problem of low water solubility. In continuation with this research activity and to solve the problem of water solubility further derivatization was undertaken. The results of these efforts have been described in this section-II.

BRIEF REVIEW OF LITERATURE:

The literature survey revealed that there are various analogues of combretastatin A-4 reported. In last few years the flow of combretastatin A-4 analogues increased due to the potent antitumor activity exhibited by this small molecule. Some of the reports describing the "*cis*-restriction approach" for synthesis of combretastatin A-4 analogues have been given on the following pages.

Shirai and coworker have reported[3] that the *cis* carbon-carbon double bond in CA-4 could be replaced by a dioxolane. In this method the dihydroxylation of *trans*-stilbene **112**, synthesized from 3,4,5-trimethoxybenzaldehyde and 3-hydroxy-4-methoxybenzaldehyde, afforded the diol **113** which was converted to 1, 3-dioxolane **114** by treatment with 50 % NaOH and dibromomethane in dichloromethane in the presence of phase transfer

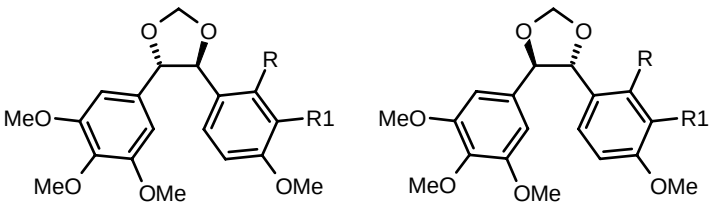
catalyst. Deprotection of MOM ether was performed by heating in 80 % acetic acid to obtain the target molecule **115** as shown in scheme-1.



Reagents and Conditions: a) KOBut, THF; **b)** AD-mix-α, $MeSO_2NH_2$, *t*-BuOH-H_2O, Na_2CO_3, CH_2Cl_2; **c)** 50 % NaOH, cetylNMe_3Br, CH_2Br_2; **d)** 80 % AcOH, Heating.

Scheme - 1

Pettit *et al*.[4] have synthesized and evaluated the 1, 3-dioxolane (*S, S*) - **116** (designated as dioxostatin) and its prodrugs (*S, S*) - **116a** and (*R, R*) - **117**. The dioxostatin was found to be the most potent inhibitor of microtubules assembly at the colchicines binding site (Fig. 2).

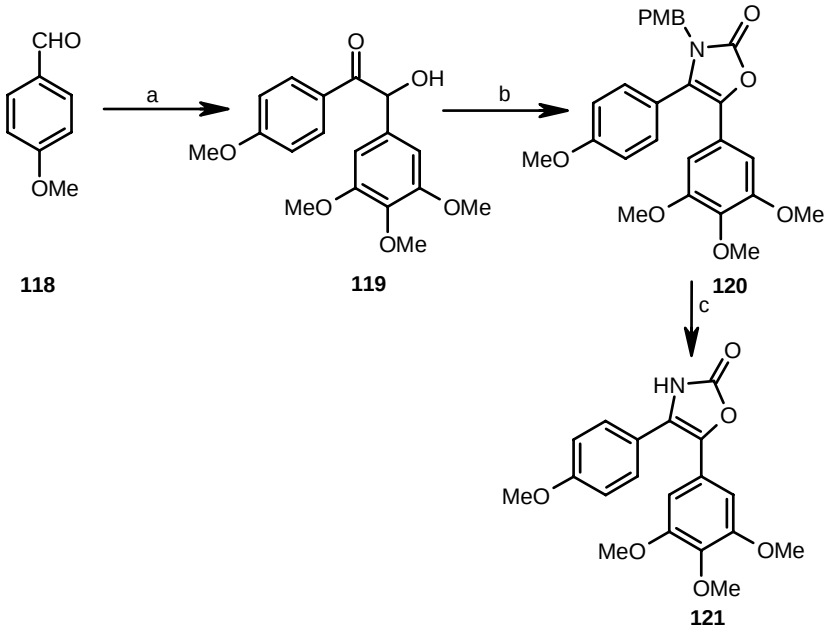


(S,S)- 116: R = R_1 = OH
(S,S)- 116a: R = R_1 = OP(O) $(ONa)_2$

(R,R)- 117: R = R1 = OH

Fig. 2

Nam *et al.* have reported[5] the combretoxazolones which showed potent cytotoxicity against a variety of tumor cell lines. Structurally these compounds are clearly *cis*-restricted and therefore, these analogues should be stable in term of isomerization. The coupling of aldehyde **118** with another aryl benzaldehyde by using TMS-CN and zinc iodide in tetrahydrofuran and then with LiHMDS in THF gave α-hydroxyketone **119**. Reaction of α-hydroxyketone **119** with PMB-isocyanate and subsequent cyclization provided the intermediate **120**. The *N*-PMB group was removed by refluxing in trifluoroacetic acid (TFA) for 3 h to give the expected combretoxazolone **121** as shown in scheme - 2.



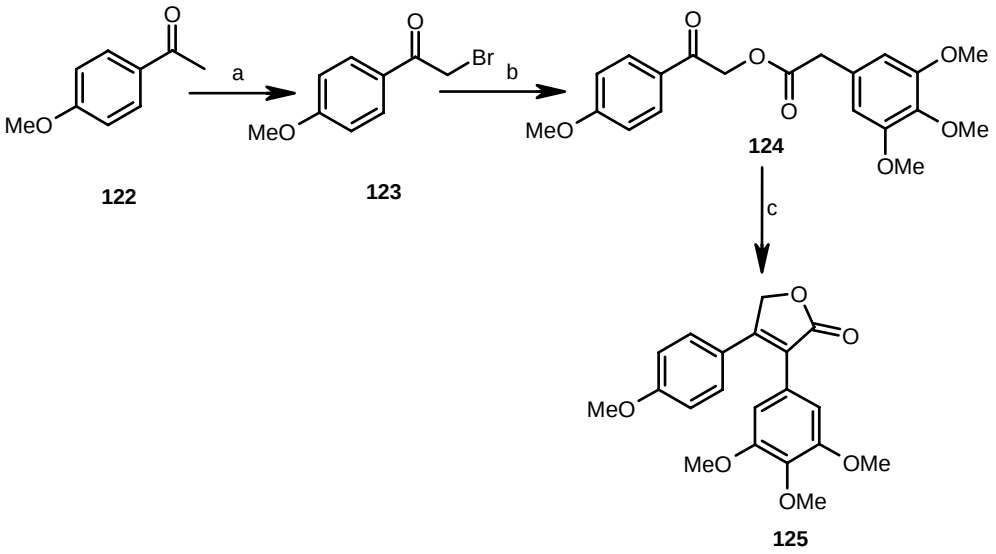
118 **119** **120** **121**

Reagents and Conditions: **a)** i) TMS-CN, ZnI_2, THF; ii) LiHMDS, 3,4,5-trimethoxy benzaldehyde, THF, -78 ^{0}C
b) i) PMB-NCO, toluene, 80 ^{0}C, 3 h; ii) AcOH, reflux, 8 h;
c) TFA, reflux, 3 h

Scheme - 2

Kim *et al*. reported[6] combretofuranones with very potent cytotoxicity and significant antitumor activity. The general method used for the synthesis of combretofuranones is outlined in scheme-3. Reaction of 3,4,5-trimethoxyphenylacetic acid with α-bromoacetophenone **123** in the presence of triethylamine gave phenylacetate **124**. The aldol type condensation and subsequent dehydration of the resulting phenylacetate with

triethylamine and *p*-toluenesulfonic acid (*p*-TsOH) gave the target molecule **125** as shown in scheme - 3.

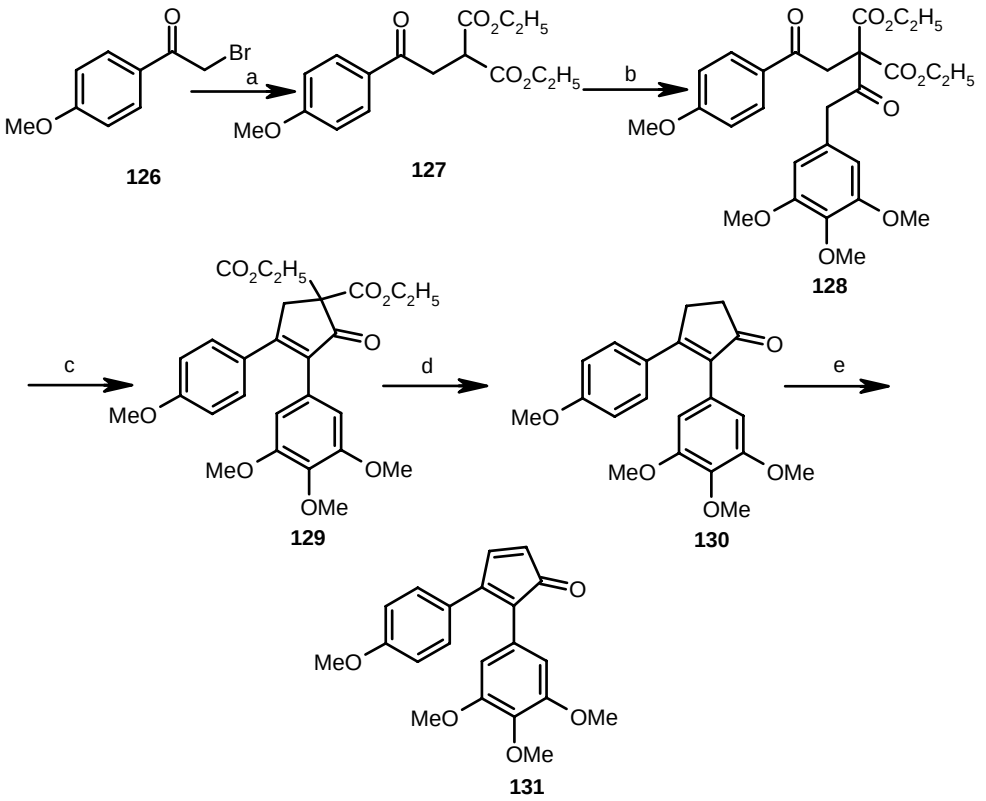


122 **123** **124** **125**

Reagents and Conditions: a) Br_2, AcOH, HCl, rt; **b)** 3,4,5-Trimethoxyphenylacetic acid, NEt_3, CH_3CN, rt; **c)** TEA, p-TsOH, 4 A^0 molecular sieves, CH_3CN, reflux.

Scheme-3

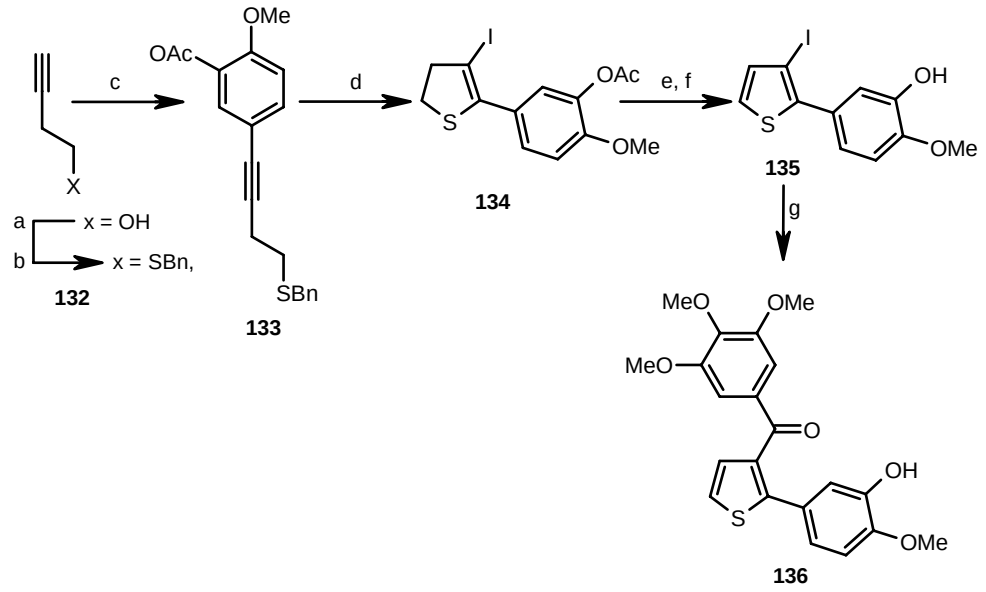
Nam, N. H. *et al.* reported[7] combretocyclopentenones and related analogues. A series of 2-(3,4,5-trimethoxyphenyl)-3-arylcyclopent-2-ene-1-one and their related analogues, including pentenone, pentenol, pentene, furan were synthesized and evaluated for cytotoxicity against murine and human tumor cell lines. Some of the compounds showed good cytotoxicity with IC_{50} values in the range of 8-34 μg/mL. Some compounds exhibited significant anti-tumor activity in BDF1 mice bearing lewis lung carcinoma cells with an inhibition ratio of 59 %. The synthetic strategy used for the synthesis of these combretocyclopentenones is shown in scheme - 4.



Reagents and Conditions: a) K_2CO_3, dimethylmalonate, 40 ^{0}C, 5 h; **b)** i) $MgBr_2.Et_2O$, pyridine, 0 ^{0}C, 3 h; ii) CH_3COCl, -25 ^{0}C, 2 h then 1 N HCl; **c)** TEA, acetonitrile, 30 min; **d)** 3 M H_2SO_4/AcOH, reflux, 3h; **e)** i) PhSeCl, EtOAc, 3 h; ii) *m*-CPBA, pyridine, 1h.

Scheme-4

Flynn, B. L. *et al.* reported[8] a number of analogues of combretastatin A-4, containing a thiophene ring interposed between the two phenyl groups. Some of the thiophene compounds also represent non-benzofused analogues of recently described tubulin binding benzothiophenes. The synthesis of thiophenes **136** began with 3-butynol, which was easily converted to the benzyl 3-butynyl sulfide (Scheme - 5). Sonogashira coupling of **132** with aryliodide afforded **133** in high yield. Treatment of **133** with iodine resulted in a rapid and efficient 5-endo-dig-iodocyclization to give **134**. Aromatization of **134** with DDQ and acetate hydrolysis afforded **135**. Treatment of **135** with 3 equivalent of *t*-Buli, lithiated the phenol and the C-3 position of thiophene ring. Reaction of this dilithiospecies with 3,4,5-trimethoxybenzoyl chloride afforded **136** upon protic workup, as shown in scheme - 5.



Reagents and Conditions: a) KOH, TosCl, CH_2Cl_2; **b)** NaH, BnSH, THF, 18 ^{0}C;
c) Iodo comp. $Pd(PPh_3)_2Cl_2$ 2.0 mol %, CuI 4.0 mol % DMF/Et_3N 3:1, 18 ^{0}C;
d) I_2, CH_2Cl_2;**e)** DDQ, CH_2Cl_2; **f)** MeOH, K_2CO_3; **g)** 3 equiv t- BuLi, -78 ^{0}C Then 3,4,5-Trimethoxybenzoyl chloride

Scheme - 5

Medarde M. *et al.* reported[9] the diarylindole derivatives **137** and **138**. Two aryl groups are maintained in the *cis* orientation required for activity by means of an indole moiety as shown in fig 3.

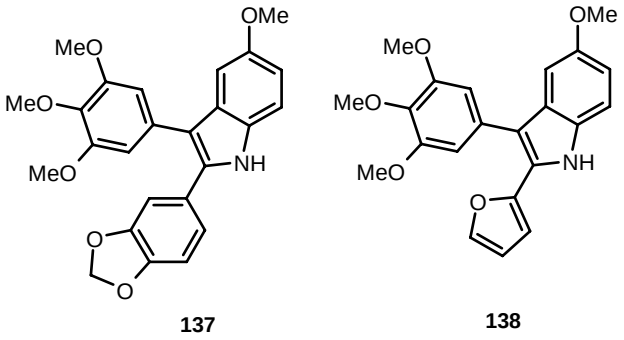


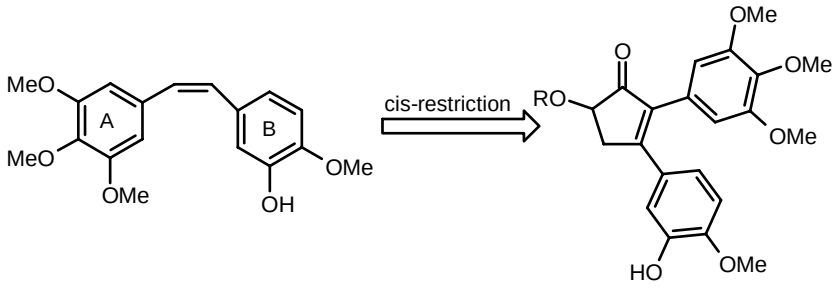
Fig. 3

1.3.2: PRESENT WORK:

We recently reported[2] the synthesis and biological studies of combretastatin A-4 analogues wherin we introduced 4/5-hydroxy-cyclopentenone ring in place of olefinic double bond between two aryl rings of combretastatin A-4, keeping 3,4,5-trimethoxy substituents on A ring, to obtain compounds with pharmaceutically acceptable properties, improved antitumor activity and also to maintain shape selectivity.

We selected the 5-membered ring with hydroxyl group to replace the *cis* double bond for synthesis of combretastatin A-4 analogues, as in prostaglandins it is well known that five membered ring having hydroxy group participates in the biological activity. Moreover, such a structure should avoid inactivation resulting from *cis*-to-*trans* isomerization of the double bond of combretastatin A-4 derivatives.

In the present work described in this section II our continued efforts to achieve a LEAD with enhanced activity and better solubility have been presented. The free hydroxy group at 5-position was derivatised with different amino acids to obtain newer analogues of 5-hydroxy -3-(4-methoxyphenyl)-2-(3, 4, 5-trimethoxyphenyl) cyclopent-2-en-1-one which would help the transport of the molecule across biological membranes.



Combretastatin A-4
16

R = o-amino acids
139

Fig. 4

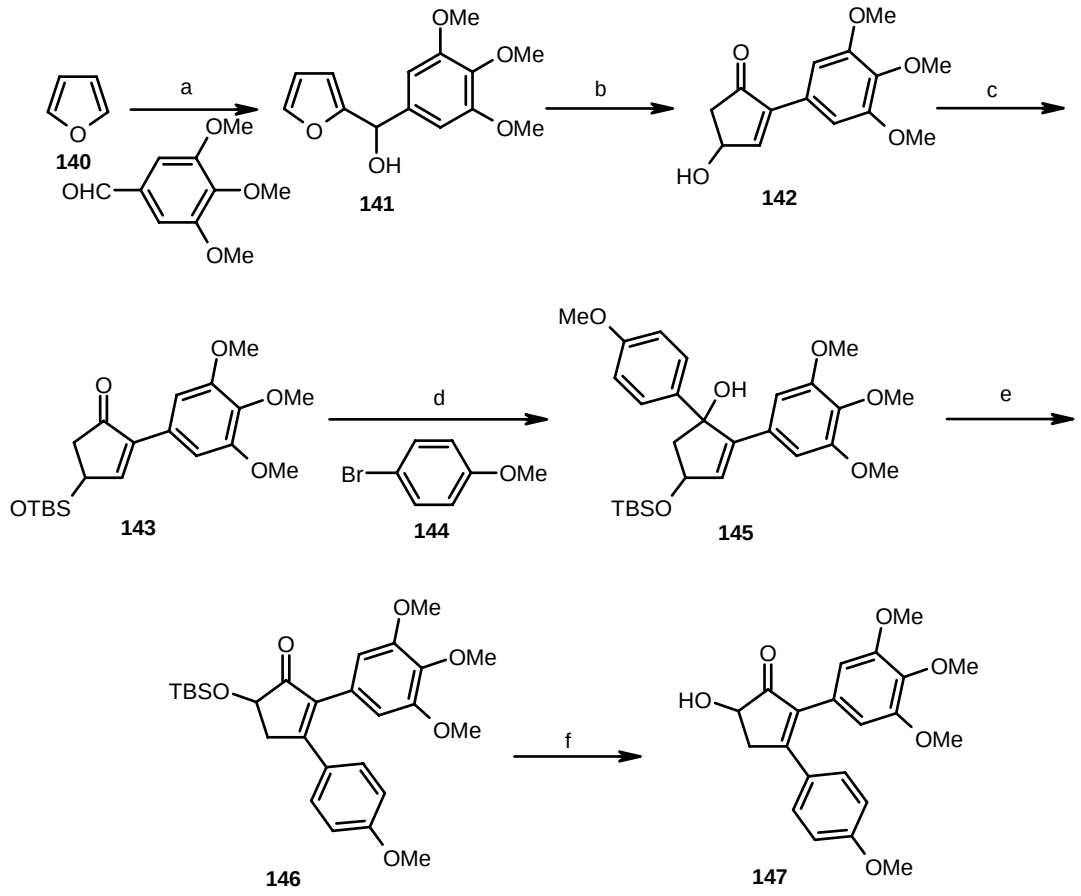
1.3.3: RESULTS AND DISCUSSION:

From the literature survey it was revealed that the synthesis of 2, 3-diaryl-cyclopent-2-en-1-one could be achieved from 1,2-diaryl-cyclopent-2-en-1-ol. We studied the rearrangement of 1,2-diphenyl (substituted)-cyclopent-2-en-1-ols using pyridinium dichromate to achieve the desired 2,3-diaryl-5-*tert*-butyldimethylsilyloxy-cyclopent-2-en-1-ones (**146**), which on deprotection should provide 2,3-diaryl-5-hydroxycyclopent-2-en-1-ones (**147**).

The synthetic strategy adapted is graphically shown in scheme-6. The intermediate **143** was prepared from commercially available 3,4,5-trimethoxybenzaldehyde as shown in shceme - 6. Reaction of furyl magnesium bromide with 3,4,5-trimethoxybenzaldehyde gave the 2-furyl-(3,4,5-trimethoxyphenyl)-methanol (**141**) which on rearrangement with $ZnCl_2$ in dioxane/water gave the intermediate **142** in excellent yield. The hydroxyl group was protected as *tert*-butyldimethylsilyl ether in the presence of dimethylaminopyridine (DMAP) and dichloromethane as a solvent to give intermediate **143** in quantitative yield.

The C-C bond forming reactions play a vital role in the synthetic organic chemistry. Among the various C-C bond forming reactions, Grignard reaction has received much attention in organic chemistry. The addition of Grignard reagent or organolithium reagent in tetrahydrofuran prepared from suitably substituted in this case it is 4-methoxy bromobenzene **144** to intermediate **143** afforded the corresponding 1,2-addition product **145** in good to excellent yield. Further treatment of cyclopentenol **145** with pyridinium dichromate (3 equivalents) in dichloromethane at 0 ^{0}C to room temperature afforded the corresponding 2, 3-diaryl-5-*tert*-butyldimethylsilyloxy-cyclopent-2-en-1-ones (**146**).

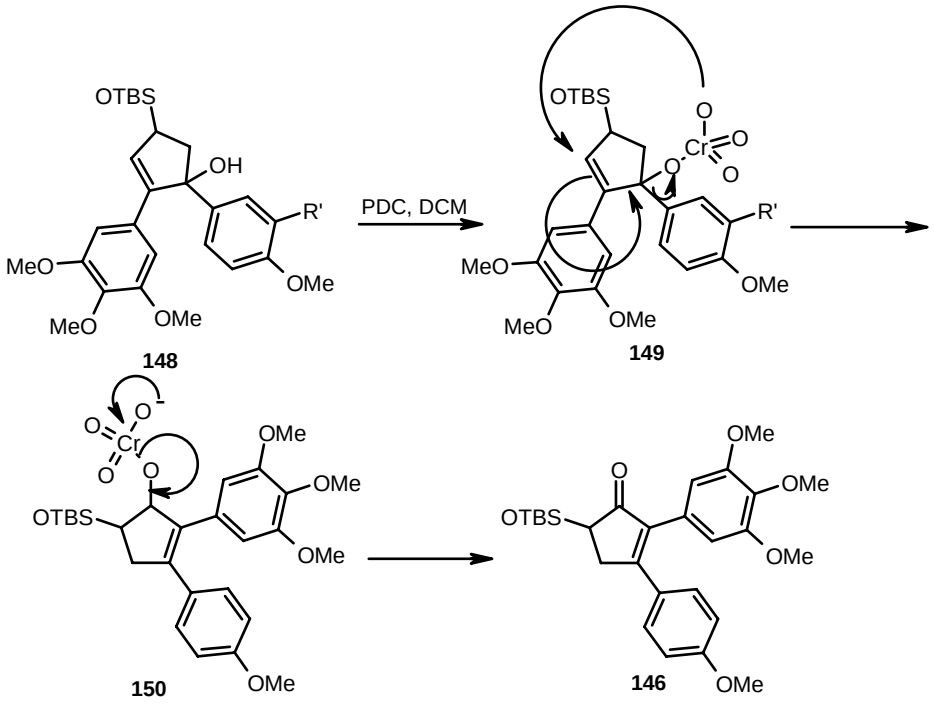
The 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)cyclopent-2-en-1-one (**147**) was obtained by the deprotection of *tert*-butyldimethylsilyl (TBDMS) derivative **146** in the presence of acetic acid, tetrahydrofuran and water at ambient temperature.



Reagents and conditions: a) i) n-BuLi, THF ii) $MgBr_2$, THF, -30 ^{0}C, 4 h. 93 % b) $ZnCl_2$, dioxan/water, reflux, 24 h, 90 % c) TBDMS-Cl, DMAP, DCM, Et_3N, 3 h, 74 % d) Mg, THF, 0 ^{0}C-rt, 2 h, 72 % e) PDC (2 eq.), DCM, r t, 12 h, 46 % f) CH_3COOH-THF-H_2O (3:1:1), 50 ^{0}C, 20 h, 84 %

Scheme - 6

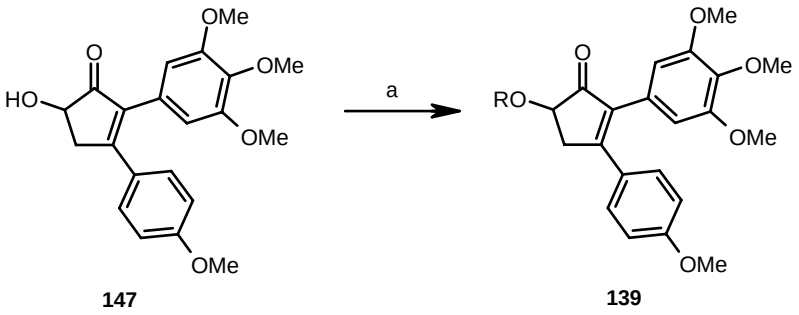
The proposed mechanism for this rearrangement is the initial formation of the chromate ester **149** from the tertiary alcohol followed by allylic rearrangement of the chromate ester of the secondary alcohol **150**. Typical fragmentation of the resultant chromate ester **150** delivers the 2,3-diaryl-5-tert-butyldimethylsilyloxy-cyclopent-2-en-1-ones (**146**) as shown in scheme - 7.



Scheme - 7

All the intermediates synthesized were characterized by spectroscopic methods such as IR, PMR, CMR etc which showed the corresponding peaks at their expected values.

The synthesis of amino acid derivatives **139** from 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)cyclopent-2-en-1-one (**147**) was achieved in one step by treating the alcohol **147** with different aminoacids such as proline, tyrosine, lysine etc in presence of EDCI in dry dichloromethane at 0 ^{0}C to room temperature to achieve the synthesis of final amino acid derivative of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-en-1-one **139** as shown in scheme - 8.



Scheme - 8

Reagents and conditions: a) amino acids, EDCI, DCM, 0 ^{0}C - rt, 7 h.

In a typical example 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-en-1-one (**147**) and boc protected-o-benzyltyrosine were dissolved in dry dichloromethane, in it EDCI dissolved in dry dichloromethane was added dropwise at 0 ^{0}C and stirred for 7 h at room temperature. After work up crude product was isolated by column chromatography using ethyl acetate and pet ether as eluent to get the pure product **139a** and **139b** The products obtained were characterized by ^{1}H NMR spectroscopy and supported by ^{13}C and IR spectroscopic methods, described as follows.

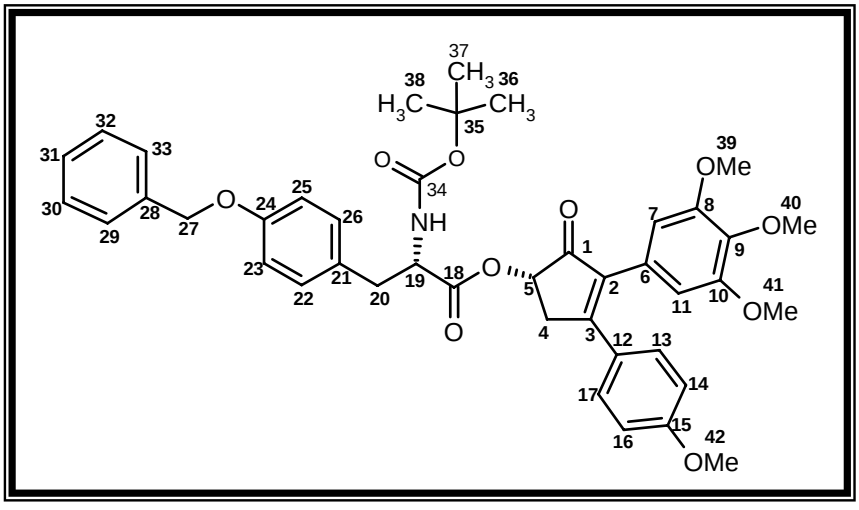


Table - 1, Comp. No. 139

^{1}H NMR spectrum of compound **139a** indicated the presence of amino acid part as well as cyclopentenone part. The upfield singlet at δ 1.44 assigned for the protons from C - 35,

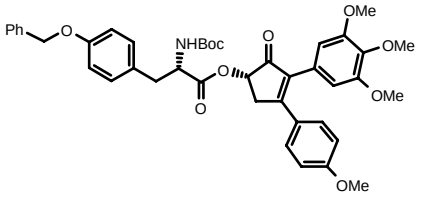
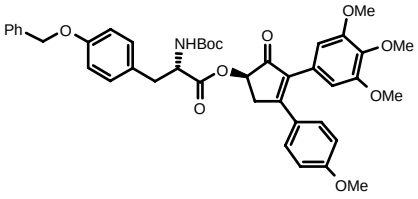
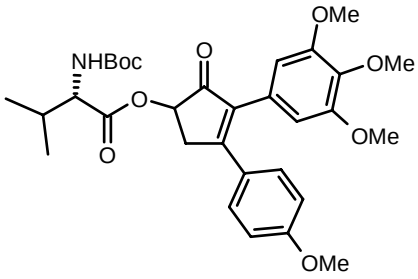
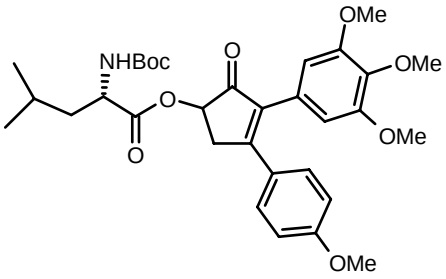
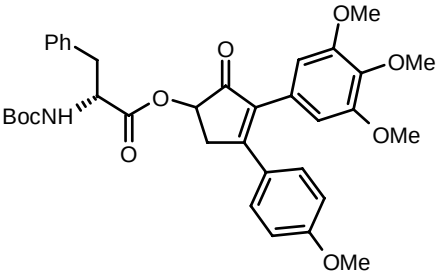
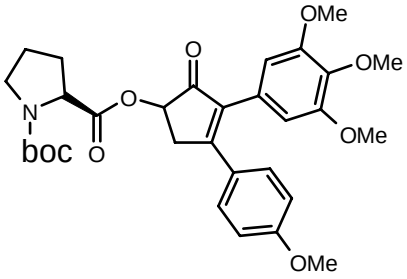
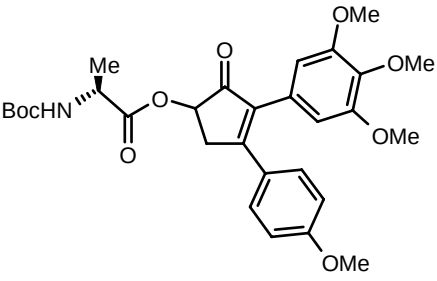
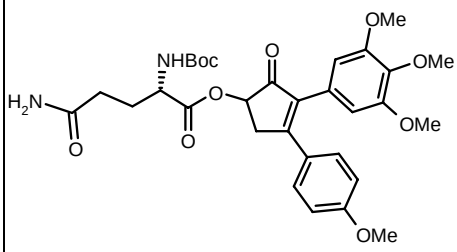
36 and 37 integrating for nine protons from *t*-butyl group in Boc derivative. A multiplet between δ 2.94 - 3.18 was assigned for the methylene protons from C - 20 and the protons from C - 4 showed a doublet of doublet at δ 3.45 (J = 24 and 8 Hz). The three singlets at δ 3.76, 3.82 and 3.88 were assigned for four methoxy groups present on C - 38, 39, 40 and 41. A multiplet at δ 4.02 - 4.16 was assigned for the proton at C - 19, a broad multiplet at δ 4.57 - 4.68 was indicated the presence of - NH group in the compound **139a**, while a sharp singlet at δ 5.03 assigned for two protons of benzylic – CH_2 in the molecule present at C - 27. The other protons from aromatic region showed the peaks at their expected chemical shifts were described in experimental part of this section.

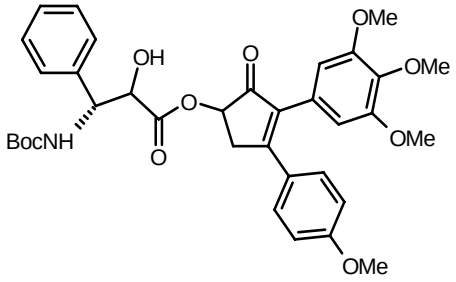
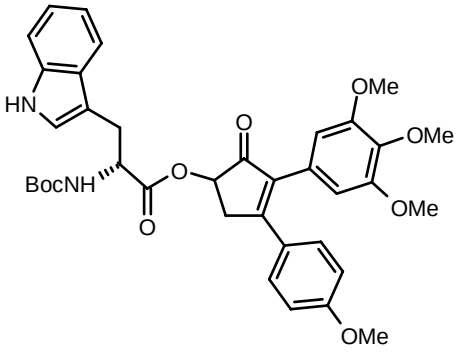
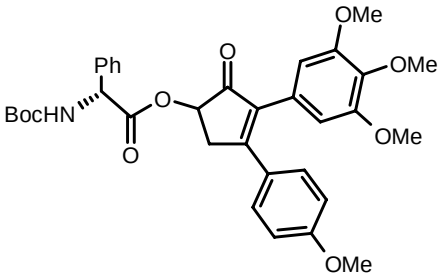
The assigned structure of compound **139a** from ^{1}H NMR spectrum was further supported by ^{13}C NMR spectrum, it exhibited 28 signals for 40 carbon atoms, the upfield signal at δ 28.33 assigned for three C - 35, 36 and 37 present in the boc group, while the three methylene carbons C - 4, 20 and 27 showed the peaks at δ 36.12, 37.10 and 70.39. The presence of carbonyl functionality in the molecule was evident by the signal at δ 200.55 it is the characteristic peak for carbonyl carbon C - 1, the presence of ester group at C - 18 was confirmed by the peak at δ 171.54. This was further supported by IR spectroscopy also the carbonyl carbon at C - 1 showed the peak at ν_{max} 1750 cm^{-1} while the ester carbon at C - 18 showed a peak at 1709 cm^{-1}. The other carbon atoms showed the peaks at their expected chemical shifts were described in experimental part of this section.

Using the same synthetic strategy we have synthesized totally 11 different amino acid esters of 5-hydroxy -3-(4-methoxyphenyl)-2-(3, 4, 5-trimethoxyphenyl) cyclopent-2-en-1-one **139** as shown in table-1. All the synthesized derivatives were characterized by spectroscopic method such as IR, ^{1}H NMR, ^{13}C NMR etc.

The synthesized amino acid esters of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-en-1-one **139** were screened for cytotoxicity against cancer cell lines were described in the third section of this chapter.

Table-1: New Chemical Entites 139

S. No.	Structure	S. No.	Structure
139a		**139b**	
139c		**139d**	
139e		**139f**	
139g		**139h**	

139i		**139j**	
139k			

1.3.4: CONCLUSION:

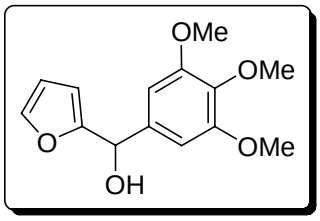
In conclusion, amino acid analogues of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-en-1-one were synthesized successfully by the rearrangement of tertiary allylic alcohols using pyridinium dichromate. Various amino acids were attached to the 5-hydroxy position of cyclopentenone were prepared by the use of EDCI, overall 11 compounds of this category was created alongwith generation of their spectral and analytical data. The water soluble amino acid esters of the lead compound **147** were successfully prepared which retained the activity *in vitro*.

1.3.5: EXPERIMENTAL:

Preparation of furan-2-yl-(3,4,5-trimethoxyphenyl)-methanol (141):

Magnesium (1.68 gm, 70 mmol) was taken in three neck round bottom flask equipped with reflux condensor and 100 ml ether followed by dibromoethane (9.5 gm, 51.02 mmol) were added with stirring at 0 ^{0}C under nitrogen atmosphere. Stirring was continued till all magnesium reacted, then ether was removed under vacuum till slurry was formed (A). In another single neck round bottom flask furan (4.76 gm, 70 mmol) in tetrahydrofuran (100 ml) was cooled with ice-salt mixture, n-butyllithium (2M, 35 ml, 70 mmol) was added dropwise, and stirred at 0 ^{0}C for 45 min (B).

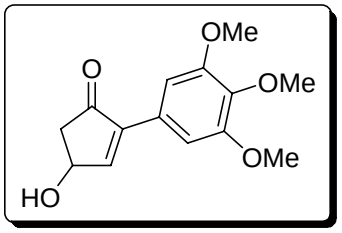
Furyllithium thus prepared in flask B was added to cold mixture in A through cannula, stirred at 0 ^{0}C for 5 min, brought to room temperature, stirred at room temperature for 1.5 h and then cooled to -20 ^{0}C (dry ice + CCl_4). Substituted benzaldehyde (51.02 mmol) in tetrahydrofuran (50 ml) was added and stirred at -20 ^{0}C for 4 h (monitored by TLC). After completion of reaction, the reaction mixture was quenched with saturated ammonium chloride solution and the mixture was allowed to warm to room temperature. Solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect pure product.



Nature: Yellow solid; **M. p.** 77 - 78 ^{0}C; **Yield:** 73 %; **IR** (chloroform)**:** ν_{max} 3433, 3017, 1595, 1216 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.72 (bs, 1H), 3.84 (s, 9H), 5.75 (bs, 1H), 6.25 (d, J = 6 Hz, 1H), 6.27 - 6.32 (m, 1H), 6.66 (d, J = 2 Hz, 2H), 7.40 (bs, 1H); **Mass** (m/e)**:** 264 (M^+, 80), 247 (60), 233 (12), 214 (15), 189 (20), 169 (70), 161 (25), 95 (100); **Anal. Calcd. for** $C_{14}H_{16}O_5$**:** C, 63.63; H, 6.10 %. **Found:** C, 63.78; H, 6.22 %.

Preparation of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (142):

In a 1 liter round bottom flask a solution of aryl furfuryl alcohol (25 gm, 94.69 mmol) $ZnCl_2$ (51.26 gm, 378.7 mmol) in dioxan (309 ml) and water (206 ml) was refluxed for 24 h at which time TLC analysis indicated the complete disappearance of starting material. The mixture was brought to room temperature, acidified to pH 1 with dilute HCl and extracted with ethyl acetate. Organic layer was washed with water, followed by brine and dried over sodium sulphate. The organic layer was concentrated under reduced pressure using rotary evaporator and chromatographed on silica gel column to collect substituted 4-hydroxy-cyclopent-2-en-1-ones as shown in scheme -1.

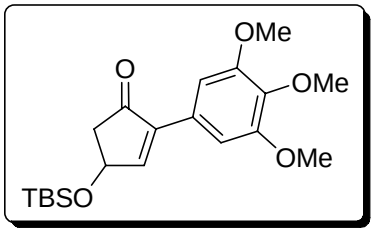


Nature: Yellow solid; **Yield:** 81 %; **M. p.** 93 - 94 ^{0}C; **IR** (chloroform)**:** ν_{max} 3464, 1709 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.46 (dd, J = 18 Hz and 4 Hz, 1H), 2.91 (dd, J = 18 Hz and 8 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 6H), 4.93 - 4.98 (m, 1H), 6.91 (s, 2H), 7.51 (d, J = 4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 45.78, 55.88 (2C), 60.58, 67.02, 104.59 (2C), 125.92 (2C), 138.34, 142.80, 152.75, 156.66, 204.48; **Mass** (m/e)**:** 264 (M^+, 100), 249 (57), 233 (10), 221 (22), 205 (32), 189 (70), 177 (20), 161 (40); **Anal. Calcd. for** $C_{14}H_{16}O_5$**:** C, 63.63; H, 6.10 %. **Found:** C, 63.71; H, 6.18 %.

Preparation of 4-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (143):

A solution of 2-aryl-4-hydroxy-cyclopent-2-en-1-one (8.7 mmol) in dry dichloromethane (30 ml) was stirred at 0 ^{0}C under inert atmosphere (maintained by using nitrogen or argon gas filled in balloon), a solution of *tert*-butyldimethylsilylchloride (1.5 gm, 9.95 mmol) and dimethylaminopyridine (0.194 gm, 1.5 mmol) in dichloromethane (10 ml) was added dropwise and stirred at same temperature for 15 min. Then triethylamine (1.77 ml, 12.7 mmol) was added and mixture was warmed to room temperature and stirred further for 3 h (monitored by TLC). The reaction mixture was filtered through Whatman filter paper, dichloromethane removed under reduced pressure and extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and

concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether - acetone as eluent) to give the title product.

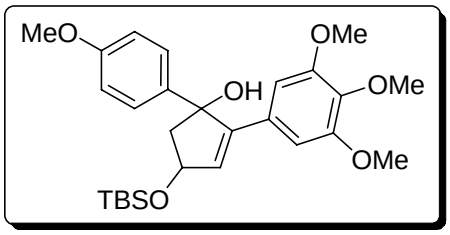


Nature: Yellow solid; **Yield:** 85 %; **M. p.** 87 - 88 ^{0}C; **IR** (chloroform)**:** ν_{max} 3014, 2935, 1704, 1602, 1504 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.16 (s, 3H), 0.17 (s, 3H), 0.94 (s, 9H), 2.47 (bd, J = 18 Hz, 1H), 2.92 (dd, J = 18 Hz and 6 Hz, 1H), 3.85 (s, 3H), 3.90 (s, 6H), 4.95 - 5.05 (m, 1H), 6.96 (s, 2H), 7.45 (d, J = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ -4.97 (2C), 17.82, 25.50 (3C), 46.49, 55.79 (2C), 60.50, 67.81, 104.57 (2C), 125.89, 138.46, 142.61, 152.79 (2C), 156.76, 203.81; **Mass** (m/e)**:** 378 (M^+, 100), 363 (10), 321 (15), 290 (40), 219 (70); **Anal. Calcd. for** $C_{20}H_{30}O_5Si$**:** C, 63.46; H, 7.99; Si, 7.42 %. **Found:** C, 63.58; H, 8.12; Si, 7.46 %.

4-(tert-butyldimethylsilanyloxy)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-en-1-ol (145):

In 100 ml two neck round bottom flask, magnesium turnings (0.19 g, 7.93 mmol) were taken under nitrogen atmosphere. Dry tetrahydrofuran (30 ml) was added followed by dropwise addition of *p*-bromoanisole (1.48 g, 7.90 mmole) and 4-*tert*-butyldimethylsilyloxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (2.00 g, 5.29 mmol). The reaction mixture was then stirred at room temperature for 2 h (TLC indicated the completion of reaction). It was then quenched with dilute hydrochloric acid (25 ml), tetrahydrofuran was removed under reduced pressure, the reaction mixture was extracted with ethyl acetate (3 x 25 ml), washed with water, dried over sodium sulfate, concentrated and purified by column chromatography over silica gel (petroleum ether-acetone as eluent) to afford 4-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxyphenyl) -2-(3,4,5- trimethoxyphenyl)-cyclopent-2-en-1-ol (1.28 g) as a thick liquid.

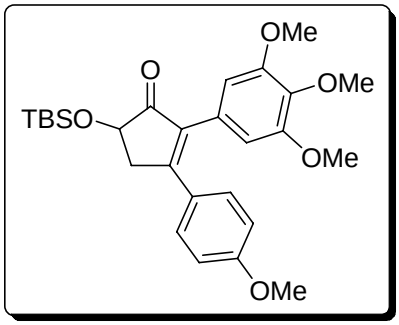
Nature: Thick yellow liquid; **Yield:** 52 %; **IR** (chloroform)**:** ν_{max} 3473, 3013, 2955, 2934, 1581, 1509, 1248 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.12 (s, 6H), 0.93 (s, 9H), 2.22 (dd, J = 16 Hz and 6 Hz, 1H), 2.61 (dd, J = 16 Hz and 6 Hz, 1H), 3.66 (s, 6H), 3.76 (s, 6H), 4.85 - 4.90 (m, 1H), 6.23 (d, J = 2 Hz, 1H), 6.57 (s, 2H), 6.80 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 4.78 (2C), 17.90, 25.70 (3C), 54.81, 55.54 (3C), 60.36, 73.26, 85.35, 104.80 (2C), 113.33 (2C), 125.71 (2C), 128.88, 131.93, 137.22, 149.35, 152.44 (2C), 158.02; **Mass** (m/e)**:** 485 (M^+); **Anal. Calcd. for** $C_{27}H_{38}O_6Si$**:** C, 66.63; H, 7.87; Si, 5.77 %. **Found:** C, 66.78; H, 7.95; Si, 5.80 %.



Prepration of 5-(tert-Butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-en-1-one (146):

In a 50 ml two neck round bottom flask, 4-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxyphenyl) -2-(3,4,5- trimethoxyphenyl)-cyclopent-2-en-1-ol (1.15 g, 2.36 mmol) was taken in dry dichloromethane (20 ml) and cooled to 0 ^{0}C. Pyridinium dichromate (1.73 g, 7.38 mmol) was then added and allowed to stir at same temperature for 1 h and then stirred at room temperature for 10 h. It was then filtered through celite (2.00 g) and washed with water(2 x 10 ml) followed by brine (5 ml), dried over sodium sulfate, concentrated on rotary evaporator and purified by column using silica gel (2-5 % acetone in pet ether) to affored the 5-(*tert*-butyldimethylsilanyloxy)-3-(4-methoxyphenyl) -2-(3,4,5- trimethoxyphenyl)-cyclopent-2-en-1-one (0.52 g) as a yellowish solid.

Nature: Yellowish solid; **Yield:** 45 %; **M. p.** 104 - 106 ^{0}C; **IR** (chloroform)**:** ν_{max} 3016, 2933, 1712, 1581, 1280, 1255 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.22 (s, 6H), 0.96 (s, 9H), 2.94 (dd, J = 16 Hz and 4 Hz, 1H), 3.30 (dd, J = 16 Hz and 8 Hz, 1H), 3.71 (s, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 4.45 - 4.52 (m, 1H), 6.44 (s, 2H), 6.78 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4)**:**

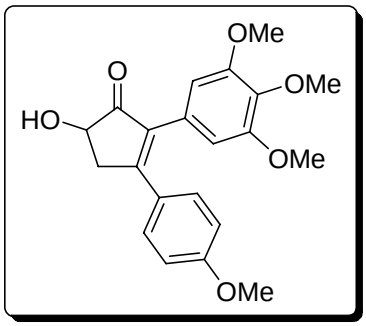


δ -5.23, -4.49, 18.26, 25.72 (3C), 39.29, 55.02, 55.75 (2C), 60.53, 72.44, 106.30 (2C), 113.57 (2C), 127.14, 127.95, 130.12 (2C), 135.44, 137.54, 153.16 (2C), 161.10, 162.43, 204.88; **Mass** (m/e)**:** 484 (M^+); **Anal. Calcd. for** $C_{27}H_{36}O_6Si$**:** C, 66.91; H, 7.49; Si, 5.79 %. **Found:** C, 66.98; H, 7.52; Si, 5.83 %.

Prepration of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-en-1-one (147):

In a 50 ml two neck round bottom flask, 5-(*tert*-butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5- trimethoxyphenyl)-cyclopent-2-en-1-one (0.950 g, 2.47 mmol) was taken and to this a mixture of acetic acid, tetrahydrofuran and water (3:1:1) (20 ml) was then added and heated at 50 ^{0}C for 20 h (reaction monitored by TLC). The reaction mixture was then cooled to 0 ^{0}C and neutralized by adding sodium bicarbonate and then extracted with cholorform (3 x 20 ml). The organic layer was washed with water followed by brine and dried over sodium sulfate. The solvent was removed under reduced pressure using rotary evaporator. The crude residue obtained was purified by column chromatography using silica gel (acetone in pet ether as eluent) to collect the pure 5-hydroxy-3-(4-methoxyphenyl) -2-(3,4,5- trimethoxyphenyl)-cyclopent-2-en-1-one (0.610 g, 84 %) as a yellowish solid.

Nature: yellowish solid; **M. p.** 205 ^{0}C; **Yield:** 84 %; **IR** (chloroform)**:** ν_{max} 3434, 3019, 1697, 1602, 1504, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.06 (dd, J = 18 Hz and 4 Hz, 1H), 3.38 (dd, J = 18 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 4.48 - 4.58 (m, 1H), 6.45 (s, 2H), 6.87 (d, J = 8 Hz, 2H), 7.38 (d, J = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 38.38, 55.55, 56.24 (2C), 60.06, 72.12, 106.57 (2C), 114.06 (2C), 127.69, 127.96, 130.72 (2C), 135.38, 138.07, 153.73 (2C), 161.78, 164.68, 207.47; **Mass** (m/e)**:** 370 (M^+); **Anal. Calcd. for** $C_{21}H_{22}O_6$**:** C, 68.10; H, 5.99 %. **Found:** C, 66.18; H, 6.12 %.

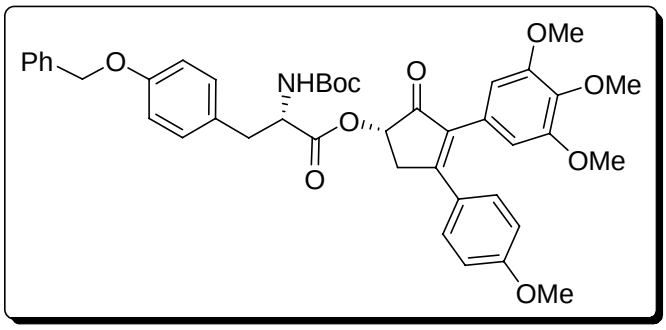


Prepration of tert-butyl-1-((3-(3,4,5-trimethoxyphenyl)-4-(4-methoxy-phenyl)-2-oxocyclopent-3-enyloxy)carbonyl)-2-(4-(benzyloxy)phenyl)ethylcarbamate (139a):

In a 50 ml two neck round bottom flask, 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.500 g, 1.35 mmol) and boc protected tyrosine (0.501 g, 1.35 mmol) were taken, reaction mixture was then cooled to 0 ^{0}C and to this EDCI (0.311 g, 1.62 mmol) dissolved in dichloromethane was added dropwise stir reaction mixture at room temperature for 7 h (reaction monitored by TLC). The reaction mixture was then extracted with dichloromethane (3 x 20 ml). The organic layer was washed with water followed by brine and dried over sodium sulfate. The solvent was removed under reduced pressure using rotary evaporator. The crude residue obtained was purified by column chromatography using silica gel (ethyl acetate in pet ether as eluent) to collect the pure *R* and *S* *tert*-butyl-1-((3-(3,4,5-trimethoxyphenyl)-4-(4-methoxy-phenyl)-2-oxocyclopent-3-enyloxy)carbonyl)-2-(4-(benzyloxy)phenyl)ethylcarbamate (**139a**)

(S)-3-(4-Benzyloxy-phenyl)-2-tertbutoxycarbonylamino-propionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy phenyl)-cyclopent-3-enyl ester (139 a):

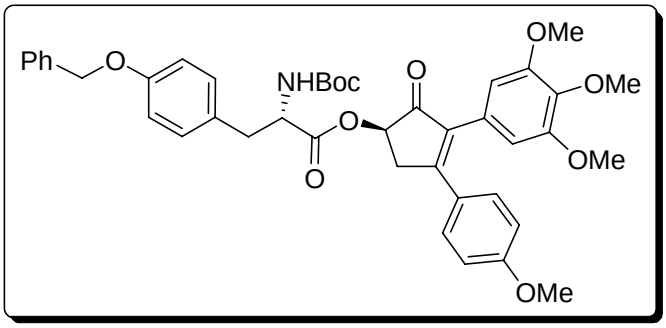
Nature: Yellow solid; **M. p.** 132 ^{0}C; $[\alpha]_D$ +17.56 (c 0.55, $CHCl_3$); **Yield:** 44 %; **IR** (chloroform)**:** ν_{max} 3370, 3006, 2971, 1749, 1708, 1602, 1582, 1512, 1454, 1413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.44 (s, 9H), 2.94 - 3.18 (m, 2H), 3.45 (dd, J = 24 Hz and 8 Hz, 1H), 3.76 (s, 6H), 3.82 (s, 3H), 3.88 (s, 3H), 4.02 - 4.16 (m, 1H), 4.57 - 4.68 (m, 1H), 4.95 - 5.07 (m, 3H), 5.52 - 5.64 (m, 1H), 6.48 (s, 2H), 6.82 (d, J = 8 Hz, 2H), 6.93 (d, J = 8 Hz, 2H), 7.15 - 7.43 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.83 (3C), 36.12, 37.10, 55.24, 56.02 (2C), 60.78, 69.92, 72.21, 79.87, 106.49 (2C), 113.93 (2C), 114.94 (2C), 126.67, 127.37 (2C), 127.95 (2C), 128.50 (2C), 130.10 (2C), 130.73 (2C), 136.13, 137.05 (2C), 138.13, 153.54 (2C), 154.90,



157.99, 161.71, 163.10, 171.54 (2C), 200.55; **Anal. Calcd. for** $C_{42}H_{45}NO_{10}$**:** C, 71.27; H, 6.41 %. **Found:** C, 71.15; H, 6.27; N, 1.84 %.

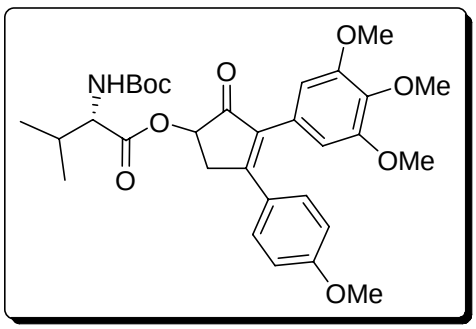
(R)-3-(4-Benzyloxy-phenyl)-2-tertbutoxycarbonylamino-propionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy phenyl)-cyclopent-3-enyl ester (139 b):

Nature: Yellow solid; **M. p.** 125 ^{0}C; $[\alpha]_D$ -17.20 (c 0.55, $CHCl_3$); **Yield:** 42 %; **IR** (chloroform)**:** ν_{max} 3369, 3007, 2935, 1747, 1707, 1602, 1582, 1511, 1454, 1413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.43 (s, 9H), 2.72 - 2.88 (m, 1H), 3.07 - 3.13 (m, 2H), 3.37 (dd, J = 26 and 8 Hz, 1H), 3.75 (s, 6H), 3.82 (s, 3H), 3.88 (s, 3H), 4.08 - 4.16 (m, 1H), 4.62 - 4.70 (m, 1H), 4.98 - 5.04 (s, 2H), 5.37 - 5.50 (m, 1H), 6.45 (s, 2H), 6.90 (d, J = 8 Hz, 2H), 7.12 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 7.28 - 7.48 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.35 (3C), 35.95, 37.74, 55.23, 56.00 (2C), 60.81, 69.88, 72.54, 79.90, 106.37 (2C), 113.92 (2C), 114.88 (2C), 126.70, 127.37 (2C), 127.92 (2C), 128.54 (2C), 130.55 (2C), 130.72 (2C), 136.10, 137.07 (2C), 138.15, 153.55 (2C), 154.94, 157.80, 161.68, 163.1, 171.52 (2C), 200.50; **Anal. Calcd. for** $C_{42}H_{45}NO_{10}$**:** C, 71.27; H, 6.41; N, 1.98 %. **Found:** C, 71.12; H, 6.32; N, 1.81 %.



2-tert-Butoxycarbonylamino-3-methyl-butyric acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy phenyl)-cyclopent-3-enyl ester (139 c):

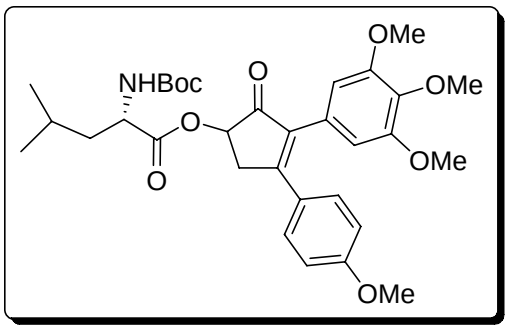
Nature: Yellow semisolid; **Yield:** 78 %; **IR** (chloroform)**:** ν_{max} 3367, 3006, 2932, 1750, 1702, 1600, 1578, 1510, 1456, 1410 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.90 - 1.10 (m, 6H), 2.15 - 2.45 (m, 1H), 1.47 (s, 9H), 2.15 - 2.45 (m, 1H), 3.00 - 3.19 (m, 1H), 3.30 - 3.51 (m, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.25 - 4.45 (m, 1H), 4.95 - 5.14 (m, 1H),



5.60 - 5.67 (m, 1H), 6.46 (s, 2H), 6.83 (d, *J* = 10 Hz, 2H), 7.32 - 7.42 (m, 2H); **Anal. Calcd. for** $C_{31}H_{39}O_9$**:** C, 65.38; H, 6.85; N, 2.47 %. **Found:** C, 65.28; H, 6.78; N, 2.40 %.

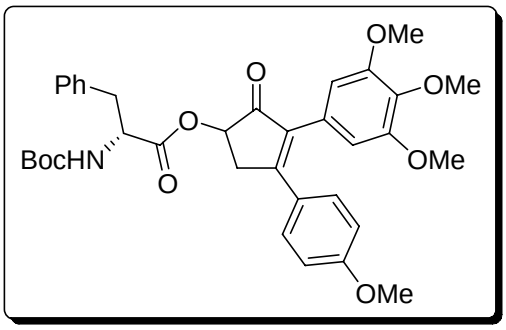
2-tert-Butoxycarbonylamino-4-methyl-pentanoic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy phenyl)-cyclopent-3-enyl ester (139 d):

Nature: Yellow semisolid; **Yield:** 80 %; **IR** (chloroform)**:** ν_{max} 3370, 3001, 2930, 1756, 1698, 1601, 1585, 1509, 1455, 1412 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.88 - 1.01 (m, 6H), 1.47 (s, 9H), 1.60 - 1.90 (m, 3H), 2.95 - 3.20 (m, 1H), 3.30 - 3.55 (m, 1H), 3.74 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 4.32 - 4.50 (m, 1H), 4.86 - 5.02 (m, 1H), 5.29 - 5.67 (m, 1H), 6.47 (s, 2H), 6.83 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H); **Anal. Calcd. for** $C_{32}H_{41}NO_9$**:** C, 65.87; H, 7.03; N, 2.40 %. **Found:** C, 65.68; H, 6.98; N, 2.32 %.



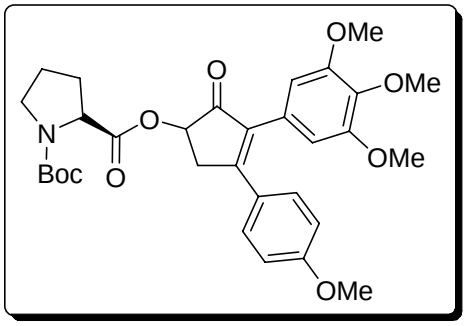
***2-tert-Butoxycarbonylamino-3-phenylpropionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy phenyl)-cyclopent-3-enyl ester (139 e)*:**

Nature: Yellow semisolid; **Yield:** 81 %; **IR** (chloroform)**:** ν_{max} 3370, 3006, 2932, 1748, 1706, 1601, 1584, 1510, 1452, 1412 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.35 (s, 9H), 2.90 - 3.10 (m, 2H), 3.28 - 3.46 (m, 1H), 3.55 - 3.15 (m, 1H), 3.68 (s, 6H), 3.76 (s, 3H), 3.80 (s, 3H), 4.55 - 4.70 (m, 1H), 4.86 - 5.00 (m, 1H), 5.32 - 5.57 (m, 1H), 6.41 (s, 2H), 6.76 (d, *J* = 10 Hz, 2H), 7.15 - 7.34 (m, 7H); **Anal. Calcd. for** $C_{35}H_{39}NO_9$**:** C, 68.07; H, 06.32; N, 02.27 %. **Found:** C, 68.01; H, 6.28; N, 02.23 %.



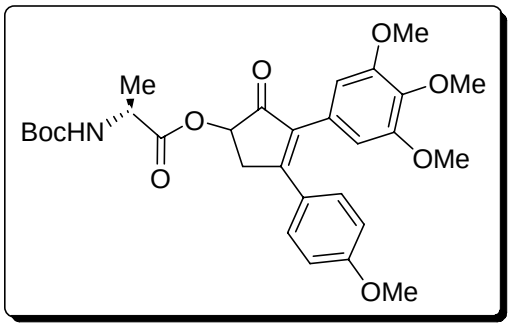
Pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester-2-[4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy-phenyl)-cyclopent-3-enyl] ester (139 f):

Nature: Yellow semisolid; **Yield:** 79 %; **IR** (chloroform)**:** ν_{max} 3004, 2933, 1751, 1708, 1604, 1585, 1509, 1450, 1415 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.38 - 1.44 (m, 9H), 1.75 - 2.20 (m, 4H), 2.85 - 3.15 (m, 3H), 3.25 - 3.50 (m, 1H), 3.67 (s, 6H), 3.75 (s, 3H), 3.79 (s, 3H), 4.25 - 4.35 (m, 1H), 5.40 - 5.60 (m, 1H), 6.38 (s, 2H), 6.74 (d, J = 10 Hz, 2H), 7.25 - 7.33 (m, 2H); **Anal. Calcd. for** $C_{31}H_{37}NO_9$**:** C, 65.61; H, 6.52; N, 2.47 %. **Found:** C, 65.47; H, 6.33; N, 2.32 %.



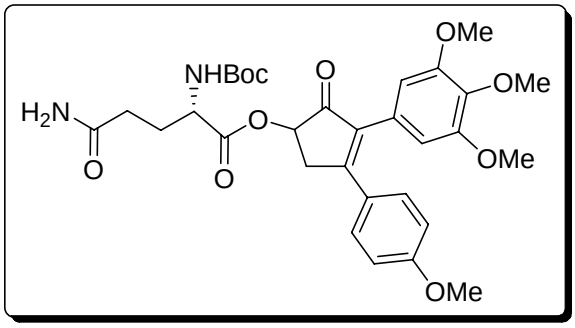
2-tert-Butoxycarbonylamino-propionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy-phenyl)-cyclopent-3-enyl ester (139 g):

Nature: Yellow semisolid; **Yield:** 79 %; **IR** (chloroform)**:** ν_{max} 3365, 3005, 2935, 1746, 1708, 1601, 1584, 1514, 1454, 1412 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.30 - 1.50 (m, 12H), 2.90 - 3.10 (m, 1H), 3.31 - 3.51 (m, 1H), 3.67 (s, 6H), 3.75 (s, 3H), 3.80 (s, 3H), 4.20 - 4.45 (m, 1H), 4.95 - 5.03 (m, 1H), 5.28 - 5.50 (m, 1H), 6.38 (s, 2H), 6.74 (d, J = 10 Hz, 2H), 7.29 (d, J = 10 Hz, 2H); **Anal. calcd for** $C_{29}H_{35}NO_9$**:** C, 64.32; H, 6.47; N, 2.59 %. **Found:** C, 64.18; H, 6.40; N, 2.48 %.



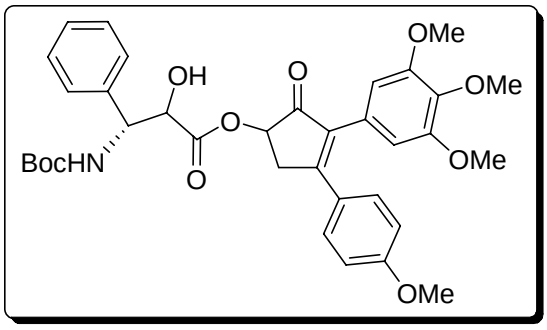
2-tert-Butoxycarbonylamino-4-carbamoyl-butyric acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy-phenyl)-cyclopent-3-enyl ester (139 h):

Nature: Yellow semisolid; **Yield:** 87 %; **IR** (chloroform)**:** ν_{max} 3368, 3006, 2934, 1745, 1706, 1602, 1583, 1510, 1456, 1413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.46 (s, 9H), 2.10 - 2.36 (m, 2H), 2.37 - 2.47 (m, 2H), 3.10 - 3.20 (m, 1H), 3.37 - 3.51 (m, 1H), 3.75 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 4.30 - 4.50 (m, 1H), 5.39 - 5.69 (m, 3H), 6.46 (s, 2H), 6.83 (d, J = 12 Hz, 2H), 7.38 (d, J = 12 Hz, 2H). **Anal. Calcd. for** $C_{31}H_{38}N_2O_{10}$**:** C, 62.20; H, 6.40; N, 4.68 %. **Found:** C, 62.07; H, 6.26; N, 4.53 %.



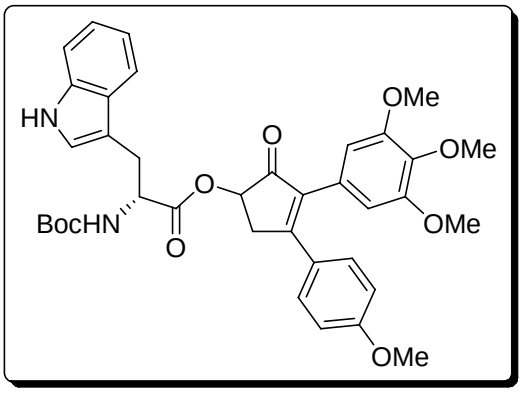
2-tert-Butoxycarbonylamino-2-hydroxy-3-phenyl-propionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy-phenyl)-cyclopent-3-enyl ester (139 i):

Nature: Yellow semisolid; **Yield:** 86 %; **IR** (chloroform)**:** ν_{max} 3368, 3006, 2934, 1745, 1706, 1602, 1583, 1510, 1456, 1413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.83 (s, 9H), 2.95 - 3.10 (m, 1H), 3.30 - 3.45 (m, 1H), 3.67 (s, 6H), 3.74 (s, 3H), 3.78 (s, 3H), 4.52 (d, J = 8 Hz, 1H), 5.05 - 5.15 (m, 2H), 5.40 - 5.60 (m, 1H), 6.37 (s, 2H), 6.76 (d, J = 8 Hz, 2H), 7.18 - 7.36 (m, 7H); **Anal. Calcd. for** $C_{35}H_{39}NO_{10}$**:** C, 66.34; H, 6.20; N, 2.21 %. **Found:** C, 66.18; H, 6.12; N, 2.05 %.



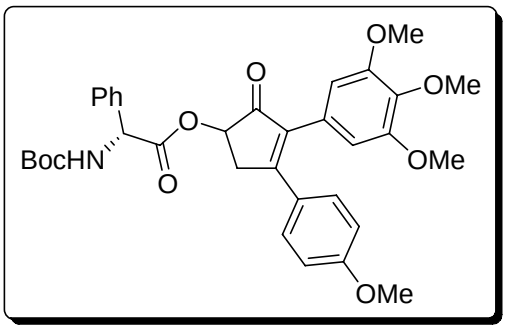
2-tert-Butoxycarbonylamino-3-(1H-indol-3-yl)-propionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy-phenyl)-cyclopent-3-enyl ester (139 j):

Nature: Pale yellow solid; **M. p.** 89 ^{0}C; **Yield:** 82 %; **IR** (chloroform)**:** ν_{max} 3369, 3005, 2930, 1747, 1700, 1601, 1585, 1513, 1455, 1412 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.37 (s, 9H), 2.50 - 2.90 (m, 1H), 3.10 - 3.40 (m, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 3.79 (s, 6H), 4.62 - 4.74 (m, 1H), 4.95 - 5.10 (m, 1H), 5.20 - 5.60 (m, 1H), 6.38 (s, 2H) 6.68 - 6.78 (m, 2H), 7.00 - 7.40 (m, 6H), 7.53 (t, J = 8 Hz, 1H), 8.21 (bs, 1H); **Anal. Calcd. for** $C_{37}H_{40}N_2O_9$**:** C, 67.79; H, 5.10; N, 4.27 %. **Found:** C, 67.70; H, 5.02; N, 4.18 %.

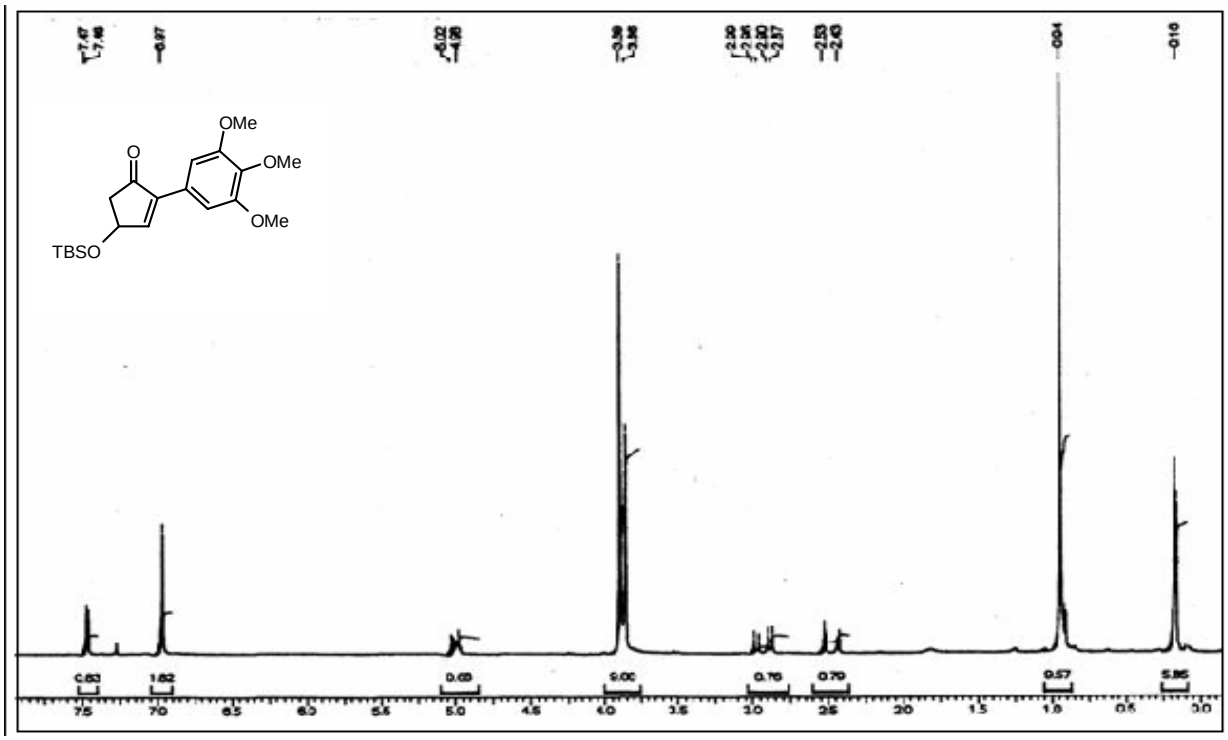


2-tert-Butoxycarbonylamino-phenyl-acetic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy-phenyl)-cyclopent-3-enyl ester (139 k):

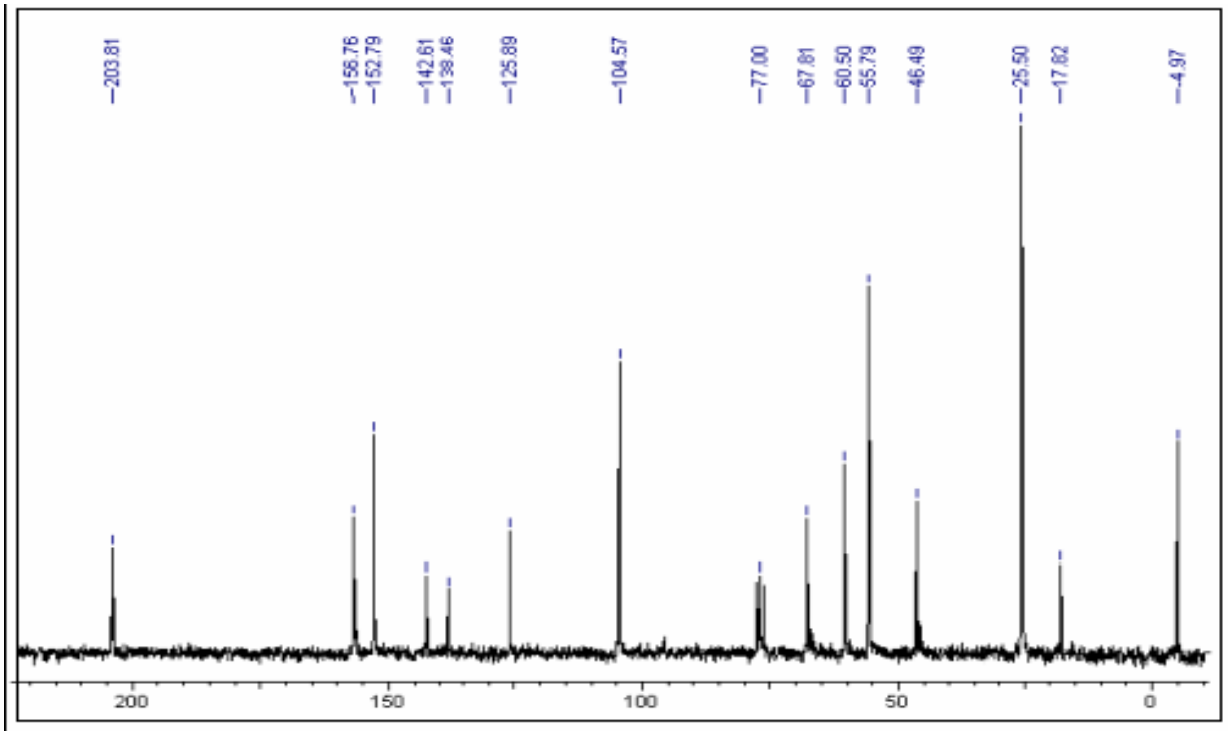
Nature: Yellow semisolid; **Yield:** 76 %; **IR** (chloroform)**:** ν_{max} 3370, 3009, 2933, 1747, 1706, 1600, 1585, 1510, 1456, 1411 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.46 (s, 9H), 3.10 - 3.24 (m, 1H), 3.36 - 3.48 (m, 1H), 3.71 (s, 6H), 3.72 (s, 3H), 3.74 (s, 3H), 4.02 - 4.16 (m, 1H), 5.46 - 5.57 (m, 2H), 6.42 (s, 2H), 6.81 (dd, J = 6 and 4 Hz, 2H), 7.29 - 7.52 (m, 7H); **Anal. Calcd. for** $C_{34}H_{37}NO_9$**:** C, 67.67; H, 6.13; N, 2.32 %. **Found:** C, 67.58; H, 6.02; N, 2.20 %.



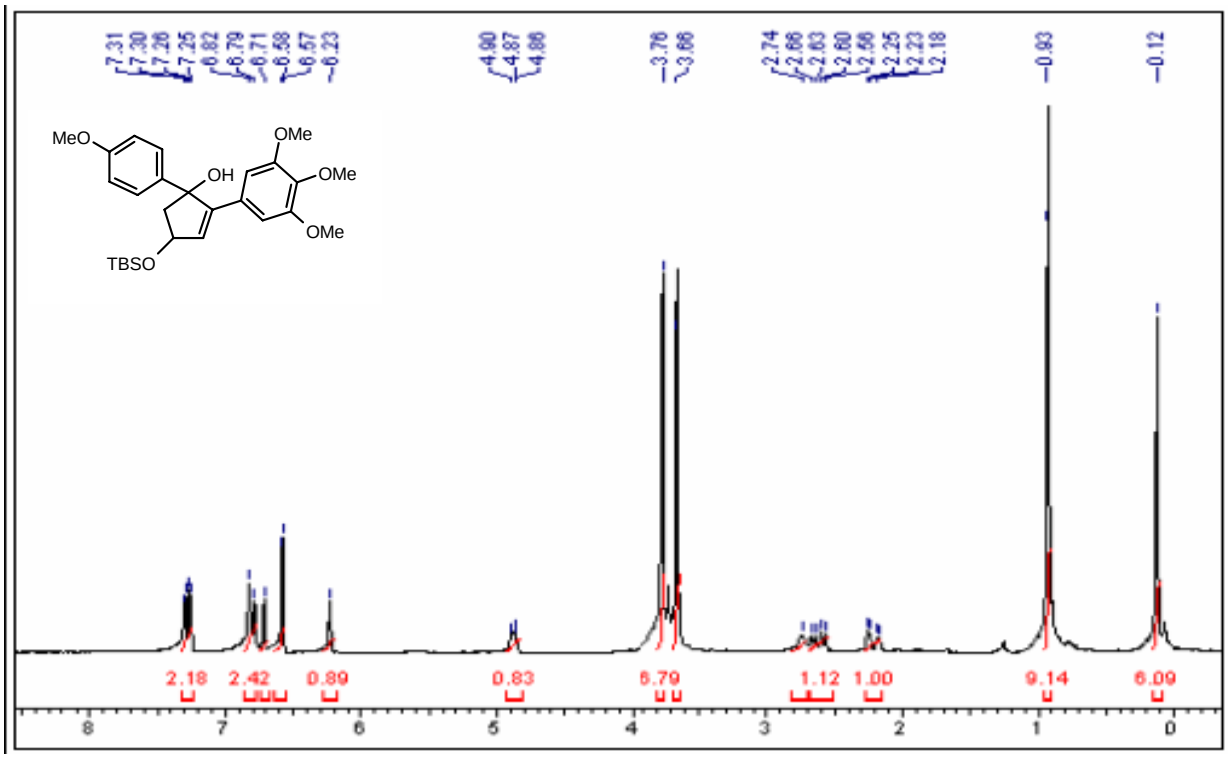
^{1}H NMR spectrum of the compound 143 ($CDCl_3$+CCl_4, 200 MHz)



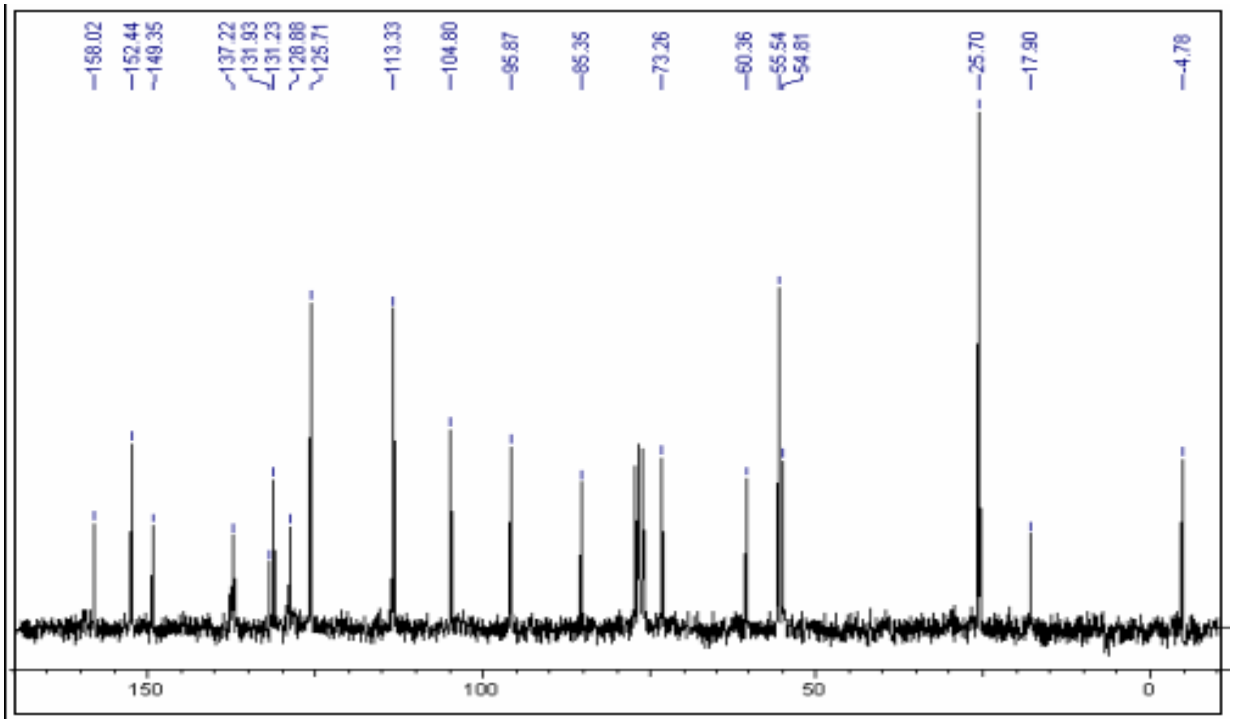
^{1}C NMR spectrum of the compound 143 ($CDCl_3$+CCl_4, 50 MHz)



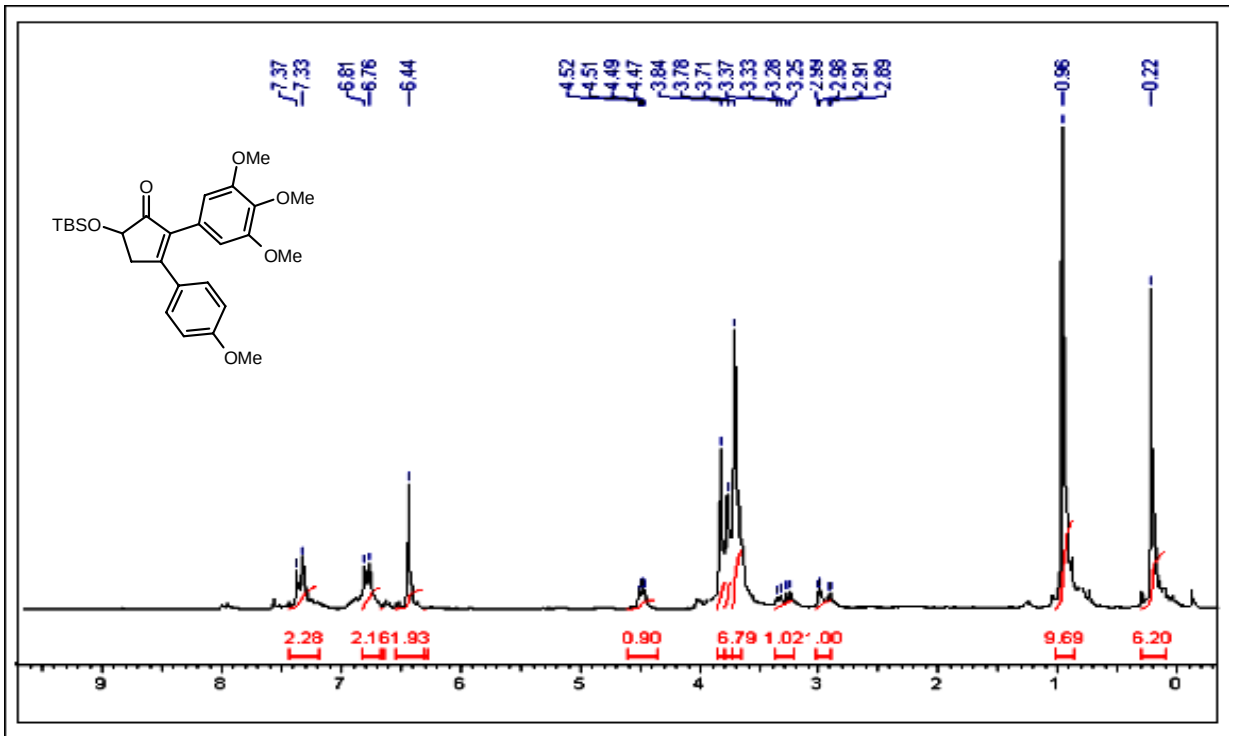
^{1}H NMR spectrum of the compound 145 ($CDCl_3$+CCl_4, 200 MHz)



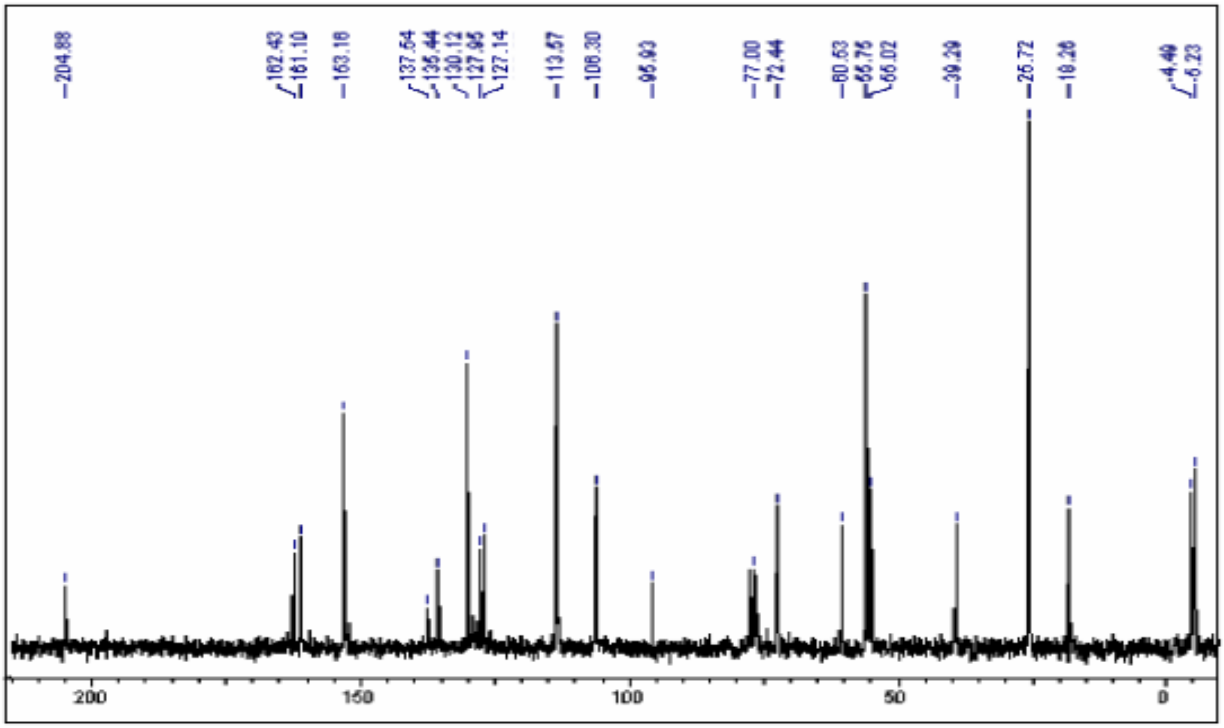
^{13}C NMR spectrum of the compound 145 ($CDCl_3$+CCl_4, 200 MHz)



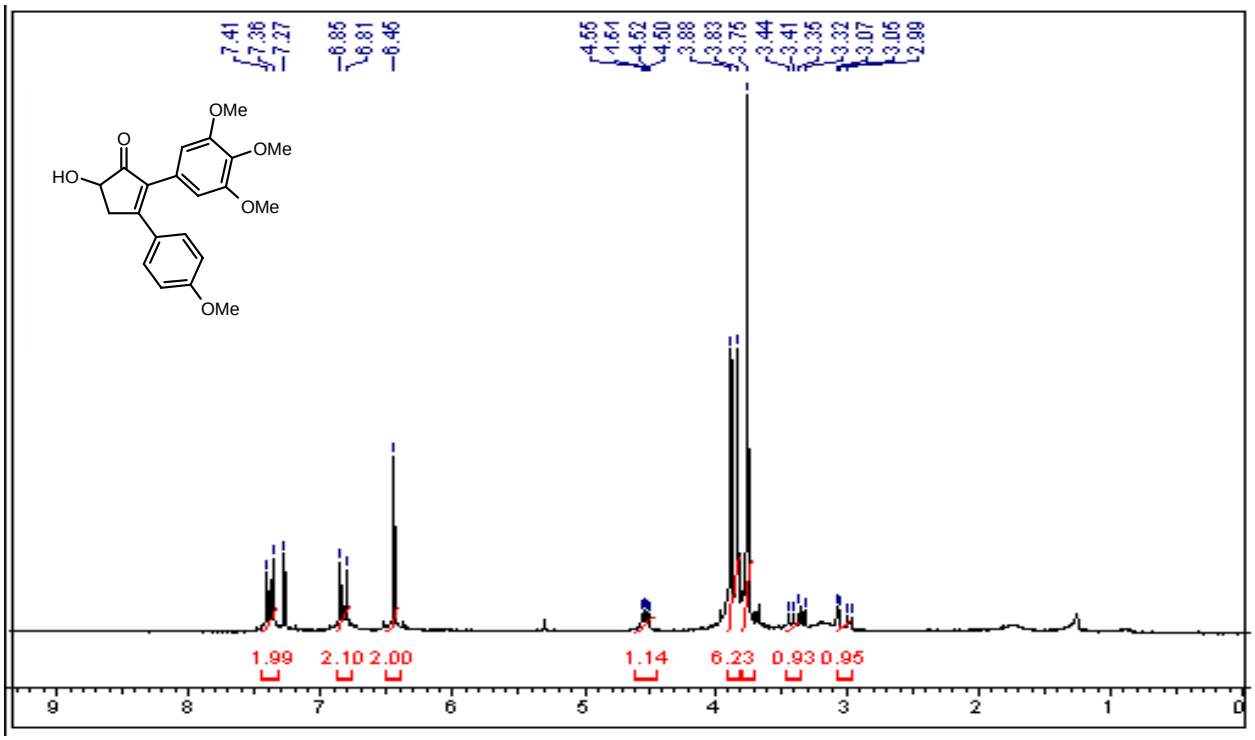
^{1}H NMR spectrum of the compound 146 ($CDCl_3$+CCl_4, 200 MHz)



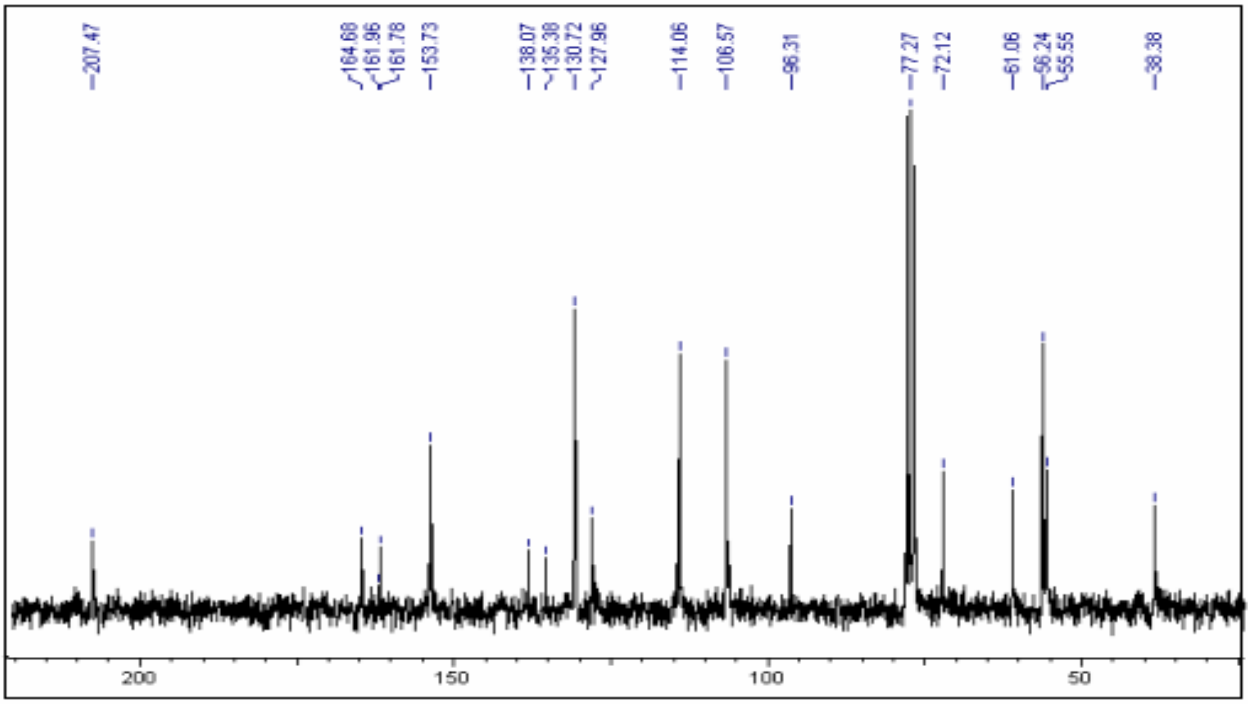
^{1}C NMR spectrum of the compound 146 ($CDCl_3$+CCl_4, 50 MHz)



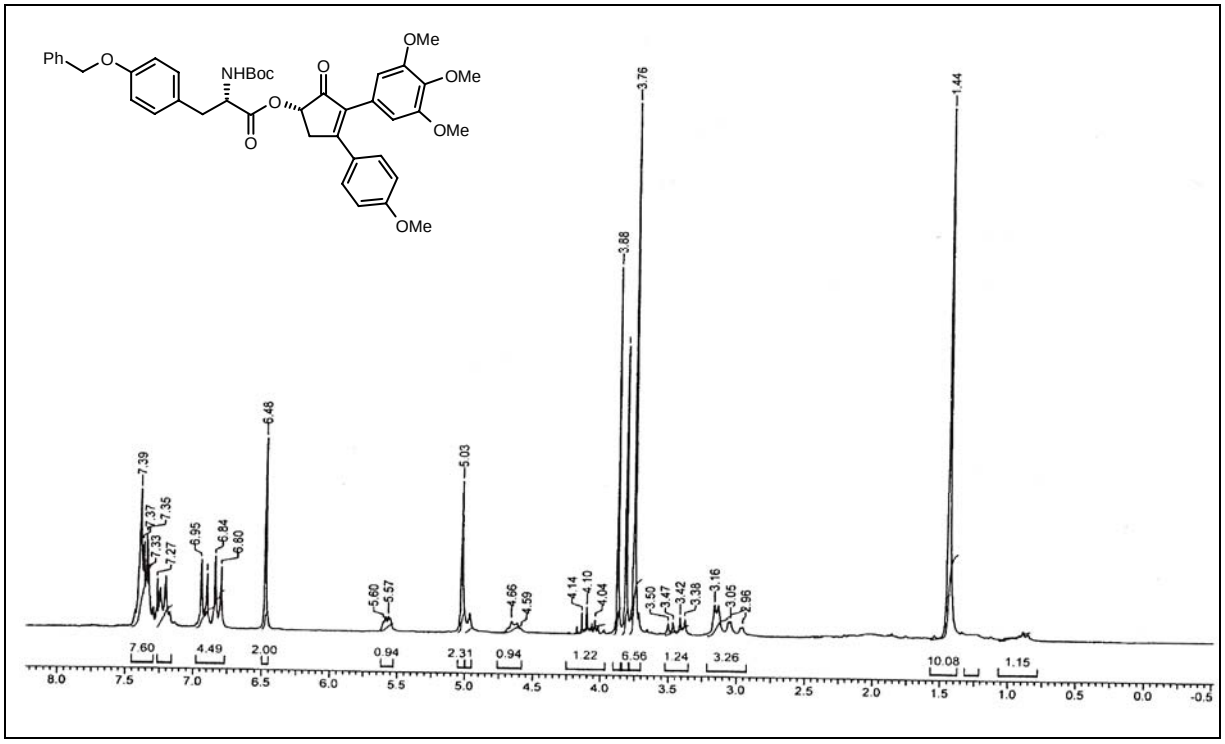
^{1}H NMR spectrum of the compound 147 ($CDCl_3$+CCl_4, 200 MHz)



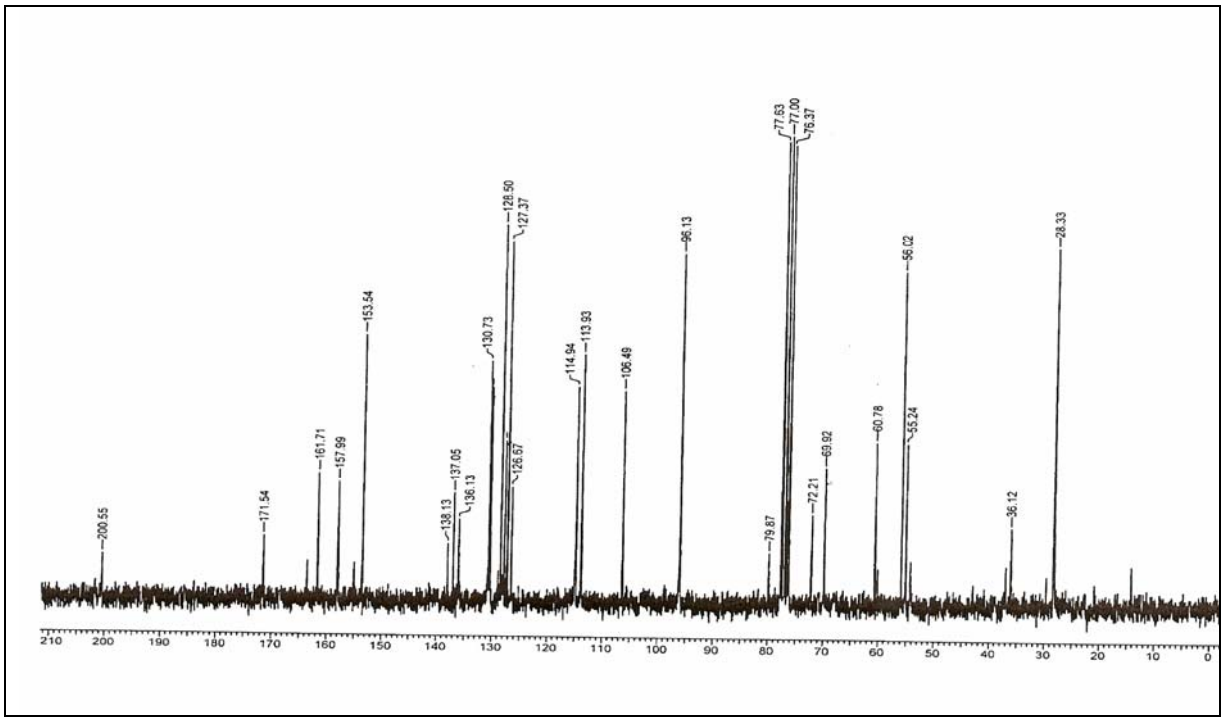
^{1}C NMR spectrum of the compound 147 ($CDCl_3$+CCl_4, 50 MHz)



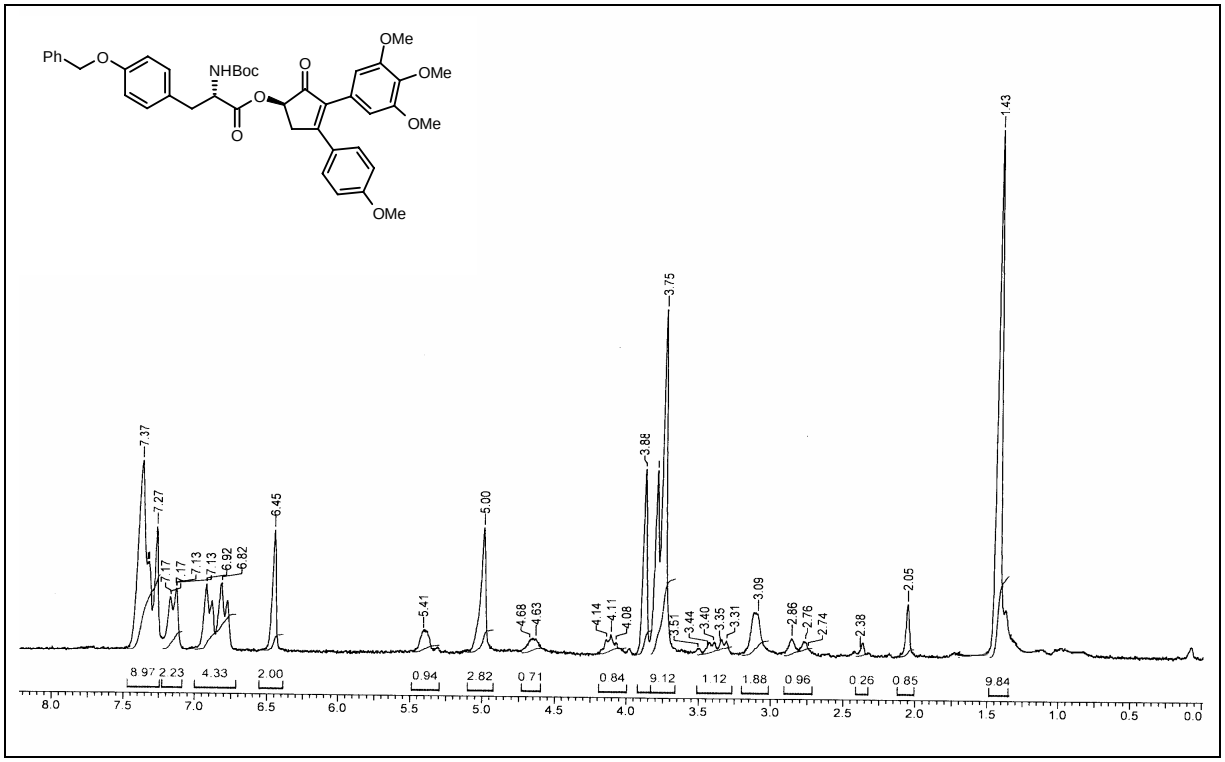
^{1}H NMR spectrum of compound 139 a ($CDCl_3$+CCl_4, 200 MHz)



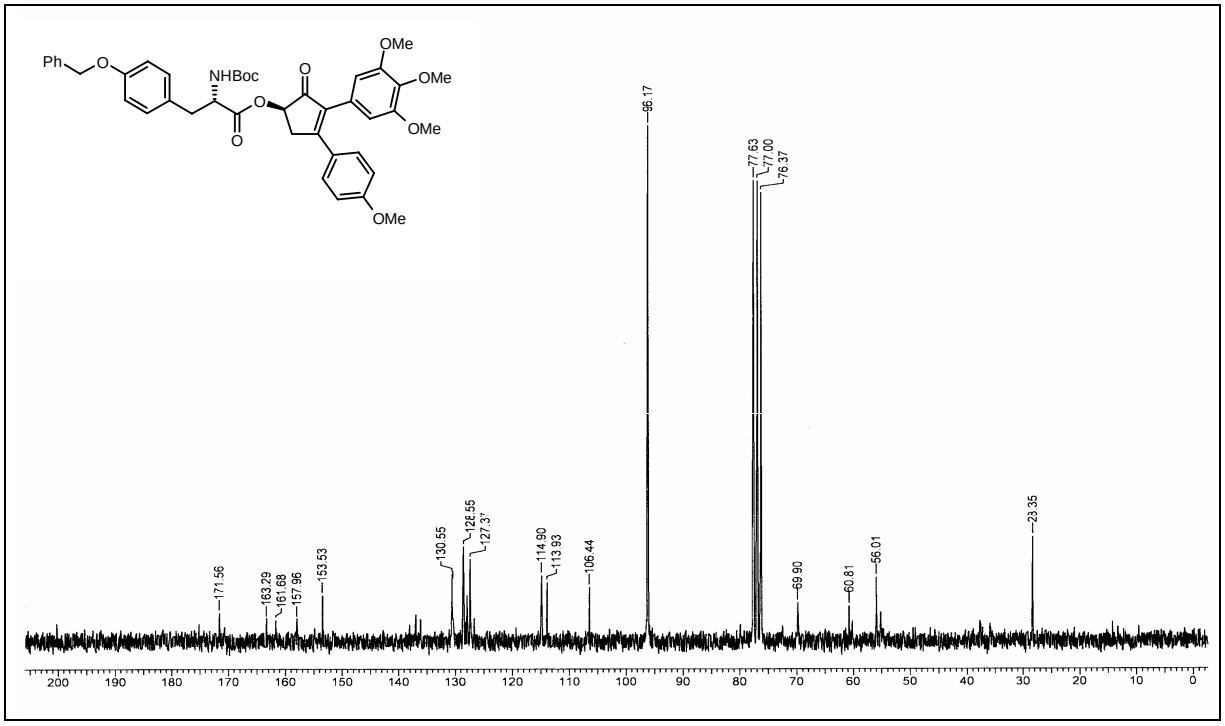
^{13}C NMR spectrum of compound 139 a ($CDCl_3$+CCl_4, 50 MHz)



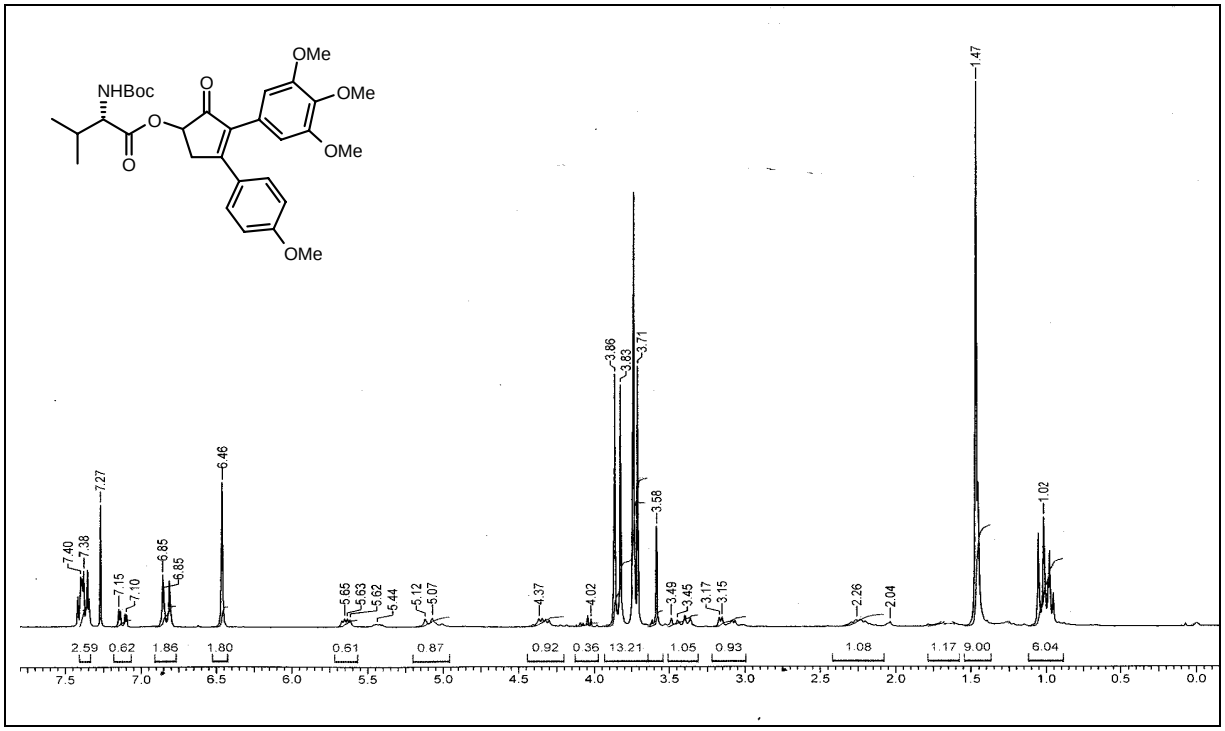
^{1}H NMR spectrum of compound 139 b ($CDCl_3$+CCl_4, 200 MHz)



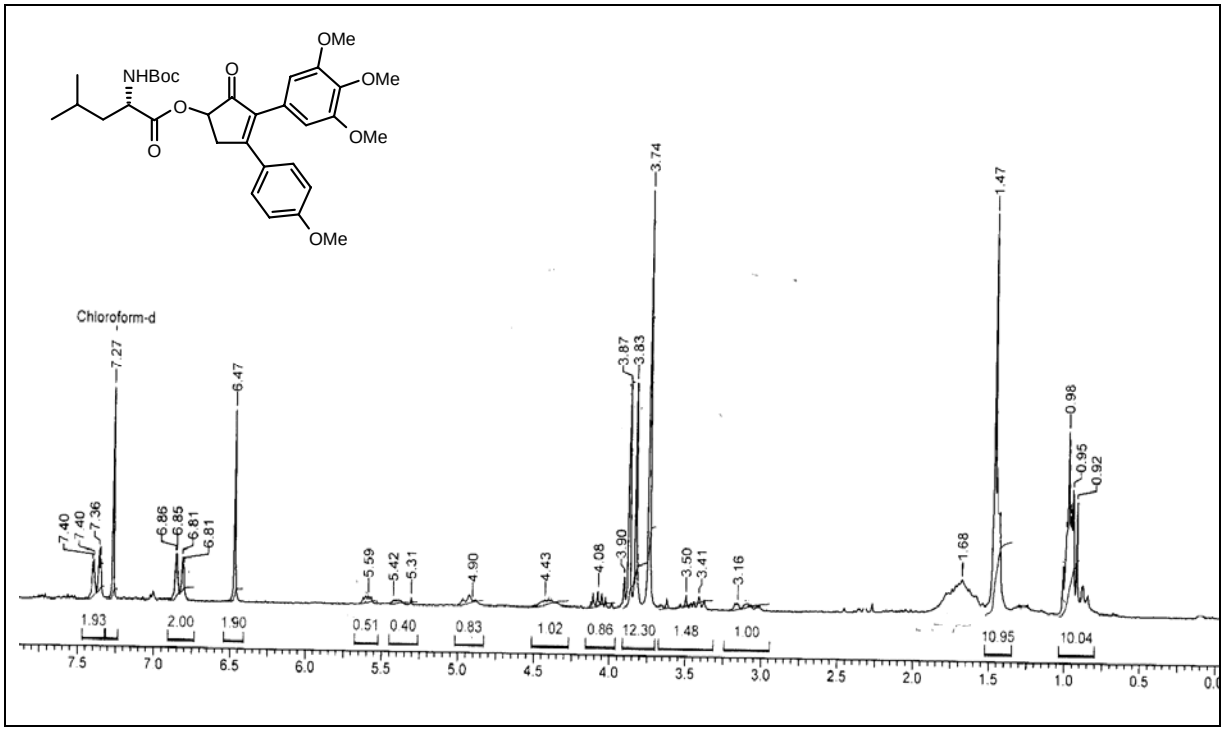
^{13}C NMR spectrum of compound 139 b ($CDCl_3$+CCl_4, 50 MHz)



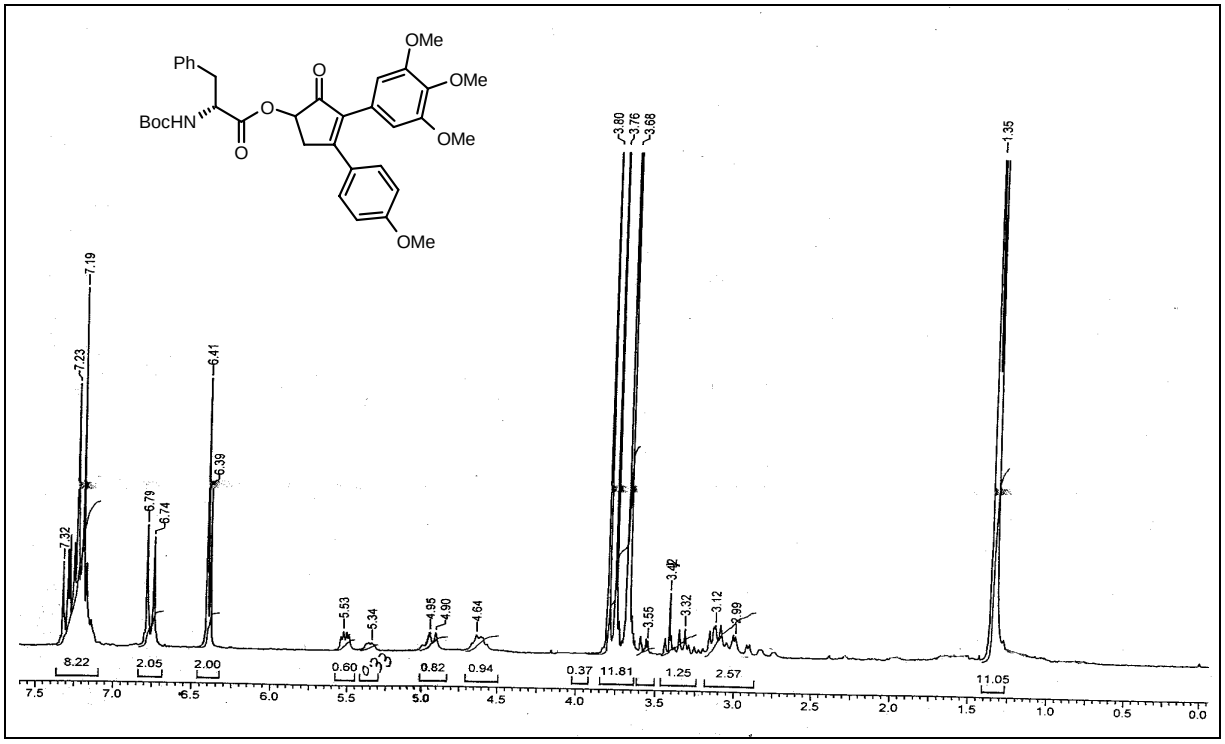
^{1}H NMR spectrum of compound 139 c ($CDCl_3$+CCl_4, 200 MHz)



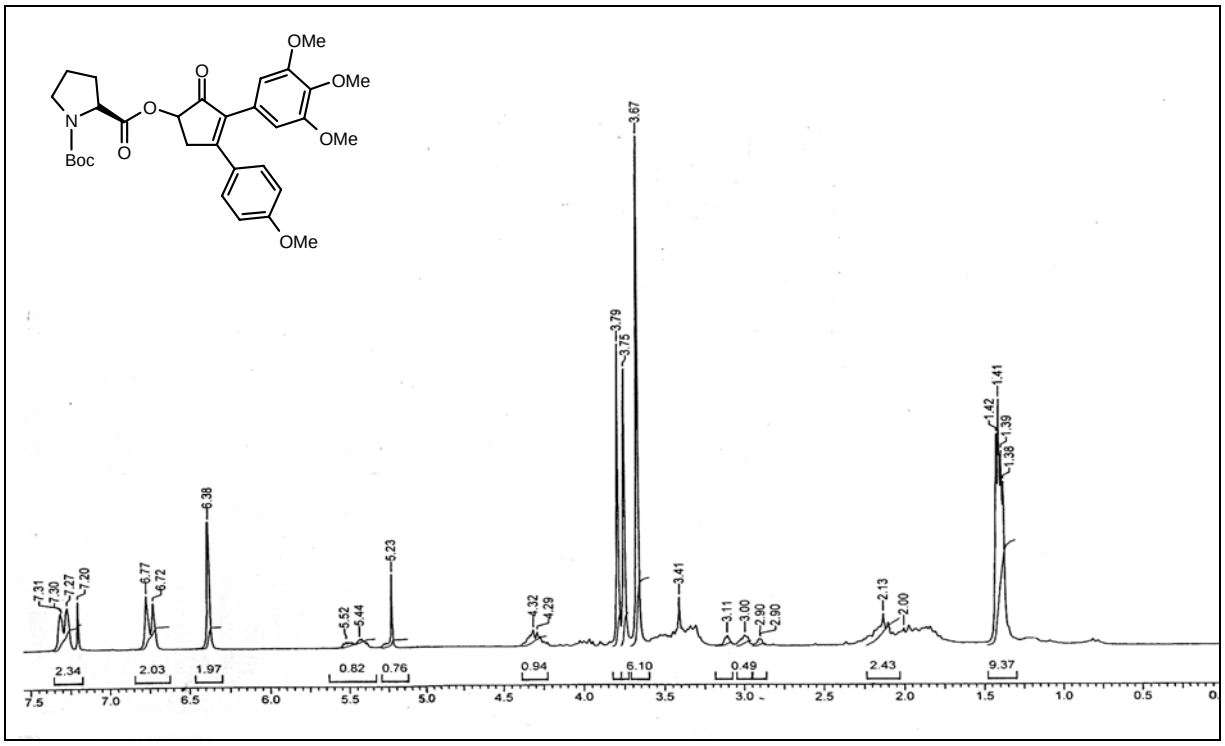
^{1}H NMR spectrum of compound 139 d ($CDCl_3$+CCl_4, 200 MHz)



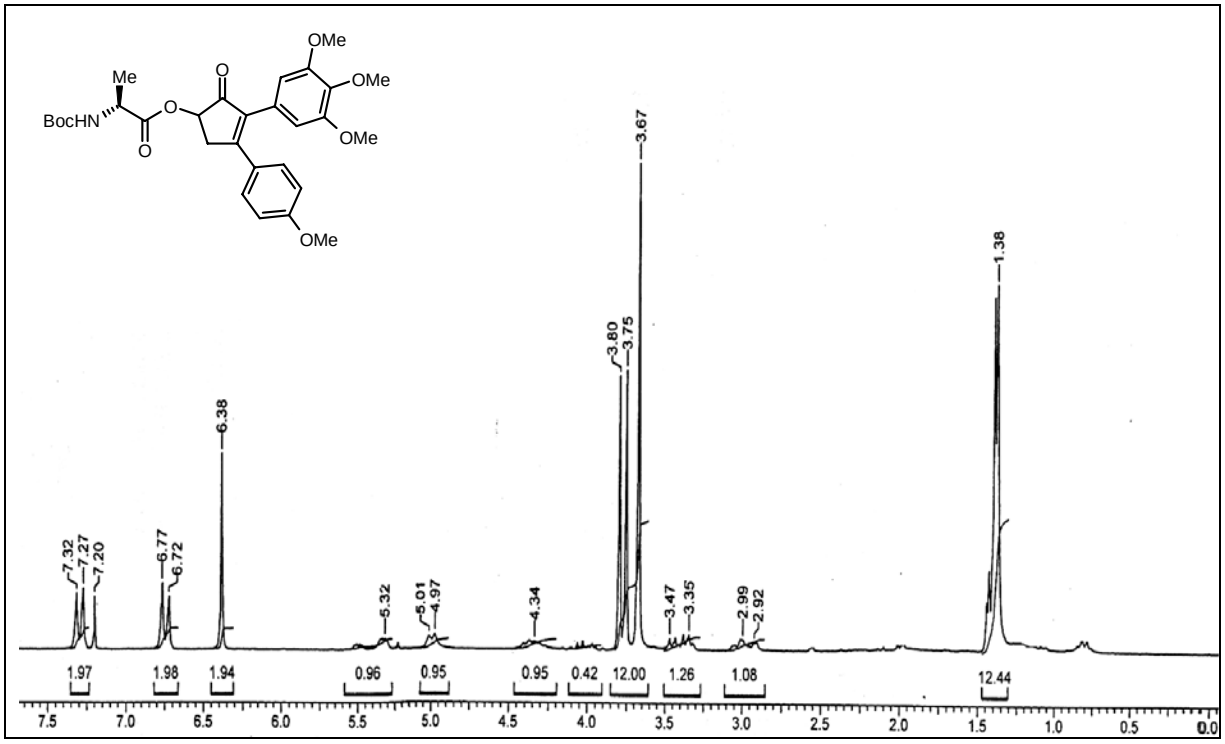
^{1}H NMR spectrum of compound 139 e ($CDCl_3$+CCl_4, 200 MHz)



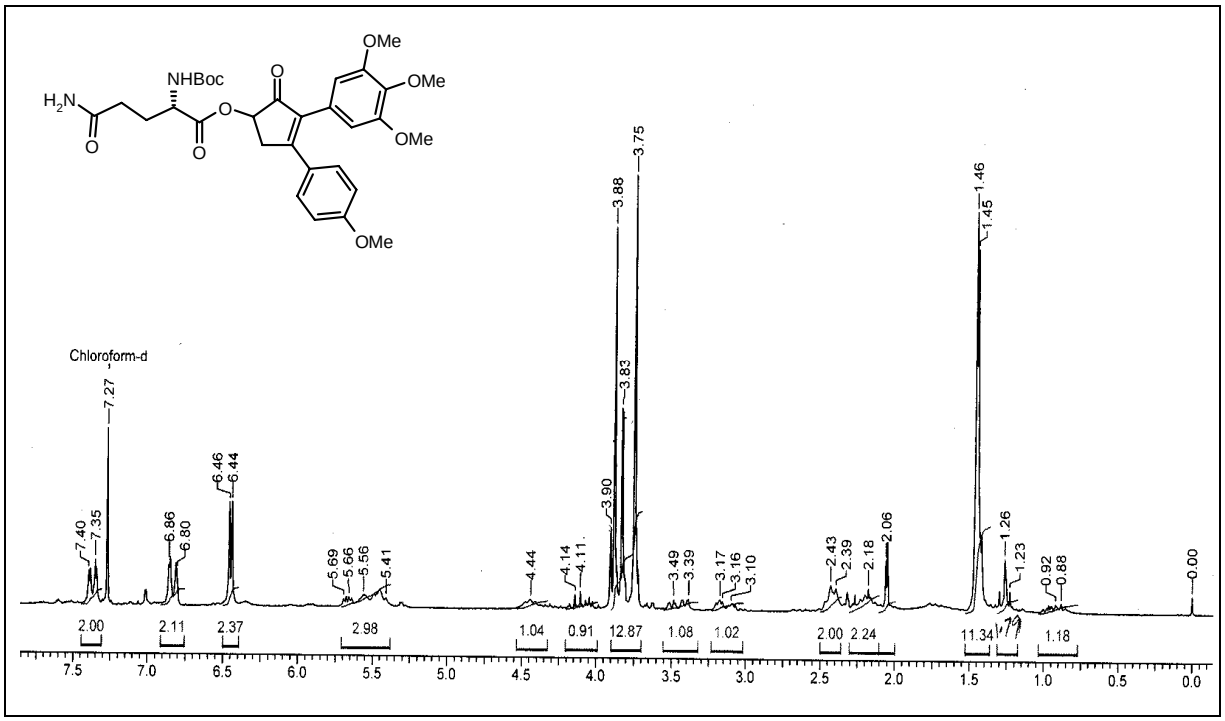
^{1}H NMR spectrum of compound 139 f ($CDCl_3$+CCl_4, 200 MHz)



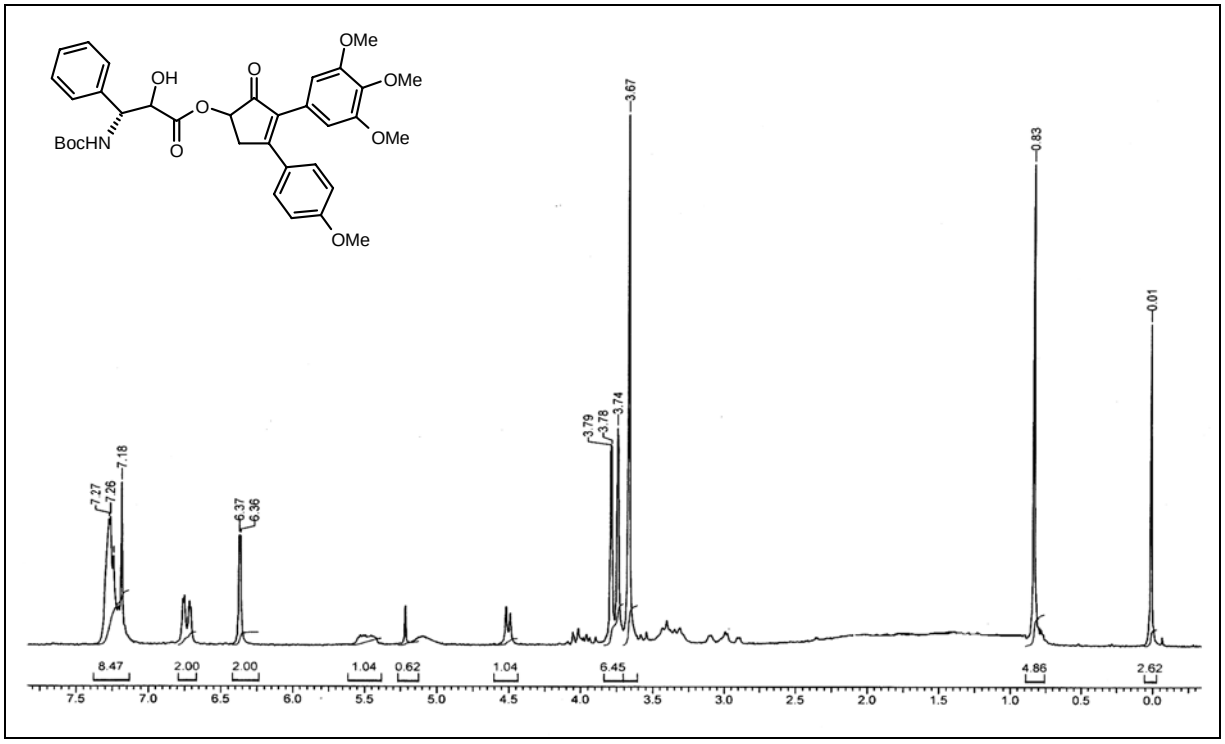
^{1}H NMR spectrum of compound 139 g ($CDCl_3$+CCl_4, 200 MHz)



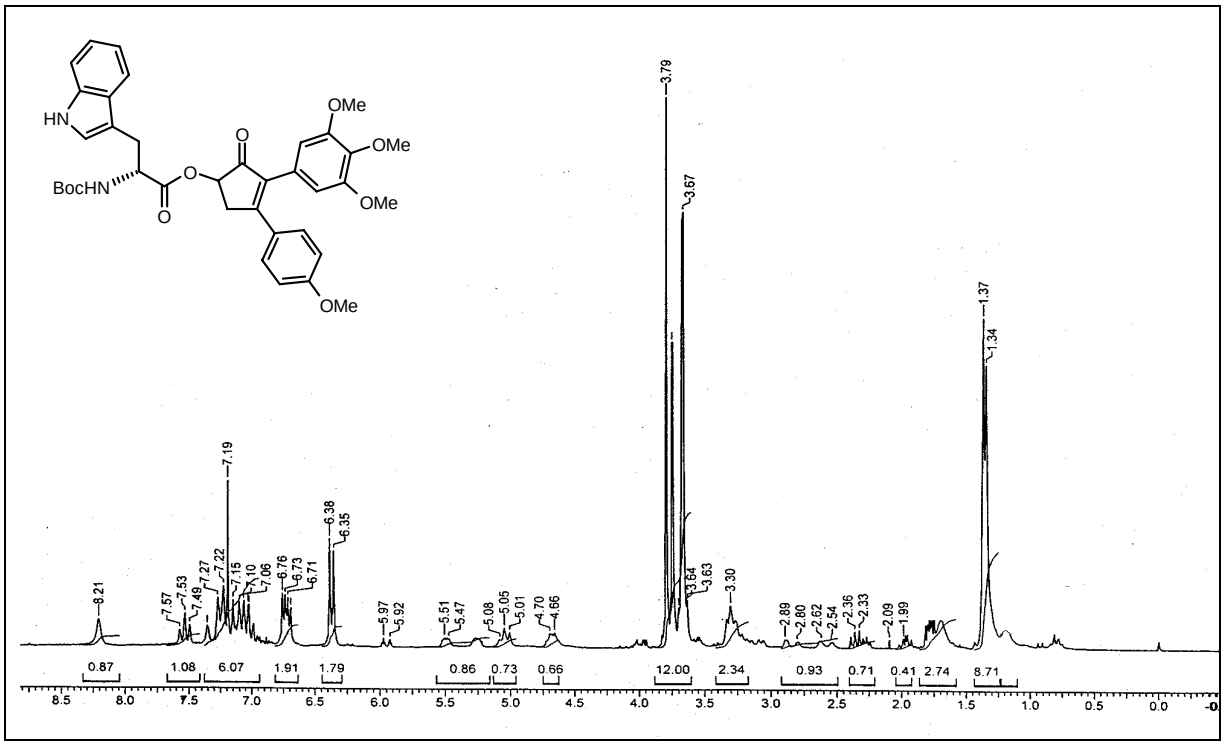
^{1}H NMR spectrum of compound 139 h ($CDCl_3$+CCl_4, 200 MHz)



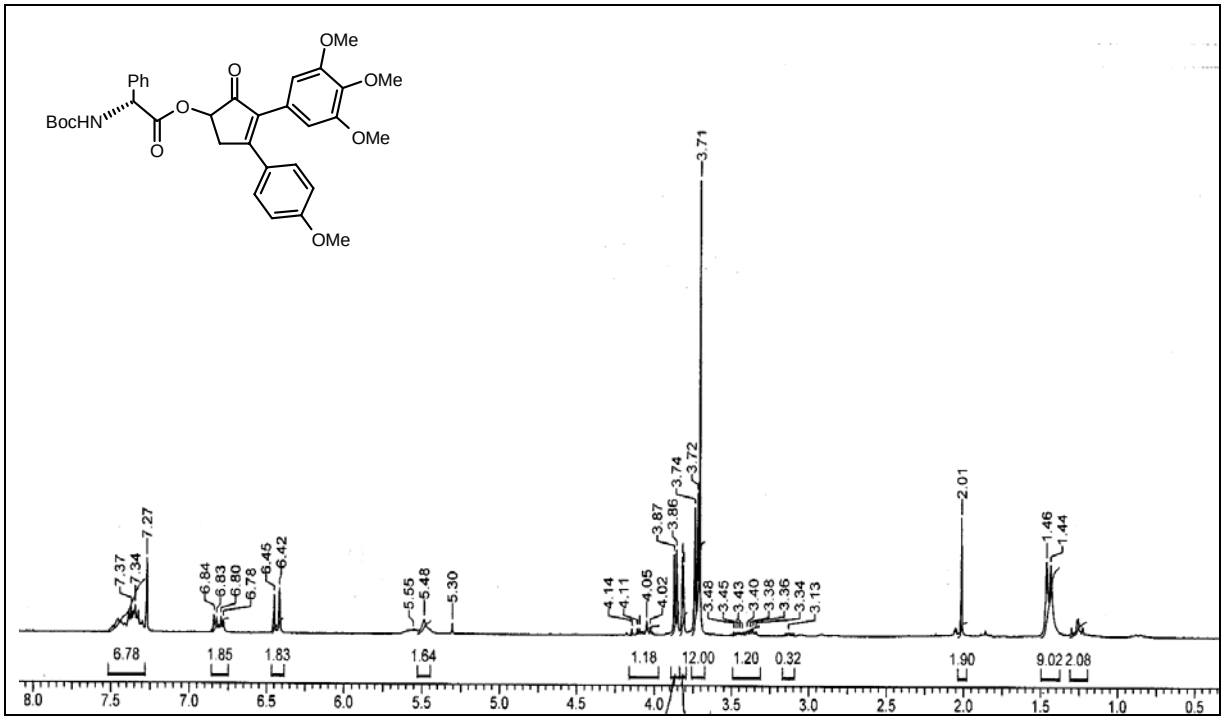
^{1}H NMR spectrum of compound 139 i ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 139 j ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 139 k ($CDCl_3$+CCl_4, 200 MHz)



1.3.6: REFERENCES:

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CHAPTER - I

SECTION - II

NEW 5- HYDROXY-3-(4-METHOXYPHENYL) 2-(3,4,5-TRIMETHOXYPHENYL)CYCLOPENT-2-EN-1-ONE DERIVATIVES WITH POTENTIAL ANTICANCER ACTIVITY

PART - B

RESOLUTION OF 5- HYDROXY-3-(4-METHOXYPHENYL) 2-(3,4,5-TRIMETHOXYPHENYL)CYCLOPENT-2-EN-1-ONE DERIVATIVES

1.4.1: INTRODUCTION:

The importance of obtaining optically pure materials hardly requires restatement. Manufacture of chemical products applied either for the promotion of human health or to combat pests that otherwise adversely impact on the human food supply is now increasingly concerned with the enantiopurity. A large proportion of such products contain at least one chiral center. To show importance of single-enantiomer drugs, Sujan Ba, Director of Chiral Chemistry Consulting Services at the consulting firm Technology Catalyst International (TCI) measured their appearance among the top-selling drugs[1]. Of the top 100 drugs world wide, 50 are single enantiomers. Their sales were $ 42.8 billion in 1997 i.e. 50 % of the total sales of $ 85.2 billion for these top 100 drugs. Single enantiomers remain important among the top 300, with 158 drugs accounting for $ 64.7 billion out of total sales of $ 124.4 billion. There is a move towards increasing single enantiomer use, wherever possible as a matter of choice as well as by dictates of regulates in bioactive materials for different reasons including the biological ones.

The reasons for producing optically pure materials include the following: i) biological activity is often associated with only one enantiomer ii) enantiomers may exhibit very different types of activity, both of which may be beneficial or one may be beneficial and other undesirable (fig.1) Racemic thalidomide consumed by expectant mothers as sedative in the early sixties created a generation of maltransformed babies because of teratogenicity of the (*S*)- enantiomer[2] which made the company to close down for ever and opened the eyes of scientists against the potential harm from the wrong enantiomer usage. Production of only one enantiomer allows the separation of the effects; iii) the unwanted isomer is at best enantiomeric ballast[3] gratuitously applied to the environment. iv) optically pure compound may be more than twice as active as the racemate because of antagonism, for example the pheromone of the Japanese beetle 144 where, as little as 1 % of the (S, Z)-isomer inhibits the (R, Z) isomer;[4] v) registration consideration;[5] vi) production of materials as the required enantiomer is now a question of law in certain countries, the unwanted enantiomer being considered as an impurity; vi) where the switch from racemate to enantiomer is feasible, there is the opportunity effectively to double the capacity of an industrial process; alternativly, in some cases, where the optically active

component of the synthesis is not very expensive, it may allow significant savings to be made in some other achiral but very expensive process intermediate; vii) improved cost benefit ratio; viii) the physical characterstics of enantiomers versus racemates may confer processing or the formulaton advantages.

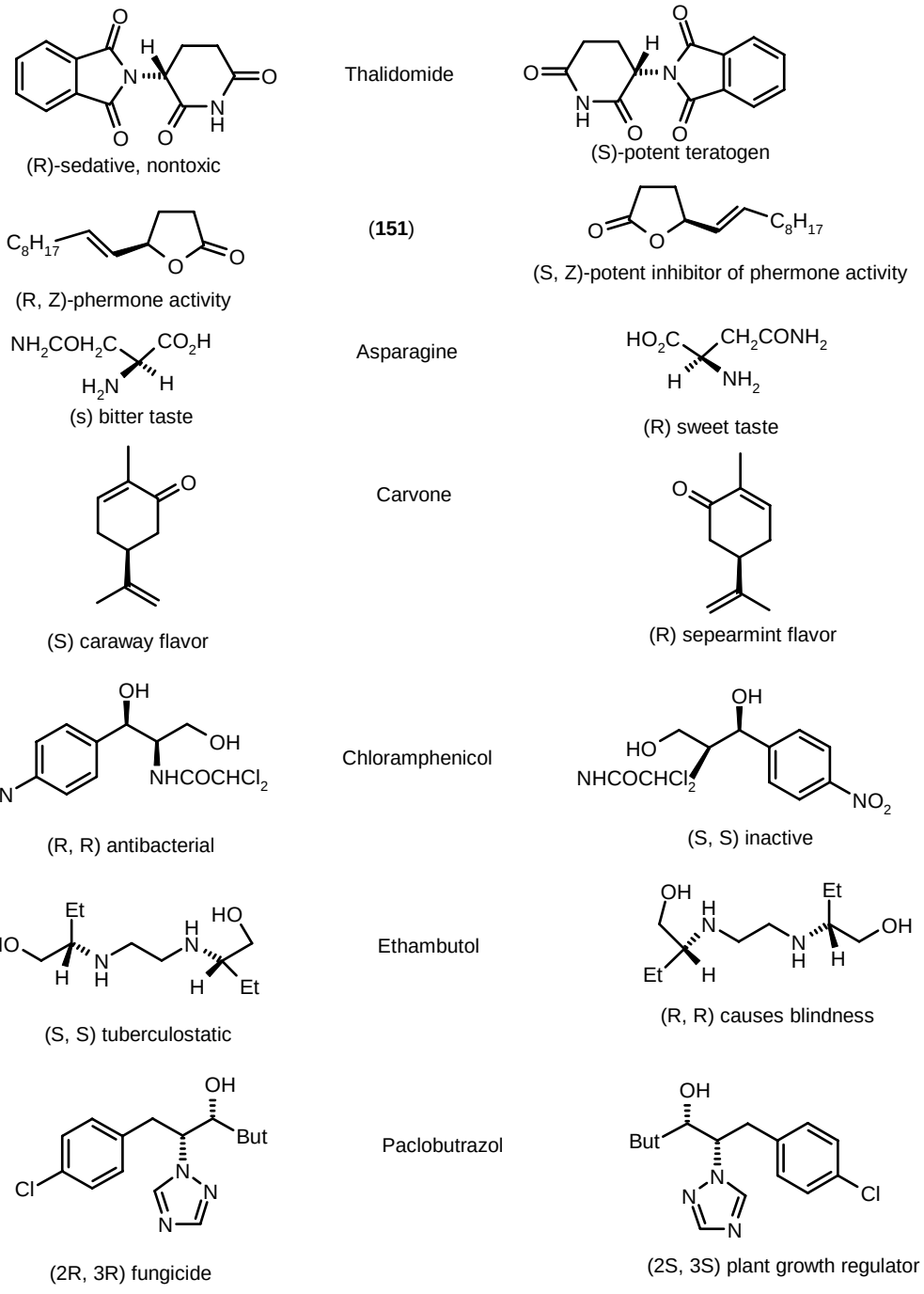


Fig 1

Methods for determination of absolute configuration of organic substances:

The determination of absolute configurations of organic compounds has become an important task of the natural products chemist as well as the synthetic chemist. There are a few physical methods, e.g. exciton chirality method[6] and X-ray crystallography that fill this need. The heavy-atom phase-shifted X-ray crystallographic analysis being the most general and reliable is nevertheless limited by the necessity to get adequate monocrystals and requires specialized equipment. There are also several chemical methods used to predict the absolute configuration of organic substances[7]. Mosher's method[8] involving study of NMR spectra of 2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid (MTPA) esters has been found very useful in many cases.

In recent years there has been a marked increase in the number of papers describing the use of NMR for the assignment of absolute stereochemistry of organic compounds. The general procedure consists of the derivatization of the substances of unknown configuration with the two enantiomers of an auxiliary reagent. The proton NMR spectra of the resulting diastereoisomeric derivatives are compared and the difference in chemical shifts is measured to give $\Delta\ \delta^{RS}$ values. Mosher proposed a configuration correlation model to assign the configuration of unknown compound from the shift difference of two diastereoisomeric derivatives. The specification of the carbonyl moiety as *R* or *S* follows from the application of the Cahn-Ingold-Prelog configurational nomenclature rules. Several auxiliary reagents (Fig 2) have been described for this purpose[9]. But very few have been subjected to detailed theoretical or experimental studies. There are many publications which guide the factors governing the efficiency of arylmethoxyacetic acids (AMAAs) for the determination of absolute configuration of alcohols by NMR[10,11] Among them, Mosher's method[8] using 2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid (MTPA) esters has been most frequently used. We have used here a chromatographic resolution method using chiral column.

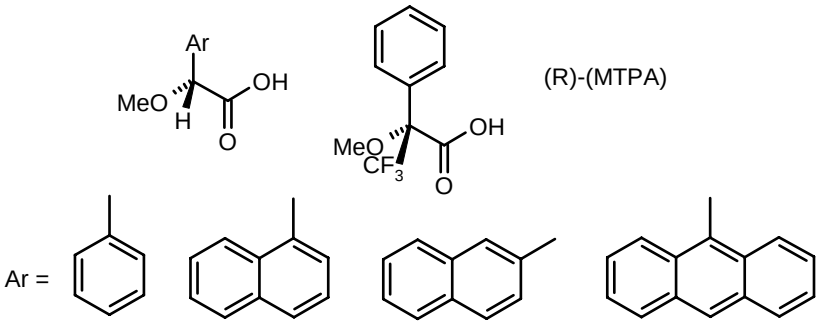
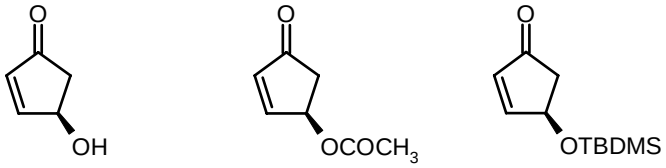


Fig 2

Methods for the preparation of optically pure hydroxycyclopentenone or its OH-protected derivatives:

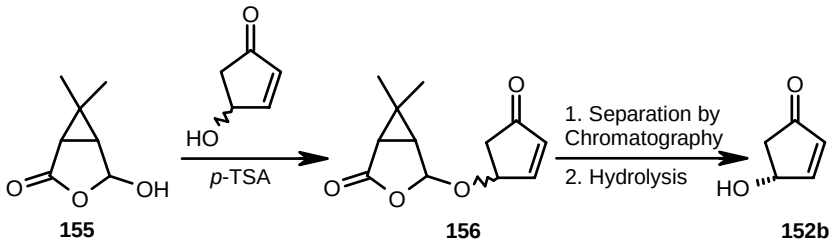
Large amount of literature is available for the preparation of optically pure 4-hydroxy-cyclopentenone building block **152a**, its O-acetate derivative **153** and its O-silylated derivative **154**. The various methods reported for the synthesis of **152a** and its derivatives **153** and **154** are mainly of two types *viz.* chemical methods and enzymatic method. Chemical methods include classical resolution of racemic **152a**, preparation from chiral natural products or resolved synthetic intermediates, by asymmetric synthesis and by kinetic resolution of (+ or -) -**152a** using chiral catalysts.



152a **153** **154**

The (*R*) cyclopentenone derivative **152a**, is obtainable by chemical[12] or chromatographic resolution,[13] transformation from D-tartaric acid (2*S*, 3*S*)-(-)- tartaric acid),[14] chemical kinetic resolution of racemic 4-hydroxycyclopent-2-en-1-one,[15] enzymatic kinetic resolution of the acetate[16] and asymmetric reduction of 2-cyclopentenone-1,3-dione[17] etc. Noyori *et al.*[18] resolved (±)-**152b** using bicyclic species caronaldehyde **155**, derived from (1*S*, 3*S*)-*trans* chrysanthemic acid. They found that diastereomeric adducts **156** of

racemic **252** with caronaldehyde could be easily separated on a silica gel column. The desired (*R*)-**152b** of 97 % ee was obtained in 88 % overall yield (scheme-1).

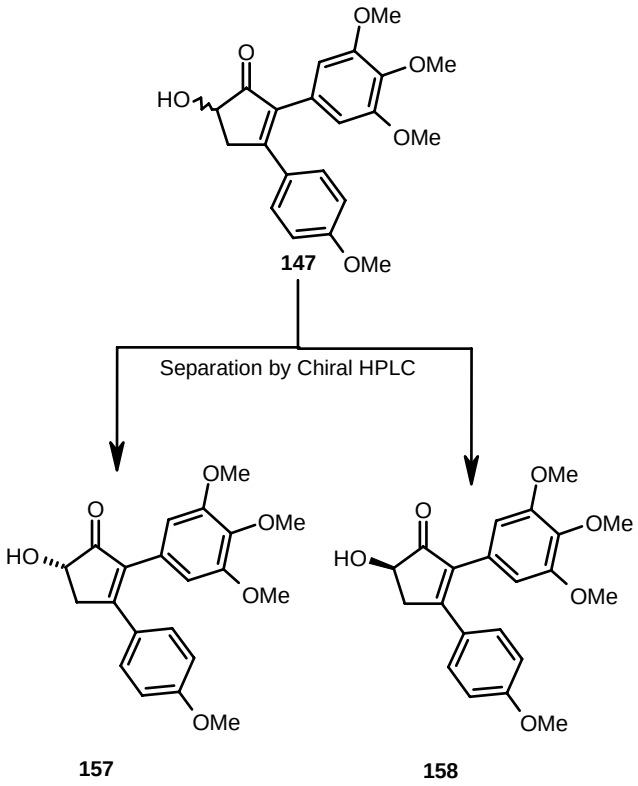


Scheme - 1

The use of caronaldehyde for the resolution of substituted 2-aryl/2, 3-diaryl-4/5-hydroxy cyclopentenone is not known. In our group the method for resolution of these compounds was explored. In continuation with this we resolved the alcohol **147** by the use of analytical chiral HPLC method we also separated its analogue **139** mixture of diastereomers could be separated by silica gel column chromatography and the purity of isomers were confirmed by chiral HPLC.

1.4.2: PRESENT WORK:

The resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**147**) was undertaken in our group by chemical method using caronaldehyde. The *R*-isomer **157** and *S*-isomer **158** were obtained by hydrolysis of the corresponding esters and chromatographic purification on silica gel. In continuation we have now developed the resolution method of alcohol **147** by using analytical chiral HPLC method, in which we have separated both the *R*-isomer **157** and *S*-isomers **158**. The analytical method was developed for alcohol **147** on CHIRALCEL OD-RH column showed separation of both enantiomers as seen in the chromatogram shown in (Fig. 3)



Scheme - 2

The enantioisomers **157** and **158** could be separated by preparative HPLC on CHIRALCEL OD-RH column and confirmed by optical rotation. The enantiomer eluted first (RT 10.4 min) showed rotation $[\alpha]^{25}_{D}$ + 21.33^{0} (c 0.55, $CHCl_3$) while the other one,

which eluted later (RT 11.1 min) had rotation $[\alpha]^{25}_{D}$ - 21.26^{0} (c 0.55, $CHCl_3$), the rotation of both the enantiomers **157** and **158** was in agreement with reported values.[19]

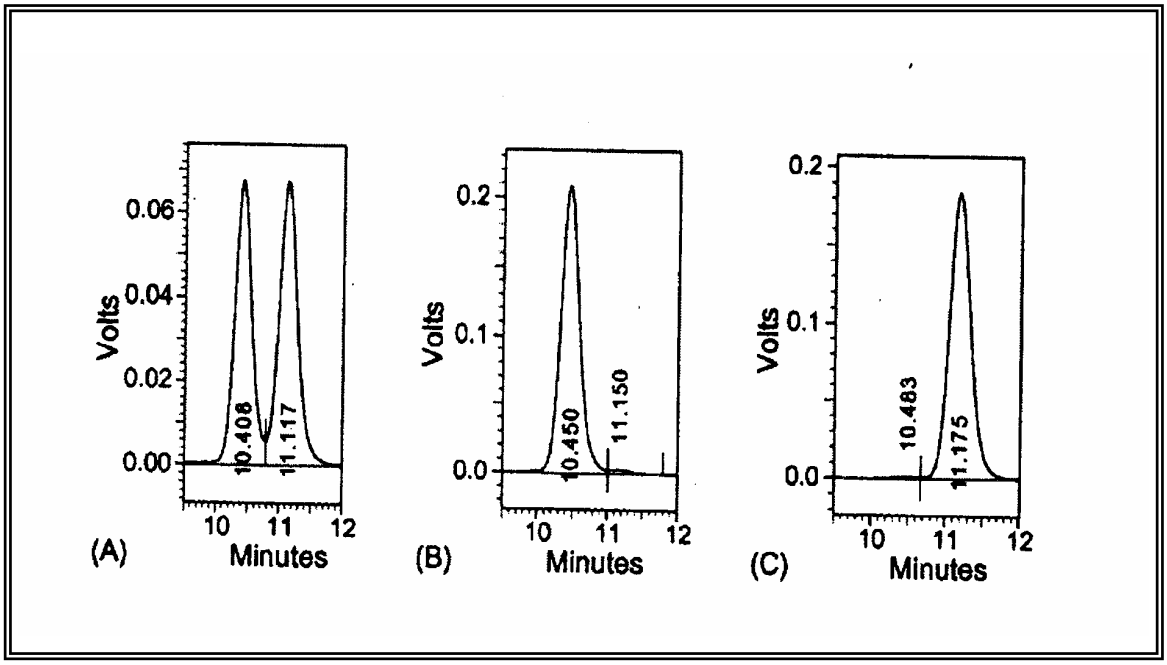
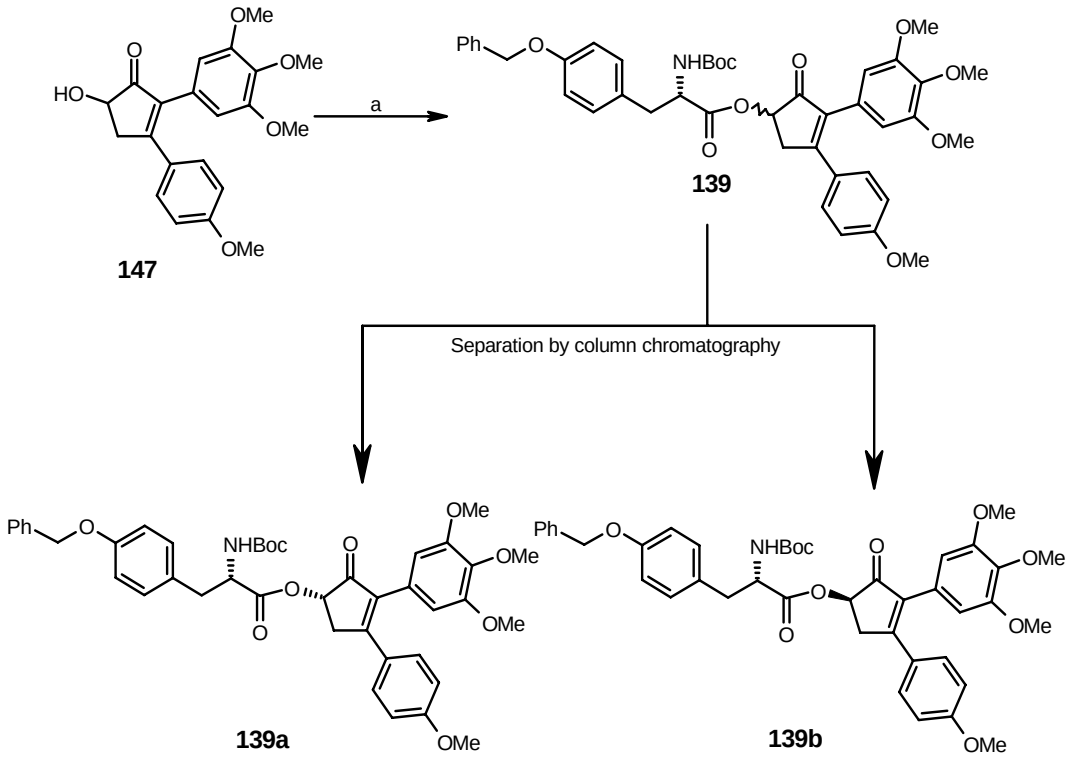


Fig. 3

We also developed a novel resolution method for the resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**147**) by using the Boc protected-O-benzyl tyrosine ester of alcohol **147**. The alcohol **147** was treated with Boc protected-O-benzyl tyrosine in the presence of EDCI in dichloromethane as a solvent at 0 ^{0}C to room temperature for 7 h the reaction was monitored by TLC, after work up the crude product was furnished (scheme - 2).

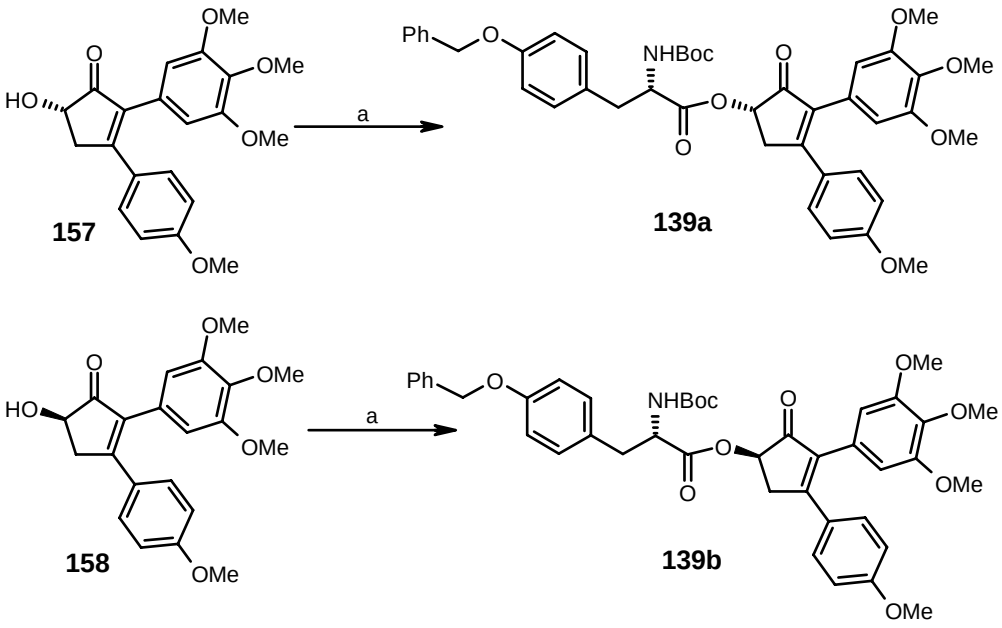
The compound **139** was separated by column chromatography using pet ether and ethyl acetate as an eluent, it provided the *R* and *S* isomers of ester as **139a** and **139b** which were fully characterized by ^{1}H NMR and ^{13}C NMR techniques and confirmed by optical rotation. The optical rotation for the isomers **139a** and **139b** are $[\alpha]^{25}_{D}$ + 17.56^{0} (c 0.55, $CHCl_3$) and $[\alpha]^{25}_{D}$ - 17.20^{0} (c 0.55, $CHCl_3$) respectively.



Reagents and conditions: a) Boc protected-O-benzyl tyrosine, EDCI, dry DCM, 0 ^{0}C - rt, 7 h

Scheme - 3

The diastereoisomers **139a** and **139b** were confirmed independently by making the esters of alcohols **157** and **158**. The alcohol **157** on esterification furnished the ester **139a** while the alcohol **158** on esterification gave ester **139b**. HPLC analysis indicated that *R*-isomer of alcohol gave diastereoisomer **139a** and *S*-isomers of alcohol **158** gave the diastereoisomer **139b** (scheme - 4) by direct comparison with the samples obtained by chiral separation of the mixture of diastereoisomers.



Reagents and conditions: a) Boc protected-O-benzyl tyrosine, EDCI, dry DCM, 0 ^{0}C - rt, 7 h

Scheme - 3

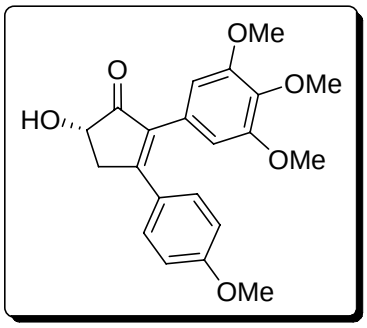
1.4.3. CONCLUSION:

Resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**147**) into its (R) and (S) isomers was achieved successfully by chiral HPLC method using CHIRALCEL OD-RH column and confirmed by optical rotation.. Similarly, resolution of amino acid derivative **139** was carried out successfully by column chromatography and confirmed HPLC and optical rotation.

1.4.4: EXPERIMENTAL:

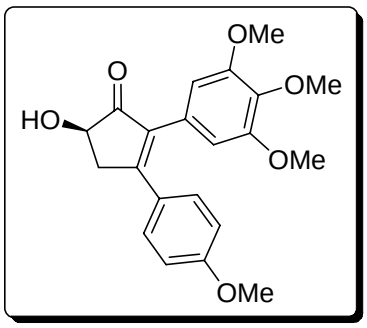
Compounds **157**, **158**, **139a** and **139b** were synthesized as per the procedures given in experimental part of section - II, part - A.

(S)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (157):



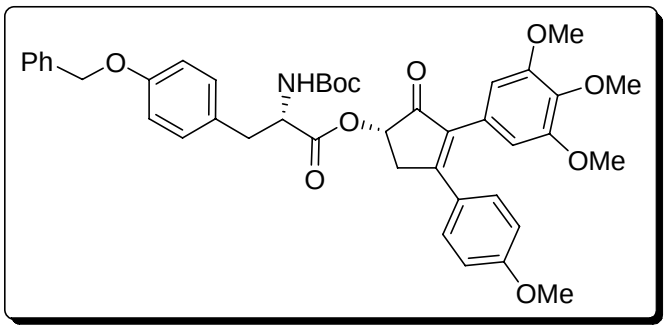
Nature: Yellow solid; **M. p.** 167 ^{0}C; [ά]$_D$ +21.33 (c 0.55, $CHCl_3$, ee > 98.64); **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.01 (dd, J = 18 Hz and 4 Hz, 1H), 3.39 (dd, J = 18 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 4.48 - 4.57 (m, 1H), 6.45 (s, 2H), 6.83 (d, J = 10 Hz, 2H), 7.39 (d, J = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 38.11, 55.28, 55.97 (2C), 60.79, 71.85, 106.30 (2C), 113.79 (2C), 126.95, 127.69, 130.45 (2C), 135.11, 137.80, 153.46 (2C), 161.51, 164.41, 207.20; **Mass** (m/e): 370 (M^+); **Anal. Calcd. for** $C_{21}H_{22}O_6$: C, 68.10; H, 5.99 %; **Found:** C, 66.18; H, 6.12 %.

(R)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (158):



Nature: yellowish solid; **M. p.** 192 ^{0}C; [ά]$_D$ +21.26 (c 0.55, $CHCl_3$, ee > 97.99).

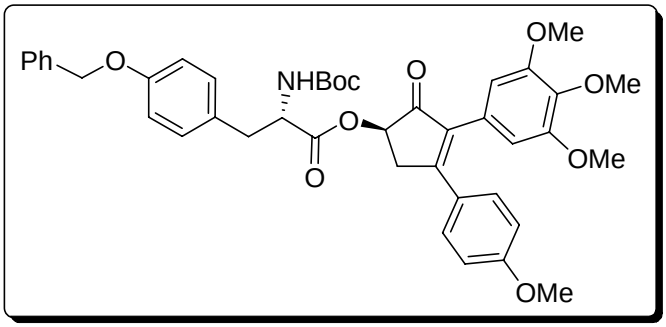
(S)-3-(4-Benzyloxy-phenyl)-2-tertbutoxycarbonylamino-propionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy phenyl)-cyclopent-3-enyl ester (139 a):



Nature: Yellow solid; **M. p.** 132 ^{0}C; $[\alpha]_D$ +17.56 (c 0.55, $CHCl_3$); **Yield:** 44 %; **IR** (chloroform)**:** ν_{max} 3370, 3006, 2971, 1749, 1708, 1602, 1582, 1512, 1454, 1413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.44 (s, 9H), 2.94 - 3.18 (m, 2H), 3.45 (dd, *J* = 24 Hz and 8 Hz, 1H), 3.76 (s, 6H), 3.82 (s, 3H), 3.88 (s, 3H), 4.02 - 4.16 (m, 1H), 4.57 - 4.68 (m, 1H), 4.95 - 5.07 (m, 3H), 5.52 - 5.64 (m, 1H), 6.48 (s, 2H), 6.82 (d, *J* = 8 Hz, 2H), 6.93 (d, *J* = 8 Hz, 2H), 7.15 - 7.43 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.83 (3C), 36.12, 37.10, 55.24, 56.02 (2C), 60.78, 69.92, 72.21, 79.87, 106.49 (2C), 113.93 (2C), 114.94 (2C), 126.67, 127.37 (2C), 127.95 (2C), 128.50 (2C), 130.10 (2C), 130.73 (2C), 136.13, 137.05 (2C), 138.13, 153.54 (2C), 154.90, 157.99, 161.71, 163.10, 171.54 (2C), 200.55; **Anal. Calcd. for** $C_{42}H_{45}NO_{10}$**:** C, 71.27; H, 6.41 %. **Found:** C, 71.15; H, 6.27; N, 1.84 %.

(R)-3-(4-Benzyloxy-phenyl)-2-tertbutoxycarbonylamino-propionic acid 4-(4-methoxy-phenyl)-2-oxo-3-(3,4,5-trimethoxy phenyl)-cyclopent-3-enyl ester (139 b):

Nature: Yellow solid; **M. p.** 125 ^{0}C; $[\alpha]_D$ -17.20 (c 0.55, $CHCl_3$); **Yield:** 42 %; **IR** (chloroform)**:** ν_{max} 3369, 3007, 2935, 1747, 1707, 1602, 1582, 1511, 1454, 1413 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.43 (s, 9H), 2.72 - 2.88 (m, 1H), 3.07 - 3.13 (m, 2H), 3.37 (dd, *J* = 26 and 8 Hz, 1H), 3.75 (s, 6H), 3.82 (s, 3H), 3.88 (s, 3H), 4.08 - 4.16 (m, 1H), 4.62 - 4.70 (m, 1H), 4.98 - 5.04 (s, 2H), 5.37 - 5.50 (m, 1H), 6.45 (s, 2H), 6.90 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 7.28 - 7.48 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 28.35 (3C), 35.95,



37.74, 55.23, 56.00 (2C), 60.81, 69.88, 72.54, 79.90, 106.37 (2C), 113.92 (2C), 114.88 (2C), 126.70, 127.37 (2C), 127.92 (2C), 128.54 (2C), 130.55 (2C), 130.72 (2C), 136.10, 137.07 (2C), 138.15, 153.55 (2C), 154.94, 157.80, 161.68, 163.1, 171.52 (2C), 200.50; **Anal. Calcd. for** $C_{42}H_{45}NO_{10}$**:** C, 71.27; H, 6.41; N, 1.98 %. **Found:** C, 71.12; H, 6.32; N, 1.81 %.

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CHAPTER - I

SECTION - III

BIOLOGICAL ACTIVTY OF DESIGNED NCEs AS ANTICANCER AGENTS

1.5.1: INTRODUCTION:

Cancer is a multi-step process in which multiple genetic alterations must occur, usually over a span of years, to have 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 sometimes failures of treatment. The search for new drugs with higher therapeutic index and lower capacity to induce 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 synthetic congeners were in the treatment and many of them are 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 which occur 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 cells and abort the life cycle have been discussed in the introduction of this chapter. In past few years different natural products were isolated and screened for their cytotoxicity and this research has brought up with number of well-known anticancer natural products such as podophyllotoxin (**8**), stignancin (**83**), paclitaxel (**20**), vinblastine (**6**), vincristine (**7**), camptothecin (**11**) 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.

Alkylating agents were one of the first cancer chemotherapeutic agents employed and are most widely 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 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 system and consequently abort the cell division.[3]

1.5.2: PRESENT WORK:

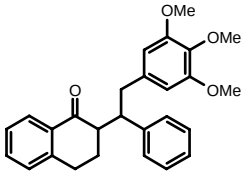
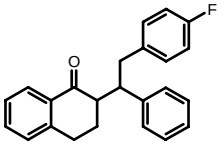
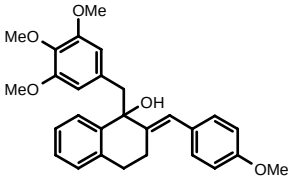
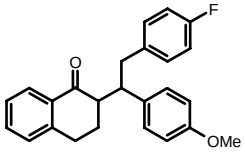
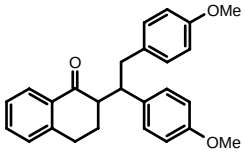
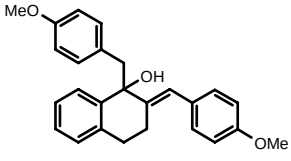
Our research aim is to come up with the synthesis of New Chemical Entities (NCEs) by a short synthetic pathway and which are featured with wide range of biological activity to contribute to global drug discovery program. With this target we have synthesized the hybrids of two small molecules which showed potential cytotoxicity. We have synthesized different analogues of the hybrids considering the different functional groups present in the NCEs as described in the section 1 and 2 of this chapter. The 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one was the lead molecule in our group,[4] to increase the solubility and cytotoxicity of this molecule we have synthesized the new analogues of this molecule with attachment of amino acids to the free hydroxy group. The present section describes structure activity relationship of arylidene tetralone derivatives as well as the analogues of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one, for which the cytotoxic activity was studied at Combichem Bioresource Center, National Chemical Laboratory, Pune and Dabur Research Foundation (DRF) Gaziabad, New Delhi respectively.

1.5.3: RESULTS AND DISCUSSION:

The synthesized new chemical entities of arylidene tetralone derivatives in section first of this chapter were tested for cytotoxicity against 3 human cell lines such as MCF-7 (breast cancer), A-431 (epidermal carcinoma) and HL-60 (leukemia). For the relevance of this chapter the methodology used for screening is MTT assay method, which is briefly described herein. The cell suspension at a concentration of 1 x 10^4 cells/ml was added in 96 well microtiter plates. Culture media used for HL-60, MCF-7 and A-431 were RPMI 1640, MEM and DMEM respectively. Plates containing culture media and tested compounds were incubated overnight for HL-60, 7-8 days for MCF-7 and 4 days for A-431 at 37 ^{0}C, 5 % v/v CO_2 and 95 % humidity. All the samples were taken in triplicates. 10 µl of MTT reagent (5 mg/ml) was added to each well and cells were incubated for 1 h at 37 ^{0}C. At the end of this period, 200 µl of acidified isopropanol was added and plates

were incubated for 4 h to solublize the purple formazan crystals produced. Absorbanc was measured at 290 nm with a Beckman coulter spectrophotometer.

Table-1: IC_{50} values (µg/ml) of NCEs derived from Grignard reaction method

Entry	Comp.	Structure	NCF-7	A-431	HL-60
1		**Combretastatin A-4**	219	275	259
2		**Taxol**	73	110	188
3		**Tamoxiphen**	75	176	168
4		**Doxorubicin**	416	428	**--**
5	**100 b**		**61.5**	>125	>125
6	**100 c**		>125	>125	>125
7	**101 e**		**62.5**	>125	>125
8	**100 f**		**72.5**	>125	>125
9	**100 g**		125	>125	>125
10	**101 g**		>125	**60**	>125

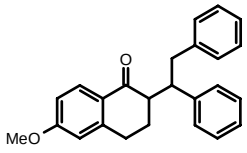
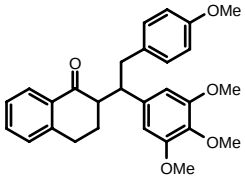
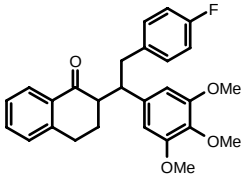
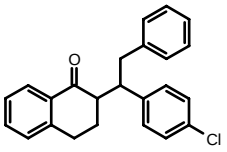
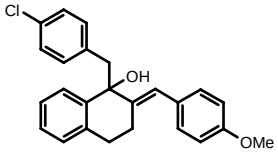
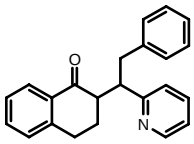
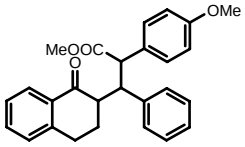
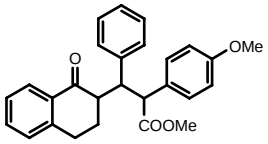
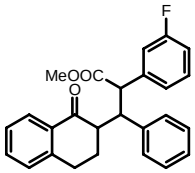
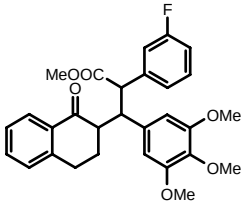
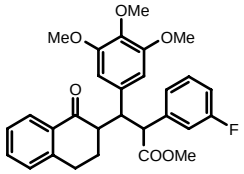
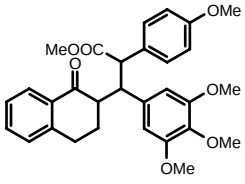
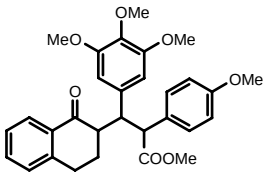
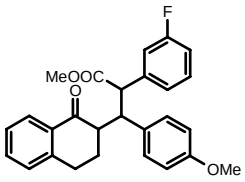
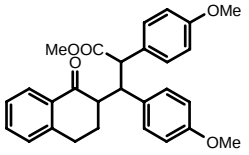
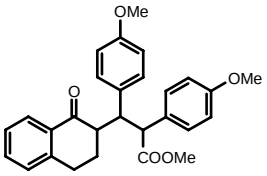
11	**101 h**		**81**	>125	>125
12	**100 k**		>125	>125	>125
13	**100 n**		>125	>125	>125
14	**100 p**		**70**	**125**	>125
15	**101 p**		**60.5**	**125**	>125
16	**100q**		**62.5**	**125**	>125

Table-1: IC_{50} values (µg/ml) of NCEs derived from LDA reaction method

Entry	Comp.	Structure	NCF-7	A-431	HL-60
1		**Combretastatin A-4**	219	275	259
2		**Taxol**	73	110	188
3		**Tamoxiphen**	75	176	168
4		**Doxorubicin**	416	428	--
5	**106 a**		>125	125	>125
6	**107 a**		>125	>125	>125
7	**106 b**		**100**	>125	>125
8	**106 c**		**75**	>125	>125
9	**107 c**		**62.5**	**125**	>125
10	**106 d**		**82.45**	>125	>125

11	**107 d**		**125**	>125	>125
12	**106 e**		>125	>125	>125
13	**106 f**		**125**	**56.2**	>125
14	**107 f**		**80**	>125	>125

All the new chemical entities (NCEs) were screened by plate assay method briefly described in the results and discussions. The data compilation of the in vitro studies has been depicted in table 1 and 2, for the compounds synthesized in section-I, A and B respectively and compared with well known anticancer agents such as combretastatin A-4, Taxol, Tamoxiphen and Doxorubicin.

Cytotoxic assay for derivatives of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one:

The cytotoxicity of amino acid derivatives of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one 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. 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 cyclopentenone derivatives in a CO_2 incubator for 72 hours. The concentrations of the cyclopentenone derivatives were in the range of 1 – 100 μg/ml. Controls, which were not treated with the cyclopentenone 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 ^{0}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).

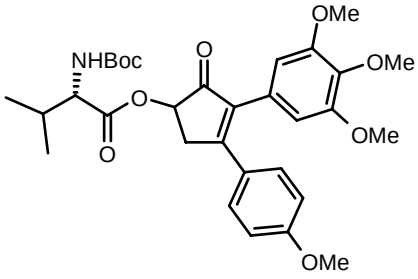
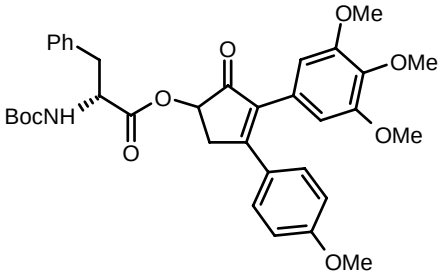
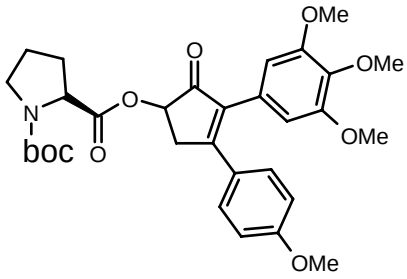
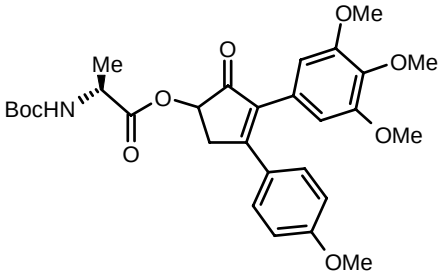
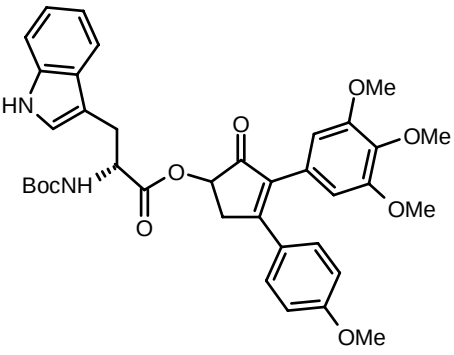
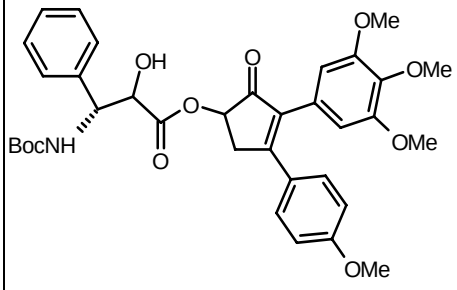
Thus, in each of the MTT cytotoxicity assays reported herein, the cytotoxicity percentage was calculated according to the above formula and was based on the proliferation of the

untreated controls, the value of which was taken as 100 %. A dose response curve was prepared and IC_{50} values determined graphically. Table 3 show the IC_{50} values with standard deviation.

Table-3: IC_{50} values of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one derivatives:

Entry	Comp.	NH3T3 (Normal)	HBL 100 (Breast)	A-549 (Lung)	Miapaca (Panc.)	K-562 (Luk.)	SW620 (Colon)	DU145 (Oral)	KB (Oral)	PAI (Ovary)	CHO (Normal)
1	**139c**	6.07	NA	2.23	NA	6.77	ND	NA	ND	**0.369**	ND
2	**139e**	8.76	4.95	NA	NA	**0.97**	**1.36**	NA	**1.23**	**0.624**	NA
3	**139f**	ND	ND	ND	ND	ND	**1.51**	NA	**0.51**	**1.65**	NA
4	**139g**	NA	NA	NA	NA	**1.68**	**1.59**	NA	**1.1**	**1.844**	NA
5	**139i**	5.39	NA	**1.51**	NA	**1.7**	ND	NA	NA	**1.916**	ND
6	**139j**	NA	NA	NA	NA	NA	NA	NA	NA	3.7	NA

Table-4: Structures of NCEs:

S. No.	Structure	S. No.	Structure
139c		**139e**	
139f		**139g**	
139i		**139j**	

1.5.4: CONCLUSION:

The presented biological data revealed that, the designed new chemical entities using hybrid technology (section-I) showed promising anticancer activity as compared to well known anticancer agents such as combretastatin A-4, Taxol, Tamoxiphen. Some of the derivatives showed considerable anticancer activity. The amino acid derivatives of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one retained their anticancer activity with solving the problem of water solubility. These results contribute a novel class of compounds with potential anticancer activity to the global drug discovery program.

1.5.5: REFERENCES:

1. *Cancer and chemotherapy*, (Academic press) **1981**, *3*, chap. 1-11, pp 1-293.
2. a) Suar, J. M.; Smith, R. L.; Bao, J.; Katting , M. J.; Kuster, R. K.; Mcclure, T. D.; Mayersohn, M.; Sipes, J. and Glenn, I. *Drug Metabolism* **1997**, *25*, 732. b) Spencer, S. R.; Xue, L.; Klenz, S. and Talahay, P. *Biochem. J.* **1991**, *273*, 711.
3. Wang, W. and Ballatori, N. *Pharmacological Reviews* **1998**, *50*, 335.
4. Gurjar, M. K.; Wakharkar, R. D.; Singh, A. T.; Jaggi, M.; Borate, H. B.; Shinde, P. D.; Verma, R.; Rajendran, P.; Dutta, S.; Singh, G.; Sanna, V. K.; Singh, M. K.; Srivastava, S. K.; Mahajan, V. A.; Jadhav, V. H.; Dutta, K.; Krishnan, K.; Chaudhary, A.; Agarwal S. K.; Mukherjee, R. and Burman, A. C. *J. Med. Chem.* **2007**, *1138*, 184.

CHAPTER - II

SYNTHESIS OF FURANONE AND AZOLE DERIVATIVES AS ANTIFUNGAL AGENTS

2.0.1: ANTIFUNGAL AGENTS: GENERAL INRODUCTION:

Fungal infections in human range from the superficial and common, such as dermatophytoses and onycomycoses, to deeply invasive and disseminated, such as candidiasis and aspergillosis. In the past 20 years the frequency of systemic fungal infections increased dramatically along with the number of invasive, mostly opportunistic species. Most of the presently used antifungal agents are associated with severe side effects mainly due to the lower degree of specificity towards the desired target. On longer use, resistance gets developed, especially in the opportunistic fungi active during the immune suppressive stage. This has attained greater importance especially because of the HIV infected patients, where the resistance goes down easing out the entry of the active fungi. The main factor for the increase is the proliferation of severely immunocompromised patients either with AIDS, undergoing cancer chemotherapy or immunosuppressive therapy for organ transplantation. The additional factors include treatment with broad spectrum antibacterial drugs or glucocorticosteroids, invasive procedures such as surgery, in-dwelling catheters or prosthetic devices; and parenteral nutrition or dialysis. The higher incidence of several fungal infections that was noted in the late 1940's with an advent of anti-bacterial agents first and steroid therapy later, continued to increase throughout ensuing decades. The more aggressive and frequently used broad spectrum antibiotics, antineoplastic and immuno-suppresssive chemotherapy also augmented systemic mycosis as mentioned earlier. Data from ongoing National Nosocomial Infection Surveillance System conducted in the United States showed an enormous increase of 487 % in candida blood stream infection between 1980 and 1989. Similar situation would prevail in other countries including India though the exact statistics are not available.[1-4]

PATHOGENS

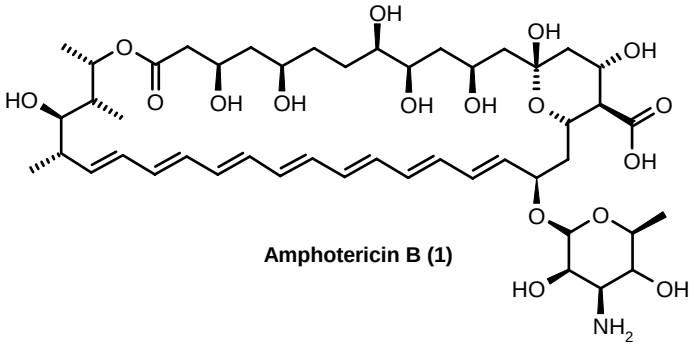
The major pathogen causing the fungal infections include *Candida ablicans* which is normally a commensal of the oral cavity and gastro-intestinal tract of humans. Non-*albicans Candida species like C. glabrata, C. tropicalis, C. krusei* have also increased

considerably. Other pathogens which are involved in serious fungal infections are *Aspergillus* (e.g. *A. niger, A. flavus* etc.), *Histoplasma capsulatum* and *Cryptococcus neoformans*. Emerging opportunistic pathogens include *Fusarium* and *Thrichosporon* both of which are known to infect neutropenic patients and which are commonly associated with disseminated infections. Other fungi like *Rhizopu* and *Mucor* are also known today to cause severe infections.[5] The fungal infections are the important causes of morbidity and mortality in hospitalized patients. Candidiasis is the 4th most common blood culture isolate in US hospitals and pulmonary aspergillosis is the leading cause of death in bone marrow transplant recipients. This clearly shows how important is the control of fungal infections in humans.[6,7] The increase in life threatening fungal infections has brought about an increased use of anti-fungal drugs and the pressing need for newer, broad spectrum, fungicidal agents that can be used empirically in immuno-compromised patients. The difficulties encountered in the diagnosis, culturing, and susceptibility testing of fungi has necessitated empirical treatment of suspected fungal infections with suitable anti-fungal drugs in order to avoid future complications.[8,9]

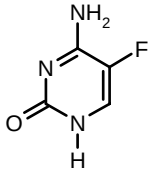
None of the existing systemic anti-fungal agents satisfies the medical need completely; there are weaknesses in the spectrum, potency, safety and pharmacokinetics properties. Each and every anti-fungal drug available today has its own advantages and disadvantages. So there is a definite need for superior anti-fungal drug to treat the ever increasing invasive fungal infections especially those caused by virulent and resistant fungi.

Significant antifungal chemotherapy began in 1903, with the successful use of potassium iodide (KI) for the treatment of sporotrichosis. There was little progress for the next 50 years until nystatin, the first useful polyene, was introduced in 1951. This was soon followed by Amphotericin B (**1**) in 1956, still the standard against which new systemic antifungals are compared. Except for the development of flurocytosine (**2**) (1964), there was little progress until the early 1970s and the development of the azole drugs, began with miconazole (**3**) (1978), econazole (**4**) and ketoconazole (**5**) (1981) and brought the agents fluconazole (**6**) (1990) and itraconazole (**7**) (1992), which can be given orally and have increasing potency, decreased toxicity and a broader spectrum of activity. Recent studies have examined ways to ameliorate the well-known toxicities of Amphotericin B

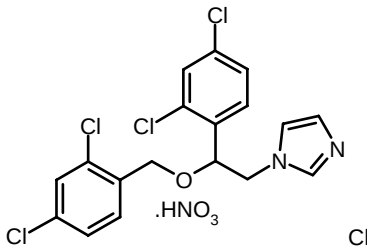
(**1**). A new approach has been to complex the drug with lipids or entrap it in liposomes. Glucans are glucose homopolymers of β-(1, 3)-linked residues with occasional sidechains involving β-(1, 6)-linkages and are major components of the fungal cell wall. Polymerization is catalyzed by β-(1,3)-glucan synthase which has at least two functional components, a catalytic component that acts on the UDP- glucose substrate, and a regulatory 21 kDa GTP-binding protein (Rholp) that is activated by cell wall defects and may link glucan synthesis to the cell cycle via a phosphorylation/dephosphorylation relay system. There are two glucan synthatase systems in S. cerevisiae, and most likely in pathogenic fungi.[10-20]



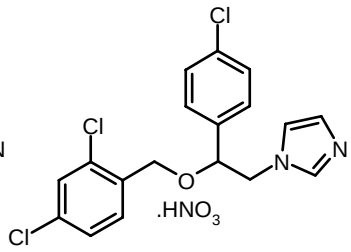
Amphotericin B (1)



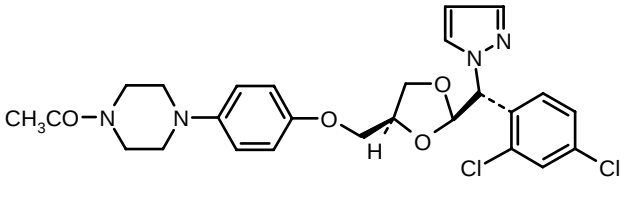
5-fluorocytosine (2)



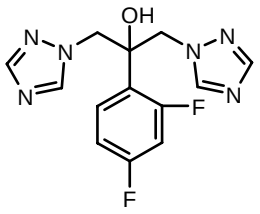
Miconazole Nitrate (3)



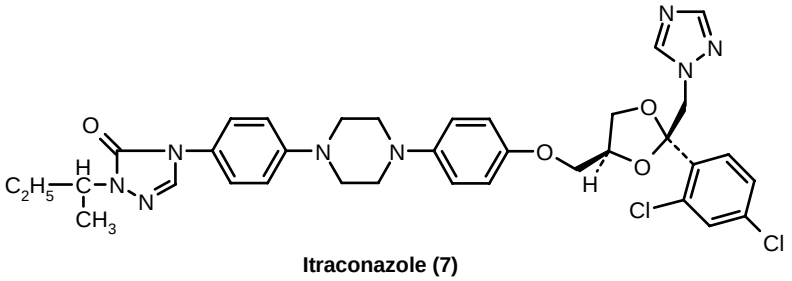
Econazole Nitrate (4)



Ketoconazole (5)



Fluconazole (6)



Itraconazole (7)

EMERGING TARGETS

Microtubules are dynamic polymers of α- and β-tubulin dimers whose aggregation / disaggregation plays a key role in cell morphology and growth. Microtubule aggregation is inhibited by griseofulvin, the agricultural fungicide benomyl, and the anticancer drugs vincristine and vinblastine, disaggregation is inhibited by taxol. This is an area of intense research for anticancer agents that has the potential of spilling over to antifungal research [21]. Topoisomerases I and II control the topological state of DNA so that it can undergo replication, transcription, repair and chromosomal segregation. They act by introducing transient, enzyme-bridged DNA breaks (single strand breaks for type I and double strand breaks for type II) that allow the passing of DNA strands. The enormous success of topoisomerase inhibitors in antibacterial and anticancer chemotherapy has underscored the potential of fungal topoisomerases as drug targets. Recent evidence suggests that fungal topoisomerase I and II can be inhibited selectively, the latter by cationic aromatic compounds that bind to the major groove of DNA.[22-24]

The discovery of the amino acid analogue cispentacin, an antifungal with excellent in vitro activity and multiple cellular targets, raised the possibility of interfering with amino acid synthesis. Other amino acid analogues with antifungal activity are RI-331, which inhibits homoserine dehydrogenase, a particularly attractive target since it is absent in mammalian cells, and azoxybacillin, which inhibits the biosynthesis of sulfur-containing amino acids [25-29]. Ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine synthesis and the target for suicide substrate analogues such as eflornithine, may also be an antifungal target. *P. carinii* ODC is far less sensitive to DFMO than the mammalian enzyme, suggesting differences in the active sites, though the available information is not

yet sufficient for rational drug design. An inhibitor of S-adenosylmethionine decarboxylase recently showed promising activity against *papulacandin carinii in vivo*.[30,31]

PROTON ATPASES AND EFFLUX PUMPS

The plasma membrane H^+-ATPase is an integral, abundant membrane protein involved in the maintenance of electro-chemical proton gradients and the regulation of intracellular pH. Plasma membrane H^+-ATPase are known in sufficient molecular detail to be targets for rational drug design, provided there are exploitable differences between the fungal and mammalian enzymes. The vesicular H^+-ATPase (V-ATpase) is inhibited specifically by folimycin, an antifungal agent structurally related to bafilomycins. These compounds block acidification of intracellular organelles and thereby affect intracellular protein trafficking and translocation to the cell surface. As with the plasma membrane ATpase, the selectivity between fungal and mammalian enzymes is presently unclear.[32]

ESTABLISHED ANTIFUNGAL AGENTS:

There are four classes of systemic antifungal compounds currently in clinical use:

a) Polyene antibiotics,
b) The azole derivatives,
c) Allylamines / thiocarbamates,
d) Fluoro pyrimidines.

a) Polyene antibiotics:

The ployene antibiotics discovered in the late 1950s, are produced by streptomyces species. They are fungicidal and have the broadest activity spectrum of any clinically useful antifungals. They complex with ergosterol in the fungal plasma membrane and thereby compromise its barrier function. In addition, they cause oxidative damage which

may contribute to their fungicidal action.[33,34] The only systemic polyene in clinical use is Amphotericin B (**1**).

It has acute and chronic side effects notably nephrotoxicity, the side effects are considerably reduced when it is used in costly lipid formulations.

b) Azole antifungals:

The azole antifungals, discovered in the late 1960s are totally synthetic and are most rapidly expanding group of antifungal agents.[35,36] They are classified as imidazoles or triazoles on the basis of whether they have two or three nitrogen atoms in the 5 membered azole ring. Systemic azoles have fungistatic, broad spectrum activity that includes most yeasts and filamentous fungi and some emerging pathogens such as *Trichosporon* species.

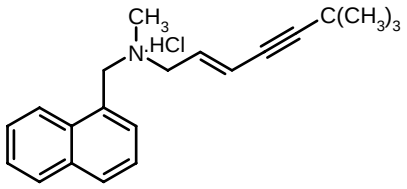
Azoles act on ergosterol biosynthesis at C-14 demethylation stage, a three step, oxidative reaction catalysed by the cytochrome P-450 enzyme 14 α – sterol demethylate (P-450 DM). The resulting ergosterol depletion and accumulation of lanasterol and other 14-methylated sterols interferes with bulk functions of ergosterol as a membrane component, it disrupts the structure of plasma membrane, making it more vulnerable to further damage and alters the activity of several membrane bound enzymes, such as those associated with nutrient transport and chitin synthesis.[34,37,38] Severe ergosterol depletion may interface with hormone like function of ergosterol, affecting cell growth and proliferation.[39] Systemic azoles are generally free of serious host toxicity, they may produce endocrine side effects, such as decrease in testosterone and glucocorticoids, stemming from their ability to interact with mammalian cytochrone P-450. Noteable examples of azole class of antifungal agents are miconazole (**3**), econazole (**4**), ketoconazole (**5**) and brought the agents fluconazole (**6**) and itraconazole (**7**).

Resistance to azoles, particularly fluconazole, is emerging in *C. ablicans* after long term suppressive therapy for oropharyngeal candidiasis in HIV-infected patients.[40] Resistance to fluconazole is also reported in other candida species particularly *C. glabrata, C. krusei* and *C. neoformans*.[41,42]

c) Allylamines and thiocarbamates:

This class of compounds, discovered in the 1970s, is totally synthetic. The only systemic allylamine antifungal in clinical use is terbinafine hydrochloride (**8**). It is reversible, non - competitive inhibitor of squalene epoxidase.

Pharmacokinetics limits the clinical efficacy of terbinafine and other compounds of this class to skin and nail infection despite broad spectrum in *vitro* activity.



(8)

d) Fluoropyrimidines:

The fluoropyrimidine 5-fluorocytosine (5-FC, **2**), though fungicidal, has a limited activity spectrum. It is mainly used in combination with amphotericin B in cryptococcal meningitis and in cases of disseminated candidiasis.

Others:

Novel antifungal agents have originated from random or target-based screening of natural products and synthetic compounds followed by lead optimization. They include:

Echinocandins, pneumocandins and papulacandins:

These are natural products discovered in 1970s. Echinocandins are fatty acid derivatives of cyclic hexapeptides whereas papulacandins are fatty acid derivatives of disaccharide β-(1, 4)-galactosylglucose. Both classes inhibit β-(1, 3)-glucan synthesis.

Two water soluble semisynthetic derivatives of echinocandin B have promising *in vitro* and *in vivo* activity against *Candida* species, *Aspergillus* species and *Papulacandin carinii.* They are currently in late clinical development. Papulacandins are no longer being pursued as antifungals because their *in vitro* activity is limited to *Candida* species and doesn't translate to *in vivo* activity.

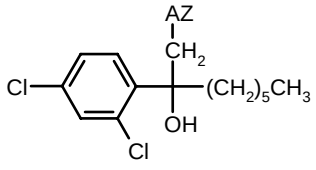
Polyoxins and nikkomycins:

These are nucleoside peptide antibiotics produced by streptomycetes and discovered in the 1960s and 1970s. They have modest activity against human pathogens due to transport limitations and work by inhibition of chitin synthesis.

Antifungal azoles related to fluconazole:

Fluconazole (**6**) as mentioned before is the most successful antimycotic developed in the 15 years. The structural development of what was to become fluconazole has been envisioned as antimycotic of good safety, effective both p.o. and i.v., with wide spectrum of activity and suitable not only for treatment but also for the prophylaxis of fungal infections. Since most azole antimycotics known so far had been rapidly and extensively metabolized, the drug of choice should not suffer along the path of p.o. doses absorption in the gastrointestinal tract passage through the liver and delivery to the site of action. In addition, complexing with protein, as a result of high lipophilicity should not be prominent.

Pfizer used compound UK-46,245 (**9**) as a corner stone in the structural development leading to fluconazole.



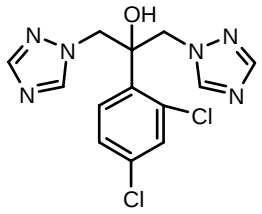
Az = 1,2,4-triazole-1-yl

(**9**)

To achieve this goal, tertiary alcohols have been selected as a starting group since they had the highest potential of good *in vivo* activity, in preference to tetrahydrofurans and dithiolanes, though they still were easily metabolized. 1,2,4-Triazoles have been preferred to imidazoles. Their greater *in vivo* activity suggested that at least one site of the molecule had been blocked against metabolism; also they show greater selectivity towards fungal cytochrome P-450 enzyme and do not affect mammalian testosterone synthesis.

The exchange of hexyl in compound **9** by CH_2 –Tr has resulted in compound **10** which is 100-fold as potent *in vivo* against systemic candidiasis than ketoconazole (**5**).

Variation of the phenyl substituents in **10** brought an optimal example with 2, 4-F_2 after comparison of water solubility, long half-life, and high urinary recovery (clearance without metabolism), thus fluconazole was born, fluconazole is *in vitro* significantly more toxic to *C. ablicans* than to dermatophytes like *T. rubrum*, *T. mentagrophytes*, *M. canis* and *E. floccosum*. In contrast, this drug is a much weaker inhibitor of *C. krusei* than ketoconazole or itraconazole, this is believed to result from a much lower intracellular accumulation.

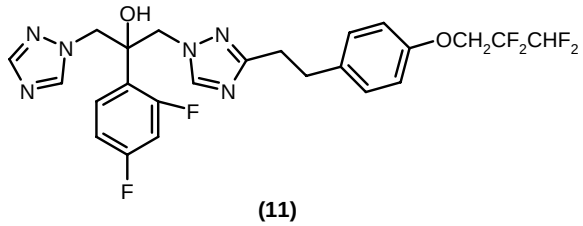


(10)

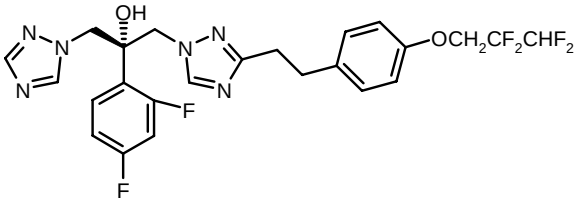
Fluconazole is 5-20 fold more active than ketoconazole against *Aspergillus* and *Cryptococcus* infections in mice. The high blood levels allow a single effective dose in the treatment of vaginal and mucocutaneous candidiasis. An excellent safety profile and good tolerance permit high doses in late stage AIDS patients against candidal esophagitis, against histoplasmosis, and against lymphocutaneous sporotrichosis.[43] Non-albicans spp. such as *C. glabrata* are intrinsically more resistant to fluconazole, and infections by these fungi seem to be on the increase in hospitals. Generally, resistance against fluconazole has developed more frequently than against ketoconazole and itraconazole. Multidrug transporters (ATP-binding cassettes) seem to be involved in the formation of this resistance. This might become a problem in the important, often very long prophylactic use of fluconazole in immunocompromised patients. Resistance to fluconazole is now considered so serious in a very recent discussion of present research efforts, that new antimycotics are qualified by the inhibition of fluconazole-resistant strains of *C. ablicans, C. krusei* and *A. fumigatus*. Fluconazole presents an excellent ocular profile which might be useful as an orally administerd agent in ocular fungal infections.

In order to overcome the limitations of fluconazole, several attempts are made to modify the structural features of fluconazole. The notable examples are compound ICI 195,739 (**11**) developed by ICI, Zeneca. ICI 195,739 shows 10-100 times the potency of

ketoconazole with good p. o. activity against vaginal candidiosis in mice and rats and against dermatophytic lesions in mice and guinea pig, but with untolerable toxicity in rat, rabbit and dog. It is freely permeable through the fungal cell walls, as experiments with whole and broken cells have shown. Compared with fluconazole, the minimal effective oral doses of this agent are lower by the factor of 5-10 against *C. ablicans* in mice, and against rodent vaginitis models. Compared with fluconazole, ICI 195,739 is several fold potent in experimental fungal diseases.



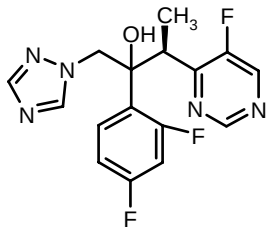
(11)



D-0870 (12) (+)-R-Enantiomer of 11

Antimycotic agents D-0870 (**12**) represent the (*R*)-(+)-enantiomer of IC 195,739 (**11**), which has been found to be the center of antimicrobial *in vitro* and *in vivo* activity. Outstanding *in vitro* inhibition of fluconazole-resistant strains of *C. albicans* and *C. neoformans* has been demonstrated with D-0870. It is also active against trichosporon beigelii in immunocompromised mice. *In vivo* activities in normal and immunocompromised mice against infections by *C. ablicans, C. neoformans,* and *A. fumigatus* are superior by a factor of 2-90 to fluconazole, and of the same order of magnitude in the second animal group. D-0870 inhibits more than half of *C. ablicans* isolates, which have drawn attention because of their elevated fluconazole and itraconazole MICs. Thus, it has potential for the therapy of infections caused by fluconazole-resistant *Candida spp*. In a similar therapeutic situation, D-0870 is superior against *C. Iusitaniae* and *T. beigelii*.

The replacements of second triazolylmethyl in fluconazole by 5-fluoro-pyrimidin-4-yl and inserting an α-methyl have resulted in Pfizer's voriconazole (**13**), an orally active broad-spectrum antimycotic with two chiral centers.

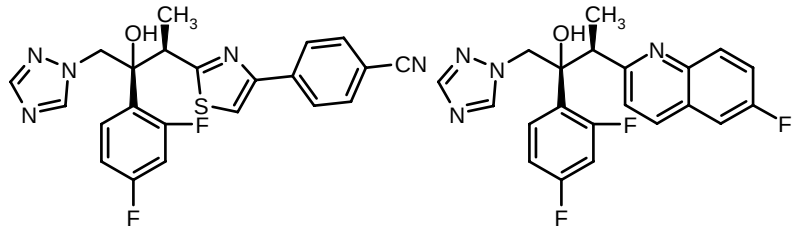


(13)

In vivo efficacy of voriconazole against systemic *C. ablicans* and pulmonary *Cryptococcus neoformans* infections has been found comparable with that of fluconazole and itraconazole, but has proved superior against systemic candidiasis caused by *C. krusei, C. glabrata* and azole-resistant *C. ablicans spp*. and against invasive aspergillosis in rabbits and guinea pigs. Clinical observations indicate efficacy against oropharyngeal candidiasis in immunocompromised patients, and against acute invasive and chronic aspergillosis in neutrotropic patients.

In a number of compounds similar to voriconazole, the pyrimidyl moiety has been replaced by thiazol-2-yl to give Eisai pharma's ER-30346 (**14**) with demonstrated superiority or equality to itraconazole and fluconazole against pulmonary aspergillosis, candidiasis, and cryptococcosis, against intercranial cryptococcosis (all in mice) and against oral candidiasis in rats. ER-30346 (**14**) shows good oral availability and does not influence pentobarbital sleeping time.

Similarly, pyrimidyl moiety in voriconazole has been replaced by qinolin-2-yl which produces Fujisawa's compound (**15**), also characterized by inhibition of *Cryptococcus neoformans*.



(14) **(15)**

The azole antifungal molecules mainly fluconazole and voriconazole offer lot of possibilities in structural modification resulting in compounds with broad-spectrum of activity, better safety profile, better bioavailability, and with better pharmacokinetic profile.

Efforts are on in various laboratories all over the world to synthesize new azole antifungals as is evident from the spate of publications appearing on the subject.

Recently US-FDA approved Pfizer's antifungal Vfend (voriconazole) for treating invasive aspergillosis. The most common adverse event was abnormal vision, which occurred in 35 % of 443 healthier volunteers who took voriconazole compared with 12 % of 135 healthy volunteers given placebo.[44] The work envisages structural modifications of flunconazole molecule using rational drug designing methodologies so as to get new antifungal compounds devoid of above mentioned drawbacks.

The following factors signify need for development of new antifungal agents:

A) Resistance of fungal strains to currently used antifungal agents. Resistance to azoles, particularly fluconazole, is emerging in *C. ablicans*, after long term suppressive therapy for oropharyngeal candidiasis in HIV infected patients. Resistance to fluconazole is also emerging in other *Candida* species, particularly *C. glabrata* and *C. krusei* and *C. neoformans*.

B) Since vast majority of life threatening mycoses occur in immunocompromised patients the importance of broad spectrum fungicidal agents of acceptable toxicity cannot be overemphasized.

C) Though antifungal agents are available to treat infections due to strains of *Candida* very few drugs are available to treat *Aspergillus* infections. The continued broad use of amphotericin B despite its nephrotoxicity to treat

aspergillosis underscores the potent need for other safer compounds with antiaspergillus activity.

D) In Indian context need for new broad spectrum antifungal agents having activity against *Candida* and *Aspergillus* strains is felt very badly due to rise in immunocompromised patients and drug resistant fungal infections. In coming years our healthcare economics will greatly depend upon indigenous availability of new drugs for treating fungal and other infections in immunocompromised patients.

The search for novel biologically active compounds involves two approaches. The first is traditional medicinal chemist's approach involving synthesis of molecules and their biological screening. The compounds synthesized are tested at random until suitable leads are obtained. This method is time consuming and tedious. It involves lot of experimental work where medicinal chemists synthesize compounds by changing the functional groups at random. These are trial and error attempts and require synthesis of very large number of compounds for biological screening purpose.

The second methodology is rational approach to discovery of new drugs which may be called as Rational Drug Designing. This is more efficient approach and involves less time as compared to traditional approach.

Thus there is always a continuous need for safer antifungals, in pursuit of this chitin synthase has been selected as a unique target, mainly due to it's absence in the human body and plant. In this work we envisage development of new chemical entities using systematic approach involving molecular modeling and QSAR methods.

CHAPTER - II

SECTION - I

DESIGN AND SYNTHESIS OF FURANONE DERIVATIVES AS ANTIFUNGAL AGENTS

2.1.1: INTRODUCTION:

Clinically, candidiasis and aspergillosis account for between 80 % and 90 % of systemic fungal infections in immunocompromised patients. While there is a multiple choice of drugs for the treatment of candidiasis, only amphotericin B (**1**) and itraconazole (**5**) come into consideration in the case of infections due to *Aspergillus fumigatus*. Although the research towards a new azole continues at an unabated pace, with examples such as TAK-187 (fig.**1a**), ER-30346 (**14**), Sankyo's amido alcohol, UR-9825 (fig. **1b**) and most notably voriconazole (**13**) and SCH-56592 (fig. **1c**) having been reported, the discovery and development of new structural types of antifungal compounds are no less desirable.

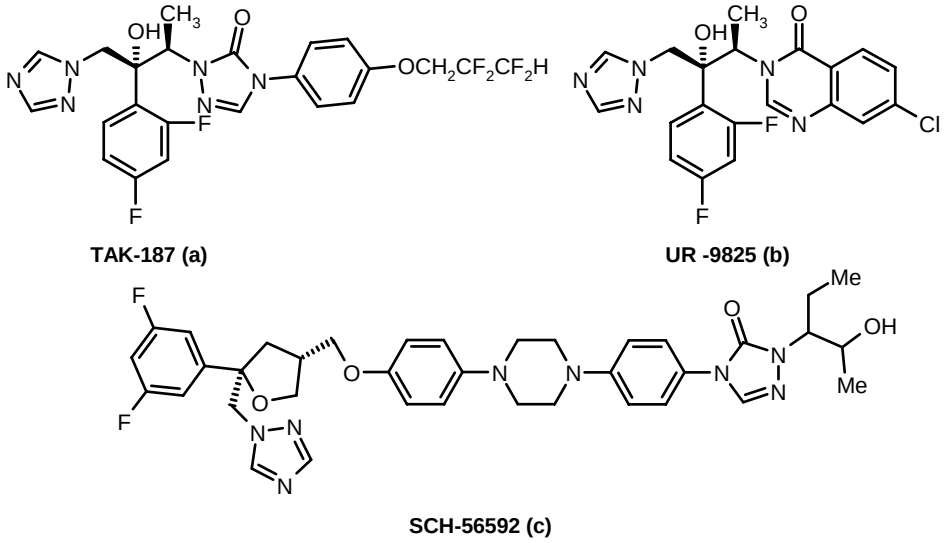


Fig. 1

As there are just a few structurally different groups of antifungal agents, which is especially true about the systemic ones, identification of new lead structures and further development to novel antifungal drugs is an important goal of current pharmaceutical research. In particular, it appears highly desirable to continue the process caused by opportunistic fungal pathogens. Furanones are important constituents of natural products[45] and useful synthetic intermediates[46] which have recently received much attention as synthetic targets[47]. Functionalized furanones are important subunits present in a large variety of natural products and biologically active compounds such as

alkaloids,[48] lignan lactones[49] and sex attractant insect pheromones.[50] Many of these compounds exhibit a variety of properties including antifungal and anticancer, insecticidal, antibacterial, phytotoxic, or anti-inflammatory activities, some of them are antibiotics, cyclooxygenase or phospholipase A2 inhibitors.

Substituted butyrolactones of furanone moiety are widely distributed in nature and exhibit a diverse spectrum of biological activity.[51-57] Many furanones have anticancer activity as well as many natural products have furanone moiety in the structural framework such as Nostoclide I (**16**), Nostoclide II (**17**), Bovolide (**18**), Thiophenebutenolide (**19**) and Rubrolides (**20**) etc. There are numerous reports describing isolation, structure determination, biological activity and synthesis of various furanones.

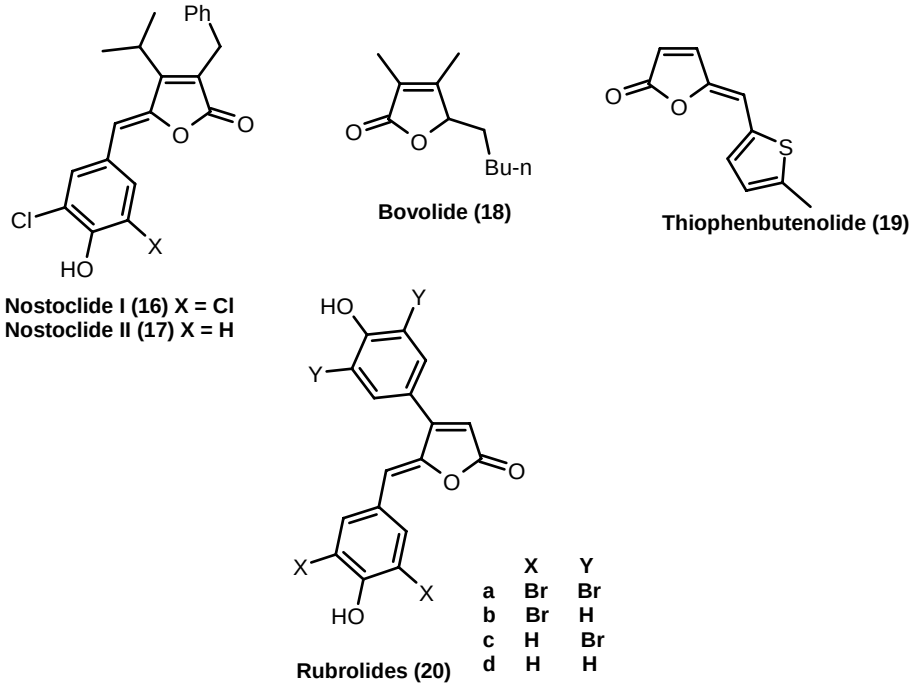
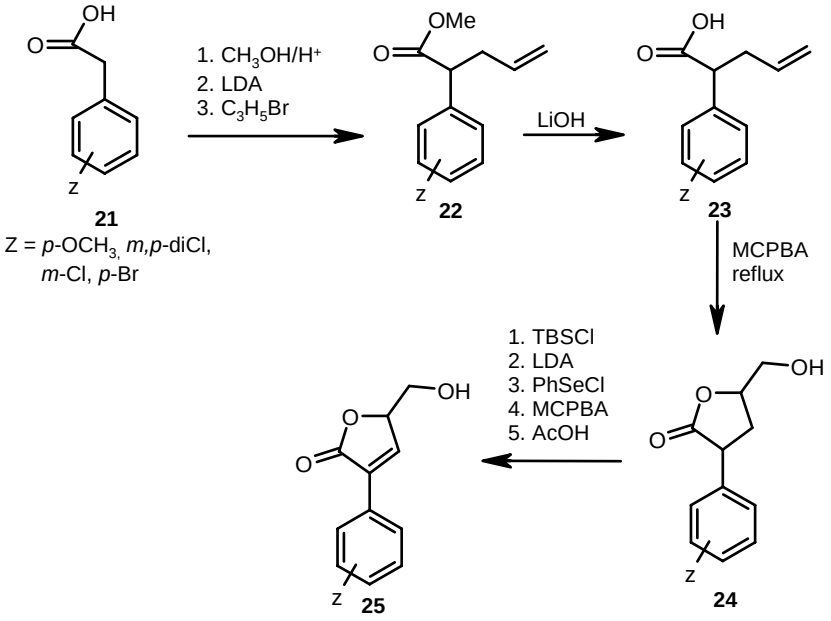


Fig. 2

BRIEF REVIEW OF LITERATURE:

Pour M. *et al* reported[58] synthesis and biological activity of 3-phenyl-5-acyloxymethyl-2*H*, 5*H*-furan-2-ones (**25**). In this synthesis the intermediate **22** was achieved from the commercially available substituted phenyl acetic acid **21** by esterfication using methanol

and catalytic amount of sulfuric acid followed by benzylic allylation in the presence of LDA. This intermediate **22** was hydrolyzed with LiOH and treated with *m*-CPBA under reflux to give the cyclized alcohol (**24**) which on further series of reactions gave the final 3-phenyl-5-acyloxymethyl-2*H*, 5*H*-furan-2-ones **25** as shown in scheme-1.



Scheme-1

2.1.2: PRESENT WORK:

In the present work furanones substituted at various positions with different groups have been synthesized and screened for antifungal activity. Starting from substituted phenylacetic acid derivatives, hydroxylmethyl furanone deriviative was synthesized. Treatment of the requisite acid chlorides with these intermediates led to the designed novel molecules. Preliminary molecular modeling study has indicated the novelty as well as potential of the above furanone molecules as antifungal agents. Keeping the substituted phenyl group at the α-position of furanone moiety, various R groups like alkyl, branched alkyl, substituted aryl, alicyclic etc. were incorporated (Fig. 3) to synthesize number of designed molecules of this type.

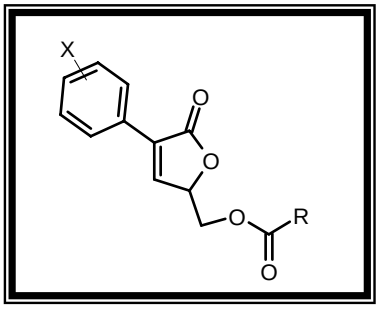


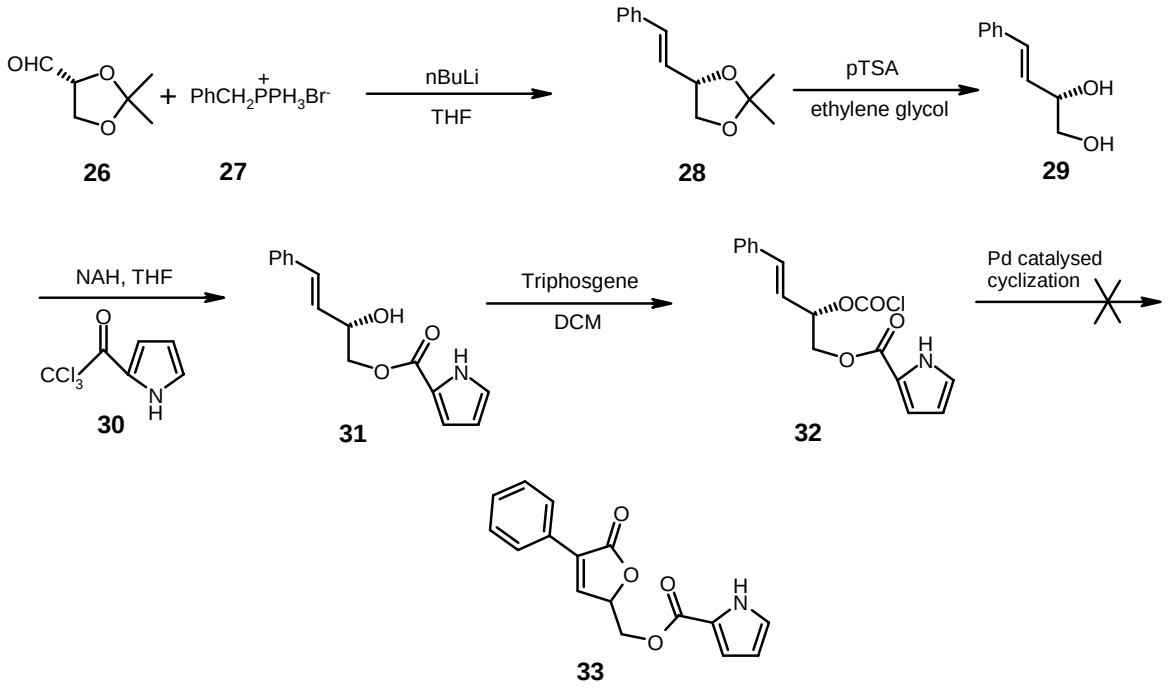
Fig. 3

2.1.3: RESULTS AND DISCUSSION:

Literature survey revealed the importance of furanones and their derivatives from medicinal as well as synthetic point of view. Huge amount of derivatization has been reported in case of different types of furanones, however the derivatization of 5*H*-furan-2-ones have attracted less attention in view of their structure activity relationship studies. It was observed that furanones with antifungal activity encompass a five membered lactone ring.

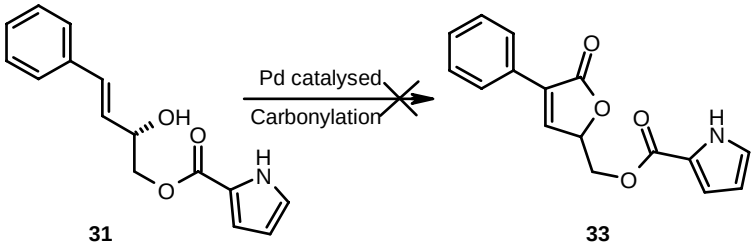
Synthetic stratagy attempted:

In the Wittig reaction approach we treated Garnar's aldehyde (**26**) with a salt **27** in the presence of n-BuLi in THF at -78 ^{0}C to give the intermediate **28**. The deprotection of intermediate **28** gave the diol **29**. This diol **29** on selective esterification using 2-trichloroacetylpyrrole in the presence of sodium hydride in tetrahydrofuran gave the ester **31**. The ester thus obtained was treated with triphosgene in dichloromethane as a solvent to collect the carbonyl chloride **32**, which was subjected to intramolecular cyclization under Heck reaction conditions using palladium salts, however this cyclisation could not be achieved (scheme - 3).



Scheme-3

Alternatively, palladium catalyzed carbonylation on the double bond of intermediate alcohol **31** was attempted which met with failure (scheme - 4).

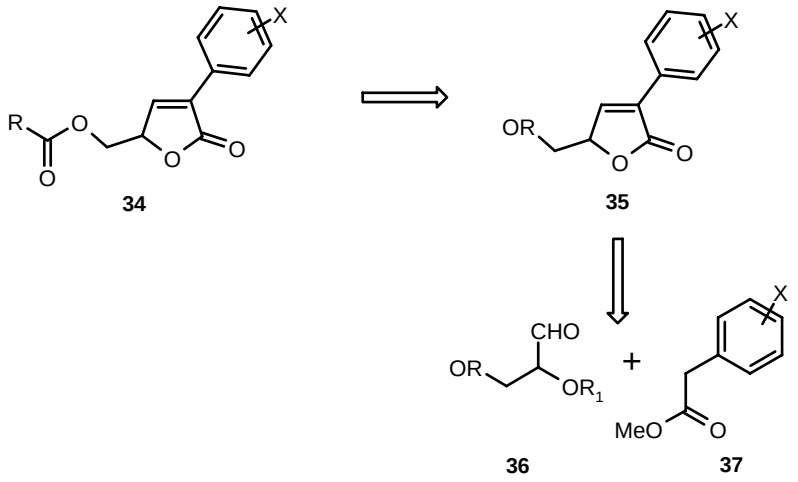


Scheme - 4

Due to the failure of cyclization of both intermediate alcohol **31** and intermediate **32,** we proposed another synthetic strategy which is described in detail on the following pages.

Proposed synthetic strategy:

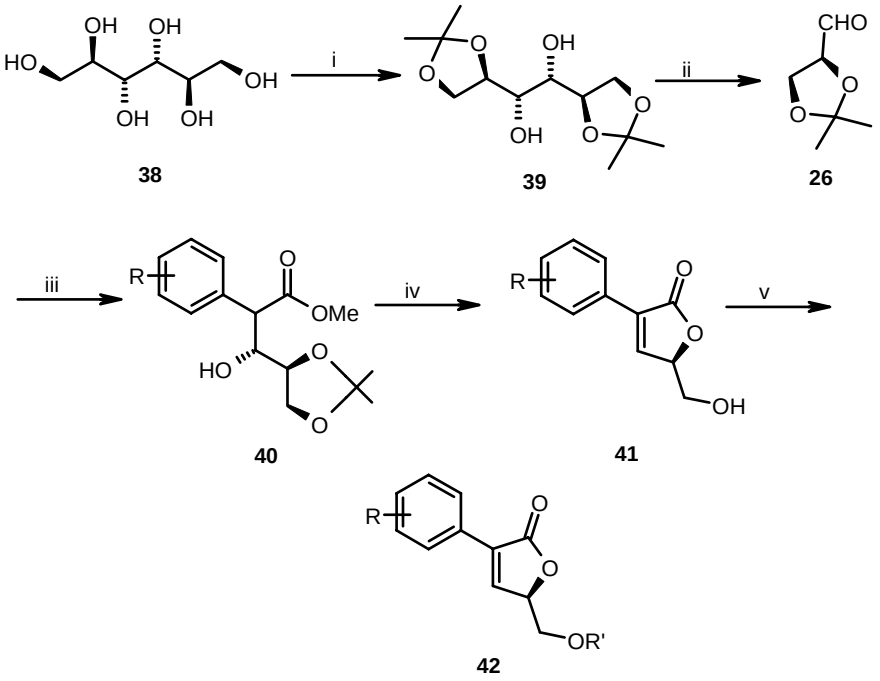
The retrosynthetic pathway for the synthesis of furanone derivatives started from glyceraldehydes (**36**) which could be treated with a methyl or ethyl ester of substituted phenyl acetic acid (**37**) to give the furanone alcohol **35** in two steps. The furanone alcohol **35** thus obtained could be derivatised as esters using various acid chlorides or their equivalents.



Scheme - 2

As stated in retrosynthetic analysis we synthesized the furanone alcohol **41** from the commercially available D-mannitol (**38**) which on diacetonide protection gave the diacetonide protected intermediate **39**. The diacetonide **39** on further treatment with

sodium periodate in dichloromethane at room temperature gave the Garnar's aldehyde (**26**) by well known repoted[59] method. The Garnar's aldehyde (**26**) was treated with the methyl or ethyl ester of substituted phenyl acetic acid in the presence of lithium diisopropyl amide (LDA) as base in dry tetrahydrofuran at -78 ^{0}C (to stabilize the anion, catalytic amount of hexamethyl phosphorous amide was used) which gave the alcohol **40**. This alcohol **40** was found to be unstable therefore was used directly for the next step. The alcohol ester **40** was hydrolysed in the presence of *p*-toluene sulphonic acid in methanol which cyclized *in situ* to furnish the alcohol **41**.



Reagents and conditions: i) 2, 2-Dimethoxy propane, *p*-TSA, dry DMSO, r t, 48 h. ii) $NaIO_4$, MeOH, H_2O, r t, 2 h. iii) Ester of substituted phenyl acetic acid, LDA, THF, HMPA, -78 ^{0}C, 4 h. iv) *p*-TSA, MeOH, 45 ^{0}C, 48 h. v) depending upon the (R'COCl) analogues synthesized.

Scheme - 5

Thus the desired alcohol **41** could be synthesized in two steps from Garnar's aldehyde. The asymmetry of the Garnar's aldehyde (at C-2) was retained in most cases however it was observed that during the cyclisation racemization took place. Pour M. *et al*[59] have studied the antifungal activity of both the enantiomers of similar derivatives and have

reported that the asymmetry in these compounds did not affect the antifungal activity. In view of this report enantiomeric purity of the products was not studied.

We synthesized 3-chloro, 3-bromo, 3-fluoro, 3, 4-dichloro and 3-bromo-4-methoxy substituted furanone alcohols **41** intermediates, and their corresponding esters **42** as shown in scheme-5. The synthesized furanones were characterised by using spectroscopic techniques such as IR, PMR, CMR and Mass etc., which clearly indicated the formation of desired products.

In a typical example 3-(3-Bromo-4-methoxy-phenyl)-5-hydroxymethyl-5*H*-furan-2-one (**41a**) was prepared as follows:

The Garnar's aldehyde was treated with the methyl or ethyl ester of 3-bromo-4-methoxy-phenyl acetic acid in the presence of lithium diisopropyl amide (LDA) as base in dry tetrahydrofuran at -78 ^{0}C (to stabilize the anion, catalytic amount of hexamethyl phosphorous amide was used) which gave the corresponding alcohol **40a**. This alcohol was found to be unstable therefore it was used for the next step as such. The alcohol ester **40a** was hydrolysed in the presence of *p*-toluene sulphonic acid in methanol which cyclized *in situ* to furnish 3-(3-Bromo-4-methoxy-phenyl)-5-hydroxymethyl-5*H*-furan-2-one (**41a**).

3-(3-Bromo-4-methoxy-phenyl)-5-hydroxymethyl-5*H*-furan-2-one (**41a**) was dissolved in dry dichloromethane and cooled to 0 ^{0}C, pyridine was added dropwise followed by *m*-iodobenzoyl chloride. The reaction mixture was stirred at room temperature overnight. The reaction was monitored by thin layer chromatography which showed complete disapperence of starting material, when the reaction mixture was quenched with dil HCl and extracted with dichloromethane and dried over sodium sulfate. The solvent was removed under reduced pressure on rotary evaporator and purification of the crude product on silica gel column chromatography by using ethyl acetate and pet ether as the eluent provided ester (**42c**) in good yield.

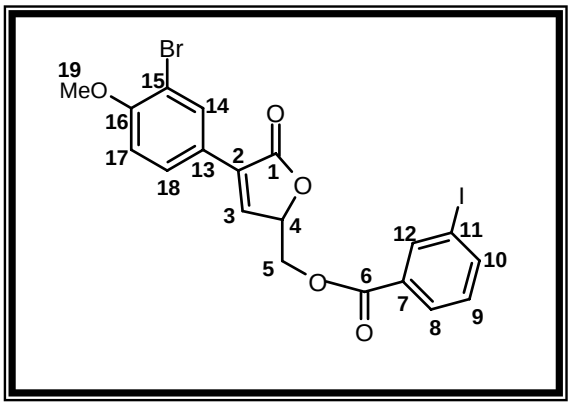


Table: 2; Compound No. 42c

The IR spectrum of compound (**42c**) showed absorption at 1766 cm^{-1} and 1727 cm^{-1} indicating the presence of carbonyl groups corresponding to ester and that of lactone ring respectively. ^{1}H NMR spectrum of the product (Table-2) showed singlet at δ 3.93 which indicated the presence of methoxy group in the molecule, a doublet of doublet at δ 4.54 for one proton (J = 12 and 4 Hz) and doublet of doublet at δ 4.67 for one proton (J = 12 and 4 Hz) which was assigned to the benzylic $–CH_2$ at C - 5 position. The proton at C - 4 showed a multiplet at δ 5.30 to 5.42, the olefinic proton at C-3 appeared as a doublet at δ 6.90 (J = 10 Hz) and the aromatic proton at C - 9 as a triplet at δ 7.17 (J = 8 Hz), a singlet at δ 7.47 due to the proton at C - 12, a multiplet at δ 7.83 to 8.01 corresponding protons at C - 8, 10 and 17, 18. The singlet at δ 8.31 was assigned to the proton present at C - 14. On the basis of this proton NMR data the structure of compound (**42c**) was assigned.

To support the structure of compound (**42c**), ^{13}C NMR spectrum of furanone (**42c**) was taken which fully supported the structure assigned from ^{1}H NMR spectrum. It displayed 19 signals for 19 carbons present in the molecule, the upfield signal at 56.22 was assigned for methoxy group present in molecule and the signal at 63.94 indicated the presence of $–CH_2$ at C - 5. The carbonyl carbon at C - 1 of the lactone ring appeared at δ 170.45 and the carbonyl carbon at C - 6 corresponding to the ester group appeared at δ 164.41 while other peaks were at their expected chemical shifts. The furanone (**42c**) showed a rotation $[\alpha]_D$+27.38, which indicated retention of configuration at C - 4, during cyclization.

By using the same synthetic strategy described above for alcohol (**41a**) and ester (**42c**) we have synthesized different alcohols (Table-1) and their corresponding esters (Table-2).

Overall 27 NCEs were synthesized and their antifungal activity was studied. The screening data of the synthesized NCEs of this furanone category indicated their potential anti-fungal activity, and the activity data of these compounds has been discussed in the third section of this chapter.

Table-1: Synthesized Alcohols (41)

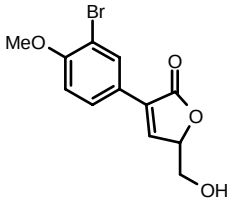
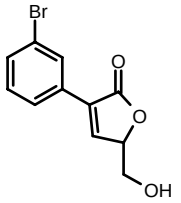
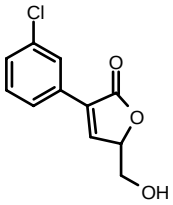
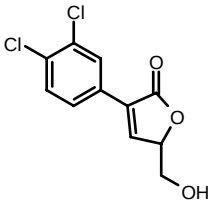
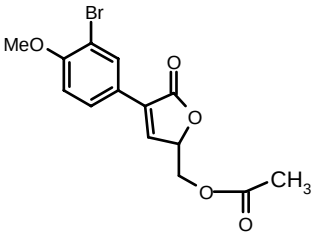
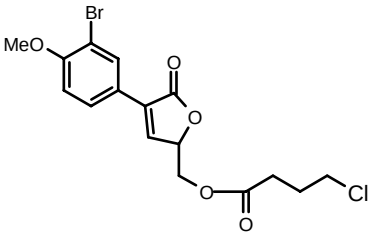
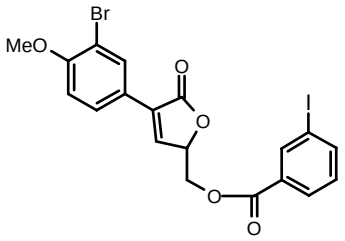
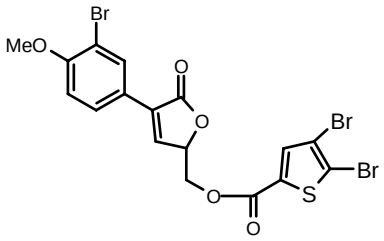
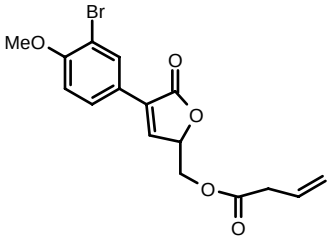
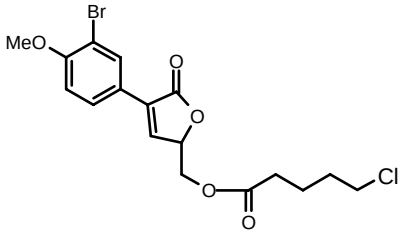
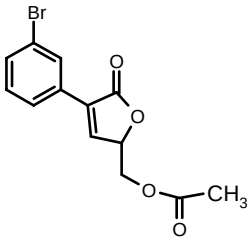
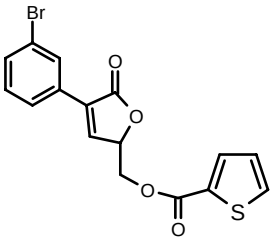
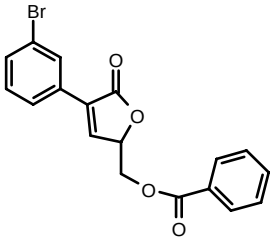
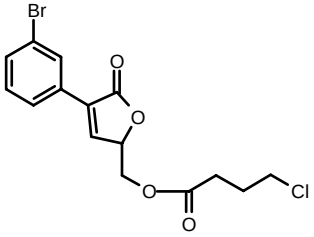
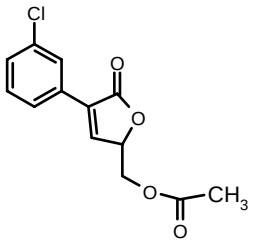
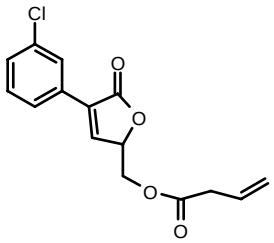
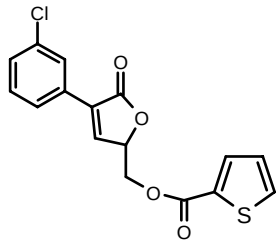
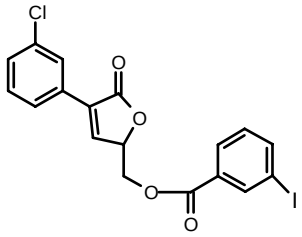
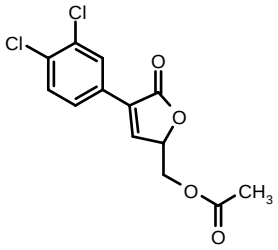
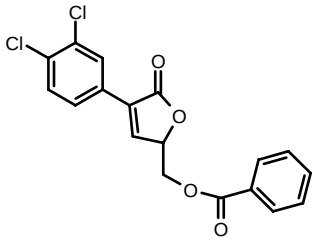
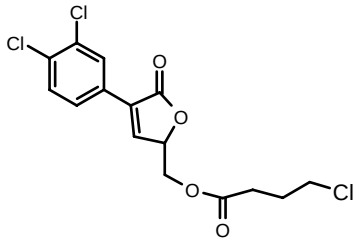
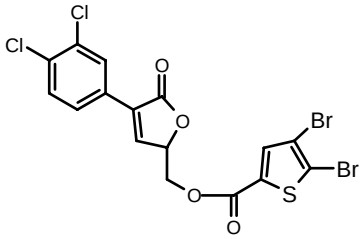
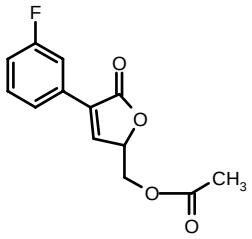
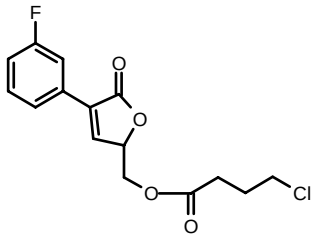
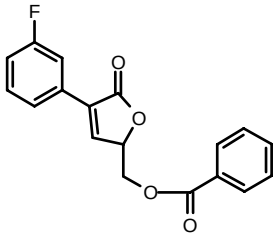
Comp. No.	Structure	Comp. No.	Structure
41a		**41b**	
41c		**41d**	

Table-2: Synthesized Esters (42)

Comp. No.	Structure	Comp. No.	Structure
42a		**42b**	

42c		**42d**	
42e		**42f**	
42g		**42h**	
42i		**42j**	
42k		**42l**	

42m		**42n**	
42o		**42p**	
42q		**42r**	
42s		**42t**	
42u			

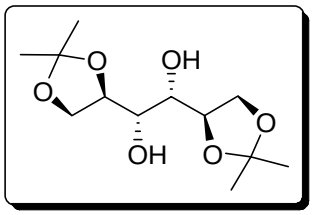
2.1.4: CONCLUSION:

We have developed an efficient method for the synthesis of (substituted) aromatic-5-hydroxymethyl-5*H*-furan-2-one (**42a-u**). The described method has the advantages of simplicity to obtain novel furanone derivatives in good yields from commercially available starting materials. In order to study the structure activity relationship we have synthesized 27 furanone analogues including substituted aromatic rings and all compounds were characterized by spectral and analytical methods.

2.1.5: EXPERIMENTAL:

Preparation of 1, 2-bis-(2,2-dimethyl-1,3-dioxolan-4-yl)-ethane-1,2-diol (39):

In a dry 500 ml round bottom flask 50 gm D-mannitol (0.267 mmol) was taken and flushed with nitrogen, 750 mg of *p*-TSA was added in it followed by 375 ml dry DMSO by using cannula and the reaction mixture was allowed to stir for 15 min till the solution became turbid. Then 2, 2-dimethoxy propane (DMP) (60 ml, 0.610 mmol) was added dropwise in 10 - 15 min. The reaction mixture was stirred at room temperature so that solution became clear, the reaction progress was monitored by TLC, the complete disapparance of starting material was observed in 12 h. In the reaction mixture 500 ml of ethyl acetate was added to get homogeneous solution, then 100 ml water was added to remove unreacted mannitol, DMSO and *p*-TSA. The aqueous layer was separated and the same procedure was repeated twice. The collected organic layer was dried over sodium sulfate and concentrated under reduced pressure on rotary evaporator to get pure product in good yield.



Nature: White solid; **Yield:** 89 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.38 (d, J = 12 Hz, 12H), 2.58 (bs, 2OH), 3.73 (d, J = 8 Hz, 2H), 3.97 (t, J = 8 Hz, 2H), 4.08 - 4.25 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 25.2 (2C), 26.7 (2C), 66.7 (2C), 71.0 (2C), 75.9 (2C), 109.3 (2C). **Anal. Calcd. for** $C_{12}H_{22}O_6$**:** C, 54.96; H, 08.40 %. **Found:** C, 54.90; H, 08.25 %.

Preparation of 2, 2-dimethyl-[1, 3]dioxolane-4-carbaldehyde (26)*:*

In a dry 100 ml round bottom flask 1, 2-bis-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethane-1,2-diol (4 gm, 19.23 mmol) was taken, dichloromethane (60 ml) was added in it, sodium periodate (5 gm, 28.84 mmol) adsorbed on silica gel (25 gm) was added in the reaction mixture at 0 ^{0}C and stirred at room temperature for 1 h. The reaction was monitored by TLC which showed completion of reaction in one and half h. 4-5 drops of water was added in the reaction mixture and filtered through sintered column by using dichloromethane. The filtrate was concentrated under reduced pressure using rotary

evaporator to get 2, 2-dimethyl-[1, 3]dioxolane-4-carbaldehyde product in excellent yield and the product was used in the next step directly.

Preparation of methyl 2-(3-bromo-4-methoxyphenyl)-3-(2,2-dimethyl-1,3-dioxoan-4-yl)propannoate (40a):

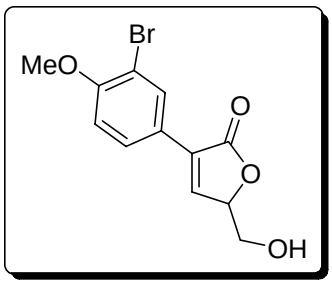
In a dry 250 ml two-necked round bottom flask evacuated and flushed with nitrogen, freshly distilled dry THF (50 ml) was added and cooled in ice salt mixture. n-BuLi (11.53 ml, 18.45 mmol) was added dropwise followed by diisopropyl amine (2.567 ml, 18.45 mmol) and the reaction mixture was stirred for 50 min at same temperature and then for additional 20 min at -78 ^{0}C. 3-bromo-4-methoxy-phenylacetic acid methyl ester (4.778 g, 18.45 mmol) dissolved in dry THF (25 ml) was added in the reaction mixture slowely, after 5 min. HMPA (2 ml) was added in it and the reaction mixture was stirred for 40 min at same temparture. Then 2, 2-dimethyl-[1, 3]dioxolane-4-carbaldehyde (2 g, 15.38 mmol) dissolved in dry THF (20 ml) was added in reaction mixture slowely and stirred for 3 h at -78 ^{0}C. The reaction mixture was quenched with ammonium chloride, extracted with ethyl acetate (3 x 75 ml), dried over sodium sulfate and concentrated under reduced pressure on rotary evaporator. The crude product (methyl 2-(3-bromo-4-methoxyphenyl)-3-(2,2-dimethyl-1,3-dioxoan-4-yl)propannoate) as such was used for cyclization step.

Preparation of 3-(3-bromo-4-methoxy-phenyl)-5-hydroxymethyl-5H-furan-2-one (41a):

In a dry 200 ml two-necked round bottom flask evacuated and flushed with nitrogen, (2 gm, 5.14 mmol) of methyl 2-(3-bromo-4-methoxyphenyl)-3-(2,2-dimethyl-1,3-dioxoan-4-yl)propannoate was taken. 15 ml of dry methanol was added in it, catalytic amount of *p*-TSA was added in the reaction mixture at 45 ^{0}C for 12 h. Monitor the reaction by thin layer chromatography which showed the complete disapperence of starting material. Remove methanol on rotary evaporator and extract reaction mixture with ethyl acetate (3 x 50 ml), dried over sodium sulfate. Concentrate under reduced pressure on rotary evaporator and purification of crude product on column chromatography by using ethyl acetate and pet ether as an eluent to gave 3-(3-bromo-4-methoxy-phenyl)-5-hydroxymethyl-5*H*-furan-2-one in good yield (1.08 g, 71 %).

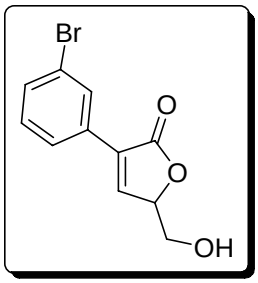
***3-(3-Bromo-4-methoxyphenyl)-5-hydroxymethyl-5H-furan-2-one (41a)*:**

Nature: White semisolid; **Yield:** 71 %; **IR** (chloroform)**:** ν_{max} 3435, 3020, 1760, 1600, 1562, 1476, 1400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4+DMSO-d_6)**:** δ 3.78 - 3.90 (m, 2H), 3.93 (s, 3H), 4.05 (bs, 1H), 5.07 - 5.17 (m, 1H), 6.95 (d, J = 16 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.87 (dd, J = 8 and 4 Hz, 1H), 8.08 (d, J = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4+DMSO-d_6)**:** δ 56.0, 61.4, 81.5, 110.9, 111.8, 123.4, 127.3, 129.2, 131.1, 146.1, 155.8, 171.3; **Anal. Calcd. for** $C_{12}H_{11}BrO_4$**:** C, 48.16; H, 3.68; Br, 26.76 %. **Found:** C, 48.10; H, 3.55; Br, 26.62 %.



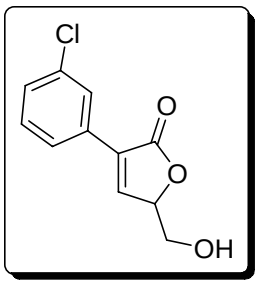
3-(3-Bromo-phenyl)-5-hydroxymethyl-5H-furan-2-one (41b):

Nature: White semisolid; **Yield:** 73 %; **IR** (chloroform): ν_{max} 3429, 3018, 1762, 1602, 1566, 1474, 1410 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.84 (dd, J = 12 and 4 Hz, 1H), 4.04 (dd, J = 12 and 4 Hz, 1H), 5.05 - 5.25 (m, 1H), 7.27 (t, J = 8 Hz, 1H), 7.51 (d, J = 8 Hz, 1H), 7.62 (s, 1H), 7.78 (d, J = 8 Hz, 1H), 7.98 (s, 1H); **Anal. Calcd. for** $C_{11}H_9BrO_3$**:** C, 49.07; H, 3.35; Br, 29.74 %. **Found:** C, 49.00; H, 3.30; Br, 29.54 %.



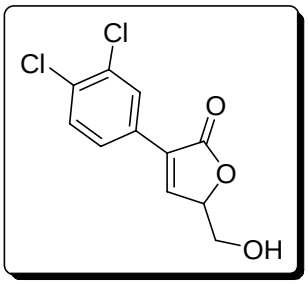
3-(3-Chloro-phenyl)-5-hydroxymethyl-5H-furan-2-one (41c):

Nature: White semisolid; **Yield:** 74 %; **IR** (chloroform)**:** ν_{max} 3436, 3019, 1760, 1595, 1567, 1476, 1404 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.75, (bs, 1H), 3.84 (dd, J = 12 and 4 Hz, 1H), 4.04 (dd, J = 12 and 4 Hz, 1H), 5.12 - 5.25 (m, 1H), 7.25 - 7.45 (m, 2H), 7.62 (s, 1H), 7.70 - 7.80 (m, 1H), 7.85 (s, 1H); **Anal. Calcd. for** $C_{11}H_9ClO_3$**:** C, 58.81; H, 4.04; Cl, 15.78 %. **Found:** C, 58.62; H, 04.00; Cl, 15.57 %.



3-(3,4-Dichloro-phenyl)-5-hydroxymethyl-5H-furan-2-one (41d):

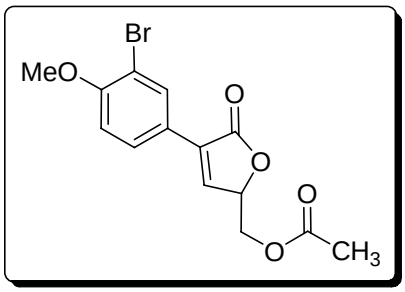
Nature: White solid; **M. p.** 122 ^{0}C; **Yield:** 70 %; **IR** (chloroform)**:** ν_{max} 3430, 3020, 1762, 1602, 1565, 1476, 1400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.87 (dd, J = 8 and 2 Hz, 1H), 4.05 (dd, J = 8 and 2 Hz, 1H), 5.16 - 5.19 (m, 1H), 7.48 (d, J = 4 Hz, 1H), 7.63 (s, 1H), 7.71 (d, J = 4 Hz, 1H), 7.99 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 61.0, 80.9, 83.7, 125.6, 127.9, 128.9, 129.8, 130.5, 131.4, 147.5, 170.3; **Anal. Calcd. for** $C_{11}H_8Cl_2O_3$**:** C, 53.14; H, 2.95; Cl, 26.20 %. **Found:** C, 53.00; H, 2.85; Cl, 26.18 %.



Preparation of *3-(3-bromo-4-methoxyphenyl)-5-(acetoxymethyl)-5H-furan-2-one (42 a):*

In a dry 200 ml two-necked round bottom flask evacuated and flushed with nitrogen, 3-(3-bromo-4-methoxy-phenyl)-5-hydroxymethyl-5*H*-furan-2-one (200 mg, 0.671 mmol) dissolved in 5 ml dry DCM cooled in ice bath and pyridine (0.066 ml, 0.805 mmol) was added dropwise followed by acetic anhydride (0.096 ml, 1.006 mmol) (or other acid chlorides e. g. acetyl chloride, benzoyl chloride, thiophene 2-carboxyl chloride, butyryl chloride etc). The reaction mixture was stirred at room temperature for overnight. The progress of the reaction was monitored by TLC which showed complete disapparance of starting material. The mixture was quenched with dil HCl, extracted with dichloromethane (3 x 20 ml) and dried over sodium sulfate. The extract was concentrated under reduced pressure on rotary evaporator and purification of crude product by column chromatography by using ethyl acetate and pet ether as an eluent to get 3-(3-bromo-4-methoxyphenyl)-5-(acetoxymethyl)-5*H*-furan-2-one.

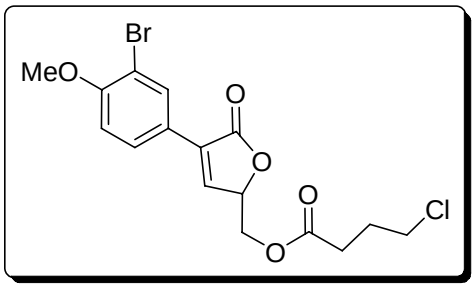
Nature: White semisolid; **Yield:** 78 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.07 (s, 3H), 3.93 (s, 3H), 4.30 - 4.45 (m, 2H), 5.15 - 5.30 (m, 1H), 6.93 (d, J = 8 Hz, 1H), 7.42 (s, 1H), 7.90 (d, J = 8 Hz, 1H), 8.02 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 20.6, 56.4, 63.1, 78.1, 111.7, 111.9, 122.9, 127.6, 131.3, 131.9, 142.4, 156.9, 170.6, 170.9;



Anal. Calcd. for $C_{14}H_{13}BrO_5$**:** C, 49.27; H, 3.12; Br, 23.46 %. **Found:** C, 49.20; H, 3.10; Br, 23.40 %.

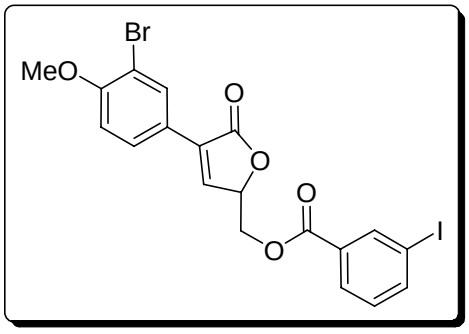
3-(3-Bromo-4-methoxyphenyl)-5-(4-chlorobutyroxymethyl)-5H-furan-2-one (42 b):

Nature: Yellow semisolid; **Yield:** 81 %; **IR** (chloroform)**:** ν_{max} 3020, 2964, 1767, 1736, 1610, 1565, 1502, 1408 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.98 - 2.15 (m, 2H), 2.52 (t, J = 8 Hz, 2H), 3.55 (t, J = 8 Hz, 2H), 3.93 (s, 3H), 4.25 - 4.50 (m, 2H), 5.10 - 5.30 (m, 1H), 6.92 (d, J = 8 Hz, 1H), 7.41 (s, 1H), 7.89 (d, J = 8 Hz, 2H), 8.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 27.3, 30.8, 43.6, 56.2, 63.0, 77.9, 111.6, 111.9, 122.8, 127.4, 131.3, 131.8, 142.0, 156.8, 170.5, 172.1; **Anal. Calcd. for** $C_{16}H_{16}BrClO_5$**:** C, 47.61; H, 4.00; Br, 19.80; Cl, 8.78 %. **Found:** C, 47.52; H, 3.87; Br, 19.58; Cl, 8.62 %.



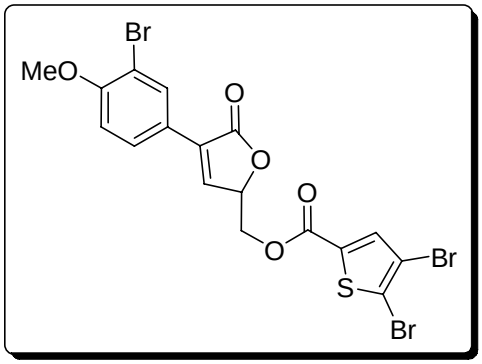
3-(3-Bromo-4-methoxyphenyl)-5-(3-iodobenzoyloxymethyl)-5H-furan-2-one (42 c):

Nature: White semisolid; **Yield:** 78 %; **IR** (chloroform)**:** ν_{max} 3020, 1766, 1727, 1599, 1498, 1419 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.93 (s, 3H), 4.50 - 4.71 (m, 2H), 5.30 - 5.38 (m, 1H), 6.90 (d, J = 10 Hz, 1H), 7.13 - 7.25 (m, 1H), 7.47 (s, 1H), 7.85 - 8.05 (m, 4H), 8.32 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 56.2, 63.9, 78.0, 93.9, 111.7, 112.1, 122.9, 127.5, 128.8, 130.1, 130.5, 130.9, 132.0, 138.6, 141.8, 142.3, 157.0, 164.4, 170.5; **Anal. Calcd. for** $C_{19}H_{14}BrIO_5$**:** C, 43.13; H, 2.67; Br, 15.10; I, 23.98 %. **Found:** C, 43.07; H, 2.53; Br, 14.97; I, 23.79 %.



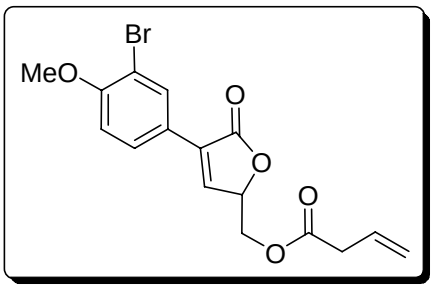
3-(3-Bromo-4-methoxyphenyl)-5-(4,5-dibromo-thiophene-2-carbonyloxymethyl)-5H-furan-2-one (42 d):

Nature: Yellow solid; **M. p.** 155 ^{0}C; $[\alpha]_D$ +49.82 (c 0.55, MeOH); **Yield:** 80 %; **IR** (chloroform)**:** ν_{max} 2925, 1757, 1713, 1600, 1500, 1461, 1404 cm^{-1} **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.93 (s, 3H), 4.49 - 4.67 (m, 2H), 5.27 - 5.38 (m, 1H), 6.93 (d, J = 8 Hz, 1H), 7.44 (s, 1H), 7.58 (s, 1H), 7.88 (d, J = 8 Hz, 1H), 8.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 56.3, 64.1, 77.7, 111.7, 112.0, 115.4, 120.2, 122.8, 127.6, 132.1, 133.0, 136.2, 141.2, 157.1, 159.7, 170.3; **Anal. Calcd. for** $C_{17}H_{11}Br_3O_5S$**:** C, 36.01; H, 1.96; Br, 42.27 %. **Found:** C, 35.92; H, 1.84; Br, 42.16 %.

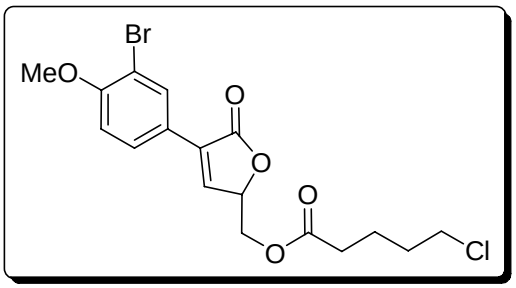


3-(3-Bromo-4-methoxyphenyl)-5-(3-butenoyloxymethyl)-5H-furan-2-one (42 e):

Nature: Yellow semisolid; **Yield:** 76 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.10 (d, J = 8 Hz, 2H), 3.94 (s, 3H), 4.40 (d, J = 8 Hz, 2H), 5.07 - 5.30 (m, 3H), 5.70 - 5.95 (m, 1H), 6.92 (d, J = 8 Hz, 1H), 7.45 (s, 1H), 7.80 (d, J = 8 Hz, 1H), 8.02 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 38.6, 56.2, 62.9, 78.0, 111.6, 111.8, 119.1, 122.8, 127.5, 129.2, 131.3, 131.8, 142.1, 156.7, 170.8, 171.0; **Anal. Calcd. for** $C_{16}H_{15}BrO_5$**:** C, 52.32; H, 4.09; Br, 21.80 %. **Found:** C, 52.30; H, 4.00; Br, 21.55 %.



3-(3-Bromo-4-methoxyphenyl)-5-(5-chloropentanoyloxymethyl)-5H-furan-2-one (42 f):

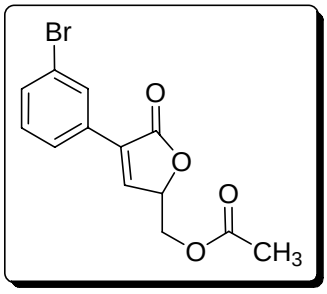


Nature: Yellow semisolid; **Yield:** 78 %; **IR** (chloroform)**:** ν_{max} 3019, 2960, 1767, 1724, 1600, 1560, 1472, 1410 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.65 - 1.85 (m, 4H), 2.25 - 2.45 (m, 2H), 3.40 - 3.55 (m, 2H), 3.94 (s, 3H), 4.35 - 4.45 (m, 2H), 5.20 - 5.32 (m,

1H), 6.94 (d, *J* = 8 Hz, 1H), 7.42 (s, 1H), 7.89 (d, *J* = 8 Hz, 1H), 8.02 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 22.2, 32.1, 33.2, 44.2, 56.5, 63.4, 78.4, 112.4, 112.6, 123.1, 127.9, 131.9, 132.1, 142.5, 157.6, 171.1, 173.1; **Anal. Calcd. for** $C_{17}H_{18}BrClO_5$**:** C, 48.86; H, 4.31 %. **Found:** C, 48.79; H, 4.25 %.

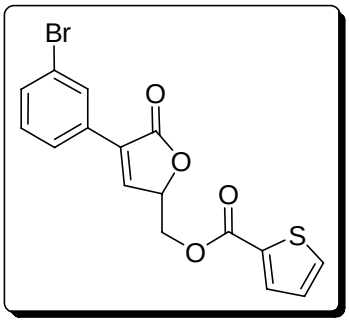
3-(3-Bromophenyl)-5-(acetoxymethyl)-5H-furan-2-one (42 g):

Nature: Yellow semisolid; **Yield:** 76 %; **IR** (chloroform)**:** ν_{max} 3019, 1767, 1732, 1602, 1565, 1470, 1410 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.08 (s, 3H), 4.35 - 4.55 (m, 2H), 5.24 - 5.30 (m, 1H), 7.33 (t, *J* = 8 Hz, 1H), 7.52 - 7.57 (m, 2H), 7.82 (d, *J* = 8 Hz, 1H), 8.01 (s, 1H); **Anal. Calcd. for** $C_{13}H_{11}BrO_4$**:** C, 50.16; H, 3.54; Br, 25.72 %. **Found:** C, 50.05; H, 3.50; Br, 25.65 %.



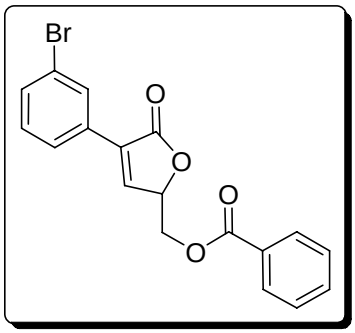
3-(3-Bromophenyl)-5-(thiophene-2-carbonyloxymethyl)-5H-furan-2-one (42 h):

Nature: Yellow semisolid; **Yield:** 81 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.54 - 4.69 (m, 2H), 5.35 - 5.44 (m, 1H), 7.25 - 7.40 (m, 2H), 7.48 - 7.65 (m, 3H), 7.77 (t, *J* = 8 Hz, 1H), 7.97 (s, 1H), 8.12 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 62.5, 78.4, 110.7, 116.6, 121.3, 122.7, 124.0, 125.7, 129.9, 130.2, 130.9, 131.1, 132.6, 145.0, 160.3, 170.6; **Anal. Calcd. for** $C_{16}H_{11}BrO_4S$**:** C, 50.67; H, 2.92; Br, 21.07; S, 8.46 %. **Found:** C, 50.46; H, 2.80; Br, 20.96; S, 8.39 %.



3-(3-Bromophenyl)-5-(benzoyloxymethyl)-5H-furan-2-one (42 i):

Nature: White semisolid; **Yield:** 77 %; **IR** (chloroform)**:** ν_{max} 3019, 1767, 1734, 1608, 1566, 1470, 1408 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.53 - 4.80 (m, 2H), 5.30 - 5.50 (m, 1H), 7.20 - 7.70 (m, 6H), 7.80 (d, *J* = 8 Hz, 1H), 7.95 - 8.20 (m, 1H); **Anal. Calcd. for** $C_{18}H_{13}BrO_4$**:** C, 57.90; H, 03.45; Br, 21.45 %. **Found:** C, 57.79; H, 03.25; Br, 21.30 %.



3-(3-Bromophenyl)-5-(4-chlorobutyroxymethyl)-5H-furan-2-one (42 j):

Nature: Yellow semisolid; $[\alpha]_D$ +5.82 (c 0.55, MeOH); **Yield:** 74 %; **IR** (chloroform)**:** *v* $_{max}$ 3020, 1770, 1742, 1592, 1561, 1474, 1398 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.05 (t, *J* = 8 Hz, 2H), 2.52 (t, *J* = 8 Hz, 2H), 3.56 (m, 2H), 4.21 - 4.55 (m, 2H), 5.26 - 5.32 (m, 1H), 7.31 (t, *J* = 8 Hz, 1H), 7.50 - 7.70 (m, 2H), 7.84 (d, *J* = 8 Hz, 1H), 7.98 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 27.3, 30.8, 43.6, 62.8, 78.0, 122.8, 125.6, 129.9, 130.2, 131.1, 132.0, 132.6, 144.6, 170.2, 172.1; **Anal. Calcd. for** $C_{15}H_{14}BrClO_4$**:** C, 48.19; H, 03.75; Br, 21.39; Cl, 9.49 %. **Found:** C, 48.15; H, 03.69; Br, 21.32; Cl, 9.38 %.

3-(3-Bromophenyl)-5-(acetoxymethyl)-5H-furan-2-one (42 k):

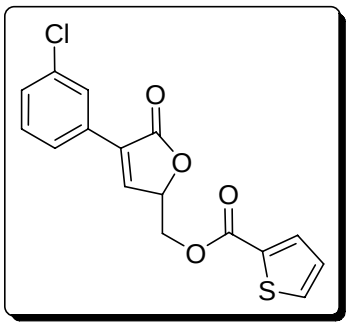
Nature: Yellow semisolid; **Yield:** 80 %; **IR** (chloroform)**:** *v* $_{max}$ 3402, 1776, 1747, 1610, 1567, 1476, 1410 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.08 (s, 3H), 4.41 (d, *J* = 6 Hz, 2H), 5.20 - 5.29 (m, 1H), 7.30 - 7.40 (m, 2H), 7.56 (s, 1H), 7.72 - 7.80 (m, 1H), 7.86 (s, 1H); **Anal. Calcd. for** $C_{13}H_{11}ClO_4$**:** C, 58.54; H, 4.13; Cl, 13.32 %. **Found:** C, 58.45; H, 4.10; Cl, 13.25 %.

3-(3-Chlorophenyl)-5-(3-butenoyloxymethyl)-5H-furan-2-one (42 l):

Nature: Yellow semisolid; **Yield:** 73 %; **IR** (chloroform)**:** *v* $_{max}$ 3021, 1765, 1723, 1603, 1562, 1470, 1404 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.10.5 (d, *J* = 6 Hz, 2H), 4.45 (d, *J* = 6 Hz, 2H), 5.10 - 5.40 (m, 3H), 5.75 - 6.00 (m, 1H), 7.30 - 7.45 (m, 2H), 7.54 (s, 1H), 7.20 - 7.30 (m, 1H), 7.85 (s, 1H); **Anal. Calcd. for** $C_{15}H_{13}ClO_4$**:** C, 61.54; H, 04.44; Cl, 12.14 %. **Found:** C, 61.50; H, 4.25; Cl, 12.05 %.

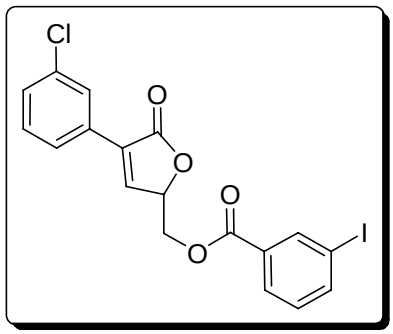
(4-(3-Chlorophenyl)-2,5-dihydro-5-oxofuran-2-yl)methyl thiophene-2-carboxylate (42 m):

Nature: White semisolid; **Yield:** 79 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.55 - 4.65 (m, 2H), 5.30 - 5.45 (m, 1H), 7.25 - 7.45 (m, 3H), 7.48 (d, *J* = 8 Hz, 1H), 7.65 (s, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.85 (s, 1H), 8.15 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 61.6, 77.5, 109.8, 115.7, 120.3, 123.1, 124.2, 126.1, 128.7, 128.9, 129.7, 131.1, 133.7, 144.1, 159.4, 169.8; **Anal. Calcd. for** $C_{16}H_{11}ClO_4$**:** C, 57.40; H, 3.31; Cl, 10.59; S, 9.58 %. **Found:** C, 57.22; H, 3.15; Cl, 10.45; S, 9.39 %.



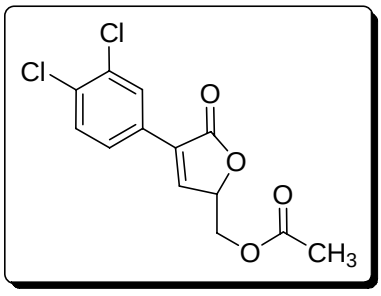
3-(3-Chlorophenyl)-5-(3-iodobenzoyloxymethyl)-5H-furan-2-one (42 n):

Nature: White semisolid; **Yield:** 81 %; **IR** (chloroform): ν_{max} 3020, 1765, 1727, 1595, 1567, 1474, 1419 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.50 - 4.75 (m, 2H), 5.30 - 5.42 (m, 1H), 7.17 (t, *J* = 8 Hz, 1H), 7.26 - 7.40 (m, 2H), 7.60 (s, 1H), 7.70 - 8.00 (m, 4H), 8.31 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 63.7, 78.1, 93.9, 125.2, 127.2, 128.8, 129.8, 130.0, 130.2, 130.6, 130.8, 132.5, 134.8, 138.5, 142.3, 144.4, 164.4, 170.2; **Anal. Calcd. for** $C_{18}H_{12}ClIO_4$**:** C, 47.55; H, 2.66; Cl, 7.80; I, 27.91 %. **Found:** C, 47.38; H, 2.48; Cl, 7.59; I, 27.83 %.



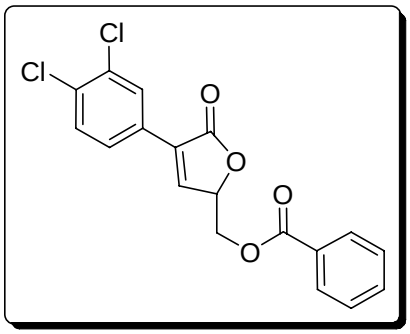
3-(3,4-Dichlorophenyl)-5-(acetoxymethyl)-5H-furan-2-one (42 0):

Nature: Yellow semisolid; **Yield:** 74 %; **IR** (chloroform)**:** ν_{max} 3020, 1770, 1740, 1600, 1561, 1470, 1400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.08 (s, 3H), 4.40 (d, *J* = 4 Hz, 2H), 5.15 - 5.30 (m, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.07 (s, 1H), 7.75 (d, *J* = 8 Hz, 1H), 8.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 20.2, 62.5,



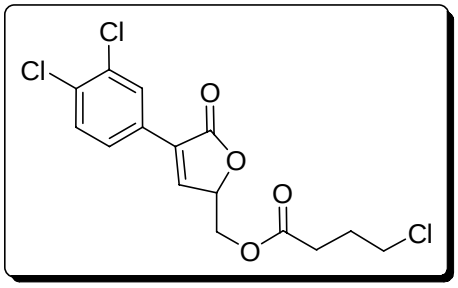
76.5, 77.8, 125.9, 128.6, 130.4, 131.1, 132.5, 133.7, 144.5, 169.7, 170.0; **Anal. Calcd. for** $C_{13}H_{10}Cl_2O_4$**:** C, 51.83; H, 3.32; Cl, 23.59 %. **Found:** C, 51.79; H, 3.25; Cl, 23.52 %.

3-(3,4-Dichlorophenyl)-5-(benzoyloxymethyl)-5H-furan-2-one (42 p):



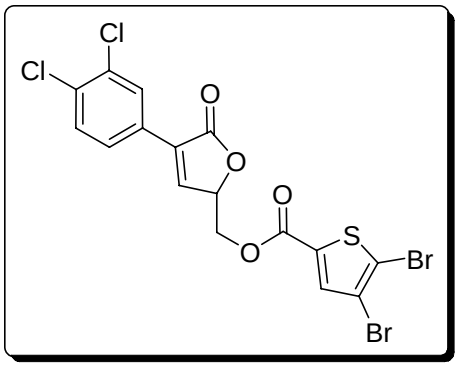
Nature: White semisolid; **Yield:** 79 %; **IR** (chloroform)**:** ν_{max} 3021, 1766, 1729, 1604, 1565, 1478, 1402 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.66 (d, J = 2 Hz, 2H), 5.40 - 5.50 (m, 1H), 7.42 - 7.46 (dd, J = 8 and 4 Hz, 2H), 7.49 (d, J = 4 Hz, 1H), 7.58 (t, J = 4 Hz, 1H), 7.64 (s, 1H), 7.70 (d, J = 4 Hz, 1H), 7.95 - 8.02 (m, 3H); **Anal. Calcd. for** $C_{18}H_{12}Cl_2O_4$**:** C, 59.50; H, 3.31; Cl, 19.56 %. **Found:** C, 59.39; H, 3.25; Cl, 19.40 %.

3-(3,4-Dichlorophenyl)-5-(4-chlorobutyroxymethyl)-5H-furan-2-one (42 q):



Nature: Yellow semisolid; **Yield:** 74 %; **IR** (chloroform)**:** ν_{max} 3018, 1778, 1730, 1602, 1564, 1476, 1408 cm^{-1} **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.01 - 2.11 (m, 2H), 2.53 (t, J = 6 Hz, 2H), 3.56 (t, J = 6 Hz, 2H), 4.43 (d, J = 4 Hz, 2H), 5.26 - 5.32 (m, 1H), 7.46 - 7.58 (m, 2H), 7.74 (d, J = 8 Hz, 1H), 8.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 27.3, 30.7, 43.6, 62.6, 78.1, 126.1, 128.6, 128.8, 130.5, 130.7, 132.8, 133.6, 145.0, 170.0, 171.9; **Anal. Calcd. for** $C_{15}H_{13}Cl_3O_4$**:** C, 49.52; H, 03.58; Cl, 29.30 %. **Found:** C, 49.39; H, 03.53; Cl, 29.14 %.

3-(3,4-Dichlorophenyl)-5-(4,5-dibromo-thiophene-2-carbonyloxymethyl)-5H-furan-2-one (42 r):

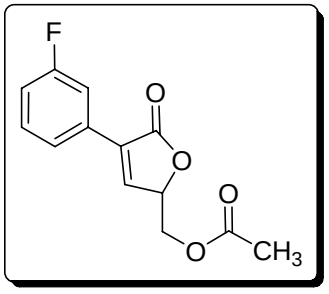


Nature: Milky solid; **Yield:** 78 %; **IR** (chloroform)**:** ν_{max} 3020, 1769, 1721, 1661, 1524, 1472, 1402 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.50 - 4.75 (m, 2H), 5.30 - 5.40 (m, 1H), 7.50 (d, J = 8 Hz, 1H), 7.56 - 7.64 (m, 2H), 7.71 (d, J = 8 Hz, 1H), 7.98 (s, 1H); **^{13}C NMR**

(50 MHz, $CDCl_3$+CCl_4)**:** δ 63.6, 78.0, 115.3, 120.3, 126.2, 128.6, 128.8, 130.7, 131.4, 132.8, 133.0, 134.1, 136.2, 144.3, 159.6, 170.0; **Anal. Calcd. for** $C_{16}H_8Br_2Cl_2O_4S$**:** C, 36.46; H, 1.53; Br, 30.32; Cl, 13.45 %. **Found:** C, 36.31; H, 1.45; Br, 30.22; Cl, 13.31 %.

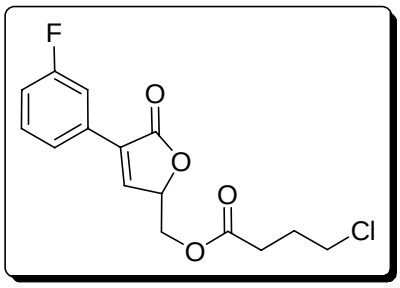
***3-(3-Fluorophenyl)-5-(acetoxymethyl)-5H-furan-2-one (42 s)*:**

Nature: Yellow semisolid; $[\alpha]_D$ +4.03 (c 0.55, MeOH); **Yield:** 81 %; **IR** (chloroform)**:** ν_{max} 3021, 1764, 1740, 1613, 1585, 1488 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 2.05 (s, 3H), 4.30 - 4.45 (m, 2H) 5.25 (m, 1H), 7.09 (t, J = 8 Hz, 1H), 7.28 - 7.44 (m, 1H), 7.52 - 7.68 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 20.5, 62.8, 78.0, 113.9, 116.3, 122.7, 130.3, 130.6, 132.0, 144.6, 160.3, 165.2, 170.3; **Anal. Calcd. for** $C_{13}H_{11}FO_4$**:** C, 62.40; H, 4.40; F, 7.59 %. **Found:** C, 62.35; H, 4.30; F, 7.43 %.



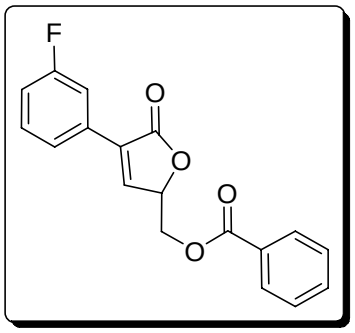
3-(3-Fluorophenyl)-5-(4-chlorobutyroxymethyl)-5H-furan-2-one (42 t):

Nature: Yellow semisolid; $[\alpha]_D$ +5.18 (c 0.55, MeOH); **Yield:** 72 %; **IR** (chloroform)**:** ν_{max} 3021, 2965, 1766, 1739, 1613, 1585, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.99 - 2.17 (m, 2H), 2.53 (t, J = 6 Hz, 2H), 3.56 (t, J = 6 Hz, 2H), 4.38 - 4.54 (m, 2H), 5.26 - 5.32 (m, 1H), 7.12 (t, J = 8 Hz, 1H), 7.37 - 7.45 (m, 1H), 7.55 - 7.67 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 27.3, 30.8, 43.7, 62.8, 78.01, 113.9, 114.2, 116.4, 122.7, 130.2, 132.0, 144.6, 164.4, 170.4, 172.1; **Anal. Calcd. for** $C_{15}H_{14}ClFO_4$**:** C, 57.60; H, 4.48; F, 06.08 %. **Found:** C, 57.50; H, 4.45; F, 06.01 %.

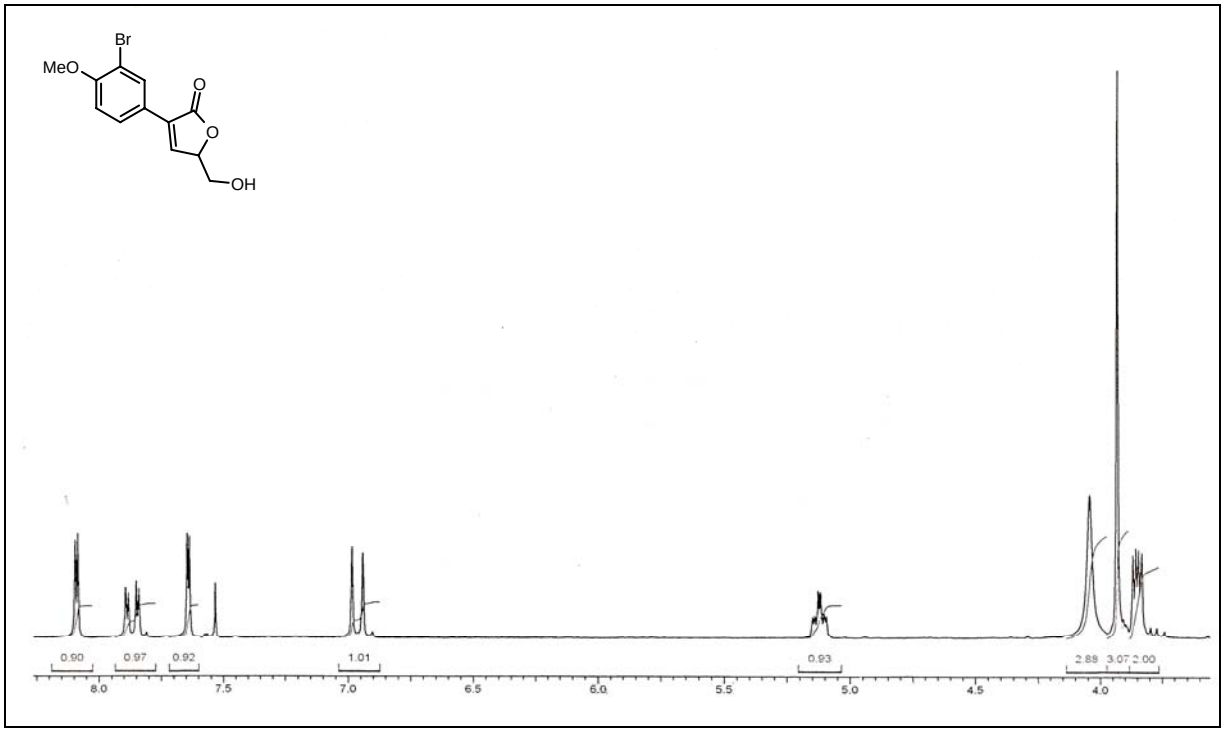


3-(3-Fluorophenyl)-5-(benzoyloxymethyl)-5H-furan-2-one (42 u):

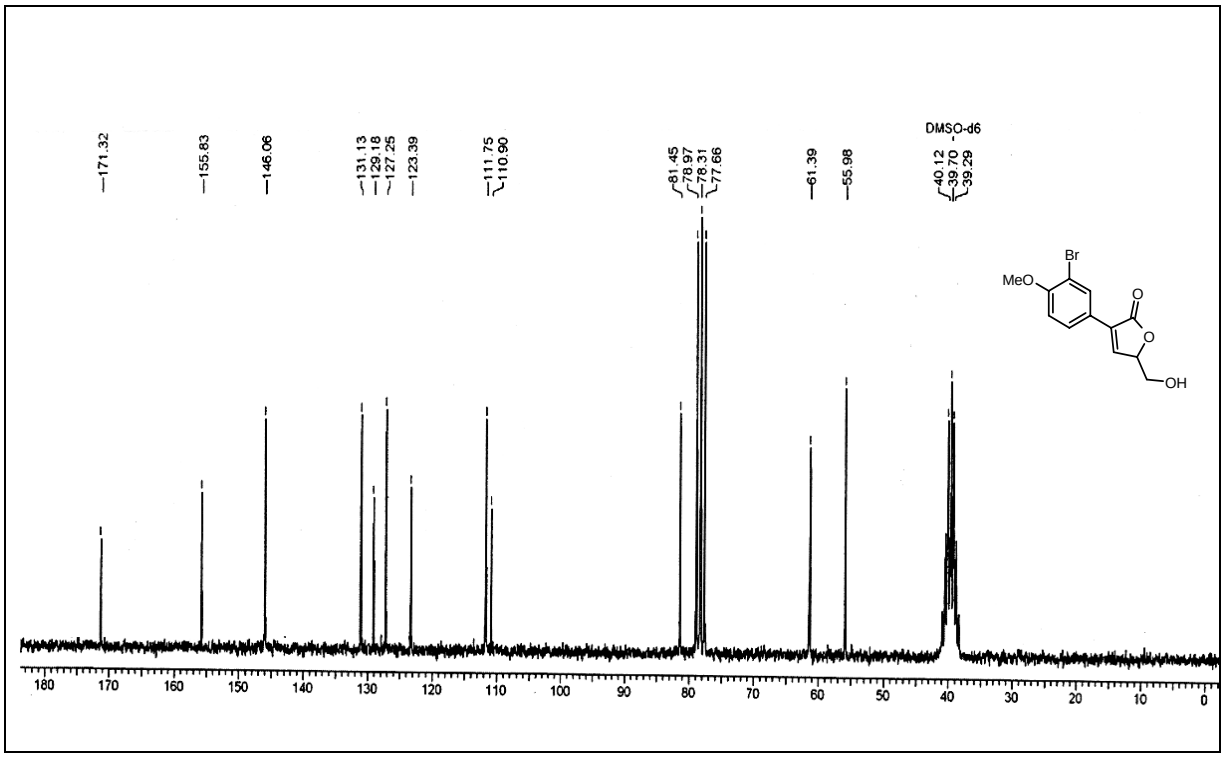
Nature: White solid; $[\alpha]_D$ +40.67 (c 0.55, MeOH); **M. p.** 68 ^{0}C; **Yield:** 79 %; **IR** (chloroform)**:** ν_{max} 3022, 1748, 1711, 1584, 1488, 1451 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$+CCl_4)**:** δ 4.61 - 4.70 (m, 2H), 5.34 - 5.43 (m, 1H), 7.10 (t, J = 6 Hz, 1H), 7.35 - 7.48 (m, 2H), 7.52 - 7.74 (m, 3H), 8.01 (d, J = 9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 63.3, 78.2, 114, 116.3, 122.8, 128.4 (2C), 129.7 (2C), 129..0, 130.1, 132.2, 133.4, 144.7, 161.1, 164.4, 165.9, 170.3; **Anal. Calcd. for** $C_{18}H_{13}FO_4$**:** C, 69.23; H, 04.16; F, 06.08 %. **Found:** C, 69.20; H, 4.10; F, 06.02 %.



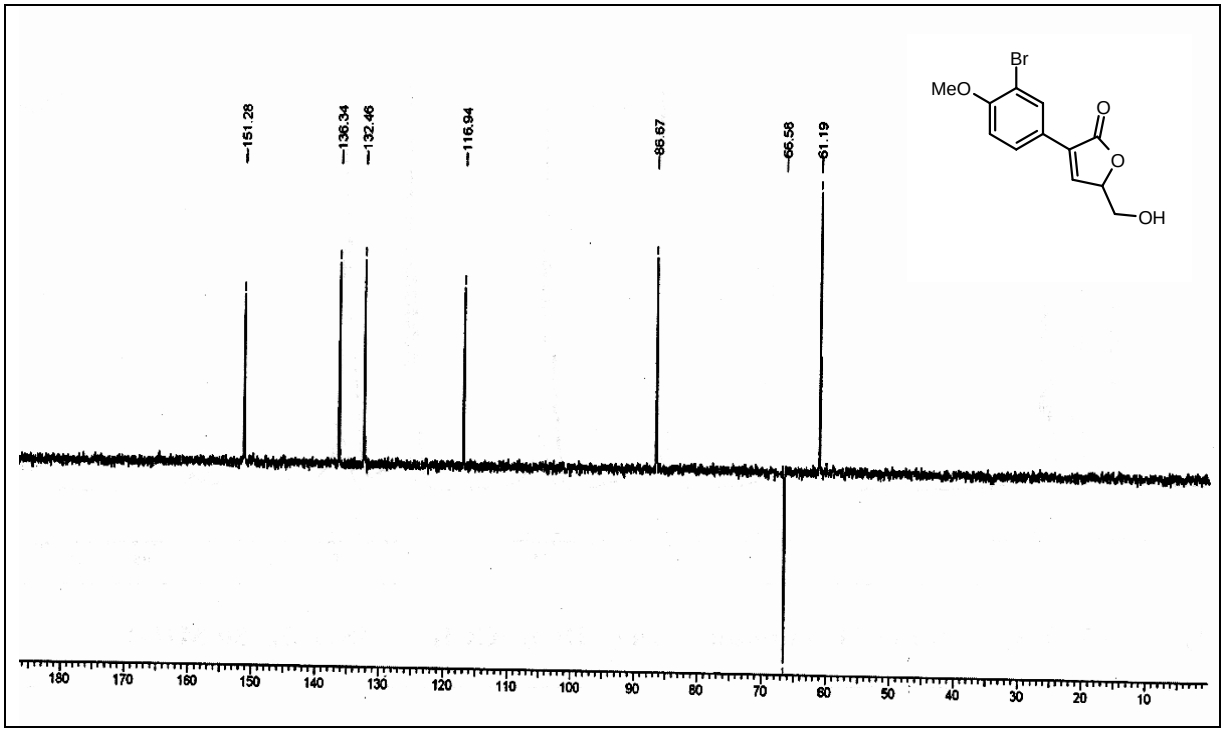
^{1}H NMR spectrum of compound 41 a ($CDCl_3$+CCl_4, 200 MHz)



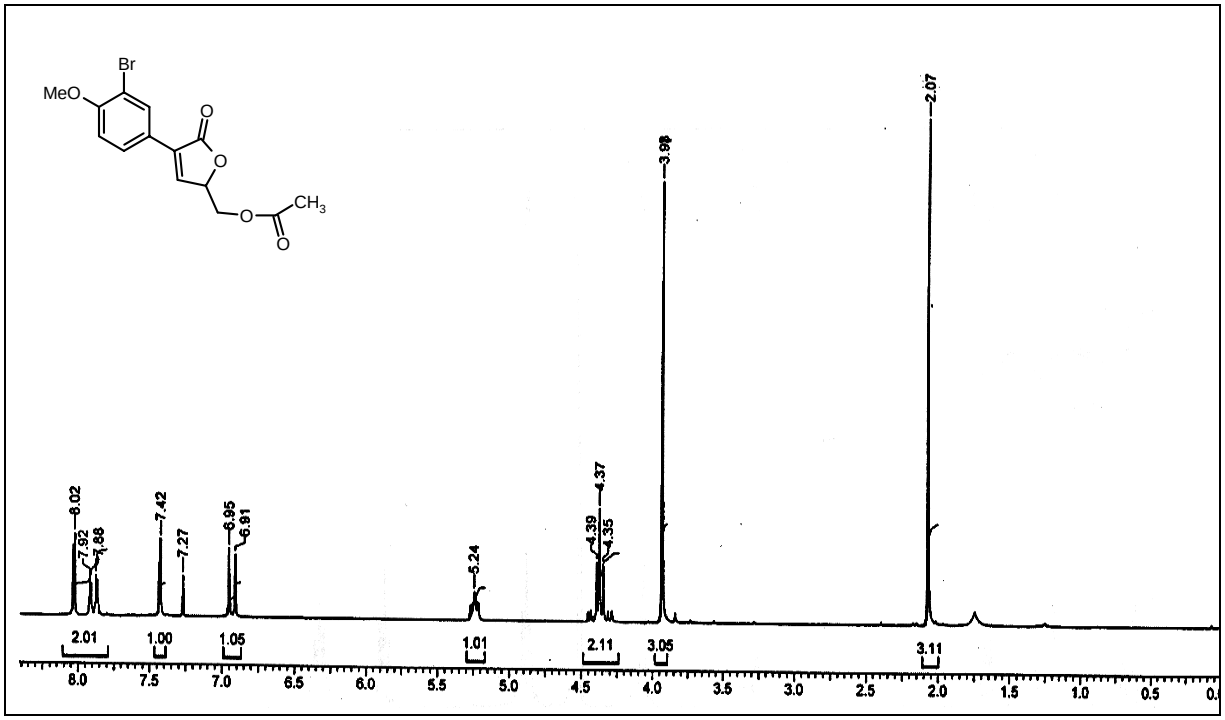
^{13}C NMR Spectrum of compound 41 a ($CDCl_3$+CCl_4+DMSO-D_6, 50 MHz)



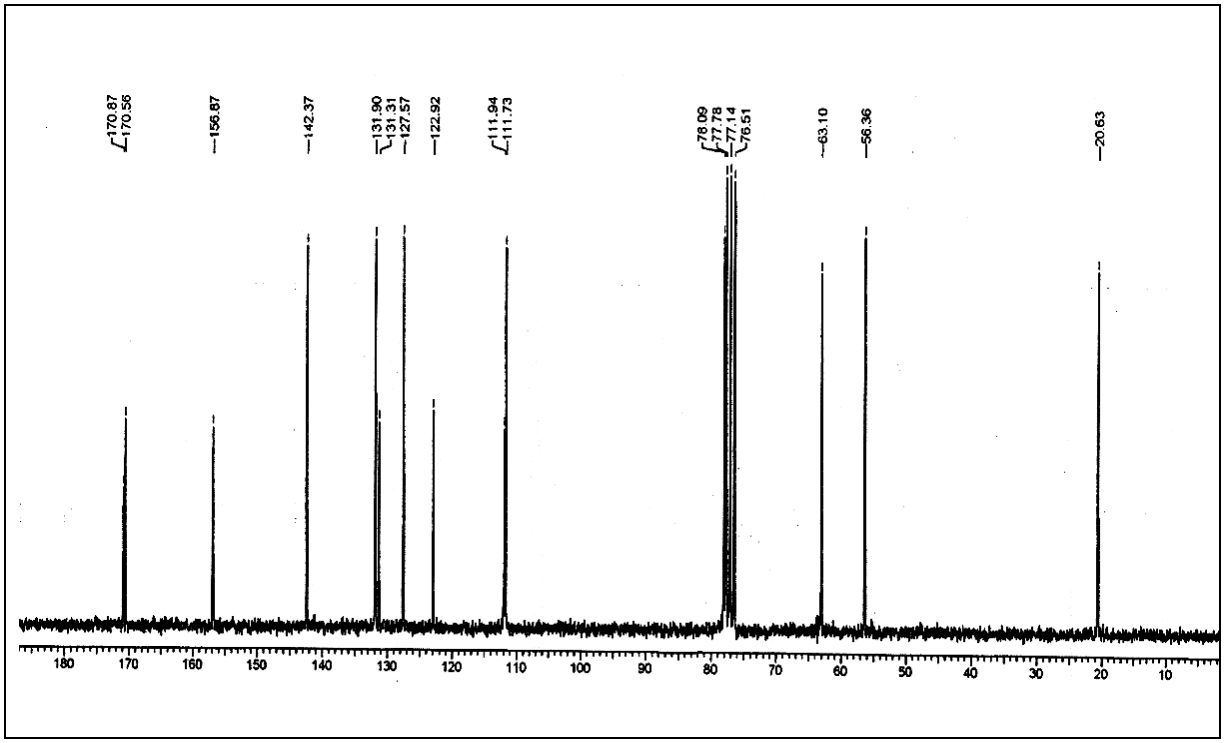
DEPT spectrum of compound 41 a ($CDCl_3$+CCl_4+DMSO-D_6, 50 MHz)



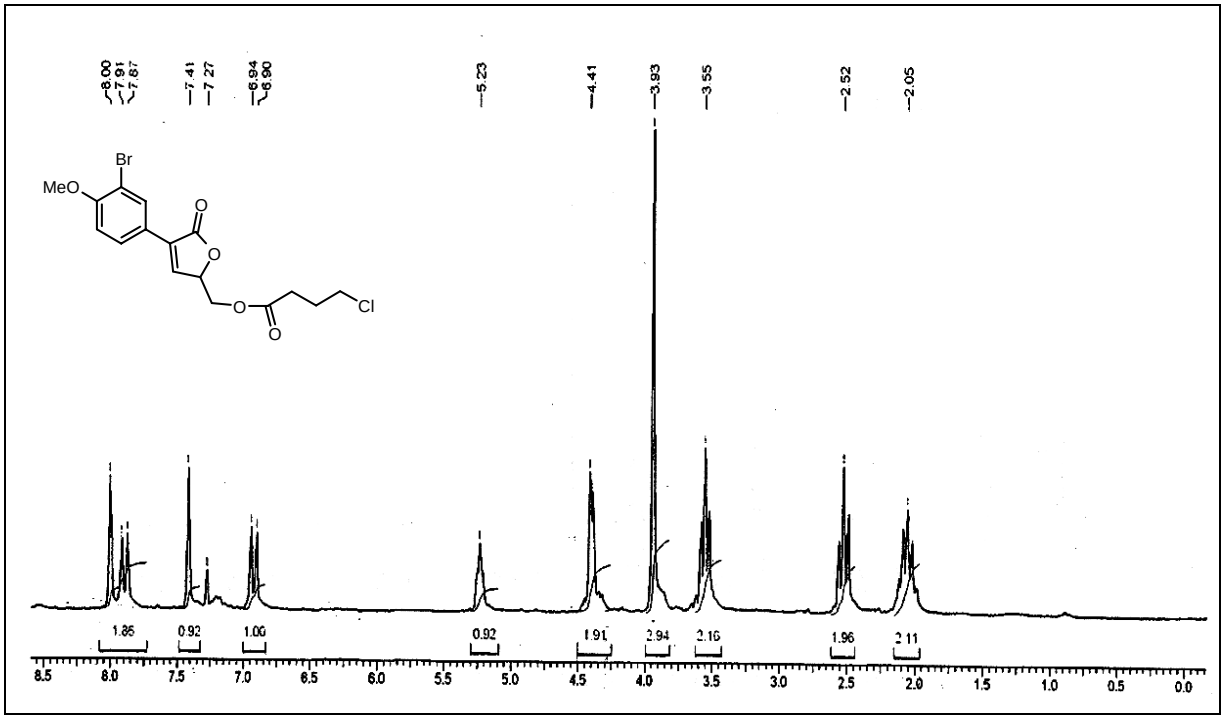
^{1}H NMR spectrum of compound 42 a ($CDCl_3$+CCl_4, 200 MHz)



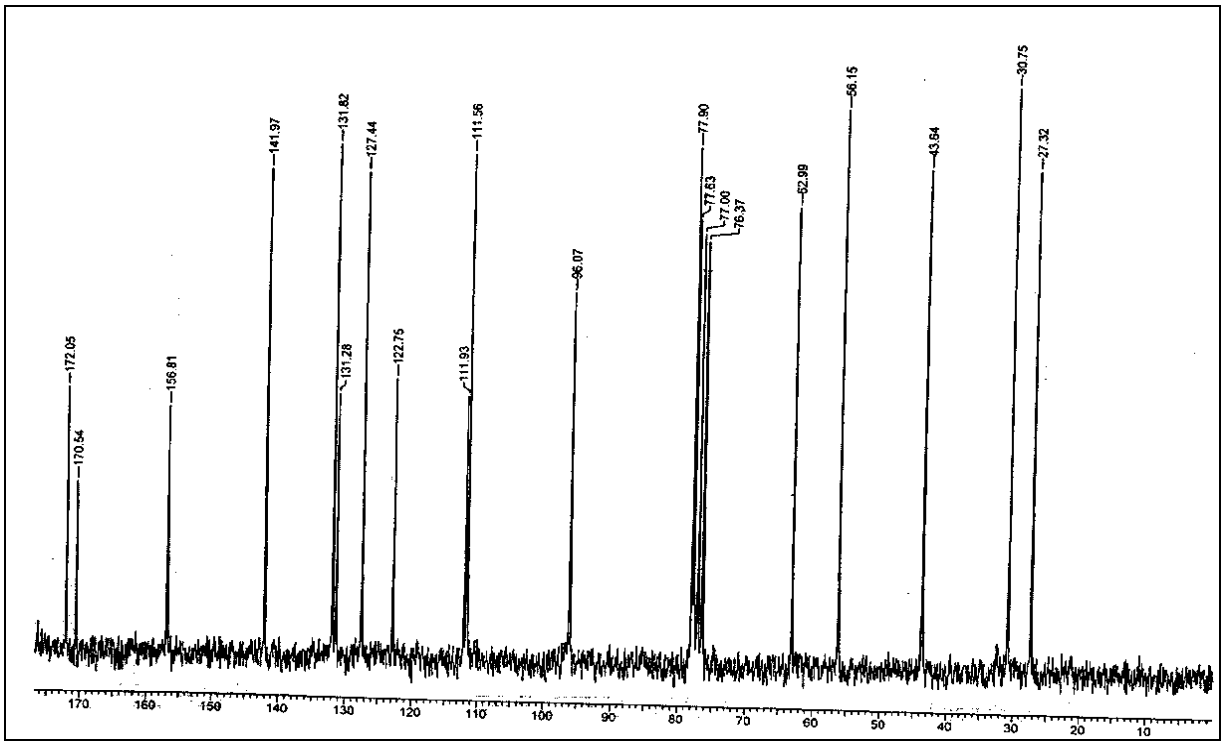
^{13}C NMR Spectrum of compound 42 a ($CDCl_3$+CCl_4, 50 MHz)



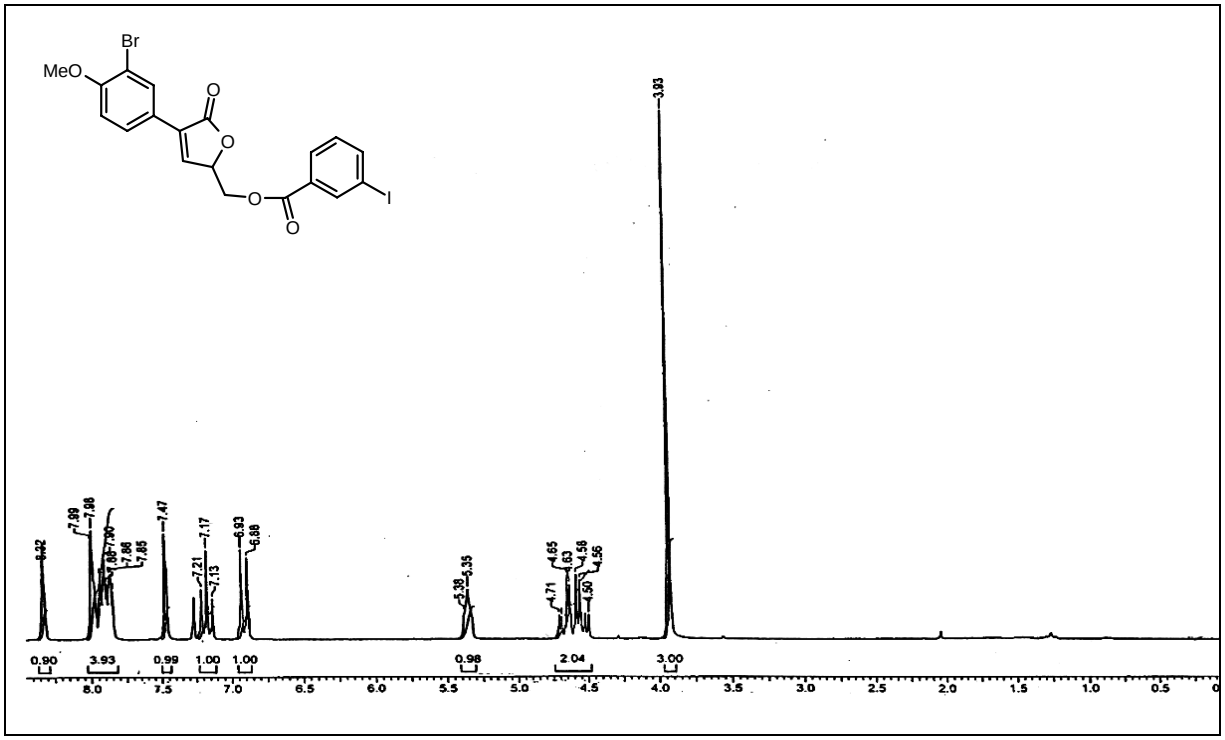
^{1}H NMR spectrum of compound 42 b ($CDCl_3$+CCl_4, 200 MHz)



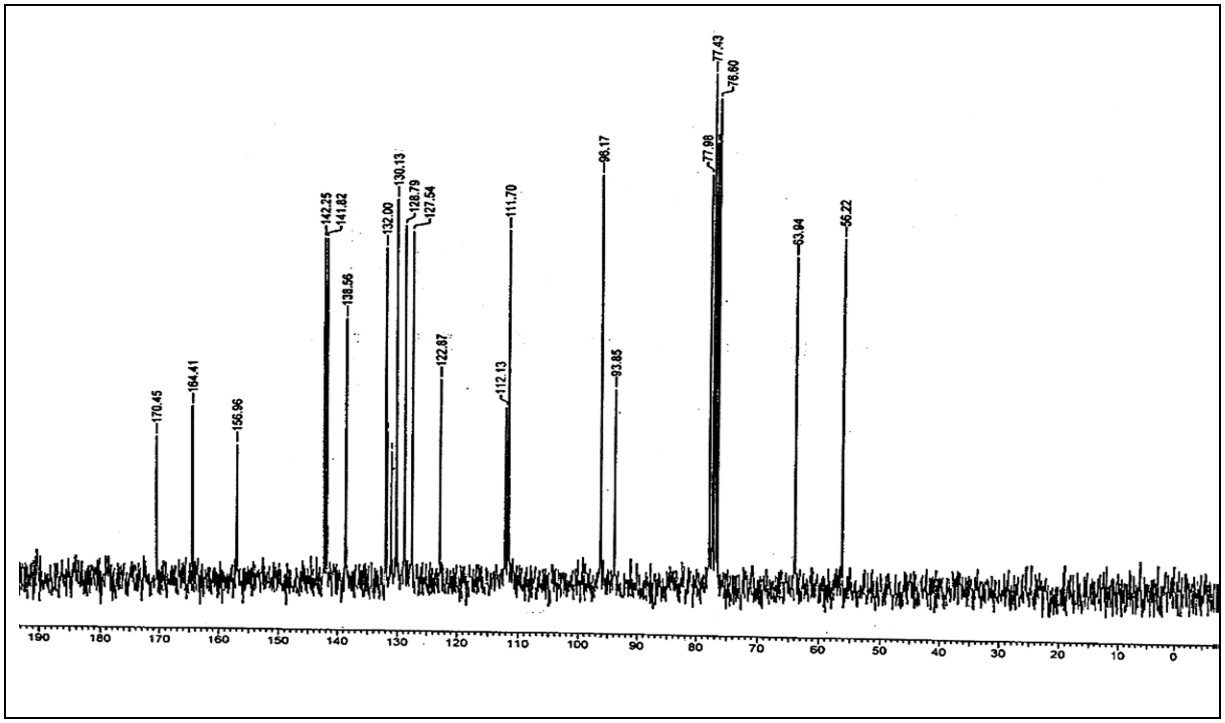
^{13}C NMR Spectrum of compound 42 b ($CDCl_3$+CCl_4, 50 MHz)



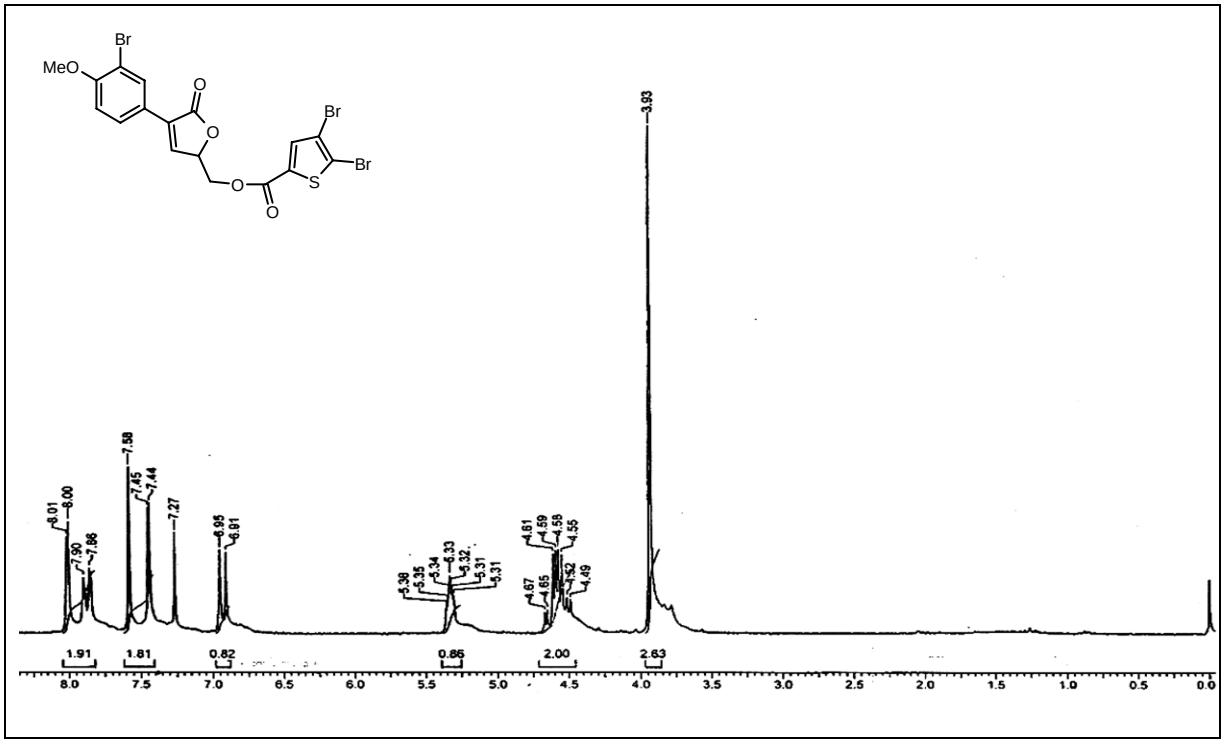
^{1}H NMR spectrum of compound 42 c ($CDCl_3$+CCl_4, 200 MHz)



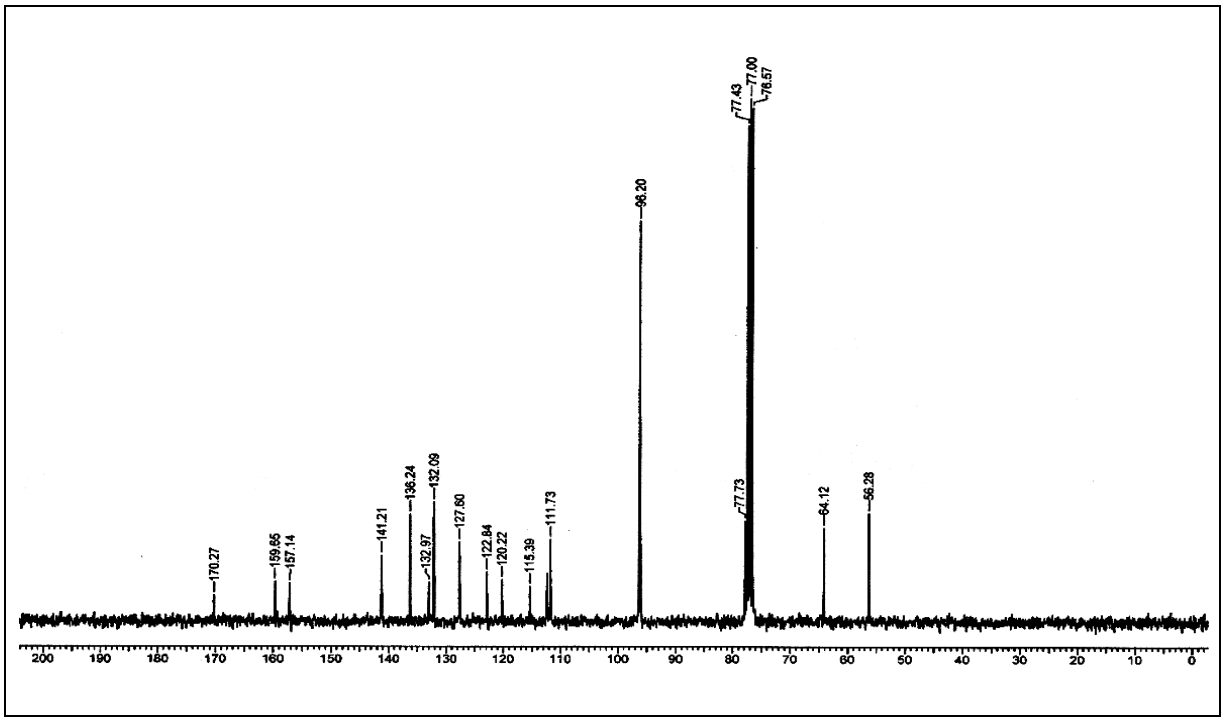
^{13}C NMR Spectrum of compound 42 c ($CDCl_3$+CCl_4, 50 MHz)



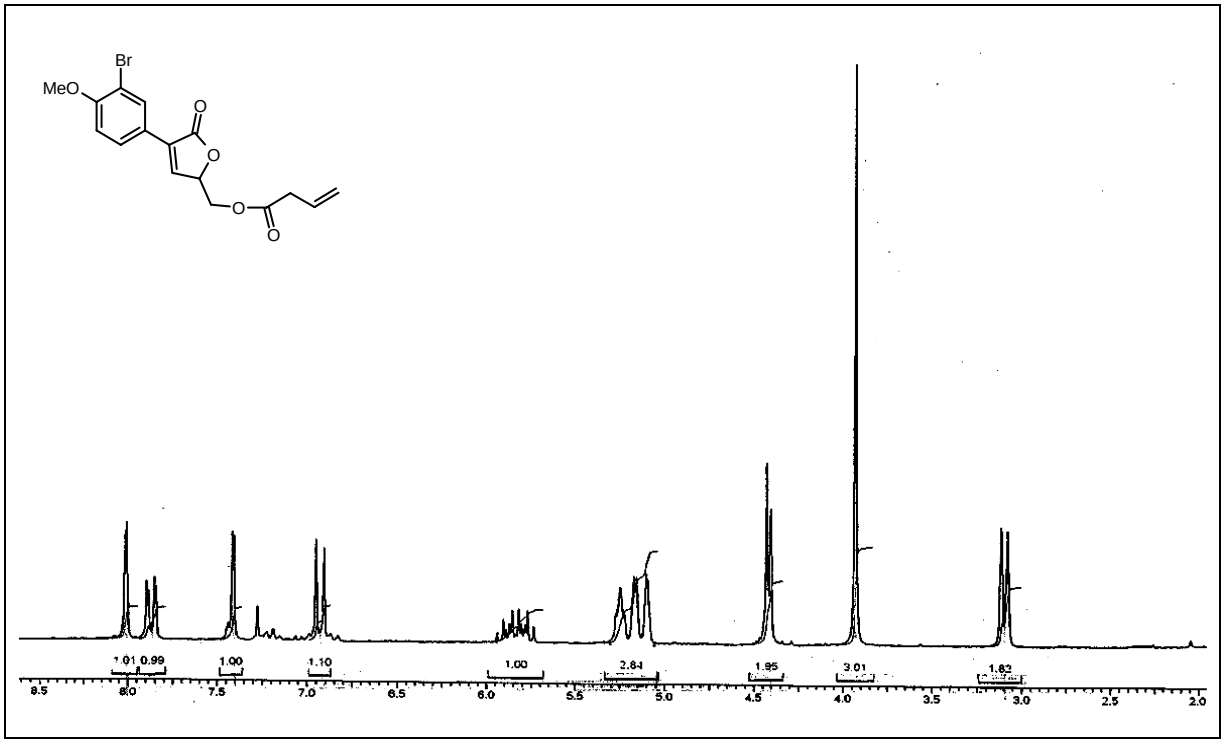
^{1}H NMR spectrum of compound 42 d ($CDCl_3$+CCl_4, 200 MHz)



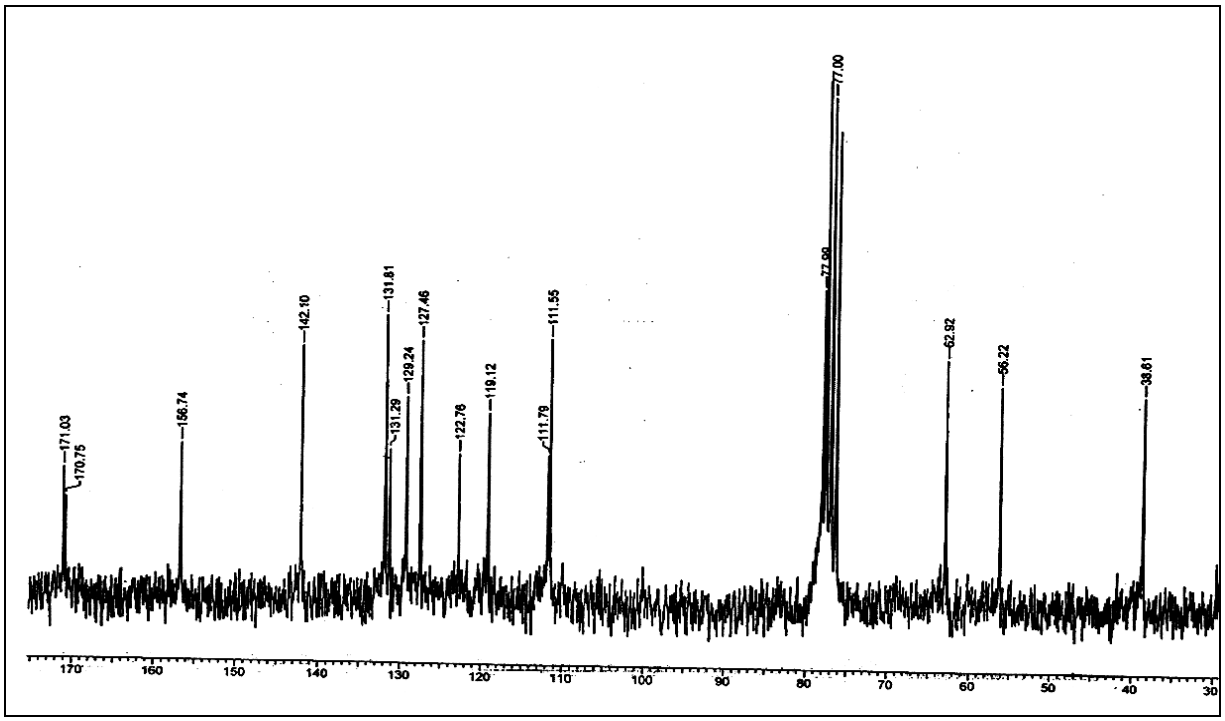
^{13}C NMR Spectrum of compound 42 d ($CDCl_3$+CCl_4, 50 MHz)



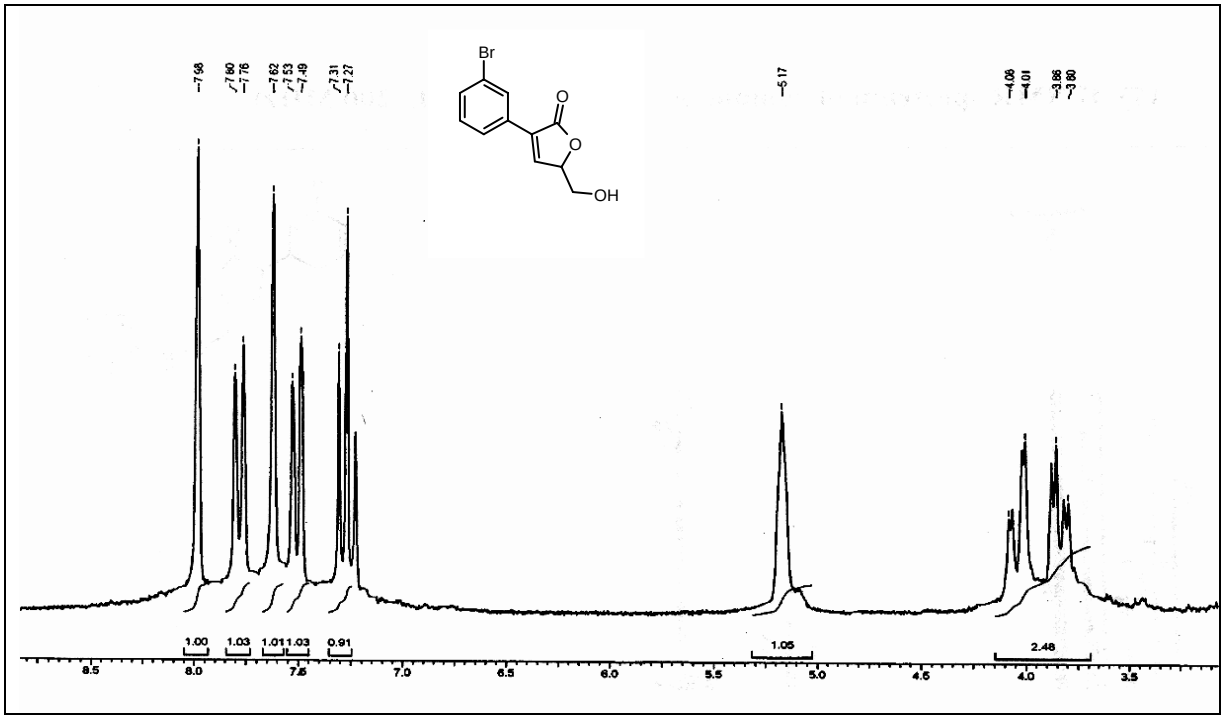
^{1}H NMR spectrum of compound 42 e ($CDCl_3$+CCl_4, 200 MHz)



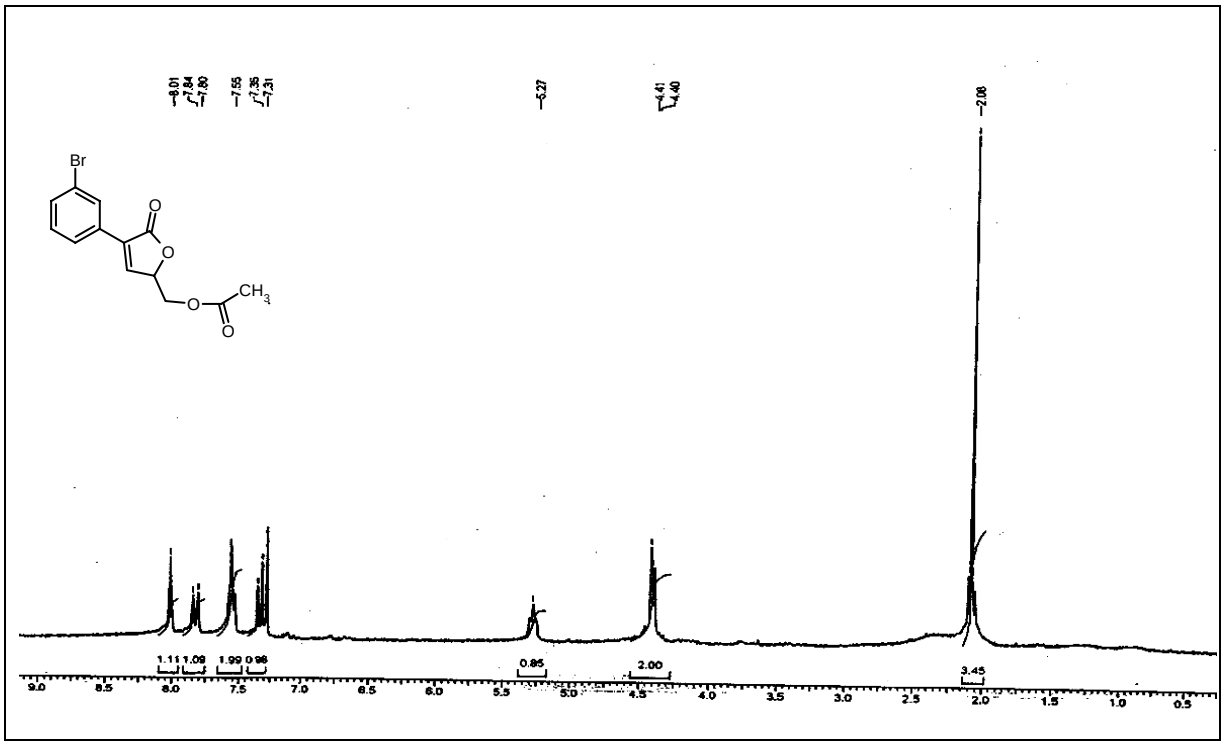
^{13}C NMR Spectrum of compound 42 e ($CDCl_3$+CCl_4, 50 MHz)



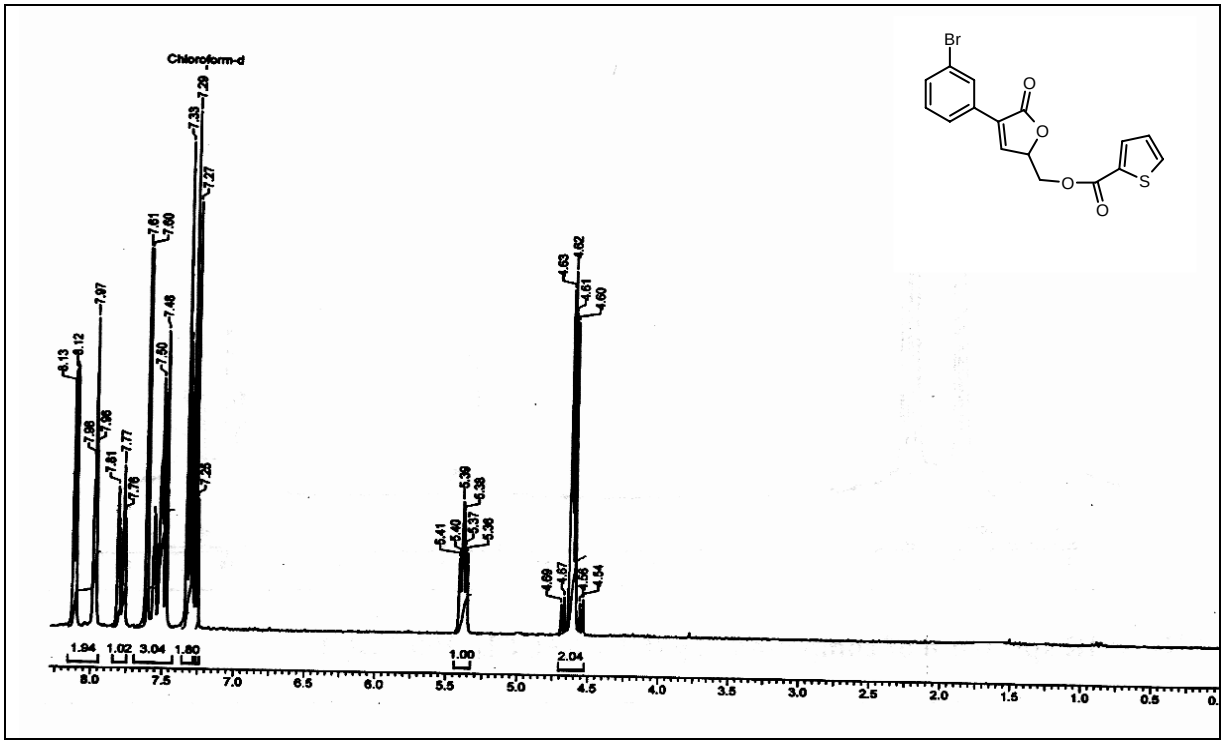
^{1}H NMR spectrum of compound 41 b ($CDCl_3$+CCl_4, 200 MHz)



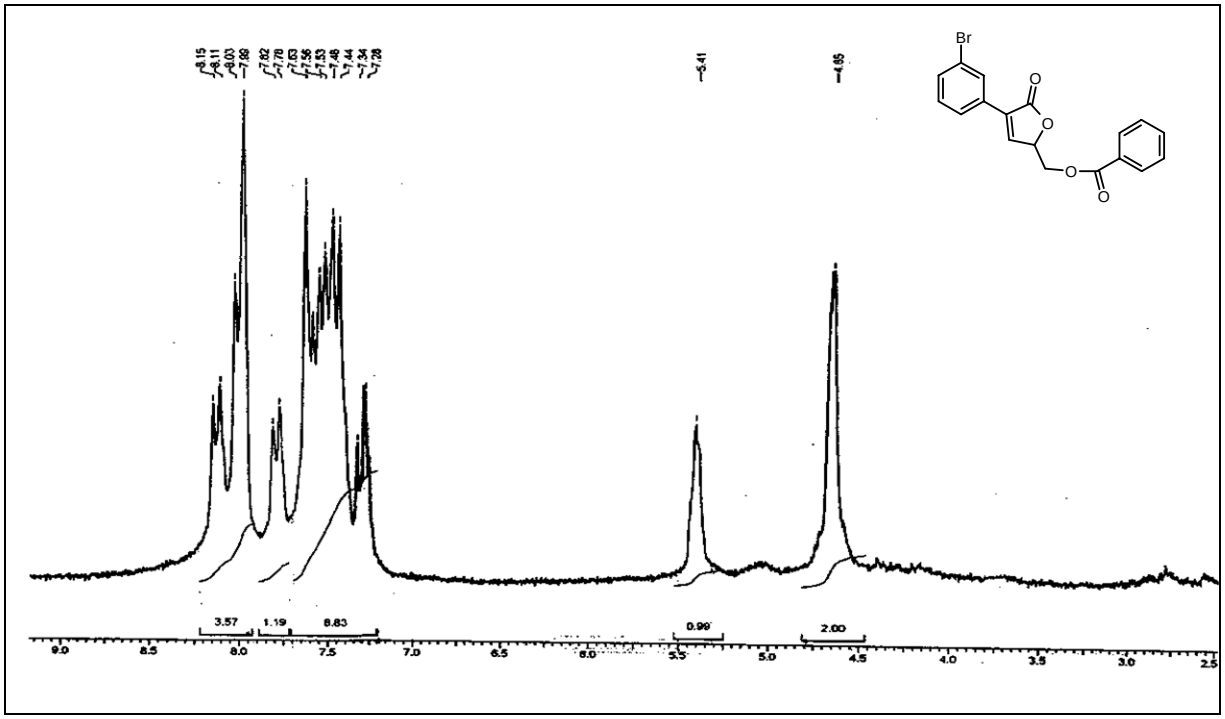
^{1}H NMR Spectrum of compound 42 g ($CDCl_3$+CCl_4, 200 MHz)



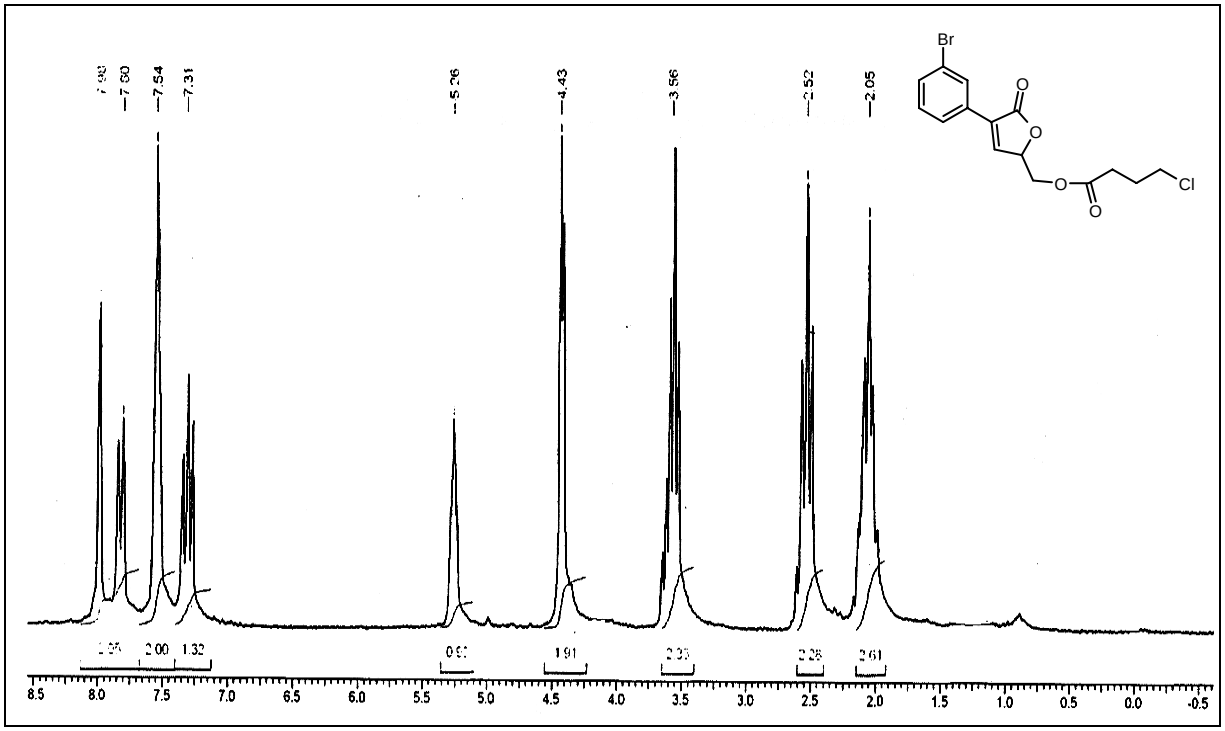
^{1}H NMR spectrum of compound 42 h ($CDCl_3$+CCl_4, 200 MHz)



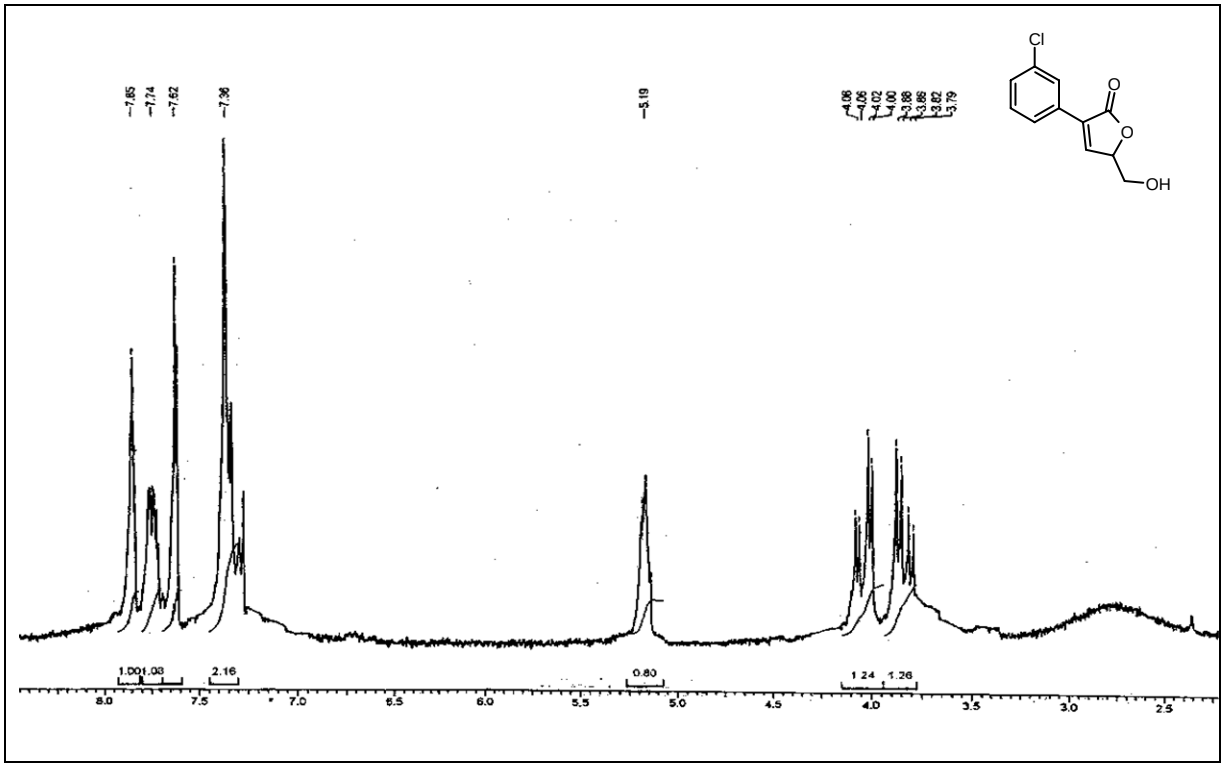
^{1}H NMR Spectrum of compound 42 i ($CDCl_3$+CCl_4, 200 MHz)



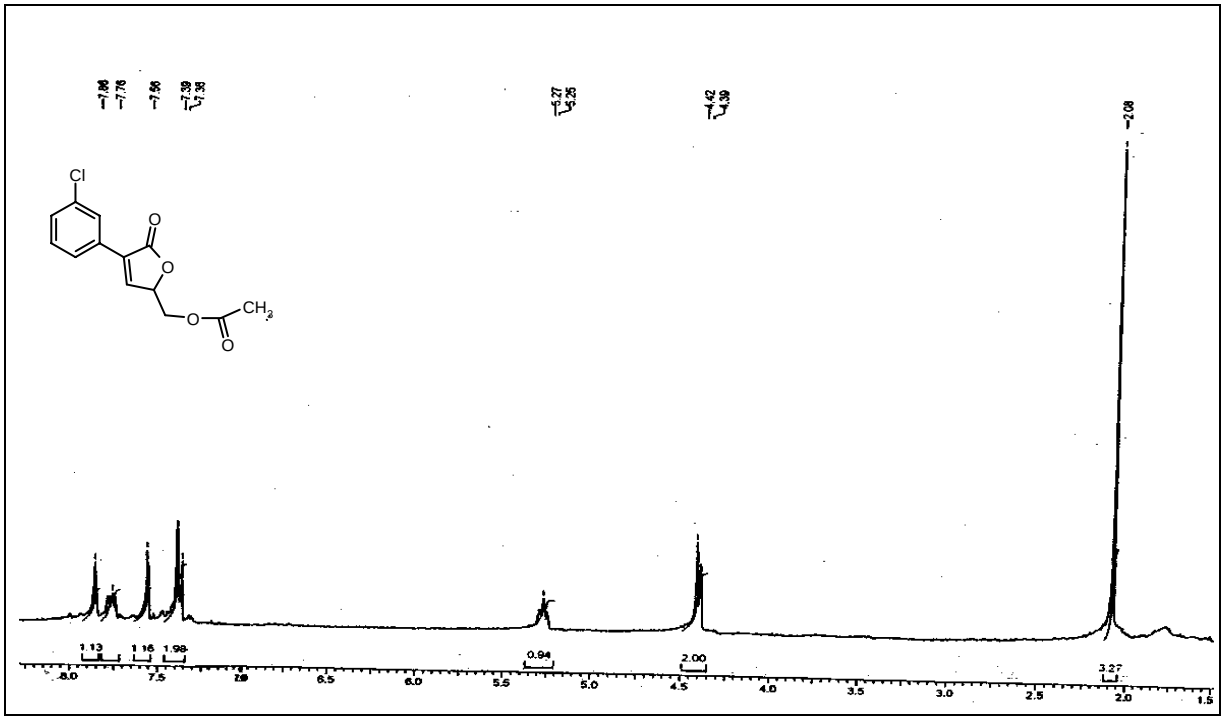
^{1}H NMR spectrum of compound 42 j ($CDCl_3$+CCl_4, 200 MHz)



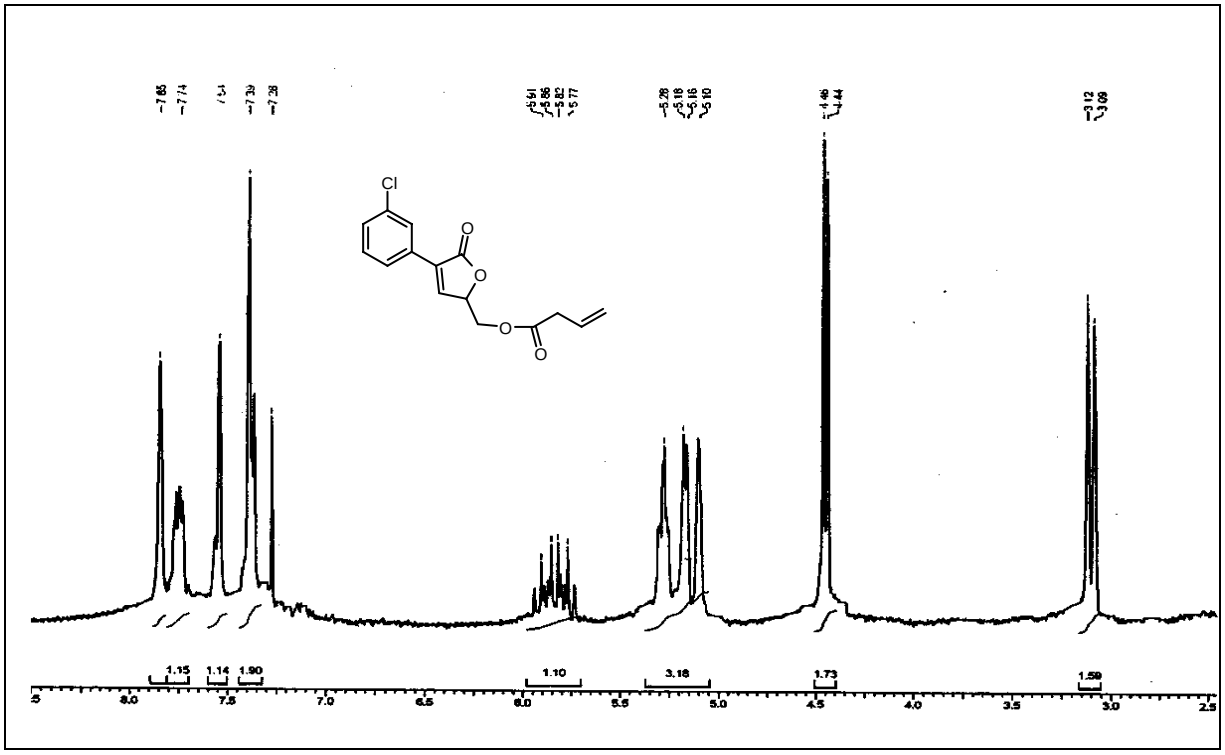
^{1}H NMR spectrum of compound 41 c ($CDCl_3$+CCl_4, 200 MHz)



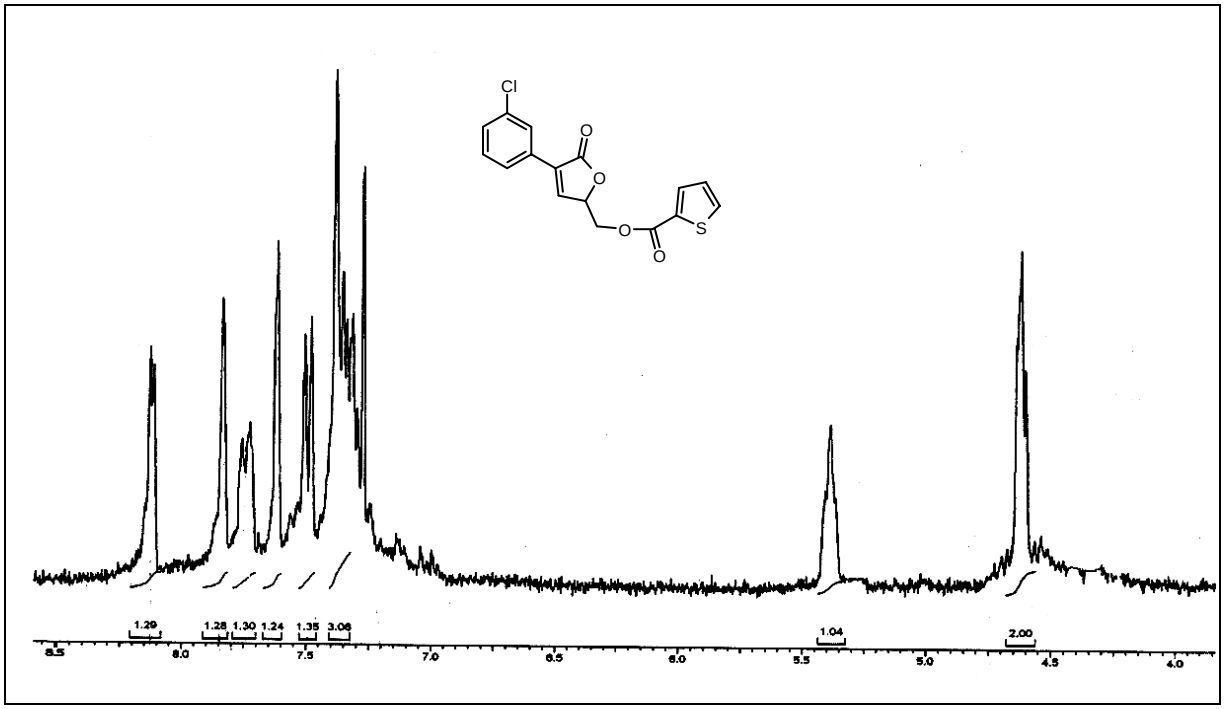
^{1}H NMR Spectrum of compound 42 k ($CDCl_3$+CCl_4, 200 MHz)



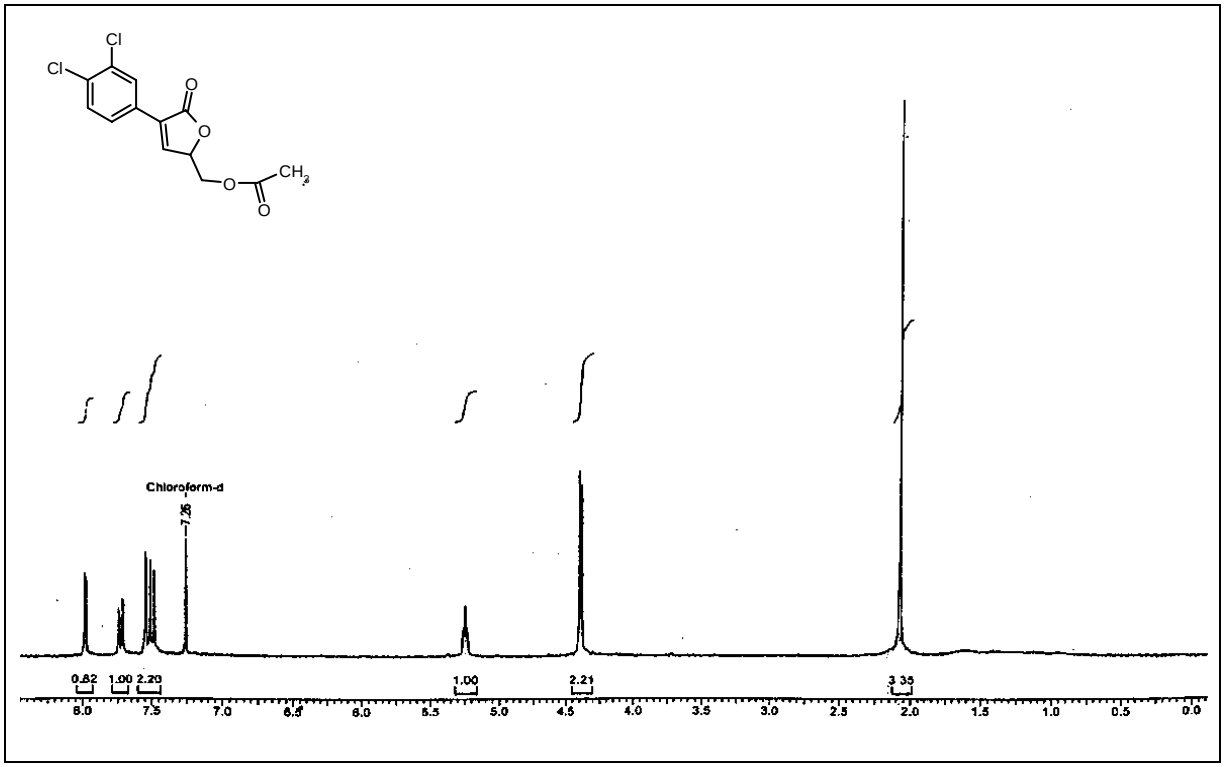
^{1}H NMR spectrum of compound 42 l ($CDCl_3$+CCl_4, 200 MHz)



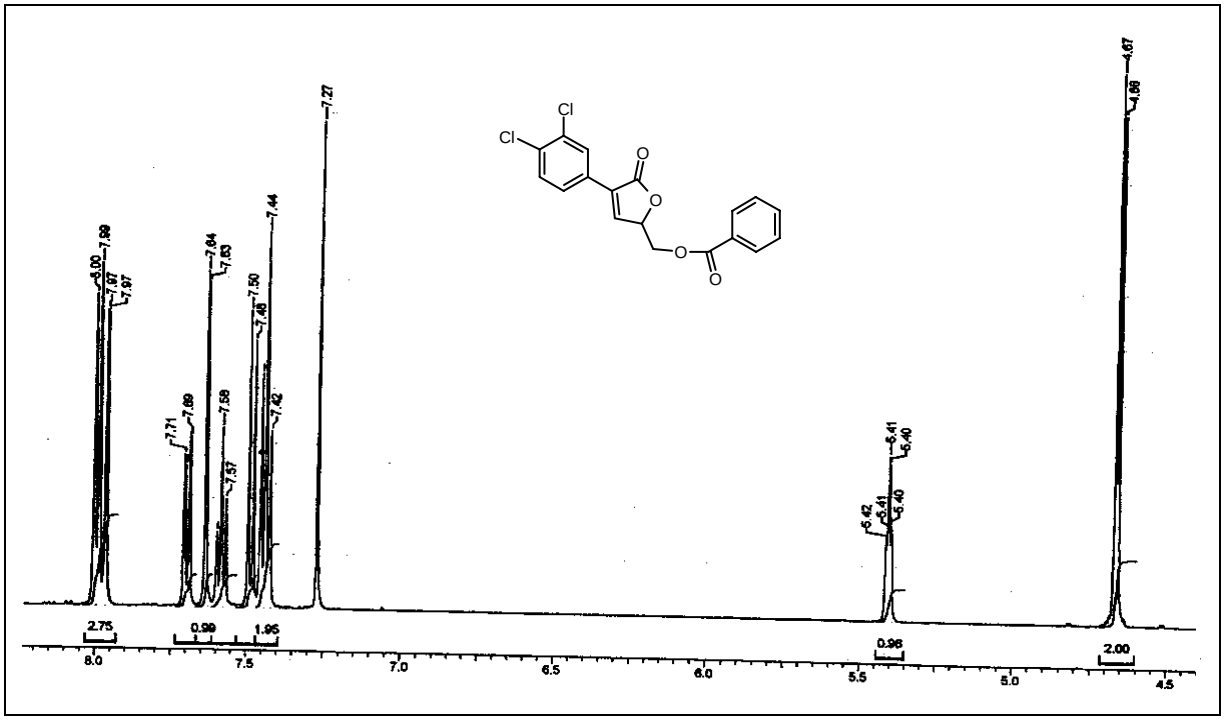
^{1}H NMR Spectrum of compound 42 m ($CDCl_3$+CCl_4, 200 MHz)



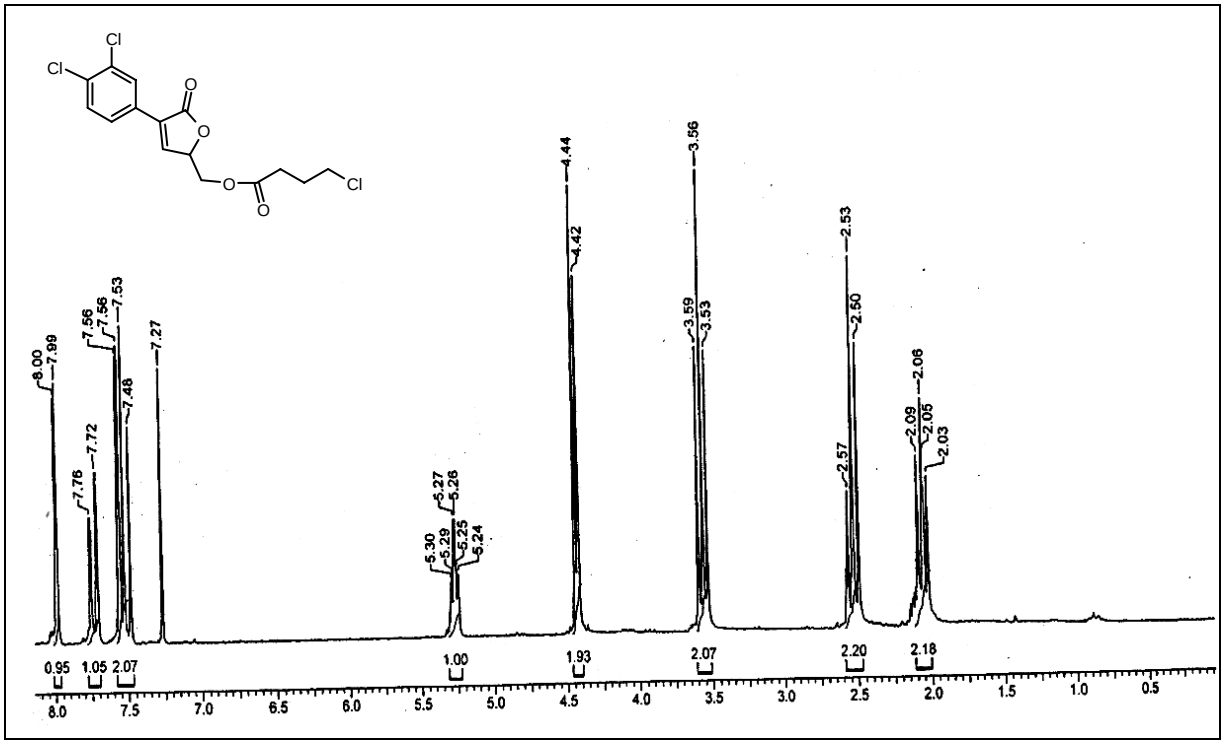
^{1}H NMR spectrum of compound 42 o ($CDCl_3$+CCl_4, 200 MHz)



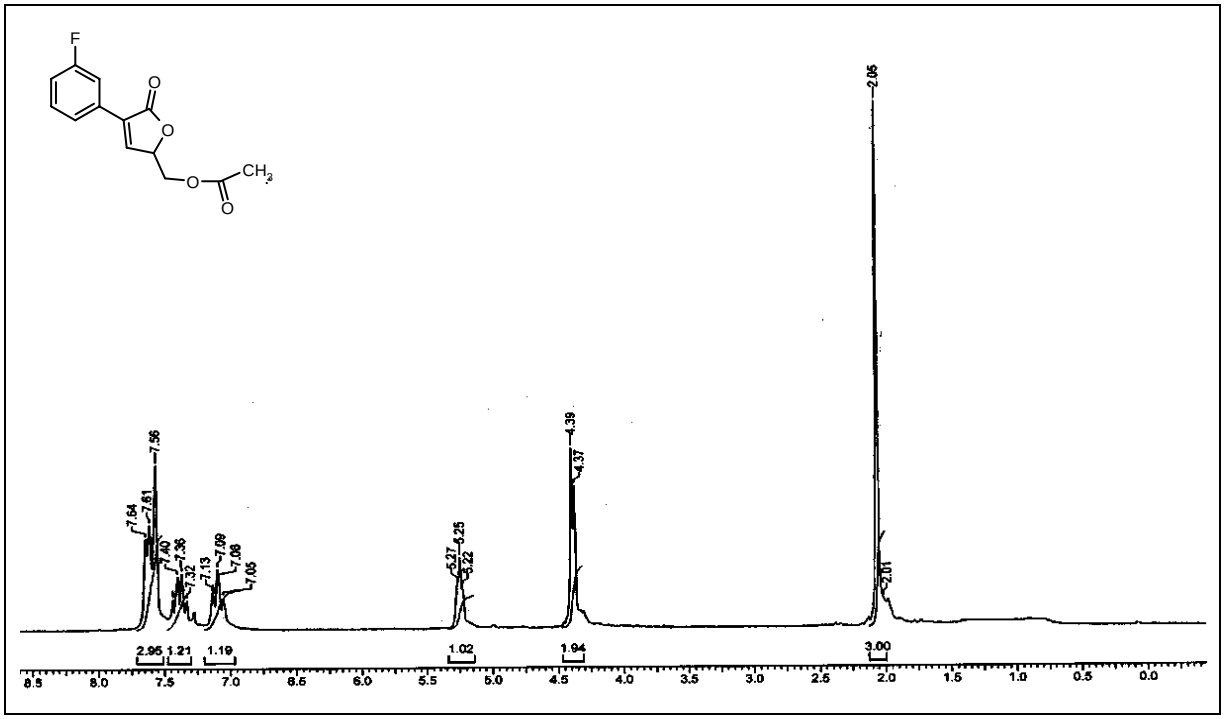
^{1}H NMR Spectrum of compound 42 p ($CDCl_3$+CCl_4, 200 MHz)



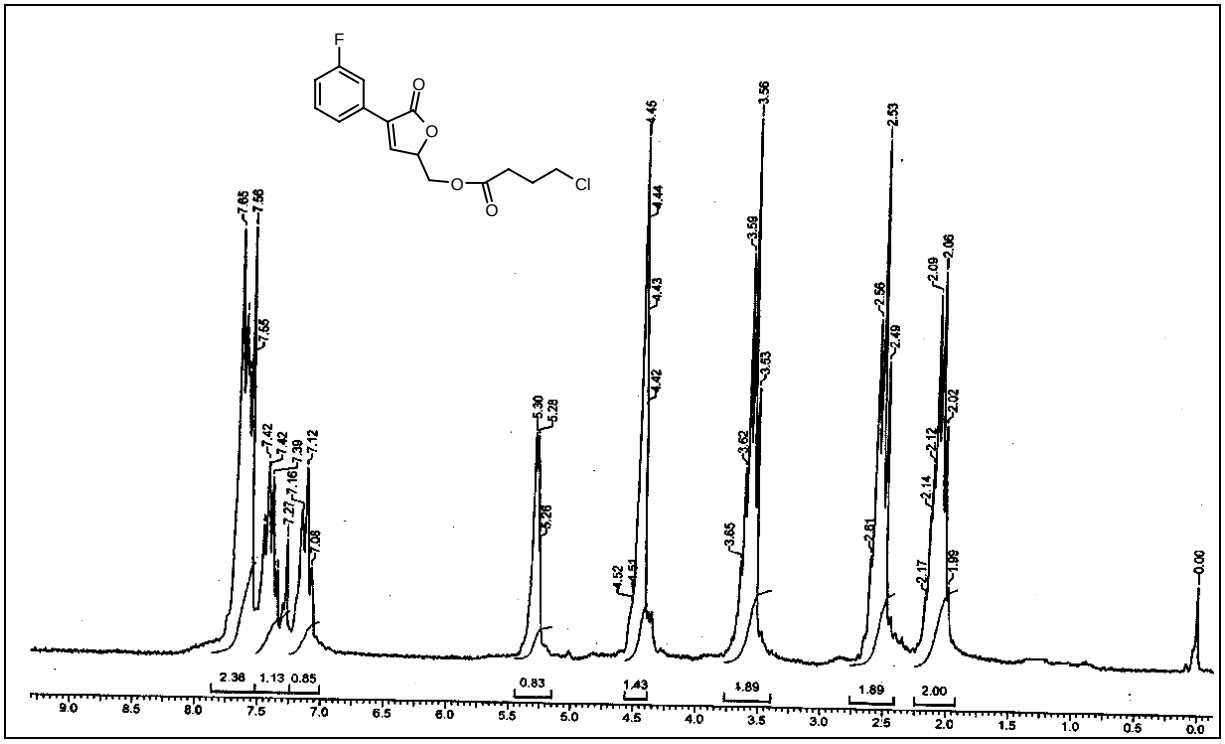
^{1}H NMR spectrum of compound 42 q ($CDCl_3$+CCl_4, 200 MHz)



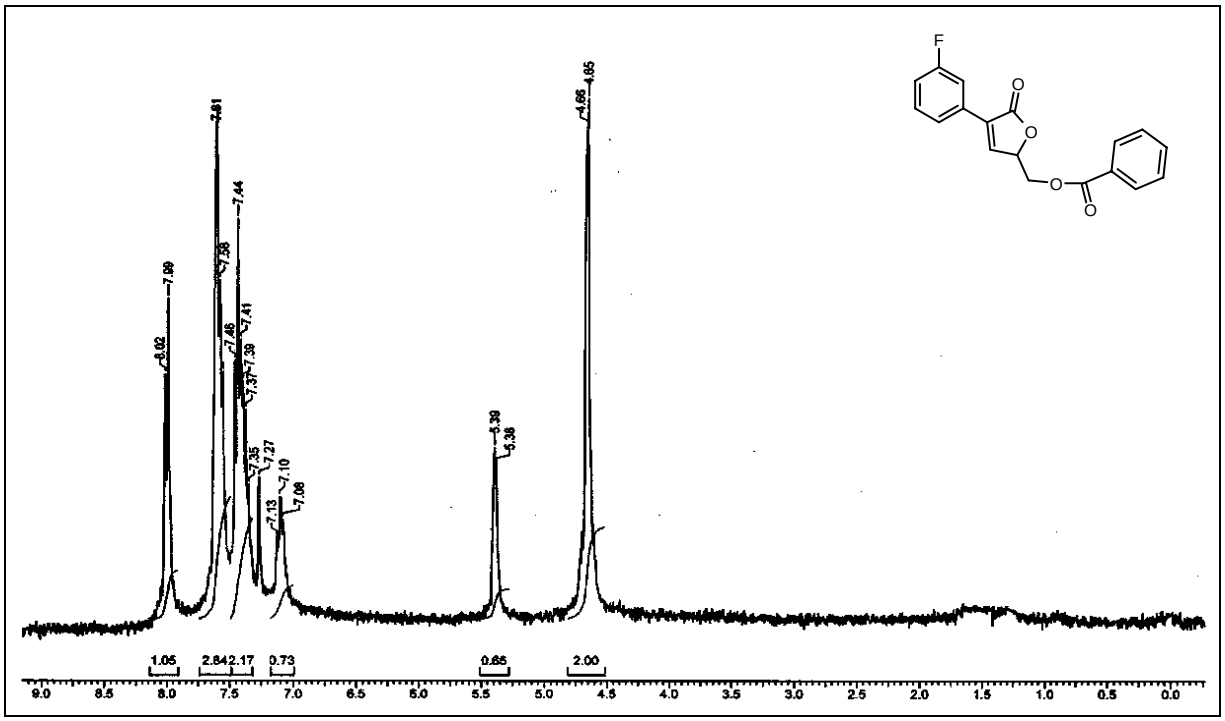
^{1}H NMR Spectrum of compound 42 s ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 42 t ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR Spectrum of compound 42 u ($CDCl_3$+CCl_4, 300 MHz)



2.1.6: REFERENCES:

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CHAPTER - II

SECTION - II

SYNTHESIS OF AZOLE DERIVATIVES AS ANTIFUNGAL AGENTS

2.2.1: INTRODUCTION:

Fungal infections are a major burden to the health and welfare of modern humans. They range from simply cosmetic, non-life-threatening skin infections to severe, systemic infections that may lead to significant debilitation or death. The selection of chemotherapeutic agents useful for the treatment of fungal infections is small. In this overview, a major chemical group with antifungal activity, the azole derivatives, is examined. Included are historical and state of the art information on the in vitro activity, experimental in vivo activity, mode of action, pharmacokinetics, clinical studies, and uses and adverse reactions of imidazoles currently marketed (clotrimazole (**43**), miconazole (**44**), econazole (**45**), ketoconazole (**6**), butoconazole (**46**), isoconazole nitrate (**47**), oxiconazole (**48**) and sulconazole nitrate (**49**) and aliconazole (**50**) as well as triazoles currently marketed (terconazole (**51**), fluconazole (**4**), voriconazole (**13**), itraconazole (**5**), alteconazole (**51**), and ICI 195,739 (**11**)).[1]

Although the first report of antifungal activity of an azole compound, benzimidazole, was already described in 1944 by Woolley, it was not until after the introduction of topical chlormidazole in 1958 that researchers became interested in the antifungal activity of azole compounds.[2] In the late 1960s, three new topical compounds were introduced, clotrimazole (**43**) developed by Bayer Ag (Germany), miconazole and econazole (**45**), both developed by Janssen Pharmaceutica (Belgium).[3] The *in-vitro* activity of clotrimazole against dermatophytes, yeasts, and dimorphic as well as filamentous fungi, is well-established and comparable to that of amphotericin B for many pathogens.[4] However, unacceptable side effects following oral administration[5] and unpredictable pharmacokinetics as a result of the induction of hepatic microsomal enzymes[6] have limited the use of clotrimazole to the topical treatment of dermatophytic infections and super-ficial candida infections, including oral thrush.

Miconazole, a phenethyl imidazole synthesized in 1969, was the first azole available for parenteral administration (although not before 1978). Like other azoles, it interferes with the biosynthesis of fungal ergosterol, but at high concentrations, miconazole may also cause direct membrane damage that results in leakage of cell constituents. The drug has a

limited spectrum of activity including dermatophytes, Candida species, dimorphic fungi, and Pseudallescheria boydii. The agent has proven to be an effective topical antifungal agent, but toxicity associated with the vehicle used for intravenous administration has limited its parenteral use[7], although it has been used successfully in the treatment of systemic candida infections, pseudallescheriasis and some refractory cases of cryptococcal meningitis.[8,9] Miconazole has recently been withdrawn from the market. In 1981, the Food and Drug Administration (FDA) approved the systemic use of ketoconazole, an imidazole derivative synthesised and developed by Janssen Pharmaceutica.[10] For almost a decade it would be regarded as the standard and was the only available oral agent for the treatment of systemic fungal infections. Until the introduction of the triazoles, ketoconazole was indicated as the drug of choice in chronic mucocutaneous candidiasis[11] and as an effective alternative to amphotericin B (**1**) in less severe (nonimmunocompromised) cases of blastomycosis,[12] histoplasmosis,[12] and paracoccidioidomycosis[13] in coccidioidomycosis, the relapse rate after discontinuation of the drug was high.[14] Ketoconazole has not been adequately evaluated in deep-seated candida infections or cryptococcosis and was ineffective in aspergillosis and mucormycosis. Over the years, a number of clinically relevant shortcomings of this compound became evident:

• The absorption of orally administered ketoconazole showed considerable interindividual variation and was markedly influenced by gastric pH.[15]
• An intravenous formulation was not available.
• The drug penetrated the blood–brain barrier poorly and could therefore not be recommended for the treatment of fungal meningitis.[16,17]
• Ketoconazole was largely fungistatic and proved to be less effective in immunocompromised patients.[3]
• The use of ketoconazole was associated with several dose-related (gastrointestinal) side effects,[12] in addition, ketoconazole could cause symptomatic, even fatal, drug-induced hepatitis.[18]

• When given in doses exceeding 400 mg daily, ketoconazole might reversibly inhibit the synthesis of testosterone and cortisol, resulting in a variety of endocrine disturbances, including rare cases of adrenal insufficiency.[19]

• A number of clinically important, often unpredictable, drug interactions (e.g. to cyclosporine) have been reported.[20] Thus, the poor response rates and frequent recurrences of major fungal infections, as well as the toxicity associated with ketoconazole therapy, led to the search for a second chemical group of azole derivatives, namely the triazoles. In general, the triazoles demonstrate a broader spectrum of antifungal activity and reduced toxicity when compared with the imidazole antifungals. Terconazole, the first triazole marketed for human use, was active in the topical treatment of dermatomycoses.

Fluconazole (**4**), a broad-spectrum triazole antifungal developed by Pfizer and approved for use in early 1990, covers many of the shortcomings of the imidazoles. In contrast to ketoconazole, fluconazole is highly water soluble and can be given intravenously to seriously ill patients. After oral administration, absorption is essentially complete (90 % bioavailability) and not influenced by gastric pH.[21] In contrast to ketoconazole, fluconazole enters the cerebrospinal fluid (CSF) extremely well, with CSF levels of almost 80% of the corresponding serum levels.[22] The serum half-life allows once-daily dosing, and, also in contrast to ketoconazole, renal clearance is the major route of elimination of fluconazole, with 70 - 80 % of unchanged drug excreted in the urine.[23] Given this favourable pharmacokinetic profile (Table 1), Fluconazole has been studied extensively in various clinical settings, both in prophylaxis and in therapy.

The drug is approved for the treatment of oropharyngeal, oesophageal, vaginal, peritoneal and genito-urinary candida infections, disseminated candidiasis (including chronic disseminated candidiasis) and cryptococcal meningitis. Fluconazole also has good activity against coccidioidomycosis and is a good alternative to ketoconazole in chronic mucocutaneous candidiasis.

Fluconazole has no clinically meaningful activity in infections caused by filamentous fungi. In addition, the drug is relatively safe (even at daily doses up to 1600 mg) and does not interfere with the synthesis of testosterone or cortisol. Also, fluconazole has fewer drug interactions than does ketoconazole. The initial enthusiasm for fluconazole,

however, has been challenged by two recent developments, the evolving spectrum of fungal pathogens and the development of azole-resistance.

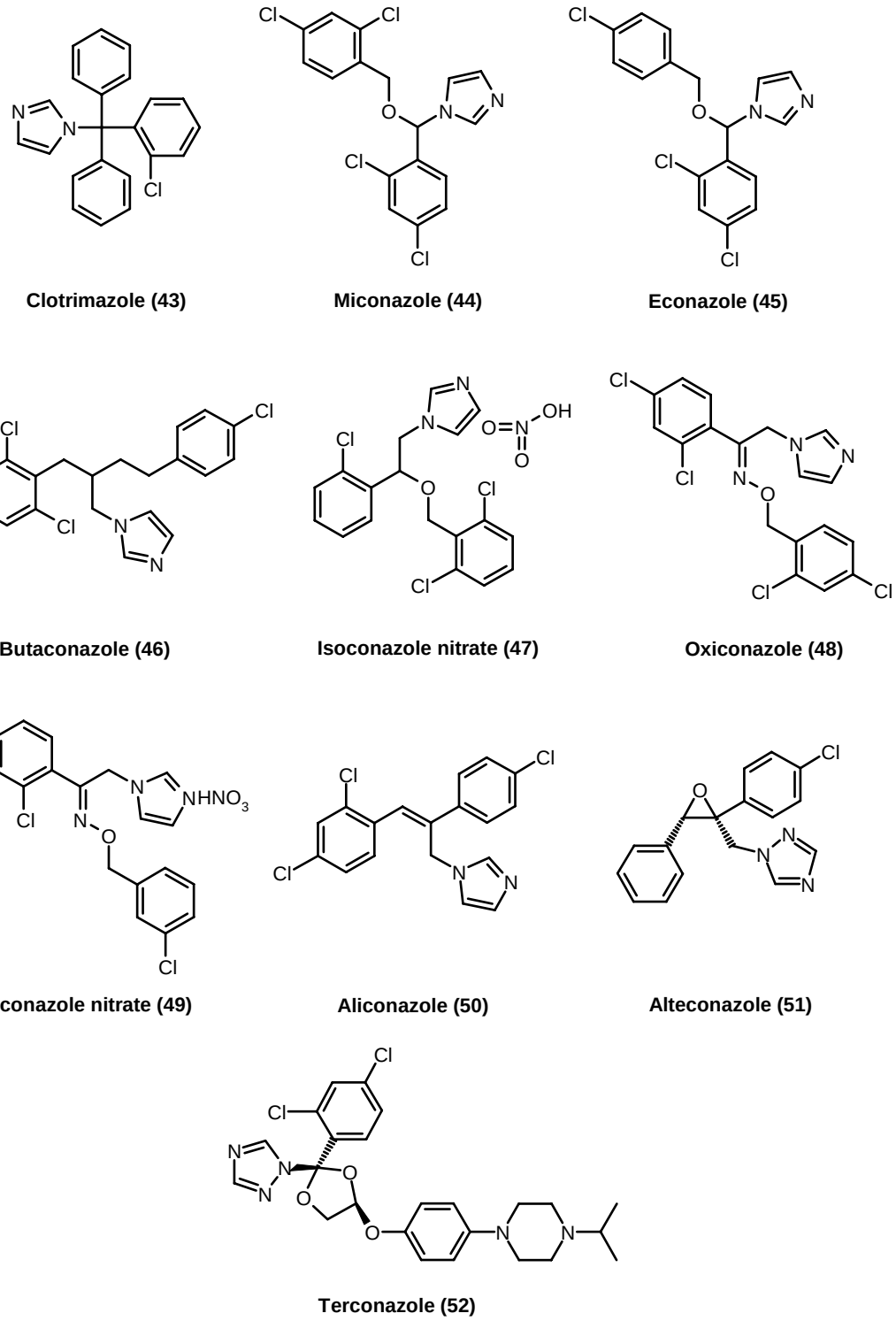


Fig. 1 Chemical Structures of Triazoles

Voriconazole (**13**), structurally related to fluconazole, was developed by Pfizer Pharmaceuticals as part of a programme designed to enhance the potency and spectrum of activity of fluconazole.[24] Voriconazole displays wide-spectrum *in-vitro* activity against fungi from all clinically important pathogenic groups such as Candida spp., Aspergillus spp., C. neoformans, dimorphic fungi, dermatophytes, and some of the emerging mould pathogens including Fusarium spp., Penicillium, Scedosporium, Acremonium and Trichosporon. Members of the zygomycetes still appear to be resistant. Compared to reference triazoles, voriconazole is several-fold more active than fluconazole and itraconazole against Candida spp. However, C. albicans isolates with decreased susceptibility to fluconazole and itraconazole also demonstrate significantly higher MICs for voriconazole, and isolates (Candida as well as Aspergillus) that are highly resistant to both fluconazole and itraconazole show apparent cross-resistance to voriconazole. The drug is orally and parenterally active but exhibits complex pharmacokinetics.

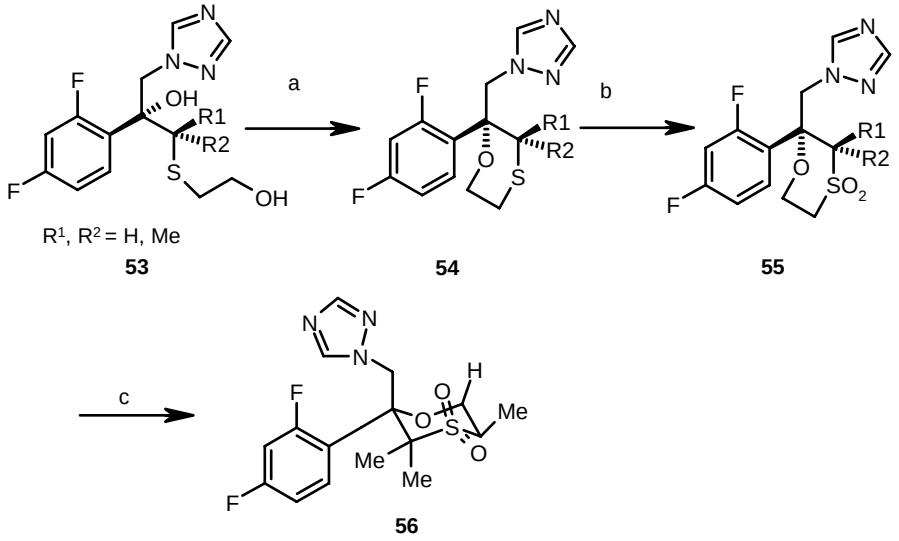
Interestingly, animal studies have revealed good penetration into the CSF and central nervous system. The promising *in-vitro* activity has been confirmed in a range of infections in immunosuppressed animal models where voriconazole proved to be more effective than amphotericin B, fluconazole and itraconazole. Data from phase - II and III clinical trials indicate that voriconazole is a promising agent for the treatment of oropharyngeal candidiasis in AIDS patients, oesophageal candidiasis, and acute and chronic invasive aspergillosis, including cerebral aspergillosis. A number of cases have reported activity in unusual mould infections, such as scedosporiosis.

Clearly, progress in the development of new antifungals has lagged behind antibacterial research, a fact that can be explained by at least two factors. First, before the HIV-era, the occurrence of fungal infections was believed to be too low to warrant aggressive research by the pharmaceutical industry. Second, the ‘apparent’ lack of a highly selective fungal target, not present in other eukaryotic (including mammalian) cells, precluded the development of new agents. Until recently, the arsenal that was available for the treatment of systemic fungal infections was limited in number and consisted mainly of the polyene antibiotic amphotericin B, some azole derivatives, the allylamines–

thiocarbamates and 5-flucytosine. Considering these limitations in the mind we have synthesized the new analogues of azole antifungals which are discussed in this section.

BRIEF REVIEW OF LITERATURE:

Miyauchi H. *et al*. reported[25] a series of azole derivatives containing an oxathiane ring. A series of triazole analogoues containing an oxathiane ring were synthesized as shown in scheme - 1. Oxathianes (**54**) were respectively oxidized with hydrogen peroxide in presence of catalytic amount of sodium tungstate to give 4,4-dioxooxathianes (**55**). Furthermore this 4,4-dioxooxathiane (**55**) was deprotonated with sodium hydride and treated with methyl iodide to afford a 5-substituted derivative (**56**) as a single isomer.

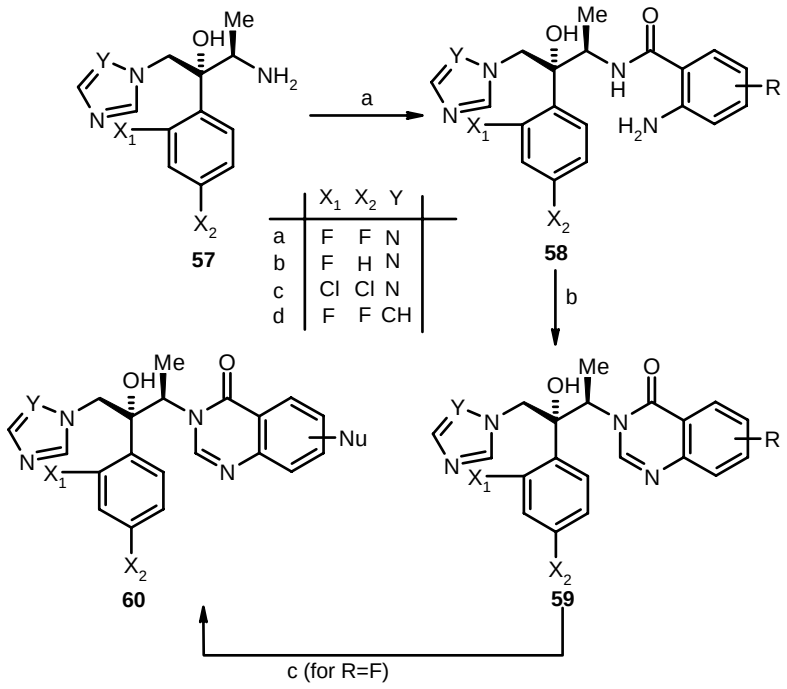


Reagents and Conditions: a) DEAD, Ph_3P, THF, rt, 4 h; b) H_2O_2, Na_2WO_4, MeOH, rt, 1 h; c) NaH, MeI, DMF, -20 ^{0}C-rt, 1 h

Scheme - 1

Bartoli J. *et al.* reported[26] a series of azole antifungal agents featuring a quinazolinone nucleus. In general, these compounds displayed higher *in vitro* activities against filamentous fungi and shorter half-lives than the previous structures. Quinazolinones were readily synthesized from enantiomerically pure amines a-c[27,28] by two-step

procedure (Scheme - 2) consisting of a DCC coupling with the corresponding anthranilic acid, followed by heating the resulting intermediate **59** with triethylorthoformate or formamidine acetate in NMP to afford the final compounds **60** carrying a NR_1R_2, OR, or SR substitutent at the 7-position.

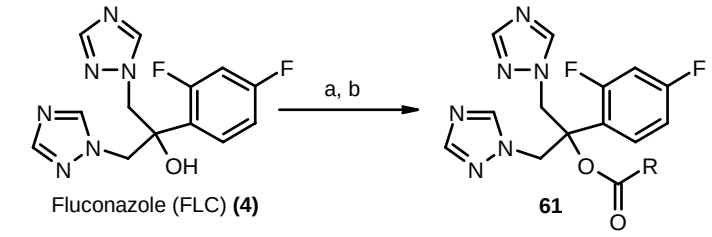


Reagents and Conditions: a) DCC, HOBT, NEt_3, DMF, room temperature, 18 h; b) $(EtO)_3CH$, NMP, 110 ^{0}C, 18 h; c) HNu, NaH, NMP, heat.

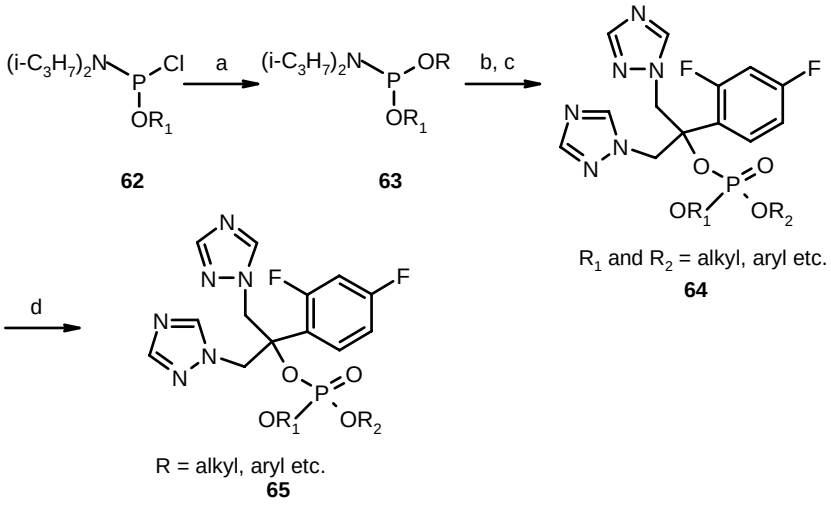
Scheme - 2

Nam N. -H. *et al*. reported[29] two classes of fluconazole derivatives, carboxylic acid esters **61** and fatty alcohol and carbohydrate phosphate esters **65**, were synthesized and evaluated *in vitro* against Cryptococcus neoformans, Candida albicans, and Aspergillus niger. All carboxylic acid ester derivatives of fluconazole, such as O-2-bromooctanoyl fluconazole (MIC = 111l g/ml) and O-11-bromoundecanoyl fluconazole (MIC = 198l g/ml), exhibited higher antifungal activity than fluconazole (MIC P4444l g/mL) against C. albicans ATCC 14053 in SDB medium. Several fatty alcohol phosphate triester derivatives of fluconazole, exhibited enhanced antifungal activities against *C. albicans*

and/or *A. niger* compared to fluconazole in SDB medium. For example, 2-cyanoethyl-x-undecylenyl fluconazole phosphate with MIC value of 122l g/ml had at least 36 times greater antifungal activity than fluconazole against *C. albicans* in SDB medium. Methyl-undecanyl fluconazole phosphate with a MIC value of 190l g/ml was at least 3-fold more potent than fluconazole against A. niger ATCC 16404. All compounds had higher estimated lipophilicity and dermal permeability than those for fluconazole. The synthetic strategy used for the synthesis of these derivatives is shown in scheme - 3.



Synthesis of carboxylic acid ester derivatives of FLC.

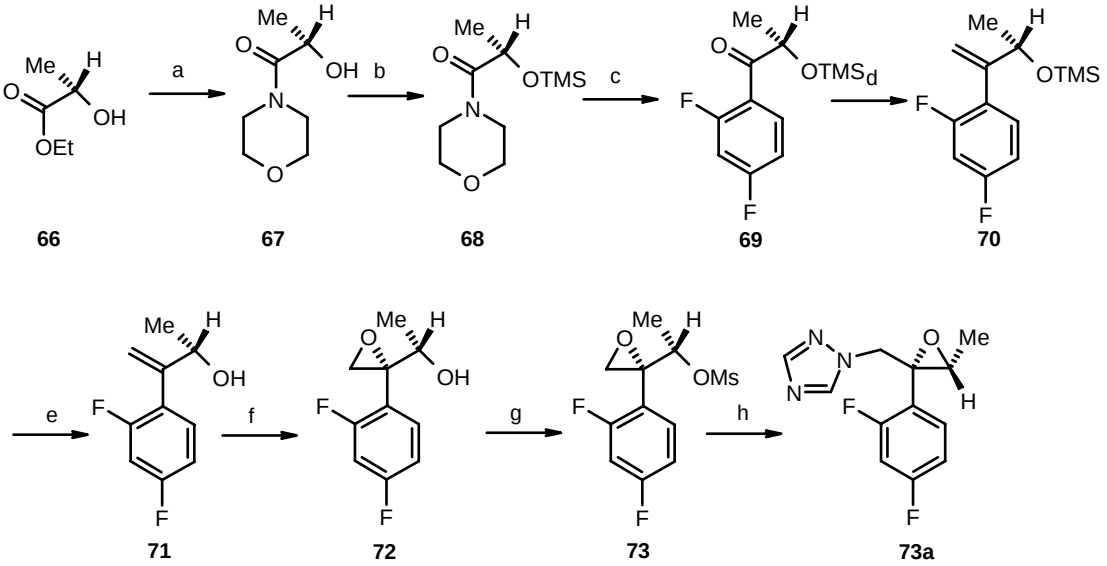


Synthesis of alkylphosphate derivatives of FLC.

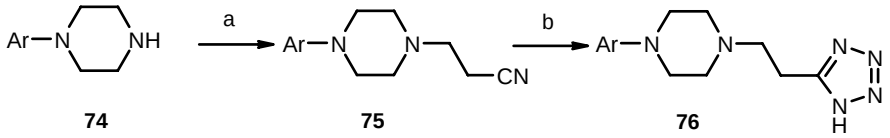
Scheme - 3

Arora S. K. *et al.* reported[30] optically active antifungal azole derivatives. The antifungal activity of compounds was evaluated by *in vitro* agar diffusion and broth dilution assay. Some compounds were having significant antifungal activity against variety of fungal cultures (Candida spp. C. neoformans and Aspergillus spp.). The synthetic strategy

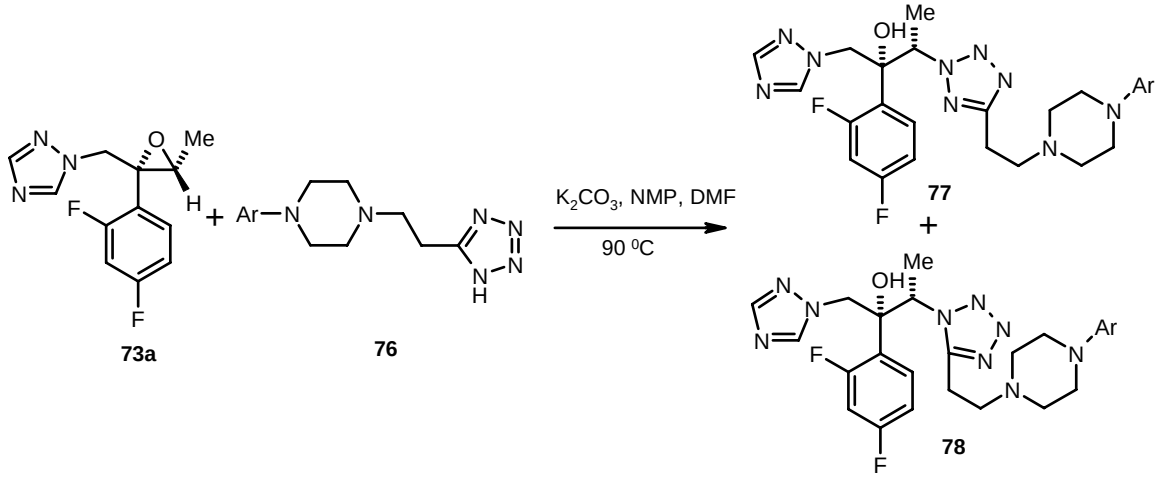
started from commercially available ethyl lactate and morpholine as shown in scheme - 4 and after a series of reactions finally it gave the azole derivative as shown in scheme - 4.



Reagents and Conditions: a) morpholine, 80 ^{0}C, 4 days; b) HMDS, Py-HBr, DCM, rt; c) 2,4-$F_2C_6H_3MgBr$, THF; d) t-BuOK, PPh_3MeI, toluene, 80 ^{0}C, 2h; e) HCOOH, EtOH, rt, 1 h; f) $Ti(i\text{-}PrO)_3$, L-(+)-DET, t-BuOOH; g) MsCl, TEA, 50 ^{0}C, 30 min; h) NaH, 1,2,4-triazol, 50 ^{0}C, 30 min.

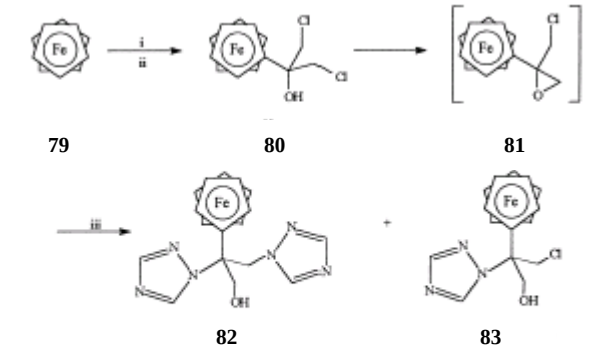


Reagents and Conditions: a) acrylonitrile, TEA, MeOH, -5 to 10 ^{0}C; b) NaN_3, TEA-HCl, toluene, reflux.



Scheme - 4

Biot C. *et al*. reported[31] ferrocene-fluconazole analogue and its antifungal properties investigated against yeast strains of medical importance, including those intrinsically resistant to fluconazole. *In vitro* tests revealed a slight increase in fungal growth and a reversal of the effect of fluconazole at minimal inhibitory concentrations. Synthetic strategy used for the synthesis of this analogue of fluconazole is shown in scheme-5.



Reagents and conditions: (i) 0.83 equiv *t*-BuLi, anhydrous THF, O°C, 15 min; (ii) 1.3 equiv $(ClCH_2)_2CO$, anhydrous Et_2O, −78 °C, 30 min, then CH_3COOH, O°C, 15 min; (iii) 6 equiv 1,2,4-triazole, 4 equiv K_2CO_3, DMF, 70°C, 19 h. Percentages indicate the yield of the reaction.

Scheme - 5

2.2.2: PRESENT WORK:

The past decade has witnessed an expansion of basic and clinical research in antifungal pharmacology and many companies have launched new compounds, including several new azole compounds and the candins.[32]

Azole antifungals are divided into the imidazoles (e.g. miconazole (**44**) and ketoconazole (**6**)) and the triazoles (e.g. itraconazole (**5**), fluconazole (**4**), voriconazole (**13**)). The latter group has three instead of two nitrogen atoms in the azole ring. All of the azoles operate *via* a common mode of action, they prevent the synthesis of ergosterol, the major sterol component of fungal plasma dermatophytes, yeasts, and dimorphic as well as filamentous fungi, is well established and comparable to that of amphotericin B for many pathogens.[33] However, unacceptable side effects following oral administration[34] and unpredictable pharmacokinetics as a result of the induction of hepatic microsomal enzymes[35] have limited the use of clotrimazole to the topical treatment of dermatophytic infections and super-ficial candida infections, including oral thrush. Considering these limitations we planned to synthesize the second group antifungal agents wherein one of the triazole in fluconazole is replaced by thienopyrimidinone. Variconazole is one of the recently introduced drugs for antifungal treatment. We synthesized voriconazole derivatives wherein the pyrimidine ring was replaced by thienopyrimidone moiety (Fig 2, wherein R1 = H (fluconazole analogues) or R1 = CH_3 (voriconazole analogues).

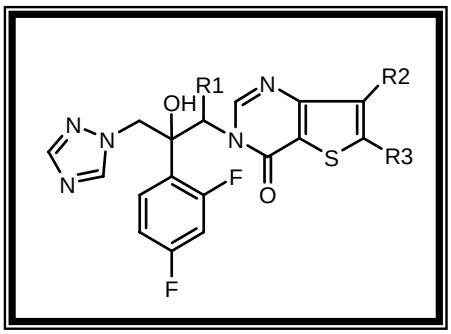
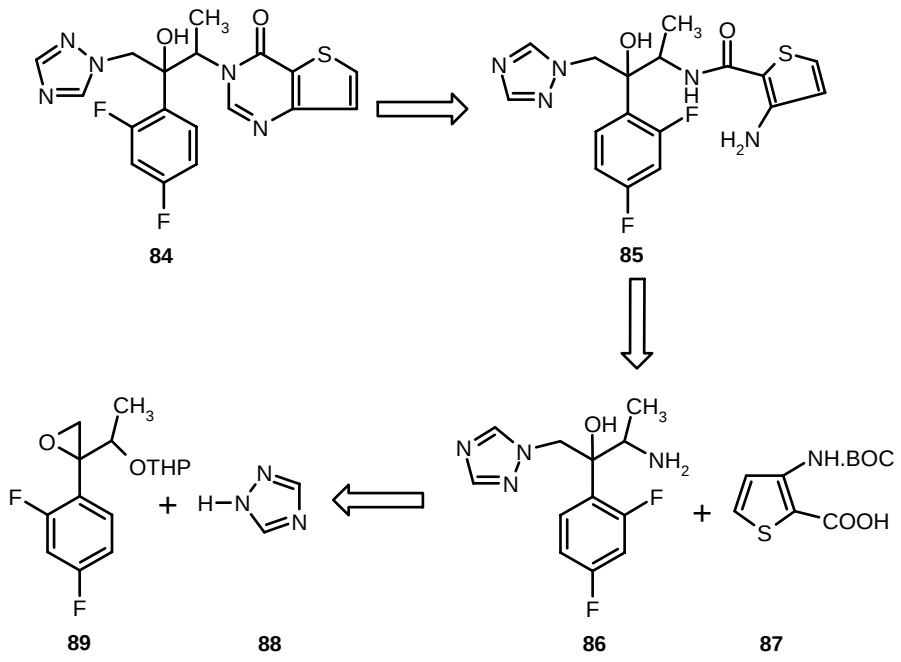


Fig. 2

2.2.3: RESULTS AND DISCUSSION:

Literature survey revealed the importance of azoles and their derivatives from synthetic as well as medicinal point of view. A large number of derivatives of the same have been synthesized and antifungal activity was reported. We planned to synthesize derivatives of azoles by using a very short synthetic route. In this section we have used the two synthetic approaches. We proposed synthetic strategy for the synthesis of azole derivatives from commercially available starting materials such as difluorobenzene and triazole as depicted in scheme - 6.

Retrosynthetic pathway:



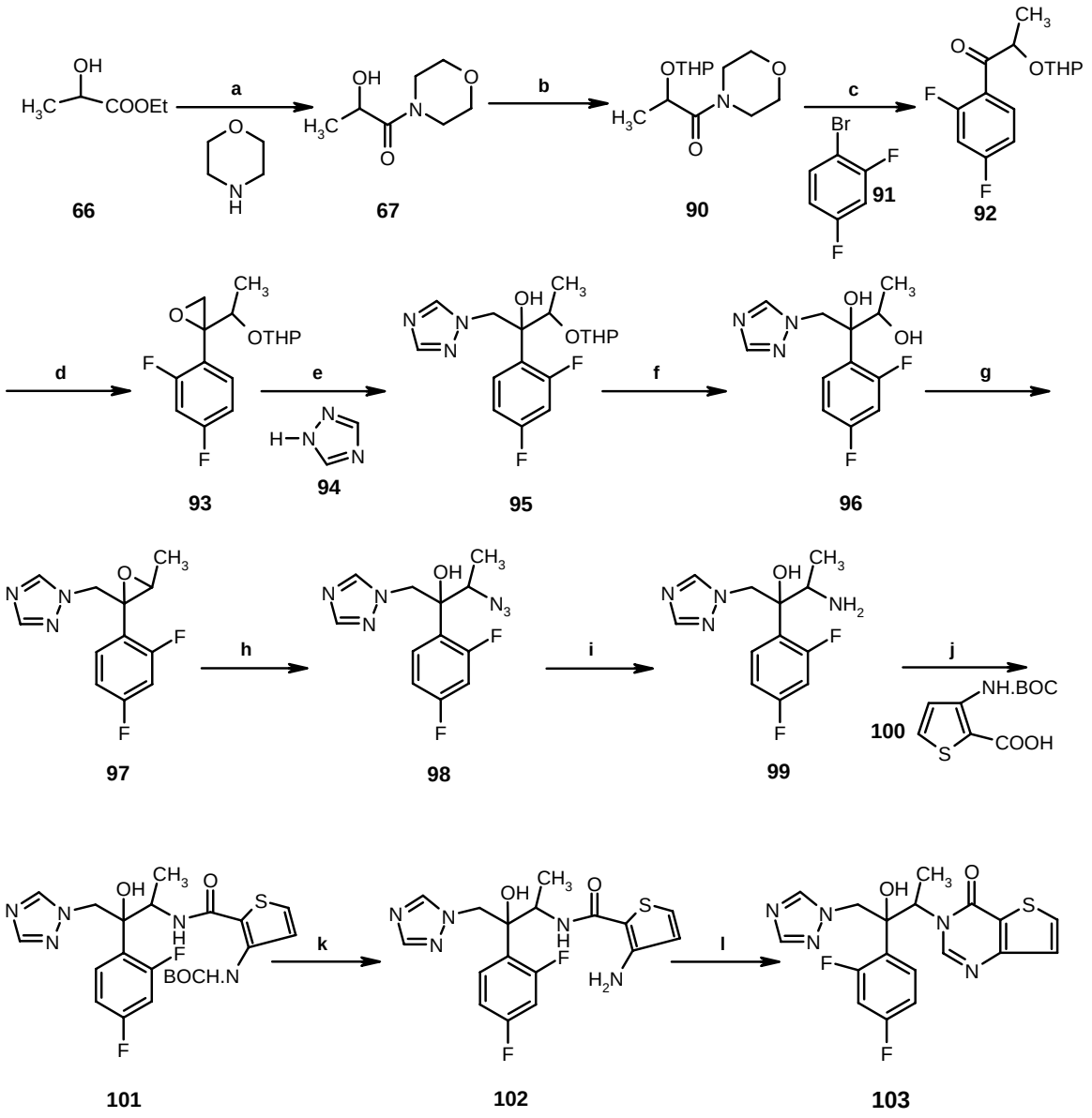
Scheme - 6

It was assumed that the intermediate **85** could be obtained from the condensation of intermdiate **86** and thiophene carboxylic acids (**87**) and the intermediate **86** could be prepared from a commercially available difluorobenzene and 1,2,4-triazole.

Accordingly we synthesized the azole derivatives by using ethyl lactate (**66**) as the starting material which was treated with morpholine at 80 ^{0}C for 60 h to get intermediate **67**. This intermediate was protected by THP group by treating it with dihydropyran. Ether **90** was treated with difluorobromobenzene (**91**) and magnesium in presence of tetrahydrofuran as a solvent to get ketone intermediate **92**. This ketone intermediate **92** on epoxidation by the use of trimethylsulphoxonium iodide furnished the epoxide **93**, this epoxide was further reacted with triazole in presence of sodium hydride as a base and dimethyl formamide as a solvent which gave the alcohol **95**.

Further this alcohol **95** on deprotection of tetrahydorpyranyl ether by PPTS gave the diol **96**, which on selective mesylation by mesyl chloride and triethyl amine, followed by treatment with sodium methoxide gave the intermediate epoxide **97**.

The epoxide **97** was further treated with sodium azide to obtain the intermediate azide **98**. The intermediate azide **98** was reduced by hydrogenation to get amine intermediate **99** which was further condensed with boc-protected 3-amino-thiophene-2-carboxylic acid to get the intermediate **101**. The deprotection of boc-derivative **101** by trifluoroacetic acid (TFA) gave the amine **102** which on cyclization by using formamidine acetate and NMP gave the final azole derivatives **103** in good yield as shown in scheme -7.

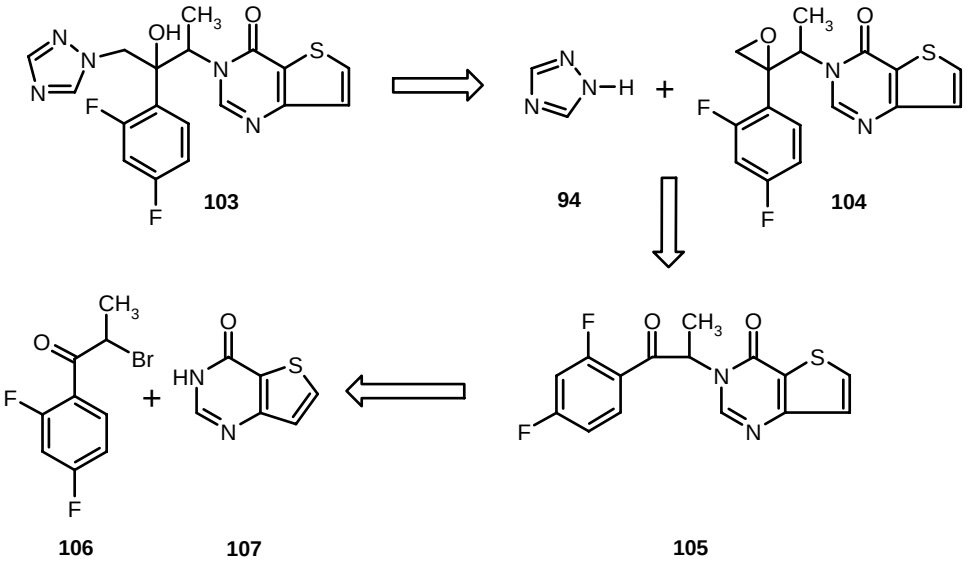


Reagents and Conditions: a) 85 ^{0}C, 60 h, 70 % b) DHP, *p*-TSA, DCM, 0 ^{0}C, 30 min, 83 % c) Mg, THF, rt, 4 h, 85 % d) Trimethylsulfoxonium iodide, NaH, DMSO, rt, 4 h, 80 % e) 1*H*-1,2,4-Triazole, NaH, DMF, 0 ^{0}C-rt, 1 h, 55 % f) PPTS, EtOH, 55 ^{0}C, 4 h, 42 % g) i) Methanesulfonyl chloride, ethyl acetate, 0 ^{0}C-rt, 45 min, ii) MeOH, 0 ^{0}C, 15 min, h) NaN_3, ammonium chloride, DMF, 110 0C, 2.5 h i) Pd/c, H_2, MeOH, rt, 4 h j) 1-hydroxybenzotriazole, DMF, DCC, rt, 18 h, 56 % k) TFA, THF, rt, 2 h, 85 % l) Formamidine acetate, NMP, 130 ^{0}C, 24 h, 60 %.

Scheme -7

In order to synthesize several analogues of this category the route described above is not practical and much shorter route is desirable. The retrosynthetic pathway for a shorter route is as shown in scheme - 8. The proposed route required commercially available starting materials and should achieve the target molecule in few steps.

Retrosynthetic pathway:

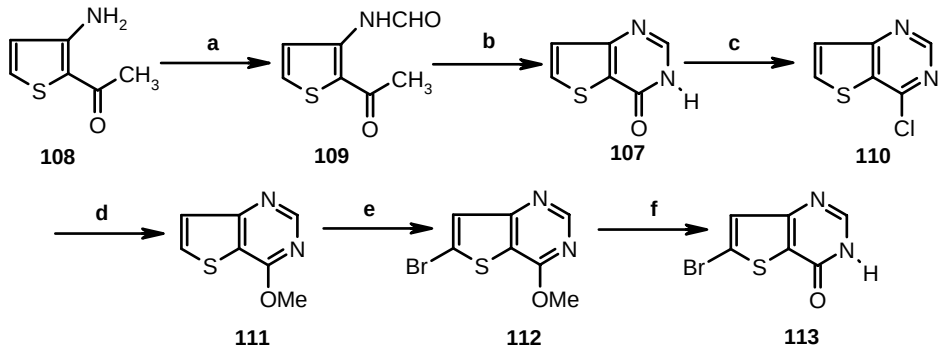


Scheme - 8

Preparation of substituted thienopyrimidinones:

As stated in retrosynthetic route we began synthetic strategy with the commercially available starting material methyl 3-aminothiophene-2-carboxylate (**108**) which on formylation in presence of ammonium acetate and formic acid gave aldehyde **109**. This aldehyde was further treated with ammonium formate and formamide at 140 ^{0}C to give the thienopyrimidone **107**. This intermediate thienopyrimidinone **107** was further reacted with $POCl_3$ to get the chlorothienopyrimidinone **110**, This intermediate **110** was further treated with sodium hydride and methanol which formed sodium methoxide insitu in 1, 4 - dioxane at room temperature overnight to get methoxy intermediate **111** which on bromination using lithium diisopropyl amine (LDA) and *N*-bromosuccinamide (NBS)

provided the 2-bromo substituted thienopyrimidinone **112**. This intermediate was further treated with hydrobromic acid in acetic acid to get thienopyrimidinone **113** as shown in scheme-9.

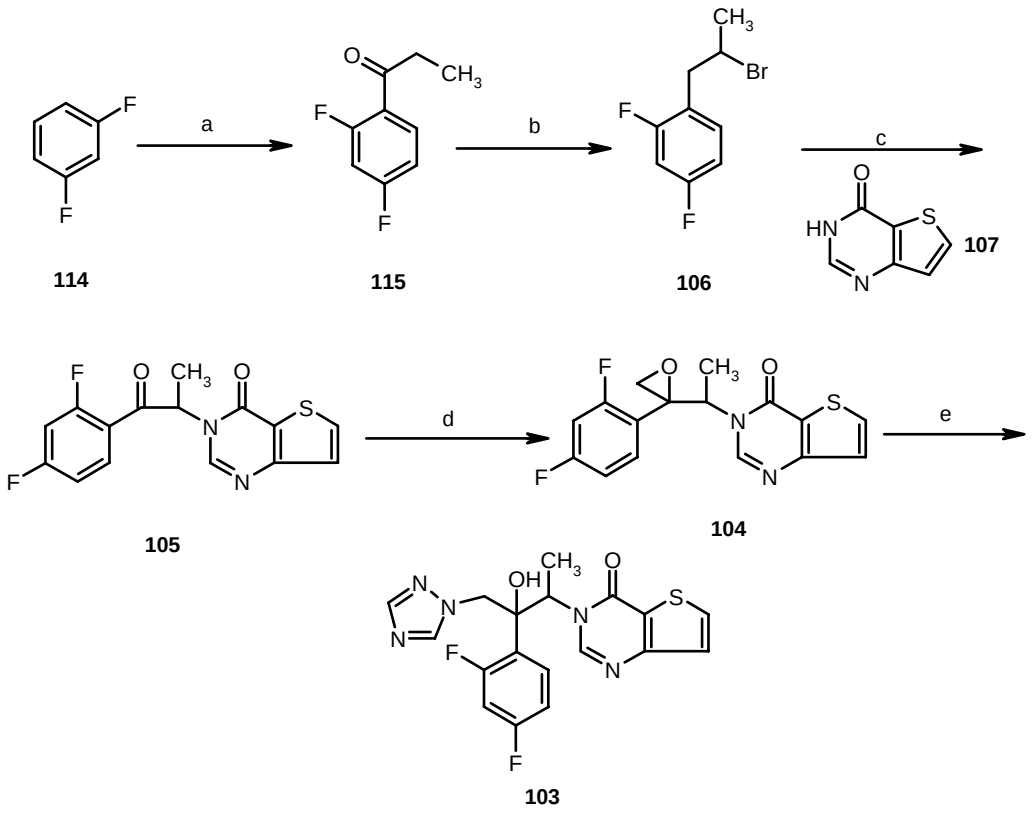


Reagents and Conditions: a) Ammonium acetate, formic acid, 115 -120 ^{0}C, 4 h
b) Ammonium formate, formamid,140 ^{0}C, 4 h. c) $POCl_3$, reflux, 5 h.
d) Sodium hydride, methanol, dioxane, room temperature, overnight
e) n-BuLi, diisopropyl amine, N-bromosuccinamide, tetrahydrofuran, -78 ^{0}C- room temperature,
f) HBr, acetic acid, reflux, 6 h

Scheme - 9

After getting the substituted thienopyrimidinones as described above (scheme-9), we synthesized the second intermediate **106.** We began synthetic strategy with the commercially available 2, 4-difluorobenzene (**114**) which on acylation with propionyl chloride in presence of aluminium chloride in dichloromethane gave 1-(2, 4-difluroro-phenyl)-propan-1-one (**115**). This 1-(2, 4-difluorophenyl)-propan-1-one (**115**) on further bromination in presence of *N*-bromosuccinamide and AIBN in carbon tetrachloride gave 2-bromo-1-(2, 4-difluorophenyl)- propan-1-one (**106**). 2-Bromo-1-(2, 4-difluorophenyl)-propan-1-one intermediate (**106**) was treated with substituted thienopyrimidinone (**107**) in presence of potassium carbonate and tetrabutyl ammonium bromide (TBAB) in dry ethyl acetate at reflux temperature to get the condensed intermediate **105**. It was further treated with trimethyl sulphoxonium iodide in the presence of cetrimide for epoxidation, using dichloromethane as a solvent at reflux condition overnight to get the epoxide **104**. Finally this epoxide **104** was reacted with sodium methoxide and 1,2,4-triazole (**94**) in

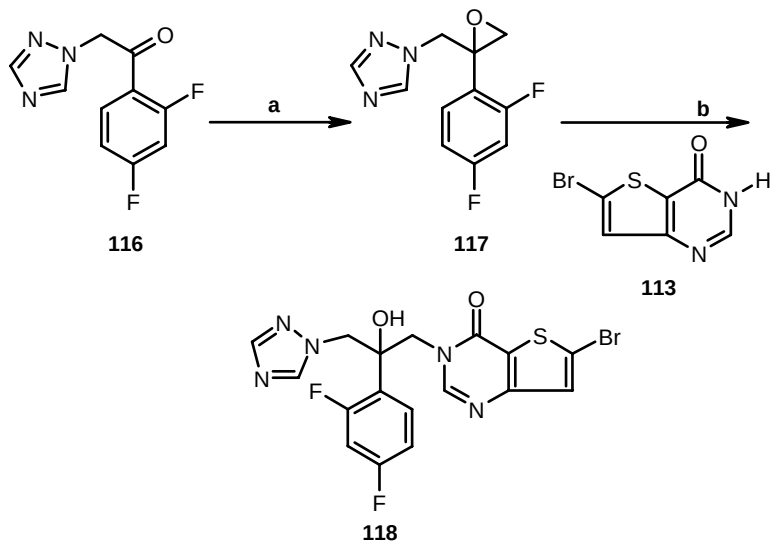
tert-butanol as a solvent at reflux conditions overnight to achieve the final derivative of voriconazole **103** in good yield as shown in scheme -10.



Reagents and Conditons: a) Propionyl chloride, $AlCl_3$, DCM, rt, 24h b) NBS, AIBN, CCl_4, uv light, 8 h. c) thienopyrimidinone, K_2CO_3, TBAB, dry ethyl acetate, reflux, ½ h d) Trimethyl sulphoxonium iodide, cetrimide, DCM, reflux, overnight e) NaOMe, *tert*-butanol, 1,2,4-triazole, reflux, overnight.

Scheme - 10

To synthesize fluconazole analogues of thienopyrimidinone derivatives we have used the intermediate **116**, which on epoxidation by trimethyl sulphoxonium iodide and potassium hydroxide in presence of cetrimide in water and dichloromethane as solvent gave the epoxide **117**. This epoxide **117** was reacted with substituted thienopyrimidinone **113** in presence of potassium carbonate and tetrabutyl ammonium bromide in dry ethyl acetate at reflux condition for 20 h to get the fluconazole derivative **118** in good yield as shown in scheme - 11.



Reagents and Conditions: a) TMSI, cetrimide, KOH, water, dichloromethane, b) Sodium methoxide, *t*-butanol, methanol (60:40), 80 ^{0}C, 20 h.

Scheme - 11

All the analogues of voriconazole and fluconazole were characterised by spectroscopic methods such as ^{1}H NMR, ^{13}C NMR and IR spectroscopy. In a typical example voriconazole drivative **103** was characterized by proton ^{1}H NMR spectroscopy method and supported by ^{13}C NMR and IR spectroscopic methods as follows.

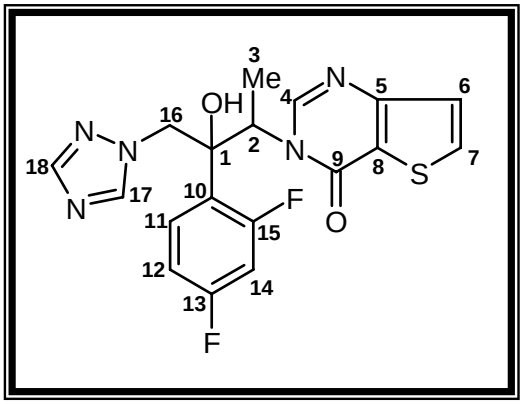


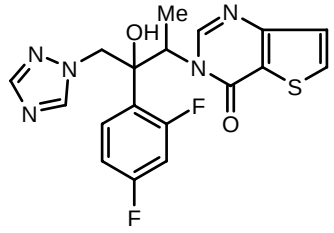
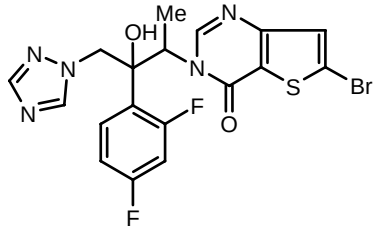
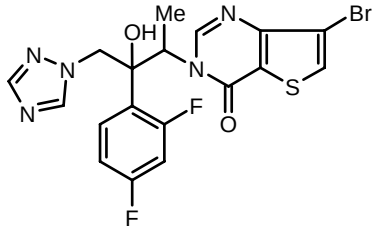
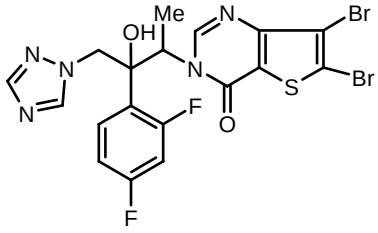
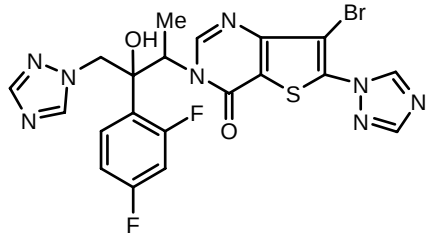
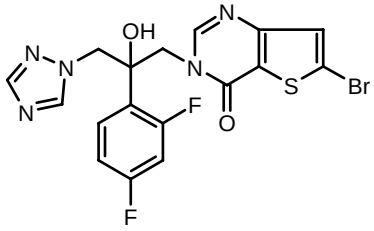
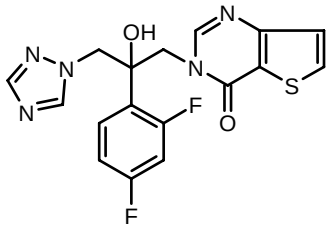
Table - 1, Compound: 103

^{1}H NMR spectrum of compound **103** showed a doublet at δ 1.49 which indicated the presence of methyl proton on C-3 which is coupled with –CH at C-2. The doublets at δ 4.42 and 5.15 (J = 10 Hz) were assigned to methylene protons present on C-16, while the

proton on C-2 showed a multiplet at δ 6.14 - 6.23 due to the presence of methyl group present on adjacent C-3. A singlet seen at δ 6.66 was assigned for the proton present at C-17, triplet at δ 7.24 (J = 5 Hz) was assigned for the proton on C-14. A multiplet at δ 7.48 - 7.62 was due to the protons present at C-11 and C-12. The proton on C-7 showed a doublet at δ 7.75 (J = 6 Hz) while singlet at δ 7.86 was assigned for the proton at C-4. A doublet at δ 8.51 (J = 6 Hz) was due to the proton at C-6 and a singlet at δ 8.74 was assigned for the proton present at C-18. The above ^{1}H NMR data supported the structure of compound **103** as shown.

By using the same synthetic strategy used for the synthesis of voriconazole analogue **103** and fluconazole analogue **118** other azole derivatives from Table - 1 were synthesized and were characterized by spectroscopic methods such as IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

Table. 1: Azole Derivatives Synthesized

Comp. No.	Structure	Comp. No.	Structure
103		**103a**	
103b		**103c**	
103d		**118**	
118a			

The synthesized azole derivatives were screened for biological activity, which is discussed in the third section of this chapter.

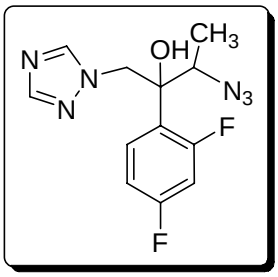
2.2.4: CONCLUSION:

In conclusion, we have synthesized novel substitutes for antifungal agents viz. Fluconazole, Voriconazole etc. We have replaced the pyrimidine ring present in reported azole derivatives by thienopyrimidone moiety, totally 7 new derivatives were synthesized and characterized by spectral and analytical methods. The desired methods has the advantages of simplicity to obtain novel azole derivatives in good yields from commercially available starting materials. Present studies have potential to contribute novel thienopyrimidone derivatives to azole family.

2.2.5: EXPERIMENTAL:

Preparation of 3-azido-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazole-1-yl)-2-butanol (98):

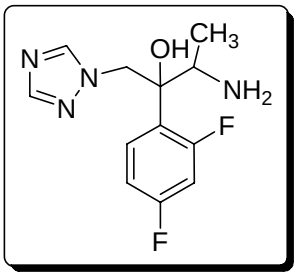
A mixture of (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-methyl)-oxirane (**97**) was synthesized by reported[36] method. Epoxide **97** (5 g, 19.8 mmol), sodium azide (3.91 g, 60.0 mmol), ammonium chloride (1.76 g, 32.5 mmol) and DMF (60 ml) was stirred at 110 ^{0}C for 2.5 h. After cooling the mixture was partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried and concentrated in vaccum. Purification of crude product on column chromatography to afford 3-azido-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazole-1-yl)-2-butanol in good yield.



Yield: 76 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.00 (d, *J* = 8 Hz, 3H), 1.89 (bs, 1H), 2.20 (q, 8 Hz, 1H), 4.05 (d, *J* = 14 Hz, 1H), 4.30 (d, *J* = 14 Hz, 1H), 6.61 (s, 1H), 6.67 (d, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 8.11 (s, 1H), 8.15 (s, 1H); **Anal. Calcd. for** $C_{12}H_{12}F_2N_6O$**:** C, 48.98; H, 4.11; N, 28.56; F, 12.19 %. **Found:** C, 48.87; H, 4.01; N, 28.37; F, 12.46 %.

Preparation of 3-amino-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazole-1-yl)-2-butan-2-ol (99):

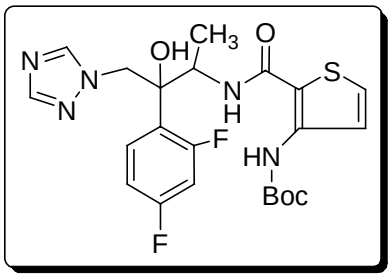
In a 100 ml round bottom flask 3-azido-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazole-1-yl)-2-butanol (1 g, 3.40 mmol) was dissolved in methanol (20 ml). Pd/C (100 mg, 10 % by wt.) was added, stirred reaction mixture under the pressure of hydrogen balloon at room temperature for 4 h. Methanol was removed under reduced pressure on rotary evaporator, reaction mixture was extracted with ethyl acetate (3 x 50 ml) organic extract was washed with water followed by brine and dried over sodium sulfate. It was then concentrated and purified on column chromatography to afford 3-amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazole-1-yl)-2-butan-2-ol.



Yield: 68 %; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4)**:** δ 0.88 (d, *J* = 6 Hz, 3H), 3.20 (q, *J* = 6 Hz, 1H), 3.65 (bs, 1H), 4.29 (bs, 2H), 4.69 (s, 2H), 6.70 - 6.86 (m, 2H), 7.41 - 7.55 (m, 1H), 7.78 (s, 1H), 7.97 (s, 1H); **Anal. calcd. for** $C_{12}H_{14}F_2N_4O$**:** C, 53.73; H, 5.26; N, 20.89; F, 14.16 %. **Found:** C, 53.67; H, 5.11; N, 20.72; F, 14.06 %.

Preparation of tert-butyl 2-(3-(2,4-difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazole-1-yl)butan-2-ylcarbamoyl)thiophen-3-ylcarbamate (101):

To a solution of 3-amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazole-1-yl)-2-butan-2-ol (1 g, 3.73 mmol) in dimethyl formamide (DMF) (15 ml) was added 1-hydroxybenzotriazole (0.503 g, 3.73 mmol). Next the boc-protected 3-amino-thiophene-2-carboxylic acid (0.906 g, 3.73 mmol) and DCC (0.845 g, 4.10 mmol) were added and the mixture was stirred at room temperature for 18 h. The reaction mixture was then cooled to 0 ^{0}C, and the dicyclohexylurea formed was filtered and washed with chloroform. The remaining solution was the evaporated to dryness and partitioned between 10 % aqueous $NaHCO_3$ solution and $CHCl_3$. The layers were separated, and the organic phase was dried over sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography to give the *tert*-butyl-2-(3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazole-1-yl)butan-2-ylcarbamoyl)thiophen-3-ylcarbamate (56 %)

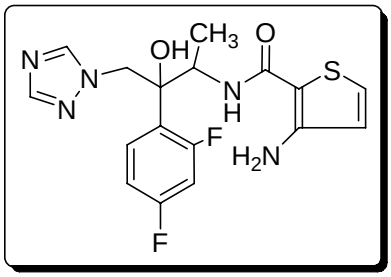


Yield: 56 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.01 (d, *J* = 8 Hz, 3H), 1.53 (s, 9H), 4.56 (d, *J* = 6 Hz, 1H), 4.93 (q, *J* = 8 Hz, 1H), 5.05 (d, *J* = 8 Hz, 1H), 6.17 (bs, 1H), 6.79 (d, *J* = 8 Hz, 2H), 7.30 - 7.50 (m, 2H), 7.82 (d, *J* = 8 Hz, 2H), 7.97 (d, *J* = 8 Hz, 1H), 10.07 (s, 1H); **Anal. Calcd. for** $C_{22}H_{25}F_2N_5O_4S$**:** C, 53.54; H, 5.11; N, 14.19; F, 7.70; S, 6.50 %. **Found:** C, 53.47; H, 5.01; N, 14.02; F, 7.62 %.

Preparation of 3-amino-N-(3-(2,4-difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazole-1-yl)butan-2-yl)thiophene-2-carboxamide (102):

To a solution of **101** (0.500 g, 1.01 mmol) in tetrahydrofuran (8 ml) was added TFA (0.175 g, 1.52 mmol) with stirring at 0 ^{0}C. The resulting mixture was stirred to room temperature for 2 h. It was then extracted ethyl acetate (2 x 10 ml), the organic layer was washed successively with water followed by brine and dried over sodium sulphate. Evoporation of the solvent under reduced pressure on rotary evaporator gave the title product in quantitative yield (85 %).

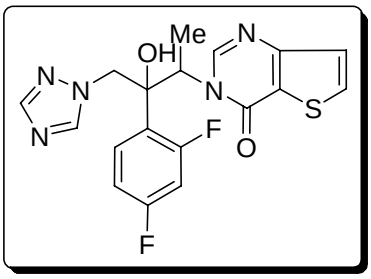
Yield: 85 %; **^{1}H NMR** (300 MHz, $CDCl_3 + CCl_4$)**:** δ 0.92 (d, *J* = 6 Hz, 3H), 4.47 (d, *J* = 9 Hz, 1H), 4.72 - 4.81 (m, 1H), 4.94 (d, *J* = 9 Hz, 1H), 5.28 (bs, 1H), 5.85 (d, *J* = 6 Hz, 1H), 6.49 (d, *J* = 3Hz, 1H), 6.64 - 6.73 (m, 2H), 7.10 (d, *J* = 3 Hz, 1H), 7.27 - 7.36 (m, 1H), 7.69 (s, 1H), 7.73 (s, 1H); **Anal. Calcd. for** $C_{17}H_{17}F_2N_5O_2S$**:** C, 51.90; H, 4.36; N, 17.80; F, 9.66; S, 8.15 %. **Found:** C, 51.78; H, 4.21; N, 17.67; F, 9.52; S, 8.02 %.



Preparation of 3-[2-(2,4-difluoro-phenyl)-2-hydroxy-1-methyl-3-[1,2,4]-triazole-1-yl-propyl]-3H-thieno[3,2-d]pyrimidin-4-one (103):

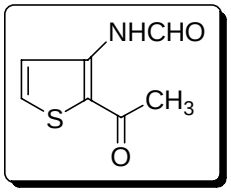
To a solution 3-amino-N-(3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazole-1-yl)butan-2-yl)thiophene-2-carboxamide (0.500 g, 1.27 mmol) in NMP (5 ml) was added formamidine acetate (0.595 g, 5.72 mmol) and the mixture was heated at 130 ^{0}C for 24 h. Water (25 ml) was added, and the solid that formed was collected by filtration and was then partitioned between aqueous 1 N NaOH solution and $CHCl_3$. The aqueous phase was discarded and the organic phase was washed with brine, dried over sodium sulphate, filtered, concentrated and the residue purified by flash column chromatography and recrystallized from ethyl acetate:pet ether to gave **103**.

Nature: Milky white solid; **Yield:** 60 %; **IR** (Chloroform)**:** ν_{max} 3002, 2934, 1675, 1601, 1502, 1456, 1301, 1247 cm^{-1}; **^{1}H NMR** (200 MHz, DMSO-d_6)**:** δ 1.49 (d, *J* = 4 Hz, 3H), 2.19 (s, 1H), 4.42 (d, *J* = 10 Hz, 1H), 5.15 (d, *J* = 10 Hz, 1H), 6.18 (q, *J* = 4 Hz, 1H), 6.66 (s, 1H), 7.24 (t, *J* = 6 Hz, 1H), 7.49 - 7.65 (m, 2H), 7.75 (d, *J* = 6 Hz, 1H), 7.86 (s, 1H), 8.48 - 8.55 (m, 1H), 8.74 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6)**:** δ 15.48, 51.04, 54.49, 77.25, 104.02, 110.82, 111.10, 121.96, 124.95, 129.59, 135.82, 147.30, 150.32, 156.27 (2C), 157.24, 163.78; **Anal. Calcd. for** $C_{18}H_{15}F_2N_5O_2S$**:** C, 53.59; H, 3.75; F, 9.42; N, 17.36 %. **Found:** C, 53.41; H, 3.67; F, 9.32; N, 17.21 %.



***Preparation of N-(2-acetylthiophen-3-yl)formamide (109)*:**

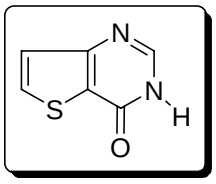
In a dry two necked 500 ml round bottom flask, methyl-3-aminothiophene-2-carboxylate (50 gm, 340 mmol) was taken. Ammonium acetate (31.90 gm, 414.28 mmol) and formic acid (250 ml) were added in it under nitrogen atmosphere. Reaction mixture was heated to 115 - 120 ^{0}C for 4 h. The reaction was monitored by thin layer chromatography which showed the completion of reaction. The reaction mixture was allowed to cool to room temperature, that solid formed was filtered, washed with water and dried to get the *N*-(2-acetylthiophen-3-yl)formamide (42 gm, 53 %) which was used for next step directly.



Yield: 53 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.20 (s, 3H), 6.78 (d, *J* = 6 Hz, 1H), 6.40 (d, *J* = 6 Hz, 1H), 7.72 (s, 1H), 9.41 (bs, 1H); **Anal. Calcd for** $C_7H_7NO_3S$**:** C, 38.92; H, 3.78; N, 7.57; S, 21.05 %. **Found:** C, 38.80; H, 3.71; N, 7.49; S, 21.00 %.

***Preparation of thieno(3,2-d)pyrimidin-4(3H)-one (107)*:**

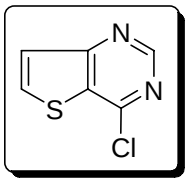
In a 500 ml round bottom flask *N*-(2-acetylthiophen-3-yl)formamide (145 gm, 857.0 mmol) was taken, ammonium formate (146 gm, 231 mmol) and formamide (150 ml) were added in it. The reaction mixture was stirred at 140 ^{0}C for about 4 h. Reaction was monitored by TLC which showed the complete disapperence of starting materials. Reaction mixture was cooled and the solid that was formed was filtered out, washed with water and dried in vacuum to afford thieno(3,2-d)pyrimidin-4(3*H*)-one (49.8 gm, 42 %).



Yield: 42 %; **IR** (Chloroform)**:** ν $_{max}$ 3020, 1660, 1478, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 7.60 (d, *J* = 6 Hz, 1H), 8.04 (d, *J* = 6 Hz, 1H), 8.98 (s, 1H); **Anal. Calcd for** $C_7H_4N_2OS$**:** C, 47.36; H, 2.63; N, 18.42; S, 21.05 %. **Found:** C, 47.31; H, 2.58; N, 18.39; S, 20.95 %.

***Preparation of 4-chlorothieno[3,2-d]pyrimidine (110)*:**

In a dry 500 ml round bottom flask thieno-(3, 2-d)pyrimidin-4(3*H*)-one (16.86 gm, 110.92 mmol) was taken, phosphorous trichloride (168.2 ml) was added in it. The reaction mixture was heated under reflux condition for 5 h on cooling the solution was evaporated to dryness and in residue ice-water was added. The reaction mixture was extracted with dichloromethane (3 x 250 ml). The organic layer was washed with sodium bicarbonate, brine and dried over sodium sulphate. It was then concentrated under reduced pressure on rotary evaporator and purified by column chromatography to get the 4-chlorothieno[3,2-d]pyrimidine (16 gm, 85 %).

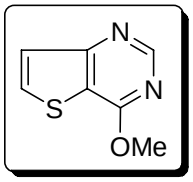


Yield: 85 %; **IR** (Chloroform)**:** ν $_{max}$ 3018, 1522, 1520, 1215 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4): δ 7.62 (d, *J* = 6 Hz, 1H), 8.06 (d, *J* = 6 Hz, 1H), 9.00 (s, 1H); **Anal. Calcd. for** $C_6H_3N_2SCl$**:** C, 42.23; H, 1.76; N, 16.42; S, 18.77; Cl, 20.82 %. **Found:** C, 42.11; H, 1.62; N, 16.36; S, 18.70; Cl, 20.61 %.

***Preparation of 4-methoxythieno[3,2-d]pyrimidine (111)*:**

In a dry 500 ml two necked round bottom flask sodium hydride (8 gm, 333 mmol) was taken under nitrogen atmosphere and dry 1, 4- dioxane (100 ml) was added in it by syringe. When effervescence had subsided, the starting material (20 gm, 117.30 mmol) in 1, 4-dioxane (150 ml) was added dropwise using syringe. Reaction mixture was stirred overnight at room temperature. Reaction was monitored by TLC which showed completion of reaction. The reaction mixture was poured into water and extracted with ethyl acetate (3 x 200 ml). The organic layer was washed with water, brine and dried over sodium sulphate. It was concentrated under reduced pressure on rotary evaporator and

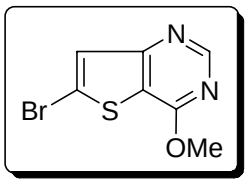
purified on column chromatography gave 3,4-dihydro-4-methoxythieno(3,2-d)-pyrimidine (17 gm, 87 %).



Yield: 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 4.17 (s, 3H), 7.48 (d, *J* = 6 Hz, 1H), 7.83 (d, *J* = 6 Hz, 1H), 8.74 (s, 1H); **Anal. Calcd. for** $C_7H_6N_2OS$**:** C, 50.60; H, 3.61; N, 16.87; S, 19.28 %. **Found:** C, 50.51; H, 3.60; N, 16.68; S, 19.23 %.

***Preparation of 6-bromo-4-methoxythieno(3,2-d)-pyrimidine (112)*:**

In a dry 250 ml two necked round bottom flask diisopropyl amine (3.65 gm, 36.13 mmol) and tetrahydrofuran was taken under nitrogen atmosphere. It was cool to 0 ^{0}C and n-BuLi (22.75 ml 1.6 M) was added dropwise by using syringe. The reaction mixture was stirred for 45 min at 0 ^{0}C and cooled to -78 ^{0}C. Then 3,4-dihydro-4-methoxythieno(3,2-d)-pyrimidine (5 gm, 30.12 mmol) in tetrahydrofuran was added dropwise and stirred for one hour at same temperature. *N*-Bromosuccinamide (5.897 gm, 33.12 mmol) dissolved in tetrahydrofuran was added dropwise at -78 ^{0}C and stirred for 2 hour at same temperature. The reaction mixture was allowed to come to room temperature and stirred overnight at room temperature. Reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate (3 x 100 ml). Organic layer was washed with water, brine and dried over sodium sulphate. It was then concentrated under reduced pressure on rotary evaporator and purified on column chromatography to afford 6-bromo-4-methoxythieno(3,2-d)-pyrimidine in good yield (6.2 gm, 83 %).

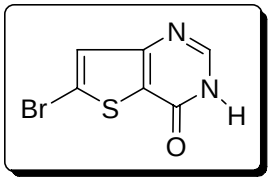


Yield: 83 %; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4)**:** δ 4.16 (s, 3H), 7.53 (s, 1H), 8.70 (s, 1H); **Anal. Calcd. for** $C_7H_5N_2SOBr$**:** C, 33.73; H, 2.00; N, 11.24; S, 12.85; Br, 32.13 %. **Found:** C, 33.69; H, 1.96; N, 11.16; S, 12.78; Br, 32.10 %.

***Preparation of 6-bromothieno[3,2-d]-pyrimidin-4(3H)-one (113)*:**

In a dry 500 ml single necked round bottom flask 6-bromo-3,4-dihydro-4-methoxythieno(3,2-d)-pyrimidine (5 gm, 20.49 mmol) was taken, hydrobromic acid in acetic acid (47 %, 50 ml) was added in it followed by glacial acetic acid (200 ml). The reaction mixture was stirred at 120 ^{0}C for 6 hours. The reaction was monitored by thin

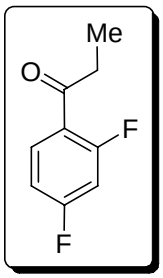
layer chromatography which showed a completion of reaction. The reaction mixture was neutralized with saturated sodium bicarbonate and extracted with ethyl acetate (3 x 100 ml), organic layer was washed with water then with brine and dried over sodium sulphate. It was then concentrated under reduced pressure on rotary evaporator and purified on column chromatography gave 6-bromothieno[3,2-d]-pyrimidin-4(3*H*)-one (2.6 gm, 70 %).



Yield: 70 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 7.22 (s, 1H), 7.27 (s, 1H), 7.85 (s, 1H); **Anal. Calcd. for** $C_6H_3N_2OSBr$**:** C, 31.17; H, 1.30; N, 12.12; S, 13.85; Br, 34.63 %. **Found:** C, 31.09; H, 1.26; N, 12.06; S, 13.71; Br, 34.54 %.

***Preparation of 1-(2, 4-difluroro-phenyl)-propan-1-one (115)*:**

In a 250 ml two necked round bottom flask fitted with a stopcock, 1, 3-difluorobenzene (10 gm, 87.7 mmol) and propionyl chloride (16.22 gm, 175.35 mmol) were taken under nitrogen atmosphere at 0 ^{0}C, to it 50 ml dry dichloromethane was added slowely. Aluminium trichloride (29.22 gm, 219.6 mmol) was added portionwise and the reaction was stirred at room temperature for 12 h. The reaction mixture was quenched with ice-water, extracted with dichloromethane and dried over sodium sulphate. It was then concentrated under reduced pressure on rotary evaporator and purified on column chromatography to afford 1-(2, 4-difluoro-phenyl)-propan-1-one (12 gm, 80.5 %).

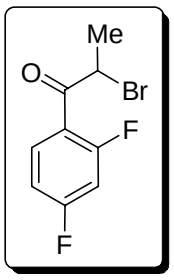


Yield: 80.5 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.20 (t, *J* = 8 Hz, 3H), 2.90 - 3.05 (m, 2H), 6.76 - 6.95 (m, 2H), 7.82 - 7.96 (m, 1H); **Anal. Calcd. for** $C_9H_8F_2O$**:** C, 63.53; H, 4.74; F, 22.23 %. **Found:** C, 63.45; H, 4.56; F, 22.16 %.

***Preparation of 2-bromo-(2, 4-difluoro-phenyl)-propan-1-one (106)*:**

1-(2, 4-Difluoro-phenyl)-propan-1-one (10 gm, 58.82 mmol) was taken in a dry two necked round bottom flask fitted with a condenser and stop cock under nitrogen atmosphere, dry carbon tetrachloride (100 ml) was added followed by catalytic amount of 2, 2'-azobisisobutyronitrile (AIBN). *N*-Bromo succinamide (26.17 gm, 147.02 mmol)

was added portionwise and the reaction mass was refluxed by exposing it to electric bulb fitted next to two necked round bottom flask. The reaction was continued for 8 h after which TLC showed completion of reaction. Reaction mixture was filtered through sintered funnel, dried over sodium sulphate, concentrated under reduced pressure on rotary evaporator and purified on column chromatography by using pet ether: ethyl acetate as eluent to yield the pure 2-bromo- (2, 4-difluoro-phenyl)-propan-1-one (13.5 gm, 92 %).

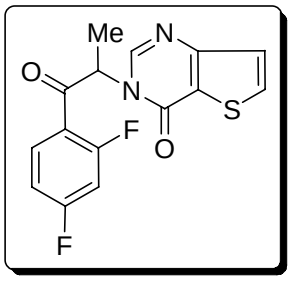


Yield: 92 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.89 (d, *J* = 4 Hz, 3H), 5.23 (q, *J* = 4 Hz, 1H), 6.84 - 7.06 (m, 3H); **Anal. Calcd. for** $C_9H_7BrF_2O$**:** C, 43.40; H, 2.83; Br, 32.08; F, 15.26 %. **Found:** C, 43.27; H, 2.69; Br, 31.96; F, 15.14 %.

Preparation of 3-(1-(2,4-difluorophenyl)-1-oxopropan-2-yl)thieno-[3,2-d]pyrimidin-4(3H)-one (105):

In a two necked round bottom flask fitted with a condenser and stopcock, thienopyrimidinone (0.641 gm, 4.2 mmol), potassium carbonate (0.969 gm, 7 mmol) and tetrabutylammonium bromide (1.089 gm, 3.3 mmol) were taken. Dry ethyl acetate (10 ml) was added in it and the mixture was refluxed for 20 min. 2-bromo- (2, 4-difluoro-phenyl)-propan-1-one (1.045 gm, 4.2 mmol) in ethyl acetate (5 ml) was added dropwise and the reaction mixture was refluxed 12 h. The reaction mixture was then extracted with ethyl acetate (3 x 25 ml), organic layer was washed with water and brine, dried over sodium sulphate, concentrated under reduced pressure on rotary evaporator and purified on column chromatography to afford 3-[2-(2, 4-difluoro-phenyl)-1-methyl-2-oxo-ethyl]-3*H*-thieno-[3, 2-d] pyrimidin-4-one (0.80 gm, 62 %)

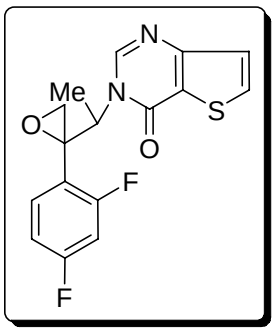
Yield: 62 %; **IR** (Chloroform)**:** ν_{max} 3019, 1677, 1612, 1580, 1502, 1428 cm^{-1}; **^{1}H NMR**



(200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.78 (d, *J* = 4 Hz, 3H), 6.09 (q, *J* = 4 Hz, 1H), 6.84 - 7.03 (m, 2H), 7.33 (d, *J* = 4 Hz, 1H), 7.88 (d, *J* = 4 Hz, 1H), 7.92 - 8.04 (m, 1H), 8.16 (s, 1H); **Anal. Calcd. for** $C_{15}H_{10}F_2N_2O_2S$**:** C, 56.24; H, 3.15; F, 11.86; N, 8.75 %. **Found:** C, 56.09; H, 3.04; F, 11.62; N, 8.63 %.

Preparation of 3-(1-(2,4-difluorophenyl)oxiran-2yl)ethyl)thieno-[3,2-d]-pyrimidin-4(3H)-one (104):

In a dry two necked round bottom flask fitted with a condenser, solution of potassium hydroxide (0.811 gm, 14.48 mmol) in water (2 ml) was taken, dichloromethane (20 ml) was added and the mixture was stirred for 15 min. Trimethyl sulphoxonium iodide (1.60 gm, 7.27 mmol) and cetrimide (0.080 gm 2.19 mmol) were added in it. 3-[2-(2, 4-Difluoro-phenyl)-1-methyl-2-oxo-ethyl]-3*H*-thieno-[3,2-d] pyrimidin-4-one (1.5 gm, 4.68 mmol) in dichloromethane (15 ml) was added and the reaction mixture was stirred at 40 ^{0}C overnight. It was then extracted with dichloromethane (3 x 75 ml), organic layer was washed with water and brine and dried over sodium sulphate. Concentrated under reduced pressure on rotary evaporator and purification of crude product on column chromatography afforeded 3-{1-[2-(2,4-difluoro-phenyl)-oxiranyl]-ethyl}-3*H*-thieno-[3, 2-d]-pyrimidin-4-one (1.3 gm, 79 %)



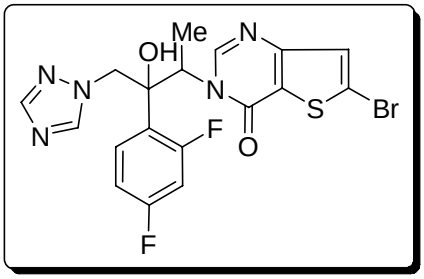
Yield: 79 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.47 (d, *J* = 6 Hz, 3H), 2.63 (q, *J* = 6 Hz, 2H), 5.89 (q, *J* = 6 Hz, 1H), 6.76 - 6.93 (m, 2H), 7.29 (d, *J* = 6 Hz, 1H), 7.37 - 7.49 (m, 1H), 7.76 (d, *J* = 4 Hz, 1H), 8.07 (s, 1H); **Anal. Calcd for** $C_{16}H_{12}F_2N_2O_2S$**:** C, 57.48; H, 3.62; F, 11.36; N, 8.38 %. **Found:** C, 57.37; H, 3.54; F, 11.19; N, 8.19 %.

Preparation of 3-[2-(2, 4-difluoro-phenyl)-2-hydroxy-1-methyl-3-[1, 2, 4]-triazol-1-yl-propyl]-3H-thieno[3, 2-d]pyrimidin-4-one (103):

In a dry two necked round bottom flask equipped with a reflux condenser 3-{1-[2-(2, 4-difluoro-phenyl)-oxiranyl]-ethyl}-3*H*-thieno-[3,2-d]-pyrimidin-4-one (0.500 gm, 1.41 mmole), sodium methoxide (0.075 gm, 1.38 mmol) and 1,2,4- triazole (0.090 gm, 1.30 mmol) were taken in it under nitrogen atmosphere. *t*-BuOH (10 ml) was added in reaction mixture by syringe and the reaction mixture was stirred at 70 ^{0}C for 12 h. *t*-BuOH was removed under reduced pressure, reaction mixture was quenched with water (10 ml) and extracted with ethyl acetate (3 x 20 ml) organic layer was washed with water, brine and dried over sodium sulphate. Concentrated under reduced pressure on rotary evaporator and purification of crude product on column chromatography afforded the pure desired

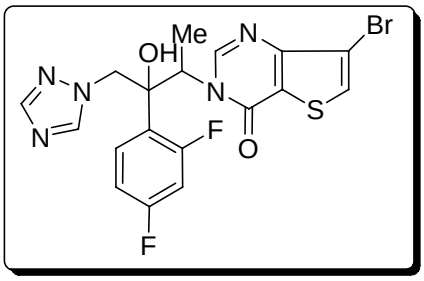
product 3-[2-(2, 4-difluoro-phenyl)-2-hydroxy-1-methyl-3-[1, 2, 4]-triazol-1-yl-propyl]-3*H*-thieno[3, 2-d]pyrimidin-4-one in good yield (0.425 gm, 73 %).

6-Bromo-3-[2-(2,4-difluoro-phenyl)-2-hydroxy-1-methyl-3-[1,2,4]-triazole-1-yl-propyl]-3H-thieno[3, 2-d]pyrimidin-4-one (103 a):



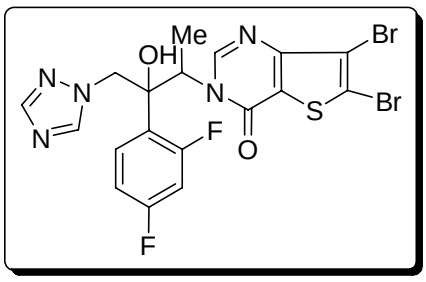
Nature: Brown semisolid; **Yield:** 71 %; **IR** (Chloroform)**:** ν $_{max}$ 3420, 1676, 1618, 1575, 1500, 1445, 1215 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.30 (d, *J* = 6 Hz, 3H), 3.97 (d, *J* = 14 Hz, 1H), 5.16 (d, *J* = 14 Hz, 1H), 5.59 (s, 1H), 5.92 (q, *J* = 6 Hz, 1H), 6.70 - 6.90 (m, 2H), 7.37 (s, 1H), 7.42 - 7.57 (m, 1H), 7.71 - 7.85 (m, 2H), 8.54 (s, 1H), 8.73 (s, 1H); **Anal. Calcd. for** $C_{18}H_{14}BrF_2N_5O_2S$**:** C, 44.83; H, 2.93; Br, 16.57; F, 7.88; N, 14.52 %. **Found:** C, 44.71; H, 2.79; Br, 16.42; F, 7.73; N, 14.37 %.

7-Bromo-3-[2-(2,4-difluoro-phenyl)-2-hydroxy-1-methyl-3-[1,2,4]-triazole-1-yl-propyl]-3H-thieno[3, 2-d]pyrimidin-4-one (103 b):



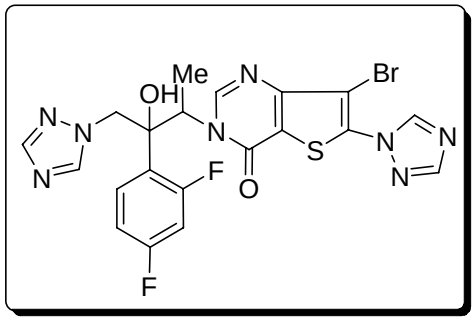
Nature: Brown semisolid; **Yield:** 69 %; **IR** (Chloroform)**:** ν $_{max}$ 3008, 2933, 1679, 1610, 1511, 1455, 1301, 1247 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.31 (d, *J* = 6 Hz, 3H), 3.96 (d, *J* = 14 Hz, 1H), 5.16 (d, *J* = 14 Hz, 1H), 5.58 (s, 1H), 5.97 (q, *J* = 6 Hz, 1H), 6.79 - 6.88 (m, 2H), 7.44 - 7.57 (m, 1H), 7.76 (d, *J* = 6 Hz, 2H), 7.85 (s, 1H), 8.75 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 15.58, 51.24, 54.12, 77.98, 104.44, 111.71, 122.16, 122.65, 130.32, 131.83, 144.04, 148.11, 151.96, 153.31, 157.31, 160.38, 165.37, 165.69; **Anal. Calcd. for** $C_{18}H_{14}BrF_2N_5O_2S$**:** C, 44.83; H, 2.93; Br, 16.57; F, 7.88; N, 14.52 %. **Found:** C, 44.71; H, 2.79; Br, 16.42; F, 7.73; N, 14.37 %.

6,7-Dibromo-3-[2-(2,4-difluoro-phenyl)-2-hydroxy-1-methyl-3-[1,2,4]-triazole-1-yl-propyl]-3H-thieno[3,2-α]pyrimidin-4-one (103 c):



Nature: White semisolid; **Yield:** 67 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.30 (d, *J* = 6 Hz, 3H), 3.95 (d, *J* = 14 Hz, 1H), 5.13 (d, *J* = 14 Hz, 1H), 5.61 (s, 1H), 5.93 (q, *J* = 4 Hz, 1H), 6.77 - 6.91 (m, 2H), 7.42 - 7.56 (m, 1H), 7.76 (dd, *J* = 8 Hz, 2H), 8.70 (s, 1H). **Anal. Calcd. for** $C_{18}H_{13}Br_2F_2N_2O_2S$**:** C, 38.52; H, 2.33; Br, 28.48; F, 6.77; N, 12.48 %. **Found:** C, 38.39; H, 2.21; Br, 28.31; F, 6.58; N, 12.37 %.

6-Bromo-3-(3-(2,4-difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazole-1-yl)butan-2-yl)-7-(1H-1,2,4-triazole-1-yl)thieno[3,2-d]pyrimidin-4(3H)-one (103 d):

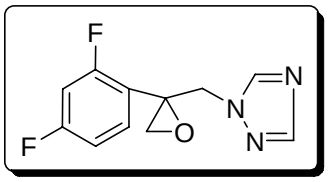


Nature: Brown semisolid; **Yield:** 71 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.32 (d, *J* = 6Hz, 3H), 4.00 (d, *J* = 14 Hz, 1H), 5.15 (d, *J* = 14 Hz, 1H), 5.65 (s, 1H), 5.96 (q, *J* = 6 Hz, 1H), 6.74 - 6.92 (m, 2H), 7.43 - 7.54 (m, 1H), 7.77 (d, *J* = 10 Hz, 2H), 8.17 (s, 1H), 8.77 (s, 1H), 8.82 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6)**:** δ 15.64, 52.16, 55.12, 77.51, 79.38, 101.92, 104.98, 111.19, 118.63, 123.77, 124.10, 130.11, 140.68, 145.53, 149.92, 152.51, 153.23, 156.81, 161.02, 161.17; **Anal. Calcd. for** $C_{20}H_{15}BrF_2N_8O_2S$**:** C, 43.73; H, 2.75; Br, 14.55; F, 6.92; N, 20.40 %. **Found:** C, 43.59; H, 2.67; Br, 14.46; F, 6.78; N, 20.12 %

Preparation of 1-((2-(2,4-difluorophenyl)oxiran-2-yl)methyl)-1H-1,2,4-triazole (117):

In a 250 ml two necked round bottom flask fitted with a condenser, a solution of potassium hydroxide (7.56 gm, 135.0 mmol) in water (10 ml) was taken, dichloromethane (60 ml) was added in it and the reaction mixture was stirred for 15 min trimethyl sulphoxonium iodide (14.932 gm, 67.87 mmol) and cetrimide (0.819 gm 2.25 mmol) were added in it. 1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (10 gm, 45.24 mmol) dissolved in dichloromethane (25 ml) was added and the reaction

mixture was stirred at 40 ^{0}C overnight. It was then extracted with dichloromethane, organic layer was washed with water, brine and then dried over sodium sulphate. Concentrated organic layer under reduced pressure on rotary evaporator and purification of crude product on column chromatography afforded 1-((2-(2,4-difluorophenyl)oxiran-2-yl)methyl)-1*H*-1,2,4-triazole in good yield (8.23 gm, 78 %).

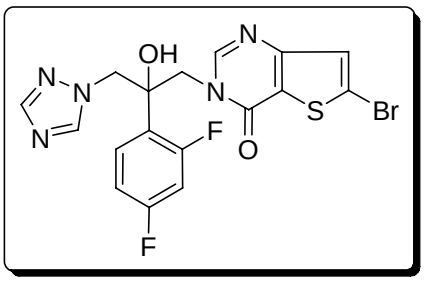


Yield: 78 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.92 (dd, *J* = 8 and 4 Hz, 2H), 4.51 (d, *J* = 14 Hz, 1H), 5.83 (d, *J* = 14 Hz, 1H), 6.78 - 6.90 (m, 2H), 7.10 - 7.25 (m, 1H), 7.88 (s, 1H), 8.07 (s, 1H); **Anal. Calcd. for** $C_{11}H_9F_2N_3O$**:** C, 55.70; H, 3.82; F, 16.02; N, 17.71 %. **Found:** C, 55.58; H, 3.73; F, 15.98; N, 17.67 %.

Preparation of 6-bromo-3-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-[1,2,4]-triazole-1-yl-propyl]-3H-thieno[3,2-d]pyrimidin-4-one (118):

In a two necked round bottom flask fitted with a condenser and stopcock, 1-((2-(2,4-difluorophenyl)oxiran-2-yl)methyl)-1*H*-1,2,4-triazole (6.083 gm, 25.56 mmol), potassium carbonate (5.903 gm, 42.78 mmol) and tetrabutyl ammonium bromide (8.290 gm, 25.66 mmol) were taken. Dry ethyl acetate (40 ml) was added in it reaction was stirred at 80 ^{0}C for 20 min, then 6-bromothieno[3,2-d]-pyrimidin-4(3*H*)-one (4 gm, 21.390 mmol) dissolved in dry ethyl acetate (20 ml) was added in reaction mixture and stirred under reflux for 15 h at 80 ^{0}C. The reaction mixture was extracted with ethyl acetate (3 x 100 ml), organic layer was washed with water and brine, dried over sodium sulphate, concentrated under reduced pressure on rotary evaporator and purified on column chromatography to afford 6-bromo-3-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-[1,2,4]-triazole-1-yl-propyl]-3*H*-thieno[3,2-d]pyrimidin-4-one (6.2 gm, 62 %).

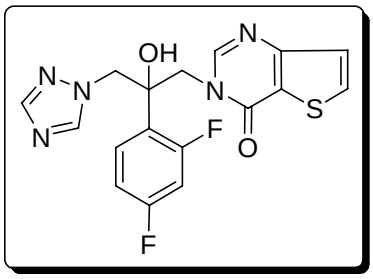
Nature: Brown semisolid; **Yield:** 62 %; **IR** (Chloroform)**:** ν_{max} 3351, 1666, 1618, 1581, 1441, 1422, cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.22 (d, *J* = 14 Hz, 1H), 4.43 (d, *J* = 14 Hz, 1H), 4.75 (d, *J* = 14 Hz, 1H), 4.85 (d, *J* = 14 Hz, 1H), 5.89 (bs, 1H), 6.70 - 6.87 (m, 2H), 7.45 - 7.50 (m, 1H), 7.77 (s, 1H), 7.80 (s, 1H), 8.01 (s, 1H), 8.18 (s, 1H); **Anal. Calcd. for** $C_{17}H_{12}BrF_2N_5O_2S$**:** C, 43.60; H,



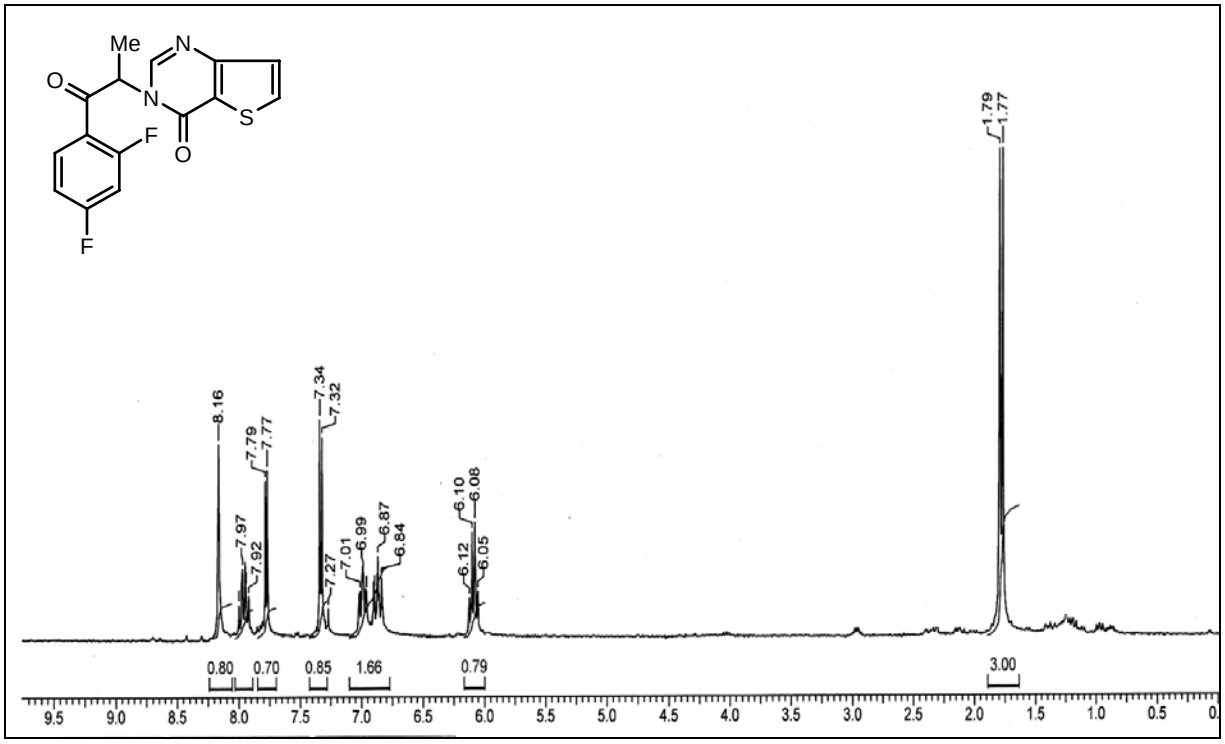
2.58; Br, 17.06; F, 8.11; N, 14.96 %. **Found:** C, 43.49; H, 2.37; Br, 17.00; F, 7.98; N, 14.78 %.

3-[2-(2,4-difluoro-phenyl)-2-hydroxy-3-[1,2,4]-triazole-1-yl-propyl]-3H-thieno[3,2-α]pyrimidin-4-one (118 a):

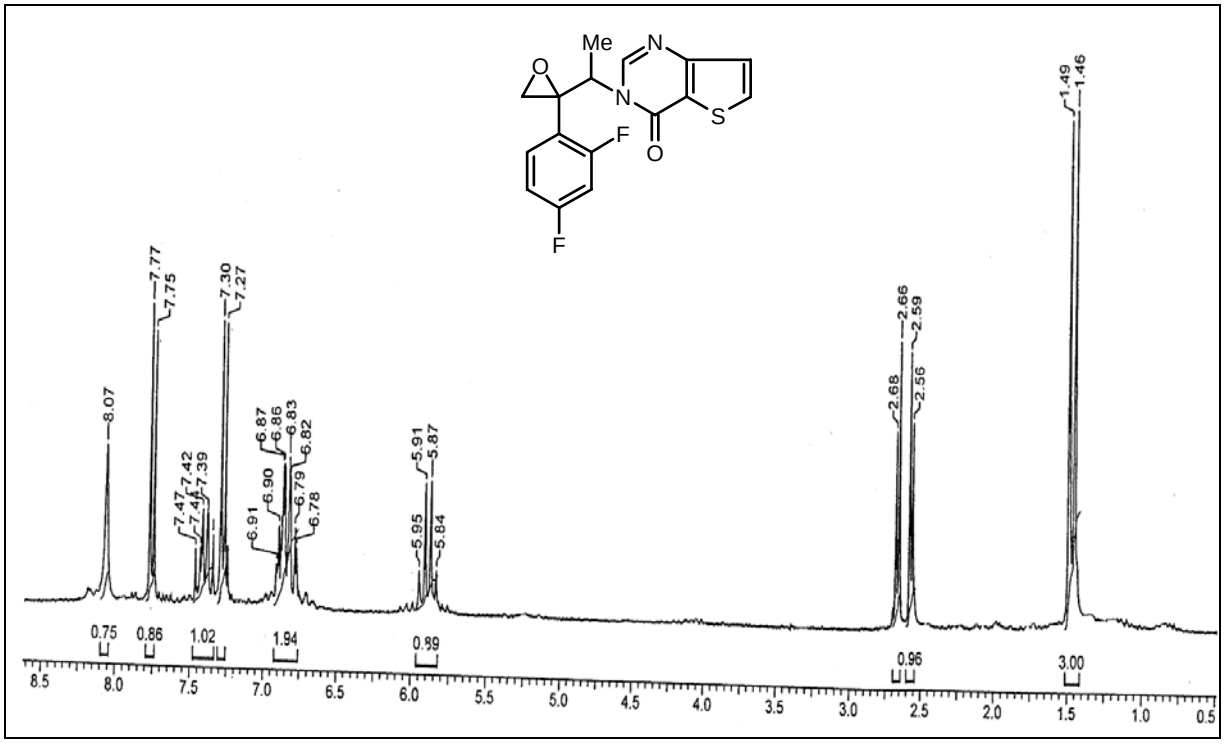
Nature: White semisolid; **Yield:** 73 %; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 4.27 (d, *J* = 14 Hz, 1H), 4.54 (d, *J* = 14 Hz, 1H), 4.77 (d, *J* = 14 Hz, 1H), 4.87 (d, *J* = 14 Hz, 1H), 6.12 (bs, 1H), 6.75 - 6.89 (m, 2H), 7.32 (d, *J* = 8 Hz, 1H), 7.49 - 7.61 (m, 1H), 7.80 - 7.86 (m, 2H), 8.08 (s, 1H), 8.13 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$)**:** δ 53.09, 53.43, 76.02, 104.32, 111.90, 112.30, 122.73, 125.19, 130.08, 135.37, 138.18, 148.40, 151.72, 155.90, 157.34, 158.94, 160.75; **Anal. Calcd. for** $C_{17}H_{13}F_2N_5O_2S$**:** C, 52.44; H, 03.37; F, 9.76; N, 17.99 %. **Found:** C, 52.27; H, 3.27; F, 9.59; N, 17.87 %.



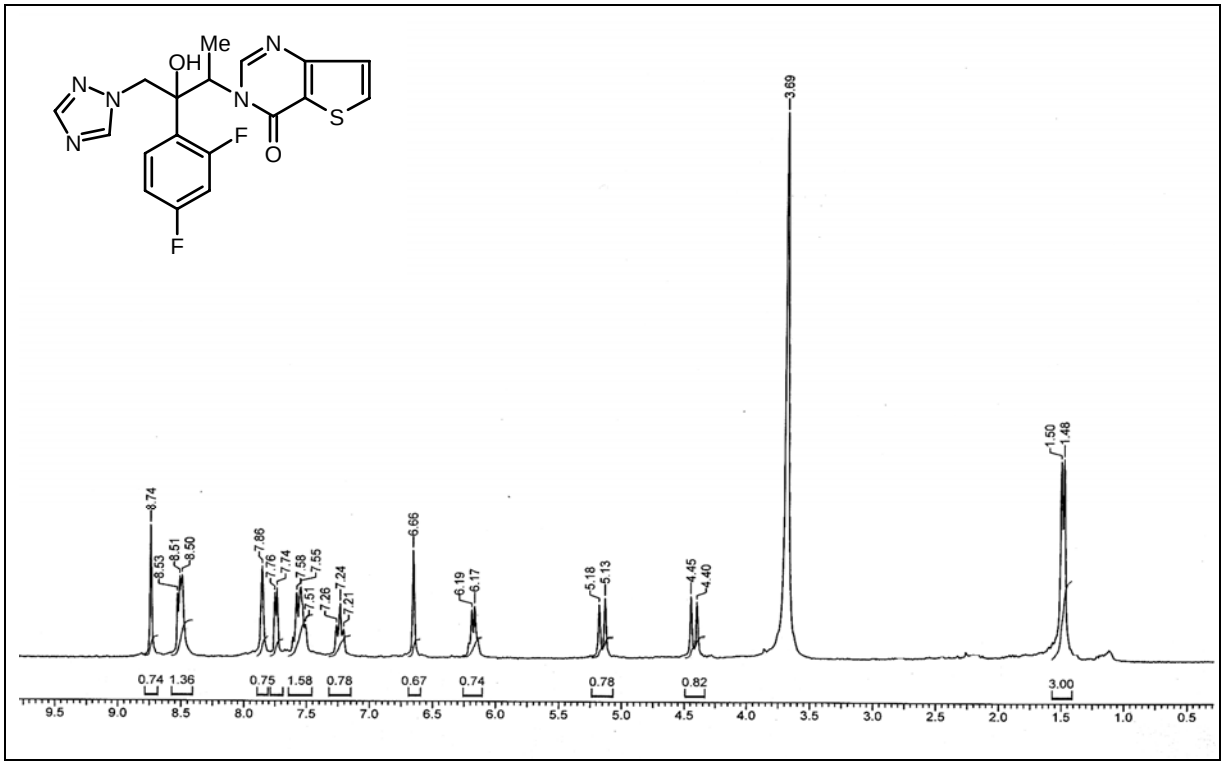
^{1}H NMR spectrum of compound 105 ($CDCl_3$+CCl_4, 300 MHz)



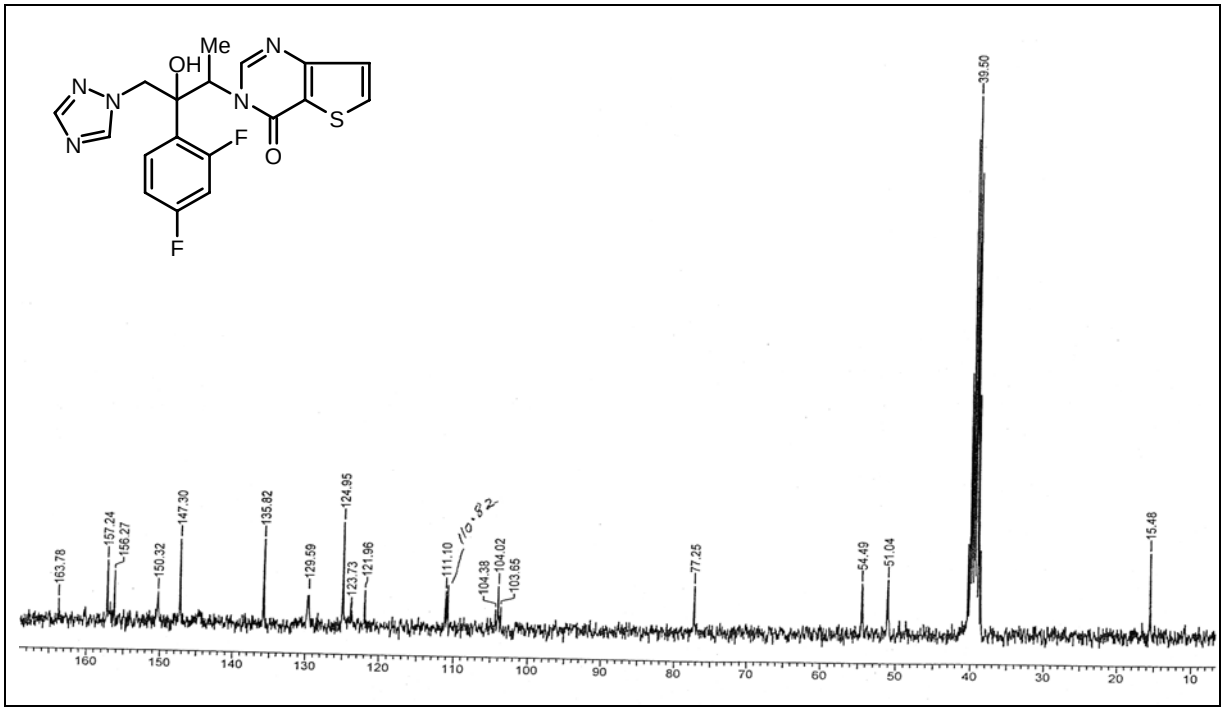
^{1}H NMR spectrum of compound 104 ($CDCl_3$+CCl_4, 200 MHz)



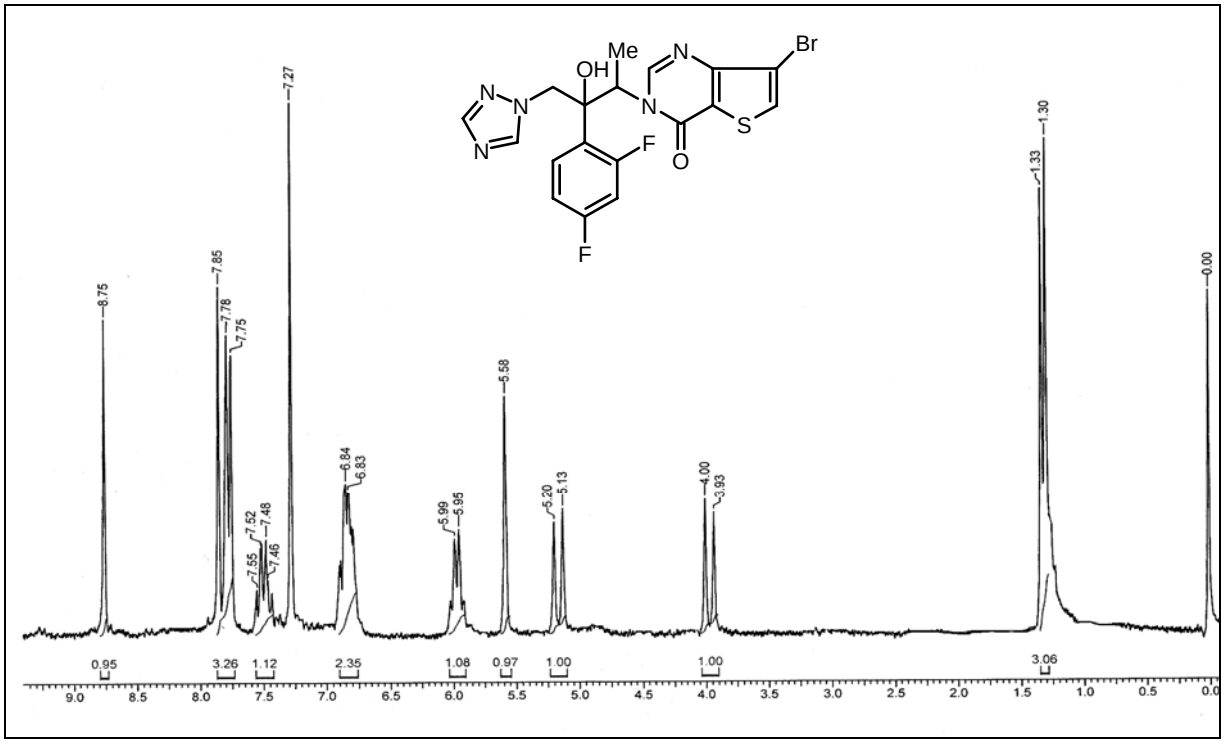
^{1}H NMR spectrum of compound 103 (DMSO-d_6, 300 MHz)



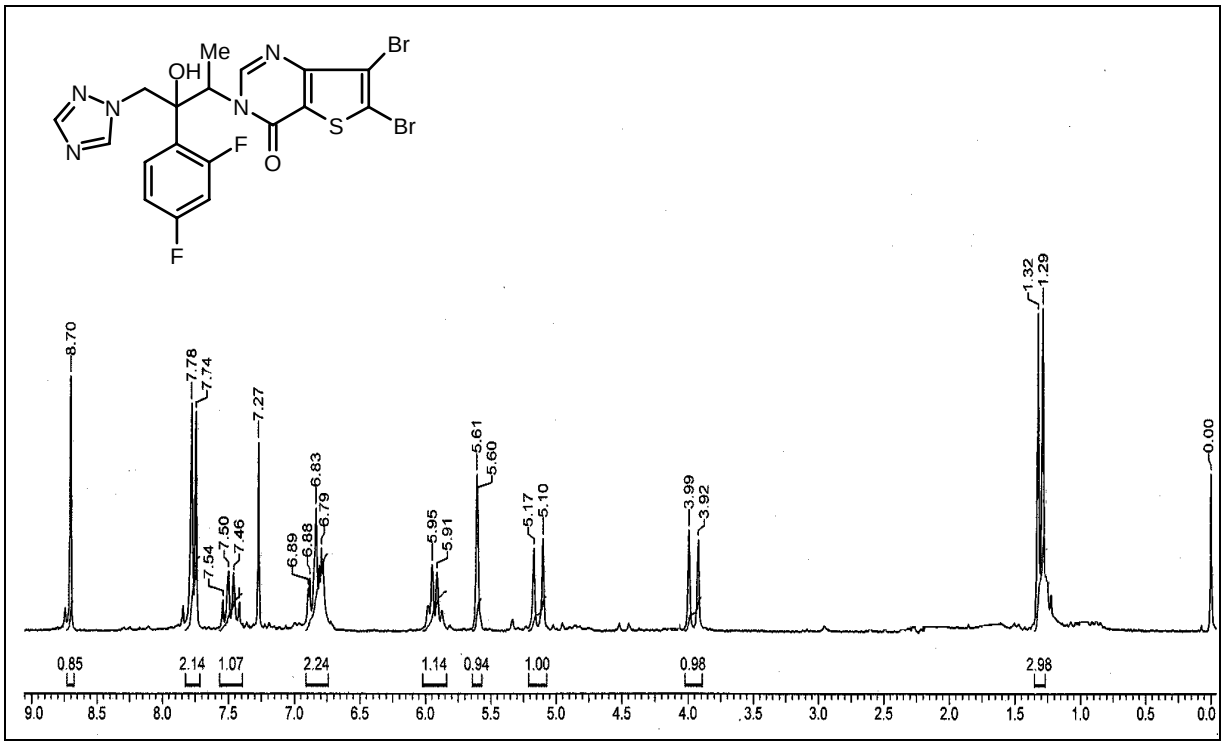
^{13}C NMR spectrum of compound 103 (DMSO-d_6, 75 MHz)



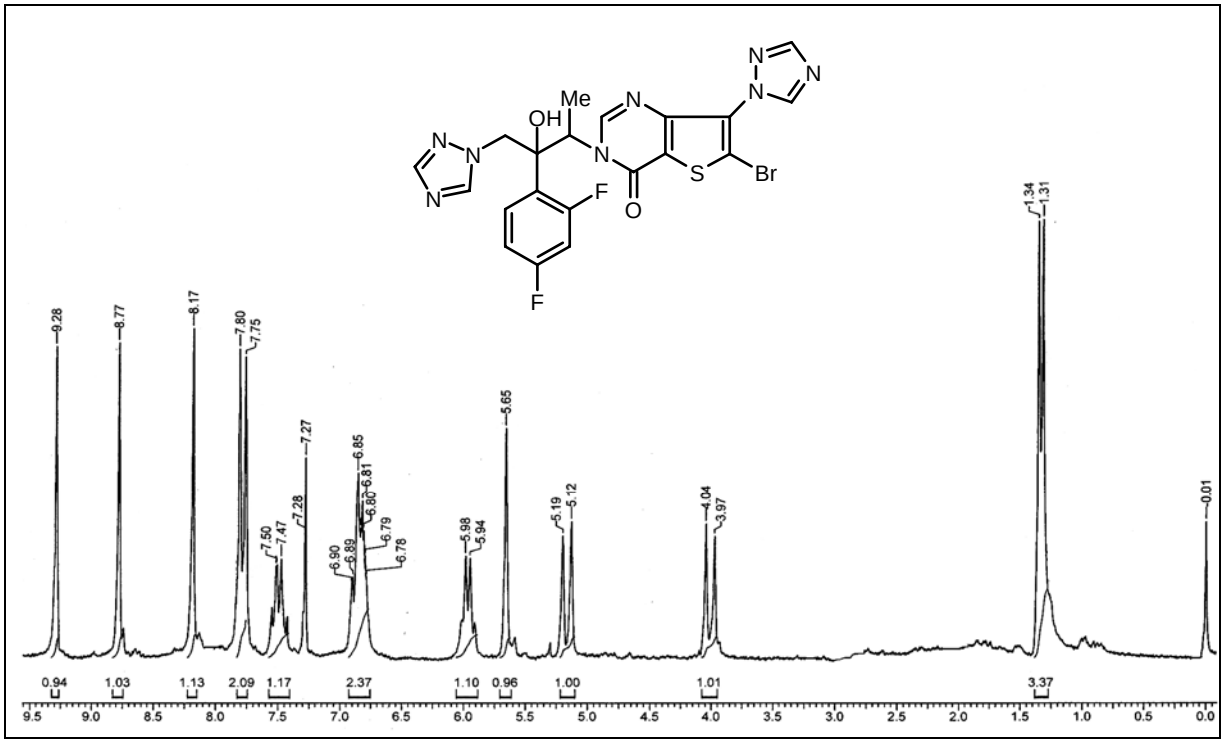
^{1}H NMR spectrum of compound 103 b ($CDCl_3$+CCl_4, 200 MHz)



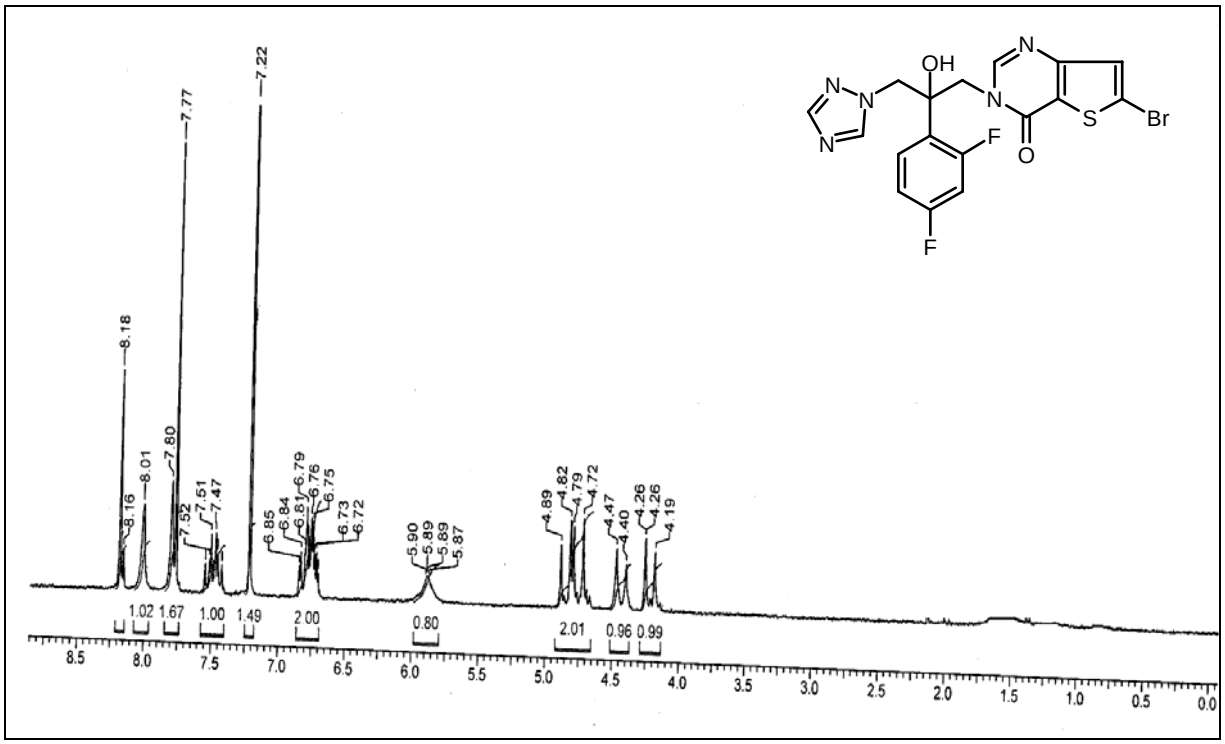
^{1}H NMR spectrum of compound 103 c ($CDCl_3$+CCl_4, 200 MHz)



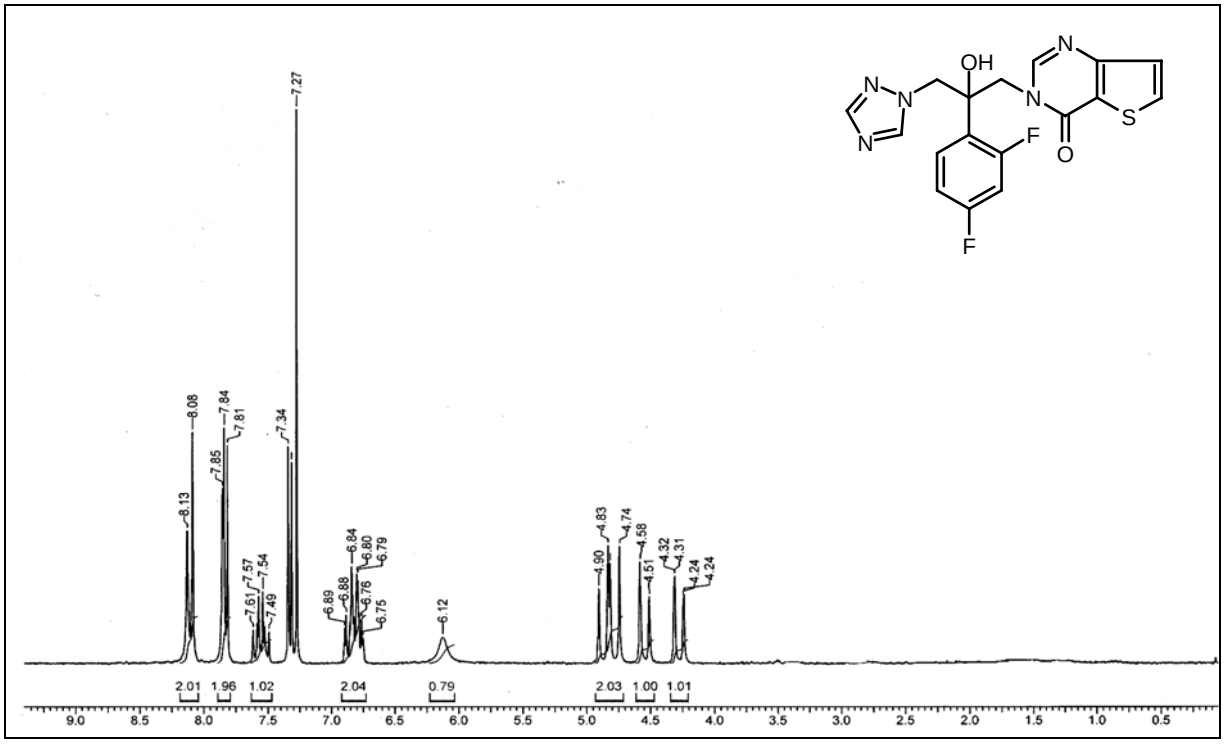
^{1}H NMR spectrum of compound 103 d ($CDCl_3$+CCl_4, 200 MHz)



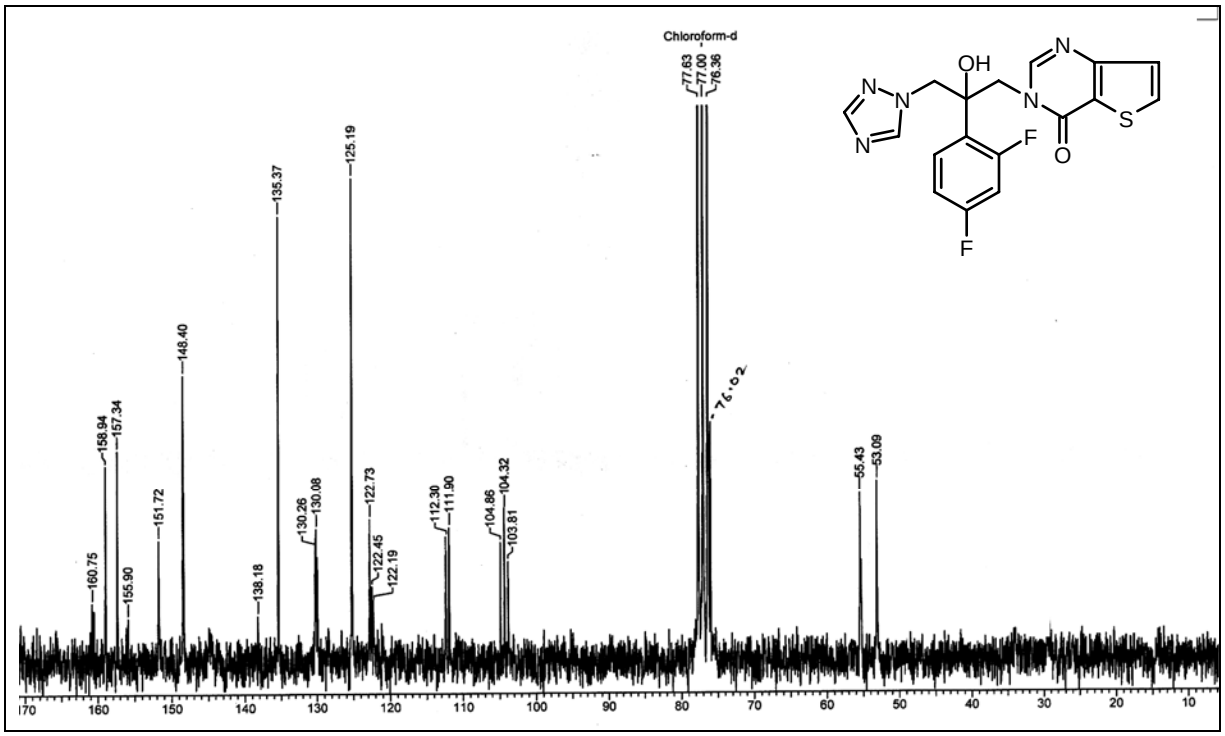
^{1}H NMR spectrum of compound 118 ($CDCl_3$+CCl_4 50 MHz)



^{1}H NMR spectrum of compound 118 a ($CDCl_3$+CCl_4, 200 MHz)



^{13}C NMR spectrum of compound 118 a ($CDCl_3$+CCl_4, 50 MHz)



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CHAPTER - II

SECTION - III

BIOLOGICAL ACTIVITY OF DESIGNED NCEs AS ANTIFUNGAL AGENTS

2.3.1: INRODUCTION:

Furanone moiety is commonly found in a number of drugs with diverse biological activities such as antifungal, antibacterial and anti-inflammatory.[1-4] A number of furanone derivatives have also been reported from nature as cytotoxic and antitumor agents. Considering the importance of furanone moiety in synthetic as well as naturally occurring compounds, we synthesized some new chemical entities having furanone moiety as discussed in first section of this chapter. Antifungal activity of designed NCEs containing furanone moiety has been discussed in this section.

The incidence of systemic fungal infections such as Candidosis, Cryptococcosis and Aspergillosis has been increasing recently due to an increase in the number of immunocompromised hosts. For the treatment of these infections, the new antifungal azoles have been developed for clinical use. Attention has been paid to triazole derivatives because of their generally broad antifungal spectrum and low toxicity. Trazole derivatives displace lanosterol from lanosterol 14-demethylase (14 DM), a cytochrome P-450-dependent enzyme, and block the biosynthesis of an essential component of fungal cell membrane, ergosterol. Fluconazole has relatively low antifungal activity *in vitro*, but it is water soluble, and has excellent pharmacokinetic properties. It is effective against candidiasis after both oral administration and injection. However, its activity against *Aspergillus* seems limited. Itraconazole has an excellent and broader antifungal spectrum. Newer triazole agents such as voriconazole, posaconazole and ravuconazole are active against Aspergillus and are currently under clinical trials. In order to seek new triazole antifungal agents we designed and synthesized a series of triazole compounds discussed in section-II of this chapter and antifungal activity has been discussed herein.

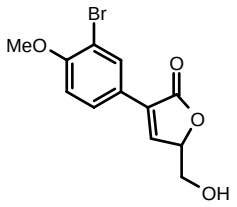
2.3.2: PRESENT WORK:

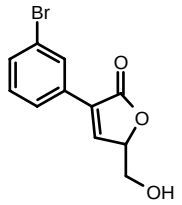
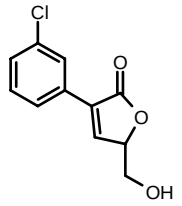
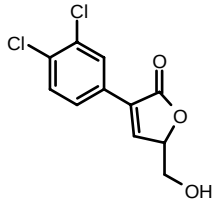
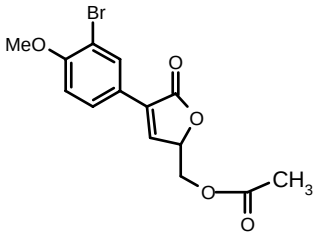
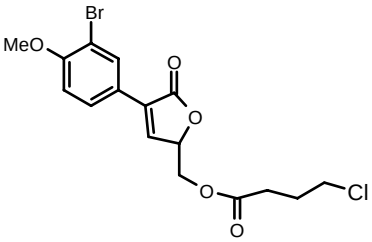
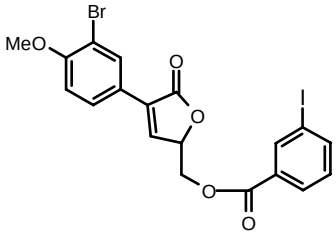
The synthesized NCEs of furanones and azole antifungals described in first and second section of this chapter were screened for antifungal activity at FDC Ltd. Mumbai. Three slandered ATCC strains of fungal cultures were used for the testing; Candida albicans ATCC 24433, Aspergillus niger ATCC 16404 and Fusarium proliferatum ATCC 10052. The activity screening was performed by macrobroth dilution method optimized by using amphotericin B and fluconazole as the standards.

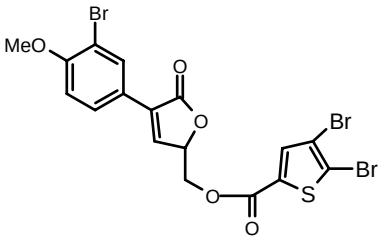
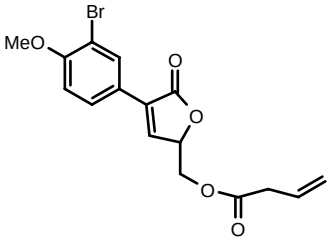
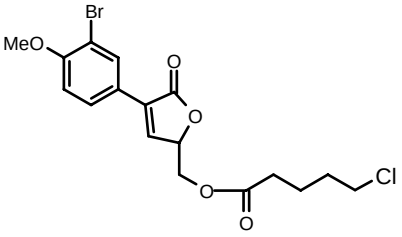
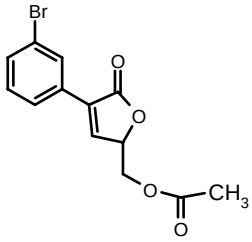
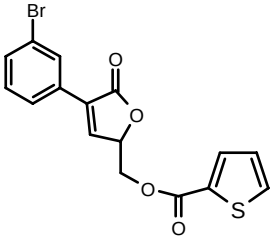
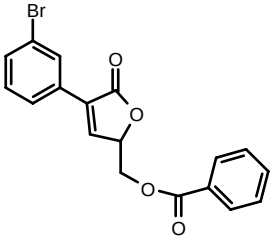
2.3.3. RESULTS AND DISCUSSION:

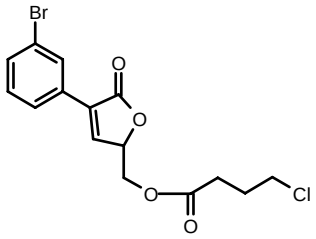
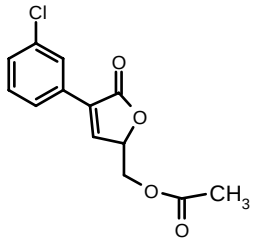
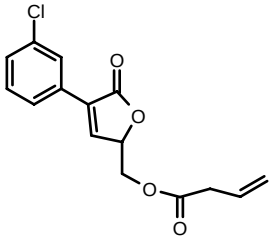
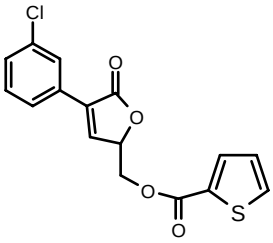
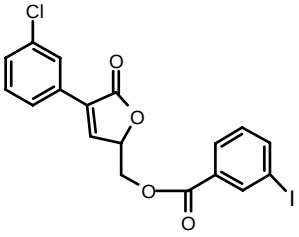
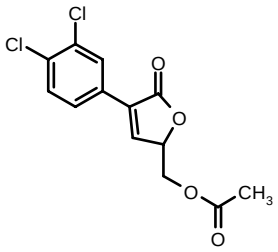
In vitro antifungal activities of the compounds amphotericin B and fluconazole were evaluated on a panel of three ATCC (Candida albicans ATCC 24433, Aspergillus niger ATCC 16404 and Fusarium proliferatum ATCC 10052) from the fungal strains deposited in the laboratory. Minimum inhibitory concentrations (MICs) were determined by microdilution format of the NCCLS M27-A guidelines. The activity data of synthesized derivatives of furanone has been depicted in table-1.

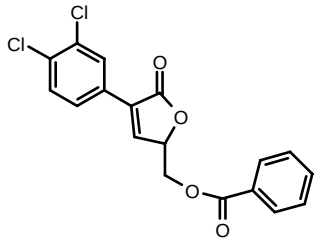
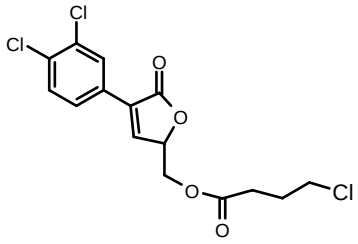
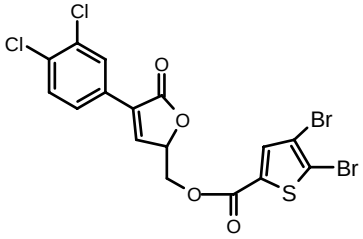
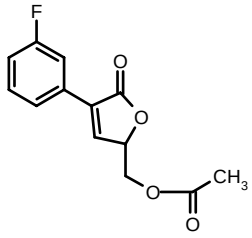
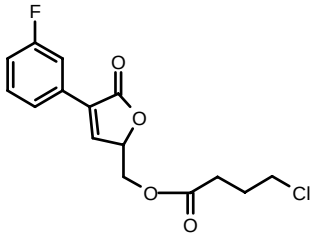
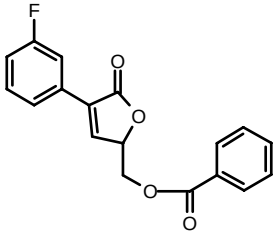
Table-1: Anti-fungal Activity Data of Furanones:

Entry	Comp	Structure	C. albicans	A. niger	F. proliferatum	Back precipitation
A		Fluconazole	0.25-	64-128	>128	
B		Amphotericin B	0.12-0.25	0.25-1	1-2	
1	**41a**		NI till 32	NI till 32	NI till 32	

2	**41b**		64	64	32	128 µg/ml
3	**41c**		32	64	32	Up to 32 µg/ml
4	**41d**		NA	2	2	Up to 32 µg/ml
5	**42a**		2-4	4-8	8-16	
6	**42b**		NI till 4	NI till 4	NI till 4	
7	**42c**		NI till 2	NI till 2	NI till 2	

8	**42d**		4-8	NI till 4	NI till 4	
9	**42e**		2-4	NI till 8	NI till 8	
10	**42f**		NI till 8	NI till 8	NI till 8	
11	**42g**		2	4	2	Up to 16 µg/ml
12	**42h**		2	8	2	Up to 4 µg/ml
13	**42i**		2	4	**0.5**	Up to 2 µg/ml

14	**42j**		1-2	4-8	1-2	
15	**42k**		2	4	**1**	Up to 16 µg/ml
16	**42l**		4	8	2	Up to 32 µg/ml
17	**42m**		2	4	1	Up to 4 µg/ml
18	**42n**		NI till 2	NI till 2	NI till 2	
19	**42o**		2	**0.5**	**0.25**	Up to 8 µg/ml

20	**42p**		4	2	**1**	Up to 8 µg/ml
21	**42q**		1-2	1-2	1-2	
22	**42r**		NI till 4	NI till 4	NI till 4	
23	**42s**		1-2	1-2	1-2	
24	**42t**		1-2	1-2	1-2	
25	**42u**		1-2	1-2	1-2	

The activity data depicted in Table 1 indicated that some of the compounds showed selectivity against *C. albicans, A. niger*, and *F. proliferatum.* Some analogues showed comparable activity for these fungi with that of amphotericin B and were found to be better than fluconazole, especially against *F. proliferatum*.

Antifungal activity data of azole derivatives:

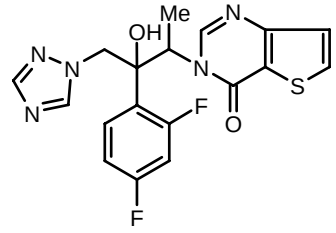
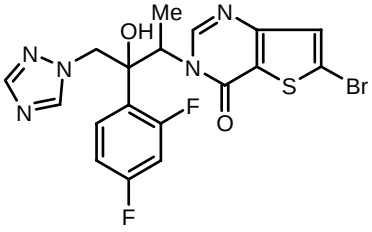
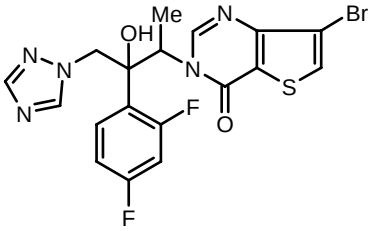
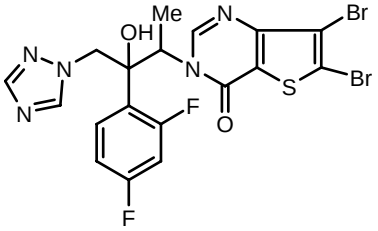
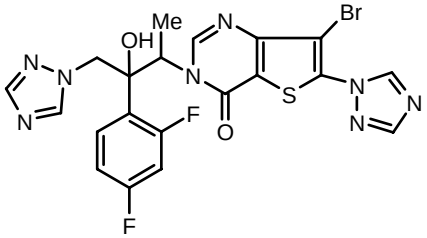
All of the azoles operate *via* a common mode of action: they prevent the synthesis of ergosterol, the major sterol component of fungal plasma membranes, through inhibition of the fungal cytochrome P450-dependent enzyme lanosterol 14-α-demethylase. The resulting depletion of ergosterol and the concomitant accumulation of 14-α-methylated precursors interfere with the bulk function of ergosterol in fungal membranes and alter both the fluidity of the membrane and the activity of several membrane-bound enzymes (e.g. chitin synthase). The net effect is an inhibition of fungal growth and replication. In addition, a number of secondary effects, such as inhibition of the morphogenetic transformation of yeasts to the mycelial form, decreased fungal adherence, and direct toxic effects on membrane phospholipids were observed.

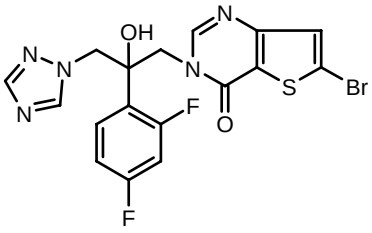
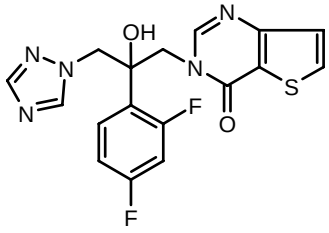
Unfortunately, as a result of the nonselective nature of the therapeutic target, cross-inhibition

of P450-dependent enzymes involved in mammalian biosynthesis has been responsible for some toxicity, although significantly lower and less severe with fluconazole, itraconazole and voriconazole than with the older compounds. The improved toxicity profile of the triazoles compared to the imidazoles (especially endocrine-related side-effects) can be explained by their greater affinity for fungal rather than mammalian P450-enzymes at therapeutic concentrations.

The synthesized derivatives of azoles showed considerable antifungal activity as compared to amphotericin-B and fluconazole.

Table-2: Antifungal activity data of azole derivatives

Entry.	Comp.	Structure	C. albicans	A. niger	F. proliferatum	Back precipitation
A		Fluconazole	0.25	64-128	>128	
B		Amphotercin-B	0.12-0.25	0.25-1	1-2	
1	**103**		**0.5**	4	64	Up to 64 µg/ml
2	**103a**		**0.12**	4	NA	Up to 32µg/ml
3	**103b**		**0.06-0.12**	NI till 8	NI till 8	--
4	**103c**		**0.06-0.12**	NI till 2	NI till 2	--
5	**103d**		**0.12-0.25**	NI till 16	NI till 16	--

6	**118**		**0.06**	32	NA	Up to 128 µg/ml
7	**118a**		**0.5**	4	54	Up to 64 µg/ml

2.3.4: CONCLUSION:

The presented data revealed that, the designed new chemical entities of furanone as well as azole derivatives showed considerable antifungal activity. Some of the NCEs showed very good antifungal activity as compared to amphotericin B and fluconazole. These results contribute a novel class of compounds with potential activity to the global drug discovery program. The results have been protected in the form of patents.

2.3.5: REFERENCES:

1. Larock, R.C. and Reifing, B. *J. Org. Chem.* **1978**, *43*, 131 and references therein.
2. Caine, D.; Stephen, F. and Ukachukawa, V.C. *J. Org. Chem.* **1983**, *48*, 740.
3. Rao, Y.S. *Chem. Rev.* **1964**, *64*, 353.
4. Rao, Y.S. *Chem. Rev.* **1976**, *76*, 625.

CHAPTER - III

SOME USEFUL ORGANIC TRANSFORMATIONS

CHAPTER - III

SECTION - I

EFFICIENT *N*-ARYLATION OF AMINES CATALYZED BY Cu-Fe HYDROTALCITE

3.1.1: INTRODUCTION:

A catalyst is a substance whose presence makes physiological and chemical reactions proceed and which itself does not get altered during the course of the reaction. In other words catalyst is a substance that accelerates rate of chemical reaction but is not consumed in the reaction; its mere presence evokes chemical actions, which would not take place in its absence.

A catalyst may control a chemical reaction by increasing the reactivity between molecules brought into play in the reaction and by facilitating the interaction between the reacting molecules, by loosening certain linkages of bonds within them. For example, in oxidation reaction, catalyst activates oxygen and helps the reactant to absorb oxygen. In catalytic hydration or dehydration, catalyst helps either addition of water or removal of water during reaction process. In catalytic hydrogenation, catalyst helps the addition of hydrogen to substance by ionizing hydrogen gas.

The basic concept of catalyst is that a substance in a small amount causes a large change; it determines the path of a reaction e.g. the decomposition of ethanol over alumina as catalyst yields ethylene and water; while over copper or silver catalysts, acetaldehyde and hydrogen are the products. In catalytic halogenation and dehalogenation catalyst helps addition or removal of halogens by radical or ionic mechanism. In alkylation or acylation reactions, catalysts assist in formation of cation as well as stabilizing it in the process. In polymerization, catalyst polarizes the double bonds or initiates the formation of free radicals. Catalyst even helps in rearrangement of groups within interacting molecules to form isomeric compounds during isomerisation.

Thus, the catalysts may be of different types, acids, bases, organometallics, enzymes, polymer supported, molecular sieves, zeolites, hydrotalcite, clays, phase transfer catalysts, metal and metal oxides, transition metal complexes etc. They have the ability to catalyze a variety of chemical reactions such as (a) coupling reactions (b) condensation (c) alkylation (d) oxidation (e) reduction (f) hydrogenation (g) dehydrogenation (h) halogenation and (i) isomerisation etc.

Catalytic reactions can either take place in solutions or on surfaces. Most of the metal ions or hydrogen ions function as acid-base catalysts in electron transfer reactions.

Several organometallic complexes have been used as single electron transfer catalyst. Enzymes are a separate class of catalysts, without them the processes of life will not take place. Enzymes, which possess complex polymeric structure catalyze biological reactions efficiently and function only at relatively mild temperatures. For example: (1) Breakdown of proteins and carbohydrates (2) Biosynthetic process that leads to growth and replacement of living organisms (3) Photosynthesis (4) Catalytic oxidation processes that convert food into CO_2, H_2O and energy etc.

Several alumino-silicates like zeolites, clays and molecular sieves are used as catalysts. Zeolites bear catalytic sites having microscopic cavities and are comparable to enzymes. Zeolites catalyze several types of reactions like oxidation, halogenation or acylation and isomerisation reactions. Molecular sieves, which are similar in structure to the zeolites, are also used in acid catalyzed reactions. Clays and other layered materials like hydrotalcite are also used in acid or base catalyzed reactions. Metals, metal oxides and metal sulfides some times used in combination with each other are important as industrial catalysts. Palladium, nickel and platinum as powders or on supports are used in olefin hydrogenation in food industries. Copper, nickel and platinum etc. are used in carbonyl reductions. The catalysts are classified into two main types: 1) Homogeneous catalysts 2) Heterogeneous catalysts.

1) **Homogeneous catalysts:** In recent years the term homogeneous catalysis is applied more specifically to the use of a solution of certain organometallic compounds in which a central metal atom is surrounded by a regular pattern of atoms or molecules, known as ligands with which it is coordinated. Homogeneous catalytic transition metal complex reactions enhance selectivity compared with heterogeneous catalytic reactions. In homogeneous catalytic reactions the catalysts and reactants are present in one phase and a major disadvantage of this arises from the difficulty in separating the product from the catalysts; this is a peculiar problem in large-scale conversions with open reaction systems. The reactions of industrial importance are primarily hydro-formylation (oxo synthesis), carbonylation, addition of HCN and olefin polymerization.

2) **Heterogeneous catalysts:** In heterogeneous catalysis, the reaction takes place in the interface between the catalysts and the less dense phase. In other words heterogeneous catalysis describes the enhancement in the rate of a chemical reaction brought about by the presence of an interface between two phases. In general, much higher temperature is used in heterogeneous catalytic reactions than in homogeneous catalytic ones. Heterogeneous catalyst can be divided naturally into two distinct groups (a) Metals and (b) Non-metals.

   Heterogeneous catalysis is widely used in petroleum refining and plays an ever increasingly important role in organic synthesis (speciality and fine chemicals). This development is quite natural, as processes employing solid catalysts are definitely more advantageous from an environmental and functional point of view than non-catalytic processes or those using soluble catalysts.

   Around 90 % of all chemicals involve a catalyst at some stage of their manufacture hence catalysis is critical to the chemical industry. The development of profitable production of already established fine chemicals could only be achieved with innovative methods, which have ecological and economical benefits. In this regard catalysts in general are of key importance due to their abilities to open up new reaction pathways and to improve all kinds of selectivity. Consequently, it is possible to use cheaper feedstock and to avoid unwanted side products.

   Heterogeneous catalysts are proved to be very effective in the synthesis of fine chemicals even on industrial scales. The main advantages of these heterogeneous catalysts are:

   1) High catalytic activity under mild reaction conditions.
   2) Easy separation of the catalyst after the reaction.
   3) Low cost, as catalyst can be recycled.

HYDROTALCITES (HT) AS A HETEROGENEOUS CATALYST:

Hydrotalcite (HT)[1-4] like synthetic anionic clays (also called as layered double hydroxides, LDHs) are more rare in nature than cationic clays (or clay minerals), but relatively simple and inexpensive to synthesize in laboratory and on industrial scale.

Hydrotalcites (HT) are composed of positively charged brucite like layers of divalent and trivalent metal hydroxides whose excess positive charge is compensated by anions and water molecules present in the interstitial positions.

The structure of these compounds consists of brucite [Cu $(OH)_2$] type layers in which a part of the M (II) cations are isomorphously substituted between M(III) cations. The excess positive charge of the layers resulting from this substitution is compensated for interstitial layers built of anions such as CO_3^{2-} and water molecules. Many names are used as a function of the composition and nature of the polytype forms[5] (Hydrotalcite, Mansseite, Sjorgenite, Stitchite etc.) They can be represented by the general formula $[M(II)_{1-x}\ M(III)x\ (OH)_2]^{x+}\ [(A^{n-})x/n\ Y\ H_2O]^{x-}$ where M (II) and M (III) are the divalent and trivalent cations such as Mg^{+2}, Cu^{+2}, Ni^{+2}, Co^{+2}, Mn^{+2}, Zn^{+2} and Al^{+3}, Fe^{+3}, Cr^{+3}, Ga^{+3}, V^{+3}, Ru^{+3}, Rh^{+3}, respectively, A^{n-} is an inter layer anion such as CO_3^{2-}, NO_3^-, SO_4^{2-} and X is the ratio of trivalent metal which is in the range from 0.1 to 0.33. The positively charged Cu-Fe double hydroxide sheets (or layers) are charge balanced by the carbonate anions residing in the inter layer section of the clay structure.[6]

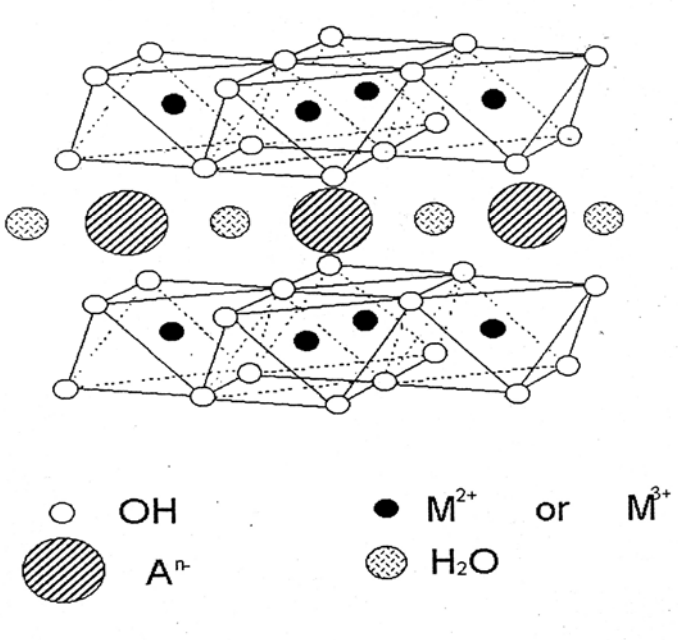


Fig 1: Hydrotalcite-like compound

$M^{2+}\ M^{3+}\ (OH)_2\ (A^{n-}) \bullet mH_2O$

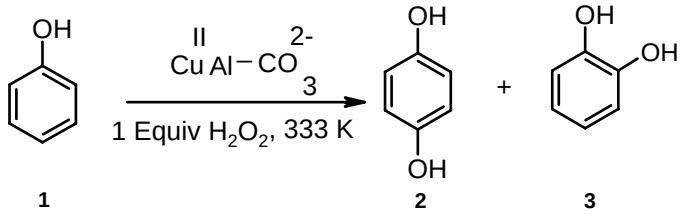
Hydrotalcites are synthetic or natural crystalline materials containing positively charged two dimensional sheets with water and exchangeable charge compensating anions in the interlayer region (Fig 1).

Their general structure is as shown in figure 1 where M^{2+} and M^{3+} represent divalent and trivalent cations in the brucite-type layers, A is the inter layer anion with charge n, x is the fraction of the trivalent cation (x values in the general formula are in the range of 0.20-0.5) and m is the water of crystallization.

The mineral hydrotalcite itself is a magnesium–aluminium hydroxycarbonate; the class of HTs comprising many isostructural and polytype forms. HTs may be used as such or they may be calcined to form mixed oxides that are useful catalysts. HTs in the uncalcined form can be used as catalyst supports but they are mainly applied because of their basic properties or as redox catalyst.

As is evident from the structural formula, HTs have a considerable anion-exchange capacity. Under proper conditions, small exchanged ions such as NO_3^- or Cl^- can be replaced completely with large anions, and an expanded layered structure with intercalated guest species is obtained. Hydrotalcites are reported to catalyze some redox reactions very effectively.

Copper (II) containing HTs were tested for the liquid-phase hydroxylation of phenol using H_2O_2 as the oxygen source.[7]



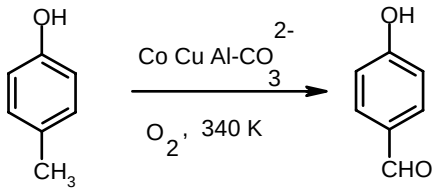
1 **2** **3**

Hydroquinone Catechol

32% yield 22% yield

Scheme - 1: *Copper (II) containing HTs catalyzed liquid-phase hydroxylation of phenol*

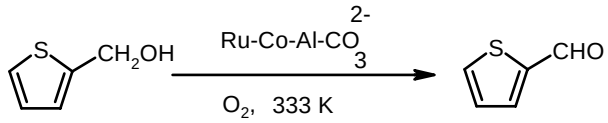
Copper (II) containing HTs catalyzed liquid-phase hydroxylation of phenol can yield *p*-hydroxybenzaldehyde, which is an important chemical for the pharmaceutical and perfume industries.



4 **5**

Scheme - 2: *Liquid phase oxidation of p-cresol with Co and Cu containing HTs*

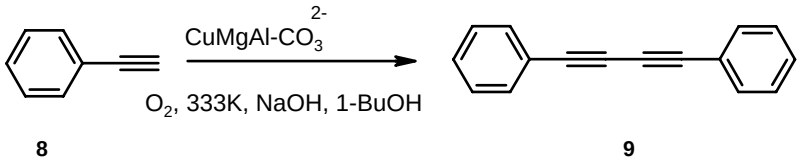
Ru-Co-Al-CO_3^{2-} and Ru-Al-Mg-CO_3^{2-} hydrotalcites were used as catalyst for the oxidation of allylic and benzylic alcohols with molecular oxygen. The reaction is chemoselective as primary allylic and benzylic alcohol groups are converted in to the corresponding aldehydes, with negligible formation of the acids. Even oxidation – sensitive functions such as thiophene are not attacked during alcohol oxidation.[8]



6 **7**

Scheme - 3: *Ru-Co-Al-CO_3^{2-} and Ru-Al-Mg-CO_3^{2-} hydrotalcites as catalyst for the oxidation of allylic and benzylic alcohols with molecular oxygen*

The synthesis of substituted conjugated alkynes, valuable components for liquid-crystal applications was reported[9] by oxidative coupling of phenylethyne, leading to 1, 4-diphenyl buta-1,3-diyne, with a calcined Cu containing Mg-Al-HT as the catalyst.



Scheme - 4: *Oxidative coupling of phenylethyne with a calcined Cu containing Mg-Al-HT as the catalyst*

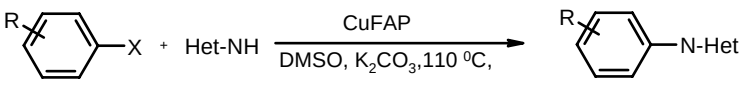
Our exploratory efforts for application of HT-catalyst have resulted in the observation that Cu-Fe-hydrotalcite is a useful catalyst for *N*-arylation of amines with aryl halides and the results discussed in the present work of this section, have been reported.[10]

3.1.2: PRESENT WORK:

BRIEF REVIEW OF LITERATURE:

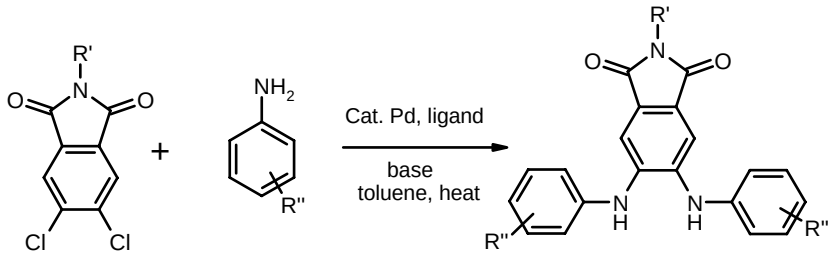
N-Arylation of various amines and amides has continued to attract synthetic chemists as the *N*-arylated products constitute the subunits of many biologically active molecules.[11,12] The different methods reported for *N*-arylation include coupling of amines or isocyanates with aryl boronic acids, aryl halides, aryl triflates etc using copper, cuprous iodide, cupric acetate, copper-diamine complexes, palladium, cobalt or nickel catalysts. Cu-catalyzed Ullmann coupling protocols and Ullmann type processes for C–N bond formation have been reported and amination of aryl iodides using various ligands has been extensively studied. Application of ionic liquids or microwave for *N*-arylation has been reported recently. Some of these methods involve use of expensive chemicals, tedious work up or sensitive catalysts / ligands, therefore it has been recognized that developing clean *N*-arylation is one of the most important challenges in green chemistry. The use of heterogeneous catalysts offers the advantages such as ease of work up, recyclability and development of environmentally benign synthetic procedures. Solid supports like KF/Al_2O_3 have been used for *N*-arylation in recent years.

Lakshmi Kantam M. *et al*. reported[13] the copper fluorapatite catalyzed *N*- arylation of heterocycles with bromo and iodoarenes. Copper exchanged fluorapatite (CuFAP) is an effective heterogeneous catalyst for *N*- arylation of heterocycles with bromo- or iodoarenes using K_2CO_3 as base as shown in scheme-5. *N*-Arylated products were isolated in good yields, demonstrating the versatility of the reaction.



Scheme - 5

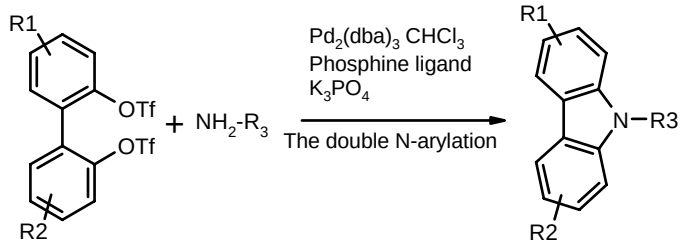
Buchwald *et al.* reported[14] the *N*-arylation of amines by using palladium and ligand in presence of a base in toluene. They have reported the synthesis of 4, 5-dianilinophthalimide and its analogues by using this methodology as shown in scheme-6. The requisite substrates are easily obtained, and their coupling with substituted anilines proceeds in high yields. Thus, a variety of DAPH analogues can be quickly accessed in a modular fashion. In addition the route described should also be amenable to the incorporation of other classes of nucleophiles into the molecular framework.



12 **13** **14**

Scheme - 6

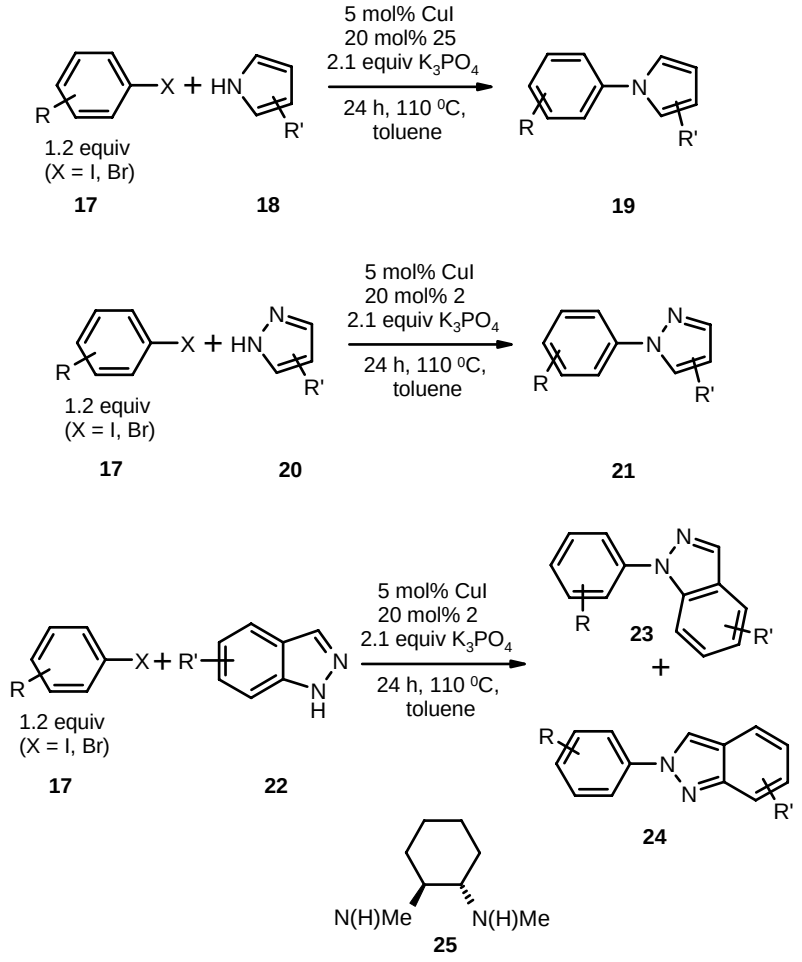
Nazaki k. *et al*. reported[15] the double *N*-arylation of primary amines with 2, 2'-biphenylene ditriflates for the synthesis of multisubstituted carbazoles. Palladium complexes supported by 2-dicyclohexylphosphino-2'-methylbiphenyl or xanthphos [4, 5-bis (diphenylphosphino)-9, 9-dimethylxanthene] were found to be efficient catalyst for the reaction as shown in scheme-7. The catalysts allow the use of anilines with an electron-donating or electron-withdrawing substitutent and multisubstituted 2, 2'-biphenylylene ditriflates as substrates.



15 **16**

Scheme - 7

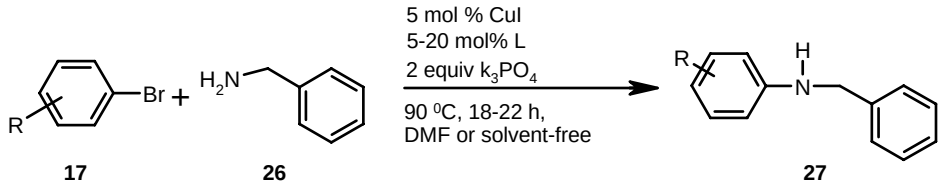
Buchwald *et al.* reported[16] the Copper-Diamine-Catalyzed *N*-arylation of pyrroles, pyrazoles, imidazoles and triazoles. A general reaction protocol for each class of heterocycles was determined, and represents a good starting point for future studies with particular substrates of interest. This work should find wide application among synthetic and medicinal chemists in industry and academics. They have made considerable inroads. The development of new catalysts that allow C-N bond formation to take place with more highly hindered substrate combinations is desirable as shown in scheme-8.



Scheme - 8

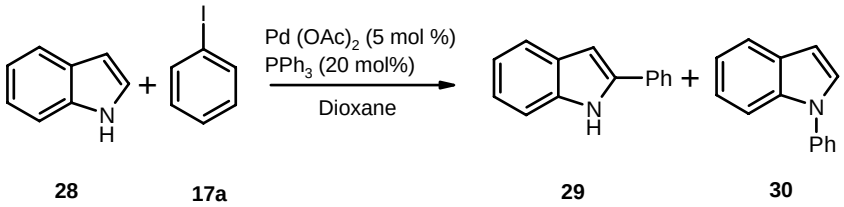
Buchwald S. L. *et al*. reported[17] a mild and efficient copper-catalyzed amination of aryl bromides with primary alkylamines. The method uses commercially available diethylsalicylamides as the ligand as shown in scheme-9. This amination reaction can be

performed at 90 ^{0}C in good yield. A variety of functional groups are compatible with these reaction conditions. Preliminary results show that this reaction can be carried out under solvent-free condition with comparable yields.



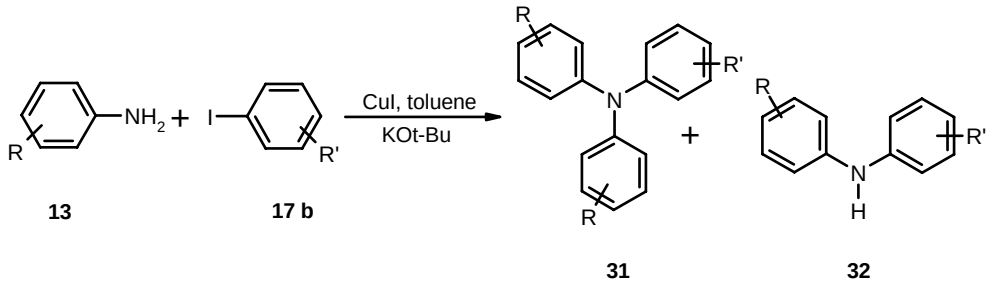
Scheme - 9

Sames D. *et al*. reported[18] the *N*-arylation in presence of palladium acetate and triphenyl phosphine in dioxane but they isolated the products of *N*-arylation as well as *C*-arylation as shown in scheme-10.



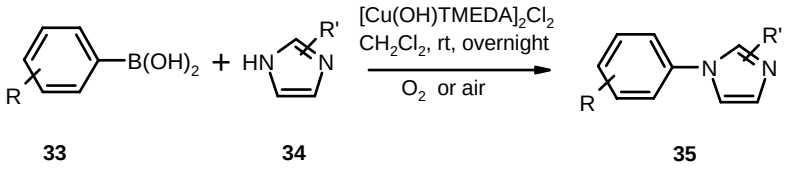
Scheme - 10

Kelkar A. A. *et al*. reported[19] copper-catalyzed amination of aryl halides. They used CuI, toluene and KO*t*-Bu as a base in this method and isolated the mixture of diaryl and triaryl amines as shown in scheme-11.



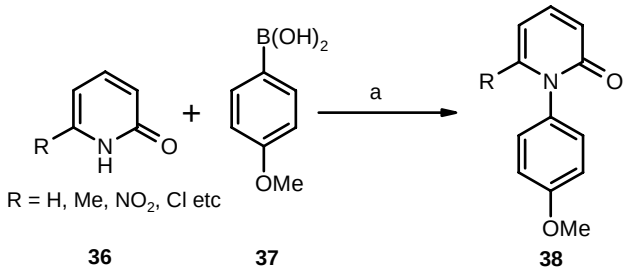
Scheme - 11

Collman *et al.* reported[20] an efficient diamine-copper complex-catalyzed coupling of arylboronic acids with imidazoles. In the presence of catalytic amount of [Cu(OH)-TMEDA]$_2$Cl$_2$, arylboronic acids react smoothly with imidazoles in dichloromethane at room temperature to give a variety of *N*-arylimidazoles in good to excellent yields as shown in scheme-12.



Scheme - 12

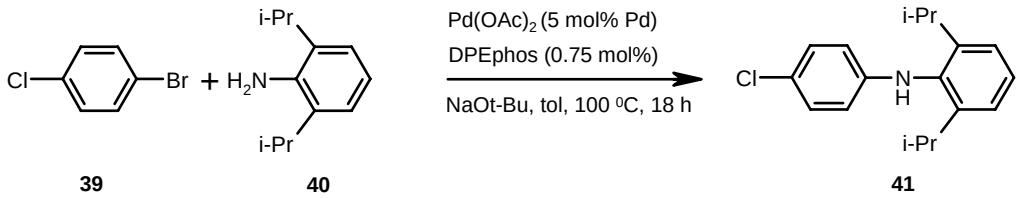
Mederski *et al.* reported[21] *N*-aryl heterocycles via coupling reactions with arylboronic acids. Here they have used various 2-pyridones and 3-pyridazinones with 4-methoxyphenylboronic acid as shown in scheme-13.



a = biphenyl-2-carbonitrile. 2 eq. boronic acid, 2.0 eq. anhydrous Cu(OAc)$_2$, N(Et)$_3$, 2.0 eq. pyridine, molecular sieve 4 A^0, CH$_2$Cl$_2$, room temperature, 48 h.

Scheme - 13

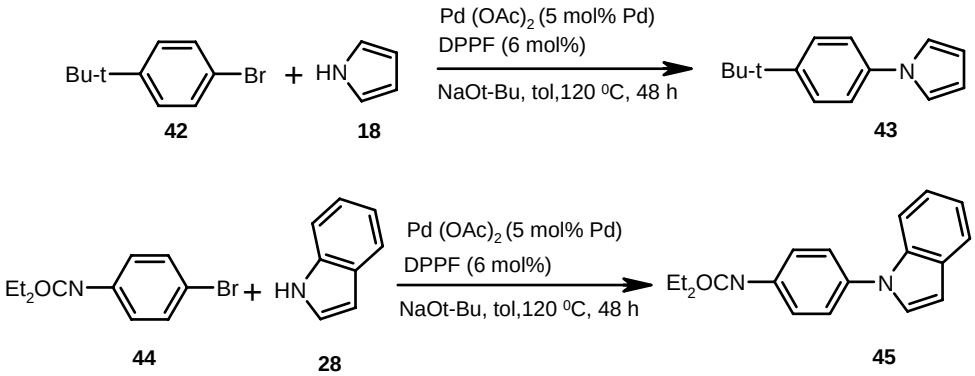
During a search for inexpensive ligands, Buchwald S. L. *et al*. reported[22] the use of bis[2-(diphenylphosphino)phenyl] ether (DPEphos). This ligand is easily prepared from diphenyl ether by double lithiation, followed by trapping with chlorodiphenylphosphine. In the comparative study, DPEphos, BINAP and DPPF were combined with Pd(OAc)$_2$, and the resulting systems were assayed for their effectiveness in catalyzing the *N*-arylation of primary anilines as shown in scheme-14. DPEphos was found to be as good as BINAP in the cases studied, and as good as or superior to DPPF.



39 **40** **41**

Scheme - 14

Mann G. *et al*. reported[23] *N*- arylation using Pd as catalyst. Pyrroles, indoles, and carbazoles constitute a special class of nitrogenous bases. Under standard Pd-catalyzed *N*-arylation conditions, these compounds can be prepared in high yield using both electron-rich and electron-poor aryl bromides as shown in scheme-15. However, the former requires long reaction times at high temperatures, and no examples of o-substituted aryl bromide substrates were reported.

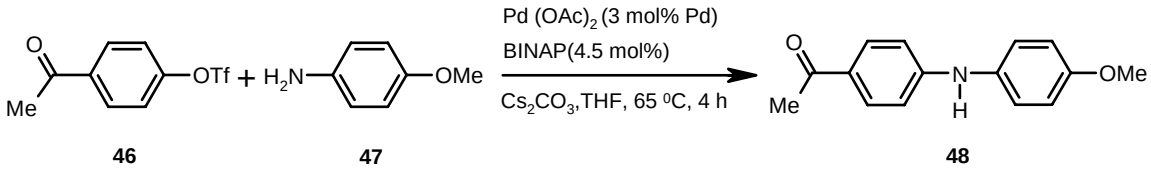


42 **18** **43**

44 **28** **45**

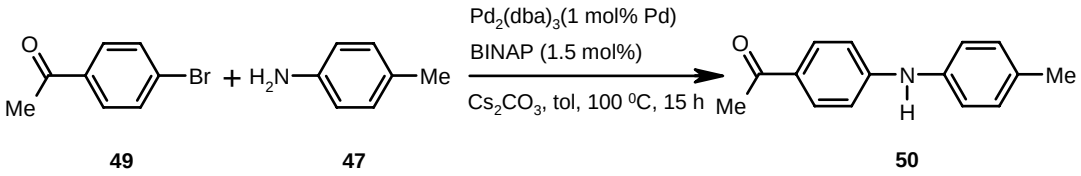
Scheme - 15

Buchwald S. L. and Ahman J. have reported[24] that under the standard conditions, [$Pd(OAc)_2$, BINAP, Cs_2CO_3 as base] primary anilines can be coupled with electron-poor triflates in high yields, even with substrates containing an enolizable ketones as shown in scheme-16.



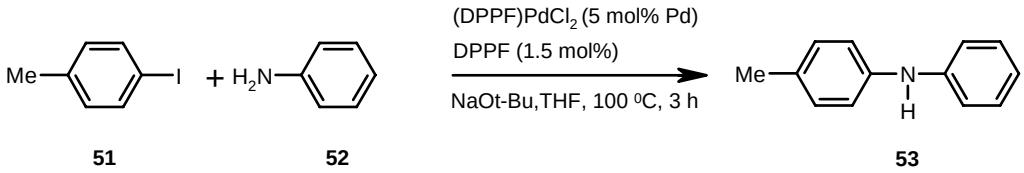
Scheme - 16

Buchwald and coworkers reported[25] the synthesis of oligoanilines by Pd-catalyzed coupling of primary anilines with aryl bromides. Using standard conditions [Pd $(OAc)_2$ and BINAP], they found that anilines were effectively coupled with a variety of aryl bromides as shown in scheme-17.



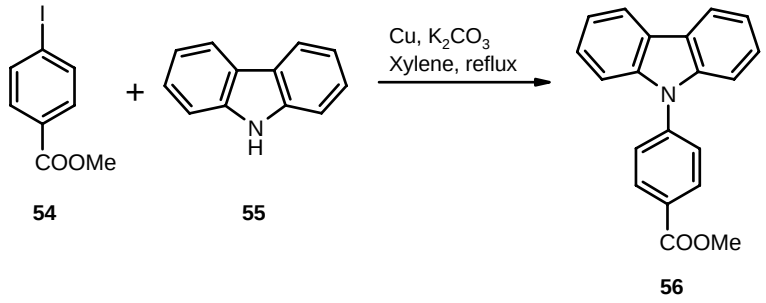
Scheme - 17

Hartwig and co-workers[26] have demonstrated the utility of (DPPF) $PdCl_2$- catalyzed reactions of aryl bromides and aryl iodides with anilines as shown in scheme-18.



Scheme - 18

Kato. Y. *et al*. reported[27] water-soluble receptors for cyclic-AMP and their use for evaluating phosphate-guanidinium interactions, in which they used *N*-arylation in presence of Cu and K_2CO_3 as a base for the synthesis of *N*-arylated product as shown in scheme-19.



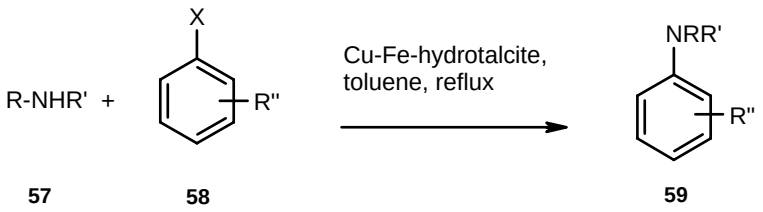
Scheme - 19

PRESENT WORK:

In continuation of our research interest in the use of heterogeneous catalysts for organic transformations, recently we synthesized a double-layered hydrotalcite catalyst containing Cu-Fe from their corresponding nitrites, potassium hydroxide and potassium carbonate. The catalyst contained not only HT phase but also mixed metal hydroxide/carbonate phases. Considering the requirement of basic conditions and the role of copper in such Ullmann-type C-N bond forming reactions we employed Cu-Fe-hydrotalcite for *N*-arylation of amines with aryl halides (Scheme 20). Cu-Fe-hydrotalcite was found to be capable of catalyzing this reaction efficiently and this environmentally friendly way for the synthesis of *N*-aryl-amines has been described herein.

3.1.3: RESULTS AND DISCUSSION:

The importance of *N*-aryl-amines and the advantages of heterogeneous catalysis prompted us to explore the possibility of arylation of various amines by reaction with aryl halides in the presence of Cu-Fe-hydrotalcite as shown in scheme - 20.



57 **58** **59**

R-NHR'=Substituted aniline, indole, cyclohexyl amine, benzyl amine

X=Br, I

R''=H, OMe, NO_2, Cl, CHO

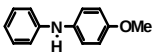
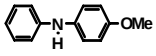
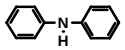
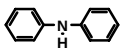
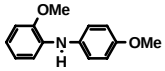
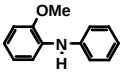
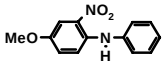
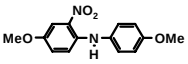
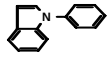
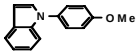
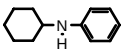
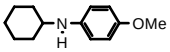
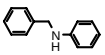
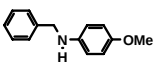
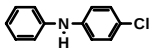
Scheme 20

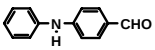
The layered double hydroxide (LDH) and/or mixed hydroxides containing Cu (II) and Fe (III) with Cu (II) / Fe (III) mole ratio of 3:1 (Cu-Fe-HT) was prepared by a known procedure[6], by adding two aqueous solutions simultaneously, one containing mixed nitrates of the divalent and trivalent metals (Cu/Fe) and second containing potassium hydroxide and potassium carbonate in deionized water, dropwise into a flask under vigorous stirring at 40 ºC, while maintaining a constant pH of 11-12. The resulting gel-like material was aged for 0.5 h, filtered, thoroughly washed with deionized water and dried at 80 ºC in vacuum oven and then further heated in air oven at 200 ºC for 12 h. The catalyst was characterized for the crystalline phase(s) and spacing between hydroxide layers [d (001) spacing] by XRD [using a Phillips Diffractometer (1730 series) and CuKα radiations]. The catalyst contained not only HT phase but also mixed HT and metal hydroxide/carbonate phases. Before carrying out the surface area measurements, the catalyst (0.1-0.5 g) was pretreated *in situ* in an U-shaped sample cell in a flow of moisture- free N_2 –He (1:3) gas mixture (30 $cm^3\ g^{-1}$) at 200ºC for 2 h. The surface area measurement was carried out by the single point N_2 adsorption method (using a Surface Area Analyser; Quanta Chrome, USA) and the observed surface area was 65.9 $m^2\ g^{-1}$. For measuring the pH of the suspension in water, 0.15 g catalyst was suspended in 10 ml deionized water at room temperature and the observed pH was 7.43. The CO_3^{2-} content of the catalyst (by treating the catalyst with 4.0 M HNO_3 and measuring quantitatively the CO_2 evolved) was observed to be 0.286 mmol g^{-1}.

Initially, aniline was reacted with one equivalent of 4-bromoanisole in toluene at room temperature in presence of Cu-Fe-hydrotalcite (10% by weight of aniline) when there was no reaction. Increase in temperature helped the reaction to occur and it was gratifying that the desired product was obtained in 80% yield when the reaction mixture was refluxed for 15 h Absence of product in a similar reaction without catalyst confirmed the role of the catalyst. When aniline was reacted with 4-iodoanisole, 85% product was obtained in 12 h A number of amines were reacted with different aryl halides to study the scope and limitations of the reaction and the results are shown in Table 1.

This newly developed Cu-Fe-hydrotalcite catalyzed *N*-arylation protocol was applied to substituted anilines like 2-methoxyaniline, 4-methoxy-2-nitroaniline, indole, cyclohexyl amine and benzyl amine which were reacted with 4-bromoanisole to afford the corresponding products in 74-87% yields. Bromobenzene, iodobenzene, 4-bromochlorobenzene and 4-bromobenzaldehyde were used as the variants on aryl halide side and it was observed that they were efficiently transformed to the corresponding products in excellent yield. To our surprise when 4-bromobenzaldehyde was subjected to this transformation with aniline no traces of Schiffs base product was observed and the reaction was highly selective for the desired transformation. It is noteworthy that the reaction was selective for primary amines and did not yield further arylation to give triarylamines. Alkylamines like cyclohexylamine and benzylamine (Table-1, entry 11 and 12) reacted equally efficiently to give the corresponding *N*-arylated products. Diarylamine was separately treated with iodoanisole to confirm this observation when the starting materials remained unchanged. Although this catalyst worked well with primary amines and indole when other heterocycles such as imidazole, triazole, benzimidazole and substituted indole derivatives were employed as substrates, the reaction did not proceed to give the expected products which indicated the high selectivity of the catalyst towards primary amines.

Table1. *N*-Arylation of amines catalyzed by Cu-Fe-hydrotalcite

Ent. No.	***Amine***	Halide	Product (59)	Time in h	% Yield
1	Aniline	4-Bromo-anisole	 **59a**	15	80
2	Aniline	4-Iodoanisole	 **59a**	12	82
3	Aniline	Bromobenzene	 **59b**	14	79
4	Aniline	Iodobenzene	 **59b**	12	81
5	2-Methoxy-aniline	4-Bromo-anisole	 **59c**	12	76
6	2-Methoxy-aniline	Bromobenzene	 **59d**	12	75
7	4-Methoxy- 2-nitroaniline	Bromobenzene	 **59e**	16	77
8	4-Methoxy -2-nitroaniline	4-Bromo-anisole	 **59f**	16	74
9	Indole	Bromobenzene	 **59g**	12	85
10	Indole	4-Bromo-anisole	 **59h**	12	87
11	Cyclohexylamine	Bromobenzene	 **59i**	12	81
12	Cyclohexylamine	4-Bromo-anisole	 **59j**	12	80
13	Benzylamine	Bromobenzene	 **59k**	12	79
14	Benzylamine	4-Bromo-anisole	 **59l**	12	81
15	Aniline	4-Bromo-chloro-benzene	 **59m**	12	76

16	Aniline	4-Bromo-benzaldehyde	 **59n**	12	79

3.1.4: CONCLUSION:

In conclusion, we have developed an efficient useful method for *N*-arylation of amines by reaction of different amines with aryl halides in presence of Cu-Fe-hydrotalcite. The reaction conditions are mild and various functional groups are tolerated. In comparison with reported protocols this method avoids the use of expensive catalysts and ligands, excess of amines or use of base and instead employs a heterogeneous catalyst that is easily removed from the product and can be recycled and reused. No hazardous chemicals are used and the reaction is performed in environmentally friendly solvent (toluene) and products are obtained simply by filtration and concentration of the filtrate. Selective *N*-arylation of primary amines is possible in case of amino benzaldehyde without formation of Schiffs base.

3.1.5: EXPERIMENTAL:

Preparation of the Cu-Fe hydrotalcite catalyst:

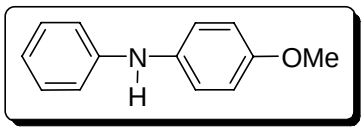
The layered double hydroxide (LDH) and/or mixed hydroxides containing Cu (II) and Fe (III) with Cu (II) / Fe (III) mole ratio of 3:1 (Cu-Fe-HT) was prepared by adding two aqueous solutions simultaneously, one containing copper nitrate (38.60 g, 159.8 mmol) and ferric nitrate (21.57 g, 53.4 mmol) in deionized water (200 ml) with the required Cu/Fe ratio and second containing potassium hydroxide (30.38 g, 541.4 mmol) and potassium carbonate (5.52 g, 39.9 mmol) in deionized water (600 ml), dropwise into a flask under vigorous stirring at 40 ºC, while maintaining a constant pH of 11-12. The resulting gel-like material was aged for 0.5 h, filtered, thoroughly washed with deionized water and dried at 80 ºC in vacuum oven and then further heated in air oven at 200 ºC for 12 h.

***Typical procedure for the preparation of (4-methoxyphenyl)-phenylamine**:*

To a solution of aniline (0.5 g, 5.3 mmol) and 4-bromoanisole (1.0 g, 5.3 mmol) in toluene (7 ml) was added Cu-Fe-hydrotalcite (50 mg, 10 % by wt. of amine). The reaction mixture was stirred under reflux at 130 °C for 15 h (monitored by TLC). It was then cooled to RT, filtered, washed with toluene (10 ml) and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel.

(4-methoxy-phenyl)-phenyl-amine (59 a):

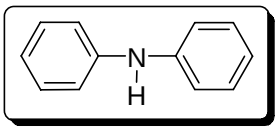
Yield: 80 %; **IR** (chloroform)**:** ν_{max} 3411, 3018, 1611, 1513, 1489, 1443 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.69 (s, 3H), 6.59 (d, J = 8 Hz, 2H), 7.40 - 7.55 (m, 5H), 7.85 (d, J = 8 Hz, 3H including N-H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 55.2, 112.7,



115.6 (2C), 122.8 (2C), 128.9 (2C), 130.9, 132.1 (2C), 152.5, 158.6. **Anal. Calcd. for** $C_{13}H_{13}NO$**:** C, 78.36; H, 6.58; N, 7.03 %. **Found:** C, 78.15; H, 6.53; N, 6.92 %.

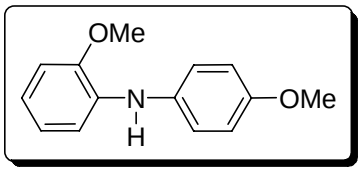
Diphenyl-amine (59 b):

Yield: 79 %; **IR** (chloroform)**:** ν_{max} 3429, 3019, 1693, 1509, 1484, 1454 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 7.40 - 7.57 (m, 6H), 7.85 - 7.96 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 122.9 (4C), 129.05 (4C), 130.9 (2C), 152.6 (2C); **Anal. Calcd. for** $C_{12}H_{11}N$**:** C, 85.17; H, 6.55; N, 8.28 %. **Found:** C, 85.07; H, 6.42; N, 8.20 %.



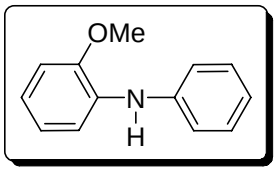
(4-methoxy-phenyl)-(2-methoxy-phenyl)-amine (59 c):

Yield: 76 %; **IR** (chloroform)**:** ν_{max} 3425, 3019, 1601, 1512, 1463, 1384 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.82 (s, 3H), 3.92 (s, 3H), 6.84 - 6.94 (m, 5H), 7.10 - 7.20 (m, 3H); **Anal. Calcd. for** $C_{14}H_{15}NO_2$**:** C, 73.34; H, 6.59; N, 6.11 %. **Found:** C, 73.21; H, 6.47; N, 6.01 %.



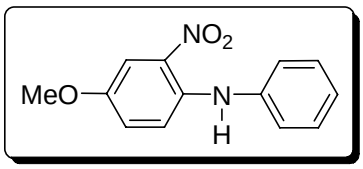
(2-methoxy-phenyl)-phenyl-amine (59 d):

Yield: 75 %; **IR** (chloroform)**:** ν_{max} 3427, 3008, 1606, 1510, 1486, 1440 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.76 (s, 3H), 6.44 - 7.05 (m, 5H), 7.10 (d, J = 8 Hz, 1H), 7.18 - 7.26 (m, 3H) **Anal. Calcd. for** $C_{13}H_{13}NO$**:** C, 78.36; H, 6.58; N, 7.03 %. **Found:** C, 78.22; H, 6.51; N, 6.95 %.



(4-methoxy-2-niitro-phenyl)-phenyl-amine (59 e):

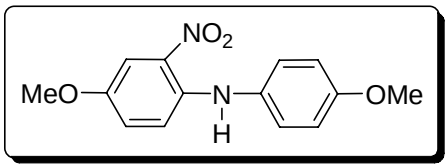
Yield: 77 %; **IR** (chloroform)**:** ν_{max} 3431, 3010, 1602, 1500, 1420, 1380 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.75 (s, 3H), 6.96 - 7.19 (m, 7H), 7.54 (s, 1H), 9.20 (broad hump, 1H); **Anal. Calcd. for**



$C_{13}H_{12}N_2O_3$**:** C, 63.93; H, 4.95; N, 11.47 %. **Found:** C, 63.88; H, 4.89; N, 11.30 %.

(4-methoxy-2-nitro-phenyl)-(4-methoxy-phenyl)-amine (59 f):

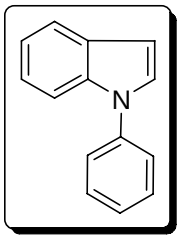
Yield: 74 %; **IR** (chloroform)**:** ν_{max} 3443, 3020, 1573, 1508, 1417, 1384 cm^{-1}; **^{1}H NMR**



(200 MHz, $CDCl_3$+CCl_4)**:** δ 3.74 (s, 3H), 3.76 (s, 3H), 6.82 - 7.00 (m, 4H), 7.10 (d, J = 10 Hz, 2H), 7.53 (s, 1H), 9.25 (broad hump, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 55.4, 55.7, 106.5, 114.9 (2C), 117.4, 126.6 (3C), 131.7 (2C), 139.8, 150.6, 157.6; **Anal. Calcd. for** $C_{14}H_{14}N_2O_4$**:** C, 61.31; H, 5.14; N, 10.21 %. **Found:** C, 61.20; H, 5.02; N, 10.11 %.

1-phenyl-1H-indole (59 g):

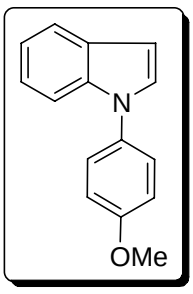
Yield: 85 %; **IR** (chloroform)**:** ν_{max} 3057, 1598, 1516, 1504, 1456 cm^{-1}; **^{1}H NMR** (200



MHz, $CDCl_3$+CCl_4)**:** δ 6.61 (d, J = 2 Hz, 1H), 7.05 - 7.20 (m, 3H), 7.22 - 7.31 (m, 1H), 7.40 - 7.55 (m, 5H), 7.62 (d, J = 6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 103.5, 110.4, 120.3, 121.1 122.3, 124.3 (2C), 126.4, 127.9, 128.7, 129.5 (2C), 139.5, 140.1; **Anal. Calcd. for** $C_{14}H_{11}N$**:** C, 87.01; H, 5.74; N, 7.25 %. **Found:** C, 86.92; H, 5.61; N, 7.12 %.

1-(4-methoxy-phenyl)-1H-indole (59 h):

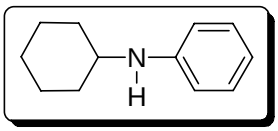
Yield: 87 %; **IR** (chloroform)**:** ν_{max} 2925, 1612, 1518, 1458, 1400 cm^{-1}; **^{1}H NMR** (200



MHz, $CDCl_3$+CCl_4)**:** δ 3.78 (s, 3H), 6.55 (d, J = 4 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 7.04 - 7.25 (m, 4H), 7.26 - 7.45 (m, 3H), 7.59 (d, J = 6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 55.6, 102.9, 110.3, 114.7 (2C), 120.0, 121.1, 122.1, 126.0 (2C), 128.3, 128.9, 132.8, 136.3, 158.2; **Anal. Calcd. for** $C_{15}H_{13}NO$**:** C, 80.69; H, 5.87; N, 6.27 %. **Found:** C, 80.52; H, 5.65; N, 6.16 %.

Cyclohexyl-phenyl-amine (59 i):

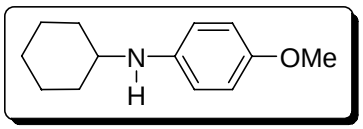
Yield: 81 %; **IR** (chloroform)**:** ν_{max} 3399, 2931, 1601, 1504, 1451, 1384 cm^{-1}; **^{1}H NMR**



(200 MHz, $CDCl_3$+CCl_4)**:** δ 0.98 - 1.35 (m, 6H), 1.63 - 2.01 (m, 4H), 3.11 - 3.24 (m, 1H), 6.49 - 6.72 (m, 3H), 7.02 - 7.13 (m, 2H); **Anal. Calcd. for** $C_{12}H_{17}N$**:** C, 82.23; H, 9.78; N, 7.99 %. **Found:** C, 82.10; H, 9.65; N, 7.81 %.

Cyclohexyl-(4-methoxy-phenyl)-amine (59 j):

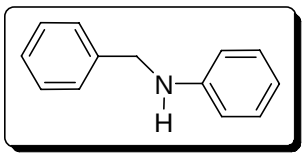
Yield: 80 %; **IR** (chloroform)**:** ν_{max} 3437, 3020, 1652, 1514, 1424, 1384 cm^{-1}; **^{1}H NMR**



(200 MHz, $CDCl_3$+CCl_4)**:** δ 1.17 - 1.39 (m, 6H), 1.74 - 2.00 (m, 4H), 3.07 - 3.25 (m, 1H), 3.79 (s, 3H), 4.02 (bs, 1H), 6.55 - 6.65 (m, 1H), 6.74 - 6.90 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 24.7, 24.9, 25.5, 25.6, 31.8, 55.3, 55.6, 114.7, 115.7 (2C), 119.5, 132.2 (2C); **Anal. Calcd. for** $C_{13}H_{19}NO$**:** C, 76.06; H, 9.33; N, 6.82 %. **Found:** C, 75.82; H, 9.25; N, 6.76 %.

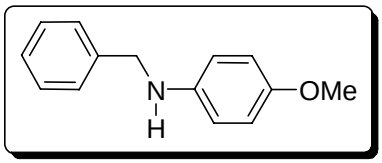
Benzyl-phenyl-amine (59 k):

Yield: 79 %; **IR** (chloroform)**:** ν_{max} 3420, 3016, 1601, 1510, 1480, 1421 cm^{-1}; **^{1}H NMR**



(200 MHz, $CDCl_3$+CCl_4)**:** δ 4.77 (s, 2H), 7.25 - 7.40 (m, 8H), 7.68 - 7.85 (m, 2H), 8.33 (s, 1H); **Anal. Calcd. for** $C_{13}H_{13}N$**:** C, 85.21; H, 7.15; N, 7.64 %. **Found:** C, 85.10; H, 7.08; N, 7.49 %.

Benzyl-(4-methoxy-phenyl)-amine (59 l):

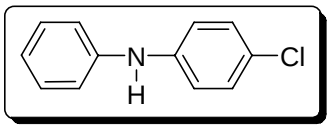


Yield: 81 %; **IR** (chloroform)**:** ν_{max} 3416, 3021, 1607, 1511, 1485, 1434 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.83 (s, 3H), 4.87 (s, 2H), 6.82 (d, J = 8

Hz, 2H), 7.30 - 7.48 (m, 5H), 7.81 - 7.96 (m, 2H); **Anal. Calcd. for** $C_{14}H_{15}NO$**:** C, 78.84; H, 7.09; N, 6.57 %. **Found:** C, 78.67; H, 6.95; N, 6.42 %.

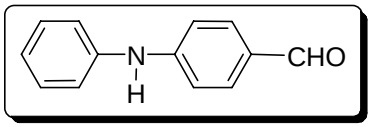
(4-chloro-phenyl)-phenyl-amine (59 m):

Yield: 76 %; **IR** (chloroform)**:** ν_{max} 3430, 3012, 1609, 1511, 1485, 1430 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 6.15 - 6.30 (m, 1H), 6.90 - 7.04 (m, 5H), 7.13 - 7.25 (m, 3H); **Anal. Calcd. for** $C_{12}H_{10}ClN$**:** C, 70.77; H, 4.95; Cl, 17.41; N, 6.88 %. **Found:** C, 70.52; H, 4.71; Cl, 17.28; N, 6.76 %.

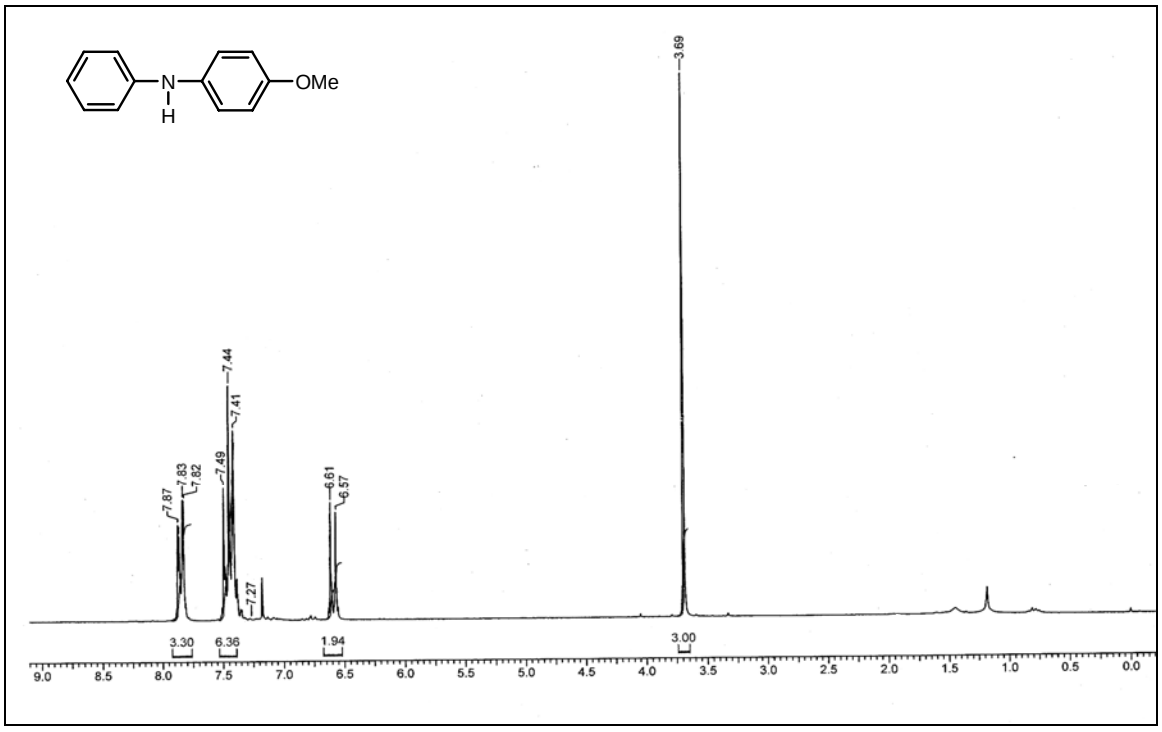


4-phenyl amino-benzaldehyde (59 n):

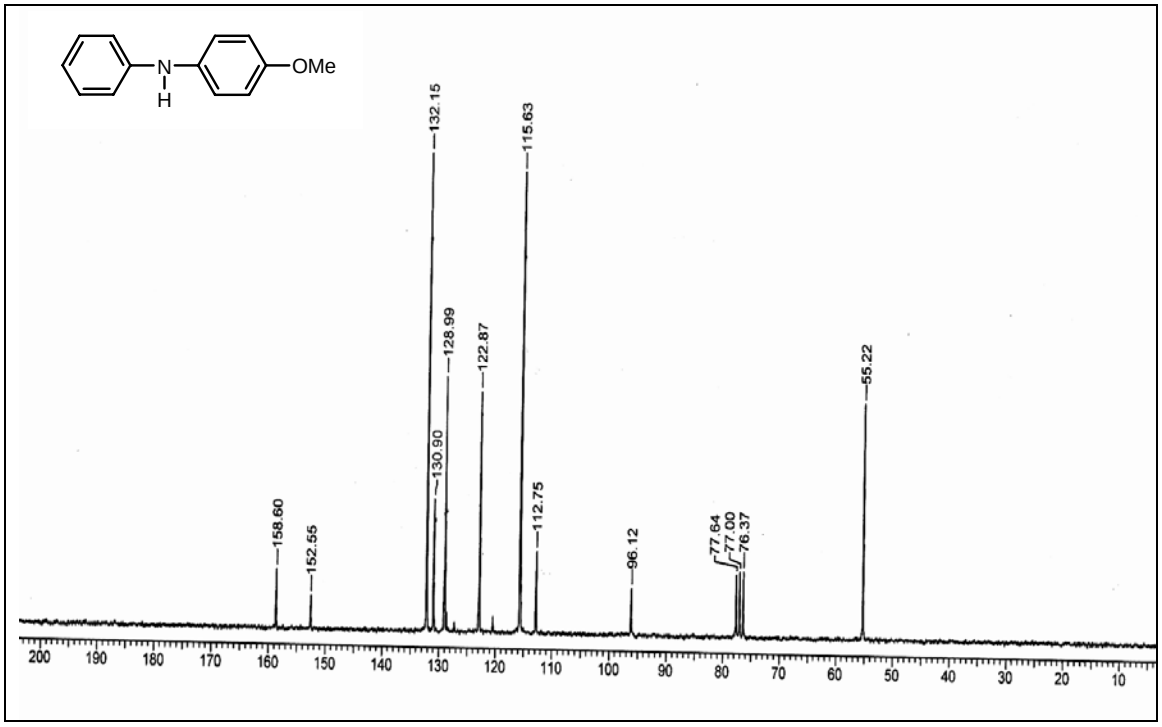
Yield: 79 %; **IR** (chloroform)**:** ν_{max} 3394, 2710, 1700, 1626, 1588, 1488 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 6.83 - 6.90 (m, 2H), 7.00 - 7.07 (m, 2H), 7.24 - 7.50 (m, 5H), 8.05 (s, 1H), 9.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4)**:** δ 120.7, 125.7, 126.0, 129.0, 130.0, 130.7, 131.8 (2C), 132.2, 134.9, 151.3, 158.5, 190.6; **Anal. Calcd. for** $C_{13}H_{11}NO$**:** C, 79.16; H, 5.62; N, 7.10 %. **Found:** C, 78.98; H, 5.54; N, 7.05 %.



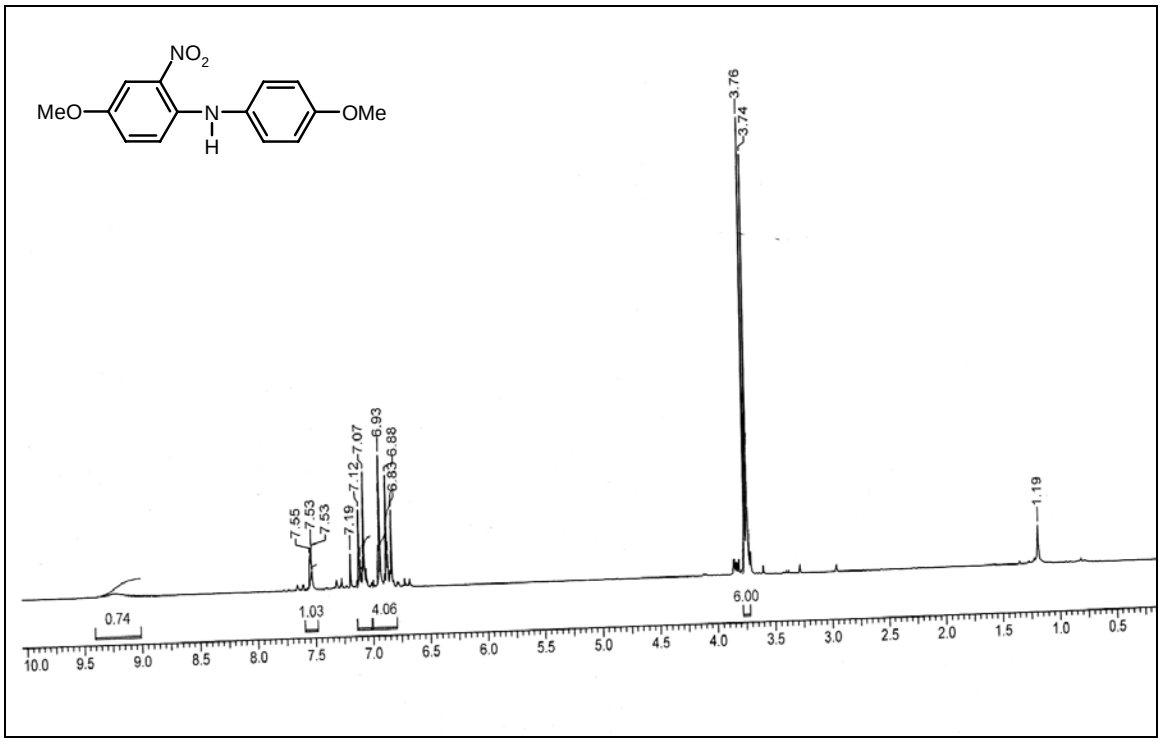
^{1}H NMR spectrum of Compound 59 a ($CDCl_3$+CCl_4, 200 MHz)



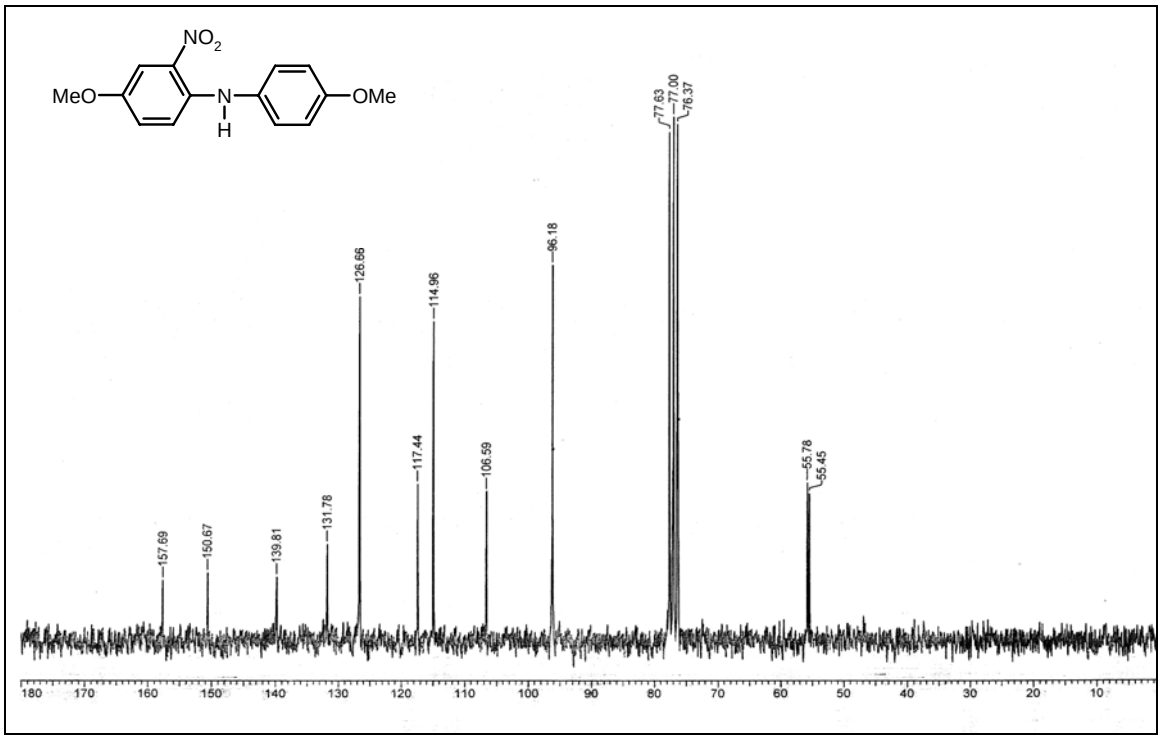
^{13}C NMR Spectrum of Compound 59 a ($CDCl_3$+CCl_4, 50 MHz)



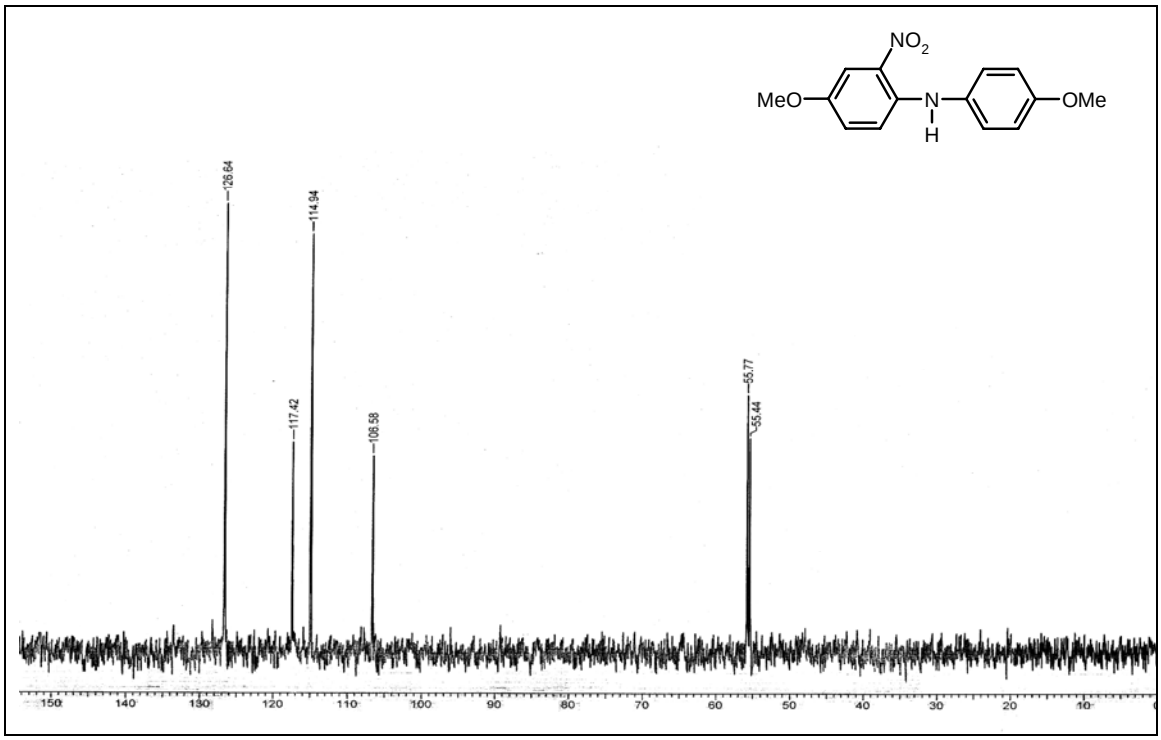
^{1}H NMR spectrum of Compound 59 f ($CDCl_3$+CCl_4, 200 MHz)



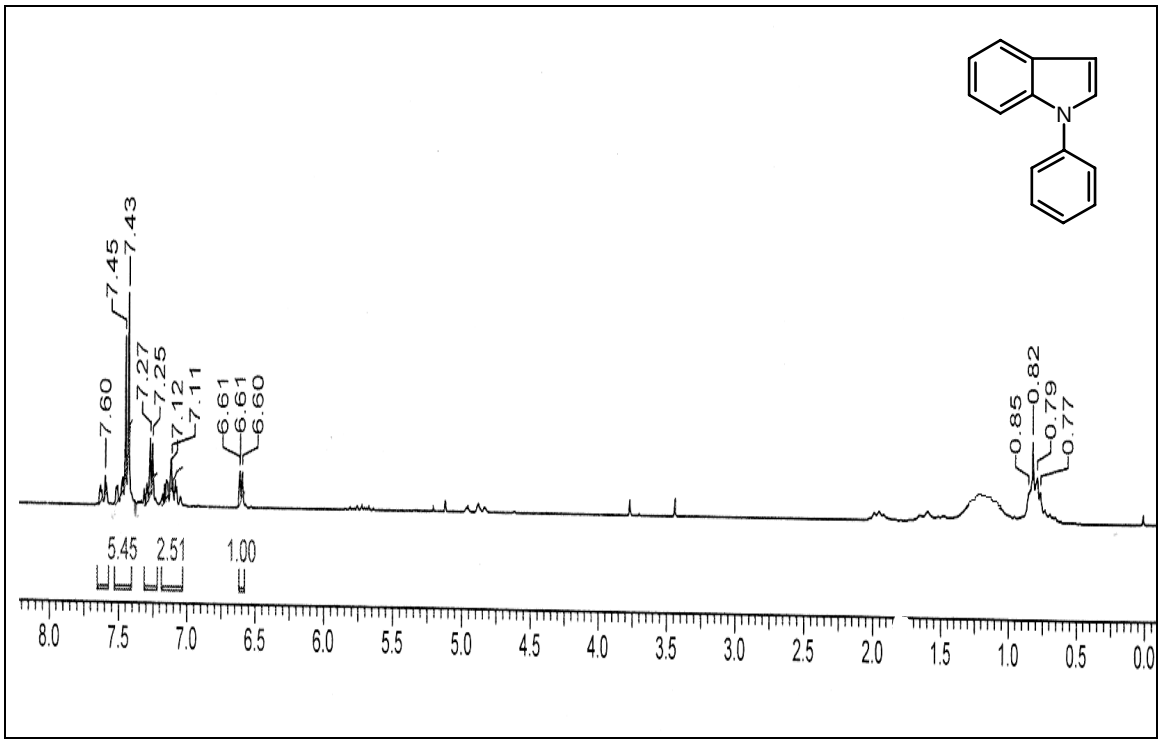
^{13}C NMR Spectrum of Compound 59 f ($CDCl_3$+CCl_4, 50 MHz)



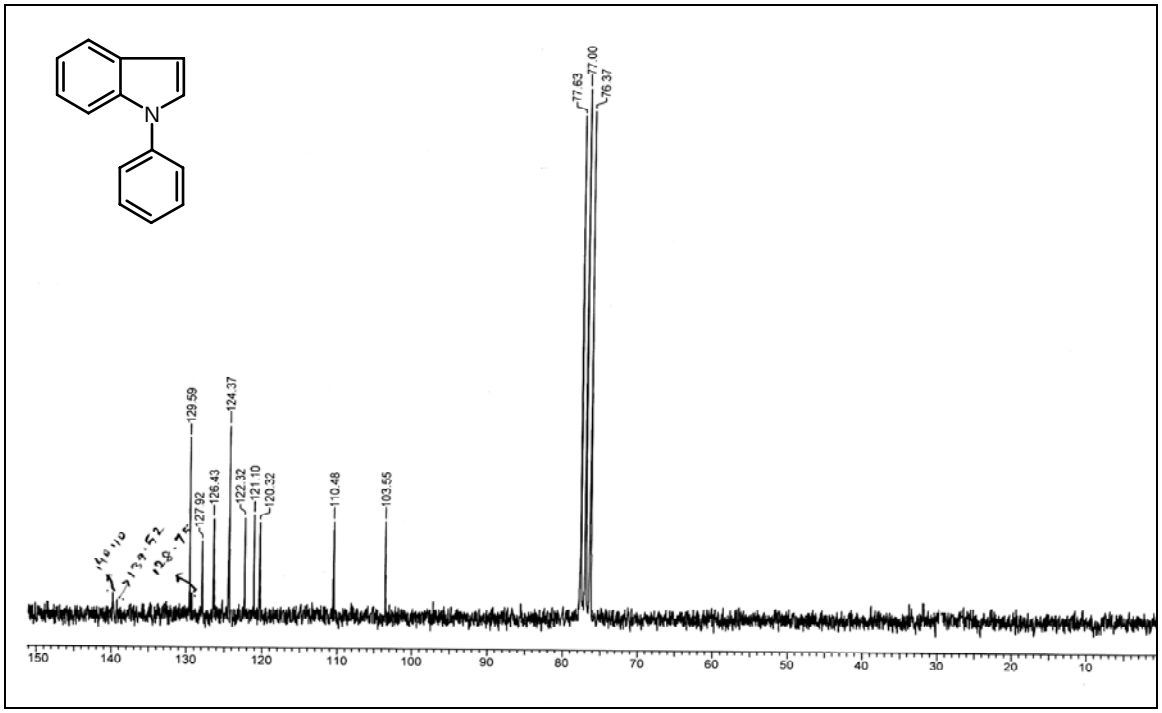
DEPT spectrum of Compound 59 f ($CDCl_3$+CCl_4, 50 MHz)



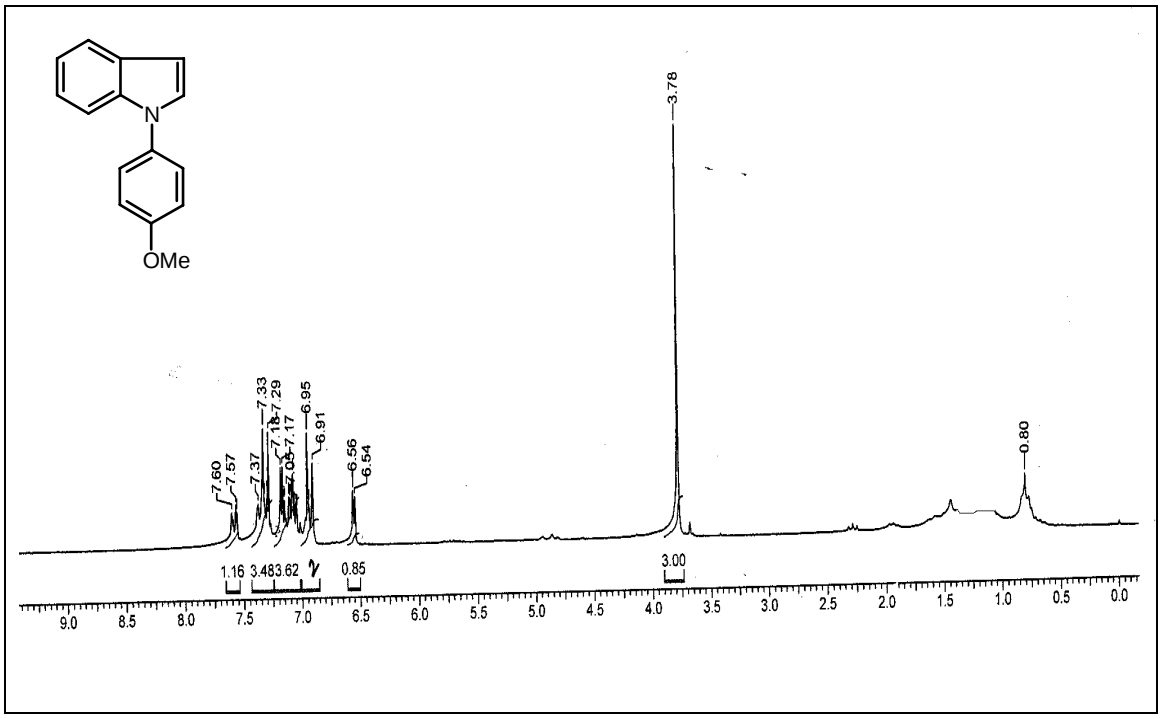
^{1}H NMR spectrum of Compound 59 g ($CDCl_3$+CCl_4, 200 MHz)



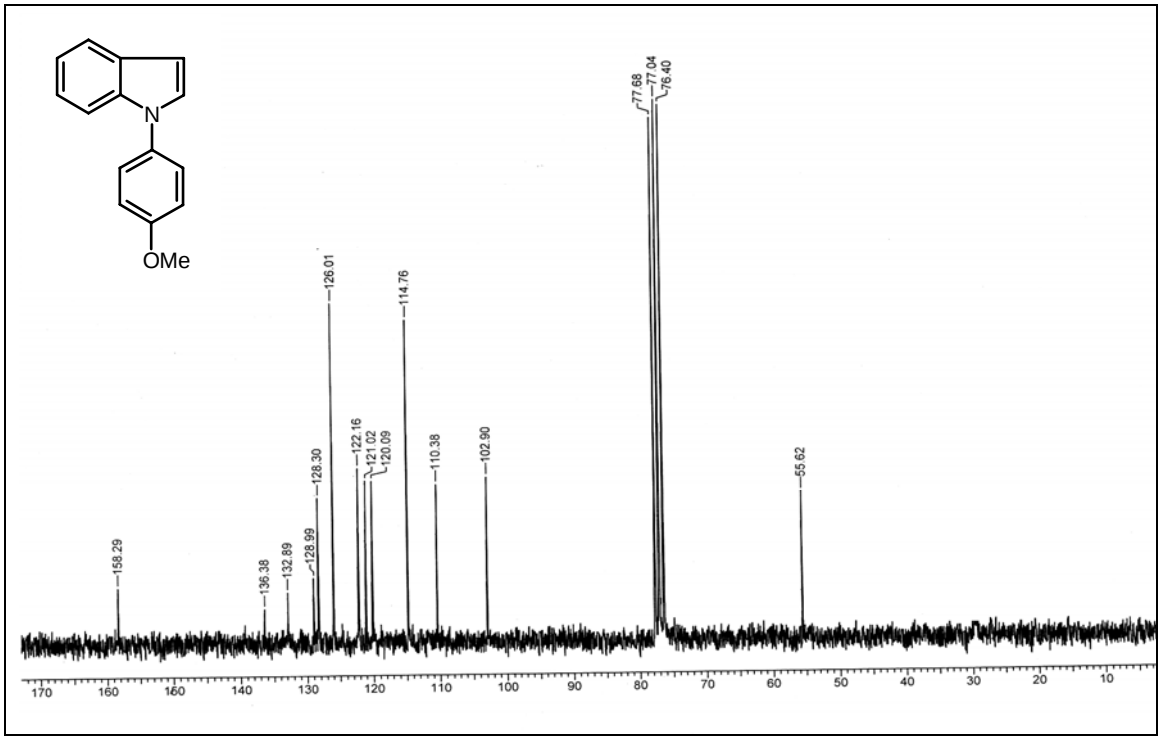
^{13}C NMR Spectrum of Compound 59 g ($CDCl_3$+CCl_4, 50 MHz)



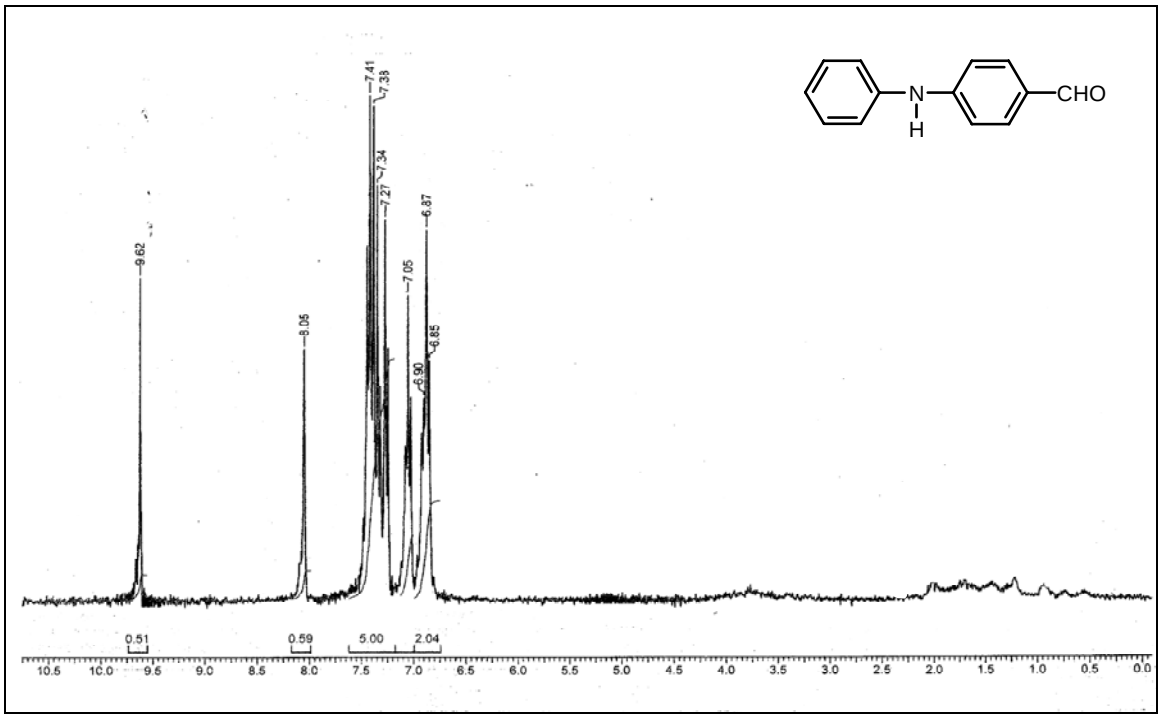
^{1}H NMR spectrum of Compound 59 h ($CDCl_3$+CCl_4, 200 MHz)



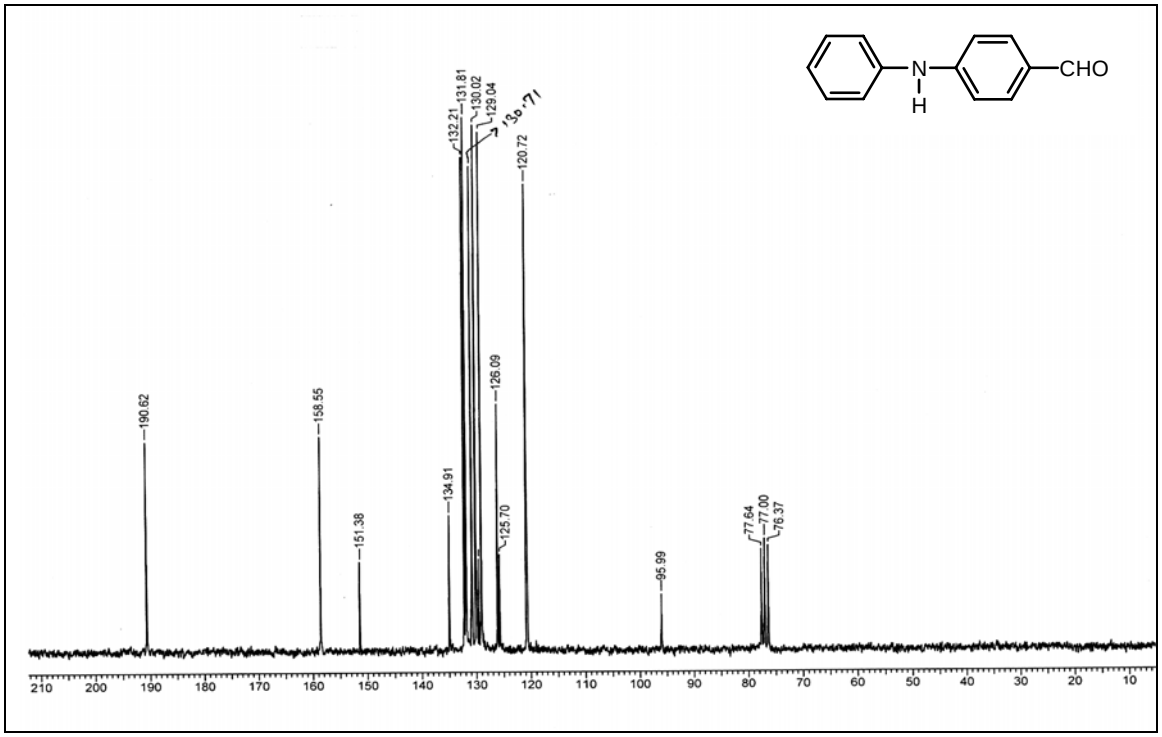
^{13}C NMR Spectrum of Compound 59 h ($CDCl_3$+CCl_4, 50 MHz)



^{1}H NMR spectrum of Compound 59 n ($CDCl_3$+CCl_4, 200 MHz)



^{13}C NMR Spectrum of Compound 59 n ($CDCl_3$+CCl_4, 50 MHz)



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CHAPTER - III

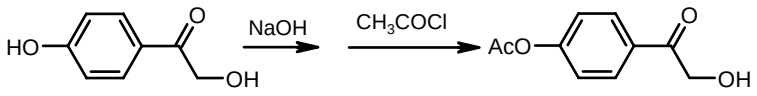
SECTION - II

A SIMPLE METHOD FOR DEPROTECTION OF *tert*-BUTYLDIMETHYLSILYL ETHERS BY USING STANNOUS CHLORIDE UNDER MICROWAVE IRRADIATION

3.2.1: INTRODUCTION:

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been, and are being, developed for this purpose. A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group. The protective group should have a minimum of additional functionality to avoid further sites of reaction.

Since a few protective groups cannot satisfy all these criteria for elaborate substrates, a large number of mutually complementary protective groups are needed and, indeed, are becoming available. In early syntheses the chemist chose a standard derivatives known to be stable to the subsequent reactions. In the synthesis of callistephin chloride the phenolic -OH group in **60** was selectively protected as an acetate as shown in scheme -1. In the presence of silver ion the aliphatic hydroxyl group in **61** displaced the bromide ion in a bromoglucoside. In a final step the acetate group was removed by basic hydrolysis.



60 **61**

Scheme - 1

Development of New Protective Groups:

As chemists proceeded to synthesize more complicated structures, they developed more satisfactory protective groups and more effective methods for the formation and cleavage of protected compounds. At first a tetrahydropyranyl acetal was prepared,[1] by an acid-catalyzed reaction with dihydropyran, to protect a hydroxyl group. The acetal is readily cleaved by mild acid hydrolysis, but formation of this acetal introduces a new stereogenic center. Formation of the 4-methoxytetrahydropyranyl ketal[2] eliminated this problem.

The protection/deprotection protocol of free hydroxyl groups has became commonplace in organic synthesis. When the protection of more than one hydroxyl group is necessary,

the traditional methodology has been to carefully select protecting groups in a manner that allows selective removal at a later stage of the synthetic scheme. Thus different protecting groups can be selectively removed, allowing unlike transformations of various hydroxyl groups in the same molecule. More traditional protection schemes involved, for example, the protection of one alcohol as an ester and another as ether. Due to their ease and recently developed selectivity of attachment, a host of di- and trialkylsilyl groups (Fig. 1) have been commonly used as protection of free hydroxyl groups over the last 20 years.[3-7]

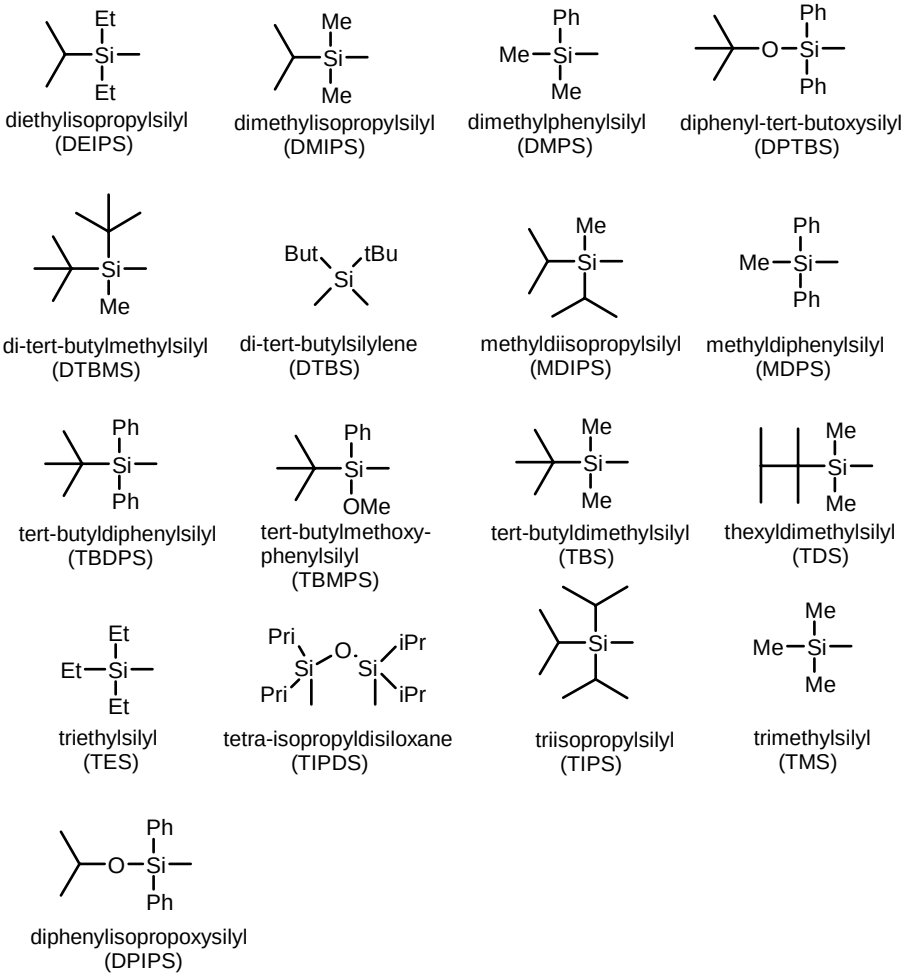


Fig. 1

As the complexity of synthetic targets has grown more demanding, selective discrimination of different silylethers in the same molecule has become increasingly important. Selective differentiation of silyl ethers is illustrated in the recently published

total syntheses of taxol,[8-10] brevetoxin,[11,12] rapamycin,[13] zaragozic acid,[14-16] and avermectins.[17] Considering the importance of deprotection of protecting groups we have developed a simple method for the deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers by using stannous chloride in ecofriendly solvent such as water, also to reduce the time of reaction, we have used the domestic microwave oven system.

Microwave Technology:

High-speed synthesis with microwaves has attracted a considerable amount of attention in recent years.[18] More than 2000 articles have been published in the area of microwave-assisted organic synthesis (MAOS) ever since the first reports on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986.[19,20] The intial slow uptake of the technology in the late 1980s and early 1990s has been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available systems for adequate temperature and pressure controls were major concerns.

Although most of the early pioneering experiments in MAOS were performed in domestic, sometimes modified, kitchen microwave ovens, the current trend is to use dedicated instruments which have only become available in the last few years for chemical synthesis. The number of publications related to MAOS has therefore increased dramatically since the late 1990s to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity. A large number of review articles[21-30] and several books[31-33] provide extensive coverage of the subject.

Microwave irradiation is electromagnetic irradiation in the frequency range of 0.3 to 300 GHz. All domestic "kitchen" microwave ovens and all dedicated microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz (which corresponds to a wavelength of 12.24 cm) to avoid interference with telecommunication and cellular phone frequency region (0.0016 eV) which is too low to break chemical bonds and is also lower than the energy of Brownian chemical reactions.[34-36]

Microwave-enhanced chemistry is based on the efficient heating of material by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material (solvents or reagent) to absorb microwave energy and convert it into heat. The electric component[37] of an electromagnetic field causes heating by two main mechanisms viz, dipolar polarization and ionic conduction. Irradiation of the sample at microwave frequencies results in the dipoles or ions aligning in the applied electric fields. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the applied field. If the dipole does not have enough time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely.[18,19]

The heating characteristics of a particular material (for example, a solvent) under microwave irradiation conditions are dependent on its dielectric properties. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so called loss factor tan δ. This loss factor is expressed as the quotient tan $\delta = \epsilon'' / \epsilon'$, where ϵ'' is the dielectric loss, which is indicative of the efficiency with which electromagnetic radiation is converted into heat, and ϵ' is the dielectric constant describing the ability of molecules to be polarized by the electric field. A reaction medium with a high tan δ value is required for efficient absorption and consequently for rapid heating. The loss factors for some common organic solvents are summarized in Table 1. In general, solvents can be classified as high (tan $\delta > 0.5$), medium (tan δ 0.1-0.5) and low microwave absorbing (tan $\delta < 0.1$).

Table1. Loss factors (tan δ) of different solvents.

Solvent	**Tan δ**	**Solvent**	**Tan δ**
Ethylene glycol	1.350	DMF	0.161
Ethanol	0.941	1,2-dichloromethane	0.127
DMSO	0.825	Water	0.123
2-propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-Butanol	0.571	Acetone	0.054
2-Butanol	0.447	Tetrahydrofuran	0.047
1,2-Dichlorobenzene	0.280	Dichloromethane	0.042
NMP	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

Traditionally, organic synthesis is carried out by conductive heating with an external heat source (for example, an oil bath). This is a comparatively slow and inefficient method for transferring energy into the system, since it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. In contrast, microwave irradiation produces efficient internal heating (in-core volumetric heating) by direct coupling of microwave energy with the molecules that are present in the reaction mixture. Since the reaction vessels employed are typically made out of microwave-transparent materials, such as borosilicate glass, quartz, or teflon, an inverted temperature gradient results compared to conventional thermal heating. The very efficient internal heat transfer results in minimized wall effects (no hot vessel surface) which may lead to the observation of so called specific microwave effects for example, in the context of diminished catalyst deactivation.

Since the early days of microwave synthesis, the observed rate accelerations and sometimes altered product distributions compared to oil-bath experiments have led to speculation on the existence of so-called “specific” or non-thermal” microwave effects.[38-

[40] Historically, such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart carried out at the same apparent temperature. Today most scientists agree that in the majority of cases the reason for the observed rate enhancements is a purely thermal/kinetic effect that is a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field. A high microwave absorbing solvent such as methanol (tan δ = 0.695) can be rapidly superheated to temperatures > 100 ^{0}C above its boiling point when irradiated under microwave conditions in a sealed vessel. The rapid increase in temperature can be even more pronounced for media with extreme loss factors, such as ionic liquids, where temperature jumps of 200 ^{0}C within a few seconds are not uncommon. Naturally, such temperature profiles are very difficult if not impossible to reproduce by standard thermal heating. Therefore, comparisons with conventionally heated processes are inherently troublesome. Dramatic rate enhancements between reactions performed at room temperature or under standard oil-bath conditions (heating under reflux) and high temperature microwave-heated processes have frequently been observed.

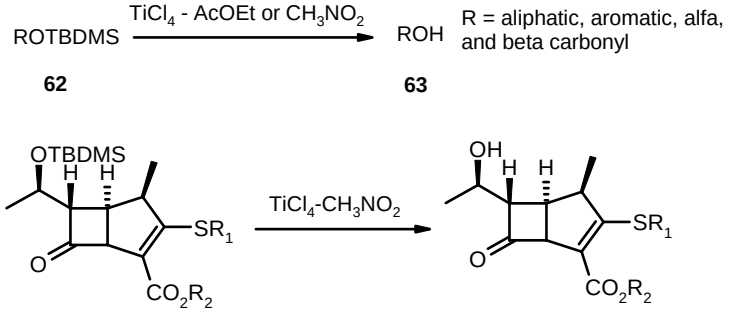
Some authors have suggested the possibility of "non-thermal microwave effects" (also referred to as athermal effects). These should be classified as accelerations that can not be raionalized by either purely thermal/kinetic or specific microwave effects. Nonthermal effects essentially result from a direct interaction of the electric field with specific molecules in the reaction medium. It has been argued that the presence of an electric field leads to orientation effects of dipolar molecules and hence changes the pre-exponential factor A or the activation energy (entropy term) in the Arrhenius equation.[38, 39] A similar effect should be observed for polar reaction mechanisms, where the polarity is increased going from the ground state to the transition state, thus resulting in an enhancement of reactivity are the subject of considerable current debate and controversy,[38-40] and it is evident that extensive research efforts will be necessary to truly understand these and related phenomena.

3.2.2: PRESENT WORK:

The scientific community uses a large number of protecting groups for various functionalities routinely as the protection-deprotection strategies are the inevitable steps in synthetic organic chemistry. *tert*-butyldimethylsilylation of alcohols and phenols is a versatile method because these silyl ethers are stable under a variety of conditions like Wittig reaction, Grignard reaction, reductions with diisobutylaluminium hydride etc. The enormous work in the silylation chemistry has resulted in the development of various methods for silylation and every year newer methods are being added for these transformations. Recently $BiCl_3$-NaI and cesium carbonate have been reported to effect the deprotection of *tert*-butyldimethylsilyl ethers.

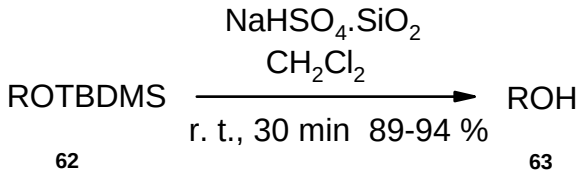
A BRIEF REVIEW OF LITERATURE:

Tanabe Y. *et al.* reported[41] the deprotection of *tert*-butyldimethylsilyl ethers with $TiCl_4$ - Lewis acid complexes in the synthesis of 1-β-methylcarbapenems. They also used the Lewis base (AcOEt or CH_3NO_2) complexes as shown in scheme-1.



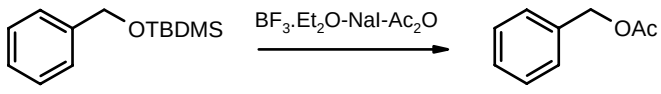
Scheme - 1

Biswanath D. *et al*. reported[42] an efficient selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers using silica supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$) as a heterogeneous catalyst at room temperature to regenerate the parent alcohols in high yields as shown in scheme-2.



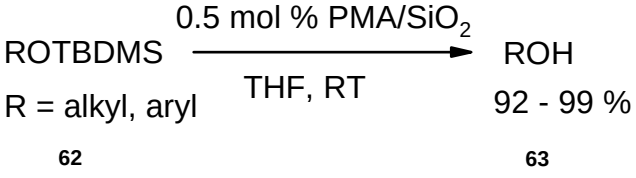
Scheme - 2

Yashwant D. V. *et al.* reported[43] an efficient selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers fallowed by acetylation of several *tert*-butyldimethylsilyl (TBDMS) ethers using the $BF_3.Et_2O$-NaI-Ac_2O reagent system as shown in scheme-3. This method is also useful for the deprotection of isopropylidene and benzylidene groups.



Scheme - 3

Sundarababu B. *et al*. reported[44] the catalytic and environmentally benign method for the selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers by using the phosphomolybdic acid supported on silica gel under very mild conditions as shown in scheme - 4. Various labile functional groups such as isopropylidene acetal, OBz, *N*-Boc, etc. are found to be stable under the reaction conditions.

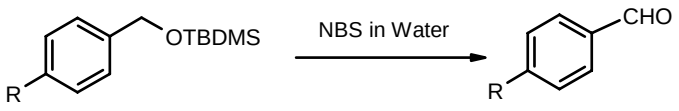


TON + 19400; TOF = 38800

PMA = Phosphomolybdic acid

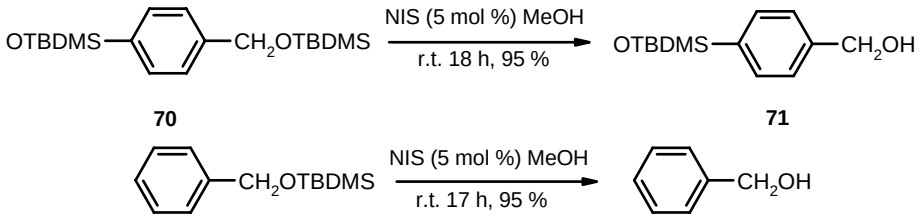
Scheme - 4

Rama Rao K. *et al*. reported[45] a facile β- cyclodextrin – catalyzed oxidative deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers with NBS in water. Treatment of TBDMS ethers with NBS in the presence of β- cyclodextrin in water results, for the first time, in the cleavage of the silicon - oxygen bond, carbonyl compounds are obtained upon oxidation as shown in scheme - 5.



68 **Scheme - 5** **69**

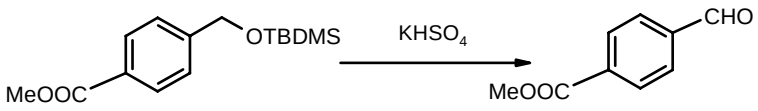
Babak K. *et al*. reported[46] a mild and highly chemoselective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers using *N*-iodosuccinimide (NIS) as a catalyst. A variety of alcoholic TBDMS ethers are easily removed in excellent yields by treatment with a catalytic amount of *N*-iodosuccinimide (NIS, 5 mol %) in methanol. This method is able to deprotect TBDMS ethers of alcohols in the presence of TBDMS ethers of phenols as shown in scheme - 6.



70 **71**

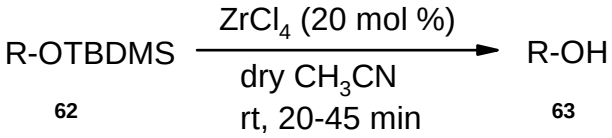
72 **Scheme - 6** **73**

Perumal P. T. *et al.* reported[47] a mild, efficient, and inexpensive protocol for the selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers by using $KHSO_4$ as shown in scheme - 7. Potassium hydrogensulfate in 30 % aqeous methanol deprotects a variety of *tert*-butyldimethylsilyl (TBDMS) ethers at room temperature in excellent yields.



74 **Scheme - 7** **75**

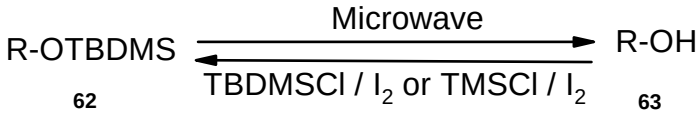
Sharma G. V. M. *et al*. reported[48] a simple and efficient protocol for the selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers using 20 % $ZrCl_4$ in 20 - 45 min and in high yields as shown in scheme - 8, wherein it is demonstrated that acid and base sensitive groups and allylic and benzylic groups are unaffected.



62 **63**

Scheme - 8

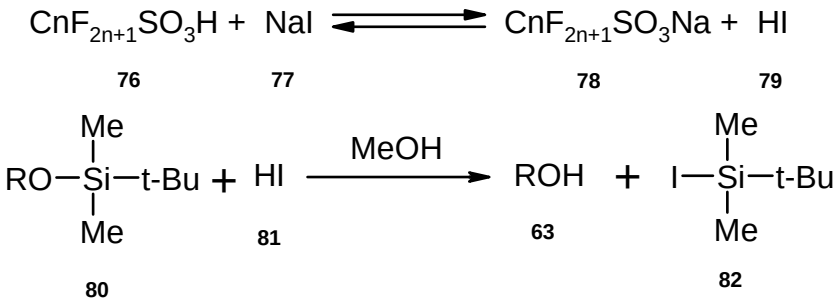
Sharma J. S. and Tsuboi S. reported[49] a convenient method for protection and deprotection of alcohols and phenols as alkylsilyl ethers catalyzed by iodine under microwave irradiation. Irradiation of alcohols or phenols with *tert*-butyldimethylsilyl chloride (TBDMSCl) or trimethylsilyl chloride (TMSCl) in presence of catalytic amount (20 mol %) of iodine in a microwave oven for 2 min gives the corresponding silyl ethers in excellent yield. Iodine in methanol deprotects the silyl ethers into its parent alcohol as shown in scheme - 9.



62 **63**

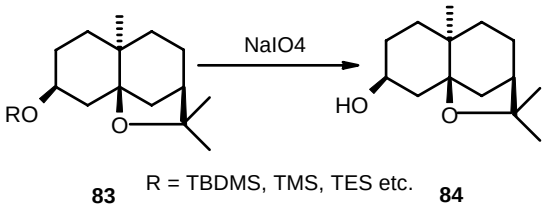
Scheme - 9

Yashwant D. V. *et al*. reported[50] a deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers by using a catalytic amounts of bromodimethyl sulfonium bromide, or Nafion – H along with NaI (1 equiv.) in methanol, which results in the expected alcohols respectively as shown in scheme - 10. Alkyl TBDMS ethers react more readily and selectively compared to phenolic TBDMS ethers, benzyl and methyl ethers.



Scheme - 10

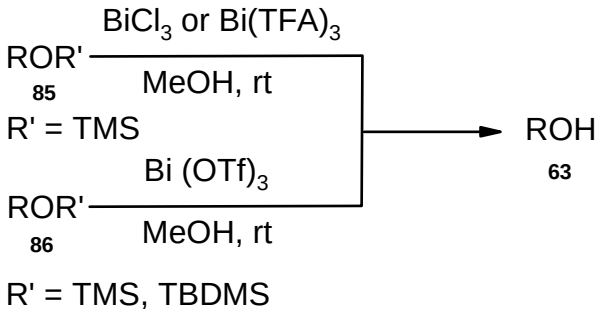
Chun L. D. *et al.* reported[51] a mild and efficient method for the deprotection of silyl ethers. The most often used silyl protecting groups such as TBDMS, TIPS, TMS, TIBS, TPS can be cleaved by $NaIO_4$ furnishing the corresponding alcohol in high yields as shown in scheme - 11. This method can be used for a wide range of substrates.



Scheme - 11

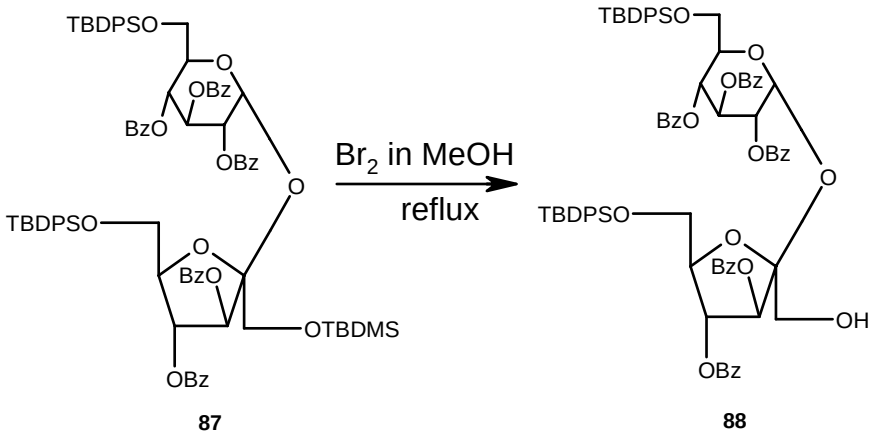
Mohammadpoor B. *et al*. reported[52] rapid, selective and efficient method for the deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers catalyzed by bismuth (III) salts. A variety of trimethylsilyl (TMS) ethers of alcohols and phenols are easily and rapidly removed in the presence of catalytic amount of bismuth (III) salts, including $BiCl_3$, $Bi(TFA)_3$, and $Bi(OTf)_3$ in methanol at room temperature in excellent yields. *tert*-Butyldimethylsilyl (TBDMS) ethers are intert towards $BiCl_3$ and $Bi(TFA)_3$, but in the

presence of $Bi(OTf)_3$, the corresponding alcohols are obtained in excellent yields as shown in scheme - 12.



Scheme -12

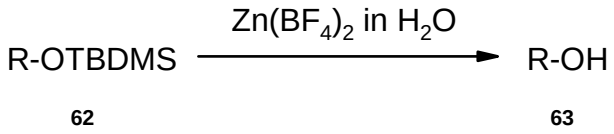
Christine T. *et al.* reported[53] a selective reagent for the deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers in the presence of other protecting groups, using bromine in methanol under reflux as shown in scheme - 13.



Scheme - 13

Brindaban C. R. *et al*. reported[54] a simple and efficient method for selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers by zinc tetrafluoroborate in water as shown in scheme - 14. A wide range of structurally varied TBDMS ethers was subjected to deprotection by this procedure. This procedure is found to be general being effective for

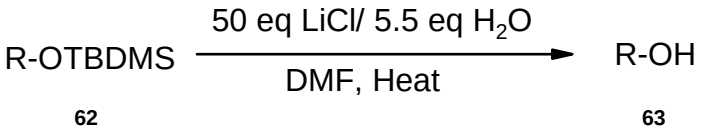
the cleavage of TBDMS ethers of primary, secondary, tertiary, allylic, propargylic and homoallylic alcohols.



62 **63**

Scheme - 14

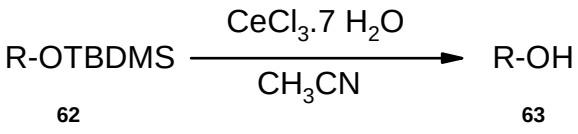
Farras J. *et al*. reported[55] a general method for the selective cleavage of *tert*-butyldimethylsilyl (TBDMS) ethers in the presence of *tert* - butyldiphenylsilyl ones using a combination of water and a concentrated solution of LiCl in DMF at 90 ^{0}C as shown in scheme - 15. Since no acids, bases, reducing or oxidizing agents are used, the method seems to be very appropriate for the deprotection of TBDMS ethers in the presence of other sensitive functional groups.



62 **63**

Scheme - 15

Bartoli, G. *et al.* reported[56] cerium (III) chloride as a mild Lewis acid, and efficient catalyst for the deprotection of alcohol protecting groups such as *tert* - butyldiphenylsilyl as shown in scheme - 16.

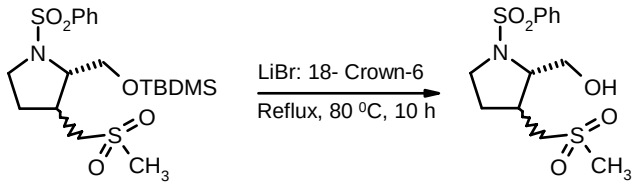


62 **63**

Scheme - 16

Tadhg P. B. *et al*. reported[57] the selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers, using lithium bromide in the presence of crown ether under controlled

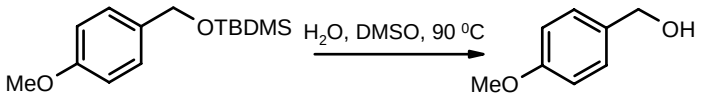
conditions as shown in scheme - 17. This selectivity has been utilized in the synthesis of deoxyuridine.



89 **90**

Scheme - 17

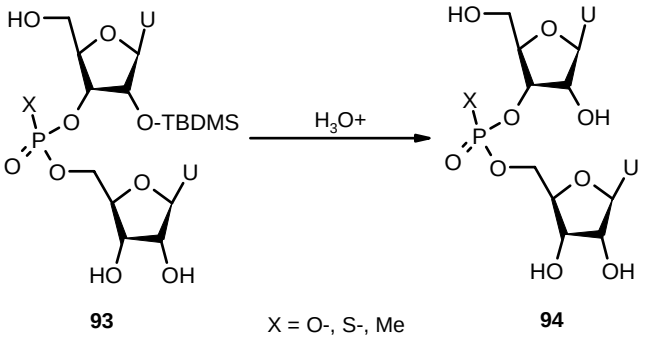
Roy C. R. *et al*. reported[58] a mild and efficient method for the selective deprotection of allylic and homoallylic, primary benzylic and aryl *tert*-butyldimethylsilyl (TBDMS) ethers by using a combination of H_2O and DMSO at 90 ^{0}C as shown in scheme - 18. All other primary and secondary TBDMS ethers remained unaffected under the reaction conditions. The method is very effective in deprotection of TBDMS ethers in the presence of other sensitive functional groups.



91 **92**

Scheme - 18

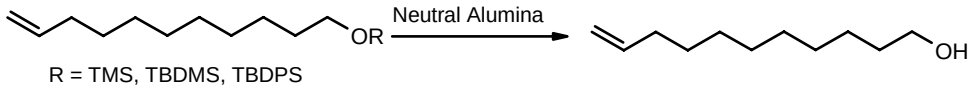
Mitsuo S. *et al.* reported[59] a mild acid-catalyzed desilylation of the 2'-O- *tert*-butyldimethylsilyl (TBDMS) group from chemically synthesized oligoribonucleotide intermediates via neighboring group participation of the internucleotidic phosphate residue as shown in scheme - 19. Hydrolytic removal of the 2'- *tert*-butyldimethylsilyl (TBDMS) group from a 2'-O- TBDMS protected UpU dimer [U (2'-Si)pU] (Si = TBDMS) and related derivatives under various acidic conditions was studied.



93 X = O-, S-, Me **94**

Scheme - 19

Angel G. *et al*. reported[60] the selective cleavage of primary and secondary *tert*-butyldimethylsilyl (TBDMS) ethers with neutral alumina under very mild conditions. The method involves utilization of the support, previously activated by heating at 80 ^{0}C/0.1 torr for 16 h and later deactivated with variable amounts of water (1.5 – 4.5 %), in 50:1 ratio with regard to the substrate and in the presence of non-polar solvents like hexane. This method was also useful for the deprotection of TMS, TIPS, TBDPS groups also.



95 **Scheme - 20** **96**

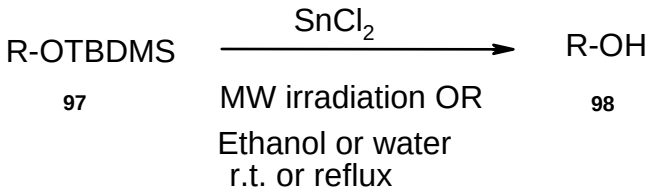
PRESENT WORK:

Stannous chloride is an easily available, stable and cheap reagent widely used in the food industry as a preservative, colour retention agent and a component in food packaging materials[61] as well as it is used for various organic conversions including reduction, dehalogenation, protection-deprotection of various functional groups etc[62]. A. D. Cort reported deprotection of *tert*-butyldimethylsilyl ether of cyclohexanol and 1-decanol with $SnCl_2$ in acetonitrile but its potential has not been exploited fully as there is no other report about deprotection of other substrates or use of other solvents. We considered that environmentally benign method for deprotection of *tert*-butyldimethylsilyl ethers could be developed using stannous chloride. In the present work deprotection of a number of

tert-butyldimethylsilyl ethers in presence of stannous chloride under microwave irradiation and solvent free conditions as well as in ecofriendly solvents such as ethanol and water has been described.

3.2.3: RESULTS AND DISCUSSION:

Various alcoholic and phenolic *tert*-butyldimethylsilyl ethers were initially treated with an equimolar quantity of $SnCl_2$ in ethanol at rt. It was observed that they were converted to the corresponding alcohols and phenols in good yields in 5 to 7 h (Table 2). When the reactions were carried out at 80 ^{0}C, the duration of the reaction was reduced to 35 - 40 min to afford the products in comparable yields as shown in scheme - 21. Similarly, replacing ethanol by water as solvent in the above experiments under reflux conditions afforded the desilylated products. Table 2 exhibits efficiency of the method under aqueous conditions leading to good yields. Further utility of $SnCl_2$ for this transformation under solvent free conditions was also explored using microwave irradiation technique wherein comparable results were achieved in much shorter time i.e. 5 to 7 min. Thus, *tert*-butyldimethylsilyl ethers of various alcohols, phenols and naphthols bearing different substituents were deprotected using $SnCl_2$ under microwave conditions. It was observed that the yields were consistent (80-90 %) under all different conditions described above. It is noteworthy that acetate of benzylic alcohol (Table 2, entry no **97** k) got cleaved whereas acetanilide (Table 2, entry no. **97** m) was stable under these reaction conditions. All the products obtained were confirmed by comparing the spectral data with those reported in literature.



Scheme 21

Table-2: Deprotection of *tert*-butyldimethylsilyl ethers with $SnCl_2$ under different conditions

Entry No.	TBDMS ether of (**97**)	*Ethanol at RT*		*Ethanol at reflux*		*Water at reflux*		*MW irrad.*	
		time (hr)	yield (%)[a]	time (min)	yield (%)[a]	time (hr)	yield (%)[a]	time (min)	yield (%)[a]
A	Cyclohexanol	6	89	40	85	4	83	5	85
B	Phenol	5	90	35	88	3	82	5	87
C	Guaiacol	5	85	35	83	3	85	5	89
D	4-Methoxyphenol	5	82	35	85	3	80	5	82
E	Benzyl alcohol	6	80	45	87	4	82	6	85
F	3-Methylphenol	5	87	35	90	3	85	5	90
G	Isovanillin	5	85	35	85	3	80	5	83
H	Vanillin	5	89	35	90	3	87	5	90
I	3-Hydroxy-4-methoxy-benzylalcohol(3-OH protected)	5	86	35	87	3	85	5	83
J	3-Hydroxy-4-methoxy benzylalcohol(di-TBDMS)	7	90	40	90	4	87	6	89
K	3-Hydroxy-4-methoxy-benzyl acetate	5	92	35	90[b]	3	90	5	91[b]
L	2-Aminophenol	5	88	35	85	3	83	5	85
M	2-OH-acetanilide	5	85	35	85[c]	3	85	5	87[c]
N	2-OH-acetophenone	5	83	35	80	3	82	5	86
O	4-Br-2-Cl-phenol	5	87	35	83	3	83	5	85
P	1-Naphthol	ND	ND	ND	ND	5	82	7	85
Q	2-Naphthol	ND	ND	ND	ND	5	85	7	83
R	2-Methoxy-1-naphthylmethanol	ND	ND	ND	ND	6	87	5	82
S	4-Methoxy-1-naphthylmethanol	ND	ND	ND	ND	6	85	5	83
T	Furfuryl alcohol	ND	ND	ND	ND	5	85	5	85

a = Isolated yields; b = Acetate group got cleaved; c = Acetate remained intact; ND = Not Done

3.2.4: CONCLUSION:

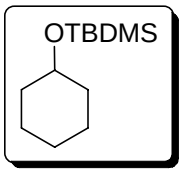
In conclusion, we have demonstrated the utility of $SnCl_2$ for deprotection of *tert*-butyldimethylsilyl ethers under various conditions. The reactions can be performed in ethanol or water. It is also noteworthy that the same efficiency is observed under solvent free conditions using microwave irradiation in much shorter time (~ 5 min).

3.2.5: EXPERIMENTAL:

General procedure for protection of alcoholic OH group as tert-butyldimethylsilyl ethers:

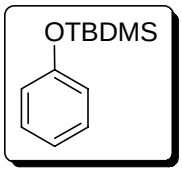
A solution of cyclohexanol (1 gm, 10.0 mmol) in dry dichloromethane (10 ml) was stirred at 0 ^{0}C under inert atmosphere (maintained by using nitrogen or argon gas filled in balloon), a solution of *tert*-butyldimethylsilylchloride (1.806 gm, 12.0 mmol) and dimethylaminopyridine (0.050 gm, 4.09 mmol) in dichloromethane (5 ml) was added dropwise and stirred at same temperature for 15 min. Then triethylamine (1.515 gm, 15.0 mmol) was added and mixture was warmed to room temperature and stirred further for 3 h (monitored by TLC). The reaction mixture was filtered through Whatman filter paper, dichloromethane removed under reduced pressure and extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether - acetone as eluent) to give the *tert*-butyl-cyclohexyloxy-dimethyl-silane in good yields.

Tert-butyl-cyclohexyloxy-dimethyl-silane (97 a):



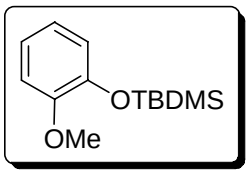
Molecular Formula: $C_{12}H_{26}OSi$; **Nature:** Colourless liquid; **Yield:** 86 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.05 (s, 6H), 0.90 (s, 9H), 1.15 - 1.40 (m, 6H), 1.65 - 1.85 (m, 5H).

Tert-butyl-dimethyl-phenoxy-silane (97 b):



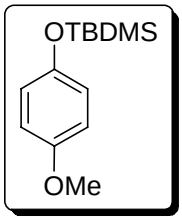
Molecular Formula: $C_{12}H_{20}OSi$; **Nature:** Colourless thick liquid; **Yield:** 91 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.08 (s, 6H), 1.0 (s, 9H), 6.73 (d, J = 8 Hz, 2H), 6.82 (t, J = 8 Hz, 1H), 7.05 - 7.13 (m, 2H).

Tert-butyl-(2-methoxy-phenoxy)-dimethyl-silane (97 c):



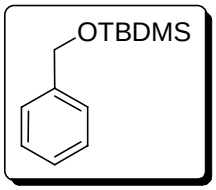
Molecular Formula: $C_{13}H_{22}O_2Si$; **Nature:** Colourless liquid; **Yield:** 90 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.17 (s, 6H), 1.02 (s, 9H), 3.82 (s, 3H), 6.80 - 6.90 (m, 4H).

Tert-butyl-(4-methoxy phenoxy)-dimethyl-silane (97 d):



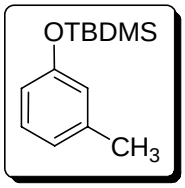
Molecular Formula: $C_{13}H_{22}O_2Si$; **Nature:** Colourless liquid; **Yield:** 89 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.17 (s, 6H), 0.98 (s, 9H), 3.76 (s, 3H), 6.70 - 6.82 (m, 4H).

Benzyloxy-tert-butyl-dimethyl-silane (97 e):



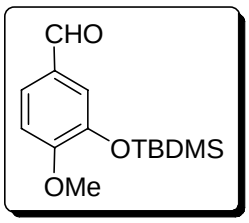
Molecular Formula: $C_{13}H_{22}OSi$; **Nature:** Thick liquid; **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.15 (s, 6H), 1.00 (s, 9H), 4.79 (s, 2H), 7.10 - 7.38 (m, 5H).

Tert-butyl-dimethyl-m-tolyloxy-silane (97 f):



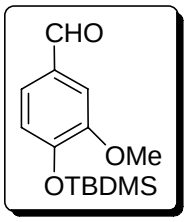
Molecular Formula: $C_{13}H_{22}OSi$; **Nature:** Thick liquid; **Yield:** 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.25 (s, 6H), 1.04 (s, 9H), 2.35 (s, 3H), 6.70 - 7.10 (m, 4H).

3-(tert-butyl-dimethyl-silanyloxy)4-methoxy-benzaldehyde (97 g):



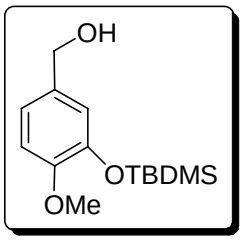
Molecular Formula: $C_{14}H_{22}O_3Si$; **Nature:** Thick white semisolid; **Yield:** 93 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.08 (s, 6H), 0.92 (s, 9H), 3.80 (s, 3H), 6.86 (d, J = 8 Hz, 1H), 7.26 (s, 1H), 7.40 (d, J = 8 Hz, 1H), 9.72 (s, 1H).

4-(tert-butyl-dimethyl-silanyloxy)-3-methoxy-benzaldehyde (97 h):



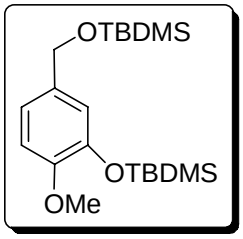
Molecular Formula: $C_{14}H_{22}O_3Si$; **Nature:** White thick semisolid; **Yield:** 92 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.08 (s, 6H), 0.90 (s, 9H), 3.95 (s, 3H), 7.02 (d, J = 8 Hz, 1H), 7.30 - 7.39 (m, 2H), 9.79 (s, 1H).

[3-(tert-butyl-dimethyl-silanyloxy)-4-methoxy-phenyl-methanol (97 i):



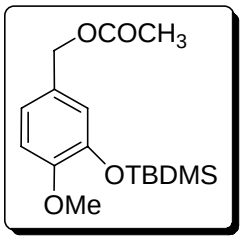
Molecular Formula: $C_{14}H_{24}O_3Si$; **Nature:** White thick semisolid; **Yield:** 84 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.16 (s, 6H), 1.01 (s, 9H), 1.75 (bs, 1H), 3.81 (s, 3H), 4.55 (s, 2H), 6.75 – 6.95 (m, 3H).

Di-tert-butyl ethers of 3-hydroxy-4-methoxy benzaldehyde (97 j):



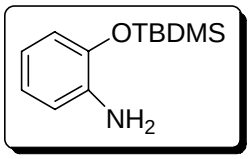
Molecular Formula: $C_{20}H_{36}O_3Si_2$; **Nature:** White thick semisolid; **Yield:** 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.07 (s, 6H), 0.09 (s, 6H), 0.92 (s, 9H), 0.93(s, 9H), 3.79 (s, 3H), 4.62 (s, 2H), 6.75 - 6.90 (m, 3H).

Acetic acid 3-(tert-butyl-dimethyl-silanyloxy)-4-methoxy benzyl ester (97 k):



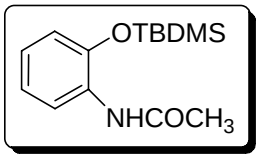
Molecular Formula: $C_{16}H_{26}O_4Si$; **Nature: W**hite thick semisolid; **Yield:** 90 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.16 (s, 6H), 1.01 (s, 9H), 2.08 (s, 3H), 3.81 (s, 3H), 4.98 (s, 2H), 6.80 - 6.95 (m, 3H).

2-(tert-butyl-dimethyl-silanyloxy)-phenylamine (97 l):



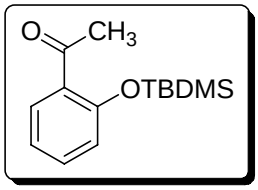
Molecular Formula: $C_{12}H_{21}NOSi$; **Nature:** Red thick semisolid; **Yield:** 88 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.25 (s, 6H), 1.03 (s, 9H), 3.49 (bs, 2H), 6.37 - 6.61 (m, 4H);

N-[2-(tert-butyl-dimethyl-silanyloxy)-phenyl]-acetamide (97 m):



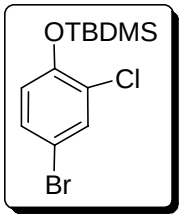
Molecular Formula: $C_{14}H_{23}NO_2Si$; **Nature:** Red thick semisolid; **Yield:** 92 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.27 (s, 6H), 1.05 (s, 9H), 2.18 (s, 3H), 6.77 - 6.98 (m, 4H), 7.69 (bs, 1H).

1-[2-(tert-butyl-dimethyl-silanyloxy)-phenyl]-ethanone (97 n):



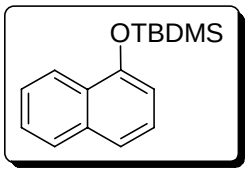
Molecular Formula: $C_{14}H_{22}O_2Si$; **Nature:** Colourless liquid; **Yield:** 91 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.25 (s, 6H), 0.99 (s, 9H), 2.58 (s, 3H), 6.80-6.95 (m, 2H), 7.30 (t, J = 10 Hz, 1H), 7.58 (d, J = 10 Hz, 1H).

(4-bromo-2-chloro-phenoxy)-tert-butyl-dimethyl-silane (97 o):



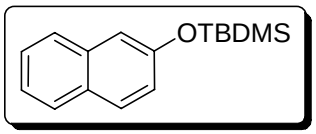
Molecular Formula: $C_{12}H_{18}BrClOSi$; **Nature:** white solid; **Yield:** 89 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.22 (s, 6H), 1.02 (s, 9H), 6.75 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 7.49 (s, 1H).

1-Naphthol (97 p):



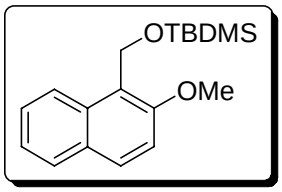
Molecular Formula: $C_{17}H_{22}OSi$; **Nature:** Red solid; **Yield:** 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.34 (s, 6H), 1.16 (s, 9H), 6.91 (d, J = 8 Hz, 1H), 7.25 – 7.55 (m, 4H), 7.78 – 7.86 (m, 1H), 8.20 - 8.28 (m, 1H);

2-Naphthol (97 q):



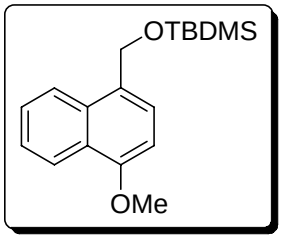
Molecular Formula: $C_{16}H_{22}OSi$; **Nature:** Red solid; **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.28 (s, 6H), 1.06 (s, 9H), 7.10 (d, J = 8 Hz, 1H), 7.19 - 7.46 (m, 3H), 7.65 - 7.80 (m, 3H).

((2-Methoxynaphthalen-1-yl)methoxy)(tert-butyl)dimethylsilane (97 r):



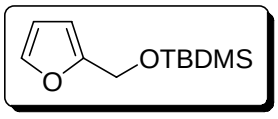
Molecular Formula: $C_{18}H_{26}O_2Si$; **Nature:** red coloured thick liquid; **Yield:** 81 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.09 (s, 6H), 0.92 (s, 9H), 3.98 (s, 3H), 5.23 (s, 2H), 7.20 - 7.54 (m, 3H), 7.70 - 7.85 (m, 2H), 8.22 (d, J = 8 Hz, 1H).

((1-Methoxynaphthalen-4-yl)methoxy)(tert-butyl)dimethylsilane (97 s):



Molecular Formula: $C_{18}H_{26}O_2Si$; **Nature:** Red coloured semisolid; **Yield:** 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.13 (s, 6H), 0.97 (s, 9H), 4.02 (s, 3H), 5.13 (s, 2H), 6.78 (d, J = 8 Hz, 1H), 7.20 - 7.35 (m, 3H), 8.04 (d, J = 8 Hz, 1H), 8.36 (d, J = 8 Hz, 1H).

tert-Butyl-(furan-2-ylmethoxy)-dimethyl-silane (97 t):



Molecular Formula: $C_{11}H_{20}O_2Si$; **Nature:** Colourless semisolid; **Yield:** 94 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 0.09 (s, 6H), 0.92 (s, 9H), 4.65 (s, 2H), 6.21 - 6.35 (m, 2H), 7.38 (d, J = 4 Hz, 1H).

General procedures for deprotection of tert-butyldimethylsilyl ethers:

A) Using ethanol as a solvent

$SnCl_2.2\ H_2O$ (1 mmole) was added to a solution of *tert*-butyldimethylsilyl ether (1 mmole) in ethanol (20 ml) and the reaction mixture was stirred at room temperature or

under reflux till it was found to be complete (monitored by TLC). The solvent was then removed under vacuum, the residue was diluted with water to dissolve the tin salts and the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was purified by column chromatography over silica gel to afford pure products in 80 to 90 % yields.

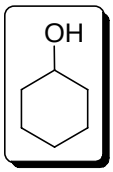
B) Using water as a solvent

A procedure as in A) above was followed under reflux using water as a solvent. After completion of reaction, the reaction mixture was diluted with water (10 ml) and worked up as in A) to isolate pure products in 80 to 90 % yields.

C) Under microwave irradiation:

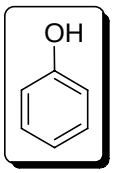
The reaction was conducted without solvent in a microwave oven. After completion of reaction, the residue was taken up in ethyl acetate (20 ml/mmol of starting *tert*-butyldimethylsilyl ether) and filtered to remove tin salts. The filtrate was concentrated and the product was purified by column chromatography to collect the pure products in 82 to 91 % yields.

Cyclohexanol (98 a):



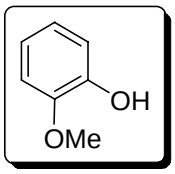
Molecular Formula: $C_6H_{12}O$; **Nature:** Colourless liquid; **Yield:** 89 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.20 - 1.50 (m, 6H), 1.70 - 1.80 (m, 4H), 3.45 (bs, 1H);

Phenol (98 b):



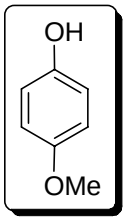
Molecular Formula: C_6H_6O; **Nature:** Colourless thick liquid; **Yield:** 90 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.5 (bs, 1H), 6.70 (d, J = 8 Hz, 2H), 6.85 (t, J = 8 Hz, 1H), 7.10 - 7.15 (m, 2H).

Guaiacol (98 c):



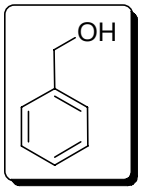
Molecular Formula: $C_7H_8O_2$; **Nature:** Colourless liquid; **Yield:** 85 %; **IR** (chloroform)**:** ν_{max} 3410, 3021, 2965, 1600, 1539, 1460, 1400, cm^{-1} **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 4.19 (s, 3H), 6.27 (bs, 1H), 7.20 - 7.45 (m, 4H).

4-methoxy phenol (98 d):



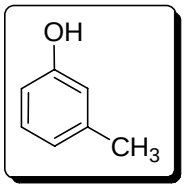
Molecular Formula: $C_7H_8O_2$; **Nature:** White solid; **M. p.** 56 ^{0}C; **Yield:** 82 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.78 (s, 3H), 4.70 (bs, 1H), 6.60 - 6.90 (m, 4H).

Benzyl alcohol (98 e):



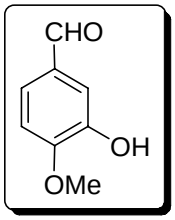
Molecular Formula: C_7H_8O; **Nature:** Colourless liquid; **Yield:** 80 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.15 (bs, 1H), 4.79 (s, 2H), 7.10-7.50 (m, 5H).

3-methyl phenol (98 f):



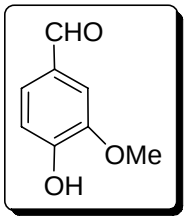
Molecular Formula: C_7H_8O; **Nature:** Red colured liquid; **Yield:** 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.43 (s, 3H), 4.75 (bs, 1H), 6.75 - 7.24 (m, 4H).

Isovanillin (98 g):



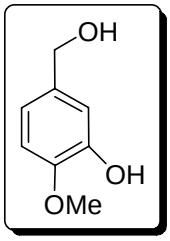
Molecular Formula: $C_8H_8O_3$; **Nature:** White solid; **M. p.** ^{0}C; **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.96 (s, 3H), 5.89 (s, 1H), 6.94 (d, J = 8 Hz, 1H), 7.36 - 7.43 (m, 2H), 9.81 (s, 1H).

Vanillin (98 h):



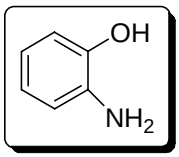
Molecular Formula: $C_8H_8O_3$; **Nature:** white solid; **M. p.** 82 ^{0}C; **Yield:** 89 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.95 (s, 3H), 6.32 (s, 1H), 7.02 (d, J = 8 Hz, 1H), 7.37 - 7.45 (m, 2H), 9.80 (s, 1H).

3-hydroxy-4-methoxy benzylacohol (98 i, j, k):



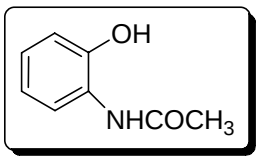
Molecular Formula: $C_8H_{10}O_3$; **Nature:** Colourless liquid; **Yield:** 92 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.86 (s, 3H), 4.55 (s, 2H), 5.60 (bs, 1H), 6.50 - 6.90. (m, 3H);

2-amino phenol (98 l):



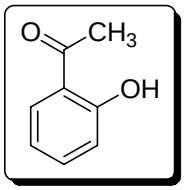
Molecular Formula: C_6H_7NO; **Nature:** Brick red solid; **M. p.** ^{0}C; **Yield:** 88 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.49 (bs, 3H), 6.37 - 6.61 (m, 4H);

N-(2-hydroxy-phenyl)-acetamide (98 m):



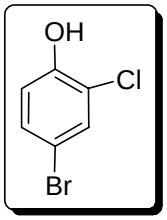
Molecular Formula: $C_8H_9NO_2$; **Nature:** Brick red semisolid; **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 1.85 (s, 3H), 2.78 (bs, 1H), 6.38 - 6.68 (m, 3H), 7.19 (d, J = 8 Hz, 1H), 9.19 (bs, 1H);

2-hydroxy acetophenone (98 n):



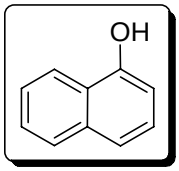
Molecular Formula: $C_8H_8O_2$; **Nature:** Milky white solid; **M. p.** 88 ^{0}C; **Yield:** 83 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.61 (s, 3H), 6.86 - 7.00 (m, 2H), 7.45 (t, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 1H), 12.24 (bs, 1H).

4-bromo-2-chloro-phenol (98 o):



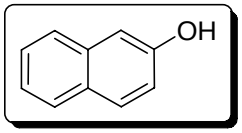
Molecular Formula: C_6H_4BrClO; **Nature:** White solid; **M. p.** 50 ^{0}C; **Yield:** 87 %; **^{1}H NMR:** (200 MHz, $CDCl_3$+CCl_4)**:** δ 5.52 (s, 1H), 6.92 (d, J = 10 Hz, 1H), 7.29 (d, J = 8 Hz, 1H), 7.47 (s, 1H).

1-naphthol (98 p):



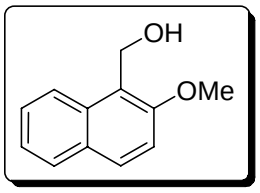
Molecular Formula: $C_{10}H_8O$; **Nature:** Dark red solid; **M. p.** 95 ^{0}C; **Yield:** 82 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 5.28 (bs, 1H), 6.81 (d, J = 6 Hz, 1H), 7.20 – 7.53 (m, 4H), 7.75 - 7.90 (m, 1H), 8.15 - 8.24 (m, 1H);

2-naphthol (98 q):



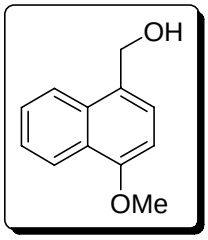
Molecular Formula: $C_{10}H_8O$; **Nature:** Dark red solid; **M. p.** 121 ^{0}C; **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 5.28 (bs, 1H), 6.81 (d, J = 6 Hz, 1H), 7.23 - 7.55 (m, 4H), 7.80 - 7.85 (m, 1H), 7.15 - 7.24 (m, 1H).

2-methoxy-1-naphthylmethanol (98 r):



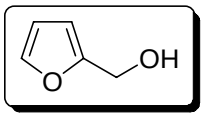
Molecular Formula: $C_{12}H_{12}O_2$; **Nature:** Brick red semisolid; **Yield:** 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.96 (s, 3H), 5.15 (s, 2H), 7.22 – 7.35 (m, 2H), 7.50 (t, J = 8 Hz, 1H), 7.80 (t, J = 8 Hz, 2H), 8.08 (d, J = 8 Hz, 1H).

4-methoxy-1-naphthylmethanol (98 s):



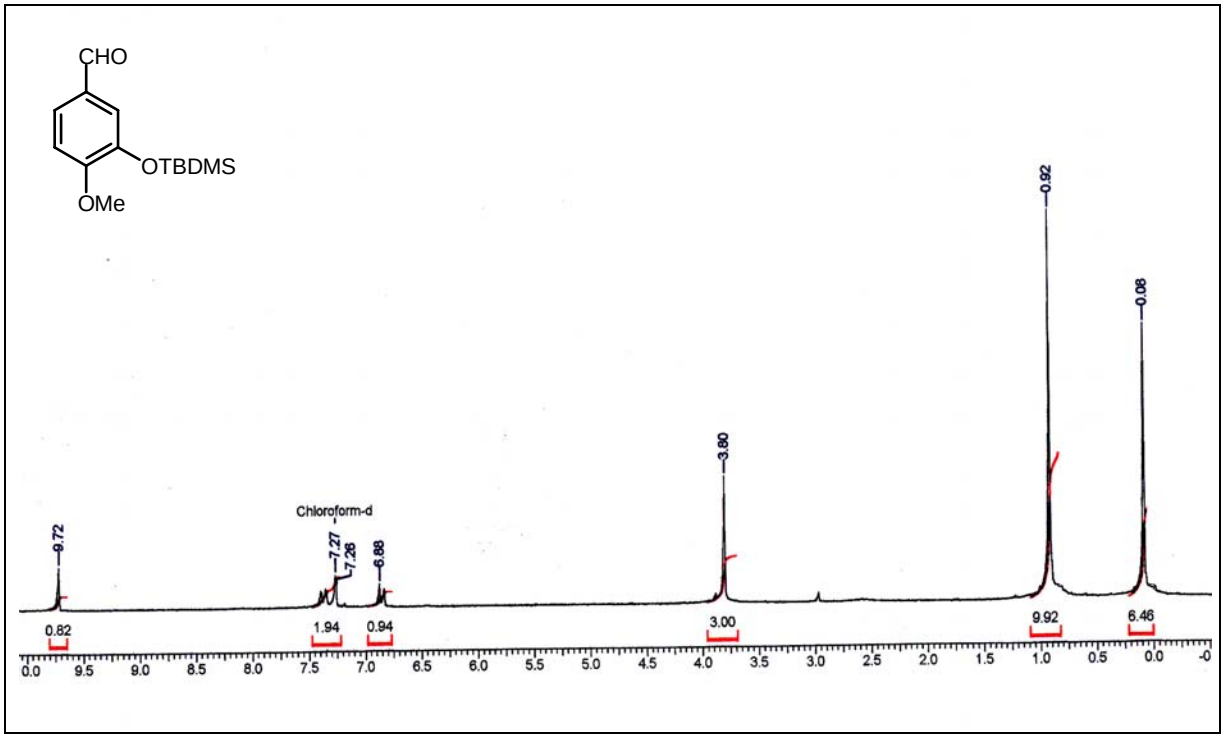
Molecular Formula: $C_{12}H_{12}O_2$; **Nature:** Brick red semisolid; **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.98 (s, 3H), 5.10 (s, 2H), 6.74 (d, J = 8 Hz, 1H), 7.25 - 7.50 (m, 3H), 8.08 (d, J = 8 Hz, 1H), 8.45 (d, J = 8 Hz, 1H).

Furfuryl alcohol (98 t):

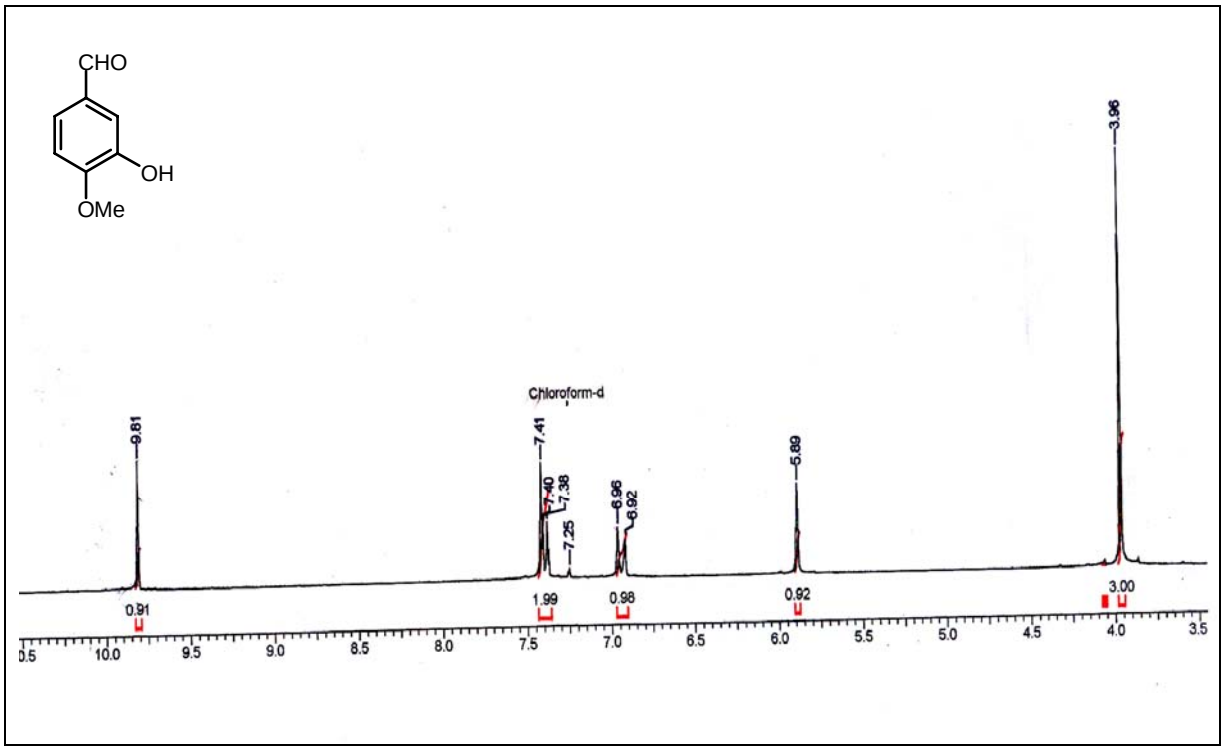


Molecular Formula: $C_5H_6O_2$; **Nature:** Colourless liquid; **Yield:** 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4)**:** δ 3.06 (bs, 1H), 4.52 (s, 2H), 6.21 - 6.34 (m, 2H), 7.35 (d, J = 4 Hz, 1H); **Anal. Calcd. for** C_5H_6O: C, 61.22; H, 6.16 %. **Found:** C, 61.02; H, 6.00 %.

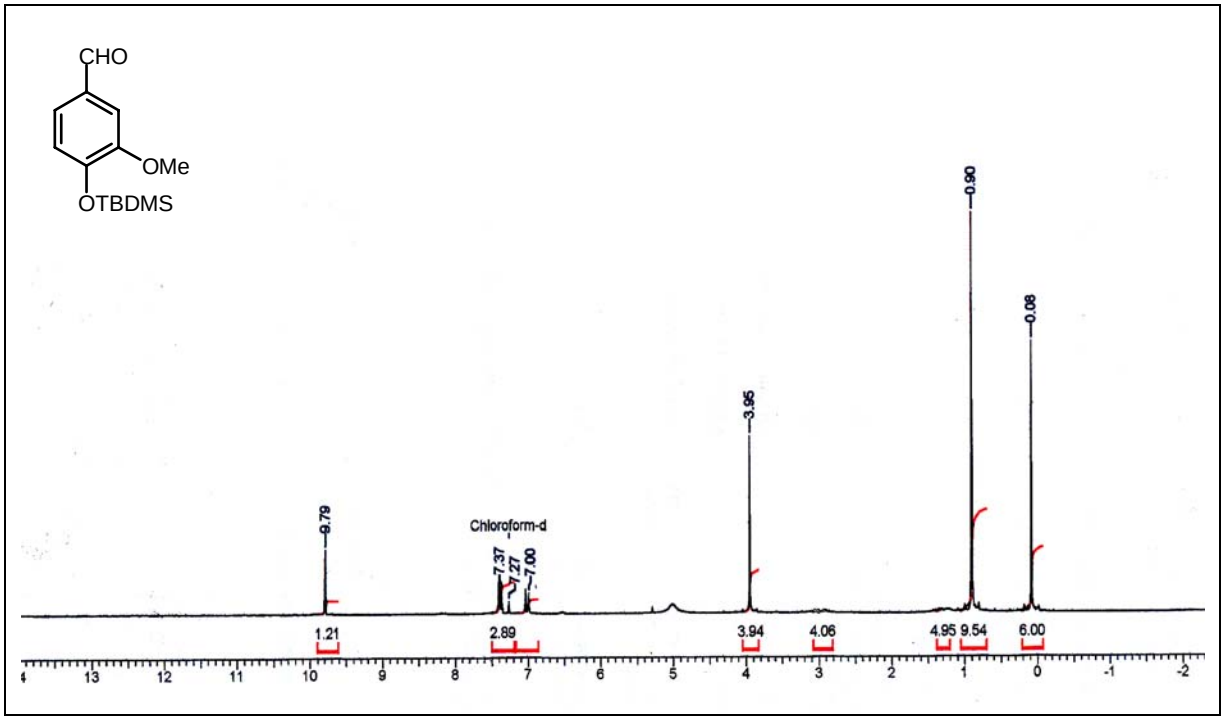
^{1}H NMR spectrum of Compound 97 g ($CDCl_3$+CCl_4, 200 MHz)



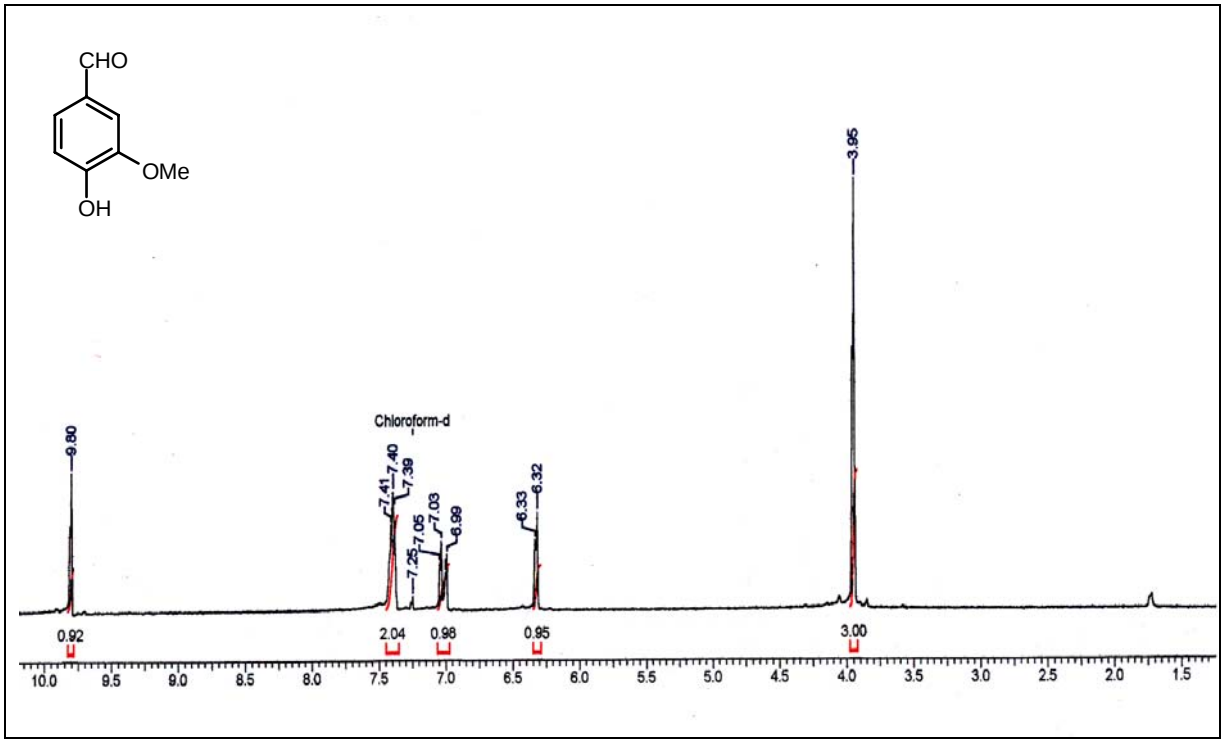
^{1}H NMR Spectrum of Compound 98 g ($CDCl_3$+CCl_4, 50 MHz)



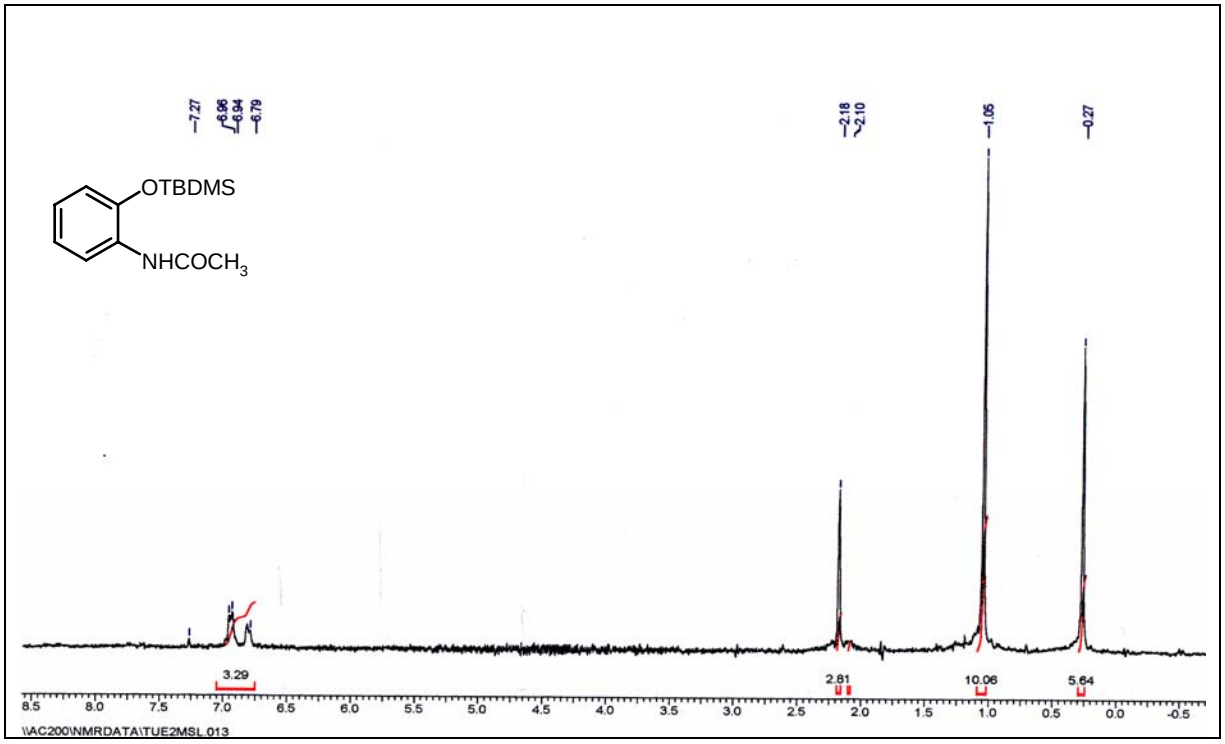
^{1}H NMR spectrum of Compound 97 h ($CDCl_3$+CCl_4, 200 MHz)



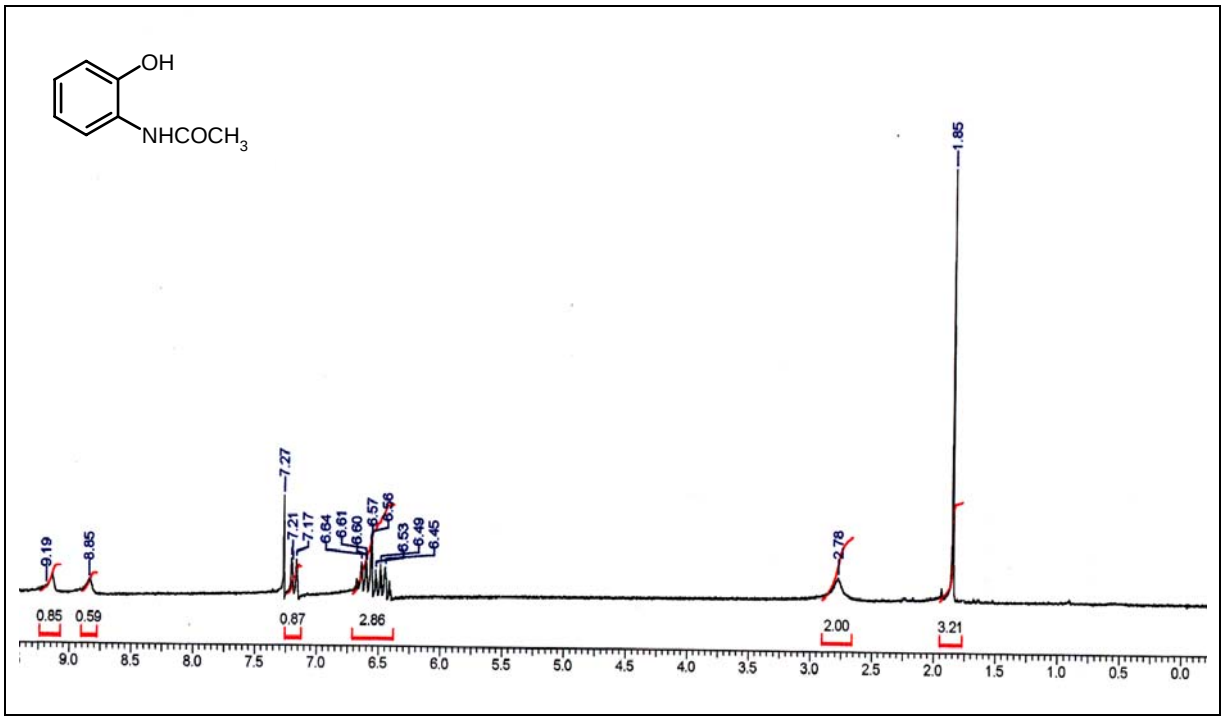
^{1}H NMR Spectrum of Compound 98 h ($CDCl_3$+CCl_4, 200 MHz)



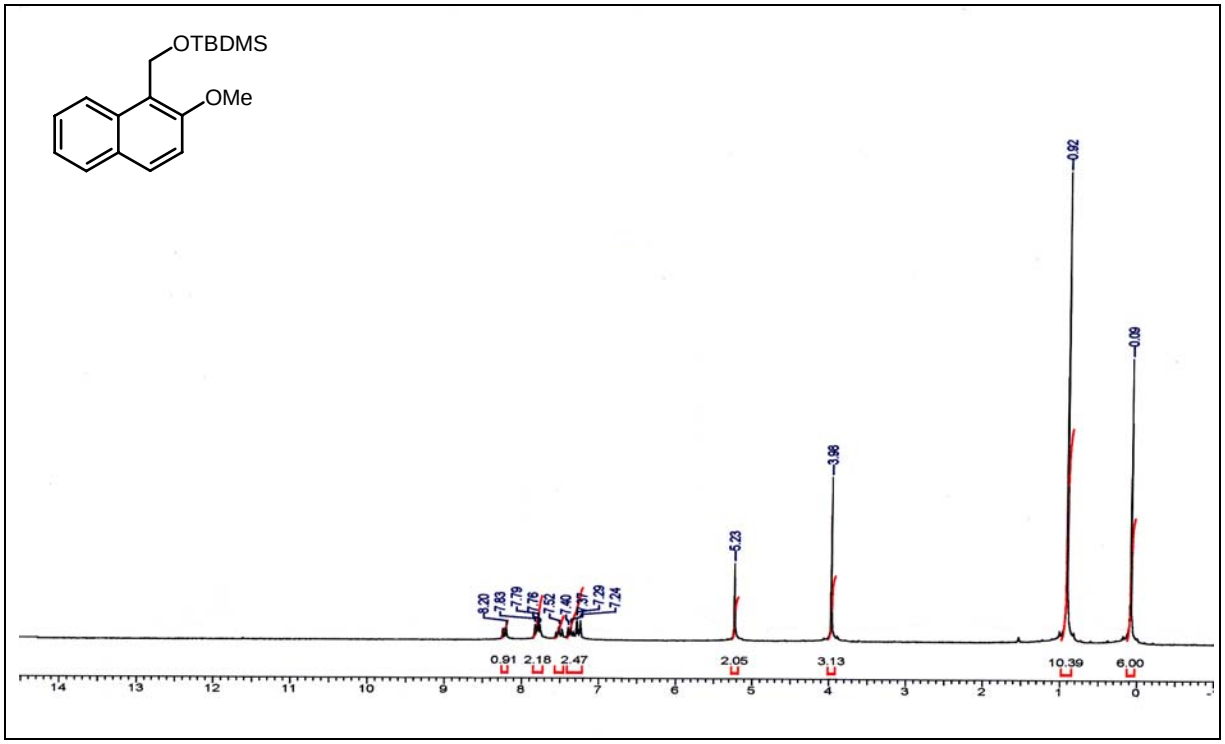
^{1}H NMR spectrum of Compound 97 m ($CDCl_3$+CCl_4, 200 MHz)



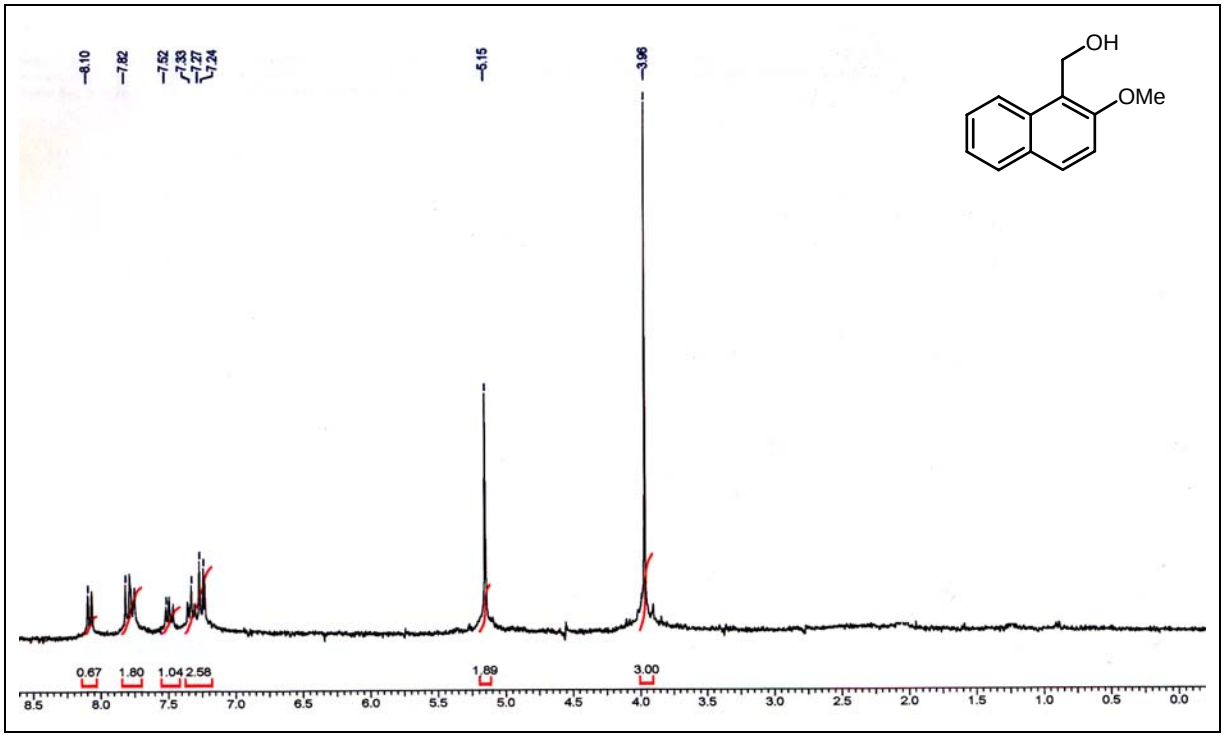
^{1}H NMR Spectrum of Compound 98 m ($CDCl_3$+CCl_4, 200 MHz)



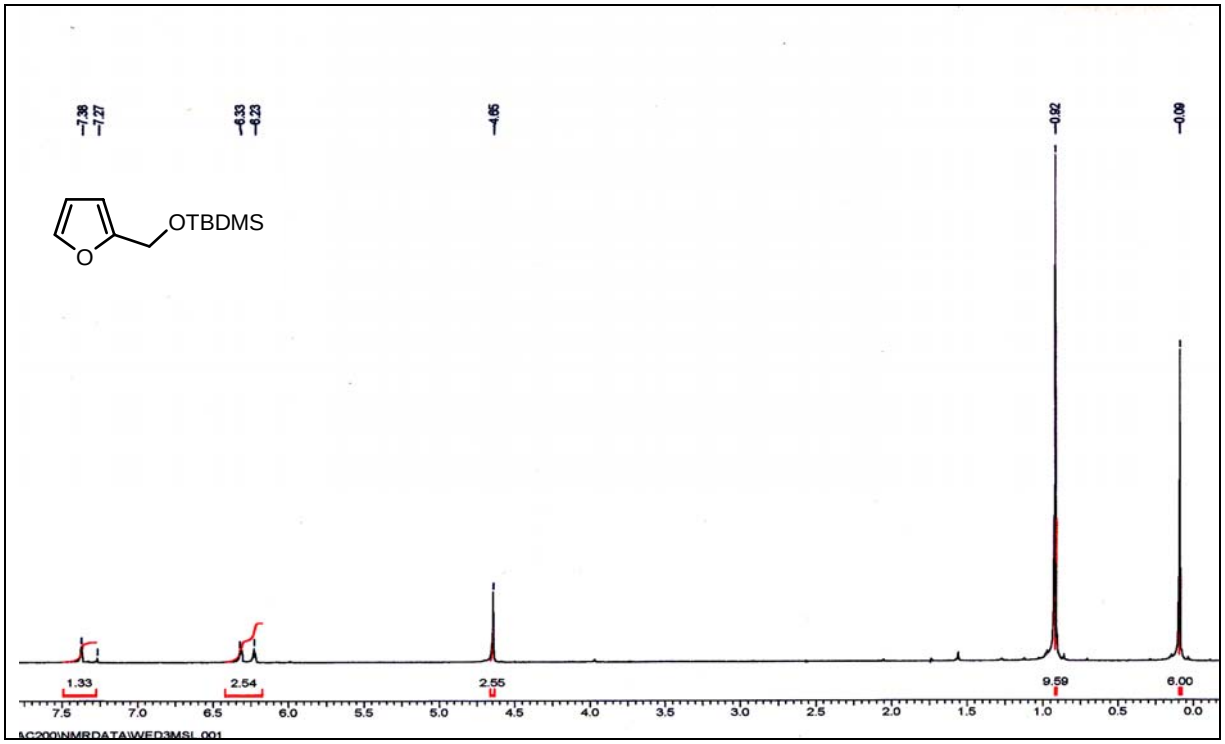
^{1}H NMR spectrum of Compound 97 r ($CDCl_3$+CCl_4, 200 MHz)



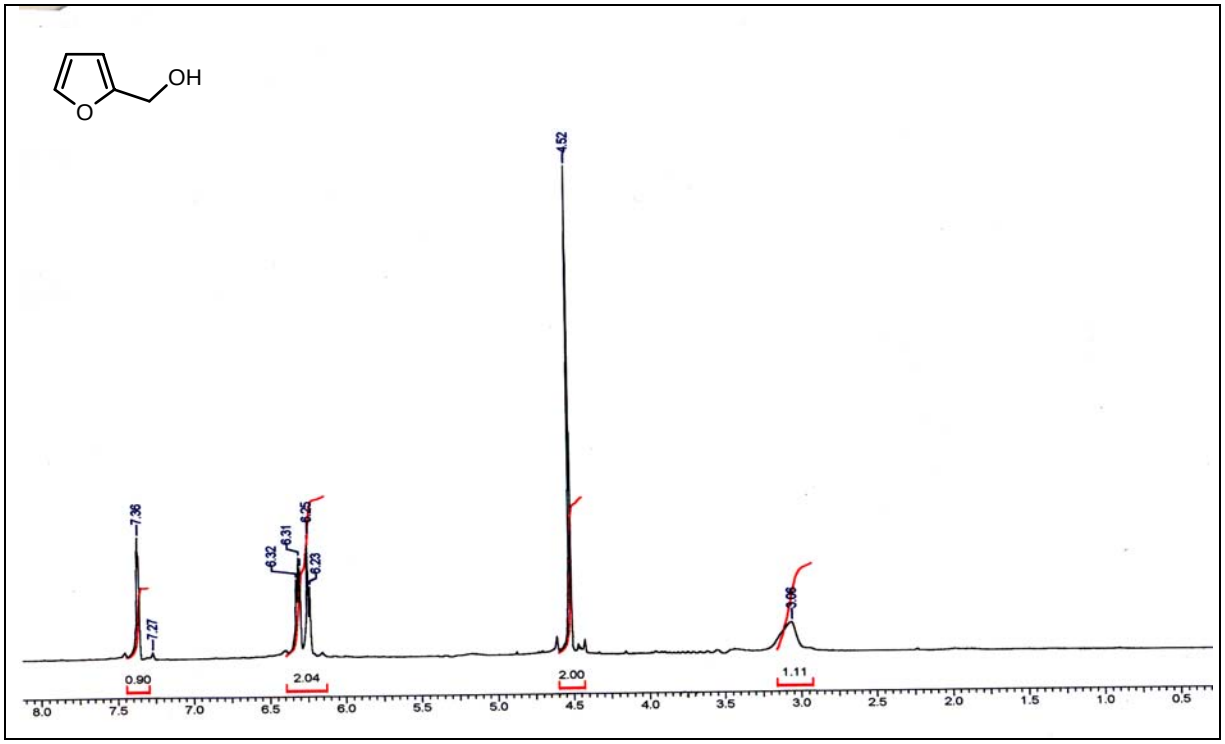
^{1}H NMR Spectrum of Compound 98 r ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR spectrum of Compound 97 t ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR Spectrum of Compound 98 t ($CDCl_3$+CCl_4, 200 MHz)



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CHAPTER - III

SECTION - III

MICROWAVE PROMOTED SOLVENT-FREE ONE-POT SYNTHESIS OF *N*, *N*'-DISUBSTITUTED UREA DERIVATIVES

3.3.1: INTRODUCTION:

Substituted ureas have been of recent interest due to the appearance of this functionality in drug candidates such as HIV protease inhibitors;[1,2] in addition, ureas have found widespread use as agricultural chemicals, resin precursors, dyes and additives to petroleum compounds and polymers.[3] For these reasons, many efforts have been made to find new efficient synthesis of ureas to replace the classical reactions of amines with phosgene[4] or related compounds.

Human immunodeficiency virus (HIV) aspartyl protease inhibitors are a major component of anti-HIV chemotherapy, the current treatment for acquired immunodeficiency syndrome (AIDS), ureido class of compounds inhibits the formation of mature viral particles and thus the infectious process. Although protease inhibitors have radically improved the life of AIDS patients and contributed in large part to the success of highly active anti-retroviral therapy (HAART), new problems have recently been identified. The rapid emergence of several viral strains resistant to one or more of the drugs currently available for the treatment of AIDS has now become the most important issue in the treatment of HIV infection.[5] Most currently available drugs are peptidomimetics containing the hydroxyethylene moiety, which mimic the hydrolytic transition state of protease substrate.[6,7] Recently discovered HIV protease inhibiting compounds devoid of the hydroxyethylene moiety of general structure as shown in Fig 1, also demonstrated interesting anti-viral activity.[8-10]

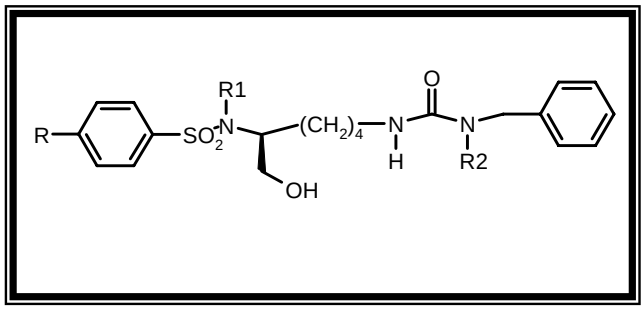


Fig. 1

N, N'-Disubstituted ureas are important subunits present in a number of naturally occurring compounds and have found numerous applications as dyes, antioxidants, pesticides, corrosion inhibitors, intermediates for the preparation of pharmaceuticals, and agricultural chemicals. *N, N'*-Unsymmetrically and symmetrically disubstituted ureas have found use in a wide variety of areas including applications in medicinal chemistry.[11] The preparation of ureas from amines is well documented[12] and it is based on the use of phosgene,[13] phosgene substitutes,[14] carbonic acid derivatives,[15,16] and isocyanates.[17] Recently, novel methods for the preparation of ureas have been described. These involve the reaction of unsymmetrical diaryl carbonates[18] or S,S-dimethyl dithiocarbonates with amines[19] and the treatment of ethyl carbonates with magnesium amides.[20] Other method involves formation of isocyanates from *tert*-butyl carbamates using DMAP[21] or a stronger base for deprotonation.[22] Processes involving the aminolysis of alkyl carbamates have been described[23] and very often require high temperature reaction conditions.[24] Formation of ureas from phenyl carbamates is also cited in the literature,[25] but procedures often call for harsh conditions, long reaction times and occasionally a large excess of amines.[26] Consequently, an improved general method was sought.

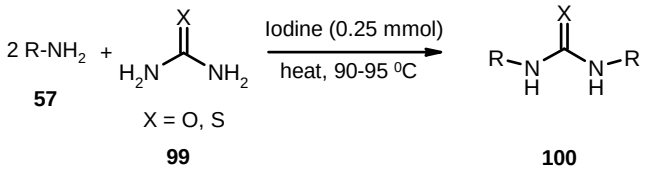
The synthesis of symmetrically disubstituted ureas from amines can be accomplished by oxidative carbonylation of amines by means of carbon monoxide and transition metal catalyst (W,[27] Ni,[28] Mn,[29] Co,[30] Rh,[31] Ru[32] and Pd[33]) among them, the most commonly used is Pd. The reaction with a Pd catalyst implies the use of a reoxidant reagent in stoichiometric amount to transform Pd(0) that results from the reaction) into Pd(II) (the reactive species of the catalyst); usually, high pressures of CO and O_2 are necessary, sometimes in combination with I_2;[34] alternatively, CO, O_2, and copper salts can be used.

Electrochemistry has also been used as reoxidizing system. Recently Deng and co-workers have applied electrochemistry to the synthesis of symmetrical dialkyl ureas using $Pd(PPh_3)_2Cl_2$ as catalyst and $Cu(OAc)_2$ as co-catalyst, instead of high pressure of CO/O_2. In this case, it is proved that $Cu(OAc)_2$ "acted as not only an electron transfer agent but also a catalyst"[35].

A brief review of literature survey for the synthesis of disubstituted ureas has been given on the following pages.

BRIEF REVIEW OF LITERATURE:

Pasha, M. A. and Jayashankara, V. P. reported[36] efficient synthesis of *N, N'* - disubstituted ureas/thioureas catalyzed by iodine. Iodine is an efficient catalyst for the synthesis of *N, N'* - disubstituted ureas/thioureas by heating respective amines or phenyl hydrazine and urea / thiourea on a preheated hot plate at 90 - 95 ^{0}C, under solvent-free conditions as shown in scheme-1. The yields are excellent, and the reactions go to completion within 5 - 10 min.



57 **99** **100**

X = O, S

Scheme - 1

Batey, R. A. and coworkers reported[37] that carbamoylimidazolium salts act as efficient *N, N'* - disubstituted carbamoylating reagents. These salts are readily prepared by the sequential treatment of secondary amines with *N, N'* - carbonyldimidazole (CDI) and iodomethane. The carbamoylimidazolium salts are more efficient carbamoyl transfer reagents than the intermediate carbamoylimidazoles, as a result of the imidazolium effect. Kinetic studies on the base promoted hydrolysis of both carbamoylimidazoles and carbamoylimidazolium salts reveal over a hundred-fold rate acceleration. The salts react with amines, thiols, phenols/alcohols, and carboxylic acids in high yields, without the need for subsequent chromatographic purification of the products, producing ureas as shown in scheme-2.

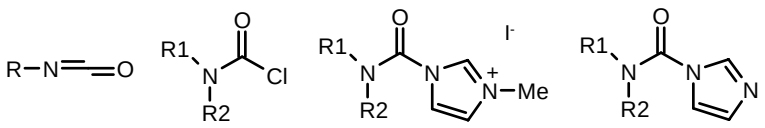
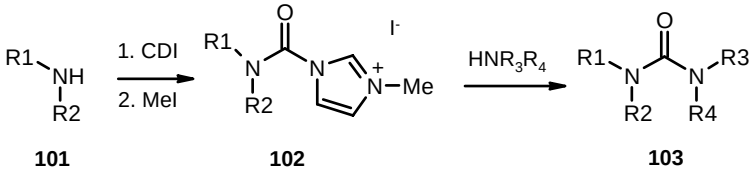
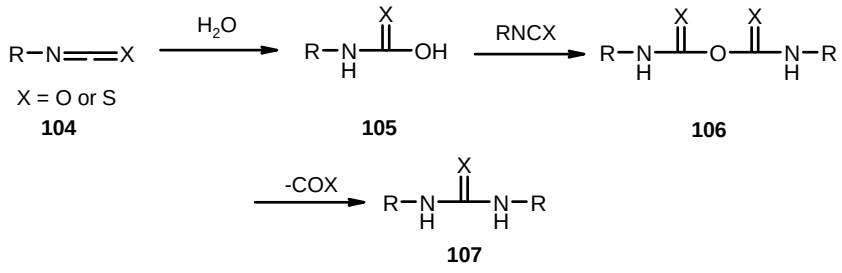


Figure 1. N-monosubstituted and N,N' - disubstituted carbamoyl cation equivalents.



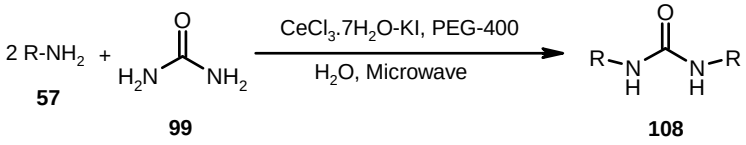
Scheme - 2

Perveen, S. and coworkers reported[38] expeditious method for the synthesis of symmetrical 1, 3 - disubstituted ureas and thioureas as shown in scheme-3. Symmetrical 1, 3-disubstituted ureas and symmetrical thioureas were synthesized from corresponding isocyanates, diisocyanates, and isothiocyanates by a new versatile, simple, and quick method in the presence of tertiary amines at room temperature. The method under discussion has several advantages over the existing techniques, as it is simple to carry out, does not require complicated equipment, has a simple workup, and does not use expensive chemicals. Moreover, the yields are almost quantitative. This method has potential in commercial applications.



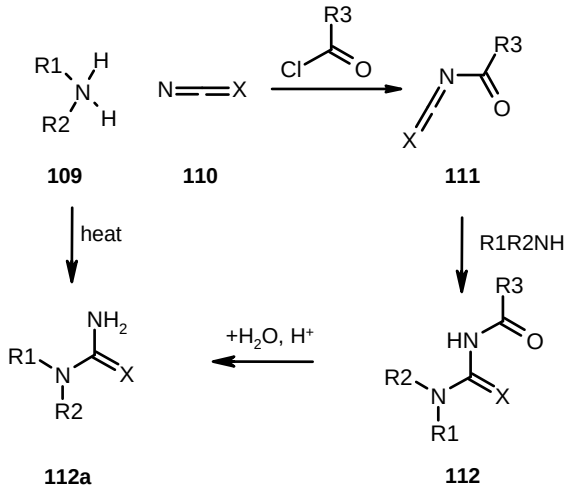
Scheme - 3

Zhao, Y. L. and coworkers reported[39] $CeCl_3.7H_2O$-KI-Catalyzed, environmentally friendly synthesis of *N, N'*-disubstituted ureas in water under microwave irradiation. *N, N'*-Disubstituted ureas were efficiently synthesized by reactions of urea with a variety of amines in water under microwave irradiation using $CeCl_3.7H_2O$-KI as catalyst as shown in scheme-4. This protocol has advantages of avoiding use of toxic phosgene and hazardous organic solvents, achieving high reaction rate, high yield, and a simple workup procedure.



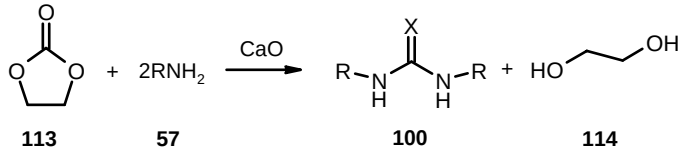
Scheme - 4

Hartmann H. and Keil D. reported[40] a simple route to synthesize *N, N*- disubstituted selenoureas from *N, N*- disubstituted cyanamides. It can be prepared from the hydrolysis of acylselenoureas (**112**) which are available by reaction of alkali or ammonia selenocynides (**110**) with acyl chlorides and subsequent reaction of the primarily formed acyl isoselenocynates (**111**) with amines as shown in scheme-5.



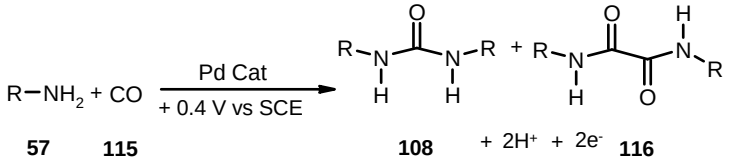
Scheme - 5

Fujita S. I. and coworkers reported[41] synthesis of *N, N'*-disubstituted ureas from ethylene carbonate and amine using CaO. Calcium oxide was an excellent solid catalyst for the synthesis of *N, N'*-disubstituted ureas from ethylene carbonate and primary amines under mild conditions as shown in scheme-6.



Scheme - 6

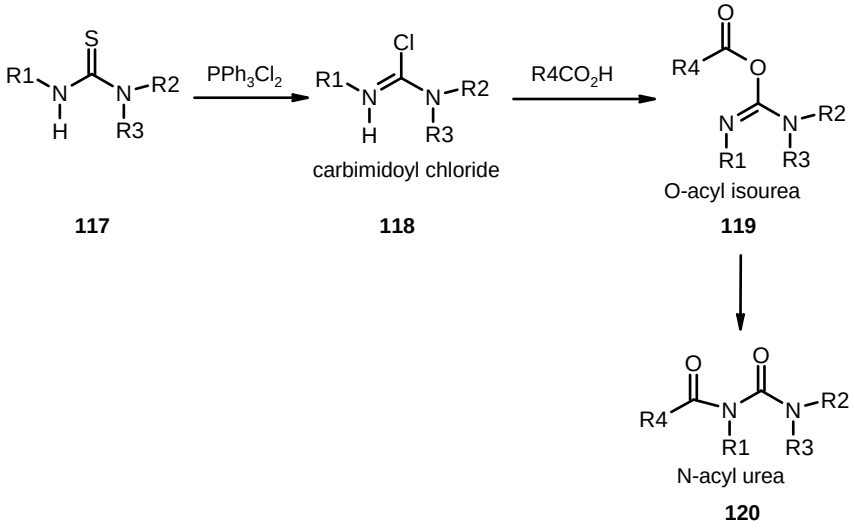
Feroci M. and Chiarotto I. Reported[42] selective and environmentally friendly methodology based on the use of electrochemistry for fine chemical preparation. A novel efficient synthesis of *N, N'*-disubstituted urea was developed. Aromatic and aliphatic primary amines undergo oxidative carbonylation under atmospheric pressure of carbon monoxide using Pd (II) catalyst in combination with its anodic recycling at a graphite electrode as shown in scheme-7.



Scheme - 7

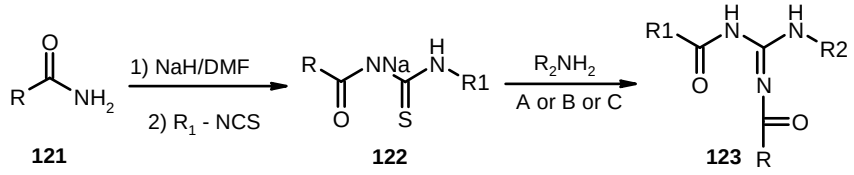
Lau J. F. *et al.* reported[43] a novel, mild method for the synthesis of di and trisubstituted *N*-acyl ureas on solid support. Addition of carboxylic acids to a resin-bound carbimidoyl chloride gave, initially, an *O*-acyl isourea which subsequently rearranged to the corresponding *N*-acyl urea as shown in scheme-8. Trisubstituted *N*-acyl ureas were assembled on a Wang resin from a wide range of Fmoc amino acids, secondary amines and carboxylic acids. Acid mediated cleavage yielded the products in good yields and

excellent purities. In addition to this the regioselective synthesis of disubstituted *N*-acyl ureas, was achieved.



Scheme - 8

Shi, Y. *et al.* reported[44] one pot synthesis of *N, N'*-disubstituted acylguanidines. Acylguanidines are isoesteres of thioureas (or ureas) and are possible prodrugs of guanidines. A convenient one-pot synthesis of *N, N'*-disubstituted acylguanidines from primary amides as shown in scheme-9, was reorted.

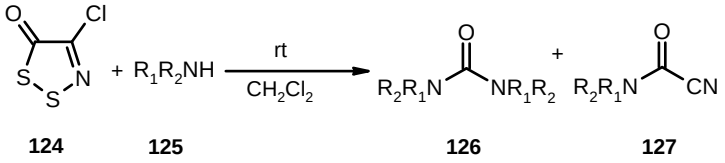


A = $HgCl_2$, B = EDCI, DMAP, Et_3N, C = 2-Chloro-1-methylpyridium iodide.

Scheme - 9

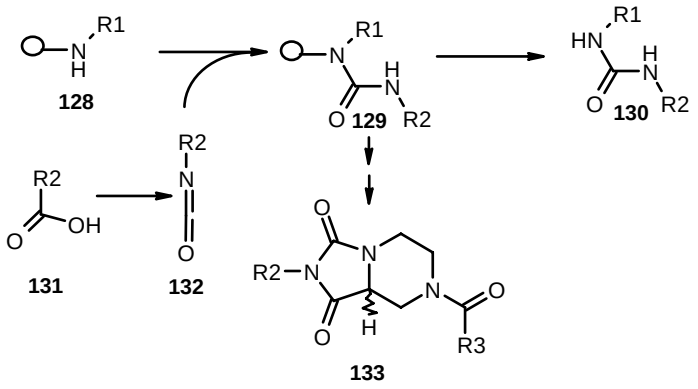
Kim K. and coworkers reported[45] a convenient synthesis of symmetrical *N, N'*-dialkylureas by the reaction of 4-chloro-5*H*-1,2,3-dithiazol-5-one with alkylamines.

Treatment of 4-chloro-5*H*-1,2,3-dithiazol-5-one with primary and secondary alkylamines (>2 equiv.) in CH_2Cl_2 at room temperature afforded *N, N'*-disubstituted ureas in moderate to good yields as shown in scheme-10. Similarly, the reactions with amino acid ester hydrochlorides in the presence of Et_3N (>3 equiv.) under the same conditions gave symmetrical ureas.



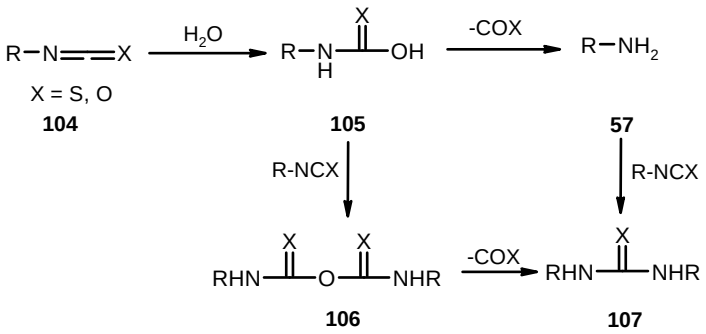
Scheme - 10

Migawa M. T. and his group reported[46] a solid-phase synthesis of *N, N'*-disubstituted ureas and perhyroimidazo [1, 5-a] pyrazines via the Curtius rearrangement. An efficient method for trapping isocyanates, generated from the Curritius rearrangement, with resin-bound amines was developed. Carboxylic acid was treated with diphenylphosphoryl azide, followed by thermal rearrangement, to give the desired product. Cleavage from the resin provided an *N, N'* –disubstituted urea in excellent purity as shown in scheme-11.



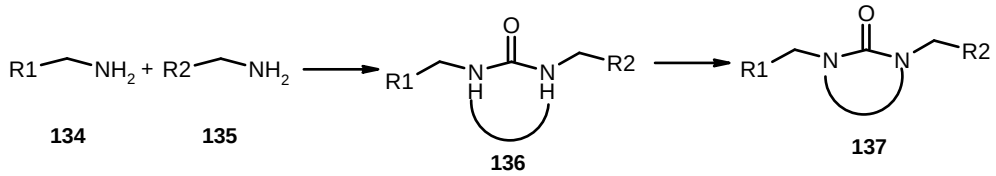
Scheme - 11

Fernandez M. G. *et al.* reported[47] a practical amine-free synthesis of urea and thioureas by self-condensation of iso (thio) cyanates. Isocyanates and isothiocyanates are readily transformed into the corresponding symmetric *N, N'* - disubstituted ureas and thioureas upon treatment with pyridine-water with no formation of side products. Evidence is shown for an amine-free mechanistic pathway, probably involving (thio) carbamic anhydrides as reaction intermediates. The methodology is compatible with in situ generation of the isocyanate precursor from an acyl azide via Curtius rearrangement and with the presence of ester and amide functional groups in the molecule as shown in scheme-12. Examples include alkyl, aryl and carbohydrate substrates. This procedure allows the high yielding preparation of (thio)ureas in those cases where the related amine is not accessible.



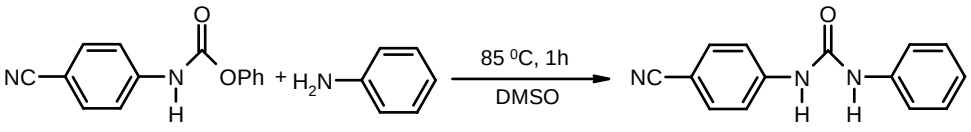
Scheme - 12

Davies S. G. and coworkers reported[48] a simple desymmetrisation approach to unsymmetric *N, N'*-disubstituted cyclic ureas. The formation of cyclic ureas via a treatment of unsymmetric *N, N'* bis protected diamines with phosgene yielded *N, N'*-disubstituted cyclic ureas in good yield as shown in scheme-13.



Scheme - 13

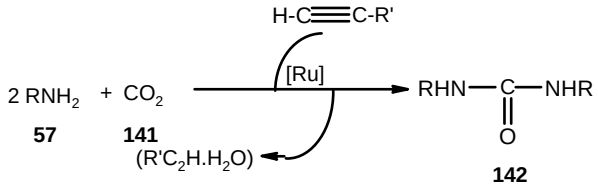
Thavonekham T. reported[49] a practical synthesis of ureas from phenyl carbamates, using DMSO as solvent. A mild and efficient procedure for the synthesis of unsymmetrical *N, N'* – disubstituted ureas by the treatment of phenyl carbamates, with a stoichiometric amount of amine at ambient temperature, was developed to collect the ureas in high yield and high purity as shown in scheme-14. The reaction was fast and could be easily scaled up.



138 **139** **140**

Scheme - 14

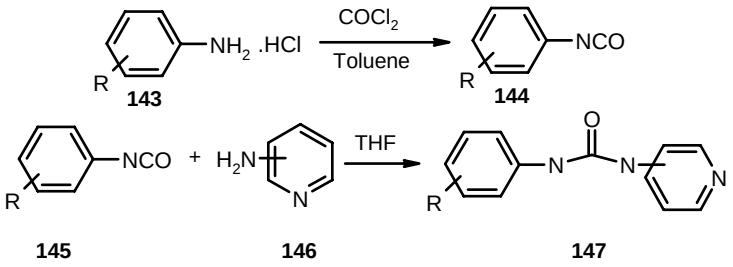
Dixneuf P. H. *et al* reported[50] ruthenium-catalyzed synthesis of symmetrical *N, N'*-dialkylureas directly from carbon dioxide and amines. Aliphatic and araliphatic primary amines react with carbon dioxide at 120-140 ^{0}C in the presence of ruthenium complexes and terminal alkynes, especially propargyl alcohols, to directly afford *N, N*'-disubstituted symmetrical ureas. The alkyne ruthenium intermediate acts as a dehydrating reagent as shown in scheme-15. This method avoids the classical use of carbonyl precursors like phosgene or isocyanates.



57 **141** **142**

Scheme - 15

Pavia M. R. and co-workers reported[51] a series of *N*-phenyl–*N'*-pyridinylureas which was examined for anticonvulsant activity. Extensive structure / activity investigation revealed optimal activity in the *N*-(2,6-disubstituted-phenyl)-*N*'-(4-pyridinyl)urea series. They synthesized the disubstituted urea derivatives as shown in scheme-16.



Scheme - 16

3.3.2: PRESENT WORK:

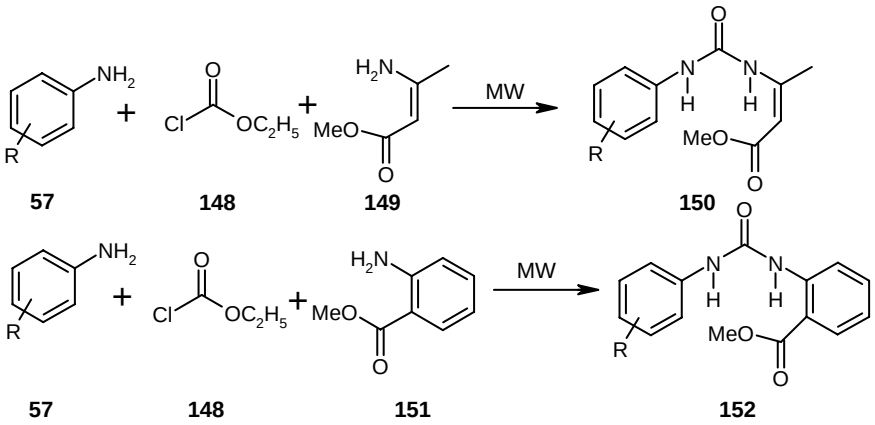
Symmetrical and unsymmetrical *N, N'*-disubstituted aryl/alkyl urea derivatives are well known for their biological activities such as herbicidal,[52-56] COX-2 inhibition,[57] fat metabolism inhibition,[58] *etc*. Symmetrical disubstituted aromatic ureas are useful as agrochemicals and their intermediates,[59] stabilizers[52,60] for smokeless gun powder, propellants and solid rocket fuels. Diaryl urea derivatives have been reported[61] recently for the treatment of disease states mediated by the chemokine, interleukin-8 and also as chloride channel blockers.[62] Diaryl ureas have been claimed[62] as Chk-1 kinase inhibitors for the treatment of cancer. Some *N, N'*-diaryl urea derivatives have been reported as complement receptor C5a antagonists[63] which are useful as remedies and preventives for diseases like rheumatism, allergic diseases such as sepsis, asthma, cardiac infarction, brain infarction, psoriasis, Alzeimer *etc*.

Literature survey for the synthesis of disubstituted urea derivatives has been reviewed and summarized as an introduction of this section. Alkyl/aryl substituted urea and thiourea derivatives have been synthesized from corresponding amines by the treatment with the requisite isocyanates and isothiocyanates respectively. Carbonylation process catalyzed by palladium salts using primary and secondary alkyl amines with carbon monoxide was found to be one of the convenient methods for the synthesis of symmetrical urea derivatives. Phosgenation of *N*-alkyl amines in presence of aqueous sodium hydroxide has been reported to provide symmetrical diaryl urea derivatives in excellent yields. Reductive carbonylation of aromatic nitro compounds, coupling of acyl azide, dihydroxy borane substrate and ruthenium catalyzed synthesis are a few other methods reported for the synthesis of substituted urea derivatives. Literature survey revealed a very few reports using simple non-hazardous chemicals such as phosgene-free synthesis of *N, N*'-diaryl ureas, use of aryl carbonic acid ester and condensation of anilines with urea. The wide spectrum of important biological activities exhibited by *N, N'*-disubstituted urea derivatives and lack of environmently friendly methods prompted us to undertake the research described this section. We performed one pot sequential condensation of aryl amines with ethyl chloroformate followed by methyl 3-amino-2-

butenoate or methyl anthranilate under solvent free microwave irradiation conditions to collect the corresponding *N*, *N'*-disubstituted urea derivatives. The scope and limitations of this protocol have been described.

3.3.3: RESULTS AND DISCUSSION:

Microwave irradiation has become a powerful synthetic tool for the rapid synthesis of a variety of biologically active compounds under solvent-free conditions[64] because of simplicity in operation, enhanced reaction rates and greater selectivity. The one - pot multi-component reaction protocol has attracted considerable attention in organic synthesis as one of the tools for environmentally benign synthetic procedures. Initially, we treated aniline, methyl 3-amino-2-butenoate and ethyl chloroformate in equal ratio under microwave solvent-free conditions for 5 min at 130 °C and found that the product was a mixture of the corresponding carbamates and urea derivatives. Aniline, methyl 3-amino-2-butenoate and methyl anthranilate were independently reacted in microwave oven with ethyl chloroformate to observe the complete conversion to their corresponding carbamate esters within 5 min. Ethyl phenylcarbamate was further treated with methyl 3-amino-2-butenoate which provided the corresponding urea derivative as the only product.



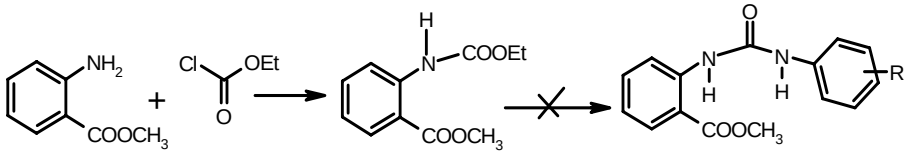
Scheme -17

The control experiments confirmed that carbamate formation is a much faster reaction than its conversion to urea derivatives. Similar sequence of reaction was observed in case

of methyl anthranilate. The one pot sequential coupling reaction under solventless microwave irradiation conditions was optimized using aniline, ethyl chloroformate and methyl 3-amino-2-butenoate or methyl anthranilate to collect *N, N'*-disubstituted urea derivatives (Scheme-17).

In order to study the scope and limitations of this protocol, several substituted anilines were subjected to this sequential addition reaction performed in one-pot (without work up) under microwave irradiation. The substituted anilines and ethyl chloroformate (1:1 ratio) were placed in a microwave oven and complete conversion to the corresponding ethyl carbamate was observed in 5 min (as monitored by TLC). Methyl anthranilate or methyl 3-amino-2-butenoate and K_2CO_3 (1.2 equivalent) were added to the above carbamate and heating in microwave was continued further till complete conversion to the urea derivatives. The reaction was best performed in presence of potassium carbonate when the product was cleaner with improved yield. It was noteworthy that the reaction selectively provided urea derivatives and did not procced further to give the corresponding cyclized products. The results are summerised in Table-1. *N, N'*-Disubstituted urea derivatives have been achieved in good yields in 15 to 25 min.

The examples exhibited in Table-1 indicated that the reaction proceeded smoothly irrespective of the electronic nature of the substituents on aniline. *o*-Phenylene diamine efficiently reacted to provide the diureido-derivative (Table-1, entry 15). The phenyl carbamate esters reacted equally efficiently with methyl anthranilate as well as methyl 3-amino-2-butenoate. 2-Aminophenol (Table-1, entry 13) gave selectively the corresponding urea derivative wherein the phenolic hydroxy remained unreacted. To study the selectivity further, condensation reactions were performed using phenol, thiophenol, ethylamine, ethanolamine, diethylamine, benzylamine, L-serine and Boc-protected L-serine in place of aniline, which remained unreacted under the present conditions described. Similarly, the ethyl phenyl carbamate and ethyl 4-methoxyphenyl carbamate were treated with methyl 3-amino-2-thiophenecarboxylate which failed to give the corresponding urea derivatives.

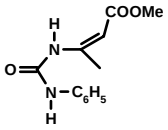
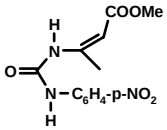
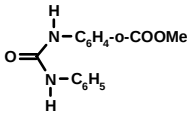
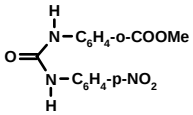
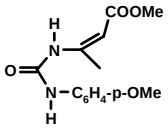
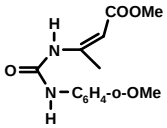
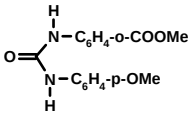
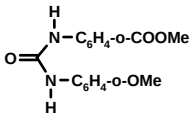
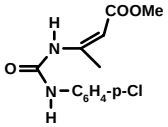
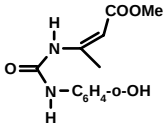
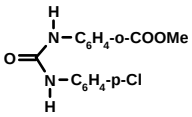
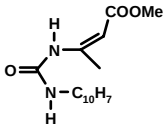
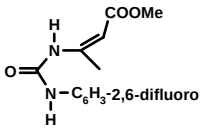
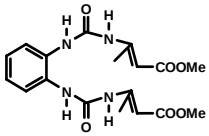
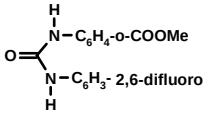
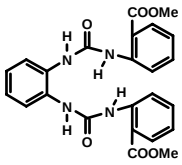


151 **148** **153** **152**

Scheme - 18

It is noteworthy that the diester obtained after condensation of methyl anthranilate and ethyl chloroformate (Scheme - 18) did not react further with anilines under similar conditions leading to the urea derivatives. Similar selectivity was observed in case of methyl 3-amino-2-butenoate.

Table 1: *N,N'*-Disubstituted urea derivatives

Sr. No.	Products	Time min	Yield %	Sr. No.	Products	Time min	Yield %
a	 **150a**	15	82	**i**	 **150e**	20	76
b	 **152a**	15	82	**j**	 **152e**	20	72
c	 **150b**	20	81	**k**	 **150f**	15	87
d	 **152b**	20	83	**l**	 **152f**	15	82
e	 **150c**	20	78	**m**	 **150g**	20	79
f	 **152c**	20	80	**n**	 **150h**	20	89
g	 **150d**	20	82	**o**	 **150i**	25	83
h	 **152d**	20	81	**p**	 **152g**	25	82

3.3.4: CONCLUSION:

In conclusion, the one-pot protocol presented in this section for the synthesis of *N, N*'-disubstituted urea derivatives under solvent-free microwave irradiation conditions was found to be highly efficient and selective. The synthetic procedure is environmentally friendly and does not require hazardous chemicals like phosgene, isocyanates and expensive metal salts for the coupling reaction described herein. A clean conversion of aniline derivatives has been optimized to their urea derivatives in good yield in a very short period of 15 to 25 min.

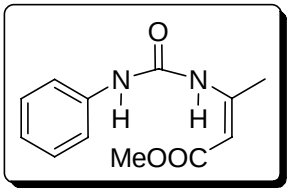
3.3.5: EXPERIMENTAL:

General Procedure using methyl-3-amino-2-butenoate:

A mixture of ethyl chloroformate (228 mg, 2.10 mmol) and aniline (200 mg, 2.10 mmol) was irradiated in a domestic microwave oven adjusted at 900W and 130 °C for 5 min. Methyl-3-amino-2-butenoate (242 mg, 2.10 mmol) and potassium carbonate (348 mg, 2.52 mmol) were then added and the mixture was irradiated for 20 min (monitored by TLC). After adding water (10 ml) to the reaction mixture, the product was extracted with ethyl acetate (3 X 15 ml). The ethyl acetate layer was dried (Na_2SO_4), concentrated and the crude product obtained was purified by column chromatography over silica gel to afford the methyl 3-(3-phenylureido)but-2-enoate (221 mg, 82 %).

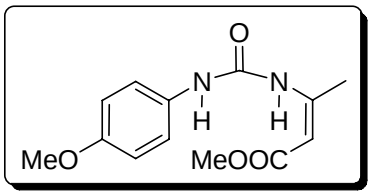
Methyl 3-(3-Phenylureido)but-2-enoate (150 a):

Molecular Formula: $C_{12}H_{14}O_3N_2$; **Nature:** White solid; **M. p.** 87 ^{0}C; **Yield:** 82 %; **IR** (Chloroform)**:** ν_{max} 3448, 3268, 1731, 1652, 1596 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.00 (s, 3H), 3.69 (s, 3H), 4.69 (s, 1H), 6.70 (bs, 1H), 7.07 - 7.19 (m, 3H), 7.27 - 7.36 (m, 2H), 10.38 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 23.0, 50.8, 96.9, 121.0 (2C), 127.0, 128.7 (2C), 139.5, 148.2, 152.8, 167.2; **Anal. Calcd. for** $C_{12}H_{14}O_3N_2$**:** C, 61.54; H, 5.98; N, 11.96 %. **Found:** C, 61.50; H, 5.95; N, 11.97 %.



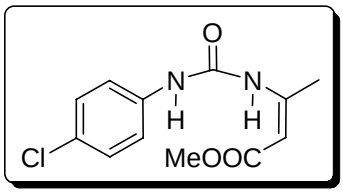
3-[3-(4-Methoxy-phenyl)-ureido]-but-2-enoic acid methyl ester (150 b):

Molecular Formula: $C_{13}H_{16}N_2O_4$; **Nature:** White solid; **M. p.** 78 ^{0}C; **Yield:** 81 %; **IR** (Chloroform)**:** ν_{max} 3475, 3210, 1745, 1690 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.11 (s, 3H), 3.82 (s, 3H), 4.00 (s, 3H), 6.09 (s, 1H), 6.90 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 8.18 (s, 1H), 10.86 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 21.5, 52.6, 52.9, 96.5, 113.8, 115.1 (2C), 122.6 (2C), 132.8, 147.2, 153.5, 166.2; **Anal. Calcd. for** $C_{13}H_{16}N_2O_4$**:** C, 59.09; H, 6.06; 10.60 %. **Found:** C, 59.20; H, 6.25; N, 10.67 %.



***Methyl 3-(3-(4-chlorophenyl)ureido)but-2-enoate (150 c)*:**

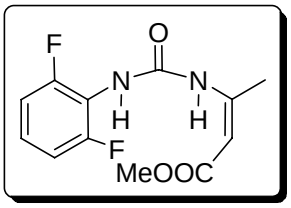
Molecular Formula: $C_{12}H_{13}ClN_2O_3$; **Nature:** White solid; **M. p.** 70 ^{0}C; **Yield:** 78 %; **IR**



(Chloroform)**:** ν_{max} 3490, 3321, 1733, 1681 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.34 (s, 3H), 3.69 (s, 3H), 4.89 (s, 1H), 6.75 (bs, 1H), 7.23 - 7.37 (m, 4H), 10.60 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 22.9, 51.7, 98.4, 122.2 (2C), 129.2 (2C), 129.4, 137.1, 146.5, 152.9, 163.2; **Anal. Calcd. for** $C_{12}H_{13}ClN_2O_3$**:** C, 53.53; H, 4.83; N, 10.41; Cl, %. **Found:** C, 53.60; H, 4.80; N, 10.45; Cl, %.

3-[3-(2, 6-difluoro-phenyl)-ureido]-but-2-enoic acid methyl ester (150 d):

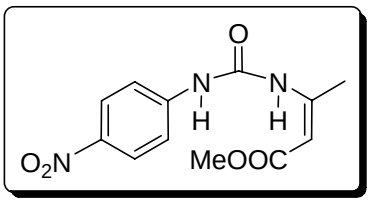
Molecular Formula: $C_{12}H_{12}F_2N_2O_3$; **Nature:** White solid; **M. p.** 73 ^{0}C; **Yield:** 82 %; **IR**



(Chloroform)**:** ν_{max} 3495, 3380, 1760, 1692 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.25 (s, 3H), 3.70 (s, 3H), 4.80 (s, 1H), 6.60 - 6.72 (m, 2H), 6.80 (d, *J* = 6 Hz, 1H), 6.95 (d, *J* = 6 Hz, 1H), 9.73 (bs, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 23.4, 51.9, 98.7, 111.3 (2C), 112.8, 126.4, 147, 151.3, 156.8 (2C), 166.2; **Anal. Calcd. for** $C_{12}H_{12}F_2N_2O_3$**:** C, 53.33; H, 4.44; N, 10.37 %. **Found:** C, 53.40; H, 4.48; N, 10.35 %.

3-[3-(4-Nitro-phenyl)-ureido]-but-2-enoic acid methyl ester (150 e):

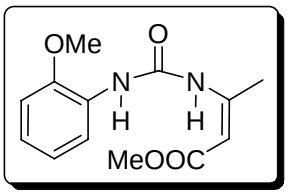
Molecular Formula: $C_{12}H_{13}N_3O_5$; **Nature:** Yellow solid; **M. p.** 104 ^{0}C; **Yield:** 76 %; **IR**



(Chloroform)**:** ν_{max} 3500, 3360, 1755, 1688 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.97 (s, 3H), 3.79 (s, 3H), 5.00 (s, 1H), 7.25 - 7.37 (m, 4H), 7.79 - 7.83 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 23.2, 50.9, 98.1, 122.4 (2C), 123.9 (2C), 144.6, 145.1, 145.6 152.9, 166.1; **Anal. Calcd. for** $C_{12}H_{13}N_3O_5$**:** C, 53.53; H, 4.83; N, 15.61. **Found:** C, 53.45; H, 4.87; N, 15.50 %.

3-[3-(2-Methoxy-phenyl)-ureido]-but-2-enoic acid methyl ester (150 f):

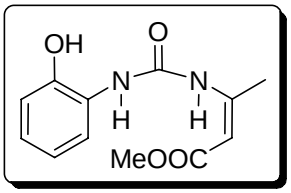
Molecular Formula: $C_{13}H_{16}N_2O_4$; **Nature:** White solid; **M. p**. 98 ^{0}C; **Yield:** 79 %; **IR**



(Chloroform)**:** ν_{max} 3502, 3300, 1768, 1695 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.12, (s, 3H), 3.78 (s, 3H), 3.95 (s, 3H), 5.50 (bs, 2H), 6.56 - 7.20 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 22.9, 51.6, 56.2, 98.0, 114.4, 121.2, 121.6, 123.9, 125.4, 145.8, 152.8, 154.6, 165.9; **Anal. Calcd. for** $C_{13}H_{16}N_2O_4$**:** C, 59.09; H, 6.06; N, 10.61 %. **Found:** C, 59.10; H, 6.15; N, 10.50 %.

3-[3-(2-Hydroxy-phenyl)-ureido]-but-2-enoic acid methyl ester (150 g):

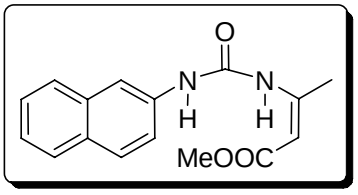
Molecular Formula: $C_{12}H_{14}N_2O_4$; **Nature:** White solid; **M. p.** 73 ^{0}C; **Yield:** 87 %; **IR**



(Chloroform)**:** ν_{max} 3480, 3235, 1757, 1693 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 2.10 (s, 3H), 3.98 (s, 3H), 4.74 (s, 1H), 6.85 - 7.05 (m, 4H), 8.10 (s, 1H), 10.87 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 23.5, 51.4, 97.9, 116.4, 122.0, 122.4, 125.6, 125.8, 145.4, 149.0, 151.5, 166.2; **Anal. Calcd. for** $C_{12}H_{14}N_2O_4$**:** C, 57.60; H, 5.60; N, 11.20 %. **Found:** C, 57.45; H, 5.71; N, 11.10 %.

3-[3- naphthalen-2- yl-ureido]- but-2-enoic acid methyl ester (150 h):

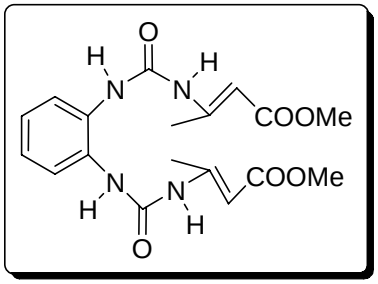
Molecular Formula: $C_{16}H_{16}N_2O_3$; **Nature:** White solid; **M. p.** 120 ^{0}C; **Yield:** 89 %; **IR**



(Chloroform)**:** ν_{max} 3498, 3280, 1758, 1682 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.98 (s, 3H), 3.65 (s, 3H), 4.72 (s, 1H), 6.50 (bs, 2H) 7.00 - 7.18 (m, 4H), 7.25 - 7.34 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 22.8, 49.9, 96.8, 107.4, 117.2, 122.3, 124.6, 125.2, 125.8, 126.4, 127.1, 133.0, 142.6, 145.2, 151.3, 165.2; **Anal. Calcd. for** $C_{16}H_{16}N_2O_3$**:** C, 67.60; H, 5.63; N, 9.86 %. **Found:** C, 67.50; H, 5.70; N, 9.81 %.

3-(3-[2-{3-(2-Methoxycarbonyl-1-methyl-vinyl)-ureido}-phenyl]-ureido)-but-2-enoic acid methyl ester (150 i):

Molecular Formula: $C_{18}H_{22}N_4O_6$; **Nature:** White solid; **M. p**. 63 ^{0}C; **Yield:** 83 %; **IR** (Chloroform)**:** ν_{max} 3490, 3287, 1761, 1694 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 1.39 (s, 3H), 1.73 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.29 (s, 2H), 4.70 (bs, 4H), 6.57 (d, *J* = 8 Hz, 1H), 7.74 - 7.98 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 22.8, 22.9, 50.5, 51.5, 96.9, 97.2, 120.4, 121.2, 124.3 (2C), 130.2 (2C), 145.8 (2C), 151.2 (2C), 166.1, 167.5; **Anal. Calcd. for** $C_{18}H_{22}N_4O_6$**:** C, 55.38; H, 5.64; N, 14.36 %. **Found:** C, 55.20; H, 5.48; N, 14.21 %.

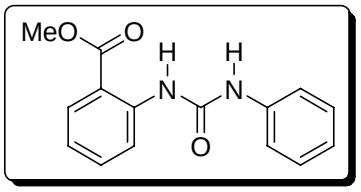


General Procedure using methyl anthranilate:

A mixture of ethyl chloroformate (228 mg, 2.10 mmol) and aniline (200 mg, 2.10 mmol) was irradiated in a domestic microwave oven adjusted at 900W and 130 °C for 5 min. Methyl anthranilate (375 mg, 2.10 mmol) and potassium carbonate (348 mg, 2.52 mmol) were then added and the mixture was irradiated for 20 min (monitored by TLC). After adding water (10 ml) to the reaction mixture, the product was extracted with ethyl acetate (3 X 15 ml). The ethyl acetate layer was dried (Na_2SO_4), concentrated and the crude product obtained was purified by column chromatography over silica gel to afford the N-(phenyl)-N'-(2- carbomethoxyphenyl) urea (221 mg, 82 %).

2-(3-Phenyl-ureido)-benzoic acid methyl ester (152 a):

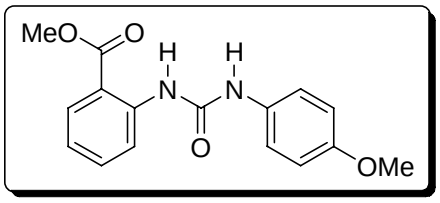
Molecular Formula: $C_{15}H_{14}N_2O_3$; **Nature:** White solid; **M. p.** 63 ^{0}C; **Yield:** 82 %; **IR** (Chloroform)**:** ν_{max} 3502, 3381, 1740, 1692 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.86 (s, 3H), 5.50 (bs, 2H), 6.54 - 6.67 (m, 3H), 6.98 - 7.45 (m, 5H), 7.81 - 7.89 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 51.1, 110.4,



115.8 (2C), 116.4, 118.6, 122.9, 128.6, 130.9 (2C), 133.7, 138.0, 150.4, 153.5, 168.2; **Anal. Calcd. for** $C_{15}H_{14}N_2O_3$**:** C, 66.66; H, 5.18; N, 10.37 %. **Found:** C, 66.40; H, 5.30; N, 10.48 %.

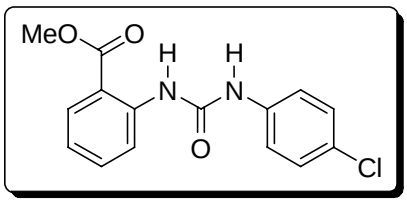
2-[3-(4-methoxy-phenyl)-ureido]-benzoic acid methyl ester (152 b):

Molecular Formula: $C_{16}H_{16}N_2O_4$; **Nature:** White solid; **M. p.** 67 ^{0}C; **Yield:** 83 %; **IR** (Chloroform)**:** ν_{max} 3430, 3190, 1750, 1691 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.87 (s, 3H), 3.90 (s, 3H) 5.10 (bs, 2H), 6.63 - 6.69 (m, 4H), 7.23 - 7.31 (m, 2H), 7.82 - 7.88 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 50.6, 56.5, 115.2 (2C), 116.4, 122.5 (2C), 123.0, 123.5, 124.9, 128.5, 131.4, 138.8, 153.0, 156.9, 169.8; **Anal. Calcd. for** $C_{16}H_{16}N_2O_4$**:** C, 64.00; H, 5.33; N, 9.33 %. **Found:** C, 64.10; H, 5.25; N, 9.40 %.



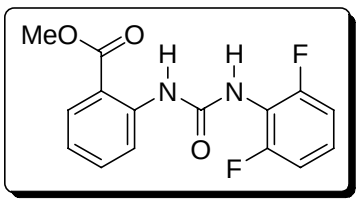
2-[3-(4-chloro-phenyl)-ureido]-benzoic acid methyl ester (152 c):

Molecular Formula: $C_{15}H_{13}ClN_2O_3$; **Nature:** White solid; **M. p.** 81 ^{0}C; **Yield:** 80 %; **IR** (Chloroform)**:** ν_{max} 3500, 3382, 1750, 1693, 1616 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.85 (s, 3H), 5.46 (bs, 2H), 6.61 - 6.67 (m, 3H), 7.21 - 7.30 (m, 3H), 7.80 - 7.88 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 52.4, 121.2 (2C), 122.8, 123.4, 124.0, 128.2 (2C), 128.9, 129.4, 131.8, 137.1, 140.2, 153.8, 169.8; **Anal. Calcd. for** $C_{15}H_{13}ClN_2O_3$**:** C, 59.01; H, 4.26; N, 9.18 %. **Found:** C, 59.15; H, 4.20; N, 9.30 %.



2-[3-(2, 6-Difluoro-phenyl)-ureido]-benzoic acid methyl ester (152 d):

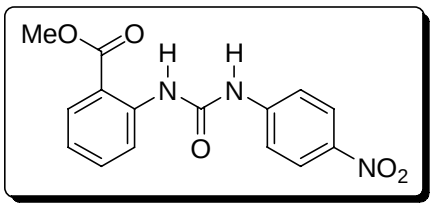
Molecular Formula: $C_{15}H_{12}F_2N_2O_3$; **Nature:** White solid; **M. p.** 64 ^{0}C; **Yield:** 81 %; **IR** (Chloroform)**:** ν_{max} 3451, 3295, 1740, 1693 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.90 (s, 3H), 6.70 (s, 1H), 6.96 - 7.04 (m, 2H), 7.44 - 7.56 (m, 2H), 7.94 - 8.02 (m, 2H), 8.44 (d, *J* = 6 Hz, 1H), 10.47 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 50.8, 112.0 (2C), 112.4, 121.2, 122.6, 124.8, 127.2, 129.9,



132.5, 139.6, 151.9, 155.4 (2C), 170.1; **Anal. Calcd. for** $C_{15}H_{12}F_2N_2O_3$**:** C, 58.82; H ,3.92; N, 9.15 %. **Found:** C, 58.65; H, 3.97; N, 9.12 %.

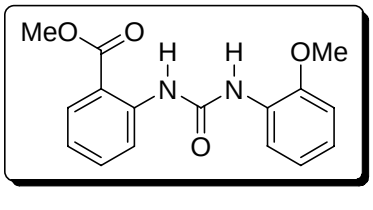
2-[3-(4-Nitro-phenyl)-ureido]-benzoic acid methyl ester (152 e):

Molecular Formula: $C_{15}H_{13}N_3O_5$; **Nature:** Yellow solid; **M. p.** 115 ^{0}C; **Yield:** 72 %; **IR** (Chloroform)**:** ν_{max} 3495, 3370, 1765, 1695 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.87 (s, 3H), 5.90 (bs, 2H), 7.47 - 7.54 (m, 2H), 7.82 - 7.89 (m, 2H), 8.74 - 8.78 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 49.8, 121.5 (2C), 122.6, 122.8 (2C), 124.2, 128.8, 129.6, 132.3, 139.9, 144.2, 145.1, 156.0, 167.9; **Anal. Calcd. for** $C_{15}H_{13}N_3O_5$**:** C, 57.14; H, 4.13; N, 13.33 %. **Found:** C, 57.18; H, 4.10; N, 13.20 %.



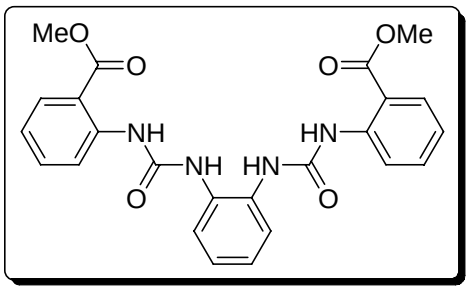
Methyl 2-(3-(2-methoxyphenyl)ureido)benzoate (152 f):

Molecular Formula: $C_{16}H_{16}N_2O_4$; **Nature:** White solid; **M. p.** 64 ^{0}C; **Yield:** 82 %; **IR** (Chloroform)**:** ν_{max} 3501, 3300, 1769, 1690 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.85 (s, 3H), 3.92 (s, 3H), 5.02 (bs, 2H), 6.60 - 6.70 (m, 4H), 7.21 - 7.29 (m, 2H), 7.80 - 7.85 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 51.2, 57.5, 115.0, 121.4, 121.9, 122.6, 123.9, 124.2, 125.5, 129.4, 130.1, 132.6, 139.5, 152.0, 153.8, 167.2; **Anal. Calcd. for** $C_{16}H_{16}N_2O_4$**:** C, 64.00; H, 5.33; N, 9.33 %. **Found:** C, 63.90; H, 5.20; N, 9.50 %.



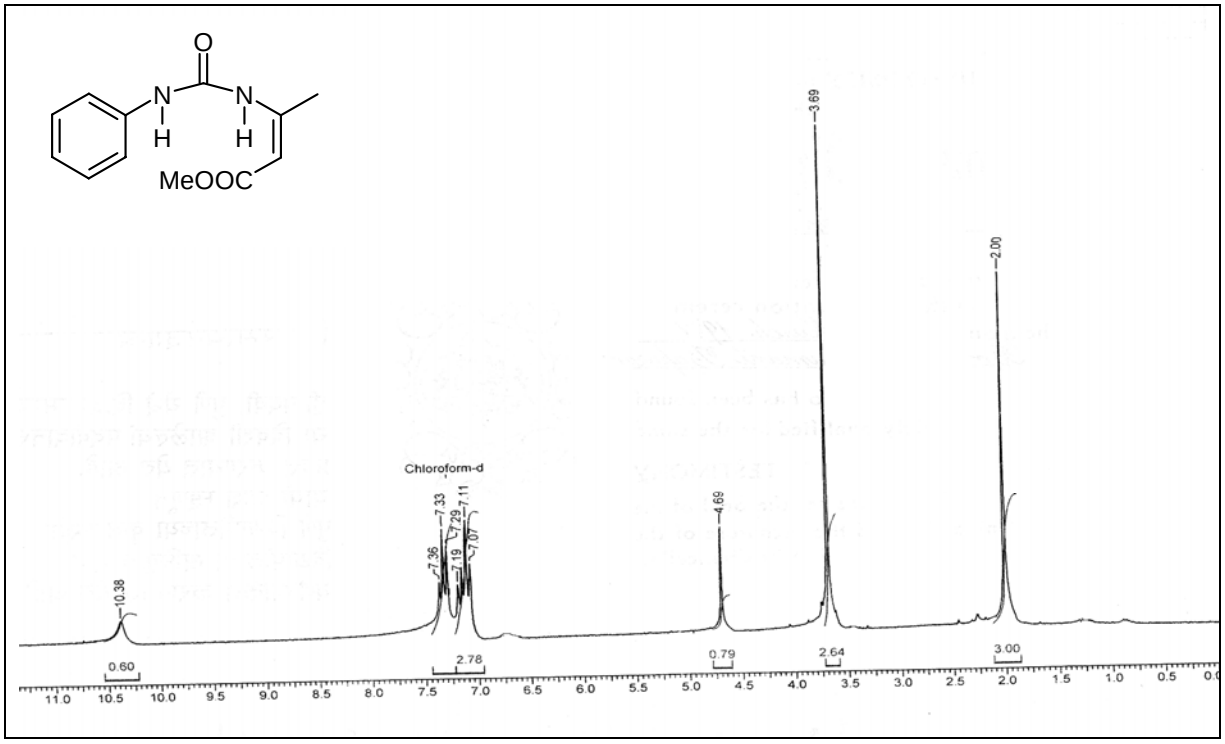
2-{3-[2-(3-o-tolyl-ureido)-phenyl]-ureido}-benzoic acid methyl ester (152 g):

Molecular Formula: $C_{24}H_{22}N_4O_6$; **Nature:** White Solid; **M. p.** 77 ^{0}C; **Yield:** 82 %; **IR** (Chloroform)**:** ν_{max} 3500, 3305, 1765, 1689 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4)**:** δ 3.88 (s, 6H), 5.60 (bs, 4H), 6.60 - 6.72 (m, 4H), 7.22 - 7.32 (m, 4H), 7.89 - 8.00 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4)**:** δ 51.7, 51.1, 110.5 (2C), 115.7 (2C), 116.0 (2C), 116.43, 116.51, 118.58, 118.60,

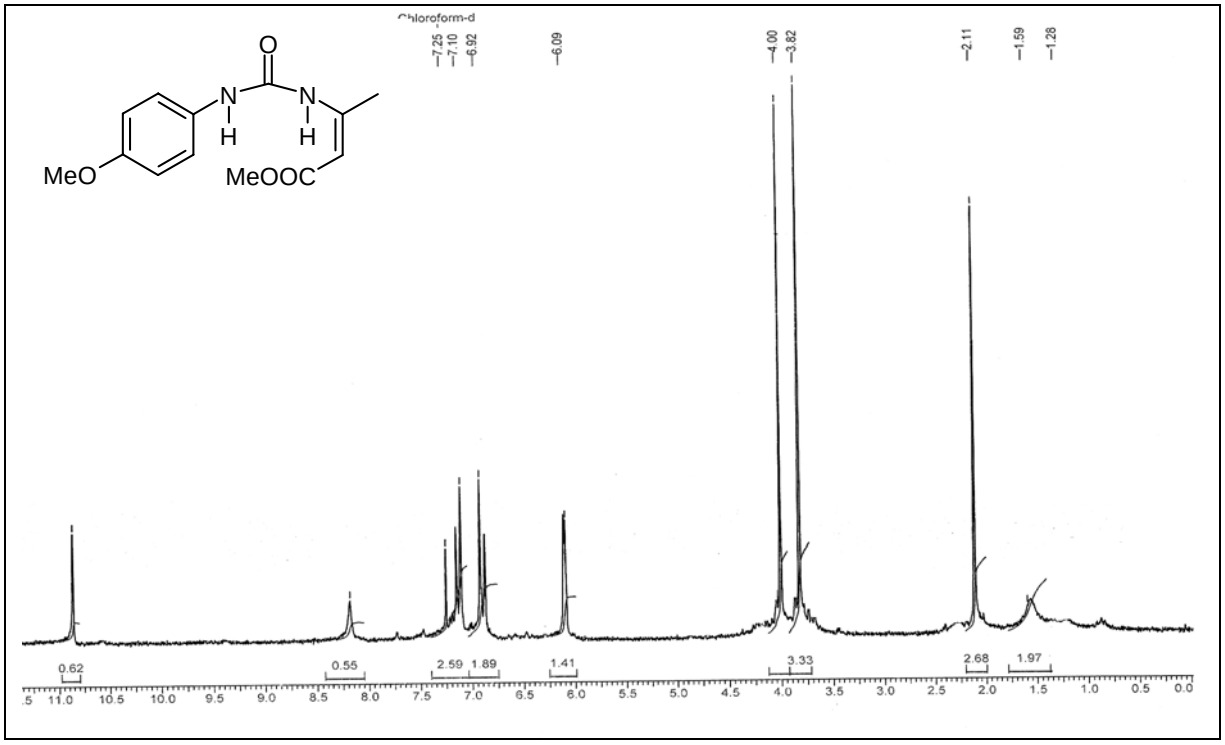


122.94, 122.96, 128.70, 131.4 (2C), 133.0, 138.5, 150.3, 154.1 (2C), 169.0 (2C); **Anal. Calcd. for** $C_{24}H_{22}N_4O_6$**:** C, 62.34; H, 4.76; N, 12.12 %. **Found:** C, 62.40; H, 4.60; N, 12.15 %.

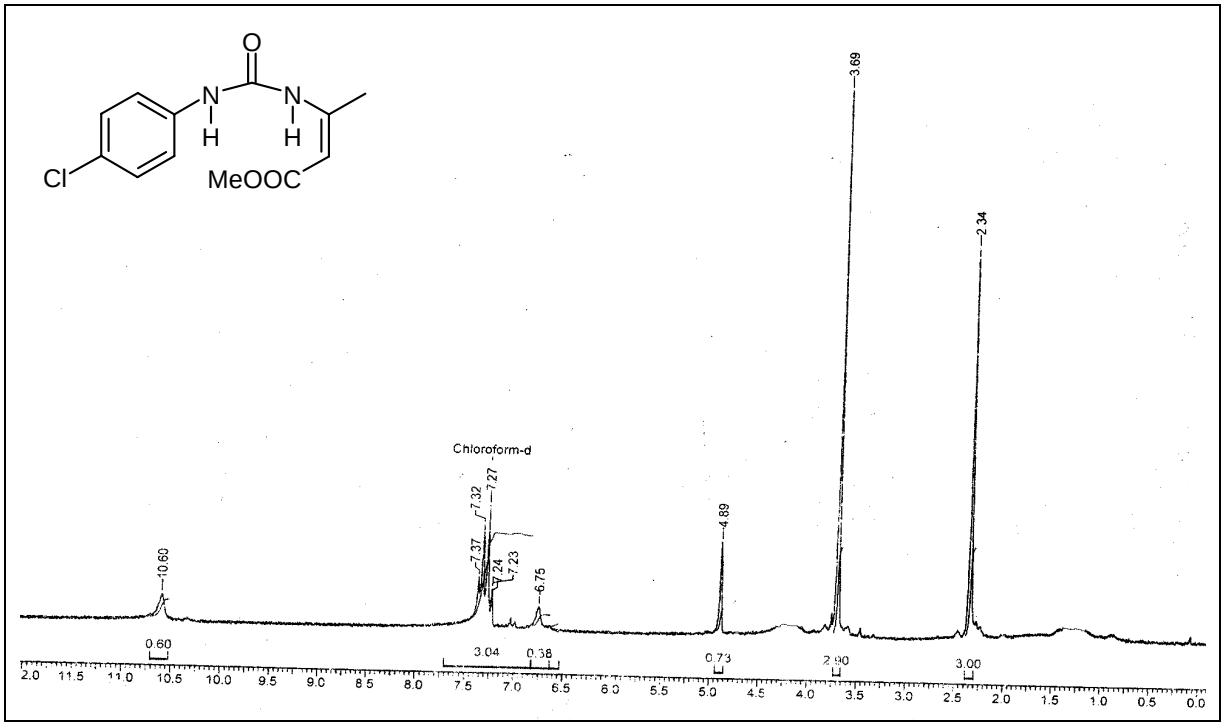
^{1}H NMR spectrum of Compound 150 a ($CDCl_3$+CCl_4, 200 MHz)



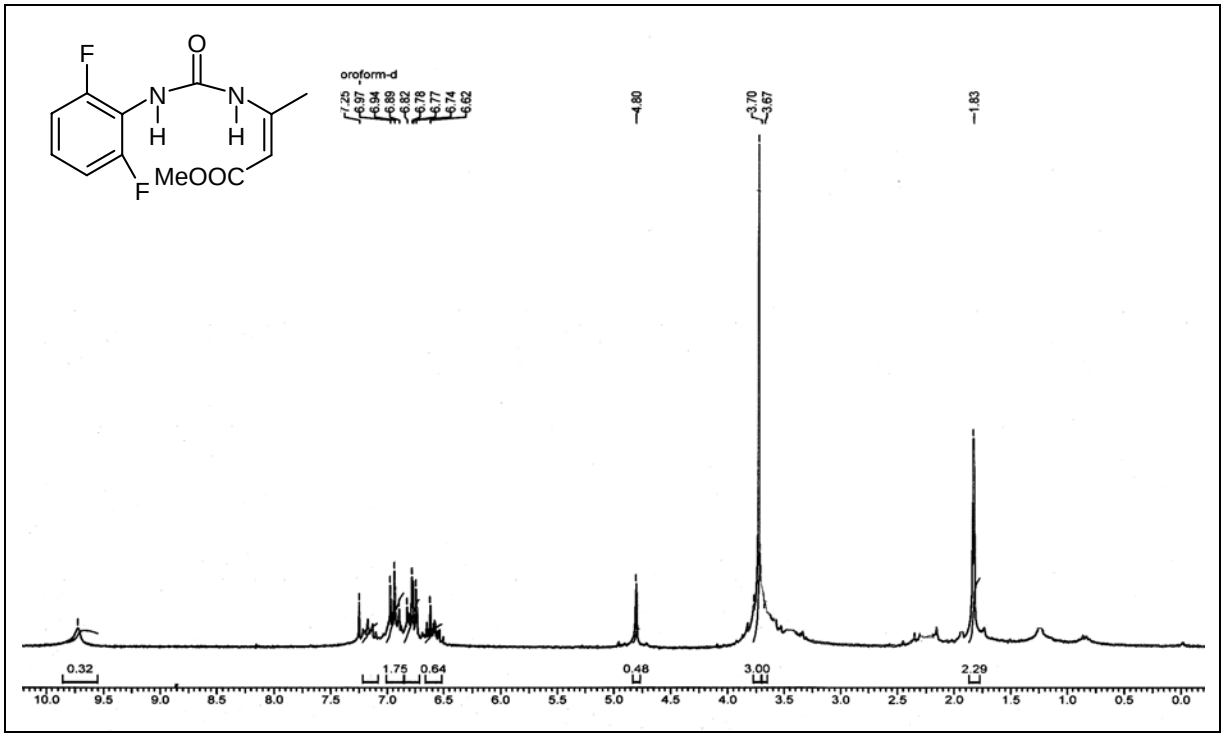
^{1}H NMR Spectrum of Compound 150 b ($CDCl_3$+CCl_4, 200 MHz)



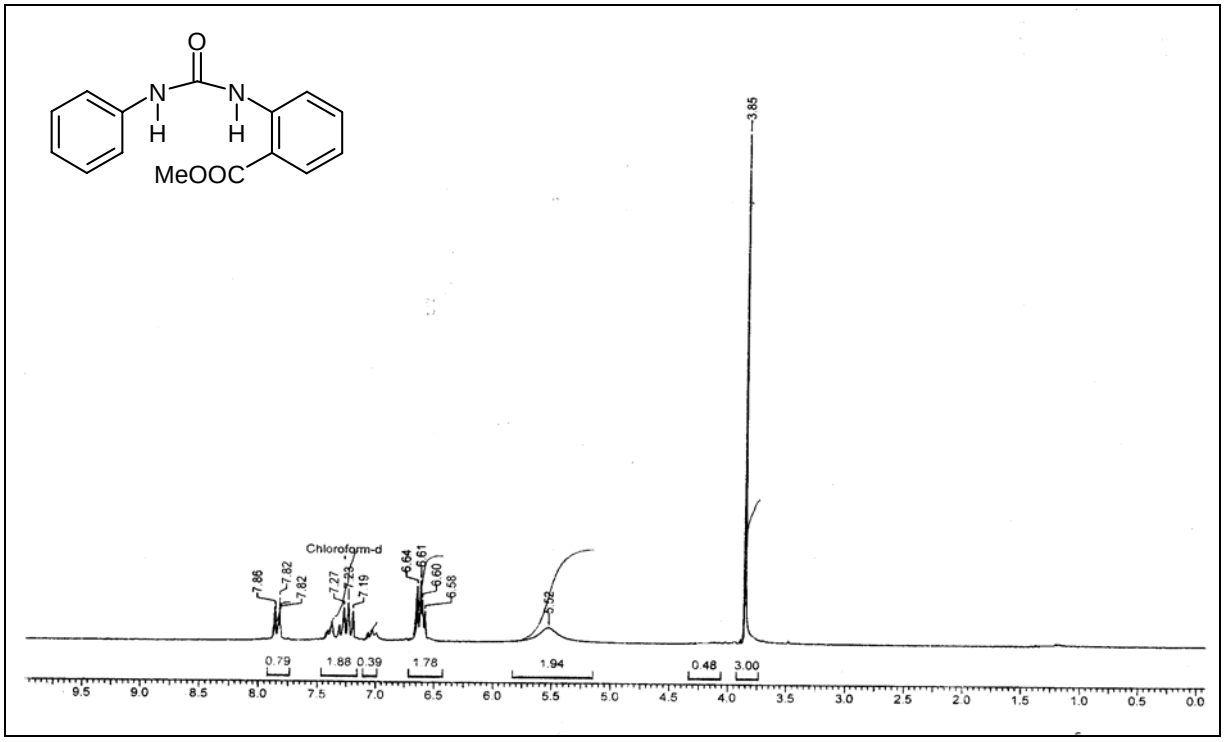
^{1}H NMR spectrum of Compound 150 c ($CDCl_3$+CCl_4, 200 MHz)



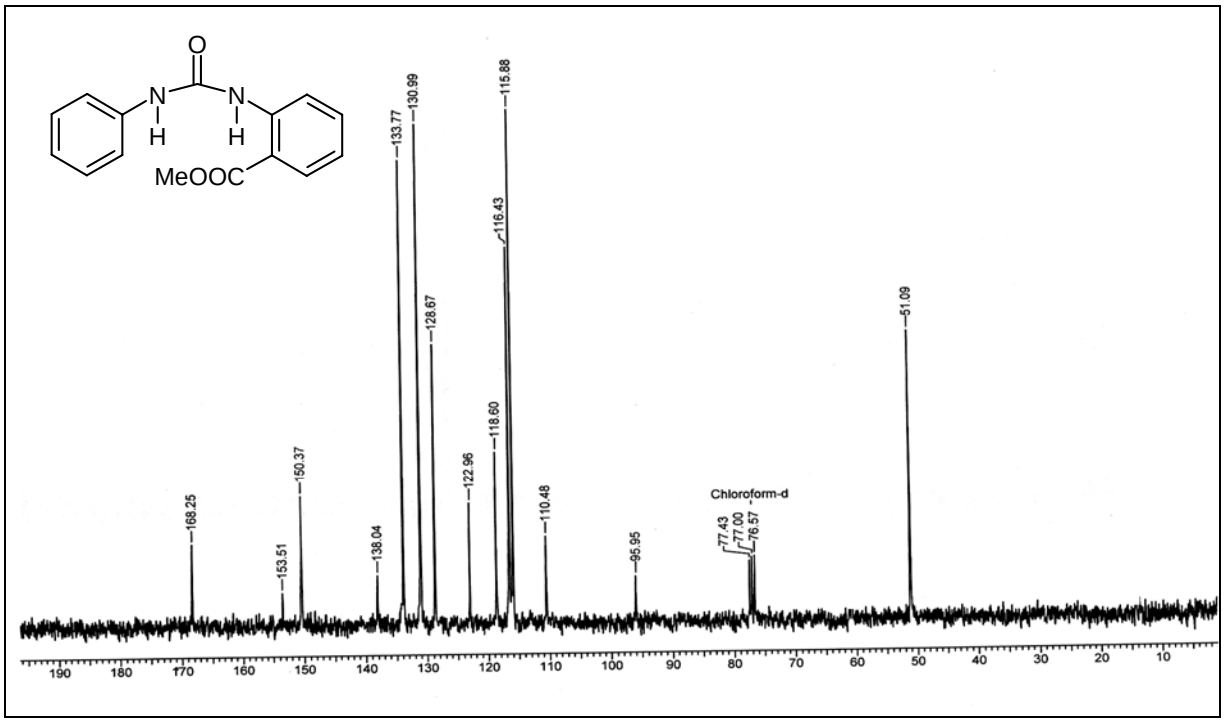
^{1}H NMR Spectrum of Compound 150 d ($CDCl_3$+CCl_4, 200 MHz)



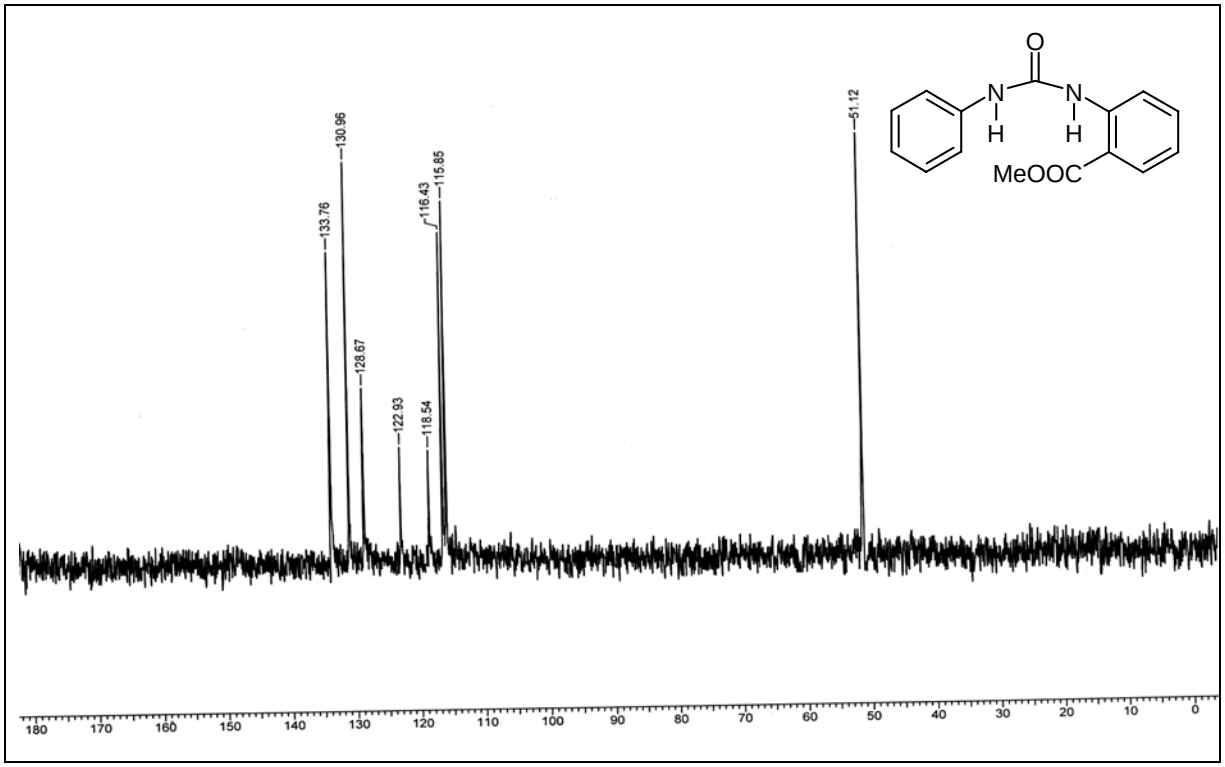
^{1}H NMR spectrum of Compound 152 a ($CDCl_3$+CCl_4, 200 MHz)



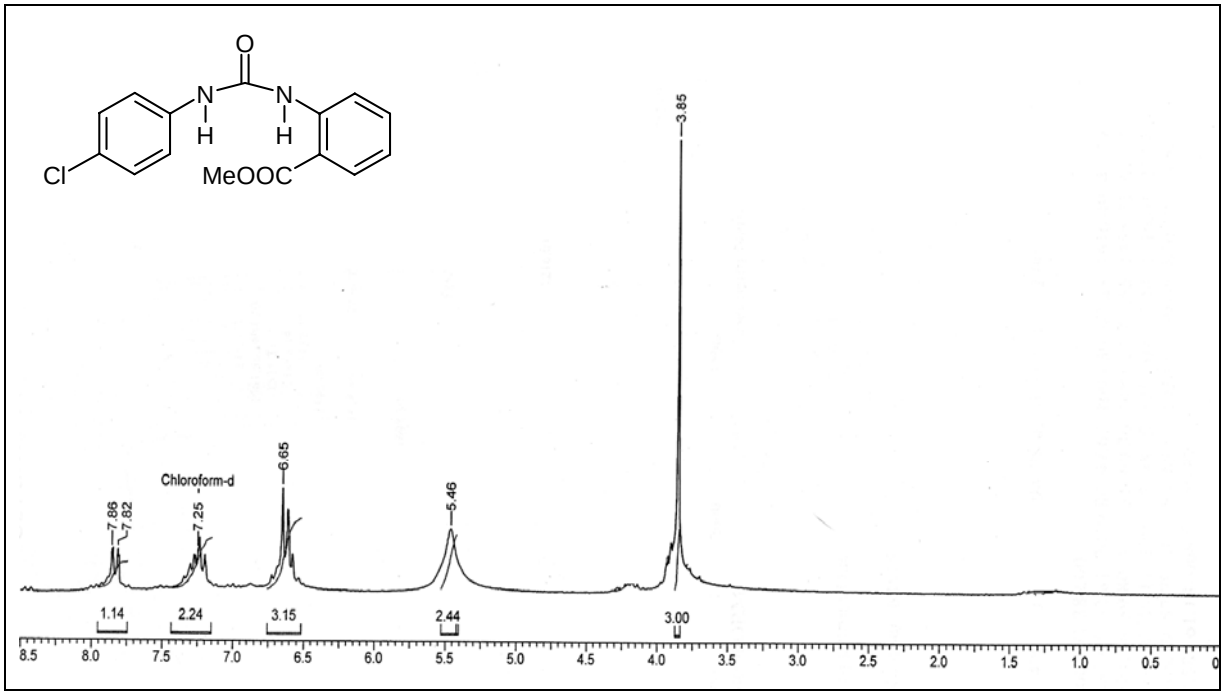
^{13}C NMR Spectrum of Compound 152 a ($CDCl_3$+CCl_4, 50 MHz)



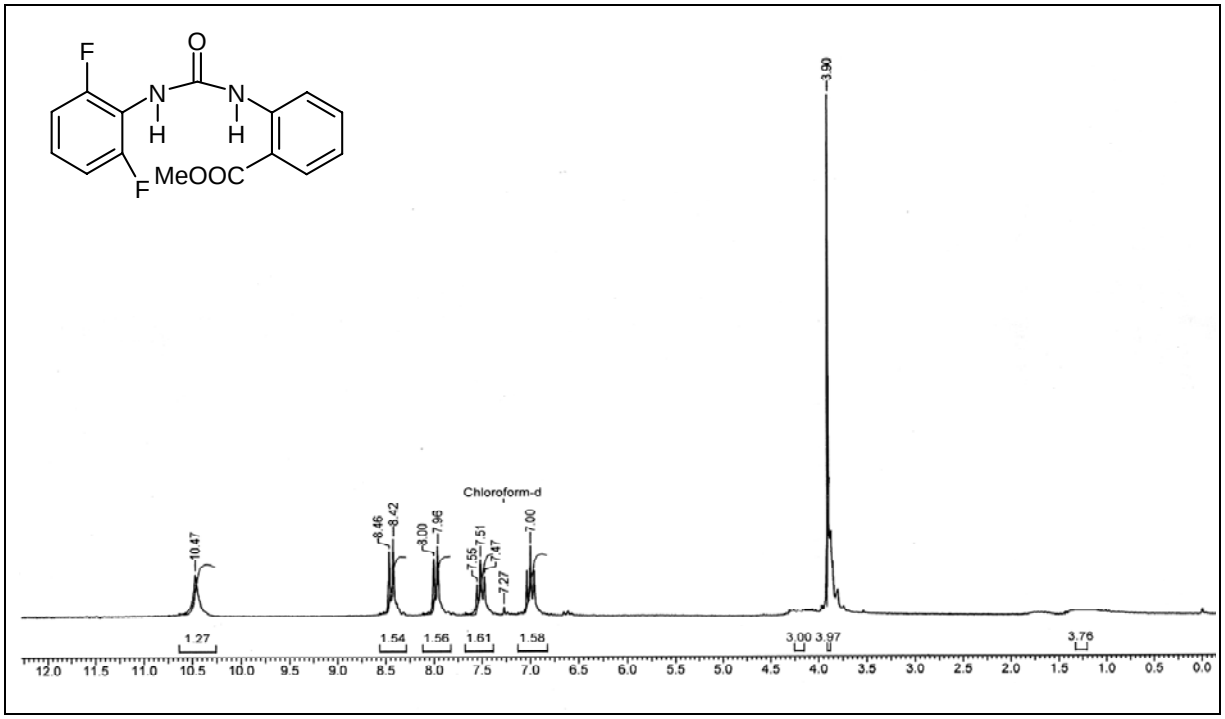
DEPT spectrum of Compound 152 a ($CDCl_3$+CCl_4, 50 MHz)



^{1}H NMR Spectrum of Compound 152 c ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR spectrum of Compound 152 d ($CDCl_3$+CCl_4, 200 MHz)



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LIST OF PUBLICATIONS:

1. Synthesis and evaluation of 4/5-hydroxy-2,3-diaryl (substituted)-cyclopent-2-en-1-ones as cis-restricted analogues of combretastatin A-4 as novel anticancer agents

   M. K. Gurjar; R. D. Wakharkar; A. T. Singh; M. Jaggi; H. B. Borate; P. D. Shinde; R. Verma; P. Rajendran; S. Dutta; G. Singh; V. K. Sanna; M. K. Singh; S. K. Srivastava; V. A. Mahajan; **V. H. Jadhav**; K. Dutta; K. Krishnan; A. Chaudhary; S. K. Agarwal; R. Mukherjee; A. C. Burman *Journal of Medicinal Chemistry.* 1138, **2007**, 184-189.

2. Enantiomeric separation of novel anticancer agent 5-hydroxy-3-(4- methoxyphenyl)-2-(3,4,5,-trimethoxyphenyl)- cyclopent-2-en-1-one

   P. D. Shinde; **V. H. Jadhav**; H. B. Borate; S. R. Bhide; K. B. Sonawane; R.D.Wakharkar *Journal of Chromatography A.* 1138, **2007**, 184-189.

3. Efficient *N*-Arylation of amine catalyzed by Cu-Fe-hydrotalcit

   V. H. Jadhav; D. K. Dumbre; V. B. Phapale; H. B. Borate; R. D. Wakharkar *Cat. Commun.* 8 (1), **2007**, 65-68.

4. A simple method for deprotection of tert-butyldimethylsilsy ethers by using stannous chloride under microwave irradiation

   V. H. Jadhav; H. B. Borate; R. D. Wakharkar *Ind. J. Chem.* (section B) 45 (1), **2006**, 322-324.

5. Microwave promoted solvent-free one-pot synthesis of N, N'-disubstituted urea derivatives

   V. H. Jadhav; S. S. Deshpande; H. B. Borate; R. D. Wakharkar *Journal of Chem. Res.* 7, **2005**, 454-456.

6. Solvent free selective silylation of alcohols, phenols and naphthols with HMDS catalyzed by H-β zeolite

   V. H. Tillu; **V. H. Jadhav**; H. B. Borate; R. D. Wakharkar *Arkivoc* 14, **2004**, 110-117.

PATENTS:

1. A process for the preparation of 2,3-diaryl-5-(*tert*-butyldimethylsilyloxy)cyclopent-2-en-1-one.
   M. K. Gurjar, R. D. Wakharkar, H. B. Borate, P. D. Shinde, V. A. Mahajan, **V. H. Jadhav**, A. M. Wagh.
   Ind. Patent Appl. No. NCL-76-2003 (**2003**).
2. A process for the preparation of 2-aryl-4-hydroxy-cyclopent-2-en-1-one.
   M. K. Gurjar, R. D. Wakharkar, H. B. Borate, P. D. Shinde, V. A. Mahajan, **V. H. Jadhav**, A. M. Wagh.
   Ind. Patent Appl. No. NF 254-2002 (**2002**).
3. A process for the preparation of 2, 3-diaryl-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-en-1-one.
   M. K. Gurjar, R. D. Wakharkar, H. B. Borate, P. D. Shinde, V. A. Mahajan, **V. H. Jadhav**, A. M. Wagh.
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4. A process for the preparation of 5-methylene-benzyl(substituted)-2-(5H)-furanone.
   M. K. Gurjar, R. D. Wakharkar, H. B. Borate, P. D. Shinde, V. A. Mahajan, **V. H. Jadhav**, A. M. Wagh.
   Ind. Patent Appl. No. NF 257-2002 (**2002**).

POSTER PRESENTED:

1. Synthesi of ± Terrin.
   P. D. Shinde, **V. H. Jadhav**, H. B. Borate, R. D. Wakharkar.
   Poster presented in sixth CRSI National symposium in Chemistry, I. I. T. Kanpur, 3-6 February **2004**.
2. Design and synthesis of new chemical entities as anticancer agents derived from arylidene tetralones.
   V. H. Jadhav, D. K. Dumbre, H. B. Borate, R. D. Wakharkar, S. Sarkar, D. Sarkar.
   Poster presented in ACS symposium at National Chemical Laboratory, Pune in January **2006**.