“Target cum Flexibility": Towards the Synthesis of Spirocyclic Nucleosides, Carbapenems and Tri-/Tetracyclic Tetrahydroisoquinoline Alkaloids

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BY

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(Research Guide)

ORGANIC CHEMISTRY DIVISION
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PUNE–411008

DECEMBER–2013

DEDICATED TO

MY PARENTS

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

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CERTIFICATE

The research work presented in thesis entitled **"Target cum Flexibility": Towards the Synthesis of Spirocyclic Nucleosides, Carbapenems and Tri-/Tetracyclic Tetrahydroisoquinoline Alkaloids."** has been carried out under my supervision and is a bonafide work of **Mr. Mangesh Pandurang Dushing**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008
December – 2013

Dr. C. V. Ramana
(Research Guide)

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Mangesh

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
Bu	–	Butyl
Cat.	–	Catalytic/catalyst
DCM	–	Dichloromethane
Conc.	–	Concentrated
DMP	–	2,2'-Dimethoxypropane
DMF	–	*N*,*N*-Dimethylformamide
DMAP	–	*N*,*N'*-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
Liq.	–	Liquid
m-CPBA	–	3-Chloroperbenzoic acid
Me	–	Methyl
MIC	–	Minimum Inhibitory Concentration
NMR	–	Nuclear Magnetic Resonance
Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
i-PrOH	–	*iso*-Propanol
rt	–	Room temperature
Sat.	–	Saturated
TBAF	–	Tetra-*n*-butylammonium fluoride
THF	–	Tetrahydrofuran
TMSOTf		Timethylsilyl trifluromethanesulfonate

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, and DRX–125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

ABSTRACT

Research Student	:	Mangesh Pandurang Dushing
Research Guide	:	Dr. C. V. Ramana
Title of Thesis	:	**"Target *cum* Flexibility": Towards the Synthesis of Spirocyclic Nucleosides, Carbapenems, and Tri-/Tetracyclic Tetrahydroisoquinoline Alkaloids.**
Registration Number	:	PGS/PhD/9004/Date: 27/08/2011
Date of Registration	:	10.11.2009
Place of Work	:	Division of Organic chemistry National Chemical Laboratory, Pune, INDIA

Abstract

The thesis entitled **"Target *cum* Flexibility": Towards the Synthesis of Spirocyclic Nucleosides, Carbapenems, and Tri-/Tetracyclic Tetrahydroisoquinoline Alkaloids** is divided into four chapters dealing with - General Introduction (Chapter 1), the synthesis of *C*(3)-spirocyclic nucleosides (Chapter 2), synthesis of trinems (Chapter 3) and the synthesis of some tri-/tetracyclic tetrahydroisoquinoline alkaloids (Chapter 4).

Chapter I: Small Molecule Libraries Synthesis: In this chapter, various approaches reported for the synthesis of focused small molecule libraries synthesis such as – i. Diversity Oriented Synthesis (DOS), Biology Oriented Synthesis (Bios), Diverted Total Synthesis (DTS) and Function Oriented Synthesis (FOS) etc have been described. In the second part, a concept of Target cum Flexibility, which is funded upon the DOS and BIOS, has been provided, along with the some recent developments on alkyne cyclotrimeriation and the catalysts employed.

Chapter-II: Synthesis of *C*(3)-Spirocyclic Nucleosides

2.1 Introduction:

Access to collections of distinctive small molecules is an important aspect in the realm of chemical genetics and for identifying new therapeutic candidates. However, flexibility in modulating the structural characteristics is the cornerstone of a successful hit to lead exploration. A strategy that integrates the conceptual advantages of DOS and the

manipulation of chemical functionality at an advanced stage in a target oriented synthesis could be a valuable tool in new drug discovery programs. This provision of manipulation/substrate flexibility at the final/penultimate steps in the forward synthesis should address the chemical functionality modulation. The objective of this thesis is to develop such strategies for the synthesis the small molecules collections. The selection of the targets was inspired either by the natural products or the new chemical entities.

2.2 Result and discussion:

Modification of the sugar back bone in nucleosides is an important therapeutic approach for developing small molecules that control genetic disorders or infections. There are several approaches for the modification of nucleosides. Spiroannulation on the sugar backbone is one of the recent approaches for the modified nucleosides. Considering the prevalence of the dihydroisobenzofuran structural unit in many of the naturally occurring substances and drug candidates, our intention has been to spiro-annulate a dihydroisobenzofuran unit on the nucleoside templates. The intended strategy is described in Figure 1.

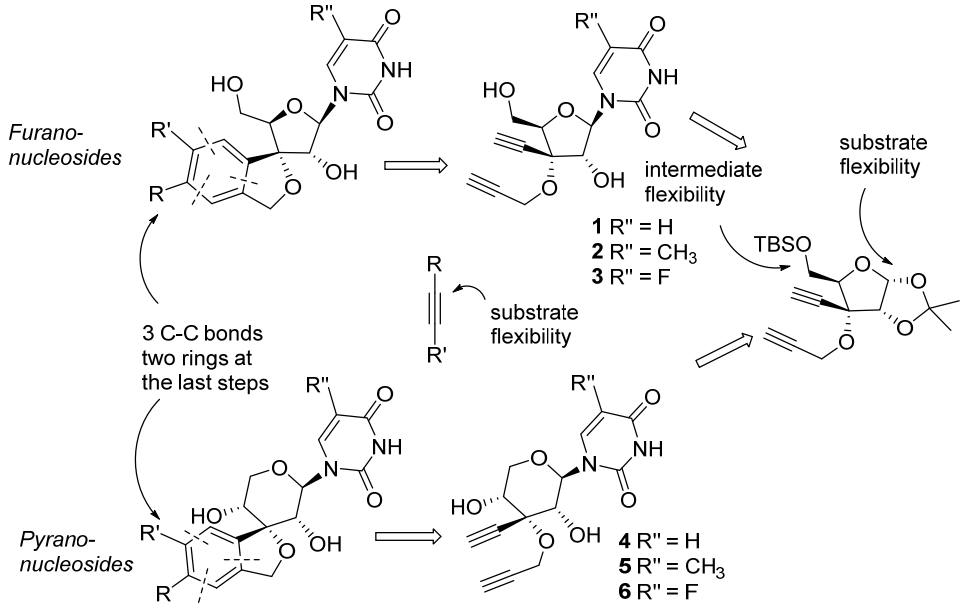


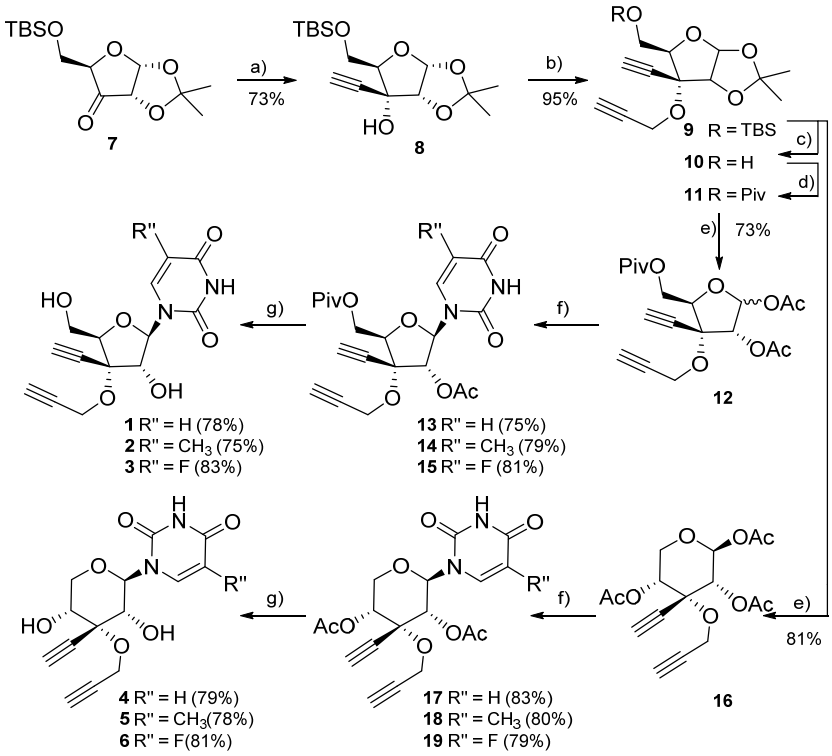
Figure 1: The key [2+2+2] cyclotrimerization transform addressing the target complexity cum substrate flexibilityat the penultimate step

The key retrosynthetic disconnections for the synthesis of *C*(3)-spiroannulated furano-/pyrano nuclesodies project a [2+2+2] co-cyclotrimerization for the isobenzofuran ring construction. The corresponding key diynes could be derived from a common intermediate **7** through selective trapping of the *C*(1)-aldehyde either as a furanoside or as a pyranoside by protecting group manipulations at the *C*(5)-OH.

2.3 Synthesis of key diyens 1–6:

The synthesis of the key diynes **1**–**6** started with the addition of ethynylmagnesium bromide to the ketone **7**. Subsequently, propargylation of 3°-hydroxyl gave the diyne intermediate (Scheme 1) **9**. Compound **9** was converted to the corresponding pivolate derivative **11** by deprotection of the TBS ether using TBAF in THF and reprotection of the resulting alcohol **10** using pivoloyl chloride and Et_3N. Selective acetonide hydrolysis of compound **11** followed by acetylation (Ac_2O/Et_3N) gave a 1:1 anomeric mixture of diacetates **12**. The glycosidation of the anomeric mixture **12** was carried out under modified Vorbrüggen conditions employing uracil, thymine and 5-fluorouracil as glycosylacceptors to afford the protected nucleosides **13**–**15**, respectively.

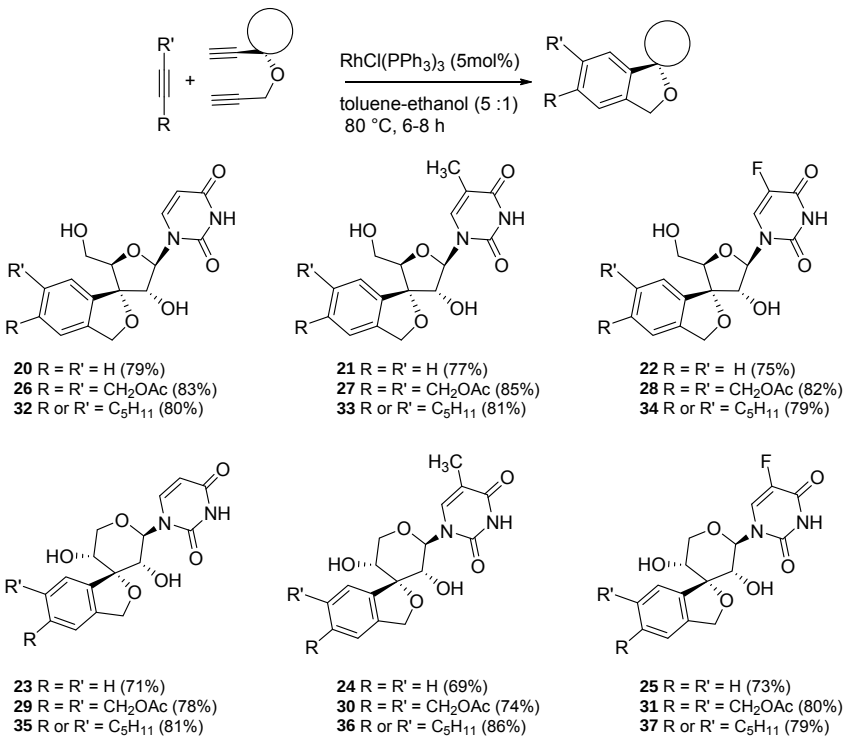
Subjecting **13**–**15** to Zemplen's deacetylation afforded the furanose nucleosides **1**–**3**, with the key diyne unit for the cycloisomerization reactions. Synthesis of the pyranosyl nucleoside precursors **4**–**6** started with the global deprotection of **9** using acetic acid followed by peracetylation, employing acetic anhydride and Et_3N in dichloromethane to afford a exclusively pyranoside **16**. Treating the compound **16** with uracil, 5-fluorouracil and thymine under modified Vorbrüggen conditions followed by deacetylation of the compounds **17**–**19** gave the pyranose nucleosides **4**–**6**.



Scheme 1: Reagents and conditions: a) Mg, nBuCl, THF, acetylene, 0 °C; b) NaH, propargyl bromide, THF, 0 °C - rt, 8 h; c) TBAF. THF, rt, 8 h; d) PivCl, DMAP, CH_2Cl_2, rt, 6 h; e) i. 60% AcOH, reflux, 2 h, ii. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; f) uracil/5-flurouracil/thymine N,O-bis(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h; g) NaOMe, MeOH, rt, 20 min.

2.4 Syntheis of Spironucleosides:

With the fully elaborated diyne frameworks in place, the cyclotrimerization of **1**–**6** with symmetric and unsymmetric alkynes has been attempted. The trimerization reactions with the acetylene proceeded effectively with Wilkinson's catalyst at 80 °C in a sealed tube to afford the corresponding products **20**–**25** respectively from **1**–**6**. The diacetate of 2-butyne-1,4-diol, *bis*-(trimethylsilyl)acetylene and dimethyl acetylenedicarboxylate were explored as the representative symmetric disubstituted alkynes for the trimerization reactions. Amongst the three, the trimerization of **1**–**6** with the diacetate of 2-butyne-1,4-diol gave the corresponding isobenzofurannulated nucleosides **26**–**31** in good yields.



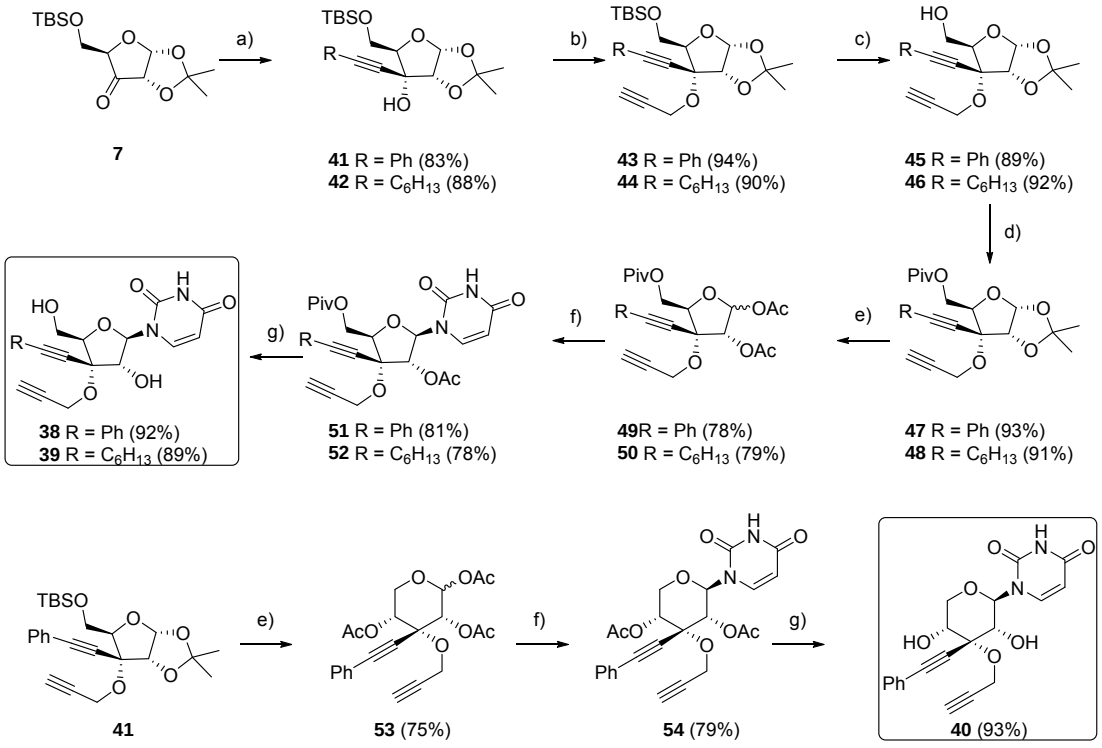
Scheme 2: Representative C(3)-spiroisobenzofurannulated nucleosides

Formation of either self dimerization products or a complex mixture was noticed with the other two alkynes. The cyclotrimerization reactions of **1**–**6** with the terminal alkyne 1-heptyne, in general are clean and the yields are good. However, the reaction gave inseparable regiomeric mixtures. A similar lack of regioselectivity was observed when phenyl acetylene and *N*-propargyl pthalimide were employed as the substrates in the cyclotrimerization of **1** and **4**. Changing to the catalysts Cp*RuCl(cod) and $[Rh(cod)_2]BF_4$/(*R*)-BINAP for cyclotrimerization with the terminal alkynes did not result in any improvement in the regioselectivity.

The regioselectivity is the critical limitation with the [2+2+2]-cyclotrimerization reactions, which has been addressed to some extent by the placement of a substituent on one of the alkynes of the diyne unit. A systematic exploration of this aspect, along with the manipulation of OH-protecting groups has been undertaken. Synthesis of the diynes **38** – **40** (figure 2) has been planned in this context.

The synthesis of the diynes **38** – **40** started with the reaction of ketone **7** with alkynylmagnesium chloride (prepared by Grignard exchange between the corresponding alkyne and n-butylmagnesium chloride) followed by propargylation of 3°-hydroxyl in the

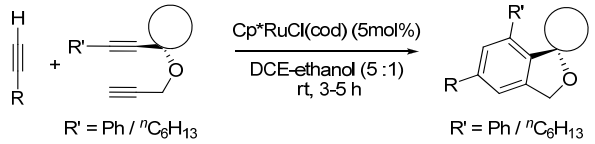
resulting alkynols **41, 42** to obtain the diyne intermediates **43** and **44** respectively. The compounds **43** and **44** are then converted to the corresponding pivolate derivatives **47** and **48** followed by a sequence of TBS deprotection and pivaloylation reactions. Subsequent acetonide hydrolysis of **45** and **46**, acetylation (Ac_2O/Et_3N) and the *N*-glycosidation with uracil, and final saponification under Zemplen's conditions yielded the furanose nucleosides **38** and **39**. Further, deprotection of **43** using acetic acid followed by peracetylation, *N*-glycosidation with uracil and deacetylation gave the pyranosyl nucleoside **40.**



Scheme 3: Reagents and Conditions: a) n-BuMgCl, phenyl acetylene/1-octyne, 0 °C 1 h; b) NaH, THF, 0 °C - rt, 3 h; c) TBAF, THF, rt, 8 h; d) PivCl, DMAP, CH_2Cl_2, 0 °C - rt, 6 h; e) i. 60% AcOH, reflux, 2 h; ii. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; f) uracil/5-flurouracil/thymine *N,O-bis*(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h; g) NaOMe, MeOH, rt, 20 min.

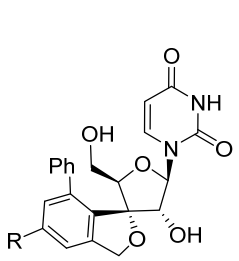
2.5 [2+2+2]-cyclotrimerisation of diynes "38 – 40":

The furanoside diynes **38** − **39** and pyranoside diyne **40** were subjected to the cyclotrimerisation reaction in the presence of catalyst Cp*RuCl(cod) and a mixture DCE-ethanol (5:1) solvents system at room temperature.

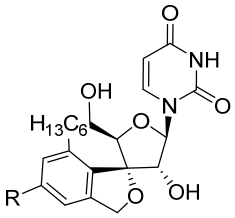


Scheme 4: Cyclotrimarization of diynes **38 – 40**

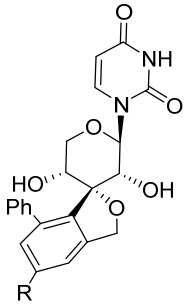
Table 2 describes the scope of the cyclotrimerization reaction with the diynes **38**–**40**. A variety of terminal alkynes have been employed for cyclotrimerization with the diyne **38**. The regioselectivity was excellent and various functional groups were found to be tolerant under these conditions. A similar regioselectivity was observed with the furanose diyne **39** too. However, for the case of the pyranose diyne **40**, its cyclotrimerization with phenyl acetylene gave a 7:1 regiomeric mixture, with the 1,3-product being the major one. On the other hand, in the case of other three alkynes employed, the 1,3-products were seen to be formed exclusively. The amine group present in the products **60** and the chloro functional group present in the products and **56**, **64**, and **68** provide a suitable handle for further diversification.



55 R = -Ph (85%)
56 R = -^{n}C$_6$H$_{13}$ (78%)
57 R = -^{n}C$_{21}$H$_{43}$ (87%)
58 R = -(CH$_2$)$_3$Cl (83%)
59 R = -CH$_2$NPht (80%)
60 R = *m*-(Ar-NH$_2$) (85%)



61 R = -Ph (78%)
62 R = -^{n}C$_6$H$_{13}$ (74%)
63 R = -^{n}C$_{21}$H$_{43}$ (73%)
64 R = -(CH$_2$)$_3$Cl (78%)



65 R = -Ph (83%, dr = 7:1)
66 R = -^{n}C$_6$H$_{13}$ (77%)
67 R = -^{n}C$_{21}$H$_{43}$ (81%)
68 R = -(CH$_2$)$_3$Cl (79%)

Table 2: Scope of the cyclotrimerization reaction of diynes **38 − 40**

2.6 Conclusion:

In conclusion, a simple protocol comprising the [2+2+2]-cyclotrimerisation of the fully deprotected nucleoside diynes as the last step of the process has been developed for a rapid access to *C*(3′)-dihydroisobenzofuran spiroannulated nucleosides. During the synthesis of the penultimate furanose-nucleoside diynes, we have shown that, proceeding with ribofuranose intermediates having a pivaloyl protection at *C*(5)-OH is a reliable approach to avoiding unwanted pyranose formation during the hydrolysis and peracetylation.

Chapter-III: Flexible Synthesis of Trinems.

3.1 Introduction:

Tricyclic β-lactam antibiotics or trinems are a new class of synthetic antibacterial agents having good resistance to β-lactamase and dehydropeptidase. Due to their biological and medicinal importance, synthesis of trinems has lately grabbed the attention of the scientific community. The challenges involved in the synthesis of tricyclic β-lactam antibiotics and the need for new methods has propelled us to find effective routes in this direction.

3.2 Results and discussions:

As a continuation of our Target cum Flexibility approach for the synthesis of focused small molecule libraries, the idea of implementing the cyclotrimerization reaction for the construction of tricyclic carbapenem framework was conceived.

Visualizing the possibility of synthesizing the 4/5/6 tricyclic framework similar to 6-(1-hydroxyethyl)cyclonocardicins **A** reported by Christensen *et al*. from Merck which show activity against a wide range of pathogens including both Gram positive (*S. aureus, Strep. Pyogenes, B. subtilis*) and Gram negative (*E. coli, Pseudomonas, Proteus morgani* etc.), we sketched our strategy as shown in figure 3.

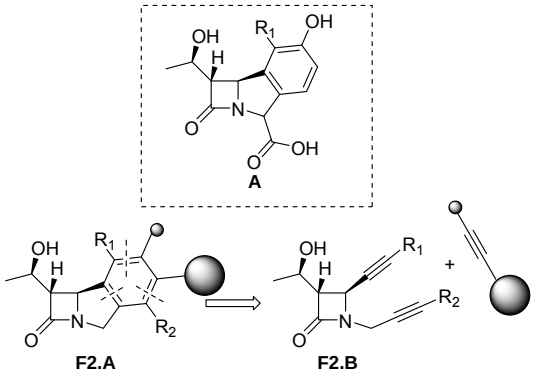


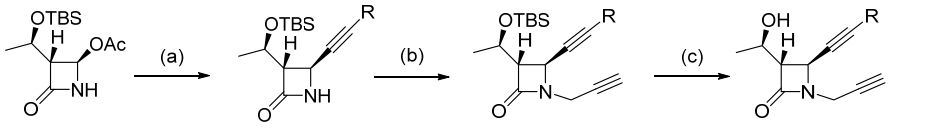
Figure 3

Keeping the substrate flexibility at the penultimate stages, the central trinem skeleton **F2.A** has been disconnected by employing the trimerization transform leading to the intermediates **F2.B**. Since the trimerization will be the final reaction, the fact that various alkynes are commercially available and also easy to synthesize, indicates that this

approach will lead to the synthesis of trinems library rapidly. Considering the regioselectivity issues with a diyne having both the terminal alkynes, we have directly selected the diynes **69** and **70,** having one internal alkyne, as the suitable penultimate substrates in this context.

3.3 Synthesis if diyens 69 and 70:

The synthesis of diynes **69** and **70** started with the Grignard reaction of 2-azitidinone **71** to access the alkyne addition products **72–73** in good yields. The N-propargylation of compound **72** and **73** with propargyl bromide under phase-transfer conditions gave the dialkyne products **74–75**. Finally, the deprotection of OTBS group gave required hydroxy dialkyne product **69** and **70**.



71

72 R = Ph (89%)
73 R = n-C_6H_{13} (83%)

74 R = Ph (77%)
75 R = n-C_6H_{13} (75%)

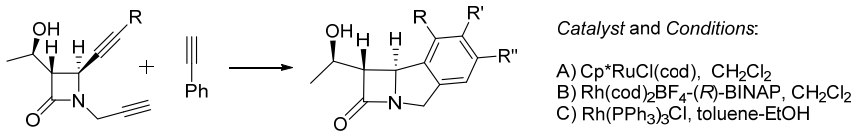
69 R = Ph (89%)
70 R = n-C_6H_{13} (78%)

Scheme 5: *Reagents and conditions*: (a) n-BuMgCl, R(Phenylacetylene/1-octyne), THF,0 °C; (b) propargyl bromide, KOH, Bu_4NI, THF, 0 °C; (c)TBAF, THF.

3.4 Cyclotrimerization of diynes 69 and 70:

Having synthesized the key diynes **69** and **70**, our next objective was to explore their cyclotrimerization with terminal alkynes. As our initial attempts using Wilkinson catalyst were unsuccessful, various catalysts reported for the alkyne cyclotrimerization have been explored in this context (See Table 3) which revealed that depending upon the alkyne substrate employed either $[Rh(cod)_2]BF_4$/(*R*)-BINAP (**A**) or Cp*RuCl(COD) (**B**) can be chosen. Table 4 reveals the scope of the trimerization reaction of diynes **69** and **70** with various terminal and internal alkynes using either **A** or **B** catalysts. In all the cases, the regioselectivity was excellent with the diyne **69** trimerizations. In case of diyne **70**, along with the anticipated 1,3-regiomer,the 1,2-isomer was also obtained as a minor product. A variety of terminal alkynes have been employed for the cyclotrimerization with diyne **70**. Various functional groups are tolerant under the reaction conditions. The

products **85** and **89** obtained from the cyclotrimerization of diyne **69** with 5-chloropent-1-yne and 3-ethynylaniline are quite attractive, as these products provide a suitable functional group handle for further diversification with simple chemical maneuvering. In case of sterically crowded alkynes like diphenyl acetylene and bis-(trimethylsilyl)-acetylene we observed the dimerised products of diyne.



69 R = Ph
70 R = C_6H_{13}

76 (R = R" = Ph, R' = H)
78 (R= $^nC_6H_{13}$, R' = H, R" = Ph)

Entry	Diyne	R =	Method	Time/temp	Product(s)	a:b	Yield
1	**69**	Ph	A	rt/4 h	**76**	--	81%
2	**69**	Ph	B	rt/7 h	**76**	--	80%
3	**69**	Ph	C	80 °C/24 h	**76**	--	No reaction
4	**70**	*n*-C_6H_{13}	A	rt/4 h	**77**	--	--
5	**70**	*n*-C_6H_{13}	B	rt/7 h	**77**	--	78%
6	**70**	*n*-C_6H_{13}	C	80 °C/18 h	**77**	--	No reaction

Table 3

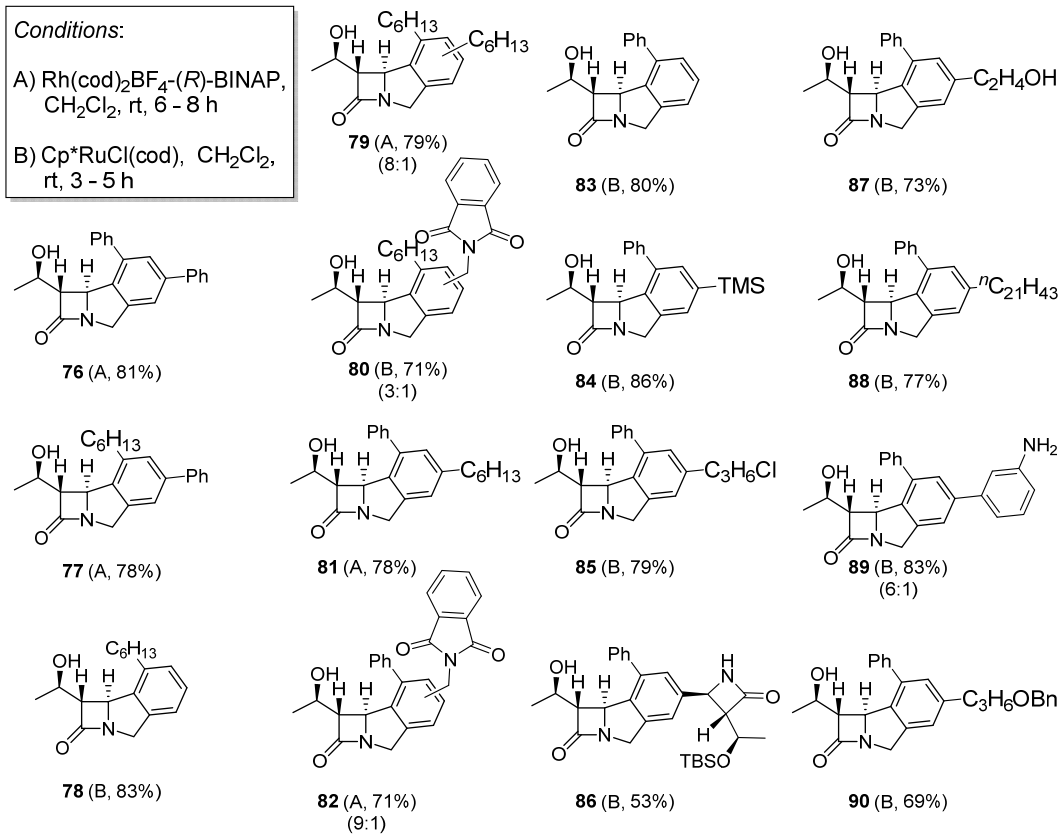


Table 4

3.5 Conclusion:

In conclusion, a [2+2+2] alkyne cyclotrimerization reaction was employed successfully to construct the central 4/5/6 tricyclic framework of 6-(1-hydroxyethyl)-cyclonocardicin trinems. Introduction of different substituents to the structure was achieved easily by simply employing a suitable alkyne at the final event of bicyclo-annulation, and thus a focussed library of trinem like small molecules has been constructed easily.

Chapter-IV: [2+2+2]-Cyclotrimerisation approach towards the synthesis of tri-/tetracyclic tetrahydroisoquinoline alkaloids.

4.1 Introduction:

Indole and tetrahydroisoquinoline skeletons are the commonly encountered sub-structural units present in a variety of alkaloids and pharmaceutical drugs. The alkaloids having both these units integrated, such as indolinoisoquinoline are also present in natural products such as Cryptausoline. In continuation of our program on the synthesis of focused small molecule libraries, the indolinoisoquinoline skeleton has attracted our attention as there are relatively few reports on the synthesis of indolo[1,2-b]isoquinoline framework and also on their biological activity. Considering this, we have taken up this skeleton as a target for applying the cycloisomerization reaction and focused small molecule library synthesis. As shown in figure 4, the intended strategy comprises overall of three steps and projects two sequential catalytic transformations – namely the Friedel-Craft type C2 alkylation of C3-substituted indole having a pendant alkyne on the ring nitrogen and then the cyclotrimerization. The synthesis of propargyl alcohols is a straightforward proposition from the Grignard reaction of the arylaldehydes. The diynes **91** and **92** have been selected as the model substrates in this context.

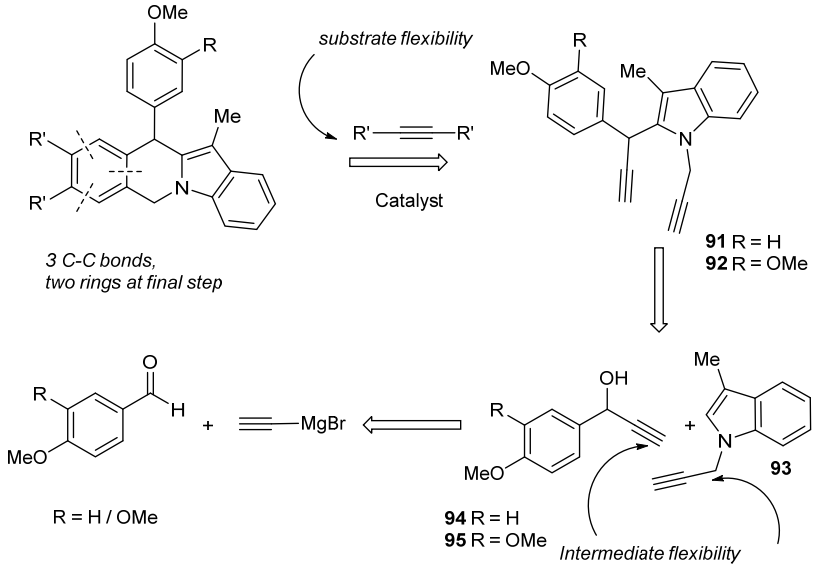
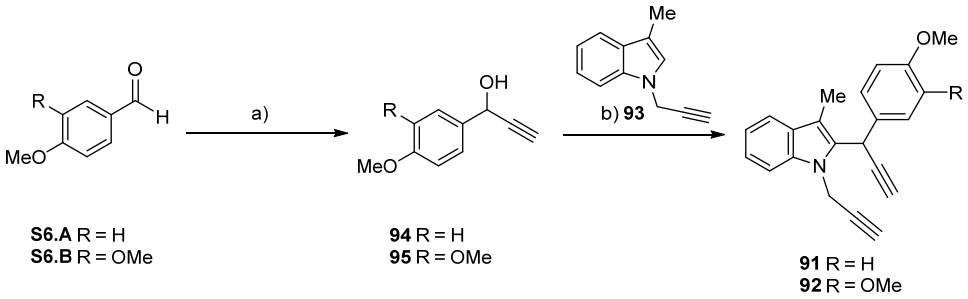


Figure 4: Retrosynthetic plan

4.2 Synthesis of diyne 91 and 92:

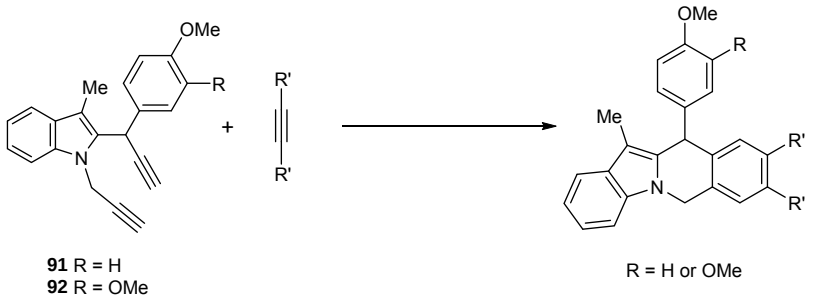
The synthesis of diynes **91** and **92** started with the addition of acetylene Grignard (prepared by Grignard exchange between the corresponding alkyne and n-butylmagnesium chloride) to aldehydes **S6.A** and **S6.B** to afford the alkynols **94** and **95**. The alkynols **94** and **95** were then used as the substrates for the Friedel-Craft alkylation of N-propargyl-3-methylindol using *p*-TSA as the catalyst and CH_2Cl_2 as the solvent. The alkylation reactions proceeded smoothly and provided the diynes products **91** and **92** in very good yields.



Scheme 6: *Reagents and conditions*: a) n-BuMgCl, acetylene, THF, 0 °C; b) **93**, PTSA, CH_2Cl_2, rt, 15 min.

4.3 Cyclotrimerization of diynes 91 and 92:

Having both the requisite diynes in hand the stage was set for their trimerization. The optimization reactions have been carried out by employing acetylene as the substrate. Unlike both the previous systems (nucleosides and beta-lactams), in the present case, both the Ru- and Rh-catalysts were found to be ineffective. The $CpCo(CO)_2$ catalyst was



Scheme 7: *Reagents and conditions*: $CpCo(CO)_2$ (20 mol%), 1,4-dioxane, PPh_3, 130 °C, 12h.

found to be the best for this purpose. The optimized conditions involve heating a mixture of diyne and alkyne and 20 mol% catalyst $CpCo(CO)_2$ in 1,4-dioxane in the presence of

TPP (PPh_3) at 130 °C for about 12 h. With propargyl alcohol, the cyclotrimerization of diyne **91** and **92** provided the requisite indolo[1,2-b]isoquinoline in **103** and **104** respectively. Table 4 shows the generality of this reaction with various internal and terminal alkynes.

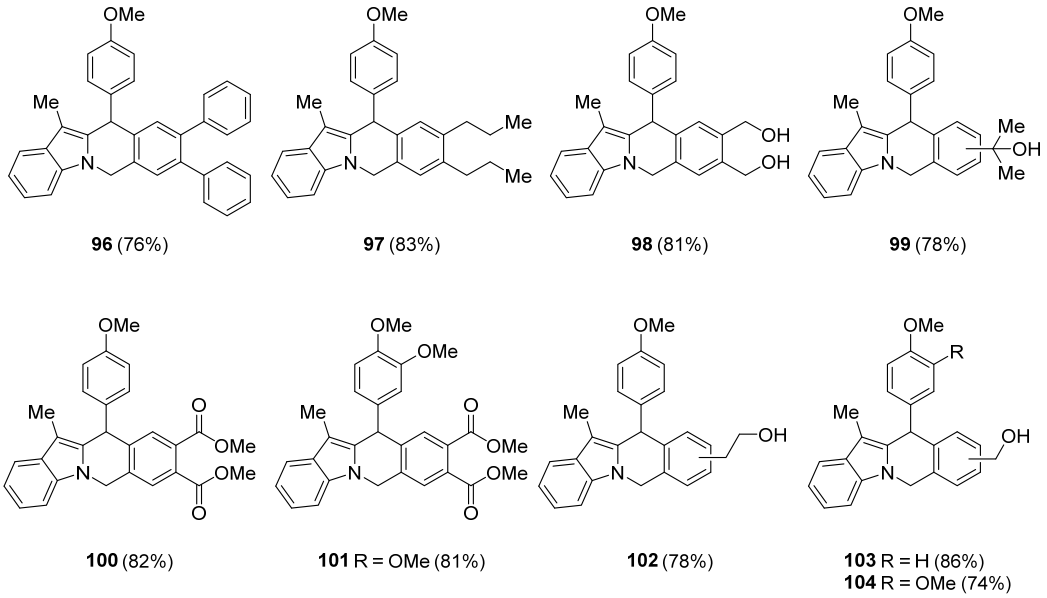


Table 4: Scope of cyclotrimerization on diynes **91** and **92.**

The 2-butyne-1,4-diol, 4-octyne, diphenyl acetylene, dimethyl butyne dicarboxylate, and 2,5-dimethyl-hex-3-yne-2,5-diol, were explored as the representative symmetric disubstituted alkynes for the trimerization reactions, which gave the corresponding tricyclic-tetrahydroisoquinoline alkaloids **96**–**104** in good yields.

4.4 Conclusion:

In conclusion, a [2+2+2]-alkyne cyclotrimerization reaction was employed successfully to construct the indolo[1,2-b]isoquinoline core. The Introduction of different substituents to the structure was achieved easily by simply employing a suitable alkyne at the final event of bicyclo-annulation, and thus allowed the preparation of focused library of tetrahydroisoquinoline alkaloids like small molecules very easily.

CHAPTER I:

Small Molecule library Synthesis

1.1 Introduction

It is indisputable that advances in the central disciplines of chemistry are essential in amalgamating chemistry, biology, material science and medicine to contribute to human progress. Organic synthesis is definitely an indispensable tool to develop the molecules with the properties desired. The continuing evolution of organic synthesis depends heavily on the design/discovery of reactions and the development of concise strategies that would allow the synthesis of natural products of varying complexity. Retrosynthetic analysis gifted the synthetic community with a unified language to foresee/explain the synthetic strategies and was recognized in 1990 by a Nobel Prize given to E.J. Corey. This has greatly contributed to the success of chemical synthesis by providing certain guidelines and principles for dissecting the target molecules that have been identified either from natural sources or from intuitional exercises to deliver either function or properties.

1.2 Part A: Small Molecule library Synthesis

"Total Synthesis" that has been rechristened as "Target Oriented Synthesis (TOS)" continues to be a valuable source for new developments and discoveries. In the words of Robert Woodward, "*in chemistry, one's ideas, however beautiful, logical, elegant, imaginative they may be in their own right, are simply without value unless they are actually applicable to one physical environment we have*". This insightful observation is particularly appropriate when applied to the field of total synthesis in the realm of the present notions: "chemical space & small-molecule probes & chemical genetics". As expressed by Schreiber, the aims of these particular TOS exercises are confined to a precise region of chemical space which is defined by complex natural products known to have a useful function. The combinatorial chemical approach for molecular libraries synthesis, conceptualized in the early 90's of the last century and practiced until recently, has been recognized as a versatile handle to populate the chemical space. However, despite the rapid speed of synthesis, no combinatorial magic bullet has been delivered. Although the reasons for this apparent lack of productivity remain unclear, it has been attributed in part to the

molecular simplicity and to too much similarity within the library. This shifted the field slowly from the numbers game to focused, biologically relevant libraries, admitting the complexity and diversity in nature's small-molecules. Several efforts to identify planning concepts for syntheses of small-molecules, inspired by structural complexity, have been reported recently.[1] These strategies include, among others, diversity oriented synthesis (DOS, Schreiber),[2] biology oriented synthesis (BIOS Waldmann),[3] "molecular editing" or "diverted total synthesis" (DTS, Danishefsky),[4] and "libraries-from-libraries" (Houghten)[5].

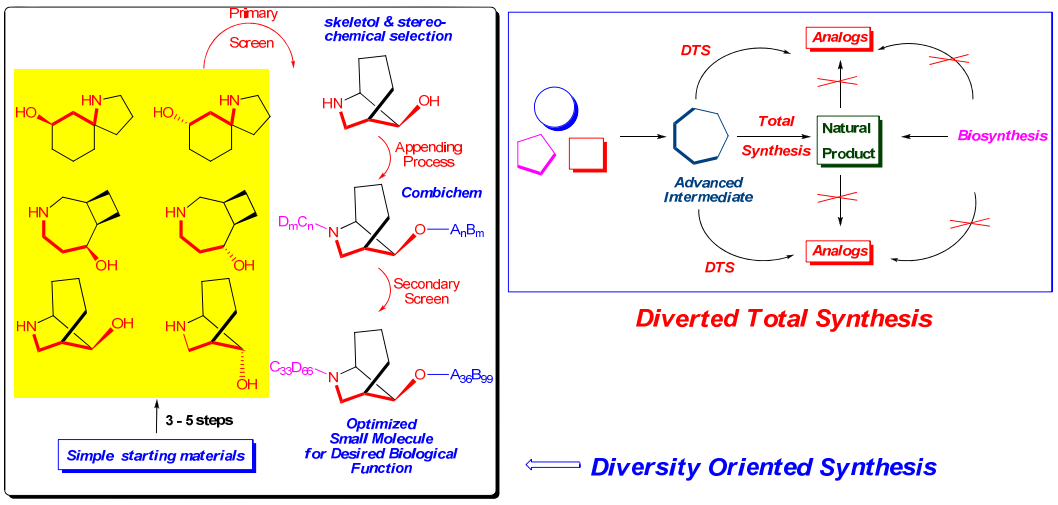


Figure 1. *DOS & DTS Approaches for Small Molecules Library Synthesis*

Function Oriented Design and Synthesis (FOS): Most synthetic studies these days are directed at targets that have interesting structural and, often even more importantly, functional properties, like biological activity or the value as a catalyst, probe, sensor or imaging agent. Phorbol, a structurally fascinating and synthetically daunting challenge, has been one of the most studied molecules of the last century in part because of its exceptional activity (function). By studying the structure of phorbol and molecules with similar function like DAG using computer modeling, our group has been proposed a simpler FOS target. Significantly, the designed FOS target exhibited the function (activity) of phorbol. This represents a powerful strategy to achieve step economy by designing targets that have function of interest but that

could be made in a practical fashion that allows synthetic innovation. Other examples of step economy achieved through function oriented design and synthesis appear below (see Bryostatin and designed bryologs).[6]

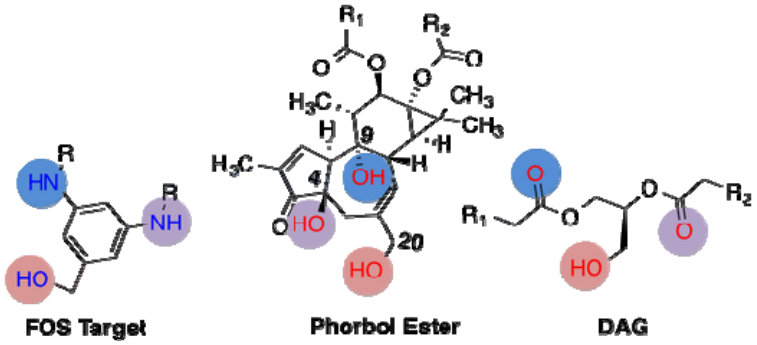


Figure 2: ***Biology-Oriented Synthesis (BIOS): (****From Natural Product to New Therapeutics)*

The structural classification of natural products (SCONP) and its extension to non-natural products and PSSC provide two complementary approaches for the identification of biologically relevant compound classes in the vast chemical space. Either applied alone or in a synergistic fashion, they define the underlying reasoning of an approach we term "biology-oriented synthesis". In BIOS, biological relevance is the prime criterion for the selection of compound classes and scaffolds that inspire the synthesis of compound collections enriched in bioactivity. BIOS-based compound libraries are typically not, and do not have to be large. Their synthesis, however, may require the application of elaborate chemistry methods and demanding multistep sequences, in particular if libraries inspired by natural products have to be synthesized. However, this investment in chemical development is well-balanced by the smaller library size needed. In a sense, BIOS offers relevant compounds, but demands more of chemistry.

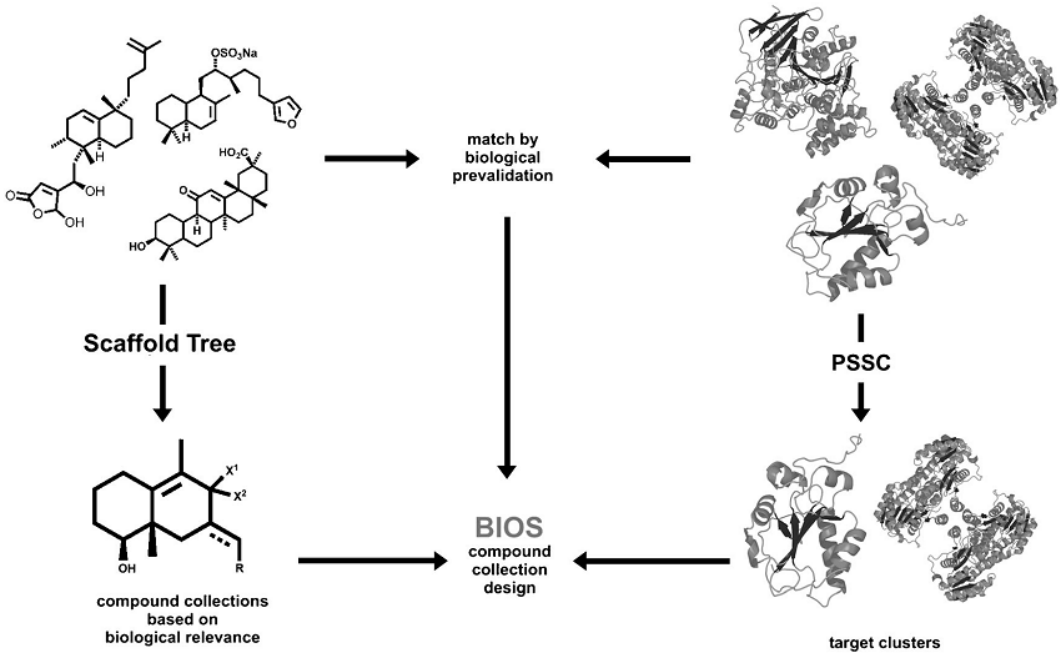


Figure: 3

Exploring the BIOS concept for medicinal chemistry and chemical biology research requires the synthesis of compound collections based on biologically relevant structural frameworks. Natural products represent a major source of bioactive molecules. However, the limited accessibility of these molecules from natural sources and/or by synthetic or semi synthetic methods often limits their further exploration in the biological sciences. This generates the need to synthesize complex natural product like molecules in sufficient amounts and numbers, and calls for the development of new strategies and methods amenable to the formats of compound library synthesis. A synergistic approach that utilizes the power of contemporary organic synthesis and the technology of combinatorial and parallel synthesis is required in order to synthesize focused libraries based on the core frameworks of natural products and other biologically relevant chemo types.

The synthesis of natural product inspired compound collections frequently requires multistep synthesis sequences in order to generate the natural product like structural complexity. This demand often hinders the synthesis of medium-sized or large libraries and calls for the development of complexity generating reactions that

rapidly and efficiently generate complex molecular skeletons based on natural products.

Diversity Oriented synthesis (DOS) and Diverted Total Synthesis (DTS):

There have been certain notable discoveries recently, wherein the natural products have served as templates for drug discoveries *en route* to new chemical entities (NCEs). In such instances, the synthesis of congeners with appropriate molecular editing of SMNPs has been integrated in parallel with the discovery total synthesis programs, thus providing molecular editing *en route* to accessing to the natural product-like small-molecule libraries with improved structural characteristics (recognized as *diverted total synthesis,* DTS). While DTS has high probability in providing potential leads for drug discovery, it is confined to improving the performance level of a natural product inspired drug by structural alterations, which, in general, need a series of long reaction sequences as the skeletal complexity increases.

Diversity oriented synthesis (DOS) conceptualized by Schreiber has certainly provided an impetus to rapidly accessing the complex small-molecule libraries. Though DTS and DOS share the aim of accessing complex structures, however, a fundamental difference is that DTS works in the backward direction to identify critical retrons/synthons for projected total synthesis and molecular editing at advanced stages, whereas DOS moves in the forward direction by identifying a set of complexity generating reactions and selection of substrates in such a way that products of each step will be the reactants for the next reaction. Moreover, the structural complexity, the function of natural products and, more importantly, the biological target have minimal role in the design of DOS libraries.[7]

As described above, though the DTS approach has the high probability to provide potential leads for drug discovery, however, structural alterations need a series of long reaction sequences as the skeletal complexity increases, or in essence, result in *a parallel total synthesis* with limited library size. DOS has an edge over the DTS approach, especially on the size of the library, as it seeks a vigorous substrate design for the follow up complex transforms that employ easily available or

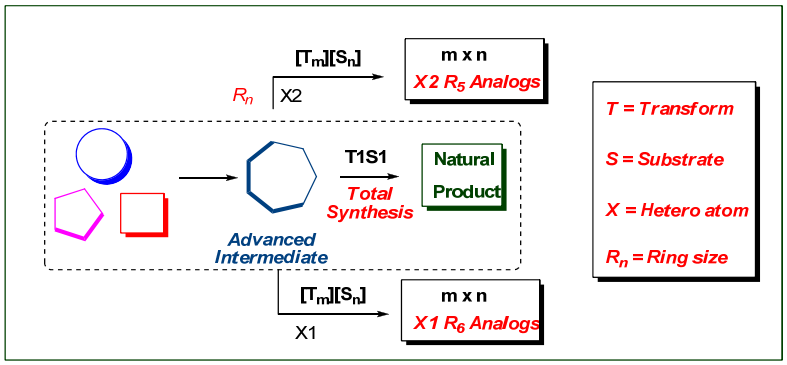


Figure 4. *Transform Oriented Flexible Synthesis*

sometimes even commercial substrates thus providing enormous flexibility at each stage. By combining the themes of DTS & DOS, i.e. parallel total synthesis and the flexibility at the advanced stage, we propose a new approach for high throughput synthesis of Natural Product-like Small-molecules (NPLSM). *The underlying motive of our approach will be the identification of complexity generating transform(s) that should address the critical skeletal construction at an advanced stage and be flexible for employing the simple, inexpensive, easily available materials so as to create natural product-like small-molecule libraries rapidly*. In essence, this approach could be identified as "Target cum Flexibility Oriented Synthesis" (TCFOS).

Synthesis of Focused Small-Molecule Libraries by Target cum Flexibility Oriented Synthesis (TCFOS) Approach

The focus of this thesis work is to develop strategies that aim to build small-molecule libraries which are designed around a target which is of natural or pharmaceutically relevance. The present approach, which we have labeled as the Target cum Flexibility Oriented Synthesis (TCFOS) approach, integrates the flexibility of the Diversity Oriented Synthesis (DOS) approach and the molecular editing of the Diverted Total Synthesis (DTS). A judicious selection of targets inspired by their biological activity, followed by appropriate substrate design and identification of suitable late stage complexity generating transformation(s) that can also address the flexibility to incorporate various physical properties like aqueous

solubility, chemical stability, and cell permeability will be the critical issues of the present approach. Some of the specific synthetic tactics to be employed have their foundation in a couple of efficient synthetic strategies developed recently in our laboratory. One amongst them is the 'alkyne trimerization" for linear and bridged bezannulated tri- and tetracyclic systems. The present focus of this thesis will be the construction of the small molecule libraries focusing mainly on (1) nucleosides (2) β-lactams and (3) indoloisoquinoline alkaloids. These developed small-molecule libraries will be screened for the projected biological activities through the established collaborations. Though the initial emphasis will be on biological targets relevant to diseases like viral infections, cancer, and antibacterial, the present program can also be extended to a number of other biological targets.

Complexity Transforms: Coming to the skeletal construct transforms, apart from the complexity, they should also address the essential requirement, i.e. flexibility, in order to incorporate various physical properties such as aqueous solubility, chemical stability and cell permeability, which may or may not be present in the natural product. This will entail either an intermolecular coupling of two or more functional units forming more than one bond' or 'pair-wise coupling of two functional units in intermolecular fashion followed by inter molecular cyclization' (Figure 3). At least one functional unit should be sufficiently simple and diverse.

Building Blocks: Like DOS, substrate design at various stages is another important exercise in our approach. The pre-qualification for the functional unit present in the penultimate advanced intermediates is its suitability for branching at the next stage with a provision to access substrates for the other skeletal constructs in order to bring in skeletal diversity in the synthesized libraries.

Following are the key steps that form the action plan of the present proposal (as explained, the identification of key skeletal constructs and that of suitable substrates for molecular alterations and also particular natural product targets will be carried out so as to complement each other):

1. targets selection and prioritization,
2. identification of advanced intermediates,
3. retrosynthetic disconnections,
4. execution of identified target synthesis,
5. small-molecule library synthesis and

Target cum Flexibility: Some Recent Examples from Our Group:

A Flexible Approach for Total Synthesis of Bruguierol and Related Small Molecules:

We have already established the feasibility of the alkyne trimerization approach for bridged bicyclic systems by taking bruguierol A as the target for total synthesis.[8] We have executed the total synthesis of the enantiomer of bruguierol A and established its relative and absolute stereochemistry. This approach has been extended to access about 20 small-molecules having the bruguierol skeleton. These compounds were tested for anti-mycobacterial activity. None of the compounds was found to be active enough. The initial lack of activity was attributed to the absolute configuration which is opposite to the natural compound. So we synthesized the natural bruguierol A and

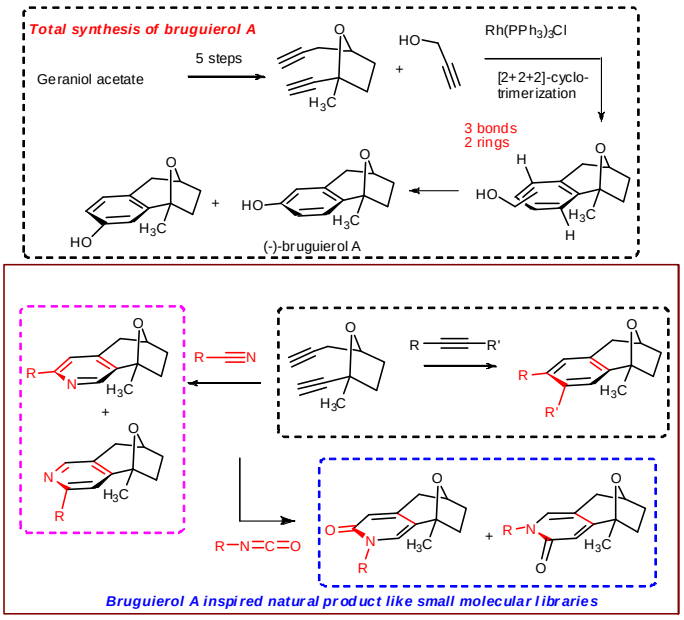


Figure 5. *Novel approach for benzene fused [3.2.1]bicyclooctane skeletonsTotal Synthesis of Bruiguierol A & Subsequent [2+2+2]cycloisomerization Transform Oriented Flexible Synthesis of bruguierol like small molecular libraries*

also some of the related small-molecules by using nitriles and isocyanates as alkyne surrogates for making aza-analogues of bruguierols (unpublished). The biological assay of these libraries against the *M. bovis* BCG strain has been carried out. Interestingly, one of the pyridine derivatives was found to inhibit the growth of *M. bovis* BCG at sub micro molar concentrations.

In essence, our approach for bruguierol clarifies and qualifies the definition of "Target cum Flexibility Oriented Synthesis" for natural product-like small-molecule libraries synthesis. The key complexity transform is characterized by the formation of three alternative C-C bonds and two rings and provides the central tricyclic framework of bruguierol and is amicable for enormous substrate flexibility.

A Simple Access to Tricyclic Sugar Derivatives: We have demonstrated the application of the [2+2+2]-cyclotrimerization reaction to the synthesis of enantiopure tricyclic systems comprising the isochroman or dihydroisobenzofuran units integrated with a sugar ring[9]. The alkyne cylotrimerization reaction has been employed with

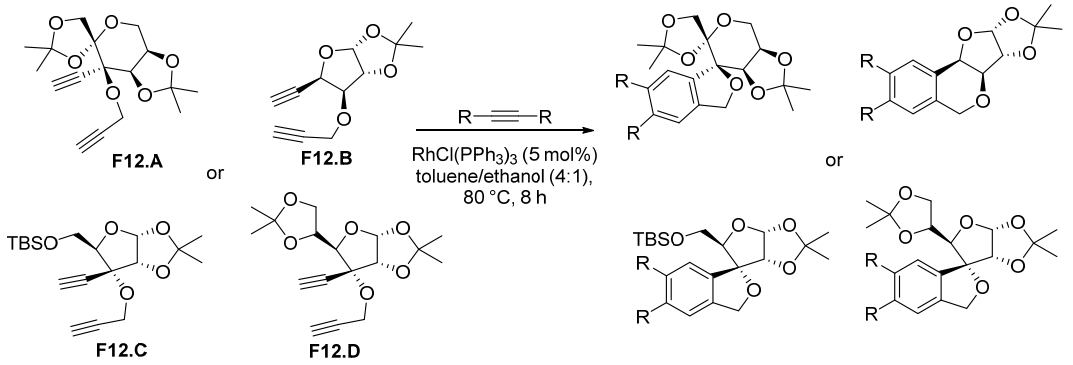


Figure 6: Flexibility in construction of isochroman and dihydroisobezofuran units

easily accessible sugar diynes which were the substrates for the key bicyclic ring construction and thus a provision to alter the functional groups on the newly formed aromatic rings with flexibility of various alkynes. The reaction between diynes **F12.A**–**F12.D** and alkynes in the presence of Wilkinson's catalyst afforded the corresponding products in moderate yields (scheme 2). These were modified, using simple synthetic steps, to give tricyclic nucleosides which are of interest for several

pharmaceutical applications (e.g., antiviral, antisense therapeutic and diagnostic agents).

In this respect, cycloaddition reactions particularly [2+2+2]-alkyne-cyclotrimerization reaction in presence of a transition metal catalyst on sugar templates have been studied and considered to be strategically useful for synthesizing library of small molecules. The unique characteristic property of [2+2+2]-alkyne-cyclotrimerization is its high synthetic efficiency (with the formation of several C-C and/or C-heteroatom bonds in a single step), complete atom-economy, and the availability of a wide range of catalysts that can tolerate a myriad of protecting/functional groups.

1.3 Part B: Introduction to Cyclotrimerization.

Designing effective routes to construct complex cyclic structures through organo-transition metal catalyzed reactions has been recognized as an attractive strategy for delivering molecular diversity. More specifically, the use of carbon-carbon bond formation reactions to generate new ring systems is a key part of contemporary organic synthesis. In this respect, cycloaddition reactions are considered to be strategically useful where more than one carbon-carbon or carbon-heteroatom bonds are formed. With this as a goal, several researchers have developed new reaction pathways aimed towards the synthesis of complex organic molecules with cycloaddition reaction as the key skeletal construct. Novel catalysts and new reaction conditions addressing the chemo- and regioselectivity aspects of various types of cycloaddition reactions have been disclosed.

The [2+2+2]-cyclotrimerization of alkynes into benzene derivatives is a powerful tool for the construction of polysubstituted aromatic compounds. Compared to traditional methods for preparing substituted benzenes, e.g. electrophilic aromatic substitution or *ortho*-metallation, the [2+2+2] cyclotrimerization can offer a more flexible approach limited solely by alkyne synthesis. In a single operation, multiple rings and three new carbon-carbon bonds can be formed.[10] [2+2+2]-cycloaddition

involving alkynes to generate annulated benzene derivatives is one of the more elegant methods for the construction of polycyclic aromatics.

Discovered by Berthelot in 1866, the first known cyclotrimerization reaction produced benzene from acetylene at ~400 °C (without the need of any metal catalyst).[11] Such high temperatures essentially preclude the thermal [2+2+2] cyclotrimerization from synthetic utility despite the reaction being exothermic in nature. A major advance came in the late 1940's when Reppe et al.[12] reported the first transition metal catalyzed [2+2+2] cyclotrimerization reaction in which acetylene was converted into benzene in the presence of $(PPh_3)_2Ni(CO)_2$. Despite the formation of cyclooctatetraene as the major product, the discovery that under certain conditions transition metals could mediate the [2+2+2]-cyclotrimerization of alkynes opened the door for the reaction to become synthetically useful. Since then, the cyclotrimerization reaction has attracted considerable attention by virtue of its intrinsic atom economy, as well as the importance of substituted and annulated benzenes as synthetic intermediates. Various transition metal catalysts based on Ni, Co, Pd, Cr, Rh, Ru, Fe, Zr, Nb, Ir, and Ta have been developed for the trimerization reaction involving alkynes. In addition to the alkynes, other unsaturated functional groups such as nitriles, isocyanates, olefins, carbonyl compounds, imines, and diimides have been shown to participate in cyclotrimerizations with alkynes to deliver useful end products. The application of the alkyne trimerization reaction for the construction of new carbo- and heterocyclic frameworks useful in the synthesis of natural products and complex polycyclic aromatic compounds have been documented recently.[13]

Cyclotrimerization of alkynes can be classified into three types, intermolecular (type **A**), partially intramolecular (type **B**) and totally intramolecular (type **C**) [2+2+2]-cyclotrimerization reactions (Figure 2), giving substituted benzene derivatives **A**−**C** respectively.

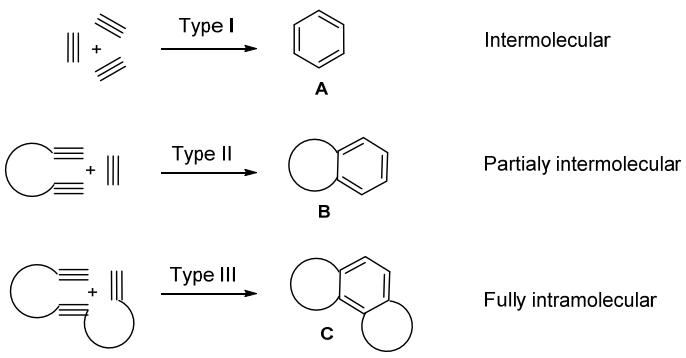


Figure 7: Three types of cyclotrimerization reactions of alkynes

For a long time the regioselectivity of the product was a primary concern for this type of reactions,[14] but little success was achieved despite enormous efforts to control regioselectivity. In general, these reactions can be performed in common organic solvents at temperatures ranging from room temperature upwards. Due to its operational simplicity, and ability to provide complex molecular structures, the transition metal catalyzed [2+2+2] alkyne cyclotrimerization has become an integral component in the armory of organic synthetic methods and has been reviewed thoroughly.[15]

[2+2+2]-cyclotrimerization in recent Organic Synthesis and Development of catalyst:

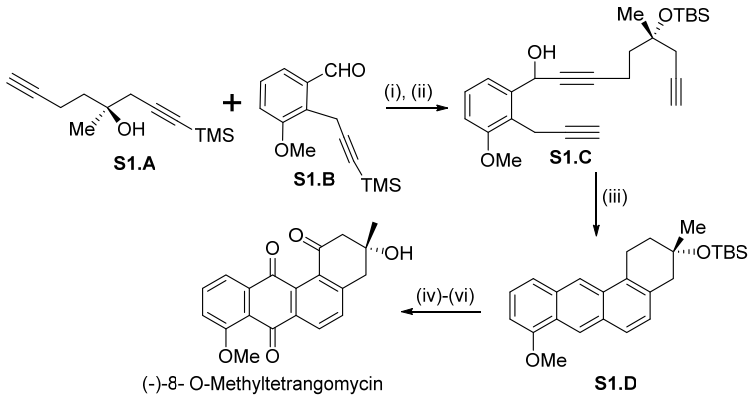
Transition metal-catalyzed [2+2+2] cyclizations of three nonconjugated π-systems exemplify synthetic organic processes that would have been considered extraordinary not all that long ago. Along with other remarkable transformations mediated by transition metals, such as cross couplings and olefin metathesis, these ring-forming reactions have rapidly become valuable synthetic tools, able to accomplish chemistry in a single step that often would have required tedious and low-yielding multistep strategies. A great variety of such transition metalcatalyzed [2+2+2] cyclizations are now well-established using a variety of metals, and these have proven to be particularly effective at producing highly substituted aromatic and nonaromatic rings.

Cobalt mediated cyclotrimerisation (Vollhardt trimerisation)

The transition metal-catalyzed [2+2+2] cycloaddition reaction is an expedient way to prepare six-membered ring systems, such as benzenes, pyridines, and cyclohexadienes, starting from alkynes, nitriles, and alkenes. In this context, cobalt complexes are widely used as catalysts, which provide extensive levels of chemo-, regio-, and diastereoselectivity. Among the commercially available cyclopentadienyl catalysts, [$CpCo(CO)_2$] is probably the most widely used. Its activation usually requires heat and/or visible light. The use of [CpCo(cod)] (cod = 1,5-cyclooctadiene), which has been used mostly for the preparation of pyridines, also requires high temperatures and/or light. Conversely, [$CpCo(C_2H_4)_2$], which is also employed frequently, is active at room temperature or lower. However, these very efficient catalysts are all very sensitive to air and require the use of distilled and thoroughly degassed solvents.

[2+2+2]-Cyclotrimerization in Organic Synthesis

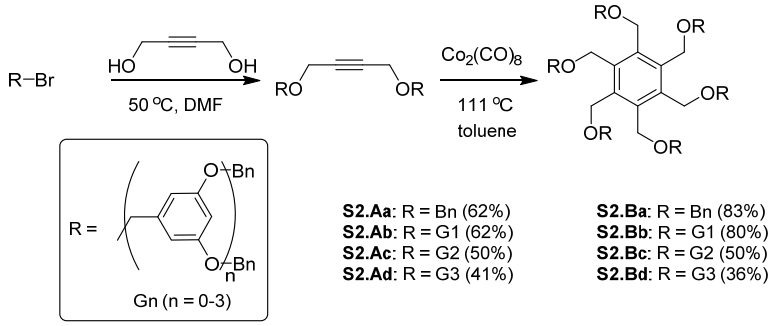
Groth and co-workers reported stereo-selective total synthesis of the natural antibiotic (–)-8-*O*-methyltetrangomycin (MM 47755).[16] The cobalt-mediated [2+2+2]-cyclotrimerization reaction of the triyne **S1.C**, prepared from geraniol, in diethyl ether at –78 °C to r.t. led to a benz[a]anthracene system **S1.A** (Scheme 1), which was oxidized with $Ag(Py)_2MnO_4$ to a benz[a]anthraquinone. Deprotection with aq. HF in acetonitrile and photo-oxidation afforded the desired natural product.



Scheme 1: *Reagents and conditions:* (i) *n*-BuLi, Et_2O, –78 °C, 3 h, $BF_3.Et_2O$, Et_2O, –78 °C, 2 h, 70%. (ii) K_2CO_3, MeOH, rt., 6 h, 90%. (iii) $CpCo(C_2H_4)_2$, Et_2O, –78 °C to rt., 4 h, then cat. AcOH,

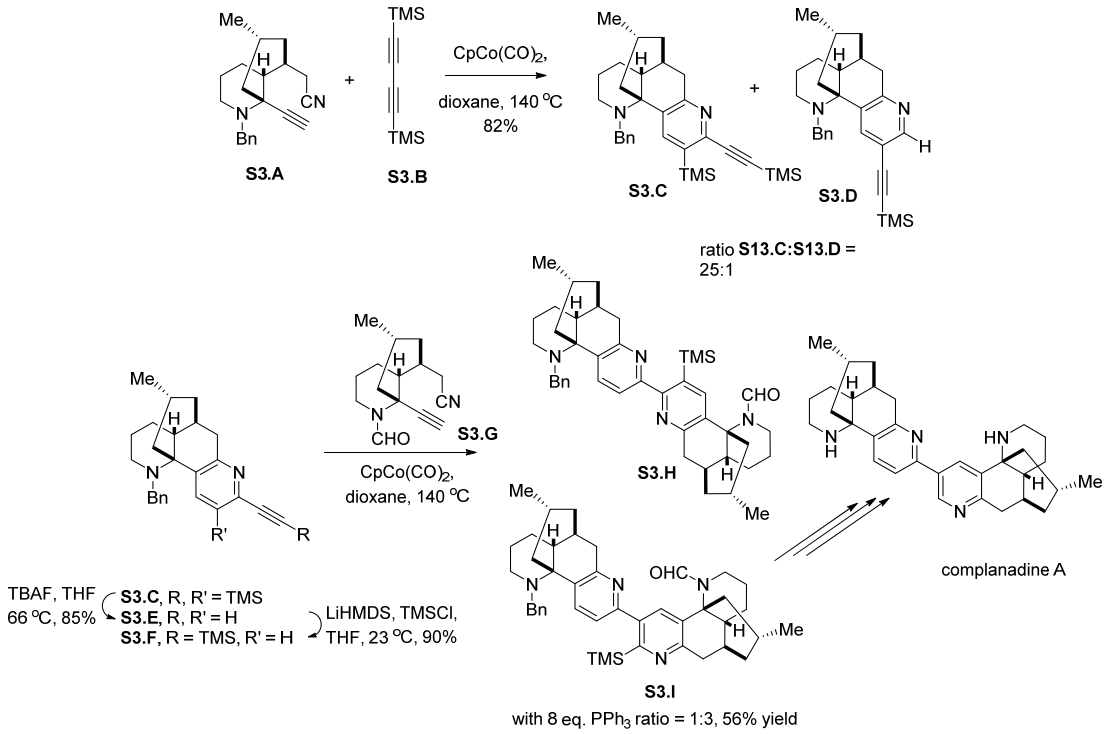
80%. (iv) $Ag(Py)_2MnO_4$, SiO_2, CH_2Cl_2, rt., 7 h, 65%. (v) aq. HF, CH_3CN, 50 °C, 5 h, 98%. (vi) hυ, air, $CHCl_3$, rt., 1 h, 58%.

Frechet and co-workers reported synthesis of novel benzene-core dendrimers *via* alkyne cyclotrimerization.[17] The substituted alkynes **S2.Aa–d** were synthesized by the Williamson ether coupling of 2-butyne-1,4-diol with appropriate polybenzyl ether-type dendritic bromides. The trimerization reaction of **S2.Aa–d** was carried out in refluxing toluene using dicobalt octacarbonyl as the catalyst to afford novel structures **S2.Ba–d** (Scheme 2).

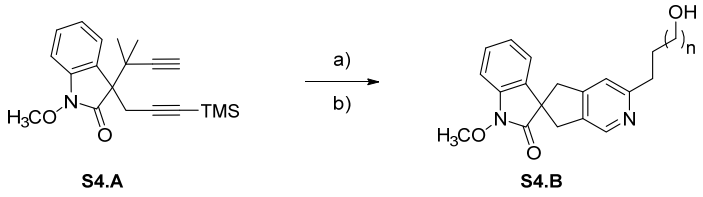


Scheme 2: Synthesis of dendritic assemblies

Dionicio Siegel and co-workers[18] reported successful synthesis of complanadine-A, two late-stage Co(I)-mediated [2+2+2] cycloadditions with good to excellent regioselectivities. The first [2+2+2]-cycloaddition of alkyne-nitrile **S3.A** and bis(trimethylsilyl) butadiyne **S3.B** proceeded smoothly under thermal conditions using $CpCo(CO)_2$, providing the [2+2+2] cycloadduct **S3.C** as the major regioisomer (25:1, **S3.C**:**S3.D**). It was discovered that a remarkable switch in regioselectivity, providing **53** as the major isomer (1:3, **S3.H:S3.I**), was possible by the addition of an excess PPh_3 to the reaction using the formyl derivative **S3.G** (Scheme 3) in the second [2+2+2] cycloaddition.



Scheme 3



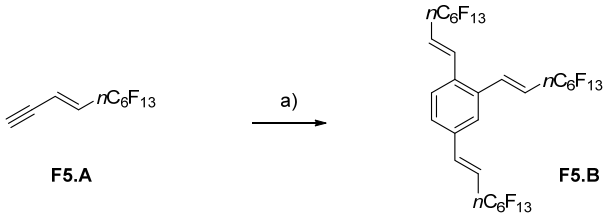
Scheme 4: a) $CpCo(CO)_2$, MW, xylene; b) KF, MW, H_2O/THF

Alexander Deiters[19] has developed an expedient route to tricyclic alkaloid core structures by using the $CpCo(CO)_2$ catalyst and conducting a microwave-mediated [2+2+2]-cyclotrimerization/intramolecular nucleophilic substitution/reduction sequence.

Nickel mediated cyclotrimerisation (Reppe trimerisation)

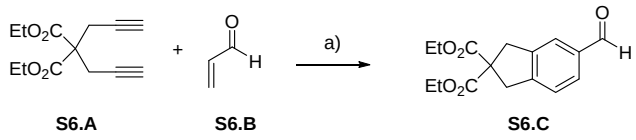
In the late 1940's when Von Walter Reppe et al. reported the first transition metal catalyzed [2+2+2] cyclotrimerization reaction in which acetylene was converted into benzene in the presence of $(PPh_3)_2Ni(CO)_2$.

Yamamoto and co-workers[20] have described a useful process involving nickel-catalyzed regioselective cyclotrimerization of 1-perfluoroalkylenynes. The (E)-perfluorohexyl-enyne derivative **F5.A**, for example, was cyclotrimerized in the presence of 10 mol-% $Ni(PPh_3)_4$, prepared from $Ni(cod)_2$ and PPh_3, to produce the 1,2,4-trisubstitutedbenzene derivative **F5.B** in good yield (Scheme 5)



Scheme 5: a) 10 mol%, $Ni(cod)_2$, 40 mol% PPh_3, toluene, 65%

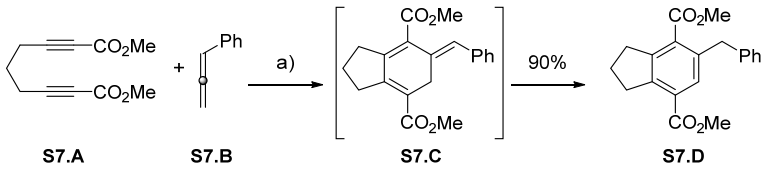
Sato *et al.*[21] have investigated Ni- and Zn-promoted [2+2+2] cycloadditions of diynes with α,β-enones to give aromatic compounds directly in good yields. Under these conditions cyclic enones also cyclize with diynes. As shown in Scheme 6, a dialkyne **S6.A** can undergo a [2+2+2] cycloaddition reaction with an α,β-enone **S6.B** in the presence of $NiCl_2/Zn/ZnCl_2$/Et 3N in acetonitrile to provide the co-trimerized product **S6.C** in good yield.



Scheme 6: a) $NiCl_2/Zn$, $ZnCl_2$, Et_3N, MeCN reflux, 77%

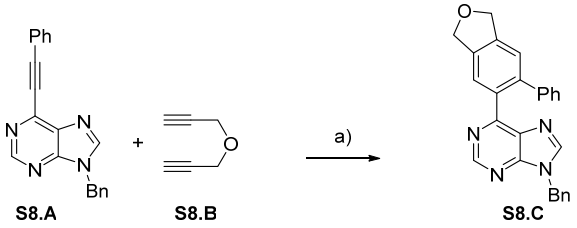
Cheng and co-workers[22] have recently reported nickel-catalyzed regio- and chemoselective [2+2+2] cycloadditions between electron-deficient diynes and allenes. The diyne **S7.A** for example, was treated with the unsymmetrical allene **S7.B** in the presence of $Ni(dppe)Br_2/Zn$ in acetonitrile to give the cyclized product **S7.D**,

presumably *via* compound **S7.C**, in excellent yields and with good regioselectivity (Scheme 7).



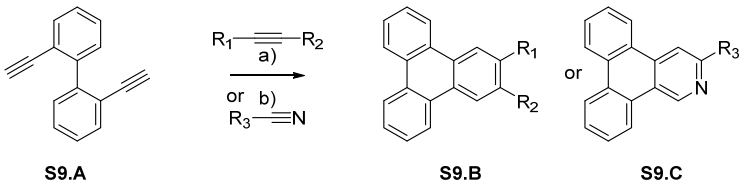
Scheme 7: a) 10 mol%, $Ni(cod)_2$, 40 mol% PPh_3, toluene, 65%

Several 6-aryl purines have been prepared by co-trimerization of 6-alkynylpurines **S8.A** with diynes such as **S8.B**. The key co-trimerization reaction was catalyzed by Ni or Rh or Co-phosphane derived catalysts. The choice of the catalyst depends on the substitution patterns of both dialkyne and mono-alkyne (Scheme 8).[23]



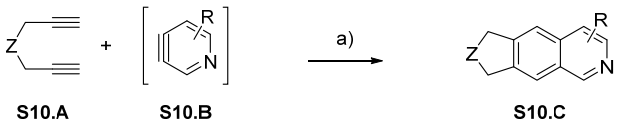
Scheme 8: a) $NiBr_2(dppe)Zn$

[2+2+2]-Cyclotrimerizations can also be used to construct polycyclic aromatic hydrocarbons. Deiters and co-workers[24] reported the cyclotrimerization of 2,2′-diethynylbiphenyl **S9.A** and alkynes or nitriles to give triphenylenes **S9.B** and azatriphenylenes **S9.C,** respectively (Scheme 9). Both reactions were conducted under microwave irradiation and provided the polycyclic aromatic products in good to excellent yields.



Scheme 9: a) $Ni(CO)_2(PPh_3)_2$, 63-94%; b) $CpCo(CO)_2$, 69-100%.

Iwayama and Sato[25] have reported the synthesis of isoquinoline derivatives involving the reaction between a 3,4-pyridyne **S10.B**, generated *in situ* from a silyl triflate precursor, and a tethered diyne **S10.A** in the presence of a nickel catalyst to afford isoquinoline derivative **S10.C** in moderate to good yields (Scheme 10).

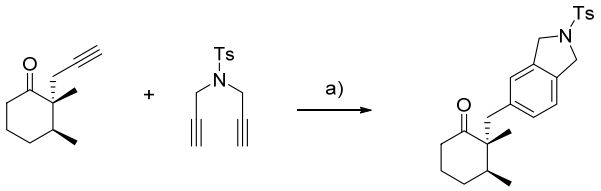


S10.A S10.B S10.C

Scheme 10: a) $[Ni(cod)_2]PPh_3$, synthesis of isoquinolene derivatives by reaction between pyridyne and tethered diyne, R = Me or $COEt_2$; Z = CH_2, NTs or $C(CO_2Me_2)$

Rhodium or Rhuthenium mediated cyclotrimerisation:

An enantioselective synthesis of the tetracyclic benzo[d]xanthene core of anti-influenza natural products has recently been reported by Cramer and co-workers.[26] Because of the growing resistance to anti-influenza agents, these sesquiterpenes and analogues are of great interest. The authors demonstrated a ruthenium-catalyzed [2+2+2]-cyclotrimerization reaction of alkyne **S11.A** and diyne **S11.B**, depicted in (Scheme 11), which could be used to access more substituted derivatives.

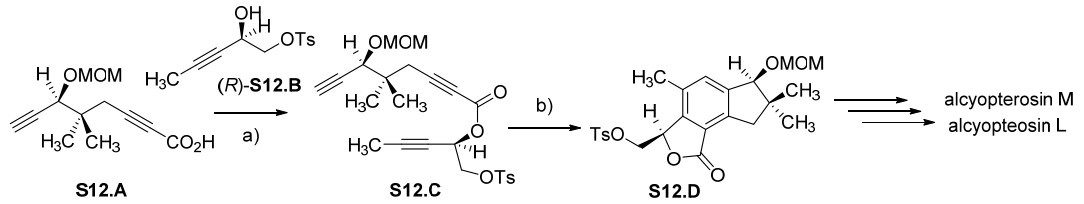


S11.A S11.B S11.C

Scheme 11: a) [Cp*Ru(cod)Cl], 78%.

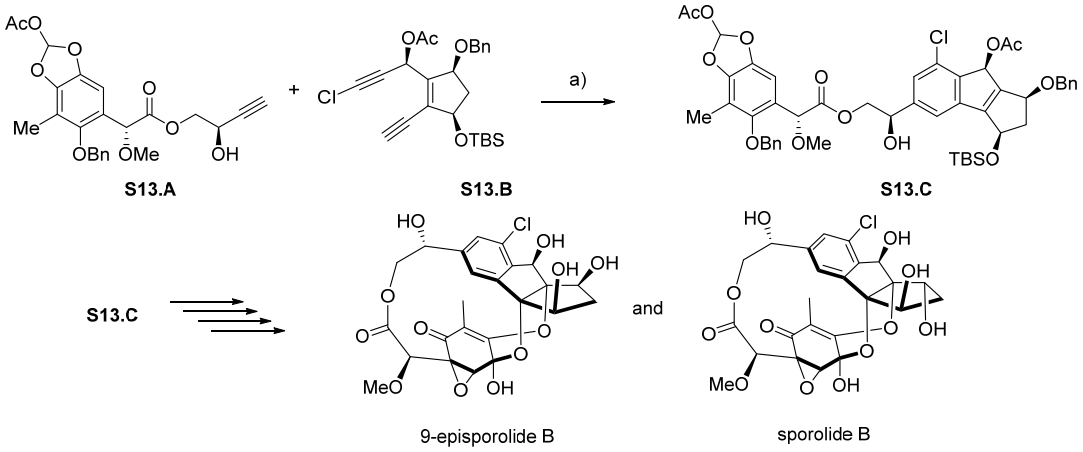
Witulski and co-workers reported the first total synthesis of the marine illudalane sesquiterpenoid alcyopterosins M and L through a concise ABC ring-formation strategy using a rhodium (I)-catalysed intramolecular alkyne cyclotrimerization as the key connection.[27] Treatment of **S12.C** with 10 mol% $RhCl(PPh_3)_3Cl$ in DCM at 40 °C gave **S12.D** as a single product in 69% yield. Finally, the synthesis of alcyopterosin M and alcyopterosin L were completed by

nucleophilic displacement of the tosyl protective group against nitrate ester functionality and chlorine respectively (Scheme 12).



Scheme 12: *Reagents and conditions:* a) DCC, DMAP, CH_2Cl_2, –78 °C to r.t., 65%. b) 10 mol% $[RhCl(PPh_3)_3Cl]$, CH_2Cl_2, 40 °C, 69%.

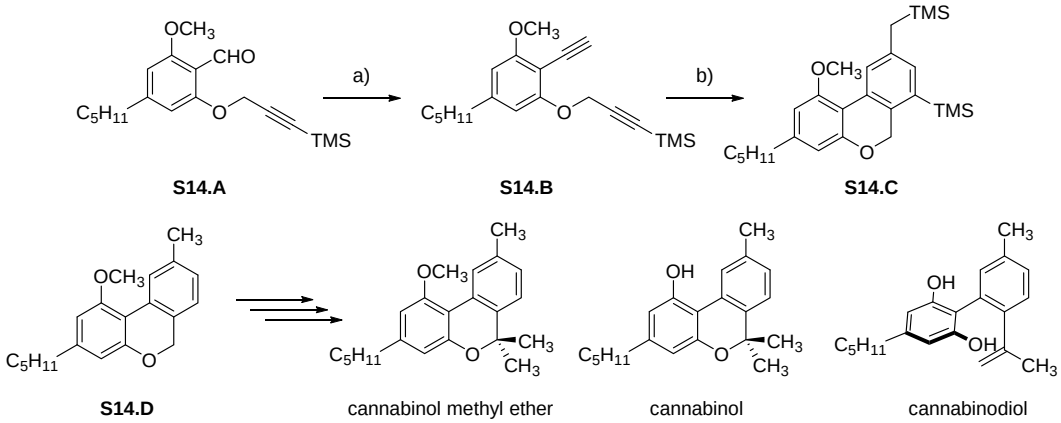
K. C. Nicolaou et al.[28] recently reported the stereocontrolled total synthesis of sporolide B designed strategy that also delivered 9-*epi*sporolide B the efficient synthesis of the [2+2+2] fusion of acetylenic fragments **S13.A** and **S13.B** under the influence of Cp*RuCl(COD) catalyst was expected to proceed regioselectively toward the desired *meta*-substituted chlorobenzyl alcohol system **S13.C** (Scheme 13). Further, a stereocontrolled total synthesis of sporolide B has been achieved through a designed strategy that also delivered 9-*epi*sporolide B from **S11.C**.



Scheme 13: *Ru-Catalyzed [2+2+2]-Cyclization* a) Cp*Ru(cod)Cl.

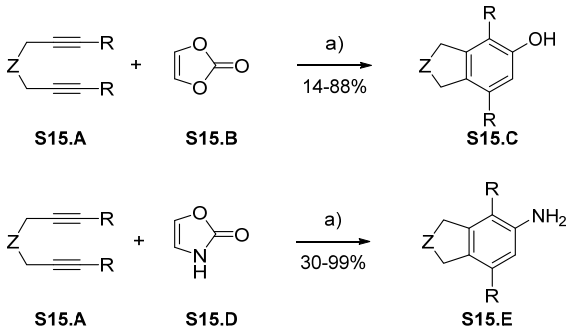
Teske and Alexander Deiters[29] reported the synthesis of three members of the cannabinoid class, cannabinol, cannabinol methyl ether, and cannabinodiol, using a microwave-mediated [2+2+2]-cyclotrimerization reaction as the key step. This approach provides a high level of synthetic flexibility allowing for the facile synthesis of cannabinoid analogues. Treatment of **S14.B** through an efficient and regioselective

Cp*Ru(cod)Cl catalyzed [2+2+2]-cyclotrimerization reaction with propargyltrimethylsilane under microwave irradiation delivered the pyran **S14.C** in 88% yield as a single regioisomer. Finally, synthesis of cannabinol methyl ether, cannabinol, and cannabinodiol was completed (Scheme 14).



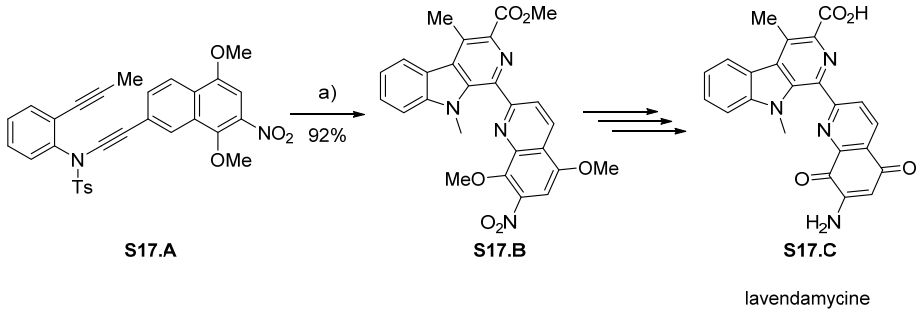
Scheme 14: *Reagents and conditions:* (a) *n*-BuLi, $TMSCHN_2$, THF, 71%. (b) Propargyl TMS, Cp*Ru(cod)Cl, toluene, MW 300W, 10 min, 88%. (c) $Bu_4N^+F^-$, THF/DMF, MW 300W, 2 min, 96%.

More recently, Tanaka and colleagues[30] reported the methodology in the synthesis of fused benzofuran derivatives. The reactions were again performed with perfect regioselectivity, albeit in moderate yields. Tanaka and co-workers also reported a similar methodology utilizing a different leaving group. This was achieved *via* a decarboxylative [2+2+2] cyclotrimerization between tethered alkynes **S15.A** and vinylene carbonate **S15.B** using the same catalyst system (Scheme 15). An interesting feature of this reaction is that it employs compound **S15.C** as a synthetic equivalent of the unstable hydroxyacetylene. Zhang and Louie[31] extended this approach to the synthesis of anilines **S15.E** using 2-oxazolone **S15.D**, which can be used as an alternative for ynamides (Scheme 15). They also demonstrated that the reaction proceeds with full regioselectivity when two different R groups are used (e.g., H, Me). The sole regioisomer formed has the amino group in the ortho-position with respect to the larger R group.



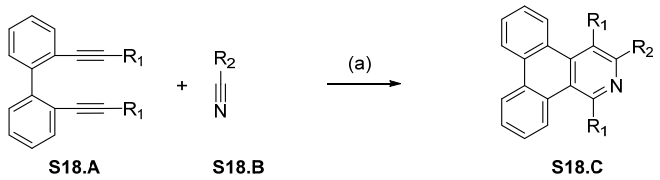
Scheme 15: *Decarboxylative [2+2+2]-cyclotrimerization reaction towards substituted benzenes.*
a) $[Ru(cod)_2]/BF_4$, *Rac*-BINAP, R = H, Me, Et or Ph; Z = O, NTs, NAc, $(CH_2)_2$, $C(CH_2OMe)_2$, CAc_2, $C(CO_2Me)_2$or $[C(CO_2Et)_2]_2$

Nissen and Detert[32] used the trimerization reaction in the total synthesis of lavendamycin (**S17.C**, Scheme 17). In this case, 2 mol% of Yamamoto's catalyst was sufficient to afford the [2+2+2]-cyclocotrimerization product **S17.B** in excellent yield as a single regioisomer.



Scheme 17: $[Cp^*RuCl(cod)]_2$ mol%, NC-CO_2Me, CH_2Cl_2, rt,

Ken Tanaka and co-worker[33] reported the substituted azatriphenylene synthesis, as shown in Scheme 18. The reaction of the terminal diyne **S18.A** and acetonitrile **S18.B** proceeded at room temperature in the presence of the cationic rhodium(I)/BINAP complex (5 mol %) to give the corresponding azatriphenylene **S18.C** in good yield. Both primary and secondary aliphatic nitriles could also participate in this reaction. Not only aliphatic nitriles but also aromatic nitriles reacted with **S18.A** at room temperature to give the corresponding conjugated azatriphenylenes in good yields.



Scheme 18: a) $[Rh(cod)_2BF_4]$ 5 mol%, $BINAP(CH_2Cl)_2$ rt or 80 °C, 16-72 h

In the following chapters, we summarize a simple and efficient protocol for the synthesis of small molecule libraries built around either pharmaceutically or naturally important scaffolds. Three diverse scaffolds, namely nucleosides, beta-lactams and indoloisoquinolines have been selected as representative platforms to examine the feasibility of the late-stage alkyne cyclotrimerization and its suitability for developing related small molecule libraries. The scaffolds that we selected have been already established as important leads for targeting life-threatening diseases such as cancer, HIV and bacterial infections. The expertise that we have already gained during the last seven years at NCL in different spheres of the field of target oriented synthesis (TOS) and our initial success that forms the foundation of our present proposal gives us confidence in believing that we will achieve the objectives that we have laid out and synthesize the varied targets that we have proposed.

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CHAPTER II:

Synthesis of *C*(3)-Spirocyclic Nucleosides

2.1 Introduction

Nucleosides are glycosylamines consisting of a nucleobase bonded to a ribose or deoxyribose sugar. Nucleosides can be phosphorylated by specific kinases in the cell on the sugar's primary alcohol group, producing nucleotides, which are the molecular building block of DNA and RNA. In medicine, several natural nucleosides and their analogs are used as antiviral or anticancer agents. Natural nucleosides are of great biological importance in metabolic pathways.[1]

For many years, D-ribose or D-deoxyribose have been recognized as the only two typical sugar moieties that are connected by a β-glycosyl linkage to different heterocyclic bases such as thymine, uracil, cytosine, adenine and guanine. However, n 1950, Bergmann et al. reported the isolation of spongouridine and spongothymidine (figure 1) from marine Caribbean sponges *Cryptotheca crypta*, which had D-arabinose as the sugar moiety.[2] In 1958, Y. Yonehara et al. reported the discovery of a metabolite of Streptomyces griseochromogenes, Blasticidin S,[3] which controls rice blast Pyricularia oryzae.[4] In 1978, K. Suetomi et al. reported the isolation of antifungal mildiomycin from a culture of Streptoverticillium rimofaciens.[5]

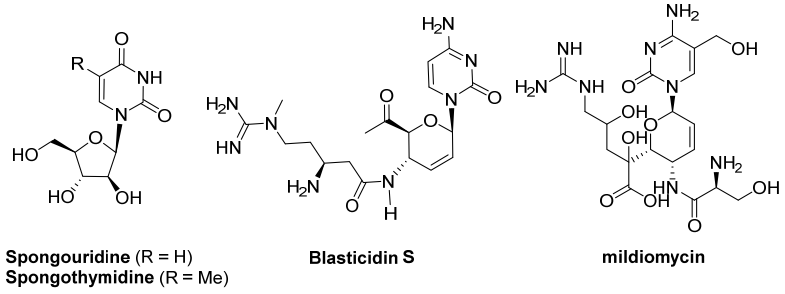


Figure 1: Natural Nucleosides having other than *ribo* sugar part

The isolation of these nucleosides having the sugar unit other than the ribose or the deoxyribose has indeed provided the foundations for the anti-viral research by use of modified nucleosides. For example, Vidarabine or 9-β-D-arabinofuranosyladenine (ara-A), is an antiviral drug which is active against herpes simplex and varicella zoster viruses, has been synthesized by Baker in 1960 as a potential anticancer agent. However, its first clinical application has been showed by Whitely in 1976, as an antiviral agent. Cytarabine was one of the early examples of the modified nucleoside that has entered the market. Cytarabine or cytosine

arabinoside (Cytosar-U or Depocyt) was first synthesized in 1959 by Richard Walwick, Walden Roberts, and Charles Dekker. In 1969, it has been approved by US FDA for the treatment of cancers of white blood cells such as acute myeloid leukemia (AML) and non-Hodgkin lymphoma. It kills cancer cells by interfering with DNA synthesis.

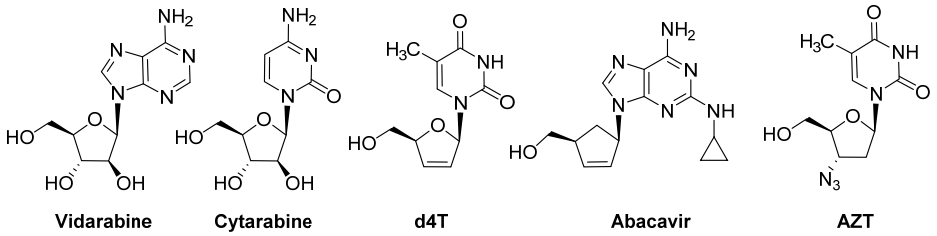


Figure 2: Structures of medicinally important modified nucleosides

These discoveries led to a large number of nucleoside analogues that were tested for the treatment of viral diseases.[6] Among the US FDA approved compounds used in the treatment of acquired immunodeficiency syndrome (AIDS), the 2',3'-didehydro-3'-deoxythymidine ***d4T***,[7–9] the carbocyclic 2-amino-6-cyclopropylaminopurine analogue ***Abacavir***[10,11] and **AZT** and showed potent anti-human immunodeficiency virus (HIV) activity (Figure. 1.5). However, side effects and drug-resistant variants remained a problem with these antiviral agents.[12–14] Moreover, the introduction of the 2',3'-double bond in compound ***d4T*** resulted in an increased lipophilicity compared to the corresponding natural and saturated 2',3'-dideoxynucleoside series but decreased the chemical stability in acidic medium.

In the course of the search for new antiviral agents with a higher therapeutic index, the obvious emphasis was on the design of drugs with potent activity, high stability, low cytotoxicity, minimal side effects. Christopher Len and co-workers reported the synthesis of pyrimidine nucleoside analogues of d4T based on the 1,3-dihydrobenzo[c]furan core (Figure 2).[15,16] This class of nucleoside with a modified glycan part was attractive because: (i) it retained the phosphorylation site; (ii) the presence of the benzene ring as electron-withdrawing group stabilized the glycosidic bond compared to the olefinic analogue: 2',3'-didehydro-2',3'-dideoxynucleoside; (iii) the introduction of the aromatic residue increased the lipophilicity compared to d4T.[17] In an attempt to expand the variety of nucleoside antiviral drugs, a novel range of

unsaturated nucleoside analogues of d4T were synthesized to explore their potential as antiviral drugs.

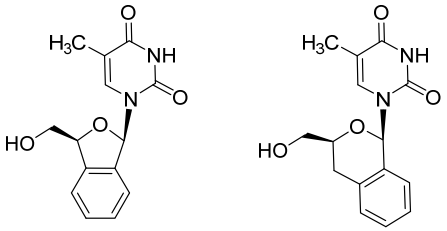


Figure 3: Modified nucleosides having Isobenzofuran and isochroman

The synthesis of structurally modified nucleosides has been emerging as an important area of research because some members show biological activities of medicinal interest.[18] The term spironucleoside was introduced in 1990 to designate a class of spiranic sugar derivatives in which the anomeric carbon belongs to both the sugar ring and to a heterocyclic base. Data on this type of compound were reported before 1990 but only recently, the term spironucleoside has been used. Of the different classes of nucleosides, the spironucleosides are probably the least well known. However, the isolation from *Streptomyces hygroscopicus*, in 1991, of (+)-hydantocidin (figure 4), the first natural spironucleoside[19], and later the discovery of its potent herbicidal and regulatory plant growth activities[20] and its low mammalian toxicity, have resulted in great interest in the chemistry of spironucleosides. Since then, there have been notable contributions from Miyasaka's and Paquette's groups in addition to others, to synthesize 1'-spiro-, 2'-spiro-, 3'-spiro- and 4'-spironucleoside derivatives[21] as conformationally restricted analogues.

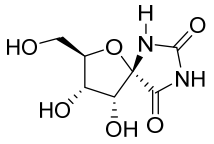
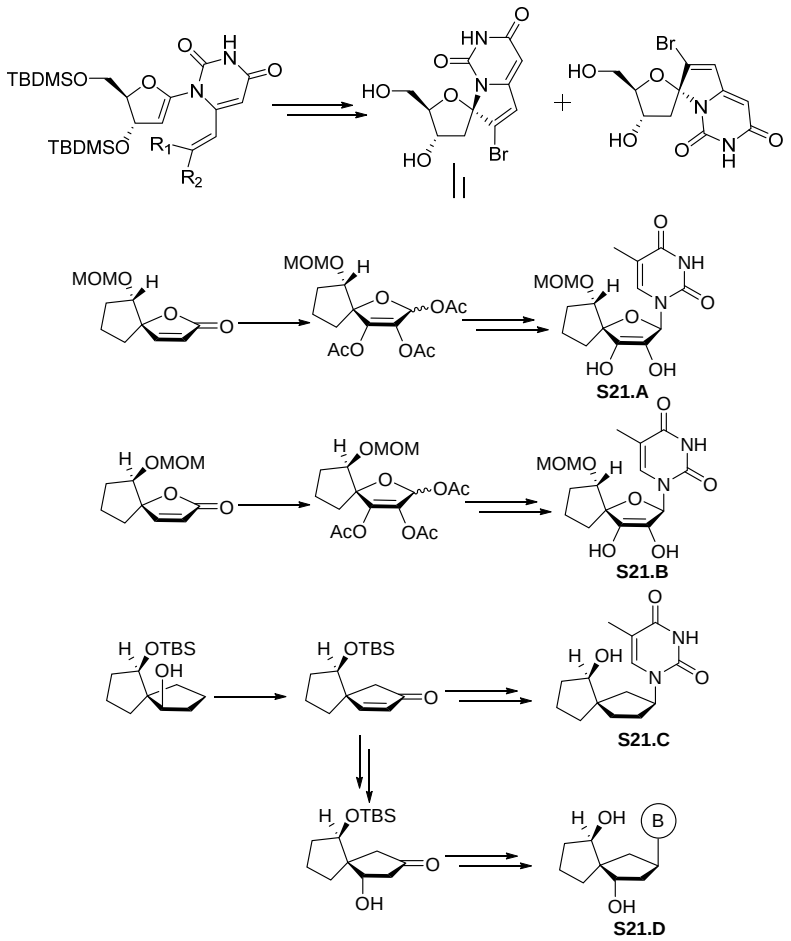


Figure 4: naturally occurring spironucleoside hydantocidin

The isolation of hydantocidin stimulated the synthesis of anomeric spiro nucleosides. Hiromichi Tanaka[22] prepared 6-bromovinyl derivatives of 1-(2-deoxy-D-erythro-pent-1-enofuranosyl)-uracils **S20.A** and developed new method for the synthesis of anomeric spiro nucleosides **S20.B** by vinyl radical-mediated reactions (Scheme 1). Later number of groups synthesized anomeric spiro nucleosides by using radical intermediate cyclizations.[23]



Scheme 2: Synthesis of *syn*, *anti*-oxaspiro[4.4]nonalyl mimic and carbaspironucleosides.

Paquette and co-workers developed spirocyclic nucleosides with different modifications on sugar ring. In 2001, this group reported the synthesis of *syn* and *anti*-oxaspiro[4.4]nonalyl mimics (**S21.A**),[25] (**S21.B**)[26] respectively and later in a couple of years made their carbocyclic analogues (**S21.C**),[27] (**S21.D**)[28] (Scheme 2).

Recently, the attention has been shifted towards the synthesis of *C*-4'-spiroalkylated nucleosides having hetero atoms like sulfur and nitrogen been incorporated. The rapidity with which 2',3'-dideoxy-3'-thiacytidine was adopted for clinical use in the treatment of AIDS,[29] and the high-level antiviral and anticancer

potency of several sulfur mimics having the heteroatom at the apex position[30] has ignited research in this area from several directions. Paquette's and Mandal's groups reported the new sulfur containing derivatives of spironucleosides (Figure 5).

Jesper Wangel and co-workers in 2003 first time reported the synthesis of bicyclic *C*-2' spiro ribo and arabinonucleosides via *C*-2' –allyl nucleosides as key intermediates.[31] As per our knowledge, except Nielsen in 1996 no report is available towards the synthesis of *C*-3' spiro nucleosides. An attempt to expand the variety of

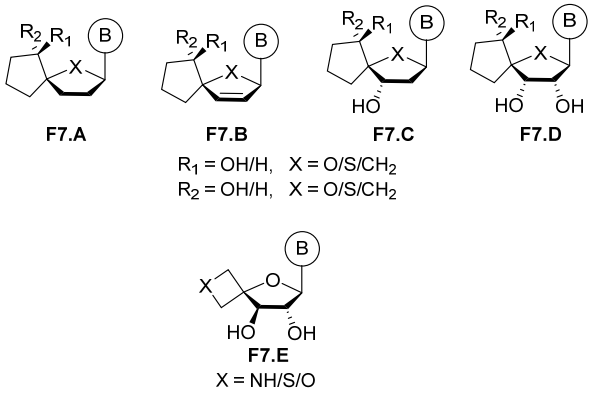


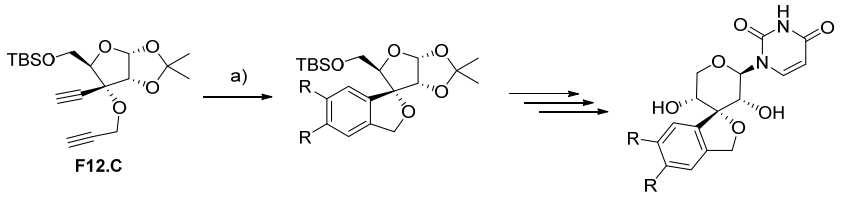
Figure 5: Some structurally unique spironucleosides

nucleoside as an antiviral drugs, a novel range of unsaturated, conformationally restricted, tricyclic nucleosides containing isochromane unit and *C*-3' spironucleosides containing isobenzofuran system were synthesized to explore their potential as antiviral drugs.

To impart some degree of conformational restriction to the natural nucleosides, several possibilities have been suggested. These include (i) synthesis of locked bicyclic and tricyclic nucleoside analogues by inserting an extra ring fused to the furanose moiety, (ii) synthesis of spironucleosides and (iii) synthesis of nucleosides of varied ring structures. Mainly researchers have reported the synthesis of fused bicyclic, tricyclic nucleosides and *C*-4' spiroannulated nucleosides, but the synthesis of *C*-3' spiroannulated nucleosides has attempted only by Nielsen and co-workers in 1996.[24] We have therefore taken up a scheme to synthesize new classes of tricyclic nucleosides containing isochromane annulated unit and *C*-3' spiroannulated nucleosides.

2.2 Present Work

Considering the prevalence of the dihydroisobenzofuran structural unit in many of the naturally occurring substances, and drug candidates, our intention has been to spiro-annulate a dihydroisobenzofuran unit on the nucleoside templates.[32] We have recently documented[33] the feasibility of cyclotrimerization of sugar derived diyens and shown that the resultant product can be transformed to the tricyclic and C(3')-spirobenzoisofuran-annulated nucleosides following the sequence of chemical transformations (Scheme 3). However, the spiro-annulated nucleosides reported contain a pentopyranose unit (6-membered sugar unit). Also, this strategy is not sufficiently effective as the number of compounds to be accessed is restricted by the limited number of nucleobases available which are introduced at the penultimate step of the synthesis. In addition, it may require additional steps if one intends to place sensitive functional groups on the isobenzopfuran ring. This has prompted us to look for an alternative approach which can effectively address the library size and the ease of alternation of the functional groups on the isobenzofuran ring. This has led us into the exploration of the key C(3')-spiroannulation as the final step of [2+2+2]-cyclotrimerization of completely free nucleoside-diynes with alkynes which is the main theme of the present work and also we address the selective synthesis of spiroannulated nucleosides having the furanoside ring also.



Scheme 3: a) RhCl(PPh3)3 (5 mol%), toluene/ethanol (4:1), 80 °C, 8 h

As mentioned earlier, the previously reported approaches for spironucleosides, have in general been executed in a target oriented way (one scheme one nucleoside). This causes a serious limitation in the collection of spironucleosides as each modification needs to be attended separately from the beginning of the synthesis. Considering the importance of the modified nucleosides in the area of anti-viral and anti-cancer drug discovery programs and as a part of our program to provide flexible methods for the synthesis of biologically active small molecules, we have identified that cyclotrimerization on sugar templates and glycosidation could be combined

effectively to address the synthesis of either conformationally restricted or spiroannulated nucleosides libraries rapidly.

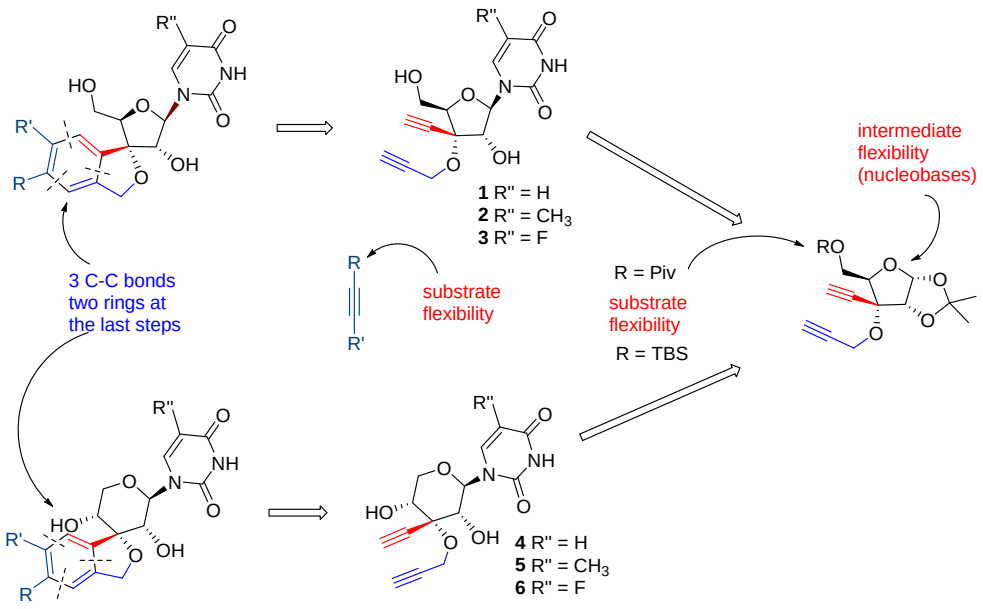


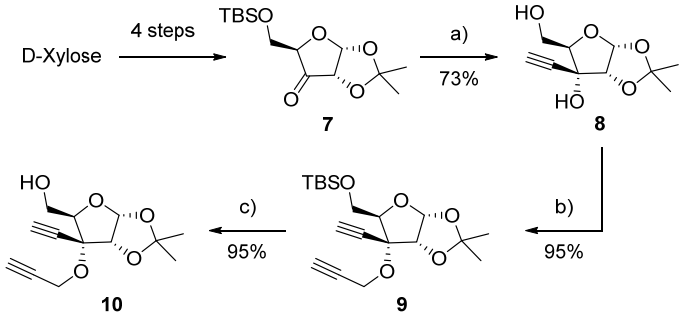
Figure 6: The key [2+2+2] cyclotrimerization transform addressing the target complexity cum substrate flexibility at the penultimate step

Figure 6, reveals our intended approach in this regard. The key cyclotrimerization reaction has been planned on a fully deprotected nucleoside diynes **1**–**6**. We have selected three furanosyl nucleosides and **1**–**3** and three pyranosyl nucleosides **4**–6 having uracil, thymidine and 5-flurourancil units. We planned to introduce the nucleobase at an advanced stage so as one have the flexibility in terms of the nucleobase to be placed (apart from the 5 parent nucleobases several of their analogues and various other nitrogen containing heterocycles could be employed as glycosyl acceptors). The proposal of keeping the cyclotrimerization on a free nucleoside is challenging and provides an opportunity to employ a wide range of easily accessible substrates (commercial availability of hundreds of alkynes and through easy synthesis).

2.2.1 Synthesis of glycosyl donors 1 – 6.

The synthesis of the nucleoside diynes **1**–**6** has been planned from the advanced intermediate **10** having the preinstalled diyne unit and free C5-OH for

further manipulation to arrive at either pyranosyl or furanosyl units. The synthesis of key intermediate **10** started from the known xylosed derived ketone **7**.[83] The ketone 7 was prepared from D- xylose following a sequence of 4 reported steps. The addition of ethynylmagnesium chloride prepared by Grignard exchange with *n*-butylmagnesium chloride at 0 °C to the ketone **7** and consequently propargylation of 3°-hydroxyl of obtained Grignard product afforded diyne **8** (Scheme 4). Diyne **9** was fully characterized by spectral and analytical data. In the 1H NMR spectrum of compound **9**, the characteristic alkyne protons resonated at δ 2.44 as a triplet with J = 2.4 Hz and at δ 2.66 as a singlet. In the ^{13}C NMR spectrum, the alkyne carbons and quaternary carbon C(3) showed singlets at 74.5, 77.8, 79.4, 79.5 and 80.6 ppm. The acetylenic C–H stretching frequency was appeared at 3307 cm^{-1} and C≡C stretching frequency at 2110 cm^{-1} in the IR spectrum of compound **9**.

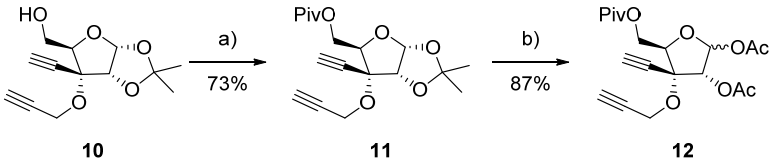


Scheme 4: *Reagents and Conditions*: a) Mg, n-BuCl, THF, acetylene, 0°C; b) NaH, propargyl bromide, THF, 0°C – rt, 8h; c) TBAF,THF, rt, 8 h.

Having the key intermediate **10** in hands our next objective was its conversion to a suitable furanosyl derivative with anomeric –OH being protected as an acetate so as it can be directly employed as a substrate for the N-glycosidation with the nucleobases. Our earlier observations have revealed that the peracetylation of fully deprotected furanose derivatives leads mainly to the formation of pyranosyl derivatives. Considering this, we have opted for suitable protecting group at C5–OH which can survive during the acid-mediated 1,2-acetonide hydrolysis as well as to the peracetylation conditions. To this end, we have selected a pivoloyl protecting group as a viable handle. The work in this direction started with the preparation of pivolate derivative **11** by treating **10** with pivaloyl chloride in the presence of DMAP and Et_3N in dichloromethane (scheme 5). The selective acetonide hydrolysis of compound **11**

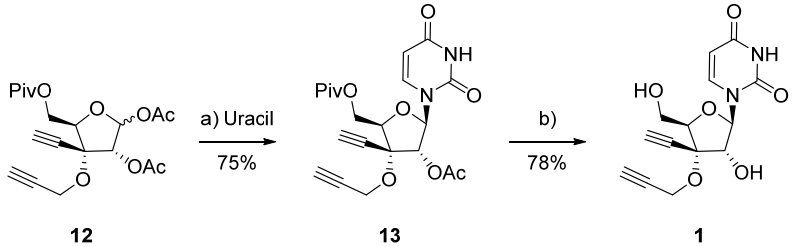
followed by acetylation (Ac_2O/Et_3N) gave a 1:1 anomeric mixture of diacetates **12** (inseparable on silica gel column).

Mixtures of diacetate **12** derivatives were characterized by spectral and analytical data. In the ^1H NMR spectrum of compound **12** the appearance of the nine carbon singlet at 1.20 ppm indicated that the pivaloyl group indeed was intact. The appearance of the anomeric protons at downfield (two doublets at δ 6.12 and 6.42 with 1.5 and 4.4 Hz coupling constants respectively) indicated the presence of a furanose unit and 7:3 α:β ratio ratio has been determined based upon the relative ^1H NMR integrations for these two signals. In the ^{13}C NMR spectrum of **12**, six carbonyl carbons resonated at 169.1, 169.2 (2C), 169.3, 177.9, and 178.0 ppm and four methyl carbons of acetyl resonated at 20.5, 20.6, 20.9, and 21.0 ppm.



Scheme 5: *Reagents and Conditions*: a) PivCl, DMAP, CH_2Cl_2, rt, 6 h; b) *i.* 60% AcOH, reflux, 2 h; *ii.* Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h.

Having the key furanosyl intermediate 12 in hand the stage was next set for its glycosidation. The glycosidation of the anomeric mixture **12** was carried out under modified Vorbrüggen[34] conditions [refluxing the diacetate with BSA *N*,*O*-bis(trimethil silyl) acetamide and base in acetonitrile, then after, adition of TMSOTf and heating at 50 °C for 2 h]. When uracil was employed as a base, the corresponding protected nucleoside **13** was obtained as a single anomer in 75% yield. Subjecting **13**to Zemplen's deacetylation [NaOMe in methanol] afforded the free nucleoside diyne **1** (Scheme 6).



Scheme 6: *Reagents and Conditions*: a) uracil, *N*,*O*-bis(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h; b) NaOMe, MeOH, rt, 20 min

The constitution as well as the configuration of the anomeric center in the compound **13** was determined with the help of extensive NMR spectral data analysis. For example, in the ^{1}H NMR spectrum of compound **13**, the anomeric–H and C(2)–H resonated at δ 6.05 and 5.40 respectively as a doublets with a characterist coupling constant J = 3.8 Hz which is indicative of a β-configutration. The olefinic C3'–H of uracil displayed a doublet of doublet at δ 5.76 with J = 1.9, 8.2 Hz and C2'–H resonated at down field δ 7.62 with J = 8.2 Hz. The amide N–H of **13** showed a broad singlet at δ 9.15. In the ^{13}C NMR spectrum of compound **13**, the anomeric–C appeared at δ 6.05 as a doublet with J = 3.8 Hz, and that of the olefinic carbons C2' and C3' resonated at 139.2 ppm and 102.5 ppm respectively. The spectral data of the free nucleoside diyne **1** was in accordance with the assigned structure. For example, the disappearance of characteristic peaks of pivaloyl, acetyl methyl group in ^{1}H-NMR was in supportive of the assigned structures of **1**.

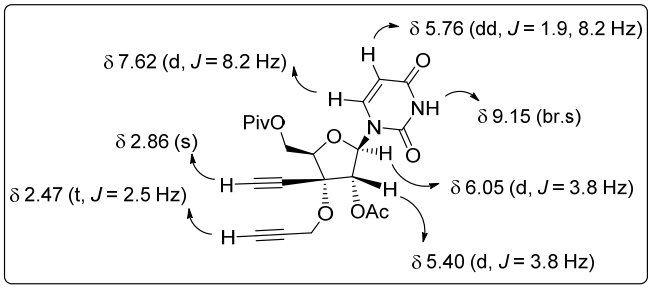
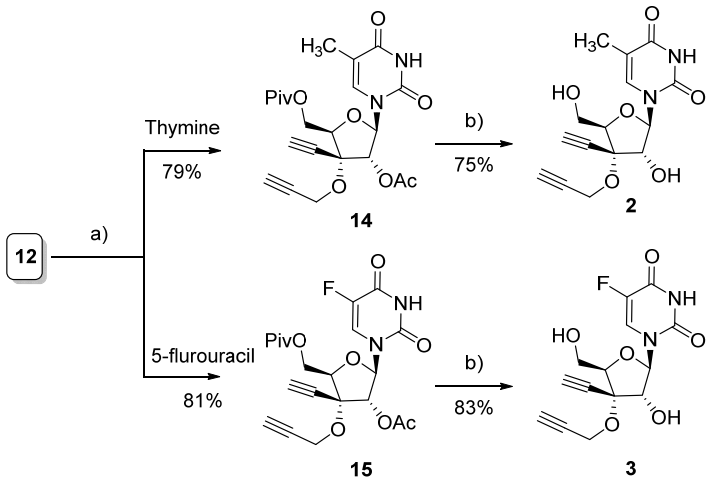


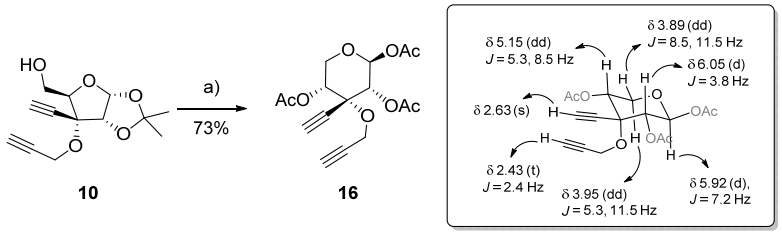
Figure 7: Selected 1H NMR chemical shifts and coupling constants in compound **13**

Having been successfully synthesized the penultimate intermediate **1**, we next proceeded for the synthesis of other key nucleoside diynes **2** and **3**. The synthesis of **2** and **3** followed a similar sequence of synthetic operations as established in the preparation of **1**. As shown in Scheme 26, the glycosidation of acetates **12** with thymine followed by the saponification of the resulting compound **14** under Zemplen conditions gave the nucleosidediyne **2**. Similarly, nucleosidediyne **3** was prepared in an overall yield of 67% by subjecting acetates **12** for glycosidation with 5-flurouracil followed by the saponification. The spectral data of compounds **14**/**15** and of **2**/**3** are comparable with that of compounds **13**/**1**.



Scheme 7: *Reagents and Conditions*: a) uracil, *N*,*O*-bis(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h; b) NaOMe, MeOH, rt, 20 min.

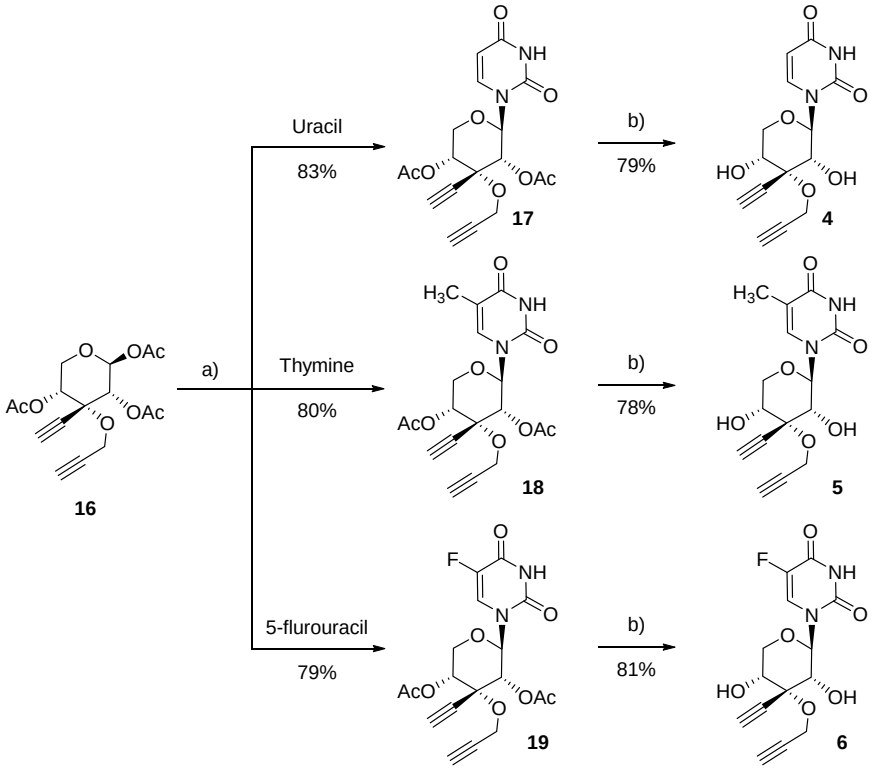
Having synthesized key diyne building blocks **1**–**3** embedded on a furanosyl nucleoside, we next focussed our attention on the synthesis of the corresponding pyranosyl nucleosides **4**–**6**. In our previous studies, as mentioned above, we have realized that the hydrolysis of a furanoside 1,2-acetonides having the C5–OH free followed by acetylation leads mainly to the peracetylated pyranosides. To encash in this direction, the intermediate acetonide **10** was subjected directly for the acid hydrolysis and then for peracetylation employing acetic anhydride and Et_3N in dichloromethane to afford the corresponding β-anomer **16** exclusively (scheme 8).



Scheme 8: *Reagents and Conditions*: a) *i.* 60% AcOH, reflux, 2 h;
ii. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h;

The constitution and the configuration of the triacetate derivative **16** was established by spectroscopic and analytical data. In the ^1H NMR spectrum of **16**, there was only a single peak for anomeric proton which appeared as doublet at δ 5.92 with 7.2 Hz coupling constant. In ^{13}C NMR spectrum of **16** three carbonyl carbons resonated at 169.0 (2C), and 169.4 ppm, three methyl carbons of acetyl resonated at

20.5, 20.6, and 20.8 ppm. Carbonyl stretching frequency of acetates gave strong absorption peak at 1752 cm^{-1} in IR spectrum.



Scheme 9: *Reagents and Conditions*: a) *N*,*O*-bis(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h; c) NaOMe, MeOH, rt, 20 min.

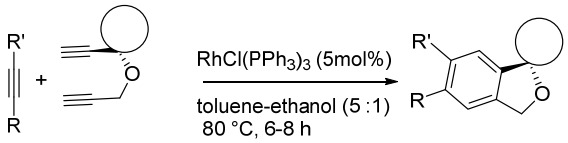
The *N*-glycosidation of **16** with uracil, 5-fluorouracil and thymine under modified Vorbrüggen conditions followed by deacetylation of the resulting compounds **17**–**19** gave the pyranose nucleosides **4**–**6**. Diacetate derivatives of nucleosides **17**–**19** were characterized by spectroscopic and analytical data. Methyl protons of thymine resonated at δ 2.14 as a singlet, anomeric proton resonated at δ 6.05 with coupling constant 9.4 Hz in the ^{1}H NMR spectrum of **18**. In the ^{13}C NMR spectrum of **18**, two triplets for methylene carbon atoms resonated at 56.5 and 63.0 ppm. Mass spectrum and elemental analysis were in well agreement with proposed structure. β-configuration of compound **18** was further confirmed with the help of coupling constants of anomeric protons. Amide hydrogen of **18** showed a broad singlet at δ 8.56. Subjecting **17**–**19** to Zemplen's deacetylation [NaOMe in methanol] afforded the free hydroxyl diyne spironucleosides **4**–**6** (Scheme 9). Pyranose nucleosides **4**–**6** were characterized by spectrometric and analytical data.

Disappearance of characteristic peaks of acetyl methyl group in ^{1}H-NMR was in supportive of the assigned structures of **4**–**6**.

2.2.2 Syntheis of Spironucleosides:

With the fully elaborated diyne frameworks in place, we attempted the cyclotrimerization of **1**–**6** with symmetric and unsymmetric alkynes. The trimerization reactions with the acetylene proceeded effectively with Wilkinson's catalyst at 80 °C in a sealed tube to afford the corresponding products **20**–**25** respectively from **1**–**6** (scheme 10). In the ^{1}H NMR spectrum of **20**, the characteristic C(1)-H and C(2)-H of the furanose ring appeared at δ 5.91 (d) and 4.45 (d) respectively with $J_{1,2}$ = 8.2 Hz. The C(4)-H appeared as a dd (δ 4.07 ppm, J = 1.2, 2.8 Hz) and the benzylic methylene hydrogens appeared at δ 5.03 (d) and 5.05 (d) respectively with J = 12.7 Hz. In the ^{13}C NMR spectrum of **20** two methylene carbons appeared as triplet at δ 60.4 and 72.2 ppm.

The diacetate of 2-butyne-1,4-diol, *bis*-(trimethylsilyl)acetylene and dimethyl acetylenedicarboxylate were explored as the representative symmetric disubstituted alkynes for the trimerization reactions. Amongst the three, the trimerization of **1**–**6** with the diacetate of 2-butyne-1,4-diol gave the corresponding isobenzofurannulated nucleosides **26**–**31** in good yields (table 1). Synthesized spirocyclic-nucleosides were characterized by extensive NMR spectroscopy. The anomeric proton of **26** resonated at δ 5.95 with coupling constant J = 8.2 Hz in ^{1}H NMR spectrum. C(2)-H showed doublet at 4.57 (J = 8.2 Hz), olefinic C3'–H proton of uracil displayed double at δ 5.71 with J = 8.2 Hz and C2'–H proton resonated at down field δ 8.09 with J = 8.2 Hz. Acetate methyls appeared at δ 2.02 (s) and 2.04 (s), methylene carbon resonated at 63.4 (t), 64.1 (t), ppm and methyl carbon resonated at 20.8 (t) ppm in ^{13}C NMR spectrum of compound **26**. Formation of either self dimerization products or a complex mixture was noticed with the other two alkynes.



Scheme 10: Cyclotrimerization of diyne **1** – **6**

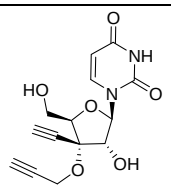
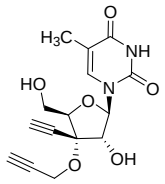
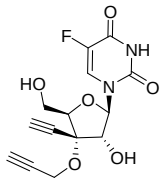
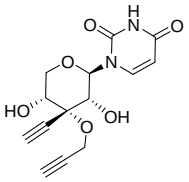
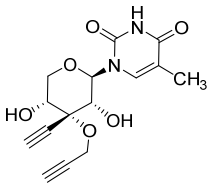
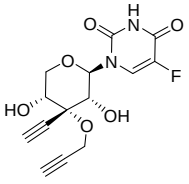
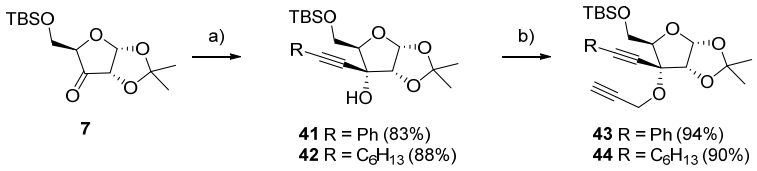
Alkyne/diyne	Acetylene	Diacetoxy-2-butyne-1,4-diol	Hexyne
 **1**	**20** (79%)	**26** (83%)	**32** (80%)
 **2**	**21** (77%)	**27** (85%)	**33** (81%)
 **3**	**22** (75%)	**28** (82%)	**34** (79%)
 **4**	**23** (71%)	**29** (78%)	**35** (81%)
 **5**	**24** (69%)	**30** (74%)	**36** (86%)
 **6**	**25** (73%)	**31** (80%)	**37** (79%)

Table 1: Representative c(3)-spiroisobenzofurannulated nucleosides

The cyclotrimerization reactions of **1**–**6** with the terminal alkyne 1-heptyne in general are clean and gave the corresponding isobenzofurannulated nucleosides **26**–**31** in good yields (table 1). However, gave inseparable regiomeric mixtures. With the catalysts Cp*RuCl(cod)[35] and $[Rh(cod)_2]BF_4$/(*R*)-BINAP,[36] the reactions do not resulting any improvement in the regioselectivity. Synthesized spirocyclic-nucleosides were characterized by extensive NMR spectroscopy. The anomeric proton of **26** resonated at δ 6.01 with coupling constant J = 8.1 Hz in ^{1}H NMR spectrum. Benzylic methylene protons resonated as doublet at δ 5.12 and 5.16 with coupling constant 12.6 Hz in ^{1}H NMR spectrum of **26**. Methylene carbon resonated at 63.4 (t), 64.1 (t), ppm and methyl carbon resonated at 20.8 (q) ppm in ^{13}C NMR spectrum of compound **26**. Formation of either self dimerization products or a complex mixture was noticed with the other two alkynes.

2.2.3 Synthesis of substituted diyens 38–40: The regioselectivity is the critical limitation with the [2+2+2]-cyclotrimerization reactions, which has been addressed to some extent in the present invention by the placement of a substituent on any of the alkynes of the diyne unit. In personification of the present work, cyclotrimerization of diynes **38–40** with the terminal alkynes is carried out to

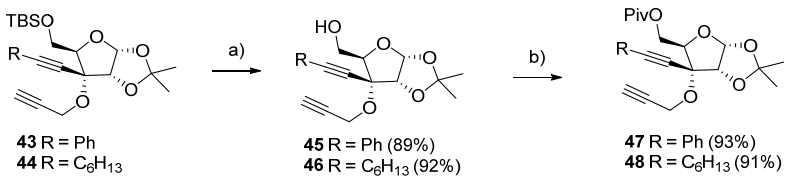


Scheme 11: *Reagents and Conditions* a) n-BuMgCl, phenyl acetylene/1-octyne, 0 °C 1 h; b) propargyl bromide, NaH, THF, 0 °C - rt, 3 h;

determine the regioselectivity. Accordingly, ketone **7**[37] is reacted with alkynylmagnesium chloride (prepared by Grignard exchange between the corresponding alkyne i.e. phenylacetylene and 1-octyne respectively with n-butylmagnesium chloride) to gave alkynols **41** and **42** respectively [37a] (scheme 11). The resonance of aliphatic protons of **42** in up-field region in ^{1}H-NMR spectrum and presence of two acetylenic singlet carbons at 76.8 and 88.3 ppm in ^{13}C-NMR were in accordance with structure **42**. The presence of aromatic protons in the region 7.29–7.45 ppm in ^{1}H-NMR and two singlets carbons at 85.7 and 87.8 ppm in ^{13}C-NMR approved the structure of **41**. Propargylation of 3°-hydroxyl by using propargyl bromide and sodium hydride in dry THF to obtain the diyne intermediates **43** and **44**

respectively in good yields. Appearance of additional triplets at 2.46 and 2.41 ppm with coupling constant 2.4 Hz for the propargylic proton in the intermediates **41** and **44** respectively in ^{1}H-NMR and additional triplet at 63.3 and 63.4 ppm in ^{13}C-NMR accounted for newly introduced alkyne in compound **43** and **44** respectively.

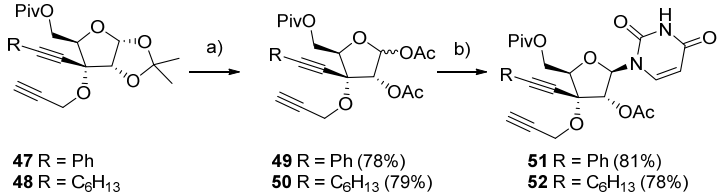
The deprotection of -OTBS group of diyne **43** and **44** by TBAF in THF furnished free hydroxyl diyne substrates **45** and **46** respectively in good yields. Disappearance of characteristic peaks of TBS group in ^{1}H-NMR was in supportive of the assigned structures of **45** and **46** respectively. Mass [*m/z* 351.47 for $(M+Na)^{+}$] for the **45** and Mass [*m/z* 375.42 for $(M+Na)^{+}$] for the compound **46** and elemental analysis further confirmed the structures. Primary hydroxyls of **45** and **46** were protected with pivaloyl group by using pivaloyl chloride and DMAP to afford pivaloyl derivatives **45** and **46** in good yields respectively. A surge in the number of protons at δ 1.20 (s, 9H) and 1.27 (s, 9H) acknowledged the presence of pivaloyl group in products **47** and **48** respectively (scheme 12).



Scheme 12: *Reagents and Conditions*: a) TBAF,THF, rt, 8 h;
b) PivCl, DMAP, CH_2Cl_2, rt, 6 h.

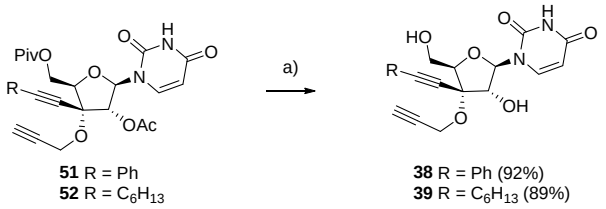
The pivaloyl diyne derivative **47** and **48** were subjected to acid catalyzed acetonide hydrolysis to deprotect the acetonide group. Thus heating compound **47** or **48** in 60% acetic acid at reflux temperature for two hours gave the corresponding lactols. Acetylation of these lactols by using acetic anhydride and Et_3N in dichloromethane afforded anomeric mixture of diacetates **49** (inseparable on silica gel column) and single isomer of **50** in 78% and 79% yields over two steps respectively (Scheme 13). Mixtures of diacetate **49** and **50** derivatives were characterized by spectral and analytical data. The ^{1}H-NMR spectrum of **49** showed two peaks for anomeric proton at δ 6.18 as doublet with 1.4 Hz coupling constant and at δ 6.53 as doublet with 4.7 Hz coupling constant in 2:3 ratio. By comparing the integrations for two isomers, α:β ratio of diacetates is 2:3. In the ^{13}C-NMR spectrum of **49** four carbonyl carbons resonated at 169.0 (s), 169.2 (s) and 169.3 (s, 2C) ppm, four methyl carbons resonated at 20.5, 20.6, 20.8 and 20.9 ppm. Carbonyl stretching frequency of

acetates gave strong absorption peak at 1741 cm^{-1} in IR spectrum. In case of **50** exclusively single i.e. β isomer. The ^{1}H NMR spectrum of **50** showed single peak for anomeric proton at δ 6.38 as a doublet with 4.3 Hz coupling constant and C(2)–H showed doublet at δ 5.40 as a doublet with 4.3 Hz coupling constant. The ^{13}C-NMR spectrum of **50** two acetyl methyl carbons resonated at 20.6 and 20.9 ppm.



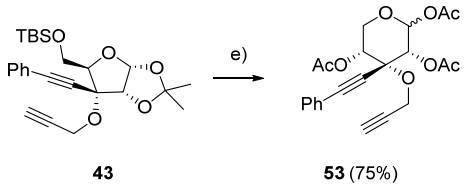
Scheme 13: *Reagents and Conditions* a) i. 60% AcOH, reflux, 2 h; ii. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; b) uracil, *N,O-bis*(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h;
.

Treatment of anomeric mixture of diacetate **49** and **50** with uracil under modified Vorbrüggen conditions [refluxing the diacetate with BSA *N,O*-bis(trimethylsilyl)acetamide and base in acetonitrile, then after adition of TMSOTf and heating at 50 °C for 2 h] afforded the protected nucleosides **51** and **52** respectively in good yields (Scheme 10). Synthesized protected nucleosides **51** and **52** were characterized by extensive NMR spectroscopy. The anomeric proton of **51** resonated as doublet at δ 6.08 with coupling constant *J* = 3.2 Hz in the ^{1}H-NMR spectrum. The C(2)–H showed doublet at 5.47 (*J* = 3.2 Hz), olefinic C3'–H proton of uracil displayed double at δ 5.65 with *J* = 8.2 Hz and C2'–H proton resonated at down field δ 7.71 with *J* = 8.2 Hz. Olefinic C3'–H carbon resonated at 102.3 ppm and C2'–H carbon resonated at 139.1 ppm in the ^{13}C-NMR spectrum of compound **51**. Similarly in the anomeric proton of **50** resonated as doublet at δ 5.98 with coupling constant *J* = 3.0 Hz in the ^{1}H-NMR spectrum. The C(2)–H showed doublet at 5.30 (*J* = 3.0 Hz), olefinic C3'–H proton of uracil displayed double at δ 5.71 with *J* = 8.2 Hz and C2'–H proton resonated at down field δ 7.65 with *J* = 8.2 Hz. Olefinic C3'–H carbon resonated at 101.9 ppm and C2'–H carbon resonated at 139.4 ppm in the ^{13}C-NMR spectrum of compound **50**.



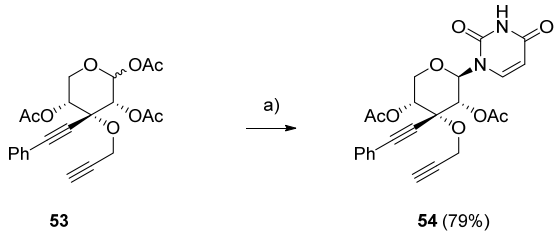
Scheme 14: a) NaOMe, MeOH, rt, 20 min

Subjecting **51** and **52** to Zemplen's deacetylation afforded the free hydroxy diyne spironucleosides **38** and **39** respectively in good yields (Scheme 14). Furanose nucleosides **38** and **39** were characterized by spectrometric and analytical data. Disappearance of characteristic peaks of pivaloyl, acetyl methyls in ^{1}H-NMR was in supportive of the assigned structures of **38** and **39**. Mass [*m/z* 405.48 for $(M+Na)^+$] for the **36** and Mass [*m/z* 413.07 for $(M+Na)^+$] for the compound **39** and elemental analysis further confirmed the structures.



Scheme 15: *Reagents and Conditions*: a) *i.* 60% AcOH, reflux, 2 h; *ii.* Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h;

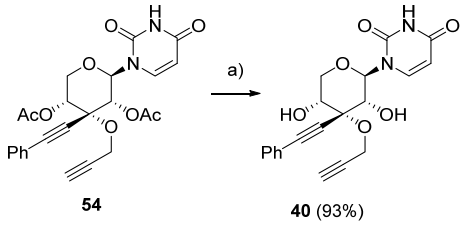
Synthesis of the pyranosyl nucleoside precursors **40** started with the global deprotection of **43** subjected to acid catalyzed acetonide hydrolysis to deprotect the acetonide and TBS groups. Thus heating compound **43** in 60% acetic acid at reflux temperature for two hours gave the corresponding lactols. Acetylation of these lactols by using acetic anhydride and Et_3N in dichloromethane afforded anomeric mixture of pyranosyl triacetate **53** (inseparable on silica gel column) derivatives in 75% yield over two steps respectively (Scheme 15).



Scheme 16: a) uracil, *N*,*O*-bis(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h;

Mixture of triacetate **53** derivatives was characterized by spectral and analytical data. The ^{1}H-NMR spectrum of **53** showed two peaks for anomeric proton at δ 6.08 as doublet with coupling constant 2.6 Hz and at δ 6.15 as doublet with 9.5 Hz coupling constant in 1:1 ratio, Observation of large coupling constants indicated the formation of pyranoside framework after hydrolysis of 1,2-acetonide and deprotection of TBS ether of compound **53.** C(2)–H showed two peaks at δ 5.69 as doublet with coupling constant 8.2 Hz and at δ 5.79 as doublet with 8.1 Hz coupling constant in 1:1 ratio. By comparing the integrations for two isomers, α:β ratio of diacetates is 1:1. In the ^{13}C-NMR spectrum of **53** six carbonyl carbons resonated at 163.1, 163.3, 169.0, 169.2, 169.4 and 170.4 ppm and prapagylic methylene carbons resonated at 55.5 and 56.1 ppm. Carbonyl stretching frequency of acetates gave strong absorption peak at 1753 cm^{-1} in IR spectrum. Mass [*m/z* 437.27 for $(M+Na)^{+}$] for the **53** and elemental analysis further confirmed the structures.

Treatment of anomeric mixture of triacetate **53** with uracil under modified



Scheme 17: a) NaOMe, MeOH, rt, 20 min.

Vorbrüggen conditions [refluxing the diacetate with BSA *N*,*O*-bis(trimethylsilyl)-acetamide and base in acetonitrile, then after adition of TMSOTf and heating at 50 °C for 2 h] afforded the protected nucleoside **54** in good yield (Scheme 16). Synthesized protected nucleoside **54** was characterized by extensive NMR spectroscopy. The anomeric proton of **54** resonated as doublet at δ 6.13 with coupling constant 9.4 Hz in the ^{1}H-NMR spectrum. The C(2)–H showed doublet at 5.25 (J = 9.4 Hz), olefinic C3'–H proton of uracil displayed double at δ 5.76 with J = 8.2 Hz. Olefinic C3'–H carbon resonated at 103.2 ppm and C2'–H carbon resonated at 139.6 ppm in the ^{13}C-NMR spectrum of compound **54**.

Subjecting **54** to Zemplen's deacetylation afforded the free hydroxy diyne pyranose spironucleosides **40** in good yield (Scheme 17). Pyranose nucleoside **40** was characterized by spectrometric and analytical data. Disappearance of characteristic peaks of acetyl methyls in ^{1}H-NMR was in supportive of the assigned structures of **40**. Mass [*m/z* 489.50 for $(M+Na)^+$] for the compound **40** and elemental analysis further confirmed the structures

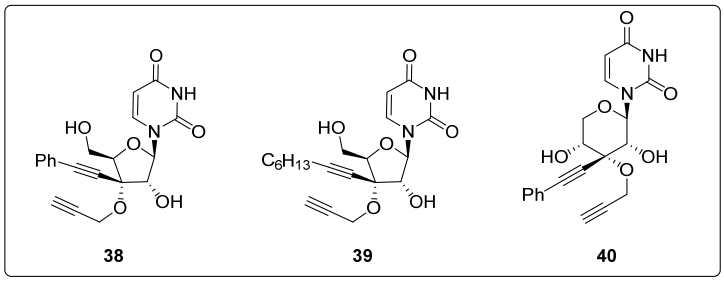


Figure 9: Diynes **38** – **40**.

With the fully elaborated diyne frameworks in place (figure 9), using 1-octyne as a substrate the feasibility of cyclotrimerization of the diynes **38**–**40** has been examined by screening available Rh- and Ru-based catalysts. With Wilkinson catalyst, the cyclotrimerization of the diynes **38**–**40** with 1-octyne are not facile. When the catalysts Cp*RuCl(cod) and $[Rh(cod)_2]BF_4$/(R)-BINAP were employed, the reactions proceeded smoothly at rt and gave the corresponding nucleosides (Figure 3) in good yields and with compelete regioselectivity. The regioselectivity noticed with the trimerization of diynes **38**–**40** endorse them for further exploration in constructing the spiro-nucleosides library.

Next, the cyclotrimerization reactions of **38**–**40** with symmetrically disubstituted alkynes such as bis-(trimethylsilyl)acetylene, dimethyl acetylenedicarboxylate and diphenyl acetylene was attempted. The reactions are sluggish and did not proceed at different temperatures under atmospheric pressure, and the starting material was intact. The scope of the cyclotrimerization reactions with the diynes **38**–**40** was explored. A variety of terminal alkynes have been employed for the cyclotrimerization with the diyne **38**. The regioselectivity was excellent and various functional groups are tolerant under these conditions. A similar regioselectivity was observed with the furanose diyne **39** too. However, for the case of the pyranose diyne **40**, its cyclotrimerization with phenyl acetylene gave a 7:1 regiomeric mixture, with the 1,3-product being the major one. On the other hand, in the case of other three alkynes employed, the 1,3-products were seen to be formed exclusively.

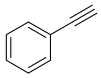
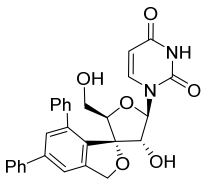
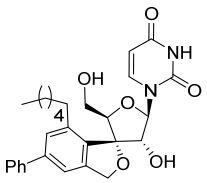
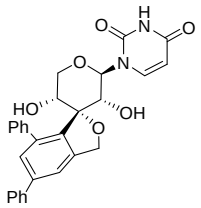
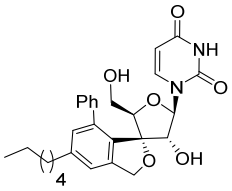
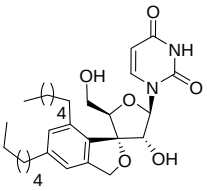
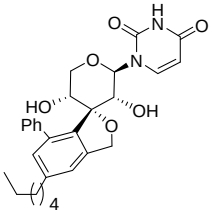
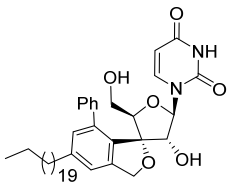
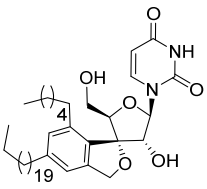
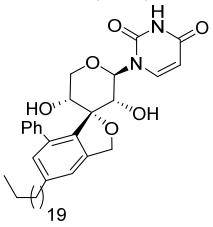
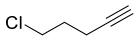
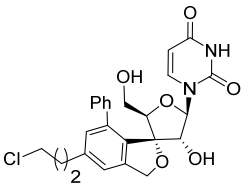
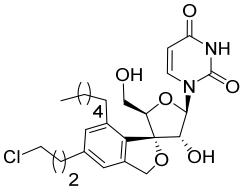
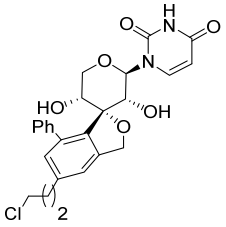
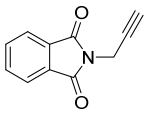
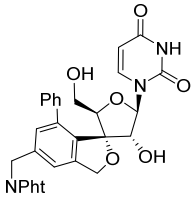
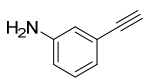
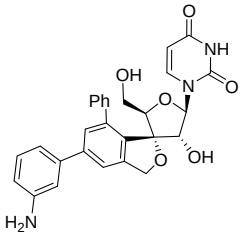
Alkyne / Diyne	**38**	**39**	**40**
	 **55** (85%)	 **61** (78%)	 **65** (83%)
	 **56** (78%)	 **62** (74%)	 **66** (77%)
	 **57** (87%)	 **63** (73%)	 **67** (81%)
	 **58** (83%)	 **64** (78%)	 **68** (79%)
	 **59** (80%)		
	 **60** (85%)		

Table 2: Scope of the cyclotrimerization reaction of diynes **38** – **40**.

The amine group present in the products **60** and the chloro functional group present in the products and **58**, **64**, and **68** provide a suitable handle for further diversification.

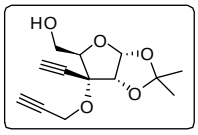
2.2.4 Conclusion:

To conclude, a simple approach with enormous flexibility for the synthesis of spiro-tricyclic nucleosides through the [2+2+2]-cyclotrimerization on sugar templates has been developed. Considering the importance of modified nucleosides as antiviral and anti-cancer agents and as potential antisense therapeutic and diagnostic agents, the results from the present investigation could be further explored for a strategic construction of these molecular skeletons. Work in this direction is ongoing in our laboratory. Also, incorporation of the spirocyclic-nucleoside monomers into oligodeoxy-nucleosides and their biological evaluation is presently progressing in our lab.

2.3 Experimental:

General Methods: Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an argon atmosphere in oven-dried glassware. All anhydrous solvents were distilled prior to use: Toluene from Na and benzophenone; CH_2Cl_2 and DMF from CaH_2; MeOH and EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (100–200 mesh). Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Specific optical rotations $[\alpha]_D^{25}$ are given in 10^{-1} deg cm^2 g^{-1}. ^1H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AC 200 MHz or Bruker DRX 400 MHz spectrometers, and TMS was used as internal standard. The ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and the coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The multiplicity of the ^{13}C NMR signals was assigned with the help of DEPT spectra and the terms s = singlet, d = doublet, t = triplet and q = quartet represent C (quaternary), CH, CH_2 and CH_3 respectively. Mass spectroscopy was carried out on an API QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) spectrometer. Elemental analysis data were obtained on a Thermo Finnigan Flash EA 1112 Series CHNS Analyzer.

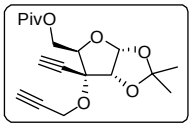
1,2-*O*-Isopropylidene-3-*C*-ethynyl-3-*O*-(2-propynyl)-α-D-ribofuranose (**10**):



To a cooled solution of **9** (12 g, 0.032 mol) in THF (350 ml) was added tetra-butyl ammonium fluoride (16.7 g 0.064 mol) and stirred at rt 2 h. The reaction was patronized in water and ethyl acetate, aqueous layer was extracted with ethyl acetate. The combined extract as dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The purification of residue by silica gel column chromatography afforded compound **10** (8.0 g, 98% yield) as a white solid; mp: 142−143 °C; $[\alpha]_D^{25}$ +62.8 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3304, 3019, 2400, 1522, 1422, 1217, 1021, 928, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3H), 1.58 (s, 3H), 2.47 (br.t, J = 2.4 Hz, 1H), 2.73 (s, 1H), 3.92 (t, J = 4.7 Hz, 2H), 4.20 (t, J = 5.5 Hz, 1H), 4.32 (dd, J = 2.4, 14.6 Hz, 1H), 4.45 (dd, J = 2.4, 14.6 Hz, 1H), 4.63 (d, J = 3.6 Hz, 1H), 5.85 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50

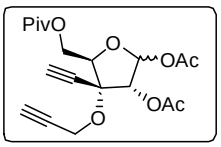
MHz): δ 26.7 (q), 26.8 (q), 54.6 (t), 62.1(t), 74.8 (d), 77.5 (s), 79.2 (s), 80.0 (d), 80.5 (s), 80.7 (d), 82.7 (d), 104.4 (d), 114.0 (s) ppm; ESI-MS (*m/z*): 275.3 (100%, $[M+Na]^+$), 291.3 (5%, $[M+K]^+$); Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39%; Found: C, 61.77; H, 6.52%.

1,2-*O*-Isopropylidene-3-*C*-ethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-α-D-ribofuranose (**11**):



At 0 °C, a solution of compound **10** (7.5 g, 29.0 mmol), TEA (8.3 ml, 60.0 mmol) and catalytic DMAP in dry DCM (100 ml) was treated with pivoloyl chloride (5.35 ml, 44.0 mmol) stirred at rt for 3 h. The reaction mixture was cooled to 0 °C and quenched with water and extracted with DCM. Combined organic phase washed with sat $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography gave compound **11** (8.09 g, 81% yield) as a white solid; mp: 125−127 °C; $[\alpha]_D^{25}$ +4.5 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3305, 3019, 2983, 2933, 2872, 2400, 1726, 1523, 1480, 1215, 1165, 669, 628 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.19 (s, 9H), 1.35 (s, 3H), 1.58 (s, 3H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.71 (s, 1H), 4.27−4.39 (m, 3H), 4.33 (dd, *J* = 2.4, 14.6 Hz, 1H), 4.46 (dd, *J* = 2.4, 14.6 Hz, 1H), 4.63 (d, *J* = 3.7 Hz, 1H), 5.86 (d, *J* = 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.7 (q), 26.8 (q), 27.0 (q, 3C), 38.6 (s), 54.5 (t), 63.5 (t), 74.8 (d), 77.1 (s), 78.5 (d), 79.1 (s), 80.1 (d), 80.6 (s), 82.2 (d), 104.6 (d), 113.8 (s), 178.1 (s) ppm; ESI-MS (*m/z*): 359.1 (100%, $[M+Na]^+$), 375.1 (17%, $[M+K]^+$); Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19%; Found: C, 64.14; H, 7.21%.

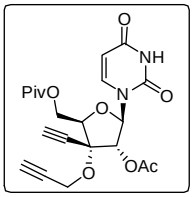
Acetyl-2-*O*-acetyl-3-*C*-ethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-α/β-D-ribofuranoside (**12**):



Compound **11** (8.0 g, 0.024 mol) in 60% acetic acid (50 mL) was heated under reflux for 2 h. The reaction mixture was neutralized by slow addition of solid K_2CO_3 and extracted in ethyl acetate. Combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude diol were dissolved in dry CH_2Cl_2 (30 mL). TEA (8 mL) and catalytic DMAP were added and the mixture was cooled to 0 °C. To this, acetic anhydride (6.8 mL, 0.072 mol) was added and the contents were stirred at 0 °C for 1 h

and then at room temperature for 1 h. The reaction mixture was quenched with cold 2 N HCl and extracted in CH_2Cl_2. Combined organic phase was washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4, and filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography gave a mixture of diacetates **12** (7.87 g, 87% yield) as a yellowish oil, IR ($CHCl_3$) *v*: 3305, 3021, 2977, 2874, 2401, 2119, 1753, 1523, 1480, 1460, 1372, 1216, 1126, 1033, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.20, 1.21 (2s, 9H), 2.07, 2.10 (2s, 3H), 2.18 (s, 3H), 2.43, 2.44 (2t, *J* = 2.4 Hz, 1H), 2.79, 2.83 (2s, 1H), 4.22 (dd, *J* = 2.4, 15.1 Hz, 1H), 4.31−4.38 (m, 3H), 4.41 (dd, *J* = 2.4, 15.1 Hz, 1H), 5.47, 5.49 (2d, *J* = 1.5, 4.4 Hz, 1H), 6.12, 6.42 (2d, *J* = 1.5, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.5 (q), 20.6 (q), 20.9 (q), 21.0 (q), 27.2 (q, 6C), 38.6 (s), 38.7 (s), 55.1 (t, 2C), 63.5 (t), 64.2 (t), 74.7 (d), 74.8 (d), 75.0 (d), 75.5 (s), 76.1(s), 77.9 (d), 78.5 (s, 2C), 78.9 (s), 79.2 (s), 80.3 (s), 80.8 (s), 82.0 (d), 82.7 (d), 94.1 (d), 98.9 (d), 169.1 (s), 169.2 (s, 2C), 169.3 (s), 177.9 (s), 178.0 (s) ppm; ESI-MS (*m/z*): 403.1 (100%, $[M+Na]^+$), 419.1 (25%, $[M+K]^+$); Anal. Calcd for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36%; Found: C, 58.11; H, 6.23%.

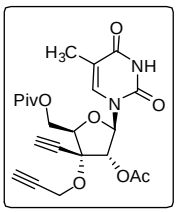
1-[2-*O*-Acetyl-3-*C*-ethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-*β*-D-ribo-pentofuranosyl]uracil (**13**):



A solution of acetates **12** (2.0 g, 5.3 mmol), uracil (1.12 g, 10.5 mmol), and *N,O-bis*(trimethylsilyl) acetamide (2.44 mL, 26.3 mmol) in anhydrous CH_3CN (5 mL) was heated to reflux for 15 min. The reaction mixture was cooled to 0 °C and TMSOTf (4.52 mL, 0.015 mol) was added. The reaction mixture was stirred at 50 °C for 2 h, quenched with cold aq. $NaHCO_3$, and extracted with EtOAc. The combined organic layer was washed with water, dried over Na_2SO_4, and filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography afforded the protected nucleoside **13** (1.7 g, 75% yield) as a white solid, mp: 174−176 °C; $[\alpha]_D^{25}$ +63.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3302, 3019, 2975, 2929, 2400, 1753, 1695, 1634, 1519, 1479, 1425, 1375, 1279, 1159, 1083, 1059, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.22 (s, 9H), 2.18 (s, 3H), 2.47 (t, *J* = 2.5 Hz, 1H), 2.86 (s, 1H), 4.25 (dd, *J* = 2.5, 15.1 Hz, 1H), 4.39 (dd, *J* = 2.6, 7.5 Hz, 2H), 4.42 (dd, *J* = 2.4, 15.1 Hz, 1H), 4.55 (dd, *J* = 5.5, 11.2 Hz, 1H), 5.40 (d, *J* = 3.8 Hz, 1H), 5.76 (dd, *J* = 1.9,

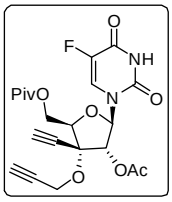
8.2 Hz, 1H), 6.05 (d, *J* = 3.8 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 9.15 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.6 (q), 27.2 (q, 3C), 38.8 (s), 55.8 (t), 63.3 (t), 75.2 (d), 75.8 (s), 77.8 (2d, 2C), 78.8 (s), 81.8 (s), 82.0 (d), 87.5 (d), 102.5 (d), 139.2 (d), 150.0 (s), 162.9 (s), 169.3 (s), 178.0 (s) ppm; ESI-MS (*m/z*): 433.4 (3%, $[M+H]^+$), 455.4 (100%, $[M+Na]^+$), 471.4 (12%, $[M+K]^+$); Anal. Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.59; N, 6.48%; Found: C, 58.13; H, 5.72; N, 6.36%.

1-[2-*O*-Acetyl-3-*C*-ethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-β-D-ribo-pentofuranosyl]thymine (**14**):



Following the above procedure, the glycosylation of acetates **12** (2.3 g, 6.0 mmol) with thymine (1.26 g, 12.1 mmol) gave **14** (1.85 g, 79% yield) as a white solid, mp: 192−194 °C; $[\alpha]_D^{25}$ +41.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3390, 3302, 3020, 2400, 1754, 1696, 1523, 1478, 1372, 1280, 1216, 1132, 924, 849, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22 (s, 9H), 1.92 (d, *J* = 1.2 Hz, 3H), 2.17 (s, 3H), 2.47 (t, *J* = 2.4 Hz, 1H), 2.86 (s, 1H), 4.28 (dd, *J* = 2.5, 15.2 Hz, 1H), 4.29–4.37 (ddd, *J* = 2.4, 4.5, 13.3 Hz, 2H), 4.43 (dd, *J* = 2.4, 15.2 Hz, 1H), 4.55 (dd, *J* = 7.2, 13.3 Hz, 1H), 5.37 (d, *J* = 4.5 Hz, 1H), 6.12 (d, *J* = 4.5 Hz, 1H), 7.40 (d, *J* = 1.2 Hz, 1H), 9.06 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.5 (q), 20.6 (q), 27.2 (q, 3C), 38.8 (s), 55.7 (t), 63.2 (t), 75.2 (d), 76.0 (d), 77.2 (s), 77.7 (d), 77.8 (s), 78.9 (s), 81.8 (d), 86.6 (d), 111.3 (s), 134.7 (d), 150.3 (s), 163.5 (s), 169.5 (s), 178.0 (s) ppm; ESI-MS (*m/z*): 447.5 (5%, $[M+H]^+$), 469.4 (100%, $[M+Na]^+$), 485.4 (5.2%, $[M+K]^+$); Anal. Calcd for $C_{22}H_{26}N_2O_8$: C, 59.19; H, 5.87; N, 6.27%; Found: C, 59.04; H, 5.98; N, 6.10%.

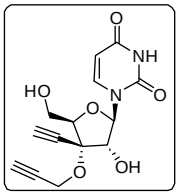
1-[2-*O*-Acetyl-3-*C*-ethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-β-D-ribo-pentofuranosyl]5-fluorouracil (**15**):



Following the procedure used for the preparation of **14**, glycosylation of acetates **12** (2.0 g, 5.2 mol) with 5-fluorouracil (1.3 g, 10.5 mol) gave the nucleoside **15** (1.91 g, 81% yield) as a white solid, mp: 191−192 °C; $[\alpha]_D^{25}$ +8.1 (*c* 1.0,$CHCl_3$); IR ($CHCl_3$) *v*: 3309, 3019, 2400, 1748, 1600, 1522, 1475, 1423, 1216, 1019, 928, 757, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.24 (s, 9H), 2.18 (s, 3H), 2.49 (t, *J* = 2.4 Hz, 1H), 2.89 (s, 1H), 4.31 (dd, *J* = 2.5, 15.2 Hz, 1H), 4.33 (dd, *J* = 2.6, 12.1 Hz, 1H), 4.43 (dd, *J* = 2.6, 12.1

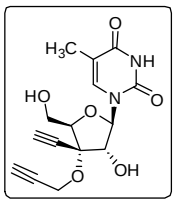
Hz, 1H), 4.45 (dd, *J* = 2.5, 15.2 Hz, 1H), 4.58 (dd, *J* = 5.5, 12.1 Hz, 1H), 5.40 (d, *J* = 4.5 Hz, 1H), 6.07 (dd, *J* = 1.6, 4.5 Hz, 1H), 7.73 (d, *J* = 6.1 Hz, 1H), 8.94 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.6 (q), 27.2 (q, 3C), 38.8 (s), 55.7 (t), 63.3 (t), 75.3 (s), 75.7 (s), 77.9 (d), 78.8 (s), 81.7 (d), 82.4 (d), 87.2 (d), 123.1 (d), 123.8 (d), 124.2 (s), 148.7 (s), 169.5 (s), 169.6 (s), 178.0 (s) ppm; ESI-MS (*m/z*): 451.5 (5%, $[M+H]^+$), 473.4 (100%, $[M+Na]^+$), 489.4 (10%, $[M+K]^+$); Anal. Calcd for $C_{21}H_{23}FN_2O_8$: C, 56.00; H, 5.15; N, 6.22%; Found: C, 56.19; H, 5.10; N, 6.12%.

1-[3-*C*-ethynyl-3-*O*-(2-propynyl)-*β*-D-ribo-pentofuranosyl]uracil (**01**):



A solution of **13** (500 mg, 1.15 mmol) and catalytic NaOMe in methanol (10 mL) was stirred at room temperature for 20 min. The reaction mixture was concentrated under reduced pressure and the crude was purified by silica gel column chromatography to afford the compound **1** (276 mg, 78% yield) as White solid, mp: 114−145 °C; $[\alpha]_D^{25}$ +28.7 (*c* 0.5, MeOH); IR ($CHCl_3$) *v*: 3684, 3308, 3019, 2399, 1598, 1216, 928, 770, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD; 3:1, 500 MHz): δ 2.45 (t, *J* = 2.4 Hz, 1H), 2.85 (s, 1H), 3.76 (dd, *J* = 3.0, 12.4 Hz, 1H), 4.82 (dd, *J* = 4.1, 12.4 Hz, 1H), 4.22 (t, *J* = 3.4 Hz, 1H), 4.31 (d, *J* = 6.3 Hz, 1H), 4.33 (dd, *J* = 2.4, 15.4 Hz, 1H), 4.40 (dd, *J* = 2.4, 15.4 Hz, 1H), 5.61 (d, *J* = 8.2 Hz, 1H), 5.82 (d, *J* = 6.2 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 125 MHz): δ 54.2 (t), 61.6 (t), 74.9 (d), 76.6 (s), 79.0 (d), 79.2 (s), 79.3 (s), 80.2 (d), 84.3 (d), 88.5 (d), 102.1 (d), 141.0 (d), 151.0 (s), 164.0 (s) ppm; ESI-MS (*m/z*): 307.3 (21%, $[M+H]^+$), 329.3 (100%, $[M+Na]^+$), 345.3 (27%, $[M+K]^+$); Anal. Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15%; Found: C, 54.72; H, 4.80; N, 9.04%.

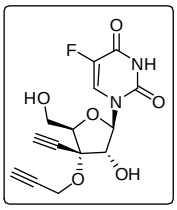
1-[3-*C*-ethynyl-3-*O*-(2-propynyl)-*β*-D-ribo-pentofuranosyl]thymine (**02**):



Deprotection of **14** (500 mg, 1.12 mmol), as followed in the preparation of **1**, afforded compound **2**, (269 mg, 75% yield) White solid, mp: 106−107 °C, $[\alpha]_D^{25}$ +13.4 (*c* 1.0, MeOH); IR ($CHCl_3$) *v*: 3684, 3303, 3019, 2400, 1693, 1600, 1521, 1476, 1423, 1216, 1018, 928, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD; 3:1, 500 MHz): δ 1.83 (s, 3H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.88 (s, 1H), 3.84 (dd, *J* = 2.7, 12.6 Hz, 1H), 3.90 (dd, *J* = 3.9, 12.6 Hz, 1H), 4.28 (t, *J* = 3.1 Hz, 1H), 4.39 (ddd, *J* = 0.7, 2.4, 15.4 Hz, 2H), 4.41(br.d, *J* = 1.0, 2.4 Hz, 1H), 4.46 (ddd, *J* = 1.0, 2.4, 15.4 Hz, 1H), 5.85 (d, *J* = 6.6 Hz, 1H), 7.57 (s,

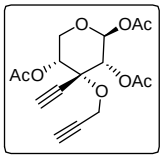
1H); ^{13}C NMR ($CDCl_3$:CD_3OD, 3:1, 125 MHz): δ 11.7 (q), 54.0 (t), 61.5 (t), 74.7 (s), 76.6 (s), 78.7 (d), 79.0 (d), 79.3 (s), 79.9 (d), 84.1 (d), 87.8 (d), 110.6 (s), 136.7 (d), 151.1 (s), 164.4 (s) ppm; ESI-MS (*m/z*): 321.3 (9.3%, $[M+H]^+$), 343.3 (100%, $[M+Na]^+$), 359.4 (11.7%, $[M+K]^+$); Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75%; Found: C, 56.02; H, 5.32; N, 8.51%

1-[3-*C*-Ethynyl-3-*O*-(2-propynyl)-β-D-ribo-pentofuranosyl]5-flurouracil (**03**):



The deprotection of compound **15** (400 mg, 0.89 mmol) was carried out according to the procedure used for the preparation of **1**, to procure nucleoside **3** (240 mg, 83% yield) as a white solid, mp: 109−111 °C; $[\alpha]_D^{25}$ +29.3 (*c* 1.4, MeOH); IR ($CHCl_3$) *v*: 3683, 3304, 3019, 2399, 1600, 1522, 1475, 1423, 1612, 1019, 928, 757, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD, 3:1, 500 MHz): δ 2.50 (t, *J* = 2.4 Hz, 1H), 2.90 (s, 1H), 3.84 (dd, *J* = 2.9, 12.3 Hz, 1H), 3.91 (dd, *J* = 3.3, 12.3 Hz, 1H), 4.29 (t, *J* = 3.1 Hz, 1H), 4.35 (d, *J* = 6.4 Hz, 1H), 4.39 (dd, *J* = 2.4, 15.4 Hz, 1H), 4.46 (dd, *J* = 2.4, 15.4 Hz, 1H), 5.92 (dd, *J* = 1.5, 6.4 Hz, 1H), 8.07 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz): δ 55.t (t), 62.8 (t), 76.1 (s), 78.1 (d), 80.5 (d), 81.1 (s), 81.7 (d), 86.2 (d), 88.8 (d), 126.35 (d, *J* = 35 Hz), 141.2 (d, *J* = 234 Hz), 151.4 (s), 159.43 (d, *J* = 26 Hz) ppm; ESI-MS (*m/z*): 325.3 (9%, $[M+H]^+$), 347.3 (100%, $[M+Na]^+$), 363.3 (25%, $[M+K]^+$); Anal. Calcd for $C_{14}H_{13}FN_2O_6$: C, 51.86; H, 4.04; N, 8.64%; Found: C, 51.92; H, 4.36; N, 8.43%.

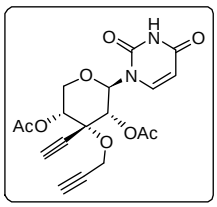
3-*C*-Ethynyl-3-*O*-(2-propynyl)-2,4,5-Tri-O-acetyl-α/β-D-ribopyranose (**16**):



Global deprotection and acetylation of **9** (8 g, 0.22 mol), as followed in the preparation of **12**, gave triacetate **16** (7.38 g, 81% yield). Yellow oil, IR ($CHCl_3$) *v*: 3022, 1752, 1374, 1217, 1154, 1071, 756, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.06 (s, 3H), 2.12, 2.13, 2.15, 2.16 (4s, 6H), 2.43 (t, *J* = 2.4 Hz, 1H), 2.63 (s, 1H), 3.89 (dd, *J* = 8.5, 11.5 Hz, 1H), 3.95 (dd, *J* = 5.3, 11.5 Hz, 1H), 4.49 (dd, *J* = 2.5, 15.4 Hz, 2H), 5.15 (dd, *J* = 5.3, 8.5 Hz, 1H), 5.18 (d, *J* = 7.2 Hz, 1H), 5.92 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.5 (q), 20.6 (q), 20.8 (q), 55.7 (t), 61.7 (t), 71.2 (d), 71.9 (d), 74.1 (d), 74.7 (s), 76.2 (d), 78.5 (s), 79.8 (d), 90.5 (s), 169.0 (s, 2C), 169.4 (s) ppm; ESI-MS (*m/z*): 361.8 (100%,

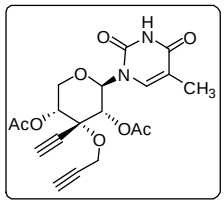
$[M+Na]^+$), 377.3 (0.8%, $[M+K]^+$); Anal. Calcd for $C_{16}H_{18}O_8$: C, 56.80; H, 5.3%; Found: C, 56.91; H, 5.19%.

1-[3-*C*-Ethynyl-3-*O*-(2-propynyl)-2,4,5-tri-*O*-acetyl-*β*-D-ribopyranosyl] uracil (**17**):



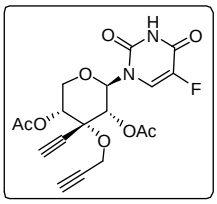
Following the procedure for the preparation of **13**, the glycosylation of acetates **16** (1.0 g, 2.9 mol) with uracil (0.734 g, 5.9 mmol) gave **17** (0.911 g, 79% yield). White solid, mp: 189−190 °C; $[\alpha]_D^{25}$ +31.2 (*c* 0.6, MeOH); IR ($CHCl_3$) *v*: 3394, 3306, 3020, 2400, 1755, 1698, 1637, 1520, 1305, 1263, 1216, 1073, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *δ* 2.08 (s, 3H), 2.14 (s, 3H), 2.50 (t, *J* = 2.4, 1H), 2.62 (s, 1H), 3.86–4.02 (m, 2H), 4.59 (d, *J* = 2.4 Hz, 2H), 5.14 (2dd, *J* = 6.1, 9.6 Hz, 2H), 5.75 (dd, *J* = 2.2, 8.2 Hz, 1H), 6.06 (d, *J* = 9.4 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 8.63 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 20.3 (q), 20.6 (q), 56.5 (t), 63.1 (t), 71.6 (d), 72.3 (d), 74.5 (s), 75.7 (d), 75.8 (d), 78.2 (d), 78.6 (s), 79.8 (s), 103.2 (d), 139.6 (d), 150.1 (s), 162.3 (s), 169.3 (s), 169.5 (s) ppm; ESI-MS (*m/z*): 391.3 (2.3%, $[M+1]^+$), 413.3 (100%, $[M+Na]^+$), 429.3 (14%, $[M+K]^+$); Anal. Calcd for $C_{18}H_{18}N_2O_8$: C, 55.39; H, 4.65; N, 7.18%; Found: C, 55.20; H, 4.76; N, 7.21%.

1-[3-*C*-Ethynyl-3-*O*-(2-propynyl)-2,4,5-tri-*O*-acetyl-*β*-D-ribopyranosyl]thymine (**18**):



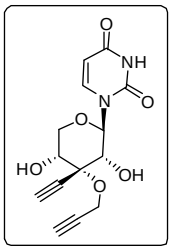
Following the procedure used for the preparation of **14**, glycosylation of acetates **16** (1.0 g, 2.9 mmol) with thymine (0.757 g, 5.9 mmol) gave the nucleoside **18** (0.932 g, 80% yield). White solid, mp: 185−186 °C; $[\alpha]_D^{25}$ –1.6 (*c* 1.0, MeOH); IR ($CHCl_3$) *v*: 3672, 3305, 3448, 3020, 1742, 1693, 1216, 1073, 757, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 1.91 (d, *J* = 1.1 Hz, 3H), 2.07 (s, 3H), 2.14 (s, 3H), 2.49 (t, *J* = 2.4 Hz, 1H), 2.62 (s, 1H), 3.88−3.99 (m, 2H), 4.58 (d, *J* = 2.4 Hz, 2H), 5.13−5.18 (m, 2H), 6.05 (d, *J* = 9.4 Hz, 1H), 7.14 (d, *J* = 1.1 Hz, 1H), 8.56 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 12.4 (q), 20.4 (q), 20.6 (q), 56.5 (t), 63.0 (t), 71.6 (d), 72.3 (d), 74.5 (s), 75.7 (s), 75.7 (d), 77.2 (s), 78.5 (d), 79.8 (d), 111.6 (s), 135.2 (d), 150.3 (s), 163.2 (s), 169.3 (s) 169.5 (s) ppm; ESI-MS (*m/z*): 405 (6.7%, $[M+H]^+$), 427.6 (100%, $[M+Na]^+$), 443.5 (26.7%, $[M+K]^+$); Anal. Calcd for $C_{19}H_{20}N_2O_8$: C, 56.43; H, 4.99; N, 6.93%; Found: C, 56.18; H, 5.10; N, 6.79%.

1-[3-*C*-Ethynyl-3-*O*-(2-propynyl)-2,4,5-tri-*O*-acetyl-*β*-D-ribopyranosyl]5-flurouracil **(19)**:



By following the procedure used for the preparation of **15**, the glycosylation of acetates **16** (1.0 g, 2.9 mmol) with 5-fluorouracil (780 mg, 5.9 mmol) gave **19** (977 mg, 81% yield) as white solid, mp: 169−171 °C; $[\alpha]_D^{25}$ +26.7 (*c* 0.8, MeOH); IR ($CHCl_3$) *v*: 3304, 3020, 1744, 1728, 1704, 1475, 1372, 1306, 1267, 1240, 1216, 1156, 1110, 1062, 928, 757, 670, 597 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *δ* 2.06 (s, 3H), 2.11 (s, 3H), 2.47 (t, *J* = 2.4 Hz, 1H), 2.64 (s, 1H), 3.89−3.99 (m, 2H), 4.54 (d, *J* = 2.4 Hz, 2H), 5.09 (d, *J* = 9.3 Hz, 1H), 5.12 (d, *J* = 8.1 Hz, 1H), 5.99 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): *δ* 20.1 (q), 20.4 (q), 56.3 (t), 62.8 (t), 71.4 (d), 72.2 (d), 74.4 (s), 75.5 (s), 78.3 (d), 78.8 (s), 79.6 (d), 87.6 (d), 124.0 (d, *J* = 35 Hz), 140.0 (d, *J* = 238 Hz), 149.2 (s), 157.3 (d, *J* = 26 Hz), 169.5 (s), 169.7 (s) ppm; ESI-MS (*m/z*): 409 (8%, $[M+H]^+$), 431.2 (100%, $[M+Na]^+$); Anal. Calcd for $C_{18}H_{17}FN_2O_8$: C, 52.94; H, 4.20; N, 6.86%; Found: C, 52.73; H, 4.35; N, 6.72%.

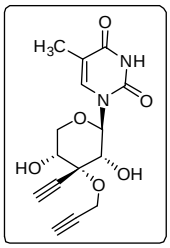
1[3-*C*-Ethynyl-3-*O*-(2-propynyl)-*β*-D-ribopyranosyl]uracil (**04**):



Deacetylation of **17** (500 mg, 1.28 mmol), as followed in the preparation of **1**, gave nucleoside **4** (306 mg, 79% yield), White solid, mp: 133−135 °C; $[\alpha]_D^{25}$ +18.9 (*c* 0.3, MeOH); IR ($CHCl_3$) *v*: 3609, 3302, 3319, 2401, 2253, 2072, 1688, 1456, 1392, 1216, 1118, 1076, 974, 909, 759, 669, 650 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD, 3:1, 200 MHz): d 2.44 (t, *J* = 2.4 Hz, 1H), 2.69 (s, 1H), 3.55 (d, *J* = 9.3 Hz, 1H), 3.66−3.73 (m, 3H), 4.56 (d, *J* = 2.4 Hz, 2H), 5.60 (d, *J* = 8.0 Hz, 1H), 5.61 (d, *J* = 9.3 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$:CD_3OD, 3:1, 50 MHz): *δ* 56.5 (t), 65.8 (t), 71.5 (d), 73.2 (d), 74.5 (s), 77.6 (s), 78.0 (d), 78.3 (s), 80.3 (d), 80.6 (d), 102.6 (d), 140.3 (d), 151.0 (s), 163.9 (s) ppm; ESI-MS (*m/z*): 307.2 (16%, $[M+H]^+$), 329.2 (100%, $[M+Na]^+$), 345.2 (20%, $[M+K]^+$); Anal. Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15% Found: C, 54.78; H, 4.69; N, 9.01%.

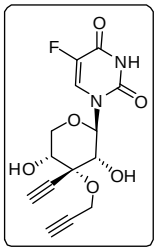
1[3-*C*-Ethynyl-3-*O*-(2-propynyl)-*β*-D-ribopyranosyl]thymine (**05**):

Deacetylation of **18** (480 mg, 1.19 mmol), as followed in the preparation of **1**, gave nucleoside **5** (285 mg, 78% yield), White solid, mp: 121−123 °C; $[\alpha]_D^{25}$ −15.3 (*c* 0.2, MeOH); IR ($CHCl_3$) *v*: 3302, 3319, 2401, 2253, 2072, 1688, 1456, 1392, 1216, 1118, 1076, 974 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 200 MHz): *δ* 1.79 (d, *J* = 1.1 Hz, 3H), 2.47 (t, *J* = 2.4 Hz, 1H), 2.72 (s, 1H), 3.57 (m, 1H), 3.70−3.83 (m, 3H), 4.59 (2d, *J* = 12.5 Hz, 2H), 5.62 (d, *J* = 9.4 Hz, 1H), 7.07 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 50 MHz): *δ* 11.1 (q), 55.9 (t), 65.3 (t), 71.2 (d), 72.4 (d), 73.7 (d), 76.4 (s), 77.2 (s), 77.9 (s), 79.8 (d), 80.0 (d), 110.4 (s), 135.9 (d), 151.9 (s), 164.2 (s) ppm; ESI-MS (*m/z*): 321.2 (7%, $[M+H]^+$), 343.3 (100%, $[M+Na]^+$); Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75%; Found: C, 56.09; H, 5.15; N, 8.62%.



1[3-*C*-Ethynyl-3-*O*-(2-propynyl)-*β*-D-ribopyranosyl]5-flurouracil (**06**):

The deacetylation of compound **19** (487 mg, 1.19 mmol) was carried out according to the procedure used for the preparation of **1**, to procure nucleoside **6** (321 mg, 81% yield). White solid, mp: 197−198 °C; $[\alpha]_D^{25}$ +6.6 (*c* 0.3, MeOH); IR ($CHCl_3$) *v*: 3675, 3302, 3319, 2401, 2253, 2072, 1688, 1456, 1392, 1216, 1118, 1076, 974, 909 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 200 MHz): *δ* 2.39 (t, *J* = 2.4 Hz, 1H), 2.67 (s, 1H), 3.46 (d, *J* = 9.4 Hz, 1H), 3.57−3.69 (m, 3H), 4.49 (s, 1H), 4.50 (s, 1H), 5.55 (dd, *J* = 1.7, 9.4 Hz, 1H), 7.33 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 125 MHz): *δ* 56.5 (t), 65.8 (t), 71.4 (d), 73.1 (d), 74.3 (d), 77.4 (d), 77.9 (s), 78.2 (s), 80.2 (s), 80.7 (d), 124.1 (d, *J* = 26 Hz), 140.0 (d, *J* = 237), 149.7 (s), 157.5 (d, *J* = 26 Hz) ppm; ESI-MS (*m/z*): 325.2 (7.1%, $[M+H]^+$), 347.2 $[M+Na]^+$), 363.2 (2.2%, $[M+K]^+$); Anal. Calcd for $C_{14}H_{13}FN_2O_6$: C, 51.86; H, 4.04; N, 8.64%; Found: C, 51.76; H, 4.15; N, 8.71%.



Representative procedures for the [2+2+2]-cyclotrimerization reactions of diynes:

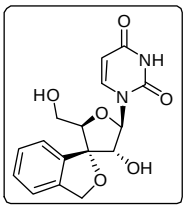
Procedure A: A solution of diyne 1 (0.5 mmol) and alkyne (1.5 mmol) in 4:1 toluene/ethanol (12 mL) was degassed with dry argon for 20 min. To this, Wilkinson's catalyst [$RhCl(PPh_3)_3$] (0.03 mmol) was added, and the mixture was

heated at 80 °C for 6 h and then allowed to cool to room temperature. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography to procure the cyclotrimerization product.

Procedure B: A solution of diyne 1 (0.5 mmol) in toluene/ethanol (12 and 3 mL, respectively) in a long glass tube was degassed with dry acetylene for 20 min; then, Wilkinson's catalyst [$RhCl(PPh_3)_3$] (0.03 mmol) was introduced into the mixture. The reaction mixture was cooled to –78 °C, and acetylene gas was condensed by continuous bubbling for 25 min. and the tube sealed by fusion. The sealed tube was transferred into steel bomb, heated at 80 °C for 6 h. After cooling to room temperature, the tube was broken and the mixture was transferred into a round-bottom flask and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford the cyclotrimerized product.

Procedure C: A solution of diyne 1 (0.5 mmol) and alkyne (0.5 mmol) in DCE (5 mL) was degassed with dry argon for 20 min. To this, Cp*RuCl(cod) catalyst (0.03 mmol) was added, and the mixture was stired for 4-6 h at room temperature. The solvent evaporated under reduced pressure. The residue was purified by silica gel chromatography to procure the cyclotrimerization product.

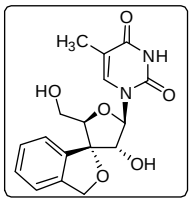
1-[3-*C*,3-*O*-(*o*-Phenylenemethylene)-*β*-D-ribofuranosyl]uracil (**20**):



Following procedure B, using diyne **1** (100 mg, 0.33 mmol) and acetylene gas were used to get a compound **20** (86 mg, 79% yield) as a white solid, mp: 234–236 °C; $[\alpha]_D^{25}$ +14.3 (*c* 0.3, MeOH); IR ($CHCl_3$): 3630, 3371, 3018, 1728, 1522, 1421, 1375, 1216, 1120, 1048, 975, 757 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 500 MHz): δ 3.38 (dd, J = 1.2, 12.1 Hz, 1H), 3.64 (dd, J = 2.8, 12.1 Hz, 1H), 4.07 (dd, J = 1.2, 2.8 Hz, 1H), 4.45 (d, J = 8.2 Hz, 1H), 5.03 (d, J = 12.7 Hz, 1H), 5.05 (d, J = 12.7 Hz, 1H), 5.60 (d, J = 8.2 Hz, 1H), 5.91 (d, J = 8.2 Hz, 1H), 7.08–7.10 (m, 1H), 7.17–7.19 (m, 2H), 7.62 (dd, J = 1.9, 6.8 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 125 MHz): δ 60.4 (t), 72.2 (t), 78.1 (d), 86.0 (d), 87.7 (d), 94.8 (s), 102.2 (d), 120.6 (d), 123.1 (d), 127.6 (d), 128.6 (d), 134.9 (s), 140.9 (s), 142.0 (d), 151.3 (s), 164.3 (s) ppm; ESI-MS (*m/z*): 333.4 (18%, $[M+H]^+$), 355.3 (100%,

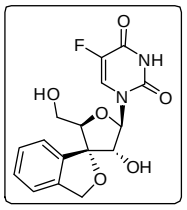
$[M+Na]^+$), 371.3 (32%, $[M+K]^+$); Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 5.85; N, 8.43%; Found: C, 57.51; H, 5.99; N, 8.21%.

1-[3-*C*,3-*O*-(*o*-Phenylenemethylene)-*β*-D-ribofuranosyl]thymine (**21**):



Procedure B was followed. Diyne **2** (50 mg, 0.163 mmol) and acetylene gas were used to afford compound **21** (41.6 mg, 77% yield). White solid, mp: 262−163 °C; $[\alpha]_D^{25}$ +4.4 (*c* 1.1 MeOH); IR ($CHCl_3$) *v*: 3421, 3019, 1660, 1404, 1216, 1035, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 400 MHz): δ 1.21 (s, 3H), 3.53 (d, *J* = 11.8 Hz, 1H), 3.80 (dd, *J* = 3.0, 11.8 Hz, 1H), 4.20 (d, *J* = 2.4 Hz, 1H), 4.52 (d, *J* = 8.1 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 5.20 (d, *J* = 12.6 Hz, 1H), 6.11 (d, *J* = 8.1 Hz, 1H), 7.23 (dd, *J* = 3.0, 8.0 Hz, 1H), 7.29–7.34 (m, 2H), 7.37–7.38 (m, 1H), 7.76 (dd, *J* = 2.5, 7.1 Hz, 1H), 8.58 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 13.7 (q), 60.3 (t), 72.2 (t), 78.5 (d), 85.9 (d), 87.0 (d), 94.9 (s), 120.6 (d), 123.1 (d), 125.4 (s), 125.7 (d), 127.6 (d), 128.6 (d), 134.7 (s), 141.0 (s), 149.9 (s), 157.8 (s) ppm**;** ESI-MS (*m/z*): 369.3 (100%, $[M+Na]^+$); Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09%; Found: C, 58.71; H, 5.39; N, 8.01%.

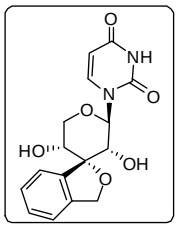
1-[3-*C*,3-*O*-(*o*-Phenylenemethylene)-*β*-D-ribofuranosyl]5-flurouracil (**22**):



General procedure B was followed. Diyne **3** (110 mg, 0.34 mmol) and acetylene gas were used to afford compound **22** (118 mg, 75% yield). White solid, mp: 262 °C; $[\alpha]_D^{25}$ +11.6 (*c* 0.2, MeOH); IR ($CHCl_3$) *v*: 3684, 3621, 3019, 2975, 2927, 2400, 1609, 520, 1476, 1423, 1215, 1031, 928 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 400 MHz): δ 3.53 (dd, *J* =1.2, 11.8 Hz, 1H), 3.80 (dd, *J* = 3.0, 11.8 Hz, 1H), 4.20 (dd, *J* = 1.2, 2.8 Hz, 1H), 4.52 (d, *J* = 8.1 Hz, 1H), 5.16 (d, *J* = 12.5 Hz, 1H), 5.20 (d, *J* = 12.5 Hz, 1H), 6.12 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.22 (dd, *J* = 2.6, 7.1 Hz, 1H), 7.28–7.37 (m, 2H), 7.73–7.81 (m, 1H), 8.60 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 60.3 (t), 72.2 (t), 78.4 (d), 85.9 (d), 87.0 (d), 94.9 (s), 120.5 (d), 123.1 (d), 125.3 (s), 125.5 (d, *J* = 34 Hz), 125.7 (d), 127.5 (d), 128.6 (d), 134.7 (s), 140.4 (d, *J* = 234 Hz,), 140.9 (s), 150.0 (s), 157.9 (d, *J* = 26 Hz) ppm; ESI-MS (*m/z*): 350.3 (3.7%, $[M+H]^+$), 373.2

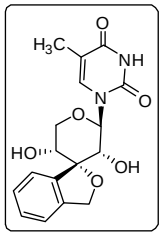
(100%, $[M+Na]^+$), 389.2 (18%, $[M+K]^+$); Anal. Calcd for $C_{16}H_{15}FN_2O_6$: C, 54.86; H, 4.32; N, 8.00%; Found: C, 54.68; H, 4.40; N, 7.92%.

1-[3-*C*,3-*O*-(*o*-Phenylenemethylene)-*β*-D-ribopyranosyl]uracil (**23**):



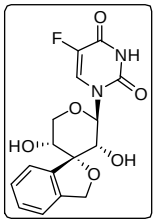
By following procedure B, cycloaddition of the diyne **4** (100 mg, 0.55 mmol) with acetylene gave compound **23** (77 mg, 71% yield) as a white solid. mp: 138–140 °C; $[\alpha]_D^{25}$ +56.5 (*c* 0.4, MeOH); IR (nujol) *v*: 3393, 3018, 2961, 2854, 1679, 1459, 1377, 1243, 1062 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz): δ 3.85 (t, *J* = 10.8 Hz, 1H), 3.94 (dd, *J* = 5.4, 10.8 Hz, 1H), 4.03 (dd, *J* = 5.4, 10.8 Hz, 1H), 4.06 (d, *J* = 9.5 Hz, 1H), 5.22 (d, *J* = 11.8 Hz, 1H), 5.27 (d, *J* = 11.8 Hz, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 5.86 (d, *J* = 9.5 Hz, 1H), 7.25 (dd, *J* = 6.1, 1.55 Hz, 1H), 7.30–7.35 (m, 2H), 7.38–7.40 (m, 1H), 7.79 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz): *δ* 68.8 (t), 71.4 (d), 72.7 (d), 75.8 (t), 83.7 (d), 93.9 (s), 103.2 (d), 121.8 (d), 122.3 (d), 128.6 (d), 129.4 (d), 139.5 (s), 142.9 (d), 143.0 (s), 152.9 (s), 166.1 (s) ppm; ESI-MS (*m/z*): 333.60 (19.12%, $[M+1]^+$), 355.60 (100%, $[M+Na]^+$), 371.57 (11.03%, $[M+K]^+$); Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43%; Found: C, 57.95; H, 4.98; N, 8.56%.

1-[3-*C*,3-*O*-(*o*-Phenylenemethylene)-*β*-D-ribopyranosyl]thymine **(24)**:



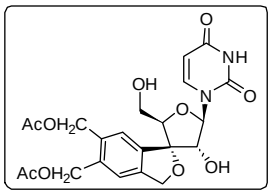
Cycloaddition of diyne **5** (130 mg, 0.40 mmol) and acetylene gas, following procedure B gave compound **24** (97 mg, 69% yield) as a white solid. mp: 116–118 °C; $[\alpha]_D^{25}$ +30.0 (*c* 0.8, MeOH); IR (nujol) *v*: 3371, 3017, 2925, 2855, 1653, 1463, 1377, 1064, 762 cm^{-1}; ^1H NMR (Acetone−D_6, 200 MHz): *δ* 1.85 (d, *J* = 1.1 Hz, 3H), 3.83 (t, *J* = 10.7 Hz, 1H), 3.91 (m, 1H), 3.93 (dd, *J* = 5.5, 10.7 Hz, 1H), 4.05−4.11 (m, 1H), 4.17 (d, *J* = 9.1 Hz, 1H), 4.23 (dd, *J* = 8.8, 9.5 Hz, 1H), 5.24 (d, *J* = 11.7 Hz, 1H), 5.29 (d, *J* = 11.7 Hz, 1H), 5.90 (d, *J* = 9.5 Hz, 1H), 7.27–7.28 (m, 1H), 7.30−7.35 (m, 2H), 7.40–7.42 (m, 1H), 7.63 (q, *J* = 1.1 Hz, 1H), 10.12 (br.s, 1H); ^{13}C NMR (Acetone−D_6, 50 MHz): *δ* 12.3 (q), 68.5 (t), 71.1 (d), 72.2 (d), 75.3 (t), 82.8 (d), 93.5 (s), 110.8 (s), 121.4 (d), 122.0 (d), 127.9 (d), 128.7 (d), 137.1 (d), 139.7 (s), 142.5 (s), 152.0 (s), 164.2 (s) ppm; ESI-MS (*m/z*): 369.03 (100%, $[M+Na]^+$), 385.99 (70%, $[M+K]^+$); Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09%; Found: C, 59.10; H, 5.06; N, 7.97%.

1-[3-*C*,3-*O*-(*o*-Phenylenemethylene)-*β*-D-ribopyranosyl]5-flurouracil (**25**):



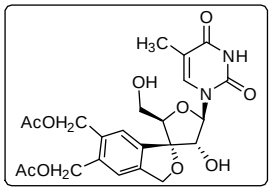
General procedure B was followed. Diyne **6** (110 mg, 0.34 mmol) and acetylene gas were used to afford compound **25** (86.7 mg, 73% yield) as a white solid. mp: 153–155 °C; $[\alpha]_D^{25}$ +44.0 (*c* 0.7, MeOH); IR (nujol) *v*: 3387, 3021, 2920, 2854, 1698, 1666, 1461, 1377, 1284, 1245, 1063, 914, 756 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz): δ 3.85 (t, *J* = 10.9 Hz, 1H), 3.95 (dd, *J* = 5.3, 10.7 Hz, 1H), 3.99–4.04 (m, 2H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.26 (d, *J* = 11.9 Hz, 1H), 5.84 (dd, *J* = 1.5, 9.5 Hz, 1H), 7.23−7.25 (m, 1H), 7.29–7.38 (m, 3H), 7.94 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (CD_3OD, 50 MHz): δ 68.5 (t), 71.0 (d), 72.5 (d), 75.6 (t), 83.6 (d), 93.5 (s), 121.7 (d, *J* = 36 Hz), 126.1 (d), 126.5 (d), 128.4 (d), 129.2 (d), 139.0 (s), 142.5 (s), 142.7 (d, *J* = 234 Hz), 151.2 (s), 159.1 (d, *J* = 26 Hz) ppm; ESI-MS (*m/z*): 351.5 (18%, $[M+H]^+$), 373.5 (100%, $[M+Na]^+$); Anal. Calcd for $C_{16}H_{15}FN_2O_6$: C, 54.86; H, 4.32; N, 8.0%; Found: C, 54.71; H, 4.48; N, 8.13%.

1-[3-*C*,3-*O*-{*o*-(3,4-Di-acetyloxymethyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**26**):



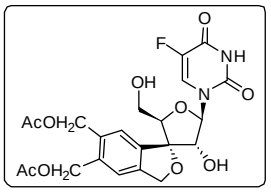
General procedure A was followed. Diyne **1** (100 mg, 0.33 mmol) and 1,4-diacetoxy-2-butyne (0.24 mL, 1.63 mmol) were used to afford compound **26** (129 mg, 83% yield) as a white solid. mp: 181−183 °C; $[\alpha]_D^{25}$ +25.0 (*c* 0.5, MeOH); IR ($CHCl_3$) *v*: 3683, 3304, 3019, 2400, 1749, 1600, 1422, 1478, 1424, 1372, 1216, 1030, 928 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 500 MHz): δ 2.02 (s, 3H), 2.04 (s, 3H), 3.45 (dd, *J* = 1.0, 11.8 Hz, 1H), 3.77 (dd, *J* = 2.9, 12.0 Hz, 1H), 4.16 (dd, *J* = 1.1, 2.7 Hz, 1H), 4.57 (d, *J* = 8.2 Hz, 1H), 5.11 (d, *J* = 12.7 Hz, 1H), 5.13 (d, *J* = 2.4, 12.7 Hz, 1H), 5.15–5.17 (m, 4H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.71 (d, *J* = 8.1 Hz, 1H), 5.95 (d, *J* = 8.2 Hz, 1H), 7.78 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 125 MHz): δ 20.8 (q, 2C) 60.6 (t), 63.4 (t), 64.1 (t), 72.3 (t), 78.2 (d), 86.0 (d), 88.3 (d), 95.1 (s), 102.7 (d), 122.1 (d), 125.5 (d), 134.1 (s), 135.7 (s), 135.8 (s), 142.0 (s), 142.1 (d), 151.3 (s), 164.0 (s), 170.9 (s), 171.3 (s) ppm; ESI-MS (*m/z*): 477.4 (5.3%, $[M+H]^+$), 499.3 (100%, $[M+Na]^+$), 515.5 (3.5%, $[M+K]^+$); Anal. Calcd for $C_{22}H_{24}N_2O_{10}$: C, 55.46; H, 5.08; N, 5.88%; Found: C, 55.30; H, 5.21; N, 5.93%.

1-[3-*C*,3-*O*-{*o*-(3,4-Di-acetyloxymethyl)phenylenemethylene}-*β*-D-ribofuranosyl]thymine (**27**):



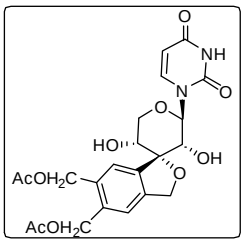
General procedure A was followed. Diyne **2** (100 mg, 0.31 mmol) and 1,4-diacetoxy-2-butyne (0.23 mL, 1.56 mmol) were used to afford a compound **27** (92 mg, 85% yield) as a white solid. mp: 228−230 °C; IR ($CHCl_3$) *v*: 3685, 3019, 2400, 1734, 1215, 1020, 928, 849, 765, 699 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 200 MHz): δ 1.91 (s, 3H), 2.06, 2.08 (2s, 6H), 3.50 (dd, *J* = 1.2, 12.1 Hz, 1H), 3.78 (dd, *J* = 2.9, 12.1 Hz, 1H), 4.17 (dd, *J* = 1.2, 2.8 Hz, 1H), 4.58 (d, *J* = 8.2 Hz, 1H), 5.15–5.24 (m, 6H), 5.99 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H), 7.85 (s, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 12.4 (q), 20.9 (q, 2C), 61.0 (t), 63.4 (t), 64.2 (t), 72.4 (t), 77.2 (d), 86.0 (d), 90.0 (d), 95.0 (s), 111.2 (s), 122.1 (d), 125.8 (d), 134.4 (s), 135.7 (s), 136.0 (s), 138.3 (d), 141.9 (s), 151.2 (s), 163.8 (s), 170.8 (s), 171.2 (s) ppm; ESI-MS (*m/z*): 503.4 (100%, $[M+Na]^+$); Anal. Calcd for $C_{23}H_{26}N_2O_{10}$: C, 56.32; H, 5.34; N, 5.71%; Found: C, 56.29; H, 5.46; N, 5.76%.

1-[3-*C*,3-*O*-{*o*-(3,4-Di-acetyloxymethyl)phenylenemethylene}-*β*-D-ribofuranosyl]5-flurouracil (**28**):



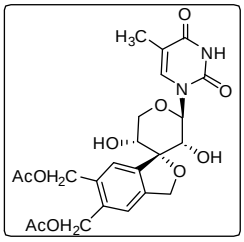
By following procedure A, cycloaddition of the diyne **3** (150 mg, 0.46 mmol) with 1,4-Diacetoxy-2-butyne (0.35 mL, 2.31mmol) gave compound **28** (187 mg, 82% yield) as a white solid. mp: 132−134 °C; $[\alpha]_D^{25}$ +25.9 (*c* 0.5, MeOH); IR ($CHCl_3$) *v*: 3684, 3532, 3019, 1681, 2400, 2236, 1521, 1476, 1215, 1117, 1029, 972, 849, 770 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 500 MHz): δ 2.14, 2.15 (2s, 6H), 3.60 (dd, *J* = 1.4, 12.1, 1H), 3.84 (dd, *J* = 3.1, 12.1 Hz, 1H), 4.24 (dd, *J* = 1.4, 2.8 Hz, 1H), 4.52 (br.s, 1H), 5.21 (d, *J* = 12.7 Hz, 1H), 5.24 (d, *J* = 12.7 Hz, 1H), 5.26–5.30 (m, 4H), 6.19 (dd, *J* = 1.6, 8.1 Hz, 1H), 7.45 (s, 1H), 7.91 (s, 1H), 8.67 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$:DMSO-D6; 3:1, 125 MHz): δ 20.9 (q), 21.00 (q), 61.4 (t), 64.3 (t), 64.7 (t), 73.1 (t), 79.7 (d), 87.0 (d), 87.2 (d), 96.2 (s), 101.0 (s), 123.0 (d), 125.6 (d), 126.18 (d, *J* = 35 Hz), 135.5 (s), 136.8 (s), 137.4 (s), 141.65 (d, *J* = 233 Hz), 143.6 (s), 151.1 (s), 158.5 (d, *J* = 26 Hz), 171.7 (2s) ppm; ESI-MS (*m/z*): 517.5 (100%, $[M+Na]^+$), 533.5 (43%, $[M+K]^+$); Anal. Calcd for $C_{22}H_{23}FN_2O_{10}$: C, 53.44; H, 4.69; N, 5.67%; Found: C, 53.35; H, 4.74; N, 5.63%.

1-[3-*C*,3-*O*-{*o*-(3,4-Di-acetyloxymethyl)phenylenemethylene}-*β*-D-ribopyranosyl]uracil (**29**):



Cycloaddition of diyne **4** (130 mg, 0.42 mmol) and 1,4-Diacetoxy-2-butyne (0.32 mL, 2.12 mmol) following procedure B gave compound **29** (164 mg, 81% yield) as a colorless liquid, $[\alpha]_D^{25}$ +15.9 (*c* 0.4, MeOH); IR ($CHCl_3$) *v*: 3687, 3650, 3567, 3019, 2930, 2400, 1732, 1693, 1612, 1517, 1474, 1423, 1386, 1216, 1075, 1028, 961, 928 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 400 MHz): δ 1.87 (s, 6H), 3.62 (t, *J* = 12.5 Hz, 2H), 3.67 (d, *J* = 9.4 Hz, 1H), 3.75 (dd, *J* = 1.8, 5.3 Hz, 1H), 3.78 (dd, *J* = 1.8, 5.3 Hz, 1H), 4.99 (s, 2H), 5.00 (s, 2H), 5.52 (d, *J* = 8.1 Hz, 1H), 5.59 (d, *J* = 9.4 Hz, 1H), 7.08 (s, 1H), 7.12 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 20.2 (q), 20.3 (q), 63.3 (t), 63.7 (t), 67.2 (t), 69.7 (d), 71.5 (d), 74.2 (t), 82.0 (d), 92.1 (s), 102.1 (d), 121.9 (d), 122.1 (d), 133.7 (s), 134.9 (s), 138.1 (s), 140.4 (d), 141.8 (s), 151.0 (s), 163.9 (s), 170.9 (s), 171.1 (s) ppm; ESI-MS (*m/z*): 477.9 (0.8%, $[M+H]^+$), 499.9 (100%, $[M+Na]^+$), 515.9 (1.3%, $[M+K]^+$); Anal. Calcd for $C_{22}H_{24}N_2O_{10}$: C, 55.46; H, 5.88; N, 5.88%; Found: C, 55.39; H, 5.96; N, 5.78%.

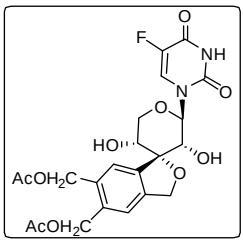
1-[3-*C*,3-*O*-{*o*-(3,4-Di-acetyloxymethyl)phenylenemethylene}-*β*-D-ribopyranosyl]thymine (**30**):



General procedure A was followed. Diyne **5** (120 mg, 0.37 mmol) and 1,4-Diacetoxy-2-butyne (0.28 mL, 1.9 mmol) were used to afford compound **30** (136 mg, 74% yield) as a colorless gum. $[\alpha]_D^{25}$ +14.8 (*c* 0.5, MeOH); IR ($CHCl_3$) *v*: 3686, 3650, 3020, 2930, 2400, 1731, 1723, 1694, 1602, 1519, 1475, 1422, 1215, 1028, 928, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.91 (d, *J* = 1.1 Hz, 3H), 2.09 (2s, 6H), 3.29 (d, *J* = 10.7 Hz, 1H), 3.75 (d, *J* = 6.9 Hz, 1H), 3.82 (d, *J* = 10.7 Hz, 1H), 3.97−4.11 (m, 2H), 5.17 (d, *J* = 12.8 Hz, 1H), 5.20 (br.s, 2H), 5.23 (d, *J* = 12.8 Hz, 1H), 5.27 (d, *J* = 12.7 Hz, 1H), 5.43 (d, *J* = 12.7 Hz, 1H), 5.82 (d, *J* = 9.3 HZ, 1H), 7.20 (d, *J* = 1.1 Hz, 1H), 7.33 (2s, 2H), 8.99 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.4 (q), 20.9 (q), 21.1 (q), 63.5 (t), 63.7 (t), 67.7 (t), 70.3 (d), 73.4 (d), 75.1 (t), 82.0 (d), 92.5 (s), 111.6 (s), 122.5 (d), 122.6 (d), 134.6 (s), 135.3 (d), 135.8 (s), 137.6 (s), 141.4 (s), 151.3 (s), 163.6 (s), 170.7 (s), 170.8 (s) ppm; ESI-MS (*m/z*):

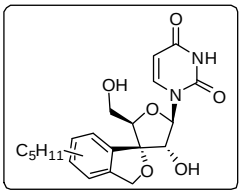
491.89 (0.6%, $[M+H]^+$), 513.97 (100%, $[M+Na]^+$), 529.96 (2.7%, $[M+K]^+$); Anal. Calcd for $C_{23}H_{26}N_2O_{10}$: C, 56.32; H, 5.34; N, 5.71%; Found: C, 56.18; H, 5.32; N, 5.52%.

1-[3-*C*,3-*O*-{*o*-(3,4-Di-acetyloxymethyl)phenylenemethylene}-*β*-D-ribopyranosyl]5-flurouracil (**31**):



General procedure A was followed. Diyne **6** (100 mg, 0.31 mmol) and 1,4-Diacetoxy-2-butyne (0.234 mL, 1.54 mmol) were used to procure compound **31** (122 mg, 80% yield) as a white gum. $[\alpha]_D^{25}$ +134.1 (*c* 0.2, MeOH) ; IR ($CHCl_3$) *v*: 3686, 3019, 2927, 2855, 2400, 1731, 1601, 1519, 1471, 1417, 1215, 1021, 928 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 400 MHz): δ 1.84 (2s, 6H), 3.56–3.65 (m, 2H), 3.71–3.77 (m, 2H), 4.96 (s, 2H), 4.98 (s, 2H), 5.00–5.08 (m, 2H), 5.56 (dd, *J* = 1.4, 9.4 Hz, 1H), 7.06 (s, 1H), 7.12 (s, 1H), 7.47 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 20.1 (q, 2C), 63.3 (t), 63.6 (t), 67.1 (t), 69.5 (d), 71.3 (d), 74.1 (t), 82.1 (d), 92.0 (s), 121.8 (d), 122.2 (d), 124.3 (d, *J* = 35 Hz), 133.6 (s), 134.8 (s), 138.1 (s), 140.3 (d, *J* = 236 Hz), 141.8 (s), 149.7 (s), 157.5 (d, *J* = 27 Hz), 170.8 (s), 171.1 (s) ppm; ESI-MS (*m/z*): 517.4 (100%, $[M+Na]^+$); Anal. Calcd for $C_{22}H_{23}FN_2O_{10}$: C, 53.44; H, 4.69; N, 5.67%; Found: C, 53.24; H, 4.95; N, 5.45%.

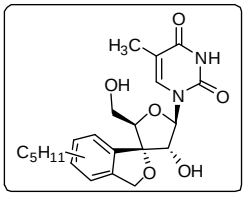
1-[3-*C*,3-*O*-{*o*-(3/4-^{n}Pentyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**32**):



General procedure A was followed. Diyne **1** (120 mg, 0.39 mmol) and 1-heptyne (0.26 mL, 1.96 mmol) were used to afford a 1:1 mixture of compounds **32** (126 mg, 80% yield) as a white solid, IR ($CHCl_3$) *v*: 3683, 3019, 2400, 1695, 1522, 1476, 1424, 1416, 1021, 908 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 400 MHz): δ 0.85 (t, *J* = 6.5 Hz, 3H), 1.27–1.29 (m, 6H), 1.56 (br.s, 3H), 2.57 (dd, *J* = 7.6, 15.4 Hz, 2H), 3.54 (d, *J* = 12.1 Hz, 1H), 3.76 (dd, *J* = 3.0, 12.1 Hz, 1H), 4.18 (m, 1H), 4.57 (t, *J* = 8.5 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 5.72 (d, *J* = 8.1 Hz, 1H), 6.01 (d, *J* = 8.1 Hz, 1H), 7.03–7.15 (m, 2H), 7.56–7.64 (m, 1H), 8.18 (dd, *J* = 1.3, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 13.6 (q), 22.2 (t), 31.0 (t), 31.2 (t), 35.5 (t), 35.6 (t), 60.5 (t), 72.1 (t), 72.2 (t), 77.3 (s), 77.9 (s), 78.0 (d), 86.0 (2d), 88.0 (d), 88.1 (d), 94.7 (s), 102.2 (d), 120.3 (s), 120.4 (d), 122.9 (d), 128.0 (d), 128.9 (d),

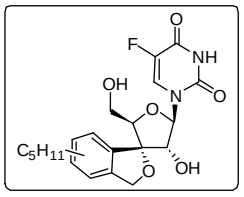
132.1 (s), 135.0 (s), 138.2 (s), 141.1 (s), 142.1 (2d), 142.7 (d), 143.8 (s), 151.3 (s), 164.3 (s) ppm; ESI-MS (*m/z*): 403.2 (2.4%, $[M+H]^+$), 425.3 (100%, $[M+Na]^+$), 441.2 (4.5%, $[M+K]^+$); Anal. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96%; Found: C, 62.58; H, 6.60; N, 7.03%.

1-[3-*C*,3-*O*-{*o*-(3/4-^{n}Pentyl)phenylenemethylene}-*β*-D-ribofuranosyl]thymine (**33**):



By following procedure A, cycloaddition of the diyne **2** (100 mg, 0.31 mmol) with 1-heptyne (0.20 mL, 1.56 mmol) gave a 1:1 mixture of compounds **33** (105 mg, 81% yield) as a white solid. mp: 210−212 °C; IR ($CHCl_3$) *v*: 3685, 3308, 3020, 2400, 1521, 1476, 1423, 1385, 1215, 1100, 1068, 1044, 909, 770, 669, 651, 626 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD, 3:1, 400 MHz): *δ* 0.85 (t, *J* = 6.1 Hz, 3H), 1.21−1.29 (m, 4H), 1.57 (br.s, 3H), 1.88 (s, 3H), 2.59 (dd, *J* = 7.6, 15.4 Hz, 2H), 3.52 (d, *J* = 12.1 Hz, 1H), 3.75 (d, *J* = 12.1 Hz, 1H), 3.92 (br.s, 1H), 4.61 (t, *J* = 6.8 Hz, 1H), 5.13 (2d, *J* = 12.6 Hz, 2H), 5.94 (d, *J* = 7.8 Hz, 1H), 7.02−7.12 (m, 2H), 7.46−7.65 (m, 2H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD, 3:1, 100 MHz): *δ* 11.9 (q), 13.6 (q), 22.2 (t), 31.0 (t), 31.2 (t, 2C), 35.5 (t), 35.6 (t), 60.5 (t), 72.1 (t), 72.2 (s), 77.2 (s), 77.9 (s), 78.0 (d), 86.0 (2d), 88.0 (d), 88.1 (d), 94.7 (s), 102.2 (d), 120.3 (s), 120.4 (d), 122.9 (d), 128.0 (d), 128.9 (d), 132.1 (s), 135.0 (s), 138.2 (s), 141.1 (s), 142.1 (2d), 142.7 (s), 143.8 (s), 151.3 (s), 164.3 (s) ppm; ESI-MS (*m/z*): 417.4 (39%, $[M+H]^+$), 439.4 (100%, $[M+Na]^+$), 455.2 (9%, $[M+K]^+$); Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78; N, 6.73%; Found: C, 63.37; H, 6.83; N, 6.82%.

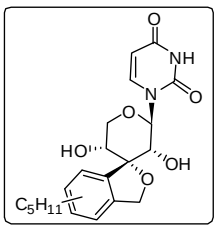
1-[3-*C*,3-*O*-{*o*-(3/4-^{n}Pentyl)phenylenemethylene}-*β*-D-ribofuranosyl]5-flurouracil (**34**):



Cycloaddition of diyne **3** (130 mg, 0.40 mmol) and 1-heptyne (0.26 mL, 2.0 mmol) following procedure A gave a 1:1 mixture of compounds **34** (133 mg, 79% yield) as a white solid. IR ($CHCl_3$) *v*: 3685, 3020, 2400, 1709, 1523, 1425, 1216, 929, 909 cm^{-1}; ^1H NMR ($CDCl_3$:CD_3OD; 3:1, 500 MHz): *δ* 0.87 (t, *J* = 6.9 Hz, 3H), 1.28−1.34 (m, 6H), 1.55−1.61 (m, 2H), 2.58−2.63 (m, 3H), 3.53 (d, *J* = 11.7 Hz, 1H), 3.77 (dd, *J* = 2.5, 11.7 Hz, 1H), 4.17 (m, 1H), 4.55 (t, *J* = 8.1 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 6.07 (d, *J* = 7.9 Hz, 1H), 7.04−7.16 (m, 2H), 7.55−7.57 (m,

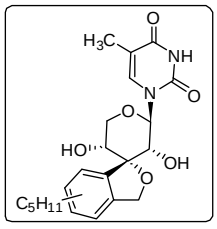
1H), 8.32 (d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 13.3 (2q), 21.9 (t), 22.0 (t), 28.7 (t), 29.0 (t), 30.7 (t), 30.9 (t, 2C), 31.3 (t), 35.1 (t), 35.3 (t), 60.2 (t), 71.7 (2t), 77.2 (d), 77.9 (d, 2C), 85.5 (2d), 87.3 (d), 94.6 (s), 99.4 (s), 119.9 (d), 120.0 (d), 122.7 (d), 124.4 (d, J = 35 Hz), 127.6 (d), 128.5 (d), 130.5 (s), 132.3 (s), 135.1 (s), 138.0 (s), 139.9 (d, J = 139 Hz), 140.9 (s), 142.2 (s), 143.3 (s), 153.8 (s) ppm; ESI-MS (*m/z*): 443.33 (100%, $[M+Na]^+$); Anal. Calcd for $C_{21}H_{25}FN_2O_6$: C, 59.99; H, 5.99; N, 6.66%; Found: C, 59.80; H, 6.11; N, 6.72%.

1-[3-*C*,3-*O*-{*o*-(3/4-^{n}Pentyl)phenylenemethylene}- β-D-ribopyranosyl]uracil (**35**):



General procedure A was followed. Diyne **4** (120 mg, 0.39 mmol) 1-heptyne (0.28 mL, 1.95 mmol) were used to afford a 1:1 mixture of compounds **35** (112 mg, 81% yield) as a colorless gum. IR ($CHCl_3$) v: 3672, 3565, 3020, 2929, 2400, 1696, 1634, 1539, 1403, 1215, 105, 1029, 929 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD; 3:1, 400 MHz): δ 0.82 (t, J = 6.4 Hz, 3H), 1.22–1.32 (m, 6H), 2.51–2.61 (m, 2H), 3.70–3.83 (m, 2H), 3.85–4.98 (m, 2H), 5.17 (d, J = 12.1 Hz, 1H), 5.27 (d, J = 12.1 Hz, 1H), 5.65 (dt, J = 1.9, 8.2 Hz, 1H), 5.79 (d, J = 9.3 Hz, 1H), 7.00 (d, J = 4.0 Hz, 1H), 7.09–7.11 (m, 2H), 7.33 (dd, J = 1.9, 8.2 Hz, 1H), 9.68 (br.s, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 13.9 (q), 14.0 (q), 22.3 (t), 22.5 (t), 22.6 (t), 29.2 (t), 31.1 (2t), 31.2 (t), 31.5 (t), 31.7 (t), 35.8 (t), 35.7 (t), 51.0 (t), 67.8 (t), 70.1 (d), 70.2 (d), 72.6 (d), 72.7 (d), 74.9 (t), 77.2 (d), 82.2 (d), 92.0 (s), 102.8 (d), 120.3 (d), 120.4 (d), 120.5 (d), 120.7 (d), 128.1 (d), 128.9 (d), 134.4 (s), 137.3 (s), 138.1 (s), 139.6 (d), 141.0 (s), 142.7 (s), 143.6 (s), 151.0 (s), 163.0 (s) ppm; ESI-MS (*m/z*): 403.3 (9%, $[M+H]^+$), 425.4 (100%, $[M+Na]^+$), 471.5 (18%, $[M+K]^+$); Anal. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96%; Found: C, 62.76; H, 6.49; N, 6.82%.

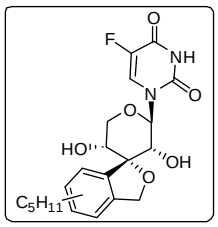
1-[3-*C*,3-*O*-{*o*-(3/4-^{n}Pentyl)phenylenemethylene}-β-D-ribopyranosyl]thymine (**36**):



General procedure A was followed. Diyne **5** (130 mg, 0.41 mmol) and 1-heptyne (0.27 mL, 2.0 mmol) were used to afford 1:1 mixture of compounds **36** (145 mg, 86% yield) as a colorless gum. IR ($CHCl_3$) v: 3747, 3673, 3647, 3196, 1690, 1646, 1539, 1506, 1403, 1219, 1046, 929, 771, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD; 3:1, 400 MHz): δ 0.87 (t, J = 6.1 Hz, 3H), 1.27−1.40 (m, 6H), 1.85 (d, J = 3.1 Hz,

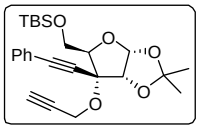
3H), 2.57 (t, *J* = 6.8 Hz, 1H), 2.59 (t, *J* = 6.8 Hz, 1H), 3.68−3.83 (m, 2H), 3.93−4.05 (m, 2H), 4.17 (t, *J* = 13.3 Hz, 1H), 5.24 (*J* = 12.1 Hz, 1H), 5.50 (d, *J* = 12.1 Hz, 1H), 5.85 (2d, *J* = 4.6 Hz, 1H), 7.05 (d, *J* = 19.1 Hz, 1H), 7.38−7.49 (m, 2H), 7.61−7.65 (m, 2H), 9.78 (br.s, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 12.3 (q), 12.4 (q), 14.1 (q), 22.5 (t), 29.7 (t), 31.1 (t), 31.2 (t), 31.6 (t), 31.6 (t), 31.9 (t), 35.8 (s), 35.9 (t), 67.6 (t), 67.7 (t), 70.3 (s), 70.4 (d), 73.7 (d), 75.1 (t), 77.3 (s), 82.0 (d), 92.3 (2s), 111.3 (s), 111.4 (s), 120.5 (d), 120.7 (d), 120.8 (d), 128.4 (2d), 128.5 (d), 129.2 (d), 131.8 (s), 132.0 (d), 132.1 (d), 132.8 (s), 134.0 (s), 135.1 (s), 135.2 (d), 136.7 (s), 137.8 (s), 140.7 (s), 143.1 (s), 142.0 (s), 151.2 (s), 151.3 (s), 163.7 (s) ppm; ESI-MS (*m/z*): 439.5 (100%, $[M+Na]^+$); Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78; N, 6.73%; Found: C, 63.52; H, 6.75; N, 6.81%.

1-[3-*C*,3-*O*-{*o*-(3/4-^{n}Pentyl)phenylenemethylene}-β-D-ribopyranosyl]5-flurouracil (**37**):



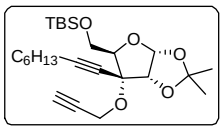
General procedure A was followed. Diyne **6** (90 mg, 0.28 mmol) and 1-heptyne (0.18 mL, 1.39 mmol) were used to afford 1:1 mixture of compounds **37** (92 mg, 79% yield) as a White gummy solid, $[\alpha]_D^{25}$ +54.8 (*c* 0.3, MeOH); IR ($CHCl_3$) *v*: 3647, 3565, 3120, 3019, 2400, 1793, 1696, 1403, 1215, 1072, 928, 771, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$:CD_3OD, 3:1, 400 MHz): δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.28−1.38 (m, 6H), 2.58 (t, *J* = 7.8 Hz, 1H), 2.61 (d, *J* = 7.8 Hz, 1H), 3.68−3.77 (m, 2H), 3.92−4.05 (m, 2H), 4.19−4.20 (m, 1H), 5.25 (d, *J* = 12.1 Hz, 1H), 5.51 (d, *J* = 12.1 Hz, 1H), 5.83 (d, *J* = 9.4 Hz, 1H), 7.05 (d, *J* = 13.1 Hz, 1H), 7.11−7.16 (m, 2H), 7.39 (dd, *J* = 2.7, 5.8 Hz, 1H), 10.11 (br.s, 1H); ^{13}C NMR ($CDCl_3$:CD_3OD; 3:1, 100 MHz): δ 14.0 (q), 14.1 (q), 14.2 (q), 22.5 (t), 22.7 (t), 29.7 (t), 31.1 (t), 31.2 (t), 31.6 (2t), 35.8 (2t), 51.1 (s), 60.4 (s), 67.6 (t), 70.3 (2d), 73.7 (d), 75.3 (t), 82.3 (d), 92.2 (2s), 120.5 (d), 120.8 (d), 120.9 (d), 127.8 (d, *J* = 38 Hz), 128.5 (d), 129.4 (d), 133.6 (s), 136.5 (s), 137.7 (s), 140.1 (d, *J* = 241 Hz), 143.3 (s), 144.2 (s), 149.7 (s), 156.7 (d, *J* = 26 Hz), 171.2 (s) ppm; ESI-MS (*m/z*): 421.5 (6%, $[M+H]^+$), 443.4 (100%, $[M+Na]^+$); Anal. Calcd for $C_{21}H_{25}FN_2O_6$: C, 59.99; H, 5.99; N, 6.66%; Found: C, 59.80; H, 5.87; N, 6.81%.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-phenylethynyl-3-*O*-(2-propynyl)-α-D-ribofuranose (**43)**:



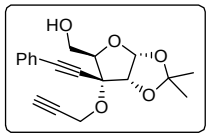
To a suspension of alcohol **41** (8.0 g, 0.02 mol), NaH (0.96 g, 0.04 mol) in DMF (60 mL), propargyl bromide (2.66 mL, 0.03 mmol) was added drop-wise at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 2 hours, quenched with slow addition of cold water at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4, concentrated and purified to give compound **43** (8.2 g, 94%) as a colorless gum. $[\alpha]_D^{25}$ +27.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3310, 3020, 2930, 2225, 1680, 1491, 1463, 1385, 1216, 1166, 1049, 880, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.08 (s, 6H), 0.89 (s, 9H), 1.36 (s, 3H), 1.61 (s, 3H), 2.46 (t, *J* = 2.4 Hz, 1H), 3.94 (dd, *J* = 6.8, 11.2 Hz, 1H), 4.01 (dd, *J* = 4.0, 11.2 Hz, 1H), 4.24 (dd, *J* = 4.0, 6.8 Hz, 1H), 4.40 (dd, *J* = 2.4, 14.9 Hz, 1H), 4.52 (dd, *J* = 2.4, 14.8 Hz, 1H), 4.70 (d, *J* = 3.6 Hz, 1H), 5.88 (d, *J* = 3.6 Hz, 1H), 7.30−7.37 (m, 3H), 7.41−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.3 (q), −5.2 (q), 18.4 (s), 25.9 (3C, q), 26.9 (q), 26.9 (q), 54.6 (t), 63.3 (t), 74.4 (s), 79.9 (s), 81.3 (s), 82.1 (d), 82.8 (s), 83.1 (d), 91.2 (s), 104.4 (d), 113.6 (s), 121.4 (s), 128.4 (2C, d), 129.2 (d), 131.8 (2C, d) ppm; ESI-MS (*m/z*): 465.77 (100%, $[M+Na]^+$); Anal. Calcd for $C_{25}H_{34}O_5Si$: C, 67.84; H, 7.74; Found: C, 67.79; H, 7.63%.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(1-octynyl)-3-*O*-(2-propynyl)-*α*-D-ribofuranose (**44)**:



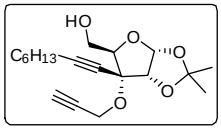
Following the above procedure, the propargylation of **42** (5.0 g, 0.012 mol) gave compound **44** (4.9 g, 90% yield) as a white solid. mp: 113−115 °C; $[\alpha]_D^{25}$ +19.7 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) *v*: 3313, 3020, 2927, 2238, 1385, 1216, 1094, 1022, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 6H), 0.87 (s, 9H), 0.90 (t, *J* = 6.8 Hz, 3H), 1.20−1.28 (m, 4H), 1.32 (s, 3H), 1.40−1.47 (m, 4H), 1.56 (s, 3H), 2.23 (t, *J* = 6.8 Hz, 2H), 2.41 (t, *J* = 2.4 Hz, 1H), 3.77−3.93 (m, 2H), 4.28 (dd, *J* = 2.4, 14.9 Hz, 1H), 4.41 (dd, *J* = 2.4, 14.9 Hz, 2H), 5.52 (d, *J* = 3.6 Hz, 1H), 5.77 (d, *J* = 3.6 Hz,1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.4 (q), −5.3 (q), 13.9 (q), 18.6 (t), 25.9 (3C, q), 22.4 (t), 26.8 (q), 28.2 (t), 28.4 (q), 28.4 (t), 31.2 (s), 54.1 (t), 63.4 (t), 73.9 (s), 74.1 (s), 80.0 (d), 80.8 (s), 81.9 (s), 83.1 (d), 92.5 (s), 104.3 (d), 113.4 (s), 178.2 (s); ESI-MS (*m/z*): 453.67 (100%, $[M+Na]^+$), 459.63 (10%, $[M+K]^+$); Anal. Calcd for $C_{25}H_{42}O_5Si$: C, 66.62; H, 9.39%; Found: C, 66.58; H, 9.28%

1,2-*O*-Isopropylidene-3-*C*-phenylethynyl-3-*O*-(2-propynyl)-*α*-D-ribofuranose (**45)**:



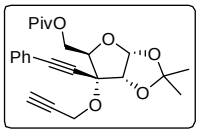
The deprotection of compound **43** (4.0 g, 9.0 mmol) was carried out according to the procedure used for the preparation of **10**, giving compound **45** (2.64 g, 89% yield) as a white solid. mp: 113–115 °C; $[\alpha]_D^{25}$ +48.7 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) *v*: 3309, 3020, 2933, 2220, 1681, 1491, 1385, 1216, 1132, 1020, 878, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *δ* 1.37 (s, 3H), 1.61 (s, 3H), 2.48 (t, *J* = 4.5 Hz, 1H), 3.41 (d, *J* = 5.6 Hz, 2H), 4.29 (t, *J* = 5.6 Hz, 1H), 4.39 (dd, *J* = 2.5, 14.8 Hz, 1H), 4.53 (dd, *J* = 2.5, 14.8 Hz, 1H), 4.72 (d, *J* = 3.6 Hz, 1H), 5.90 (d, *J* = 3.6 Hz, 1H), 7.32−7.38 (m, 2H), 7.41−7.47 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 26.7 (q), 26.8 (q), 54.6 (t), 62.4 (t), 74.7 (s), 79.5 (s), 81.0 (s), 81.1 (d), 82.4 (s), 82.8 (d), 91.6 (s), 104.5 (d), 113.8 (s), 121.0 (s), 128.4 (2C, d), 129.3 (d), 131.9 (2C, d) ppm; ESI-MS (*m/z*): 351.47 (100%, $[M+Na]^+$); Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14%; Found: C, 69.45; H, 6.07%.

1,2-*O*-Isopropylidene-3-*C*-(1-octynyl)-3-*O*-(2-propynyl)-*α*-D-ribofuranose (**46)**:



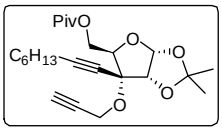
The desilylation of compound **44** (7.0 g, 0.016 mol) was carried out according to the procedure used for the preparation of **10**, giving compound **46** (4.8 g, 92% yield) as a colorless liquid. $[\alpha]_D^{25}$ +39.9 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3309, 3020, 2933, 2231, 1733, 1457, 1385, 1216, 1166, 1086, 1023, 874, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 0.87 (t, *J* = 6.7 Hz, 3H), 1.21−1.24 (m, 4H), 1.33 (s, 3H), 1.35−1.40 (m, 2H), 1.51 (quint, *J* = 7.2 Hz, 2H), 1.57 (s, 3H), 2.24 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 2.3 Hz, 1H), 3.39 (d, *J* = 5.5 Hz, 2H), 4.17 (t, *J* = 5.5 Hz, 1H), 4.29 (dd, *J* = 2.3, 14.8 Hz, 1H), 4.41 (dd, *J* = 2.3, 14.8 Hz, 1H), 4.56 (d, *J* = 3.5 Hz, 1H), 5.80 (d, *J* = 3.5 Hz,1H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 14.0 (q), 18.7 (t), 22.5 (t), 26.8 (q), 26.8 (q), 28.2 (t), 28.5 (t), 31.2 (t), 54.2 (t), 62.4 (t), 73.6 (s), 74.5 (s), 79.7 (s), 80.7 (d), 80.8 (d), 83.0 (s), 93.3 (s), 104.5 (d), 113.7 (s); ESI-MS (*m/z*): 359.39 (100%, $[M+Na]^+$), 375.42 (0.9%, $[M+K]^+$); Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39%; Found: C, 67.71; H, 8.30%

1,2-*O*-Isopropylidene-3-*C*-phenylethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-*α*-D-ribofuranose (**47)**:



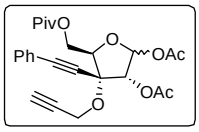
The pivoloyl protection of compound **45** (2.0 g, 6.1 mmol) was carried out according to the procedure used for the preparation of **11**, giving a compound **47** (2.5 g, 93% yield) as a white solid. mp: 103−105 °C; $[\alpha]_D^{25}$ +24.6 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) *v*: 3308, 3020, 2214, 1727, 1385, 1216, 1057, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.20 (s, 9H), 1.37 (s, 3H), 1.60 (s, 3H), 2.47 (t, *J* = 2.5 Hz, 1H), 4.35 (d, *J* = 7.3 Hz, 1H), 4.38 (t, *J* = 7.3 Hz, 1H), 4.39 (dd, *J* = 2.5, 14.7 Hz, 1H), 4.49 (d, *J* = 7.3 Hz, 1H), 4.53 (dd, *J* = 2.5, 14.7 Hz, 1H), 4.71 (d, *J* = 3.6 Hz, 1H), 5.91 (d, *J* = 3.6 Hz, 1H), 7.28−7.37 (m, 3H), 7.43−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.8 (q), 27.0 (q), 27.1 (3C, q), 38.7 (s), 54.6 (t), 63.9 (t), 74.7 (s), 79.1 (d), 79.5 (s), 81.2 (s), 81.9 (s), 82.5 (d), 91.6 (s), 104.8 (d), 113.8 (s), 121.0 (s), 128.4 (2C, d), 129.4 (d), 131.9 (2C, d), 178.3 (s) ppm; ESI-MS (*m/z*): 435.43 (100%, $[M+Na]^+$); Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84%; Found: C, 69.76; H, 6.79%.

1,2-*O*-Isopropylidene-3-*C*-(1-octynyl)-3-*O*-(2-propynyl)-5-*O*-pivaloyl-*α*-D-ribofuranose **(48)**:



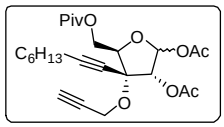
The pivoloyl protection of compound **46** (2.0 g, 6.1 mmol) was carried out according to the procedure used for the preparation of **11**, giving compound **48** (2.27 g, 91% yield) as a white solid. mp: 94−96 °C; $[\alpha]_D^{25}$ +16.7 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) *v*: 3313, 3020, 2929, 1725, 1385, 1216, 1094, 1022, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.86 (t, *J* = 6.5 Hz, 3H), 1.27 (s, 9H), 1.19−1.28 (m, 6H), 1.32 (s, 3H), 1.38−1.50 (m, 2H), 1.55 (s, 3H), 2.22 (t, *J* = 6.8 Hz, 2H), 2.42 (t, *J* = 2.5 Hz, 1H), 4.17−4.24 (m, 2H), 4.30 (dd, *J* = 3.4, 5.8 Hz, 2H), 4.40 (dd, *J* = 2.3, 14.8 Hz, 1H), 5.54 (d, *J* = 3.6 Hz, 1H), 5.80 (d, *J* = 3.6 Hz,1H) ppm^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.9 (q), 18.6 (t), 22.4 (t), 26.7 (q), 26.8 (q), 26.9 (q), 27.1 (3C, q), 28.2 (t), 28.4 (t), 31.1 (s), 54.2 (t), 64.1 (t), 73.2 (s), 74.4 (s), 78.8 (d), 79.6 (s), 80.8 (s), 82.6 (d), 93.2 (s), 104.7 (d), 113.6 (s), 178.2 (s); ESI-MS (*m/z*): 453.67 (100%, $[M+Na]^+$), 459.63 (10%, $[M+K]^+$); Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63%; Found: C, 68.40; H, 8.58%

Acetyl-2-*O*-acetyl-3-*C*-phenylethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-*α*/*β*-D-ribofuranoside (**49)**:



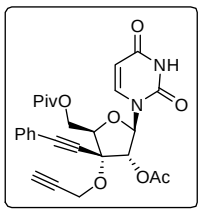
Deprotection of acetonide and acetylation of **47** (1.8 g, 4.4 mmol), as followed in the preparation of **12**, gave compound **49** (1.55 g, 78% yield) as a colorless liquid. IR ($CHCl_3$) *v*: 3310, 3020, 2930, 1741, 1733, 1473, 1433, 1394, 1216, 1118, 1053, 930, 879, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.21 (s, 5.5H), 1.22 (s, 3.5H), 2.04 (s, 1.3H), 2.12 (s, 1.7H), 2.21 (s, 3H), 2.47 (t, *J* = 2.5 Hz, 0.4H), 2.48(t, *J* = 2.5 Hz, 0.6H), 4.26−4.65 (m, 5H), 5.56 (d, *J* = 1.4 Hz, 0.4H), 5.59 (d, *J* = 4.4 Hz, 0.6H), 6.18 (d, *J* = 1.4 Hz, 0.4H), 6.49 (d, *J* = 4.4 Hz, 0.6H), 7.31-7.40 (m, 3H), 7.44-7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.5 (q), 20.6 (q), 20.8 (q), 20.9 (q), 27.0 (q), 38.6 (s), 38.6 (s), 55.0 (t), 55.1 (t), 63.7 (t), 64.4 (t), 74.6 (s), 74.7 (s), 75.2 (d), 78.0 (d), 79.1 (s), 79.2 (s), 79.5 (s), 80.4 (s), 80.8 (s), 82.3 (d), 82.9 (d), 91.7 (s), 92.3 (s), 94.3 (d), 98.9 (d), 120.6 (s), 120.9 (s), 128.4 (d), 128.4 (d), 129.4 (d), 129.4 (d), 131.7 (d), 131.9 (d), 169.0 (s), 169.2 (s), 169.3 (s), 169.3 (s), 177.9 (s), 178.0 (s); ESI-MS (*m/z*): 479.56 (100%, $[M+Na]^+$); Anal. Calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.18%; Found: C, 65.70; H, 6.03%.

Acetyl-2-*O*-acetyl-3-*C*-(1-octynyl)-3-*O*-(2-propynyl)-5-*O*-pivaloyl-α/β-D-ribofuranoside (**50)**:



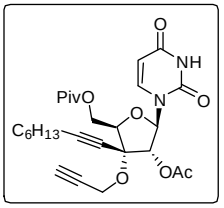
Deprotection of acetonide and acetylation of **48** (2.0 g, 4.7 mmol), as followed in the preparation of **12**, gave compound **50** (1.74 g, 79% yield) as a colorless liquid. IR ($CHCl_3$) *v*: 3310, 3020, 2930, 1740, 1735, 1394, 1216, 1118, 1053, 930, 879, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.85 (t, *J* = 6.6 Hz,3H), 1.18 (s, 9H), 1.21−1.38 (m, 6H), 1.43−1.57 (m, 2H), 2.07 (s, 3H), 2.12 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 2.5 Hz, 1H), 4.21 (dd, *J* = 6.3, 11.9 Hz, 1H), 4.24 (dd, *J* = 2.5, 15.4 Hz, 1H), 4.29 (dd, *J* = 11.9, 15.4 Hz, 1H), 4.37 (dd, *J* = 2.5, 15.4 Hz, 1H), 4.44 (dd, 3.4, 6.4 Hz, 1H), 5.40 (d, *J* = 4.3 Hz, 1H), 6.38 (d, *J* = 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.9 (q), 18.7 (t), 20.6 (q), 20.9 (q), 22.4 (t), 27.1 (3C, q), 28.1 (t), 28.5 (t), 31.1 (t), 38.7 (s), 54.7 (t), 63.9 (t), 72.2 (s), 74.3 (s), 75.0 (d), 78.9 (s), 79.6 (s), 81.8 (d), 93.8 (s), 94.5 (d), 169.4 (2C, s), 178.0 (s); ESI-MS (*m/z*): 487.71 (100%, $[M+Na]^+$); Anal. Calcd for $C_{25}H_{36}O_8$: C, 64.64; H, 7.81%; Found: C, 64.50; H, 7.97%

1-[2-*O*-Acetyl-3-*C*-phenylethynyl-3-*O*-(2-propynyl)-5-*O*-pivaloyl-β-D-ribo-pentofuranosyl]uracil (**51)**:



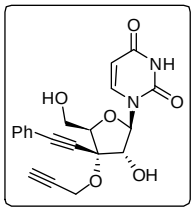
Following the procedure used for the preparation of **13**, glycosylation of **49** (1.0 g, 2.2 mmol) with uracil (493 mg, 4.4 mmol) gave the compound **51** (1.11 g, 81% yield) as a colorless liquid. $[\alpha]_D^{25}$ +65.4 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) *v*: 3488, 3020, 2931, 1733, 1698, 1473, 1433, 1385, 1216, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.19 (s, 9H), 2.20 (s, 3H), 2.47 (t, *J* = 2.4 Hz, 1H), 4.27 (dd, *J* = 2.4, 14.1 Hz, 1H), 4.37−4.47 (m, 2H), (dd, 4.46 (dd, *J* = 2.4, 15.1 Hz, 1H), 4.63 (dd, *J* = 7.8, 13.2 Hz, 1H), 5.47 (d, *J* = 3.2 Hz, 1H), 5.65 (d, *J* = 8.2 Hz, 1H), 6.08 (d, *J* = 3.2 Hz, 1H), 7.32−740 (m 5H), 7.71 (d, *J* = 8.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.6 (q), 27.1 (3C, q), 38.7 (s), 55.7 (t), 63.4 (t), 75.0 (s), 78.0 (d), 78.3 (s), 79.1 (s), 80.5 (s), 82.3 (d), 87.9 (d), 93.5 (s), 102.3 (d), 120.0 (s), 128.6 (2C, d), 130.0 (d), 131.9 (2C, d), 139.1 (d), 150.2 (s), 163.2 (s), 169.3 (s), 178.1 (s); ESI-MS (*m/z*): 530.42 (100%, $[M+Na]^+$); Anal. Calcd for $C_{27}H_{27}N_2O_8$: C, 63.90; H, 5.36; N, 5.52%; Found: C, 63.85; H, 5.45; N, 5.45%

1-[2-*O*-Acetyl-3-*C*-(1-octynyl)-3-*O*-(2-propynyl)-5-*O*-pivaloyl-*β*-D-ribo-pentofuranosyl]uracil (**52)**:



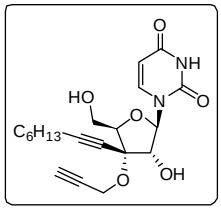
Following the procedure used for the preparation of **13**, glycosylation of **50** (1.1 g, 2.4 mmol) with uracil (89 mg, 4.7 mmol) gave the compound **52** (95 mg, 78% yield) as a colorless liquid. $[\alpha]_D^{25}$ +130.9 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3309, 3020, 2934, 1694, 1457, 1384, 1216, 1163, 1062, 928, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.85 (t, *J* = 6.5 Hz, 3H), 1.20 (s, 9H), 1.25−1.35(m, 6H), 1.47 (quin, *J* = 7.0 Hz, 2H), 2.16 (s, 3H), 2.19 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 2.4 Hz, 1H), 4.14 (dd, *J* = 2.4, 15.0 Hz, 1H), 4.25−4.32 (m, 2H), 4.34 (dd, , *J* = 2.4, 15.0 Hz, 1H), 4.51 (dd, *J* = 7.6, 12.6 Hz, 1H), 5.30 (d, *J* = 3.0 Hz, 1H), 5.71 (d, *J* = 8.2 Hz, 1H), 5.98 (d, *J* = 3.0 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.9 (q), 18.7 (t), 20.6 (q), 22.4 (t), 27.1 (3C, q), 28.0 (t), 28.5 (t), 31.0 (t), 38.7 (s), 55.3 (t), 63.5 (t), 72.1 (s), 74.7 (s), 77.9 (s), 78.1 (d), 79.2 (s), 82.1 (d), 88.0 (d), 95.4 (s), 101.9 (d), 139.4 (d), 150.1 (s), 163.3 (s), 169.3 (s), 178.1 (s); ESI-MS (*m/z*): 538.61 (100%, $[M+Na]^+$); Anal. Calcd for $C_{27}H_{35}N_2O_8$: C, 62.90; H, 6.84; N, Found: C, 62.75; H, 6.97; N, 5.53%

1-[3-*C*-Phenylethynyl-3-*O*-(2-propynyl)-*β*-D-ribo-pentofuranosyl]uracil (**38)**:



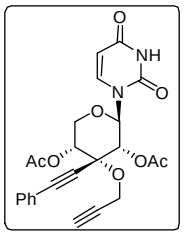
Deprotection of **51** (480 mg, 0.94 mmol), as followed in the preparation of **1**, gave compound **38** (332 mg, 92% yield) as a white solid. mp: 206−208 °C; $[\alpha]_D^{25}$ +3.6 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2923, 2236, 1697, 1385, 1216, 928, 879, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.46 (t, *J* = 2.5 Hz, 1H), 3.78-3.84 (m, 1H), 4.30 (dd, *J* = 3.3, 4.3 Hz, 1H), 4.37 (d, *J* = 5.5 Hz, 1H), 4.42 (dd, *J* = 1.0, 2.5 Hz, 2H), 5.55 (d, *J* = 8.1 Hz, 1H), 5.85 (d, *J* = 5.5 Hz, 1H), 7.21−7.35 (m, 5H), 7.82 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 54.1 (t), 61.7 (t), 74.8 (s), 79.0 (d), 79.5 (s), 81.7 (s), 84.6 (d), 89.0 (d), 91.7 (s), 101.8 (d), 120.8 (s), 128.2 (2C, d), 129.2 (d), 131.6 (2C, d), 140.8 (d), 150.9 (s), 155.4 (s), 164.1 (s); ESI-MS (*m/z*): 405.48 (100%, $[M+Na]^+$); Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33%; Found: C, 62.73; H, 4.82; N, 7.42%;

1-[3-*C*-(1-Octynyl)-3-*O*-(2-propynyl)-*β*-D-ribo-pentofuranosyl]uracil (**39)**:



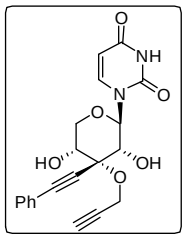
The hydrolysis of compound **52** (400 mg, 0.77 mmol) was carried out according to the procedure used for the preparation of **1**, giving compound **39** (269 mg, 89% yield) as a white solid. mp: 157−159 °C; $[\alpha]_D^{25}$ +20.7 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) *v*: 3488, 3020, 2931, 1733, 1694, 1473, 1433, 1394, 1216, 1118, 1053, 930, 879, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.73 (t, *J* = 6.8 Hz, 3H), 1.21−1.25 (m, 6H), 1.37 (quin, *J* = 7.2 Hz, 2H), 2.11 (t, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 2.4 Hz, 1H), 3.72 (dd, *J* = 3.1, 12.3 Hz, 1H), 3.74 (dd, *J* = 5.0, 12.3 Hz, 1H), 4.14 (dd, *J* = 3.1, 5.0 Hz, 1H), 4.16 (d, *J* = 5.0 Hz, 1H), 4.25 (dd, *J* = 2.4, 15.4 Hz, 1H), 4.30 (dd, *J* = 2.4, 15.4 Hz, 1H), 5.55 (d, *J* = 8.2 Hz, 1H), 5.73 (d, *J* = 5.0 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.6 (q), 18.4 (t), 22.2 (t), 27.9 (t), 28.3 (t), 30.9 (t), 53.7 (t), 61.8 (t), 72.9 (s), 74.6 (s), 79.0 (d), 79.1 (s), 79.5 (s), 84.3 (d), 89.2 (d), 93.6 (s), 101.5 (d), 140.8 (d), 150.8 (s), 164.2 (s) ppm; ESI-MS (*m/z*): 413.07 (100%, $[M+Na]^+$); Anal. Calcd for $C_{20}H_{25}N_2O_6$: C, 61.68; H, 6.47; N, 7.19%; Found: C, 51.55; H, 6.59; N, 7.25%.

1-[3-*C*-phenylethynyl-3-*O*-(2-propynyl)-4,5-di-*O*-acetyl-*β*-D- ribopyranosyl]uracil (**54)**:



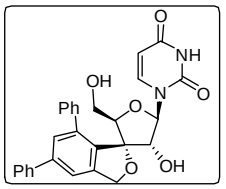
Following the procedure used for the preparation of **13**, glycosylation of triacetates **53** (2.5 g, 6.0 mmol) with uracil (1.35 g, 12.1 mmol) gave the product **54** (2.22 g, 79% yield) as a colorless liquid. $[\alpha]_D^{25}$ +11.9 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) *v*: 668, 874, 1020, 1131, 1214, 1283, 1384, 1451, 1480, 1725, 1745, 2219, 2861, 2933, 3021, 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.09 (s, 3H), 2.15 (s, 3H), 2.51 (t, *J* = 2.4 Hz, 1H), 3.94−4.03 (m, 2H), 4.64 (d, *J* = 2.4 Hz, 2H), 5.24 (dd, *J* = 5.4, 10.3 Hz, 1H), 5.25 (d, *J* = 9.4 Hz, 1H), 5.76 (d, *J* = 8.2 Hz, 1H), 6.13 (d, *J* = 9.4 Hz, 1H), 7.30−7.39 (m, 6H), 9.20 (br.s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.4 (q), 20.7 (q), 56.4 (t), 63.2 (t), 71.7 (d), 72.5 (d), 74.3 (s), 78.2 (d), 80.2 (s), 80.6 (s), 90.2 (s), 103.2 (d), 120.8 (s), 128.5 (d, 2C), 129.5 (d), 131.8 (d, 2C), 139.6 (d), 150.3 (s), 162.8 (s), 169.3 (s), 169.6 (s) ppm; ESI-MS (*m/z*): 489.50 (100%, $[M+Na]^+$); Anal. Calcd for $C_{24}H_{22}N_2O_8$: C, 61.80; H, 4.75; N, 6.01 %; Found: C, 61.71; H, 4.87; N, 6.24%

1-[3-*C*-Phenylethynyl-3-*O*-(2-propynyl)-*β*-D-ribopyranosyl]uracil (**40)**:



The deprotection of compound **54** (360 mg, 0.87 mmol) was carried out according to the procedure used for the preparation of **1**, giving compound **40** (252 mg, 93% yield) as a White solid, mp: 170−172 °C; $[\alpha]_D^{25}$ +15.8 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) *v*: 3309, 3020, 2933, 2862, 2220, 1725, 1481, 1457, 1385, 1284, 1216, 1131, 1022, 874, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.60 (t, *J* = 2.3 Hz, 1H), 3.70−3.84 (m, 4H), 4.80 (d, *J* = 2.3 Hz, 2H), 5.74 (d, *J* = 7.7 Hz, 1H), 5.79 (d, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.31−7.39 (m, 3H), 7.50−5.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 57.0 (t), 66.4 (t), 71.5 (d), 74.3 (d), 75.3 (d), 79.3 (s), 80.6 (s), 81.1 (d), 83.6 (s), 89.5 (s), 102.8 (d), 121.4 (s), 128.5 (2C, d), 129.3 (d), 131.9 (2C, d), 140.1 (d), 151.1 (s), 164.0 (s) ppm; ESI-MS (*m/z*): 405.54 (100%, $[M+Na]^+$); Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33%; Found: C, 62.71; H, 4.87; N, 7.44%

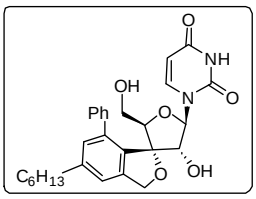
1-[3-*C*,3-*O*-{*o*-(2,4-Diphenyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**55)**:



By following procedure C, cycloaddition of the diyne **38** (20 mg, 0.052 mmol) with phenyl acetylene (5 mmL, 0.052 mmol) gave compound **55** (22 mg, 85%) as a white solid. mp: 270−272 °C; $[\alpha]_D^{25}$ +35.0 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2925, 1694,

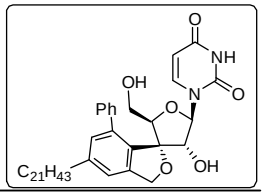
1526, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 400 MHz): δ 3.29 (dd, J = 6.6, 12.1 Hz,1H), 3.35 (dd, J = 4.0, 12.1 Hz, 1H), 4.20 (dd, J = 4.2, 6.4 Hz, 1H), 4.47 (d, J = 8.2 Hz, 1H), 5.25 (s, 2H), 5.58 (d, J = 8.2 Hz, 1H), 6.07 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 7.36−7.51 (m, 10H), 7.60 (dd, J = 1.2, 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz): δ 61.8 (t), 70.4 (t), 76.4 (d), 85.4 (d), 86.6 (d), 93.1 (s), 102.7 (d), 118.8 (d), 127.0 (3C, d), 127.8 (d), 128.0 (d), 128.3 (d), 128.7 (2C, d), 129.4 (2C, d), 130.0 (s), 130.8 (d), 138.5 (s), 139.5 (s), 139.8 (s), 139.8 (d), 142.0 (s), 142.9 (s), 151.0 (s), 163.7 (s) ppm; ESI-MS (*m/z*): 507.02 (70%, $[M+Na]^+$), 522.97 (100%, $[M+K]^+$); Anal. Calcd for $C_{28}H_{24}N_2O_6$: C, 69.41; H, 4.99; N, 5.78%; Found: C, 69.30; H, 5.18; N, 5.87%;

1-[3-*C*,3-*O*-{*o*-(2-Phenyl-4-^{n}hexyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**56)**:



Procedure C was followed. Diyne **38** (20 mg, 0.052 mmol) and 1-octyne (7.67 mmL, 0.052 mmol) were used to afford compound **56** (19.7 mg, 52%) as a colorless gu., $[\alpha]_D^{25}$ +29.3 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) *v*: 2924, 2853, 1686, 1466, 1385, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, J = 6.5 Hz, 3H), 1.29−1.39 (m, 6H), 1.57−1.63 (m, 2H), 2.63 (t, J = 7.9 Hz, 2H), 3.09−3.36 (m, 3H), 4.10 (t, J = 4.5 Hz, 1H), 4.50 (dd, J = 8.0, 10.9 Hz, 1H), 5.13 (s, 2H), 5.57 (d, J = 8.1 Hz, 1H), 6.08 (d, J = 8.1 Hz, 1H), 6.97 (s, 1H), 7.06 (d, J = 2.8, 8.0 Hz, 1H), 7.09 (s, 1H), 7.41−7.49 (m, 5H), 8.54 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.5 (t), 29.0 (t), 31.3 (t), 31.6 (t), 35.5 (t), 61.8 (t), 70.3 (t), 84.6 (d), 87.2 (d), 93.8 (s), 103.0 (d), 120.5 (d), 127.2 (d), 127.9 (d), 128.3 (d), 128.7 (s), 128.7 (2C, d), 129.3 (2C, d), 131.5 (d), 138.1 (s), 140.0 (d), 142.5 (s), 144.6 (s), 150.7 (s), 162.7 (s); ESI-MS (*m/z*): 531.04 (100%, $[M+K]^+$); Anal. Calcd for $C_{28}H_{32}N_2O_6$: C, 68.28; H, 6.55; N, 5.69%; Found: C, 68.31; H, 6.63; N, 5.78%;

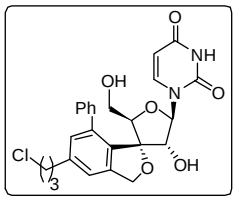
1-[3-*C*,3-*O*-{*o*-(2-Phenyl-4-^{n}henicosyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**57)**:



General procedure C was followed. Diyne **38** (20 mg, 0.052 mmol) and 1-tricosyne (15.9 mg, 0.052 mmol) were used to afford compound **57** (32 mg, 87% yield) as a colorless gum.

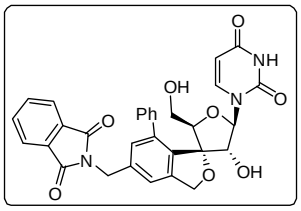
$[\alpha]_D^{25}$ +26.9 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) *v*: 2924, 2853, 1686, 1466, 1385, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.86 (t, *J* = 6.4 Hz, 3H), 1.24 (m, 36H), 1.52−1.70 (m, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 3.28 (d, *J* = 2.8 Hz, 2H), (m, 3H), 4.10 (t, *J* = 4.5 Hz, 1H), 4.50 (dd, *J* = 8.1, 10.5 Hz, 1H), 5.13 (s, 2H), 5.57 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.08 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 1.2 Hz, 1H), 7.04 (d, 8.0 Hz, 1H), 7.09 (d, *J* = 1.2 Hz, 1H), 7.41−7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t), 29.3 (2C, t), 29.4 (t), 29.6 (t), 29.7 (12C, t), 31.3 (t), 31.9 (t), 35.5 (t), 61.8 (t), 70.3 (t), 77.2 (s), 76.8 (d), 84.6 (d), 87.2 (d), 93.7 (s), 103.0 (d), 120.5 (d), 128.3 (d), 128.7 (2C, d), 129.3 (2C, d), 131.4 (d), 138.1 (s), 140.0 (s), 140.1 (d), 142.5 (s), 144.5 (s), 150.8 (s), 162.9 (s); ESI-MS (*m/z*): 725.3 (80%, [M+Na]),741.20 (100%, $[M+K]^+$); Anal. Calcd for $C_{43}H_{62}N_2O_6$: C, 73.47; H, 8.89; N, 3.99%; Found: C, 73.38; H, 8.97; N, 4.10%.

1-[3-*C*,3-*O*-{*o*-(2-Phenyl-4-chloropropyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**58)**:



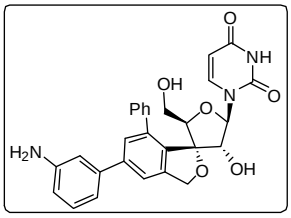
Procedure C was followed. Diyne **38** (20 mg, 0.052 mmol) and 1-chloro-4-pentyne (5.33 mmL, 0.052 mmol) were used to afford compound **58** (21.0 mg, 83% yield) as a white solid. mp: 172−174 °C; $[\alpha]_D^{25}$ +12.7 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2925, 1694, 1462, 1385, 1216, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.08 (quin, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 3.23 (dd, *J* = 5.8, 12.1 Hz, 1H), 3.30 (dd, *J* = 3.3, 12.1 Hz, 1H), 3.53 (t, *J* = 6.3 Hz, 2H), 3.70 (d, *J* = 8.9 Hz, 1H), 4.11 (t, *J* = 4.5 Hz, 1H), 4.47 (br t, *J* = 7.4 Hz, 1H), 5.12 (s, 2H), 5.55 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.96 (s, 1H), 7.10 (s, 1H), 7.36−7.48 (m, 5H), 9.45 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.2 (t), 33.7 (t), 44.1 (t), 61.9 (t), 70.3 (t), 77.2 (s), 84.9 (d), 87.0 (d), 93.5 (s), 103.0 (d), 120.6 (d), 128.3 (d), 128.6 (2C, d), 129.4 (2C, d), 129.5 (d), 131.4 (d), 138.4 (s), 139.8 (s), 140.0 (d), 142.1 (s), 142.7 (s), 151.0 (s), 163.2 (s); ESI-MS (*m/z*): 507.09 (100%, $[M+Na]^+$); Anal. Calcd for $C_{25}H_{25}ClN_2O_6$: C, 61.92; H, 5.20; Cl, 7.31; N, 5.78%; Found: C, 61.82; H, 5.34; N, 5.88%;

1-[3-*C*,3-*O*-{*o*-(2-Phenyl-4-phthalimidomethyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**59)**:



General procedure C was followed. Diyne **38** (20 mg, 0.052 mmol) and *N*-propargyl pthalimide (9.4 mg, 0.052 mmol) were used to afford compound **59** (23.7 mg, 80% yield) as a white solid. mp: 196−198 °C; $[\alpha]_D^{25}$ +8.2 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) *v*: 3393, 3020, 2929, 1771, 1717, 1469, 1394, 1346, 1216, 1107, 1047, 947, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.15−3.33 (m, 2H), 3.48 (br s, 1H), 4.07 (t, *J* = 4.9 Hz, 1H), 4.44 (br s, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 5.09(s, 2H), 5.52 (d, *J* = 8.1 Hz, 1H), 6.02 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 1.3 Hz, 1H), 7.33 (d, *J* = 1.3 Hz, 1H), 7.36−7.49 (m, 5H), 7.66–7.75 (m, 2H), 7.79–7.88 (m, 2H), 9.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 40.9 (t), 61.7 (t), 70.2 (t), 76.6 (s), 84.7 (d), 87.0 (d), 93.6 (s), 103.0 (d), 120.7 (d), 123.5 (3C, d), 128.4 (d), 128.7 (2C, d), 129.4 (2C, d), 131.3 (d), 131.9 (s), 134.2 (3C, d), 137.5 (s), 138.7 (s), 139.4 (s), 140.0 (s), 143.1 (s), 150.9 (s), 163.0 (s), 168.0 (2C, s); ESI-MS (*m/z*): 589.98 (40%, $[M+Na]^+$), 605.94 (100%, $[M+K]^+$); Anal. Calcd for $C_{31}H_{25}N_3O_8$: C, 65.60; H, 4.44; N, 7.40%; Found: C, 65.51; H, 4.59; N, 7.31%

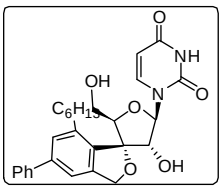
1-[3-*C*,3-*O*-{*o*-(2-Phenyl-4-(3-aminophenyl))phenylenemethylene}-β-D-ribofuranosyl]uracil (**60)**:



By following procedure C, cycloaddition of the diyne **38** (20 mg, 0.052 mmol) with 3-amino phenyl acetylene (3.77 μL, 0.052 mmol) gave compound **60** (22.2 mg, 85% yield) as a yellowish liquid. $[\alpha]_D^{25}$+15.8 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) *v*: 3437, 3020, 2925, 1695, 1524, 1385, 1217, 1018, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 400 MHz): δ 3.07 (dd, *J* = 7.3, 11.9 Hz, 1H), 3.14 (dd, *J* = 4.2, 11.9 Hz 1H), 4.04 (dd, *J* = 4.2, 7.3 Hz, 1H), 4.28 (d, *J* = 8.2 Hz, 1H), 5.04 (d, *J* = 13.0 Hz, 1H), 5.08 (d, *J* = 13.0 Hz, 1H), 5.09 (s, 2H), 5.40 (d, *J* = 8.1 Hz, 1H), 5.90 (d, *J* = 8.2 Hz, 1H), 6.58 (dd, *J* = 1.8, 8.2 Hz, 1H), 6.60 (d, *J* = 1.3, 8.1 Hz, 1H), 6.80 (s, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 7.16 (s, 1H), 7.30 (s, 6H); ^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz): δ 61.7 (t), 70.2 (t), 76.2 (d), 85.5 (d), 86.3 (d), 92.7 (s), 102.4 (d), 113.9 (d), 114.9 (d), 117.5 (d), 118.5 (d), 127.7 (d), 129.0 (2C, d), 129.3 (2C, d), 129.4 (d), 129.6 (d), 130.7 (s), 138.1 (s), 139.7 (d), 139.7 (s), 140.5 (s), 141.9 (s), 142.6 (s), 146.3 (s), 150.9 (s), 163.8 (s); ESI-

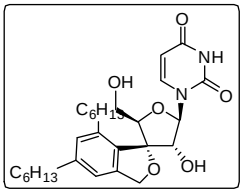
MS (*m/z*): 522.01 (20%, $[M+Na]^+$), 537.98 (100%, $[M+K]^+$); Anal. Calcd for : $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N, 8.41%; Found: C, 67.31; H, 5.17; N, 8.53%

1-[3-*C*,3-*O*-{*o*-(2-^{n}Hexyl-4-phenyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**61)**:



Procedure C was followed. Diyne **39** (50 mg, 0.128 mmol) and phenyl acetylene (13.1 μL, 0.128 mmol) were used to afford compound **61** (49.2 mg, 78% yield) as a white solid. mp: 143−145 °C; $[\alpha]_D^{25}$ +20.9 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) *v*: 2924, 2853, 1686, 1466, 1385, 1045, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *δ* 0.88 (t, *J* = 6.5 Hz, 3H), 1.26−1.47 (m, 6H), 1.56−1.76 (m, 2H), 2.65−2.89 (m, 2H), 3.51 (dd, *J* = 3.9 Hz, 2H), 3.81 (dd, *J* = 7.5, 12.1 Hz, 1H), 4.38 (dd, *J* = 3.9, 7.2 Hz, 1H), 4.62 (d, *J* = 8.1 Hz, 1H), 5.14 (d, *J* = 12.7 Hz, 1H), 5.22 (d, *J* = 12.7 Hz, 1H), 5.80 (dd, *J* = 1.5, 8.1 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 7.37−7.57 (m, 7H), 9.33 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 14.1 (q), 22.6 (t), 29.7 (t), 31.7 (t), 31.9 (t), 33.5 (t), 61.7 (t), 72.0 (t), 76.4 (d), 86.5 (d), 89.2(d), 92.3 (s), 103.2 (d), 117.5 (d), 127.2 (2C, d), 127.7 (d), 128.6 (d), 128.8 (2C, d), 132.3 (s), 138.0 (s), 140.3 (s), 140.4 (d), 141.6 (s), 142.6 (s), 150.8 (s), 163.0 (s); ESI-MS (*m/z*): 515.07 (40%, $[M+Na]^+$), 531.03 (100%, $[M+K]^+$); Anal. Calcd for $C_{28}H_{32}N_2O_6$: C, 68.28; H, 6.55; N, 5.69%; Found: C, 68.17; H, 6.67, N, 5.73%

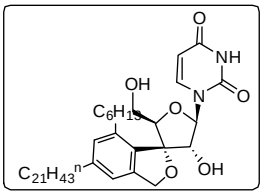
1-[3-*C*,3-*O*-{*o*-(2- ^{n}Hexyl-4- ^{n}hexyl)phenylenemethylene}-*β*-D-ribofuranosyl] uracil (**62)**:



General procedure C was followed. Diyne **39** (20 mg, 0.051 mmol) and 1-octyne (7.5 μL, 0.051 mmol) were used to afford a compound **62** (19.2 mg, 75% yield) as a colorless liquid. $[\alpha]_D^{25}$ +4.4 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2930, 2858, 1698, 1521, 1462, 1385, 1216, 1045, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 0.87 (t, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H), 1.26−1.38 (m, 12H), 1.53−1.71 (m, 4H), 2.47 (dd, *J* = 7.7, 8.1 Hz, 2H), 2.60−2.66 (m, 1H), 2.72−2.74 (m, 1H), 3.43 (dd, *J* = 3.8, 12.0 Hz, 1H), 3.75 (dd, *J* = 7.6, 12.0 Hz, 1H), 4.32 (dd, *J* = 3.8, 7.6 Hz, 1H), 4.56 (t, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.76 (d, *J* = 8.0 Hz, 1H), 5.87 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.95 (s, 1H), 7.45 (d, 8.0 Hz, 1H),

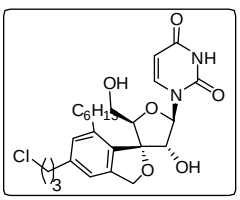
9.25 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 14.2 (q), 22.6 (t), 22.6 (t), 29.0 (t), 29.7 (t), 31.4 (t), 31.6 (t), 31.7 (t), 31.9 (t), 33.4 (t), 35.6 (t), 61.8 (t), 72.0 (t), 76.3 (d), 86.5 (d), 89.2 (d), 92.1 (s), 103.2 (d), 118.7 (d), 129.7 (d), 130.4 (s), 137.2 (s), 140.3 (d), 140.8 (s), 144.4 (s), 150.7 (s), 162.9 (s) ESI-MS (*m/z*): 523.11 (100%, $[M+Na]^+$), 539.08 (90%, $[M+K]^+$); Anal. Calcd for : $C_{28}H_{40}N_2O_6$: C, 67.18; H, 8.05; N, 5.60%; Found: C, 67.06; H, 8.17; N, 5.71%;

1-[3-*C*,3-*O*-{*o*-(2-^{n}Hexyl-4-^{n}henicosyl)-phenylenemethylene}-*β*-D-ribo-furanosyl]uracil (**63)**:



Procedure C was followed. Diyne **39** (50 mg, 0.138 mmol) and 1-tricosyne (42.3 mg, 0.138 mmol) were used to afford compound **63** (66.5 mg, 73% yield) as a colorless liquid. $[\alpha]_D^{25}$ +1.9 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2930, 2858, 1698, 1521, 1462, 1385, 1216, 1045, 929, 669 cm^{-1}; ^{1H} NMR ($CDCl_3$, 200 MHz): δ 0.86 (t, *J* = 6.5 Hz, 3H), 0.88 (t, *J* = 6.5 Hz, 3H), 1.24 (s, 36H), 1.30−1.36 (m, 8H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.60−2.66 (m, 1H), 2.70−2.79 (m, 1H), 3.33 (br s, 1H), 3.44 (dd, *J* = 4.0, 12.1 Hz, 1H), 3.75 (dd, *J* = 7.7, 12.1 Hz, 1H), 4.32 (dd, *J* = 4.0, 7.1 Hz, 1H), 4.59 (t, *J* = 7.8 Hz, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 5.29 (s, 1H), 5.78 (d, *J* = 8.1 Hz, 1H), 5.85 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 6.96 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 8.94 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (q), 14.1 (q), 22.6 (t), 22.7 (t), 29.3 (t), 29.5 (t), 29.6 (t), 29.7 (13C, t), 31.4 (t), 31.7 (t), 31.9 (t), 31.9 (t), 33.4 (t), 35.6 (t), 53.4 (t), 61.8 (t), 72.0 (t), 76.2 (d), 86.4 (d), 89.3 (d), 92.1 (s), 103.2 (d), 118.7 (d), 129.7 (d), 130.3 (s), 137.3 (s), 140.4 (d), 140.8 (s), 144.5 (s), 150.6 (s), 162.7 (s) ppm; ESI-MS (*m/z*): 733.51 (10%, $[M+Na]^+$); Anal. Calcd for $C_{43}H_{70}N_2O_6$: C, 72.64; H, 9.92; N, 3.94; Found: C, 72.51; H, 9.97; N, 4.01%.

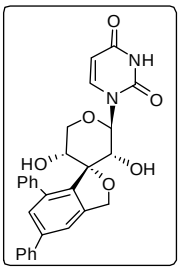
1-[3-*C*,3-*O*-{*o*-(2-^{n}Hexyl-4-chloropropyl)phenylenemethylene}-*β*-D-ribofuranosyl]uracil (**64)**:



General procedure C was followed. Diyne **39** (20 mg, 0.051 mmol) and 1-chloro-4-pentyne (4.67 mmL, 0.051 mmol) were used to afford **64** (19.7 mg, 78% yield) as a colorless liquid. $[\alpha]_D^{25}$ +5.7 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2929, 1698,

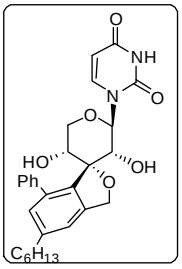
1385, 1216, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, J = 6.8 Hz, 3H), 1.24−1.37 (m, 6H), 1.53−1.66 (m, 2H), 2.05 (quint, J = 7.3 Hz, 2H), 2.59−2.66 (m, 1H), 2.75 (t, J = 7.3 Hz, 3H), 3.43 (dd, J = 3.3, 12.1 Hz, 1H), 3.51 (t, J = 6.3 Hz, 3H), 3.75 (dd, J = 7.5, 12.1 Hz, 1H), 4.33 (dd, J = 3.3, 7.3 Hz, 1H), 4.56 (t, J = 8.2 Hz, 1H), 5.06 (d, J = 12.3 Hz, 1H), 5.13 (d, J = 12.3 Hz, 1H), 5.78 (d, J = 8.1 Hz, 1H), 5.87 (d, J = 8.1 Hz, 1H), 6.88 (s, 1H), 6.98 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 9.40 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.6 (t), 29.7 (t), 31.7 (t), 31.9 (t), 32.3 (t), 33.4 (t), 33.8 (t), 44.1 (t), 61.7 (t), 71.9 (t), 76.3 (d), 86.5 (d), 89.0 (d), 92.1 (s), 103.2 (d), 118.9 (d), 129.8 (d), 131.1 (s), 137.7 (s), 140.4 (d), 141.2 (s), 142.1 (s), 150.7 (s), 163.0 (s); ESI-MS (*m/z*): 515.03 (82%, $[M+Na]^+$), 531.00 (100%, $[M+K]^+$); Anal. Calcd for $C_{25}H_{33}ClN_2O_6$: C, 60.91; H, 6.75; Cl, 7.19%; Found: C, 61.09; H, 6.61; N, 7.07%.

1-[3-*C*,3-*O*-{*o*-(2,4-Diphenyl)phenylenemethylene}-*β*-D-ribopyranosyl]uracil (**65)**:



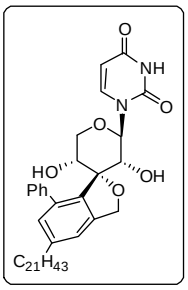
By following procedure C, cycloaddition of the diyne **40** (20 mg, 0.052 mmol) with phenyl acetylene (5 mmL, 0.052 mmol) gave a regiomeric mixture of compound **65** (7:1) (21.0 mg, 83% yield) colorless liquid. $[\alpha]_D^{25}$ +117.5 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2925, 1694, 1526, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 400 MHz): δ 3.24 (d, J = 9.4 Hz, 0.3H), 3.37 (d, J = 9.4 Hz, 0.7H), 3.64 (dd, J = 5.8, 10.2 Hz, 1H), 3.69−3.77 (m, 2H), 5.29 (d, J = 10.1 Hz, 1H), 5.30 (s, 1H), 5.60 (d, J = 8.1 Hz, 0.3H), 5.63 (d, J = 8.1 Hz, 0.7H), 5.68 (d, J = 9.4 Hz, 0.3H), 5.71 (d, J = 9.4 Hz, 0.7H), 6.66 (d, J = 8.1 Hz, 0.3H), 6.77 (d, J = 8.1 Hz, 0.7H), 7.03−7.43 (m, 11H), 7.55 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.8 (t), 66.9 (t), 69.4 (d), 70.4 (d), 71.2 (d), 73.4 (t), 73.7 (t), 77.2 (s), 81.5 (d), 81.6 (d), 92.8 (s), 93.2 (s), 102.4 (d), 102.5 (d), 118.3 (d), 118.5 (s), 119.7 (d), 126.0 (d), 126.8 (d), 127.1 (d), 127.3 (d), 127.4 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.4 (s), 128.5 (s), 128.8 (s), 129.4 (s), 129.5 (s), 130.2 (d), 130.3 (d), 130.3 (d), 132.5 (s), 133.9 (s), 135.6 (s), 137.1 (s), 137.6 (s), 139.1 (s), 139.2 (d), 139.3 (d), 140.0 (s), 140.5 (s), 140.7 (s), 141.3 (s), 141.4 (s), 142.4 (s), 151.0 (s), 163.8 (s); ESI-MS (*m/z*): 506.99 (25%, $[M+Na]^+$), 522.96 (100%, $[M+K]^+$); Anal. Calcd for $C_{28}H_{24}N_2O_6$: C, 69.41; H, 4.99; N, 5.78%; Found: C, 69.35; H, 5.15; N, 5.98%;

1-[3-*C*,3-*O*-{*o*-(2-phenyl-4-*n*hexyl)phenylenemethylene}-*β*-D-ribopyranosyl]uracil (**66)**:



By following procedure C, cycloaddition of the diyne **40** (25 mg, 0.065 mmol) with 1-octyne (7.2 mmL, 0.065 mmol) gave compound **65** (24.8 mg, 77% yield) as a white solid. mp: 124−126 °C; $[\alpha]_D^{25}$ +85.4 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) *v*: 2924, 2853, 1686, 1466, 1385, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.27−1.40 (m, 6H), 1.60 (quint, *J* = 7.8, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 3.48 (br s, 1H), 3.58 (br s, 1H), 3.65 (t, *J* = 10.5 Hz, 1H), 3.71 (dd, *J* = 5.6, 10.5 Hz, 1H), 5.23 (d, *J* = 12.3 Hz, 1H), 5.45 (d, *J* = 12.3 Hz, 1H), 5.61 (d, *J* = 8.2 Hz, 1H), 5.74 (d, *J* = 9.3 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.94 (s, 1H), 7.03 (s, 1H), 7.32−7.43 (m, 5H), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.5 (t), 22.7 (t), 31.3 (t), 31.6 (t), 35.6 (t), 67.0 (t), 69.4 (d), 73.0 (d), 74.3 (t), 81.8 (d), 93.3 (s), 103.2 (d), 119.9 (d), 128.0 (3C, d), 129.2 (2C, d), 130.1 (d), 130.1 (s), 137.5 (s), 139.0 (d), 139.3 (s), 141.3 (s), 143.7 (s), 151.1 (s), 163.0 (s); ESI-MS (*m/z*): 515.08 (75%, $[M+Na]^+$), 531.02 (100%, $[M+K]^+$); Anal. Calcd for $C_{28}H_{32}N_2O_6$: C, 68.28; H, 6.55; N, 5.69; Found: C, 68.31; H, 6.60; N, 5.76;

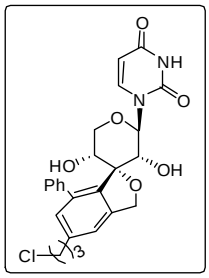
1-[3-*C*,3-*O*-{*o*-(2-phenyl-4-*n*henicosyl)phenylenemethylene}-*β*-D-ribopyranosyl]uracil (**67)**:



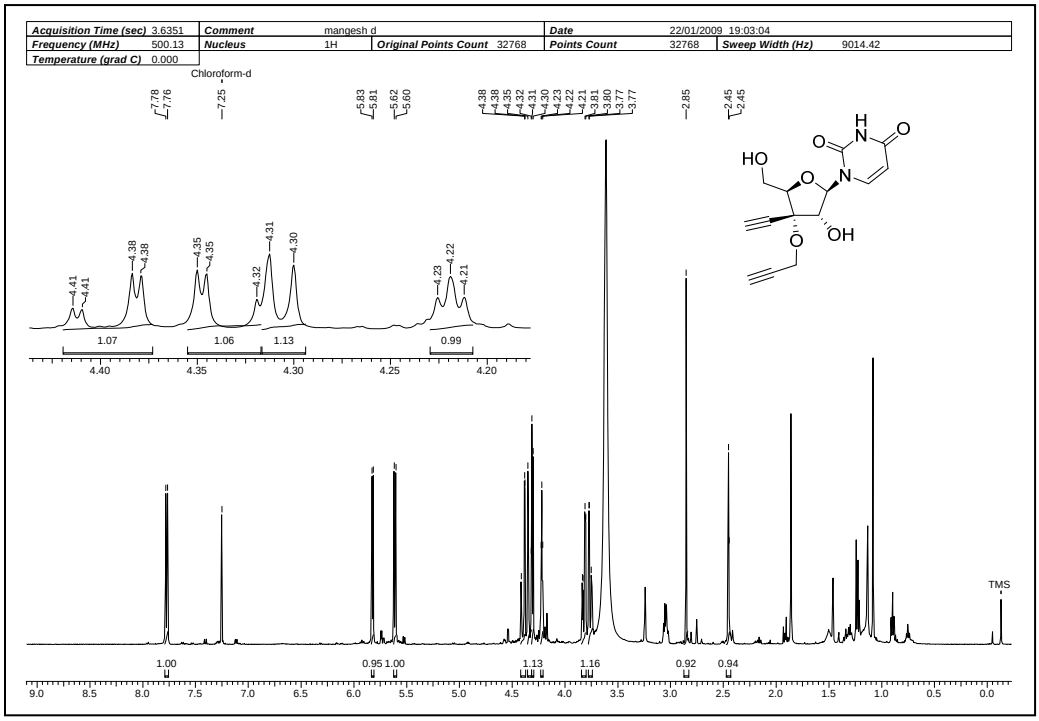
Procedure C was followed. Diyne **40** (30 mg, 0.078 mmol) and 1-tricoxyne (24 mg, 0.078 mmol) were used to afford compound **67** (31.3 mg, 81% yield) as a white solid. mp: 102−104 °C; $[\alpha]_D^{25}$ +55.3 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) *v*: 2924, 2853, 1686, 1466, 1385, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 6.4 Hz, 3H), 1.24 (s, 36H), 1.45−1.64 (m, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 3.48−3.75 (m, 5H), 5.23 (d, *J* = 12.3 Hz, 1H), 5.45 (d, *J* = 12.3 Hz, 1H), 5.62 (dd, *J* = 1.8, 8.2 Hz, 1H), 5.64 (d, *J* = 8.9 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.95 (s, 1H), 7.04 (s, 1H), 7.34−7.47 (m, 5H), 9.36 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t), 29.3 (t), 29.5 (t), 29.7 (14C, t), 31.4 (t), 31.9 (t), 35.7 (t), 67.0 (t), 69.4 (d),

73.1 (d), 74.4 (t), 81.8 (d), 93.2 (s), 103.2 (d), 119.6 (d), 128.0 (2C, d), 129.2 (3C, d), 130.0 (s), 130.2 (d), 137.5 (s), 138.9 (d), 139.2 (s), 141.2 (s), 143.8 (s), 151.0 (s), 162.8 (s); ESI-MS (*m/z*): 741.16 (100%, $[M+K]^+$); Anal. Calcd for $C_{43}H_{62}N_2O_6$: C, 73.47; H, 8.89; N, 3.99%; Found: C, 73.31; H, 8.97; N, 4.07%;

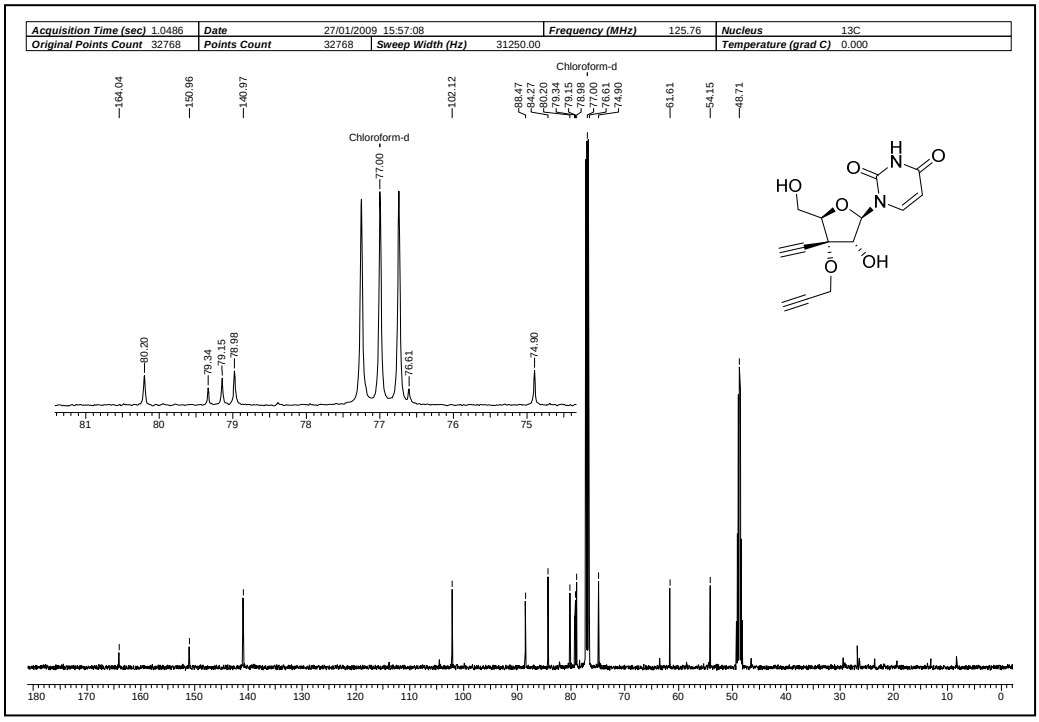
1-[3-*C*,3-*O*-{*o*-(2-phenyl-4-chloropropyl)phenylenemethylene}-*β*-D-ribopyranosyl]uracil (**68)**:



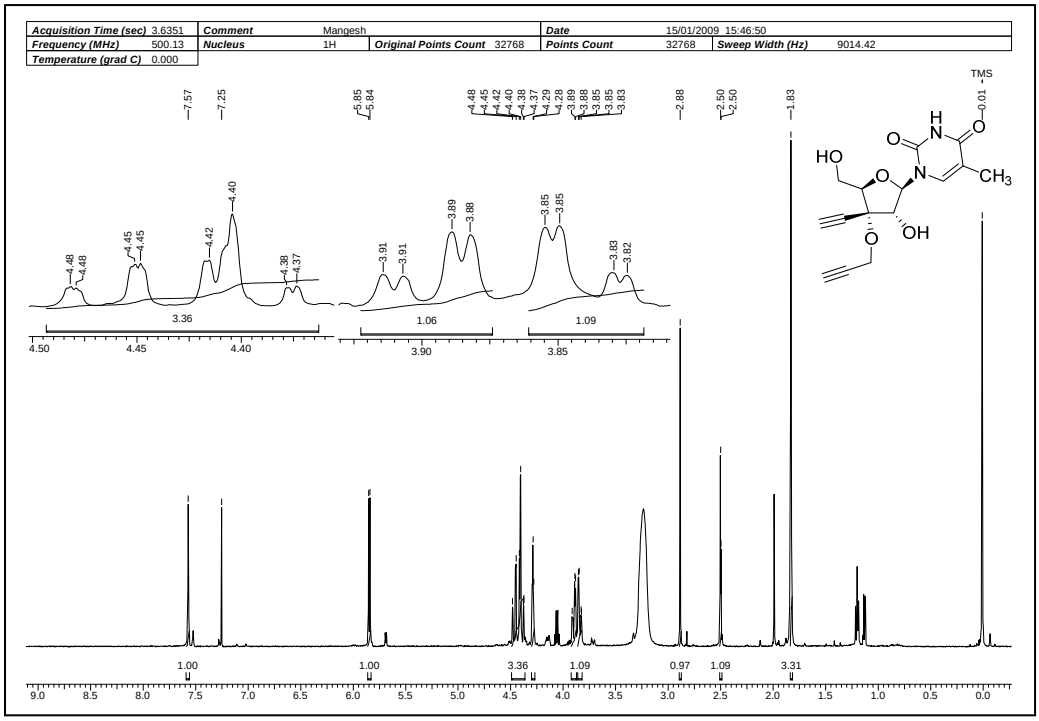
General procedure C was followed. Diyne **40** (20 mg, 0.052 mmol) and 1-chloro-4-pentyne (5.51 mmL, 0.052 mmol) were used to afford compound **68** (20 mg, 79% yield) as a white solid. mp: 176−178 °C; $[\alpha]_D^{25}$ +114.2 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2925, 1694, 1462, 1385, 1215, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3CD_3OD$, 500 MHz): δ 1.98 (quint, J = 7.5 Hz, 2H), 2.70 (t, J = 7.5 Hz, 2H), 3.24 (d, J = 9.5 Hz, 1H), 3.45 (t, J = 6.4 Hz, 2H), 3.51 (t, J = 8.3 Hz, 1H), 3.61 (d, J = 12.1 Hz, 1H), 3.65 (d, J = 12.1 Hz, 1H), 5.14 (s, 2H), 6.55 (d, J = 8.2 Hz, 1H), 5.60 (d, J = 9.5 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.85 (s, 1H), 6.98 (s, 1H), 7.24−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$+CD_3OD, 125 MHz): δ 32.2 (t), 33.7 (t), 44.0 (t), 66.9 (t), 69.4 (d), 71.4 (d), 73.8 (t), 81.6 (d), 92.8 (s), 102.7 (d), 119.9 (d), 127.7 (2C, d), 127.8 (d), 128.8 (2C, d), 129.7 (d), 131.3 (d), 137.4 (s), 139.1 (s), 139.3 (s), 141.0 (s), 141.9 (s), 151.1 (s), 163.7 (s); ESI-MS (*m/z*): 506.98 (60%, $[M+Na]^+$), 522.94 (100%, $[M+K]^+$); Anal. Calcd for $C_{25}H_{25}ClN_2O_6$: C, 61.92; H, 5.20; Cl, 7.31; N, 5.78% Found: C, 61.88; H, 5.09; Cl, 7.47; N, 5.81%.



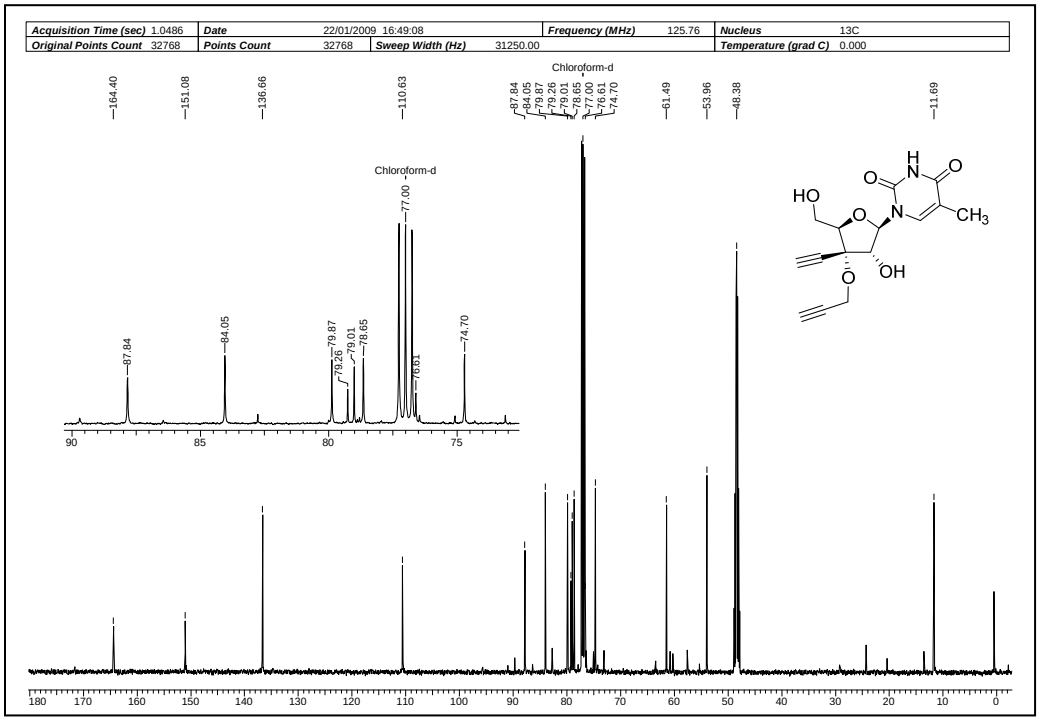
^{1}H NMR Spectrum of 1 in $CDCl_3$



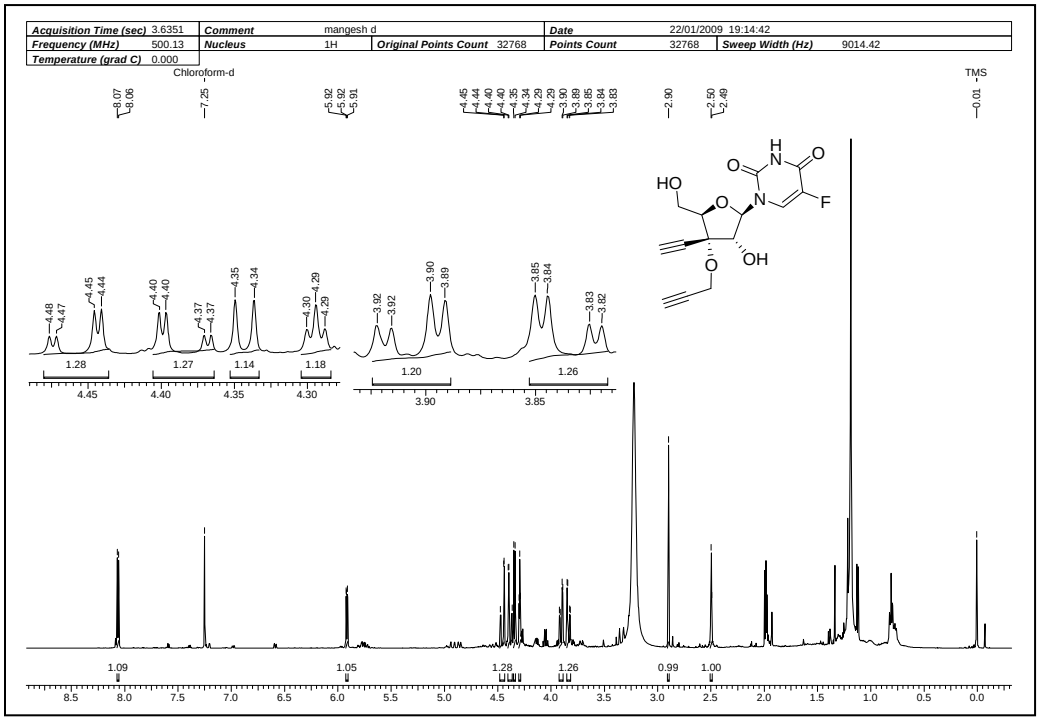
^{13}C NMR Spectrum of 1 in $CDCl_3$



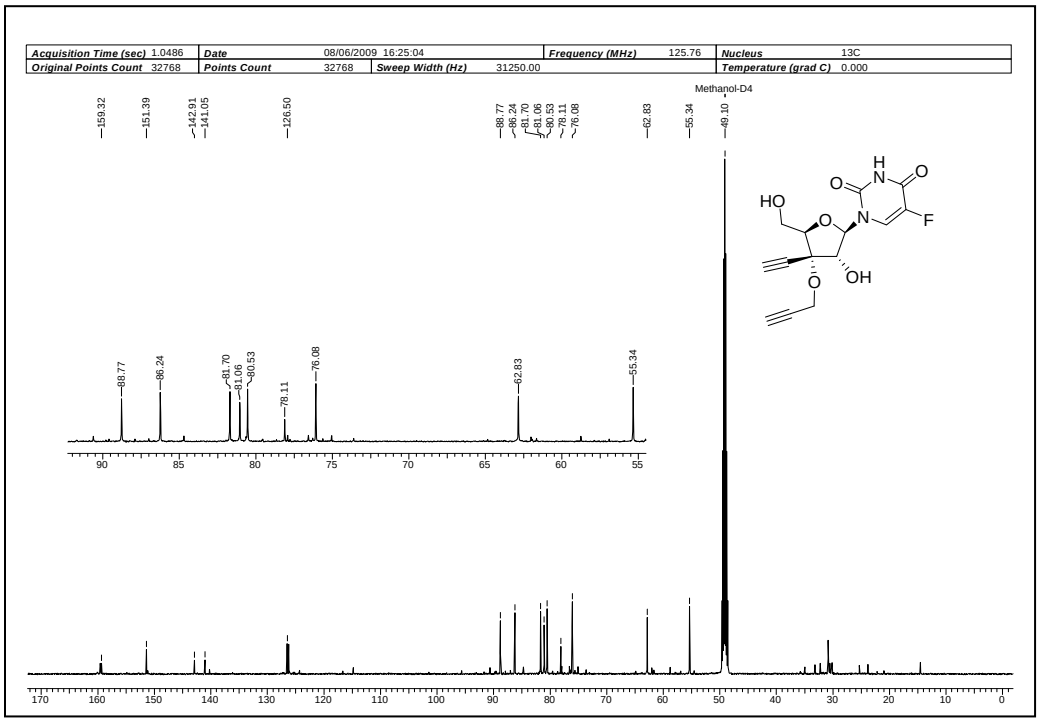
^{1}H NMR Spectrum of 2 in $CDCl_3$



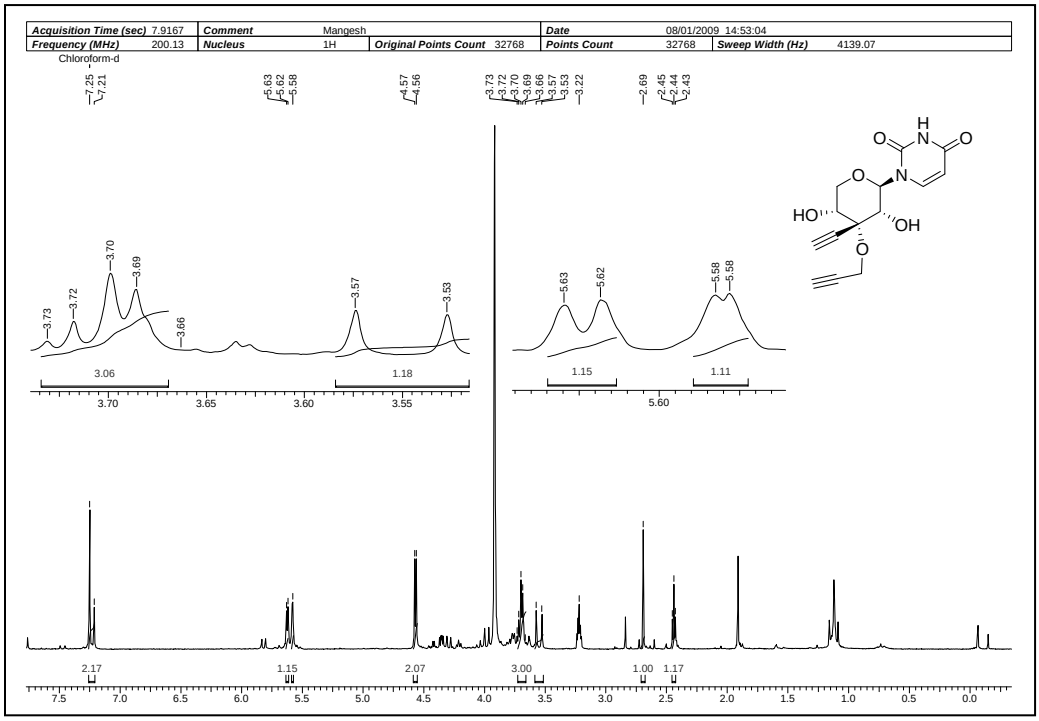
^{13}C NMR Spectrum of 2 in $CDCl_3$



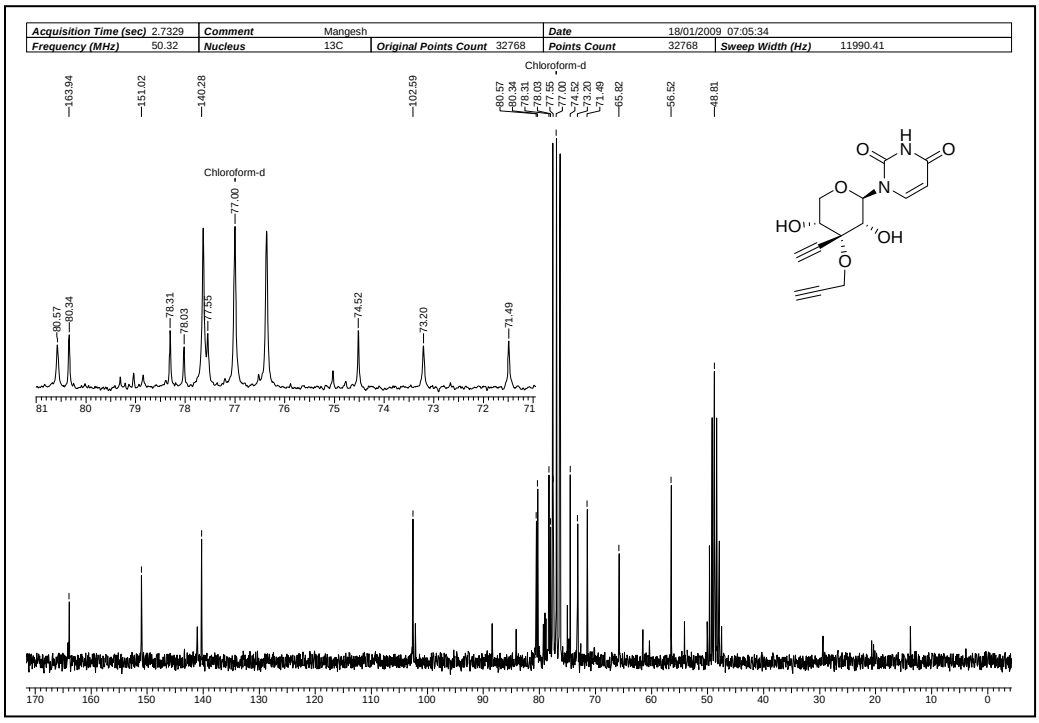
^{1}H NMR Spectrum of 3 in $CDCl_3$



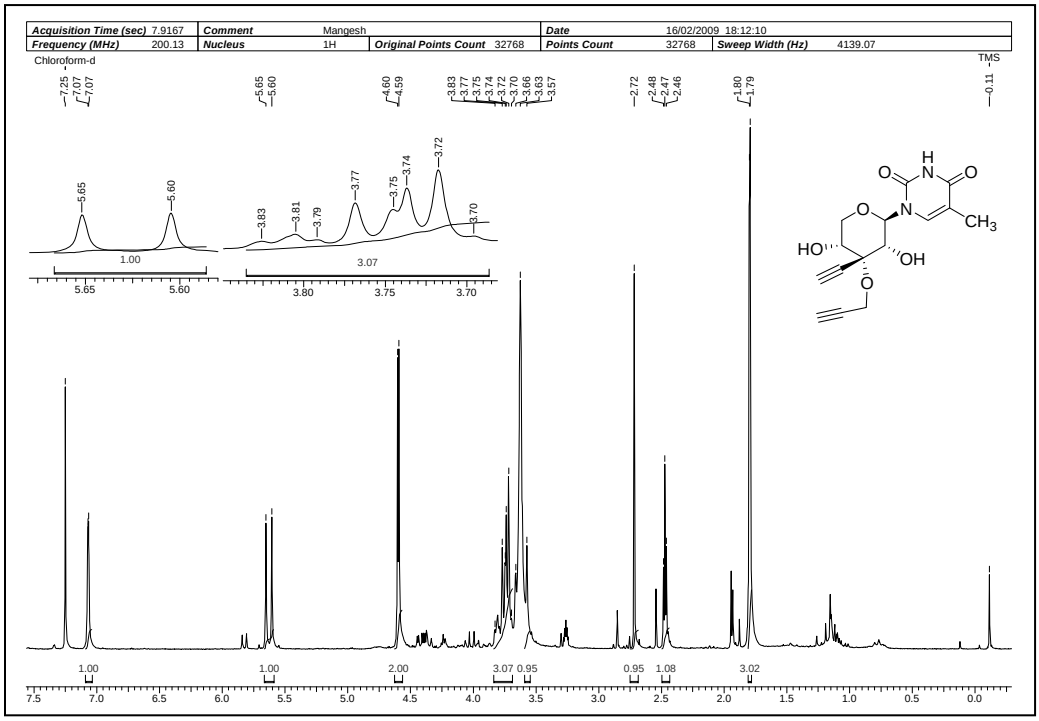
^{13}C NMR Spectrum of 3 in $CDCl_3$



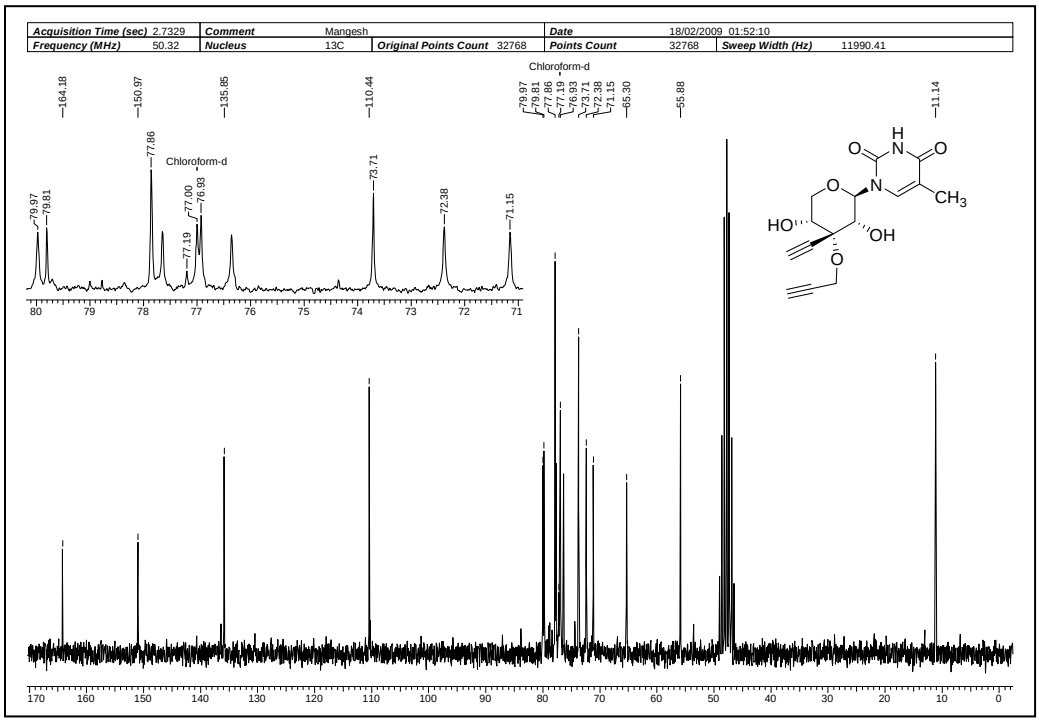
^{1}H NMR Spectrum of 4 in $CDCl_3$



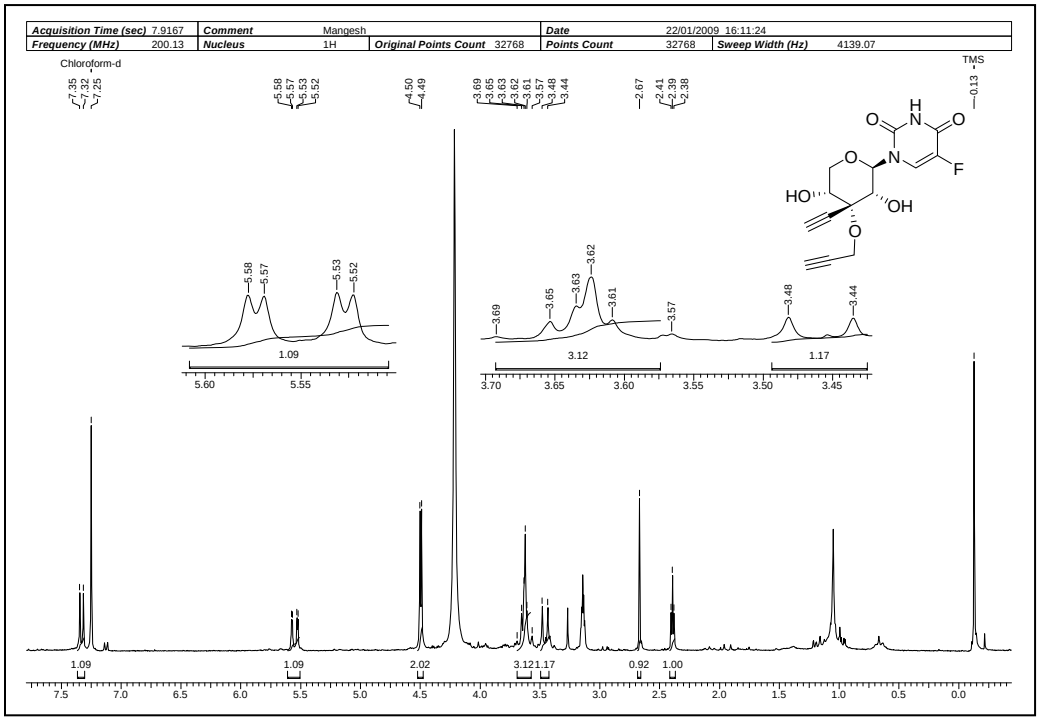
^{13}C NMR Spectrum of 4 in $CDCl_3$



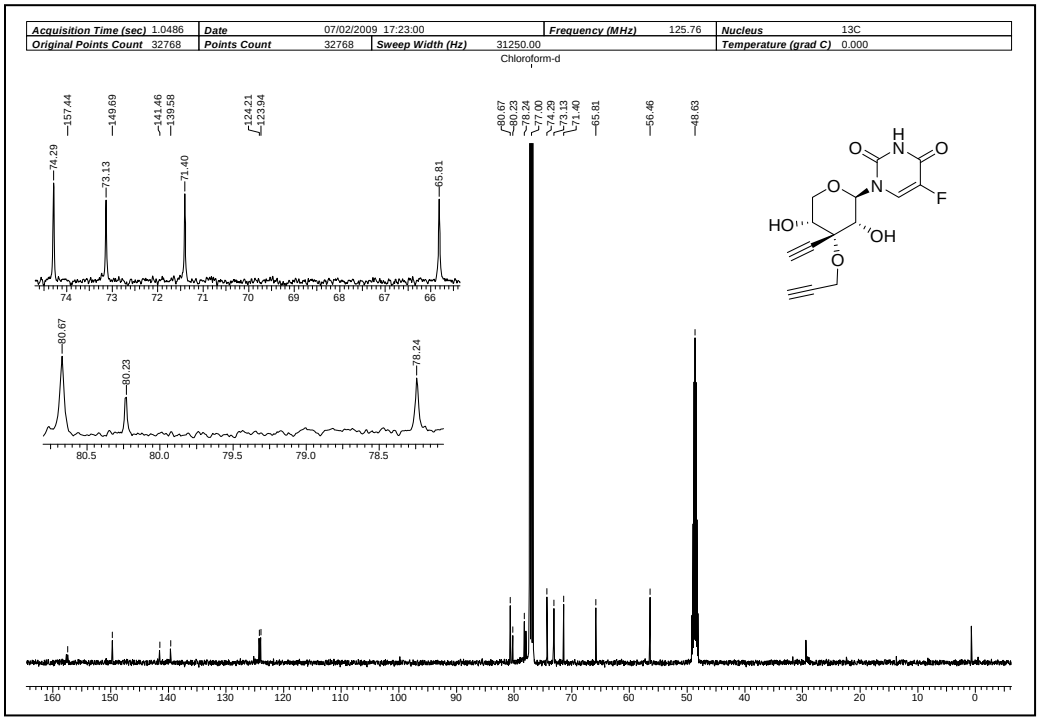
^{1}H NMR Spectrum of 5 in $CDCl_3$



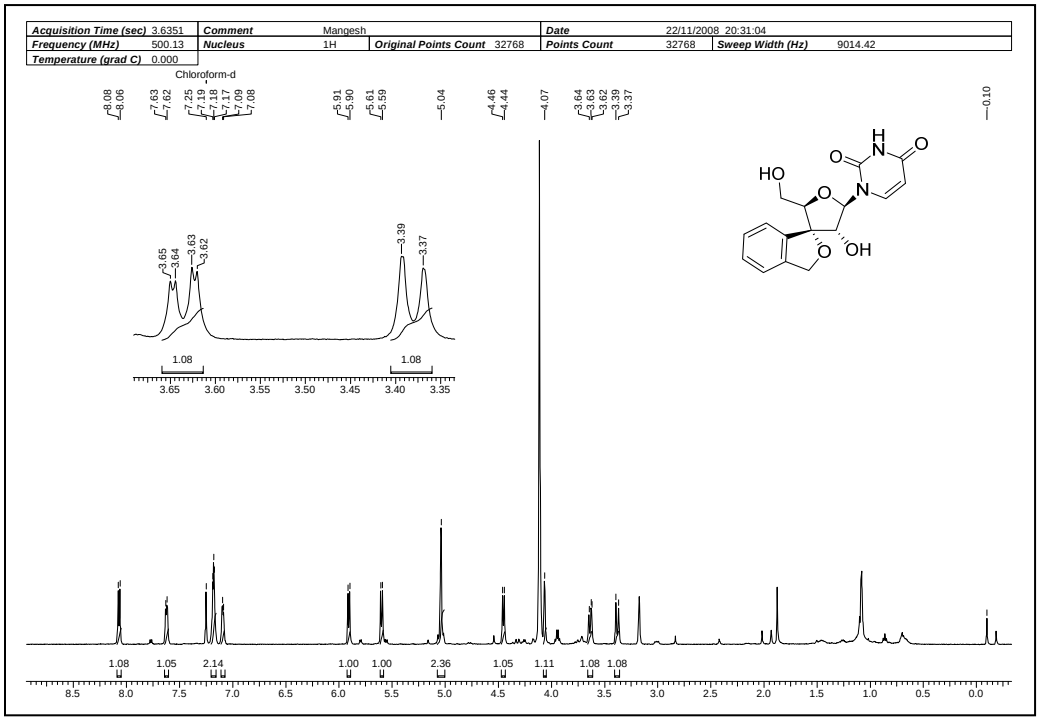
^{13}C NMR Spectrum of 5 in $CDCl_3$



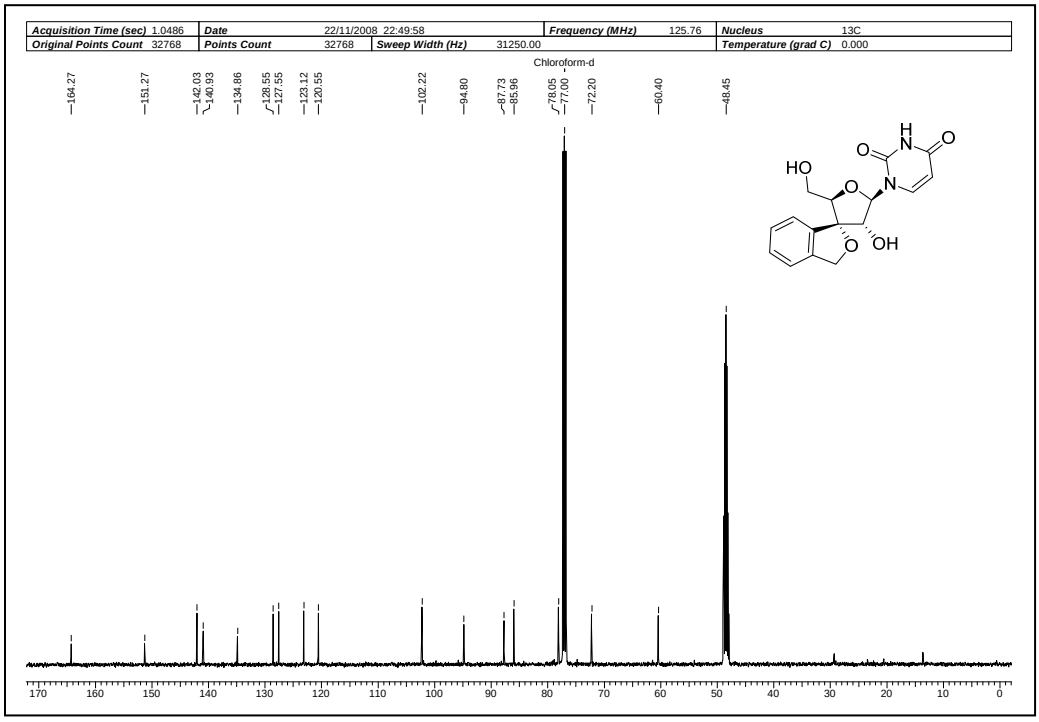
^{1}H NMR Spectrum of 6 in $CDCl_3$



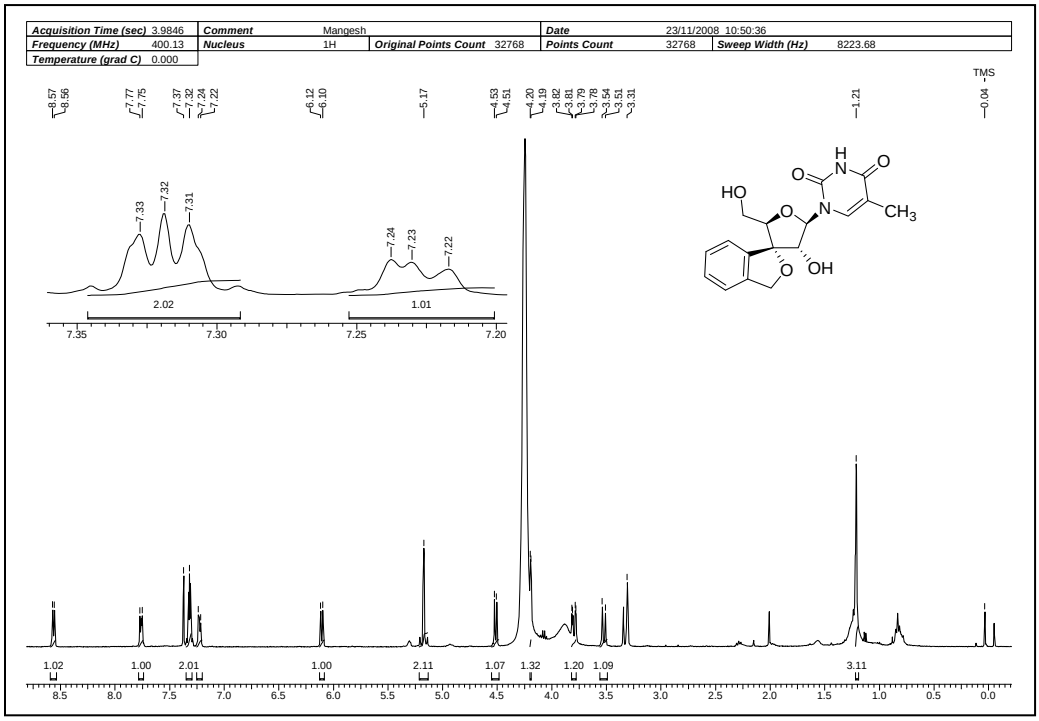
^{13}C NMR Spectrum of 6 in $CDCl_3$



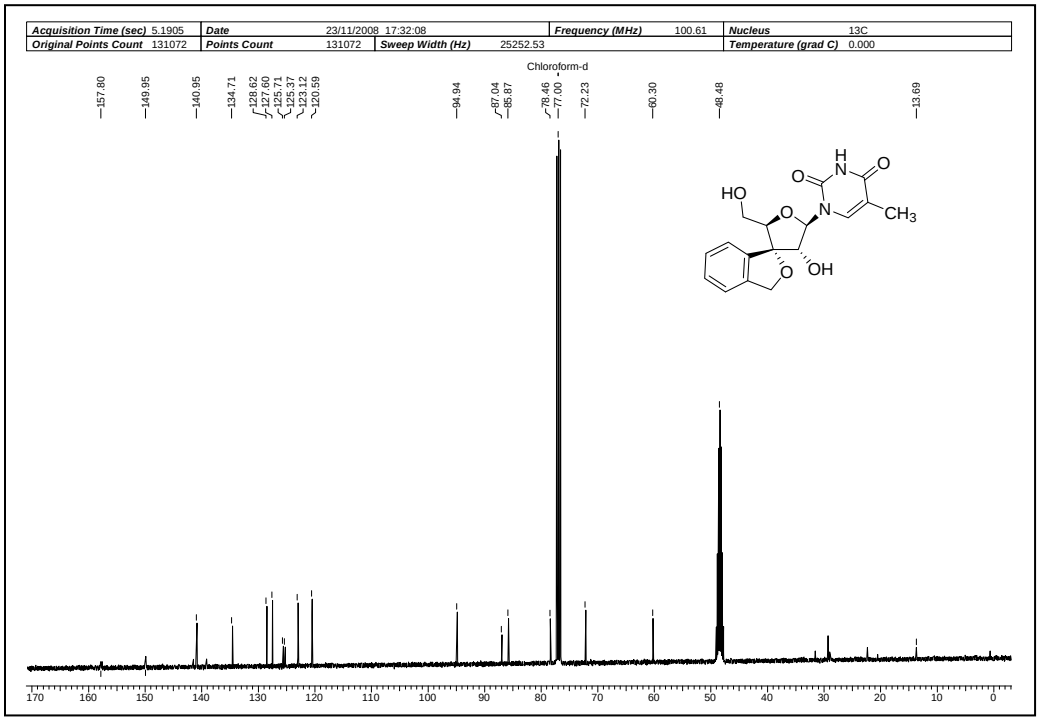
^{1}H NMR Spectrum of 20 in $CDCl_3$



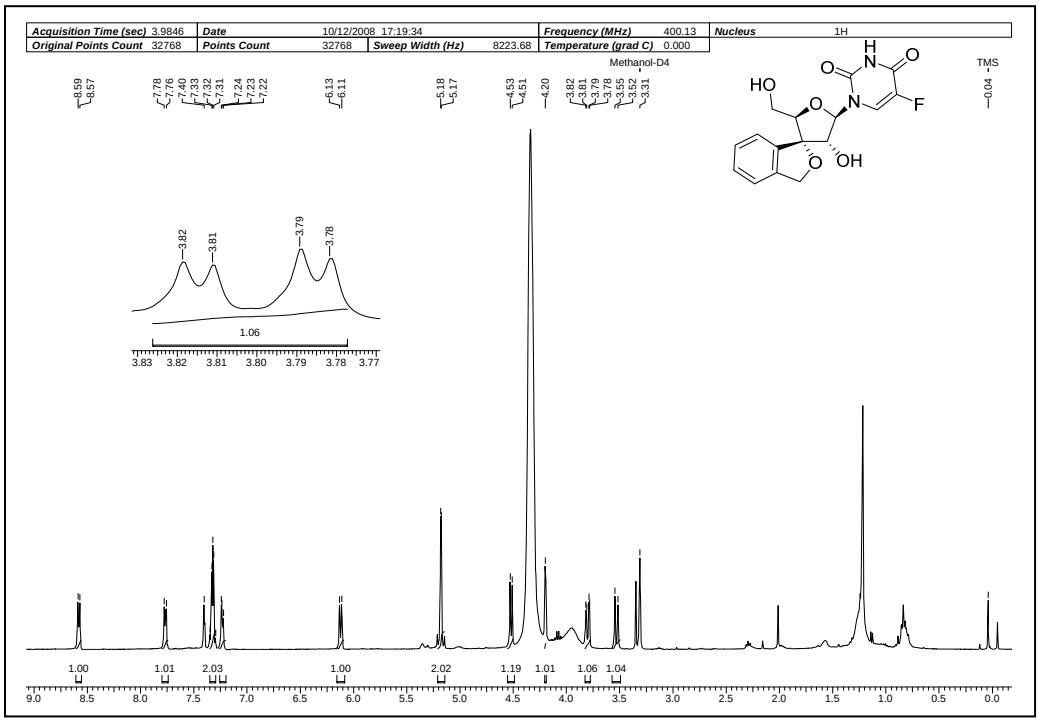
^{13}C NMR Spectrum of 20 in $CDCl_3$



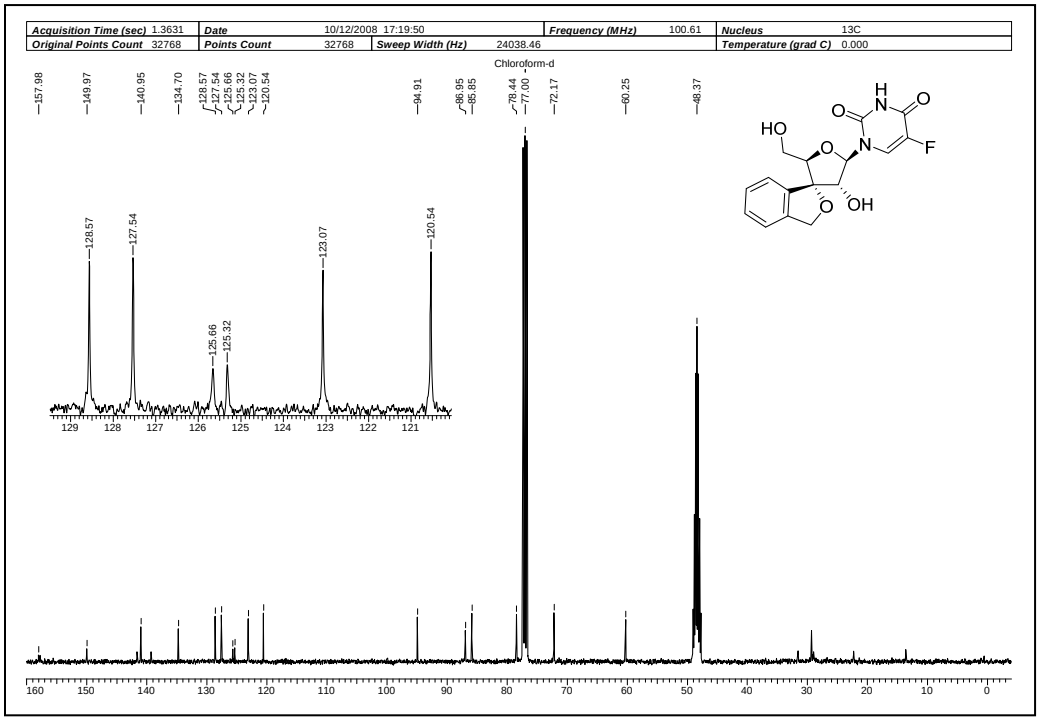
^{1}H NMR Spectrum of 21 in $CDCl_3$



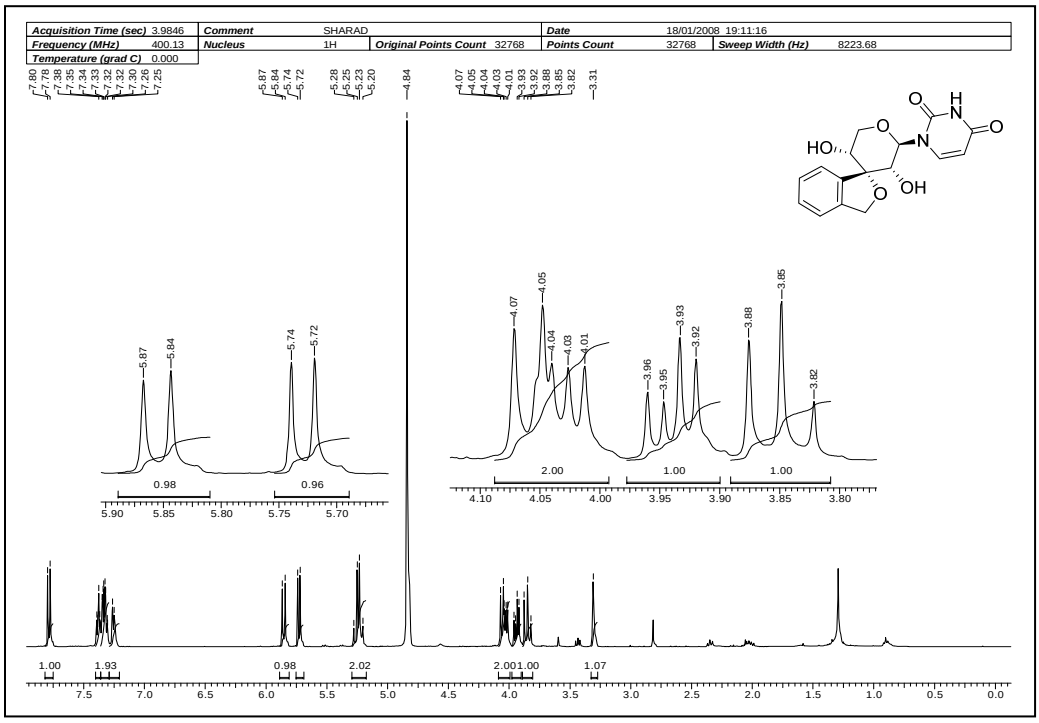
^{13}C NMR Spectrum of 21 in $CDCl_3$



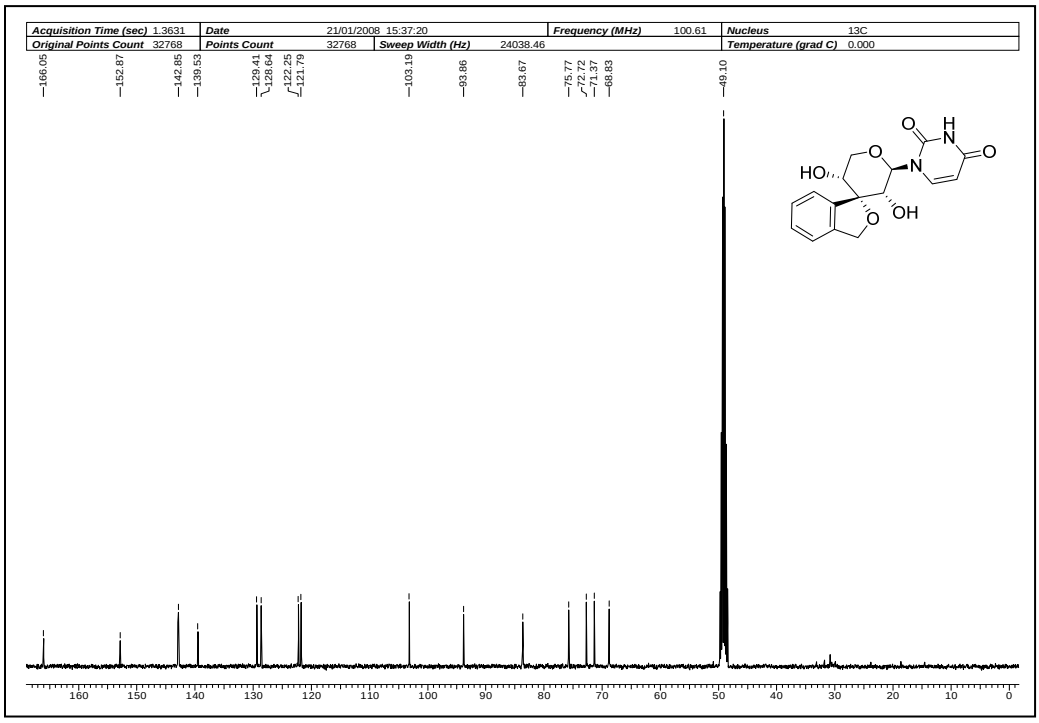
^{1}H NMR Spectrum of 22 in $CDCl_3$



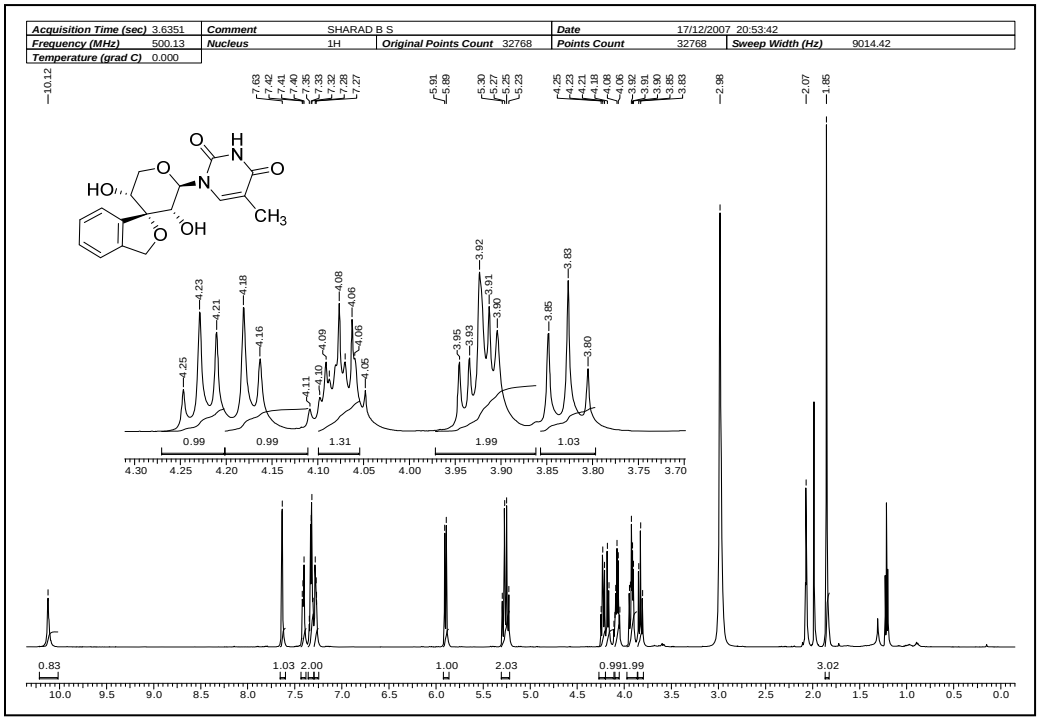
^{13}C NMR Spectrum of 22 in $CDCl_3$



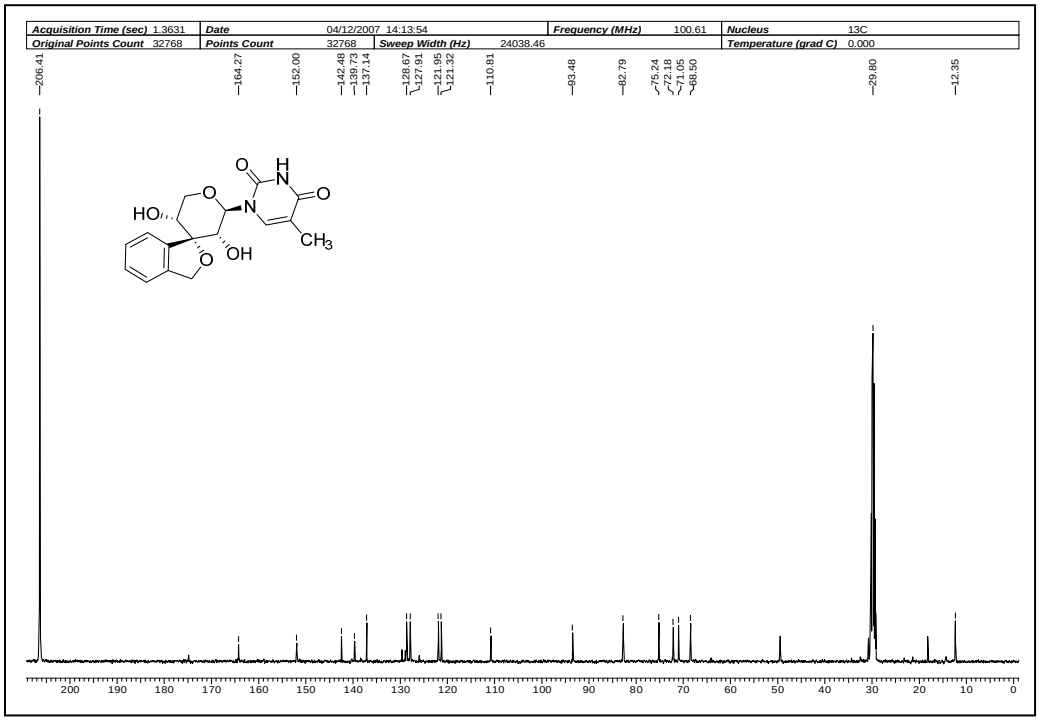
^{1}H NMR Spectrum of 23 in $CDCl_3$



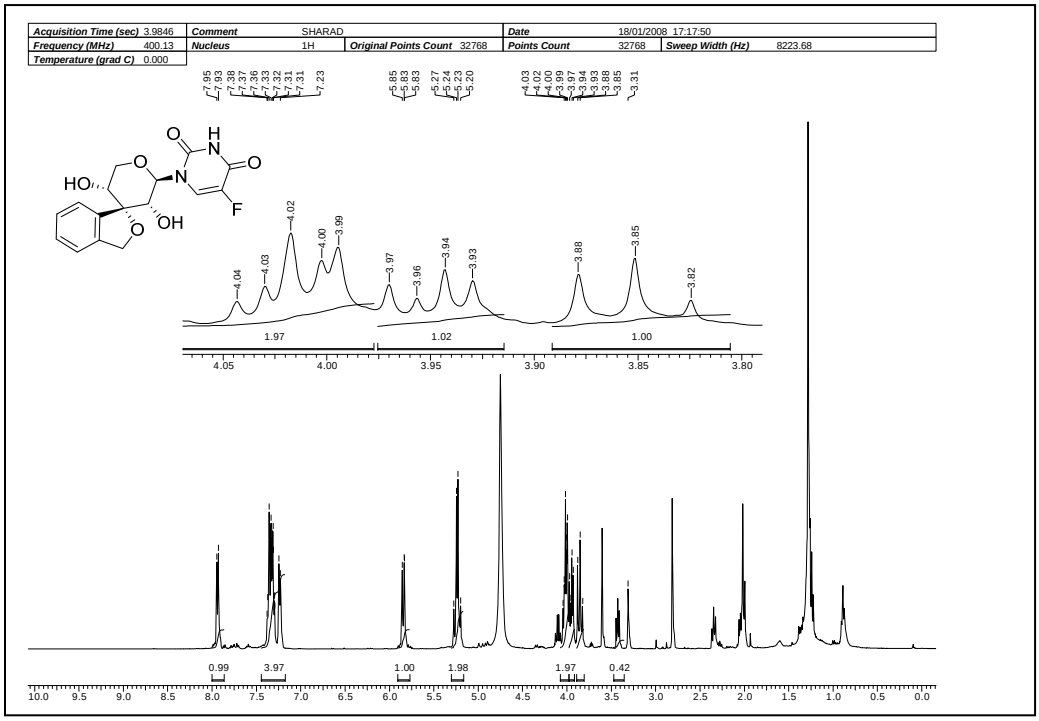
^{13}C NMR Spectrum of 23 in $CDCl_3$



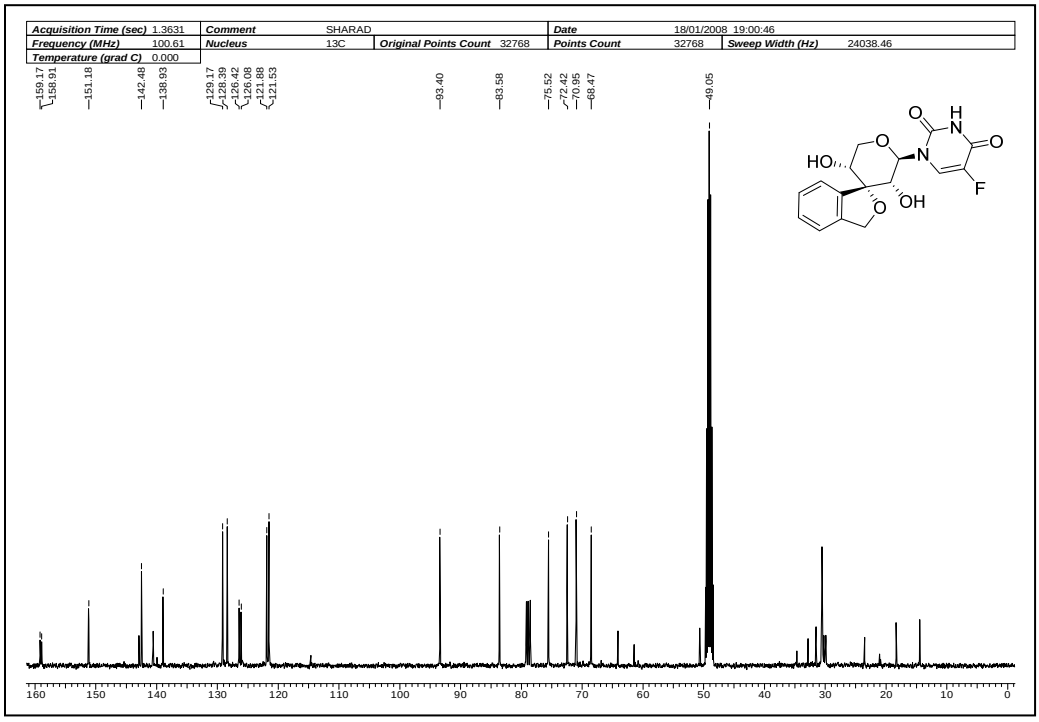
^{1}H NMR Spectrum of 24 in $CDCl_3$



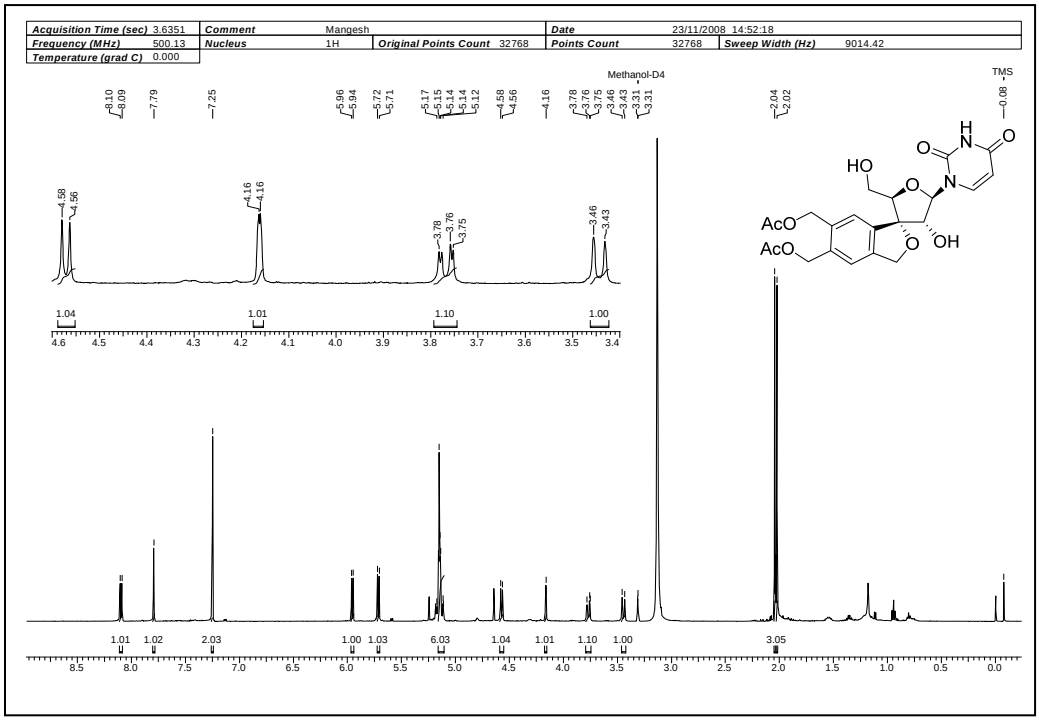
^{13}C NMR Spectrum of 24 in $CDCl_3$



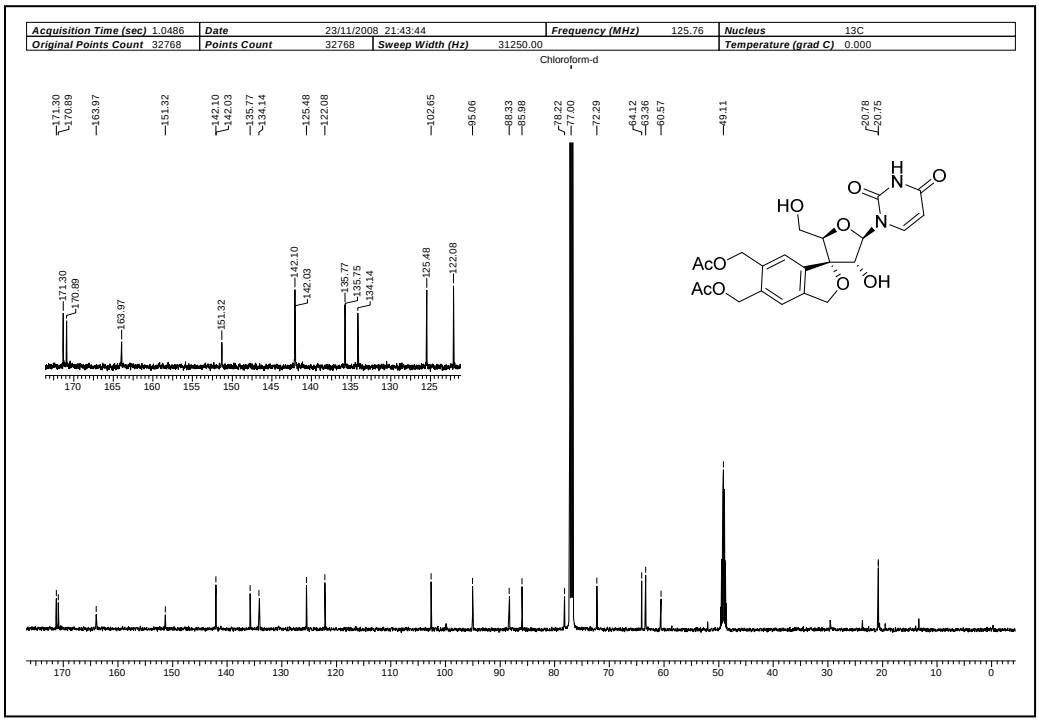
^{1}H NMR Spectrum of 25 in $CDCl_3$



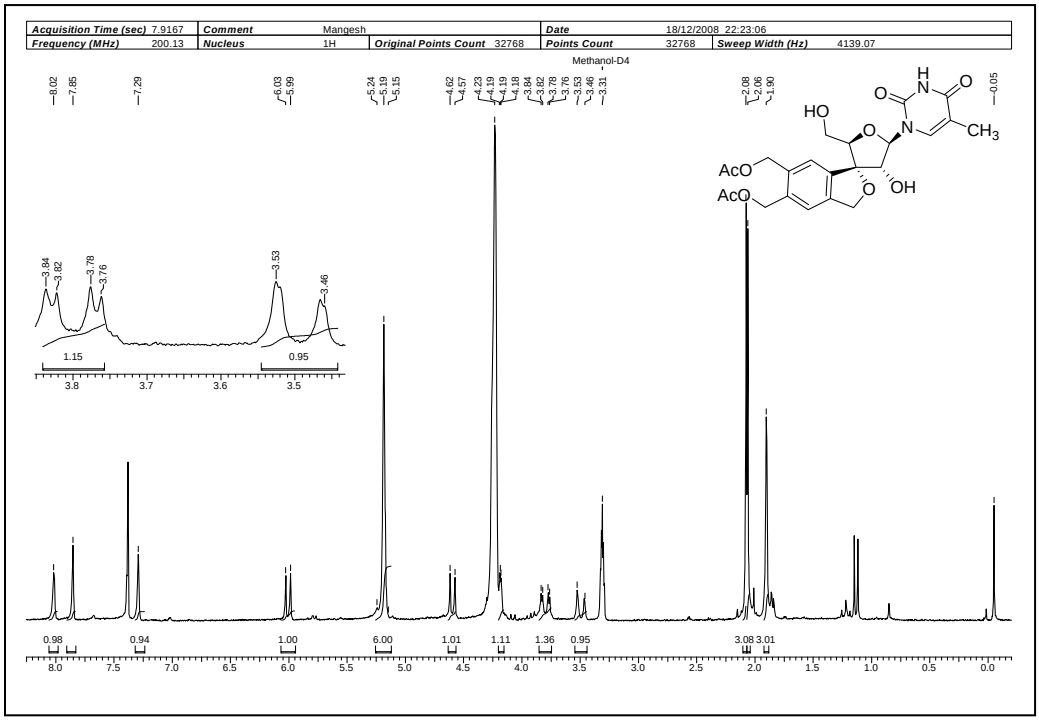
^{13}C NMR Spectrum of 25 in $CDCl_3$



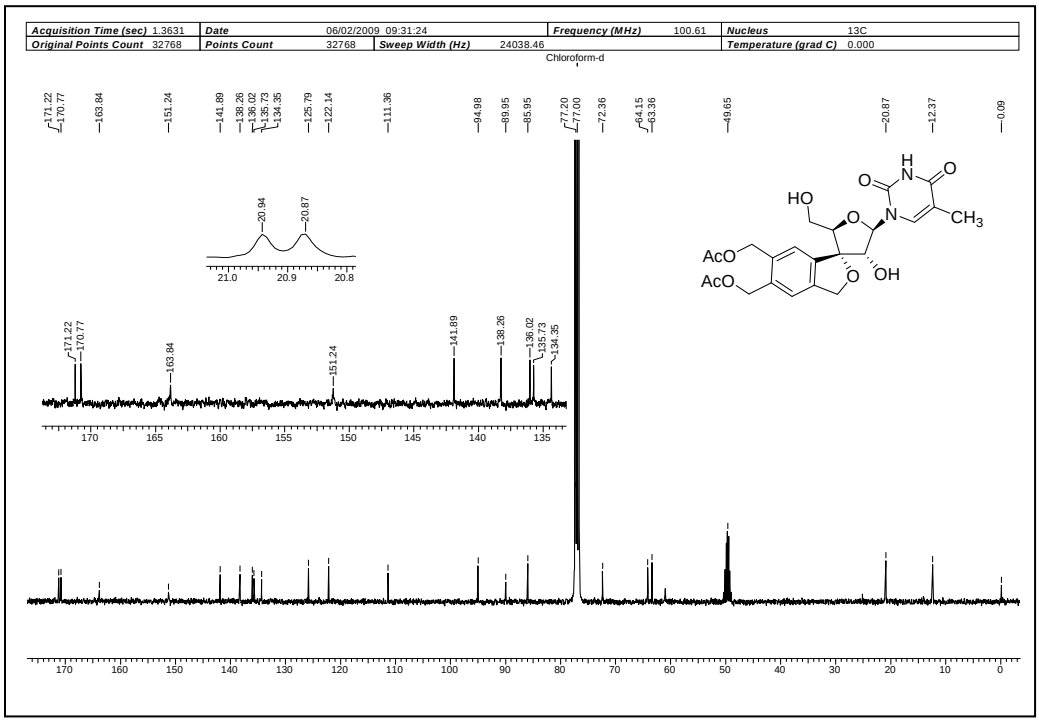
^{1}H NMR Spectrum of 26 in $CDCl_3$



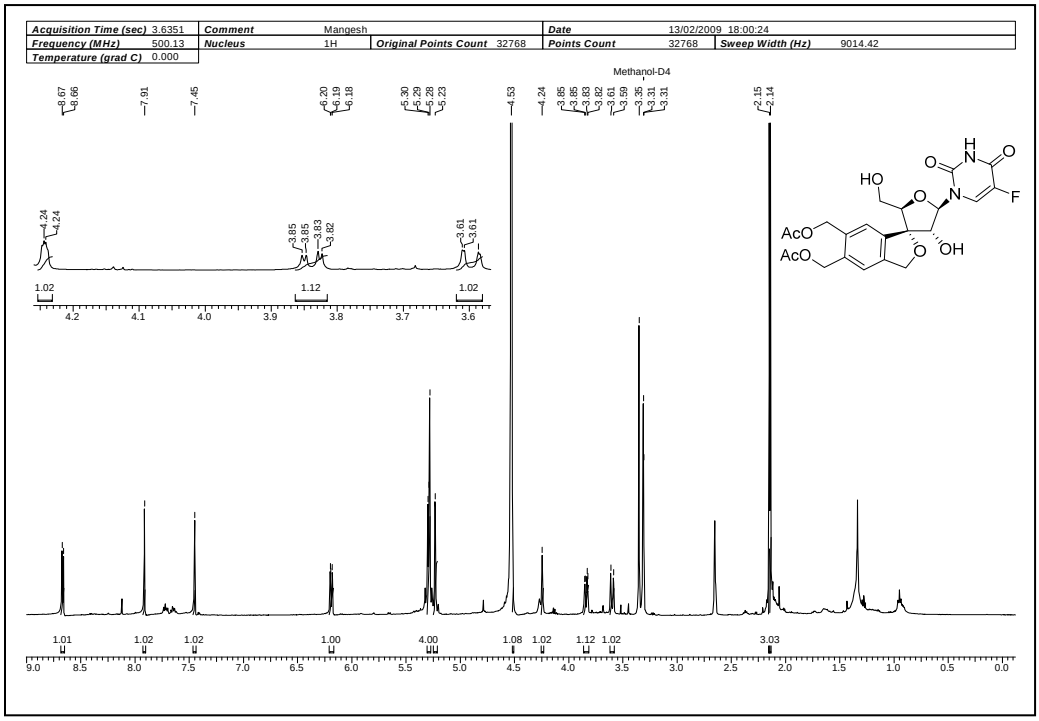
^{13}C NMR Spectrum of 26 in $CDCl_3$



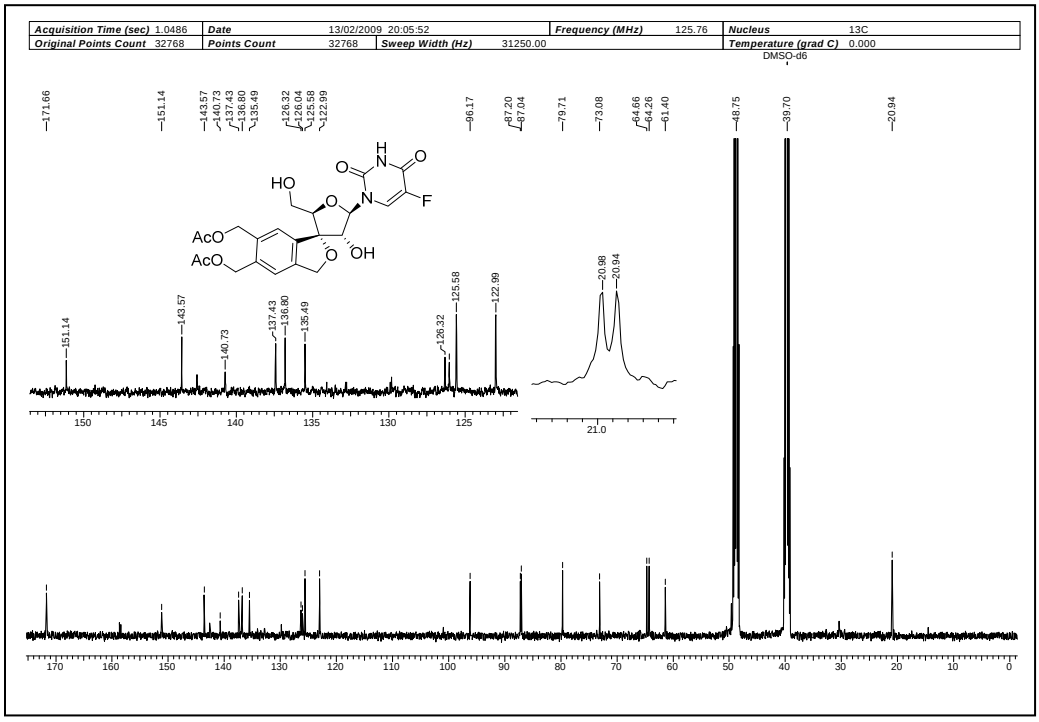
^{1}H NMR Spectrum of 27 in $CDCl_3$



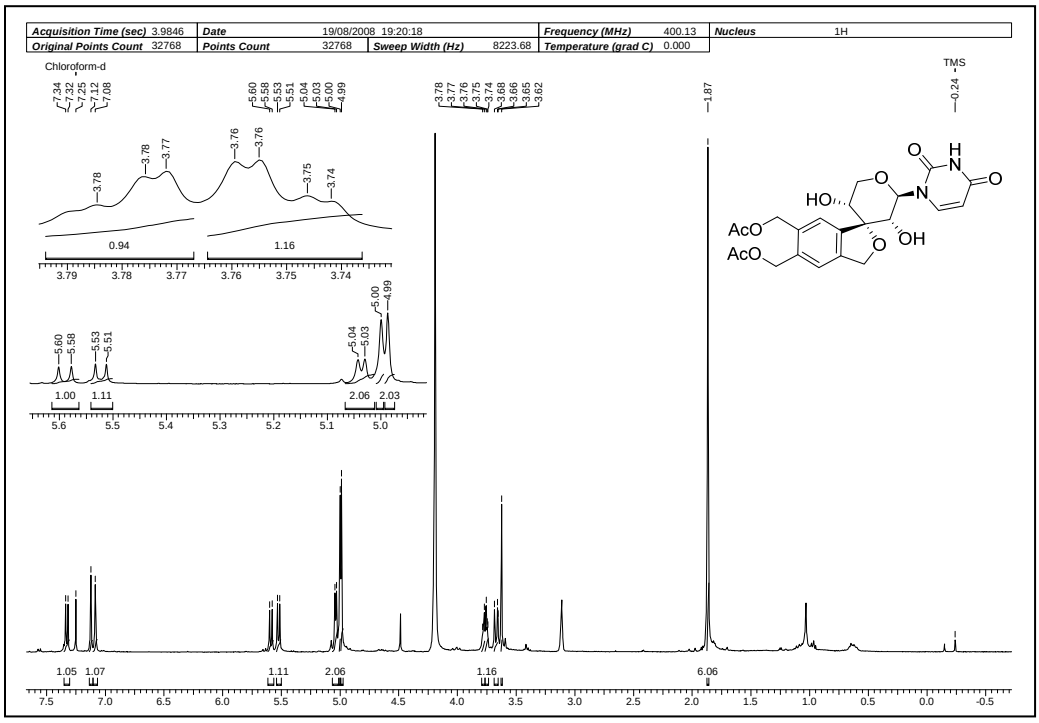
^{13}C NMR Spectrum of 27 in $CDCl_3$



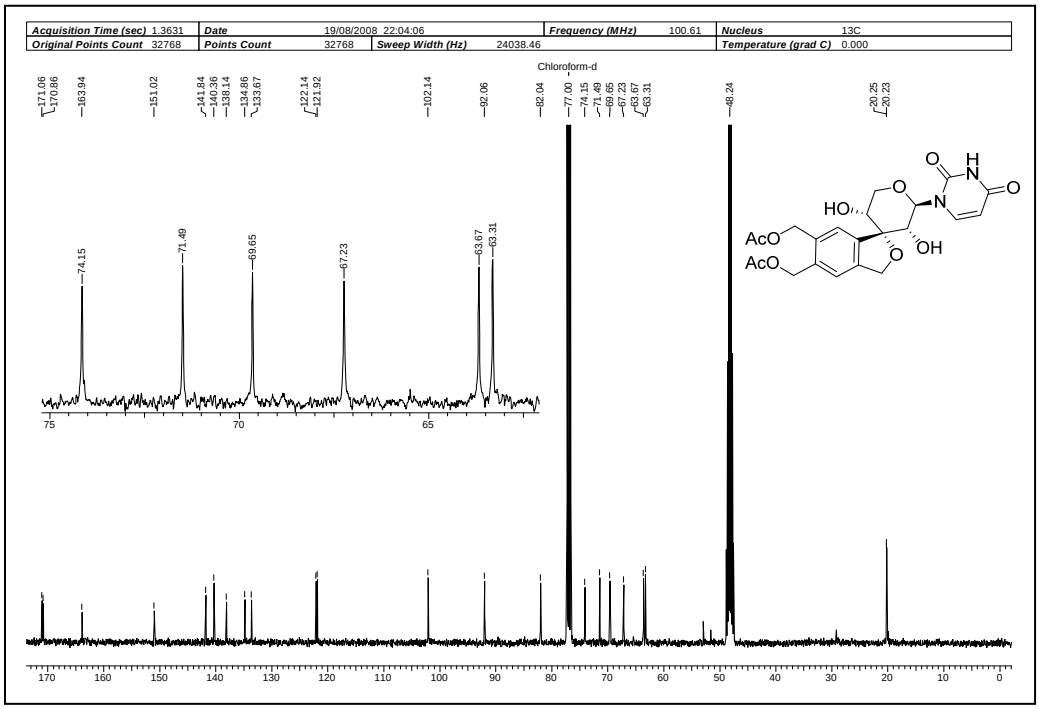
^{1}H NMR Spectrum of 28 in $CDCl_3$



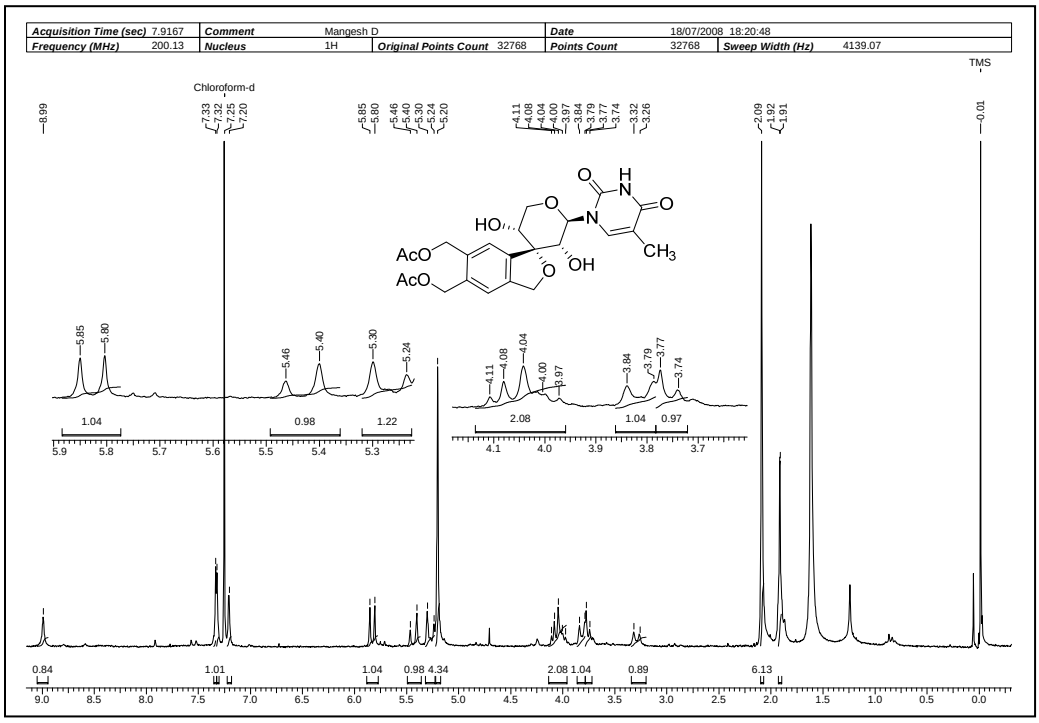
^{13}C NMR Spectrum of 28 in $CDCl_3$



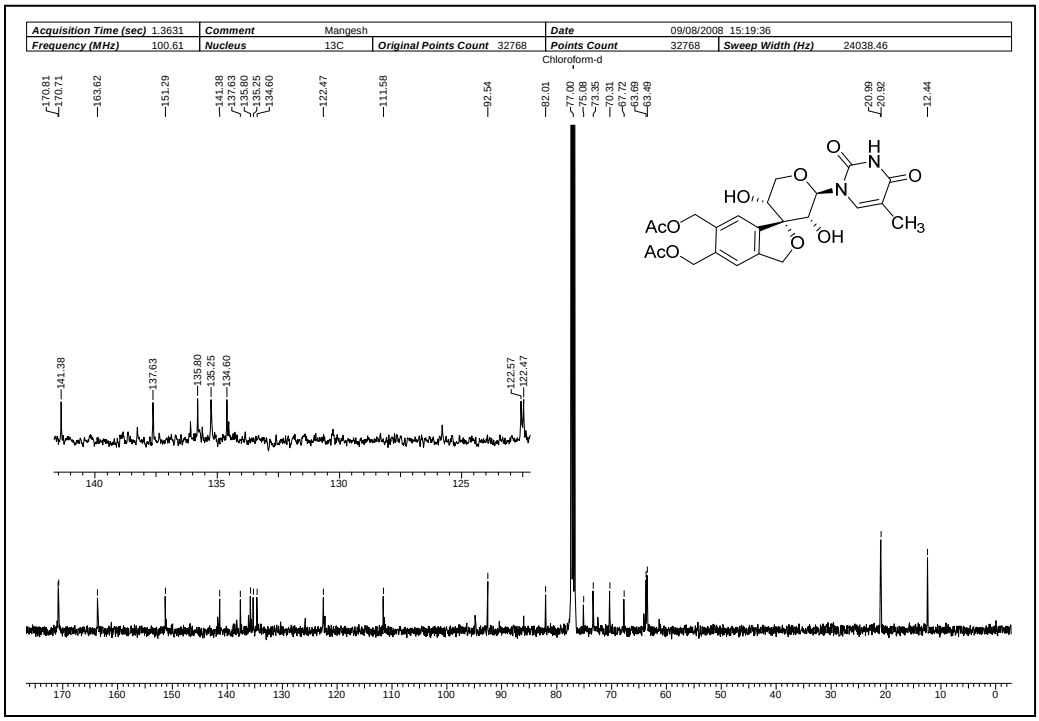
^{1}H NMR Spectrum of 29 in $CDCl_3$



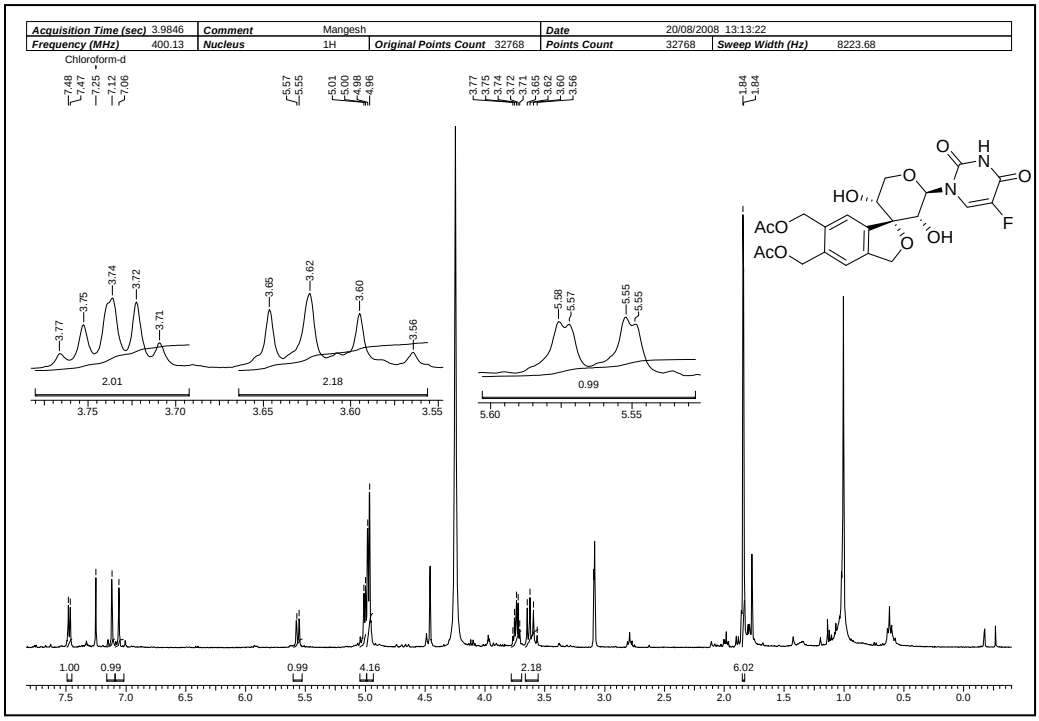
^{13}C NMR Spectrum of 29 in $CDCl_3$



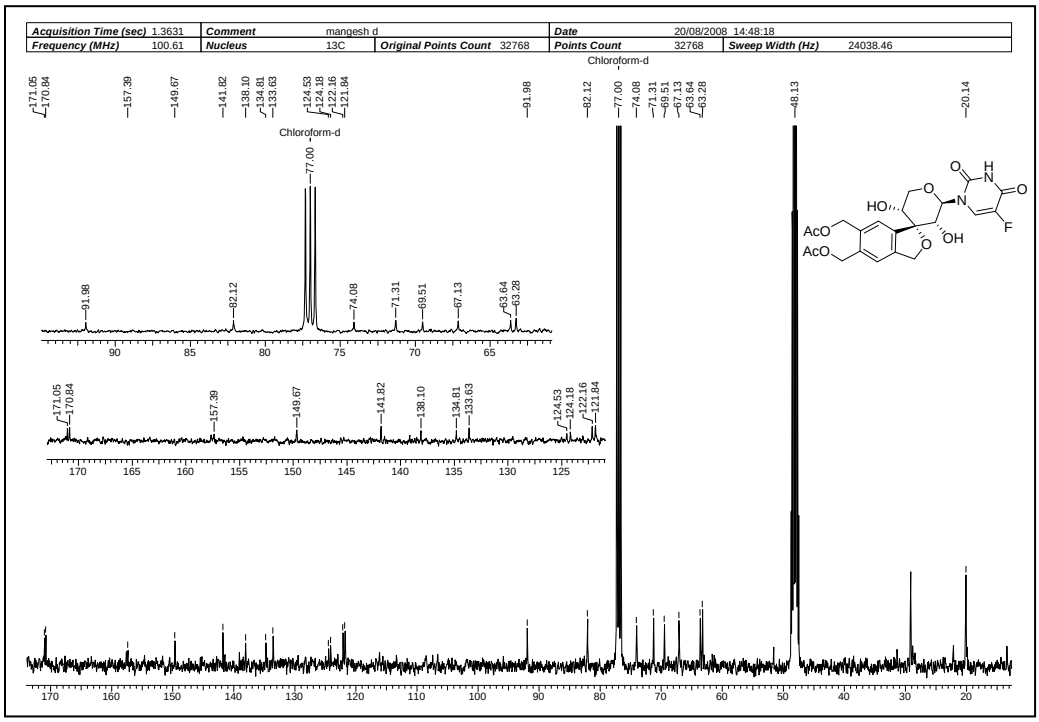
^{1}H NMR Spectrum of 30 in $CDCl_3$



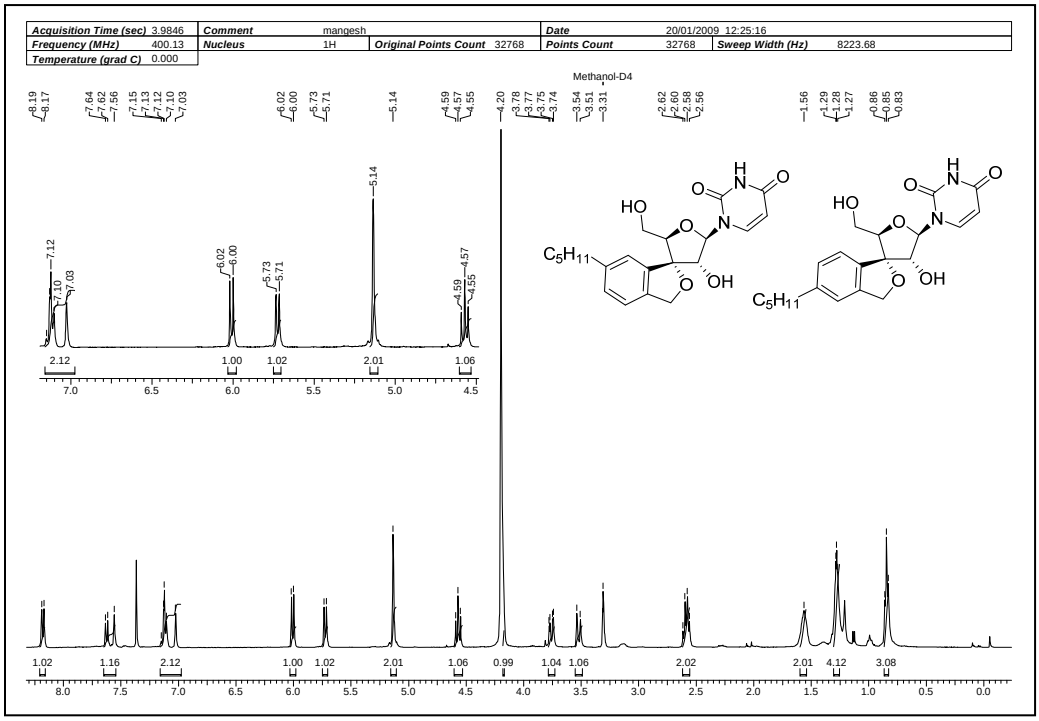
^{13}C NMR Spectrum of 30 in $CDCl_3$



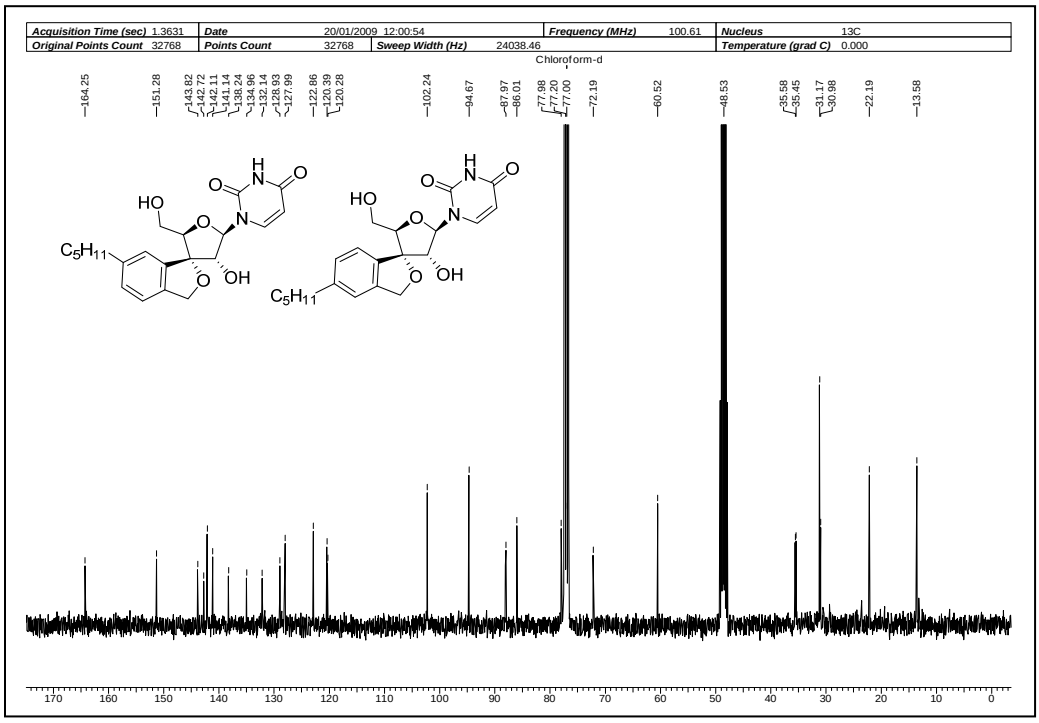
^{1}H NMR Spectrum of 31 in $CDCl_3$



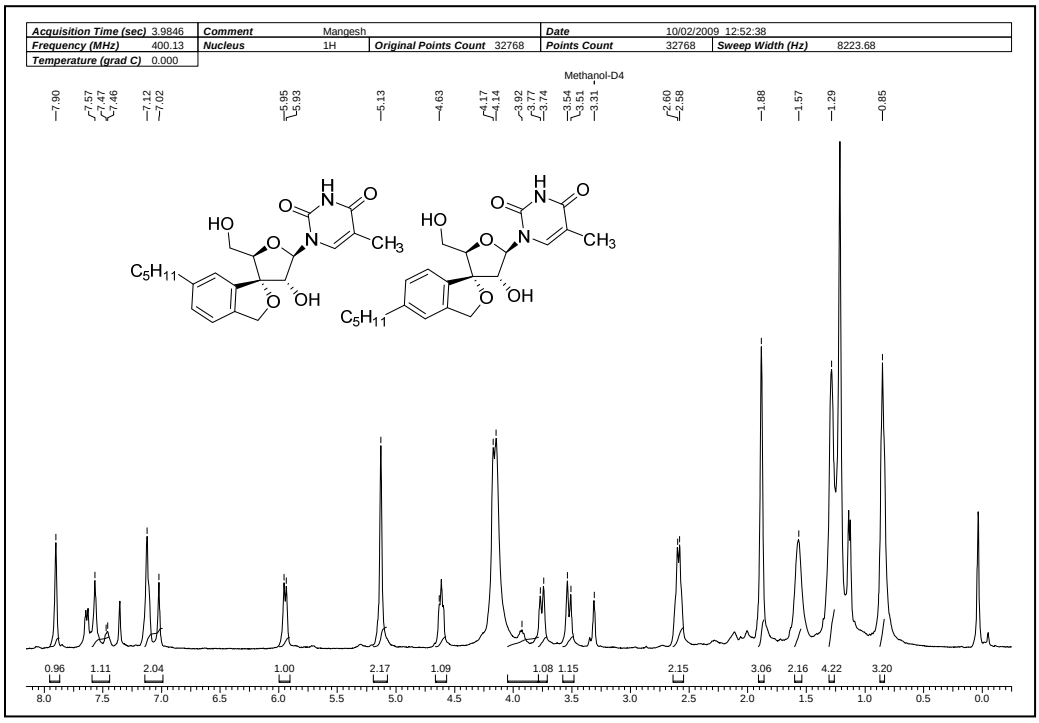
^{13}C NMR Spectrum of 31 in $CDCl_3$



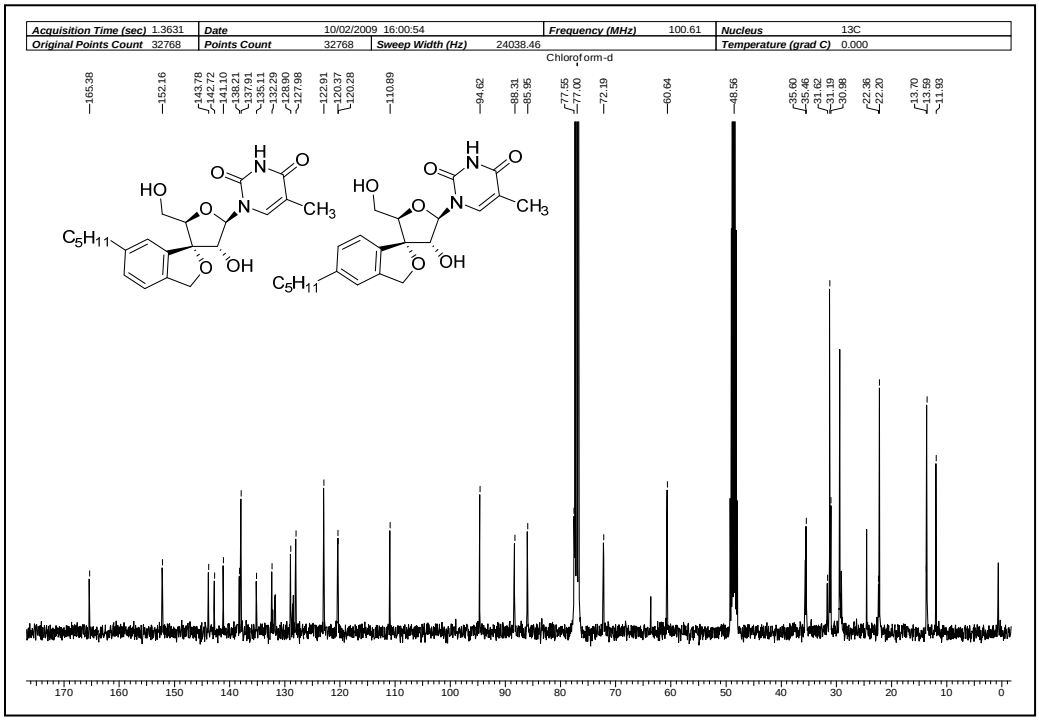
^{1}H NMR Spectrum of 32 in $CDCl_3$



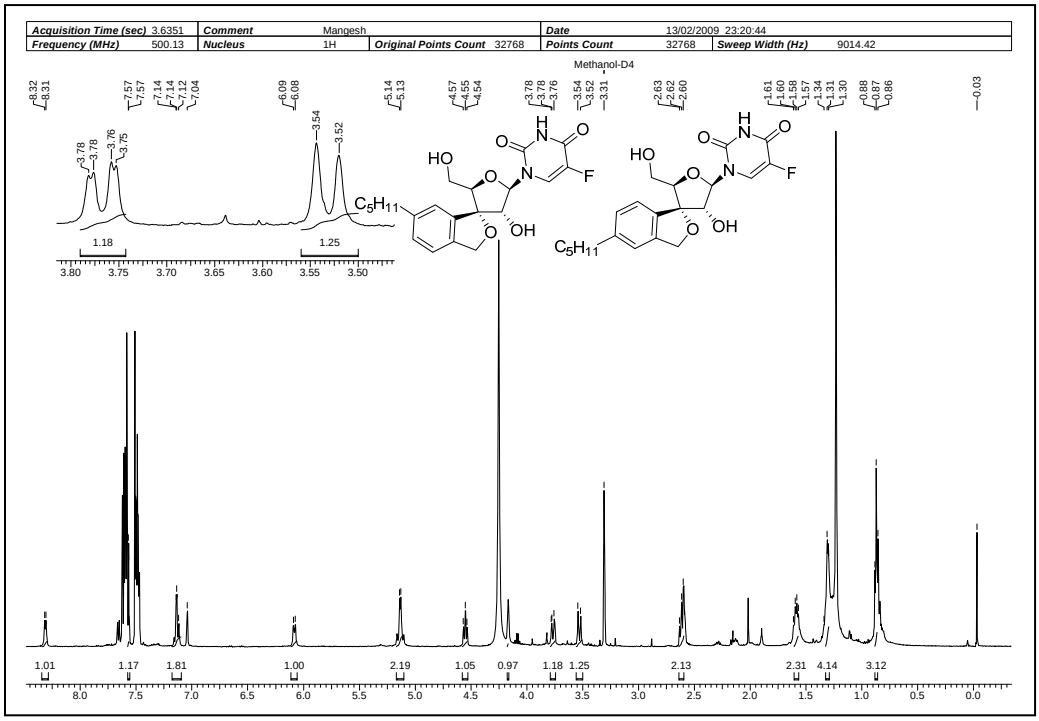
^{13}C NMR Spectrum of 32 in $CDCl_3$



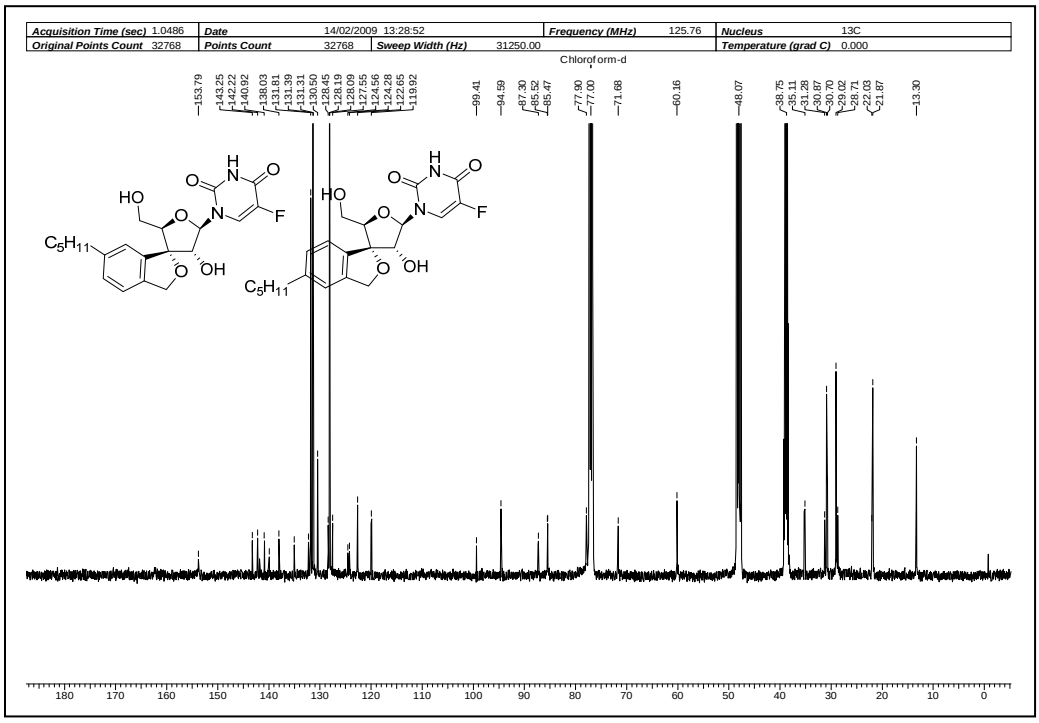
^{1}H NMR Spectrum of 33 in $CDCl_3$



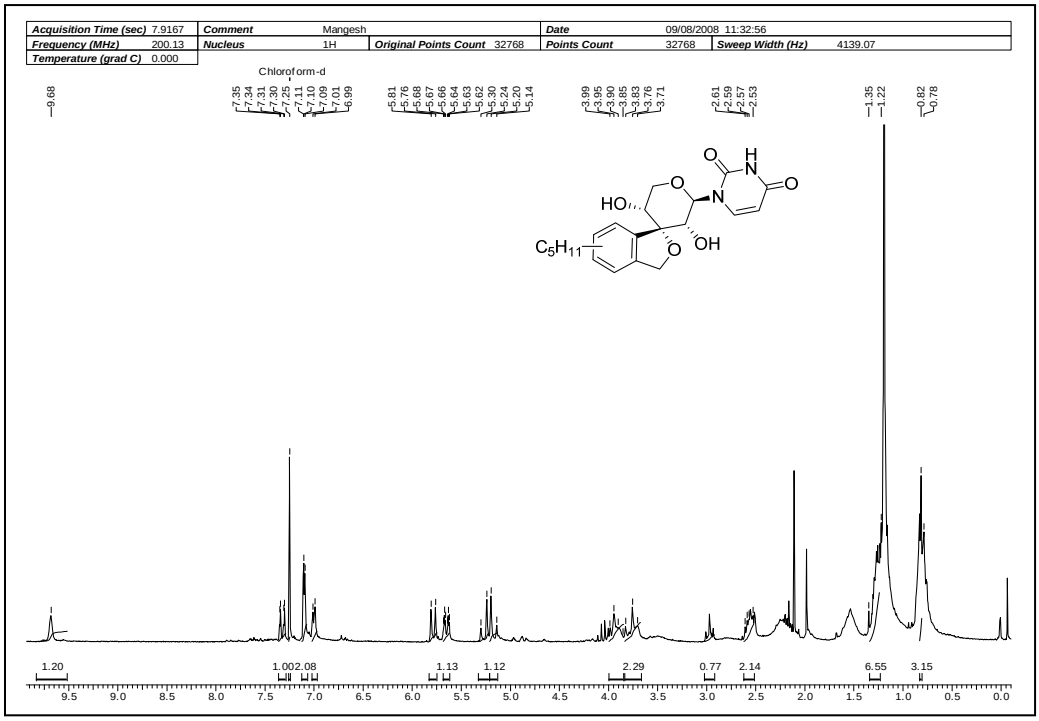
^{13}C NMR Spectrum of 33 in $CDCl_3$



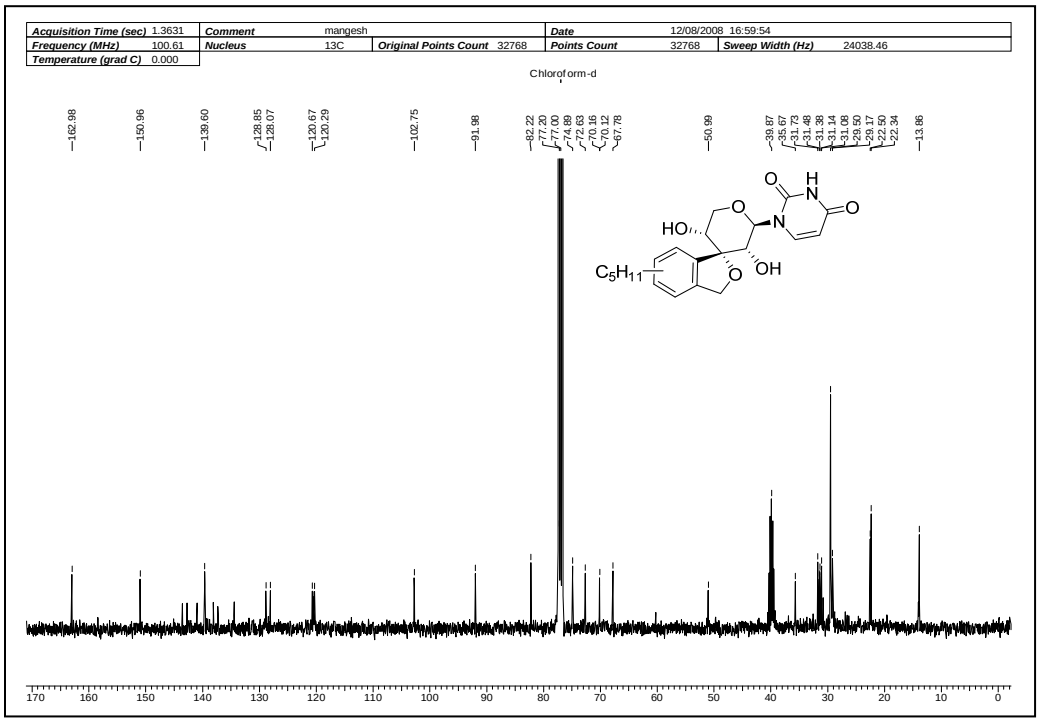
^{1}H NMR Spectrum of 34 in $CDCl_3$



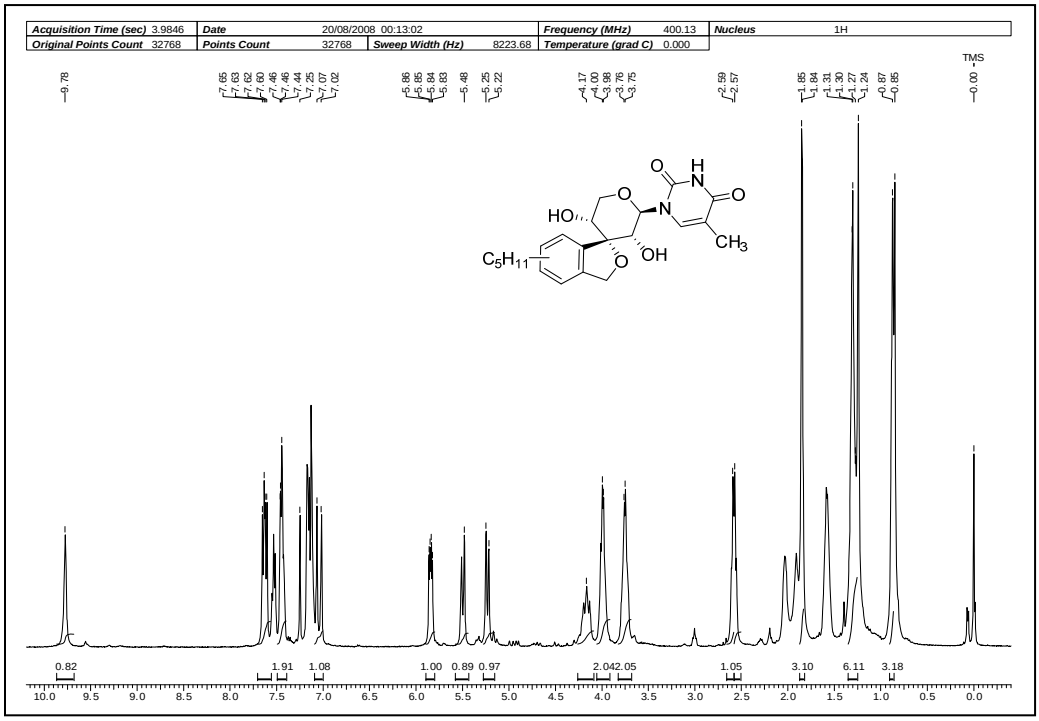
^{13}C NMR Spectrum of 34 in $CDCl_3$



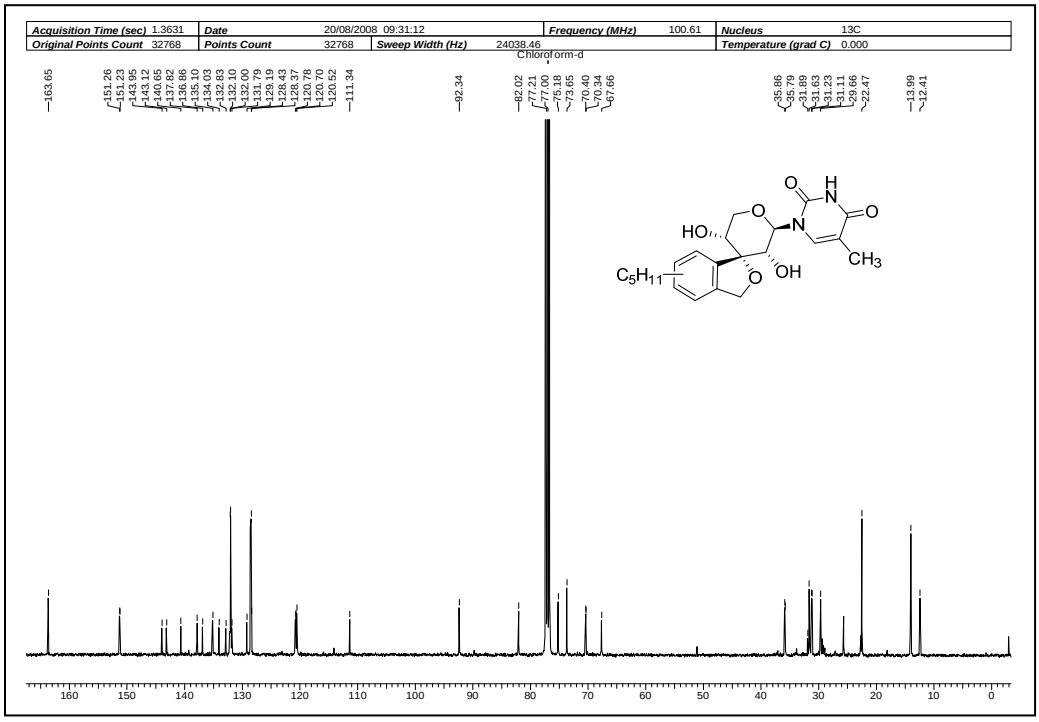
^{1}H NMR Spectrum of 35 in $CDCl_3$



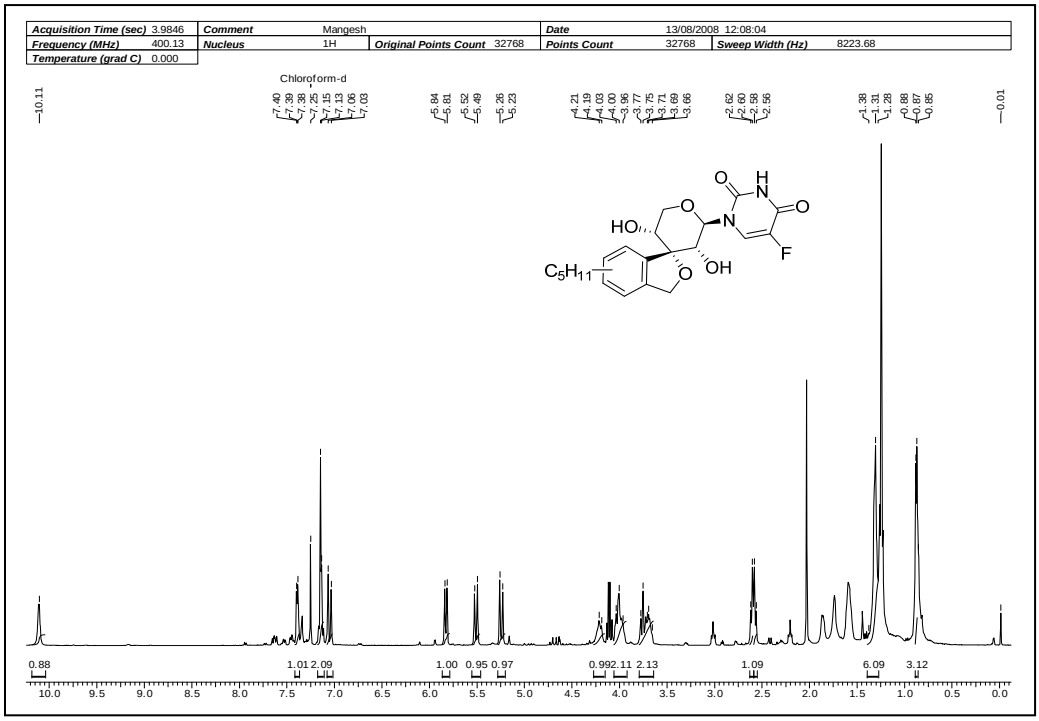
^{13}C NMR Spectrum of 35 in $CDCl_3$



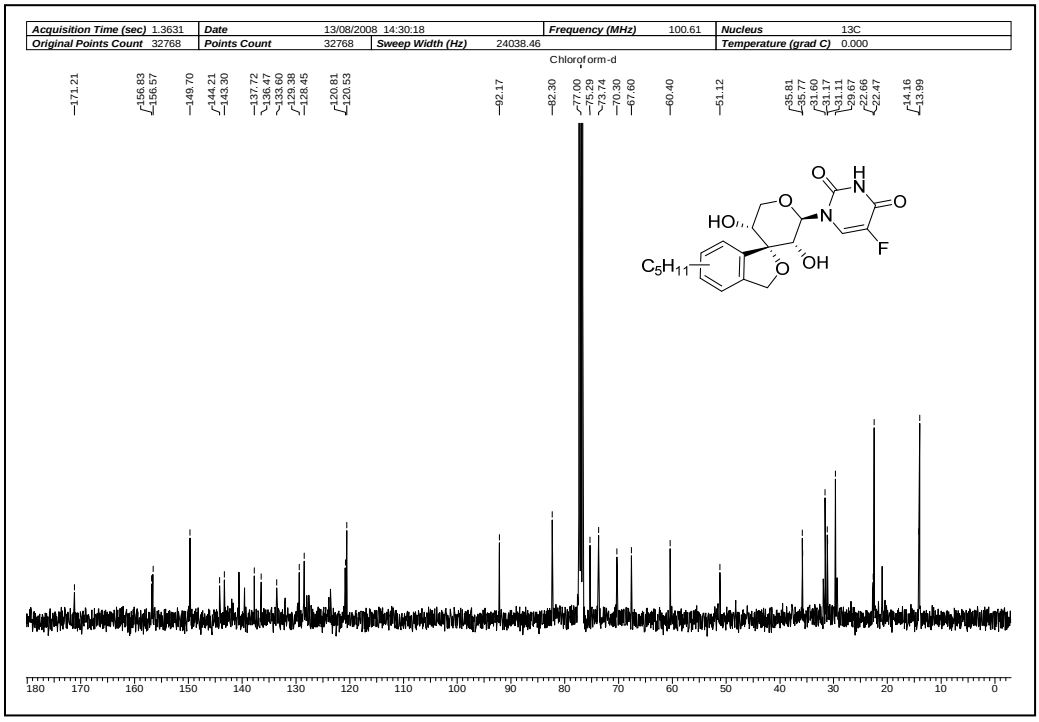
^{1}H NMR Spectrum of 36 in $CDCl_3$



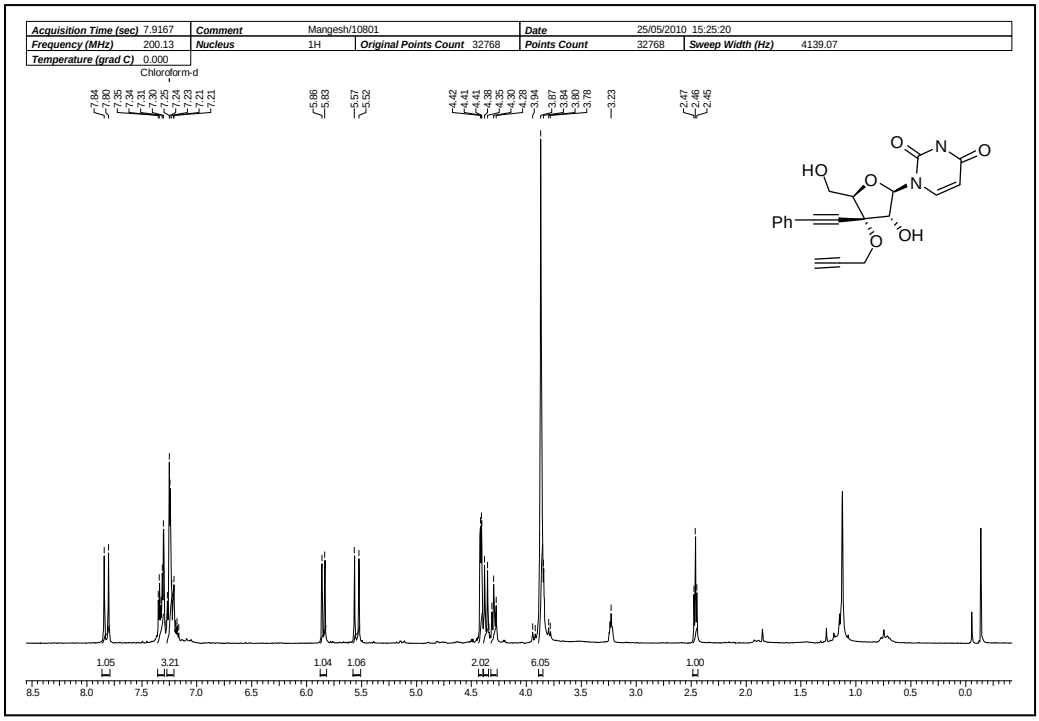
^{13}C NMR Spectrum of 36 in $CDCl_3$



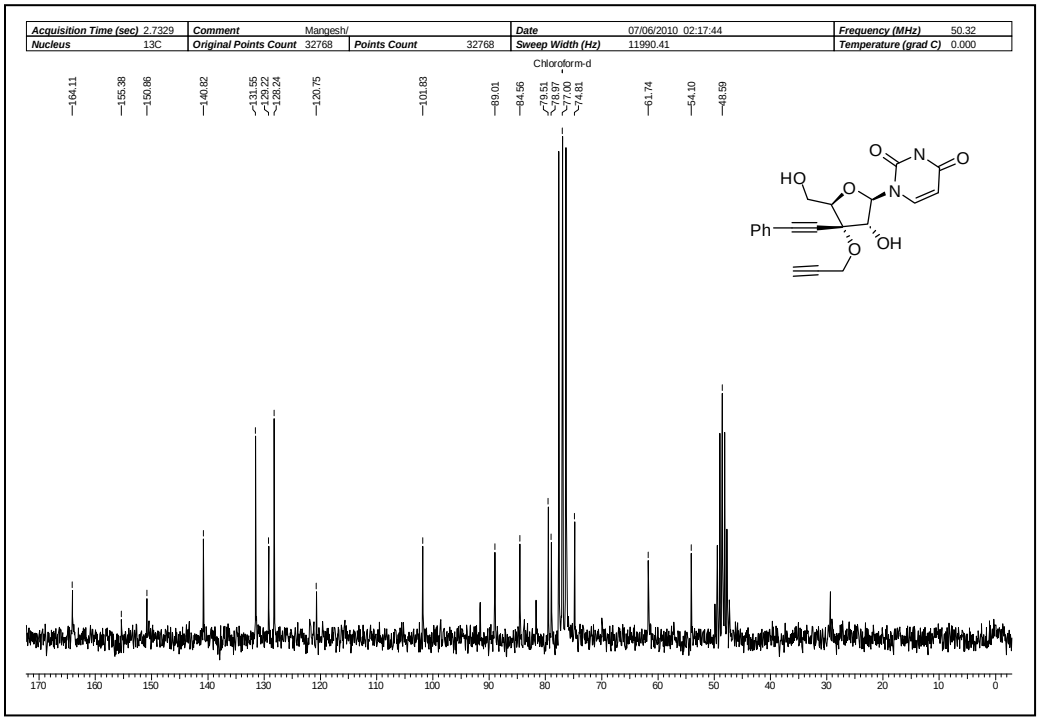
^{1}H NMR Spectrum of 37 in $CDCl_3$



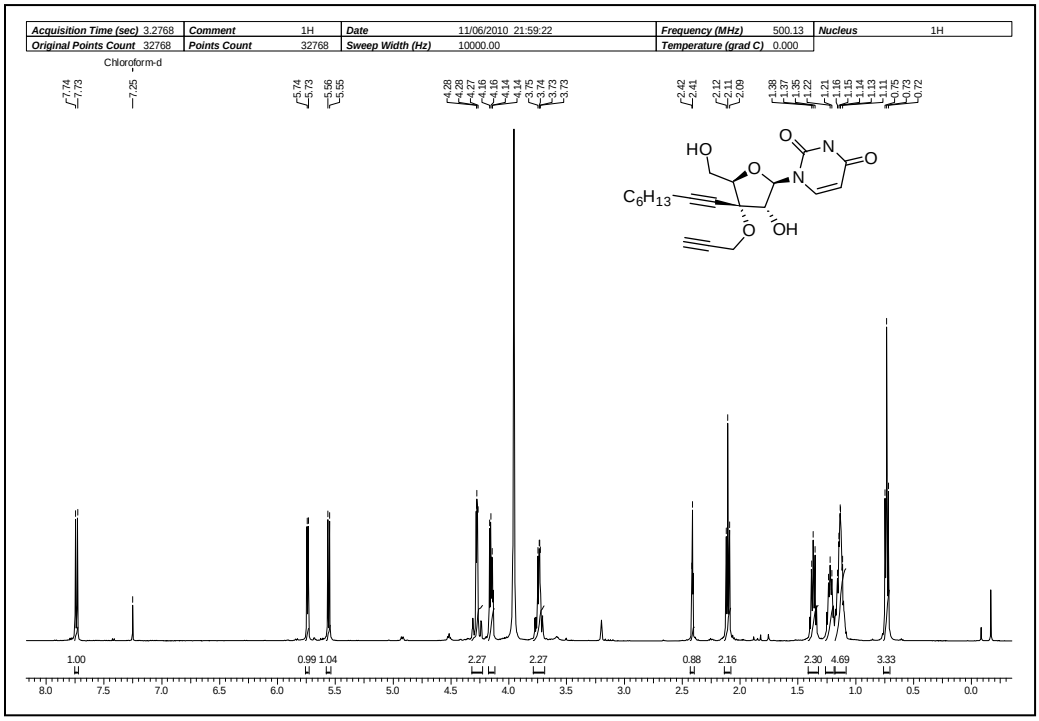
^{13}C NMR Spectrum of 37 in $CDCl_3$



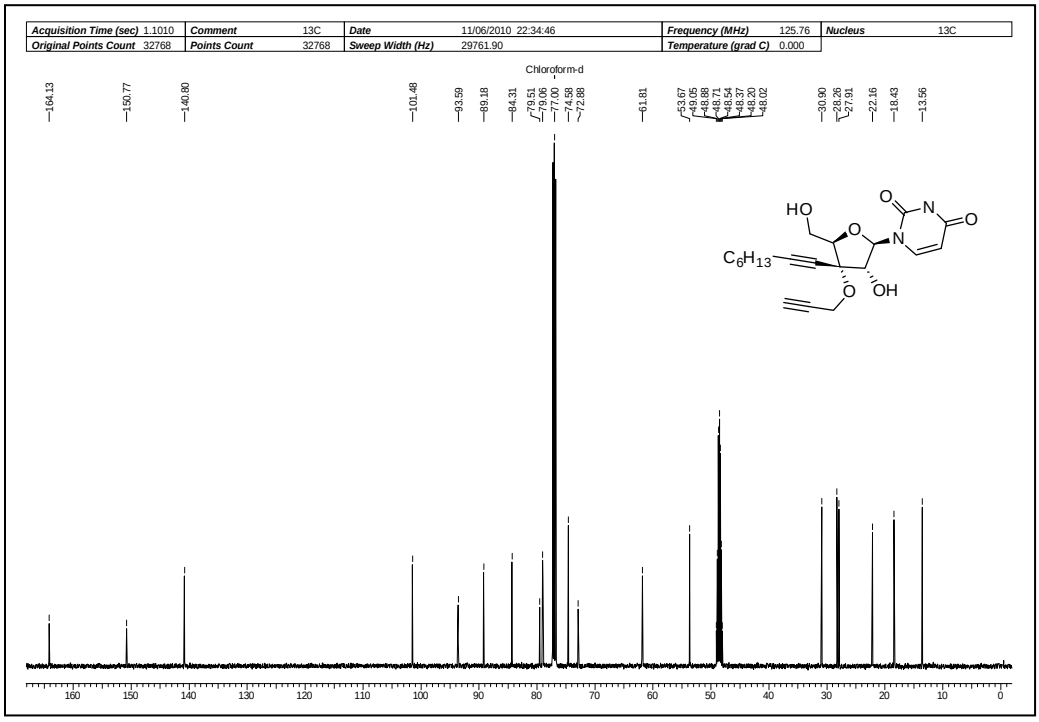
^{1}H NMR Spectrum of 38 in $CDCl_3$



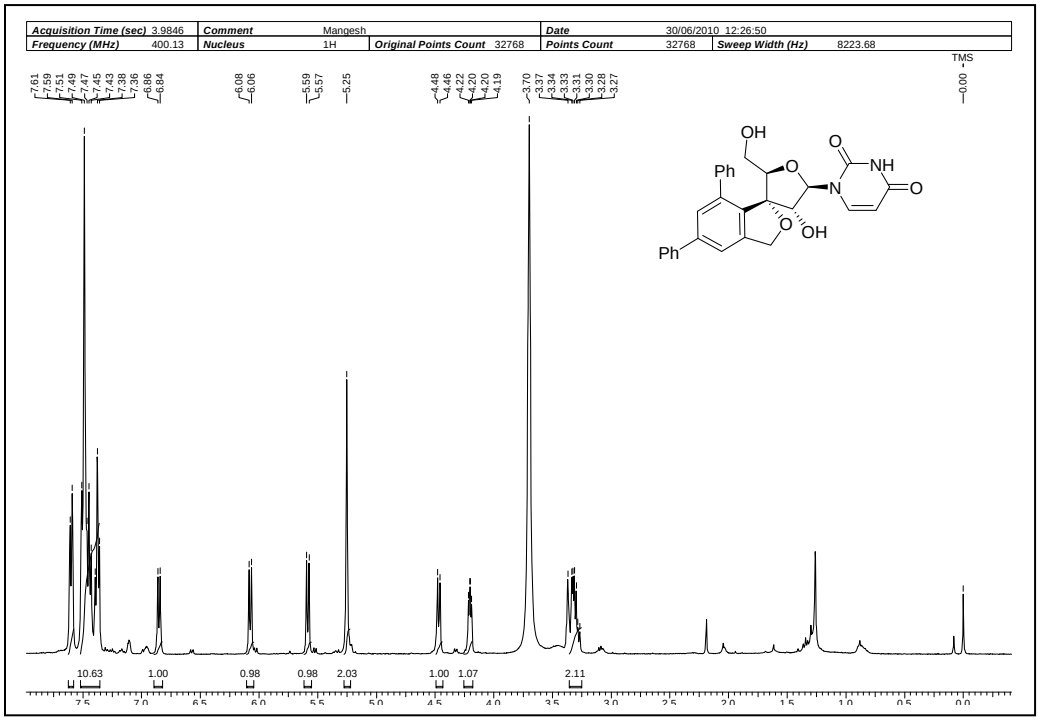
^{13}C NMR Spectrum of 38 in $CDCl_3$



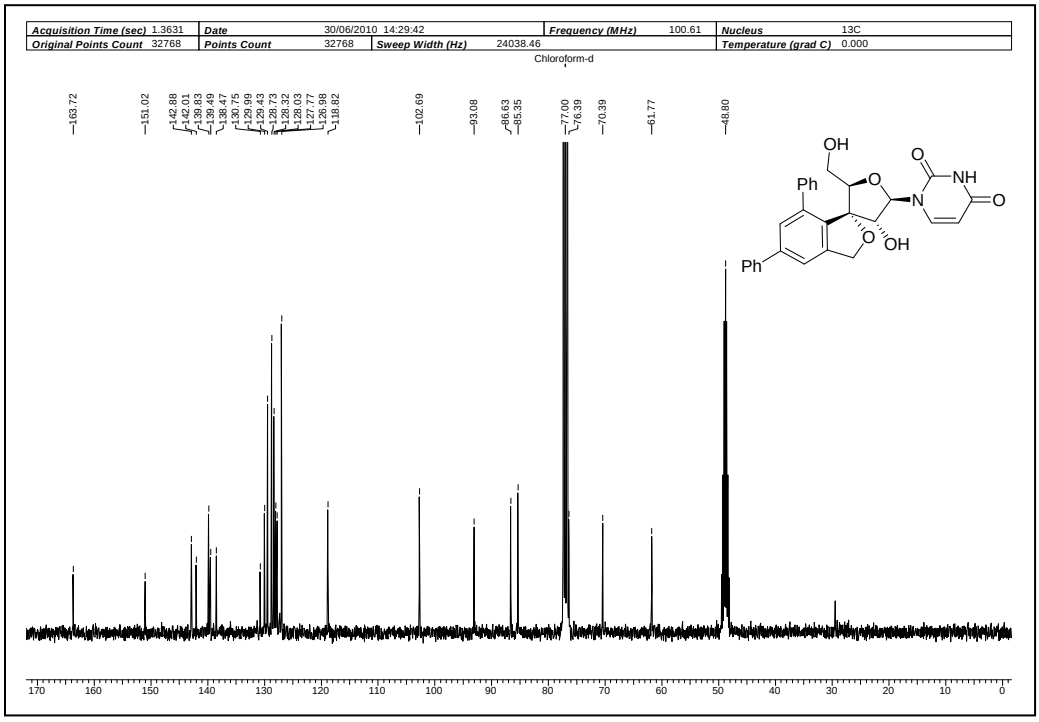
^{1}H NMR Spectrum of 39 in $CDCl_3$



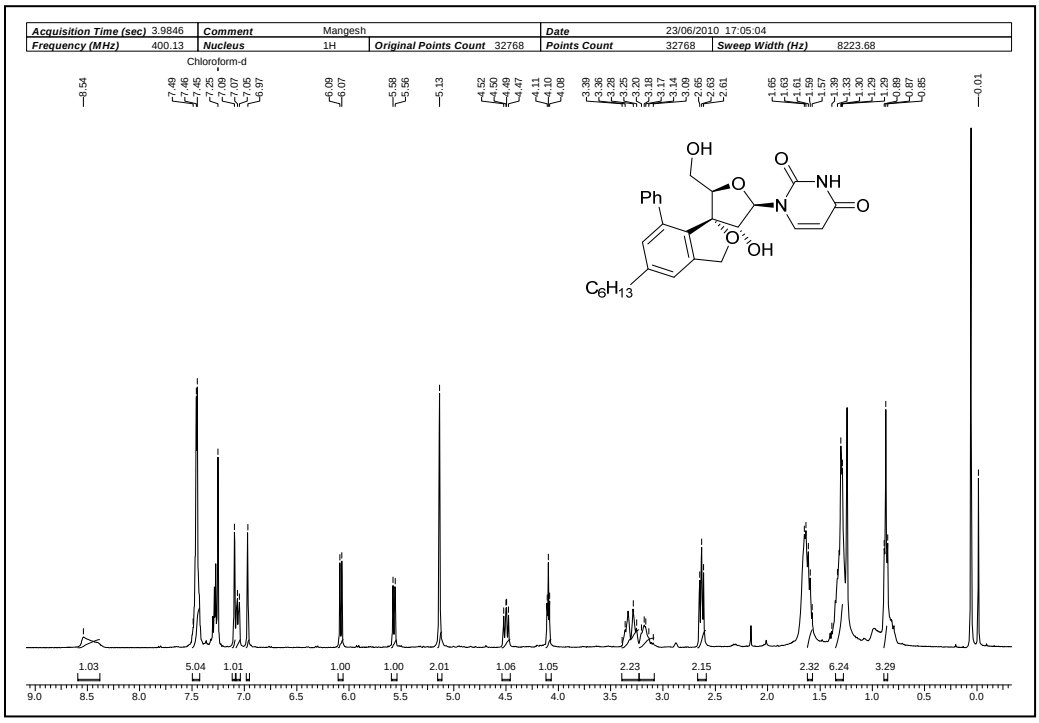
^{13}C NMR Spectrum of 39 in $CDCl_3$



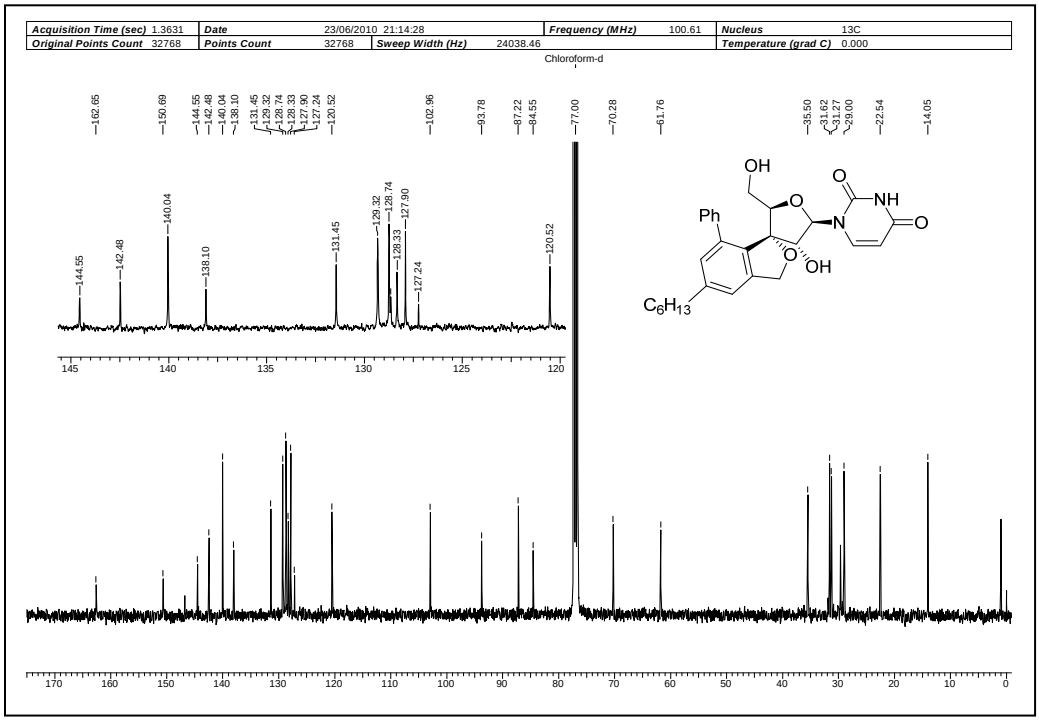
^{1}H NMR Spectrum of 55 in $CDCl_3$



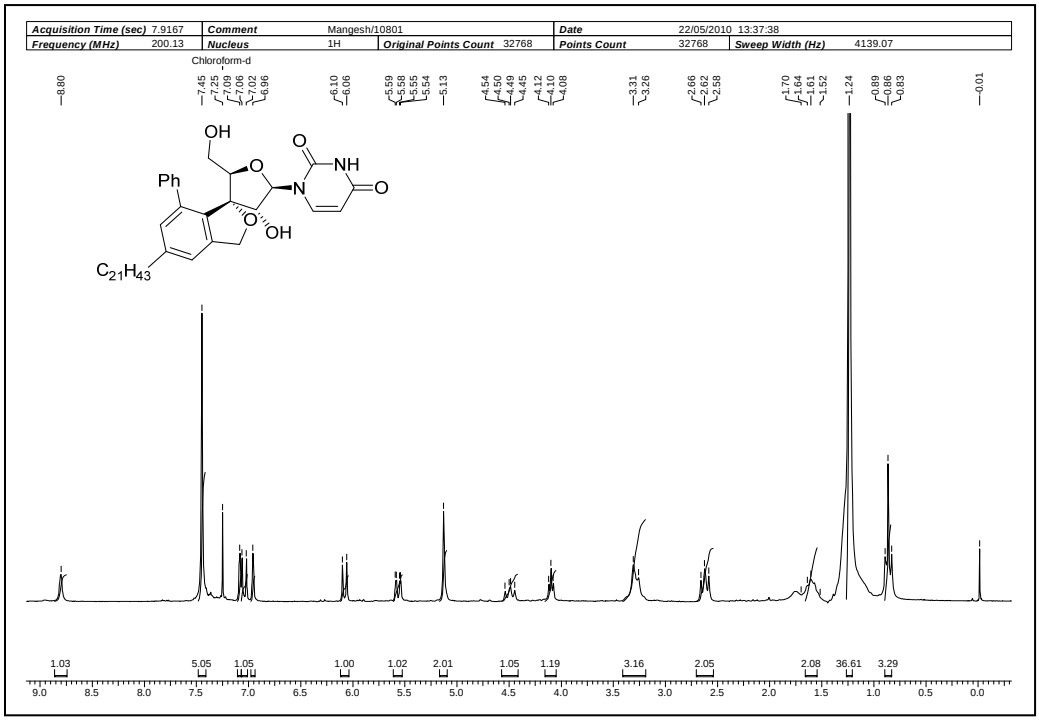
^{13}C NMR Spectrum of 55 in $CDCl_3$



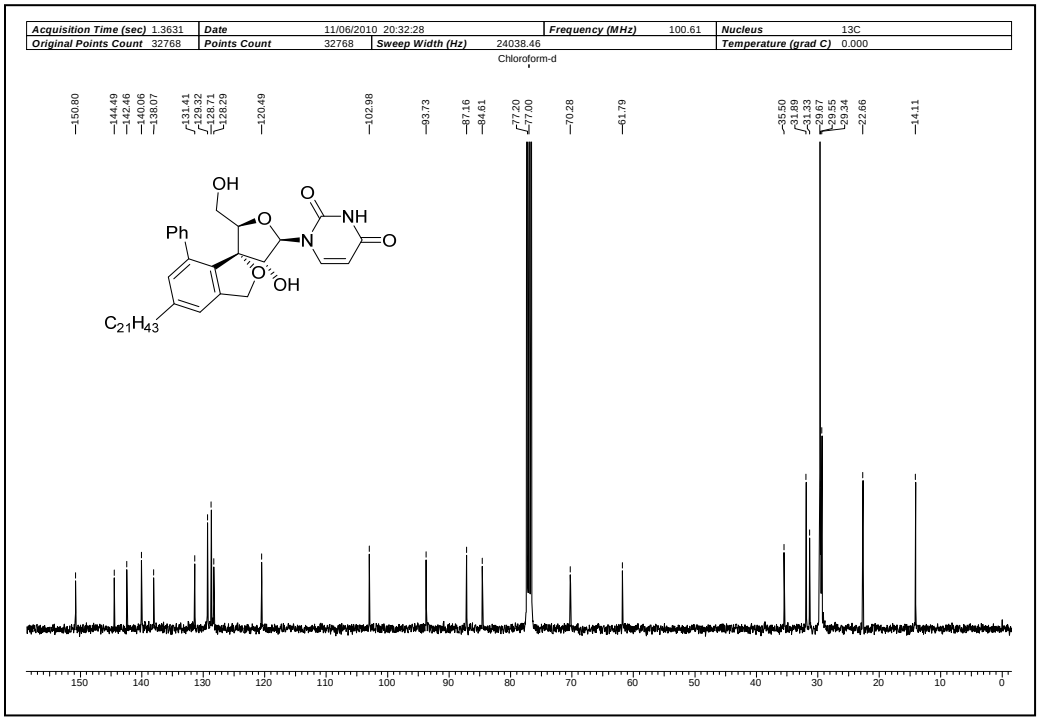
^{1}H NMR Spectrum of 56 in $CDCl_3$



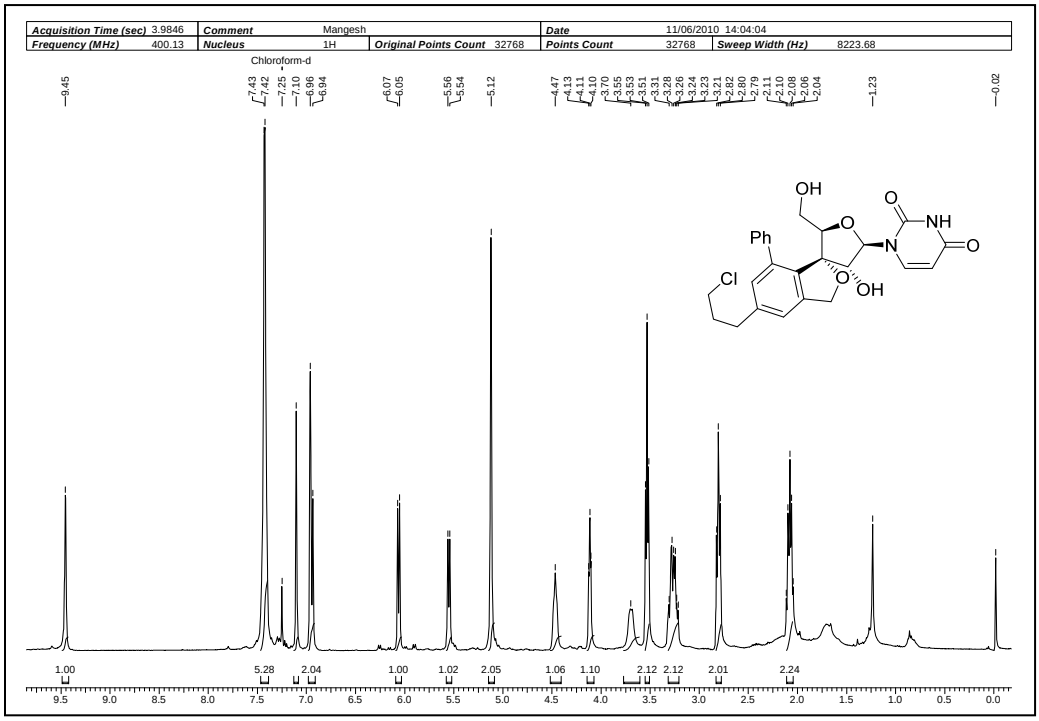
^{13}C NMR Spectrum of 56 in $CDCl_3$



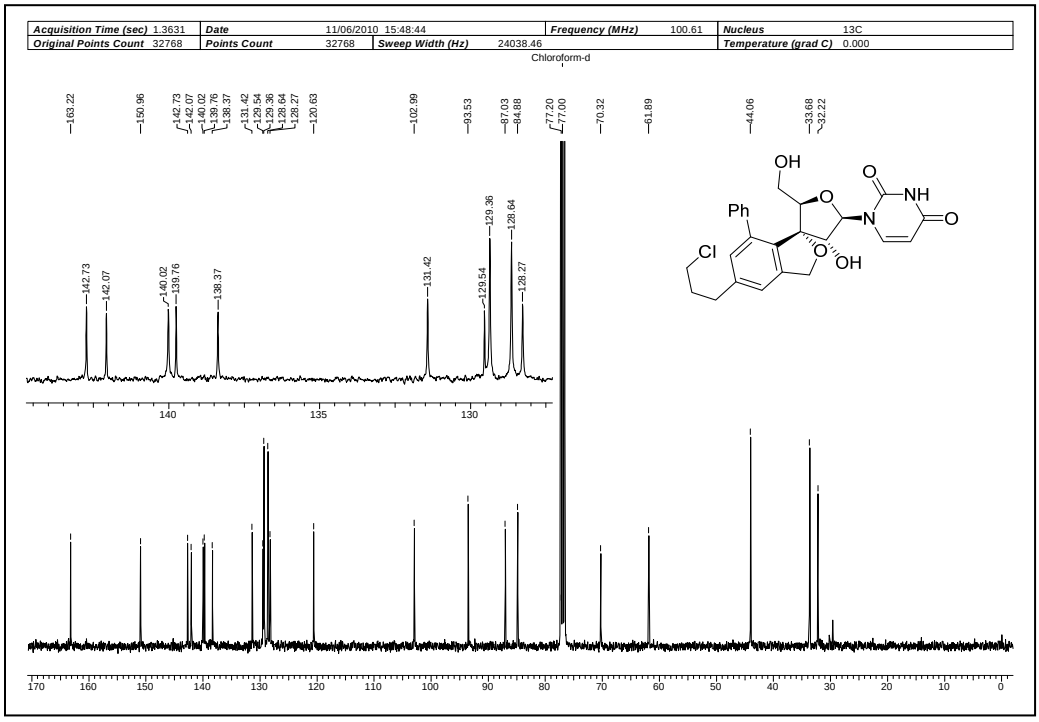
^{1}H NMR Spectrum of 57 in $CDCl_3$



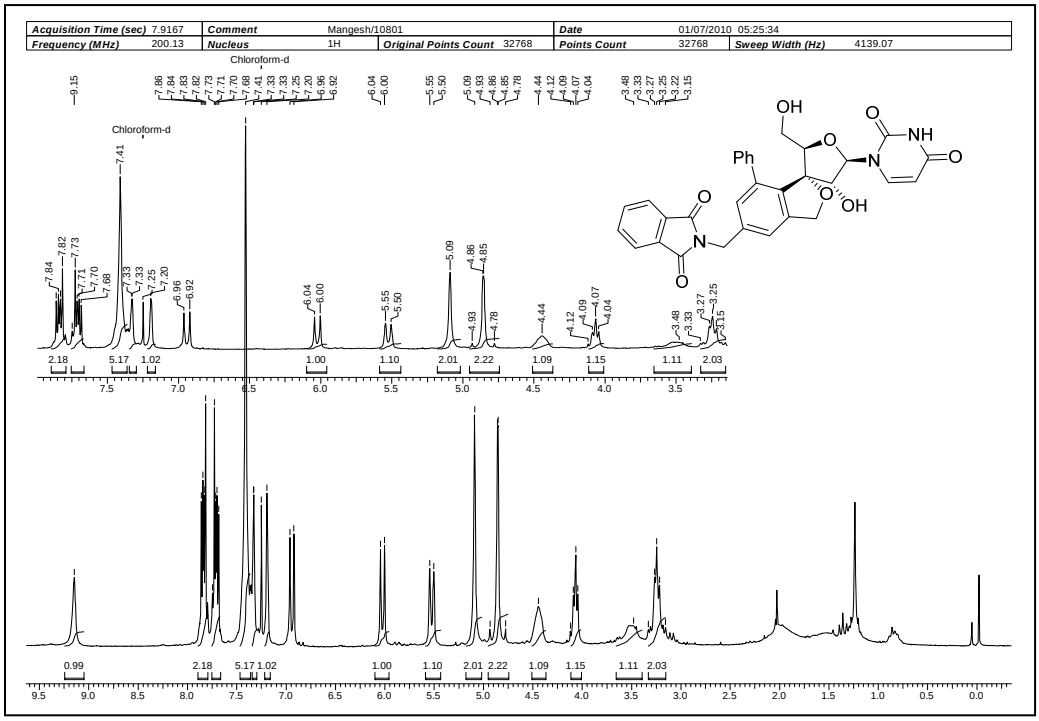
^{13}C NMR Spectrum of 57 in $CDCl_3$



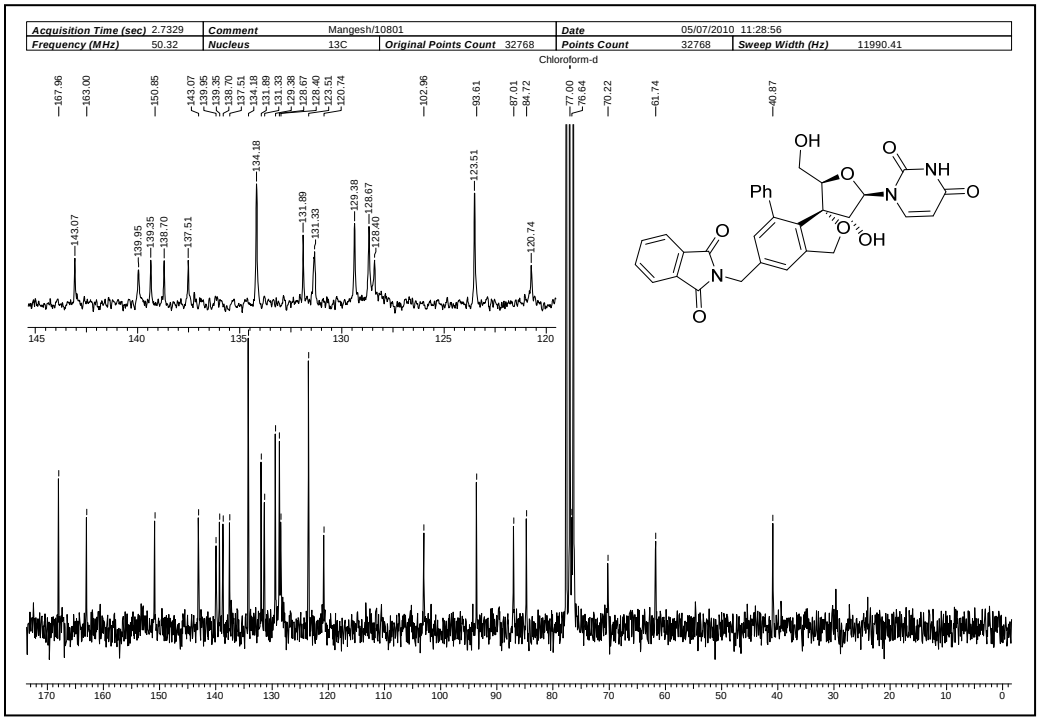
^{1}H NMR Spectrum of 58 in $CDCl_3$



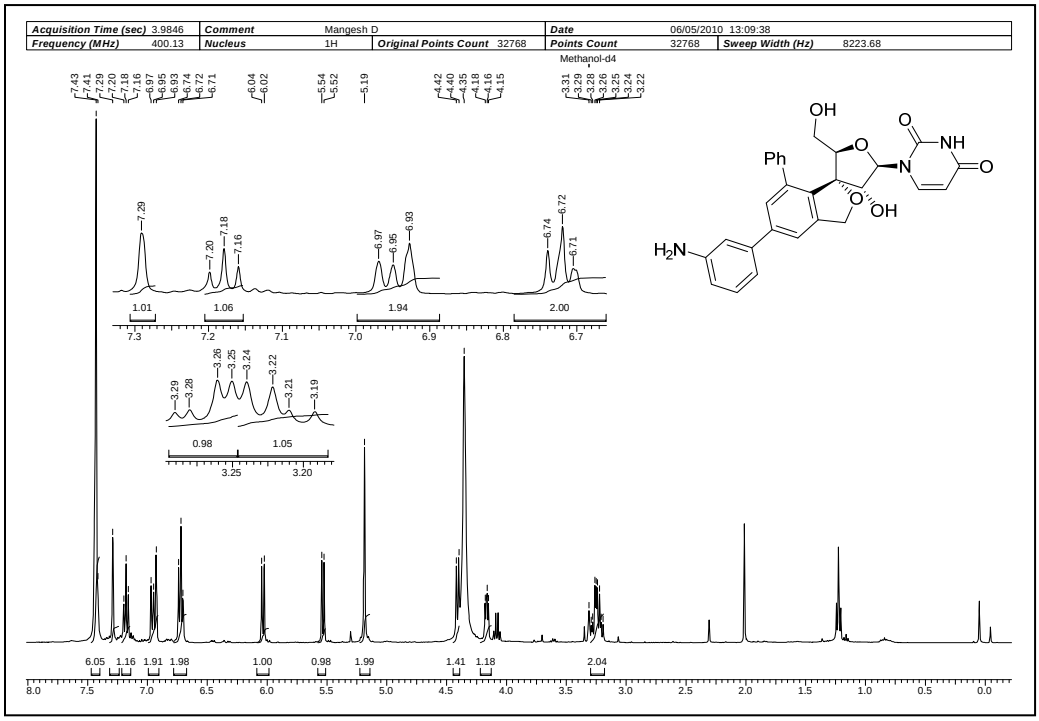
^{13}C NMR Spectrum of 58 in $CDCl_3$



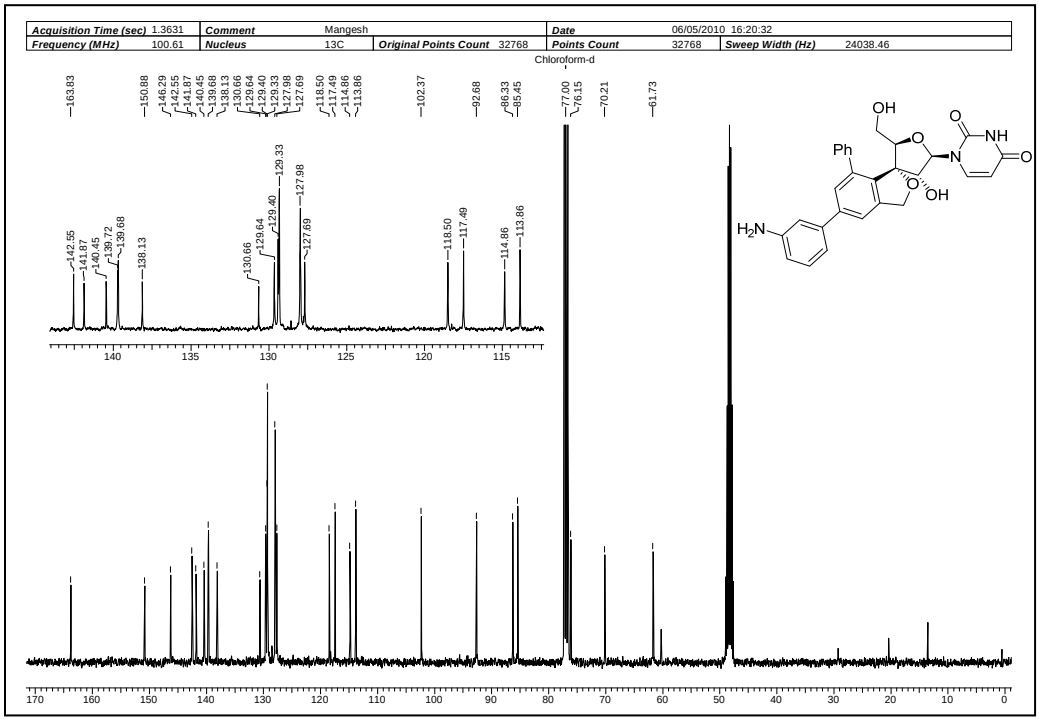
^{1}H NMR Spectrum of 59 in $CDCl_3$



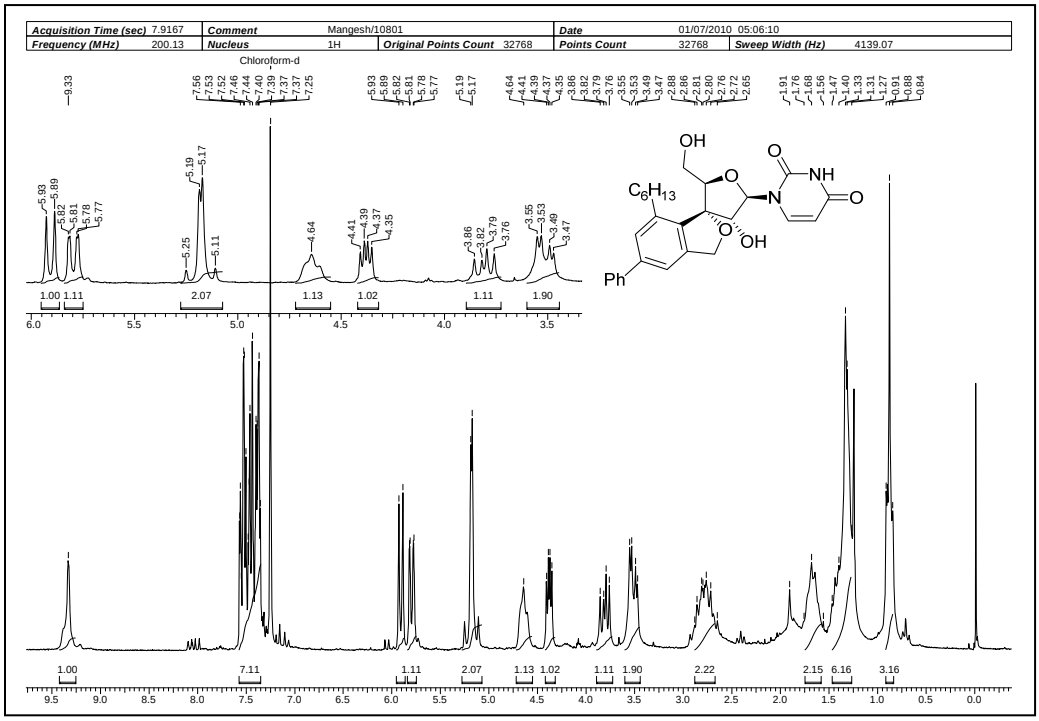
^{13}C NMR Spectrum of 59 in $CDCl_3$



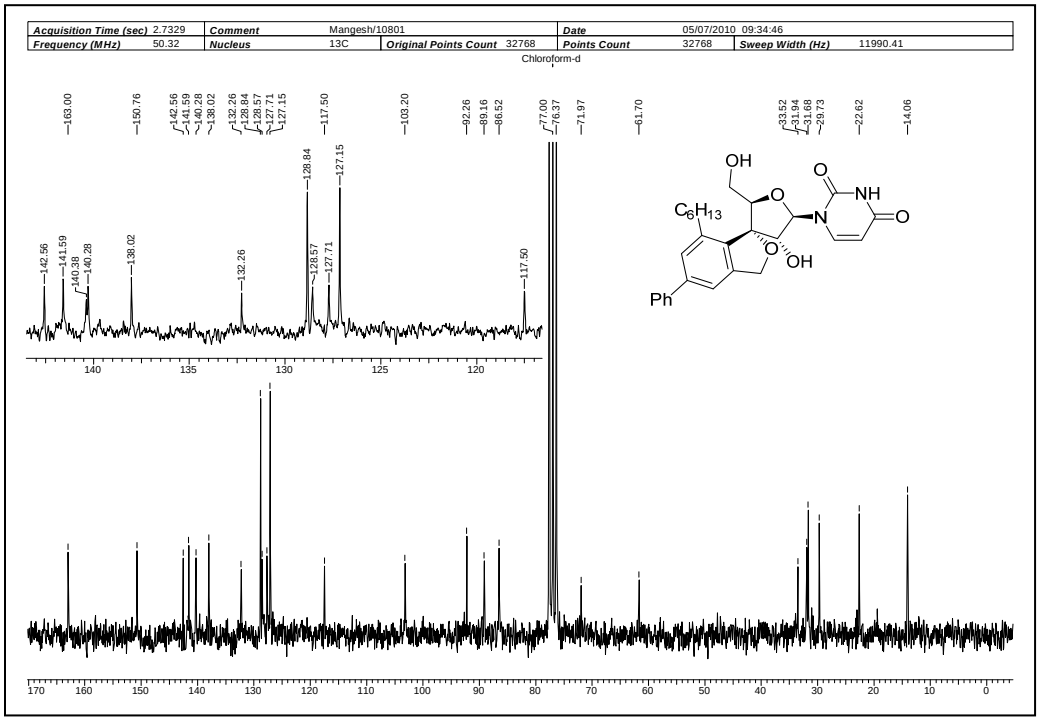
^{1}H NMR Spectrum of 60 in $CDCl_3$



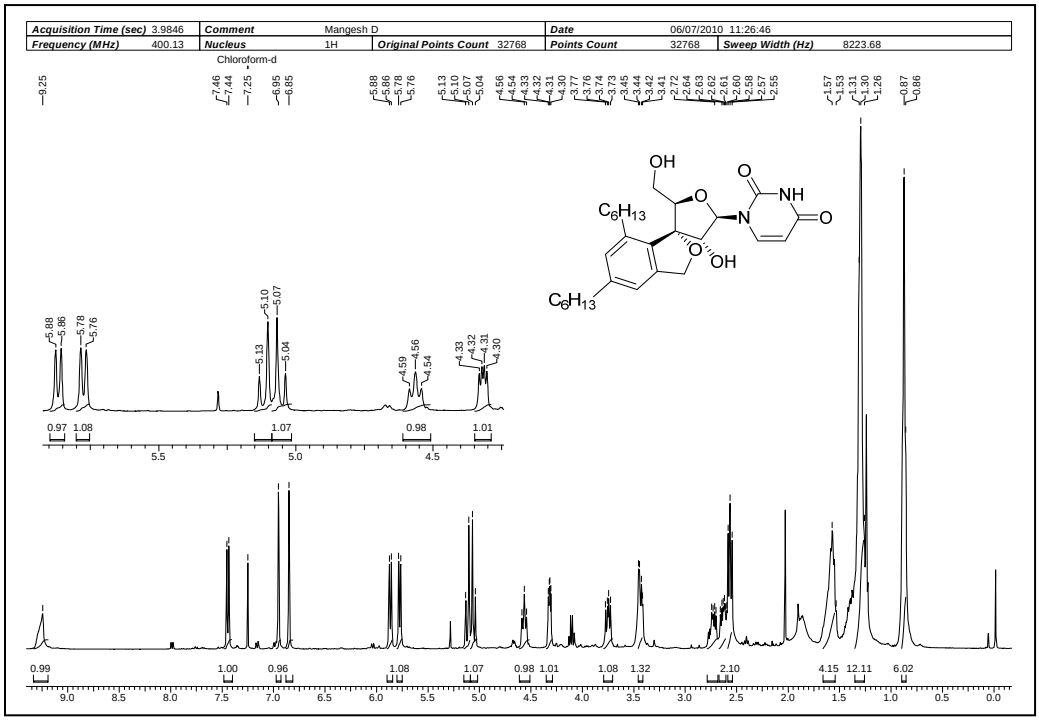
^{13}C NMR Spectrum of 60 in $CDCl_3$



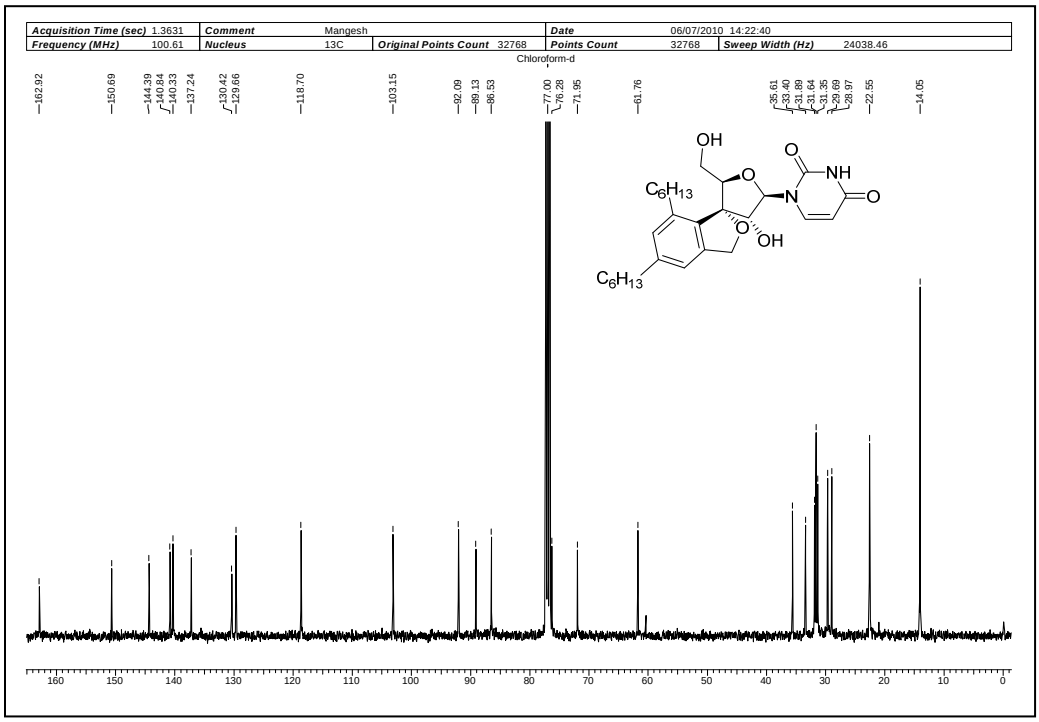
^{1}H NMR Spectrum of 61 in $CDCl_3$



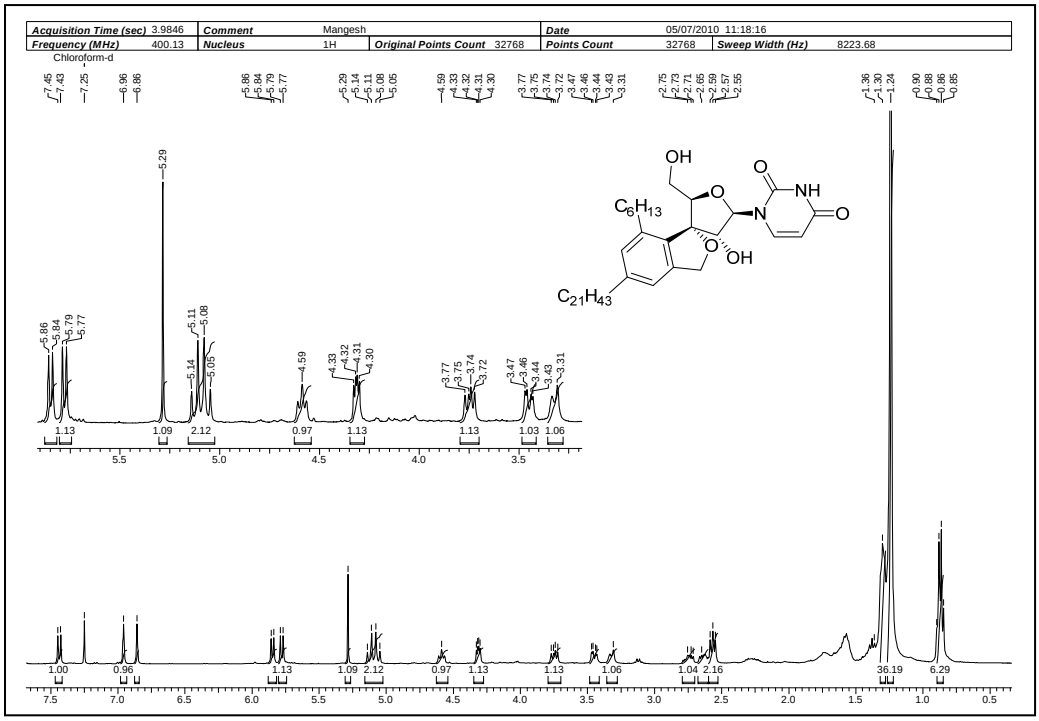
^{13}C NMR Spectrum of 61 in $CDCl_3$



^{1}H NMR Spectrum of 62in $CDCl_3$



^{13}C NMR Spectrum of 62 in $CDCl_3$



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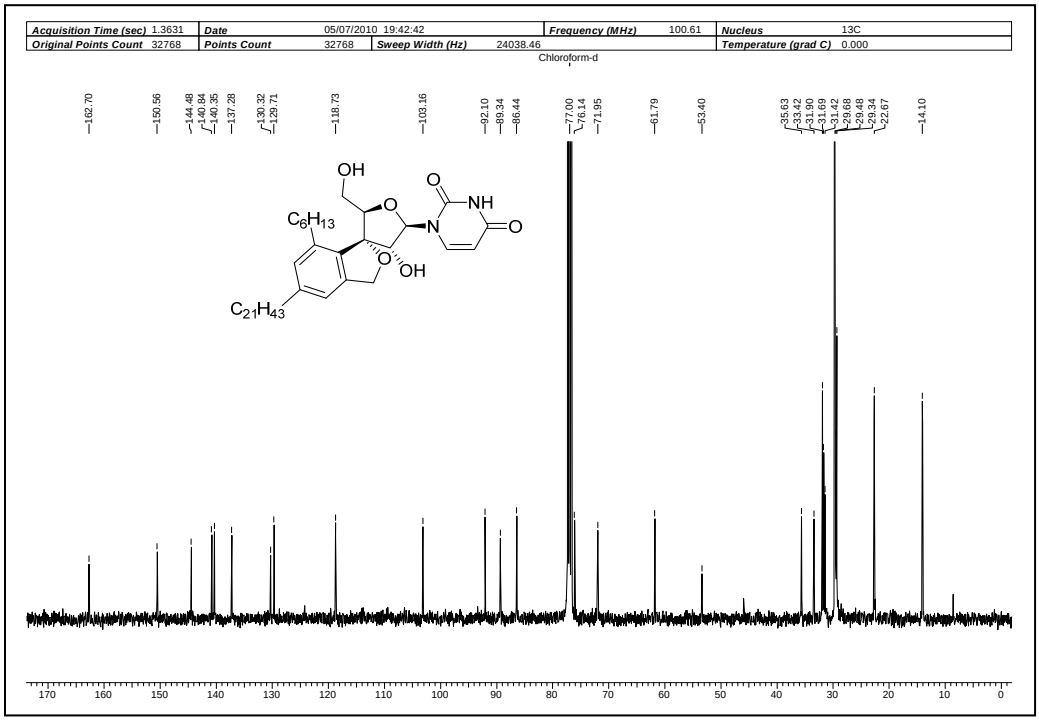

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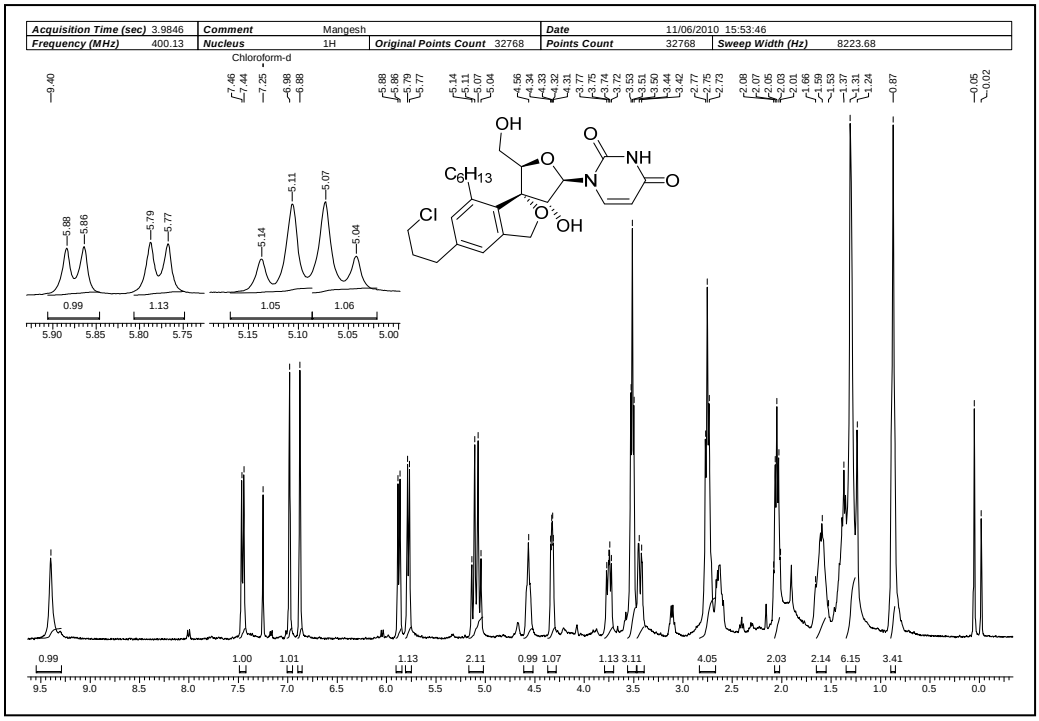

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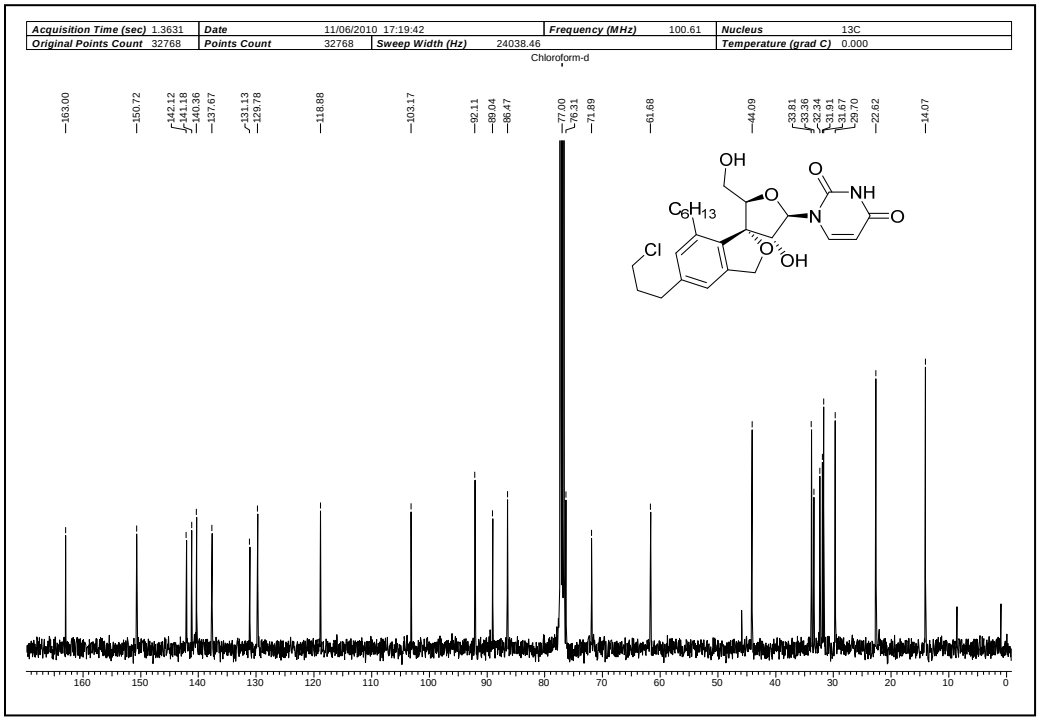

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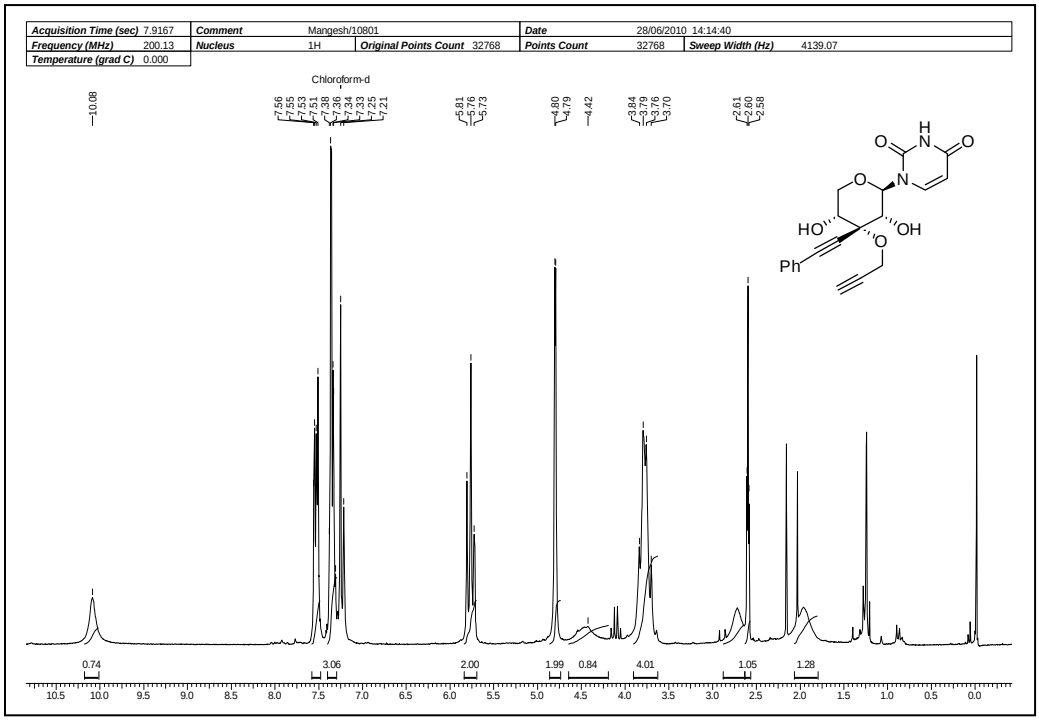

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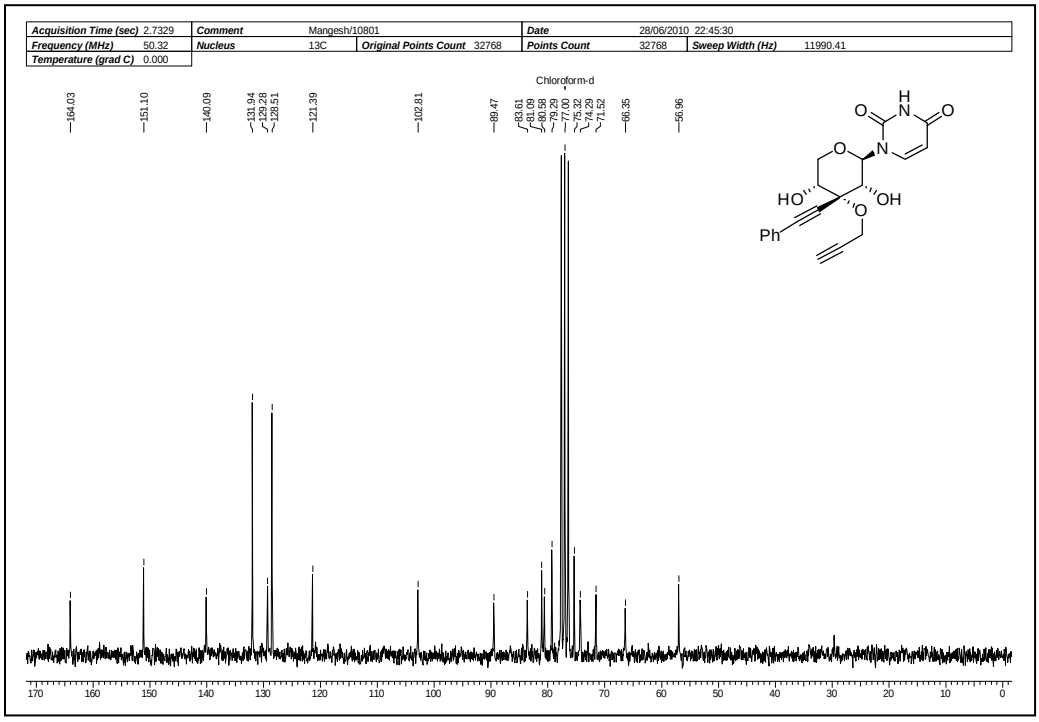

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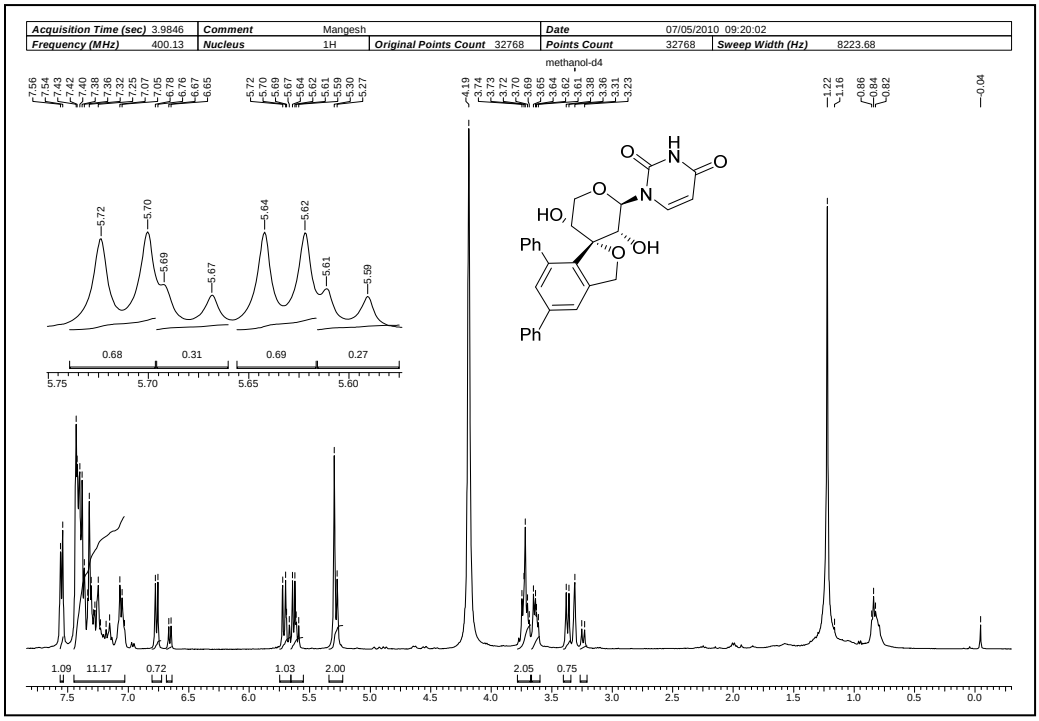

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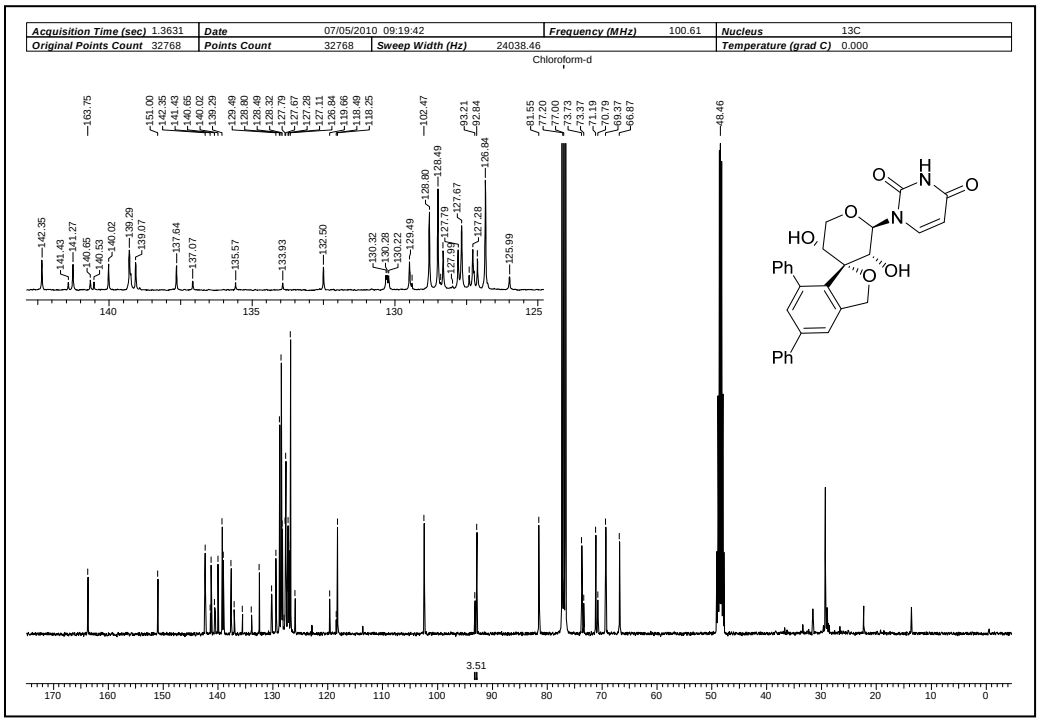

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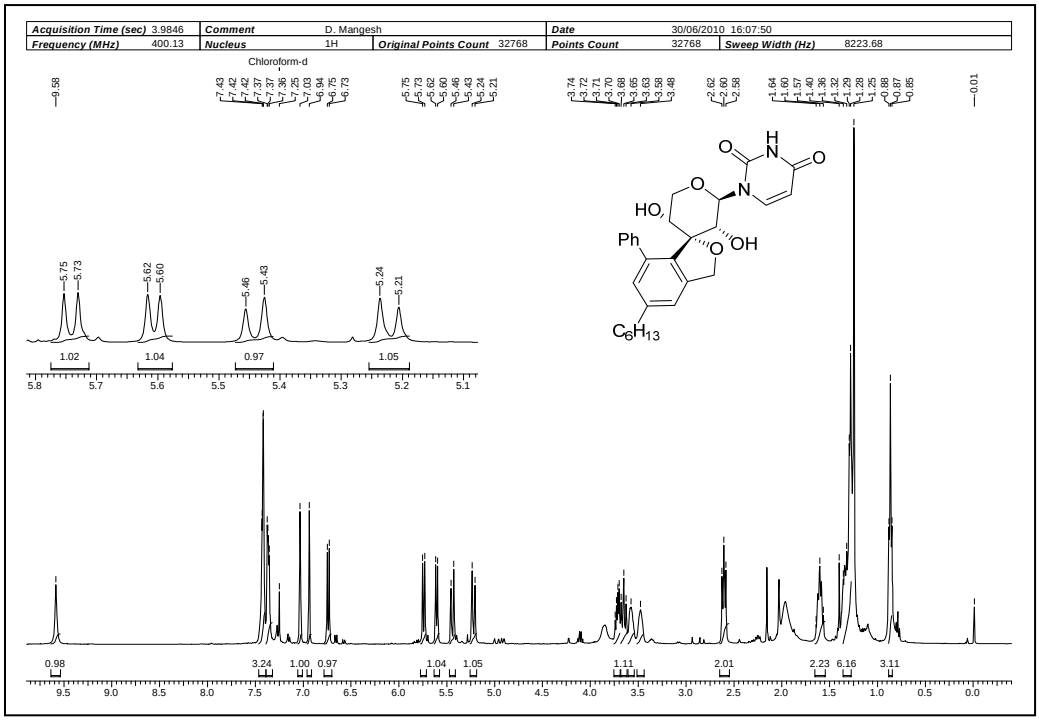

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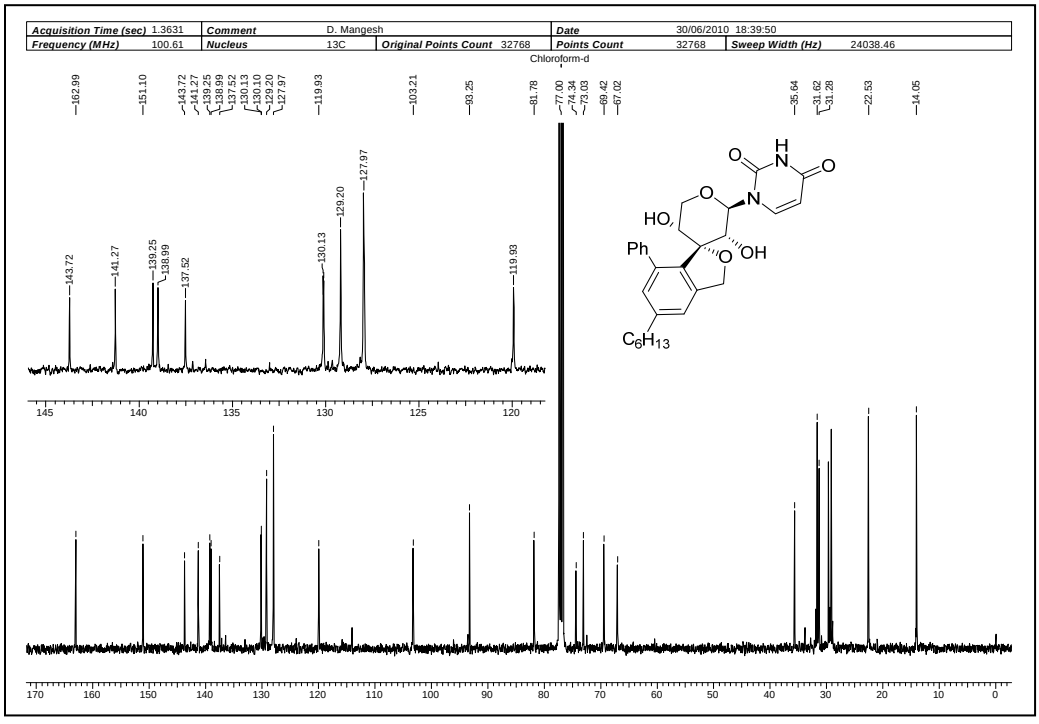

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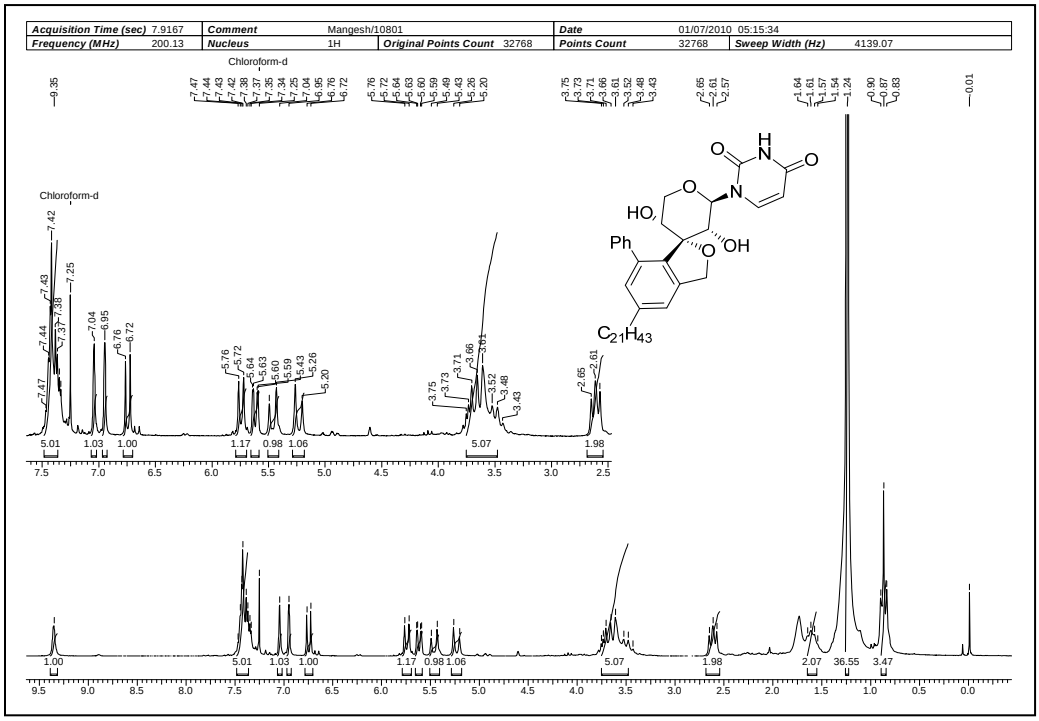

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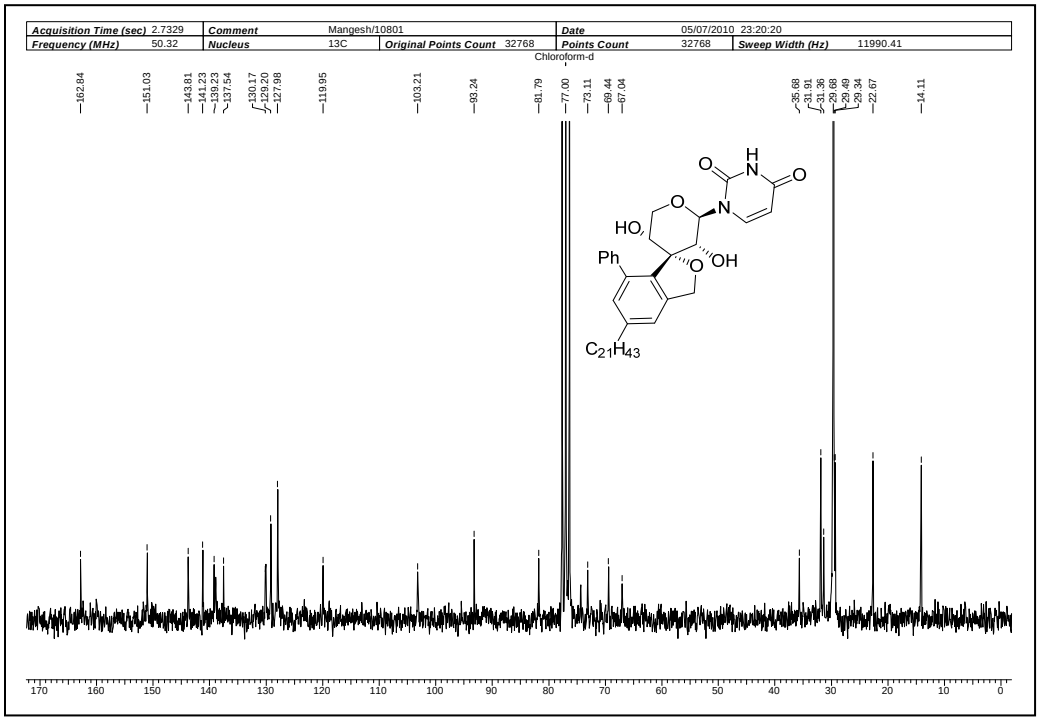

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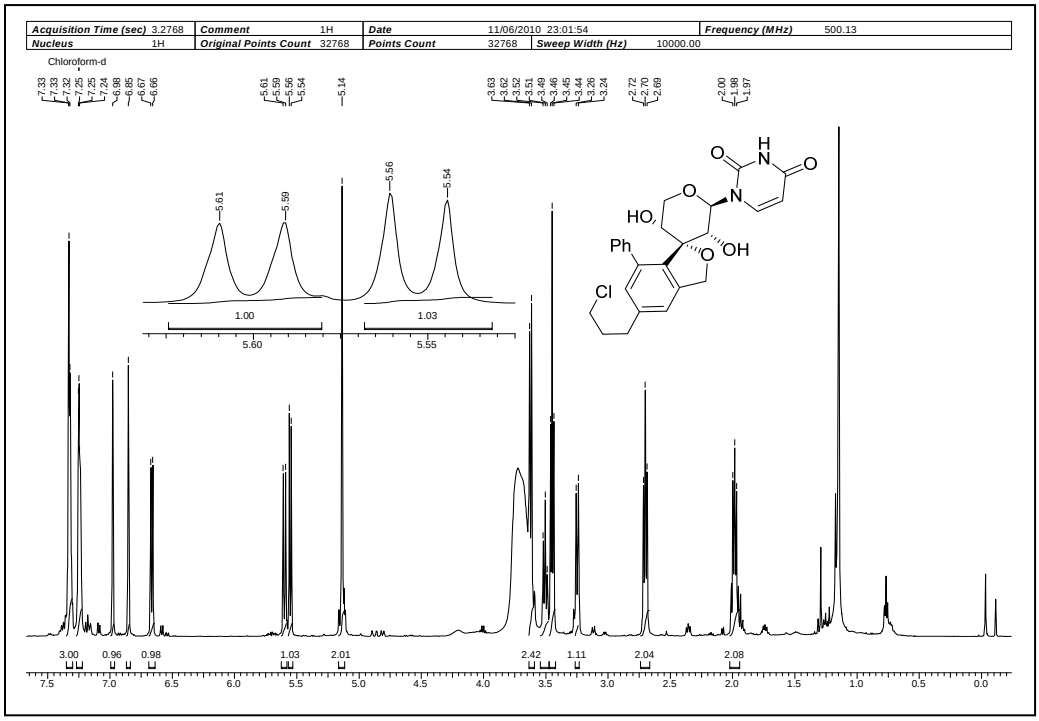

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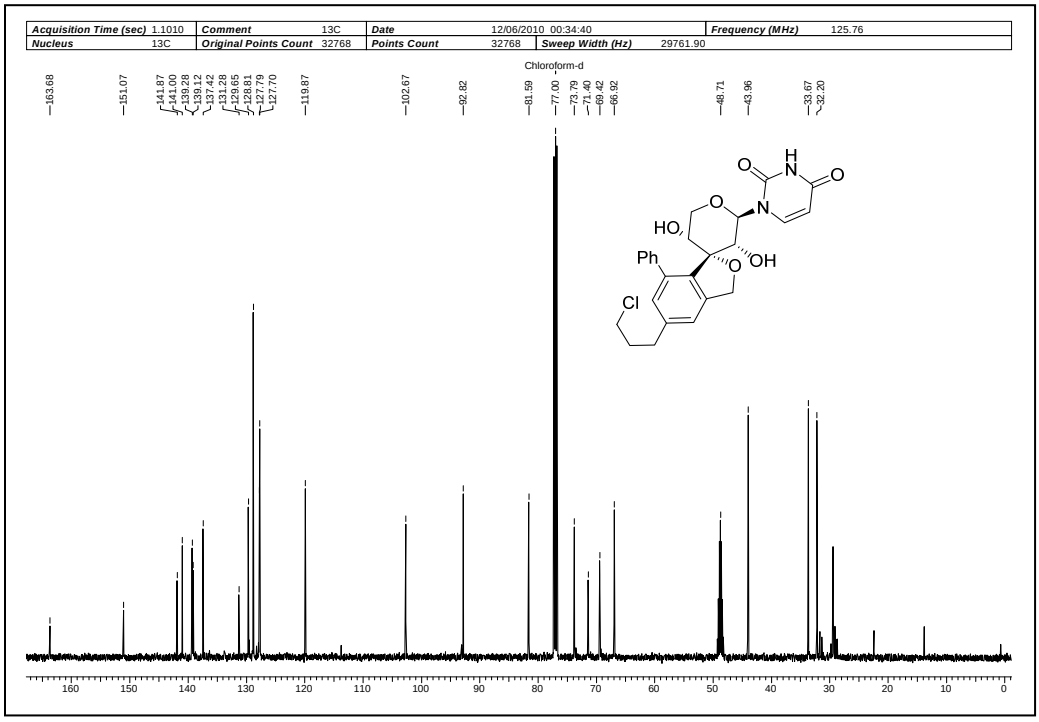

^{13}C NMR Spectrum of 68 in $CDCl_3$

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CHAPTER III:

Flexible Synthesis of Trinems

3.1 Introduction

β-Lactam antibiotics have proved to be chemotherapeutics of incomparable effectiveness, possessing a broad spectrum of biological activities with low host toxicity [1]. First synthesized in 1907 by Staudinger,[2] the four membered cyclic amide derivatives of 3-aminopropionic acids known as β-lactams, did not come to the forefront in organic chemistry until Fleming's landmark discovery of penicillin in 1929[3]. The serendipitous discovery of penicillin by Fleming was a great breakthrough in the history of antibiotics, which brought solace to both patients suffering from bacterial infections and doctors alike and began the modern era of antibiotic discovery. Since then, some new classes of antibiotics have been found from natural sources, such as cephalosporins, cephamycins, monobactams and carbapenems. On the other hand, different kinds of synthetic antibiotics such as carbacephems, oxacephems, penems, cephalosporins, oxacephams, as well as monocyclic and spirocyclic ring systems have been developed in the last three decades.[4] From a structural point of view, these classes are broadly divided as penams, cephams, cephems and penems (Figure 1); although all of them come under a broader genre called β-lactam antibiotics, as these compounds contain a central 4-membered β-lactam ring.

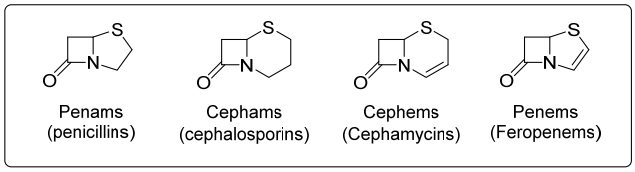


Figure 1: Classification of synthetic antibiotics

In the early 90's, the discovery of penicillin began the antibiotic era. The introduction of β-lactam antibiotics into the health care system, about 60 years ago, represents a major contribution to modern medicine. Today this class still includes the clinically most widely used agents and counts half of all the prescribed antibacterial drugs (cephalosporins: 30%; penicillins: 16%; penams: 5%; macrolides: 18%; quinolones: 19%; others: 12%).[5] During the last several decades, the quest for an expanded antimicrobial spectrum has prompted several synthetic endeavours aimed at the skeleton modification of the naturally occurring β-lactam antibiotics (figure 2).

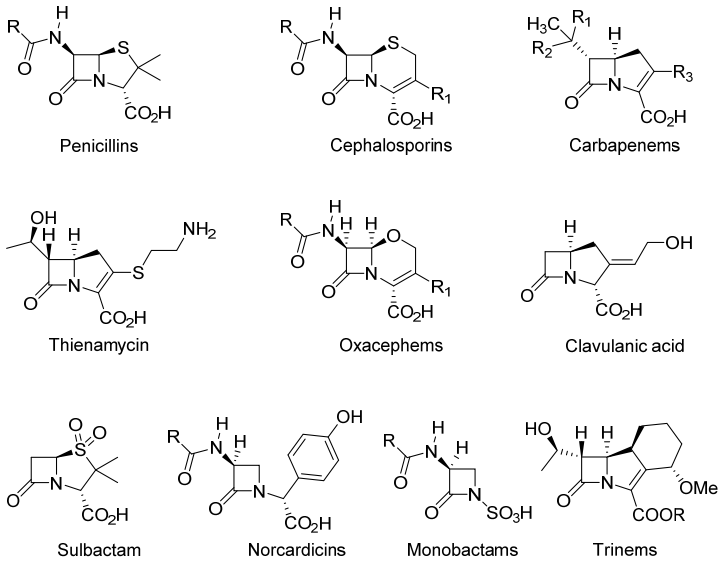


Figure 2: β-Lactam antibiotics

Till quite recently penicillins and cephalosporins were the commonly used β-lactam antibiotics. Extensive use of these antibiotics in medicine has resulted in an increasing number of resistant strains of bacteria, which has become a serious problem in clinical practice.

The most common form of bacterial resistance to the β-lactam antibiotics involves the ability to produce one or more types of β-lactamase[6]. More than 300 β-lactamase have been characterized. Clavulanic acid,[7] sulbactam and tazobactam are the examples of commercial inhibitors of β-lactamases (figure 2). Interestingly, all known classes (with the exception of the monocyclic β-lactams) of β-lactam antibiotics share a common structural feature in that the lactam nitrogen is at the ring fusion. The nuclear sulphur of the penicillin and cephalosprins has been replaced by (O, N, C) and chemo physical and the microbiological effects of these substitution have become primary objects of investigation. Also, there is a considerable interest in the modification of the ring system of β-lactam by placing fused or spiro rings as well as substituted bi-/tricyclic rings.

3.1.1 Cell wall structure of bacteria:

The activity of any antibacterial compound depends upon how effectively it penetrates into the bacterial cell wall. Bacteria are divided into two categories namely Gram-positive and Gram-negative bacteria, depending upon their cell wall structure.[8] A relatively simple cell wall (A) of Gram positive bacteria allows lipophilic molecules to penetrate the cytoplasmic membrane. Gram negative organisms have a complex 5-layer cell wall (B) which makes penetration of large antibiotic molecules rather difficult (Figure 3). But the porin channels present in the lipid bi-layer outer membrane allow polar compounds to pass through. To generalize the lipophilicity of a molecule makes it active against Gram positive organisms whereas hydrophilicity of a molecule enhances activity against Gram negative organisms.

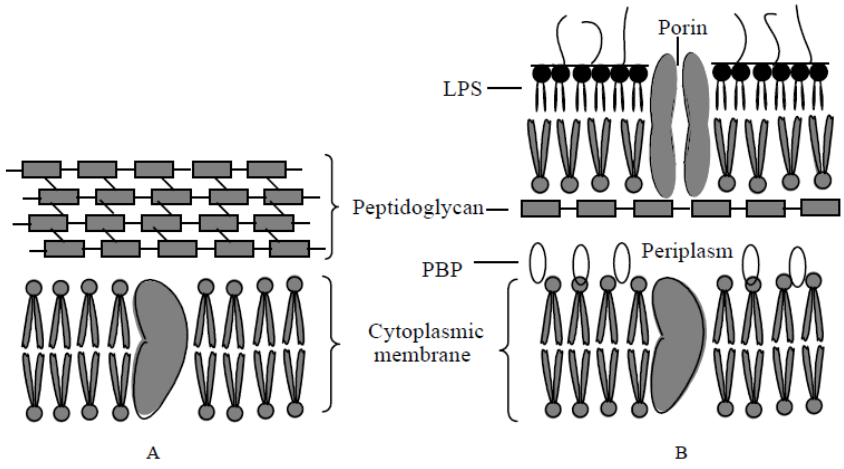


Figure 3: Cell wall structure of Gram-positive and Gram-negative bacteria

Penicillin inhibit bacterial growth by interfering with the synthesis of the bacterial cell wall after binding to Penicillin binding proteins (PBPs) which are present in periplasmic space and are involved in cell wall biosynthesis. Though β-lactam antibiotics have a wide range of antibacterial activity for both Gram-positive and Gram-negative bacteria, the appearance of resistant strains has become the matter of much concern in recent years. Resistance has occurred because of impaired entry into bacteria, instability to bacterial serine- or metallo-β-lactamases or inability to saturate penicillin-binding proteins (PBPs).[9] The most important mechanism of bacterial resistance to penicillin is enzymatic hydrolysis of the β-lactam bond by β-lactamases, which is the most common resistance process in Gram-negative bacilli.[10]

Cephalosporins work in the same way as penicillins but are inactive against enterococci and *P. aeruginosa*. Hence the need to look beyond penicillins and cephalosporins and search for new classes of antibiotic agents has arisen. This has led to the isolation of thienamycin by Merck[11] and thus led to the emergency of Carbapenem, a new generation of antibiotics.

3.1.2 Development of Carbapenems antibiotics:

Carbapenems were found to be exceptionally broad-spectrum agents. Unfortunately, thienamycin proved to be chemically unstable due to β-lactam ring cleavage of one molecule by the primary amine in the 2' side chain of another. This led to the development of imipenem, bearing more basic amidine functionalities, which protonates at physiological pH. But it was found to be unstable to renal dehydropeptidase-I (DHP-I), a β-lactamase. Hence an additional compound, cilastatin[4c] has been co-administrated with imipenem to prevent hydrolysis by (DHP-I). Though imipenem/cilastatin is an excellent broad-spectrum agent, its potential is limited due to toxicity. Also it lacks activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa*. Sankyo group in Japan marketed Panipenem[12] which also needs to be co-administrated with an additive Betamipron to reduce nephrotoxicity. The introduction of 1-β-methyl substituent into the structure of Meropenem[13] enhanced its stability to human renal DHP-I. This is chemically less prone to hydrolysis by DHP-I and thus marketed as a single product. Though it is a little less potent than imipenem against Gram-positive aerobes, it is more active against Gram-negative aerobes (i.e.-*P. aeruginosa*) as well as anaerobes. It is tolerable at higher doses and can be used for serious infections. Like Imipenem, Meropenem is

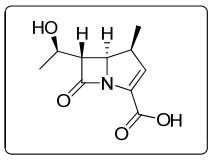


Figure 4: General structure of carbapenem

also inactive against methicillinresistant *Staphylococci*. As the activity against Gram-positive organisms favored by more lipophilic molecules, L-786392 is active *in vitro* against Gram-positive aerobes, including MRSA and enterococci,[14] but it has reduced

activity against enterobacteriaceae and it lacks anti-psedomonal activity. Biapenem is a case of a hydrophilic molecule in which the 2' side chain is permanently charged. Biapenem and Doripenem have typical carbapenem pharmacokinetics with a broad spectrum and tested against resistant strains of *P. aeruginosa* and have recently made their entry into the market. Most of the above cited compounds are for parenteral use (inject able).

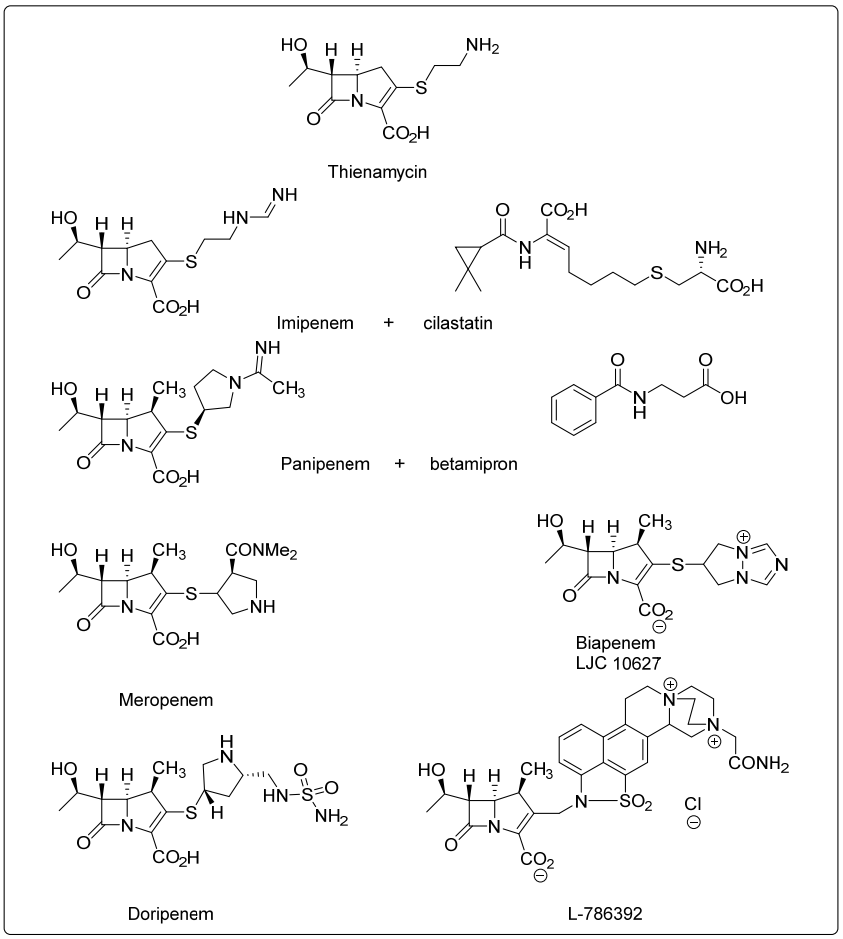


Figure 5

3.1.3 Oral carbapenems:

Due to their instability in gastric juices and even in neutral conditions, the development process of carbapenems as orally administrable drugs is fairly slow. Also β- lactam antibiotics are known to be difficult to absorb from the intestine. Recently, several orally active carbapenems without stability problems have been developed as prodrug esters or prodrug peptides (Figure 6). Faropenem is a novel

class of oral penem (not a carbapenem) which is more active than other β-lactam antibiotics.[15]

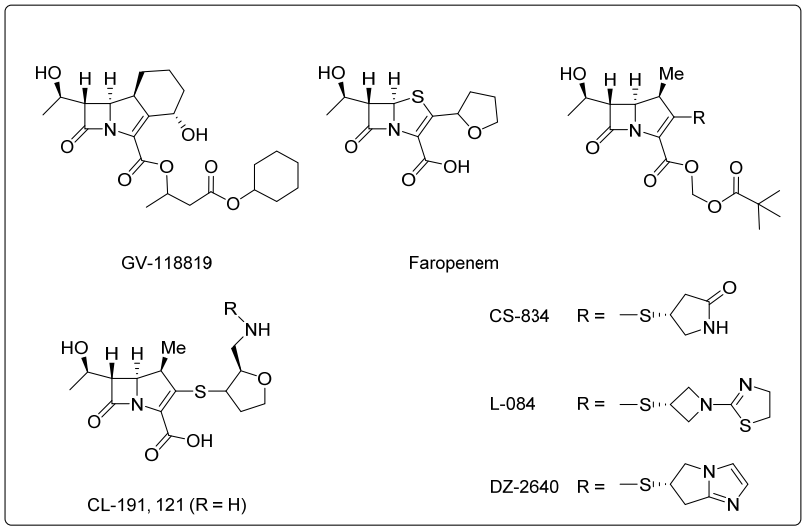


Figure 6: Some classes of oral penems

3.1.4 Tricyclic β-lactam (Trinem):

Tricyclic β-lactam antibiotics, referred to as trinems are a new class of synthetic antibacterial agents with the general structure of a 4/5/6 fused tricyclic system as shown in figure 7.

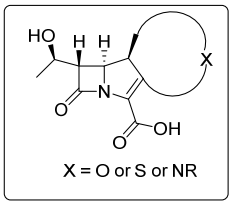


Figure 7: General structure of trinems

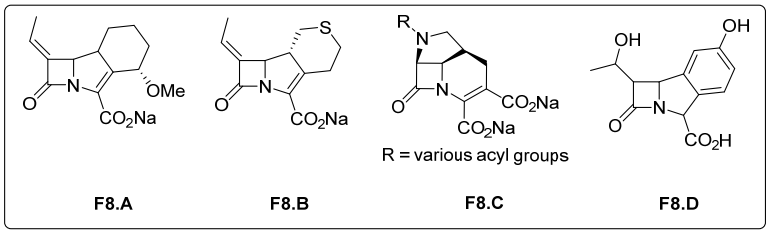


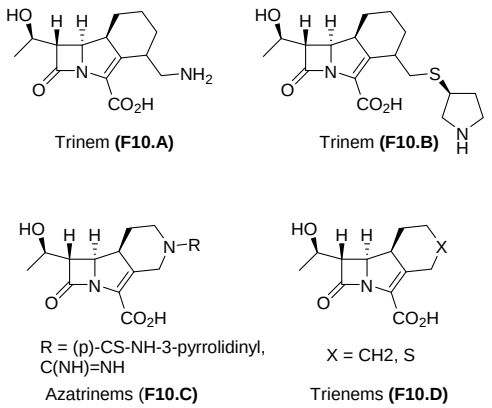
Figure 8: Some tricyclic β-lactams

This is a novel class of synthetic antibiotics, having good resistance to β-lactamases and dehydropeptidases which was first reported by the Glaxo Welcome

group. Sanfetrinem (GV-104326) and Sanfetrinem cilexetil (GV-118819), developed by the same group, were until recently, undergoing phase-II clinical trials as oral trinems.[16] Apart from these two, some other tricyclic carbapenems and their analogs have been developed and patented by various research groups. Trinems **F8.A** and **F8.B** were patented by Lek[17], **F8.C** by Hoffmann-La Roache[18], and **F8.D** by Merck[19] (figure 8).

From the model studies of enzyme-substrate interactions, it has been found that the incorporation of a third fused ring to carbapenem introduces some interesting differences in chemical reactivity. Also, if an appropriate substituent is incorporated, the reaction mechanism is very similar to that for cephalosporins, which can be related to an interesting antimicrobial spectrum. The results from molecular modelling studies[20] reveal that subtle differences between the β-lactamases results in substantial differences with regards to the recognition of various substrates at the active site.

Trinems are a class of fused tricyclic totally synthetic antibiotics. These are potent antibacterial agents with a broad spectrum of activity against both aerobic and anaerobic Gram-(+) and Gram-(–) bacteria. Kanno et al.[21] have reported that tricyclic β-lactam **F10.A** showed antibacterial activity against both Gram-(+) and Gram-(–) bacteria (MIC = 0.01–6.2 mg mL^{-1}). However, tricyclic β-lactam **F10.B** having pyrrolidinylthiomethyl moiety exhibit the most potent anti-MRSA activity (MIC = 1.5 mg mL^{-1}) against Gram-(+) bacteria S. aureus 209P. [22]



Tricyclic-β-lactams: Antibcterial and β-lactmase inhibitors
Figure 9: Biologically active tricyclic β-lactams

Recently, Mori et al.[23] have reported the stereoselective synthesis and antibacterial activity of tricyclic β-lactams with the azacyclohexane ring (**F10.C**). These 5-azatrinems (**F10.C**) showed high potency and well-balanced spectrum against

Gram-(+) and Gram-(–) bacteria. In continuation to this study, Copar *et al*.[24] have designed biologically active tricyclic β-lactams **F10.D** using computational and molecular modelling. These trinems have been shown to possess inhibitory activity against Class C β-lactamase (Figure 9).

3.1.5 Reported methods for the synthesis of tricyclic carbapenems:

GV-118819 is the first tricyclic carbapenem developed by Glaxo Welcome group as a prodrug ester.[25]

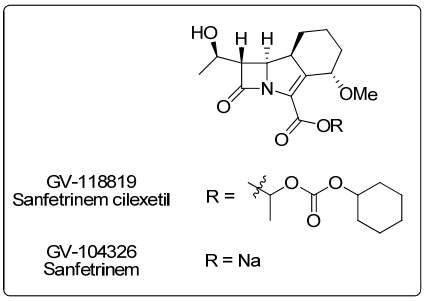
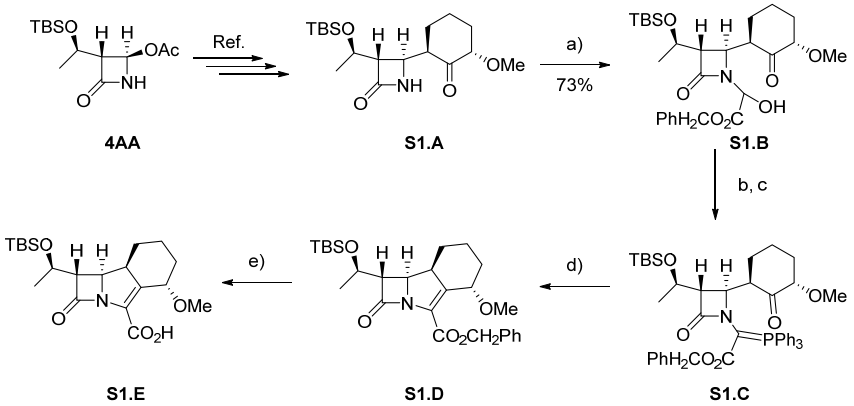


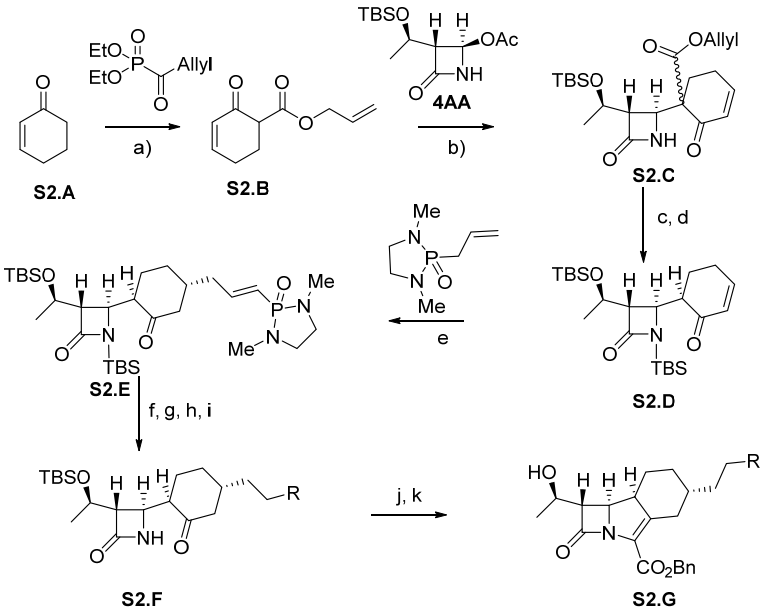
Figure 10

They started the synthesis from acetoxyazetidin-2-one **4AA** and achieved the racemic key intermediate **S1.A** by reacting with 6-methoxy-1–trimethylsilyloxycyclohexene[26a] and again stereoselectively by using 1-(trimethylsilyloxy)-cyclohexene in presence of $ZnCl_2$ or $SnCl_4$.[26b]

In 1997 Hanessian *et al.* reported the synthesis of 4α- and 5α-methoxy trinems and their structural variants.[27]

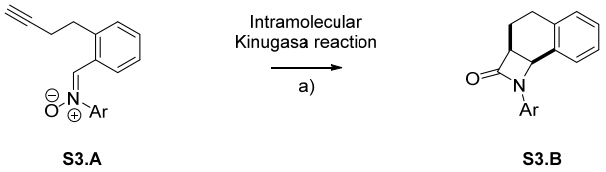


Scheme 1: *Reagents and conditions*: a) $HCOCO_2CH_2Ph$, C_6H_6, reflux; b) $SOCl_2$, 2,6- lutidine, THF; c) PPh_3, 2,6-lutidine, THF; d) PhMe, reflux; e) H_2, Pd/C, *i*-PrOH, EtOAc.



Scheme 2: *Reagents and conditions:* a) LDA, THF, allyl diethylphosphonoformate –78 °C; b) NaH, THF, **4AA**, –20 °C; c) TBSOTf, TEA, DCM, 0 °C; d) $Pd(OAc)_2$, PPh_3, formic acid, EtOAc; e) 2-allyl-1,3-dimethyl-[1,3,2]-diazaphospholidine, *n*-BuLi, THF, –78 °C; f) O_3, DCM, DMS, –78 °C; g) 9-BBN, THF, rt; h) TBSCl, Imidazole, DMF, rt; i) TBAF, AcOH, THF, rt; j) BnOCOCOCl, Pyridine, DCM, 0 °C; k) $P(OEt)_3$, *o*-xylene, 140 °C.

Ryo Shintani and G. C. Fu reported a ligand based intramolecular Kinugasa reaction[28] of alkyne-nitrone to form tricyclic β-lactam framework.[29] Among the various catalysts used, they found **B** to be more effective.



Scheme 3: *Reagents and conditions*: a) CuBr (5%), Ligand (5.5%), $(C_6H_{11})_2NMe$ (0.5 eqv) MeCN, 0ºC

Savingac *et al.* reported an efficient route for constructing 4/5/6 fused polycyclic β-lactams using enyne metathesis and Diels-Alder cycloaddition as the key reactions.[30]

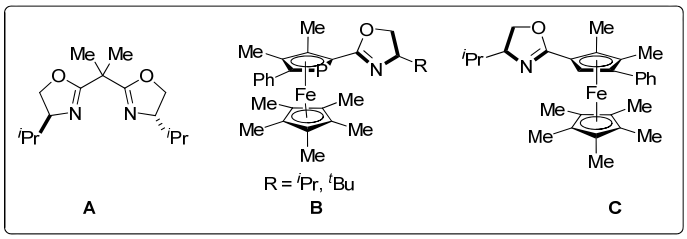
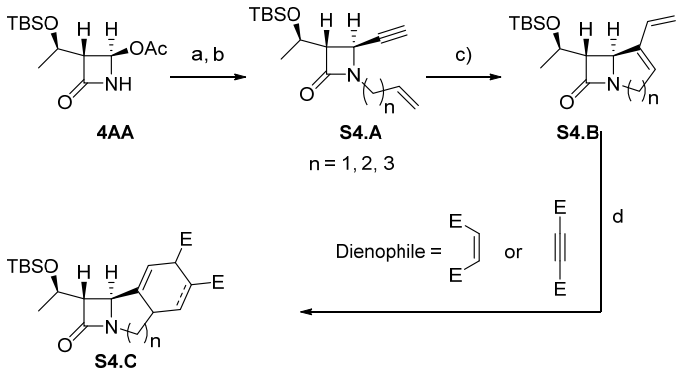


Figure 11: Ligands used for Kinugasa reaction

In case of enyne metathesis, though 4/6 and 4/7 fused bicyclic dienes were readily obtained with Grubb's 1st generation catalyst, 4/5 fused bicyclic system could be achieved only by Grubb's 2nd generation catalyst. Also to get the 4/5/6 system, the use of ionic liquid as solvent was more preferable than DCM (Scheme 4).



Scheme 4: *Reagents and conditions*: a) Trimethylsilylacetylene, *n*-BuLi, THF, –70 ºC to –30 C, b) Bromoalkenes, Bu_4NHSO_4, NaI, KOH, THF, rt, c) Grubb's catalyst, d) Dienophile, LPDE/ionic liquid/DCM, 80 ºC.

3.1.6 Conclusion:

The development of carbapenem antibiotics and the emergence of new drug resistant strains of bacteria are two parallel processes boosted by each other and thus making the drug development process a double-edged sword. The drugs which are now in use as common antibiotics are flawed with limited efficacy and inadequate safety profiles, some of which are used along with additives (Imipenem, Panipenem). Also apart from the gene mutation, some of the resistant strains evolve due to prolonged clinical use and improper dosage.[31] This calls for development of new class of futuristic antibiotics and efficient synthetic methods so that a vast number of

related compounds can be synthesized and studied for potential antibacterial properties.

3.2 Present Work

The extensive use of common β-lactam antibiotics such as penicillins and cephalosporins as broad spectrum antibiotics has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. The development and synthesis of new classes of β-lactam antibiotics has been a matter of much investigation and research for both industrial and academic sectors. Tricyclic β-lactam antibiotics or trinems are a new class of synthetic antibacterial agents having good resistance to β-lactamase and dehydropeptidase. Due to their biological and medicinal importance, synthesis of trinems has been lately grabbed the attention of scientific community. The challenges involved in the synthesis of tricyclic β-lactam antibiotics and the need of new methods propelled us to find effective routes in this direction.

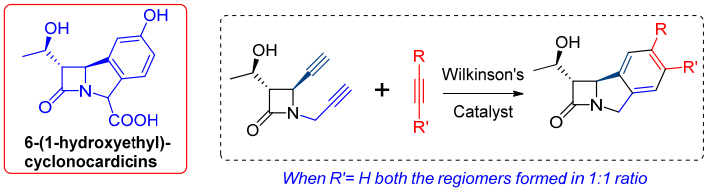


Figure 12. The structure of Merck's novel benzannulated trinem and our earlier report on the synthesis of central core

In continuation of efforts in implementing cyclotrimerization reaction for the construction of focused small molecule libraries, we have conceived the construction of the 4/5/6 tricyclic framework of 6-(1-hydroxyethyl)cyclonocardicins. The 6-(1-hydroxyethyl)cyclonocardicin has been reported by Christensen *et al*. from Merck that showed promising activity against a wide range of pathogens including both Gram positive (*S.aureus, Strep. Pyogenes, B. subtilis*) and Gram negative (*E. coli, Pseudomonas, Proteus morgani* etc.). As a preliminary effort, in our lab we have earlier shown that the cyclotrimerization with Wilkinson catalyst is facile on a diyne derived from the 4AA albeit limited mainly to the symmetric alkynes. When a terminal alkyne was employed as a partner, the trimerization reaction gave a 1:1 regiomeric mixture.

As a continuation of our efforts in this direction, we have been interested in providing a strategy which can facilitate the placement of a wide range of functional groups and appendages on the aromatic ring without having any regioselectivity issues. Keeping this in mind, we have planned to place a substituent on one of the

alkyne unit on aryl ring so that the less sterically hindered meta-isomer will be the favored.[32–34] Since the cyclotrimerization was planned as the final step (figure 13), this strategy should effectively address a rapid synthesis of the trinem library as various alkynes are commercially available and are easy to synthesize. In order to investigate in this direction, the diynes **69** and **70** (scheme 5) were selected as the model substrates in order to check the feasibility of this approach and also to understand the substituent influence on the regioselectivity.[35]

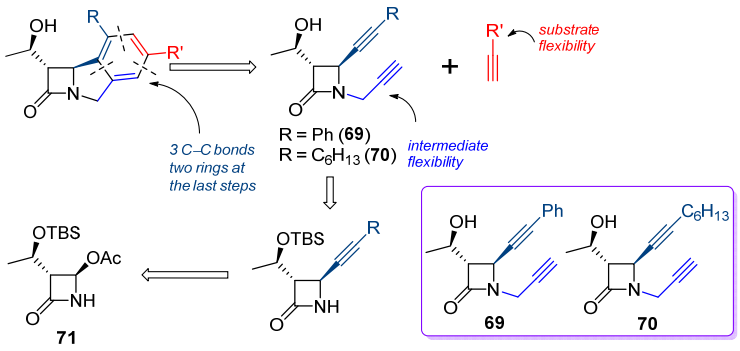
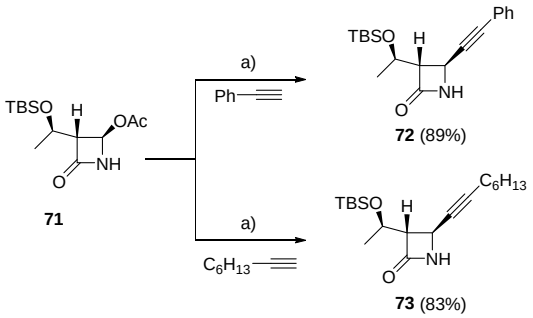


Figure 13

Since the cyclotrimerization was planed as the final step (figure 13), this strategy should effectively address a rapid synthesis of the trinem library.



Scheme 5: *Reagents and conditions:* (a) *n*-BuMgCl, THF, 0 ºC

Synthesis of alkynes **72** and **73** was started from 2-azitidinone **71**. The selective introduction of the alkyne group at the C4 position was the first challenge that we had to meet. In literature, there are only a few reports are available, which mostly employ a transition metal catalyzed reaction with TMS protected acetylene.[36] To have a simple method that can be viable on large scales, we opted for the addition

of an alkynyl Grignard reagent as it will also address the flexibility on keeping the substituent on the first introducting alkyne unit. Accordingly, 2-azitidinone **71** is reacted with alkynylmagnesium chloride (prepared by Grignard exchange between the corresponding alkyne i.e. phenylacetylene and 1-octyne respectively with n-butylmagnesium chloride) to gave **72** and **73** respectively in good yields.

The structure of the product was confirmed from the spectral and analytical data. The presence of aromatic protons in the region 7.30–7.48 ppm in ^{1}H-NMR and two singlet carbons at 84.8 and 86.9 ppm in ^{13}C-NMR approved the structure of **72**. The resonance of aliphatic protons of **73** in up-field region in ^{1}H-NMR spectrum and presence of two acetylenic singlet carbons at 78.0 and 85.6 ppm in ^{13}C-NMR were in accordance with structure **73**. Mass [*m/z* 360.2 for $(M+Na)^{+}$] for the **72** and Mass [*m/z* 350.2 for $(M+Na)^{+}$] for the compound **73** and elemental analysis further confirmed the structures (Scheme 5).

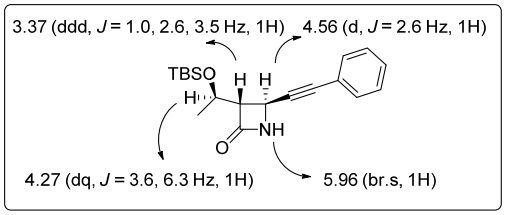
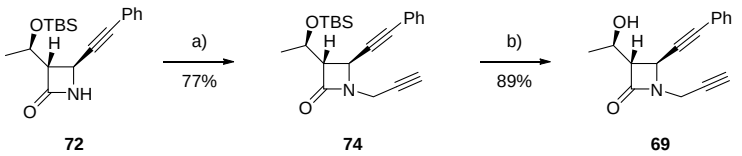


Figure 14: Characteristic peaks of **72** in ^{1}H NMR

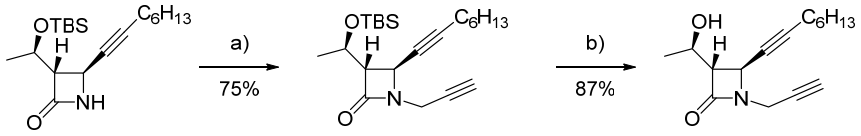
Compound **72** was then subjected to propargylation reaction by using propargyl bromide and KOH in the presence of a phase transfer catalyst Bu_4NI in THF. The propargylation reaction proceeded smoothly and provided **74** in good yields. The appearance of an additional triplet at 2.23 ppm for the propargylic proton in ^{1}H NMR and two additional signals at 84.8 and 86.9 ppm in ^{13}C NMR accounted for newly introduced alkyne in **74**. The structure was further proved by mass [*m/z* 389.9 for $(M+Na)^{+}$] and elemental analysis. The deprotection of the OTBS group by TBAF in THF furnished our required diyne substrate **69**. The disappearance of the characteristic peaks of the TBS group (singlets at 0.08, and 0.88 ppm) in ^{1}H NMR was supportive of the assigned structure of **69**. Mass [*m/z* 276.4 for $(M+Na)^{+}$] and elemental analysis further confirmed the structure (Scheme 6).



72 **74** **69**

Scheme 6: a) Propargyl bromide, KOH, Bu_4NI, THF, 0 ºC, b) TBAF, THF, 0 ºC – rt, 2h.

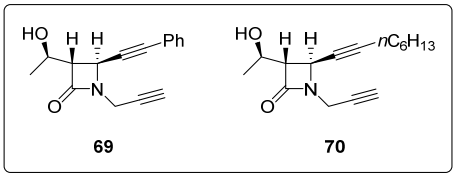
Similarly, the *N*-propargylation of compound **73** using propargyl bromide and KOH in the presence of catalytic amount of Bu_4NI in THF provided the diyne intermediate **73** in good yield. A triplet at 2.18 ppm (J = 2.5 Hz) corresponding to the propargylic proton in the intermediate **75** in ^{1}H-NMR and an additional triplet at 29.4 ppm in ^{13}C-NMR accounted for the newly introduced alkyne in compound **75**. The structure of the **75** was further proved by mass [*m/z* 398.4 for $(M+Na)^+$] as well as through elemental analysis (scheme 7).



73 **75** **70**

Scheme 7: a) Propargyl bromide, KOH, Bu_4NI, THF, 0 ºC, b) TBAF, THF, 0 ºC – rt, 2h.

The deprotection of the OTBS group by TBAF in THF furnished our required diyne substrate **70.** The disappearance of the characteristic peaks of the TBS group (quartets at –5.1, –4.5, and 25.7 ppm) was supportive of the assigned substrate **70**. Mass [*m/z* 284.4 for $(M+Na)^+$] for the compound **70** and elemental analysis further confirmed the structure (Scheme 6).

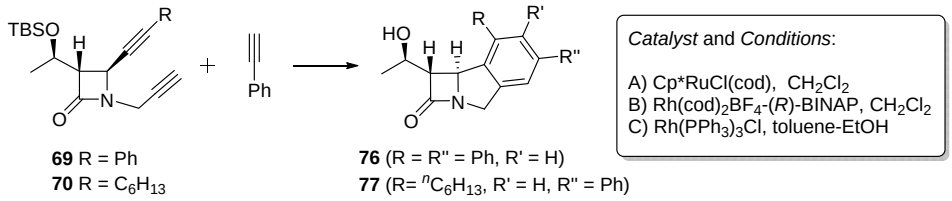


69 **70**

Figure 15: Diynes **69** and **70**

Having synthesized both the requisite diynes, our next concern was the cyclotrimerization reaction with symmetric internal diynes and importantly with the terminal diynes. Our experiments in this regard began with exploration of the

trimerization of diynes **69** and **70** with phenyl acetylene as a substrates, various Rh- and Ru-based catalysts have been explored in this context. The cyclotrimerization of the diynes **69** and **70** with phenyl acetylene were not facile with Wilkinson's catalyst. When the catalysts Cp*RuCl(cod) (B)[37] and $[Rh(cod)_2]BF_4$/(*R*)-BINAP (C)[38] were employed, the reactions proceeded smoothly at room temperature and gave the corresponding trinems (Table 1) in good yields. The trimerization of n-hexyl substituted diyne **70** gave mainly the 1,3-isomer **77**. Formation of the trimerized product **77** was evident from the absence of the propargyl proton (–C≡CH) and the appearance of peaks in aromatic region (7.27−7.57 ppm). Mass [m/z 386.7 for $(M+Na)^+$] and elemental analysis.



69 R = Ph
70 R = C_6H_{13}

76 (R = R'' = Ph, R' = H)
77 (R= $^nC_6H_{13}$, R' = H, R'' = Ph)

Entry	Diyne	R =	Method	Time/temp	Product(s)	a:b	Yield
1	**69**	Ph	A	rt/4 h	**76**	--	81%
2	**69**	Ph	B	rt/7 h	**76**	--	80%
3	**69**	Ph	C	80 °C/24 h	**76**	--	No reaction
4	**70**	*n*-C_6H_{13}	A	rt/4 h	**77**	--	--
5	**70**	*n*-C_6H_{13}	B	rt/7 h	**77**	--	78%
6	**70**	*n*-C_6H_{13}	C	80 °C/18 h	**77**	--	No reaction

Table 1

further confirmed the assigned structure. The product distribution was independent of the catalyst employed. With the phenyl substituted diyne **69**, the trimerization gave exclusively the 1,3-product **76**. Similarly, formation of the trimerized product **76** was evident from the absence of the propargyl proton (–C≡CH) and the appearance of additional seven proton peaks in aromatic region (7.32−7.62 ppm). A clear ^1H NMR spectrum and the appearance of a single peak for the all basic β-lactam ring protons indicate the formation of a single compound, rather than a mixture of products. β-lactam's α-proton appeared as a sharp single doublet of doublet at δ 2.88 with a

coupling constant 2.4 and 5.4 Hz (figure 16). The benzylic methylene carbon resonated as triplet at 51.9 ppm in the ^{13}C NMR spectrum of compound **76**. Mass [m/z 378.3 for $(M+Na)^+$] and elemental analysis further confirmed the assigned structure.

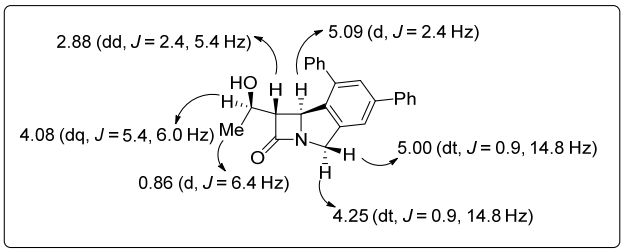


Figure 16: Characteristic peaks of **76** in ^{1}H-NMR

The regioselectivity noticed with the trimerization of diynes **69** and **70** endorse them for further exploration in constructing the homochiral trinem libraries. The attempted cyclotrimerization reactions of the alkynes **69** and **70** with symmetrically disubstituted akynes bis-(trimethylsilyl)acetylene, dimethyl acetylenedicarboxylate, and diphenylacetylene met with failure. With the optimized catalyst and conditions of the cyclotrimerization reactions with phenylacetylene, we next proceeded with the synthesis of a small collection of trinems by employing easily available alkynes as the

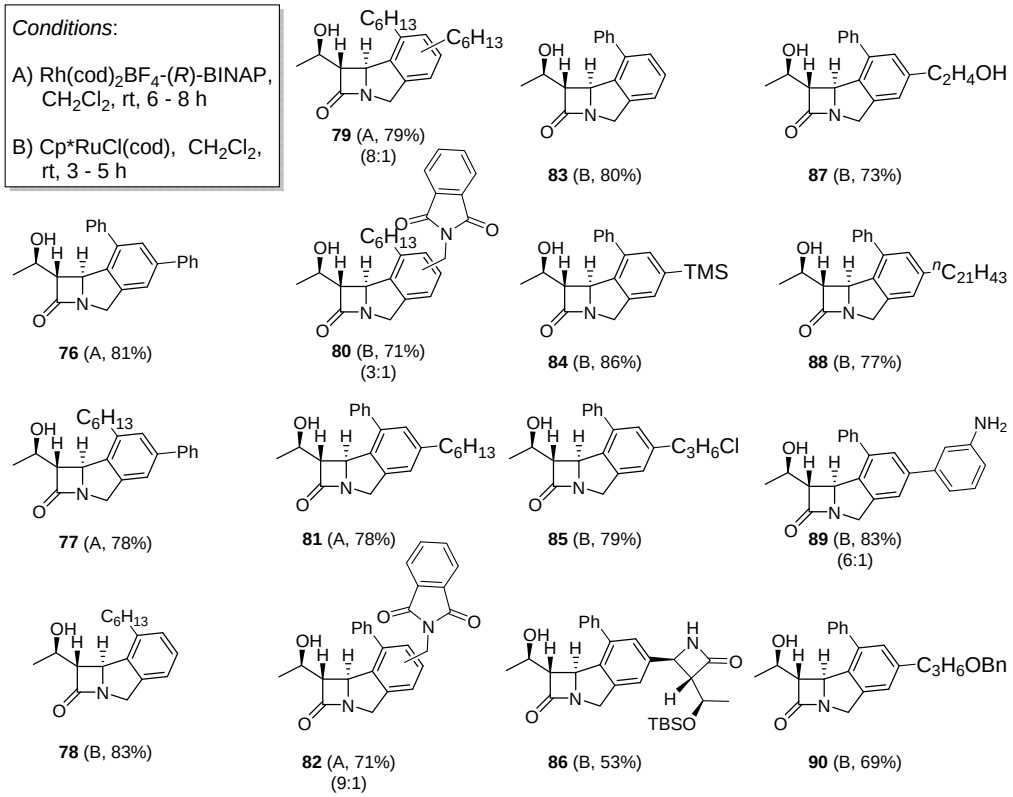


Table 2

co-partners for the cyclotrimerization. Tables 1 and 2 show the versatility of our strategy. The scope of the cyclotrimerization reactions with the substituted diynes **69** and **70** was explored.

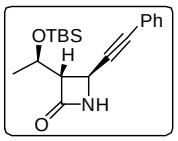
With terminal alkynes, the cyclotrimerization of diynes **69** and **70** were achieved smoothly at room temperature. The regioselectivity was excellent with the diyne **69** trimerizations. In case of diyne **70**, along with the anticipated 1,3-regiomer, the 1,2-isomer was also obtained as a minor product. A variety of terminal alkynes have been employed for the cyclotrimerization with diyne **69**. Various functional groups are tolerant under the reaction conditions. The products **85** and **89** obtained from the cyclotrimerization of diyne **69** with 5-chloropent-1-yne and 3-ethynylaniline are quite attractive, as these products provide a suitable functional group handle for further diversification with simple chemical manoeuvring.

Conclusion:

In conclusion, a [2+2+2] alkyne cyclotrimerization reaction was employed successfully to construct the central 4/5/6 tricyclic framework of 6-(1-hydroxyethyl)-cyclonocardicin trinems. Introduction of different substituents to the structure was achieved easily by simply employing a suitable alkyne at the final event of bicycloannulation, and thus allowed the preparation of a focussed library of trinem like small molecules easily. Further studies towards the synthesis of carboxylate appended trinems and ring size modifications are in progress. Their synthesis and the biological activities will be reported in due course.

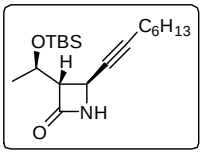
3.3 Experimental:

3-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-(phenylethynyl)azetidin-2-one (72):



Mg (4.2 g, 173 mmol) was flame dried in a two neck R.B. flask fitted with a reflux condenser and cooled to room temperature in dry argon atmosphere. Dry THF (150 mL) was introduced followed by a few crystals of iodine. Half the total volume of *n*-BuCl (18 mL, 173 mmol) was added and the contents were refluxed till the generation of Grignard reagent. The reaction temperature was brought to rt and the rest of *n*-BuCl was added. Stirring continued at room temperature till all the magnesium was consumed. Then the reaction mixture was cooled to 0 °C and phenylacetylene (16.4 mL, 173.95 mmol) in THF (20 mL) was added into it for 15 min. Compound **71** (10 g, 39.5 mmol) in THF (50 mL) was added at 0 °C and stirred for 20 min. The reaction was quenched with saturated NH_4Cl solution, diluted with water and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated and purified on silica gel (10% ethyl acetate in light petroleum) to get alkyne compound **72** as a white solid yield: 89%; mp: 113 °C; $[\alpha]_D^{25}$: +62.8 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) ν: 3020, 2929, 1764, 1471, 1338, 1216, 1157, 1106, 1065, 967, 929, 834, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.08 (s, 6H), 0.88 (s, 9H), 1.26 (d, J = 6.3 Hz, 3H), 3.37 (ddd, J = 1.0, 2.6, 3.5 Hz, 1H), 4.27 (dq, J = 3.6, 6.3 Hz, 1H), 4.56 (d, J = 2.6 Hz, 1H), 5.96 (br.s, 1H), 7.27–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.1 (q), –4.3 (q), 17.9 (s), 22.3 (q), 25.7 (q, 3C), 39.6 (d), 64.6 (d), 67.7 (d), 84.8 (s), 86.9 (s), 122.2 (s), 128.3 (d, 2C), 128.6 (d), 131.7 (d, 2C), 168.1 (s) ppm; ESI-MS (*m/z*): 352.1 (100%, $[M+Na]^+$), 368.1 (8%, $[M+K]^+$); Anal. Calcd for C, 69.26; H, 8.26; N, 4.25%; Found: C, 69.32; H, 8.19; N, 4.31%.

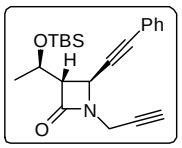
3-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-(oct-1-ynyl)azetidin-2-one (73):



Following the above procedure, the Grignard reaction of **67** (4.0 g, 13.8 mmol) gave compound **73** as a yellow liquid, yield: 83%; $[\alpha]_D^{25}$: +5.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν: 3433, 3020, 1714, 1600, 1394, 1216, 757, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 0.87–0.91 (m, 3H), 1.22 (d, J = 6.3 Hz, 3H), 1.28–1.38 (m, 6H), 1.41–1.51 (m, 2H), 2.18 (dt, J

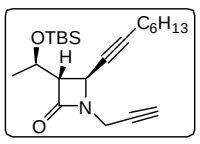
= 1.9, 6.9 Hz, 2H), 3.19 (ddd, *J* = 1.0, 1.5, 2.5 Hz, 1H), 4.21 (dq, *J* = 3.8, 6.3 Hz, 1H), 4.31 (dd, *J* = 2.5, 4.3 Hz, 1H), 5.87 (br.s 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.2 (q), –4.4 (q), 14.0 (q), 17.9 (s), 18.6 (t), 22.2 (q), 22.4 (t), 25.6 (q, 3C), 28.4 (t, 2C), 31.2 (t), 39.4 (d), 64.6 (d), 67.5 (d), 78.0 (s), 85.6 (s), 168.4 (s) ppm; ESI-MS (*m/z*): 360.2 (100%, $[M+Na]^+$); Anal. Calcd for C, 67.60; H, 10.45; N, 4.15%; Found: C, 67.47; H, 10.49; N, 4.26%.

3-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-(phenylethynyl)-1-(prop-2-ynyl)azetidin-2-one (74):



Compound **72** (4 g, 12.15 mmol) was taken in dry THF under argon. Propargyl bromide (1.32 mL, 31.56 mmol), tetrabutyl ammonium iodide (2.3 g, 6.3 mmol) and crushed KOH (2.2 g, 39.46 mmol) were added subsequently at 0 °C and stirred for 2.5 h at room temperature. The reaction was quenched with saturated NH_4Cl solution. After usual workup and concentration, the crude product was purified by column chromatography (10% ethyl acetate in light petroleum) to obtain **74** as a thick yellow liquid, yield: 77%; $[\alpha]_D^{25}$: –49.9 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν: 3681, 3309, 3019, 2957, 2896, 1752, 1625, 1596, 1472, 1217, 947, 758, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.08 (s, 6H), 0.88, (s, 9H), 1.26 (d, *J* = 6.3 Hz, 3H), 2.23 (t, *J* = 2.5 Hz, 1H), 3.30 (ddd, *J* = 0.7, 2.5, 3.2 Hz, 1H), 3.83 (ddd, *J* = 0.8, 2.5, 17.8 Hz, 1H), 4.27 (dq, *J* = 3.3, 6.4 Hz, 1H), 4.30, (dd, *J* = 2.5, 17.8 Hz, 1H), 4.63 (d, *J* = 2.5 Hz, 1H), 7.28–7.35 (m, 3H), 7.39–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.1 (q), –4.5 (q), 17.8 (s), 22.3 (q), 25.7 (q, 3C), 29.6 (t), 42.7 (d), 64.3 (d), 66.4 (d), 72.4 (d), 76.6 (s), 84.8 (s), 86.2 (s), 122.0 (s), 128.3 (d, 2C), 128.6 (d), 131.7 (d, 2C), 166.4 (s) ppm; ESI-MS (*m/z*): 367.9 (5%, $[M+1]^+$), 389.9 (100%, $[M+Na]^+$), 405.9 (3%, $[M+K]^+$); Anal. Calcd for C, 71.89; H, 7.95; N, 3.81%; Found: C, 71.76; H, 8.02; N, 3.79%.

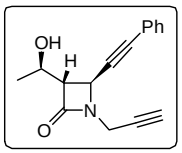
3-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-(oct-1-ynyl)-1-(prop-2-ynyl)azetidin-2-one (75):



Following the above procedure to synthesis compound **74**, the propargylation of **73** (4.0 g, 0.012 mol) gave compound **75** as a yellow

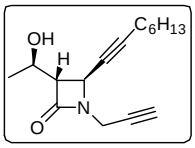
liquid, yield: 75%; $[\alpha]_D^{25}$: –29.7 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) *ν*: 3415, 3020, 2931, 1760, 1600, 1518, 1424, 1216, 1046, 929, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 6H), 0.85 (s, 9H), 0.86–0.90 (m, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.24–1.38 (m, 6H), 1.42–1.52 (m, 2H), 2.18 (t, *J* = 2.5 Hz, 1H), 2.19 (dd, *J* = 1.9, 6.9 Hz, 2H), 3.12 (ddd, *J* = 0.7, 2.5, 3.3 Hz, 1H), 3.70 (ddd, *J* = 0.8, 2.5, 17.8 Hz, 1H), 4.20 (dq, *J* = 3.5, 6.3 Hz, 1H), 4.25 (dd, *J* = 2.5, 17.8 Hz, 1H), 4.38 (q, *J* = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –5.1 (q), –4.5 (q), 14.0 (q), 17.8 (s), 18.7 (t), 22.2 (q), 22.5 (t), 25.7 (q, 3C), 28.4 (t, 2C), 29.4 (t), 31.2 (t), 42.6 (d), 64.3 (d), 66.1 (d), 72.1 (d), 75.7 (s), 76.6 (s), 87.4 (s), 166.9 (s) ppm; ESI-MS (*m/z*): 376.4 (15%, $[M+1]^+$), 398.4 (100%, $[M+Na]^+$), 414.3 (28%, $[M+K]^+$); Anal. Calcd for C, 70.35; H, 9.93; N, 3.73%; Found: C, 70.41; H, 9.77; N, 3.59%.

03. 3-((*R*)-1-Hydroxyethyl)-4-(phenylethynyl)-1-(prop-2-ynyl)azetidin-2-one (69):



Compound **74** (2.0 g, 5.4 mmol) was taken in THF (15 mL) under argon. TBAF (2.1 g, 8.0 mmol) was added subsequently at 0 °C and stirred for 1 h at room temperature. The reaction was quenched with saturated NH_4Cl solution. After usual workup and concentration, the crude product was purified by column chromatography (60% ethyl acetate in light petroleum) to obtain **69** as a white solid, yield: 89%; mp: 108.3 °C; $[\alpha]_D^{25}$: –86.1 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) *ν*: 3621, 3020, 1753, 1523, 1425, 1216, 1045, 929, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35 (d, *J* = 6.4 Hz, 3H), 1.93 (d, *J* = 4.6 Hz, 1H), 2.29 (t, *J* = 2.5 Hz, 1H), 3.38 (ddd, *J* = 0.5, 2.4, 4.8 Hz, 1H), 3.87 (ddd, *J* = 0.8, 2.4, 17.8 Hz, 1H), 4.23–4.34 (m, 1H), 4.33 (dd, *J* = 2.4, 17.8 Hz, 1H), 4.61 (d, *J* = 2.4 Hz, 1H), 7.30–7.37 (m, 3H), 7.41–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.3 (q), 30.0 (t), 43.5 (d), 64.6 (d), 66.0 (d), 72.6 (d), 76.5 (s), 77.2 (s), 84.4 (s), 122.0 (s), 128.4 (d, 2C), 128.9 (d), 131.8 (d, 2C), 166.5 (s) ppm; ESI-MS (*m/z*): 254.4 (4%, $[M+H]^+$), 276.4 (100%, $[M+Na]^+$), 292.4 (5%, $[M+K]^+$); Anal. Calcd for C, 75.81; H, 5.97; N, 5.53%; Found: C, 75.79; H, 5.87; N, 5.47%.

3-((*R*)-1-Hydroxyethyl)-4-(oct-1-ynyl)-1-(prop-2-ynyl)azetidin-2-one (70):



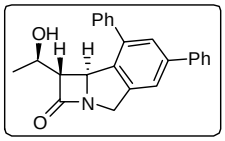
The deprotection of compound **75** (4.0 g, 10.6 mmol) was carried out according to the above procedure used for the preparation of **69**, giving compound **70** as a pale yellow liquid, yield: 78%; $[\alpha]_D^{25}$: –45.3 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν: 3621, 3309, 3020, 1752, 1523, 1424, 1216, 1046, 929, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.26–1.39 (m, 9H), 1.47–1.52 (m, 2H), 2.20 (dt, *J* = 1.9, 7.2 Hz, 2H), 2.24 (t, *J* = 2.5 Hz, 1H), 3.20 (dd, 2.5, 4.6 Hz, 1H), 3.75 (dd, *J* = 2.5, 17.8 Hz, 1H), 4.19–4.22 (m, 1H), 4.25 (dd, *J* = 2.5, 17.8 Hz, 1H), 4.30–4.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0 (q), 18.7 (t), 21.1 (q), 22.5 (t), 28.4 (t), 28.5 (t), 29.7 (t), 31.3 (t), 43.3 (d), 64.5 (d), 65.8 (d), 72.4 (d), 75.4 (s), 76.6 (s), 87.8 (s), 166.8 (s) ppm; ESI-MS (*m/z*): 262.3 (8%, $[M+H]^+$), 284.4 (100%, $[M+Na]^+$), 300.4 (10%, $[M+K]^+$); Anal. Calcd for C, 73.53; H, 8.87; N, 5.36%; Found: C, 73.38; H, 8.78; N, 5.44%.

Representative procedures for the [2+2+2]-cyclotrimerization reactions of diynes:

Procedure A: A solution of diyne (0.5 mmol) and alkyne (0.5 mmol) in DCM (10 mL) in a long glass tube was degassed with dry argon for 20 min; then, $[Rh(cod)_2]BF_4$/(*R*)-BINAP catalyst (0.03 mmol) was introduced into the mixture. The tube sealed by airtight cap. The mixture was stirred at room temperature for 2-4 h. After complition of reaction, the reaction mixture was transferred into a round-bottom flask and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford the cyclotrimerized product.

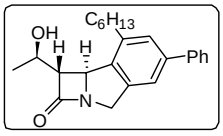
Procedure B: A solution of diyne 1 (0.5 mmol) and alkyne (0.5 mmol) in DCE (5 mL) was degassed with dry argon for 20 min. To this, Cp*RuCl(cod) catalyst (0.03 mmol) was added, and the mixture was stired for 4-6 h at room temperature. The solvent evaporated under reduced pressure. The residue was purified by silica gel chromatography to procure the cyclotrimerization product.

1-((*R*)-1-Hydroxyethyl)-6,8-diphenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (76):



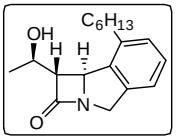
General procedure A was followed. Diyne **69** (100 mg, 0.40 mmol) and phenylacetylene (0.24 mL, 2.3 mmol) were used to afford compound **76** as a white solid, yield: 83%; mp: 159 °C; $[\alpha]_D^{25}$: –54.2 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) ν: 3412, 2929, 3024, 1755, 1523, 1428, 1211, 1049, 929, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.86 (d, *J* = 6.4 Hz, 3H), 1.33 (d, *J* = 4.7 Hz, 1H), 2.88 (dd, *J* = 2.4, 5.4 Hz, 1H), 4.08 (dq, *J* = 5.4, 6.0 Hz, 1H), 4.25 (dt, *J* = 0.9, 14.8 Hz, 1H), 5.00 (dt, *J* = 0.9, 14.8 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 7.35–7.51 (m, 10H), 7.56–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.7 (q), 51.9 (t), 59.4 (d), 65.3 (d), 67.2 (d), 120.8 (d), 127.3 (d, 2C), 127.6 (d), 127.7 (d), 128.0 (d), 128.5 (d, 2C), 128.9 (d, 4C), 136.9 (s), 139.2 (s), 139.8 (s), 140.3 (s), 142.4 (s), 143.7 (s), 178.7 (s) ppm; ESI-MS (*m/z*): 378.3 (100%, $[M+Na]^+$), 394.3 (20%, $[M+K]^+$); Anal. Calcd for C, 81.10; H, 5.96; N, 3.94%; Found: C, 81.01; H, 5.89; N, 3.91%.

8-Hexyl-1-((*R*)-1-hydroxyethyl)-6-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (77):



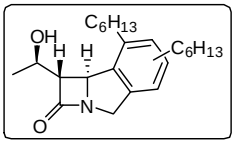
General procedure A was followed. Diyne **70** (100 mg, 0.38 mmol) and phenylacetylene (0.13 mL, 1.24 mmol) were used to afford a compound **77** as a white gummy liquid, yield: 80%; $[\alpha]_D^{25}$: –4.6 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν: 3620, 3019, 2930, 1758, 1600, 1518, 1424, 1216, 1045, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25–1.38 (m, 6H), 1.47 (d, *J* = 6.3 Hz, 3H), 1.55–1.73 (m, 2H), 2.57–2.81 (m, 2H), 3.22 (dd, *J* = 2.4, 6.3 Hz, 1H), 4.14 (br.d, *J* = 14.0 Hz, 1H), 4.39 (q, *J* = 6.3 Hz, 1H), 4.88–5.03 (m, 2H), 7.27 (s, 1H), 7.31 (s, 1H), 7.34–7.48 (m, 3H), 7.51–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 22.2 (q), 22.6 (t), 29.2 (t), 30.6 (t), 31.7 (t), 33.0 (t), 51.9 (t), 59.5 (d), 65.9 (d), 66.4 (d), 119.3 (d), 127.0 (d), 127.2 (d, 2C), 127.5 (d), 128.8 (d, 2C), 137.0 (s), 139.2 (s), 140.8 (s), 142.3 (s), 143.2 (s), 178.8 (s) ppm; ESI-MS (*m/z*): 364.7 (52%, $[M+1]^+$), 386.7 (100%, $[M+Na]^+$); Anal. Calcd for C, 79.30; H, 8.04; N, 3.85%; Found: C, 79.19; H, 8.21; N, 3.77%.

8-Hexyl-1-((*R*)-1-hydroxyethyl)-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (78):



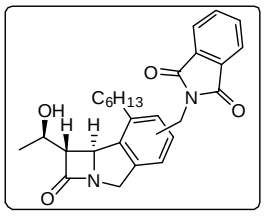
General procedure B was followed. Diyne **70** (110 mg, 0.42 mmol) and acetylene gas were used to afford compound **78** white gummy liquid, yield: 83%; $[\alpha]_D^{25}$: –62.7 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) ν: 3410, 3020, 2930, 1753, 1459, 1216, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.24–1.38 (m, 6H), 1.45 (d, *J* = 6.3 Hz, 3H), 1.53–1.68 (m, 2H), 2.51–2.75 (m, 2H), 3.18 (dd, *J* = 2.4, 6.3 Hz, 1H), 4.11 (br.d, *J* = 13.5 Hz, 1H), 3.37 (q, *J* = 6.3 Hz, 1H), 4.90 (br.d, *J* = 15.2 Hz, 2H), 7.07 (br.t, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 22.2 (q), 22.6 (t), 29.2 (t), 30.5 (t), 31.7 (t), 32.8 (t), 51.8 (t), 59.7 (d), 66.0 (d), 66.2 (d), 120.5 (d), 127.7 (d), 128.8 (d), 137.9 (s), 139.0 (s), 142.4 (s), 178.9 (s) ppm; ESI-MS (*m/z*): 288.3 (9%, $[M+1]^+$), 310.3 (100%, $[M+Na]^+$), 326.3 (16%, $[M+K]^+$); Anal. Calcd for C, 75.22; H, 8.77; N, 4.87%; Found: C, 75.26; H, 8.69; N, 4.73%.

6,8-Dihexyl-1-((*R*)-1-hydroxyethyl)-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (79):



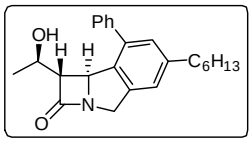
Cycloaddition of diyne **70** (130 mg, 0.50 mmol) and 1-octyne (0.22 mL, 2.0 mmol) following procedure A gave a 8:1 mixture of compounds **79** as a colorless gummy liquid, yield: 79%; $[\alpha]_D^{25}$: +62.8 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) ν: 3020, 2930, 2400, 1753, 1523, 1425, 1216, 1046, 929, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, *J* = 6.4 Hz, 6H), 1.24–1.38 (m, 12H), 1.44, 1.45 (2d, *J* = 6.3 Hz, 3H), 1.58 (br.s, 4H), 2.47–2.67 (m, 4H), 3.16, 3.20 (2dd, *J* = 2.4, 6.2 Hz, 1H), 4.04 (br.d, *J* = 13.7 Hz, 1H), 4.35 (q, *J* = 6.3 Hz, 1H), 4.86 (br.d, *J* = 14.7 Hz, 2H), 6.87–7.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q, 2C), 22.1 (q), 22.6 (t, 2C), 29.0 (t), 29.2 (t), 30.5 (t), 31.6 (t), 31.7 (t, 2C), 32.9 (t), 35.8 (t), 51.8 (t), 59.4 (d), 65.9 (d), 66.2 (d), 120.4 (d), 128.0 (d), 135.2 (s), 138.5 (s), 142.6 (s), 143.0 (s), 179.0 (s) ppm; ESI-MS (*m/z*): 372.4 (5%, $[M+H]^+$), 390.4, (100%, $[M+Na]^+$), 410.4 (4%, $[M+K]^+$); Anal. Calcd for C, 77.58; H, 10.04; N, 3.77%; Found: C, 77.49; H, 10.19; N, 3.59%.

2-((8-Hexyl-1-((*R*)-1-hydroxyethyl)-2-oxo-1,2,4,8b-tetrahydroazeto[2,1-a]isoindol-6-yl)methyl)isoindoline-1,3-dione (80):



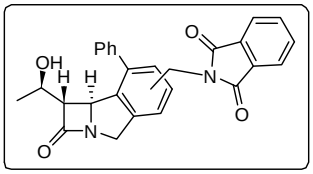
General procedure B was followed. Diyne **69** (120 mg, 0.56 mmol) and N-propargyl pthalimide (92.5 mg, 0.50 mmol) were used to procure a 3:1 mixture of compounds **80** as a white gummy solid, yield: 71%; $[\alpha]_D^{25:}$ –13.2 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν: 3584, 3019, 1769, 1718, 1518, 1394, 1216, 1046, 929, 759, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.85 (br.t, *J* = 6.5 Hz, 3H), 1.24–1.31 (m, 6H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.49–1.65 (m, 2H), 2.47–2.70 (m, 2H), 3.12 (dd, *J* = 2.4, 6.3 Hz, 0.9H), 3.21 (dd, *J* = 2.4, 6.3 Hz, 0.1H), 4.03 (br.d, *J* = 14.2 Hz, 1H), 4.34 (qui, *J* = 6.3 Hz, 1H), 4.74–4.88 (br.m, 5H), 7.12 (br.s, 1H), 7.17 (br.s, 1H), 7.66–7.47 (m, 2H), 7.80–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (q), 22.2 (q), 22.6 (t), 29.2 (t), 30.5 (t), 31.7 (t), 32.8 (t), 41.4 (t), 51.7 (t), 59.4 (d), 65.9 (d), 66.3 (d), 120.8 (d), 123.4 (d), 128.4 (d), 132.0 (s), 133.9 (d), 134.1 (d, 2C), 137.3 (s), 137.7 (s), 139.3 (s, 2C), 143.1 (s), 168.0 (s, 2C), 178.6 (s) ppm; (*m/z*): 469.3 (100%, $[M+Na]^+$), 485.3 (21%. $[M+K]^+$). Anal. Calcd for C, 72.62; H, 6.77; N, 6.27%**;** Found: C, 72.58; H, 6.88; N, 6.22%.

6-Hexyl-1-((*R*)-1-hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (81):



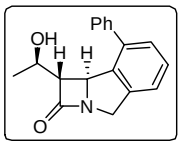
General procedure A was followed. Diyne **69** (100 mg, 0.40 mmol) and 1-octyne (0.18 mL, 1.20 mmol) were used to afford a compound **81** (92 mg, 85% yield as a white solid, yield: 78%; mp: 195 °C; $[\alpha]_D^{25}$: –80.4 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) ν: 3019, 2929, 1753, 1605, 1518, 1523, 1424, 1215, 1045, 929, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.85 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 1.26–1.37 (m, 6H), 1.55–1.64 (m, 2H), 2.64 (t, *J* = 7.4 Hz, 2H), 2.81 (dd, *J* = 2.5, 5.6 Hz, 1H), 3.98–4.08 (m, 1H), 4.15 (br.d, *J* = 14.8 Hz, 1H), 4.89 (br.d, *J* = 14.8 Hz, 1H), 4.97–5.02 (m, 1H), 7.06 (br.s, 2H), 7.32–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 20.7 (q), 22.6 (t), 29.0 (t), 31.6 (t), 31.7 (t), 35.8 (t), 51.8 (t), 59.5 (d), 65.5 (d), 67.0 (d), 122.1 (d), 127.8 (d), 128.4 (d, 2C), 128.6 (d), 128.8 (d, 2C), 135.1 (s), 138.5 (s), 140.1 (s), 143.1 (s), 144.2 (s), 178.8 (s) ppm; ESI-MS (*m/z*): 364.3 (9%, $[M+1]^+$), 386.2 (100%, $[M+Na]^+$), 402.3 (12%, $[M+K]^+$); Anal. Calcd for C, 79.30; H, 8.04; N, 3.85%; Found: C, 79.26; H, 8.16; N, 3.75%.

2-((1-((*R*)-1-Hydroxyethyl)-2-oxo-8-phenyl-1,2,4,8b-tetrahydroazeto[2,1-a]isoindol-6-yl)methyl)isoindoline-1,3-dione (82)



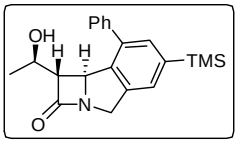
By following procedure A, cycloaddition of the diyne **69** (150 mg, 0.59 mmol) with N-propargyl pthalimide (110 mg, 0.59 mmol) gave a 3:1 mixture of compounds **82** as a white solid, yield: 71%; mp: 208 °C; $[\alpha]_D^{25}$: –50.5 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν: 3433, 3020, 1714, 1600, 1394, 1216, 757, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.66 (d, *J* = 6.4 Hz, 0.5 H), 0.80 (d, *J* = 6.4 Hz, 2.5 H), 2.78 (dd, *J* = 2.5, 5.5 Hz, 0.8 H), 2.88 (dd, *J* = 2.5, 5.5 Hz, 0.2 H), 4.03 (m, *J* = 6.3 Hz, 1H), 4.13 (dt, *J* = 0.9, 15.0 Hz, 1H), 7.72 (dd, *J* = 24.6 Hz, 1H), 4.85–4.99 (m, 3H), 7.31–7.48 (m, 7H), 7.67–7.75 (m, 2H), 7.78–7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7 (q), 41.2 (t), 51.7 (t), 59.3 (d), 65.3 (d), 67.0 (d), 122.4 (d), 123.5 (d, 2C), 128.0 (d), 128.4 (d, 2C), 128.8 (d, 3C), 132.0 (s, 2C), 134.1 (d, 2C), 137.4 (s), 137.6 (s), 139.1 (s), 139.4 (s), 143.6 (s), 168.0 (s, 2C), 178.6 (s) ppm; ESI-MS (*m/z*): 461.3 (100%, $[M+Na]^+$), 477.4 (23%, $[M+K]^+$); Anal. Calcd for C, 73.96; H, 5.06; N, 6.39%; Found: C, 73.78; H, 5.11; N, 6.18%.

1-((*R*)-1-Hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (83):



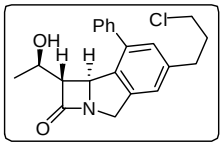
Following procedure B, using diyne **69** (100 mg, 0.40 mmol) and acetylene gas were used to get a compound **83** as a white solid, yield: 80%; mp: 146 °C; $[\alpha]_D^{25}$: –123.6 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν: 3409, 3020, 1751, 1524, 1423, 1216, 1047, 929, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.86 (d, *J* = 6.4 Hz, 3H), 2.83 (dd, *J* = 2.5, 5.5 Hz, 1H), 3.98–4.11 (m, 1H), 4.19 (dt, *J* = 1.1, 14.8 Hz, 1H), 4.94 (dt, *J* = 1.1, 14.8 Hz, 1H), 5.03 (br.q, *J* = 1.1 Hz, 1H), 7.24 (br.d, *J* = 7.5 Hz, 3H), 7.33–7.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.6 (q), 51.8 (t), 59.5 (d), 65.3 (d), 67.0 (d), 122.2 (d), 127.9 (d), 128.3 (d), 128.4 (d, 2C), 128.8 (d, 2C), 128.9 (d), 137.8 (s), 138.9 (s), 139.8 (s), 142.8 (s), 178.8 (s) ppm; ESI-MS (*m/z*): 280.3 (18%, $[M+1]^+$), 302.2 (100%, $[M+Na]^+$), 318.2 (9%, $[M+K]^+$); Anal. Calcd for C, 77.40; H, 6.13; N, 5.01%; Found: C, 77.34; H, 6.21; N, 5.13%.

(*1S,8bS*)-1-((*R*)-1-Hydroxyethyl)-8-phenyl-6-(trimethylsilyl)-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (84):



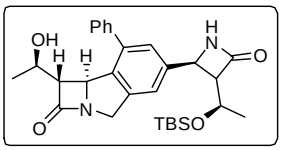
General procedure B was followed. Diyne **69** (130 mg, 0.51 mmol) and TMS-acetylene (0.15 mL, 1.5 mmol) were used to afford compound **84** as a colorless gum, yield: 86%; IR ($CHCl_3$) ν: 3437, 3019, 3010, 2401, 1757, 1517, 1384, 1216, 1045, 926, 841, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.29 (s, 9H), 0.81 (d, J = 6.4 Hz, 3H), 2.84 (dd, J = 2.5, 5.2 Hz, 1H), 4.05 (dq, J = 5.8, 6.2 Hz, 1H), 4.20 (dd, J = 0.8, 14.7 Hz, 1H), 4.95 (br.d, J = 14.7 Hz, 1H), 5.03 (br.q, J = 1.5 Hz, 1H), 7.34–7.49 (m, 7H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ–1.1 (s, 3C), 20.6 (s), 51.8 (t), 59.5 (d), 65.1 d), 67.0 (d), 126.9 (d), 127.8 (d), 128.5 (d, 2C), 128.8 (d, 2C), 133.2 (d), 138.2 (q), 138.5 (q), 140.1 (q), 141.9 (q), 142.2 (q), 178.9 (q); ESI-MS (*m/z*): 374.35 (100%, $[M+Na]^+$); Anal. Calcd for $C_{21}H_{25}NO_2Si$: C, 71.75; H, 7.17; N, 3.98; Found C, 71.66; H, 7.21; N, 8.79%.

(*1S,8bS*)-6-(3-Chloropropyl)-1-((*R*)-1-hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (85):



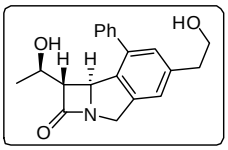
General procedure B was followed. Diyne **69** (200 mg, 0.28 mmol) and 5-chloro-1-pentyne (0.18 mL, 1.39 mmol) were used to afford compound **85** as a coloreless thick liquid, yield: 79%; IR ($CHCl_3$) ν: 3446, 3011, 1759, 1385, 1216, 1045, 930, 703, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.79 (d, J = 6.4 Hz, 3H), 2.10 (tt, J = 6.4, 7.6 Hz, 2H), 2.13 (d, J = 6.3 Hz, 1H), 2.82 (dd, J = 2.6, 4.6 Hz, 1H), 2.83 (dd, J = 3.6, 7.6 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 4.05 (dq, J = 5.3, 6.3 Hz, 1H), 4.14 (br.d, J = 15.2 Hz, 1H), 4.90 (br.d, J = 15.2 Hz, 1H), 5.03 (br.q, J = 1.6 Hz, 1H), 7.08 (s, 2H), 7.31–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ20.5 (s), 32.4 (t), 33.9 (t), 44.0 (t), 51.6 (t), 59.0 (d), 64.7 (d), 66.9 (d), 122.1 (d), 127.7 (d), 128.3 (d), 128.6 (d), 128.7 (d), 135.7 (q), 138.8 (q), 139.7 (q), 141.7 (q), 143.3 (q), 179.1 (q) ppm; ESI-MS (*m/z*): 378.28 (100%, $[M+Na]^+$); Anal. Calcd for $C_{21}H_{22}ClNO_2$: C, 70.88; H, 6.23; N, 3.94; Found: C, 70.79; H, 6.12; N, 3.78%.

(*1S,8bS*)-6-((*2S,3S*)-3-((*R*)-1-((tert-Butyldimethylsilyl)oxy)ethyl)-4-oxoazetidin-2-yl)-1-((R)-1-hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (86):



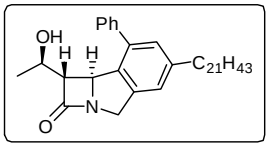
General procedure B was followed. Diyne **69** (120 mg, 0.47 mmol) and compound **BL** (126 mg, 0.50 mmol) were used to afford a compound **86** as a white gummy liquid, yield: 53%; IR ($CHCl_3$) ν: 3411, 3020, 2930, 1760, 1385, 1216, 1045, 669, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.81 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 2.82 (dd, 3.05 (dd, J = 2.4, 5.2 Hz, 1H), 2.77 (dd, J = 2.3, 4.1 Hz, 1H), 4.05 (dq, J = 5.9, 6.3 Hz, 1H), 4.17 (dq, J = 5.9, 6.3 Hz, 1H), 4.07 (br.d, J = 14.9 Hz, 1H), 4.85 (br.d, J = 14.9 Hz, 1H), 4.96 (br.s, 1H), 6.57 (ddd, J = 0.8, 2.2, 7.9 Hz, 1H), 6.79 (t, J = 1.9 Hz, 1H), 6.86 (ddd, J = 0.8, 1.6, 7.9 Hz, 1H), 7.06–7.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ –4.9 (s), –4.2 (s), 18.0 (s), 20.7 (s), 22.7 (d), 25.7 (s, 3C), 29.7 (q), 51.7 (t), 52.6 (d), 59.3 (d), 65.2 (d), 65.4 (d), 67.1 (d), 69.0 (d), 119.5 (d), 126.0 (d), 128.2 (d), 128.4 (d, 2C), 128.9 (d, 2C), 137.7 (q), 139.3 (q, 2C), 141.8 (q), 143.8 (q), 168.7 (q), 178.7 (q) ppm; ESI-MS (*m/z*): 529.54 (100%, $[M+Na]^+$); Anal. Calcd for $C_{29}H_{38}N_2O_4Si$: C, 68.74; H, 7.57; N, 5.53; Found: C, 68.37; H, 7.68; N, 5.44%.

(*1S,8bS*)-1-((*R*)-1-Hydroxyethyl)-6-(2-hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (87):



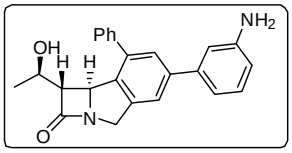
General procedure B was followed. Diyne **69** (100 mg, 0.40 mmol) and 3-butyn-1-ol (0.12 mL, 1.6 mmol) were used to procure compound **87** as a gummy liquid, yield: 73%; IR ($CHCl_3$) ν: 3446, 3020, 1756, 1385, 1216, 1045, 669, cm^{-1}; ^1H NMR: ($CDCl_3$, 200 MHz): δ 0.79 (d, J = 6.4 Hz, 3H), 1.82 (br.s, 2H), 2.80 (dd, J = 2.5, 5.1 Hz, 1H), 2.90 (t, J = 6.5 Hz, 2H), 3.87 (t, 6.5 Hz, 2H) 4.03 (dq, J = 5.5, 6.3 Hz, 1H), 4.13 (dd, J = 0.8, 15.1 Hz, 1H), 4.89 (br.d, J = 0.8, 15.1 Hz, 1H), 5.00 (br.q, J = 0.8 Hz, 1H), 7.10 (s, 2H), 7.31–7.46 (m, 5H); ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 20.6 (s), 38.8 (t), 51.7 (t), 59.2 (d), 63.4 (t), 65.0 (d), 66.9 (d), 122.7 (d), 127.8 (d), 128.4 (d), 128.8 (d), 129.2 (d), 136.0 (q), 138.9 (q), 139.7 (q), 139.8 (q), 143.3 (q), 179.0 (q) ppm; ESI-MS (*m/z*): 324.58 (5%, $[M+H]^+$], 346.61 (100%, $[M+Na]^+$); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33; O, 14.84; Found: C, 74.14; H, 6.61; N, 5.19%.

(*1S,8bS*)-6-Henicosyl-1-((*R*)-1-hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (88):



Cycloaddition of diyne **69** (130 mg, 0.51 mmol) and 1-tricosyne (164 mg, 0.51 mmol) following procedure B gave a compound **88** as a white thick liquid, yield: 77%; IR ($CHCl_3$) ν: 3020, 2928, 1755, 1604, 1520, 1529, 1426, 1225, 1055, 939, 768, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.84 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 6.4 Hz, 3H), 1.24 (s, 34H), 1.55–1.65 (m, 4H), 2.64 (t, J = 7.7 Hz, 2H), 2.82 (dd, J = 2.5, 5.4 Hz, 1H), 4.05 (dq, J = 5.5, 6.1 Hz, 1H), 4.14 (dd, J = 1.5, 14.8 Hz, 1H), 4.89 (br.d, J = 14.8 Hz, 1H), 5.00 (br.q, J = 1.5 Hz, 1H), 7.06 (br.s, 2H), 7.32–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (s), 20.7 (s), 22.7 (t), 29.3 (t, 2C), 29.5 (t), 29.6 (t), 29.7 (t, 13C), 31.6 (t), 31.9 (t), 35.7 (t), 51.8 (t), 59.3 (d), 65.2 (d), 67.0 (d), 122.0 (d), 127.7 (d), 128.4 (d, 2C), 128.6 (d), 128.7 (d, 2C), 135.1 (q), 138.5 (q), 140.1 (q), 143.1 (q), 144.1 (q), 179.0 (q) ppm; ESI-MS (*m/z*): 576.6 (100%, $[M+Na]^+$); Anal. Calcd for $C_{39}H_{59}NO_2$: C, 81.62; H, 10.36; N, 2.44; Found: C, 81.57; H, 10.28; N, 2.53%.

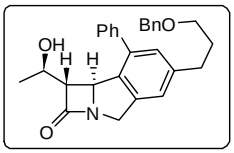
(*1S,8bS*)-6-(3-Aminophenyl)-1-((*R*)-1-hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (89):



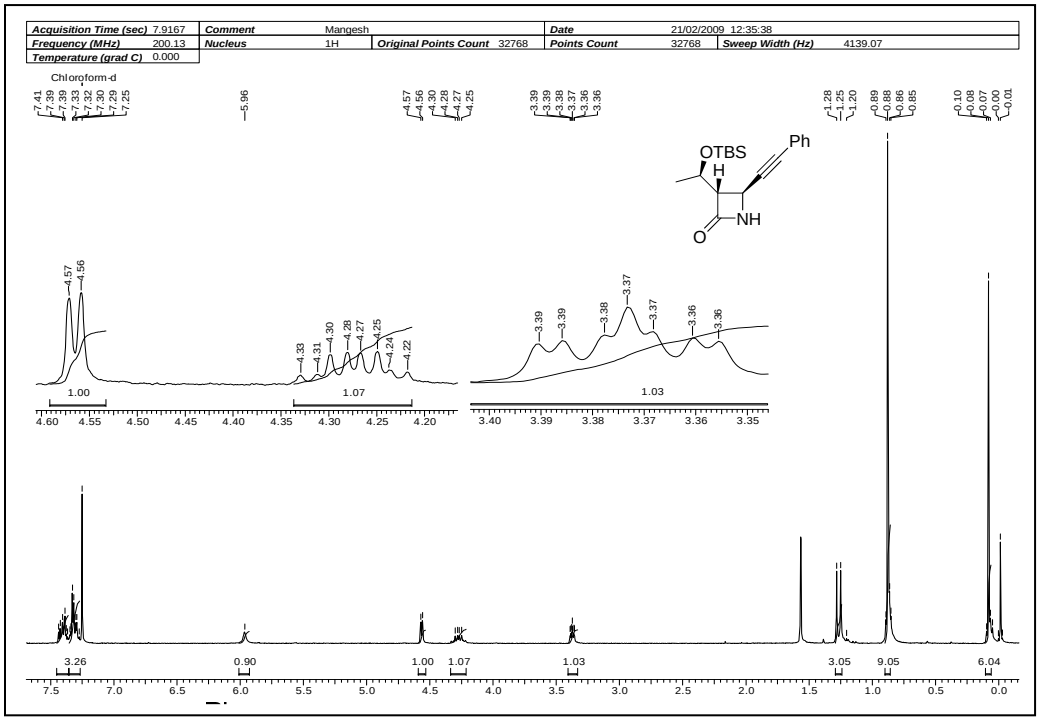
By following procedure B, cycloaddition of the diyne **69** (100 mg, 0.40 mmol) with 3-ethynylaniline (0.19 mL, 1.6 mmol) gave a 6:1 mixture of compounds **89** as a gummy liquid, yield: 83%; IR ($CHCl_3$) ν: 3448, 3020, 2929, 2401, 1758, 1619, 1385, 1216, 1045, 930, 702, 669, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.55 (d, J = 6.5 Hz, 0.25H), 0.69 (d, J = 6.5 Hz, 2.75H), 2.72 (dd, J = 2.5, 4.8 Hz, 0.1H), 2.77 (dd, J = 2.5, 4.8 Hz, 0.9H), 3.15 (br.s, 2H), 3.96 (dq, J = 5.1, 6.5 Hz, 1H), 4.07 (br.d, J = 14.9 Hz, 1H), 4.85 (br.d, J = 14.9 Hz, 1H), 4.96 (br.s, 1H), 6.57 (ddd, J = 0.8, 2.2, 7.9 Hz, 1H), 6.79 (t, J = 1.9 Hz, 1H), 6.86 (ddd, J = 0.8, 1.6, 7.9 Hz, 1H), 7.06–7.38 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.5 (s), 51.7 (t), 59.0 (d), 64.7 (d), 67.0 (d), 113.8 (d), 114.4 (d), 117.5 (d), 120.5 (d), 127.4 (d), 127.8 (d), 128.3 (d, 2C), 128.7 (d, 2C), 129.7 (d), 136.7 (q), 138.9 (q), 139.7 (q), 141.3 (q), 142.4 (q), 143.4 (q), 146.8 (q), 179.1 (q) ppm; ESI-MS (*m/z*): 393.6584 (100%,

$[M+Na]^+$); Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56; Found: C, 77.78; H, 5.81; N, 7.43%.

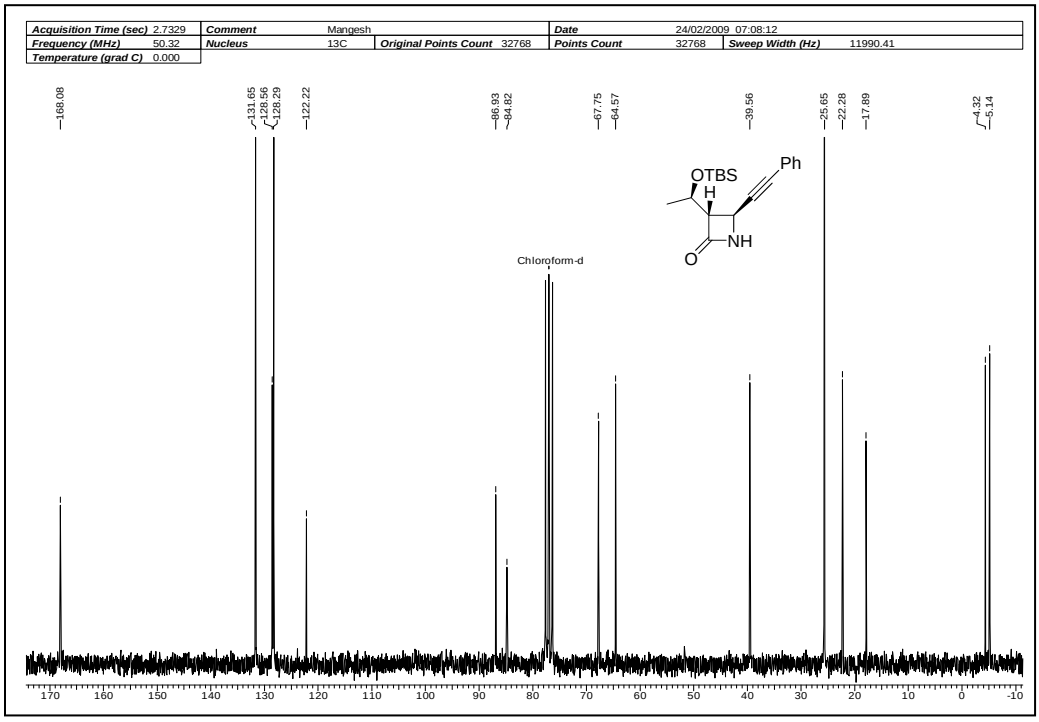
(*1S,8bS*)-6-(3-(Benzyloxy)propyl)-1-((*R*)-1-hydroxyethyl)-8-phenyl-1,8b-dihydroazeto[2,1-a]isoindol-2(4H)-one (90):



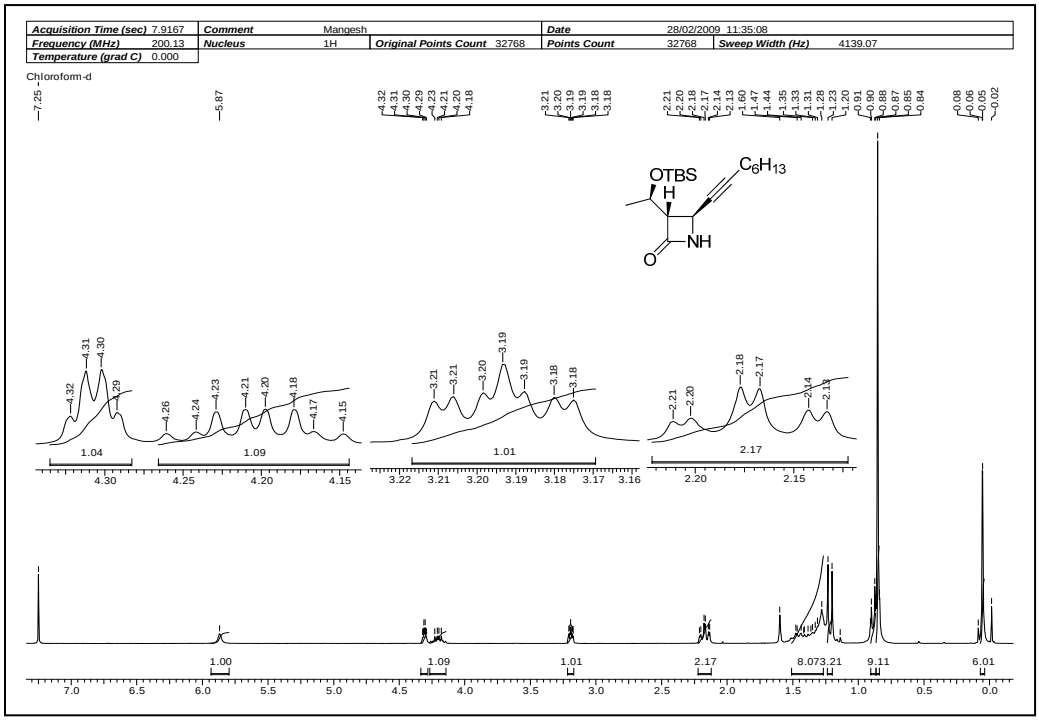
General procedure B was followed. Diyne **69** (120 mg, 0.47 mmol) 1-benzyloxy-4-pentyne (0.17 mL, 1.0 mmol) were used to afford compound **90** as a colorless thick liquid, yield: 69%; IR ($CHCl_3$) ν., 3437, 3020, 2400, 2929, 1760, 1619, 1385, 1216, 1045, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.84 (d, J = 6.4 Hz, 3H), 1.88–2.02 (m, 2H), 2.77 (dd, J = 6.4, 8.1 Hz, 2H), 2.81 (dd, J = 2.5, 5.4 Hz, 1H), 3.50 (t, J = 6.2 Hz, 2H), 4.05 (dq, J = 5.5, 6.1 Hz, 1H), 4.13 (dd, J = 0.9, 15.1 Hz, 1H), 4.51(s, 2H), 4.89 (br.d, J = 15.1 Hz, 1H), 5.00 (br.q, J = 1.5 Hz, 1H), 7.04 (br.d, J = 7.0 Hz, 2H), 7.29–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ20.7 (s), 31.4 (t), 32.1 (t), 51.7 (t), 59.3 (d), 65.2 (d), 66.9 (d), 69.2 (t), 72.9 (t), 122.1 (d), 127.6 (d), 127.7 (d, 2C), 127.8 (d), 128.3 (d, 2C), 128.4 (d, 2C), 128.6 (d), 128.7 (d, 2C), 135.3 (q), 138.4 (q), 138.6 (q), 140.0 (q), 143.1 (q), 143.2 (q), 178.9 (q) ppm; ESI-MS (*m/z*): 450.12 (100%, $[M+Na]^+$); Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28; Found: C, 78.54; H, 6.91; N, 3.21%.



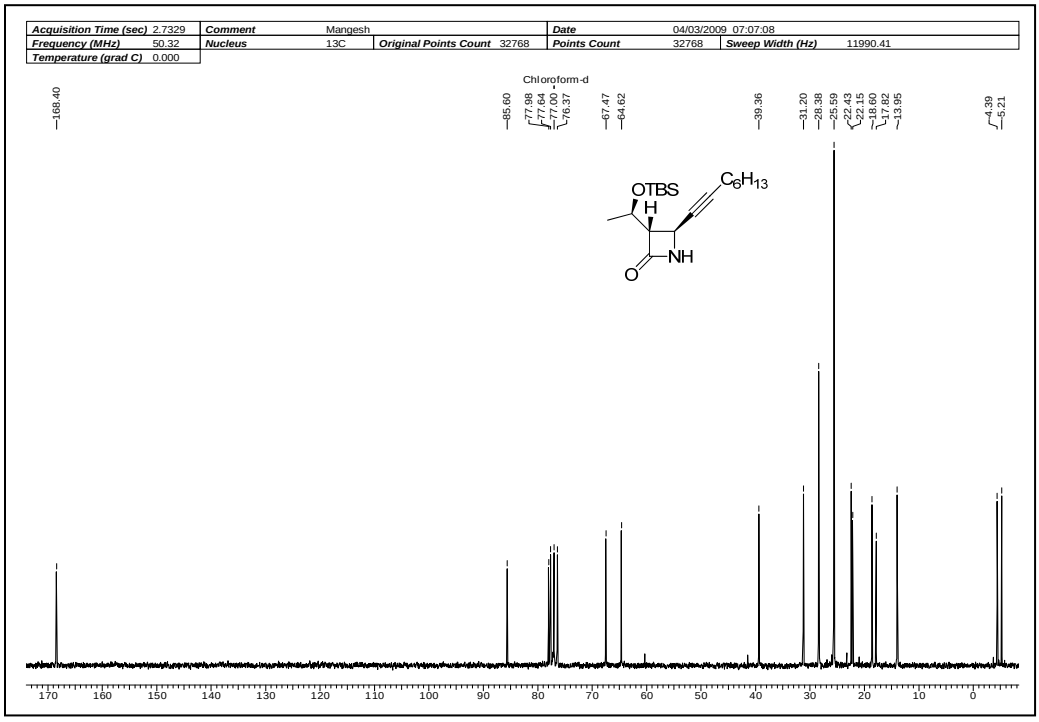
^{1}H NMR Spectrum of 72 in $CDCl_3$



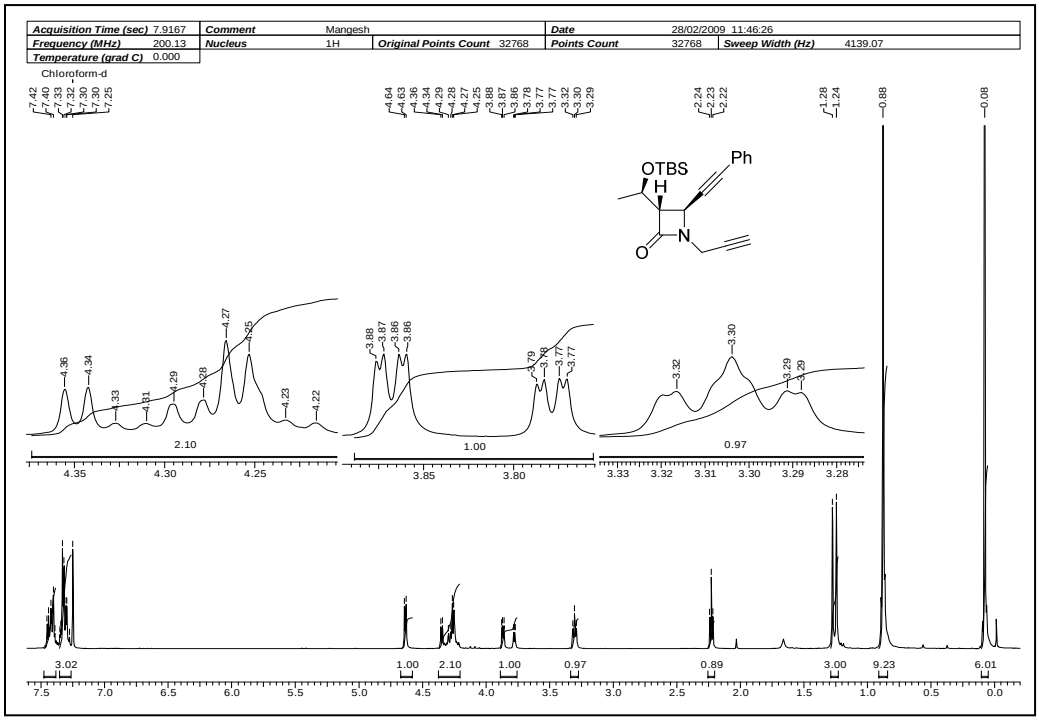
^{13}C NMR Spectrum of 72 in $CDCl_3$



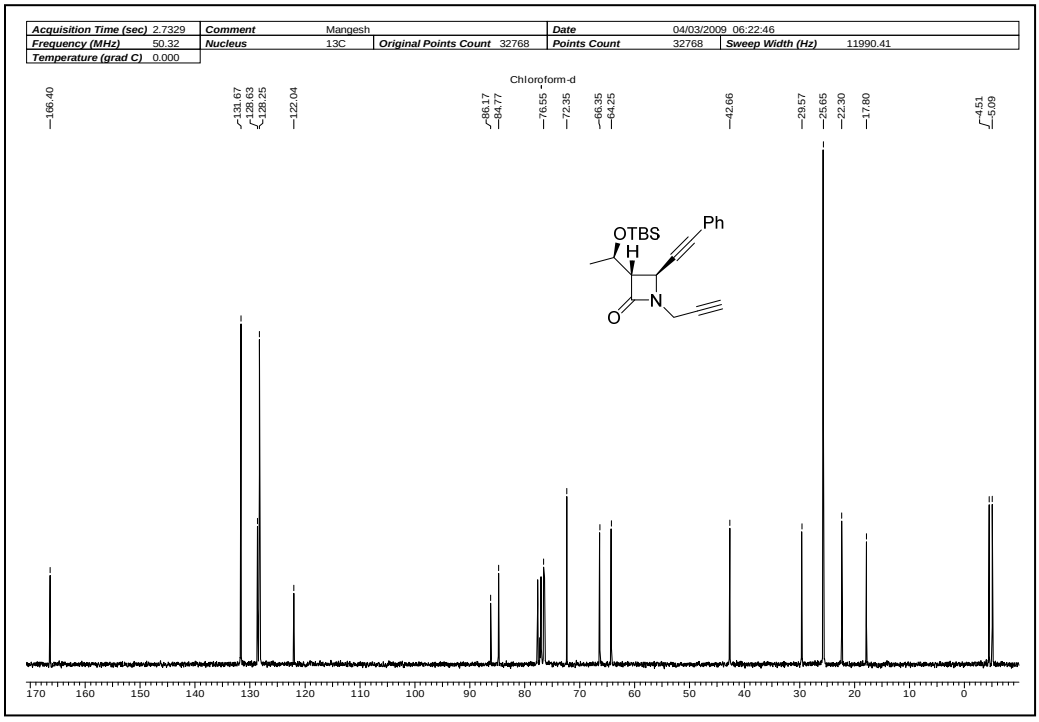
^{1}H NMR Spectrum of 73 in $CDCl_3$



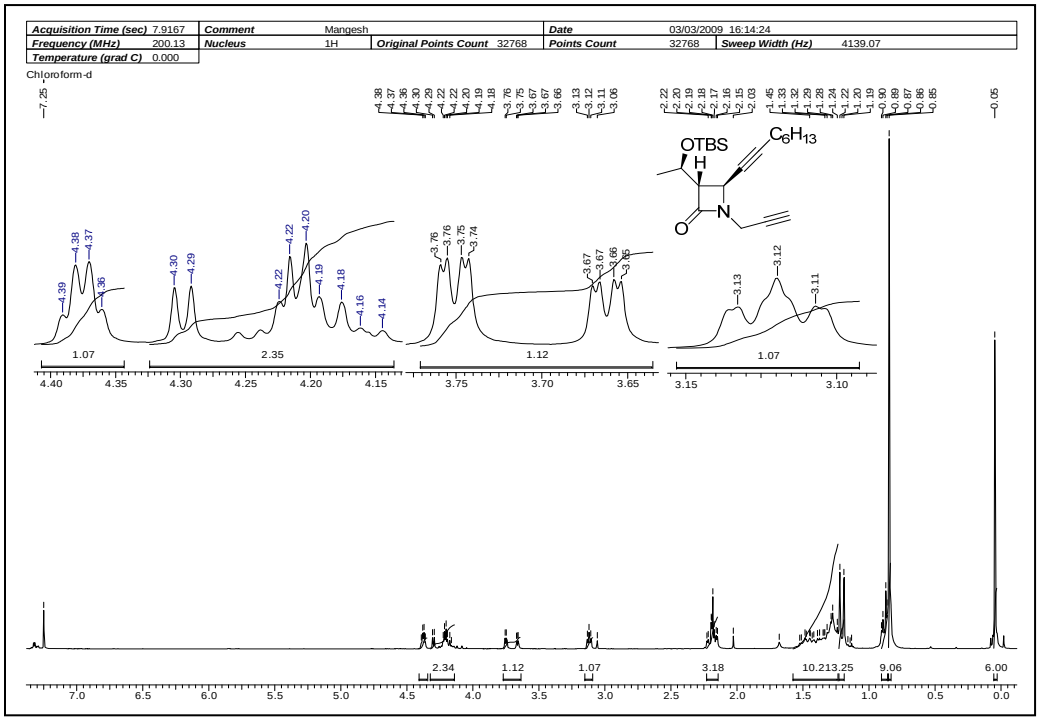
^{13}C NMR Spectrum of 73 in $CDCl_3$



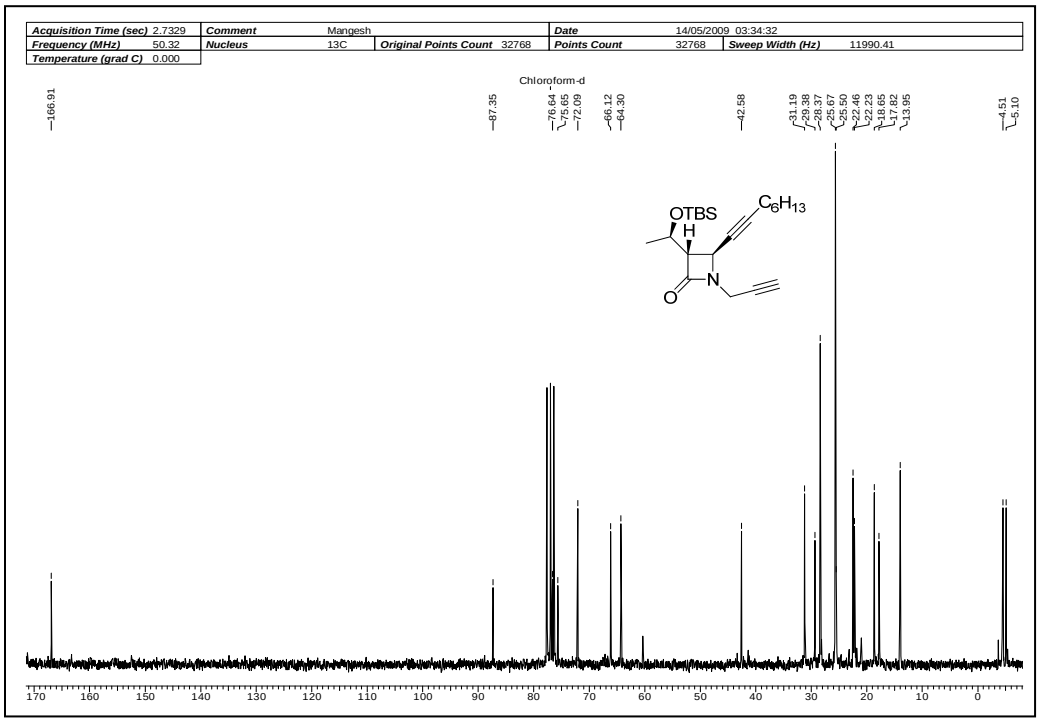
^{1}H NMR Spectrum of 74 in $CDCl_3$



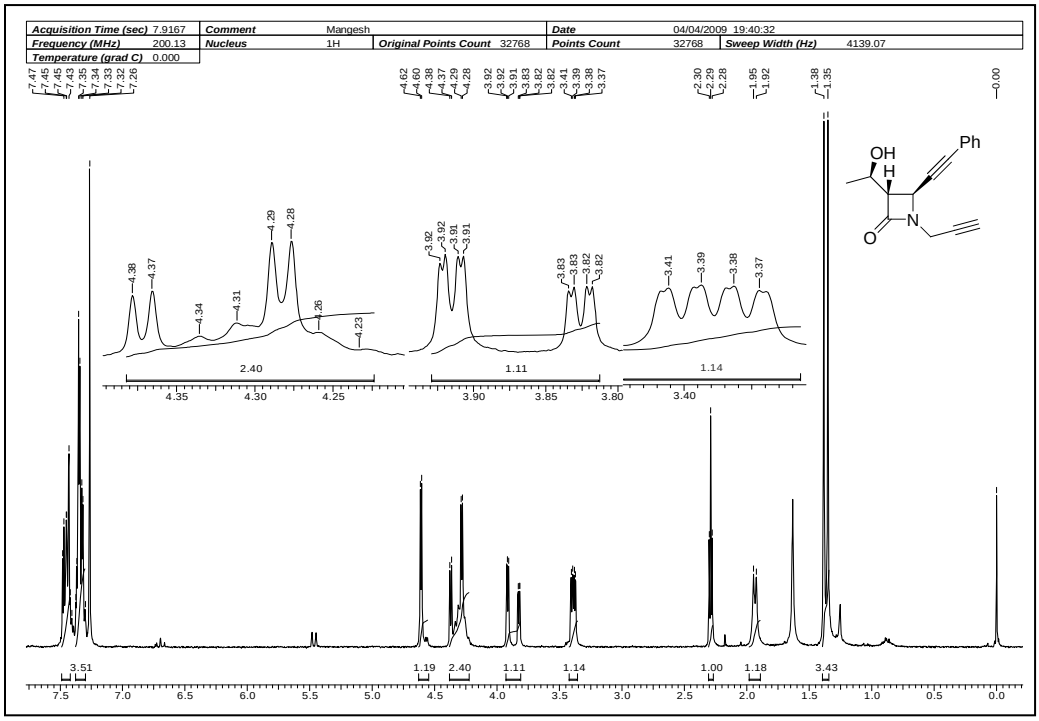
^{13}C NMR Spectrum of 74 in $CDCl_3$



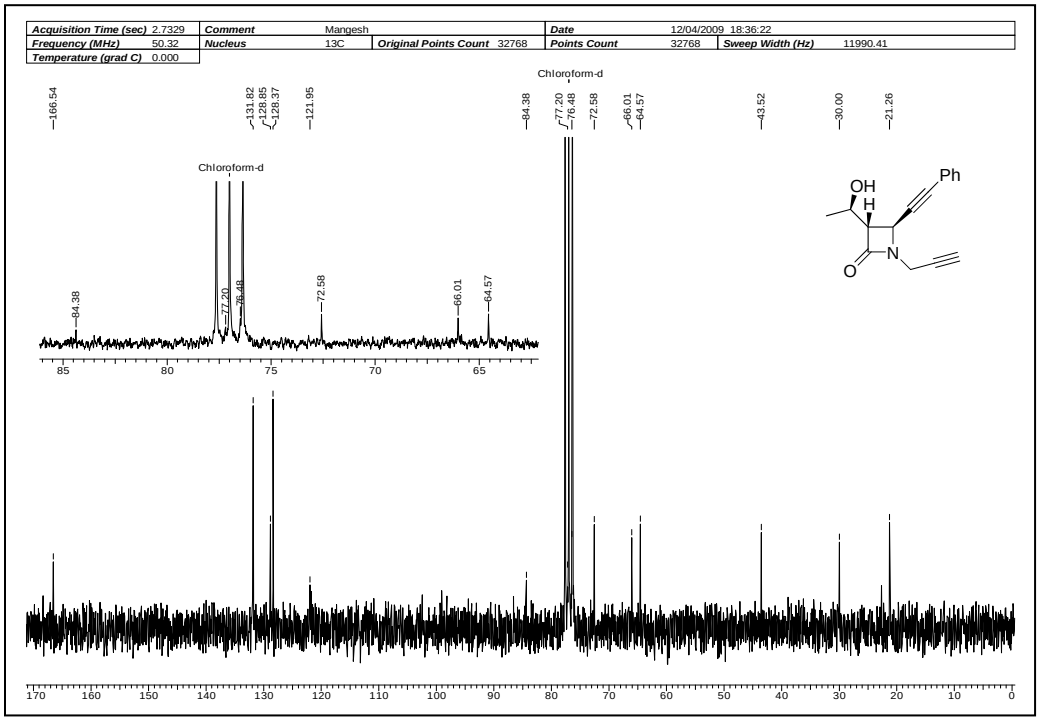
^{1}H NMR Spectrum of 75 in $CDCl_3$



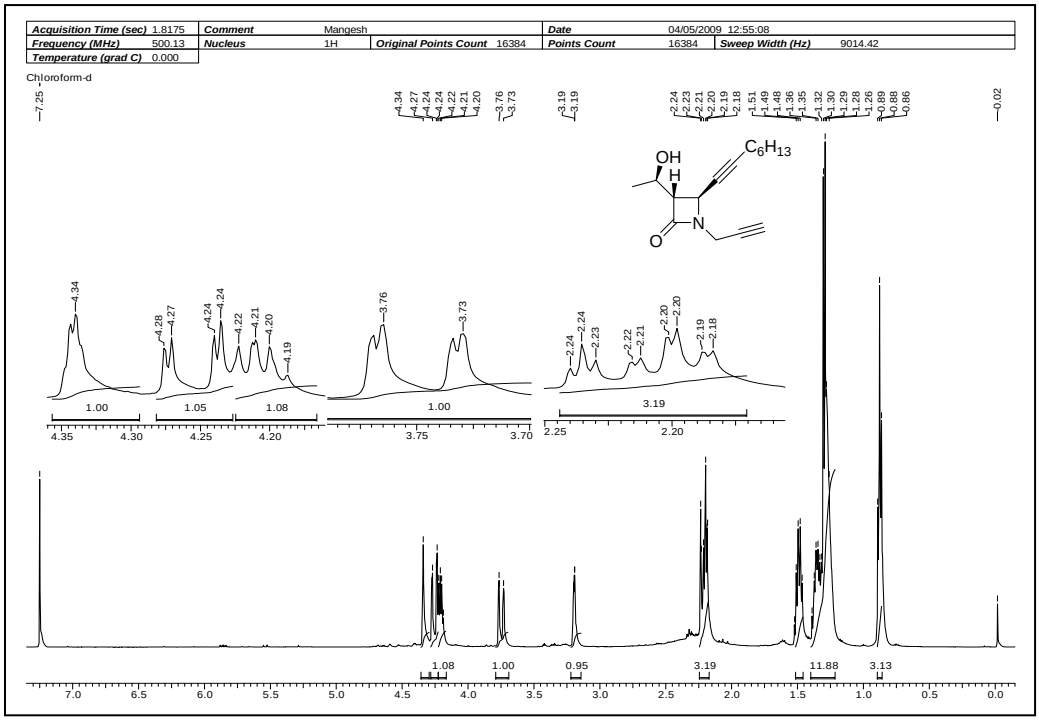
^{13}C NMR Spectrum of 75 in $CDCl_3$



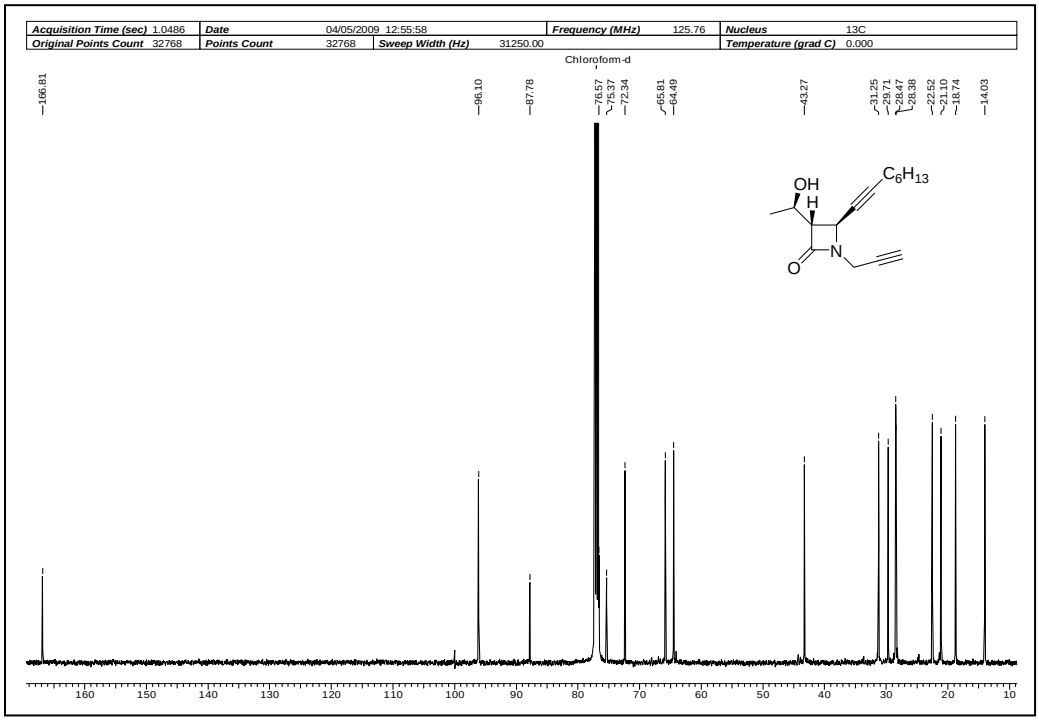
^{1}H NMR Spectrum of 69 in $CDCl_3$



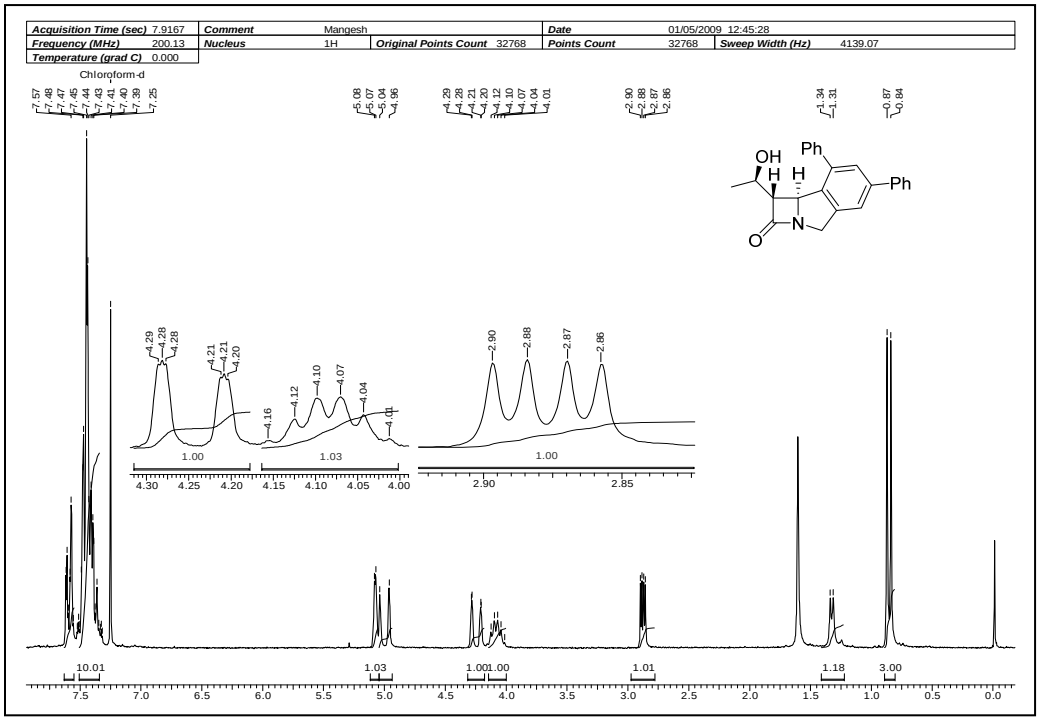
^{13}C NMR Spectrum of 69 in $CDCl_3$



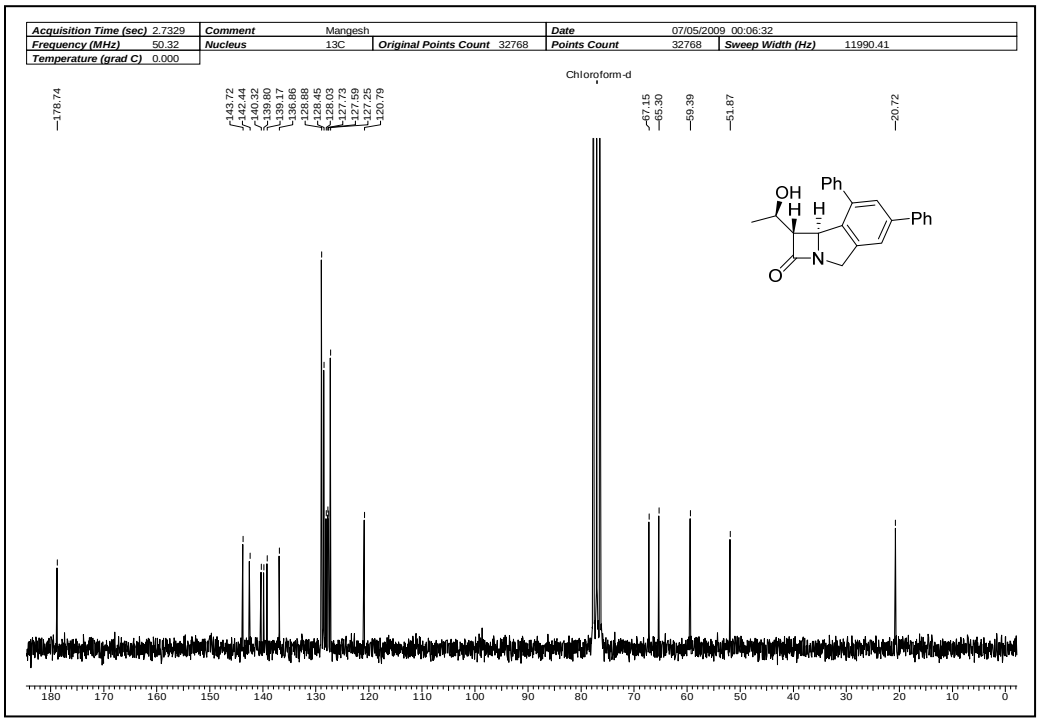
^{1}H NMR Spectrum of 70 in $CDCl_3$



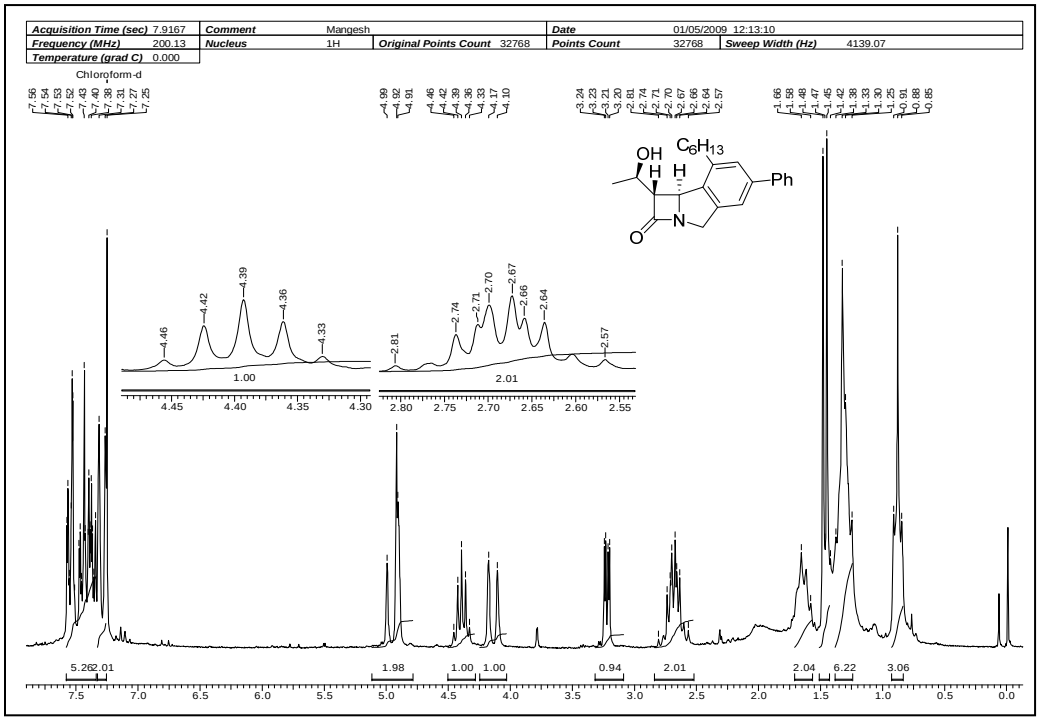
^{13}C NMR Spectrum of 70 in $CDCl_3$



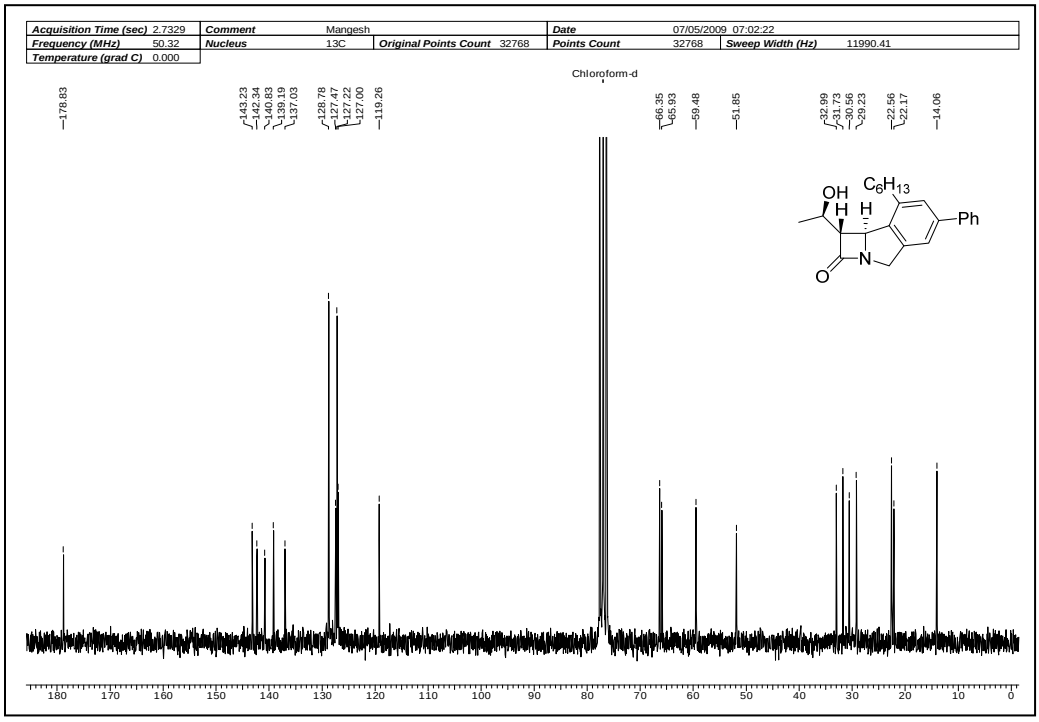
^{1}H NMR Spectrum of 76 in $CDCl_3$



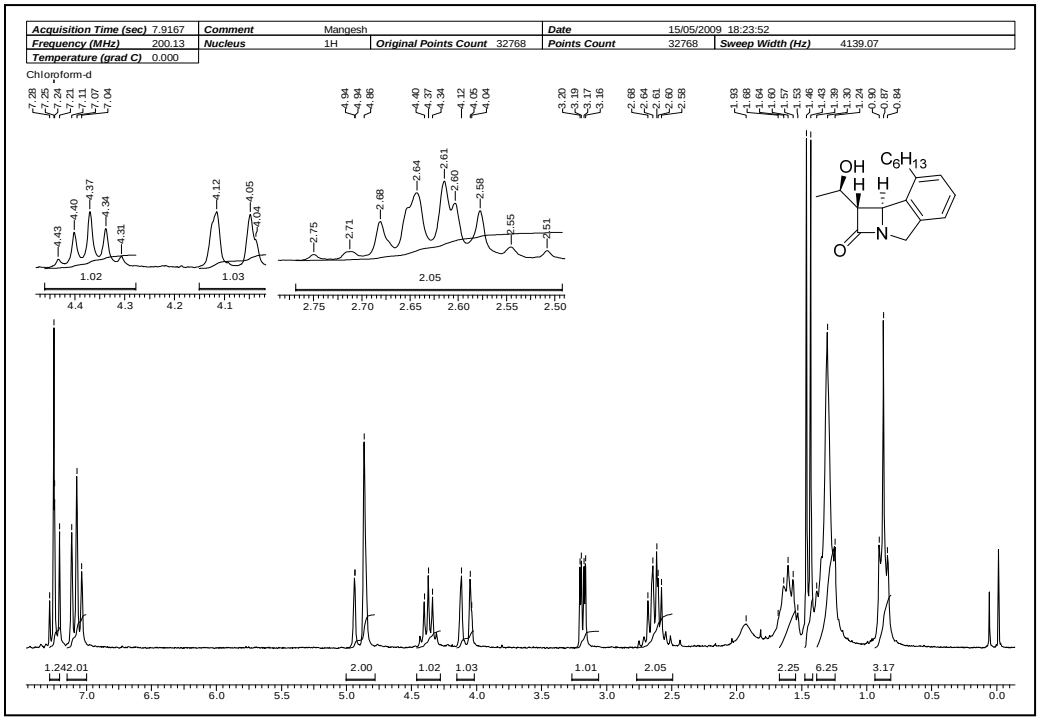
^{13}C NMR Spectrum of 76 in $CDCl_3$



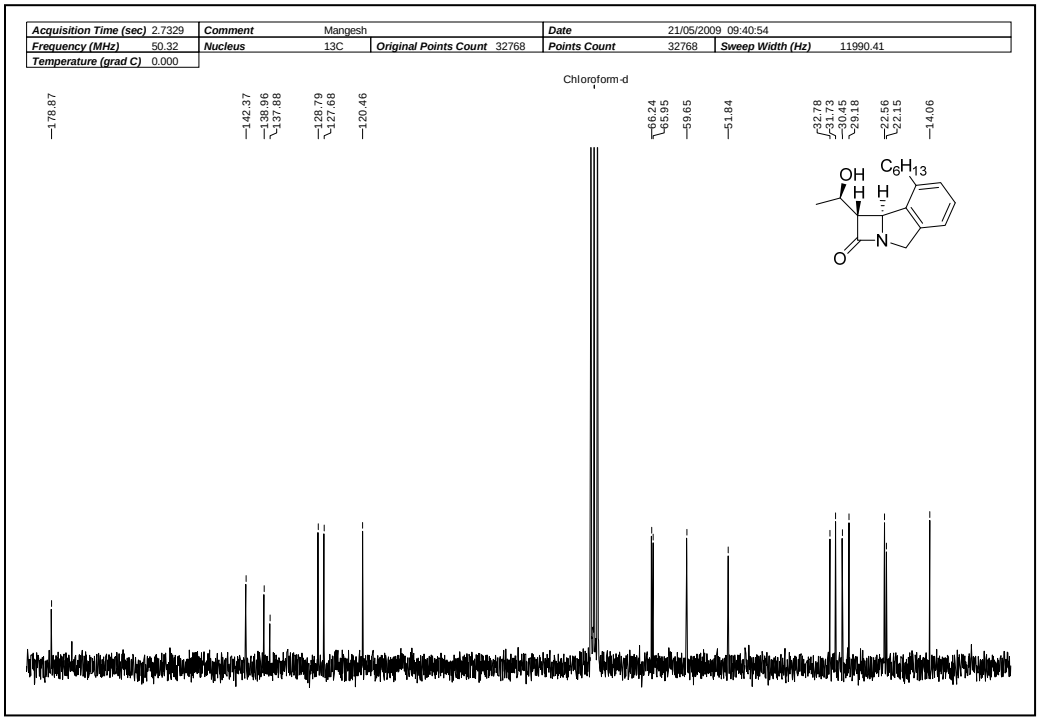
^{1}H NMR Spectrum of 77 in $CDCl_3$



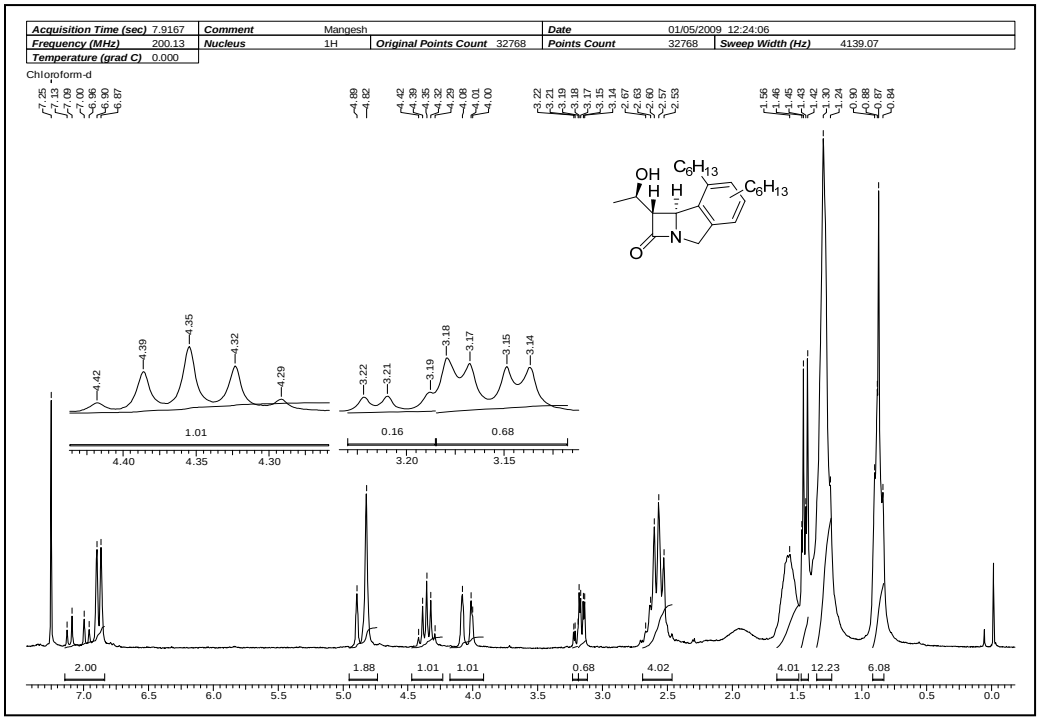
^{13}C NMR Spectrum of 77 in $CDCl_3$



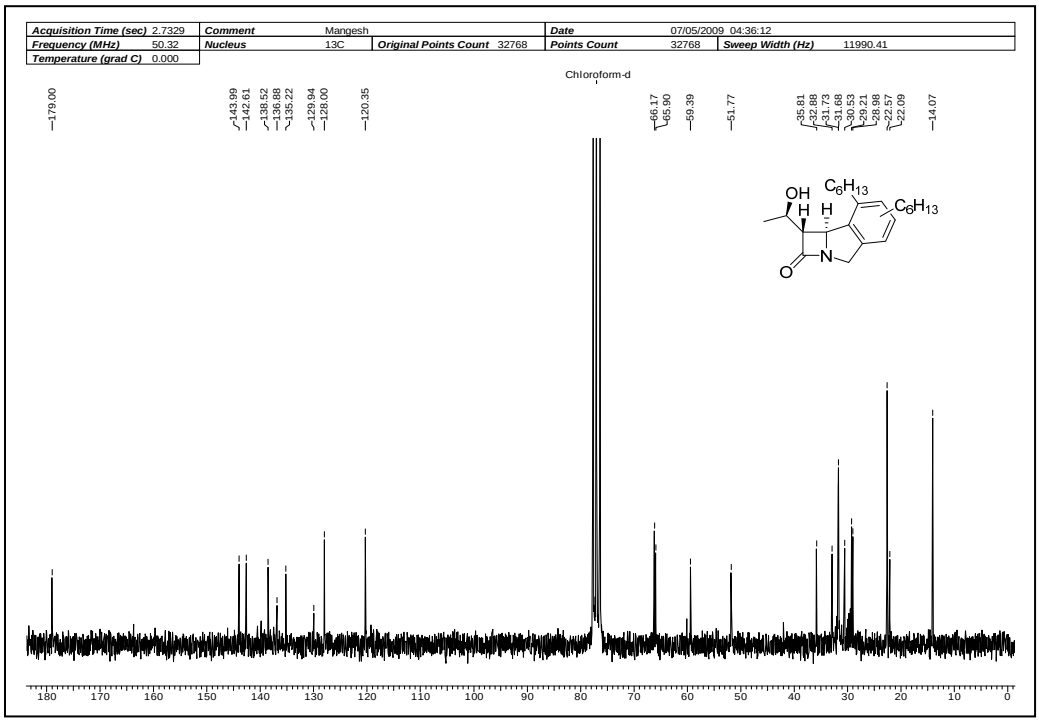
^{1}H NMR Spectrum of 78 in $CDCl_3$



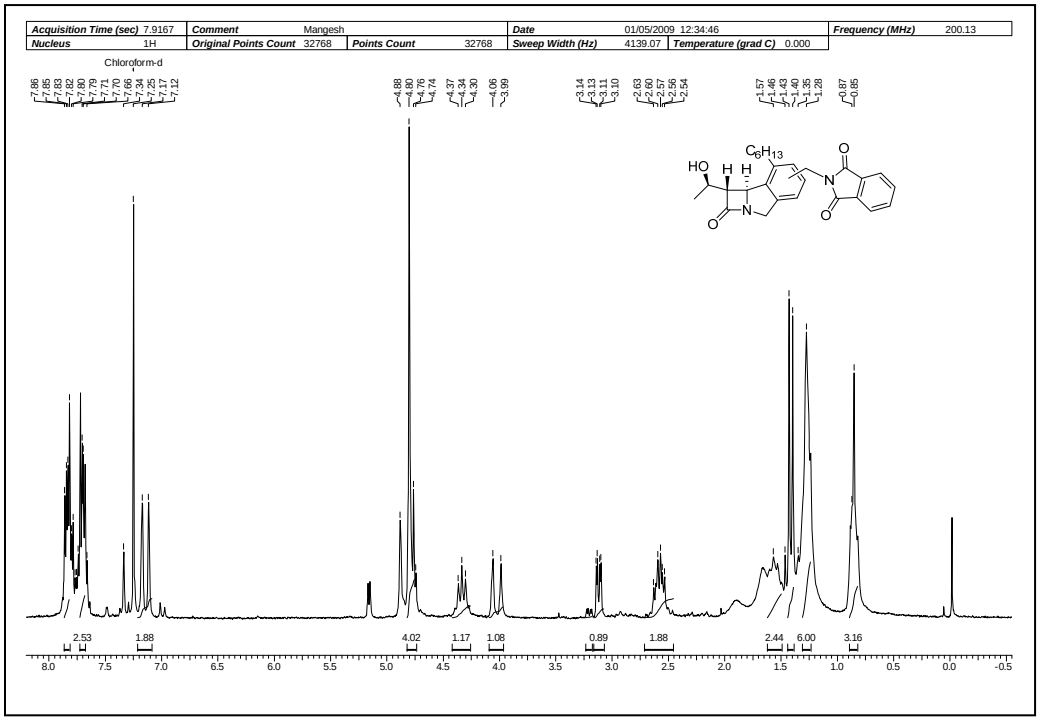
^{13}C NMR Spectrum of 78 in $CDCl_3$



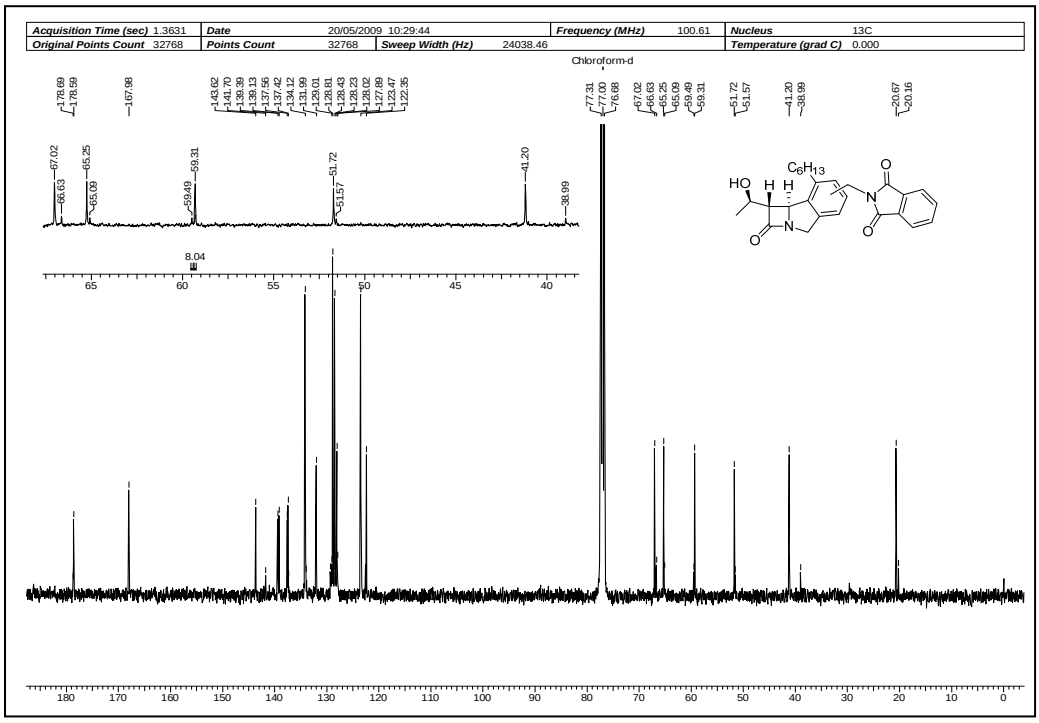
^{1}H NMR Spectrum of 79 in $CDCl_3$



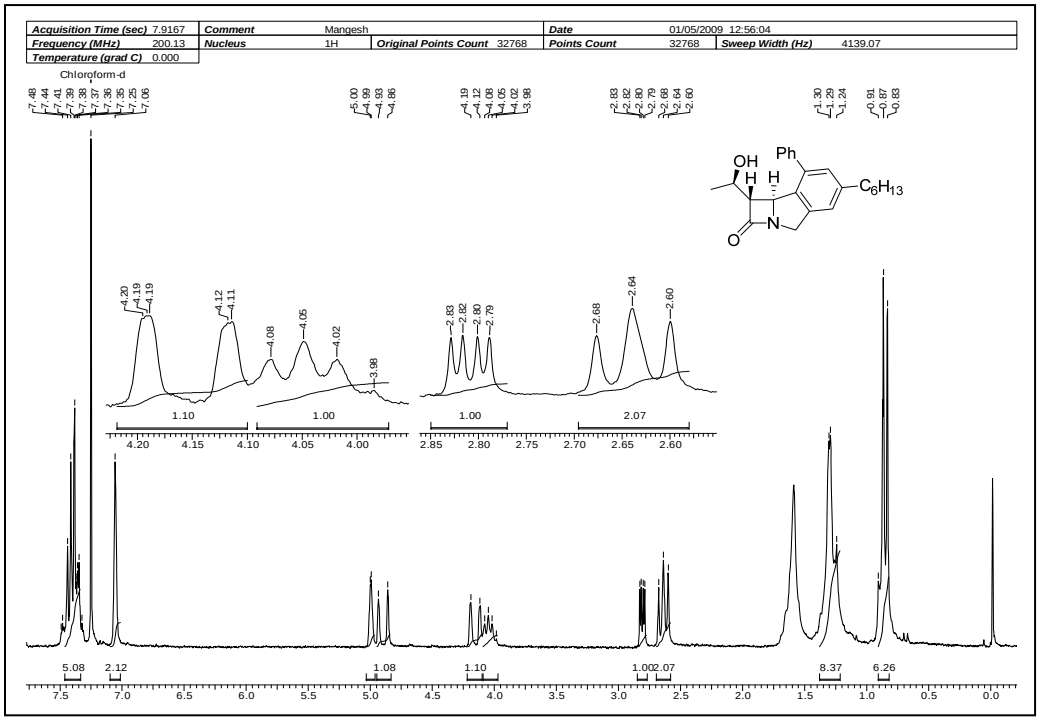
^{13}C NMR Spectrum of 79 in $CDCl_3$



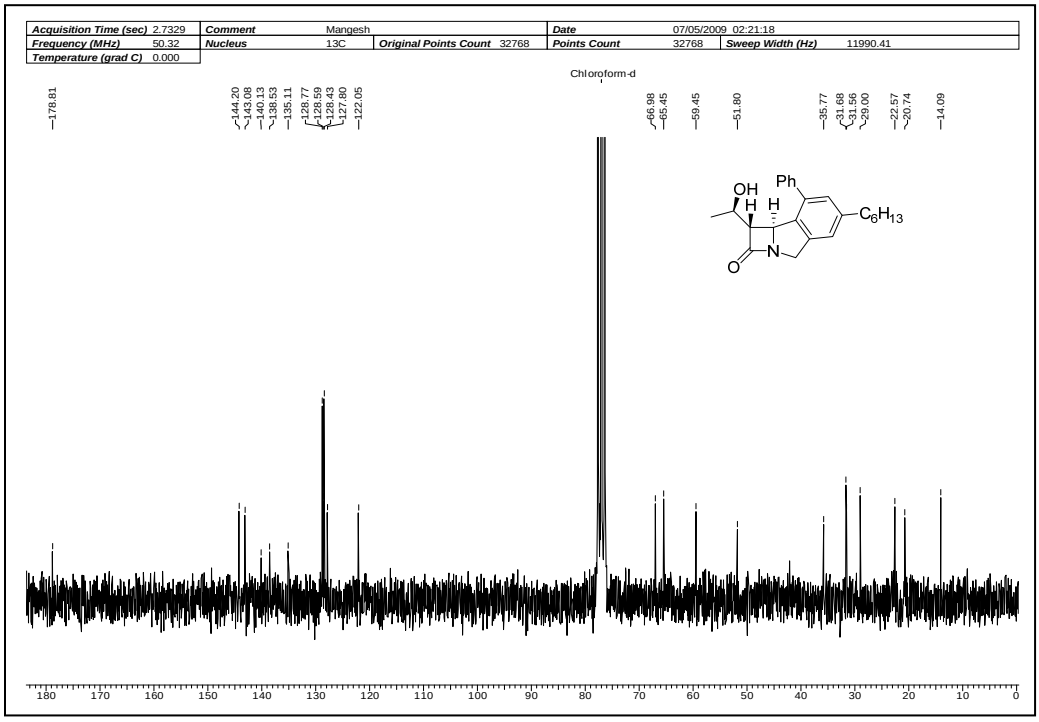
^{1}H NMR Spectrum of 80 in $CDCl_3$



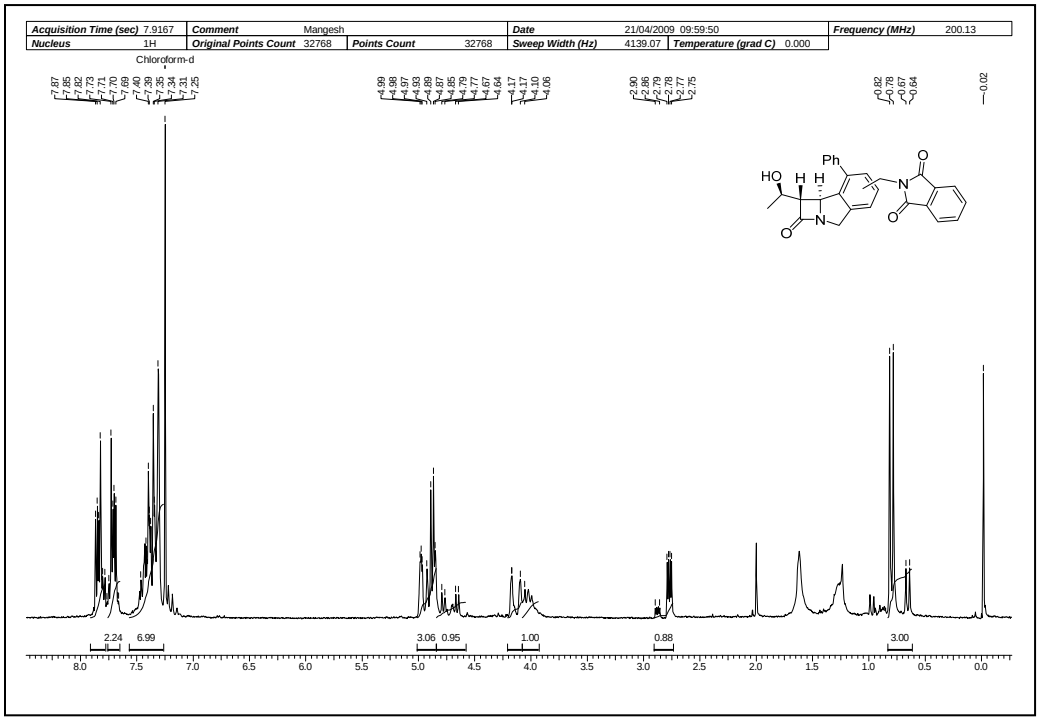
^{13}C NMR Spectrum of 80 in $CDCl_3$



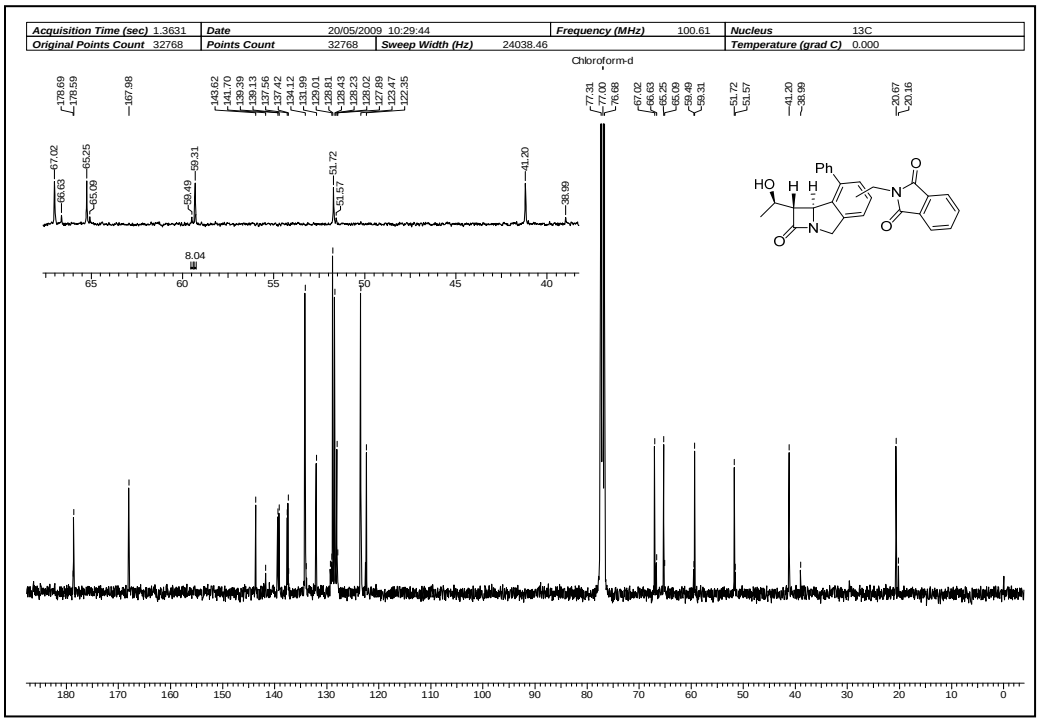
^{1}H NMR Spectrum of 81 in $CDCl_3$



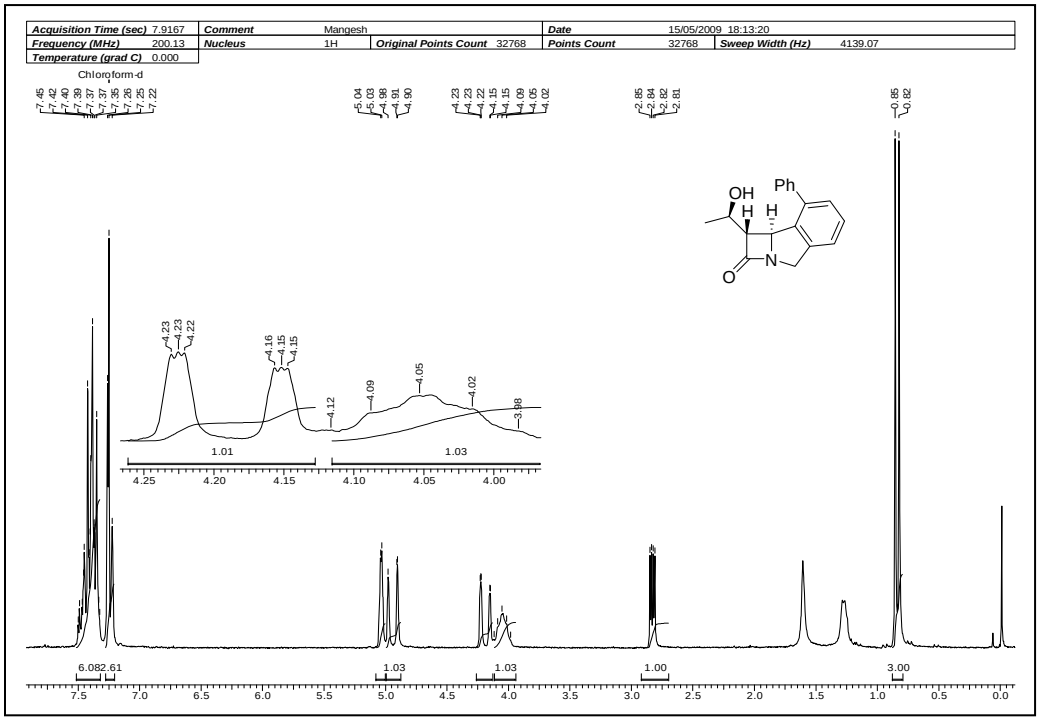
^{13}C NMR Spectrum of 81 in $CDCl_3$



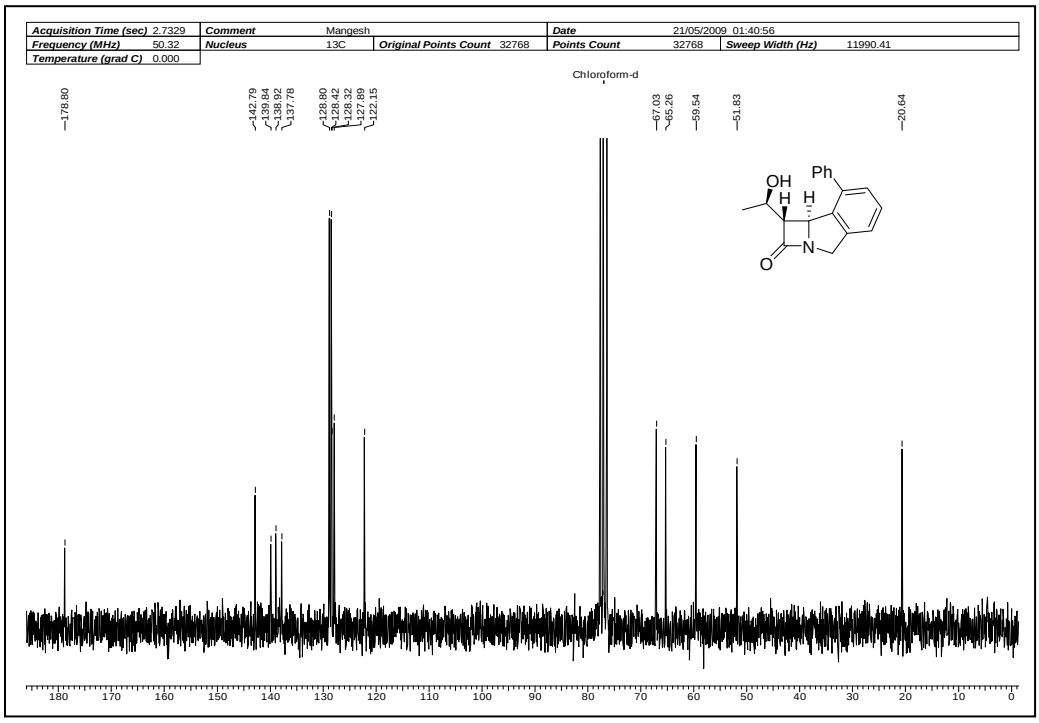
^{1}H NMR Spectrum of 82 in $CDCl_3$



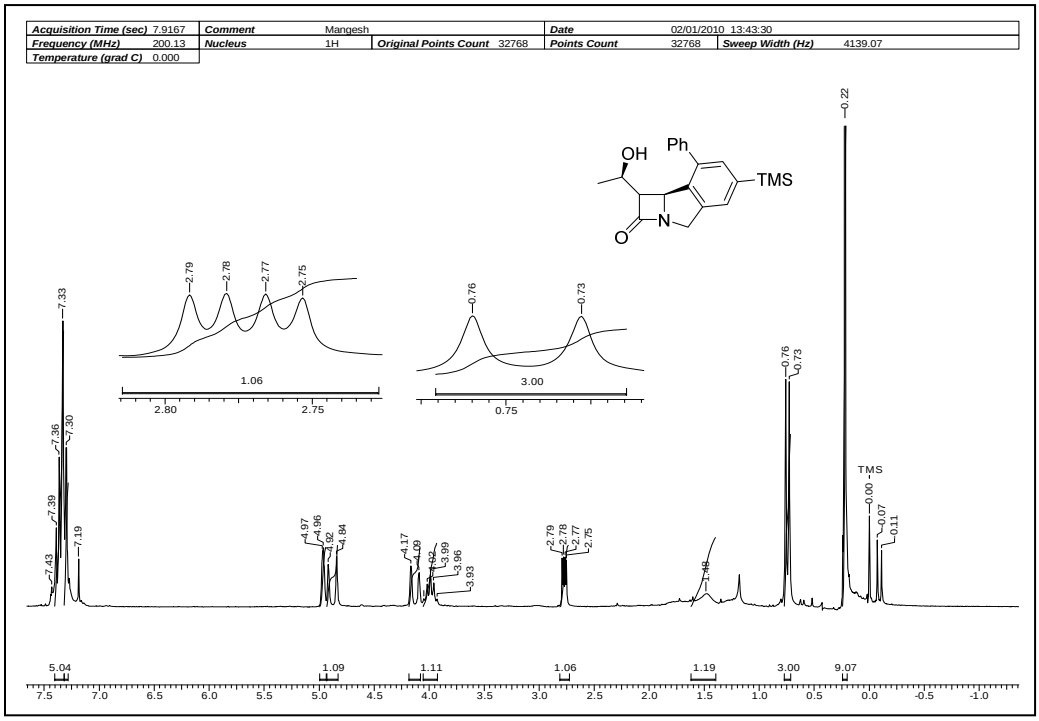
^{13}C NMR Spectrum of 82 in $CDCl_3$



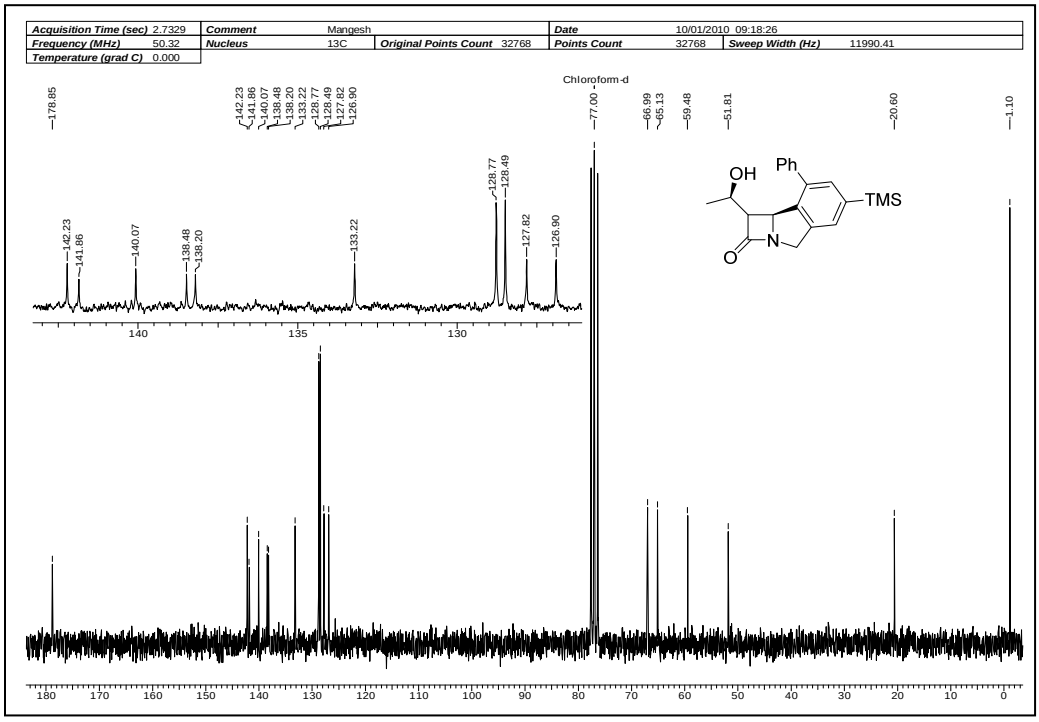
^{1}H NMR Spectrum of 83 in $CDCl_3$



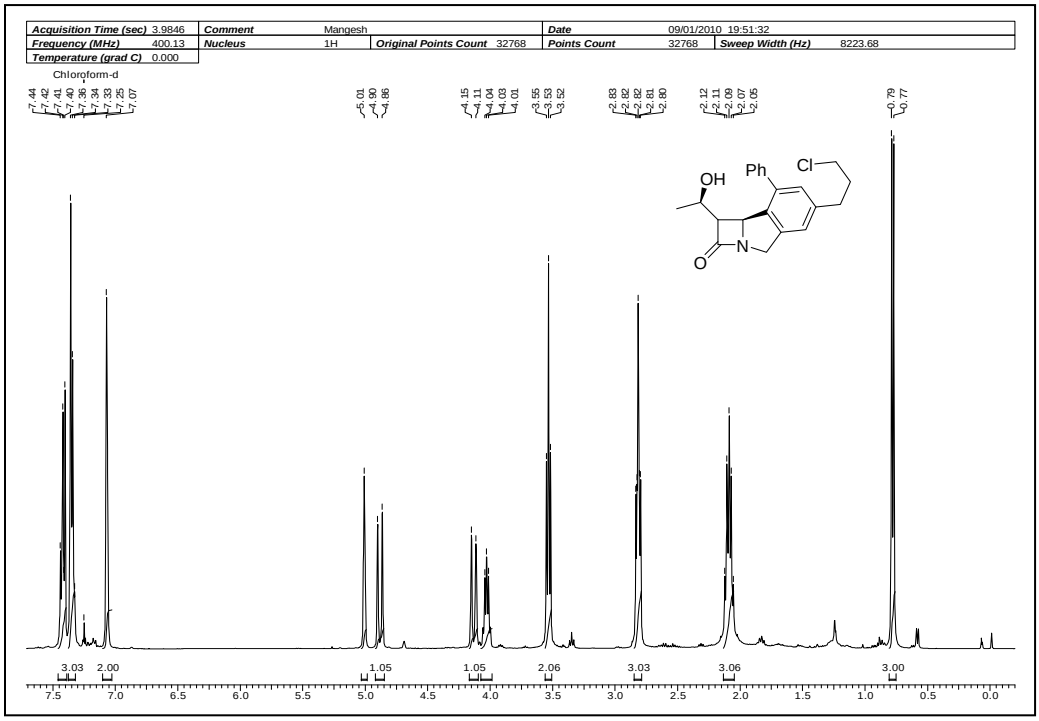
^{13}C NMR Spectrum of 83 in $CDCl_3$



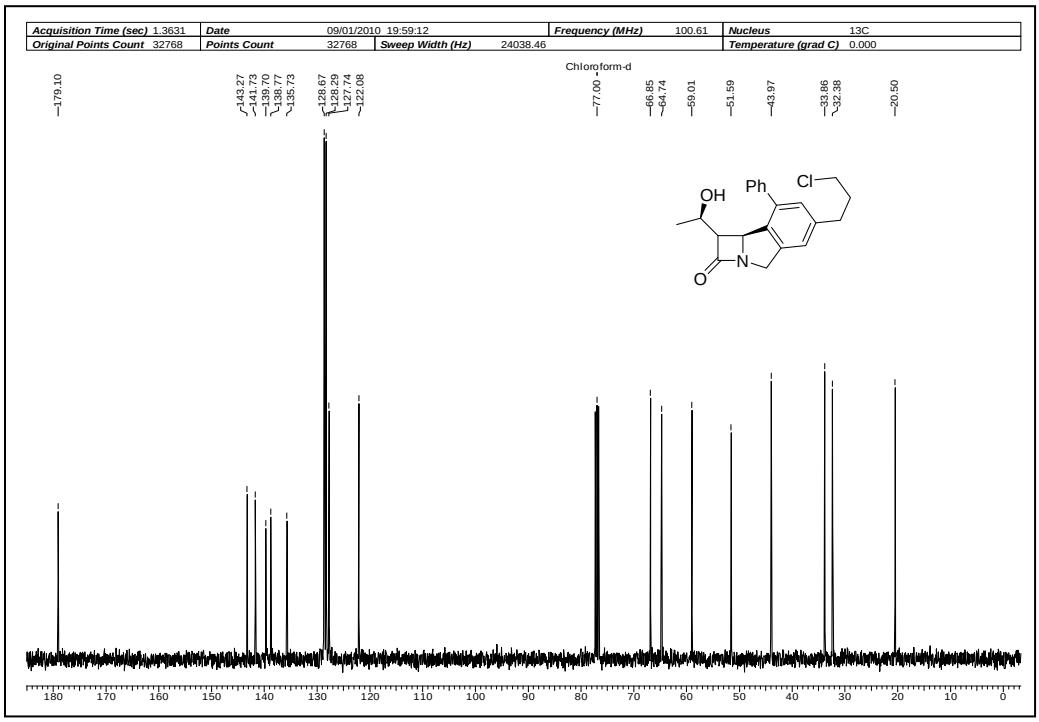
^{1}H NMR Spectrum of 84 in $CDCl_3$



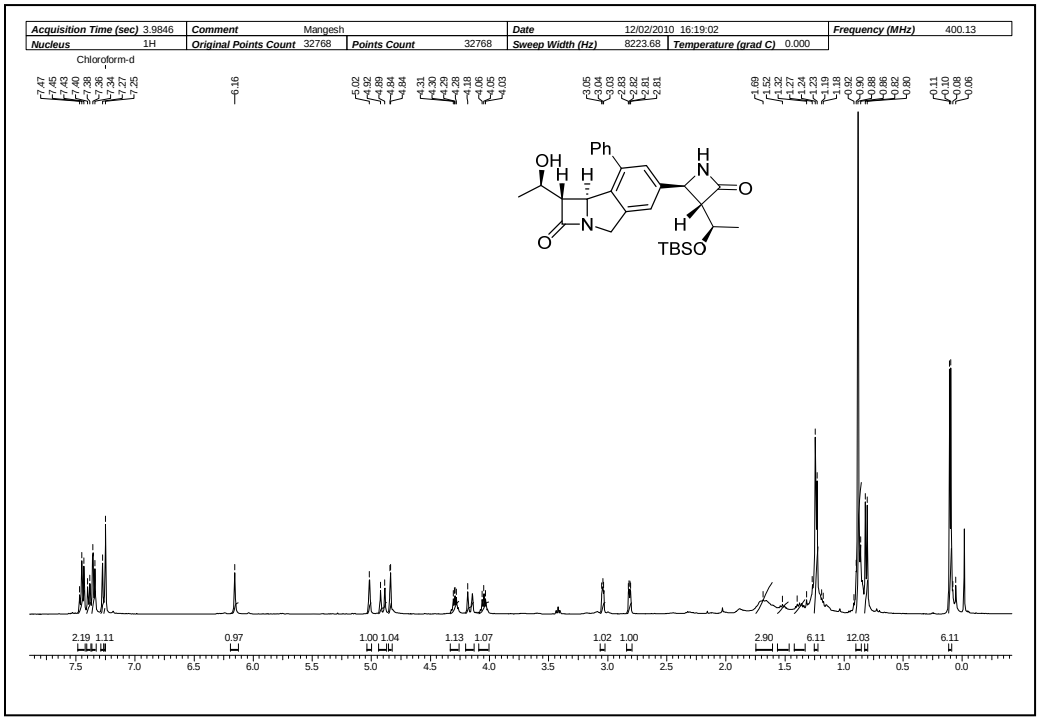
^{13}C NMR Spectrum of 84 in $CDCl_3$



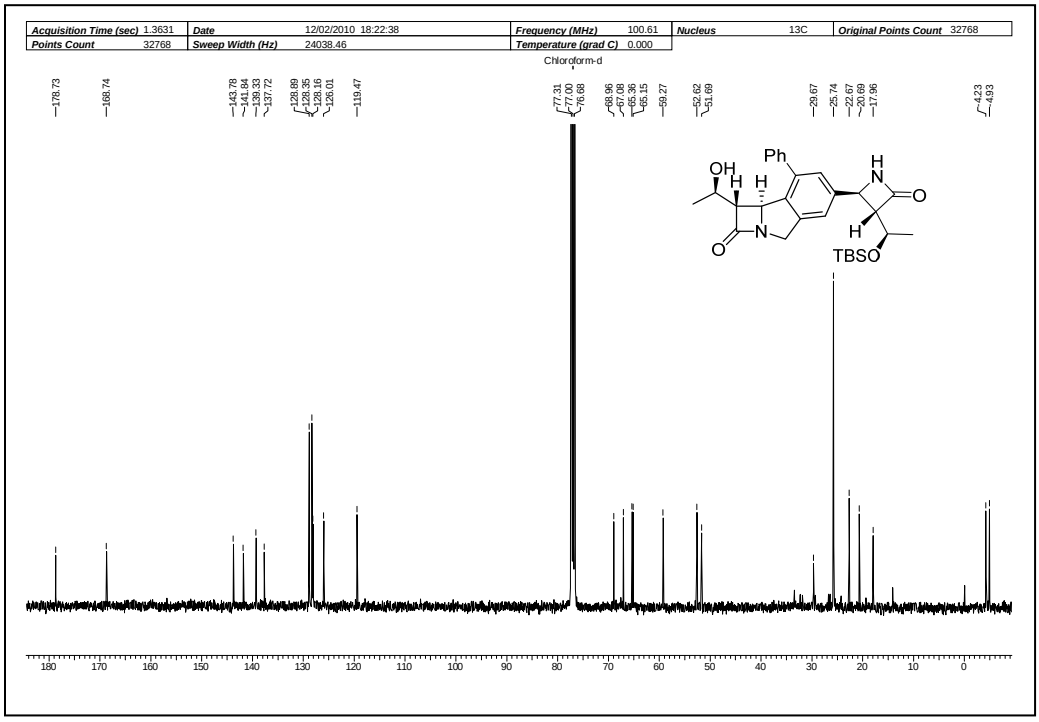
^{1}H NMR Spectrum of 85 in $CDCl_3$



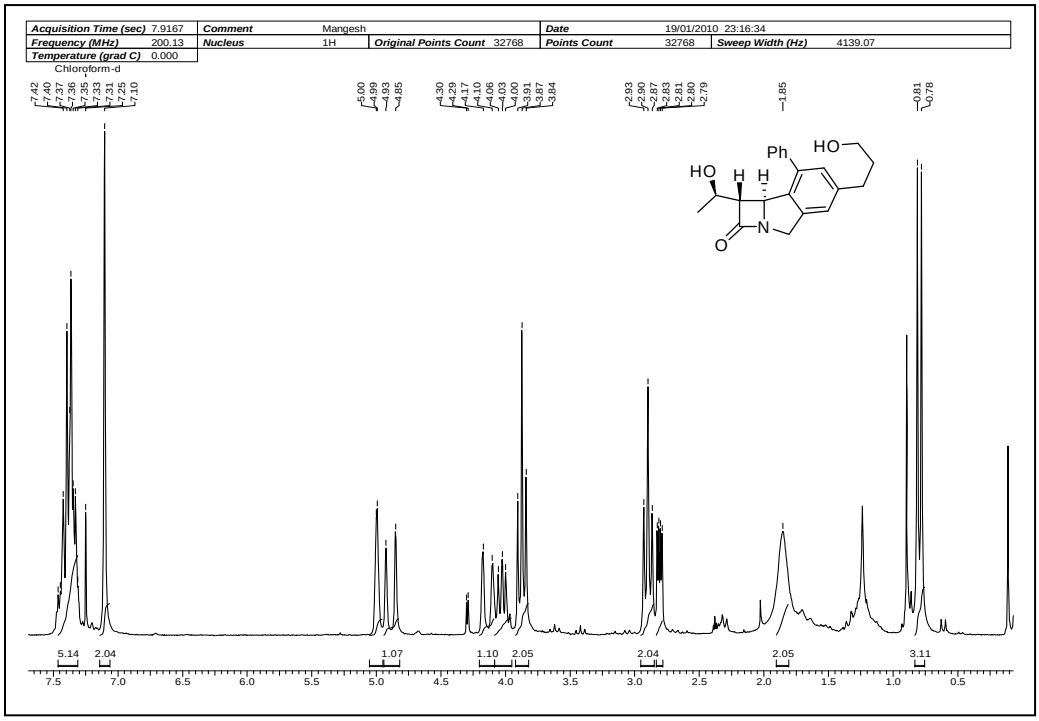
^{13}C NMR Spectrum of 85 in $CDCl_3$



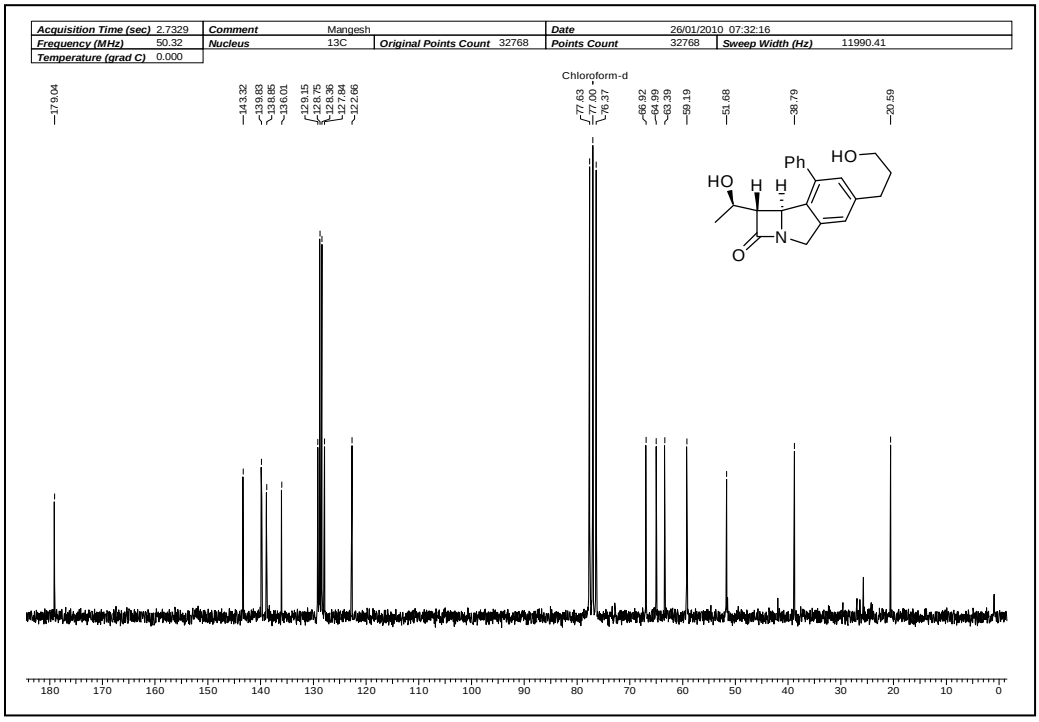
^{1}H NMR Spectrum of 86 in $CDCl_3$



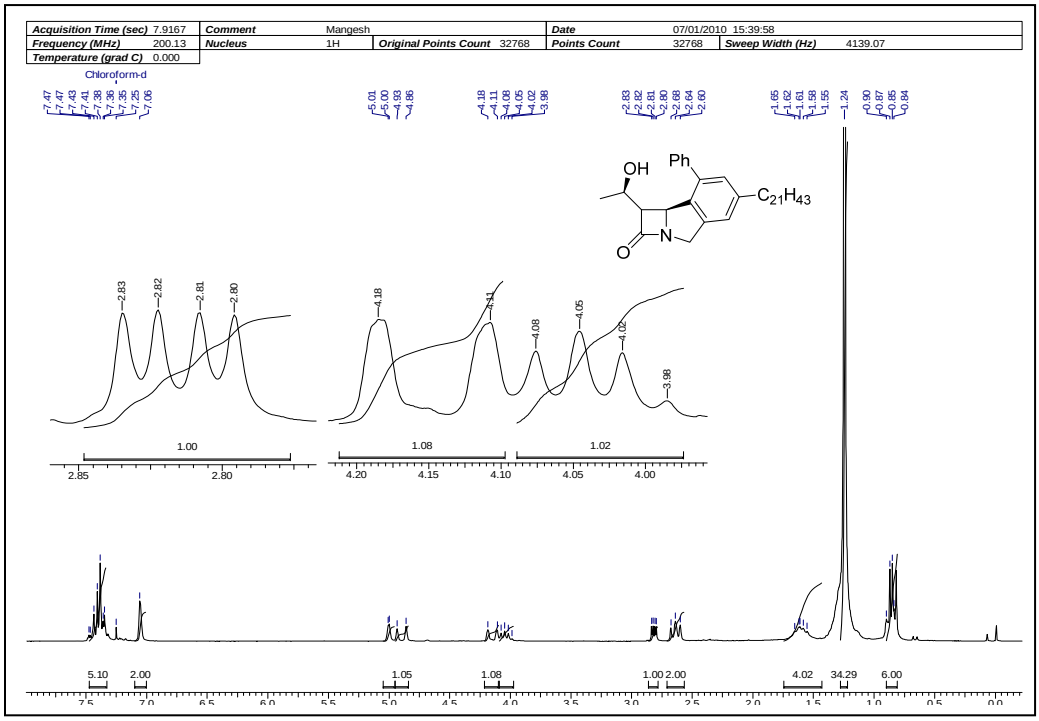
^{13}C NMR Spectrum of 86 in $CDCl_3$



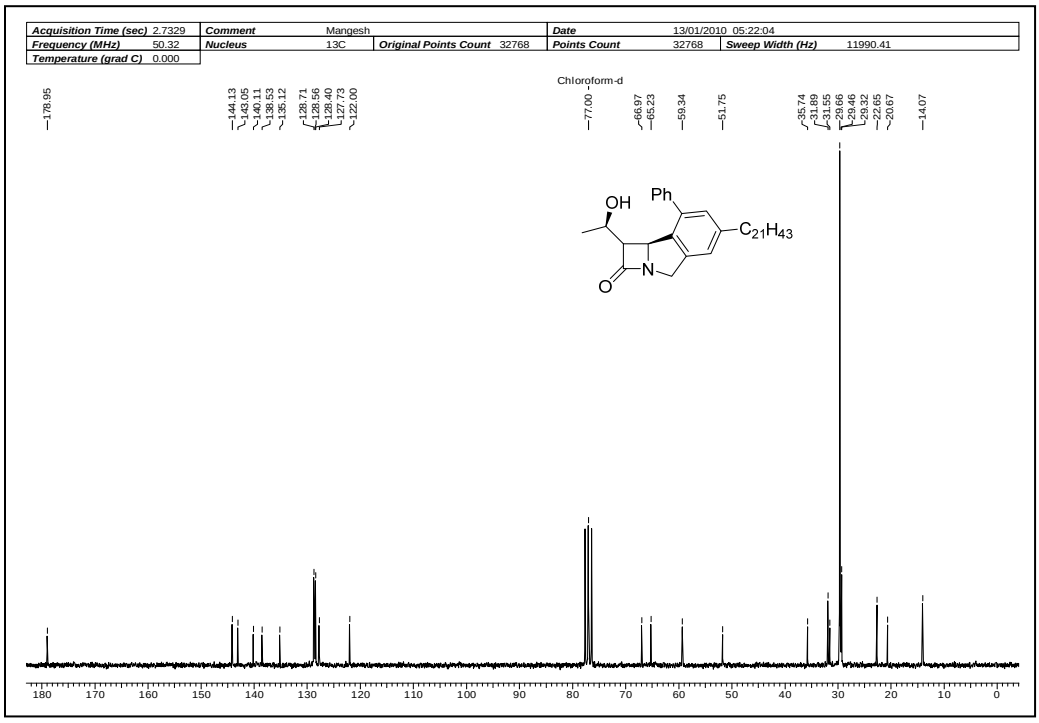
^{1}H NMR Spectrum of 87 in $CDCl_3$



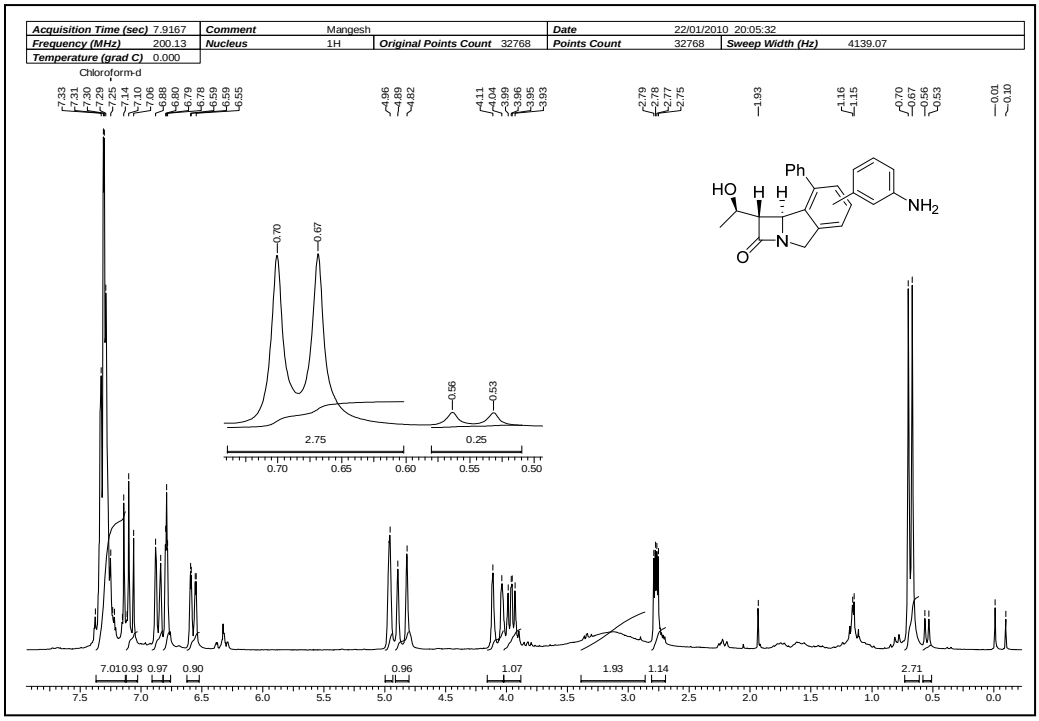
^{13}C NMR Spectrum of 87 in $CDCl_3$



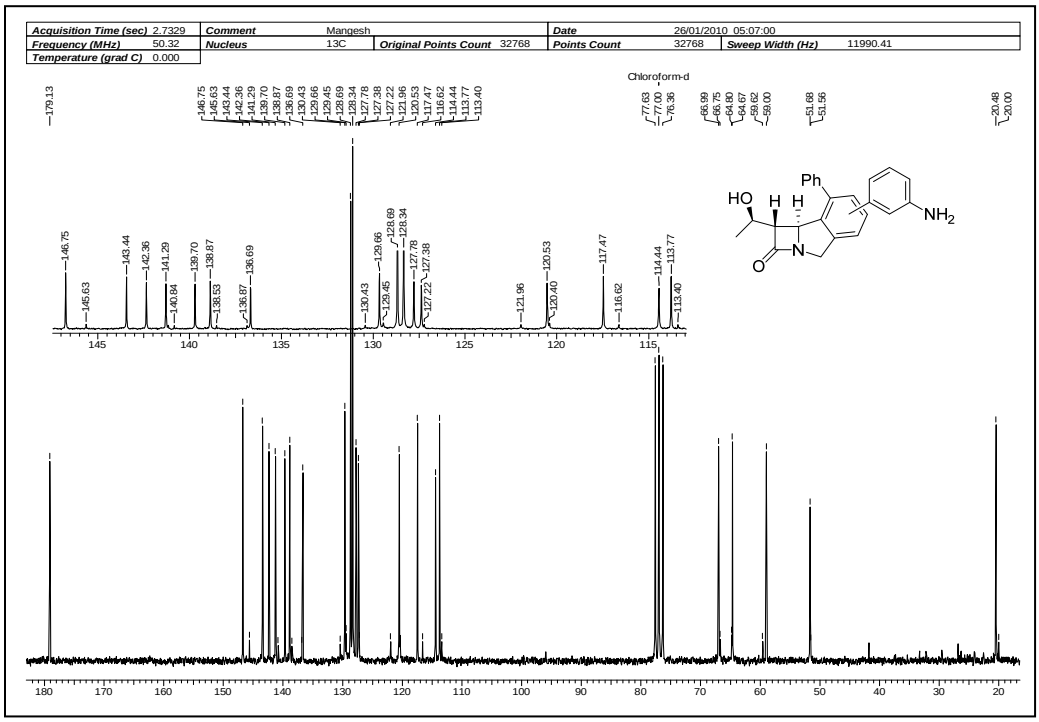
^{1}H NMR Spectrum of 88 in $CDCl_3$



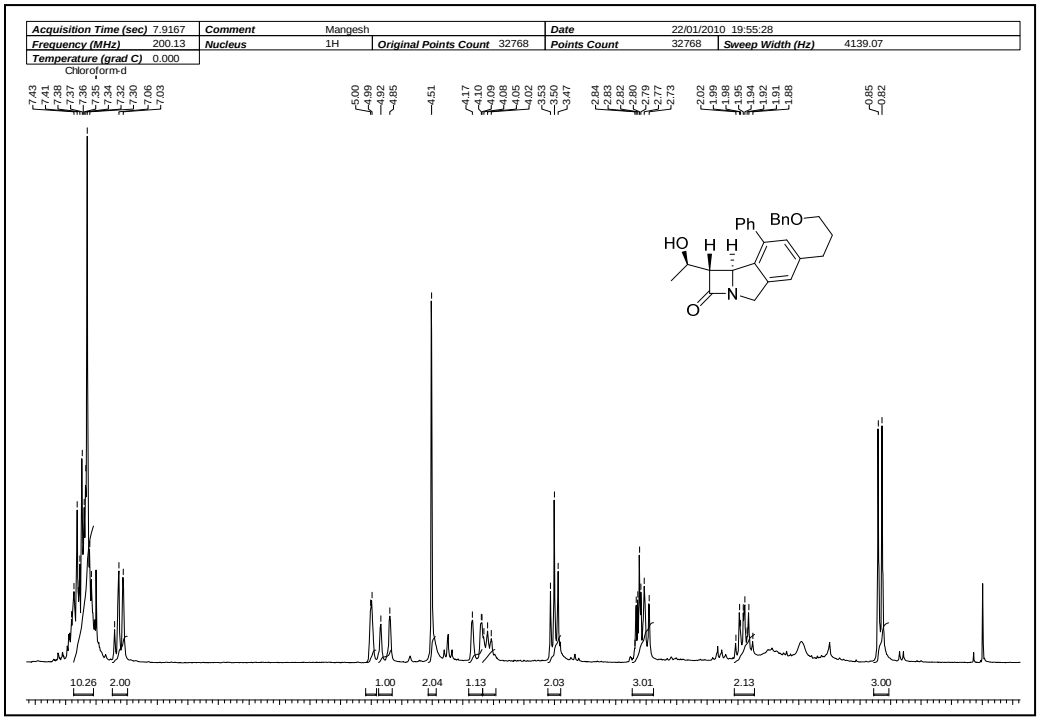
^{13}C NMR Spectrum of 88 in $CDCl_3$



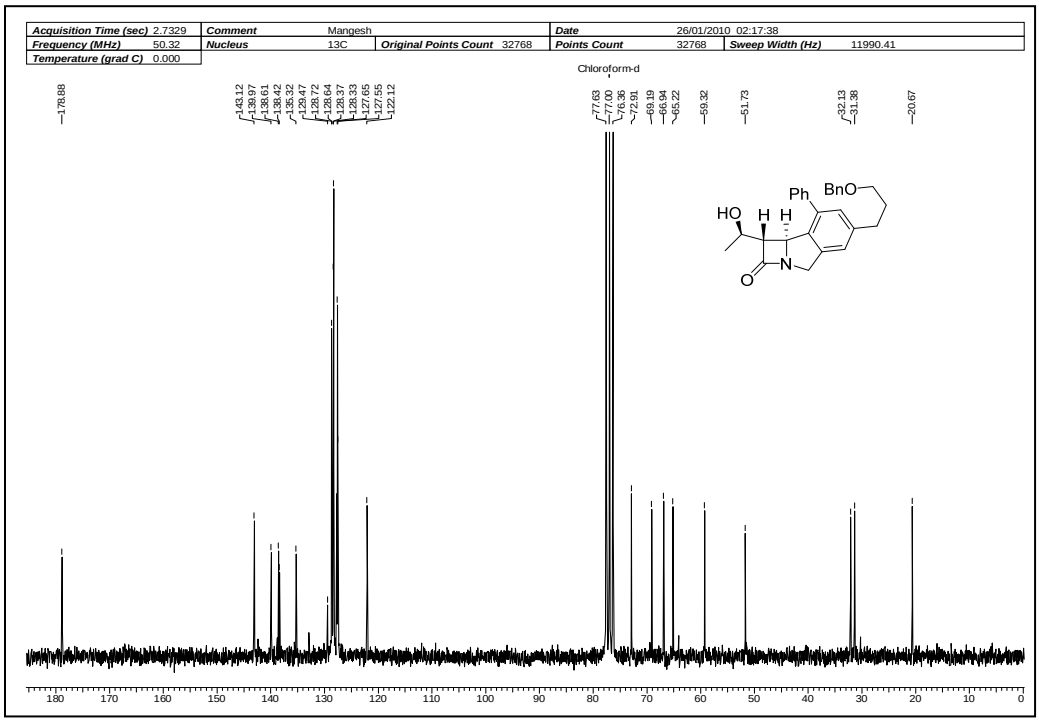
^{1}H NMR Spectrum of 89 in $CDCl_3$



^{13}C NMR Spectrum of 89 in $CDCl_3$



^{1}H NMR Spectrum of 90 in $CDCl_3$



^{13}C NMR Spectrum of 90 in $CDCl_3$

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CHAPTER IV:

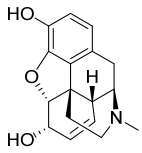
[2+2+2]-Cyclotrimerisation approach towards the synthesis of tri-/tetracyclic tetrahydroisoquinoline alkaloids.

4.1 Introduction:

4.1.1 Alkaloids

Alkaloids are low-molecular weight nitrogenous compounds and constitute as one of the major secondary metabolite families. The biosynthesis of a majority of the plant alkaloids utilizes mainly the amino acids - tyrosine, tryptophan and phenylalanine. The classification of alkaloids is based on their carbon-nitrogen skeletons. The common alkaloid ring structures include the pyridines, pyrroles, indoles, pyrrolidines, isoquinolines and piperidines.[1]

In nature, plant alkaloids are mainly involved in plant defense against herbivores and pathogens. The alkaloids are known for their wide range of pharmacological activities, which include analgesics, antimalarial, antispasmodics, for pupil dilation, and the treatment of hypertension, mental disorders and tumors, to name a few. Many of these compounds have been known and used as stimulants (nicotine, caffeine), pharmaceuticals (vinblastine), narcotics (cocaine, morphine) and poisons (tubocurarine).



morphine

Figure: 1

Morphine was one of the earliest alkaloids that was introduced by the German pharmacist Sertürner in 1806 and led the foundations to the field of plant alkaloid biochemistry. Quite interestingly, the structure of morphine was determined 150 years after its isolation. Quinine is another important alkaloid of the same time that has been widely used for the treatment of malaria. Indeed, even though its structure was unknown, quinine has served as an inspiration for the total synthesis. One of the first commercial dyes Move, has been prepared by Perking in the middle of the 19th century when he trying to synthesis quinine, the disconnections of which is based upon dividing the molecular formula. There are a wide variety of structural types of alkaloids, e.g. monocyclic, dicyclic, tricyclic and tetracyclic, as well as cage structures.

4.1.2. Monocyclic alkaloids.

Coniine, whose structure is based on piperidine, is highly toxic. It may be extracted from hemlock and it was used by the ancient Greeks for state executions Socrates being the most famous victim. On the other hand, nicotine, the main alkaloid constituent of tobacco, is based on the five membered pyrrolidine and six membered pyridine structures. It is without doubt the most well known alkaloid, and its calming effect, together with its addictiveness, has probably caused the death of more people in the world than any other compound. Epibatidine has a high analgesic potency, as stated above. Studies show it has potency at least 200 times that of morphine.[2] As the compound was not addictive and also did not suffer the effects of habituation, it was very promising to replace morphine as a painkiller. Unfortunately for its therapeutic uses, the therapeutic concentration is very close to the toxic concentration.

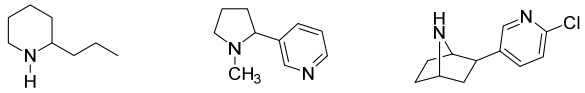


Figure: 2

4.1.3. Bicyclic alkaloids.

The tropane alkaloids are based on a 1,4 nitrogen bridged cycloheptane structure. Atropine is isolated from Belladonna plants, commonly known as "Deadly Nightshade". Atropine is widely used in medicine in doses of about 0.1 mg for its muscle relaxant properties. Thus, it is used as an antispasmodic including the dilation of the pupil by relaxing the eye muscles, and so assists eye treatment, and it is available for the treatment of organophosphate/nerve gas poisoning. Not surprisingly cocaine, which comes from the coca plant, has similar properties to atropine and, at one time, it was used as a local anesthetic, but is rarely used medically nowadays due to its toxic and addictive effects.

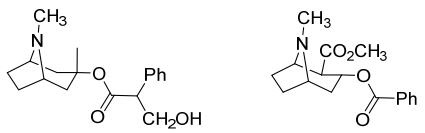


Figure: 3

There are a number of alkaloids which are derivatives of quinoline, isoquinoline and their hydrogenated analogues. Papaverine, an opium constituent, has antispasmotic properties and has also been used as an analgesic (Figure 4). Today it is used as a minor constituent usually with morphine to enhance the analgesic properties of a weaker drug such as aspirin.

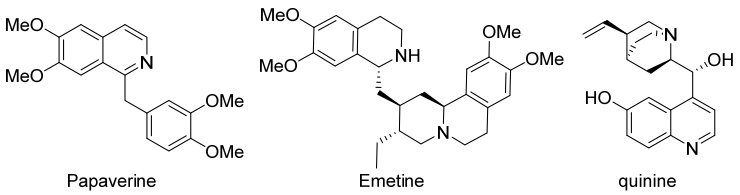


Figure: 4

Emetine is a derivative of tetrahydro isoquinoline which is isolated from the root of a S. African creeper. It has been used as an expectorant, but now replaced by codeine and other non alkaloid drugs such as ephedrine and diphenylhydramine. The most widely used of the quinoline alkaloids is quinine which is isolated from the bark of the cinchona tree. It is used as an antimalarial drug in 0.6 g doses. As a skeletal muscle relaxant it is used in 0.2 g doses to relieve nocturnal cramps and, at trace levels as a bitter flavouring in tonic water.

4.1.4. Polycyclic alkaloids:

The indole structure is also a common feature of alkaloid structures and can be identified as part of polycyclic alkaloids such as reserpine, vinblastine, and strychnine.

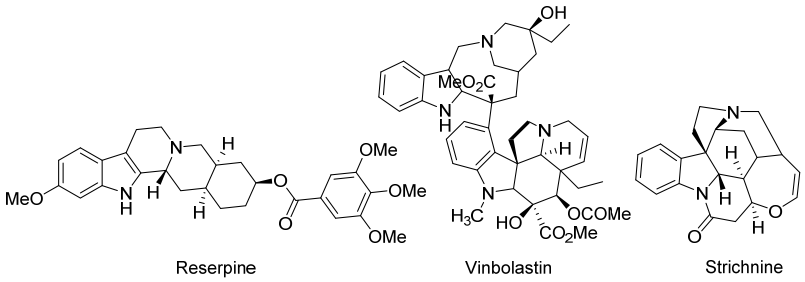


Figure: 5

Of this reserpine has the most important clinical use i.e. for the treatment of high blood pressure and as a tranquillizer. Vinoblastine and its analogues are used to treat acute leukemia, lymphomas and some solid breast and lung tumors.

Strychnine is very poisonous and was once used to control rodents, but it has been replaced by poisons which are less toxic to man.

Morphine is the most abundant opiate found in opium. It is one of the most potent alkaloids. It is a very effective pain killer and is used in medicine when the pain is absolutely intolerable. On the other hand, its acetyl derivative, heroin, is widely abused because of its short-term production of an overwhelming relaxing feeling of well-being. Both are highly addictive and, with prolonged use, produce very harmful physiological effects on the body.

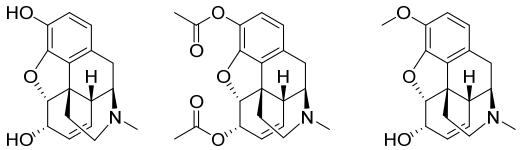


Figure: 6

The most commonly used of this class of opioids in medicine is codeine. It is a minor constituent of opium but is made by the methylation of morphine. It is a fairly good analgesic but causes constipation. Thus, about 8 mg is often added to either 0.4 or 0.5 g. tablets of aspirin or paracetamol. It is also used as a cough suppressant and as an antidiarrhoeal drug. It must be used with care since it is still addictive, although to a lesser extent than morphine.

4.1.5. Tetrahydroisoquinoline Alkaloids

The tetrahydroisoquinoline (TIQ) group is one of the prominent groups of alkaloids with nearly 60 isolated members and over a hundred analogs showing a wide range of biological activities.[3] The well-known CNS agents such as dopamine (DA), norepinephrine (NE) and epinephrine (E) are related structurally to the catecholamines (CA) belonging to the group of tetrahydroisoquinoline alkaloids. The compounds are biosynthesized in humans during alcohol intake, and these substances can then function as false adrenergic transmitters. By interfering with the adrenergic mechanism in the brain and in the periphery, biosynthesized TIQ alkaloids may be capable of altering mood and behavior. In this way, they may play a role during alcohol intoxication and in post intoxication states.

The tetrahydroisoquinoline ring system is present in numerous structurally diverse natural products exhibiting a wide range of biological and pharmacological activities such as antitumor, anti-microbial, anti-inflammatory, anti-HIV, and analgesic activities.[4] For example, tetrahydroisoquinoline alkaloid Et-743 (Trabectedin, Yondelis) has received considerable attention recently due to its potent *in vivo* activity. It shows greater anti-proliferative activity than taxol and is currently marketed in Europe and South Korea for the treatment of soft-tissue sarcoma, and is in Phase II/III clinical trials for the treatment of other cancer types.

The synthesis of simple 1-substituted tetrahydroisoquinoline derivatives is of great interest not only as alkaloids themselves but also as useful key intermediates in the synthesis of more complex alkaloids. This has stimulated the development of a number of methodologies aimed at the enantioselective synthesis of 1-substituted tetrahydroisoquinoline derivatives (Figure 8). [5]

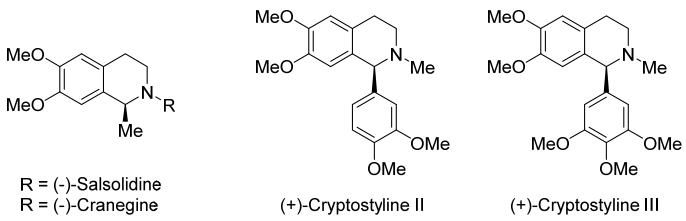
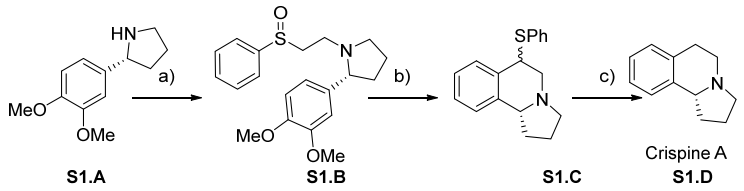


Figure 7: Tetrahydroisoquinoline derivatives

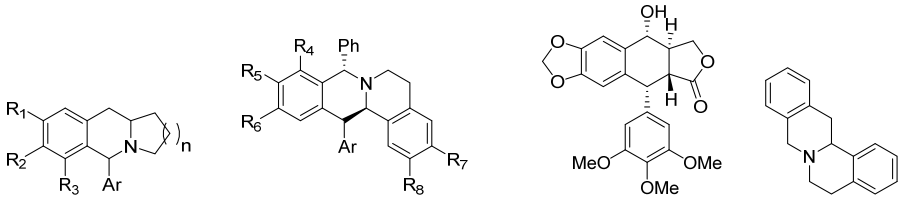
Coming to the tricyclic tetrahydroisoquinoline derivatives, crispine is one of the simple alkaloids with promising anti-cancer activity. There are several reports on the total synthesis of crispine. Following is the recent six step total synthesis of crispine reported by Chittiboyina and co-workers. The Michael addition of compound (+)-**S1.A** with a phenyl vinyl sulfoxide in the presence of triethylamine was successful and furnished an N-alkylated product (+)-**S1.B** in good yield. The Pummerer cyclization of compound (+)-**S1.B** was reacted under Lewis acidic conditions and yielded the Pummerer cyclization product (+)-**S1.C** with very good yields. The reductive radical elimination of the thiophenyl group using Bu_3SnH and cat. AIBN in toluene at refluxing conditions yielded target compound *R*(+)-crispine A in excellent yield (Scheme 7). [6]



Scheme1:

The benzo[b]indolizidine and benzo[b]quinolizidine ring systems represent the main structural subunits of a wide variety of highly condensed alkaloids which have been shown to display unique and interesting biological properties. When these fused heterocyclic models are further equipped with a pendant aromatic unit at the 5 or 6 position of the central nucleus, i. e. **F8.A** (n=1) or **F8.B** (n=2), these new skeletons constitute the framework of an array of tetrahydroprotoberberine (berbine) alkaloids as exemplified by the 8-phenyl derivatives of tetrahydrocoptisine **F8.C**, tetrahydropalmatine **F8.D**, and the 8-phenyl analogues of coralydine **F8.E** and O-methylcorytenchirine **F8.F** (Figure 8).

On the other hand, 6-arylbenzo[b]quinolizidine derivatives **F8.B** (n=2) have been recently suggested as promising alternative models to podophyllotoxin **F8.G**,which has long been known to display antitumor and mitotoxic activities but also known to have ill-fated toxic side effects. Indeed, such compounds in which the sp^3 C-2 atom is replaced by a sp^3 nitrogen atom embedded in the fused hydrocarbon rings, offer the double advantage of avoiding epimerization at this site and eliminating any deleterious effects attributable to the highly reactive nature of the γ-lactone moiety. [7]



F8.A n = 1
F8.B n = 2

F8.C R_4 = H, R_5, R_6, = R_7, R_8 = OCH_2O
F8.D R_4 = R_5 = R_7 = R_8 = OMe, R_6 = H
F8.E, **F8.F** R_5 = R_6 = R_7 = R_8 = OMe, R_4 = H

F8.G Podophyllotoxin

berbine

Figure 8

Podophylotoxin **F8.G** and related compounds, including α- and β-peltatin **F9.A** and **F9.B** (Figure 9) are a class of cyclolignan type compounds characterized by several vicinal oxygen functions on the dierently substituted aromatic moieties and/or

in the central carbocyclic unit. They have been obtained from the rhizoma resin of *Podophyllum peltatum* L[8] and have long been known to display anti-tumour [9] and mitotoxic activities.[10] However due to toxic side effects they have in most cases, failed to give satisfactory clinical trial results. In fact, the clinical utility of these compounds is compromised by the highly reactive nature of the fused γ-lactone moiety present in these molecules and by epimerization at C2 under physiological conditions. This has been shown to be deleterious to the therapeutic action by giving rise to products devoid of anti-tumour activity.[11] Consequently, a number of groups have carried out modifications at this stereogenic centre. New analogues which are incapable of loss of configurational integrity at the C2 centre, which encompass a broad spectrum of antineoplastic activities and thus overcome clinical limitations, have been explored.[12] In particular, ingenious variations have been proposed by several groups which have notably designed and synthesized a variety of analogues in which the sp^3 carbon is replaced by a sp^2 nitrogen, anticipating configurational integrity and avoiding any problems of epimerization. Paradoxically, despite the fact that they retain anti-tumour activities, to our knowledge, such modifications have been mainly confined to the aza-analogues of podophyllotoxin **F9.C–F9.F**,[13] (Figure 9).[14]

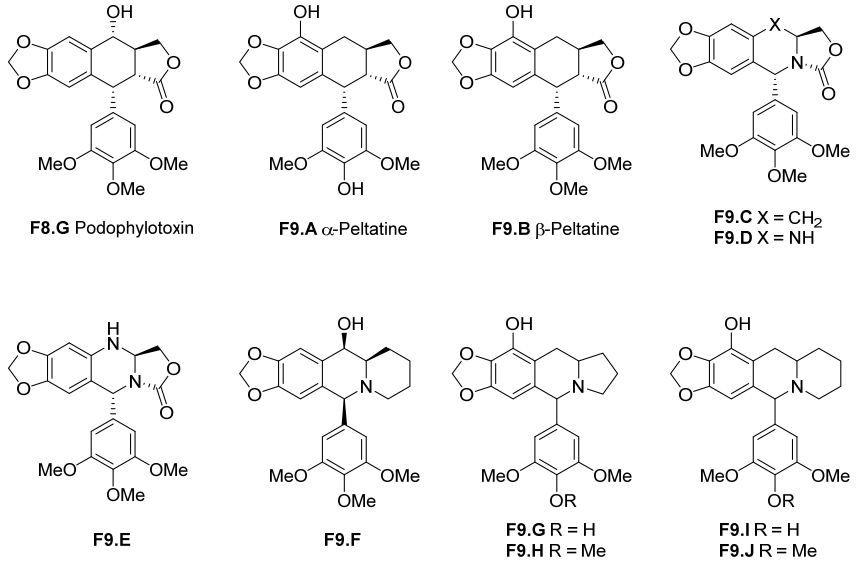
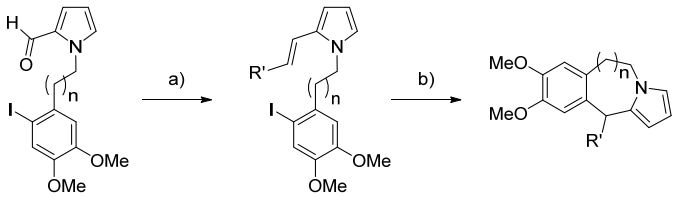


Figure 9

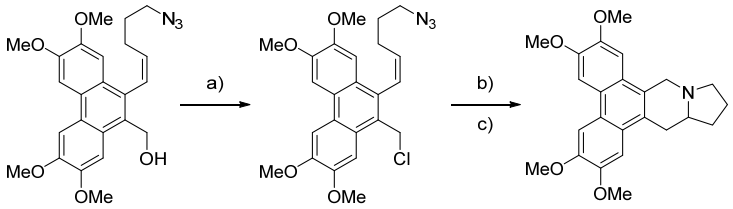
Lete and co-workers reported intramolecular carbolithiation reactions of 2-alkenylsubstituted N-benzylpyrroles **S2.Ba** and **S2.Bb** constitute an efficient route to pyrrolo[1,2-b]isoquinolines **S2.Ca** and **S2.Cb**, when the internal alkene bears an

electron-withdrawing group and a nonnucleophilic metalating agent, such as MesLi, is used. The procedure is applicable to the construction of six-, seven-, and eight membered rings, thus, opening new routes to benzazepines and benzazocines. Similarly, the 6-exocarbolithiation of 2-alkenylpyrrolidines takes place with complete diastereoselectivity, allowing the synthesis of enantiomerically pure hexahydropyrrolo[1,2-b]isoquinolines in high yields.[15]



Scheme 2: a) Ph_3P=CHR', CH_2Cl_2, reflux b) MesLi, –105 °C, TMEDA

Pearson and Walavalkar reported the synthesis of tylophorine **S3.C** using a method which represents a new disconnection for this pentacyclic alkaloid in that the indolizidine ring was assembled in one step from a 9,10-disubstituted phenanthrine. Azid **S3.A** was converted to the benzylic chloride **S3.B** in one operation using Meyers' method. Heating **S3.B** in a sealed tube at 120 °C produced an iminium ion which was reduced with methanolic sodium borohydride to afford the benzolndollzidlne **S3.C** in good yield.[16]

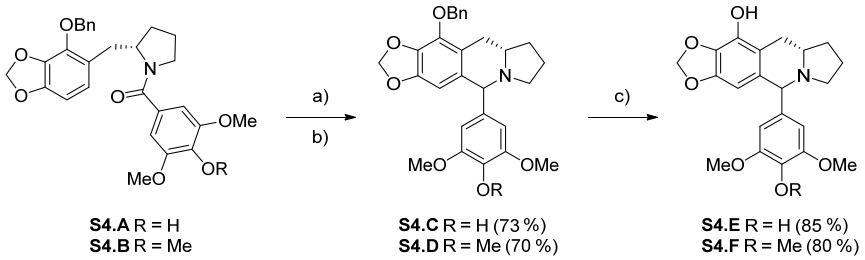


Synthesis of (±)-Tylophorine

Scheme3: a) MsCl, 2eq 2,6-Lutidine, 2eq LiCl DMF, 0 °C b) C_6D_6, 120 °C, c) 6 eq $NaBH_4$, MeOH,

Couture et al. reported the synthesis of the benzoindolizidine and quinolizidine analogues of α- and β-peltatin by different synthetic routes involving Bischler-Napieralski cyclization as the key step. Thus constitutes suitably substituted N-acyl-2-

arylmethylpyrrolidine and -piperidine derivatives. Compounds **S4.A**, **S4.B** were then subjected to Bischler-Napieralski conditions by standard treatment with phosphorus



Scheme 4: a) $POCl_3$, Toluene, heat b) $NaBH_4$, MeOH, 0 °C; c) Pd/C, $HCOONH_4$, MeOH, Heat

oxichloride ($POCl_3$) in toluene at reflux and subsequent reduction with sodium borohydride ($NaBH_4$) in methanol (Scheme 6). This afforded the cyclized products **S4.C** and **S4.D**, in 73% and 70% yield respectively, as a mixture of diastereomers in the ratio 10:1. Final removal of the benzyl protecting group of the major isomers delivered the benzoindolizidine analogues of α-and β-peltatin **S4.E** and **S4.F** with very acceptable yields.[17]

4.1.6 N-Fused Tetrahdyo Indoloisoquinoline alkaloids:

The indoloisoquinoline alkaloids are tetracyclic condensed heterocyclic compounds. The *N*-fusion of indole and isoquinoline units leads to two possible structural units (A and B, Figure 10). Whilst very few natural products having the structural unit A are known, the structural unit B is an unprecedented one and there are only two reports on the synthesis of corresponding derivatives.

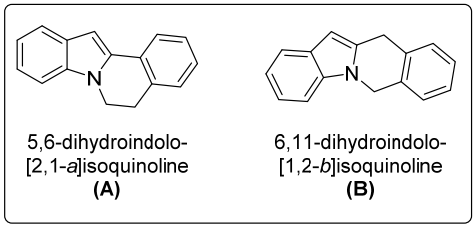
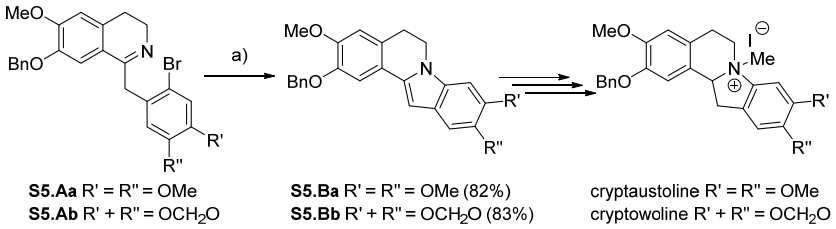


Figure 10.

In 2000 Kazuhiko Orito *et al*.,[18] reported a formal synthesis of cryptaustoline and cryptowoline alkaloids. The key reaction that has been studied is the application of cyclization on 7-benzyloxy-3,4-dihydroisoquinoline. **S2.Aa** and **S2.Ab** were heated

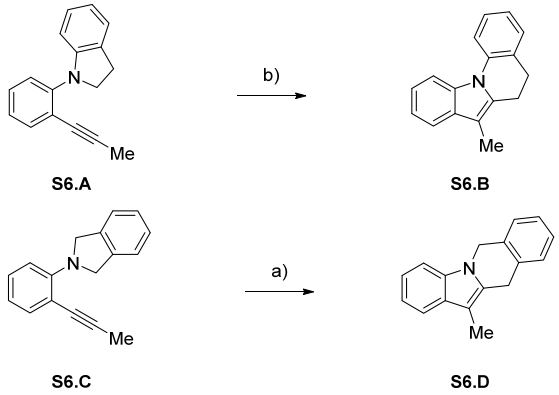
in the presence of 2 mol equiv of K_2CO_3 in boiling DMF for 3 days, gave 5,6-dihydroindolo[2,1-*a*]isoquinolines **S5Ba**, and **S5.Bb** quantitatively (Scheme 7).



Synthesis of dibenzopyrrocoline Alkaloids Cryptaustoline and Cryptowoline

Scheme 5: a) K_2CO_3, DMF, reflux N_2, 3d.

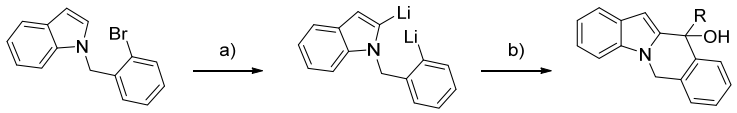
Nobuharu Iwasawa *et al*.[19] have developed a method for the preparation of *N*-fused tricyclic indole derivatives through a tandem [1,2] Stevens-type rearrangement/1,2-alkyl migration reaction through the intermediate metal-containing ammonium ylides generated by the cycloaddition of a tertiary amine to a metal coordinated alkyne. $[W(CO)_6]$ and $[ReBr(CO)_5]$ have been employed as the catalysts. Thus the treatment of alkynes **S6.A** and **S6.C** $[W(CO)_6]$ under photolysis led to the formation of tetracyclic indole derivatives **S6.B** and **S6.D**, respectively, in good yields.



Scheme 6: Reaction conditions: a) $[W(CO)_6]$ (10 mol %),5 Å M.S.,toluene, hυ, room temperature. b) 1 equivalent $[W(CO)_6]$.

In 2007, Sanz and co-workers reported a simple method for the synthesis of N-fused indoloisoquinoline derivatives of type B *via* double lithiation of ***N***-benzylindole derivatives and subsequent addition to an ester. Thus, as shown in Scheme 3, a wide range of aliphatic or aromatic carboxylic esters were useful electrophiles for the

trapping of dianion **S7.B**, and dihydroindolo[1,2-*b*]isoquinolin-11-ol derivatives **S7.C,** which were isolated in good yields.[20]



S7.A **S7.B** **S7.C**

Scheme 7: a) *t*-BuLi (3.5 equiv), TMEDA (3.5 equiv), Et_2O, –78 to 0 °C. b) i. RCO_2Et, –78 to 20 °C. ii. H_2O

Thus, a brief examination of literature related to the *N*-fused indoloisoquinoline derivatives revealed that amongst two structural types A and B which mainly vary at where the indole C2 is positioned, the structural type B is unprecedented and there are very few methods reported for their synthesis. Importantly, their biological activity has been not yet been examined. Considering these factors and founded upon the suitability of [the isquinoline core] construction *via* cyclotrimerization, we conceived this as a potential template around which a focused library could be synthesized.

4.2 Present work:

In the continuation of the ongoing research interest in transition metal mediated cyclotrimerization reactions and their utilization in synthesizing biologically active molecules in our laboratory, the idea of implementing the cyclotrimerization reaction for the construction of tetracyclic isoquinoline framework was conceived. Considering the fact that the structural type B is unprecedented in natural products as well as the fact that no information about the biological activity of this type compounds we have planned to execute a simple approach for the synthesis of type B compounds.

The proposed strategy for the synthesis of compounds of type **F10.G/F10.H** has its own origins from the concepts of target cum flexibility oriented synthesis. As mentioned above, a route will be highly effective if it involves the coupling of different structural units in sequence without involving any intermediate functionalization.

Keeping the substrate flexibility at the penultimate stages, the isoquinoline skeleton been disconnected by employing the cyclotrimerization transform. Since the trimerization will be the penultimate reaction, and since that various alkynes are commercially available the synthesis is easy, this approach will lead to the synthesis of tricyclic isoquinoline alkaloid library rapidly (figure 11).

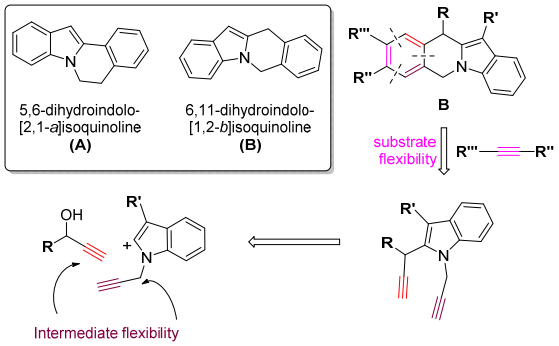


Figure 11: Two possible types of *N*-fused indoloisoquinolines and & proposed Retrosynthetic plan for **Type B** Structural Unit

4.2.1 Result and Discussion:

Our journey in this direction started with choosing the diynes **F12.A** and **F12.C** as simple targets to be synthesized. As shown in Scheme 12, the synthesis of diynes **F12.A** and **F12.C** was planned *via* the Friedel-Crafts type C2-alkylation of N-propargyl-3-methyl indole. The alkynol **F12.B** is commercially available whereas the alynol **F12.D** is synthesized by addition of the alkynyl magnesium bromide to benzaldehyde.

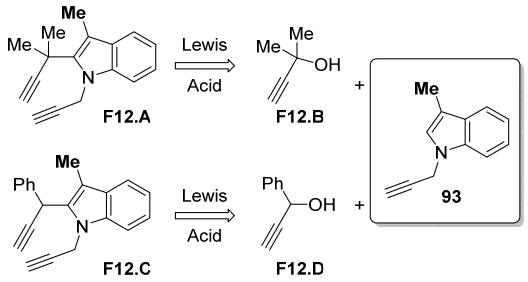
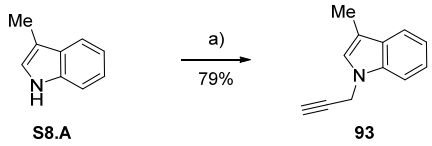


Figure 12: Retrosynthetic plan for making diyne precursors

Coming to the synthesis of indole partner **93**,[21] the propargylation reaction needs a special mention. The attempted propargylation with NaH in solvents like THF or DMF resulted in a complex mixture and the requisite product **93** was isolated in poor yields. However, when switched to DMSO, the reaction proceeded smoothly and provided the N-propargylated indole **93** in very good yields (scheme 8). Appearance of the triplet at 2.40 ppm with coupling constant 2.5 Hz for the propargylic proton and doublet at 4.83 ppm for the methylene in the ^{1}H-NMR and additional triplet at 35.4 and acetylenic carbons at 73.1 and 78.1 ppm in ^{13}C-NMR accounted for the newly introduced alkyne in compound **93.**



Scheme 8: a) Propargyl bromide, NaH. DMSO, 0 °C to rt

The C2 alkylation of indole **93** was next attempted initially with the alkynol **F12.A**. However, a wide range of Lewis acids employed the alkylation reaction met with a failure. A similar observation was made with the alkynol **F12.C** also. These initial failures with simple alkynols have prompted us to revisit the design of the alkynol. Since the C2 alkylation of indole is not as facile as that of C3, we need to

apply the alkynols where the resulting carbocation is well stabilized. Considering this, we have switched to aryl groups having a methoxy group at the para-position. By virtue of the p-donation from the methoxy oxygen, the generation of a carbocation at the benzylic position, as well as its stabilization in alkynol, is facile. Considering this, we have designed the following two alkynols **94** and **95** as suitable coupling partners.

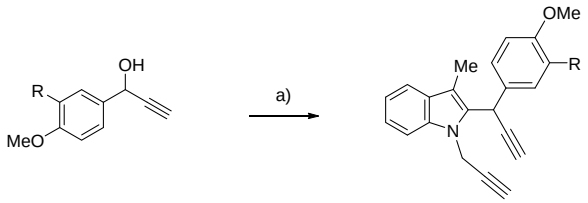
Our journey in this context started with the preparation of alkynol **94** and **95**, from 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde respectively. The acetylene Grignard reaction was performed [Grignard reagent was generated *in situ* by passing the acetylene gas into a solution of *n*-BuMgCl in THF] on p-methoxy benzaldehyde and 3,4-dimethoxybenzaldehyde to provide the **94** and **95** respectively in good yields (Scheme 9).

The structure of the products **94** and **95** was confirmed with the help of the spectral and analytical data. The resonance of hydroxyl proton of **94** resonated at δ 2.28 as a broad singlet and the presence of acetylenic proton as a doublet at 2.65 and 2.66 with a coupling constant 2.3 Hz in the ^{1}H-NMR spectra of compounds **94** and **95** confirmed their assigned structures

Scheme 9: a) *n*-BuMgCl, THF, 0 °C to rt

The presence of acetylenic singlet carbons at 83.7 and 83.6 ppm in ^{13}C-NMR were in accordance with structure **94** and **95** respectively. Mass [*m/z* 185.34 for $(M+Na)^{+}$] for the **94** and Mass [*m/z* 215.24 for $(M+Na)^{+}$] for the compound **94** and elemental analysis further confirmed the structures.

As expected, the alkylation[22] of indole **93** with the the alkynols **94** and **95** proceeded smoothly by employing catalytic amounts of p-TSA and provided **91** and **92** respectively (scheme 10).



Scheme 10: a) PTSA, DCM, rt, 15 min

Synthesized diynes **91** and **92** were characterized by extensive NMR spectral data analysis. Appearance of the doublets at 2.81 and 2.78 ppm with a coupling constant 2.4 Hz for the propargylic methylene protons in the intermediates **91** and **92** respectively in ^{1}H NMR spectra and an additional triplet at 33.7 and 33.7 ppm in ^{13}C-NMR accounted for newly introduced alkyne in compound **94** and **95** respectively. The structure was further proved by mass [*m/z* 336.36 for $(M+Na)^{+}$] for **91** and Mass [*m/z* 366.46 for $(M+Na)^{+}$] for the compound **92** and elemental analysis further confirmed the structures.

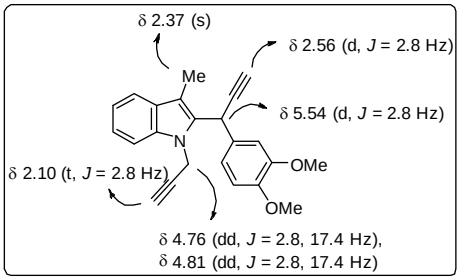


Figure 13: ^{1}H-NMR of Compound **92**

Having both the requisite diynes in hand, the stage was set for their trimerization. The optimization reactions have been carried out by employing biphenyl acetylene as the substrate. Unlike both the previous systems (nucleosides and beta-lactams), in the present case, both the Ru- and Rh-catalysts were found to be ineffective. The $CpCo(CO)_2$ catalyst was found to be the best for this purpose. The optimized conditions involve heating a mixture of diyne and alkyne and 20 mol% catalyst $CpCo(CO)_2$ in 1,4-dioxane in the presence of PPh_3 at 130 ºC for about 12 h (scheme 11).

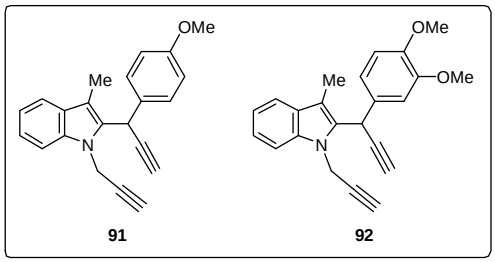
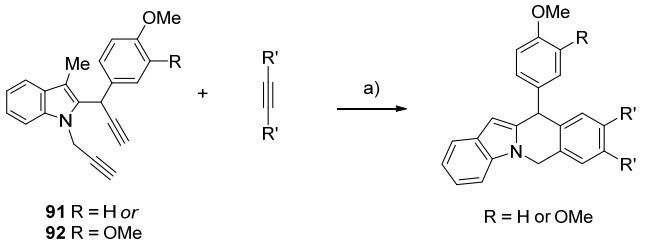


Figure 14: Diyne Precursors



Scheme 11: $CpCo(CO)_2$, 1,4 dioxane, PPh_3, 130 °C, 12h

In the ^{1}H NMR spectrum of **96**, the characteristic CH of the newly formed 1,2,3,4-tetrahydroisoquinoline ring appeared at δ 5.57 (s) and benzylic methylene hydrogens appeared at 5.18 (d) and 5.40 (d) respectively with a coupling constant 15.7 Hz (figure 13). In the ^{13}C NMR spectrum of **96** methylene carbon appeared as triplet at δ 44.5 ppm. Similarly, formation of the trimerized product **96** was evident from the absence of the propargyl proton (–C≡CH) and the appearance of additional twelve proton peaks in the aromatic region (6.75−7.58 ppm). Mass [m/z 514.36 for $(M+Na)^+$] and elemental analysis further confirmed the assigned structure of compound **96**.

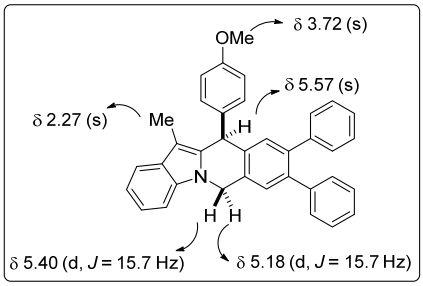


Figure 15: Characteristic peaks of compound **96**

Next, the scope of the trimerization reaction of diynes **91** and **92** was explored in a wide range of symmetric and terminal alkynes. 2-Butyne-1,4-diol, 4-octyne, biphenyl acetylene, and dimethyl acetylenedicarboxylate, were explored as the representative symmetric disubstituted alkynes for the trimerization reactions. Propargyl alcohol, homopropargyl alcohol have been employed as representative terminal alkynes.

The reactions with all the symmetric internal alkynes proceeded smoothly. On the other hand, the cyclotrimerization reactions of **91** and **92** with the terminal alkynes, although are clean, led to good yields but resulted in an inseparable regiomeric mixtures.

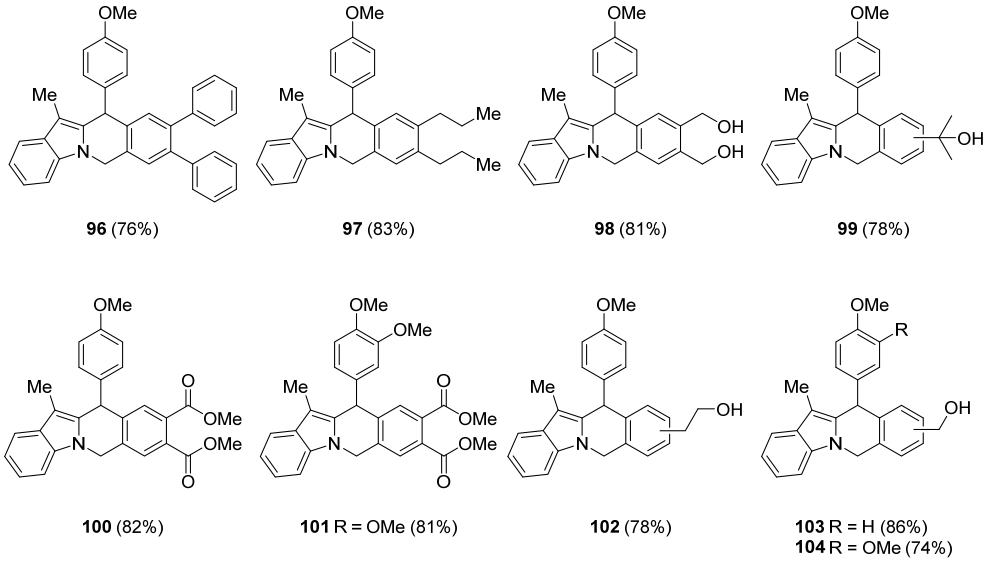


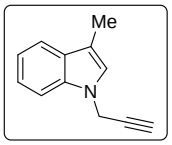
Table 1: Scope of cyclotrimerization on diynes **91** and **92.**

4.2.2 Conclusion:

In conclusion, a [2+2+2]-alkyne cyclotrimerization reaction was employed successfully to construct the central tricyclic-isoquinoline alkaloids. The introduction of different substituents to the structure was achieved easily by simply employing a suitable alkyne at the final event of bicyclo-annulation, and thus allowed the facile preparation of prepare a focused library of tetrahydroisoquinoline alkaloids like small molecules.

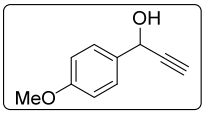
4.3 Experimental:

3-Methyl-1-(prop-2-yn-1-yl)-1H-indole **(93):**



3-methyl-indol **S8.A** (4.0 g, 30.5 mmol) was taken in dry DMSO under argon. Propargyl bromide (2.8 mL, 36.6 mmol), and NaH (0.9 g, 36.6 mmol) were added subsequently at 0 °C and stirred for 4 h at room temperature. The reaction was quenched with ice cold water. After usual workup and concentration, the crude product was purified by column chromatography (10% ethyl acetate in light petroleum) to obtain **93** as a dark brown liquid yield: 79%; IR ($CHCl_3$) ν: 2933, 2544, 1613, 1511, 1469, 1374, 1250, 1226, 1129, 1163, 1017, 858, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (d, J = 1.0 Hz, 3H), 2.40 (t, J = 2.5 Hz, 1H), 4.83 (d, J = 2.5 Hz, 2H), 7.00 (d, J = 1.0 Hz, 1H), 7.17 (ddd, 1.3, 6.9, 7.8 Hz, 1H), 7.29 (dt, J = 1.3, 6.9 Hz, 1H), 7.33 – 7.42 (m, 1H), 7.62 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.5 (q), 35.4 (t), 73.1 (d), 78.1 (s), 109.1 (d), 111.4 (s), 119.2 (d, 2C), 121.8 (d), 124.8 (d), 129.2 (s), 136.1 (s) ppm; ESI-MS (*m/z*): 192.16 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{12}H_{11}N$ C, 85.17; H, 6.55; N, 8.28% Found: C, 85.06; H, 6.48; N, 8.32%.

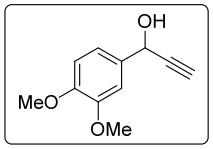
1-(4-Methoxyphenyl)prop-2-yn-1-ol (**94**):



Mg (4.2 g, 175 mmol) was flame dried in a two neck R.B. flask fitted with a reflux condenser and cooled to room temperature in dry argon atmosphere. Dry THF (150 mL) was introduced followed by a few crystals of iodine. Half the total volume of *n*-BuCl (18 mL, 175 mmol) was added and the contents were refluxed till the generation of Grignard reagent. The reaction temperature was brought to rt and the rest of *n*-BuCl was added. Stirring continued at room temperature till all the magnesium was consumed. Then the reaction mixture was cooled to 0 °C and dry acetylene gas was bubbled into it for 15 min. Compound **S6.A** (10 g, 73.5 mmol) in THF (50 mL) was added at 0 °C and stirred for 20 min. The reaction was quenched with saturated NH_4Cl solution, diluted with water and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated and purified on silica gel (10% ethyl acetate in light petroleum) to get alkynol compound **92** as a yellowish thick liquid: 75%; mp: 113 °C; IR ($CHCl_3$) ν: 3621, 3020, 2935, 1600, 1518,

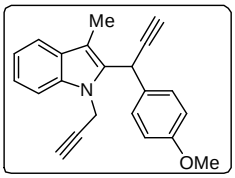
1425, 1218, 1040, 930, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (br.s, 1H), 2.65 (d, J = 2.3 Hz, 1H), 3.80 (s, 3H), 5.40 (dd, J = 1.9, 5.6 Hz, 1H), 6.90 (ddd, 2.1, 2.9, 8.8 Hz, 2H), 7.46 (ddd, 2.1, 2.9, 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3 (q), 63.9 (d), 74.6 (d), 83.7 (s), 114.0 (d, 2C), 128.0 (d, 2C), 132.4 (s), 159.7 (s) ppm; ESI-MS (*m/z*):185.34 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{10}H_{10}O_2$ C, 74.06; H, 6.22% Found: C, 74.12; H, 6.35%.

1-(3,4-Dimethoxyphenyl)prop-2-yn-1-ol **(95):**



Following the above procedure, the Grignard reaction of **S6.B** (4.0 g, 24 mmol) gave compound **93** as a yellowish liquid: 80%; bp: 133 °C; IR ($CHCl_3$) ν: 3620, 3020, 2930, 1606, 1520, 1428, 1216, 1045, 929, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.30 (d, J = 5.8 Hz, 1H), 2.66 (d, J = 2.3 Hz, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 5.40 (dd, J = 2.0, 3.6 Hz, 1H), 6.84 (dd, J = 4.2, 8.8 Hz, 1H), 7.07 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8 (q), 55.9 (q), 64.2 (d), 74.6 (d), 83.6 (s), 109.7 (d), 110.8 (d), 119.0 (d), 132.6 (s), 149.0 (s), 149.2 (s) ppm; ESI-MS (*m/z*): 215.24 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{11}H_{12}O_3$ C, 68.74; H, 6.29% Found: C, 68.88; H, 6.36%.

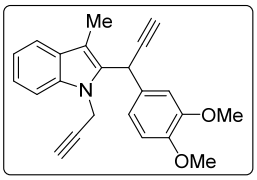
2-(1-(4-Methoxyphenyl)prop-2-yn-1-yl)-3-methyl-1-(prop-2-yn-1-yl)-1H-indole **(91):**



3-methyl-1-(prop-2-yn-1-yl)-1H-indole (**93**) (1.8 g, 10.6 mmol) was placed in a two necked flask with solution in DCM (20 ml) and was cooled to 0 °C. Then *p*-toluenesulphonic acid (0.6 g, 3.2 mmol) was added slowly under stirring. The mixture was stirred for 2 h, and then solution of compound **94** (1.15 g, 8.5 mmol) in DCM (20 mL) was added slowly by using syring pump over the period of 2 hrs. After complication, the reaction was quenched with saturated $NaHCO_3$ solution, diluted with water and extracted with DCM. The combined organic layer was dried over Na_2SO_4, concentrated and purified on silica gel (10% ethyl acetate in light petroleum) to get diyne compound **89** as a brown solid yield: 72%; mp: 85 °C; IR ($CHCl_3$) ν: 2933, 2530, 1613, 1518, 1461, 1375, 1250, 1211, 1130, 1160, 1012, 859, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.14 (dd, J = 0.6, 2.4 Hz, 1H), 2.41 (s, 3H), 2.61 (t, J = 2.7 Hz, 1H), 3.83 (s, 3H), 4.81 (d, J = 2.4 Hz, 2H), 5.58 (s, 1H), 6.87 –

6.92 (d, J = 8.6 Hz 2H), 7.18 – 7.47 (m, 5H), 7.64 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.9 (q), 31.9 (d), 33.7 (t), 55.3 (q), 72.0 (d), 73.4 (d), 78.6 (s), 81.7 (s), 109.3 (s), 109.4 (d), 114.0 (d, 2C), 118.9 (d), 119.5 (d), 122.1 (d), 128.2 (d, 2C), 128.5 (s), 129.6 (s), 132.4 (s), 136.3 (s), 158.7 (s) ppm; ESI-MS (*m/z*): 336.36 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{22}H_{19}NO$ C, 84.31; H, 6.11; N, 4.47; Found: C, 84.42; H, 6.52; N, 4.47 %.

2-(1-(3,4-Mimethoxyphenyl)prop-2-yn-1-yl)-3-methyl-1-(prop-2-yn-1-yl)-1H-indole **(92):**

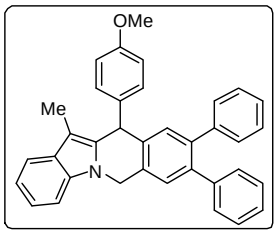


Following the above procedure to synthesis compound **91**, the Friedel-Craft alkylation of **94** (2.0 g, 0.012 mol) gave compound **92** as a brown solid yield: 79%; mp: 99 °C; IR ($CHCl_3$) ν: 2933, 2794, 1610, 1510, 1463, 1374, 1252, 1212, 1128, 1161, 1012, 856, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (t, J = 2.8 Hz, 1H), 2.37 (s, 3H), 2.56 (d, J = 2.8 Hz, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 4.76 (dd, J = 2.8, 17.4 Hz, 1H), 4.81 (dd, J = 2.8, 17.4 Hz, 1H), 5.54 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1 H), 6.92 – 6.96 (m, 2H), 7.18 (dt, J = 0.9, 7.8 Hz, 1H), 7.26 (dt, J = 0.9, 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 1.4, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.9 (q), 32.2 (d), 33.7 (t), 55.9 (q, 2C), 72.0 (d), 73.4 (d), 78.2 (s), 81.6 (s), 109.5 (d), 110.6 (d), 111.2 (d), 118.9 (d), 119.3 (d), 119.5 (d), 122.1 (d, 2C), 128.5 (s), 130.0 (s, 2C), 132.2 (s), 136.3 (s), 148.2 (s), 149.0 (s) ppm; ESI-MS (*m/z*): 366.46 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{23}H_{21}NO_2$ C, 80.44; H, 6.16; N, 4.08; Found: C, 80.51; H, 6.10; N, 4.12%.

General procedure for [2+2+2]-cyclotrimerization:

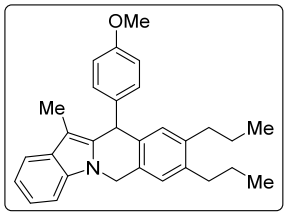
A solution of diyne (0.3 mmol) and alkyne (0.6 mmol) in 1,4-dioxane (5 mL) in a flame dried long glass tube was degassed with dry argon for 20 min; then, 0.2 M solution of $[CpCo(CO)_2]$ (20 mol%) catalyst in toluene was introduced into the mixture. The tube sealed by airtight cap. The mixture was stirred at 130–135 °C for 10–12 hrs. After complition of reaction, the reaction mixture was transferred into a round-bottom flask and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether) to afford the cyclotrimerized product.

11-(4-Methoxyphenyl)-12-methyl-8,9-diphenyl-6,11-dihydroindolo[1,2-b]isoquinoline: (**96**)



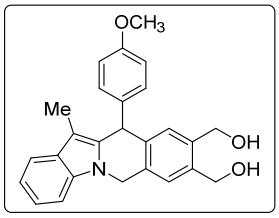
Colourless thick liquid: 76%; IR ($CHCl_3$) *v*: 3020, 1529, 1471, 1338, 1216, 1157, 1106, 1066, 969, 929, 834, 757, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ2.27 (s, 3H), 3.72 (s, 3H), 5.18 (d, *J* = 15.7 Hz, 1H), 5.40 (d, *J* = 15.7 Hz, 1H), 5.57 (s, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 7.11 – 7.29 (m, 12H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.50 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 8.6 (q), 42.7 (d), 44.6 (t), 55.2 (q), 105.6 (s), 108.6 (d), 114.0 (d, 2C), 118.5 (d), 119.1 (d), 120.8 (d), 126.6 (d, 2C), 127.9 (d, 3C), 128.6 (d), 128.8 (d, 2C), 129.2 (d), 129.8 (d, 2C), 129.9 (d, 2C), 131.0 (s, 2C), 131.3 (d), 133.8 (s), 135.2 (s), 135.6 (s), 136.3 (s), 139.0 (s), 139.9 (s), 140.9 (s), 141.0 (s), 158.2 (s) ppm; ESI-MS (*m/z*): 514.78 (100%, $[M+Na]^+$); Anal. Calcd for $C_{36}H_{29}NO$ C, 87.95; H, 5.95; N, 2.85; Found: C, 87.82; H, 5.89; N, 2.71%.

11-(4-Methoxyphenyl)-12-methyl-8,9-dipropyl-6,11-dihydroindolo[1,2-b]isoquinoline **(97):**



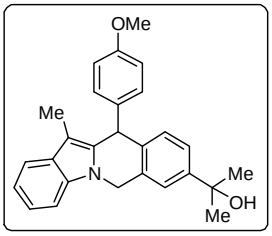
White solid yield: 83%; IR ($CHCl_3$) *v*: 2930, 2784, 1616, 1517, 1461, 1379, 1251, 1225, 1130, 1161, 1012, 856, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 1.54 – 1.65 (m, 4H), 2.26 (s, 3H), 2.58 (t, *J* = 7.9 Hz, 4H), 3.71 (s, 3H), 5.07 (d, *J* = 15.2 Hz, 1H), 5.26 (d, *J* = 15.2 Hz, 1H), 5.42 (s, 1H), 6.71 (ddd, *J* = 1.8, 2.8, 8.5 Hz, 2H), 6.99 (dd, *J* = 1.8, 2.8, 8.5 Hz, 2H), 7.07 – 7.23 (m, 4H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7 (q), 14.2 (q), 14.2 (q), 24.7 (t), 24.3 (t), 34.4 (t), 34.5 (t), 42.5 (d), 44.5 (t), 55.3 (q), 105.2 (s), 108.5 (d), 113.8 (d, 2C), 118.4 (d), 118.9 (d), 120.5 (d), 127.1 (d), 128.4 (d, 2C), 129.1 (s), 129.7 (d), 132.0 (s), 134.2 (s), 134.5 (s), 135.1 (s), 136.0 (s), 138.9 (s), 139.8 (s), 157.9 (s) ppm; ESI-MS (*m/z*): 446.58 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{30}H_{33}NO$ C, 85.06; H, 7.85; N, 3.31; Found: 85.11; H, 7.78; N, 3.40%.

(11-(4-Methoxyphenyl)-12-methyl-6,11-dihydroindolo[1,2-b]isoquinoline-8,9-diyl)dimethanol **(98)**:



Brown thick liquid: 81%; IR ($CHCl_3$) ν: 2933, 2794, 1610, 1510, 1463, 1374, 1252, 1212, 1128, 1161, 1012, 856, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.65 (s, 3H), 4.51 (d, J = 12.3 Hz, 2H), 4.60 (d, J = 12.3 Hz, 2H), 5.11 (d, J = 15.8 Hz, 1H), 5.24 (d, J = 15.8 Hz, 1H), 5.40 (s, 1H), 6.68 (ddd, J = 2.1, 2.9, 8.7 Hz, 2H), 6.85 (ddd, J = 2.1, 2.9, 8.7 Hz, 2H), 7.10 – 7.29 (m, 4H), 7.38 (d, J = 7.3 Hz, 1H), 7.57 (dd, J = 1.1, 7.0 Hz, 1H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.6 (q), 42.6 (d), 44.4 (t), 55.1 (d), 63.4 (t), 63.6 (t), 105.5 (s), 108.6 (d), 114.0 (d, 2C), 118.4 (d), 119.2 (d), 120.8 (d), 127.7 (d), 128.5 (d, 2C), 129.1 (s), 130.2 (d), 131.3 (s), 133.6 (s), 135.0 (s), 135.8 (s), 136.8 (s), 137.7 (s), 138.4 (s), 158.0 (s) ppm; ESI-MS (*m/z*): 422.37 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{26}H_{25}NO_3$ C, 78.17; H, 6.31; N, 3.51; Found: C, 78.09; H, 6.40; N, 3.63%.

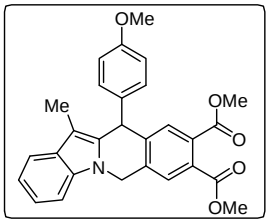
2-(11-(4-Methoxyphenyl)-12-methyl-6,11-dihydroindolo[1,2-b]isoquinolin-8-yl)propan-2-ol **(99)**:



1:1 Mixture of product, Brown thick liquid: 78%; IR ($CHCl_3$) ν: 3020, 2930, 1764, 1472, 1338, 1216, 1157, 1106, 1065, 967, 929, 834, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.54 – 1.62 (m, 6H), 2.24 (s, 0.5H), 2.28 (s, 0.5H), 3.71 (s, 1.5H), 3.72 (s, 1.5H), 5.11 (d, J = 15.3 Hz, 0.5H), 5.16 (d, J = 15.3 Hz, 0.5H), 5.29 (d, J = 12.8 Hz, 0.5H), 5.32 (d, J = 13.3 Hz, 0.5H), 5.47 (s, 0.5H), 5.50 (s, 0.5H), 6.72 (dd, J = 3.7, 8.6 Hz, 2H), 6.99 (dd, J = 5.3, 8.6 Hz, 2H), 7.11 – 7.15 (m, 1H), 7.21 (dt, J = 3.3, 7.9 Hz, 1H), 7.29 – 7.40 (m, 3H), 7.49 (s, 0.5H), 7.55 (s, 0.5H), 7.57 (s, 0.5H), 7.59 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 8.7 (q), 31.7 (q), 31.8 (q), 31.8 (q), 31.8 (q), 42.5 (d), 43.1 (d), 44.5 (t), 44.9 (t), 55.2 (q), 72.4 (s), 72.4 (s), 105.3 (s), 105.4 (s), 108.5 (d), 108.5 (d), 113.9 (d), 118.4 (d), 118.5 (d), 119.0 (d), 119.0 (d), 120.7 (d), 122.7 (d), 122.9 (d), 123.8 (d), 125.2 (d), 126.5 (d), 128.4 (d), 128.5 (d), 129.0 (d), 129.1 (s), 130.5 (s), 131.5 (s), 134.0 (s), 134.1 (s), 135.1 (s), 135.4 (s), 135.5 (s), 135.7 (s),

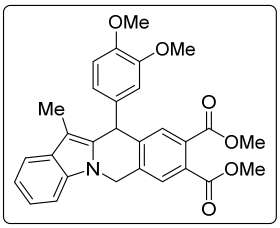
137.0 (s), 147.6 (s), 148.6 (s), 158.0 (s) ppm; ESI-MS (*m/z*): 420.25 (100%, $[M+Na]^+$); Anal. Calcd for $C_{27}H_{27}NO_2$ C, 81.58; H, 6.85; N, 3.52; Found: C, 81.45; H, 6.78; N, 3.48%.

dimethyl 11-(4-Methoxyphenyl)-12-methyl-6,11-dihydroindolo[1,2-b]isoquinoline-8,9-dicarboxylate **(100):**



Brown solid yield: 82%; mp: 124-126 °C; IR ($CHCl_3$) *v*: 3030, 2921, 1742, 1764, 1471, 1338, 1216, 1157, 1110, 1067, 967, 929, 834, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.23 (s, 3H), 3.72 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 5.30 (d, *J* = 16.3 Hz, 1H), 5.36 (d, *J* = 16.3 Hz, 1H), 5.51 (s, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.14 (dt, *J* = 1.1, 6.9 Hz, 1H), 7.24 (dt, 1.1, 6.9 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.56 (d *J* = 7.6 Hz, 1H), 7.72 (s, 1H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 8.6 (q), 42.8 (d), 44.5 (t), 52.7 (q, 2C), 55.2 (q), 106.1 (s), 108.5 (d), 114.2 (d, 2C), 118.6 (d), 119.4 (d), 121.1 (d), 127.5 (d), 128.5 (d, 2C), 129.2 (s), 130.0 (d), 130.2 (s), 131.2 (s), 132.5 (s), 134.5 (s), 134.9 (s), 135.0 (s), 140.5 (s), 158.4 (s), 167.6 (s, 2C) ppm; ESI-MS (*m/z*): 478.32 (100%, $[M+Na]^+$); Anal. Calcd for $C_{28}H_{25}NO_5$ C, 73.83; H, 5.53; N, 3.08; Found: C, 73.79; H, 5.42; N, 3.11%. (11-(3,4-

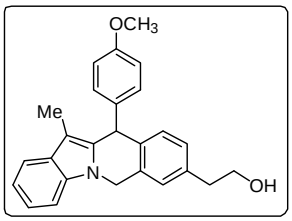
Dimethyl-11-(3,4-dimethoxyphenyl)-12-methyl-6,11-dihydroindolo[1,2b]isoquinoline -8,9-dicarboxylate **(101):**



Yellowish spongy mass, yield 81%; IR ($CHCl_3$) *v*: 2939, 2796, 1756, 1748, 1610, 1510, 1463, 1374, 1252, 1212, 1128, 1161, 1012, 856, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.73 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 5.23 (d, *J* = 16.2 Hz, 1H), 5.35 (d, *J* = 16.2 Hz, 1H), 5.49 (s, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 1.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.74 (s, 1H), 7.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7 (q), 43.2 (d), 44.5 (t), 52.7 (q), 52.7 (q), 55.8 (q), 55.9 (q), 106.3 (s), 108.5 (d), 110.9 (d), 111.2 (d), 118.6 (d), 119.5 (d), 119.8 (d), 121.2 (d), 127.5 (d), 129.2 (s), 130.0 (d), 130.2 (s), 131.2 (s), 132.4 (s), 134.8

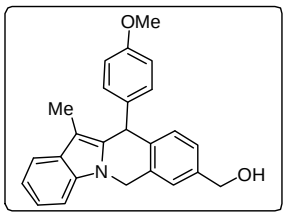
(s), 134.9 (s), 135.0 (s), 140.3 (s), 148.0 (s), 149.2 (s), 167.6 (s), 167.6 (s) ppm; ESI-MS (*m/z*): 508.36 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{29}H_{27}NO_6$ C, 71.74; H, 5.61; N, 2.88; Found: C, 71.77; H, 5.69; N, 2.93%.

2-(11-(4-Methoxyphenyl)-12-methyl-6,11-dihydroindolo[1,2-b]isoquinolin-8-yl)ethan-1-ol **(102):**



Yellowish thick liquid: 78%; IR ($CHCl_3$) ν: 3020, 2929, 1764, 1471, 1338, 1216, 1157, 1106, 1065, 967, 929, 834, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.65 (br.s, 1H), 2.26 (d, J = 3.9 Hz, 3H), 2.87 (t, J = 6.5 Hz, 2H), 3.71 (s, 3H), 3.85 (dt, J = 2.6, 6.5 Hz, 2H), 5.13 (dd, J = 3.9, 15.6 Hz, 1H), 5.28 (t, J = 15.6 Hz, 1H), 5.47 (s, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 7.09 – 7.41 (m, 6H), 7.56 (dd, J = 1.1, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 8.7 (q), 38.7 (t), 38.8 (t), 42.6 (s), 42.9 (s), 44.6 (t), 44.7 (t), 55.2 (q), 63.5 (t), 63.6 (t), 105.4 (s), 105.4 (s), 108.5 (d), 113.9 (s), 113.9 (s), 118.4 (s), 119.0 (s), 119.0 (s), 120.7 (d), 126.9 (d), 127.2 (d), 127.4 (d), 128.3 (d), 128.4 (d), 128.5 (d), 129.2 (s), 129.4 (d), 129.8 (d), 130.1 (s), 131.9 (s), 133.9 (s), 134.0 (s), 135.1 (s), 135.3 (s), 135.7 (s), 135.8 (s), 137.0 (s), 137.3 (s), 137.9 (s), 158.1 (s), ppm; ESI-MS (*m/z*): 406.51 (100%, $[M+Na]^+$); Anal. Calcd for $C_{26}H_{25}NO_2$ C, 81.43; H, 6.57; N, 3.65; Found: C, 81.39; H, 6.66; N, 3.58%.

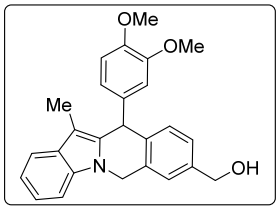
(11-(4-Methoxyphenyl)-12-methyl-6,11-dihydroindolo[1,2-b]isoquinolin-8-yl)methanol **(103)**



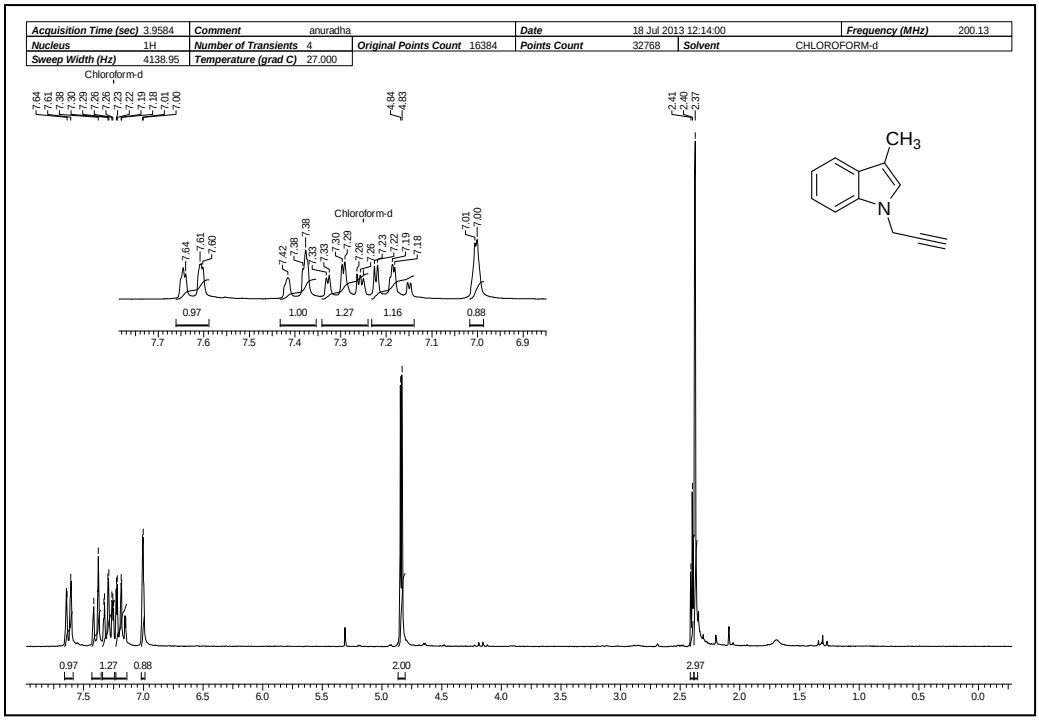
1:1 Mixture of regioisomers: brown think liquid, yield: 86%; IR ($CHCl_3$) ν: 3621, 3020, 2925, 1601, 1519, 1425, 1226, 1055, 930, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.70 (s, 3H), 4.68 (d, J = 4.6 Hz, 2H), 5.14 (d, J = 15.6 Hz, 1H), 5.30 (d, J = 15.6 Hz, 1H), 5.47 (s, 1H), 6.71 (d, J = 8.2 Hz, 2H), 6.98 (dd, J = 6.4, 8.2 Hz, 2H), 7.12 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.35 (s, 1H), 7.37 – 7.41 (m, 2H), 7.55 (d, J = 7.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.63 (q), 42.64 (d), 42.93 (d), 44.60 (t), 44.72 (t), 55.17 (q), 64.84 (t), 64.93 (t), 105.41 (s), 105.45 (s), 108.53 (d), 113.94 (d), 118.44 (d), 119.07 (d), 120.70 (d), 125.19 (d), 125.32

(d), 126.25 (d), 126.85 (d), 127.68 (d), 128.47 (d), 129.12 (s), 129.40 (d), 131.07 (s), 131.94 (s), 133.86 (s), 135.05 (s), 135.67 (s), 136.42 (s), 139.34 (s), 140.32 (s), 158.05 (s), ppm; ESI-MS (*m/z*): 392.32 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{25}H_{23}NO_2$ C, 81.27; H, 6.28; N, 3.79; Found: C, 81.25; H, 6.23; N, 3.83%.

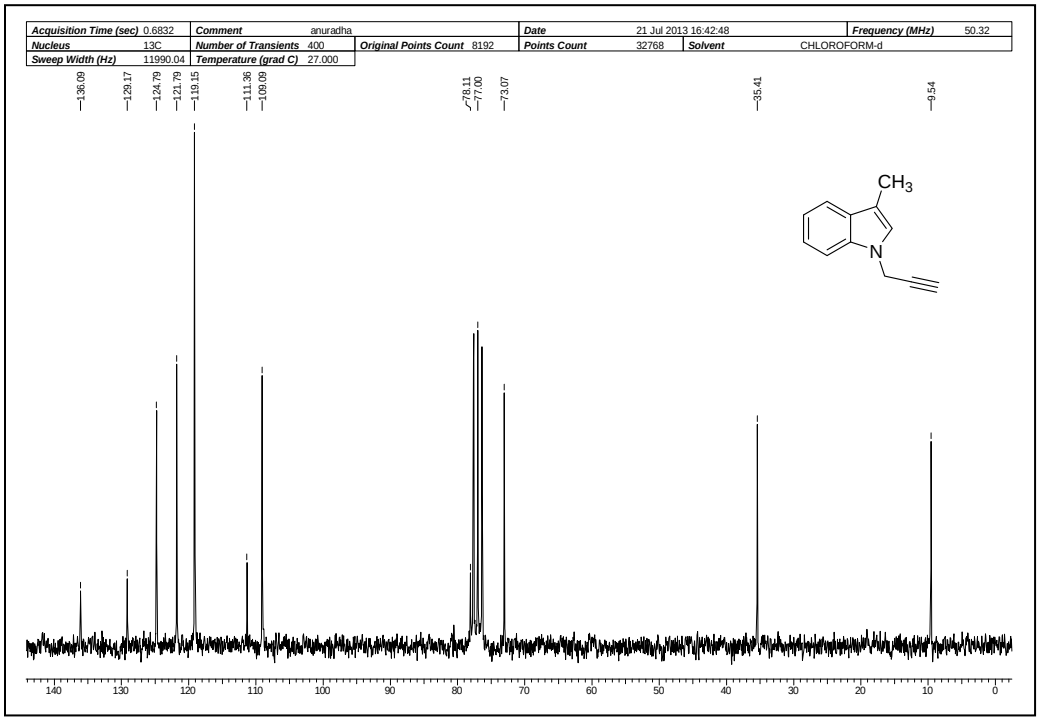
Dimethoxyphenyl)-12-methyl-6,11-dihydroindolo[1,2-b]isoquinolin- 8-yl)methanol **(104)**:



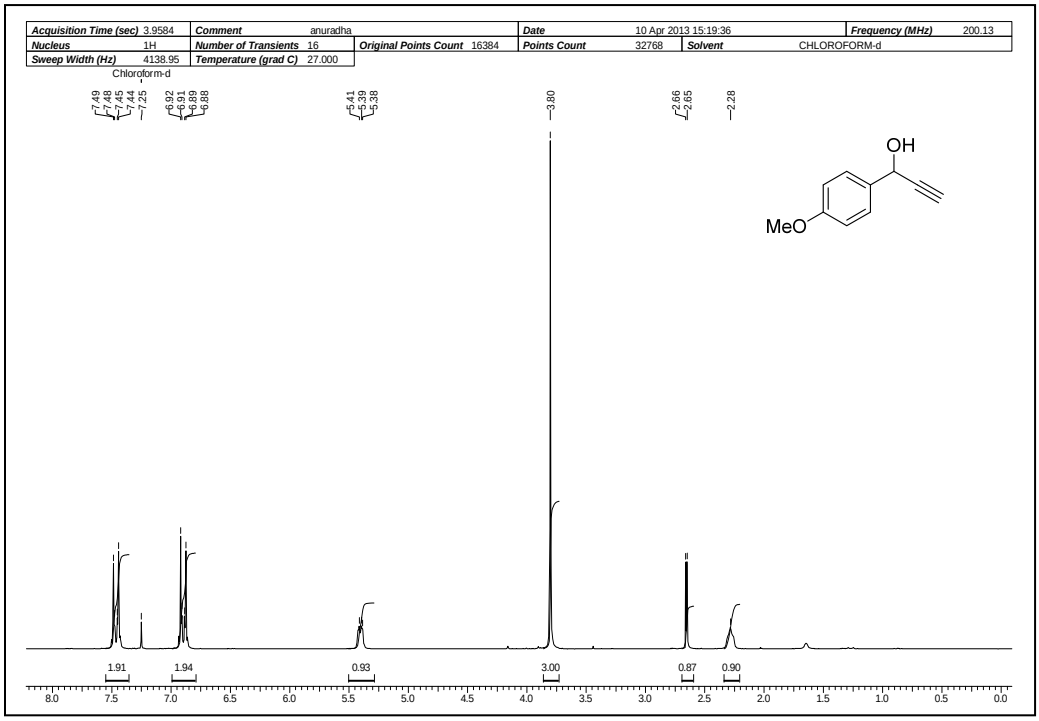
1:1 Mixture of regioisomers: brown spongy mass, yield: 74%; IR ($CHCl_3$) ν: 3620, 3019, 2930, 1600, 1518, 1424, 1216, 1045, 929, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.74 (br.s, 1H), 2.27 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 4.69 (d, J = 7.6 Hz, 2H), 5.16 (d, J = 3.9, 15.6 Hz, 1H), 5.31 (dd, J = 15.6 Hz, 1H), 5.46 (s, 1H), 6.56 (dd, J = 1.5, 9.5 Hz, 1H), 6.64 – 6.70 (m, 2H), 7.13 (t, J = 7.4 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 9.5 Hz, 1H), 7.31 – 7.44 (m, 3H), 7.55 (d, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7 (q), 43.1 (d), 43.4 (d), 44.6 (t), 44.8 (t), 55.8 (q, 2C), 64.8 (t), 64.9 (t), 105.5 (s), 105.6 (s), 108.5 (d), 111.1 (d), 118.5 (d), 119.1 (d), 119.6 (d), 119.6 (d), 120.8 (d), 125.2 (d), 125.4 (d), 126.2 (d), 126.8 (d), 127.7 (d), 129.1 (s), 129.4 (d), 131.1 (s), 132.0 (s), 133.7 (s), 135.1 (s), 136.0 (s), 136.1 (s), 136.2 (s), 137.1 (s), 139.4 (s), 140.3 (s), 147.7 (s), 149.0 (s) ppm; ESI-MS (*m/z*): 400.49 (10%, $[M+H]^+$), 422.23 (100%, $[M+Na]^+$); Anal. Calcd for: $C_{26}H_{25}NO_3$ C, 78.17; H, 6.31; N, 3.51; Found: C, 78.25; H, 6.32; N, 3.39%.



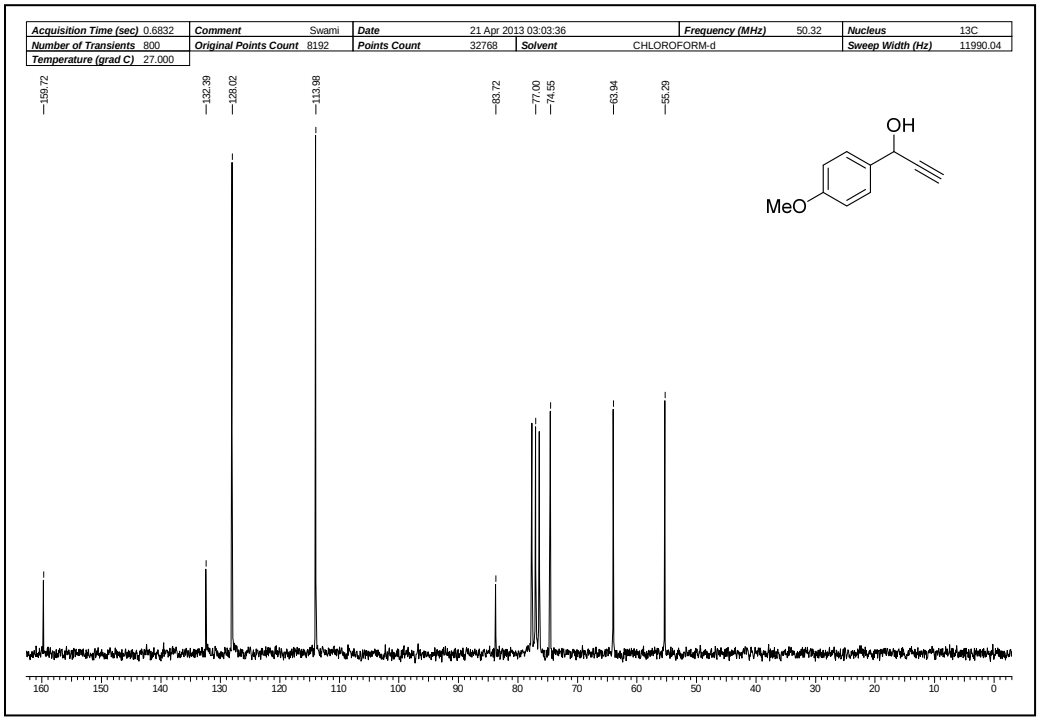
^{1}H NMR Spectrum of 93 in $CDCl_3$



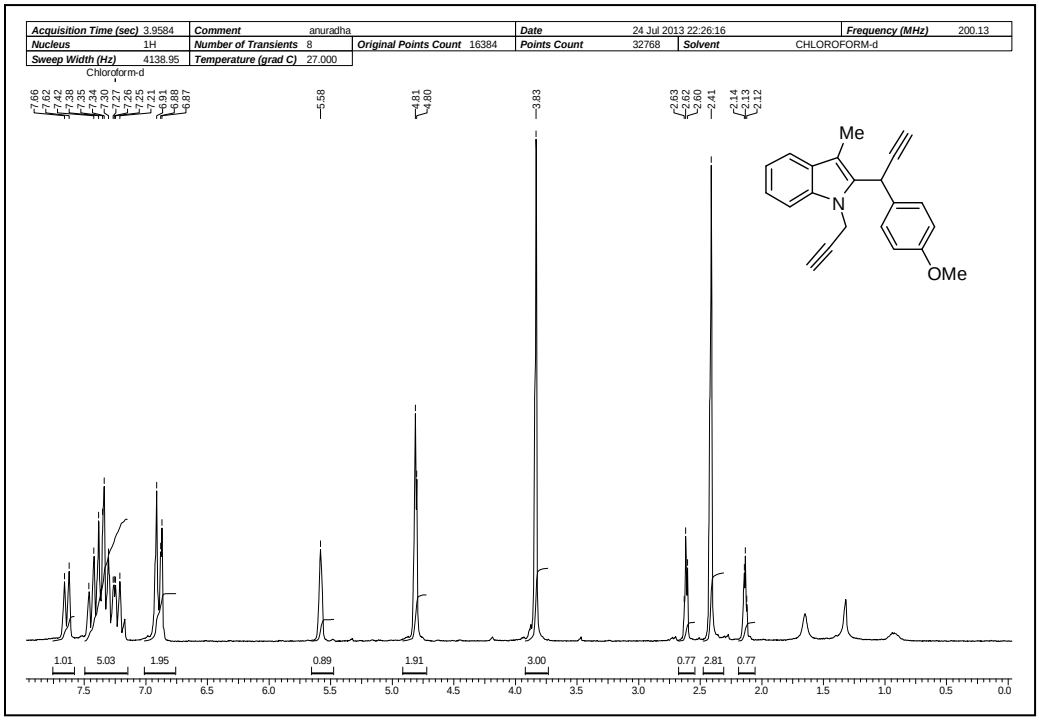
^{13}C NMR Spectrum of 93 in $CDCl_3$



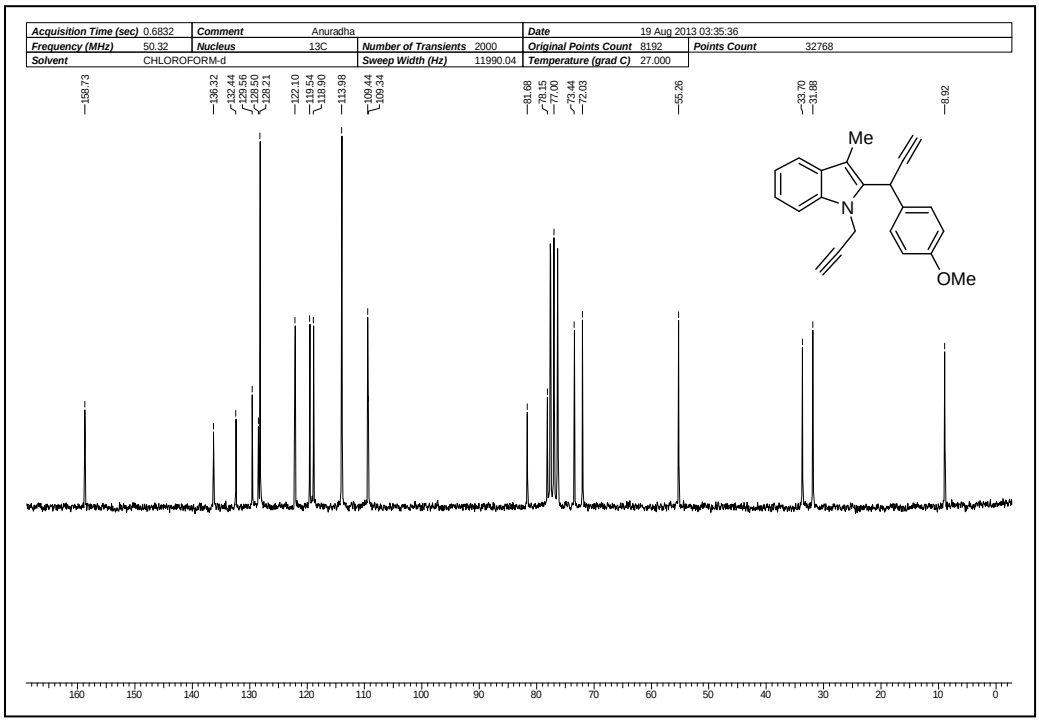
^{1}H NMR Spectrum of 94 in $CDCl_3$



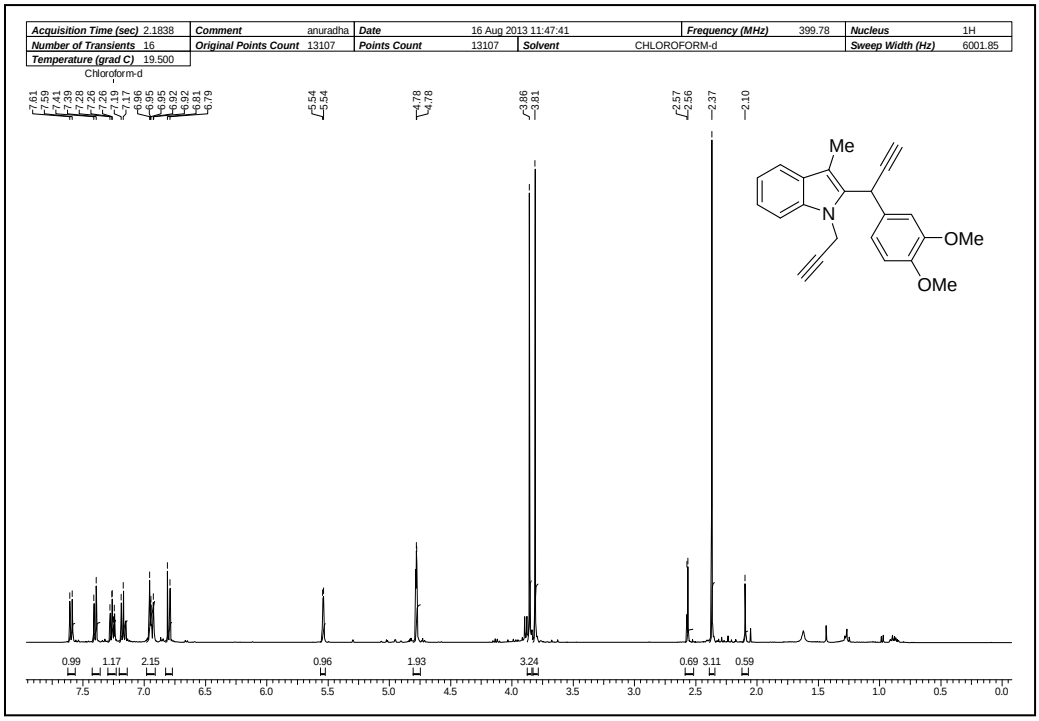
^{13}C NMR Spectrum of 94 in $CDCl_3$



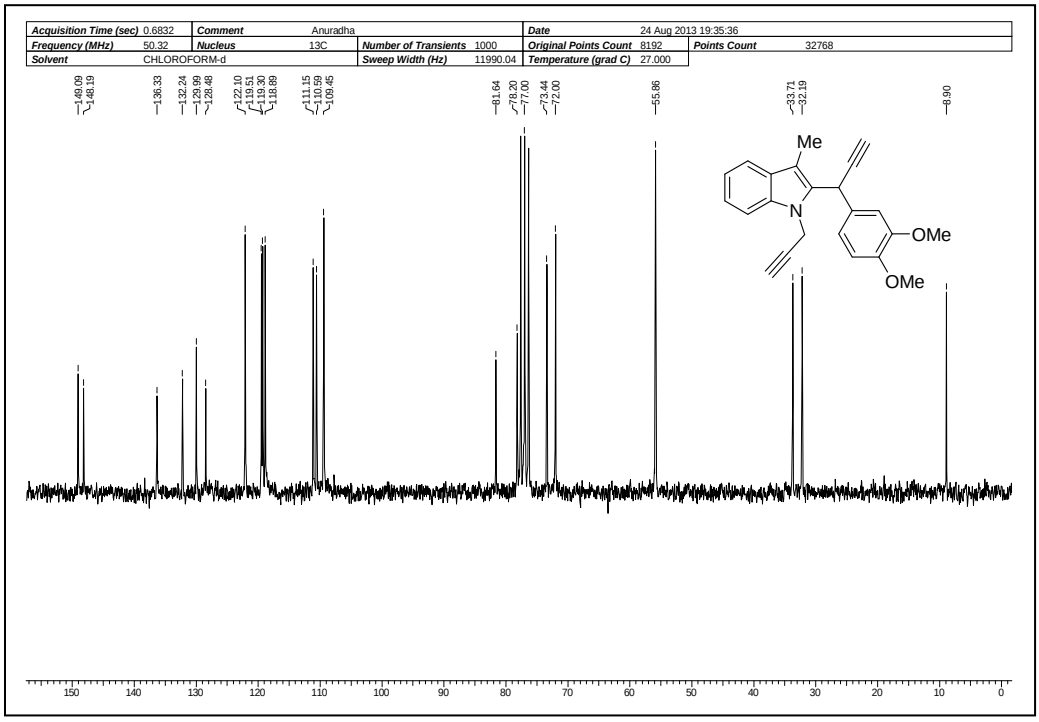
^{1}H NMR Spectrum of 91 in $CDCl_3$



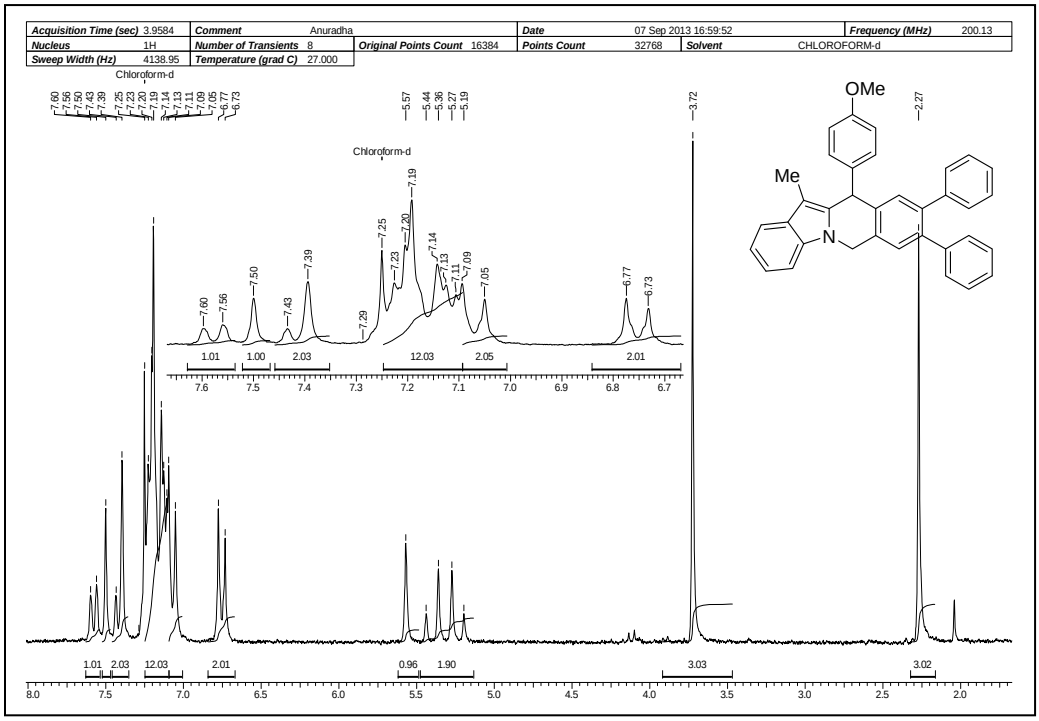
^{13}C NMR Spectrum of 91 in $CDCl_3$



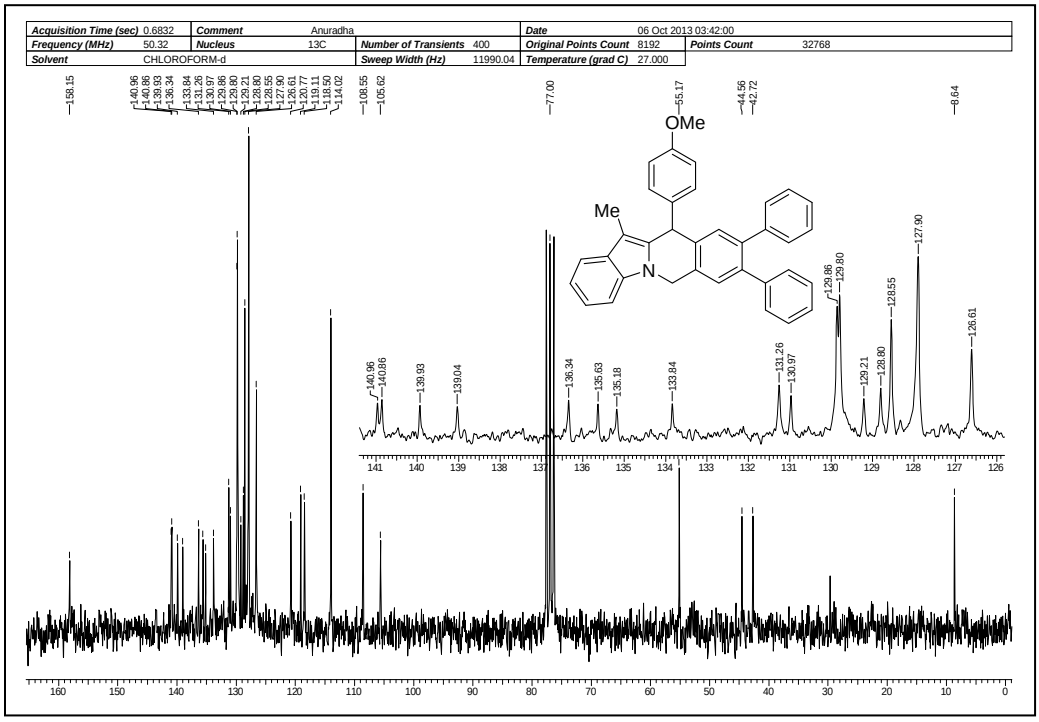
^{1}H NMR Spectrum of 92 in $CDCl_3$



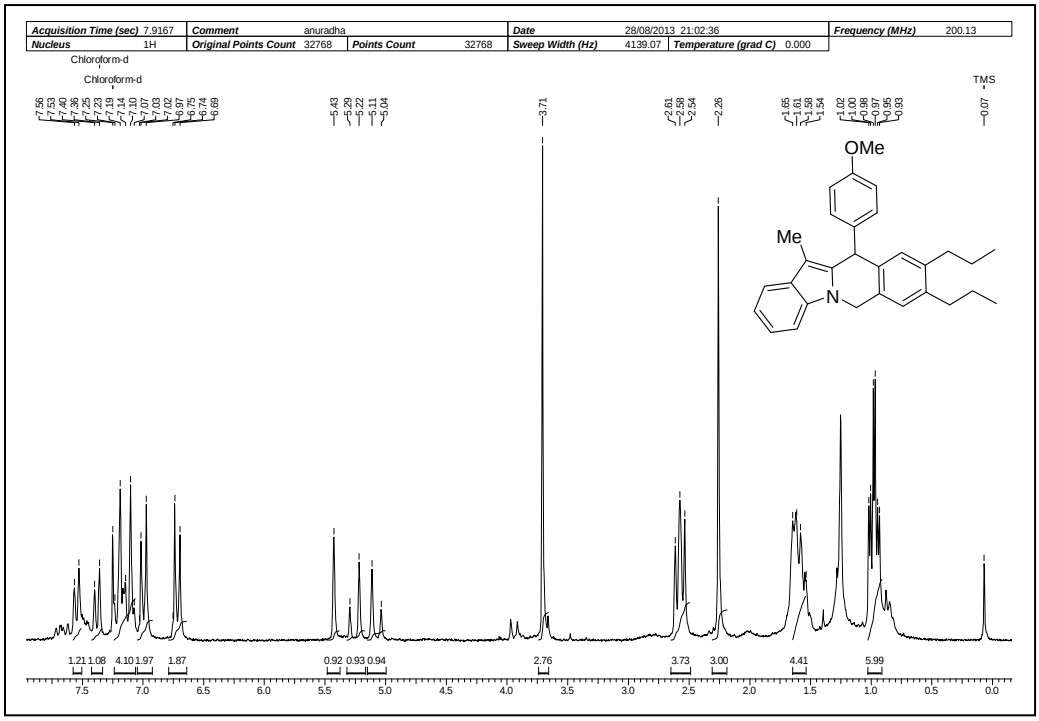
^{13}C NMR Spectrum of 92 in $CDCl_3$



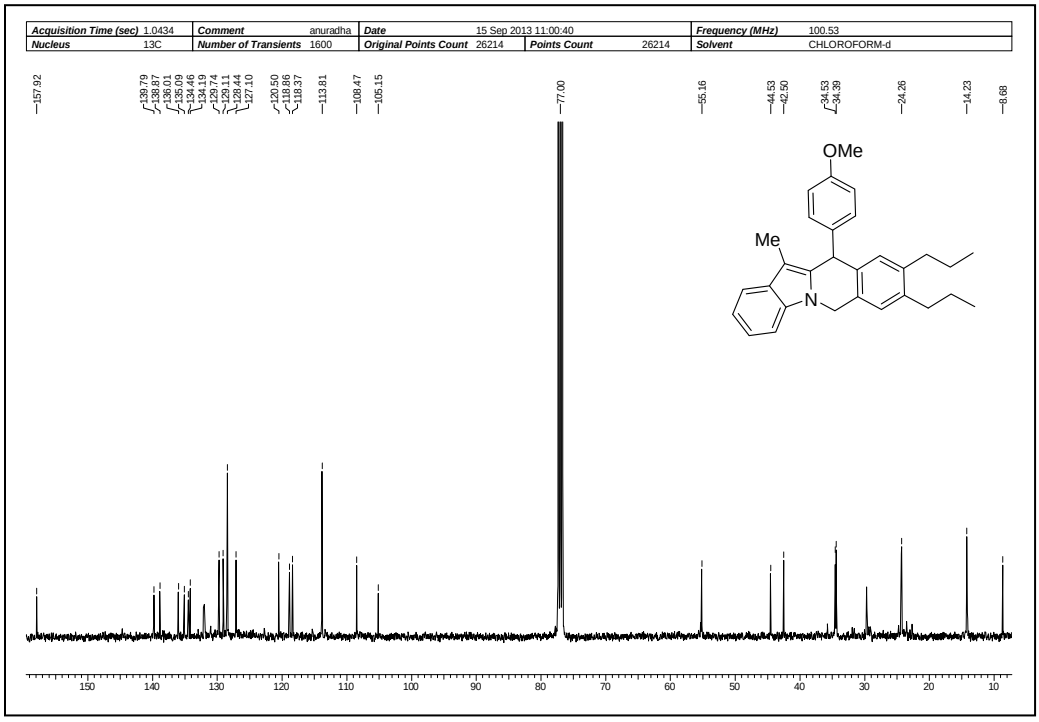
^{1}H NMR Spectrum of 96 in $CDCl_3$



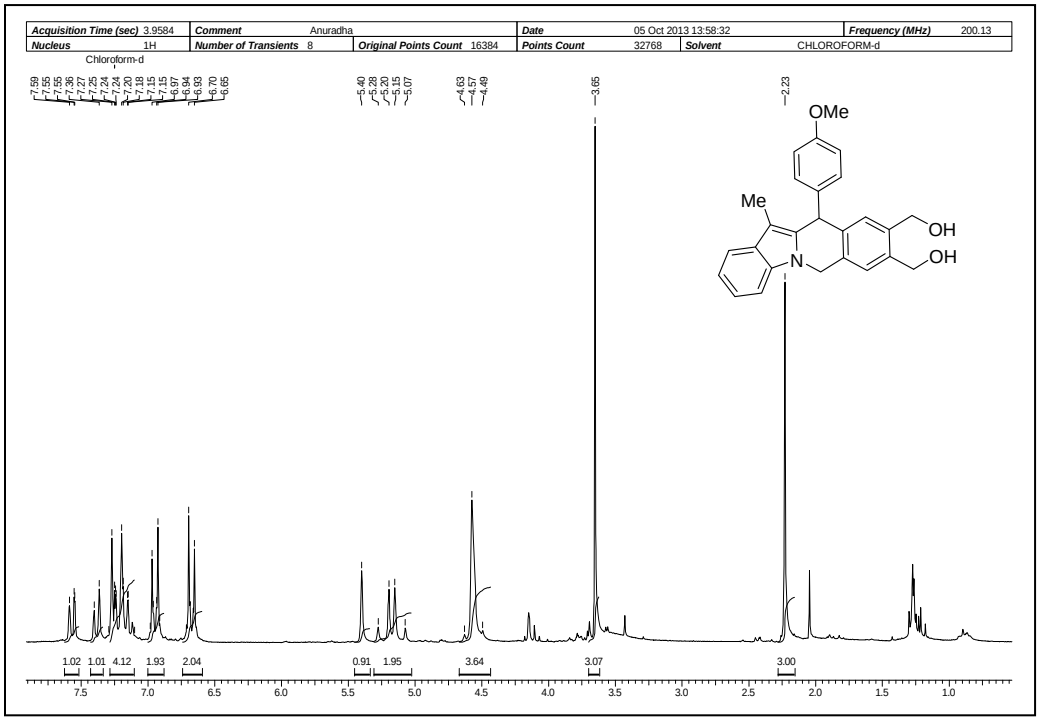
^{13}C NMR Spectrum of 96 in $CDCl_3$



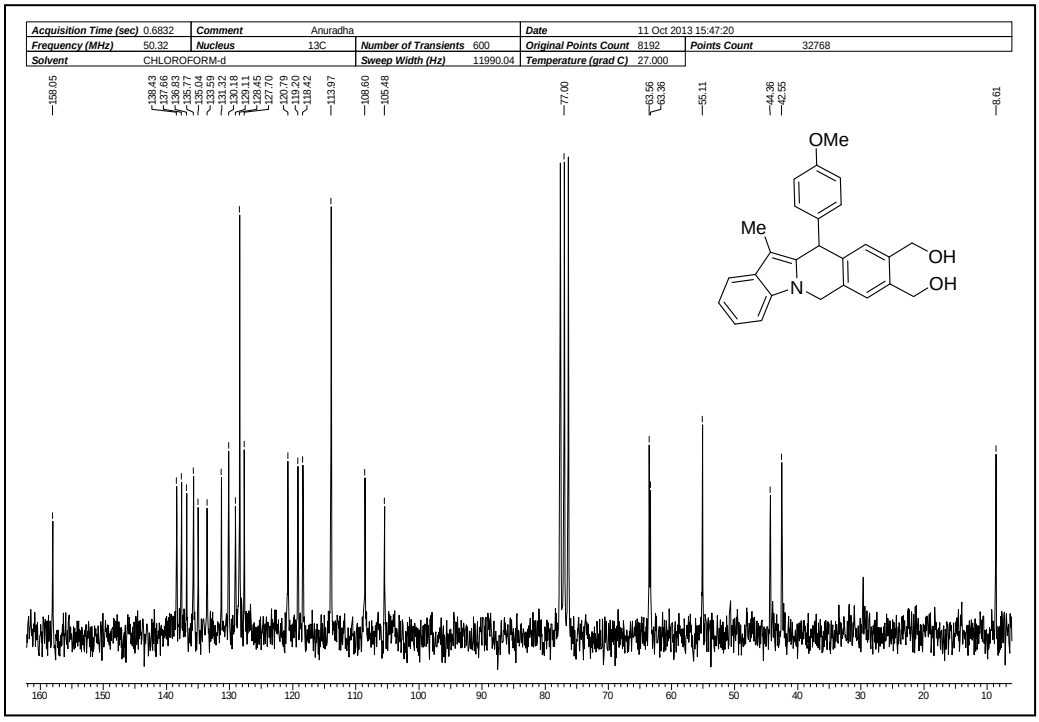
^{1}H NMR Spectrum of 97 in $CDCl_3$



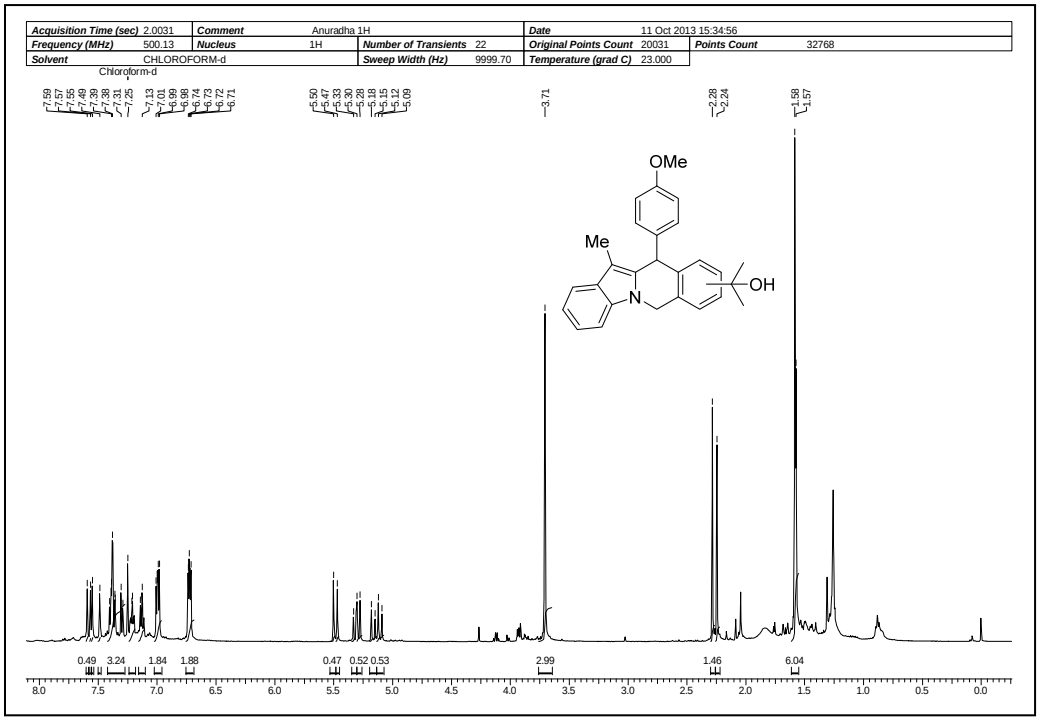
^{13}C NMR Spectrum of 97 in $CDCl_3$



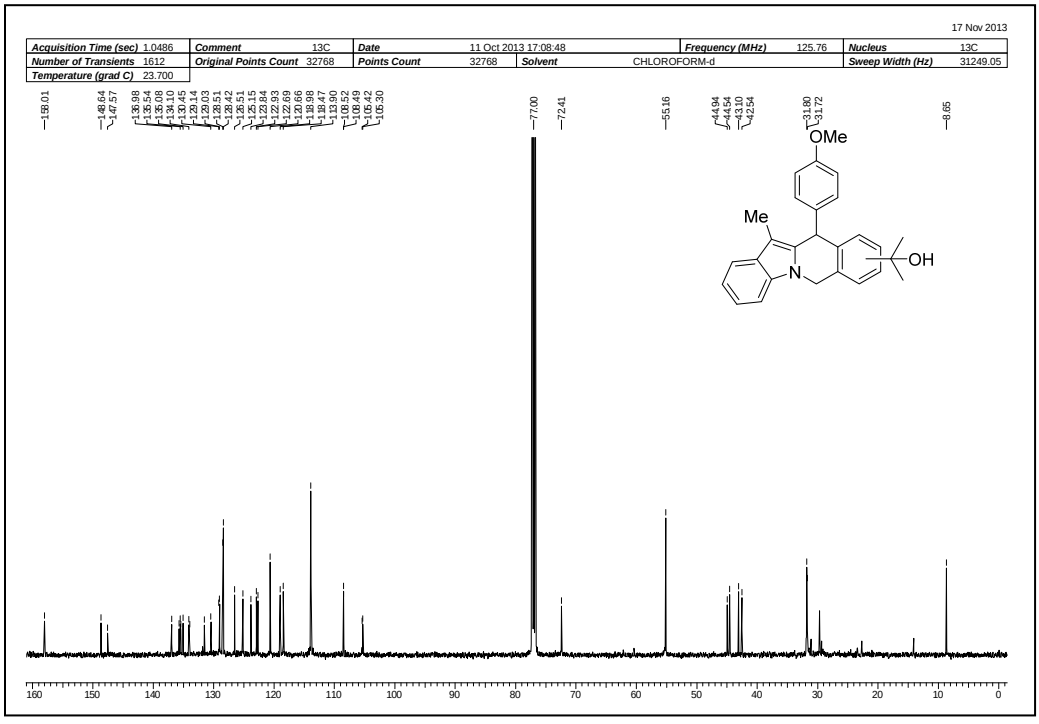
^{1}H NMR Spectrum of 98 in $CDCl_3$



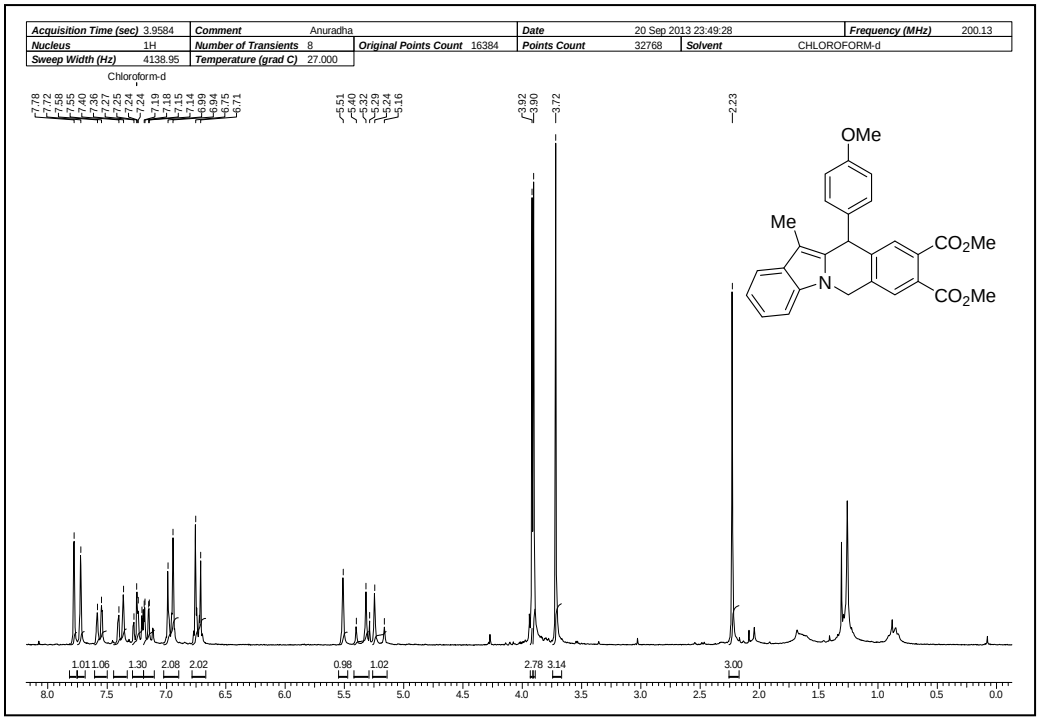
^{13}C NMR Spectrum of 98 in $CDCl_3$



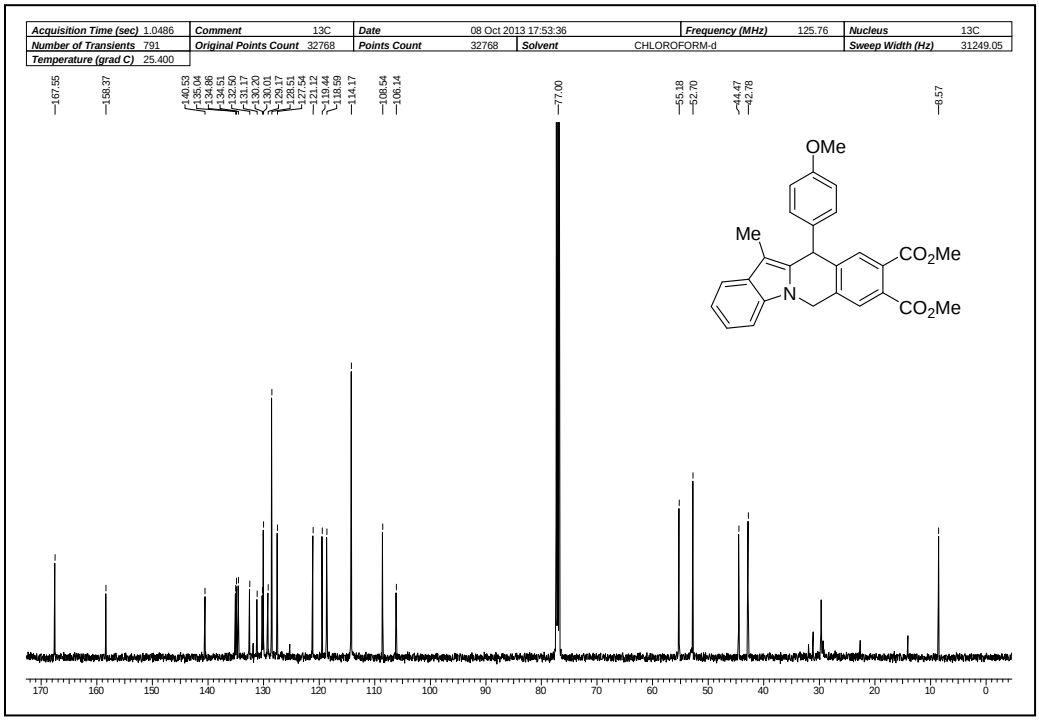
^{1}H NMR Spectrum of 99 in $CDCl_3$



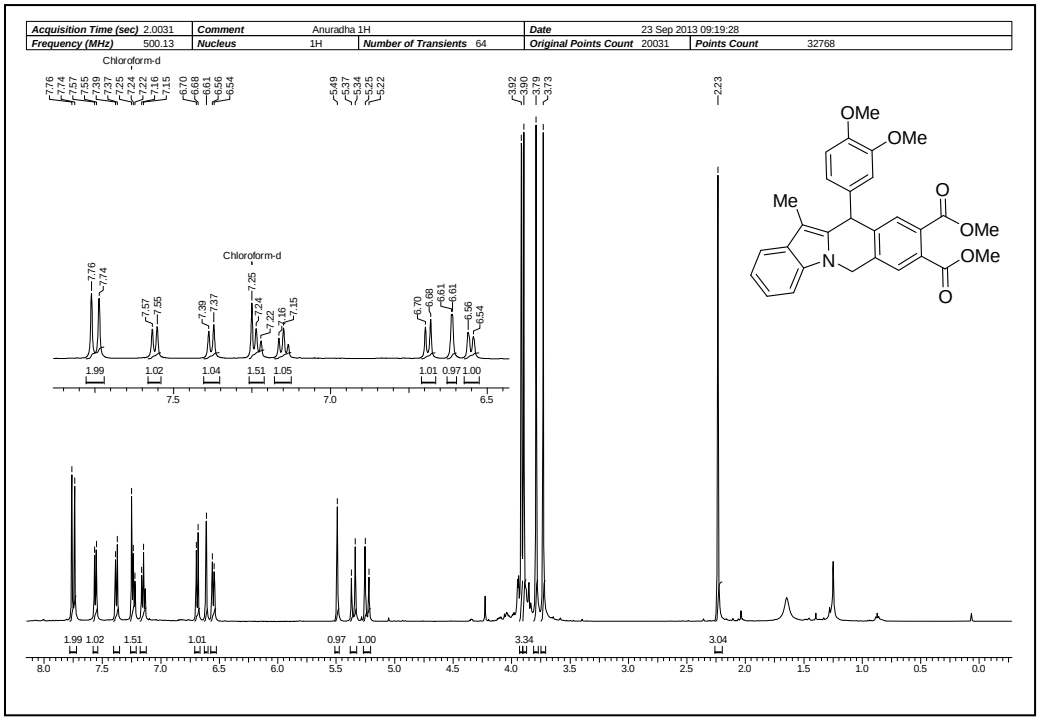
^{13}C NMR Spectrum of 99 in $CDCl_3$



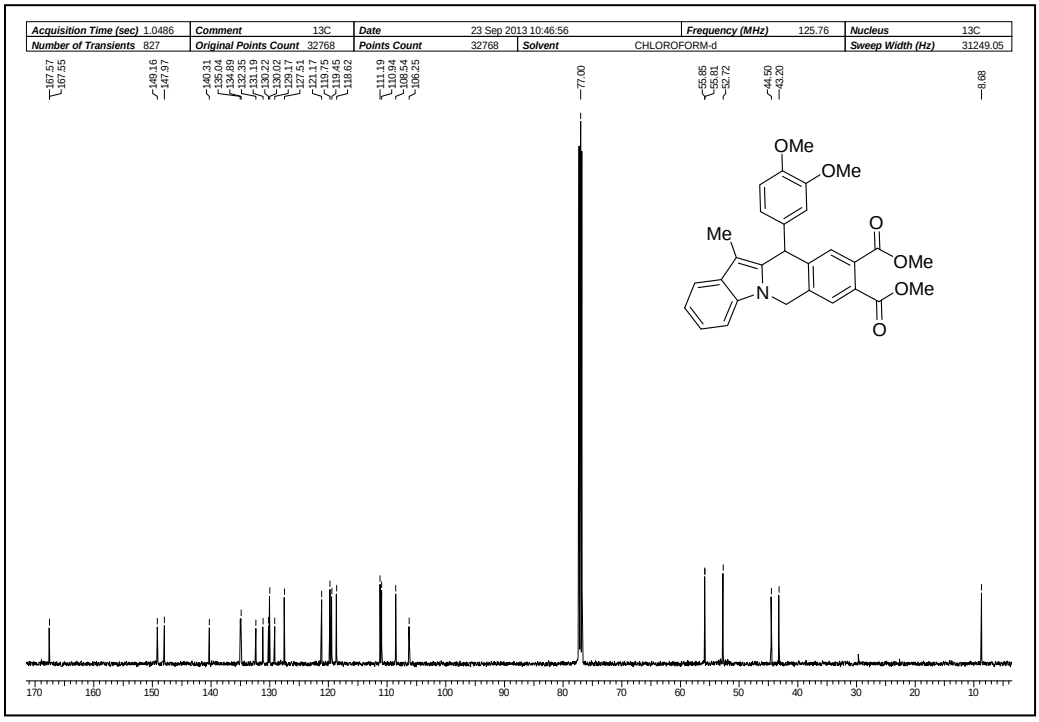
^{1}H NMR Spectrum of 100 in $CDCl_3$



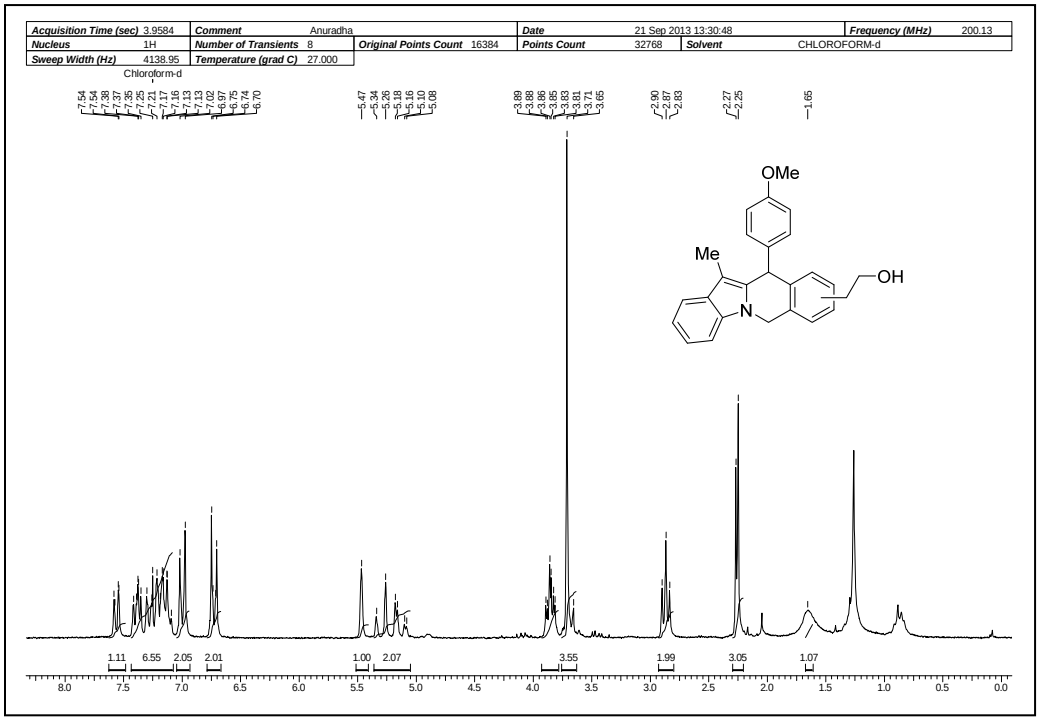
^{13}C NMR Spectrum of 100 in $CDCl_3$



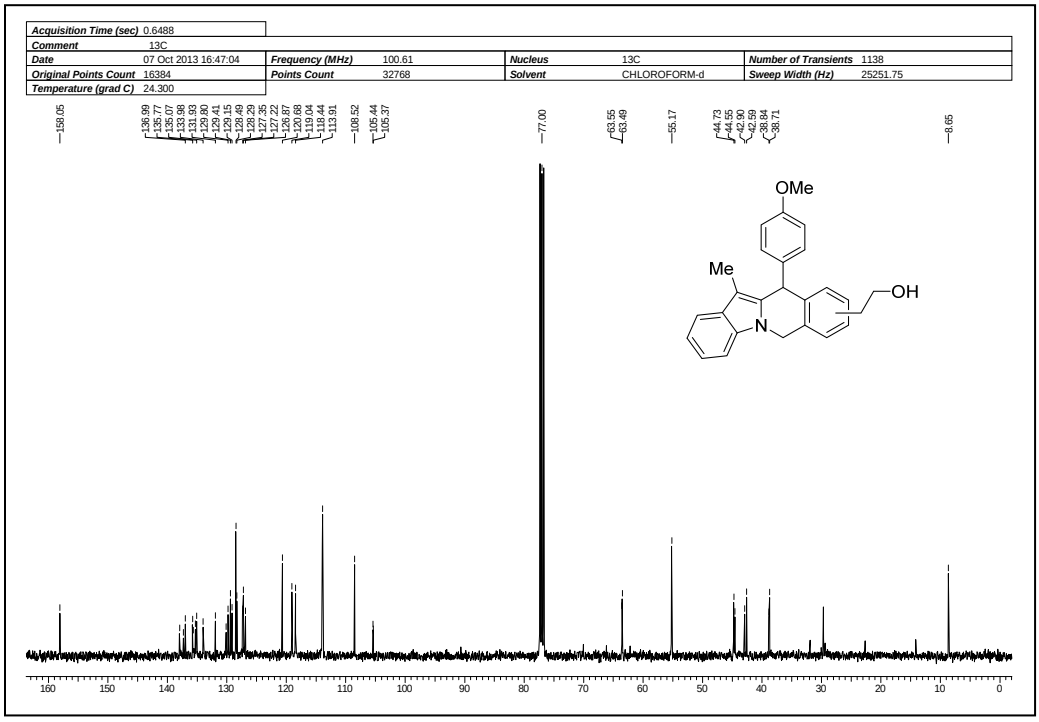
^{1}H NMR Spectrum of 101 in $CDCl_3$



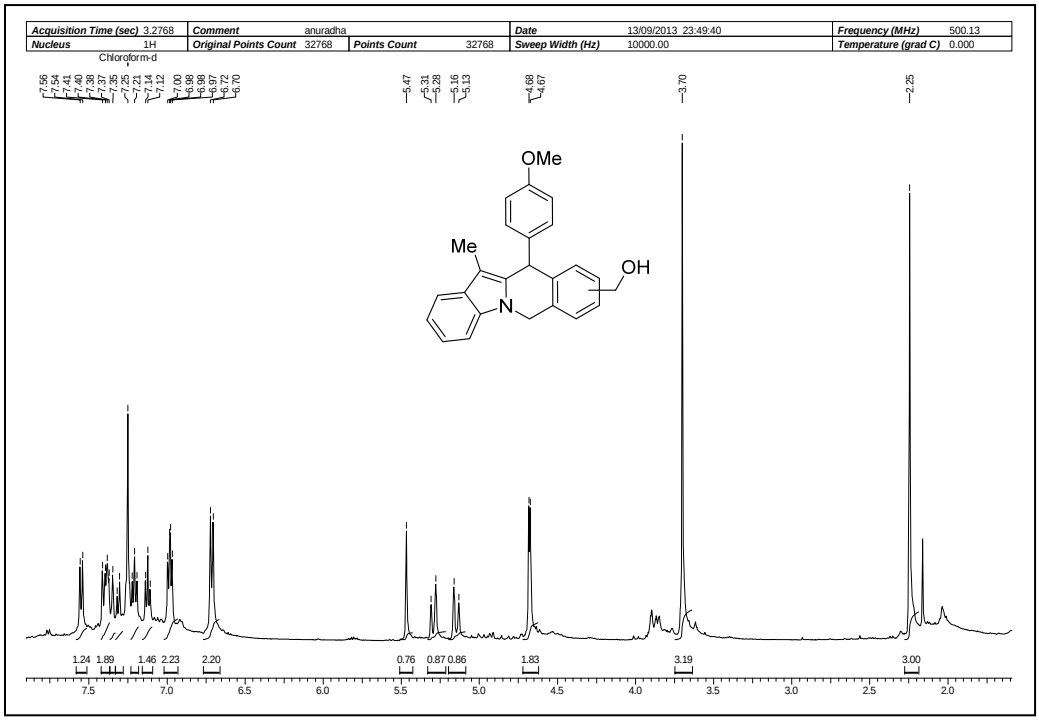
^{13}C NMR Spectrum of 101 in $CDCl_3$



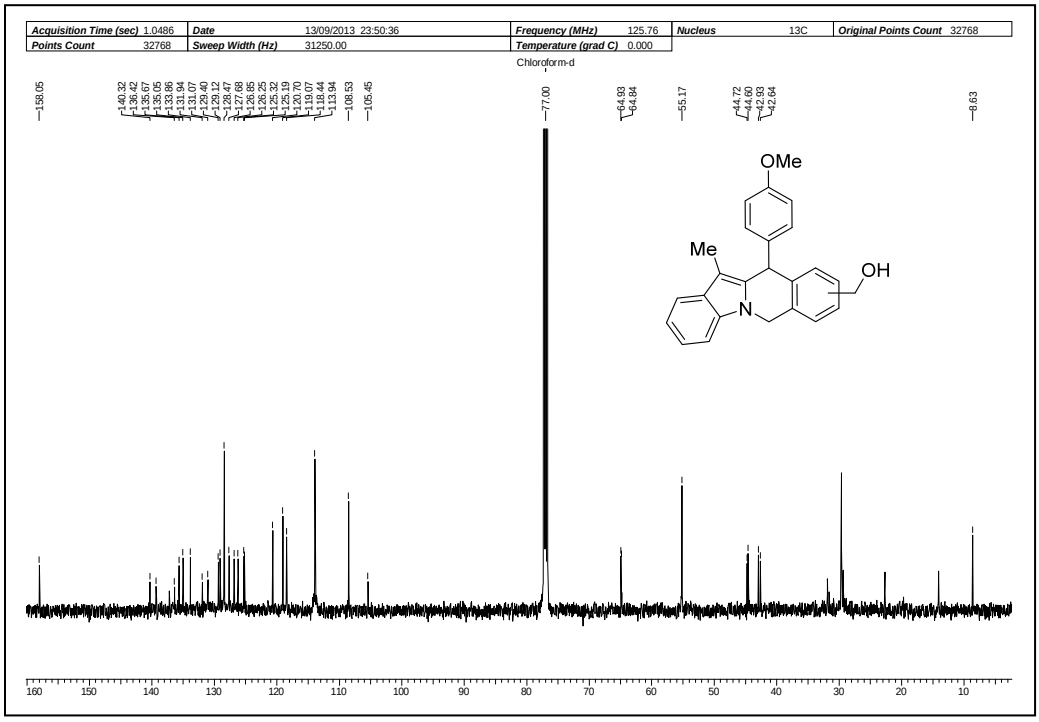
^{1}H NMR Spectrum of 102 in $CDCl_3$



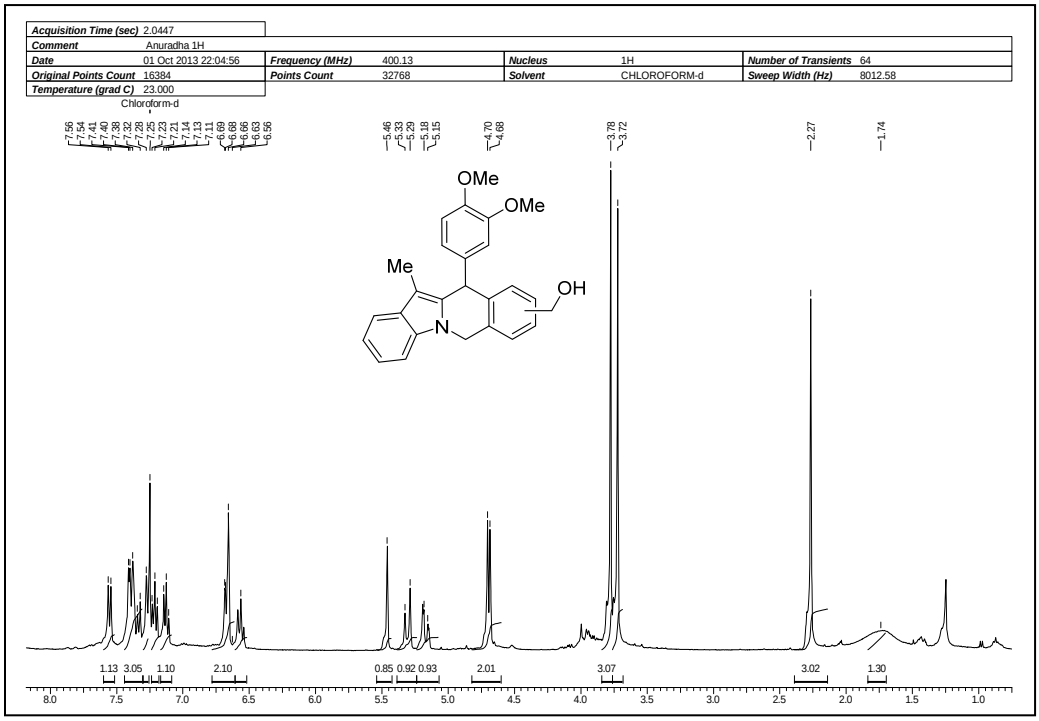
^{13}C NMR Spectrum of 102 in $CDCl_3$



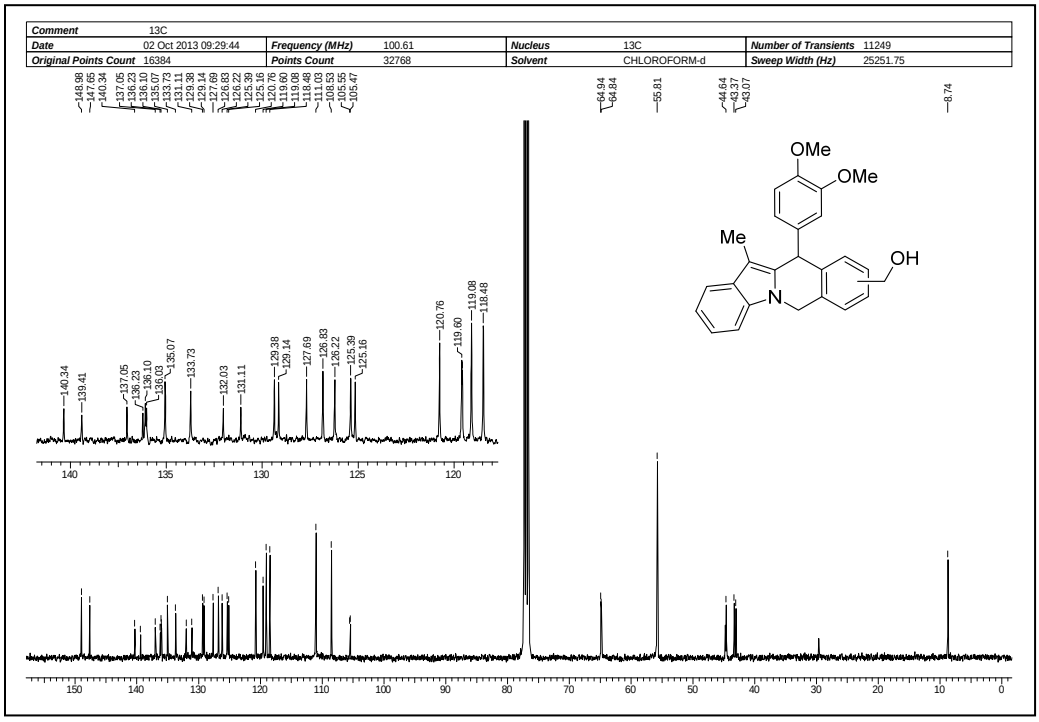
^{1}H NMR Spectrum of 103 in $CDCl_3$



^{13}C NMR Spectrum of 103 in $CDCl_3$



^{1}H NMR Spectrum of 104 in $CDCl_3$



^{13}C NMR Spectrum of 104 in $CDCl_3$

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Curriculum Vitae

Educational Qualifications

M.Sc. (Master of Science)	**Organic Chemistry ("A" Grade) 2007** Dept. of Chemistry, University of pune, Pune, Maharashtra, India.
B.Sc. (Bachelor of Science)	**Chemistry**, **(Distinction) 2005**. K.T.H.M. College, Nashik Maharashtra, India

Examinations Qualified

- Qualified National Eligibility Test (NET), Eligibility test for the lecturership/JRF Conducted by Council of Scientific and Industrial Research (CSIR) and University Grant Commission, **June 2007, Dec-2007**
- Graduate Aptitude Test in Engineering Exam **(GATE): 2007**

Award and Fellowships

- Junior Research Fellowship Awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in) **2008-2010**

- Senior Research Fellowship Awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in) **2010-2013**

Publications

1. "The isochroman- and 1,3-dihydroisobenzofuran-annulation on carbohydrate templates via [2+2+2]-cyclotrimerization and synthesis of some tricyclic nucleosides" Sharad B. Suryawanshi, **Mangesh P. Dushing**, Rajesh G. Gonnade, C.V. Ramana *Tetrahedron* **2010**, *66*, 6085–6096.
2. "Target cum flexibility: an alkyne [2+2+2]-cyclotrimerization strategy for synthesis of trinem library" C.V. Ramana,* **Mangesh P. Dushing**, Sradhanjali Mohapatra, Rosy Mallik, Rajesh G. Gonnade *Tetrahedron Letters* **2011**, *52*, 38–41.
3. "Target cum flexibility: synthesis of C(3)-spiroannulated nucleosides" **Mangesh P. Dushing**, C.V. Ramana* *Tetrahedron Letters* **2011**, *52*, 4627–4630.
4. "Spiroannuleted nucleosides and process for the preparation thereof" WO/**2012**/090155

Symposia / conferences attended

- Attended 4th INSA-KOSEF symposium in Organic Chemistry: Contemporary Organic Chemistry and its Future directions, **Jan 2009** conducted at National Chemical Laboratory, Pune, India.
- Attended 11th CRSI National Symposium in Chemistry 2010 held at National Chemical Laboratory (NCL), Pune in **February 2009**.
- Participated and presented oral presentation in the "6th J-NOST Conference" at School of Chemistry, University of Hyderabad, (AP) in **Jan 2010**.
- Participated and presented a poster in the "National Science Day poster Presentation" at National Chemical Laboratory, Pune(MS) in **Feb. 2011.**
- Participated and presented oral presentation in the "National Seminar on Advances in Synthetic and Applied Chemistry" at Sangamner College, Sangmaner, Dist. Ahemadnagar (MS) in **Sept 2012**.

Erratum