Synthesis of Carbo- and Nitrogen Hetero-cyclic Compounds

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Doctor of Philosophy in Chemistry

Submitted by

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This thesis is dedicated to

My Parents, Brothers, Sisters

and all those who have supported me throughout my education

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "**Synthesis of Carbo- and Nitrogen Hetero-cyclic Compounds**" is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Anil K. Saikia.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that Miss **Archana Kumari Sahu** has been working under my supervision since July 2016 as a regular registered Ph. D. student. I am forwarding her thesis entitled "**Synthesis of Carbo- and Nitrogen Hetero-cyclic Compounds**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

8th June, 2022
IIT Guwahati

Prof. Anil K. Saikia
Supervisor

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Finally, I feel a deep sense of gratitude to my loving parents, my dearest brother Ajit and all my kins. Without their love, care, support and sympathetic ears, it would have not been possible. It is rightly said “Happiness is a journey, not destination.” I thank you all for making this possible for me and I wish the best for you all.

Archana Kumari Sahu

LIST OF ABBREVIATIONS

Ac	Acetyl	mp	melting point
ACN	Acetonitrile	MS	molecular sieves
Ar	Aryl	mw	microwave
Bu	butyl	m/z	mass to charge ratio
Bu	butyl	NHC	Nucleophilic heterocyclic carbene
CCDC	cambridge crystallographic data centre	NMO	N-Methylmorpholine N-oxide
CuTc	Copper(I) thiophene-2-carboxylate	NMR	nuclear magnetic resonance
DAC	Donor-acceptor cyclopropane	NRO	nucleophilic ring opening
DCE	1,2-dichloroethane	Ns	2-nitrobenzenesulfonyl
DCM	Dichloromethane	ORTEP	oak ridge thermal ellipsoid plot
de	diastereomeric excess	$P(Bu)_3$	*tri n*-butylphosphine
DEAD	Diethyl azodicarboxylate	Ph	Phenyl
DFT	Density Functional Theory	PMB	*p*-methoxy benzyl
DMAc	Dimethylacetamide	*p*-TSA	*p*-toluenesulfonic acid
DMEDA	*N*,*N'*-dimethylethylenediamine	PPh_3	triphenyphosphine
DMF	*N*, *N*-dimethylformamide	ppm	parts per million
DMSO	dimethylsulfoxide	rt	room temperature
dppp	1,3-bis(diphenylphosphino)propane	SET	Single electron transfer
dr	diastereomeric ratio	TBAB	tetrabutylammonium bromide
ee	enantiomeric excess	TBAI	tetrabutylammonium iodide
HRMS	high resolution mass spectrometry	TBHP	*tert*-Butyl hydroperoxide
HFIP	Hexafluoroisopropanol	TBME	Methyl tert-butyl ether
^{i}Pr	Iso-propyl	*t*Bu	*tert*- Butyl
IR	*Infrared*	TFA	trifluoroacetic acid
LA	Lewis acid	TfOH	Triflic acid
LAH	lithiumaluminium hydride	THF	tetrahydrofuran

TLC	thin layer chromatography	TMSOTf	Trimethylsilyltriflate
TMS	Trimethylsilyl	Ts	*p*-toluenesulfonyl

Abbreviations for intensities of ^{1}H-NMR signals

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	brs	broad signal
dddd	doublet of doublet of doublet of doublet	Hz	Hertz
dt	doublet of triplet	MHz	Mega-Hertz

Abstract

The contents of this thesis have been divided into five chapters based on the results of experimental work performed during complete course of research period. Chapter 1 mainly discusses about tandem reactions and use of alkynes and donor-acceptor cyclopropanes in tandem reactions. Chapter 2 describes the synthesis of dibenzocyclohepta[1,2-*a*]naphthalene derivatives from alkynyl benzyl alcohols and phenylacetaldehydes *via* sequential electrophilic addition and double Friedel–Crafts reactions. Chapter 3 illustrates $In(OTf)_3$-catalyzed one-pot tandem Mannich/Conia-ene cyclization reaction for the construction of tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindolone-1,1-dicarboxylates from *N*-propargyl amido alcohols with 1,3-dicarbonyl compounds. Chapter 4 discloses a direct method for the synthesis of dibenzoyl tetrahydro-[1,5]diazocinodiisoindolediones from *N*-propargyl amido alcohols employing $Bi(OTf)_3$ as catalyst. Chapter 5 demonstrates the synthesis of 3*C*-homologated active methylene substituted 2*H*-indazoles *via* a sequential Ni(II) catalysed ring opening of donor acceptor cyclopropanes with arylamines followed by Sn(II) mediated reductive cyclization reaction.

Chapter 1: Tandem reactions in organic synthesis: use of alkynes and donor-acceptor cyclopropanes (DACs) in tandem reactions

Organic chemists have developed ample number of methods to synthesize enormous range of cyclic compounds that are often used in pharmaceuticals, agrochemicals, natural products etc. Above all, the major efforts reside on the lowering generation of waste. In other words the modern organic synthetic community focuses on atom economy, avoidance of hazardous reagents and management of waste, labor and time along with achieving the desired compounds with excellent selectivity. To reach these objectives, tandem reactions have been used to synthesize structurally diverse compounds. Different authors use different terminology to address these reactions like domino, cascade, concurrent, or sequential processes.

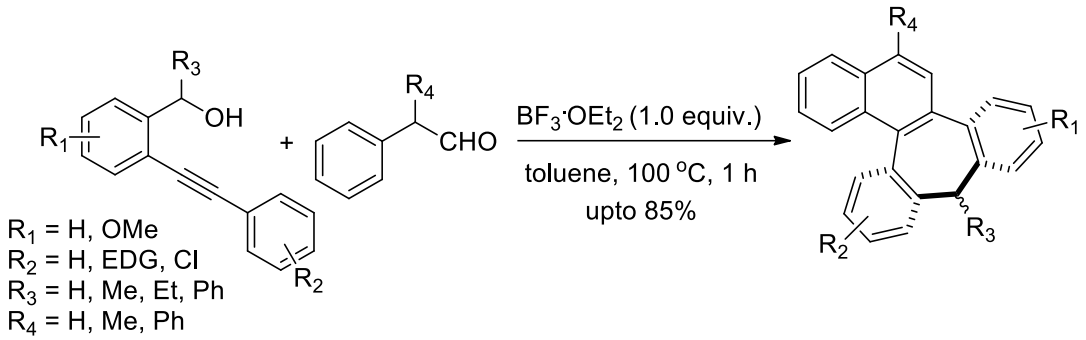
In this thesis, our research emphasizes the synthesis of carbo- and nitrogen-heterocyclic compounds using tandem cyclization employing mainly alkynes and donor acceptor cyclopropanes. Alkynes are important and well-known starting precursors used in all areas of organic synthesis to develop simple to complex moieties. The triple bond is observed in

readily participating in both nucleophilic, electrophilic as well as radical cyclizations. Literature survey reveals a wide range of organic compounds that have been accessed from starting materials with alkyne precursors such as isoindoloquinazolinones, benzofluorene derivatives, functionalized pentalenes, indole fused bicycle[3,2,1]octanes, cycloheptanones, substituted isochromenes, triazolo isoquinolines, indole fused pthalazines etc. using metal catalyst as well as metal free conditions.

Cyclopropanes are smallest carbocycles that have high angle strain of about 115 kJ mol^{-1} and cyclopropanes accompanied with donor and acceptor groups, positioned vicinal to each other facilitate easy cleavage of *C-C* bond in presence of Lewis acid thereby leading to 1,3 zwitterion formation. Henceforth, the DACs have been extensively utilized in ring opening reactions with different nucleophiles, involve in ring expansion reactions, annulations and rearrangements etc., to provide different membered carbo- and heterocyclic compounds as well as biologically important molecules.

Chapter 2: Synthesis of dibenzocyclohepta[1,2-*a*]naphthalene derivatives from alkynyl benzyl alcohols and phenylacetaldehydes *via* sequential electrophilic addition and double Friedel–Crafts reactions.

Dibenzocycloheptane is an important structural motif encountered in some biologically active molecules such as, allocolchicine, tenuifolin, subavenoside E and subamol. On the other hand, substituted naphthalenes are also present in many biologically important compounds, optical as well as electronic materials and constitute the backbone of many chiral ligands. Although there are very few strategies reported for the synthesis of dibenzocycloheptene unit and most of the methods mainly suffer from drawbacks such as multistep synthesis, use of costly catalysts etc. Herein, a concise methodology for the synthesis of substituted 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene derivatives *via* sequential electrophilic addition and double Friedel-Crafts cyclization between arylacetaldehydes and alkynyl benzyl alcohols as starting materials has been described (*scheme 1*).



Scheme 1: *Synthesis of 9H-dibenzo[3,4:6,7]-cyclohepta[1,2-a] naphthalenes* and *substrate scope*

The compound 7-methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene was determined from ^{1}H, ^{13}C NMR and mass spectrometry experiments. Further, the structure of the compound was confirmed from X-ray analysis (***Figure 1***). It was observed that the compound shows bend structure which is due to the repulsion among three aromatic rings attached to the cycloheptane ring.

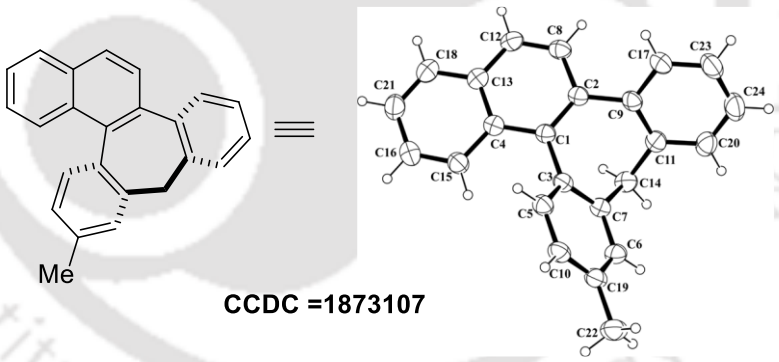


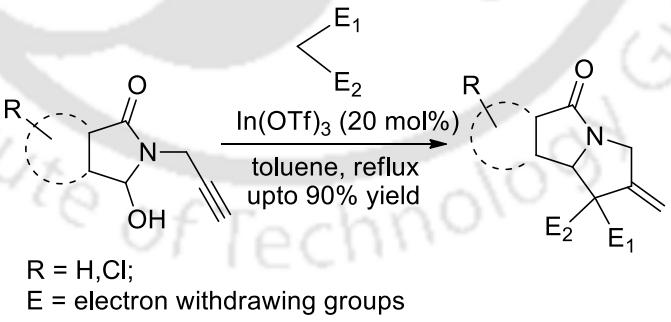
Figure 1**:** ORTEP diagram of compound *7-methyl-9H-dibenzo[3,4:6,7]cyclohepta[1,2-a]naphthalene*

In conclusion we have developed a methodology for the synthesis of unsymmetrical 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene *via* sequential electrophilic addition of alkynes to aldehyde and double Friedel-Crafts cyclization reactions in moderate to good yields in a short time span. The reaction is highly regioselective and produces equal amount of enantiomers.

Chapter 3: $In(OTf)_3$-catalyzed one-pot tandem Mannich/Conia-ene cyclization reaction of *N*-propargyl amido alcohols with 1,3-dicarbonyl compounds: An approach to construct tetrahydro-pyrroloisoindolone-1,1-dicarboxylate derivatives and its application

α- C-H function of carbonyl compounds adds to alkene/alkynes to form a new carbon-carbon bond under thermal conditions is the fundamental phenomena of Conia-Ene reaction. Several carbo- and hetero-cyclic compounds has been developed using this strategy. Moreover, to increase the applicability Conia-Ene reaction has been targeted in variety of cascade/tandem cyclization reactions (like ring-opening/Conia-Ene, Michel/Conia-Ene, and Prins/Conia-Ene reactions etc.).

Tetrahydropyrolloisoindolone and its derivatives are important core structures found in many natural products, pharmaceuticals and biologically active molecules. Based on importance of these derivatives development of new methods are always in high demand. In this regard, herein we report indium(III)triflate catalyzed tandem one-pot reaction for the synthesis of highly substituted tetrahydropyrroloisoindolone having *exo*-cyclic double bond *via* tandem Mannich reaction of substituted 3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-one and 1,3-dicarbonyl compounds followed by Conia-ene cyclization reaction (*scheme 2*).



Scheme 2: *Synthesis of substituted tetrahydropyrroloisoindolones and substrate scope*

The compound diethyl 2-methylene-5-oxo-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1(5*H*,9*bH*)-dicarboxylate was determined from ^{1}H, ^{13}C NMR and mass spectrometry experiments. Further, the structure of the compound was confirmed from X-ray analysis (*Figure 2*).

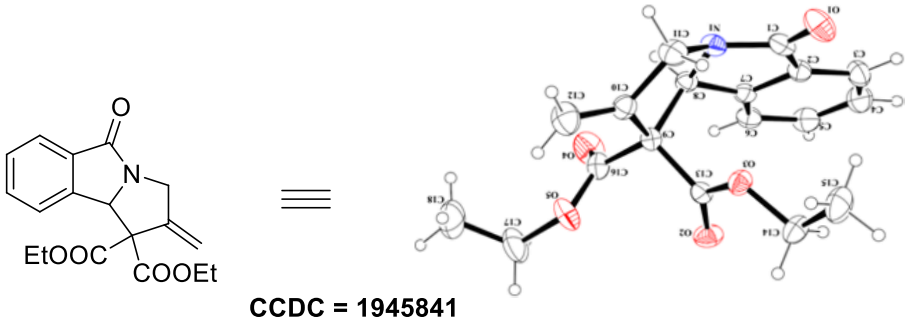
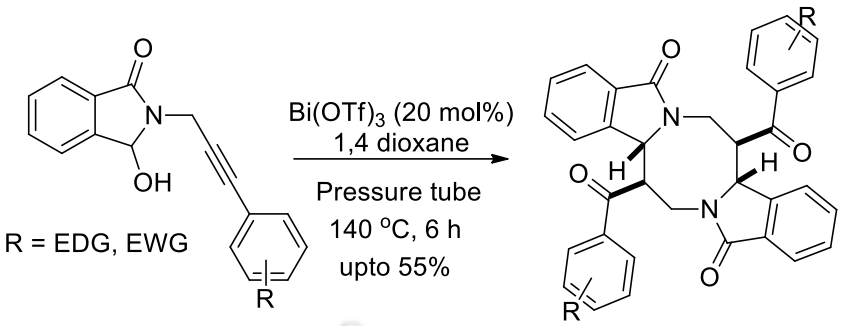


Figure 2: ORTEP diagram of compound *diethyl 2-methylene-5-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-1,1(5H,9bH)-dicarboxylate*

In conclusion, we have developed a methodology for the synthesis of substituted tetrahydropyrroloisoindolone using one-pot tandem Mannich and Conia-ene cyclization reaction with moderate to high yields. The reaction is highly regioselective with an exocyclic double bond in the pyrrolidine ring. The reaction can also be used for the synthesis of tetrahydropyrido[2,1-*a*]isoindolone and dihydro-oxazino[3,2-*a*]isoindolone derivatives. The methodology can be further extended for the synthesis of 5*H*-pyrrolo[2,1-*a*]isoindol-5-ones *via* Krapcho dealkoxycarbonylation followed by aromatization in moderate yields.

Chapter 4: $Bi(OTf)_3$-catalyzed one-pot dimerization of *N*-propargyl amido alcohols to construct dibenzoyl tetrahydro-[1,5]diazocinodiisoindolediones

Diazocanes based molecules more often occurs in many important bioactive compounds, electronic materials, supramolecular receptors, Troger's base, and naturally occurring alkaloids. The synthesis of diazocanes are relatively less explored compared to other 5-/6-/7-membered ring due to the their instability caused by rise in angle strain (strain energy) in the molecule. However, methods for synthesis of substituted 1,5 diazocanes suffers from multistep synthesis and use of costly reagents. Hence, it is exclusively challenging task to synthesize these scaffolds using an efficient method. In continuation of previous work, herein we report $Bi(OTf)_3$ catalysed one-pot dimerization of *N*-propargyl amido alcohols to provide benzoyltetrahydro-[1,5]diazocinodiisoindolediones in moderate yields (*scheme 3*).



Scheme 3: *Dibenzoyl tetrahydro-[1,5]diazocino[2,1-a:6,5-a']diisoindole diones and substrate scope*

The structure of the compounds was determined by NMR and mass spectrometry. It was further confirmed by X-ray crystallographic analysis of compound (8*S*,8*aS*,16*S*,16*aS*)-8,16-dibenzoyl-8,8*a*,16,16*a*-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (*Figure 3*).

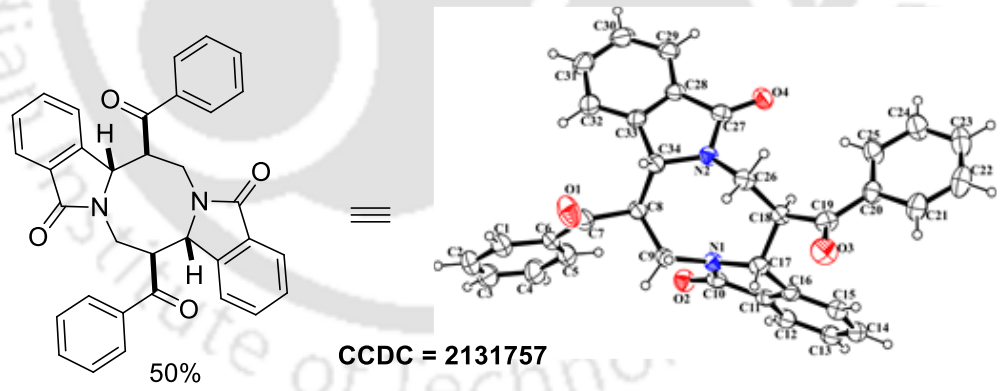


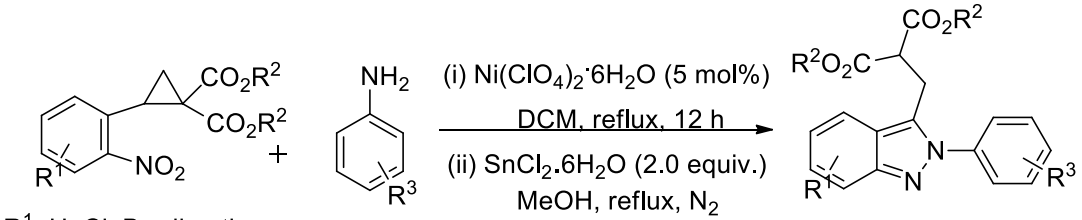
Figure 3: ORTEP diagram of compound *(8S,8aS,16S,16aS)-8,16-dibenzoyl-8,8a,16,16a-tetrahydro-[1,5]diazocino[2,1-a:6,5-a']diisoindole-5,13(7H,15H)-dione*

In conclusion, a simple and direct protocol has been developed for the synthesis of uncommon dibenzoyltetrahydro-[1,5]diazocinodiisoindoledione derivatives from *N*-propargylamido alcohols using $Bi(OTf)_3$ as catalyst. The reaction proceeds through *N*-acyliminium ion formation and nucleophilic attack from alkynes leading to dimerization.

Chapter 5: Synthesis of 3*C*-homologated active methylene substituted 2*H*-Indazole Derivatives via Sequential Ring Opening of Donor Acceptor Cyclopropanes and Reductive cyclization Reaction

2*H*-indazoles with different functionalities show many pharmacological and therapeutical properties such as, anticancer, antiangiogenic, antitumor, antiatherosclerotic, 5-HT_{1A} receptor etc. More interestingly, a few 3*C*-alkylated 2*H*-indazole motifs are clinically approved as promising drug candidates. For example, pazopanib, estrogen receptor ER-16b etc. The methods for synthesis of 3*C*-alkylated 2*H*-indazole are limited. Even though, there are few strategies developed for the synthesis of 3*C*-alkylated 2*H*-indazole, these methods suffer from draw backs, such as the use of expensive metal catalyst like Pd, require pre-synthesized indazoles and multistep process.

On the other hand, donor acceptor cyclopropanes (DACs) are also well-known molecular entities and they have been successfully utilized in nucleophilic ring-opening, as well as ring expansion reactions, annulations and rearrangements for the sysnthesis of various carbo- and hetero-cyclic compounds. In this regard, construction of substituted heterocycles from DACs with primary arylamines in presence of Lewis acid is less studied. Till date substituted dihydropyrroles, pyrroles, 2-substituted 4-hydroxy indole, poly-substituted azetidines etc. have been achieved. To the best of our knowledge 3*C*- alkylated 2*H*-indazoles are not yet synthesized from DACs and primary aryl amines. Here in, we report a facile sequential protocol for the synthesis of 2*H*-indazoles containing 3*C*-homologated active methylene group *via* $Ni(ClO_4)_2{\cdot}6H_2O$ catalyzed nucleophilic ring-opening (NRO) reaction of *o*-nitro having DACs with arylamines followed by $SnCl_2{\cdot}2H_2O$ mediated reductive cyclisation reaction (*Scheme 4*).



R^1=H, Cl, Br, dimethoxy
R^2= Me, Et
$R^{3=}$ ERG, EWG,

Scheme 4: *Synthesis of 3C-alkylated 2H-indazole and substrate scope*

The structure of the compounds was determined by ^{1}H, ^{13}C NMR and mass spectrometry. The compound dimethyl 2-((2-(4-(methylthio)phenyl)-2*H*-indazol-3-yl)methyl)malonate was confirmed by X-ray crystallographic analysis (*Figure 4*).

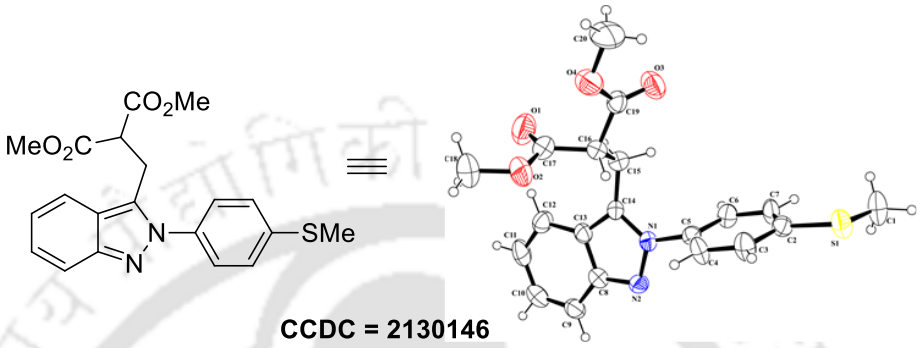


Figure 4: ORTEP diagram of *dimethyl 2-((2-(4-(methylthio)phenyl)-2H-indazol-3-yl)methyl)malonate*

In conclusion, a simple and sequential protocol has been developed to synthesize 3*C*-homologated active methylene substituted 2*H*-indazole derivatives from *o*-nitro DACs and primary arylamines in moderate to good yields. The present strategy follows $Ni(ClO_4)_2.6H_2O$ catalysed NRO reaction of *o*-nitro DACs with primary arylamines followed by $SnCl_2.2H_2O$ mediated intramolecular reductive cyclisation. For further utility, of one of the synthesized compounds was extended for few functional group transformations to provide 2*N*-arylated 3-indazolyl-propanoate, propanoic acid, propanols and propanamide.

Index

CHAPTER 1

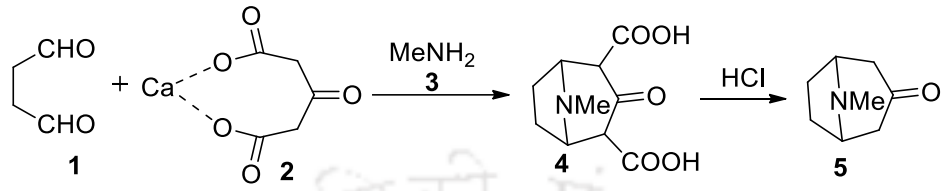
Tandem reactions in organic synthesis: use of alkynes and donor-acceptor cyclopropanes (DACs) in tandem reaction

1.1 Introduction

The organic compounds which constitutes a cyclic system with carbon atoms only in its core is referred as carbocyclic compounds whereas, if any of the carbon atoms in the cyclic system is replaced with other atoms (*O, N, S* etc.) is named as heterocyclic compounds. Organic chemists use ample number of methods to synthesize enormous range of cyclic compounds that are often used in many pharmaceuticals,[1a-e] agrochemicals,[1f] natural products[1g-h] etc. Above all, the major efforts reside on lowering the generation of waste. In other words, the modern organic synthetic community focus on atom economy, avoidance of hazardous reagents and management of waste, labor, time along with achieving the desired compound with excellent selectivity. To reach these objectives, tandem reactions have been used to synthesize structurally diverse compounds.[2] Different authors use different terminology to address these reactions like domino, cascade, concurrent or sequential processes. Discrete definitions of this procedure has been given by separate individuals to contemporize the context. For example, according to Tietze,[3] the domino reaction is a process where multiple C-C bonds form in a sequence without altering reaction conditions and isolating intermediates or adding additional reagents/catalysts. Here the subsequent reactions result from the functionality developed in the previous step. Similarly, Nicolaou[4] described cascade reactions as multiple transformations occurring in one synthetic operation. Furthermore, Bazan[5] and Winkler[6] used the terms "sequential" and "concurrent" respectively. In both these cases, reactions were carried out in single reaction vessel whether or not the reaction demands additional reagents.

In 1917, Robert Robinson reported the first tandem reaction for the synthesis of the alkaloid tropinone.[7] A three component reaction of succindialdehyde **1**, calcium salt of

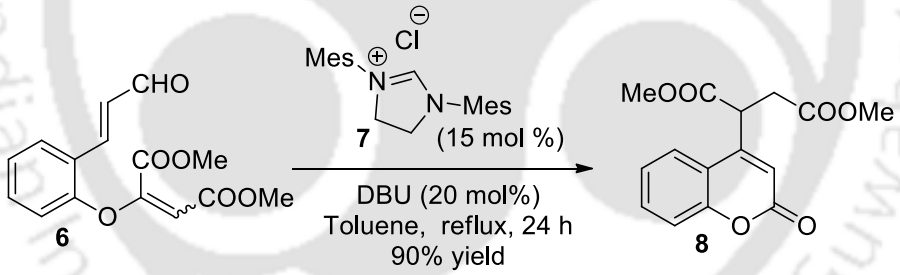
acetonedicarboxylic acid **2** and methylamine **3** gave carboxylic group substituted compound **4** which on acidification with HCl gave bridged bicyclic alkaloid tropinone **5**. The reaction proceeds through a tandem double Mannich reaction (*scheme 1.1.1*).



Scheme 1.1.1

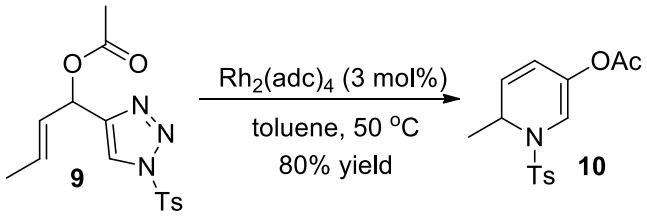
1.2 Few examples of tandem reaction

Nair and group demonstrated an efficient methodology to synthesize coumarin derivatives **8** in moderate to good yields. The reaction of *o*-alkenoates substituted enals **6** and nucleophilic heterocyclic carbene (NHC) **7** in presence of base generate carbene that reacts in tandem double Michael addition fashion to give the desired compounds (*Scheme 1.2.1*).[8]



Scheme 1.2.1

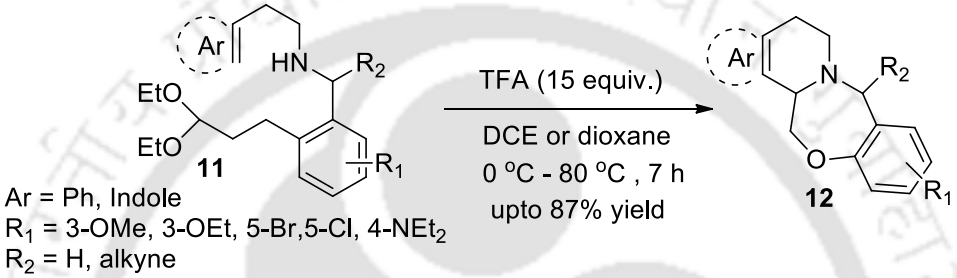
Li and co-workers reported a tandem reaction of 4-(1-acetoxyallyl)-1-sulfonyl-1,2,3-triazole **9** to form 3-acetyl substituted dihydropyridine **10** *via* formation of an imino rhodium carbene



Scheme 1.2.2

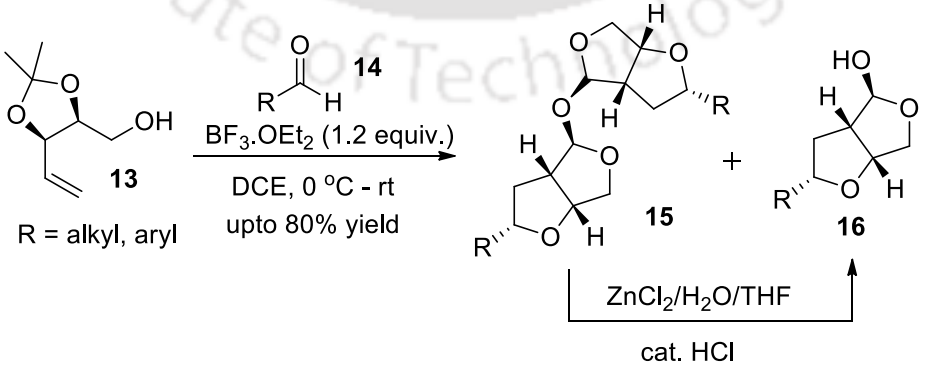
followed by 1,2-migration of acetoxy group and six electron electrocyclic ring closure process (*Scheme 1.2.2*).[9]

Synthesis of benzo[1,4]oxazepino-fused tetrahydroisoquinoline/tetrahydro-*β*-carboline derivatives **12** were made possible *via* one-pot cascade reaction sequence using propargyl amines having substituted diethylacetal **11** in excess amount of TFA. This reaction involves an acid mediated deprotection of acetal, *in situ* iminium ion formation followed by intramolecular Pictet–Spengler reaction of cyclic iminium ions (*Scheme 1.2.3*).[10]



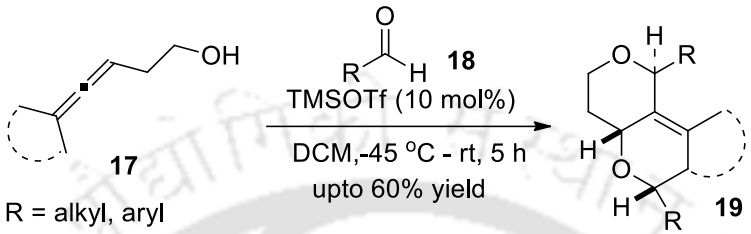
Scheme 1.2.3

A new synthetic route was demonstrated for the cyclization of ((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol **13** with aldehydes **14** to give hexahydrofuro[3,4-*b*]furan-4-ol **16** and its dimer **15** using $BF_3{\cdot}OEt_2$. The reaction proceeds through a domino Prins-cyclization reaction from the *in situ* generated *oxo*-carbenium ion followed by pinocol rearrangement. The dimer produced could further be converted into their corresponding monomer using mild reaction conditions such as $ZnCl_2$ in catalytic amount of HCl (*Scheme 1.2.4*).[11]



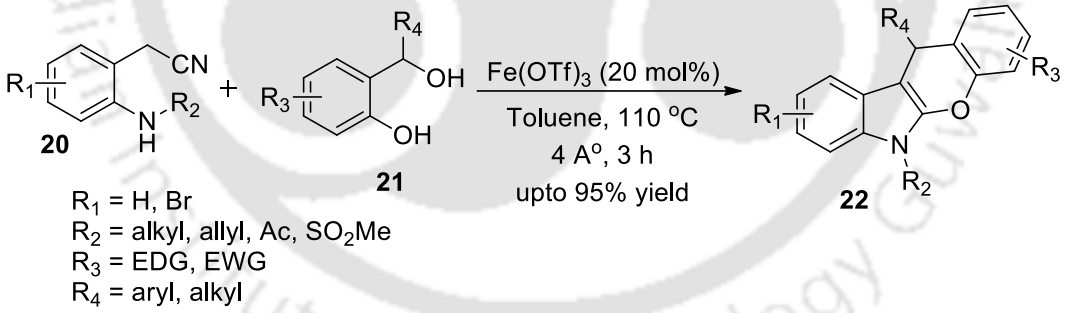
Scheme 1.2.4

A tandem reaction of *β*-allenols **17** and aldehydes **18** furnished substituted pyranopyrans **19** in presence of TMSOTf. The tandem reaction involves nucleophilic attack of allene on *oxo*-carbenium ion which is generated *in situ* from hydroxyl group and the activated aldehydes to produce a *cis*-diene at lower temperature, which further involves in concomitant Diels-Alder reaction with aldehydes to provide desired compounds **19** (*Scheme 1.2.5*).[12]

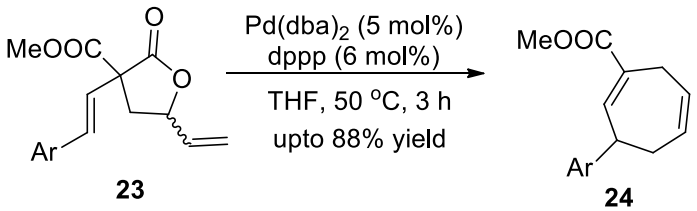


Scheme 1.2.5

An approach to access dihydrochromeno[2,3-*b*]indoles **22** from cascade cyclisation of substituted 2-(aminophenyl)acetonitriles **20** and 2-hydroxyl benzylalcohols **21** in presence of catalytic amount of $Fe(OTf)_3$ was reported by Liu and group. The intramolecular nucleophilic attack, Friedel-Crafts alkylation, cycloaddition and deaminization are the main steps involved in this reaction (*Scheme 1.2.6*).[13]



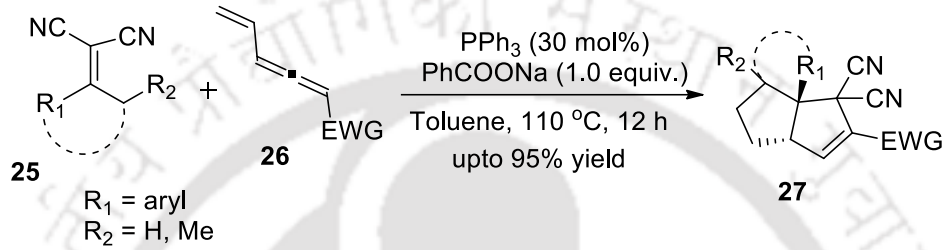
Scheme 1.2.6



Scheme 1.2.7

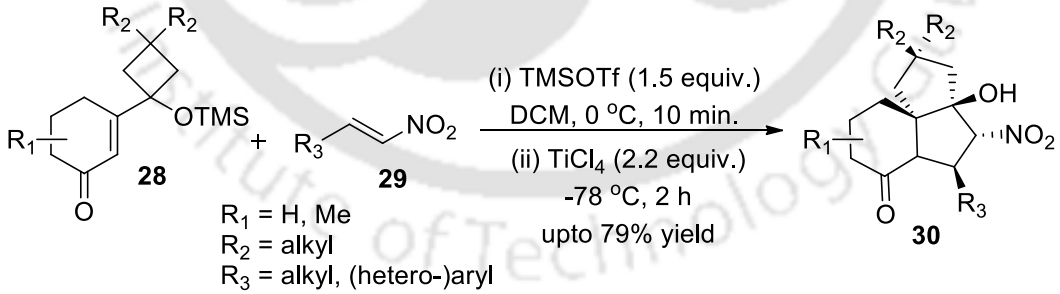
Tsuruda *et al.* demonstrated the synthesis of cycloheptadienes **24** from substituted lactones **23** using Pd(II) catalyst in moderate to good yields. The reaction initiates with a domino intramolecular cyclization, isomerization followed by Cope rearrangement (*Scheme 1.2.7*).[14]

A PPh_3 catalysed sequential annulation reaction of alkylidenemalononitriles **25** and γ-vinyl allenoates **26** was demonstrated by Huang and co-workers to produce fused cyclopentane derivatives **27** *via* two consecutive [3+2] nucleophilic addition reactions (*Scheme 1.2.8*).[15]



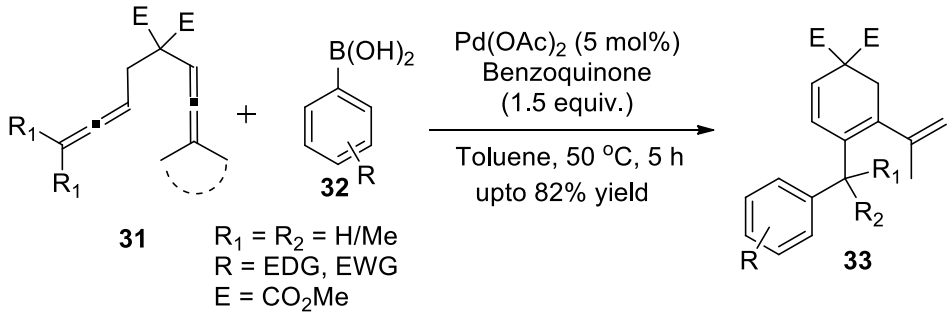
Scheme 1.2.8

Tu and co-workers reported a sequential method for the synthesis of fused multi-functionalized tricyclic carbocycles **30** from vinylogous ketols **28** and nitroolefins **29** using double Lewis acids TMSOTf and $TiCl_4$ at lower temperatures in DCM. The reaction proceeds with *in situ* generation of spirocyclic enol ethers *via* semipinacol rearrangement followed by Michael addition and Henry reaction (*scheme 1.2.9*).[16]



Scheme 1.2.9

A tandem oxidative carbocyclization-arylation protocol for the synthesis of cyclohexadiene derivatives **33** in good yields was reported by Backvall and Volla from bisallenes **31** and aryl boronic acids **32** employing catalytic amounts of Pd(II) catalyst and benzoquinone in toluene at 50 °C (*scheme 1.2.10*).[17]



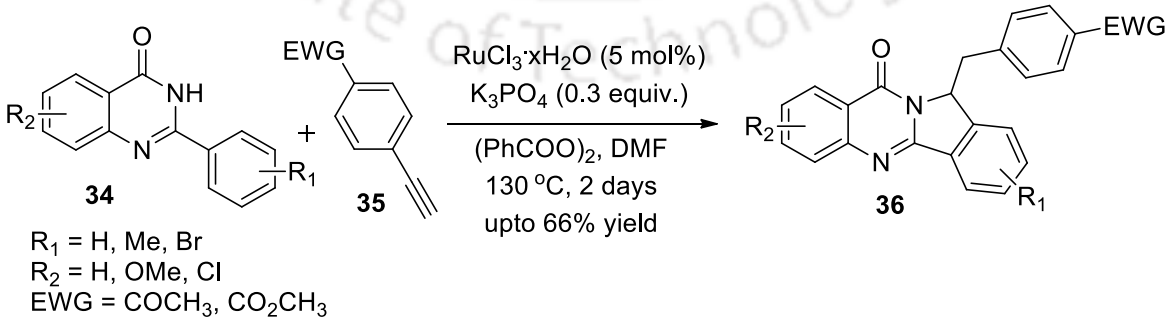
Scheme 1.2.10

1.3 Alkynes in tandem reactions

Alkynes are important and well-known starting precursors used in all areas of organic synthesis to develop simple to complex moieties.[18] The triple bond is already observed in readily participating in both nucleophilic, electrophilic as well as radical cyclizations.[19] However in transition metal catalyzed reactions, alkynes are popularly found to bond in two distinct ways *i.e.* formation of α- and π- bonded metal-alkyne complexes to form new molecules.[20] It is noteworthy that, alkynes are preferentially utilized as starting precursors in many tandem reactions to synthesize a variety of carbo-/hetero-cyclic molecules in synthetic organic chemistry. Moreover, classification of these tandem reactions is done on the basis of reagents and catalysts used and the examples are enlisted below.

1.3.1 Metal catalyzed tandem cyclizations

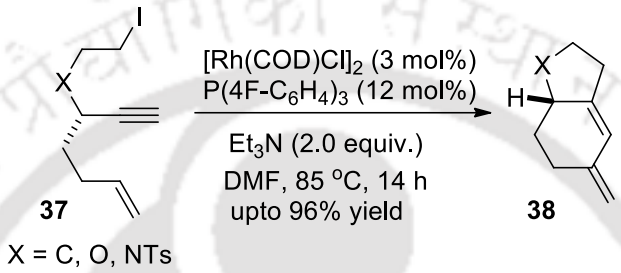
Many transition metals have been used regularly for triggering tandem reaction by activating the alkynic site on a molecule. Mhaske and group described a ruthenium catalysed regioselective



Scheme 1.3.1.1

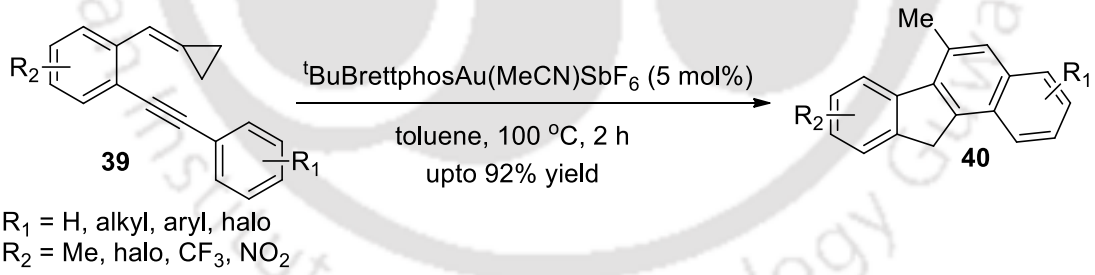
tandem hydroamidation cyclizations of substituted quinazolinones **34** and terminal alkynes **35** in presence of base/oxidant at high temperature to provide fused isoindoloquinazolinones **36** (*Scheme 1.3.1.1*).[21]

Joo *et al*. reported an efficient cascade cyclisation of iodoenynes **37** for the synthesis of hexahydrobenzofuran, hexahydroindole and hexahydroindene **38** in good to excellent yields, using rhodium catalyst and arylphosphines in presence of a base at 85 °C (*Scheme 1.3.1.2*).[22]



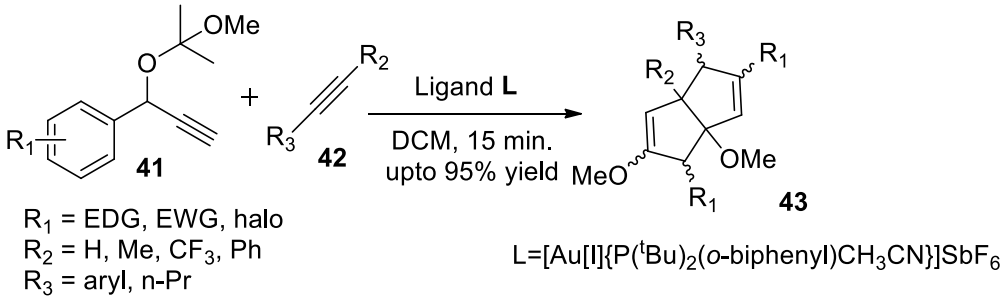
Scheme 1.3.1.2

Shi and co-workers demonstrated an efficient protocol for synthesis of benzofluorene derivatives **40** through a gold catalyzed intramolecular tandem cyclisation of aryl alkynes containing *o*-substituted methylene cyclopropanes **39** in moderate to good yields (*Scheme 1.3.1.3*).[23]



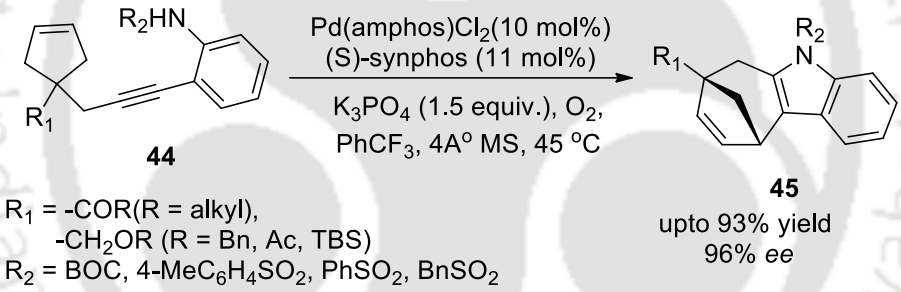
Scheme 1.3.1.3

Siah *et al*. reported a tandem cyclisation for the synthesis of bicyclic highly substituted and poly functionalized pentalenes **43** from various propargylacetals **41** and substituted aryl alkynes **42** using gold(I) catalyst in excellent yields. The reaction proceeds *via* two subsequent cycloaddition reactions *i.e.* [2+2]-/[2+3]-cycloadditions followed by rearrangements in the transition state (*Scheme 1.3.1.4*).[24]

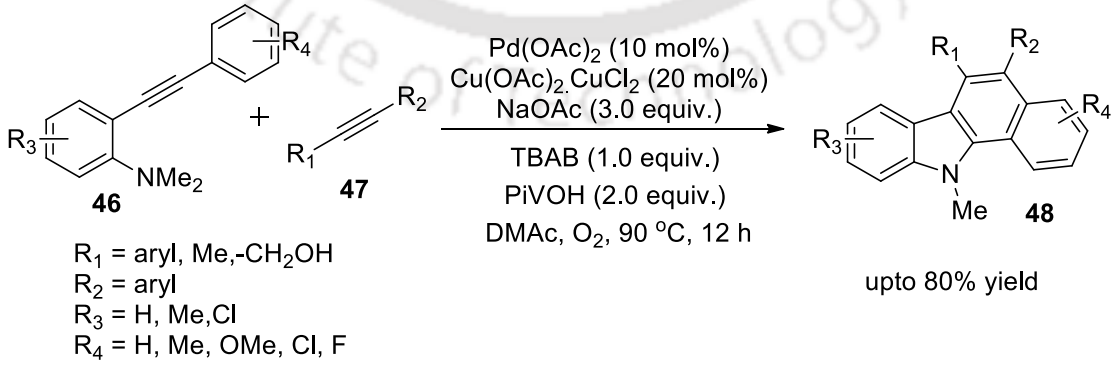


Scheme 1.3.1.4

Wang *et al*. described an enantioselective synthesis of substituted indole fused bicycle[3,2,1]octanes **45** from *N*-sulfonyl-2-alkynylanilide **44** *via* aminopalladition followed by Heck-type reaction carried out in presence of palladium catalyst using (*S*)-synphos ligand and base. The reaction provided the product **45** in moderate to good yield with an excellent enantioselectivity (*Scheme 1.3.1.5*).[25]



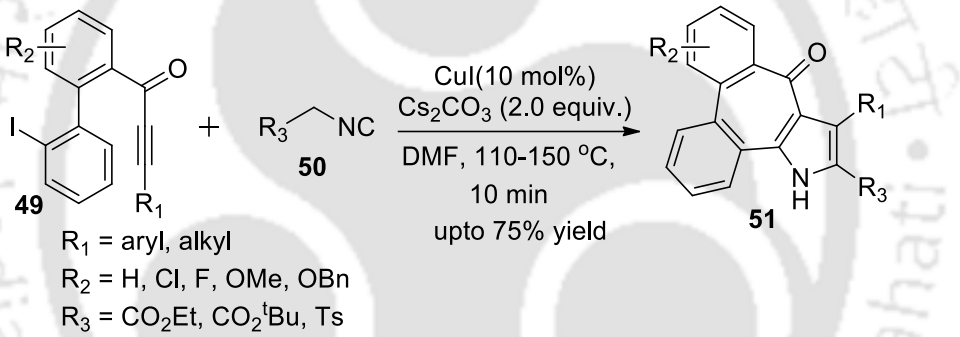
Scheme 1.3.1.5



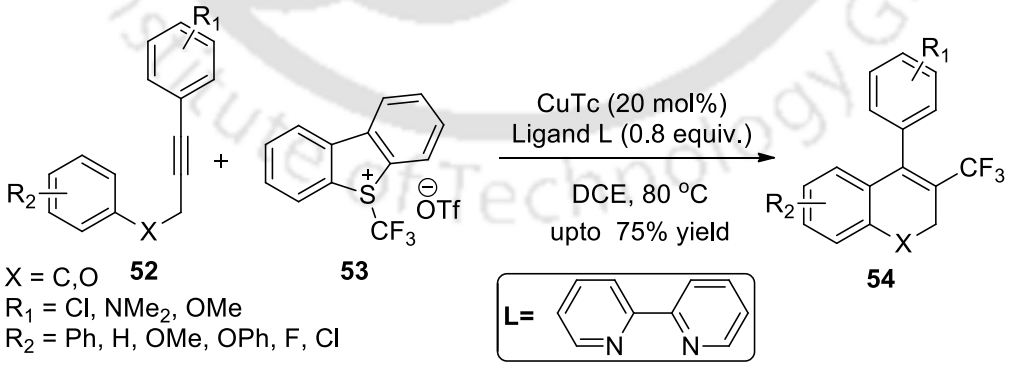
Scheme 1.3.1.6

Liang and co-workers reported a straight forward method for the synthesis of regioselective polycyclic functionalized indoles **48** through palladium and copper co-catalyzed tandem cyclisation followed by *C-H* functionalization of *o*-alkynyl anilines **46** and disubstituted alkynes **47**. Molecuclar oxygen was used as an oxidant to efficiently regenerate palladium catalyst during the reaction (*Scheme 1.3.1.6*).[26]

A convenient procedure for the synthesis of tetracyclic skeleton having fused pyrrole and cycloheptanone **51** was accessed from biphenyl with iodo substitution at *ortho* position in one phenyl ring and alkynoyl group at the other **49** and isocyanoacetates **50** in presence of catalytic amount of CuI and base, was described by Cai and group. The tandem reaction follows through a [3+2]-cycloaddition/*C–C* coupling reactions (*Scheme 1.3.1.7*).[27]



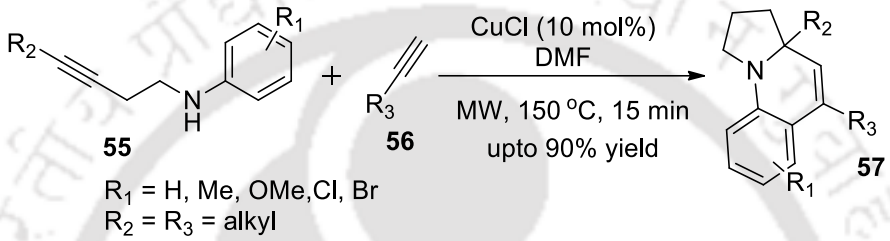
Scheme 1.3.1.7



Scheme 1.3.1.8

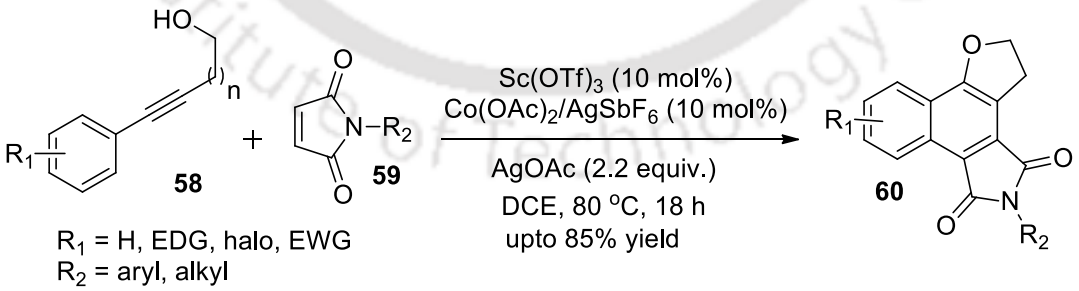
Ji *et al*. described the synthesis of 3-trifluoromethyl-1,2-dihydronaphthalene derivatives **54** *via* domino trifluoromethylation and cyclization of internal alkynes **52** with Umemoto's reagent **53** in moderate to good yields (*Scheme 1.3.1.8*).[28]

Ma *et al*. developed a cascade cyclisation of internal aminoalkynes **55** and alkynes **56** catalyzed by copper(I) catalyst under microwave radiation for synthesis of tetrahydropyrrolo[1,2-*a*]quinolines **57** in convenient yields (*Scheme 1.3.1.9*).[29]



Scheme 1.3.1.9

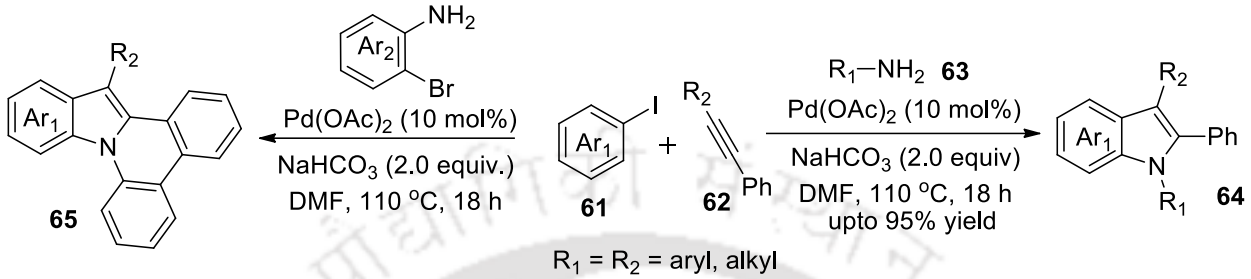
Reddy and co-workers very recently published a convenient method for the synthesis of pyrano- and heteroaryl fused pthalimides **60** from readily available maleimides **59** and substituted alkynols **58** catalyzed by combined Sc(III) and Co(III) catalysts. The reaction proceeds through Sc(III) catalyzed domino electrophilic cyclization, ligand exchange with Co(III), and *C−H* activation followed by maleimide insertion (*Scheme 1.3.1.10*).[30]



Scheme 1.3.1.10

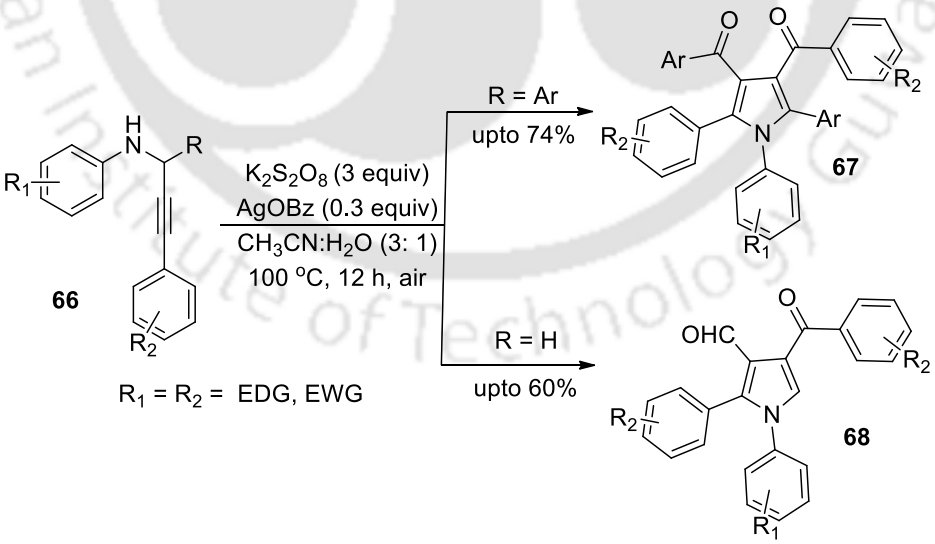
An effective approach for the synthesis of substituted indoles **64** as well as indolo[1,2-*f*]phenanthridine scaffolds **65** was described by Habibi and co-workers from commercially

available iodoarenes **61**, aryl amines **63** and disubstituted alkynes **62** using palladium(II) catalyst and base in DMF at 110 °C. The reaction followed a sequential pathway of palladium-catalyzed alkyne insertion, *C−H* activation and palladacycle amination respectively (*Scheme 1.3.1.11*).[31]



Scheme 1.3.1.11

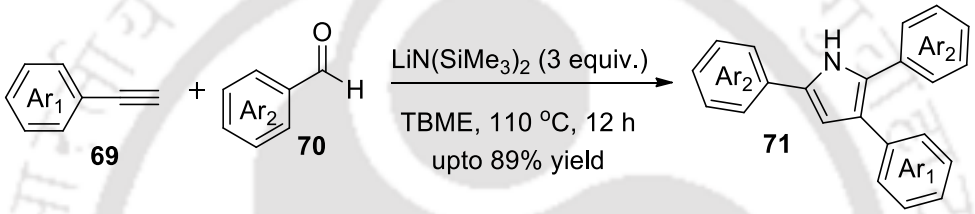
A radical mediated protocol for oxidative dimerization of *N*-propargylamines **66** was reported to provide carbonyl groups having both tetra- and pentasubstituted pyrroles (**67**/**68**) in good yields, catalyzed by silver benzoate in the presence of $K_2S_2O_8$. The reaction proceeds through *in situ* generation of imine *via* SET mechanism which coupled with *N*-propargyamines to produce the target products. The methodology was further extended toward the synthesis of pyrrolo- [3,4-*d*]pyridazine (*Scheme 1.3.1.12*).[32]



Scheme 1.3.1.12

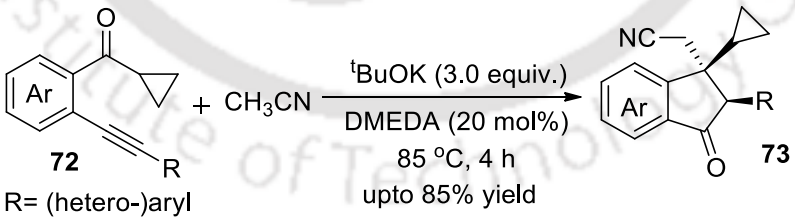
1.3.2 Metal free tandem cyclizations

Metal free reactions have always gained importance in organic synthesis as it reduces the cost of synthesis as compared to metal catalysts. Chen *et al*. described a one-pot procedure for synthesis of trisubstituted pyrroles **71** from arylalkynes **69** and aryl aldehydes **70** in presence of base $LiN(SiMe_3)_2$. The reaction move along *via* nucleophilic attack of acetylide anion to *N*-(trimethylsilyl)imines to form allenyllithium which further involves in intramolecular nucleophilic attack on *in situ* generated *N*-(trimethylsilyl)imines and subsequent cyclization to yield the compounds **71** (*Scheme 1.3.2.1*).[33]



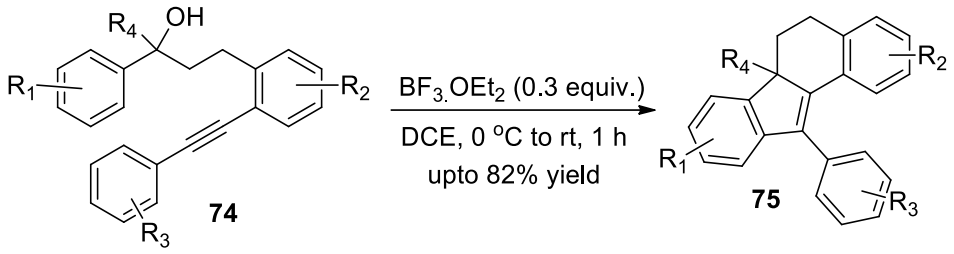
Scheme 1.3.2.1

Jiang and group reported a cascade 1,4-*oxo*-migration and intramolecular cyclization of *β*-alkynyl ketones **72** and acetonitrile co-promoted by double base to afford substituted indanones **73** in moderate to good yields. Acetonitrile serves as the source of cyanomethylene for nucleophilic attack at carbonyl center (*Scheme 1.3.2.2*).[34]



Scheme 1.3.2.2

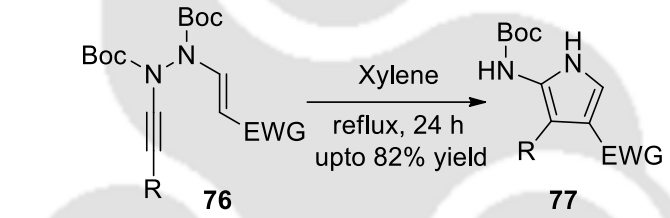
Satyanarayana and group reported a facile method *via* domino intramolecular cyclization of alkynols **74** under Lewis acidic conditions to afford dihydrobenzo[*a*]fluorenes **75** regioselectively in moderate to good yields (*Scheme 1.3.2.3*).[35]



R_1 = R_3 =H, alkyl, OMe, halo;
R_2 = H, OMe, F; R_4= H, alkyl

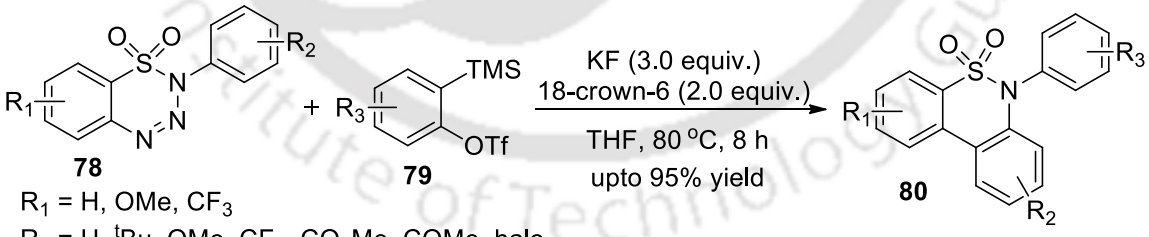
Scheme 1.3.2.3

Tejedor and co-workers described a simple cascade procedure involving diaza-Cope rearrangement, isomerization and 5-*exo*-*dig* cyclization reaction of alkynyl vinyl hydrazides **76** to afford mono protected 2-aminopyrroles **77** in moderate to good yields (*Scheme 1.3.2.4*).[36]



R = alkyl, Ph, Cyclopropyl
EWG = -COPh, -$CONMe_2$, -COC_5H_{11}

Scheme 1.3.2.4



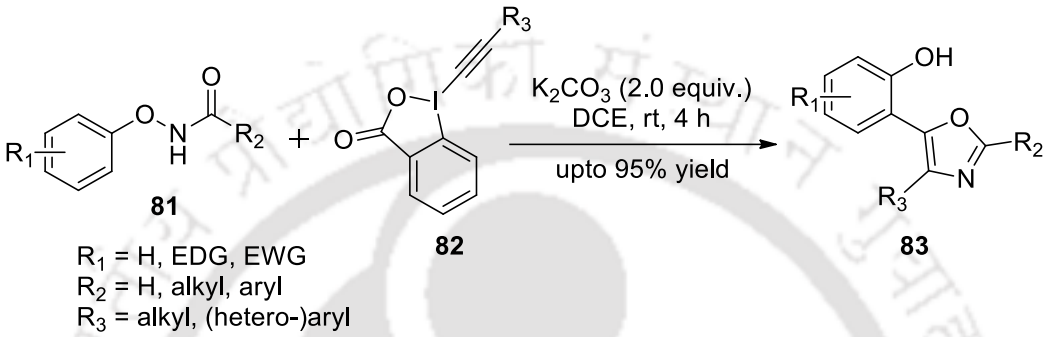
R_1 = H, OMe, CF_3
R_2 = H, ^{t}Bu, OMe, CF_3, CO_2Me, COMe, halo
R_3 = alkyl, aryl, halo

Scheme 1.3.2.5

A tandem transition-metal-free intramolecular homolytic cyclization of diradical species generated from thermal decomposition of benzothiatriazine-1,1-dioxide **78** followed by *N*-

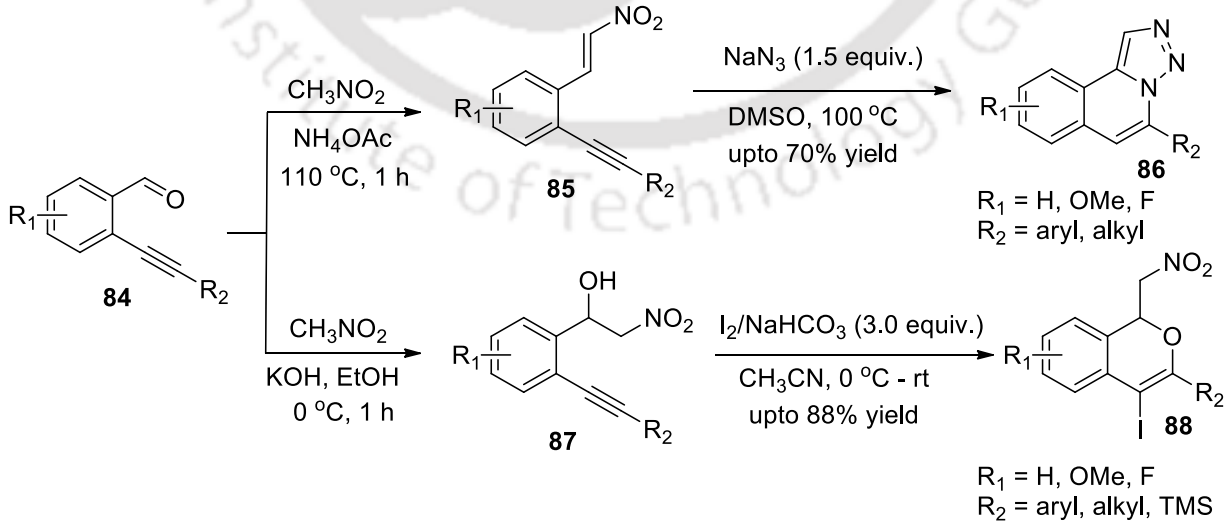
arylation reaction with aryne source **79** was proposed by Thorat *et al*. to afford biarylsultam derivatives **80** in moderate to excellent yields (*Scheme 1.3.2.5*).[37]

A base mediated, mild domino reaction condition was developed by Wen and group for the generation of oxazolylphenols **83** from *N*-phenoxyamides **81** and alkynylbenziodoxolones **82** in excellent yields. The reaction chooses to follow a sequence of [3,3]-rearrangement, carbene insertion afterwards Michael addition and finally cyclization (*Scheme 1.3.2.6*).[38]



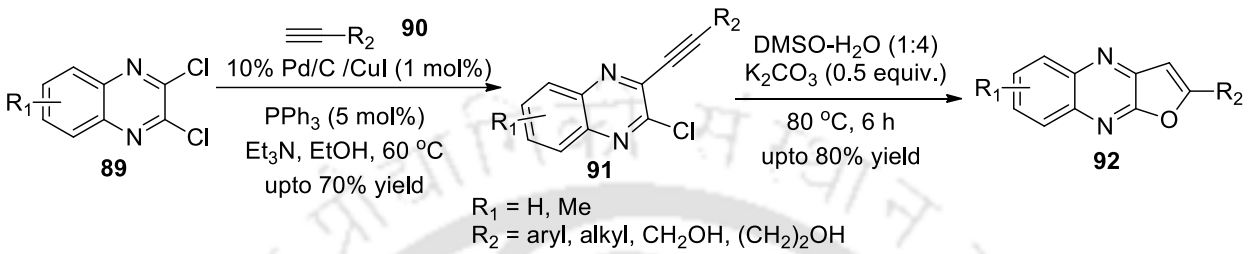
Scheme 1.3.2.6

Kundu and co-workers developed straight forward approach for the synthesis of substituted triazoloisoquinolines **86** and isochromenes **88** from akynylbenzaldehydes **84** in moderate to good yields. Both the strategies include condensation with nitromethane followed by [3+2]-cycloaddition with extrusion of nitro group in the former whereas electrophilic iodocyclizations using base in the latter (*Scheme 1.3.2.7*).[39]



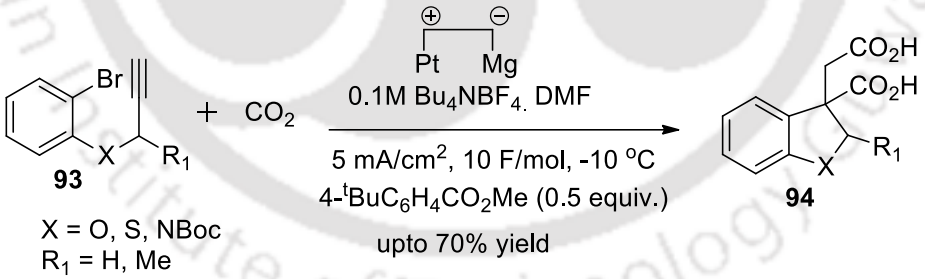
Scheme 1.3.2.7

Pal and co-workers described a two-step strategy for the synthesis of furan fused *N*-heterocycles **92** from 2-chloro-3-alkynyl quinoxalines **91** using base and DMSO as a solvent. Initially 2-chloro-3-alkynyl quinoxalines undergo hydrolysis and subsequent *in situ* cyclization leading to the formation of desired products upto 80% yield (*Scheme 1.3.2.8*).[40]



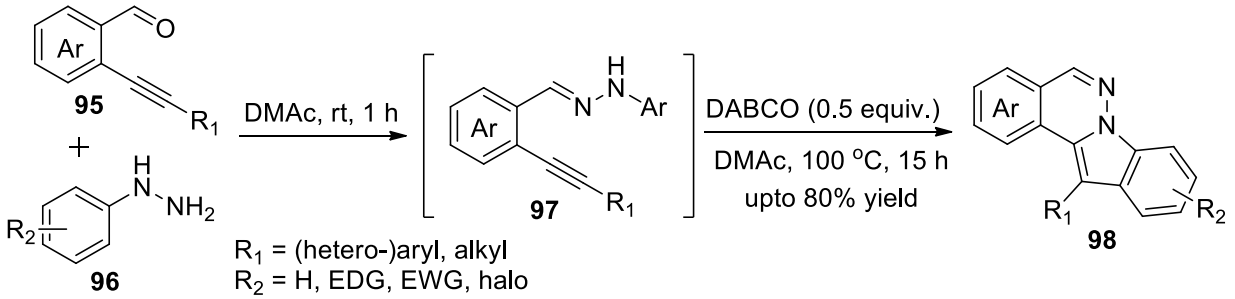
Scheme 1.3.2.8

Katayama *et al.* synthesized 2,2-ring fused succinic acid derivatives **94** using tandem radical cyclisation of 2-(2-propynyloxy)bromobenzenes **93** and carboxylation implementing electrochemical reduction with an undivided cell having Pt and Mg as cathode and anode, respectively. The reaction was also successful in producing dihydrobenzofurans and dihydrobenzothiophenes (*Scheme 1.3.2.9*).[41]



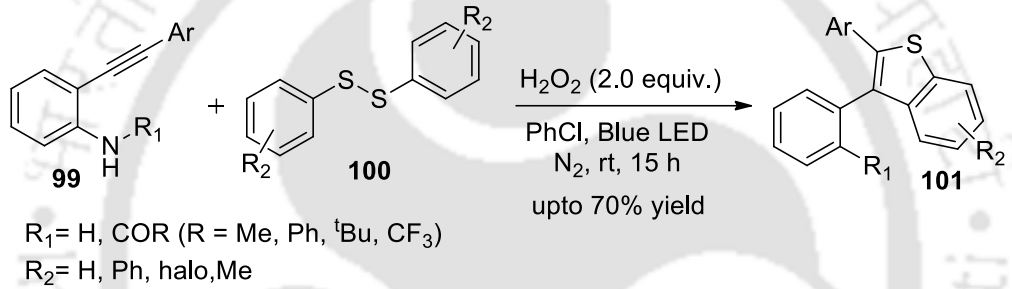
Scheme 1.3.2.9

A base mediated tandem 6-*exo*-*dig* radical cyclization to synthesize indole fused pthalazines **98** from alkynylbenzylidenehydrazines **97** was demonstrated by Cui and co-workers in good yields. The corresponding alkynylbenzylidenehydrazines **97** were prepared *via* a condensation reaction of aldehydes **95** and hydrazines **96.** (*Scheme 1.3.2.10*).[42]



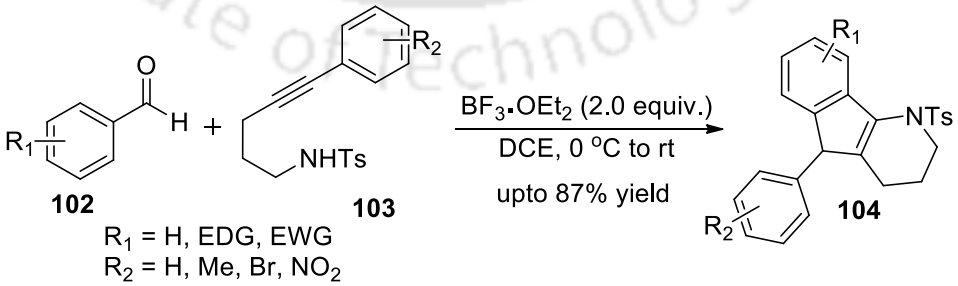
Scheme 1.3.2.10

Wang and co-workers reported a convenient metal and photocatalyst free tandem cyclisation of *o*-alkynyl anilines **99** and disulfides **100** to access diversely substituted benzothiophenes **101** in moderate to good yields induced by visible light conditions (*Scheme 1.3.2.11*).[43]



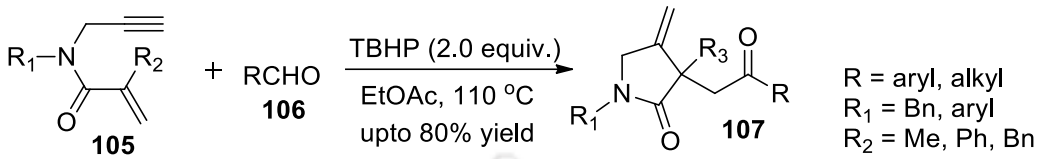
Scheme 1.3.2.11

Saikia and co-workers reported the synthesis of fused tetrahydroindenopyridines **104** from α-sulfonamido alkynes **103** and aldehydes **102** using $BF_3.OEt_2$ at room temperature (*Scheme 1.2.1.1*).[1b] The nucleophilic attack of alkyne on activated aldehyde followed by Friedel-Crafts reaction are the key steps involved in this reaction (*Scheme 1.3.2.12*).[1b]



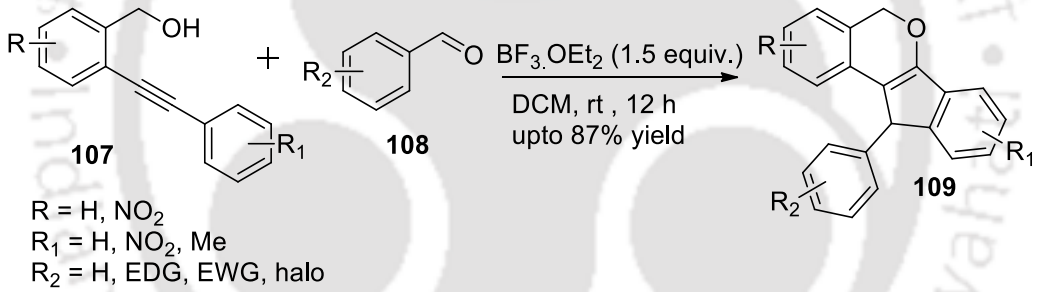
Scheme 1.3.2.12

tert-Butyl hydroperoxide (TBHP)-mediated regioselective one-pot, cascade radical cyclization of 1,6-enynes **105** and aldehydes **106** to produce substituted 2-pyrrolidinones **107** in moderate to good yields was reported by Xu *et al.* (*Scheme 1.3.2.13*).[44]



Scheme 1.3.2.13

A mild and efficient method for the synthesis of dihydroindeno[1,2-*c*]isochromene **109** was developed from alkynol **107** and aldehydes **108** using boron trifuoride etherate in good yields. The reaction proceeded *via* cascade cyclization from the alkyne and the activated aldehydes followed by Friedel-Crafts reaction (*Scheme 1.3.2.14*).[45]



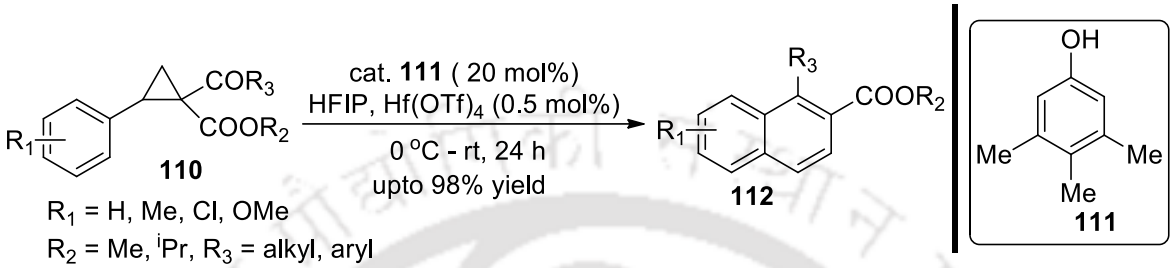
Scheme 1.3.2.14

1.4 Brief description on DAC

Donor–acceptor cyclopropanes (DACs) serve as tool box to organic synthetic community. Owing to its high ring strain and the donor and acceptor groups positioned vicinal to each other further aids the easy cleavage of *C*-*C* bond in presence of Lewis acid thereby leading to 1,3 zwitterion formation.[46] Henceforth, the DACs have been extensively utilized in ring opening reactions with different nucleophiles,[47] which involve in ring expansion reactions, annulations and rearrangements etc.,[48] to provide differently membered carbo- and heterocyclic compounds.[46,49] Apart from this, the ring opening along with different consecutive reactions are quite well studied, a few them are enlisted below.

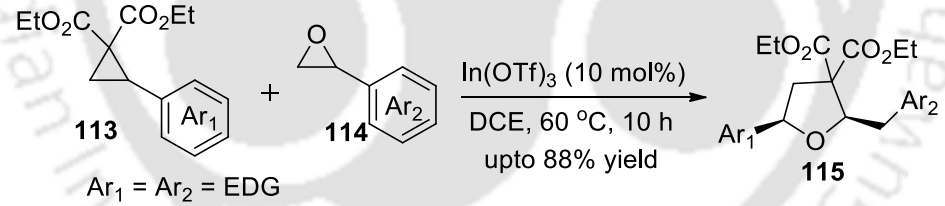
1.4.1 Tandem reactions using DACS

Xu and group reported a domino ring-opening and cyclization reaction of differently substituted DACs **110** catalyzed by 3,4,5-trimethylphenol **111** and Lewis acid for direct synthesis of substituted naphthalenes **112** in excellent yields (*Scheme 1.4.1.1*).[50]

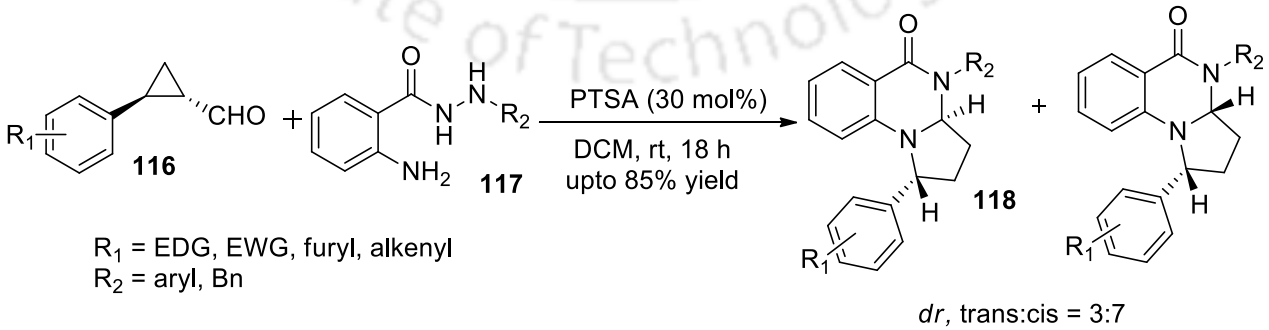


Scheme 1.4.1.1

$In(OTf)_3$ catalyzed one-pot synthesis of *cis*-2,5-aryl-benzyl substituted tetrahydrofurans **115** was explained by Banerjee and group employing epoxides **114** and DACs **113** as starting precursors. The reaction proceeds through a domino Meinwald rearrangement/[3+2]-cycloaddition to provide functionlized tetrahydrofurans **115** in moderate to good yields with *cis*-selectivity (*Scheme 1.4.1.2*).[51]



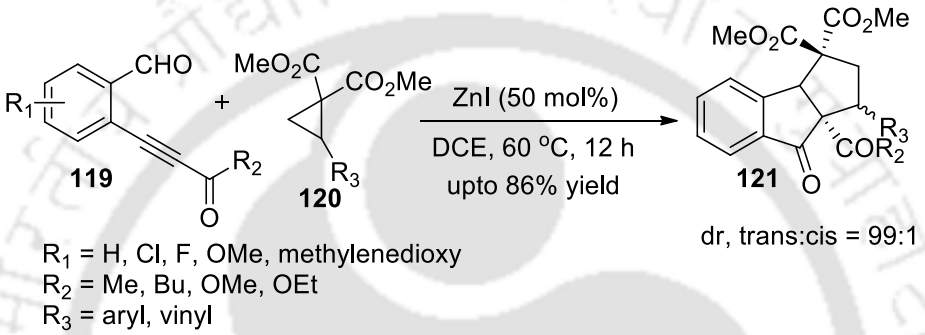
Scheme 1.4.1.2



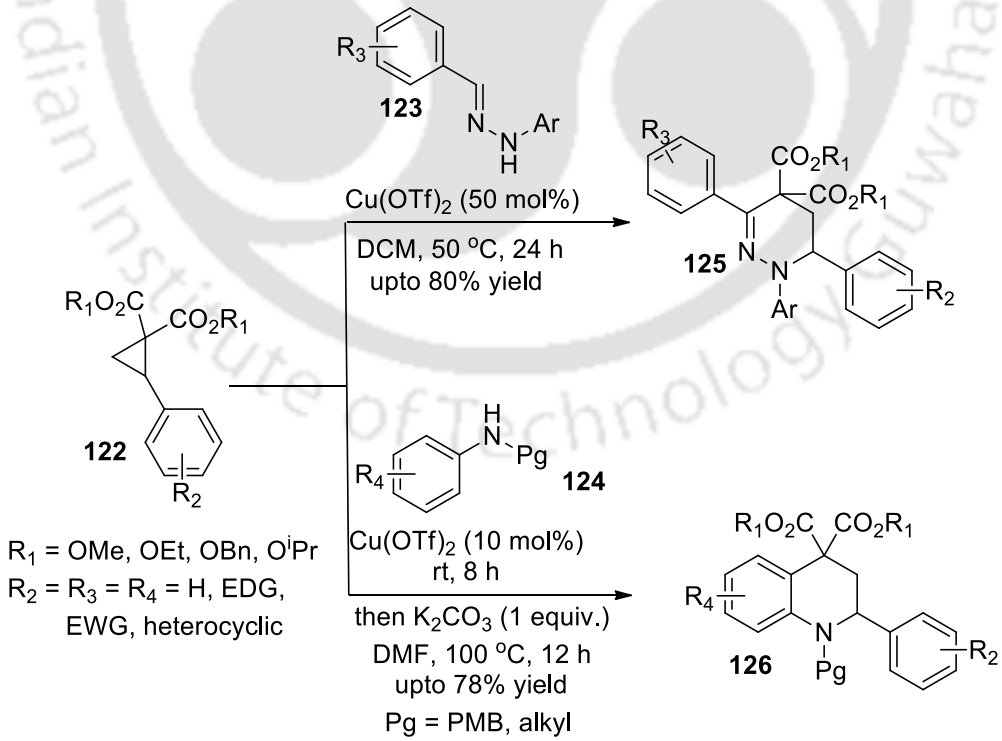
Scheme 1.4.1.3

Same group reported a protocol for regioselective synthesis of tetrahydropyrrolo[1,2-a]quinazolin-5(1*H*)one derivatives **118** by reacting cyclopropane aldehydes **116** with substituted anthranil hydrazides **117** in the presence of PTSA. The reaction involves tandem imine formation/intramolecular cyclization followed by nucleophilic ring opening of the cyclopropyl ring to furnish desired compound in good to excellent yield (*Scheme 1.4.1.3*).[52]

Zhu and group developed a one-pot cascade Zn(II) catalyzed hydrolysis/Knoevenagel condensation/[3+2]-cycloaddition reaction sequence by using DACs **120** and enynals **119** to give substituted indanone fused cyclopentanes **121** in moderate to good yields (*Scheme 1.4.1.4*).[53]



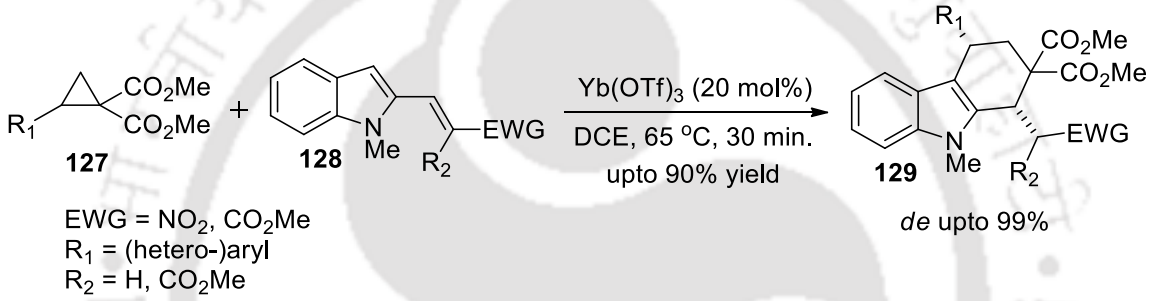
Scheme 1.4.1.4



Scheme 1.4.1.5

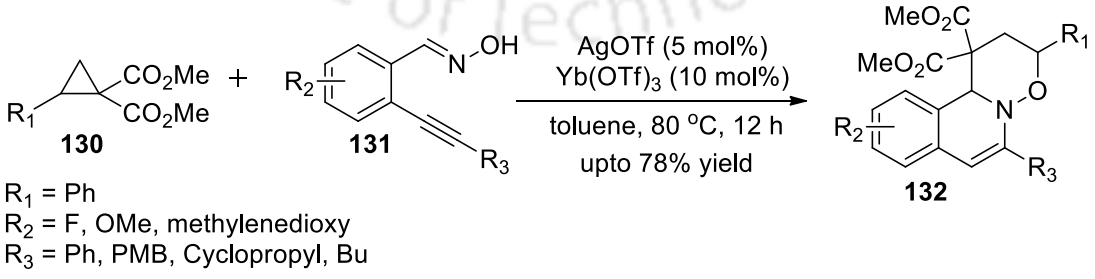
Tetrahydropyridazines **125** and tetrahydroquinolines **126** were synthesized by Punniyamurthy and group employing bisarylhydrazones **123** or *N*-alkyl anilines **124** with DACs **122** catalyzed by Cu(II) triflate. The reaction transformation was explained as tandem ring-opening followed by SET leading to oxidative alkylation for the former and oxidative cyclization sequence for the latter to provide corresponding targets (*Scheme 1.4.1.5*).[54]

Ghorai and co-workers reported a diastereoselective synthesis of highly functionalized tetrahydrocarbazoles **129** from DACs **127** and indole substituted alkylidenes **128** under catalytic Lewis acidic conditions. The domino ring-opening of cyclopropanes with consecutive nucleophilic attack of indole followed by ring closure from active methylene in Michael addition fashion are the key steps of this reaction (*Scheme 1.4.1.6*).[55]



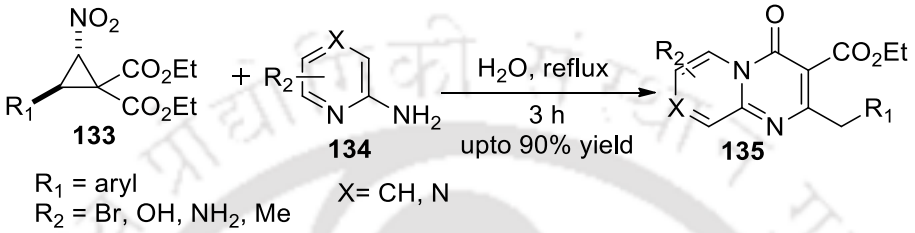
Scheme 1.4.1.6

Wu and co-workers described the synthesis of tetrahydro-1,2-oxazine fused 1,2-dihydroisoquinolines **132** from DACs **130** and 2-alkynylbenzaldoximes **131** in presence of dual catalysts Ag(I)/Yb(III) triflates in toluene at 80 °C. The reaction follows a sequence of Lewis acid catalyzed ring-opening of DAC, [3+3]-cycloaddition and Ag(I) catalyzed alkyne activation leading to *6-endo-dig* cyclization to afford the targets (*Scheme 1.4.1.7*).[56]



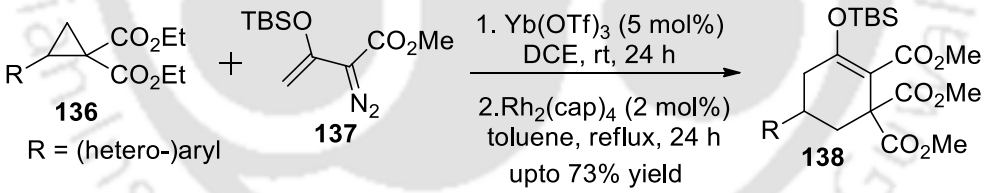
Scheme 1.4.1.7

Srinivasan and co-workers reported an efficient strategy to synthesize pyrido[1,2-*a*]-pyrimidin-4-one/pyrazinopyrimidinone derivatives **135** using 2-aryl-3-nitrocyclopropane-1,1-dicarboxylates **133** and aminopyridine/aminopyrazines **134** in water. The reaction proceeds *via in situ* generation of *α,β*-unsaturated intermediate from cyclopropane, which involves in addition-elimination reaction with **134** followed by cyclization to give the final compounds **135** (*Scheme 1.4.1.8*).[57]

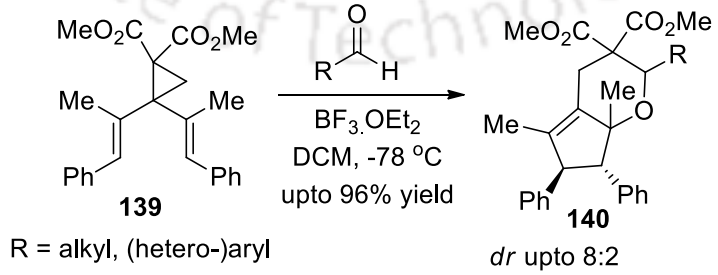


Scheme 1.4.1.8

Doyle and group demonstrated a sequential formal [3+2]-cycloaddition of enoldiazoacetates **137** with DACs **136** in presence of 5 mol% of $Yb(OTf)_3$ to generate diazo-substituted cyclopentane which undergoes Rh(II) catalyzed ring expansion to deliver highly substituted cyclohexenes **138** in moderate to good yields (*Scheme 1.4.1.9*).[58]



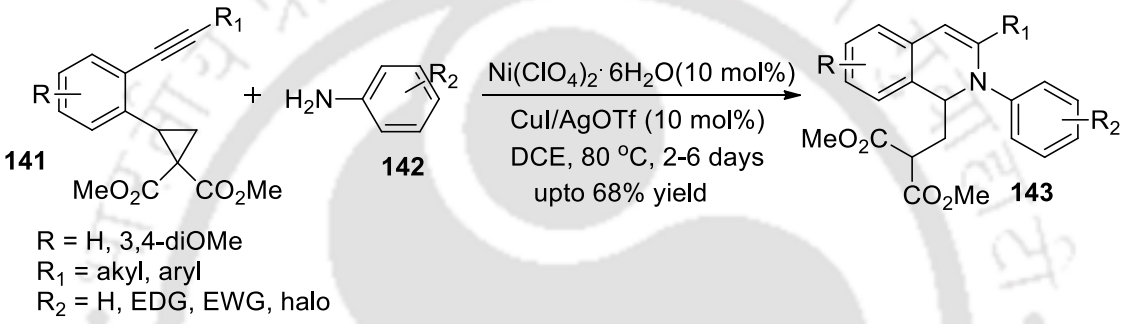
Scheme 1.4.1.9



Scheme 1.4.1.10

Sudhakar and co-workers reported a Lewis acid catalyzed tandem Nazarov cyclization/[4+2]-cycloaddition reaction sequence for the synthesis of fused pyrans **140** from divinyl DACs **139**. Reaction involves initial ring-opening of cyclopropane ring forming a pentadienyl cation that subsequently transforms into cyclic allylic cation by 4π-electrocyclization which on [4+2]-cycloaddition reaction with carbonyl form target compounds **140** (*Scheme 1.4.1.10*).[59]

Unnava *et al.* reported an efficient protocol for the synthesis of substituted 1,2-dihydroisoquinolines **143** *via* tandem ring opening reaction of *o*-alkynyl donor–acceptor cyclopropanes **141** with arylamines **142** followed by intramolecular hydroamination reaction using Ni(II) and Cu(I)/Ag(I) catalytic system (*Scheme 1.4.1.11*).[60]



Scheme 1.4.1.11

1.5. References

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CHAPTER 2

Synthesis of dibenzocyclohepta[1,2-*a*]naphthalene derivatives from alkynyl benzyl alcohols and phenylacetaldehydes *via* sequential electrophilic addition and double Friedel–Crafts reactions

2.1 Introduction

Carbocyclic compounds are frequently found in many natural products and biologically active molecules.[1] Amidst the limitless carbocycles, dibenzocycloheptane is an important structural motif also encountered in some biologically active molecules.[2] For instance, (±)allocolchicine[3] (**A**) is active against many cancer cell lines, tenuifolin[4] (**B**), shows antiproliferative activity against tumor cell line DU145, subavenoside E[5] (**C**) dibenzocycloheptadiene dihydroisosubamol,[5] and subamol[6] (**C**) show inhibitory activity against α-glucosidase type IV (*Figure 2.1.1*). On the other hand, substituted naphthalenes are present in many biologically important compounds[7], optical as well as electronic materials[8] and constitute the backbone of many chiral ligands.[9]

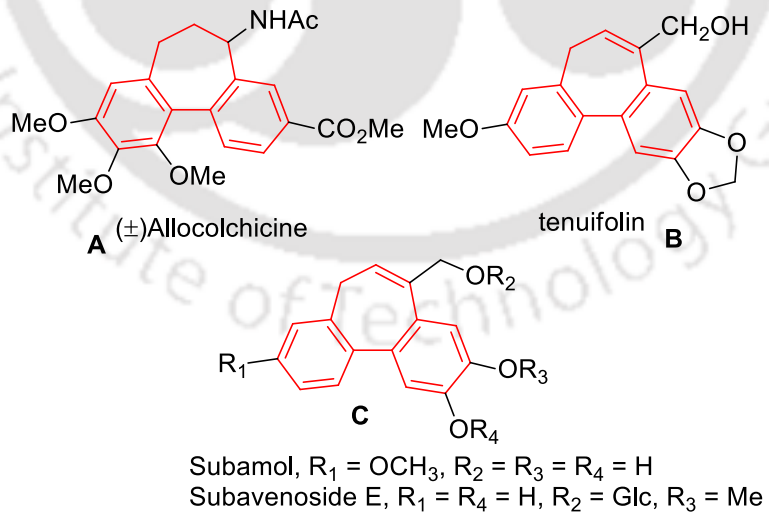
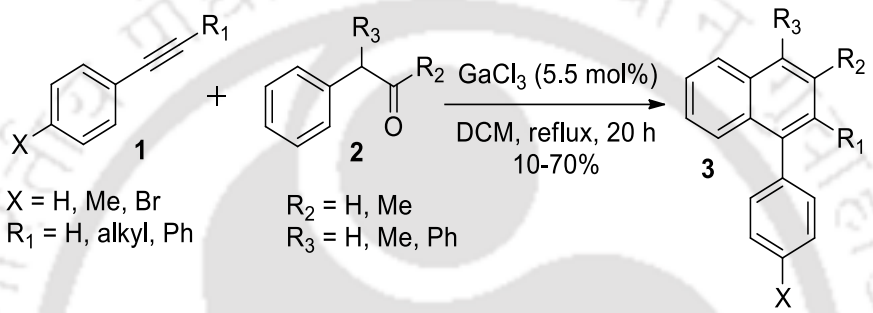


Figure 2.1.1 Examples of bioactive dibenzocycloheptanes

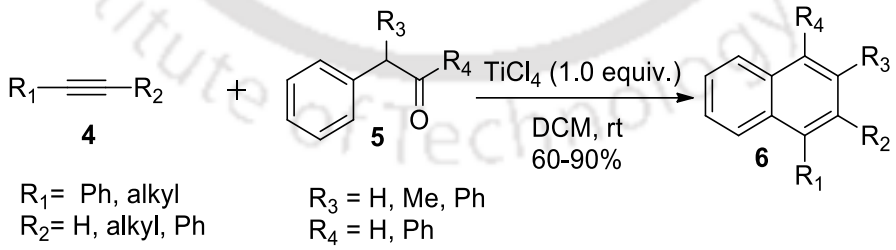
2.2 Literature survey for the synthesis of substituted naphthalenes

Several methods have been employed for the synthesis of substituted/fused naphthalenes from substituted phenyl acetaldehydes and disubstituted alkynes in presence of variety of Lewis acids. For example, Ganapathy and co-workers in 2002 developed a highly regioselective approach for the synthesis of polysubstituted naphthalenes **3** in moderate to good yields, from aromatic alkynes **1** and *α*-aryl substituted carbonyl compounds **2** using catalytic amount of gallium(III) chloride (*scheme 2.2.1*).[10]



Scheme 2.2.1

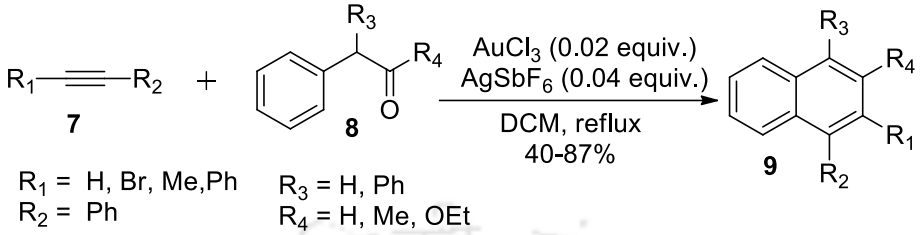
In the succeeding year Kabalka *et al.* reported the reaction of *α*-aryl-substituted carbonyl compounds **5** with terminal as well as internal alkynes **4** in the presence of $TiCl_4$ at room temperature that resulted substituted naphthalene derivatives **6** with high regioselectivity in good to excellent yields (*scheme 2.2.2*).[11]



Scheme 2.2.2

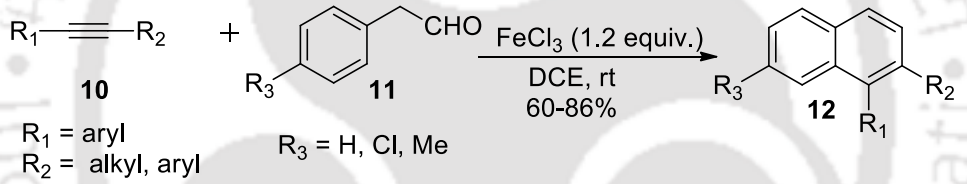
Balamurugan and co-workers demonstrated a protocol for the synthesis of substituted naphthalenes **9** *via* electrophilic addition of arylalkynes **7** to *α*-aryl-substituted carbonyl

compounds **8** followed by benzannulation catalysed by $AuCl_3/AgSbF_6$ system in good to excellent yields (*scheme 2.2.3*).[12]



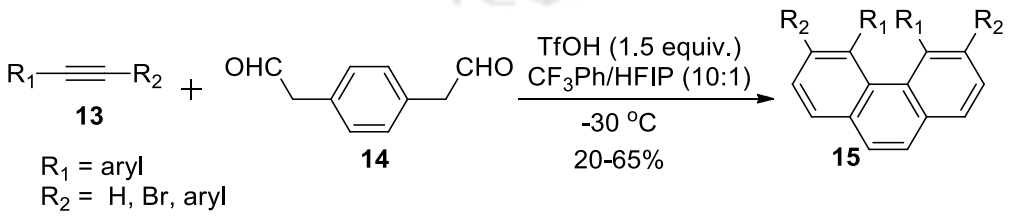
Scheme 2.2.3

Furthermore, a versatile straightforward regioselective method for the synthesis of substituted naphthalenes **12** from arylacetaldehydes **11** and alkynes **10** using green catalyst $FeCl_3$, in good yields was designed by Zhou and co-workers (*scheme 2.2.4*).[13]



Scheme 2.2.4

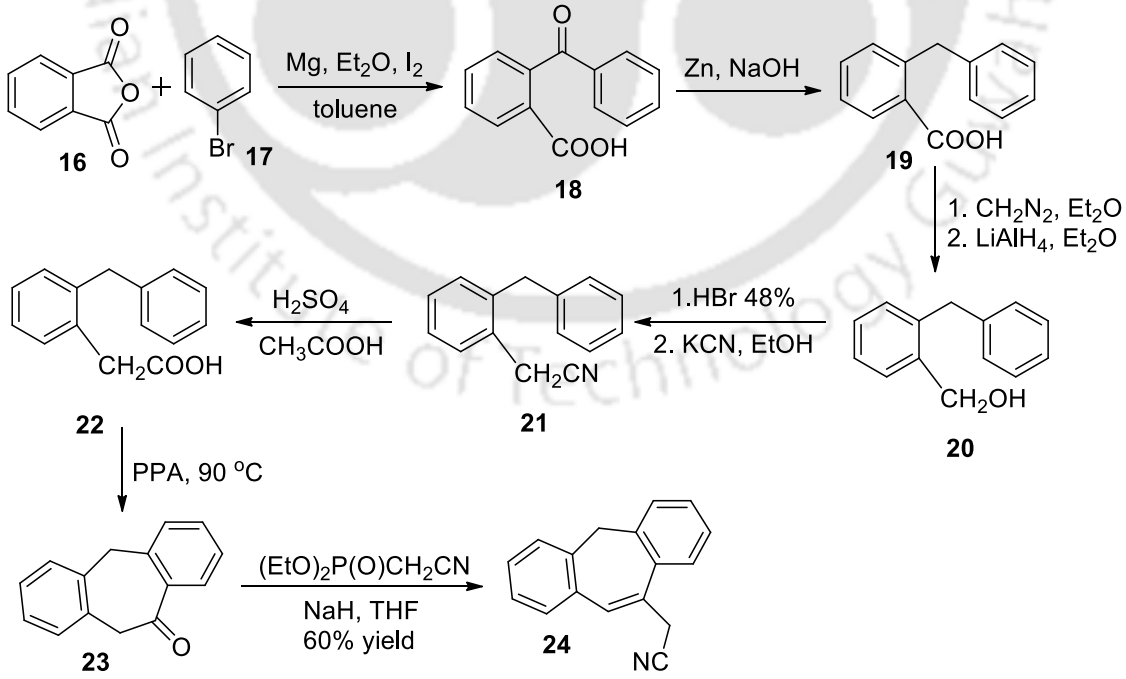
Itami and group reported an efficient approach for the synthesis of sterically hindered phenanthrenes **15** *via* triflic acid-catalyzed bisannulation reaction of benzene diacetaldehydes **14** and alkynes **13** in low to good yields. The sterically hindered 3,4,5,6-tetrasubstituted phenanthrenes display augmented backbone helicity (*scheme 2.2.5*).[14]



Scheme 2.2.5

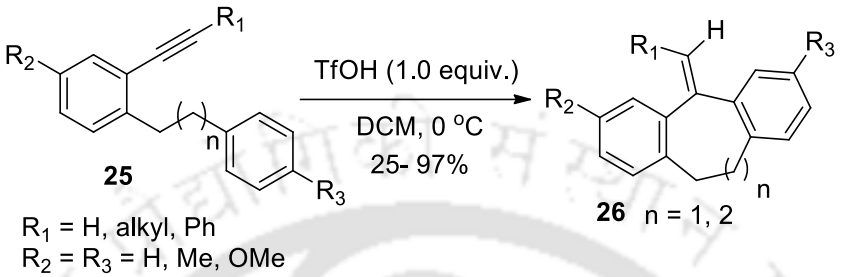
2.3 Literature survey for the synthesis of fused dibenzocycloheptene

As already revealed, highly substituted carbocyclic seven-membered rings are frequently found in natural products and their synthesis possess a significant challenge to the synthetic chemist. In past years, Rivara and Tarzia in 2004 reported a multi-step reaction procedure for the synthesis of substituted dibenzocycloheptene from commercially available phthalic anhydride **16** and bromobenzene **17**. Initally, Grignard reagent which is prepared from bromobenzene on addition to phthalic anhydride gave the 2-benzoylbenzoic acid derivative **18**. Thereafter, reduction of **18** gave **19** which was further involved in a two-step procedure such as esterfication followed by reduction resulted in alcohol **20**. Upon subsequent treatment with hydrogen bromide and potassium cyanide; the benzyl alcohol derivative **20** could be converted into cyanomethyl derivatives **21**. Later, hydrolysis of **21** produced carboxylic acids **22**. Finally, the compound **22** undergoes intramolecular Friedel-Crafts acylation in presence of polyphosphoric acid (PPA) to form dibenzocycloheptanone **23**. The compound **23** was further utilized in synthesis of methyl nitrile substituted dibenzocycloheptenes **24** *via* Wittig-Horner reaction with diethyl (cyanomethyl)phosphonate followed by isomerisation reaction with an overall yield of 60% (*scheme 2.3.1*).[15]



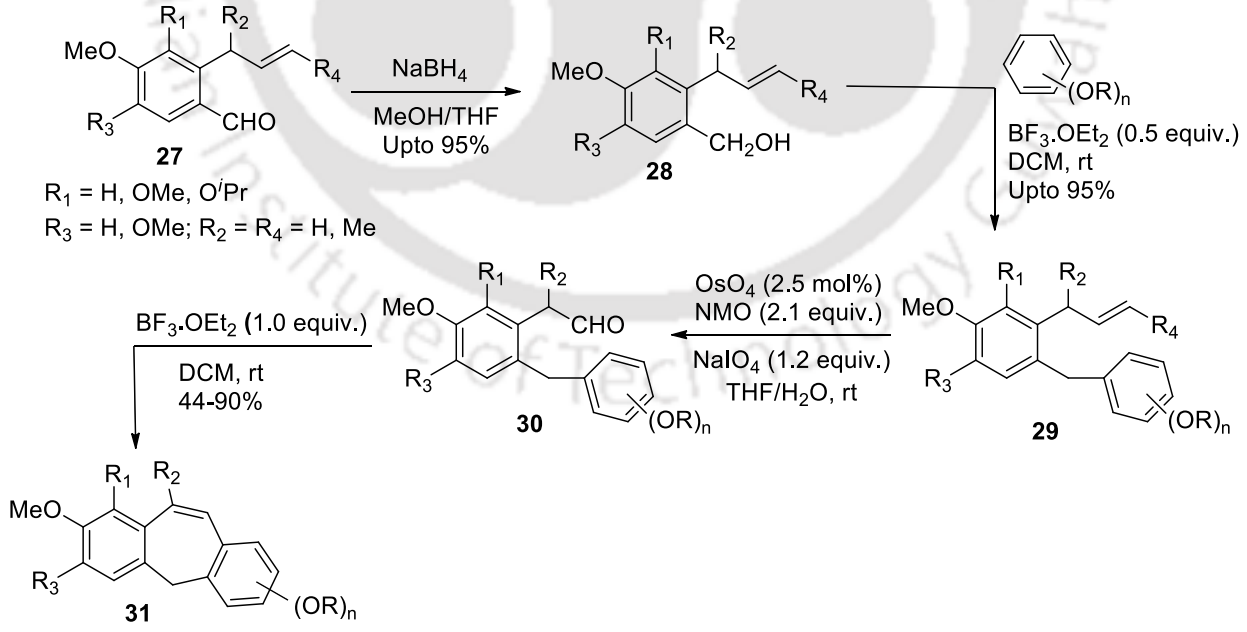
Scheme 2.3.1

Saito and group developed a mild and efficient methodology for the synthesis of seven- to nine-membered dibenzo fused carbocycles **26** from alkynylbenzenes carrying an arylalkyl group at the *ortho*-position *via* Brønsted acid-promoted intramolecular Friedel-Crafts-type alkenylation in quantitative yields (*scheme 2.3.2*).[16]



Scheme 2.3.2

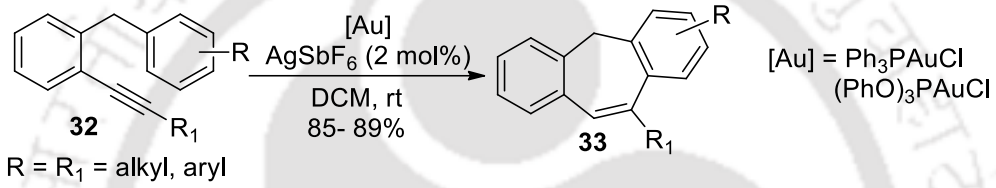
A facile multi step procedure for the synthesis of substituted dibenzocycloheptatrienes was established by Chang and his group from 2-allylbenzaldehydes in good to excellent yields. The successive route constitutes reduction of 2-allylbenzaldehydes **27** to give allylphenylmethanols **28** which undergoes $BF_3.OEt_2$ mediated Friedel-Crafts alkylation with oxygenated benzenes to



Scheme 2.3.3

produce **29**. Oxidative cleavage of **29** lead to *in situ* generation of **30**, followed by Lewis acid mediated intramolecular ring closure furnished the fused dibenzocycloheptatrienes **31** (*scheme 2.3.3*).[17]

Very recently, Alcarazo and co-workers demonstrated a facile synthesis of dibenzocycloheptenes **33** from hydroarylation of substituted 1-benzyl-2-ethynylbenzenes **32** with the use of catalytic system of highly carbophilic gold(I) in combination with $AgSbF_6$. The size of the Au atom has an added advantage that made simultaneous activation of both carbon atoms of the alkyne possible thus, the cyclization at the more sterically available carbon was enabled (*scheme 2.3.4*).[18]



Scheme 2.3.4

2.4 Results and Discussions

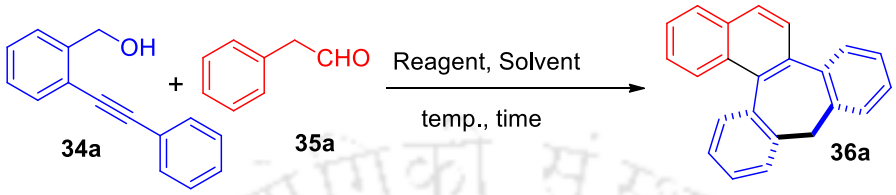
Despite existing literature reports, synthesis of dibenzofused cycloheptenes is always an uphill battle. The methods mainly suffer with drawbacks such as multistep synthesis, use of costly catalysts etc. However, development of new strategies and chemical reactions to synthesize this kind of molecules continues to be a major focus in the modern synthetic organic community.

In this chapter, a concise methodology for the synthesis of substituted 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene *via* sequential electrophilic addition and double Friedel-Crafts cyclization between arylacetaldehydes and alkynyl benzyl alcohols as starting materials has been described.

Considering (2-(phenylethynyl)phenyl)methanol (**34a**) and phenyl acetaldehyde (**35a**) as model substrates, the reaction was performed with 0.5 equivalents of $BF_3{\cdot}OEt_2$ in dichloromethane (DCM) at room temperature (entry 1, *Table 2.4.1*). To our delight, compound **36a** was obtained

in 34% yield without formation of any side products. Encouraged with the result, the reaction was subjected to different conditions as shown in *Table 2.4.1*. The reaction was performed in

Table 2.4.1: Optimization of the reaction[a]

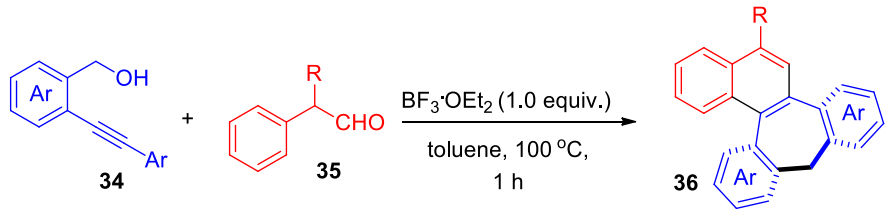


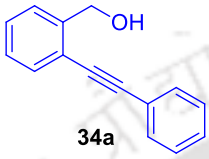
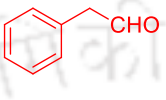
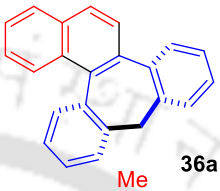
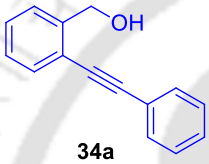
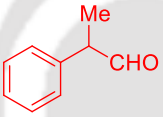
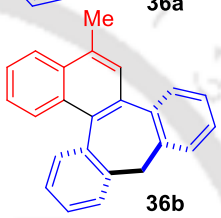
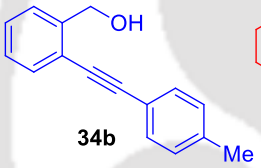
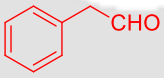
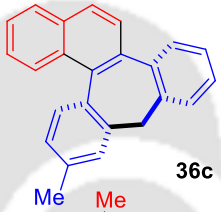
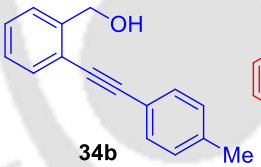
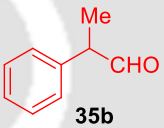
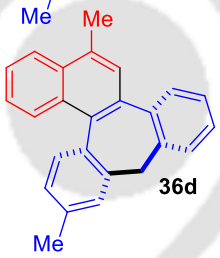
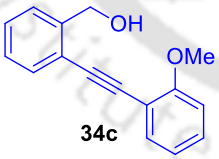
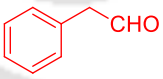
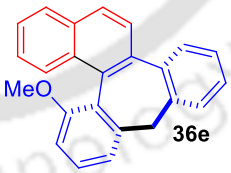
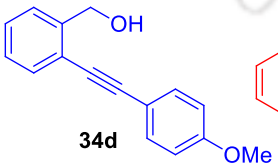
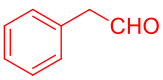
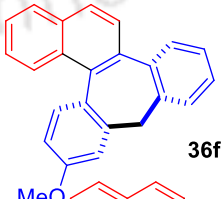
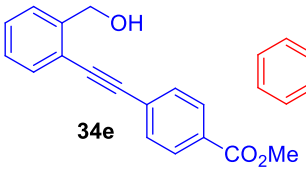
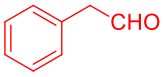
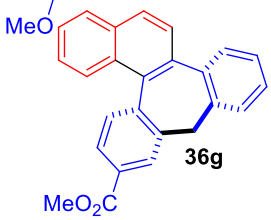
Entry	Reagent (equiv.)	Solvent	Temp.(°C)	Time(h)	Yield(%)[b]
1	$BF_3.OEt_2$(0.5)	DCM	rt	1.5	34
2	$BF_3.OEt_2$(0.5)	DCE	rt	2.0	33
3	$BF_3.OEt_2$(0.5)	CH_3CN	rt	4.0	--[c]
4	$BF_3.OEt_2$(0.5)	Toluene	rt	1.5	41
5	$BF_3.OEt_2$(0.5)	Toluene	60	1.5	44
6	$BF_3.OEt_2$(0.5)	Toluene	100	0.5	48
7	**$BF_3.OEt_2$(1.0)**	**Toluene**	**100**	**0.5**	**70**
8	$BF_3.OEt_2$(1.5)	Toluene	100	0.5	69
9	$InCl_3$(0.1)	Toluene	100	2.0	47
10	$FeCl_3$(0.1)	Toluene	100	2.0	46
11	$FeCl_3$(1.0)	Toluene	100	1.0	65
12	$In(OTf)_3$(0.1)	Toluene	100	2.0	31
13	$Sc(OTf)_3$(0.2)	Toluene	100	2.5	17
14	$Cu(OTf)_2$(1.2)	Toluene	100	2.5	21
15	TMSOTf(1.2)	Toluene	100	2.0	29
16	TfOH(1.2)	Toluene	100	2.5	28
17	PTSA(1.2)	Toluene	100	3.0	8

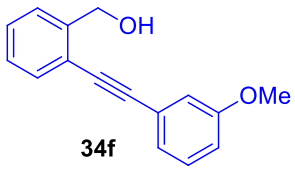
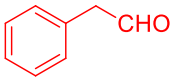
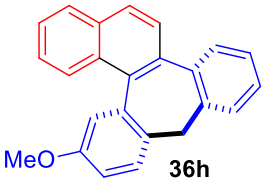
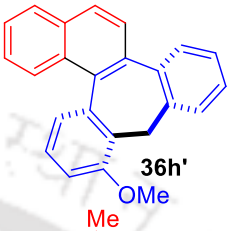
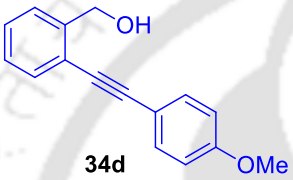
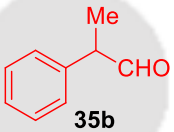
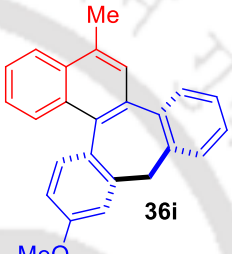
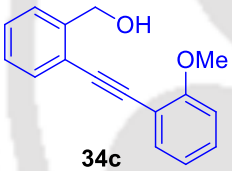
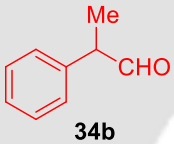
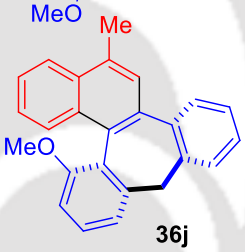
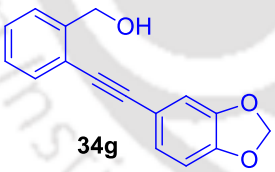
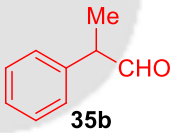
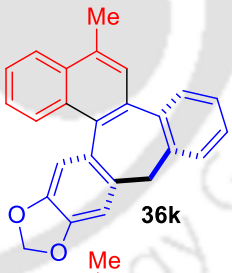
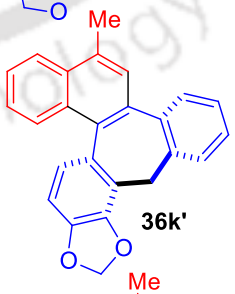
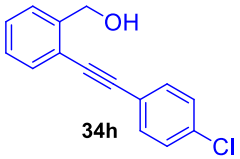
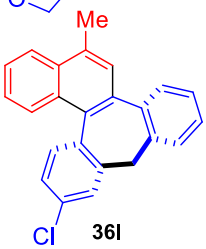
[a]Reaction conditions: **34a** (1.0 equiv), **35a** (1.1 equiv); [b]Yield refers to isolated yield. Compounds are characterised by ^1H, ^{13}C NMR, IR and Mass spectrometry.
[c]No reaction, starting material was recovered.

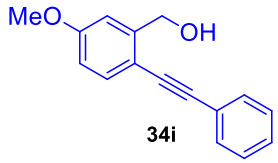
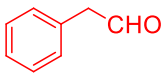
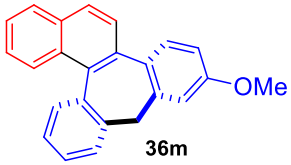
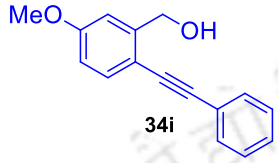
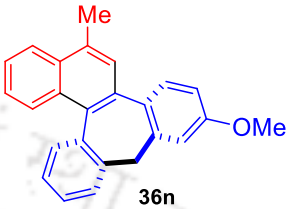
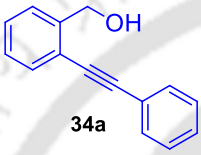
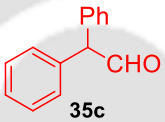
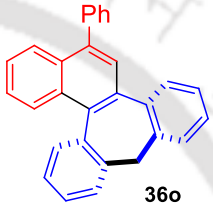
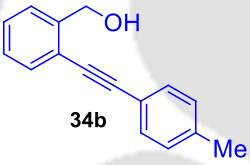
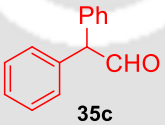
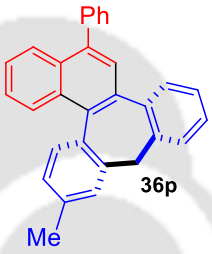
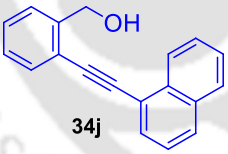
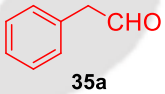
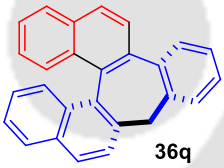
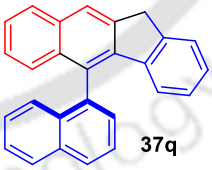
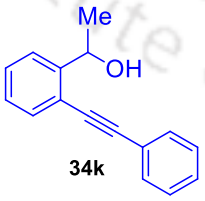
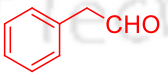
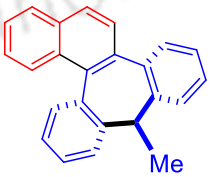
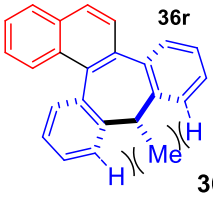
dichloroethane (DCE), acetonitrile and toluene at room temperature (entries 2-4, *Table 2.4.1*). Reactions in DCE and toluene gave 33% and 41% yields respectively, whereas in acetonitrile no product was noticed. At higher temperature such as 60 and 100 °C (entries 5-6, *Table 2.4.1*) the

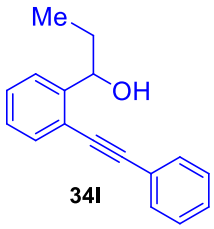
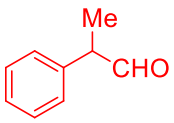
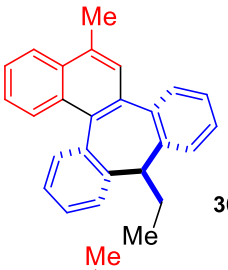
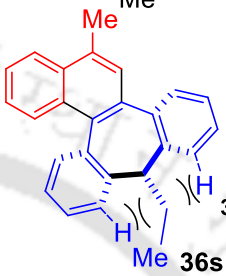
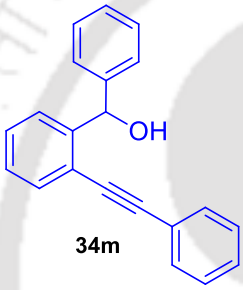
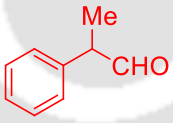
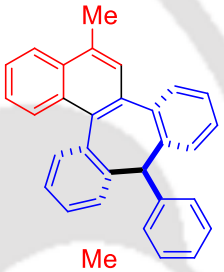
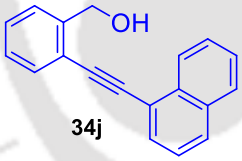
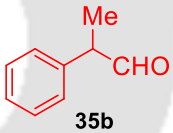
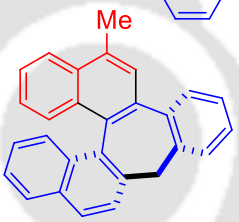
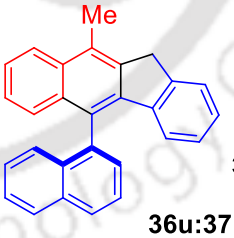
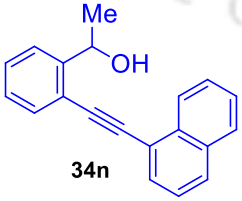
Table 2.4.2 Synthesis of 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene



Entry	Alcohol **34**	Aldehyde **35**	Product **36**	(%)Yield[a]
1				70
2				50
3				60
4				40
5				48
6				50
7				0

Entry	Alcohol **34**	Aldehyde **35**	Product **36**	(%)Yield[a]
8	 **34f**	 **35a**	 **36h**	48
			 **36h'**	29
9	 **34d**	 **35b**	 **36i**	48
10	 **34c**	 **34b**	 **36j**	30
11	 **34g**	 **35b**	 **36k**	25
			 **36k'**	15
12	 **34h**	 **35b**	 **36l**	15

Entry	Substrates	Product **36**	(%)Yield[a]
13	 **34i** +  **35a**	 **36m**	85
14	 **34i** +  **35b**	 **36n**	78
15	 **34a** +  **35c**	 **36o**	40
16	 **34b** +  **35c**	 **36p**	48
17	 **34j** +  **35a**	 **36q**	35
		 **37q**	45
18	 **34k** +  **35a**	 **36r** +  **36r'**	40 (**36r:36r' :: 4:1**)

Entry	Substrates	Product **3**	(%)Yield[a]
19	 **34l** +  **35b**	 **36s** +  **36s'** **36s**:**36s'** :: 2:1	85
20	 **34m** +  **35b**	 **36t**	55
21	 **34j** +  **35b**	 **36u** +  **37u** **36u**:**37u** :: **2:3**	84
22	 **34n** +  **35b**	----	0[c]

[a]Yield refers to isolated yield. The compounds were characterized by IR, NMR and mass spectrometry.
[b]No reactions. Starting material was recovered in 95% yield, [c]complex mixture.

yield increased to 44 and 48%, respectively. After observing the effect of temperature on the yield, the quantity of reagent was increased from 0.5 equivalents to 1.0 equivalent (entry 7, *Table 2.4.1*) and it was observed that the yield increased to 70%. At higher loading of the Lewis acid to 1.5 equivalents did not improve the yield (entry 8, *Table 2.4.1*). Other Lewis acids such as $InCl_3$, $FeCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$ and TMSOTf could not afford higher yields (entries 9-15, *Table 2.4.1*). Similarly, Brønsted acids, trifluoromethanesulfonic acid (TfOH) and *p*-toluenesulfonic acids (PTSA) (entries 16-17, *Table 2.4.1*) were found to be inefficient reagents for this transformation. Thus 1.0 equivalent of $BF_3{\cdot}OEt_2$ in toluene at 100 ^oC is found to be the optimum conditions for the reaction.

With this optimum reaction conditions in hand, the scope of the reaction was investigated with variety of substrates as shown in *Table 2.4.2*. It was observed that the success of the reaction depend upon the substituents in alkyne side chain. Substrates having electron donating group on the aromatic ring (entries 3-6, 8-11, *Table 2.4.2*) gave 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene in moderate yields. On the other hand, moderately electron-withdrawing group such as chlorine on the aromatic group gave very low yield (entry 12, *Table 2.4.2*), which is due to the destabilization of the carbocation **A** (*Scheme 2.4.1*). Similarly, strong electron-withdrawing group such as carboxylate on the aromatic ring (entry 7, *Table 2.4.2*) failed to give any product due to strong destabilizing effect of carboxylate group. On the other hand, phenylacetaldehyde gave good yields (entries 1 and 3, *Table 2.4.2*) compared to 2-phenyl propionaldehyde (entry 2, 4, 9-11, *Table 2.4.2*). *Meta* substituted alkyne alcohol **34f** and benzo[*d*][1,3]dioxole substituted alkyne alcohol **34g** gave two regioisomeric products. It was also observed that substitution on the aromatic ring of alkyne alcohol (entries 13-14, *Table 2.4.2*) afforded the desired product with high yields, which is attributed to the enhancement of nucleophilicity of alkyne **34i**. 2,2-Diphenyl acetaldehyde, on the other hand, gave moderate yields (entries 15-16, *Table 2.4.2*). Similarly, naphthyl substituted alkyne alcohol **34j** with phenylacetaldehyde **35a** produced two products **36q** and **37q** in 35% and 45% of the yields, respectively. However, 2-phenylpropanal **35b** produced inseparable mixture of **36u** and **37u** with a ratio of 2:3 with 84% overall yield. To our dismay, the secondary alcohol **34n** with **35b** resulted in complex mixture. Interestingly, naphthyl substituted alkynes (entries 17, 21, *Table 2.4.2*) gave high yields which might be due to the more stabilization of carbocation **A** (*Scheme 2.4.1*). Secondary benzylic alcohol **34k** gave diastereomeric mixture **36r** and **36r′** with a ratio of

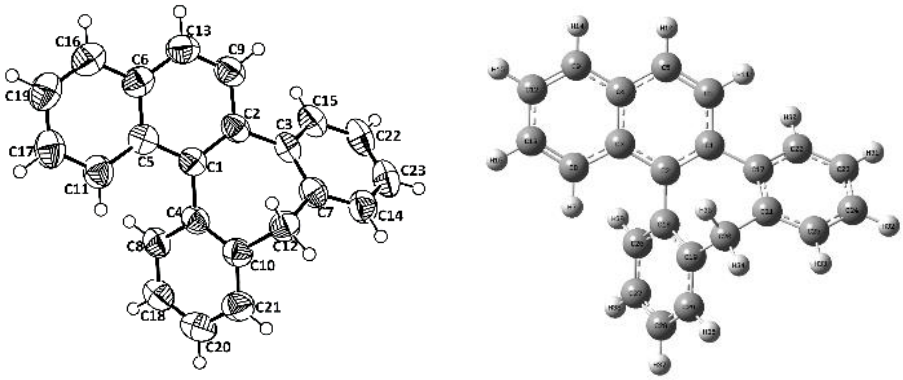


Figure 2.4.1 X-ray crystallographic and energy optimized structure of **36a** at [DFT-B3LYP/6-311++G(d,p)] level of theory

4:1 in 40% overall yield. The formation of minor product **36r′** can be explained on the basis of steric congestion between methyl and two nearby hydrogens of two phenyl rings, which are aligned in the same plane. Same is true for the formation of **36s** and **36s′** as diastereomeric mixture with a ratio of 2:1.In this case the methylene group is less crowded as compared to methyl group and therefore, the ratio is increased from 4:1 to 2:1. The phenyl substituted secondary alcohol **34m** provided only single diastereomer **36t** in 55% yield. This is due to the

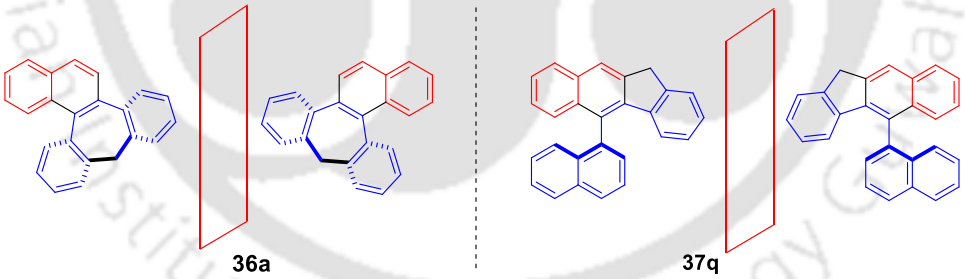


Figure 2.4.2 Enantiomers: non-superimposable mirror images

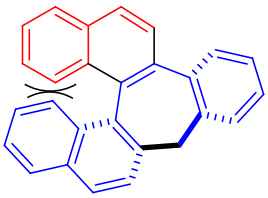
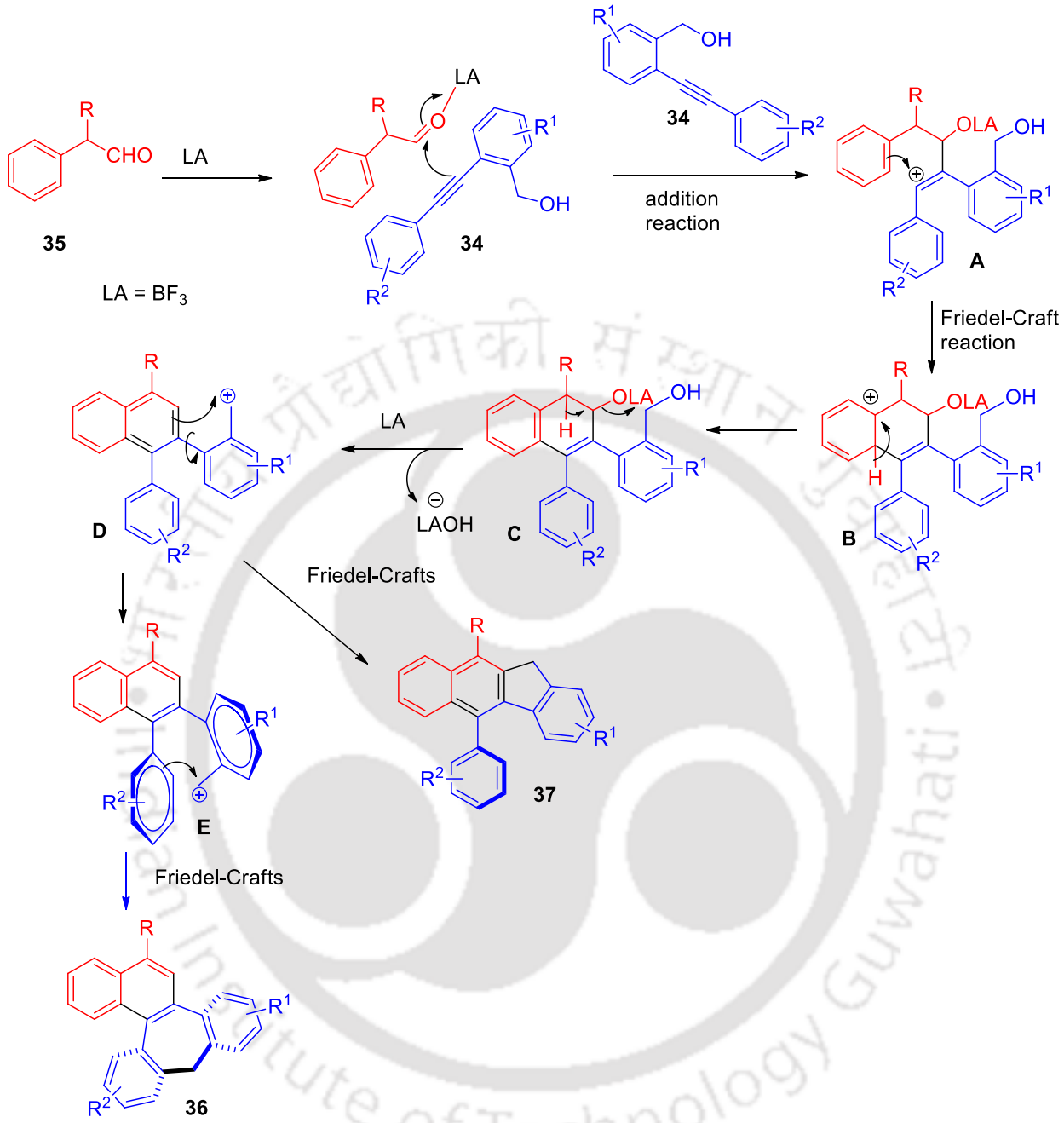


Figure 2.4.3 Repulsive forces experienced by two hydrogens of two naphthyl groups of **36q**



Scheme 2.4.1

sterically hindered phenyl group prefers opposite side of the two adjacent aryl groups to reduce the steric repulsion. The structure of all compounds was determined with the help of ^{1}H and ^{13}C NMR and mass spectrometry. Finally it was confirmed by X-ray crystallographic analysis of **36a** and **36c** and DFT calculation of compound **36a** (*Figure 2.4.1*).[19] Both X-ray crystallography and

DFT (DFT-B3LYP/6-31+G(d,p)) optimized structures of **36a** shows bend structure for **36a**, which is due to the repulsion among three aromatic rings attached to the cycloheptane ring. Compound **37q** is similar to chiral biaryl compound where naphthalene and benzo[*b*]fluorene rings are in a different plane and have restricted rotation about a single bond, which is termed as atropisomerism.[20] Due to the dissymmetry in the molecules **36** and **37**, these compounds might have two enatiomeric forms (*Figure 2.4.2*). To ascertain this, compounds **36a**, **36f**, **36q** and **37q** were subjected to HPLC analysis and it was observed that they are mixture of equal amounts (1:1 ratio) of enantiomers. It may be noted that these chiral molecules are important chiral ligands in asymmetric synthesis and possess chiroptical properties.[20b,21]

The mechanism is proposed on the basis of our findings and previous report (*Scheme 2.4.1*).[10] Under the Lewis acidic condition the aldehyde **35** is activated for the nucleophilic attack by alkyne **34** to give intermediate **A**, which after Friedel-Crafts reaction generates intermediate **B** (*Scheme 2.4.1*). The intermediate **B** after aromatization and subsequent Friedel-Crafts reaction gives final compounds **36** and **37**. In most of the cases the reaction provided compound **36** with a seven membered ring in the system. On the other hand, starting material with naphthalene derivative **34j** in the alkyne side chain gave both seven-membered **36q** and five-membered **37q** system with **37q** in higher yield. This may be due to the steric repulsion between the two nearby naphthalene rings (*Figure 2.4.3*). This is validated by the energy difference obtained from DFT calculation, where compound **36q** is higher in energy by almost 3.4 kcal/mole than that of the compound **37q**. In other words, compound **37q** is more stable than that of compound **36q**. The reaction is highly regioselective.

Conclusion

In conclusion we have developed a methodology for the synthesis of unsymmetrical 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene *via* sequential electrophilic addition of aldehyde to alkynes and double Friedel-Crafts cyclization reactions in moderate to good yields in a short time span. The reaction is highly regioselective and produces equal amount of enantiomers. The reaction provides a new type of dibenzocycloheptane with an additional naphthalene ring in the molecule. The application of the synthesized compounds is under investigation.

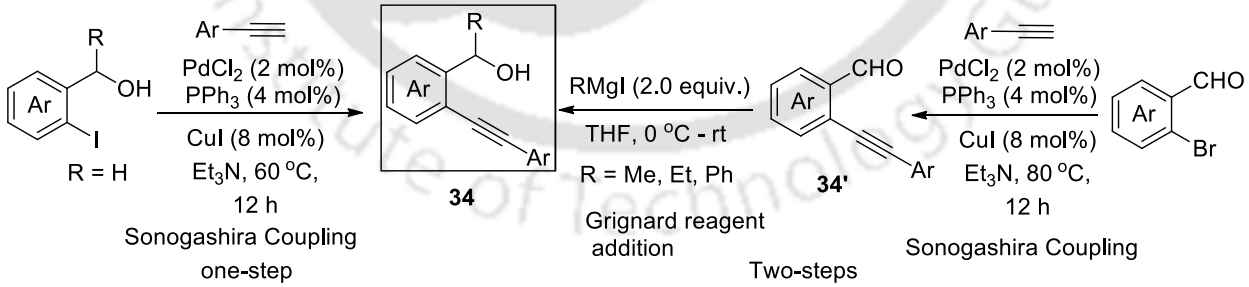
2.5 Experimental Section

2.5.1 Instrumentation and characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded with a Büchi B-540 melting point apparatus. Fourier transform-infra red (FTIR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF premier mass spectrometer. The ratio of enantiomers was determined by HPLC analysis using Chiracel OD columns on Waters 1525 Binary HPLC system.

2.5.2 General procedure for the synthesis of *o*-alkynyl benzyl alcohols 34

The corresponding starting materials having primary alcohols **34(a-j)** were synthesized in a single-step procedure *i.e.* Sonogashira coupling reaction and the starting materials having secondary alcohols **34(k-m)** were synthesized in a two-step procedure *i.e.* Sonogashira coupling reaction followed by Grignard reagent addition reaction (*Scheme 2.5.2.1*).



Scheme 2.5.2.1 Starting material preparation

The starting material *o*-alkynyl alcohols (**34a, 34b, 34d, 34h, 34i)**,[22a] **34j,**[22b] **34k**,[22c] **34l,**[22d] **34m**[22d], and **35c**[22e] were prepared as per the literature procedure and the spectroscopic data are in good agreement with the literature one.

2.5.2.1 General Experimental procedure for synthesis of *o*-alkynyl benzyl alcohols (34)

To a stirred solution of substituted 2-iodobenzylalcohol (1.0 mmol, 1.0 equiv.), palladium (II) chloride (2 mol%, 0.02 equiv.), triphenylphosphine (4 mol%, 0.04 equiv.) and copper(I) iodide (8 mol%, 0.08 equiv.) in triethylamine (4 mL) was added 1-ethynyl-benzene derivatives (1.2 mmol, 1.2 equiv.) under nitrogen atmosphere. Then, the reaction was heated at 60 ^{o}C for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated NH_4Cl solution. The organic layer was extracted with EtOAc (3x20 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the *o*-alkynyl benzyl alcohols (**34**).

2.5.3 General procedure for synthesis of 9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene derivatives (36)

To a solution of (2-(phenylethynyl)phenyl)methanol (0.5 mmol, 1.0 equiv.) and phenylacetaldehyde (0.55 mmol, 1.1 equiv.) in toluene was added $BF_3{\cdot}OEt_2$ (0.5 mmol, 1.0 equiv.) dropwise at 0 ^{o}C under nitrogen atmosphere. The reaction was stirred at 0 ^{o}C for 15 minutes and then brought to room temperature over a period of 15 minutes and then heating at 100 ^{o}C for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3x10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel eluted with hexane to give the desired targets.

2.6 References

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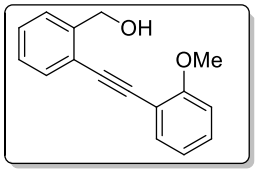
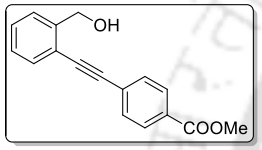
2.7 Characterization data

(2-((2-Methoxyphenyl)ethynyl)phenyl)methanol(34c)



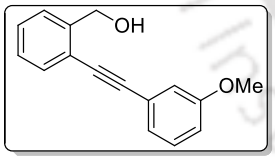
Colorless oil; R_f (hexane/EtOAc 5:1) 0.50; yield 209 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (t, *J* = 7.2 Hz, 1 H), 3.92 (s, 3 H), 4.83 (d, *J* = 7.2 Hz, 2 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 7.25-7.36 (m, 4 H), 7.48 (dd, *J* = 7.6 and 1.6 Hz, 1 H), 7.54 (dd, *J* = 8.0 and 2.4 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 55.9, 64.9, 90.8, 91.9, 110.7, 112.3, 120.9, 122.3, 127.8, 128.3, 128.7, 130.2, 132.0, 132.7, 143.5, 160.2; HRMS (ESI) calcd. for $C_{16}H_{15}O_2$ $(M + H)^+$ 239.1067, found 239.1066.

Methyl 4-((2-(hydroxymethyl)phenyl)ethynyl)benzoate (34e):



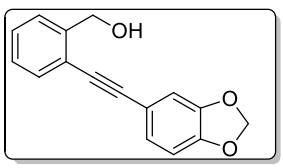
Colorless solid; R_f (hexane/EtOAc 5:1) 0.40; mp 108-110 ºC; yield 220 mg, 83%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.06 (t, *J* = 5.4 Hz, 1 H), 3.96 (s, 3 H), 4.95 (d, *J* = 6.6 Hz, 2 H), 7.33 (dt, *J* = 7.6 and 1.2 Hz, 1 H), 7.42 (dt, *J* = 7.6 and 1.2 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.58 (dd, *J* = 7.6 and 1.0 Hz, 1 H), 7.61 (d, *J* = 8.6 Hz, 2 H), 8.06 (d, *J* = 8.6 Hz, 2 H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ52.5, 64.1, 89.9, 93.5, 121.0, 127.5, 127.8, 129.5, 129.8, 130.0, 131.7, 132.6, 142.9, 166.7; HRMS (ESI) calcd. for $C_{17}H_{15}O_3$ $(M + H)^+$ 267.1016, found 267.1034.

(2-((3-Methoxyphenyl)ethynyl)phenyl)methanol (34f):



Colorless oil; R_f (hexane/EtOAc 5:1) 0.50; yield 207 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 1 H), 3.78 (s, 3 H), 4.87 (s, 2 H), 6.88 (dd, *J* = 8.4 and 2.4 Hz, 1 H), 7.03 (s, 1 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 7.20-7.25 (m, 2 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.50 (d, J = 7.6 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 55.4, 63.8, 86.7, 94.2, 115.2, 116.4, 121.2, 124.0, 124.3, 127.2, 127.5, 128.9, 129.6, 132.2, 142.7, 159.5; HRMS (ESI) calcd. for $C_{16}H_{15}O_2$ $(M + H)^+$ 239.1067, found 239.1067.

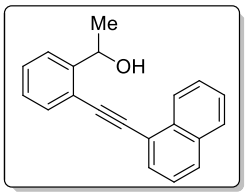
(2-(Benzo[*d*][1,3]dioxol-5-ylethynyl)phenyl)methanol (34g):



Colorless oil; R_f (hexane/EtOAc 5:1) 0.60; yield 216 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (bs, 1 H), 4.87 (s, 2 H), 5.98 (s, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.96 (s, 1 H), 7.05 (dd, *J* = 8.0 and 1.5 Hz, 1 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 7.33 (t, *J* = 7.4 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H),

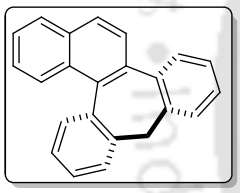
7.50 (d, *J* = 7.6 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 64.2, 85.4, 94.4, 101.6, 108.8, 111.7, 116.3, 121.6, 126.5, 127.4, 127.7, 128.7, 132.2, 142.6, 147.8, 148.4; HRMS (ESI) calcd. for $C_{16}H_{13}O_3$ $(M + H)^+$ 253.0859, found 253.0839.

1-(2-(Naphthalen-1-ylethynyl)phenyl)ethanol (34n):



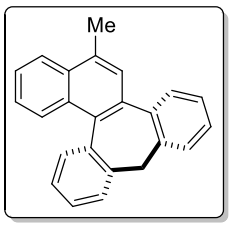
Brown solid; R_f (hexane/EtOAc 4:1) 0.50; mp 105-107 °C; yield 244 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (d, *J* = 6.4 Hz, 3 H), 2.19 (bs, 1 H), 5.53-5.59 (m, 1 H), 7.30 (dt, *J* = 7.6 and 1.5 Hz, 1 H), 7.41 (dt, *J* = 7.6 and 1.5 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.58-7.65 (m, 3 H), 7.76 (d, *J* = 7.6 Hz, 1 H), 7.87 (t, *J* = 7.6 Hz, 2 H), 8.40 (d, *J* = 7.6 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 24.5, 68.9, 92.0, 92.8, 120.8, 121.0, 125.0, 125.5, 126.3, 126.7, 127.2, 127.4, 128.6, 129.2, 129.3, 130.7, 132.7, 133.4, 133.5, 147.8; HRMS (ESI) calcd. for $C_{20}H_{17}O$ $(M + H)^+$ 273.1274, found 273.1284.

9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36a)



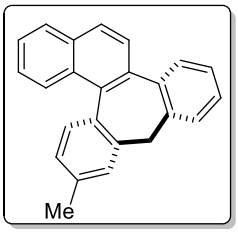
Colorless solid; R_f (hexane) 0.60; mp 75-77 °C; yield 102 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (d, J_{ab} = 3.6 Hz, 2 H), 7.33-7.35 (m, 1 H), 7.40-7.43 (m, 4 H), 7.51-7.53 (m, 1 H), 7.61-7.68 (m, 3 H), 7.80-7.82 (m, 1 H), 7.89-7.91 (m, 1 H), 8.05-8.10 (m, 2 H), 8.32 (d, *J* = 8.0 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 40.7, 125.2, 126.0, 126.3, 126.5, 126.6, 126.7, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 129.6, 132.0, 132.7, 133.4, 134.2, 135.8, 136.2, 138.2, 143.6, 144.4; HRMS (ESI) calcd. for $C_{23}H_{17}$ $(M + H)^+$ 293.1325, found 293.1323.

15-Methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36b):



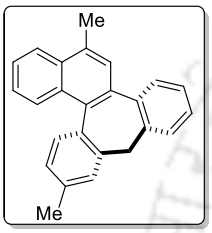
Colorless solid; R_f (hexane) 0.60; mp 74-76 °C; yield 76 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (s, 3 H), 3.66 (d, J_{ab} = 2.8 Hz, 2 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.24-7.32 (m, 4 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.44-7.50 (m, 2 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.63 (s, 1 H), 7.67-7.70 (m, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 8.17 (d, *J* = 8.4 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 20.0, 40.8, 124.4, 125.2, 125.9, 126.0, 126.4, 126.5, 126.6, 127.9, 128.0, 128.4, 128.9, 129.5, 132.2, 132.6, 132.9, 134.0, 134.3, 134.4, 135.8, 138.2, 143.7, 144.3; HRMS (ESI) calcd. for $C_{24}H_{19}$ $(M + H)^+$ 307.1481, found 307.1488.

7-Methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36c):



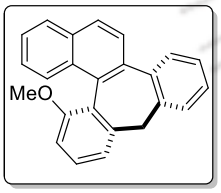
Colorless solid; R_f (hexane) 0.70; mp 182-184 °C; yield 92 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.53 (d, *J* = 5.4 Hz, 3 H), 3.79 (s, 2 H), 7.20 (d, *J* = 7.2 Hz, 1 H), 7.36-7.39 (m, 1 H), 7.40-7.44 (m, 2 H), 7.45-7.48 (m, 1 H), 7.58-7.67 (m, 3 H), 7.82-7.85 (m, 1 H), 7.91-7.94 (m, 1 H), 8.04-8.08 (m, 2 H), 8.37 (t, *J* = 7.8 Hz, 1 H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 21.3, 40.7, 125.9, 126.1, 126.2, 126.4, 126.6, 127.3, 127.7, 127.8, 127.9, 128.1, 128.3, 129.6, 131.3, 132.1, 132.6, 133.4, 135.8, 136.1, 137.9, 138.3, 143.7, 144.3; HRMS (ESI) calcd. for $C_{24}H_{22}N$ $(M + NH_4)^+$ 324.1747, found 324.1755.

7,15-Dimethyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36d):



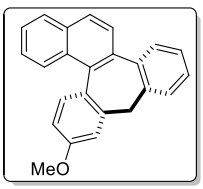
Colorless solid; R_f (hexane) 0.70; mp 87-89 °C; yield 64 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 2.81 (s, 3 H), 3.64 (s, 2 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 7.21 (s, 1 H), 7.27-7.32 (m, 3 H), 7.38 (d, *J* = 11.4 Hz, 1 H), 7.47 (t, *J* = 6.8 Hz, 1 H), 7.56 (t, *J* = 6.8 Hz, 1 H), 7.63 (s, 1 H), 7.68-7.71 (m, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 8.20 (d, *J* = 8.4 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.0, 21.4, 40.9, 124.4, 125.8, 125.9, 126.1, 126.5, 126.6, 127.3, 127.9, 128.5, 129.0, 129.6, 131.5, 132.2, 132.6, 132.8, 133.7, 134.4, 135.8, 137.8, 138.4, 143.7, 144.2; HRMS (ESI) calcd. for $C_{25}H_{24}N$ $(M + NH_4)^+$ 338.1903, found 338.1885.

5-Methoxy-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36e):



Colorless solid; R_f (hexane/EtOAc 98:2) 0.50; mp 187-189 °C; yield 77 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 3 H), 3.53-3.63 (m, 2 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 7.2 Hz, 1 H), 7.22-7.32 (m, 4 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 6.8 Hz, 1 H), 7.70 (t, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.90 (t, *J* = 8.4 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 40.8, 55.4, 109.1, 119.0, 122.8, 125.6, 125.7, 126.5, 126.7, 127.8, 128.0, 128.2, 128.4, 129.2, 129.3, 131.7, 132.2, 132.6, 136.9, 138.6, 143.8, 146.7, 157.7; HRMS (ESI) calcd. for $C_{24}H_{19}O$ $(M + H)^+$ 323.1430, found 323.1419.

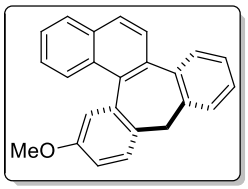
7-Methoxy-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36f):



Colorless solid; R_f (hexane) 0.40; mp 168-170 °C; yield 81 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73-3.75 (m, 2 H), 3.91 (s, 3 H), 6.87-6.89 (m, 1 H), 7.05 (s, 1 H), 7.37-7.42 (m, 3 H), 7.53-7.61 (m, 3 H), 7.76-7.79 (m, 1 H), 7.85-

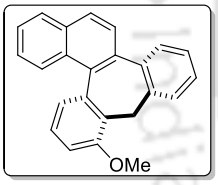
7.87 (m, 1 H), 7.98-8.02 (m, 2 H), 8.26-8.29 (m, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 41.0, 55.4, 110.8, 111.8, 125.9, 126.2, 126.5, 126.7, 126.8, 127.5, 127.8, 127.9, 128.1, 128.3, 129.6, 132.1, 133.4, 133.7, 135.6, 136.0, 138.4, 143.3, 145.7, 159.7; HRMS (ESI) calcd. for $C_{24}H_{19}O$ $(M + H)^+$ 323.1430, found 323.1438.

6-Methoxy-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36h):



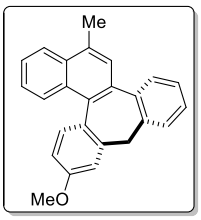
Colorless solid; R_f (hexane/EtOAc 98:2) 0.50; mp 124-126 °C; yield 77 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 2 H), 3.70 (s, 3 H), 6.85 (dd, J = 8.4 and 2.4 Hz, 1 H), 7.08 (d, J = 2.0 Hz, 1 H), 7.25-7.29 (m, 4 H), 7.44-7.52 (m, 2 H), 7.65-7.68 (m, 1 H), 7.75 (d, J = 8.4 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 2 H), 8.23 (d, J = 8.0 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 39.8, 55.5, 114.1, 118.0, 126.0, 126.3, 126.4, 126.6, 127.4, 127.6, 128.0, 128.2, 128.3, 129.6, 131.9, 133.4, 135.1, 135.7, 136.3, 137.3, 138.2, 144.0, 157.1; HRMS (ESI) calcd. for $C_{24}H_{19}O$ $(M + H)^+$ 323.1430, found 323.1437.

8-Methoxy-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36h′):



Colorless solid; R_f (hexane/EtOAc 98:2) 0.55; mp 158-160 °C; yield 46 mg, 29%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (d, J_{ab} = 12.5 Hz, 1 H), 3.91 (s, 3 H), 4.39 (d, J_{ab} = 12.5 Hz, 1 H), 6.90-6.93 (m, 1 H), 7.14-7.19 (m, 2 H), 7.28-7.34 (m, 2 H), 7.42-7.45 (m, 1 H), 7.47-7.56 (m, 2 H), 7.71-7.73 (m, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 8.4 Hz, 2 H), 8.21 (d, J = 8.4 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 31.1, 56.1, 109.7, 125.1, 125.2, 125.9, 126.2, 126.5, 126.8, 127.8, 127.9, 128.0, 128.1, 128.2, 129.4, 132.0, 133.0, 133.3, 135.8, 135.9, 136.3, 138.6, 143.8, 155.5; HRMS (ESI) calcd. for $C_{24}H_{19}O$ $(M + H)^+$ 323.1430, found 323.1428.

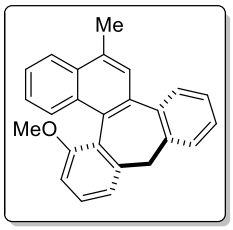
7-Methoxy-15-methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36i):



Colorless oil; R_f (hexane/EtOAc 98:2) 0.5; yield 81 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3 H), 3.60-3.71 (m, 2 H), 3.83 (s, 3 H), 6.77 (dd, J = 8.8 and 2.8 Hz, 1 H), 6.93 (d, J = 2.8 Hz, 1 H), 7.25-7.32 (m, 3 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.45-7.49 (m, 1 H), 7.53-7.57 (m, 1 H), 7.62 (s, 1 H), 7.67-7.69 (m, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 8.18 (t, d = 8.0 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR

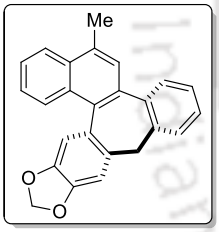
(100 MHz, $CDCl_3$) δ 19.9, 41.1, 55.5, 110.9, 111.8, 124.4, 125.8, 126.6, 126.7, 127.1, 127.9, 128.4, 128.9, 129.6, 132.3, 132.6, 133.5, 133.9, 134.1, 135.6, 138.4, 143.3, 145.6, 159.5; HRMS (ESI) calcd. for $C_{25}H_{21}O$ $(M + H)^+$ 337.1587, found 337.1606.

5-Methoxy-15-methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36j):



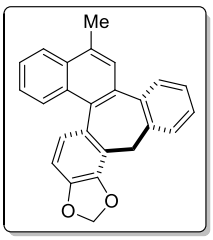
Colorless solid; R_f (hexane/EtOAc 99:1) 0.60; mp 196-198 °C; yield 50 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 3 H), 3.55 (s, 3 H), 3.58-3.66 (m, 3 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 7.27-7.34 (m, 3 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.64 (s, 1 H), 7.75 (d, *J* = 7.6 Hz, 2 H), 8.09 (d, *J* = 8.2 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 19.9, 40.8, 55.4,109.0, 119.0, 123.0, 124.1, 125.3, 125.6, 126.5, 126.7, 127.8, 128.9, 129.0, 129.1, 129.2, 130.9, 131.5, 131.7, 134.1, 136.5, 138.5, 143.8, 146.6, 157.7; HRMS (ESI) calcd. for $C_{25}H_{21}O$ $(M + H)^+$ 337.1587, found 337.1607.

5-Methyl-11*H*-benzo[4',5']naphtho[2'',1'':6',7']cyclohepta[1',2':4,5]benzo[1,2-*d*][1,3]dioxole (36k):



Colorless solid; R_f (hexane, eluted twice) 0.2; mp 102-104 °C; yield 44 mg, 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (s, 3 H), 3.56 (s, 2 H), 5.87 (d, *J* = 1.2 Hz, 1 H), 6.00 (d, *J* = 1.2 Hz, 1 H), 6.88 (s, 1 H), 6.95 (s, 1 H), 7.29-7.32 (m, 3 H), 7.50 (t, *J* = 6.8 Hz, 1 H), 7.56 (t, *J* = 6.8 Hz, 1 H), 7.62 (s, 1 H), 7.69-7.71 (m, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 8.21 (t, *J* = 8.0 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.0, 40.5, 101.3, 106.9, 112.8, 124.4, 125.9, 126.0, 126.2, 126.7, 127.6, 128.0, 128.3, 128.9, 129.5, 132.2, 132.6, 133.7, 134.1, 135.7, 138.2, 138.3, 143.9, 145.4, 147.6; HRMS (ESI) calcd. for $C_{25}H_{22}NO_2$ $(M + NH_4)^+$ 368.1645, found 368.1657.

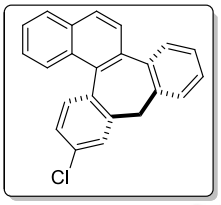
16-Methyl-10*H*-benzo[5',6']naphtho[1'',2'':3',4']cyclohepta[1',2':3,4]benzo[1,2-*d*][1,3]dioxole (36k′):



Colorless solid; R_f (hexane, eluted twice) 0.3; mp 188-190 °C; yield 26 mg, 15%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (s, 3 H), 3.43 (d, J_{ab} = 12.8 Hz, 1 H), 4.02 (dd, J_{ab} = 12.8 and 1.6 Hz, 1 H), 6.07 (d, *J* = 3.6 Hz, 2 H), 6.75 (dd, *J* = 8.0 and 2.8 Hz, 1 H), 7.02 (dd, *J* = 8.0 and 2.0 Hz, 1 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.42 (d, *J* = 6.8 Hz, 1 H), 7.55 (t, *J* = 6.8 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 1 H), 7.65 (s, 1 H), 7.74 (d, *J* = 7.2 Hz, 1 H), 8.13 (d, *J* = 8.4 Hz, 1 H), 8.28 (d,

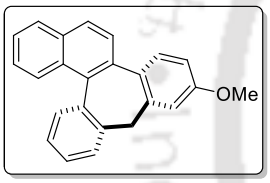
J = 8.4 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 19.9, 32.5, 101.3, 105.5, 124.3, 125.9, 126.0, 126.1, 126.2, 126.8, 126.9, 127.8, 128.5, 129.1, 129.3, 129.8, 132.5, 132.7, 133.7, 133.9, 135.7, 139.0, 142.6, 143.9, 146.7; HRMS (ESI) calcd. for $C_{25}H_{22}NO_2$ $(M + NH_4)^+$ 368.1645, found 368.1659.

7-Chloro-15-methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36l):



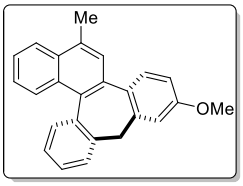
Colorless solid; R_f (hexane) 0.60; mp 130-132 °C; yield 24 mg, 15%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (d, J_{ab} = 2.8 Hz, 2 H), 7.23 (dd, *J* = 8.4 and 2.0 Hz, 1 H), 7.33-7.37 (m, 3 H), 7.43-7.58 (m, 4 H), 7.70-7.73 (m, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.96-7.99 (m, 2 H), 8.12 (d, *J* = 8.4 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 40.5, 125.5, 126.2, 126.5, 126.6, 126.7, 127.0, 127.4, 128.1, 128.3, 128.4, 129.7, 131.9, 132.7, 133.4, 133.8, 133.9, 134.6, 136.3, 138.1, 143.0, 145.8; HRMS (ESI) calcd. for $C_{23}H_{19}ClN$ $(M + NH_4)^+$ 344.1201, found 344.1209.

11-Methoxy-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36m):



Colorless gum; R_f (hexane) 0.50; yield 140 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (d, J_{ab} = 2.8 Hz, 2 H), 3.86 (s, 3 H), 6.87 (dd, *J* = 8.4 and 2.6 Hz, 1 H), 6.91 (d, *J* = 2.6 Hz, 1 H), 7.27 (t, *J* = 8.4 Hz, 1 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.48-7.55 (m, 4 H), 7.63 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 8.16 (d, *J* = 8.4 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 41.1, 55.6, 112.0, 112.1, 125.3, 125.8, 126.3, 126.7, 127.7, 127.9, 128.1, 128.2, 128.3, 130.7, 131.1, 132.2, 133.2, 134.5, 135.2, 136.0, 144.0, 145.0, 159.7; HRMS (ESI) calcd. for $C_{24}H_{19}O$ $(M + H)^+$ 323.1430, found 323.1432.

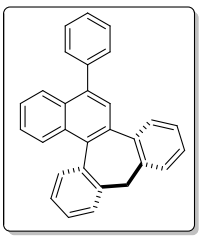
11-Methoxy-15-methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36n):



Colorless gum; R_f (hexane) 0.50; yield 130 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (s, 3 H), 3.63 (d, J_{ab} = 2.8 Hz, 2 H), 3.82 (s, 3 H), 6.83 (dd, *J* = 8.4 and 2.6 Hz, 1 H), 6.87 (d, *J* = 2.6 Hz, 1 H), 7.21 (t, *J* = 8.4 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 7.38 (d, *J* = 7.4 Hz, 1 H), 7.44-7.49 (m, 2 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.60 (s, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 8.07 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 8.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 20.0, 41.2, 55.5, 111.9, 112.1, 124.3, 125.3, 125.7, 125.9, 126.6, 127.9, 128.3, 128.9, 130.6, 131.1, 132.3, 132.4, 132.9,

133.7, 133.9, 134.7, 135.6, 143.9, 145.0, 159.7; HRMS (ESI) calcd. for $C_{25}H_{21}O$ $(M + H)^+$ 337.1587, found 337.1589.

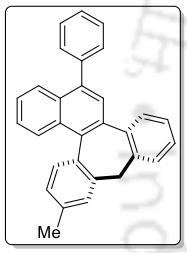
15-Phenyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36o):



Colorless gum; R_f (hexane) 0.50; yield 74 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 2 H), 7.25-7.33 (m, 4 H), 7.35-7.38 (m, 2 H), 7.44-7.51 (m, 4 H), 7.54-7.62 (m, 4 H), 7.72-7.74 (m, 1 H), 7.77 (s, 1 H), 8.01-8.04 (m, 1 H), 8.23-8.26 (m, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 40.9, 125.3, 126.1, 126.2, 126.4, 126.5, 126.7, 127.6, 128.1, 128.2, 128.3, 128.6, 129.2, 129.7, 130.4, 131.7, 132.5, 132.8, 134.3, 135.4, 135.7, 138.1, 140.0, 141.0, 143.8, 144.5; HRMS (ESI) calcd. for $C_{29}H_{21}$ $(M + H)^+$ 369.1638, found 369.1645.

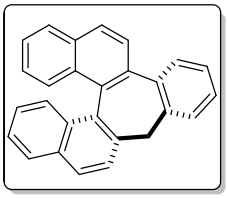
7-Methyl-15-phenyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36p):

Colorless gum; R_f (hexane) 0.50; yield 92 mg, 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H),



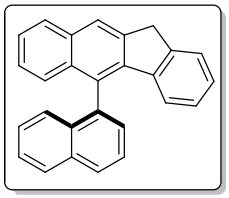
3.73 (d, J_{ab} = 6.7 Hz, 2 H), 7.10 (d, J = 8.0 Hz, 1 H), 7.28-7.34 (m, 3 H), 7.36-7.39 (m, 1 H), 7.47-7.51 (m, 4 H), 7.57 (t, J = 7.2 Hz, 2 H), 7.64 (d, J = 7.2 Hz, 2 H), 7.78 (s, 1 H), 8.01-8.04 (m, 1 H), 8.27-8.30 (m, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.4, 40.9, 126.0, 126.1, 126.2, 126.4, 126.6, 126.7, 127.4, 127.6, 128.1, 128.3, 128.6, 129.2, 129.7, 130.4, 131.4, 131.7, 132.6, 132.7, 135.5, 135.6, 138.1, 138.2, 139.8, 141.0, 143.8, 144.3; HRMS (ESI) calcd. for $C_{30}H_{23}$ $(M + H)^+$ 383.1794, found 383.1792.

11*H*-Benzo[5,6]cyclohepta[2,1-*a*:3,4-*a*′]dinaphthalene (36q):



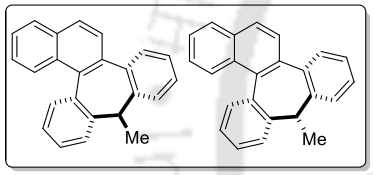
Colorless solid; R_f (hexane) 0.80; mp 190-192 °C; yield 60 mg, 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (d, J_{ab} = 13.4 Hz, 1 H), 4.45 (d, J_{ab} = 13.4 Hz, 1 H), 6.90 (d, J = 8.6 Hz, 1 H), 7.08 (dd, J = 7.2 and 1.0 Hz, 1 H), 7.14-7.17 (m, 2 H), 7.22-7.28 (m, 2 H), 7.35-7.47 (m, 4 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.61 (d, J = 7.2 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 7.83 (dd, J = 8.4 and 1.0 Hz, 1 H), 7.91 (d, J = 8.4 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 42.0, 124.7, 125.7, 125.8, 126.1, 126.6, 127.0, 127.3, 127.4, 127.6, 127.7, 127.8, 127.9, 128.1, 128.6, 129.3, 132.9, 133.1, 133.6, 133.7, 134.8, 135.0, 135.4, 136.1, 136.9, 137.3, 138.3, 139.2, 139.5, 140.5, 141.4, 142.1; HRMS (ESI) calcd. for $C_{27}H_{19}$ $(M + H)^+$ 343.1481, found 343.1463.

5-(Naphthalen-1-yl)-11*H*-benzo[*b*]fluorene (37q):



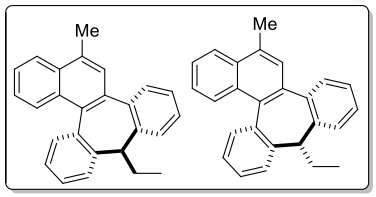
Colorless solid; R_f (hexane) 0.80; mp 90-92 ^oC; yield 76 mg, 45%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (d, J_{ab} = 12.6 Hz, 1 H), 3.79 (d, J_{ab} = 12.6 Hz, 1 H), 7.10-7.12 (m, 1 H), 7.17 (d, *J* = 8.4 Hz, 1 H), 7.22 (dd, *J* = 7.2 and 1.5 Hz, 1 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.27-7.30 (m, 1 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 7.44-7.51 (m, 2 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.72 (dd, *J* = 7.2 and 1.5 Hz, 1 H), 7.79-7.88 (m, 3 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 41.2, 124.8, 125.6, 125.8, 125.9, 126.0, 126.4, 126.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.8, 129.0, 129.1, 130.0, 130.5, 132.4, 132.5, 133.2, 134.0, 137.8, 138.5, 142.8, 144.1; HRMS (ESI) calcd. for $C_{27}H_{19}$ $(M + H)^+$ 343.1481, found 343.1481.

9-Methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (diastereomeric mixture; 36r:36r′:: 4:1):



Colorless gum; R_f (hexane) 0.80; yield 60 mg, 40%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 7.2 Hz, 3 H, minor), 1.86 (d, *J* = 7.2 Hz, 3 H, major), 3.79 (q, *J* = 7.2 Hz, 1 H, major), 4.18 (q, *J* = 7.2 Hz, 1 H, minor), 7.22-7.34 (m, 2 H), 7.36-7.44 (m, 3 H), 7.48-7.58 (m, 4 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.95-8.00 (m, 2 H), 8.21 (d, *J* = 8.4 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 13.9, 37.4, 121.6, 121.8, 124.8, 126.0, 126.1, 126.4, 127.8, 127.9, 128.0, 128.1, 128.4, 129.5, 131.7, 131.8, 132.4, 133.4, 134.3, 135.8, 136.2, 138.4, 146.7, 147.5; HRMS (ESI) calcd. for $C_{24}H_{19}$ $(M + H)^+$ 307.1481, found 307.1462.

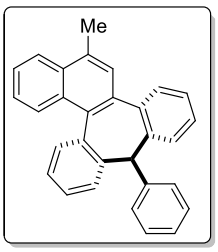
9-Ethyl-15-methyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (diastereomeric mixture; 36s:36s′:: 2:1):



Yellow gum; R_f (hexane) 0.60; yield 162 mg, 85%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (t, *J* = 7.2 Hz, 3 H, minor), 1.01 (t, *J* = 7.2 Hz, 3 H, major), 1.34-1.41 (m, 2 H, minor), 2.36-2.41 (m, 2 H, major), 2.77 (s, 3 H, minor), 2.80 (s, 3 H, major), 3.44 (t, *J* = 8.0 Hz, 1 H, major), 3.81 (t, *J* = 8.0 Hz, 1 H, minor), 7.12-7.37 (m, 11 H), 7.43-7.56 (m, 5 H), 7.60-7.71 (m, 3 H), 8.04-8.15 (m, 2 H), 8.22 (d, *J* = 8.4 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 12.6, 13.6, 19.9, 20.0, 20.9, 22.6, 45.2, 57.9, 121.9, 122.1, 124.3, 124.4, 124.6, 125.3, 125.8, 125.85, 125.9, 126.0, 126.8, 127.8, 127.85, 127.89, 127.9, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.6, 130.6, 131.9, 132.3, 132.6, 132.65, 132.7, 133.7,

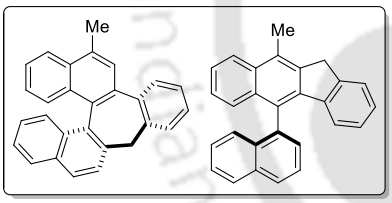
133.8, 133.9, 134.0, 134.3, 134.5, 134.9, 135.4, 135.8, 137.5, 138.7, 145.7, 146.5, 146.7, 147.2 ; Anal. Calcd for $C_{26}H_{22}$: C, 93.37; H, 6.63. Found: C, 93.32; H, 6.70.

15-Methyl-9-phenyl-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*a*]naphthalene (36t):



Yellow gum; R_f (hexane) 0.60; yield 118 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3 H), 5.35 (s, 1 H), 6.48 (d, *J* = 7.8 Hz, 1 H), 7.01 (t, *J* = 7.6 Hz, 1 H), 7.15 (d, *J* = 7.4 Hz, 1 H), 7.18(d, *J* = 7.6 Hz, 2 H), 7.21-7.26 (m, 1 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 7.44-7.51 (m, 2 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.27-7.32 (m, 3 H), 7.41-7.47 (m, 2 H), 7.50-7.58 (m, 2 H), 7.62-7.68 (m, 4 H), 8.09 (d, *J* = 8.4 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.8, 54.1, 123.8, 123.9, 125.3, 125.5, 126.7, 127.1, 127.2, 127.7, 128.0, 128.3, 129.0, 129.3, 130.2, 130.6, 130.7, 132.1, 132.6, 133.6, 137.3, 139.5, 140.4, 143.0, 143.2, 149.4; HRMS (ESI) calcd. for $C_{30}H_{23}$ $(M + H)^+$ 383.1794, found 383.1801.

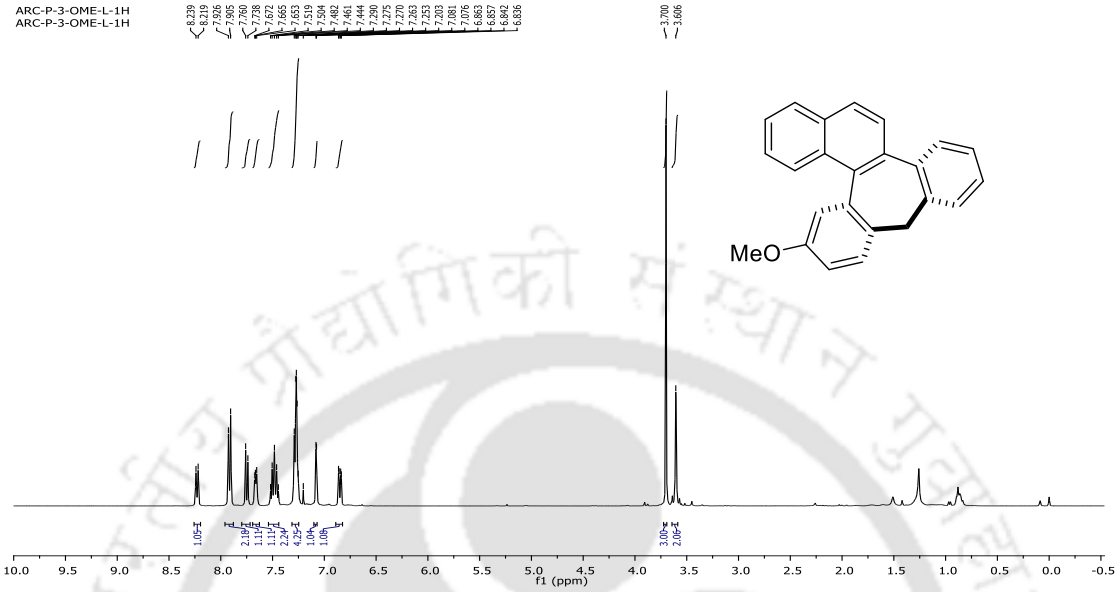
17-Methyl-11*H*-benzo[5,6]cyclohepta[2,1-*a*:3,4-*a'*]dinaphthalene (36u) and 10-Methyl-5-(naphthalen-1-yl)-11*H*-benzo[*b*]fluorine (37u) (36u:37u::2:3):



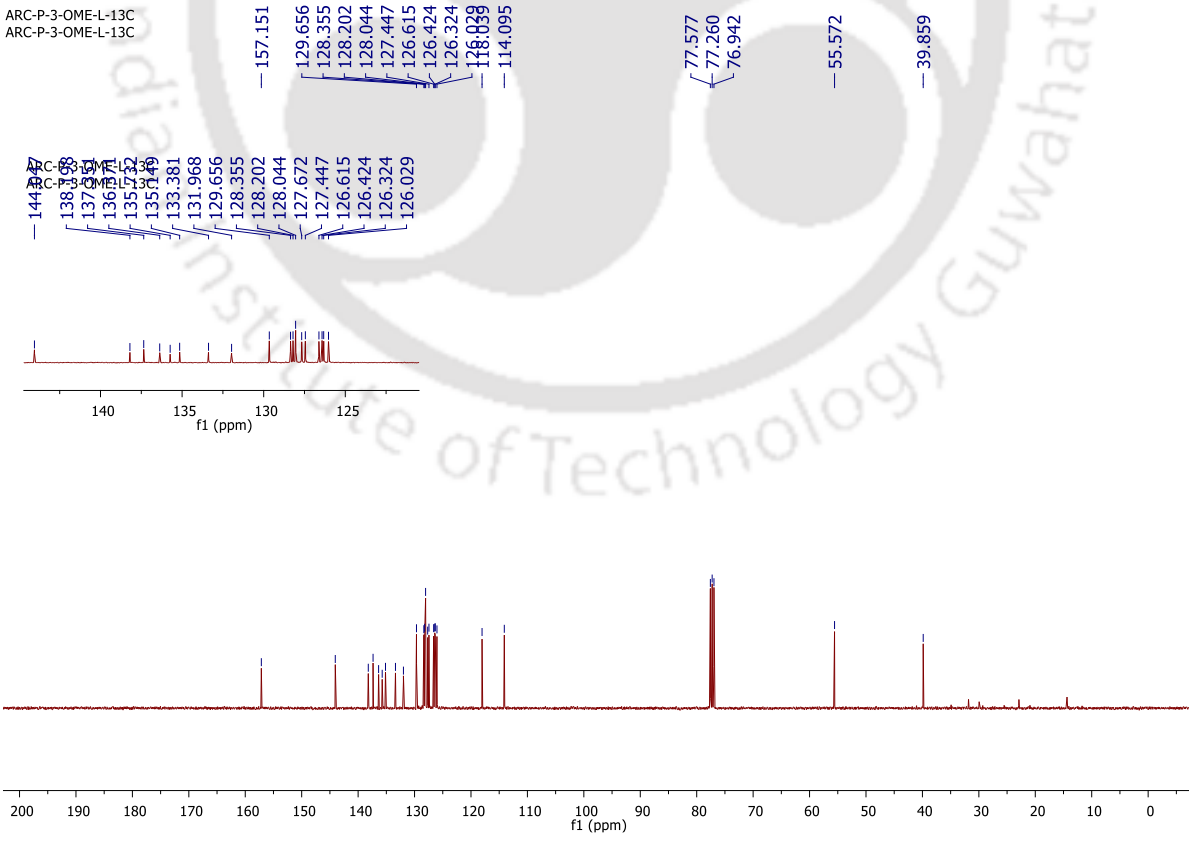
Yellow solid; R_f (hexane) 0.60; mp 180-182-92 ^{o}C; yield 140 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 3 H, **3u**), 2.84 (s, 3 H, **4u**), 3.67 (d, *J* = 13.2 Hz, 1 H, **3u**), 3.71 (d, *J* = 12.6 Hz, 1 H, **4u**), 3.78 (d, *J* = 12.6 Hz, 1 H, **4u**), 4.44 (d, *J* = 13.2 Hz, 1 H, **3u**), 6.90 (d, *J* = 8.6 Hz, 1 H), 7.02-7.12 (m, 3 H), 7.15-7.36 (m, 11 H), 7.38-7.62 (m, 7 H), 7.67-7.72 (m, 3 H), 7.78 (t, *J* = 8.0 Hz, 3 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.0, 20.0, 37.0, 37.9, 120.4, 121.3, 121.6, 124.0, 124.3, 124.4, 124.7, 125.3, 125.4, 125.5, 125.6, 125.7, 125.74, 125.8, 125.9, 126.2, 126.3, 127.0, 127.2, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 128.7, 128.76, 128.8, 129.3, 129.5, 130.3, 131.7, 132.1, 132.3, 132.5, 132.9, 133.1, 133.6, 134.0, 134.2, 134.9, 135.2, 136.1, 136.7, 137.2, 138.7, 141.0, 143.2, 145.1, 145.4, 147.2; HRMS (ESI) calcd. for $C_{28}H_{21}$ $(M + H)^+$ 357.1638, found 357.1636.

2.8 Selected Spectra

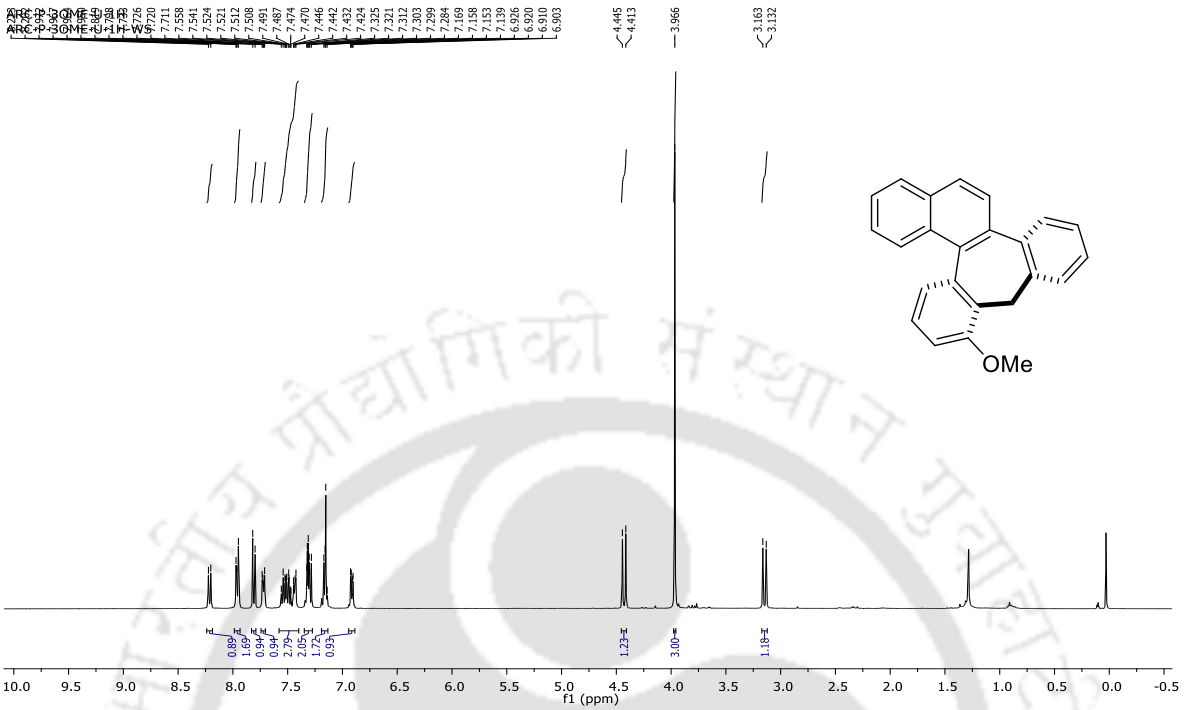
^{1}H spectrum of compound **36h** (400 MHz, $CDCl_3$)



^{13}C{^{1}H} spectrum of compound **36h** (100 MHz, $CDCl_3$)

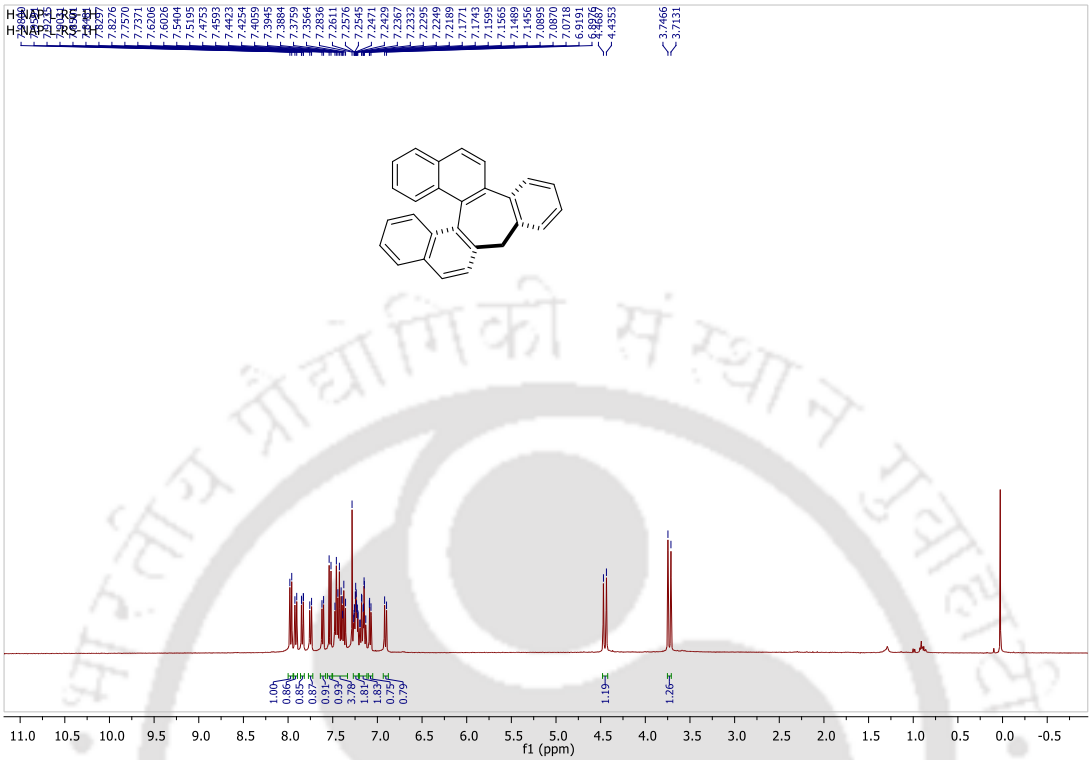


^{1}H spectrum of compound **36h'** (400 MHz, $CDCl_3$)

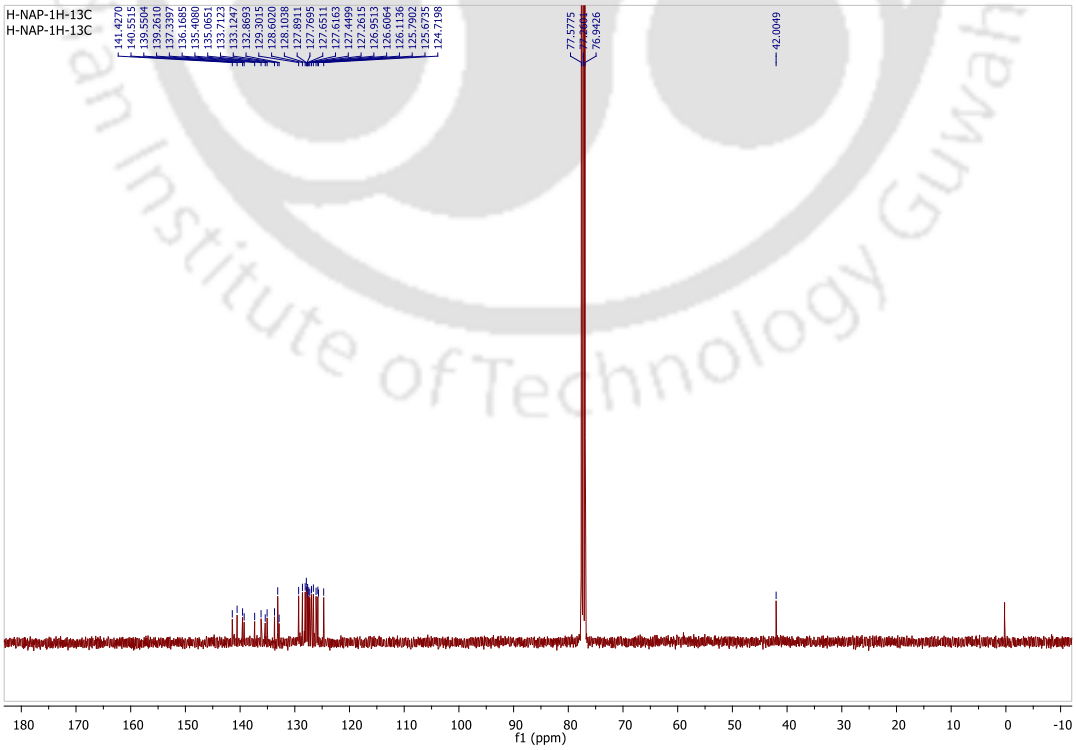


^{13}C{^{1}H} spectrum of compound **36h'** (100 MHz, $CDCl_3$)

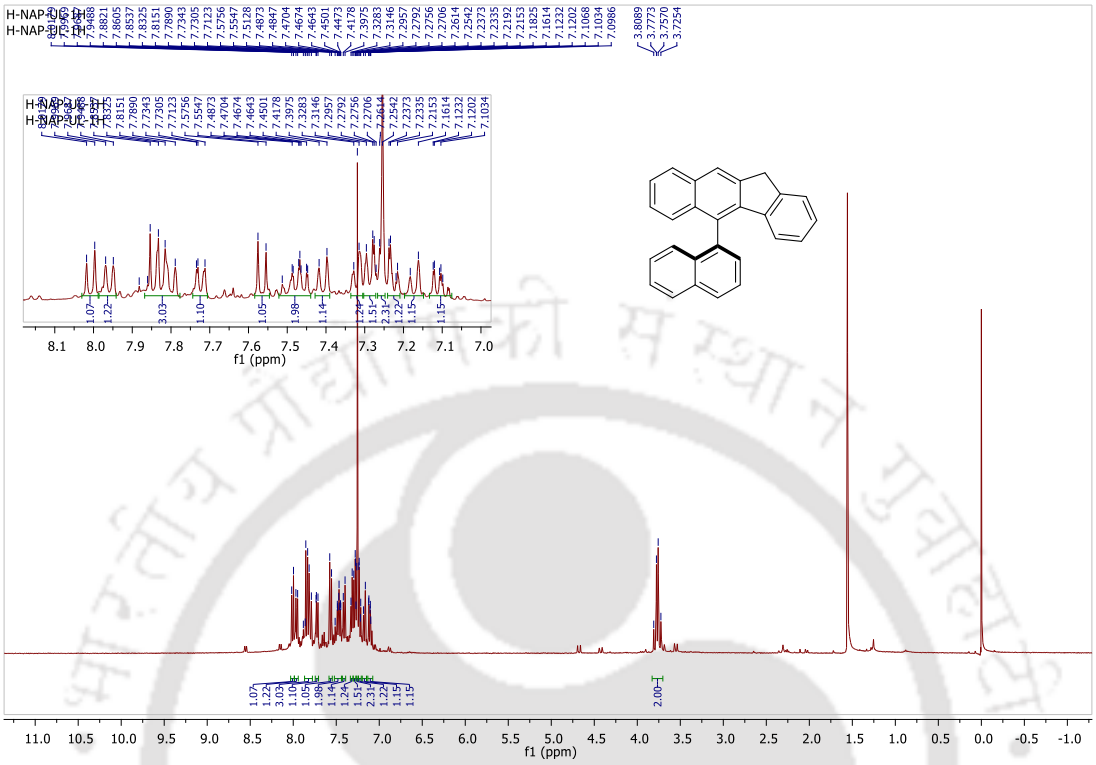
^{1}H spectrum of compound **36q** (400 MHz, $CDCl_3$)



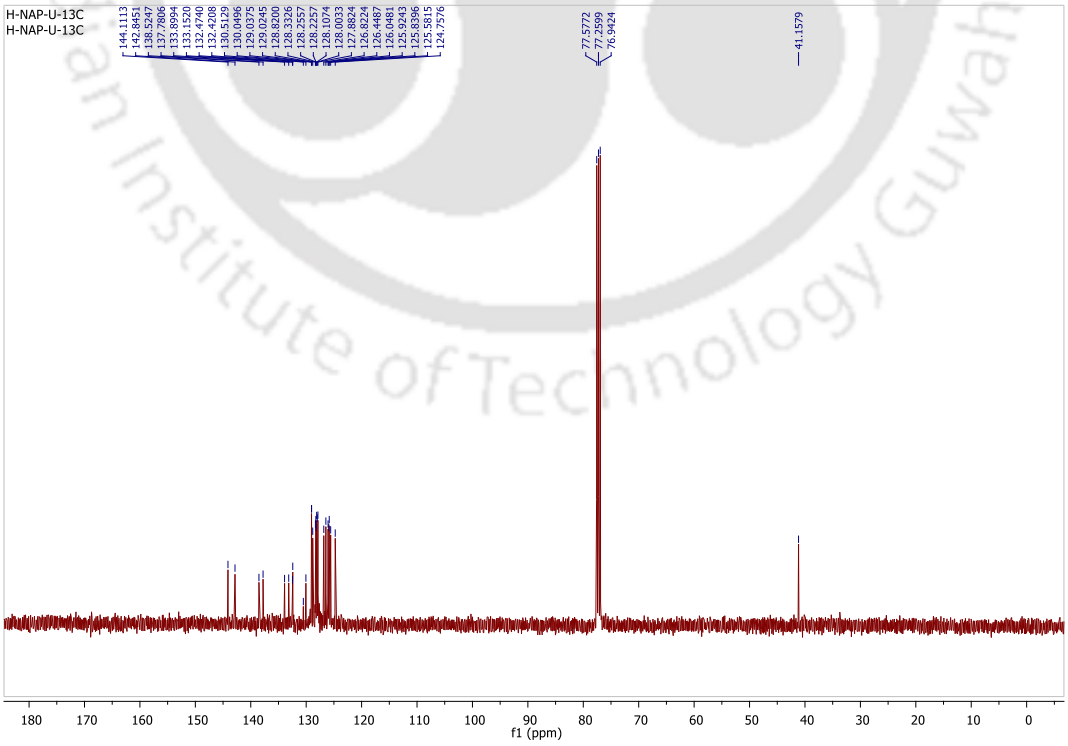
^{13}C{^{1}H} spectrum of compound **36q** (100 MHz, $CDCl_3$)



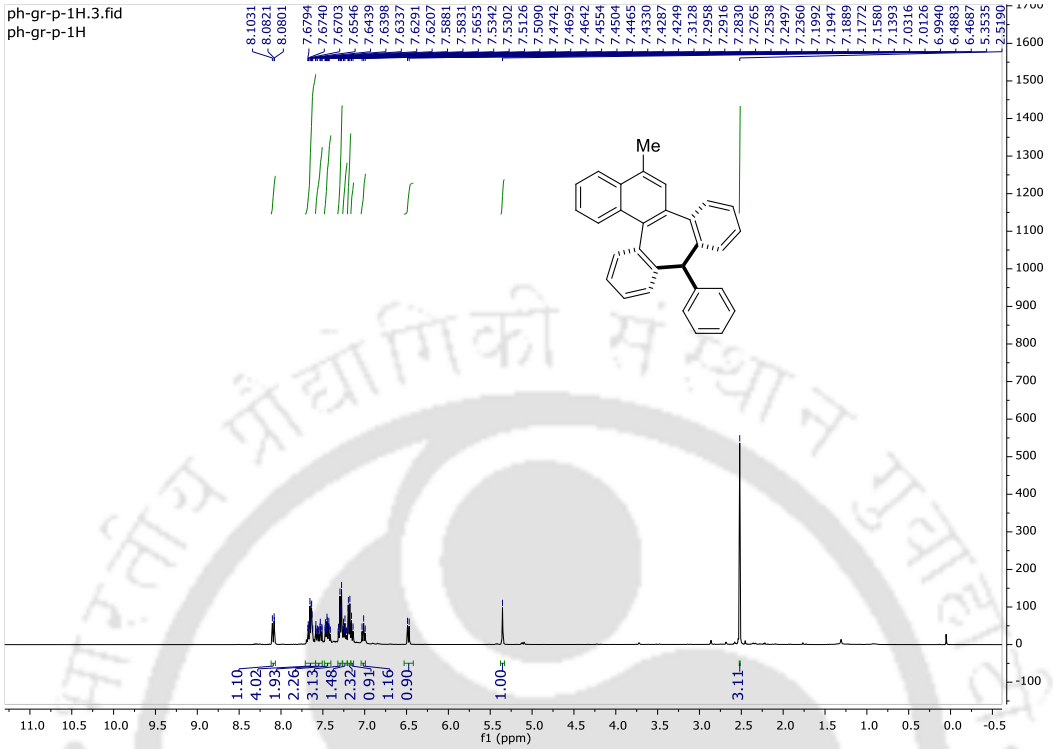
^{1}H spectrum of compound **37q** (400 MHz, $CDCl_3$)



^{13}C{^{1}H} spectrum of compound **37q** (100 MHz, $CDCl_3$)



^{1}H spectrum of compound **36t** (400 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ spectrum of compound **36t** (100 MHz, $CDCl_3$)

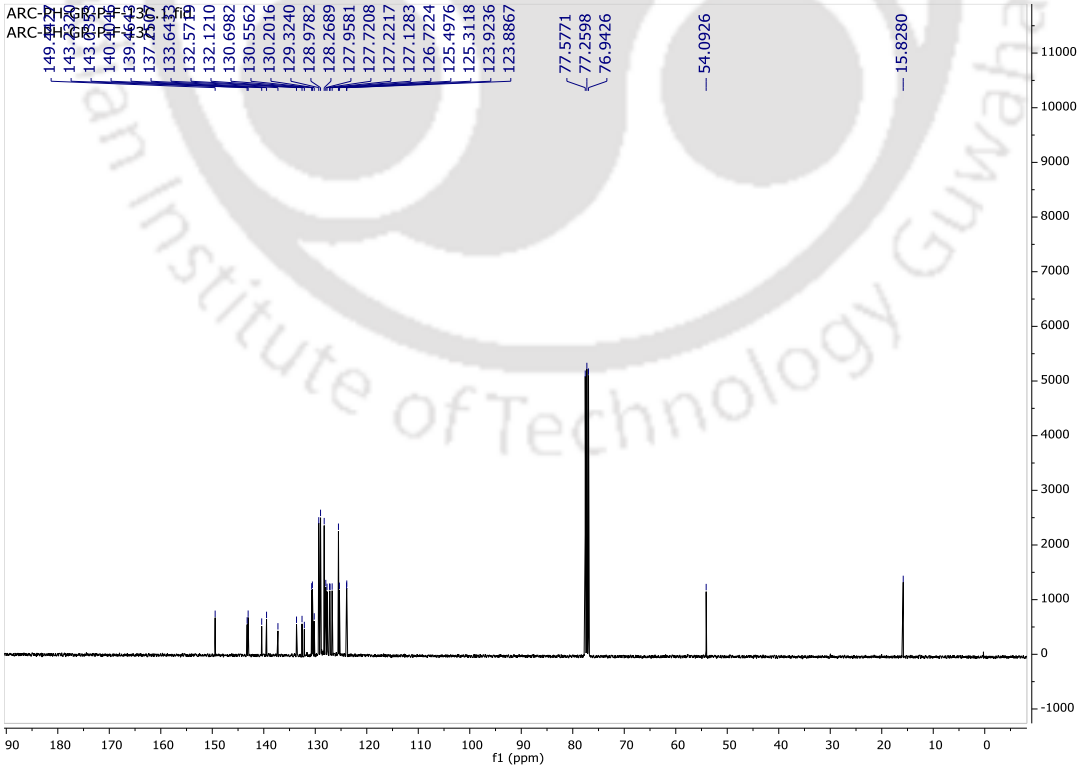
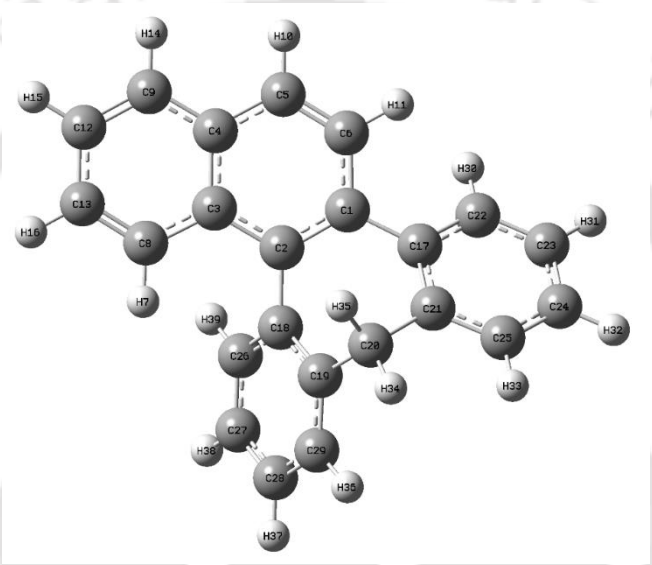


Table 2.8.1 Energy optimized structure of **36a** at [DFT-B3LYP/6-311++G(d,p)] level of theory

Compound Name	Method used	Energy (Hartree)
36a	DFT-B3LYP/6-31+G(d,p)	-886.168565
36a	DFT-B3LYP/6-311++G(d,p)	-886.325690

Figure 2.8.1: Optimized Structure of compound **36a**



Compound 36a [DFT-B3LYP/6-311++G(d,p)]

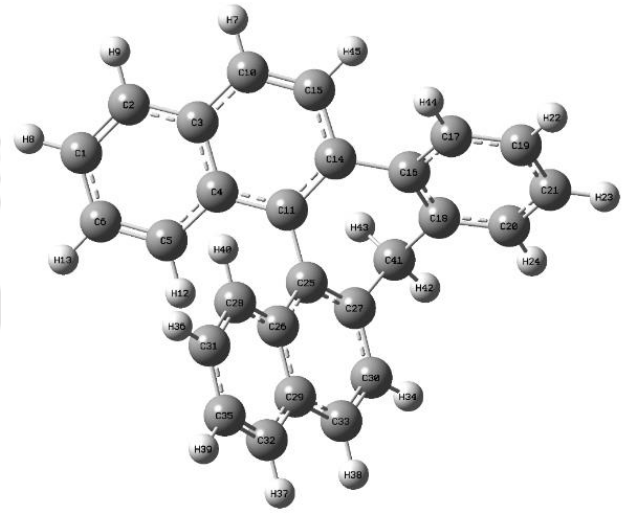
Table 2.8.2 Energy optimized structures of compounds 36q and 37q and their comparison

Compound Name	**Method used**	**Energy (Hartree)**
36q	DFT-B3LYP/6-31+G(d,p)	-1039.815027
37q	DFT-B3LYP/6-31+G(d,p)	-1039.820533
$\Delta E = E_{36q} - E_{37q}$	**DFT-B3LYP/6-31+G(d,p)**	**0.005506 (3.45 kcal/mol)**
36q	DFT-B3LYP/6-311++G(d,p)	-1039.998898
37q	DFT-B3LYP/6-311++G(d,p)	-1040.004372
$\Delta E = E_{36q} - E_{37q}$	**DFT-B3LYP/6-311++G(d,p)**	**0.005474 (3.43 kcal/mol)**

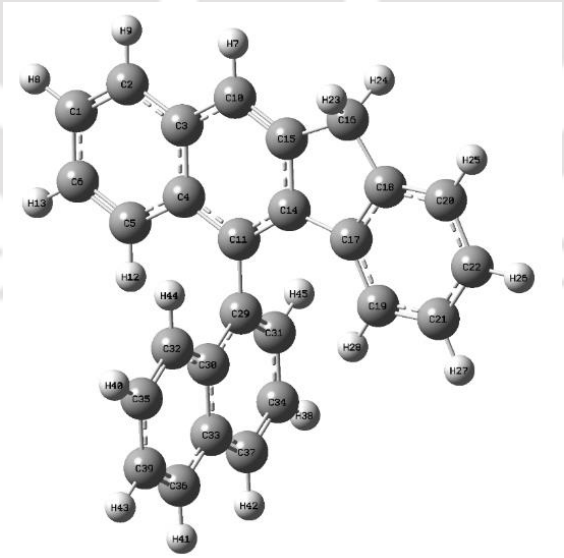
As we can see from *Table 2.8.2*, in DFT-B3LYP/6-31+G(d,p) method, Compound **36q** is 0.005506 Hartree (3.45 kcal/mol) higher in energy than that of the Compound **37q**. Similarly, in

DFT-B3LYP/6-311++G(d,p) method, Compound **36q** is 0.005474 Hartree (3.43 kcal/mole) higher in energy than that of the Compound **37q**. In other words, Compound **37q** is more stable than that of Compound **36q**. (1 Hartree = 627.51 kcal/mole)

Figure 2.8.2 Optimized Structure of compounds **36q** and **37q**



Compound **36q** [DFT-B3LYP/6-311++G(d,p)]



Compound **37q** [DFT-B3LYP/6-311++G(d,p)]

HPLC spectrum of compound **36a**

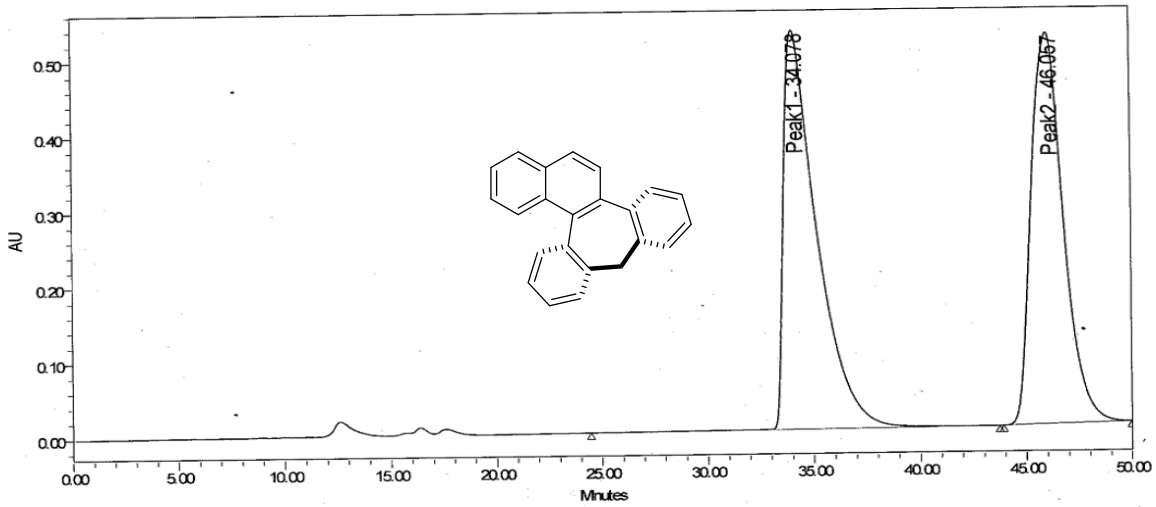
IIT-Guwahati
Project Name: Demo 20022018
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	Arc-h-ph	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/26/2020 2:39:30 PM IST
Vial:	1	Acq. Method:	Hex_ARC
Injection #:	1	Processed By:	Breeze
Injection Volume:	20.00 ul	Date Processed:	11/26/2020 3:34:13 PM IST
Run Time:	50.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name:	

Sample Values Used in Calculations: Injection Volume = 20.00 SampleWeight = 1.00000 Dilution = 1.00000



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	%Area	Height (µV)	%Height	Integration Type	Response	Peak Codes	Points Across Peak	Start Time (min)	End Time (min)	Baseline Start (min)
1	Peak1	34.078	Found	57105388	51.25	529209	50.48	BB	5.711e+007	QP0	1155	24.467	43.733	24.467
2	Peak2	46.057	Found	54326008	48.75	519057	49.52	BB	5.433e+007	QP0	364	43.917	49.983	43.917

Report Method: Detailed Individual Report
Page: 1 of 2

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HPLC spectrum of compound **36f**

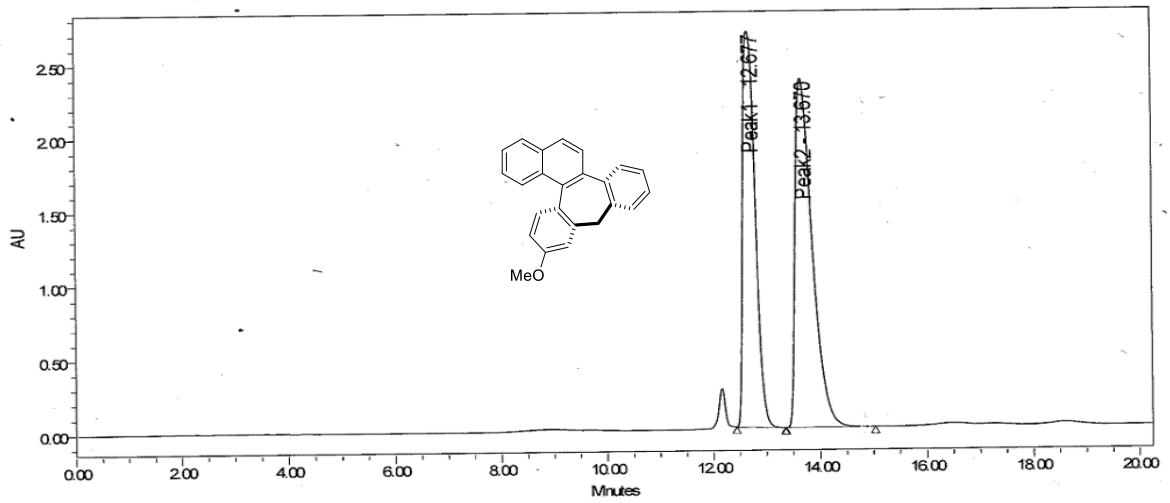
IIT-Guwahati
Project Name: Demo 20022018
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	Arc-p-OMe	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/26/2020 4:54:48 PM IST
Vial:	1	Acq. Method:	Hex_ARC
Injection #:	1	Processed By:	Breeze
Injection Volume:	20.00 ul	Date Processed:	11/26/2020 7:31:43 PM IST
Run Time:	50.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name:	

Sample Values Used in Calculations: Injection Volume = 20.00 SampleWeight = 1.00000 Dilution = 1.00000



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	%Area	Height (µV)	%Height	Integration Type	Response	Peak Codes	Points Across Peak	Start Time (min)	End Time (min)
1	Peak1	12.677	Found	43759208	45.64	2683837	53.12	BB	4.376e+007	QP0	55	12.433	13.350
2	Peak2	13.670	Found	52118795	54.36	2368867	46.88	BB	5.212e+007	QP0	100	13.367	15.033

Report Method: Detailed Individual Report
Page: 1 of 2

Printed: 11/26/2020 7:33:02 PM Asia/Calcutta

HPLC spectrum of compound **36q**

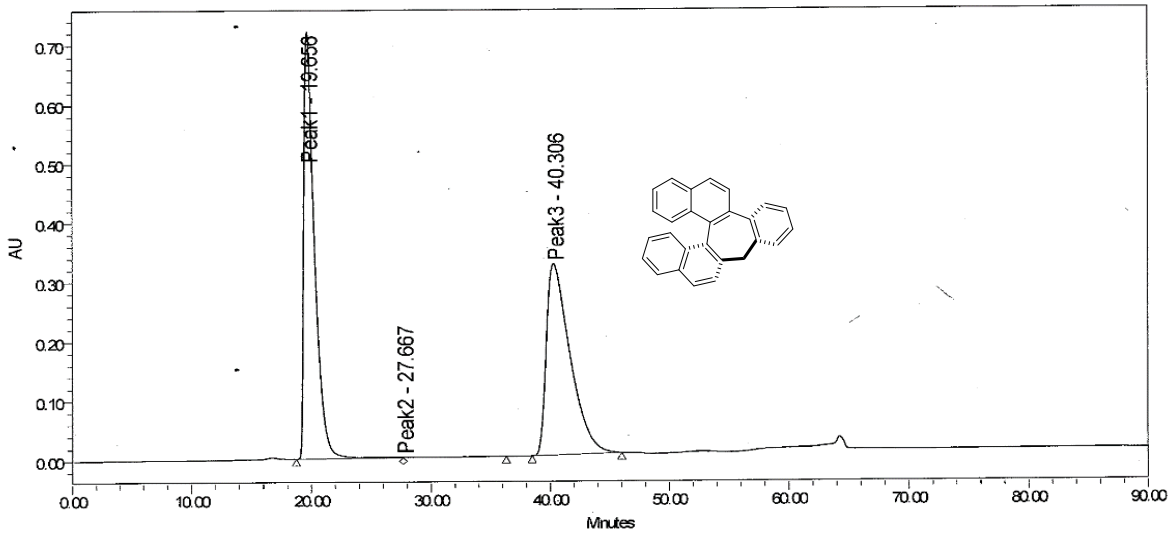
IIT-Guwahati
Project Name: Demo 20022018
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	Arc-h-nap-7	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/27/2020 4:54:34 PM IST
Vial:	1	Acq. Method:	Hex_ARC
Injection #:	2	Processed By:	Breeze
Injection Volume:	20.00 ul	Date Processed:	11/27/2020 8:13:28 PM IST
Run Time:	90.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name:	

Sample Values Used in Calculations: Injection Volume = 20.00 SampleWeight = 1.00000 Dilution = 1.00000



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	%Area	Height (µV)	%Height	Integration Type	Response	Peak Codes	Points Across Peak	Start Time (min)	End Time (min)
1	Peak1	19.65	Found	44978169	50.2	718952	69.0	BV	4.498e+007	Q20	53	18.733	27.667
2	Peak2	27.667	Found	139750	0.1	1273	0.12	VB	1.397e+005	I06 Q20	51	27.667	36.317
3	Peak3	40.30	Found	44485602	49.6	321250	30.8	BB	4.449e+007	Q20	45	38.483	46.017

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HPLC spectrum of compound **37q**

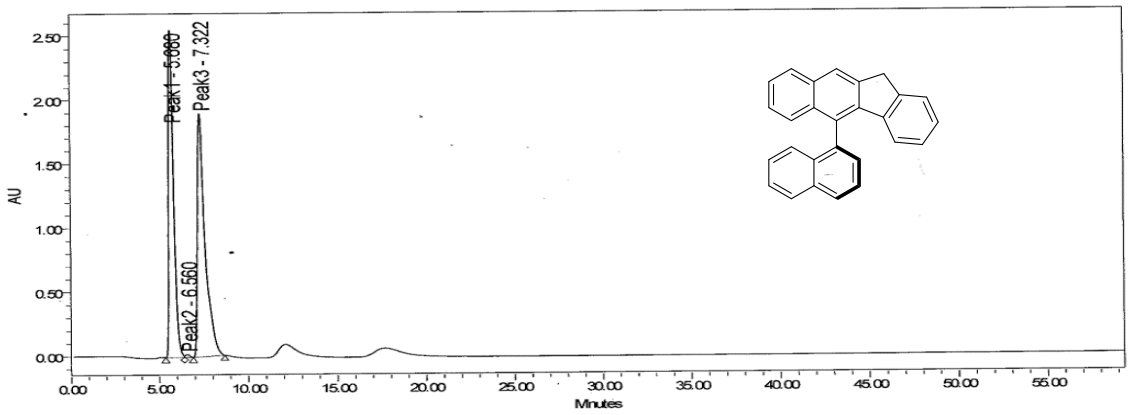
IIT-Guwahati
Project Name: Demo 20022018
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	Arc-h-nap-6	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/27/2020 6:55:09 PM IST
Vial:	1	Acq. Method:	Hex_ARC
Injection #:	3	Processed By:	Breeze
Injection Volume:	20.00 ul	Date Processed:	11/27/2020 8:15:35 PM IST
Run Time:	90.00 Minutes	Channel Name:	W2489 ChA
Sampling Rate:	1.00 per sec	Channel Desc.:	W2489 ChA 254nm
		Sample Set Name:	

Sample Values Used in Calculations: Injection Volume = 20.00 SampleWeight = 1.00000 Dilution = 1.00000



	Peak Name	RT (min)	Peak Type	Area (µV*sec)	%Area	Height (µV)	%Height	Integration Type	Response	Peak Codes	Points Across Peak	Start Time (min)	End Time (min)	Baseline Start (min)
1	Peak1	5.680	Found	49855349	46.62	256604	57.04	BV	4.986e+007	Q20	63	5.350	6.400	5.350
2	Peak2	6.560	Found	405762	0.38	24236	0.54	VB	4.058e+005	Q20	30	6.400	6.900	5.350
3	Peak3	7.322	Found	56667964	53.00	190110	42.42	BB	5.667e+007	Q20	105	6.900	8.667	6.900

Report Method: Detailed Individual Report
Page: 1 of 2

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2.9 Crystal parameters

Table 2.9.1.The crystal parameters of compound **36a**

	CCDC 1873106
Formula	$C_{23}H_{16}$
Formula weight	292.36
T/K	293(2)
Crystal system	Triclinic
Space group	P-1
a/Å	8.7105(6)
b/Å	9.7870(7)
c/Å	10.2324(12)
α/°	107.954(7)
β/°	100.920(7)
γ/°	104.829(5)
V/Å^3	767.28(12)
Z	2
Abs. Coeff./mm^{-1}	0.072
Abs. Correction	Multi-Scan
GOF on F^2	1.031
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0606
	wR2 = 0.1172
R indices [all data]	*R1* = 0.1672
	wR2 = 0.1977

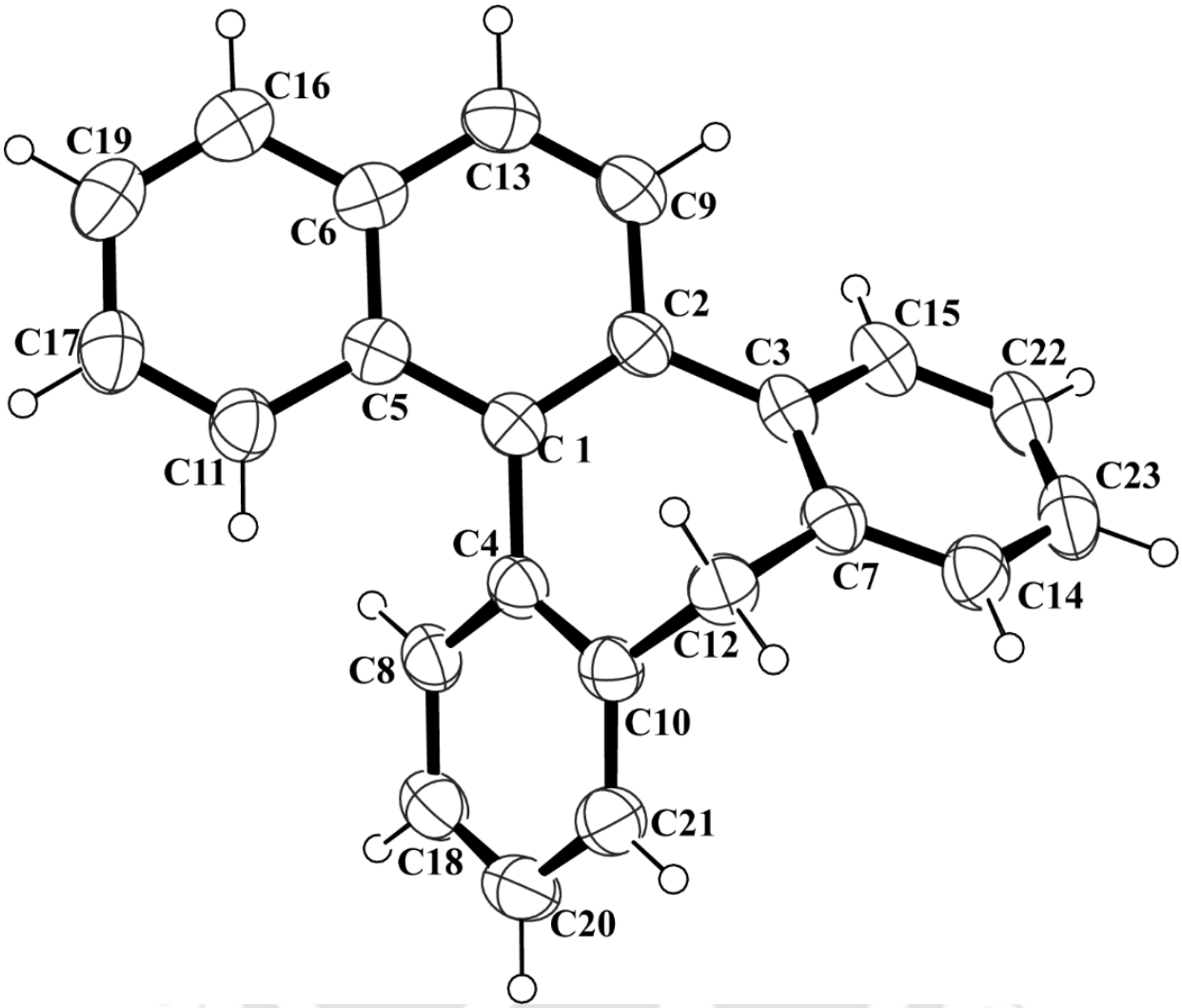


Figure 2.9.1 ORTEP diagram of compound **36a**, thermal ellipsoids are drawn on 35% probability level

Table 2.9.2 The crystal parameters of compound **36c**

	CCDC 1873107
Formula	$C_{24}H_{18}$
Formula weight	306.38
T/K	293(2)
Crystal system	Monoclinic
Space group	P2(1)/n
a/Å	9.8016(6)
b/Å	12.5556(7)
c/Å	14.0526(8)
α/°	90.00
β/°	108.162(3)
γ/°	90.00
V/Å^3	1643.22(17)
Z	4
Abs. Coeff./mm^{-1}	0.070
Abs. Correction	Multi-Scan
GOF on F^2	1.074
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0517
	wR2 = 0.0715
R indices [all data]	*R1* = 0.1455
	wR2 = 0.1611

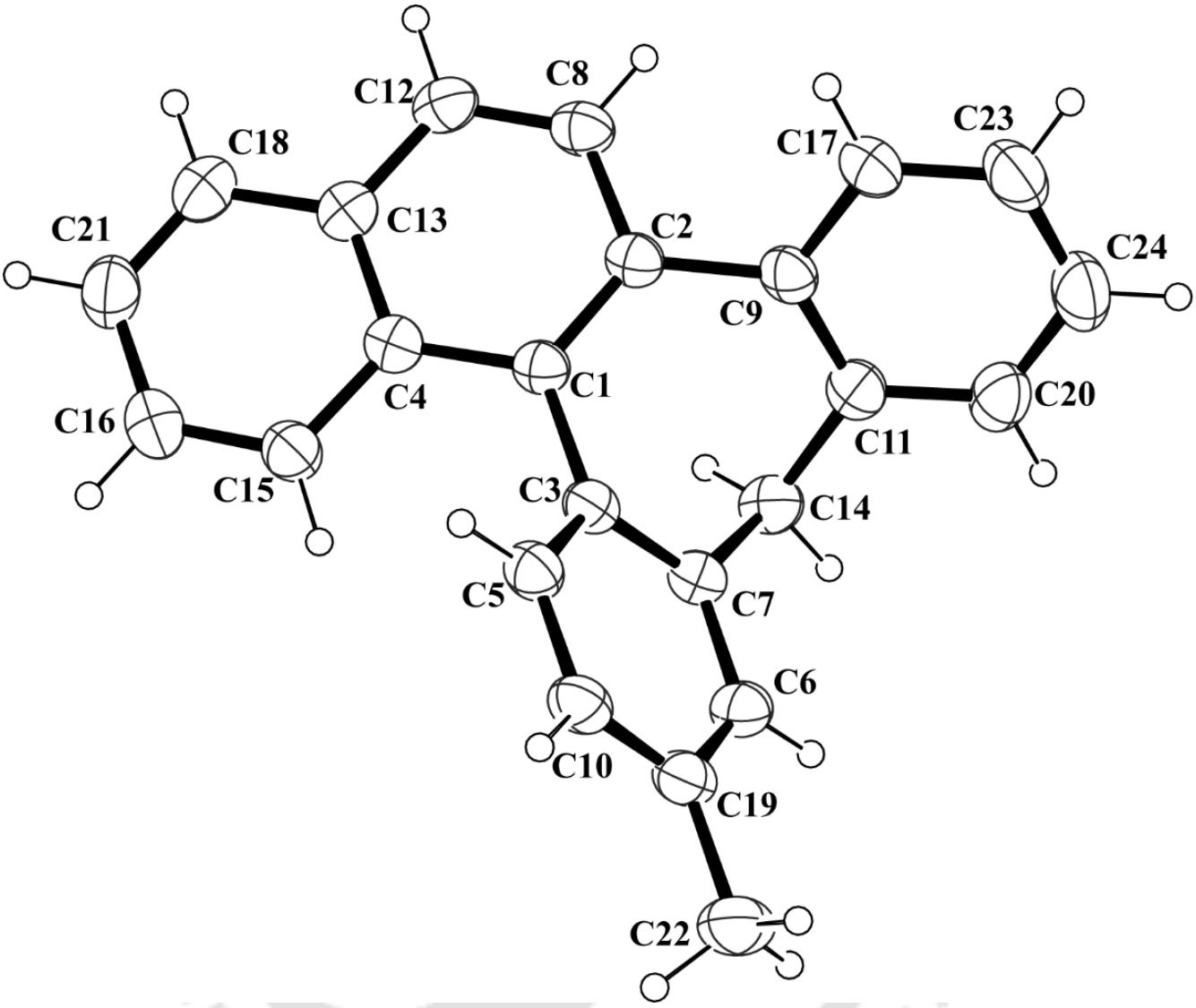


Figure 2.9.2 ORTEP diagram of compound **36c**, thermal ellipsoids are drawn on 35% probability level

CHAPTER 3

In(OTf)$_3$-catalyzed one-pot tandem Mannich/Conia-ene cyclization reaction of *N*-propargyl amido alcohols with 1,3-dicarbonyl compounds: An approach to construct tetrahydro-pyrroloisoindolone-1,1-dicarboxylate derivatives and its application

3.1 Introduction

Tetrahydropyrroloisoindolone and its derivatives are important core structures found in many natural products, pharmaceuticals and biologically active molecules. For example, (*R*)-1-(5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindol-9-yl)-3-(pyridin-2-yl)urea (**A**) is found to be potent Cdk$_4$ inhibitor,[1a] as well as shows cytotoxicity against HCT-116 colon carcinoma cells (*Figure 3.1.1*).[1b] Similarly, (*R*)-9*b*-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9*bH*)-one (**B**) contains thiazoloisoindolone moiety, exhibits antiretroviral properties and also act as high affinity ligand for the melatonin MT3 binding site (*Figure 3.1.1*).[2] The pyrroloisoindolone skeleton containing compound (**C**), (-)-chlorizidine A is a marine natural product (*Figure 3.1.1*).[3]

However, the different substitution pattern in these heterocycles explores new opportunities for synthetic organic chemists in drug discovery. Thus, the need of efficient methodologies to prepare new set of heterocycles is always in high demand.

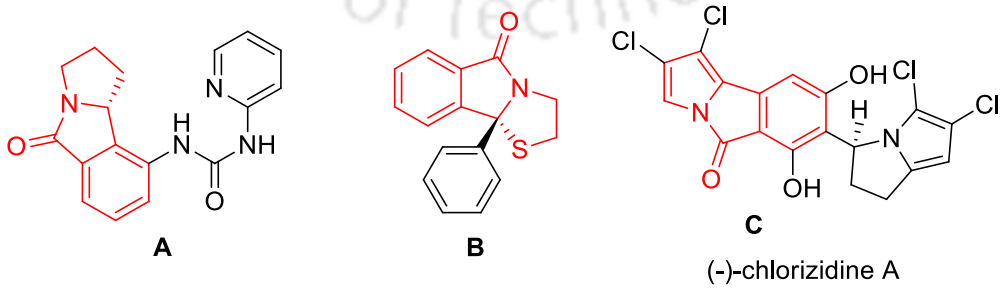


Figure 3.1.1 Examples of bioactive isoindolinones.

Tandem reactions, in general are unrivalled tool in organic chemistry[4] because it allows multiple transformation in one operation with minimal operational cost, reagents, reduce wastage of solvents and improve the yields of products in shorter reaction time. Synthetic chemist's repertoire contains numerous reactions to synthesize complex nitrogen containing heterocycles, Conia-ene reaction is one among them.

Conia-ene reaction is an atom economic, special ene-type of thermal intramolecular cyclization reaction of enolizable carbonyl compounds with a tethered alkyne or alkene group (*Figure*

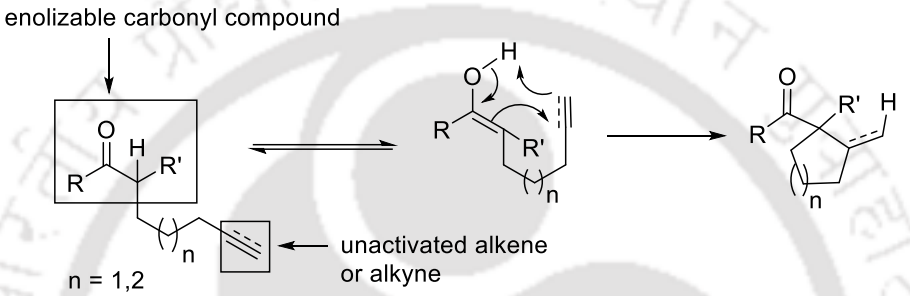
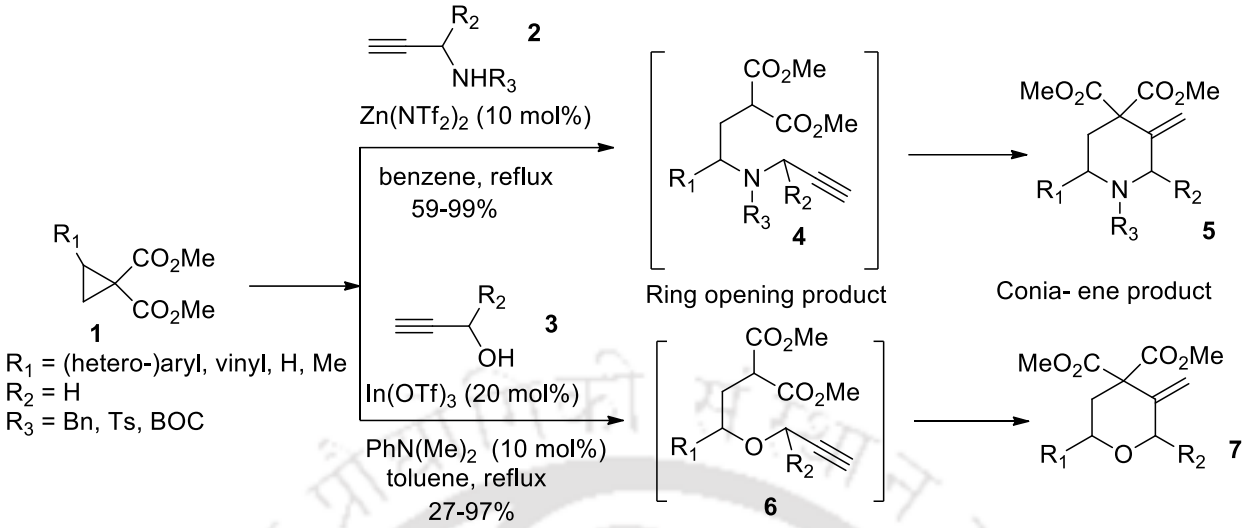


Figure 3.1.2 Schematic representation of Conia-ene cyclization reaction.

3.1.2). Further, this method was also modified to ambient reactions by using transition metal catalysts.[5a] In past years, this strategy has been utilized to synthesize many carbo- and hetero-cyclic compounds varying from five to nine membered ring systems.[5] Moreover, this method has also been applied in synthesis of complex natural products.[6] Additionally to increase the applicability, Conia-ene reaction has been targeted in variety of cascade/tandem cyclization reactions and they are dissucssed below.

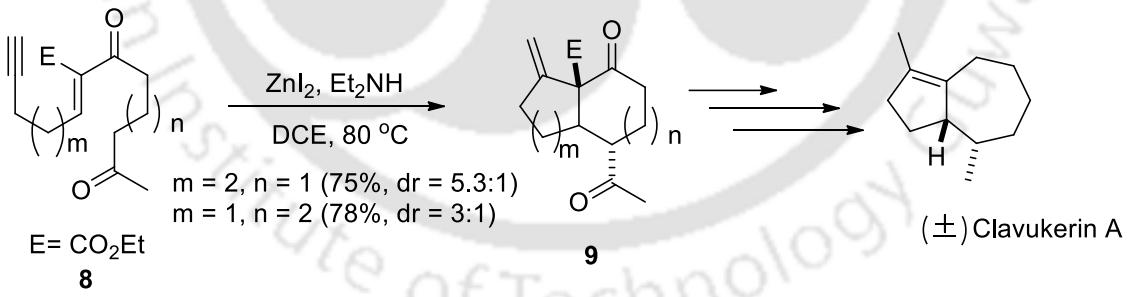
3.2 Literature survey befitting tandem Conia-ene reactions

Kerr and co-workers in 2009 reported a convenient method for the synthesis of highly substituted piperidines **5** and tetrahydropyrans **7** from 1,1-cyclopropanediesters **1** with propargyl amines **2** and propargyl alcohols **3** respectively.[7] The sequence of the reaction involves tandem nucleophilic ring opening of cyclopropanediesters by propargyl amines or alcohols, followed by Conia-ene reaction catalysed by Lewis acid and often a mild base (*scheme 3.2.1*).



Scheme 3.2.1

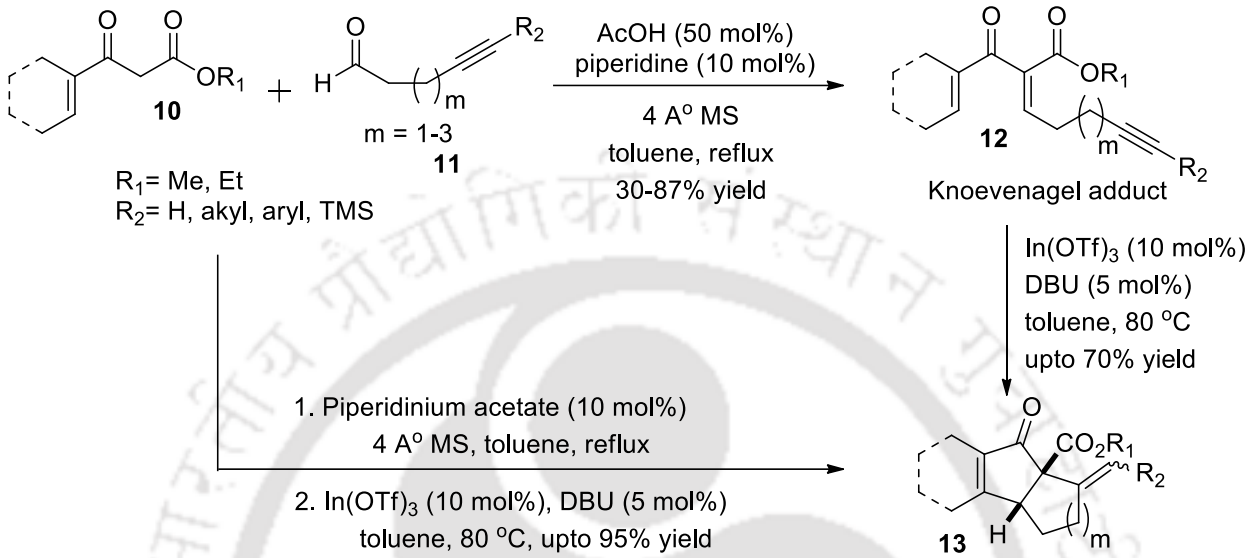
Lee and his group explored the applicability of Conia-ene reaction for the synthesis of fused carbocycles in 2010. Simple *β*-ketoesters **8** tethered with alkyne at one end and aldehyde at the other were successfully converted into fused 6,6 and 5,7 bicyclic carbocycles **9** using secondary amines in stoichiometric amount *via* cascade Michael and Conia-ene reaction. Infact, use of zinc iodide proceeded the reaction with good diastereoselectivity (*scheme 3.2.2*). Moreover, this method was further utilized for the formal synthesis of a sesquiterpenoid (±) Clavukerin A.[8]



Scheme 3.2.2

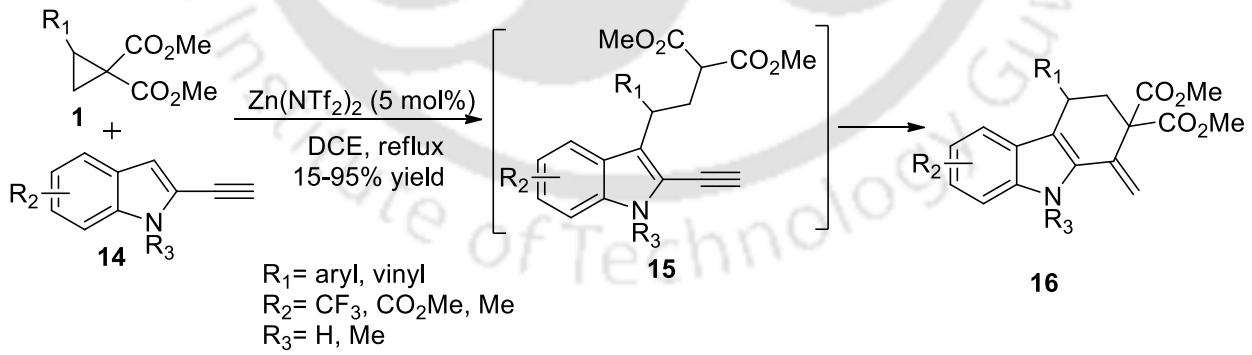
In the same year, fused carbocycles were synthesized by Zhang and co-workers from *β*-ketoesters **10** and alkynyl aldehydes **11** as starting precursors (*scheme 3.2.3*).[9] The reaction was accomplished using two strategies. At first, synthesis of Knoevenagel condensation product **12** from β-ketoester **10** with alkynyl aldehyde **11** followed by conversion into fused carbocyclic compound **13** *via* tandem Nazarov cyclisation and Conia-ene type reaction catalysed by

indium(III) triflate. In the second strategy, they achieved all the three reactions (Knoevenagel condensation, Nazarov cyclisation and intramolecular Conia-ene reaction) concisely in one pot which resulted in *exo*-double bond having *cis*–selectivity in excellent yields.



Scheme 3.2.3

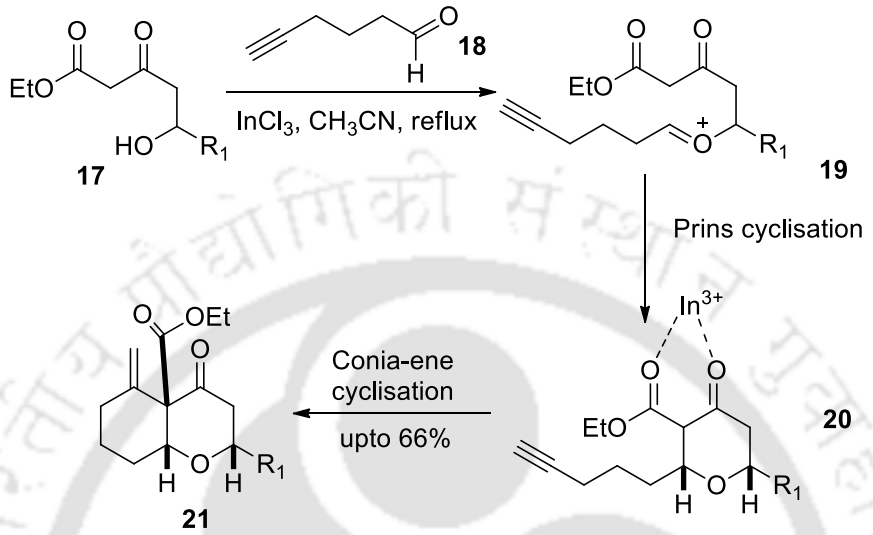
An efficient $Zn(NTf_2)_2$ catalyzed, one-step domino Friedel-Crafts ring opening reaction of 1,1-cyclopropanediesters **1** by 2-alkynyl indoles **14** followed by Conia-ene ring closure resulted in tetrahydrocarbazoles **16** was proposed by Kerr and his group in 2011 (*scheme 3.2.4*).[10]



Scheme 3.2.4

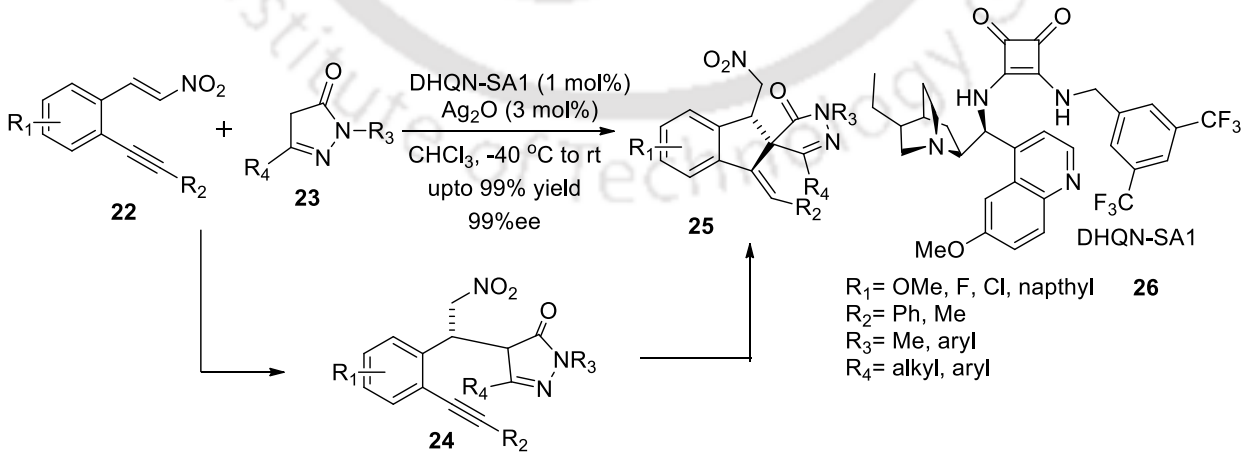
In 2011 Lee and his group reported a Prins/Conia-ene cascade cyclization of acyclic *β* ketoesters **17** and alkynyl aldehyde **18** catalyzed by Indium(III) salts in refluxing acetonitrile to get 1-oxadecalin **21** in moderate to good yields. The reaction mechanism explains the initial generation

of oxocarbenium ion **19** followed by Prins cyclisation reaction to generate substituted tetrahydropyran intermediate **20** which undergoes subsequent Conia-ene cyclization to install the target compounds (*scheme 3.2.5*).[11]



Scheme 3.2.5

Enders and co-workers in 2016 developed a stereoselective synthesis of spiropyrazolones **25** from alkyne bearing *β*-nitrostyrenes **22** and substituted pyrazolones **23** through a consecutive organocatalytic asymmetric Michael addition followed by Conia-ene approach in single step



Scheme 3.2.6

process (*scheme 3.2.6*).[12] In this reaction, alkyne activation was achieved by silver catalysis which promoted *5-exo-dig* cyclization to give the desired spiropyrazolones **25** in moderate to good yields with excellent enantioselectivitity.

Apart from this, Mannich reaction is one of the classical *C-C* bond forming reactions in which nucleophilic attack of enolizable carbonyls or their equivalents takes place on iminium ion intermediates and this has been investigated widely in organic synthesis.[13]

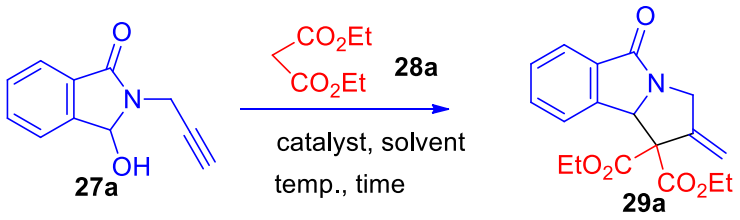
3.3 Results and discussions

Literature reports revealed the existence of tandem ring-opening/Conia-ene, Nazarov/Conia-ene, Prins/Conia-ene and Michael/Conia-ene along with its asymmetric version for the synthesis of variety of fused and complex carbo-/hetero-cyclic compounds. In this sequence, to the best of our knowledge, tandem Mannich/Conia-ene is not reported till date.

In continuation of our interest to explore *N*-acyliminium ion reactions in synthesis of various nitrogen containing bicyclic compounds,[14] in this chapter, an indium(III) triflate catalyzed tandem one-pot reaction for the synthesis of highly substituted tetrahydropyrroloisoindolone having *exo*-cyclic double bond *via* tandem Mannich reaction of substituted 3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-one and 1,3-dicarbonyl compounds followed by Conia-ene cyclization reaction is described.

In the beginning, 3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-one (**27a**) was reacted with diethylmalonate (**28a**) in presence of 0.1 equivalent of $In(OTf)_3$ in DCE at room temperature under an inert nitrogen atmosphere for 48 h (*Table 3.3.1*, entry 1). Unfortunately, no desired product was observed, instead starting material was recovered in 95%. Later on, the same reaction under reflux conditions gave diethyl 2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*] isoindole-1,1-dicarboxylate (**29a**) in 21% yield (*Table 3.3.1*, entry 2). A moderate38% yield of the target compound was observed when the reaction was performed in toluene at reflux temperature (*Table 3.3.1*, entry 3). To our delight, when the amount of $In(OTf)_3$ was increased from 0.1 to 0.2 equivalents the yield increased to 68% in 5 h (*Table 3.3.1*, entry 4). Moreover, to improve the yield, the reaction was examined with other solvents such as xylene,

Table 3.3.1 Optimization of the reaction[a]



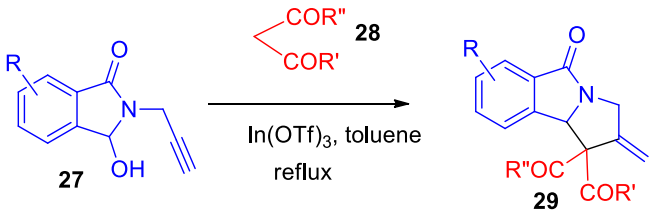
entry	catalyst (in equiv.)		solvent	temp.	time (h)	yield[b](%)
1	$In(OTf)_3$	0.1	DCE	rt	48	nr[c]
2	$In(OTf)_3$	0.1	DCE	reflux	8	21
3	$In(OTf)_3$	0.1	Toluene	reflux	5	38
4	$In(OTf)_3$	0.2	Toluene	reflux	5	68
5	$In(OTf)_3$	0.2	CH_3CN	reflux	7	e[d]
6	$In(OTf)_3$	0.2	1,4 dioxane	reflux	6	e[d]
7	$In(OTf)_3$	0.2	Xylene	reflux	12	e[d]
8	$In(OTf)_3$	0.3	Toluene	reflux	5	65
9	$In(OTf)_3$	1.0	Toluene	reflux	5	65
10	AgOTf	0.1	DCE	reflux	12	10
11	$Bi(OTf)_3$	0.2	Toluene	reflux	48	trace
12	TMSOTf	0.2	Toluene	reflux	7	e[d]
13	$Sc(OTf)_3$	0.5	Toluene	reflux	12	e[d]
14	$BF_3{\cdot}OEt_2$	1.0	Toluene	reflux	6	e[d]
15	$AlCl_3$	1.0	Toluene	reflux	12	e[d]
16	$InCl_3$	0.2	Toluene	reflux	12	32
17	$InBr_3$	0.2	Toluene	reflux	7	30
18	$FeCl_3$	1.0	Toluene	reflux	7	8
19	CuCl	0.2	Toluene	reflux	48	trace
20	$In(OTf)_3/Sc(OTf)_3$	0.1/0.1	Toluene	reflux	12	20
21	$BF_3{\cdot}OEt_2/In(OTf)_3$	1.0/0.1	Toluene	reflux	12	21
22	PTSA	0.2	Toluene	reflux	24	8
23	TfOH	0.2	Toluene	reflux	7	e[d]

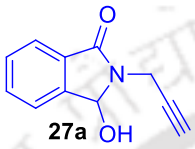
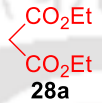
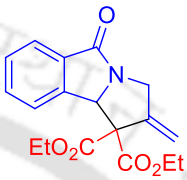
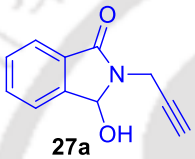
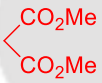
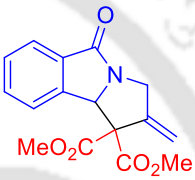
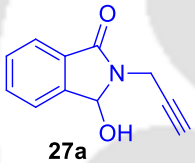
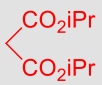
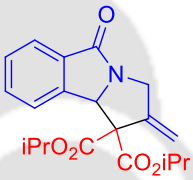
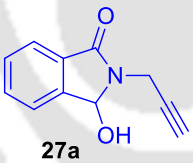
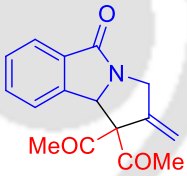
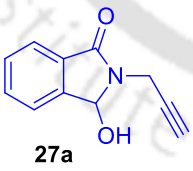
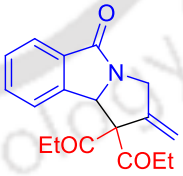
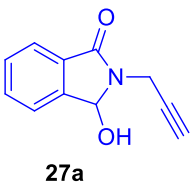
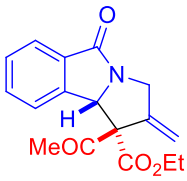
[a]All the reactions carried out in (0.3 mmol) **27a**, (0.33 mmol) **28a** in 3.0 mL solvent, [b]Isolated yields, [c]nr = No reaction, [d]e = Decomposed

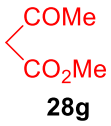
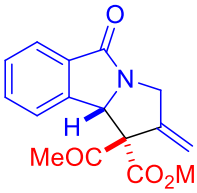
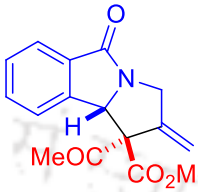
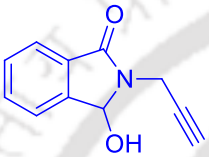
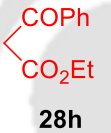
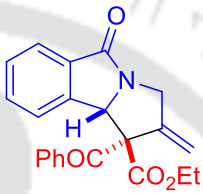
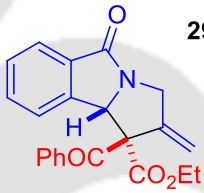
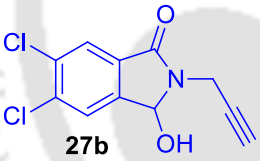
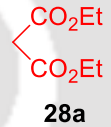
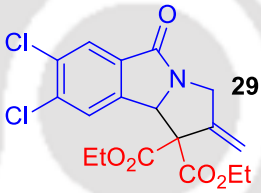
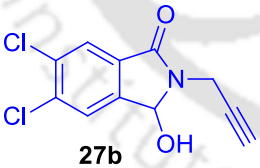
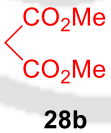
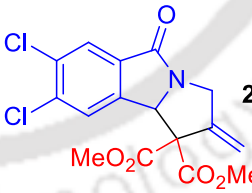
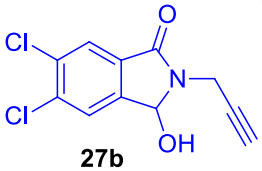
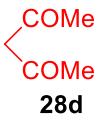
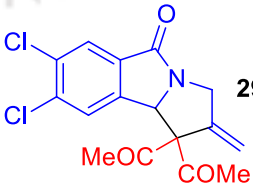
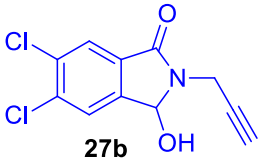
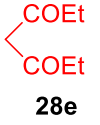
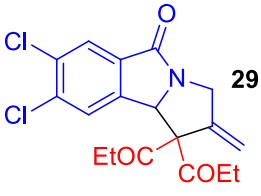
acetonitrile, 1,4-dioxane under reflux conditions but resulted in decomposed products (*Table 3.3.1*, entries 5-7). Among all the solvents inspected, toluene emerged out as the best solvent for the reaction. In an effort to increase yield, the reaction was carried out with varying amount of catalyst loadings such as 0.3 and 1.0 equivalents of $In(OTf)_3$ in toluene and they failed to afford higher yields (*Table 3.3.1*, entries 8-9). The reaction was also screened with other triflates such as Ag(OTf) and $Bi(OTf)_3$ afforded the trace amount of yields; trimethylsilyltriflate (TMSOTf) and $Sc(OTf)_3$ were not fruitful (*Table 3.3.1*, entries 10-13). Whereas, the use of strong Lewis acids such as Borontrifluoride etherate ($BF_3{\cdot}OEt_2$) and aluminium (III) chloride ($AlCl_3$) afforded decomposed products (*Table 3.3.1*, entries 14-15). Similarly, indium(III), iron(III) and copper(I) halides didn't show much effect on yield of the reaction, (*Table 3.3.1*, entries 16-19). On the other hand, the reaction with double Lewis acids also resulted in low yields (*Table 3.3.1*, entries 20-21). Brønsted acids were found to be totally inefficient for this transformation (*Table 3.3.1*, entries 22-23). From the overall observations we could infer that 0.2 equivalents of $In(OTf)_3$ in toluene under reflux conditions is the optimum conditions for this reaction.

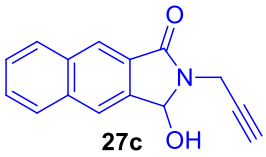
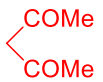
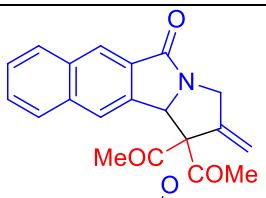
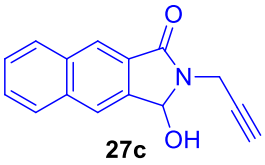
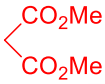
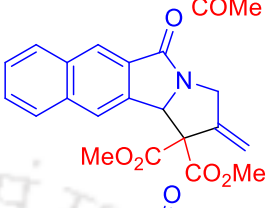
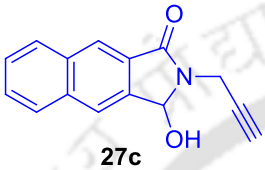
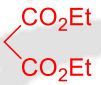
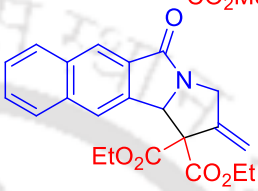
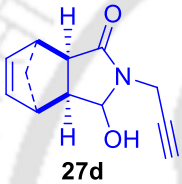
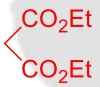
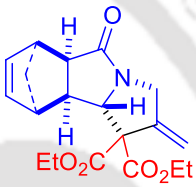
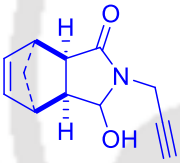
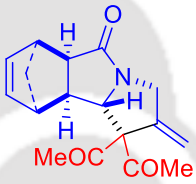
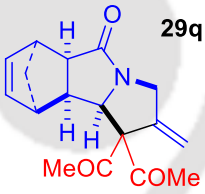
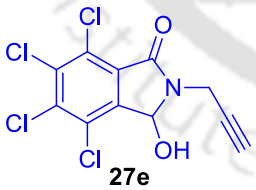
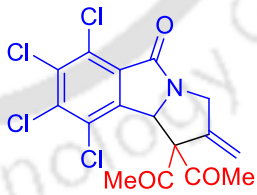
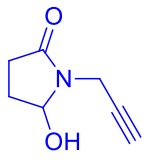
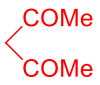
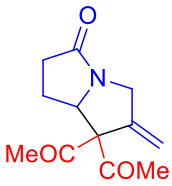
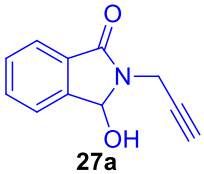
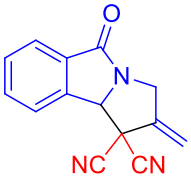
With the established optimal, the scope of this reaction was investigated with other *N*-propargyl amido alcohols and dicarbonyls and the results are summarized in *Table 3.3.2.* The *N*-propargyl amido alcohol **27a** was treated with dimethyl- **28b** and diisopropyl-malonates **28c** and gave products **29b** and **29c** with 65 and 35% yields respectively (*Table 3.3.2*, entries 2-3). The low yield in the case of diisopropylmalonate (35%), may be attributed to the steric and electronic effects of two isopropyl groups. Similarly, reaction with pentane-2,4-dione (**28d)** and heptane-3,5-dione (**28e)** produced **29d** and **29e** with 65 and 60% yields (*Table 3.3.2*, entries 4-5). But in case of unsymmetrical active methylene compounds **28f**-**28g**, an inseparable mixture of diastereomers with a ratio of 1:1 were obtained with 80% overall yields (*Table 3.3.2*, entries 6-7). In the same way, 1-phenylpentane-1,3-dione (**28h)** produced inseparable diastereomers **29h** and **29h′** in 75% yield with high diastereoselectivity (*dr*, 93:7). The formation of major compound **29h** might be due to the steric repulsion between the phenyl ring of the benzoyl group on the tetrahydropyrrole ring and the phenyl group of the isoindolinone ring. The repulsive π-π stacking between the two phenyl rings which makes them move apart from each other cannot be ruled out (*Table 3.3.2*, entry 8). The structure of **29h** is determined by nOe correlation (*Figure 3.3.1* and *3.8.1*).[15] There is a strong interaction between the phenyl ring of the benzoyl group and the olefinic proton of the *exo*-cyclic double bond of the tetrahydropyrrole ring. To examine the

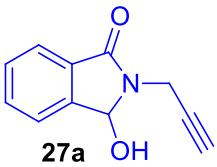
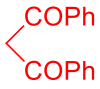
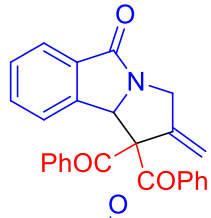
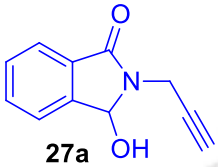
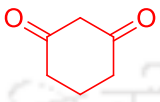
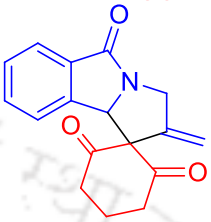
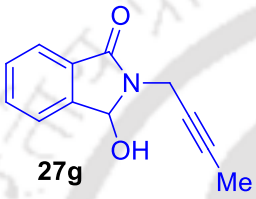
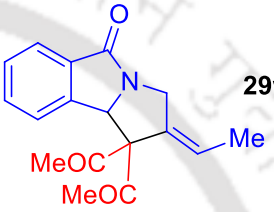
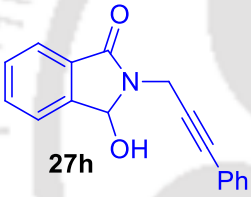
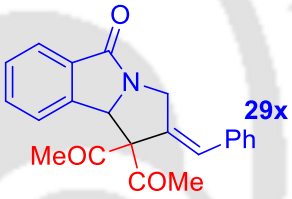
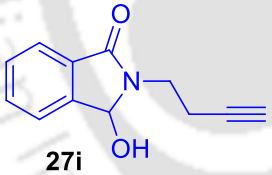
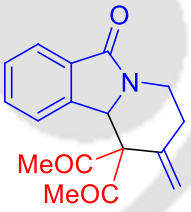
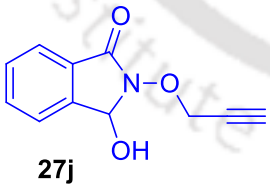
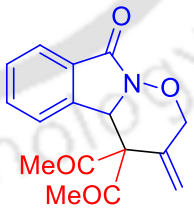
Table 3.3.2 Synthesis of Pyrroloisoindolone



Entry	1	2	Product	%Yield[a]
1				68
2				65
3				35
4				65
5				60
6				80[b]

Entry	1	2	Product	%Yield[a]
7	 **27a**	 **28g**	 **29g**  **29g:29g' =** 1:1 **29g'**	80[b]
8	 **27a**	 **28h**	 **29h**  **29h:29h' =** 93:7 **29h'**	75[b]
9	 **27b**	 **28a**	 **29i**	45
10	 **27b**	 **28b**	 **29j**	68
11	 **27b**	 **28d**	 **29k**	70
12	 **27b**	 **28e**	 **29l**	80

Entry	1	2	Product		%Yield[a]
13	 **27c**	 **28d**		**29m**	57
14	 **27c**	 **28b**		**29n**	60
15	 **27c**	 **28a**		**29o**	43
16	 **27d**	 **28a**		**29p**	57
17	 **27d**	 **28d**		**29q**	55[b]
				**29q'**	**29q**:**29q'** = 86:14
18	 **27e**	 **28d**		**29r**	90
19	 **27f**	 **28d**		**29s**	d[c]
20	 **27a**	 **28i**		**29t**	nr[d]

Entry	1	2	Product		%Yield[a]
21	 **27a**	 **28j**		**29u**	40
22	 **27a**	 **28k**		**29v**	d[c]
23	 **27g**	 **28d**		**29w**	30
24	 **27h**	 **28d**		**29x**	d[c]
25	 **27i**	 **28d**		**29y**	64
26	 **27j**	 **28d**		**29z**	37

[a]Yields refer to isolated yield. Reaction conditions: **27** (1.0 equiv.), **28** (1.1 equiv.), $In(OTf)_3$ (0.2 equiv.), 110 °C; [b]Ratio is determined by ^1H NMR; [c]d = decomposed products. [d]nr = no reaction.

further substrate scope of the reaction, dichloro substituted 3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-ones **27b** was reacted with malonates **28a**-**28b** and 1,3-diketones **28d**-**28e** and furnished the corresponding products in 45-80% yields (*Table 3.3.2*, entries 9-12). On the other

hand, *N*-propargyl amido alcohol **27c** derived from 1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione gave moderate yields (*Table 3.3.2*, entries 13-15).

Furthermore, the reaction was successfully carried out with *N*-propargyl norbornene skeleton **27d** with dicarbonyls **28a** and **28d** to give the respective products in 57 and 55% yields, respectively (*Table 3.3.2*, entries 16-17). The reaction of **27d** with diethylmalonate **28a** gave compound **29p** as single diastereomer whereas with pentane-2,4-dione (**28d**) gave diastereomeric mixture of **29q** and **29q′** with a ratio of 86:14. The structure of **29p** and **29q** is determined by nOe analysis of **29q** (*Figure 3.3.1* and *3.8.2*). Formation of low yield in the case of **29q′** may be attributed to the steric repulsion between acetyl groups on tetrahydropyrrole ring and norbornene skeleton in which tetrahydropyrrole ring is *cis* to norbornene ring. The absence of other diastereoisomer in the former case might be due to the steric repulsion between the more bulky ester groups on tetrahydropyrrole ring and the norbonene ring compared to acetyl groups of the latter. Importantly, highly chloro substituted *N*- propargyl amido alcohol **27e** (*Table 3.3.2*, entry 18) gave highest yield (90%). Interestingly, 5-hydroxy-1-(prop-2-yn-1-yl)pyrrolidin-2-one (**27f**) failed to give desired product, instead some decomposed products were obtained. Malononitrile failed to provide desired product because of its inability to form enol. Other bulkier dicarbonyl compounds 1,3-diphenylpropane-1,3-dione (**28j**) and cyclohexane-1,3-dione (**28k**) were also screened for this reaction, while **28j** gave 40% yield, **28k** failed to give the desired product instead inseparable complex mixture was observed under the reaction conditions (*Table 3.3.2*, entries 21-22).

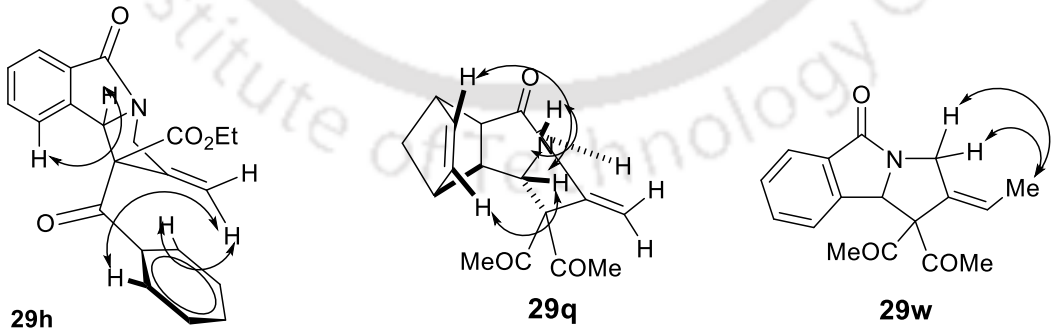
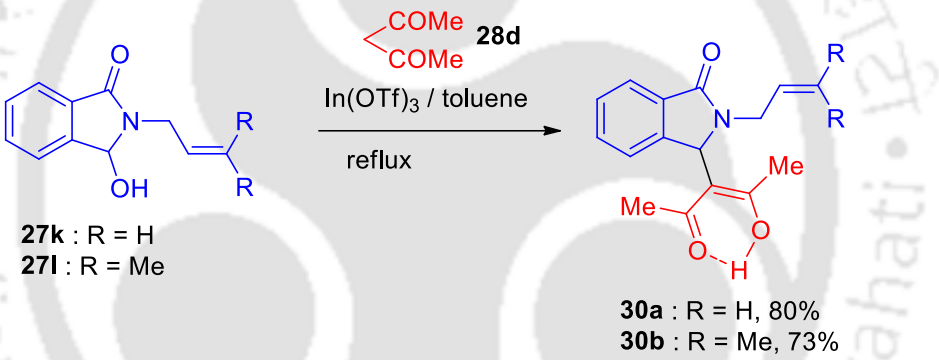


Figure 3.3.1 nOe correlation of compounds **29h**, **29q** and **29w**

The substrates with internal alkyne having methyl group **27g** produced compound **29w** only in 30% yield (Table 2, entry 23) with *Z* selectivity, which is confirmed by nOe correlation (*Figure 3.3.1* and *3.8.3*), whereas, phenyl substituted internal alkyne **27h** afforded decomposed products (*Table 3.3.2*, entry 24). *N*-homopropargyl amido alcohol **27i** when subjected to react with **28d** gave tetrahydropyrido[2,1-*a*]isoindolone derivative **29y** in 64% yield (*Table 3.3.2*, entry 25). The reaction is also applicable to 3-hydroxy-2-(prop-2-yn-1-yloxy)isoindolin-1-one (**27i)**, which produced dihydro-oxazino[3,2-*a*]isoindolone derivative **29z** in 37% yield (*Table 3.3.2*, entry 26). In order to access the feasibility of reaction with terminal and internal *N*-allyl amido alcohols, **27k** and **27l** were reacted with **28d** and to our dismay they gave only intermediate Mannich products **30a** and **30b** as keto-enol tautomer in 80 and 73% yields, respectively (*Scheme 3.3.1*).

3.3.1 Reaction with *N*-allyl amido alcohols



Scheme 3.3.1

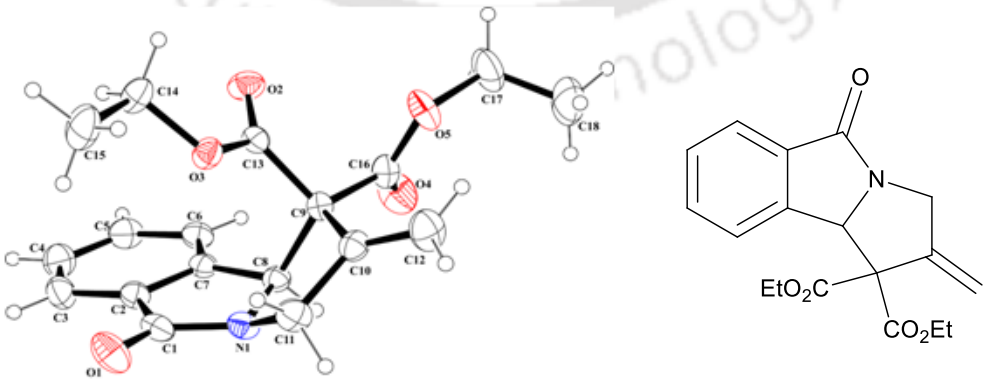
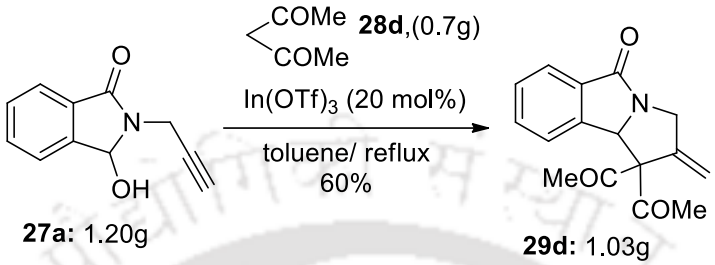


Figure 3.3.2 ORTEP diagram of compound **29a** using thermal ellipsoids of 30% probability

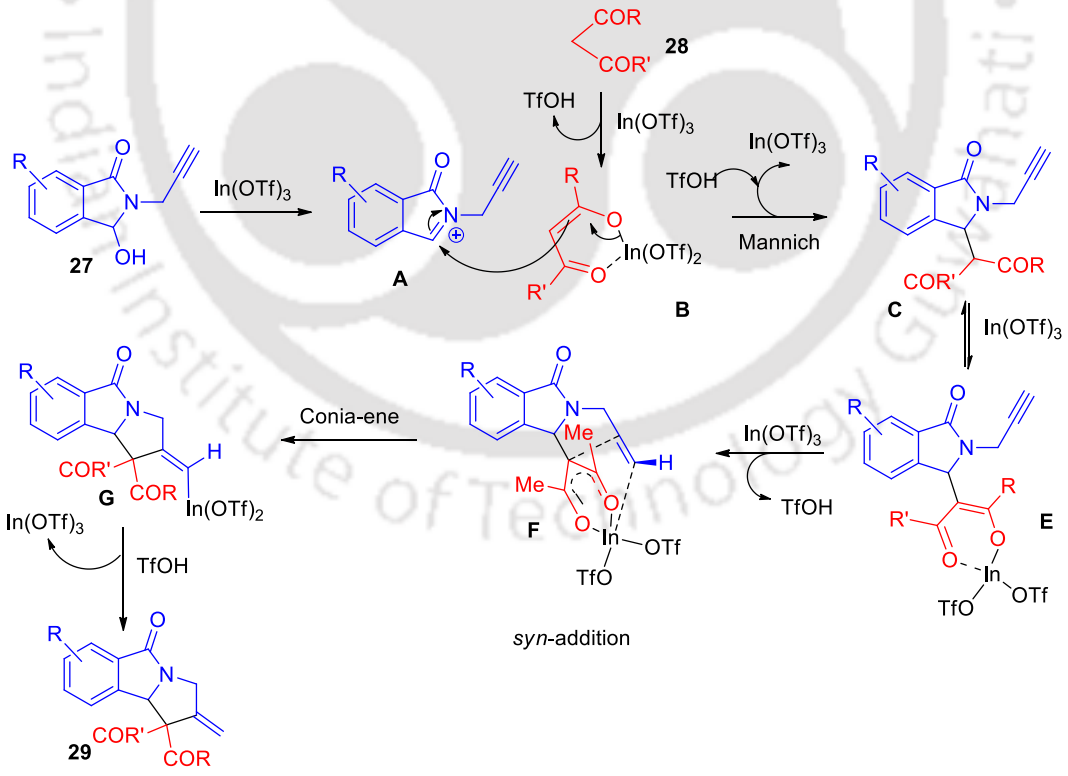
The structure of all compounds was confirmed by ^{1}H & ^{13}C NMR, IR, mass spectrometry and finally by X-ray crystallographic analysis of compound **29a** (*Figure 3.3.2*, *Table 3.9.1*).[16]

3.3.2 Reaction in gram scale



Scheme 3.3.2

To demonstrate the practical utility of the methodology a gram scale reaction has been carried out as shown in *Scheme 3.3.2*. Thus the reaction of **27a** (1.2 g, 6.4 mmol) with **28d** (0.7g, 7.0 mmol) in presence of $In(OTf)_3$ (720 mg, 1.28 mmol) in refluxing toluene gave **29d** in 60% yield.



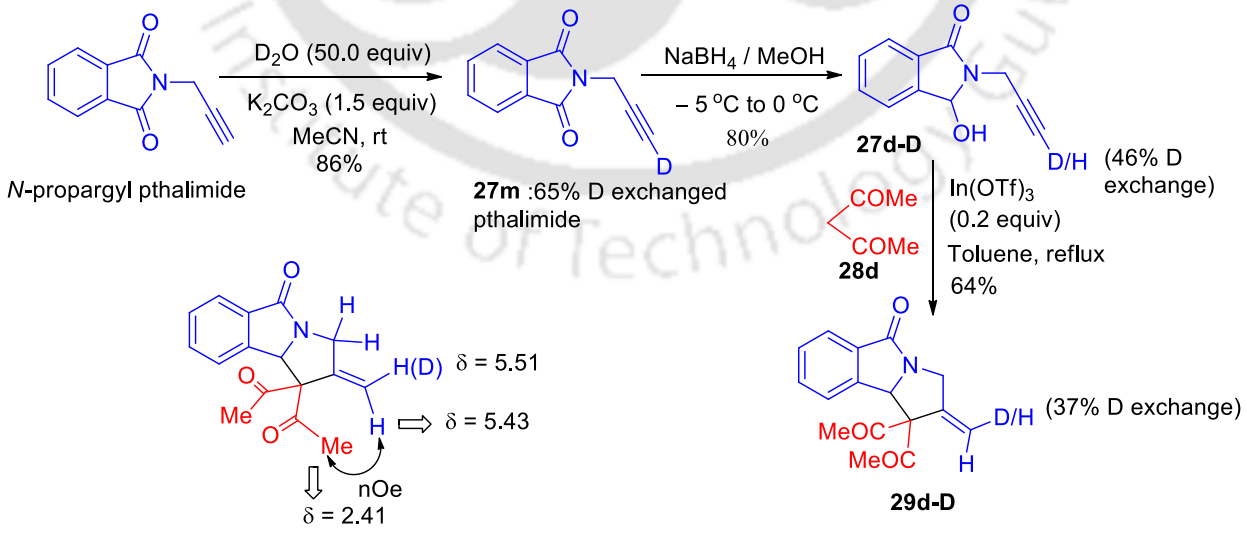
Scheme 3.3.3

3.3.3 Plausible mechanism of the reaction

The plausible mechanism of the reaction is proposed in *Scheme 3.3.3*. The amido alcohol **27** under Lewis acidic conditions forms *N*-acyliminium ion **A**, which is attacked by indium enolate **B** to give Mannich product **C**. The compound **C** after double activation by $In(OTf)_3$ forms transition state **F** *via* **E,** which after *syn*- addition gives intermediate **G**.[5b] Protonation of **G** provides final compound **29** (*Scheme 3.3.3*).

3.3.4 Deuterium exchange reaction

To prove the *syn*-addition mechanism, a deuterium exchange experiment has been conducted as shown in *scheme 3.3.4*. Thus, the reaction of *N*-propargyl pthalimide (185 mg, 1.0 mmol) with D_2O (0.9 mL, 50 mmol) in the presence of K_2CO_3 (207 mg, 1.5 mmol) in acetonitrile (2 mL) under nitrogen atmosphere for 12 h gave deuterated compound **27m**. The compound **27m** (160 mg, 0.86 mmol) is then reduced to **27d-D** with $NaBH_4$ (80 mg, 2.15 mmol) in MeOH (2 mL), which after cyclization with pentane-2,4-dione (**28d**) (75 mg, 0.75 mmol) provides deuterated product **29d-D** with 37% deuterium exchange. The 1D nOe analysis revealed that there is a strong interaction between the acetyl methyl group and undeuterated olefinic proton which confirms the *syn*-addition and *Z* configuration (*scheme 3.3.4*, *Figure 3.8.4*). This also explains the *Z* configuration of compound **29w**.

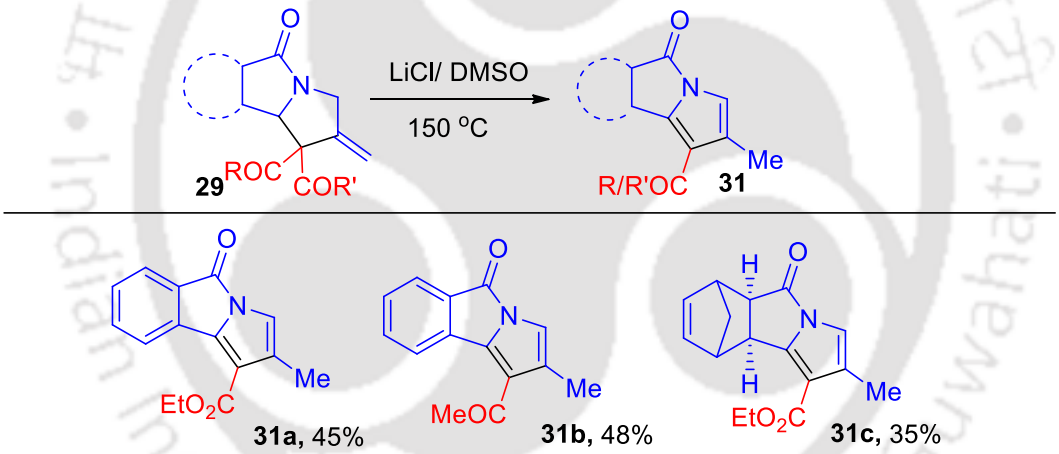


Scheme 3.3.4

3.4 Post synthetic modification

The utility of the methodology is extended towards the synthesis of pyrroloisoindolones **31a-31c**. It may be noted that pyrroloisoindolone moiety is found in biologically active molecules and natural products.[3] Thus the reaction of tetrahydropyrroloisoindolone **29a, 29f/29f′**and **29p** with lithium chloride in DMSO at 150 °C resulted in 5*H*-pyrrolo[2,1-*a*]isoindol-5-ones **31a**, **31b** and **31c** in 45, 48 and 35% yields, respectively (*Scheme 3.4.1*). The structure of the compounds was confirmed by ^{1}H & ^{13}C NMR, IR, mass spectrometry and finally by X-ray crystallographic analysis of compound **31a** (*Figure 3.4.1, Table 3.9.2*).[16]

3.4.1 Synthesis of 5*H*-pyrrolo[2,1-*a*]isoindol-5-one[a]

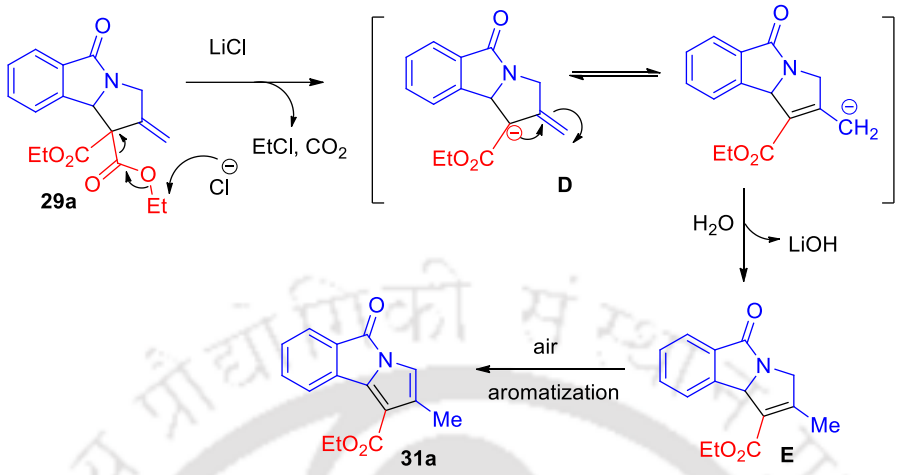


[a]Yields refer to isolated yield, reaction conditions: **29** (1.0 equiv.), LiCl (5.0 equiv.), 150 °C.

Scheme 3.4.1

The mechanism for the formation of **31a-31c** is similar to Krapcho dealkoxycarbonylation (*Scheme 3.4.2*).[17] The chloride ion abstracts one of the ethyl groups from **29a** to form anion **D**, which abstracts one proton from water followed by oxidative aromatization forms desired ethyl 2-methyl-5-oxo-5*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (**31a**).

3.4.2 Mechanism of formation of pyrroloisoindolone



Scheme 3.4.2

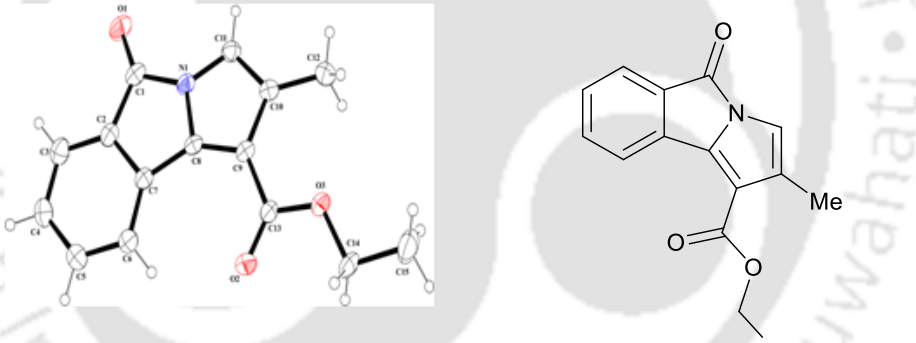


Figure 3.4.1. ORTEP diagram of compound **31a** using thermal ellipsoids of 30% probability

Conclusion

In conclusion, we have developed a methodology for the synthesis of substituted tetrahydropyrroloisoindolone using one-pot tandem Mannich and Conia-ene cyclization reaction with moderate to high yields. The reaction is highly regioselective with an exocyclic double bond in the pyrrolidine ring. The reaction can also be used for the synthesis of tetrahydropyrido[2,1-*a*]isoindolone and dihydro-oxazino[3,2-*a*]isoindolone derivatives. The

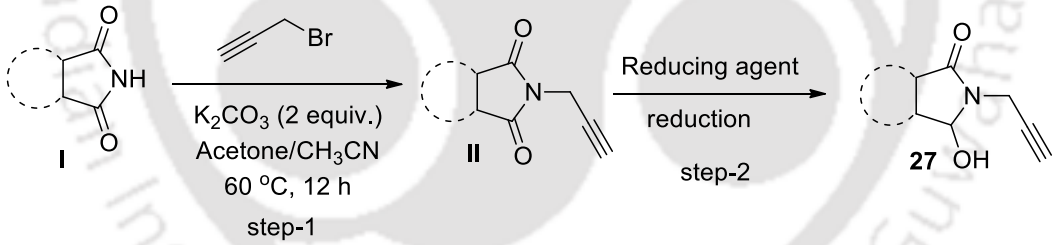
methodology can be further extended for the synthesis of 5*H*-pyrrolo[2,1-*a*]isoindol-5-ones *via* Krapcho dealkoxycarbonylation followed by aromatization in moderate yields.

3.5 Experimental Section

3.5.1 Instrumentation and characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

3.5.2 General procedure for the synthesis of amidoalcohols 27



Scheme 3.5.2.1 Starting material preparation

The starting material amido alcohols **27a**,[18] **27c-27d**,[18] **27g-27h**,[18] **27i**,[14c] **27l**,[19] were prepared in two-steps *i.e*. propargylation and reduction as per the literature procedure and the spectroscopic data are in good agreement with the literature one.

3.5.2.1 Experimental procedure for the synthesis of amido alcohol 27f

To a stirred solution of 1-(prop-2-yn-1-yl)pyrrolidine-2,5-dione (137 mg, 1.0 mmol) in methanol (1.5 mL) and 1,4 dioxane (0.5 mL) at -5 °C was added $NaBH_4$ (92 mg, 2.5 mmol). Then, the

reaction was stirred at same temperature for 10 minutes. The reaction was monitored by TLC. After completion of the starting material, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3x10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **27f**.

3.5.3 Experimental procedure for the synthesis of tetrahydropyrroloisoindolones 29a-29z

To a solution of *N*-alkyl amido alcohol (0.3 mmol, 1.0 equiv.) and $In(OTf)_3$ (0.06 mmol, 0.2 equiv.) in toluene (2 mL) at room temperature was added active methylene compound (0.33 mmol, 1.1 equiv.) dissolved in dry toluene (1.0 mL) under nitrogen atmosphere. Then, the reaction was refluxed on an oil bath for 5-12 h. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. The organic layer was extracted with EtOAc (3x10mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude product was subjected to column chromatography over silica gel to give the corresponding product.

Gram scale preparation of 29d: To a solution of $In(OTf)_3$ (720 mg, 1.28 mmol) in toluene (12 mL) at room temperature was added 3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-one (1.20g, 6.40 mmol) and pentane-2,4-dione (704 mg, 7.04 mmol) under nitrogen atmosphere. Then, the reaction was refluxed for 10 h. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ (10 mL) solution. Then the organic layer was extracted with EtOAc (3x100 mL). The organic layer was further washed with brine solution (10 mL) for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **29d** in 60% yield (1.03g).

3.5.4 Experimental procedure for the synthesis of pyrroloisoindolones 31a-31c

To a solution of dihydropyrroloisoindole (0.3 mmol, 1.0 equiv) in wet DMSO (5 mL) at room temperature was added LiCl (1.5 mmol, 5.0 equiv.). Then, the reaction was stirred for 20 h at 150 ^{o}C. After completion of the reaction, the reaction mixture was washed with brine solution and then extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluents to give the corresponding products.

3.6 References

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15. Compounds **29h** and **29q** are inseparable diastereoisomers. Small amount of pure compounds are obtained by thin layer chromatography (TLC) for nOe experiment.
16. The crystallographic data for compounds **29a** and **31a** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication nos. CCDC 1945841 and CCDC 1945842, respectively.
17. (a) Krapcho, A. P. *Synthesis* **1982**, 805-822. (b) Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett*. **1999**, *40*, 1297-1300.
18. (a) Qi, C.; Gandon, V.; Leboeuf, D. *Adv. Synth. Catal*. **2017**, *359*, 2671-2675. (b) Maury, J.; Force, G.; Darses, B.; Leboeuf, D *Adv. Synth. Catal*. **2018**, *360*, 2752-2756.
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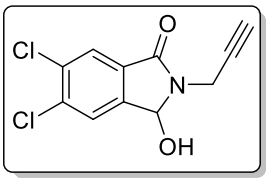
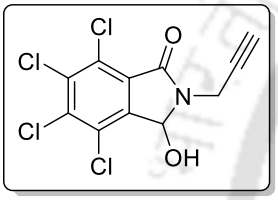
3.7 Characterization data

5,6-Dichloro-3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-one (27b)



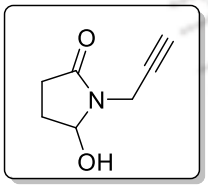
Colourless solid; R_f (hexane/EtOAc, 9:1) 0.45; mp 185-187 ^oC. Yield 204 mg, 80%; ^1H NMR (400 MHz, $CDCl_3$/DMSO-d_6) δ 2.23 (s, 1 H), 4.02 (d, *J* = 17.6 Hz, 1 H), 4.63 (d, *J* = 17.6 Hz, 1 H), 5.92 (d, *J* = 9.2 Hz, 1 H), 5.99 (dd, *J* = 9.2 and 5.0 Hz, 1 H), 7.69 (s, 1 H), 7.78 (s, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$/DMSO-d_6) δ 28.8, 72.2, 78.3, 80.1, 125.3, 126.0, 131.4, 134.4, 136.9, 143.9, 164.6; IR (KBr, neat) 3292, 2918, 2212, 1658, 1616, 1071, 676 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_8Cl_2NO_2$ $(M + H)^+$ 255.9927, found 255.9952.

4,5,6,7-Tetrachloro-3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-one (27e):



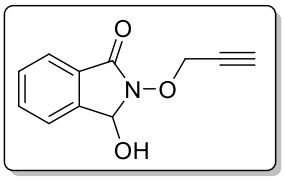
Colourless solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 220-222 ^oC. Yield 162 mg, 50%; ^1H NMR (400 MHz, $CDCl_3$/Acetone-d_6) δ 2.69 (t, *J* = 2.8 Hz, 1 H), 3.96 (dd, *J* = 17.6 and 2.4 Hz, 1 H), 4.50 (dd, *J* = 17.6 and 2.6 Hz, 1 H), 5.92 (d, *J* = 7.6 Hz, 1 H), 5.97 (s, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$/Acetone-d_6) δ 29.2, 73.48, 78.8, 79.7, 129.3, 129.5, 129.6, 135.6, 137.1, 143.6, 162.0; IR (KBr, neat) 3200, 2918, 2090, 1699, 1642, 1428, 1148, 1088, 735 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_6Cl_4NO_2$ $(M + H)^+$ 323.9147, found 323.9152.

5-Hydroxy-1-(prop-2-yn-1-yl)pyrrolidin-2-one (27f):



Colourless oil; R_f (hexane/EtOAc, 3:7) 0.42; Yield 42 mg, 30%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84-1.94 (m, 1 H), 2.19 (t, *J* = 2.4 Hz, 1 H), 2.22-2.35 (m, 2 H), 2.48-2.54 (m, 1 H), 3.83 (dd, *J* = 17.4 and 1.8 Hz, 1 H), 3.96 (brs, 1 H), 4.32 (dd, *J* = 17.4 and 2.4 Hz, 1 H), 5.37 (d, *J* = 4.8 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 28.0, 29.1, 29.4, 72.4, 78.1, 82.5, 174.6; IR (KBr, neat) 3287, 2927, 2121, 1677, 1458, 1175, 1068, 666 cm^{-1}; HRMS (ESI) calcd. for $C_7H_{10}NO_2$ $(M + H)^+$ 140.0706, found 140.0731.

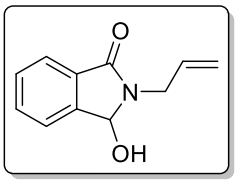
3-Hydroxy-2-(prop-2-yn-1-yloxy)isoindolin-1-one (27j):



Colourless solid; R_f (hexane/EtOAc, 2:3) 0.50; mp 140-142 ^oC. Yield 92 mg, 46%; ^1H NMR (400 MHz, DMSO-d6) δ 3.61 (t, *J* = 2.4 Hz, 1 H), 4.69 (dd, *J* = 15.0 and 2.4 Hz, 1 H), 4.74 (dd, *J* = 15.0 and 2.4 Hz, 1 H), 5.96 (d, *J* = 6.4 Hz, 1 H), 7.11 (d, *J* = 8.6 Hz, 1 H), 7.52 (dd, *J* = 7.2 and

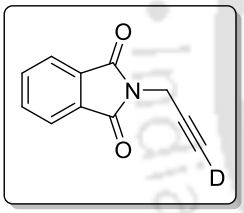
2.4 Hz, 2 H), 7.63 (dd, *J* = 7.2 and 1.0 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d6) δ 64.0, 78.7, 79.9, 82.0, 123.1, 124.2, 129.1, 130.2, 133.5, 142.6, 164.0; IR (KBr, neat) 3149, 2927, 2115, 1708, 1616, 1403, 1175, 1064, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{10}NO_3$ $(M + H)^+$ 204.0655, found 202.0644.

2-Allyl-3-hydroxyisoindolin-1-one (27k):



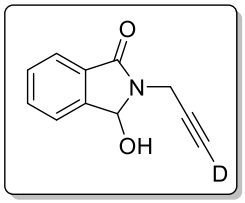
Colourless solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 138-140 °C. Yield 103 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (dd, *J* = 15.4 and 7.2 Hz, 1 H), 4.05 (dt, *J* = 12.5 and 3.0 Hz, 1 H), 4.32 (d, *J* = 11.2 Hz, 1 H), 5.14-5.29 (m, 2 H), 5.68-5.96 (m, 2 H), 7.40-7.44 (m, 1 H), 7.52-7.61 (m, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 41.5, 81.4, 118.1, 123.4, 123.7, 129.9, 131.4, 132.5, 132.6, 144.2, 167.6; IR (KBr, neat) 3224, 2923, 2112, 1674, 1468, 1175, 1056, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}NO_2$ $(M + H)^+$ 190.0863, found 190.0853.

Deuterated 2-(Prop-2-yn-1-yl)isoindoline-1,3-dione (27m):



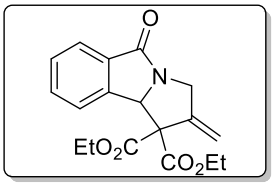
Colourless solid; R_f (hexane/EtOAc, 4:1) 0.60; mp 138-140 °C. Yield 160 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (t, *J* = 2.4 Hz, 0.35 H), 4.46 (d, *J* = 1.8 Hz, 2 H), 7.73-7.78 (m, 2 H), 7.86-7.90 (m, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 27.2, 71.7, 77.5, 123.8, 132.2, 134.5, 134.6, 167.2; IR (KBr, neat) 3136, 2964, 2130, 1688, 1397, 1050, 717 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_7DNO_2$ $(M + H)^+$ 187.0612, found 187.0603.

Deuterated 3-hydroxy-2-(prop-2-yn-1-yl)isoindolin-1-one (27d-D):



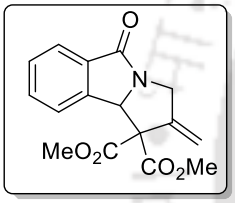
Colourless solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 150-152 °C. Yield 130 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (t, *J* = 2.4 Hz, 0.54 H), 3.31 (d, *J* = 11.2 Hz, 1 H), 3.96 (d, *J* = 17.6 Hz, 1 H), 4.43 (d, *J* = 17.6 Hz, 1 H), 5.97 (d, *J* = 11.0 Hz, 1 H), 7.50 (dt, *J* = 7.2 and 1.2 Hz, 1 H), 7.59-7.66 (m, 2 H), 7.70 (d, *J* = 7.2 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 28.9, 72.4, 77.6, 78.3, 123.7, 123.8, 130.3, 131.3, 132.9, 143.9, 166.8; IR (KBr, neat) 3264, 2949, 2121, 1686, 1401, 1138, 1046, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_9DNO_2$ $(M + H)^+$ 189.0769, found 189.0762.

Diethyl 2-methylene-5-oxo-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-a]isoindole-1,1-dicarboxylate (29a):



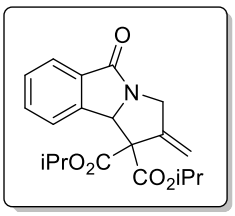
White solid; R_f (hexane/EtOAc, 7:3) 0.59; mp 110-112 ^oC. Yield 68 mg, 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (t, *J* = 7.0 Hz, 3 H), 1.35 (t, *J* = 7.0 Hz, 3 H), 3.44-3.52 (m, 2 H), 4.00 (d, *J* = 15.4 Hz, 1 H), 4.35-4.40 (m, 2 H), 4.67 (d, *J* = 18.0 Hz, 1 H), 5.30 (s, 1 H), 5.46 (s, 1 H), 5.70 (s, 1 H), 7.40-7.49 (m, 2 H), 7.57 (d, *J* = 7.4 Hz, 1 H), 7.72 (d, *J* = 7.4 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 13.3, 14.3, 48.0, 62.1, 62.6, 64.8, 68.4, 113.1, 123.8, 124.9, 129.5, 131.9, 134.5, 142.0, 145.8, 166.8, 167.6, 170.9; IR (KBr, neat) 2983, 2930, 2854, 1715, 1705, 1650, 1461, 1098, 1011, 730 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{20}NO_5$ $(M + H)^+$ 330.1336, found 330.1365.

Dimethyl 2-methylene-5-oxo-2,3-dihydro-1*H*-pyrrolo[2,1-a]isoindole-1,1(5*H*,9*bH*)-dicarboxylate (29b):



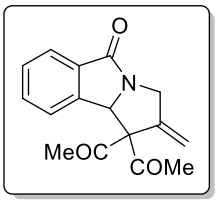
Yellow solid; R_f (hexane/EtOAc, 7:3) 0.52; mp 135-137 ^oC. Yield 58 mg, 65%;^1H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 3 H), 3.92 (s, 3 H), 4.02 (d, *J* = 15.6 Hz, 1 H), 4.68 (d, *J* = 15.6 Hz, 1 H), 5.32 (s, 1 H), 5.49 (s, 1 H), 5.67 (t, *J* = 2.0 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.55 (d, *J* = 7.4 Hz, 1 H), 7.74 (d, J = 7.4 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 47.9, 52.5, 53.4, 64.9, 68.3, 113.2, 123.7, 124.7, 129.5, 131.9, 134.0, 141.7, 145.4, 167.1, 168.0, 171.0; IR (KBr, neat) 2954, 2291, 2251, 1725, 1691, 1645, 1438, 1070, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{16}NO_5$ $(M + H)^+$ 302.1023, found 302.1024.

Diisopropyl 2-methylene-5-oxo-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1(*5H*,9*bH*)-dicarboxylate (29c):



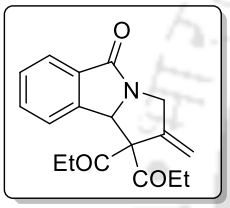
Colourless oil; R_f (hexane/EtOAc, 7:3) 0.60; yield 35 mg, 35%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.67 (d, *J* = 6.2 Hz, 3 H), 0.74 (d, *J* = 6.2 Hz, 3 H), 1.39 (d, *J* = 6.2 Hz, 3 H), 1.42 (d, *J* = 6.2 Hz, 3 H), 4.08 (d, *J* = 15.4 Hz, 1 H), 4.43-4.49 (m, 1 H), 4.72 (d, *J* = 15.4 Hz, 1 H), 5.27-5.36 (m, 1 H), 5.36 (s, 1 H), 5.49 (s, 1 H), 5.76 (t, *J* = 2.2 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ20.8, 21.0, 21.7, 22.0, 48.0, 64.6, 68.3, 70.2, 70.5, 112.8, 123.9, 125.0, 129.4, 131.9, 134.8, 142.1, 146.1, 166.3, 167.1, 170.8; IR (KBr, neat) 2926, 2853, 1719, 1658, 1376, 1060, 748 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_5$ $(M + H)^+$ 358.1649, found 358.1668.

1,1'-(2-Methylene-5-oxo-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29d):



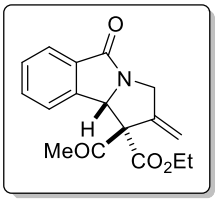
Yellow gum; R_f (hexane/EtOAc, 7:3) 0.45; yield 52 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3 H), 2.43 (s, 3 H), 4.11 (d, *J* = 15.9 Hz, 1 H), 4.83 (d, *J* = 15.9 Hz, 1 H), 5.46 (s, 1 H), 5.54 (s, 1 H), 5.80 (s, 1 H), 7.32 (d, *J* = 7.0 Hz, 1 H), 7.48-7.57 (m, 2 H), 7.81 (d, *J* = 7.0 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 28.5, 28.7, 48.0, 66.8, 77.6, 114.1, 124.3, 124.6, 129.5, 132.6, 133.8, 142.3, 147.3, 170.1, 202.1, 203.8; IR (KBr, neat) 2925, 2850, 1782, 1698, 1629, 1395, 1078, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{16}NO_3$ $(M + H)^+$ 270.1125, found 270.1128.

1,1'-(2-Methylene-5-oxo-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)bis(propan-1-one) (29e):



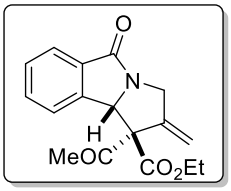
Yellow gum; R_f (hexane/EtOAc, 7:3) 0.50; yield 53 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33 (t, *J* = 7.2 Hz, 3 H), 1.17-1.28 (m, 4 H), 2.17-2.23 (m, 1 H), 2.65-2.76 (m, 2 H), 4.10 (dt, *J* = 15.8 and 2.0 Hz, 1 H), 4.83 (d, *J* = 15.8 Hz, 1 H), 5.43 (s, 1 H), 5.49 (d, *J* = 1.6 Hz, 1 H), 5.84 (s, 1 H), 7.32 (d, *J* = 7.0 Hz, 1 H), 7.47-7.55 (m, 2 H),7.80 (d, *J* = 7.0 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 7.3, 8.9, 34.6, 35.0, 48.2, 67.0, 77.7, 113.8, 124.2, 125.0, 129.4, 132.5, 133.8, 142.4, 147.3, 170.3, 205.4, 207.2; IR (KBr, neat) 2924, 2853, 1735, 1684, 1642, 1465, 1059, 748 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}NO_3$ $(M + Na)^+$ 320.1257, found 320.1276.

(1*S,9*bS**)-Ethyl 1-acetyl-2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (29f):**



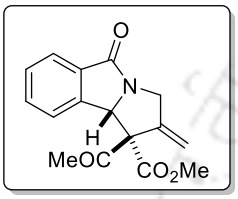
Yellow oil; R_f (hexane/EtOAc, 7:3) 0.50; yield 71 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (t, *J* = 7.2 Hz, 3 H), 1.56 (s, 3 H), 3.49-3.58 (m, 1 H), 4.00 (d, *J* = 16.0 Hz, 1 H), 4.36-4.45 (m, 1 H), 4.69-4.76 (m, 1 H), 5.35 (s, 1 H), 5.38 (s, 1 H), 5.64 (s, 1 H), 7.36-7.58 (m, 3 H), 7.75-7.79 (m, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 13.4, 28.6, 47.8, 62.1, 67.5, 70.8, 112.1, 123.8, 124.6, 129.4, 132.0, 134.3, 141.6, 146.4, 167.8, 170.0, 200.4; IR (KBr, neat) 2987, 1707, 1650, 1610, 1389, 1075, 748 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{17}NNaO_4$ $(M + Na)^+$ 322.1050, found 322.1080.

(1*R,9*bS**)-Ethyl 1-acetyl-2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (29f′):**



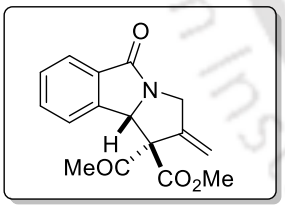
Yellow oil; R_f (hexane/EtOAc, 7:3) 0.50; yield 71 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3 H), 2.49 (s, 3 H), 3.49-3.58 (m, 1 H), 4.11 (d, *J* = 16.0 Hz, 1 H), 4.36-4.45 (m, 1 H), 4.69-4.76 (m, 1 H), 5.35 (s, 1 H), 5.52 (s, 1 H), 5.64 (s, 1 H), 7.36-7.58 (m, 3 H), 7.75-7.79 (m, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.3, 29.8, 48.5, 62.7, 68.0, 71.0, 113.8, 124.3, 124.7, 129.6, 132.3, 134.4, 142.2, 147.6, 168.9, 171.1, 200.9; IR (KBr, neat) 2987, 1707, 1650, 1610, 1389, 1075, 748 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{17}NNaO_4$ $(M + Na)^+$ 322.1050, found 322.1080.

(1*S,9*bS**)-Methyl 1-acetyl-2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (29g):**



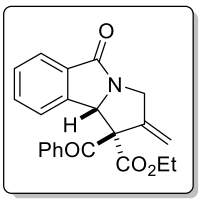
Yellow oil; R_f (hexane/EtOAc, 7:3) 0.50; yield 71 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3 H), 3.10 (s, 3 H), 4.00 (d, *J* = 16.0 Hz, 1 H), 4.73-4.79 (m, 1 H), 5.40 (s, 1 H), 5.43 (s, 1 H), 5.67 (s, 1 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 7.49-7.54 (m, 1 H), 7.55-7.61 (m, 1 H), 7.79 (t, *J* = 7.5 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 28.4, 47.6, 52.3, 67.3, 70.7, 112.2, 123.6, 124.4, 129.2, 131.8, 133.7, 141.3, 146.0, 168.0, 169.8, 200.2; IR (KBr, neat) 2927, 1736, 1708, 1615, 1387, 1076, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{16}NO_4$ $(M + H)^+$ 286.1074, found 286.1100.

(1*R,9*bS**)-Methyl 1-acetyl-2-methylene-5-oxo-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (29g′):**



Yellow oil; R_f (hexane/EtOAc, 7:3) 0.50; yield 71 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3 H), 3.98 (s, 3 H), 4.14 (d, *J* = 16.0 Hz, 1 H), 4.73-4.79 (m, 1 H), 5.40 (s, 1 H), 5.56 (s, 1 H), 5.71 (s, 1 H), 7.44-7.49 (m, 1 H), 7.49-7.54 (m, 1 H), 7.55-7.61 (m, 1 H), 7.79 (t, *J* = 7.5 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 29.5, 48.2, 53.3, 67.8, 70.8, 113.8, 124.1, 124.5, 129.5, 132.2, 134.2, 142.0, 147.0, 169.2, 171.0, 200.5; IR (KBr, neat) 2927, 1736, 1708, 1615, 1387, 1076, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{16}NO_4$ $(M + H)^+$ 286.1074, found 286.1100.

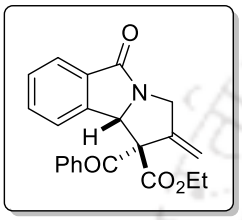
(1*R,9*bS**)-Ethyl 1-benzoyl-2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (29h):**



White solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 190-192 °C. Yield 81 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (t, *J* = 7.2 Hz, 3 H), 3.43-3.53 (m, 2 H),

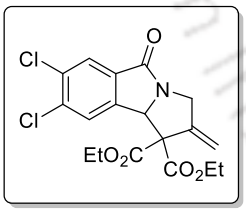
4.12 (d, *J* = 14.7 Hz, 1 H), 4.90 (d, *J* = 14.7 Hz, 1 H), 5.10 (s, 1 H), 5.41 (s, 1 H), 5.88 (s, 1 H), 7.45-7.53 (m, 4 H), 7.58-7.62 (m, 2 H), 7.82 (d, *J* = 7.2 Hz, 1 H), 7.94 (d, *J* = 7.2 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 13.2, 49.2, 62.0, 68.9, 69.3, 114.8, 123.9, 125.8, 128.8, 129.4, 130.1, 131.8, 134.0, 134.2, 136.1, 142.2, 147.7, 167.8, 171.0, 192.7; IR (KBr, neat) 2987, 1730, 1704, 1674, 1383, 1094, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{20}NO_4$ $(M + H)^+$ 362.1387, found 362.1414.

(1*S,9*bS**)-Ethyl 1-benzoyl-2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (29h′):**



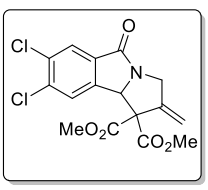
White solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 190-192 °C. Yield 81 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (t, *J* = 7.2 Hz, 3 H), 4.12 (d, *J* = 14.7 Hz, 1 H), 4.33-4.44 (m, 2 H), 4.90 (d, *J* = 14.7 Hz, 1 H), 5.50 (s, 1 H), 5.66 (s, 1 H), 5.76 (s, 1 H), 7.45-7.53 (m, 4 H), 7.58-7.62 (m, 2 H), 7.82 (d, *J* = 7.2 Hz, 1 H), 7.94 (d, *J* = 7.2 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 13.2, 49.2, 62.0, 68.9, 69.3, 114.8, 123.9, 125.8, 128.8, 129.4, 130.1, 131.8, 134.0, 134.2, 136.1, 142.2, 147.7, 167.8, 171.0, 192.7; IR (KBr, neat) 2987, 1730, 1704, 1674, 1383, 1094, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{20}NO_4$ $(M + H)^+$ 362.1387, found 362.1414.

Diethyl 7,8-dichloro-2-methylene-5-oxo-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1(5*H*,9*bH*)-dicarboxylate (29i):



Offwhite solid; R_f (hexane/EtOAc, 7:3) 0.62; mp 110-112 °C. Yield 53 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 3.63-3.72 (m, 2 H), 4.06 (d, *J* = 15.6 Hz, 1 H), 4.42-4.47 (m, 2 H), 4.69 (d, *J* = 15.6 Hz, 1 H), 5.38 (s, 1 H), 5.44 (s, 1 H), 5.78 (s, 1 H), 7.74 (s, 1 H), 7.86 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 13.6, 14.4, 48.2, 62.5, 63.0, 64.7, 67.7, 113.8, 125.7, 127.1, 134.4, 134.5, 136.6, 141.1, 144.8, 166.5, 167.4, 168.7; IR (KBr, neat) 2984, 2878, 1715, 1642, 1065, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}Cl_2NO_5$ $(M + H)^+$ 398.0557, found 398.0574.

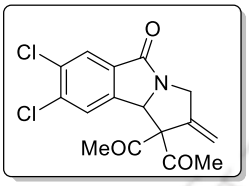
Dimethyl 7,8-dichloro-2-methylene-5-oxo-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1(5*H*,9*bH*)-dicarboxylate (29j):



White solid; R_f (hexane/EtOAc, 4:1) 0.45; mp 147-149 °C. Yield 75 mg, 68%;^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (s, 3 H), 3.99 (s, 3 H), 4.06 (d, *J* =

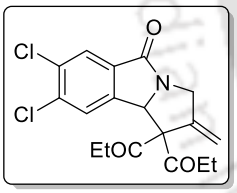
15.6 Hz, 1 H), 4.72 (d, *J* = 15.6 Hz, 1 H), 5.40 (s, 1 H), 5.46 (s, 1 H), 5.75 (s, 1 H), 7.72 (s, 1 H), 7.87 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 48.1, 53.0, 53.8, 64.8, 67.8, 114.0, 125.7, 126.9, 134.1, 134.6, 136.7, 140.9, 144.6, 166.9, 167.8, 168.6; IR (KBr, neat) 2922, 2856, 1750, 1656, 1103, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{14}Cl_2NO_5$ $(M + H)^+$ 370.0244, found 370.0259.

1,1'-(7,8-Dichloro-2-methylene-5-oxo-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29k):



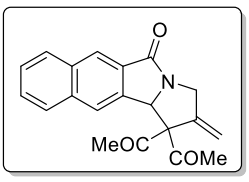
Yellow gum; R_f (hexane/EtOAc, 3:2) 0.50; yield 70 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 3 H), 2.40 (s, 3 H), 4.09 (d, *J* = 16.0 Hz, 1 H), 4.78 (d, *J* = 16.0 Hz, 1 H), 5.51 (t, *J* = 2.0 Hz, 1 H), 5.56 (t, *J* = 2.0 Hz, 1 H), 5.67 (s, 1 H), 7.41 (s, 1 H), 7.84 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 28.7, 28.9, 48.1, 66.3, 77.5, 114.6, 126.1, 126.8, 133.6, 134.6, 137.4, 141.4, 146.6, 167.8, 201.9, 203.3; IR (KBr, neat) 2991, 1762, 1701, 1645, 1055, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{14}Cl_2NO_3$ $(M + H)^+$ 338.0345, found 338.0353.

1,1'-(7,8-Dichloro-2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)bis(propan-1-one) (29l):



Colourless solid; R_f (hexane/EtOAc, 4:1) 0.45; mp 149-151 °C. Yield 87 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.49 (t, *J* = 7.2 Hz, 3 H), 1.18-1.30 (m, 4 H), 2.26-2.33 (m, 1 H), 2.59-2.74 (m, 2 H), 4.08 (d, *J* = 16.0 Hz, 1 H), 4.78 (d, *J* = 16.0 Hz, 1 H), 5.45 (d, *J* = 1.6 Hz, 1 H), 5.50 (d, *J* = 1.6 Hz, 1 H), 5.70 (s, 1 H), 7.43 (s, 1 H), 7.84 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 7.6, 8.8, 34.7, 34.9, 48.2, 66.6, 77.6, 114.3, 125.9, 127.0, 133.6, 134.4, 137.2, 141.6, 146.6, 167.7, 205.3, 206.5; IR (KBr, neat) 2984, 1760, 1701, 1649, 1397, 1056, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}Cl_2NO_3$ $(M + H)^+$ 366.0658, found 366.0678.

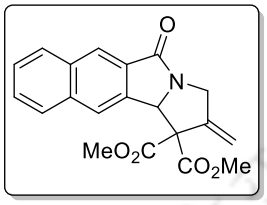
1,1'-(2-Methylene-5-oxo-2,3,5,11*b*-tetrahydro-1*H*-benzo[*f*]pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29m):



Yellow oil; R_f (hexane/EtOAc, 3:2) 0.42; yield 99 mg, 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 2.47 (s, 3 H), 4.15 (d, *J* = 16.0 Hz, 1 H), 4.86 (d, *J* = 16.0 Hz, 1 H), 5.47 (d, *J* = 1.6 Hz, 1 H), 5.55 (d, *J* = 1.6 Hz, 1 H), 5.91 (s, 1 H), 7.55-7.59 (m, 2 H), 7.76 (s, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H),

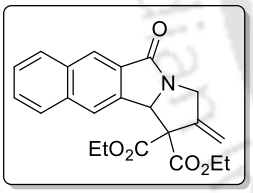
7.97 (d, *J* = 8.0 Hz, 1 H), 8.30 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 28.4, 28.9, 48.3, 66.6, 78.0, 114.2, 124.0, 124.9, 127.2, 128.4, 128.8, 129.8, 131.4, 133.5, 135.5, 136.6, 147.0, 169.7; 202.6, 203.8; IR (KBr, neat) 2992, 1761, 1667, 1642, 1378, 1056, 751 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{18}NO_3$ $(M + H)^+$ 320.1281, found 320.1276.

Dimethyl 2-methylene-5-oxo-2,3-dihydro-1*H*-benzo[*f*]pyrrolo[2,1-*a*]isoindole-1,1(5*H*,11*bH*)-dicarboxylate (29n):



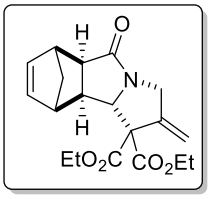
Yellow gum; R_f (hexane/EtOAc, 19:1) 0.53; yield 63 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (s, 3 H), 4.03 (s, 3 H), 4.13 (d, *J* = 15.6 Hz, 1 H), 4.82 (d, *J* = 15.6 Hz, 1 H), 5.40 (s, 1 H), 5.69 (s, 1 H), 5.77 (s, 1 H), 7.56-7.60(m, 2 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 8.00 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 8.33 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 48.2, 52.7, 53.6, 65.3, 68.3, 113.5, 124.1, 124.2, 127.1, 128.1, 128.8, 129.8, 131.8, 133.6, 135.3, 136.3, 145.2, 167.4, 168.4, 170.8; IR (KBr, neat) 2993, 1737, 1701, 1642, 1380, 1062, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{18}NO_5$ $(M + H)^+$ 352.1179, found 352.1206.

Diethyl 2-methylene-5-oxo-2,3-dihydro-1*H*-benzo[*f*]pyrrolo[2,1-*a*]isoindole-1,1(5*H*,11*bH*)-dicarboxylate (29o):



Colourless gum; R_f (hexane/EtOAc, 4:1) 0.50; yield 50 mg, 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (t, *J* = 7.2 Hz, 3 H), 1.46 (t, *J* = 7.2 Hz, 3 H), 3.36-3.41 (m, 1 H), 3.47-3.52 (m, 1 H), 4.13 (d, *J* = 15.6 Hz, 1 H), 4.46-4.53 (m, 2 H), 4.82 (d, *J* = 15.6 Hz, 1 H), 5.39 (s, 1 H), 5.66 (s, 1 H), 5.80 (s, 1 H), 7.56-7.59 (m, 2 H), 7.92 (d, *J* = 7.8 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 8.10 (s, 1 H), 8.30 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 13.3, 14.4, 48.3, 62.1, 62.8, 65.1, 68.3, 113.3, 124.1, 124.3, 127.0, 128.1, 128.8, 129.8, 132.2, 133.6, 135.3, 136.6, 145.5, 167.0, 167.9, 170.7; IR (KBr, neat) 2959, 2926, 1740, 1656, 1637, 1377, 1062, 649 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}NO_5$ $(M + H)^+$ 380.1492, found 380.1499.

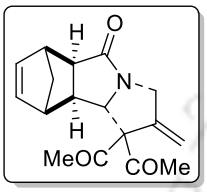
(5*aR,6*S**,9*R**,9*aS**,9*bS**)-Diethyl-2-methylene-5-oxo-2,3,5*a*,6,9,9*a*-hexahydro-1*H*-6,9-methano-pyrrolo[2,1-*a*]isoindole-1,1(5*H*,9*bH*)-dicarboxylate (29p):**



Colourless oil; R_f (hexane/EtOAc, 3:2) 0.50; yield 59 mg, 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.35 (d, *J* = 8.4 Hz, 1 H), 1.55 (d, *J* = 8.4 Hz, 1 H), 2.81 (dd, *J* = 4.4 and 2.0 Hz,, 1 H),

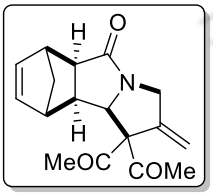
2.94 (dd, *J* = 9.2 and 4.4 Hz, 1 H), 3.07 (s, 1 H), 3.16 (s, 1 H), 3.56 (d, *J* = 15.6 Hz, 1 H), 3.63 (s, 1 H), 4.05-4.10 (m, 2 H), 4.23-4.27 (m, 3 H), 5.16 (d, *J* = 1.2 Hz, 1 H), 5.60 (d, *J* = 1.2 Hz, 1 H), 6.17 (d, *J* = 1.2 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 13.8, 14.1, 41.4, 45.1, 45.9, 47.5, 51.5, 53.0, 62.0, 62.3, 64.6, 68.9, 112.6, 134.6, 136.7, 143.5, 167.5, 168.4, 176.8; IR (KBr, neat) 2985, 1771, 1757, 1654, 1371, 1063, 720 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_5$ $(M + H)^+$ 346.1649, found 346.1655.

1,1'-((5*aR,6*S**,9*R**,9*aS**,9*bS**)-(2-Methylene-5-oxo-2,3,5,5*a*,6,9,9*a*,9*b*-octahydro-1*H*-6,9-methano-pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29q)**:



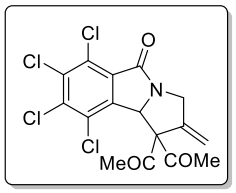
Colourless oil; R_f (hexane/EtOAc, 1:1) 0.40; yield 47 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 8.2 Hz, 1 H), 1.61 (dd, *J* = 8.2 and 1.6 Hz, 1 H), 2.06 (s, 3 H), 2.27 (s, 3 H), 2.77-2.80 (m, 1 H), 3.00-3.06 (m, 1 H), 3.15-3.18 (m, 1 H), 3.18-3.25 (m, 1 H), 3.63 (dt, *J* = 16.2 and 1.2 Hz, 1 H), 3.69 (d, *J* = 4.0 Hz, 1 H), 4.31 (dd, *J* = 16.2 and 1.8 Hz, 1 H), 5.38 (dt, *J* = 6.8 and 0.8 Hz, 2 H), 6.22 (dd, *J* = 6.2 and 1.6 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 28.5, 29.0, 41.1, 45.2, 45.9, 47.2, 51.7, 53.8, 68.5, 77.6, 114.1, 134.6, 137.1, 144.8, 176.1, 202.8, 204.1; IR (KBr, neat) 2925, 2654, 1715, 1693, 1681, 1427, 1131, 715 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{20}NO_3$ $(M + H)^+$ 286.1438, found 286.1442.

1,1'-((5*aR,6*S**,9*R**,9*aS**)-2-Methylene-5-oxo-2,3,5,5*a*,6,9,9*a*,9*b*-octahydro-1*H*-6,9-methano-pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29q′):**



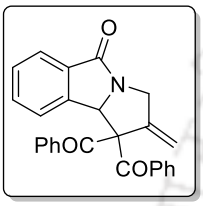
Colourless oil; R_f (hexane/EtOAc, 1:1) 0.40; yield 47 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 8.2 Hz, 1 H), 1.61 (d, *J* = 8.2 Hz, 1 H), 2.05 (s, 3 H), 2.33 (s, 3 H), 2.95-3.04 (m, 1 H), 3.01-3.06 (m, 1 H), 3.22-3.33 (m, 2 H), 4.01-4.09 (m, 1 H), 4.10-4.14 (m, 1 H), 4.36-4.41 (m, 1 H), 5.17-19 (m, 2 H), 6.31 (dd, *J* = 5.8 and 2.8 Hz, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 29.8, 30.7, 43.0, 46.1, 46.2, 52.2, 52.4, 56.9, 70.5, 77.1, 114.1, 135.9, 136.1, 150.7, 176.2, 202.9, 204.1; IR (KBr, neat) 2925, 2654, 1715, 1693, 1681, 1427, 1131, 715 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{20}NO_3$ $(M + H)^+$ 286.1438, found 286.1442.

1,1'-(6,7,8,9-Tetrachloro-2-methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29r):



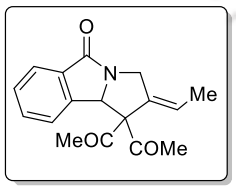
Yellow solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 150-152 ºC. Yield 110 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3 H), 2.50 (s, 3 H), 4.10 (d, *J* = 16.2 Hz, 1 H), 4.70 (d, *J* = 16.2 Hz, 1 H), 5.32 (d, *J* = 1.8 Hz, 1 H), 5.54 (d, *J* = 1.8 Hz, 1 H), 5.64 (s, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 28.2, 29.2, 47.3, 66.3, 76.7, 114.8, 128.5, 130.1, 130.3, 135.4, 137.1, 141.8, 147.5, 165.6, 201.8, 202.3; IR (KBr, neat) 2928, 1705, 1647, 1392, 1046, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{12}Cl_4NO_3$ $(M + H)^+$ 407.9537, found 407.9536.

(2-Methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)bis (phenylmethanone) (29u):



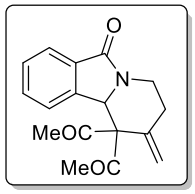
Orange gum; R_f (hexane/EtOAc, 7:3) 0.50; Yield 47 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (d, *J* = 15.0 Hz, 1 H), 4.85 (d, *J* = 15.0 Hz, 1 H), 5.15 (d, 1 H), 5.48 (d, *J* = 1.4 Hz, 1 H), 6.06 (s, 1 H), 7.06 (t, *J* = 7.6 Hz, 2 H), 7.19-7.28 (m, 5 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.60 (d, *J* = 6.8 Hz, 1 H), 7.99 (d, *J* = 7.6 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 49.1, 69.2, 75.9, 115.5, 123.6, 126.2, 128.2, 128.9, 129.1, 130.7, 131.5, 132.9, 134.2, 134.3, 136.6, 137.6, 141.2, 149.4, 169.8, 194.7, 196.1; IR (KBr, neat) 2927, 1704, 1653, 1397, 1181, 1046, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{20}NO_3$ $(M + H)^+$ 394.1438, found 394.1425.

(*Z*)-1,1'-(2-Ethylidene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29w):



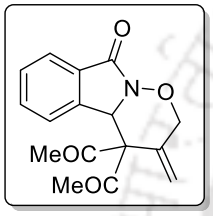
Colourless gum; R_f (hexane/EtOAc, 3:2) 0.40; Yield 25 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.82 (d, *J* = 6.8 Hz, 3 H), 2.42 (s, 3 H), 4.04 (d, *J* = 16.0 Hz, 1 H), 4.86 (d, *J* = 16.0 Hz, 1 H), 5.79 (s, 1 H), 5.82-5.88 (m, 1 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 7.32-7.56 (m, 2 H), 7.81 (d, *J* = 7.2 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.7, 28.4, 29.0, 45.3, 66.7, 76.9, 124.2, 124.6, 124.8, 129.3, 132.5, 133.8, 139.4, 142.4, 170.1, 202.9, 204.5; IR (KBr, neat) 2857, 1710, 1694, 1403, 1142, 1097, 705 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{18}NO_3$ $(M + H)^+$ 284.1281, found 284.1289.

1,1'-(2-Methylene-6-oxo-1,2,3,4,6,10*b*-hexahydropyrido[2,1-*a*]isoindole-1,1-diyl)diethanone (29y):



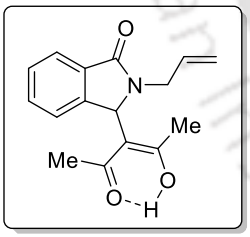
Colourless gum; R_f (hexane/EtOAc, 1:1) 0.45; Yield 54 mg, 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3 H), 2.39 (s, 3 H), 2.63-2.69 (m, 2 H), 3.69-3.75 (m, 1 H), 3.97-4.05 (m, 1 H), 5.10 (s, 1 H), 5.53 (s, 1 H), 5.61 (s, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.45-7.52 (m, 2 H), 7.83 (dd, *J* = 8.0 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 27.9, 28.0, 30.3, 41.0, 57.9, 76.5, 118.7, 123.6, 124.8, 129.0, 132.0, 133.1, 141.5, 142.2, 168.1, 204.7, 205.3; IR (KBr, neat) 2927, 1770, 1690, 1403, 1189, 1025, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{18}NO_3$ $(M + H)^+$ 284.1281, found 284.1299.

1,1'-(3-Methylene-9-oxo-3,4,4*a*,9-tetrahydro-2*H*-[1,2]oxazino[3,2-*a*]isoindole-4,4-diyl)diethanone (29z):

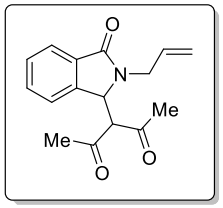


Brown gum; R_f (hexane/EtOAc, 3:7) 0.40; Yield 31 mg, 37%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3 H), 2.48 (s, 3 H), 4.59 (d, *J* = 12.2 Hz, 1 H), 4.81 (d, *J* = 12.2 Hz, 1 H), 5.23 (s, 1 H), 5.32 (s, 1 H), 5.63 (s 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.48-7.57 (m, 2 H), 7.88 (d, *J* = 7.6 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 29.4, 30.2, 60.3, 74.5, 75.6, 119.9, 123.8, 124.5, 129.4, 130.5, 132.4, 138.9, 139.0, 161.8, 201.9, 204.0; IR (KBr, neat) 2925, 1702, 1647, 1398, 1192, 1099, 708 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{16}NO_4$ $(M + H)^+$ 286.1074, found 286.1071.

3-(2-Allyl-3-oxoisoindolin-1-yl)pentane-2,4-dione (30a, keto-enol tautomer, 12:88):



Major (enol form): Colourless gum; R_f (hexane/EtOAc, 3:2) 0.50; Yield 65 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3 H), 2.38 (s, 3 H), 3.57 (dd, *J* = 15.6 and 7.6 Hz, 1 H), 4.67 (dd, *J* = 15.6 and 2.0 Hz, 1 H), 5.17 (d, *J* = 17.2 Hz, 1 H), 5.24 (d, *J* = 10.2 Hz, 1 H), 5.51 (s, 1 H), 5.82-5.92 (m, 1 H), 7.34 (d, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.90 (d, *J* = 7.4 Hz, 1 H), 17.57 (s, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.1, 24.4, 42.6, 58.1, 105.3, 118.2, 122.4 (2C), 124.2, 128.9, 132.5, 133.5, 145.2, 168.0, 190.0, 197.8; IR (KBr, neat) 2917, 1704, 1686, 1401, 1171, 1005, 730 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1281, found 272.1275.

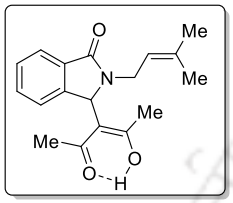


Minor (keto form): Colourless gum; R_f (hexane/EtOAc, 3:2) 0.50; Yield 65 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3 H), 2.12 (s, 3 H), 3.77 (dd, *J* = 15.8 and 7.0 Hz, 1 H), 4.32 (d, *J* = 3.0 Hz, 1 H), 5.20 (d, *J* = 11.8 Hz, 2 H), 5.35 (d, *J* = 2.8 Hz, 1 H), 5.51 (s 1 H), 5.82-5.92 (m, 1 H), 7.44 (d, *J* =

7.4 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.85 (d, *J* = 7.4 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 31.0, 31.4, 43.7, 57.2, 67.3, 118.5, 122.4 (2C), 124.1, 129.2, 132.3, 132.9, 142.8, 168.7, 202.3, 202.6; IR (KBr, neat) 2917, 1704, 1686, 1401, 1171, 1005, 730 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1281, found 272.1275.

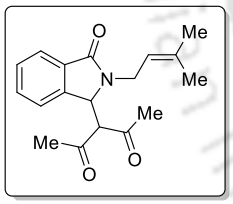
3-(2-(3-Methylbut-2-en-1-yl)-3-oxoisoindolin-1-yl)pentane-2,4-dione (30b, keto-enol tautomer; 17:83):

Major (enol form): Colourless gum; R_f (hexane/EtOAc, 7:3) 0.60; Yield 65 mg, 73%; ^{1}H NMR



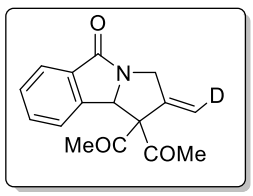
(400 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.67 (s, 3 H), 1.73 (s, 3 H), 2.36 (s, 3 H), 3.66 (dd, *J* = 15.0 and 8.8 Hz, 1 H), 4.56 (dd, *J* = 15.0 and 5.2 Hz, 1 H), 5.18-5.21 (m, 1 H), 5.49 (s, 1 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.47-4.52 (m, 1 H), 7.56 (dt, *J* = 7.4 and 1.0 Hz, 1 H), 7.88 (d, *J* = 7.4 Hz, 1 H), 17.54 (s, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 17.9, 22.8, 24.3, 25.9, 37.9, 58.1, 105.4, 119.9, 122.2 (2C), 123.9, 128.8, 132.2, 137.3, 145.1, 167.8, 189.8, 197.7; IR (KBr, neat) 2976, 1792, 1688, 1464, 1021, 722 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_3$ $(M + H)^+$ 300.1594, found 300.1604.

Minor (keto form): Colourless gum; R_f (hexane/EtOAc, 7:3) 0.60; Yield 65 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.76 (s, 3 H), 1.88 (s, 3 H), 2.17 (s, 3 H), 3.81 (dd, *J* = 15.4



and 7.2 Hz, 1 H), 4.31 (d, *J* = 3.0 Hz, 1 H), 4.59 (dd, *J* = 15.4 Hz, 1 H), 5.18-5.21 (m, 1 H), 5.22 (d, *J* = 1.2 Hz, 1 H), 7.41 (d, *J* = 7.4 Hz, 1 H), 7.47-4.52 (m, 1 H), 7.56 (dt, *J* = 7.4 and 1.0 Hz, 1 H), 7.83 (d, *J* = 7.4 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 18.2, 30.8, 31.4, 38.8, 57.3, 67.0, 119.1, 122.4, 124.0, 124.4, 129.0, 132.0, 132.6, 137.5, 142.7, 168.5, 202.4, 202.7; IR (KBr, neat) 2976, 1792, 1688, 1464, 1021, 722 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{22}NO_3$ $(M + H)^+$ 300.1594, found 300.1604.

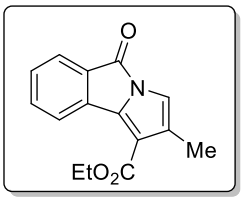
Deuterated 1,1'-(2-Methylene-5-oxo-2,3,5,9*b*-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole-1,1-diyl)diethanone (29d-D):



Yellow gum; R_f (hexane/EtOAc, 7:3) 0.45; yield 120 mg, 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 2.44 (s, 3 H), 4.12 (d, *J* = 15.9 Hz, 1 H), 4.84 (d, *J* = 15.9 Hz, 1 H), 5.45 (s, 1 H), 5.54 (s, 0.63 H), 5.81 (s, 1 H), 7.32 (d, *J* = 7.0 Hz, 1 H), 7.48-7.57 (m, 2 H), 7.81 (d, *J* = 7.0 Hz, 1 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 28.4, 28.7, 47.9, 66.7, 77.6, 114.0, 124.2, 124.5, 129.4,

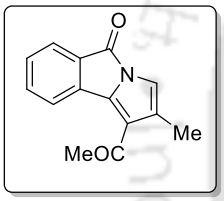
132.5, 133.7, 142.2, 147.1, 170.0, 202.1, 203.8; IR (KBr, neat) 2925, 2850, 1706, 1698, 1399, 1171, 1097, 767 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{15}DNO_3$ $(M + H)^+$ 271.1187, found 271.1171.

Ethyl 2-methyl-5-oxo-5*H*-pyrrolo[2,1-*a*]isoindole-1-carboxylate (31a):



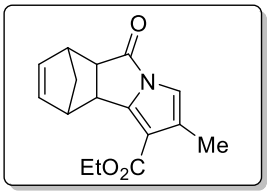
Orange solid; R_f (hexane/EtOAc, 47:3) 0.50; mp 105-107 ^oC. Yield 35 mg, 45%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, *J* = 7.2 Hz, 3 H), 2.21 (d, *J* = 1.2 Hz, 3 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 6.79 (d, *J* = 1.2 Hz, 1 H), 7.27 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.2 Hz, 1 H), 7.65 (d, *J* = 7.4 Hz, 1 H), 8.02 (d, *J* = 7.4 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 13.0, 14.7, 60.7, 114.5, 114.9, 124.0, 125.9, 128.8, 128.9, 131.8, 135.2, 135.7, 140.0, 163.0, 164.4; IR (KBr, neat) 2932, 1745, 1658, 1378, 1094, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{14}NO_3$ $(M + H)^+$ 256.0969, found 256.0998.

1-Acetyl-2-methyl-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (31b):



Yellow solid; R_f (hexane/EtOAc, 47:3) 0.50; mp 110-112 ^oC Yield 33 mg, 48%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (d, *J* = 1.0 Hz, 3 H), 2.52 (s, 3 H), 6.80 (d, *J* = 1.0 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.2 Hz, 1 H), 7.64 (d, *J* = 7.4 Hz, 1 H), 8.14 (d, *J* = 7.4 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1, 31.3, 115.2, 124.3, 124.4, 126.0, 126.4, 129.2, 131.7, 135.6, 135.8, 139.9, 163.3, 195.2; IR (KBr, neat) 2928, 1751, 1655, 1376, 1060, 718 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{12}NO_2$ $(M + H)^+$ 226.0863, found 226.0868.

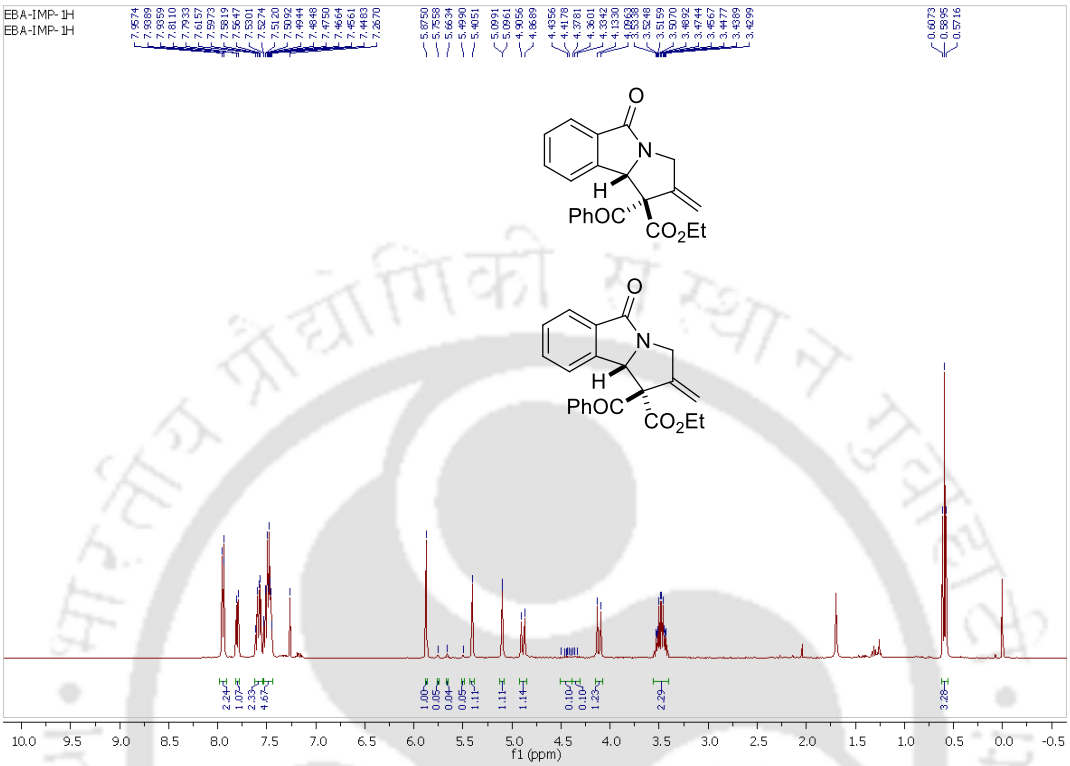
Ethyl 2-methyl-5-oxo-5*a*,6,9,9*a*-tetrahydro-5*H*-6,9-methanopyrrolo[2,1-*a*]isoindole-1-carboxylate (31c):



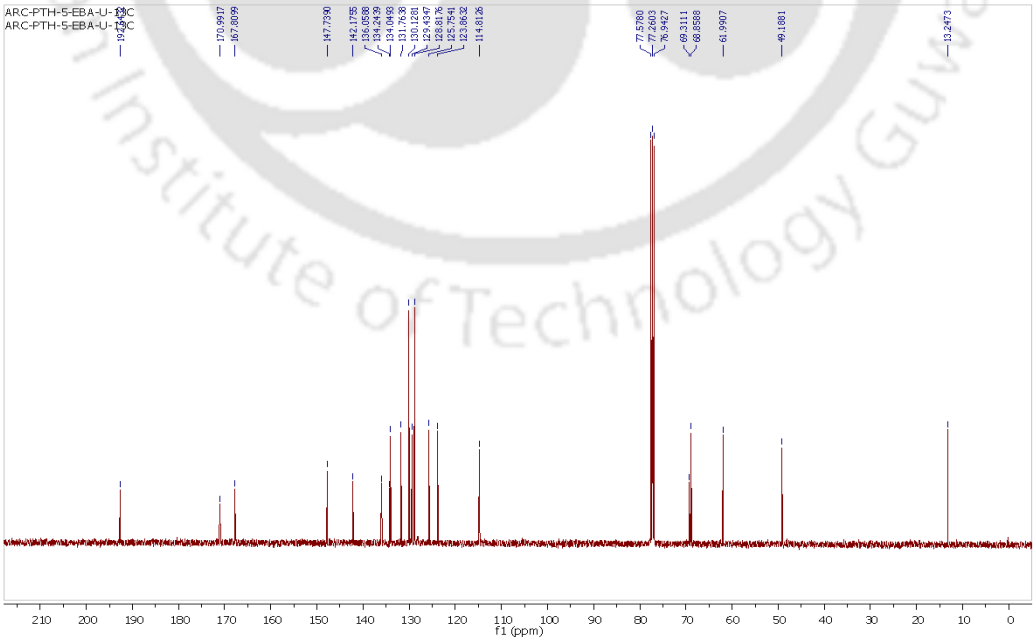
Colourless oil; R_f (hexane/EtOAc, 47:3) 0.50; yield 28 mg, 35%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.2 Hz, 3 H), 1.59 (d, *J* = 8.7 Hz, 1 H), 1.71 (d, *J* = 8.7 Hz, 1 H), 2.15 (s, 3 H), 3.30 (s, 1 H), 3.40 (s, 1 H), 3.45 (dd, *J* = 6.7 and 2.2 Hz, 1 H), 3.80 (dd, *J* = 6.7 and 4.2 Hz, 1 H), 4.21-4.31 (m, 2 H), 5.74 (dd, *J* = 5.6 and 3.0 Hz, 1 H), 5.95 (dd, *J* = 5.6 and 2.8 Hz, 1 H), 6.54 (s, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 12.8, 14.8, 41.1, 45.0, 45.5, 52.2, 52.4, 60.0, 109.6, 111.6, 130.0, 133.5, 135.6, 148.6, 164.7, 172.6; IR (KBr, neat) 2989, 2873, 1710, 1651, 1384, 1183, 1079, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1281, found 272.1296.

3.8 Selected Spectra

^{1}H spectrum of compound **29h/29h′** (Diastereomeric mixture) (400 MHz, $CDCl_3$)



^{13}C{^{1}H } spectrum of compound **29h/29h′** (Diastereomeric mixture) (100 MHz, $CDCl_3$)



400 MHz, $CDCl_3$

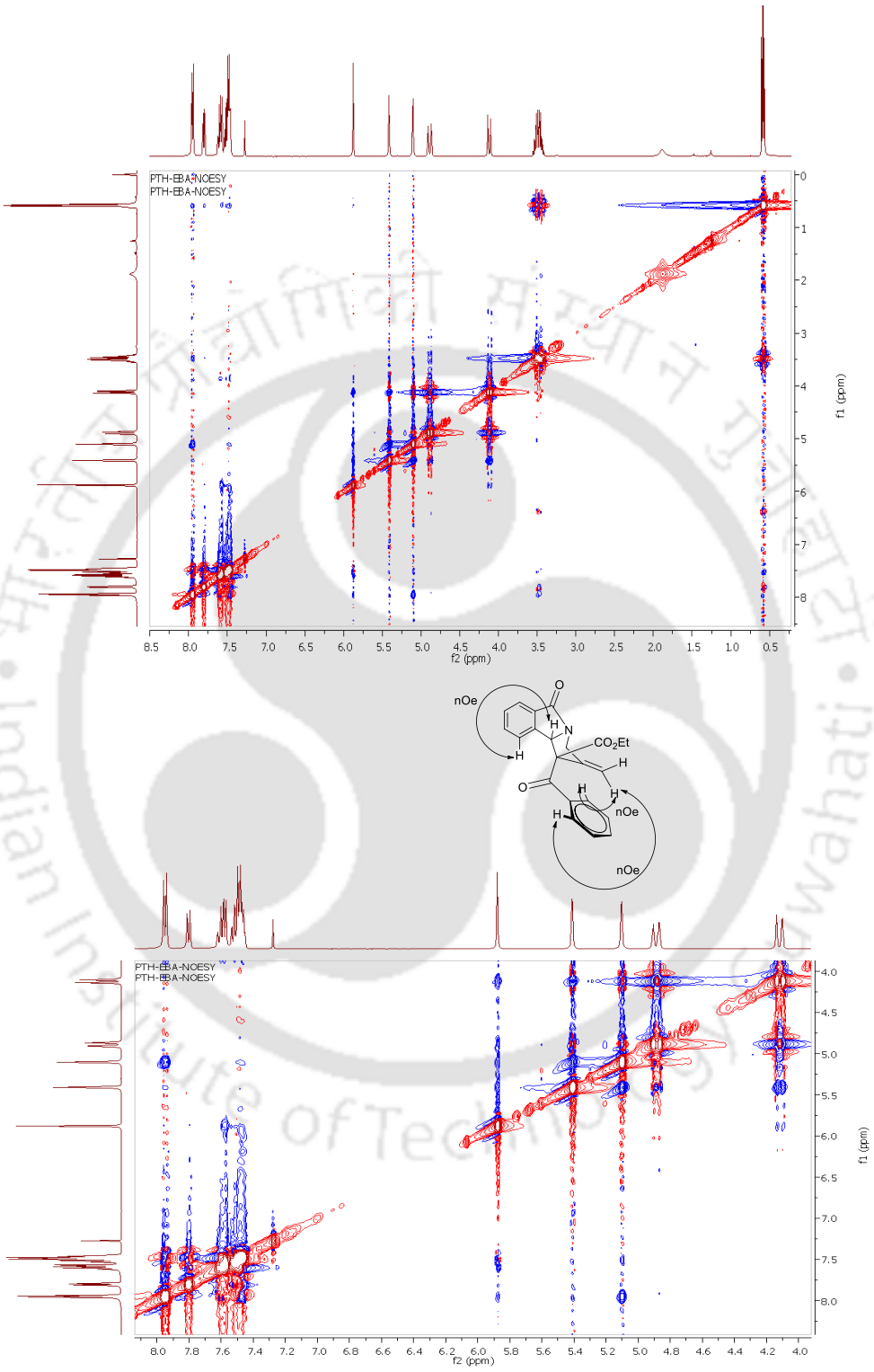
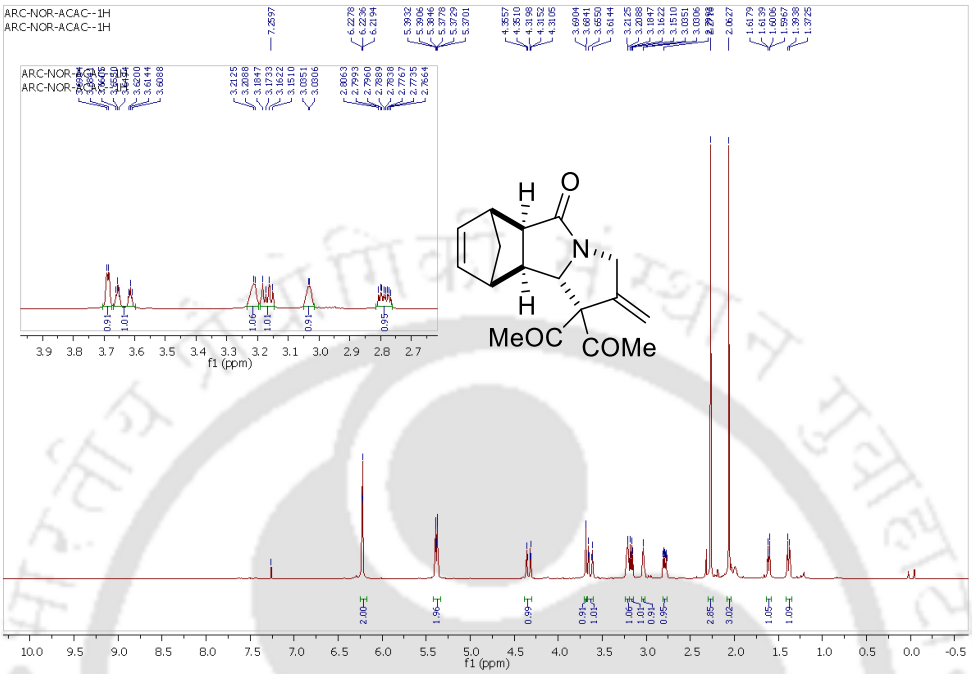
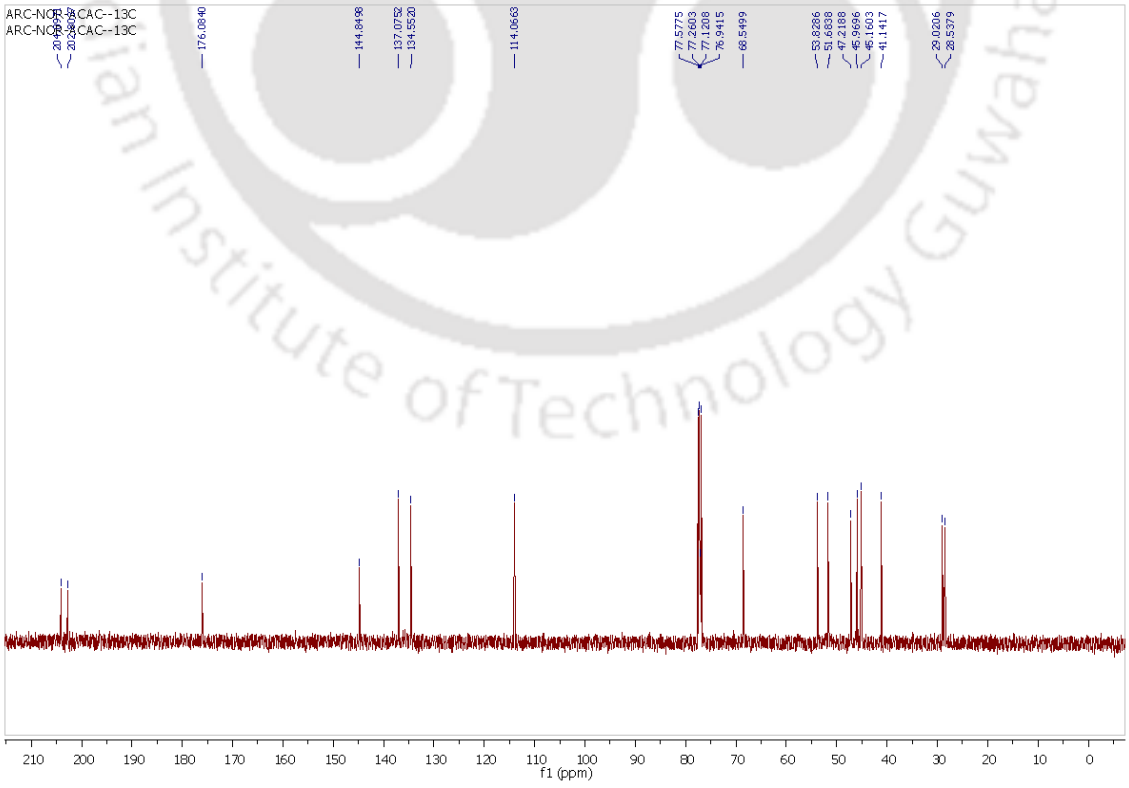


Figure 3.8.1 NOE of compound **29h**

^{1}H spectrum of pure compound **29q** (400 MHz, $CDCl_3$)



^{13}C{^{1}H } spectrum of pure compound **29q** (100 MHz, $CDCl_3$)



400 MHz, $CDCl_3$

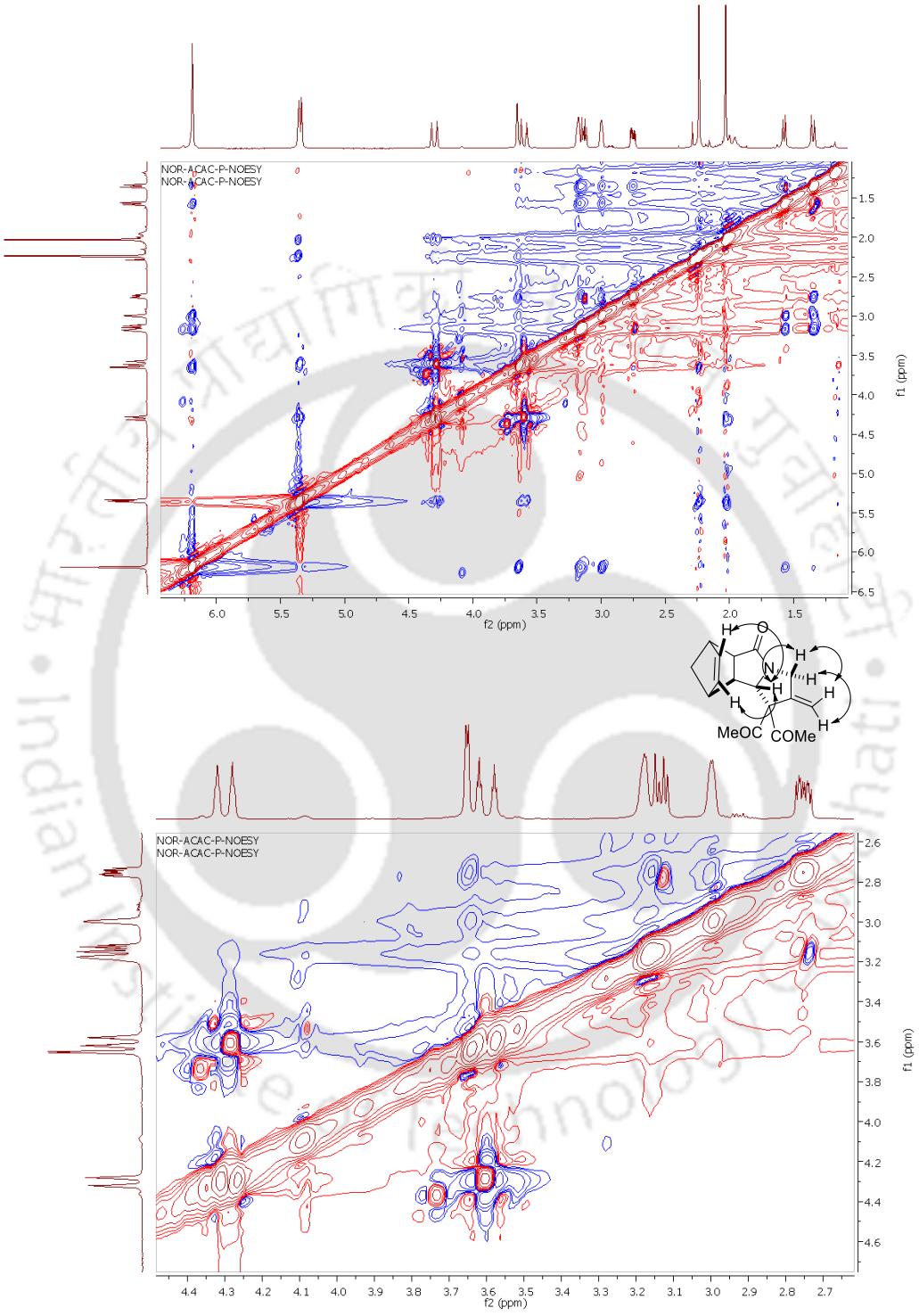
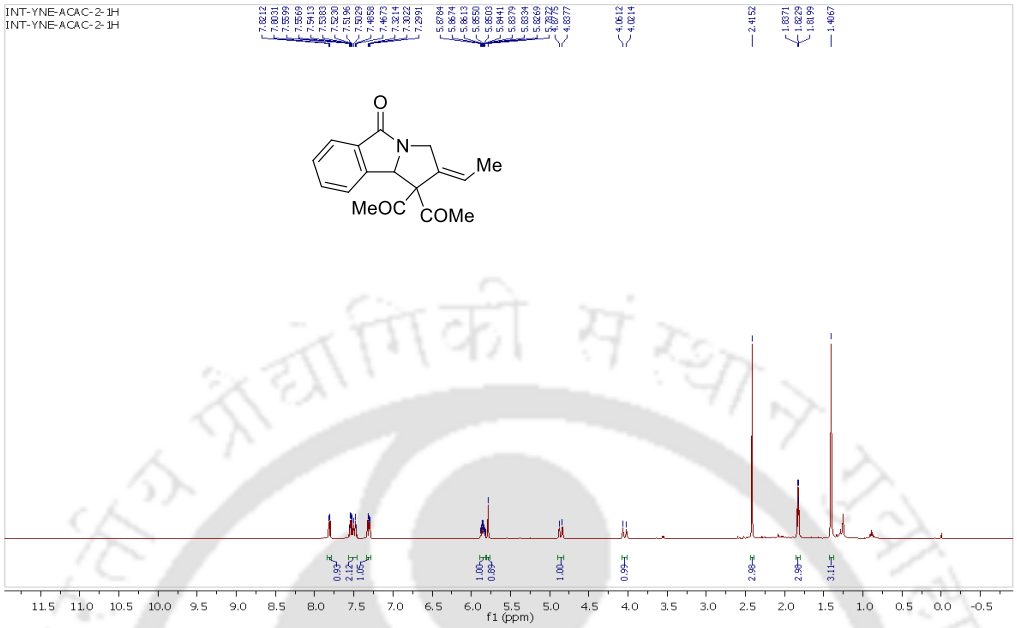
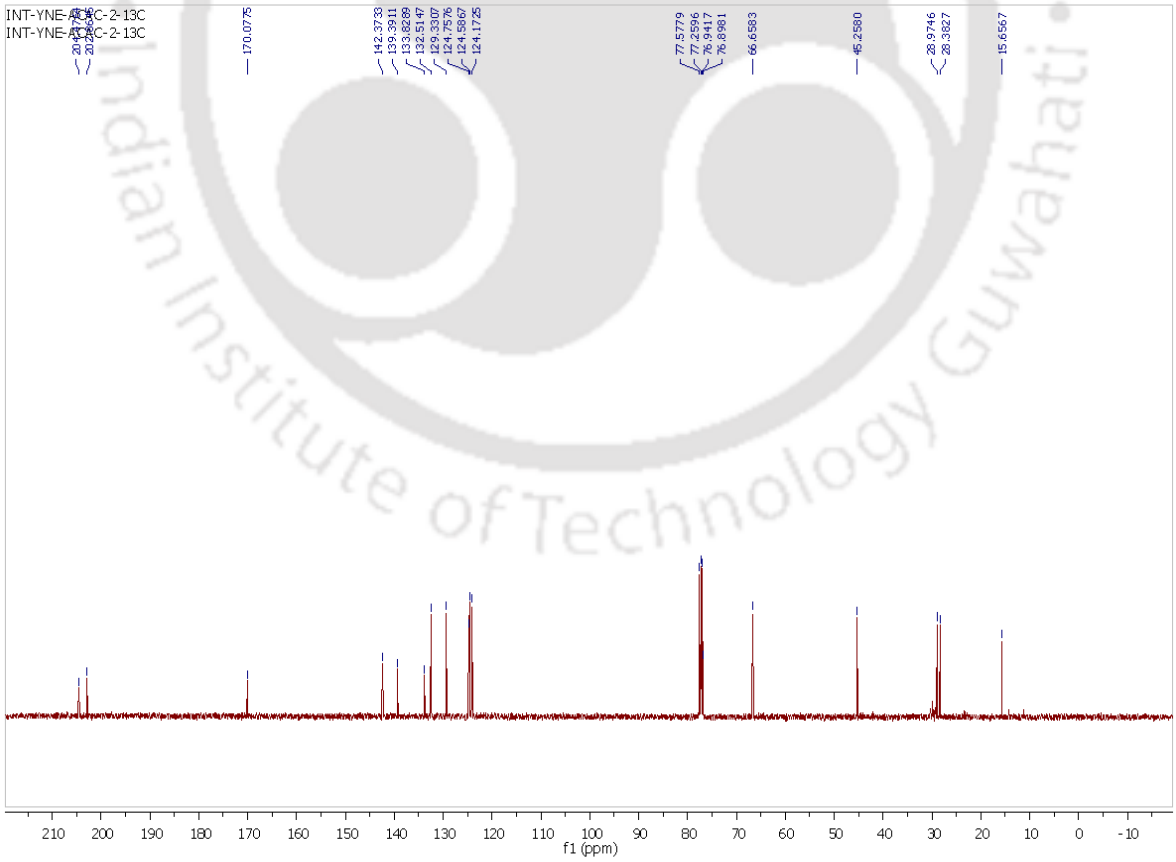


Figure 3.8.2 NOE of compound **29q**

^{1}H spectrum of compound **29w** (400 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ spectrum of compound **29w** (400 MHz, $CDCl_3$)



400 MHz, $CDCl_3$

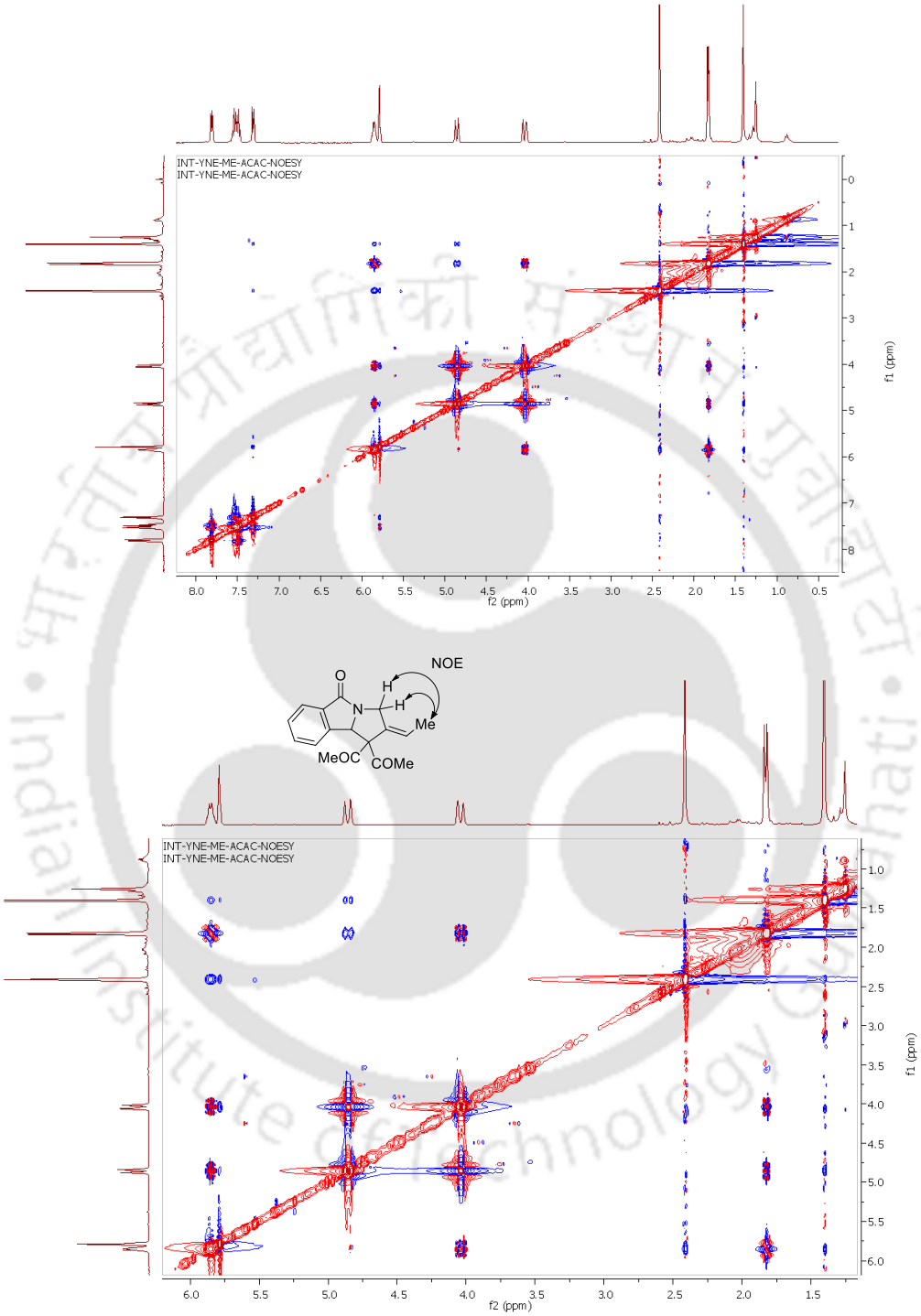
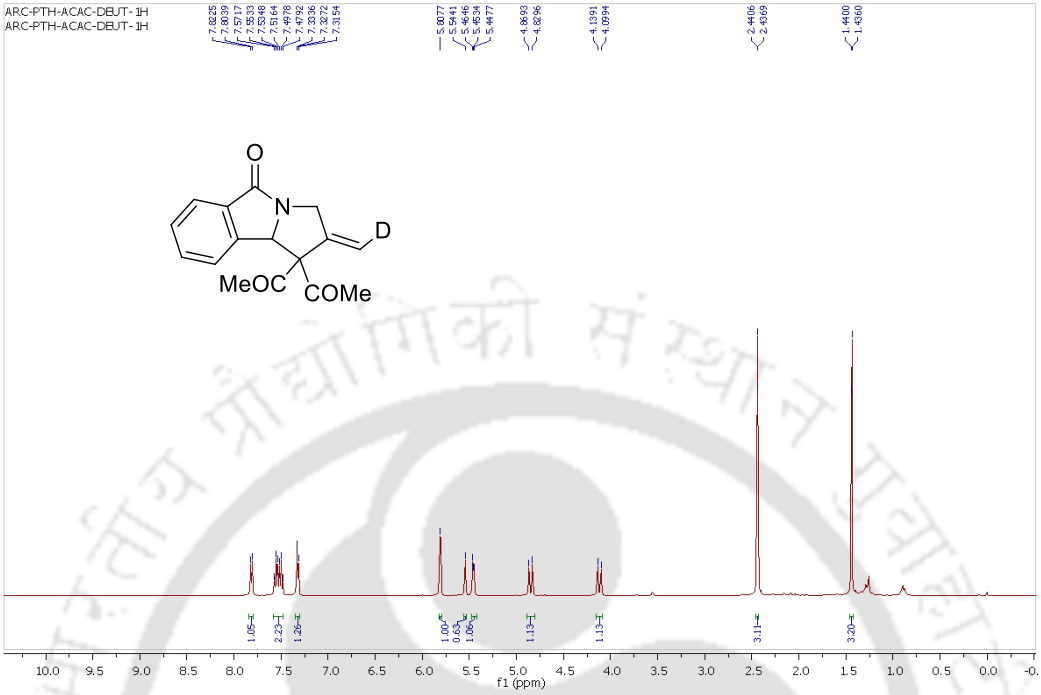
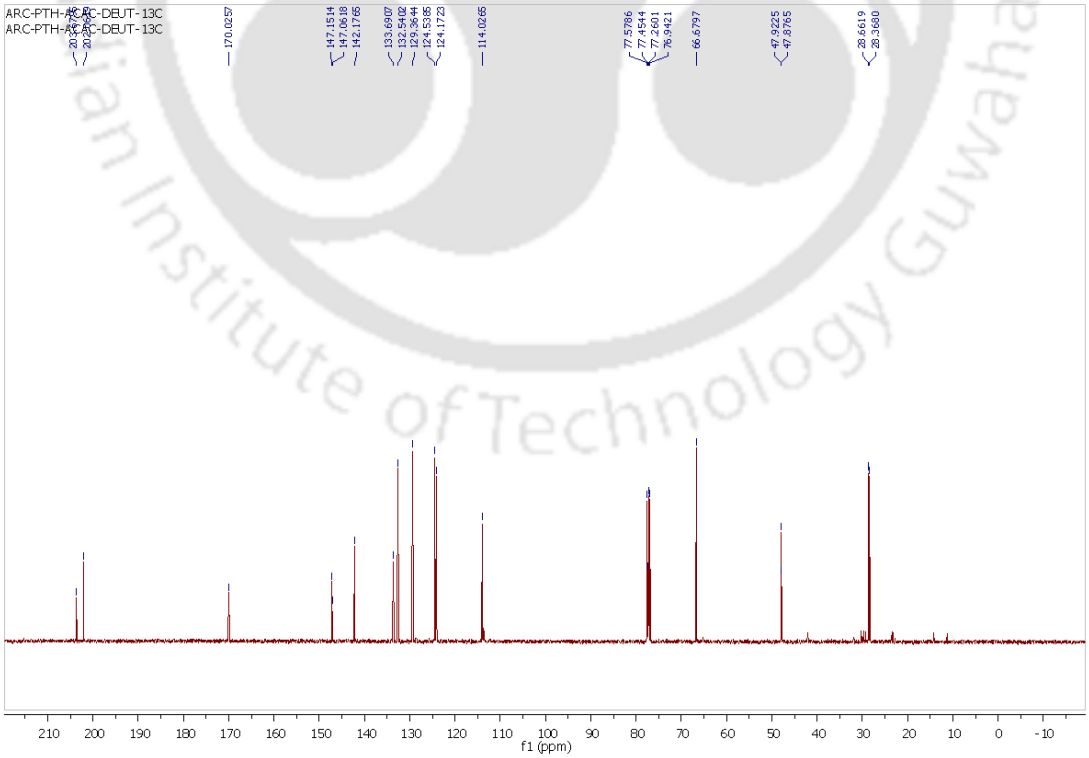


Figure 3.8.3 nOe of compound **29w**

^{1}H spectrum of compound **29d-D** (400 MHz, $CDCl_3$)



^{13}C{^{1}H } spectrum of compound **29d-D** (100 MHz, $CDCl_3$)



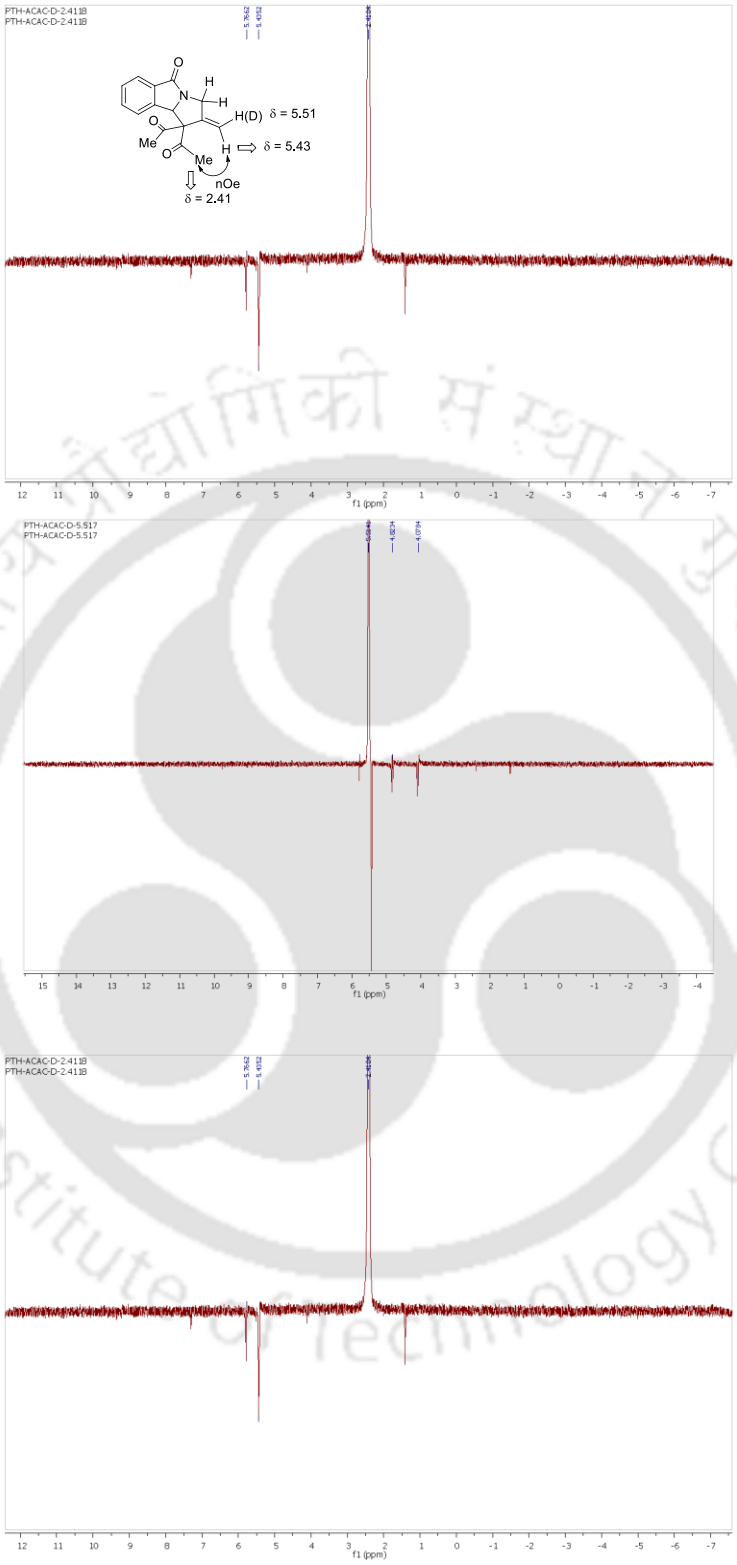


Figure 3.8.4 1D-nOe of compound **29d-D**

3.9 Crystal parameters

Table 3.9.1 The crystal parameters of compound **29a**

	CCDC 1945841
Formula	$C_{18}H_{19}NO_5$
Formula weight	329.34
T/K	296(2)
Crystal system	Monoclinic
Space group	P2(1)
a/Å	8.4181(8)
b/Å	10.0355(9)
c/Å	10.2655(10)
α/°	90.00
β/°	107.956(2)
γ/°	90.00
V/Å^3	824.99(13)
Z	2
Abs. Coeff./mm^{-1}	0.097
Abs. Correction	none
GOF on F^2	1.073
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0369
	wR2 = 0.0911
R indices [all data]	*R1* = 0.0404
	wR2 = 0.0941

Table 3.9.2 The crystal parameters of compound **31a**

	CCDC 1945842
Formula	$C_{15}H_{13}NO_3$
Formula weight	255.26
T/K	293(2)
Crystal system	Triclinic
Space group	P-1
a/Å	7.8165(11)
b/Å	8.0726(15)
c/Å	11.7190(15)
α/°	97.711(13)
β/°	101.614(12)
γ/°	116.715(16)
V/Å^3	625.31(17)
Z	2
Abs. Coeff./mm^{-1}	0.095
Abs. Correction	multi-scan
GOF on F^2	1.099
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0567
	wR2 = 0.1184
R indices [all data]	*R1* = 0.0911
	wR2 = 0.1467

CHAPTER 4

Bi(OTf)$_3$-catalyzed one-pot dimerization of *N*-propargyl amido alcohols to construct dibenzoyl tetrahydro-[1,5]diazocinodiisoindolediones

4.1 Introduction

Diazocanes are saturated eight membered heterocycles containing two nitrogen atoms usually exist in three isomeric forms *i.e*. 1,3-, 1,4- and 1,5-diazocanes named after different position of nitrogen atoms. Diazocane based molecules more often occurs in many important bioactive compounds,[1] electronic materials,[2a] supramolecular receptors, Troger's base[2b] etc. Interestingly, 1,5-diazocane nucleus with varying functionalities has been found in pharmacological important compounds.[3] For example, compound **A** is a novel interleukine-1β converting inhibitors[3a] and compound **B** is a ligand that shows high affinity for $\alpha_4\beta_2$ nicotinic acetylcholine receptors facilitating easy transmission of message within neurons.[3b] Cytisine (**C**) is a naturally occurring alkaloid that acts as an agonist for nicotinic acetylcholine receptors.[3c] Similarly, sparteine (**D**) act as both antiarrhythmic agent as well as anticonvulsant drug (*Figure 4.1.1*).[3d]

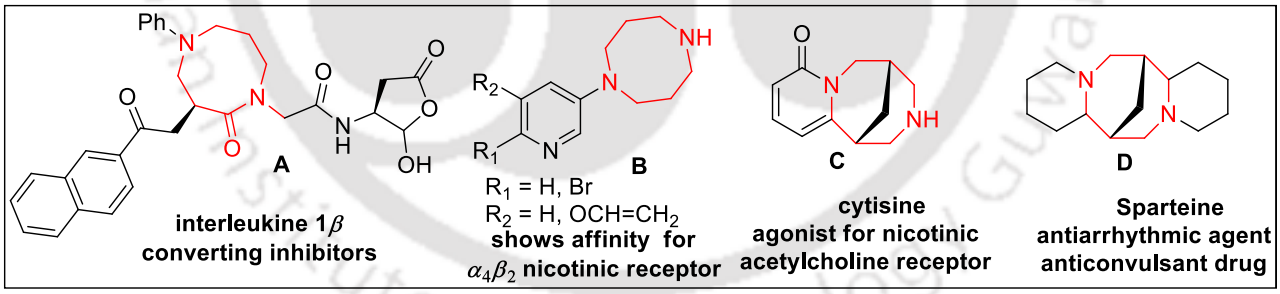
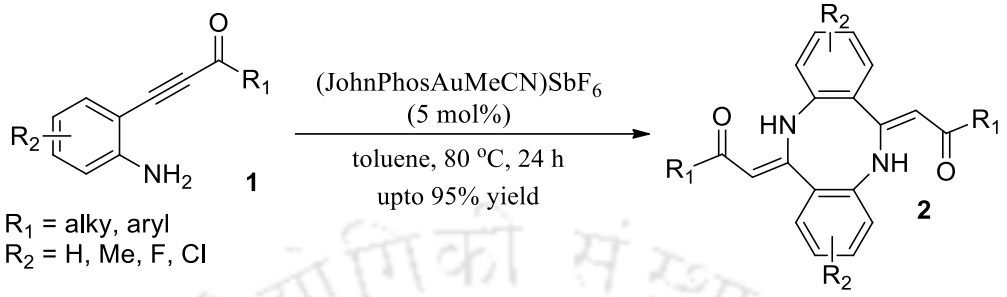


Figure 4.1.1 Examples of bioactive 1,5-diazocane based molecules.

4.2 Literature methods for substituted 1,5-diazocanes:

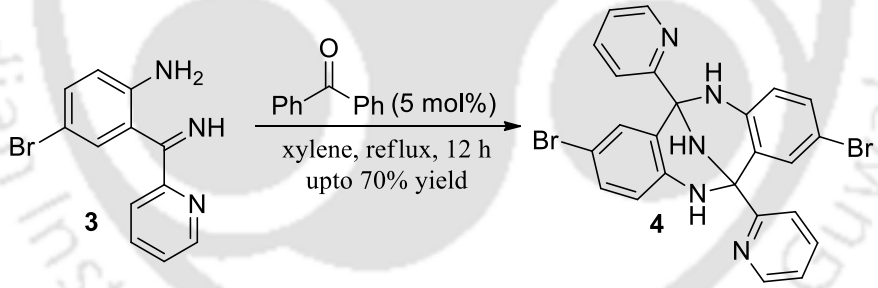
Rode *et al.* described a procedure for the synthesis of dibenzo[1,5]diazocines **2** from *ortho*-amino-ynones **1** using Au(I) catalyst in toluene at 80 ^{o}C. The corresponding amino-ynones

undergoes auto-intermolecular hydroamination under these conditions to afford the target **2** in moderate to good yields (*Scheme 4.2.1*).[4]



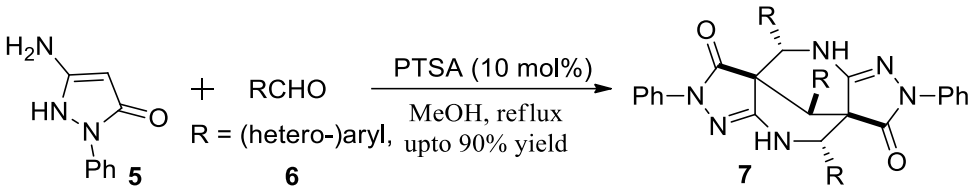
Scheme 4.2.1

A metal free cyclisation of 2-amino phenylketimines **3** was demonstrated by Linden and group to produce substituted iminodibenzo[1,5]diazocine **4** in good yields catalyzed by benzophenone. The synthesized compounds could form complex with $PdCl_2$ that found application in supramolecular chemistry (*Scheme 4.2.2*).[5]



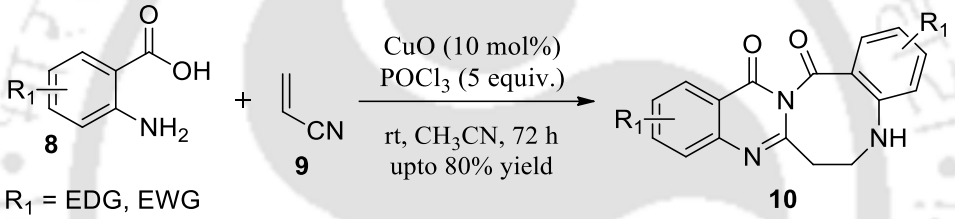
Scheme 4.2.2

Kiamehr and group explained a Bronsted acid catalysed one pot procedure for the synthesis of pyrazolo[1,5]diazocinediones **7** from 3-aminopyrazolones **5** and substituted aldehydes **6** in moderate to good yields. Formation of imine from compounds **5** and **6** followed by cycloaddition reaction are the key steps to deliver the compounds **7** (*Scheme 4.2.3*).[6]



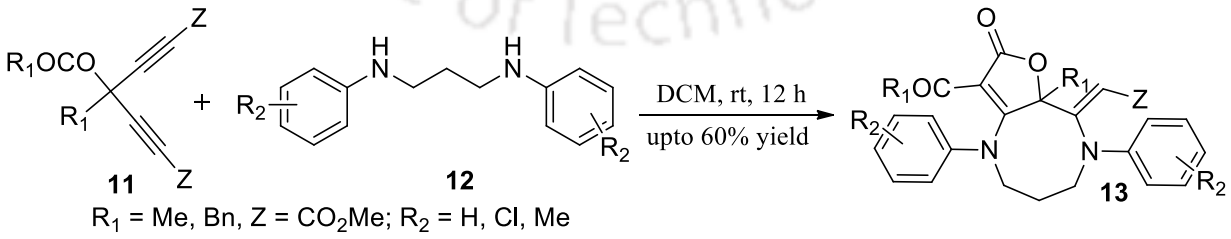
Scheme 4.2.3

Yamada and his group accessed quinazolone fused [1,5]diazocanes **10** *via* one pot cascade reaction of antranilic acids **8** and acrylonitrile **9** by employing catalytic CuO and excess amount of $POCl_3$ in ACN at ambient conditions. The reaction headed through Ritter-type reaction/condensation/intramolecular anti-Markovnikov hydroamination (*scheme 4.2.4*).[7]



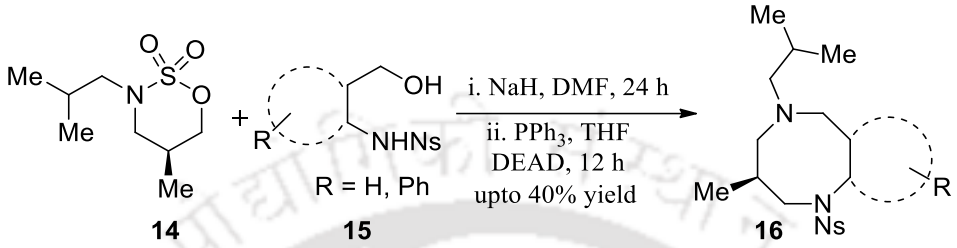
Scheme 4.2.4

A domino reaction for synthesis of butenolide fused [1,5]diazocanes **13** was developed by Tellado and co-workers from diarylated 1,3-diamines **12** and activated diynes **11** in good yields. The reaction mechanism explains consecutive aza-Michael addition of amines on alkynes, Morita–Baylis–Hillman-type reaction and lactonization *via* aza addition and elimination are the key steps for this transformation (*scheme 4.2.5*).[8]



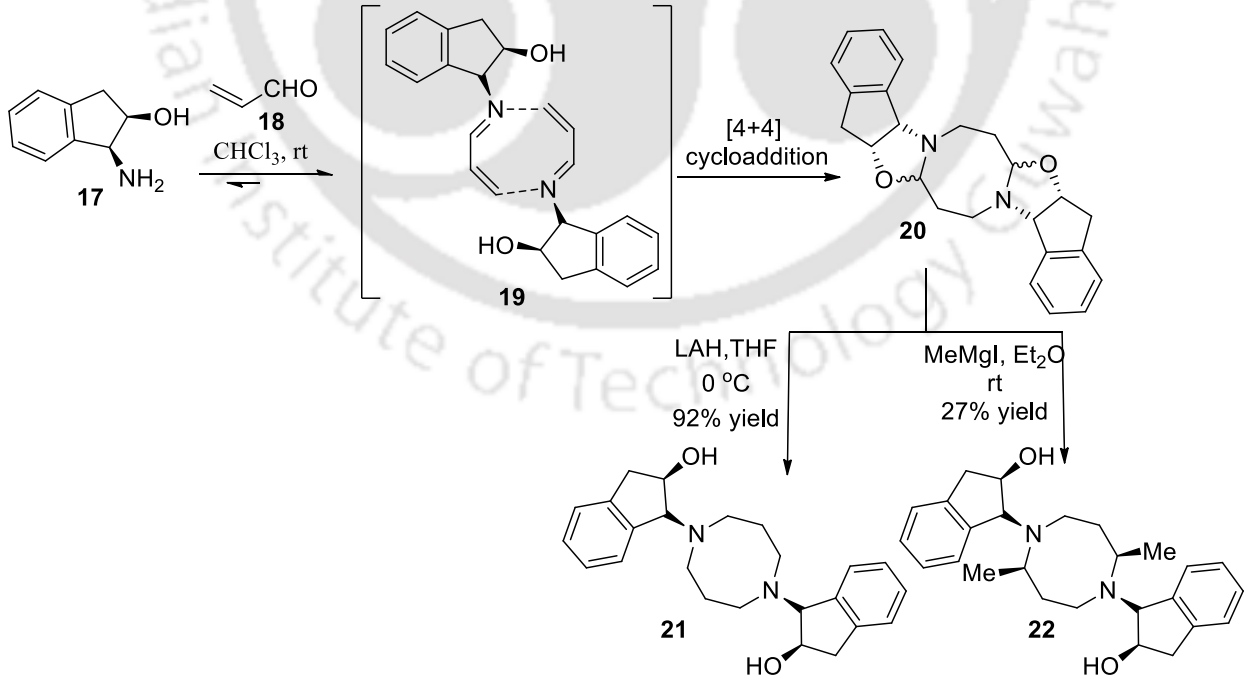
Scheme 4.2.5

Nelson and co-workers developed a two-step protocol for the synthesis of [1,5]diazocane scaffolds **16** using cyclic sulfamidate **14** and hydroxy sulfonamide **15** as building blocks in moderate yields. The reaction involves nucleophilic substitution with removal of SO_3 followed by Mitsunobu type reaction to afford **16** (*Scheme 4.2.6*).[9]



Scheme 4.2.6

Chiral auxiliary bearing [1,5]diazocanes **20** were obtained by Tanaka and group from the formal [4+4]-cycloaddition of *N*-alkyl-*α*,*β*-unsaturated imines **19** that was further derivatized into different chiral substituted 1,5-diazocane derivatives (**21**/**22**) by the reduction of Lithium aluminium hydride as well as nucleophilic alkylation reaction in moderate yields (*Scheme 4.2.7*).[10]

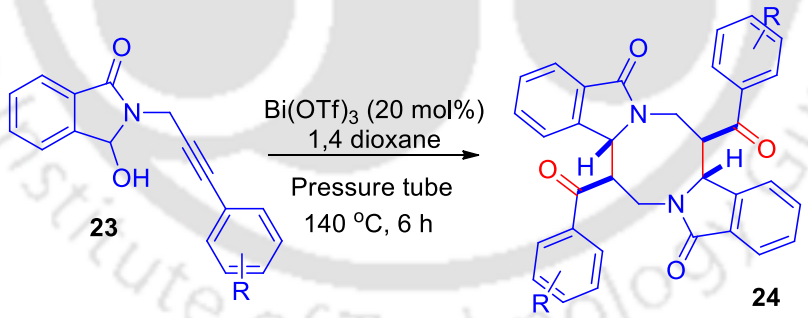


Scheme 4.2.7

The corresponding *N*-alkyl-*α*,*β*-unsaturated imine **19** was obtained from the condensation reaction of *cis*-aminol **17** and acrolein **18.**

4.3 Results and Discussions

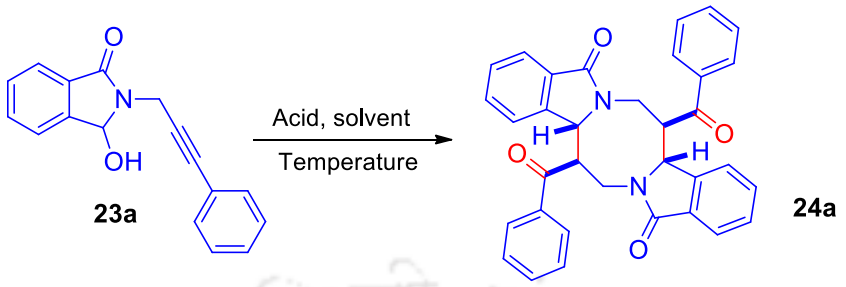
The chemistry of 1,5-diazocanes are relatively less explored compared to other 5-/6-/7-membered ring due to the their instability caused by rise in angle strain (strain energy) in the molecule. Moreover, methods for synthesis of substituted [1,5]diazocanes suffer from multistep synthesis, using expensive metal catalysts.[4,11] Hence, it is exclusively challenging task to synthesize such scaffolds in an efficient method. In a verge to synthesize different nitrogen heterocyclic compounds, our group has been lately using *N*-acyliminium ions as a key intermediate.[12] In the previous chapter, we described the synthesis of tetrahydropyrroloisoindolones and pyridoisoindolones from *N*-propargylamidoalcohols in presence of catalytic amount of $In(OTf)_3$. To the best of our knowledge there is no literature findings for synthesis of dibenzoyltetrahydro-[1,5]diazocinodiisoindolediones using the same starting material *N*-propargylamido alcohols till date. In this chapter, we demonstrate $Bi(OTf)_3$ catalysed one-pot dimerization of *N*-propargylamido alcohols **23** to provided benzoyltetrahydro-[1,5]diazocinodiisoindolediones **24** (*Scheme 4.3.1*).



Scheme 4.3.1

Considering 3-hydroxy-2-(3-phenylprop-2-yn-1-yl)isoindolin-1-one (**23a**) as model substrate, the reaction was carried out in a pressure tube in presence of 1.0 equiv of TfOH in toluene at reflux temperature. To our delight 8,16-dibenzoyl-8,8a,16,16a-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (**24a**) was obtained but only in trace amounts (*Table 4.3.1*, entry 1). In order to increase the yield, same reaction was again performed at an elevated

Table 4.3.1 Optimization of the reaction[a]

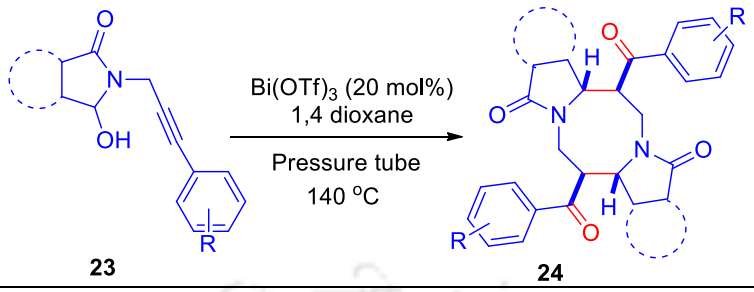


Entry	Reagent (equiv.)	Solvent	Temp.(°C)	Time(h)	Yield(%)[b]
1	TfOH(1.0)	toluene	110	12	trace
2	TfOH(1.0)	toluene	140	12	20
3	TfOH(1.0)	CH_3CN	140	1.5	--[d]
4	TfOH(1.0)	DCE	140	1.5	--[d]
5	TfOH(1.0)	xylene	140	1.5	--[d]
6	TfOH(1.0)	1,4 dioxane	140	1.5	35
7	PTSA(1.0)	1,4 dioxane	140	1.5	--[c]
8	$BF_3.OEt_2$(1.0)	1,4 dioxane	140	1.5	--[d]
9	Tf_2NH(2.0)	1,4 dioxane	140	1.5	20
10	TMSOTf(1.0)	1,4 dioxane	140	1.5	35
11	**$Bi(OTf)_3$(0.2)**	**1,4 dioxane**	**140**	**1.5**	**50**
12	$In(OTf)_3$(0.2)	1,4 dioxane	140	1.5	42
13	$Sc(OTf)_3$(0.2)	1,4 dioxane	140	1.5	--[d]
14	$FeCl_3$(0.1)	1,4 dioxane	140	1.5	--[d]
15	$InCl_3$(0.3)	1,4 dioxane	140	1.5	--[c]

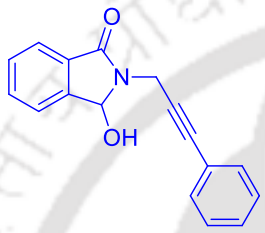
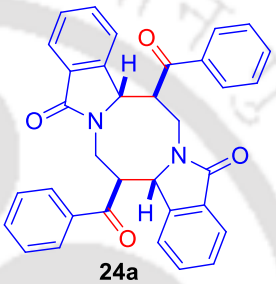
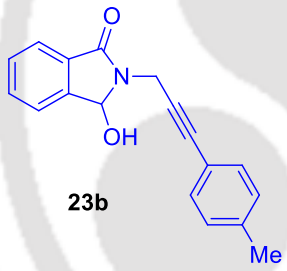
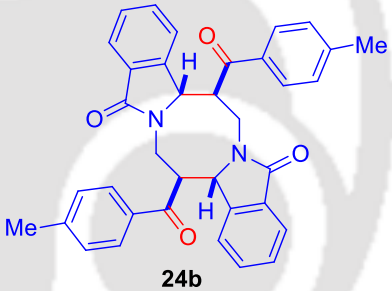
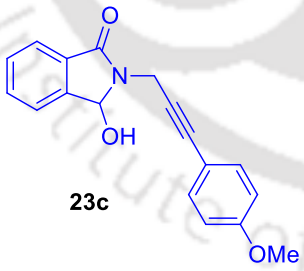
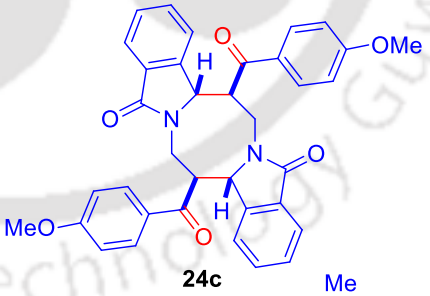
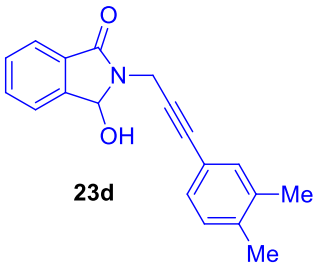
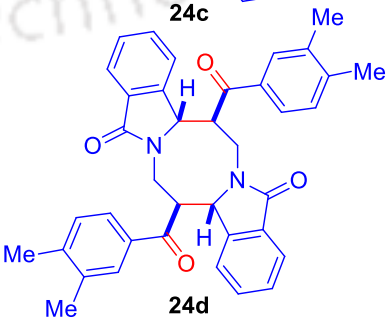
[a]Reaction conditions: **23a (**1 equiv); in a pressure tube [b]Yield refers to isolated yield. Compounds are characterised by ^1H, ^{13}C NMR, IR and Mass spectrometry. [c]No reaction, starting material was recovered.[d]decomposed.

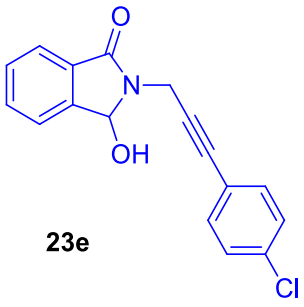
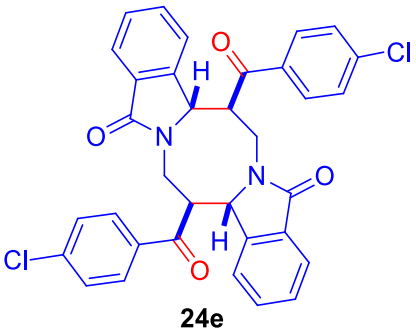
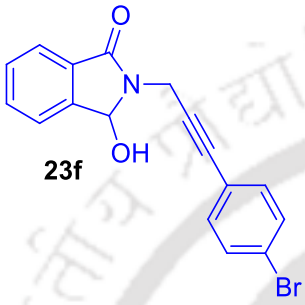
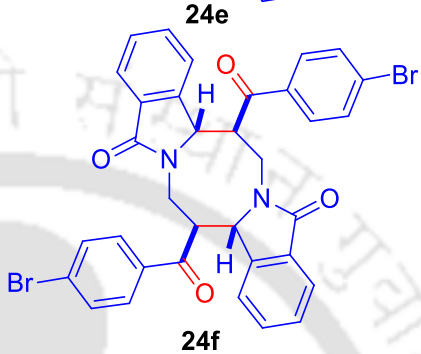
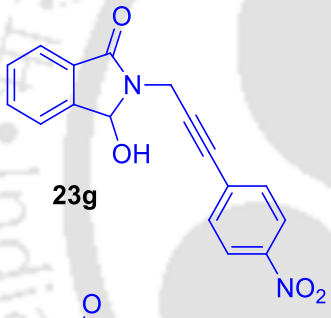
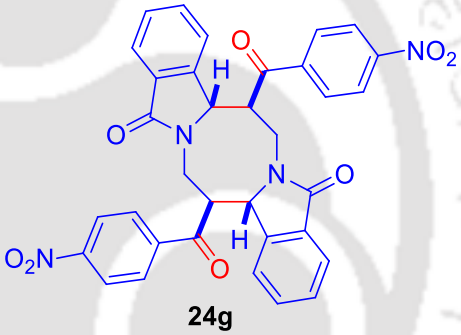
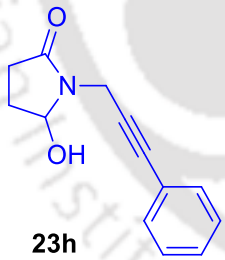
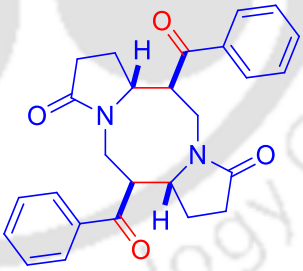
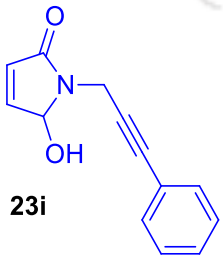
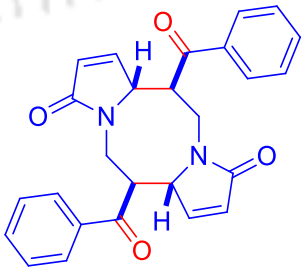
temperature of 140 °C and we are pleased to obtain the desired product in 20% yield (*Table 4.3.1*, entry 2) and it was further confirmed by ^1H and ^{13}C NMR, IR, mass spectrometry as well as crystallographic analysis of compound **24a.**[13] To study the effect of other solvents, the

Table 4.3.2 Synthesis of dibenzoyltetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindolediones.

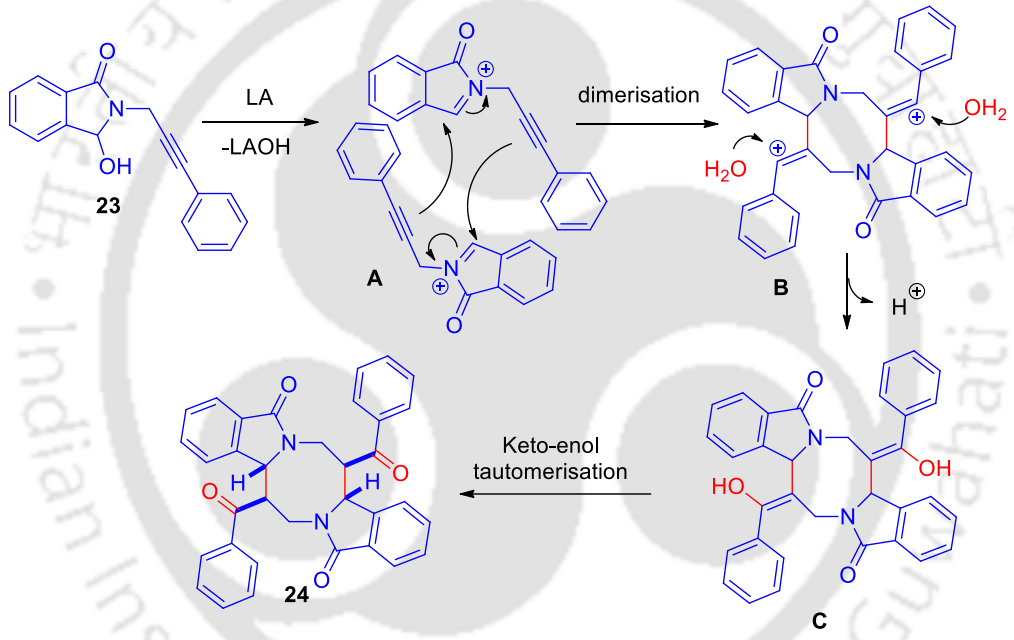


23 **24**

Entry	Starting material	Product	%Yield[a]
1	 **23a**	 **24a**	50
2	 **23b**	 **24b**	55
3	 **23c**	 **24c**	52
4	 **23d**	 **24d**	48

5	 **23e**	 **24e**	45
6	 **23f**	 **24f**	43
7	 **23g**	 **24g**	d
8	 **23h**	 **24h**	52
9	 **23i**	 **24i**	0

reaction was further performed in DCE, CH_3CN and xylene but gave decomposed products (*Table 4.3.1*, entries 3-5). However, the use of 1,4 dioxane as a solvent, the reaction gave inflation of reaction yield to 35% (*Table 4.3.1*, entry 6). Other Bronsted acid such as PTSA was found inefficient for the conversion (*Table 4.3.1*, entry 7). From the results we then envisaged Lewis acid could be beneficial for this process. Lewis acids such as metal triflates, metal halides, $BF_3.OEt_2$, Tf_2NH, TMSOTf etc. were used for further screening of our reaction (*Table 4.3.1*, entries 8-15). Thus, 0.2 equiv. of $Bi(OTf)_3$ in 1,4 dioxane at 140 ^oC was found to be the optimum conditions for our reaction. With this optimum conditions in hand, the scope of the reaction is being investigated. The 1,5-diazocanes synthesized has been shown in *Table 4.3.2*.



Scheme 4.3.2

Both side chains having electron-donating as well as electron-withdrawing groups were able to produce the target products in moderate to good yields. Compound **23b** under standard reaction conditions provided compound **24b** in 55% yield. Similarly, other electron-donating group having compounds **23c-23d** furnished the corresponding target products **24c-24d** in 52 and 48% yields, respectively. On the other hand, moderately electron-withdrawing group having *N*-propargylamido alcohols **23e** and **23f** proceeded sluggishly and gave respective products **24e** and

24f in 45 and 43% yields. This might be due to less stabilization of carbocation formed during the reaction compared to the stabilization from electron-donating groups. Strongly electron-withdrawing group having compound **23g** gave complex mixture. 5-Hydroxy-1-(3-phenylprop-2-yn-1-yl)pyrrolidin-2-one (**23h**) was also successfully produced **24h** in 52% yield. But to our dismay, compound **23i** which was derived from *N*-propargyl maleimide found to be inefficient in this transformation.

The mechanism is proposed on the basis of previous report (*Scheme 4.3.2*).[12a] Lewis acid generates *N*-acyliminium ion **A** from *N*-propargylamidoalcohol **23**. The *N*-acyliminium ion **A** dimerizes resulting in intermediate **B**. The carbocation **B** is trapped by water in the reaction to generate enols **C.** The enols **C** after tautomerization give more stable product with the benzoyl group *exo* to the isoindolone ring system.

Conclusion

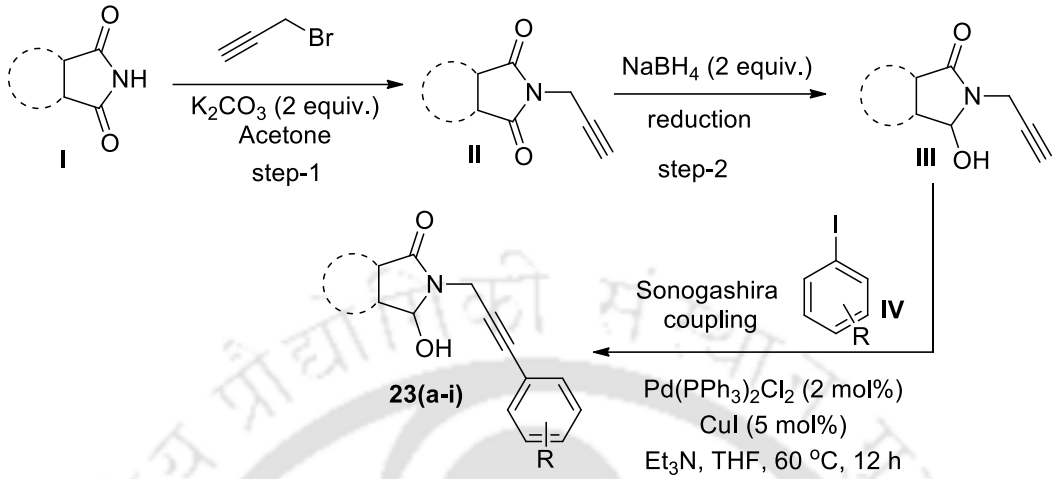
In conclusion, a simple and direct protocol has been developed for the synthesis of uncommon dibenzoyltetrahydro-[1,5]diazocinodiisoindoledione derivatives from *N*-propargylamido alcohols using $Bi(OTf)_3$ as catalyst. The reaction proceeds through *N*-acyliminium ion formation and nucleophilic attack from alkynes leading to dimerization. Further applications of this protocol are under investigation.

4.4 Experimental Section

4.4.1 Instrumentation and characterization:

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

4.4.2 General procedure for the synthesis of amidoalcohols 23



Scheme 4.4.2.1 Starting material preparation

The corresponding starting materials were synthesized in a three-step procedure *i.e.* propargylation, reduction followed by Sonogashira coupling reaction (*Scheme 4.4.2.1*). The starting material amido alcohols **23a**,[14] was prepared as per the literature procedure and the spectroscopic data are in good agreement with the literature one.

4.4.2.1 General procedure for the synthesis of 23b-23h:

Compound **IV** (1.2 mmol, 1.2 equiv.) was added to a stirred solution of $Pd(PPh_3)_2Cl_2$ (0.02 mmol, 0.02 equiv.) and CuI (0.05 mmol, 0.05 equiv.), TEA (1.0 mmol, 1.0 equiv.) in 3 mL of dry THF under nitrogen atmosphere at room temperature. After 15 min. *N*-propargylamido alcohols **III** (1.0 mmol, 1.0 equiv.) in dry THF was added over a period of 10 min. The resulting solution was subjected to heat for 60 ^oC for 12 h. After completion of the starting material (monitored by TLC) the solvent was removed under reduced pressure and diluted with saturated NH_4Cl solution. The organic layer was extracted with EtOAc (3x20 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the compounds **23**.

4.4.3 General procedure for the synthesis of 1,5-diazocanes 24:

An oven dried pressure tube was charged with compound **23** (0.5 mmol, 1.0 equiv.) and $Bi(OTf)_3$ (0.1 mmol, 0.2 equiv.) in 1,4 dioxane (6.0 mL) at room temperature. Then, the resulting suspension was heated for 6 h then, the solution was cooled to room temperature. The solvent was then removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. The organic layer was extracted with EtOAc (3x20 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the compounds **24**.

4.5 References

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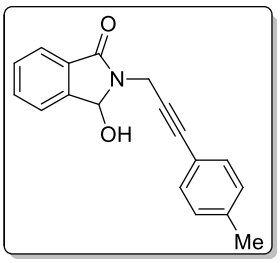
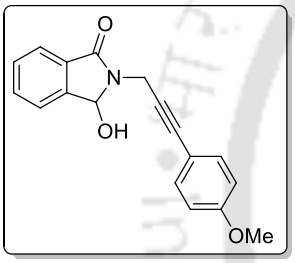
4.6 Characterization data

3-Hydroxy-2-(3-(*p*-tolyl)prop-2-yn-1-yl)isoindolin-1-one (23b):



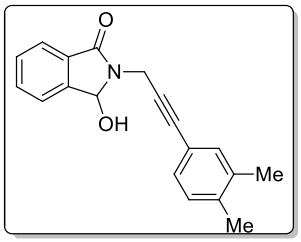
Offwhite solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 150-152 ^oC Yield 188 mg, 68%;^1H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2 H), 7.59 – 7.54 (m, 1 H), 7.50 – 7.39 (m, 1 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 6.01 (d, *J* = 7.5 Hz, 1 H), 4.62 – 4.52 (m, 1 H), 4.12 – 4.07 (m, 1 H), 3.91 (bs, 1 H), 2.31 (s, 3 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.1, 144.2, 138.8, 132.7, 131.9, 131.2, 129.9, 129.2, 123.7, 123.5, 119.5, 84.0, 82.8, 81.3, 29.4, 21.6.; IR (KBr, neat) 2954, 1649, 1527, 1440, 1343, 1285, 1133, 983, 891, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{16}NO_2$ $(M + H)^+$ 278.1176, found 278.1199.

3-Hydroxy-2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)isoindolin-1-one (23c):



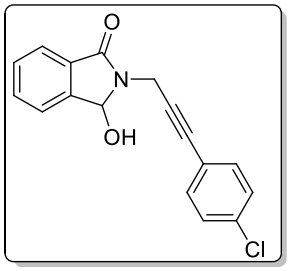
White solid; R_f (hexane/EtOAc, 3:2) 0.40; mp 148-150 ^oC Yield 160 mg, 55%;^1H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.37 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.70 (d, *J* = 8.5 Hz, 2 H), 5.93 (s, 1 H), 4.48 (dd, *J* = 17.5 and 3.5 Hz, 1 H), 4.01 (d, *J* = 17.5 Hz, 2 H), 3.68 (s, 3 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.1, 159.3, 144.2, 133.5, 132.8, 131.3, 129.9, 123.8, 123.6, 114.7, 114.1, 83.9, 82.1, 81.4, 54.5. 29.5.; IR (KBr, neat) 3325, 2972, 1671, 1527, 1392, 1215, 1132, 923, 880, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{16}NO_3$ $(M + H)^+$ 294.1125, found 294.1119.

2-(3-(3,4-Dimethylphenyl)prop-2-yn-1-yl)-3-hydroxyisoindolin-1-one (23d):



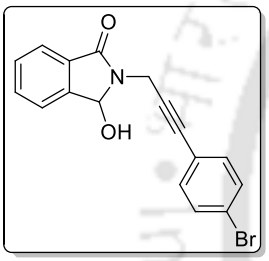
Orange gum; R_f (hexane/EtOAc, 3:2) 0.50; mp 160-162 ^oC Yield 168 mg, 58%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (t, *J* = 7.5 Hz, 2 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 6.99 (s, 2 H), 6.89 (s, 1 H), 6.00 (s, 1 H), 4.54 (d, *J* = 17.5 Hz, 1 H), 4.07 (d, *J* = 17.5 Hz, 1 H), 2.21 (s, 6 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 167.1, 144.2, 137.9, 132.7, 131.1, 130.5, 129.8, 129.6, 123.7, 123.4, 122.2, 84.2, 82.8, 81.3, 29.3, 21.2.; IR (KBr, neat) 3323, 2953, 1675, 1447, 1312, 1219, 1032, 935, 882, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$ $(M + H)^+$ 292.1332, found 292.1349.

2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-3-hydroxyisoindolin-1-one (23e):



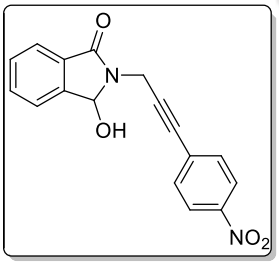
White solid; R_f (hexane/EtOAc, 3:2) 0.60; mp 178-180 ^oC Yield 193 mg, 65%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (t, *J* = 7.5 Hz, 2 H), 7.59 (td, *J* = 7.5 and 1.0 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.33 – 7.28 (m, 2 H), 7.26 – 7.21 (m, 2 H), 5.99 (d, *J* = 10.5 Hz, 1 H), 4.58 (d, *J* = 17.5 Hz, 1 H), 4.12 (d, *J* = 17.5 Hz, 1 H), 3.83 (bs, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.8, 143.9, 134.9, 133.3, 132.9, 131.4, 130.3, 128.9, 123.8, 123.7, 121.1, 84.7, 82.9, 81.5, 29.6.; IR (KBr, neat) 3250, 2927, 2131, 1671, 1392, 1310, 1214, 1073, 923, 880, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{13}ClNO_2$ $(M + H)^+$ 298.0626, found 298.0649.

2-(3-(4-Bromophenyl)prop-2-yn-1-yl)-3-hydroxyisoindolin-1-one (23f):



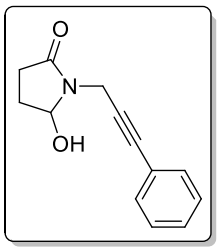
Brown solid; R_f (hexane/EtOAc, 3:2) 0.60; mp 173-175 ^oC Yield 210 mg, 62%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.5 Hz, 1 H), 7.64 (d, *J* = 7.5 Hz, 1 H), 7.60 (td, *J* = 7.5 and 1.0 Hz, 1 H), 7.48 (td, *J* = 7.5 and 1.0 Hz, 1 H), 7.40 – 7.38 (m, 2 H), 7.26 – 7.23 (m, 2 H), 6.00 (s, 1 H), 4.63 (d, *J* = 17.5 Hz, 1 H), 4.16 (d, *J* = 17.5 Hz, 1 H), 3.49 (bs, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.9, 144.0, 133.5, 132.9, 131.8, 131.3, 130.2, 123.8, 123.7, 123.1, 121.6, 84.8, 82.9, 81.5, 29.5.; IR (KBr, neat) 3230, 2950, 2251, 1668, 1389, 1118, 1214, 1071, 932, 860, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{13}BrNO_2$ $(M + H)^+$ 342.0124, found 342.0138.

3-Hydroxy-2-(3-(4-nitrophenyl)prop-2-yn-1-yl)isoindolin-1-one (23g):



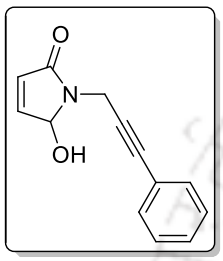
Pale yellow solid; R_f (hexane/EtOAc, 2:3) 0.50; mp 170-172 ^oC Yield 140 mg, 45%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 11.0 Hz, 2 H), 7.42 (t, *J* = 9.5 Hz, 1 H), 7.50–7.59 (m, 3 H), 8.07 (d, J = 11.0 Hz, 2 H).6.00 (s, 1 H), 4.62 (d, *J* = 17.5 Hz, 1 H), 4.13 (d, *J* = 17.5 Hz, 1 H), 3.46 (bs, 1 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.9, 146.2, 144.0, 133.5, 132.9, 131.3, 130.2, 123.8, 123.7, 123.1, 121.6, 84.8, 82.9, 81.5, 29.5.; IR (KBr, neat) 3430, 2934, 1679, 1523, 1432, 1383, 1287, 1133, 933, 851, 726 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{13}N_2O_4$ $(M + H)^+$309.0870, found 309.0892.

5-Hydroxy-1-(3-phenylprop-2-yn-1-yl)pyrrolidin-2-one (23h):



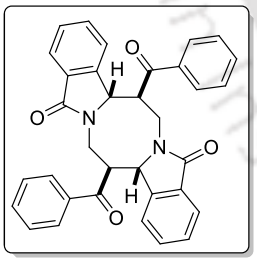
Orange gum; R_f (hexane/EtOAc, 3:7) 0.50; Yield 140 mg, 65%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2 H), 7.34 – 7.27 (m, 3 H), 5.51 (s, 1 H), 4.61 (d, *J* = 17.5 Hz, 1 H), 4.15 – 4.10 (m, 1 H), 2.70 – 2.54 (m, 1 H), 2.45 – 2.27 (m, 2 H), 2.00 – 1.91 (m, 1 H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 174.4, 132.0, 128.8, 128.6, 122.6, 84.3, 83.3, 82.7, 30.4, 29.1, 28.1.; IR (KBr, neat) 3200, 2954, 2329, 1669, 1527, 1453, 1343, 1279, 1175, 1066, 983, 891, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{14}NO_2$ $(M + H)^+$ 216.1019, found 216.1021.

5-Hydroxy-1-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-2(5*H*)-one (23i):



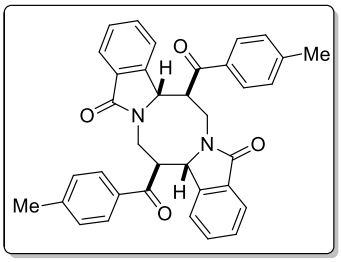
Colorless gum; R_f (hexane/EtOAc, 1:1) 0.50; mp 150-152 ^{o}C Yield 120 mg, 59%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2 H), 7.35 – 7.25 (m, 3 H), 6.99 (d, *J* = 6.0 Hz, 1 H), 6.18 – 6.08 (m, 1 H), 5.67 (d, *J* = 9.5 Hz, 1 H), 4.67 (dd, *J* = 17.5 and 2.0 Hz, 1 H), 4.17 (dd, *J* = 17.5 and 2.0 Hz, 1 H), 3.67 (s, 1 H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.3, 146.6, 132.0, 128.8, 128.5, 128.4, 122.6, 83.9, 83.7, 83.0, 29.5.; IR (KBr, neat) 3100, 2952, 2224, 1679, 1550, 1468, 1323, 1276, 1173, 1056, 983, 882, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{12}NO_2$ $(M + H)^+$ 214.0863, found 214.0888.

(8S,8*a*S,16S,16*a*S)-8,16-dibenzoyl-8,8*a*,16,16*a*-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (24a):



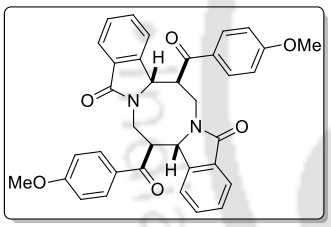
Orange solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 280-282 ^{o}C Yield 65 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 7.6 Hz, 4 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 7.67 (t, *J* = 7.2 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 4 H), 7.39 (t, *J* = 7.2 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 2 H), 6.98 (d, *J* = 7.2 Hz, 2 H), 5.38 (d, *J* = 10.4 Hz, 2 H), 4.35 (d, *J* = 14.8 Hz, 2 H), 4.29 (d, *J* = 10.8 Hz, 2 H), 3.80 (dd, *J* = 14.8 and 10.8 Hz, 2 H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.6, 171.3, 146.5, 135.9, 134.7, 132.7, 130.6, 129.8, 129.4, 129.0, 123.8, 122.5, 64.0, ,52.4, 46.8.; IR (KBr, neat) 2924, 2343, 1697, 1681, 1595, 1583, 1402, 1330, 1277, 1156, 1097, 986, 843, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{34}H_{27}N_2O_4$ $(M + H)^+$ 527.1965, found 527.1989.

(8S,8*a*S,16S,16*a*S)-8,16-bis(4-methylbenzoyl)-8,8*a*,16,16*a*-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (24b):



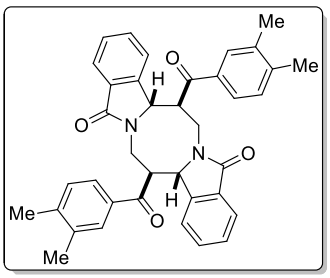
Orange solid; R_f (hexane/EtOAc, 1:1) 0.50; mp 197-199 °C Yield 75 mg, 55%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 6.0 Hz, 1 H), 7.78 (d, *J* = 6.0 Hz, 2 H), 7.68 (d, *J* = 5.2 Hz, 1 H), 7.63 (d, *J* = 6.0 Hz, 2 H), 7.44 (t, *J* = 6.0 Hz, 1 H), 7.40 – 7.35 (m, 2 H), 7.29 - 7.23 (m, 5 H), 7.14 – 7.09 (m, 3 H), 5.50 (d, *J* = 8.0 Hz, 1 H), 5.20 (t, *J* = 8.0 Hz, 1 H), 5.16 (s, 1 H), 4.97 (d, *J* = 12.8 Hz, 1 H), 4.62 (dd, *J* = 11.6 and 6.4 Hz, 1 H), 4.18 (dd, *J* = 12.8 and 6.4 Hz, 1 H), 4.09 (t, *J* = 10.0 Hz, 1 H), 3.66 (t, *J* = 7.6 Hz, 1 H), 2.38 (s, 3 H), 2.34 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.1, 197.9, 170.1, 168.2, 145.6, 145.5, 144.6, 142.2, 135.2, 132.7, 132.6, 131.7, 131.5, 131.2, 130.1, 129.4, 129.0, 128.6, 128.4, 124.1, 123.9, 123.6, 122.6, 64.1, 57.9, 52.1, 46.3, 44.1, 41.9, 21.9, 21.8.; IR (KBr, neat) 2957, 2511, 1798, 1697, 1667, 1605, 1468, 1293, 1202, 1181, 1071, 904, 824, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{36}H_{31}N_2O_4$ $(M + H)^+$ 555.2278, found 555.2289.

(8S,8*a*S,16S,16*a*S)-8,16-bis(4-methoxybenzoyl)-8,8*a*,16,16*a*-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (24c):



Orange solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 290-292 °C Yield 77 mg, 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.4 Hz, 4 H), 7.78 (d, *J* = 7.6 Hz, 2 H), 7.36 (m, 4 H), 7.07 (d, *J* = 8.4 Hz, 4 H), 7.00 (d, *J* = 7.6 Hz, 2 H), 5.39 (d, *J* = 9.6 Hz, 2 H), 4.33 (d, *J* = 14.4 Hz, 2 H), 4.22 (t, *J* = 10.4 Hz, 2 H), 3.90 (s, 6 H), 3.79 (dd, *J* = 14.4 and 10.4 Hz, 2 H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 198.7, 171.4, 164.9, 146.6, 132.6, 132.3, 130.7, 129.0, 128.9, 123.7, 122.6, 114.6, 64.1, 55.8, 52.1, 46.9.; IR (KBr, neat) 2965, 2349, 1685, 1665, 1592, 1570, 1400, 1330, 1257, 1177, 1019, 946, 838, 732 cm^{-1}; HRMS (ESI) calcd. for $C_{36}H_{31}N_2O_6$ $(M + H)^+$ 587.2177, found 587.2179.

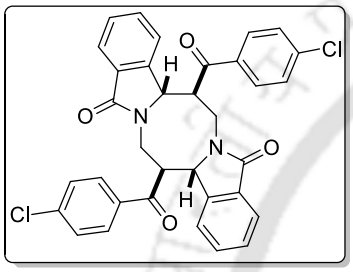
(8S,8*a*S,16S,16*a*S)-8,16-bis(3,4-dimethylbenzoyl)-8,8*a*,16,16*a*-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (24d):



White solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 220-222 °C Yield 70 mg, 48%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 6.0 Hz, 1 H), 7.70 - 7.65 (m, 1 H), 7.46 (s, 2 H), 7.39 - 7.33 (m, 3 H), 7.26 (s, 2 H), 7.24 – 7.21 (m, 3 H), 7.13 (d, J = 6.0 Hz, 1 H), 7.06 (s, 1 H), δ 5.50 (d, *J* = 8.4 Hz, 1 H), 5.21 – 5.16 (m, 2 H), δ 4.95 (d, *J* = 12.8

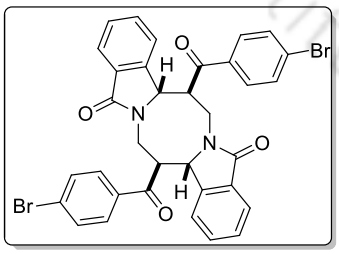
Hz, 1 H), 4.66 – 4.60 (m, 1 H), 4.19 – 4.10 (m, 2 H), 3.68 – 3.62 (m, 1 H), 2.30 (s, 6 H), 2.27 (s, 6 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 199.1, 198.9, 170.1, 168.1, 146.1, 145.5, 142.2, 139.2, 139.1, 138.3, 138.0, 136.3, 135.3, 135.2, 132.7, 132.5, 131.7, 131.3, 131.2, 129.1, 128.5, 128.6, 126.7, 125.9, 124.0, 123.9, 123.6, 122.7, 64.3, 57.9, 52.2, 46.8, 44.0, 41.9, 29.9, 29.5, 21.4, 21.3.; IR (KBr, neat) 2923, 2854, 1677, 1595, 1466, 1404, 1350, 1304, 1183, 1097, 986, 842, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{38}H_{35}N_2O_4$ $(M + H)^+$ 583.2591, found 583.2597.

(8S,8*a*S,16S,16*a*S)-8,16-bis(4-chlorobenzoyl)-8,8*a*,16,16*a*-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (24e):



Yellow gum; R_f (hexane/EtOAc, 2:3) 0.50; mp 270-272 ^{o}C Yield 64 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 7.69 – 7.66 (m, 1 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.50 – 7.39 (m, 4 H), 7.38 – 7.31 (m, 2 H), 7.29 – 7.24 (m, 3 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 5.50 (d, *J* = 10.4 Hz, 1 H), 5.16 (s, 2 H), 4.94 (d, *J* = 16.0 Hz, 1 H), 4.64 – 4.58 (m, 1 H), 4.22 – 4.13 (m, 2 H), 3.61 (dd, *J* = 10.4 and 8.0 Hz, 1 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 197.4, 197.3, 170.1, 168.1, 145.4, 141.9, 141.4, 140.2, 136.2, 133.4, 132.9, 131.8, 131.1, 130.3, 129.9, 129.5, 129.3, 129.1, 128.9, 124.3, 124.2, 124.1, 123.4, 122.6, 64.0, 57.9, 52.4, 46.8, 44.0, 41.6.; IR (KBr, neat) 2854, 2357, 1683, 1642, 1585, 1468, 1400, 1298, 1215, 1095, 1076, 969, 842, 722 cm^{-1}; HRMS (ESI) calcd. for $C_{34}H_{25}Cl_2N_2O_4$ $(M + H)^+$ 595.1186, found 595.1188.

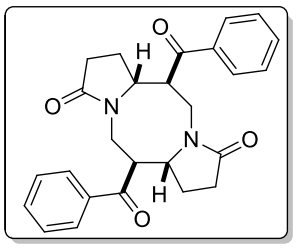
(8S,8*a*S,16S,16*a*S)-8,16-bis(4-bromobenzoyl)-8,8*a*,16,16*a*-tetrahydro-[1,5]diazocino[2,1-*a*:6,5-*a*']diisoindole-5,13(7*H*,15*H*)-dione (24f):



Yellow solid; R_f (hexane/EtOAc, 2:3) 0.40; mp 284-286 ^{o}C Yield 74 mg, 43%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.0 Hz, 1 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 7.70 - 7.63 (m, Hz, 2 H), 7.60 (d, *J* = 8.5 Hz, 2 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 7.50 – 7.42 (m, 3 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.36 – 7.33 (m, 1 H), 7.28 – 7.25 (m, 1 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 5.50 (d, *J* = 10.5 Hz, 1 H), 5.18 (d, *J* = 12.5 Hz, 2 H), 4.93 (d, *J* = 16.5 Hz, 1 H), 4.63 – 4.56 (m, 1 H), 4.21 – 4.08 (m, 2 H), 3.62 (t, *J* = 8.5 Hz, 1 H).$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 197.6, 197.5, 170.1, 168.1, 145.3, 141.8, 136.5, 133.7, 132.9, 132.8, 132.0, 131.8, 131.4, 131.0, 130.3, 130.1, 129.6, 129.3, 129.0, 128.9, 124.2, 124.1, 123.3, 122.6, 63.9, 57.8, 52.2, 46.7, 43.9, 41.5.; IR (KBr, neat) 2854, 2367, 1673, 1642, 1583, 1468, 1430, 1287, 1215,

1115, 1076, 969, 844, 732 cm^{-1}; HRMS (ESI) calcd. for $C_{34}H_{25}Br_2N_2O_4$ $(M + H)^+$ 683.0176, found 683.0192.

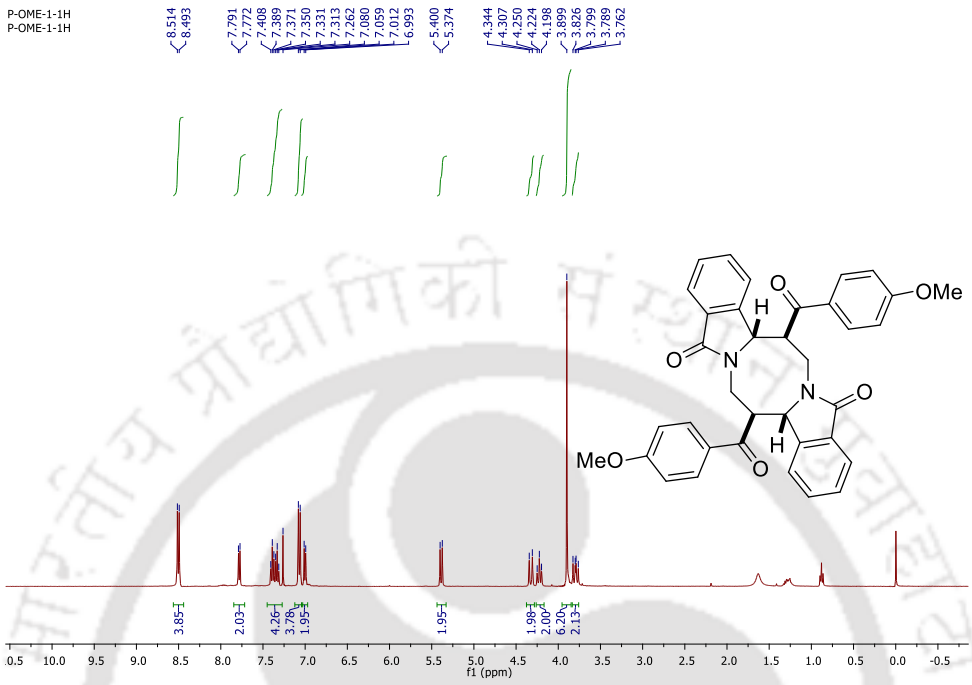
(6S,6*a*R,12S,12*a*R)-6,12-dibenzoyloctahydrodipyrrolo[1,2-*a*:1',2'-*e*][1,5]diazocine-3,9(2*H*,5*H*)-dione (24h):



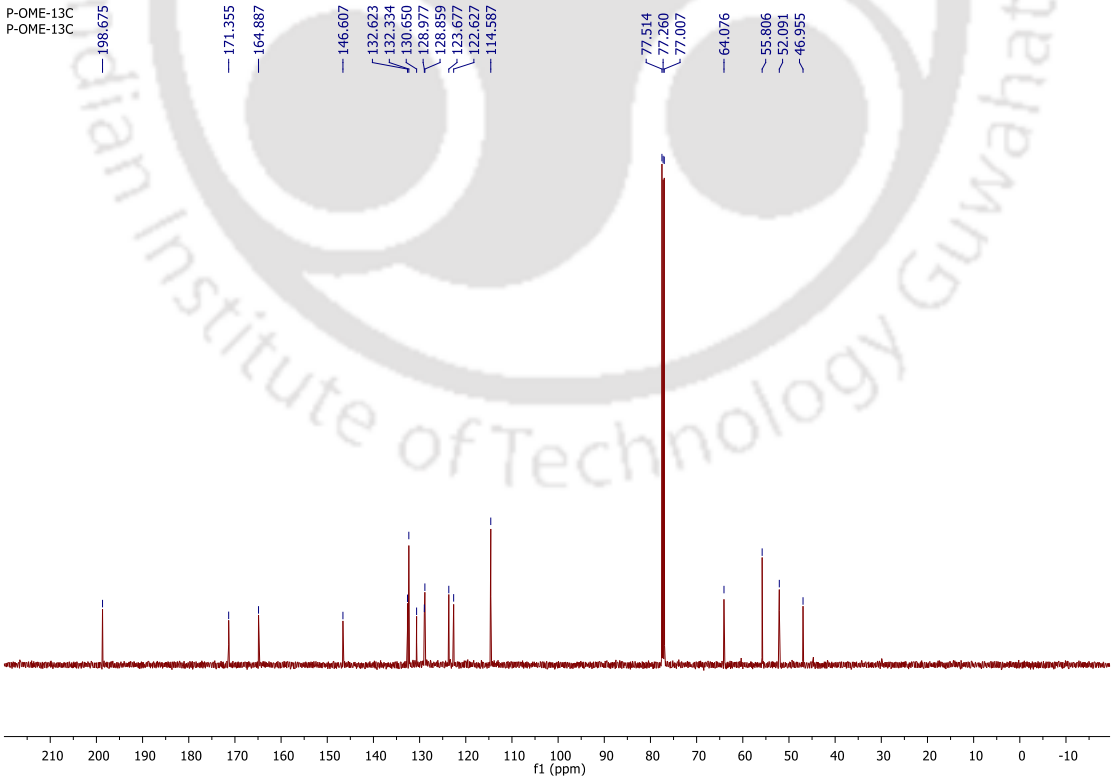
Yellow gum; R_f (hexane/EtOAc, 3:7) 0.50; Yield 56 mg, 52%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.5 Hz, 2 H), 7.91 (d, *J* = 9.5 Hz, 2 H), 7.62 (t, *J* = 9.0 Hz, 1 H), 7.55 – 7.50 (m, 3 H), 7.44 (t, *J* = 9.0 Hz, 2 H), 4.43 – 4.39 (m, 1 H), 4.22 – 4.16 (m, 1 H), 4.06 (d, *J* = 9.0 Hz, 1 H), 3.85 – 3.77 (m, 2 H), 3.66 – 3.56 (m, 1 H), 3.52 – 3.42 (m, 1 H), 3.25 – 3.16 (m, 2 H), 2.60 – 2.55 (m, 1 H), 2.54 – 2.50 (m, 1 H), 2.48 – 2.38 (m, 2 H), 2.35 (s, 1 H), 2.32 – 2.21 (m, 2 H) $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 199.7, 198.4, 175.9, 174.2, 136.6, 135.5, 134.3, 133.6, 129.4, 128.9, 128.8, 128.3, 64.7, 59.1, 47.7, 44.8, 42.7, 37.3, 36.9, 30.2, 29.9, 28.6, 21.5.; IR (KBr, neat) 2854, 2343, 1679, 1595, 1402, 1285, 1220, 1161, 1006, 956, 898, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{27}N_2O_4$ $(M + H)^+$ 431.1965, found 431.1966.

4.7 Selected Spectra

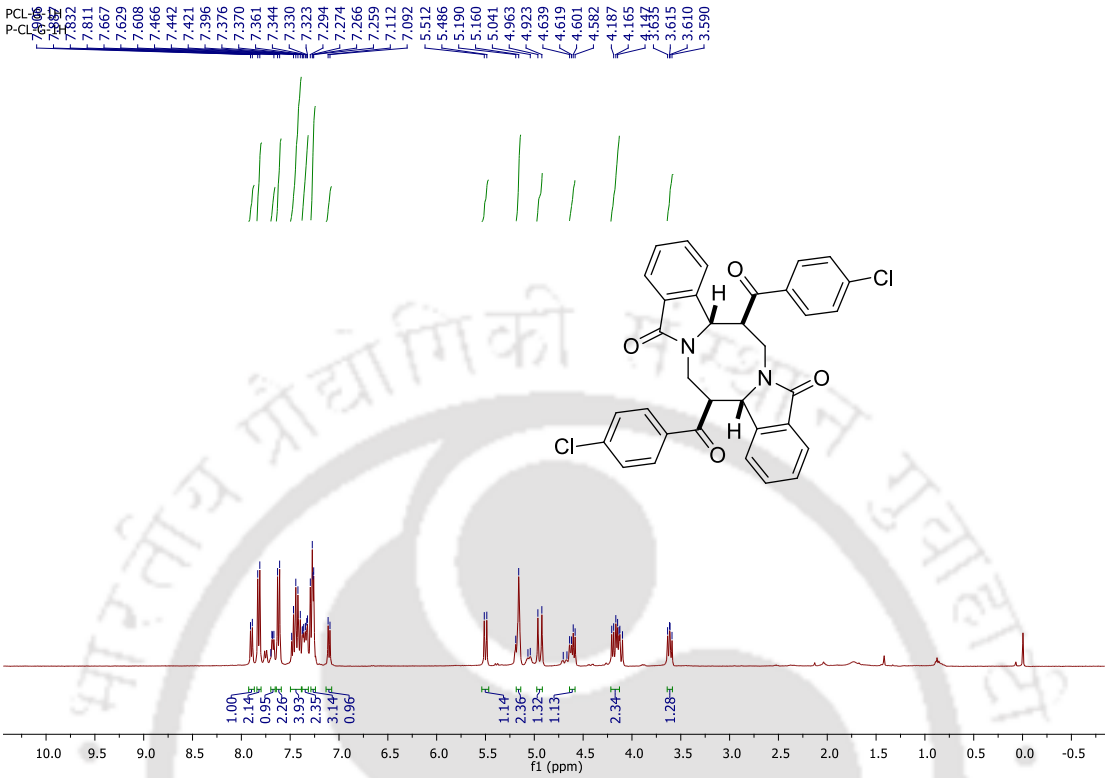
^{1}H spectrum of compound **24c** (400 MHz, $CDCl_3$)



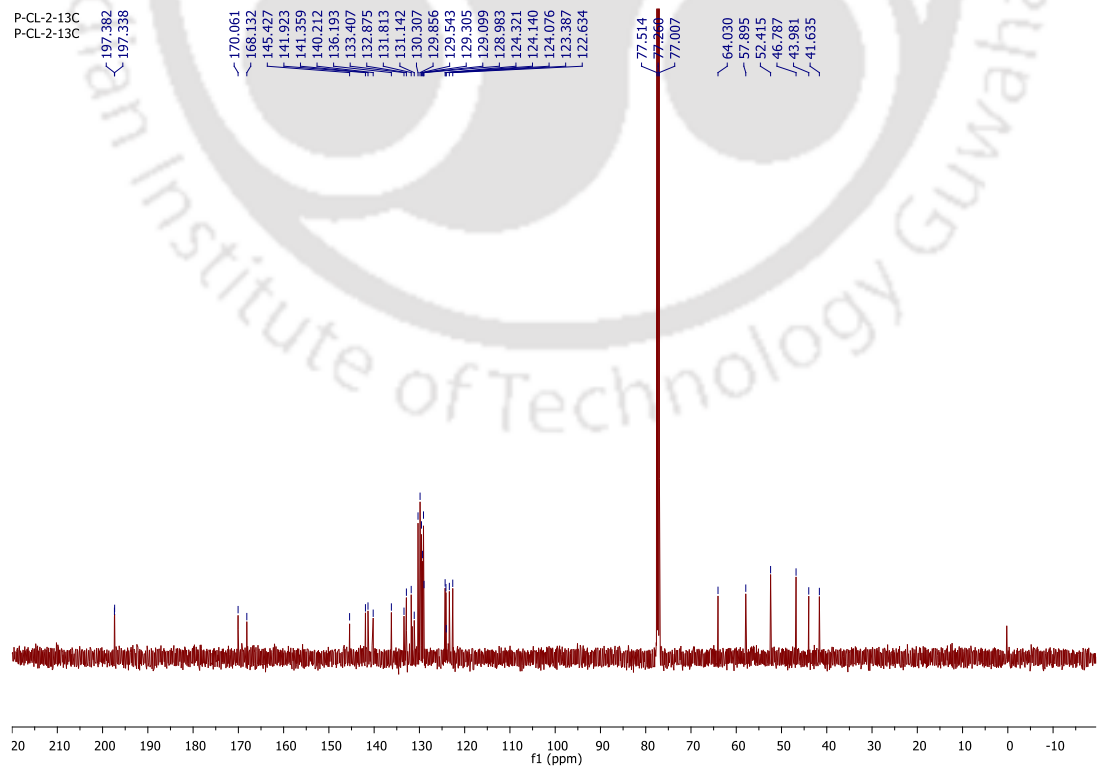
^{13}C{^{1}H } spectrum of compound **24c** (125 MHz, $CDCl_3$)



^{1}H spectrum of compound **24e** (400 MHz, $CDCl_3$)



^{13}C spectrum of compound **24e**(125 MHz, $CDCl_3$)



4.8 Crystal parameters

Table 4.8.1. The crystal parameters of compound **24a**

	CCDC 2131757
Formula	$C_{34}H_{26}N_2O_4$
Formula weight	526.57
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	5.3690(3)
b/Å	13.6673(10)
c/Å	17.5932(12)
α/°	89.856(2)
β/°	89.448(2)
γ/°	86.202(2)
V/Å^3	1288.09(15)
Z	2
Abs. Coeff./mm^{-1}	0.090
Abs. Correction	none
GOF on F^2	1.087
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0519
	wR2 = 0.0914
R indices [all data]	*R1* = 0.1427
	wR2 = 0.1046

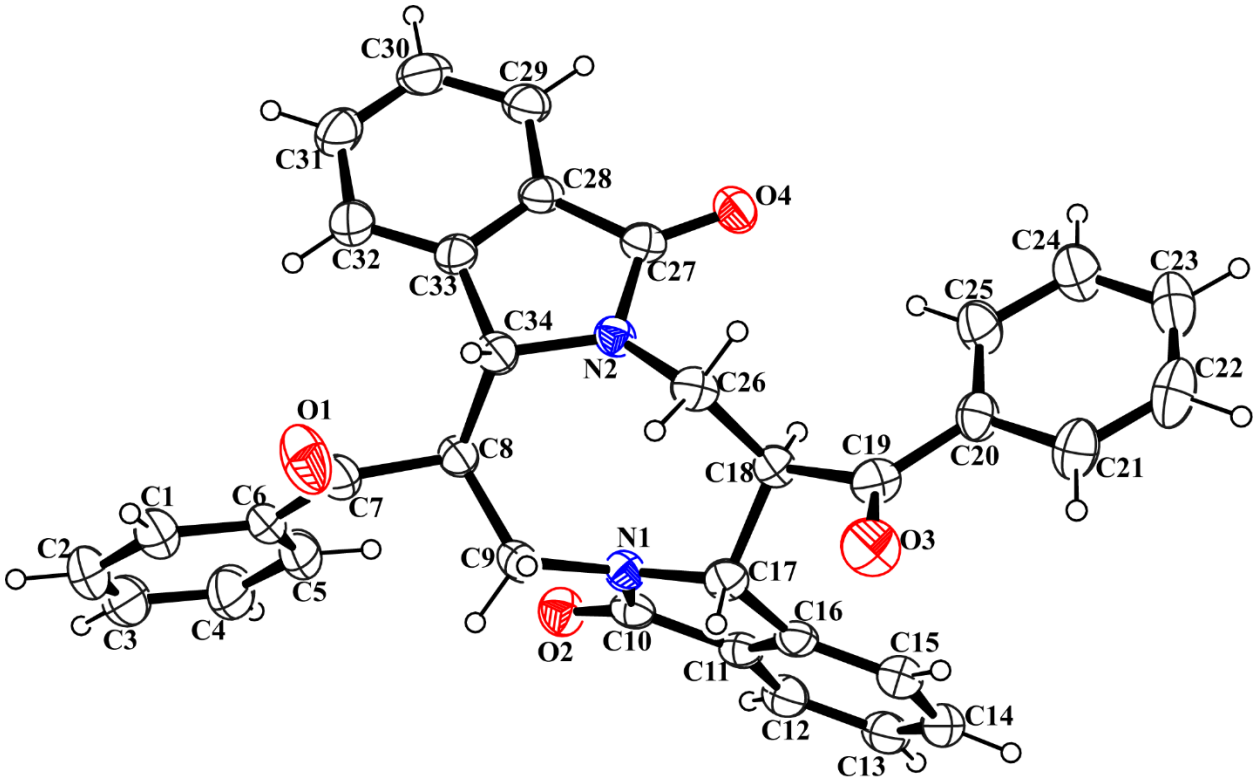


Figure 4.8.1 ORTEP diagram of compound **24a** using thermal ellipsoids of 30% probability

CHAPTER 5

Synthesis of 3*C*-homologated active methylene substituted 2*H*-Indazole Derivatives *via* Sequential Ring Opening of Donor Acceptor Cyclopropanes and Reductive cyclization Reaction

5.1 Introduction

Indazoles are highly privileged scaffolds rarely found in nature.[1a] The structurally diverse indazoles and one of its isomers, 2*H*-indazoles with different functionalities has showed many pharmacological and therapeutical properties,[1] such as, anticancer,[2a] antiangiogenic,[2b] antitumor,[2c] antiatherosclerotic,[2d] 5-HT_{1A}[2e] receptor etc.[2] More interestingly, a few 3*C*-alkylated 2*H*-indazole motifs are clinically approved as promising drug candidates. For example pazopanib (**A**) is used to treat renal cell carcinoma (*Figure 5.1.1*).[3a] Compound **B** is an antiparasitic drug[3b] and ER-16b (**C**) is a selective ligand of estrogen receptor *β*.[3c] Similarly, 3-propanamide substituted 2*H*-indazole (**D**) act as an agonist for G-protein coupled niacin receptor 109A.[3d] (*Figure 5.1.1*).

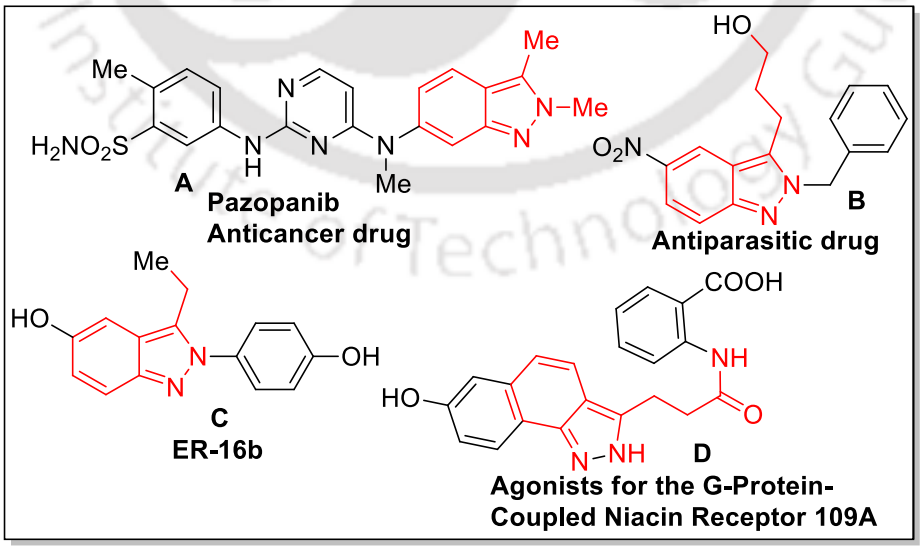
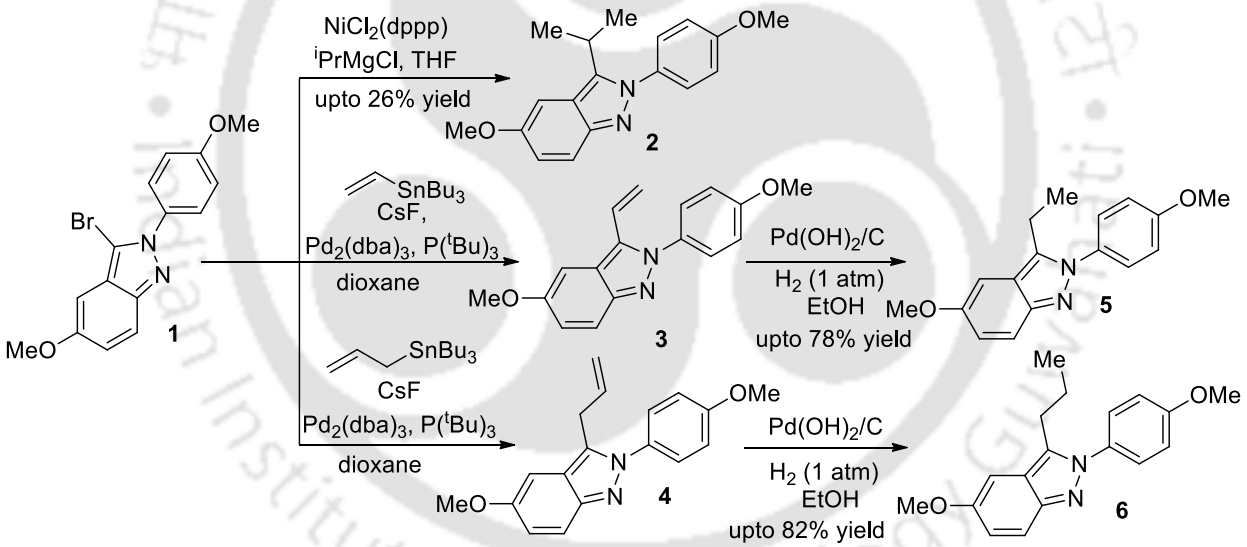


Figure 5.1.1: Biologically active 3*C*-alkylated 2*H*-indazole scaffolds

Various methods have been developed for the construction of 2*N*,3*C*-substituted 2*H*-indazoles in last two decades.[1b,4] However, literature methods for 3*C*-alkylated 2*H*-indazoles are rarely encountered and these are enlisted below.

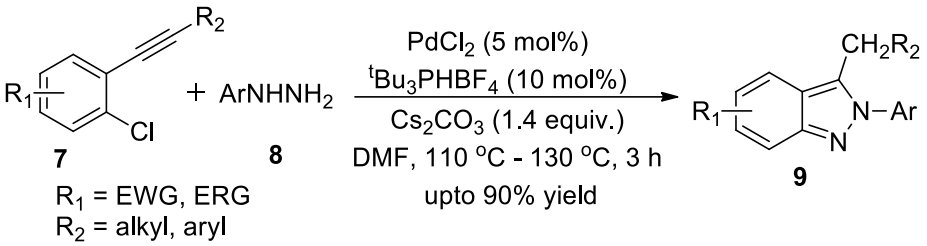
5.2 Literature methods for 3*C*-alkylated 2*H*-indazoles

Traditionally, 3*C*-alkylated 2*H*-indazoles were synthesized *via* transition metal catalyzed Kumuda coupling as well as Stille coupling reactions by using 3-halo substituted 2*H*-indazoles as starting precursors. For example, 3-bromo substituted 2*H*-indazole (**1**) with ^{i}PrMgCl under Ni(II) catalysed Kumuda coupling reaction resulted in 3-isopropyl-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (**2).** Same as, Pd(0) catalyzed Stille coupling reaction by using vinyl/allyl stannanes followed by hydrogenation gave 3*C*-ethyl/propyl substituted 2*H*-indazoles (**5/6**) (*scheme 5.2.1*).[5]



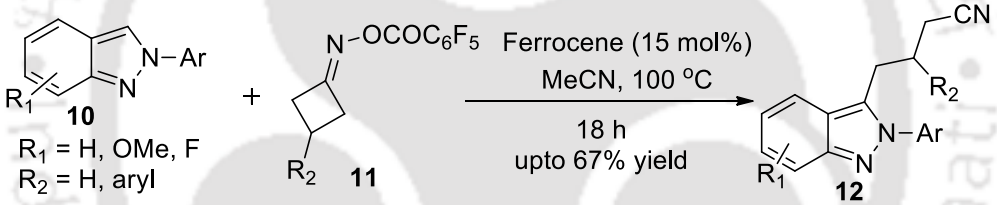
Scheme 5.2.1

An efficient $PdCl_2$ and base catalyzed, one-pot domino regioselective cross-coupling followed by intramolecular hydroamination/isomerization reaction of 2-halophenylacetylenes **7** and hydrazines **8** resulted in 3*C*-alkylated aromatic 2*H*-indazoles **9** was reported by Linden Schmidt and his group in 2009 (*Scheme 5.2.2*).[6]



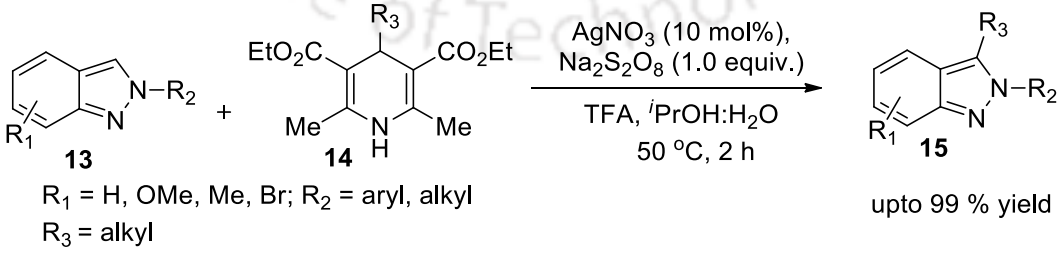
Scheme 5.2.2

In 2019, Duan and group reported a methodology for regioselective 3*C*-cyanoalkylation of 2*H*-indazoles from pre-synthesised 2*H*-indazoles **10** and cyclobutanone oxime esters **11** in presence of iron(II) catalyst. The reaction mechanism explains that, initial generation of iminyl radical *via* single-electron reduction of cyclobutanone oxime ester catalyzed by Fe(II), which subsequently involved in *C*-*C* bond cleavage providing a cyanoalkyl radical which is the key step for the formation of compounds **12** (*scheme 5.2.3*).[7]



Scheme 5.2.3

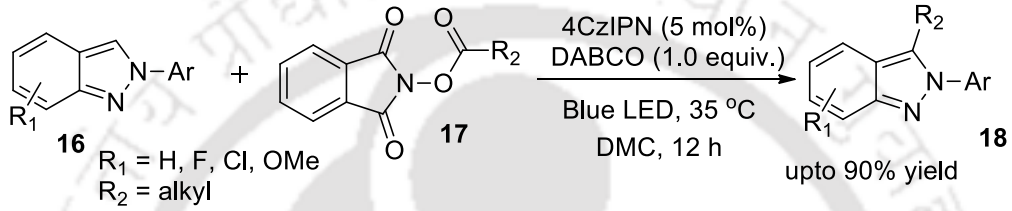
Tan and his group explored regioselective 3*C*-alkylation of 2*N*-substituted 2*H*-indazoles **13** by using substituted 1,4-dihydropyridines **14** as alkylating source in presence of catalytic $AgNO_3$, sodium persulfate as oxidant and TFA. The reaction was initiated by $Na_2S_2O_8$ mediated SET



Scheme 5.2.4

oxidation of substituted 1,4-dihydropyridines to form the corresponding radical species, that added up to protonated 2*H*-indazoles followed by oxidation afforded target compounds **15** (*scheme 5.2.4*).[8]

In the same year, photocatalytic decarboxylative 3-alkylation reaction of 2-aryl-2*H*-indazoles **16** was developed by Yu and co-workers under visible-light irradiation to provide 3*C*- alkylated 2*H*-indazoles **18** implementing alkyl *N*-hydroxyphthalimide esters **17** as alkylating reagents in excellent yields (*scheme 5.2.5*).[9]



Scheme 5.2.5

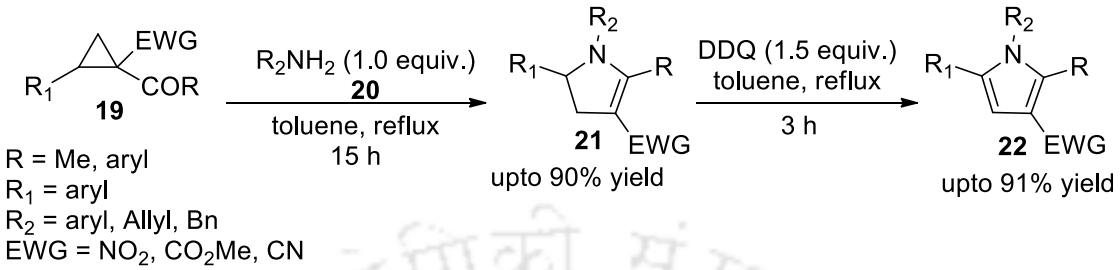
On the other hand, owing to the high ring strain donor–acceptor cyclopropanes (DACs) are well-known reactive molecular entities in modern organic synthesis and they have been extensively utilized in ring opening,[10a-b] ring expansion reactions,[10a] annulations[10a-d] and rearrangements[10b,10e] as well, to provide various ring sized carbo-/heterocyclic compounds and biologically active molecules.[10]

The nucleophilic ring opening (NRO) reaction of DACs have been widely studied with various nucleophiles.[11] Among them, primary arylamines are more commonly used which along with concomitant cyclisation with additional functionalities have been gaining significant attention for building various *N*-containing compounds in recent years. Here are a few examples that cites the formation of different *N*-containing heterocycles shown below.

5.3 Literature survey on construction of *N*-heterocycles from DACs with primary arylamines

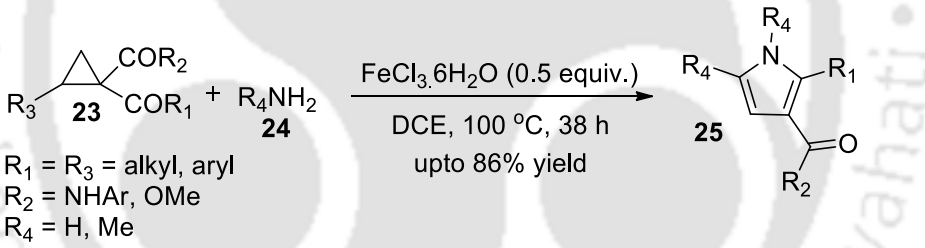
Charette and co-workers developed a protocol for the regiospecific synthesis of dihydropyrroles **21** using ring opening reaction of doubly activated cyclopropanes **19** with primary amines **20** in

good yields. Further oxidation of dihydropyrroles yielded multi-functionalized pyrroles **22** (*Scheme 5.3.1*).[12]



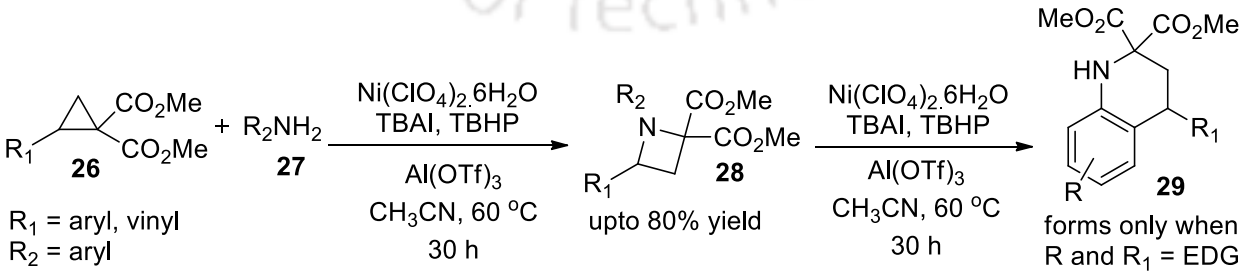
Scheme 5.3.1

Similarly, doubly activated cyclopropanes **23** and substituted anilines **24** were used as starting precursors by Zhang and co-workers to synthesize multi-substituted pyrrole derivatives **25** in presence of Fe(III) catalyst. The reaction proceeds in a domino reaction fashion involving a sequential ring-opening, cyclization, and dehydrogenation reactions (*Scheme 5.3.2*).[13]



Scheme 5.3.2

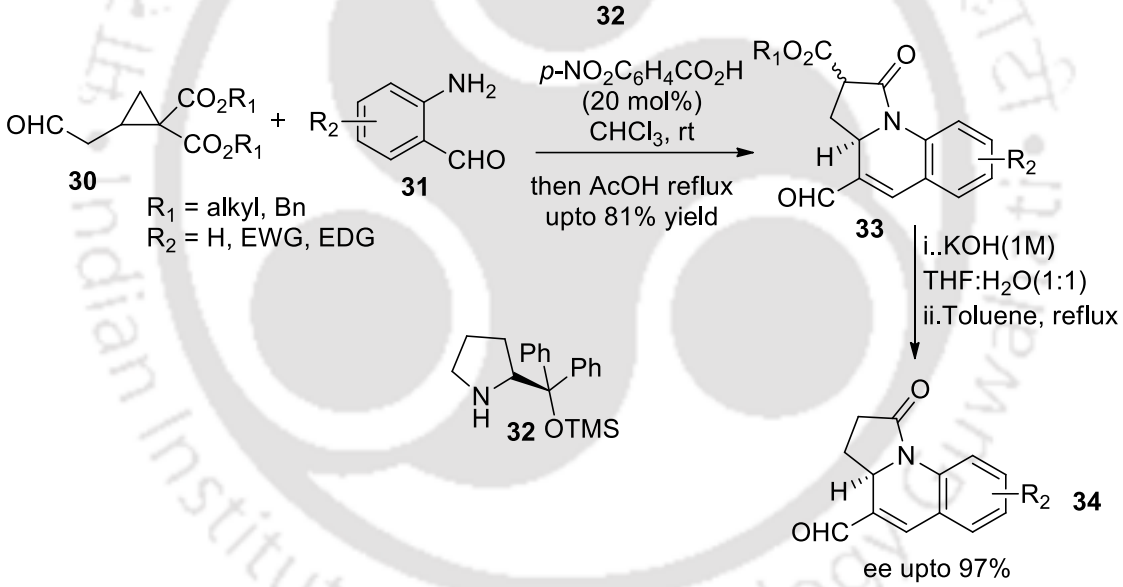
A relay catalysis strategy involving catalytic [3+1]-annulation reaction between cyclopropane 1,1-diester **26** and aromatic amines **27** was developed by Luo and group to synthesize substituted



Scheme 5.3.3

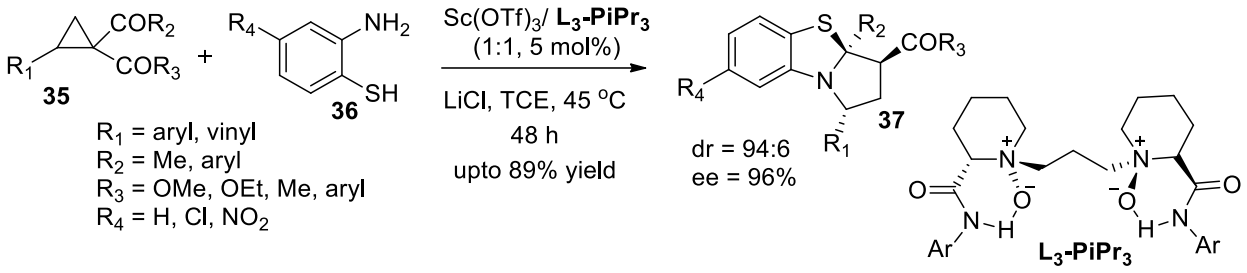
azetidines **28** in presence of Ni(II) and TBAI/TBHP (tetrabutylammonium iodide/tert-butyl hydroperoxide). The key steps of this strategy involves, $Ni(ClO_4)_2.6H_2O$ catalyzed NRO (nucleophilic ring-opening) reaction with subsequent (hypo)iodite and TBAB (tetrabutylammonium bromide) mediated intramolecular *C-N* bond formation reaction to install compound **28**. Further, the azetidine derivatives were successfully converted into tetrahydroquinolines **29** under same Lewis acidic conditions (*Scheme 5.3.3*).[14]

Vicario and his group demonstrated a straight forward synthesis of substituted pyrrolo-[1,2-*a*]quinolines **33** from cyclopropaneacetaldehydes **30** and *o*-amino benzaldehydes **31** through a domino cyclopropane ring opening, aza-Michael and aldol reaction followed by acid-promoted lactamization. Moreover, further hydrolysis and decarboxylation of compound **33** provided enantioselective pyrroloquinolines **34** with enantiomeric excess of about 97% (*Scheme 5.3.4*).[15]



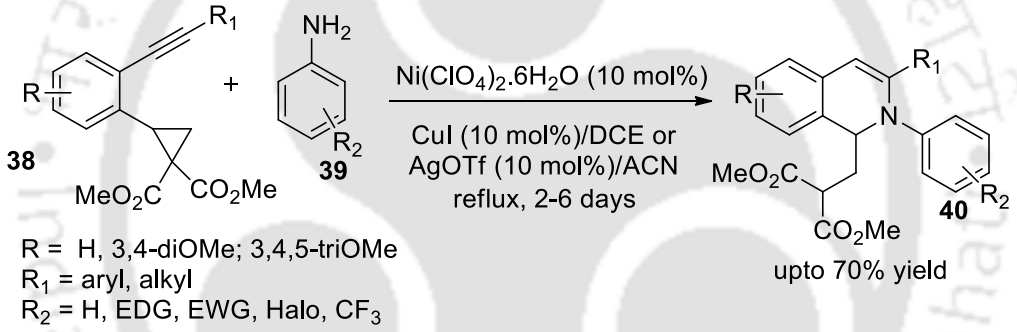
Scheme 5.3.4

Feng and his group synthesized enantiomerically pure benzothiazole derivatives **37** from cyclopropyl ketones **35** and 2-aminothiophenol **36** employing a $Sc(OTf)_3$ and chiral *N*,*N*-dioxide-scandium(III) complex as a catalyst. The reaction is shown to follow ring-opening, cyclization and thio-Michael cascade cyclization reactions (*Scheme 5.3.5*).[16]



Scheme 5.3.5

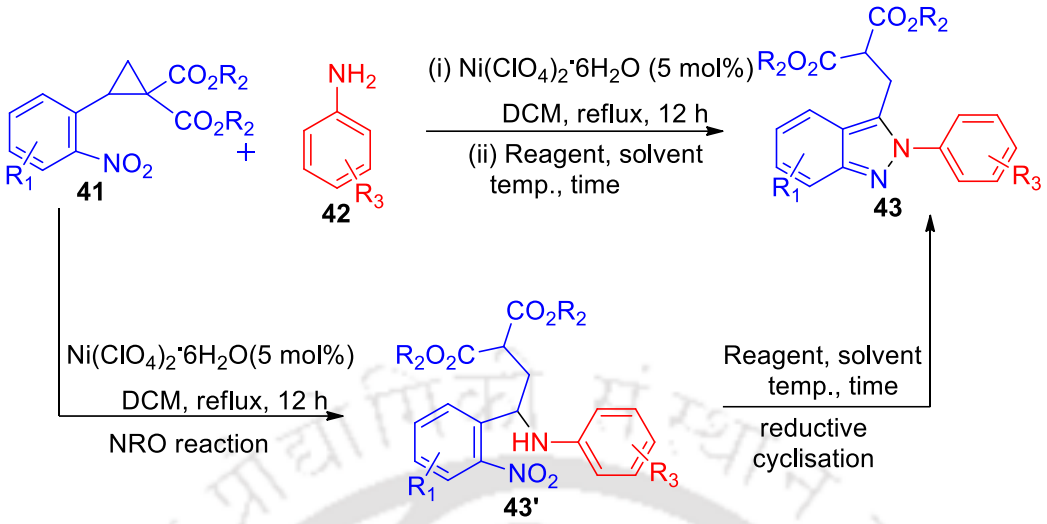
Very recently, Reddy and his group implemented a concise approach to synthesize substituted 1,2-dihydroisoquinolines **40** *via* double nucleophilic addition of primary arylamines **39** to *o*-alkynyl donor–acceptor cyclopropanes **38** in the presence of a catalytic $Ni(ClO_4)_2 \cdot 6H_2O$ and CuI/AgOTf system (*Scheme 5.3.6*). [17]



Scheme 5.3.6

5.4 Results and Discussions

Based on literature survey, it could be seen that 3*C*-alkylated 2*H*-indazoles are not yet synthesized by utilizing DACs. Also the existing literature for synthesizing 3*C*-alkylated 2*H*-indazoles suffer from major drawbacks such as, the use of expensive metal catalyst like Pd, require pre-synthesized indazoles and multistep process. Our interest was additionally stimulated looking at the conclusive medicinal applications due to the *C*-3 alkylations of 2*H*-indazoles. Thus, we anticipate that, new substitution pattern in the alkyl group at *C*-3 position would



Scheme 5.4.1

enhance their biological properties and hence assist in drug discovery. In this regard, development of new methodologies for synthesis of 3*C*-alkylated 2*H*-indazoles are always in high demand.

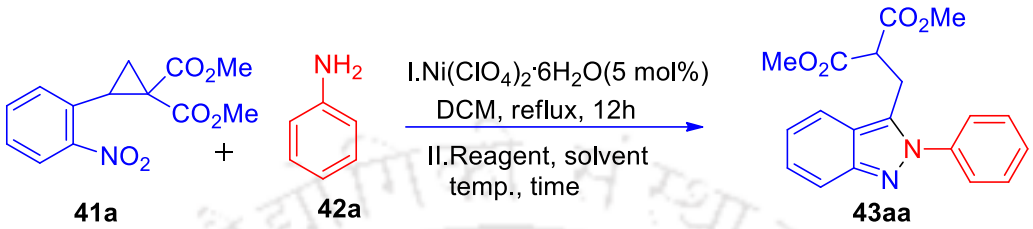
In pursuit of synthesizing nitrogen heterocycles as per our continuing interest,[18] we envisioned that *o*-nitro having DACs **41** could undergo ring-opening reaction with primary arylamines **42** in presence of $Ni(ClO_4)_2.6H_2O$ and further can be cyclized to get 3*C*-alkylated 2*H*-indazoles **43** (*scheme 5.4.1*).

Thus, in this chapter we report a facile sequential protocol for the synthesis of 2*H*-indazoles containing 3*C*-homologated active methylene *via* $Ni(ClO_4)_2.6H_2O$ catalysed NRO reaction of *o*-nitro aryl compounds having DACs with arylamines followed by $SnCl_2.2H_2O$ mediated reductive cyclisation reaction. Moreover, homologated active methylene side-chain could be further manipulated into other functionalities which add to its advantage.

Since the success of NRO reactions of DACs and arylamines with nickel catalyst is demonstrated evidently[19] for preliminary investigation, we used dimethyl 2-(2-nitrophenyl)cyclopropane-1,1-dicarboxylate (**41a**) and anilne (**42a**) as our model substrates. As presumed, With the use of 5mol% $Ni(ClO_4)_2.6H_2O$ in DCM at 40 ^oC the ring opening product dimethyl 2-(2-(2-

nitrophenyl)-2-(phenylamino)ethyl)malonate (**43aa′**) was obtained in 93% yield (*Scheme 5.4.1*). Compound **43aa′** was then treated with 2.0 equivalents of $SnCl_2.2H_2O$ in MeOH at 40 °C under

Table 5.4.1 Optimization of the reaction[a]



41a **42a** **43aa**

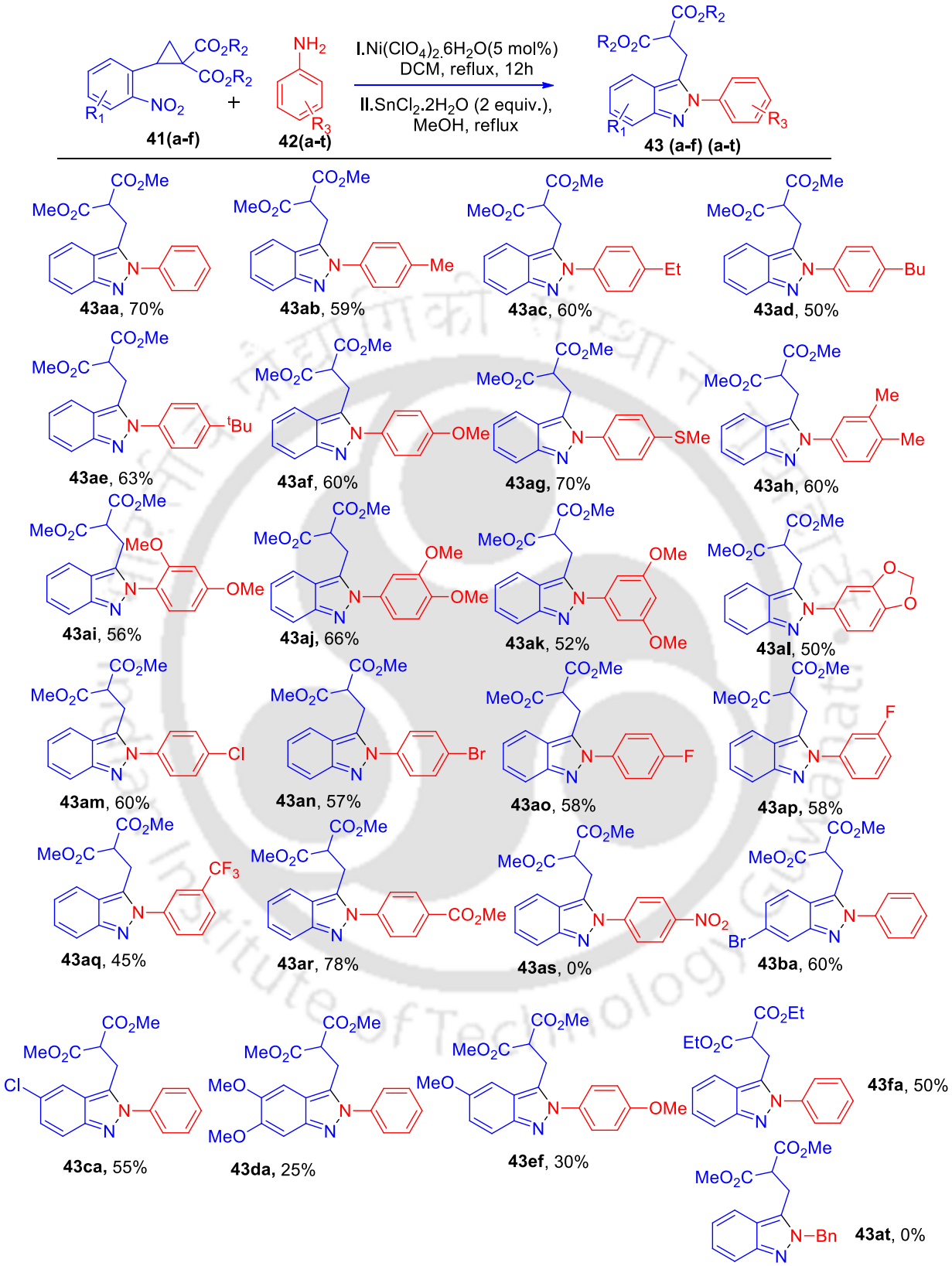
Entry	Reagent	(in equiv.)	Solvent	Temp.	Time (h)	Yield[b](%)
1	$SnCl_2·2H_2O$	2.0	MeOH	40	12	15
2	$SnCl_2·2H_2O$	2.0	MeOH	reflux	12	25
3[c]	**$SnCl_2·2H_2O$**	**2.0**	**MeOH**	**reflux**	**5**	**70** **64[f]**
4[c]	$SnCl_2·2H_2O$	2.0	EtOH	reflux	12	68
5[c]	$SnCl_2·2H_2O$	4.0	MeOH	reflux	12	65
6[c]	$SnCl_2·2H_2O$	1.0	MeOH	reflux	12	40
7	Zn	6.0	EtOH:H_2O(2:1)	reflux	5	nr
8[c]	Zn/$TiCl_4$	1.0,2.0	Et_3N/THF(1:2)	reflux	12	30
9[c]	Zn/$HCOONH_4$	5.0,1.0	Toluene	reflux	8	e[d]
10[c]	P(n-Bu)$_3$	5.0	Toluene	reflux	12	40
11	P(OEt)$_3$	5.0	MeOH	rt	12	21

[a]All the reactions carried out in (0.3 mmol) **41a**, (0.33 mmol) **42a** in 3.0 mL solvent, [b]Isolated yields, c = N_2 atmosphere, nr = No reaction, [d]e = Decomposed, f = Gram scale synthesis with **41a** (1g)

air, to our delight dimethyl 2-((2-phenyl-2*H*-indazol-3-yl)methyl)malonate (**43aa**) was formed in 20% yield. Encouraged by this result, we investigated for a sequential reaction procedure where the ring opening product was subjected to reductive cyclization without any further purification and the desired product formed successfully in 15 % yield (*Table 5.4.1*, entry 1). From these findings, we focused on increasing yield of reductive cyclisation step. There was no satisfactory increment in yield was observed even though temperature was raised to its reflux conditions (entry 2). To our surprise, a sudden rise in the yield was noted when the same reaction was carried out under nitrogen atmosphere (entry 3). With further elevation in temperature with

switching solvent from MeOH to EtOH, similar yield was noticed (entry 4). To our dismay, the yield of the reaction reduced to 65 and 40 % respectively, with changing the load of reagent from 2.0 equivalents to 4.0 and 1.0 equivalents (entries 5-6). Examination with other reducing agents like Zn was proved inefficient for this transformation (entries 7). Whereas, the concomitant use of $TiCl_4$, Zn and base in THF under reflux conditions furnished product **43aa** in 30% yield (entry 8). On the contrary, combination of Zn and $HCOONH_4$ gave decomposed products (entry 9). Furthermore, organophosphorus reagents were able to produce the target in very low yield (entries 10-11). From all the above discussed results, entry 3 of *Table 5.4.1* is the optimum reaction conditions. The scalability of the present method was determined from a gram scale synthesis carried out under standard reaction conditions to give compound **43aa** in 64% yield (*Table 5.4.1*, entry 3).

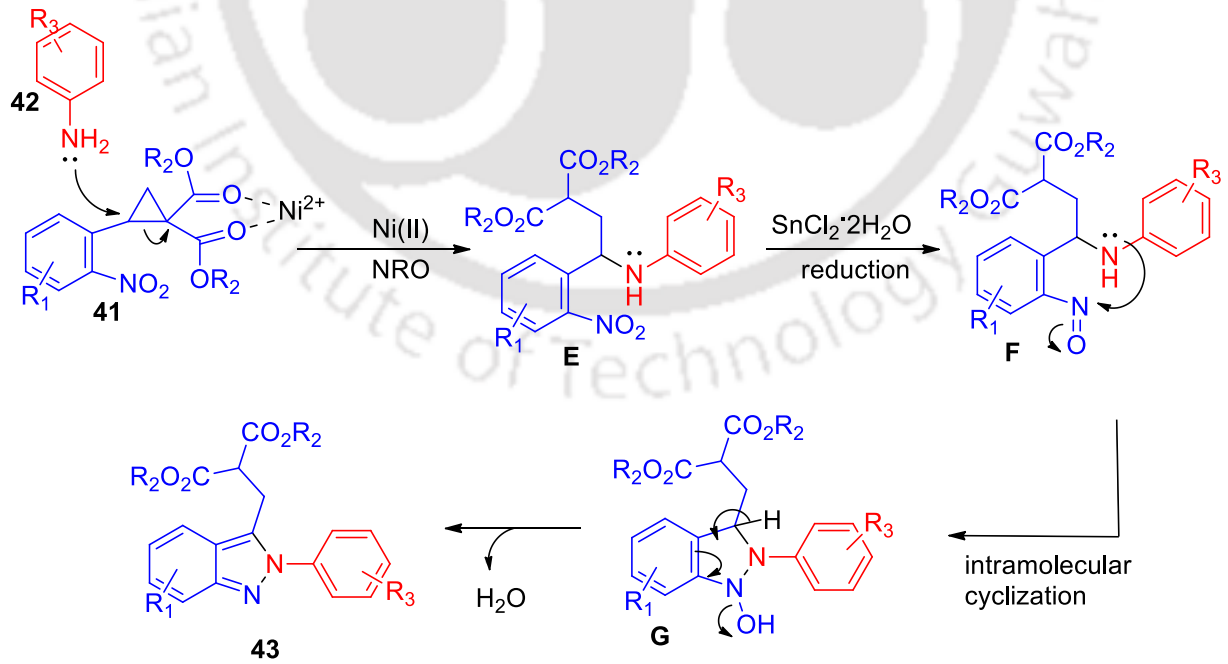
With this optimum conditions, the scope of the reaction was explored with variety of primary aromatic amines as well as differently substituted *o*-nitro DACs that are summarized in *scheme 5.4.2*. Initial investigations were started using various aromatic amines with **41a**. It was observed that, the reaction proceeds well with anilines having both electron-donating as well as electron-withdrawing groups at different positions of the aromatic ring. Electron rich groups at the *para* position such as 4-Me, 4-Et, 4-OMe and 4-SMe in anilines produced the corresponding products **43ab**, **43ac, 43af** and **43ag** in 59-70% yields. Similarly, both straight/branched alkyl chain having anilines **42d** and **42e** successfully produced desired products **43ad** and **43ae** in good yields. In continuation, disubstituted arylamines such as 3,4-Me, 2,4-OMe, 3,4-OMe and 3,5-OMe **42h-42k** smoothly provided **43ah-43ak** in moderate to good yields as shown in *scheme 5.4.2*. Fused aniline like 3,4-(methylenedioxy)aniline (**42l**) also gave product **43al** in 50% yield. Substituted anilines with moderate electron withdrawing groups at *para*- as well as *meta*-positions **42m-42p** provided the anticipated products **43am-43ap** up to 60% yield whereas, 3-(trifluoromethyl)aniline (**42q**) resulted in **43aq** with 45% of yield. Reaction of **42r** with **41a** furnished **43ar** in good yields. However, strong electron withdrawing group having *p*-nitro aniline (**42s)** failed to give desired product **43as**, even no ring opening product was observed, which is due to the deactivation of aniline by nitro group. To our pleasure, reaction of chloro- and bromo substituted *o*-nitro DACs **41b** and **41c** with aniline deliberately delivered product **43ba** and **43ca** in 60 and 55% yields, respectively. On the other hand, electron-donating methoxy



Scheme 5.4.2 Synthesis of 3*C*-homologated active methylenes having 2*H*-indazole

group on aromatic ring of substituted *o*-nitro DAC **41d** with **42a** found to hinder reductive cyclisation due to +R effect of methoxy group and henceforth, 25% yield of **43da** was observed. Similarly, reaction of **41e** with 4-methoxyaniline yielded the target product **43ef** in 30% yield only, which is a derivative of biologically active compound **C** (*Figure 5.1.1*). The reaction was also surveyed using other ester functionality, such as diethyl malonate **41f** with **42a** resulted in **43fa** 50% yield. Unfortunately, the reaction of **41a** with benzyl amine (**42t**) was found unsuccessful.The structure of all the compounds was determined with the help of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and finally X-ray crystallographic analysis of **43ag** (*Figure 5.9.1*)**.**[20]

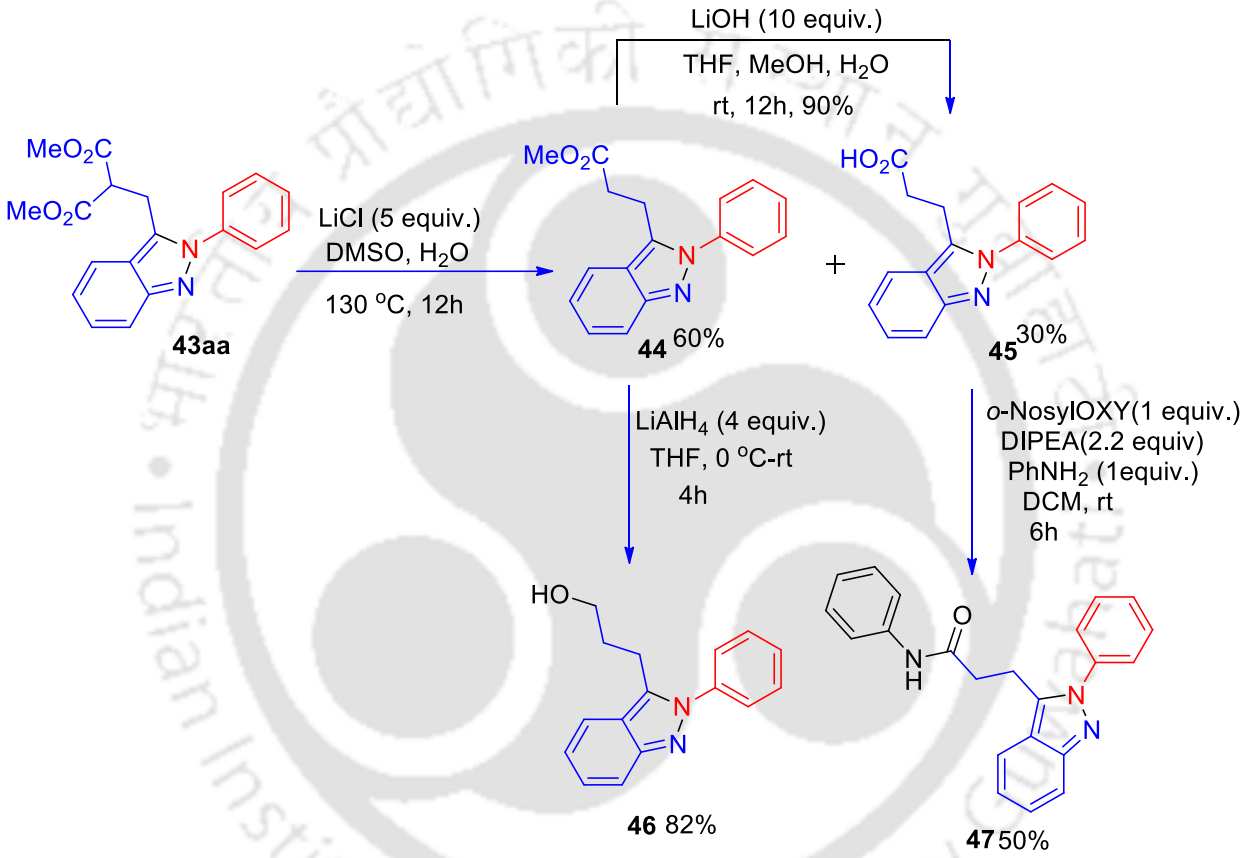
The mechanism is proposed on the basis of previous report (*Scheme 5.4.3*).[19b, 21] Under the Lewis acidic condition, nucleophilic attack of arylamines **42** readily open up *o*-nitro DAC **41** to provide γ-amino ester intermediate **E**. Upon treatment with $SnCl_2.2H_2O$, the intermediate **E** undergoes reduction to produce nitroso intermediate **F**, which undergoes intramolecular nucleophilic attack from amine to generate intermediate **G.** Finally, intermediate **G** involves in aromatization with elimination of water molecule to offer target **43**.



Scheme 5.4.3

5.5 Post synthetic modifications

To demonstrate the practical utility of this method, compound **43aa** was subjected to few post synthetic modifications (*Scheme 5.5.1*). The Krapcho decarboxylation reaction of compound **43aa** produced both decarboxylated product **44** and its hydrolysed product **45**. However, compound **44** can be efficiently hydrolysed into **45** using LiOH. Further compound **44** upon



Scheme 5.5.1 Post synthetic applications

reduction produced 3-indazolyl-propanol **46.** It is worth mentioning that the 3-indazolyl-propanol is a core unit of antiparasitic drug **B** as shown in *Figure 5.1.1*. Moreover, amidation of compound **45** gave 3-indazolyl-propanamide **47** in good yields and the said motif is found in compound **D** (*Figure 5.1.1*). To our delight, current methodology greatly shorten the synthetic

route and improving the overall efficiency for preparing derivative of compound **D** which adds to the advantage of the present methodology.[3d]

Conclusion

In conclusion, a simple and sequential protocol has been developed to synthesize 3*C*-homologated active methylene substituted 2*H*-indazole derivatives from *o*-nitro DACs and primary arylamines in moderate to good yields. The present finding is a direct method for the synthesis of 3*C*-alkylated 2*H*-indazole derivatives in a short route. For further utility, one of the synthesized compounds was extended for few functional group transformations to provide 2*N*-arylated 3-indazolyl-propanoate, propanoic acid, propanols and propanamide. The biological studies of the synthesized compounds are under investigation.

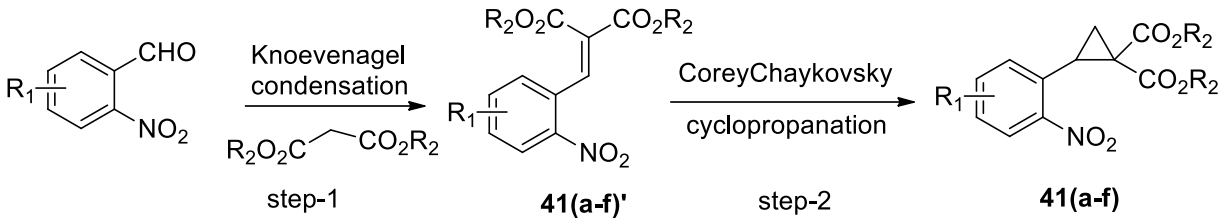
5.6 Experimental Section

5.6.1 Instrumentation and Characterisation

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 500 MHz, 400 MHz) or ^{13}C (150 MHz, 125 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

5.6.2 General procedure for the synthesis of *o*-nitro DACs 41

The corresponding starting materials were synthesized in a two-step procedure *i.e.* Knoevenagal condensation followed by Corey-Chaykovsky cyclopropanation (*Scheme 5.6.2*).



Scheme 5.6.2. Starting material preparation

The starting material *o*-nitro DACs **41a′**,[22] **41f′**,[23] **41a**,[24] was prepared as per the literature procedure and the spectroscopic data are in good agreement with the literature one.

5.6.2.1 General procedure for the synthesis of 41b′-41e′

To a solution of substituted *o*-nitrobenzaldehydes (2.2 mmol, 1.1 equiv.) in benzene (5 mL) at room temperature was added active methylene compound (2.0 mmol, 1.0 equiv.), piperidine (0.4 mmol, 0.2 equiv.) and AcOH (0.4 mmol, 0.2 equiv.) under nitrogen atmosphere. Then, the reaction was refluxed on an oil bath for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and the crude was subjected to column chromatography over silica gel to give the corresponding product.

5.6.2.2 General procedure for the synthesis of 41b-41f

Sodium hydride (1.2 mmol, 1.2 equiv.) was added slowly to a stirred solution of trimethyl sulfoxoniumiodide (TMSOI) (1.2 mmol, 1.2 equiv.) in dry DMF (4.0 mL/mmol) under nitrogen atmosphere at room temperature. Thereafter, the mixture is continued to stir for another 1 h. After getting a clear solution, the condensation product **1′** (1.0 mmol, 1.0 equiv.) dissolved in dry DMF (1 mL/mmol) was added at once to the mixture. The reaction was monitored by TLC. After completion of starting material the reaction mixture was quenched with saturated ammonium chloride and diluted with ice cold water. The organic layer was extracted with ethyl acetate and washed with brine. The combined organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure. Finally the crude mixture was purified by column chromatography over a silica gel to obtain the corresponding compound **41**.

5.6.3 Experimental procedure for the synthesis of 43aa′

To a solution of $Ni(ClO_4)_2.6H_2O$ (9 mg, 0.025 mmol) in DCM (5 mL) at room temperature was added dimethyl 2-(2-nitrophenyl)cyclopropane-1,1-dicarboxylate (**41a**) (140 mg, 0.5 mmol) and aniline (56 mg, 0.6 mmol). Then, the reaction was refluxed for 12 h. After completion of the reaction, the solvent was removed under reduced pressure. The crude was subjected to column chromatography over silica gel to give the corresponding product **43aa′**in 93% yield.

5.6.4 General procedure for the synthesis of 43

To a solution of $Ni(ClO_4)_2.6H_2O$ (0.015 mmol, 0.05 equiv.) in DCM (3 mL)at room temperature was added o-*nitro* aryl compounds having DACs **41** (0.3 mmol, 1.0 equiv.) and primary arylamines **42** (0.36 mmol, 1.2 equiv.). Then, the reaction was refluxed for 12 h. After completion of the reaction as indicated by TLC analysis, the solvent was removed under reduced pressure and the crude was used for further reaction without any purification. In continuation, to a solution of $SnCl_2.2H_2O$ (0.6 mmol, 2.0 equiv.) in dry MeOH (3 mL)at room temperature was added the crude product isolated earlier under nitrogen atmosphere and refluxed till the starting material consumes completely. The reaction mixture was then quenched with saturated NH_4Cl solution, organic layer was extracted with ethyl acetate and washed with brine. The combined organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure. Finally the crude mixture was purified by column chromatography over a silica gel to obtain the corresponding compound **43**.

5.6.5 Experimental procedure for the synthesis of 44 and 45

To a stirred solution of LiCl (65 mg, 1.5 mmol) in DMSO (2 mL) and H_2O (10 µL) at room temperature was added compound **43aa** (100 mg, 0.3 mmol) under nitrogen atmosphere. Then, the reaction was refluxed for 10 h. After completion of starting material, the reaction was cooled to room temperature; diluted with cold water and then extracted with DCM (3x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding products **44** and **45** in 60% and 30% yield respectively.

5.6.6 Experimental procedure for the synthesis of 45 from 44

To a stirred solution of compound **44** (84 mg, 0.3 mmol) in THF (5 mL) was added a solution of $LiOH.H_2O$ (72 mg, 3.0 mmol) in MeOH and H_2O (4:1, 5 mL) and the resulting mixture was allowed to stir at room temperature for overnight. After complete consumption of starting material, the reaction mixture was quenched with 1N HCl and *p*H 1-2 was maintained, and then organic layer was extracted with DCM. Thereafter, the organic layer was washed brine solution 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to obtain the corresponding product **45** in 90% yields.

5.6.7 Experimental procedure for the synthesis of 46

To a stirred solution of LAH (45 mg, 1.2 mmol) in THF (5 mL) kept at 0 ^oC, compound **44** (84 mg, 0.3 mmol) was added dropwise. The reaction mixture was slowly brought to room temperature and allowed to stir for 4 h. After complete consumption of starting material, the reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl solution. The organic layer was extracted, dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to obtain the corresponding product **46** in 82% yield.

5.6.8 Experimental procedure for the synthesis of 47

Compound **47** was prepared as per literature[25], to a stirred solution of compound **45** (45 mg, 0.3 mmol), DIPEA (45 mg, 0.66 mmol) in DCM (5 mL), NosylOXY(45 mg, 0.3 mmol) was added. The reaction mixture was stirred for 15 min followed by addition of aniline (84 mg, 0.3 mmol) dropwise. Stirring of the reaction mixture was continued till 6 h. After completion of the reaction, the reaction mixture was diluted with 50 mL of ethyl acetate; the organic phase was washed with 1N HCl (3 × 10 mL) and saturated $NaHCO_3$ (3 × 10mL). The organic layer was extracted, dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to obtain the corresponding product **47** in 50% yield.

5.7 References

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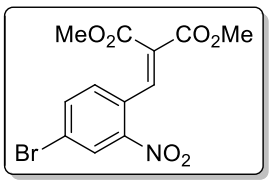
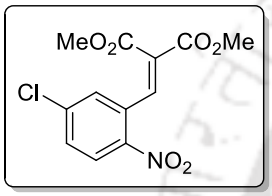
5.8 Characterization data:

Dimethyl 2-(4-bromo-2-nitrobenzylidene)malonate (41b′):



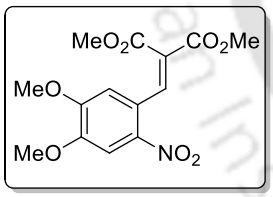
Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 300 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 8.10 (s, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 3.88 (s, 3 H), 3.65 (s, 3 H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.3, 136.8, 147.7, 140.7, 137.0, 131.5, 129.3, 129.2, 128.4, 124.1, 53.2, 52.8. IR (KBr, neat) 2954, 1727, 1643, 1522, 1432, 1350, 1225, 1156, 1073, 981, 843, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{11}BrNO_6$ $(M + H)^+$ 343.9764, found 343.9775.

Dimethyl 2-(5-chloro-2-nitrobenzylidene)malonate (41c′):



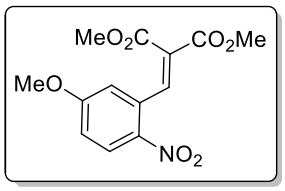
Yellow gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 275 mg, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 1 H), 8.13 (s, 1 H), 7.53 (dd, J = 8.4 and 2.0 Hz, 1 H), 7.39 (d, J = 2.0 Hz, 1 H), 3.88 (s, 3 H), 3.66 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.0, 163.6, 145.6, 140.6, 140.5, 132.2, 130.4, 130.0, 129.4, 126.7, 53.2, 52.8. IR (KBr, neat) 2957, 1724, 1605, 1565, 1435, 1343, 1220, 1181, 1071, 986, 844, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{11}ClNO_6$ $(M + H)^+$ 300.0269, found 300.0285.

Dimethyl 2-(4,5-dimethoxy-2-nitrobenzylidene)malonate (41d′):



Orange gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 292 mg, 45%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.77 (s, 1 H), 6.88 (s, 1 H), 3.99 (s, 3 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 3.67 (s, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.2, 164.1, 153.5, 149.8, 142.0, 140.3, 127.9, 124.6, 111.6, 108.2, 56.8, 56.7, 53.0, 52.8. IR (KBr, neat) 2965, 1732, 1610, 1504, 1427, 1330, 1279, 1171, 1086, 946, 845, 742 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO_8$ $(M + H)^+$ 326.0870, found 326.0879.

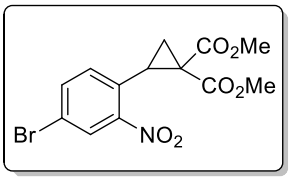
Dimethyl 2-(5-methoxy-2-nitrobenzylidene)malonate (41e′):



Yellow gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 384 mg, 65%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 2 H), 6.99 (dd, *J* = 8.5 and 2.5 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1 H), 3.89 (s, 6 H), 3.64 (s, 3 H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.6, 164.0, 163.8, 142.5, 140.4, 133.2, 128.3, 128.0, 115.3, 114.9, 56.4, 53.1, 52.7 IR (KBr, neat) 2854, 1734, 1642, 1555,

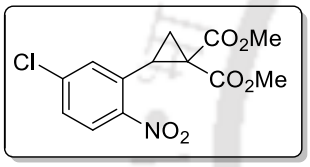
1432, 1350, 1215, 1161, 1076, 956, 842, 742 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{14}NO_7$ $(M + H)^+$ 296.0765, found 296.0789.

Dimethyl 2-(4-bromo-2-nitrophenyl)cyclopropane-1,1-dicarboxylate (41b):



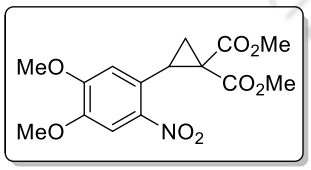
Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 160 mg, 45%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.24 (d, J = 8.5 Hz, 1 H), 3.82 (d, J = 1.5 Hz, 3 H), 3.63 (t, J = 9.0 Hz, 1 H), 3.43 (d, J = 1.5 Hz, 3 H), 2.07 (dd, J = 8.5 and 5.5 Hz, 1 H), 1.90 – 1.87 (m, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.5, 167.2, 150.8, 136.4, 132.8, 130.1, 128.1, 122.2, 53.3, 52.9, 35.9, 30.4, 19.6. IR (KBr, neat) 2954, 1729, 1527, 1440, 1343, 1285, 1133, 983, 891, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{13}BrNO_6$ $(M + H)^+$ 357.9921, found 357.9942.

Dimethyl 2-(5-chloro-2-nitrophenyl)cyclopropane-1,1-dicarboxylate (41c):



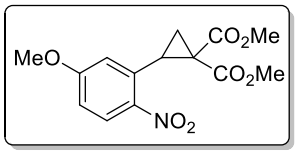
Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 150 mg, 48%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.8 Hz, 1 H), 7.41 (dd, J = 8.8 and 2.0 Hz, 1 H), 7.34 (d, J = 2.0 Hz, 1 H), 3.83 (s, 3 H), 3.69 (t, J = 8.8 Hz, 1 H), 3.44 (s, 3 H), 2.07 (dd, J = 8.4 and 5.6 Hz, 1 H), 1.90 (dd, J = 8.4 and 5.6 Hz, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 167.2, 148.7, 139.9, 133.2, 131.6, 129.1, 126.6, 53.4, 52.9, 35.9, 30.7, 19.8. IR (KBr, neat) 2954, 1724, 1602, 1522, 1437, 1340, 1275, 1128, 1063, 931, 881, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{13}ClNO_6$ $(M + H)^+$ 314.0426, found 314.0444.

Dimethyl 2-(4,5-dimethoxy-2-nitrophenyl)cyclopropane-1,1-dicarboxylate (41d):



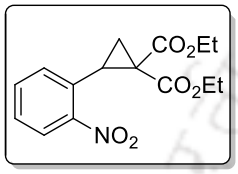
Yellow gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 170 mg, 50%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1 H), 6.74 (s, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.83 (s, 3 H), 3.78 – 3.72 (m, 1 H), 3.43 (s, 3 H), 2.11 (dd, *J* = 8.4 and 5.2 Hz, 1 H), 1.90 (dd, *J* = 8.4 and 5.2 Hz, 1 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 167.5, 153.0, 148.5, 142.9, 125.5, 112.7, 108.4, 56.6, 56.5, 53.2, 52.8, 36.0, 31.7, 20.2. IR (KBr, neat) 2932, 1727, 1517, 1435, 1333, 1218, 1063, 871, 794 cm^{-1} HRMS (ESI) calcd. for $C_{15}H_{18}NO_8$ $(M + H)^+$ 340.1027, found 340.1039.

Dimethyl 2-(5-methoxy-2-nitrophenyl)cyclopropane-1,1-dicarboxylate (41e):



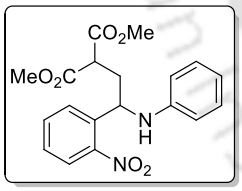
Colourless gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 154 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.8 Hz, 1 H), 6.88 (dd, *J* = 8.8 and 2.8 Hz, 1 H), 6.80 (d, *J* = 2.8 Hz, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.77 (t, *J* = 8.8 Hz, 1 H), 3.41 (s, 3 H), 2.10 (dd, *J* = 8.8 and 5.6 Hz, 1 H), 1.88 (dd, *J* = 8.8 and 5.6 Hz, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.9, 167.4, 163.4, 143.3, 133.9, 127.8, 116.9, 113.0, 56.1, 53.2, 52.8, 35.9, 31.7, 19.9. IR (KBr, neat) 2987, 1714, 1605, 1517, 1437, 1345, 1280, 1136, 1038, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{16}NO_7$ $(M + H)^+$ 310.0921, found 310.0939.

Diethyl 2-(2-nitrophenyl)cyclopropane-1,1-dicarboxylate (41f):



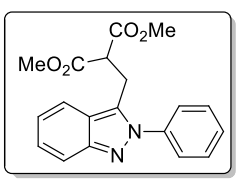
Colourless gum; R_f (hexane/EtOAc, 4:1) 0.45; Yield 187 mg, 61%;; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.0 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 4.29 – 4.22 (m, 2 H), 3.89-3.82 (m, 1 H), 3.81 – 3.71 (m, 2 H), 2.11 (dd, *J* = 8.8 and 5.2 Hz, 1 H), 1.84 (dd, *J* = 8.8 and 5.2 Hz, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.4, 166.9, 150.5, 133.4, 131.2, 131.1, 128.8, 125.1, 62.1, 61.8, 36.4, 30.6, 19.2, 14.3, 13.8. IR (KBr, neat) 2984, 1727, 1612, 1530, 1370, 1275, 1136, 1031,850, 786 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{18}NO_6$ $(M + H)^+$ 308.1129, found 308.1125.

.**Dimethyl 2-(2-(2-nitrophenyl)-2-(phenylamino)ethyl)malonate (43aa′):**



Colourless gum; R_f (hexane/EtOAc, 4:1) 0.40; Yield 172 mg, 93%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 7.41 (t, *J* = 7.8 Hz, 1 H), 7.09 (t, *J* = 8.4 Hz, 2 H), 6.68 (t, *J* = 7.8 Hz, 1 H), 6.45 (d, *J* = 7.8 Hz, 2 H), 5.20 (t, *J* = 6.6 Hz, 1 H), 4.43 (d, *J* = 6.6 Hz, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 2.52 - 2.47 (m, 1 H), 2.45 - 2.37 (m, 1 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 170.5, 169.5, 148.9, 146.1, 139.0, 134.1, 129.6, 128.6, 128.1, 125.3, 118.5, 113.3, 53.2, 53.1, 52.7, 50.3, 36.7, IR (KBr, neat) 2953, 1750, 1729, 1605, 1520, 1350, 1277, 1155, 852, 753 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}N_2O_6$$(M + H)^+$ 373.1394, found 373.1389.

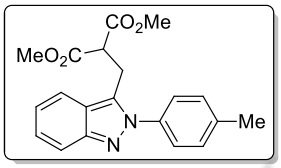
Dimethyl 2-((2-phenyl-2*H*-indazol-3-yl)methyl)malonate (43aa):



Orange gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 70 mg, 70%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 1 H), 7.65 (d, *J* = 8.5 Hz, 1 H),

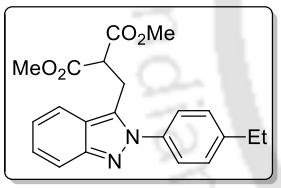
7.53 (m, 5 H), 7.30 (t, *J* = 8.5 Hz, 1 H), 7.09 (t, *J* = 8.5 Hz, 1 H), 3.70 (d, J = 7.8 Hz, 2 H), 3.59 (d, *J* = 7.8 Hz, 1 H), 3.55 (s, 6 H).; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.5, 148.8, 139.9, 131.8, 129.6, 129.5, 126.9, 126.5, 122.0, 121.6, 120.0, 118.0, 52.9, 50.9, 24.7.; IR (KBr, neat) 2954, 1734, 1595, 1435, 1375, 1265, 1118, 1021, 731, 696 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{19}N_2O_4$ $(M + H)^+$ 339.1339, found 339.1352.

Dimethyl 2-((2-(p-tolyl)-2*H*-indazol-3-yl)methyl)malonate (43ab):



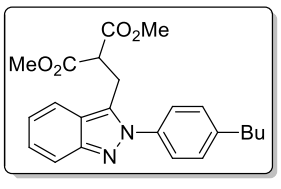
Orange gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 62 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 1 H), 7.65 (d, *J* = 8.5 Hz, 1 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.31 (t, *J* = 6.8 Hz, 1 H), 7.10 (t, *J* = 6.8 Hz, 1 H), 3.69 (d, J = 7.6 Hz, 2 H), 3.61 (d, J = 7.6 Hz, 1 H), 3.57 (s, 6 H), 2.46 (s, 3 H).; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 148.7, 139.6, 137.3, 131.7, 130.1, 126.8, 126.2, 121.8, 121.5, 119.9, 117.9, 52.9, 50.9, 24.7, 21.4.; IR (KBr, neat) 2957, 1734, 1520, 1435, 1378, 1245, 1161, 1043, 821, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O_4$ $(M + H)^+$ 353.1496, found 353.1497.

Dimethyl 2-((2-(4-ethylphenyl)-2*H*-indazol-3-yl)methyl)malonate (43ac):



Brown solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 98-100 ºC Yield 66 mg, 60%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.5 Hz, 1 H), 7.64 (d, *J* = 8.5 Hz, 1 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 7.36 (d, *J* = 8.5 Hz, 2 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 3.69 (d, *J* = 8.0 Hz, 2 H), 3.61 (t, *J* = 8.0 Hz, 1 H), 3.56 (s, 6 H), 2.76 (q, *J* = 7.5 Hz, 2 H), 1.30 (t, *J* = 7.5 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 148.8, 145.9, 137.5, 131.7, 129.0, 126.8, 126.3, 121.9, 121.6, 120.0, 118.0, 52.9, 51.0, 28.8, 24.7, 15.6.; IR (KBr, neat) 2957, 1732, 1625, 1520, 1435, 1380, 1225, 1153, 1016, 844, 741 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_4$ $(M + H)^+$ 367.1652, found 367.1655.

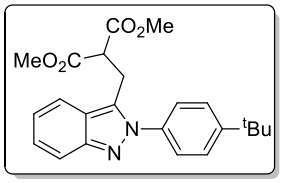
Dimethyl 2-((2-(4-butylphenyl)-2*H*-indazol-3-yl)methyl)malonate (43ad):



Yellow gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 60 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.8 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H), 7.31 (t, J = 6.8 Hz, 1 H), 7.1 (t, J = 6.8 Hz, 1 H), 3.71 (d, *J* = 7.6 Hz, 2 H), 3.62 (dd, *J* = 8.4 and 6.8 Hz, 1 H), 3.58 (s, 6 H), 2.73 (t, *J* = 7.6 Hz, 2 H), 1.71 – 1.64 (m, 2 H), 1.41 (q, *J* = 14.8

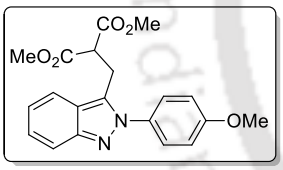
and 7.2 Hz, 2 H), 0.97 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 148.7, 144.6, 137.5, 131.7, 129.5, 126.8, 126.2, 121.9, 121.5, 120.0, 117.9, 52.9, 50.9, 35.5, 33.6, 24.7, 22.4, 14.1.; IR (KBr, neat) 2932, 1737, 1627, 1517, 1435, 1268, 1153, 1046, 916, 734 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{27}N_2O_4$ $(M + H)^+$ 395.1965, found 395.1979.

Dimethyl 2-((2-(4-(tert-butyl)phenyl)-2*H*-indazol-3-yl)methyl)malonate (43ae):



Orange gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 74 mg, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.32 (t, *J* = 6.8 Hz, 1 H), 7.11 (t, *J* = 6.8 Hz, 1 H), 3.72 (d, *J* = 7.2 Hz, 2 H), 3.68-3.64 (m, 1 H), 3.58 (s, 6 H), 1.40 (s, 9 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 152.8, 148.8, 137.3, 131.7, 126.8, 126.6, 126.0, 122.0, 121.5, 120.0, 117.9, 53.0, 50.9, 35.1, 31.5, 24.7.; IR (KBr, neat) 2952, 1734, 1623, 1520, 1435, 1378, 1220, 1153, 1106, 841, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{27}N_2O_4$ $(M + H)^+$ 395.1965, found 395.1968.

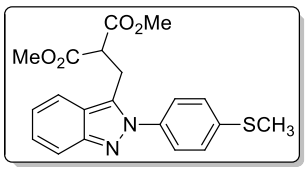
Dimethyl 2-((2-(4-methoxyphenyl)-2*H*-indazol-3-yl)methyl)malonate (43af):



Orange Solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 97-99 ºC Yield 66 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 7.30 (dd, *J* = 15.6 and 6.8 Hz, 1 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 3.91 (s, 3 H), 3.68 (d, *J* = 6.8 Hz, 2 H), 3.62 (t, *J* = 6.8 Hz, 1 H), 3.59 (s, 6 H).; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 160.4, 148.7, 132.8, 131.8, 127.7, 126.8, 121.9, 121.5, 120.0, 117.9, 114.8, 55.8, 53.0, 50.1, 24.7.; IR (KBr, neat) 2957, 1732, 1620, 1510, 1437, 1383, 1245, 1023, 836, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O_5$ $(M + H)^+$ 369.1445, found 369.1441.

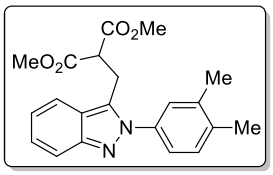
Dimethyl 2-((2-(4-(methylthio)phenyl)-2*H*-indazol-3-yl)methyl)malonate (43ag):

Brown solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 85-87 ºC Yield 82 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.8 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 3.70 (d, *J* = 6.8 Hz, 2 H), 3.64 (dd, *J* = 6.8 and 2.4 Hz, 1 H), 3.59 (s, 6 H), 2.57 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 148.9, 140.9, 136.7, 131.8, 127.0, 126.9, 126.7, 122.0, 121.6, 120.0, 118.0, 53.0,



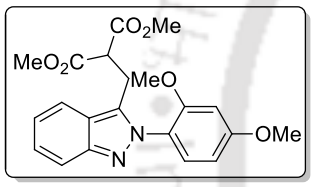
50.9, 24.7, 15.8.; IR (KBr, neat) 2952, 1734, 1520, 1435, 1378, 1223, 1151, 1093, 834, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O_4S$ $(M + H)^+$ 385.1217, found 385.1219.

Dimethyl 2-((2-(3,4-dimethylphenyl)-2*H*-indazol-3-yl)methyl)malonate (43ah):



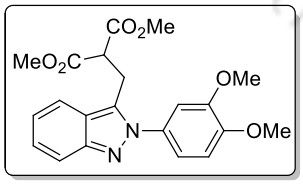
Orange gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 66 mg, 60%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.34 – 7.24 (m, 4 H), 7.14 – 7.08 (t, *J* = 7.2 Hz, 1 H), 3.71 (d, *J* = 7.2 Hz, 2 H), 3.63 (dd, *J* = 7.2 and 2.0 Hz, 1 H), 3.59 (s, 6 H), 2.37 (d, *J* = 4.4 Hz, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 148.7, 138.3, 137.6, 131.6, 130.5, 127.4, 126.8, 123.5, 121.8, 121.5, 120.0, 118.0, 52.9, 50.9, 24.7, 20.0, 19.8. IR (KBr, neat) 2952, 1732, 1627, 1505, 1435, 1380, 1210, 1153, 1062, 903, 824, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_4$ $(M + H)^+$ 367.1652, found 367.1689.

Dimethyl 2-((2-(2,4-dimethoxyphenyl)-2*H*-indazol-3-yl)methyl)malonate (43ai):



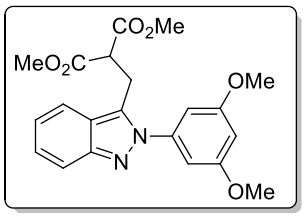
Orange gum; R_f (hexane/EtOAc, 7:3) 0.60; Yield 67 mg, 56%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 1 H), 7.66 (d, J = 8.4 Hz, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.32-7.29 (m, 1 H), 7.09 (t, J = 8.4 Hz, 1 H), 6.66 – 6.62 (m, 2 H), 3.91 (s, 3 H), 3.77 (s, 3 H), 3.65 – 3.57 (m, 7 H), 3.54 (d, J = 1.0 Hz, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.9, 162.1, 155.6, 149.0, 133.7, 130.0, 126.6, 121.8, 121.5, 121.0, 120.2, 118.0, 105.0, 99.7, 56.1, 55.9, 52.9, 50.8, 24.7.; IR (KBr, neat) 2952, 1732, 1612, 1517, 1435, 1375, 1243, 1158, 1023, 918, 836, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_6$ $(M + H)^+$ 399.1551, found 399.1550.

Dimethyl 2-((2-(3,4-dimethoxyphenyl)-2*H*-indazol-3-yl)methyl)malonate (43aj):



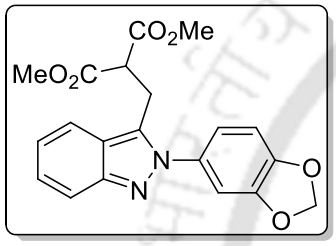
Orange gum; R_f (hexane/EtOAc, 7:3) 0.60; Yield 67 mg, 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.13 – 7.09 (m, 3 H), 7.02 – 6.99 (m, 1 H), 3.99 (s, 3 H), 3.95 (s, 3 H), 3.70 (d, *J* = 6.4 Hz, 2 H), 3.64 (dd, *J* = 6.4 and 9.2 Hz, 1 H), 3.60 (s, 6 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 161.3, 148.7, 41.3, 131.7, 127.0, 122.0, 121.6, 120.0, 118.0, 104.9, 101.9, 55.9, 53.0, 50.9, 24.8.; IR (KBr, neat) 2837, 1734, 1627, 1517, 1437, 1375, 1235, 1026, 898, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_6$ $(M + H)^+$ 399.1551, found 399.1565.

Dimethyl 2-((2-(3,5-dimethoxyphenyl)-2*H*-indazol-3-yl)methyl)malonate (43ak):



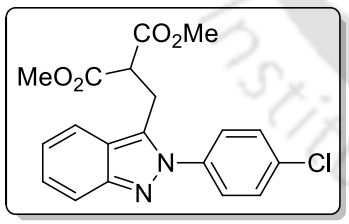
Orange gum; R_f (hexane/EtOAc, 7:3) 0.60; Yield 62 mg, 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 6.70 (d, *J*= 2.4 Hz, 2 H), 6.61 (t, *J* = 2.4 Hz, 1 H), 3.86 (s, 6 H), 3.73 (d, *J* = 8.4 Hz, 2 H), 3.68 (dd, *J* = 8.4 and 6.8 Hz, 1 H), 3.60 (s, 6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.6, 161.3, 148.7, 141.3, 131.7, 127.0, 122.0, 121.6, 120.0, 118.0, 104.9, 101.9, 55.9, 53.0, 50.9, 24.8.; IR (KBr, neat) 2954, 1732, 1612, 1432, 1343, 1205, 1153, 1063, 839, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_6$(M + H)$^+$ 399.1551, found 399.1554.

Dimethyl 2-((2-(benzo[d][1,3]dioxol-5-yl)-2*H*-indazol-3-yl)methyl)malonate (43al):



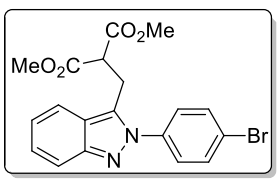
Brown solid; R_f (hexane/EtOAc, 7:3) 0.60; mp 93-95 ºC Yield 57 mg, 50%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.5 Hz, 1 H), 7.62 (d, J = 8.5 Hz, 1 H), 7.29 (t, *J* = 8.5 Hz, 1 H), 7.08 (t, *J* = 7.5 Hz, 1 H), 6.98 (t, *J* = 7.5 Hz, 2 H), 6.92 (d, *J* = 8.5 Hz, 1 H), 6.09 (s, 2 H), 3.68 – 3.62 (m, 3 H), 3.58 (s, 6 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.6, 148.7, 148.5, 140.1, 133.7, 131.9, 127.0, 122.0, 121.4, 120.3, 120.0, 118.0, 108.5, 107.9, 102.3, 53.0, 50.9, 24.7.; IR (KBr, neat) 2902, 1729, 1625, 1500, 1435, 1343, 1213, 1038, 931, 744, 639 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{19}N_2O_6$ (M + H)$^+$ 383.1238, found 383.1233.

Dimethyl 2-((2-(4-chlorophenyl)-2*H*-indazol-3-yl)methyl)malonate (43am):



Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 67 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 3.70 (d, *J* = 6.8 Hz, 2 H), 3.66-.362 (m, 1 H), 3.60 (s, 6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5, 149.0, 138.4, 135.5, 131.9, 129.8, 127.8, 127.2, 122.2, 121.6, 119.9, 118.0, 53.0, 51.9, 24.7.; IR (KBr, neat) 2952, 1737, 1625, 1500, 1435, 1378, 1275, 1153, 1091, 839, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}ClN_2O_4$ (M + H)$^+$ 373.0950, found 373.0955.

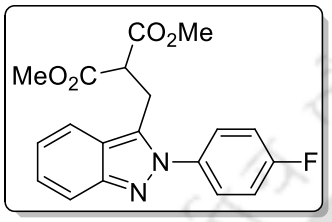
Dimethyl 2-((2-(4-bromophenyl)-2*H*-indazol-3-yl)methyl)malonate (43an):



Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 71 mg, 57%; ^{1}H NMR (500 MHz, $CDCl_3$) 7.68 (d, *J* = 8.0 Hz, 3 H), 7.62 (d, *J* = 8.5 Hz, 1 H),

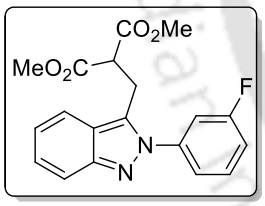
7.43 (d, *J* = 8.5 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 1 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 3.68 (d, *J* = 8.0 Hz, 2 H), 3.62 (dd, *J* = 6.5 and 8.0 Hz 1 H), 3.57 (s, 6 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.4, 149.0, 138.9, 132.8, 131.8, 128.0, 127.2, 123.6, 122.2, 121.6, 120.0, 118.0, 53.0, 50.9, 24.7.; IR (KBr, neat) 2952, 1740, 1625, 1495, 1380, 1223, 1181, 1071, 834, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}BrN_2O_4$ $(M + H)^+$ 417.0444, found 417.0442.

Dimethyl 2-((2-(4-fluorophenyl)-2*H*-indazol-3-yl)methyl)malonate (43ao):



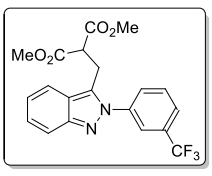
Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 62 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.57 – 7.53 (m, 2 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.30 – 7.25 m, 2 H), 7.13 (t, *J* = 7.2 Hz, 1 H), 3.70 – 3.68 (m, 2 H), 3.66 – 3.62 (m, 1 H), 3.61 (s, 6 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.5, 163.0 (d, *J* = 249.0 Hz), 148.9, 136.0, 132.0, 128.4 (d, *J* = 8.8 Hz), 127.1, 122.2, 121.5, 120.0, 118.0, 116.6 (d, *J* = 23.5 Hz), 53.0, 51.1, 24.7. ^{19}F NMR (471 MHz, $C_6F_6/CDCl_3$) δ 50.6; IR (KBr, neat) 2954, 1740, 1627, 1515, 1437, 1223, 1153, 1091, 846, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}FN_2O_4$ $(M + H)^+$ 357.1245, found 357.1254.

Dimethyl 2-((2-(3-fluorophenyl)-2*H*-indazol-3-yl)methyl)malonate (43ap):



Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 62 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.59 – 7.51 (m, 1 H), 7.39 – 7.31 (m, 3 H), 7.29 – 7.23 (m, 1 H), 7.15 (t, *J* = 6.8 Hz, 1 H), 3.73 (d, *J* = 7.2 Hz, 2 H), 3.66 (dd, *J* = 8.4 and 6.8 Hz, 1 H), 3.60 (s, 6 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5, 163.0 (d, *J* = 247.8 Hz), 149.0, 141.2(d, *J* = 9.8 Hz), 131.9, 130.9 (d, *J* = 8.9 Hz), 127.3, 122.3, 122.2 (d, *J* = 3.3 Hz), 121.7, 120.0, 118.1, 116.7 (d, *J* = 20.8 Hz), 114.4 (d, *J* = 24.1 Hz), 53.0, 50.9, 24.7. ^{19}F NMR (377 MHz, $C_6F_6/CDCl_3$) δ 51.5.; IR (KBr, neat) 2952, 1729, 1607, 1497, 1435, 1345, 1268, 1188, 1023, 896, 741 cm^{-1} HRMS (ESI) calcd. for $C_{19}H_{18}FN_2O_4$ $(M + H)^+$ 357.1245, found 357.1249.

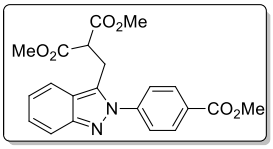
Dimethyl 2-((2-(3-(trifluoromethyl)phenyl)-2*H*-indazol-3-yl)methyl)malonate (43aq):



Orange gum; R_f (hexane/EtOAc, 9:1) 0.45; Yield 55 mg, 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.81 (t, *J* = 8.4 Hz, 2 H), 7.74 (dd, *J* = 7.2 and 6.8 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.36 (t, *J* = 6.8 Hz, 1 H), 7.15 (t, *J* =

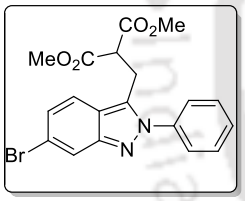
7.2 Hz, 1 H), 3.76 – 3.65 (m, 3 H), 3.61 (s, 6 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5, 149.3, 140.5, 132.3 (q, *J* = 35 Hz), 130.3, 129.8, 127.5, 126.3 (q, *J* = 3.7 Hz), 125.0, 123.8 (q, *J* = 3.7 Hz), 122.5, 122.2, 121.7, 120.0, 118.1, 53.1, 51.0, 24.8. ^{19}F NMR (471 MHz, $C_6F_6/CDCl_3$) δ 99.1.; IR (KBr, neat) 2954, 1734, 1612, 1530, 1437, 1330, 1278, 1128, 1071, 906, 751 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{18}F_3N_2O_4$ $(M + H)^+$ 407.1213, found 407.1219.

Dimethyl 2-((2-(4-(methoxycarbonyl)phenyl)-2*H*-indazol-3-yl)methyl)malonate (43ar):



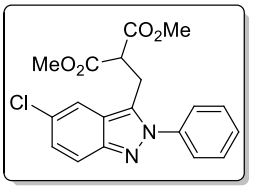
Orange gum; R_f (hexane/EtOAc, 1:4) 0.40; Yield 93 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) 8.25 (d, *J* = 8.4 Hz, 2 H), 7.72-7.64 (m, 4 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 3.98 (s, 3 H), 3.74 (d, *J* = 8.0 Hz, 2 H), 3.62 (t, J = 8.0 Hz 1 H), 3.58 (s, 6 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.4, 166.3, 149.2, 143.6, 131.9, 131.1, 131.0, 127.4, 126.3, 122.4, 121.9, 120.0, 118.1, 53.0, 52.7, 50.9, 24.8.; IR (KBr, neat) 2957, 1729, 1605, 1517, 1437, 1373, 1275, 1108, 866, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{21}N_2O_6$ $(M + H)^+$ 397.1394, found 397.1409.

Dimethyl 2-((6-bromo-2-phenyl-2*H*-indazol-3-yl)methyl)malonate (43ba):



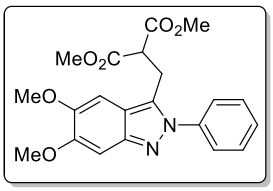
Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 75 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.58 – 7.51 (m, 6 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 3.67 (d, *J* = 8.0 Hz, 2 H), 3.58 (s, 6 H), 3.54 (t, *J* = 8.0 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.5, 149.4, 139.5, 132.6, 129.9, 129.8, 126.4, 125.9, 121.6, 121.1, 120.4, 120.2, 53.1, 50.8, 24.6. IR (KBr, neat) 2954, 1734, 1622, 1502, 1435, 1373, 1258, 1181, 1036, 918, 764, 696 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}BrN_2O_4$ $(M + H)^+$ 417.0444, found 417.0469.

Dimethyl 2-((5-chloro-2-phenyl-2*H*-indazol-3-yl)methyl)malonate (43ca):



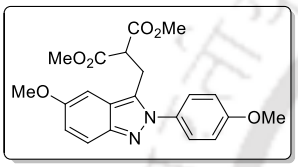
Orange gum; R_f (hexane/EtOAc, 9:1) 0.50; Yield 61 mg, 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.8 Hz, 2 H), 7.59 – 7.51 (m, 5 H), 7.27 – 7.23 (m, 1 H), 3.65 (d, *J* = 8.0 Hz, 2 H), 3.60 (s, 6 H), 3.55 (t, *J* = 8.0 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.4, 147.2, 139.6, 131.7, 129.8, 129.7, 128.4, 127.7, 126.4, 122.0, 119.7, 118.8, 53.1, 50.9, 24.6. IR (KBr, neat) 2952, 1734, 1600, 1505, 1437, 1340, 1268, 1156, 1043, 916, 801, 766 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}ClN_2O_4$ $(M + H)^+$ 373.0950, found 373.0971.

Dimethyl 2-((5,6-dimethoxy-2-phenyl-2*H*-indazol-3-yl)methyl)malonate (43da):



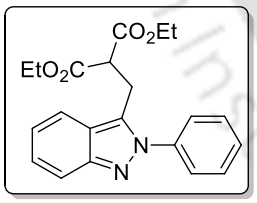
Brown gum; R_f (hexane/EtOAc, 7:3) 0.40; Yield 30 mg, 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 5 H), 6.98 (s, 1 H), 6.85 (s, 1 H), 3.97 (d, *J* = 2.0 Hz, 6 H), 3.65 (d, *J* = 8.0 Hz, 2 H), 3.59 (s, 6 H), 3.52 (t, *J* = 8.0 Hz, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.8, 152.2, 148.2, 145.6, 140.1, 130.5, 129.6, 129.2, 126.4, 116.3, 97.0, 95.9, 56.3, 56.1, 53.0, 50.9, 24.7. IR (KBr, neat) 2929, 1732, 1596, 1510, 1437, 1330, 1218, 1166, 1013, 769 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_6$ $(M + H)^+$ 399.1551, found 399.1554.

Dimethyl 2-((5-methoxy-2-(4-methoxyphenyl)-2*H*-indazol-3-yl)methyl)malonate (43ef):



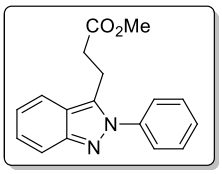
Colourless liquid; R_f (hexane/EtOAc, 7:3) 0.45; Yield 36 mg, 30%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 9.0 Hz, 1 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 7.04 (d, *J* = 8.5 Hz, 2 H), 7.01 (dd, *J* = 9.0 and 2.0 Hz, 1 H), 6.82 (s, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.61 (d, *J* = 7.5 Hz, 2 H), 3.58 (s, 6 H), 3.53 (t, *J* = 7.5 Hz, 1 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.8, 160.3, 155.2, 145.5, 132.9, 130.6, 127.7, 121.9, 121.4, 119.3, 114.7, 96.1, 55.8, 55.7, 53.0, 50.8, 24.7. IR (KBr, neat) 2942, 1755, 1737, 1596, 1581, 1436, 1330, 1216, 1024, 842, 769 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_6$ $(M + H)^+$ 399.1551, found 399.1566.

Diethyl 2-((2-phenyl-2*H*-indazol-3-yl)methyl)malonate (43fa):



Colourless gum; R_f (hexane/EtOAc, 4:1) 0.50; Yield 55 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 13.6 and 8.8 Hz, 2 H), 7.59 – 7.52 (m, 5 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 4.06 – 3.96 (m, 4 H), 3.70 (d, *J* = 8.0 Hz, 2 H), 3.55 (t, *J* = 8.0 Hz, 1 H), 1.08 (t, *J* = 7.2 Hz, 6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.3, 148.9, 140.0, 132.0, 129.7, 129.5, 127.0, 126.5, 121.9, 121.7, 120.2, 118.0, 62.0, 51.1, 24.6, 14.0. IR (KBr, neat) 2984, 1729, 1597, 1502, 1455, 1370, 1273, 1156, 1028, 856, 746 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_4$ $(M + H)^+$ 367.1652, found 367.1679.

Methyl 3-(2-phenyl-2*H*-indazol-3-yl)propanoate (44):

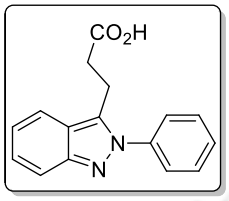


Colourless gum; R_f (hexane/EtOAc, 4:1) 0.60; Yield 51 mg, 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 17.6 and 8.8 Hz, 2 H), 7.59 – 7.51 (m, 5 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 7.2 (t, *J* = 8.0 Hz, 1 H), 3.62 (s, 3 H), 3.42 (t, *J* =

8.0 Hz, 2 H), 2.64 (t, *J* = 8.0 Hz, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 148.9, 140.1, 134.5, 129.6, 129.4, 127.0, 126.4, 121.7, 121.2, 120.1, 118.0, 52.1, 33.5, 21.0. IR (KBr, neat) 2952, 1732, 1597, 1437, 1373, 1198, 1073, 916, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{17}N_2O_2$ $(M + H)^+$ 281.1285, found 281.1288.

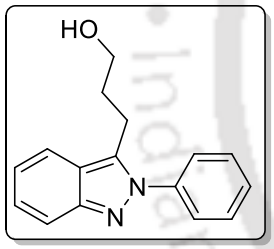
3-(2-Phenyl-2*H*-indazol-3-yl)propanoic acid (45):

White solid; R_f (EtOAc, 100%) 0.80; mp 188-187 ºC Yield 24 mg, 30%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (bs, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.65 – 7.56 (m, 6 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.07 (t, *J* = 8.0 Hz, 1 H), 3.30 (t, *J* = 7.6 Hz, 2 H), 2.57 (t, *J* = 7.6 Hz, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 173.5, 148.4, 140.1, 135.4, 129.8, 129.5, 126.9, 126.6, 121.2, 121.1, 117.6, 33.2, 21.0. IR (KBr, neat) 3319, 2949, 2830, 1667, 1457, 1250, 1021, 819, 759 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{15}N_2O_2$ $(M + H)^+$ 267.1128, found 267.1135.



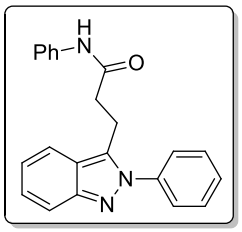
3-(2-Phenyl-2*H*-indazol-3-yl)propan-1-ol (46):

Colourless gum; R_f (hexane/EtOAc, 1:1) 0.40; Yield 62 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.68 (m, 2 H), 7.52-7.50 (m, 5 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 3.56-3.53 (m, 2 H), 3.20-3.12 (m, 2 H), 2.02 (bs, 1 H), 1.89 – 1.80 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 148.8, 140.1, 136.4, 129.4, 129.2, 127.0, 126.4, 121.3, 120.3, 117.8, 61.6, 32.2, 21.8. IR (KBr, neat) 3069, 2937, 1627, 1600, 1505, 1457, 1375, 1280, 1181, 1066, 936, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{17}N_2O$ $(M + H)^+$ 253.1335, found 253.1352.



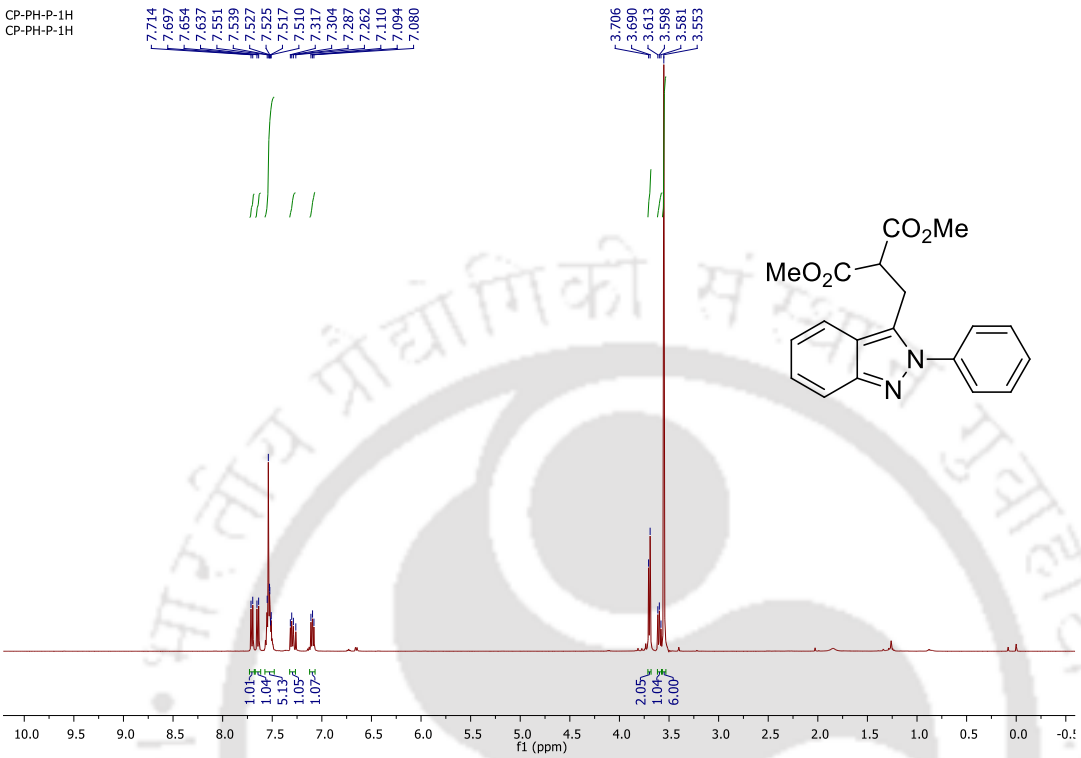
***N*-phenyl-3-(2-phenyl-2*H*-indazol-3-yl)propanamide (47):**

Orange gum; Rf (hexane/EtOAc, 2:3) 0.40; mp 185-187 ºC Yield 52 mg, 50%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (m, 2 H), 7.42 – 7.31 (m, 7 H), 7.27 – 7.23 (m, 3 H), 7.10 – 7.05 (m, 2 H), 3.46 – 3.36 (m, 2 H), 2.54 – 2.43 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 169.4, 148.9, 139.7, 138.0, 135.5, 129.6, 129.4, 129.1, 127.3, 126.2, 124.5, 121.8, 121.2, 120.4, 120.1, 117.7, 36.6, 21.0. IR (KBr, neat) 3193, 2902, 1684, 1598, 1499, 1441, 1378, 1249, 1046, 751, 695 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{20}N_3O$ $(M + H)^+$ 342.1601, found 342.1621.

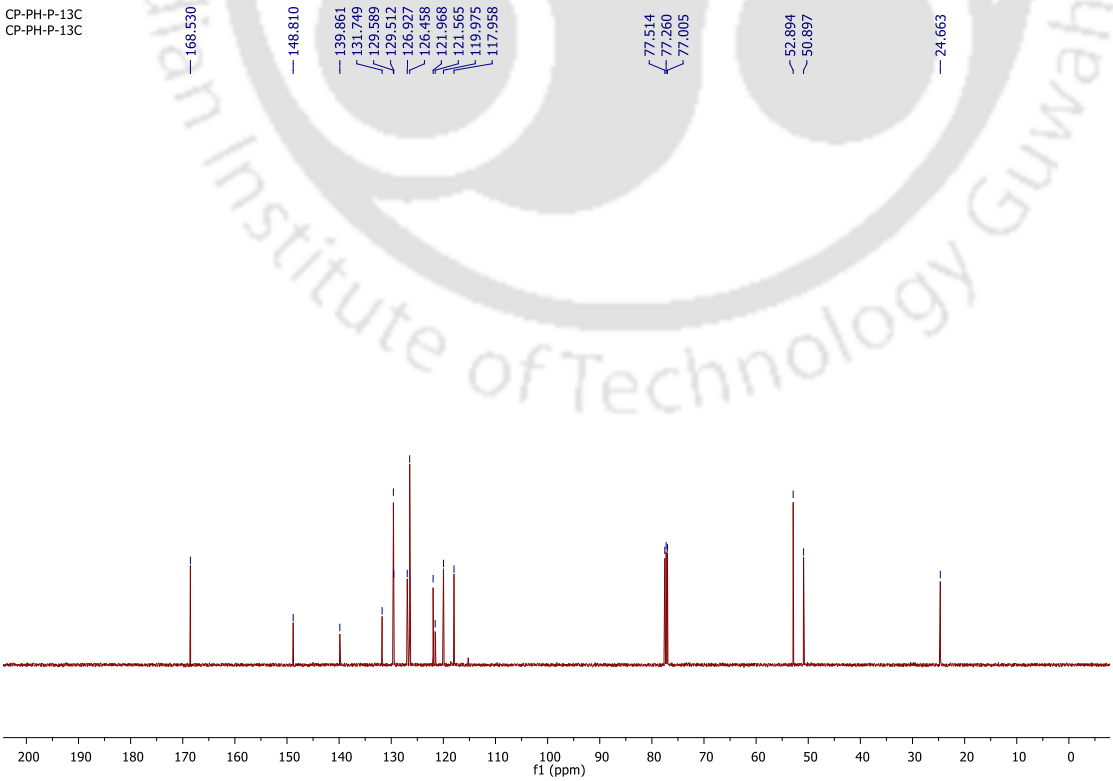


5.9 Selected Spectra

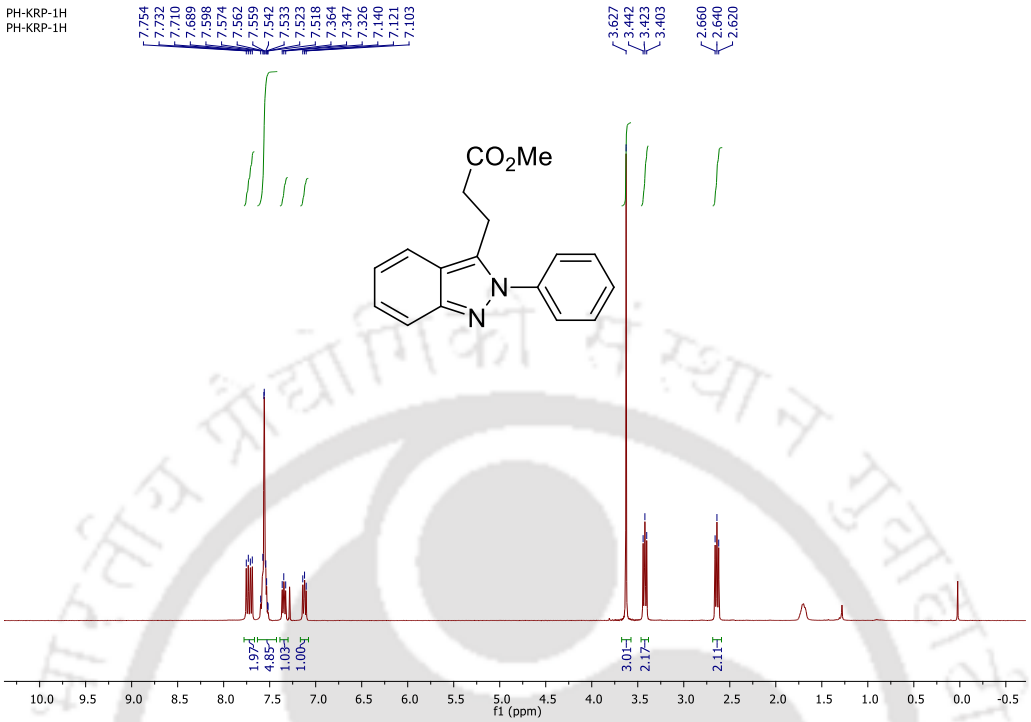
^{1}H spectrum of compound **43aa** (500 MHz, $CDCl_3$)



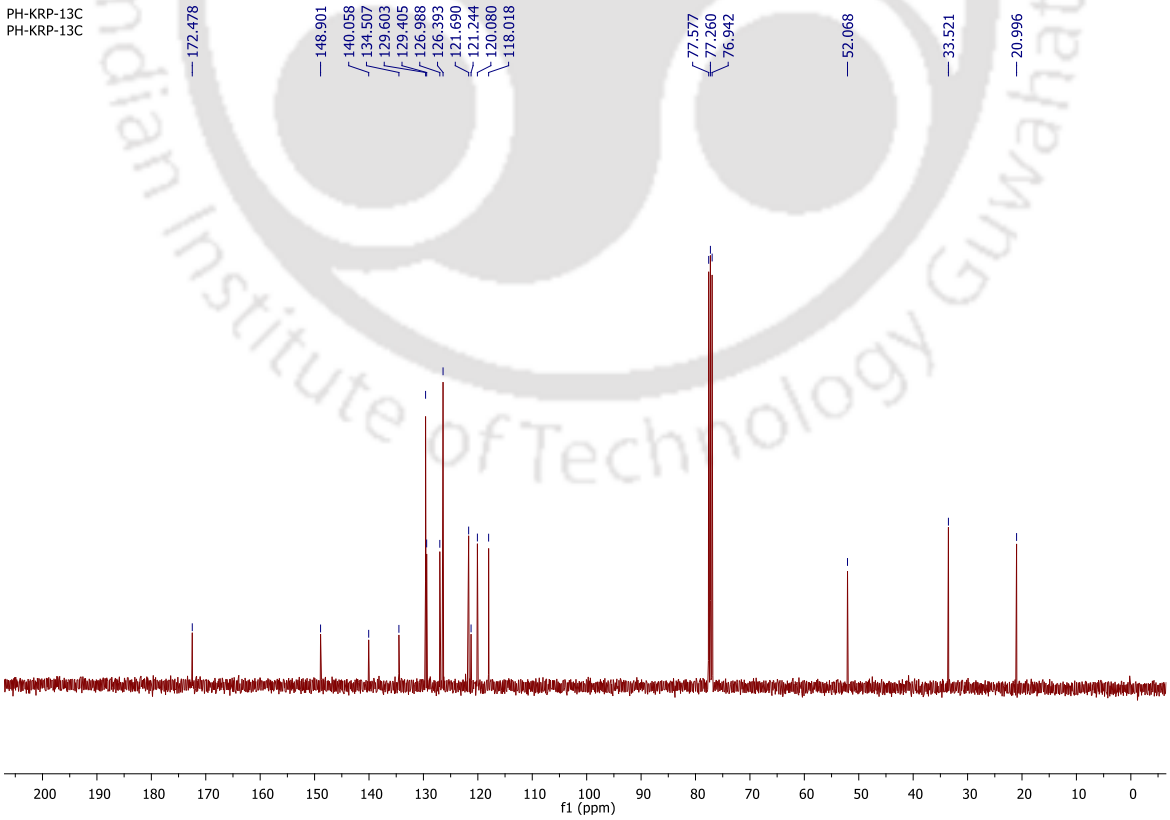
^{13}C{^{1}H } spectrum of compound **43aa** (125 MHz, $CDCl_3$)



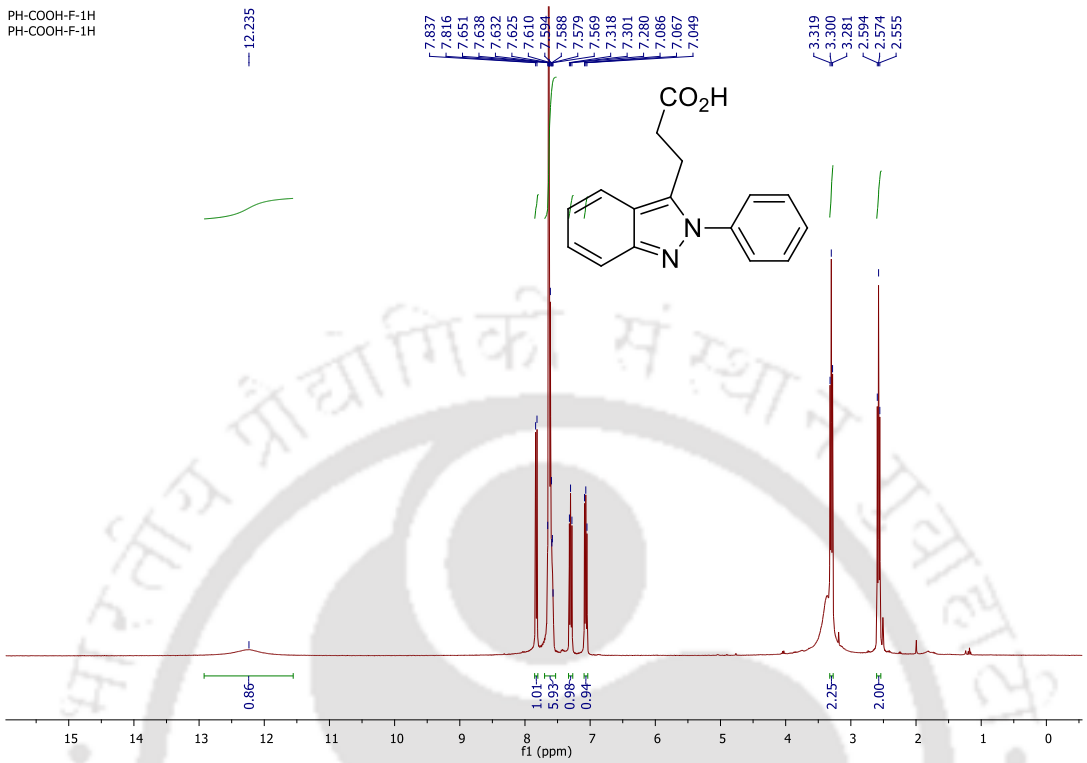
^{1}H spectrum of compound **44** (400 MHz, $CDCl_3$)



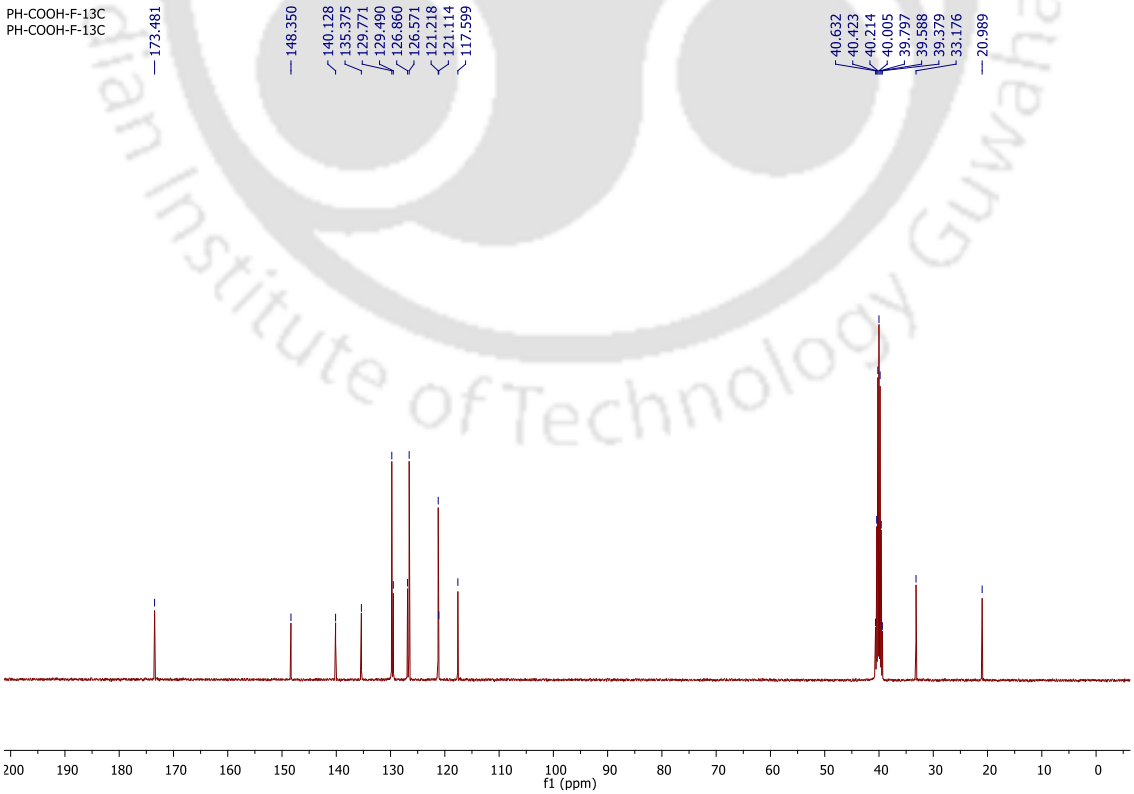
$^{13}C\{^{1}H\}$ spectrum of compound **44** (100 MHz, $CDCl_3$)



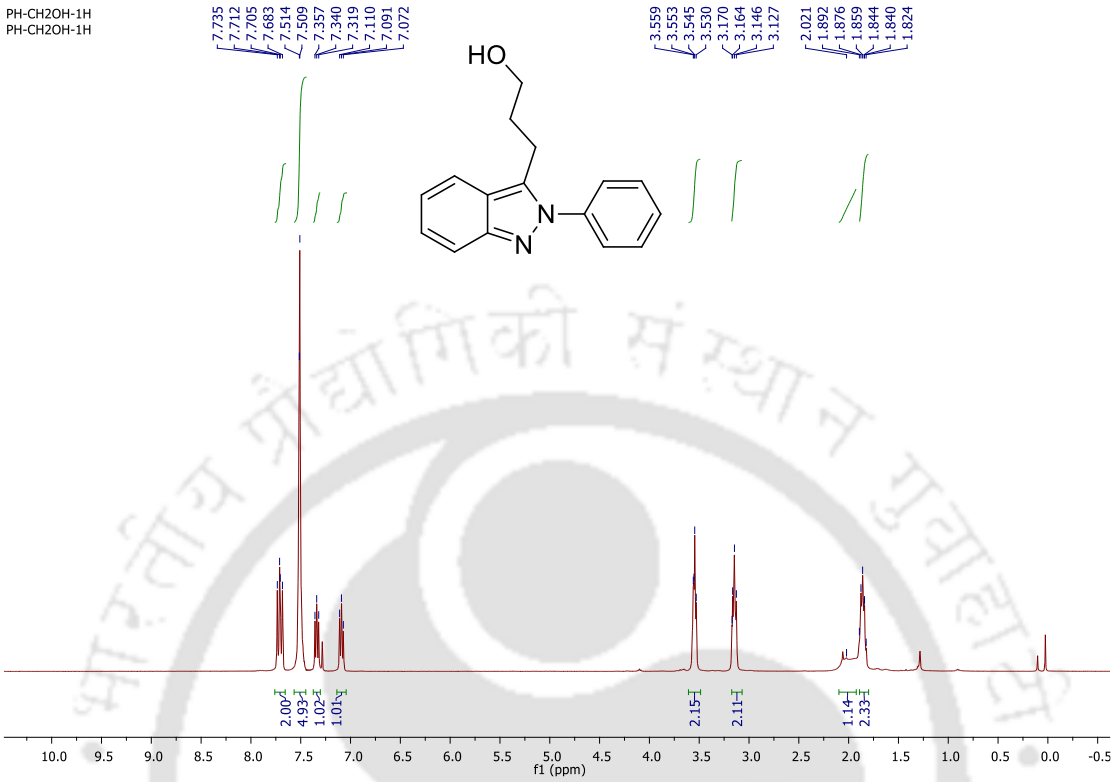
^{1}H spectrum of compound **45** (400 MHz, DMSO-d_6)



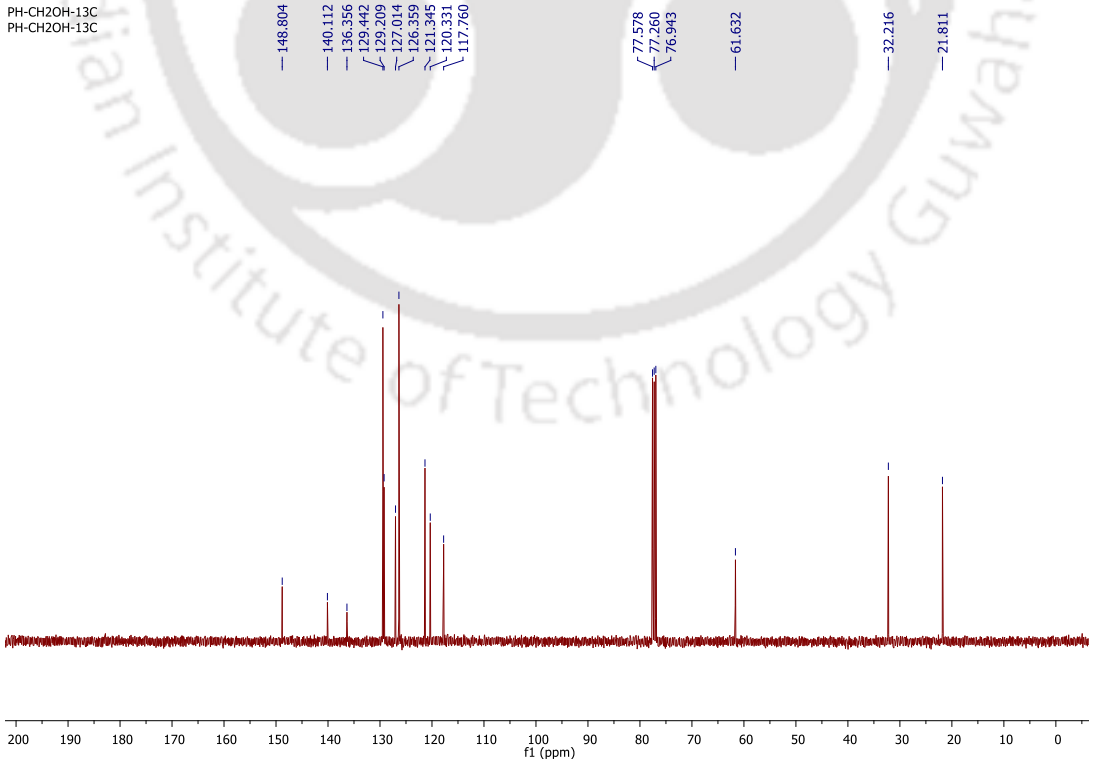
^{13}C{^{1}H } spectrum of compound **45** (100 MHz, DMSO-d_6)



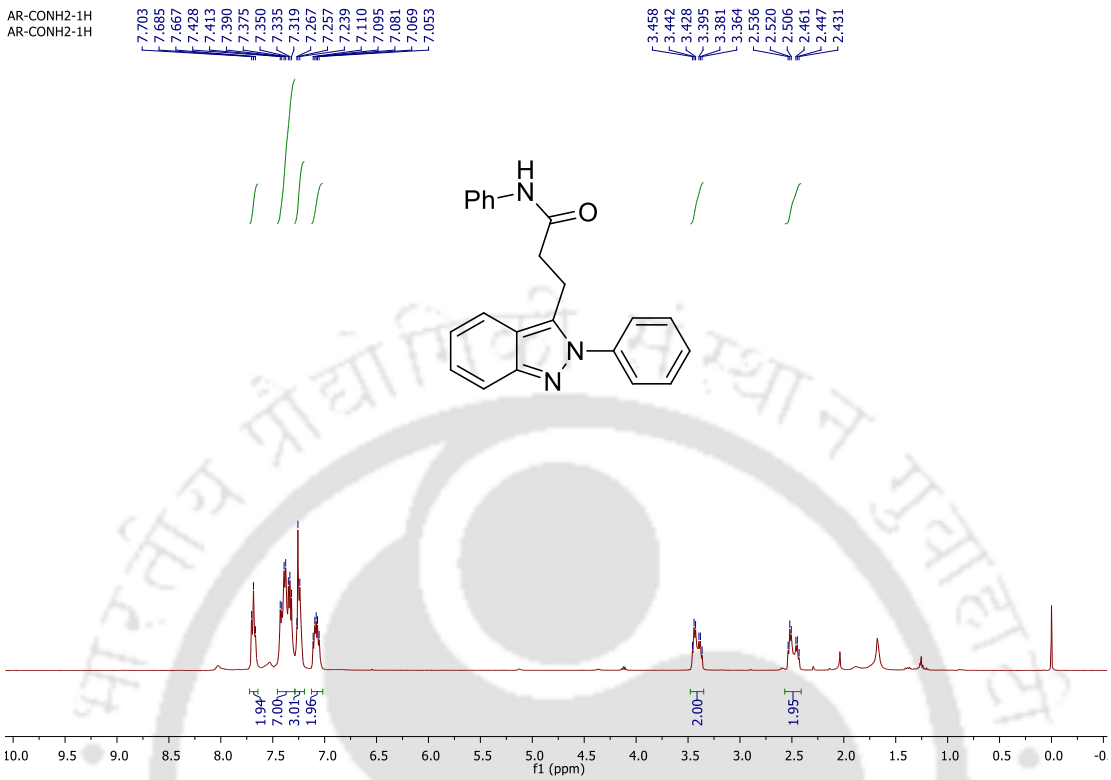
^{1}H spectrum of compound **46** (400 MHz, $CDCl_3$)



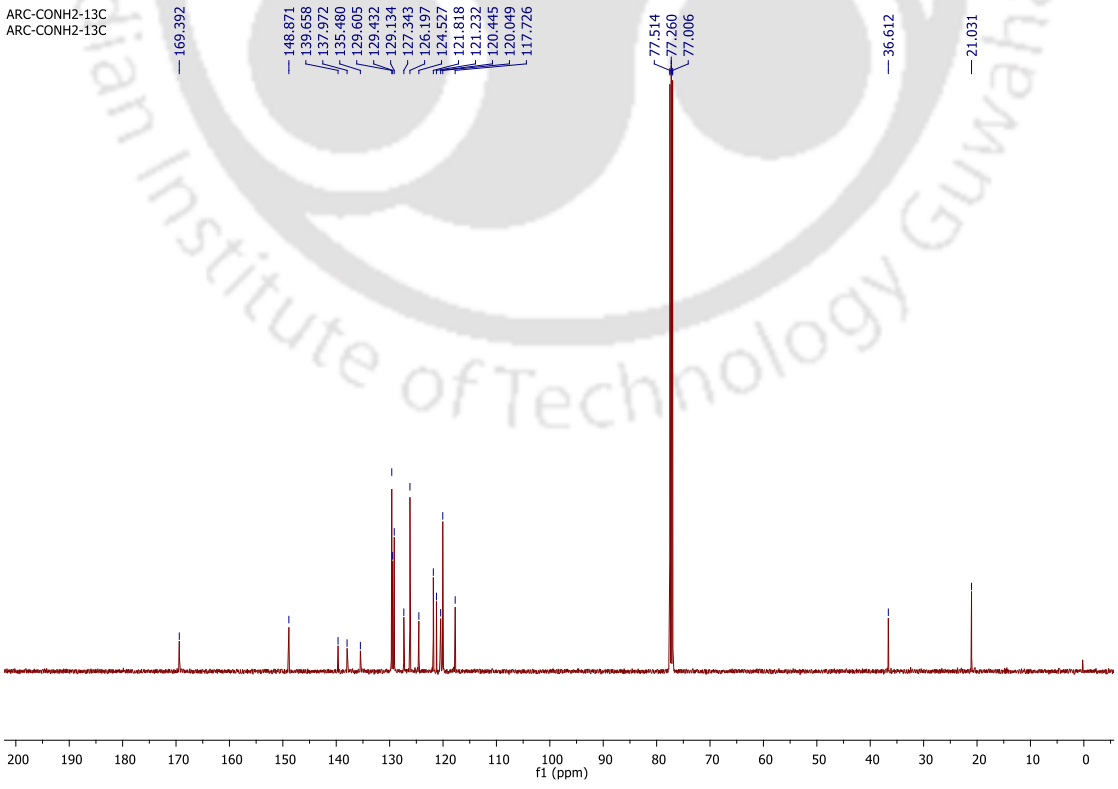
$^{13}C\{^{1}H\}$ spectrum of compound **46**(100 MHz, $CDCl_3$)



^{1}H spectrum of compound **47** (500 MHz, $CDCl_3$)



^{13}C{^{1}H } spectrum of compound **47** (125 MHz, $CDCl_3$)



5.9.1 Crystal parameters

Table 5.9.1. The crystal parameters of compound **43ag**

	CCDC 2130146
Formula	$C_{20}H_{20}N_2O_4S$
Formula weight	384.44
T/K	273(2)
Crystal system	monoclinic
Space group	P 21
a/Å	5.2570(8)
b/Å	13.741(2)
c/Å	13.614(2)
α/°	90
β/°	94.765(4)
γ/°	90
V/Å^3	980.0(3)
Z	2
Abs. Coeff./mm^{-1}	0.193
Abs. Correction	none
GOF on F^2	1.318
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0892
	wR2 = 0.1055
R indices [all data]	*R1* = 0.1953
	wR2 = 0.2045

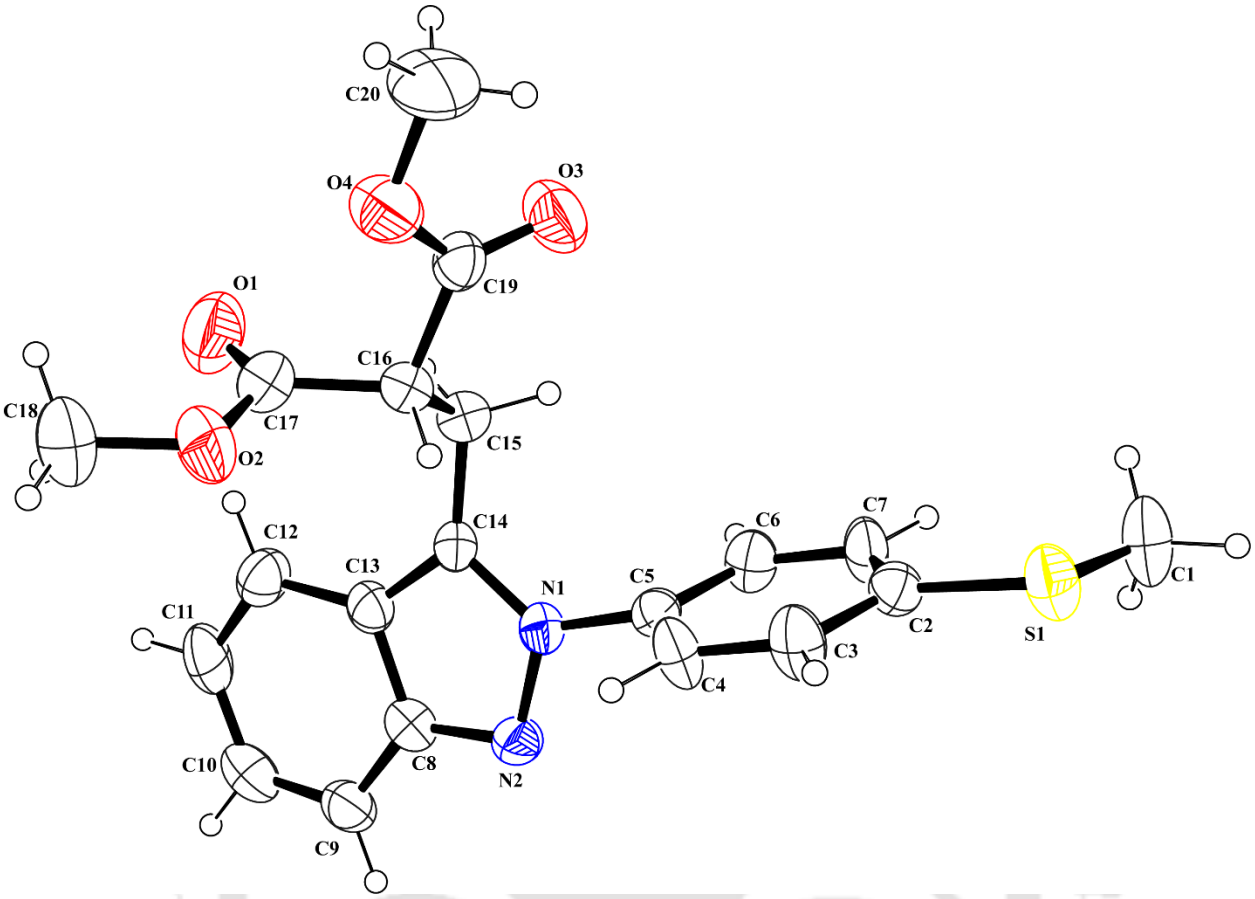


Figure 5.9.1 ORTEP diagram of compound **43ag** using thermal ellipsoids of 35% probability

List of publications

1. "Synthesis of 3*C*-alkylated active methylene substituted 2*H*-indazole derivatives *via* sequential ring opening of donor–acceptor cyclopropanes and reductive cyclization reaction" Sahu, A. K.; Biswas S.; Bora, S. K.; Saikia, A. K. *New J. Chem.* **2022,** *XX*, XXXX-XXXX (Advance).
2. "Synthesis of dibenzocyclohepta[1,2-*a*]naphthalene derivatives from phenylacetaldehyde and alkynyl benzyl alcohols *via* sequential electrophilic addition and double Friedel–Crafts reactions." Sahu, A. K.; Unnava, R.; Behera, B. K.; Saikia, A. K. *Org. Biomol. Chem*. **2021**, *19*, 2430-2435.
3. "$In(OTf)_3$-catalyzed one-pot tandem Mannich and Conia-ene cyclization reaction of *N*-propargyl amido alcohols with 1,3-dicarbonyl compounds: an approach to construct tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindolone-1,1-dicarboxylate and its application." Sahu, A. K.; Unnava, RShit, S.; Saikia, A. K. *J. Org. Chem*. **2020**, *85*, 1961-1971.
4. "$K_2S_2O_8$-mediated synthesis of highly functionalized pyrroles *via* oxidative self-dimerization of *N*-propargylamines." Behera, B. K.; Sahu, A. K.; Devi, N. R.; Saikia, A. K. *J. Org. Chem*. **2021**, *86*, 12481-12493.
5. "Intramolecular Pictet–Spengler reaction of cyclic iminium ions: a novel access to benzo [1,4] oxazepine-fused tetrahydroisoquinoline and tetrahydro-*β*-carboline analogues."Unnava, R.; Sahu, A. K.; Saikia, A. K. *Asian. J. Org. Chem*. **2017**, *6*, 1003-1007.