SYNTHESIS OF HETEROARYLCARBAZOLES, BENZONAPHTHYRIDINES, AZEPINOINDOLES AND TOTAL SYNTHESIS OF THE MARINE ALKALOIDS MANSOURAMYCIN D, CAULIBUGULONES A, D AND PUTATIVE STRUCTURE OF HYRTIOERECTINE E USING ALKYNYLALDEHYDE HETEROANNULATIONS

A Thesis
Submitted for the Degree of
Doctor of Philosophy

By

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STATEMENT

I hereby declare that the matter embodied in this thesis entitled "**SYNTHESIS OF HETEROARYLCARBAZOLES, BENZONAPHTHYRIDINES, AZEPINOINDOLES AND TOTAL SYNTHESIS OF THE MARINE ALKALOIDS MANSOURAMYCIN D, CAULIBUGULONES A, D AND PUTATIVE STRUCTURE OF HYRTIOERECTINE E USING ALKYNYLALDEHYDE HETEROANNULATIONS**" is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad under the supervision of **Dr. R. NAGARAJAN.**

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

Date: **(K. S. PRAKASH)**

Hyderabad

CERTIFICATE

Certified that the work "**SYNTHESIS OF HETEROARYLCARBAZOLES, BENZONAPHTHYRIDINES, AZEPINOINDOLES AND TOTAL SYNTHESIS OF THE MARINE ALKALOIDS MANSOURAMYCIN D, CAULIBUGULONES A, D AND PUTATIVE STRUCTURE OF HYRTIOERECTINE E USING ALKYNYLALDEHYDE HETEROANNULATIONS**" has been carried out by **K. S. PRAKASH** under my supervision and that the same has not been submitted elsewhere for a degree.

DEAN
School of Chemistry
University of Hyderabad

(Dr. R. NAGARAJAN)
Thesis Supervisor

List of Publications

1. **Prakash, K. S.;** Nagarajan, R. A General Method for Synthesis of 5*H*-Benzo[*b*]-, Carbazolo[2,3-*b*]- and Indolo[2,3-*b*]carbazole Derivatives *via* Copper(II) Triflate-Catalyzed Heteroannulation, *Adv. Synth. Catal.* **2012**, *354*, 1566.
2. **Prakash, K. S.;** Nagarajan, R. Synthesis of solid state fluorescent quino[2,3-*b*]carbazoles via copper(II) triflate-catalyzed heteroannulation: application to detection of TNT, *Tetrahedron* **2013**, *69*, 8269.
3. **Prakash, K. S.;** Nagarajan, R. An efficient synthesis of indol-3-yl benzonaphthyridines via copper(II) triflate-catalyzed heteroannulation, *Tetrahedron Lett.* **2013**, *54*, 3635.
4. **Prakash, K. S.;** Nagarajan, R. Total Synthesis of the Marine Alkaloid Mansouramycin D, *Org. Lett.* **2014**, *16*, 244.
5. **Prakash, K. S.;** Nagarajan, R. Total synthesis of the marine alkaloids Caulibugulones A and D, *Tetrahedron* **2015**, *71*, 801.
6. **Prakash, K. S.;** Nagarajan, R. Synthesis of Azepino[4,5-*b*]indoles via 7-*endo* Selective Cyclization of Isocyanoacetates and indole-1,2-alkynylaldehydes; An Approach Towards the Synthesis of Chromoazepinone Core, *Synlett* **2015**, (Accepted)
7. **Prakash, K. S.;** Nagarajan, R. Total synthesis of the putative structure of the Marine Alkaloid Hyrtioerectine E, **2015**, (Manuscript Communicated)

Other Publications

8. **Prakash. K. S.;** Nagarajan, R. Copper-catalyzed heteroannulation: a simple route to the synthesis of pyrrolo[2,3-*b*]carbazole and pyrrolo[2,3-*b*]quinoline derivatives, *Tetrahedron Lett.* **2015**, *56*, 69.
9. Chaitanya, T. K.; **Prakash, K. S.;** Nagarajan, R., Metal-free synthesis of benzimidazo[2,1-*a*]ellipticines via tandem inter and intramolecular cyclization, *Tetrahedron* **2011**, *67*, 6934.

Posters and Presentations

1. Presented poster on "Synthesis of benzimidazo[2,1-*a*]ellipticines *via* tandem inter and intramolecular cyclization" in the **Chennai Chemistry Conference** held at **IIT Madras** (Feb-2011).

2. Presented poster on "Synthesis of 5*H*-Benzo[*b*]-, Carbazolo[2,3-*b*]- Quino[2,3-*b*]- and Indolo[2,3-*b*]carbazoles" in the **International Symposium on Chemistry & Chemical Biology of Natural Products** held at CSIR-IICT - Hyderabad (Aug-2012).

3. Presented poster on "Copper(II) triflate-catalyzed heteroannulation: An efficient protocol for the synthesis of 5*H*-Benzo[*b*]-, Carbazolo[2,3-*b*]- Quino[2,3-*b*]- and Indolo[2,3-*b*]carbazoles" in the **VIII JNOST** conference held at IIT Guwahati (Dec-2012).

4. Presented poster on "Total synthesis of Marine Alkaloid Mansouramycin D *via* iminoannulation" in **16th CRSI National Symposium in Chemistry** held at IIT-Bombay (Feb-2014).

5. Given Oral talk and presented poster on "Total Synthesis of Mansouramycin D" in **ChemFest In House Symposium** held at University of Hyderabad (Feb-2014).

6. Given oral talk on "Total synthesis of the Marine Alkaloids Mansouramycin D and Caulibugulones *via* iminoannulation" in **X JNOST Conference** held at IIT Madras (Dec 2014)

7. Presented poster on "Total Synthesis of the putative structure of the Marine Alkaloid Hyrtioerectine E" in **ChemFest In House Symposium** held at University of Hyderabad. (Feb-2015)

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K. S. Prakash

To

My Family and Teachers

This thesis is affectionately dedicated

Table of Contents

List of acronyms used

Å	Angstrom
Ac	Acetyl
Anal. Calcd	Analytically calculated
Aq.	Aqueous
Ar	Aryl
Bn	Benzyl
bs	Broad singlet (spectral)
t-Bu	*tert*-Butyl
Boc	*tert*-Butyloxycarbonyl
^{o}C	Degree Celsius
Cacld	Calculated
CAN	Ceric Ammonium Nitrate
Cat.	Catalytic
cm^{-1}	Wavenumber(s)
conc.	Concentrated
δ	Chemical shift in parts per million
d	Doublet
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets (spectral)
DIBAL	Diisobutylaluminium Hydride
dil.	Dilute
DMF	*N*,*N*-Dimethylformamide
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMSO	Dimethylsulfoxide
DMAP	4-Dimethylaminopyridine
dppp	1,3-*Bis*(diphenylphosphino)propane
dr	Diastereomeric ratio
dt	Doublet of triplets (Spectral)
ee	Enantiomeric excess
equiv.	Equivalent
Et	Ethyl

EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
EWG	Electron Withdrawing Group
ESI	Electrospray Ionization
FT	Fourier transformation
g	Gram(s)
h	Hour(s)
HRMS	High resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant (in NMR Spectroscopy)
K	Kelvin (Temperature)
LA	Lewis acid
LCMS	Liquid chromatography-mass spectrometry
M	Molar (Solution concentration)
m	Multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
mg	Milligram(s)
MHz	Megahertz
min.	Minute(s)
mL	Millilitre (s)
mmol	Millimole(s)
MOM	Methoxymethyl
Mp	Melting point
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
ORTEP	Oak ridge thermal ellipsoid plot
OTf	Trifluoromethanesulfonate
Ph	Phenyl
PG	Protecting group
PIFA	Phenyliodine(III) *bis*(trifluoroacetate)
PPA	Polyphospharic acid

PTSA/*p*-TsOH	*p*-Toluenesulfonic acid
Py	Pyridine
q	Quartet (spectral)
R_f	Retardation factor
rt	Room temperature
s	Singlet (spectral)
t	Triplet (spectral)
TBAI	Tetrabutylammonium Iodide
TBDMS	*tert*-Butyldimethylsilyl
TCCA	trichloroisocyanuric acid
Tf	Triflate
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	2,2,6,6-Tetramethylpiperidine
TNT	Trinitrotoluene
UV	Ultra-Violet

Introduction

General background

Synthetic organic chemistry is one of the most important branch of organic chemistry, concerns with the synthesis of organic compounds from easily accessible starting materials. There are two main research fields within the general area of synthetic organic chemistry: total synthesis of natural products and development of the new synthetic methodology.

More specifically, nitrogen heterocycles are worth, in particular, for their biological activities. They have been considered as privileged structures in drug discovery. Designing and testing new heterocyclic compounds have often contributed significant advances in medicinal chemistry. Moreover, most of the pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products which are in significant need of human life.

From past few decades, alkynes are extremely versatile motif,[1] which are ubiquitously found in functional materials,[2] supramolecules,[3] and natural products.[4] Further, they are also useful synthetic intermediates from which a wide variety of saturated and unsaturated compounds can be obtained *via* addition reactions across their C-C triple bonds.[5] In particular, recent advances in the transition metal-catalyzed transformations of alkynes have provided rapid and concise access to many useful architectures.[6] More specifically, those containing functional groups such as –OR, -COOR, -CHO, -NH_2, -CN, -N_3, -NOH, etc. in the 1,2-position (*ortho*) proved to be versatile precursor for the synthesis of many useful natural products or bioactive molecules or their derivatives.[5]

A brief literature review on annulation reactions of *ortho*-alkynylaldehyde and their application in the total synthesis of natural products is provided.

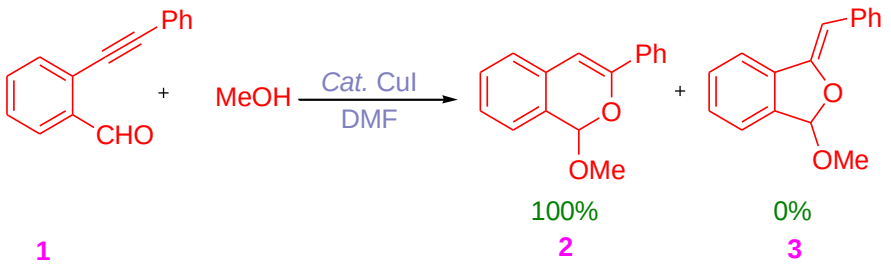
Application of Alkynylaldehyde Heteroannulations

Synthesis of cyclic alkenyl ethers

Yamamoto *et al.* reported the synthesis of cyclic alkenyl ethers from *o*-alkynylbenzaldehydes in 2004.[6] They utilized CuI as a catalyst for this regioselective cyclization of *o*-alkynylaldehyde. The reaction most probably proceeds *via* the nucleophilic addition of alcohols to *o*-alkynylbenzaldehydes **1** to generate the corresponding hemiacetals, and subsequent nucleophilic attack of the hemiacetal oxygen to the copper coordinated alkyne would give the annulated products **2** and **3**. In all cases, the reaction preceded in a regiospecific manner, gives six membered *endo* cyclic products *via* 6-*endo*-dig cyclization. The yields were essentially quantitative or very high in most cases and the regioselectivity

was always 100% favoring the 6-*endo*-mode annulation. The scope of this methodology is good, terminal alkynes were tolerated under the reaction conditions (**Eq. 1**).

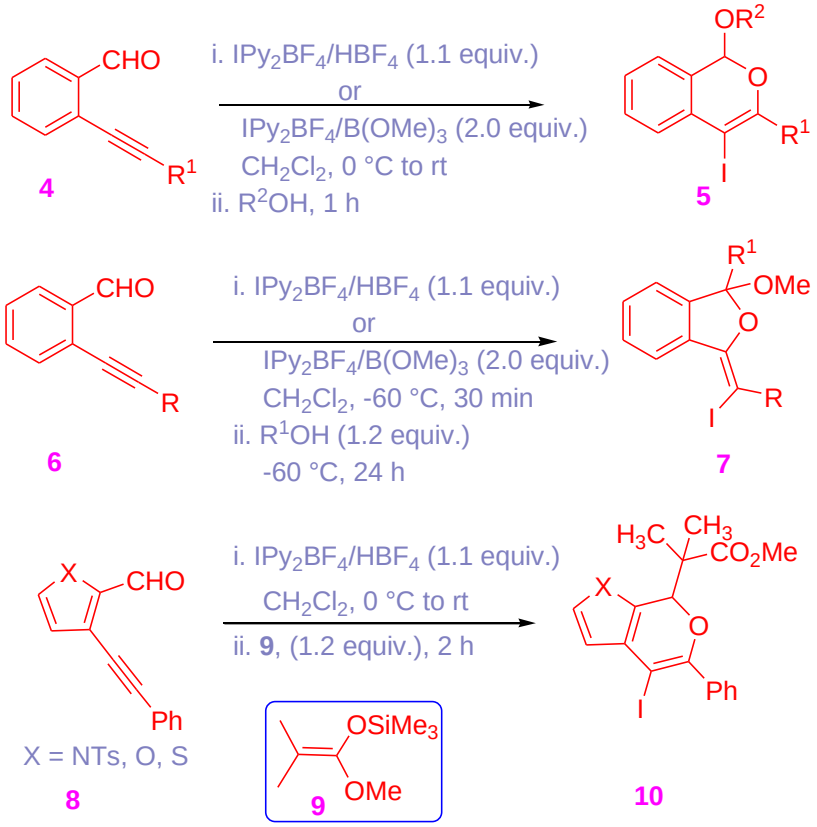
Eq. 1

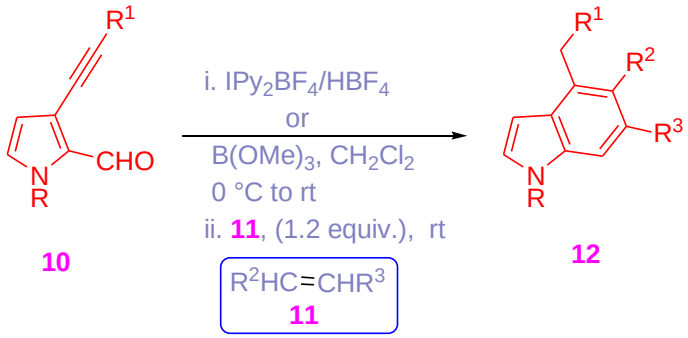


Synthesis of 1*H*-isochromene, napthalene, indole, benzofuran, and benzothiophene

Barluenga *et al.* demonstrated the synthesis of different types of substituted indoles, naphthalenes, benzoheterocycles and isochromenes from *o*-alkynylarylaldehyde.[7] They utilized the benzannulation/heteroannulation of *o*-alkynylarylaldehyde derivatives with corresponding reagents, say, alcohols, silylated nucleophiles, alkynes, or alkenes in presence of iodonium ions (**Eq. 2**).

Eq. 2

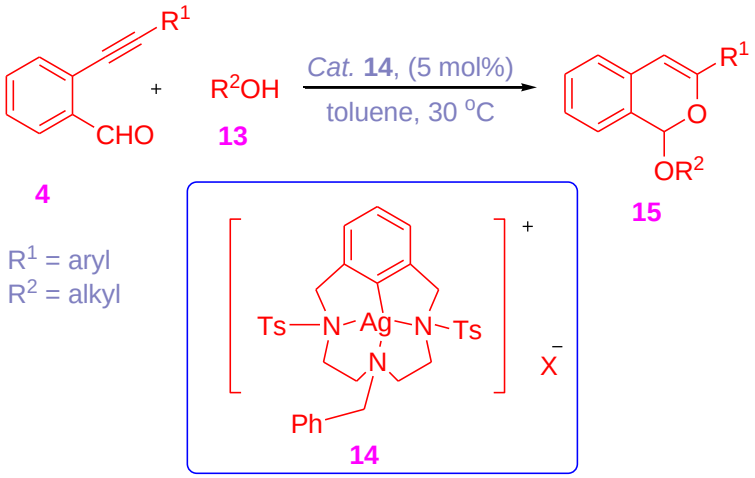




Synthesis of 1-alkoxy-isochromenes

Abbiati *et al.* reported the synthesis of 3-substituted-1-alkoxyisochromenes **15** by cylisation of 2-alkynylbenzaldehydes **4** and different alcohols (**Eq. 3**).[8] They utilized a silver(I) complex **14** with an macrocyclic pyridine containing ligand as catalyst for this cyclization. They have proved the reaction mechanism very clearly by NMR experiments. The reaction was proceeded through isochromenilium ion is presumably the main intermediate.

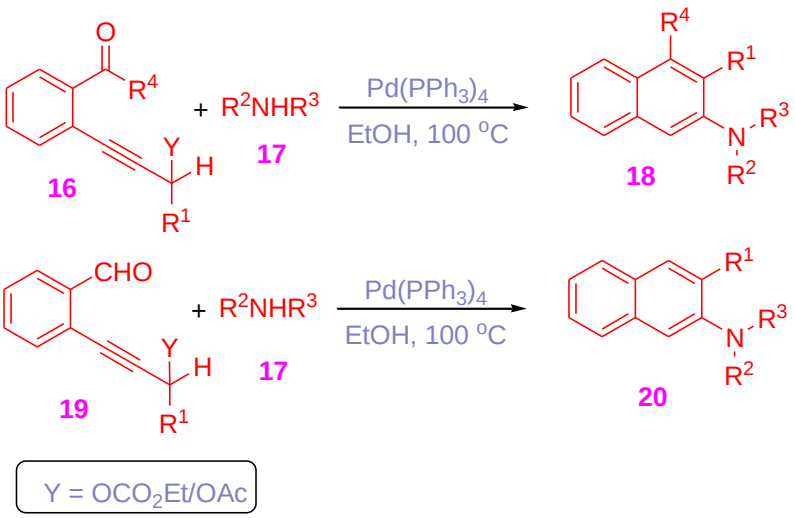
Eq. 3



Synthesis of substituted amine derivatives

Liang *et al.* developed a novel route to synthesize the highly substituted aromatic amine by Pd(0)-catalyzed amino-benzannulation with propargylic compounds (**Eq. 4**).[9] The reaction proceeded *via* the transformation of propargylic compound by Pd(0) catalyst generates allenylpalladium intermediate, followed by the nucleophile attacks the center *sp*-carbon of propargylic compound, finally 6-*endo* cyclization, using the carbonyl group, to form alkenylpalladium(II) intermediate, and the elimination of palladium(II) gives the desired products **17**, **18** and **20**.

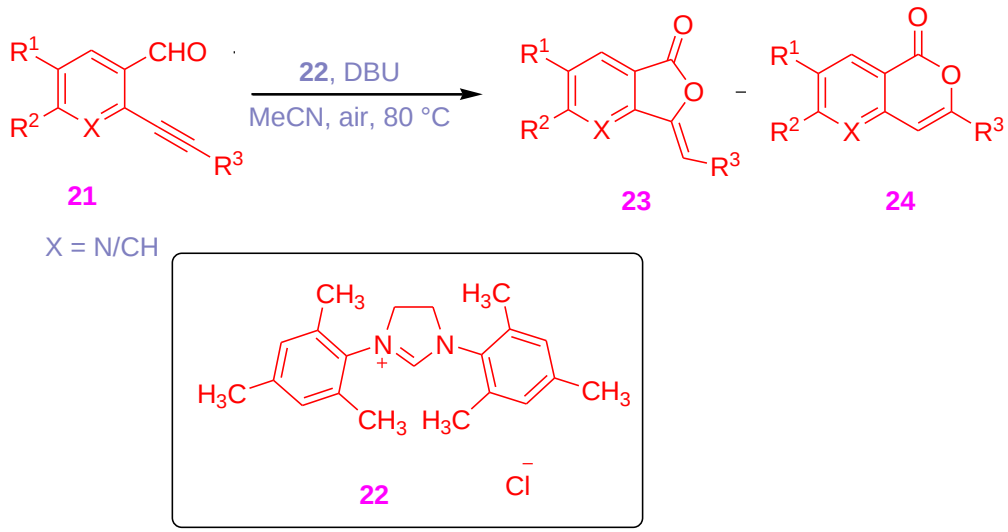
Eq. 4



Synthesis of phthalide and isocoumarines

Youn *et al.* developed a regio- and stereoselective oxidative cyclization of *o*-alkynylbenzaldehydes to afford phthalides **23** and isocoumarins **24** (**Eq. 5**).[10] Here, they used NHC as single organic catalytic system **22** and DBU as a base to generate the catalyst. For the first time, molecular oxygen in air was utilized as a source of an oxygen atom for the oxidation of benzaldehydes to the corresponding benzoic acids under their newly developed reagent system.

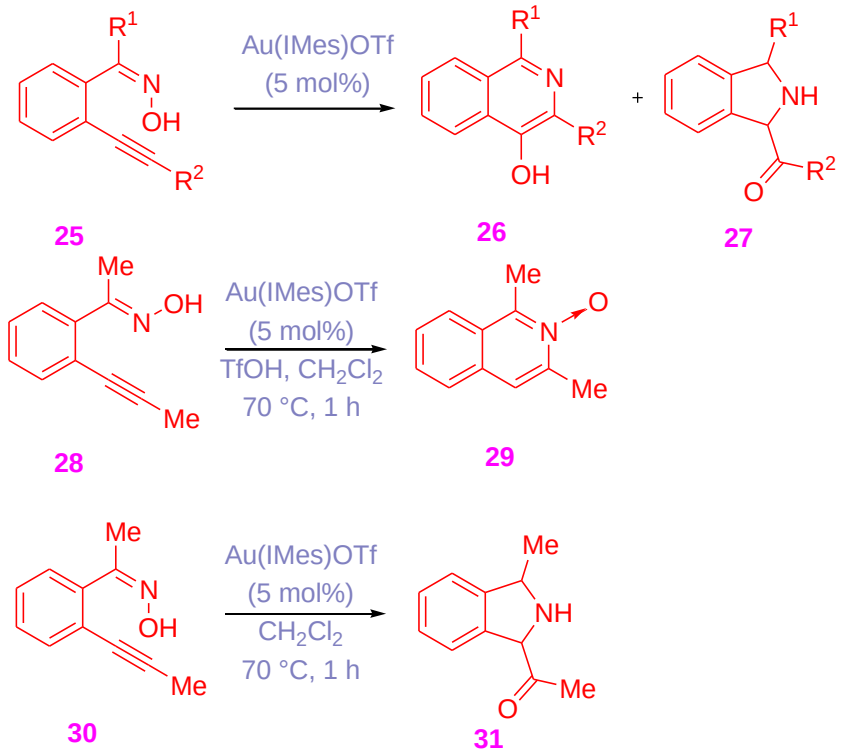
Eq. 5



Synthesis of isoindoles, isoquinolines and isoquinoline-*N*-oxides

Shin *et al*. developed the synthesis of isoquinoline, their -*N*-oxides, and isoindoles *via* gold complex catalyzed geometry-dependent annulation of *o*-alkynylaryl ketoximes and nitrones (**Eq. 6**).[11] They synthesized isoquinoline-*N*-oxides **29** from (*E*)-ketoximes **28** whereas they observed that, (*Z*)-ketoximes and nitrones unprecetedly gave isoindoles **31**.

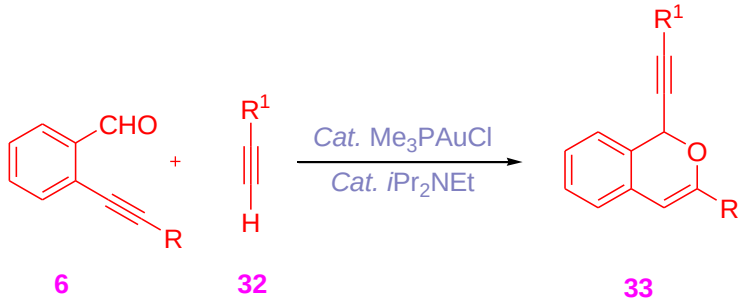
Eq. 6



Synthesis of 1-alkynyl-1*H*-isochromenes

Li *et al*. demonstrated the synthesis of 1-alkynyl-1*H*-isochromenes **33** by the cyclization of *ortho*-alkynylaryl aldehydes with terminal alkynes in water using gold-phosphine complex as catalytic system (**Eq. 7**).[12] These reactions were dually promoted an electron-donating phosphine ligand and water.

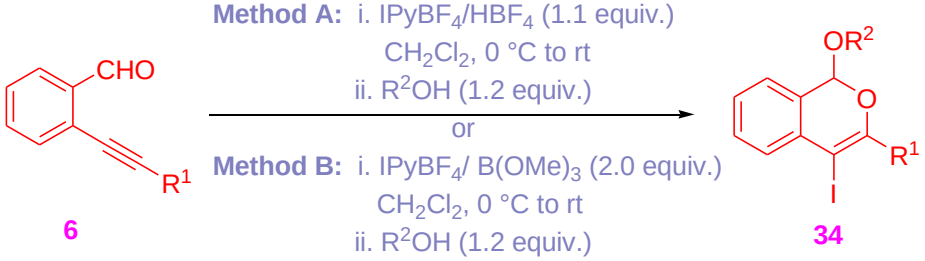
Eq. 7



Synthesis of 4-iodo-1*H*-isochromenes

Barluenga *et al.* explored the synthesis of iodo adducts of 1*H*-isochromene *via* iodine mediated annulations (**Eq. 8**).[13] Their strategy involves iodonium *tetra*-fluoroborate $(IPy_2BF_4)_6$ mediated formation of oxonium intermediate followed by the attack of nucleophiles such as alcohols, as well as different *C*-nucleophiles.

Eq. 8

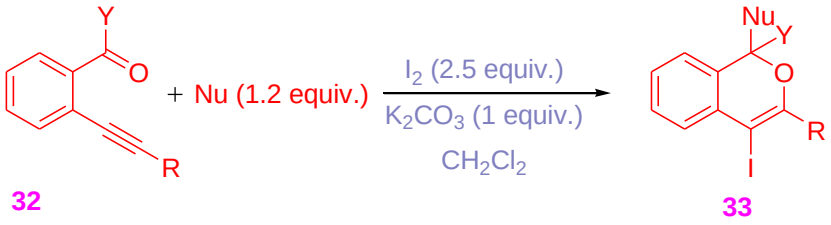


R^1 = alkyl, aryl and alkenyl

Synthesis of isochromenes and naphthalenes

Larock *et al.* reported the synthesis of 1*H*-isochromenes, isobenzofurans, and pyranopyridines naphthyl ketones and iodides by the reaction of *o*-(1-alkynyl)arenecarboxaldehydes with respective reagents, I_2, ICl, NIS/I_2 and simple alkynes/alkenes (**Eq. 9**).[14] They showed that these cyclizations proceed by *anti*-attack of the electrophile and the carbonyl to produce a pyrilium intermediate, this intermediate is immediately trapped by the nucleophile present in the reaction mixture.

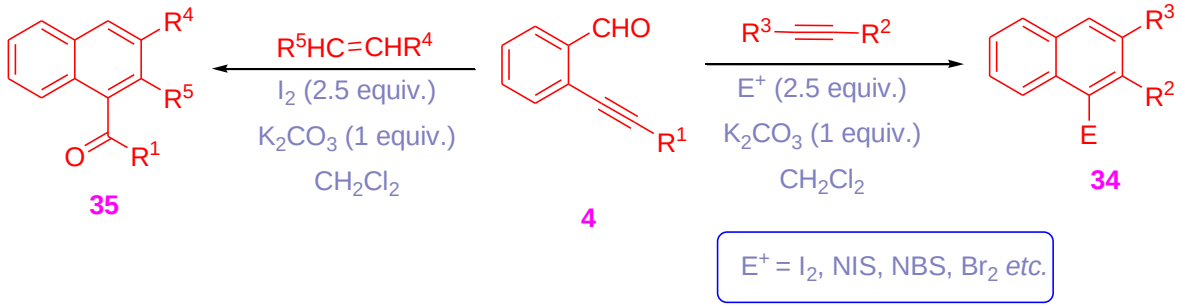
Eq. 9



Y = H, CH_3

R = alkyl, vinylic, aryl, etc.

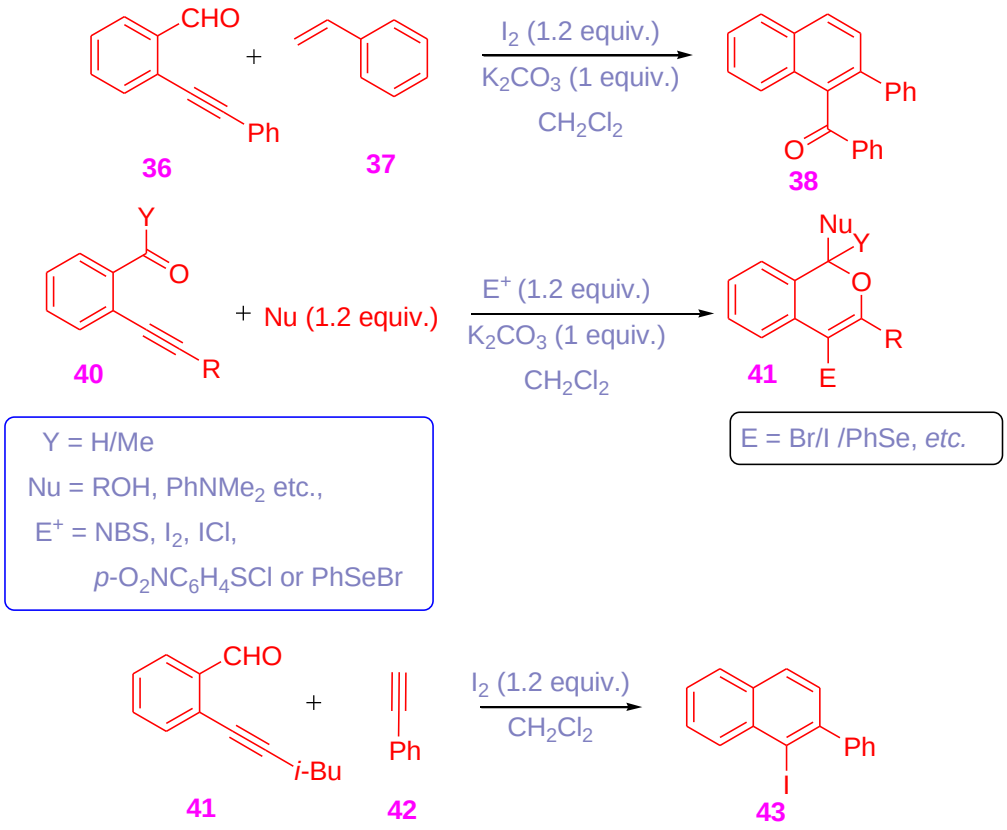
Nu = MeOH, EtOH, PhOH



Synthesis of isochromene and napthylketone

Larock *et al.* demonstrated the synthesis of substituted isochromene from *o*-alkynylaldehydes. It involves reaction of *o*-(1-alkynyl)-substituted arene carbonyl compounds with NBS, I_2, ICl, *p*-$O_2NC_6H_4SCl$, or PhSeBr and various alcohols or carbon-based nucleophiles to afford the desired products **38**, **41** and **43** (**Eq. 10**).[15] They also demonstrated the synthesis of substituted naphthalene derivatives with alkene and alkyne as trapping reactions.

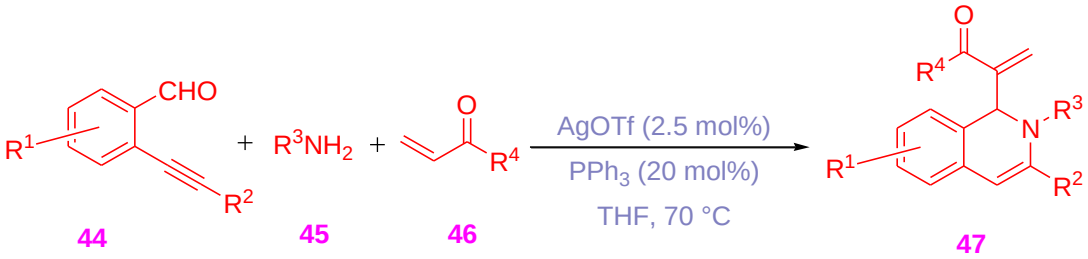
Eq. 10



Synthesis of 1, 2-dihydroisoquinoline derivatives

Wu *et al.* demonstrated the synthesis of 1,2-dihydroisoquinolines **47** by the three-component reaction of *ortho*-alkynylbenzaldehyde, amine, and α, β-unsaturated ketones (**Eq. 11**).[16] They utilized the combined catalytic system of an inorganic catalyst AgOTf and catalytic amount of an organic catalyst, PPh_3. The reaction proceeds under mild reaction conditions and gave the desired products in good yields.

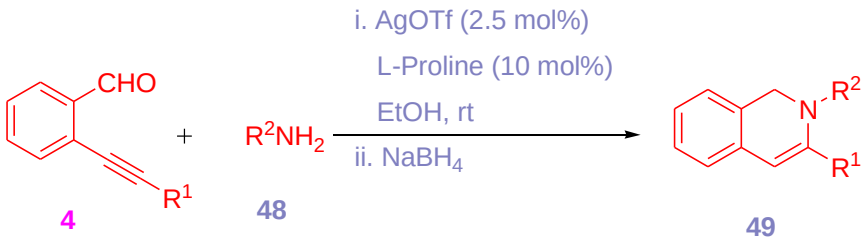
Eq. 11



44 45 46 47

Wu *et al.* developed the facile protocol for the synthesis of 1,2-dihydroisoquinoline derivatives (**49**) by the one-pot reactions of 2-alkynylbenzaldehydes, amines, and sodium borohydride catalyzed by AgOTf (**Eq. 12**).[17]

Eq. 12

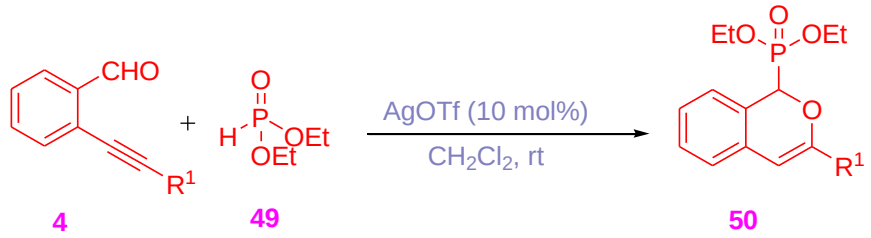


4 48 49

Synthesis 1*H*-isochromen-1-ylphosphonates

Wu *et al.* reported the tandem cyclization-addition reaction of *ortho*-alkynylbenzaldehyde with diethyl phosphate to synthesis 1*H*-isochromen-1-ylphosphonates **50** in room temperature using AgOTf as catalyst (**Eq. 13**).[18] They used various *ortho*-alkynylaldehydes to prove the scope and generality of the methodology.

Eq. 13

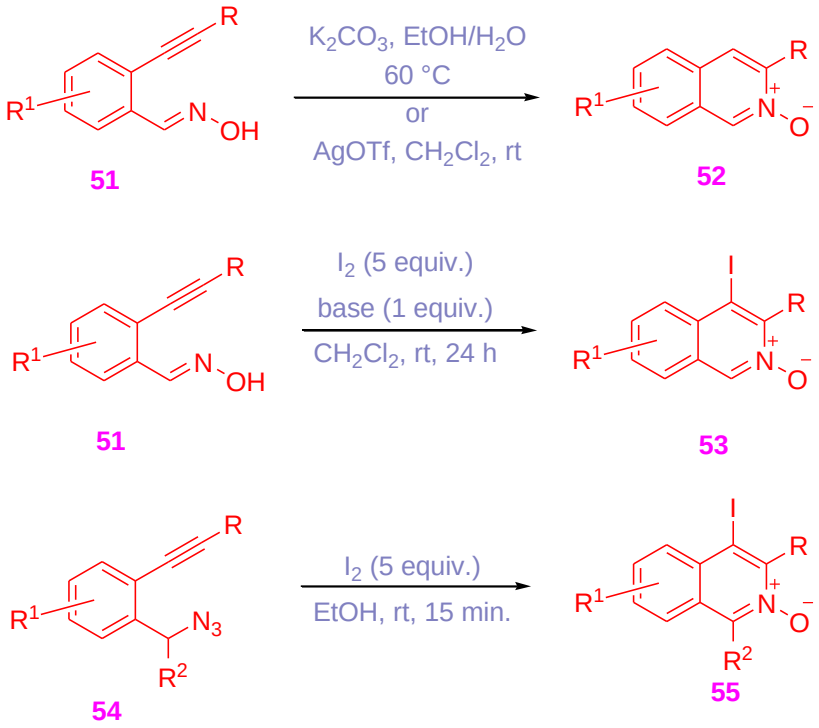


4 49 50

Synthesis of isoquinoline-*N*-oxides and iodoisoquinoline-*N*-oxide

Yamamoto *et al.* reported the synthesis of isoquinoline *N*-oxides under very mild, metal free conditions from *ortho*-alkynylbenzaldoximes and iodine in EtOH (**Eq. 14**).[19]

Eq. 14

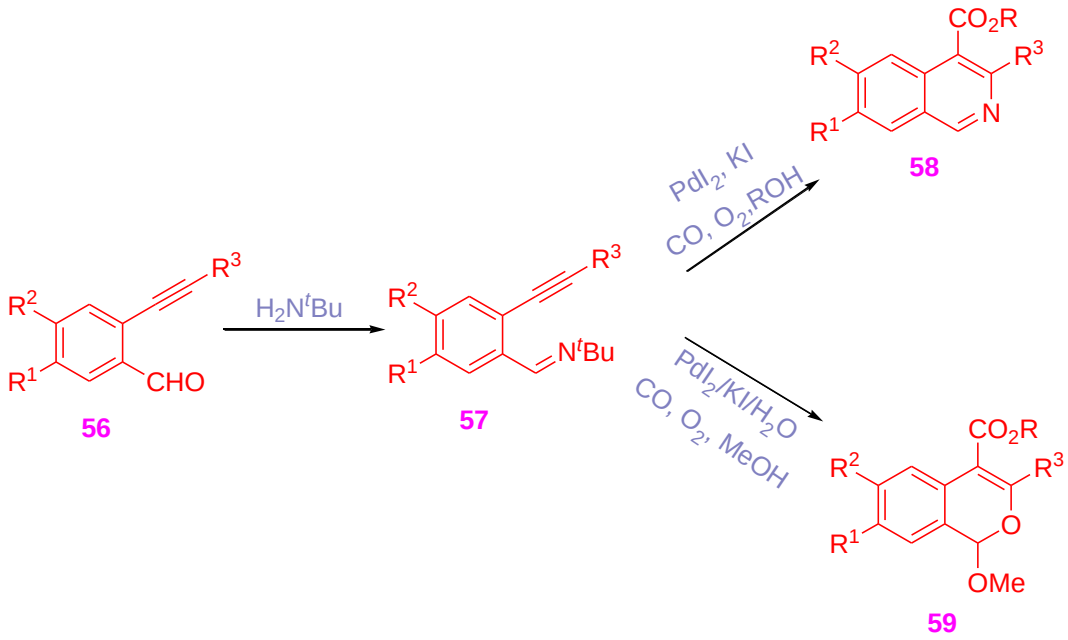


51 52 51 53 54 55

Synthesis of isoquinolines and isochromenes

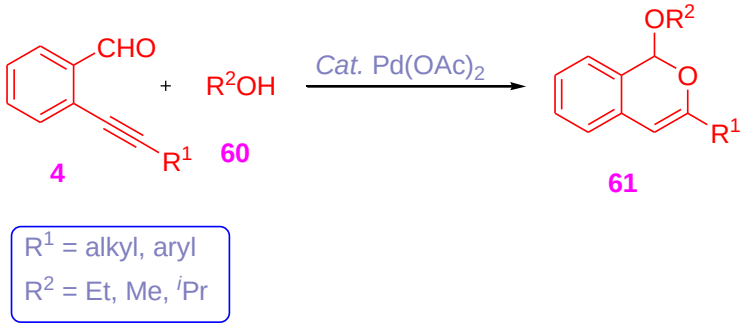
Gabriele *et al.* disclosed the synthesis of isoquinoline-4-carboxylic esters **58** and isochromene-4-carboxylic esters **59** from PdI_2-catalyzed oxidative heterocyclization/alkoxycarbonylation of (2-alkynylbenzylidene)amine derivatives **57** (**Eq. 15**).[20]

Eq. 15



Yamamoto *et al.* explored the synthesis of 1*H*-isochromenes by palladium catalyzed cyclization *o*-(1-alkynyl)arenecarboxaldehydes in ethanol as solvent (**Eq. 16**).[21]

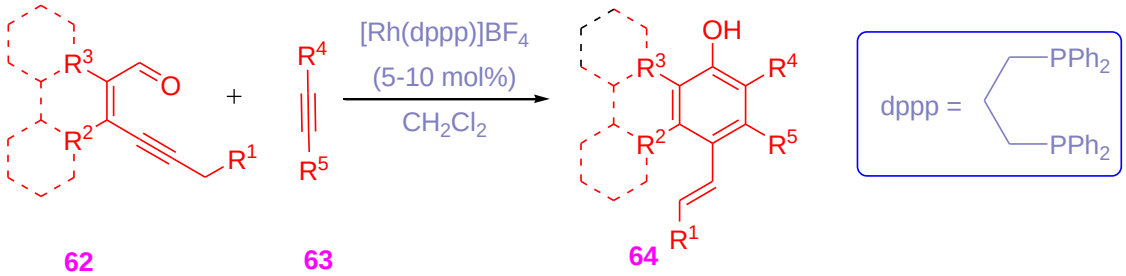
Eq. 16



Synthesis of phenol, naphthol, phenanthrenol and triphenylenol derivatives

Tanaka *et al.* demonstraded the synthesis of phenol, naphthol, phenanthrenol, and triphenylenol derivatives from *o*-alkynyl aldehydes and alkynes through a rhodium complex catalyzed C-H bond activation strategy (**Eq. 17**).[22]

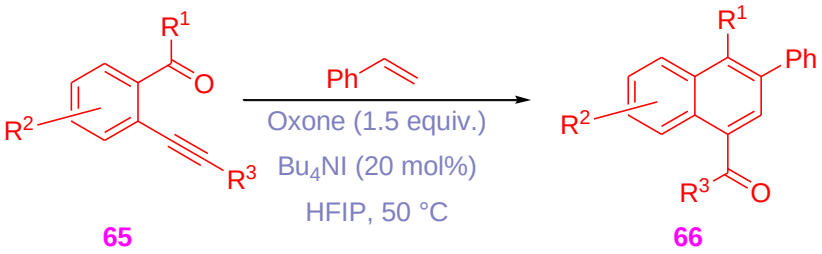
Eq. 17



Synthesis of highly substituted 1-naphthalenones

Nachtsheim *et al.* developed catalytic iodonium-mediated benzannulation protocol for the synthesis of highly substituted 1-naphthalenones (**66**, **Eq. 18**).[23] They accomplished the efficient iodine-catalyzed transformation with use of fluorinated protic solvents, in particular, HFIP and oxone as the co-oxidant. In this report, the first application of (hypo)iodite catalysis in Barluenga's iodocyclization/cycloaddition/elimination cascade reaction is demonstrated.

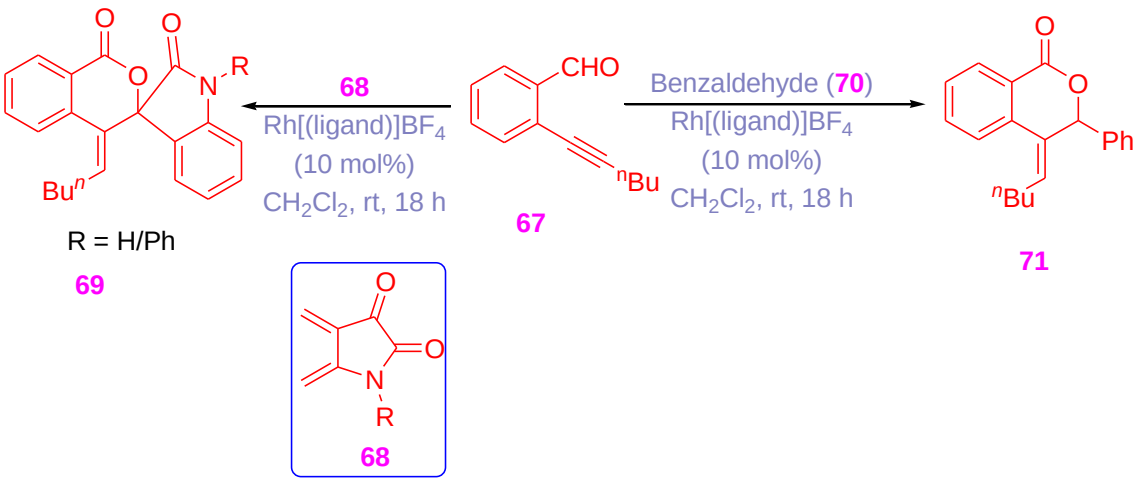
Eq. 18



Synthesis of spirocyclic benzopyranones and isatin

Tanaka *et al.* developed a cationic rhodium(I)/(*R*,*R*)-walphos-catalyzed highly enantioselective-[4+2] annulation of *ortho*-alkynylbenzaldehydes with cyclic electron-deficient carbonyl compounds to afford enantio-enriched spirocyclic benzopyranones and isatin derivatives **69, 71** (**Eq. 19**).[24] This methodology serves as a two-step route to formation of products starting from commercially available precursor.

Eq. 19



Synthesis of tetrahydro-1, 2-oxazine fused 1, 2-dihydroisoquinolines

Wu *et al.* reported the synthesis of tetrahydro-1,2-oxazine fused 1,2-dihydroisoquinolines **74** (**Eq. 20**).[25] Their protocol involves the combined AgOTf and $Yb(OTf)_3$ catalyzed tandem cyclization [3+3]-cycloaddition of *ortho*-alkynylbenzaldoximes with dimethyl cyclopropane-1,1-dicarboxylate. It is believed that, in the reaction process, initially the intermediate

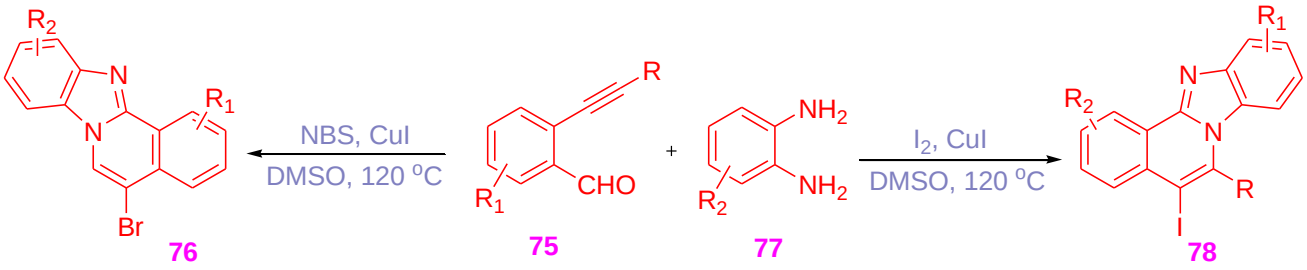
isoquinoline-*N*-oxide could be formed from 2-alkynylbenzaldoxime in the presence of silver triflate then it could be reacted with dimethyl cyclopropane-1,1-dicarboxylate in a [3+3] fashion to afford the desired product, 1,2-dihydroisoquinolines **74**.

Eq. 20

Synthesis of iodoisoquinoline-fused benzimidazoles

Li and co-workers reported an efficient tandem route to the synthesis of iodoisoquinoline-fused benzimidazole derivatives including an iodocyclization strategy (**Eq. 21**).[26] 2-Ethynylbenzaldehydes **75** underwent the tandem reaction with benzenediamines **77** in the presence of CuI and iodine/NBS to afford the corresponding iodoisoquinoline-substituted benzimidazoles **78**/bromoisoquinoline fused benzimidazoles **76** respectively. This protocol allows the formation of two heterocyclic rings in a one-pot reaction through the electrophilic annulation.

Eq. 21

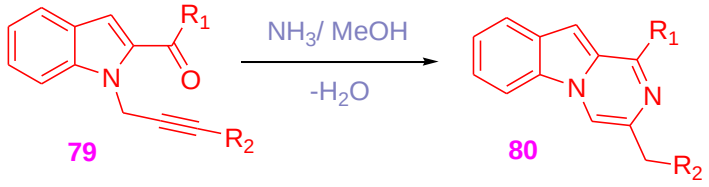


Synthesis of pyrazino[1,2-*a*]indoles

Abbiati *et al.* developed the methodology for the synthesis of pyrazino[1,2-*a*]indoles **80** in the presence of ammonia *via* intramolecular cyclization of several 2-carbonyl-1-propargylindoles **79** under heating. They demonstrated the reaction under microwave heating, where they could reduce the reaction time and improve overall yields (**Eq. 22**).[27] They showed the utility of $TiCl_4$ for the synthesis of pyrazinoindoles from 1-alkynyl-2-acetylindoles. It has been demonstrated that $TiCl_4$ catalysis drastically modifies the

cyclization kinetics for the 1-alkynyl-2-acetylindoles, allowing for the almost selective isolation of both isomers by appropriate choice of the reaction times.

Eq. 22

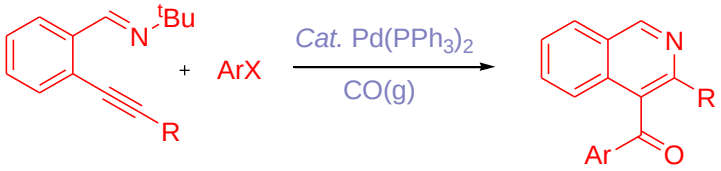


79 80

Synthesis of isoquinoline derivatives

Larock *et al.* developed 3-substituted-4-aroylisoquinolines **82** by the reaction of *o*-(1-alkynyl)benzaldimines (**81**) with aryl iodides and 1 atm of CO in the presence of tri-*n*-butylamines and $Pd(PPh_3)_2$ in good yields (**Eq. 23**).[28]

Eq. 23



81 82

Synthesis of quinoxalines and benzimidazoles

A green and operationally simple approach for the diverse synthesis of fused quinoxalines and benzimidazoles (**85**) from *o*-alkynylaldehydes and diamines using silver catalyst in water reported by A. K. Verma *et al.* (**Eq. 24**).[29]

Eq. 24

83 84 85

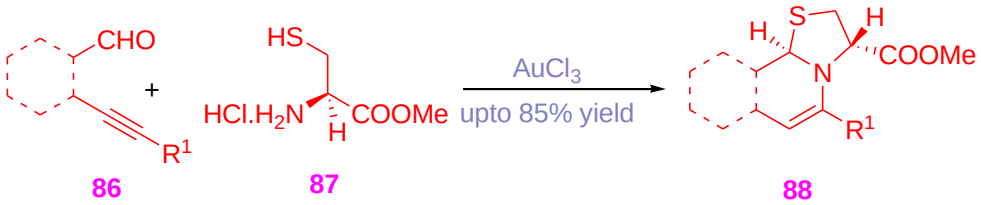
X = CH, N, S

Synthesis of thiazolo fused naphthyridines and thienopyridines

A. K. Verma *et al.* developed an operationally simple approach for the stereoselective tandem synthesis of thiazolo fused naphthyridines and thienopyridines **88** by the reaction of *ortho*-alkynylaldehydes **86** with *L*-Cystine methyl ester hydrochloride (**87**) *via* gold-catalyzed regioselective 6-*endo* annulation under mild reaction condition in good yields (**Eq. 25**).[30]

Alkynes bearing electron donating and electron withdrawing, alkyl, and acyl groups successfully afforded the corresponding products in good yield. Scope and generality of the reaction is well studied.

Eq. 25

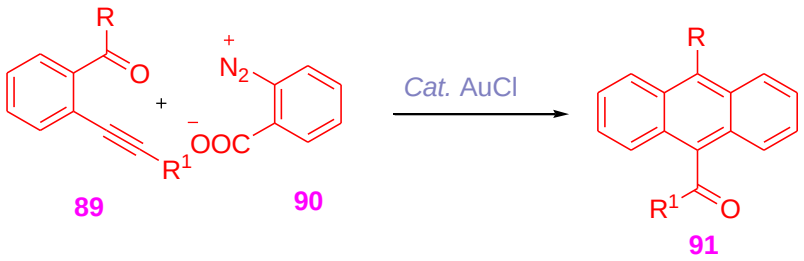


86 87 88

Synthesis of anthracene derivatives

Asao *et al.* reported the synthesis of a variety of anthracene derivatives by gold catalyzed benzannulation between *o*-alkynyl(oxo)benzene **89** and benzenediazonium-2-carboxylate **90** in good to high yield (**Eq. 26**). This reaction most probably proceeds through the reverse electron demand type Diels-Alder reaction between the benzopyrylium type intermediate and *in situ* generated benzyne.

Eq. 26

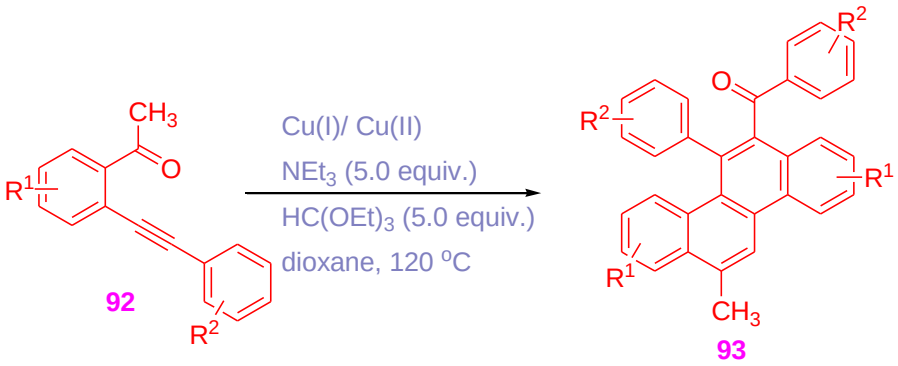


89 90 91

Synthesis of highly substituted chrysene derivatives

An efficient synthesis for highly substituted chrysene derivatives **93** was reported by Hua and co-workers (**Eq. 27**).[31] They have developed copper catalyzed dimerization of 2-alkynyl-1-acetylbenzene (**92**) in good yields. The reaction proceeds via isobenzopyrylium intermediate and then the intermolecular Diels-Alder reaction afforded the desired products.

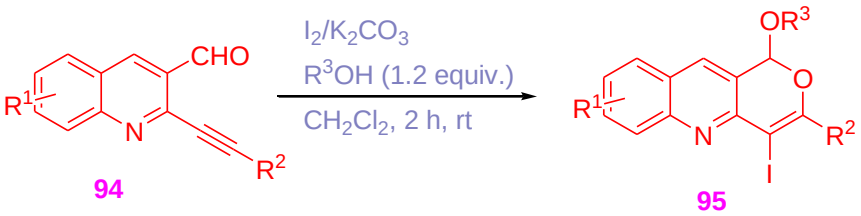
Eq. 27



Synthesis of pyrano[4,3-*b*]quinolines

A. K. Verma *et al.* reported the synthesis of pyrano[4,3-*b*]quinolines by electrophilic iodocyclization of corresponding *ortho*-alkynylaldehydes in good to excellent yields (**Eq. 28**).[32] Subsequently a diverse set of libraries were synthesized by employing palladium-catalyzed coupling reactions.

Eq. 28



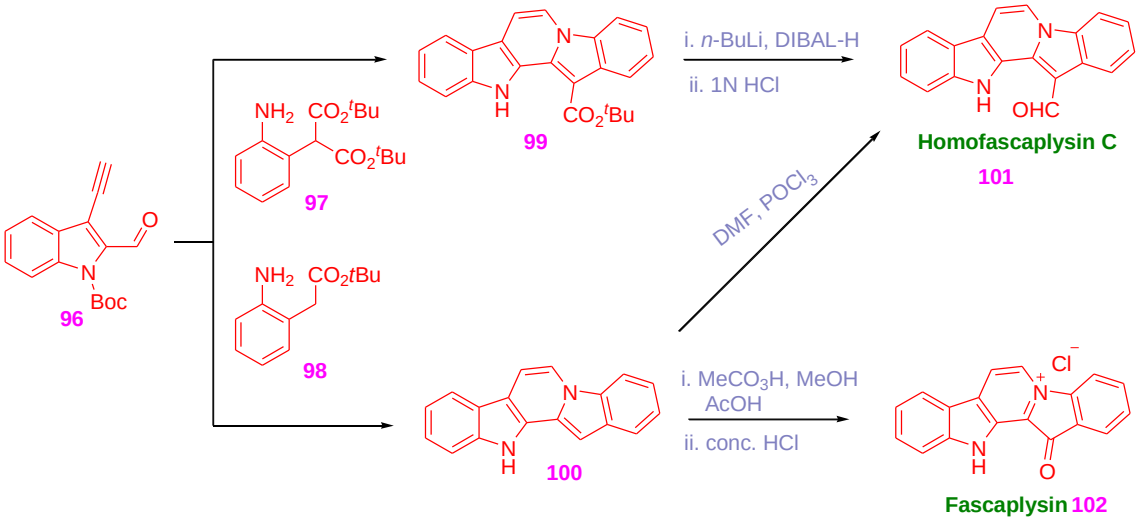
The literature reports depicted above is clearly established that *ortho*-alkynylaldehydes are versatile and powerful tool in organic synthesis. Next part of introduction, we discussed the total synthesis of natural products using alkynylaldehyde annulation as key step.

Total synthesis of natural products using alkynylaldehyde chemistry

Total synthesis of Fascaplysin and Homofascaplysin C

In 1988, Fascaplysin (**102**) was isolated from the marine sponge *fascaplysinopsis Bergquist* species collected in the south pacific near the Fiji Islands. It shows anti-microbial and cytotoxic activities.[33] Gribble *et al.* reported the first total synthesis of Fascaplysin and Homofascaplysin B and C.[34] Waldmann *et al.* employed Boc-protected 3-ethynyl-indole-2-carbaldehyde **96** as a common precursor for the natural products Fascaplysin (**102**) and Homofascaplysin C (**101**) (**Eq. 29**). Key step in the total synthesis involves alkynylaldehyde heteroannulation.

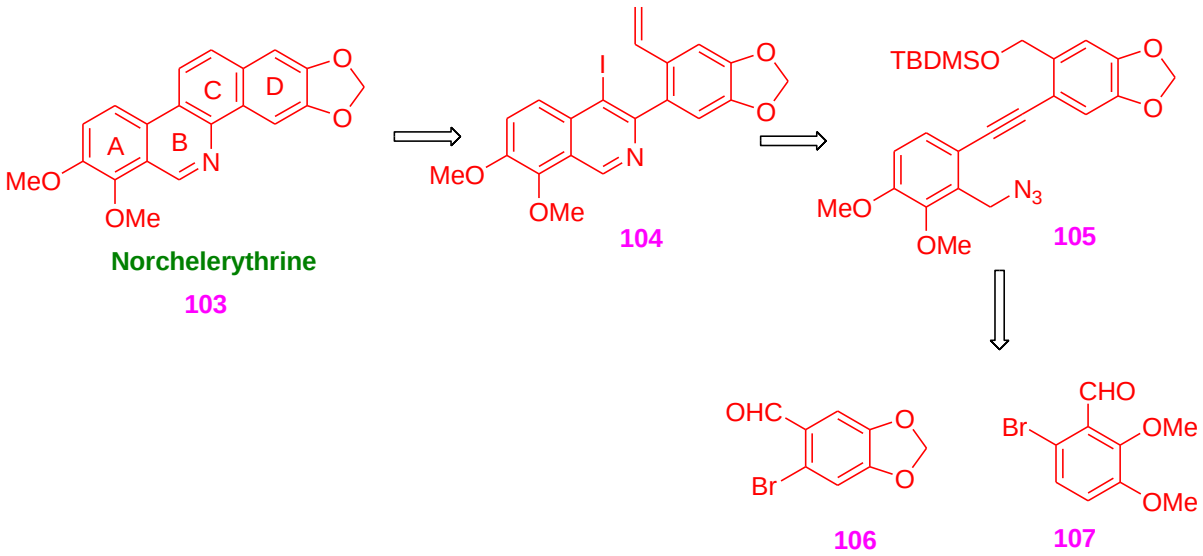
Eq. 29



Total synthesis of Norchelerythrine

Yamamoto *et al.* reported the total synthesis of Norchelerythrine[35] (**103**) (antitumor and antiviral agent) based on iodine mediated annulation of 2-alkynyl-1-methylene azide aromatics **105**. Key step for the total synthesis involves the annulation of alkynylazide. Their retrosynthetic approach is shown in **Eq. 30**, which involved the construction of a key fragment containing a 3,4-disubstituted isoquinoline **104**.

Eq. 30

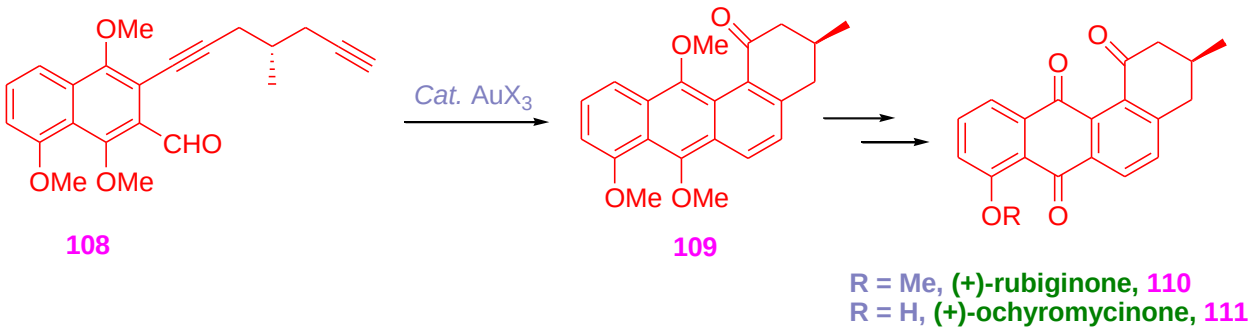


Total synthesis of (+)-Rubiginone and (+)-Ochyromycinone

In 2005, an efficient synthetic approach to the total synthesis of angucyclinone antibiotics, (+)-Rubiginone (**110**) and (+)-Ochromycinone (**111**) was reported by Yamamoto group (**Eq. 31**).[36] The key step involves in the total synthesis is the facile formation of 2,3-

dihydrophenantren-4(1*H*)-one skeleton, an important framework of angucyclinone natural products, by using gold-catalyzed intramolecular [4+2]-benzannulation reaction using alkynylaldehyde annulation.

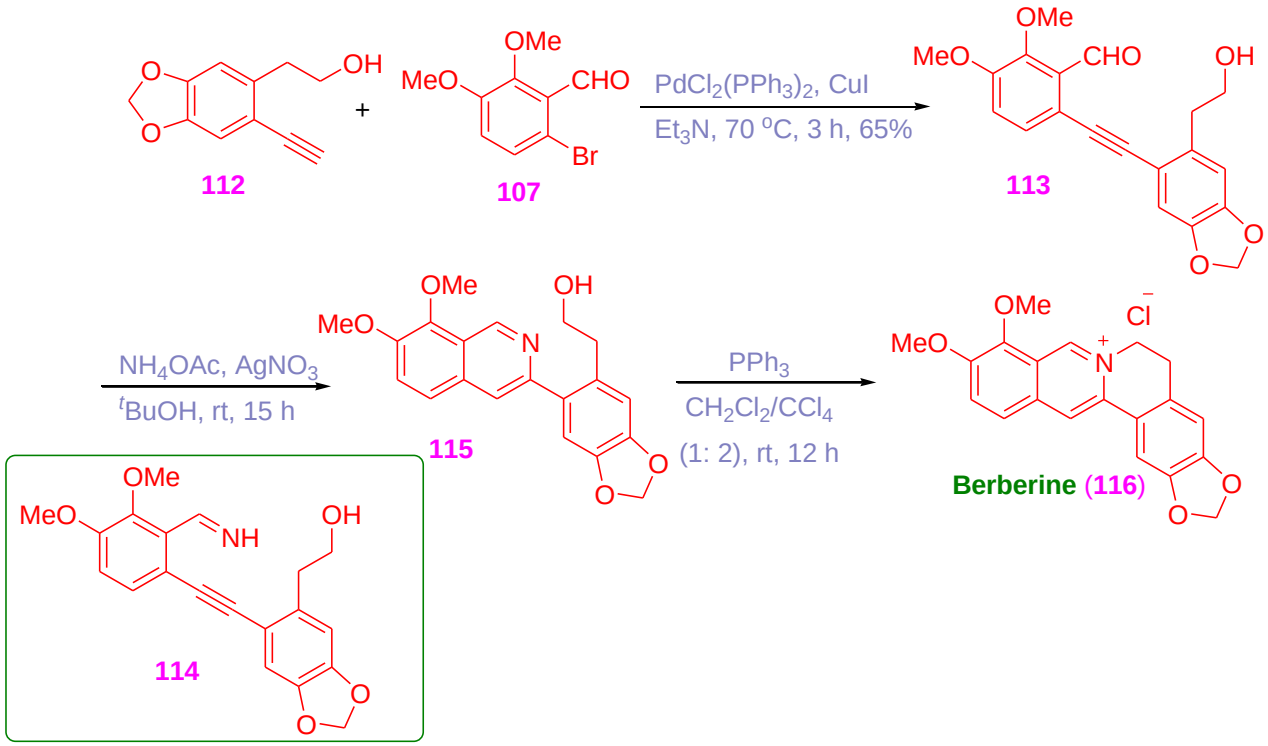
Eq. 31



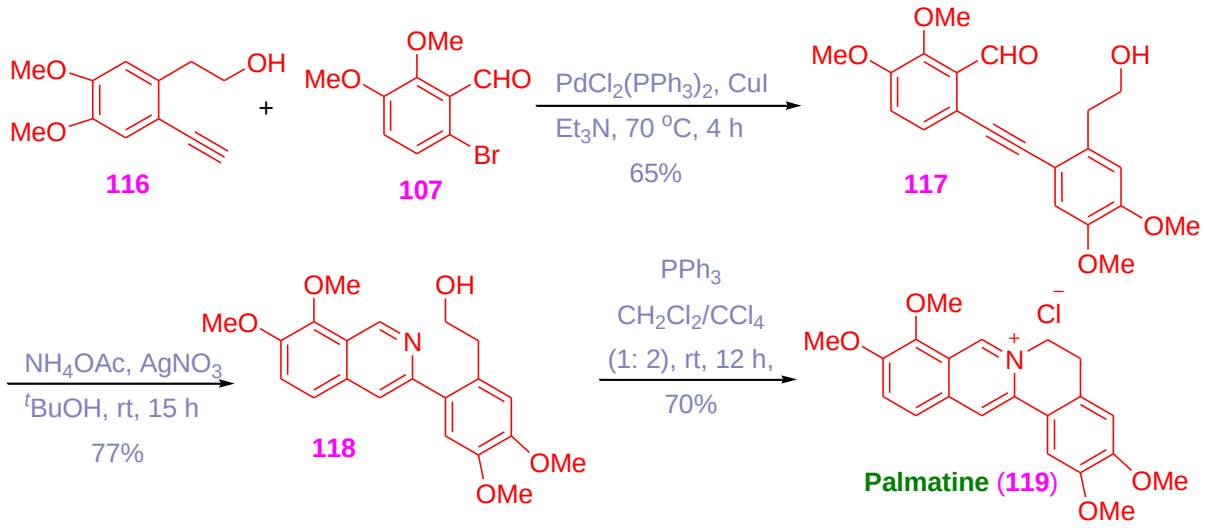
Total synthesis of Berberine and Palmatine

Recently, Anand and co-workers utilized the alkynylaldehyde chemistry to form the isoquinoline core in the total synthesis of Berberine **116** (**Eq. 32**) and Palmatine **119** (**Eq. 33**).[37] In this total synthesis, they prepared the corresponding alkynylaldehyde starting materials, then cyclized to afford the isoquinoline core of **116** and **119**.

Eq. 32



Eq. 33



From the above reports we decided to explore the *ortho*-alkynylaldehyde heteroannulation on various heterocyclic systems to synthesize various new biologically active compounds. To date, this chemistry on heterocyclic system is less explored. The investigation of this heteroannulation, would create the great scope in scientific community.

Objectives of the present investigation

In this thesis, the goal is to explore the synthetic utility of *ortho*-alkynylaldehyde heteroannulation chemistry towards the synthesis of nitrogen heterocycles and total synthesis of the marine natural products.

Thesis Organization

In the present study, we focused on exploring the synthesis of heteroarylcarbazoles (benzo[*b*]carbazoles, indolo[2,3-*b*]carbazoles, carbazolo[2,3-*b*]carbazoles and quino[2,3-*b*]carbazoles), benzonapthyridine derivatives, azepinoindole derivatives utilizing the alkynylaldehyde annulations (**Chapter 1-3**). The alkynylaldehyde annulation chemistry was used as key step for the total synthesis of the marine alkaloids; Mansouramycin D, Caulibugulone A, D and Hyrtioerectine E (**Chapter 4-6**).

Chapters are organized as follows;

1. In chapter 1, To develop an efficient synthesis of 5*H*-benzo[*b*]-, carbazolo[2,3-*b*]-, indolo[2,3-*b*]-and quino[2,3-*b*]carbazole derivatives *via* copper(II)-triflate catalyzed heteroannulation using corresponding heteroaryl-*ortho*-alkynylaldehydes. Application of

quino[2,3-*b*]carbazoles has been demonstrated as sensing of TNT using titration of quino[2,3-*b*]carbazole and various concentration of TNT and other nitroaromatics. Sensing behavior and physical properties (solid state absorbance and emission) are studied and are clearly explained by the crystal packing studies from single crystal X-ray analysis.

2. In chapter 2, we developed the convenient method for the synthesis of indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines *via* copper(II)-triflate catalyzed heteroannulation using corresponding quinoline-1,2-alkynylaldehydes.

3. In chapter 3, we reported the synthesis of indolodiazepenes *via* 7-*endo* selective cyclization using indole-1,2-alkynylaldehydes and isocyanides, and the same methodology has been applied to the synthesis of Chromoazepinone core using corresponding alkynylaldehydes.

4. In chapter 4, we described the first successful and concise total synthesis of Mansouramycin D (a marine alkaloid) involving intramolecular iminoannulation as key ring closure step. The overall yield of the total synthesis is very high; 54.5 to 60.9%.

5. In chapter 5, we reported a new route to the total synthesis of the marine alkaloids Caulibugulone A and D *via* alkynylaldehyde iminoannulation with overall yield of 62% and 60% respectively.

6. In chapter 6, we demonstrated the first total synthesis of the putative structure of the marine alkaloid Hyrtioerectine E, key features of the total synthesis involves intermolecular iminoannulation followed by deprotection sequence.

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CHAPTER 1

Synthesis of 5*H*-benzo[*b*]-, carbazolo[2,3-*b*]-, indolo[2,3-*b*]-and quino[2,3-*b*]carbazole derivatives *via* heteroannulation

1.1. Introduction

Over the past few years, carbazole and its fused aromatic systems were found to display a wide range of attractive biological activities.[38] Of its fused aromatic systems, syntheses of benzannulated and heteroannulated carbazole analogues are vital as they are not found in abundance in natural sources. They exhibit promising biological activities,[39] especially antitumor activity.[40] In particular, benzo[*a*]carbazole derivatives have been found to have binding affinities for the estrogen receptor, and inhibit the mammary tumors of rats.[41a] Benzo[*b*]carbazole derivatives **120** and 1**21** (Figure 1) show cytostatic activity against leukemia type L 1210 cell culture[41b] and potential bifunctional nucleic acid intercalating property[41c] respectively.

Ever since the first isolation of indolocarbazole in 1977, organic chemists are interested in the synthesis of indolocarbazole and its derivatives due to their biological activities.[42] 6-Formylindolo[3,2-*b*]carbazole **122** and 6,12-diformylindolo[3,2-*b*]carbazole **123** (Figure 1) are reported to be highly efficient ligands for the Ah receptor.[43] Carbazolocarbazole derivatives are explored in the field of organic electronics,[44] anion binding studies[45] and organic dyes.[46] Although the structure of carbazolocarbazole was first reported in 1965, these derivatives did not receive much attention and only a few reports were available for their synthesis.[44-46]

In recent years, there has been an immense interest in the cyclization of phenylacetylenes that have a halo[47] or a carbonyl or an imino group in *ortho* position by employing various catalysts.[48,49,52] Similarly, Lewis-acid-mediated domino reaction has been proven to be a powerful method in the synthesis of a wide variety of polycyclic heterocycles.[51,56] Yamamoto group described iodine-mediated electrophilic cyclization of 2-alkynyl-1-methyleneazide,[50] Lewis acid catalyzed benzannulation of *o*-alkynyl(oxo)benzenes with alkynes,[51a] alkenes[51b] and enols.[51c] Barluenga *et al.* developed a new metal free protocol for consecutive C-O and C-C bond formation using IPy_2BF_4.[52] Especially, Larock *et al.* reported the reaction of alkynes having *tert*-butylimino group

close to the carbon-carbon triple bond catalysed by copper,[53a-c] palladium;[53d, e] and cyclization induced by electrophile.[53f] Jana *et al.* developed intramolecular alkyne-carbonyl metathesis under iron catalyzed condition.[54] Very recently, Cao and colleagues have reported Pd-catalyzed sequential reaction for the synthesis of *δ*-carbolines using Larock heteroannulation/elimination/electrocyclization and oxidative aromatization.[55]

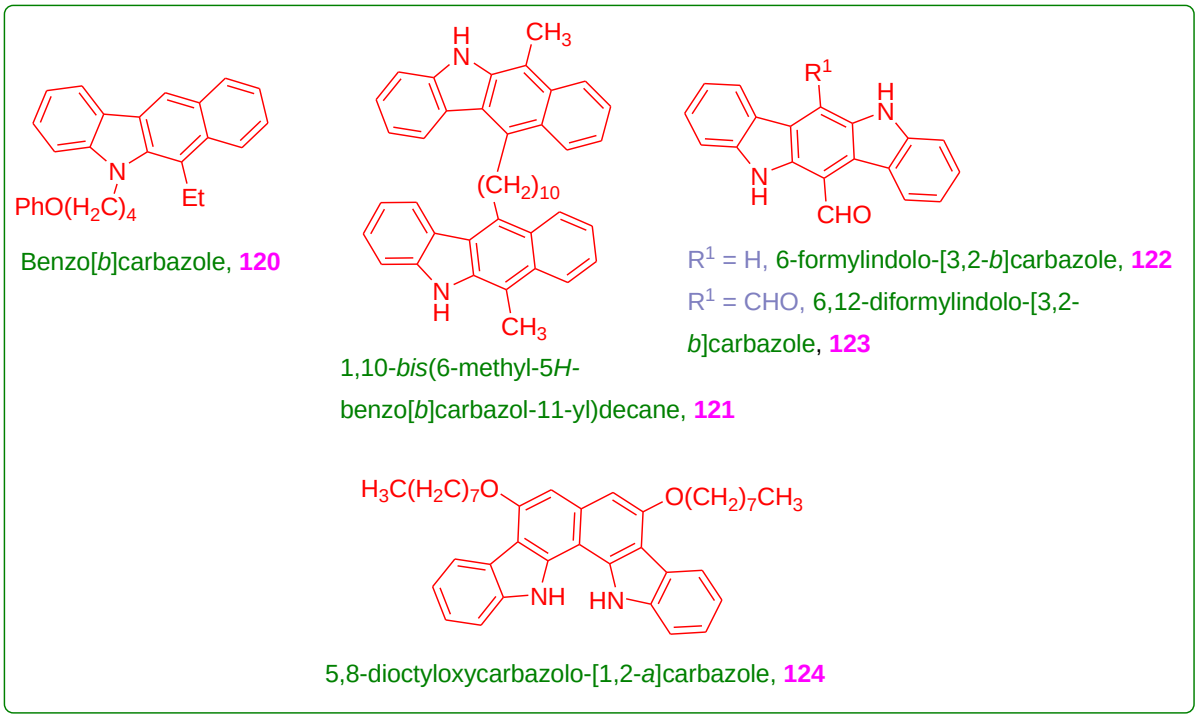


Fig. 1. Structures of important benzo, indolo, and carbazolocarbazole derivatives

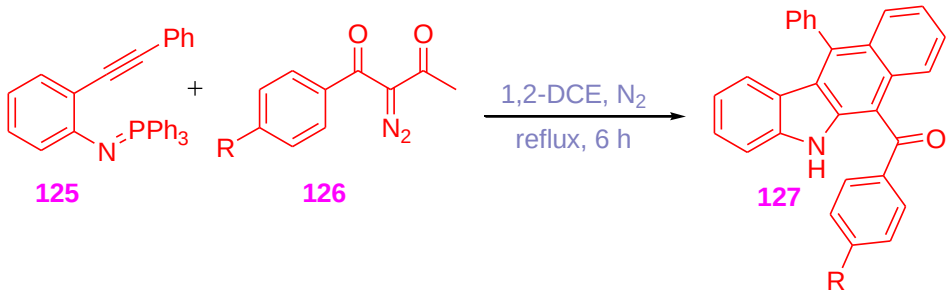
However, to the best of our knowledge, very few reports have been in the literature for the annulation of indole and 2-ethynylbenzaldehyde,[57a-b] and hetero-aryl alkynylaldehyde with indoles was unexplored. Thus, development of synthetic methods for annulated carbazole is sure to open up new opportunities to utilize these compounds as organic materials as well as in their biological applications. In this chapter, we successfully synthesised the 5*H*-benzo[*b*]-, carbazolo[2,3-*b*]-, indolo[2,3-*b*]- and quino[2,3-*b*]-carbazole derivatives *via* copper(II) triflate-catalyzed annulation and the quino[2,3-*b*]carbazole analogues are proved that the new analogues of solid state fluorescent candidates and their preliminary photophysical properties are studied and application as chemosensory material for detection of trinitrotoluene (TNT) was demonstrated.

In the following section of this chapter, literature survey on the synthesis of benzocarbazoles, indolocarbazoles, carbazolocarbazoles and quinocarbazoles is presented.

Synthesis of benzocarbazoles

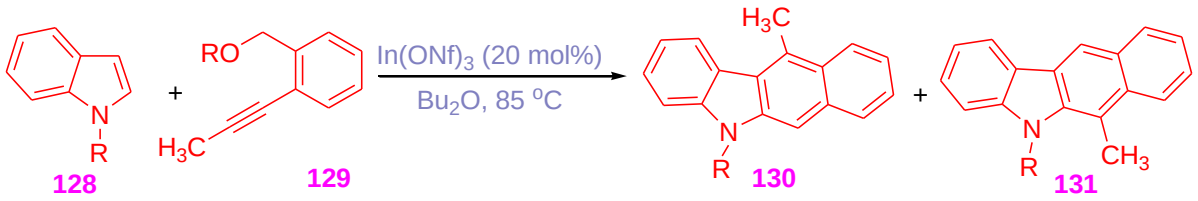
Wang *et al.* developed a strategy to synthesis of 5*H*-benzo[*b*]carbazoles *via* a tandem reaction between 2-ethynyl-*N*-triphenylphosphoranylidene anilines **125** and *α*-diazoketones **126** *via* ketenimine intermediates (**Eq. 34**).[58] This reaction involved a tandem Wolff-rearrangement/aza-Wittig-reaction/biradical-cyclization/1,5-H shift process.

Eq. 34



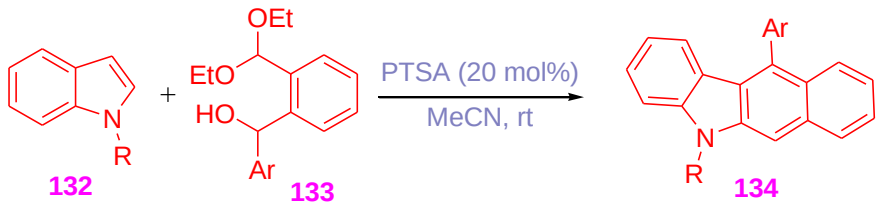
Tsuchimoto *et al.* developed a new synthetic method of heteroaryl-carbazoles **130** and **131** by the indium-catalyzed annulation of indoles with ethyl(2-ethynylaryl)methyl carbonates **129** (**Eq. 35**).[59] The reaction proceeds in one pot through the two carbon-carbon bond forming cascade. They reported the photoluminescent properties of the benzocarbazoles and compared with those of the corresponding [*a*]- and [*c*]-types, thereby they found, light-emitting efficiency as [*a*]- < [*b*]- < [*c*]-type.

Eq. 35



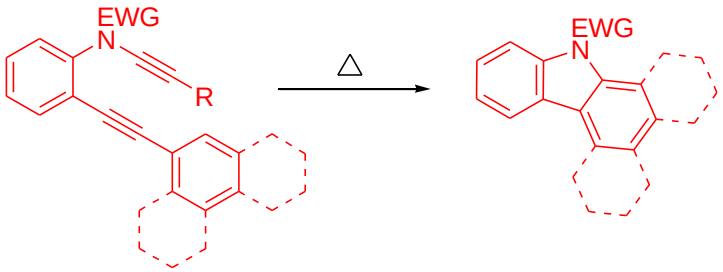
Sanz and co-workers demonstrated an efficient metal free synthesis of benzo[*b*]carbazoles **134** by Brønsted acid-catalyzed reactions between C-2, C-3-unsubstituted indoles **132** and *ortho*-[*α*-(hydroxy)benzyl]benzaldehyde acetals **133** (**Eq. 36**).[60] Key step involved is highly selective migration processes, and the overall cascade sequence which involves the one-pot formation of two new bonds and the annulation by regioselective fashion.

Eq. 36



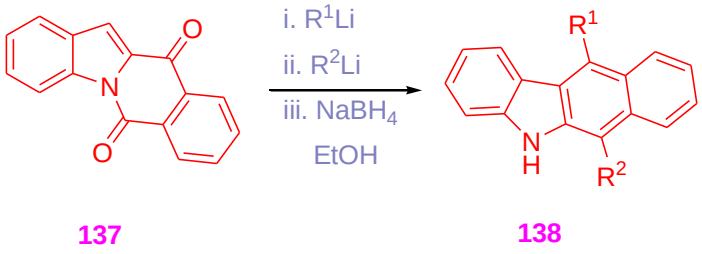
Saa *et al.* developed a new protocol for the synthesis carbazoles and benzocarbazole analogues by intramolecular dehydro Diels-Alder reactions of ynamides **135**. (**Eq. 37**).[61]

Eq. 37



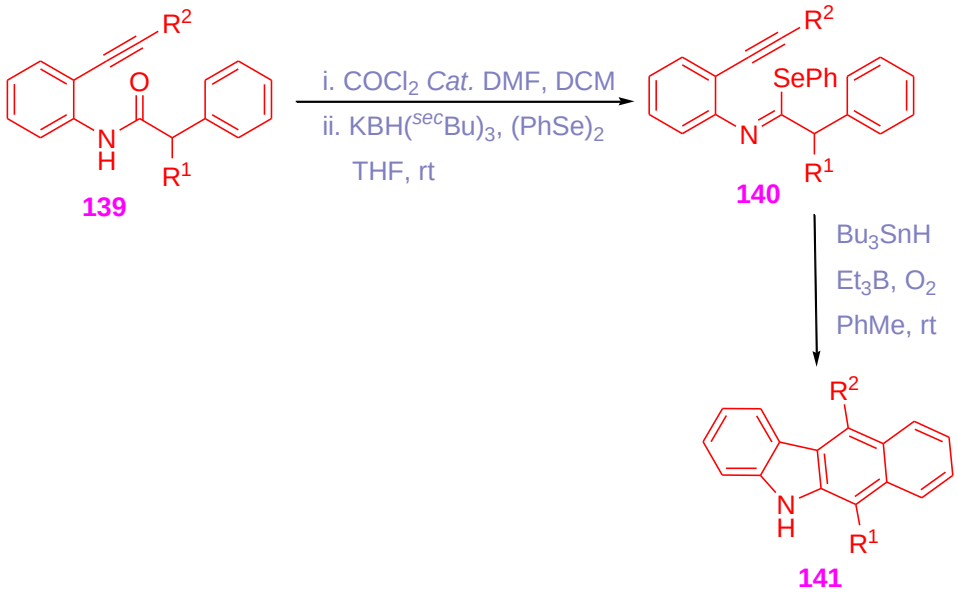
Gribble *et al.* reported the synthesis of 6,11-disubstituted 5*H*-benzo[*b*]carbazoles **138** by the sequential regioselective addition of organolithium reagents to indolo[1,2-*b*]isoquinoline-6,11-quinone **137** followed by sodium borohydride reduction of the intermediate diol (**Eq. 38**).[62]

Eq. 38



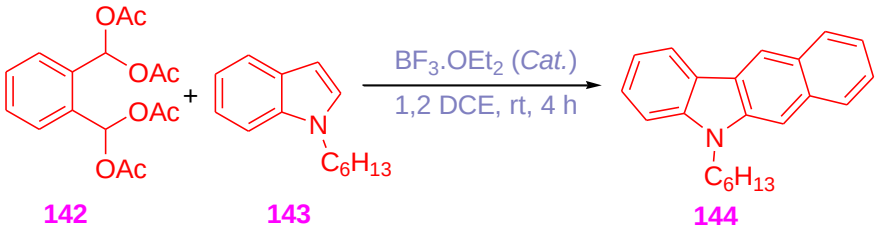
Bowman *et al.* developed a novel radical cascade protocol for the synthesis of aryl- and heteroaryl fused[*b*]carbazoles, this protocol has been applied to the total synthesis of the anticancer alkaloid ellipticine. (**Eq. 39**).[63]

Eq. 39



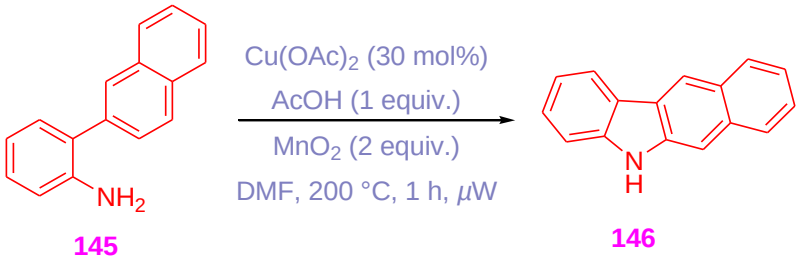
Mohanakrishnan *et al.* demonstrated a simple and one-pot synthesis of annulated heterocycles (**Eq. 40**).[64] Their strategy involves a Lewis-acid-mediated domino reaction of *bis*(diacetoxymethyl)-substituted arenes and heteroarenes. In this reaction, tetraacetates react with arenes and heteroarenes afforded the annulated product **144**.

Eq. 40



Miura *et al.* developed a method to synthesis of carbazole, benzocarbazole family ring systems by C-H activation under 30 mol% of $Cu(OAc)_2$ catalysis in conjunction with an MnO_2 as oxidant (**Eq. 41**).[65] The key to success is the incorporation of the picolinamide-based directing group, which was removed once the coupling occurs.

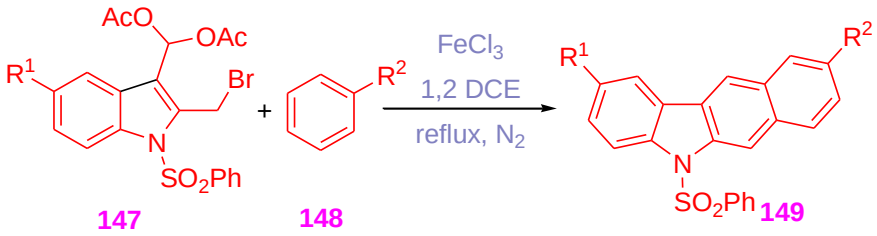
Eq. 41



Mohanakrishnan *et al.* reported a three-step and one-pot synthesis of annulated carbazoles (**Eq. 42**).[66] The protocol involves a Lewis-acid-mediated domino reaction of 2/3-(bromomethyl)

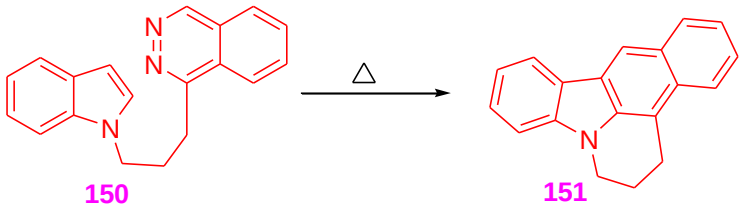
indoles with arenes/heteroarenes furnish the heteroarylcarbazoles (**149**). This three-step transformation proceeded by sequential Lewis acid catalysed Friedel-Crafts alkylation, electrocyclization and aromatization.

Eq. 42



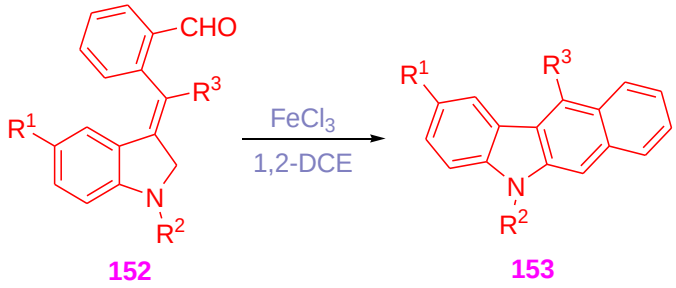
Kaferbock *et al.* developed a method for synthesis of multi ring condensed carbazoles by thermally induced intramolecular Diels-Alder reactions of 1,2-diazines tethered to indole dienophiles and alkylene chains (**Eq. 43**).[67] The reaction proceeds *via* [4+2]-cycloaddition.

Eq. 43



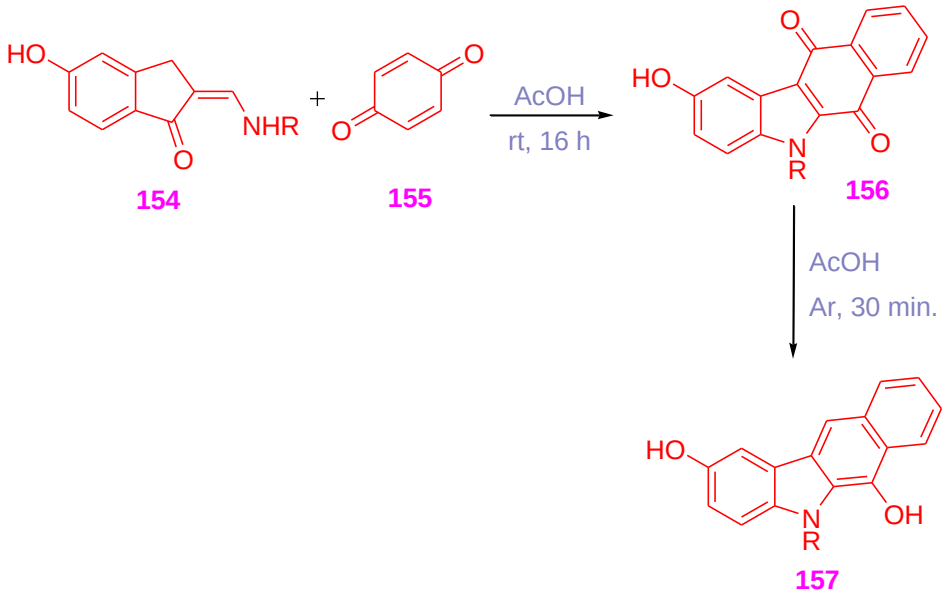
Jana *et al.* demonstrated an iron-catalyzed new protocol for the synthesis of benzocarbazoles **153** and the strategy involving domino isomerization/cyclodehydration sequences from substituted 2-[(indoline-3-ylidene)(methyl)]benzaldehyde derivatives **152** (**Eq. 44**).[68] This protocol was extended to other aromatics also.

Eq. 44



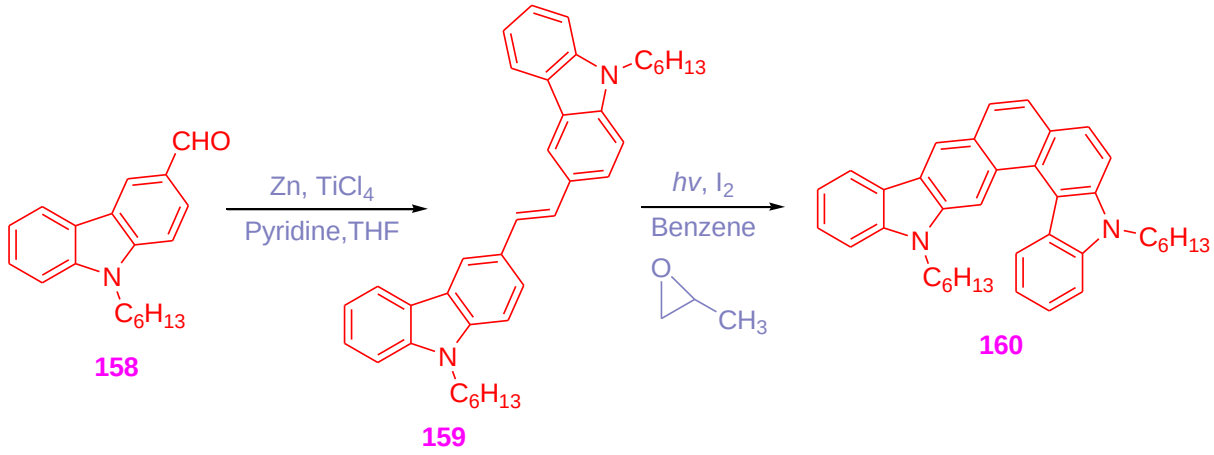
Asche *et al.* reported the synthesis of variety of benzocarbazole derivatives **157** by the reaction of *p*-benzoquinones **155** with 2-aminomethylene-1-indanones **154** in presence of acetic acid (**Eq. 45**).[69]

Eq. 45



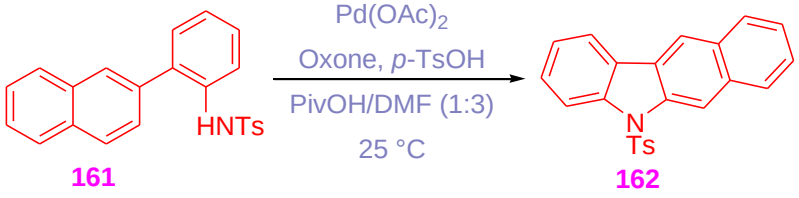
Liu *et. al.* developed the synthesis of a new carbazole-based diaza[7]helicene **160**, those are new carbazole based diaza[7]helicene using photochemical synthesis (**Eq. 46**).[70] Their physical properties were well studied and reported.

Eq. 46



Youn *et al.* reported Pd mediated oxidative C-H amination of *N*-Ts-2-arylanilines under ambient temperature using Oxone as an oxidant to afford carbazole, benzocarbazoles and their analogues (**Eq. 47**).[71]

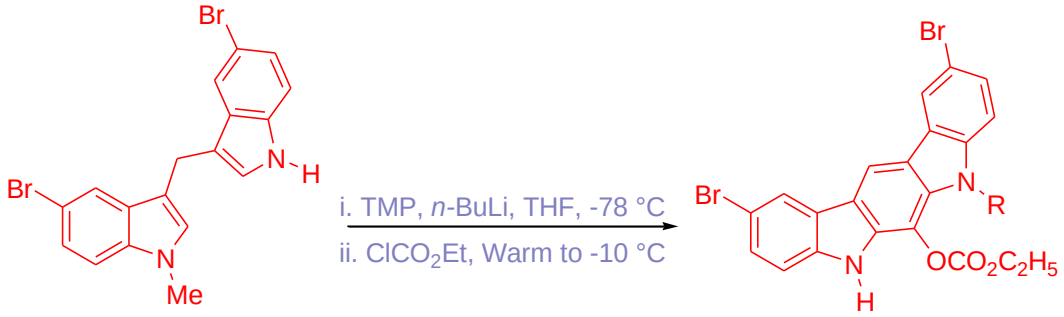
Eq. 47



Synthesis of indolocarbazoles

Jong *et al.* reported the synthesis of indolo[2,3-*b*]carbazole from *bis*(indol-3-yl)methane **163** (**Eq. 48**).[72] It involves the treatment of *bis*-indolylmethane with *n*-BuLi followed by ethylchloroformate /$(C_3F_7CO)_2O$ leads to formation of indolo[2,3-*b*]carbazole derivatives **164**.

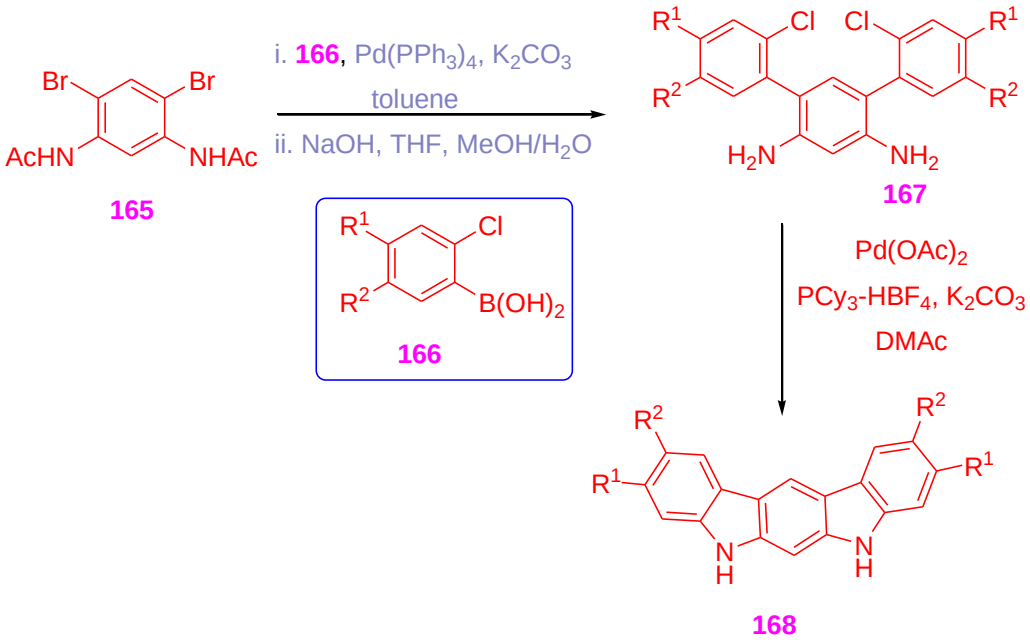
Eq. 48



163 164

Wong *et al.* developed a new strategy for the synthesis of indolo[2,3-*b*]carbazole **168** *via* a double intramolecular Buchwald-Hartwig reaction (**Eq. 49**).[73]

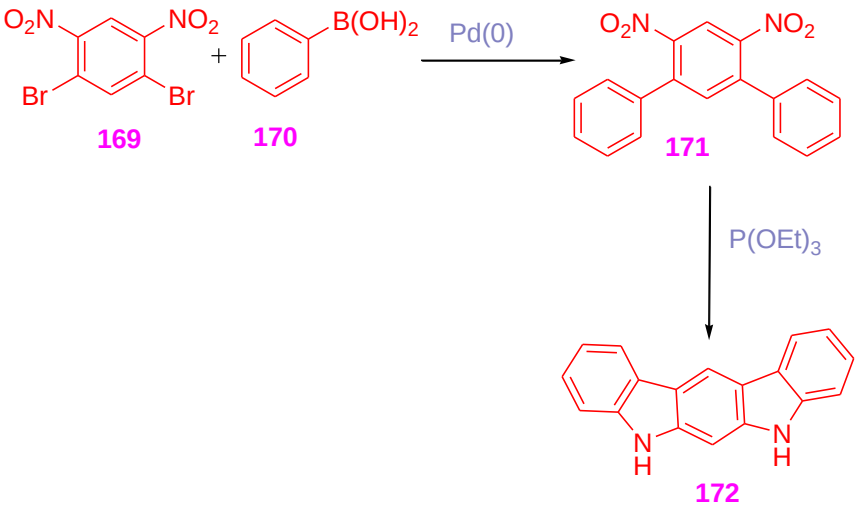
Eq. 49



165 166 167 168

Mullen *et al.* developed the methodology for the synthesis of 5,7-dihydroindolo[2,3-*b*]carbazole and 5,11-dihydroindolo[2,3-*b*]carbazole **172** by reductive cyclization of dinitrophenyl benzene **169** with triethyl phosphite as reducing agent (**Eq. 50**).[74]

Eq. 50

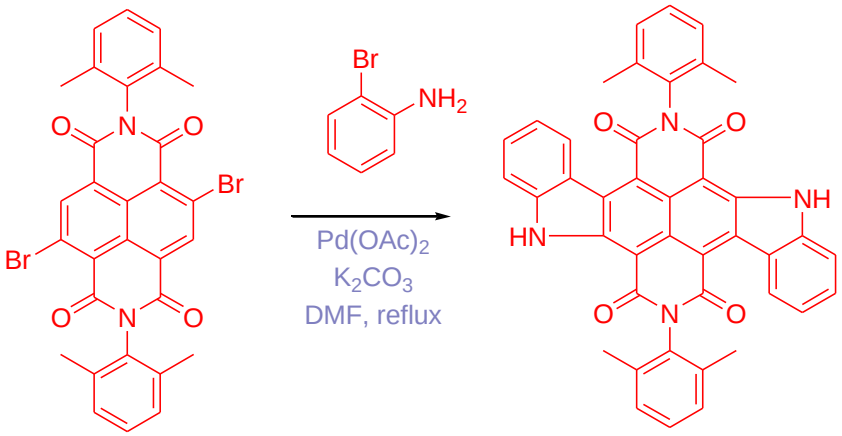


169 170 171 172

Synthesis of carbazolocarbazoles

In 2011, Würthner *et al.* developed a one-pot, two-step reaction synthesis of carbazolocarbazole diimide **174** (**Eq. 51**).[75] Their planning involves a substitution reaction followed by intramolecular coupling catalyst by palladium. They have studied this novel carbazolocarbazole diimide for semiconductor activity.

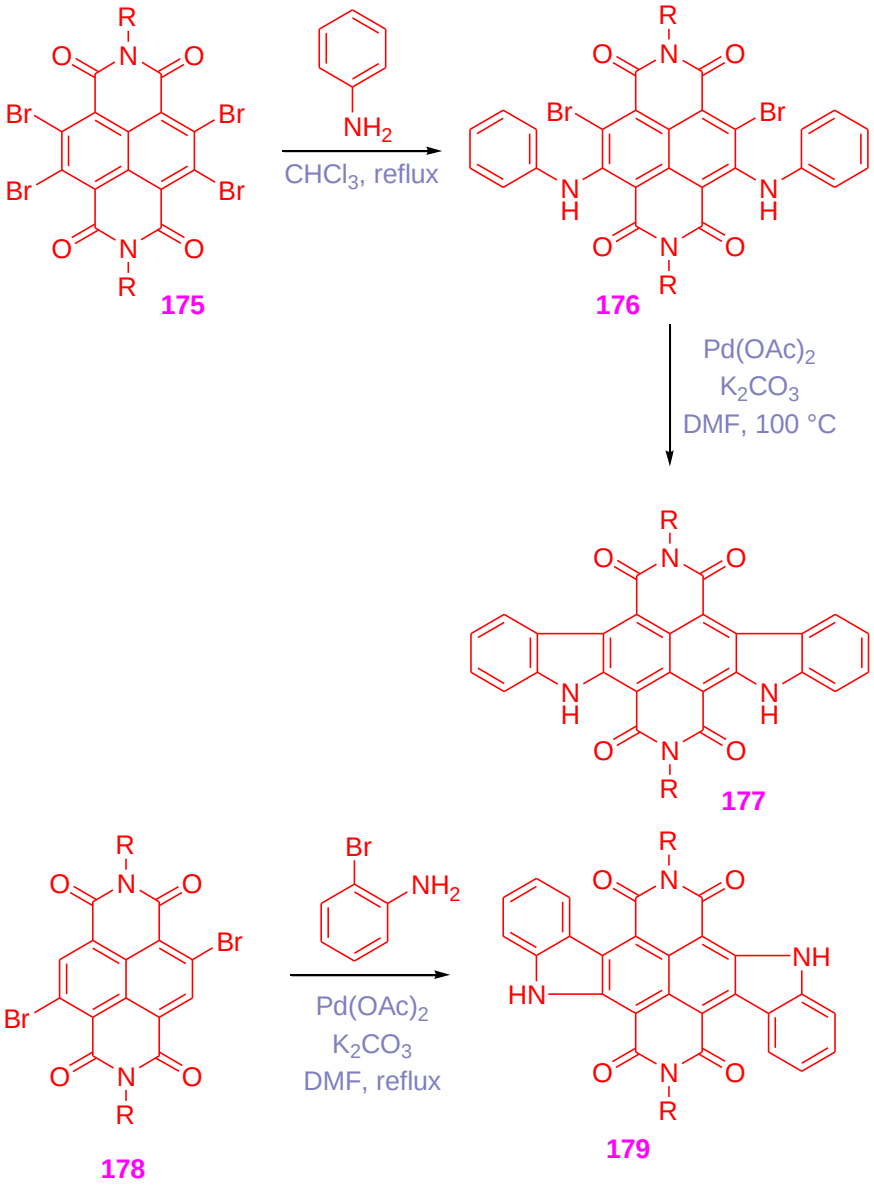
Eq. 51



173 174

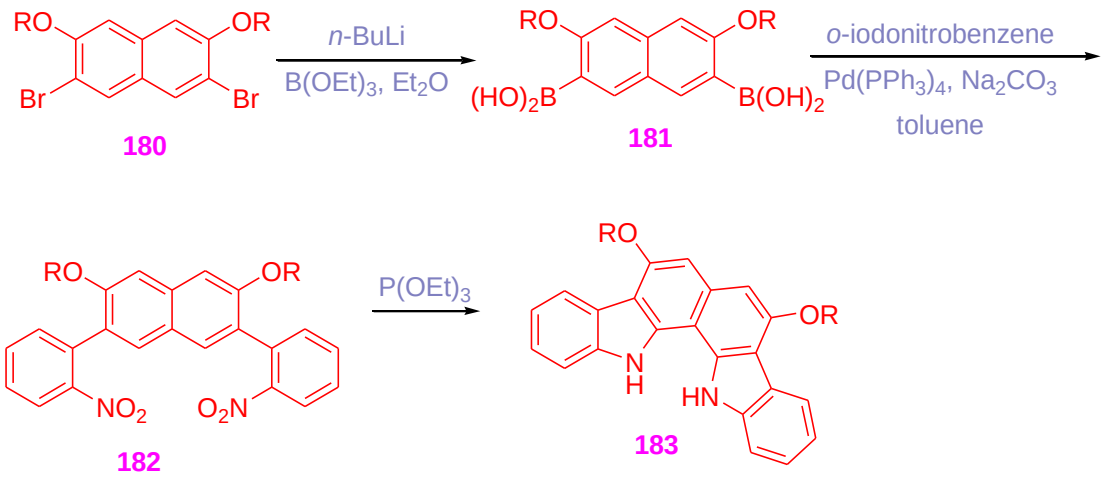
A few years later, Würthner *et. al.* again reported a synthesis of carbazolocarbazole derivative **179** from naphthalenediimide (NDI) (**Eq. 52**).[76] Their strategy involves regioselective nucleophilic substitution reaction of *tetra*-bromo-NDI with arylamines, followed by palladium-catalyzed intramolecular C-C coupling. They also synthesised other regio-isomer by using corresponding dibromo-NDI. They studied the semiconductor behaviour of the synthesised compounds.

Eq. 52



Molina *et al.* demonstrated the synthesis of carbazolo[1,2-*a*]carbazole **183** by a regiospecific reductive coupling 3,6-*bis*(2-nitrophenyl)naphthalene derivatives **182** (**Eq. 53**).[77] The corresponding nitro compounds were derived from the 2,7-naphthalene-diol, by bromination, conversion into boronic acid followed by Suzuki-Miyaura cross coupling with corresponding *o*-iodonitrobenzene. They also found that these compounds might be used as an organic material with evident from their optical and electrochemical characterization.

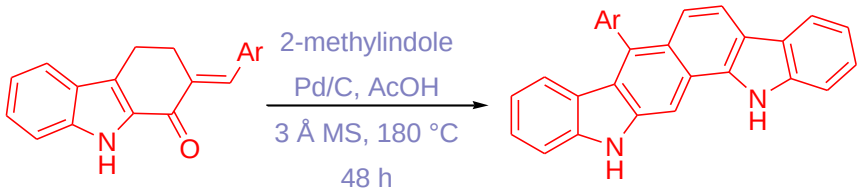
Eq. 53



180 181 182 183

Recently our group also devised a strategy to synthesis carbazolo[1,2-*b*]carbazole derivatives **185**. The reaction sequence involved are Michael addition of 2-methylindole, condensation of methyl group with the carbonyl, dehydration followed by aromatization (**Eq. 54**).[78]

Eq. 54

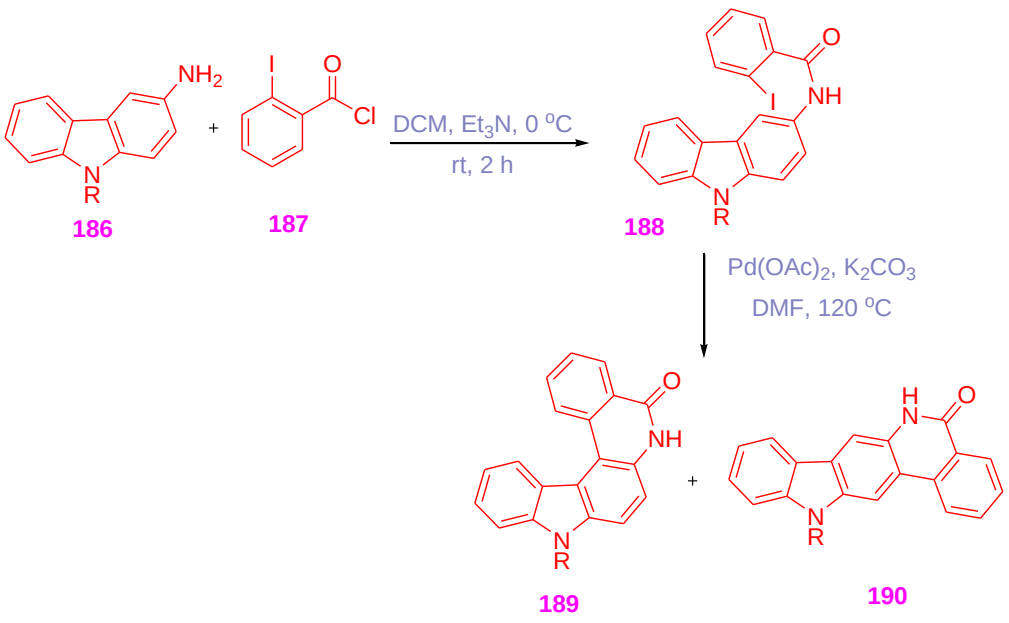


184 185

Synthesis of quinocarbazole

Our group reported a simple route for the synthesis of quinocarbazoles **189**, **190** *via* palladium catalyzed intermolecular arylation involving *ortho* C-H activation (**Eq. 55**).[79]

Eq. 55

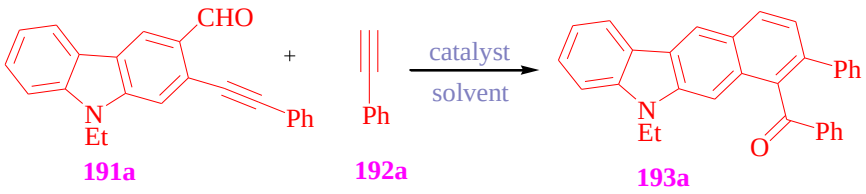


186 187 188 189 190

1.2. Synthesis of benzo[*b*]carbazole derivatives

From the literature reports, we observed that *ortho*-alkynylaldehyde is a versatile starting material for various useful biologically active analogues. So, we planned to utilize the alkynylaldehyde chemistry on the heterocyclic systems which is less explored. In this chapter, we presented successfully synthesized the hetero-arylcarbazoles (5*H*-benzo[*b*]-, carbazolo[2,3-*b*]-, indolo[2,3-*b*]-and quino[2,3-*b*]carbazoles) using alkynylaldehyde heteroannulation. First, we synthesized benzo[*b*]carbazoles. We began our synthesis of benzo[*b*]carbazoles, by optimizing the reaction between **191a** and **192a** using various catalysts and solvents. The results are summarized in table 1.

Table 1. Optimization of the Reaction Conditions[a]



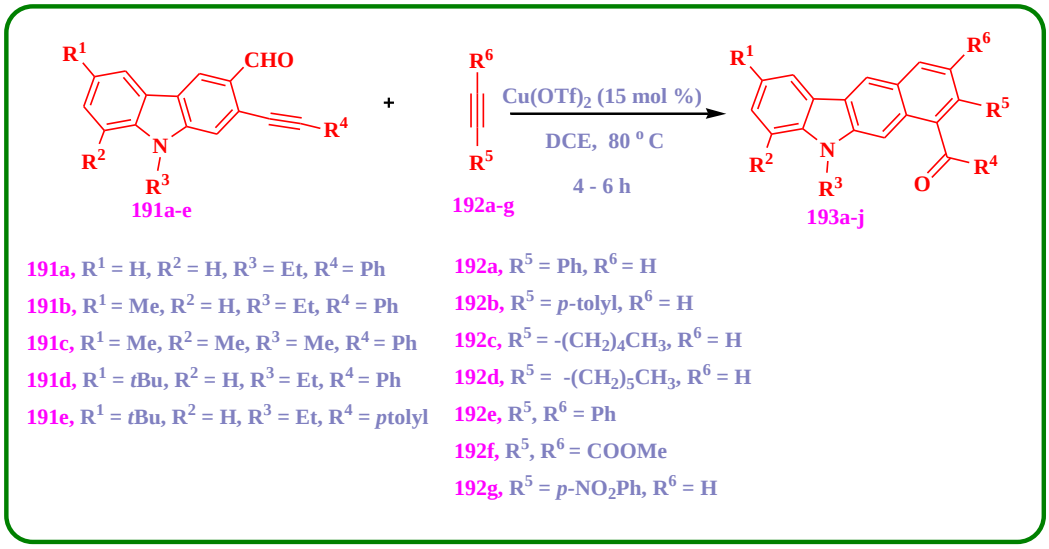
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1[c]	$Cu(OTf)_2$	DCE	10	70
2	$Cu(OTf)_2$	DCE	5	92
3	$Cu(OTf)_2$	CH_3CN	5	68
4	$Cu(OTf)_2$	THF	5	70
5	$Cu(OTf)_2$	toluene	5	45
6	$CuBr_2$	DCE	5	64
7	$CuCl_2$	DCE	5	53
8	CuBr	DCE	5	62
9	CuI	DCE	5	68
10	AgOTf	DCE	5	51
11	$FeCl_3$	DCE	5	NR
12	$La(OTf)_3$	DCE	5	Trace
13	-	DCE	5	NR
14	$Cu(OTf)_2$	DCE	5	NR[d]/Trace[e]

[a] Reaction conditions: 191a (0.5 mmol), 192a (1.0 mmol), solvent (5 mL), catalyst (15 mol %), 80 °C. [b]Isolated yields. [c] 10 mol% catalyst was used. [d] Reaction was carried out at room temperature. [e] Reaction was carried out at 50 °C. NR: no reaction.

While using 10 mol % $Cu(OTf)_2$, we got the product **193a** with lower yield in longer reaction time (Table 1, entry 1). So, we increased the amount of catalyst to 15 mol%. Under these conditions, the reaction proceeded smoothly and benzocarbazole **193a** was obtained in 92% yield (Table 1,

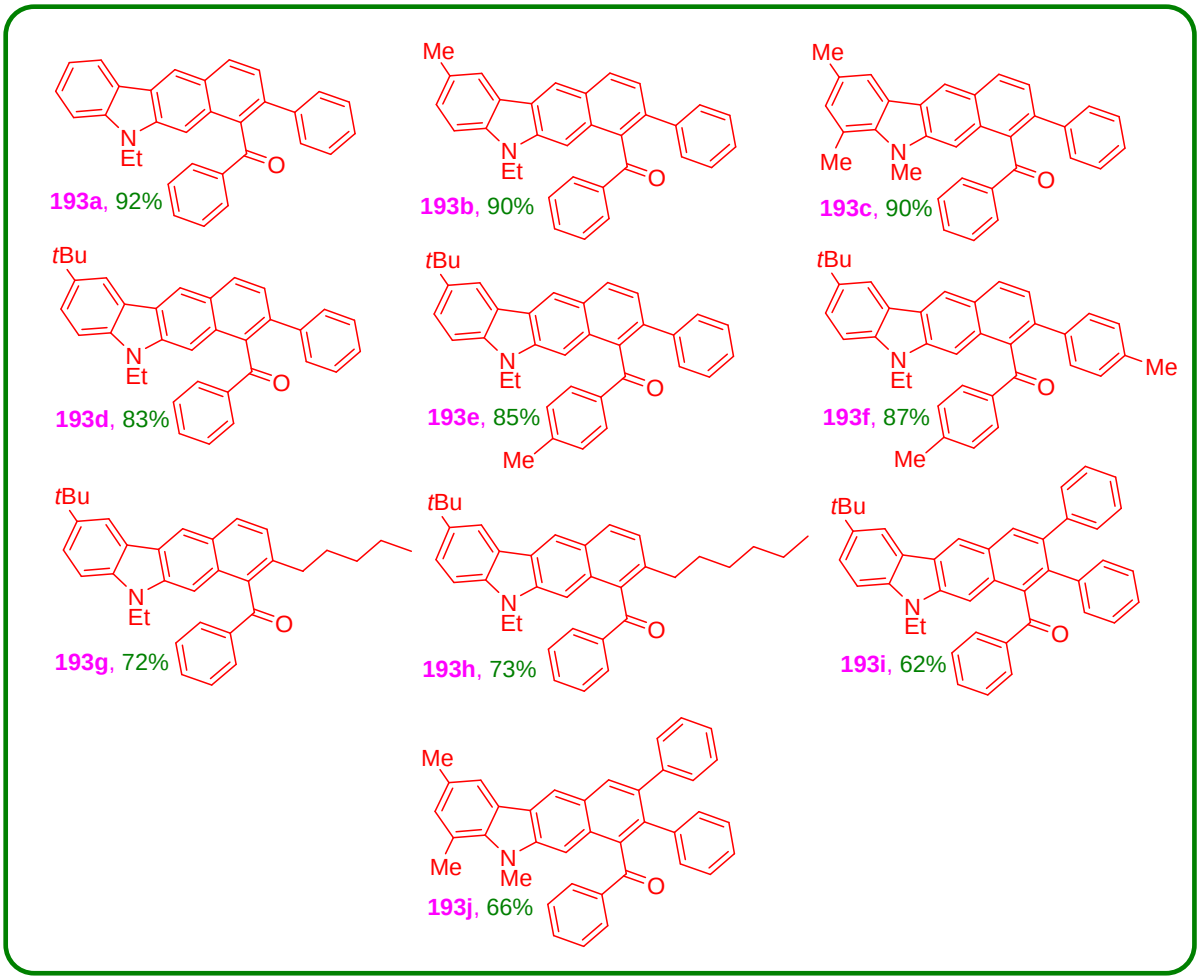
entry 2). We also screened other solvents, such as CH_3CN, THF, toluene etc. (Table 1, entries 3, 4, and 5), however only inferior results were observed. Other catalysts gave the product in low yield (Table 1, entries 6-12). In the absence of a catalyst, no cyclization was observed (Table 1, entry 13). As shown in table 1, we conclude that best result was obtained with 15 mol% $Cu(OTf)_2$ as a catalyst and dichloroethane as solvent at 80 °C. Employing the optimized reaction conditions, we successfully synthesized various benzo[*b*]carbazole derivatives **193a-j**.

Scheme 1. $Cu(OTf)_2$ catalyzed cyclization of 2-(alkynyl) carbazole-3-carbaldehydes (191a-e) with different arylacetylenes (192a-g)[a]



191a, R^1 = H, R^2 = H, R^3 = Et, R^4 = Ph
191b, R^1 = Me, R^2 = H, R^3 = Et, R^4 = Ph
191c, R^1 = Me, R^2 = Me, R^3 = Me, R^4 = Ph
191d, R^1 = *t*Bu, R^2 = H, R^3 = Et, R^4 = Ph
191e, R^1 = *t*Bu, R^2 = H, R^3 = Et, R^4 = *p*tolyl

192a, R^5 = Ph, R^6 = H
192b, R^5 = *p*-tolyl, R^6 = H
192c, R^5 = $-(CH_2)_4CH_3$, R^6 = H
192d, R^5 = $-(CH_2)_5CH_3$, R^6 = H
192e, R^5, R^6 = Ph
192f, R^5, R^6 = COOMe
192g, R^5 = *p*-NO_2Ph, R^6 = H



[a] Unless otherwise noted, all the reactions were carried out in dichloroethane (5.0 mL) as a solvent at 80 °C using **191a-e** (0.5 mmol) and **192a-g** (1.0 mmol) in presence of $Cu(OTf)_2$ (15 mol%). Isolated yields after column chromatography.

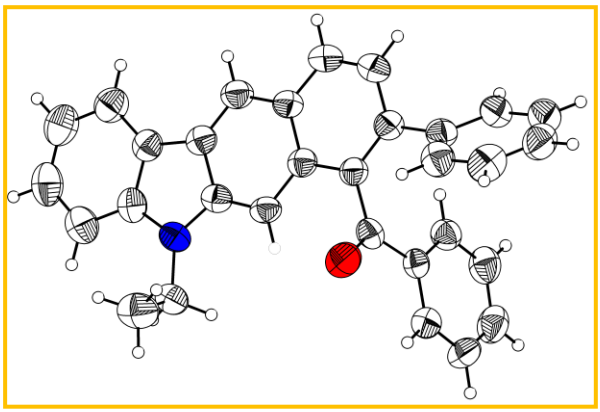
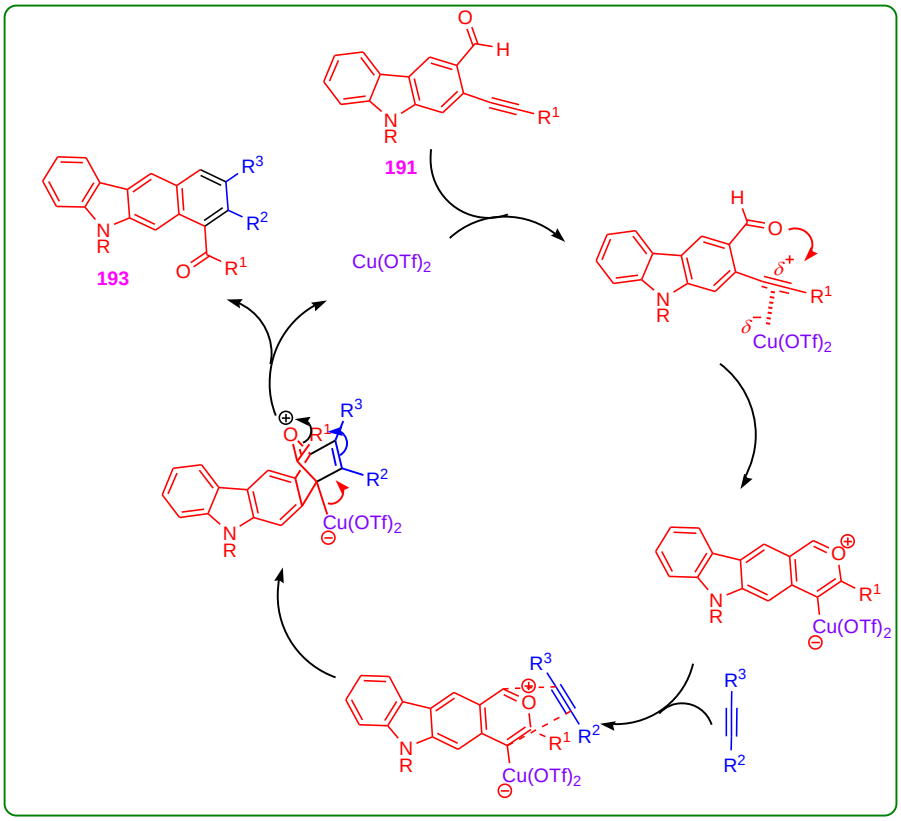


Fig. 2. ORTEP diagram of **193a**.

As shown in Scheme 1, substrates containing substituents like, phenyl, *p*-tolyl, diphenyl , alkyl, on the acetylene (Scheme 1, **192a-e**) could be handled without any trouble and also gave the products in good yields. With arylalkynes bearing electron withdrawing group (Scheme 1, **192f** and **192g**), we were unable to separate the corresponding product due to a complex mixtures as found in TLC. The structure of the product **193a** was unambiguously confirmed by the single crystal X-ray diffraction analysis and ORTEP diagram of **193a** is shown in Fig. 2.

Based on the reported literature,[57] possible mechanism for the formation of benzocarbazole derivatives **193a-j** has been proposed in Scheme 2. As outlined in Scheme 2, $Cu(OTf)_2$ coordinates with triple bond of **191** to enhance the electrophilicity of alkyne. Subsequently, nucleophilic attack of the carbonyl oxygen followed by cycloaddition with alkyne delivers benzo[*b*]carbazole derivatives **193**.

Scheme 2. Possible mechanism for the formation of benzo[*b*]carbazole derivatives (193a-j)

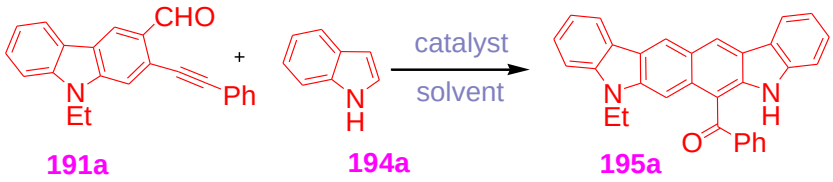


1.3. Synthesis of carbazolo[2,3-*b*]carbazole derivatives

We expected that a similar kind of cyclization could be done with 2-alkynylcarbazole-3-carbaldehydes (**191a-f**) and indoles (**194a-g**) using copper catalyst. As expected, we got the

desired product **195a** in good yield (85%) by employing $Cu(OTf)_2$ (10 mol%) as a catalyst and dichloroethane as a solvent at 80 °C (table 2, entry 3).

Table 2. Optimization of the reaction conditions[a]

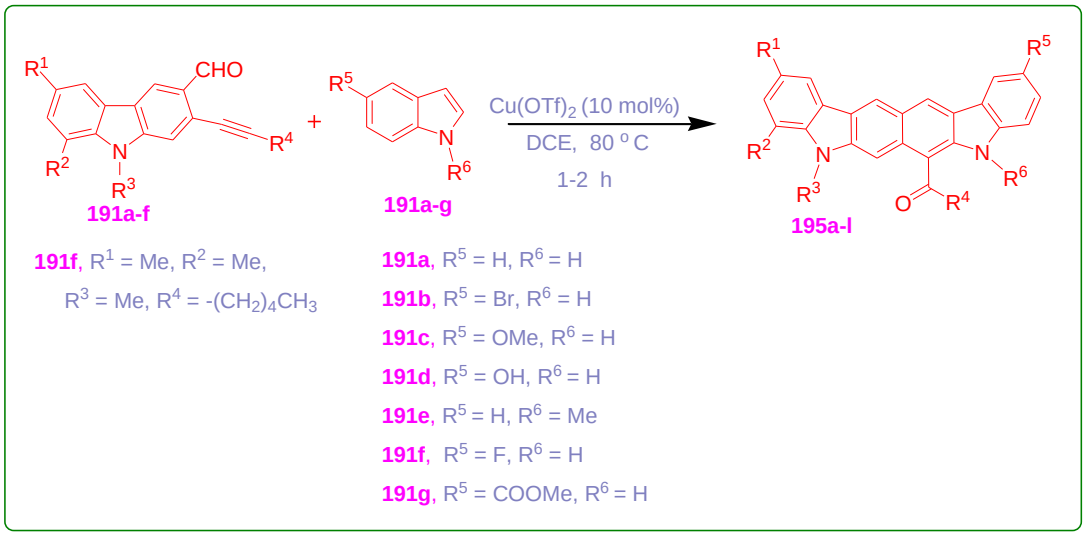


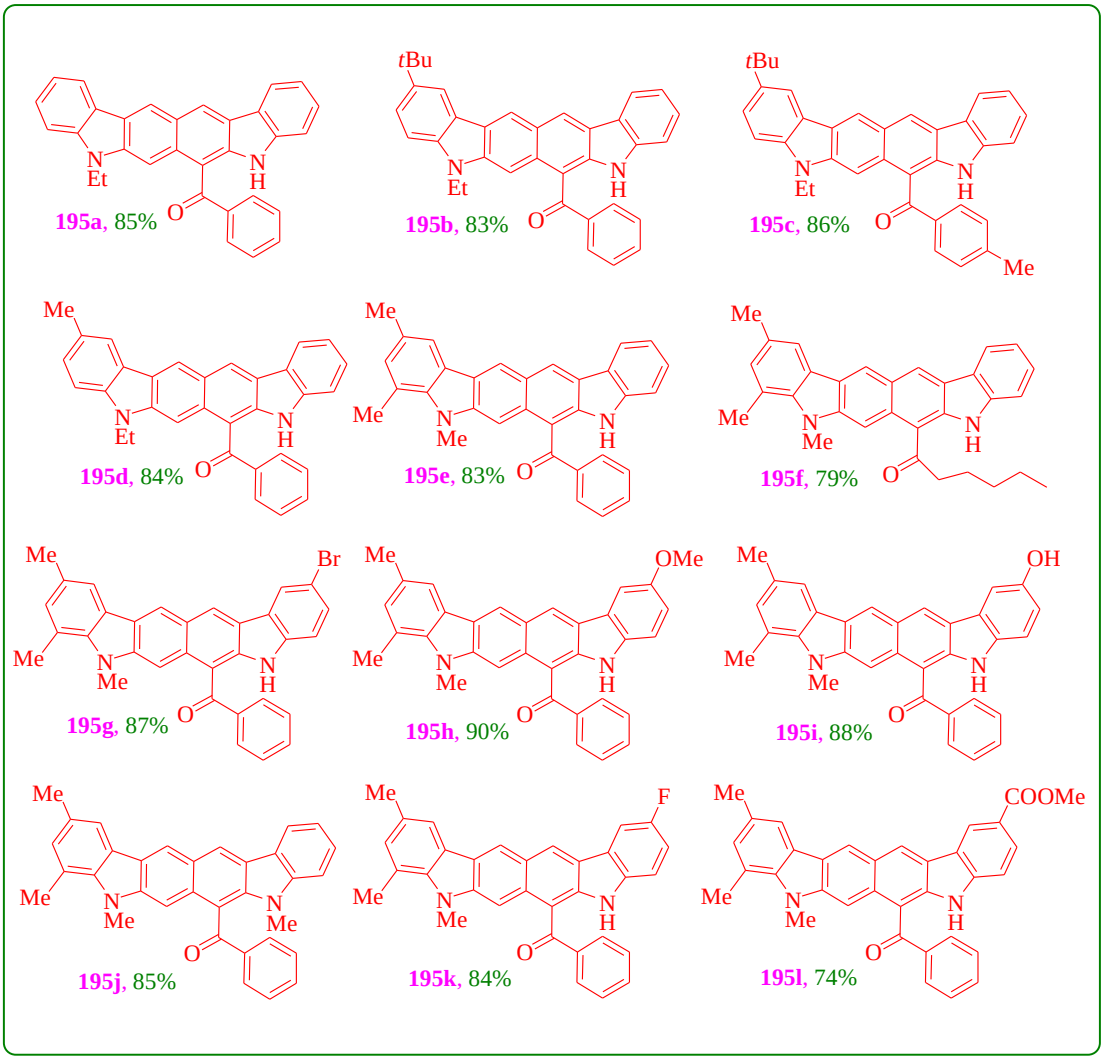
191a **194a** **195a**

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	$Cu(OTf)_2$	DCE	rt	12	0
2	$Cu(OTf)_2$	DCE	50	10	68
3	$Cu(OTf)_2$	DCE	80	1	85
4	$Cu(OTf)_2$	CH_3CN	80	3	60
5	$Cu(OTf)_2$	THF	80	3	62
6	$Cu(OTf)_2$	toluene	80	5	52
7	$CuBr_2$	DCE	80	3	71
8	CuBr	DCE	80	3	68
9	CuI	DCE	80	3	63
10	CuCl	DCE	80	3	48
11	$CuCl_2$	DCE	80	3	54
12	-	DCE	80	3	Trace

[a]Reaction conditions: 191a (0.5 mmol), 194a (0.5 mmol), solvent (5 mL), catalyst (10 mol%). [b]Isolated yields.

Scheme 3. $Cu(OTf)_2$ catalyzed cyclization of 2-alkynyl carbazole-3-carbaldehyde (191a-f) with indoles (194a-g)

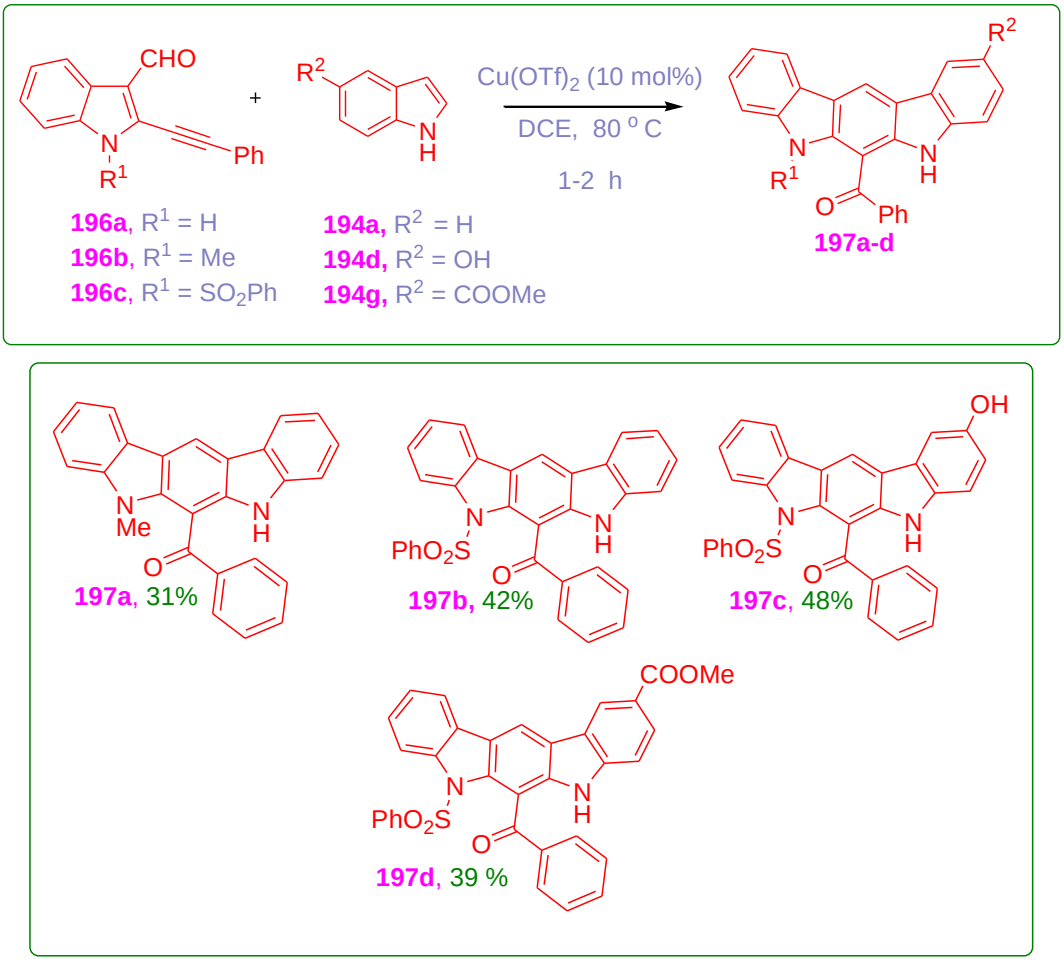




This result prompted us to optimize the reaction conditions. When using $CuBr_2$ as a catalyst, yield of the anticipated product was low with trace amount of inseparable by-products (table 2, entry 7). We could not improve the yield of the product while screening other copper catalysts. To extend this methodology further, we carried out the reaction of 2-alkynylcarbazole-3-carbaldehydes (**191a-f**) with various indoles (**194a-g**) in the presence of $Cu(OTf)_2$ (10 mol%) under optimized conditions. The scope of this reaction was outlined in Scheme 3.

1.4. Synthesis of indolo[2,3-*b*]carbazole derivatives

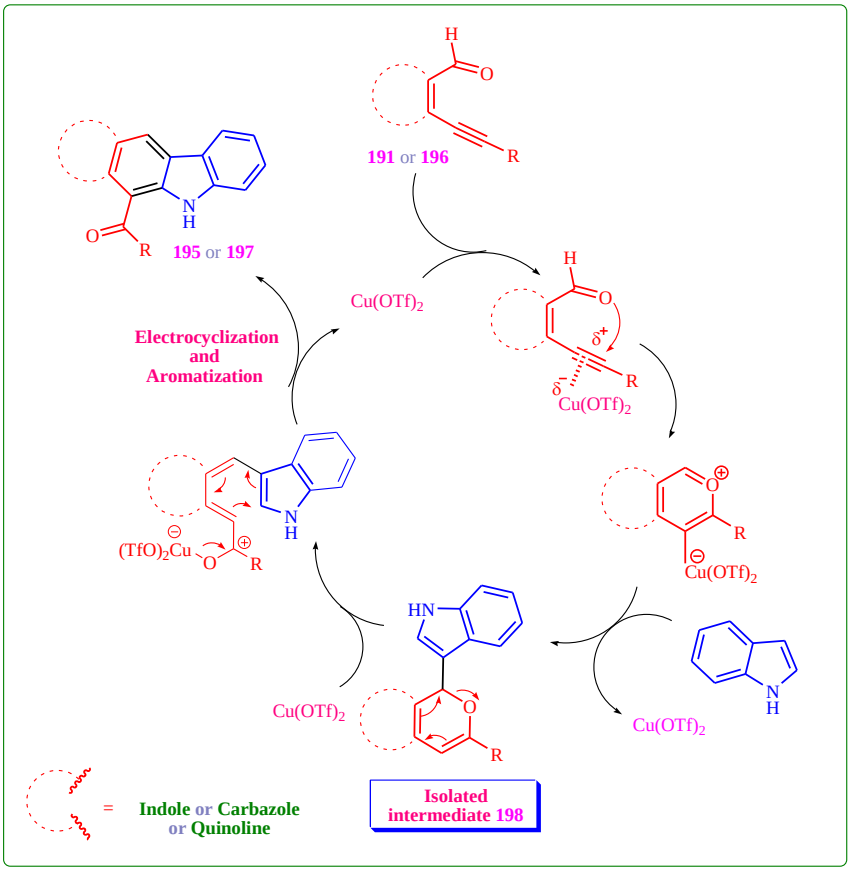
Scheme 4. $Cu(OTf)_2$ catalyzed cyclization of 2-alkynylindole-3-aldehydes (196a-c) with indoles (194a, 194d and 194g)



Motivated by these results, we turned our attention next to the synthesis of indolo[2,3-*b*]carbazole derivatives using 2-alkynylindole-3-aldehyde and indole. Here again, we started our synthesis by screening various copper catalysts. Among them, 10 mol% $Cu(OTf)_2$ gave the expected product

197a in DCE as a solvent. After careful column chromatography, indolo[2,3-*b*]carbazole **197a** was isolated in moderate yield. It was possible to slightly increase the yield of the product as R^1 was the electron withdrawing substituent (Scheme 4, **197b-d**). In ^{1}H NMR spectra of **197a-d**, a singlet around δ = 8.50-9.30 ppm which corresponds to C-12 proton of the indolo[2,3-*b*]carbazole derivatives clearly indicate the formation of products. Reaction of **196a** with indole did not afford the desired product. The possible mechanism for the coupling of indole and 2-alkynylcarbazole-3-carbaldehydes **191a-f**, 2-alkynylindole-3-aldehydes **196a-c** is depicted in Scheme 5 based on the literature.[51, 57]

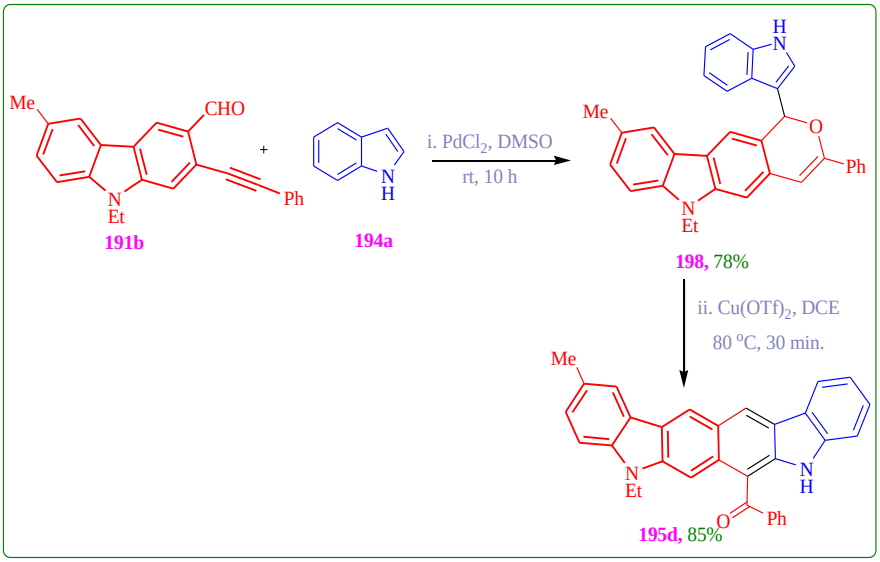
Scheme 5. Possible mechanism for the formation of indolo[2,3-*b*]- and carbazolo[2,3-*b*]carbazole derivatives



In order to understand the reaction pathway, we trapped the intermediate **198** (Scheme 6) by performing a reaction between 2-alkynylcarbazole-3-carbaldehyde (**191b**) and indole (**194a**). Employing 10 mol% $Cu(OTf)_2$ in 1,2-DCE as a solvent at room temperature gave the intermediate **198** in trace amount. While heating, we were unable to trap the intermediate **198** because **195d** was formed at faster rate. So, we changed the reaction condition (10 mol% $PdCl_2$, DMSO as a

solvent at room temperature) to trap the intermediate **198**. As shown in Scheme 6, the intermediate **198** was prepared in 78% yield and subjected it to reaction with standard conditions (10 mol% $Cu(OTf)_2$ and 1,2-dichloroethane as a solvent), and this also gave carbazolocarbazole **195d** in good yield (85%). These results clearly lead to the conclusion that the domino process proceeds through the trapped intermediate **198.**

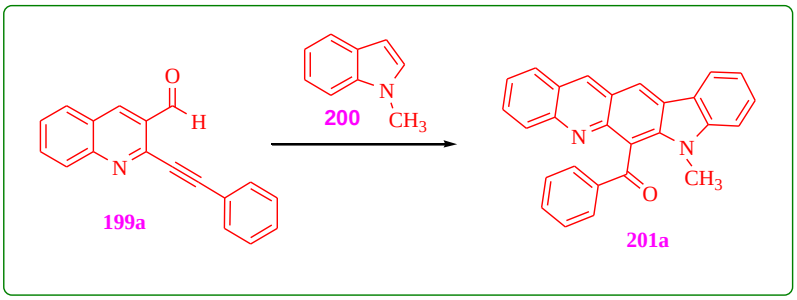
Scheme 6. Formation of intermediate 198 and cyclization.



1.5. Synthesis of quino[2,3-*b*]carbazole derivatives

Next, we planned to synthesis quinocarbazoles using same annulation with quinoline alkynylaldehydes with indole. So, we investigated the model reaction of *N*-methyl indole with 2-(2-phenylethynyl)quinoline-3-carbaldehyde using metal catalysts and solvents. The results are summarized in optimization table 3.

Table 3. Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Time (h)/ Temp (°C)	Yield (%)[b]
1	$Cu(OTf)_2$	DCE	10/80	35
2	CuBr	DCE	10/80	30
3	CuCl	DCE	10/80	20
4	CuI	DCE	10/80	35
5	$Cu(OTf)_2$	DCM	10/80	30
6	$Cu(OTf)_2$	THF	10/80	20
7	$Cu(OTf)_2$	dioxane	10/80	25
8	$Cu(OTf)_2$	toluene	12/100	35
9	$Cu(OTf)_2$	DMF	12/120	51
10	$Cu(OTf)_2$	DMA	6/120	63
11	$Cu(OTf)_2$	DMA	6/120	60
12	CuI	DMA	6/120	53
13	$Cu(OTf)_2$	CH_3CN	12/80	40
14	-	DMA	24/120	NR
15	$CuCl_2$	DMA	10/120	25

Reaction conditions: 199a (0.5 mmol), *N*-methylindole 200 (0.5 mmol) and solvent 5.0 mL. catalyst 5 mol % [b] Isolated yields. [NR] No reaction.

While using $Cu(OTf)_2$ (5 mol%) and 1,2-dichloroethane as solvent, the expected quinocarbazole (QC) is formed only in 35% yield (table 1, entry 1). Other copper catalysts CuCl, CuBr, CuI and $CuCl_2$ did not improve the yield of the product (table 1, entries 2-4 and entry 15). Screening various metal catalysts also gave only inferior results ($La(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$). However, we also screened other solvents. Gratifyingly, when DMA (as solvent) and 5 mol% of copper(II) triflate were employed, the yield of expected product was significantly enhanced to 63% after 6 h heating at 120 ^oC (table 1, entry 10). Reaction did not occur in absence of catalyst. By using the above mentioned optimized reaction conditions, the substrate scope of the heteroannulation and the optical properties of the products were studied (table 4). The yield was decreased, when unprotected indoles were used as substrate (**201a**, **201b**, **201h** and **201i**). No reaction occurred, when reaction between *N*-sulfonylindole and **199a**. The structures of compounds **201a**, **201e** and **201l** were also unambiguously confirmed by single crystal X-ray diffraction analysis (table 8).

The mechanism for formation of products is explained in scheme 5. As depicted in scheme 5, copper(II) triflate activates the triple bond and then 6-*endo*-dig cyclization and subsequent electrocyclization and followed by aromatization deliver quino[2,3-*b*]carbazoles.

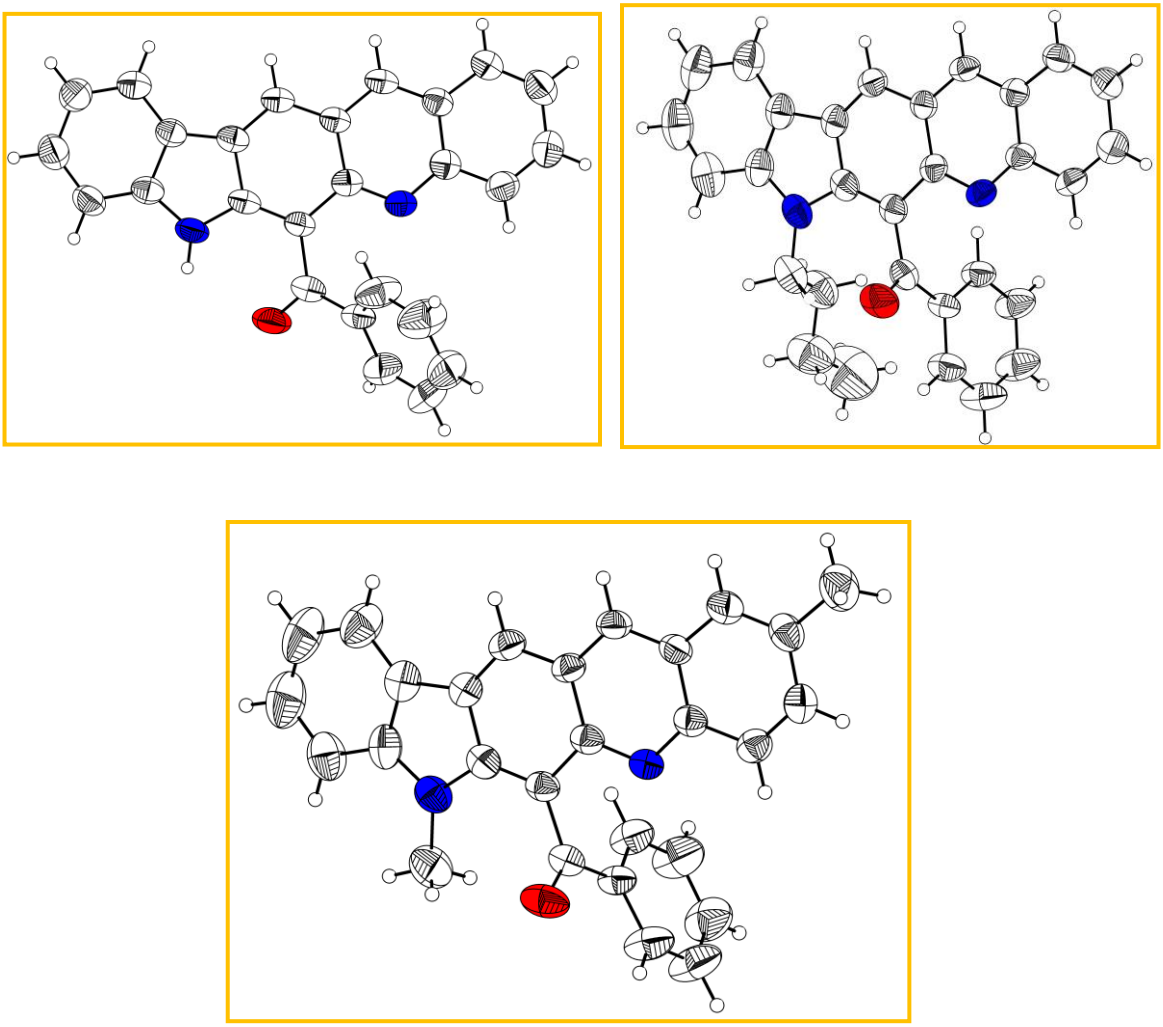
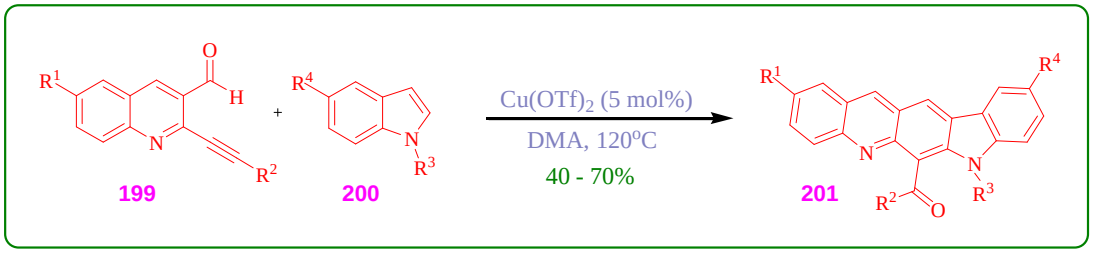


Fig. 3. ORTEP diagrams of **201a, 201e** and **201l**

Table 4. Heteroannulation of various indoles with quinoline alkynylaldehyde[a] and optical properties of QCs



entry	substrate	product	yield (%) / time (h)	λ_{abs} (nm)		λ_{em} (nm)	
				Liquid	**Solid**	**Liquid**	**solid**
1[b]	R^1 = H, R^2 = Ph, R^3 = H, R^4 = H	**201a**	42/8	-	-	-	-
2	R^1 = H, R^2 = Ph, R^3 = CH_3, R^4 = H	**201b**	63/6	384	355	530	626
3[b]	R^1 = H, R^2 = Ph, R^3 = H, R^4 = Br	**201c**	40/8	-	-	-	-
4	R^1 = H, R^2 = Ph, R^3 = C_2H_5, R^4 = H	**201d**	62/6	382	358	531	600
5	R^1 = H, R^2 = Ph, R^3 = C_4H_9, R^4 = H	**201e**	60/6	384	324	518	630
6	R^1 = H, R^2 = Ph, R^3 = C_6H_{13}, R^4 = H	**201f**	61/6	384	333	531	590
7	R^1 = H, R^2 = Ph, R^3 = Bn, R^4 = H	**201g**	58/6	383	313	519	611
8[b]	R^1 = H, R^2 = *p*-tolyl, R^3 = H, R^4 = H	**201h**	43/6	-	-	-	-
9[b]	R^1 = H, R^2 = *p*-tolyl, R^3 = H, R^4 = Br	**201i**	41/6	-	-	-	-
10	R^1 = H, R^2 = p-tolyl, R^3 = CH_3, R^4 = H	**201j**	64/6	384	333	533	600
11	R^1 = H, R^2 = *p*-tolyl, R^3 = Bn, R^4 = H	**201k**	62/6	382	323	532	590
12	R^1 = CH_3, R^2 = Ph, R^3 = CH_3, R^4 = H	**201l**	68/5	384	318	527	600
13	R^1 = OCH_3, R^2 = Ph, R^3 = CH_3, R^4 = H	**201m**	70/5	384	321	527	544

[a] Unless otherwise noted, all the reactions were carried out in DMA as a solvent at 120 °C in presence of $Cu(OTf)_2$ (5 mol%). Isolated yields. [b] No fluorescence was observed

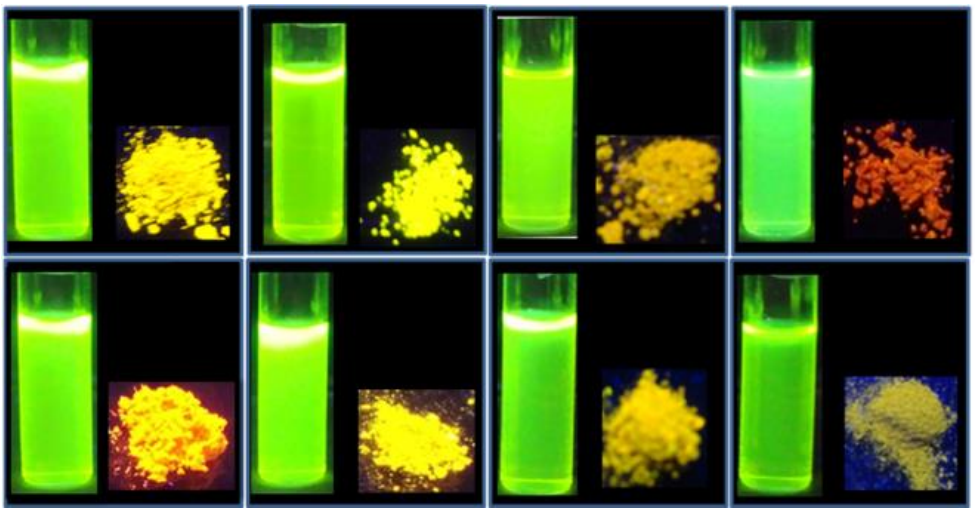


Fig. 4. The photographs of QCs

It is noteworthy that all *N*-Protected QCs show intense fluorescence in liquid as well as in solid states. The photographs of QCs are shown in figure 4. These compounds emit light in red region in solid state and green region in liquid state (figure 4). It is observed that, unprotected derivatives of QCs (**201a**, **201c**, **201h** and **201i**) did not fluoresce, neither in solution nor in the solid state.

Fluorescence behavior is explained from the crystal packing. We expected that fluorescence of unprotected QCs is quenched by hydrogen bonding interaction between free -*NH* and carbonyl oxygen. As we expected, strong inter and intramolecular hydrogen bonding are observed in **201a**. The H(1)-O(1) distance is 2.202 (2) Å (intermolecular), 2.458 (2) Å (intramolecular) (figure 5). Such strong intermolecular hydrogen bonding was not possible in *N*-protected QCs. It is known that, emissive nature in the solid state of the protected derivatives is more related to the lack of effective π-stacking rather than intermolecular hydrogen bonding. In crystal structure for an unprotected derivative (**201a**), the molecules are effectively π-stacked along the crystallographic *b* axis. But, in crystal structures **201e** and **201l**, only isolated pairs of π-stacked molecules can be found. Surprisingly, fluorescent QCs showed significant quenching of fluorescence in the presence of nitrobenzene; this interesting result led us to an investigation on the efficiency of sensing for TNT. We have thus extended our work on sensing of fluorescence using such nitroaromatic explosives.

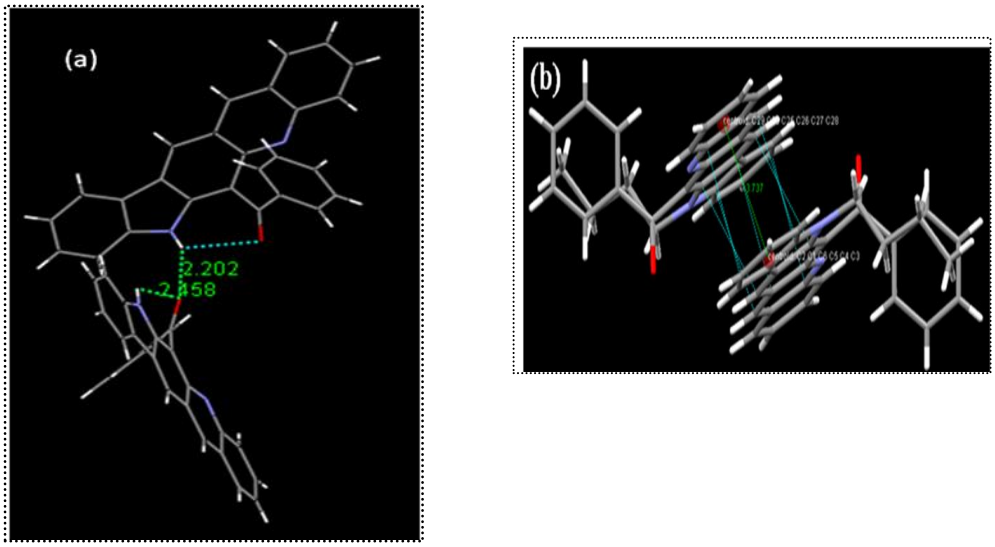


Fig. 6. X-ray crystal packing, Intermolecular hydrogen bonding in **201a** distance is (H(1)-O(1) = 2.202(2) Å)

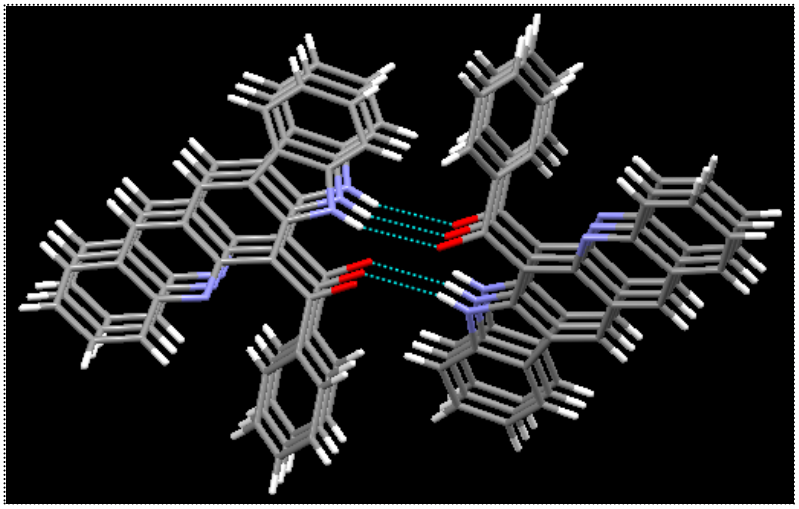
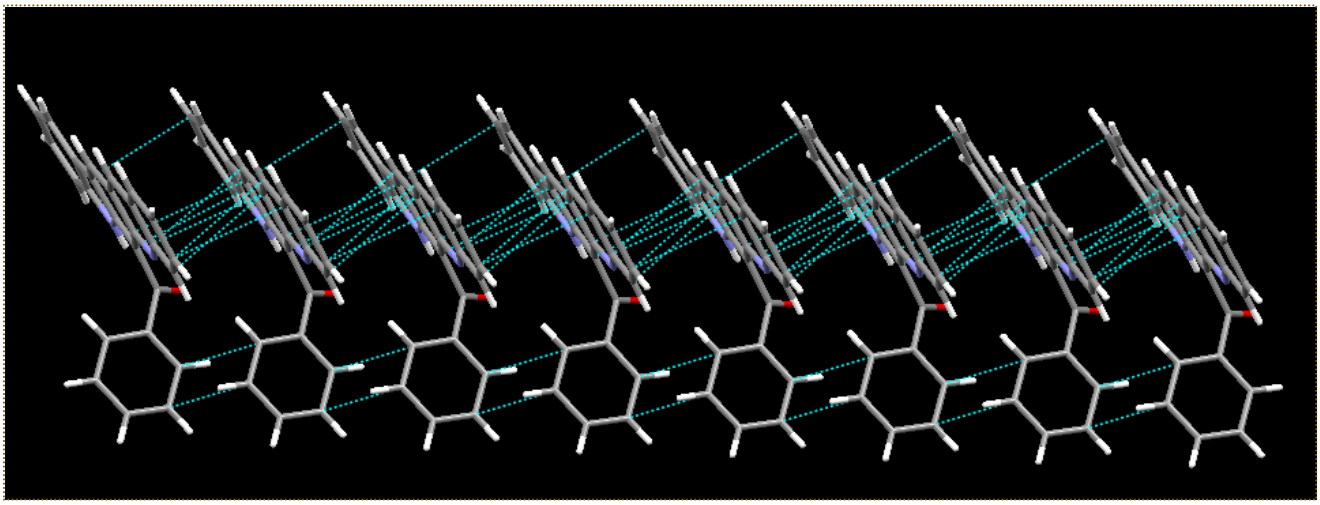
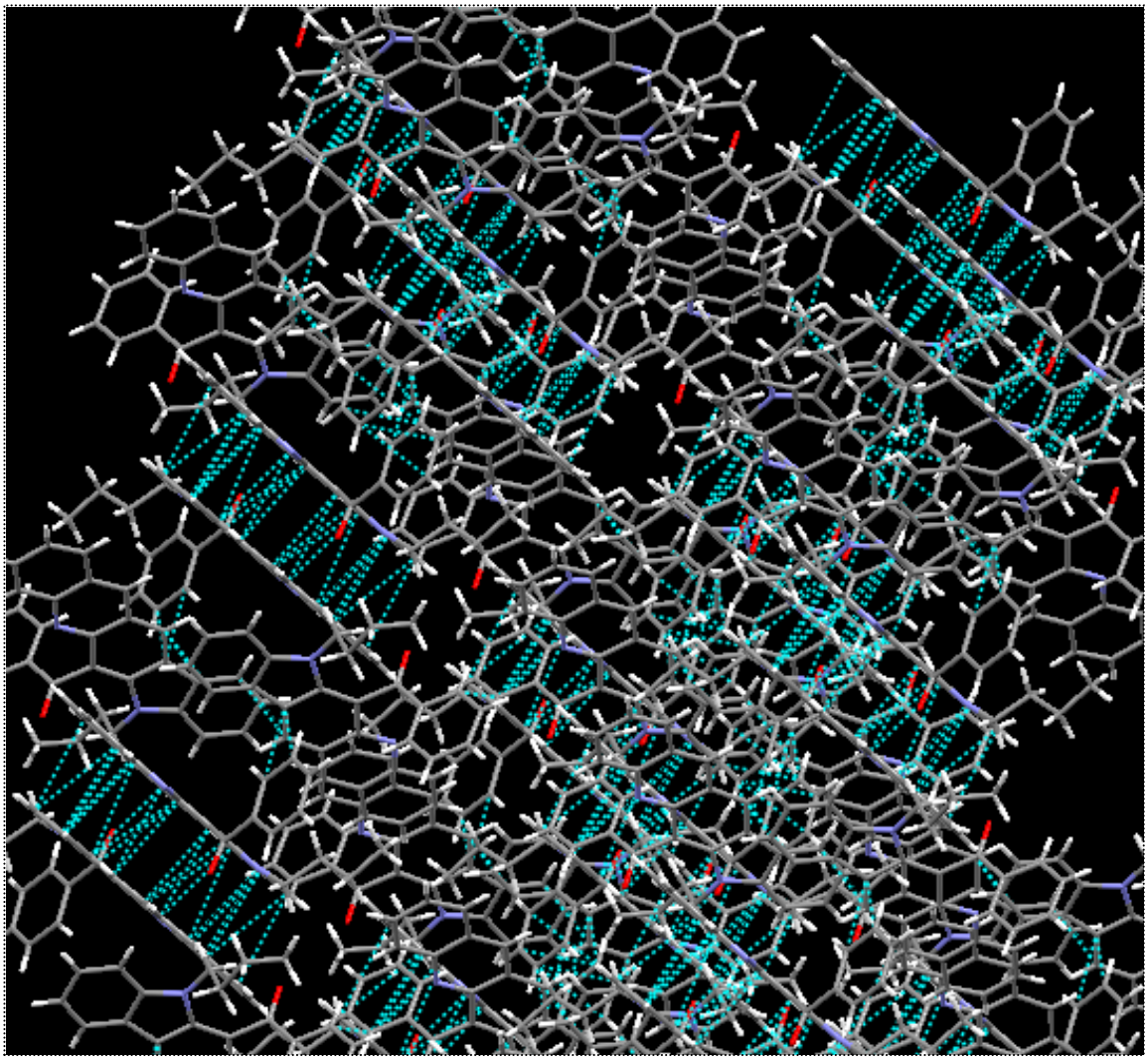


Fig. 5. Perspective view of strong inter- (H(1)-O(1) = 2.202(2) Å) and intramolecular hydrogen bonding interaction (H(1)-O(1) = 2.458(2) Å) in **201a.** (b) Centroid-to-centroid distance (c1, c2, c3, c4, c5, c6 to c25, c26, c27, c28, c29 = 3.737 Å) in **201e** is shown.

Crystal packing of 201a



Crystal packing of 201e



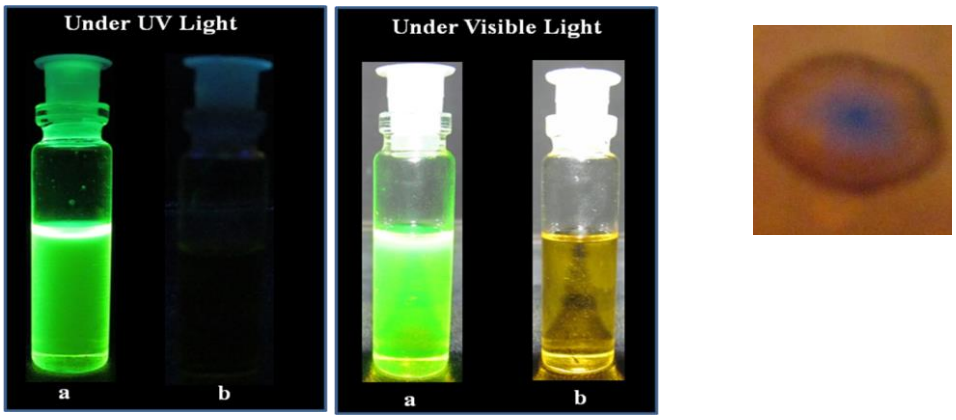


Fig. 7. Visual sensing of quino[2,3-*b*]carbazole **(201b)** (a) 10 mM solution of quino[2,3-*b*]carbazole **(201b)**. (b) 10 mM solution of quino[2,3-*b*]carbazole **(201b)** + 10 mM solution of 2,6-dinitrotoluene (DNT)

We studied TNT sensing and the results are given in figure 8. Quenching of fluorescence was observed from other nitroaromatics (2,6-dinitrotoluene, 1,3-dinitrobenzene, 1-chloro-2,4-dinitrobenzene, nitrobenzene) in 10 μM level, while doing fluorescence titration of compound **201b** in CH_3CN. Upon addition of incremental amount of 10 μM solution of TNT, fluorescence sensing was observed (figure 8 and figure 7). Visual changes of color is also observed, when TNT is spotted in quinocarbazole coated whatman filter paper (figure 7). No sensing was observed with nitromethane. The fluorescence intensity of **201b** decreases linearly with increasing concentration of nitroaromatic compounds. Visual sensing of nitrocompound also observed. There is clear color change while addition of DNT (10 mM) in quinocarbazole (**201b**). After addition of nitrocompound, fluorescent behaviour of QC was fully disappeared (figure 7). We expect that there is an occurance of electron transfer between **201b** and electron deficient nitroaromatics by formation of a π-donor-acceptor (D-A) complex.

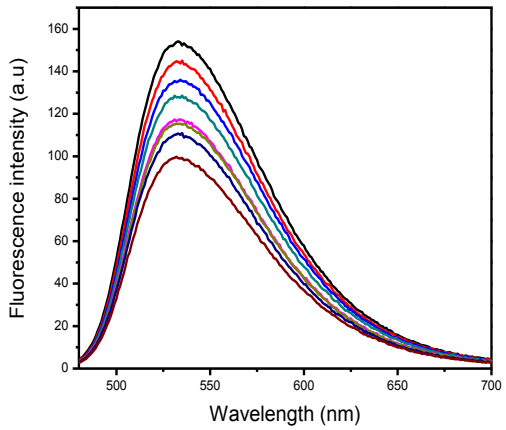


Fig. 8. Emission spectral change (λ_{ex} = 384 nm) of **201b** with titration of 10 μM solution of TNT in CH_3CN (Showing variation of emission intensity).

1.6. Experimental Section

General Information

^{1}H and ^{13}C-NMR spectra were recorded at 400 and 100 MHz, respectively, or at 500 and 125 MHz, respectively. Chemical shifts were calculated in ppm downfield from TMS ($\delta = 0$) for ^{1}H NMR, and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) and DMSO-d_6 ($\delta = 39.51$) for ^{13}C-NMR. Data are presented as follows: chemical shift, multiplicity (br = broad signal, bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz) and integration. HRMS (ESI) was carried out at School of Chemistry, University of Hyderabad. UV-Vis spectra were performed in a conventional quartz cell on UV-VIS-NIR spectrophotometer (UV-3600). Fluorescence spectra were recorded in a conventional quartz cell at 25 °C on spectrofluorometer. X-ray diffraction measurements were carried out at 298 K on an automated diffractometer using graphite-monochromated Mo-K_α (l = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on an instrument equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (l = 0.71073 Å). Melting points were measured in open capillary tubes and are uncorrected. All the obtained products were purified by column chromatography using silica gel (100-200 mesh). All reaction solvents used were of GR grade and used without drying unless mentioned. All other commercial reagents were used as received.

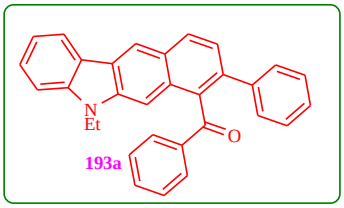
2-Alkynylcarbazole-3-carbaldehydes (**191a-f**) were prepared from 2-bromocarbazoles as methods developed from our laboratory[80] and 2-alkynylindole-3-aldehydes (**196a-c**) were prepared according to reported literature.[53c, 81a] Quinoline alkynyl aldehydes were prepared according to methods already reported in the literature.[81b]

General procedure for the synthesis of benzo[*b*]carbazole derivatives:

An oven dried 10 mL round-bottomed flask equipped with a teflon-coated magnetic stirring bar was charged with 0.5 mmol of 9- ethyl-2-(2-phenylethynyl)-9*H*-carbazole-3-carbaldehyde (**191a**), 15 mol% of $Cu(OTf)_2$, (15 mol%) 1.0 mmol of phenylacetylene (**192a**) and 5 mL of dry 1,2-dichloroethane. The reaction mixture was stirred at 80 °C. After 5 h, solvent and excess of phenylacetylene were removed under reduced pressure. The crude reaction mixture was then poured over water and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed. The residue was purified by column chromatography on silica gel to afford the product **193a** in 92%

yield. (10% ethyl acetate in hexanes). we followed the same procedure for the synthesis of other benzo[*b*]carbazole derivatives (**193b-193j**).

(5-Ethyl-8-phenyl-5*H*-benzo[*b*]carbazol-7-yl)phenyl)methanone (193a):



Yield: 92%

R_f 0.60 (10% EtOAc/hexanes)

Mp: 168-170 °C

IR (KBr) ν_{max} cm^{-1}: 2910, 1720, 1590, 1060, 790

^1H NMR (400 MHz) δ: 8.68 (s, 1H), 8.24 (t, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.61 (s, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.42-7.36 (m, 4H), 7.30-7.22 (m, 5H), 7.18-7.16 (m, 1H), 4.27 (q, *J* = 6.8 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H)

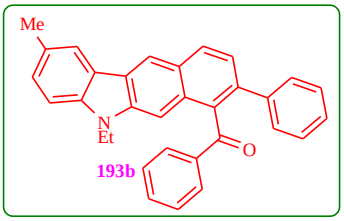
^{13}C NMR (100 MHz) δ: 200.8, 142.8, 140.9, 140.7, 138.5, 137.1, 134.3, 133.0, 130.3, 129.7, 129.6, 128.2, 128.1, 127.5, 127.2, 127.0, 125.6, 124.3, 122.5, 121.2, 119.2, 119.0, 108.3, 101.0 (aromatic C); 37.5, 13.1 (aliphatic C)

LCMS (m/z): 426 ($M+H^+$), positive mode

Anal. Calcd for $C_{31}H_{23}NO$: C, 87.50; H, 5.45; N, 3.29%

Found: C, 87.41; H, 5.51; N, 3.22%

(5-Ethyl-2-methyl-8-phenyl-5*H*-benzo[*b*]carbazol-7-yl)(phenyl)methanone (193b):



Yield: 90%

R_f 0.62 (10% EtOAc/hexanes)

Mp: 156-158 °C

IR (KBr) ν_{max} cm^{-1}: 2909, 1729, 1560, 1060, 881, 850

^1H NMR (400 MHz) δ: 8.64 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.08 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.41-7.37

(m, 4H), 7.28-7.23 (m, 5H), 7.19 (t, *J* = 7.0 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 2.59 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H);

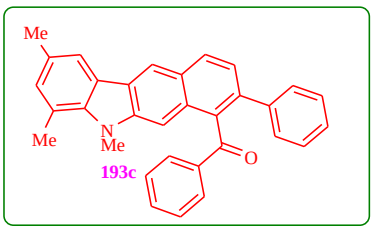
^{13}C NMR (100 MHz) *δ*: 200.6, 141.0, 140.9, 138.6, 137.0, 134.3, 132.9, 130.2, 129.7, 129.6, 129.5, 128.7, 128.5, 128.4, 128.2, 128.1, 127.2, 126.9, 125.5, 124.1, 122.6, 121.3, 118.9, 108.0, 100.9 (aromatic C); 37.5, 21.3, 13.1(aliphatic C)

LCMS (m/z): 440 ($M+H^+$), positive mode

Anal. Calcd for $C_{32}H_{25}NO$: C, 87.44; H, 5.73; N, 3.19%

Found: C, 87.61; H, 5.68; N, 3.25%

Phenyl(2,4,5-trimethyl-8-phenyl-5*H*-benzo[*b*]carbazol-7-yl)(phenyl)methanone (193c):



Yield: 90%

R_f 0.58 (10% EtOAc/hexanes)

Mp: 152-154 °C

IR (KBr) ν_{max} cm^{-1}: 2928, 1722, 1490, 1070, 900

^{1}H NMR (400 MHz) *δ*: 8.58 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.53 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.39-7.37 (m, 3H), 7.27-7.21 (m, 4H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.10 (s, 1H), 3.98 (s, 3H), 2.80 (s, 3H), 2.51 (s, 3H)

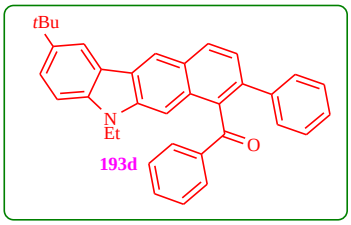
^{13}C NMR (100 MHz) *δ*: 200.8, 142.9, 140.9, 140.5, 138.4, 136.8, 134.4, 133.0, 132.2, 130.1, 129.7, 129.6, 128.7, 128.2, 128.1, 127.2, 127.0, 125.5, 124.1, 123.2, 119.9, 119.0, 118.5, 101.1 (aromatic C); 32.6, 21.0, 20.1 (aliphatic C)

LCMS (m/z): 440 ($M+H^+$), positive mode

Anal. Calcd for $C_{32}H_{25}NO$: C, 87.44; H, 5.73; N, 3.19%

Found: C, 87.32; H, 5.68; N, 3.25%

(2-*Tert*-butyl-5-ethyl-8-phenyl-5*H*-benzo[*b*]carbazol-7-yl)(phenyl)methanone (193d):



Yield: 83%

R_f 0.55 (10% EtOAc/hexanes)

Mp: 124-126 °C

IR (KBr) ν_{max} cm^{-1}: 2920, 1722, 1585, 1290, 1060, 850

^1H NMR (400 MHz) δ: 8.69 (s, 1H), 8.28 (d, *J* = 1.8 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.65 (m, 2H), 7.63 (dd, *J* = 8.8 & 2.0 Hz, 1H), 7.57 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.40-7.36 (m, 3H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.25-7.21 (m, 4H), 7.18 (d, *J* = 7.2 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.50 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H)

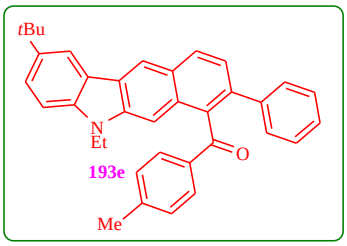
^{13}C NMR (100 MHz) δ: 200.7, 142.2, 141.1, 140.9, 138.6, 137.0, 134.3, 132.9, 130.2, 129.7, 129.6, 128.3, 128.2, 128.1, 127.2, 127.0, 125.9, 125.3, 124.1, 122.2, 118.9, 117.5, 107.8, 107.5, 100.9 (aromatic C), 37.5, 34.7, 32.0, 13.2 (aliphatic C)

LCMS (m/z): 482 ($M+H^+$), positive mode

Anal. Calcd for $C_{35}H_{31}NO$: C, 87.28; H, 6.49; N, 2.91%

Found: C, 87.14; H, 6.38; N, 3.05%

(2-*Tert*-butyl-5-ethyl-8-phenyl-5*H*-benzo[*b*]carbazol-7-yl)(*p*-tolyl)methanone (193e):



Yield: 85%

R_f 0.58 (10% EtOAc/hexanes)

Mp: 120-122 °C

IR (KBr) ν_{max} cm^{-1}: 2910, 1720, 1590, 1060, 850

^1H NMR (400 MHz) δ: 8.70 (s, 1H), 8.31 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.64 (dd, *J* = 8.0 & 2.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.57 (s, 1H), 7.50

(d, *J* = 8.5 Hz, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.29-7.26 (m, 2H), 7.20 (t, *J* = 7.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 1.52 (s, 9H), 1.34 (t, *J* = 7.0 Hz, 3H)

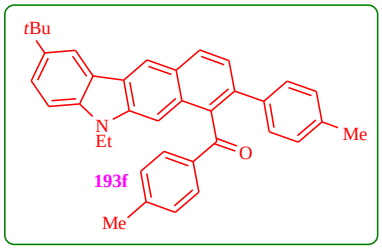
^{13}C NMR (100 MHz) *δ*: 200.3, 143.8, 142.1, 141.1, 141.0, 140.9, 136.7, 136.0, 134.5, 130.0, 129.8, 129.6, 129.0, 128.9, 128.1, 127.1, 127.0, 125.8, 125.2, 124.2, 122.2, 118.9, 117.5, 107.8, 101.0 (aromatic C), 37.5, 34.7, 32.0, 21.6, 13.2 (aliphatic C)

LCMS (m/z): 496 (M+H$^+$), positive mode

Anal. Calcd for $C_{36}H_{33}NO$: C, 87.24; H, 6.71; N, 2.83%

Found: C, 87.09; H, 6.78; N, 2.76%

(2-*Tert*-butyl-5-ethyl-8-*p*-tolyl-5*H*-benzo[*b*]carbazol-7-yl)(*p*-tolyl)methanone (193f):



Yield: 87%

R_f 0.65 (10% EtOAc/hexanes)

Mp: 116-118 °C

IR (KBr) ν_{max} cm^{-1}: 2910, 1720, 1470, 1580, 1080, 950

^{1}H NMR (400 MHz) *δ*: 8.67 (s, 1H), 8.28 (d, *J* = 1.6 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.61 (m, 3H), 7.51 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.32 (m, 2H), 7.06 (m, 5H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 1.50 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H)

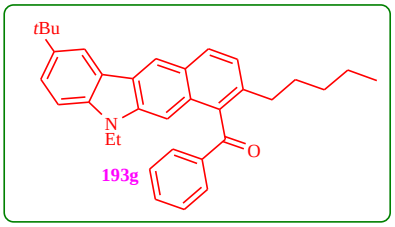
^{13}C NMR (100 MHz) *δ*: 200.5, 143.9, 142.1, 141.0, 140.9, 138.1, 137.5, 136.8, 136.6, 136.0, 134.3, 129.9, 129.4, 129.0, 128.9, 126.8, 125.7, 125.2, 124.4, 122.2, 120.7, 118.9, 117.5, 107.7, 100.9 (aromatic C); 37.5, 34.7, 32.0, 21.7, 21.1, 13.2 (aliphatic C)

LCMS (m/z): 510 (M+H$^+$), positive mode

Anal. Calcd for $C_{37}H_{35}NO$: C, 87.19; H, 6.92; N, 2.75%

Found: C, 87.25; H, 6.85; N, 2.71%

(2-*Tert*-butyl-5-ethyl-8-pentyl-5*H*-benzo[*b*]carbazol-7-yl)(phenyl)methanone (193g):



Yield: 72%

R_f 0.68 (10% EtOAc/hexanes)

Mp: 104-106 °C

IR (KBr) ν_{max} cm^{-1}: 2910, 1720, 1420, 1590, 1060, 850

^{1}H NMR (400 MHz) δ: 8.62 (s, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.62-7.57 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.29-7.27 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 8.0 Hz, 2H), 1.65 (m, 2H), 1.50 (s, 9H), 1.48-1.45 (m, 4H), 1.26 (m, 3H), 0.84 (t, *J* = 6.8 Hz, 3H)

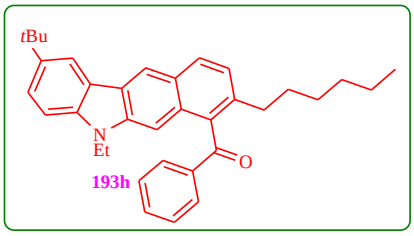
^{13}C NMR (100 MHz) δ: 201.3, 142.0, 140.7, 140.6, 138.3, 136.7, 134.2, 133.6, 129.9, 129.8, 129.7, 128.7, 126.3, 125.1, 125.0, 124.0, 122.3, 118.8, 117.4, 107.6, 100.6 (aromatic C); 37.5, 34.7, 34.0, 32.0, 31.8, 31.0, 22.4, 13.9, 13.0 (aliphatic C)

LCMS (m/z): 476 ($M+H^+$), positive mode

Anal. Calcd for $C_{34}H_{37}NO$: C, 85.85; H, 7.84; N, 2.94%

Found: C, 85.68; H, 7.91; N, 2.85%

(2-*Tert*-butyl-5-ethyl-8-hexyl-5*H*-benzo[*b*]carbazol-7-yl)(phenyl)methanone (193h):



Yield: 73%

R_f 0.72 (10% EtOAc/hexanes)

Mp: 102-104 °C

IR (KBr) ν_{max} cm^{-1}: 2915, 1710, 1580, 1110, 650

^{1}H NMR (400 MHz) δ: 8.61 (s, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.59 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 2H),

7.34 (d, *J* = 8.4 Hz, 1H), 7.26-7.29 (m, 2H), 4.91 (q, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 8.0 Hz, 2H), 1.63 (t, *J* = 7.6 Hz, 2H), 1.49-1.47 (m, 11H), 1.24 (m, 7H), 0.85 (t, *J* = 6.8 Hz, 3H)

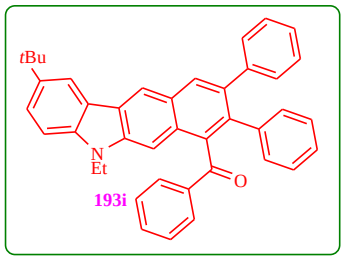
^{13}C NMR (100 MHz) *δ*: 201.3, 142.0, 140.7, 140.6, 138.9, 136.7, 134.2, 133.6, 129.9, 129.7, 129.6, 128.7, 126.2, 125.1, 125.0, 124.0, 122.3, 118.8, 117.4, 107.6, 100.6 (aromatic C); 37.5, 34.7, 34.0, 32.0, 31.5, 31.3, 29.3, 22.5, 14.1, 13.1 (aliphatic C)

LCMS (m/z): 490 ($M+H^+$), positive mode

Anal. Calcd for $C_{35}H_{39}NO$: C, 85.84; H, 8.03; N, 2.86%

Found: C, 85.92; H, 8.12; N, 2.75%

(2-*Tert*-butyl-5-ethyl-8,9-dipentyl-5*H*-benzo[*b*]carbazol-7-yl)(phenyl)methanone (193i):



Yield: 62%

R_f 0.42 (10% EtOAc/hexanes)

Mp: 142-144 °C

IR (KBr) ν_{max} cm^{-1}: 2915, 1720, 1590, 1469, 1060, 850

^{1}H NMR (400 MHz) *δ*: 9.14 (d, *J* = 1.6 Hz, 1H), 7.74 (s, 1H), 7.71 (dd, *J* = 8.8 & 2.0 Hz, 1H), 7.60-7.58 (m, 2H), 7.53 (s, 1H), 7.41-7.20 (m, 14H), 7.00 (t, *J* = 7.2 Hz, 1H), 4.25 (q, *J* = 8.0 Hz, 2H), 1.52 (s, 9H), 1.30 (t, *J* = 8.0 Hz, 3H)

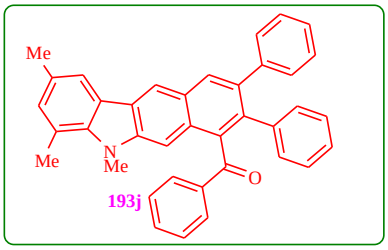
^{13}C NMR (100 MHz) *δ*: 200.3, 142.2, 141.2, 141.1, 141.07, 138.4, 137.2, 136.6, 136.4, 133.0, 131.6, 130.3, 129.4, 129.3, 129.0, 128.3, 128.25, 128.1, 127.7, 126.8, 126.4, 126.1, 125.7, 125.2, 122.3, 120.8, 117.0, 107.5, 100.5 (aromatic C); 37.6, 34.8, 32.0, 13.0 (aliphatic C);

LCMS (m/z): 558 ($M+H^+$), positive mode

Anal. Calcd for $C_{41}H_{35}NO$: C, 88.29; H, 6.33; N, 2.51%

Found: C, 88.12; H, 6.39; N, 2.48%

Phenyl(2,4,5-trimethyl-8,9-diphenyl-5*H*-benzo[*b*]-carbazol-7-yl)methanone (193j):

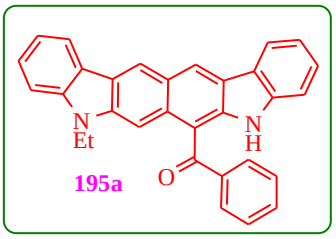


Yield:	66%
R_f	0.44 (10% EtOAc/hexanes)
Mp:	154-156 °C
IR (KBr) ν_{max} cm^{-1}:	2910, 1725, 1500, 1600, 1060, 850
^{1}H NMR (400 MHz) δ:	8.62 (s, 1H), 8.22 (s, 1H), 8.16 (m, 1H), 7.95 (m, 1H), 7.92 (s, 1H), 7.60 (m, 3H), 7.49 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.25-7.15 (m, 8H), 7.11 (s, 1H), 6.74 (t, *J* = 7.0 Hz, 1H), 4.00 (s, 3H), 2.82 (s, 3H), 2.53 (s, 3H)
^{13}C NMR (100 MHz) δ:	200.7, 142.9, 141.3, 140.6, 138.9, 138.5, 136.4, 135.8, 132.8, 132.2, 131.1, 130.9, 130.1, 129.4, 128.8, 128.7, 128.6, 128.0, 127.6, 127.2, 126.6, 126.2, 125.9, 123.2, 119.9, 119.0, 118.6, 118.1, 100.8 (aromatic C); 32.7, 21.0, 20.1 (aliphatic C)
LCMS (m/z):	516 ($M+H^+$), positive mode
Anal. Calcd for $C_{38}H_{29}NO$:	C, 88.51; H, 5.67; N, 2.72%
Found:	C, 88.39; H, 5.63; N, 2.81%

General procedure for the synthesis of carbazolo[2,3-*b*]carbazole derivatives:

An oven dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 0.5 mmol 9-ethyl-2-(2-phenylethynyl)-9*H*-carbazole-3-carbaldehyde (**191a**), 10 mol% of $Cu(OTf)_2$, and 5 mL of dry 1,2-dichloroethane. To it 0.5 mmol of indole (**194a**) was added. Then the reaction mixture was stirred at 80 °C. After 1 h, solvent was removed under reduced pressure. The crude reaction mixture was then poured over water and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed. The residue was purified by column chromatography using silica gel with hexanes-ethyl acetate mixture (eluent: 15% ethyl acetate in hexanes) to afford the product **195a** in 85% yield. We followed the same procedure for the synthesis of other carbazolo[2,3-*b*]carbazole derivatives **(195b-195l)**.

(8-Ethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(phenyl)methanone (195a):



Yield: 85%

R_f 0.32 (15% EtOAc/hexanes)

Mp: 236-238 °C

IR (KBr) ν_{max} cm^{-1}: 3395, 2950, 1688, 1633, 1555, 1222, 698

^1H NMR (400 MHz) δ: 9.90 (bs, 1H), 8.90 (s, 1H), 8.73 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.58-7.42 (m, 7H), 7.34-7.24 (m, 3H), 3.95 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H);

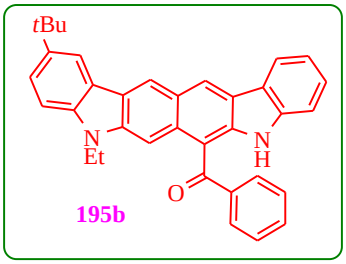
^{13}C NMR (100 MHz) δ: 198.3, 142.8, 142.4, 141.7, 141.5, 140.0, 131.9, 130.7, 129.4, 128.7, 127.3, 127.0, 126.3, 123.7, 123.0, 122.6, 120.8, 120.6, 120.4, 120.3, 119.1, 111.1, 110.8, 108.0, 102.8 (aromatic C); 37.3, 13.1 (aliphatic C)

LCMS (m/z): 439 ($M+H^+$), positive mode

Anal. Calcd for $C_{31}H_{22}N_2O$: C, 84.91; H, 5.06; N, 6.39%

Found: C, 84.79; H, 5.12; N, 6.28%

(11-*Tert*-butyl-8-ethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(phenyl)methanone (195b):



Yield: 83%

R_f 0.34 (15% EtOAc/hexanes)

Mp: 186-188 °C

IR (KBr) ν_{max} cm^{-1}: 3390, 2978, 1712, 1622, 1545, 1295, 840

^1H NMR (400 MHz) δ: 9.91 (bs, 1H), 8.92 (s, 1H), 8.77 (s, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.79-7.78 (m, 2H), 7.60-7.41 (m, 7H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.26 (m, 1H), 3.94 (q, *J* = 7.2 Hz, 2H), 1.51 (s, 9H), 1.09 (t, *J* = 7.2 Hz, 3H)

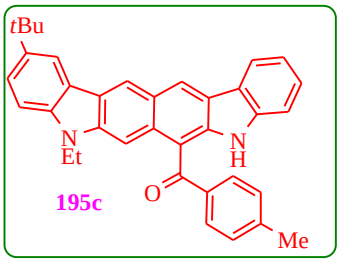
^{13}C NMR (100 MHz) δ: 198.3, 142.8, 142.2, 143.7, 141.5, 140.5, 140.4, 131.8, 130.6, 129.5, 128.6, 127.2, 126.3, 124.7, 123.6, 123.5, 123.3, 123.0, 122.3, 120.5, 120.2, 117.2, 111.1, 110.8, 107.5, 102.7 (aromatic C); 37.3, 34.7, 32.0, 13.2 (aliphatic C)

LCMS (m/z): 495 ($M+H^+$), positive mode

Anal. Calcd for $C_{35}H_{30}N_2O$: C, 84.99; H, 6.11; N, 5.66%

Found: C, 84.91; H, 6.15; N, 5.58%

(11-*Tert*-butyl-8-ethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(*p*-tolyl)methanone (195c):



195c

Yield: 86%

R_f 0.38 (15% EtOAc/hexanes)

Mp: 180-182 °C

IR (KBr) ν_{max} cm^{-1}: 3400, 2985, 1675, 1628, 1535, 1295, 700

^{1}H NMR (400 MHz) δ: 9.72 (bs, 1H), 8.90 (s, 1H), 8.77 (s, 1H), 8.25 (d, J = 1.6 Hz, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.58 (dd, J = 8.4 & 1.2 Hz, 1H), 7.51-7.40 (m, 3H), 7.32 (t, J = 7.6 Hz, 1H), 7.25-7.22 (m, 3H), 3.98 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.49 (s, 9H), 1.11 (t, J = 7.2 Hz, 3H)

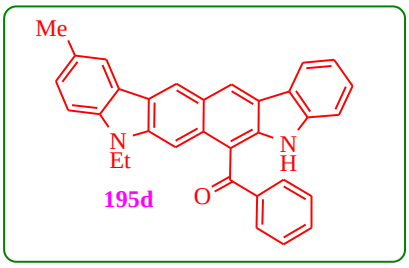
^{13}C NMR (100 MHz) δ: 198.1, 142.6, 142.4, 142.2, 141.7, 140.6, 140.4, 138.6, 130.6, 129.7, 129.3, 127.2, 125.8, 124.6, 123.6, 123.5, 123.3, 123.0, 122.3, 120.5, 120.2, 120.1, 117.2, 111.0, 110.7, 107.4, 102.5 (aromatic C); 37.3, 34.7, 32.0, 21.6, 13.0 (aliphatic C)

LCMS (m/z): 509 ($M+H^+$), positive mode

Anal. Calcd for $C_{36}H_{32}N_2O$: C, 85.01; H, 6.34; N, 5.51%

Found: C, 85.15; H, 6.29; N, 5.63%

(8-Ethyl-11-methyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(phenyl)methanone (195d):



Yield: 84%

R_f 0.30 (15% EtOAc/hexanes)

Mp: 212-214 °C

IR (KBr) ν_{max} cm^{-1}: 3397, 2980, 1688, 1638, 1527, 1292, 700

^1H NMR (400 MHz) δ: 9.91 (bs, 1H), 8.88 (s, 1H), 8.69 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.03 (s, 1H), 7.78 (m, 2H), 7.59-7.44 (m, 5H), 7.39 (s, 1H), 7.35-7.31 (m, 2H), 7.20 (d, J = 8.4 Hz, 1H), 3.92 (q, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H)

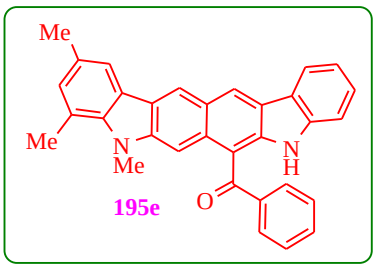
^{13}C NMR (100 MHz) δ: 198.3, 142.8, 141.7, 141.6, 140.6, 140.2, 131.8, 130.7, 129.4, 128.7, 128.4, 128.1, 127.2, 126.3, 123.6, 123.5, 123.0, 122.9, 122.7, 121.0, 120.5, 120.3, 120.25, 111.0, 110.8, 107.7, 102.6 (aromatic C); 37.3, 21.4, 13.1 (aliphatic C)

LCMS (m/z): 452 (H^+), negative mode

Anal. Calcd for $C_{32}H_{24}N_2O$: C, 84.93; H, 5.35; N, 6.19%

Found: C, 85.12; H, 5.31; N, 6.25%

Phenyl(8,9,11-trimethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)methanone (195e):



Yield: 83%

R_f 0.28 (15% EtOAc/hexanes)

Mp: 218-220 °C

IR (KBr) ν_{max} cm^{-1}: 3384, 2987, 1688, 1527, 1292, 700

^1H NMR (400 MHz) δ: 9.84 (bs, 1H), 8.87 (s, 1H), 8.63 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.86 (s, 1H), 7.78 (m, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.52-

7.44 (m, 4H), 7.34-7.33 (m, 2H), 7.05 (s, 1H), 3.63 (s, 3H), 2.76 (s, 3H), 2.53 (s, 3H)

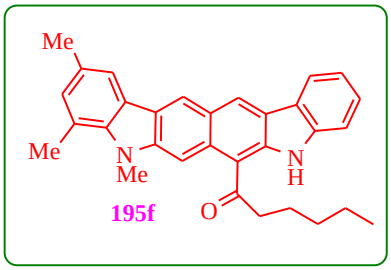
^{13}C NMR (100 MHz) δ: 198.2, 142.7, 142.2, 141.7, 141.6, 140.1, 131.8, 131.6, 130.3, 129.4, 128.7, 128.6, 127.2, 126.1, 123.7, 123.5, 123.4, 123.0, 120.5, 120.2, 119.7, 119.6, 118.7, 111.1, 110.7, 102.6 (aromatic C); 31.9, 21.1, 20.0 (aliphatic C)

LCMS (m/z): 452 (H^+), negative mode

Anal. Calcd for $C_{32}H_{24}N_2O$: C, 84.93; H, 5.35; N, 6.19%

Found: C, 84.85; H, 5.31; N, 6.25%

1-(8,9,11-Trimethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)hexan-1-one (195f):



195f

Yield: 79%

R_f 0.38 (15% EtOAc/hexanes)

Mp: 196-198 °C

IR (KBr) ν_{max} cm^{-1}: 3387, 2980, 1710, 1527,1292, 800

^{1}H NMR (400 MHz) δ: 10.50 (bs, 1H), 8.80 (s, 1H), 8.70 (s, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.95 (s, 1H), 7.89 (s, 1H), 7.46 (m, 2H), 7.29 (m, 1H), 7.10 (s, 1H), 4.13 (s, 3H), 3.38 (m, 2H), 2.85 (s, 3H), 2.55 (s, 3H), 2.01 (m, 2H), 1.42 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H)

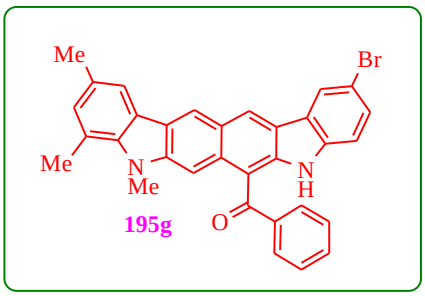
^{13}C NMR (100 MHz) δ: 204.9, 143.1, 142.1, 141.7, 140.1, 131.7, 130.0, 128.9, 127.2, 126.3, 123.7, 123.6, 123.4, 122.9, 122.8, 120.6, 120.5, 120.2, 119.8, 118.7, 113.5, 110.8, 100.7 (aromatic C); 44.1, 32.5, 31.8, 25.8, 22.7, 21.1, 20.1, 14.0 (aliphatic C)

LCMS (m/z): 447 ($M+H^+$), positive mode

Anal. Calcd for $C_{31}H_{30}N_2O$: C, 83.37; H, 6.77; N, 6.27%

Found: C, 83.25; H, 6.71; N, 6.35%

(2-Bromo-8,9,11-trimethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(phenyl)methanone (195g):



195g

Yield: 87%

R_f 0.42 (15% EtOAc/hexanes)

Mp: 232-234 °C

IR (KBr) ν_{max} cm^{-1}: 3399, 2976, 1670, 1537,1292, 860

^{1}H NMR (400 MHz) δ: 9.81 (bs, 1H), 8.77 (s, 1H), 8.59 (s, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 7.86 (s, 1H), 7.76 (m, 2H), 7.55 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.29 (m, 2H), 7.05 (s, 1H), 3.62 (s, 3H), 2.75 (s, 3H), 2.53 (s, 3H)

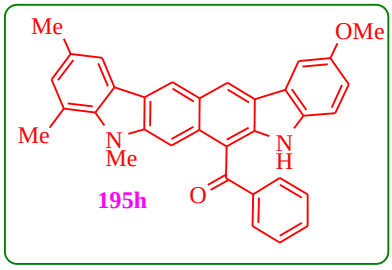
^{13}C NMR (100 MHz) δ: 198.2, 142.6, 142.4, 141.4, 140.3, 140.1, 131.9, 131.8, 130.8, 129.7, 129.4, 128.8, 128.6, 126.4, 124.9, 123.7, 123.3, 123.2, 122.2, 119.7, 118.7, 112.8, 112.0, 111.3, 102.6 (aromatic C); 31.9, 21.0, 20.0 (aliphatic C)

LCMS (m/z): 530 (M^+), 532 (M+2), negative mode

Anal. Calcd for $C_{32}H_{23}BrN_2O$: C, 72.32; H, 4.36; N, 5.27%

Found: C, 72.45; H, 4.41; N, 5.18%

(2-Methoxy-8,9,11-trimethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(phenyl) methanone (195h):



195h

Yield: 90%

R_f 0.44 (15% EtOAc/hexanes)

Mp: 228-230 °C

IR (KBr) ν_{max} cm^{-1}: 3388, 2980, 1705, 1638, 1527,1292, 700

^{1}H NMR (400 MHz) δ: 9.77 (bs, 1H), 8.80 (s, 1H), 8.60 (s, 1H), 7.85 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H),

7.45 (t, *J* = 8.0 Hz, 2H), 7.35-7.30 (m, 2H), 7.12 (dd, *J* = 8.4 & 2.4 Hz, 1H), 7.04 (s, 1H), 3.99 (s, 3H), 3.61 (s, 3H), 2.74 (s, 3H), 2.52 (s, 3H)

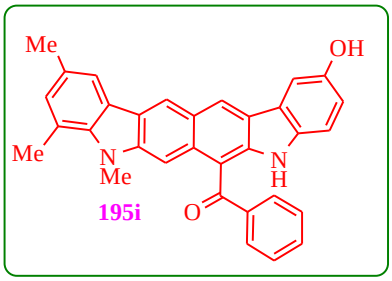
^{13}C NMR (100 MHz) *δ*: 198.1, 154.5, 143.4, 142.2, 141.7, 136.3, 131.7, 131.6, 130.8, 129.4, 128.7, 128.6, 126.3, 123.6, 123.5, 123.4, 123.3, 122.8, 119.7, 119.6, 118.6, 115.2, 111.3, 110.9, 104.5, 102.6 (aromatic C); 56.2, 31.9, 21.0, 20.0 (aliphatic C)

LCMS (m/z): 483 ($M+H^+$), positive mode

Anal. Calcd for $C_{33}H_{26}N_2O_2$:C, 82.13; H, 5.43; N, 5.81%

Found: C, 82.23; H, 5.48; N, 5.76%

(2-Hydroxy-8,9,11-trimethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(phenyl) methanone (195i):



Yield: 88%

R_f 0.44 (15% EtOAc/hexanes)

Mp: 242-244 °C

IR (KBr) ν_{max} cm^{-1}: 3390, 3300, 2916, 1660, 1638, 1527,1292, 700

^{1}H NMR (400 MHz) *δ*: 10.73 (s, 1H), 9.12 (s, 1H), 8.95 (s, 1H), 8.82 (s, 1H), 7.89 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.65 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.03 (s, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H), 2.43 (s, 3H)

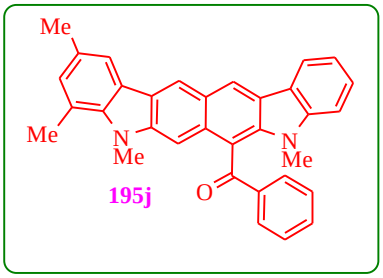
^{13}C NMR (100 MHz) *δ*: 197.6, 151.6, 142.1, 140.5, 140.1, 139.7, 136.5, 133.4, 131.9, 129.9, 129.86, 129.3, 128.4, 124.0, 123.8, 123.2, 122.9, 122.6, 120.2, 120.1, 118.9, 116.2, 112.1, 112.0, 106.4, 100.5 (aromatic C); 32.2, 21.1, 19.9 (aliphatic C)

LCMS (m/z): 469 ($M+H^+$), positive mode

Anal. Calcd for $C_{32}H_{24}N_2O$: C, 82.03; H, 5.16; N, 5.98%

Found: C, 82.12; H, 5.22; N, 6.07%.

Phenyl(5,8,9,11-tetramethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)methanone (195j):



195j

Yield: 85%

R_f 0.52 (15% EtOAc/hexanes)

Mp: 208-210 °C

IR (KBr) ν_{max} cm^{-1}: 2970, 1658, 1630, 1505,1287, 870

^1H NMR (400 MHz) δ: 8.88 (s, 1H), 8.73 (s, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 7.0 Hz, 1H), 7.87 (s, 1H), 7.79 (m, 3H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.49 (m, 2H), 7.33 (s, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.04 (s, 1H), 3.89 (s, 3H), 3.55 (s, 3H), 2.78 (s, 3H), 2.50 (s, 3H)

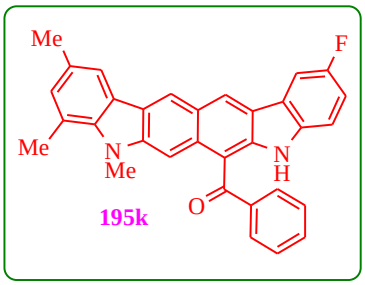
^{13}C NMR (100 MHz) δ: Due to limited solubility, ^{13}C NMR spectrum could not be taken.

LCMS (m/z): 469 ($M+H^+$), positive mode

Anal. Calcd for $C_{33}H_{26}N_2O$: C, 84.95; H, 5.62; N, 6.00%

Found: C, 84.85; H, 5.56; N, 6.08%

(2-Fluoro-8,9,11-trimethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)(phenyl) methanone (195k):



195k

Yield: 84%

R_f 0.54 (15% EtOAc/hexanes)

Mp: 226-228 °C

IR (KBr) ν_{max} cm^{-1}: 3405, 2850, 1648,1610, 1507, 1315, 750

^1H NMR (400 MHz) δ: 11.07 (s, 1H), 9.09 (s, 1H), 8.84 (s, 1H), 8.30 (s, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 7.95 (s, 1H), 7.77 (dd, *J* = 7.0 & 1.5 Hz, 2H), 7.68 (t, *J* = 7.0 Hz, 1H), 7.54-7.45 (m, 2H), 7.29 (m, 2H), 7.06 (s, 1H), 3.73 (s, 3H), 2.73 (s, 3H), 2.45 (s, 3H)

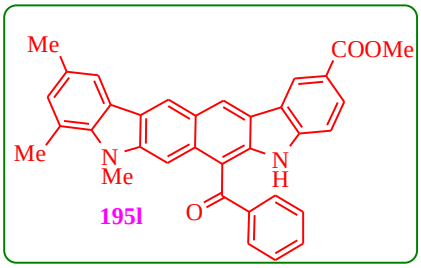
^{13}C NMR (100 MHz) δ: Due to limited solubility, ^{13}C NMR spectrum could not be taken.

LCMS (m/z): 469 ($M+H^+$), positive mode

Anal. Calcd for $C_{32}H_{23}FN_2O$: C, 81.68; H, 4.93; N, 5.95%

Found: C, 81.52; H, 4.89; N, 5.88%

Methyl-6-benzoyl-8,9,11-trimethyl-5,8-dihydrocarbazolo[2,3-*b*]carbazol-6-yl)carbazole-2-carboxylate (195l):



Yield: 74%

R_f 0.50 (15% EtOAc/hexanes)

Mp: 234-236 °C

IR (KBr) ν_{max} cm^{-1}: 3399, 2970, 1710, 1650, 1628, 1507,1272, 815

^{1}H NMR (400 MHz) δ: 11.36 (s, 1H), 9.08 (s, 1H), 8.88 (s, 1H), 8.78 (s, 1H), 8.15 (t, *J* = 7.0 Hz, 1H), 7.95-7.49 (m, 7H), 7.27 (s, 1H), 7.02 (s, 1H), 3.94 (s, 3H), 3.74 (s, 3H), 2.74 (s, 3H), 2.45 (s, 3H)

^{13}C NMR (100 MHz) δ: Due to limited solubility, ^{13}C NMR spectrum could not be taken.

LCMS (m/z): 486 ($M-H^+$), negative mode

Anal. Calcd for $C_{34}H_{26}N_2O_3$: C, 79.98; H, 5.13; N, 5.49%

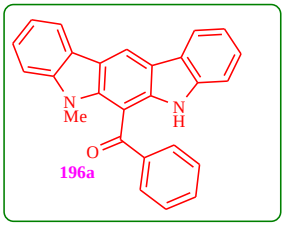
Found: C, 79.85; H, 5.21; N, 5.56%

General procedure for the synthesis of indolo[2,3-*b*]carbazole derivatives:

An oven dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 0.5 mmol of 1-methyl-2-(2-phenylethynyl)-1*H*-indole-3-carbaldehyde (**196b**), 10 mol% of $Cu(OTf)_2$, and 5mL of dry 1,2-dichloroethane. To it 0.5 mmol of indole (**194a**) was added. Then, the reaction mixture was stirred at 80 °C for 2 h. Then, solvent was removed under reduced pressure. The crude reaction mixture was then poured over water and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and

the solvent was removed. The residue was purified by column chromatography using silica gel with hexanes-ethyl acetate mixture (eluent: 15% ethyl acetate in hexane). The product **12a** was eluted in 15% eluent as a light yellow solid. Yield: 31%. We followed the same procedure for the synthesis of other indolo[2,3-*b*]carbazole derivatives (**196b-196d**).

(5-Methyl-5,7-dihydroindolo[2,3-*b*]carbazol-6-yl)(phenyl)methanone (196a):



Yield: 31%

R_f 0.54 (20% EtOAc/hexanes)

Mp: 266-268 °C

IR (KBr) ν_{max} cm^{-1}: 3435, 2968, 1518, 1455, 1010, 805

^1H NMR (400 MHz) δ: 9.58 (bs, 1H), 8.90 (s, 1H), 8.21-8.17 (m, 2H), 7.75 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.44-7.39 (m, 5H), 7.34-7.29 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 3.19 (s, 3H)

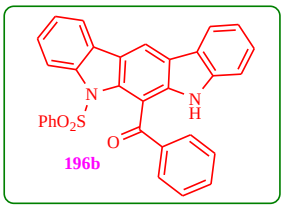
^{13}C NMR (100 MHz) δ: 195.6, 142.6, 140.8, 140.2, 139.8, 133.0, 129.5, 125.4, 125.2, 123.8, 123.4, 120.2, 120.0, 119.6, 119.3, 118.7, 118.4, 116.7, 110.8, 109.1, 103.4 (aromatic C); 35.1 (aliphatic C)

LCMS (m/z): 375 ($M+H^+$), positive mode

Anal. Calcd for $C_{26}H_{18}N_2O$: C, 83.40; H, 4.85; N, 7.48%

Found: C, 83.31; H, 4.81; N, 7.56%

Phenyl(5-(phenylsulfonyl)-5,7-dihydroindolo[2,3-*b*]carbazol-6-yl)methanone (196b):



Yield: 42%

R_f 0.56 (20% EtOAc/hexanes)

Mp: 254-256 °C

IR (KBr) ν_{max} cm^{-1}: 3415, 2970, 1718, 1650, 1628, 1537,1292, 908

^1H NMR (400 MHz) δ: 10.80 (s, 1H), 8.60 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.90 (m, 1H), 7.82 (m, 1H), 7.66-7.60 (m, 4H), 7.47 (t, J = 7.2 Hz, 1H), 7.39-7.31 (m, 4H), 7.20 (m, 2H), 7.00-6.95 (m, 4H)

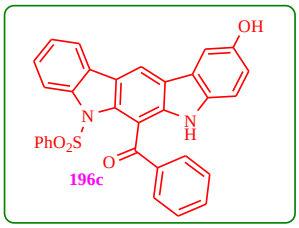
^{13}C NMR (100 MHz) δ: 193.3, 141.2, 139.6, 139.1, 138.1, 135.4, 134.4, 133.4, 132.1, 129.3, 129.1, 128.0, 127.9, 126.3, 125.9, 125.5, 123.2, 121.7, 121.5, 119.8, 119.5, 119.1, 117.9, 114.1, 111.8, 111.2, 110.7 (aromatic C)

LCMS (m/z): 501 ($M+H^+$), positive mode

Anal. Calcd for $C_{31}H_{20}N_2O_3S$: C, 74.38; H, 4.03; N, 5.60%

Found: C, 74.26; H, 4.10; N, 5.52%

(2-Hydroxy-7-(phenylsulfonyl)-5,7-dihydroindolo[2,3-*b*]carbazol-6-yl)(phenyl) methanone (196c):



Yield: 48%

R_f 0.60 (20% EtOAc/hexanes)

Mp: 242-244 °C

IR (KBr) ν_{max} cm^{-1}: 3418, 3320, 2990, 1728, 1670, 1638, 1437,1382, 710

^{1}H NMR (400 MHz) δ: 11.15 (s, 1H), 9.17 (bs, 1H), 8.92 (s, 1H), 8.31 (s, 1H), 8.05-7.93 (m, 2H), 7.62-7.43 (m, 9H), 7.17-6.97 (m, 5H)

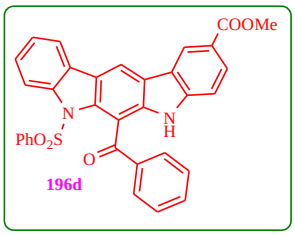
^{13}C NMR (100 MHz) δ: 193.2, 151.8, 151.8, 139.8, 138.5, 135.7, 135.5, 134.7, 133.1, 129.7, 129.3, 129.1, 128.9, 126.7, 126.4, 123.6, 122.9, 121.1, 120.2, 119.7, 118.3, 116.6, 115.6, 113.2, 112.7, 111.5, 105.4 (aromatic C)

LCMS (m/z): 515 ($M-H^+$), negative mode;

Anal. Calcd for $C_{31}H_{20}N_2O_4S$: C, 72.08; H, 3.90; N, 5.42%

Found: C, 72.15; H, 3.95; N 5.36%

Methyl-6-benzoyl-7-(phenylsulfonyl)-5,7-dihydroindolo[2,3-*b*]carbazol-6-yl)carbazole-2-carboxylate (196d):



Yield: 39%

R_f 0.64 (20% EtOAc/hexanes)

Mp: 248-250 °C

IR (KBr) ν_{max} cm^{-1}: 3433, 2890, 1738, 1722, 1612, 1427,1282, 708

^{1}H NMR (400 MHz) δ: 11.84 (s, 1H), 9.26 (s, 1H), 8.95 (s, 1H), 8.09-8.05 (m, 2H), 7.96-7.93 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.49-7.42 (m, 4H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 3.91 (s, 3H)

^{13}C NMR (100 MHz) δ: 192.9, 167.2, 144.7, 139.8, 139.7, 138.2, 135.9, 134.9, 134.6, 133.3, 129.7, 129.4, 129.3, 129.0, 128.0, 127.3, 126.7, 126.5, 123.4, 123.1, 122.7, 122.1, 121.4, 120.4, 118.2, 116.2, 112.4, 112.3 (aromatic C); 52.4 (aliphatic C)

LCMS (m/z): 557 ($M-H^+$), negative mode

Anal. Calcd for $C_{33}H_{22}N_2O_5S$: C, 70.95; H, 3.97; N, 5.01%

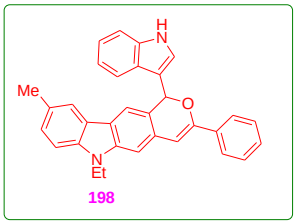
Found: C, 70.89; H, 3.91; N, 5.10%

Procedure for the synthesis of 6-ethyl-1,6-dihydro-1-(1*H*-indol-3-yl)-9-methyl-3-phenylpyrano[4,3-*b*]carbazole (198):

An oven dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 0.5 mmol of 9-ethyl-6-methyl-2-(2-phenylethynyl)-9*H*-carbazole-3-carbaldehyde (**191b**), 10 mol% of $PdCl_2$, and 5 mL of DMSO. To it 0.5 mmol of indole (**194a**) was added. Then, the reaction mixture was stirred at room temperature. After completion of reaction as monitored by TLC, the crude reaction mixture was then poured over water and extracted with dichloromethane (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography using silica gel with hexanes-ethyl acetate mixture

(eluent: 20% ethyl acetate in hexanes). The product **198** was eluted in 20% eluent as a viscous liquid.

6-Ethyl-1,6-dihydro-1-(1*H*-indol-3-yl)-9-methyl-3-phenylpyrano[4,3-*b*]carbazole (198)



198

Yield: 78%

R_f 0.62 (25% EtOAc/hexanes)

Mp: viscous liquid

IR (KBr) ν_{max} cm^{-1}: 3056, 2965, 2912, 1457, 1045, 1035, 769

^{1}H NMR (400 MHz) δ: 8.03 (bs, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.71-7.69 (m, 3H), 7.66 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.29-7.28 (m, 3H), 7.27 (s, 1H), 7.23-7.20 (m, 2H), 7.18-7.16 (m, 2H), 6.87 (s, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.67 (s, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 2.46 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 152.3, 140.4, 138.5, 136.6, 135.1, 130.3, 128.4, 128.2, 128.1, 126.7, 126.5, 125.3, 125.0, 123.4, 122.3, 122.2, 121.2, 120.3, 120.1, 120.0, 117.1, 116.4, 111.2, 108.1, 103.2, 102.0 (aromatic C); 74.8, 37.7, 21.3, 13.9 (aliphatic C)

LCMS (m/z): 453 ($M-H^+$), 454 (M^+), negative mode

Anal. Calcd for $C_{32}H_{26}N_2O$: C, 84.55; H, 5.77; N, 6.16%

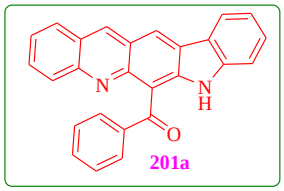
Found: C, 84.41; H, 5.71; N, 6.25%

General procedure for synthesis of quino[2,3-*b*]carbazoles:

An oven-dried 10-mL round-bottomed flask equipped with a teflon-coated magnetic stirring bar was charged with 0.5 mmol 2-(2-phenylethynyl)quinoline-3-carbaldehyde (**199a**) 5 mol% of $Cu(OTf)_2$, and 5 mL DMA. To this 0.5 mmol of *N*-methyl indole (**200a**) was added. Then the reaction mixture was stirred at 120 °C until the complete consumption of starting materials as monitored by TLC. Then, solvent was removed under reduced pressure. The crude reaction mixture was then poured over water and extracted with EtOAc (3 × 20 mL). The organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed. The residue was purified by column chromatography using silica gel with hexanes-ethyl acetate

mixture (eluent: 5% ethyl acetate in hexanes) to afford the product **201b**; the product **201b** was eluted as fluorescent solid. Yield: 63%. The same procedure was followed for the synthesis of other quino[2,3-*b*]carbazoles (**201a-201m**).

(7*H*-Indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201a):



201a

Yield: 42%

R_f 0.62 (20% EtOAc/hexanes)

Mp: 274-276 °C

IR (KBr) ν_{max} cm^{-1}: 3395, 2955, 2910, 2850, 1655, 1594, 1468, 1400, 1250, 1100, 805

^{1}H NMR (400 MHz) δ: 10.21 (s, 1H), 8.98 (s, 1H), 8.86 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.71 (m, 2H), 7.60-7.66 (m, 1H), 7.52-7.58 (m, 3H), 7.46-7.49 (m, 2H), 7.35-7.41 (m, 3H)

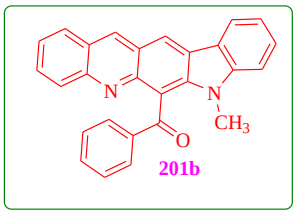
^{13}C NMR (100 MHz) δ: 198.8, 147.9, 146.4, 146.2, 142.9, 142.4, 136.7, 131.1, 130.2, 129.3, 129.2, 129.0, 128.1, 127.9, 127.5, 124.8, 124.7, 124.4, 122.3, 121.8, 121.4, 121.0, 111.6, 111.1 (Aromatic C)

HRMS (ESI-MS)

Calculated for $C_{26}H_{16}N_2O$: 373.1341 (M+H), positive mode

Found: 373.1341

(7-Methyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201b):



201b

Yield: 63%

R_f 0.64 (20% EtOAc/hexanes)

Mp: 252-254 °C

IR (KBr) ν_{max} cm^{-1}: 3400, 2945, 2890, 2750, 1559, 1500, 1400, 1250, 1128, 790

^{1}H NMR (400 MHz) δ: 8.94 (s, 1H), 8.76 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 7.97-8.00 (m, 3H), 7.92 (d, J = 9.0 Hz, 1H), 7.54-7.67 (m, 3H), 7.43 (t, J

= 8.0 Hz, 2H), 7.30-7.35 (m, 2H), 7.24-7.27 (m, 1H), 3.66 (s, 3H)

^{13}C NMR (100 MHz) δ: 199.3, 148.6, 147.2, 145.0, 141.2, 140.0, 135.8, 133.0, 130.0, 129.6, 129.55, 128.8, 128.6, 128.5, 127.9, 127.6, 124.7, 124.4, 122.1, 121.1, 120.0, 119.3, 115.2, 108.4, (Aromatic C), 31.9 (Aliphatic C)

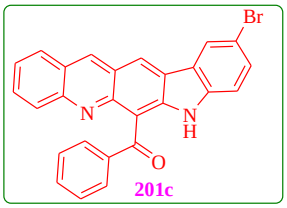
HRMS (ESI-MS)

Calculated for $C_{27}H_{18}N_2O$: 387.1497 (M+H), positive mode

Found: 387.1497

(10-Bromo-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201c):

Yield: 40%



201c

R_f 0.62 (20% EtOAc/hexanes)

Mp: 262-264 °C

IR (KBr) ν_{max} cm^{-1}: 3380, 2955, 2870, 2690, 1555, 1490, 1256, 790

^{1}H NMR (400 MHz) δ: 10.16 (s, 1H), 8.98 (s, 1H), 8.82 (s, 1H), 8.36 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 6.5 Hz, 2H), 7.53-7.58 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.35-7.40 (m, 3H)

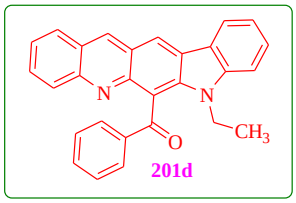
^{13}C NMR (100 MHz) δ: 198.7, 148.2, 146.3, 145.9, 142.0, 141.6, 136.9, 131.6, 131.3, 130.5, 129.3, 129.2, 127.9, 127.6, 126.9, 125.0, 124.7, 124.3, 124.2, 121.8, 113.6, 112.5, 112.0 (Aromatic C)

HRMS (ESI-MS)

Calculated for $C_{26}H_{15}BrN_2O$: 451.0466 (M+H)

Found: 451.0464 (M+H), 453.0466 (M+2)

(7-Ethyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201d)



201d

Yield: 62%

R_f 0.60 (20% EtOAc/hexanes)

Mp: 258-260 °C

IR (KBr) ν_{max} cm^{-1}: 3742, 2958, 2915, 2860, 1660, 1594, 1468

^{1}H NMR (400 MHz) δ: 8.96 (s, 1H), 8.78 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.93-8.00 (m, 4H), 7.53-7.63 (m, 3H), 7.40-7.44 (m, 3H), 7.32-7.36 (m, 2H), 4.21 (q, *J* = 7.0 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 3H)

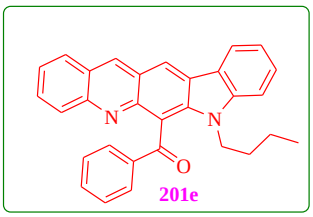
^{13}C NMR (100 MHz) δ: 199.3, 148.6, 147.2, 144.1, 139.9, 139.4, 135.7, 133.1, 129.9, 129.6, 129.57, 128.6, 128.5, 127.9, 127.8, 124.8, 124.4, 122.5, 121.1, 121.0, 120.1, 119.2, 115.0, 108.7 (Aromatic C), 39.6, 13.2 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{28}H_{20}N_2O$: 401.1654 (M+H)

Found: 401.1654

(7-Butyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201e):



201e

Yield: 60%

R_f 0.58 (20% EtOAc/hexanes)

Mp: 230-232 °C

IR (KBr) ν_{max} cm^{-1}: 3739, 2988, 2900, 2880, 1657, 1590, 1448

^{1}H NMR (400 MHz) δ: 8.95 (s, 1H), 8.77 (s, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 7.93-7.99 (m, 4H), 7.53-7.64 (m, 3H),7.39-7.43 (m, 3H), 7.30-7.34 (m, 2H), 4.10 (t, *J* = 8.0 Hz, 2H), 1.53 (br, 2H), 1.18 (sextet, *J* = 7.2 Hz, 2H), 0.74 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 199.1, 148.6, 147.2, 144.5, 140.1, 139.2, 135.7, 133.1, 130.0, 129.6, 128.6, 128.5, 127.9, 124.7, 124.4, 122.3, 121.1, 121.0,

120.0, 119.1, 115.0, 108.8 (Aromatic C), 44.7, 30.5, 20.0, 13.6 (Aliphatic C)

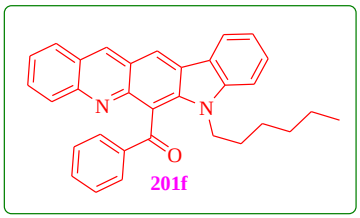
HRMS (ESI-MS)

Calculated for $C_{30}H_{24}N_2O$: 429.1967 (M+H)

Found: 429.1967

(7-Hexyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201f):

Yield: 61%



201f

R_f 0.60 (20% EtOAc/hexanes)

Mp: 224-226 °C

IR (KBr) ν_{max} cm^{-1}: 3749, 2955, 2900, 2850, 1647, 1490

^{1}H NMR (400 MHz) δ: 8.94 (s, 1H), 8.75 (s, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.90-7.98 (m, 4H), 7.50-7.61 (m, 3H), 7.36-7.42 (m, 3H), 7.29-7.31 (m, 2H), 4.07 (t, *J* = 8.5 Hz, 2H), 1.50 (br, 2H), 1.09-1.17 (m, 4H), 1.01-1.05 (m, 2H), 0.80 (t, *J* = 7.5 Hz, 3H)

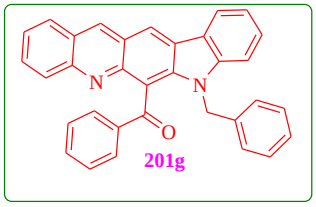
^{13}C NMR (100 MHz) δ: 199.0, 148.6, 147.3, 144.5, 140.1, 139.2, 135.7, 133.0, 130.0, 129.6, 129.55, 128.6, 128.5, 127.9, 127.8, 124.8, 124.4, 122.3, 121.0, 120.0, 119.1, 115.0, 108.8 (Aromatic C), 44.9, 31.3, 28.4, 26.3, 22.5, 14.0 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{32}H_{28}N_2O$: 457.2280 (M+H)

Found: 457.2280

(7-Benzyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201g):



Yield: 58%

R_f 0.70 (20% EtOAc/hexanes)

Mp: 252-254 °C

IR (KBr) ν_{max} cm^{-1}: 2998, 2920, 2840, 1656, 1580, 1438

^{1}H NMR (400 MHz) δ: 8.97 (s, 1H), 8.83 (s, 1H), 8.31 (d, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.60-7.64 (m, 3H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.31-7.38 (m, 2H), 7.25 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 2H), 6.96-6.97 (m, 3H), 6.79-6.81 (m, 2H), 5.48 (s, 2H)

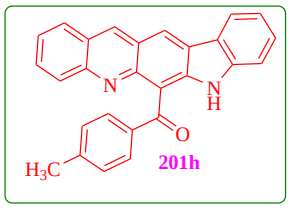
^{13}C NMR (100 MHz) δ: 198.9, 148.5, 147.3, 145.1, 140.4, 139.2, 136.4, 135.7, 132.4, 129.7, 129.6, 128.8, 128.3, 128.0, 127.8, 127.1, 126.1, 124.8, 124.5, 122.3, 121.2, 121.1, 120.5, 119.4, 115.8, 109.3 (Aromatic C), 48.1 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{33}H_{22}N_2O$: 463.1810 (M+H)

Found: 463.1810

(7*H*-Indolo[3,2-*b*]acridin-6-yl)(*p*-tolyl)methanone (201h):



Yield: 43%

R_f 0.52 (20% EtOAc/hexanes)

Mp: 276-278 °C

IR (KBr) ν_{max} cm^{-1}: 3023, 2998, 2920, 2890, 1647, 1690, 1548

^{1}H NMR (400 MHz) δ: 10.10 (bs, 1H), 8.96 (s, 1H), 8.81 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.02-8.03 (m, 4H), 7.66-7.67 (m, 1H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.45-7.47 (m, 2H), 7.34 (t, *J* = 7.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H)

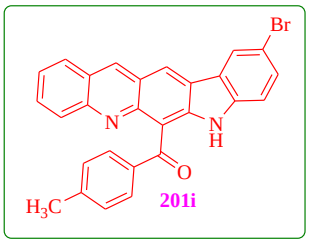
^{13}C NMR (100 MHz) δ: 198.3, 148.0, 146.3, 145.7, 144.4, 143.1, 142.1, 138.9, 136.6, 130.3, 130.1, 129.8, 129.2, 128.9, 128.3, 127.9, 124.7, 123.7, 122.3, 121.8, 121.4, 120.8, 112.2, 111.1 (Aromatic C), 21.7 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{27}H_{18}N_2O$: 387.1497 (M+H)

Found: 387.1497

(10-Bromo-7*H*-indolo[3,2-*b*]acridin-6-yl)(*p*-tolyl)methanone (201i):



Yield: 41%

R_f 0.55 (20% EtOAc/hexanes)

Mp: 282-284 °C

IR (KBr) ν_{max} cm^{-1}: 3740, 3005, 2950, 2850, 1627, 1490, 1348

^{1}H NMR (400 MHz) δ: 9.93 (s, 1H), 8.99 (s, 1H), 8.81 (s, 1H), 8.35 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.65-7.68 (m, 5H), 7.48-7.51 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H)

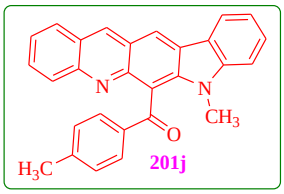
^{13}C NMR (100 MHz) δ: 198.1, 148.3, 146.3, 145.4, 142.4, 141.6, 138.7, 136.9, 131.5, 130.5, 130.2, 129.9, 129.2, 128.4, 128.0, 126.8, 125.0, 124.8, 124.3, 124.2, 121.8, 113.4, 112.7, 112.4 (aromatic C), 21.7 (aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{27}H_{17}BrN_2O$: 465.0602 (M+H)

Found: 465.0602 (M+H), 467.0585 (M+2)

(7-Methyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(*p*-tolyl)methanone (201j):



Yield: 64%

R_f 0.60 (20% EtOAc/hexanes)

Mp: 258-260 °C

IR (KBr) ν_{max} cm^{-1}: 3739, 2958, 2905, 2860, 1657, 1540, 1468

^{1}H NMR (400 MHz) δ: 8.89 (s, 1H), 8.71 (s, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.92 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.53-7.57 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.24-7.30 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.62 (s, 3H), 2.37 (s, 3H)

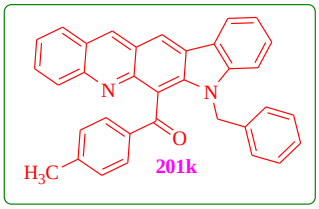
^{13}C NMR (100 MHz) δ: 198.9, 148.6, 147.1, 145.0, 143.9, 141.0, 137.6, 135.8, 130.1, 129.6, 129.5, 129.3, 128.6, 127.9, 127.6, 124.8, 124.4, 122.1, 121.2, 121.1, 120.0, 119.2, 115.5, 108.4 (Aromatic C), 31.8, 21.7 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{28}H_{20}N_2O$: 401.1654 (M+H)

Found: 401.1654

(7-Benzyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(*p*-tolyl)methanone (201k):



Yield: 62%

R_f 0.62 (20% EtOAc/hexanes)

Mp: 262-264 °C

IR (KBr) ν_{max} cm^{-1}: 3735, 2991, 2900, 2480, 1647, 1690, 1458

^{1}H NMR (400 MHz) δ: 8.87 (s, 1H), 8.74 (s, 1H), 8.24 (d, *J* = 6.8 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.50-7.52 (m, 2H), 7.30-7.37 (m, 4H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.87-6.94 (m, 5H), 6.79 (m, 2H), 5.40 (s, 2H), 2.24 (s, 3H)

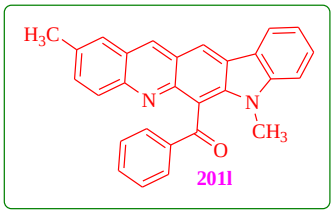
^{13}C NMR (100 MHz) δ: 198.6, 148.6, 147.2, 145.0, 143.3, 140.3, 136.7, 136.6, 135.7, 129.9, 129.7, 129.6, 128.8, 128.76, 128.3, 127.9, 127.8, 126.8, 126.1, 124.8, 124.5, 122.3, 121.2, 121.1, 120.4, 119.2, 116.1, 109.3 (Aromatic C), 48.1, 21.6 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{34}H_{24}N_2O$: 477.1967 (M+H)

Found: 477.1967

(2,7-Dimethyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201l):



201l

Yield: 68%

R_f 0.60 (20% EtOAc/hexanes)

Mp: 290-292 °C

IR (KBr) ν_{max} cm^{-1}: 3759, 2968, 2940, 2870, 1647, 1590, 1448

^{1}H NMR (400 MHz) δ: 8.77 (s, 1H), 8.69 (s, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.97-7.99 (m, 2H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.67 (s, 1H), 7.53-7.58 (m, 2H), 7.43 (m, 3H), 7.31 (t, *J* =7.0 Hz, 1H), 7.27-7.30 (m, 1H), 3.64 (s, 3H), 2.52 (s, 3H)

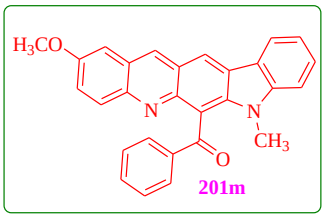
^{13}C NMR (100 MHz) δ: 199.4, 147.5, 146.6, 144.9, 140.8, 139.9, 139.3, 134.6, 134.0, 132.9, 132.5, 129.9, 129.1, 128.5, 127.3, 125.8, 122.1, 121.2, 121.0, 119.9, 115.1, 114.1, 108.3 (Aromatic C), 31.8, 21.7 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{28}H_{20}N_2O$: 401.1654 (M+H)

Found: 401.1654

(2-Methoxy-7-methyl-7*H*-indolo[3,2-*b*]acridin-6-yl)(phenyl)methanone (201m):



Yield: 70%

R_f 0.64 (20% EtOAc/hexanes)

Mp: 302-304 °C

IR (KBr) ν_{max} cm^{-1}: 3012, 2950, 2980, 1647, 1595, 1458, 1110

^{1}H NMR (400 MHz) δ: 8.61 (s, 1H), 8.59 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 9.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.29-7.30 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 3.92 (s, 3H), 3.60 (s, 3H)

^{13}C NMR (100 MHz) δ: 199.5, 156.1, 145.7, 145.6, 144.9, 140.3, 139.9, 133.4, 133.0, 131.0, 129.9, 128.5, 128.4, 127.3, 125.3, 124.8, 122.0, 121.3, 121.1, 119.7, 118.7, 115.2, 108.3, 102.7 (Aromatic C), 55.4, 31.8 (Aliphatic C)

HRMS (ESI-MS)

Calculated for $C_{28}H_{20}N_2O_2$: 417.1603 (M+H)

Found: 417.1603

Table 5. Crystal data and structure refinement for 193a.

Identification code	**193a**	
Empirical formula	$C_{31}H_{23}N\ O$	
Formula weight	425.50	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 13.9895(14) Å	α = 90°.
	b = 20.393(2) Å	β = 92.568(2)°.
	c = 15.7545(16) Å	γ = 90°.
Volume	4490.2(8) $Å^3$	
Z	8	
Density (calculated)	1.259 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	1792	
Crystal size	0.24 x 0.18 x 0.14 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	42932	
Independent reflections	7917 [R(int) = 0.0747]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9895 and 0.9821	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7917 / 0 / 598	
Goodness-of-fit on F^2	1.137	
Final R indices [I>2sigma(I)]	R1 = 0.0721, wR2 = 0.1299	
R indices (all data)	R1 = 0.1052, wR2 = 0.1426	
Extinction coefficient	0.00060(13)	
Largest diff. peak and hole	0.220 and -0.182 e.$Å^{-3}$	
CCDC number	**84727**	

Table 6. Crystal data and structure refinement for 201a.

Identification code	**201a**	
Empirical formula	$C_{26}H_{16}N_2O$	
Formula weight	372.41	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 17.4997(15) Å	α = 90°.
	b = 4.9148(4) Å	β = 104.273 (2)°.
	c = 21.8498(16) Å	γ = 90°.
Volume	1821.2(2) $Å^3$	
Z	4	
Density (calculated)	1.358 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	776	
Crystal size	0.22 x 0.18 x 0.12 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	42932	
Independent reflections	7917 [R(int) = 0.0747]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9895 and 0.9821	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7917 / 0 / 598	
Goodness-of-fit on F^2	1.137	
Final R indices [I>2sigma(I)]	R1 = 0.065, wR2 = 0.1277	
R indices (all data)	R1 = 0.0992, wR2 = 0.1445	
Extinction coefficient	0.00061(13)	
Largest diff. peak and hole	0.227 and -0.172 e.$Å^{-3}$	
CCDC number	**900312**	

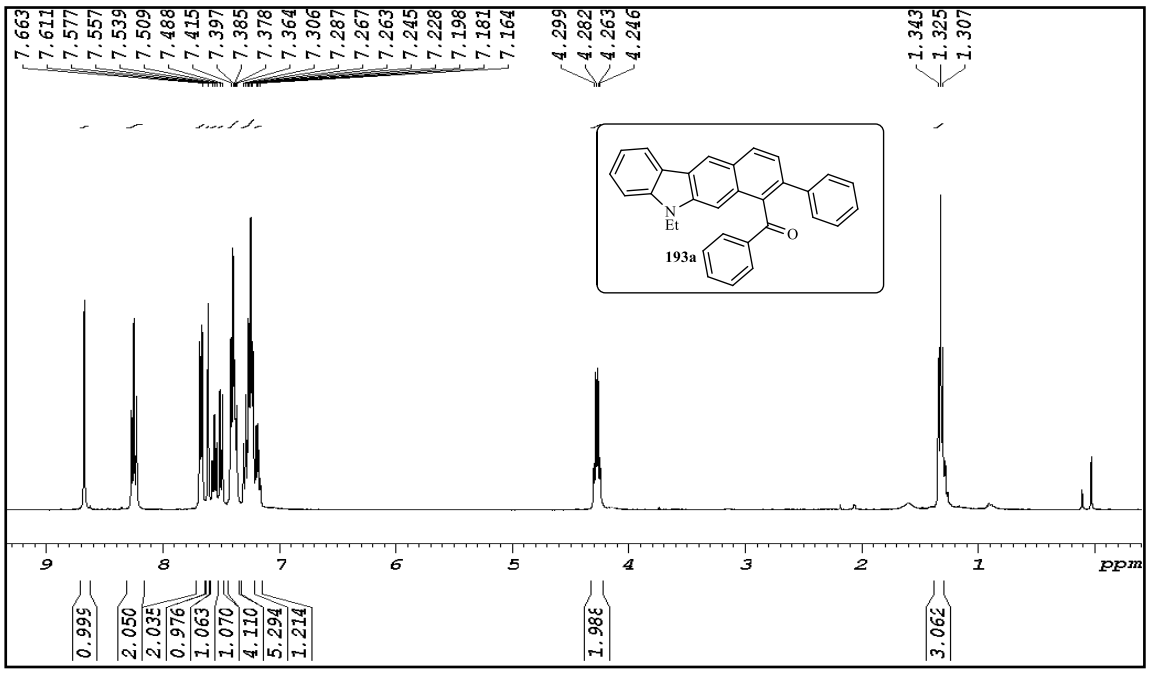
Table 7. Crystal data and structure refinement for 201e.

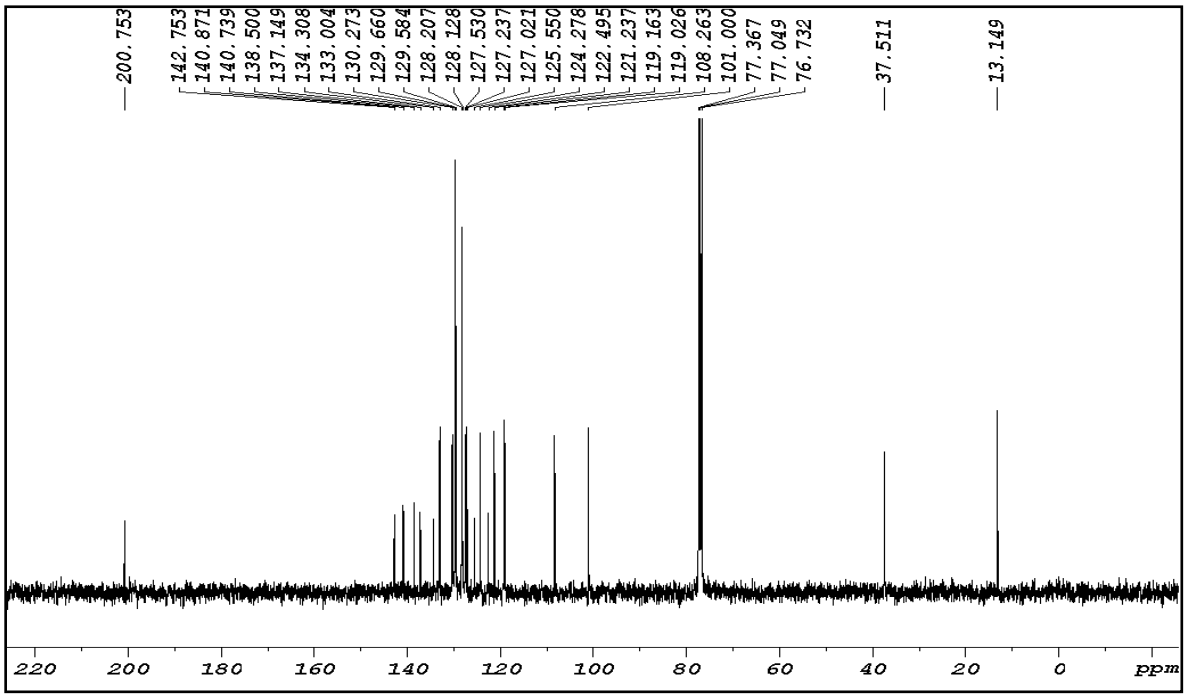
Identification code	**201e**	
Empirical formula	$C_{30}H_{24}N_2O$	
Formula weight	428.51	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 12.0524(17) Å	α = 104.180°.
	b = 13.4942(19) Å	β = 100.035(2)°.
	c = 15.342(2) Å	γ = 107.384°.
Volume	2224.6(5) $Å^3$	
Z	4	
Density (calculated)	1.308 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	604	
Crystal size	0.24 x 0.18 x 0.14 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	42932	
Independent reflections	7917 [R(int) = 0.0747]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9816 and 0.9892	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7917 / 0 / 598	
Goodness-of-fit on F^2	1.137	
Final R indices [I>2sigma(I)]	R1 = 0.086, wR2 = 0.1795	
R indices (all data)	R1 = 0.2078, wR2 = 0.2458	
Extinction coefficient	0.00051(12)	
Largest diff. peak and hole	0.224 and -0.162 $e.Å^{-3}$	
CCDC number	**900313**	

Table 8. Crystal data and structure refinement for 201l.

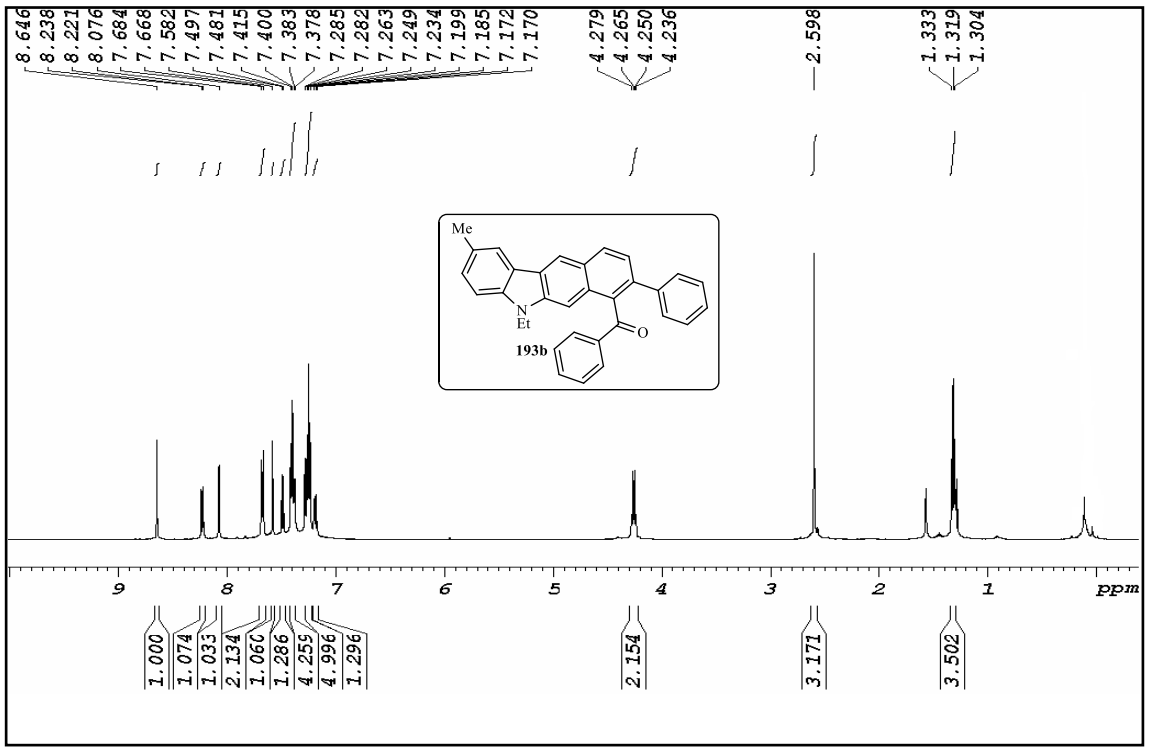
Identification code	**201l**	
Empirical formula	$C_{28}H_{20}N_2O$	
Formula weight	400.46	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	F d d 2	
Unit cell dimensions	a = 33.695(3) Å	α = 90°.
	b = 30.274(2) Å	β = 90°.
	c = 8.2167(7) Å	γ = 90°.
Volume	8381.7(12) $Å^3$	
Z	16	
Density (calculated)	1.528 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	3360	
Crystal size	0.22 x 0.20 x 0.16 mm^3	
Theta range for data collection	1.72 to 25.00°.	
Reflections collected	42932	
Independent reflections	7917 [R(int) = 0.0747]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9816 and 0.9892	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7917 / 0 / 598	
Goodness-of-fit on F^2	1.137	
Final R indices [I>2sigma(I)]	R1 = 0.0621, wR2 = 0.1145	
R indices (all data)	R1 = 0.0903, wR2 = 0.1068	
Extinction coefficient	0.00061(11)	
Largest diff. peak and hole	0.234 and -0.102 $e.Å^{-3}$	
CCDC number	**900314**	

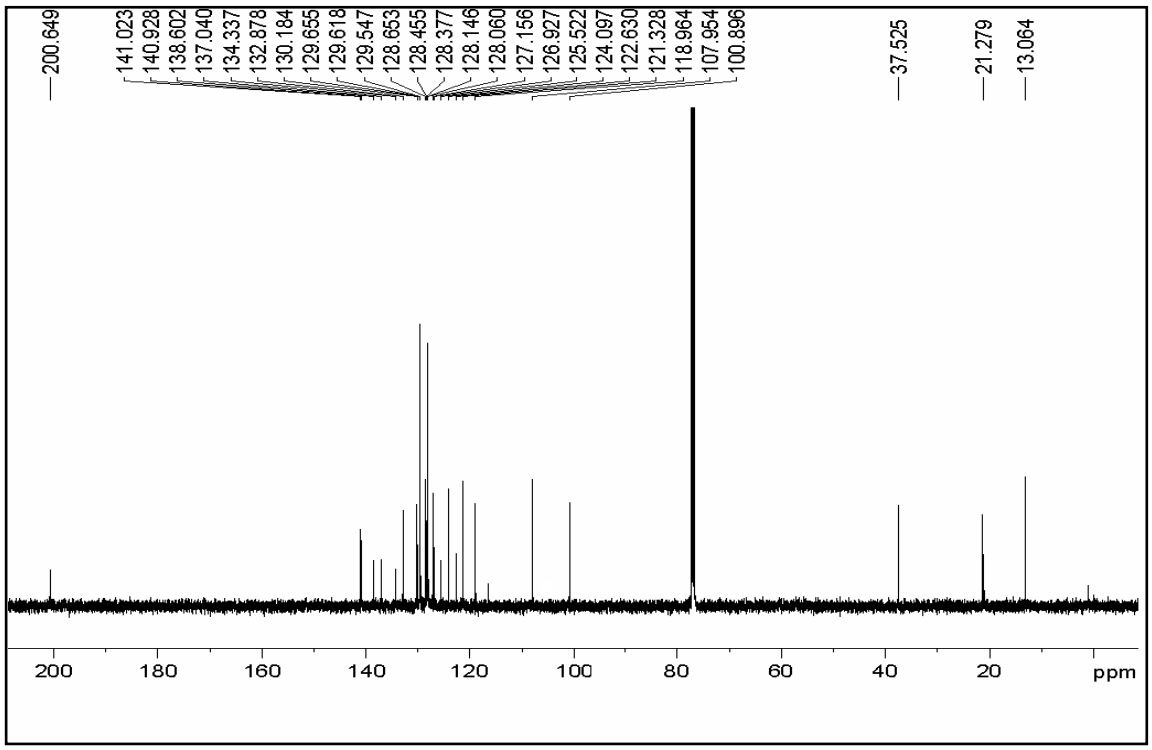
Spectra No. 1: ^{1}H and ^{13}C spectra of Compound 193a.



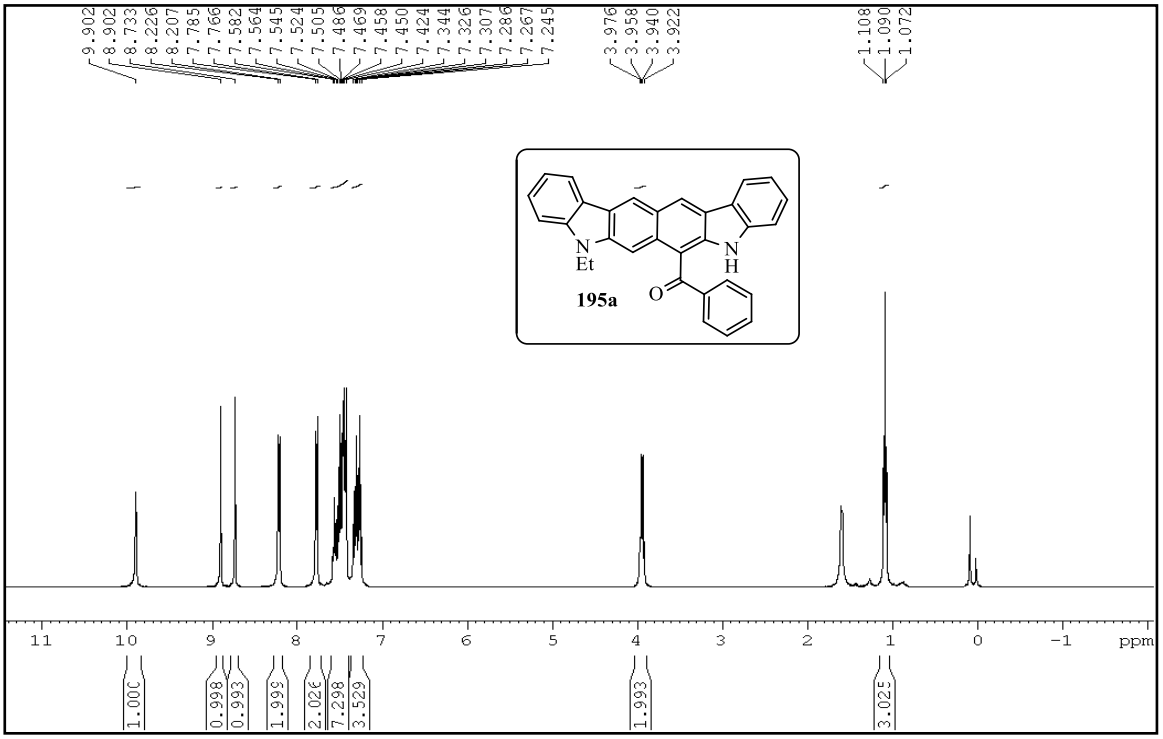


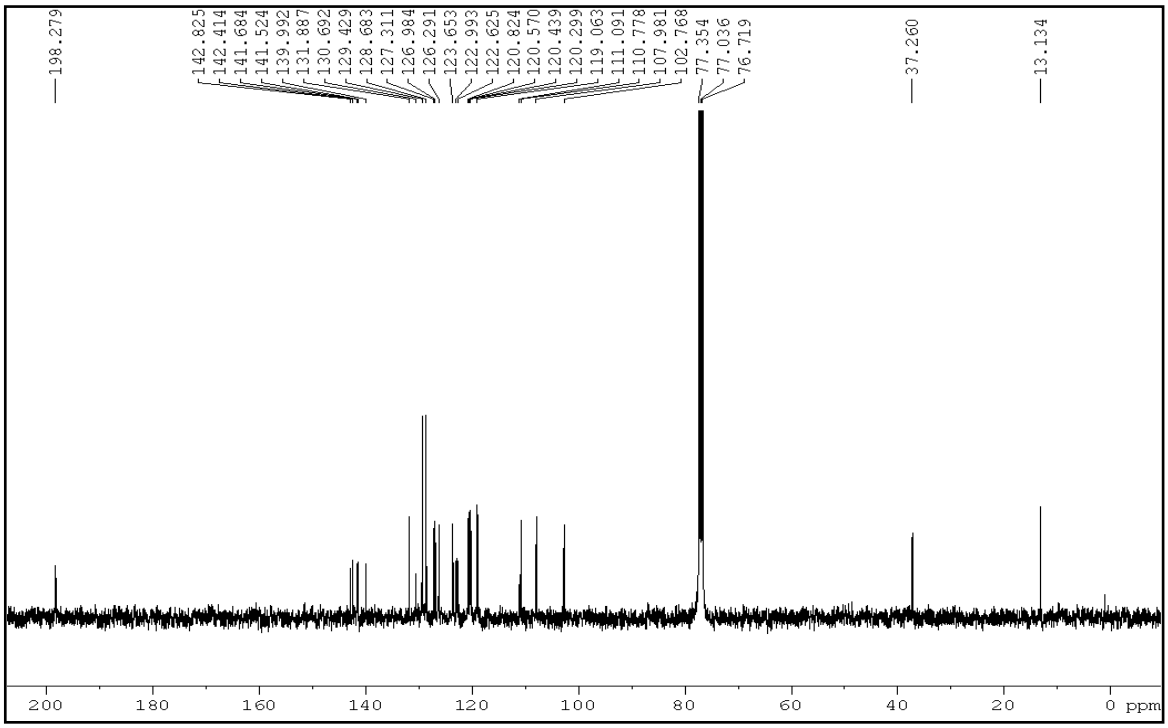
Spectra No. 2: ^{1}H and ^{13}C spectra of Compound 193b



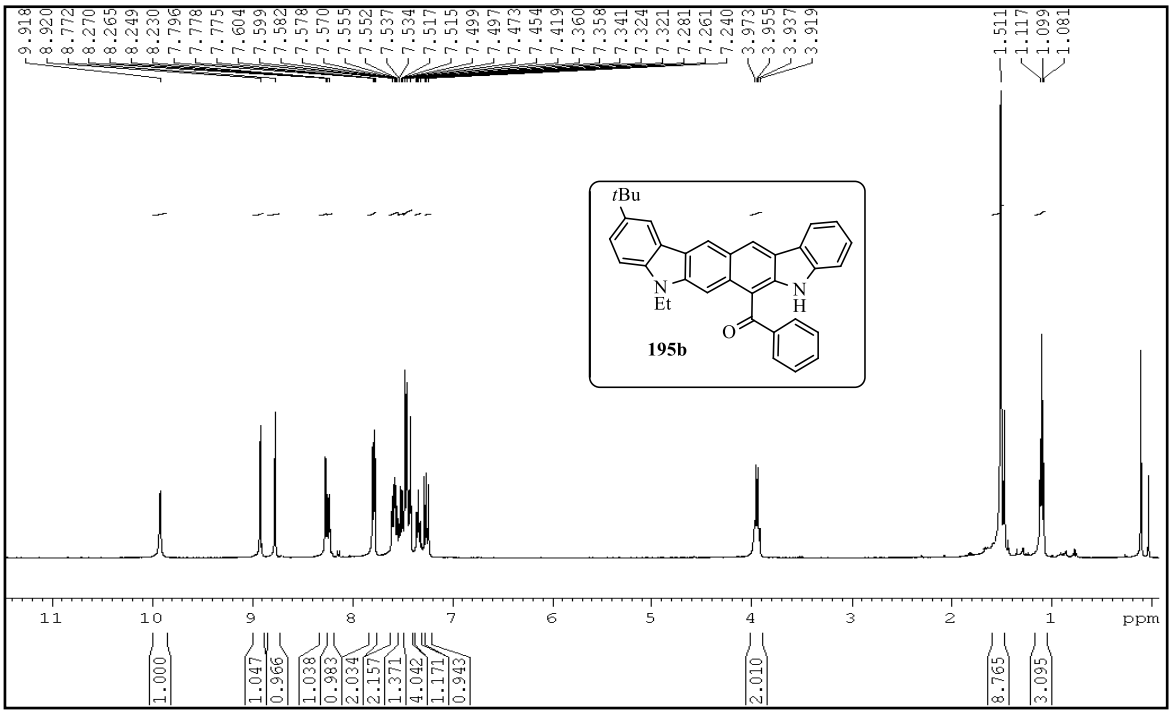


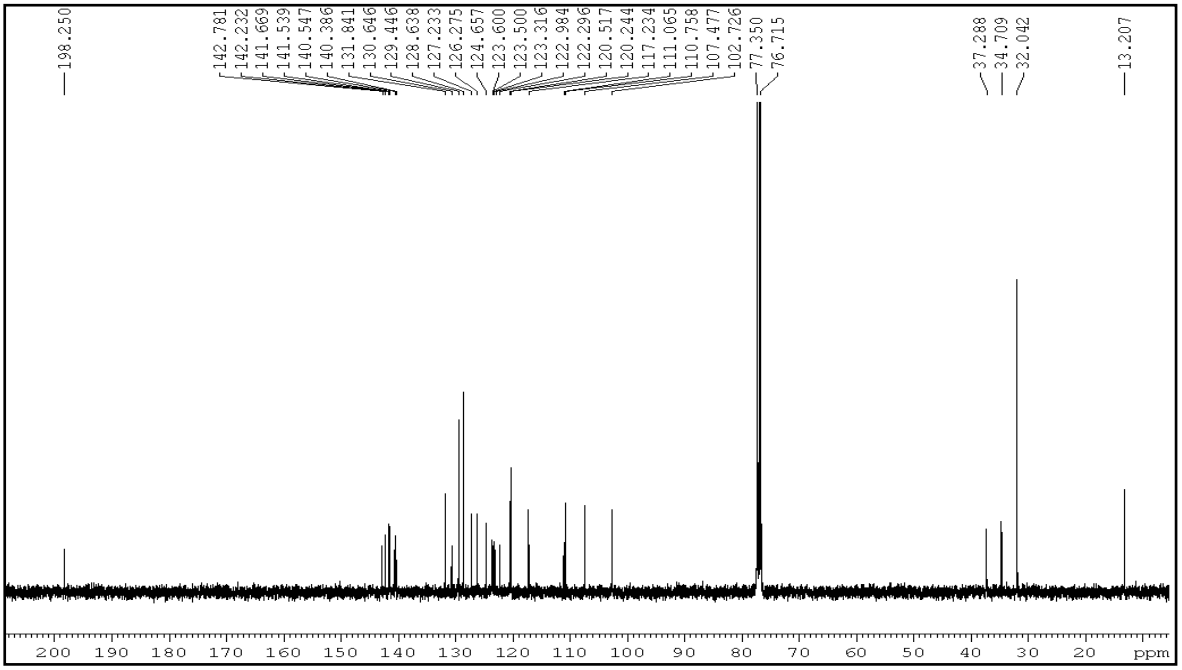
Spectra No. 3: ^{1}H and ^{13}C spectra of Compound 195a



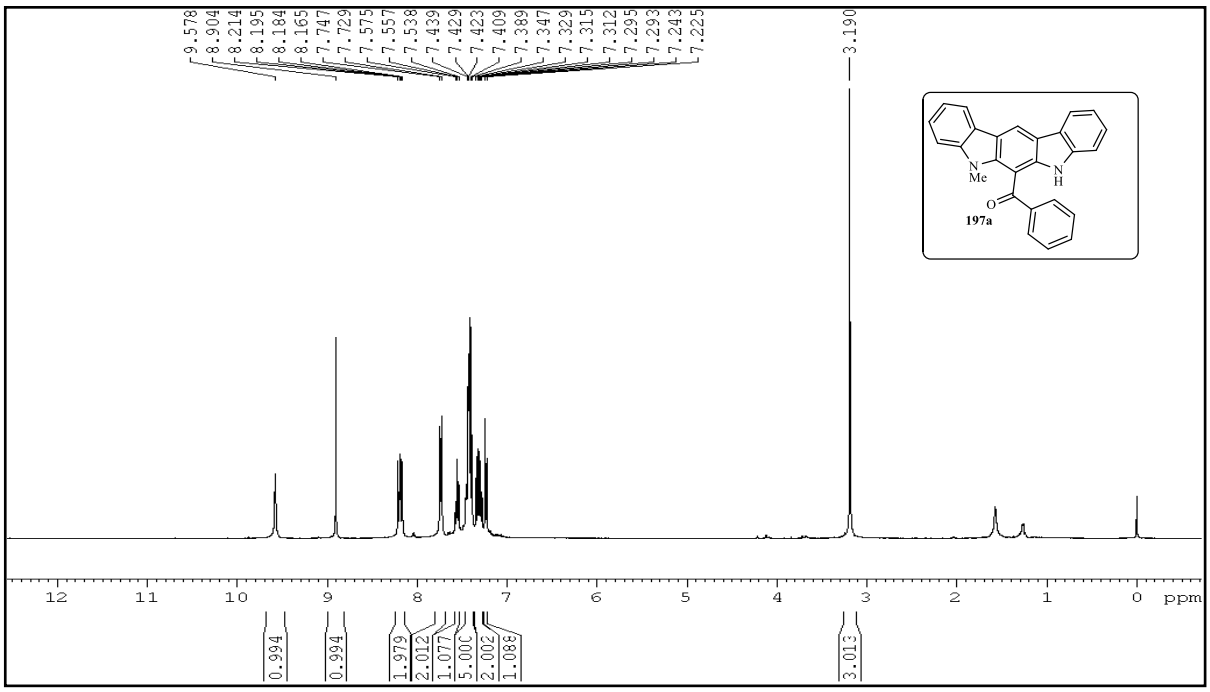


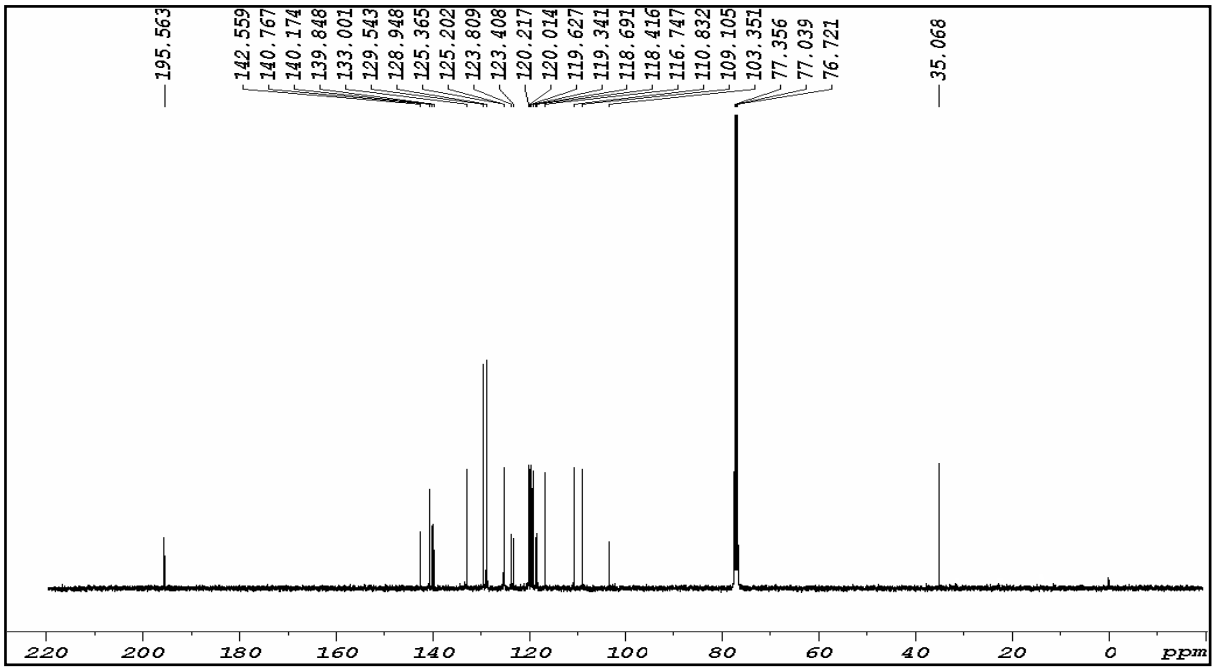
Spectra No. 4: ^{1}H and ^{13}C spectra of Compound 195b



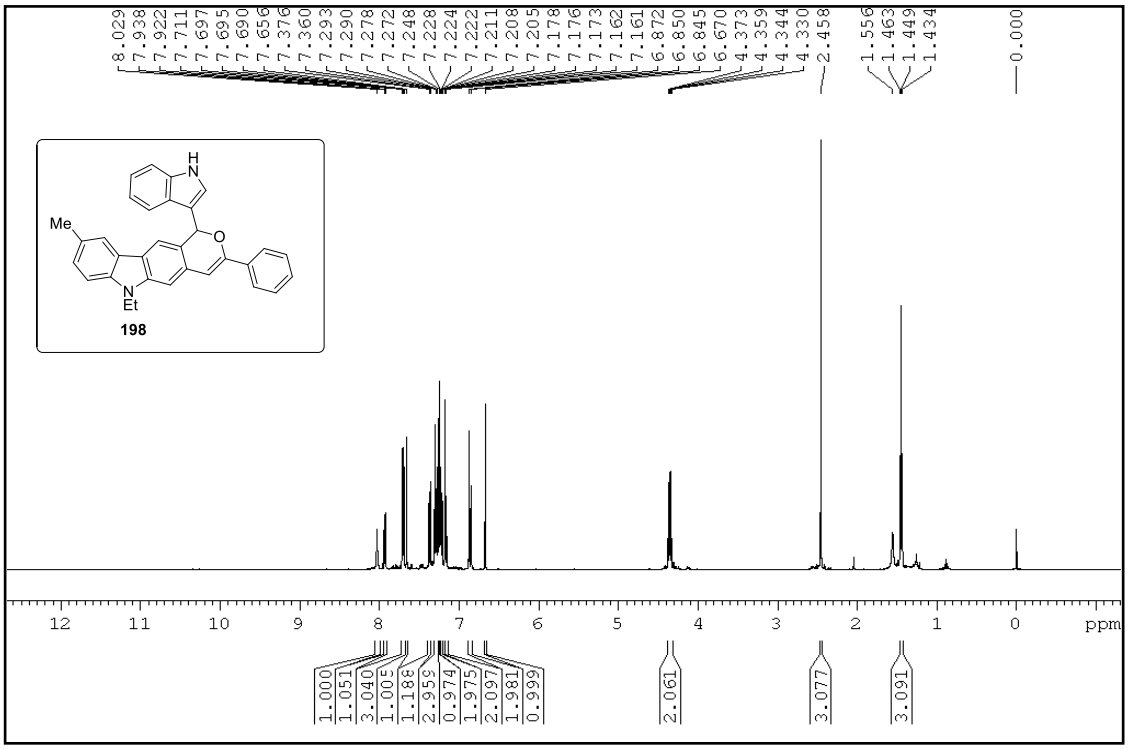


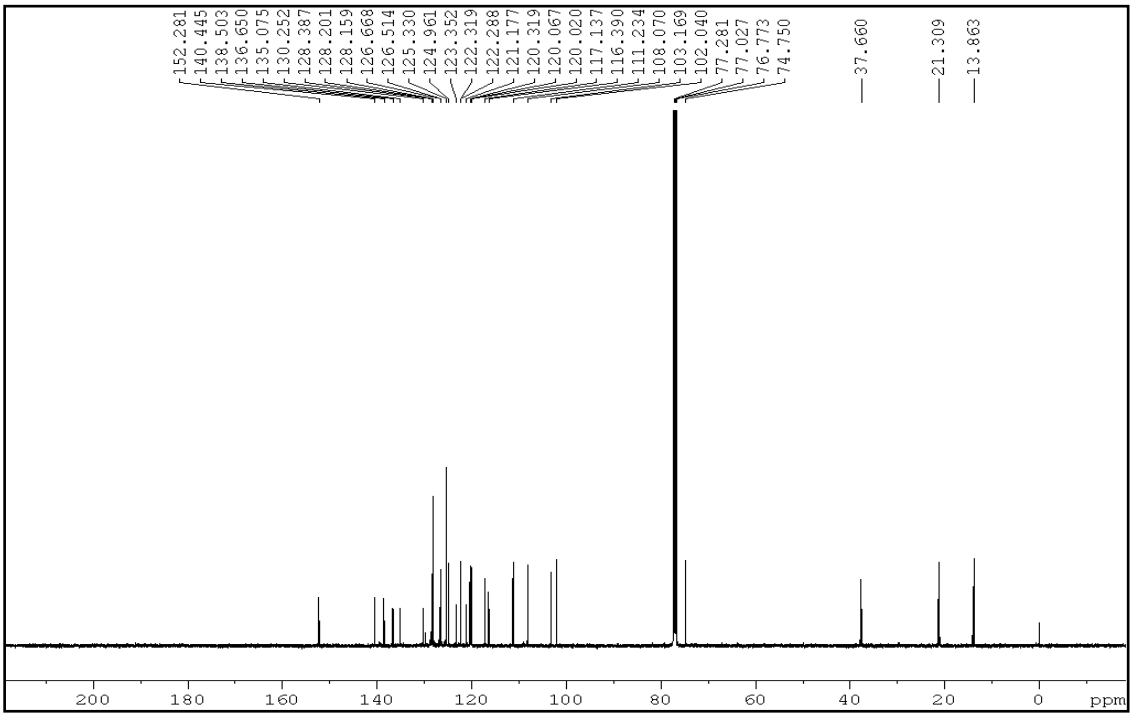
Spectra No. 5: ^{1}H and ^{13}C spectra of Compound 197a



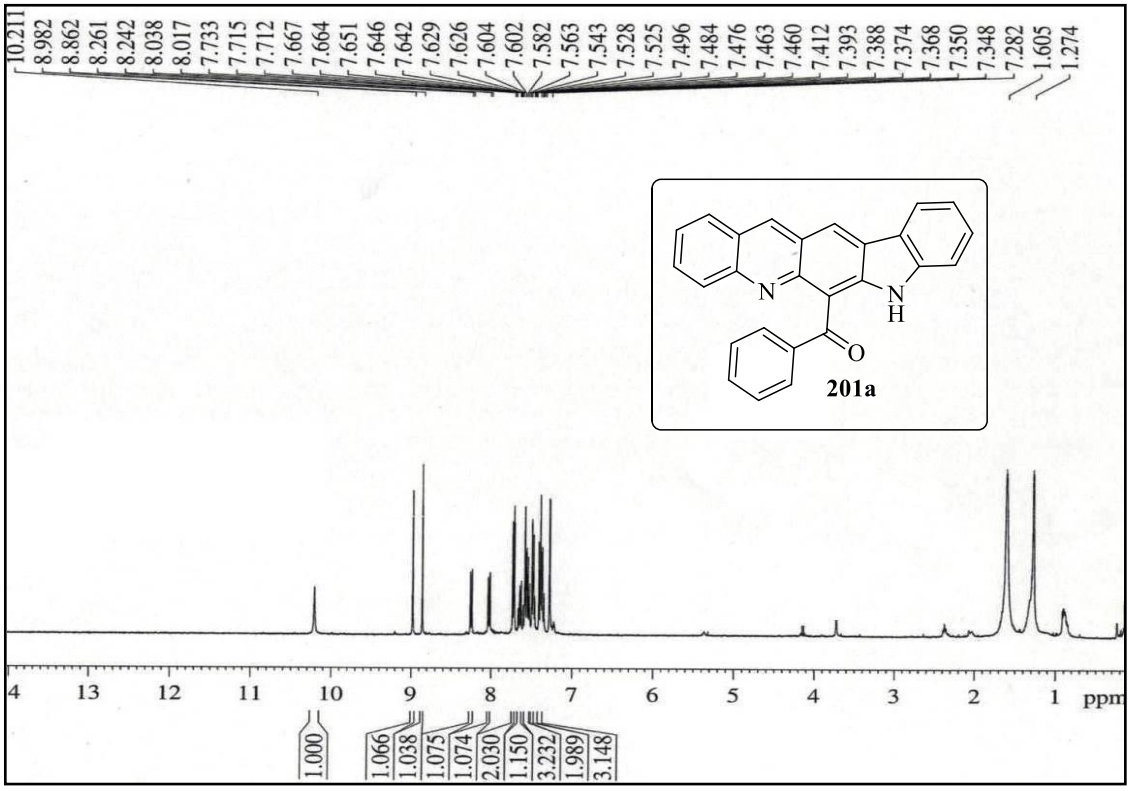


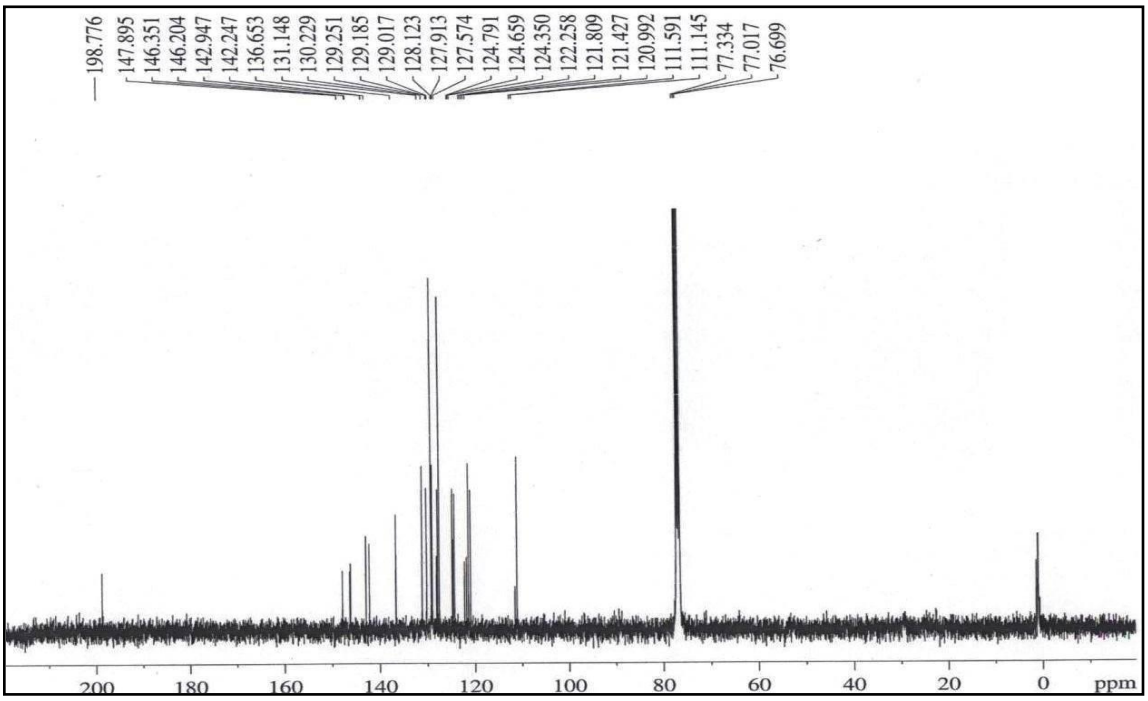
Spectra No. 6: ^{1}H and ^{13}C spectra of Compound 198





Spectra No. 7: ^{1}H and ^{13}C spectra of Compound 201a





1.7. Conclusions

In this chapter, we have demonstrated a simple and efficient methodology for the synthesis of benzo[*b*]-, carbazolo[2,3-*b*]-, and indolo[2,3-*b*]carbazole derivatives in moderate to good yields. The scope of this synthetic route is general. This process can be applicable to wide range of functional groups and affording benzo[*b*]-, carbazolo[2,3-*b*]-, and indolo[2,3-*b*]carbazole derivatives.

Mechanism for the formation of the product is clearly explained by the isolation of the intermediate.

Synthesis of a family of quino[2,3-*b*]carbazoles and the study of their photochemical behaviour in solution and in the solid state is reported. Their fluorescent nature has been utilized for the sensing of TNT.

1.8. References

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CHAPTER 2

Synthesis of indol-3-yl benzonaphthyridines *via* copper(II)-triflate catalyzed heteroannulation

2.1. Introduction

Marine sponges are the source of many biologically active nitrogen heterocyclic constituents, which possess a series of 1*H*-benzo[*de*][1,6]-naphthyridines.[82] Aaptamine (**202**) was first isolated in 1982 by Nakamura and co-workers.[83] Naphthyridines and their benzo/hetero fused analogues gained considerable attention due to their wide spectrum of biological activities[84] such as anticancer,[84a-b] anti-HIV-1 integrase inhibitors,[84c] antiproliferative activity[3d] antimicrobial,[84e] and adrenoceptor blocking activities.[84f] These are reported as allosteric inhibitors of Akt1 and Akt2,[84g] and antagonists of 5-HT_4 receptors.[84h] Furthermore, isoaaptamine, was isolated from sponge in the genus *Suberites* by Fedoreev.[85] Later, it was isolated from *Aaptos aaptos*[86a-b] and it has been found to have a PKC inhibitor[86c] and inhibit growth of cancer cells.[86a-b] Pettit *et al.* showed that isoaaptamine has significant activity against murine P388 lymphocytic leukemia cells (ED50 0.28 *ί*g/mL) and a panel of six human cancer cell lines.[87]

Most recently, 5-(3-chlorophenylamino)-benzo[*c*][2,6]naphthyridine-8-carboxylic acid (CX-4945), found to be the first clinical stage inhibitor of protein kinase CK2 for the treatment cancer[88] and dibenzo[*c*,*h*][1,5]naphthyridinediones were reported as topoisomerase I (Top1) inhibitors.[89] Lophocladine A (**205**) and Lophocladine B (**206**) are 2,7-naphthyridine alkaloids, in which, **205** exhibited affinity for NMDA receptors and it was found to be a δ-opioid receptor antagonist. Lophocladine B (**206**) showed cytotoxicity to NCI-H460 human lung tumor and MDA-MB-435 breast cancer cell lines.[90]

Very recently, *bis*-aaptamine alkaloids (suberitine A-D) were isolated from the marine sponge *Aaptos suberitoides* and showed that they have potent cytotoxicity against P388 cell lines.[91] These remarkable biological applications of naphthyridine molecules prompted us to synthesize benzonaphthyridine derivatives. Representative molecules of related naphthyridine are shown in Figure 9.

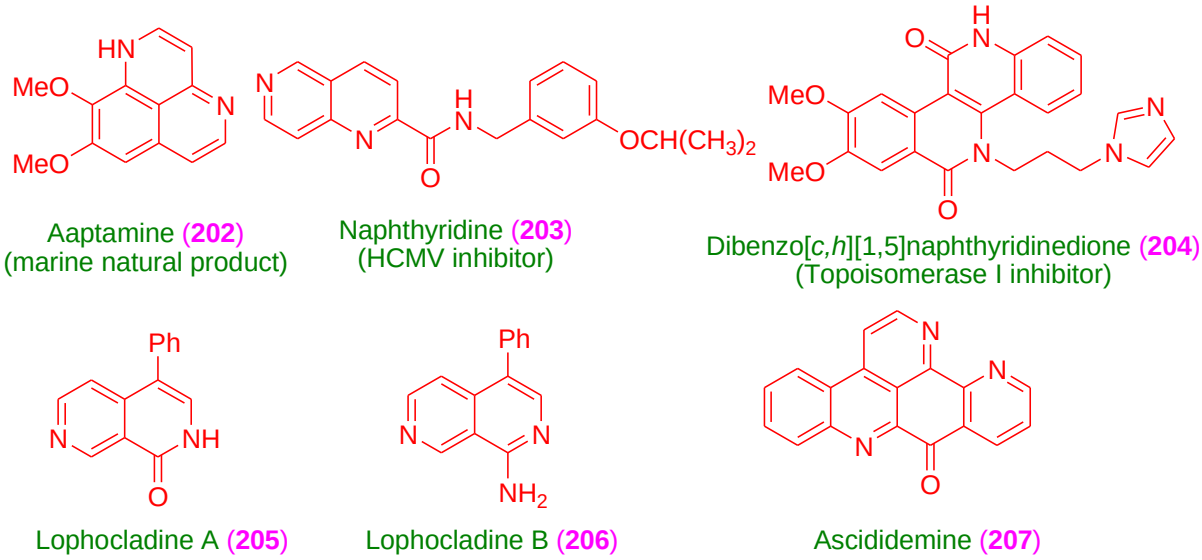


Fig. 9. Representative structures of related bioactive molecules

We envisioned that benzonaphthyridines can be synthesized by 6-*endo* mode iminoannulation of quinoline alkynyl aldehydes. Electrophilic activation of alkynes followed by annulation toward intramolecular addition reactions of heteronucleophiles has become a useful tool for the synthesis of new heterocyclic compounds.[92] Recently, there has been immense synthetic interest in the 6-*endo*-mode cyclization of 2-(1-alkynyl)arylaldimine using various transition metals and Lewis acid catalysis for the synthesis of isoquinolines and 1,2-dihydroisoquinolines motif.[93] A wide variety of functionalized terminal acetylenes participate in this metal-catalyzed and Lewis acid catalyzed cyclization process to afford the desired nitrogen heterocycles.[94]

In chapter 1, we demonstrated the synthesis of benzo[*b*]-, indolo[2,3-*b*]-, carbazolo[2,3-*b*]carbazole derivatives, and our group has reported the synthesis of ellipticinium, ellipticine derivatives[95b] and benzimidazoellipticine derivatives[95c] by 6-*endo*-mode type cyclization of carbazole alkynyl aldehydes. In continuation of our research interest in heteroannulation,[95] in this chapter, we present a convenient synthesis of indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines *via* copper(II)-triflate catalyzed heteroannulation (table 9 and 10).

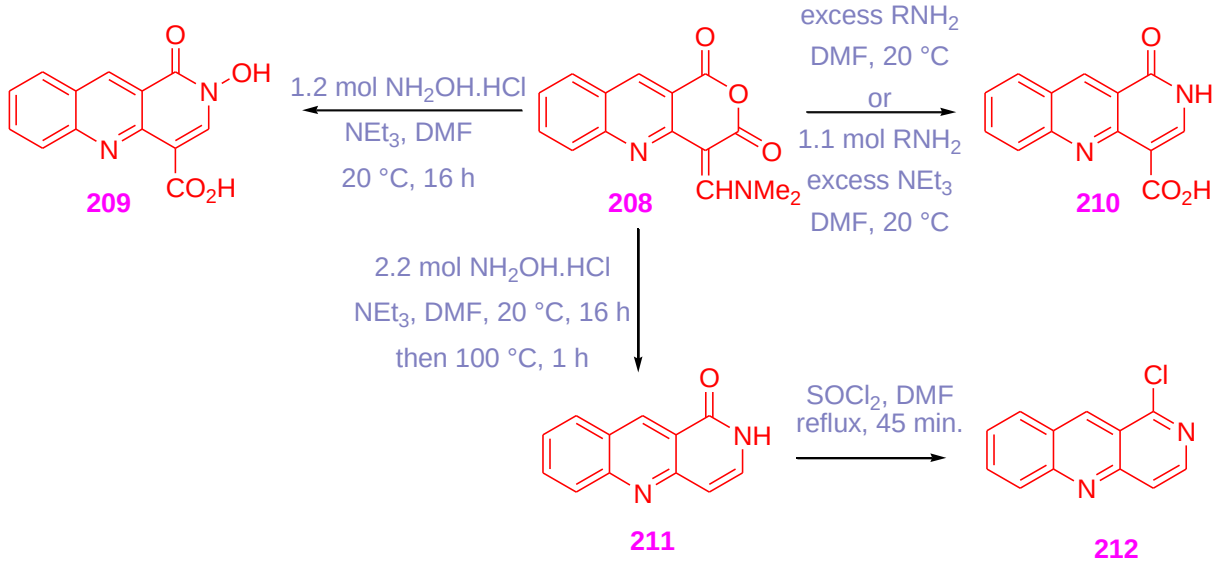
Syntheses of the benzonapthyridine derivatives reported in the literature are given below.

Synthesis of benzo[*b*][1,6]naphthyridin-1(2*H*)-ones

Rogers *et al.* reported the synthesis of benzo[*b*][1,6]naphthyridin-1(2*H*)-ones, from 4-((dimethylamino)methylene)-1*H*-pyrano[4,3-*b*]quinoline-1,3(4*H*)-dione (**208**) (**Eq. 56**).[96]

Their strategy involved treatment of dione **208** with different hydroxylamine equivalence showing different naphthyridine derivatives.

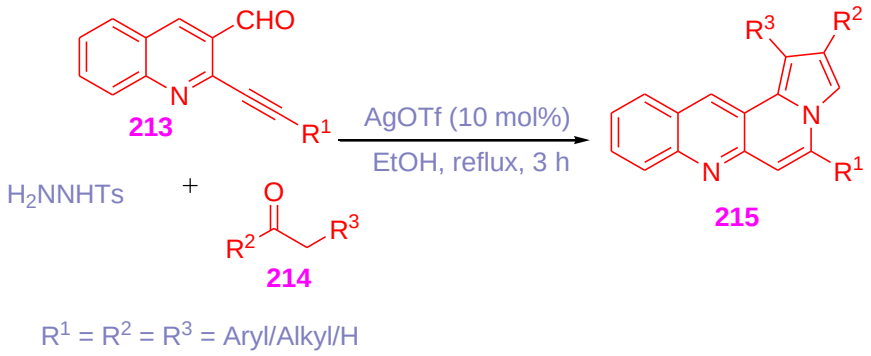
Eq. 56



Synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines

Langer *et al.* devised the synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines by the silver triflate catalyzed one-pot coupling of tosylhydrazine, carbonyl compounds **214** with 2-alkynyl-3-formylquinolines **213** (**Eq.57**).[97]

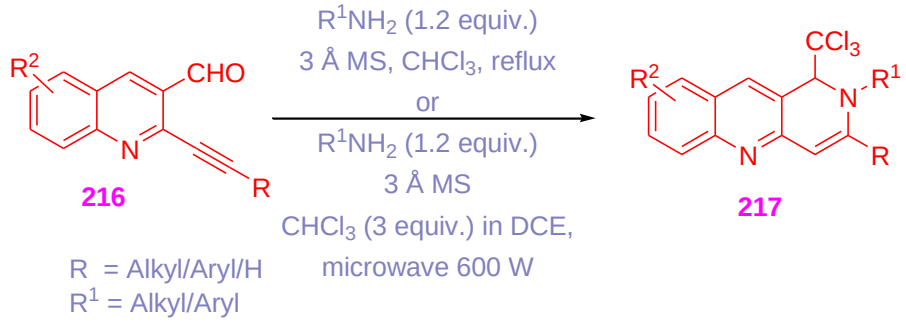
Eq. 57



Synthesis of 1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridines

Cikotiene *et al.* developed a three-component reaction of 2-alkynylquinoline-3-carbaldehydes, primary amines, and chloroform under microwave initiation condition to afford 1-(trichloromethyl)-1,2-dihydrobenzo[*b*][1,6]naphthyridines **217** (**Eq. 58**).[98] It is believed that the transformation involves the formation of imines followed by nucleophilic attack of the imine nitrogen at the triple bond and form zwitterion salt. Proton abstraction from chloroform and attack of corresponding anion would give the desired products.

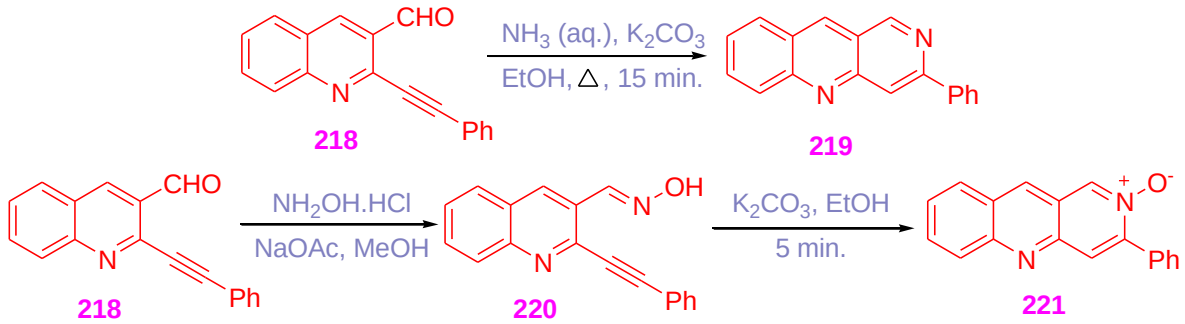
Eq. 58



Synthesis of 3-phenylbenzo[*b*][1,6]naphthyridines and 3-phenylbenzo[*b*][1,6] naphthyridines-2-oxide

M. Singh *et al.* demonstrated the synthesis of 3-phenylbenzo[*b*][1,6]naphthyridines **219** and 3-phenylbenzo[*b*][1,6]naphthyridines-2-oxide **221** from 2-(phenylethynyl)quinoline-3-carbaldehyde with aqueous ammonia and hydroxylamine hydrochloride (**Eq. 59**).[99] The reaction involves the imine or oxime formation and subsequent attack of the imine nitrogen at the activated triple bond leads to the heteroannulation and desired product was formed.

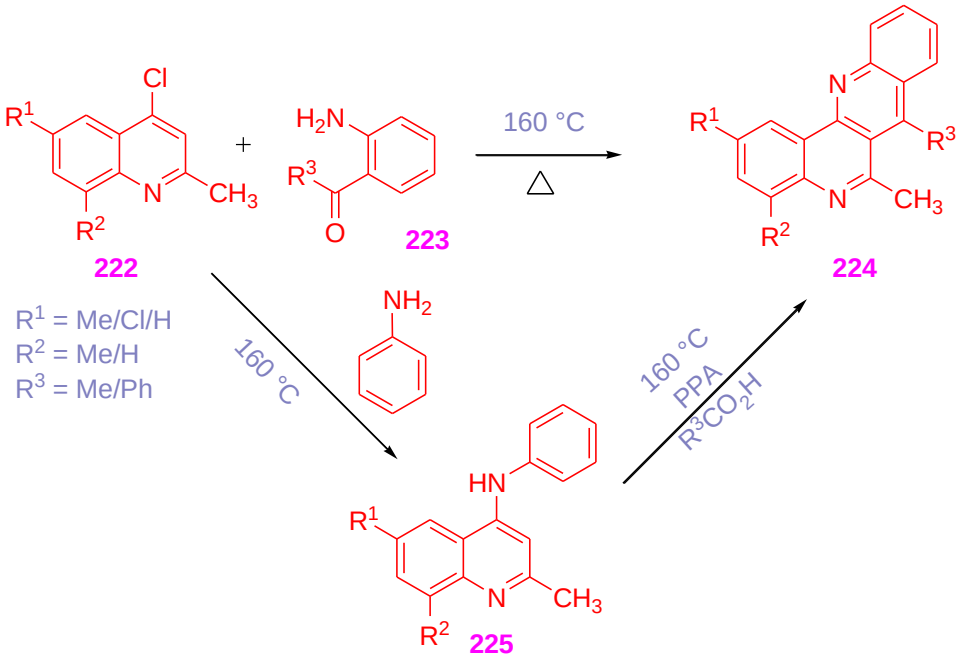
Eq. 59



Synthesis of Dibenzo[*b,h*][1,6]naphthyridines

Prasad *et. al.* reported the synthesis of dibenzo[*b,h*][1,6]naphthyridines **224** from the reaction of 4-chloro-2-methylquinolines **222** and alkyl/aryl substituted amino ketones **223**, it involves a nucleophilic substitution followed by cyclization (**Eq. 60**).[100] Due to the poor yield of the product, they moved to another strategy, which involved cyclization of anilinoquinolines with alkyl and aryl carboxylic acids using the acid mediated condition, which improved the yields.

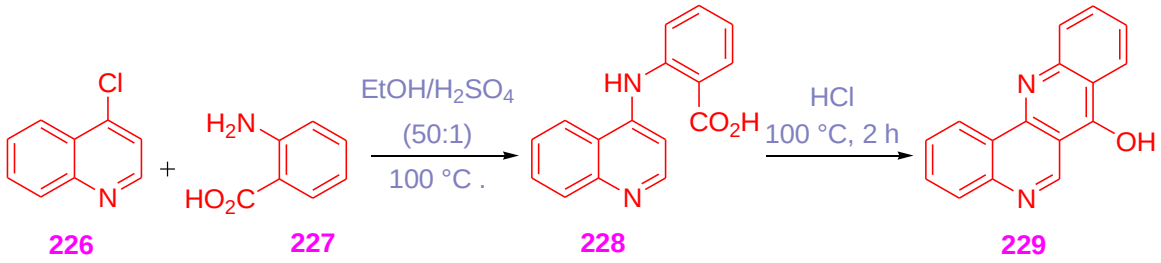
Eq. 60



Synthesis of Dibenzo[*b*,*h*][1,6]naphthyridin-7-ol

Ambartsumyan *et al.* developed the synthesis of dibenzo[*b*,*h*][1,6]naphthyridin-7-ol by concentrated sulfuric acid mediated cyclization of 4-(2-carboxyphenylamino)-2-methylquinoline (**Eq. 61**).[101] The reaction involved here is intramolecular cyclization at the free C-3 position of the quinoline ring to form the desired product **229**.

Eq. 61

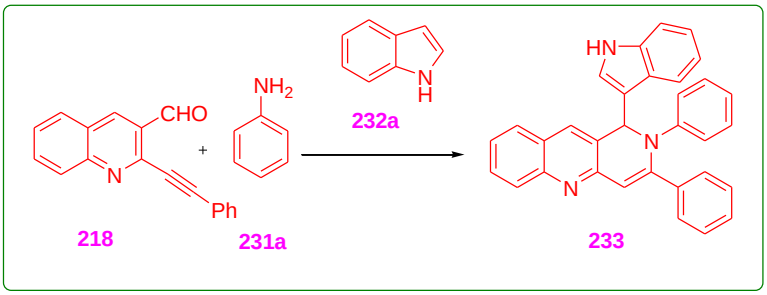


2.2. Synthesis of benzo[*b*][1,6]naphthyridines

In this chapter, we planned to synthesize the benzonaphthyridine derivatives using quinoline alkynylaldehydes, anilines and indole. For that we optimized the reaction condition. The results are summarized below. At the outset, we optimized reaction condition using various catalysts and solvents. The results are summarized in table 9. Initially, we started with CuI in THF solvent at room temperature (table 9, entry 1) and the expected product was obtained in 35% yield. Hence, we screened other catalysts and solvents as shown in table 9. CuBr gave a low yield of 40% in

THF (Table 9, entry 2). Other catalysts, such as $Cu(OTf)_2$, AgOTf and $AgNO_3$ gave moderate yield 55%, 52% and 50% in THF (table 9, entries 3-5). Without catalyst no reaction was observed (Table 5, entry 11). For all the above optimization, we used 5 mol% catalyst loading. Increasing the amount of catalyst also did not improve the yield of product. Hence, 5 mol% $Cu(OTf)_2$ was used for further solvent optimization.

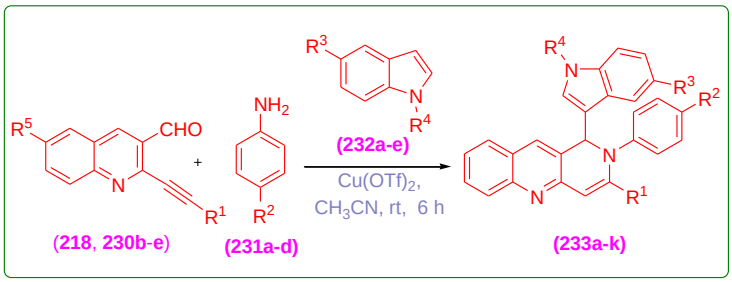
Table 9. Optimization of reaction conditions[a]



entry	catalyst	solvent	yield (%)[b]	time (h)
1	CuI	THF	35	6
2	CuBr	THF	40	8
3	$Cu(OTf)_2$	THF	55	6
4	Ag(OTf)	THF	52	7
5	$AgNO_3$	THF	50	8
6	$Cu(OTf)_2$	CH_3CN	62	6
7	$Cu(OTf)_2$	$CHCl_3$	58	6
8	$Cu(OTf)_2$	dioxane	56	6
9	$Cu(OTf)_2$	toluene	30	6
10	$Cu(OTf)_2$	DMF	35	6
11	-	CH_3CN	-	6

[a] Reaction conditions: 0.5 mmol of 218, 0.5 mmol of 231a, 0.7 mmol of indole (232) catalyst 5 mol % and 1 mmol of Na_2SO_4 as additive at room temperature. [b] Isolated yields.

Table 10. Synthesis of benzo[*b*][1,6]naphthyridines and substrate scope[a]



entry	R^1	R^2	R^3	R^4	R^5	product	yield (%)[b]
1	Ph	H	H	H	H	**233a**	62
2	Ph	Me	H	H	H	**233b**	60
3	Ph	Cl	H	H	H	**233c**	64
4	Ph	OMe	H	H	H	**233d**	68
5	Ph	Br	H	H	H	**233e**	70
6	Ph	H	H	Me	H	**233f**	72
7	Ph	H	OH	H	H	**233g**	74
8	Ph	H	OMe	H	H	**233h**	73
9	*p*-tolyl	H	H	H	H	**233i**	68
10	n-hexyl	H	H	H	H	**233j**	58
11[c]	TMS	H	H	H	H	-	-
12	Ph	H	H	H	OMe	**233k**	72

[a] Unless otherwise noted, all reactions were carried out in 5 mL of CH_3CN under optimized reaction conditions. 0.5 mmol of quinoline alkynylaldehydes 218, 230b-e, 0.5 mmol of anilines 231a-d and 0.7 mmol of indoles 232a-e were stirred at room temperature. 5 mol% of $Cu(OTf)_2$ was used, Additive: 1 mmol of Na_2SO_4

[b] Isolated yields after column chromatography.

[c] Complex mixture found in TLC.

We screened other solvents such as, toluene, dioxane, chloroform and DMF (table 9, entries 7-10). Here, the best result was obtained in acetonitrile as solvent (table 9, entry 6). Under optimized conditions, with in 6 h, complete conversion of starting material was observed in TLC. Having optimized reaction conditions in hand, we focused our attention on the exploration of the substrate scope. With other substrates, such as various anilines and indoles, the corresponding products were isolated successfully (table 10, entries 2-8). Similarly, other quinoline alkynylaldehyde substrates could be handled without any trouble and also gave the corresponding benzo[*b*][1,6]naphthyridines in good yields (table 10, entries 9, 10 and 12)

When we attempted the reaction with R^1 as trimethyl silyl group, an inseparable mixture of products were obtained. (table 10, entry 11). The structure of the product **233f** was unambiguously

confirmed by the single crystal X-ray diffraction analysis. The ORTEP diagram is shown in figure 10.

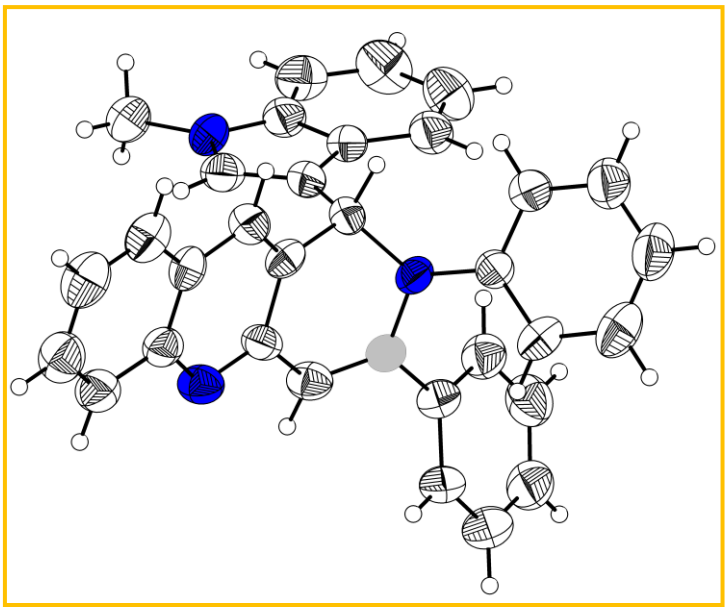


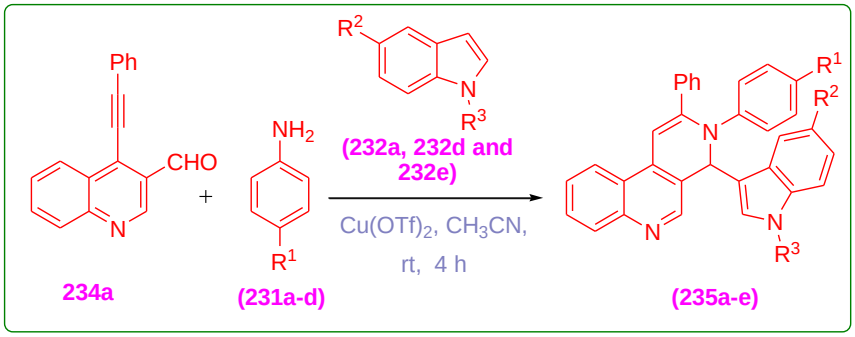
Fig. 10. ORTEP diagram of 233f.

2.3. Synthesis of benzo[*c*][2,7]naphthyridines

Considering the biological importance of 2,7-naphthyridine core (Fig. 9), we planned to synthesize 3,4-dihydro-4-(1*H*-indol-3-yl)-2,3-diphenylbenzo[*c*][2,7]naphthyridine (**235a**), by performing the reaction with 4-(2- phenylethynyl)quinoline-3-carbaldehyde (**234a**), aniline and indole derivatives under the same optimized condition, which we used in the table 9.

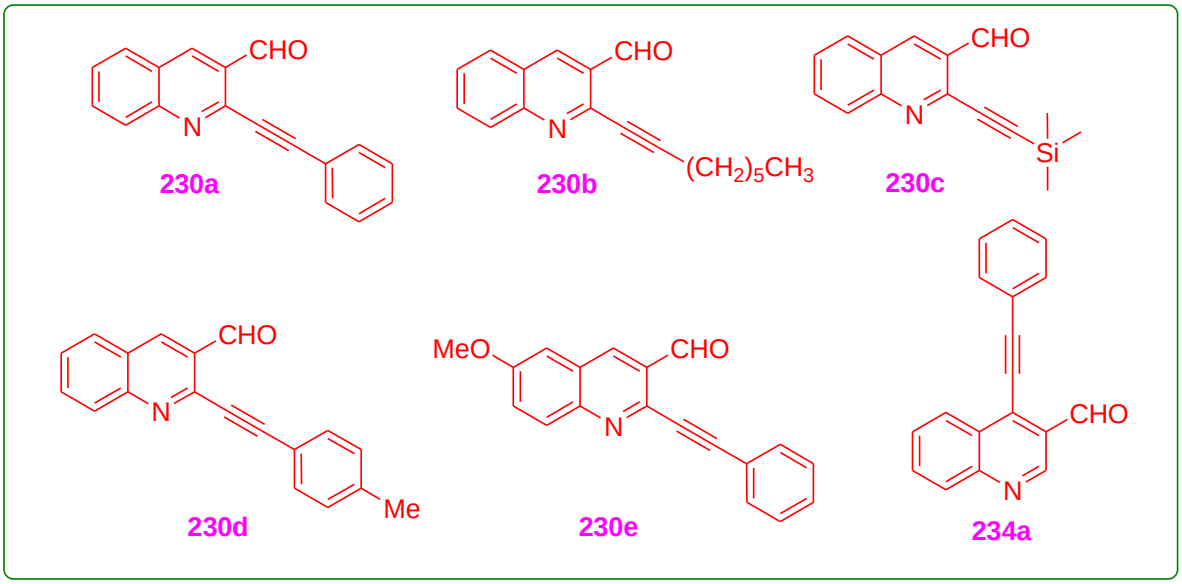
The requisite precursor **234a** was prepared from Sonogashira coupling of 4-chloroquinoline-3-carbaldehyde and phenylacetylene.[102] In this case, the expected product is formed in excellent yield (92%) with lesser reaction time (table 11, entry 1). Then, we examined the scope of this reaction by changing the substrates such as various substituted anilines and indoles. These substrates were well tolerated and excellent yields were obtained and substrate scope of this reaction was studied. The results are summarized in table 11.

Table 11. Synthesis of benzo[*c*][2,7]naphthyridines and substrate scope[a]



entry	R^1	R^2	R^3	product	yield (%)[b]
1	H	H	H	**235a**	92
2	Me	H	H	**235b**	90
3	Cl	H	H	**235c**	94
4	H	OMe	H	**235d**	90
5	H	H	*n*-butyl	**235e**	92

[a] Unless otherwise noted, all reactions were carried out in 5 mL of CH_3CN under optimized conditions. 0.5 mmol of quinoline alkynylaldehyde 234a, 0.5 mmol of anilines 231a-d and 0.7 mmol of indoles 232a, 232d and 232e were stirred at room temperature. 5 mol% of $Cu(OTf)_2$ was used. [b] Isolated yields



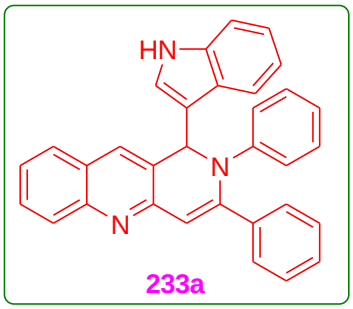
2.4. Experimental Section

2-(2-Arylethynyl)quinoline-3-carbaldehydes (**230a-230e**) and 4-(2-phenylethynyl) quinoline-3-carbaldehyde (**234a**) were prepared according to reported literature methods.[103]

General procedure for the synthesis of benzonaphthyridines:

An oven-dried 10 mL round-bottomed flask equipped with a teflon coated magnetic stirring bar is charged with 0.5 mmol of 2-(2-phenylethynyl)quinoline-3-carbaldehyde, 0.5 mmol of amine and 1 mmol of Na_2SO_4, 5 mL of acetonitrile. Then, 0.7 mmol of indole and copper(II) triflate (5 mol%) added to the reaction mixture. The reaction mixture is allowed to stir until complete conversion was observed by TLC. The reaction mass is poured into crushed ice slowly and extracted with ethyl acetate. The organic layer is washed with water, dried over anhydrous sodium sulfate and the solvent is removed under vacuum. The crude product is purified using column chromatography (eluent: 30% ethyl acetate in hexanes). The product is eluted in 30% eluent as a light yellow solid. We followed the same procedure for synthesis of other benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines (**233a-233k** and **235a-235e**).

1,2-Dihydro-1-(1*H*-indol-3-yl)-2,3-diphenylbenzo[*b*][1,6]naphthyridine (233a):



233a

Yield: 62%

R_f 0.52 (30% EtOAc/hexanes)

Mp: 156-158 °C

IR (KBr) ν_{max} cm^{-1}: 3052, 1600, 1577, 1434, 1403, 1386, 1263, 1094, 749

^{1}H NMR (400 MHz) δ: 8.24 (bs, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.71-7.69 (m, 1H), 7.64-7.58 (m, 3H), 7.41-7.36 (m, 2H), 7.26-7.21 (m, 5H), 7.19-7.11 (m, 5H), 6.95-6.93 (m, 2H), 6.63 (s, 1H)

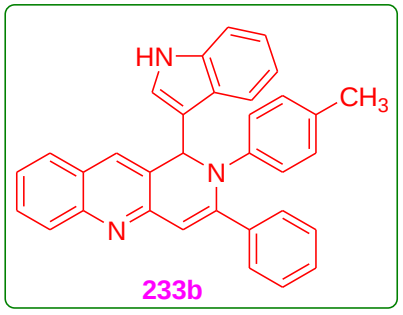
^{13}C NMR (100 MHz) δ: 151.9, 148.9, 147.9, 147.0, 137.3, 136.4, 131.9, 129.3, 128.8, 128.7, 128.5, 128.3, 128.2, 127.6, 127.5, 127.4, 125.1, 125.0, 122.9, 122.8, 122.3, 120.1, 118.9, 117.9, 112.0, 111.7, 102.6 (aromatic C), 62.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{32}H_{23}N_3$: 450.1970 (M+H)

Found: 450.1970

1,2-Dihydro-1-(1*H*-indol-3-yl)-3-phenyl-2-*p*-tolylbenzo[*b*][1,6]naphthyridine (233b):



233b

Yield: 60%

R_f 0.50 (30% EtOAc/hexanes)

Mp: 172-174 °C

IR (KBr) ν_{max} cm^{-1}: 3043, 2942, 2914, 1574, 1473, 1454, 1405, 1376, 1267, 1120, 705

^{1}H NMR (400 MHz) δ: 10.79 (bs, 1H), 8.11-8.08 (m, 1H), 8.02-8.01 (m, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 7.0 Hz, 1H), 7.53-7.52 (m, 2H), 7.37 (t, J = 7.0 Hz, 1H), 7.36-7.35 (m, 1H), 7.24-7.21 (m, 3H), 7.08-7.06 (m, 2H), 6.96-6.90 (m, 4H), 6.86 (s, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 2.15 (s, 3H)

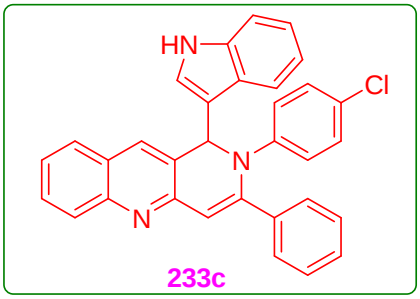
^{13}C NMR (100 MHz) δ: 151.9, 148.8, 147.9, 144.8, 137.5, 136.9, 132.2, 132.0, 129.6, 129.3, 128.9, 128.7, 128.3, 128.2, 127.9, 127.8, 127.5, 125.2, 123.4, 123.0, 121.6, 119.4, 119.2, 117.0, 112.1, 111.7 (aromatic C), 62.3, 20.7 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3$: 464.2124 (M+H)

Found: 464.2124

2-(4-Chlorophenyl)-1,2-dihydro-1-(1*H*-indol-3-yl)-3-phenylbenzo[*b*][1,6]naphthyridine (233c):



233c

Yield: 64%

R_f 0.42 (30% EtOAc/hexanes)

Mp: 162-164 °C

IR (KBr) ν_{max} cm^{-1}: 3400, 3060, 1610, 1587, 1443, 1395, 1388, 1204, 1094, 710

^{1}H NMR (400 MHz) δ: 8.11-8.05 (m, 3H), 7.94 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.65-7.63 (m, 2H), 7.57-7.55 (m, 2H), 7.41-7.37 (m, 2H), 7.26-7.24 (m, 4H), 7.09 (m, 2H), 7.04 (m, 2H), 6.96 (s, 2H), 6.56 (s, 1H)

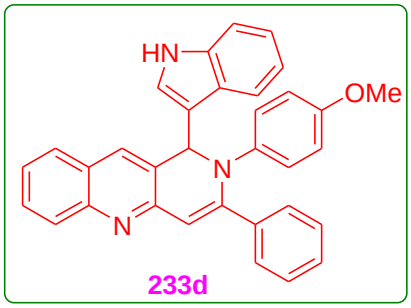
^{13}C NMR (100 MHz) δ: 145.6, 136.9, 136.8, 136.3, 132.0, 131.5, 129.4, 128.9, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.6, 127.43, 127.4, 125.3, 125.1, 124.0, 122.9, 122.4, 120.2, 118.8, 117.7, 111.7 (aromatic C), 62.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{32}H_{22}ClN_3$: 484.1580 (M+H)

Found: 484.1580

1,2-Dihydro-1-(1*H*-indol-3-yl)-2-(4-methoxyphenyl)-3-phenylbenzo[*b*][1,6] naphthyridine (233d):



233d

Yield: 68%

R_f 0.62 (30% EtOAc/hexanes)

Mp: 176-178 °C

IR (KBr) ν_{max} cm^{-1}: 3038, 2952, 2904, 1555, 1467, 1433, 1400, 1255, 1123, 690

^{1}H NMR (400 MHz) δ: 8.56 (s, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.86 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60-7.55 (m, 3H), 7.34-7.37 (m, 2H), 7.26-7.20 (m, 5H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.97 (s, 1H), 6.86 (s, 1H), 6.67 (d, *J* = 9.0 Hz, 2H), 6.48 (s, 1H), 3.69 (s, 3H)

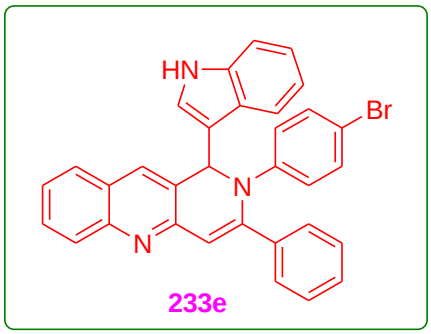
^{13}C NMR (100 MHz) δ: 155.8, 152.1, 149.9, 147.7, 140.6, 137.4, 136.4, 132.1, 129.3, 128.7, 128.4, 128.3, 127.9, 127.6, 127.5, 127.4, 125.2, 124.9, 124.8, 122.9, 122.2, 120.0, 118.9, 118.1, 114.1, 111.7, 110.1 (aromatic C), 62.6, 55.3 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3O$: 480.2076 (M+H)

Found: 480.2076

2-(4-Bromophenyl)-1,2-dihydro-1-(1*H*-indol-3-yl)-3-phenylbenzo[*b*][1,6]naphthyridine (233e):



Yield: 70%

R_f 0.66 (30% EtOAc/hexanes)

Mp: 168-170 °C

IR (KBr) ν_{max} cm^{-1}: 3078, 2976, 2971, 1535, 1460, 1433, 1401, 1275, 1121, 735

^{1}H NMR (400 MHz) δ: 8.21 (bs, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.67-7.64 (m, 1H), 7.56-7.55 (m, 2H), 7.43-7.36 (m, 3H), 7.27-7.24 (m, 7H), 6.99-6.92 (m, 3H), 6.57 (s, 1H)

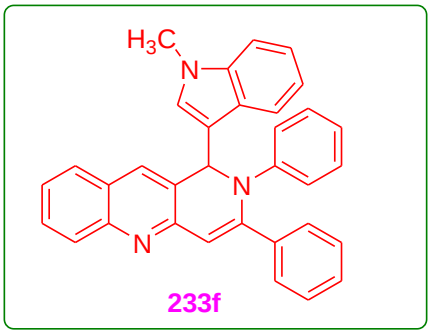
^{13}C NMR (100 MHz) δ: 151.7, 148.4, 146.0, 136.9, 136.4, 132.0, 131.8, 129.6, 129.0, 128.6, 128.4, 128.3, 128.1, 127.6, 127.4, 126.0, 125,3, 125.1, 124.4, 123.0, 122.5, 120.2, 118.8, 117.6, 115.6, 112.7, 111.7 (aromatic C), 62.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{32}H_{22}BrN_3$: 528.1075 (M+H)

Found: 528.1048, 530.1031 (M+2)

1,2-Dihydro-1-(1-methyl-1*H*-indol-3-yl)-2,3-diphenylbenzo[*b*][1,6]naphthyridine (233f):



233f

Yield: 72%

R_f 0.50 (30% EtOAc/hexanes)

Mp: 174-176 °C

IR (KBr) ν_{max} cm^{-1}: 3405, 3068, 2972, 2961, 1525, 1470, 1453, 1421, 1265, 1127, 745

^{1}H NMR (400 MHz) δ: 7.86 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.69 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.38-7.28 (m, 3H), 7.14 (m, 1H), 7.04-6.99 (m, 6H), 6.94-6.87 (m, 4H), 6.66 (s, 2H), 6.54 (s, 1H), 6.37 (s, 1H), 3.38 (s, 3H)

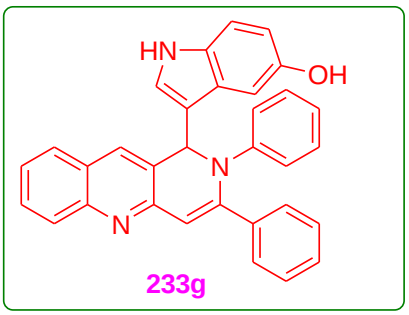
^{13}C NMR (100 MHz) δ: 151.7, 148.6, 147.8, 146.8, 137.1, 136.9, 131.6, 129.1, 128.7, 128.6, 128.3, 128.1, 127.9, 127.5, 127.3, 127.2, 125.3, 124.9, 122.7, 122.6, 121.7, 119.4, 118.9, 116.2, 111.9, 109.6 (aromatic C), 61.9, 32.6 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3$: 464.2126 (M+H)

Found: 464.2126

3-(1,2-Dihydro-2,3-diphenylbenzo[*b*][1,6]naphthyridin-1-yl)-1*H*-indol-5-ol (233g):



233g

Yield: 74%

R_f 0.56 (30% EtOAc/Hexanes)

Mp: 186-188 °C

IR (KBr) ν_{max} cm^{-1}: 3068, 2972, 2961, 1525, 1470, 1453, 1421, 1265, 1127, 745

^{1}H NMR (400 MHz) δ: 10.64 (bs, 1H), 8.83 (s, 1H), 8.18 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.68-7.65 (m, 1H), 7.58-7.57 (m,

2H), 7.46-7.43 (m, 2H), 7.27-7.25 (m, 3H), 7.19-7.09 (m, 5H), 6.91 (t, *J* = 7.0 Hz, 1H), 6.88 (s, 1H), 6.66 (s, 1H), 6.65-6.63 (m, 2H)

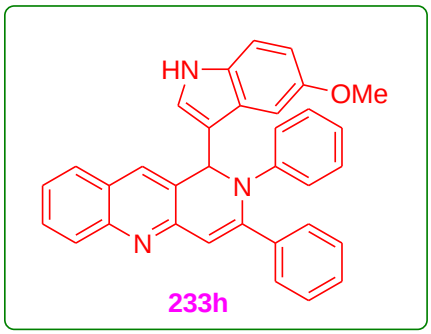
^{13}C NMR (100 MHz) δ: 152.1, 151.1, 148.4, 147.9, 147.2, 137.5, 132.2, 131.5, 129.6, 129.4, 129.3, 129.0, 128.5, 128.2, 128.1, 127.6, 126.2, 125.6, 124.3, 122.8, 116.1, 112.9, 112.6, 112.2, 103.6 (aromatic C), 61.9 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{32}H_{23}N_3O$: 466.1919 (M+H)

Found: 466.1919

1,2-Dihydro-1-(5-methoxy-1*H*-indol-3-yl)-2,3-diphenylbenzo[*b*][1,6]naphthyridine (233h):



Yield: 73%

R_f 0.56 (30% EtOAc/hexanes)

Mp: 172-174 °C

IR (KBr) ν_{max} cm^{-1}: 3400, 3058, 2956, 2901, 1565, 1470, 1435, 1402, 1265, 1103, 730

^{1}H NMR (400 MHz) δ: 8.29 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.91 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.58-7.57 (m, 2H), 7.23-7.21 (m, 2H), 7.15-7.10 (m, 4H),7.02-7.05 (m, 4H), 6.96-6.87 (m, 4H), 6.56 (s, 1H), 3.87 (s, 3H)

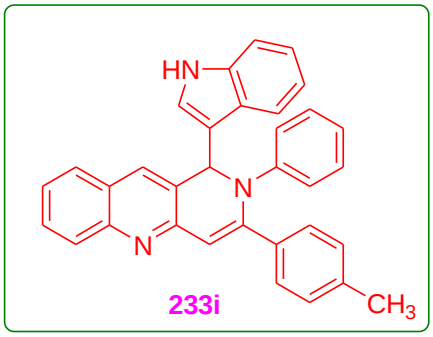
^{13}C NMR (100 MHz) δ: 154.3, 151.7, 149.6, 147.0, 137.2, 132.2, 131.6, 129.5, 129.3, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.5, 127.4, 125.5, 125.1, 123.6, 123.2, 123.1, 117.9, 112.4, 112.3, 101.3 (aromatic C), 62.3, 55.9 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3O$: 480.2076 (M+H)

Found: 480.2076

1,2-Dihydro-1-(1*H*-indol-3-yl)-2-phenyl-3-*p*-tolylbenzo-[*b*][1,6]naphthyridine (233i):



Yield: 68%

R_f 0.60 (30% EtOAc/hexanes)

Mp: 162-164 °C

IR (KBr) ν_{max} cm^{-1}: 3058, 2975, 2965, 1535, 1480, 1451, 1431, 1280, 725

^{1}H NMR (400 MHz) δ: 8.15 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.64 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.37 (m, 2H), 7.25 (m, 2H), 7.14 (m, 5H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (m, 1H), 6.93 (m, 2H), 6.62 (s, 1H), 2.29 (s, 3H)

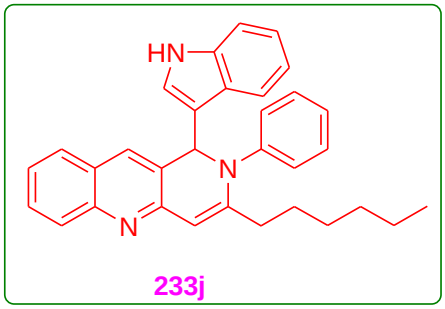
^{13}C NMR (100 MHz) δ: 152.0, 149.1, 147.2, 138.9, 136.3, 134.4, 131.9, 129.3, 129.2, 128.8, 128.1, 127.6, 127.5, 127.4, 125.1, 124.9, 123.0, 122.9, 122.8, 122.3, 120.7, 120.1, 118.9, 117.9, 117.8, 111.6, 111.0 (aromatic C), 62.1, 21.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3$: 464.2126 (M+H)

Found: 464.2126

3-Hexyl-1,2-dihydro-1-(1*H*-indol-3-yl)-2-phenylbenzo[*b*][1,6]naphthyridine (233j):



Yield: 58%

R_f 0.58 (30% EtOAc/hexanes)

Mp: 158-160 °C

IR (KBr) ν_{max} cm^{-1}: 3025, 2984, 2953, 2940,

1515, 1450, 1431, 1280, 730

^{1}H NMR (400 MHz) δ: 8.25 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.24-7.26 (m, 2H), 7.15-7.19 (m, 2H), 7.08-7.12 (m, 3H), 6.91 (s, 1H), 6.29 (s, 1H), 6.20 (s, 1H), 2.16-2.29 (m, 2H), 1.34-1.41 (m, 2H), 1.01-1.14 (m, 6H), 0.77 (t, J = 6.8 Hz, 3H)

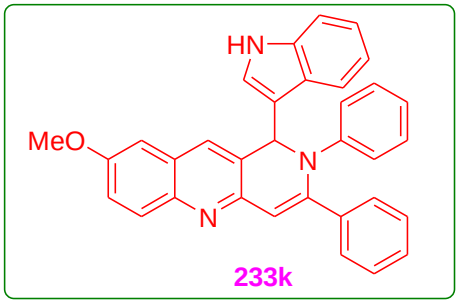
^{13}C NMR (100 MHz) δ: 145.5, 136.3, 131.7, 129.5, 129.4, 129.35, 129.2, 129.0, 128.8, 127.8, 127.3, 127.0, 126.7, 126.4, 125.3, 124.1, 123.1, 122.1, 119.9, 119.8, 118.7, 111.3, 104.3 (aromatic C), 62.4, 33.9, 31.3, 28.8, 27.9, 22.4, 14.0 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{32}H_{31}N_3$: 458.2596 (M+H)

Found: 458.2598

1,2-Dihydro-1-(1*H*-indol-3-yl)-8-methoxy-2,3-diphenylbenzo[*b*][1,6]naphthyridine (233k):



Yield: 72%

R_f 0.46 (30% EtOAc/hexanes)

Mp: 170-172 °C

IR (KBr) ν_{max} cm^{-1}: 3038, 2974, 2968, 2965, 1525, 1470, 1453, 1421, 1290, 716

^{1}H NMR (400 MHz) δ: 8.36 (bs, 1H), 8.15 (d, J = 6.0 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 7.56 (s, 2H), 7.35-7.12 (m, 10H), 6.98-6.92 (m, 5H), 6.60 (s, 1H), 3.88 (s, 3H)

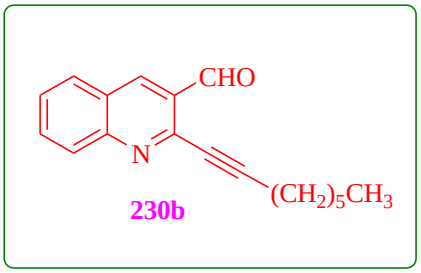
^{13}C NMR (100 MHz) δ: 156.9, 149.9, 147.7, 147.1, 143.9, 137.4, 136.4, 130.8, 129.7, 128.8, 128.6, 128.4, 128.3, 128.1, 125.2, 123.1, 122.8, 122.6, 122.3, 121.8, 120.0, 118.9, 117.9, 112.3, 111.7, 105.6 (aromatic C), 62.0, 55.5 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3O$: 480.2076 (M+H)

Found: 480.2076

2-(Oct-1-ynyl)quinoline-3-carbaldehyde (230b):



230b

Yield: 88%

R_f 0.60 (5% EtOAc/hexanes)

Mp: 110-112 °C

IR (KBr) ν_{max} cm^{-1}: 3450, 3325, 3062, 2208, 1710, 1652, 1400, 1350, 732

^1H NMR (400 MHz) δ: 10.69 (s, 1H), 8.69 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.83 (dt, J = 1.5 and 8.5 Hz, 1H), 7.59 (t, J = 7.0 Hz, 1H), 2.59 (t, J = 7.0 Hz, 2H), 1.72 (quintet, J = 8.0 Hz, 2H), 1.48-1.51 (m, 2H), 1.32-1.36 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H)

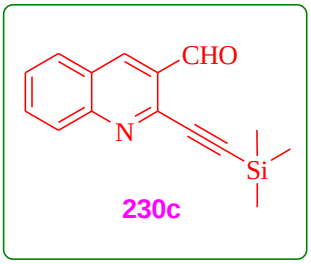
^{13}C NMR (100 MHz) δ: 191.3, 150.1, 144.5, 136.8, 132.8, 129.5, 129.2, 128.8, 127.8, 126.3, 98.2, 77.5 (Aromatic C), 31.3, 28.8, 28.2, 22.5, 19.7, 14.1 (Aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{18}H_{19}NO$: 266.1545 (M+H)

Found: 266.1544

2-(2-(Trimethylsilyl)ethynyl)quinoline-3-carbaldehyde (230c):



230c

Yield: 85%

R_f 0.60 (5% EtOAc/hexanes)

Mp: 102-104 °C

IR (KBr) ν_{max} cm^{-1}: 3460, 3250, 3012, 2190, 1730, 1642, 1420, 1370, 772

^{1}H NMR (400 MHz) δ: 10.72 (s, 1H), 8.74 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.95-7.97 (m, 1H), 7.85-7.89 (m, 1H), 7.63-7.66 (m, 1H), 0.36 (s, 9H)

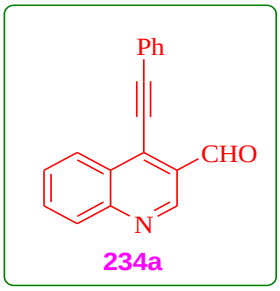
^{13}C NMR (100 MHz) δ: 190.9, 150.1, 143.6, 136.7, 132.9, 129.6, 129.4, 128.8, 128.3, 126.5, 100.4, 100.1 (Aromatic C), 0.4 (Aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{15}H_{15}NOSi$: 254.1001 (M+H)

Found: 254.1003

4-(2-Phenylethynyl)quinoline-3-carbaldehyde (234a):



234a

Yield: 90%

R_f 0.59 (5% EtOAc/hexanes)

Mp: 104-106 °C

IR (KBr) ν_{max} cm^{-1}: 3446, 3051, 2202, 1704, 1682, 1435, 1386, 1309, 761

^{1}H NMR (400 MHz) δ: 10.83 (s, 1H), 9.37 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 7.2 Hz, 1H), 7.76-7.46 (m, 3H), 7.51-7.46 (m, 3H)

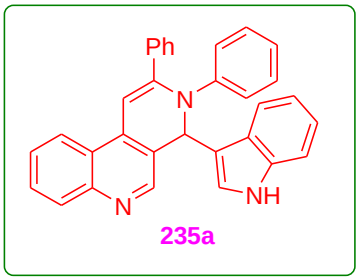
^{13}C NMR (100 MHz) δ: 190.9, 150.0, 148.0, 134.8, 132.7, 132.2, 130.4, 130.2, 128.8, 128.2, 127.1, 127.0, 126.8, 121.3, 106.8, 81.1

HRMS (ESI-MS):

Anal. calcd. for $C_{18}H_{11}NO$: 258.0919 (M+H)

Found: 258.0919

3,4-Dihydro-4-(1*H*-indol-3-yl)-2,3-diphenylbenzo[*c*][2,7]naphthyridine (235a):



235a

Yield: 92%

R_f 0.64 (20% EtOAc/hexanes)

Mp: 164-166 °C

IR (KBr) ν_{max} cm^{-1}: 3050, 1794, 1538, 1464, 1435, 1423, 1385, 1245, 1005, 729

^1H NMR (400 MHz) δ: 8.78 (s, 1H), 8.52 (bs, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.14-8.12 (m, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.62-7.58 (m, 3H), 7.35-7.33 (m, 1H), 7.26-7.25 (m, 3H), 7.23-7.20 (m, 2H), 7.15-7.14 (m, 5H), 6.96-6.94 (m, 2H), 6.65 (s, 1H)

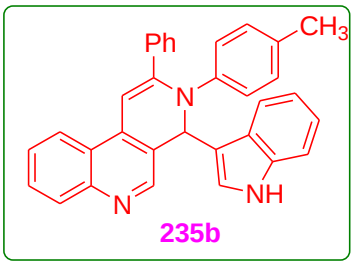
^{13}C NMR (100 MHz) δ: 148.4, 147.6, 147.0, 146.7, 137.6, 136.6, 135.1, 129.6, 129.3, 128.8, 128.5, 128.5, 128.2, 126.2, 125.0, 123.2, 123.15, 123.1, 123.0, 122.2, 121.7, 120.0, 119.3, 118.2, 111.7, 104.6 (aromatic C), 60.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{23}N_3$: 450.1970 (M+H)

Found: 450.1971

3,4-Dihydro-4-(1*H*-indol-3-yl)-2-phenyl-3-*p*-tolylbenzo[*c*][2,7]naphthyridine (235b):



235b

Yield: 90%

R_f 0.58 (20% EtOAc/hexanes)

Mp: 188-190 °C

IR (KBr) ν_{max} cm^{-1}: 3065, 1594, 1574, 1541, 1425, 1388, 1268, 1100, 725

^1H NMR (400 MHz) δ: 8.75 (s, 1H), 8.57 (bs, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.13-8.12 (m, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.0 Hz, 1H), 7.62-7.58 (m, 3H), 7.35-7.33 (m, 1H), 7.28-7.27 (m, 3H), 7.23-7.20

(m, 2H), 7.11 (s, 1H), 7.06 (s, 1H), 7.04 (s, 1H), 6.97-6.95 (m, 3H), 6.60 (s, 1H), 2.24 (s, 3H)

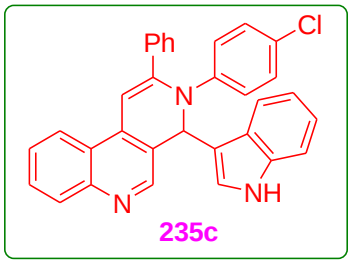
^{13}C NMR (100 MHz) δ: 148.2, 147.5, 147.3, 144.3, 137.7, 136.6, 135.4, 133.1, 129.4, 128.8, 128.7, 128.65, 128.6, 128.5, 126.2, 125.0, 123.5, 123.1, 123.08, 123.05, 122.2, 121.2, 120.0, 119.3, 118.5, 111.6, 103.8 (aromatic C), 60.3, 20.7 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3$: 464.2126 (M+H)

Found: 464.2124

3-(4-Chlorophenyl)-3,4-dihydro-4-(1*H*-indol-3-yl)-2-phenylbenzo[*c*][2,7]naphthyridine (235c):



235c

Yield: 94%

R_f 0.620 (20% EtOAc/hexanes)

Mp: 180-182 °C

IR (KBr) ν_{max} cm^{-1}: 3062, 1594, 1567, 1484, 1441, 1413, 1386, 1265, 1095, 739

^{1}H NMR (400 MHz) δ: 8.78 (s, 1H), 8.42 (bs, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.10-8.07 (m, 2H), 7.72-7.68 (m, 1H), 7.64-7.56 (m, 3H), 7.37-7.35 (m, 1H), 7.31-7.29 (m, 3H), 7.25-7.22 (m, 2H), 7.18 (s, 1H), 7.13-7.11 (m, 2H), 7.08-7.05 (m, 2H), 6.96 (d, J = 2.4 Hz, 1H), 6.59 (s, 1H)

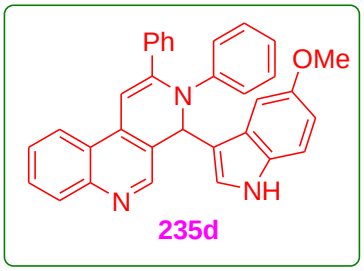
^{13}C NMR (100 MHz) δ: 148.3, 147.6, 146.5, 145.2, 137.1, 136.5, 134.9, 129.7, 129.0, 128.9, 128.7, 128.4, 126.4, 124.9, 124.2, 123.1, 123.1, 123.0, 122.4, 121.7, 120.2, 119.1, 118.0, 111.7, 105.1 (aromatic C), 60.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{32}H_{22}ClN_3$: 484.1580 (M+H)

Found: 484.1580

3,4-Dihydro-4-(5-methoxy-1*H*-indol-3-yl)-2,3-diphenylbenzo[*c*][2,7]naphthyridine (235d):



Yield: 90%

R_f 0.56 (20% EtOAc/hexanes)

Mp: 168-170 °C

IR (KBr) ν_{max} cm^{-1}: 3060, 1554, 1463, 1434, 1400, 1386, 1266, 1110, 715

^{1}H NMR (400 MHz) δ: 8.76 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.15 (bs, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.68-7.66 (m, 1H), 7.59 (m, 2H), 7.50 (s, 1H), 7.22-7.20 (m, 3H), 7.13-7.11 (m, 6H), 7.00 (s, 1H), 6.95 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 3.81 (s, 3H)

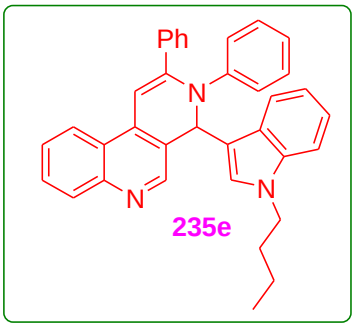
^{13}C NMR (100 MHz) δ: 154.3, 148.1, 147.3, 147.2, 146.7, 137.7, 137.5, 135.3, 131.9, 131.6, 129.4, 128.9, 128.8, 128.5, 127.4, 126.3, 125.3, 123.5, 123.4, 123.0, 121.4, 118.5, 112.6, 112.2, 104.2, 101.3 (aromatic C), 60.2, 55.8 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{33}H_{25}N_3O$: 480.2076 (M+H)

Found: 480.2077

4-(1-Butyl-1*H*-indol-3-yl)-3,4-dihydro-2,3-diphenylbenzo[*c*][2,7]naphthyridine (235e):



Yield: 92%

R_f 0.65 (20% EtOAc/hexanes)

Mp: 186-188 °C

IR (KBr) ν_{max} cm^{-1}: 3038, 2942, 2871, 1585, 1535, 1460, 1455, 1422, 1255, 1124, 708

^{1}H NMR (400 MHz) δ: 8.80 (s, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.17-8.12 (m, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.66-7.62 (m, 3H), 7.36-7.25 (m, 6H), 7.18-

7.17 (m, 5H), 6.97-6.94 (m, 2H), 6.69 (s, 1H), 3.98 (t, J = 6.8 Hz, 2H), 1.73 (m, 2H), 1.26 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 148.5, 147.6, 147.1, 146.7, 139.3, 137.8, 136.5, 135.0, 129.7, 128.8, 128.7, 128.5, 128.4, 126.7, 126.2, 125.6, 123.3, 123.2, 123.15, 123.1, 121.9, 121.7, 119.6, 119.5, 116.9, 114.1, 109.9, 104.5 (aromatic C), 60.0, 46.1, 29.8, 20.1, 13.6 (aliphatic C)

HRMS (ESI-MS):

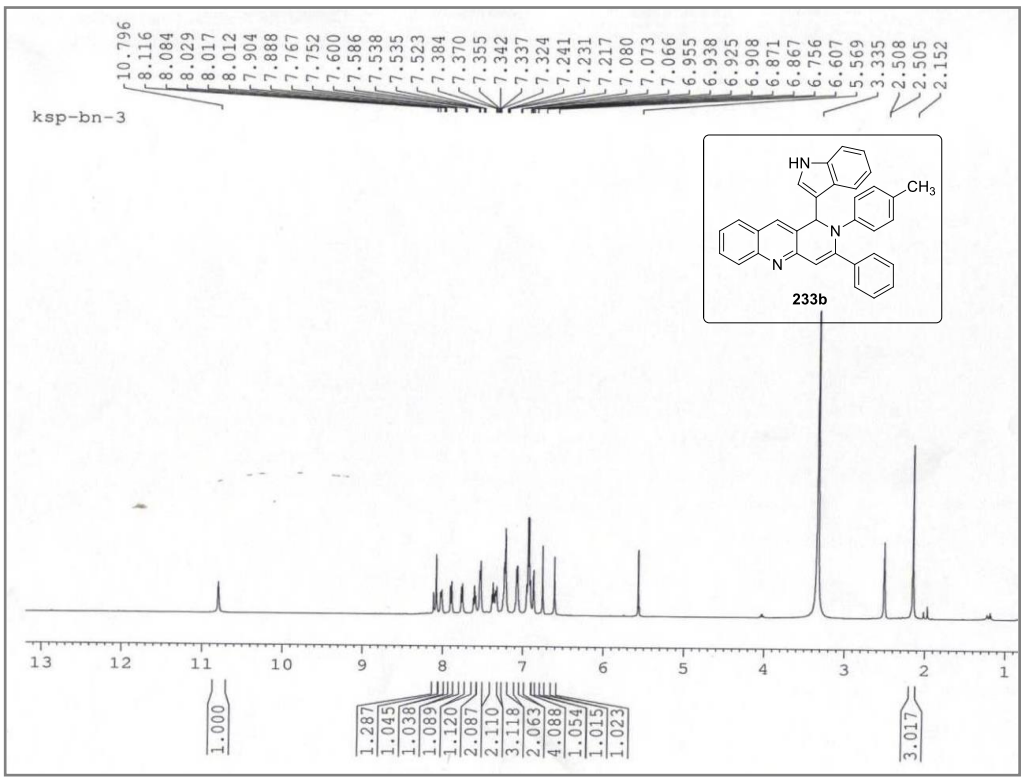
Anal. calcd. for $C_{36}H_{31}N_3$; 506.2596 (M+H)

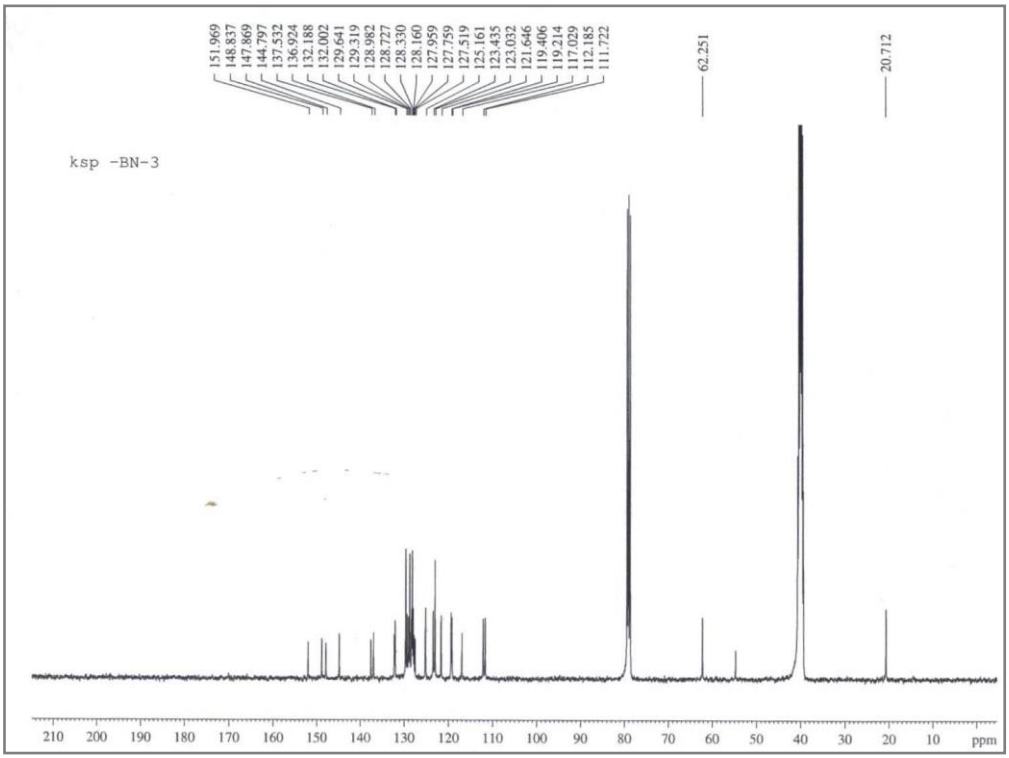
Found: 506.2596

Table 12. Crystal data and structure refinement for 233f.

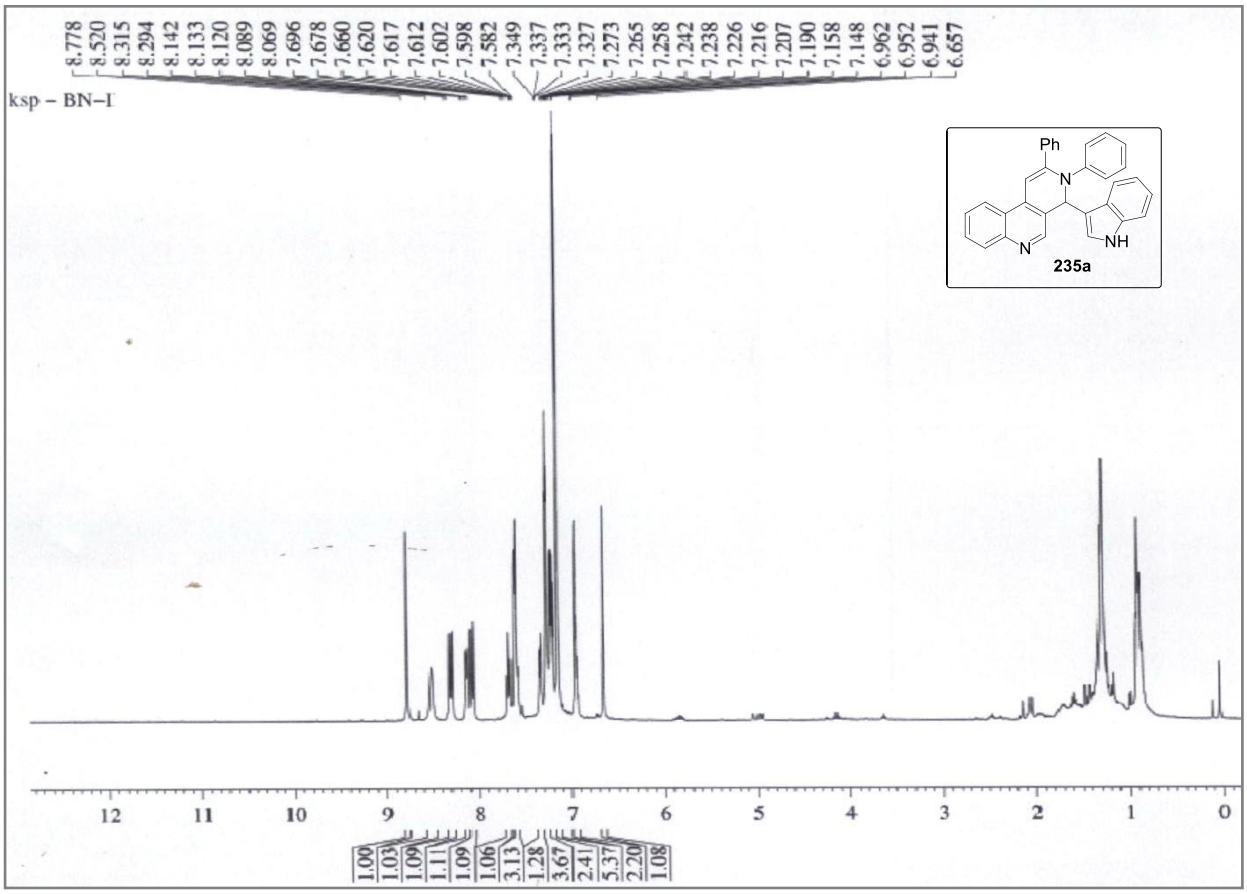
Identification code	**233f**	
Empirical formula	$C_{33}H_{25}N_3$	
Formula weight	463.56	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 15.190(4) Å	α = 90.00 °.
	b = 10.3275(17) Å	β = 108.46(3) °.
	c = 16.424(4) Å	γ = 90.00°.
Volume	2443.9(10) $Å^3$	
Z	4	
Density (calculated)	1.358 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	976	
Crystal size	0.20 x 0.12 x 0.16 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	42932	
Independent reflections	7917 [R(int) = 0.0747]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	2.7078 and 28.9572	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7917 / 0 / 598	
Goodness-of-fit on F^2	1.137	
Final R indices [I>2sigma(I)]	R1 = 0.070, wR2 = 0.2600	
R indices (all data)	R1 = 0.0908, wR2 = 0.1571	
Extinction coefficient	0.00068 (10)	
Largest diff. peak and hole	0.247 and -0.152 $e.Å^{-3}$	
CCDC number	**908173**	

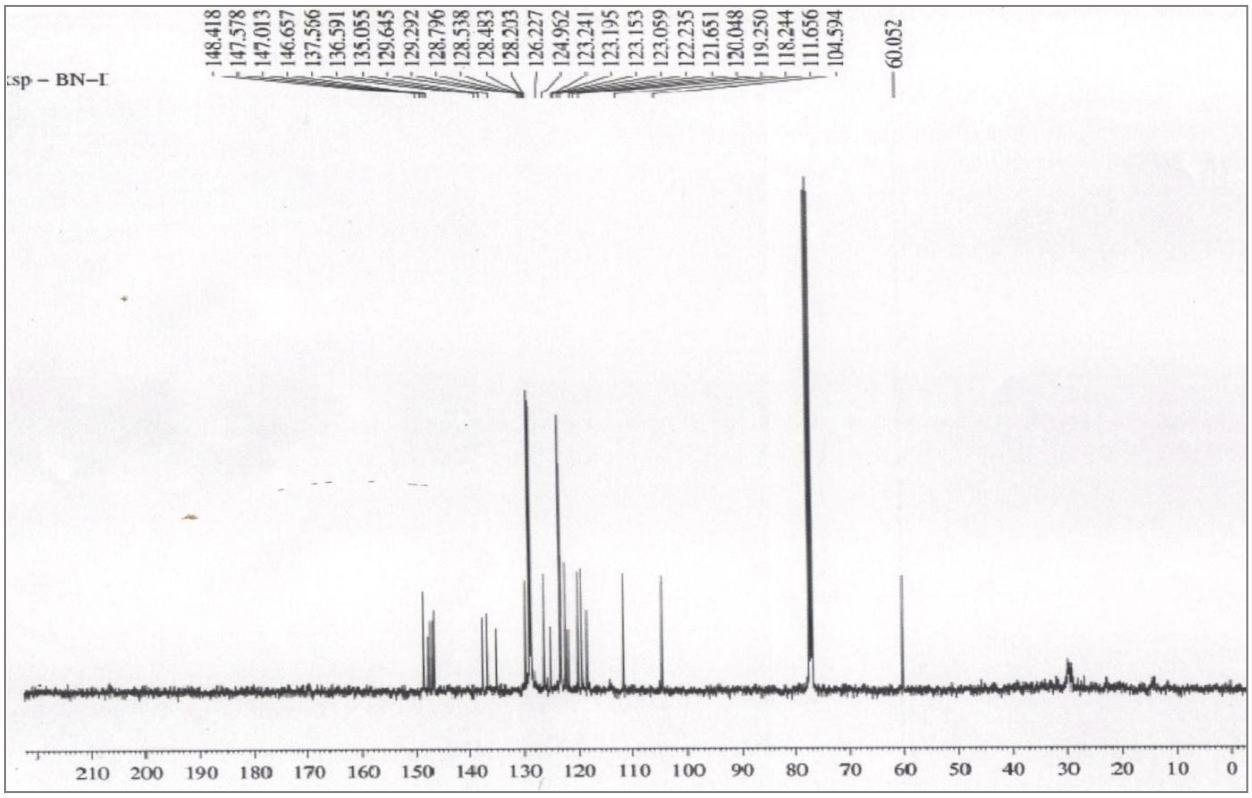
Spectra No. 8: ^{1}H and ^{13}C Spectra of Compound 233b





Spectra No. 9: ^{1}H and ^{13}C Spectra of Compound 235a





2.5. Conclusions

In summary, we have developed an efficient methodology for the synthesis of new indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines in moderate to excellent yields *via* copper(II) triflate-catalyzed heteroannulation.

On the other hand, all of the synthesized compounds have yet another vital nucleus, indole, which is known to be part of many biologically important molecules.

This approach is general and an efficient method for construction of diverse indol-3-yl benzonaphthyridine skeletons under mild reaction conditions. Moreover, generality and biological significance of naphthyridine motif make it highly valuable.

2.6. References

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CHAPTER 3

Synthesis of azepino[4,5-*b*]indole analogues and Chromoazepinone core *via* 7-*endo* dig cyclization

3.1. Introduction

Indole nucleus is one of the main core of various natural products those possess wide range of biological profiles.[104] The azepino[4,5-*b*]indole ring system containing a seven membered C ring, has recently been found in several biological active molecules[105] and have been identified as potent agonists of the farnesoid X receptor (FXR)[106] and possesses activity against some central nerves system diseases.[105a-c] Representing azepino[4,5-*b*]indole core containing alkaloids is shown in figure 1. Various reported synthetic methodologies in the literature, this is a new method for the synthesis of azepino[4,5-*b*]indoles using 7-*endo* dig annulation of alkynyl-1,2-aldehyde and isocycnoacetate.

The similar approach was recently disclosed by Wu and co-workers,[107] in which they synthesized isoquinolines *via* an unexpected silver triflate catalyzed 6-*exo* cyclization of 2-alkynylbenzaldehyde with 2-isocyanoacetate. Intrigued by their result, we anticipated the formation of corresponding carboline by the similar kind of reaction with indole-1,2-alkynylaldehydes and 2-isocyanoacetates. But unfortunately, we observed the formation of 7-membered product rather than carbolines *via* selective 7-*endo* cyclization. This novel result prompted us to investigate this 7-*endo* selective annulation further. During last few decades, similar alkynylaldehyde heteroannulation was reported in the literature as a powerful tool for making new biologically active molecules.[108]

Representative structures of azepino[4,5-*b*]indole core containing alkaloids **236-240** are shown in figure 11. Considering the biological activity of these molecules and very few reports are known for the synthesis of indolodiazepene containing molecules, we herein report the synthesis of azepino[4,5-*b*]indoles *via* 7-*endo* selective cyclization and Chromoazepinone core.[109]

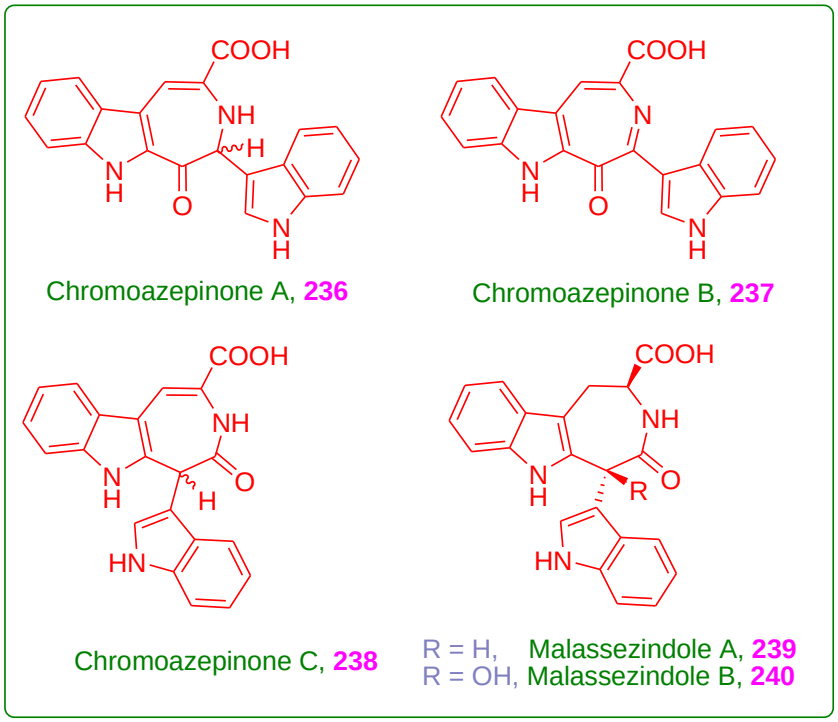
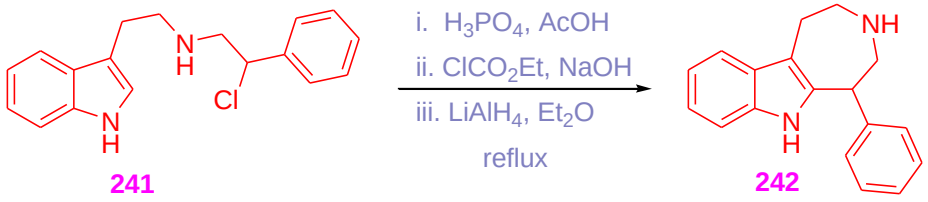


Fig. 11. Representative structures of azepino[4,5-*b*]indole core containing alkaloids

Synthesis of azepinoindole analogues

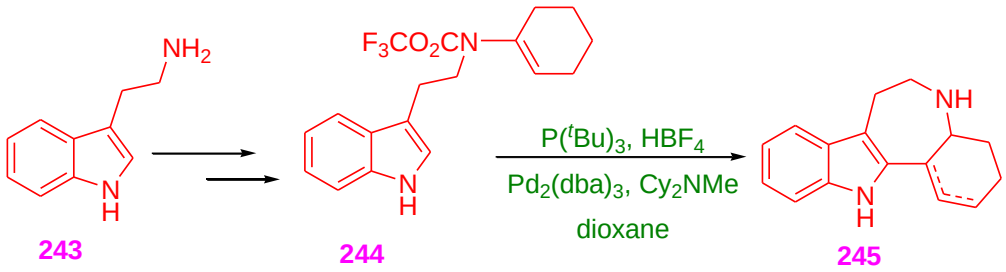
Elliott *et al.* reported the synthesis of 5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole **242** from *N*-[2-(5-methoxy-3-indolyl)ethyl]-2-chloro-2-phenylacetamide by acid catalyzed cyclization, by treatment with ethylchloroformate followed by LAH reduction (**Eq. 62**).[110]

Eq. 62



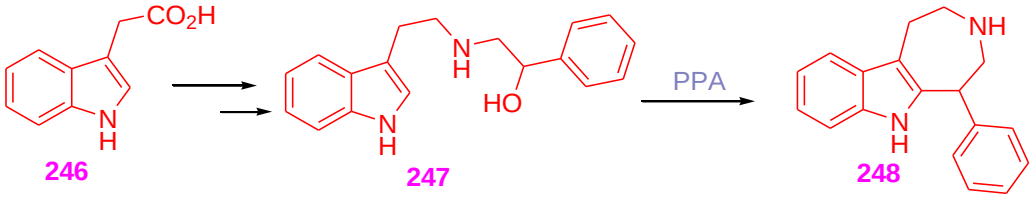
Stewart *et al.* reported the formation and reactivity of several azepino[4,5-*b*]indole heterocycles **245**. The key reaction for the formation of the azepino[4,5-*b*]indole seven membered ring containing an exocyclic double bond is intramolecular Heck reaction (**Eq. 63**).[111]

Eq. 63



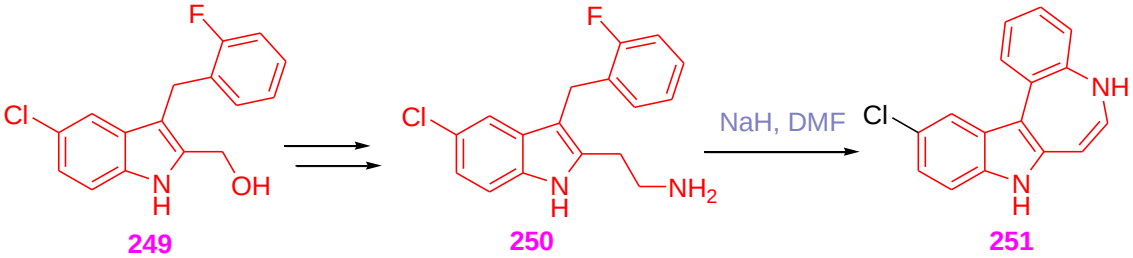
Decker *et al.* reported a method for the synthesis of 3-substituted 5-phenyl-1,2,3,4,5,6-hexahydro-azepino-[4,5-*b*]indoles **248** from *N*-(2-hydroxy-2-phenylethyl)-2-(1*H*-indol-3-yl)acetamide by acid catalyzed annulation (**Eq. 64**).[112]

Eq. 64



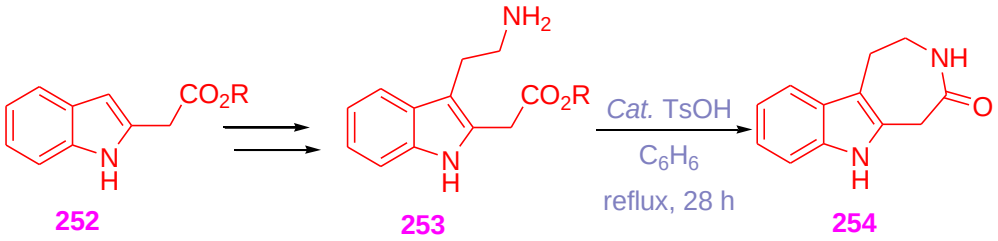
Walster *et al.* developed a simple strategy for the synthesis of indolo[2,3-*d*]azipine **251** using 2(2-aminoethyl)-5-chloro-3-(2-fluorophenyl)-methylindole hydrochloride by an intramolecular nucleophilic substitution (**Eq. 65**).[113]

Eq. 65



Bernauer *et al.* developed a method for the synthesis indoloazepinone **254** the acid catalyzed intramolecular lactonization of methyl 3-(2-aminoethyl)-l*H*-indole-2-acetate (**Eq. 66**).[114]

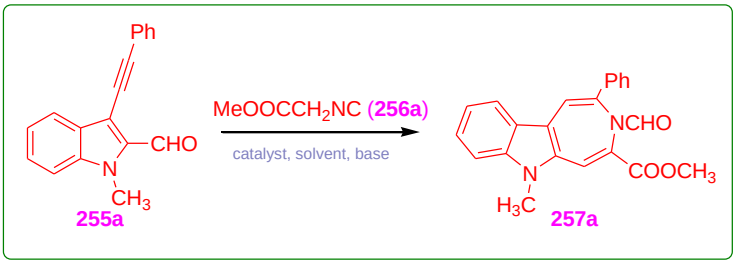
Eq. 66



3.2. Synthesis of azepino[4,5-*b*]indole analogues

We began our investigation by the reaction of 1-methyl-3-(2-phenylethynyl)-1*H*-indole-2-carbaldehyde (**255a**) and methyl isocyanoacetate (**256a**) in the presence of silver triflate as a catalyst. The new product is observed (TLC), we expected the formation of carboline by 6-*exo* mode cyclization, unfortunately, exclusive formation of 7-*endo* cyclized product is identified.

Table 13. Optimization of the reaction conditions



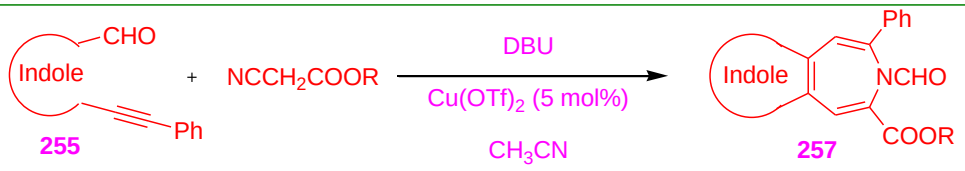
entry	solvent	catalyst	base	time (h) /yield(%)
1	CH_3CN	AgOTf	DBU	5/55
2	CH_3CN	$Cu(OTf)_2$	DBU	5/63
3	CH_3CN	CuI	DBU	5/52
4	CH_3CN	$PdCl_2$	DBU	5/40
5	CH_3CN	$Pd(OAc)_2$	DBU	5/42
6	CH_3CN	$Sc(OTf)_3$	DBU	5/32
7	CH_3CN	$Cu(OTf)_2$	NaOH	5/trace
8	CH_3CN	$Cu(OTf)_2$	KOtBu	5/trace
9	CH_3CN	$Cu(OTf)_2$	TEA	7/30
10	MeOH	$Cu(OTf)_2$	DBU	5/NR
11	toluene	$Cu(OTf)_2$	DBU	8/NR
12	DMSO	$Cu(OTf)_2$	DBU	8/35
13	DMF	$Cu(OTf)_2$	DBU	8/NR
14	THF	$Cu(OTf)_2$	DBU	8/20
15	Dioxane	$Cu(OTf)_2$	DBU	8/45
16	CH_3CN	-	DBU	8/30

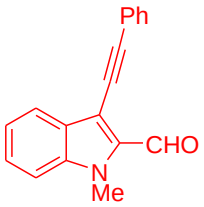
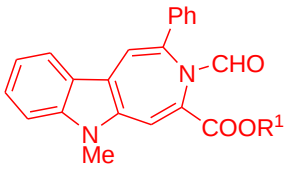
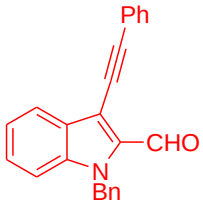
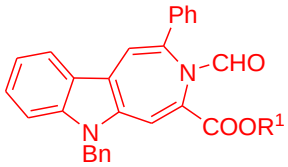
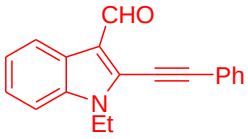
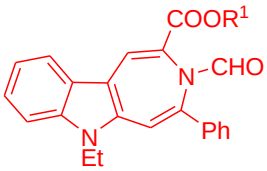
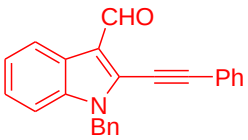
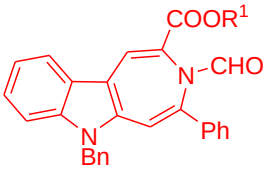
With this novel result in hand, our first attempt to find optimal condition by changing various solvents and catalysts (table 13). Then we concluded that the formation of 7-*endo* product is formed exclusively and 6-*exo* product is not at all formed in various conditions. Optimization table for this reaction is shown in table 13. We first optimized the reaction by changing the catalysts AgOTf, $Cu(OTf)_2$ and CuI. Among them, $Cu(OTf)_2$ gave the product in 63% of yield (table 13, entry 2). Other catalysts $Pd(OAc)_2$, $PdCl_2$ and $Sc(OTf)_3$ did not improve the yield of the product (table 13, entries 4-6). Other bases like NaOH, KO^{t}Bu gave the products only in trace amounts. While using triethylamine as a base, only 30% yield of the product was observed. So, we optimized the base and catalyst for this reaction. Then we changed solvent for knowing optimal solvent. But yield of the products are not improved while using other solvents (table 13, entries 10-15). Without catalyst, only 30% yield of the product was obtained (table 13, entry 16).

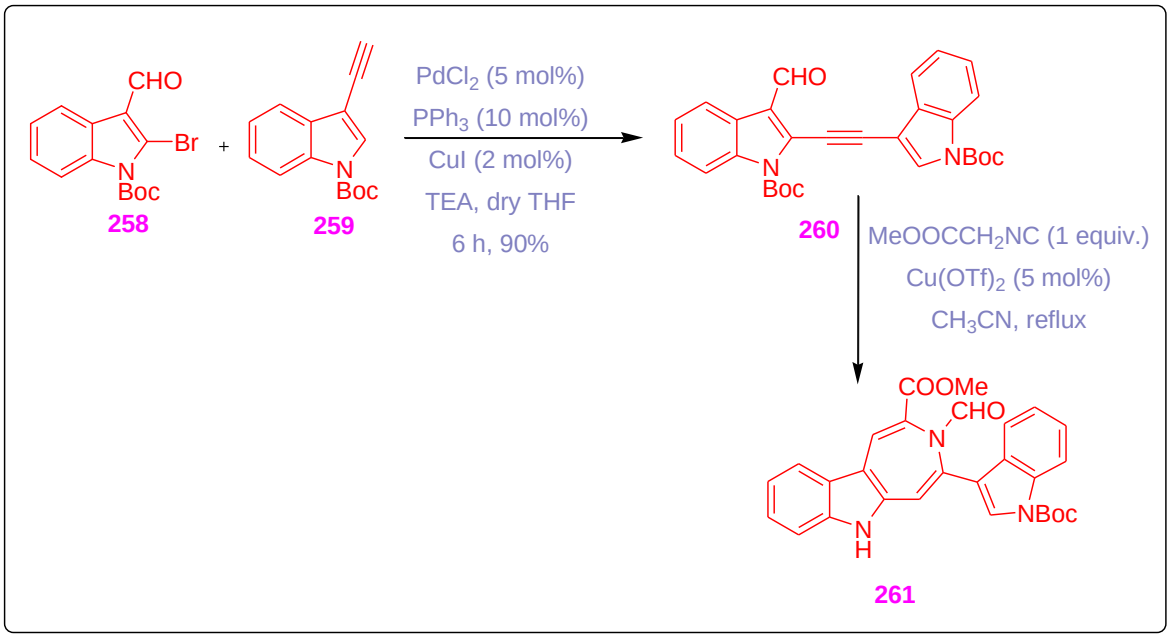
With this optimized condition in hand, we investigated the substrate scope of the reaction by varying substrates and shown in table 14. As expected all the substrates were gave in good the product yields (table 14, entries 1-8). One of the product **257d** was confirmed unambiguously by single crystal X-ray analysis. The crystal structure of **257d** is shown in figure 12.

After optimizing the 7-membered ring formation, we planned to construct the Chromoazepinone core. Scheme 1 shows the synthesis of Chromoazepinone core *via* corresponding alkynylaldehyde isocyanide heteroannulation. The requisite starting material **260** was prepared from indole bromoaldehyde[115] and indole acetylene[116] by Sonogashira cross coupling reaction. This reaction proceeded very smoothly and gave the coupled product in 90% yield. Then we performed the isocyanide heteroannulation with the substrate, it gave the product **261** with good yield. It should be noted that, removal of Boc group is observed in the reaction. This product has been confirmed by single crystal X-ray analysis.

Table 14. Synthesis of azepino[4,5-*b*]indole analogues and substrate scope



Entry	Alkynylaldehyde	Isocyanoacetate	Product	Yield (%)/ Time (h)
1	 (255a)	$NCCH_2COOMe$ (256a)	 R^1 = Me, **257a**	72/6
2	255a	$NCCH_2COOEt$ (256b)	R^1 = Et, **257b**	70/6
3	 (255b)	256a	 R^1 = Me, **257c**	70/6
4	255b	256b	R^1 = Et, **257d**	68/6
5	 (255c)	256a	 R^1 = Me, **257e**	65/5
6	255c	256b	R^1 = Et, **257f**	67/5
7	 (255d)	256a	 R^1 = Me, **257g**	67/5
8	255d	256b	R^1 = Et, **257h**	66/5



Scheme 7. An approach towards the synthesis of Chromoazepinone core

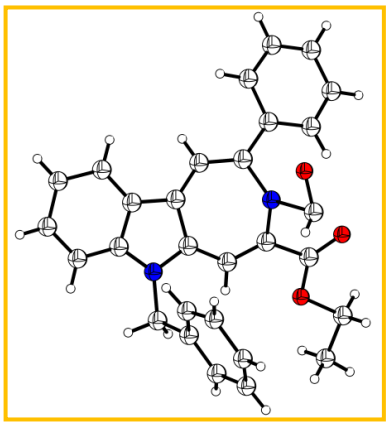


Fig 12. X-ray crystal structure of 257d.

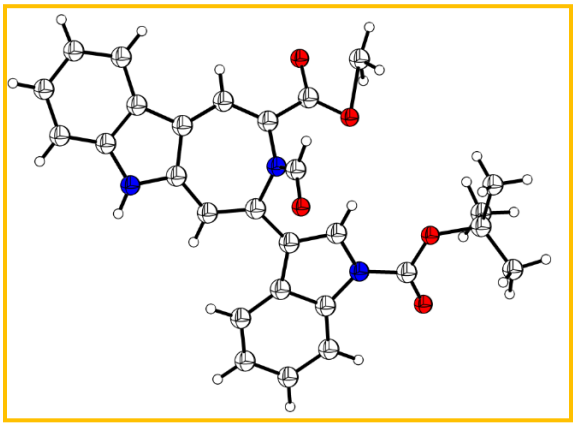
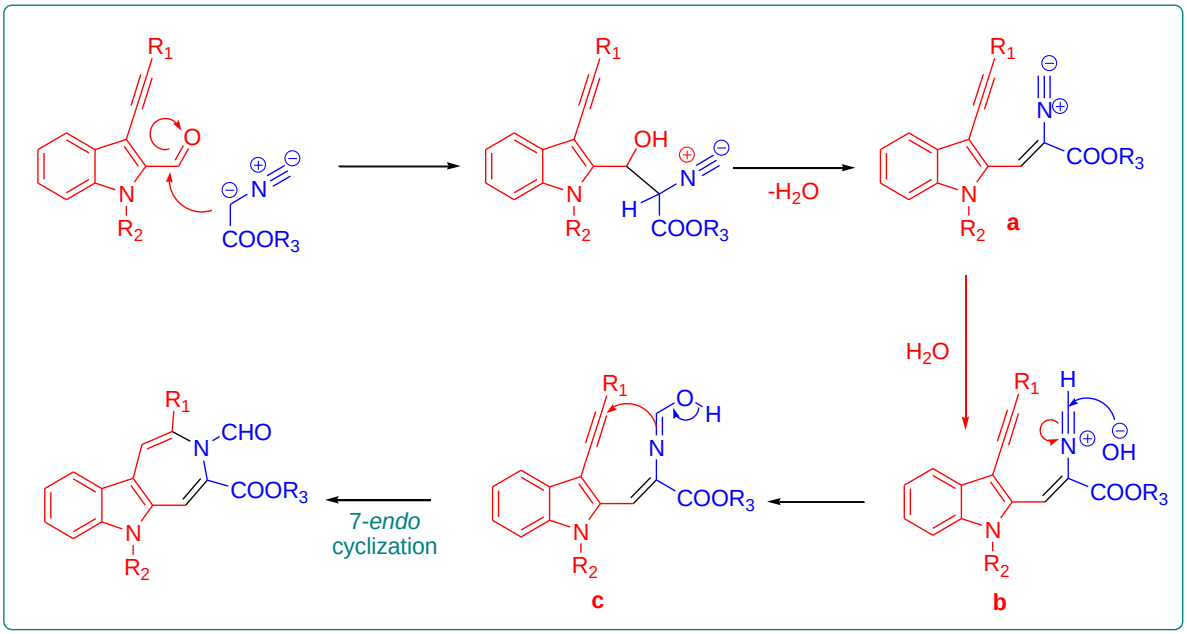


Fig. 13. X-ray crystal structure of 261.

The crystal structure of **261** is shown in figure 13. So, we successfully synthesized the Chromoazepinone core by utilizing the developed methodology.

On the basis of literature reports,[107, 117] we proposed the possible mechanism for the formation of products and shown in Scheme 8. The first step involves Knoevenagel type condensation, isocyanoacetate would be involved to afford the intermediate **a**, followed by the addition of water would lead to afford **b.** The subsequent 7-*endo* dig cyclization in the presence of copper(II) triflate would generate the products.



Scheme 8. Proposed mechanism

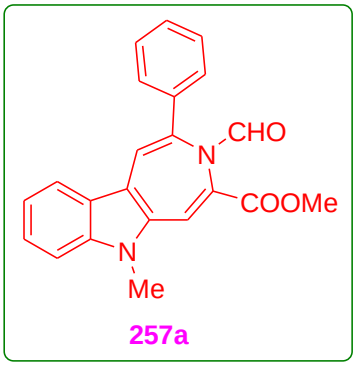
3.3. Experimental Section

General procedure for synthesis of azepino[4,5-*b*]indole derivatives (257a-h and 261):

An oven dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 0.19 mmol of 1-methyl-3-(phenylethynyl)-1*H*-indole-2-carbaldehyde (**255a**) (0.05 g) in acetonitrile (2 mL), were added methylisocyanoacetate (**256a**) (0.021 g, 0.21 mmol), $Cu(OTf)_2$ (7 mg, 5 mol%) and DBU (0.43 g, 0.29 mmol). The mixture was stirred at 90 °C for 6 h. After completion of reaction (TLC), was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude reaction mixture was then poured over water and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4. The residue was purified by column chromatography on silica gel to afford the product **257a** in 72% (0.05 g) yield. (20% ethyl acetate in hexanes). We followed the same experimental procedure for the synthesis of other azepinoindole derivatives (**257b-h** and **261**).

Note: In ^{13}C NMR spectra of the products extra peaks came due to rotamer

Methyl 3-formyl-6-methyl-2-phenyl-3,6-dihydroazepino[4,5-*b*]indole-4-carboxylate (257a)



257a

Yield: 72%

R_f 0.32 (hexanes/EtOAc = 1:1)

Mp: 160-162 °C

IR (KBr) ν_{max} cm^{-1}: 3151, 2936, 2874, 1692, 1648, 1578, 1457

^1H NMR (400 MHz) δ: 8.13-8.10 (m, 2H), 8.08 (s, 1H), 8.05-7.98 (m, 1H), 7.86 (s, 1H), 7.84-7.82 (m, 2H), 7.68 (s, 1H), 7.48-7.30 (m, 4H), 3.95 (s, 3H), 3.87 (s, 3H)

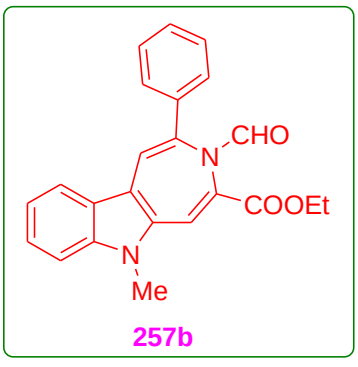
^{13}C NMR (100 MHz) δ: 163.9, 162.8, 138.4, 137.0, 134.2, 132.3, 129.0, 128.7, 128.4, 126.5, 126.0, 125.5, 123.0, 121.0, 119.5, 118.3, 117.3, 116.8, 109.9 (aromatic) 52.6, 30.4 (aliphatic)

HRMS (ESI-MS):

Anal. calcd. for $C_{22}H_{18}O_3N_2$: 359.1396 (M+H)

Found: 359.1395

Ethyl 3-formyl-6-methyl-2-phenyl-3,6-dihydroazepino[4,5-*b*]indole-4-carboxylate (257b)



257b

Yield: 70%

R_f 0.30 (hexanes/EtOAc = 1:1)

Mp: 164-166 °C

IR (KBr) ν_{max} cm^{-1}: 3173, 2936, 2473, 1682, 1573, 1429, 1387

^1H NMR (400 MHz) δ: 8.12 (d, J = 9.5 Hz, 2H), 8.08, (s, 1H), 8.03, (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.73 (s, 1H), 7.50-7.41 (m, 5H), 4.43 (q, J = 9.0 Hz, 2H), 3.91 (s, 3H), 1.46 (t, J = 9.5 Hz, 3H)

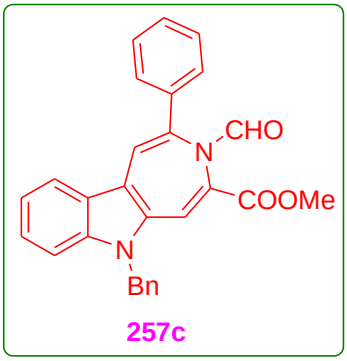
^{13}C NMR (100 MHz) δ: 164.0, 163.8, 162.6, 138.7, 138.4, 137.1, 134.7, 134.4, 133.6, 132.2, 129.0, 128.6, 128.4, 128.2, 127.6, 126.3, 126.2, 126.1, 126.0, 125.9, 125.5, 123.6, 121.1, 120.3, 119.6, 118.3, 117.4, 116.9, 109.9, 109.8, 77.36, 62.2, 61.9, 30.5, 14.3

HRMS (ESI-MS):

Anal. calcd. for $C_{23}H_{20}O_3N_2$: 395.1372 (M+Na)

Found: 395.1366

Methyl 6-benzyl-3-formyl-2-phenyl-3,6-dihydroazepino[4,5-*b*]indole-4-carboxylate (257c)



257c

Yield: 70%

R_f 0.34 (hexanes/EtOAc = 1:1)

Mp: 156-158 °C

IR (KBr) ν_{max} cm^{-1}: 3127, 2978, 2481, 1649, 1498, 1337

^{1}H NMR (400 MHz) δ: 8.11 (d, *J* = 5.5 Hz, 2H), 8.04 (s, 1H), 7.99 (s, 1H), 7.92-7.88 (m, 1H), 7.74 (s, 1H), 7.49-7.44 (m, 2H), 7.39-7.35 (m, 2H), 7.34-7.28 (m, 5H), 7.09 (d, *J* = 7Hz, 2H), 5.56-5.47 (m, 2H), 3.90 (s, 3H)

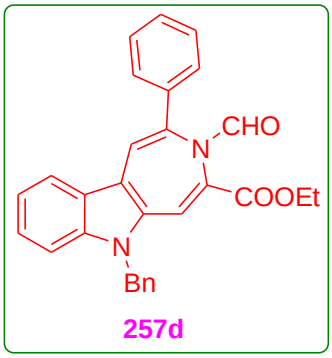
^{13}C NMR (100 MHz) δ: 163.9, 163.7, 162.8, 198.2, 137.0, 136.2, 134.3, 130.0, 129.2, 129.1, 129.09, 129.0, 128.7, 128.5, 128.3, 128.0, 127.9, 127.7, 127.5, 126.5, 126.48, 126.4, 126.3, 126.2, 126.14, 126.1, 126.0, 12508, 123.8, 121.3, 121.0, 119.7, 118.8, 117.3, 110.5, 110.2, 104.4, (aromatic C) 52.6, 47.6 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{28}H_{22}O_3N_2$: 457.1528 (M+Na)

Found: 457.1523

Ethyl 6-benzyl-3-formyl-2-phenyl-3,6-dihydroazepino[4,5-*b*]indole-4-carboxylate (257d)



257d

Yield: 68%

R_f 0.42 (hexanes/EtOAc = 1:1)

Mp: 160-162 °C

IR (KBr) ν_{max} cm^{-1}: 3159, 2950, 2476, 1662, 1609, 1387

^1H NMR (400 MHz) δ: 8.12 (J = 8.0 Hz, 2H), 8.09 (s, 1H), 8.05 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.93-7.92 (m, 1H), 7.74 (s, 1H), 7.49-7.44 (m, 2H), 7.38-7.34 (m, 2H), 7.33-7.29 (m, 4H), 7.10 (d, J = 7.0 Hz, 2H), 5.57-5.49 (m, 2H), 4.40-4.35 (m, 2H), 1.41-1.38 (m, 3H)

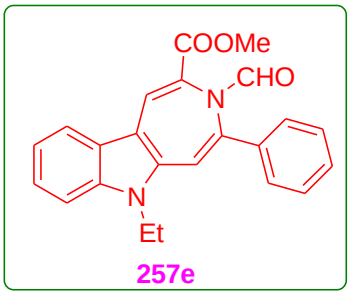
^{13}C NMR (100 MHz) δ: 163.8, 163.7, 163.2, 162.4, 138.1, 136.9, 136.2, 136.1, 134.3, 133.4, 132.6, 129.02, 129.0, 128.9, 128.6, 128.4, 128.2, 127.9, 127.8, 127.5, 126.2, 126.17, 126.15, 126.1, 126.03, 126.0, 125.6, 123.9, 121.2, 120.3, 119.6, 118.6, 117.3, 116.7, 110.4, 110.1 (aromatic C) 62.02, 61.7, 47.6, 47.5, 14.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{29}H_{24}O_3N_2$: 471.1685 (M+Na)

Found: 471.1679

Methyl 6-ethyl-3-formyl-4-phenyl-3,6-dihydroazepino[4,5-*b*]indole-2-carboxylate (257e)



257e

Yield: 65%

R_f 0.33 (hexanes/EtOAc = 1:1)

Mp: 158-160 °C

IR (KBr) ν_{max} cm^{-1}: 3146, 2947, 2462, 1671, 1619, 1421

^1H NMR (400 MHz) δ: 8.46 (s, 1H), 8.37 (s, 1H), 8.16 (d, J = 10.5 Hz, 1H), 8.06-8.00 (m, 2H), 7.89-7.80 (m, 1H), 7.54-7.39 (m, 6H), 4.44-4.35 (m, 2H), 3.86 (s, 3H), 1.53-1.48 (m, 3H)

^{13}C NMR (100 MHz) δ: 164.5, 164.4, 163.4, 163.2, 139.5, 137.6, 136.8, 136.7, 134.4, 133.1, 131.6, 129.6, 123.3, 129.2, 128.9, 126.9, 126.7, 126.6, 126.4, 124.7, 124.6, 121.7, 121.5, 119.5, 119.1, 117.4, 113.9, 113.3, 112.6, 112.2, 109.9, 109.7 (aromatic C) 52.5, 52.3, 39.0, 38.7, 15.1, 14.9 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{23}H_{20}O_3N_2$: 395.1372 (M+Na)

Found: 395.1366

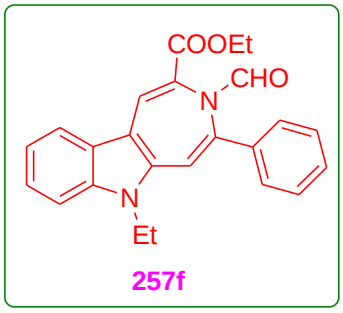
Ethyl 6-ethyl-3-formyl-4-phenyl-3,6-dihydroazepino[4,5-*b*]indole-2-carboxylate (257f)

Yield: 67%

R_f 0.31 (hexanes/EtOAc = 1:1)

Mp: 170-172 °C

IR (KBr) ν_{max} cm^{-1}: 3189, 2932, 2439, 1687, 1628, 1492, 1376



257f

^{1}H NMR (400 MHz) δ: 8.47 (s, 1H), 8.16 (d, J = 7.2 Hz, 1H), 8.03-8.00 (m, 2H), 7.87-7.83 (m, 1H), 7.52-7.38 (m, 6H), 7.32 (s, 1H), 4.46-4.36 (m, 4H), 1.52-1.42 (m, 6H)

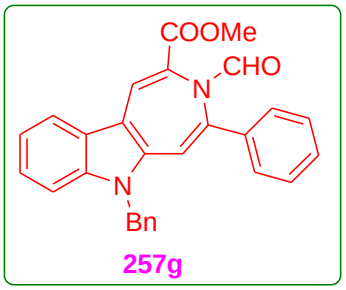
^{13}C NMR (100 MHz) δ: 164.6, 164.0, 163.2, 163.0, 139.5, 138.0, 137.6, 137.4, 136.8, 136.76, 136.7, 134.4, 132.9, 131.3, 129.6, 129.3, 129.2, 128.8, 126.9, 126.8, 126.6, 126.4, 124.7, 124.0, 121.6, 121.5, 119.6, 119.2, 119.0, 117.7, 114.0, 113.4, 112.7, 112.2, 109.9, 109.6 (aromatic C) 39.0, 38.7, 15..1, 14.9, 14.4, 1.0 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{24}H_{22}O_3N_2$: 409.1528 (M+Na)

Found: 409.1523

Methyl 6-benzyl-3-formyl-4-phenyl-3,6-dihydroazepino[4,5-*b*]indole-2-carboxylate (257g)



257g

Yield: 67%

R_f 0.38 (hexanes/EtOAc = 1:1)

Mp: 164-166 °C

IR (KBr) ν_{max} cm^{-1}: 3158, 2967, 2439, 1657, 1637, 1428, 1397

^1H NMR (400 MHz) δ: 8.50 (s, 1H), 8.01-7.99 (m, 2H), 7.90-7.87 (m, 2H), 7.46-7.33 (m, 10H), 7.13-7.08 (m, 2H), 5.64-5.48 (m, 2H), 3.95 (s, 3H)

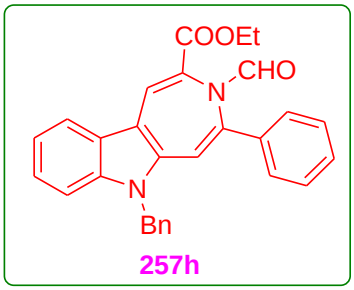
^{13}C NMR (100 MHz) δ: 164.5, 164.4, 163.3, 163.1, 163.2, 140.5, 138.6, 137.7, 137.6, 136.5, 136.1, 135.9, 133.0, 131.5, 129.6, 129.4, 129.2, 129.17, 128.8, 128.1, 126.8, 126.6, 126.5, 126.1, 126.0, 125.0, 124.9, 121.9, 121.8, 119.5, 119.2, 112.4, 110.3, 110.0 (aromatic) 52.6, 52.4, 47.7, 47.5, 29.7 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{28}H_{22}O_3N_2$: 457.1528 (M+Na)

Found: 457.1523

Ethyl 6-benzyl-3-formyl-4-phenyl-3,6-dihydroazepino[4,5-*b*]indole-2-carboxylate (257h)



257h

Yield: 66%

R_f 0.39 (hexanes/EtOAc = 1:1)

Mp: 168-170 °C

IR (KBr) ν_{max} cm^{-1}: 3167, 2914, 2478, 1689, 1652, 1467, 1351

^1H NMR (400 MHz) δ: 8.51 (s, 1H), 8.01 (m, 1H), 7.93-7.86 (m, 2H), 7.49-7.31 (m, 11H), 7.14-7.09 (m, 2H), 5.65-5.50 (m, 2H), 4.46-4.35 (m, 2H), 1.48-1.42 (m, 3H)

^{13}C NMR (100 MHz) δ: 163.9, 163.1, 162.9, 140.4, 138.5, 137.7, 137.65, 136.6, 136.2, 135.9, 134.3, 132.9, 131.2, 129.6, 129.3, 129.2, 129.1, 128.7, 128.1, 128.0, 126.9, 126.7, 126.5, 126.3, 126.1, 126.05, 125.0, 124.9, 121.9, 121.7, 119.6, 119.2, 118.1, 114.5, 113.7, 113.0, 112.4, 110.3, 111.0 (aromatic C) 61.6, 61.4, 47.7, 47.5, 29.7, 29.4, 14.4 (aliphatic C)

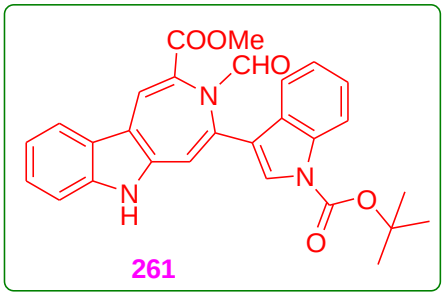
HRMS (ESI-MS):

Anal. calcd. for $C_{29}H_{24}O_3N_2$: 471.1685 (M+Na))

Found: 471.1679.

Methyl 3-formyl-4-(1*H*-indol-3-yl)-3,6-dihydroazepino[4,5-*b*]indole-2-carboxylate (261)

Yield: 71%



261

R_f 0.43 (hexanes/EtOAc = 1:1)

Mp: 168-170 °C

IR (KBr) ν_{max} cm^{-1}: 3162, 2964, 2887, 1738, 1674, 1562, 1249

^{1}H NMR (400 MHz) δ: 10.75 (s, 1H), 8.59 (s, 1H), 8.40 (s, 1H), 8.22 (s, 1H), 7.51 (d, *J* = 8.5Hz, 1H), 7.37-7.33 (m, 2H), 7.24-7.17 (m, 1H), 7.01-7.00 (m, 2H), 6.90-6.86 (m, 1H), 6.67 (t, *J* = 9.0 Hz, 1H), 6.56-6.54 (m, 1H), 3.98 (s, 3H), 1.79 (s, 9H)

^{13}C NMR (100 MHz) δ: 166.3, 164.4, 149.3, 139.9, 136.2, 134.1, 129.9, 128.2, 126.2, 125.9, 125.3, 124.4, 124.0, 122.8, 120.8, 118.7, 118.0, 116.4, 115.2, 115.16, 115.1, 112.5, 110.6, 84.3, 52.5, 28.3

HRMS (ESI-MS):

Anal. calcd. for $C_{28}H_{25}O_3N_2$: 484.1872 (M+H)

Found: 484.1857

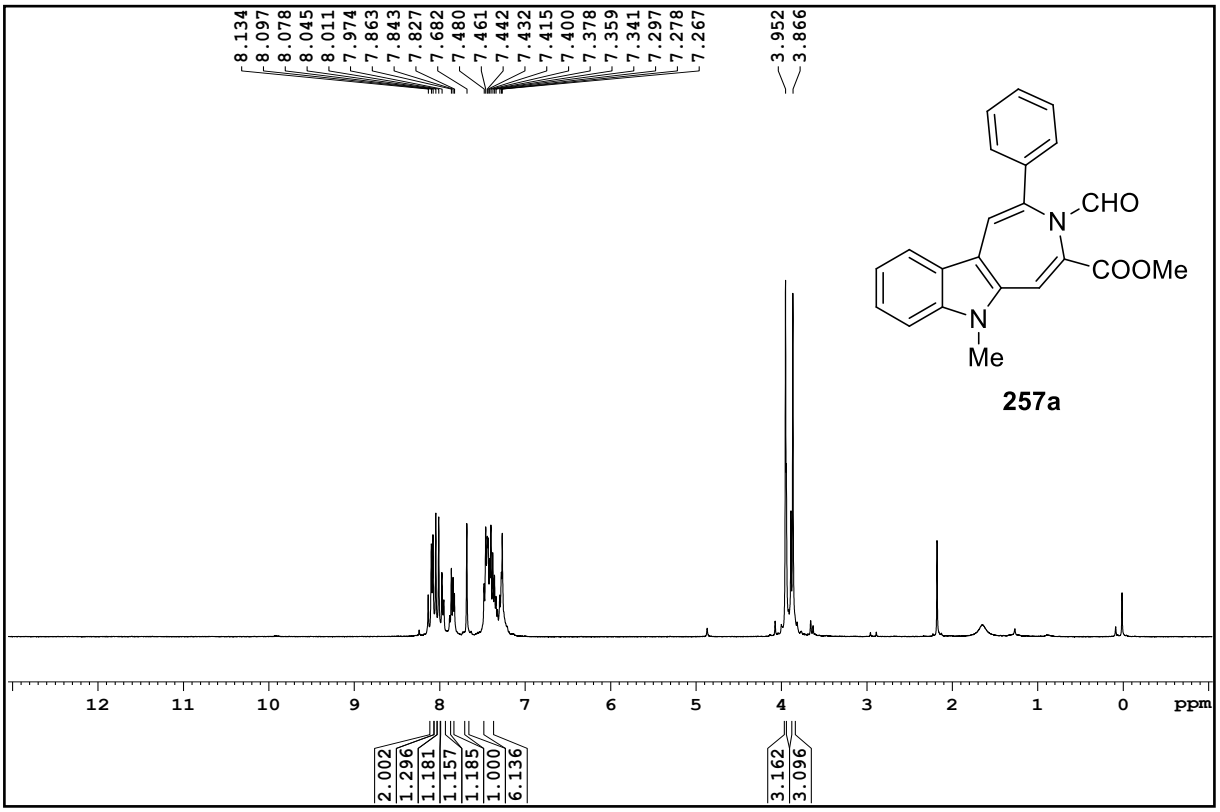
Table 15. Crystal data and structure refinement for 257d.

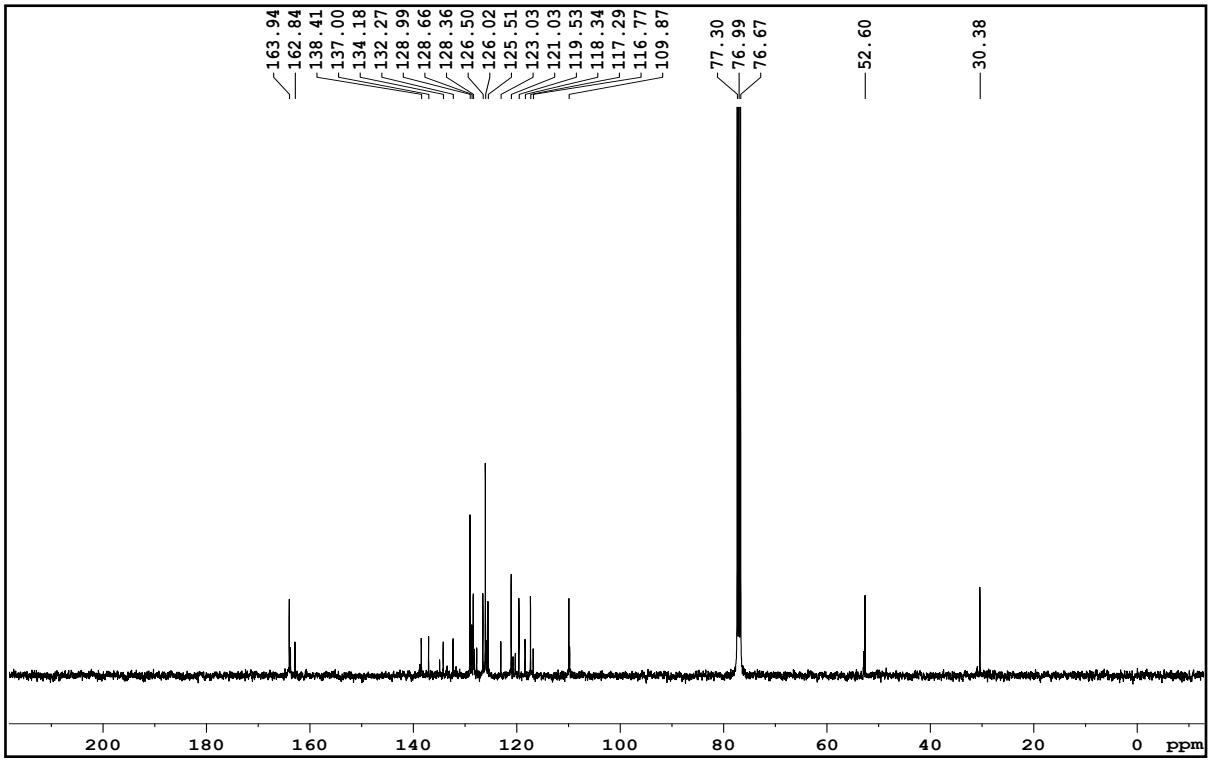
Identification code	**257d**	
Empirical formula	$C_{29}H_{24}N_2O_3$	
Formula weight	448.50	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.811(3) Å	α = 90.00 °.
	b = 14.735(2) Å	β = 112.12(2) (2)°.
	c = 13.872(3) Å	γ = 90.00 °.
Volume	2425.8 $Å^3$	
Z	4	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	944	
Crystal size	0.20 x 0.20 x 0.15 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	40932	
Independent reflections	7817 [R(int) = 0.0817]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9850 and 0.9801	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7927 / 0 / 560	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.1811, wR2 = 0.4077	
R indices (all data)	R1 = 0.6292, wR2 = 0.5345	
Extinction coefficient	0.00061(13)	
Largest diff. peak and hole	0.237 and -0.182 $e.Å^{-3}$	
CCDC number	**1040333**	

Table 16. Crystal data and structure refinement for 261.

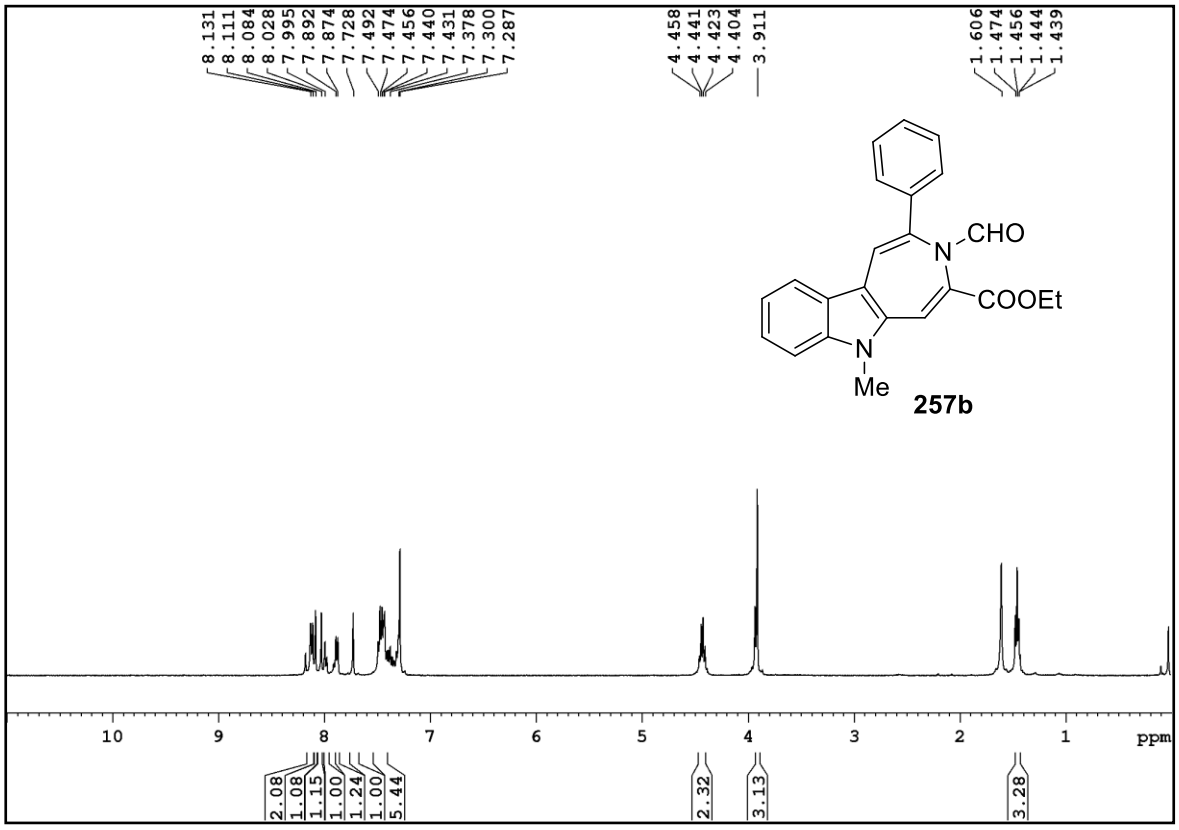
Identification code	**261**	
Empirical formula	$C_{28}H_{25}N_3O_5$	
Formula weight	483.51	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.8146(11) Å	α = 102.624 (8) °.
	b = 12.3195(11) Å	β = 108.483 (7) °.
	c = 18.619(2) Å	γ = 90.00 °.
Volume	2500.9(4) $Å^3$	
Z	4	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.062 mm^{-1}	
F(000)	944	
Crystal size	0.20 x 0.20 x 0.15 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	39932	
Independent reflections	7867 [R(int) = 0.0617]	
Completeness to theta = 25.00°	100%	
Absorption correction	Empirical	
Max. and min. transmission	0.9750 and 0.9301	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7937 / 0 / 540	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.1043, wR2 = 0.3143	
R indices (all data)	R1 = 0.2394, wR2 = 0.3551	
Extinction coefficient	0.00051(10)	
Largest diff. peak and hole	0.238 and -0.162 e.$Å^{-3}$	
CCDC number	**1040332**	

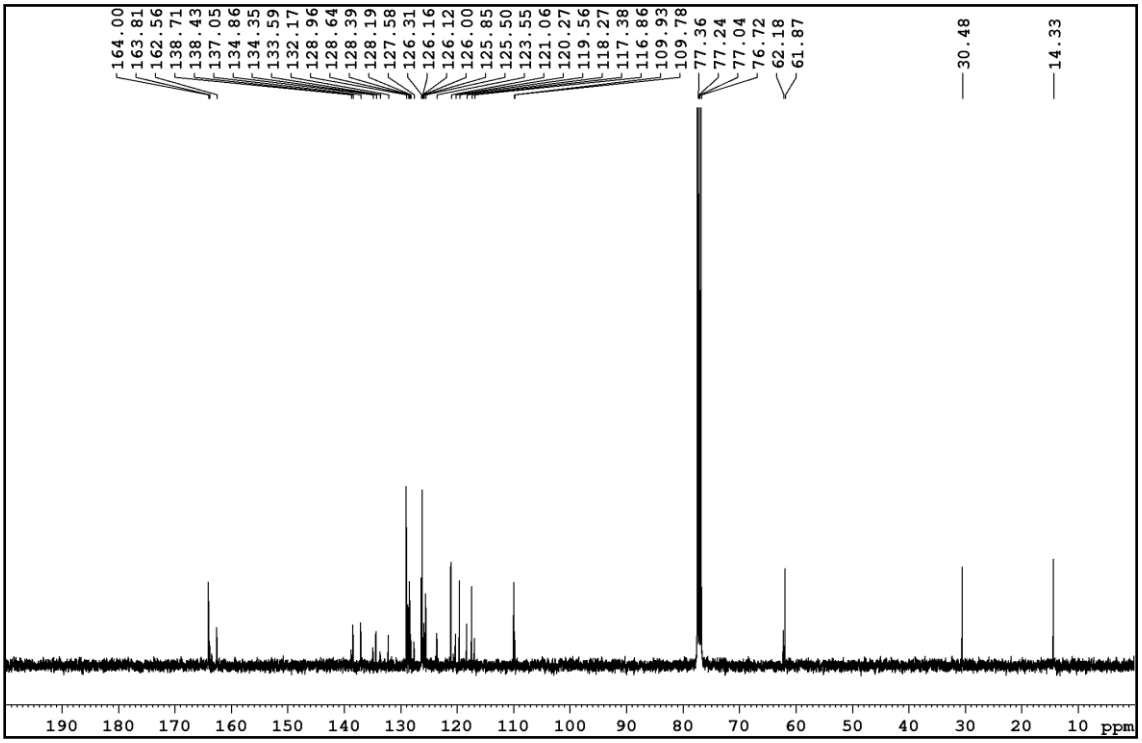
Spectra No. 10: ^{1}H and ^{13}C spectra of Compound 257a





Spectra No. 11: ^{1}H and ^{13}C spectra of Compound 257b





4.4. Conclusions

We have developed a convenient and straightforward methodology for the synthesis of indolodiazepenes and Chromoazepinone core *via* copper(II) triflate catalyzed 7-*endo* dig cyclization in moderate yield.

This novel methodology provides the first idea for the synthesis of Chromoazepinone core.

4.5. References

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CHAPTER 4

Total synthesis of the marine alkaloid Mansouramycin D

4.1. Introduction

Mansouramycin D (**262**), an isoquinoline quinone, was isolated from the ethyl acetate extract of marine *Streptomyces* sp. isolate Mei37 by Laatsch and co-workers in 2009.[118] The structure of compound **262** has been confirmed as 3-(1*H*-indol-3-yl)-7-methylaminoisoquinoline-5,8-dione by NMR and mass spectrometry. Marine isoquinoline alkaloids have received substantial attention from the scientific community due to their rich biological activities.[118-121] Mansouramycin A-D (**262-265**) showed cytotoxicity against cancer cell lines and strong antimicrobial activity. Mansouramycin A-D (**262-265**) showed cytotoxicity against 36 cancer cell lines and were found to have significant activity against non-small cell lung cancer, breast cancer, melanoma and prostate cancer cells. Specifically, high cytotoxicity was shown against many human cancer cell lines with an IC_{50} value up to 0.089 μM for lung cancer.[118]

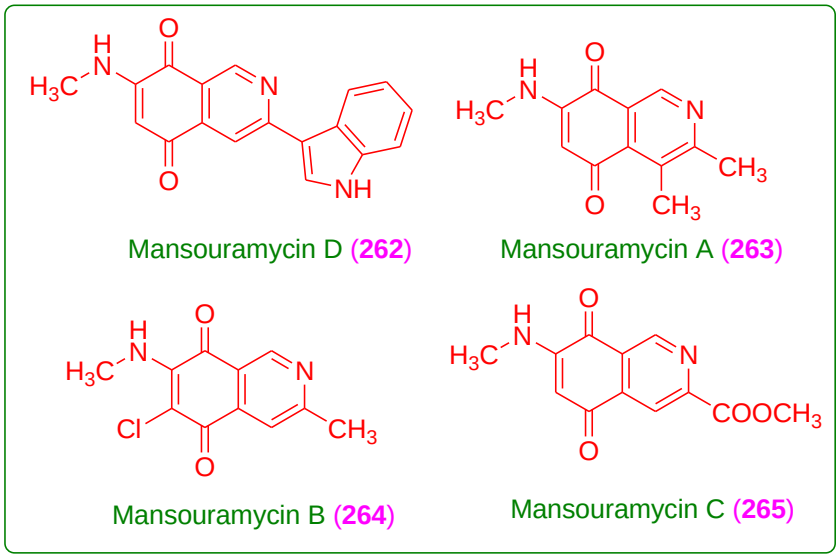


Fig. 13. Structures of Mansouramycin A-D

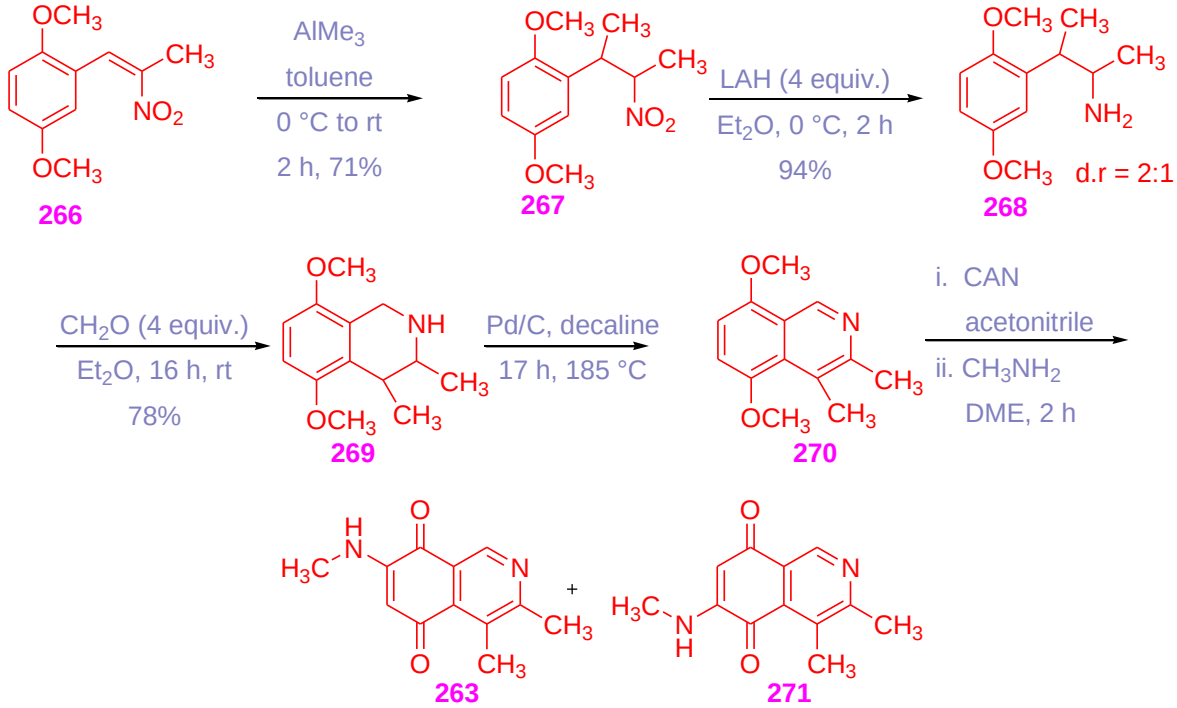
Considering the biological importance of Mansouramycin D and the lack of synthetic methods to date, we focused our interest on its synthesis. There was an unsuccessful attempt to synthesize

Mansouramycin D (**262**) involving Pictet-Spengler cyclization.[120] They were not able to reach the requisite amine for the cyclization.

Total synthesis of Mansouramycin A-C

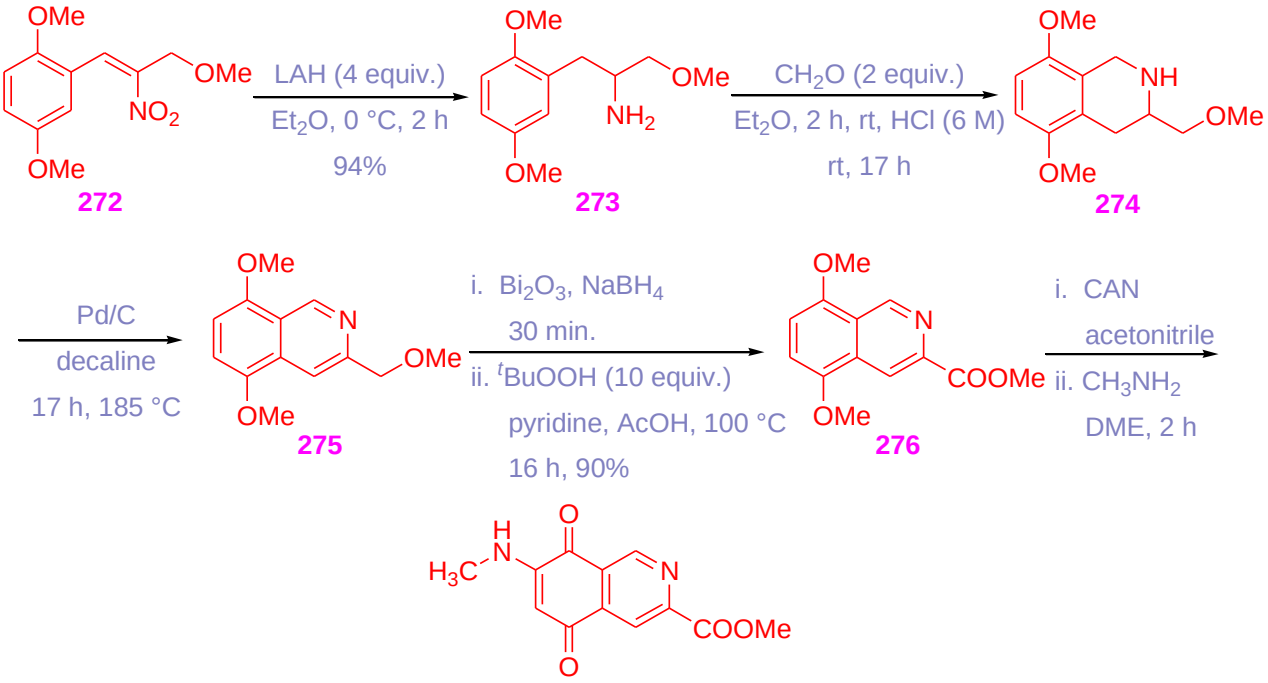
Total synthesis of Mansouramycin A, B and C were reported.[118c] In that report, key step is Pictet-Spengler cyclization followed by oxidation and oxidative amination. The schemes are given below (**Eq. 67** and **Eq. 68**). Synthesis of Mansouramycin A began with reaction of 2,5-dimethoxyacetophenone was treated with nitromethane. Then the methyl group addition by the solution of trimethylaluminium at 0 °C and methyl lithium to the solution containing methyl adduct (**266**). The reaction was stopped after 2 hours by the addition of 1 molar hydrochloric acid. Then the resulting product reduced by using LAH to afford corresponding amine which is required for Pictet-Spengler cyclization. After the Pictet-Spengler cyclization the product is further aromatized using Pd/C to get the Mansouramycin core (isoquinoline core). Finally, the total synthesis of Mansouramycin A was completed by the dione formation followed by the oxidative amination. This step gives the regioisomer, major isomer is expected Mansouramycin A (**263**).

Eq. 67. Total synthesis of Mansouramycin A (263)

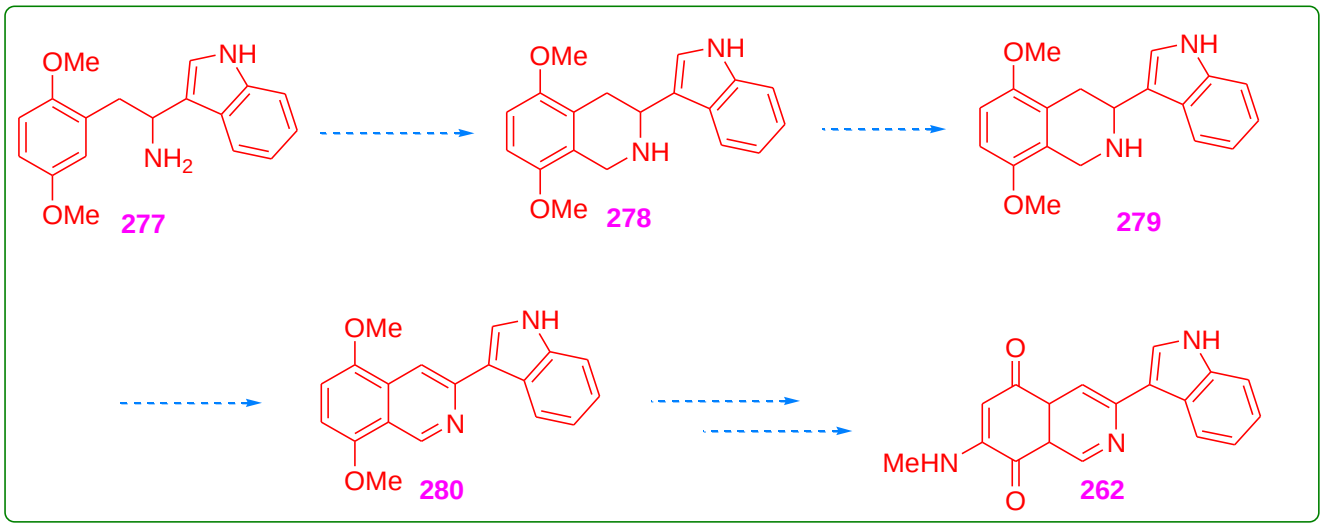


Mansouramycin B was synthesized the same reaction sequence by starting material. Compound **266** subjected to LAH reduction followed by the same reactions as in Mansouramycin A. The similar protocol was applied and successfully completed the total synthesis of other alkaloids, Mansouramycin C (**Eq. 68**).[118c]

Eq. 68. Total synthesis of Mansouramycin C (272)



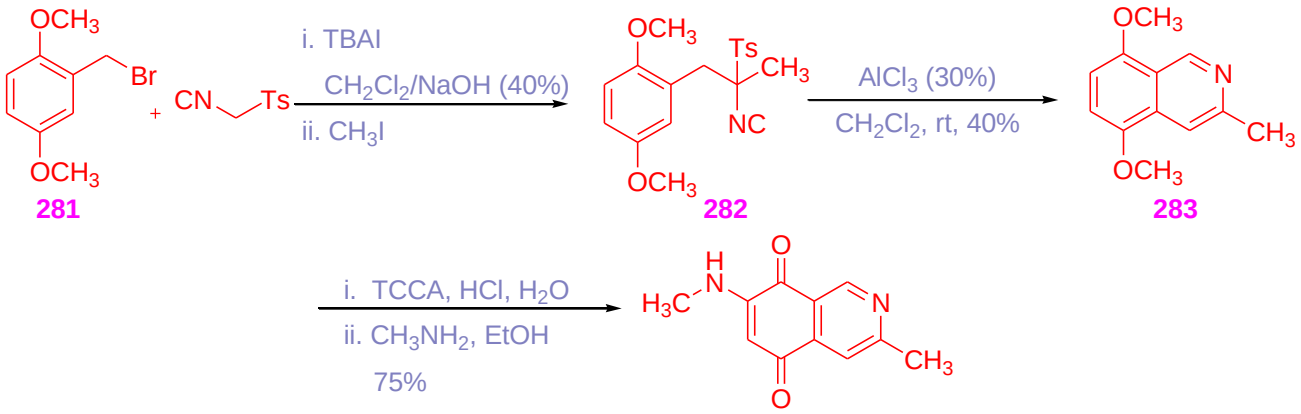
Eq. 69. Unsuccessful attempt of Mansouramycin D



But similar protocol for the total synthesis of Mansouramycin D was unsuccessful. They have planned the strategy as depicted in Eq. 69. They concluded that the routes which planned were unsuccessful to implement the amine required for proceed Pictet-Spengler cyclization. The access of Mansouramycin D, was denied. Thus, they were not possible to complete the total synthesis of marine alkaloid Mansouramycin D.[118c]

In 2015, a new method for the synthesis of isoquinolines through catalytic acid mediated cyclization of α-benzyl tosyl methylisocyanide (TosMIC) derivatives has been developed. This new methodology has been successfully applied to the total synthesis of the Mansouramycin B. This synthesis started with the preparation of TosMIC derivative **282**, then sequential addition of 2-(bromomethyl)-1,4-dimethoxybenzene and methyl iodide to TosMIC. The resulting compound is cyclized by the treatment of catalytic medium. Finally, the total synthesis was completed by the reaction of with trichloroisocyanuric acid (TCCA) in H_2O/HCl at room temperature followed by oxidative methyl amination using methylamine. Overall yield in this total synthesis is 23% (**Eq. 70**).[122]

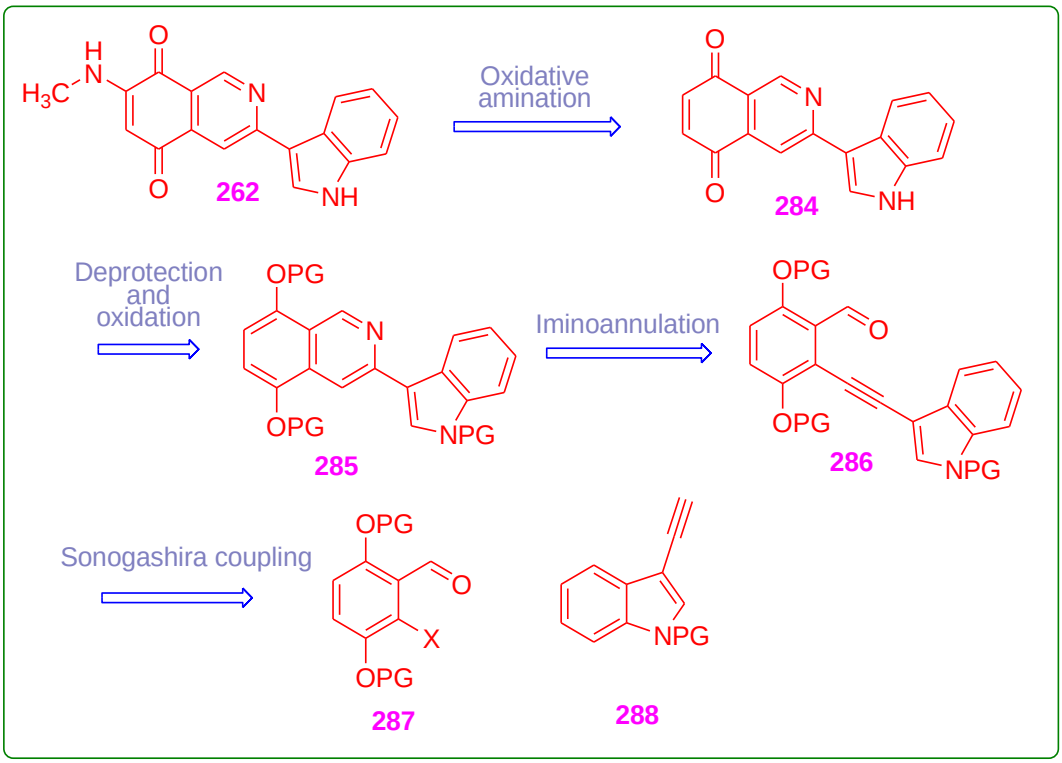
Eq. 70. Total synthesis of Mansouramycin B (285)



Synthesis of isoquinoline heterocycles has received much attention due to the presence of isoquinoline skeleton in numerous alkaloids.[123] Synthesis of isoquinoline systems by various methods is known, classical methods are, mainly, Bischler-Napieralski reaction,[124] Pomeranz-Fritsch reaction,[125] Pictet-Spengler reaction and Pictet-Games reaction.[126] Numerous elegant protocols for isoquinoline synthesis have been reported to date.[127]

4.2. Total synthesis of Mansouramycin D

In this chapter, we describe the first successful and concise total synthesis of Mansouramycin D (**262**) involving intramolecular iminoannulation as key ring closure step, which resulted in an overall yield of 54.5 to 60.9%. The retrosynthetic disconnection for the synthesis of **262** is depicted in Scheme 9.



Scheme 9. Retrosynthetic approach to Mansouramycin D

The core structure of **262** contains an isoquinoline moiety substituted with the indole at the third position. Among the reported synthetic methods, iminoannulation (key step) followed by subsequent deprotection, oxidation, and oxidative amination would be the simplest and concise route to the synthesis of this valuable marine alkaloid, Mansouramycin D (**262**).

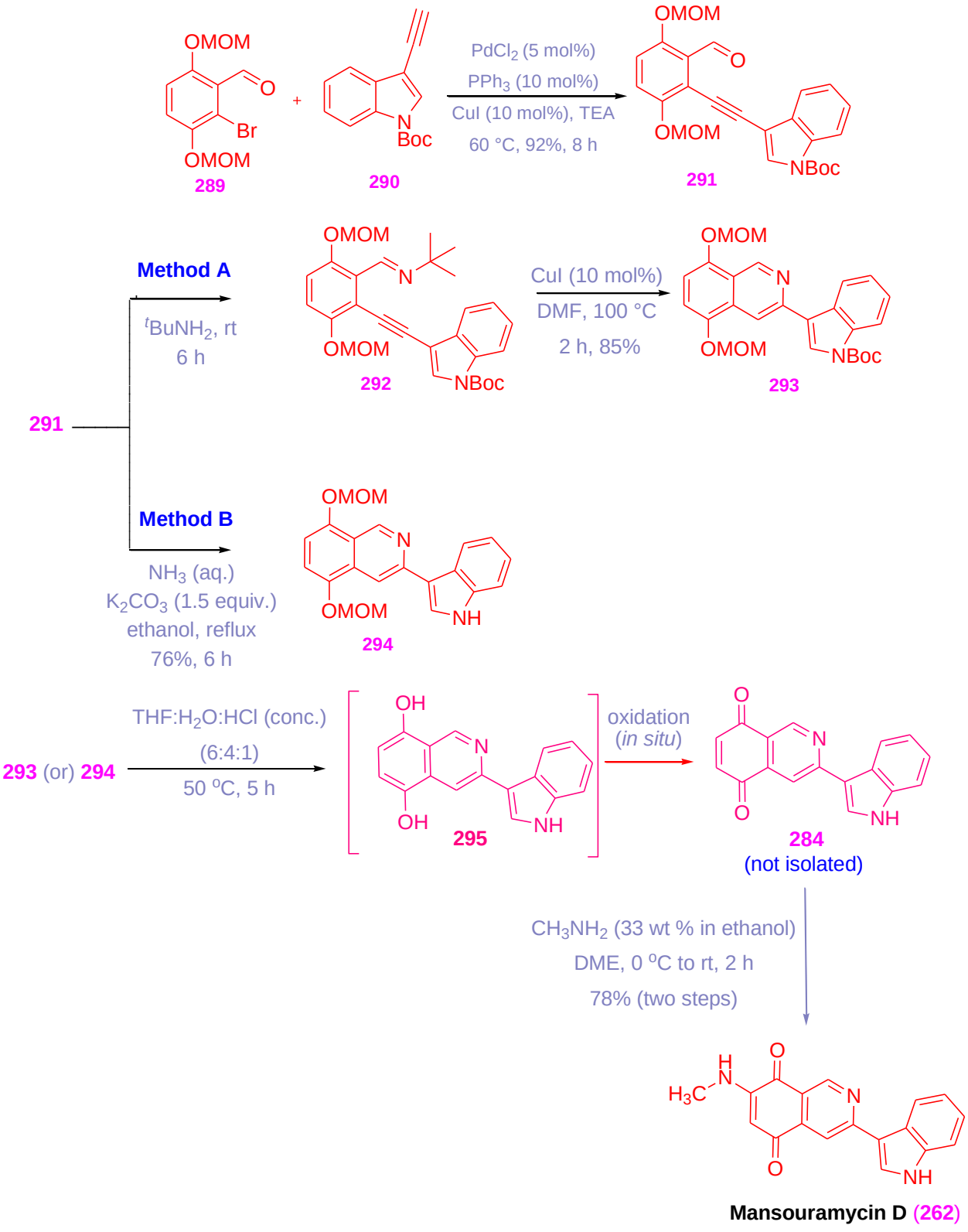
At the outset, we focused on Sonogashira coupling of 2-bromo-3,6-dihydroxybenzaldehyde and Boc protected 3-ethynyl-1*H*-indole (**290**). Unfortunately, the expected product was not formed. This might be due to the presence of free hydroxy groups in 2-bromo-3,6-dihydroxybenzaldehyde. Then, both hydroxyl groups of 2-bromo-3,6-dihydroxybenzaldehyde were protected by MOM group using MOM chloride and diisopropylethylamine (DIPEA) as base.[128] To our advantage after this modification, the Sonogashira reaction with MOM ether (**289**) of 2-bromo-3,6-dihydroxybenzaldehyde and *N*-Boc protected 3-ethynyl-1*H*-indole (**290**) using $PdCl_2$ (5 mol%), PPh_3 (10 mol%), CuI (10 mol%) and triethylamine as solvent underwent smoothly at 60 °C and

yielded in 92% of coupled product **291** as brown oil (Scheme 10). If the reaction was carried out at more than 60 °C, the yield of the product was decreased.

The isoquinoline ring closure was accomplished from product **191** *via* intramolecular iminoannulation. Iminoannulation can be performed in two ways, (i) Larock annulation with $^{t}BuNH_2$ and (ii) with aqueous ammonia. In method A (Scheme 10), iminoalkyne **292** was synthesized by the treatment of alkynylaldehyde **291** at room temperature with excess *tert*-butylamine for 6 h. After evaporation of *tert*-butylamine, the obtained crude imine **292** was then dissolved in DMF and 10 mol% copper iodide was added as a catalyst. To our delight, the expected product **293** was achieved in 85% yield. In method B, isoquinoline core **294** was synthesized *via* ammonia mediated ring closure of **291** with a treatment of excess aqueous ammonia and 1.5 equivalent of potassium carbonate. A new polar spot was observed in TLC. Surprisingly, during this reaction, Boc group was removed and the product **294** was obtained in 76% yield.

At this juncture, having the core structure **293** and **294** in hand, we further performed functional group modification, consisting of removal of MOM or Boc using THF, H_2O, and conc. HCl (6:4:1) mixture heating at 50 °C. It is also to be noted that **294** having the MOM groups and in case of **293** having both MOM and Boc groups are removed under the same conditions. To our surprise, the product **293** underwent oxidation *in situ* without the use of any oxidizing agents and with the complete conversion of the starting material (TLC). It furnished the oxidized product **284** and we utilized the compound without further purification. Finally, the aminomethylation was accomplished using ethanolic solution of methylamine (33 wt %) in 1,2-dimethoxyethane at 0 °C. It is noteworthy to mention that the reaction proceeded in regioselective manner and gave only the finally targeted molecule in 78% yield.

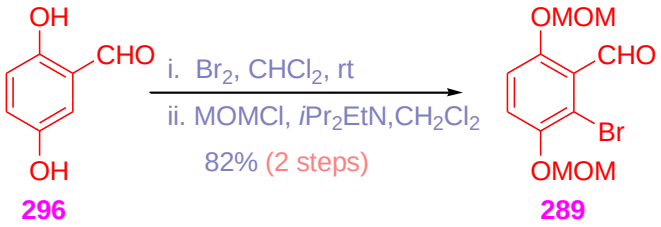
Thus, we have completed the first total synthesis of Mansouramycin D in three steps with overall yield of 54.5 to 60.9%. Spectral data of **262** is fully consistent with those of Mansouramycin D isolated from the natural source[118a] (Comparison of NMR data; see, table 17 and 18). Hence, the structure of **262** is rigorously verified by the present total synthesis.



Scheme 9. Total synthesis of Mansouramycin D

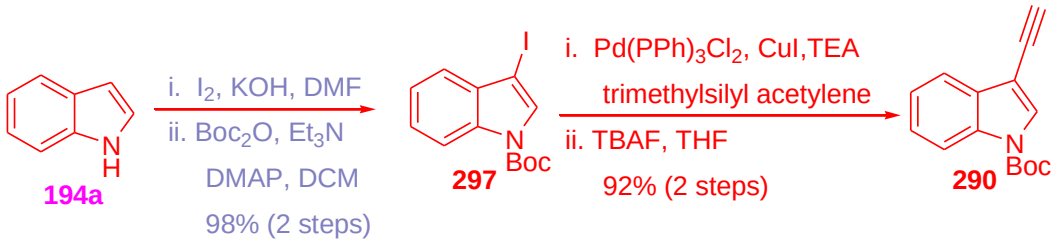
4.3. Experimental Section

Preparation of starting materials (289)



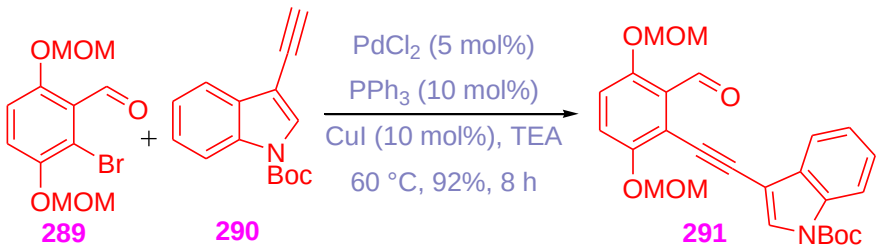
Bis-MOM protected bromoaldehyde (**289**) was prepared from bromination of 2,4-dihydroxybenzaldehyde (**296**) followed by protected as *bis* MOM ether **289** in 82% yield over two steps.[127]

Preparation of starting materials (290)



Another starting material indoleacetelyne[128] **290** preparation began with iodination and Boc production of indole to form Boc protected iodo indole in excellent yield over two steps. Then Sonogashira coupling with trimethylsilyl acetylene followed by TMS cleavage afforded corresponding alkyne required for coupling.

Synthesis of *tert*-butyl 3-((2-formyl-3,6-*bis*(methoxymethoxy)phenyl) ethynyl)-1*H*-indole-1-carboxylate (291):



To a mixture of CuI (31 mg, 10 mol%) and triphenylphosphine (42 mg, 10 mol%), freshly distilled triethylamine (5 mL) was added under nitrogen atmosphere. To this, 5 mol% of $PdCl_2$ (15 mg), 2-bromo-3,6-*bis*(methoxymethoxy)benzaldehyde (**289**) (500 mg, 1.63 mmol)

and *tert*-butyl 3-ethynyl-1*H*-indole-1-carboxylate (**290**) (435 mg, 1.80 mmol) were added and the mixture was heated at 60 °C for 8 h. After completion of reaction (indicated by TLC), reaction mixture was diluted with 50 mL of $CHCl_3$ and filtered with celite bed. Then, water (10 mL) was added to the diluted solution, which was then extracted with $CHCl_3$ (2 × 50 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum and purified by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes) to afford the *tert*-butyl 3-((2-formyl-3,6-*bis*(methoxymethoxy)phenyl)ethynyl)-1*H*-indole-1-carboxylate (**291**) as viscous oil (698 mg) in 92% yield.

Compound 291:

Yield: 92%

R_f 0.44 (10% EtOAc/hexanes)

Mp: Viscous Oil

IR (KBr) ν_{max} cm^{-1}: 3120, 2950, 2900, 2900, 2200, 950, 695

^1H NMR (400 MHz) δ: 10.71 (d, *J* = 1.4 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.91-7.90 (m, 2H), 7.30-7.31 (m, 3H), 7.16 (dd, *J* = 9.1 Hz & 1.0 Hz, 1H), 5.30 (d, *J* = 1.3 Hz, 2H), 5.25 (d, *J* = 1.3 Hz, 2H), 3.57 (d, *J* = 1.3 Hz, 3H), 3.52 (d, *J* = 1.3 Hz, 3H), 1.69 (d, *J* = 1.2 Hz, 9H)

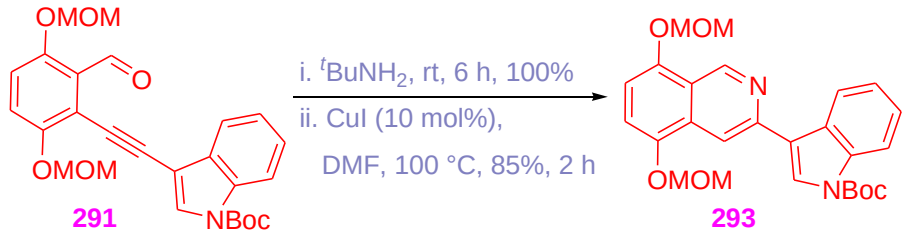
^{13}C NMR (100 MHz) *δ*: 189.8, 153.8, 153.2, 149.0, 134.7, 130.6, 129.3, 126.3, 125.2, 123.4, 122.1, 120.4, 116.4, 116.3, 115.2, 103.4 (aromatic C); 95.8, 95.4, 92.5, 86.3, 84.4, 56.4, 28.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{26}H_{27}NO_7$: 466.1866 (M+H)

Found: 466.1866

Synthesis of *tert*-butyl 3-(5,8-*bis*(methoxymethoxy)isoquinolin-3-yl)-1*H*-indole-1-carboxylate (293)



An oven-dried 10 mL round-bottomed flask equipped with a teflon-coated magnetic stirring bar was charged with 0.2 mmol of *tert*-butyl 3-((2-formyl-3,6-*bis*(methoxymethoxy)phenyl) ethynyl)-1*H*-indole-1-carboxylate (**291**) (100 mg) and 1 mL of *tert*-butylamine. The reaction mixture was stirred at room temperature for 6 hours. After complete conversion of starting material was observed by TLC, excess of *tert*-butylamine were removed under vacuum. The residue was dissolved in 3 mL of DMF, CuI (0.03 mmol) was added and heated at 100 ˚C for 2 hours. The reaction was allowed to cool to room temperature, poured into ice and extracted with $CHCl_3$ (2 × 20 mL). The organic layer was washed with 10 mL of water and 5 mL of brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude material was purified by column chromatography using silica (eluent: 10% ethyl acetate in hexanes). The product **293** was eluted as a pale yellow solid (85 mg).

Compound 293:

Yield:	85%
R_f	0.42 (10% EtOAc/hexanes)
Mp:	132-134 ˚C
IR (KBr) ν_{max} cm^{-1}:	3130, 2982, 2925, 2900, 2120, 850, 635
^{1}H NMR (400 MHz) δ:	8.29-8.28 (m, 2H, a doublet is merged with singlet), 8.10 (d, J = 7.2 Hz, 1H), 7.42-7.40 (m, 3H), 6.96-6.94 (m, 2H), 6.77 (d, J = 8.8 Hz, 1H), 5.17 (s, 2H), 4.46 (d, J = 6.8 Hz, 1H), 4.33 (d, J = 6.8 Hz, 1H), 3.49 (s, 3H), 2.81 (s, 3H), 1.72 (s, 9H)
^{13}C NMR (100 MHz) δ:	149.5, 148.3, 145.9, 145.2, 136.0, 127.1, 124.9 (two carbons), 123.5, 122.0, 120.9, 116.7, 116.0, 115.8, 115.7, 112.3, 96.2,

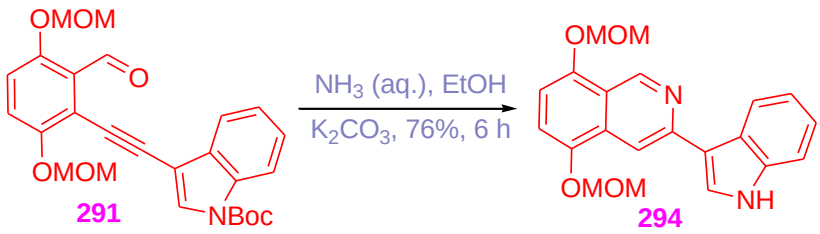
87.6 (aromatic C); 95.5, 93.7, 84.5, 56.0, 54.9, 28.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{26}H_{28}N_2O_6$: 465.2025 (M+H)

Found: 465.2026

Synthesis of 3-(1*H*-indol-3-yl)-5,8-*bis*(methoxymethoxy)isoquinoline (294)



An oven-dried 10 mL round-bottomed flask equipped with a teflon-coated magnetic stirring bar was charged with *tert*-butyl 3-((2-formyl-3,6-*bis*(methoxymethoxy)phenyl) ethynyl)-1*H*-indole-1-carboxylate (**291**) (100 mg, 0.21 mmol) and K_2CO_3 (45 mg, 0.32 mmol), 2 mL of ethanol and 1 mL of aqueous ammonia (27% ammonia in water). The reaction mixture was refluxed for 2 hours. The complete conversion of starting material was observed by TLC. The reaction was allowed to cool to room temperature, poured into ice and extracted with $CHCl_3$ (10 mL). The organic layer was washed with 10 mL of water and 5 mL of brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude product **294** was purified by column chromatography (eluent: 10% ethyl acetate in hexanes). The product was eluted in 20% eluent as a pale yellow solid (60 mg).

Compound 294:

Yield: 76%

R_f 0.40 (10% EtOAc/hexanes)

Mp: 146-148 °C

IR (KBr) ν_{max} cm^{-1}: 3110, 3010, 2900, 2890, 930, 690

^1H NMR (400 MHz) δ: 9.66 (s, 1H), 8.91 (s, 1H), 8.37-8.35 (m, 2H, a doublet is merging with singlet), 7.97 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 7.5

Hz, 1H), 7.30-7.25 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 5.37 (s, 4H), 3.57 (s, 6H)

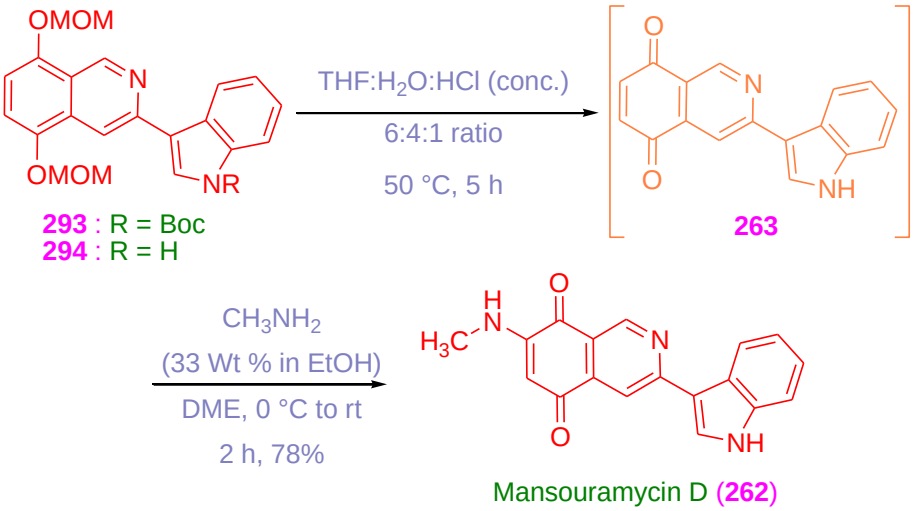
^{13}C NMR (100 MHz) δ: 149.0, 148.7, 147.2, 146.6, 137.1, 130.7, 125.4, 124.9, 122.4, 120.7, 120.6, 119.7, 117.8, 112.7, 111.6, 109.7, 107.8 (aromatic C); 95.3, 95.1, 56.3, 56.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{21}H_{20}N_2O_4$: 365.1501 (M+H)

Found: 365.1502

Synthesis of 3-(1*H*-indol-3-yl)-7-(methylamino)isoquinoline-5,8-dione (Mansouramycin D) (262)



To a solution of THF, H_2O and conc. HCl (6:4:1 ratio) (1 mL), *tert*-butyl 3-(5,8-*bis*(methoxymethoxy)isoquinolin-3-yl)-1*H*-indole-1-carboxylate (**294**) (30 mg, 0.06 mmol) in 1 mL THF was added drop wisely. Then reaction mixture was allowed to stir for 2 h at 50 °C. The complete conversion of starting material was observed. Reaction mass was poured in water and extracted with ethyl acetate (3 × 10 mL). This crude material was then used for next step. The residue was diluted with 5 mL of 1,2-dimethoxymethane. The reaction mixture was then cooled to 0 ˚C and 33% wt. absolute ethanolic solution of methylamine (0.3 mL, 0.28 mmol) was added dropwise. Then it was allowed to stir at room temperature. After 2h complete conversion was observed in TLC. After removing the solvent in reduced pressure, the reaction mixture was poured in 10 mL of water and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with water (10 mL) and brine (5 mL), dried over

anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: 10% ethyl acetate in hexanes). The product **262** was eluted in 50% eluent as a dark red solid (15 mg).

Compound 262:

Yield: 78%

R_f 0.60 (7% MeOH in DCM)

Mp: 152-154 °C

IR (KBr) ν_{max} cm^{-1}: 3150, 2950, 2880, 1620, 880, 670

^1H NMR (400 MHz) δ: 11.97 (s, 1H), 9.11 (s, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 7.88 (bs, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.21 (m, 2H), 5.71 (s, 1H), 2.83 (d, J = 5.2 Hz, 3H)

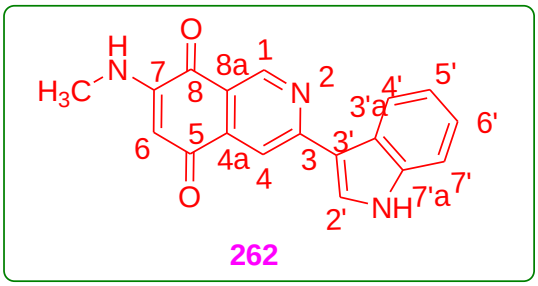
^{13}C NMR (100 MHz) δ: 180.0, 179.9, 161.8, 150.3, 148.0, 139.4, 137.4, 130.1, 125.3, 122.7, 122.1, 121.2, 120.4, 115.4, 113.4, 112.3, 99.7 (aromatic C); 29.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{18}H_{13}N_3O_2$: 304.1086 (M+H)

Found: 304.1085

Table 17. ^{1}H NMR Chemical Shift (in ppm); Spectroscopic Data Comparison of Natural and Synthetic Mansouramycin D **(262)**



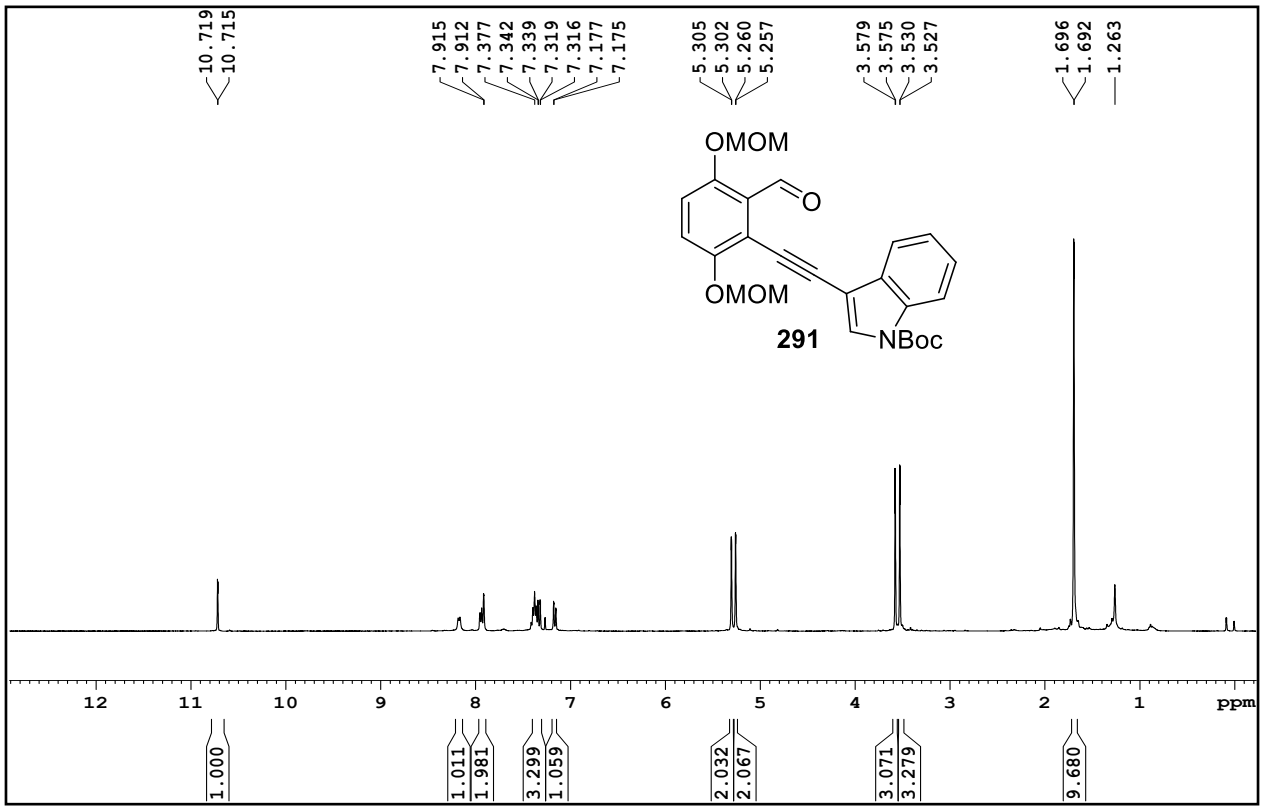
262

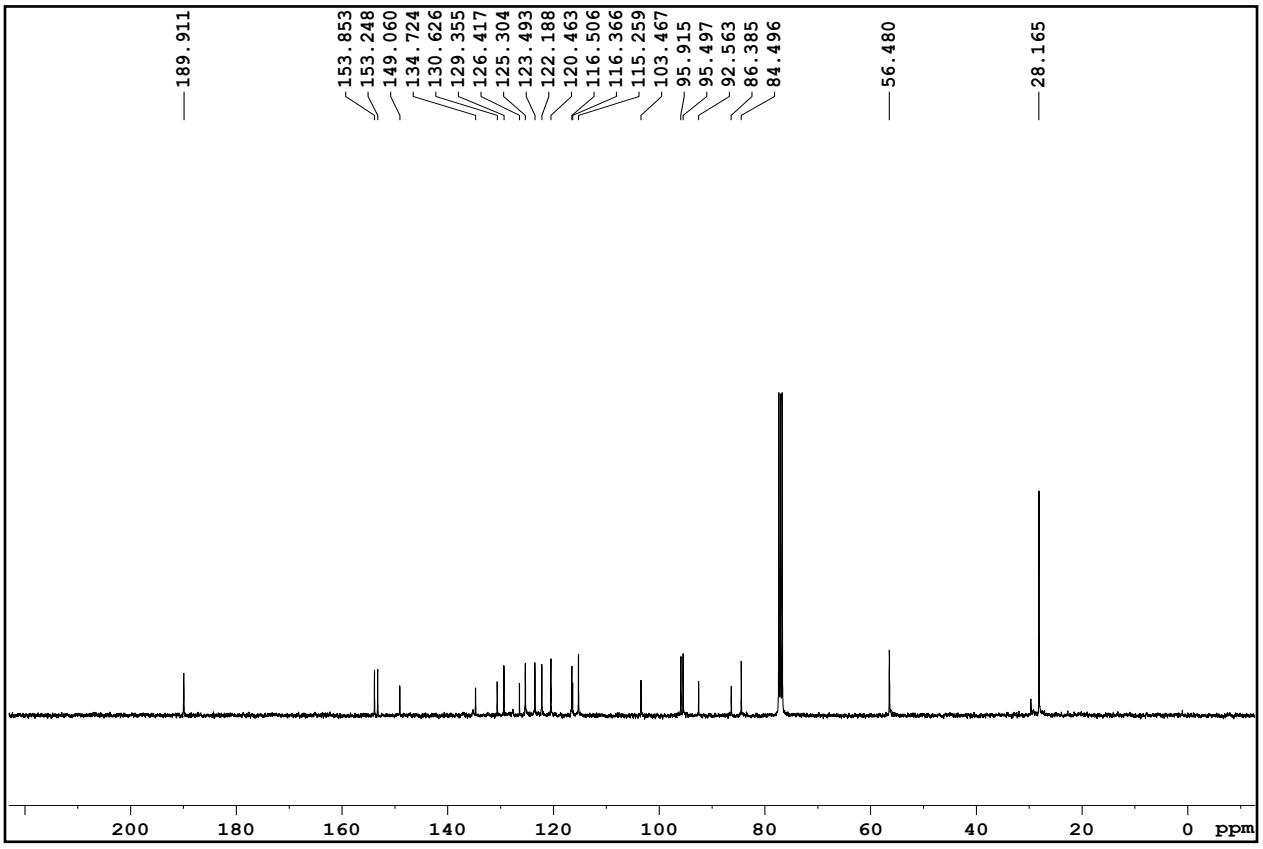
No	Mansouramycin D (Natural Compound; Reported by Laatsch *et al.*)[118] ^{1}H NMR (600 MHz, DMSO-d_6)	Mansouramycin D (Synthetic Compound; Our Sample ^{1}H NMR (500 MHz, DMSO-d_6)
1	9.11 (s)	9.11 (s)
4	8.18 (s)	8.18 (s)
6	5.71 (s)	5.71 (s)
7-*NH*	7.82 (br s)	7.88 (br s)
1'-*NH*	11.91 (s)	11.97 (s)
2'	8.50 (s)	8.51 (s)
4'	8.53 (d, *J* = 7.5 Hz)	8.53 (d, *J* = 8.0 Hz)
5'	7.21 (m)	7.21 (m)
6'		
7'	7.48 (d, *J* = 7.5 Hz)	7.48 (d, *J* = 8 Hz)
N-CH$_3$	2.83 (d, *J* = 5.2 Hz)	2.83 (d, *J* = 5.2 Hz)

Table 18. ^{13}C NMR Chemical Shift (in ppm); Spectroscopic Data Comparison of Natural and Synthetic Mansouramycin D **(262)**

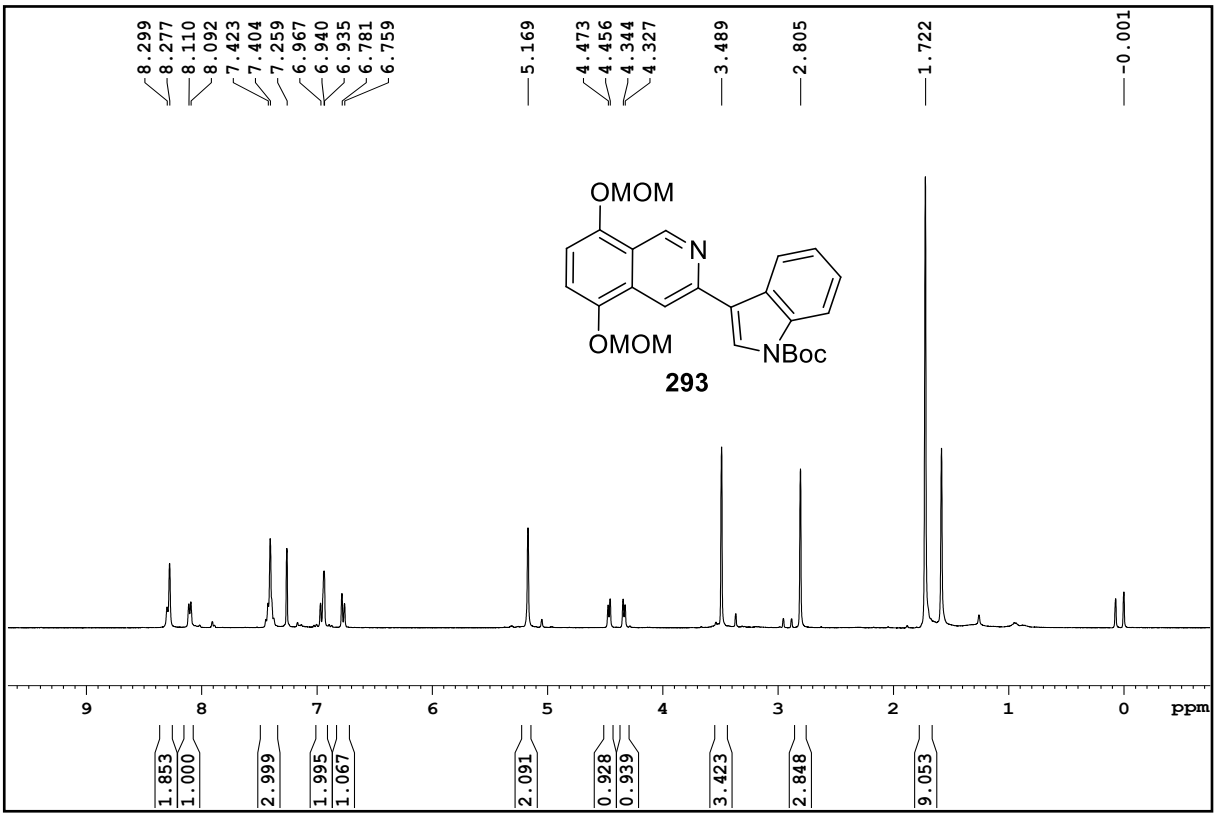
No	Mansouramycin D (Natural Compound; Reported by Laatsch *et al.*)[118] ^{13}C NMR (600 MHz, DMSO-d_6)	Mansouramycin D (Synthetic Compound; Our Sample ^{13}C NMR (500 MHz, DMSO-d_6)
1	147.8	148.0
3	161.6	161.8
4	113.3	113.4
4a	120.3	120.4
5	179.7	179.9
6	99.6	99.7
7	150.1	150.3
8	179.8	180.0
8a	139.2	139.4
2'	129.8	130.1
3'	115.2	115.4
3'a	125.1	125.3
4'	122.4	122.7
5'	121.0	121.2
6'	121.8	122.1
7'	112.1	112.3
7'a	137.3	137.4
***NH*-Me**	28.9	29.1

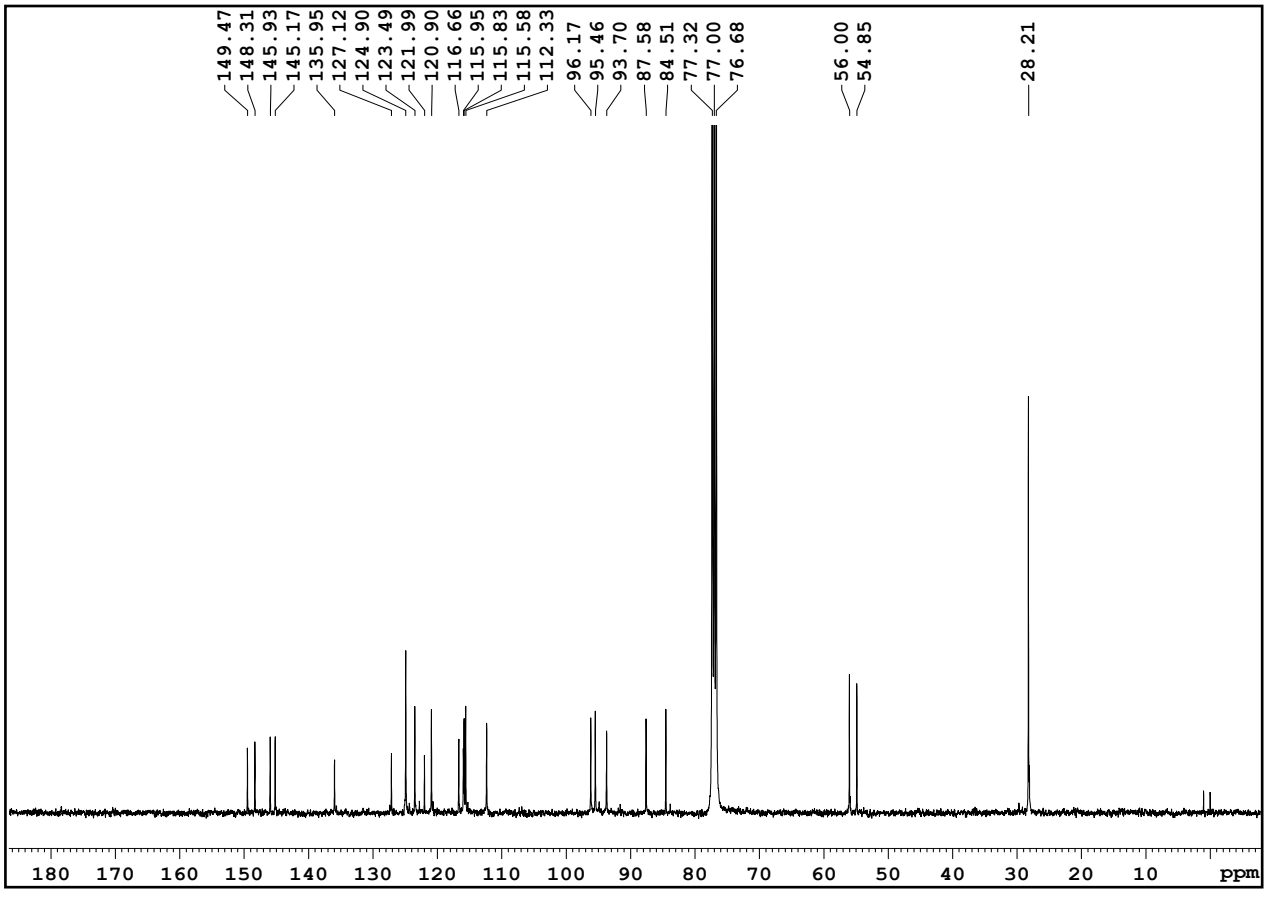
Spectra No. 12: ^{1}H and ^{13}C spectra of Compound 291



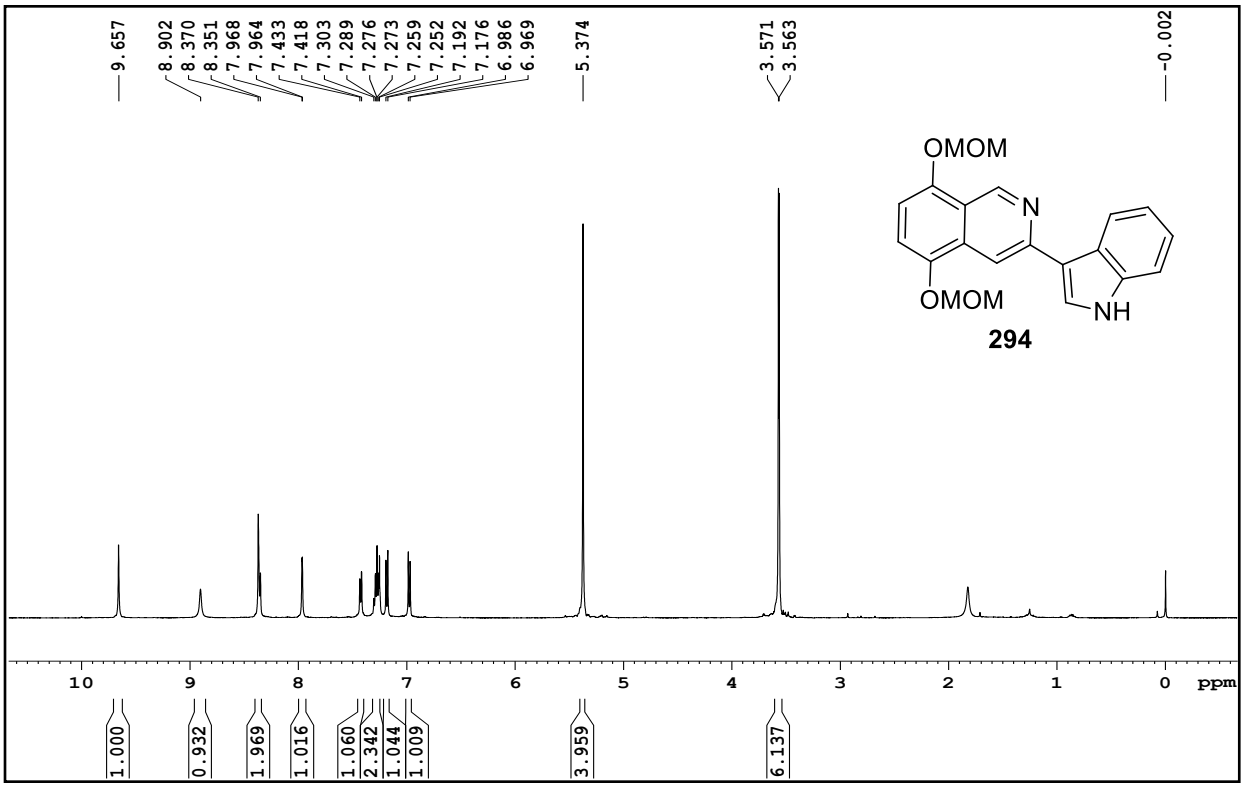


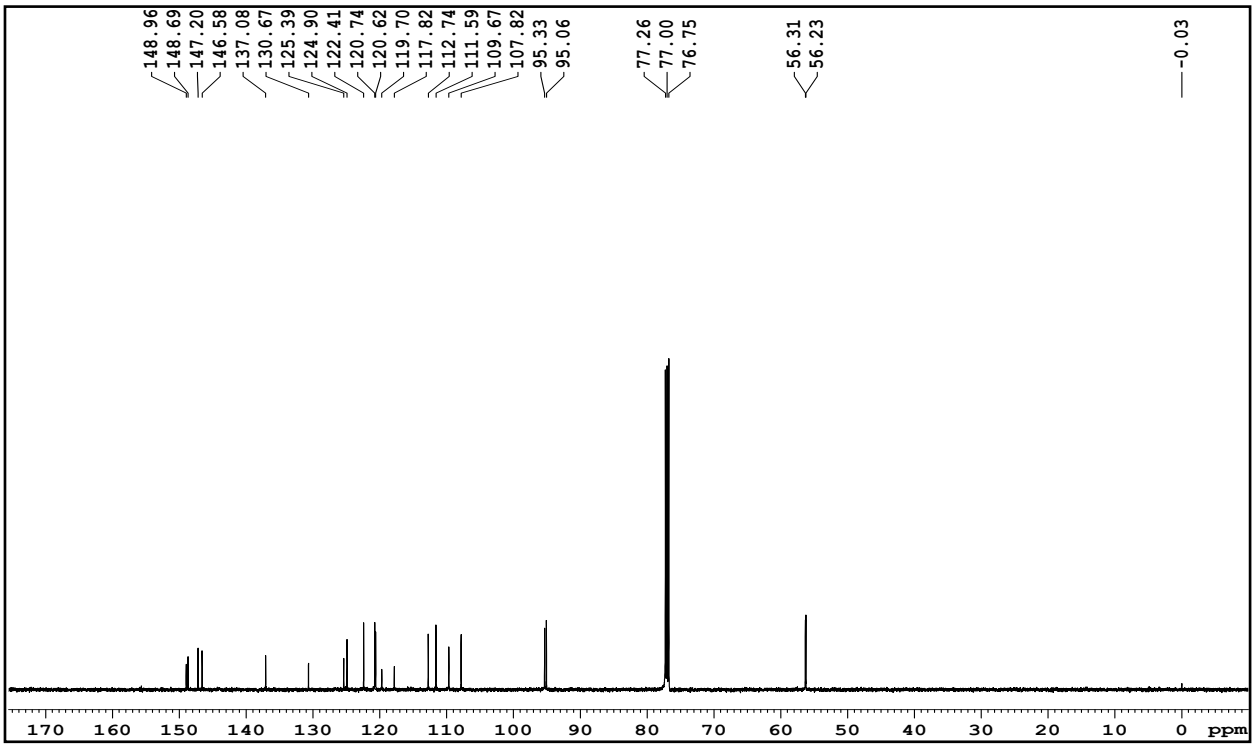
Spectra No. 13: ^{1}H and ^{13}C spectra of Compound 293



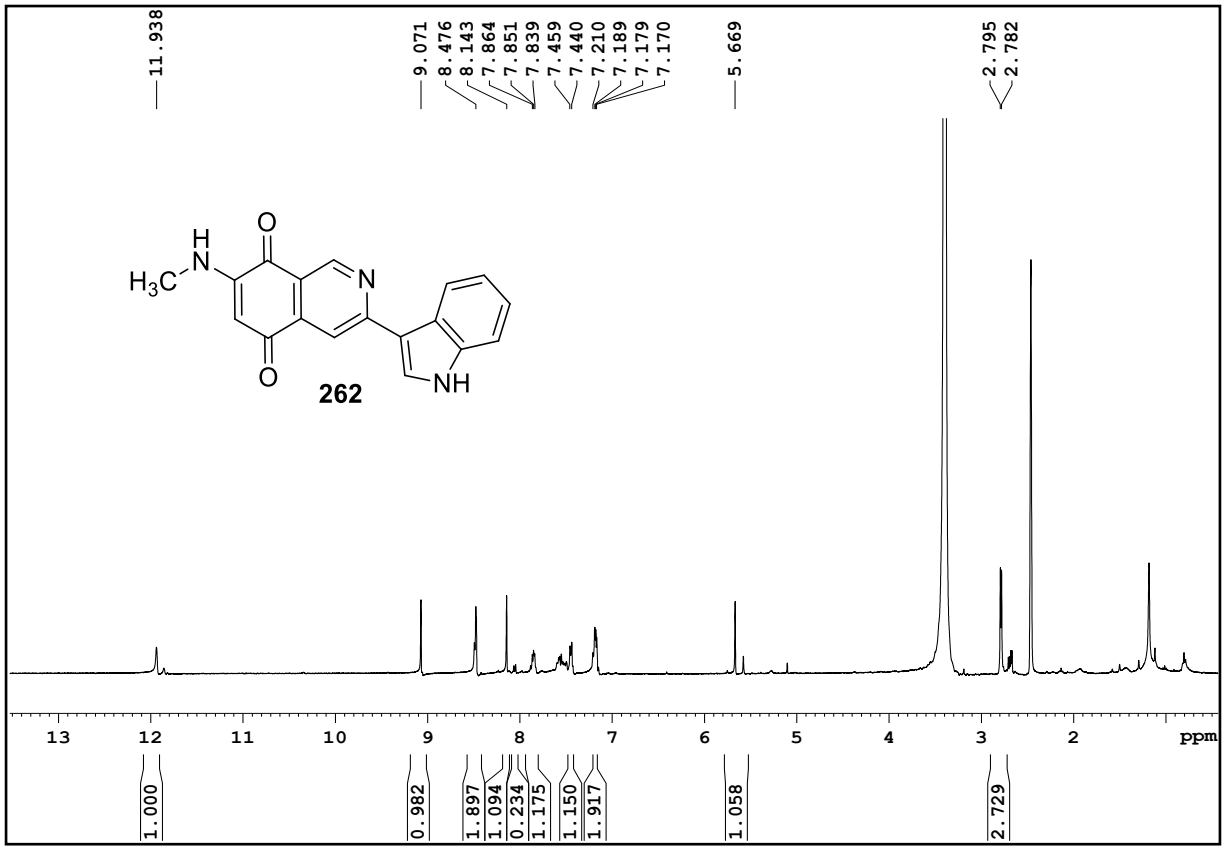


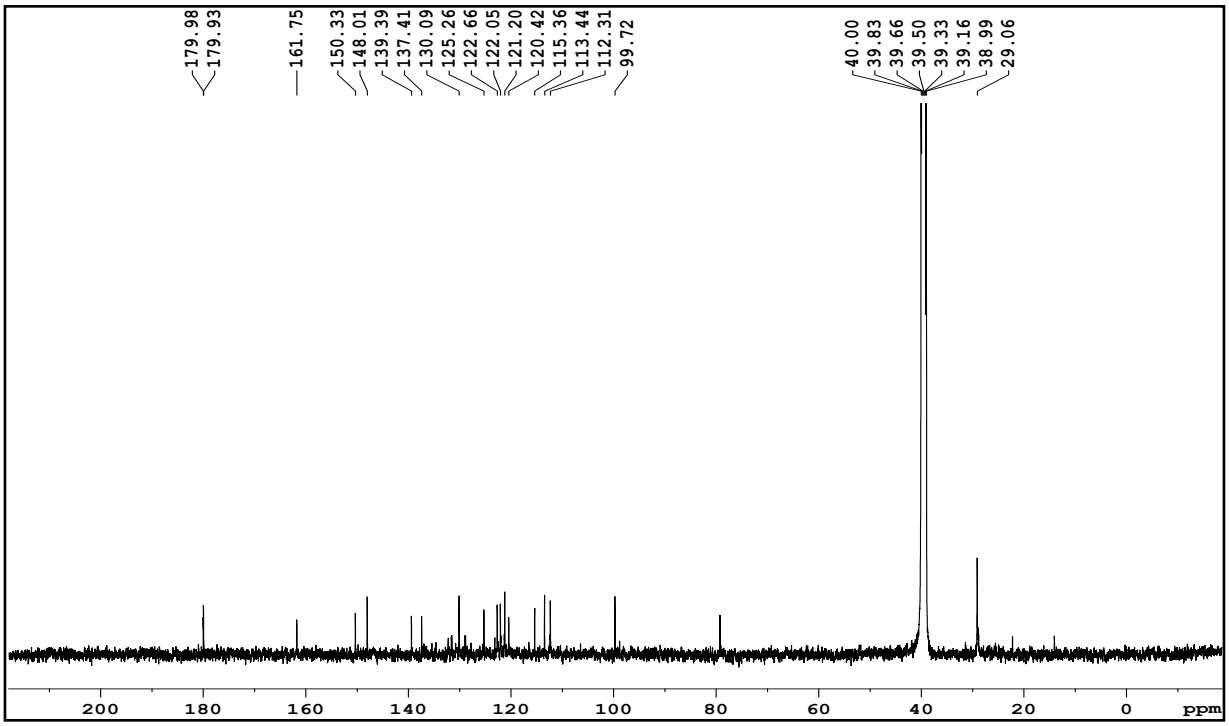
Spectra No. 14: ^{1}H and ^{13}C spectra of Compound 294





Spectra No. 15: ^{1}H and ^{13}C spectra of Compound 262 (Mansouramycin D)





4.4. Conclusions

We have accomplished a concise, first total synthesis of Mansouramycin D in overall yield of 54.5 to 60.9%.

The core isoquinoline ring has been constructed by iminoannulation in two different methods. It will likely find applications for other related alkaloids and provide an inroad to further

4.5. References

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CHAPTER 5

Total synthesis of the marine alkaloids Caulibugulones A and D

5.1. Introduction

Caulibugulones A-F (Fig. 14, **298-303**) are isoquinoline quinone alkaloids,[129] isolated from an extract of the marine bryozoan *Caulibugula intermis* collected in the Indo-Pacific off Palau, by Milanowski and co-workers in 2004.[130] Compounds **298-303** were found to have interesting cytotoxic activity ($IC_{50's}$ of 0.03-1.67 μg/mL) against murine tumor cells.[130] Valderrama *et al.* reported the synthesis of 4-methoxycarbonyl-3-methylisoquinoline-5,8-quinone (which contains the Caulibugulone core) and their analogues which expressed valuable in vitro cytotoxic activity against MRC-5 (healthy lung fibroblasts), and human cancer cell lines: AGS (gastric), SK-MES-1 (lung), J82 (bladder), and HL-60 (leukemia).[131] The Brission group reported that Caulibugulones are selective in vitro inhibitor of the Cdc25 family of cell cycle-controlling protein phosphatases.[132]

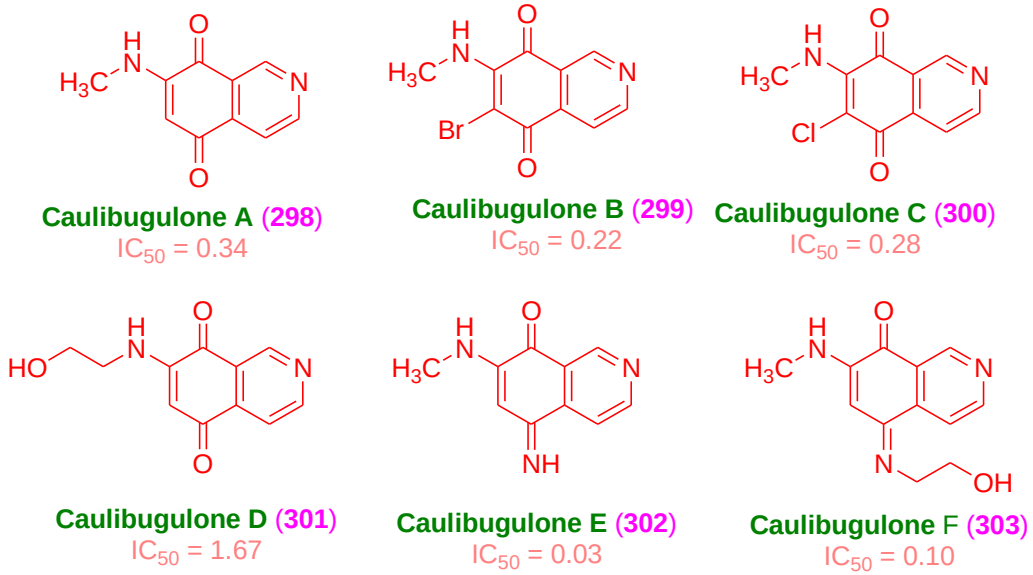
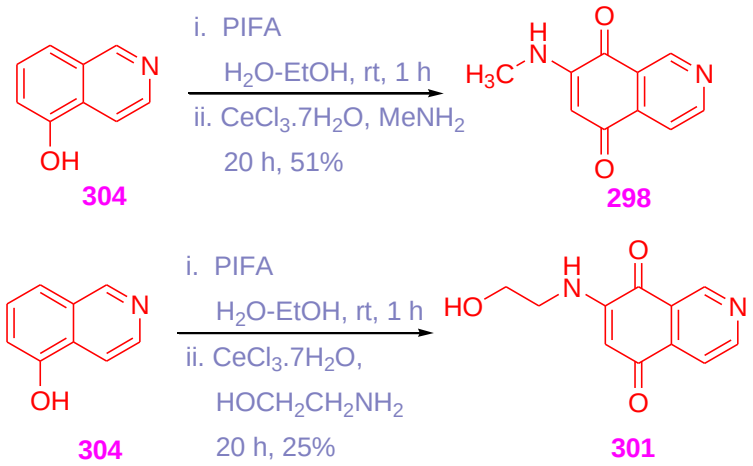


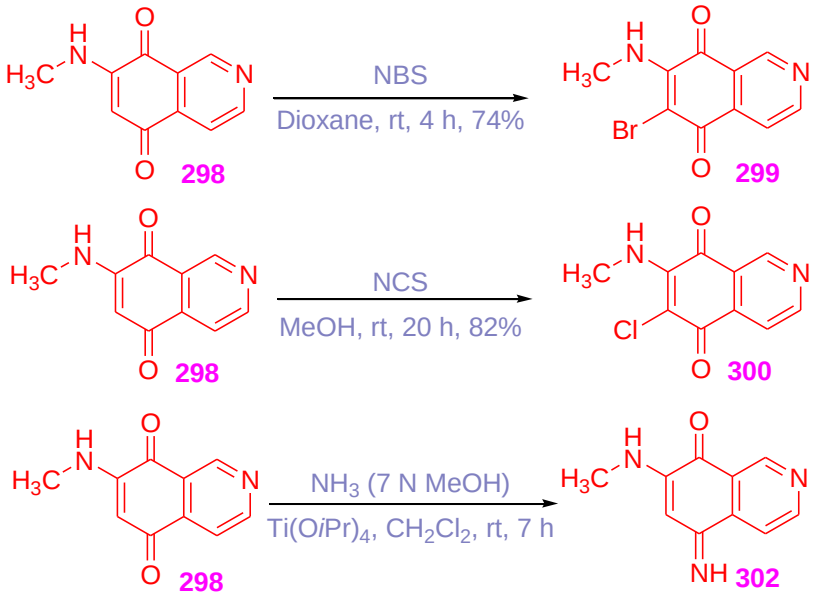
Fig. 14. Structure of Caulibugulones A-F. (IC_{50} are expressed in μg/mL against the murine tumor cell line).[130]

However, to the best of our knowledge, there are only three reports on the total synthesis of Caulibugulones.[133-135] In 2004, Tamagnan *et al.* reported the first total synthesis of Caulibugulones from 5,8-isoquinolinedione, which was prepared 30% overall yield from 5-aminoisoquinoline.[133] In the same year, Wipf and co-workers reported the synthesis of **298-303** from oxidation of 5-hydroxyisoquinoline by iodobenzene *bis*(trifluoroacetate) PIFA in a H_2O-EtOH and the subsequent *in situ* addition of methylamine, and they reported that compounds **298-303** are potent and selective inhibitors of the dual specificity phosphatase Cdc25B (**Eq. 71** and **Eq. 72**).[134]

Eq. 71. Total synthesis of Caulibugulones A, D

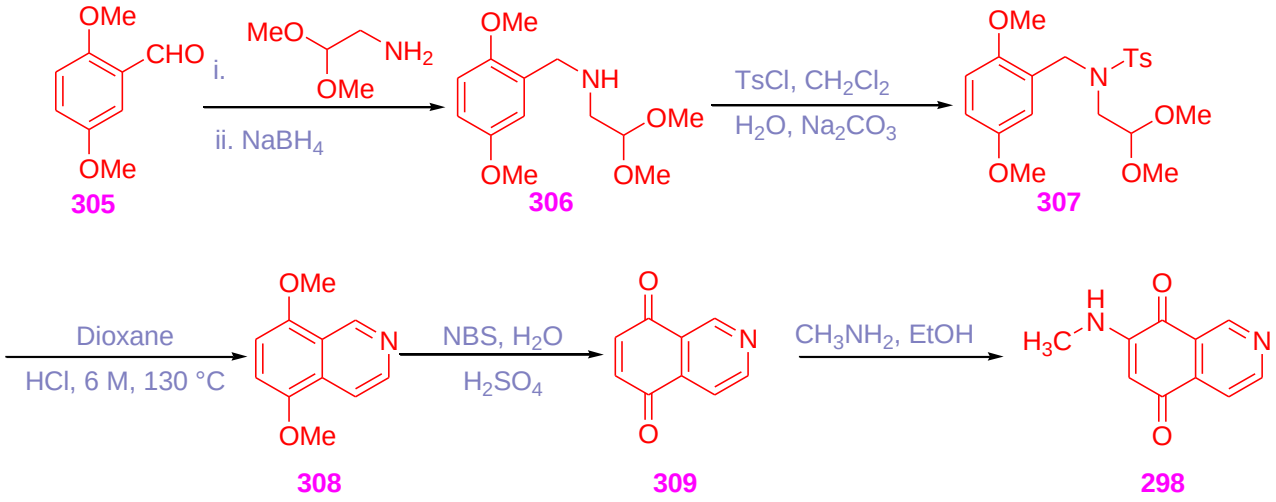


Eq. 72. Total synthesis of Caulibugulones B, C and E



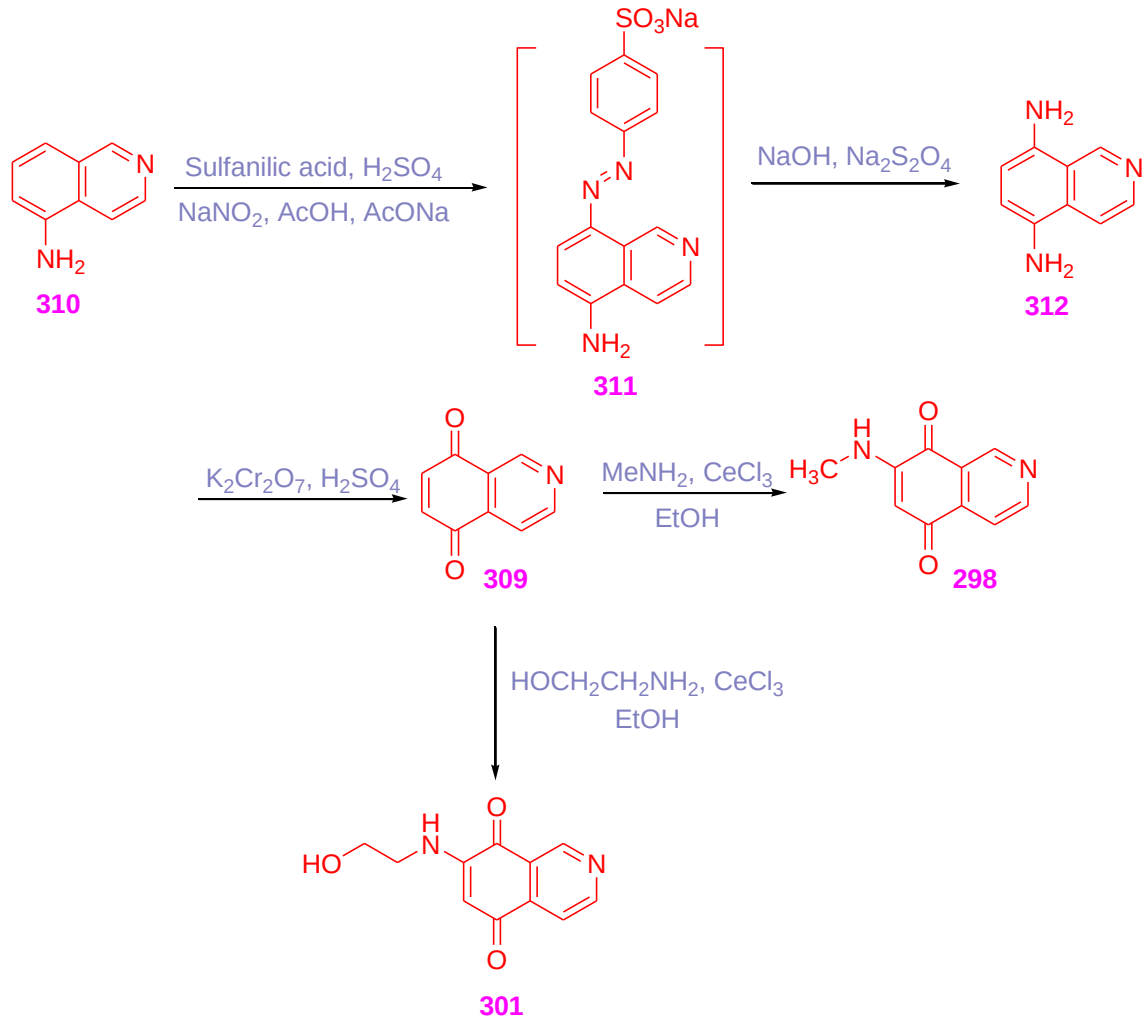
Another recent report on the total synthesis in literature. These alkaloids were synthesized in six steps starting from readily available 2,5-dimethoxybenzaldehyde. In that report Pomeranz-Fritsch reaction of *N*-(2,5-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfoamide **307** proceeded smoothly to give 5,8-dimethoxyisoquinoline, then it was oxidized to isoquinoline diones **309** followed by oxidative amination to furnish the Caulibugulone A **298** (**Eq. 73**).[135]

Eq. 73. Total synthesis of Caulibugulone A



In the following report the key intermediate 5,8-isoquinolinedione was synthesized in three steps starting from 5-aminoisoquinoline. Then the dione was converted into Caulibugulone A and D by oxidative amination with methylamine (or) 2-aminoethanol in ethanol in the presence of $CeCl_3$ (**Eq. 74**). [133]

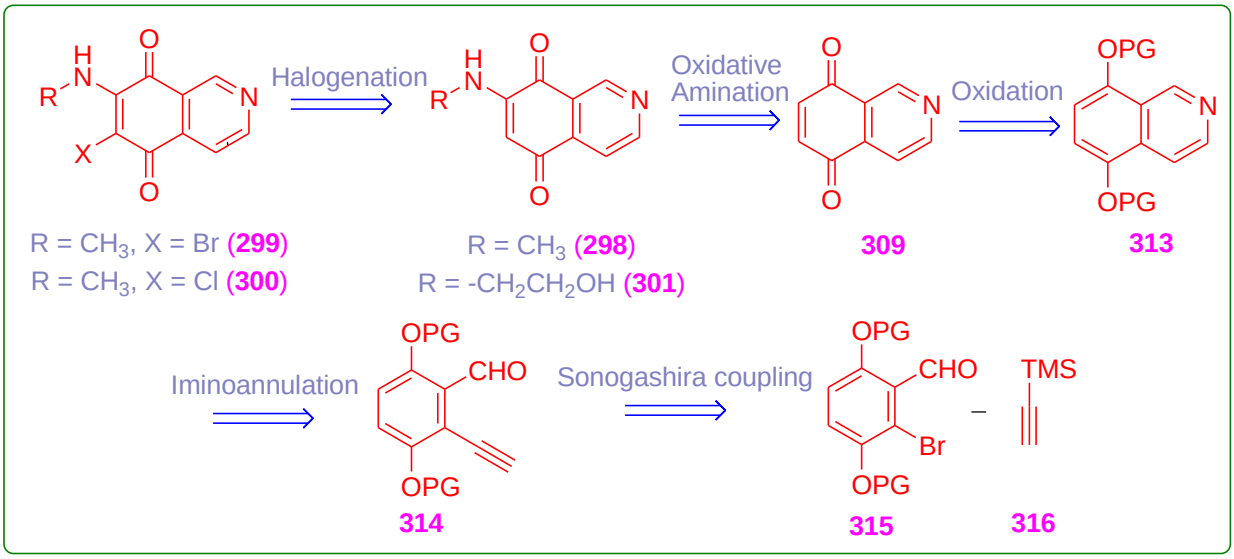
Eq. 74. Total synthesis of Caulibugulones A and D



We planned a different efficient and simple route for the synthesis of key intermediate 5,8-dihydroxyisoquinoline by utilizing ammonia mediated iminoannulation of the corresponding 1,2-alkynylaldehyde. The significant biological activity and very few methods for the synthesis of Caulibugulones[133-135] prompted us to find a new approach towards the synthesis of these marine alkaloids.

5.2. Total synthesis of Caulibugulones A and D

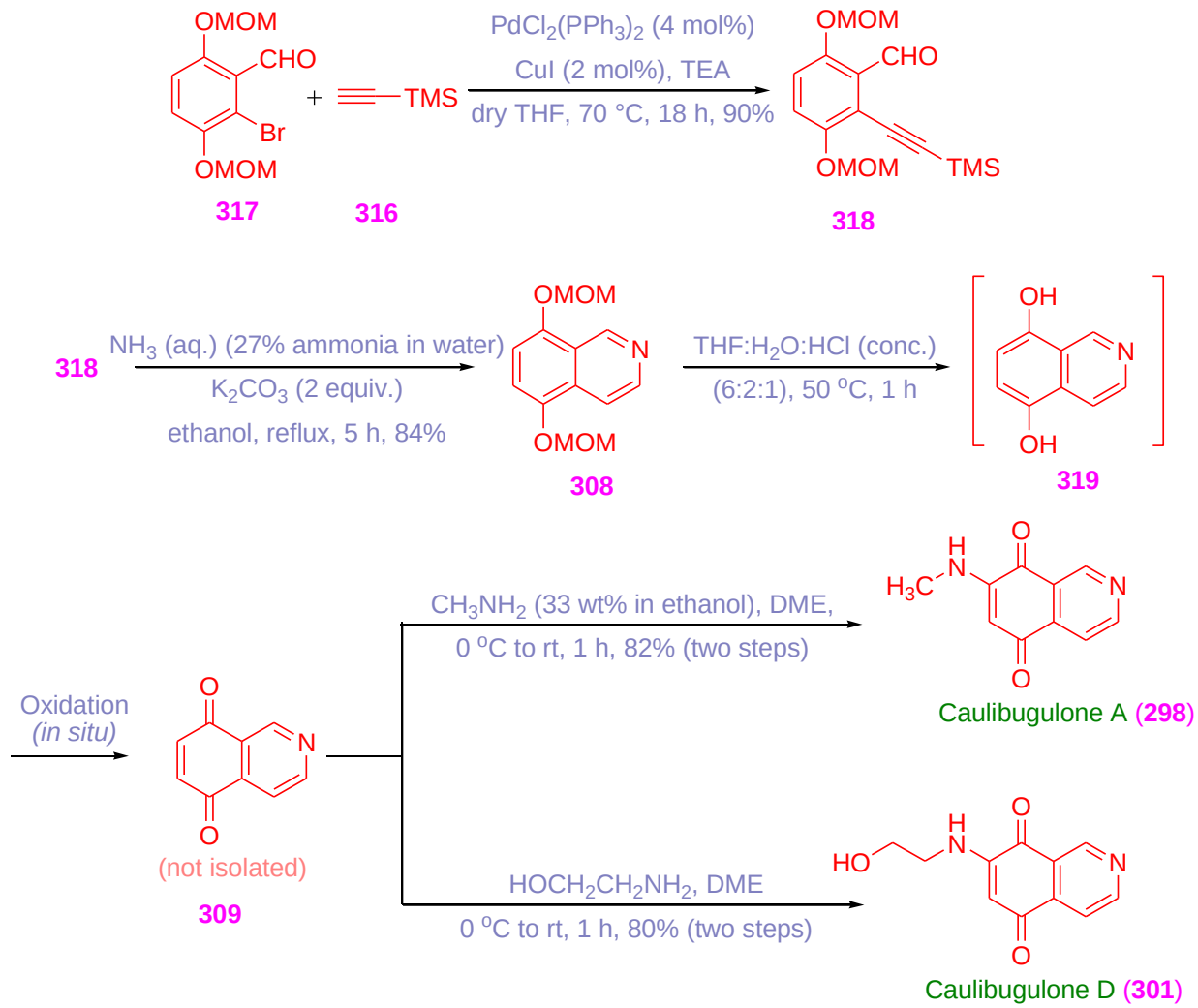
In chapter 4, we presented the first total synthesis of the marine alkaloid Mansouramycin D *via* iminoannulation. In the continuation of the previous chapter, we present a simple and concise total synthesis of Caulibugulones A and D *via* iminoannulation with an overall yield of 62% and 60% over three steps from an easily accessible known starting material.



Scheme 11. Retrosynthetic analysis of Caulibugulones A-D

Scheme 10 shows the retrosynthetic analysis for the synthesis of **298, 301, 299** and **300**. Caulibugulone A and D (**298** and **301**) are the direct product of aminolysis of isoquinoline-5,8-dione (**302**) with methylamine and 2-aminoethanol respectively. In addition, Caulibugulone A (**298**) would be extended to Caulibugulone B (**299**) C (**300**) and E (**302**) by halogenation using NBS or NCS or imination.[134] The dione **309** could easily be synthesized from the 5,8-dihydroxyisoquinoline **313**.

The formation of protected 5,8-dihydroxyisoquinoline from corresponding alkynylaldehyde **314** would be the key step in this report. The alkynylaldehyde **314** would be accessed from Sonogashira cross coupling[136] of bromoaldehyde **317** with trimethylsilylacetylene followed by removal of trimethylsilyl group. 2-Bromo-3,6-*bis*(methoxymethoxy)benzaldehyde (**317**) was readily prepared by bromination, followed by MOM protection of 2,5-dihydroxybenzaldehyde in 82% yield over two steps.[127] The selection of the MOM group was designed to be easily tailored to provide isoquinoline-5,8-diol. Then, Sonogashira coupling of **317** with trimethylsilylacetylene in the presence of 4 mol% of $PdCl_2(PPh_3)_2$, 2 mol% of CuI provided the coupled product **318** as pale yellow oil in 90% yield. With compound **318** in hand, the reaction was proceeded with the trimethylsilyl (TMS) group, because we anticipated its removal after cyclization under K_2CO_3 in ethanol reaction condition.



Scheme. 12. Total synthesis of Caulibugulones A-D

The cyclization underwent smoothly with an excess of aqueous ammonia (27% ammonia in water), 2 equivalent of K_2CO_3, in ethanol under reflux conditions and gave the expected product 5,8-*bis*(methoxymethoxy)isoquinoline (**308**) in 84% yield. In a parallel study, we attempted the synthesis of **308** by Larock iminoannulation[137] *via* preparation of *tert*-butyl imine of **318**, followed by copper catalyzed cyclization, but this was unsuccessful. The completion of total synthesis Caulibugulones A (**298**) and D (**301**) is shown in Scheme 12, Compound **308** is further subjected to removal of the MOM group by treating with THF:H_2O:conc. HCl (6:2:1 ratio) with heating at 50 °C to afford the required isoquinoline-5,8-diol, which was further converted into isoquinoline-5,8-dione **309** by *in situ* oxidation. Unfortunately, the dione **309** has insufficient stability, the next step was proceeded after a water work up and sodium bicarbonate wash without further purification and isolation of **309**. This observation is consistant with the previous literature reports on difficulties of isolating and characterizing of **309**.[134, 135] Therefore, crude compound **309** is directly subjected to aminolysis[138] using 3 equiv. of methylamine (33 wt% in

ethanol). After complete conversion as monitored by TLC (1 h), the product was purified by column chromatography using silica gel to afford Caulibugulone A (**298**) in a yield of 82% over the two steps (Scheme 11). Caulibugulone D (**301**) was also synthesized with 80% yield from dione **309** by aminolysis with ethanolamine (2 equiv.) in DME. The structure of Caulibugulone D (**301**) was unambiguously confirmed by single crystal X-ray diffraction analysis,[141] the ORTEP of **301** is shown in Figure 15.

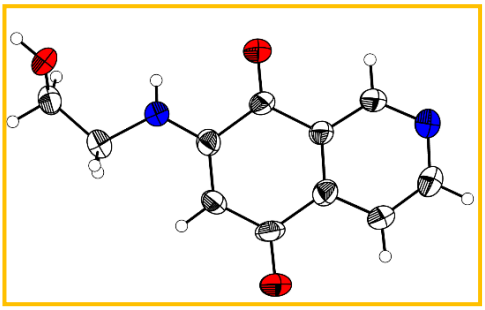
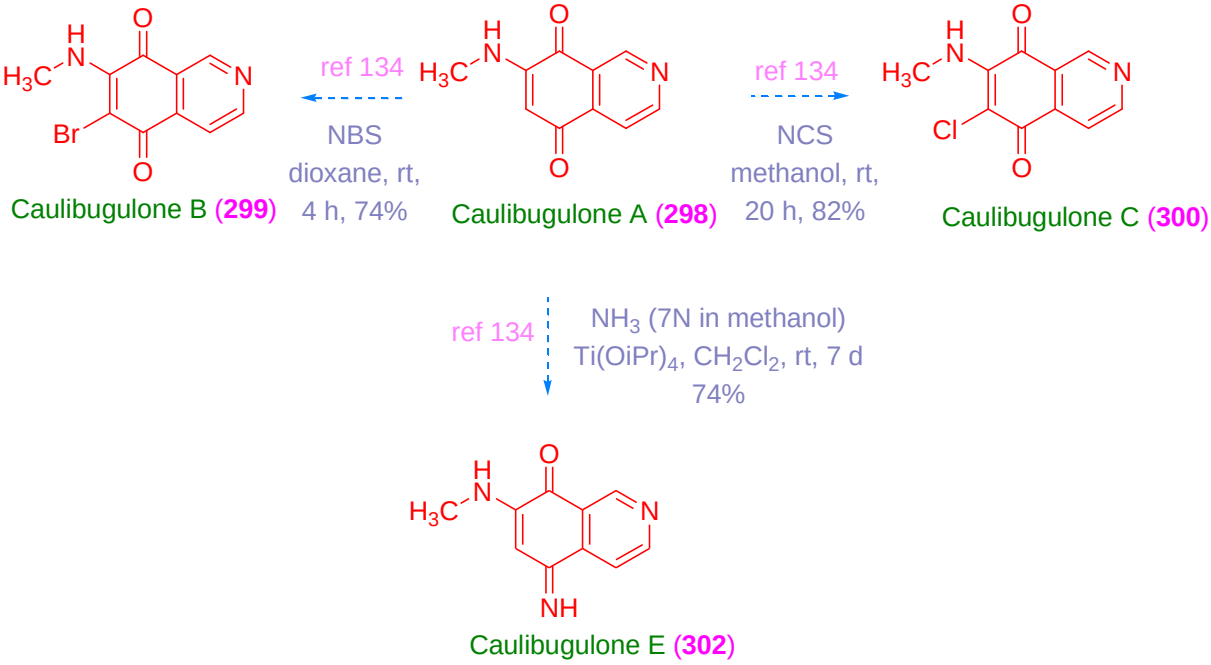


Fig 15. ORTEP diagram of Caulibugulone D (301).

The regioselective oxidative amination of **309** and formation of the major isomer is explained by the resonance stabilization of compound **309**.[133] C-7 position of isoquinoline-5,8-dione is more favorable for oxidative amination than C-6 and so that the required regioisomer was formed as a sole product. With Caulibugulone A in hand, it would be converted into Caulibugulone B (**299**), C (**300**) and E (**302**) potentially by following the previously reported studies by Wipf and co-workers (**Eq. 75**).[134]

Eq. 75. Formal synthesis of Caulibugulones B, C and E

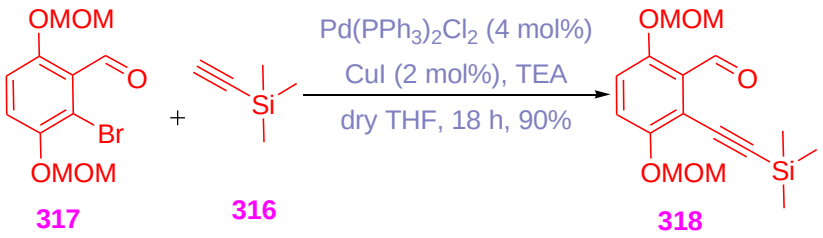


Thus, we have completed the total synthesis of Caulibugulones A and D with an overall yield of 62% and 60% respectively, the highest overall yields so far. NMR and high-resolution mass data of the synthesized compounds (**298** and **301**) are in full accordance with natural Caulibugulone A (**298**) and D (**301**). Spectroscopic data comparison is given in table 20 and table 21.

5.3. Experimental Section

Starting materials required for the total synthesis were prepared as experimental procedure reported in the literature.[127] The scheme for the preparation is given below. The required MOM ether (**317**) was prepared by following the literature and the same is shown in the chapter 4.[127]

Synthesis of 3,6-*bis*(methoxymethoxy)-2-(2-(trimethylsilyl)ethynyl) benzaldehyde (318):



An oven-dried 50 mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar is charged with 2-bromo-3,6-*bis*(methoxymethoxy)benzaldehyde (**317**) (1 g, 3.2 mmol), CuI (12 mg, 2 mol%) and $PdCl_2(PPh_3)_2$ (91 mg, 4 mol%), freshly distilled triethylamine (0.5 mL), dry THF (4 mL) and trimethylsilylacetylene (1.8 mL, 12.8 mmol) was added under nitrogen atmosphere and the resulting mixture was heated at 70 °C. After 18 h, the complete conversion of starting material was observed by TLC. The reaction mixture was cooled to room temperature, it was diluted with 50 mL of $CHCl_3$ and filtered through celite bed. Then, water (10 mL) was added to the diluted solution, which was then extracted with $CHCl_3$ (2 × 50 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum and purified by column chromatography on silica gel (eluent: 5% ethyl acetate in hexanes) to afford the 3,6-*bis*(methoxymethoxy)-2-(2-(trimethylsilyl)ethynyl)benzaldehyde (**318**) as a viscous oil 0.95 g. 20% ethyl acetate in hexanes).

Compound 318:

Yield: 90%

R_f 0.41 (20% EtOAc/hexanes)

Mp: Viscous Oil

IR (KBr) ν_{max} cm^{-1}: 2925, 2853, 2154, 1698, 1576, 1468, 1441, 1393, 1000, 922, 752

^{1}H NMR (400 MHz) δ: 10.59 (s, 1H), 7.25 (d, J = 9.2 Hz, 1H), 7.15 (d, J = 9.2 Hz, 1H), 5.22 (s, 2H), 5.21 (s, 2H), 3.56 (s, 3H), 3.51 (s, 3H), 0.29 (s, 9H)

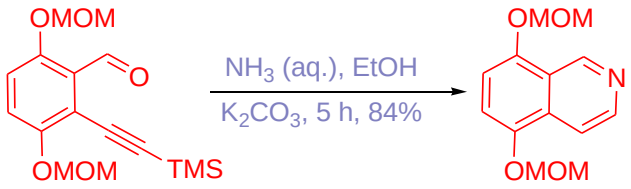
^{13}C NMR (100 MHz) δ: 190.4, 153.8, 152.9, 127.2, 122.6, 117.6, 117.3, 107.1 (aromatic C), 96.9, 96.0, 95.6, 56.4, 0.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{16}H_{22}O_5Si$: 345.1134 (M+Na)

Found: 345.1131

Synthesis of 5,8-*bis*(methoxymethoxy)isoquinoline (308):



318 308

An oven-dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 3,6-*bis*(methoxymethoxy)-2-(2-(trimethylsilyl)ethynyl)benzaldehyde (**318**) (100 mg, 0.31 mmol) and K_2CO_3 (128 mg, 0.93 mmol), 2 mL of ethanol and excess of aqueous ammonia (0.5 mL) (27% ammonia in water). The reaction mixture was allowed to stir under reflux for 2 h. The complete conversion of starting material was observed (TLC). Then, the reaction was allowed to cool to room temperature and extracted with $CHCl_3$ (2 × 10 mL). The organic layer was washed with 10 mL of water and 5 mL of brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes). The product was eluted in 10% eluent as a thick pale yellow liquid 65 mg.

Compound 308:

Yield: 84%

R_f 0.20 (20% EtOAc/hexanes)

Mp: yellow liquid

IR (KBr) ν_{max} cm^{-1}: 2954, 2827, 1625, 1575, 1491, 1453, 1375, 1273, 1110, 1024, 920, 821, 716

^1H NMR (400 MHz) δ: 9.63 (s, 1H), 8.59 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 6.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 5.38 (s, 2H), 5.34 (s, 2H), 3.56 (s, 3H), 3.55 (s, 3H)

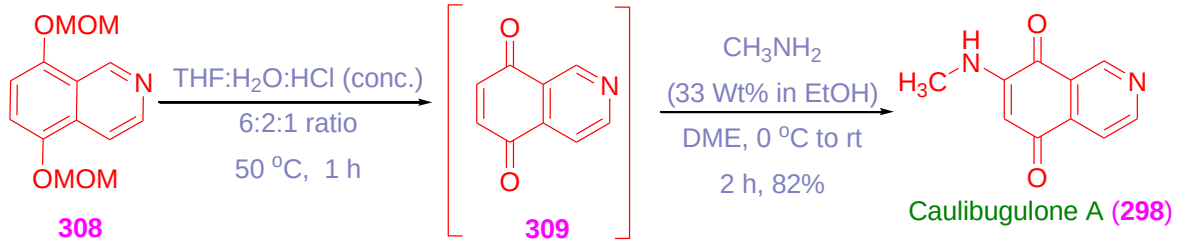
^{13}C NMR (100 MHz) δ: 148.3, 147.2, 146.5, 143.3, 129.5, 114.5, 112.6, 109.1 (aromatic C), 95.3, 95.1, 56.3, 56.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{13}H_{15}NO_4$: 250.1079 (M+H)

Found: 250.1075

Synthesis of Caulibugulone A



An oven-dried 10 mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 5,8-*bis*(methoxymethoxy)isoquinoline (**308**) (50 mg, 0.20 mmol) in 1 mL THF. Solution of THF, H_2O and conc. HCl (6:2:1 ratio) (1 mL) was added dropwisely to the reaction mixture. Then reaction mixture was allowed to stir at 50 °C for 2 h. The reaction mass turned in dark yellow color after 30 min. The complete conversion observed by TLC. The solvent THF was removed under reduced pressure. The resultant residue was extracted with ethyl acetate (2 × 10 mL), washed with saturated sodium bicarbonate solution, water,

brine and concentrated under reduced pressure. This crude material (red color residue) was then taken for next step without further purification. The residue was diluted with 2 mL of 1,2-dimethoxymethane (1,2-DME). The reaction mixture was then cooled to 0 °C and 33 wt. % absolute ethanolic solution of methylamine (0.6 mL, 0.06 mmol) was added dropwise. Then it was allowed to stir at room temperature. After 2h complete conversion was observed in TLC. After removing the solvent under reduced pressure, the reaction mixture was poured in 10 mL of water and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with water (10 mL) and brine (5 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: 20% ethyl acetate in hexanes). The product was eluted in 20% eluent as a red solid (31 mg).

Compound 298:

Yield: 82%

R_f 0.37 (20% EtOAc/hexanes)

Mp: 218-220 °C

IR (KBr) ν_{max} cm^{-1}: 3371, 2958, 2922, 2852, 2362, 1733, 1683, 1603, 1585, 1362, 1261 1078, 797

^{1}H NMR (400 MHz) δ: 9.19 (s, 1H), 8.94 (d, J = 5.0 Hz, 1H), 7.84 (d, J = 5.0 Hz, 1H), 6.02 (bs, 1H), 5.75 (s, 1H), 2.89 (d, J = 5.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 181.2, 180.9, 156.3, 148.8, 147.9, 139.3, 124.2, 119.0, 101.2 (aromatic C), 29.2 (aliphatic C)

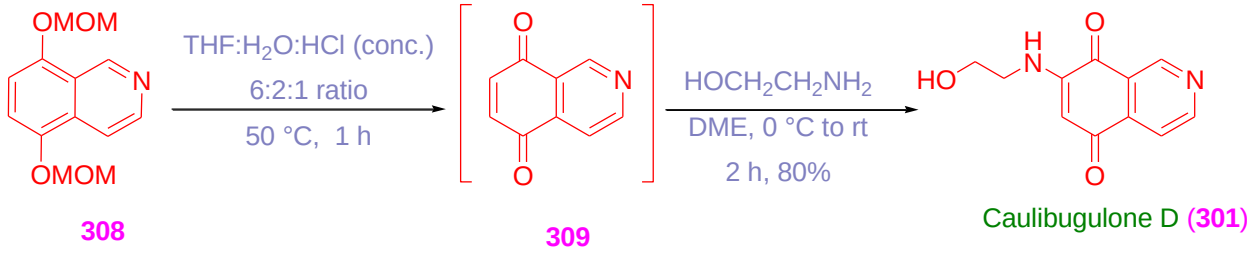
HRMS (ESI-MS):

Anal. calcd. for $C_{10}H_8N_2O_2$: 189.0664 (M+H)

Found: 189.0661

R_f value and other spectroscopic properties were found to be identical with the Caulibugulone A (**298**) reported earlier.[133-135]

Synthesis of Caulibugulone D



308 309 Caulibugulone D (301)

Same experimental protocol as adopted in the synthesis of Caulibugulone A (**298**) was followed. To a solution of THF, H_2O and conc. HCl (6:2:1 ratio) (1 mL), 5,8-*bis*(methoxymethoxy)isoquinoline (**308**) (50 mg, 0.20 mmol) in 1 mL THF was added dropwise. Resulting residue was diluted with 2 mL of 1,2-dimethoxymethane. The reaction mixture was then cooled to 0 °C and 2-aminoethanol (36 mg, 0.60 mmol) in 1 mL of 1,2-DME was added dropwise. Then it was allowed to stir at room temperature. After 2h, complete conversion was observed in TLC. After removing the solvent in reduced pressure, the reaction mixture was poured in 10 mL of water and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with water (10 mL) and brine (5 mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: 40% ethyl acetate in hexanes). The product was eluted in 40% eluent as an orange solid (35 mg).

Compound 301:

Yield:	80%
R_f	0.42 (5% methanol in EtOAc)
Mp:	180-182 ˚C
IR (KBr) ν_{max} cm^{-1}:	3312, 3193, 3015, 2973, 1689, 1633, 1594, 1561, 1524, 1354, 1327, 1101, 991, 753
^{1}H NMR (400 MHz) δ:	9.16 (s, 1H), 8.97 (d, J = 5.0 Hz, 1H), 7.81 (d, J = 5.0 Hz, 1H), 6.57 (bs, 1H), 5.83 (s, 1H), 3.71 (t, J = 5.5 Hz, 2H), 3.31 (dt, J = 5.0, 5.5 Hz, 2H)
^{13}C NMR (100 MHz) δ:	182.3, 181.5, 156.9, 149.6, 148.2, 140.0, 125.5, 119.2, 101.4 (aromatic C), 59.7, 45.3 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{11}H_{10}N_2O_3$: 219.0769 (M+H)

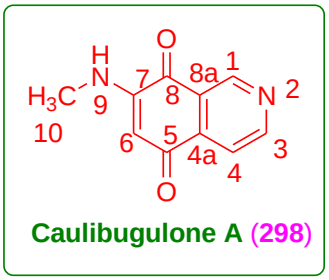
Found: 219.0768

R_f value and other spectroscopic properties were found to be identical with the Caulibugulone D (**301**) reported earlier.[133-135]

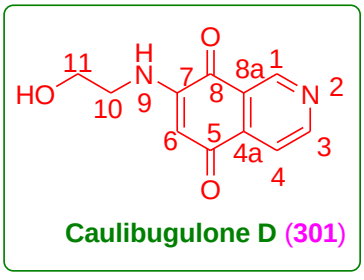
Table 19. Crystal data and structure refinement for 301.

Identification code	**301**	
Empirical formula	$C_{11}H_{10}N_2O_3$	
Formula weight	218.21	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 4.054(4) Å	α = 101.949(15)°.
	b = 10.691(10) Å	β = 90.025(16)°.
	c = 23.15(2) Å	γ = 100.646(16)°.
Volume	963.9(15) $Å^3$	
Z	4	
Density (calculated)	1.328 Mg/m^3	
Absorption coefficient	0.052 mm^{-1}	
F(000)	944	
Crystal size	0.20 x 0.20 x 0.15 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	8532	
Independent reflections	7852 [R(int) = 0.0617]	
Completeness to theta = 25.00°	100%	
Absorption correction	Empirical	
Max. and min. transmission	0.9750 and 0.9301	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7945 / 0 / 540	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0782, wR2 = 0.2190	
R indices (all data)	R1 = 0.1784, wR2 = 0.2604	
Extinction coefficient	0.00041 (10)	
Largest diff. peak and hole	0.234 and -0.152 e.$Å^{-3}$	
CCDC number	**1026827**	

Table 20. ^{1}H NMR Chemical shift (in ppm); spectroscopic data comparison of Caulibugulone A **(298)** and D **(301)**



Caulibugulone A (298)



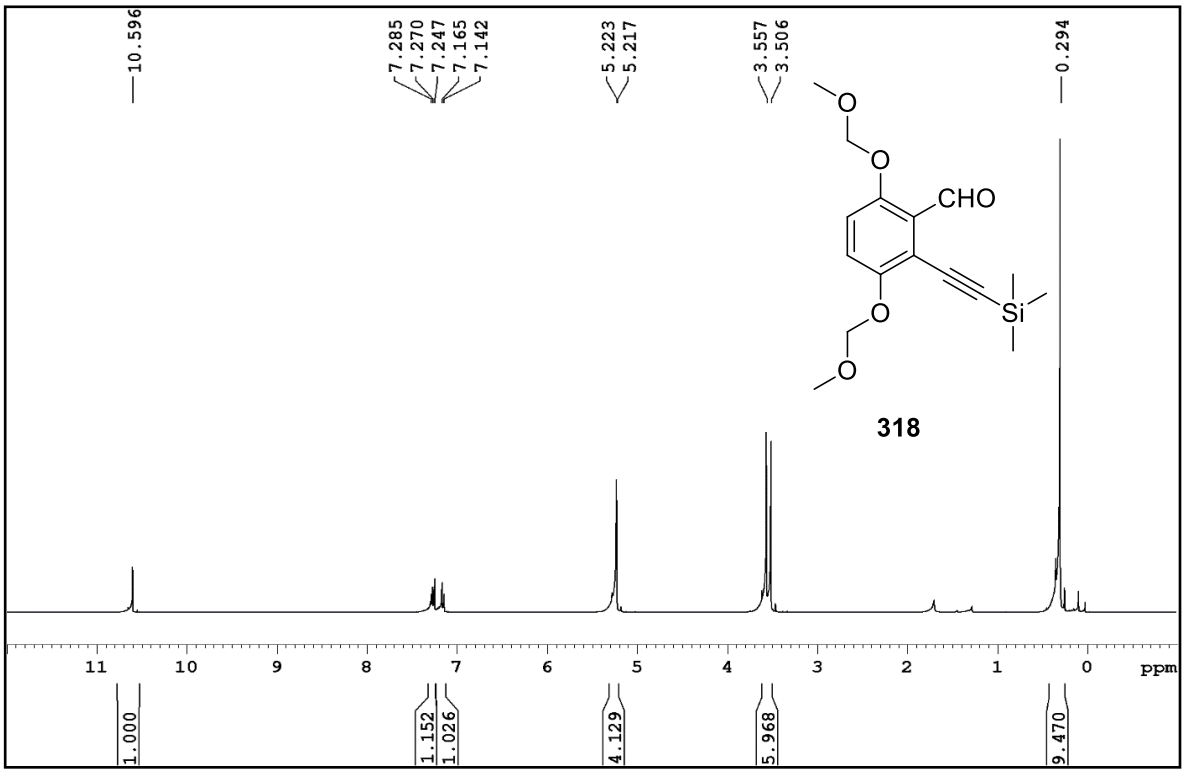
Caulibugulone D (301)

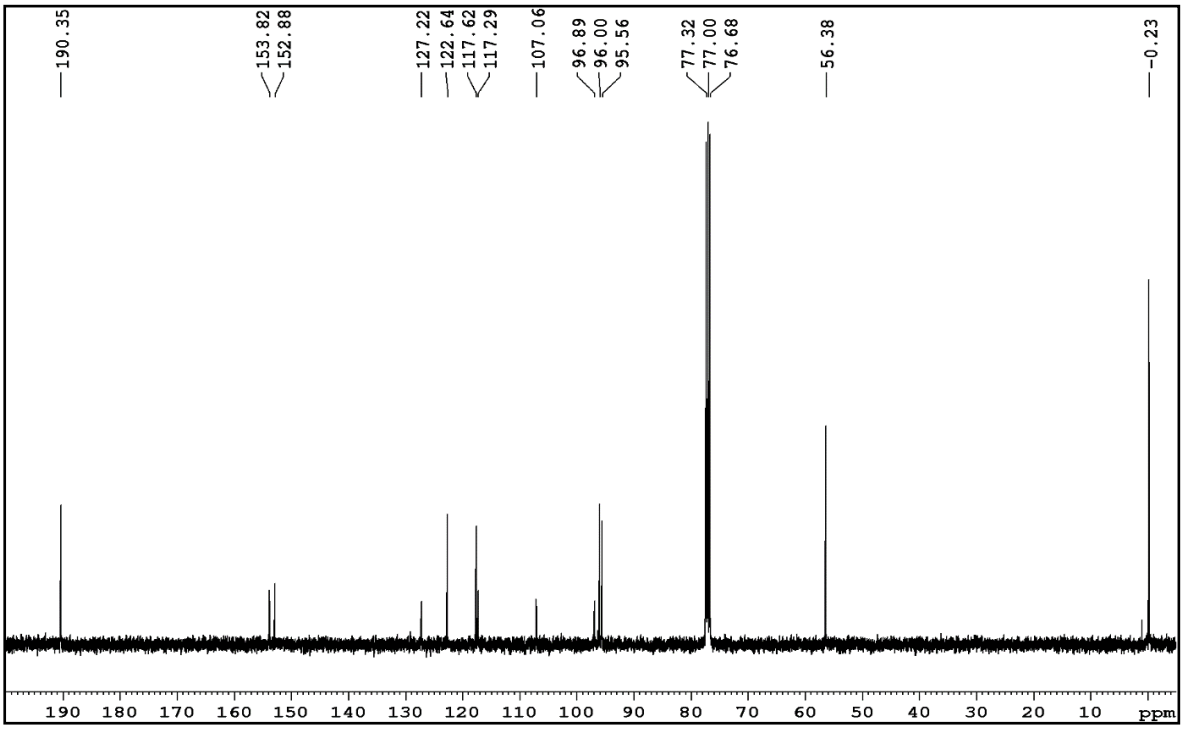
No	Caulibugulone A (Reported by Miranda *et al.*)[142] ^{1}H NMR (500 MHz, $CDCl_3$)	Caulibugulone A (298) (Our Sample) ^{1}H NMR (500 MHz, $CDCl_3$)	Caulibugulone D (Reported by Gustafson *et al.*)[130] ^{1}H NMR (500 MHz, CD_3CN)	Caulibugulone D (301) (Our Sample) ^{1}H NMR (500 MHz, CD_3CN)
1	9.19 (s)	9.19 (s)	9.17 (s)	9.16 (s)
3	8.94 (d, *J* = 5.0 Hz)	8.94 (d, *J* = 5.0 Hz)	8.97 (d, *J* = 5.0 Hz)	8.97 (d, *J* = 5.0 Hz)
4	7.85 (d, *J* = 5.0 Hz)	7.84 (d, *J* = 5.0 Hz)	7.81 (d, *J* = 5.0 Hz)	7.81 (d, *J* = 5.0 Hz)
6	5.75 (s)	5.75 (s)	5.84 (s)	5.83 (s)
9 (*NH*)	6.05 (bs)	6.02 (bs)	6.32 (bs)	6.57 (bs)
10	2.90 (d, *J* = 5.0 Hz)	2.89 (d, *J* = 5.0 Hz)	3.37 (dt, *J* = 5.0, 5.5 Hz)	3.31 (dt, *J* = 5.0, 5.5 Hz)
11	-	-	3.71 (t, *J* = 5.5)	3.71 (t, *J* = 5.5 Hz)

Table 21. ^{13}CNMR Chemical Shift (in ppm); spectroscopic data comparison of Caulibugulone A **(298)** and D **(301)**

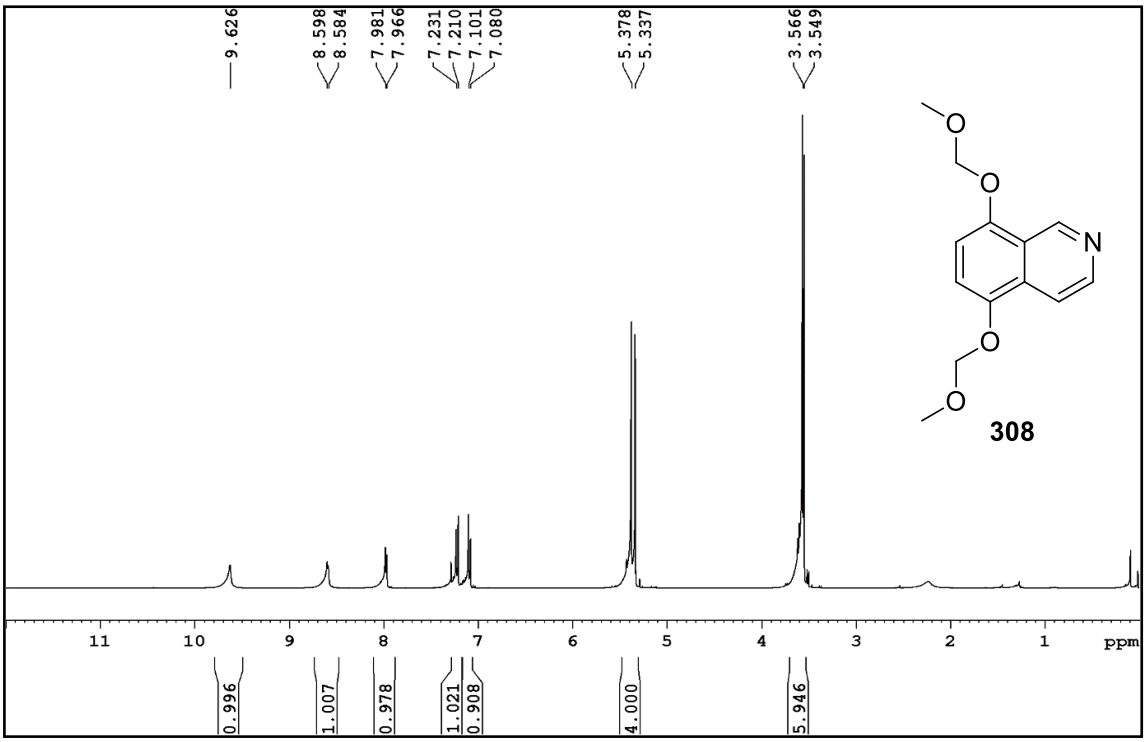
No	Caulibugulone A (Reported by Miranda *et al.*)[142] ^{13}C NMR (125 MHz, $CDCl_3$)	Caulibugulone A (298) (Our Sample) ^{13}C NMR (125 MHz, $CDCl_3$)	Caulibugulone D (Reported by Gustafson *et al.*)[130] ^{13}C NMR (125 MHz, CD_3CN)	Caulibugulone D (301) (Our Sample) ^{13}C NMR (125 MHz, CD_3CN)
1	147.9	147.9	148.3	148.2
3	156.3	156.3	156.9	156.9
4	119.0	119.0	119.3	119.2
4a	139.3	139.3	140.1	140.0
5	180.9	180.9	181.5	181.5
6	101.2	101.2	101.0	101.4
7	148.8	148.8	149.6	149.6
8	181.2	181.2	182.2	182.3
8a	124.4	124.2	125.6	125.5
10	29.2	29.2	45.2	45.3
11	-	-	59.7	59.7

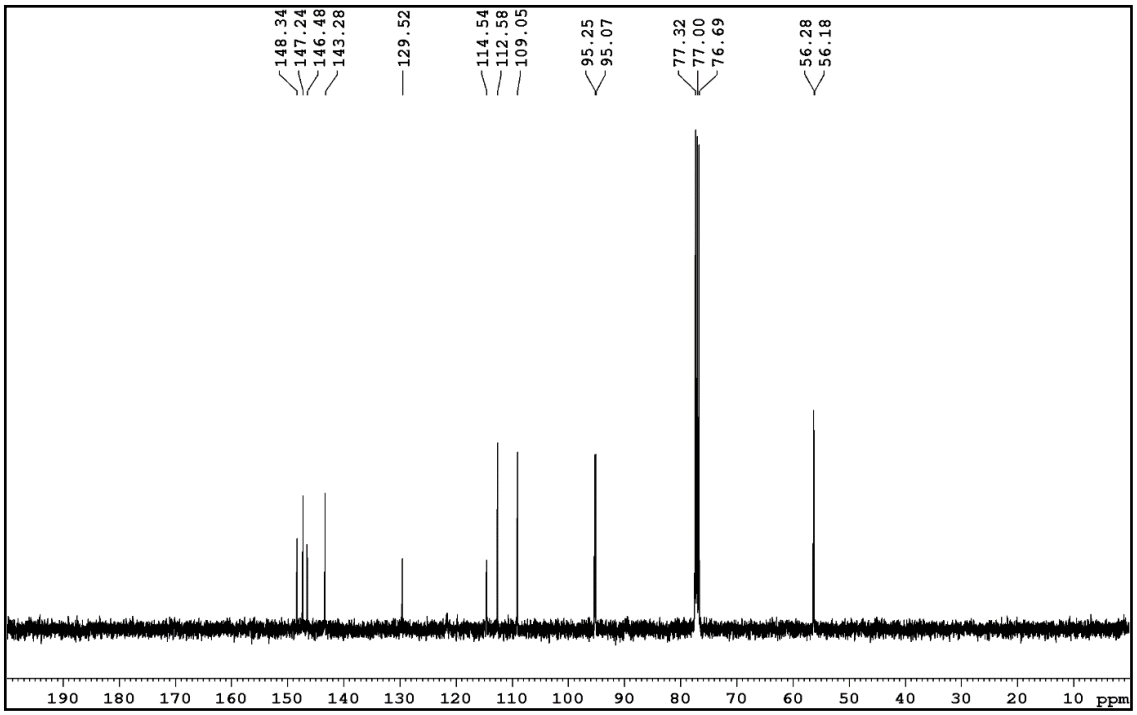
Spectra No. 16. ^{1}H and ^{13}C spectra of Compound 318



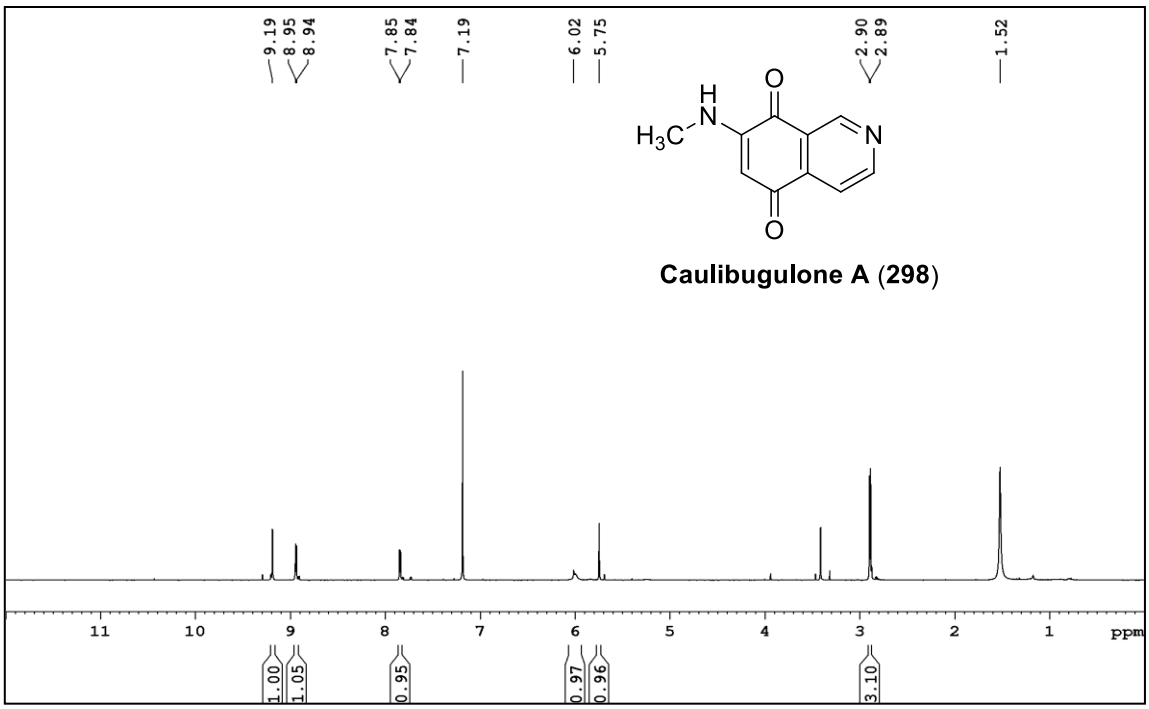


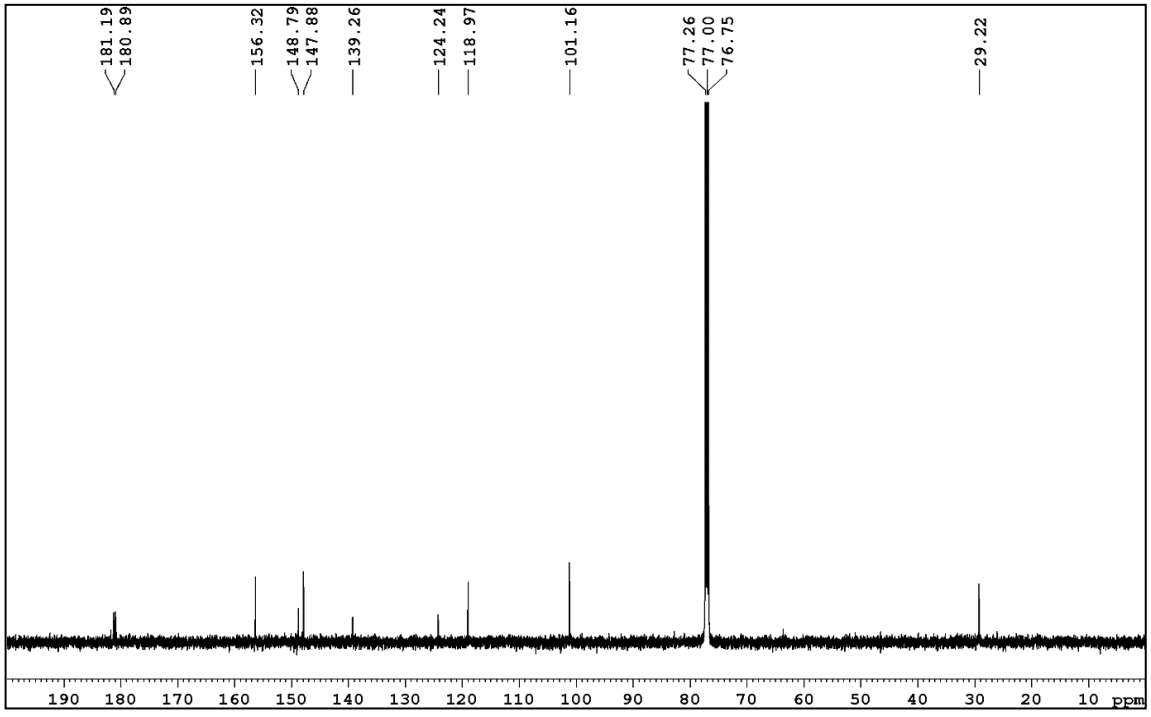
Spectra No. 17. ^{1}H and ^{13}C spectra of Compound 308



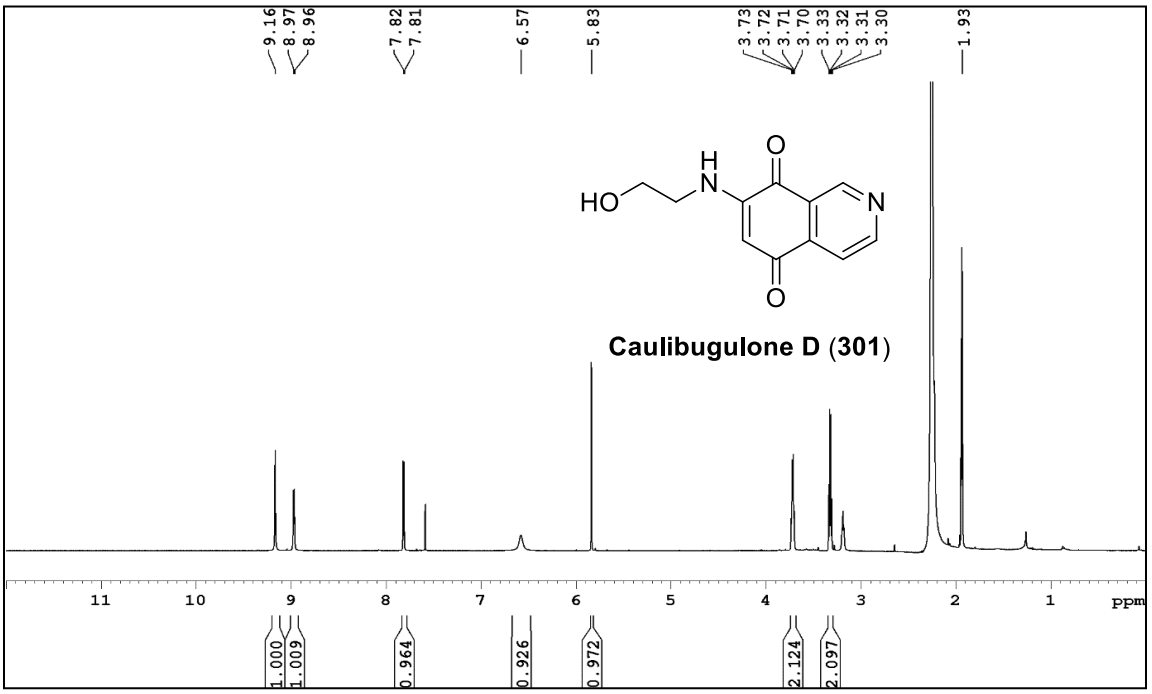


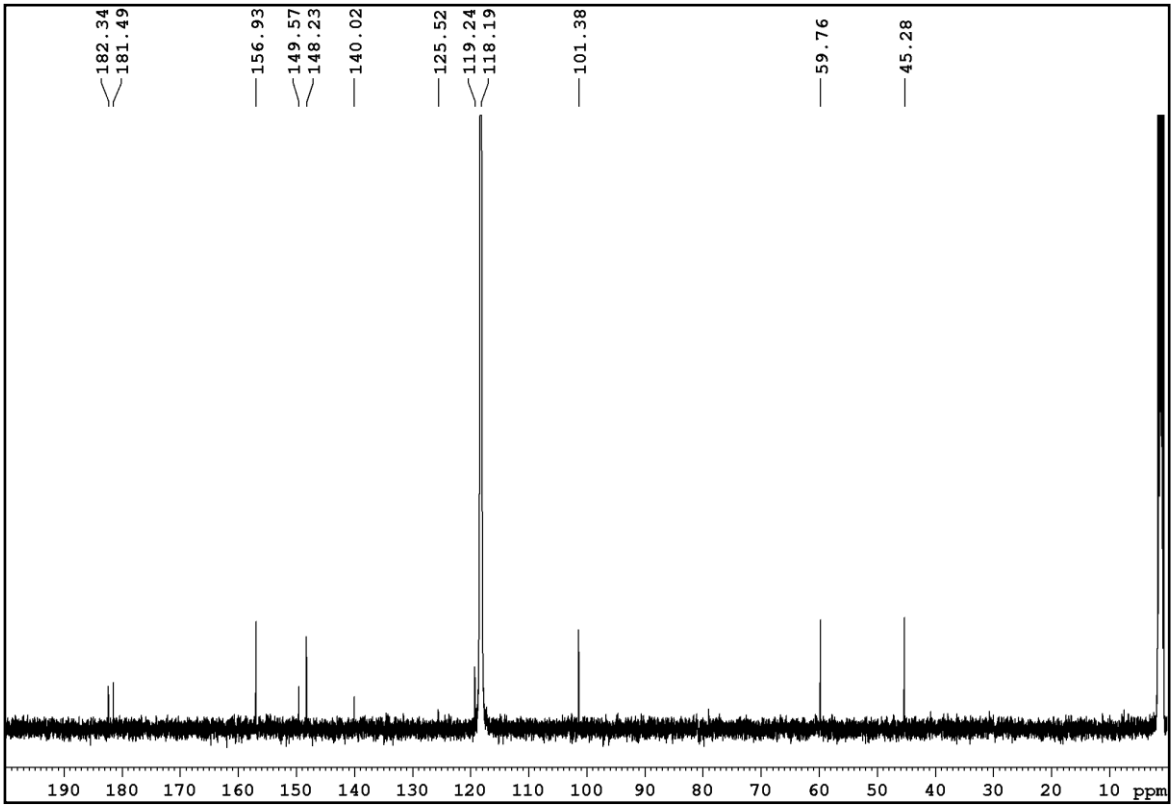
Spectra No. 18: ^{1}H and ^{13}C spectra of Compound 298





Spectra No. 19. ^{1}H and ^{13}C spectra of Compound 301





5.4. Conclusions

In this chapter, we have disclosed a concise synthesis of Caulibugulones A (**298**) and D (**301**) *via* three steps with overall yield of 62% and 60%, respectively.

Noteworthy features of this synthesis include;

(a) the effective preparation of isoquinoline-5,8-diol core *via* ammonia mediated iminoannulation,

(b) *in situ* oxidation and regioselective oxidative amination,

(c) Generally excellent yield, (d) over all operational simplicity,

(e) Caulibugulones B, C and E (**299**, **300** and **302**) can easily be synthesized from Caulibugulone A (**298**) by following the literature procedure.

(f) The protocol presented herein potentially allows the preparation of biologically active Caulibugulones for further biological screening and evaluation.

5.5. References

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CHAPTER 6

Total synthesis of putative structure of the marine alkaloid Hyrtioerectine E

6.1. Introduction

The β–carboline core containing natural products possess interesting biological profiles[139] such as antimalarial and cytotoxic,[139b] antiviral,[139c] antimicrobial and topoisomerase-II inhibitors,[139d-e] central nervous system, their affinity with benzodiazepine receptors, 5-HT2A and 5-HT2C receptors.[139f-h] From the past few decades, these core containing natural products have been isolated from the marine sources. Among them, Hyrtioerectines, (**320-322**, Fig. 16) which are extracted from the ethyl acetate fraction of red sea marine sponge *hyrtios* (family, Thorectidae, order Dictyoceratia) species, are biologically active compounds.[140]

In 2013, the structural elucidation of Hyrtioerectine E was reported by Youssef and coworkers (figure 16). The structure was elucidated from one-, two-dimensional NMR and high resolution mass spectral studies.[141] Despite compounds **320-322** (figure 16) showed antimicrobial, free radical scavenging and cancer growth inhibition activities, there is no reports on total synthesis. Considering the biological importance of Hyrtioerectine E (**321**),[141] we focused our attention towards the total synthesis. In the course of our ongoing interest on the total synthesis of biologically active alkaloids,[142] specifically total synthesis of marine alkaloids using alkynylaldehyde annulation as key step (Chapter 4 and Chapter 5), in this chapter, we demonstrated the first total synthesis of putative structure of the marine alkaloid Hyrtioerectine E. The strategy for the total synthesis of Hyrtioerectine E is based on the retrosynthetic approach as depicted in Scheme 13. The total synthesis was designed as intermolecular iminoannulation followed by removal of protecting groups. The key step was carried out by preparing corresponding imine (**326**) and internal alkyne (**331**). The similar annulations play a vital role in the synthesis of biologically active molecules.[143] To the best of our knowledge, there are no reports on the total synthesis of Hyrtioerectines.

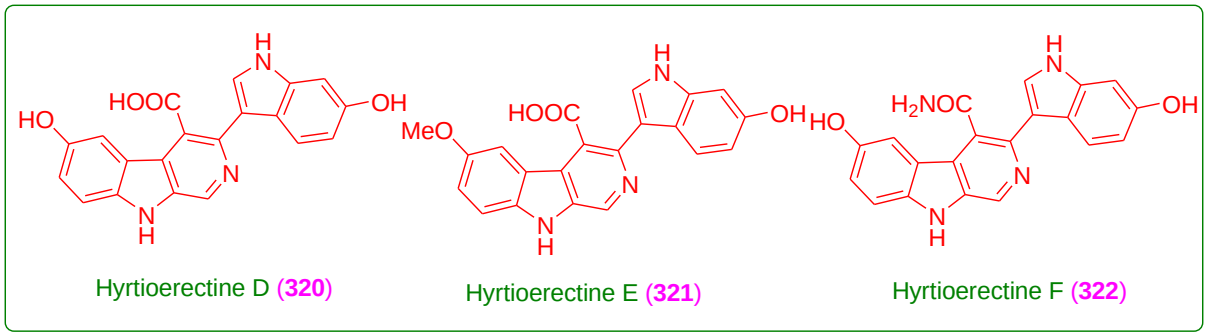
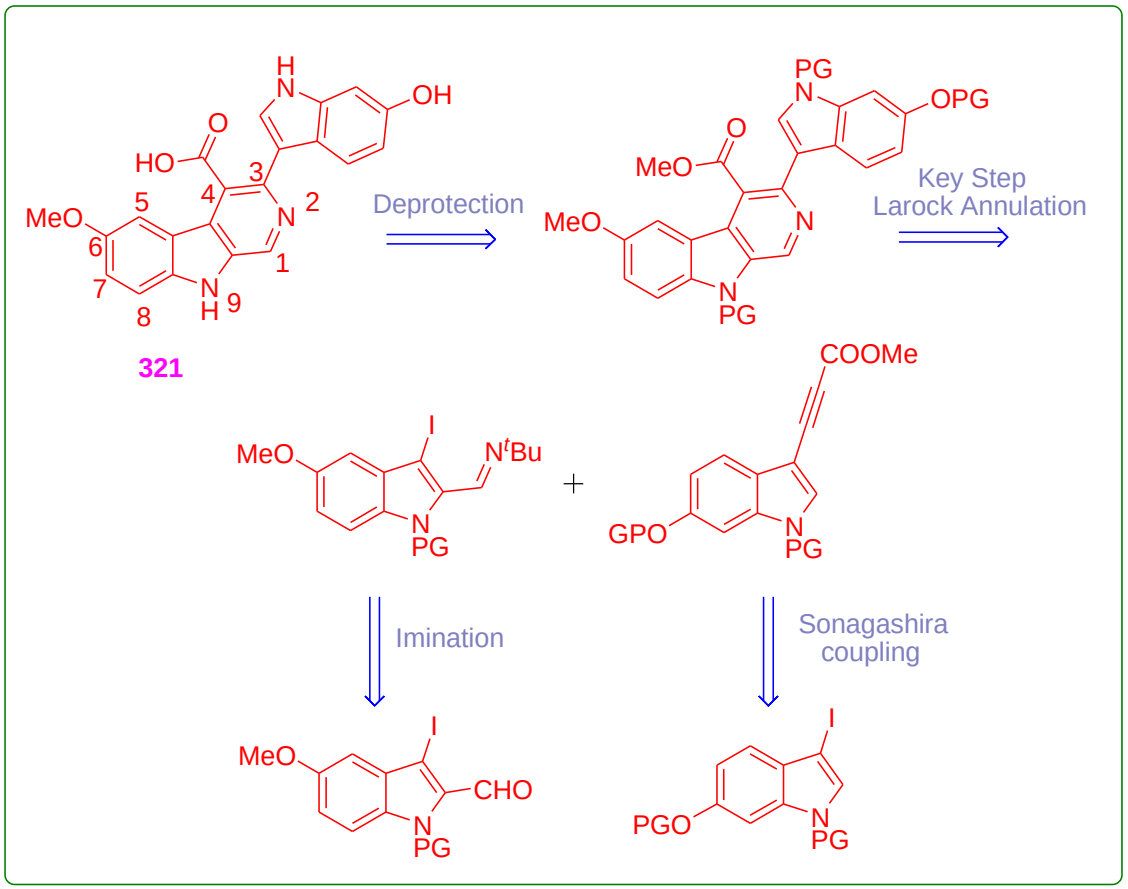


Fig. 16. Structures of marine alkaloids Hyrtioerectines D-F

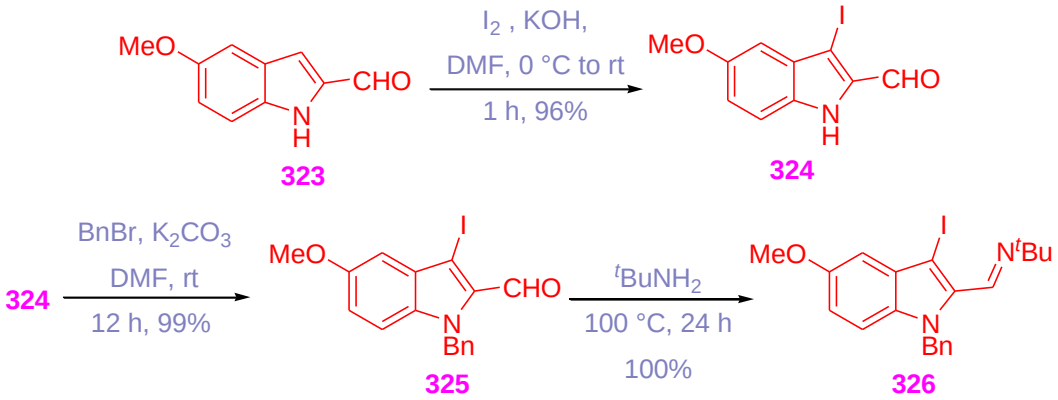
6.2. Total synthesis of Hyrtioerectine E

Our target molecule is a substituted *β*-carboline, containing a methoxy at C-6, carboxylic acid at C-4 and 6-hydroxyindole functionality at C-3. Hence, we envisioned a synthetic approach involving, intermolecular iminoannulation,[144] ester hydrolysis and deprotection. For this purpose, 3-iodoindoleimine **326** and methyl 3-(1*H*-indol-3-yl)propiolate (**331**) were taken as the starting precursor which would easily be prepared as depicted in scheme 14 and 15, respectively.



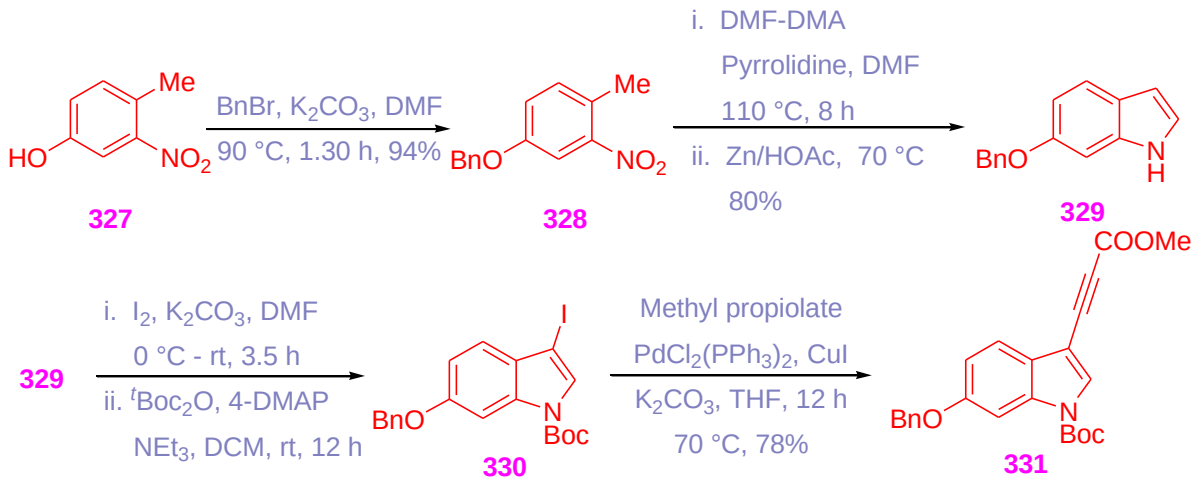
Scheme 13. Retrosynthetic analysis of putative Hyrtioerectine E

To construct β-carboline core, we synthesized the starting material **326.** As depicted in scheme 14, 5-methoxyindole-2-carboxaldehyde (**323**) was converted into iodo compound **324** by iodination. Then benzylation was carried out using benzyl bromide in DMF at room temperature stirring to achieve the product **325** with 99% yield. The imine of **325** was prepared by *tert*-butylimination using *tert*-butylamine in a sealed tube by heating at 100 °C for 24 h to get the required starting material **326** in 100% yield.



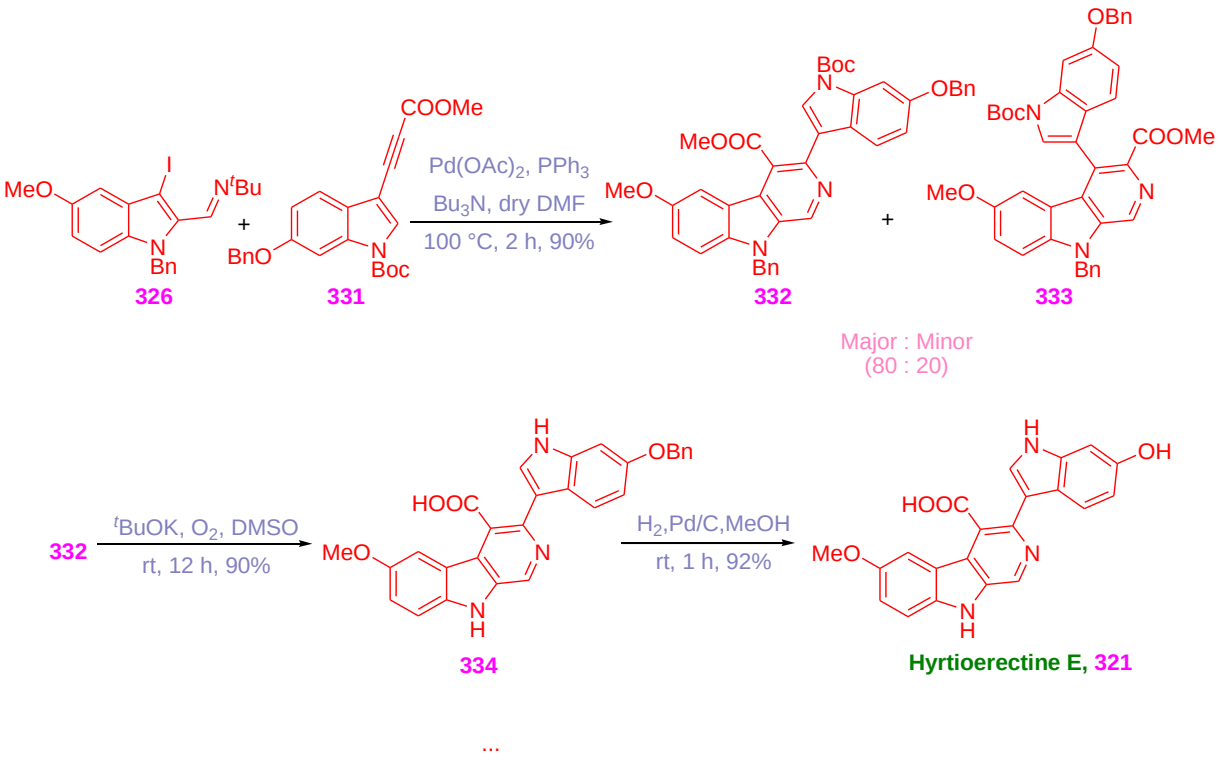
Scheme 14. Synthesis of starting material 326

Next we synthesized another coupling partner, internal alkyne **331**. Following a modified Leimgruber-Batcho indole synthesis,[145] we synthesized benzyl ether of 6-hydroxy indole. 4-methyl-3-nitrophenol was first protected with benzyl group, followed by condensation of the corresponding nitro toluene with *N*,*N*-dimethylformamide dimethyl acetal and pyrrolidine to give the intermediate **328**. Without further purification of **328**, reductive cyclization of **328** using Zn/AcOH were achieved in 80% yield. Fortunately, this step proceeded without elimination of the benzyl group. Then, the C-3 indole of **329** was iodinated using I_2 in DMF, followed by Boc protection using Boc anhydride, catalytic DMAP in DCM to afford **330**. Compound **330** is further subjected into Sonogashira coupling[136] using methyl propiolate as a alkyne, $Pd(PPh_3)Cl_2$ (5 mol%) as catalyst, CuI (2 mol%) as co catalyst and 1.5 equivalent of K_2CO_3 as base to give the coupled product **331** in 78% of yield.



Scheme 15: Synthesis of starting material 331

At this juncture, both fragments for key step in hand, we performed the iminoannulation using starting precursor **326** and **331**. In this case we got two spots (TLC), major product in this key step is our expected regioisomer, which was unambiguously confirmed by the single crystal X-ray diffraction analysis. The crystal structure of the compound **332** is shown in figure 17.



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Scheme 16. Key step and completion of total synthesis

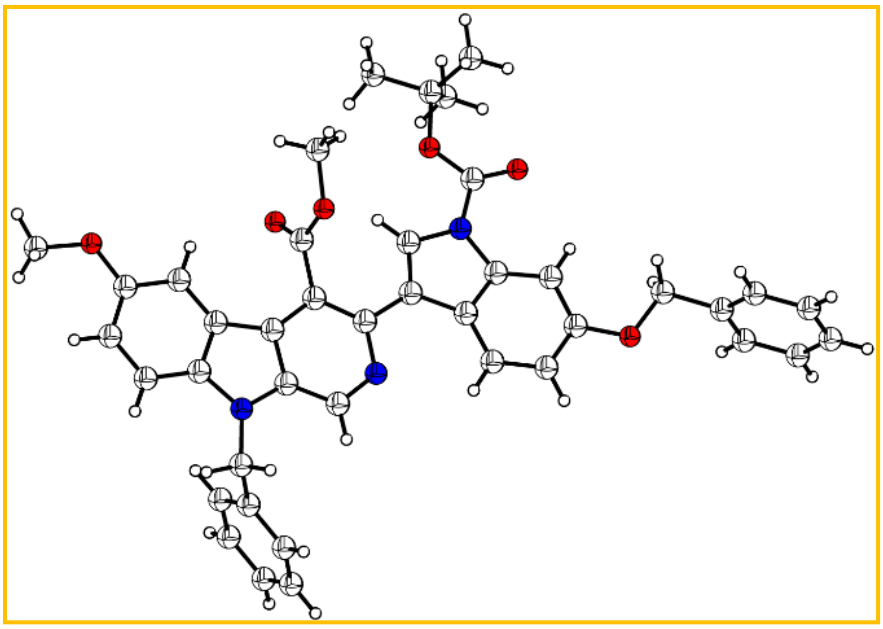


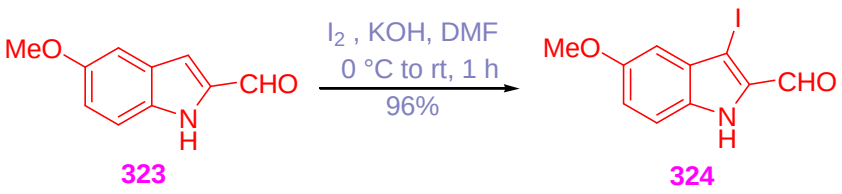
Fig. 17. X-Ray structure of 332

For the completion of the total synthesis we only need to remove the protecting groups from **332**, both benzyl, Boc followed by the saponification of ester. **332** was further subjected to deprotection of *N*-benzyl group using 5 equiv. KO^{t}Bu under O_2 baloon in DMSO as solvent and room temperature stirring gives the deprotected compound **334** in 90% yield. To our advantage after this reaction, yielded the product **334** by the removal of *N*-benzyl, *N*-Boc and saponification of methyl ester. After this step, deprotection of the *O*-benzyl is only needed for reaching the final target marine natural product Hyrtioerectine E (**321**). Finally the removal of *O*-benzyl group is performed by Pd/C, hydrogenation condition, the product formed smoothly in 1 h with yield of 92%.

6.3. Experimental Section

Starting materials required for the total synthesis of putative Hyrtioerectine E is given below.

3-Iodo-5-methoxy-1*H*-indole-2-carbaldehyde (324):



An ice-cooled solution of I_2 (1 g, 6.9 mmol) in DMF (10 mL) was added to a ice cold solution of 5-methoxy-1*H*-indole-2-carbaldehyde (1 g, 5.7 mmol) and powdered KOH (0.64 g, 11.4 mmol) in DMF (10 mL). After stirring at 0 °C - rt for 1 h, the mixture was poured into a solution of 28% NH_4OH (100 mL) and $NaHSO_3$ (1 g, 9.6 mmol) in water (1.5 L). The precipitates were separated by filtration to give the 3-iodo-5-methoxy-1*H*-indole-2-carbaldehyde (**324**) as brown solid, 1.65 g.

Compound 324:

Yield: 96%

R_f 0.17 (5% EtOAc/hexanes)

Mp: 180-182 °C

IR (KBr) ν_{max} cm^{-1}: 2944, 2856, 1725, 1555, 1481, 1675, 1263, 1210, 920, 821

^1H NMR (400 MHz) δ: 11.57 (s, 1H), 9.44-9.41 (m, 1H), 7.03-6.99 (m, 1H), 6.66-6.63 (m, 1H), 6.50-6.48 (m, 1H), 3.50 (s, 3H)

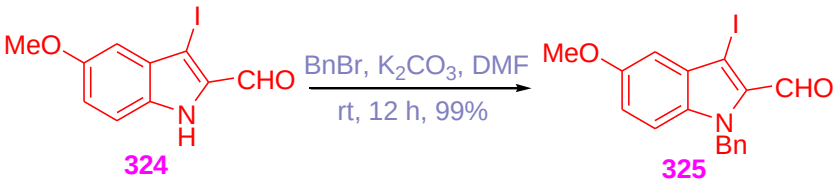
^{13}C NMR (100 MHz) δ: 182.4, 155.1, 133.7, 133.5, 130.3, 119.7, 114.5, 101.5, 70.5 (aromatic C), 55.3 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{10}H_8O_2NI$: 301.9672 (M+H)

Found: 301.9678.

Synthesis of 1-benzyl-3-iodo-5-methoxy-1*H*-indole-2-carbaldehyde (325):



324 325

A solution of 3-iodo-5-methoxy-1*H*-indole-2-carbaldehyde (**324**) (1 g, 3.3 mmol) in dry DMF (10 mL) was added slowly to a suspension of 3 equivalent of K_2CO_3 (1.4 g, 10.1 mmol) in dry DMF (5 mL) at room temperature. After complete addition, benzyl bromide (0.48 mL, 4 mmol) added drop wisely to the reaction mixture, stirred at room temperature for 10 h. After completion, the reaction was carefully quenched with water (50 mL), and the aqueous

layer was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (hexanes: ethylacetate = 99:1) afforded pure product 1-benzyl-3-iodo-5-methoxy-1*H*-indole-2-carbaldehyde (**325)** as a pale yellow solid.

Compound 325:

Yield: 99%

Mp: 178-180 °C

R_f 0.37 (5% EtOAc/hexanes)

IR (KBr) ν_{max} cm^{-1}: 2854, 2846, 1715, 1500, 1471, 1674, 1234, 1220, 1110, 879

^1H NMR (400 MHz) δ: 9.99 (d, J = 1.5 Hz, 1H) 7.29-7.25 (m, 4H), 7.12-7.10 (m, 3H), 6.95 (s, 1H), 5.83 (s, 2H), 3.92 (s, 3H)

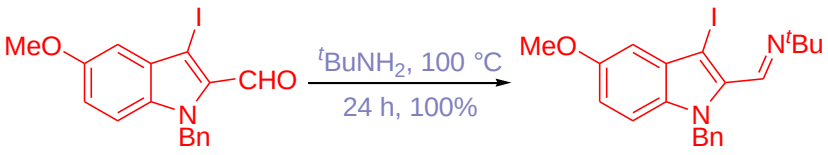
^{13}C NMR (100 MHz) δ: 184.1, 155.7, 137.3, 135.7, 131.1, 130.4, 128.6, 127.5, 126.5, 120.8, 112.5, 102.7, 75.3 (aromatic C), 55.7, 48.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{17}H_{14}O_2NI$: 413.9967 (M+Na)

Found: 413.9961.

Synthesis of *N*-((1-benzyl-3-iodo-5-methoxy-1*H*-indol-2-yl)methylene)-2-methylpropan-2 amine (326):



325 326

To 1-benzyl-3-iodo-5-methoxy-1*H*-indole-2-carbaldehyde (0.50 g, 1.3 mmol) was added *tert*-butylamine (2.6 mL, 2mL/mmol). The mixture was flushed with Nitrogen and the vial was carefully sealed. The reaction mixture was stirred at 100 °C for 12 h, diluted with ether, and dried over anhydrous Na_2SO_4. Resulting solution was dried under high vacuum to afford the imine **326** as a yellow solid 0.57 g.

Compound 326:

Yield: 100%

Mp: 192-194 ˚C

R_f 0.60 (5% EtOAc/hexanes)

IR (KBr) ν_{max} cm^{-1}: 2746, 1635, 1490, 1461, 1576, 1334, 1210, 1105, 650

^1H NMR (400 MHz) δ: 8.46 (s 1H), 7.22-7.19 (m, 4H), 7.04-7.03 (m, 2H), 6.94-6.90 (m, 2H), 6.03 (s, 2H), 3.89 (s, 3H), 1.22 (s, 9H)

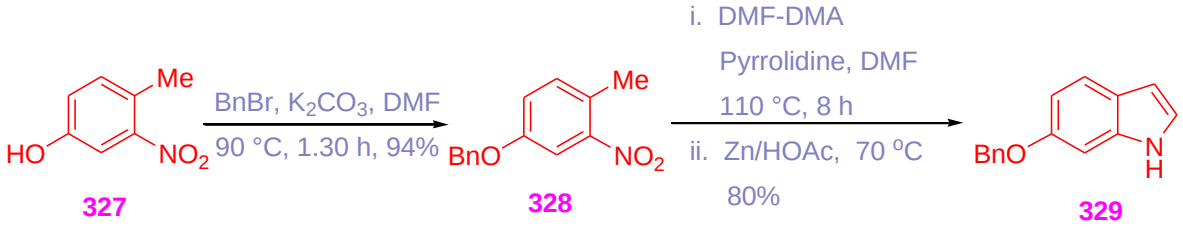
^{13}C NMR (100 MHz) δ: 155.1, 148.7, 138.7, 134.8, 133.1, 130.5, 128.3, 126.8, 126.6, 116.2, 111.6, 102.6 (aromatic C), 58.2, 55.8, 48.2, 29.5 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{21}H_{23}ON_2I$: 447.0933 (M+H)

Found: 447.0928

Synthesis of 6-(Benzyloxy)-1*H*-indole (329):[145]



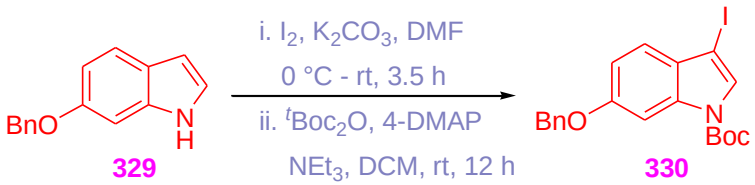
327 328 329

Step 1: K_2CO_3 (5.4 g, 39 mmol) was added to a solution of 4-methyl-3-nitrophenol **327** (2g, 13 mmol) in DMF (20 mL) and stirred for 10 minutes. Then, benzyl bromide (2 mL, 17 mmol) was added, stirred at 90 °C for 1.30 h under an nitrogen atmosphere, after cooling to room temperature the reaction mixture was quenched with water (50 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (eluted with hexanes/EtOAc = 19:1) to afford benzyl ether (3.92 g, 94%) as a white solid.

Step 2: To the solution of 4-(benzyloxy)-1-methyl-2-nitrobenzene (2 g, 7.7 mmol) in DMF (20 mL) were added *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (3.1 mL, 23.2 mmol) and pyrrolidine (0.95 mL, 11.6 mmol). The mixture was stirred at 110 °C for 8 h then cooled, poured into EtOAc and washed with water. The aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure to obtain deep red oil. This red oil is further subjected into the next step without further purification.

Step 3: To the above resulted deep red oil was added 95% HOAc (80 mL). It was heated to 70 °C, added zinc powder (6 g) pinch by pinch and stirred for 2 h. After cooling to room temperature, zinc powder is filtered through the filter paper and the excess of HOAc was removed under reduced pressure then water (200 mL) was added to the reaction mixture and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water, added water followed by Na_2CO_3 until gas evolution was over. The layers were separate, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The resulted brown mass was purified using column chromatography (eluted with hexanes/EtOAc = 19:1). Analytical data matches the reported one in the literature.[148]

Synthesis of *tert*-butyl 6-(benzyloxy)-3-iodo-1*H*-indole-1-carboxylate (330):



Step 1: A solution of I_2 (1.70 g, 6.7 mmol) in DMF (10 mL) was added to a ice cooled solution of 6-(benzyloxy)-1*H*-indole (1 g, 4.5 mmol) and powdered K_2CO_3 (3.1 g, 22.5 mmol) in DMF (5 mL). After stirring at 0 °C - rt for 3 h, the mixture was poured into cold water (200 mL). The precipitates were separated by filtration to give the 6-(benzyloxy)- 3-iodo-1*H*-indole.

Step 2: The crude 6-(benzyloxy)-3-iodo-1*H*-indole (1.5 g) was then dissolved in DCM (10 mL) and added triethylamine (2 mL), 4-(dimethylamino)pyridine (53 mg, 0.43 mmol) and di-*tert*-butyl dicarbonate (1.98 ml, 8.6 mmol) sequentially. The reaction was stirred at room temperature for 12 h, quenched with water (50 mL), extracted with DCM (3 × 50 mL) and concentrated *in vacuo*. Purification by column chromatography (eluted with hexanes/EtOAc = 1:99) afford **330,** 1.85 g.

Compound 330:

Yield: 93%

R_f 0.67 (5% EtOAc/hexanes)

Mp: 172-174 °C

IR (KBr) ν_{max} cm^{-1}: 2836, 1645, 1480, 1471, 1586, 1344, 1200, 1005, 715

^1H NMR (400 MHz) δ: 7.86 (s, 1H), 7.63 (s, 1H), 4.49 (dd, J = 7.0 & 2.0 Hz, 2H), 7.43-7.40 (m, 2H), 7.37-7.34 (m, 1H), 7.30-7.28 (m, 1H), 7.05-7.03 (m, 1H), 5.16 (s, 2H), 1.66 (s, 9H)

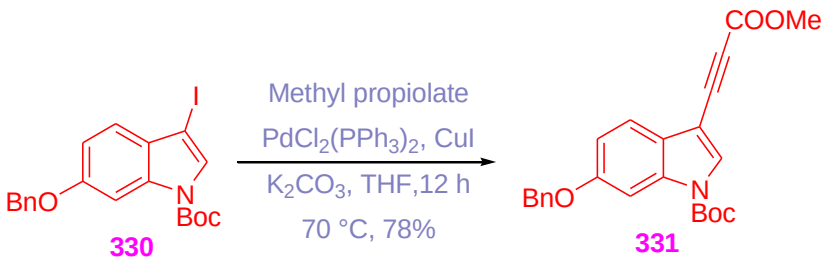
^{13}C NMR (100 MHz) δ: 157.8, 148.7, 136.9, 128.9, 128.6, 128.5, 128.0, 127.6 126.11, 122.0, 113.5, 100.1 (aromatic C), 84.2, 70.5, 65.2, 28.1 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{20}H_{20}NO_3I$: 472.0386 (M+Na)

Found: 472.0380

Synthesis of *tert*-Butyl 6-(benzyloxy)-3-(3-methoxy-3-oxoprop-1-yn-1-yl)-1*H*-indole-1-carboxylate (331):



To a solution of **330** (0.50 g, 1.1 mmol**)** in dry THF (10 mL) were added K_2CO_3 (1.10 g, 8 mmol), $Pd(PPh_3)_2Cl_2$ (39 mg, 0.056 mmol), CuI (11 mg, 0.058 mmol) and methyl propiolate (0.6 mL, 6.7 mmol) sequentially. It was sealed carefully under nitrogen atmosphere and stirred overnight at 70 °C. After cooling to room temperature, diluted with EtOAc (20 mL), filtered through celite bed, washed with water (2 × 20 mL) followed by brine solution and dried over Na_2SO_4. The solvent was evaporated under reduced pressure,

the brown mass obtained was column chromatographed (eluted with hexanes/EtOAc = 49:1) to afford **331** as a white solid 0.36 g.

Compound 331:

Yield: 78%

R_f 0.30 (5% EtOAc /hexanes)

Mp: 192-194 ˚C

IR (KBr) ν_{max} cm^{-1}: 2676, 1685, 1478, 1461, 1534, 1360, 1005, 735

^1H NMR (400 MHz) δ: 7.91 (s, 1H) 7.86 (s 1H), 7.62 (d, J = 8.50, 2H), 7.50-7.43 (m, 2H), 7.43-7.40 (m, 1H), 7.37-7.36 (m, 1H), 7.10-7.06 (m, 1H), 5.15 (s, 2H), 3.88 (s, 3H), 1.68 (s, 9H)

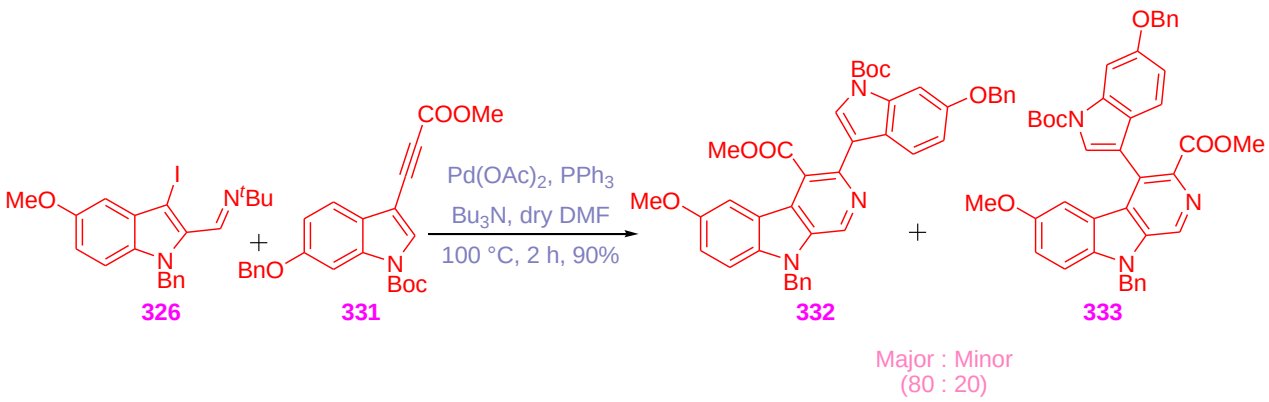
^{13}C NMR (100 MHz) δ: 157.9, 154.5, 148.6, 136.7, 135.6, 132.0, 128.5, 128.0, 127.6, 123.5, 120.6, 113.9, 100.5, 99.8 (aromatic C), 85.0, 84.1, 80.3, 70.4, 52.7, 28.0 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{24}H_{23}NO_5$: 428.1474 (M+Na)

Found: 428.1463

Synthesis of methyl 9-benzyl-3-(6-(benzyloxy)-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-6-methoxy-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (332):



To a solution of imine **326** (0.20 g, 0.45 mmol) in DMF (5 mL) were added the alkyne **333** (0.22 g, 0.54 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), Bu_3N (130 mg, 0.8 mmol) and PPh_3 (24 mg, 0.09 mmol), flushed with nitrogen, sealed carefully and stirred at 100 ˚C for 2 hours. After cooling to room temperature, diluted with EtOAc, washed with saturated NH_4Cl, filtered, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure and purified by column chromatography to afford **332** as yellow solid (0.22 g). (**332** was obtained when eluted with hexanes/EtOAc = 1:6, whereas **333** was eluted as yellow solid (0.054 g) with hexanes/EtOAc = 2:3), yield : 90%, ratio of **332**:**333** is 80:20.

Compound 332:

Yield: 90%

R_f 0.18 (30% EtOAc /hexanes)

Mp: 232-234 ˚C

IR (KBr) ν_{max} cm^{-1}: 2946, 2765, 1705, 1660, 1650, 1480, 1467, 1500, 1324, 1200, 1155, 790, 630

^{1}H NMR (400 MHz) δ: 8.99 (s, 1H), 7.96 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.70 (s, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.52-7.50 (m, 2H), 7.43-7.38 (m, 3H), 7.33-7.25 (m, 5H), 7.17-7.15 (m, 2H), 7.02 (dd, J = 8.7 & 2.2 Hz, 1H), 5.62 (s, 2H), 5.19 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 1.71 (s, 9H)

^{13}C NMR (100 MHz) δ: 169.6, 152.7, 154.3, 149.7, 139.9, 137.2, 137.1, 136.5, 136.1, 133.2, 129.0, 128.5, 128.0, 127.8, 127.6, 126.4, 125.8, 123.7, 123.3, 121.5, 120.9, 120.6, 120.1, 119.2, 113.2, 110.7, 105.4, 100.3 (aromatic C), 83.6, 55.9, 52.7, 47.1, 28.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{41}H_{37}N_3O_6$: 668.2761 (M+H)

Found: 668.2755

Compound 333:

Yield: 90%

R_f 0.82 (30% EtOAc /hexanes)

Mp: 246-248 ˚C

IR (KBr) ν_{max} cm^{-1}: 2956, 2735, 1710, 1650, 1460, 1367, 1314, 1190, 1157, 830, 670

^{1}H NMR (400 MHz) δ: 8.94 (s, 1H), 8.05 (s, 1H), 7.64 (s, 1H), 7.51-7.42 (m, 2H), 7.41-7.35 (m, 2H), 7.34-7.26 (m, 2H), 7.31-7.28 (m, 3H), 7.19 (d, J = 6.5 Hz, 2H), 7.15-7.09 (m, 2H), 6.92 (dd, J = 8.5 & 2.0 Hz, 1H), 6.62 (s, 1H), 5.66 (s, 2H), 5.19 (s, 2H), 3.82 (s, 3H), 3.38 (s, 3H), 1.69 (s, 9H)

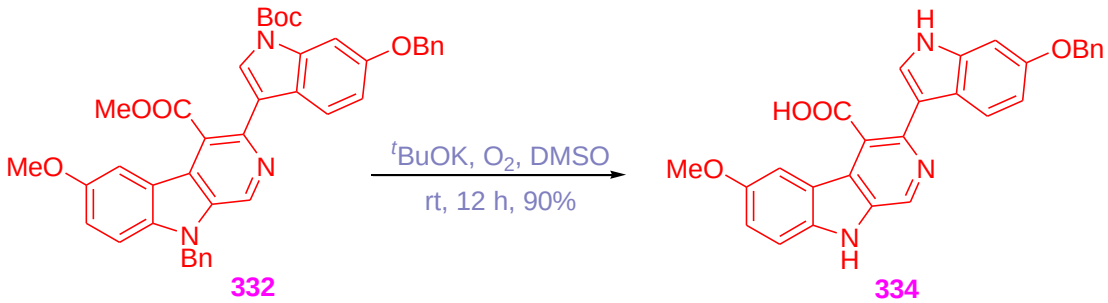
^{13}C NMR (100 MHz) δ: 166.9, 157.4, 154.2, 149.8, 138.2, 137.5, 137.1, 136.7, 135.9, 131.2, 129.1, 128.6, 128.1, 127.9 127.6, 127.5, 126.5, 126.4, 125.0, 124.1, 122.6, 121.7 120.7, 118.9, 117.0, 113.3, 110.6, 105.6, 100.8 (aromatic C). 83.9, 70.5, 55.2, 52.5, 47.3, 28.2 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{41}H_{37}N_3O_6$: 668.2761 (M+H)

Found: 668.2755

Synthesis of 3-(6-(benzyloxy)-1*H*-indol-3-yl)-6-methoxy-9*H*-pyrido[3,4-*b*] indole-4-carboxylic acid (334):



To a solution of **332** (50 mg, 0.07 mmol) in DMSO (1 mL), ^{t}BuOK (42 mg, 0.37 mmol) was added with stirring. After completion of addition, it was stirred under O_2 atmosphere (using

O_2 balloon) for 12 hours at room temperature. After completion of the reaction (TLC), was quenched with saturated ammonium chloride solution. The product was extracted with EtOAc (3 × 20 mL). The organic phase were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The product **334** was separated as yellow solid (31 mg).

Compound 334:

Yield: 90%

R_f 0.37 (10% methanol/EtOAc)

Mp: 256-258 ˚C

IR (KBr) ν_{max} cm^{-1}: 3410, 2946, 2810, 1620, 1569, 1470, 1337, 1305, 1180, 1134, 880, 600

^{1}H NMR (400 MHz) δ: 12.14 (s, 1H), 11.27 (bs, 1H), 8.99 (s, 1H), 8.58 (s, 1H), 8.34 (s, 1H), 7.88 (s, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.49-7.47 (m, 3H), 7.42 (t, J = 7.5 Hz, 2H), 7.37-7.32 (m, 2H), 6.78 (dd, J = 8.9 & 2.2 Hz, 1H), 5.20 (s, 2H), 3.83 (s, 3H)

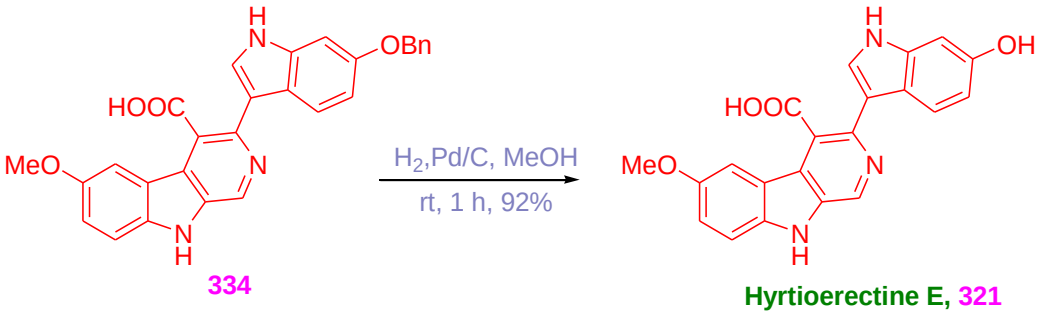
^{13}C NMR (100 MHz) δ: 168.8, 154.1, 144.8, 142.1 137.4, 137.1, 138.7, 134.4, 129.0, 128.9, 128.6 128.3, 128.1, 124.8, 123.5, 120.3, 119.7, 117.2, 113.8, 109.2, 107.2, 107.1, 101.2, 106.2 (aromatic C), 70.1, 56.0 (aliphatic C)

HRMS (ESI-MS):

Anal. calcd. for $C_{28}H_{21}N_3O_4$: 464.1610 (M+H)

Found: 464.1605

Completion of total synthesis and Synthesis of Hyrtioerectine E (321):



A solution of **334** (31 mg, 0.07 mmol) in methanol was added Pd/C pinch by pinch and stirred for 1 hour at room temperature. After completion of reaction, the reaction mass was filtered in celite bed, evaporated under reduced pressure and resulted brown mass was chromatographed (eluted with MeOH/EtOAc = 1:9) to afford pure Hyrtioerectine E **(321)** as yellow solid.

Compound 321:

Yield: 92%

R_f 0.30 (30% methanol/EtOAc)

Mp: 258-260 ˚C

IR (KBr) ν_{max} cm^{-1}: 3548, 3008, 2985, 1717, 1622, 1265, 1126, 978, 895

^{1}H NMR (400 MHz) δ: 8.73 (s, 1H), 8.44 (s, 1H), 8.11 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.2 Hz, 1H) 7.48 (d, J = 8.9 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.21 (dd, J = 8.9 & 2.0 Hz, 1H), 6.44 (dd, J = 8.7 & 2.0 Hz, 1H), 3.84 (s, 3H)

^{13}C NMR (100 MHz) δ: 174.8, 164.0, 161.9, 155.1, 144.6, 142.9, 138.2, 138.1, 138.0, 137.9, 133.0, 132.9, 131.9, 126.1, 121.4, 120.4, 113.2, 110.9, 108.3, 106.7 (aromatic C), 55.8 (aliphatic C)

HRMS (ESI-MS):

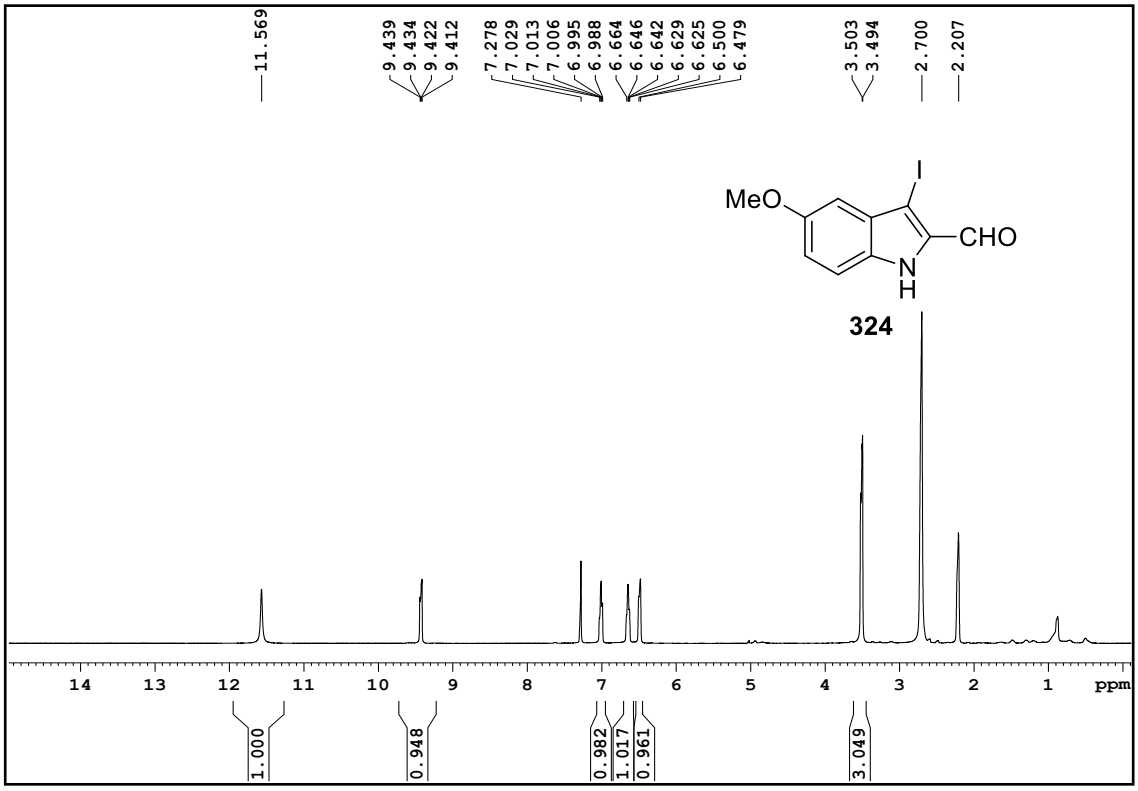
Anal. calcd. for $C_{21}H_{15}N_3O_4$: 396.0960 (M+H)

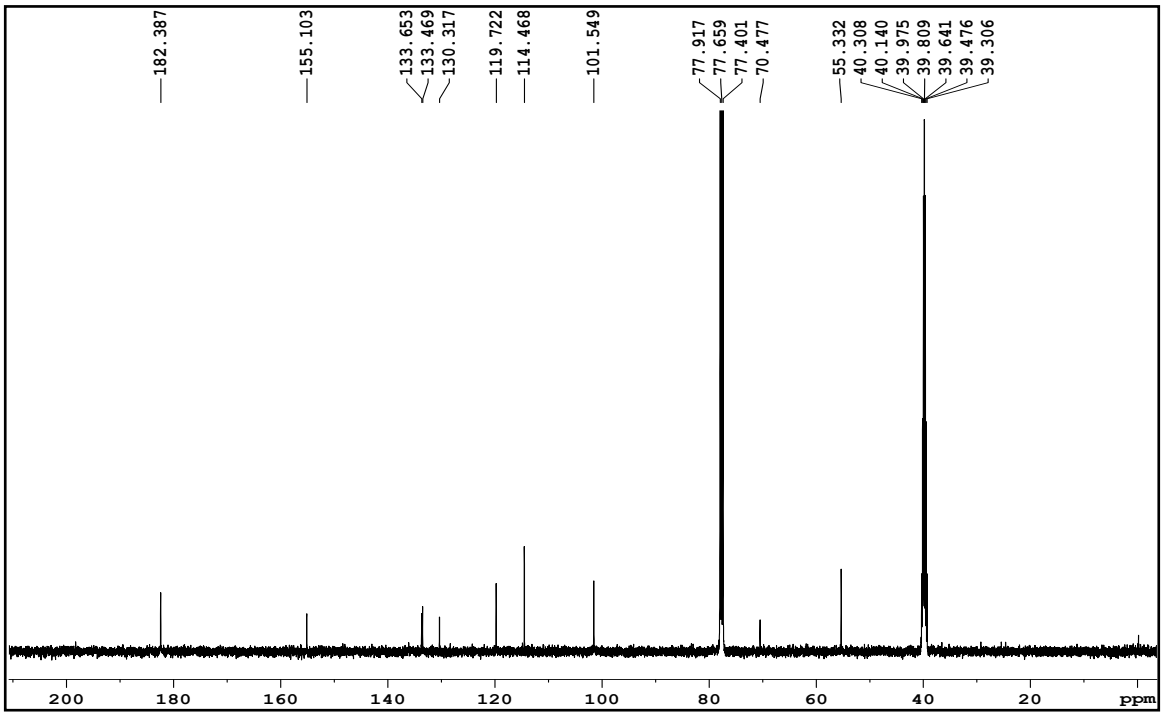
Found: 396.0955

Table 22. Crystal data and structure refinement for 332

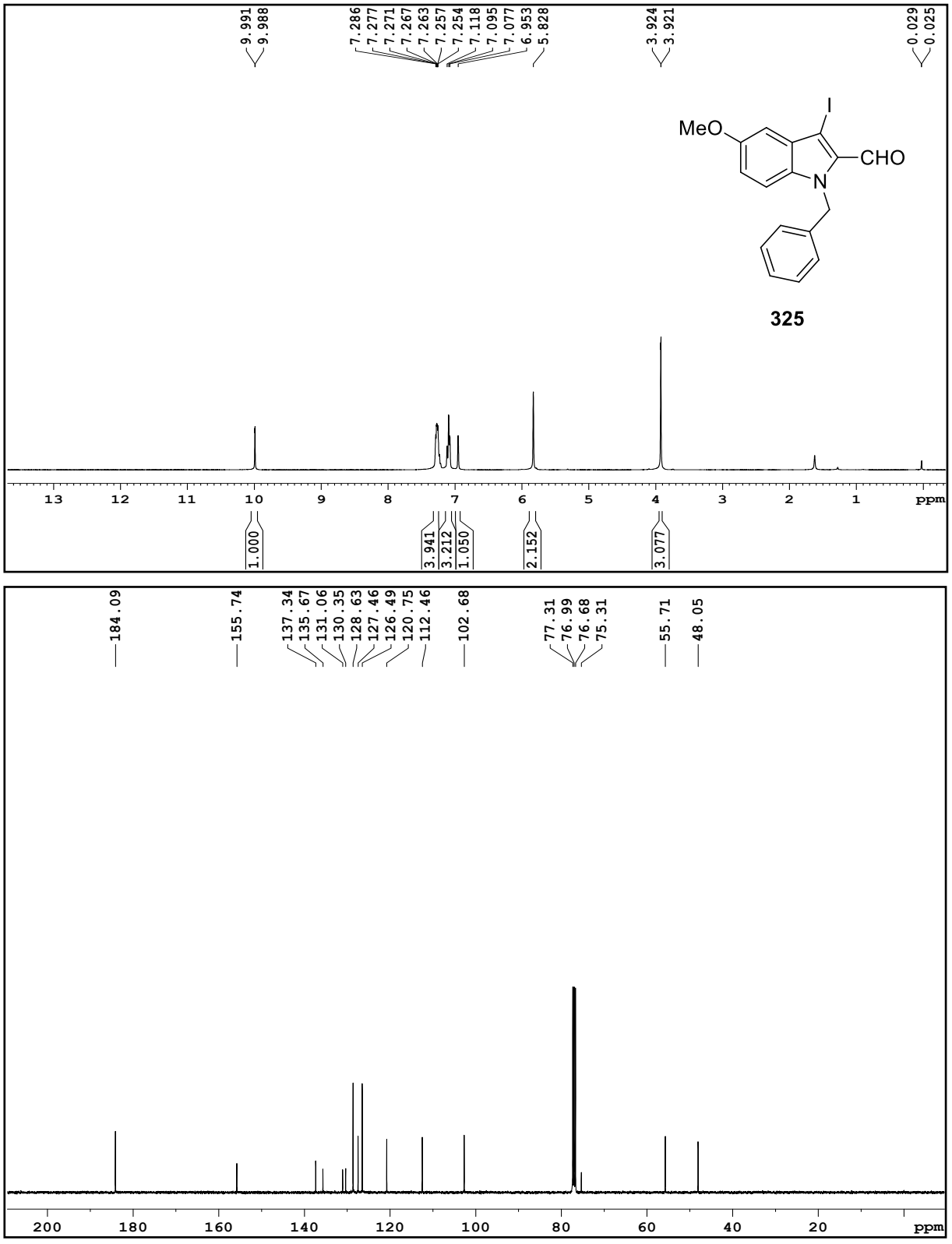
Identification code	**332**	
Empirical formula	$C_{41}H_{37}N_3O_6$	
Formula weight	667.74	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.3036(15) Å	α = 89.243(11)°.
	b = 12.3192(17) Å	β = 80.398(13)°.
	c = 15.440(2) Å	γ = 73.843(13)°.
Volume	1674.8(4) $Å^3$	
Z	2	
Density (calculated)	1.280 Mg/m^3	
Absorption coefficient	0.052 mm^{-1}	
F(000)	704	
Crystal size	0.22 x 0.22 x 0.12 mm^3	
Theta range for data collection	1.68 to 25.00°.	
Reflections collected	8432	
Independent reflections	7842 [R(int) = 0.0617]	
Completeness to theta = 25.00°	99.9%	
Absorption correction	Empirical	
Max. and min. transmission	0.9750 and 0.9301	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7945 / 0 / 540	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0782, wR2 = 0.2684	
R indices (all data)	R1 = 0.1095, wR2 = 0.1755	
Extinction coefficient	0.00062 (11)	
Largest diff. peak and hole	0.282 and -0.132 $e.Å^{-3}$	
CCDC number	**1048776**	

Spectra No. 20. ^{1}H and ^{13}C spectra of Compound 324

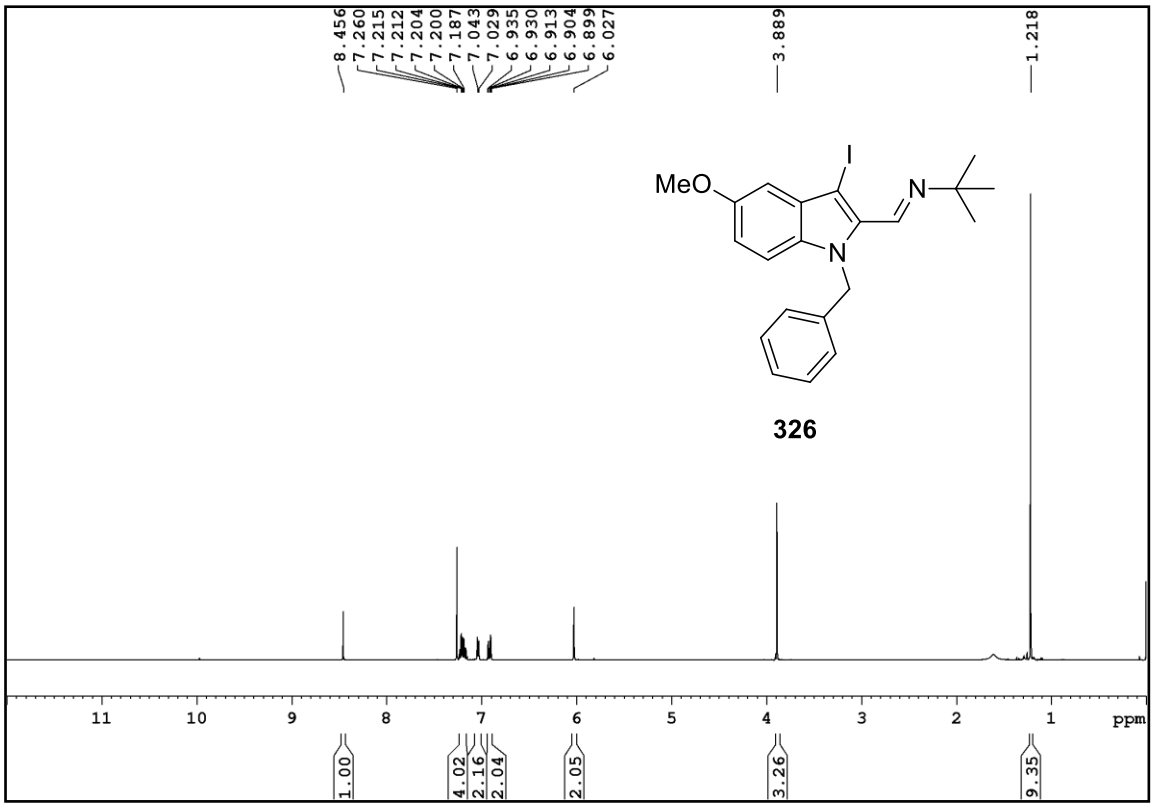


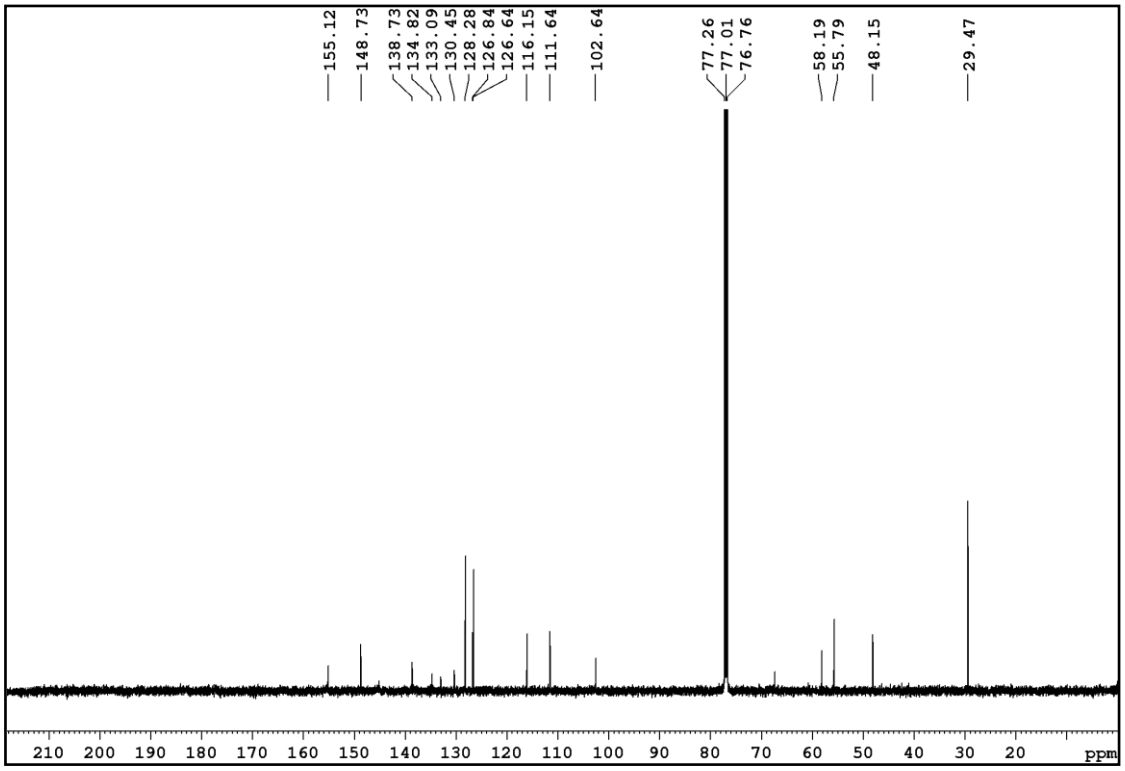


Spectra No. 21. ^{1}H and ^{13}C spectra of Compound 325

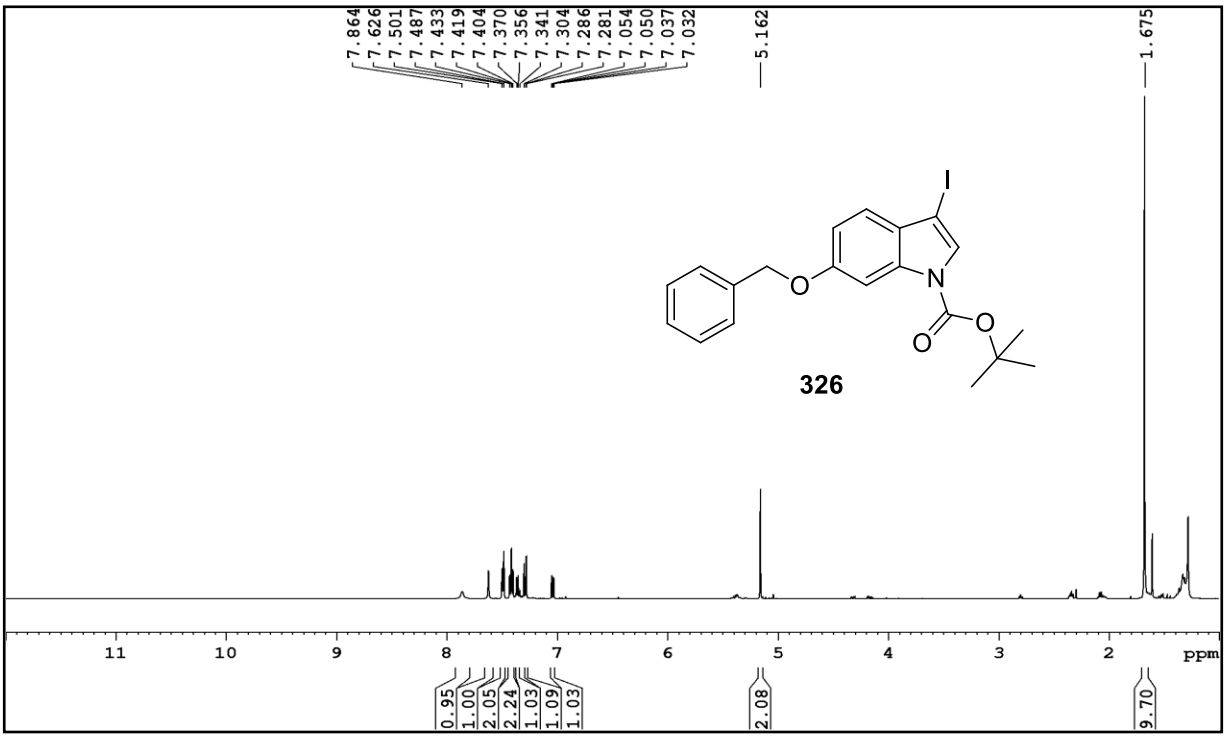


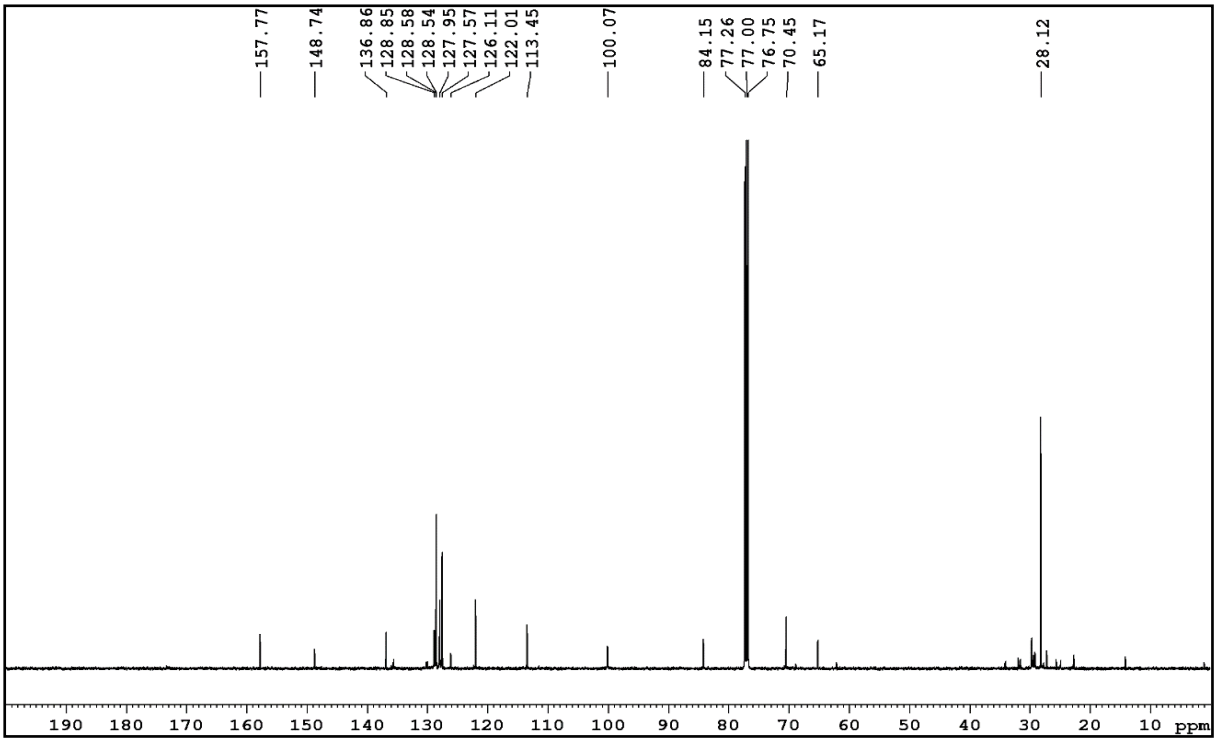
Spectra No. 22. ^{1}H and ^{13}C spectra of Compound 326



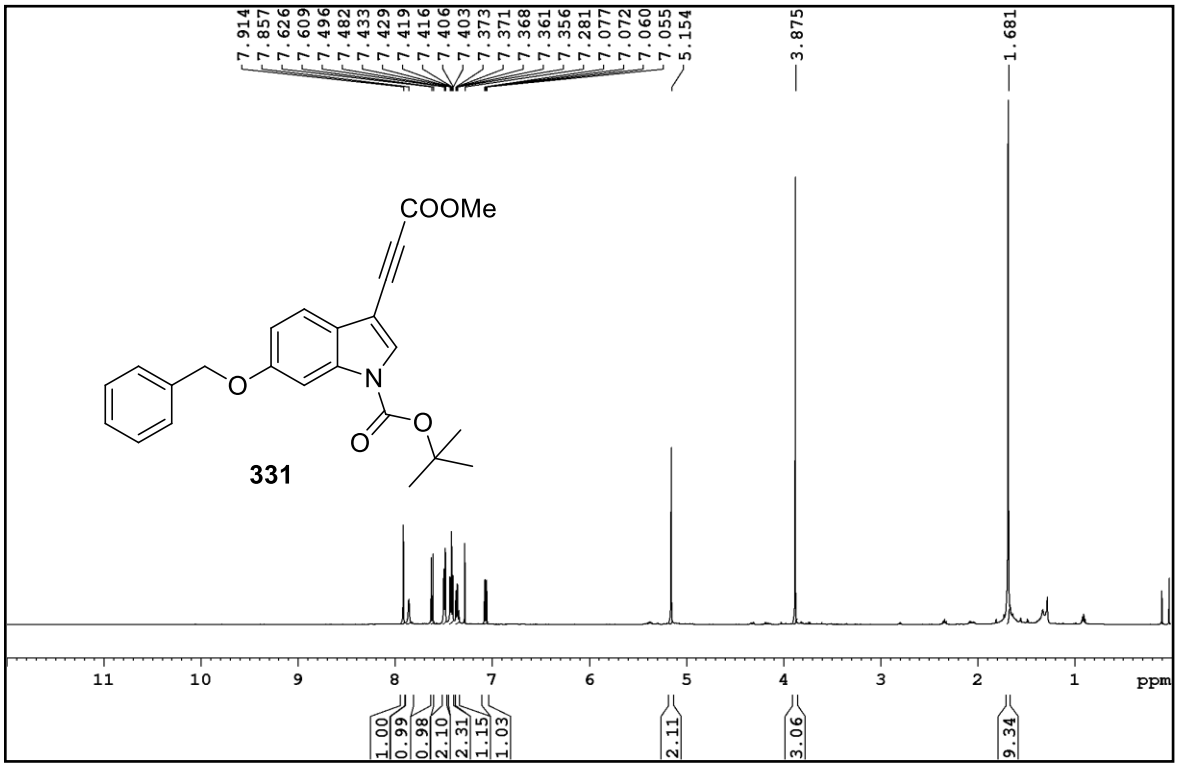


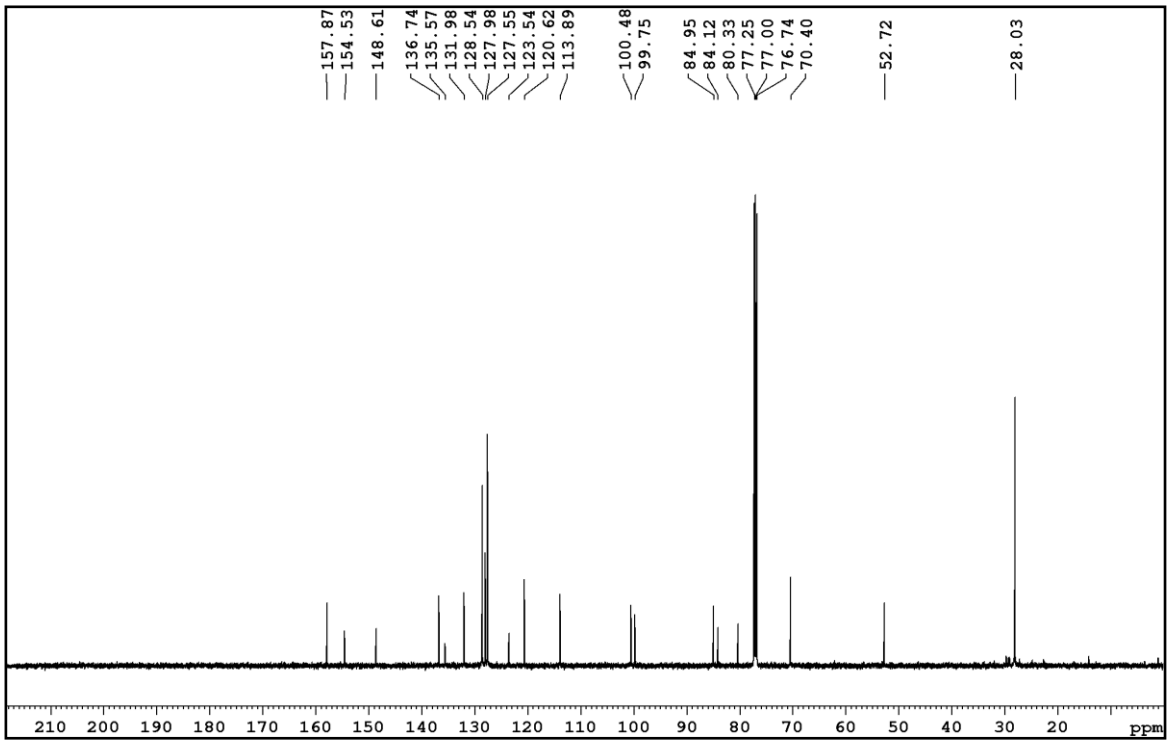
Spectra No. 23. ^{1}H and ^{13}C spectra of Compound 326



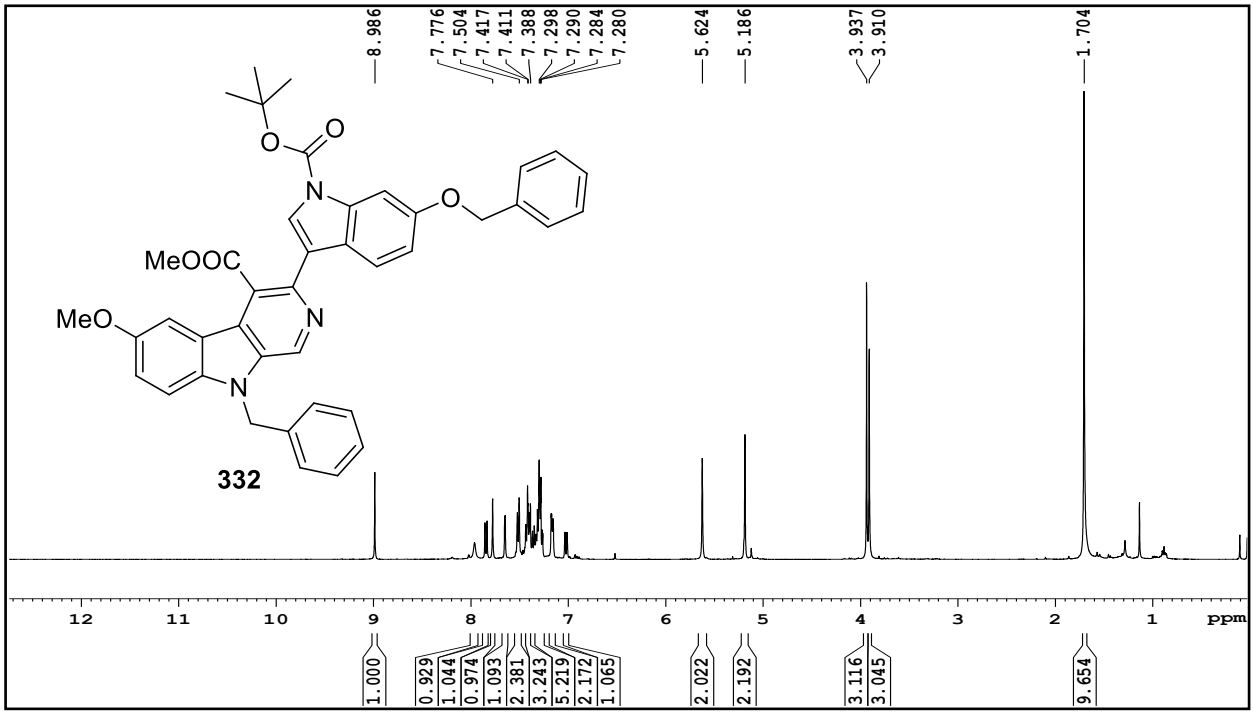


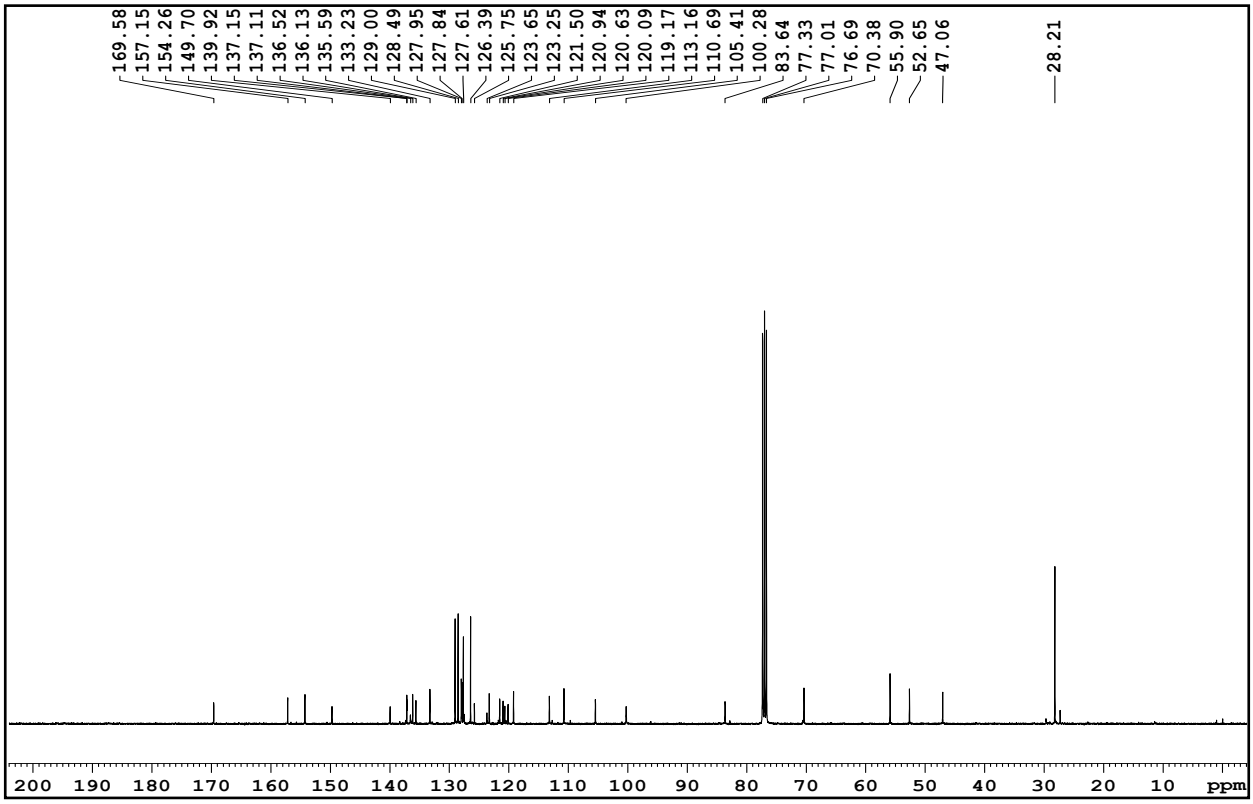
Spectra No. 24. ^{1}H and ^{13}C spectra of Compound 331



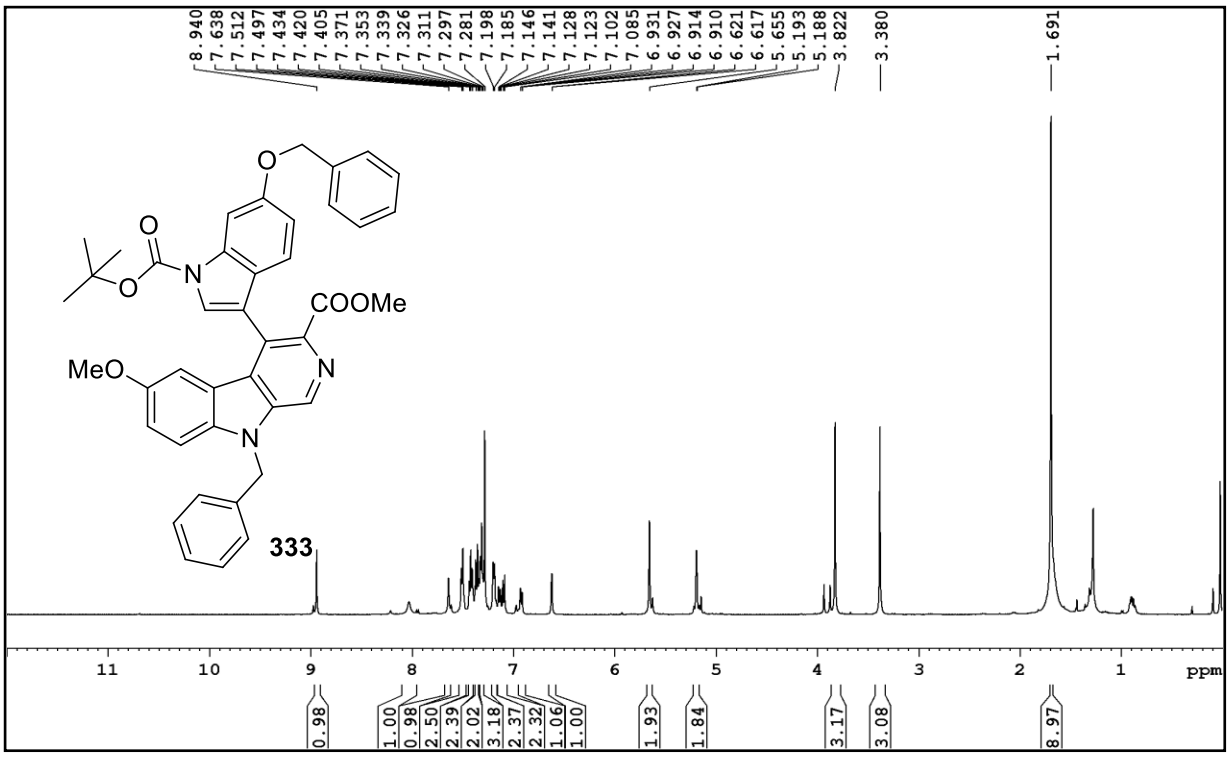


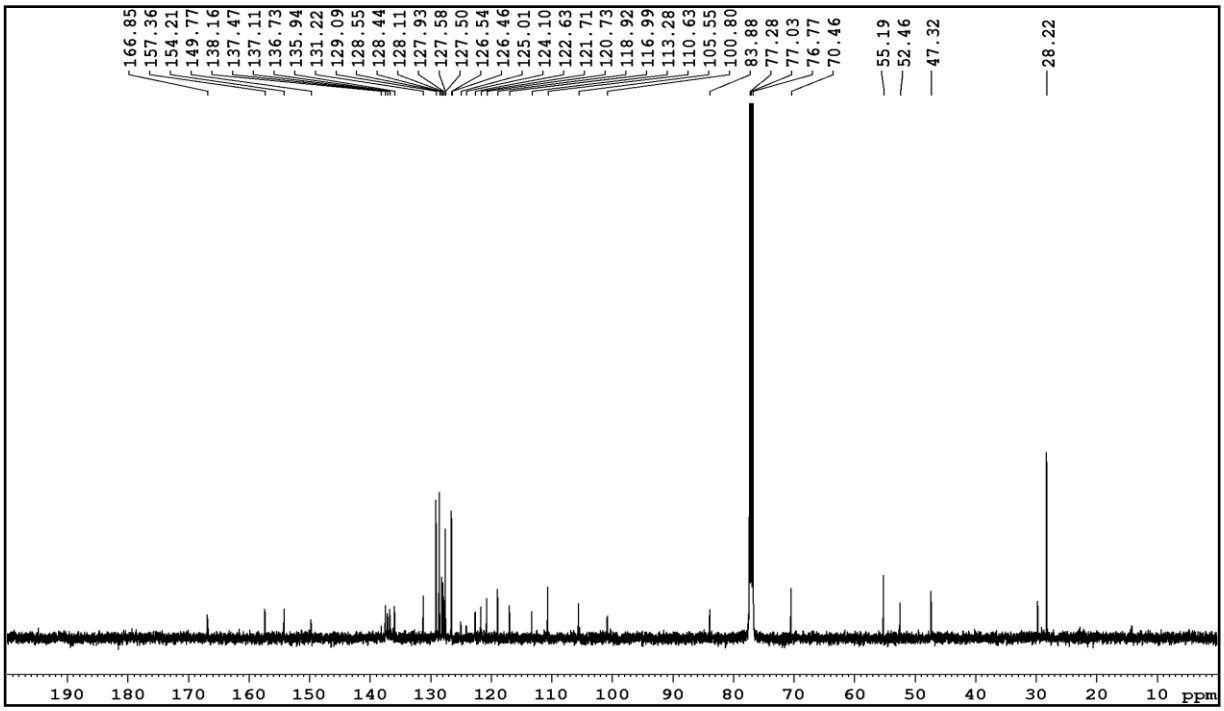
Spectra No. 25. ^{1}H and ^{13}C spectra of Compound 332



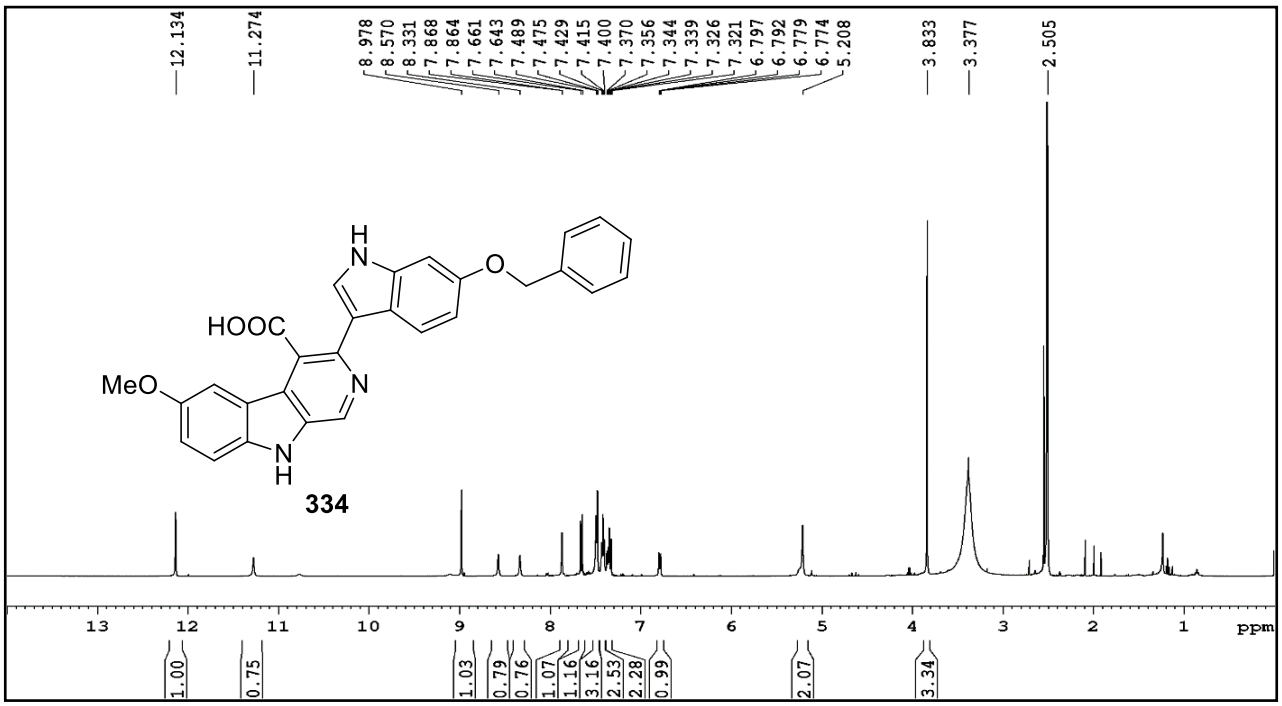


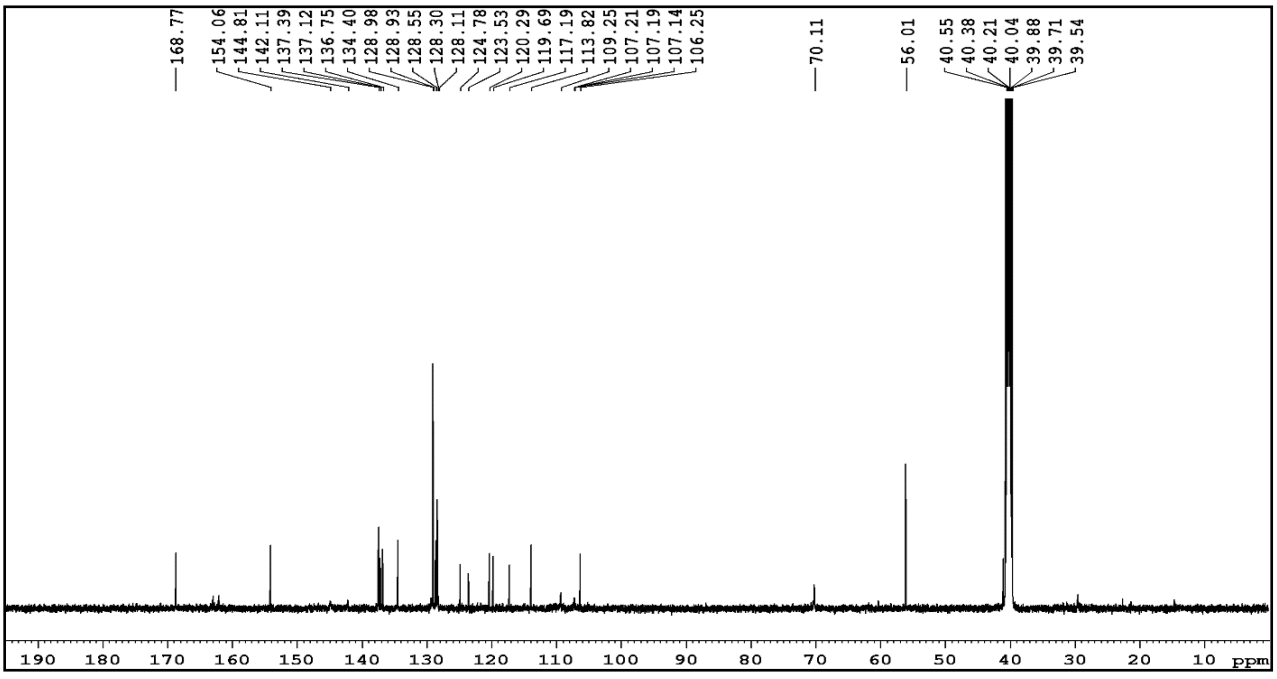
Spectra No. 26. ^{1}H and ^{13}C spectra of Compound 333



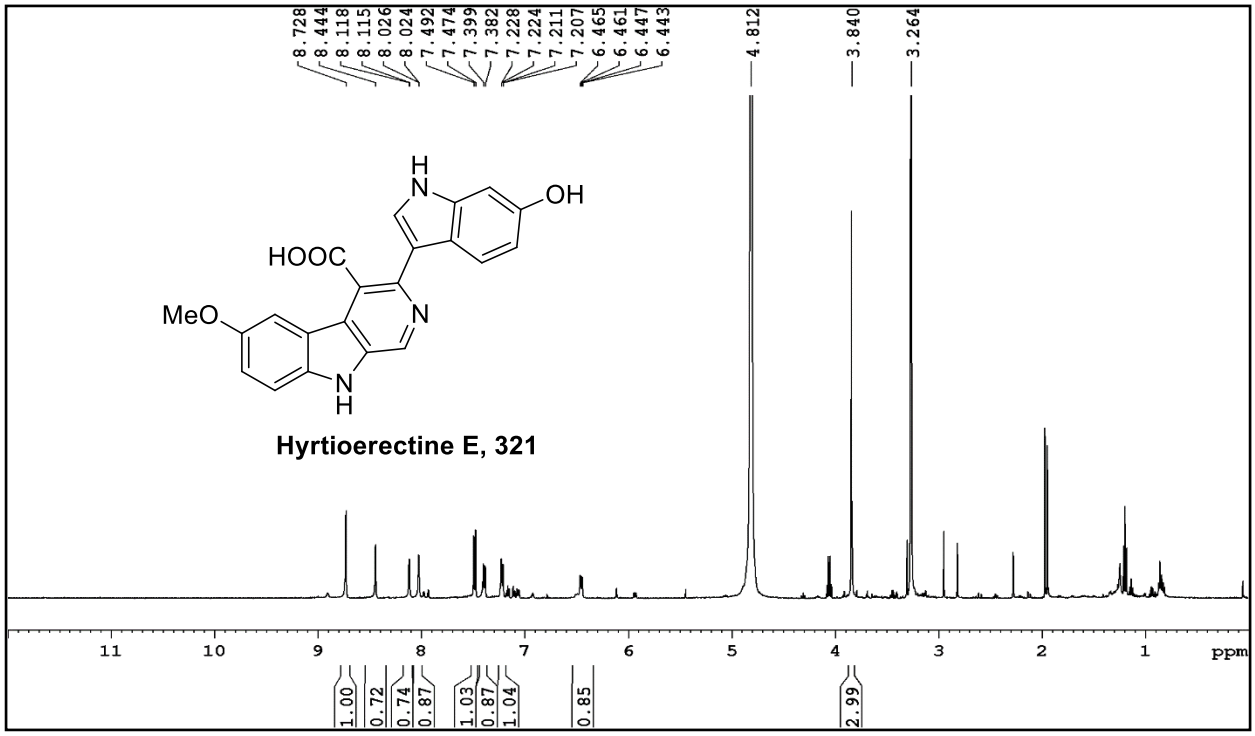


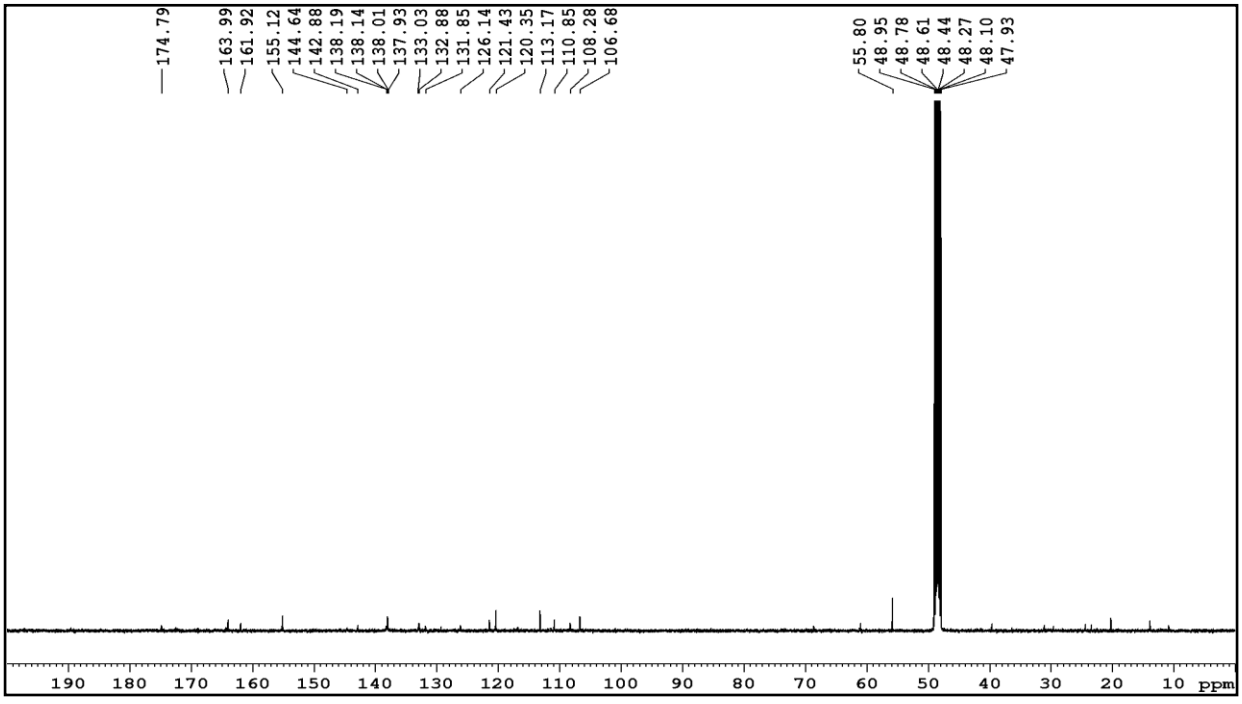
Spectra No. 27. ^{1}H and ^{13}C spectra of Compound 334





Spectra No. 28. ^{1}H and ^{13}C spectra of Hyrtioerectine E (321)





6.4. Conclusions

In this Chapter, we have completed the first total synthesis of putative structure of Hyrtioerectine E by using iminoannulation as a key step and followed by the deprotection of protective groups and saponification sequence.

In this total synthesis all the steps give the product in good yields.

But unfortunately the spectral data of the synthetic product did not match with the natural Hyrtioerectine E. In this total synthesis, unambiguous confirmation of the key step by the single crystal analysis (compound **332**) which contains core structure of Hyrtioerectine E and NMR spectral analysis and High Resolution Mass Spectral data of the all new compounds clearly evident the formation of putative structure of Hyrtioerectine E.

6.5. References

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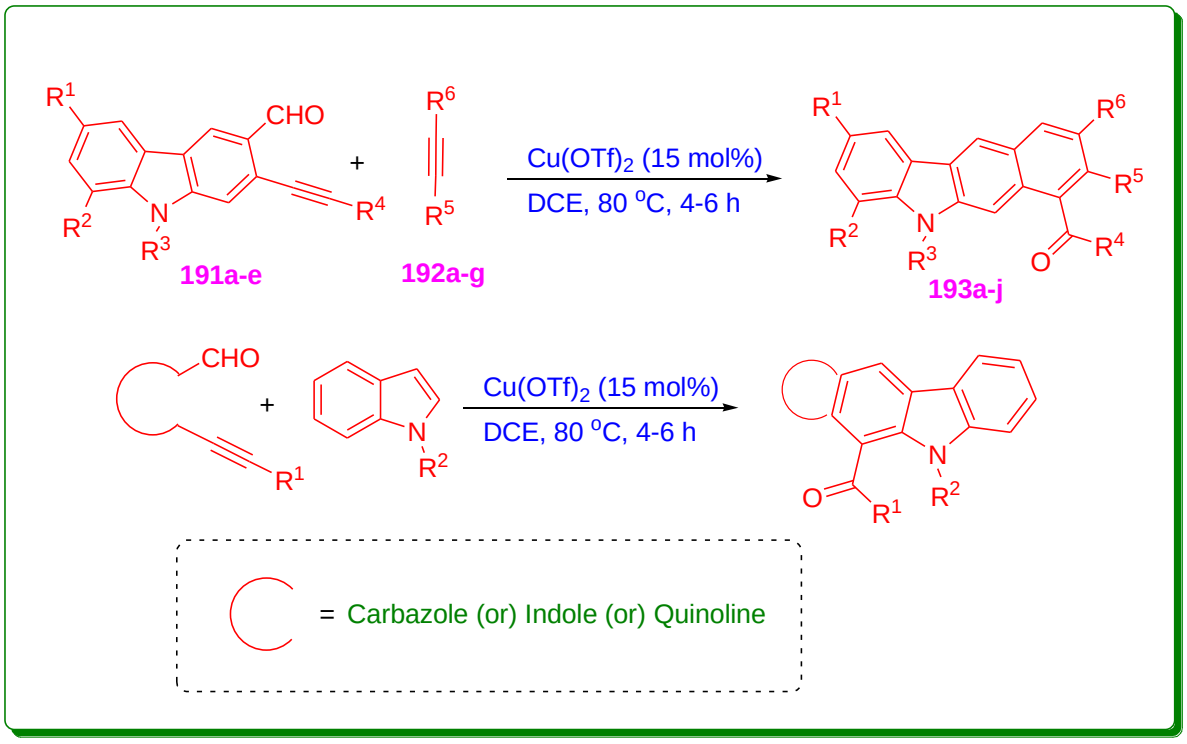
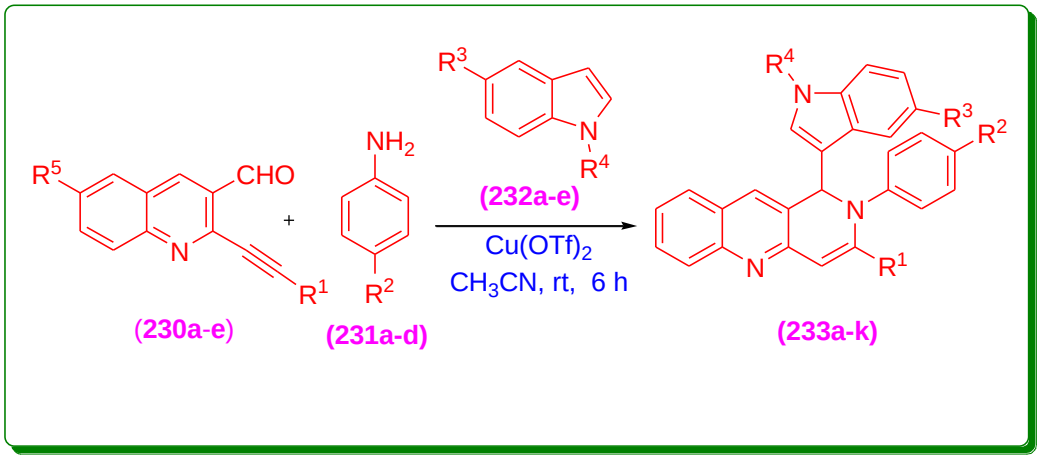
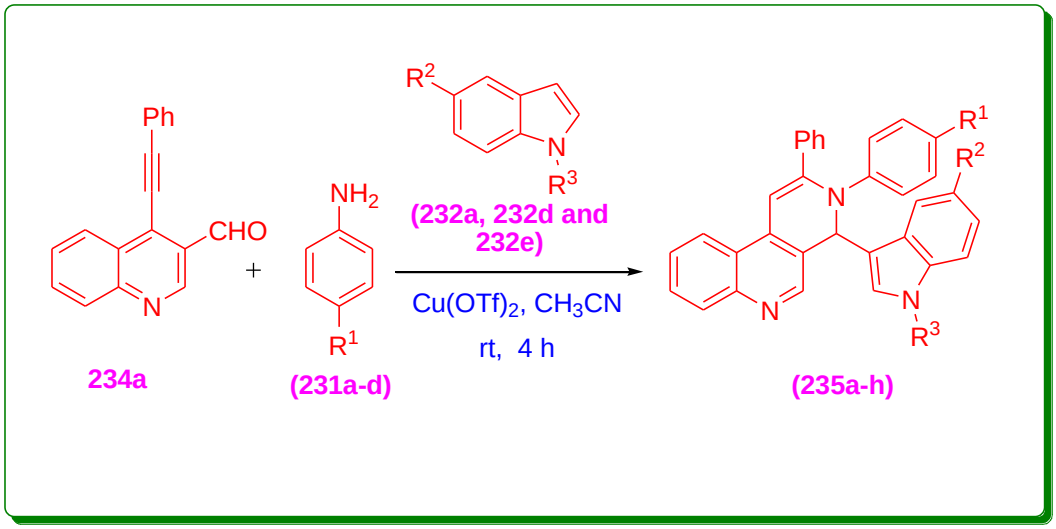
Graphical abstract

CHAPTER 1: Synthesis of 5*H*-benzo[*b*]-, carbazolo[2,3-*b*]-, indolo[2,3-*b*]- and quino[2,3-*b*]carbazole derivatives *via* heteroannulation

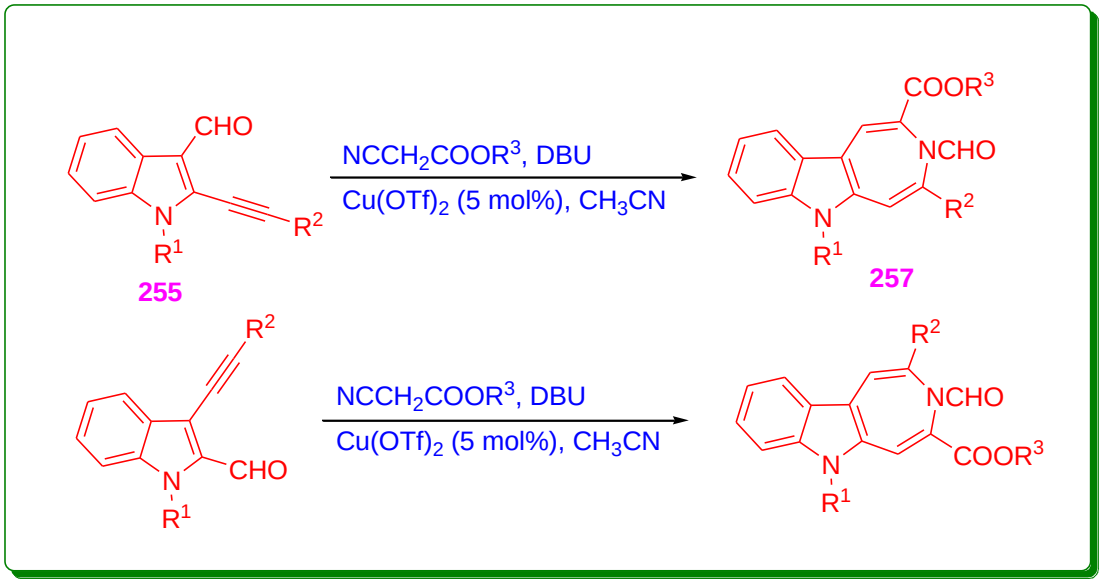


CHAPTER 2: Synthesis of indol-3-yl benzonaphthyridines *via* copper(II)-triflate catalyzed heteroannulation

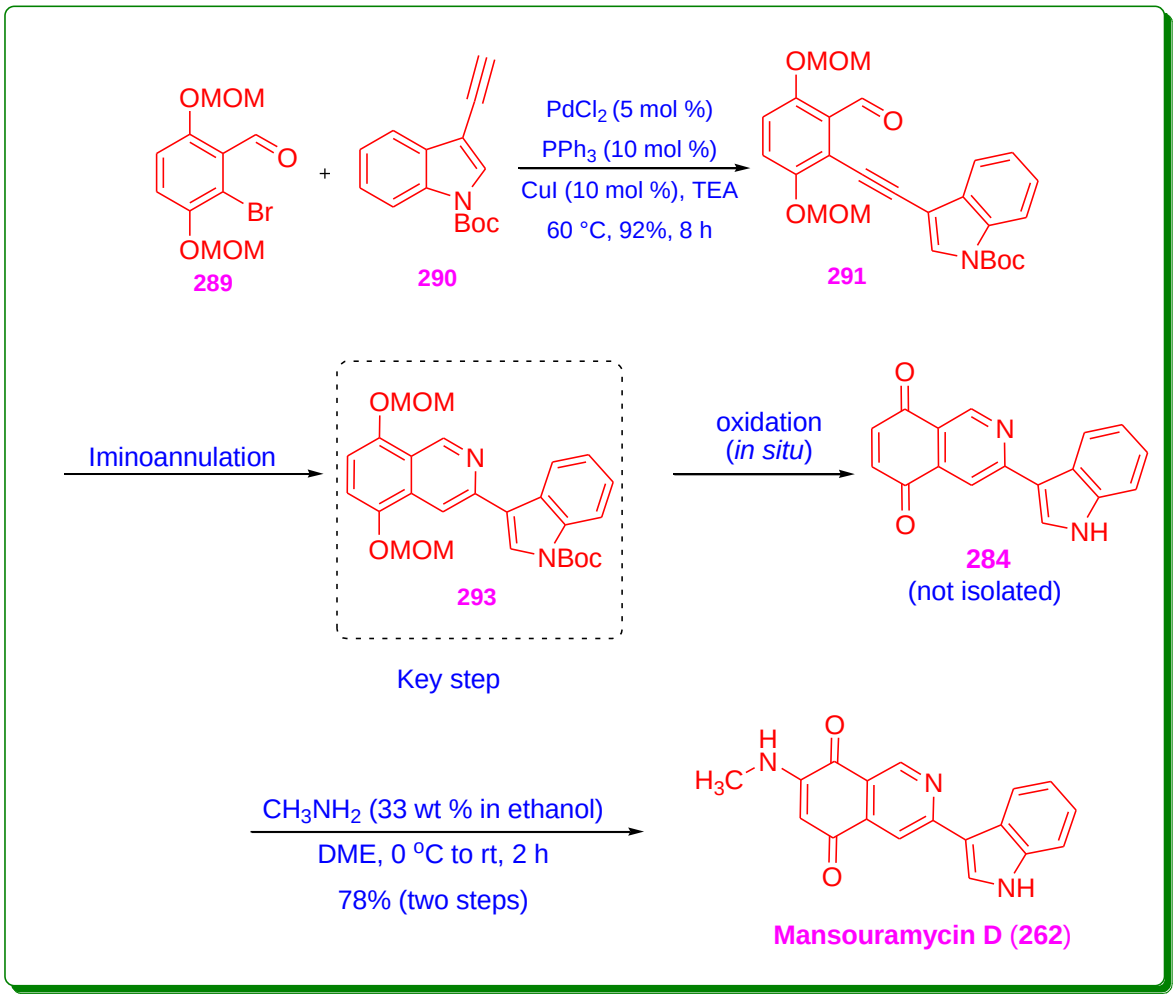




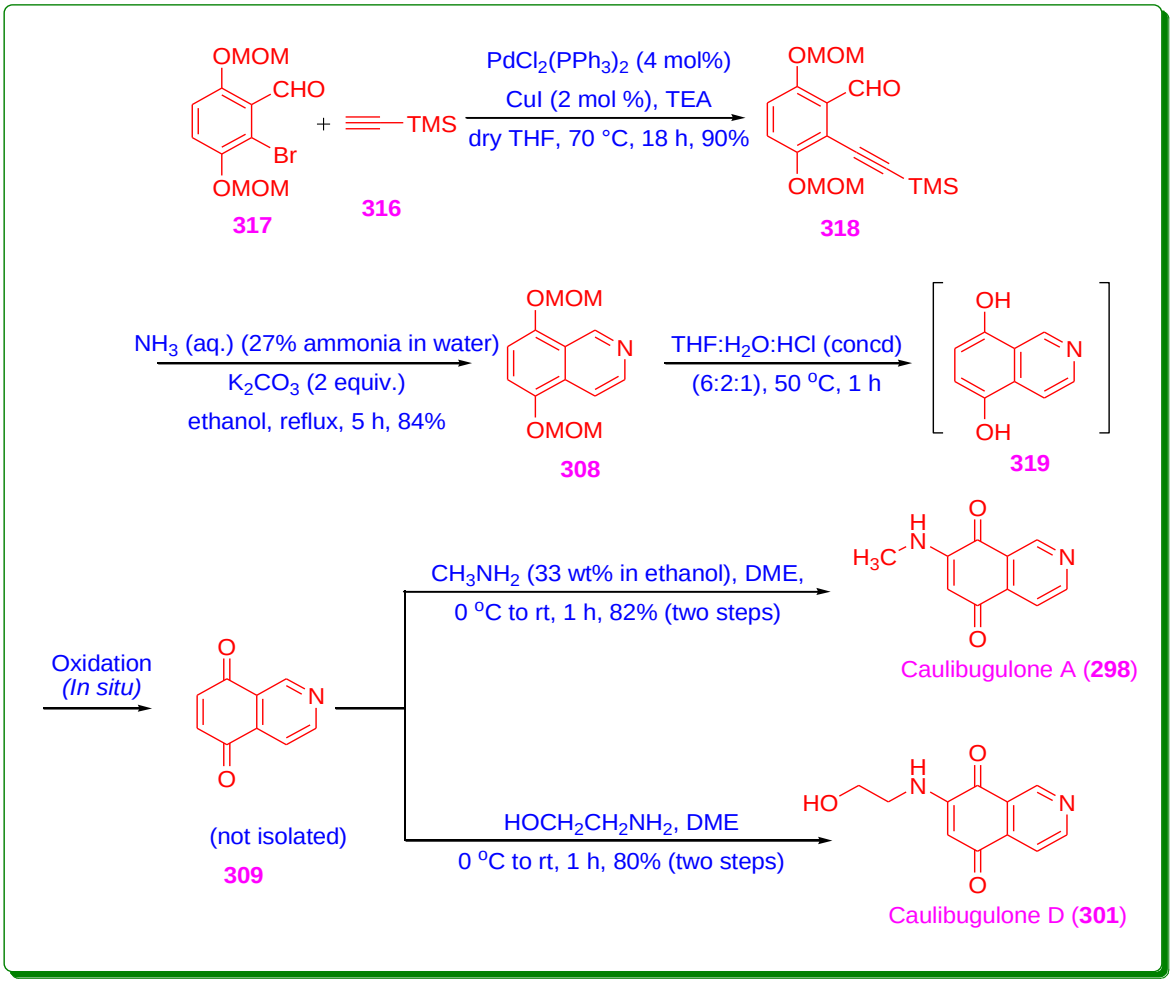
CHAPTER 3: Synthesis of indol-3-yl benzonaphthyridines *via* copper(II)-triflate catalyzed heteroannulation



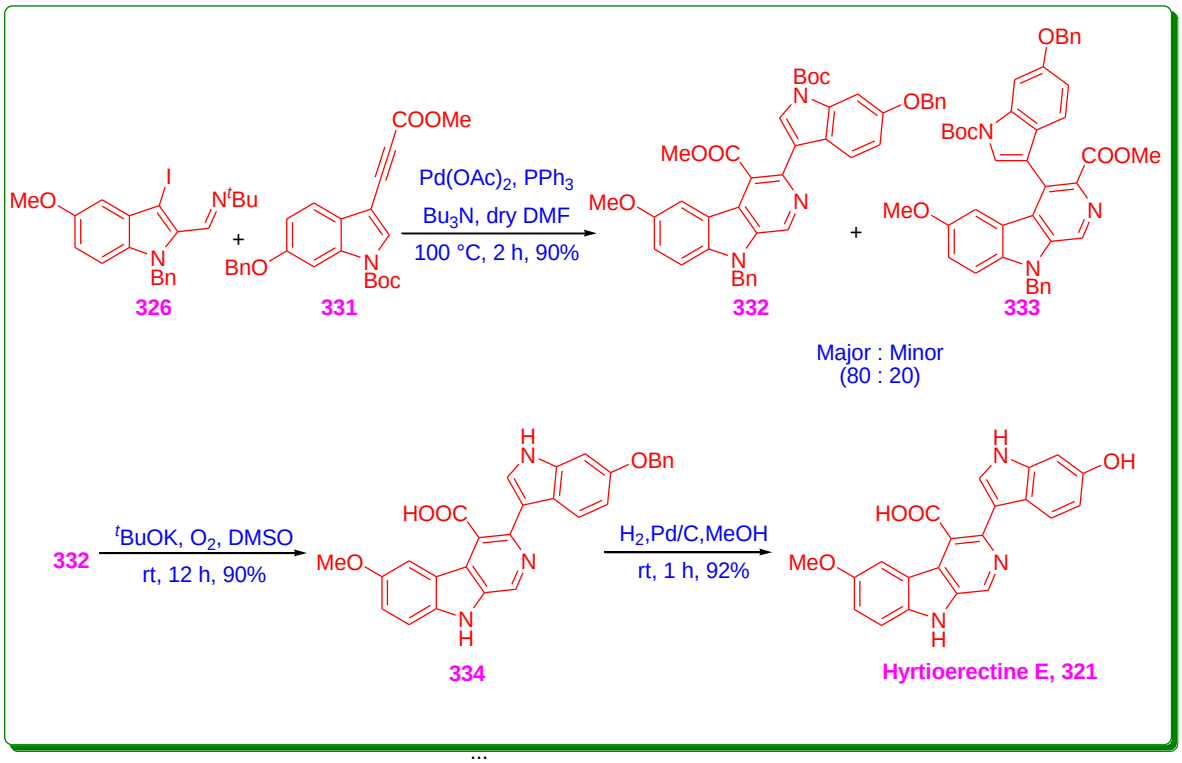
CHAPTER 4. Total synthesis of the marine alkaloid Mansouramycin D



CHAPTER 5. Total synthesis of the marine alkaloids Caulibugulones A and D



CHAPTER 6. Total synthesis of putative structure of the marine alkaloid Hyrtioerectine E



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Conclusions

In this thesis, we have made considerable success in our objectives on the alkynylaldehyde heteroannulations for the synthesis of biologically important molecules, heteroarylcarbazoles, benzonaphthyridines, azepinoindoles and the same kind of heteroannulation as key step for the total synthesis of marine alkaloids.

We have developed a new method for the synthesis of heteroarylcarbazoles (benzo[2,3-*b*]carbazoles, carbazole[2,3-*b*]carbazoles, indolo[2,3-*b*]carbazoles and quino[2,3-*b*]carbazoles). One of the above heteroarylcarbazole, quino[2,3-*b*]carbazoles is utilized for the sensing of TNT and their physical properties are studied. The mechanism for the heteroannulation is clearly studied by trapping the intermediate.

We demonstrated the convenient synthesis of indol-3-yl benzo[*b*][1,6]- and benzo[*c*][2,7]naphthyridines via copper(II)-triflate catalyzed heteroannulation.

We have described the reaction of 1-methyl-3-(2-phenylethynyl)-1*H*-indole-2-carbaldehyde and methyl isocyanoacetate in the presence of copper or silver triflate as a catalyst. The new product was identified, we expected the formation of carboline by 6-*exo* mode cyclization, unfortunately, exclusive formation of 7-*endo* cyclized product is identified. This novel observation, we developed the synthesis of azepino[4,5-*b*]indole analogues and Chromoazepinone core *via* corresponding alkynylaldehyde isocyanide heteroannulation.

We described the first successful and concise total synthesis of Mansouramycin D involving intramolecular iminoannulation as key ring closure step, which resulted in an overall yield of 54.5 to 60.9%. The core isoquinoline ring has been constructed by iminoannulation in two different methods.

We have developed a simple and concise total synthesis of Caulibugulones A and D *via* iminoannulation with an overall yield of 62% and 60% over three steps from an easily accessible known starting material.

We have completed the first total synthesis of putative structure of Hyrtioerectine E by using iminoannulation as a key step and followed by the deprotection of protective groups and saponification sequence.