SYNTHESIS OF POLYCYCLIC AMINOANTHRAQUINONE, INDOLE AND PYRIDOCARBAZOLE DERIVATIVES THROUGH INTER AND INTRAMOLECULAR HETERO DIELS-ALDER REACTION

A Thesis
Submitted for the Degree of
Doctor of Philosophy

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STATEMENT

I hereby declare that the matter embodied in this thesis entitled "**SYNTHESIS OF POLYCYCLIC AMINOANTHRAQUINONE, INDOLE AND PYRIDOCARBAZOLE DERIVATIVES THROUGH INTER AND INTRAMOLECULAR HETERO DIELS-ALDER REACTION**" 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: **(VIKRAM GADDAM)**

Hyderabad

CERTIFICATE

Certified that the work "**SYNTHESIS OF POLYCYCLIC AMINOANTHRAQUINONE, INDOLE AND PYRIDOCARBAZOLE DERIVATIVES THROUGH INTER AND INTRAMOLECULAR HETERO DIELS-ALDER REACTION**" has been carried out by **VIKRAM GADDAM** under my supervision and that the same has not been submitted elsewhere for a degree.

DEAN
School of Chemistry
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(Dr. R. NAGARAJAN)
Thesis Supervisor

LIST OF PUBLICATIONS

1. Highly diastereoselective synthesis of new chromenylaminoanthraquinones through a one pot, three-component hetero Diels-Alder reaction
   Vikram Gaddam, Devanga K. Sreenivas and Rajagopal Nagarajan, *Tetrahedron Lett*. **2006**, *47*, 9291-9295.

2. A New Entry to Polycyclic Indole Derivatives via Intramolecular Imino Diels-Alder reaction: Observation of Unexpected reaction
   Vikram Gaddam and Rajagopal Nagarajan, *J. Org. Chem*. **2007**, *72*, 3573-3576.

3. A Rapid Intramolecular Imino Diels-Alder Reaction of Aminoanthraquinones with Citronellal or Prenylated Salicylaldehydes: Substituent Effect on Changing the Reaction Pathway from Diels–Alder to Ene-Type Cyclization
   Vikram Gaddam, Ramu Meesala and Rajagopal Nagarajan, *Synthesis* **2007**, 2503-2512.

4. Highly diastereoselective synthesis of new indolopyrroloquinolines through intramolecular imino Diels–Alder reactions
   Vikram Gaddam and Rajagopal Nagarajan, *Tetrahedron Lett*. **2007**, *48*, 7335-7338.

5. An Efficient, One-Pot Synthesis of Isomeric Ellipticine Derivatives through Intramolecular Imino-Diels-Alder Reaction
   Vikram Gaddam and Rajagopal Nagarajan, *Org. Lett*. **2008**, *10*, 1975-1978.

6. A one-pot synthetic approach to the functionalized isomeric ellipticine derivatives through an imino Diels–Alder reaction
   Vikram Gaddam and Rajagopal Nagarajan, *Tetrahedron Lett*. **2009**, *50*, 1243-1248.

7. A Flexible Approach to the Chromenoquinoline Derivatives under Copper/Lewis acid Catalysis
   Subburethinam Ramesh, **Vikram Gaddam** and Rajagopal Nagarajan, *Synlett* **2010** (*in press*).

8. CuI/La(OTf)$_3$ catalyzed, one-pot synthesis of isomeric ellipticine derivatives in ionic liquid
   Vikram Gaddam, Subburethinam Ramesh and Rajagopal Nagarajan (*Communicated*).

Posters and Presentations

1. Presented a poster entitled "Intramolecular imino Diels-Alder reactions of aminoanthraquinones with citronellal or *O*-prenyl salicylaldehydes: Facile, one-pot synthesis of anthraquinone-quinoline heterocycles" in 3rd in-house symposium "***Chemfest-2006***" held at University of Hyderabad, Hyderabad, India on March 4, 2006.

2. Presented a poster entitled "A new entry to polycyclic indole derivatives *via* intramolecular imino Diels-Alder reaction: Observation of an unexpected reaction" in 4th in-house symposium "***Chemfest-2007***" held at University of Hyderabad, Hyderabad, India on March 3-4, 2007.

3. Presented a poster entitled "Synthesis of new isoellipticine derivatives through imino Diels-Alder reaction" in 5th in-house symposium "***Chemfest-2008***" held at University of Hyderabad, Hyderabad, India on March 1-2, 2008.

4. Presented a poster entitled "Synthesis of new isoellipticine derivatives through imino Diels-Alder reaction" in 10th CRSI national symposium in chemistry "***NSC-10***" held at Indian Institute of Science, Bangalore, India on February 2-3, 2008.

5. Given a flash oral presentation entitled "An facile one-pot synthesis of isomeric ellipticine derivatives through inter and intramolecular imino Diels-Alder reaction" in 6th in-house symposium "***Chemfest-2009***" held at University of Hyderabad, Hyderabad, India on March 7-9, 2009.

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First and foremost, I would like to thank my parents, Mr. G. Prasada Rao and Neelamma, and my dear brothers Mr. Kiran and Mr. Ramesh for always being there for me. The unconditional love of my parents and their blessings made me what I am today and I owe everything to them. Dedicating this thesis to them is a minor recognition for their relentless support and love. My profound gratitude and love to my wife **Prashanthi** for her understanding, cooperation and encouragement for the completion of my research work. I am thankful to my grandfather Pedapapaiah and grandmother Manikyam.

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---VIKRAM GADDAM

This thesis is dedicated to

My parents Gaddam Prasada Rao, Neelamma

and

My teachers

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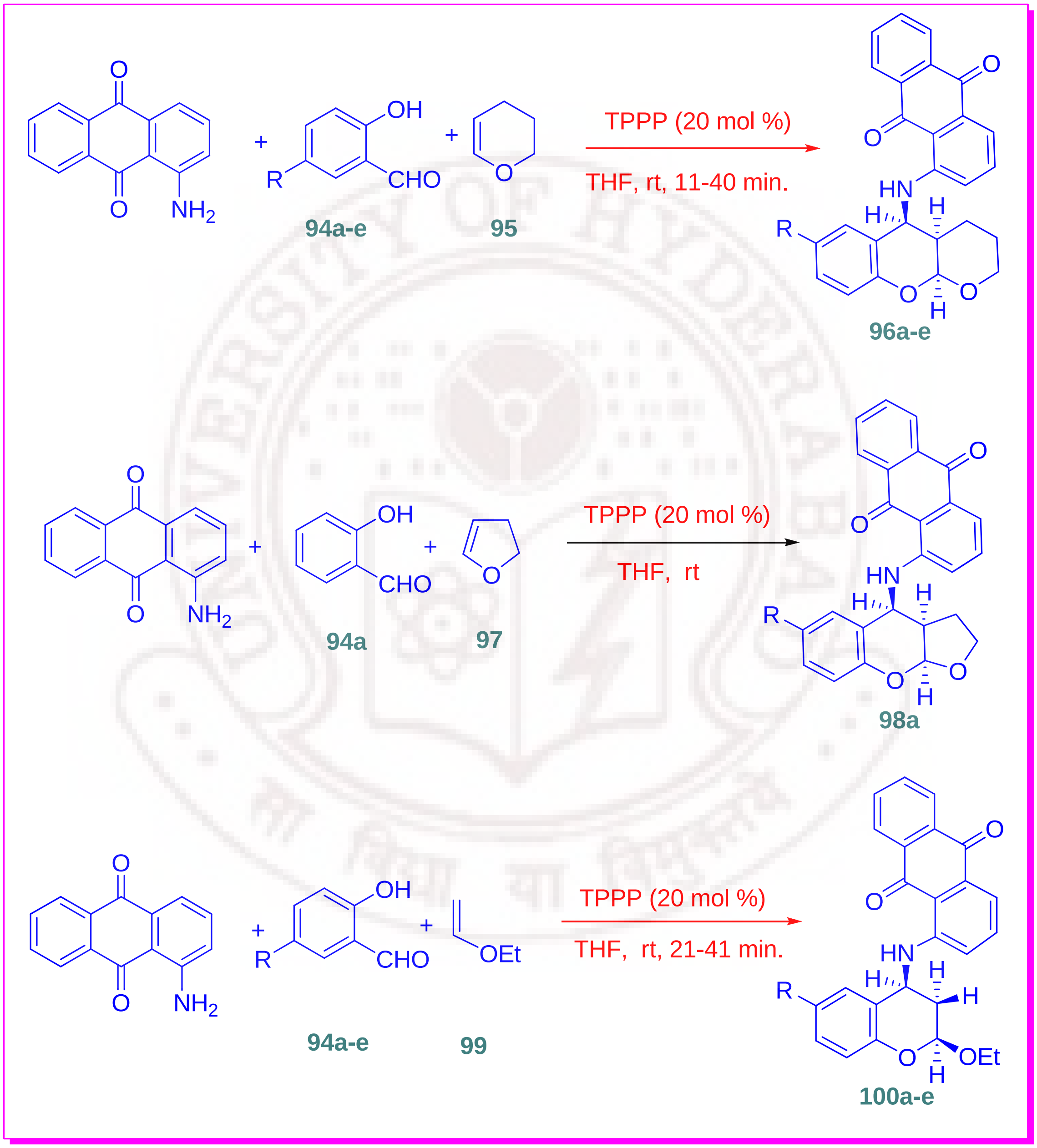
Graphical Abstracts

List of Abbreviations

Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
CAN	Ceric Ammonium nitrate
CBz	Benzyloxycarbonyl
DCM	Dichloromethane
CDI	1,1’-carbonyldiimidazole
DMA	Dimethyl ethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Eq.	Equation
i-Pr	*iso*-propyl
LDA	Lithium Diisopropylamide
LiTMP	Lithium tetramethylpiperidide
m-CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
MOM	Methoxy methyl ether
Mp	Melting point
MS	Molecular sieves
Ph	Phenyl
Pr	Propyl
p-TSA	*para*-Toluenesulfonic acid
rt	Room temperature
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethyl silyl
TMTU	Tetramethylthiourea
TPPP	Triphenylphosphonium perchlorate

Graphical Abstracts

CHAPTER 1. Synthesis of Polycyclic Aminoanthraquinones



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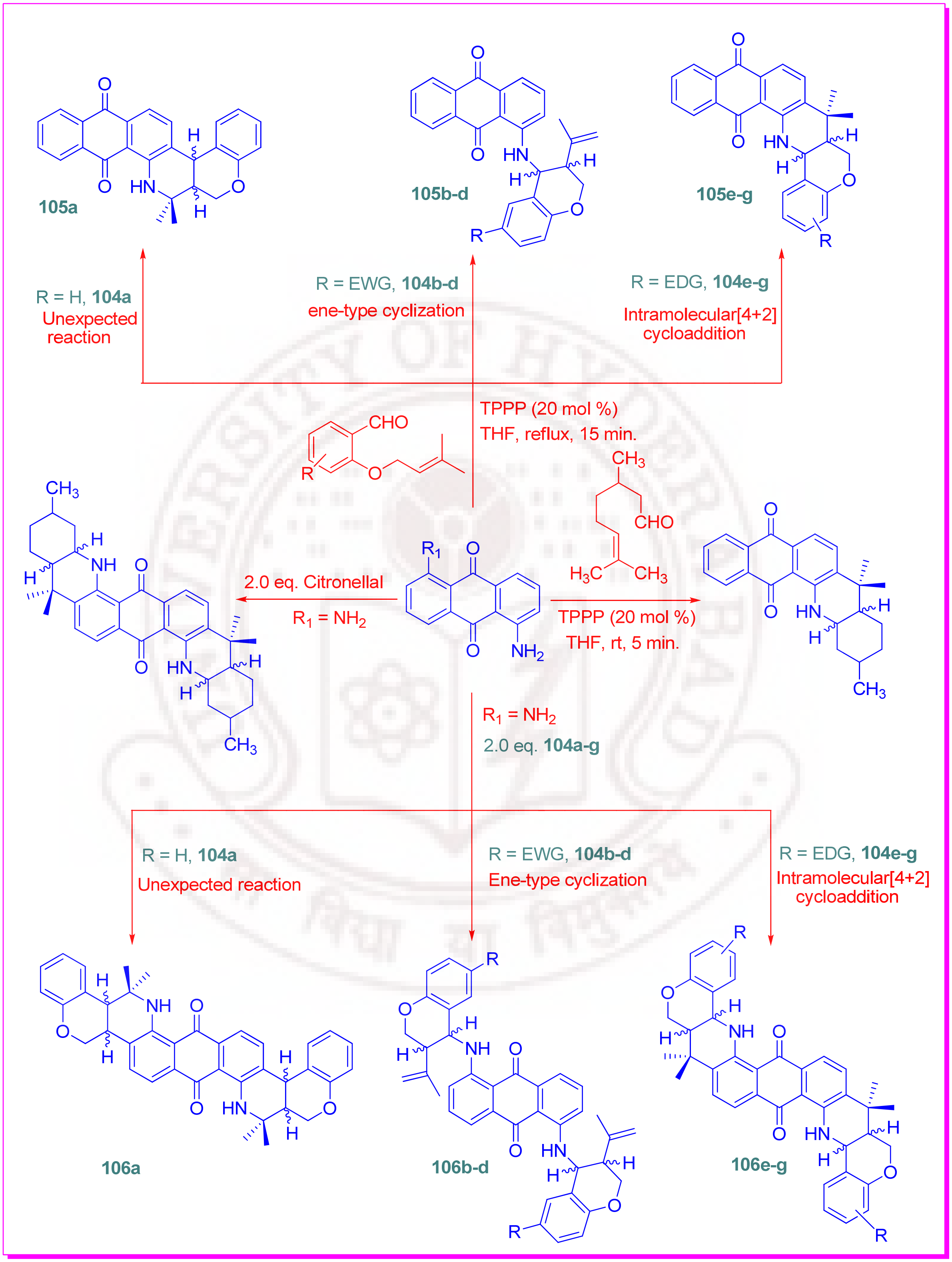
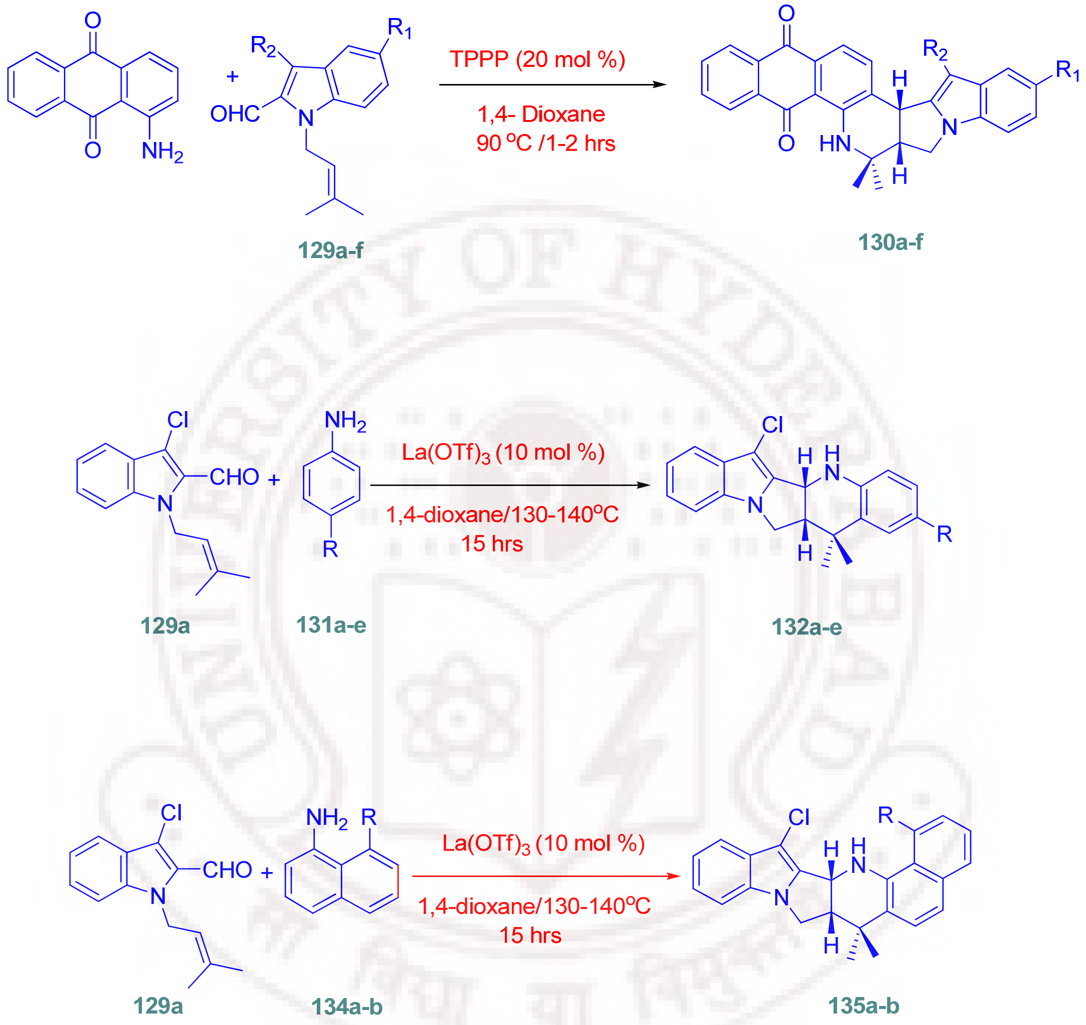
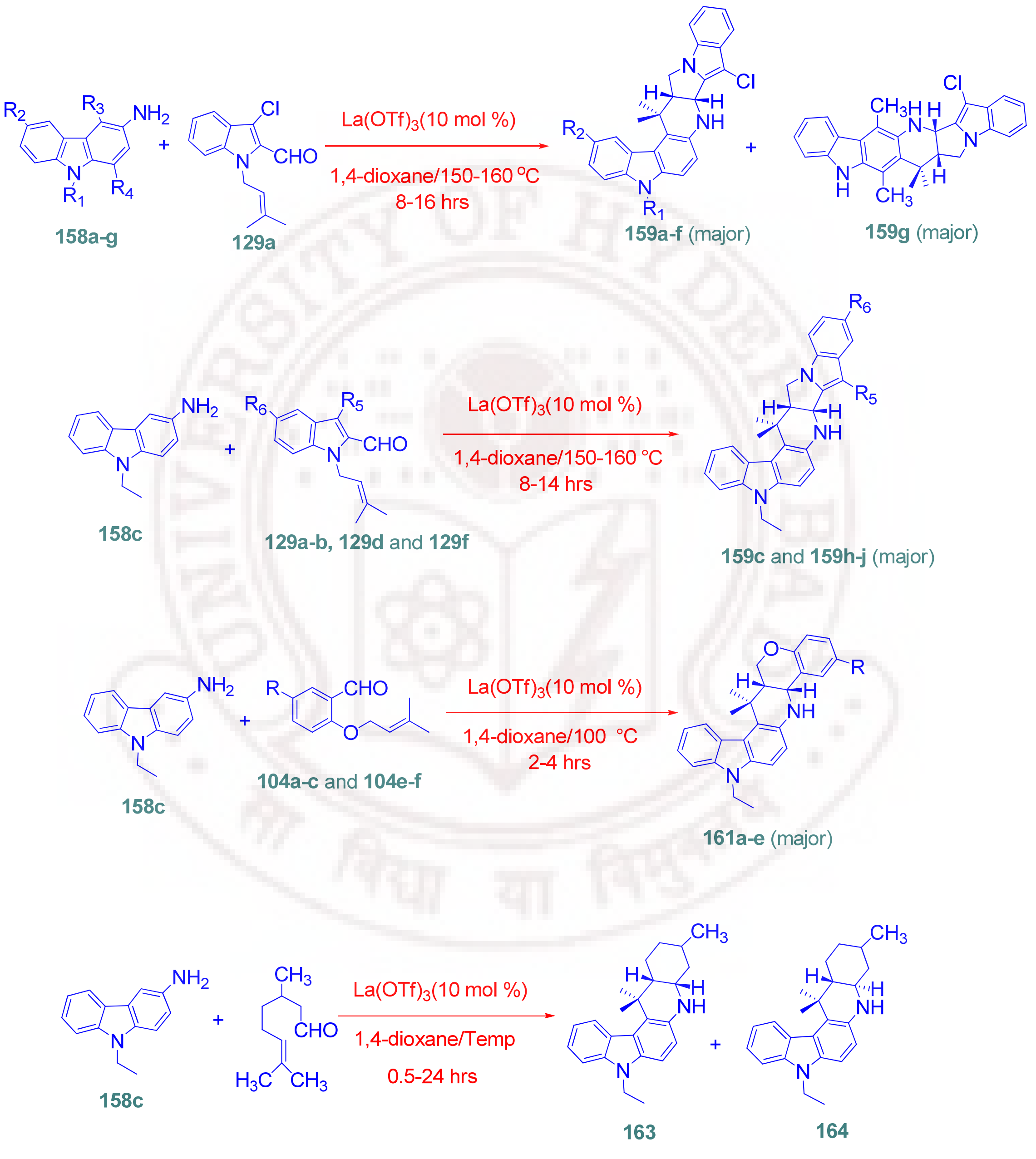

105a
105b-d
105e-g
R = H, 104a
Unexpected reaction
R = EWG, 104b-d
ene-type cyclization
R = EDG, 104e-g
Intramolecular[4+2] cycloaddition
TPPP (20 mol %)
THF, reflux, 15 min.
CHO
R
O
R1
NH2
2.0 eq. Citronellal
R1 = NH2
CH3
H3C
TPPP (20 mol %)
THF, rt, 5 min.
R1 = NH2
2.0 eq. 104a-g
R = H, 104a
Unexpected reaction
R = EWG, 104b-d
Ene-type cyclization
R = EDG, 104e-g
Intramolecular[4+2] cycloaddition
106a
106b-d
106e-g
HN
NH
H


O
O
NH2
+
R2
R1
OHC
N
129a-f
TPPP (20 mol %)
1,4- Dioxane
90 °C /1-2 hrs
O
O
R2
R1
H
HN
N
H
130a-f
Cl
CHO +
N
129a
NH2
R
131a-e
La(OTf)3 (10 mol %)
1,4-dioxane/130-140°C
15 hrs
Cl
H H
N
N
H
R
132a-e
Cl
CHO +
N
129a
NH2 R
134a-b
La(OTf)3 (10 mol %)
1,4-dioxane/130-140°C
15 hrs
Cl
R
H H
N
N
H
135a-b

CHAPTER 3. Synthesis of Polycyclic Pyridocarbazole Derivatives through inter and intramolecular imino Diels-Alder reaction



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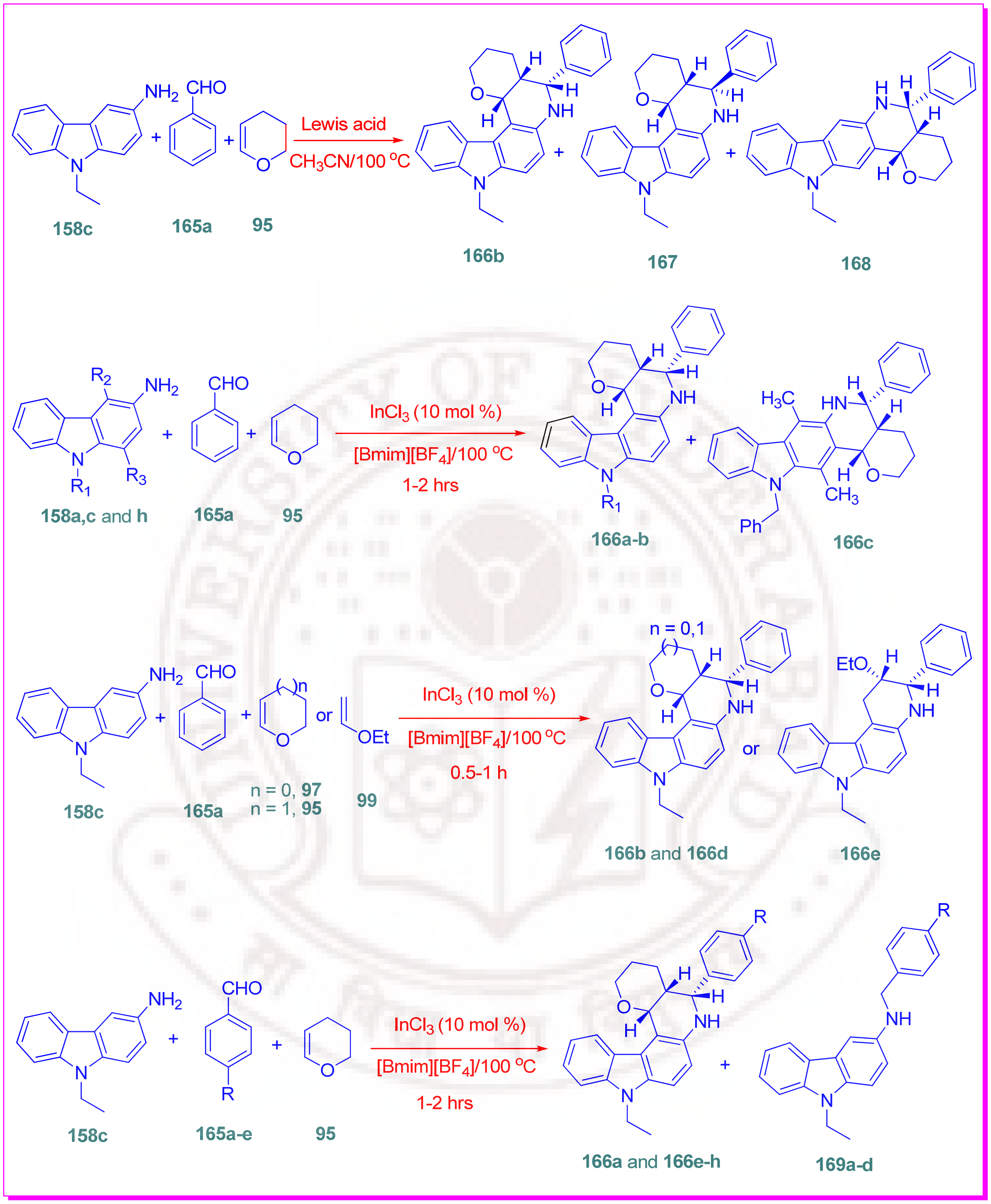
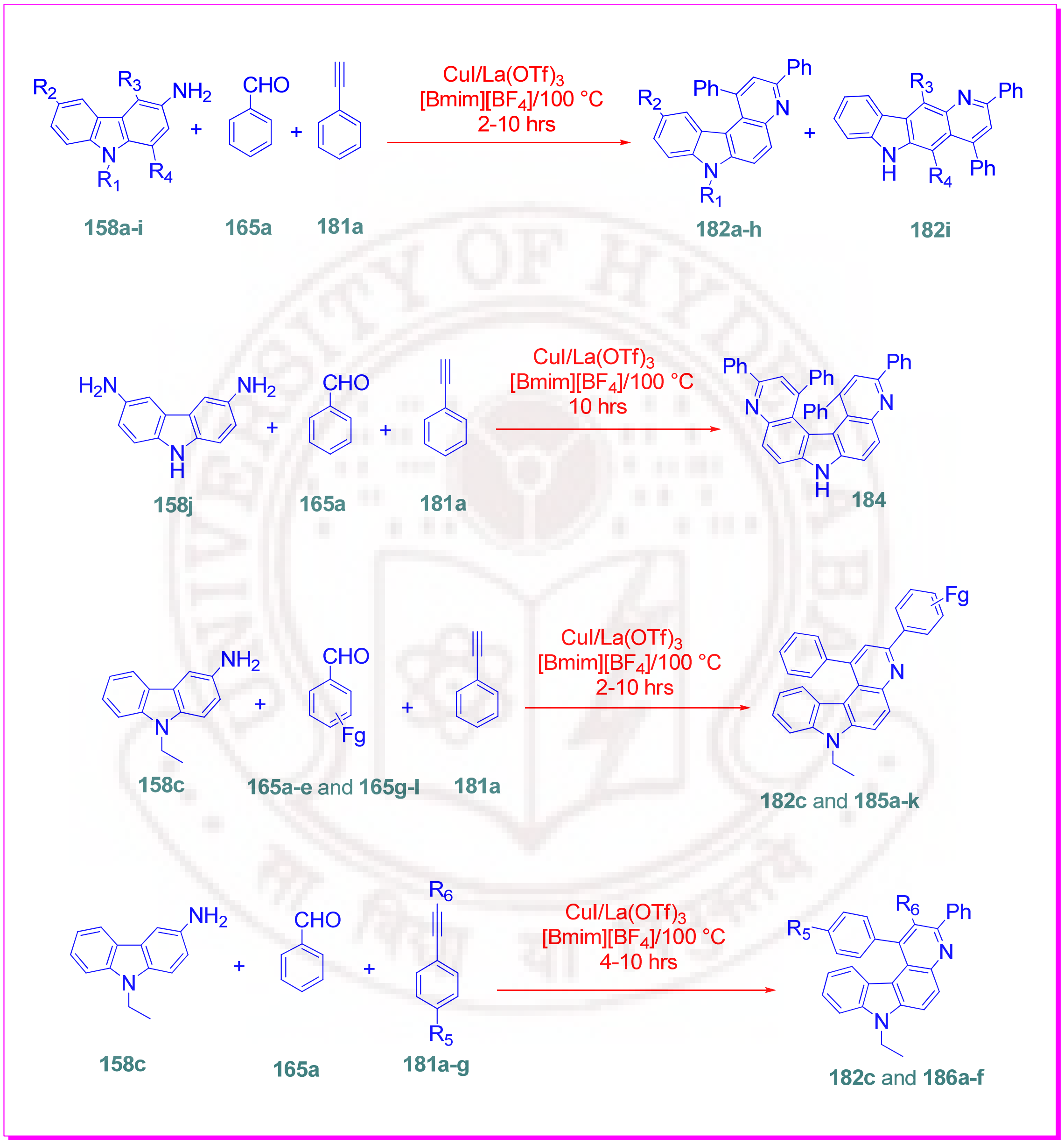

NH2
CHO
Lewis acid
CH3CN/100 °C
158c
165a
95
166b
167
168
R2
NH2
CHO
InCl3 (10 mol %)
[Bmim][BF4]/100 °C
1-2 hrs
R1
R3
158a,c and h
165a
95
166a-b
H3C
CH3
Ph
166c
NH2
CHO
( )n
or
OEt
InCl3 (10 mol %)
[Bmim][BF4]/100 °C
0.5-1 h
n = 0, 97
n = 1, 95
99
158c
165a
n = 0,1
or
EtO
166b and 166d
166e
NH2
CHO
R
InCl3 (10 mol %)
[Bmim][BF4]/100 °C
1-2 hrs
158c
165a-e
95
166a and 166e-h
169a-d

CHAPTER 4. Synthesis of Pyridocarbazole Derivatives Catalyzed by CuI/La(OTf)$_3$



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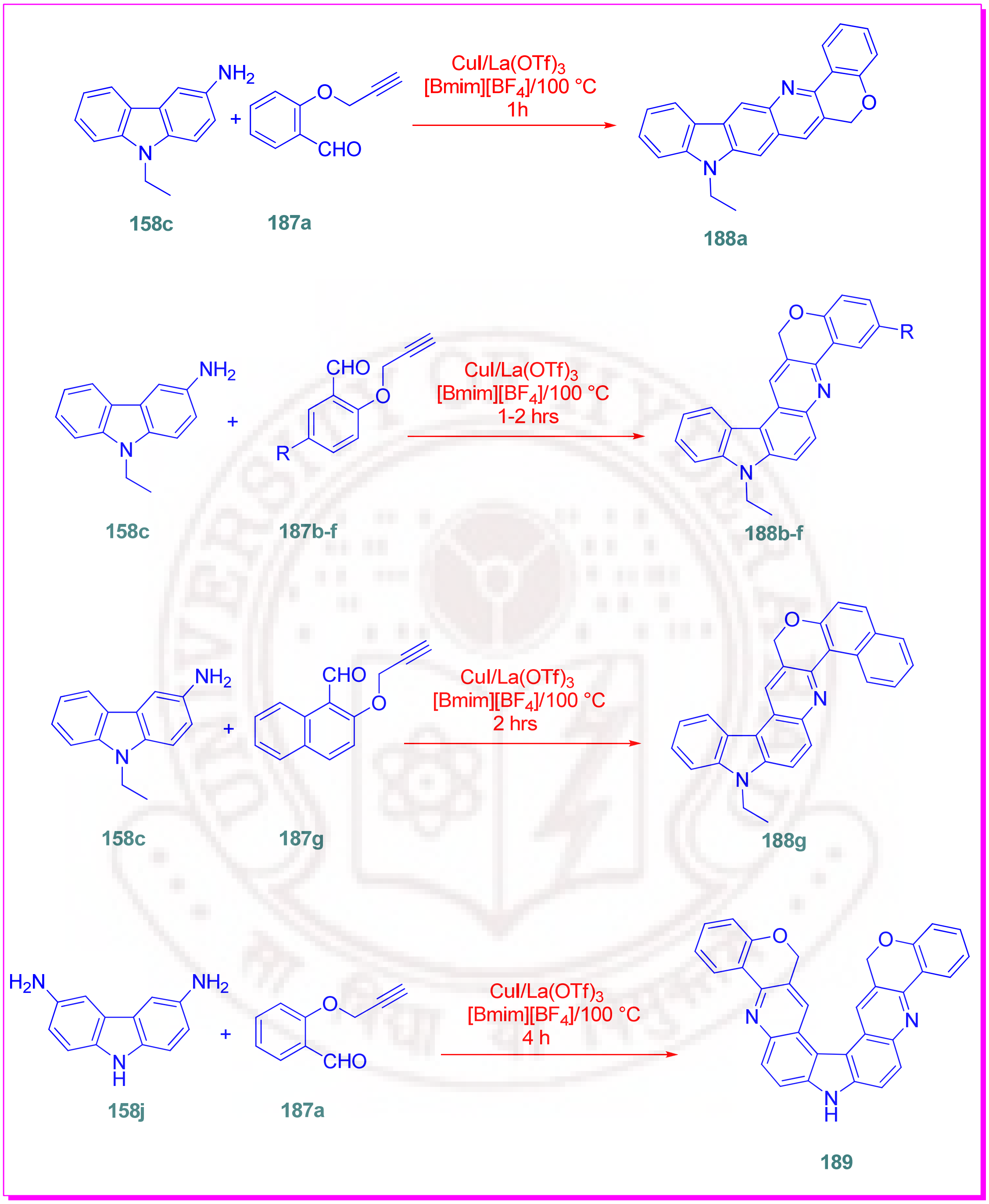
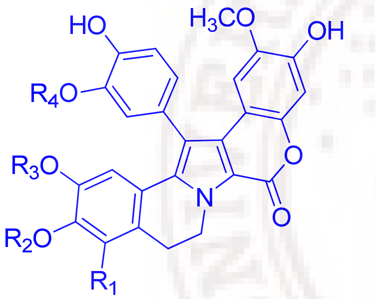

NH2
CHO
O
N
CuI/La(OTf)3
[Bmim][BF4]/100 °C
1h
158c
187a
188a
R
1-2 hrs
187b-f
188b-f
2 hrs
187g
188g
H2N
H
4 h
158j
189

Introduction

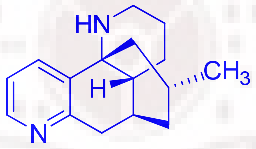
• General background

Polycyclic structures in which two or more rings are fused together have long occupied an important place in synthesis, since they are common and widely distributed in nature, especially for five- and six-membered rings. Polycyclic nitrogen heterocycles are considered to be 'privileged structures' in the pharmaceutical and agrochemical industries.[1]

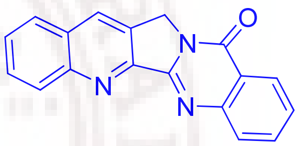


Lamellarins D, H, K and M

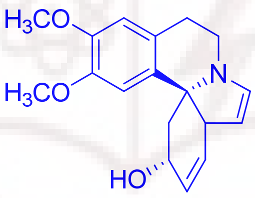
$R_1 = R_2 = H, R_3 = R_4 = CH_3$, **D**
$R_1 = R_2 = R_3 = R_4 = H$, **H**
$R_1 = OH, R_2 = R_3 = CH_3, R_4 = H$, **K**
$R_1 = OH, R_2 = R_3 = R_4 = CH_3$, **M**



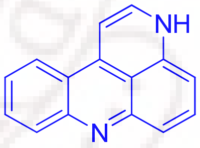
Lycodine



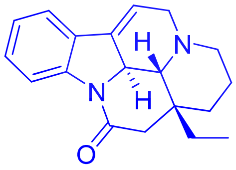
Luotonin A



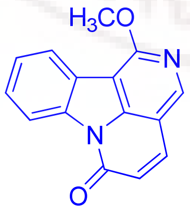
Erythravine



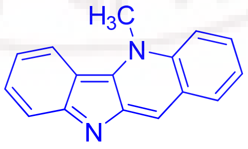
3*H*-pyrido[2,3,4-*kl*]acridine



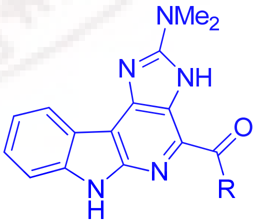
Eurnamonine



Antileukemic alkaloid



Cryptolepine



Grossularine-1, R = 3-indolyl
Grossularine-2, R = 4-hydroxyphenyl

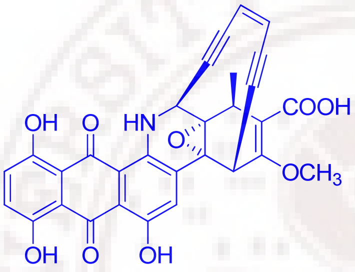
Some of the biologically important polycyclic pyrrole, pyridine, quinoline, isoquinoline, acridine and carbolines are shown above. The explorations of privileged structures in drug discovery are a rapidly emerging theme in medicinal chemistry. The exploitation of these molecules should allow the medicinal chemist to rapidly discover biologically active compounds across a broad range of therapeutic areas on a reasonable time scale. For this reason, methods of producing a diverse range of such compounds with a relatively low molecular weight are invaluable in the search for bioactive lead compounds.

Polycyclic pyrrole derivatives, lamellarins exhibit interesting biological activities including cell division inhibition, cytotoxicity and immunomodulatory activity including the recently discovered multidrug resistant (MDR) reversal and HIV-1 integrase inhibition.[2] Polycyclic pyridine derivatives are an important class of molecules due to its beneficial medicinal properties such as antipyretic and anticholinesterase activity.[3] Quinoline derivatives have a wide range of biological activities including antimalarial, and antianxiety activities including Luotonin A. Erythravine, a variety of pharmacological effects are associated with this polycyclic isoquinoline derivative including sedative, hypotensive, neuromuscular blocking and CNS activities.[4]

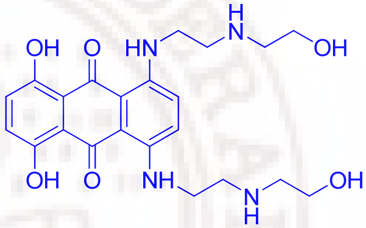
In recent years the DNA binding properties and topoisomerase II inhibitory activities of polycyclic acridines have been exploited in the development of clinically active antitumour agents.[5] The carboline moiety is an important structural subunit which occur as component of many biologically interesting, natural as well as non-natural, compounds. These polycyclic α-carbolines protects neurons against L-glutamate toxicity and a modulator of the $GABA_A$ receptor of the central nervous system[6] where as β-carbolines exhibit antidepressant activity due to their ability to inhibit an enzyme called monoamine oxidase and some of the derivatives inhibits DNA polymerase and antitumour activity.[7]

- ## Polycyclic aminoanthraquinone derivatives

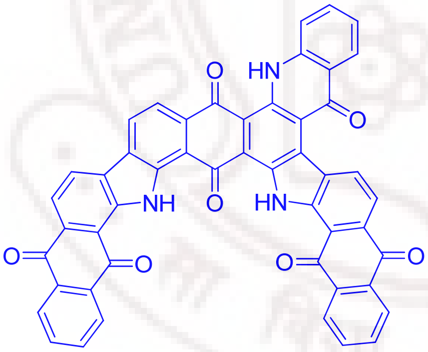
Polycyclic aminoanthraquinones have attracted considerable attention from both synthetic and medicinal chemists due to their biological activities covering a wide range of applications. The presence of five- or six-membered heterocyclic ring(s) fused with the anthraquinone moiety is essential for the ability to overcome multidrug resistance.[8] The aminoalkyl-functionalized anthraquinone series of synthetic compounds has been the subject of much study in the quest for more active and less toxic analogs of the anthracycline antitumour antibiotics daunomycin and adriamycin.[9] Anthraquinone derivatives have been utilized for the activation of human telomerase reverse transcriptase expression.[10] Several aminoanthraquinone derivatives have been identified as DNA intercalating agents.[11] Polycyclic aminoanthraquinone derivatives in the dyestuffs industry have been well established for many decades ago. Some of the important polycyclic aminoanthraquinone derivatives are shown below.



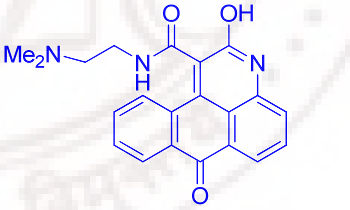
Dynemicin A



Mitoxantrone

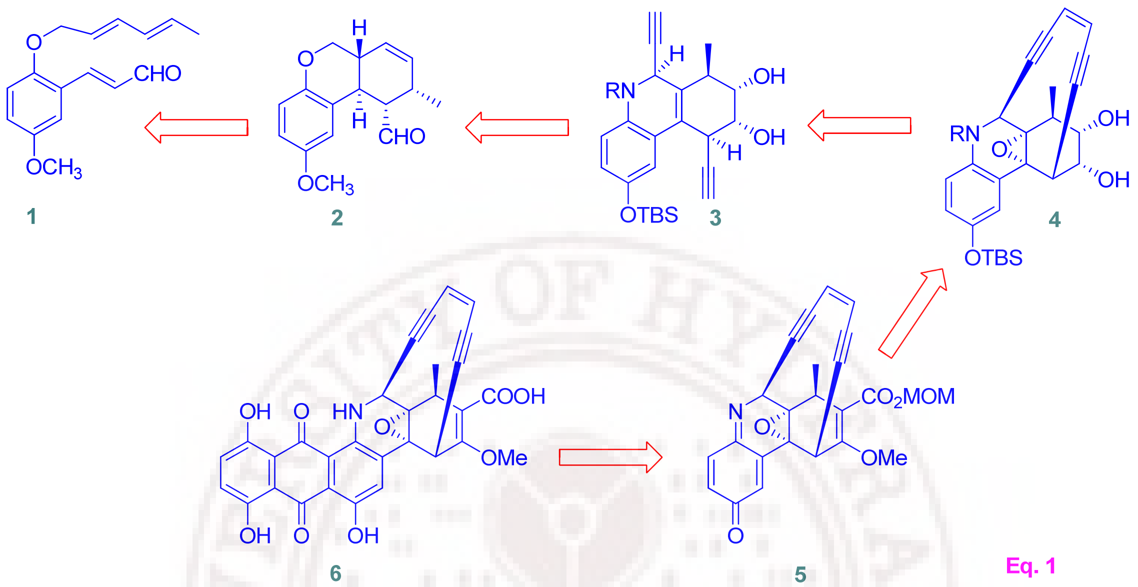


Indanthrene kaki



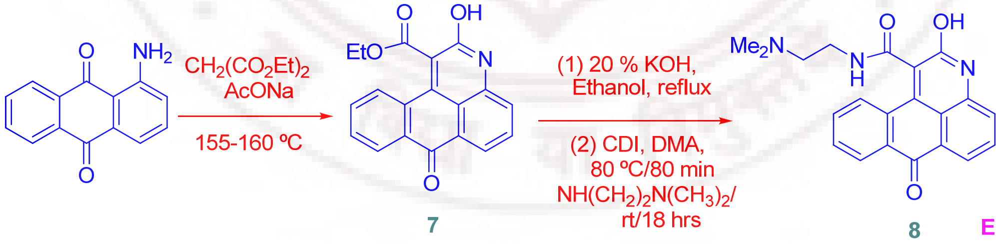
Anthrapyridone derivatives

Dynemicin A, a potent antibacterial and anticancer agent has been found to be isolated from *Micromonospora chersina* by Konishi and his colleagues at Research Institute of Bristol-Myers in Tokyo. Dynemicin A appeared to undergo bioreduction with concomitant ring-opening of the epoxide to generate the 1,4-benzenoid biradicals. Hydrogen abstraction by the radicals from the bound DNA causes cleavage of the DNA strand.[12] A number of synthetic approaches have appeared in the literature[13] for the total synthesis of Dynemicin A. Retrosynthetic analyses of the dynemicin A is shown in **Eq. 1**



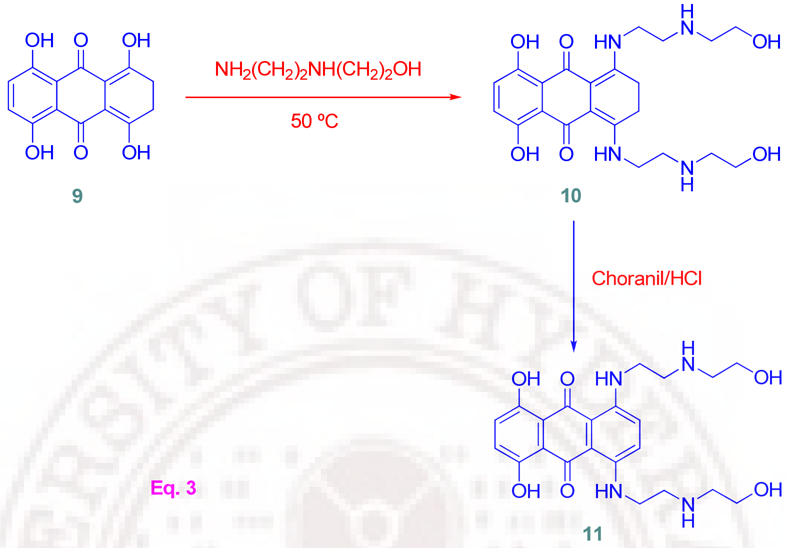
Eq. 1

Synthesis of anthrapyridone derivative is reported (**Eq. 2**)[14] from aminoanthraquinone. This derivative is showing cytotoxicity activity toward resistant tumor cell lines. It is holding only an 1-amido chain and is devoid of cytotoxicity.



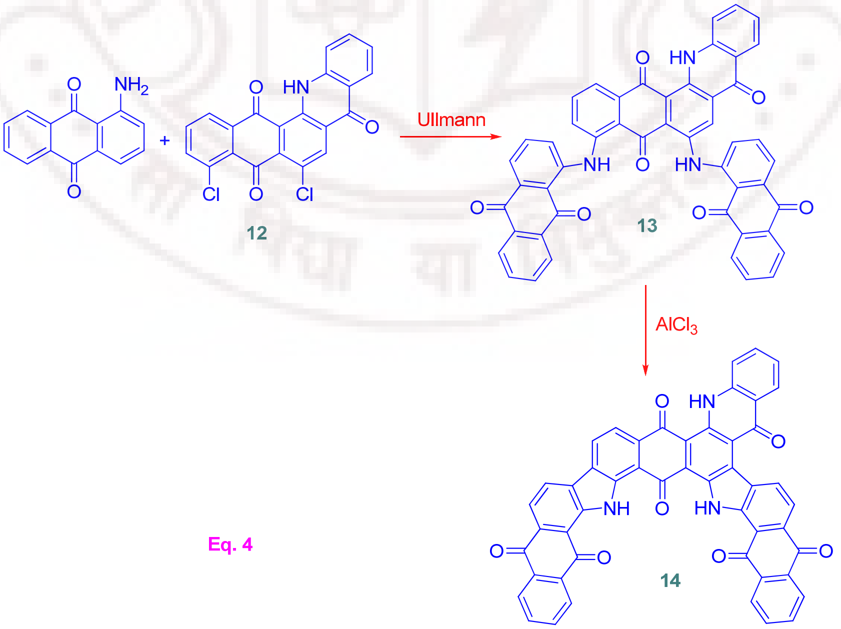
Eq. 2

Mitoxantrone is used clinically either alone or in combination with other chemotherapeutic agents to treat a variety of human cancers, particularly lung carcinoma, leukemia, melanoma and lymphoma, Hodgkin's disease and breast cancer.[9-11] Mitoxantrone inhibits RNA and DNA synthesis and intercalates with DNA, although some researchers showed that non-intercalative mechanisms were involved in its cytotoxicity against L1210 leukemia cells. Mitoxantrone synthesis was well established and one of the simple synthesis was shown in **Eq. 3**.[15]



Eq. 3

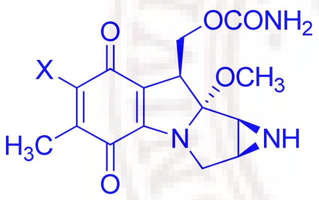
Polycyclic aminoanthraquinones are strong dye ingredients. The use of mono and di-aminoanthraquinones in the dyestuffs industry has been well established. Synthesis of Indanthrene kaki is reported[16] (**Eq. 4**) by Fox *et al.* in 1949.



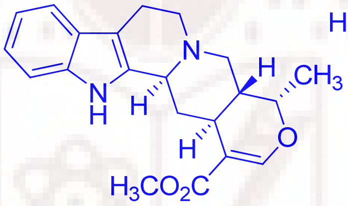
Eq. 4

• Polycyclic indole derivatives

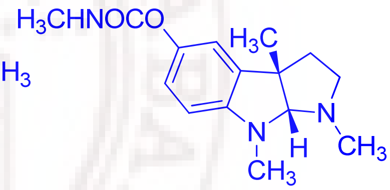
Polycyclic indole structure containing alkaloids are found in numerous natural products and synthetic compounds of vital medicinal values.[17] The indole ring system is probably the most ubiquitous heterocycle in nature. Some of these polycyclic indoles are potent inhibitors of blood platelet aggregation and thromboxane synthetase,[18a] 5HT4-receptor antagonists,[18b] antimelanoma, mycosis fungoides, and brain tumors.[18c-d] These compounds have antimicrobial activity against gram-positive bacteria and are cytotoxic to mammalian tumor cell lines *in vitro*. They were also active against both murine P388 leukemia and B16 melanoma and antibacterial activity as well as affinity for adrenergic, muscarinic and bradykinin receptors.[17a] Polycyclic indoles show antibiotic and antitumour activity and inhibit bacterial cell division through a mechanism involving DNA alkylation.[19] Some of the polycyclic indole derivatives are shown below.



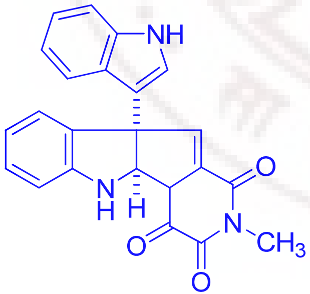
Mitomycine A X = OCH$_3$
Mitomycine C X = NH$_2$



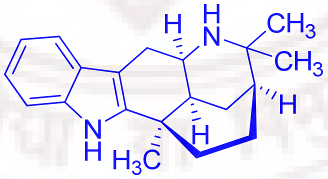
Ajmalicine



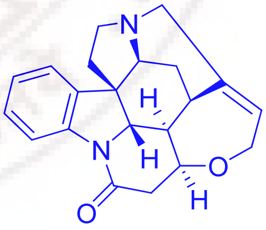
Physostigmine



Gliocladin C

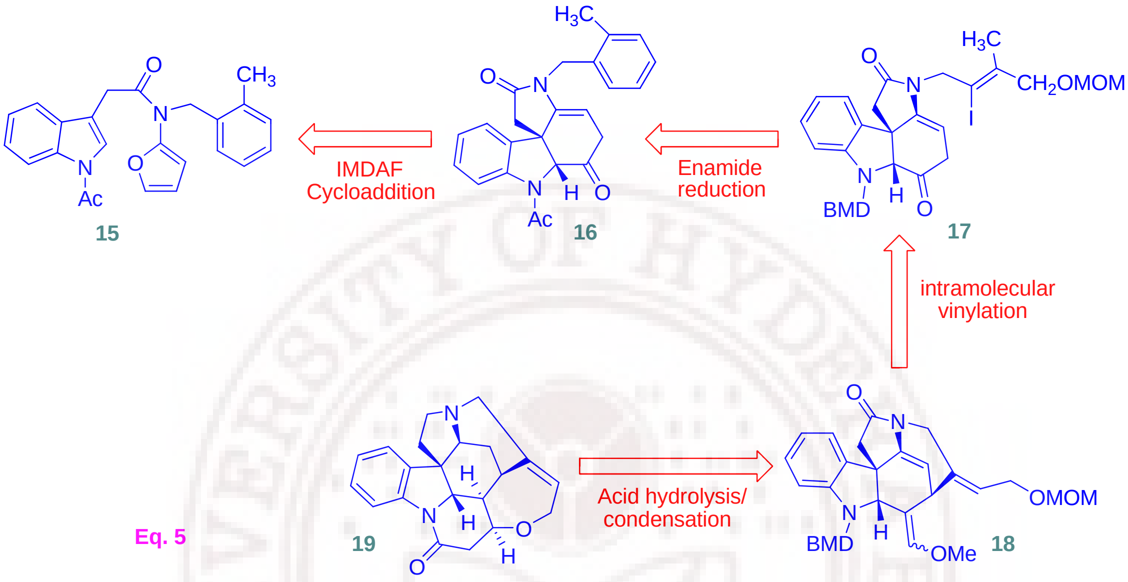


Aristoteline



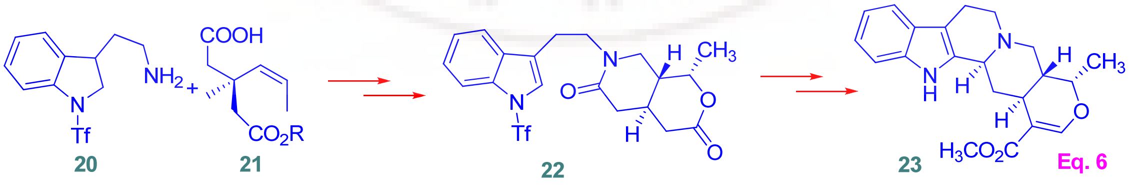
Strychnine

Strychnine was first isolated from the beans of *Strychnos ignatii* by Pierre Joseph Pelletier and Joseph Bienaimé Caventou in 1818. Strychnine acts as a blocker or antagonist at the inhibitory or strychnine-sensitive glycine receptor (GlyR), a ligand-gated chloride channel in the spinal cord and the brain. *Strychnos* alkaloids belonging to the curane type constitute an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids with highly biologically important molecule.[20] Total synthesis of strychnine was well established, one of the retrosynthetic approach is shown in **Eq. 5**.[21]



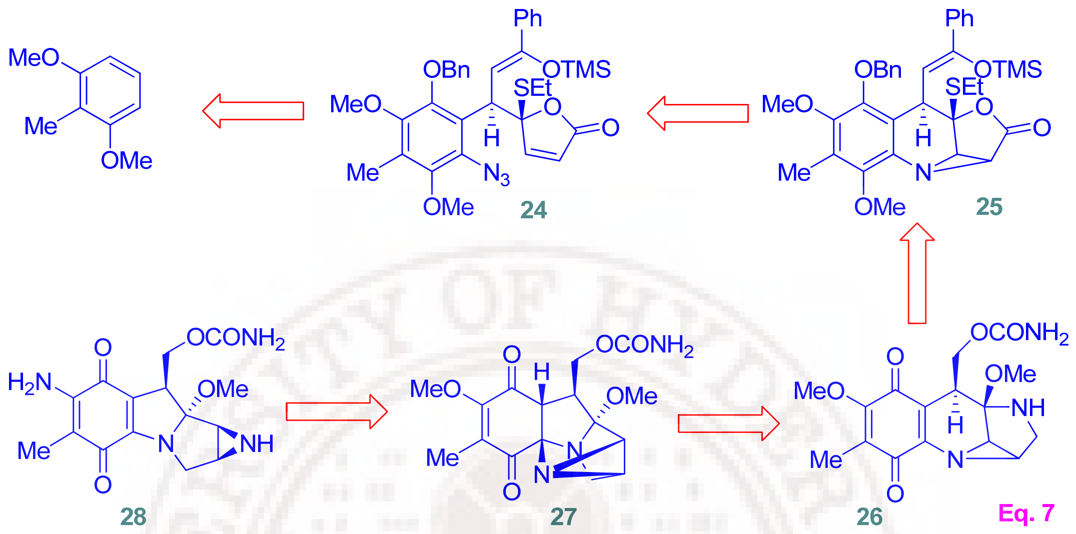
Eq. 5

Ajmalicine is a potent peripheral vasodilating agent and increases muscle caliber for short periods.[22a] Ajmalicine also reduces platelet aggregation in patients at risk due to complications of atherosclerosis and also has been prescribed for the treatment of Raynaud's disease.[22] The isolation of ajmalicine from the roots of commercially grown *Catharanthus roseus* took place in 1931. Overman and co-workers reported the total synthesis of ajmalicine (**Eq. 6**).[23]



Eq. 6

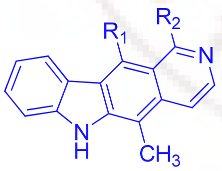
Mitomycine C finds use as a chemotherapeutic agent by virtue of its antitumour antibiotic activity. It is given intravenously to treat upper gastro-intestinal (e.g. esophageal carcinoma) and breast cancers, as well as by bladder instillation for superficial bladder tumours.[18] Fukuyama and co-workers reported[24] the synthesis as shown in Eq. 7.



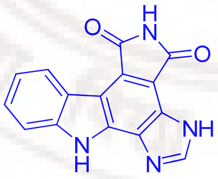
Eq. 7

• Polycyclic pyridocarbazole derivatives

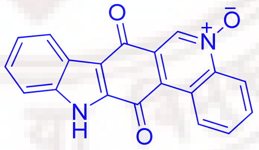
Polycyclic pyridocarbazole derivatives are endowed with antitumour and anticancer properties. They are DNA intercalating molecules, and their high DNA binding affinity is thought to be responsible in part for this pharmacological properties.[25-26]



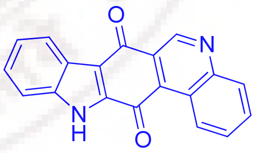
$R_1 = CH_3$, R_2 = H, **Ellipticine**
R_1 = H, $R_2 = CH_3$, **Olivacine**



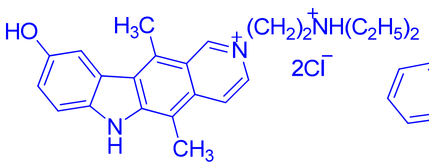
Granulatimide



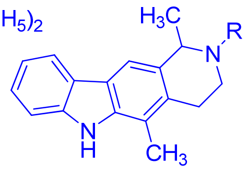
Calothrixin A



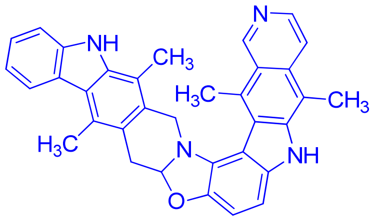
Calothrixin B



Datelliptium



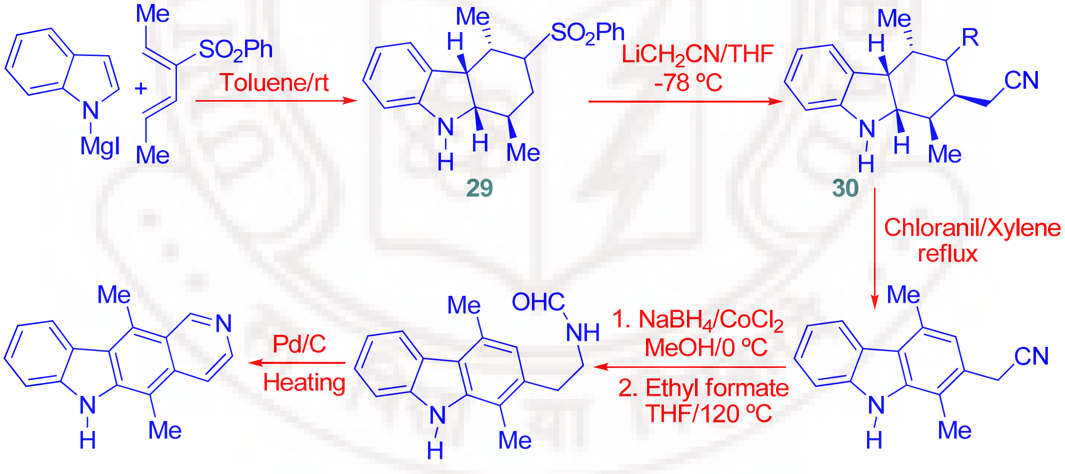
R = H, **Janetine**
R = CH_3, **Guatambuine**



Strellidimine

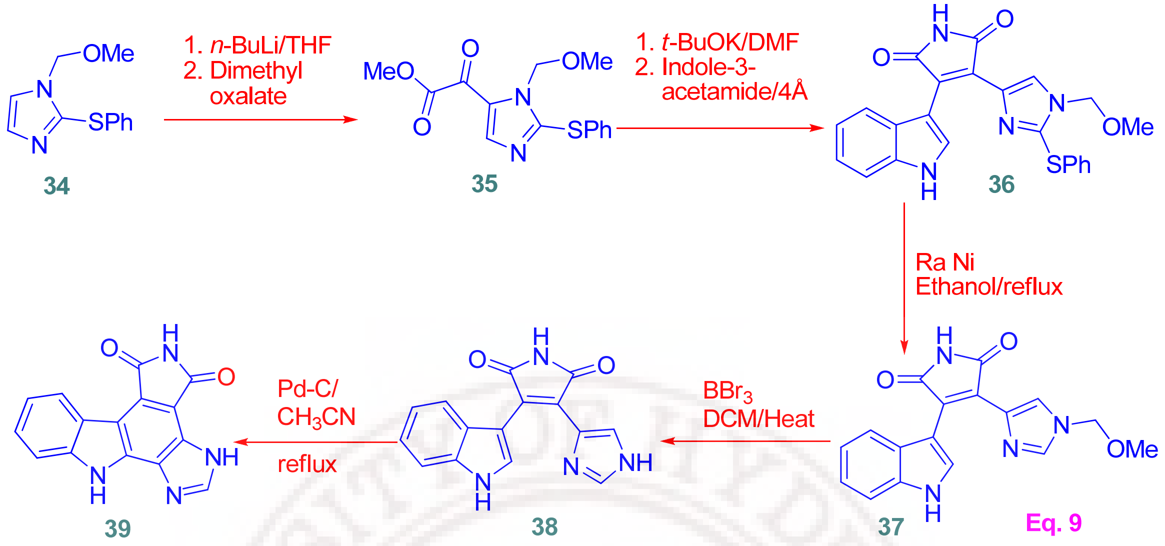
The main reason for the interest in polycyclic derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects, and complete lack of hematological toxicity[27] and several of its derivatives exhibit promising results in the treatment of osteolytic breast cancer metastases, brain tumors, kidney sarcoma, and myeloblastic leukemia.[28] More recent studies have also indicated activity against HIV.[29] Some of the important polycyclic pyridocarbazole derivatives are shown above.

In 1959, Goodwin *et al*. isolated ellipticine, a pyrido[4,3-*b*]carbazole, from the leaves of *Ochrosia elliptica* Labill.[30] In the same year Woodward *et al.* assigned this plant alkaloid as 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, confirmed by the first total synthesis.[31] One of the total synthesis was reported by Ojikawa and co-workers is shown in **Eq. 8**.[32] Bischler-Napieralski cyclization of **32** led to the ellipticine (**33**).



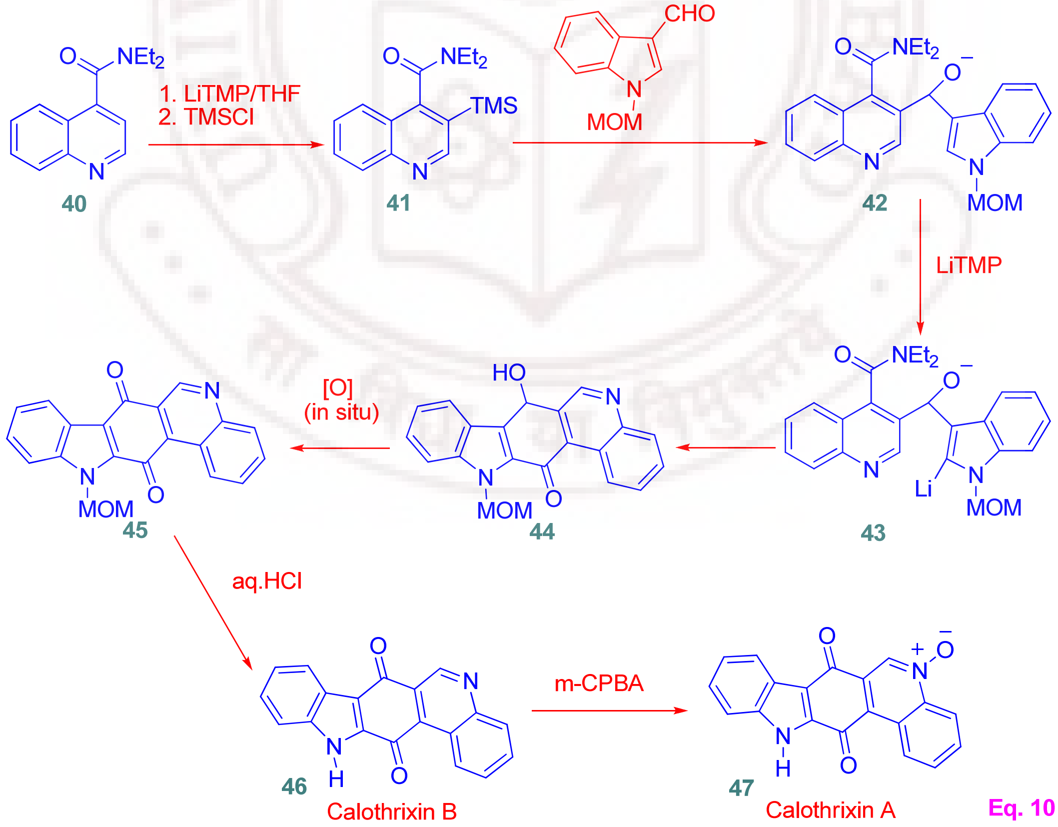
Eq. 8

The ultimate goal in the chemotherapeutic treatment of cancer is to develop drugs that are highly effective against tumor cells and have little or no effect on healthy cells. In that aspect granulatimide displayed the activity as an inhibitor of the G2 cell cycle checkpoint.[33] Reported total synthesis is shown in **Eq. 9**.[34]



Eq. 9

In 1999 Rickards, Smith, and colleagues reported the isolation and structure determination of calothrixin A and B.[35]



Eq. 10

Both compounds have exceptional (nanomolar) antimalarial activity, as well as activity against human HeLa cancer cells, and inhibition of RNA polymerase activity.[36] Kelly and co-workers have reported the synthesis of Calothrixin A and B (**Eq. 10**).[37]

• The Diels-Alder reaction

The Diels-Alder reaction is a cycloaddition reaction between a conjugated diene and a substituted alkene, commonly termed the dienophile to form a substituted cyclohexene system. **Otto Paul Hermann Diels** and **Kurt Alder** first documented the novel reaction in 1928 as 'diene synthesis' for which they were awarded the Nobel Prize in Chemistry in 1950 for their work on the eponymous reaction.[38] It presents an unrivalled opportunity for the formation of six-membered ring systems, carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds with excellent regio-, diastereo-, and enantio-selective controls.[39]

Figure 1

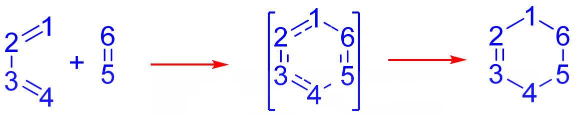
Diels-Alder reactions take place either thermally, at ambient temperatures or by Lewis acid catalysis. Among the most useful features that make the Diels-Alder reaction is primary choice to organic chemists for total synthesis of natural products are: (1) versatility of the reaction (2) simultaneous formation of two sigma bonds (3) generation of six membered ring (4) and creation of up to four stereogenic centers in one step along with high degree of regio- and stereoselectivity.

• Mechanism and reactivity

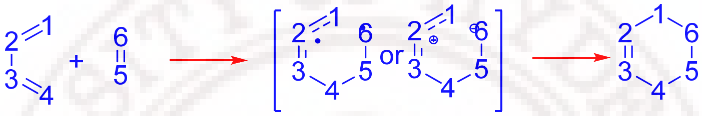
A number of mechanisms have been proposed for Diels-Alder reactions and modeled by *ab initio* or quantum mechanical calculations. Depending on the nature of the reacting partners, concerted mechanisms with symmetrical transition states, or concerted mechanisms with dipolar transition states, or even two-step mechanisms have been proposed. Finally, the theoretical and experimental evidence shows that this [4+2] cycloaddition can be concerted or stepwise (**Fig. 2**).[40]

Figure 2

one-step (concerted):



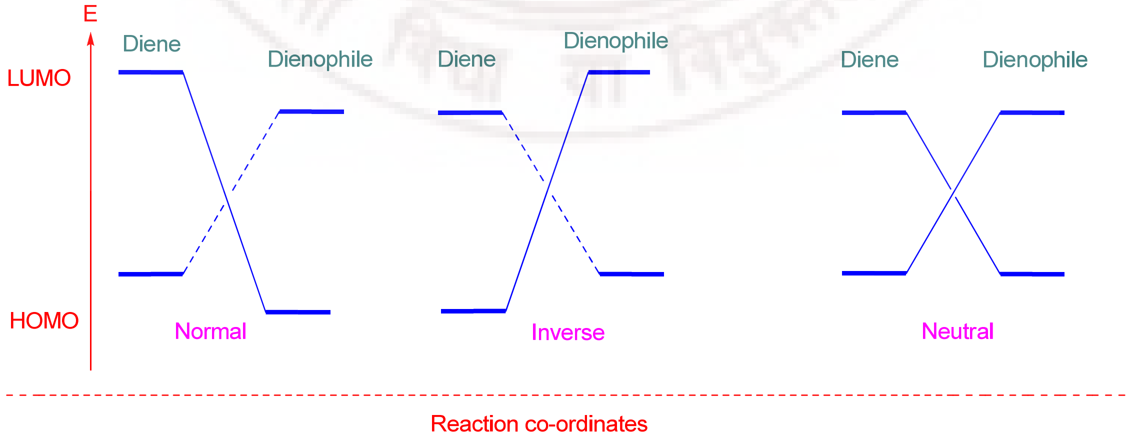
Two-step (nonconcerted):



biradical or zwitterionic

According to frontier molecular orbital theory (FMO), the reactivity, regioselectivity and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial *in phase* interaction of the highest occupied molecular orbital (HOMO) of the one component and the lowest unoccupied molecular orbital (LUMO) of the other. These orbitals are the closest in energy; **Fig. 3** illustrates the two dominant orbital interactions of the symmetry allowed Diels-Alder cycloaddition.

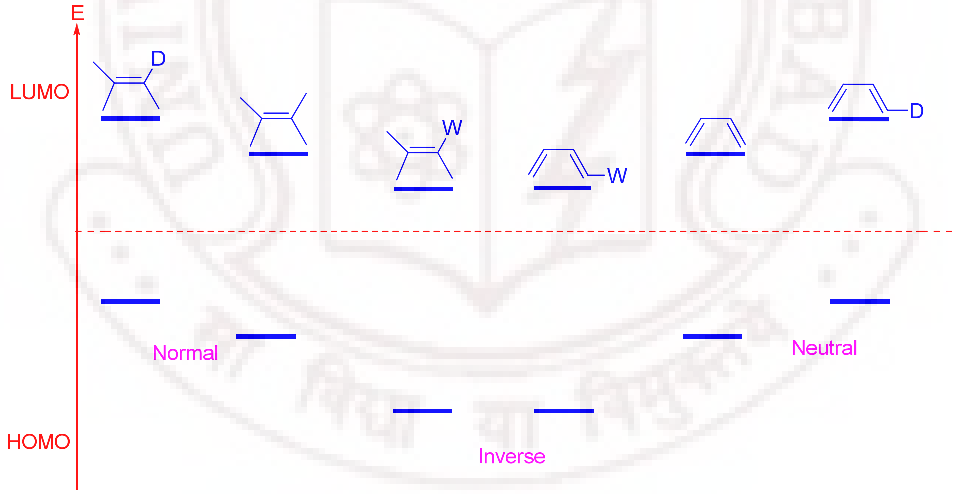
Figure 3



The normal Diels-Alder reactions are accelerated by electron donating substituents in the diene and by electron withdrawing substituents in the dienophile but in the **inverse Diels-Alder reactions** are influenced by electronic effects of the substituents in the opposite way. **The neutral Diels-Alder reactions** are insensitive to substituents in either the diene or dienophile.

The reactivity of the Diels-Alder reaction depends on the HOMO-LUMO energy separation of components: the lower the energy difference, the lower is the transition state energy of the reaction. Electron withdrawing substituents lower the energy of both HOMO and LUMO, while electron donating groups increase their energies. Factors that lower the HOMO-LUMO distance (i.e. substituent effects) increase the reaction rate due to the fact that the smaller energy difference allows for a greater contribution to the stabilization of the transition state (**Fig. 4**).

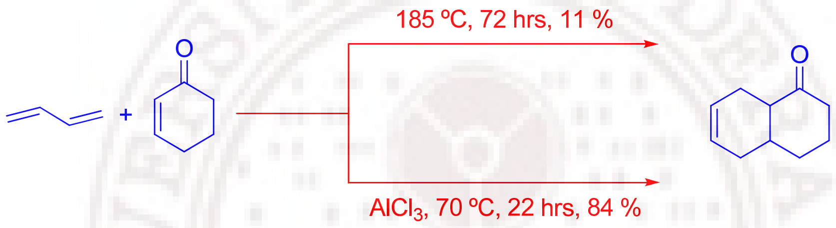
Figure 4



Lewis acid can greatly accelerate the Diels-Alder cycloaddition reaction. The catalytic activity explained by FMO theory considering that the coordination of carbonyl oxygen by Lewis acid increase the electron withdrawing effect of the carbonyl group on the carbon-carbon double bond and lower the LUMO dienophile energy.

Many Diels-Alder reactions have been conducted at high reaction temperatures without catalysts, heat-sensitive compounds cannot be employed in complex multistep syntheses. So in these cases, Lewis acid catalysts enable the reactions to proceed at room temperature, or below, with good yields. For example thermal Diels-Alder reaction of 1,3-butadiene and 2-cyclohexenone requires high temperatures and long reaction times with poor yield. With discovery of Lewis acid catalysis of the Diels-Alder reaction the reactivity of ketone towards diene increased and the reaction condition becomes milder with the good yield (**Fig 5**).

Figure 5

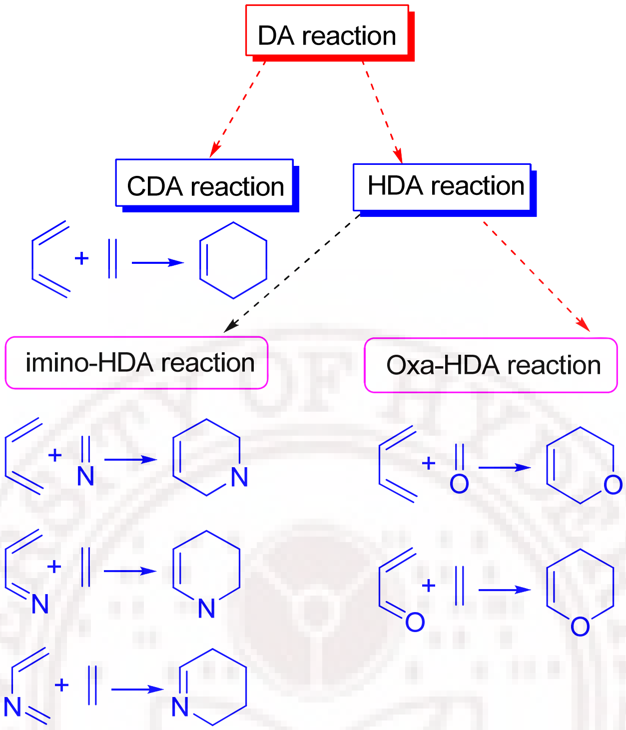


Much of the activity in imino Diels-Alder reactions has involved activation by Lewis acids. For example, La(OTf)$_3$, Yb(OTf)$_3$, Sc(OTf)$_3$, and In(OTf)$_3$ are effective and can tolerate the presence of small amounts of water.

• The imino Diels-Alder reaction

The Diels-Alder reaction methodology contains two basic variants of reaction, which can be classified as carbon-Diels-Alder reaction (CDA) and hetero-Diels-Alder reaction (HDA), which could be also subdivided as like oxa-Diels-Alder reaction and imino-Diels-Alder reaction. Hetero Diels-Alder reactions are becoming a mainstay of heterocycles and natural product synthesis.[41] Among these reactions, the imino Diels-Alder provides a useful method for the incorporation of a nitrogen atom in the ring structure. It provides a rapid construction of functionalized heterocyclic rings with control of regio-, diastereo- and enantio-selectivity.[42-44] The key to realizing this potential has been the substantial progress in recent years to activate the imine system toward cycloaddition. In the first and most common method the imine function appears as the dienophile. In the second and third variants the imine is found in the diene as either 1-azadiene or 2-azadiene structures (**Fig. 6**).

Figure 6



Imines are readily available from the corresponding aldehydes and ketones. This allows a variety of imine dienophile substrates to be available. The imine dienophile generally needs to be activated or used in conjunction with active dienes. The advance of the azadiene imino Diels-Alder reaction to the status of a general synthetic method owes much to the development of methods to activate the azadiene system. With appropriate substitution on both 1-aza-1,3-butadienes and 2-aza-1,3-butadienes are reactive as either electron-rich or electron-deficient Diels-Alder dienes. Reviews featuring the general synthetic utility of azadienes in the Diels-Alder reaction specifically have appeared in recent years.[45]

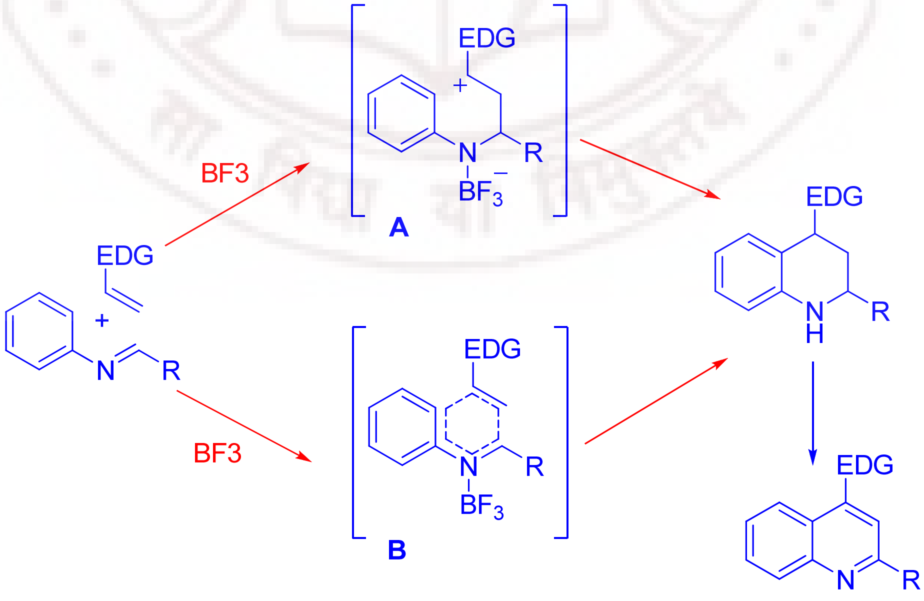
• Mechanistic aspects

The reactivity of the imines can be increased by activating groups such as sulfonyls or carbonyls and are commonly used to promote imine reactivity in Diels-Alder reactions. These activating groups may be attached either to the imine carbon or the nitrogen atom or to both. The cycloaddition type and corresponding reaction rate correlate with the magnitude of the smallest diene-dienophile HOMO-

LUMO energy difference. Electronic and structural features of the reagents determine the size of this energy difference and consequently the nature of the reaction. Azadienes generally require some form of activation to achieve general synthetic utility. The advance of the azadiene imino Diels-Alder reaction to the status of a general synthetic method owes much to the development of methods to activate the azadiene system. With appropriate substitution both 1-aza-1,3-butadienes and 2-aza-1,3-butadienes are reactive as either electron rich or electron deficient Diels-Alder dienes.

Two limiting mechanisms are possible in the imino Diels-Alder reaction. The reaction may take place in a concerted fashion, with partial formation of the two new bonds in the single transition state. If both bonds are formed to exactly the same extent in the transition state, this is called a synchronous concerted reaction; otherwise, it is asynchronous. The other extreme is a stepwise process, involving first the formation of an intermediate with a single bond formed between diene and dienophile; subsequent formation of the second bond gives the cycloadduct. Both step may be rate determining, and such an intermediate may be either diradical or zwitterionic.

Figure 7

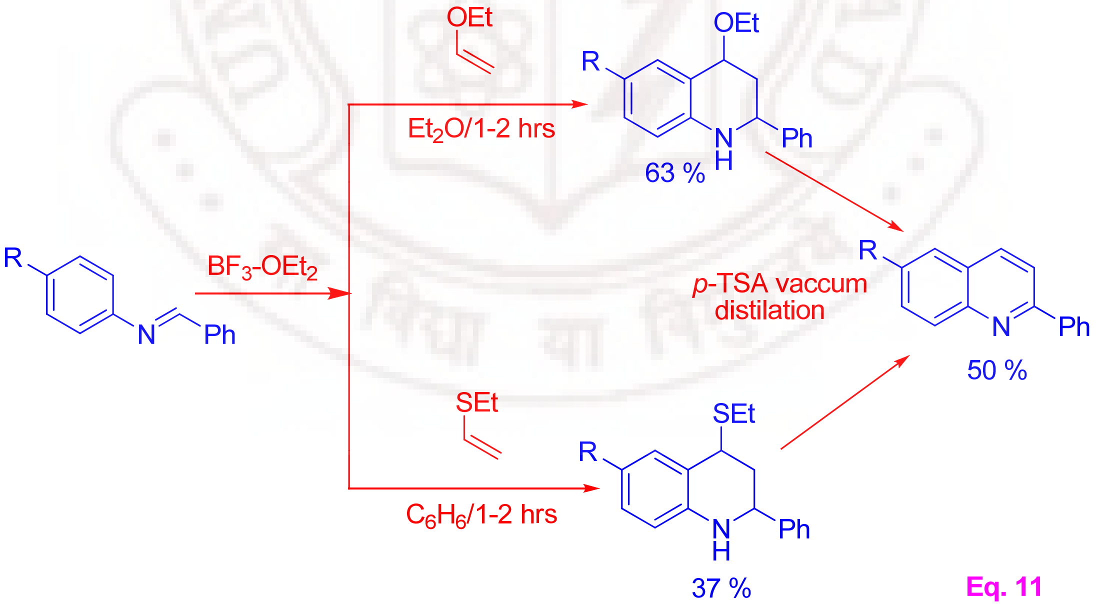


A stepwise mechanism via ionic intermediates (A) with the final step being an intramolecular electrophilic substitution of a carbenium ion was proposed as a more probable mechanism than a concerted one where a concerted asynchronous transition state (B) was suggested (**Fig. 7**).[46]

• Examples of imino Diels-Alder reaction.

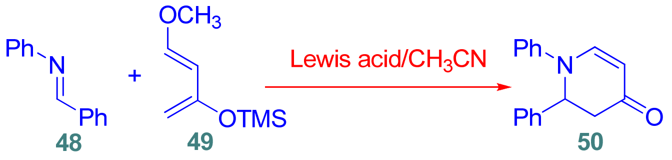
Interaction between *N*-aryl imines and electron-rich dienophiles was first discovered by Povarov in 1967. So the reaction between electron deficient Schiff bases and electron-rich alkenes are called Povarov reaction.[47]

The first works of Povarov[48] described reactions of ethyl vinyl ether or ethyl vinyl sulfide and *N*-aryl aldimine under BF_3-OEt_2 to obtain 2,4-substituted tetrahydroquinolines which were converted into corresponding quinoline product. Depending on the reaction conditions the tetrahydroquinolines or quinolines, formed by Lewis acid, become the main products of the Povarov reaction (**Eq. 11**).



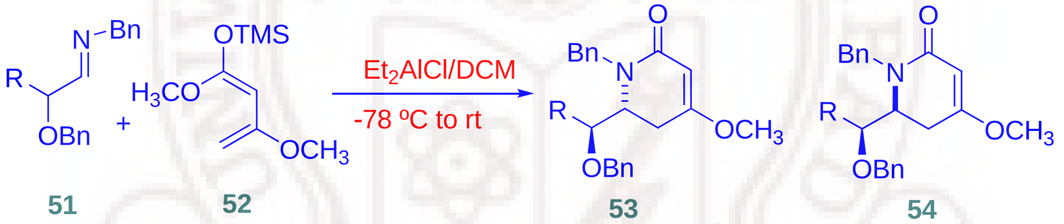
Eq. 11

Much of the activity in imino Diels-Alder reactions has involved activation by Lewis acids. Rare earth metal triflates have been investigated under various conditions. For example, $Yb(OTf)_3$, $Sc(OTf)_3$, and $In(OTf)_3$ are effective and can tolerate the presence of small amounts of water (Eq. 12).[49]



Eq. 12

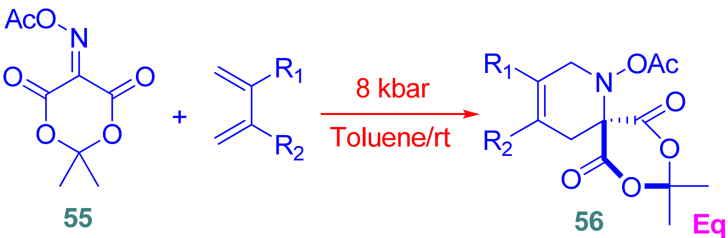
Stereoselective cycloadditions of imines and dienes have been extensively investigated recently. Some of the first stereoselective cycloadditions were of imines derived from α-alkoxyaldehydes.[50] Cycloaddition of α-alkoxy imine **51** with diene **52** gave the best selectivities when promoted by Et_2AlCl (Eq. 13). Two equivalents of Et_2AlCl gave the highest ratios of stereoisomers. The highest selectivity was observed with *tert*. butyl group.



R = *i*-propyl, 40:60
R = *n*-pentyl, 10:90
R = *t*-butyl, 01:99

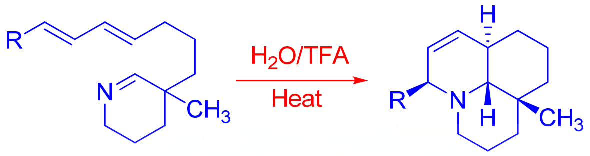
Eq. 13

There are few new examples of imino Diels-Alder reactions with imines derived from ketones. Oximinoacetate **55** derived from Meldrum's acid undergoes cycloaddition with dienes under high-pressure (Eq. 14).[51]



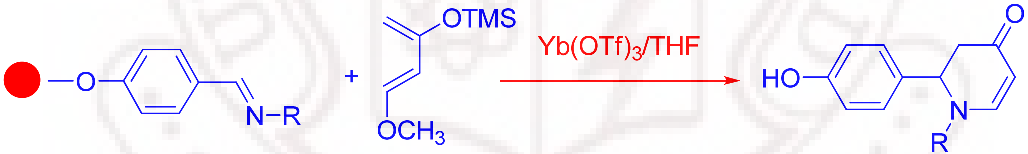
Eq. 14

In an effort to synthesize imino tricyclic compound **58** by intramolecular imino Diels-Alder reaction, Grieco synthesized **58** by heating **57** with TFA/H_2O in 55 % yield (**Eq. 15**).[52]



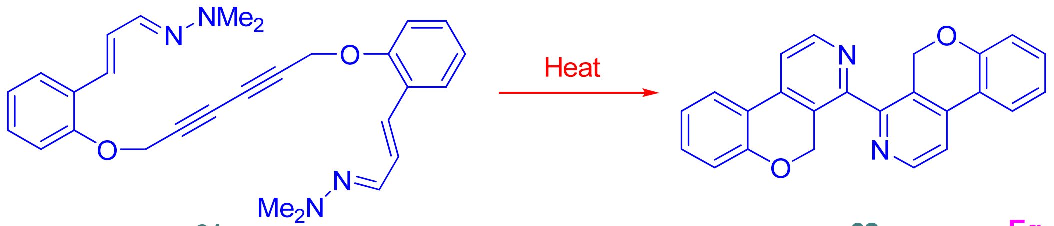
57 58 **Eq. 15**

Imines supported on polymers undergo imino Diels-Alder cycloaddition. The imine has been generated from polymer supported aldehyde or amines. Survey of different Lewis acids shows that $Yb(OTf)_3$ gave the highest yields (**Eq. 16**).[53] The resulting cycloadducts were removed from the bead. In the case of imines derived from polymer bound aldehydes, the product cleavage incorporated the aromatic group from the polymer. In the case of imines derived from polymer bound amine, the cycloadducts cleavage took place at the nitrogen atom of the cycloadduct.



59 49 60 **Eq. 16**

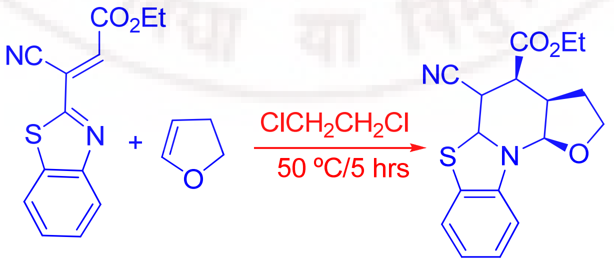
Theoretical studies of the transition state for the Diels-Alder reactions of unsubstituted 1-azabutadienes support the conclusion that the terminal nitrogen lowers the LUMO of the diene to allow for an inverse electron demand type reaction. The introduction of electron donor groups to the imine nitrogen reverses the natural electron-deficient character of the 1-azadienes. Sufficient donation raises the HOMO of the azadiene and causes the reaction to proceed through the $HOMO_{diene}$-controlled manifold.



61 62 **Eq. 17**

Ghosez *et al*. demonstrated the utility of 1-dimethylamino-1-azadienes in some of the addition of electron donor groups to facilitate normal electron demand Diels-Alder reactions (**Eq. 17**).[54] In these reactions the conjugative interaction between the lone pair of the amine nitrogen with the enimine system is critical to the activation. The importance of interaction of the tertiary nitrogen lone pair with the azadiene is manifested in the yields of the intramolecular double imino Diels-Alder reaction of compound **61**. Even with the introduction of the electron releasing dimethylamino group the necessary conditions for reactions to simple dienophiles are generally relatively harsh.

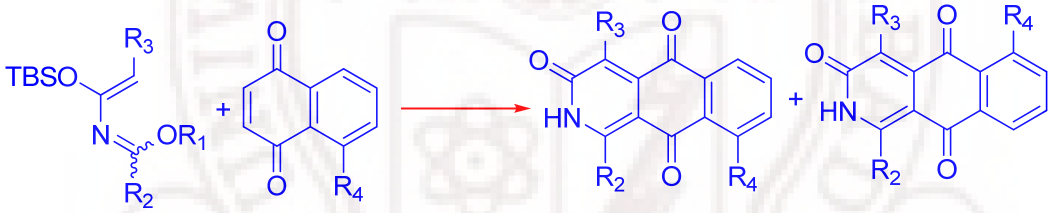
In subsequent studies, electron-withdrawing carboxylic ester functionality replaced the aromatic ring at C-4. This species proved to be a highly reactive azadiene with cycloadditions to electron-rich dienophiles proceeding in good to excellent regio- and endo-selective yield at ambient temperatures to 50 ºC (**Eq. 18**). Reactions with electron poor dienophiles proved much less facile, suggesting that the reaction proceeds through an inverse-electron demand manifold.



63 64 **Eq. 18**

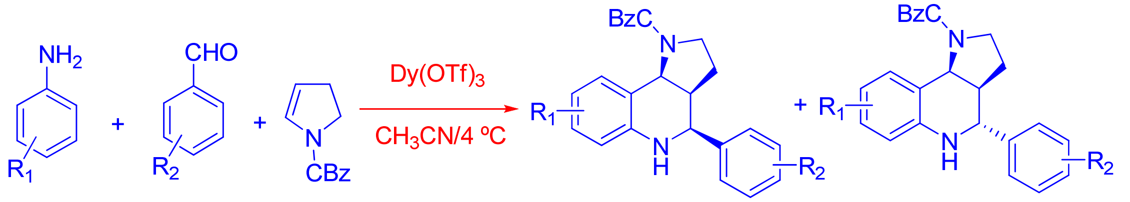
Like the 1-aza-1,3-butadienes, 2-aza-1,3-butadienes have proven to be useful reagents for the imino Diels-Alder based synthesis of pyridones, isoquinolones and pyrimidones of defined substitution patterns. While generally more reactive they mirror the behavior of the 1-aza-1,3-butadienes in that appropriate substitution renders them electron-rich or electron-deficient. A major difference between the two systems is the efficacy of Lewis acid catalysis in the 2-azadiene cycloadditions. The success of Lewis acid mediated cycloadditions depends on the identification of a Lewis acid which, by complexing an appropriate functional group, activates the dienophile and does not irreversibly complex the azadiene nitrogen.

The cycloaddition of 3-siloxy-2-azadienes to 5-substituted naphthoquinones produces the biologically interesting 2-azaanthraquinon-3-ones (**Eq. 19**).[55] As in the cycloadditions to 1-azadienes, the regiochemistry of the addition is subject to the directing effect of the C-5 group. Substituent groups that are not sufficiently electron donating often lead to the formation of mixtures of products that are difficult to separate.



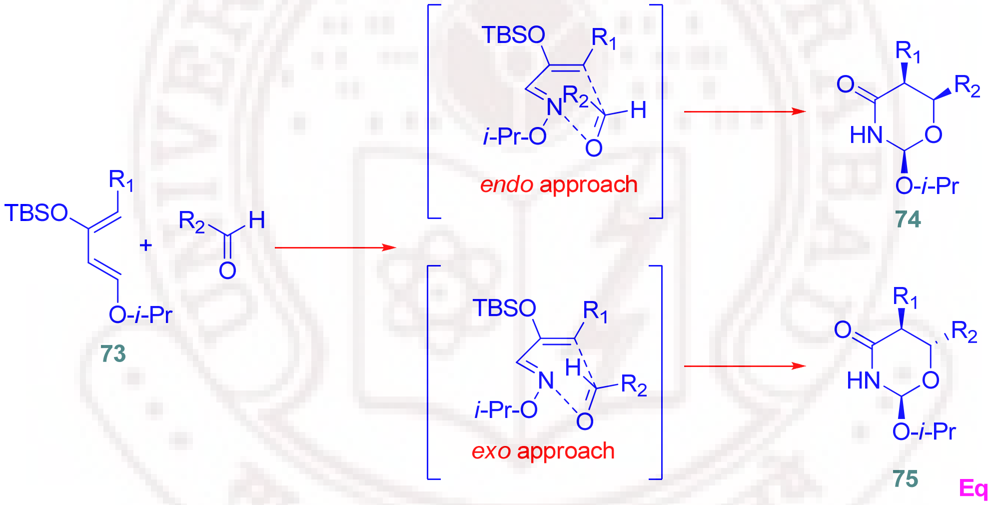
65 **66** **67** **68** **Eq. 19**

Batey *et al.*[56] utilized the CBz protected enamide as the dienophile in their study and they also employed *in situ* generation of the N-arylimine (**Eq. 20**). Using a variety of aromatic aldehydes the cycloaddition yields in acetonitrile were moderate to excellent. The diastereoselectivity proved to be strongly solvent dependent. With water as a co-solvent it was markedly improved. The source of the increased diastereoselectivity was suggested to be due to the hydrophobic effect by which a more compact transition state induces *endo*-selectivity.



70 71 72 **Eq. 20**

Cycloadditions of 2-azadienes with electron-deficient olefins show an interesting stereoselectivity. In the reactions with cyclic dienophiles, *endo*-selectivity is observed, while with acyclic dienophiles *exo*-selectivity predominates. The selectivity has been attributed to the reacting conformations. The *endo*-transition state stabilized by secondary orbital interactions and lacking electrostatic repulsion between the hetero atoms would be preferred over the *exo* transition state in reactions of cyclic dienophiles constrained to the s-*trans* conformation (**Eq. 21**).



73 74 75 **Eq. 21**

In the acyclic case, reaction would proceed through the s-*cis* conformation. The *exo*-transition state is preferred largely due to electrostatic repulsion between the hetero atoms, which would overcome the stabilization due to secondary orbital interactions in the *endo*-transition state. Asymmetric imino Diels-Alder reactions of electron-rich 3-silyloxy-2-azadienes and aldehydes have been studied.[57] These azadienes are more reactive toward aldehydes than the Danishefsky's diene counterparts, and therefore do not require Lewis acid catalysis. The reactions are predominately *endo*-selective in accord with the general trend of cycloadditions to aldehydes.

• The Lewis acid

"A Lewis acid is a species with a vacant orbital and that can accept a pair of electrons from a Lewis base", G. N. Lewis proposed this definition in his chemical bonding theory in 1923.[58] A wide varieties of elements (Al, Sb, B, Cd, Ce, Co, Cu, Eu, Ge, Hf, Fe, La, Mg, Mo, Ni, Pd, P, Si, Ag, S, Tl, Sn, Ti, Va, Yb, Zn, and Zr) can be used as Lewis acid reagents and each metal has its own characteristic features. The acidity of Lewis acids of the type MXn has been suggested, where X is a halogen atom or an inorganic radical: $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$. Lewis acidity depends on the nature of the base and any solvent that can function as a base.

Lewis acid promoted carbon-carbon bond formation is one of the most important processes in modern organic synthesis. Classically, the Friedel-Crafts reaction, the ene reaction, the Diels-Alder reaction, and the Mukaiyama aldol synthesis are catalyzed by ordinary Lewis acids such as $AlCl_3$, $TiCl_4$, BF_3-OEt_2, or $SnCl_4$ but later more sophisticated systems have been developed. These classical Lewis acids activate the functional groups of substrates, and the reactions proceed with relatively low stereo-, regio-, or chemoselectivity. When coordinated with a well-designed ligand(s), a Lewis acid has substantially different reactivity. Furthermore, designer Lewis acids lead to isolation of monomeric Lewis acid species with structural features that can be easily understood and extended to selective new designer chiral catalysts for asymmetric syntheses. Thus, metal ligand tuning is the most essential component in the design of Lewis-acid reagents.

Lewis acid-mediated reactions can be classified into two groups. In the first (type 1) the complex between substrate and Lewis-acid reagent produces the product. Claisen rearrangement promoted by a Lewis-acid catalyst is a typical example of this type. Some complexes formed between Lewis acids and substrates are, however, stable enough to react with a variety of reagents from outside the system to generate the product (type 2). The Diels-Alder reaction between Lewis acid activated unsaturated carbonyl compounds and dienes is an example of type 2 reactions.

• The Ionic liquid

The continuing depletion of natural resources and growing environmental awareness has necessitated changes in the practices of both the chemical industry and academia. Solvents are high on the list of damaging chemicals for two simple reasons: (i) they are used in huge amounts and (ii) they are usually volatile liquids that are difficult to contain. One strategy that addresses these issues is the replacement of deleterious molecular solvents with environmentally more benign, reaction enhancing alternatives i.e., ionic liquids.

Definition of ionic liquid is fused salts or liquids containing only ions. Ionic liquids also can be defined as pure compounds, consisting only of cations and anions (i.e., salts), which melt at or below 100 ºC.[59] It is possible, by careful choice of starting materials, to prepare ionic liquids that are liquid at and below room temperature. It is these "*room temperature ionic liquids*" that are widely used in organic synthesis. It is noteworthy that while the term ionic liquid, used to describe a low temperature molten salt, has only moved into common usage relatively recently, reports of 'fused salts' [60] and 'molten salt solvents' [61] are also comes under this category only. Ionic liquids are not new; some of them have been known for many years[62], for instance $[EtNH_3][NO_3]$, which has a melting point of 12 °C, was first described in 1914. Higher melting salts in synthesis are also available.[63]

Some simple physical properties of the ionic liquids that make them interesting as potential solvents for synthesis are the following: (1) they are good solvents for a wide range of both inorganic and organic materials, and unusual combinations of reagents can be brought into the same phase. (2) They are often composed of poorly coordinating ions, so they have the potential to be highly polar yet noncoordinating solvents. (3) They are immiscible with a number of organic solvents and provide a nonaqueous, polar alternative for two-phase systems. Hydrophobic ionic liquids can also be used as immiscible polar phases with water. (4) Ionic liquids are nonvolatile, hence they may be used in high-vacuum systems and eliminate many containment problems.

The most common ionic liquids in use are those with alkylammonium, alkylphosphonium, *N*-alkylpyridinium, and *N*,*N*'-dialkylimidazolium cations (**Fig. 8**).

Figure 8. (a) Alkylammonium (b) alkylphosphonium (c) *N*,*N*'-dialkylimidazolium and (d) *N*-alkylpyridinium cations.

There are two basic methods for the preparation of ionic liquids: metathesis of a halide salt with, for instance, a silver, group 1 metal or ammonium salt of the desired anion and acid-base neutralization reactions. Many alkylammonium halides are commercially available or they can be prepared simply by the reaction of the appropriate halogenoalkane and amine. Preparation of the pyridinium and imidazolium halides can be achieved similarly.[64] Other ionic liquids are made by the quarternerization of the appropriate amine.

Their negligible vapour pressure, ease of handling and potential for recycling, circumvent many of the problems associated with volatile organic solvents. Furthermore, their high compatibility with transition metal catalysts and limited miscibility with common solvents enables easy product and catalyst separation with the retention of the stabilized catalyst in the ionic phase. These and related ionic liquids have been successfully employed as the media in a number of reactions, which include the Baylis–Hillman reaction, Knoevenagel condensation, Claisen–Schmidt condensation, Horner–Wadsworth–Emmons reaction, Heck reaction, Suzuki coupling, Stille coupling, Sonogashira reaction, Nitration, Elimination reactions, hydrogenations, alkene dimerizations, Diels–Alder and Friedel–Crafts reactions.[65]

The chemistry of room-temperature ionic liquids is at an incredibly exciting stage in its development. No longer are mere curiosities, ionic liquids beginning to be used as solvents for a wide range of synthetic procedures. The solvent environment that is provided by the ionic liquids is quite unlike any other available at or close to room temperature. Already, starting differences have been seen between reactions in ionic liquids and molecular solvents. As the number of investigations increases, we will be able to tell if there is any general "ionic liquid effect". Potentially any reaction may produce interesting results in ionic liquids, and the discovery of the new chemistry waiting to be found will be a mammoth task.

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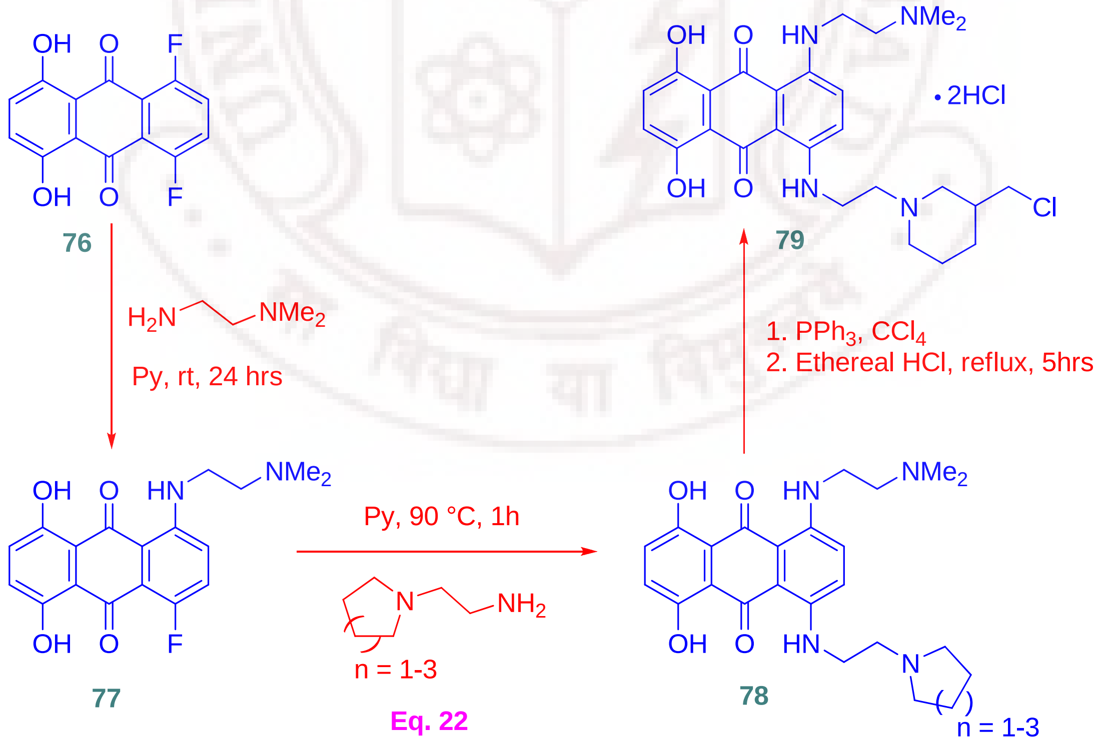
Synthesis of Polycyclic Aminoanthraquinones

CHAPTER 1

1.1. Introduction

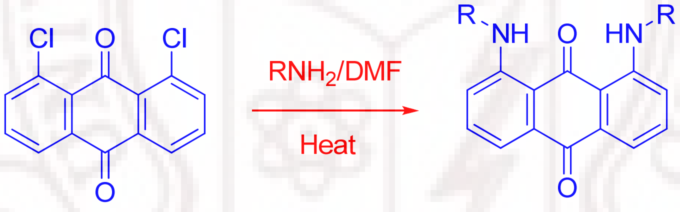
Development of efficient and convenient methodologies for the synthesis of polycyclic aminoanthraquinone derivatives has been and continues to be an attractive and challenging endeavor in organic and medicinal chemistry because of the presence of these frameworks in a number of bio-active natural products. Symmetrically (identical side chains) 1,4-disubstituted derivative, mitoxantrone was a clinically utilized aminoanthraquinone that is DNA intercalator and topomerase II inhibitor.[66]



Eq. 22

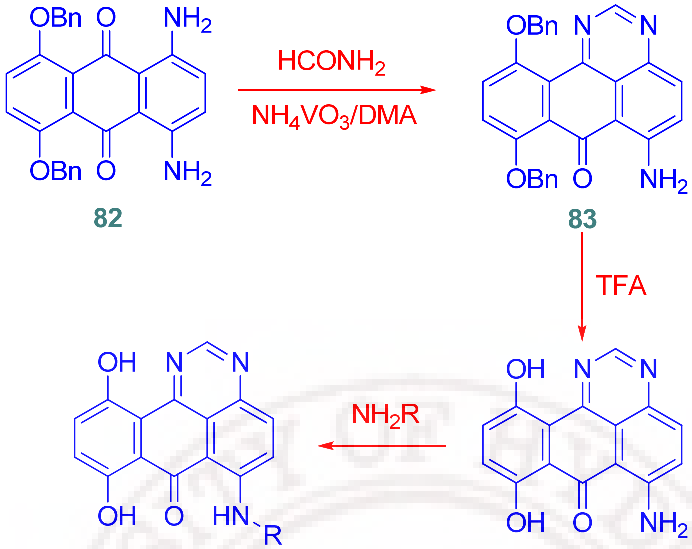
Peterson and co-workers proved that non-symmetrically 1,4-disubstituted aminoanthraquinones also possess enhanced cytotoxic potential under the conditions of over expression of topo II.[67] Krapcho *et al.* have shown that these unsymmetrical molecules are more cytotoxic than mitoxantrone in a colon carcinoma cell line and its doxorubicin-resistant variant.[68] So the synthesis of unsymmetrical 1,4-disubstitued aminoanthraquinones are considered to be very important. Peterson and co-workers developed a simple methodology, starting with 1,4-difluoro-5,8-dihydroxyanthraquinone (**76**) for this unsymmetrical molecules was shown in **Eq. 22**.[8b]

1,8-disubstituted aminoanthraquinone derivatives also enhanced the anticancer properties and showed the superior cytotoxicity. These anthraquinones were synthesized by condensing an excess of the appropriate amine with commercially available 1,8-dichloroanthraquinone and gave rise to the desired diaminoanthraquinones in good overall yield (**Eq. 23**).[69]



80 **81** Eq. 23

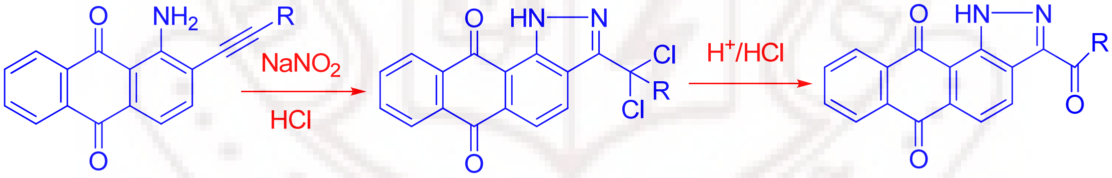
Mitoxantrone is an important antitumor agent with demonstrated clinical efficacy in the treatment of leukemia, lymphomas, and breast cancer.[9-11] However, some undesired side effects have been reported, principally cardiotoxicity.[70] In recent years the problem of multidrug resistance (MDR) toward numerous antitumor compounds has also become important. For this purpose aminoanthraquinone derivatives with unsymmetrical side chains and aza analogues containing pyridine or pyridazine rings are noteworthy. Borowski and co-workers reported a facile synthesis for MDR molecules as shown in **Eq. 24**.[71]



82 83 84 85

Eq. 24

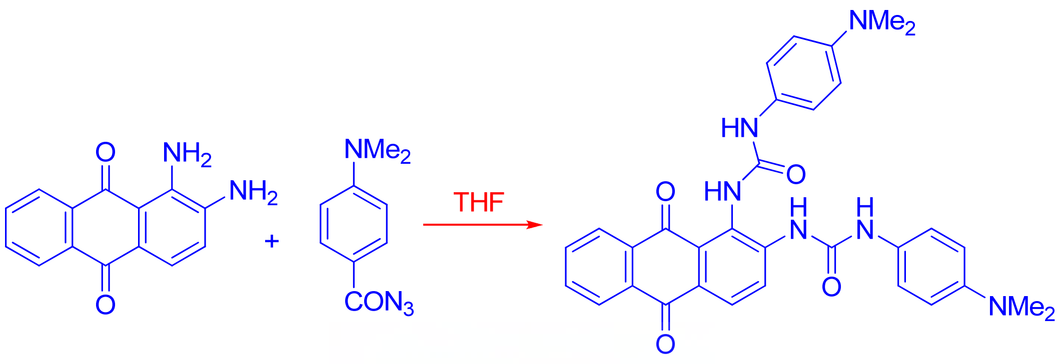
Fedenok and co-workers reported[72] the synthesis of pyrazole fused anthraquinone derivative as shown in **Eq. 25**.



86 87 88

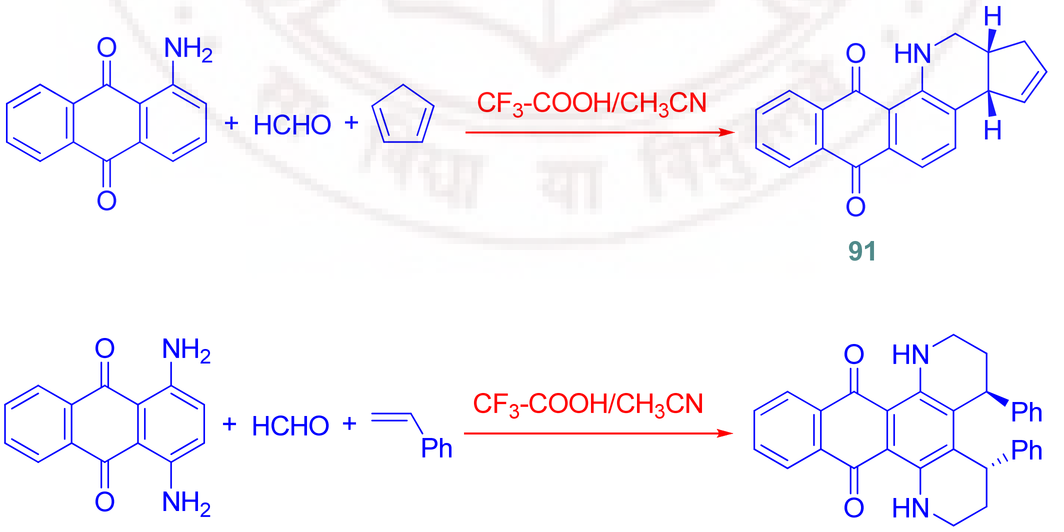
Eq. 25

Aminoanthraquinone derivatives can also be used as chemosensors for transition and heavy metal ions. Hg^{2+} is one of the most important environmental pollutants and an essential trace element in various biological systems. So the Hg^{2+} recognition in particular has received more attention. Huang and co-workers[73] reported a procedure for the Hg^{2+} ion recognition starting from 1,2-diaminoanthraquinone (**Eq. 26**).



89 **90** Eq. 26

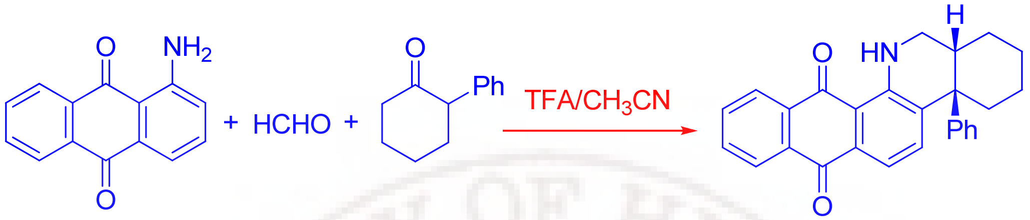
Mellor and co-workers[74] studied the reaction of aminoanthraquinone with formaldehyde and cyclopentadiene. The imine generated from the reaction of aminoanthraquinone and formaldehyde followed by cycloaddition with cyclopentadiene leads to the cycloadduct (**91**). Reactions with 1-aminoanthraquinone, 2-aminoanthraquinone, 1,4-diaminoanthraquinone and 1,5-diaminoanthraquinone gave the corresponding cycloadducts. In this reaction 1,3-butadiene, 3,4-dihydro-2*H*-pyran and styrene derivatives were also used as electron-rich dienophiles (**Eq. 27**).



91

92 Eq. 27

The same group also reported an interesting protocol for the synthesis of polycyclic aminoanthraquinone derivatives *via* the aza Diels-Alder reaction of 1-aminoanthraquinone with formaldehyde and 1-phenylcyclohexanone. One representative example was presented in **Eq. 28**.[75]



93 Eq. 28

1.2. Synthesis of pyranochromenylaminoanthraquinones

Pyranoquinoline moiety is present in many alkaloids.[76] Pyranoquinoline derivatives possess wide range of biological activities such as psychotropic activity, antiallergic activity, anti-inflammatory activity, estrogenic activity and are used as potential pharmaceuticals.[77] Acridine derivatives have attracted the attention of medicinal chemists because of their broad-ranging biological properties. Notably, DNA binding propensities and topoisomerase II inhibitory activities.[78]

Biological studies of the aminoanthraquinone further emphasize the need to establish efficient routes to a variety of aminoanthraquinones and related compounds. The hetero Diels–Alder reaction is an important carbon–carbon bond forming process in organic chemistry. It is also a versatile tool for the synthesis of six-membered heterocyclic compounds and biologically active natural products.[79] For instance, the hetero Diels-Alder reaction provides a rapid means for the construction of functionalized rings containing nitrogen with control of regio-, diastereo-, and enantioselectivity.[80-83] The appropriate choice of aldehyde and amine in the hetero Diels–Alder reaction provides a facile entry to heterocyclic systems, which is an essential moiety in many active pharmaceuticals.

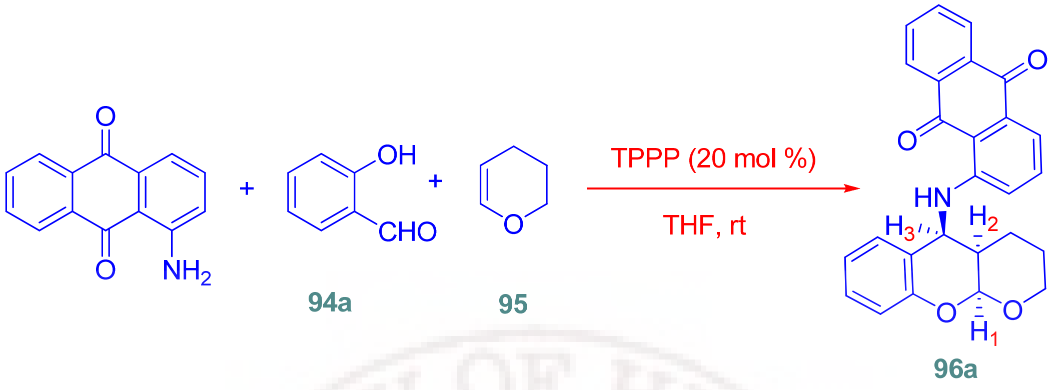
The reactions of imines with electron-rich dienophiles have been reported to be catalyzed by Lewis acids such as BF_3-OEt_2,[84] lanthanide triflates,[85] $AlCl_3$,[86] and

$LiClO_4$.[87] However, some of these reagents suffer from disadvantages such as expense, long reaction time, and low yield. Moreover, many Lewis acids are either decomposed or deactivated as a result of the formation of water during imine formation. Despite improvements by performing these hetero Diels–Alder reactions in one-pot through coupling with aldehydes catalyzed by Lewis acids, efficient and mild reaction conditions are still required for these transformations. Some of the imines are hygroscopic, unstable at high temperature and are difficult to purify through distillation or column chromatography. Therefore, developing simple and convenient procedures for preparing imines in one-pot is important.

The use of a convergent three-component reaction between aldehydes, amine and alkenes in which the heterocycle is assembled in one-pot is of particular note and especially valuable for its potential application in combinatorial synthesis. Based on this idea, the pyranochromenylaminoanthraquinones were synthesized in a one-pot way by using the hetero Diels-Alder reaction of aminoanthraquinone, salicylaldehyde and 3,4-dihydro-2*H*-pyran catalyzed by $PPh_3.HClO_4$. Triphenylphosphonium perchlorate (TPPP)[88] is inexpensive, readily available and found to retain its activity even in the presence of amines, water and other active functional groups such as NO_2 and COOH present in the substrates. Due to its efficiency and the ready availability of starting materials, this reaction constitutes the most attractive strategy for the synthesis of chromenylaminoanthraquinone derivatives.

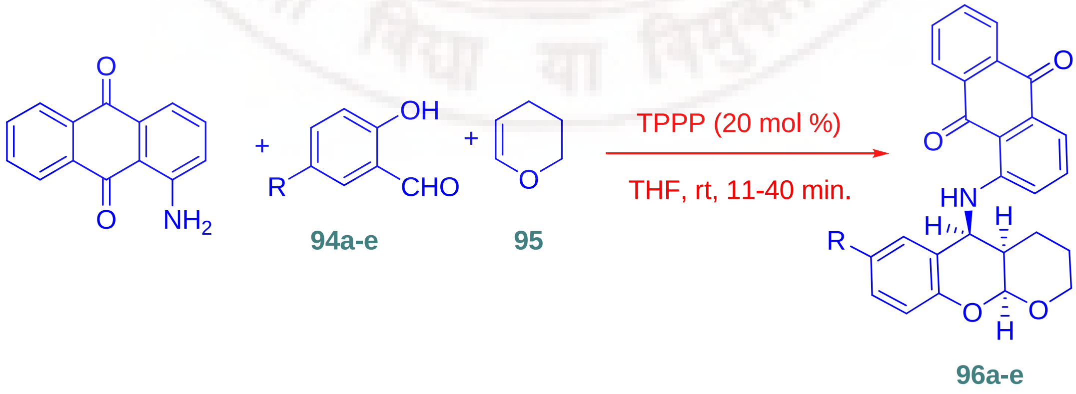
The reaction of an imine, generated *in situ* from salicylaldehyde and 1-aminoanthraquinone with 3,4-dihydro-2*H*-pyran (**95**) is catalyzed by TPPP (20 mol %) affords exclusively *cis* pyranochromenylaminoanthraquinone in good yield. Procedure is very simple. To a stirred solution of 1-aminoanthraquinone, salicylaldehyde (**94a**) and 3,4-dihydro-2*H*-pyran (**95**) in THF, was added a catalytic amount of TPPP (20 mol %) at room temperature and was stirred the mixture for about 20 minutes. The reaction proceeded smoothly and afforded the corresponding pyranochromeny-laminoanthraquinone 1-(3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromen-5-ylamino)-9,10-dihydro-9,10-anthracenedione (**96a**) in 71 % yield (**Scheme 1**).

Scheme 1



Structure of the product was confirmed by IR, ^1H NMR (spectrum 1), ^{13}C NMR (spectrum 2), mass (LCMS) spectral data and elemental analysis. The IR spectrum of **96a** showed the *NH* stretching frequency at 3238 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 10.22. Proton NMR showed the aromatic proton signals in the range between δ 6.95-8.29. Mass spectrum of the compound **96a** showed the molecular ion peak m/z at 412 in positive mode. The stereochemistry of **96a** was assigned based on the coupling constant values and also by NOE studies. The six-membered tetrahydropyran rings are *cis* fused, $J_{1\text{-}2}$ = 2.4 Hz between H_1 (δ 5.69) and H_2 (δ 2.52). Also, $J_{2\text{-}3}$ = 5.9 Hz H_3 (δ 5.27) in **96a** and the presence of NOE's between H_1-H_2 and H_2-H_3, confirms that H_1 is *cis* to H_2 and also that H_2 is *cis* to H_3.

Scheme 2



This strategy fascinated us because it involves three component reactions in a single step with high diastereoselectivity. Encouraged by these results, we have directed our attention towards understanding the generality of this methodology. Hence, we have selected different substituted salicylaldehydes (**94a-e**) and performed the reaction outlined in (**Scheme 2**).

Table 1. TPPP catalyzed synthesis of pyranochromenylaminoanthraquinones

Entry	R	Aldehyde	Product	Time (min.)	Yield (%)
1	H	**94a**	**96a**	20	71
2	Cl	**94b**	**96b**	27	65
3	Br	**94c**	**96c**	40	53
4	CH_3	**94d**	**96d**	15	80
5	OCH_3	**94e**	**96e**	11	90

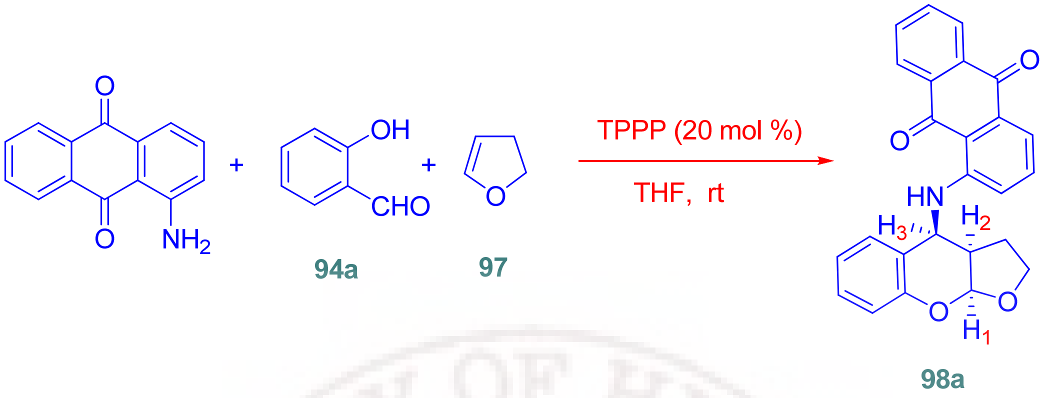
In all cases, the three component, one-pot reaction yielded the products as single diastereomers with *cis*-configuration. Several examples illustrating this procedure for the synthesis of *cis*-fused pyranochromenylaminoanthraquinones are summarized in **Table 1**. Structures of all the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, LCMS and elemental analysis.

1.3. Synthesis of furanochromenylaminoanthraquinones

Extending the methodology further, we examined the reactivity of 2,3-dihydrofuran (**97**) with salicylaldehydes and 1-aminoanthraquinone catalyzed by TPPP. The reaction is highly diastereoselective and afforded the corresponding *cis*-fused furanochromenylaminoanthraquinone 1-(2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-4-ylamino)-9,10-dihydro-9,10-anthracenedione (**98a**) in good yield (**Scheme 3**).

The structure of the product was confirmed by IR, ^{1}H NMR (spectrum 3 for compound **98a**), ^{13}C NMR (spectrum 4 for compound **98a**), LCMS, and elemental analysis. The IR spectrum of **98a** showed the *NH* stretching frequency at 3250 cm^{-1}

Scheme 3



and the proton NMR exhibits the *NH* peak at δ 10.31. Proton NMR showed the aromatic proton signals in the range between δ 6.90-8.32. Mass spectrum of the compound **98a** showed the molecular ion peak m/z at 398 in positive mode. The structure of this compound (**98a**) was further established by single crystal X-ray data (for ORTEP diagram see **Fig. 9**).

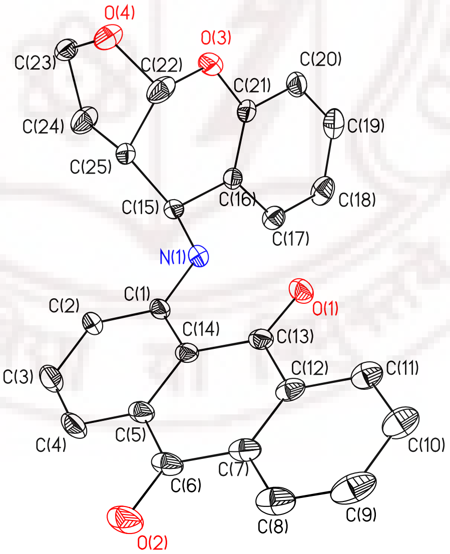


Figure 9. ORTEP diagram of compound **98a**

The stereochemistry of the product was confirmed by ^{1}H NMR and NOE studies. The six-membered tetrahydropyran and five-membered tetrahydrofuran rings were *cis*-fused, as indicated by the coupling constant $J_{1\text{-}2}$ = 5.9 Hz between H_1 (δ 6.02) and H_2 (δ 3.26) for product **98a**. Also, $J_{2\text{-}3}$ = 3.3 Hz H_3 (δ 5.18) for **98a** and the presence of NOE's between H_1–H_2 and H_2–H_3, supports that H_1 is *cis* to H_2 and H_2 is *cis* to H_3.

We have also checked with various substituted salicylaldehydes (**94a-e**) in this reaction (**Scheme 4**). The results are summarized in **Table 2**.

Scheme 4

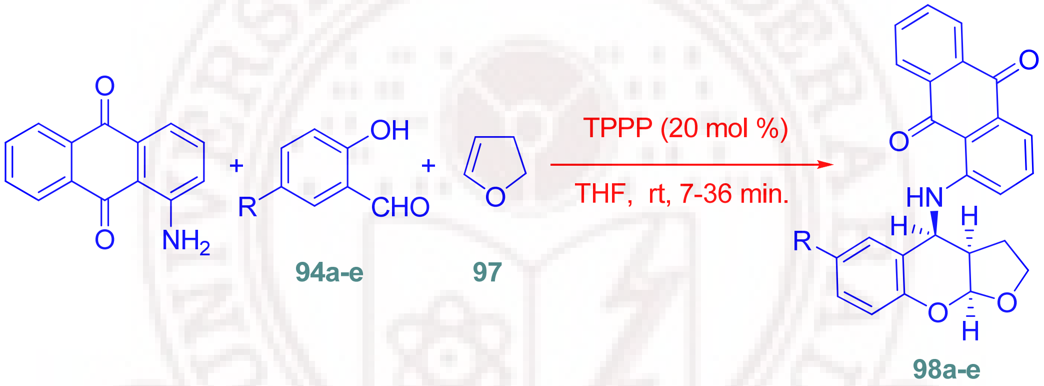


Table 2. TPPP catalyzed synthesis of furanochromenylaminoanthraquinones

Entry	R	Aldehyde	Product	Time (min.)	Yield (%)
1	H	**94a**	**98a**	12	82
2	Cl	**94b**	**98b**	20	68
3	Br	**94c**	**98c**	36	55
4	CH_3	**94d**	**98d**	10	88
5	OCH_3	**94e**	**98e**	7	92

Reactions proceeded smoothly with moderate to good yields (55-92 %). In the case of **98c** yield was 55 % but when electron donating groups such as methyl and methoxy are present yield was higher (**Table 2**). In all the cases, only *cis* diastereoselective products were observed. The structure of **98e** was also confirmed by single crystal X-ray analysis (**Fig. 10**).

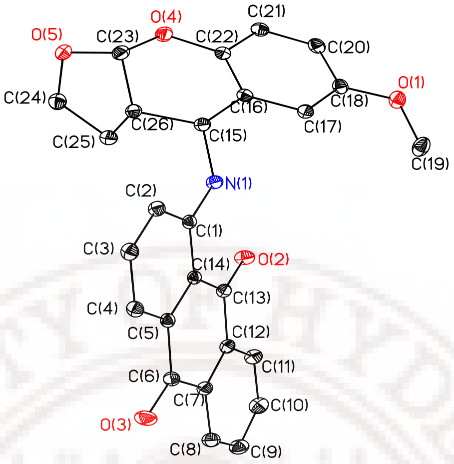


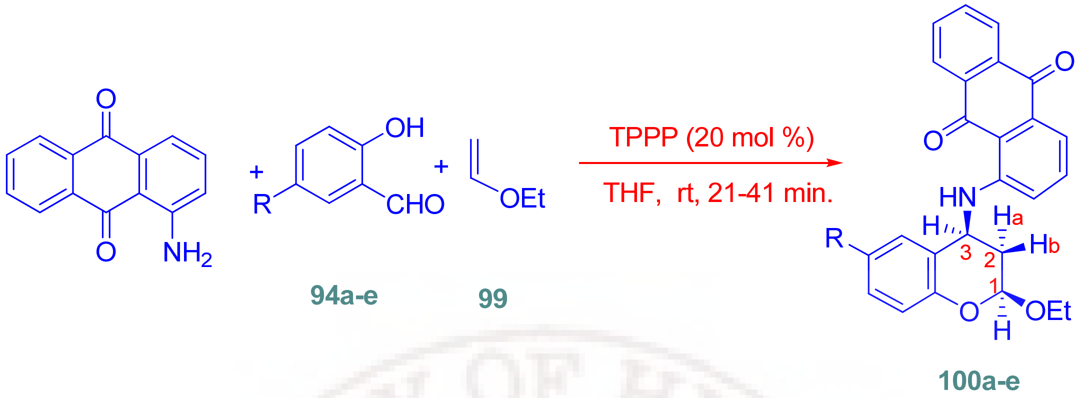
Figure 10. ORTEP diagram of compound **98e**

1.4. Synthesis of chromenylaminoanthraquinones

Annulated arene heterocycles and carbocycles such as chromanones,[89] chromans,[90] quinolones,[91] and tetrahydroquinolines[92] are present as important core structures in many biologically active natural products and pharmaceuticals. 2*H*-1-Benzopyrans (chromenes) and 3,4-dihydro-2*H*-1-benzopyrans (chromans) are important classes of oxygenated heterocycles that have attracted much synthetic interest because of the biological activity of naturally occurring representatives.[93] Numerous 4-aminobenzopyrans and their derivatives have drawn considerable attention in the last decade as modulators of potassium channels influencing the activity of the heart and blood pressure.[94]

We are interested to synthesize chromenylaminoanthraquinones by the Diels-Alder reaction of imine derived from 1-aminoanthraquinone with substituted salicylaldehydes with ethyl vinyl ether. The reaction between the imine generated from 1-aminoanthraquinone and **94a** with ethyl vinyl ether (**99**) afforded 1-(2-ethoxy-6-methyl-3,4-dihydro-2*H*-4-chromenylamino)-9,10-dihydro-9,10-anthracenedione (**100a**) in 60 % yield (**Scheme 5**).

Scheme 5



The structure of the product was confirmed by IR, ^{1}H NMR (spectrum 5 for compound **100a**), ^{13}C NMR (spectrum 6 for compound **100a**), LCMS, and elemental analysis. The IR spectrum of **100a** showed the *NH* stretching frequency at 3246 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 10.41. Proton NMR showed the aromatic proton signals in the range between δ 6.97-8.24. Mass spectrum of the compound **100a** showed the molecular ion peak m/z at 422 with sodium ion adduct.

Table 3. TPPP catalyzed synthesis of chromenylaminoanthraquinones

Entry	R	Aldehyde	Product	Time (min.)	Yield (%)
1	H	**94a**	**100a**	30	60
2	Cl	**94b**	**100b**	41	52
3	Br	**94c**	**100c**	50	45
4	CH_3	**94d**	**100d**	26	70
5	OCH_3	**94e**	**100e**	21	72

Ethyl vinyl ether also exhibited analogous behavior to that of dihydropyran and dihydrofuran with respect to the stereochemistry of the products (**100a-e**). The stereochemistry of the products was assigned by ^{1}H NMR spectroscopy based on their chemical shift and coupling constant value $J_{H1\text{-}2a}$ = 3.2 Hz between H_1 (δ 5.44) and H_{2a} (δ 4.01) for **100a**. In the case of different substituted salicylaldehydes (**94a-e**), the reaction works well with moderate to good yield and only *cis* diastereoselective products were observed (**Table 3**). The structure of products **100c**, **100d** and **100e** were also confirmed by single crystal X-ray analysis (**Fig. 11, 12** and **13**).

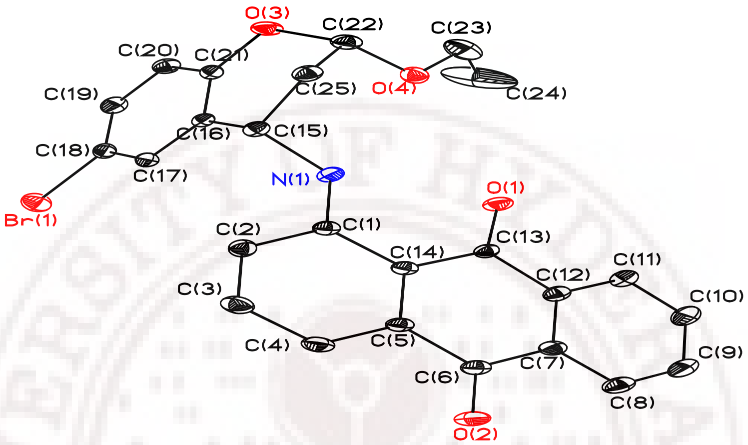


Figure 11. ORTEP diagram of compound **100c**

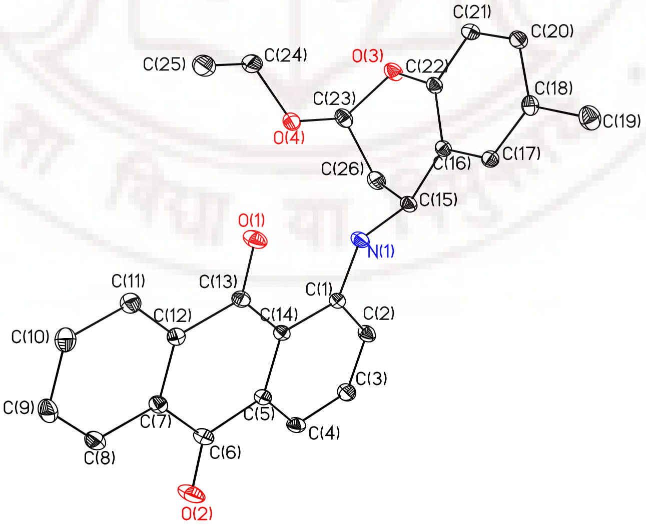
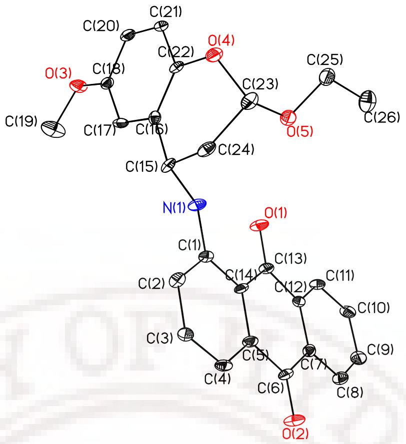


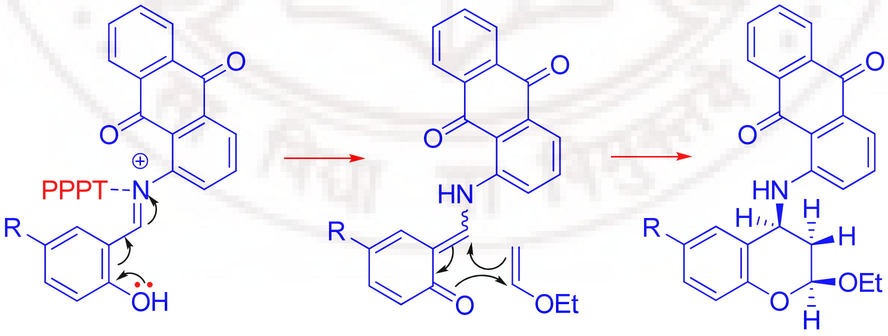
Figure 12. ORTEP diagram of compound **100d**

Figure 13. ORTEP diagram of compound **100e**



Mechanism of the reaction was given in **Scheme 6**. The reaction probably proceeds through activation of the imine by the catalyst followed by the generation of oxa-diene and subsequent [4+2] cycloaddition of the enol ether resulting in the formation of product. Same mechanism could be applicable for other electron-rich dienophiles such as 3,4-dihydro-2*H*-pyran (**95**) and 2,3-dihydrofuran (**97**).

Scheme 6: Expected mechanism of the product



In conclusion, we have developed a convenient, one-pot procedure for the synthesis of *cis*-fused pyrano and furanochromenylaminoanthraquinones by using hetero Diels-Alder reaction. In addition to its simplicity and mild reaction conditions, this procedure has advantages of high yields, easy availability and flexibility of starting materials, short reaction times, and useful diastereoselectivity.

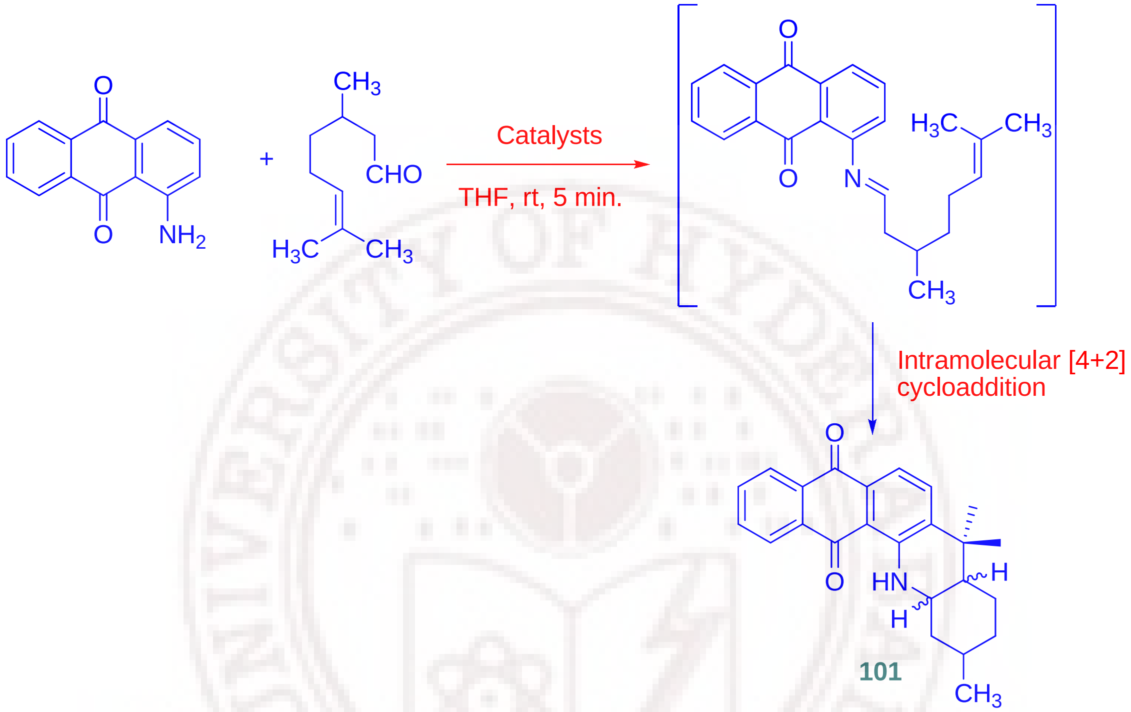
1.5. Synthesis of mono and *bis*-naptho[2,3-*c*]acridines

In recent years synthetic chemists have become increasingly aware of the power of intramolecular cycloadditions for construction of complex polycyclic molecules. In particular, the intramolecular imino Diels-Alder reaction has been the subject of intensive study.[95] The imino Diels-Alder reaction of imines derived from aromatic amines with electron-rich alkenes has emerged as a powerful tool for the synthesis of tetrahydroquinolines.[96] The chemistry of tetrahydroquinoline derivatives has long been an area of intense interest for organic chemists due to the presence of these scaffolds within the framework of numerous biologically interesting natural products and pharmaceutical agents. Many new methods for the synthesis of tetrahydroquinoline derivatives have also been developed.[97] The most attractive strategy for these derivatives is the acid-promoted imino Diels-Alder reaction between *N*-arylaldimines and electron-rich alkenes that have been a topic of continuing interest for nearly four decades.[98-99]

We have synthesized several new anthraquinone-quinoline heterocycles through the imino Diels-Alder reaction of 1-aminoanthraquinone, citronellal or substituted *O*-prenylated salicylaldehydes catalyzed by TPPP. The reactions were carried out in one-pot procedure without isolating the imine and reaction goes to completion within 5-15 minutes. A solution of 1-aminoanthraquinone, citronellal, and 20 mol % of TPPP in THF was stirred at room temperature for 5 minutes. The imine formed undergoes cycloaddition immediately and furnished the octahydro naphtho[2,3-*c*]acridine-5,14-dione (**101**) in 94 % yield (**Scheme 7**)

The product was found to be an inseparable mixture of diastereomers in 22:78 ratio, determined by ^{1}H NMR spectroscopy. Structure of the product was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass (LCMS) spectral data and elemental analysis. The IR spectrum of **101** showed the *NH* stretching frequency at 3537 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 10.14. Proton NMR showed the aromatic proton signals in the range between δ 7.42-8.27. Mass spectrum of the compound **101** showed the molecular ion peak m/z at 360 in positive mode. The structure of the product **101** was characterized by single crystal X-ray analysis. ORTEP diagram was shown in **Fig.14**

Scheme 7



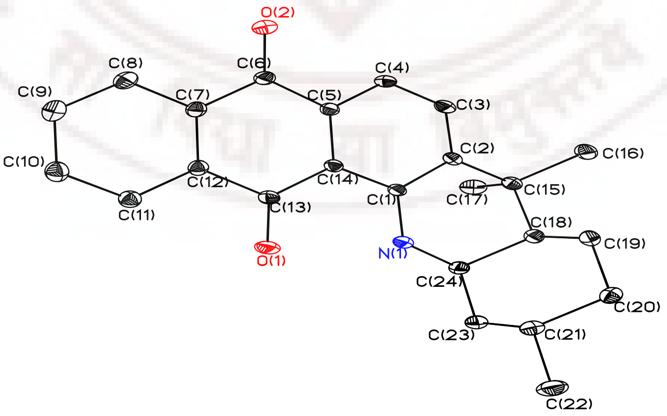


Figure 14. ORTEP diagram of compound **101**

Table 4. Screening of different substituted Lewis/Brønsted acids in intramolecular imino Diels-Alder reaction

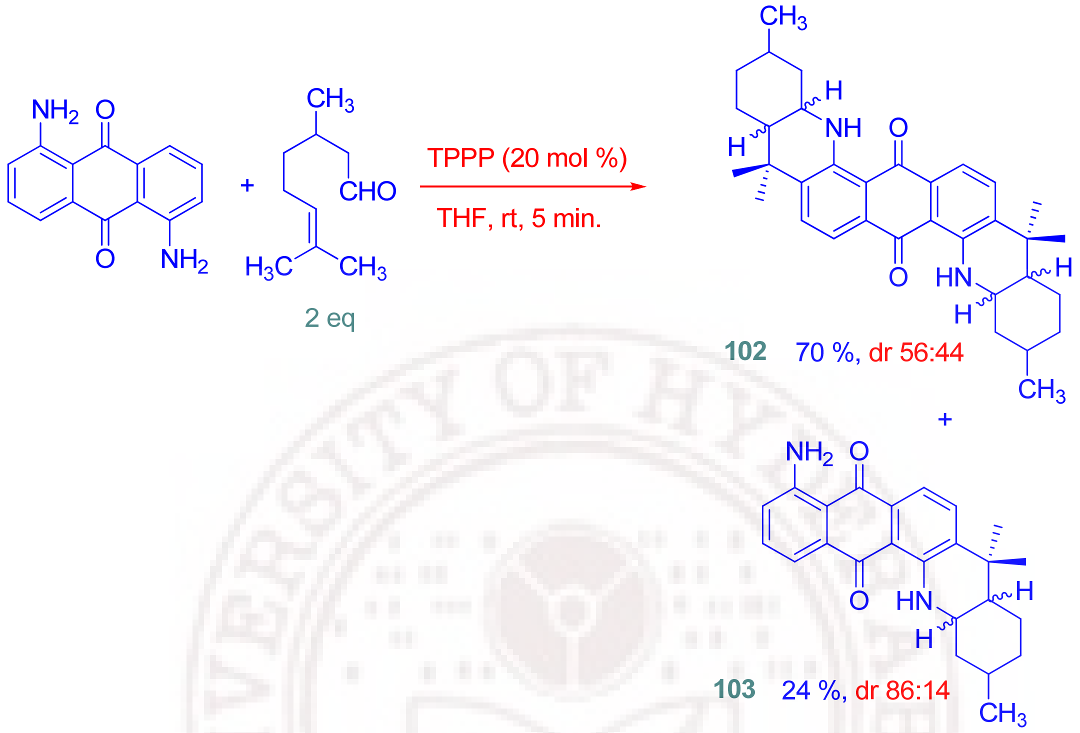
Entry	Catalyst[a]	Yield (%)[b]	dr ratio[c]
1	BF_3-OEt_2	85	46:44
2	$LiClO_4$	80	42:58
3	$BiCl_3$	87	40:60
4	CF_3-COOH	90	45:55
5	$InCl_3$	90	25:75
6	$In(OTf)_3$	90	24:76
7	[Bmim][BF_4]	68	30:70
8	[Bmim][$AlCl_3$]	66	33:67
9	**TPPP**	**94**	**22:78**

[a] All the cases 20 mol % of catalyst was used except entry 7 and 8 where 1.0 mL of ionic liquid was used. [b] Yields were calculated after column purification. [c] dr ratio was calculated from ^1H NMR with respect to the *N*<u>*H*</u> peak which comes at 10.14 ppm.

The reaction is also catalyzed by several other catalysts as given in **Table 4**. With most of the catalysts, good yield were observed. Moderate yields were observed with imidazolinium ionic liquid is due to the limited solubility of aminoanthraquinone in ionic liquid (Entry 7 and 8). With TFA and $BiCl_3$, the reaction proceeded with good yield but poor diastereoselectivity was observed (Entry 3 and 4). But the diastereoselectivity with TPPP catalyst is comparatively better than other catalysts. So we utilized TPPP for the other reactions also.

We have also studied the cycloaddition of 1,5-diaminoanthraquinone with citronellal catalyzed by TPPP resulting in the formation of the *bis*-adduct 3,9,9,12,18,18-hexamethyl-1,2,3,4,4a,5,9,9a,10,11,12,13,13a,14,18,18a-hexadecahydro-5,14-diazanaphtho[2,3-*c*]pentaphene-6,15-dione (**102**) (70 % yield, diastereomeric ratio is 56:44) along with the mono adduct 4-amino-8,8,11-trimethyl-8,8a,9,10,11,12,12a,13-octahydronaphtho[2,3-*c*]acridine-5,14-dione (**103**) (24 % yield, 86:14 diastereomeric ratio) within 5 minutes at room temperature (**Scheme 8**).

Scheme 8



1,5-Diaminoanthraquinone reacts with citronellal resulting in the formation of monoimine and *bis*-imine both of them underwent intramolecular cycloaddition leads to the corresponding monoadduct **103** and *bis*-adduct **102**.

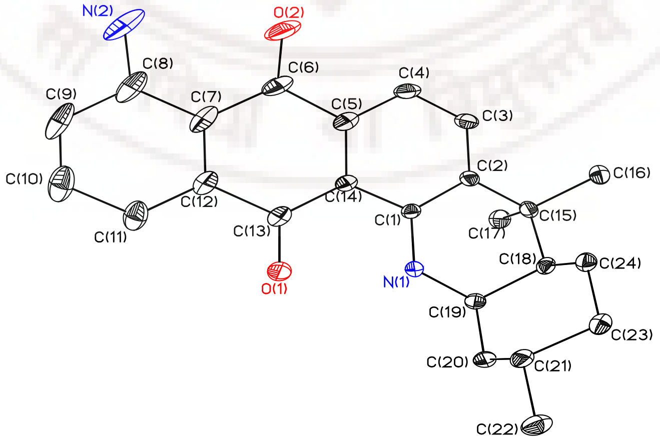


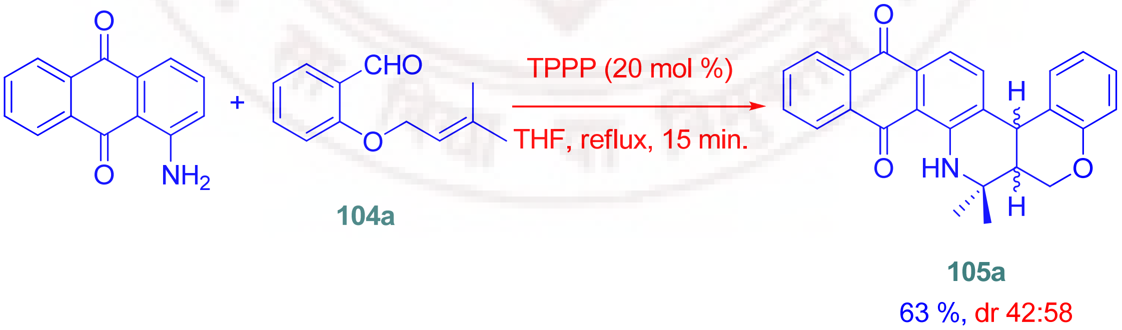
Figure 15. ORTEP diagram of compound **103**

The IR spectrum of **102** showed the *NH* stretching frequency at 3445 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 10.11. Proton NMR showed the aromatic proton signals in the range between δ 7.38-7.46. Mass spectrum of the *bis*-product (**102**) showed the molecular ion peak m/z at 511 in positive mode. In the case of monocyclized product (**103**) molecular ion peak observed at 375 in positive mode. The structure of the monoadduct **103** was also confirmed by X-ray analysis (**Fig. 15**). Prolonged reaction conditions and excess of citronellal did not improve the ratio of the products.

1.6. Synthesis of chromanoquinolo naphthaquinones from unexpected reaction

After developing a simple one-pot methodology for the synthesis of mono and *bis*-naphtho[2,3-*c*]acridine-5,14-dione, we have directed our attention towards the synthesis of chromanoquinolo naphthaquinone derivatives. The chromane moiety form the important classes of oxygenated heterocycles that has attracted much synthetic interest because of the biological activity.[81] It appeared to us that this can in principle be achieved *via* the treatment of 1-aminoanthraquinone with *O*-prenylated salicylaldehyde (**Scheme 9**). This *O*-prenylated salicylaldehydes (**104a-g**) were prepared from salicylaldehydes (**94a-g**) by the reaction of prenyl bromide in the presence of K_2CO_3 in acetone at reflux temperature.

Scheme 9



The reaction is carried out by reacting the 1-aminoanthraquinone with **104a** in THF catalyzed by 20 mol % TPPP at refluxing conditions for 15 minutes afforded the product 16,16-dimethyl-6b,9,14,15,16,16a-hexahydro-1*H*-chromeno[3,4-*c*]naphtho[2,3-*h*]quinoline-9,14-dione (**105a**) with 62 % yield (**Scheme 9**).

The IR spectrum of **102a** showed the *NH* stretching frequency at 3433 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 10.22. Proton NMR showed the aromatic proton signals in the range between δ 6.86-8.27. Two methyl peaks were observed as singlets at δ 1.52 and 1.50. Mass spectrum of the compound **105a** showed the molecular ion peak m/z at 396 in positive mode. The spectral data appears to be similar to the expected structure, but X-ray analysis shows that the structure of the product is same as expected, except with respect to the position of the methyl groups. Here we observed a interesting and unexpected reaction. ORTEP diagram of the compound **105a** was shown **fig. 16**.

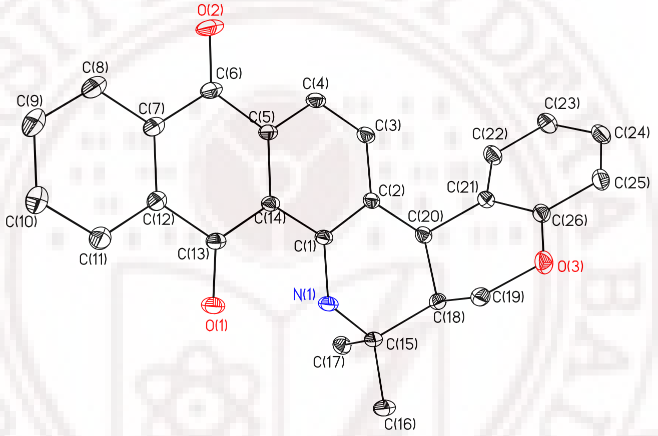
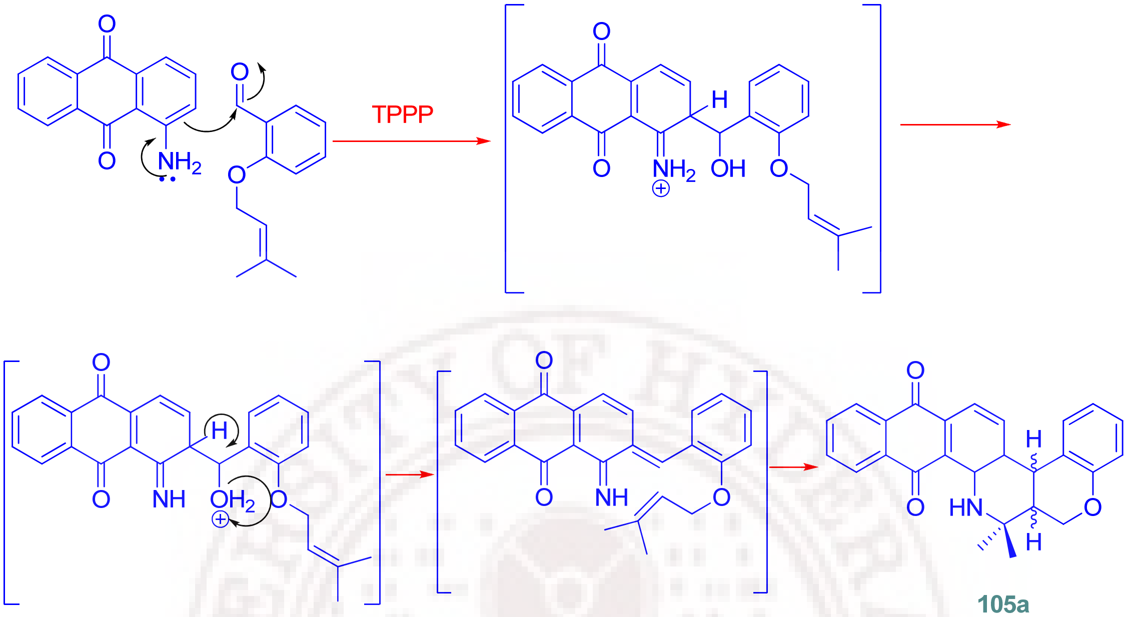


Figure 16. ORTEP diagram of compound **105a**

Formation of this type of products is unusual in the Diels-Alder reaction, especially in intramolecular cycloaddition where it proceeds with highly regioselective manner. Expected mechanism of the reaction was shown in **Scheme 10**. Initial schiff base formation was not observed and rather it undergoes nucleophilic addition of aminoanthraquinone with the salicylaldehyde and followed by dehydration, generating the imino diene. The imino diene further undergoes to imino Diels-Alder reaction which leads to cycloadduct. The compound **105a** was also characterized by NOE experiment by irradiating the hydrogen attached with nitrogen with two methyl groups and found 17 % of NOE, which confirms adjacent proximity of the dimethyl groups with amino hydrogen. This clearly shows that the compound **105a** is the unexpected reaction product.

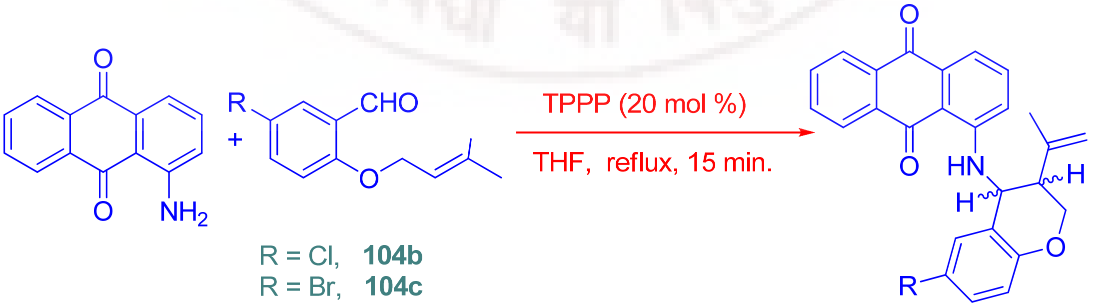
Scheme 10. Mechanism for unexpected reaction.



1.7. Synthesis of chromanoquinolo naphthaquinones from ene-type reaction

In order to verify the reaction pathway several substituted salicylaldehydes were studied and results are surprising since the nature of substituents could change the mechanism of the reaction from normal pathway to ene-type cyclization.

Scheme 11



R = Cl, **104b**
R = Br, **104c**
R = NO_2,**104d**

105b, 44 %, dr 77:33
105c, 56 %, dr 48:52
105d, 40 %, dr 56:44

Electron withdrawing substituents such as Cl, Br and NO_2 change the mechanism from Diels-Alder to ene-type cyclization. The reaction of *O*-prenylated salicylaldehyde (**104b**) with 1-aminoanthraquinone in the presence of TPPP in THF was completed within 15 minutes at reflux temperature with ene-type product 1-(6-chloro-3-isopropenyl-chroman-3-ylamino)-anthraquinone (**105b**) in 44 % yield (**Scheme 11**).

Same ene-type products (**105c** and **105d**) were observed with other substituted salicylaldehydes (**104c** and **104d**). All the products were characterized by ^{1}H NMR, ^{13}C NMR, LC-MS and elemental analysis. The IR spectrum of **105b** showed the *NH* stretching frequency at 3414 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 10.29. Proton NMR showed the aromatic proton signals in the range between δ 6.82-8.22. Mass spectrum of the compound **105b** showed the molecular ion peak m/z at 430 in positive mode. The structure of the compound (**105b**) was further established by single crystal X-ray data (**Fig. 17**).

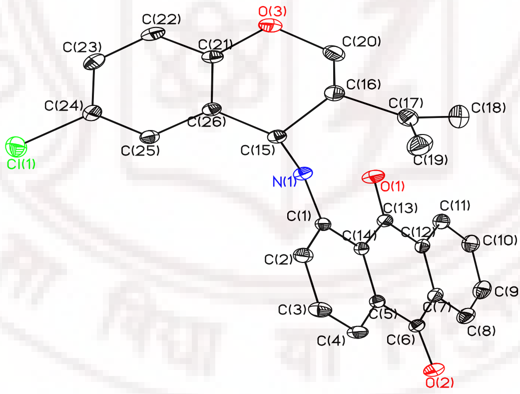
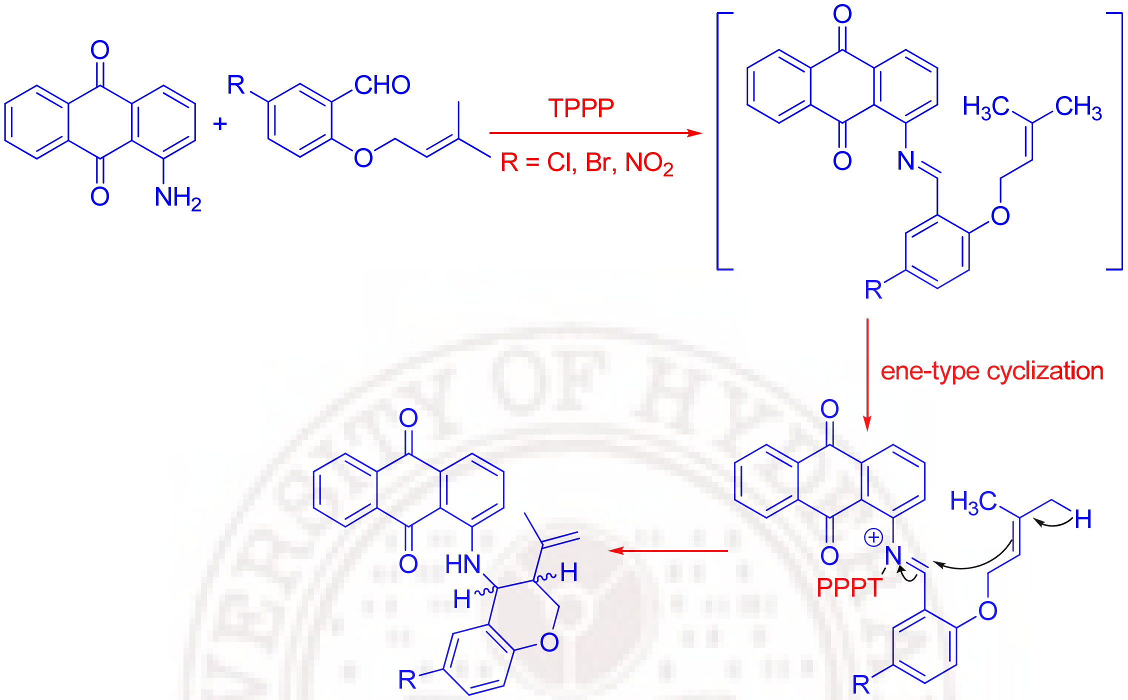


Figure 17. ORTEP diagram of compound **105b**

A plausible mechanism is presented in **Scheme 12**. It is important to mention that this type of behavior was observed only in salicylaldehydes (**104b-d**) and not in the case of citronellal, an aldehyde equivalent. This suggests that electron withdrawing nature of the aromatic ring of salicylaldehyde influenced by its substituents, and plays a primary role in changing the mechanistic pathway.

Scheme 12. Mechanism for ene-type cyclization



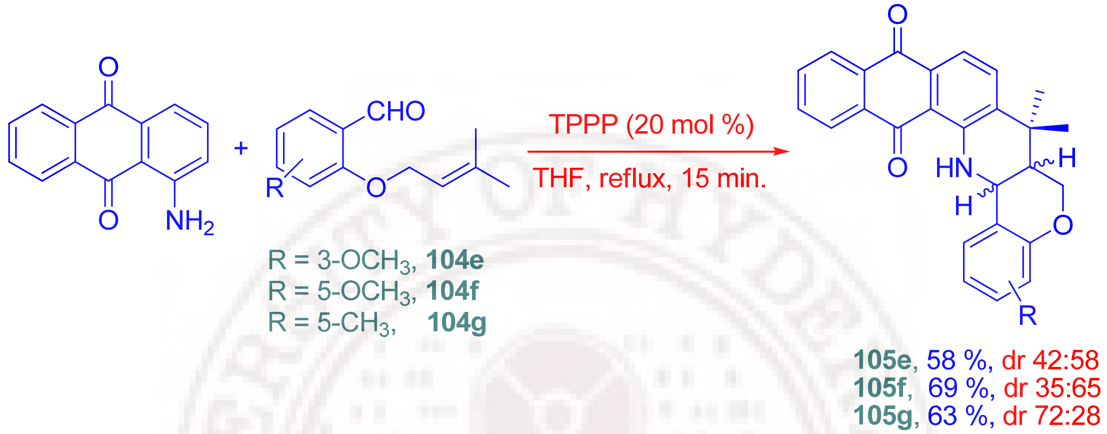
We believe that the effect is not only due to substituted salicylaldehydes but also the aminoanthraquinone ring. Anthraquinone can be in equilibrium with its tautomeric form (keto-enol). The enol form makes the adjacent benzene ring more electron-deficient and this electron deficiency drives the electron-rich amino group to donate its electron density to the aromatic system. This donation of electrons become significant when salicylaldehyde is substituted with electron withdrawing group which alters the energy levels of LUMO-HOMO and hence instead of expected normal imino Diels-Alder pathway, it undergoes ene-type cyclization. This can also be evidenced by the expected normal product formation when salicylaldehydes are substituted with electron donating groups (**104e-g**).

1.8. Synthesis of chromanoquinolo naphthaquinones from Diels-Alder reaction

Electron donating substituents like CH_3 and OCH_3 follow the normal imino Diels-Alder pathway, with the expected cycloadduct (**Scheme 13**). Product 4-methoxy-7,7-dimethyl-6a,7,10,15,16,16a-hexahydro-6*H*-chromeno[4,3-*b*]naphtho

[2,3-*h*]quinoline-10,15-dione (**105e**) was obtained by the reaction of 1-aminoantraquinone to *O*-prenylated salicylaldehyde (**104e**) in THF at reflux temperature with 20 mol % TPPP in 58 % yield.

Scheme 13



All the Compounds **105e-g** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, LCMS, and elemental analysis. In the case of **105e**, IR spectrum showed the *NH* stretching frequency at 3431 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 10.90. Proton NMR showed the aromatic proton signals in the range between δ 6.88-8.33. Two methyl peaks were observed as singlets at δ 1.26 as a singlet. Mass spectrum of the compound **105e** showed the molecular ion peak m/z at 426 in positive mode.

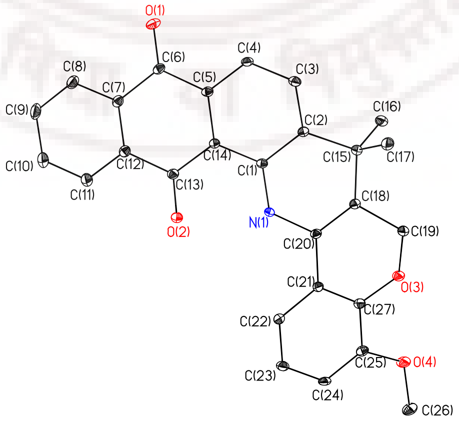


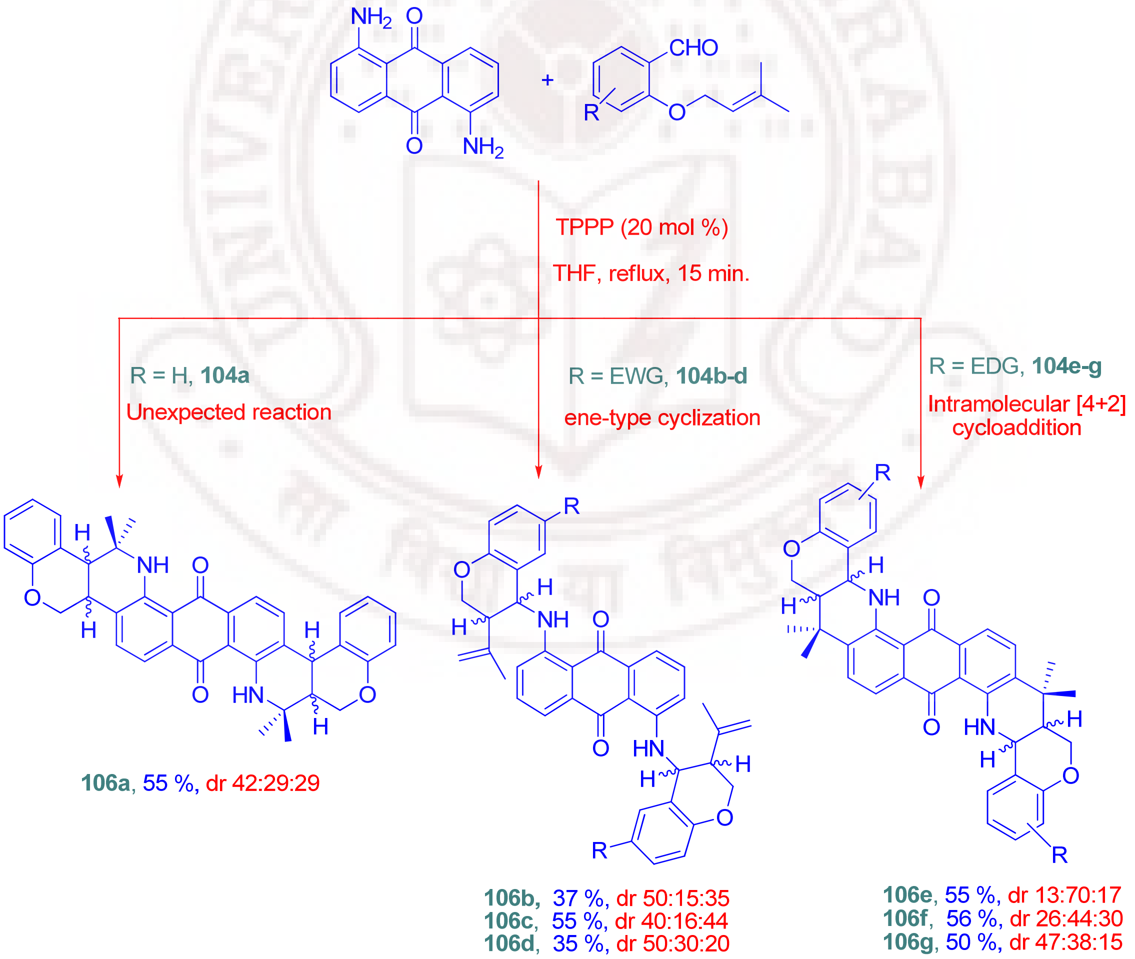
Figure 18. ORTEP diagram of compound **105e**

The structure of this compound (**105e**) was further established by single crystal X-ray data (for ORTEP diagram see **Fig. 18**). In the case of **105f**, the yield is higher (69 %) with 35:65 dr ratio, however in the case of **105g**, slightly lower yield (63 %) was observed with 72:28 dr ratio.

1.9. Synthesis of *bis*- chromanoquinolo naphthaquinones

To understand the generality of this reaction, we also carried out the reaction of 1,5-diaminoanthraquinone with substituted salicylaldehydes (**104a-g**) for the corresponding *bis*-products. In this case too, same mechanistic pathway was observed similar to monosubstituted aminoanthraquinone (**Scheme 14**).

Scheme 14



The reaction of 1,5-diaminoanthraquinone with two eq. of unsubstituted salicylaldehyde (**104a**) was observed unexpected reaction and the corresponding product 11,11,22,22-tetramethyl-1,6b,9,10,11,11a,12,17b,20,21,22,22a-dodeca-hydrochromeno[3,4-*c*]chromeno[4'',3'':4',5']pyrido[3',2':7,8]naphtha[2,3-*h*]quinol-ine-9,20-dione (**106a**) obtained in 55 % yield. In all the *bis*-analogue cases, we obtained three diastereomers. All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, LCMS and elemental analysis. A possible explanation for this observation can be given with respect to the smaller size of hydrogen atom. Electron density of hydrogen atom is small and hence it does not play a significant role in controlling the mechanism of the product. This could be a reason why unsubstituted salicylaldehyde (**104a**) does not undergo either normal Diels-Alder or ene-type cyclization.

When electron withdrawing groups such as Cl, Br and NO_2 are present on salicylaldehyde (**104b-d**) it underwent ene-type mechanism, similar to 1-aminoanthraquinone. Electron donating groups on salicylaldehyde (**104e-g**) with 1,5-diaminoanthraquinone follows the similar trend like 1-aminoanthraquinone with normal Diels-Alder cycloaddition pathway.

In summary we have presented the novel observation which originates from the reaction of aminoanthraquinones with salicylaldehydes. The nature of the substituents in the salicylaldehyde primarily determines the mechanistic pathway from the normal Diels-Alder to ene-type cyclization or unexpected reaction pathway. This unusual observation is novel and so far not reported in the literature. We have also explained the observation through the possible mechanism. The reactions are rapid and the products were obtained in moderate to excellent yields.

1.10. Experimental Section

Melting Points: The melting point of the products was recorded on a Superfit (India) capillary melting point apparatus and is uncorrected.

IR: Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in DCM.

NMR Spectra: ^1H NMR and ^{13}C NMR spectrums were recorded on BRUKER-AVANCE-400 spectrometers. ^1H NMR (400 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (δ = 2.50 ppm for ^1H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-$d_{6,}$ δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard.

Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer. All the cases DCM or MeOH were used to dissolve the compounds.

Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) software package.

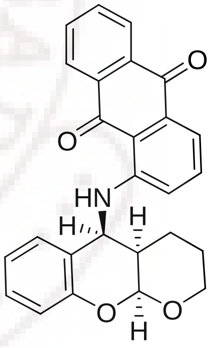
General: THF and 1,4-dioxane were dried and distilled using suitable drying agents. All the reactions were monitored using Thin Layer Chromatography (TLC). All the above general information is also applicable to other chapters 2,3 and 4.

General procedure A

To a stirred solution of 1-aminoanthraquinone (1.0 mmol), salicylaldehyde (1.0 mmol), 3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran or ethyl vinyl ether (2.5 mmol) in THF, was added TPPP (20 mol %) and the reaction stirred at room temperature for the appropriate time. After completion of the reaction, as indicated by the TLC, excess THF was distilled off and the residue was poured into water (20 mL) and extracted with DCM (3 x 20 mL). The organic layer was dried over anhy. Na$_2$SO$_4$ and distilled under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh size) and eluted with hexanes-ethyl acetate to afford pure *cis*-fused chromenylaminoanthraquinones as red solids.

Cis-1-(3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromen-5-ylamino)-9,10-dihydro-9,10-anthracenedione (96a)

Obtained **96a** by the reaction of salicylaldehyde (**94a**) with 1-aminoantraquinone and **95** in THF following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes as a red solid.



96a

Yield:	71 %
Mp:	222 ^{o}C
IR (KBr) ν_{max} cm^{-1}:	3238, 3063, 2945, 2885, 1720, 1666, 1452, 1267, 1093, 979
^{1}H NMR (400 MHz) δ:	10.22 (1H, d, *J* = 7.9 Hz, N*H*); 8.29 (2H, t, *J* = 7.2 Hz); 7.74-7.78 (2H, m); 7.62-7.71 (2H, m); 7.34 (1H, d, *J* = 7.2 Hz); 7.21-7.27 (2H, m); 6.95-6.98 (2H, m); 5.69 (1H, d, *J* = 2.4 Hz, OC*H*O); 5.27 (1H, t, *J* = 5.9 Hz, NH-C*H*); 3.81-4.12 (2H, m, OC*H*$_2$); 2.52 (1H, q, *J* = 5.3 Hz); 1.69-1.84 (3H, m); 1.53-1.60 (1H, m)
^{13}C NMR (100 MHz) δ:	185.5, 183.6, 152.9, 151.3, 135.7, 135.0, 134.8, 134.1, 133.2, 132.9, 132.2, 129.3, 126.9, 126.8,

126.6, 121.4, 120.6, 117.7, 116.4, 113.6 (aromatic C), 96.1, 60.9, 50.9, 35.8, 24.2, 17.7 (aliphatic C)

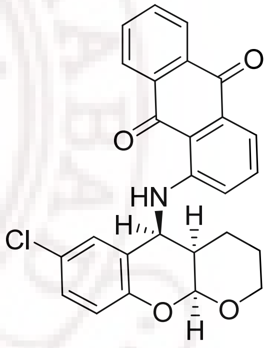
LCMS (m/z): 412 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.14; N, 3.40 %

Found: C, 75.92; H, 5.16; N, 3.33 %

Cis-1-(7-chloro-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromen-5-ylamino)-9,10-dihydro-9,10-anthracenedione (96b)

Obtained **96b** by the reaction of 5-chloro salicylaldehyde (**94b**) with 1-aminoantraquinone and **95** in THF following the *general procedure A*. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.



96b

Yield: 65 %

Mp: 183 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 3271, 3067, 2941, 1722, 1666, 1265, 1072, 997, 904

^1H NMR (400 MHz) δ: 10.21 (1H, d, *J* = 8.0 Hz, N<u>*H*</u>); 8.30 (2H, t, *J* = 7.6 Hz); 7.73-7.82 (3H, m); 7.64 (1H, t, *J* = 7.7 Hz); 7.28 (1H, d, *J* = 7.6 Hz); 7.21 (1H, d, *J* = 8.3 Hz); 6.91 (2H, m); 5.68 (1H, d, *J* = 2.5 Hz, OC<u>*H*</u>O); 5.23 (1H, t, *J* = 5.9 Hz, NH-C<u>*H*</u>); 3.81-4.07 (2H, m, OC<u>*H*</u>$_2$); 2.49 (1H, q, *J* = 6.0 Hz); 1.75-2.51 (3H, m); 1.50-1.54 (1H, m)

^{13}C NMR (100 MHz) δ: 185.6, 183.4, 151.7, 149.9, 135.9, 135.7, 134.1, 133.3, 133.2, 129.9, 129.4, 129.3, 126.9, 126.7, 126.2, 118.7, 117.9, 117.2, 116.7, 113.8 (aromatic C), 96.3, 62.7, 51.1, 37.2, 24.9, 17.6 (aliphatic C)

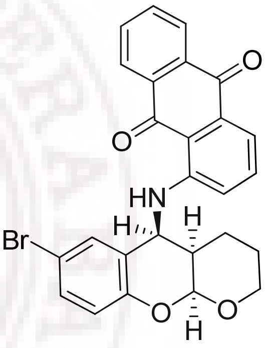
LCMS (m/z): 445 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{20}ClNO_4$: C, 70.04; H, 4.52; N, 3.14 %

Found: C, 70.05; H, 4.51; N, 2.97 %

Cis-1-(7-bromo-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromen-5-ylamino)-9,10-dihydro-9,10-anthracenedione (96c)

Obtained **96c** from 5-bromo salicylaldehyde (**94c**) by the reaction of 1-aminoanthraquinone and 3,4-dihydro-2*H*-pyran (**95**) in THF following the *general procedure A*. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.



96c

Yield: 65 %

Mp: 183 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 3271, 3067, 2941, 1722, 1666, 1265, 1072, 997, 904

^1H NMR (400 MHz) δ: 10.21 (1H, d, *J* = 8.0 Hz, N<u>*H*</u>); 8.30 (2H, t, *J* = 7.6 Hz); 7.73-7.82 (3H, m); 7.64 (1H, t, *J* = 7.7 Hz); 7.28 (1H, d, *J* = 7.6 Hz); 7.21 (1H, d, *J* = 8.3 Hz); 6.91 (2H, m); 5.68 (1H, d, *J* = 2.5 Hz, OC<u>*H*</u>O); 5.23 (1H, t, *J* = 5.9 Hz, NH-C<u>*H*</u>); 3.81-4.07 (2H, m, OC<u>H_2</u>); 2.49 (1H, q, *J* = 6.0 Hz); 1.75-2.51 (3H, m); 1.50-1.54 (1H, m)

^{13}C NMR (100 MHz) δ: 185.6, 183.4, 151.7, 149.9, 135.9, 135.7, 134.1, 133.3, 133.2, 129.9, 129.4, 129.3, 126.9, 126.7, 126.2, 118.7, 117.9, 117.2, 116.7, 113.8 (aromatic C), 96.3, 62.7, 51.1, 37.2, 24.9, 17.6 (aliphatic C)

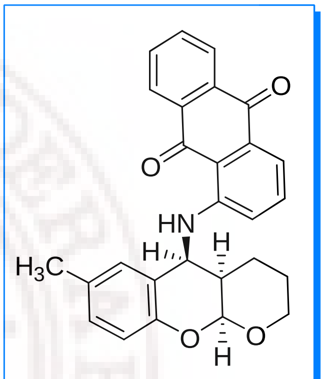
LCMS (m/z): 445 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{20}BrNO_4$: C, 63.69; H, 4.11; N, 2.86 %

Found: C, 63.75; H, 4.16; N, 3.02 %

Cis-1-(7-methyl-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromen-5-ylamino)-9,10-dihydro-9,10-anthracenedione (96d)

Reaction of 5-methyl salicylaldehyde (**94d**) in the presence of TPPP (20 mol %) with 1-aminoanthraquinone and 3,4-dihydro-2*H*-pyran (**95**) in THF following the *general procedure A* provided the title compound as a red solid. The crude product was purified by silica gel column chromatography with 2 % ethyl acetate in hexanes.



96d

Yield: 80 %

Mp: 201 °C

IR (KBr) ν_{max} cm^{-1}: 3462, 3240, 2943, 1666, 1265, 1068, 976, 906

^{1}H NMR (400 MHz) δ: 10.18 (1H, d, *J* = 8.4 Hz, N*H*); 8.26-8.30 (2H, m); 7.69-7.78 (3H, m); 7.61 (1H, t, *J* = 8.2 Hz); 7.21 (1H, d, *J* = 8.4 Hz); 7.11 (1H, s); 7.04 (1H, d, *J* = 8.2); 6.85 (1H, d, *J* = 8.2 Hz); 5.64 (1H, d, *J* = 3.1 Hz, OC*H*O); 5.23 (1H, t, *J* = 5.6 Hz, NH-C*H*); 3.78-4.08 (2H, m, OC*H*$_2$); 2.47 (1H, q, *J* = 6.4 Hz); 2.25 (3H, ArC–C*H*$_3$); 1.70-1.80 (3H, m); 1.51-1.55 (1H, m)

^{13}C NMR (100 MHz) δ: 185.4, 183.5, 151.3, 150.7, 135.7, 135.5, 134.9, 134.0, 133.2, 132.9, 130.7, 130.6, 129.9, 126.8, 120.2, 117.7, 117.4, 116.9, 116.3, 113.6 (aromatic C), 96.0, 60.9, 50.9, 44.5, 35.9, 24.2, 17.7 (aliphatic C)

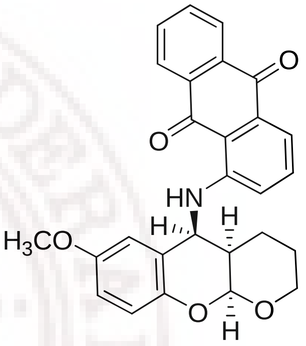
LCMS (m/z): 424 (M-H)$^+$

Anal. Calcd. for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29 %

Found: C, 76.15; H, 5.46; N, 3.16 %

Cis-1-(7-methoxy-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromen-5-ylamino)-9,10-dihydro-9,10-anthracenedione (96e)

Pyranochromenylaminoanthraquinone (**96e**) was obtained by the reaction of 5-methoxy salicylaldehyde (**94e**) with 1-aminoanthraquinone and 3,4-dihydro-2*H*-pyran (**95**) in the presence of TPPP (20 mol %) in THF following the *general procedure A*. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.



96e

Yield: 90 %

Mp: 114 °C

IR (KBr) ν_{max} cm^{-1}: 3462, 3240, 2943, 1666, 1265, 1068, 976, 906

^{1}H NMR (400 MHz) δ: 10.19 (1H, d, *J* = 8.5 Hz, NH); 8.26-8.29 (2H, m); 7.69-7.78 (3H, m); 7.62 (1H, t, *J* = 8.0 Hz); 7.21 (1H, d, *J* = 8.4 Hz); 6.88-6.91 (2H, m); 6.82 (1H, d, *J* = 8.2 Hz); 5.62 (1H, d, *J* = 3.2 Hz, OCHO); 5.24 (1H, t, *J* = 4.5 Hz, NH-CH); 3.77-4.05 (2H, m, OCH_2); 3.71 (3H, ArC–OCH_3); 2.48 (1H, q, *J* = 6.0 Hz); 1.70-1.79 (3H, m); 1.51-1.55 (1H, m)

^{13}C NMR (100 MHz) δ: 185.1, 183.4, 154.2, 150.0, 146.6, 135.7, 134.9, 134.7, 134.0, 133.2, 132.9, 126.7, 120.1, 117.9, 117.4, 117.2, 116.4, 113.7, 113.6, 111.6 (aromatic C), 95.9, 62.5, 55.6, 51.8, 37.5, 24.3, 17.7 (aliphatic C)

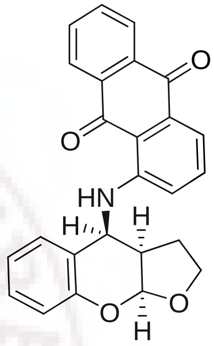
LCMS (m/z): 440 $(M-H)^+$

Anal. Calcd. for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17 %

Found: C, 73.40; H, 5.29; N, 3.23 %

Cis-1-(2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-4-ylamino)-9,10-dihydro-9,10-anthracenedione (98a)

Obtained as a red coloured solid by the reaction of salicylaldehyde (**94a**) with 1-aminoanthraquinone and 2,3-dihydrofuran (**97**) in THF following the *general procedure A*. The crude product was purified by silica gel column chromatography with 3 % ethyl acetate in hexanes.



98a

Yield: 82 %

Mp: 111 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3250, 3069, 2959, 1668, 1265, 1039, 802, 707

^{1}H NMR (400 MHz) δ: 10.31 (1H, d, *J* = 8.0 Hz, N*H*); 8.32 (2H, t, *J* = 7.7 Hz); 7.71-7.83 (3H, m); 7.60 (1H, t, *J* = 8.0 Hz); 7.16-7.30 (2H, m); 7.01 (1H, t, *J* = 8.4 Hz); 6.90-6.93 (2H, m); 6.02 (1H, d, *J* = 5.9 Hz, OC*H*O); 5.18 (1H, t, *J* = 3.3 Hz, NH-C*H*); 3.19-3.95 (2H, m, OCH_2); 3.26 (1H, sept, *J* = 5.6 Hz); 2.17-2.25 (1H, m); 1.79-1.89 (1H, m)

^{13}C NMR (100 MHz) δ: 185.7, 183.5, 152.9, 151.4, 135.8, 135.2, 134.9, 134.1, 133.3, 133.0, 129.2, 126.9, 126.8, 125.9, 124.2, 122.3, 118.3, 118.2, 117.6, 116.6 (aromatic C), 102.5, 68.2, 48.8, 44.1, 24.8 (aliphatic C)

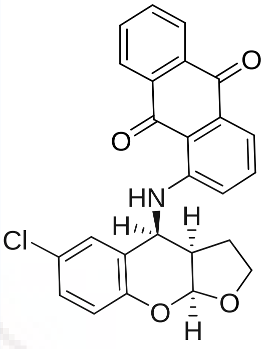
LCMS (m/z): 398 $(M+H)^{+}$

Anal. Calcd. for $C_{25}H_{19}NO_4$: C, 75.55; H, 4.82; N, 3.52 %

Found: C, 75.54; H, 4.87; N, 3.64 %

Cis-1-(6-chloro-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-4-ylamino)-9,10-dihydro-9,10-anthracenedione (98b)

The compound obtained by the reaction of **94b** with 1-aminoanthraquinone and 2,3-dihydrofuran (**97**) in THF following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 3 % ethyl acetate in hexanes.



98b

Yield: 68 %

Mp: 160 °C

IR (KBr) ν_{max} cm^{-1}: 3248, 3074, 2947, 2881, 1666, 1265, 1028, 856, 798

^{1}H NMR (400 MHz) δ: 10.27 (1H, d, *J* = 7.6 Hz, N*H*); 8.28-8.33 (2H, m); 7.72-7.83 (3H, m); 7.61 (1H, t, *J* = 8.0 Hz); 7.21-7.28 (2H, m); 7.11 (1H, d, *J* = 8.4 Hz); 6.94 (1H, d, *J* = 8.4 Hz); 6.00 (1H, d, *J* = 6.0 Hz, OC*H*O); 5.09 (1H, t, *J* = 3.6 Hz, NH-C*H*); 3.91-3.95 (2H, m, OCH_2); 3.20-3.27 (1H, m); 2.06-2.10 (1H, m); 1.75-1.84 (1H, m)

^{13}C NMR (100 MHz) δ: 185.8, 183.4, 151.6, 150.9, 135.9, 135.6, 134.8, 134.1, 133.4, 132.9, 130.1, 129.1, 128.6, 127.3, 126.8, 125.9, 119.5, 117.9, 116.8, 113.6 (aromatic C), 102.7, 68.2, 48.8, 44.0, 25.9 (aliphatic C)

LCMS (m/z): 432 (M+H)$^+$

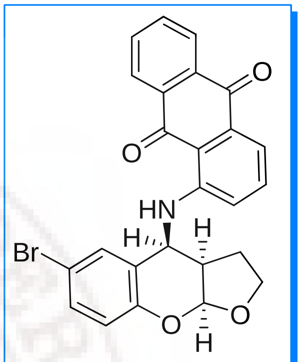
Anal. Calcd. for $C_{25}H_{18}ClNO_4$: C, 69.53; H, 4.20; N, 3.24 %

Found: C, 69.78; H, 4.19; N, 3.53 %

Cis-1-(6-bromo-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-4-ylamino)-9,10-dihydro-9,10-anthracenedione (98c)

Obtained **98c** from **94c** by the reaction with 1-aminoanthraquinone and 2,3-dihydrofuran (**97**) in THF following the *general procedure A*. The crude product was purified by silica gel column chromatography with 3 % ethyl acetate in hexanes.

Yield:	55 %
Mp:	181 °C
IR (KBr) ν_{max} cm^{-1}:	3248, 2955, 1766, 1666, 1267, 1079, 978, 862
^{1}H NMR (400 MHz) δ:	10.26 (1H, d, *J* = 7.8 Hz, N*H*); 8.30 (2H, t, *J* = 8.0 Hz); 7.76-7.82 (2H, m); 7.72 (1H, d, *J* = 7.4 Hz); 7.60 (1H, t, *J* = 8.0 Hz); 7.34-7.38 (2H, m); 7.10 (1H, d, *J* = 8.5 Hz); 6.89 (1H, d, *J* = 8.4 Hz); 6.00 (1H, d, *J* = 5.9 Hz, OC*H*O); 5.11 (1H, t, *J* = 5.5 Hz, NH-C*H*); 3.91-3.96 (2H, m, OC*H*$_2$); 3.20-3.24 (1H, m); 2.22-2.27 (1H, m); 1.81-1.86 (1H, m)
^{13}C NMR (100 MHz) δ:	185.7, 183.3, 152.1, 150.9, 135.8, 135.6, 134.8, 134.0, 132.9, 131.5, 128.8, 126.8, 119.9, 119.4, 117.8, 117.1, 116.8, 116.5, 114.6, 113.6 (aromatic C), 102.7, 68.3, 49.5, 44.4, 27.3 (aliphatic C)
LCMS (m/z):	476 (M+H)$^+$, 478 (M+2+H)$^+$
Anal. Calcd. for $C_{25}H_{18}BrNO_4$:	C, 63.04; H, 3.81; N, 2.94 %
Found:	C, 63.07; H, 3.86; N, 2.85 %



98c

Cis-1-(6-methyl-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-4-ylamino)-9,10-dihydro-9,10-anthracenedione (98d)

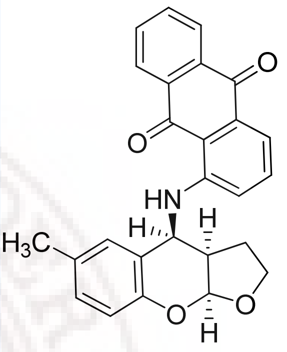
Reaction of 5-methyl salicylaldehyde (**94d**) in the presence of TPPP (20 mol %) with 1-aminoanthraquinone and 2,3-dihydrofuran (**97**) in THF following the *general procedure A* provided the title compound as a red solid. Pure product was obtained by silica gel column chromatography with 3 % ethyl acetate in hexanes.

Yield: 88 %

Mp: 210 °C

IR (KBr) ν_{max} cm^{-1}: 3240, 3065, 2949, 1666, 1269, 1091, 976, 798

^{1}H NMR (400 MHz) δ: 10.27 (1H, d, *J* = 7.6 Hz, N*H*); 8.25-8.30 (2H, m); 7.72-7.80 (2H, m); 7.68 (1H, d, *J* = 6.8 Hz); 7.56 (1H, t, *J* = 8.8 Hz); 7.11 (1H, d, *J* = 8.4 Hz); 6.94 (1H, d, *J* = 8.4 Hz); 6.76-6.79 (2H, m); 5.96 (1H, d, *J* = 6.4 Hz, OC*H*O); 5.05 (1H, t, *J* = 5.1 Hz, NH-C*H*); 3.84-3.87 (2H, m, OC*H*$_2$); 3.69 (3H, s, ArC–C*H*$_3$); 3.20-3.27 (1H, m); 2.19-2.22 (1H, m); 1.75-1.84 (1H, m)



98d

^{13}C NMR (100 MHz) δ: 185.5, 183.4, 151.3, 150.7, 135.7, 135.5, 134.0, 133.2, 133.0, 131.7, 130.6, 129.1, 126.7, 124.1, 118.2, 117.7, 117.4, 116.5, 116.2, 113.4 (aromatic C), 102.5, 68.1, 49.9, 44.7, 27.5, 20.9 (aliphatic C)

LCMS (m/z): 412 (M+H)$^+$

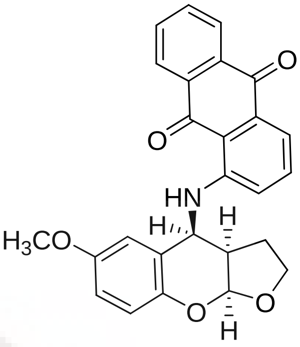
Anal. Calcd. for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.14; N, 3.40 %

Found: C, 75.97; H, 5.10; N, 3.22 %

Cis-1-(6-methoxy-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-4-ylamino)-9,10-dihydro-9,10-anthracenedione (98e)

Furanochromenylaminoanthraquinone (**98e**) was obtained by the reaction of 5-methoxy salicylaldehyde (**94e**) with 1-aminoanthraquinone and 2,3-dihydrofuran

(**97**) in the presence of TPPP (20 mol %) in THF following the *general procedure A*. The crude product was purified by silica gel column chromatography with 3 % ethyl acetate in hexanes.

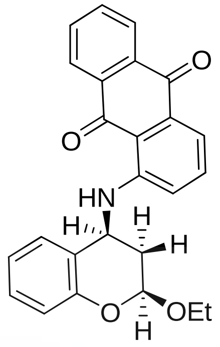


98e

Yield:	92 %
Mp:	173 °C
IR (KBr) ν_{max} cm^{-1}:	3242, 3069, 2953, 2885, 1668, 1267, 1033, 804, 736
^{1}H NMR (400 MHz) δ:	10.28 (1H, d, *J* = 7.5 Hz, N$\underline{H}$); 8.26-8.31 (2H, m); 7.75-7.81 (2H, m); 7.69 (1H, d, *J* = 7.4 Hz); 7.57 (1H, t, *J* = 8.3 Hz); 7.12 (1H, d, *J* = 8.5 Hz); 6.95 (1H, d, *J* = 8.4 Hz); 6.77-6.80 (2H, m); 5.98 (1H, d, *J* = 6.5 Hz, OC$\underline{H}$O); 5.06 (1H, t, *J* = 5.7 Hz, NH-C$\underline{H}$); 3.85-3.88 (2H, m, OC$\underline{H}_2$); 3.70 (3H, s, ArC–OC$\underline{H}_3$); 3.24 (1H, q, *J* = 5.8 Hz); 2.18-2.21 (1H, m); 1.78-1.83 (1H, m)
^{13}C NMR (100 MHz) δ:	185.6, 183.3, 155.0, 151.2, 146.5, 135.6, 134.8, 134.0, 133.8, 133.2, 132.0, 128.6, 128.5, 126.7, 126.2, 118.4, 118.2, 116.6, 113.5, 113.4 (aromatic C), 103.7, 68.1, 55.6, 49.1, 44.3, 25.0 (aliphatic C)
LCMS (m/z):	428 $(M+H)^+$
Anal. Calcd. for $C_{26}H_{21}NO_5$:	C, 73.06; H, 4.95; N, 3.28 %
Found:	C, 73.06; H, 4.94; N, 3.75 %

Cis-1-(2-ethoxy-6-methyl-3,4-dihydro-2*H*-4-chromenylamino)-9,10-dihydro-9,10-anthracenedione (100a)

Obtained as a red coloured solid by the reaction of **94a** with 1-aminoanthraquinone and ethyl vinyl ether (**99**) in THF following the *general procedure A*. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.


100a

Yield: 60 %

Mp: 153 °C

IR (KBr) ν_{max} cm^{-1}: 3246, 3069, 2968, 2885, 1664, 1267, 1111, 1020, 952, 895

^{1}H NMR (400 MHz) δ: 10.41 (1H, d, *J* = 9.0 Hz, N$\underline{H}$); 8.24 (2H, t, *J* = 7.7 Hz); 7.58-7.76 (4H, m); 7.36 (2H, t, *J* = 7.2 Hz); 7.26 (1H, t, *J* = 8.5 Hz); 6.97 (2H, t, *J* = 7.6 Hz); 5.44 (1H, t, *J* = 3.2 Hz, $OC\underline{H}OCH_2CH_3$); 5.01-5.05 (1H, m, NH-C$\underline{H}$); 4.01 (1H, p, *J* = 6.8 Hz); 3.63-3.71 (1H, m); 2.39-2.42 (2H, m, $OC\underline{H_2}CH_3$); 1.32 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 184.4, 183.9, 151.4, 150.4, 135.2, 135.1, 133.9, 132.9, 132.8, 131.5, 129.4, 129.1, 126.7, 126.6, 123.4, 121.6, 117.7, 117.3, 115.6, 113.5 (aromatic C), 96.7, 64.4, 44.1, 33.1, 15.0 (aliphatic C)

LCMS (m/z): 422 (showing +23 sodium ion adduct)

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51 %

Found: C, 75.17; H, 5.31; N, 3.83 %

Cis-1-(6-chloro-2-ethoxy-3,4-dihydro-2*H*-4-chromenylamino)-9,10-dihydro-9,10-anthracenedione (100b)

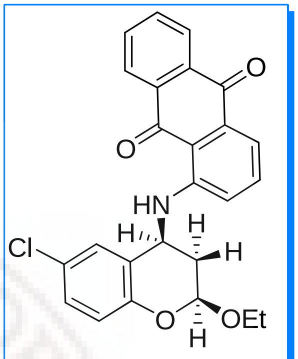
The compound (**97b**) was obtained by the reaction of 5-chloro salicylaldehyde (**94b**) with 1-aminoanthraquinone and ethyl vinyl ether (**99**) in THF following the *general procedure A*. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 52 %

Mp: 149 °C

IR (KBr) ν_{max} cm^{-1}: 3450, 3229, 3074, 2928, 1734, 1664, 1267, 1113, 881, 825

^{1}H NMR (400 MHz) δ: 10.40 (1H, d, *J* = 9.2 Hz, N*H*); 8.24 (2H, t, *J* = 6.2 Hz); 7.68-7.76 (2H, m); 7.59-7.67 (2H, m); 7.32-7.34 (2H, m); 7.20 (1H, d, *J* = 8.5 Hz); 6.89 (1H, d, *J* = 8.7 Hz); 5.43 (1H, t, *J* = 3.1 Hz, OC*H*OCH$_2$CH$_3$); 4.95-4.98 (1H, m, NH-C*H*); 3.93-4.01 (1H, m); 3.63-3.69 (1H, m); 2.37-2.38 (2H, m, OC*H*$_2$CH$_3$); 1.31 (3H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$)



100b

^{13}C NMR (100 MHz) δ: 184.6, 183.8, 150.1, 149.9, 135.3, 135.2, 134.9, 133.9, 132.9, 132.2, 129.5, 128.8, 126.8, 126.6, 126.3, 125.0, 119.2, 117.0, 115.9, 113.7 (aromatic C), 96.7, 64.6, 43.8, 32.8, 15.0 (aliphatic C)

LCMS (m/z): 434 (M+H)$^+$

Anal. Calcd. for $C_{25}H_{20}ClNO_4$: C, 69.21; H, 4.65; N, 3.23 %

Found: C, 69.33; H, 4.66; N, 3.10 %

Cis-1-(6-bromo-2-ethoxy-3,4-dihydro-2*H*-4-chromenylamino)-9,10-dihydro-9,10-anthracenedione (100c)

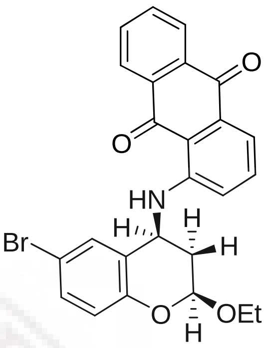
Obtained **100c** from **94c** by treating with 1-aminoanthraquinone and ethyl vinyl ether (**99**) in THF following the *general procedure A*. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 45 %

Mp: 170 °C

IR (KBr) ν_{max} cm^{-1}: 3225, 2964, 2922, 1664, 1267, 1113, 1068, 952, 879

^{1}H NMR (400 MHz) δ: 10.40 (1H, d, *J* = 9.1 Hz, N*H*); 8.23-8.26 (2H, m); 7.71-7.75 (2H, m); 7.62-7.67 (2H, m); 7.46 (1H, s); 7.28-7.35 (2H, m); 6.85 (1H, d, *J* = 8.7 Hz); 5.44 (1H, d, *J* = 2.4 Hz, OC*H*OCH$_2$CH$_3$); 4.95-5.00 (1H, m, NH-C*H*); 3.93-4.01 (1H, m); 3.63-3.69 (1H, m); 2.36-2.37 (2H, m, OC*H*$_2$CH$_3$); 1.31 (3H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$)



100c

^{13}C NMR (100 MHz) δ: 184.6, 183.8, 150.6, 150.1, 135.3, 135.1, 133.9, 133.4, 132.9, 132.4, 131.8, 131.2, 129.4, 126.8, 126.6, 125.6, 119.6, 117.1, 115.9, 113.7 (aromatic C), 96.8, 64.6, 43.8, 32.9, 15.0 (aliphatic C)

LCMS (m/z): 478 (M+H)$^+$, 480 (M+2+H)$^+$

Anal. Calcd. for $C_{25}H_{20}BrNO_4$: C, 62.77; H, 4.21; N, 2.93 %

Found: C, 62.80; H, 4.21; N, 3.14 %

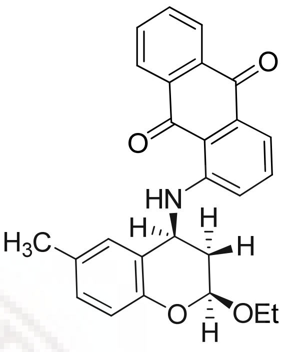
***Cis*-1-(2-ethoxy-6-methyl-3,4-dihydro-2*H*-4-chromenylamino)-9,10-dihydro-9,10-anthracenedione (100d)**

Reaction of **94d** in the presence of TPPP (20 mol %) with 1-aminoanthraquinone and ethyl vinyl ether (**99**) in THF following the *general procedure A* provided as a red solid. The crude product was purified by silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 70 %

Mp: 151 °C

IR (KBr) ν_{max} cm^{-1}: 3250, 3069, 2974, 2922, 1666, 1265, 1113, 1070, 951



100d

^{1}H NMR (400 MHz) δ: 10.40 (1H, d, *J* = 8.9 Hz, N*H*); 8.23-8.25 (2H, m); 7.69-7.75 (2H, m); 7.58-7.67 (2H, m); 7.36 (1H, d, *J* = 8.1 Hz); 7.13 (1H, s); 7.06 (1H, d, *J* = 8.0 Hz); 6.85 (1H, d, *J* = 7.9 Hz); 5.41 (1H, t, *J* = 3.0 Hz, OC*H*OCH$_2$CH$_3$); 4.96-4.99 (1H, d, *J* = 4.5 Hz, NH-C*H*); 3.96-4.01 (1H, m); 3.62-3.66 (1H, m); 2.36-2.38 (2H, m, OC*H*$_2$CH$_3$); 2.25 (3H, s, ArC-C*H*$_3$); 1.30 (3H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$)

^{13}C NMR (100 MHz) δ: 184.4, 183.9, 150.4, 149.1, 135.2, 135.0, 133.9, 132.9, 132.8, 131.5, 130.9, 130.2, 129.4, 126.8, 126.6, 123.0, 117.5, 117.3, 115.6, 113.5 (aromatic C), 96.6, 64.2, 44.2, 33.2, 20.7, 15.1 (aliphatic C)

LCMS (m/z): 414 (M+H)$^+$

Anal. Calcd. for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39 %

Found: C, 75.59; H, 5.68; N, 3.31 %

Cis-1-(2-ethoxy-6-methoxy-3,4-dihydro-2*H*-4-chromenylamino)-9,10-dihydro-9,10-anthracenedione (100e)

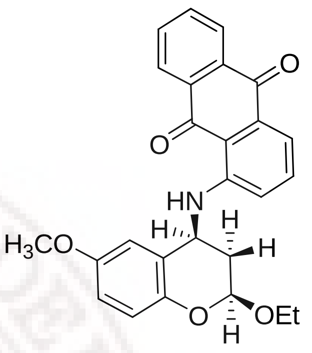
The furanochromenylaminoanthraquinone (**100e**) was obtained by the reaction of 5-methoxy salicylaldehyde (**94e**) with 1-aminoanthraquinone and ethyl vinyl ether (**99**) in the presence of TPPP (20 mol %) in THF following the *general procedure A*. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 72 %

Mp: 154 °C

IR (KBr) ν_{max} cm^{-1}: 3254, 2968, 2870, 1662, 1589, 1267, 1114, 1020, 952

^{1}H NMR (400 MHz) δ: 10.40 (1H, d, *J* = 9.0 Hz, N*H*); 8.24 (2H, t, *J* = 7.2 Hz); 7.70-7.76 (2H, m); 7.58-7.65 (2H, m); 7.35 (1H, d, *J* = 8.2 Hz); 6.83-6.90 (3H, m); 5.39 (1H, d, *J* = 2.7 Hz, OC*H*OCH$_2$CH$_3$); 4.98 (1H, t, *J* = 4.2 Hz, NH-C*H*); 3.95-4.00 (1H, m); 3.72 (3H, s, ArC-OC*H*$_3$); 3.62-3.66 (1H, m); 2.35-2.39 (2H, m, OC*H*$_2$CH$_3$); 1.30 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$)



100e

^{13}C NMR (100 MHz) δ: 184.4, 183.8, 154.1, 150.3, 145.1, 135.2, 135.1, 135.0, 133.9, 132.8, 132.7, 126.7, 126.5, 123.9, 118.3, 117.3, 115.7, 115.6, 113.5, 113.3 (aromatic C), 96.6, 64.2, 55.7, 44.4, 33.1, 15.0 (aliphatic C)

LCMS (m/z): 452 (showing +23 sodium adduct ion)

Anal. Calcd. for $C_{26}H_{23}NO_5$: C, 72.71; H, 5.40; N, 3.26 %

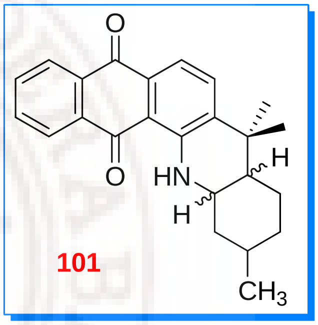
Found: C, 72.75; H, 5.39; N, 3.46 %

General procedure B

To a stirred solution of 1-aminoanthraquinone (1.0 mmol) in THF (50 mL), citronellal (1.2 mmol) or *O*-prenylated salicylaldehydes (**104a-g**) was added followed by TPPP (20 mol %). The reaction was monitored by TLC. After completion of the reaction, as indicated by the TLC, the excess THF was distilled off and the residue was poured over water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and distilled under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh size) and eluted with hexanes: ethyl acetate mixture yielded the products as red solids.

8,8,11-Trimethyl-8,8a,9,10,11,12,12a,13-octahydro-naphtho[2,3-*c*] acridine-5,14-dione (101)

The compound (**101**) was prepared by the reaction of 1-aminoanthraquinone and citronellal in the presence of TPPP (20 mol %) in THF at room temperature following the *general procedure B.* The crude product was purified by silica gel column chromatography with 1 % ethyl acetate in hexanes.

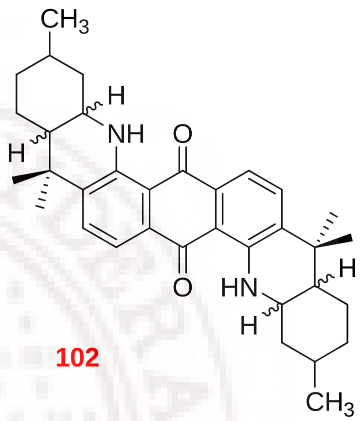


101

Yield:	94 %
Mp:	115-116 °C
IR (KBr) ν_{max} cm^{-1}:	3537, 3238, 2951, 2872, 1711, 1622, 1265, 898
^{1}H NMR (400 MHz) δ:	10.14 (1H, s, N*H*); 8.27 (1H, d, *J* = 7.7 Hz); 8.22 (1H, d, *J* = 7.6 Hz); 7.74 (1H, t, *J* = 7.6 Hz); 7.67 (1H, t, *J* = 7.6 Hz); 7.53 (1H, d, *J* = 7.6 Hz); 7.42 (1H, d, *J* = 7.6 Hz); 2.04-2.20 (1H, m, NH–C*H*); 1.80–1.94 (1H, m); 1.60–1.72 (3H, m); 1.38 (6H, s); 1.15–1.30 (4H, m); 0.93 (3H, d, *J* = 6.6 Hz)
^{13}C NMR (100 MHz) δ:	184.6, 183.6, 148.4, 140.4, 137.9, 135.3, 133.7, 132.5, 130.8, 130.5, 126.5, 126.4, 115.7, 110.8 (aromatic C), 50.7, 46.9, 42.3, 40.5, 34.1, 32.0, 25.9, 25.7, 23.0, 22.1 (aliphatic C)
LCMS (m/z):	360 $(M+H)^+$
Anal. Calcd. for $C_{24}H_{25}NO_2$:	C, 80.19; H, 7.01; N, 3.90 %
Found:	C, 80.40; H, 7.00; N, 3.85 %

3,9,9,12,18,18-Hexamethyl-1,2,3,4,4a,5,9,9a,10,11,12,13,13a,14,18,18a-hexadecahydro-5,14-diaza-naphtho-[2,3-*c*]pentaphene-6,15-dione **(102)**

Reaction of 2.0 eq. of citronellal in the presence of TPPP (20 mol %) with 1-aminoanthraquinone in THF following the *general procedure B* provided the title compound as a red solid. Pure product was obtained by silica gel column chromatography with 4 % ethyl acetate in hexanes.

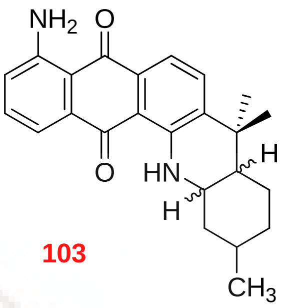


102

Yield:	70 %
Mp:	160-161 °C
IR (KBr) ν_{max} cm^{-1}:	3445, 3225, 2916, 1876, 1618, 1589, 1257, 779
^{1}H NMR (400 MHz) δ:	10.11 (2H, s, N*H*); 7.46 (2H, d, *J* = 7.9 Hz); 7.38 (2H, d, *J* = 7.7 Hz); 2.02-2.20 (2H, m, NH–C*H*); 1.78–1.93 (2H, m); 1.55–1.76 (6H, m); 1.36 (12H, s); 1.12–1.34 (8H, m); 0.91 (6H, d, *J* = 6.4 Hz)
^{13}C NMR (100 MHz) δ:	185.2, 185.1, 147.9, 147.4, 138.2, 135.7, 135.6, 134.3, 130.7, 130.6, 130.4, 114.4, 114.3, 111.1 (aromatic C), 50.6, 46.8, 45.1, 42.9, 42.5, 40.5, 36.4, 35.6, 34.9, 34.2, 32.2, 31.1, 29.7, 25.9, 25.6, 25.4, 25.3, 24.4, 22.9, 22.1 (aliphatic C)
LCMS (m/z):	511 (M+H)$^+$
Anal. Calcd. for $C_{34}H_{42}N_2O_2$:	C, 79.96; H, 8.29; N, 5.49 %
Found:	C, 79.91; H, 8.21; N, 5.47 %

4-Amino-8,8,11-Trimethyl-8,8a,9,10,11,12,12a,13-octahydro-naphtho[2,3-*c*]acridine-5,14-dione **(103)**

The compound was prepared by taking the 2.0 eq. of citronellal with 1-aminoanthraquinone at room temperature in THF following the *general procedure B*. The crude product was purified by silica gel column chromatography with 2 % ethyl acetate in hexanes.



103

Yield: 24 %

Mp: 104-105 °C

IR (KBr) ν_{max} cm^{-1}: 3447, 3325, 2924, 2856, 1714, 1597, 1257, 771

^{1}H NMR (400 MHz) δ: 10.09 (1H, s, N<u>H</u>); 7.60 (1H, d, *J* = 7.2 Hz); 7.39–7.49 (3H, m); 6.85 (1H, d, *J* = 8.2 Hz); 6.77 (2H, bs, N$\underline{H_2}$); 2.03-2.28 (1H, m, NH–C<u>H</u>); 1.82–2.00 (1H, m); 1.52–1.76 (3H, m); 1.37 (6H, s); 1.32–1.18 (4H, m); 0.92 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 185.7, 184.9, 148.1, 140.6, 136.5, 136.4, 134.3, 133.6, 130.8, 130.5, 126.3, 125.8, 114.8, 110.9 (aromatic C), 50.6, 46.8, 42.8, 40.5, 34.5, 32.1, 25.9, 25.3, 23.0, 22.4 (aliphatic C)

LCMS (m/z): 375 $(M+H)^{+}$

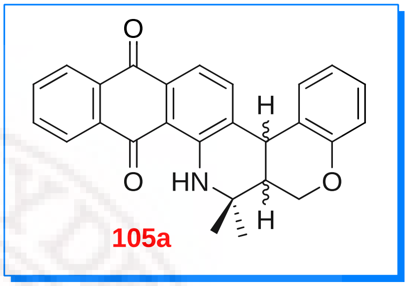
Anal. Calcd. for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48 %

Found: C, 76.97; H, 7.04; N, 7.56 %

16,16-Dimethyl-6b,9,14,15,16,16a-hexahydro-1*H*-chromeno[3,4-*c*]naphtho[2,3-*h*]quinoline-9,14-dione (105a)

This interesting compound was prepared by the addition of 1-aminoanthraquinone to *O*-prenylated salicylaldehyde (**104a**) in THF following the *general procedure B*. After 15 min reflux, reaction was over and the pure product was separated through silica gel column chromatography with 2 % ethyl acetate in hexanes.

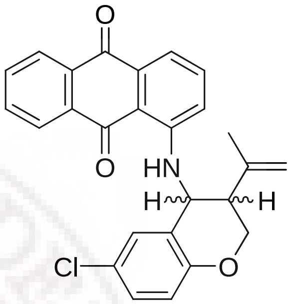
Yield:	63 %
Mp:	142-143 °C
IR (KBr) ν_{max} cm^{-1}:	3433, 3234, 2924, 1722, 1624, 1367, 1222, 754
^{1}H NMR (400 MHz) δ:	10.22 (1H, s, N*H*); 8.27 (1H, d, *J* = 7.7 Hz); 8.21 (1H, d, *J* = 7.6 Hz); 7.69–7.75 (2H, m); 7.48 (1H, d, *J* = 7.8 Hz); 7.42 (1H, d, *J* = 7.7 Hz); 7.32 (1H, d, *J* = 7.5 Hz); 7.24 (1H, t, *J* = 7.1 Hz); 7.01 (1H, t, *J* = 7.0 Hz); 6.86 (1H, d, *J* = 8.1 Hz); 4.74 (1H, d, *J* = 9.6 Hz); 4.39-4.43 (1H, m); 4.23-4.25 (1H, m); 2.26–2.31 (1H, m); 1.52 (3H, s); 1.50 (3H, m)
^{13}C NMR (100 MHz) δ:	185.1, 183.4, 153.5, 146.3, 141.8, 135.4, 133.9, 132.9, 130.8, 129.3, 126.8, 121.8, 119.8, 117.8, 116.0, 115.6, 114.5, 112.8, 112.7, 111.7 (aromatic C), 63.9, 49.9, 48.5, 33.1, 31.9, 28.2, 27.1 (aliphatic C)
LCMS (m/z):	396 (M+H)$^{+}$
Anal. Calcd. for $C_{26}H_{21}NO_3$:	C, 78.97; H, 5.35; N, 3.54 %
Found:	C, 79.01; H, 5.38; N, 3.66 %



105a

1-(6-Chloro-3-isopropenyl-chroman-3-ylamino)-anthraquinone (105b)

Prepared by the reaction of 1-aminoanthraquinone and **104b** in THF at reflux temperature for 15 minutes following the *general procedure B*. The crude product was purified by silica gel column chromatography with 6 % ethyl acetate in hexanes.

Yield:	44 %
Mp:	165-166 ^{o}C
IR (KBr) ν_{max} cm^{-1}:	3414, 3229, 3072, 2962, 2926, 1658, 1116, 978
^{1}H NMR (400 MHz) δ:	10.29 (1H, s, N$\underline{H}$); 8.22 (2H, t, J = 7.3 Hz); 7.69–7.74 (2H, m); 7.61 (1H, d, J = 7.9 Hz); 7.51 (1H, d, J = 7.3 Hz); 7.37 (1H, s); 7.23 (1H, d, J = 7.2 Hz); 7.15 (1H, d, J = 7.4 Hz); 6.82 (1H, t, J = 8.4 Hz); 4.77 (2H, d, J = 3.6 Hz); 4.41 (2H, d, J = 6.1 Hz); 2.89 (1H, d, J = 5.2 Hz); 2.12–2.15 (1H, m); 1.78 (3H, s)  **105b**
^{13}C NMR (100 MHz) δ:	185.3, 183.6, 152.4, 146.2, 145.1, 140.9, 135.5, 133.9, 133.0, 131.2, 130.8, 129.9, 128.9, 126.8, 126.5, 125.2, 118.5, 118.4, 116.1, 115.6 (aromatic C), 113.2, 111.8, 64.2, 49.9, 32.4, 27.1 (aliphatic C)
LCMS (m/z):	430 (M+H)$^{+}$
Anal. Calcd. for $C_{26}H_{20}ClNO_3$:	C, 72.64; H, 4.69; N, 3.26 %
Found:	C, 72.59; H, 4.69; N, 3.26 %

1-(6-Bromo-3-isopropenyl-chroman-3-ylamino)-anthraquinone (105c)

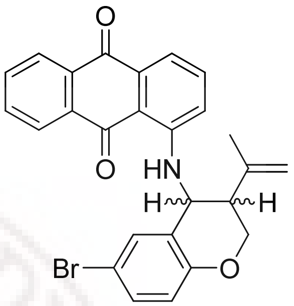
The ene-type product was prepared by the addition of 1-aminoanthraquinone to **104c** in THF following the *general procedure B*. After 15 min reflux, reaction was over and the pure product separated through silica gel column chromatography with 4 % ethyl acetate in hexanes.

Yield:	56 %

Mp: 60-61 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 3069, 2972, 2918, 1662, 1269, 1022, 978

^{1}H NMR (400 MHz) δ: 10.29 (1H, s, N*H*); 8.23 (2H, t, *J* = 6.4 Hz); 7.60–7.70 (3H, m); 7.59 (1H, s); 7.51 (1H, d, *J* = 7.7 Hz); 7.36 (1H, d, *J* = 7.2 Hz); 7.27 (1H, d, *J* = 6.9 Hz); 6.78 (1H, d, *J* = 8.7 Hz); 4.78 (2H, s); 4.27 (2H, d, *J* = 11.0 Hz); 3.63 (1H, t, *J* = 11.5 Hz); 2.11–2.14 (1H, m); 1.41 (3H, s)



105c

^{13}C NMR (100 MHz) δ: 185.4, 184.7, 154.2, 144.3, 135.4, 134.9, 133.9, 133.0, 132.8, 132.3, 132.2, 130.9, 126.7, 124.8, 118.9, 118.3, 117.4, 116.2, 114.2, 113.9 (aromatic C), 112.9, 111.8, 66.8, 45.5, 32.4, 25.6 (aliphatic C)

LCMS (m/z): 475 (M+H)$^+$, 477 (M+2+H)$^+$

Anal. Calcd. for $C_{26}H_{20}BrNO_3$: C, 65.83; H, 4.25; N, 2.95 %

Found: C, 65.97; H, 4.27; N, 2.88 %

1-(3-Isopropenyl-6-nitro-chroman-4-ylamino)-anthraquinone (105d)

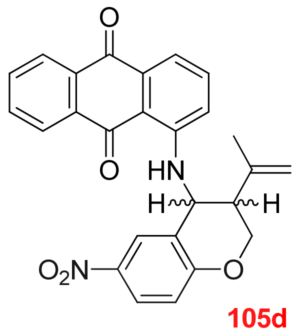
The compound (**105d**) was prepared by the addition of 1-aminoanthraquinone with 5-nitro-*O*-prenylated salicylaldehyde (**104d**) in THF following the *general procedure B*. After 15 minutes reflux, reaction was over and the pure product separated through silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 40 %

Mp: 128-130 °C

IR (KBr) ν_{max} cm^{-1}: 3429, 3027, 1662, 1624, 1257, 1091, 898

^{1}H NMR (400 MHz) δ: 10.31 (1H, s, N*H*); 8.25 (1H, s); 8.23 (1H, d, *J* = 7.2 Hz); 8.09–8.12 (2H, m); 7.72–7.75 (2H, m); 7.71 (1H, t, *J* = 7.2 Hz); 7.65 (1H, d, *J* = 8.1 Hz); 7.40 (1H, d, *J* = 8.2 Hz); 6.90 (1H, d, *J* = 8.2 Hz); 5.21–5.24 (1H, m); 4.94 (1H, s); 4.77 (1H, s); 4.55 (2H, d, *J* = 6.4 Hz); 2.94 (1H, q, *J* = 5.1 Hz); 1.80 (3H, s)



105d

^{13}C NMR (100 MHz) δ: 185.2, 183.2, 159.3, 150.9, 141.2, 140.2, 135.4, 134.7, 134.5, 133.8, 133.0, 132.7, 126.7, 126.5, 125.3, 124.9, 123.6, 117.6, 117.4, 116.5 (aromatic C), 115.1, 113.3, 66.7, 48.8, 42.7, 22.9 (aliphatic C)

LCMS (m/z): 441 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36 %

Found: C, 71.06; H, 4.53; N, 6.37 %

4-Methoxy-7,7-dimethyl-6a,7,10,15,16,16a-hexahydro-6*H*-chromeno[4,3-*b*]naphtho[2,3-*h*]quinoline-10,15-dione (105e)

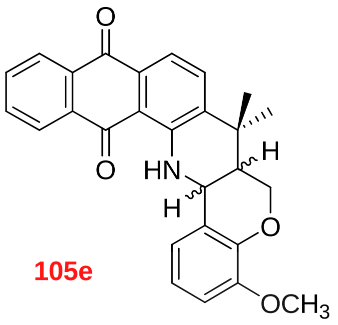
105e was prepared by the reaction of 1-aminoanthraquinone with **104e** in THF. After 15 minutes reflux following the *general procedure B*. The pure product separated through silica gel column chromatography with 5 % ethyl acetate in hexanes.

Yield: 58 %

Mp: 191-192 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 2966, 2833, 1655, 1585, 1296, 1070, 760

^{1}H NMR (400 MHz) δ: 10.90 (1H, s, N*H*); 8.33 (1H, d, *J* = 7.7 Hz); 8.24 (1H, d, *J* = 7.2 Hz); 7.63–7.78 (4H, m); 7.31 (1H, d, *J* = 7.7); 7.10 (1H, d, *J* = 7.9 Hz); 6.88 (1H, d, *J* = 8.0 Hz); 4.67 (2H, d, *J* = 2.8 Hz); 4.09 (1H, t, *J* = 10.9 Hz); 2.90 (3H, s, ArC-OC*H*$_3$); 2.17–2.22 (1H, m); 1.26 (6H, s)



105e

^{13}C NMR (100 MHz) δ: 185.2, 183.4, 148.5, 147.7, 145.1, 138.9, 135.1, 133.9, 132.9, 132.8, 132.5, 131.8, 126.8, 126.7, 123.4, 121.1, 117.1, 116.2, 113.1 (aromatic C), 66.0, 55.9, 47.1, 41.4, 35.2, 32.6, 26.7 (aliphatic C)

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

Anal. Calcd. for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29 %

Found: C, 76.36; H, 5.49; N, 3.35 %

2-Methoxy-7,7-dimethyl-6a,7,10,15,16,16a-hexahydro-6*H*-chromeno[4,3-*b*]naphtho[2,3-*h*]quinoline-10,15-dione (105f)

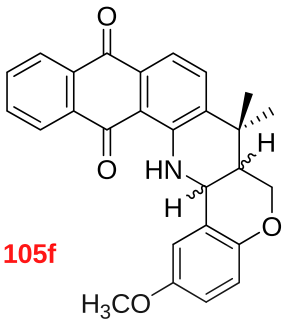
105f was prepared by the reaction of 1-aminoanthraquinone with *O*-prenylated 5-methoxy salicylaldehyde (**104f**) in THF following the *general procedure B*. After 15 minutes reflux, reaction was over and the pure product separated through silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 69 %

Mp: 108 °C

IR (KBr) ν_{max} cm^{-1}: 3238, 2922, 1664, 1271, 1149, 1043, 814

^{1}H NMR (400 MHz) δ: 10.37 (1H, s, N*H*); 8.29 (1H, d, *J* = 7.8 Hz); 8.24 (1H, d, *J* = 7.4 Hz); 7.73–7.78 (2H, m); 7.65 (1H, d, *J* = 7.2); 7.51 (1H, d, *J* = 3.1 Hz); 7.10 (1H, s); 6.82–6.90 (2H, m); 4.81 (1H, d, *J* = 3.9 Hz); 4.37–4.41 (1H, m); 4.23–4.26 (1H, m); 3.87 (3H, s, ArC-C*H*$_3$); 2.27-2.30 (1H, m); 1.53 (3H, s); 1.52 (3H, s)



105f

^{13}C NMR (100 MHz) δ: 185.1, 183.4, 153.0, 147.6, 146.5, 135.3, 133.8, 132.9, 130.7, 128.7, 126.6, 122.4, 117.6, 116.9, 116.3, 115.6, 115.1, 114.7, 113.2, 111.8 (aromatic C), 63.9, 55.9, 50.0, 37.2, 35.8, 32.3, 27.1 (aliphatic C)

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

Anal. Calcd. for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29 %

Found: C, 76.12; H, 5.59; N, 3.35 %

2,7,7-Trimethyl-6a,7,10,15,16,16a-hexahydro-6*H*-chromeno[4,3-*b*] naphtho[2,3-*h*] quinoline-10,15-dione (105g)

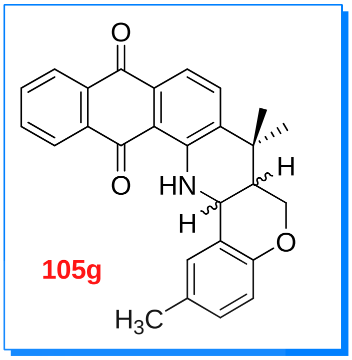
105g was prepared by the reaction of 1-aminoanthraquinone to *O*-prenylated 5-methyl salicylaldehyde (**104g**) in THF at reflux temperature for 15 minutes following the *general procedure B*. The crude product was purified by silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 63 %

Mp: 71-73 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 2922, 1664, 1502, 1269, 1147, 1024, 815

^{1}H NMR (400 MHz) δ: 10.22 (1H, s, N*H*); 8.27 (1H, d, *J* = 7.6 Hz); 8.21 (1H, d, *J* = 8.4 Hz); 7.67−7.77 (2H, m); 7.49 (1H, d, *J* = 8.0 Hz); 7.44 (1H, d, *J* = 7.6 Hz); 7.12 (1H, s); 7.04 (1H, d, *J* = 9.6 Hz); 6.76 (1H, d, *J* = 8.0 Hz); 4.39 (2H, d, *J* = 6.4 Hz); 4.36 (1H, d, *J* = 6.0 Hz); 3.75 (1H, t, *J* = 10.8 Hz); 2.38 (3H, s, ArC-C*H*$_3$); 1.51 (3H, s); 1.49 (3H, s)


105g

^{13}C NMR (100 MHz) δ: 185.1, 183.4, 151.4, 146.5, 135.4, 135.2, 133.8, 133.2, 132.9, 132.3, 131.5, 130.5, 130.1, 129.6, 129.0, 126.6, 121.6, 116.8, 115.6, 111.8 (aromatic C), 63.9, 50.0, 37.2, 35.5, 31.9, 27.1, 20.6 (aliphatic C)

LCMS (m/z): 432 (showing M+23 sodium adduct ion)

Anal. Calcd. for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42 %

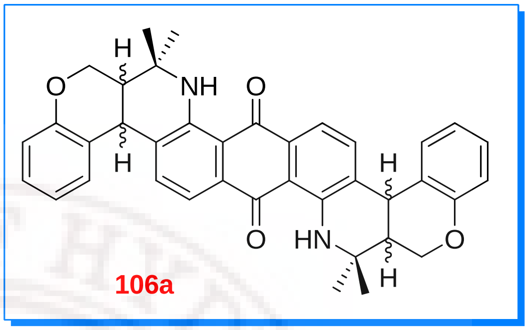
Found: C, 79.12; H, 5.59; N, 3.36 %

11,11,22,22-Tetramethyl-1,6b,9,10,11,11a,12,17b,20,21,22,22a-dodecahydrochromeno[3,4-c]chromeno[4'',3'':4',5']pyrido[3',2':7,8]naphtha [2,3-*h*]quinoline-9,20-dione (106a)

Reaction of 2.0 eq. of *O*-prenylated salicylaldehyde (**104a**) in the presence of TPPP (20 mol %) with 1,5-diaminoanthraquinone in THF following the following the *general procedure B* provided the title compound as a red solid. The pure product was separated through silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 55 %

Mp:	210-211 °C
IR (KBr) ν_{max} cm^{-1}:	3231, 2924, 1734, 1618, 1589, 1249, 1114, 846
^{1}H NMR (400 MHz) δ:	10.16 (2H, s, N*H*); 7.51–7.57 (4H, m); 7.19 (2H, d, *J* = 7.8 Hz); 6.98–7.04 (4H, m); 6.87 (2H, d, *J* = 7.3 Hz); 4.81 (2H, d, *J* = 4.3 Hz); 4.30 (4H, d, *J* = 4.0 Hz); 1.81–2.10 (2H, m); 1.28 (12H, s)
^{13}C NMR (100 MHz) δ:	185.4, 185.3, 154.5, 154.4, 150.4 , 150.2, 148.2, 146.1, 142.4, 138.3, 137.1, 135.3, 133.4, 132.9, 132.2, 129.4, 129.2, 127.3, 124.6, 122.3, 121.3, 121.1, 116.9, 116.8, 115.3, 113.8 (aromatic C), 66.6, 64.0, 63.0, 50.9, 45.7, 40.6, 37.0, 35.3, 31.8, 29.7, 28.3, 21.9 (aliphatic C)
LCMS (m/z):	583 (M+H)$^{+}$
Anal. Calcd. for $C_{38}H_{34}N_2O_4$:	C, 78.33; H, 5.88; N, 4.81 %
Found:	C, 78.26; H, 5.90; N, 4.88 %



106a

1,5-*Bis*-(6-chloro-3-isopropenyl-chroman-3-ylamino)-anthraquinone (106b)

Reaction of 5-chloro *O*-prenylated salicylaldehyde (**104b**) in the presence of TPPP (20 mol %) with 1,5-diaminoanthraquinone in THF following the *general procedure B*. The crude product was purified by silica gel column chromatography with 6 % ethyl acetate in hexanes.

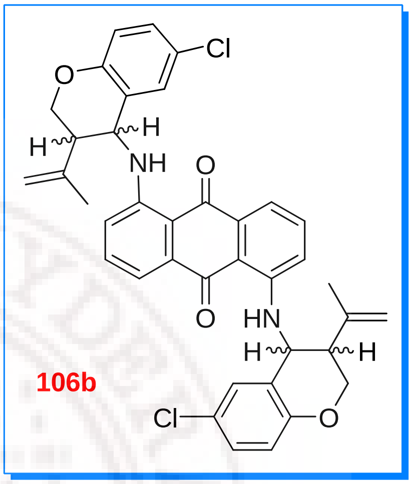
Yield:	37 %

Mp: 65-66 °C

IR (KBr) ν_{max} cm^{-1}: 3437, 3078, 2924, 1728, 1620, 1257, 1091, 895

^{1}H NMR (400 MHz) δ: 10.23 (2H, s, N*H*); 7.54–7.58 (4H, m); 7.48 (2H, s); 7.13 (2H, d, *J* = 7.8 Hz); 6.73–6.76 (4H, m); 4.78 (4H, d, *J* = 6.0 Hz); 4.39 (4H, d, *J* = 6.0 Hz); 2.45–2.61 (2H, m); 1.81 (2H, d, *J* = 6.4 Hz); 1.25 (6H, s)

^{13}C NMR (100 MHz) δ: 185.4, 184.7, 153.1, 152.5, 151.0, 150.2, 145.9, 141.9, 141.0, 135.5, 135.4, 130.8, 129.9, 129.3, 129.1, 128.8, 127.9, 126.0, 125.7, 123.9, 118.5, 118.3, 117.8, 116.2, 115.9, 115.7 (aromatic C), 115.6, 115.5, 114.7, 114.1, 66.8, 66.0, 50.8, 49.1, 44.5, 43.4, 29.7, 27.0 (aliphatic C)



106b

LCMS (m/z): 652 $(M+H)^+$

Anal. Calcd. for $C_{38}H_{32}Cl_2N_2O_4$: C, 70.05; H, 4.95; N, 4.30 %

Found: C, 70.00; H, 5.07; N, 4.48 %

1,5-*Bis*-(6-bromo-3-isopropenyl-chroman-3-ylamino)-anthraquinone (106c)

This *bis*-ene-type product was prepared by the addition of 1,5-diaminoanthraquinone to 2.0 eq. of **104c** in THF following the *general procedure B*. After 15 minutes reflux, reaction was over and the pure product was obtained by silica gel column chromatography with 3 % ethyl acetate in hexanes.

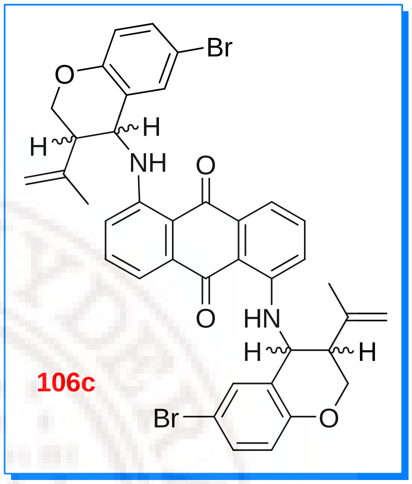
Yield: 55 %

Mp: 85-86 $^{\circ}$C

IR (KBr) ν_{max} cm^{-1}: 4358, 3232, 2964, 1620, 1591, 1257, 1028, 879

^{1}H NMR (400 MHz) δ: 10.23 (2H, s, N*H*); 7.54–7.58 (4H, m); 7.39 (2H, s); 7.36 (2H, d, *J* = 6.0 Hz); 6.68–6.79 (4H, m); 5.03 (4H, s); 4.39 (4H, d, *J* = 4.28 Hz); 4.08 (2H, t, *J* = 9.8 Hz); 2.05–2.06 (2H, m); 1.81 (6H, s)

^{13}C NMR (100 MHz) δ: 185.5, 185.2, 153.6, 153.1, 151.3, 150.2, 145.6, 141.8, 141.6, 135.7, 135.4, 132.8, 132.2, 131.9, 131.8, 131.7, 130.8, 126.6, 124.5, 118.9, 118.8, 118.3, 116.4, 116.2, 115.9, 115.7 (aromatic C), 114.8, 114.2, 113.1, 112.8, 66.7, 65.9, 48.9, 47.4, 44.6, 43.4, 23.0, 21.4 (aliphatic C)



106c

LCMS (m/z): 652 (M+H)$^{+}$, 654 (M+2+H)$^{+}$

Anal. Calcd. for $C_{38}H_{32}Br_2N_2O_4$: C, 61.64; H, 4.36; N, 3.78 %

Found: C, 61.63; H, 4.35; N, 3.81 %

1,5-*Bis*-(3-isopropenyl-6-nitro-chroman-4-ylamino)-anthraquinone (106d)

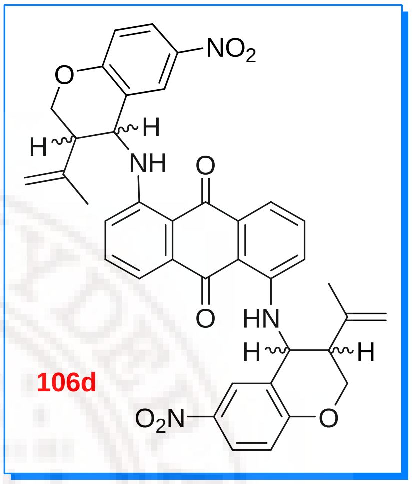
Reaction of 5-nitro *O*-prenylated salicylaldehyde (**104d**) in the presence of TPPP (20 mol %) with 1,5-diaminoanthraquinone in THF following the *general procedure B* provided the title compound as a red solid. The crude product was purified by silica gel column chromatography with 4 % ethyl acetate in hexanes.

Yield: 35 %

Mp: 117-118 °C

IR (KBr) ν_{max} cm^{-1}: 3443, 3254, 2982, 2876, 1716, 1612, 1257, 1090, 967

^{1}H NMR (400 MHz) δ: 10.98 (2H, s, N*H*); 8.59 (2H, s); 8.10–8.24 (2H, m); 7.77 (2H, t, *J* = 7.5 Hz); 7.60 (2H, d, *J* = 7.0 Hz); 7.53 (2H, d, *J* = 6.0 Hz); 6.97 (2H, d, *J* = 8.7 Hz); 5.21–5.26 (2H, m); 4.97 (2H, s); 4.91 (2H, s); 4.40 (4H, d, *J* = 3.8 Hz); 2.04–2.14 (2H, m); 1.28 (3H, s); 1.25 (3H, s)



106d

^{13}C NMR (100 MHz) δ: 185.1, 184.2, 153.7, 153.3, 152.8, 151.0, 150.3, 146.9, 144.7, 141.9, 141.7, 141.0, 137.2, 136.5, 135.2, 134.6, 134.1, 132.7, 132.2, 131.7, 130.9, 128.4, 124.6, 118.8, 118.3, 116.2 (aromatic C), 114.8, 113.7, 112.8, 111.8, 66.8, 64.2, 50.8, 49.1, 44.7, 43.4, 23.7, 21.3 (aliphatic C)

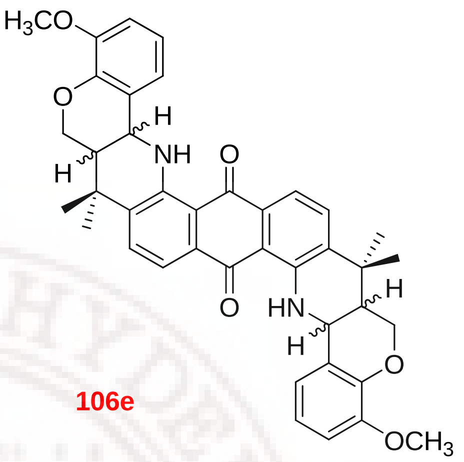
LCMS (m/z): 673 (M+H)$^+$

Anal. Calcd. for $C_{38}H_{32}N_4O_8$: C, 67.85; H, 4.79; N, 8.33 %

Found: C, 67.88; H, 4.79; N, 8.29 %

3,14-Dimethoxy-11,11,22,22-tetramethyl-1,6b,7,8,11,11a,12,17b,18,19,22,22a-dodecahydrochromeno[4,3-*b*]chromeno[3'',4'':5',6']pyrido[3',2':7,8]naphtho[2,3-*h*]quinoline-8,19-dione (106e)

Obtained **106e** from **104e** by the reaction of 1,5-diaminoanthraquinone in the presence of TPPP (20 mol %) in THF following the *general procedure B*. Reaction was completed after 15 minutes at reflux temperature. Pure product was obtained by silica gel column chromatography with 15 % ethyl acetate in hexanes.

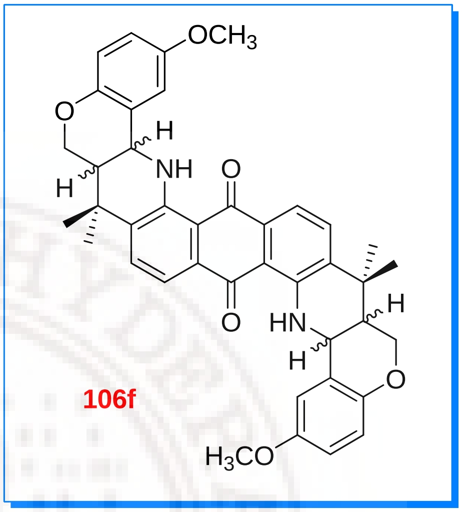


106e

Yield:	55 %
Mp:	94-95 °C
IR (KBr) ν_{max} cm^{-1}:	3441, 3317, 2987, 2876, 1734, 1599, 1261, 769
^{1}H NMR (400 MHz) δ:	10.11 (2H, s, N*H*); 7.50–7.58 (4H, m); 6.93–7.40 (4H, m); 6.83 (2H, d, *J* = 11.7 Hz); 4.04–4.19 (6H, m); 3.87 (6H, s, ArC-OC*H*$_3$); 2.02–2.16 (2H, m); 1.26 (12H, s)
^{13}C NMR (100 MHz) δ:	185.3, 185.0, 148.6, 148.4, 147.2, 147.1, 146.9, 144.8, 137.3, 135.2, 131.5, 130.6, 127.1, 123.9, 123.6, 123.2, 121.3, 119.4, 117.3, 115.5, 114.9, 113.8, 112.9, 111.8 (aromatic C), 66.9, 64.4, 63.8, 63.1, 55.9, 49.8, 47.1, 45.5, 41.5, 36.9, 35.2, 33.9, 31.8, 26.3 (aliphatic C)
LCMS (m/z):	643 (M+H)$^+$
Anal. Calcd. for $C_{40}H_{38}N_2O_6$:	C, 74.75; H, 5.96; N, 4.36 %
Found:	C, 74.65; H, 5.89; N, 4.35 %

5,16-Dimethoxy-11,11,22,22-tetramethyl-1,6b,7,8,11,11a,12,17b,18,19,22,22a-dodecahydrochromeno[4,3-*b*]chromeno[3'',4'':5',6']pyrido[3',2':7,8]naphtho[2,3-*h*]quinoline-8,19-dione (106f)

Reaction of 5-methoxy *O*-prenylated salicylaldehyde (**104f**) in the presence of TPPP (20 mol %) with 1,5-diaminoanthraquinone in THF following the *general procedure B* provided the title compound as a red solid. The crude product was purified by silica gel column chromatography with 4 % ethyl acetate in hexanes.

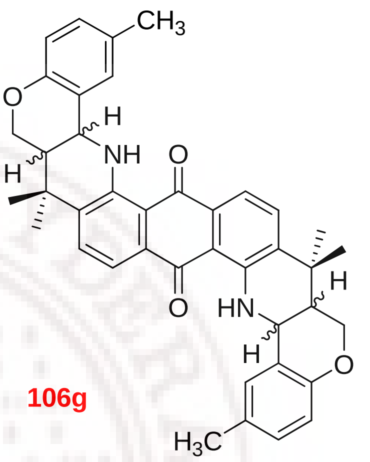

106f

Yield:	56 %
Mp:	105 °C
IR (KBr) ν_{max} cm^{-1}:	3248, 2966, 1620, 1589, 1257, 1043, 814
^{1}H NMR (400 MHz) δ:	10.26 (2H, s, N*H*); 7.45–7.68 (4H, m); 7.08–7.21 (2H, m); 6.89 (2H, d, *J* = 6.0 Hz); 6.81–6.83 (2H, m); 4.83 (2H, d, *J* = 7.0 Hz); 4.20–4.38 (4H, m); 3.84–4.0 (6H, m, ArC-OC*H*$_3$); 2.25 (2H, d, *J* = 6.9 Hz); 1.48–1.53 (12H, m)
^{13}C NMR (100 MHz) δ:	185.2, 184.8, 153.9, 152.9, 151.7, 150.4, 148.6, 147.6, 147.2, 145.9, 144.9, 142.2, 137.3, 136.7, 135.3, 134.8, 131.9, 130.5, 126.9, 122.9, 120.4, 117.6, 116.3, 114.9, 113.7, 110.5 (aromatic C), 66.6, 65.5, 63.9, 63.0, 55.9, 49.8, 47.4, 45.1, 41.8, 37.3, 35.6, 32.4, 27.1, 22.0 (aliphatic C)
LCMS (m/z):	643 (M+H)$^+$
Anal. Calcd. for $C_{40}H_{38}N_2O_6$:	C, 74.75; H, 5.96; N, 4.36 %
Found:	C, 75.70; H, 6.11; N, 4.45 %

5,11,11,16,22,22-Hexamethyl-1,6b,7,8,11,11a,12,17b,18,19,22,22a-dodecahydrochromeno[4,3-*b*]chromeno[3'',4'':5',6']pyrido[3',2':7,8]

naphtho[2,3-*c*]quinoline-8,19-dione (106g)

Reaction of **104g** in the presence of TPPP (20 mol %) with 1,5-diaminoanthraquinone in THF following the *general procedure B* provided the title compound as a red solid. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.



106g

Yield:	50 %
Mp:	96-97 °C
IR (KBr) ν_{max} cm^{-1}:	3224, 2922, 1734, 1620, 1500, 1259, 1030, 814
^{1}H NMR (400 MHz) δ:	10.24 (2H, s, N*H*); 7.65 (2H, d, *J* = 7.7 Hz); 7.52-7.57 (2H, m); 7.31 (2H, s); 6.90-7.05 (2H, m); 6.75-6.78 (2H, m); 4.65-4.80 (2H, m); 3.87 (4H, s); 3.50 (2H, m); 2.44 (6H, s, ArC-C*H*$_3$); 1.52 (12H, s)
^{13}C NMR (100 MHz) δ:	185.3, 185.0, 152.4, 151.4, 150.4, 150.2, 147.2, 146.0, 144.7, 142.6, 141.3, 137.4, 132.3, 131.3, 130.0, 129.5, 127.3, 125.7, 122.0, 116.7, 115.3, 113.7 (aromatic C), 66.5, 64.0, 51.1, 49.9, 47.3, 45.1, 38.3, 37.3, 35.4, 31.8, 27.1, 21.9, 20.9, 20.6 (aliphatic C)
LCMS (m/z):	611 (M+H)$^+$
Anal. Calcd. for $C_{40}H_{38}N_2O_4$:	C, 78.66; H, 6.27; N, 4.59 %
Found:	C, 78.54; H, 6.22; N, 4.55 %

Table 5. Crystal data and structure refinement for 98a

Empirical formula	: $C_{25}H_{19}NO_4$	
Formula weight	: 397.41	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 13.164(4) Å	α = 90°
	: b = 11.071(3) Å	β = 114.476(5)°
	: c = 14.675(4) Å	γ = 90°
Volume	: 1946.4(10) Å^3	
Z	: 4	
Density (calculated)	: 1.356 Mg/m^3	
Absorption coefficient	: 0.092 mm^{-1}	
F (000)	: 832	
Crystal size	: 0.30 x 0.14 x 0.05 mm^3	
Theta range for data collection	: 1.70 to 25.87°	
Index ranges	: -16<=h<=15, -13<=k<=12, -17<=l<=17	
Reflections collected	: 12274	
Independent reflections	: 3748 [R(int) = 0.0567]	
Completeness to theta = 26.04°	: 99.4 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9954 and 0.9728	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 3748 / 0 / 275	
Goodness-of-fit on F^2	: 1.027	
Final R indices [I>2sigma (I)]	: R1 = 0.0901, wR2 = 0.2562	
R indices (all data)	: R1 = 0.2022, wR2 = 0.3155	
Largest diff. peak and hole	: 0.516 and -0.299 e.Å^{-3}	
CCDC number	: 615199	

Table 6. Crystal data and structure refinement for 98e

Empirical formula	: $C_{26}H_{21}NO_5$	
Formula weight	: 427.44	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 7.8621(9) Å	α = 90°
	: b = 27.052(3) Å	β = 99.510(2)°
	: c = 9.8538(11) Å	γ = 90°
Volume	: 2067.0(4) $Å^3$	
Z	: 4	
Density (calculated)	: 1.374 Mg/m^3	
Absorption coefficient	: 0.096 mm^{-1}	
F (000)	: 896	
Crystal size	: 0.40 x 0.22 x 0.20 mm^3	
Theta range for data collection	: 1.51 to 25.98°	
Index ranges	: -8<=h<=9, -33<=k<=33, -12<=l<=12	
Reflections collected	: 13099	
Independent reflections	: 4051 [R(int) = 0.0254]	
Completeness to theta = 26.04°	: 99.6 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9811 and 0.9627	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 4051 / 0 / 290	
Goodness-of-fit on F^2	: 1.027	
Final R indices [I>2sigma (I)]	: R1 = 0.0466, wR2 = 0.1148	
R indices (all data)	: R1 = 0.0689, wR2 = 0.1271	
Largest diff. peak and hole	: 0.183 and -0.172 e.$Å^{-3}$	
CCDC number	: 615200	

Table 7. Crystal data and structure refinement for 100c

Empirical formula	: $C_{100}H_{79}Br_4N_4O_{16}$
Formula weight	: 1912.31
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/n
Unit cell dimensions	: a = 15.056(11) Å α = 90°
	: b = 31.951(2) Å β = 106.929(10)°
	: c = 18.368(13) Å γ = 90°
Volume	: 8452.6(11) $Å^3$
Z	: 4
Density (calculated)	: 1.503 Mg/m^3
Absorption coefficient	: 1.978 mm^{-1}
F (000)	: 3900
Crystal size	: 0.36 x 0.12 x 0.04 mm^3
Theta range for data collection	: 1.27 to 26.03°
Index ranges	: -18<=h<=18, -37<=k<=39, -19<=l<=22
Reflections collected	: 54208
Independent reflections	: 16614 [R(int) = 0.0708]
Completeness to theta = 26.04°	: 99.6 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9251 and 0.5362
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 16614 / 0 / 1121
Goodness-of-fit on F^2	: 0.947
Final R indices [I>2sigma (I)]	: R1 = 0.0622, wR2 = 0.1303
R indices (all data)	: R1 = 0.1813, wR2 = 0.1740
Largest diff. peak and hole	: 0.622 and -0.323 e.$Å^{-3}$
CCDC number	: 615198

Table 8. Crystal data and structure refinement for 100d

Empirical formula	$C_{26}H_{23}NO_4$	
Formula weight	413.45	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 15.508(4) Å	α = 90°
	b = 11.162(3) Å	β = 105.454(4)°
	c = 12.383(3) Å	γ = 90°
Volume	2066.1(8) $Å^3$	
Z	4	
Density (calculated)	1.329 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F (000)	872	
Crystal size	0.44 x 0.26 x 0.20 mm^3	
Theta range for data collection	1.36 to 26.06°	
Index ranges	-18<=h<=19, -13<=k<=11, -15<=l<=14	
Reflections collected	8900	
Independent reflections	3994 [R(int) = 0.0268]	
Completeness to theta = 26.04°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9823 and 0.9616	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3994 / 0 / 286	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma (I)]	R1 = 0.0472, wR2 = 0.1115	
R indices (all data)	R1 = 0.0772, wR2 = 0.1259	
Largest diff. peak and hole	0.189 and -0.176 e.$Å^{-3}$	
CCDC number	615201	

Table 9. Crystal data and structure refinement for 100e

Empirical formula	$C_{78}H_{69}N_3O_{15}$
Formula weight	1288.36
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 11.662(6) Å α = 86.591(8)° b = 12.589(6) Å β = 78.809(8)° c = 22.418(11) Å γ = 83.774(8)°
Volume	3207(3) $Å^3$
Z	2
Density (calculated)	1.334 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F (000)	1356
Crystal size	0.30 x 0.29 x 0.11 mm^3
Theta range for data collection	1.63 to 26.05°
Index ranges	-14<=h<=14, -15<=k<=15, -27<=l<=27
Reflections collected	33299
Independent reflections	12513 [R(int) = 0.0474]
Completeness to theta = 26.04°	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9899 and 0.9727
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12513 / 0 / 871
Goodness-of-fit on F^2	0.874
Final R indices [I>2sigma (I)]	R1 = 0.0598, wR2 = 0.1485
R indices (all data)	R1 = 0.2074, wR2 = 0.2201
Largest diff. peak and hole	0.218 and -0.202 e.$Å^{-3}$
CCDC number	619659

Table 10. Crystal data and structure refinement for 101

Empirical formula	: $C_{24}H_{25}NO_2$
Formula weight	: 359.45
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 14.5594(14) Å α = 90°
	: b = 8.4736(8) Å β = 104.635(2)°
	: c = 15.8853(16) Å γ = 90°
Volume	: 1896.2(3) $Å^3$
Z	: 4
Density (calculated)	: 1.259 Mg/m^3
Absorption coefficient	: 0.079 mm^{-1}
F (000)	: 768
Crystal size	: 0.36 x 0.13 x 0.08 mm^3
Theta range for data collection	: 1.45 to 26.04°.
Index ranges	: -17<=h<=17, -10<=k<=10, -19<=l<=19
Reflections collected	: 19107
Independent reflections	: 3729 [R (int) = 0.0450]
Completeness to theta = 26.04°	: 99.7 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.994 and 0.972
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3729 / 0 / 248
Goodness-of-fit on F^2	: 0.840
Final R indices [I>2sigma (I)]	: R1 = 0.0431, wR2 = 0.0985
R indices (all data)	: R1 = 0.0869, wR2 = 0.1130
Largest diff. peak and hole	: 0.166 and -0.130 e.$Å^{-3}$
CCDC number	: 611480

Table 11. Crystal data and structure refinement for 103

Empirical formula	: $C_{24}H_{26}N_2O_2$	
Formula weight	: 374.47	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Orthorhombic	
Space group	: Pca2(1)	
Unit cell dimensions	: a = 16.8420(15) Å	α = 90°
	: b = 11.2255(10) Å	β = 90°
	: c = 10.4503(9) Å	γ = 90°
Volume	: 1975.7(3) $Å^3$	
Z	: 4	
Density (calculated)	: 1.259 Mg/m^3	
Absorption coefficient	: 0.080 mm^{-1}	
F (000)	: 800	
Crystal size	: 0.40 x 0.20 x 0.18 mm^3	
Theta range for data collection	: 1.81 to 26.01°.	
Index ranges	: -20<=h<=20, -11<=k<=13, -12<=l<=12	
Reflections collected	: 10290	
Independent reflections	: 2057 [R (int) = 0.0390]	
Completeness to theta = 26.04°	: 100 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9857 and 0.9686	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2057 / 1 / 260	
Goodness-of-fit on F^2	: 1.176	
Final R indices [I>2sigma (I)]	: R1 = 0.0863, wR2 = 0.1862	
R indices (all data)	: R1 = 0.1123, wR2 = 0.2006	
Largest diff. peak and hole	: 0.235 and -0.130 e.$Å^{-3}$	
CCDC number	: 611481	

Table 12. Crystal data and structure refinement for 105a

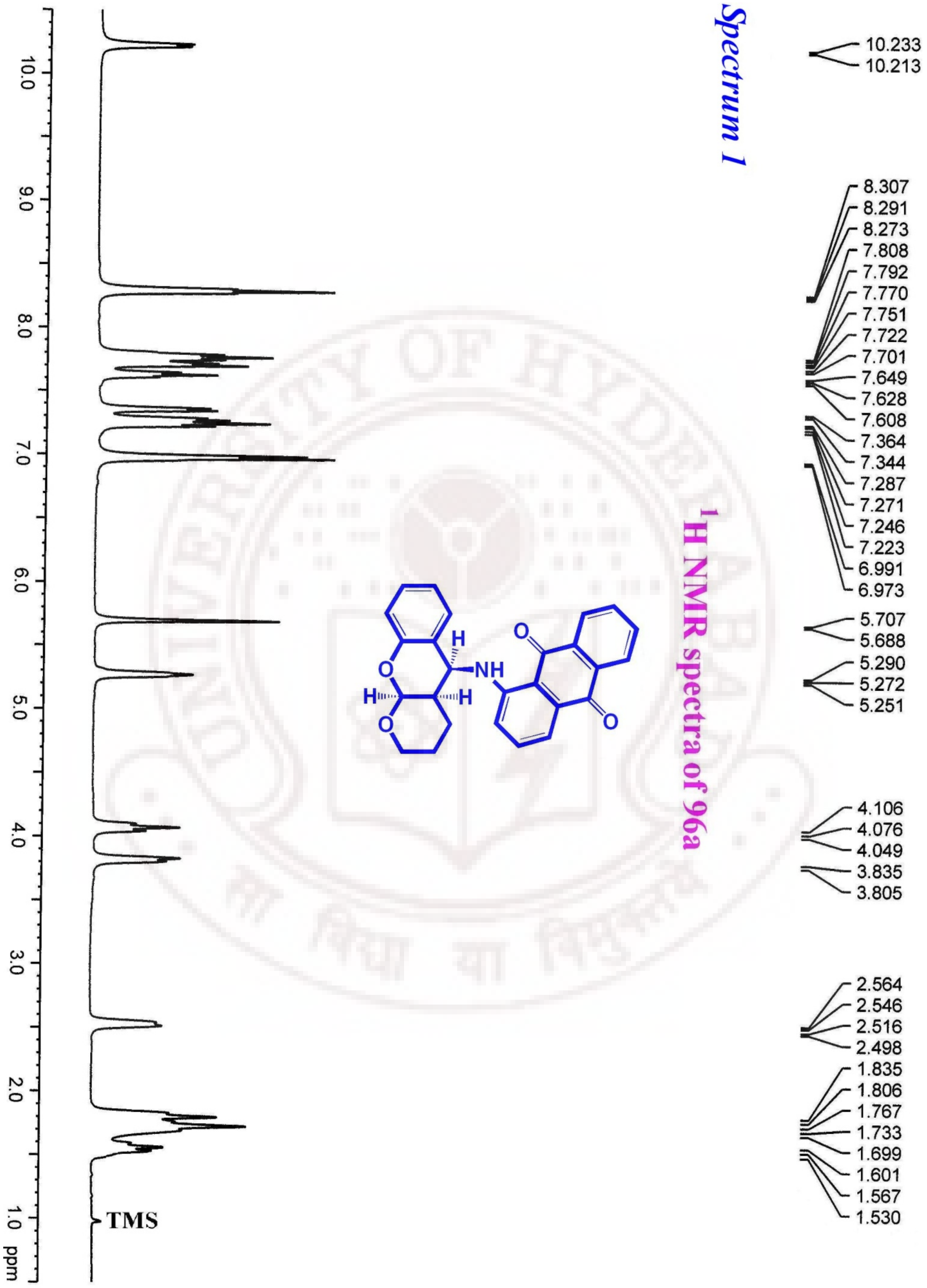
Empirical formula	: $C_{26}H_{21}NO_3$	
Formula weight	: 395.44	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Triclinic	
Space group	: P-1	
Unit cell dimensions	: a = 7.1683(8) Å	α = 92.427(2)°
	: b = 11.0149(12) Å	β = 104.027(2)°
	: c = 12.9380(14) Å	γ = 98.775(2)°
Volume	: 976.14(19) $Å^3$	
Z	: 2	
Density (calculated)	: 1.345 Mg/m^3	
Absorption coefficient	: 0.088 mm^{-1}	
F (000)	: 416	
Crystal size	: 0.42 x 0.34 x 0.03 mm^3	
Theta range for data collection	: 1.63 to 26.05°.	
Index ranges	: -8<=h<=8, -13<=k<=13, -15<=l<=15	
Reflections collected	: 10183	
Independent reflections	: 3822 [R(int) = 0.0257]	
Completeness to theta = 26.04°	: 99.4 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9974 and 0.9640	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 3822 / 0 / 281	
Goodness-of-fit on F^2	: 1.020	
Final R indices [I>2sigma (I)]	: R1 = 0.0498, wR2 = 0.1202	
R indices (all data)	: R1 = 0.0863, wR2 = 0.1391	
Largest diff. peak and hole	: 0.161 and -0.128 e.$Å^{-3}$	
CCDC number	: 611482	

Table 13. Crystal data and structure refinement for 105b

Empirical formula	: $C_{28}H_{25}Cl_2NO_4$
Formula weight	: 510.39
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/n
Unit cell dimensions	: a = 7.2367(11) Å α = 90°
	: b = 27.623(4) Å β = 102.816(3)°
	: c = 12.2850(18) Å γ = 90°
Volume	: 2394.6(6) $Å^3$
Z	: 4
Density (calculated)	: 1.416 Mg/m^3
Absorption coefficient	: 0.308 mm^{-1}
F (000)	: 1064
Crystal size	: 0.40 x 0.32 x 0.04 mm^3
Theta range for data collection	: 1.47 to 26.03°
Index ranges	: -8<=h<=5, -34<=k<=32, -15<=l<=15
Reflections collected	: 13072
Independent reflections	: 4703 [R(int) = 0.0423]
Completeness to theta = 26.04°	: 99.7 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9878 and 0.8867
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 4703 / 0 / 322
Goodness-of-fit on F^2	: 1.213
Final R indices [I>2sigma (I)]	: R1 = 0.1104, wR2 = 0.2136
R indices (all data)	: R1 = 0.1493, wR2 = 0.2315
Largest diff. peak and hole	: 0.531 and -0.419 e.$Å^{-3}$
CCDC number	: 611484

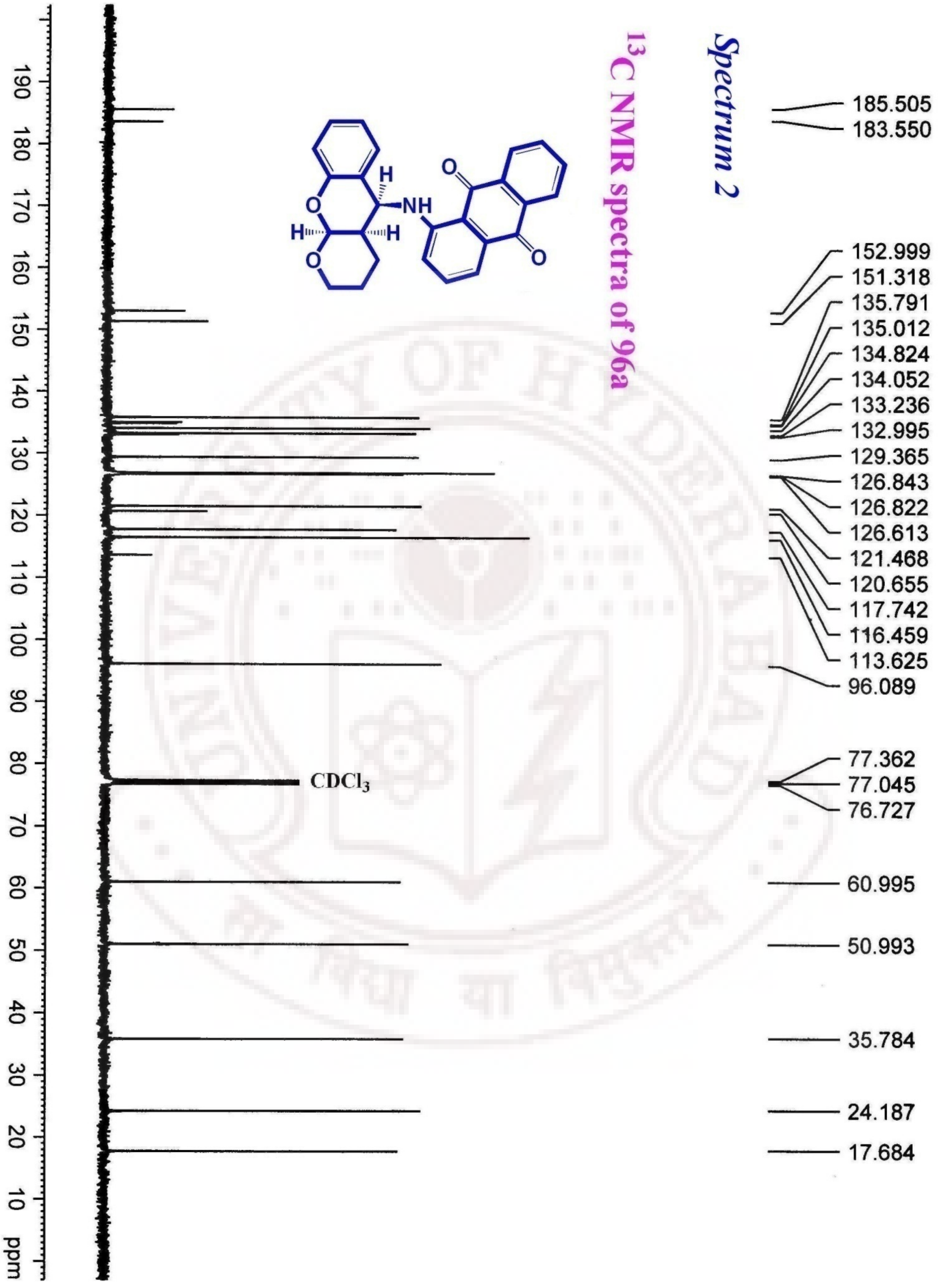
Table 14. Crystal data and structure refinement for 105e

Empirical formula	: $C_{26}H_{20}ClNO_3$	
Formula weight	: 429.88	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 13.2240(17) Å	α = 90°
	: b = 13.4610(17) Å	β = 115.528(2)°
	: c = 12.9530(17) Å	γ = 90°
Volume	: 2080.6(5) $Å^3$	
Z	: 4	
Density (calculated)	: 1.372 Mg/m^3	
Absorption coefficient	: 0.213 mm^{-1}	
F (000)	: 896	
Crystal size	: 0.26 x 0.12 x 0.10 mm^3	
Theta range for data collection	: 1.71 to 25.00°	
Index ranges	: -15<=h<=15, -16<=k<=16, -15<=l<=15	
Reflections collected	: 15351	
Independent reflections	: 3663 [R(int) = 0.0488]	
Completeness to theta = 26.04°	: 99.9 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9790 and 0.9468	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 3663 / 0 / 289	
Goodness-of-fit on F^2	: 1.092	
Final R indices [I>2sigma (I)]	: R1 = 0.0690, wR2 = 0.1365	
R indices (all data)	: R1 = 0.1127, wR2 = 0.1543	
Largest diff. peak and hole	: 0.233 and -0.229 e.$Å^{-3}$	
CCDC number	: 611483	



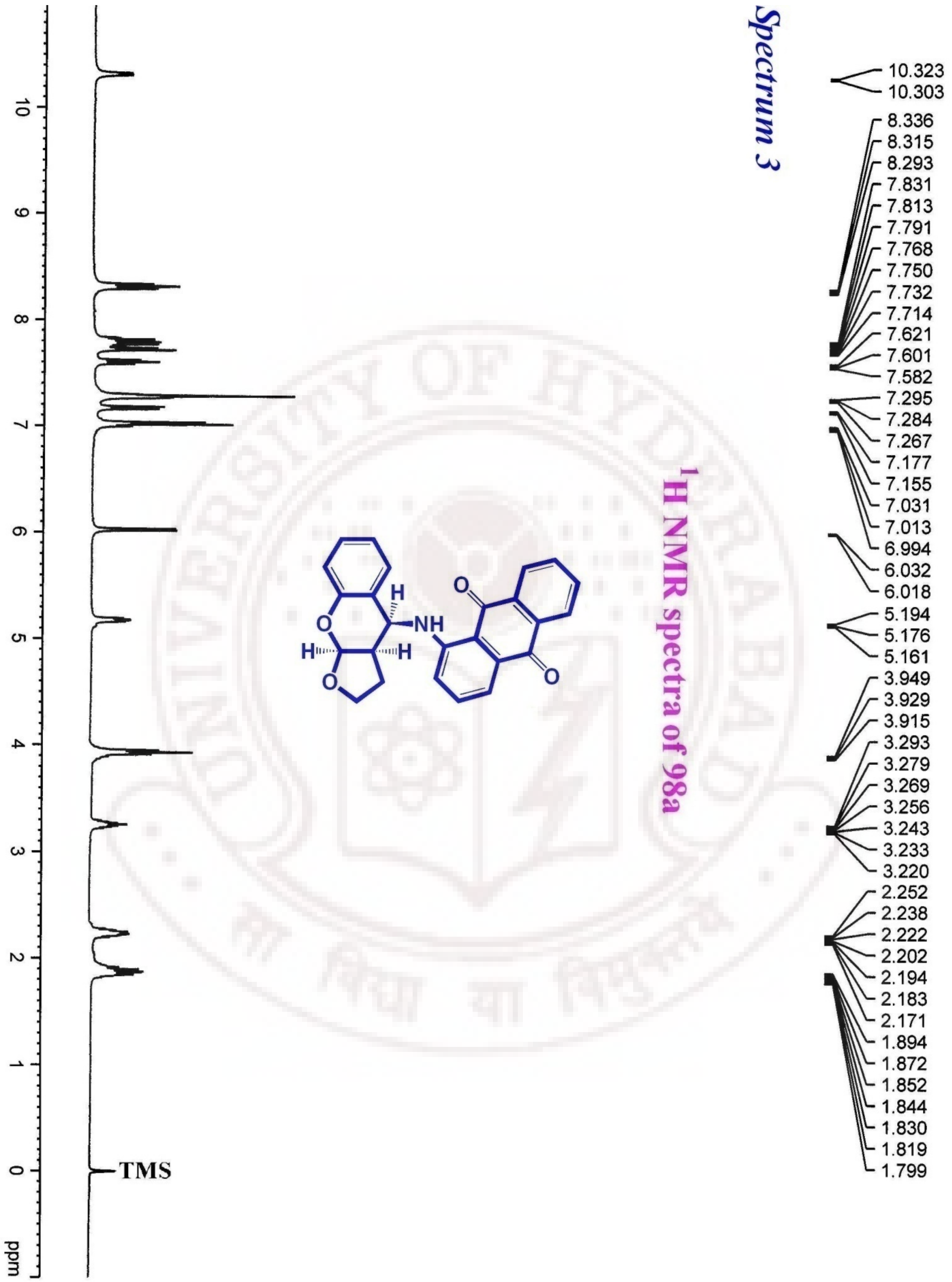
Spectrum 1

^{1}H NMR spectra of 96a

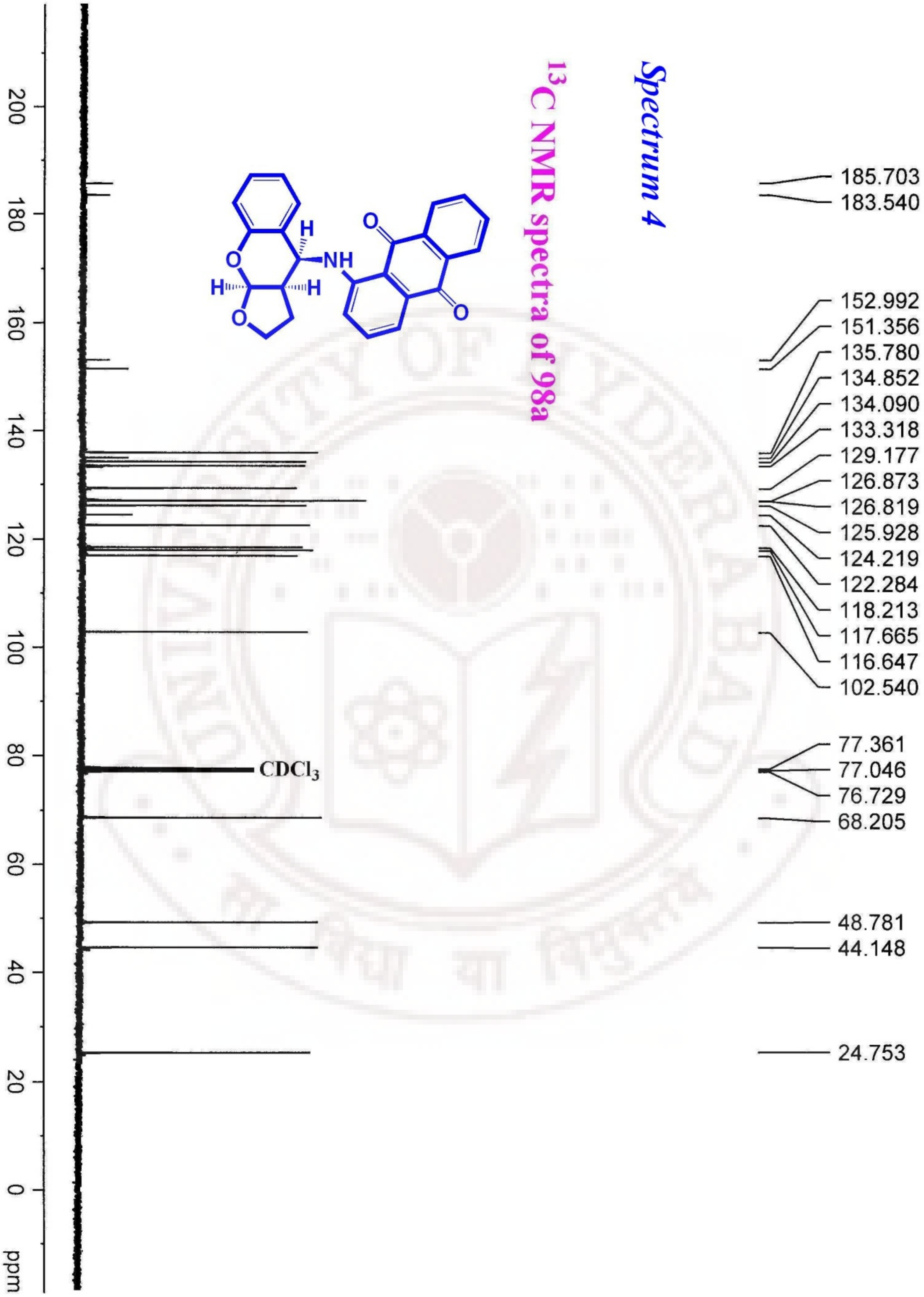


Spectrum 2

^{13}C NMR spectra of 96a

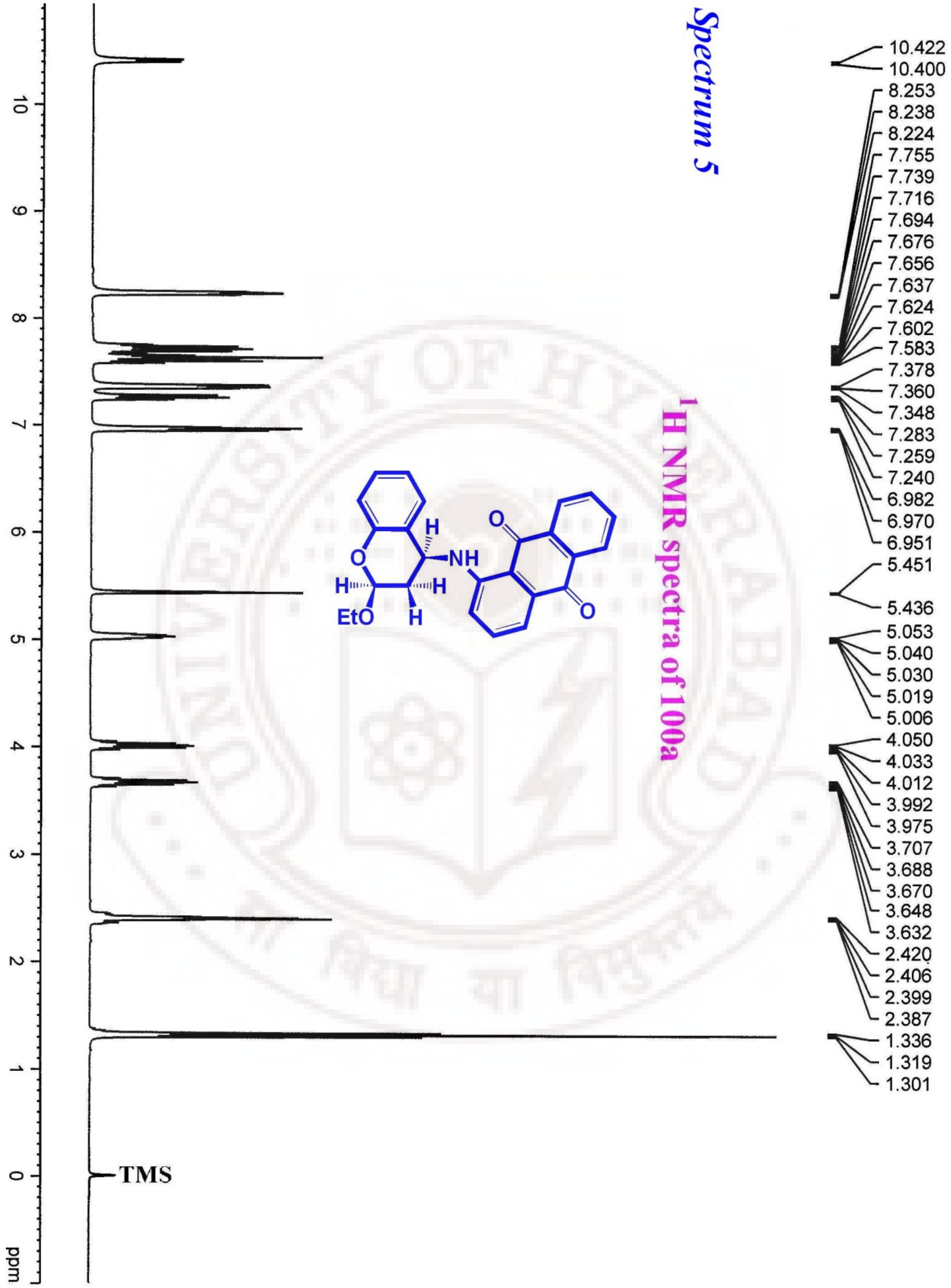

Spectrum 3

^{1}H NMR spectra of 98a



Spectrum 4

^{13}C NMR spectra of 98a

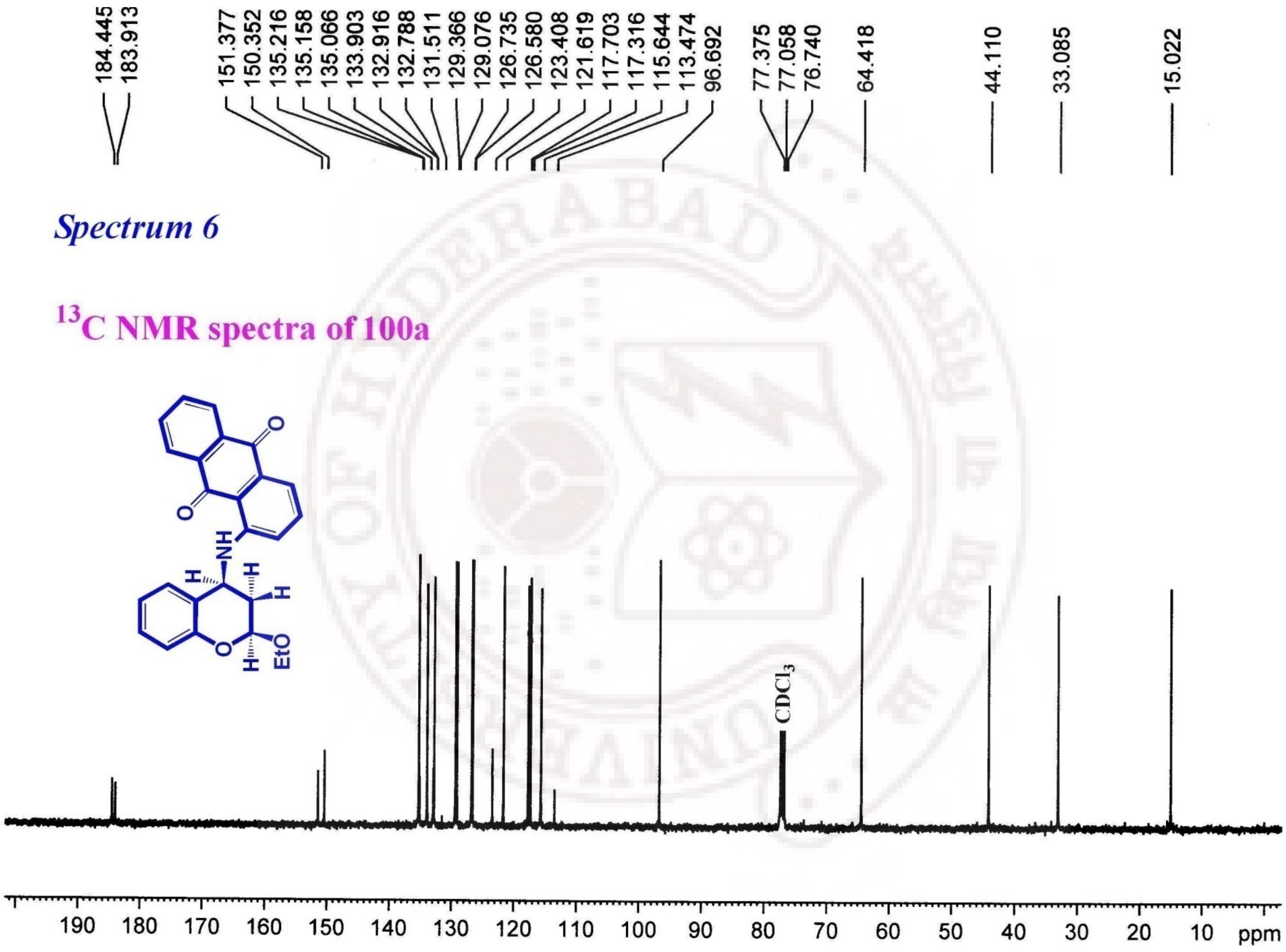


Spectrum 5

^{1}H NMR spectra of 100a

Spectrum 6

^{13}C NMR spectra of 100a



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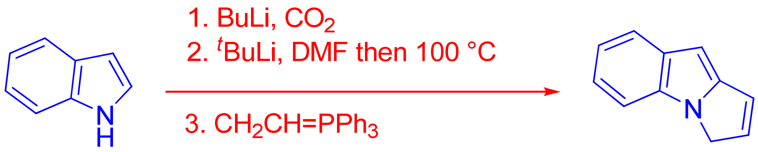
Synthesis of Polycyclic Indole Derivatives

CHAPTER 2

2.1. Introduction

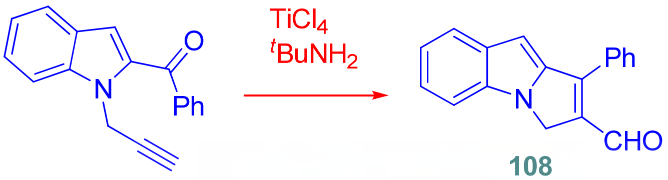
In the vast heterocyclic structural space, the indole nucleus occupies a position of major importance. Many indole derivatives, including the fused derivatives, form the basis of a range of pharmaceuticals and a high level of activity continues in the search for new indole-based medicinal agents. The study of the synthesis and activity of polycyclic indoles is a research field in continuous growth. The importance of these derivatives is related to the widespread occurrence of an indole subunit in a plethora of natural and synthetic compounds characterized by a variety of biological and pharmacological activities.[17-19] From a synthetic point of view, the opportunity to prepare complex polycyclic molecules by means of a small number of steps is an exciting goal for every modern organic chemist. Moreover, the demand to decrease the consumption of reagents, solvents, and energy together with the requirement to reduce reaction times and waste production prompt every researcher sensible to economical and environmental issues to explore the pathway of imino Diels-Alder reactions. Pyrroloindoles and pyrroloquinolines, an important family of alkaloids isolated from marine source, recently received considerable attention due to their biological activities.[100]

Katritzky and co-workers prepared this pyrroloindoles from indole *via* metalation procedure (**Eq. 29**).[101]



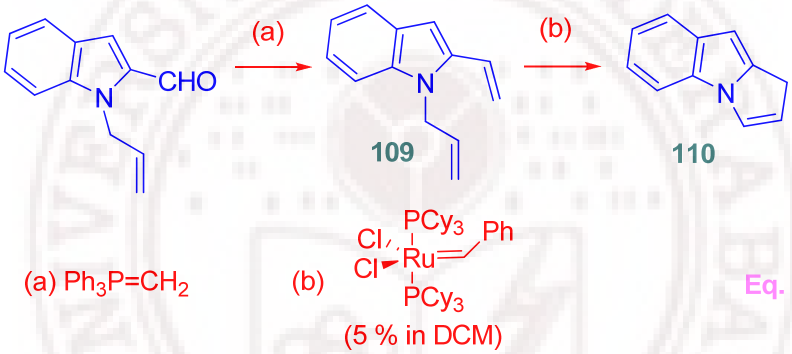
107 Eq. 29

Abbiati and co-workers[102] developed a general methodology for cyclization of *N*-propargyl-2-ketoindoles in the presence of $TiCl_4$ leading to the synthesis of pyrroloindole derivatives. Representative example was presented in **Eq. 30**.



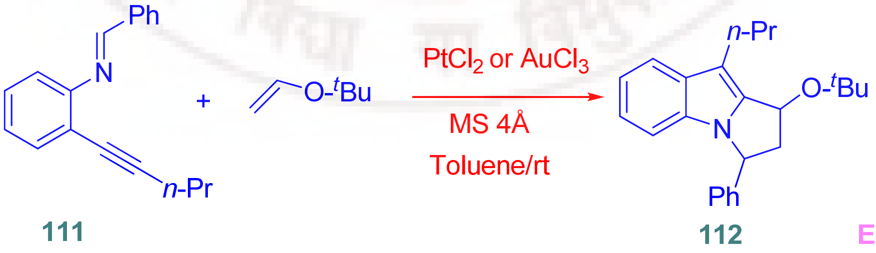
Eq. 30

Javier and co-workers[103] reported an RCM reaction of 1-allyl-2-vinylindoles leading to a synthesis of pyrroloindoles (**Eq. 31**).



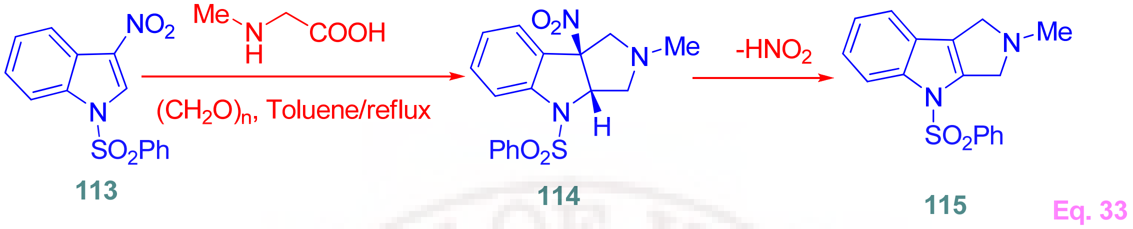
Eq. 31

Iwasawa and co-workers[104] reported [3+2] cycloaddition of transition metal containing azomethine ylides derived from *N*-(*o*-alkynylphenyl)imines (**111**) bearing an internal alkyne moiety. Only 1-3 mol % of $PtCl_2$ or $AuBr_3$ has been found sufficient to promote the reaction (**Eq. 32**).



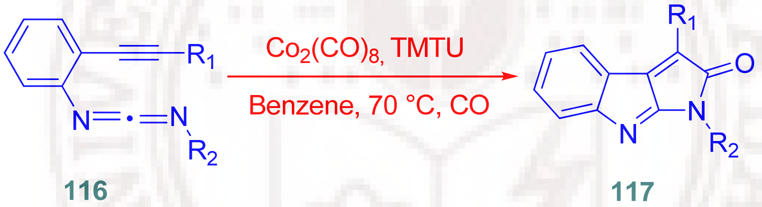
Eq. 32

Gribble and co-workers[105] developed a facile methodology for 1,3-dipolar cycloaddition reaction between 2- and 3-nitroindoles and unstabilized azomethine ylides. Treatment of 3-nitro-1-(phenylsulfonyl)indole (**113**) with the azomethine ylide generated *in situ* from sarcosine and paraformaldehyde in refluxing toluene affords the desired hexahydropyrroloindole cycloadduct **114** in 61 % yield (**Eq. 33**), followed by the loss of nitrous acid from the initial cycloadduct **114** to furnish **115** as the final product.



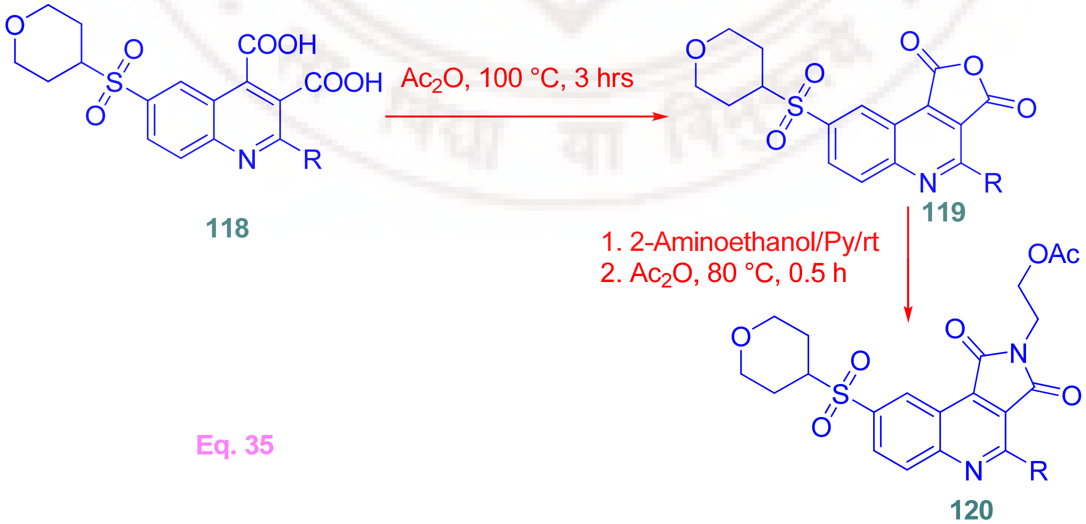
Eq. 33

Mukai and co-workers[106] described a novel $Co_2(CO)_8$ catalyzed intramolecular aza-Pauson-Khand-type reaction of alkynecarbodiimide derivatives affords pyrrolo[2,3-*b*]indol-2-one ring systems in reasonable yields as shown in **Eq. 34**.



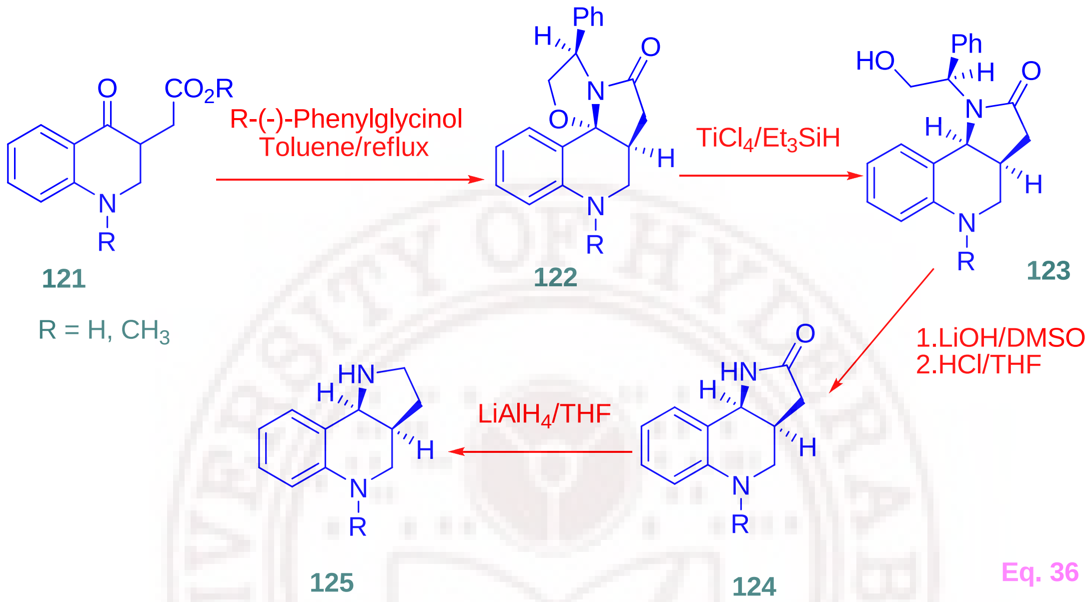
Eq. 34

Ivachtchenko and co-workers[107] reported a procedure for the synthesis of 4-substituted pyrrolo[3,4-*c*]quinoline-1,3-dione ring system was accomplished according to a sequence of reactions shown in **Eq. 35**.



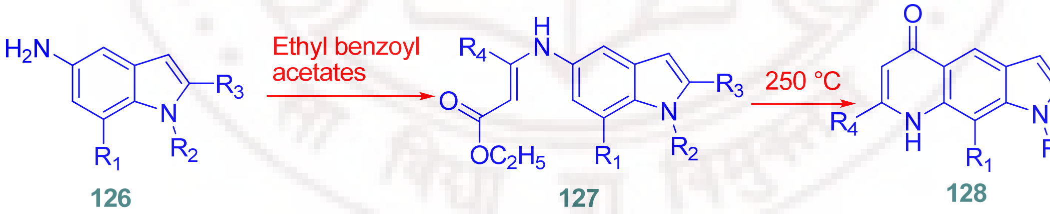
Eq. 35

Scientists at Merck reported[108] a synthesis of pyrroloquinoline derivatives from easily available starting materials (**Eq. 36**). These derivatives containing biologically important martinelline core unit.



Eq. 36

Ferlin and co-workers[109] described a synthesis of dihydro-3*H*-pyrrolo[3,2-*f*]quinolin-9-ones, which are a new class of antimitotic agents devoid of aromatase activity (**Eq. 37**).



Eq. 37

2.2. Synthesis of pyrroloindole fused aminoanthraquinone derivatives

Indole ring system has become an important structural component in many pharmaceutical agents.[17-19] Polycyclic indoles have been referred to as "privileged structures" since they are capable of binding to many receptors with high affinity.[110] For well over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists. The preparation of polyfunctional indoles is therefore an important research field, and numerous methods have been developed.[111-115] As the core structure of [*a*]-annealed indole is present in a number of biologically active indole derivatives such as mitomycin and vincamine, the development of methods for the construction of [*a*]-annealed indole nuclei have been the subject of a number of reports.[116]

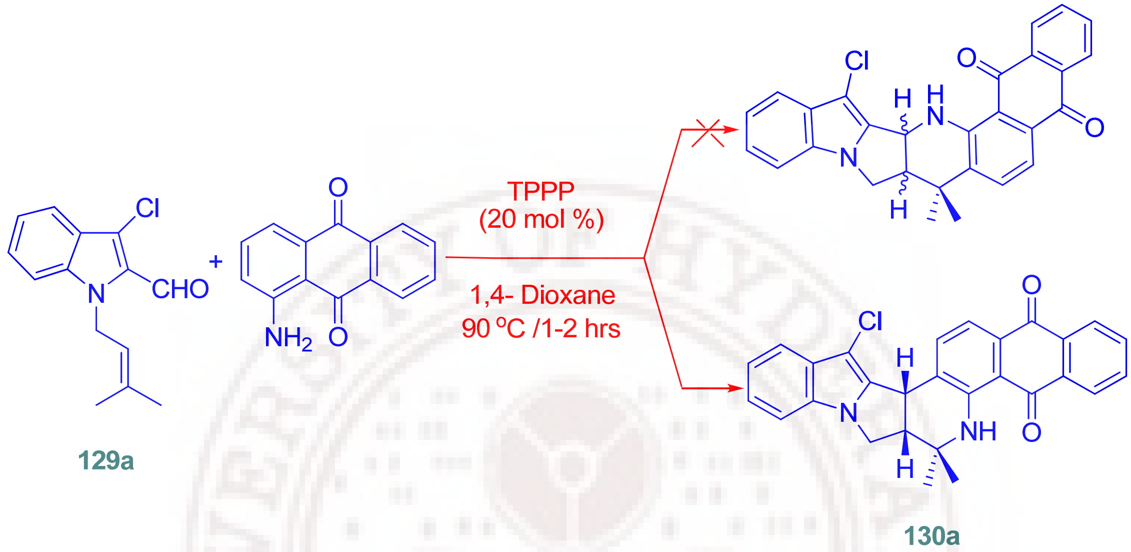
The pyrroloindole heterocyclic system is present in a growing class of alkaloid natural products, for example, physostigmine,[117] flustramines,[118] urochordamines,[119] mollenines,[120] himastatin,[121] and the numerous group of diketopiperazine derivatives.[122] Although a variety of methods have been developed to generate derivatives of this heterocycle and to modify its substitution pattern, new methods that stereoselectively provide indole derivatives are still of high interest in synthetic organic chemistry.[123] In recent years the problem of multidrug resistance (MDR) towards numerous antitumor compounds has also become important. The presence of five- or six-membered heterocyclic ring(s) fused with the anthraquinone or acridine moiety is essential for the ability to overcome multidrug resistance.[8] Construction of polycyclic indoles usually requires multistep approaches. The exploration of new methodologies that allow rapid establishment of these indole skeletons in a single operation remains an important challenge facing the organic chemists.

Our objective is to synthesize new polycyclic indole derivatives by the imino Diels-Alder reaction of 1-aminoanthraquinone with substituted *N*-prenylated indole-2-carboxaldehydes (**129a-f**) catalyzed by triphenylphosphonium perchlorate (TPPP) to provide highly functionalized products with excellent diastereoselectivity in a single step. The reactions were conducted in one-pot procedure at 90 °C and the reactions are normally completed within 1-2 hours. The heptacyclic ring system was obtained by this process. We have carried out our reactions with Lewis acid, BF_3-OEt_2 and triphenylphosphonium perchlorate and best results were obtained with triphenylphosphonium perchlorate (TPPP) as a catalyst.

The TPPP catalyzed reaction of 1-aminoanthraquinone and *N*-prenylated indole carboxaldehyde (**129a**) leads to the novel pyrrolizinoquinoline ring system

14-chloro-7,7-dimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo[5,6]pyrrolizino[2,1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (**130a**) in 80 % yield (**Scheme 15**).

Scheme 15



The IR spectrum of **130a** showed the *NH* stretching frequency at 3248 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 9.85. Proton NMR showed the aromatic proton signals in the range between δ 7.12-8.26. Two methyl peaks observed as singlets at δ 1.46 and 1.52. ^{13}C NMR showed the two keto peaks at δ 185.3, 183.2. Mass spectrum of the compound **130a** showed the molecular ion peak m/z at 451 in negative mode.

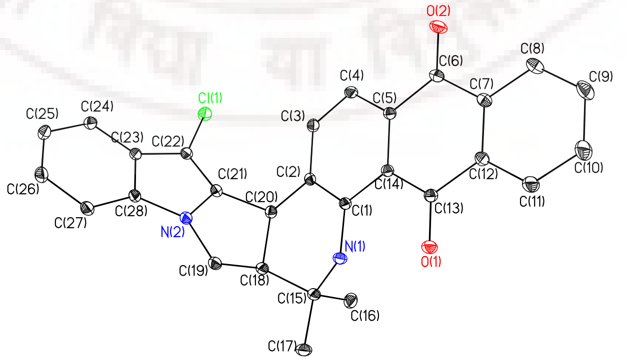


Figure 19. ORTEP diagram of compound **130a**

But single crystal X-ray structure of the product **130a** (**Fig. 19**) shows a different structure than the expected Diels-Alder product. The structure of the product is same as expected, except with respect to the position of the methyl groups. Formation of this type of products is unusual in the Diels-Alder reaction and especially the intramolecular cycloaddition which is highly regioselective. The stereochemistry of the product **130a** was assigned based on the coupling constants and NOE studies. Both six-membered tetrahydropyridine and five membered pyrrolidine rings are *cis* fused, as depicted by the coupling constant $J_{1\text{-}2}$ = 7.2 Hz between H_1 (δ 4.75) and H_2 (δ 3.24) for **130a**. The compound **130a** was also characterized by NOE experiment by irradiating the hydrogen attached to nitrogen with two methyl groups and found 30 % of NOE, which confirms adjacent proximity of the two methyl groups with amino hydrogen (**Fig. 20**). This clearly shows that the compound **130a** is the unexpected reaction product. ^{1}H NMR (spectrum 7) and ^{13}C NMR (spectrum 8) of **130a** were presented.

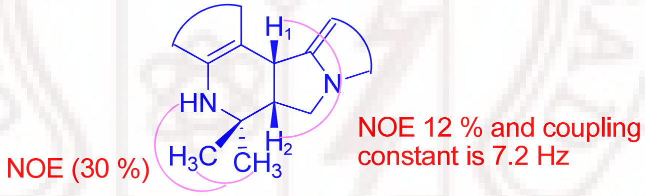
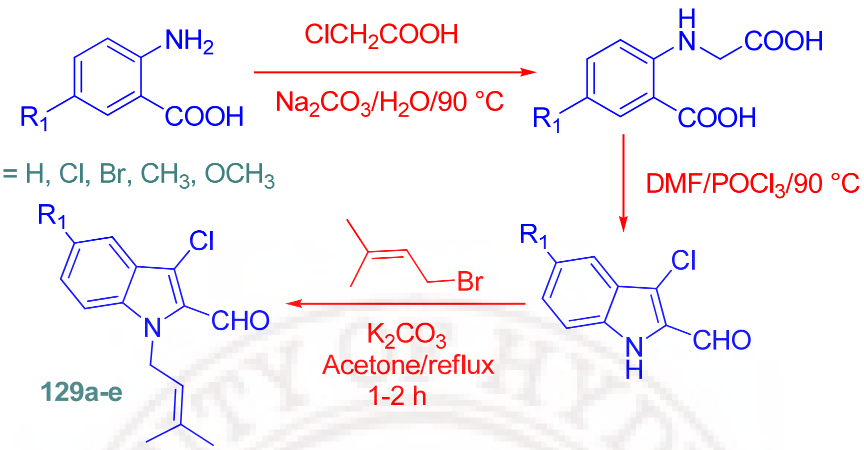


Figure 20. NOE of compound **130a**

Prepared the different substituted *N*-prenylated indole-2-carboxaldehydes (**129a-e**) from anthranilic acid (**Scheme 16**). The substituted 2-[(carboxymethylamino]benzoic acids[124] were prepared by the treatment of corresponding substituted anthranilic acids with chloroacetic acid in alkaline medium. Cyclization of these diacids under Vilsmeier-Haack reaction led to the 2-formyl-3-chloroindoles.[125] *N*-prenylation of these indoles were prepared according to the reported procedure.[126] **129f** was prepared from formylation[127] of 3-methylindole with DMF/$POCl_3$ and followed by *N*-prenylation with prenyl bromide with K_2CO_3 in acetone.

Scheme 16



In **Scheme 17** under the similar conditions, several 2-formyl indoles (**129b-f**) were treated with the aminoanthraquinone to illustrate the novelty of the present strategy and the results are summarized in **Table 15**.

Scheme 17

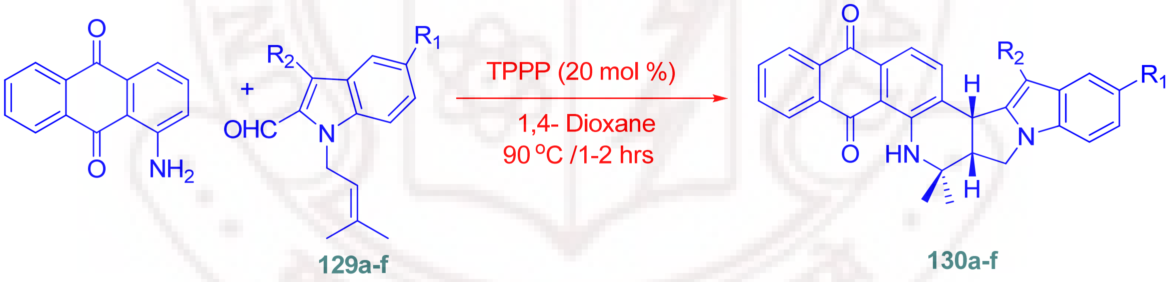


Table 15. TPPP catalyzed synthesis of polycyclic indole derivatives

Entry	R_1	R_2	Reactant	Product	Time (min.)	Yield (%)
1	H	Cl	**129a**	**130a**	70	80
2	Cl	Cl	**129b**	**130b**	90	75
3	Br	Cl	**129c**	**130c**	82	78
4	CH_3	Cl	**129d**	**130d**	100	70
5	OCH_3	Cl	**129e**	**130e**	120	66
6	H	CH_3	**129f**	**130f**	60	85

In all the cases the reactions are highly stereoselective, leading to the exclusive formation of *cis* isomers. The single crystal X-ray analysis of the compounds **130b** and **130c** were also achieved in order to confirm their molecular structure (**Fig. 21** and **22**).

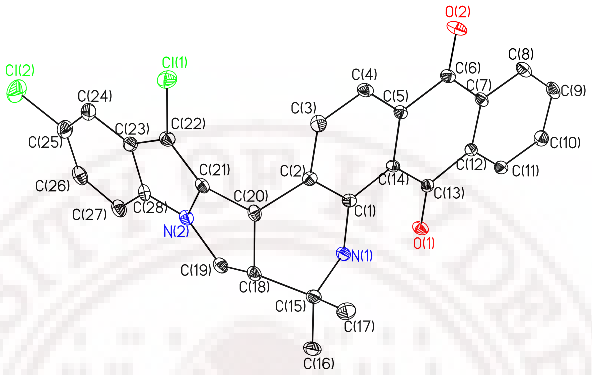


Figure 21. ORTEP diagram of compound **130b**

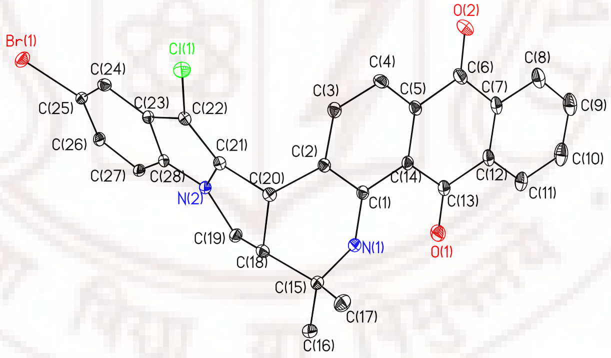
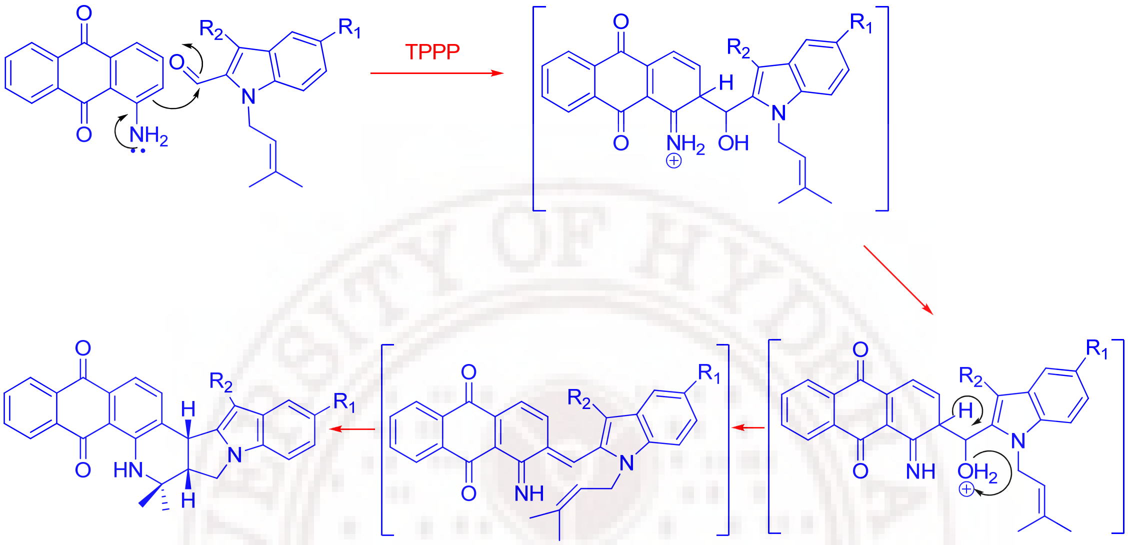


Figure 22. ORTEP diagram of compound **130c**

The two methyl groups are observed at different chemical shift values around δ 1.52 (3H, s) and δ 1.45 (3H, s), because 6-memberd ring exists in chair form and thereby axial and equatorial methyl groups were observed at different chemical shift values. N-H peak was observed at δ 9.83-9.84 as a sharp singlet. With all substitutions, reaction proceeded to afford moderate to good yields (66-85

%). In the case of **130f**, reaction finished within 1 hour with good yield (85 %) where as **130e** has given only 66 % yield after 2 h reflux.

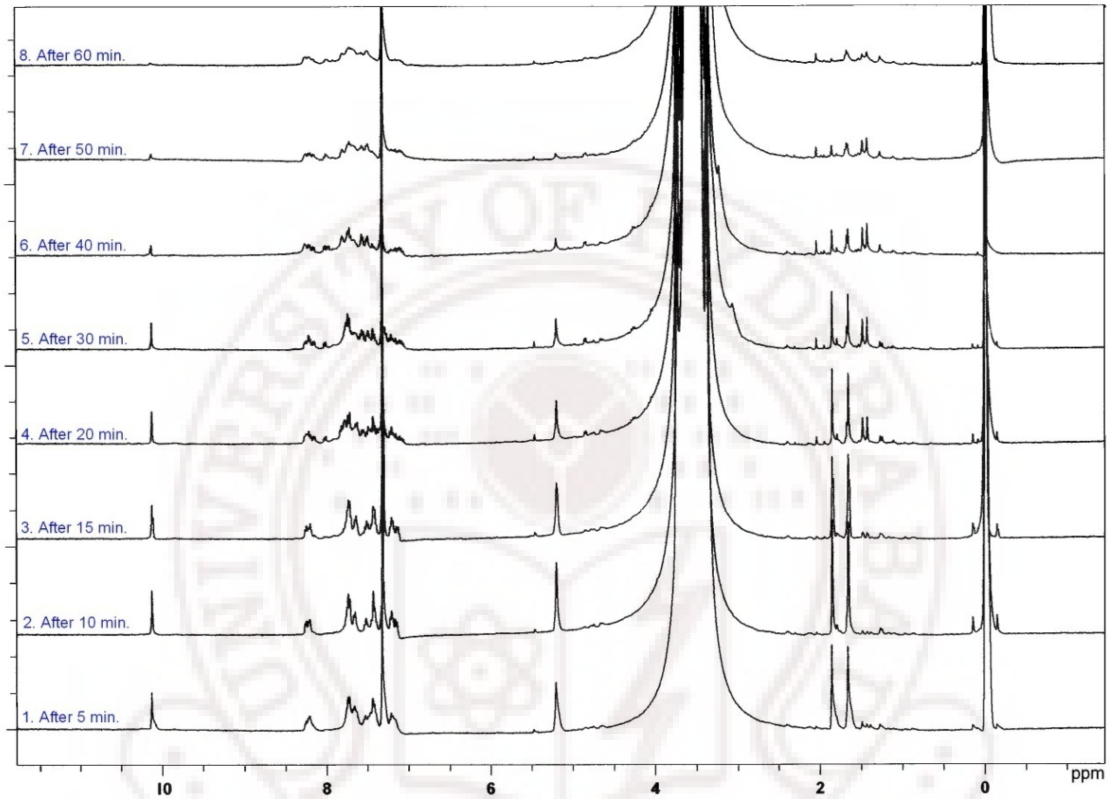
Scheme 18. Expected mechanism of the product



Expected mechanism of the reaction was shown in **Scheme 18**. Initial Schiff base formation is not observed and rather it undergoes nucleophilic addition from amino group of aminoanthraquinone with the 2-formyl indole derivative and followed by dehydration, generating imino diene. The imino diene further undergoes non-concerted cycloaddition which leads to imino Diels-Alder adduct. The enol form of aminoanthraquinone makes the adjacent benzene ring more electron-deficient and this electron deficiency drives the electron-rich amino group to donate its electron density to the aromatic system.

NMR experiments also supported the proposed mechanism (**Fig. 23**). The reaction of 1-aminoanthraquinone, *N*-prenylated indole-2-carboxyaldehyde and TPPP in dry 1,4-dioxane was heated to 90 °C. From this reaction, 0.5 mL of crude reaction mixture has taken into the NMR tube. To this a drop of TMS was added and ^{1}H NMR spectra was recorded. This procedure was repeated at every 5/10 minutes and recorded for ^{1}H NMR spectra. During the investigation, we clearly observed steady decrease of aldehyde signal as well as gem methyl and alkene proton signals. We also found the decrease in the intensity of the peaks at δ 7.2 ppm which may be corresponds to the olefinic proton formed by the dehydration of aldol product.

Figure 23.NMR study of the mechanism



One of the most important reactions for the anthracyclinone synthesis using anthraquinone as starting materials is the reaction of aldehyde with anthraquinones called Marschalk reaction.[128] This reaction is used for the introduction of various side chains on the anthraquinone skeleton. In our case, initial step is an unexpected variation of the Marschalk reaction and once the tethered azadiene system is assembled then the imino-Diels-Alder reaction was observed.

In conclusion, we have described a novel, highly efficient and highly diastereoselective method for the synthesis of polycyclic indole derivatives through intramolecular imino Diels-Alder reaction. The method is simple and straightforward starting from easily accessible starting materials.

2.3. Synthesis of pyrroloindole fused quinoline derivatives

Pyrroloquinoline systems have been found in nature and their syntheses have been reviewed.[129] The presence of pyrroloquinoline nucleus of the martinelline has attracted attention due to their antibacterial activity as well as affinity for adrenergic, muscarinic, and bradykinin receptors.[130] Pyrroloquinoline quinone (PQQ) is an important redox-active co-factor used by a number of bacterial dehydrogenases.[131]

Interest in the pyrrolo[1,2-*a*]indole skeleton is connected with its structural relationship with mitomycins,[132] an important class of antibiotics characterized by noteworthy antitumor activity.[133] In particular, mitomycin C is used in clinical cancer chemotherapy. Subsequent to the discovery and total synthesis of mitomycin C, a number of compounds have been synthesized by molecular modifications at the pyrrolo[1,2-*a*]indole without significant loss of biological activity.[134] Therefore, considerable efforts have been directed towards the synthesis of functionalized pyrrolo[1,2-*a*]indole derivatives as mitomycin analogues and as a result, numerous heterocycle-annulated pyrrolo[1,2-*a*]indole derivatives have been reported.[135]

We are interested in annulation at the 1,2-position of the indole ring in light of the fact that pyrroloindole units are present in mitosenes and mitomycins. These compounds show antibiotic and antitumor activity and inhibit bacterial cell division through a mechanism involving DNA alkylation.[136] Herein, we report the synthesis of biologically important pyrroloquinoline and pyrroloindole in a single step reaction (**Fig. 24**).

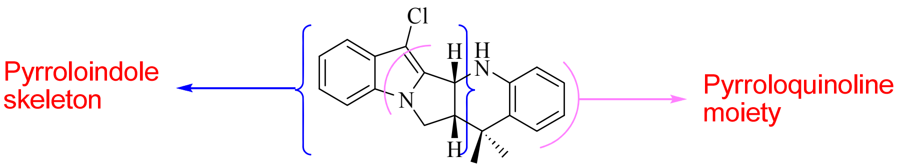
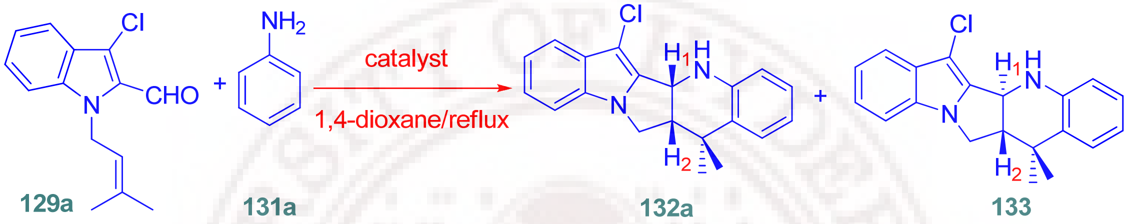


Figure 24

The imine derived from *N*-prenylated-2-formyl-3-chloroindole (**129a**) with aniline in 1,4-dioxane at reflux temperature underwent intramolecular [4+2] cycloaddition in the presence of a Lewis acid to yield the indolopyrroloquinolines *cis* and *trans*-6-chloro-13,13-dimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6]pyrrolizino[1,2-*b*]quinoline (**132a** and **133**) as a mixture of diastereomers where the *cis* isomer was the major product (**Scheme 19**).

Scheme 19



The diastereomers were readily separated by column chromatography on silica gel, and their stereochemistry was assigned based on ^{1}H NMR and NOE studies. The five-membered pyrrolidine and six-membered tetrahydro pyridine rings were *cis* fused, as indicated by the coupling constant $J_{1\text{-}2}$ = 7.2 Hz between H_1 (δ 5.08) and H_2 (δ 3.21) in product **132a** and also the strong NOE (8.0 %) enhancement of H_2 upon irradiation of H_1. Structure of the product (**132a**) was confirmed by IR, ^{1}H NMR (spectrum 9), ^{13}C NMR (spectrum 10), LCMS, and elemental analysis.

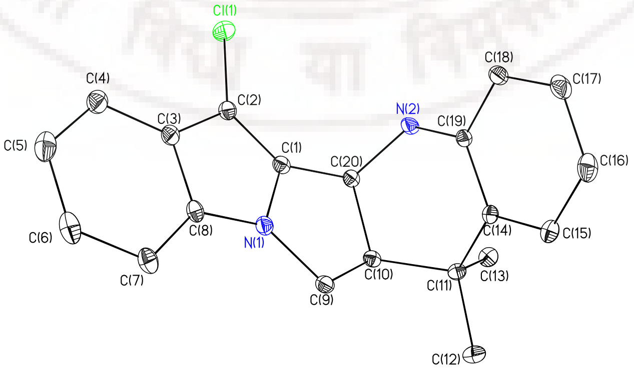


Figure 25. ORTEP diagram of compound **132a**

The stereochemistry of the *cis*-isomer was also confirmed by single crystal X-ray diffraction of **132a** (**Fig. 25**). The high coupling constant, $J_{1\text{-}2}$ = 10.4 Hz between H_1 (δ 4.77) and H_2 (δ 3.02) supported the *trans* configuration the structure of product **133** and there was no considerable NOE between these two protons.

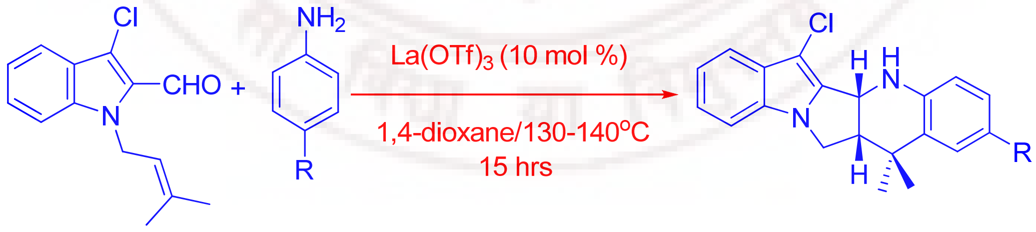
Table 16. Screening of catalysts

Entry	Catalyst	Time (h)	dr ratio	Yield (%)[a]
1	$PPh_3.HClO_4$ (20 mol %)	18	80:20	65
2	$PPh_3.CF_3SO_3H$ (20 mol %)	18	82:18	68
3	$InCl_3$ (20 mol %)	20	85:15	70
4	$BiCl_3$ (20 mol %)	20	75:25	60
5	$LiClO_4$ (20 mol %)	24	70:30	57
6	CF_3-COOH (20 mol %)	24	74:26	60
7	BF_3-OEt_2 (20 mol %)	24	71:29	50
8	Salen (Mn)H_2 (20 mol %)	48	85:15	40
9	*N*-Boc L-proline (20 mol %)	96	90:10	30
10	Dowex 20-50 mesh (0.1 g)	48	70:30	30
11	Montmorillonite K10 (0.1 g)	48	75:25	33
12	Amberlite IR 120 (0.1 g)	48	75:25	20
13	Iodine (20 mol %)[b]	48	70:30	40
14	$AlCl_3$(20 mol %)[b]	48	74:26	50
15	[Bmim][BF_4][c]	24	75:25	50
16	[Bmim][PF_6][c]	24	80:10	60
17	$In(OTf)_3$ (10 mol %)	20	90:10	70
18	$Sc(OTf)_3$ (10 mol %)	16	95:05	75
19	$Yb(OTf)_3$ (10 mol %)	16	94:04	76
20	$La(OTf)_3$ (10 mol %)	16	96:04	76
21	**$La(OTf)_3$ (10 mol %)[d]**	**15**	**100:00**	**80**

[a] Reactions were carried out at 100 °C and the yields are based on isolated yield. [b] Temperature was 50 °C and above this temperature side products were obtained. [c] 0.5 g of ionic liquid was used as solvent as well as catalyst. [d] Temperature of the reaction was 130-140 °C

The diastereoselectivity is varied with respect to the nature of the catalyst (**Table 16**). However, in all the cases, the *cis* diastereomer (**132a**) was the major product. Amberlite, Montmorillonite, Dowex, Salen, Proline catalysts have given less yields (20-40 %), but proline catalyst yielded good diastereoselectivity (90:10) with longer reaction time (Entry 9). Molecular iodine also has given 40 % yield with 70:30 diastereoselectivity after 48 hours (Entry 13). Ionic liquid catalysts ([Bmim][BF_4] and [Bmim][PF_6]) have produced moderate yields (60-70 %) after 24 hours at 100 °C (Entry 15 and 16). With TFA, 60 % yield was obtained with 74:26 diastereoselectivity after 24 hours (Entry 6). Several catalysts were screened. Among them, $Sc(OTf)_3$, $Yb(OTf)_3$ and $La(OTf)_3$ were found to be better since they provided excellent diastereoselectivity and also have similar reactivities in terms of reaction yield, diastereomer ratio and reaction time (Entries 18-20). The diastereoselectivity was further improved by maintaining the reaction temperature at 130-140°C and only the *cis* diastereomer was obtained with $La(OTf)_3$ (10 mol %). $La(OTf)_3$ has been used to catalyze a variety of reactions.[137] It is stable under aqueous conditions, and catalyzes aldol and allylation reactions in aqueous media.[138] An increase in temperature did not improve the diastereomer ratio with the other catalysts listed in **Table 16**, except for $Sc(OTf)_3$ and $Yb(OTf)_3$. The reaction was faster in 1,4-dioxane than CH_3CN and THF. Moderate yield were obtained with DMSO or toluene as solvent.

Scheme 20



129a **131a-e** **132a-e**

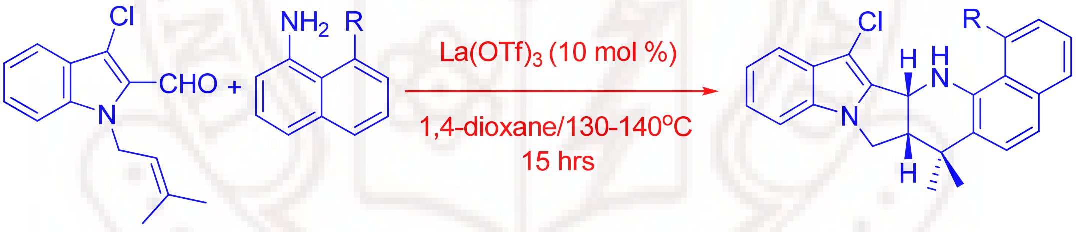
Encouraged by these results, we have focused our attention to understand the generality of this strategy. The preparation of indolopyrroloquinoline derivatives with other *p*-substituted anilines (**131a-e**) under the optimized conditions were studied (**Scheme 20**).

Table 17. Synthesis of new indolopyrroloquinoline derivatives

Entry	R	Reactant	Product	Yield (%)
1	H	**131a**	**132a**	80
2	Cl	**131b**	**132b**	92
3	Br	**131c**	**132c**	88
4	CH_3	**131d**	**132d**	65
5	OCH_3	**131e**	**132e**	52

Results are summarized in **Table 17**. In all cases, the one-pot cycloaddition reaction proceeded smoothly and yielded the corresponding products (**132a-e**) as a single diastereomer having the *cis*-configuration. When the electron donating groups were present on aniline, yields are less (52-65 %), where as electron withdrawing groups were present on aniline, yields are high (88-92 %).

Scheme 21



129a 134a-b 135a-b

Extending the methodology further, we examined the reactivity of napthylamine (**134a**) with **129a** in 1,4-dioxane at 130-140 °C. The reaction was clean, highly diastereoselective and afforded the corresponding *cis*-fused indolopyrroloquinoline 14-chloro-7,7-dimethyl-7a,8,14b,15-tetrahydro-7*H*-benzo [*h*]benzo[5,6]pyrrolizino[1,2-*b*] quinoline (**135a**) in 85 % yield (**Scheme 21**).

The structure of the product was established by IR, ^{1}H NMR (spectrum 11), ^{13}C NMR (spectrum 12), LCMS, and elemental analysis. We have also obtained single crystals for the compound (**135a**) and further confirmed the structure by single crystal X-ray data (see **Fig. 26** for ORTEP diagram). In the case of (R = OH, **134b**) product **135b** also obtained in good yield (80 %).

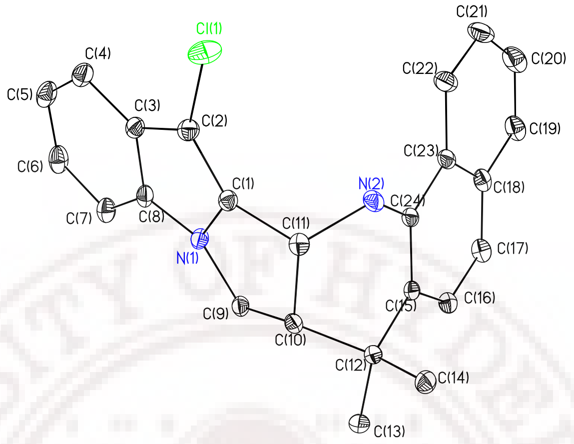


Figure 26. ORTEP diagram of compound **135a**

In summary, we have successfully synthesized indolopyrroloquinolines *via* intramolecular imino Diels-Alder [4+2] cycloaddition. This method provides synthetically useful indole annulated pyrroloquinolines in good yields.

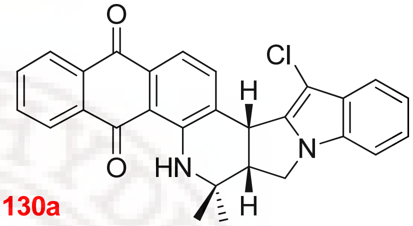
2.4. Experimental Section

General procedure C

To a stirred solution of 1-aminoanthraquinone (1.0 mmol) and 2-formyl indole derivatives (**129a-f**) (1.2 mmol) in dry 1,4-dioxane, TPPP (20 mol %) was added and the reaction mixture was heated to 90 °C for appropriate time. The reaction was monitored by TLC. After completion of the reaction, as indicated by the TLC, the excess solvent was distilled off and the crude reaction mixture was poured over water and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over anhy. Na_2SO_4 and the solvent was removed. The residue was chromatographed over neutral silica gel (prepared by eluting hexane+NEt_3 solution up to pH 7.0, 100-200 mesh size) and eluted with hexane-ethyl acetate mixture to afford the products (**130a-f**) as pink colored solids.

Cis-14-chloro-7,7-dimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo[5,6]pyrrolizino[2,1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (130a)

The compound (**130a**) was prepared by the reaction of 1-aminoanthraquinone and 3-chloro-1-(3-methylbut-2-ene)-1*H*-indole-2-carboxaldehyde (**129a**) in the presence of TPPP (20 mol %) in 1,4-dioxane following the *general procedure C.* The crude product was purified by neutral silica gel column chromatography with 4 % ethyl acetate in hexanes.



130a

Yield: 80 %

Mp: 238 °C

IR (KBr) ν_{max} cm^{-1}: 3248, 3052, 2962, 2987, 1666, 1624, 1574, 1259, 1228, 1021, 987

^{1}H NMR (400 MHz) δ: 9.85 (1H, s, N<u>*H*</u>), 8.26 (1H, d, *J* = 7.6 Hz), 8.20 (1H, d, *J* = 7.6 Hz), 8.03 (1H, d, *J* = 7.7 Hz), 7.69-7.76 (2H, m), 7.55-7.59 (2H, m), 7.12-7.16 (3H, m), 4.75 (1H, d, *J* = 7.2 Hz), 4.05-4.24 (2H, m, N-C$\underline{H_2}$), 3.24 (1H, q, *J* = 8.5 Hz), 1.52 (3H, s), 1.46 (3H, s)

^{13}C NMR (100 MHz) δ: 185.3, 183.2, 147.3, 140.9, 136.6, 134.8, 133.9, 133.2, 133.1, 133.0, 131.5, 129.0, 128.3, 126.7, 126.6, 126.5, 122.3, 119.9, 118.4, 116.5, 113.3, 109.6, 96.9 (aromatic C), 51.9, 49.7, 45.4, 36.9, 29.0, 27.5 (aliphatic C)

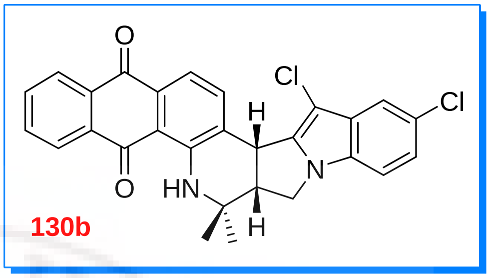
LCMS (m/z): 451 $(M-H)^+$

Anal. Calcd. for $C_{28}H_{21}ClN_2O_2$: C, 74.25; H, 4.67; N, 6.18 %

Found: C, 74.30; H, 4.72; N, 6.41 %

Cis-12,14-dichloro-7,7-dimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo[5,6]pyrrolizino[2,1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (130b)

The compound was obtained by the reaction of 1-aminoanthraquinone with **129b** in 1,4-dioxane following the *general procedure C.* Pure product was obtained through neutral silica gel column chromatography with 4 % ethyl acetate in hexane.

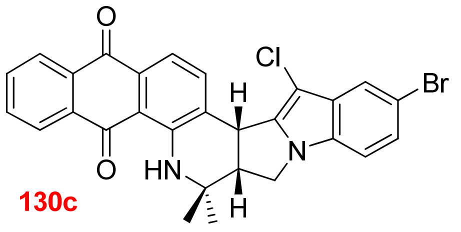


130b

Yield:	75 %
Mp:	208 °C
IR (KBr) ν_{max} cm^{-1}:	3250, 3056, 2964, 1664, 1630, 1575, 1261, 1230, 1099, 796
^{1}H NMR (400 MHz) δ:	9.83 (1H, s, N*H*); 8.26 (1H, d, *J* = 7.6 Hz), 8.21 (1H, d, *J* = 7.6 Hz), 8.01 (1H, d, *J* = 7.6 Hz), 7.70-7.77 (2H, m), 7.60 (1H, d, *J* = 7.6 Hz), 7.53 (1H, s), 7.03-7.11 (2H, m), 4.76 (1H, d, *J* = 7.2 Hz), 4.05-4.23 (2H, m, N-CH_2), 3.27 (1H, q, *J* = 8.4 Hz), 1.51 (3H, s), 1.45 (3H, s)
^{13}C NMR (100 MHz) δ:	185.3, 183.1, 147.3, 142.4, 136.5, 134.7, 133.9, 133.4, 133.2, 132.9, 129.9, 129.8, 127.9, 126.6, 126.5, 125.8, 122.6, 117.9, 116.4, 113.4, 110.6, 96.6 (aromatic C), 52.0, 49.7, 45.7, 37.1, 28.9, 27.5 (aliphatic C)
LCMS (m/z):	486 (M-H)$^+$
Anal. Calcd. for $C_{28}H_{20}Cl_2N_2O_2$:	C, 69.00; H, 4.14; N, 5.75 %
Found:	C, 69.12; H, 4.10; N, 5.70 %

Cis-12-bromo-14-chloro-7,7-dimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo[5,6] pyrrolizino[2,1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (130c)

Obtained **130c** by the reaction of 1-aminoanthraquinone with **129c** in 1,4-dioxane in the presence of 20 mol % TPPP following the *general procedure C.* The crude product was purified by neutral silica gel column chromatography with 4 % ethyl acetate in hexanes.



130c

Yield: 78 %

Mp: 199-200 °C

IR (KBr) ν_{max} cm^{-1}: 3250, 3049, 2959, 2871, 1666, 1624, 1572, 1259, 1228, 1147, 981

^{1}H NMR (400 MHz) δ: 9.74 (1H, s, N*H*), 8.16 (1H, d, *J* = 7.8 Hz), 8.11 (1H, d, *J* = 7.8 Hz), 7.90 (1H, d, *J* = 7.7 Hz), 7.58-7.66 (3H, m), 7.50 (1H, d, *J* = 7.7 Hz), 7.13 (1H, d, *J* = 7.7 Hz), 6.88 (1H, d, *J* = 8.6 Hz), 4.62 (1H, d, *J* = 7.6 Hz), 3.94-4.10 (2H, m, N-CH_2), 3.15 (1H, q, *J* = 8.0 Hz), 1.42 (3H, s), 1.36 (3H, s)

^{13}C NMR (100 MHz) δ: 185.3, 183.1, 147.3, 142.2, 136.5, 134.8, 133.9, 133.5, 132.9, 130.5, 130.1, 127.9, 126.7, 126.6, 125.2, 120.9, 120.7, 116.5, 113.8, 113.3, 111.1, 96.4 (aromatic C), 51.9, 49.7, 45.6, 37.0, 28.9, 27.5 (aliphatic C)

LCMS (m/z): 530 $(M-H)^+$

Anal. Calcd. for $C_{28}H_{20}BrClN_2O_2$: C, 63.23; H, 3.79; N, 5.27 %

Found: C, 63.23; H, 3.80; N, 5.66 %

***Cis*-14-chloro-7,7,12-trimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo[5,6]pyrrolizino[2,1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (130d)**

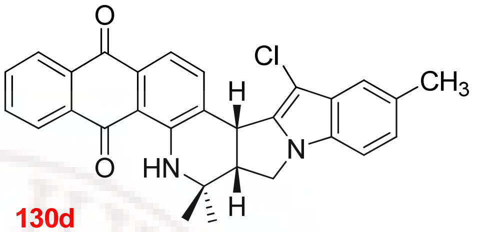
Reaction of **129d** in the presence of TPPP (20 mol %) with 1-aminoanthraquinone in 1,4-dioxane following the *general procedure C* provided the title compound as a pink solid. Pure product was obtained by neutral silica gel column chromatography with 4 % ethyl acetate in hexanes.

Yield: 70 %

Mp: 230 °C

IR (KBr) ν_{max} cm^{-1}: 3248, 3050, 2962, 2922, 1732, 1664, 1261, 1228, 1140, 987

^{1}H NMR (400 MHz) δ: 9.74 (1H, s, N*H*), 8.11-8.19 (2H, m), 8.03 (1H, d, *J* = 7.7 Hz), 7.68-7.77 (2H, m), 7.65 (1H, d, *J* = 7.4 Hz), 7.59 (1H, d, *J* = 7.6 Hz), 6.96-7.02 (2H, m), 4.63 (1H, d, *J* = 7.3 Hz), 3.92-4.10 (2H, m, N-C*H*$_2$), 3.22 (1H, q, *J* = 8.1 Hz), 2.34 (3H, s, ArC-C*H*$_3$), 1.57 (3H, s), 1.43 (3H, s)



130d

^{13}C NMR (100 MHz) δ: 185.3, 183.1, 148.8, 140.8, 136.6, 136.2, 134.9, 133.9, 133.4, 129.4, 126.8, 126.7, 126.5, 124.0, 123.9, 117.9, 117.8, 116.5, 115.9, 109.3, 108.6, 96.3 (aromatic C), 51.8, 51.4, 49.7, 45.4, 36.9, 29.0, 27.5 (aliphatic C)

LCMS (m/z): 468 (M+H)$^+$

Anal. Calcd. for $C_{29}H_{23}ClN_2O_2$: C, 74.59; H, 4.96; N, 6.00 %

Found: C, 74.40; H, 4.91; N, 6.21 %

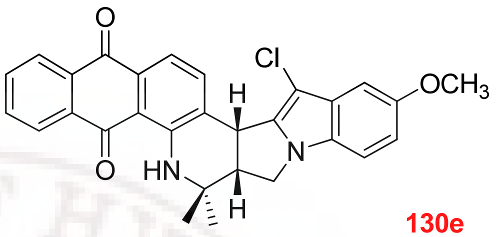
Cis-14-chloro-12-methoxy-7,7-dimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo[5,6]pyrrolizino[2,1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (130e)

The pyrrolizinonaphthoquinoline was obtained by the reaction of **129e** with 1-aminoanthraquinone in the presence of TPPP (20 mol %) in 1,4-dioxane following the *general procedure C*. The crude product was purified by neutral silica gel column chromatography with 6 % ethyl acetate in hexanes.

Yield: 66 %

Mp: 234 °C

IR (KBr) ν_{max} cm^{-1}: 3253, 3052, 2967, 2920, 1722, 1661, 1261, 1227, 1141, 986



130e

^{1}H NMR (400 MHz) δ: 9.95 (1H, s, N*H*), 8.28-8.30 (2H, m), 8.01 (1H, d, *J* = 7.5 Hz), 7.65-7.79 (2H, m), 7.62 (1H, d, *J* = 7.4 Hz), 7.52 (1H, d, *J* = 7.5 Hz), 6.92-7.09 (2H, m), 4.65 (1H, d, *J* = 7.4 Hz), 4.01-4.21 (2H, m, N-C*H*$_2$), 3.21 (1H, q, *J* = 8.0 Hz), 2.60 (3H, s, ArC-OC*H*$_3$), 1.58 (3H, s), 1.54 (3H, s)

^{13}C NMR (100 MHz) δ: 186.1, 184.0, 148.4, 143.2, 136.2, 136.0, 134.9, 133.8, 133.2, 129.2, 126.5, 126.5, 126.2, 124.0, 123.7, 117.8, 117.6, 116.5, 115.7, 109.3, 102.9, 96.4 (aromatic C), 52.9, 50.4, 49.5, 45.3, 37.5, 30.3, 28.4 (aliphatic C)

LCMS (m/z): 482 (M-H)$^+$

Anal. Calcd. for $C_{29}H_{23}ClN_2O_3$: C, 72.12; H, 4.80; N, 5.80 %

Found: C, 72.10; H, 4.62; N, 5.81 %

Cis-7,7,14-trimethyl-6,7,7a,8,14b,17-hexahydro-5*H*-benzo[5,6]pyrrolizino [2, 1-*c*]naphtho[2,3-*h*]quinoline-5,17-dione (130f)

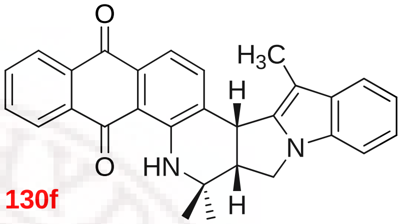
Obtained as a pink coloured solid by the reaction of **129f** with 1-aminoanthraquinone in 1,4-dioxane following the *general procedure C*. Pure product was obtained by neutral silica gel column chromatography with 4 % ethyl acetate in hexanes.

Yield: 85 %

Mp: 210 °C

IR (KBr) ν_{max} cm^{-1}: 3231, 3059, 2920, 1734, 1660, 1255, 1142, 954

^{1}H NMR (400 MHz) δ: 9.95 (1H, s, NH), 8.29 (1H, d, *J* = 7.5 Hz), 8.23 (1H, d, *J* = 7.5 Hz), 7.71-7.79 (2H, m), 7.66 (1H, d, *J* = 7.7 Hz), 7.53-7.57 (2H, d, *J* = 7.6 Hz), 7.06-7.14 (3H, m), 4.65 (1H, d, *J* = 7.1 Hz), 4.01-4.22 (2H, m, N-CH_2), 3.20 (1H, q, *J* = 8.0 Hz), 2.60 (3H, s, ArC-CH_3), 1.54 (3H, s), 1.49 (3H, s)



130f

^{13}C NMR (100 MHz) δ: 185.2, 183.3, 147.6, 142.2, 136.4, 134.9, 133.9, 133.2, 133.0, 132.6, 132.2, 129.4, 126.7, 126.6, 121.2, 118.9, 118.6, 118.5, 116.2, 113.1, 109.2, 109.0 (aromatic C), 102.1, 52.0, 49.8, 44.4, 36.6, 29.5, 27.5 (aliphatic C)

LCMS (m/z): 433 (M+H)$^+$

Anal. Calcd. for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48 %

Found: C, 80.50; H, 5.99; N, 6.69 %

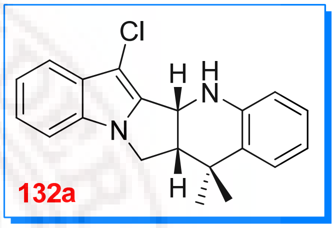
General procedure D

La(OTf)$_3$ (10 mol %) was added to a mixture of amines (**131a-e** and **134a-b**) (1 mmol) and 3-chloro-1-(3-methylbut-2-ene)-1*H*-indole-2-carboxaldehyde (**129a**) (1 mmol) in 1,4-dioxane (5 mL). The reaction mixture was heated at 130-140 °C and stirred for the appropriate time. After completion of the reaction, as indicated by TLC, excess 1,4-dioxane was distilled off and the residue was poured into water (20 mL) and extracted with DCM (3 x 20 mL). The organic layer was dried over anhy.

Na_2SO_4 and distilled under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh size) and eluted with hexane-ethyl acetate to afford pure *cis*-fused pyrroloquinoline derivatives as solids.

Cis-6-chloro-13,13-dimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6] pyrrolizino[1,2-*b*]quinoline (132a)

Obtained **132a** by the reaction of aniline (**131a**) with 3-chloro-1-(3-methylbut-2-ene)-1*H*-indole-2-carboxaldehyde (**129a**) in 1,4-dioxane following the *General procedure D.* The crude product was purified by silica gel column chromatography with 1 % ethyl acetate in hexanes.

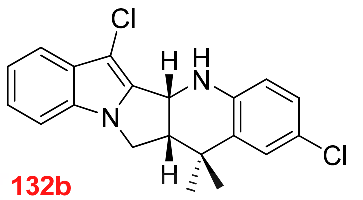


132a

Yield:	80 %
Mp:	170-171 °C
IR (KBr) ν_{max} cm^{-1}:	3337, 3061, 2926, 2854, 1711, 1668, 1614, 1510, 1460, 877, 742
^1H NMR (400 MHz) δ:	7.56 (1H, d, *J* = 7.2 Hz); 7.09-7.17 (4H, m); 6.94 (1H, t, *J* = 7.2 Hz); 6.67 (1H, t, *J* = 7.2 Hz); 6.38 (1H, d, *J* = 8.0 Hz); 5.08 (1H, d, *J* = 7.2 Hz); 4.13 (1H, t, *J* = 9.2 Hz); 3.98 (1H, s); 3.59 (1H, t, *J* = 9.6 Hz); 3.21 (1H, q, *J* = 8.4 Hz); 1.51 (3H, s); 1.49 (3H, s)
^{13}C NMR (100 MHz) δ:	142.3, 141.6, 131.7, 129.1, 127.3, 126.6, 125.1, 122.3, 120.0, 118.5, 117.8, 113.8, 110.0 (aromatic C), 54.1, 49.3, 47.1, 34.3, 28.6, 25.6 (aliphatic C)
LCMS (m/z):	323 $(M+H)^+$
Anal. Calcd. for $C_{20}H_{19}ClN_2$:	C, 74.41; H, 5.93; N, 8.68 %
Found:	C, 74.44; H, 5.93; N, 9.04 %

Cis-2,6-dichloro-13,13-dimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6] pyrrolizino[1,2-*b*]quinoline (132b)

Obtained **132b** by the reaction of 4-chloroaniline (**131b**) with **129a** in 1,4-dioxane following the *General procedure D.* Pure product was obtained by silica gel column chromatography with 3 % ethyl acetate in hexanes.



132b

Yield: 92 %

Mp: 147-148 °C

IR (KBr) ν_{max} cm^{-1}: 3393, 3057, 2962, 1755, 1666, 1284, 1170, 1093, 989, 925

^{1}H NMR (400 MHz) δ: 7.61 (1H, d, *J* = 7.2 Hz); 7.15-7.22 (4H, m); 6.93 (1H, d, *J* = 8.0 Hz); 6.34 (1H, d, *J* = 8.4 Hz); 5.05 (1H, d, *J* = 6.8 Hz); 4.14 (1H, t, *J* = 9.2 Hz); 3.99 (1H, s) ; 3.55 (1H, t, *J* = 9.6 Hz); 3.22 (1H, q, *J* = 8.0 Hz); 1.48 (3H, s); 1.46 (3H, s)

^{13}C NMR (100 MHz) δ: 141.1, 140.8, 131.6, 129.1, 128.3, 127.1, 125.2, 122.5, 122.3, 120.1, 118.6, 114.9, 110.1 (aromatic C), 53.7, 49.3, 47.0, 34.6, 28.4, 25.5 (aliphatic C)

LCMS (m/z): 357 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{18}Cl_2N_2$: C, 67.24; H, 5.08; N, 7.84 %

Found: C, 67.44; H, 5.05; N, 7.81 %

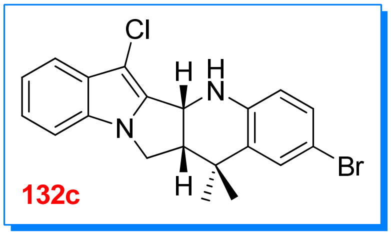
Cis-2-bromo-6-chloro-13,13-dimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6]pyrrolizino[1,2-*b*]quinoline (132c)

Reaction of 4-bromoaniline (**131c**) in the presence of La(OTf)$_3$ with **129a** in 1,4-dioxane following the *General procedure D* provided the title compound as a white solid. The crude product was purified by silica gel column chromatography with 1 % ethyl acetate in hexanes.

Yield: 88 %

Mp: 142-143 °C

IR (KBr) ν_{max} cm^{-1}: 3400, 2964, 2922, 1707, 1618, 1456, 1087, 873, 802



132c

^{1}H NMR (400 MHz) δ: 7.59 (1H, d, *J* = 7.6 Hz); 7.05-7.27 (5H, m); 6.31 (1H, d, *J* = 8.4 Hz); 5.06 (1H, d, *J* = 7.2 Hz); 4.16 (1H, t, *J* = 8.0 Hz); 4.00 (1H, s); 3.56 (1H, t, *J* = 9.6 Hz); 3.24 (1H, q, *J* = 9.2 Hz); 1.48 (3H, s); 1.46 (3H, s)

^{13}C NMR (100 MHz) δ: 141.3, 140.9, 131.6, 129.9, 129.1, 128.7, 128.0, 122.5, 120.1, 118.6, 115.4, 110.1, 109.4 (aromatic C), 53.7, 49.2, 47.0, 34.6, 28.4, 25.5 (aliphatic C)

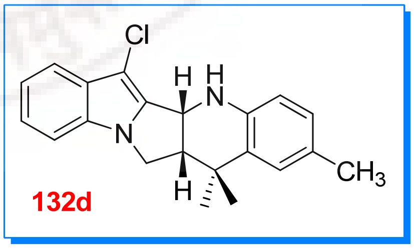
LCMS (m/z): 403 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{18}ClBrN_2$: C, 59.80; H, 4.52; N, 6.97 %

Found: C, 59.86; H, 4.50; N, 7.16 %

***Cis*-6-chloro-2,13,13-trimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6] pyrrolizino[1,2-*b*] quinoline (132d)**

The pyrroloindole fused quinoline was obtained by the reaction of 4-methylaniline (**131d**) with **129a** in the presence of La(OTf)$_3$ in 1,4-dioxane following the *General procedure D.* Pure product was obtained by silica gel column chromatography with 1 % ethyl acetate in hexanes.



132d

Yield: 65 %

Mp: 139-140 °C

IR (KBr) ν_{max} cm^{-1}: 3400, 3057, 2964, 2924, 1745, 1614, 1456, 1099, 883, 808

^{1}H NMR (400 MHz) δ: 7.60 (1H, d, *J* = 7.2 Hz); 7.12-7.19 (3H, m); 7.00 (1H, s); 6.80 (1H, d, *J* = 8.0 Hz); 6.35 (1H, d, *J* = 8.0 Hz); 5.06 (1H, d, *J* = 7.2 Hz); 4.14 (1H, t, *J* = 8.0 Hz); 3.87

(1H, s); 3.58 (1H, t, *J* = 8.8 Hz); 3.24 (1H, q, *J* = 8.0 Hz); 2.26 (3H, s, ArC-C*H*$_3$); 1.49 (3H, s); 1.48 (3H, s)

^{13}C NMR (100 MHz) δ: 141.8, 139.6, 131.6, 129.2, 127.7, 126.8, 126.7, 125.7, 122.3, 119.9, 118.5, 113.9, 110.1 (aromatic C), 54.1, 49.5, 47.2, 34.4, 28.5, 25.6, 20.6 (aliphatic C)

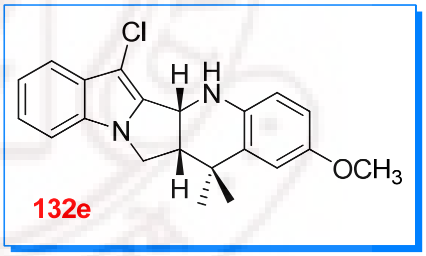
LCMS (m/z): 337 (M+H)$^+$

Anal. Calcd. for $C_{21}H_{21}ClN_2$: C, 74.88; H, 6.28; N, 8.32 %

Found: C, 74.78; H, 6.29; N, 8.36 %

Cis-6-chloro-2-methoxy-13,13-trimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6] pyrrolizino[1,2-*b*]quinoline (132e)

Obtained as a white colour solid by the reaction of **129a** with 4-methoxyaniline (**131e**) in 1,4-dioxane following the *General procedure D.* The crude product was purified by silica gel column chromatography with 1 % ethyl acetate in hexanes.



132e

Yield: 52 %

Mp: 115-116 °C

IR (KBr) ν_{max} cm^{-1}: 3368, 3051, 2962, 1616, 1510, 1456, 1259, 1035, 815, 740

^{1}H NMR (400 MHz) δ: 7.59 (1H, d, *J* = 7.2 Hz); 7.12-7.21 (3H, m); 6.82 (1H, s); 6.58 (1H, t, *J* = 5.6 Hz); 6.37 (1H, d, *J* = 8.4 Hz); 5.06 (1H, d, *J* = 7.6 Hz); 4.13 (1H, t, *J* = 8.8 Hz); 3.78 (1H, s); 3.76 (3H, s, ArC-OC*H*$_3$); 3.54 (1H, t, *J* = 9.2 Hz); 3.27 (1H, q, *J* = 8.0 Hz); 1.49 (3H, s); 1.48 (3H, s)

^{13}C NMR (100 MHz) δ: 152.4, 141.9, 136.5, 131.6, 129.2, 128.6, 122.3, 119.9, 118.5, 114.5, 112.2, 111.9, 110.1 (aromatic

C), 55.8, 53.9, 49.8, 47.2, 34.9, 27.9, 25.6 (aliphatic C)

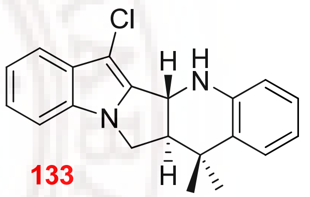
LCMS (m/z): 353 $(M+H)^+$

Anal. Calcd. for $C_{21}H_{21}ClN_2O$: C, 71.48; H, 6.00; N, 7.94 %

Found: C, 71.56; H, 6.05; N, 8.02 %

Trans-6-chloro-13,13-dimethyl-5,12,12a,13-tetrahydro-5a*H*-benzo[5,6]pyrrolizino[1,2-*b*]quinoline (133)

The compound was obtained by the reaction of **129a** with aniline (**131a**) in 1,4-dioxane following the *General procedure D.* Pure product was obtained through silica gel column chromatography with 1 % ethyl acetate in hexane as a minor product.



133

Mp: 129-130 °C

IR (KBr) ν_{max} cm^{-1}: 3337, 3059, 2962, 2856, 1709, 1668, 1614, 1510, 1460, 877, 742

^{1}H NMR (400 MHz) δ: 7.63 (1H, d, *J* = 7.6 Hz); 7.34 (1H, d, *J* = 8.0 Hz); 7.21-7.27 (2H, m); 7.18 (1H, d, *J* = 6.4 Hz); 7.12 (1H, t, *J* = 7.2 Hz); 6.88 (1H, t, *J* = 7.6 Hz); 6.80 (1H, d, *J* = 7.6 Hz); 4.77 (1H, d, *J* = 10.4 Hz); 4.55 (1H, s); 4.37 (1H, t, *J* = 8.0 Hz); 3.94 (1H, t, *J* = 10.0 Hz); 3.02 (1H, q, *J* = 7.6 Hz); 1.52 (3H, s); 1.46 (3H, s)

^{13}C NMR (100 MHz) δ: 143.7, 137.7, 132.1, 132.0, 128.9, 127.3, 127.2, 122.3, 119.9, 119.6, 118.4, 116.9, 109.7 (aromatic C), 57.7, 51.7, 43.8, 35.5, 29.3, 28.1 (aliphatic C)

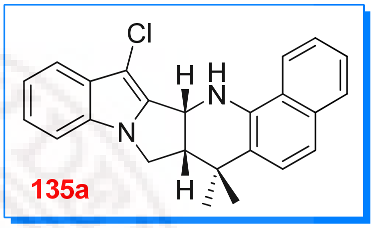
LCMS (m/z): 323 $(M+H)^+$

Anal. Calcd. for $C_{20}H_{19}ClN_2$: C, 74.41; H, 5.93; N, 8.68 %

Found: C, 74.61; H, 5.92; N, 8.59 %

Cis-14-chloro-7,7-dimethyl-7a,8,14b,15-tetrahydro-7*H*-benzo[*h*]benzo[5,6]pyrrolizino[1,2-*b*] quinoline (135a)

The compound was obtained by the reaction of 1-aminonaphthalene (**134a**) with **129a** in 1,4-dioxane in the presence of 10 mol % of La(OTf)$_3$ following the *General procedure D.* The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.



135a

Yield: 85 %

Mp: 240-241 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 3053, 2961, 1666, 1521, 1261, 1111, 989, 875

^{1}H NMR (400 MHz) δ: 7.76 (1H, d, *J* = 6.8 Hz); 7.39-7.75 (2H, m); 7.25-7.28 (3H, m); 7.12-7.19 (4H, m); 5.28 (1H, d, *J* = 6.8 Hz); 4.81 (1H, s); 4.18 (1H, t, *J* = 8.0 Hz); 3.64 (1H, t, *J* = 9.6 Hz); 3.30 (1H, q, *J* = 9.2 Hz); 1.59 (3H, s); 1.53 (3H, s)

^{13}C NMR (100 MHz) δ: 141.5, 136.7, 133.1, 131.7, 129.1, 128.5, 125.3, 124.9, 123.7, 122.4, 121.8, 120.0, 119.8, 119.5, 118.6, 117.2, 110.1 (aromatic C), 54.2, 49.4, 47.2, 34.4, 29.3, 26.1 (aliphatic C)

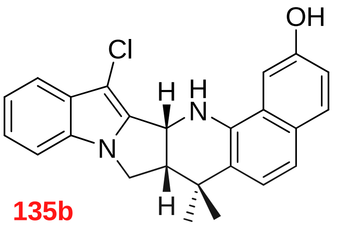
LCMS (m/z): 373 (M+H)$^+$

Anal. Calcd. for $C_{24}H_{21}ClN_2$: C, 77.30; H, 5.68; N, 7.51 %

Found: C, 77.40; H, 5.63; N, 7.59 %

Cis-14-chloro-7,7-dimethyl-7a,8,14b,15-tetrahydro-7*H*-benzo[*h*]benzo[5,6]pyrrolizino [1,2-*b*]quinoline-2-ol (135b)

Obtained **135b** from **129a** by treating with 1-amino-5-hydroxynaphthalene (**134b**) in 1,4-dioxane following the *General procedure D.* Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.



135b

Yield:	80 %
Mp:	127-128 °C
IR (KBr) ν_{max} cm^{-1}:	3375, 3051, 2959, 1630, 1523, 1452, 1377, 1209, 831, 738
^{1}H NMR (400 MHz) δ:	7.59-7.67 (2H, m); 6.91-7.35 (7H, m); 5.27 (1H, d, *J* = 6.8 Hz); 4.96-4.98 (2H, m); 4.19 (1H, t, *J* = 8.4 Hz); 3.63 (1H, t, *J* = 9.6 Hz); 3.32 (1H, q, *J* = 8.8 Hz); 1.58 (3H, s); 1.52 (3H, s)
^{13}C NMR (100 MHz) δ:	153.1, 141.6, 135.5, 130.4, 130.3, 129.1, 128.4, 122.9, 122.7, 122.4, 122.3, 121.4, 120.5, 119.9, 118.5, 117.4, 110.1 (aromatic C), 54.3, 49.4, 47.2, 34.4, 29.4, 26.1 (aliphatic C)
LCMS (m/z):	389 (M+H)$^+$
Anal. Calcd. for $C_{24}H_{21}ClN_2O$:	C, 74.12; H, 5.44; N, 7.20 %
Found:	C, 74.12; H, 5.45; N, 7.38 %

Table 18. Crystal data and structure refinement for 130a

Empirical formula	: $C_{28}H_{21}ClN_2O_2$
Formula weight	: 452.92
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P-1
Unit cell dimensions	: a = 9.2070(6) Å α = 62.6740(10)°
	: b = 11.4137(8) Å β = 88.6850(10)°
	: c = 11.9039(8) Å γ = 81.2650(10)°
Volume	: 1096.89(13) $Å^3$
Z	: 2
Density (calculated)	: 1.371 Mg/m^3
Absorption coefficient	: 0.204 mm^{-1}
F (000)	: 472
Crystal size	: 0.38 x 0.20 x 0.16 mm^3
Theta range for data collection	: 1.93 to 26.01°
Index ranges	: -11<=h<=11, -14<=k<=14, -14<=l<=14
Reflections collected	: 11409
Independent reflections	: 4273 [R (int) = 0.0233]
Completeness to theta = 26.04°	: 99.1 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9681 and 0.9266
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 4273 / 0 / 304
Goodness-of-fit on F^2	: 1.026
Final R indices [I>2sigma (I)]	: R1 = 0.0448, wR2 = 0.1121
R indices (all data)	: R1 = 0.0580, wR2 = 0.1203
Largest diff. peak and hole	: 0.191 and -0.232 e.$Å^{-3}$
CCDC number	: 621081

Table 19. Crystal data and structure refinement for 130b

Empirical formula	: $C_{56}H_{40}Cl_4N_4O_4$	
Formula weight	: 974.72	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 11.9652(14) Å	α = 90°
	: b = 23.078(3) Å	β = 102.416(2)°
	: c = 17.208(2) Å	γ = 90°
Volume	: 4640.8(9) $Å^3$	
Z	: 4	
Density (calculated)	: 1.395 Mg/m^3	
Absorption coefficient	: 0.309 mm^{-1}	
F (000)	: 2016	
Crystal size	: 0.22 x 0.16 x 0.04 mm^3	
Theta range for data collection	: 1.50 to 26.10°	
Index ranges	: -14<=h<=14, -28<=k<=28, - 20<=l<=21	
Reflections collected	: 33905	
Independent reflections	: 9115 [R(int) = 0.1435]	
Completeness to theta = 26.04°	: 98.9 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9877 and 0.9351	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 9115 / 0 / 621	
Goodness-of-fit on F^2	: 0.926	
Final R indices [I>2sigma (I)]	: R1 = 0.0653, wR2 = 0.0951	
R indices (all data)	: R1 = 0.2182, wR2 = 0.1329	
Largest diff. peak and hole	: 0.221 and -0.200 e.$Å^{-3}$	
CCDC number	: 621082	

Table 20. Crystal data and structure refinement for 130c

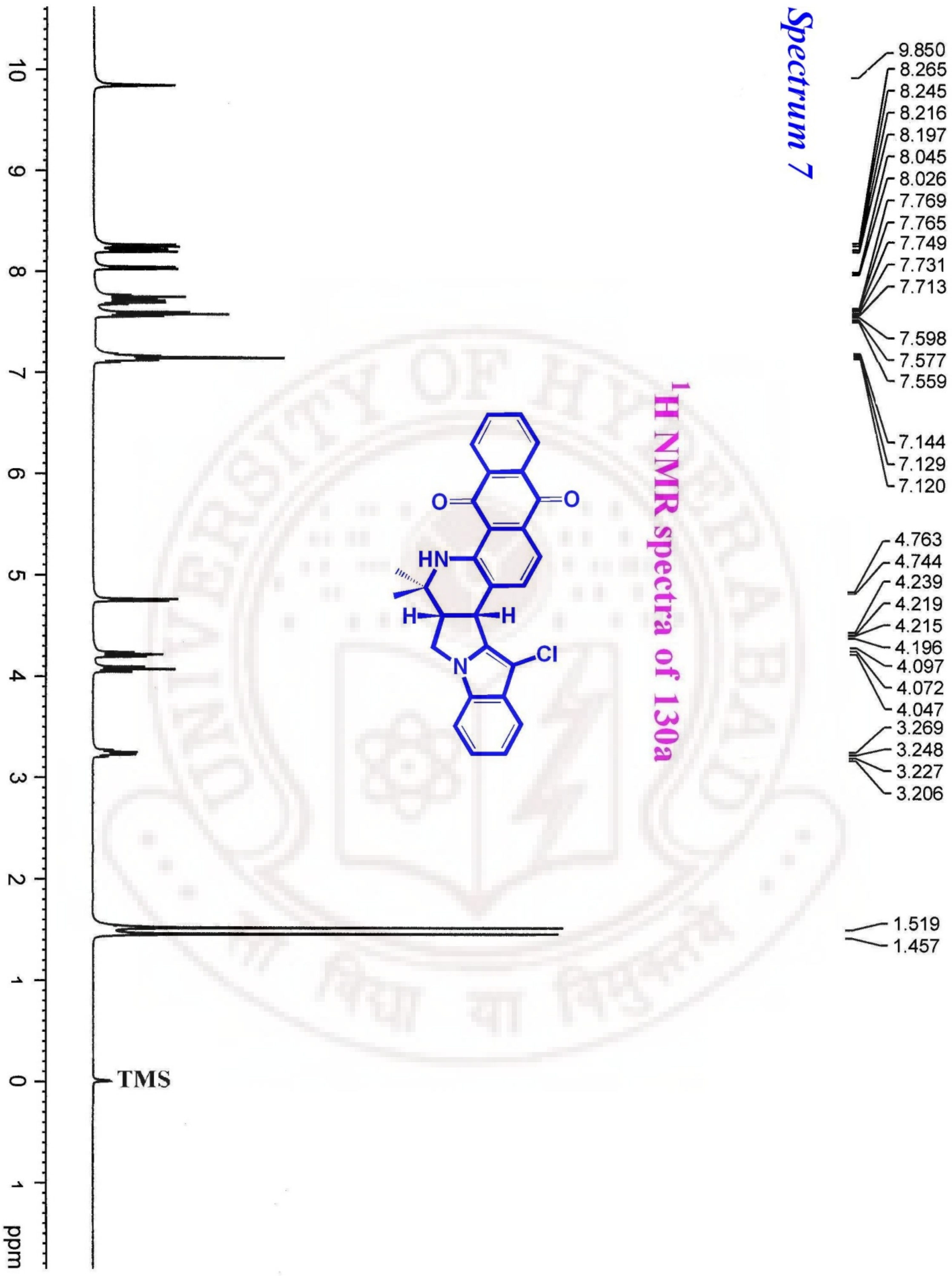
Empirical formula	: $C_{28}H_{20}BrClN_2O_2$	
Formula weight	: 531.82	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 21.701(7) Å	α = 90°
	: b = 13.626(5) Å	β = 98.523(6)°
	: c = 7.846(3) Å	γ = 90°
Volume	: 2294.2(13) $Å^3$	
Z	: 4	
Density (calculated)	: 1.540 Mg/m^3	
Absorption coefficient	: 1.938 mm^{-1}	
F (000)	: 1080	
Crystal size	: 0.48 x 0.04 x 0.03 mm^3	
Theta range for data collection	: 1.77 to 26.01°	
Index ranges	: -26<=h<=26, -16<=k<=16, -9<=l<=9	
Reflections collected	: 16410	
Independent reflections	: 4494 [R(int) = 0.0755]	
Completeness to theta = 26.04°	: 99.5 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9441 and 0.4564	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 4494 / 0 / 319	
Goodness-of-fit on F^2	: 0.976	
Final R indices [I>2sigma (I)]	: R1 = 0.0521, wR2 = 0.0985	
R indices (all data)	: R1 = 0.1124, wR2 = 0.1177	
Largest diff. peak and hole	: 0.403 and -0.239 e.$Å^{-3}$	
CCDC number	: 621083	

Table 21. Crystal data and structure refinement for 132a

Empirical formula	: $C_{20}H_{19}ClN_2$	
Formula weight	: 322.82	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Orthorhombic	
Space group	: Pbca	
Unit cell dimensions	: a = 14.8375(10) Å	α = 90°
	: b = 10.6479(8) Å	β = 90°
	: c = 20.4659(15) Å	γ = 90°
Volume	: 3233.4(4) $Å^3$	
Z	: 8	
Density (calculated)	: 1.326 Mg/m^3	
Absorption coefficient	: 0.237 mm^{-1}	
F (000)	: 1360	
Crystal size	: 0.30 x 0.28 x 0.20 mm^3	
Theta range for data collection	: 1.99 to 25.00°	
Index ranges	: $-14<=h<=17$, $-12<=k<=12$, $-24<=l<=20$	
Reflections collected	: 14559	
Independent reflections	: 2855 [R(int) = 0.0510]	
Completeness to theta = 26.04°	: 100.0 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9541 and 0.9322	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2855 / 0 / 210	
Goodness-of-fit on F^2	: 1.037	
Final R indices [I>2sigma (I)]	: R1 = 0.0515, wR2 = 0.1280	
R indices (all data)	: R1 = 0.0716, wR2 = 0.1369	
Largest diff. peak and hole	: 0.408 and -0.327 e.$Å^{-3}$	
CCDC number	: 648978	

Table 22. Crystal data and structure refinement for 135a

Empirical formula	: $C_{24}H_{21}ClN_2$
Formula weight	: 372.88
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 8.6556(10) Å α = 90°
	: b = 21.084(2) Å β = 96.368(2)°
	: c = 10.6112(12) Å γ = 90°
Volume	: 1924.6(4) $Å^3$
Z	: 4
Density (calculated)	: 1.287 Mg/m^3
Absorption coefficient	: 0.209 mm^{-1}
F (000)	: 784
Crystal size	: 0.58 x 0.22 x 0.12 mm^3
Theta range for data collection	: 1.93 to 25.95°
Index ranges	: -10<=h<=10, -24<=k<=25, -13<=l<=13
Reflections collected	: 12122
Independent reflections	: 3749 [R(int) = 0.0257]
Completeness to theta = 26.04°	: 99.7 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9753 and 0.8883
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3749 / 0 / 250
Goodness-of-fit on F^2	: 1.054
Final R indices [I>2sigma (I)]	: R1 = 0.0579, wR2 = 0.1419
R indices (all data)	: R1 = 0.0791, wR2 = 0.1526
Largest diff. peak and hole	: 0.390 and -0.248 e.$Å^{-3}$
CCDC number	: 648977

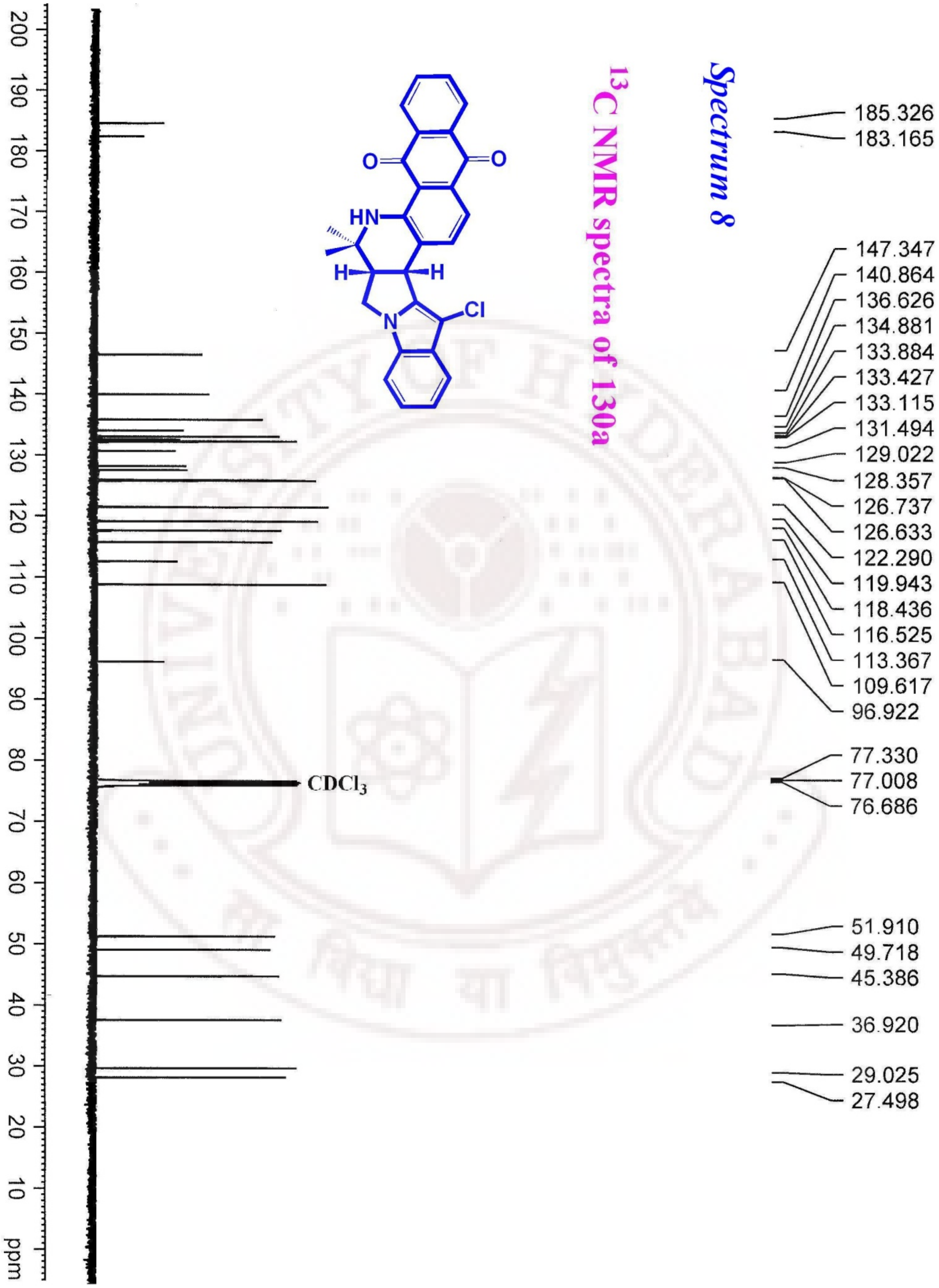


Spectrum 7

^{1}H NMR spectra of 130a

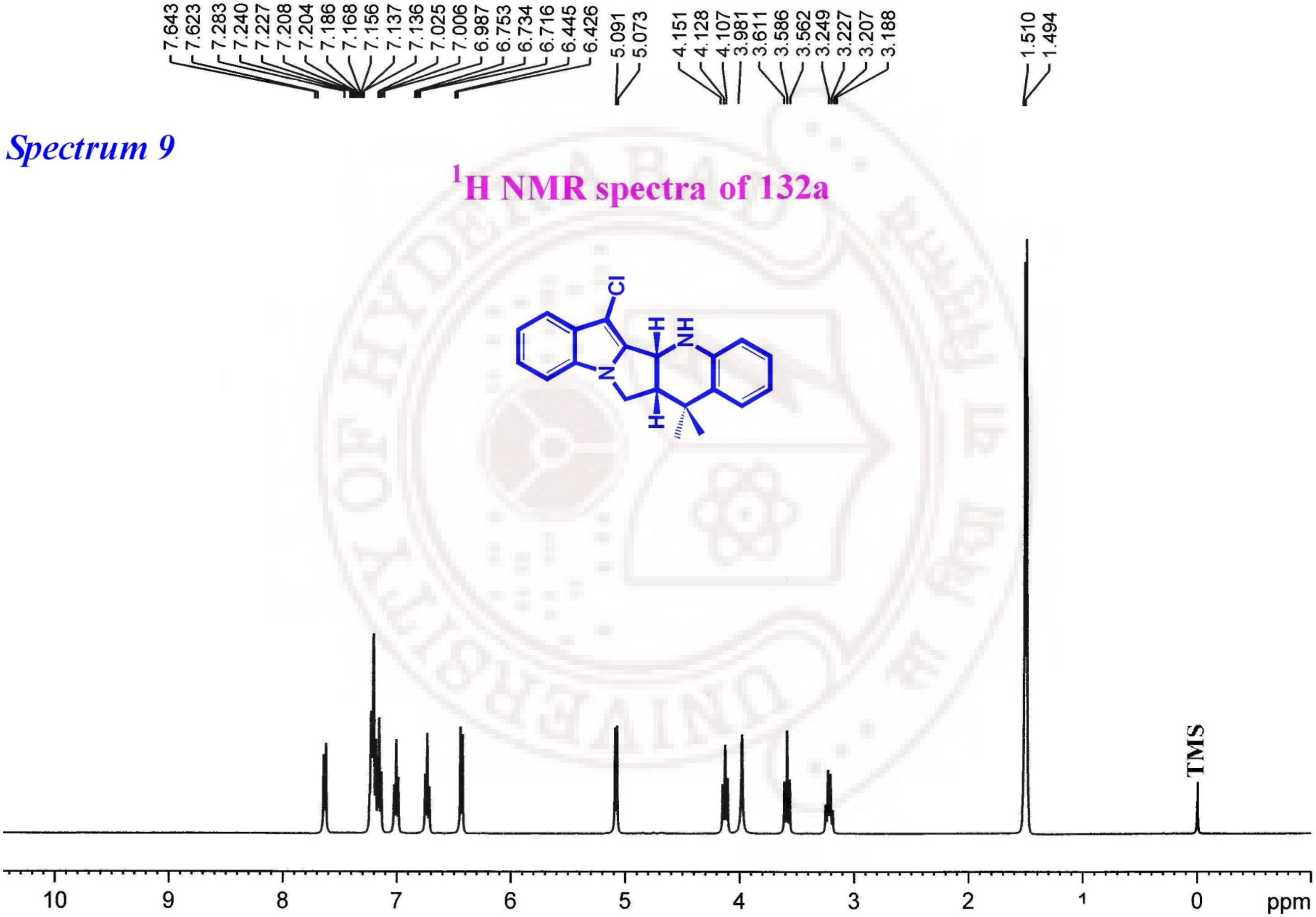
Spectrum 8

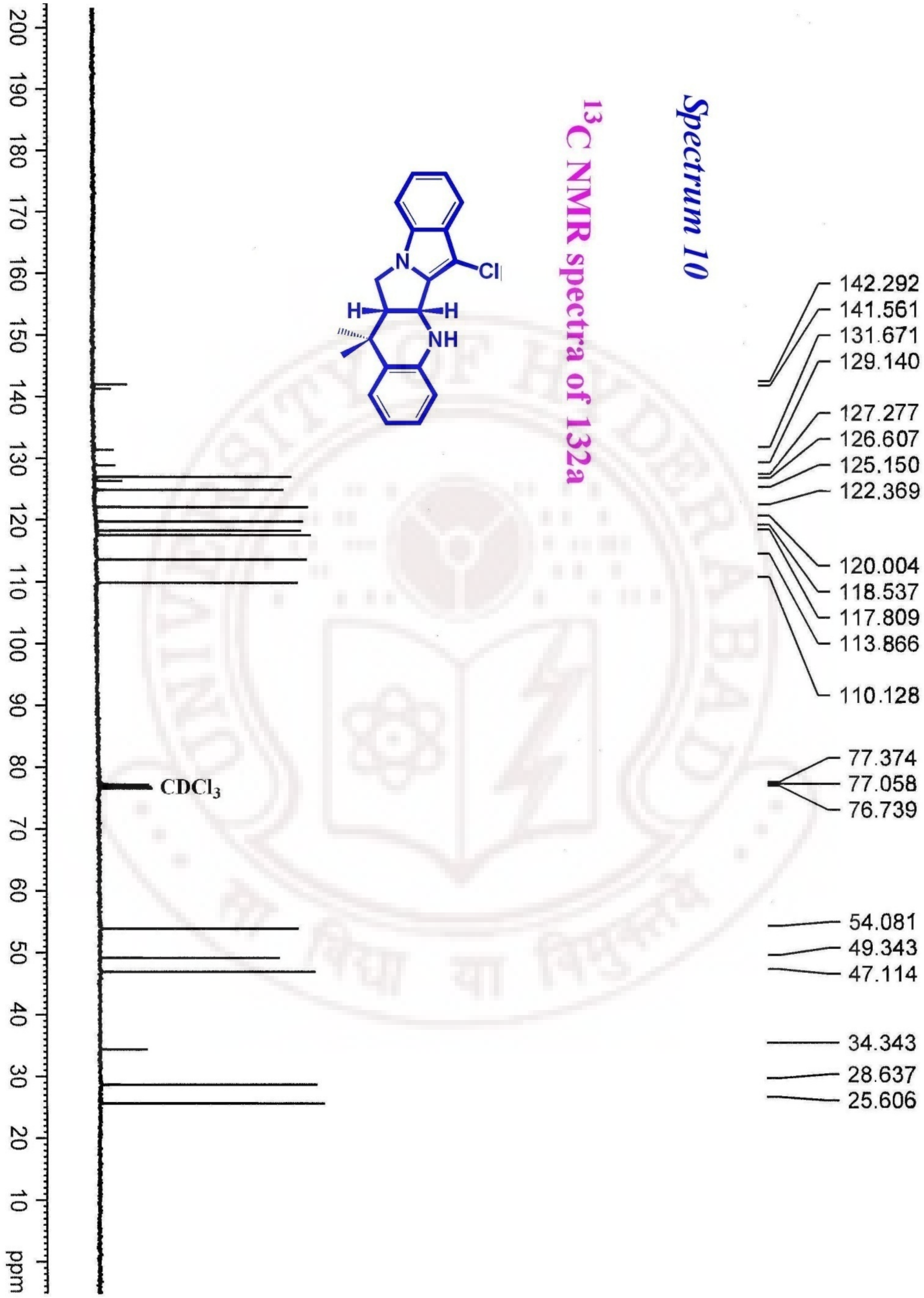
^{13}C NMR spectra of 130a



Spectrum 9

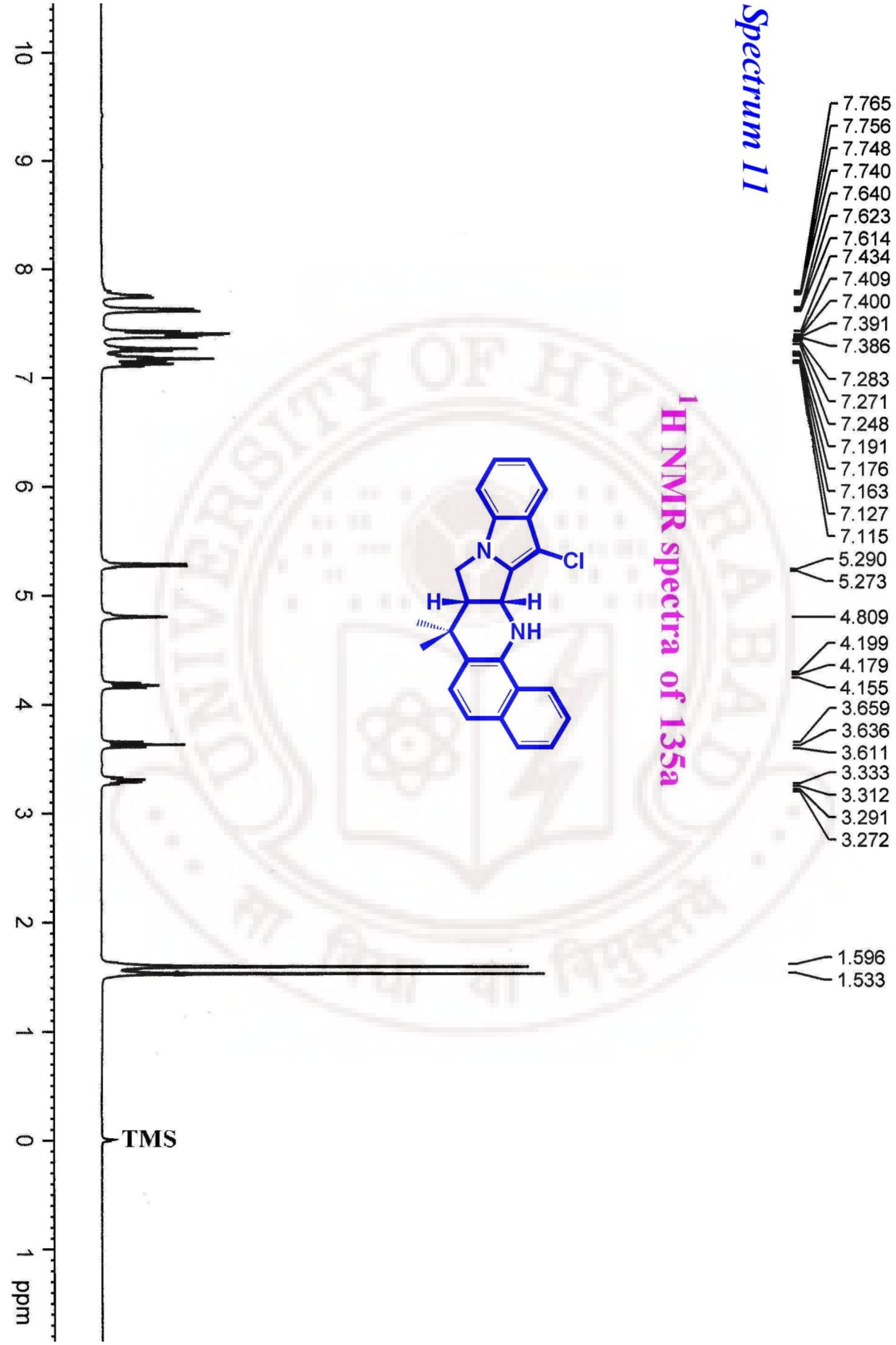
^{1}H NMR spectra of 132a





Spectrum 10

^{13}C NMR spectra of 132a

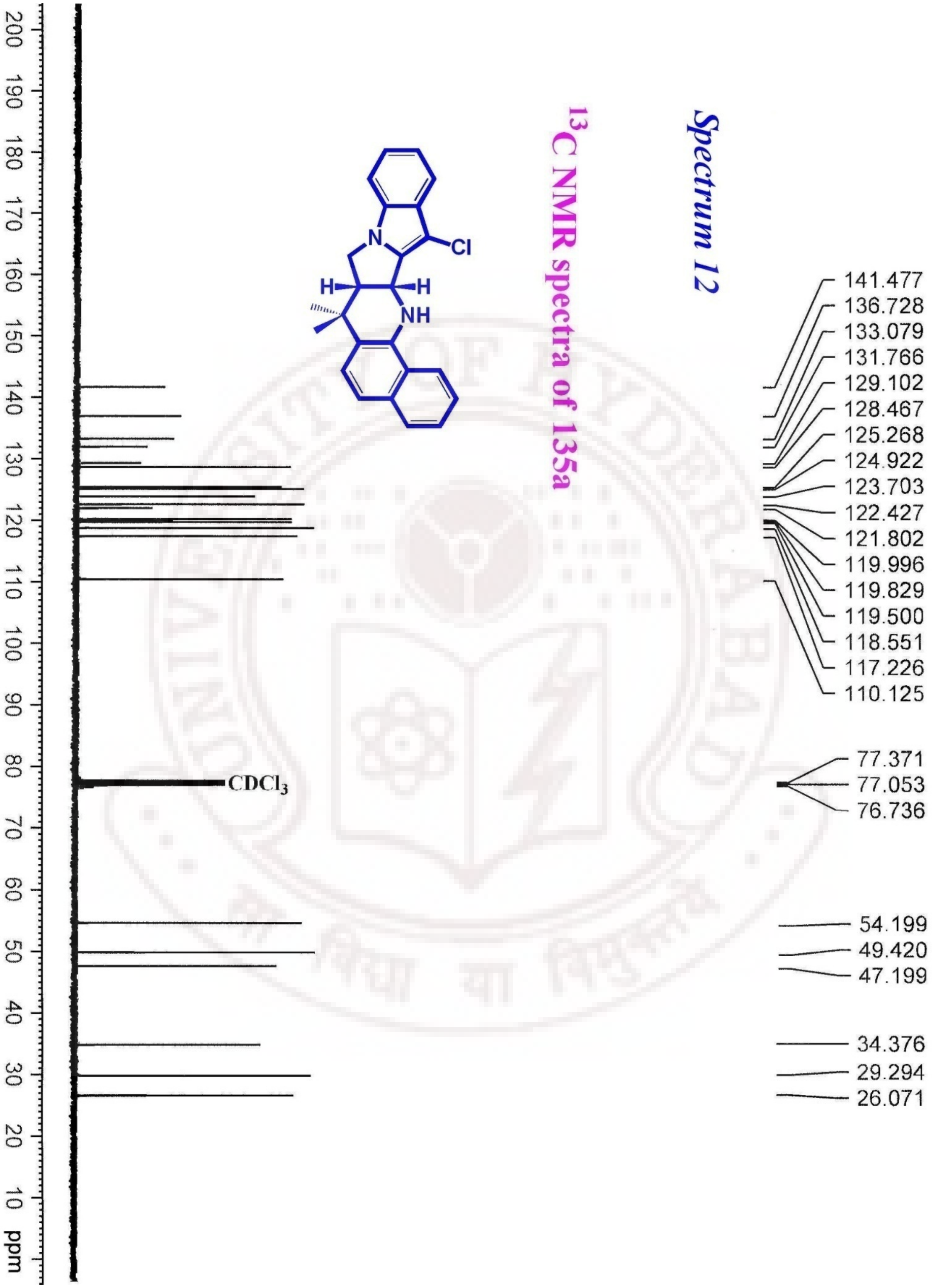


Spectrum 11

^{1}H NMR spectra of 135a

Spectrum 12

^{13}C NMR spectra of 135a



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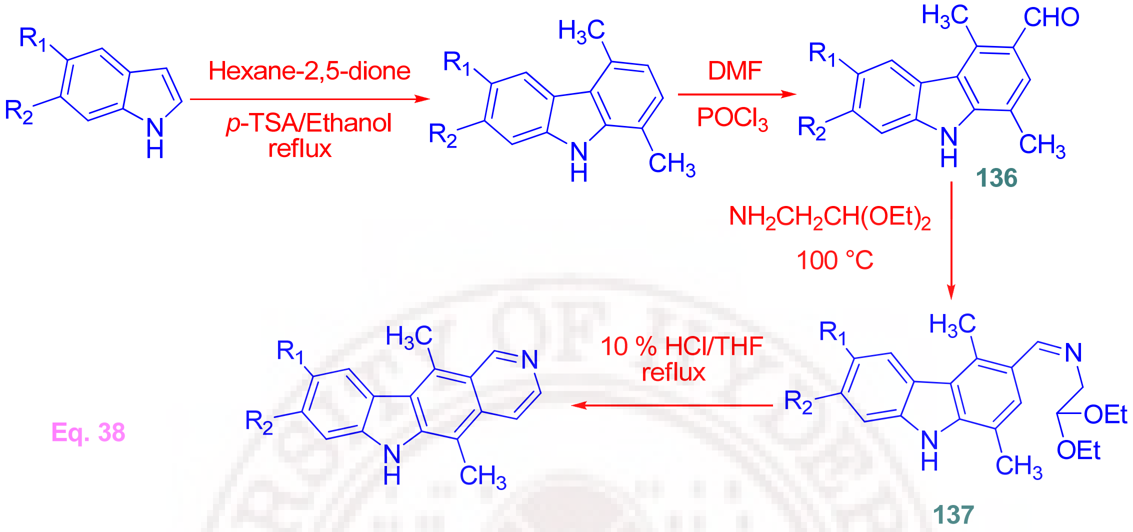
Synthesis of Polycyclic Pyridocarbazole Derivatives through inter and intramolecular imino Diels-Alder reaction

CHAPTER 3

3.1. Introduction

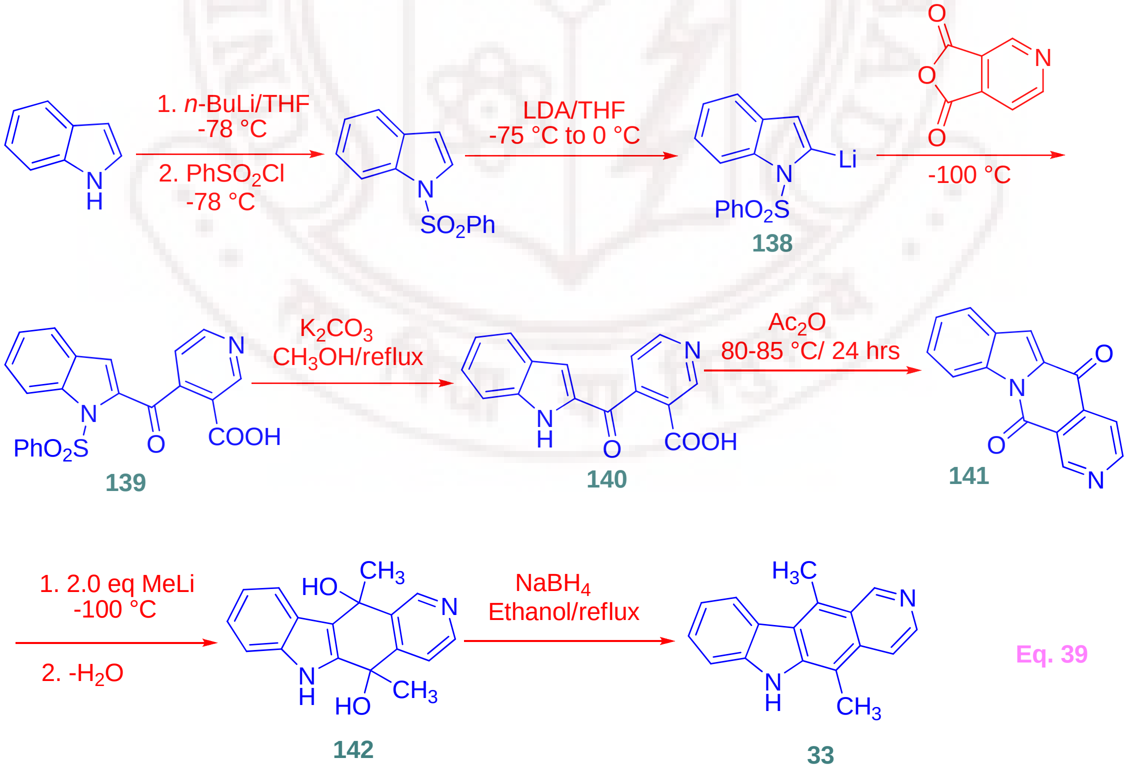
Polycyclic nitrogen-containing heterocycles form the basic skeleton of numerous alkaloids and physiologically active compounds.[139] Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole), an alkaloid having the basic structure of pyridocarbazole isolated from Apocyanaceae plants and several of its derivatives exhibit promising results in the treatment of osteolytic breast cancer metastases, kidney sarcoma, brain tumors and myeloblastic leukemia and solid tumors.[140] The antineoplastic property of ellipticine was considered to be based mainly on DNA intercalation and/or inhibition of topoisomerase II.[141-145] Recently, it was demonstrated that ellipticine covalently binds to DNA *in vitro* and *in vivo* after being enzymatically activated with cytochrome P450 or peroxidases.[146-149] Ellipticine derivatives also have tyrosine kinase-inhibiting activity. The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects, and complete lack of hematological toxicity.[150]

So the development of useful methods for the preparation of these molecules is highly desirable. Ellipticine has proven to be a popular target for synthesis, and a wide variety of strategies have been reported.[151-153] Some of the interesting synthetic schemes have been given below.



Eq. 38

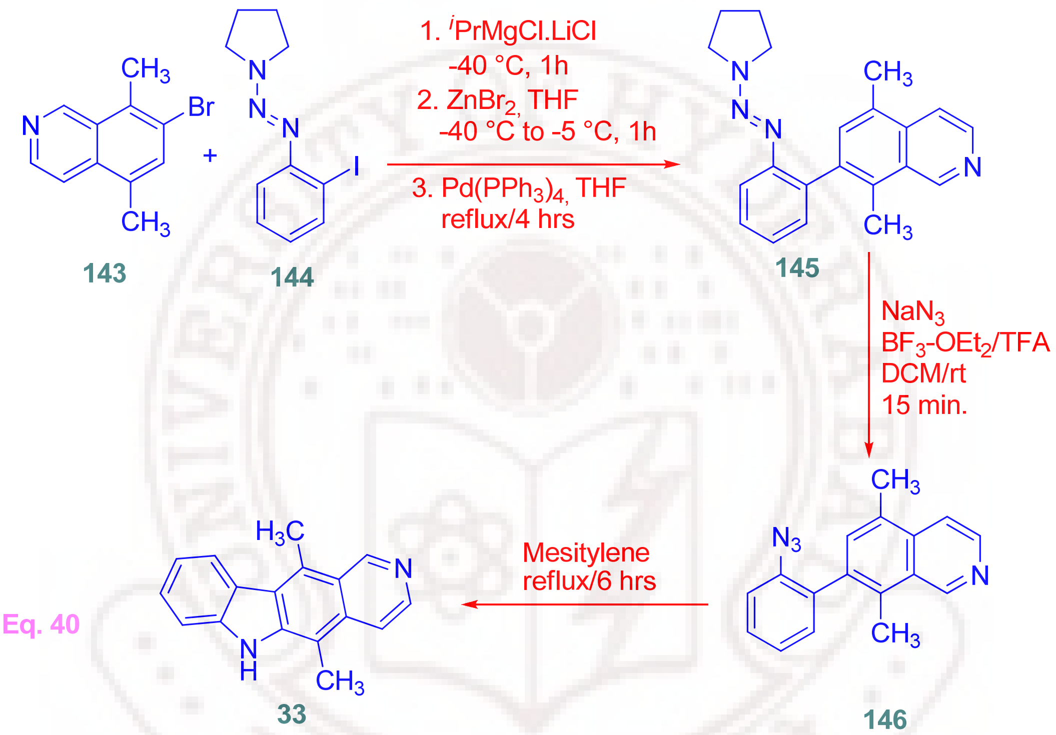
Thus far, the most versatile and efficient method for the syntheses of ellipticine and its analogs has been that as shown in **Eq. 38** developed by Dalton *et.al*.[154]



Eq. 39

Gribble and co-workers[155] developed an interesting synthesis of ellipticine framework starting from indole following the reaction as shown in **Eq. 39**.

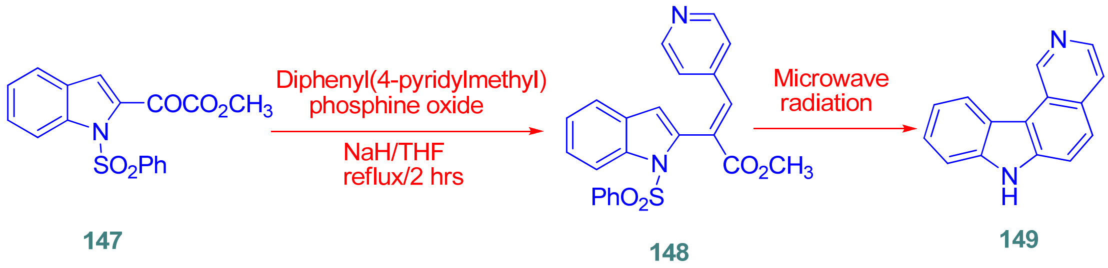
Knochel and co-workers[156] reported a simple and convenient synthesis of ellipticine by starting with the triazene **144** after thermal decomposition of azide **146** in refluxing mesitylene gave ellipticine (**33**) in overall 57 % yield (**Eq. 40**).



Eq. 40

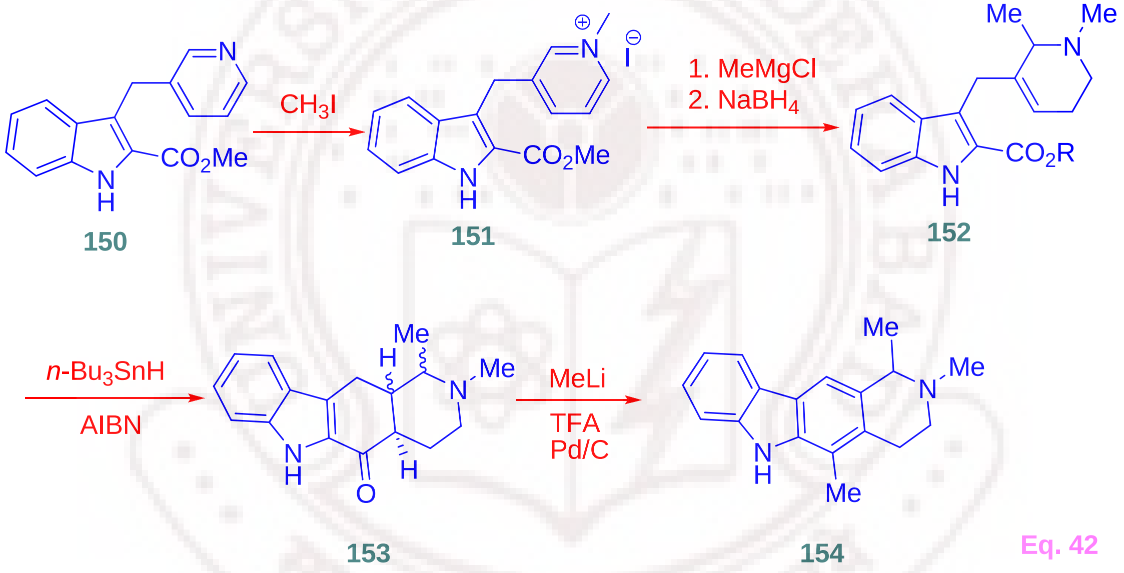
Similarly, the structurally related aryl- and heteroaryl annulated carbazoles have also received considerable synthetic attention.[157-158] Despite the great interest that has given rise to much synthetic work on ellipticine and its derivatives, very little attention has been focused on the synthesis of its isomers and fused with other biologically important molecules.[159] Some of the recent methods have given below.

Archer and co-workers[160] developed a facile methodology for the synthesis of pyridocarbazole derivatives using microwave irradiation (**Eq. 41**).



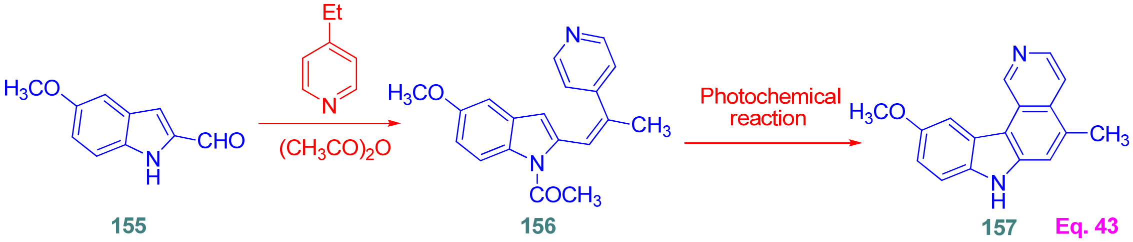
Eq. 41

Bennasar and co-workers[161] reported a regioselective 6-endo reductive cyclization of 2-indolylacyl radicals constitutes the key step of a straightforward synthetic entry to the olivacine skeleton, illustrated by a total synthesis of the tetrahydropyridine alkaloid guatambuine **154** (**Eq. 42**).



Eq. 42

A simple methodology for the synthesis of pyridocarbazole derivatives in good yields by using photochemical reaction as the key step as shown **Eq. 43** was developed by Roques and co-workers.[162]



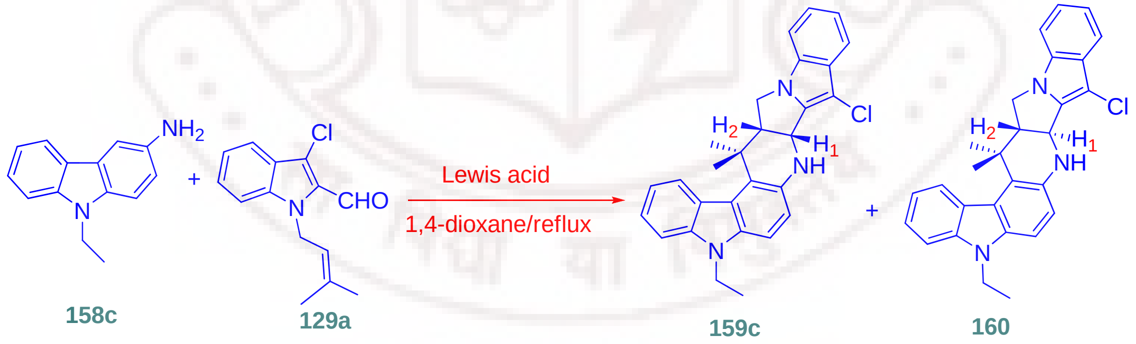
Eq. 43

Although a variety of reports are available for the synthesis, most of these methods required harsh reaction conditions and large number of steps involved for preparation of requisite starting materials. Still, general and facile synthetic approaches are required to obtain analogues for pharmacological evaluation.

3.1. Synthesis of polycyclic pyridocarbazole derivatives through intramolecular imino Diels-Alder reaction

Annulation processes have proven quite valuable in organic synthesis because of the ease with which a variety of complicated hetero- and carbocycles can be rapidly constructed.[163] We have thus focused our attention towards the construction of the polycyclic isomeric ellipticine ring systems employing the cycloaddition of imine derived from *N*-prenylated-2-formyl-3-chloroindole (**129a**) with 9-ethyl-3-aminocarbazole in 1,4-dioxane at reflux temperature, underwent intramolecular [4+2] cycloaddition in the presence of a Lewis acid to yield 9-chloro-5-ethyl-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5′,6′]pyrrolizino[2′,1′:5,6]pyrido[2,3-*c*]carbazoles (**159c** and **160**) as a mixture of diastereomers, where the *cis* isomer (**159c**) is the major product (**Scheme 22**).

Scheme 22



The products were confirmed by IR, ^1H NMR (spectrum 13 for compound **159c**), ^{13}C NMR (spectrum 14 for compound **159c**), LCMS, and elemental analysis. In the case of **159c**, the IR spectrum showed the *NH* stretching frequency at 3398 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 8.41. Proton NMR showed the aromatic proton signals in the range between δ 7.09-7.66. Two methyl peaks observed as singlets at δ 1.96 and 1.98. Mass spectrum of the compound **159c** showed the molecular ion peak m/z at 438 in positive mode.

The diastereomers were readily separated by column chromatography on silica gel, and their stereochemistry was assigned based on the coupling constant values and also by NOE studies. The five-membered pyrrolidine and six-membered tetrahydro pyridine rings were *cis* fused, as indicated by the coupling constant $J_{1\text{-}2}$ = 7.2 Hz between H_1 (δ 4.79) and H_2 (δ 3.12) in product **159c** and also the strong NOE (34 %) enhancement of H_2 upon irradiation of H_1. The high coupling constant, $J_{1\text{-}2}$ = 10.6 Hz between H_1 (δ 4.68) and H_2 (δ 2.93) supported the *trans* configuration the structure of product **160** and there was no considerable NOE between these two protons. The stereochemistry of the *trans* isomer was also confirmed by single crystal X-ray diffraction analysis (**Fig. 27**).

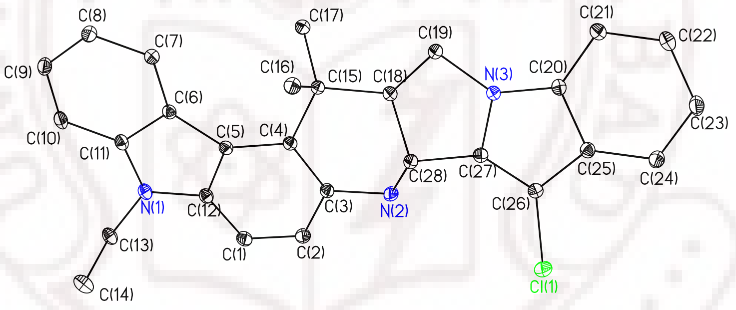


Figure 27. ORTEP diagram of compound **160**

The reactions proceed smoothly in the presence of Lewis acids or Brønsted acids, but diastereoselectivity depends on the nature of the catalyst (**Table 23**). However, the *cis* diastereomer is always the major product. When acidic polymer catalysts (Entry 1 and 4) used, yields were low even after 24 hours reflux. However, the use of Montmorillonite K10 clay as a catalyst gave only 33 % yield of the desired product with almost equal dr ratio (Entry 2). Using 20 mol % of *N*-Boc L-proline afforded the desired product only 40 % yield but with good diastereoselectivity after 96 hours reflux (Entry 3).

Table 23. Effects of various Lewis acids or Brønsted acids

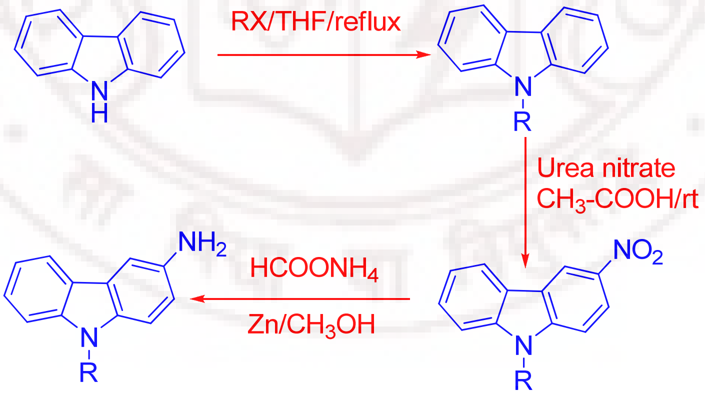
Entry	Catalyst	Time (h)	dr ratio	Yield (%)[a]
1	Amberlite IR 120 (0.1 g)	24	60:40	30
2	Montmorillonite K10 (0.1 g)	24	55:45	33
3	*N*-Boc L-proline (20 mol %)	96	90:10	40
4	Dowex 20-50 mesh (0.1 g)	24	54:46	47
5	$LiClO_4$ (20 mol %)	24	71:29	48
6	Salen $(Mn)H_2$ (20 mol %)	24	89:11	49
7	BF_3-OEt_2 (20 mol %)	24	68:32	51
8	CF_3-COOH (20 mol %)	24	62:38	60
9	CAN (20 mol %)	24	74:26	65
10	$BiCl_3$ (20 mol %)	24	77:23	70
11	Molecular Iodine (20 mol %)	48	71:29	71
12	$InCl_3$ (20 mol %)[b]	24	84:16	82
13	$[Bmim][BF_4]$[c]	24	70:30	80
14	$[Bmim][PF_6]$[c]	24	75:25	85
15	$PPh_3.HClO_4$ (20 mol %)	24	77:23	70
16	$PPh_3.CF_3SO_3H$ (20 mol %)	24	73:27	75
17	$In(OTf)_3$ (10 mol %)	20	87:13	83
18	$Sc(OTf)_3$ (10 mol %)	12	87:13	85
19	$Yb(OTf)_3$ (10 mol %)	12	88:12	85
20	$La(OTf)_3$ (10 mol %)	12	91:09	87
21	$La(OTf)_3$ (10 mol %)[d]	12	94:06	85
22	**$La(OTf)_3$ (10 mol %)[e]**	**10**	**97:03**	**88**

[a] Reactions were carried out at 100 °C, and isolated yields are reported. [b] The temperature was 50 °C; above this temperature, side products were formed. [c] 0.5 g of ionic liquid was used as solvent as well as catalyst. [d] The temperature of the reaction was 130-140 °C. [e] The temperature of the reaction was 150-160 °C.

Brønsted acid such as, CF_3-COOH gave **159c** in 60 % yield with 62:38 diastereoselectivity (Entry 8). The use of CAN (20 mol %) afforded 65 % yield with 74:26 diastereoselectivity after 24 hours reflux. Surprisingly, 20 mol % of $InCl_3$ produced 82 % yield after 24 hours reflux with good diastereoselectivity. Ionic liquids, such as [Bmim][BF_4] and [Bmim][PF_6] gave product in 80 % and 85 % yields, respectively (Entries 13 and 14). TPPP (20 mol %) gave 70 % yield with 77:23 diastereoselectivity after 24 hours reflux. Our previous work has shown that transition metal triflate La$(OTf)_3$ usually work better for [4+2] cycloaddition.

Several catalysts were screened and among them, Sc$(OTf)_3$, Yb$(OTf)_3$ and La$(OTf)_3$ were found to be better since they provided excellent diastereoselectivity and also have similar reactivity in terms of reaction yield, diastereomer ratio and reaction time. The diastereoselectivity was further improved by maintaining the reaction at 130-140 ^oC or 150-160 ^oC with La$(OTf)_3$ (10 mol %) as catalyst. Further increase in temperature did not improved the diastereomer ratio with the other catalysts listed in **Table 23**, except for Sc$(OTf)_3$ and Yb$(OTf)_3$. After several experiments, we found that good yield and excellent diastereoselectivity were obtained when the reaction was carried out in 1,4-dioxane at 150-160 ^oC. We have also explored effects of different solvents. The reaction was faster in 1,4-dioxane than CH_3CN and THF. Moderate yields were obtained with DMSO or toluene as the solvent.

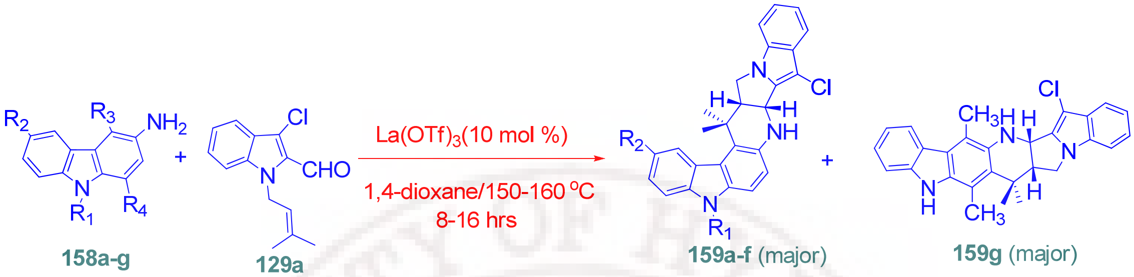
Scheme 23



Application of this methodology, with subsequent functional group manipulations, to the synthesis of new pyrroloindole fused isoellipticine derivatives, is now described in this chapter. Different substituted aminocarbazoles (**158a-g**) were prepared from carbazole (**Scheme 23**). Different substituted carbazoles[164] and nitrocarbazoles[165] were prepared with a simple procedure. Reduction of nitrocarbazoles were achieved with Zn/$HCOONH_4$ with suitable solvent.[166]

We have carried out the imino Diels-Alder reaction of **129a** with various substituted amines (**158a-g**) in the presence of La(OTf)$_3$ (10 mol %) under the optimized conditions (**Scheme 24**) and the results are summarized in **Table 24**.

Scheme 24



The reaction of 3-aminocarbazole (**158a**) and **129a** afforded 86 % yield of the expected product 9-chloro-16,16-dimethyl-5,8,8a,15,15,16-hexahydrobenzo-[5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (**159a**) with 97:03 diastereoselectivity. The X-ray crystal structure of **159a** was elucidated in **Fig. 28**.

Table 24. The imino Diels-Alder reaction of various amines (**158a-g**) with **129a** in the presence of La(OTf)$_3$ (10 mol %)

Entry	R$_1$	R$_2$	R$_3$	R$_4$	Amine	Product	Time (h)	Yield (%)	dr ratio
1	H	H	H	H	**158a**	**159a**	12	86	97:03
2	CH$_3$	H	H	H	**158b**	**159b**	10	89	99:01
3	C$_2$H$_5$	H	H	H	**158c**	**159c**	10	88	97:03
4	C$_6$H$_5$CH$_2$	H	H	H	**158d**	**159d**	8	90	96:04
5	C$_2$H$_5$	Br	H	H	**158e**	**159e**	12	85	94:06
6	C$_2$H$_5$	CH$_3$	H	H	**158f**	**159f**	10	92	96:04
7	H	H	CH$_3$	CH$_3$	**158g**	**159g**	16	51	90:10

In most cases, the corresponding imino Diels-Alder products **159a-f** were obtained in excellent yields with good diastereoselectivity (**Table 24**, entries 1-6). The fact that the amine **158g**, having a substituent on first and fourth position ($R_3 = R_4 = CH_3$), has the slower rate of reaction and the corresponding product **159g** was obtained in only 51 % yield. This may be due to the steric hindrance of two methyl substituents (Entry 7).

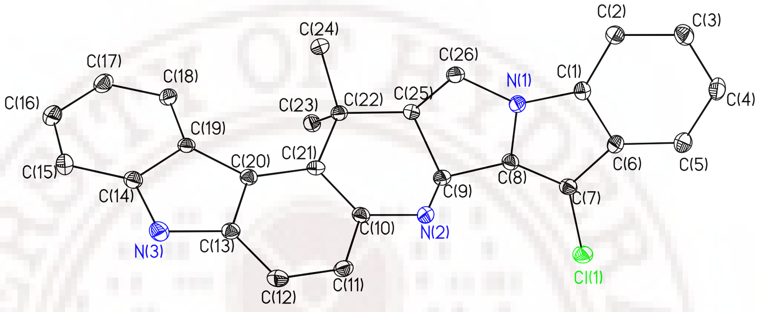
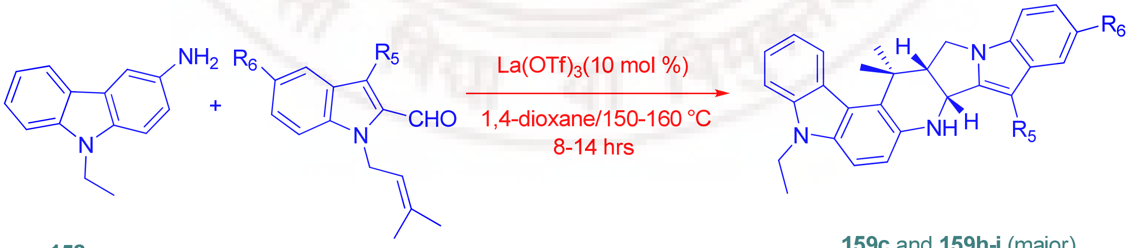


Figure 28. ORTEP diagram of compound **159a**

We, next carried out the imino Diels-Alder reaction of **158c** with prenylated indole-2-aldehydes (**129a-b**, **129d** and **129f**) in the presence of $La(OTf)_3$ (10 mol %) under the optimized conditions (**Scheme 25**).

Scheme 25



158c

129a-b, 129d and 129f

159c and 159h-j (major)

The results are summarized in **Table 25**. In all cases, the corresponding cycloaddition products (**159c** and **159h-j**) were obtained in excellent yields (**Table 25**). The electron donating or electron-withdrawing substituents (R_5 and R_6) did not significantly affect the reaction rate. The X-ray crystal structures of **159h-j** were obtained to confirm their structures (**Figs. 29-31**).

Table 25. Synthesis of isomeric ellipticine derivatives with different substituted aldehydes

Entry	Aldehyde	Product	Time (h)	Yield (%)	dr ratio
1	**129a**	**159c**	10	88	97:03
2	**129b**	**159h**	14	85	98:02
3	**129d**	**159i**	8	93	97:03
4	**129f**	**159j**	8	92	95:05

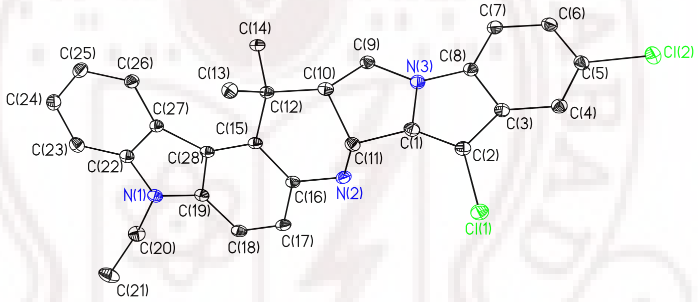


Figure 29. ORTEP diagram of compound **159h**

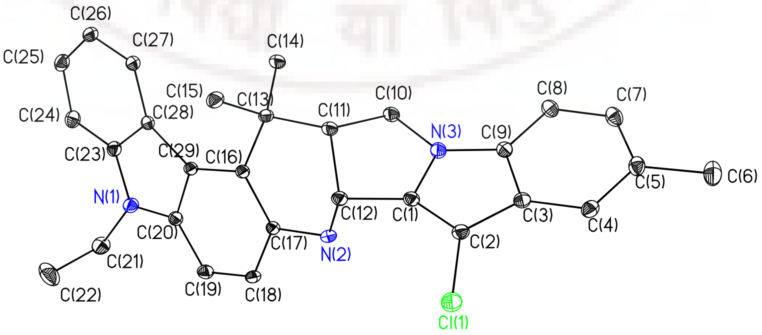
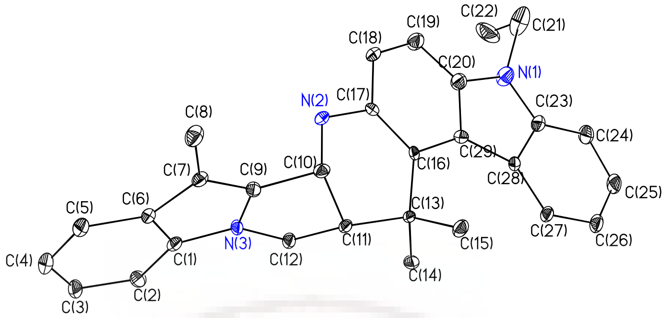


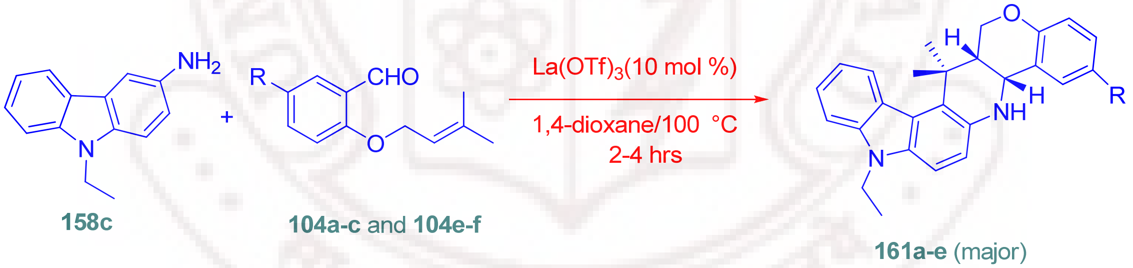
Figure 30. ORTEP diagram of compound **159i**

Figure 31. ORTEP diagram of compound **159j**



In this reaction, depending on the choice of aldehyde, a large variety of novel heterocyclic systems can be generated. To prove the generality of this reaction, we have also examined the reactions of *O*-prenylated salicylaldehydes (**104a-c** and **104e-f**) with aminocarbazole (**158c**) under the same reaction conditions and the corresponding chromene fused isoellipticine derivatives were obtained (**Scheme 26**).

Scheme 26



The cycloaddition of **158c** with **104a** at 100 °C proceeded efficiently in 1,4-dioxane to afford 8-ethyl-13,13-dimethyl-4b,5,8,13,13a,14-hexahydrochromeno [3',4':5,6]pyrido[2,3-*c*]carbazole (**161a**) in excellent yield (88 %, **Table 26**) with higher diastereoselectivity ratio; the *cis* isomer is the major product. Increase in temperature further decreases the reaction yield. The structure of the product was confirmed by IR, ^{1}H NMR (spectrum 15 for **161a**), ^{13}C NMR (spectrum 16 for **161a**), LCMS, and elemental analysis. The IR spectrum of **161a** showed the *NH* stretching frequency at 3391 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 7.99. Proton NMR showed the aromatic proton signals in the range between δ 6.89-

7.46. Two methyl peaks observed as singlets at δ 1.77 and 1.79. Mass spectrum of the compound **161a** showed the molecular ion peak m/z at 383 in positive mode.

Table 26. The reaction of **158c** with various substituted aldehydes

Entry	R	Aldehyde	Product	Time (h)	Yield (%)	dr ratio
1	H	**104a**	**161a**	3	88	97:03
2	Cl	**104b**	**161b**	2	92	95:05
3	Br	**104c**	**161c**	2	93	97:03
4	CH_3	**104e**	**161d**	4	85	98:02
5	OCH_3	**104f**	**161e**	4	85	98:02

In the case of products derived from **104c**, both *cis* (**161c**) and *trans* (**162**) isomers were separated; their structures were also confirmed by single crystal X-ray analysis (**Fig. 32**, **161c**). The results are summarized in **Table 26**. When electron withdrawing groups present on aldehyde, yields are excellent (Entries 2-3, 92-93 %) where as electron donating groups present, yields are comparatively less (Entries 4-5, 85 %). But all the cases diastereoselectivity is more than 95 %. We have also obtained single crystal for the compound **161d** further to confirm the molecular structure (**Fig. 33** for ORTEP diagram).

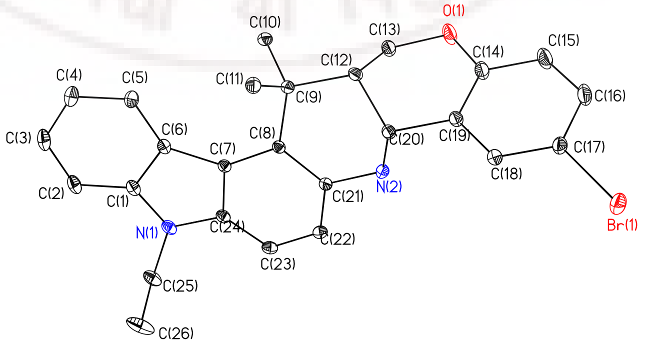
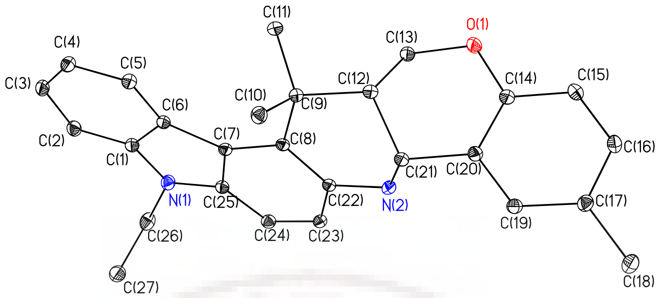


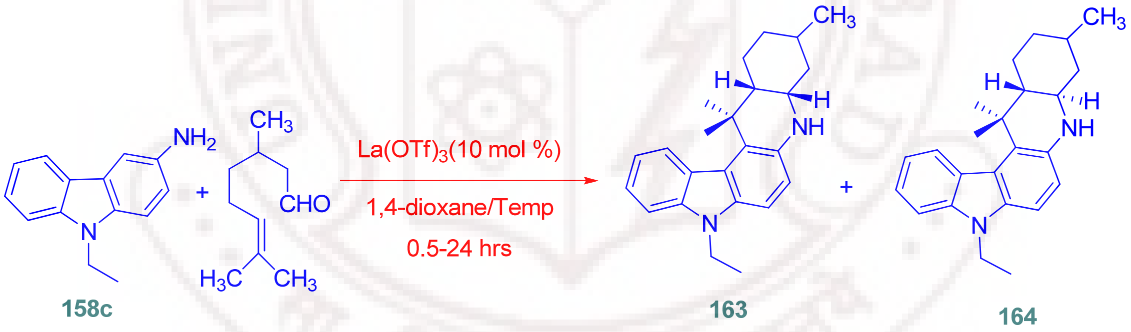
Figure 32. ORTEP diagram of compound **161c**

Figure 33. ORTEP diagram of compound **161d**



We have also examined the imine derived from aliphatic aldehyde (citronellal) as a dienophile, and the reaction proceeded very smoothly and afforded 8-ethyl-3,13,13-trimethyl-2,3,4,4a,5,8,13,13a-octahydro-1*H*-indolo[3,2-*a*]acridine as a *cis* and *trans* isomers (**163** and **164**) with good yield (**Scheme 27**).

Scheme 27



The structure of the products (**163** and **164**) were confirmed by IR, ^{1}H NMR (spectrum 17 for compound **164**), ^{13}C NMR (spectrum 18 for compound **164**), LCMS, and elemental analysis. In the case of **163**, the IR spectrum showed the *NH* stretching frequency at 3387 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 8.29. Proton NMR showed the aromatic proton signals in the range between δ 6.76-7.39. Mass spectrum of the compound **163** showed the molecular ion peak m/z at 347 in positive mode. We have also obtained single crystals for the compounds **163** and **164** further confirmed the structures by single crystal X-ray data (**Fig. 34** for ORTEP diagram of **163**).

Figure 34. ORTEP diagram of compound **163**

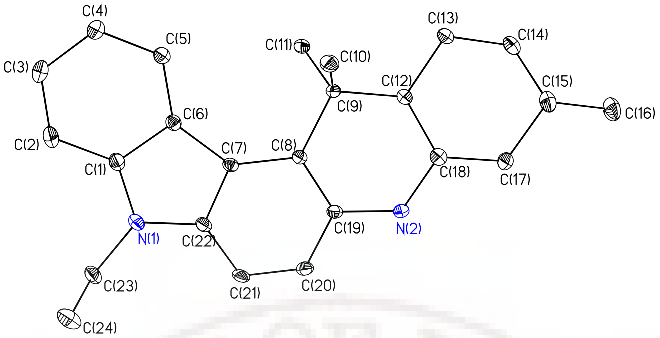


Table 27. The imino Diels-Alder reaction of **158c** with aliphatic aldehyde

Entry	Temp (°C)	Time (h)	Yield (%)	dr ratio
1	150-160	0.5	97	47:53
2	100	1.0	95	40:60
3	RT	6.0	91	21:79
4	0	12.0	90	15:85
5	**-50**	**24.0**	**95**	**10:90**

Interestingly, the *trans* isomer is the major product (**164**). The diastereoselectivity dramatically changes with respect to temperature. At 150-160 °C, almost equal ratio of diastereomers with 97 % yield was observed (Entry 1). At room temperature *trans* diastereomer ratio increased with increased time (6 h). That means, better diastereoselectivity was obtained at lower temperature (**Table 27**). Further decrease in temperature (0 °C) gave 15:85 diastereoselectivity after 12 hours stirring. At -50 °C, reaction proceeded with 10:90 diastereoselectivity in THF solvent with 95 % yield.

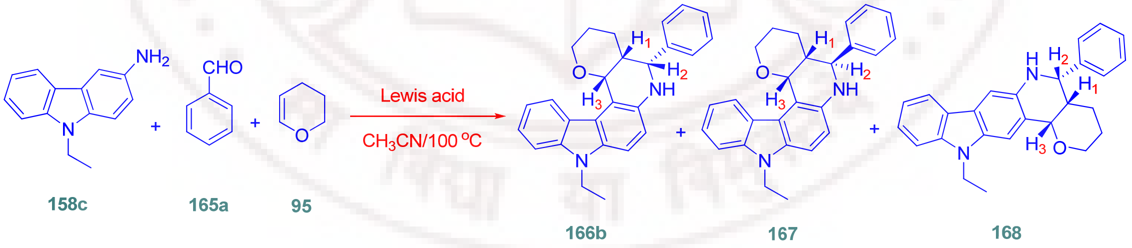
In conclusion, we described a useful method for the preparation of various polycyclic isomeric ellipticine derivatives or isomeric ellipticine derivatives fused with biologically important pyrroloindole or chromene moiety, utilizing a novel [4+2] cycloaddition reaction.

3.2. Synthesis of pyridocarbazole derivatives through intermolecular imino Diels-Alder reaction

After developing a simple intramolecular imino Diels-Alder methodology for the synthesis of polycyclic isoellipticine derivatives or isoellipticine fused pyrroloindole and chromene derivatives, we have directed our attention towards the synthesis of these derivatives through intermolecular imino Diels-Alder fashion. For that imines derived from substituted benzaldehydes and 3-aminocarbazoles are excellent substrates for an intermolecular imino Diels–Alder reaction with electron-rich dienophiles catalyzed by $InCl_3$ (10 mol %) in $[Bmim][BF_4]$ to provide highly functionalized isomeric ellipticine derivatives with high diastereoselectivity.

Construction of the polycyclic isomeric ellipticine ring systems employing the cycloaddition of imine derived from 9-ethyl-3-aminocarbazole (**158c**) and benzaldehyde (**165a**) in $[Bmim][BF_4]$ at 100 °C underwent an intermolecular [4+2] cycloaddition reaction with 3,4-dihydro-2*H*-pyran (**95**) in the presence of Lewis acid to yield 9-ethyl-5-phenyl-2,3,4,4a,5,6,9,13d-octahydropyrano[20,30:4,5]pyrido [2,3-*c*]carbazole (**166b** and **167**) as a mixture of diastereomers, where the *cis* isomer (**166b**) is the major product along with regioisomer **168** (**Scheme 28**).

Scheme 28



The diastereomers were readily separated by column chromatography on silica gel, and their stereochemistry was assigned based on the coupling constant values, NOE and also by 2D NOESY studies. The tetrahydro pyran and six-membered tetrahydro pyridine rings were *cis* fused, as indicated by the coupling constant $J_{1\text{-}2}$ = 2.3 Hz between H_1 (δ 2.39) and H_2 (δ 4.58); $J_{1\text{-}3}$ = 5.7 Hz between H_1 and H_3 (δ 5.85) in product **166b**. The strong NOE (18 %) enhancement of H_1 upon irradiation of H_3 and NOE (15 %) between H_1 and H_2 confirm that these three protons are *cis* to each other. The structure of this molecule was confirmed by IR, ^{1}H NMR (spectrum 19 for compound **166b**), ^{13}C NMR (spectrum 20 for compound **166b**), LCMS, and elemental analysis. 2D NOESY also supports this stereochemistry (spectrum 21). The IR spectrum of **166b** showed the *NH* stretching frequency at 3369 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 8.61. Proton NMR showed the aromatic proton signals in the range between δ 6.81-7.46. Mass spectrum of the compound **166b** showed the molecular ion peak m/z at 383 in positive mode. The stereochemistry of this isomer (**166b**) was also confirmed by single crystal X-ray diffraction analysis (**Fig. 35**).

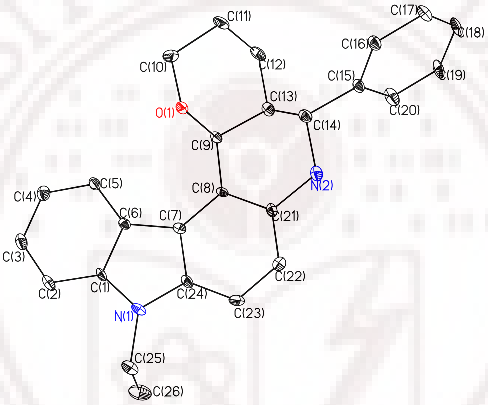


Figure 35. ORTEP diagram of compound **166b**

In the case of **167**, J_{3-1} = 3.5 Hz between H$_3$ (δ 5.21) and H$_1$ (δ 2.28) show *cis* coupling but J_{1-2} = 15.2 Hz where H$_2$ (δ 4.82) are *trans* and NOE also confirms that H$_{3-1}$ are *cis* to each other and H$_{1-2}$ are in *trans*. 2D NOESY also supports this stereochemistry (spectrum 22). This *trans* isomer (**167**) is ultimately confirmed by single crystal X-ray analysis. In the case of regio isomer **168**, The tetrahydro pyran and tetrahydro pyridine rings were *cis* fused, by showing the coupling constant J_{1-2} = 2.4 Hz between H$_1$ (δ 2.27) and H$_2$ (δ 4.73); J_{1-3} = 4.9 Hz between H$_1$ and H$_3$ (δ 5.56) in product **168**. The strong NOE (13 %) enhancement of H$_1$ upon irradiation of H$_3$ and NOE (12 %) between H$_1$ and H$_2$ confirm that these three protons are *cis* to each other. 2D NOESY also supports this stereochemistry. The structure of **168** was confirmed by IR, ^{1}H NMR (spectrum 23 for compound **168**), ^{13}C NMR (spectrum 24 for compound **168**), LCMS, and elemental analysis. The IR spectrum of **168** showed the *NH* stretching frequency at 3381 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 7.97. Proton NMR showed the aromatic proton signals in the range between δ 7.14-7.52. Mass spectrum of the compound **168** showed the molecular ion peak m/z at 383 in positive mode. The stereochemistry of this isomer (**168**) was also confirmed by single crystal X-ray diffraction analysis (**Fig. 36**).

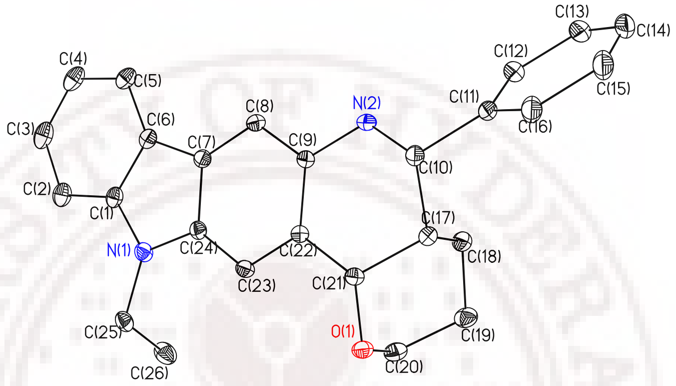


Figure 36. ORTEP diagram of compound **168**

The reactions proceed smoothly in the presence of Lewis acids or Brønsted acids, but diastereoselectivity depends on the nature of the catalyst (**Table 28**). In all cases *cis* diastereomer **166b** is the major product. Surprisingly, we have also observed a minor product **168**, which occurs through cyclization with the second position of aminocarbazole.

In the first attempt, the reaction of **158c**, **95** and benzaldehyde (**165a**) was performed in CH_3CN with BF_3-OEt_2 as a catalyst at reflux temperature (**Table 28**, Entry 1) gave only 65 % yield after 24 hours reflux with three isomers. Interestingly with CAN (20 mol %) obtained 86 % yield within 12 hours (Entry 3). Lower yields and longer reaction time are observed in [Bmim][BF_4], without the catalyst (Entry 4). When 10 mol % of $InCl_3$ was added along with ionic liquid, yield was randomly increased to 76 % at room temperature (Entry 5). Then we started increasing the temperature from room temperature to 100 °C, yield raised to 90 % with only two isomers (Entry 5-9). Among the catalysts screened, $InCl_3$ and

$La(OTf)_3$ were found to be better in $[Bmim][BF_4]$. However, compared to $InCl_3$, $La(OTf)_3$ gives a low yield (80 %) and requires a longer reaction time (2 hours). The positive role of indium chloride in the imino Diels–Alder reaction was reported earlier.[167] After the addition of $InCl_3$ (10 mol %), the reaction rate is faster and better diastereoselectivity is observed at 100 °C. Ionic liquids having the counter ion $[PF_6^-]$ have a lower yield as compared with $[BF_4^-]$. Further increase in the temperature did not improve the regioisomer ratio.

Table 28. Optimization of reaction conditions

Entry	Catalyst	Time (h)	Yield (%)	dr ratio (166b:167:168)
1	BF_3-OEt_2 (20 mol %)	24	65	62:23:15
2	CF_3-COOH (20 mol %)	24	70	67:17:16
3	CAN (20 mol %)	12	86	83:11:06
4	$[Bmim][BF_4]$	24	41	61:29:10
5	$[Bmim][BF_4]$/ $InCl_3$/ rt	24	76	77:20:03
6	$[Bmim][PF_6]$/ $InCl_3$/ rt	24	72	74:22:04
7	$[Bmim][BF_4]$/ $InCl_3$/ 50 ºC	12	81	70:25:05
8	$[Bmim][BF_4]$/ $InCl_3$/ 70 ºC	05	85	77:19:04
9	**$[Bmim][BF_4]$/ $InCl_3$/ 100 °C**	**01**	**90**	**78:22:00**
10	$[Bmim][BF_4]$/ $La(OTf)_3$/ 100 ºC	02	80	76:24:00

Extending this methodology further, we have carried out the imino Diels–Alder reaction with various substituted amines in the presence of $InCl_3$ (10 mol %) under optimized conditions (**Scheme 29**). The results are summarized in **Table 29**. In most cases, the corresponding imino Diels–Alder products **166a–c** were obtained in good yields (**Table 29**). But in the case of **166c**, having substituents on the first and fourth positions ($R_2 = R_3 = CH_3$), the corresponding product (**166c**) was obtained in only 71 % yield, and this may be due to the steric hindrance caused by the methyl groups. The X-ray crystal structure of (**166c**) is presented in **Fig. 37**.

Scheme 29

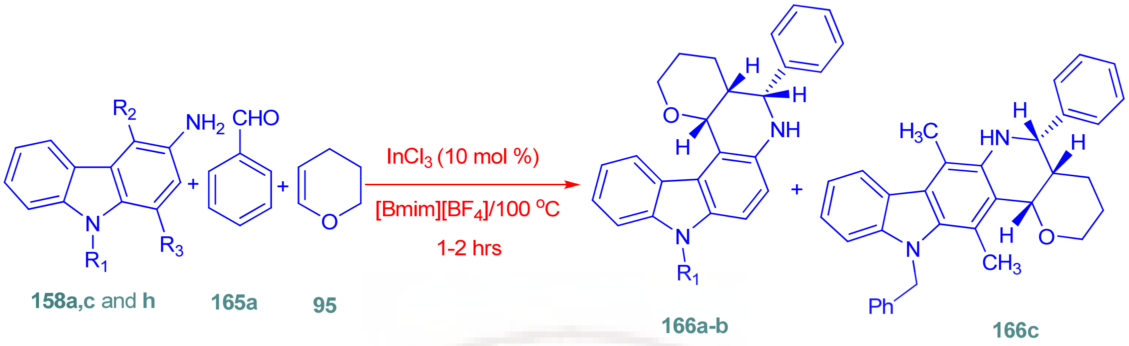


Table 29. The intermolecular imino Diels-Alder reaction of various aminocarbazoles

Entry	R_1	R_2	R_3	Amine	Product	Time (h)	Yield (%)	dr ratio
1	H	H	H	**158a**	**166a**	2	89	95:05
2	C_2H_5	H	H	**158c**	**166b**	1	90	78:22
3	$C_6H_5CH_2$	CH_3	CH_3	**158h**	**166c**	2	71	93:07

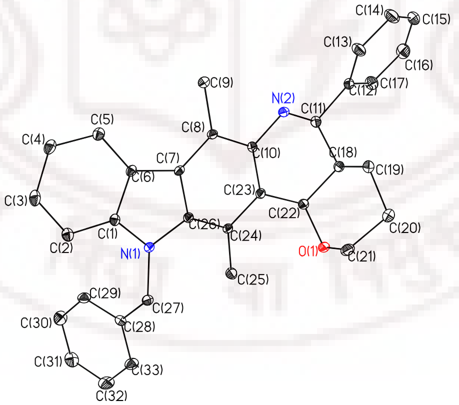
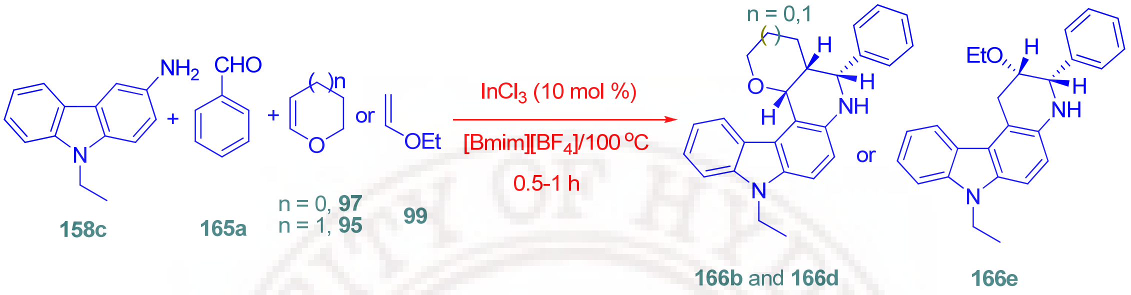


Figure 37. ORTEP diagram of compound **166c**

To prove the generality of the reaction, we have checked the different electron-rich dienophiles in this reaction (**Scheme 30**). 2,3-Dihydrofuran undergoes a cycloaddition reaction with electron deficient dienes generated from 9-

ethyl-3-aminocarbazole (**158c**) and benzaldehyde to give 8-ethyl-4-phenyl-3,3a,4,5,8,12d-hexahydro-2*H*-furo[2',3':4,5]pyrido[2,3-*c*]carbazole (**166d**) in 85 % yield with 97:03 diastereoselectivity (**Table 30**).

Scheme 30



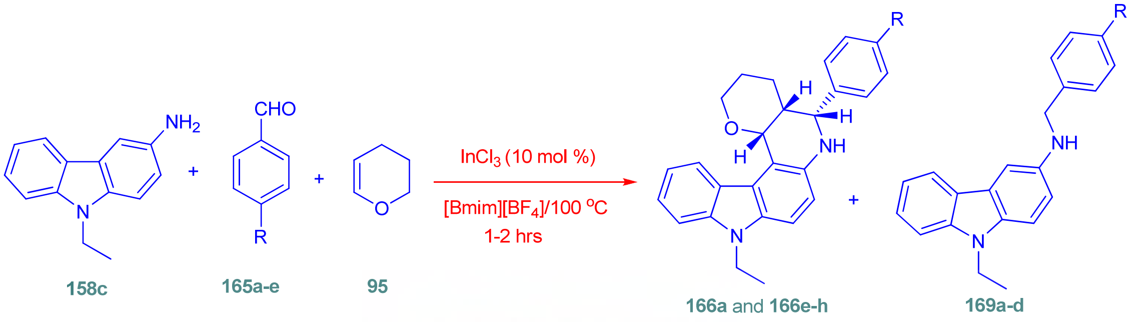
The structures of the products were confirmed by IR, ^{1}H NMR (spectrum 25 for **166d**), ^{13}C NMR (spectrum 26 for **166d**), LCMS, and elemental analysis. The IR spectrum of **166d** showed the *NH* stretching frequency at 3431 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 8.25. Proton NMR showed the aromatic proton signals in the range between δ 6.78-7.55. Mass spectrum of the compound **166d** showed the molecular ion peak m/z at 369 in positive mode. Other electron-rich dienophile such as, ethyl vinyl ether (**99**) have participated in this reaction with good yield and high diastereoselectivity (**Table 30**).

Table 30. The intermolecular imino Diels-Alder reaction of various electron-rich dienophiles

Entry	Reactant	Product	Time (h)	Yield (%)	dr ratio
1	**95**	**166b**	1.0	90	78:22
2	**97**	**166d**	0.5	85	97:03
3	**99**	**166e**	0.5	92	96:04

We have also examined the reactions of substituted benzaldehydes (**165a-e**) under the same reaction conditions to prove the generality of the reaction (**Scheme 31**) and the results are summarized in **Table 31**.

Scheme 31



The reaction of 4-chlorobenzaldehyde (**165b**) with 9-ethyl-3-aminocarbazole (**158c**) and 3,4-dihydro-2*H*-pyran (**95**) in the presence of $InCl_3$ (10 mol %) in ionic liquid afforded 5-(4-chlorophenyl)-9-ethyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole (**166f**) and also surprisingly reductive amination product *N*3-(4-chlorobenzyl)-9-ethyl-9*H*-3-carbazolamine (**169a**) as a side product. The structure of reductive amination product (**169a**) was confirmed by IR, ^1H NMR (spectrum 27), ^{13}C NMR (spectrum 28), LCMS, and elemental analysis. The IR spectrum of **169a** showed the *NH* stretching frequency at 3416 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 7.95. Proton NMR showed the aromatic proton signals in the range between δ 6.83-7.39 and CH_2 peak shows the δ value at 4.25. Mass spectrum of the compound **169a** showed the molecular ion peak m/z at 335 in positive mode.

Table 31. Synthesis of isomeric ellipticine derivatives with substituted benzaldehydes (**165b-e**).

Entry	R	Reactant	Product	Time (h)	Yield (%)	Reduced Product	Yield (%)
1	**Cl**	**165b**	**166f**	1.0	60	**169a**	21
2	**Br**	**165c**	**166g**	1.5	55	**169b**	25
3	$\mathbf{CH_3}$	**165d**	**166h**	2.0	52	**169c**	40
4	$\mathbf{OCH_3}$	**165e**	**166i**	2.0	48	**169d**	40

With other substituted benzaldehydes (**165c-e**) also reaction proceeded and exhibited both [4+2] cycloaddition products (**166g-i**) and reductive amination products (**169b-d**) were observed (**Table 31**). In the case of electron-rich benzaldehydes (**165d-e**), reaction yields are better compared to electron-deficient benzaldehydes (**165b-c**). In the case of **165e**, reductive amination product (**169d**) was confirmed by single crystal X-ray analysis (**Fig. 38**).

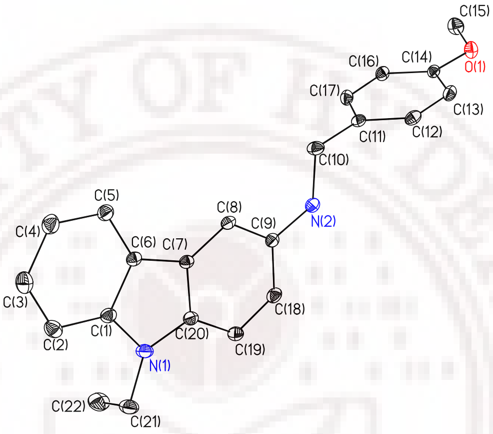


Figure 38. ORTEP diagram of compound **169d**

Same products were obtained in acetonitrile as a solvent without use of ionic liquid and $InCl_3$ as a catalyst (with $La(OTf)_3$ also similar reactivity was observed). This indicates the reductive amination is not happening due to ionic liquid and the catalyst. We assume this reduction may be due to the oxidation of 3,4-dihydro-2*H*-pyran (**95**) since without the use of 3,4-dihydro-2*H*-pyran, no reductive amination was observed. By using larger amount of dihydropyran (10 equiv.), the yield of cycloadduct **166f** improved from 60 % to 88 %. From this observation, we may assume that the excess of 3,4-dihydro-2*H*-pyran decreases the reductive amination and thereby increases the rate of [4+2] cycloaddition. Instead of substituted benzaldehydes, we have also checked with 1-methylindole-2-carboxaldehyde (**165f**) which gave only single product **166j** after 2 hours in 67 % yield under the same reaction conditions. This may be due to steric hindrance and the product (**166j**) was further confirmed by single crystal X-ray analysis (**Fig. 39**).

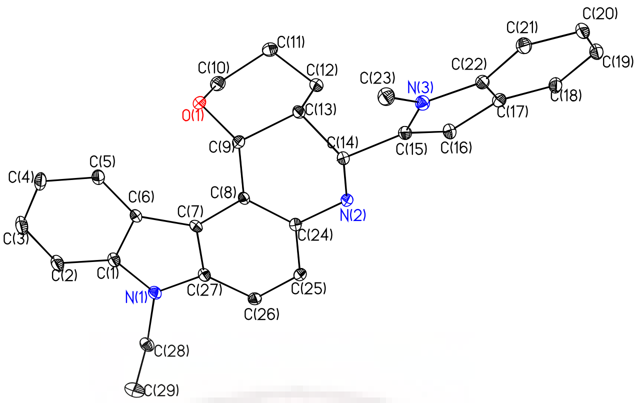


Figure 39. ORTEP diagram of compound **166j**

In summary, we have described a novel and practical method for the synthesis of new isomeric ellipticine derivatives through intermolecular imino Diels–Alder reaction with high diastereoselectivity. This procedure has advantages of high yields, easy availability and flexibility of starting materials, short reaction times and good diastereoselectivity.

3.4. Experimental Section

General procedure E

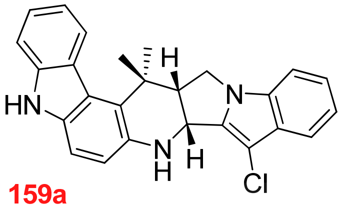
To a stirred solution of aminocarbazole (1.0 mmol) and 2-formyl indole (1.0 mmol) in dry 1,4-dioxane, La(OTf)$_3$ (10 mol %) was added and the reaction mixture was heated to 150-160 ºC for appropriate time. The reaction was monitored by TLC. After completion of the reaction, as indicated by the TLC, the excess solvent was distilled off and the crude reaction mixture was poured over water and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over anhy. Na_2SO_4 and the solvent was removed. The residue was chromatographed silica gel and eluted with hexane-ethyl acetate mixture to afford the corresponding product.

***Cis*-9-chloro-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6'] pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159a)**

The compound was obtained by the reaction of 3-aminocarbazole (**158a**) with **129a** in 1,4-dioxane following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5 % ethyl acetate in hexanes.

Yield: 86 %

IR (KBr) ν_{max} cm^{-1}: 3402, 3047, 2922, 1716, 1616, 1261, 1186, 1089, 933, 800



159a

^{1}H NMR (400 MHz) δ: 8.32 (1H, d, *J* = 8.0 Hz); 7.80 (1H, s); 7.62 (1H, d, *J* = 7.6 Hz); 7.15-7.35 (6H, m); 7.05 (1H, d, *J* = 6.2 Hz); 6.58 (1H, bs); 4.92 (1H, d, *J* = 3.2 Hz); 4.21 (1H, t, *J* = 8.8 Hz); 3.93 (1H, t, *J* = 10.1 Hz); 3.69 (1H, s); 3.06 (1H, bs); 1.90 (3H, s); 1.85 (3H, s)

^{13}C NMR (100 MHz) δ: 141.6, 139.9, 131.8, 128.9, 127.9, 127.3, 125.3, 124.3, 122.9, 122.8, 122.5, 120.2, 120.0, 119.6, 118.5, 117.3, 111.1, 110.2, 109.9, 96.1 (aromatic C), 54.7, 48.9, 47.0, 34.2, 30.2, 26.4 (aliphatic C)

LCMS (m/z): 412 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{22}ClN_3$: C, 75.81; H, 5.38; N, 10.20 %

Found: C, 75.89; H, 5.39; N, 10.21 %

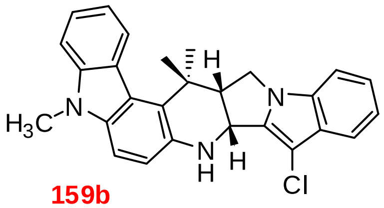
Cis-9-chloro-5,16,16-trimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6'] pyrrolizino [2',1':5,6]pyrido[2,3-*c*]carbazole (159b)

The compound was obtained by the reaction of 9-methyl-3-aminocarbazole (**158b**) with **129a** in 1,4-dioxane following the *general procedure E*. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.

Yield: 89 %

IR (KBr) ν_{max} cm^{-1}: 3414, 3047, 2962, 1728, 1618, 1261, 1190, 1022, 933, 798

^{1}H NMR (400 MHz) δ: 8.34 (1H, d, *J* = 4.9 Hz); 7.58 (1H, d, *J* = 7.8 Hz); 7.09-7.42 (7H, m); 6.62 (1H, bs); 4.90 (1H, bs); 4.23 (2H, bs); 3.76-3.96 (4H, m); 3.10 (1H, bs, N-C*H*$_3$); 1.91 (3H, s); 1.87 (3H, s)



159b

^{13}C NMR (100 MHz) δ: 142.1, 141.7, 131.8, 128.9, 127.7, 127.4, 125.8, 124.7, 122.4, 122.3, 121.7, 120.8, 120.5, 119.8, 118.9, 117.9, 110.2, 109.9, 109.3, 97.1 (aromatic C), 57.8, 46.9, 41.1, 34.1, 30.4, 24.9, 21.1 (aliphatic C)

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

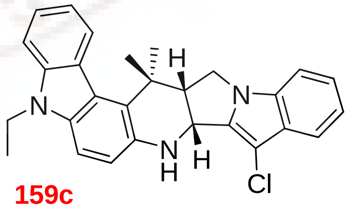
Anal. Calcd. for $C_{27}H_{24}ClN_3$: C, 76.13; H, 5.68; N, 9.86 %

Found: C, 76.14; H, 5.70; N, 10.13 %

Cis-9-chloro-5-ethyl-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo [5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159c)

Obtained **159c** by treating with **158c** and **129a** in 1,4-dioxane in the presence of 10 mol % La(OTf)$_3$ following the *general procedure E*. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 88 %



159c

IR (KBr) ν_{max} cm^{-1}: 3398, 3045, 2972, 2897, 1616, 1267, 1195, 1086, 923, 794

^{1}H NMR (400 MHz) δ: 8.41 (1H, d, *J* = 8.2 Hz); 7.66 (1H, d, *J* = 7.7 Hz); 7.46 (2H, t, *J* = 7.8 Hz); 7.17-7.25 (5H, m); 7.09 (1H, d, *J* = 7.2 Hz); 4.79 (1H, d, *J* = 7.2 Hz); 4.36-4.51

(4H, m); 4.13 (1H, t, *J* = 10.1 Hz); 3.12 (1H, q, *J* = 7.6 Hz); 1.98 (3H, s); 1.96 (3H, s); 1.47 (3H, t, *J* = 8.0 Hz, N-$CH_2C\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 140.3, 138.1, 137.1, 136.2, 132.2, 127.2, 126.6 124.7, 122.3, 121.3, 120.3, 119.9, 118.7, 118.4, 117.8, 110.4, 109.9, 108.9, 108.7, 97.4 (aromatic C), 62.0, 51.5, 44.1, 37.6, 35.7, 28.1, 24.6, 13.8 (aliphatic C)

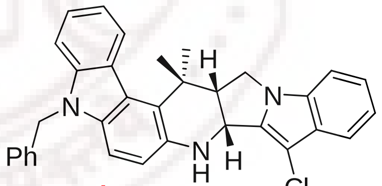
LCMS (m/z): 438 $(M+H)^+$

Anal. Calcd. for $C_{28}H_{26}ClN_3$: C, 76.44; H, 5.96; N, 9.55 %

Found: C, 76.43; H, 5.99; N, 9.87 %

Cis-14-chloro-5-benzyl-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159d)

Reaction of **158d** in the presence of La(OTf)$_3$ with **129a** in 1,4-dioxane following the *general procedure E* provided the title compound as a white solid. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.



159d

Yield: 90 %

Mp: 124 °C

IR (KBr) ν_{max} cm^{-1}: 3402, 3059, 2924, 1722, 1651, 1267, 1151, 1089, 925, 796

^{1}H NMR (400 MHz) δ: 8.41 (1H, bs); 7.61 (1H, d, *J* = 7.6 Hz); 7.10-7.38 (12H, m); 6.62 (1H, bs); 5.45-5.52 (2H, m); 4.94 (1H, bs); 4.26 (1H, bs); 3.97 (1H, t, *J* = 9.8 Hz); 3.72 (1H, bs); 3.10 (1H, bs);1.96 (3H, s); 1.91 (3H, s)

^{13}C NMR (100 MHz) δ: 141.5, 141.2, 137.4, 136.2, 136.0, 132.4, 128.9, 128.8, 128.6, 127.4, 126.3, 126.1, 124.7, 122.5, 121.7, 120.5, 119.8, 118.8, 117.9, 115.7, 110.3, 109.9, 108.9, 108.6, 96.5 (aromatic C), 57.8, 46.9, 46.4, 34.1, 30.4, 26.9, 24.9 (aliphatic C)

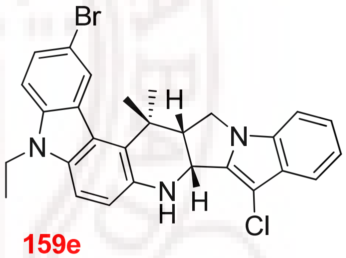
LCMS (m/z): 501 $(M+H)^+$

Anal. Calcd. for $C_{33}H_{28}ClN_3$: C, 78.95; H, 5.62; N, 8.37 %

Found: C, 78.88; H, 5.65; N, 8.35 %

Cis-2-bromo-9-chloro-5-ethyl-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159e)

The pyrroloindole fused isoellipticine was obtained by the reaction of **158e** with **129a** in the presence of La(OTf)$_3$ (10 mol %) in 1,4-dioxane following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes.



159e

Yield: 85 %

Mp: 242-243 °C

IR (KBr) ν_{max} cm^{-1}: 3408, 3053, 2974, 2922, 1722, 1616, 1205, 1163, 1089, 885

^{1}H NMR (400 MHz) δ: 8.47 (1H, s); 7.62 (1H, d, *J* = 7.8 Hz); 7.49 (1H, d, *J* = 8.6 Hz); 7.10-7.27 (5H, m); 6.69 (1H, d, *J* = 8.3 Hz); 4.94 (1H, bs); 4.23-4.29 (3H, m); 3.93 (1H, t, *J* = 10.0 Hz); 3.74 (1H, s); 3.10 (1H, bs); 1.91 (3H, s); 1.85 (3H, s); 1.37 (3H, t, *J* = 7.08 Hz, N-$CH_2C\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 141.4, 138.8, 136.2, 135.6, 132.4, 128.7, 128.6, 127.1, 123.3, 122.5, 120.3, 119.8, 119.5, 118.8, 116.4, 110.2, 109.9, 109.8, 108.4, 96.5 (aromatic C), 57.7, 53.4, 46.3, 37.4, 34.0, 30.2, 24.9, 13.6 (aliphatic C)

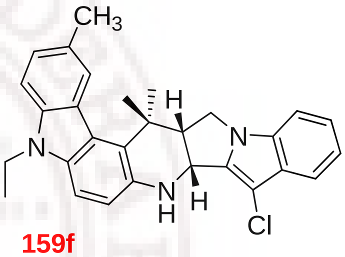
LCMS (m/z): 518 $(M+H)^+$, 520 $(M+2+H)^+$

Anal. Calcd. for $C_{28}H_{25}BrClN_3$: C, 64.81; H, 4.86; N, 8.10 %

Found: C, 64.75; H, 4.85; N, 8.44 %

Cis-9-chloro-5-ethyl-2,16,16-trimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159f)

Obtained as a white colour solid by the reaction of **129a** with **158f** in 1,4-dioxane following the *general procedure E*. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.



159f

Yield: 92 %

Mp: 295-296 °C

IR (KBr) ν_{max} cm^{-1}: 3400, 3053, 2918, 2922, 1716, 1612, 1203, 1153, 1089, 794

^1H NMR (400 MHz) δ: 8.16 (1H, bs); 7.62 (1H, d, *J* = 7.7 Hz); 7.15-7.35 (6H, m); 6.68 (1H, bs); 4.90 (1H, bs); 4.25-4.36 (3H, m); 3.97 (1H, t, *J* = 10.0 Hz); 3.70 (1H, bs); 3.10 (1H, bs); 2.56 (3H, bs, ArC-C$\underline{H}_3$); 1.88 (6H, s); 1.36 (3H, t, *J* = 7.08 Hz, N-$CH_2C\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 141.6, 138.5, 135.6, 132.4, 128.6, 126.9, 126.4, 125.8, 122.4, 121.7, 120.5, 120.0, 119.7, 118.7, 115.5, 109.9, 108.4, 108.1, 107.7, 96.4 (aromatic C), 57.9, 53.4, 46.4, 41.1, 37.6, 34.1, 30.4, 24.9, 13.6 (aliphatic C)

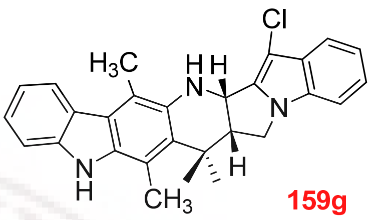
LCMS (m/z): 454 $(M+H)^+$

Anal. Calcd. for $C_{29}H_{28}ClN_3$: C, 76.72; H, 6.22; N, 9.26 %

Found: C, 76.79; H, 6.28; N, 9.25 %

Cis-14-chloro-6,7,7,16-tetramethyl-5,7,7a,8,14b,15-hexahydrobenzo[5',6']pyrrolizino[2',1':5,6]pyrido[3,2-*b*]carbazole (159g)

Obtained by the reaction of **129a** with **158g** in 1,4-dioxane following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 3 % ethyl acetate in hexanes.

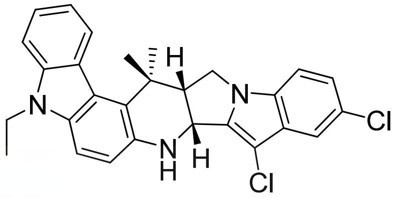


159g

Yield:	51 %
Mp:	172-173 °C
IR (KBr) ν_{max} cm^{-1}:	3429, 3059, 2962, 1722, 1612, 1261, 1151, 1095, 800
^{1}H NMR (400 MHz) δ:	8.22 (1H, d, *J* = 7.8 Hz); 7.72 (1H, s); 7.62 (1H, d, *J* = 7.6 Hz); 7.34-7.41 (2H, m); 7.17-7.24 (4H, m); 4.74 (1H, d, *J* = 10.4 Hz); 4.59 (1H, bs); 4.36 (1H, t, *J* = 8.4 Hz); 4.02 (1H, t, *J* = 10.2 Hz); 3.04 (1H, q, *J* = 7.6 Hz); 2.76 (3H, s, ArC-C$\underline{H}_3$); 2.71 (3H, s, ArC-C$\underline{H}_3$); 1.67 (6H, s)
^{13}C NMR (100 MHz) δ:	140.5, 138.7, 136.2, 135.3, 132.2, 129.9, 129.1, 125.2, 124.2, 122.8, 122.2, 120.9, 119.9, 118.9, 118.4, 116.4, 116.0, 110.5, 109.7, 97.2 (aromatic C), 60.3, 51.7, 44.1, 36.8, 29.5, 25.2, 16.7, 14.0 (aliphatic C)
LCMS (m/z):	440 (M+H)$^+$
Anal. Calcd. for $C_{28}H_{26}ClN_3$:	C, 76.44; H, 5.96; N, 9.55 %
Found:	C, 76.43; H, 5.98; N, 9.54 %

Cis-9,11-dichloro-5-ethyl-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159h)

Obtained **159h** by treating with **158c** and **129b** in 1,4-dioxane in the presence of 10 mol % La(OTf)$_3$ following the *general procedure E*. The crude product was purified by silica gel column chromatography with 2 % ethyl acetate in hexanes.



159h

Yield: 85 %

IR (KBr) ν_{max} cm^{-1}: 3369, 3043, 2972, 2901, 1718, 1614, 1265, 1155, 1091, 796

^{1}H NMR (400 MHz) δ: 8.35 (1H, d, *J* = 8.2 Hz); 7.58 (1H, s); 7.41 (2H, d, *J* = 7.1 Hz); 7.07-7.22 (4H, m); 6.70 (1H, d, *J* = 7.8 Hz); 4.91 (1H, bs); 4.30 (2H, q, *J* = 6.3 Hz, N-C$\underline{H}_2$CH$_3$); 4.19 (1H, t, *J* = 9.1 Hz); 3.95 (1H, t, *J* = 10.1 Hz); 3.70 (1H, bs); 3.07 (1H, bs); 1.92 (3H, s); 1.87 (3H, s); 1.38 (3H, t, *J* = 7.0 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 143.1, 140.3, 135.7, 135.4, 130.8, 129.5, 126.4, 125.7, 124.5, 122.8, 121.5, 120.6, 120.3, 118.3, 117.5, 115.6, 111.0, 108.5, 108.2, 96.1 (aromatic C), 57.9, 46.6, 37.3, 34.0, 31.6, 30.4, 24.8, 13.7 (aliphatic C)

LCMS (m/z): 474 (M+H)$^+$

Anal. Calcd. for $C_{28}H_{25}Cl_2N_3$: C, 70.89; H, 5.31; N, 8.86 %

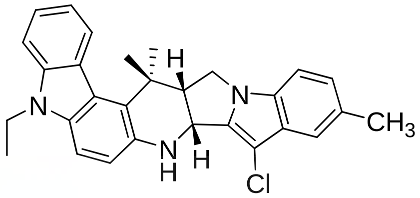
Found: C, 70.92; H, 5.32; N, 8.82 %

Cis-9-chloro-5-ethyl-11,16,16-trimethyl-5,8,8a,15,15a,16-hexahydro-benzo[5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159i)

Reaction of **158c** in the presence of La(OTf)$_3$ with **129d** in 1,4-dioxane following the *general procedure E* provided the title compound as a white solid. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 93 %

IR (KBr) ν_{max} cm^{-1}: 3385, 3047, 2966, 2901, 1718, 1579, 1278, 1155, 1084, 748



159i

^{1}H NMR (400 MHz) δ: 8.25 (1H, d, *J* = 8.2 Hz); 7.52 (1H, s, *J* = 8.2 Hz); 7.35 (1H, t, *J* = 7.3 Hz); 7.25 (3H, d, *J* = 8.4 Hz); 7.13 (1H, t, *J* = 7.4 Hz); 7.00 (1H, d, *J* = 8.0 Hz); 6.92 (1H, d, *J* = 8.8 Hz); 5.59 (1H, s); 4.78 (1H, d, *J* = 3.8 Hz); 4.34-4.36 (3H, m); 3.79 (1H, t, *J* = 10.0 Hz); 3.05 (1H, bs); 2.40 (3H, s, ArC-C$\underline{H}_3$); 1.81 (3H, s); 1.75 (3H, s); 1.24 (3H, t, *J* = 7.1 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 141.6, 140.3, 137.5, 137.1, 130.8, 129.2, 128.8, 126.4, 124.5, 124.1, 121.6, 120.5, 118.3, 117.5, 115.6, 109.7, 108.5, 108.1, 95.8 (aromatic C), 57.8, 46.4, 37.2, 34.1, 31.6, 30.2, 24.9, 21.5, 13.7 (aliphatic C)

LCMS (m/z): 454 (M+H)$^+$

Anal. Calcd. for $C_{29}H_{28}ClN_3$: C, 76.72; H, 6.22; N, 9.26 %

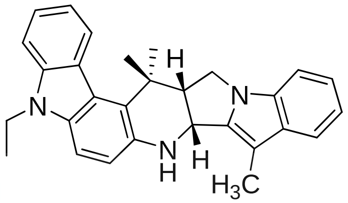
Found: C, 76.71; H, 6.26; N, 9.18 %

Cis-5-ethyl-9,16,16-trimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6'] pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (159j)

The pyrroloindole fused isoellipticine was obtained by the reaction of **129f** with **158c** in the presence of 10 mol % La(OTf)$_3$ in 1,4-dioxane following the *general procedure E*. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield: 92 %

IR (KBr) ν_{max} cm^{-1}: 3398, 3047, 2924, 1728, 1614, 1269, 1192, 1089, 792



159j

^{1}H NMR (400 MHz) δ: 8.34 (1H, d, *J* = 7.8 Hz); 7.53 (1H, d, *J* = 7.5 Hz); 7.34-7.37 (2H, m); 7.04-7.12 (5H, m); 6.59 (1H, d, *J* = 5.7 Hz); 4.80 (1H, bs); 4.10-4.24 (3H, m); 3.84 (1H, t, *J* = 9.8 Hz); 3.54 (1H, bs); 2.96 (1H, bs); 2.39 (3H, s, ArC-C$\underline{H}_3$); 1.89 (3H, s); 1.82 (3H, s); 1.33 (3H, t, *J* = 6.5 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 143.1, 140.4, 136.2, 135.2, 133.3 131.7, 126.5, 124.4, 121.8, 121.5, 120.5, 119.4, 118.5, 117.4, 115.7, 109.4, 108.5, 108.1, 101.9 (aromatic C), 58.1, 46.7, 45.4, 37.3, 34.1, 30.3, 24.8, 13.8, 9.0 (aliphatic C)

LCMS (m/z): 420 (M+H)$^+$

Anal. Calcd. for $C_{29}H_{29}N_3$: C, 83.02; H, 6.97; N, 10.02 %

Found: C, 83.05; H, 6.97; N, 10.34 %

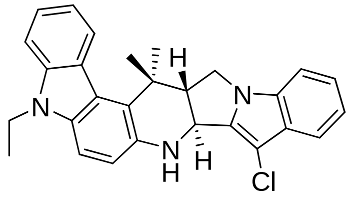
***Trans*-9-chloro-5-ethyl-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5',6']pyrrolizino[2',1':5,6]pyrido[2,3-*c*]carbazole (160)**

Reaction of **158c** in the presence of La(OTf)$_3$ with **129a** in 1,4-dioxane following the *general procedure E* provided the title compound as a minor product. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes.

Mp: 280-281 °C

IR (KBr) ν_{max} cm^{-1}: 3371, 3057, 2966, 1770, 1647, 1263, 1151, 1089, 954, 806

^{1}H NMR (400 MHz) δ: 8.27 (1H, d, *J* = 8.3 Hz); 7.58 (1H, d, *J* = 8.2 Hz); 7.39-7.52 (4H, m); 7.14-7.24 (4H, m); 5.87 (1H, s); 4.68 (1H, d, *J* = 10.6 Hz); 4.58 (1H, t, *J* = 8.4 Hz); 4.42 (2H, q, *J* = 7.1 Hz, N-C$\underline{H_2}$CH$_3$); 4.10 (1H, t, *J* = 10.4 Hz); 2.93 (1H, q, *J* = 7.6 Hz); 1.84 (3H, s); 1.80 (3H, s); 1.28 (3H, t, *J* = 6.9 Hz, N-CH$_2$C$\underline{H_3}$)



160

^{13}C NMR (100 MHz) δ: 141.6, 140.3, 135.9, 132.4, 128.6, 126.4, 124.5, 122.5, 121.6, 120.4, 119.8, 118.8, 117.5, 115.6, 110.0, 108.6, 108.2, 96.5 (aromatic C), 57.8, 46.9, 46.4, 37.3, 34.1, 30.4, 24.9, 22.7 (aliphatic C)

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

Anal. Calcd. for $C_{28}H_{26}ClN_3$: C, 76.44; H, 5.96; N, 9.55 %

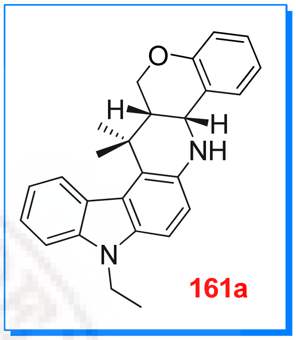
Found: C, 76.57; H, 5.79; N, 9.77 %

General Procedure F

To a stirred solution of 9-ethyl-3-aminocarbazole **158c** (1.0 mmol) and *O*-prenylated salicylaldehyde **104a-e** (1.0 mmol) in dry 1,4-dioxane, La(OTf)$_3$ (10 mol %) was added and the reaction mixture was heated to 100 °C for appropriate time (2-4 h). The reaction was monitored by TLC. After completion of the reaction, as indicated by the TLC, the excess solvent was distilled off and the crude reaction mixture was poured over water and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and the solvent was removed. The residue was chromatographed silica gel and eluted with hexane-ethyl acetate mixture to afford the corresponding products (**161a-e**).

Cis-8-ethyl-13,13-dimethyl-4b,5,8,13,13a,14-hexahydrochromeno[3',4':5,6]pyrido[2,3-*c*]carbazole (161a)

The compound was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with **104a** in 1,4-dioxane following the *general procedure F*. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes.

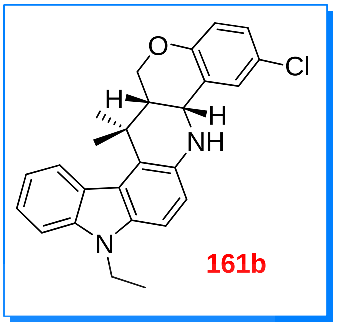


161a

Yield:	88 %
Mp:	145-146 °C
IR (KBr) ν_{max} cm^{-1}:	3391, 3043, 2970, 2926, 1610, 1259, 1151, 1064, 790
^{1}H NMR (400 MHz) δ:	7.99 (1H, d, *J* = 8.0 Hz); 7.22-7.46 (6H, m); 7.13 (1H, t, *J* = 7.8 Hz); 6.89 (2H, d, *J* = 7.7 Hz); 5.53 (1H, bs); 4.60 (2H, d, *J* = 7.8 Hz); 4.45 (2H, s, $OC\underline{H_2}$); 4.29 (2H, q, *J* = 7.6 Hz, $N\text{-}C\underline{H_2}CH_3$); 1.79 (3H, s); 1.77 (3H, s); 1.38 (3H, t, *J* = 7.2 Hz, $N\text{-}CH_2C\underline{H_3}$)
^{13}C NMR (100 MHz) δ:	154.6, 140.2, 135.3, 135.2, 129.7, 129.5, 126.5, 124.4, 124.1, 123.4, 121.5, 120.3, 120.0, 117.5, 116.5, 116.2, 108.5, 108.2 (aromatic C), 64.3, 46.4, 44.1, 37.2, 34.8, 31.1, 23.4, 13.7 (aliphatic C)
LCMS (m/z):	383 $(M+H)^+$
Anal. Calcd. for $C_{26}H_{26}N_2O$:	C, 81.64; H, 6.85; N, 7.32 %
Found:	C, 81.71; H, 6.83; N, 7.12 %

Cis-3-chloro-8-ethyl-13,13-dimethyl-4b,5,8,13,13a,14-exahydrochromeno[3',4':5,6]pyrido[2,3-*c*]carbazole (161b)

The compound was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with **104b** in 1,4-dioxane following the *general procedure F*. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.



161b

Yield: 92 %

Mp: 182-183 °C

IR (KBr) ν_{max} cm^{-1}: 3302, 2964, 1616, 1575, 1236, 1190, 1095, 814

^{1}H NMR (400 MHz) δ: 8.28 (1H, d, *J* = 7.8 Hz); 7.41-7.46 (3H, m); 7.14-7.24 (3H, m); 6.98 (1H, d, *J* = 8.3 Hz); 6.83 (1H, d, *J* = 8.5 Hz); 4.59 (1H, d, *J* = 10.0 Hz); 4.30-4.32 (3H, m); 4.04 (1H, t, *J* = 11.0 Hz); 3.94 (1H, bs); 2.07 (1H, t, *J* = 10.6 Hz); 1.91 (3H, s); 1.69 (3H, s); 1.39 (3H, t, *J* = 6.3 Hz, $N\text{-}CH_2C\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 153.2, 140.2, 136.1, 128.5, 126.9, 126.6, 126.5, 125.8, 125.7, 124.5, 121.3, 119.9, 118.8, 118.5, 117.7, 108.6, 108.3 (aromatic C), 65.8, 48.9, 47.2, 37.3, 35.0, 27.0, 23.6, 13.8 (aliphatic C)

LCMS (m/z): 416 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{25}ClN_2O$: C, 74.90; H, 6.04; N, 6.72 %

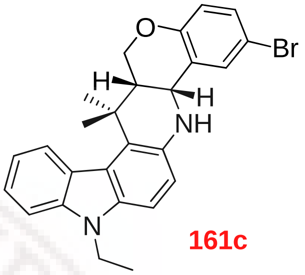
Found: C, 74.91; H, 6.06; N, 6.73 %

***Cis*-3-bromo-8-ethyl-13,13-dimethyl-4b,5,8,13,13a,14-hexahydrochromeno[3',4':5,6]pyrido[2,3-*c*]carbazole (161c)**

Reaction of **158c** in the presence of La(OTf)$_3$ with **104c** in 1,4-dioxane following the *general procedure F* provided the title compound as a white solid. Pure product was obtained through silica gel column chromatography with 3 % ethyl acetate in hexanes.

Yield: 93 %

Mp:	161-162 ^{o}C
IR (KBr) ν_{max} cm^{-1}:	3371, 2964, 1709, 1575, 1263, 1191, 1091, 800
^{1}H NMR (400 MHz) δ:	8.40 (1H, d, *J* = 8.0 Hz); 7.31-7.41 (4H, m); 7.17-7.22 (2H, m); 6.76 (2H, d, *J* = 8.6 Hz); 4.31-4.43 (5H, m); 3.74 (1H, bs); 2.17 (1H, d, *J* = 10.7 Hz); 1.93 (3H, s); 1.76 (3H, s); 1.39 (3H, t, *J* = 6.9 Hz, N-CH$_2$C$\underline{H}_3$)



161c

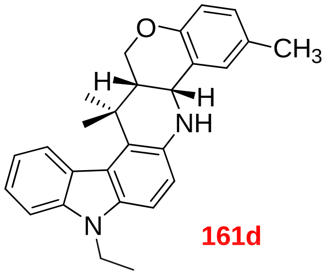
^{13}C NMR (100 MHz) δ:	153.8, 140.3, 135.5, 134.9, 132.4, 131.9, 126.5, 126.1, 124.5, 123.4, 121.4, 120.2, 118.4, 117.6, 116.2, 111.5, 108.6, 108.3 (Aromatic C), 64.5, 46.3, 43.9, 37.2, 34.8, 31.1, 23.4, 13.7 (Aliphatic C)
LCMS (m/z):	462 (M+H)$^{+}$
Anal. Calcd. for $C_{26}H_{25}BrN_2O$:	C, 67.68; H, 5.46; N, 6.07 %
Found:	C, 67.61; H, 5.42; N, 6.29 %

Cis-8-ethyl-3,13,13-trimethyl-4b,5,8,13,13a,14-hexahydrochromeno[3',4':5,6]pyrido[2,3-*c*]carbazole (161d)

Obtained **161d** by treating **158c** with **104d** in 1,4-dioxane following the *general procedure F*. The crude product was purified by silica gel column chromatography with 2 % ethyl acetate in hexanes.

Yield:	85 %
Mp:	168-169 ^{o}C
IR (KBr) ν_{max} cm^{-1}:	3389, 3043, 2974, 2926, 1616, 1595, 1261, 1153, 1091, 817

^{1}H NMR (400 MHz) δ: 8.41 (1H, d, *J* = 8.2 Hz); 7.37-7.43 (2H, m); 7.15-7.21 (2H, m); 7.05 (2H, d, *J* = 7.2 Hz); 6.74-6.80 (2H, m); 4.28-4.41 (5H, m); 3.77 (1H, bs); 2.30 (3H, s, ArC-C<u>*H*</u>$_3$); 2.19 (1H, d, *J* = 11.5 Hz); 1.94 (3H, s); 1.77 (3H, s); 1.38 (3H, t, *J* = 7.1 Hz, N-CH$_2$C<u>*H*</u>$_3$)



161d

^{13}C NMR (100 MHz) δ: 152.3, 140.2, 135.3, 135.2, 130.2, 129.8, 129.2, 126.5, 124.4, 123.8, 123.4, 121.5, 120.3, 117.5, 116.3, 116.2, 108.5, 108.2 (aromatic C), 64.2, 46.4, 44.3, 37.2, 34.8, 31.1, 23.5, 20.5, 13.7 (aliphatic C)

LCMS (m/z): 397 (M+H)$^+$

Anal. Calcd. for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06 %

Found: C, 81.70; H, 7.16; N, 7.16 %

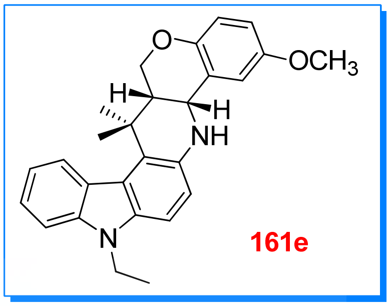
***Cis*-8-ethyl-3-methoxy-13,13-dimethyl-4b,5,8,13,13a,14-hexahydrochromeno[3',4':5,6]pyrido[2,3-*c*]carbazole (161e)**

Reaction of **158c** in the presence of La(OTf)$_3$ with **104e** in 1,4-dioxane following the *general procedure F* provided the title compound as a white solid. Pure product was obtained through silica gel column chromatography with 3 % ethyl acetate in hexanes.

Yield: 85 %

Mp: 155-156 °C

IR (KBr) ν_{max} cm^{-1}: 3389, 2974, 1747, 1684, 1577, 1259, 1149, 1062, 846



161e

^{1}H NMR (400 MHz) δ: 8.41 (1H, d, *J* = 8.0 Hz); 7.39 (2H, s); 7.16-7.22 (2H, m); 6.75-6.82 (4H, m); 4.27-4.42 (5H, m); 3.79 (4H, bs); 2.20 (1H, d, *J* = 10.9 Hz); 1.94 (3H, s); 1.77 (3H, s); 1.39 (3H, t, *J* = 6.7 Hz, N-$CH_2C\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 153.2, 148.4, 140.2, 135.3, 135.1, 126.5, 124.4, 123.4, 121.5, 120.3, 117.5, 117.1, 116.3, 115.6, 114.2, 108.5, 108.2 (aromatic C), 64.1, 55.9, 46.7, 44.2, 37.2, 34.7, 31.1, 23.5, 13.7 (aliphatic C)

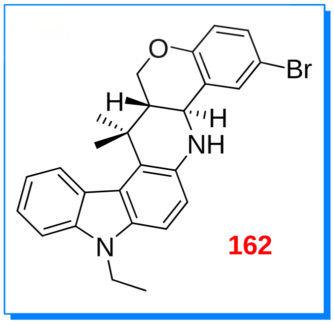
LCMS (m/z): 413 $(M+H)^+$

Anal. Calcd. for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79 %

Found: C, 78.56; H, 6.88; N, 6.67 %

Trans-3-bromo-8-ethyl-13,13-dimethyl-4b,5,8,13,13a,14-hexahydro-chromeno[3',4':5,6]pyrido[2,3-*c*]carbazole (162)

The chromene fused isoellipticine derivative was obtained by the reaction of **158c** with **104c** in the presence of La(OTf)$_3$ in 1,4-dioxane following the *general procedure F* as a minor product. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.



162

Mp: 182-183 °C

IR (KBr) ν_{max} cm^{-1}: 3302, 2974, 1869, 1614, 1574, 1265, 1159, 1095, 812

^{1}H NMR (400 MHz) δ: 8.19 (1H, d, *J* = 7.8 Hz); 7.53 (1H, s); 7.13-7.32 (5H, m); 6.89 (1H, d, *J* = 8.2

Hz); 6.69 (1H, d, *J* = 8.4 Hz); 4.50 (1H, d, *J* = 9.7 Hz); 4.21-4.24 (3H, m); 3.95 (1H, t, *J* = 10.9 Hz); 3.85 (1H, bs); 1.99 (1H, t, *J* = 10.1 Hz); 1.82 (3H, s); 1.65 (3H, s); 1.30 (3H, t, *J* = 7.1 Hz, N-$CH_2C\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 153.7, 140.2, 136.1, 131.4, 129.4, 126.9, 126.6, 126.3, 124.5, 121.3, 119.9, 118.9, 118.8, 117.7, 113.0, 108.6, 108.3 (aromatic C), 65.8, 48.9, 47.1, 37.3, 35.0, 27.1, 23.6, 13.8 (aliphatic C)

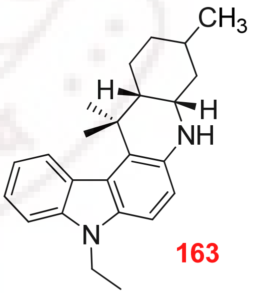
LCMS (m/z): 462 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{25}BrN_2O$: C, 67.68; H, 5.46; N, 6.07 %

Found: C, 67.61; H, 5.42; N, 6.29 %

Cis-8-ethyl-3,13,13-trimethyl-2,3,4,4a,5,8,13,13a-octahydro-1*H*-indolo [3,2-*a*]acridine (163)

This molecule was obtained as a white colour solid by the reaction of **158c** with citronellal in THF following the *general procedure F* at -50 °C as a minor isomer. Pure product was obtained through silica gel column chromatography with 1 % ethyl acetate in hexanes.



163

Mp: 127-128 °C

IR (KBr) ν_{max} cm^{-1}: 3387, 2910, 1579, 1246, 1153, 1091, 790

^{1}H NMR (400 MHz) δ: 8.36 (1H, d, *J* = 8.0 Hz); 7.28 (2H, s); 7.02-7.12 (2H, m); 6.69 (1H, d, *J* = 6.8 Hz); 4.20 (2H, q, *J* = 6.4 Hz, N-$C\underline{H}_2CH_3$); 3.62 (1H, bs); 3.33 (1H, bs); 1.59-1.82 (10H, m); 1.19-1.39 (6H, m); 0.83-0.88 (4H, m).

^{13}C NMR (100 MHz) δ: 140.2, 126.8, 124.1, 123.9, 121.9, 119.5, 117.1, 116.3, 108.3, 107.5 (aromatic C), 48.6, 47.2, 41.0, 37.2, 36.4, 35.6, 31.1, 26.0, 24.1, 22.8, 22.5, 13.7 (aliphatic C)

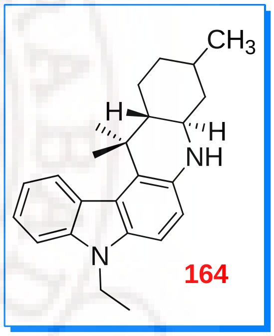
LCMS (m/z): 347 $(M+H)^+$

Anal. Calcd. for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08 %

Found: C, 83.19; H, 8.71; N, 8.09 %

Trans-8-ethyl-3,13,13-trimethyl-2,3,4,4a,5,8,13,13a-octahydro-1*H*-indolo[3,2-*a*]acridine (164)

The compound was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with citronellal in THF in the presence of 10 mol % of La(OTf)$_3$ following the *general procedure F* at -50 °C. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.



164

Yield: 95 %

Mp: 139-140 °C

IR (KBr) ν_{max} cm^{-1}: 3387, 2926, 1734, 1660, 1579, 1265, 1155, 1078, 794

^{1}H NMR (400 MHz) δ: 8.29 (1H, d, *J* = 8.2 Hz); 7.35-7.39 (2H, m); 7.11-7.21 (2H, m); 6.76 (1H, d, *J* = 8.5 Hz); 4.30 (2H, q, *J* = 7.2 Hz); 3.03 (2H, bs); 1.94-1.97 (2H, m); 1.80-1.84 (4H, m); 1.49-1.65 (9H, m); 1.04-1.11 (5H, m)

^{13}C NMR (100 MHz) δ: 140.2, 136.9, 135.2, 126.9, 126.7, 121.6, 120.4, 117.2, 116.4, 108.2, 107.6 (aromatic C), 53.2, 49.3, 42.7, 37.2, 35.2, 30.9, 27.3, 24.6, 22.4, 13.7 (aliphatic C)

LCMS (m/z): 347 $(M+H)^+$

Anal. Calcd. for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08 %

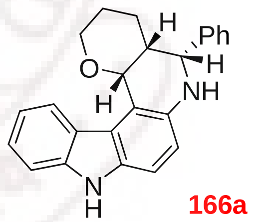
Found:	C, 83.14; H, 8.73; N, 8.19 %

General procedure G

To a solution of aldehydes (1.0 mmol), 3-aminocarbazoles (1.0 mmol), electron-rich dienophiles (3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran or ethyl vinyl ether) (2.5 mmol) in 0.5 g of [Bmim][BF$_4$] ionic liquid, was added InCl$_3$ (10 mol %) and the reaction stirred at 100 ºC for an appropriate time. After the completion of the reaction, as indicated by the TLC, the crude reaction mass was poured into water (50 mL) and extracted with DCM (3 X 20 mL). The organic layer was dried over anhy. Na$_2$SO$_4$ and distilled under reduced pressure. The residue was chromatographed over basic alumina or silica gel and eluted with hexane–ethyl acetate to afford the corresponding products.

Cis-5-phenyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*] carbazole (166a)

The compound was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) in [Bmim][BF$_4$] ionic liquid following the *general procedure G*. Pure product was obtained through basic alumina column chromatography with 3 % ethyl acetate in hexanes.



166a

Yield:	89 %
Mp:	95-96 °C
IR (KBr) ν_{max} cm^{-1}:	3400, 3026, 2935, 2862, 1614, 1585, 1089, 1066, 920, 868
^{1}H NMR (400 MHz) δ:	8.55 (1H, bs); 8.31 (1H, bs); 7.49 (2H, bs); 7.31-7-41 (5H, m); 7.14-7.28 (2H, m); 6.85 (1H, bs); 5.76 (1H, d, *J* = 5.6 Hz); 4.63 (1H, bs); 3.54 (1H, d, *J* = 8.5 Hz); 3.21 (1H, t, *J* = 7.8 Hz); 2.44 (1H, bs); 1.92-1.95 (1H, m); 1.47-1.57 (2H, m); 1.22-1.29 (2H, m)
^{13}C NMR (100 MHz) δ:	141.5, 140.4, 134.7, 129.6, 128.6, 127.5, 127.1, 125.9, 125.3, 123.5, 123.2, 122.5, 121.8, 120.1,

118.9, 115.7, 111.4, 110.2 (aromatic C), 72.4, 59.9, 38.8, 24.3, 19.4, 14.2 (aliphatic C)

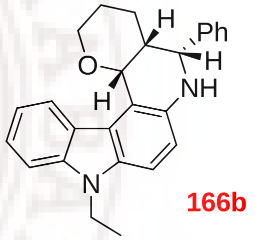
LCMS (m/z): 355 $(M+H)^+$

Anal. Calcd. for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90 %

Found: C, 81.39; H, 6.25; N, 7.95 %

Cis-9-ethyl-5-phenyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole **(166b)**

The compound was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) in [Bmim][BF_4] following the *general procedure G*. The crude product was purified through basic alumina column chromatography with 5 % ethyl acetate in hexanes.



166b

Yield: 90 %

Mp: 158-159 °C

IR (KBr) ν_{max} cm^{-1}: 3369, 3026, 2941, 1585, 1153, 1086, 983, 929

^{1}H NMR (400 MHz) δ: 8.61 (1H, d, *J* = 8.1 Hz); 7.46 (2H, d, *J* = 7.4 Hz); 7.36-7-44 (4H, m); 7.25-7.33 (2H, m); 7.14-7.18 (1H, m); 6.81 (1H, d, *J* = 8.6 Hz); 5.85 (1H, d, *J* = 5.7 Hz); 4.58 (1H, d, *J* = 2.3 Hz); 4.31 (2H, bs); 3.78 (1H, bs); 3.54 (1H, d, *J* = 7.7 Hz); 3.16-3.21 (1H, bs); 2.39 (1H, bs); 1.92-1.95 (1H, m); 1.32-1.53 (6H, m)

^{13}C NMR (100 MHz) δ: 142.1, 140.4, 139.4, 134.8, 128.3, 128.1, 127.3, 127.2, 126.2, 124.9, 122.6, 122.1, 118.1, 115.1, 114.9, 109.1, 107.8 (aromatic C), 72.7, 61.9, 59.9, 39.0, 37.3, 24.5, 19.3, 13.9 (aliphatic C)

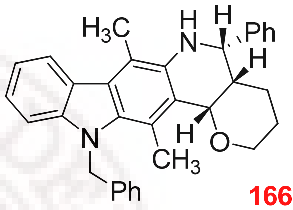
LCMS (m/z): 383 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32 %

Found:	C, 81.68; H, 6.89; N, 7.22 %

Cis-12-benzyl-7,13-dimethyl-5-phenyl-2,3,4,4a,5,6,12,13b-octahydro-pyrano[2',3':4,5]pyrido[3,2-*b*]carbazole (166c)

Obtained **166c** by treating with **158h** and **165a** in ionic liquid in the presence of 10 mol % $InCl_3$ following the *general procedure G*. Pure product was obtained by basic alumina column chromatography with 5 % ethyl acetate in hexanes.

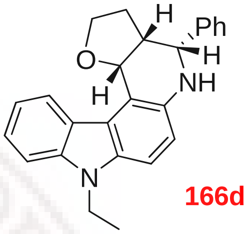


166c

Yield:	71 %
Mp:	175-176 ^{o}C
IR (KBr) ν_{max} cm^{-1}:	3391, 3024, 2955, 2908, 1602, 1575, 1078, 1028, 800, 752
^{1}H NMR (400 MHz) δ:	8.27 (1H, d, *J* = 7.7 Hz); 7.71 (2H, d, *J* = 6.9 Hz); 7.51-7.53 (3H, m); 7.44-7.48 (4H, m); 7.29-7.37 (2H, m); 7.15-7.26 (2H, m); 5.85-5.90 (1H, m); 5.78 (1H, d, *J* = 2.4 Hz); 4.49-5.59 (1H, m); 5.42 (1H, bs); 4.66 (1H, bs); 3.48-3.55 (2H, m); 3.26 (1H, t, *J* = 9.6 Hz); 2.77 (3H, s, ArC-C$\underline{H}_3$); 2.66 (3H, s, ArC-C$\underline{H}_3$); 2.55-2.62 (1H, m); 1.90 (1H, d, *J* = 10.1 Hz); 1.40-1.43 (1H, m); 1.27 (1H, bs)
^{13}C NMR (100 MHz) δ:	143.7, 139.1, 136.3, 133.8, 131.6, 129.9, 129.7, 129.4, 129.0, 128.9, 128.6, 128.4, 127.6, 127.4, 127.1, 125.9, 125.7, 125.4, 123.8, 123.1, 122.9, 119.9, 119.0, 109.3 (aromatic C), 73.3, 59.6, 49.8, 38.5, 24.0, 19.6, 17.0, 15.6, 14.1 (aliphatic C)
LCMS (m/z):	473 $(M+H)^+$
Anal. Calcd. for $C_{33}H_{32}N_2O$:	C, 83.86; H, 6.82; N, 5.93 %
Found:	C, 83.65; H, 6.85; N, 6.04 %

Cis-8-ethyl-4-phenyl-3,3a,4,5,8,12d-hexahydro-2*H*-furo[2',3':4,5]pyrido[2,3-*c*]carbazole (166d)

Reaction of **97** in the presence of $InCl_3$ (10 mol %) with **158c** in [Bmim][BF_4] following the *general procedure G* provided the title compound as a light yellow solid. The crude product was purified through basic alumina column chromatography with 4 % ethyl acetate in hexanes.

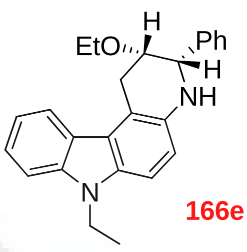


166d

Yield:	85 %
Mp:	120 °C
IR (KBr) ν_{max} cm^{-1}:	3431, 2968, 1601, 1267, 1153, 1041, 800, 734
^1H NMR (400 MHz) δ:	8.25 (1H, d, *J* = 7.8 Hz); 7.55 (2H, d, *J* = 7.0 Hz); 7.31-7-41 (5H, m); 7.14-7.21 (2H, m); 6.78 (1H, d, *J* = 8.4 Hz); 5.18 (1H, d, *J* = 4.5 Hz); 4.28 (2H, q, *J* = 7.0 Hz, N-C$\underline{H}_2$$CH_3$); 4.08-4.14 (2H, m); 4.00 (1H, q, *J* = 6.2 Hz); 3.86 (1H, d, *J* = 11.1 Hz); 2.55-2.60 (1H, m); 2.05-2.14 (1H, m); 1.73-1.76 (1H, m); 1.32 (3H, t, *J* = 7.9 Hz, N-CH_2C$\underline{H}_3$)
^{13}C NMR (100 MHz) δ:	142.1, 140.4, 138.8, 134.3, 128.6, 128.5, 128.1, 125.1, 123.7, 122.9, 122.2, 118.4, 114.4, 113.5, 109.5, 108.1 (aromatic C), 74.8, 65.1, 58.4, 43.5, 37.4, 28.6, 13.8 (aliphatic C)
LCMS (m/z):	369 $(M+H)^+$
Anal. Calcd. for $C_{25}H_{24}N_2O$:	C, 81.49; H, 6.56; N, 7.60 %
Found:	C, 81.51; H, 6.57; N, 7.44 %

Cis-4-ethoxy-6-ethyl-2-phenyl-2,3,4,6-tetrahydro-1*H*-pyrido[3,2-*b*]carbazole (166e)

The pyridocarbazole derivative was obtained by the reaction of **158c** with ethyl vinyl ether (**99**) and **165a** in the presence of $InCl_3$ (10 mol %) in $[Bmim][BF_4]$ following the *general procedure G*. Pure product was obtained through basic alumina column chromatography with 5 % ethyl acetate in hexanes.



166e

Yield: 92 %

Mp: 96-97 °C

IR (KBr) ν_{max} cm^{-1}: 3352, 2970, 1601, 1585, 1153, 1078, 925, 798

^1H NMR (400 MHz) δ: 8.04 (1H, d, *J* = 8.0 Hz); 7.45 (2H, d, *J* = 7.6 Hz); 7.32 (1H, d, *J* = 8.1 Hz); 7.25-7.31 (3H, m); 7,21 (1H, d, *J* = 7.4 Hz); 7.06-7.18 (2H, m); 6.84 (1H, d, *J* = 8.6 Hz); 5.47 (1H, t, *J* = 7.2 Hz); 4.35-4.40 (1H, m); 4.20 (2H, q, *J* = 7.1 Hz, N-$C\underline{H_2}CH_3$); 3.47-3.51 (1H, m); 3.37-3.41 (1H, m); 2.51 (2H, t, *J* = 6.9 Hz, $O C\underline{H_2}CH_3$); 1.23-1.30 (4H, m); 0.94 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 140.4, 139.4, 129.2, 128.7, 127.8, 127.2, 126.9, 125.1, 124.9, 124.4, 123.0, 122.5, 122.0, 121.9, 118.1, 110.0, 109.4, 108.1 (aromatic C), 71.8, 61.1, 56.6, 37.4, 18.4, 15.4, 13.9 (aliphatic C)

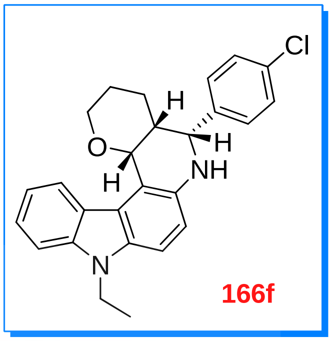
LCMS (m/z): 369 $(M-H)^+$

Anal. Calcd. for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56 %

Found: C, 81.25; H, 7.27; N, 7.50 %

Cis-5-(4-chlorophenyl)-9-ethyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole (166f)

Reaction of **158c** in the presence of $Incl_3$ (10 mol %) with 4-chlorobenzaldehyde (**165b**) in $[Bmim][BF_4]$ following the *general procedure G* provided the title compound as a product. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.



166f

Yield:	60 %
Mp:	150 °C
IR (KBr) ν_{max} cm^{-1}:	3369, 3043, 2953, 2912, 1593, 1087, 1068, 931, 846
^{1}H NMR (400 MHz) δ:	8.52 (1H, d, *J* = 7.6 Hz); 7.09-7.38 (8H, m); 6.76 (1H, d, *J* = 4.9 Hz); 5.73 (1H, d, *J* = 4.8 Hz); 4.46 (1H, bs); 4.26 (2H, q, *J* = 6.1 Hz, N-C$\underline{H_2}$CH$_3$); 3.68 (1H, bs); 3.50 (1H, d, *J* = 10.7 Hz); 3.18 (1H, t, *J* = 9.8 Hz); 2.31 (1H, bs); 1.85 (1H, q, *J* = 10.0 Hz); 1.23-1.44 (6H, m)
^{13}C NMR (100 MHz) δ:	140.8, 140.4, 138.9, 134.8, 132.9, 128.6, 128.4, 125.9, 125.1, 122.5, 122.1, 118.2, 114.9, 109.2, 107.9 (aromatic C), 72.5, 62.2, 59.3, 38.8, 37.3, 24.3, 19.5, 13.9 (aliphatic C)
LCMS (m/z):	417 (M+H)$^+$
Anal. Calcd. for $C_{26}H_{25}ClN_2O$:	C, 74.90; H, 6.04; N, 6.72 %
Found:	C, 74.91; H, 6.05; N, 6.51 %

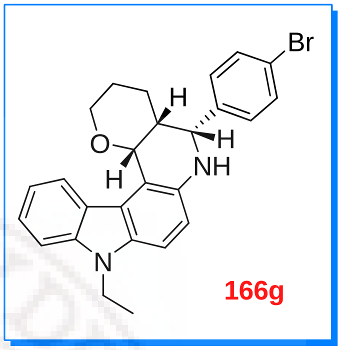
Cis-5-(4-bromophenyl)-9-ethyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole (166g)

The pyran fused pyridocarbazole derivative was obtained by the reaction of **158c** with 4-bromobenzaldehyde (**165c**) and **95** in the presence of InCl$_3$ (10 mol %) in [Bmim][BF$_4$] following the *general procedure G*. Pure product was obtained through basic alumina column chromatography with 3 % ethyl acetate in hexanes.

Yield: 55 %

Mp: 159-160 °C

IR (KBr) ν_{max} cm^{-1}: 3369, 3057, 2910, 2849, 1581, 1091, 1068, 929, 833



166g

^{1}H NMR (400 MHz) δ: 8.55 (1H, d, *J* = 5.9 Hz); 7.45 (2H, d, *J* = 6.8 Hz); 7.34-7.40 (4H, m); 7.22 (1H, d, *J* = 6.8 Hz); 7.15 (1H, s); 6.81 (1H, d, *J* = 7.9 Hz); 5.78 (1H, bs); 4.51 (1H, bs); 4.31 (2H, q, *J* = 6.2 Hz, N-$C\underline{H_2}CH_3$); 3.74 (1H, bs); 3.55 (1H, d, *J* = 8.8 Hz); 3.22 (1H, bs); 2.36 (1H, bs); 1.89 (1H, d, *J* = 9.8 Hz); 1.29-1.49 (6H, m)

^{13}C NMR (100 MHz) δ: 141.3, 140.4, 138.9, 134.8, 131.4, 129.0, 125.9, 125.1, 122.5, 122.1, 121.0, 118.2, 114.9, 109.2, 107.6 (aromatic C), 72.5, 62.2, 59.4, 38.7, 37.3, 24.3, 19.5, 13.9 (aliphatic C)

LCMS (m/z): 461 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{25}BrN_2O$: C, 67.68; H, 5.46; N, 6.07 %

Found: C, 67.72; H, 5.41; N, 6.22 %

Cis-9-ethyl-5-(4-methylphenyl)-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole (166h)

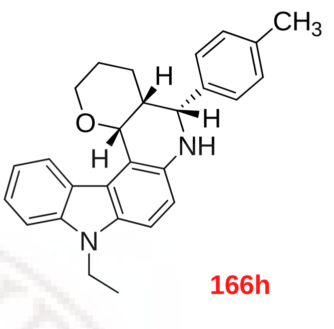
The product was obtained as a light yellow coloured solid by the reaction of **158c** with **165d** in [Bmim][BF_4] following the *general procedure G*. The crude product was purified through silica gel column chromatography with 5 % ethyl acetate in hexanes.

Yield: 52 %

Mp: 131-132 °C

IR (KBr) ν_{max} cm^{-1}: 3368, 3047, 2943, 2912, 1616, 1585, 1084, 1022, 927, 827

^{1}H NMR (400 MHz) δ: 8.61 (1H, d, *J* = 7.8 Hz); 7.33-7.42 (4H, m); 7.13-7.22 (4H, m); 6.81 (1H, d, *J* = 8.4 Hz); 5.85 (1H, d, *J* = 4.8 Hz); 4.57 (1H, bs); 4.31 (2H, q, *J* = 7.0 Hz, N-C$\underline{H}_2$CH$_3$); 3.75 (1H, bs); 3.53 (1H, d, *J* = 10.6 Hz); 3.18 (1H, t, *J* = 10.3 Hz); 2.36 (4H, s); 1.92 (1H, q, *J* = 10.8 Hz, N-CH$_2$C$\underline{H}_3$); 1.34-1.54 (6H, m)



166h

^{13}C NMR (100 MHz) δ: 140.4, 139.5, 139.0, 136.9, 134.8, 129.0, 127.1, 126.2, 124.9, 122.6, 118.1, 115.1, 114.9, 109.1, 108.8 (aromatic C), 72.7, 61.8, 59.7, 39.1, 37.3, 24.6, 21.2, 19.2, 13.9 (aliphatic C)

LCMS (m/z): 397 $(M+H)^+$

Anal. Calcd. for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06 %

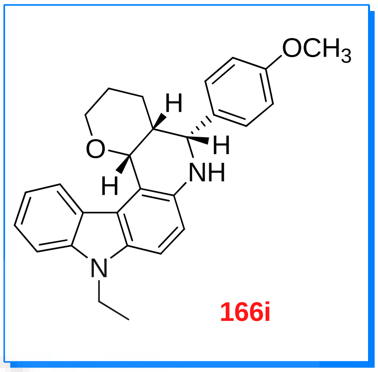
Found: C, 81.67; H, 7.15; N, 7.27 %

Cis-9-ethyl-5-(4-methoxylphenyl)-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole (166i)

Reaction of **158c** in the presence of $Incl_3$ with **165e** in [Bmim][BF_4] following the *general procedure G* provided the title compound as a product. Pure product was obtained through silica gel column chromatography with 3 % ethyl acetate in hexanes.

Yield: 48 %

IR (KBr) ν_{max} cm^{-1}: 3391, 3051, 2934, 2862, 1608, 1575, 1032, 800, 746



166i

^1H NMR (400 MHz) δ: 7.92 (1H, d, *J* = 7.6 Hz); 7.25-7.35 (4H, m); 7.16 (2H, d, *J* = 8.9 Hz); 7.06 (1H, t, *J* = 7.0 Hz); 6.81 (2H, d, *J* = 8.1 Hz); 6.74 (1H, d, *J* = 7.9 Hz); 4.40 (1H, bs); 4.28 (1H, bs); 4.22 (2H, q, *J* = 7.1 Hz, N-C$\underline{H}_2$CH$_3$); 3.78 (3H, s, ArC-OC$\underline{H}_3$); 3.29 (1H, bs); 1.18-1.74 (9H, m)

^{13}C NMR (100 MHz) δ: 158.9, 141.9, 140.5, 134.1, 131.9, 129.1, 125.4, 123.7, 122.7, 120.4, 117.9, 114.5, 114.1, 113.9, 109.2, 108.9, 108.4, 103.5 (aromatic C), 67.6, 62.4, 55.4, 49.5, 37.6, 30.8, 25.6, 19.8, 13.9 (aliphatic C)

LCMS (m/z): 441 $(M-H)^+$

Anal. Calcd. for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79 %

Found: C, 78.40; H, 6.91; N, 6.68 %

***Cis*-9-ethyl-5-(1-methyl-1*H*-2-indolyl)-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole (166j)**

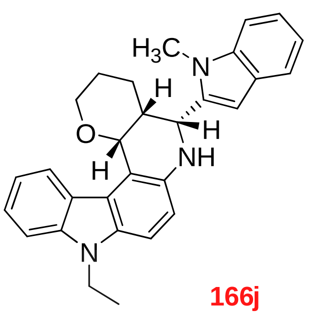
Reaction of **158c** in the presence of $InCl_3$ (10 mol %) with 1-methyl-2-formylindole (**165f**) and **95** in [Bmim][BF_4] following the *general procedure G* provided the title compound as a white solid. The crude product was purified through basic alumina column chromatography with 10 % ethyl acetate in hexanes.

Yield: 67 %

Mp: 202 °C

IR (KBr) ν_{max} cm^{-1}: 3379, 3042, 2937, 2895, 1618, 1581, 1087, 1066, 927, 794

^{1}H NMR (400 MHz) δ: 8.67 (1H, d, *J* = 8.1 Hz); 7.58 (1H, d, *J* = 7.7 Hz); 7.40 (1H, t, *J* = 7.7 Hz); 7.27-7.32 (2H, m); 7.09-7-22 (4H, m); 6.82 (1H, d, *J* = 8.6 Hz); 6.63 (1H, s); 5.89 (1H, d, *J* = 5.9 Hz); 4.73 (1H, bs); 4.23 (2H, q, *J* = 7.2 Hz, N-C$\underline{H_2}$CH$_3$); 3.81 (1H, bs); 3.63 (3H, s, N-C$\underline{H_3}$); 3.49-3.52 (1H, m); 3.10 (1H, t, *J* = 11.3 Hz); 2.41-2.44 (1H, m); 1.92-1.96 (1H, m); 1.53-1.58 (2H, m); 1.37 (4H, t, *J* = 7.1 Hz)



166j

^{13}C NMR (100 MHz) δ: 140.4, 139.6, 139.3, 137.7, 134.9, 127.5, 126.4, 125.0, 122.6, 122.1, 121.4, 120.3, 119.7, 118.1, 115.1, 109.1, 108.9, 107.8, 100.2 (aromatic C), 72.3, 61.2, 53.4, 37.3, 36.8, 29.8, 24.9, 19.1, 13.8 (aliphatic C)

LCMS (m/z): 436 (M+H)$^+$

Anal. Calcd. for $C_{29}H_{29}N_3O$: C, 79.97; H, 6.71; N, 9.65 %

Found: C, 79.86; H, 6.71; N, 9.83 %

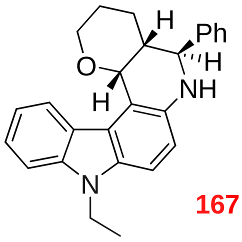
9-Ethyl-5-phenyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2',3':4,5]pyrido[2,3-*c*]carbazole (167)

The product was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with **165a** and **95** in [Bmim][BF$_4$] following the *general procedure G* as a minor isomer. Pure product was obtained through basic alumina column chromatography with 3 % ethyl acetate in hexanes.

Mp: 178 °C

IR (KBr) ν_{max} cm^{-1}: 3377, 3057, 2930, 1601, 1147, 1070, 902, 800

^{1}H NMR (400 MHz) δ: 8.03 (1H, d, *J* = 7.6 Hz); 7.52 (2H, d, *J* = 7.6 Hz); 7.34-7-45 (5H, m); 7.18-7.26 (2H, m); 6.77 (1H, d, *J* = 8.2 Hz); 5.21 (1H, d, *J* = 3.5 Hz); 4.82 (1H, d, *J* = 15.2 Hz); 4.24-4.36 (3H, m); 3.99-4.03 (1H, m); 2.22-2.28 (1H, m); 1.91-2.02 (1H, m); 1.77-1.85 (1H, m); 1.56-1.59 (2H, m); 1.35-1.43 (4H, m)



167

^{13}C NMR (100 MHz) δ: 142.5, 140.4, 138.4, 134.1, 128.6, 128.2, 127.9, 124.9, 123.2, 122.1, 121.9, 118.3, 114.7, 109.9 108.3 (aromatic C), 72.4, 68.8, 55.1, 39.7, 37.4, 24.3, 22.1, 13.8 (aliphatic C)

LCMS (m/z): 383 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32 %

Found: C, 81.63; H, 6.83; N, 7.39 %

Cis-12-ethyl-5-phenyl-2,3,4,4a,5,6,12,13b-octahydropyrano[2',3':4,5] pyrido[3,2-*b*]carbazole (168)

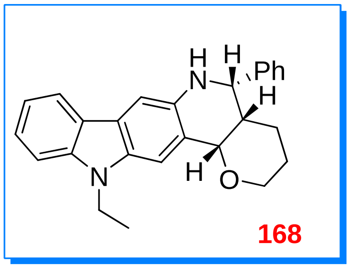
This interesting second position cyclized product was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with **165a** and **95** in [Bmim][BF_4] following the *general procedure G* as a minor isomer. The crude product was purified through basic alumina column chromatography with 3 % ethyl acetate in hexanes.

Mp: 182-183 °C

IR (KBr) ν_{max} cm^{-1}: 3381, 3051, 2939, 1604, 1230, 1199, 1082, 912, 848

^{1}H NMR (400 MHz) δ: 7.97 (1H, d, *J* = 7.5 Hz); 7.45-7.52 (3H, m); 7.40-7-44 (3H, m); 7.26-7.35 (3H, m); 7.14 (1H, t, *J* = 7.4

Hz); 5.56 (1H, d, *J* = 4.9 Hz); 4.73 (1H, d, *J* = 2.4 Hz); 4.33 (2H, q, *J* = 7.0 Hz, N-C$\underline{H}_2$CH$_3$); 3.88 (1H, bs); 3.65-3.67 (1H, m); 3.51-3.57 (1H, m); 2.25-2.27 (1H, m); 1.56-1.67 (3H, m); 1.35-1.42 (4H, m)



168

^{13}C NMR (100 MHz) δ: 141.8, 140.8, 138.7, 135.0, 128.4, 127.5, 127.0, 125.6, 123.4, 122.5, 120.5, 120.4, 117.9, 108.3, 106.9, 104.9 (aromatic C), 73.9, 60.9, 59.9, 39.7, 37.6, 25.6, 18.0, 13.9 (aliphatic C)

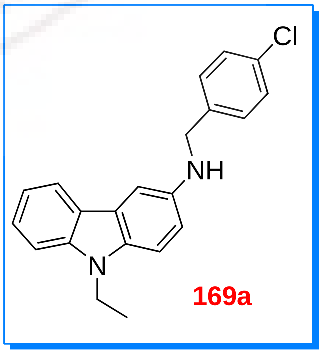
LCMS (m/z): 383 (M+H)$^+$

Anal. Calcd. for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32 %

Found: C, 81.69; H, 6.82; N, 7.58 %

*N*3-(4-Chlorobenzyl)-9-ethyl-9*H*-3-carbazolamine (169a)

Reaction of **158c** in the presence of $InCl_3$ (10 mol %) with 4-chlorobenzaldehyde (**165b**) and **95** in [Bmim][BF_4] following the *general procedure G* provided the title compound as a minor reduced amination product. Pure product was obtained through silica gel column chromatography with 3 % ethyl acetate in hexanes.



169a

Yield: 21 %

IR (KBr) ν_{max} cm^{-1}: 3416, 3049, 2974, 2930, 1631, 1604, 1089, 1014, 939, 796

^{1}H NMR (400 MHz) δ: 7.95 (1H, d, *J* = 7.7 Hz); 7.39 (1H, t, *J* = 7.8 Hz); 7.27-7.34 (7H, m); 7.20 (1H, t, *J* = 8.4 Hz); 7.13 (1H, t, *J* = 7.4 Hz); 6.83 (1H, q, *J* = 6.8 Hz); 4.35 (2H, s, NH-C*H*$_2$); 4.25 (2H, q, *J* = 7.2 Hz, N-C*H*$_2$CH$_3$); 1.35 (3H, t, *J* = 7.9 Hz, N-CH$_2$C*H*$_3$)

^{13}C NMR (100 MHz) δ: 141.4, 140.4, 138.5, 134.2, 132.8, 128.9, 128.7, 125.4, 123.7, 122.6, 120.4, 118.0, 114.4, 109.2, 108.4, 103.5 (aromatic C), 49.1, 37.5, 13.9 (aliphatic C)

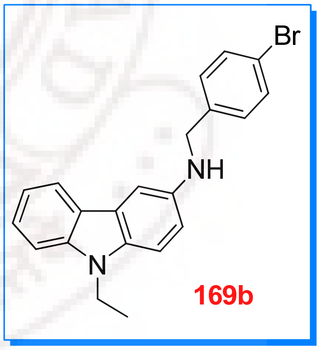
LCMS (m/z): 335 (M+H)$^+$

Anal. Calcd. for $C_{21}H_{19}ClN_2$: C, 75.33; H, 5.72; N, 8.37 %

Found: C, 75.39; H, 5.73; N, 8.56 %

*N*3-(4-Bromobenzyl)-9-ethyl-9*H*-3-carbazolamine (169b)

Reaction of **158c** in the presence of InCl$_3$ (10 mol %) with 4-bromobenzaldehyde (**165c**) and **95** in [Bmim][BF$_4$] following the *general procedure G* provided the title compound as a minor reduced amination product. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.



169b

Yield: 25 %

IR (KBr) ν_{max} cm^{-1}: 3414, 3047, 2968, 2930, 1631, 1579, 1087, 1012, 798, 744

^{1}H NMR (400 MHz) δ: 7.89 (1H, d, *J* = 7.0 Hz); 7.37 (2H, d, *J* = 6.9 Hz); 7.23-7.33 (6H, m); 7.14 (1H, d, *J* = 8.3 Hz); 7.06 (1H, d, *J* = 6.8 Hz); 6.77 (1H, d, *J* = 7.8 Hz); 4.29 (2H, s, NH-C*H*$_2$); 4.20 (2H, q, *J* = 6.6 Hz, N-C*H*$_2$CH$_3$); 1.29 (3H, t, *J* = 7.6 Hz, N-CH$_2$C*H*$_3$)

^{13}C NMR (100 MHz) δ: 141.4, 140.4, 139.1, 134.2, 131.7, 129.3, 125.5, 123.7, 122.6, 120.9, 120.4, 118.0, 114.4, 109.2, 108.4, 103.5 (aromatic C), 49.2, 37.6, 13.9 (aliphatic C)

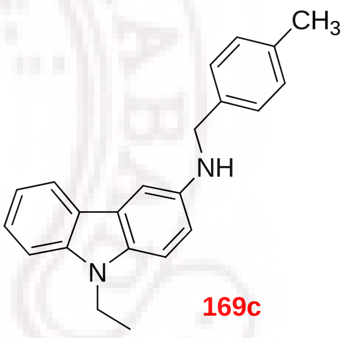
LCMS (m/z): 379 $(M+H)^+$

Anal. Calcd. for $C_{21}H_{19}BrN_2$: C, 66.50; H, 5.05; N, 7.39 %

Found: C, 66.49; H, 5.11; N, 7.19 %

*N*3-(4-Methylbenzyl)-9-ethyl-9*H*-3-carbazolamine (169c)

Reaction of **158c** in the presence of $InCl_3$ (10 mol %) with 4-methylbenzaldehyde (**165d**) and **95** in [Bmim][BF_4] following the *general procedure G* provided the title compound as a minor reduced amination product. Pure product was obtained through basic alumina column chromatography with 5 % ethyl acetate in hexanes.



169c

Yield: 40 %

IR (KBr) ν_{max} cm^{-1}: 3400, 3043, 2966, 2930, 1631, 1606, 1086, 798, 744

^{1}H NMR (400 MHz) δ: 7.93 (1H, d, *J* = 7.6 Hz); 7.26-7.36 (6H, m); 7.01-7.17 (4H, m); 6.81 (1H, d, *J* = 8.2 Hz); 4.32 (2H, s, NH-C$\underline{H}_2$); 4.21 (2H, q, *J* = 7.1 Hz, N-C$\underline{H}_2$CH$_3$); 2.29 (3H, s, ArC-C$\underline{H}_3$); 1.31 (3H, t, *J* = 7.1 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 141.9, 140.4, 136.8, 134.1, 129.3, 129.1, 127.8, 126.9, 125.3, 123.7, 122.7, 120.4, 117.9, 114.4, 109.2, 108.4, 103.4 (aromatic C), 49.6, 37.5, 21.2, 13.9 (aliphatic C)

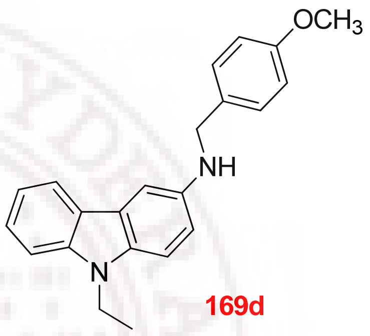
LCMS (m/z): 315 $(M+H)^+$

Anal. Calcd. for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91 %

Found: C, 84.03; H, 7.07; N, 9.12 %

*N*3-(4-Methoxylbenzyl)-9-ethyl-9*H*-3-carbazolamine (169d)

Reaction of **158c** in the presence of $InCl_3$ (10 mol %) with 4-methoxybenzaldehyde (**165e**) and **95** in [Bmim][BF_4] following the *general procedure G* provided the title compound as a minor reduced amination product. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.



169d

Yield: 40 %

Mp: 107-108 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3391, 3051, 2934, 2862, 1608, 1575, 1032, 800, 746

^{1}H NMR (400 MHz) δ: 7.98 (1H, d, *J* = 7.5 Hz); 7.31-7.41 (5H, m); 7.11-7.22 (2H, m); 6.87 (3H, d, *J* = 7.2 Hz); 4.34 (2H, s, NH-C$\underline{H_2}$); 4.28 (2H, q, *J* = 6.6 Hz, N-C$\underline{H_2}$CH$_3$); 3.78 (4H, s); 1.37 (3H, t, *J* = 6.8 Hz, N-CH$_2$C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 158.9, 141.9, 140.4, 134.1, 132.0, 129.1, 125.4, 123.7, 122.7, 120.4, 117.9, 114.5, 109.2, 108.4, 103.4 (aromatic C), 55.4, 49.4, 37.6, 13.9 (aliphatic C)

LCMS (m/z): 331 (M+H)$^+$

Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48 %

Found: C, 79.67; H, 6.90; N, 8.74 %

Table 32. Crystal data and structure refinement for 159a

Empirical formula	$C_{52}H_{44}Cl_2N_6$	
Formula weight	823.83	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.840(2) Å	α = 67.11(3)°
	b = 14.299(3) Å	β = 75.27(3)°
	c = 15.854(3) Å	γ = 85.97(3)°
Volume	2188.3(8) Å^3	
Z	2	
Density (calculated)	1.250 Mg/m^3	
Absorption coefficient	0.192 mm^{-1}	
F (000)	864	
Crystal size	0.42 x 0.10 x 0.02 mm^3	
Theta range for data collection	1.44 to 25.00°	
Index ranges	-12<=h<=12, -17<=k<=17, -18<=l<=18	
Reflections collected	21101	
Independent reflections	7671 [R(int) = 0.0846]	
Completeness to theta = 26.04°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9962 and 0.9238	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7671 / 4 / 562	
Goodness-of-fit on F^2	0.899	
Final R indices [I>2sigma (I)]	R1 = 0.0716, wR2 = 0.1394	
R indices (all data)	R1 = 0.1674, wR2 = 0.1707	
Largest diff. peak and hole	0.184 and -0.181 e.Å^{-3}	
CCDC number	678467	

Table 33. Crystal data and structure refinement for 159h

Empirical formula	: $C_{28}H_{25}Cl_2N_3$	
Formula weight	: 474.41	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 10.912(2) Å	α = 90°
	: b = 16.114(3) Å	β = 98.575(4)°
	: c = 13.277(3) Å	γ = 90°
Volume	: 2308.5(8) $Å^3$	
Z	: 4	
Density (calculated)	: 1.365 Mg/m^3	
Absorption coefficient	: 0.304 mm^{-1}	
F (000)	: 992	
Crystal size	: 0.40 x 0.26 x 0.20 mm^3	
Theta range for data collection	: 1.89 to 25.00°	
Index ranges	: -12<=h<=12, -19<=k<=19, -14<=l<=15	
Reflections collected	: 13410	
Independent reflections	: 4056 [R(int) = 0.0301]	
Completeness to theta = 26.04°	: 100.0 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9418 and 0.8882	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 4056 / 0 / 305	
Goodness-of-fit on F^2	: 1.035	
Final R indices [I>2sigma (I)]	: R1 = 0.0478, wR2 = 0.1138	
R indices (all data)	: R1 = 0.0715, wR2 = 0.1242	
Largest diff. peak and hole	: 0.186 and -0.262 e.$Å^{-3}$	
CCDC number	: 678470	

Table 34. Crystal data and structure refinement for 159i

Empirical formula	: $C_{29}H_{28}ClN_3$	
Formula weight	: 453.99	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: C2/c	
Unit cell dimensions	: a = 21.572(12) Å	α = 90°
	: b = 10.274(5) Å	β = 100.722(9)°
	: c = 21.695(12) Å	γ = 90°
Volume	: 4725(4) $Å^3$	
Z	: 8	
Density (calculated)	: 1.277 Mg/m^3	
Absorption coefficient	: 0.184 mm^{-1}	
F (000)	: 1920	
Crystal size	: 0.40 x 0.32 x 0.08 mm^3	
Theta range for data collection	: 1.91 to 25.00°	
Index ranges	: -25<=h<=25, -9<=k<=12, -25<=l<=25	
Reflections collected	: 10664	
Independent reflections	: 4045 [R(int) = 0.0368]	
Completeness to theta = 26.04°	: 97.1 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9854 and 0.9300	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 4045 / 0 / 306	
Goodness-of-fit on F^2	: 1.023	
Final R indices [I>2sigma (I)]	: R1 = 0.0793, wR2 = 0.1158	
R indices (all data)	: R1 = 0.1083, wR2 = 0.1264	
Largest diff. peak and hole	: 0.170 and -0.193 e.$Å^{-3}$	
CCDC number	: 678469	

Table 35. Crystal data and structure refinement for 159j

Empirical formula	: $C_{29}H_{29}N_3$
Formula weight	: 419.55
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: C2/c
Unit cell dimensions	: a = 25.180(7) Å α = 90° : b = 6.0388(17) Å β = 104.905(4)° : c = 30.338(9) Å γ = 90°
Volume	: 4458(2) $Å^3$
Z	: 8
Density (calculated)	: 1.250 Mg/m^3
Absorption coefficient	: 0.074 mm^{-1}
F (000)	: 1792
Crystal size	: 0.60 x 0.22 x 0.06 mm^3
Theta range for data collection	: 1.67 to 25.00°
Index ranges	: -29<=h<=28, -7<=k<=7, -31<=l<=36
Reflections collected	: 12794
Independent reflections	: 3926 [R(int) = 0.2282]
Completeness to theta = 26.04°	: 99.9 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9956 and 0.9571
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3926 / 0 / 297
Goodness-of-fit on F^2	: 0.863
Final R indices [I>2sigma (I)]	: R1 = 0.0969, wR2 = 0.1795
R indices (all data)	: R1 = 0.2742, wR2 = 0.2275
Largest diff. peak and hole	: 0.268 and -0.244 e.$Å^{-3}$
CCDC number	: 678468

Table 36. Crystal data and structure refinement for 160

Empirical formula	: $C_{28}H_{26}ClN_3$
Formula weight	: 439.97
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 15.3230(18) Å α = 90°
	: b = 12.4769(15) Å β = 104.483(2)°
	: c = 11.8279(14) Å γ = 90°
Volume	: 2189.4(5) $Å^3$
Z	: 4
Density (calculated)	: 1.335 Mg/m^3
Absorption coefficient	: 0.196 mm^{-1}
F (000)	: 928
Crystal size	: 0.40 x 0.18 x 0.16 mm^3
Theta range for data collection	: 1.37 to 26.00°
Index ranges	: -18<=h<=18, -15<=k<=14, -14<=l<=14
Reflections collected	: 15479
Independent reflections	: 4277 [R(int) = 0.0276]
Completeness to theta = 26.04°	: 99.0 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9693 and 0.9256
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 4277 / 0 / 296
Goodness-of-fit on F^2	: 1.021
Final R indices [I>2sigma (I)]	: R1 = 0.0535, wR2 = 0.1341
R indices (all data)	: R1 = 0.0660, wR2 = 0.1423
Largest diff. peak and hole	: 0.696 and -0.376 e.$Å^{-3}$
CCDC number	: 678466

Table 37. Crystal data and structure refinement for 161c

Empirical formula	: $C_{26}H_{25}BrN_2O$
Formula weight	: 461.39
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/n
Unit cell dimensions	: a = 10.2548(7) Å α = 90°
	: b = 10.9487(8) Å β = 103.838(10)°
	: c = 19.587(14) Å γ = 90°
Volume	: 2135.4(3) $Å^3$
Z	: 4
Density (calculated)	: 1.435 Mg/m^3
Absorption coefficient	: 1.946 mm^{-1}
F (000)	: 952
Crystal size	: 0.50 x 0.26 x 0.10 mm^3
Theta range for data collection	: 2.07 to 25.00°
Index ranges	: -12<=h<=12, -12<=k<=13, -23<=l<=23
Reflections collected	: 19961
Independent reflections	: 3757 [R(int) = 0.0293]
Completeness to theta = 26.04°	: 99.9 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.8292 and 0.4429
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3757 / 0 / 278
Goodness-of-fit on F^2	: 1.038
Final R indices [I>2sigma (I)]	: R1 = 0.0405, wR2 = 0.1032
R indices (all data)	: R1 = 0.0531, wR2 = 0.1094
Largest diff. peak and hole	: 0.619 and -0.474 e.$Å^{-3}$
CCDC number	: 678471

Table 38. Crystal data and structure refinement for 161d

Empirical formula	$C_{27}H_{28}N_2O$	
Formula weight	396.51	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.1868(9) Å	α = 90°
	b = 11.0925(8) Å	β = 90.0730(10)°
	c = 15.474(11) Å	γ = 90°
Volume	2091.8(3) $Å^3$	
Z	4	
Density (calculated)	1.259 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F (000)	848	
Crystal size	0.44 x 0.40 x 0.30 mm^3	
Theta range for data collection	2.13 to 25.00°	
Index ranges	-14<=h<=14, -13<=k<=13, -18<=l<=18	
Reflections collected	19686	
Independent reflections	3688 [R(int) = 0.0261]	
Completeness to theta = 26.04°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9774 and 0.9671	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3688 / 0 / 279	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma (I)]	R1 = 0.0437, wR2 = 0.1113	
R indices (all data)	R1 = 0.0508, wR2 = 0.1160	
Largest diff. peak and hole	0.236 and -0.206 e.$Å^{-3}$	
CCDC number	678473	

Table 39. Crystal data and structure refinement for 162

Empirical formula	: $C_{26}H_{25}BrN_2O$
Formula weight	: 461.39
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/n
Unit cell dimensions	: a = 14.839(4) Å α = 90°
	: b = 8.785(2) Å β = 91.424(4)°
	: c = 15.888(4) Å γ = 90°
Volume	: 2070.5(9) $Å^3$
Z	: 4
Density (calculated)	: 1.480 Mg/m^3
Absorption coefficient	: 2.006 mm^{-1}
F (000)	: 952
Crystal size	: 0.20 x 0.20 x 0.17 mm^3
Theta range for data collection	: 1.85 to 25.00°
Index ranges	: -17<=h<=17, -10<=k<=10, -18<=l<=18
Reflections collected	: 19134
Independent reflections	: 3650 [R(int) = 0.0276]
Completeness to theta = 26.04°	: 99.8 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.7266 and 0.6897
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3650 / 0 / 278
Goodness-of-fit on F^2	: 1.044
Final R indices [I>2sigma (I)]	: R1 = 0.0396, wR2 = 0.1076
R indices (all data)	: R1 = 0.0510, wR2 = 0.1136
Largest diff. peak and hole	: 1.181 and -0.417 e.$Å^{-3}$
CCDC number	: 678472

Table 40. Crystal data and structure refinement for 163

Empirical formula	: $C_{24}H_{30}N_2$
Formula weight	: 346.50
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 12.680(3) Å ɑ = 90°
	: b = 7.8737(17) Å β = 103.194(4)°
	: c = 20.108(4) Å γ = 90°
Volume	: 1954.6(7) $Å^3$
Z	: 4
Density (calculated)	: 1.178 Mg/m^3
Absorption coefficient	: 0.068 mm^{-1}
F (000)	: 752
Crystal size	: 0.42 x 0.10 x 0.10 mm^3
Theta range for data collection	: 1.65 to 25.00°
Index ranges	: -15<=h<=13, -9<=k<=9, -20<=l<=23
Reflections collected	: 10054
Independent reflections	: 3417 [R(int) = 0.0482]
Completeness to theta = 26.04°	: 100.0 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9932 and 0.9719
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3417 / 0 / 243
Goodness-of-fit on F^2	: 1.185
Final R indices [I>2sigma (I)]	: R1 = 0.1004, wR2 = 0.2085
R indices (all data)	: R1 = 0.1350, wR2 = 0.2258
Largest diff. peak and hole	: 0.435 and -0.183 e.$Å^{-3}$
CCDC number	: 678474

Table 41. Crystal data and structure refinement for 164

Empirical formula	$C_{24}H_{30}N_2$
Formula weight	346.50
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 9.456(4) Å α = 90°
	b = 9.538(4) Å β = 94.887(6)°
	c = 21.796(8) Å γ = 90°
Volume	1958.7(13) Å^3
Z	4
Density (calculated)	1.175 Mg/m^3
Absorption coefficient	0.068 mm^{-1}
F (000)	752
Crystal size	0.60 x 0.22 x 0.20 mm^3
Theta range for data collection	1.88 to 25.00°
Index ranges	-11<=h<=11, -11<=k<=11, -25<=l<=25
Reflections collected	17953
Independent reflections	3448 [R(int) = 0.0312]
Completeness to theta = 26.04°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9865 and 0.9602
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3448 / 0 / 243
Goodness-of-fit on F^2	1.149
Final R indices [I>2sigma (I)]	R1 = 0.0878, wR2 = 0.2138
R indices (all data)	R1 = 0.0995, wR2 = 0.2219
Largest diff. peak and hole	0.714 and -0.260 e.Å^{-3}
CCDC number	678475

Table 42. Crystal data and structure refinement for 166b

Empirical formula	: $C_{26}H_{26}N_2O$	
Formula weight	: 382.49	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 12.171(4) Å	α = 90°
	: b = 19.615(6) Å	β = 99.583(5)°
	: c = 8.481(3) Å	γ = 90°
Volume	: 1996.5(11) Å^3	
Z	: 4	
Density (calculated)	: 1.272 Mg/m^3	
Absorption coefficient	: 0.078 mm^{-1}	
F (000)	: 816	
Crystal size	: 0.60 x 0.10 x 0.06 mm^3	
Theta range for data collection	: 1.70 to 25.00°	
Index ranges	: -14<=h<=14, -23<=k<=23, -10<=l<=10	
Reflections collected	: 18400	
Independent reflections	: 3517 [R(int) = 0.0430]	
Completeness to theta = 26.04°	: 100.0 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9954 and 0.9550	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 3517 / 0 / 271	
Goodness-of-fit on F^2	: 1.013	
Final R indices [I>2sigma (I)]	: R1 = 0.0433, wR2 = 0.0995	
R indices (all data)	: R1 = 0.0702, wR2 = 0.1106	
Largest diff. peak and hole	: 0.157 and -0.159 e.Å^{-3}	
CCDC number	: 700692	

Table 43. Crystal data and structure refinement for 166c

Empirical formula	$C_{33}H_{32}N_2O$
Formula weight	472.61
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 12.009(2) Å α = 90°
	b = 23.983(5) Å β = 91.916(4)°
	c = 8.8101(17) Å γ = 90°
Volume	2536.0(8) Å^3
Z	4
Density (calculated)	1.238 Mg/m^3
Absorption coefficient	0.074 mm^{-1}
F (000)	1008
Crystal size	0.60 x 0.20 x 0.03 mm^3
Theta range for data collection	1.70 to 25.00°
Index ranges	-14<=h<=14, -28<=k<=28, -10<=l<=10
Reflections collected	24115
Independent reflections	4464 [R(int) = 0.0841]
Completeness to theta = 26.04°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9978 and 0.9568
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4464 / 0 / 331
Goodness-of-fit on F^2	1.093
Final R indices [I>2sigma (I)]	R1 = 0.0768, wR2 = 0.1325
R indices (all data)	R1 = 0.1310, wR2 = 0.1504
Largest diff. peak and hole	0.185 and -0.163 e.Å^{-3}
CCDC number	700696

Table 44. Crystal data and structure refinement for 166j

Empirical formula	$C_{29}H_{29}N_3O$	
Formula weight	435.55	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.694(3) Å	α = 91.585(5)°
	b = 10.223(4) Å	β = 107.682(5)°
	c = 14.049(5) Å	γ = 107.141(5)°
Volume	1127.3(7) $Å^3$	
Z	2	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F (000)	464	
Crystal size	0.48 x 0.24 x 0.20 mm^3	
Theta range for data collection	1.53 to 25.00°	
Index ranges	-10<=h<=10, -12<=k<=12, -16<=l<=16	
Reflections collected	8195	
Independent reflections	3948 [R(int) = 0.1319]	
Completeness to theta = 26.04°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9845 and 0.9633	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3948 / 0 / 304	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma (I)]	R1 = 0.0525, wR2 = 0.1458	
R indices (all data)	R1 = 0.4872, wR2 = 0.2169	
Largest diff. peak and hole	0.619 and -0.692 e.$Å^{-3}$	
CCDC number	700695	

Table 45. Crystal data and structure refinement for 167

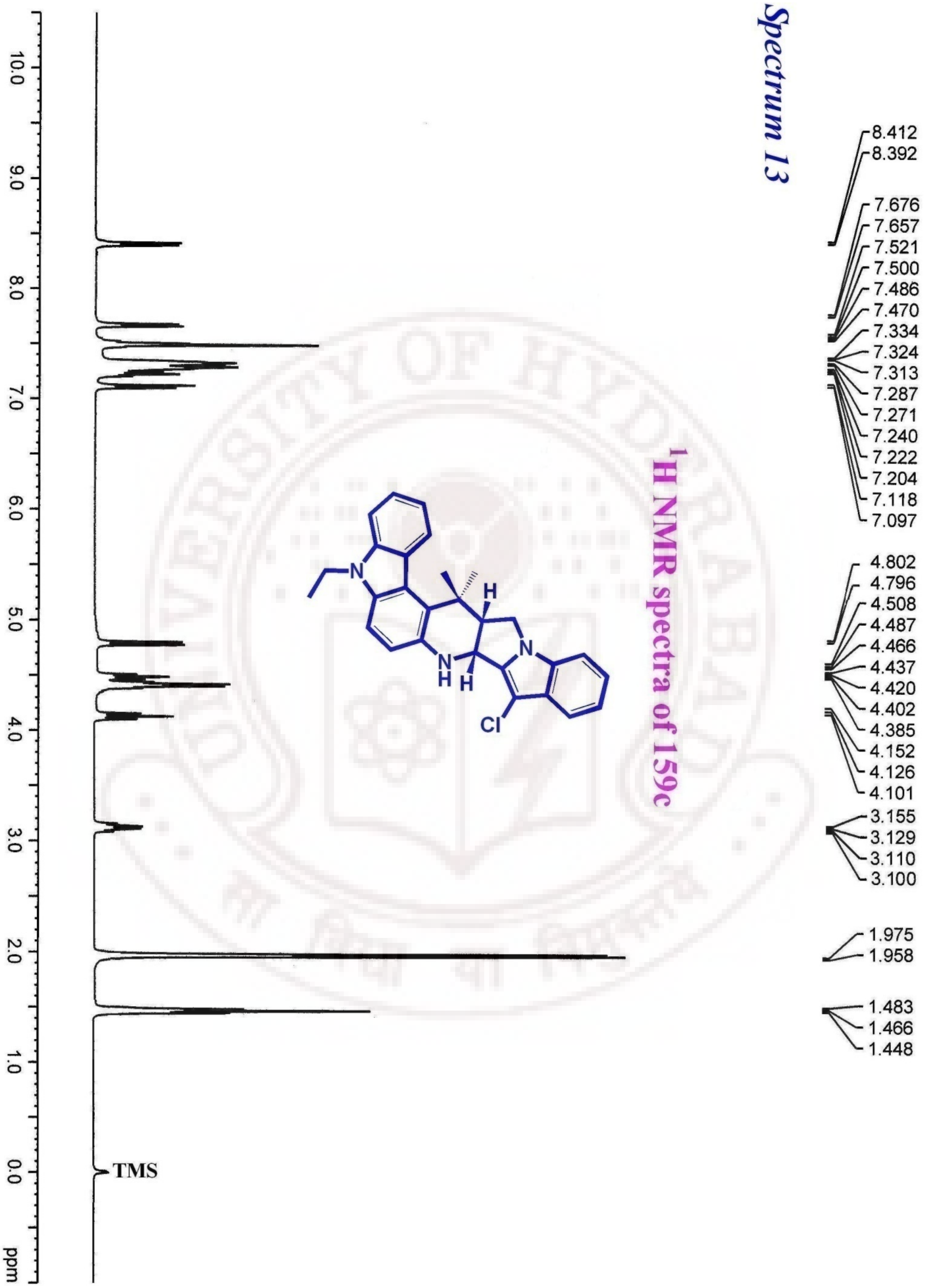
Empirical formula	$C_{52}H_{54}N_4O_2$	
Formula weight	766.99	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 17.345(6) Å	α = 90°
	b = 9.953(3) Å	β = 124.743(14)°
	c = 28.955(7) Å	γ = 90°
Volume	4107(2) $Å^3$	
Z	4	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F (000)	1640	
Crystal size	0.60 x 0.15 x 0.02 mm^3	
Theta range for data collection	1.43 to 25.00°	
Index ranges	-20<=h<=20, -11<=k<=11, -34<=l<=34	
Reflections collected	38437	
Independent reflections	7234 [R(int) = 0.1709]	
Completeness to theta = 26.04°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9985 and 0.9561	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7234 / 0 / 533	
Goodness-of-fit on F^2	0.946	
Final R indices [I>2sigma (I)]	R1 = 0.0840, wR2 = 0.1351	
R indices (all data)	R1 = 0.2440, wR2 = 0.1815	
Largest diff. peak and hole	0.188 and -0.194 e.$Å^{-3}$	
CCDC number	700691	

Table 46. Crystal data and structure refinement for 168

Empirical formula	$C_{26}H_{26}N_2O$
Formula weight	382.49
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 12.448(3) Å α = 90°
	b = 8.554(2) Å β = 95.512(4)°
	c = 19.291(5) Å γ = 90°
Volume	2044.7(9) $Å^3$
Z	4
Density (calculated)	1.243 Mg/m^3
Absorption coefficient	0.076 mm^{-1}
F (000)	816
Crystal size	0.28 x 0.18 x 0.10 mm^3
Theta range for data collection	1.87 to 25.00°
Index ranges	-14<=h<=14, -10<=k<=10, -22<=l<=22
Reflections collected	18849
Independent reflections	3584 [R(int) = 0.0575]
Completeness to theta = 26.04°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9925 and 0.9791
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3584 / 0 / 267
Goodness-of-fit on F^2	1.006
Final R indices [I>2sigma (I)]	R1 = 0.0554, wR2 = 0.1171
R indices (all data)	R1 = 0.0983, wR2 = 0.1330
Largest diff. peak and hole	0.122 and -0.176 e.$Å^{-3}$
CCDC number	700693

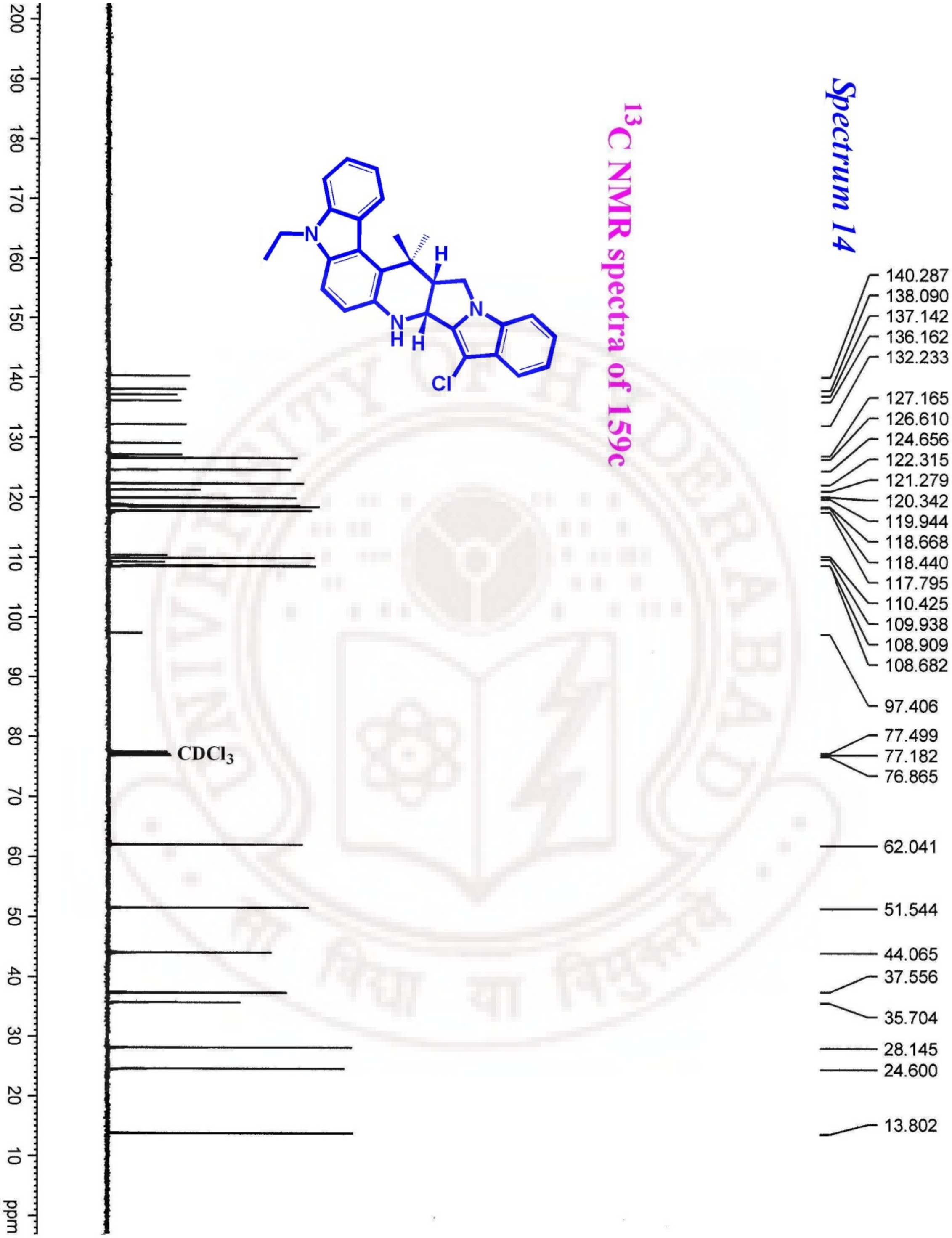
Table 47. Crystal data and structure refinement for 169d

Empirical formula	: $C_{22}H_{22}N_2O$
Formula weight	: 330.42
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 21.435(4) Å α = 90°
	: b = 10.400(2) Å β = 92.72(3)°
	: c = 8.2300(16) Å γ = 90°
Volume	: 1832.6(6) $Å^3$
Z	: 4
Density (calculated)	: 1.198 Mg/m^3
Absorption coefficient	: 0.074 mm^{-1}
F (000)	: 704
Crystal size	: 0.36 x 0.20 x 0.02 mm^3
Theta range for data collection	: 1.90 to 25.00°
Index ranges	: -25<=h<=25, -12<=k<=12, -9<=l<=9
Reflections collected	: 16226
Independent reflections	: 3216 [R(int) = 0.1000]
Completeness to theta = 26.04°	: 99.7 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9985 and 0.9739
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3216 / 0 / 232
Goodness-of-fit on F^2	: 1.262
Final R indices [I>2sigma (I)]	: R1 = 0.1143, wR2 = 0.1775
R indices (all data)	: R1 = 0.1719, wR2 = 0.1991
Largest diff. peak and hole	: 0.202 and -0.142 e.$Å^{-3}$
CCDC number	: 700694



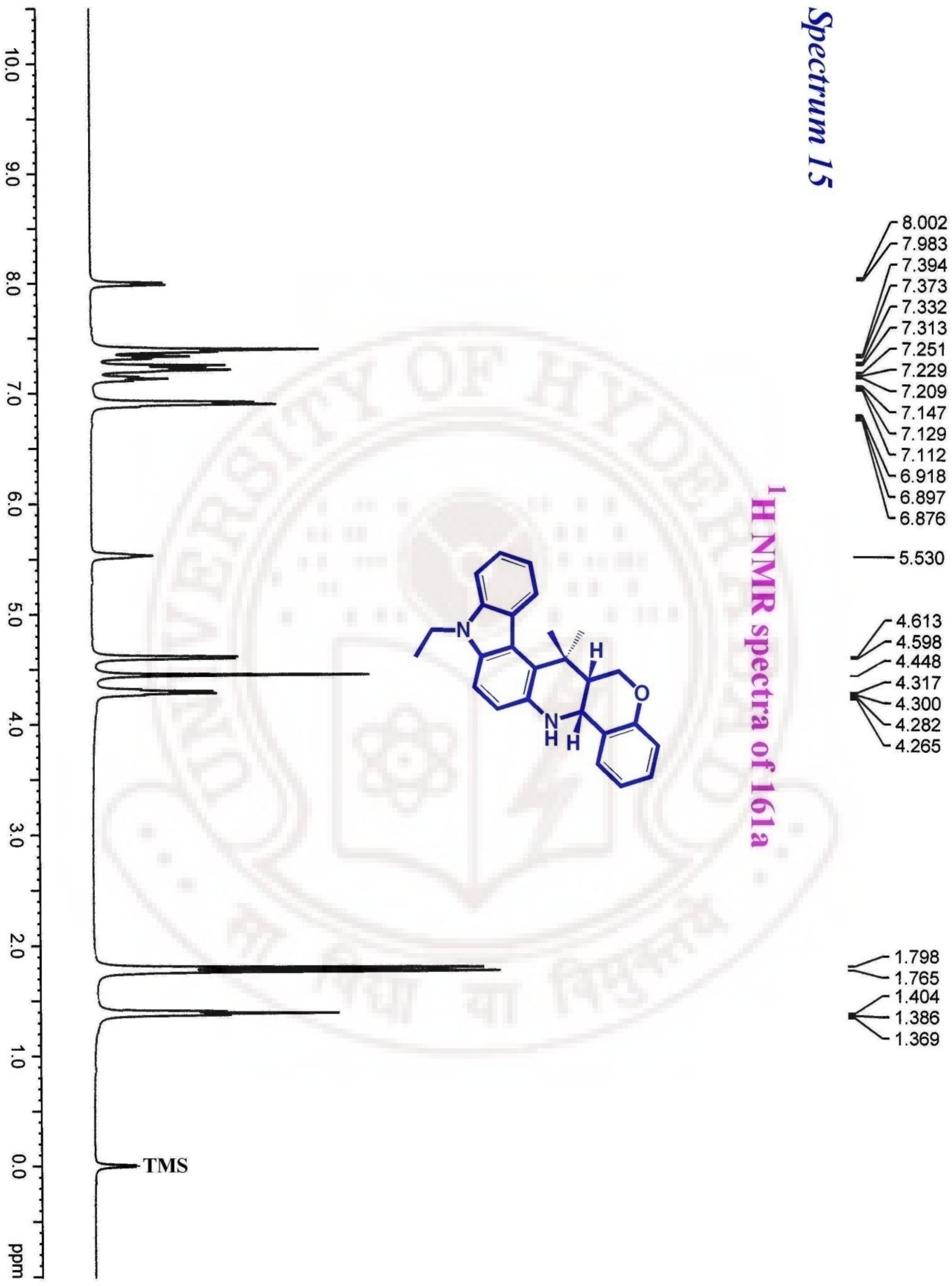
Spectrum 13

^{1}H NMR spectra of 159c



Spectrum 14

^{13}C NMR spectra of 159c

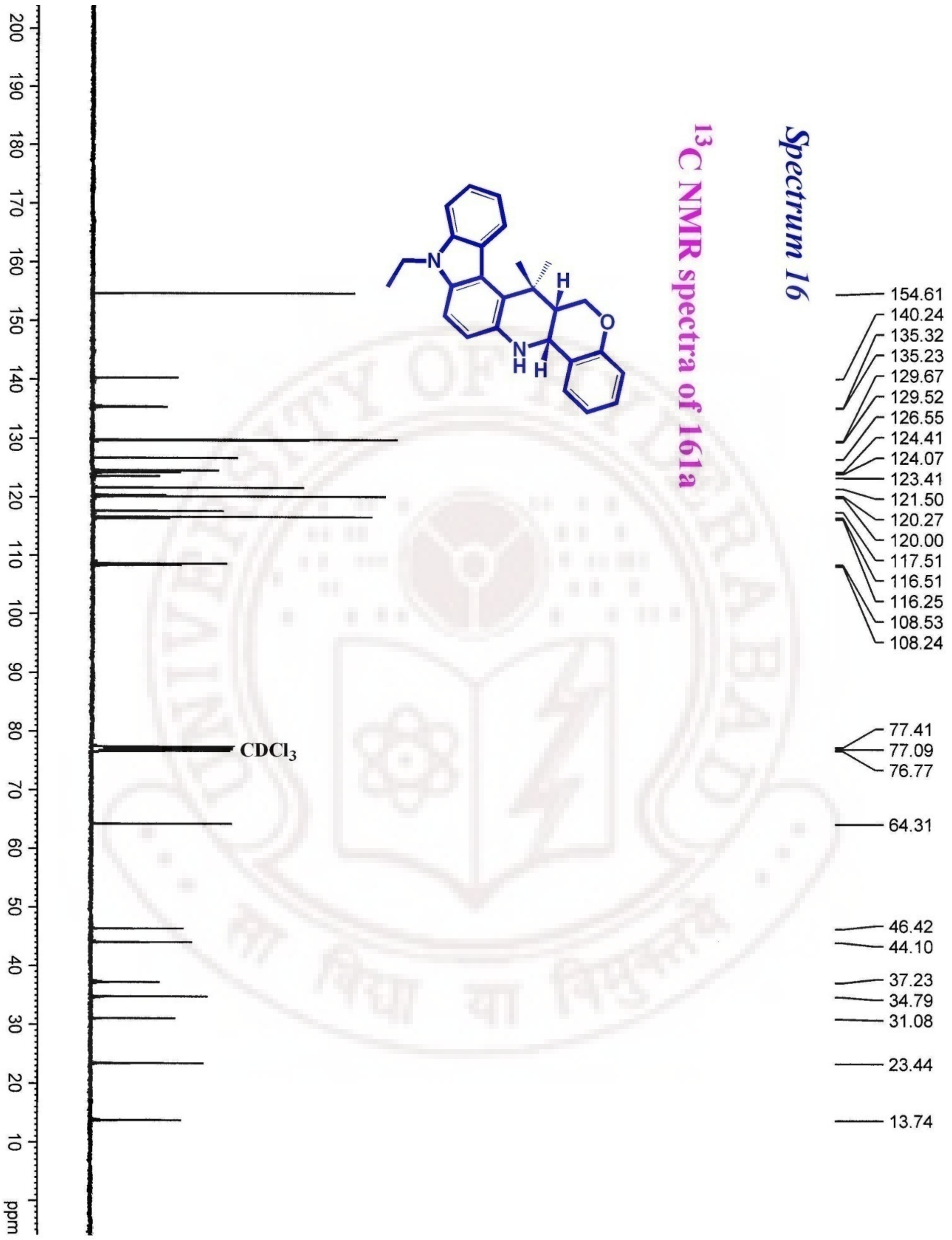


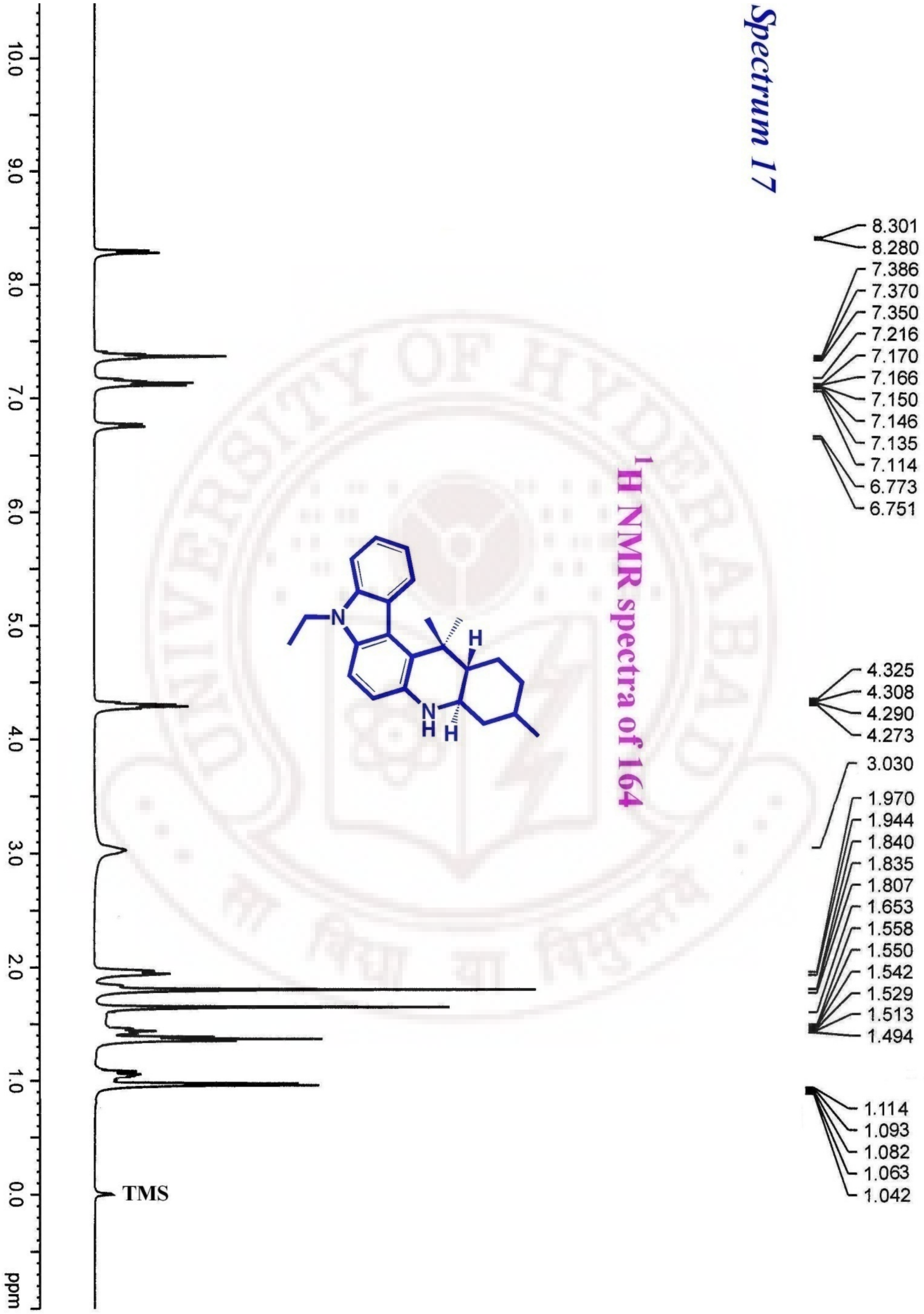
Spectrum 15

^{1}H NMR spectra of 161a

Spectrum 16

^{13}C NMR spectra of 161a



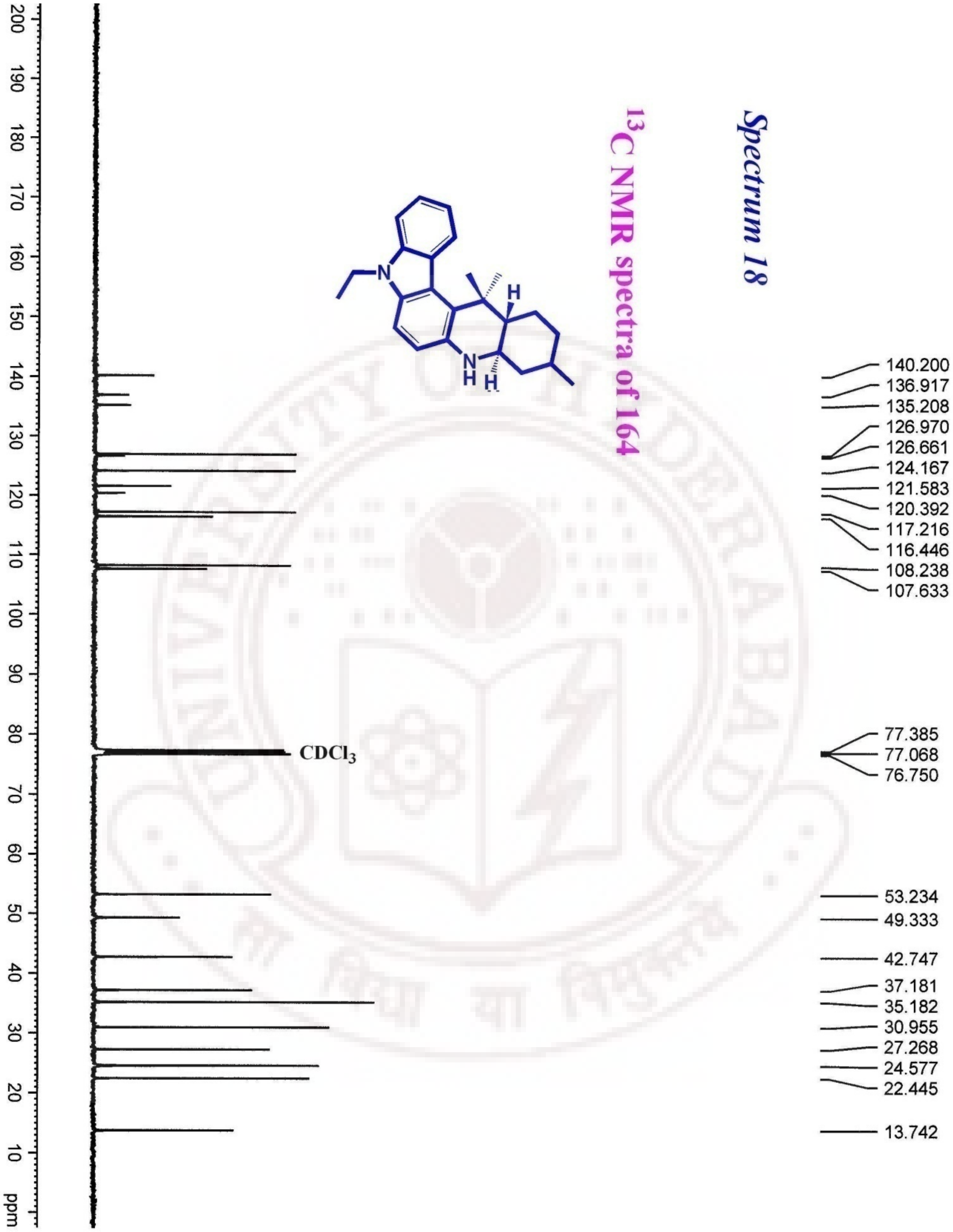


Spectrum 17

^{1}H NMR spectra of 164

Spectrum 18

^{13}C NMR spectra of 164



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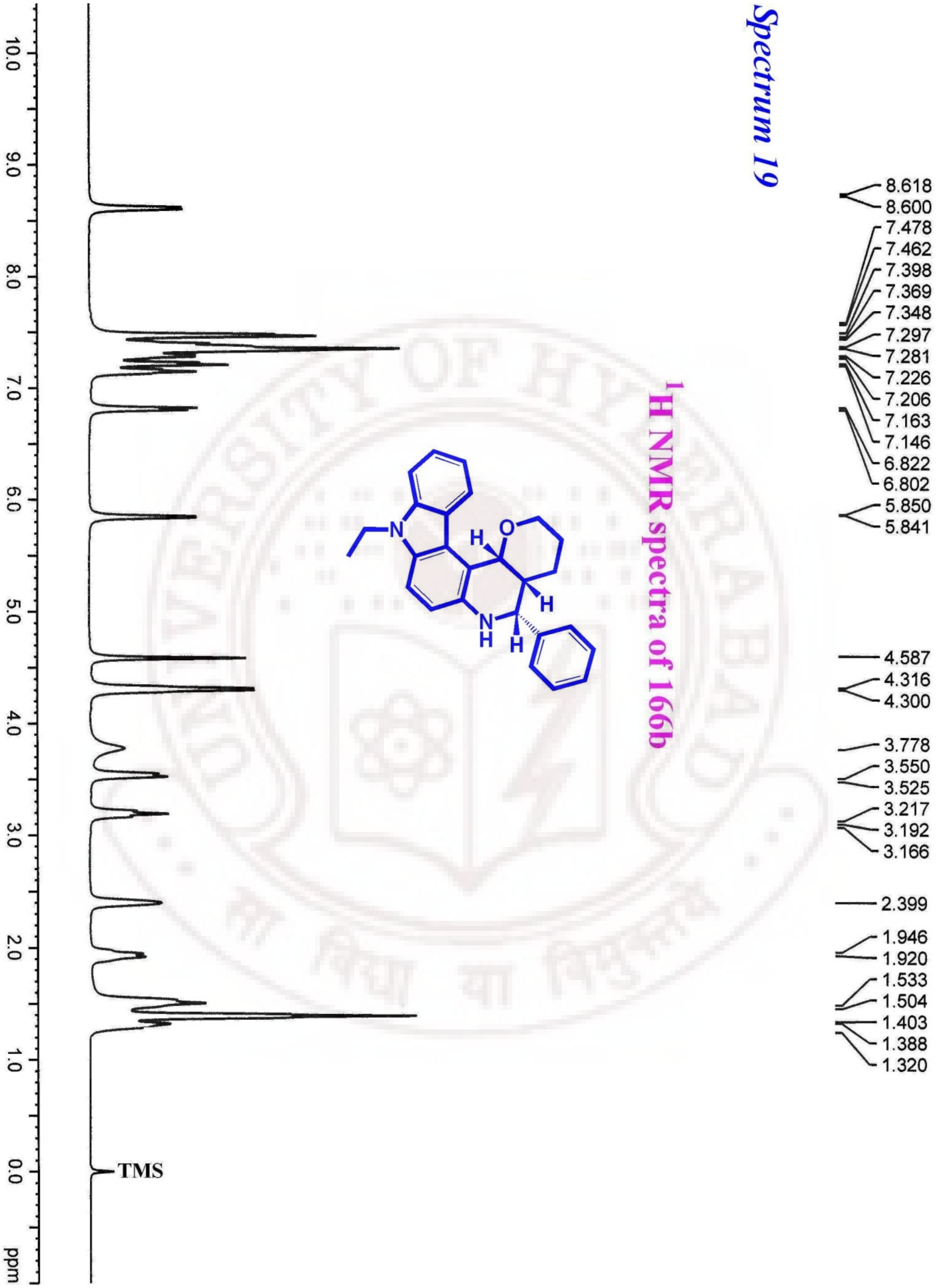
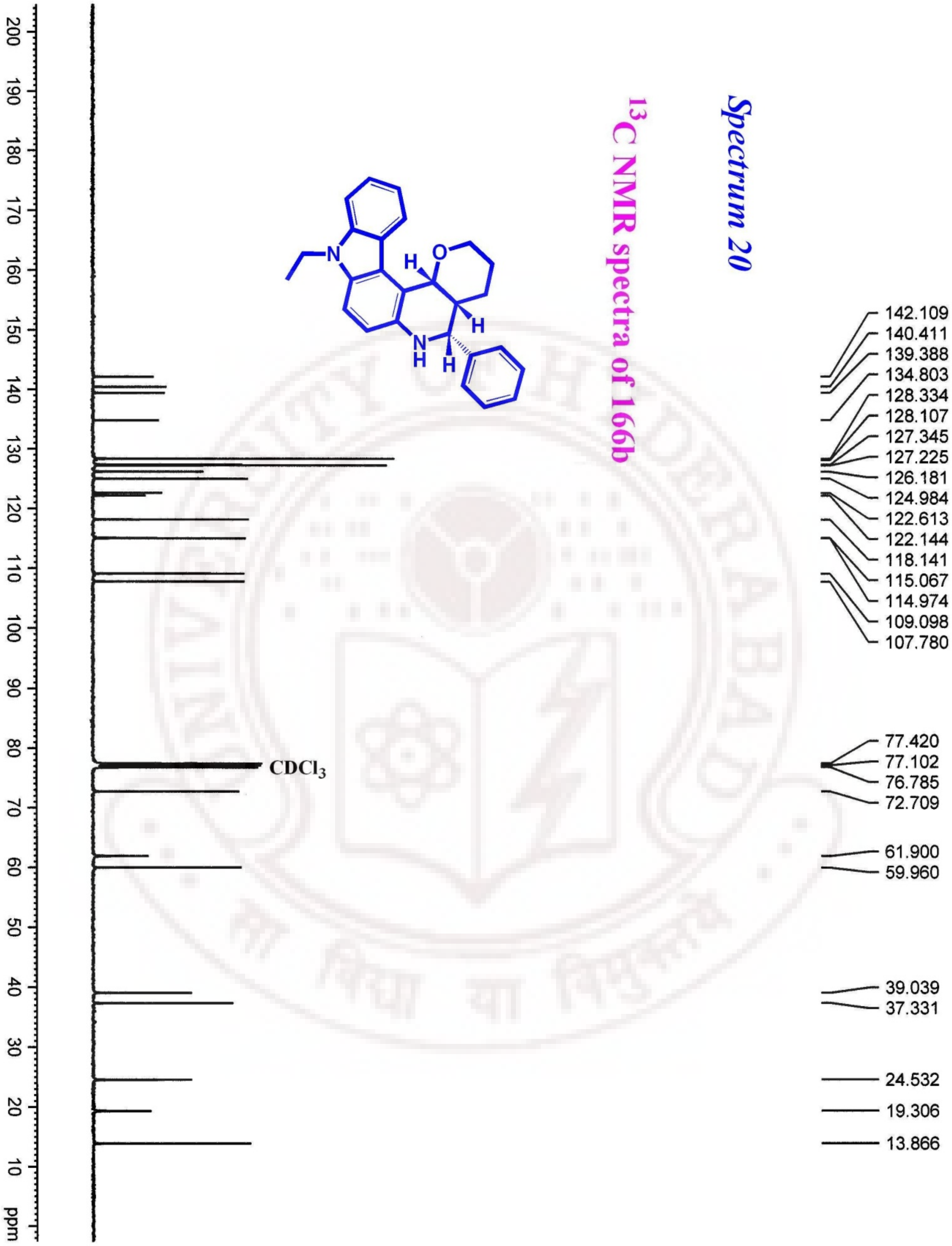


^{1}H NMR spectra of 166b

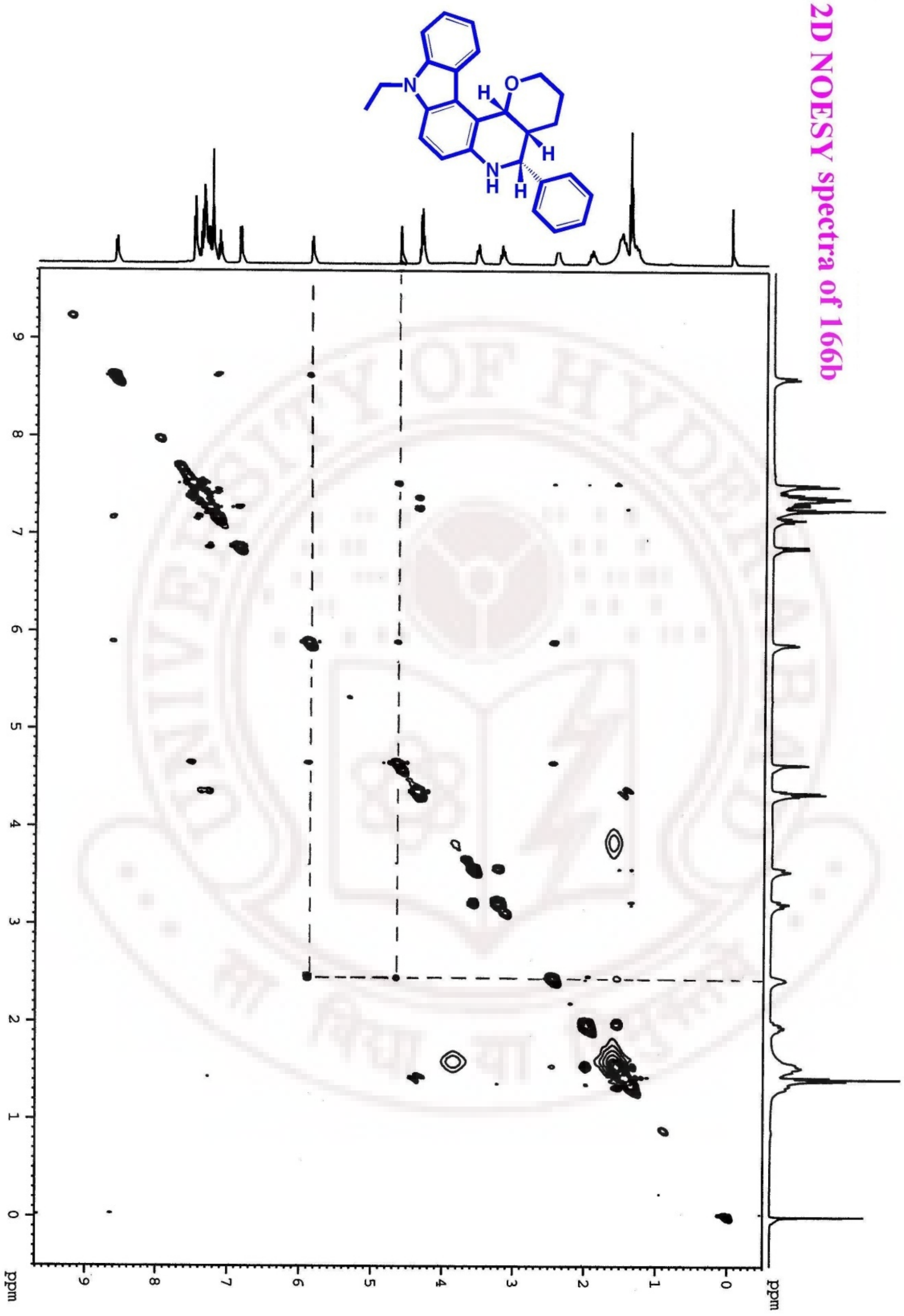


Spectrum 20

^{13}C NMR spectra of 166b

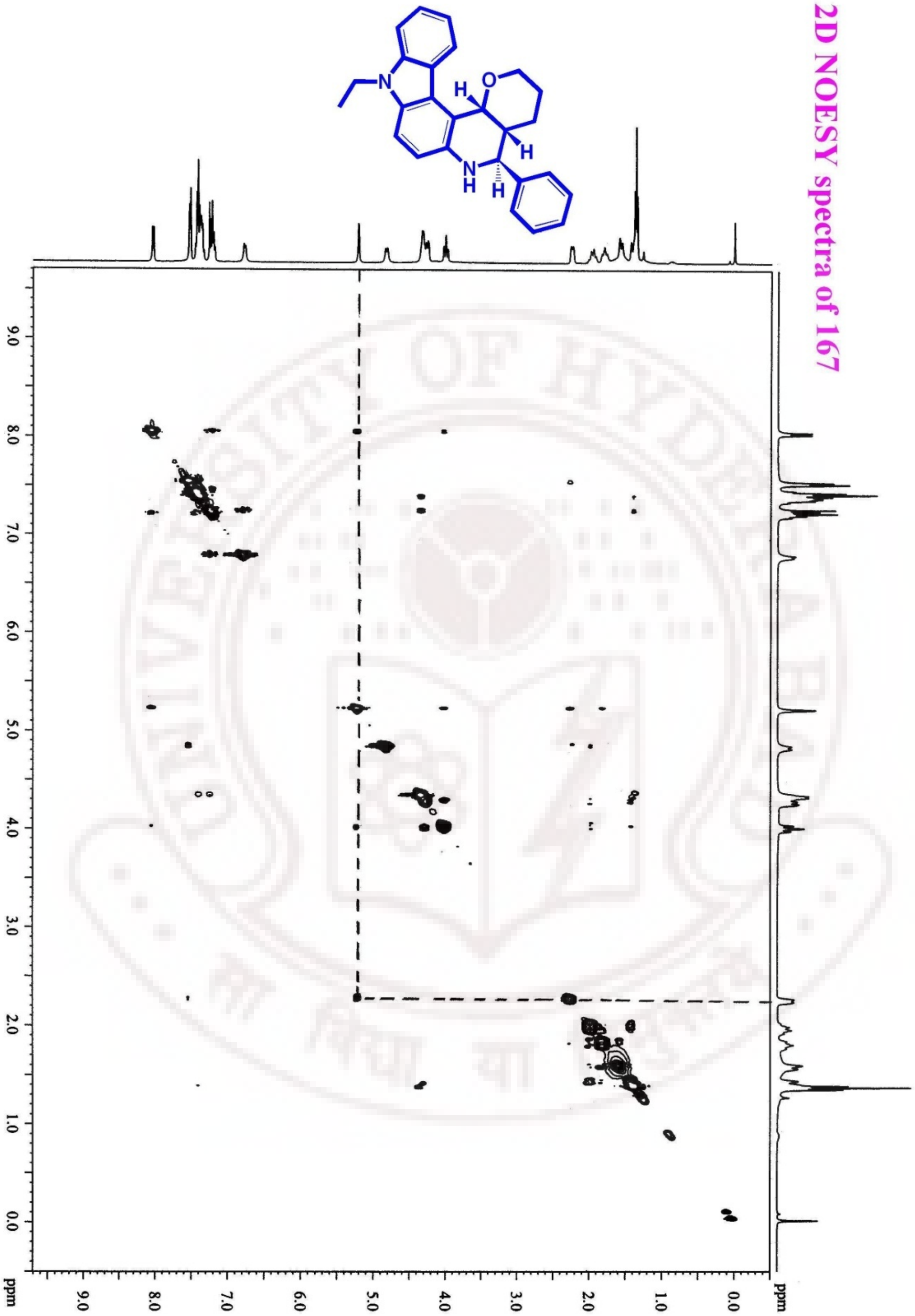
Spectrum 21

2D NOESY spectra of 166b

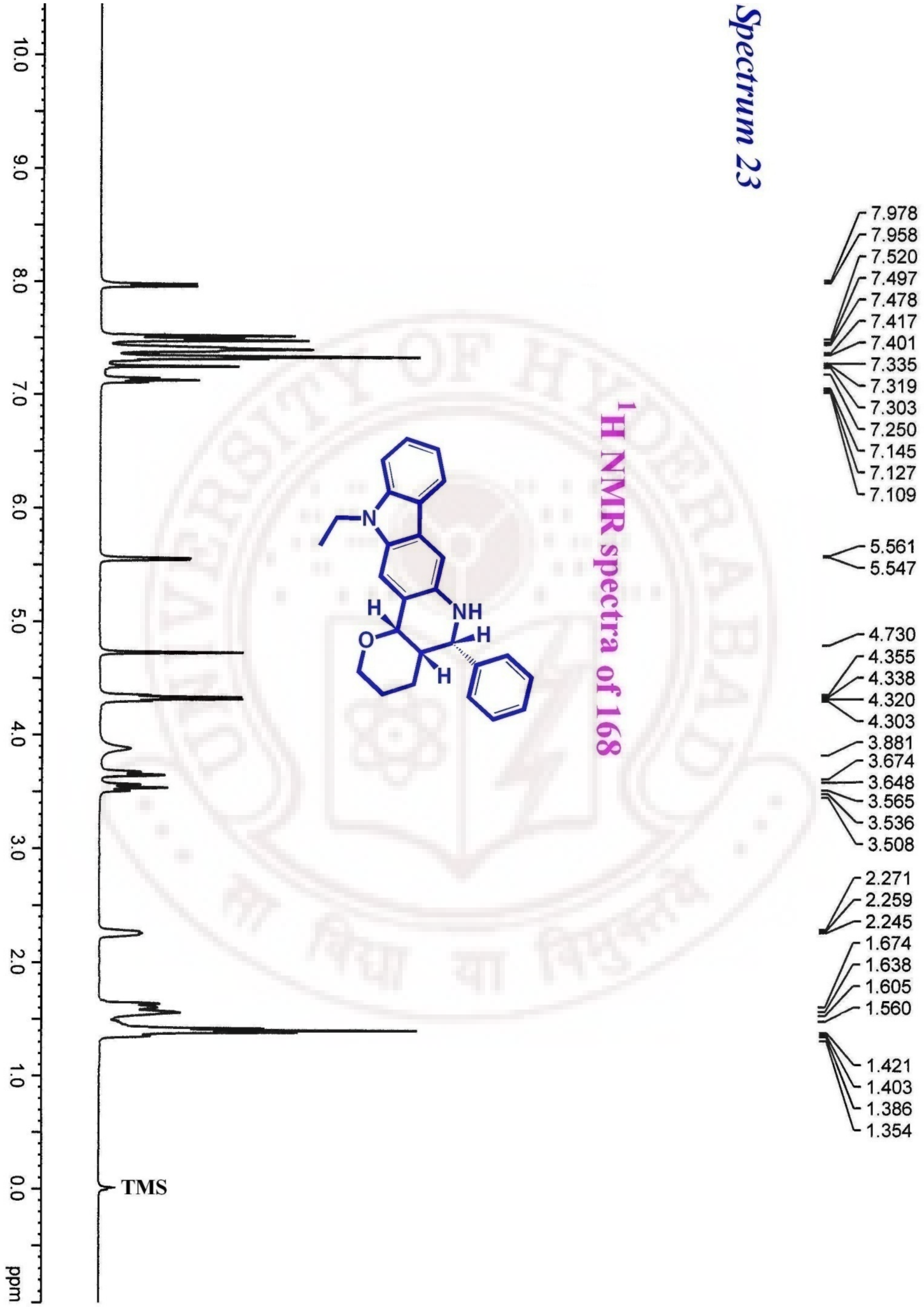


Spectrum 22

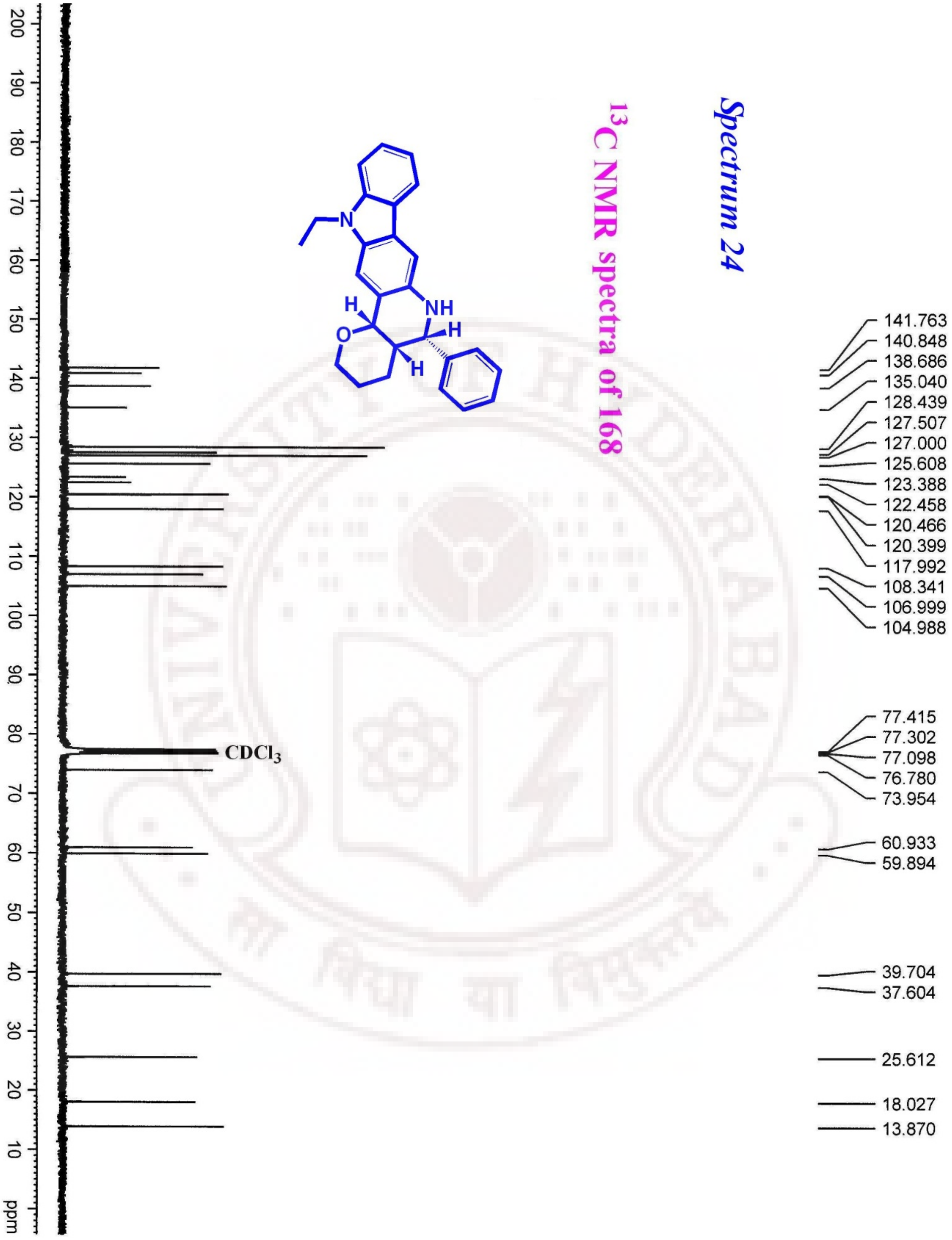
2D NOESY spectra of 167



Spectrum 23



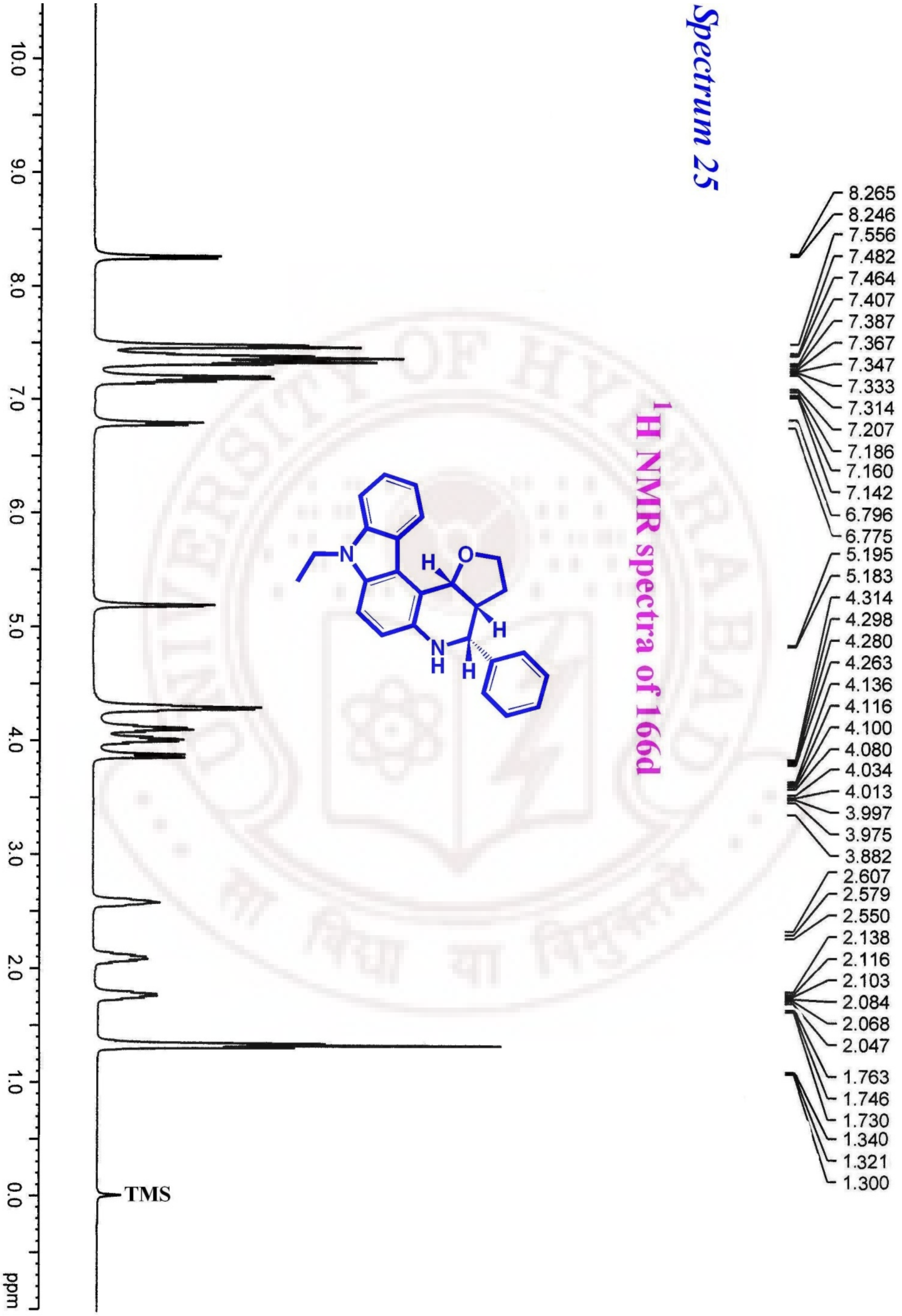
^{1}H NMR spectra of 168



Spectrum 24

^{13}C NMR spectra of 168

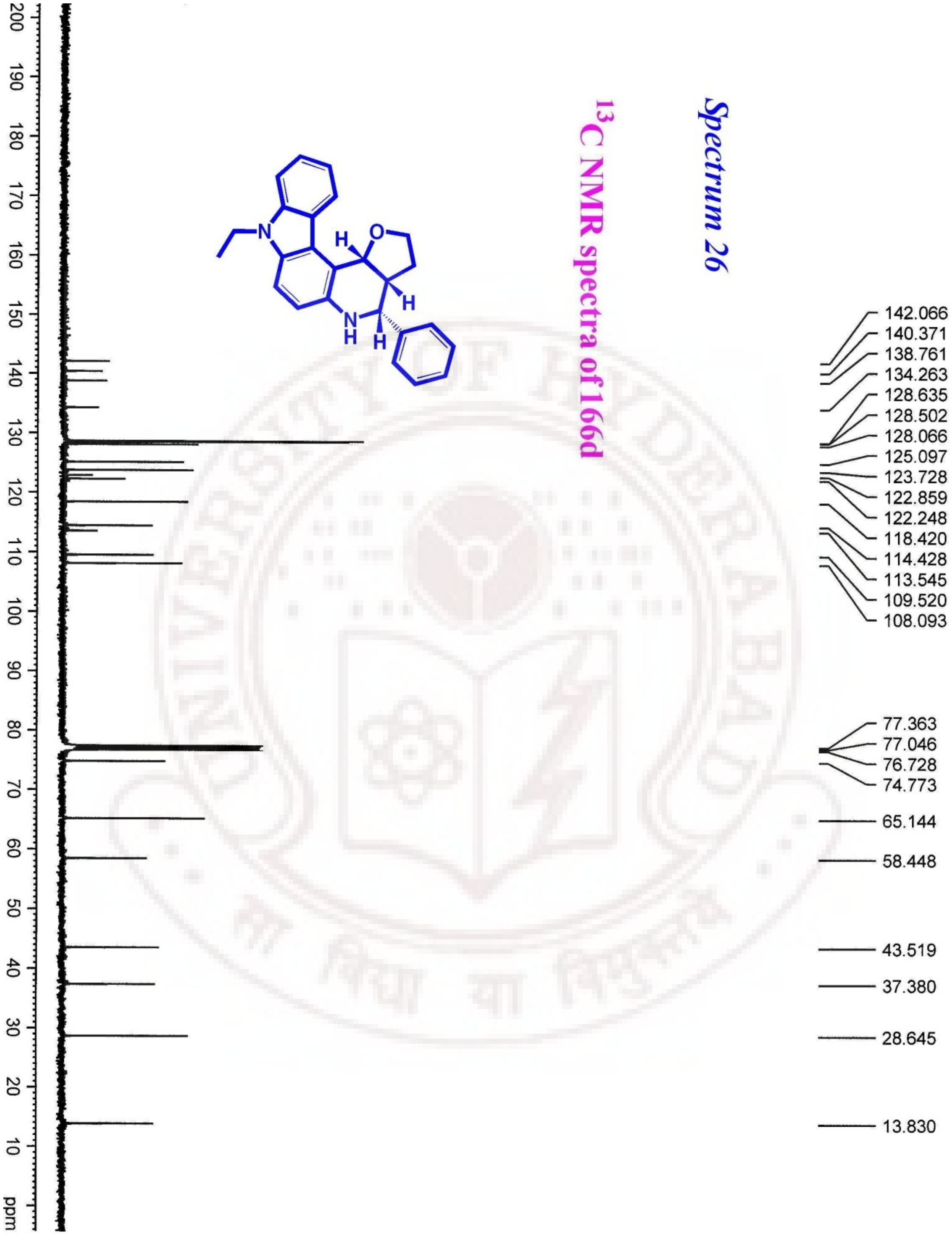
Spectrum 25

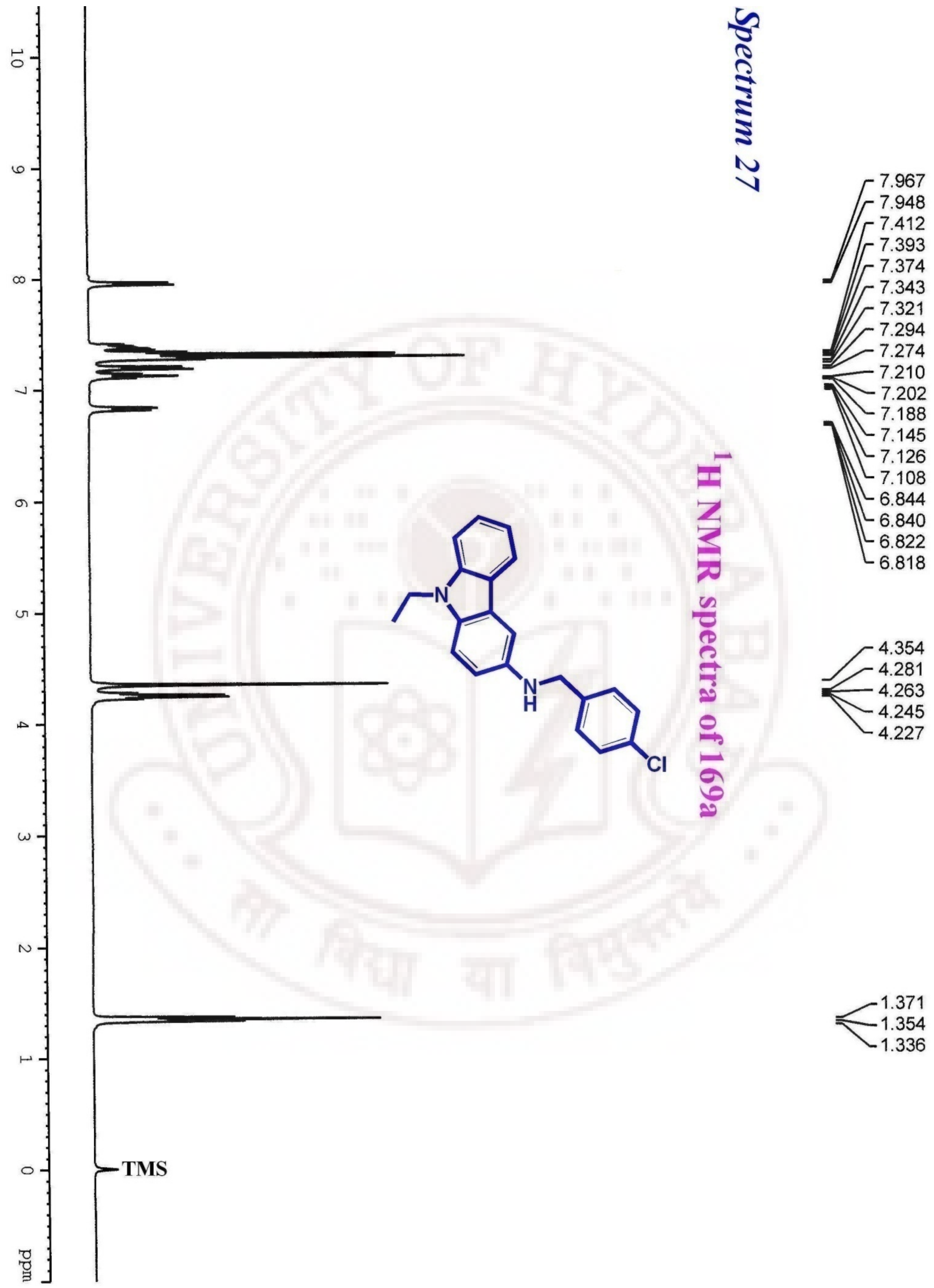


^{1}H NMR spectra of 166d

Spectrum 26

^{13}C NMR spectra of 166d



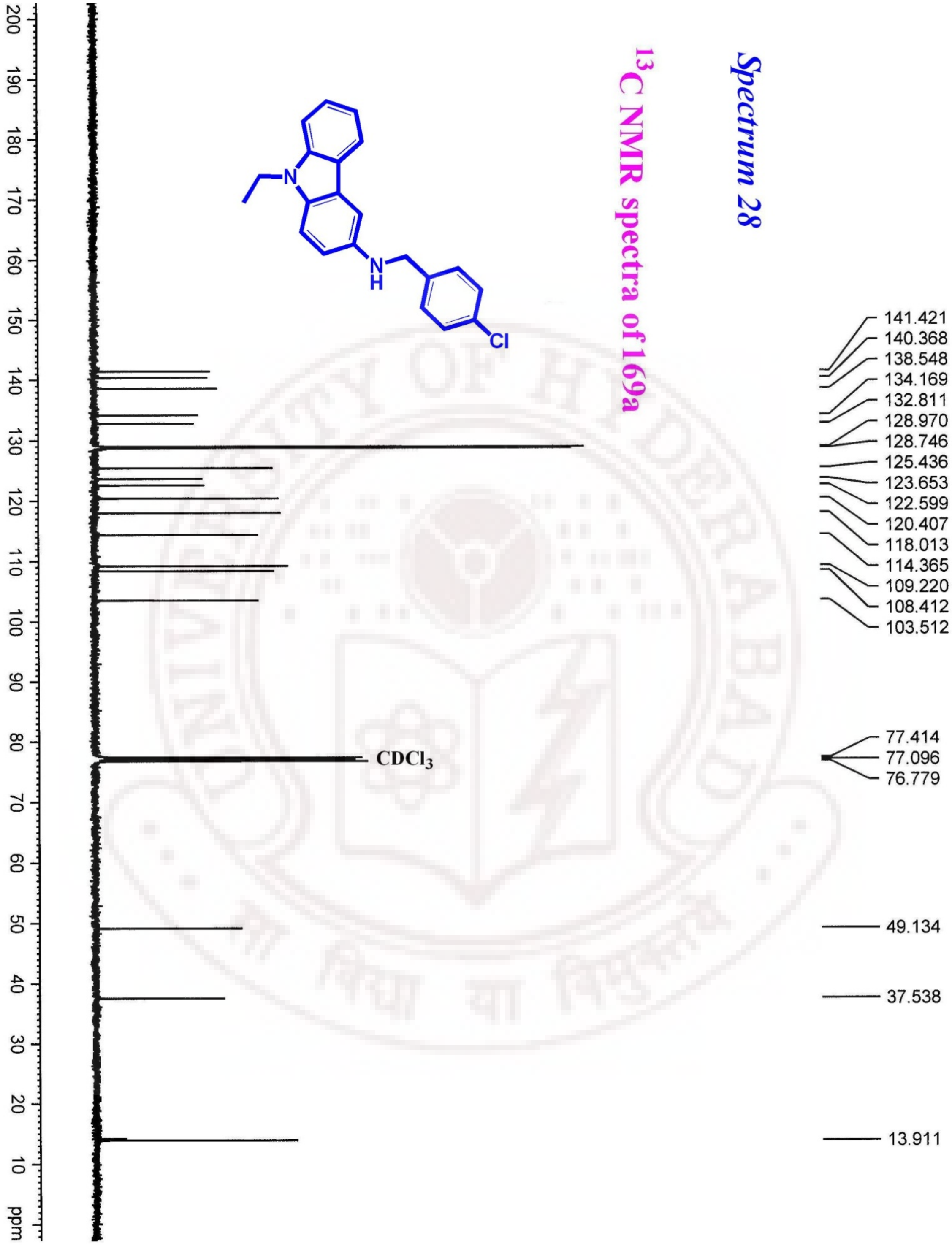


Spectrum 27

^{1}H NMR spectra of 169a

Spectrum 28

^{13}C NMR spectra of 169a



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Synthesis of Pyridocarbazole Derivatives Catalyzed by CuI/La(OTf)$_3$

CHAPTER 4

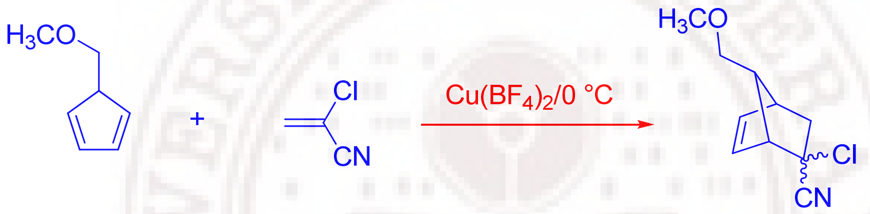
4.1. Introduction

Ellipticine and its analogues have received a vast amount of attention because of their anticancer properties due to interaction with DNA. Its derivative exhibit promising results in the treatment of osteolytic breast cancer metastasis, kidney sarcoma, brain tumours and myeloblastic leukemia.[140] The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects and complete lack of hematological toxicity.[150] So the synthesis of ellipticine and isoellipticine derivatives is an important area in organic chemistry.

In recent years, transition metal catalyzed coupling reactions have emerged as a powerful tool for the synthesis of heterocyclic compounds.[168-169] Chan *et al*. have developed Ag or Cu catalyzed efficient alkynylation of α-imino ester with aryl acetylenes.[170] These methods provide an effective route to propargylic amines, which are key intermediates to the construction of new pyridine ring. The numerous advantages of copper catalysts make them highly attractive for chemical synthesis from environmental and economic points of view. Copper(I) iodide is an inexpensive, nontoxic catalyst, insensitive to air in comparison to other transition metals such as Pd, Pt, Ru and Au. Therefore, CuI catalyzed cyclization has been accepted as a convenient tool for the preparation of heterocycles.[171] On the other hand, the use of single catalytic system to mediate two or more transformations in a single synthetic operation has recently emerged as a new research area.

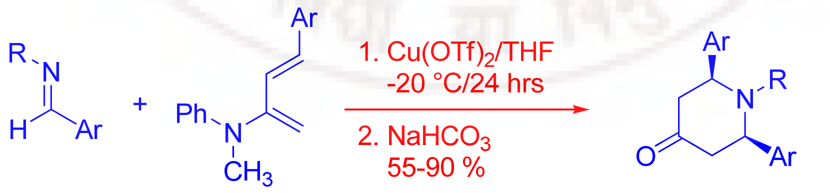
The very first Diels-Alder reaction promoted by copper species was presented by Bota *et al*.[172] They reported the cycloaddition of cyclopentadiene with acetylene to produce 2,5-norbornadiene by continuous flow reaction through a CuCl/NH_4Cl/activated carbon catalyst; however, the authors were not clear about the role of the catalyst.

In 1969, Corey *et al*. introduced the use of a copper salt [$Cu(BF_4)_2$] to catalyze the Diels-Alder reaction of diene **170** and 2-chloro-acrylonitrile **171**.[173] The use of this catalyst accelerated the Diels-Alder reaction at 0 °C without isomerization of diene (**Eq. 44**).



170 **171** **172** **Eq. 44**

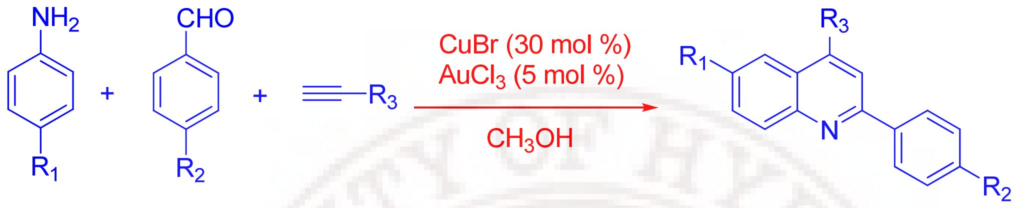
Simple non-activated Schiff bases display low reactivities in hetero-Diels-Alder reactions. However, imino-Diels-Alder reactions of 2-amino-1,3-butadiene of type **174** with imines of type **173**, in the presence of a catalytic amount of $Cu(OTf)_2$, led to 2,6-disubstituted 4-piperidinones of type **175** in good yields and with good diastereoselectivities (**Eq. 45**).[174]



173 **174** **175** **Eq. 45**

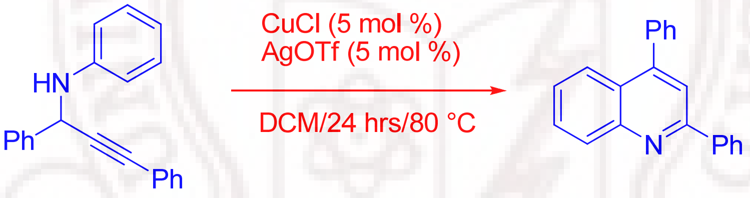
Ar = Ph, *p*-OMe-Ph, *p*-Br-Ph
R = Ph, Bn, Bu, Allyl

Wang and co-workers developed[175] a sequential catalytic process based on copper catalyzed nucleophilic addition of terminal alkynes to imines, and copper catalyzed intramolecular reaction of aromatic ring to alkynes. This one-pot reaction of aldehydes, amines, and alkynes gives quinoline derivatives in good yields (**Eq. 46**).



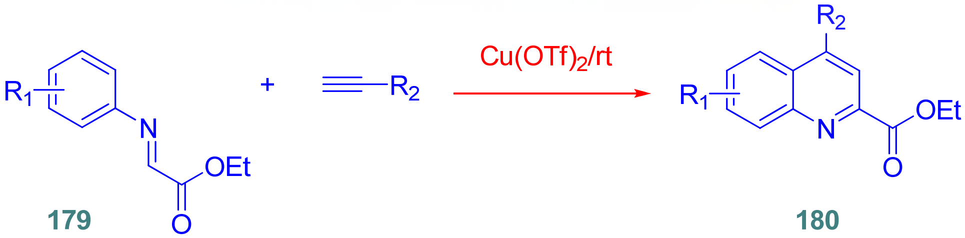
176 Eq. 46

Takai and co-workers[176] prepared 2,4-Disubstituted quinoline derivatives from *N*-aryl-2-propynylamines catalyzed by copper(I) and gold(I) complexes (**Eq. 47**).



177 **178** Eq. 47

Liu and co-workers[177] developed a simple and convenient copper-catalyzed method for the synthesis of quinoline-2-carboxylate derivatives through sequential intermolecular addition of alkynes onto imines and subsequent intramolecular ring closure by arylation (**Eq. 48**).



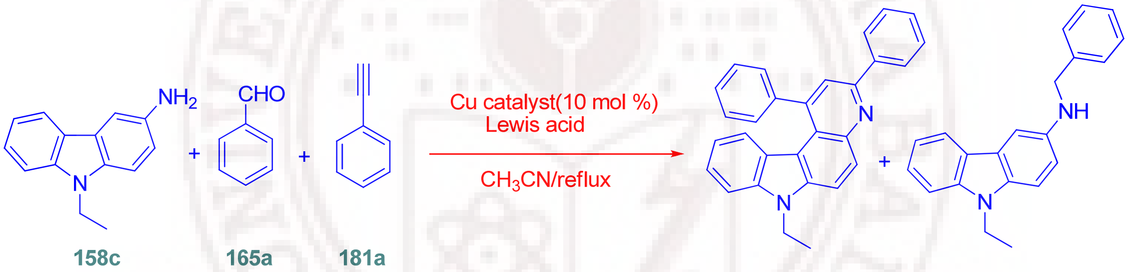
179 **180** Eq. 48

4.2. Synthesis of pyridocarbazole derivatives through intermolecular imino Diels-Alder reaction

The synthesis of pyridocarbazole derivatives with different substituents at specific locations starting from easily available materials is far from being well established. So, general and facile synthetic approaches are required to obtain analogues for pharmacological evaluation.

Herein, we represent a straightforward CuI/La(OTf)$_3$ catalyzed tandem reaction for the efficient synthesis of pyridocarbazole derivatives in ionic liquid [Bmim][BF_4]. Ionic liquids are increasingly used as reaction media in organic synthesis as they offer a wide range of advantages over classical organic solvents.

Scheme 32



158c **165a** **181a** **182c** **183**

The reaction of imine derived from **158c** (2.0 mmol) and **165a** (2.0 mmol) with phenylacetylene **181a** (1.0 mmol) in the presence of CuI/La(OTf)$_3$ catalyst gave 7-ethyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (**182c**) along with the side product 3-benzyl-9-ethyl-9*H*-3-carbazolamine (**183**) in [Bmim][BF_4] ionic liquid (**Scheme 32**). In this reaction, one equivalent of imine underwent the cyclization with phenylacetylene to dihydropyridocarbazole which further aromatized to the product **182c** (another equivalent of imine acted as a hydrogen acceptor and underwent reductive amination ie, **183**).

The structures of these molecules were confirmed by IR, ^{1}H NMR (spectrum 29 for compound **182c**), ^{13}C NMR (spectrum 30 for compound **182c**), LCMS, and elemental analysis. In the case of **182c**, Proton NMR showed the aromatic proton signals in the range between δ 6.16-8.40. Mass spectrum of the compound **182c** showed the molecular ion peak m/z at 399 in positive mode. In the case of **183**, the IR spectrum showed the *NH* stretching frequency at 3356 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 8.07. Proton NMR showed the aromatic proton signals in the range between δ 6.97-7.54 and CH_2 peak appeared at δ 4.54. Mass spectrum of the compound **183** showed the molecular ion peak m/z at 301 in positive mode. These two molecules were also confirmed by single crystal X-ray diffraction analysis (**Fig. 40** and **41**).

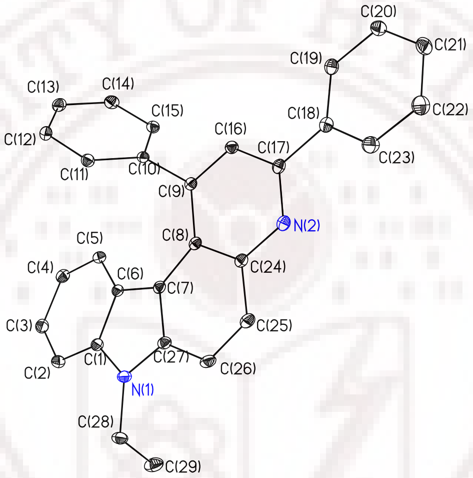


Figure 40. ORTEP diagram of compound **182c**

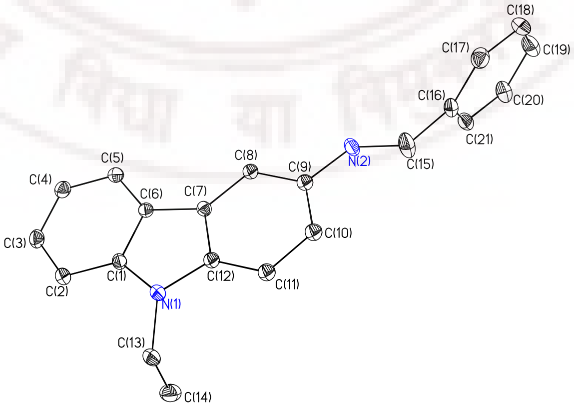


Figure 41. ORTEP diagram of compound **183**

Table 48. Screening of various Lewis acids or Brønsted acids

Entry	Catalyst	Time (h)	Yield (%)[a]
1	BF_3-OEt_2 (20 mol %)	24	---
2	CuI/BF_3-OEt_2 (20 mol %)	24	40
3	CuI/CF_3-COOH (20 mol %)	24	42
4	CuI/$InCl_3$ (20 mol %)	12	70
5	CuI/$In(OTf)_3$ (10 mol %)	12	75
6	CuI/AgOTf (10 mol %)	12	52
7	CuI/$Cu(OTf)_2$ (10 mol %)	12	72
8	CuI/$Sc(OTf)_3$ (10 mol %)	8	83
9	CuI/$Yb(OTf)_3$ (10 mol %)	8	82
10	CuI/$La(OTf)_3$ (10 mol %)	8	85
11	CuBr/$La(OTf)_3$ (10 mol %)	10	62
12	CuCl/$La(OTf)_3$ (10 mol %)	12	51
13	CuI/$La(OTf)_3$ (10 mol %)/THF	8	72
14	CuI/$La(OTf)_3$ (10 mol %)/Toluene	8	75
15	CuI/$La(OTf)_3$ (10 mol %)/DMSO[b]	8	73
16	CuI/$La(OTf)_3$ (10 mol %)/[Bmim][Cl]	6	88
17	**CuI/$La(OTf)_3$ (10 mol)/[Bmim][BF_4]**	**4**	**93**
18	CuI/$La(OTf)_3$ (10 mol %)/[Bmim][PF_6]	4	90
19	CuI(10 mol %)/[Bmim][BF_4]	6	60
20	CuI(30 mol %)/[Bmim][BF_4]	6	62

[a] Yield refers to column purified product. For the entries 1-12, acetonitrile was used as a solvent. For the entries 13 and 14 reflux temperature of the corresponding solvent was maintained. [b] Temperature was maintained at 100 °C and above the temperature, yield was low. For the entries 16-20, 1.0 mL of ionic liquid was used. In all entries, catalyst mol % was calculated relative to phenylacetylene.

We screened different Lewis and Brønsted acids to obtain a good yield of the product. The experimental results are summarized in **Table 48**. In the first attempt, the reaction of **158c**, **165a** and **181a** was performed in CH_3CN with BF_3-OEt_2 as a catalyst at reflux temperature (**Table 48**, Entry 1). In the absence of

CuI, (10 mol %) only imine formation was observed. In the presence of CuI (10 mol %) employed as a catalyst, the desired product **182c** was obtained with 40 % yield after 24 hours reflux in CH_3CN (Entry 2). Therefore CuI (10 mol %) has been found necessary to activate the triple bond by coordination.

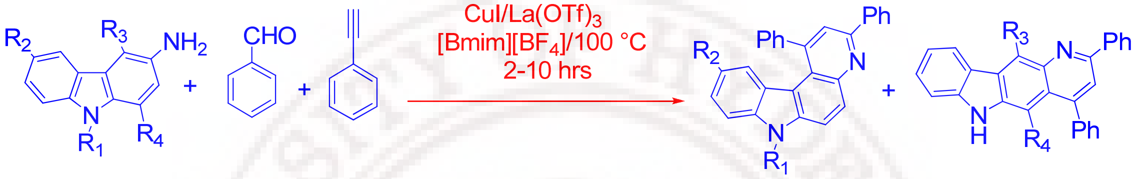
Then a series of different Lewis and Brønsted acids were investigated to improve the reaction yield. With TFA (20 mol %) only 42 % yield was observed after 24 hours reflux (Entry 3). Interestingly, when $InCl_3$ was used as a Lewis acid, yield was randomly increased to 70 % in 12 hours (Entry 4). Use of $Cu(OTf)_2$ and $In(OTf)_3$ increased the reaction yield further (Entry 5 & 7). Transition metal triflates such as scandium triflate, ytterbium triflate and lanthanum triflate catalysts also furnished the reaction with good yields (Entry 8-10). These three triflates have similar reactivity in terms of reaction yield. However we preferred $La(OTf)_3$ for the further optimization of the reaction due its to low cost and stability under moisture. The catalytic activity of CuBr and CuCl were also examined (Entry 11-12).

We have also screened different solvents THF, DMSO, Toluene and CH_3CN, of which CH_3CN gave good yield (Entry 13-15). Interestingly, when acetonitrile was replaced by [Bmim][Cl] ionic liquid, yield increased to 88 % (Entry 16). The yield further improved by replacing the counter ion [Cl^-] with [BF_4^-] (Entry 17) but when [BF_4^-] was replaced by [PF_6^-], yield was not increased (Entry 18). We also tried the reaction only with CuI (10 mol %) and without using $La(OTf)_3$ and it gave only 60 % yield (Entry 19). This indicates that the reaction can proceed without $La(OTf)_3$, but not without CuI. Increasing the mol % of CuI did not improved the yield further (Entry 20). Finally the optimal reaction conditions for this cycloaddition reaction is as follows: a mixture of CuI (10 mol %) and $La(OTf)_3$ (10 mol %) as catalysts in [Bmim][BF_4] ionic liquid at 100 °C for 4 hours (Entry 17).

We next carried out the copper catalyzed imino Diels-Alder reaction of different substituted aminocarbazoles **158a-i** under the optimized conditions (**Scheme 33**) and the results are summarized in **Table 49**. In most cases, the corresponding products **182a-i** were obtained in excellent yields (72-94 %). Except **158i**, which has the slower rate of reaction and that the corresponding product

182i was obtained in only 72 % yield, due to the steric hindrance caused by two methyl substituents (**Table 49**, Entry 7). The electron donating or withdrawing groups did not significantly alter the reaction rate and yield. The structures of the all the products (**182a-i**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR, LCMS and elemental analysis.

Scheme 33



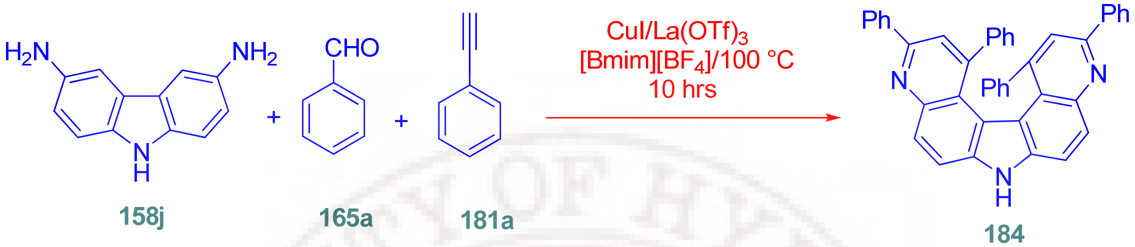
158a-i **165a** **181a** **182a-h** **182i**

Table 49. Synthesis of pyridocarbazole derivatives with different substituted aminocarbazoles (**158a-i**)

Entry	R_1	R_2	R_3	R_4	Amine	Product	Time (h)	Yield (%)
1	H	H	H	H	**158a**	**182a**	8	83
2	CH_3	H	H	H	**158b**	**182b**	5	88
3	C_2H_5	H	H	H	**158c**	**182c**	4	93
4	$C_6H_5CH_2$	H	H	H	**158d**	**182d**	4	87
5	C_2H_5	Br	H	H	**158e**	**182e**	9	86
6	C_2H_5	CH_3	H	H	**158f**	**182f**	3	94
7	H	H	CH_3	CH_3	**158g**	**182g**	10	72
8	*n*-C_4H_9	H	H	H	**158h**	**182h**	6	90
9	$C_6H_5CH_2$	CH_3	H	H	**158i**	**182i**	6	92

To prove the generality of this reaction, we also examined the reaction of 3,6-diaminocarbazole (**158j**) with benzaldehyde (**165a**) and phenylacetylene (**181a**) under the same reaction conditions (**Scheme 34**).

Scheme 34



158j 165a 181a 184

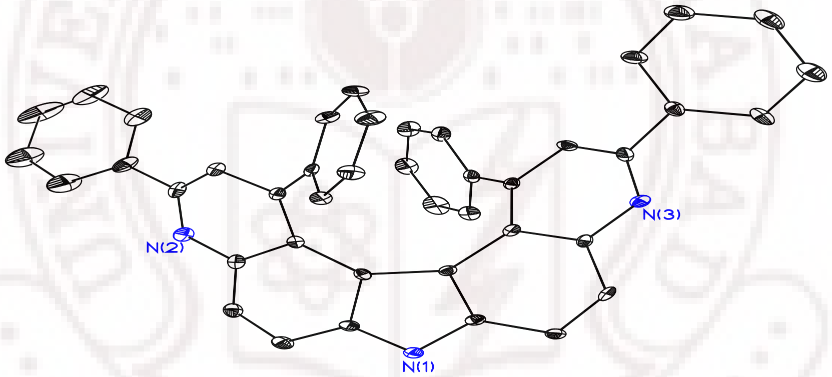
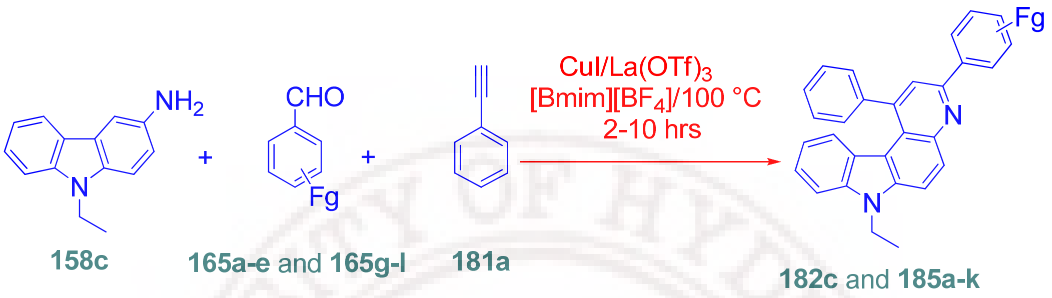


Figure 42. ORTEP diagram of compound **184**

After 10 hours at reflux temperature furnished the *bis*-product 1,3,11,13-tetraphenyl-7*H*-dipyrido[2,3-*c*:3,2-*g*]carbazole (**184**) with 62 % yield. This *bis*-product (**184**) was confirmed by IR, ^{1}H NMR, ^{13}C NMR, LCMS, and elemental analysis. The IR spectrum of **184** showed the *NH* stretching frequency at 3423 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 9.33. Proton NMR showed the aromatic proton signals in the range between δ 6.77-8.14. Mass spectrum of the compound **184** showed the molecular ion peak m/z at 574 in positive mode. The structure of this molecule (**184**) was also confirmed by single crystal X-ray diffraction analysis (**Fig. 42**).

Having optimized the reaction conditions, the reproducibility of the reaction with CuI/La(OTf)$_3$ in [Bmim][BF$_4$] with different substituted aldehydes was examined (**Scheme 35**).

Scheme 35



It was noted that the substituents did not significantly affect the reaction. Substrates bearing functional groups such as F, Cl, Br and OCH$_3$ were tolerated. This made possible the further derivatization of the products. Product **185f** was also confirmed by single crystal X-ray analysis (**Fig. 43**).

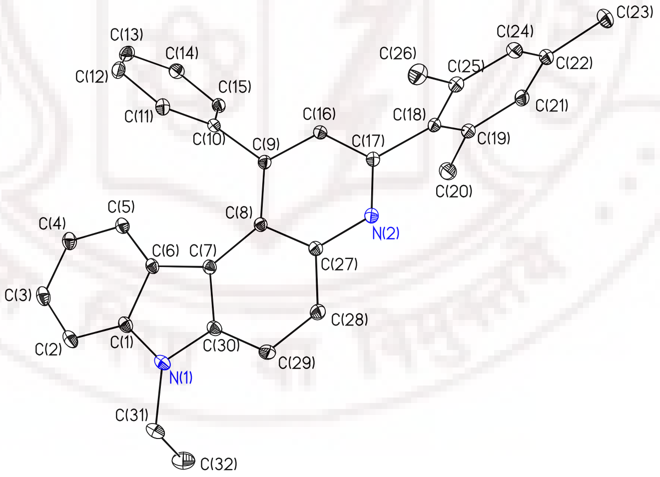


Figure 43. ORTEP diagram of compound **185f**

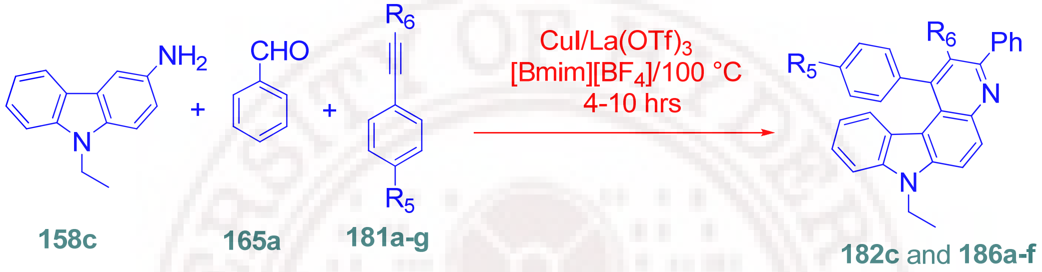
Reactions using an electron-poor or electron-rich or heteroaromatic aldehyde gave the desired products in good to excellent yields (65-96 %). Even in the case of strong electron deficient 4-fluorobenzaldehyde (**165g**) also gave **185e** with 86 % yield (**Table 50**, Entry 6). Electron rich aldehyde, 2,4,6-trimethyl benzaldehyde (**165h**) produced highest yield (96 %) in this intermolecular imino Diels-Alder reaction (Entry 7). Piperonal (**165i**), which has the powerful aroma therapeutic quality was also participated in this reaction, gave 82 % yield (Entry 8). The structure of piperonal annulated pyridocarbazole product (**185g**) was confirmed by IR, ^{1}H NMR (spectrum 31), ^{13}C NMR (spectrum 32), LCMS, and elemental analysis. Proton NMR of **185g** showed the aromatic proton signals in the range between δ 6.07-8.28 and CH_2 peak shows the δ value at 6.03. Mass spectrum of the compound **185g** showed the molecular ion peak m/z at 443 in positive mode. When we used 1-napthaldehyde (**165j**) in this reaction furnished 80 % yield (Entry 9). Saturated aldehyde, cyclohexanal (**165k**) produced 92 % yield within 3 hours (Entry 10). But in the case of heteroaromatic aldehyde such as 2-chloro-quinoline-3-carboxyaldehyde (**165l**) furnished only 65 % yield (Entry 11).

Table 50. Synthesis of pyridocarbazole derivatives with different substituted aldehydes (**165a-e** and **165g-l**)

Entry	Aldehyde	Product	Time (h)	Yield (%)
1	**165a**	**182c**	4	93
2	**165b**	**185a**	7	85
3	**165c**	**185b**	8	82
4	**165d**	**185c**	4	95
5	**165e**	**185d**	3	91
6	**165g**	**185e**	7	86
7	**165h**	**185f**	2	96
8	**165i**	**185g**	8	82
9	**165j**	**185h**	6	80
10	**165k**	**185i**	3	92
11	**165l**	**185j**	10	65

Having established suitable reaction conditions, we explored the scope and generality of the methodology with substituted alkynes also (**Scheme 36**). The reaction of 9-ethyl-3-aminocarbazole (**158c**), benzaldehyde (**165a**) with diphenyl acetylene (**181b**) in the presence of 10 mol % of CuI and 10 mol % La(OTf)$_3$ in [Bmim][BF$_4$] ionic liquid furnished 7-ethyl-1,2,3-triphenyl-7*H*-pyrido[2,3-*c*]carbazole (**186a**) with 75 % yield (**Table 51**, Entry 2).

Scheme 36



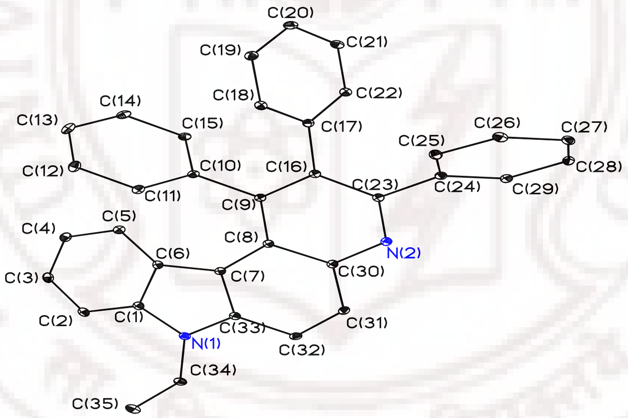
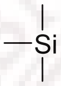


Figure 44. ORTEP diagram of compound **186a**

The structure of diphenyl acetylene product (**186a**) was confirmed by IR, ^{1}H NMR (spectrum 33), ^{13}C NMR (spectrum 34), LCMS, and elemental analysis. Proton NMR of **186a** showed the aromatic proton signals in the range between δ 5.84-8.41 and CH$_2$, CH$_3$ peaks shows the δ values at 4.54, 1.53 respectively. Mass spectrum of the compound **186a** showed the molecular ion peak m/z at 475 in positive mode. Ultimately, the structure of this molecule was also confirmed by single crystal X-ray analysis (**Fig. 44**).

Table 51. Synthesis of pyridocarbazole derivatives from different substitued alkynes (**181a-g**).

Entry	R_5	R_6	Alkyne	Product	Time (h)	Yield (%)
1	H	H	**181a**	**182c**	4	93
2	H	Ph	**181b**	**186a**	10	75
3	H	CH_3	**181c**	**186b**	5	90
4	H	*n*-C_3H_7	**181d**	**186c**	5	91
5	H	*n*-C_4H_9	**181e**	**186d**	5	94
6	OCH_3		**181f**	**186e**	7	95

The substituted aromatic alkynes containing electron rich groups proceeded well (Entry 6). When diphenylacetylene was used as alkyne, only 75 % yield was obtained (Entry 2). Substitution on the other side of the alkyne with electron donating groups (Entry 3-5) furnished excellent yields. Even with trimethylsilyl acetylene (2.0 eq), also reaction proceeded smoothly within 8 hours in 72 % yield.

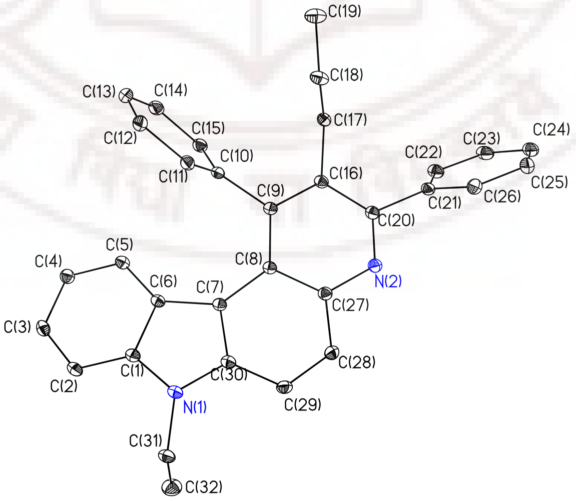


Figure 45. ORTEP diagram of compound **186c**

As silyl end groups on the alkynes are lost upon the work-up, access to the unfunctionlized products was secured. The loss of trimethylsilyl (TMS) group after work-up was ascribed to cleavage mechanism assisted by the soft transition metal cation as previously reported.[178] Crystal structures of **186c**, **186d**, and **186e** were achieved in order to confirm their regiochemistry. ORTEP diagrams of **186c**, **186d** and **186e** were shown in **Figs. 45, 46** and **47**.

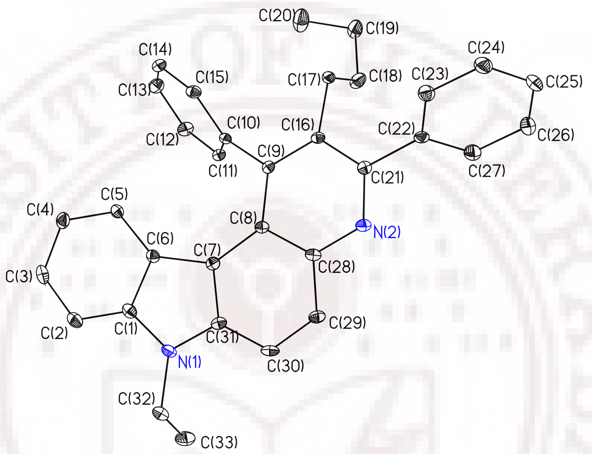


Figure 46. ORTEP diagram of compound **186d**

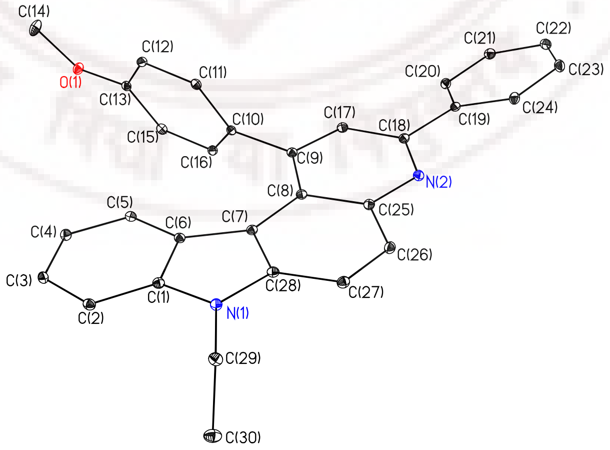
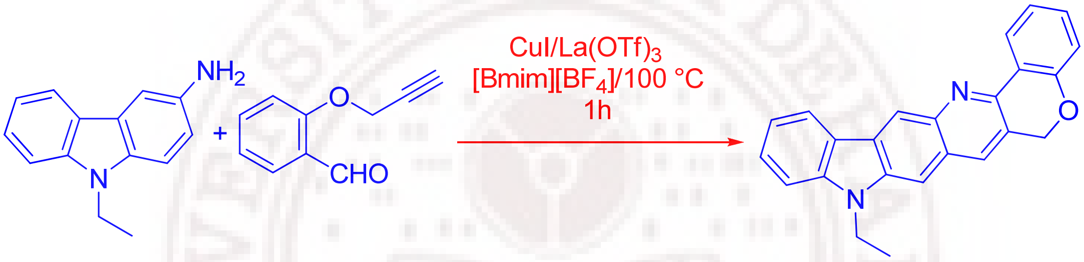


Figure 47. ORTEP diagram of compound **186e**

4.3. Synthesis of polycyclic pyridocarbazole derivatives through intramolecular imino Diels-Alder reaction

An intramolecular version of this reaction could provide a valuable route for polycyclic compounds like isomeric ellipticine fused with dihydrochromene derivatives. We carried out the reaction of *O*-propargylated salicylaldehyde (**187a**) with 9-ethyl-3-aminocarbazole (**158c**) in the presence of CuI/La(OTf)$_3$ in ionic liquid furnished 9-ethyl-6,9-dihydrochromeno[3',4':5,6]pyrido[3,2-*b*]carbazole (**188a**) (**Scheme 37**).

Scheme 37



158c 187a 188a

Surprisingly the reaction was completed within one hour and gave 95 % yield. The structure of intramolecular imino Diels-Alder product (**188a**) was confirmed by IR, ^{1}H NMR (spectrum 35), ^{13}C NMR (spectrum 36), LCMS, and elemental analysis. Proton NMR of **188a** showed the aromatic proton signals in the range between δ 7.07-8.87 and OCH$_2$ peak shows the δ value at 5.40. Mass spectrum of the compound **188a** showed the molecular ion peak m/z at 351 in positive mode. But while analyzing the ^{1}H NMR of this compound (**188a**), we observed two unexpected siglet peaks at δ 7.93 and 8.87. After careful analysis, we conclude the cyclization occurred through second position of the aminocarbazole. The same was proved by single crystal X-ray analysis. ORTEP diagram was shown in **fig. 48**. Generally cyclization occurs through fourth position of the carbazole since it is most reactive position compared to second position. In the case of unsubstituted salicylaldehyde (**187a**), cyclization occurred through second position and this may be due to less steric factor.

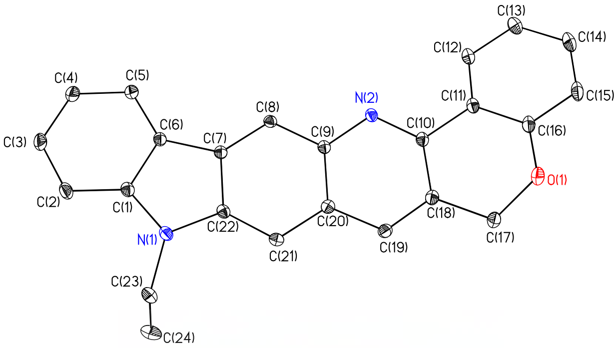
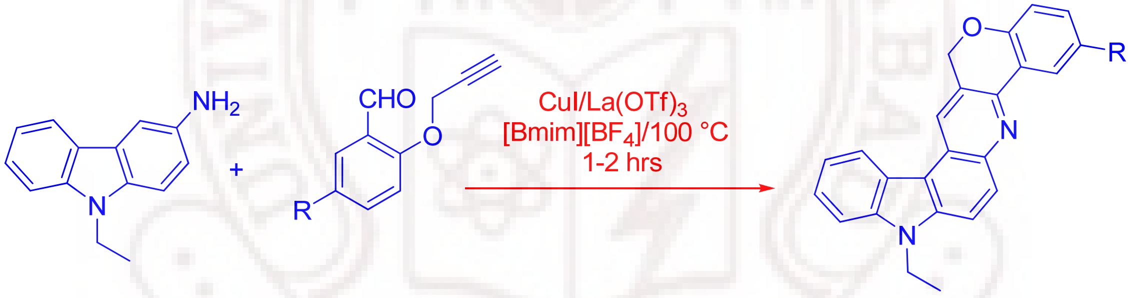


Figure 48. ORTEP diagram of compound **188a**

With substituted *O*-propargyl salicylaldehydes (**187b-g**), reaction proceeds smoothly under the optimized conditions (**Scheme 38**). In all the cases, cyclization proceeds through fourth position of the aminocarbazole.

Scheme 38

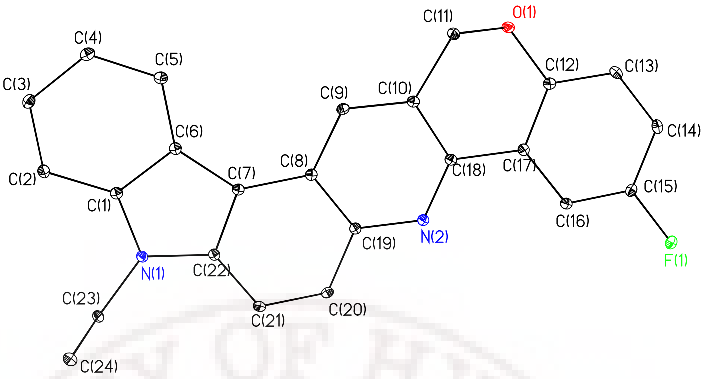


158c 187b-f 188b-f

Table 52. Synthesis of chromene fused pyridocarbazole derivatives with different substituted aldehydes (**187b-f**)

Entry	R	Aldehyde	Product	Time (h)	Yield (%)
1	**F**	**187b**	**188b**	2.0	85
2	**Cl**	**187c**	**188c**	2.0	84
3	**Br**	**187d**	**188d**	1.5	80
4	**CH_3**	**187e**	**188e**	1.0	96
5	**OCH_3**	**187f**	**188f**	1.0	93

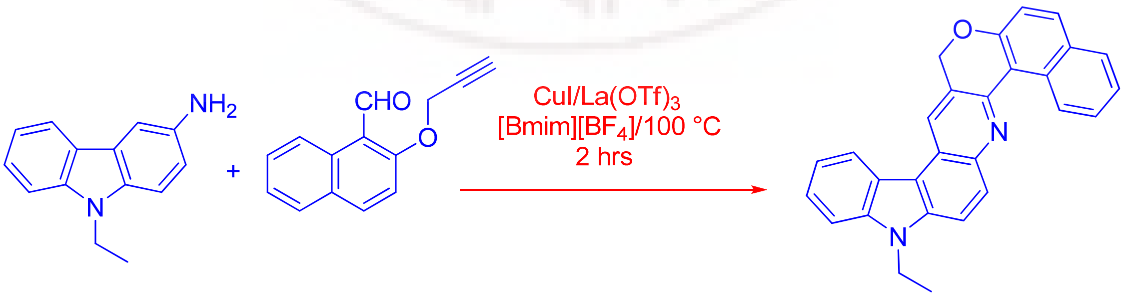
Figure 49. ORTEP diagram of compound **188b**



The results are summarized in **Table 52**. In all the cases, the corresponding cycloadducts (**188b-f**) were obtained in excellent yields (80-96 %). The electron donating or withdrawing groups did not significantly affect the reaction rate and yield. Bromo substituted aldehyde (**187d**) gave 80 % yield (**Table 52**, Entry 3), where as methyl substituted aldehyde (**187e**) produced 96 % yield (Entry 4). The X-ray crystal structure of compound **187b** was elucidated in **Fig. 49**.

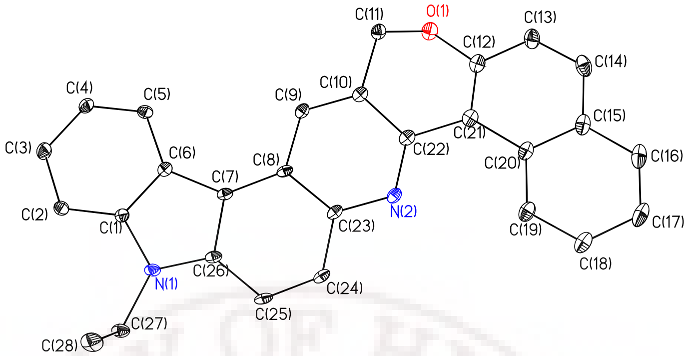
The reaction of *O*-propargylated napthaldehyde (**187g**) with 9-ethyl-3-aminocarbazole (**158c**) in the presence of Cu/La(OTf)$_3$ in ionic liquid afforded 10-ethyl-7a,10,14c,16-tetrahydrobenzo[5',6']chromeno[3',4':5,6]pyrido[3,2-*c*] carbazole (**188g**) with 84 % yield (**Scheme 39**).

Scheme 39



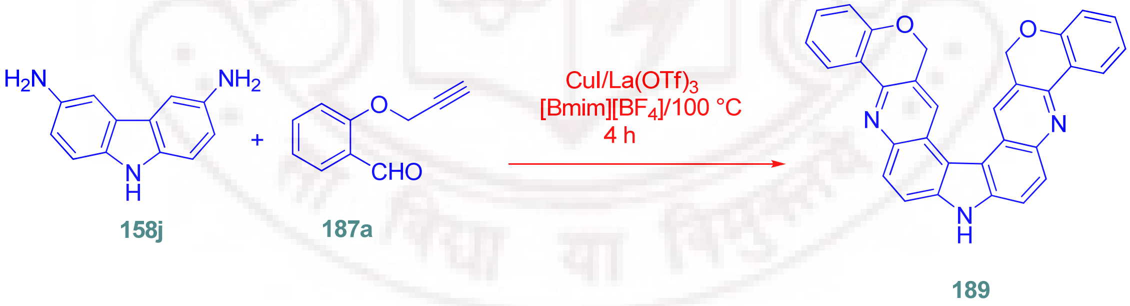
158c 187g 188g

Figure 50. ORTEP diagram of compound **188g**



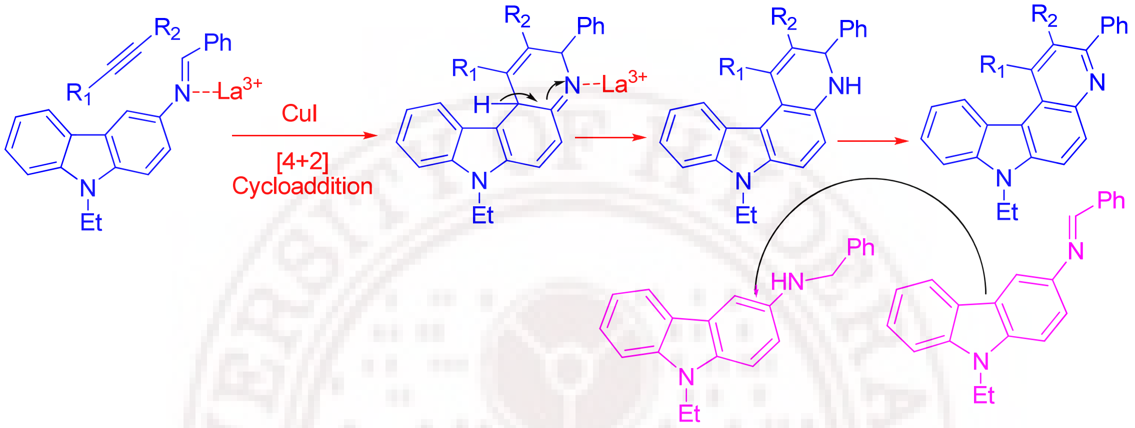
The structure of the heptacyclic product (**188g**) was confirmed by IR, ^{1}H NMR (spectrum 37), ^{13}C NMR (spectrum 38), LCMS, and elemental analysis. Proton NMR of **188g** showed the aromatic proton signals in the range between δ 7.30-10.12 and OCH_2 peak shows the δ value at 5.42. Mass spectrum of the compound **188g** showed the molecular ion peak m/z at 401 in positive mode. This molecule (**188g**) was further confirmed by single crystal X-ray analysis (**Fig. 50**)

Scheme 40



We have also tried the reaction of 3,6-diaminocarbazole (**158j**) in intramolecular pathway. Treatment of diamine with *O*-propargylated salicylaldehyde (**187a**)in the presence of CuI (10 mol %) and La(OTf)$_3$ (10 mol %) gave 11,20-dihydro-2*H*-dichromeno[3',4':5,6]pyrido[2,3-*c*:3,2-*g*] carbazole (**189**) with 76 % yield (**Scheme 40**). Monocyclized product was not observed in this reaction. The structure of this *bis*-intramolecular imino Diels-Alder product (**189**) was confirmed by IR, ^{1}H NMR, ^{13}C NMR, LCMS, and elemental analysis. The IR spectrum of **189** showed the *NH* stretching frequency at 3414 cm^{-1} and the proton NMR exhibits the *NH* peak at δ 12.68. Proton NMR showed the aromatic proton signals in the range between δ 7.09-9.16 and OCH_2 peak shows the δ value at 5.65. Mass spectrum of the compound **189** showed the molecular ion peak m/z at 476 in negative mode.

Scheme 41. Expected mechanism of the reaction



When coming to the mechanism of the reaction, copper catalyzed Diels-Alder reaction was well reported.[179] But with alkyne as a dienophile very less reports are available.[180] When the terminal alkyne was used in this reaction, reaction can be proceeded through Grignard type imine addition is followed by a Friedal-Crafts alkenylation of arens with alkynes followed by aromatization as previously reported[181-183] but in case of disubstituted alkynes, the reported mechanism may not be suitable since there is no terminal hydrogen. According to HSAB theory hard Lewis acid, La^{3+} coordinates the hard Lewis base site of nitrogen lone pair and increases the electron deficiency of the imine, [4+2] cycloaddition followed by aromatization (**Scheme 41**).

In summary, we have described for the first time the synthesis of pyridocarbazole derivatives with inter and intramolecular imino Diels-Alder reaction catalyzed by Cu/La(OTf)$_3$. Different substituents may be introduced to different positions of pyridocarbazole by just installing these substituents on any of three components. This method will be of high interest to synthetic as well as medicinal chemists.

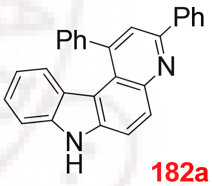
4.4. Experimental Section

General procedure H

In a round bottom flask equipped with a magnetic stirring bar, 2.0 mmol of aminocarbazoles, 2.0 mmol of aldehydes, 1.0 mmol of alkynes in 1.0 mL of [Bmim][BF_4] ionic liquid, was added 10 mol % of La$(OTf)_3$ and 10 mol % of CuI and the reaction mixture was stirred at 100 °C for 4 hours. After completion of the reaction, as indicated by the TLC, water (20 mL) was added to the crude reaction mass. Then aqueous layer was extracted with dichloromethane (3 X 20 mL) and the combined organic layers were dried over anhy. Na_2SO_4, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate) afforded the corresponding products.

1,3-Diphenyl-7*H*-pyrido[2,3-*c*]carbazole (182a)

The compound was obtained by the reaction of 3-aminocarbazole (**158a**) with **165a** and phenylacetylene (**181a**) in [Bmim][BF_4] ionic liquid following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 8 % ethyl acetate in hexanes.



182a

Mp: 222 °C

Yield: 83 %

IR (KBr) ν_{max} cm^{-1}: 3395, 3057, 1556, 1412, 796, 625

^{1}H NMR (400 MHz) δ: 8.68 (1H, s); 8.28 (3H, d, *J* = 7.8 Hz); 7.95 (1H, s); 7.81 (1H, d, *J* = 8.0 Hz); 7.45-7.61 (8H, m); 7.38 (1H, d, *J* = 7.2 Hz); 7.22 (1H, t, *J* = 7.8 Hz); 6.70 (1H, t, *J* = 7.6 Hz); 6.02 (1H, d, *J* = 7.7 Hz)

^{13}C NMR (100 MHz) δ: 153.3, 147.0, 146.8, 142.8, 139.7, 138.7, 138.4, 129.7, 129.2, 129.0, 128.9, 128.3, 127.4, 124.9, 124.2, 123.9, 122.5, 121.3, 121.0, 119.2, 116.5, 115.0, 110.3 (aromatic C)

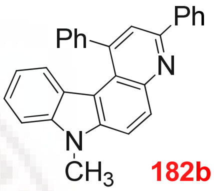
LCMS (m/z): 371 $(M+H)^+$

Anal. Calcd. for $C_{27}H_{18}N_2$: C, 87.54; H, 4.90; N, 7.56 %

Found: C, 87.45; H, 4.88; N, 7.61 %

7-Methyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (182b)

The compound was obtained by the reaction of 9-methyl-3-aminocarbazole (**158b**) with **165a** and phenylacetylene (**181a**) in [Bmim][BF_4] following the *general procedure H*. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.



182b

Mp: 206-207 °C

Yield: 88 %

IR (KBr) ν_{max} cm^{-1}: 3057, 2920, 1552, 1487, 792, 625

^1H NMR (400 MHz) δ: 8.30-8.36 (3H, m); 7.96 (1H, s); 7.90 (1H, d, *J* = 7.7 Hz); 7.95 (1H, s); 7.50-7.59 (7H, m); 7.40 (1H, d, *J* = 8.0 Hz); 7.29 (1H, t, *J* = 8.1 Hz); 6.72 (1H, t, *J* = 7.8 Hz); 6.10 (1H, d, *J* = 8.0 Hz); 3.95 (3H, s, N-$C\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 152.9, 146.7, 146.5, 142.8, 140.0, 139.7, 139.5, 129.6, 129.1, 128.9, 128.5, 128.2, 127.3, 124.9, 123.9, 123.2, 122.3, 121.2, 118.7, 114.4, 114.2, 108.4 (aromatic C), 29.3 (aliphatic C)

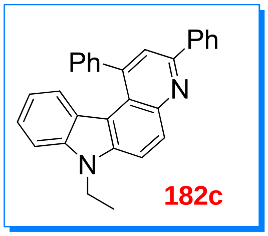
LCMS (m/z): 385 $(M+H)^+$

Anal. Calcd. for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29 %

Found: C, 87.55; H, 5.21; N, 7.33 %

7-Ethyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (182c)

Obtained **182c** by treating with **158c**, **165a** and **181a** in ionic liquid in the presence of 10 mol % $La(OTf)_3$ and CuI (10 mol %) following the *general procedure H*. Pure product was obtained by silica gel column chromatography with 2 % ethyl acetate in hexanes.



182c

Mp: 168 °C

Yield: 93 %

IR (KBr) ν_{max} cm^{-1}: 3049, 2974, 1554, 1487, 792, 625

^{1}H NMR (400 MHz) δ: 8.40 (1H, d, J = 7.8 Hz); 8.33 (2H, d, J = 8.0 Hz); 7.98 (2H, t, J = 7.7 Hz); 7.57-7.66 (4H, m); 7.45-7.54 (4H, m); 7.40 (1H, d, J = 7.7 Hz); 7.31 (1H, t, J = 7.8 Hz); 6.74 (1H, t, J = 7.7 Hz); 6.16 (1H, d, J = 7.6 Hz); 4.53 (2H, q, J = 7.8 Hz, N-C$\underline{H}_2$CH$_3$); 1.54 (3H, t, J = 8.0 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 152.8, 146.6, 146.4, 142.8, 139.6, 138.8, 138.4, 129.5, 129.4, 129.1, 128.7, 128.1, 127.2, 125.0, 123.7, 123.3, 122.4, 121.1, 118.5, 114.4, 114.1, 108.3 (aromatic C), 37.6, 14.2 (aliphatic C)

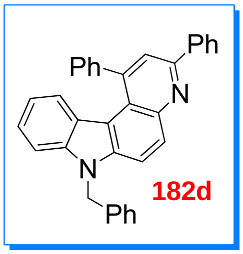
LCMS (m/z): 399 $(M+H)^+$

Anal. Calcd. for $C_{29}H_{22}N_2$: C, 87.41; H, 5.56; N, 7.03 %

Found: C, 87.35; H, 5.51; N, 7.12 %

7-Benzyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (182d)

The pyridocarbazole derivative (**182d**) was obtained by the reaction of **158d** with **165a** and phenylacetylene in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$] following the *general procedure H*. The crude product was purified through silica gel column chromatography with 4 % ethyl acetate in hexanes.



182d

Mp: 221-222 °C

Yield: 87 %

IR (KBr) ν_{max} cm^{-1}: 3028, 2916, 1552, 1487, 794, 625

^{1}H NMR (400 MHz) δ: 8.29 (3H, bs); 7.90 (2H, d, *J* = 8.0 Hz); 7.09-7.66 (15H, m); 6.74 (1H, d, *J* = 7.2 Hz); 6.13 (1H, bs); 5.66 (2H, s, N-C$\underline{H}_2$)

^{13}C NMR (100 MHz) δ: 153.1, 146.8, 146.7, 142.9, 139.8, 139.7, 139.3, 136.9, 129.8, 129.6, 129.2, 128.9, 128.8, 128.3, 127.7, 127.3, 126.3, 125.1, 124.2, 123.5, 122.4, 121.3, 119.1, 114.8, 114.5, 108.8 (aromatic C), 46.6 (aliphatic C)

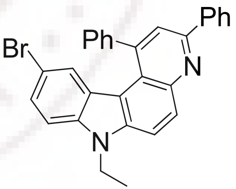
LCMS (m/z): 461 $(M+H)^+$

Anal. Calcd. for $C_{34}H_{24}N_2$: C, 88.67; H, 5.25; N, 6.08 %

Found: C, 88.61; H, 5.22; N, 6.15 %

7-Ethyl-10-bromo-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (182e)

Obtained as a white coloured solid by the reaction of **158e** with **165a** and **181a** in ionic liquid following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5 % ethyl acetate in hexanes.



182e

Mp: 213-214 °C

Yield: 86 %

IR (KBr) ν_{max} cm^{-1}: 3057, 2974, 1552, 1487, 785, 686

^{1}H NMR (400 MHz) δ: 8.28-8.35 (3H, m); 7.95 (1H, s); 7.86 (1H, d, *J* = 8.0 Hz); 7.46-7.63 (8H, m); 7.35 (1H, d, *J* = 7.8 Hz); 7.24 (1H, d, *J* = 8.6 Hz); 5.95 (1H, d, *J* = 7.7 Hz); 4.42 (2H, q, *J* = 7.6 Hz, N-C$\underline{H}_2$CH$_3$); 1.47 (3H, t, *J* = 8.0 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 153.1, 146.6, 146.5, 142.3, 139.5, 138.7, 137.4, 130.3, 129.5, 129.2, 128.9, 128.8, 127.8, 127.3, 126.5, 124.6, 124.4, 122.4, 121.2, 114.0, 113.6, 111.8, 109.6 (aromatic C), 37.8, 14.3 (aliphatic C)

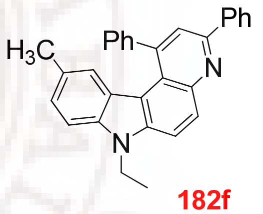
LCMS (m/z): 477 $(M+H)^+$, 479 $(M+2+H)^+$

Anal. Calcd. for $C_{29}H_{21}N_2Br$: C, 72.96; H, 4.43; N, 5.87 %

Found: C, 72.85; H, 4.48; N, 5.95 %

7-Ethyl-10-methyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*] carbazole (182f)

Obtained as a white coloured solid by the reaction of **158f** with **165a** and phenylacetylene in [Bmim][BF_4] following the *general procedure H*. The crude product was purified through silica gel column chromatography with 4 % ethyl acetate in hexanes.



182f

Mp: 219-220 °C

Yield: 94 %

IR (KBr) ν_{max} cm^{-1}: 3057, 2974, 1556, 1485, 767, 688

^{1}H NMR (400 MHz) δ: 8.33-8.35 (3H, m); 8.01 (1H, s); 7.93 (1H, d, *J* = 8.2 Hz); 7.51-7.63 (8H, m); 7.33 (1H, d, *J* = 8.1 Hz); 7.15 (1H, d, *J* = 7.6 Hz); 5.81 (1H, s); 4.47 (2H, q, *J* = 7.8 Hz, N-C$\underline{H}_2$CH$_3$); 2.13 (3H, s, ArC-C$\underline{H}_3$); 1.50 (3H, t, *J* = 8.0 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 152.7, 146.6, 146.5, 143.2, 139.8, 137.2, 130.1, 129.9, 129.4, 129.0, 128.9, 128.0, 127.4, 127.3, 125.4, 125.2, 123.4, 122.6, 121.4, 121.1, 120.9, 114.5, 114.2, 114.1, 107.9 (aromatic C), 37.7, 21.4, 14.3 (aliphatic C)

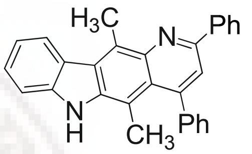
LCMS (m/z): 413 $(M+H)^+$

Anal. Calcd. for $C_{30}H_{24}N_2$: C, 87.35; H, 5.86; N, 6.79 %

Found: C, 87.28; H, 5.85; N, 6.73 %

5,11-Dimethyl-2,4-diphenyl-6*H*-pyrido[2,3-*c*]carbazole (182g)

The pyridocarbazole derivative (**182g**) was obtained by the reaction of **158g** with benzaldehyde and **181a** in the presence of CuI/La(OTf)$_3$ in ionic liquid following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5 % ethyl acetate in hexanes.



182g

Mp: 231-232 °C

Yield: 72 %

IR (KBr) ν_{max} cm^{-1}: 3034, 2916, 1539, 1487, 760, 684

^{1}H NMR (400 MHz) δ: 8.27 (2H, d, *J* = 8.0 Hz); 8.05 (1H, s); 7.90 (1H, s); 7.38-7.57 (9H, m); 7.27 (1H, s); 6.68 (1H, t, *J* = 7.8 Hz); 6.31 (1H, d, *J* = 7.7 Hz); 4.23 (3H, s, ArC-C$\underline{H}_3$); 3.06 (3H, s, ArC-C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 153.2, 146.5, 146.2, 142.9, 140.7, 139.8, 139.2, 131.3, 129.3, 129.1, 128.8, 128.1, 127.4, 127.3, 127.2, 126.3, 124.7, 123.8, 123.1, 120.7, 120.6, 118.6, 115.4, 108.5 (aromatic C), 32.8, 21.9 (aliphatic C)

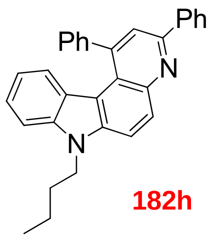
LCMS (m/z): 399 $(M+H)^+$

Anal. Calcd. for $C_{29}H_{22}N_2$: C, 87.41; H, 5.56; N, 7.03 %

Found: C, 87.35; H, 5.51; N, 7.12 %

7-Butyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (182h)

Reaction of **158h** in the presence of CuI/La(OTf)$_3$ with benzaldehyde and **181a** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a white solid. The crude product was purified through silica gel column chromatography with 5 % ethyl acetate in hexanes.



182h

Mp: 148 °C

Yield: 90 %

IR (KBr) ν_{max} cm^{-1}: 3057, 2955, 1566, 1487, 794, 625

^{1}H NMR (400 MHz) δ: 8.37 (1H, d, *J* = 7.9 Hz); 8.31 (2H, d, *J* = 8.0 Hz); 7.96 (2H, t, *J* = 7.8 Hz); 7.43-7.63 (9H, m); 7.29 (1H, t, *J* = 7.6 Hz); 6.72 (1H, t, *J* = 8.0 Hz); 6.14 (1H, d, *J* = 7.8 Hz); 4.44 (2H, t, *J* = 7.6 Hz, N-C$\underline{H_2}$CH$_2$CH$_2$CH$_3$); 1.94 (2H, t, *J* = 7.5 Hz, N-CH$_2$C$\underline{H_2}$CH$_2$CH$_3$); 1.49 (2H, q, *J* = 8.0 Hz, N-CH$_2$CH$_2$C$\underline{H_2}$CH$_3$); 1.02 (3H, t, *J* = 7.8 Hz, N-CH$_2$CH$_2$CH$_2$C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 152.9, 146.7, 146.5, 142.9, 139.7, 139.4, 139.0, 129.9, 129.6, 129.2, 128.8, 128.6, 128.2, 127.8, 127.3, 125.1, 123.8, 123.3, 122.4, 121.5, 121.3, 118.6, 114.4, 108.6 (aromatic C), 43.0, 31.5, 20.6, 13.9 (aliphatic C)

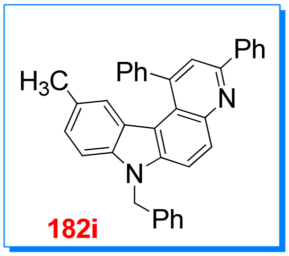
LCMS (m/z): 427 (M+H)$^+$

Anal. Calcd. for $C_{31}H_{24}N_2$: C, 87.29; H, 6.14; N, 6.57 %

Found: C, 87.21; H, 6.10; N, 6.62 %

7-Benzyl-10-methyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (182i)

Reaction of **158i** in the presence of La(OTf)$_3$ and CuI with **165a** and **181a** in ionic liquid following the *general procedure H* provided the title compound as a white solid. Pure product was obtained through silica gel column chromatography with 8 % ethyl acetate in hexanes.



182i

Mp: 230 °C

Yield: 92 %

IR (KBr) ν_{max} cm^{-1}: 3036, 2922, 1568, 1487, 765, 696

^{1}H NMR (400 MHz) δ: 8.23 (2H, d, *J* = 8.0 Hz); 8.05 (1H, s); 7.93 (1H, s); 7.44-7.63 (8H, m); 7.24-7.31 (4H, m); 7.19 (1H, t, *J* = 7.7 Hz); 7.00 (2H, d, *J* = 7.2 Hz); 6.68 (1H, t, *J* = 8.0 Hz); 6.36 (1H, d, *J* = 7.8 Hz); 5.95 (2H, s, N-C$\underline{H_2}$); 2.87 (3H, s, ArC-C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 153.4, 146.7, 146.4, 142.9, 140.6, 139.8, 139.0, 138.4, 131.7, 129.4, 129.2, 129.1, 128.9, 128.2, 127.4, 127.3, 127.2, 127.1, 126.2, 125.4, 124.9, 124.1, 123.4, 120.9, 120.8, 119.2, 115.9, 106.0 (aromatic C), 49.1, 21.0 (aliphatic C)

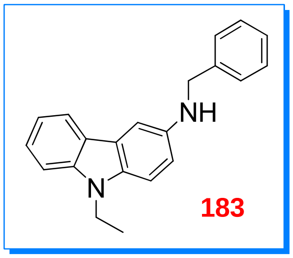
LCMS (m/z): 475 (M+H)$^+$

Anal. Calcd. for $C_{35}H_{26}N_2$: C, 88.58; H, 5.52; N, 5.90 %

Found: C, 88.46; H, 5.54; N, 5.95 %

3-Benzyl-9-ethyl-9*H*-3-carbazolamine (183)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with benzaldehyde (**165a**) and **181a** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a minor reduced amination product. The crude product was purified through silica gel column chromatography with 4 % ethyl acetate in hexanes.



183

Mp: 87-88 °C

IR (KBr) ν_{max} cm^{-1}: 3356, 3049, 2970, 1577, 1471, 792, 698

^{1}H NMR (400 MHz) δ: 8.07 (1H, d, *J* = 8.0 Hz);

7.35-7.54 (10H, m); 7.23 (1H, t, *J* = 7.8 Hz); 6.97 (1H, d, *J* = 7.5 Hz); 4.50 (2H, s, NH-C$\underline{H}_2$); 4.54 (2H, q, *J* = 7.6 Hz, N-C$\underline{H}_2$CH$_3$); 1.45 (3H, t, *J* = 8.0 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 141.5, 140.4, 139.8, 134.2, 128.7, 127.9, 127.3, 125.4, 123.7, 122.7, 120.5, 118.0, 114.6, 109.2, 108.4, 103.7 (aromatic C), 50.1, 37.5, 13.9 (aliphatic C)

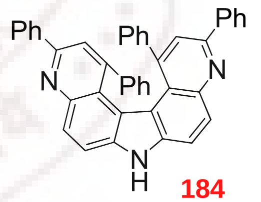
LCMS (m/z): 301 $(M+H)^+$

Anal. Calcd. for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33 %

Found: C, 83.85; H, 6.75; N, 9.45 %

1,3,11,13-Tetraphenyl-7*H*-dipyrido[2,3-*c*:3,2-*g*]carbazole (184)

Obtained *bis*-intermolecular imino Diels-Alder product as a light yellow coloured solid by the reaction of **158j** with **165a** and phenylacetylene in [Bmim][BF$_4$] following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 16 % ethyl acetate in hexanes.



184

Mp: 212 °C

Yield: 62 %

IR (KBr) ν_{max} cm^{-1}: 3423, 3034, 2920, 1554, 1489, 1323, 628

^{1}H NMR (400 MHz) δ: 9.33 (1H, s, N$\underline{H}$); 8.14 (7H, t, *J* = 7.8 Hz); 7.88 (3H, d, *J* = 7.7 Hz); 7.58 (5H, t, *J* = 7.8 Hz); 7.44-7.51 (2H, m); 7.28 (3H, s); 6.77 (6H, t, *J* = 7.9 Hz)

^{13}C NMR (100 MHz) δ: 153.9, 145.9, 144.7, 140.2, 138.1, 135.9, 129.7, 128.8, 128.7, 128.2, 127.5, 127.0, 122.4, 118.0, 117.4, 115.5 (aromatic C) (Due to limited solubility and steric hindrance of the molecule, we could not get the some of carbon δ values)

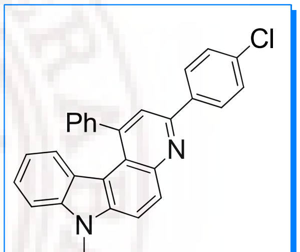
LCMS (m/z): 574 $(M+H)^+$

Anal. Calcd. for $C_{42}H_{27}N_3$: C, 87.93; H, 4.74; N, 7.32 %

Found: C, 87.95; H, 4.71; N, 7.36 %

7-Ethyl-3-(4-chlorophenyl)-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185a)

Obtained **185a** by treating with **158c, 165b** and **181a** in [Bmim][BF_4] in the presence of 10 mol % La$(OTf)_3$ and CuI (10 mol %) following the *general procedure H*. The crude product was purified by silica gel column chromatography with 3 % ethyl acetate in hexanes.



185a

Mp: 175 °C

Yield: 85 %

IR (KBr) ν_{max} cm^{-1}: 3038, 2961, 1618, 1487, 800, 738

^{1}H NMR (400 MHz) δ: 8.33 (1H, d, *J* = 7.8 Hz); 8.25 (2H, d, *J* = 8.0 Hz); 7.92-7.97 (2H, m); 7.45-7.63 (8H, m); 7.30 (1H, t, *J* = 7.8 Hz); 6.74 (1H, t, *J* = 7.8 Hz); 6.13 (1H, d, *J* = 8.0 Hz); 4.52 (2H, q, *J* = 7.8 Hz, N-C$\underline{H}_2$CH$_3$); 1.54 (3H, t, *J* = 8.1 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 151.4, 146.8, 146.4, 142.8, 138.9, 138.6, 138.1, 134.9, 129.6, 129.4, 129.2, 128.9, 128.5, 128.3, 125.1, 123.9, 123.3, 122.6, 120.8, 119.7, 114.5, 114.3, 108.4 (aromatic C), 37.7, 14.3 (aliphatic C)

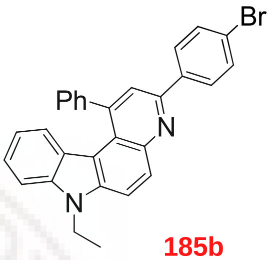
LCMS (m/z): 433 $(M+H)^+$

Anal. Calcd. for $C_{29}H_{21}N_2Cl$: C, 80.45; H, 4.89; N, 6.47 %

Found: C, 80.36; H, 4.94; N, 6.55 %

7-Ethyl-3-(4-bromophenyl)-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185b)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with 4-bromobenzaldehyde (**165c**) and Phenylacetylene (**181a**) in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a white solid. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes.



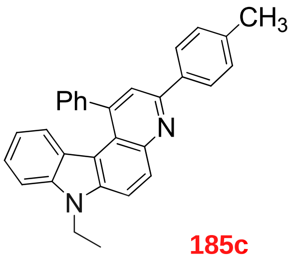
185b

Mp:	161 °C
Yield:	82 %
IR (KBr) ν_{max} cm^{-1}:	3049, 2968, 1612, 1489, 823, 698
^{1}H NMR (400 MHz) δ:	8.32 (1H, d, *J* = 7.9 Hz); 8.17 (2H, d, *J* = 8.1 Hz); 7.91-7.96 (2H, m); 7.68 (2H, d, *J* = 7.8 Hz); 7.60-7.62 (2H, m); 7.51-7.54 (3H, m); 7.45 (1H, d, *J* = 7.8 Hz); 7.31 (1H, t, *J* = 7.8 Hz); 6.73 (1H, t, *J* = 7.7 Hz); 6.12 (1H, d, *J* = 7.8 Hz); 4.52 (2H, q, *J* = 7.9 Hz, N-C$\underline{H}_2$CH$_3$); 1.54 (3H, t, *J* = 8.0 Hz, N-CH$_2$C$\underline{H}_3$)
^{13}C NMR (100 MHz) δ:	151.4, 146.8, 146.4, 142.7, 138.9, 138.6, 138.5, 131.9, 129.6, 129.4, 129.2, 128.8, 128.3, 125.1, 123.9, 123.3, 123.2, 122.6, 120.7, 118.7, 114.5, 114.3, 108.4 (aromatic C), 37.7, 14.3 (aliphatic C)
LCMS (m/z):	477 (M+H)$^+$, 479 (M+2+H)$^+$
Anal. Calcd. for $C_{29}H_{21}N_2Br$:	C, 72.96; H, 4.43; N, 5.87 %
Found:	C, 72.86; H, 4.48; N, 5.95 %

7-Ethyl-3-(4-methylphenyl)-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185c)

The pyridocarbazole derivative (**185c**) was obtained by the reaction of **158c** with **165d** and phenylacetylene (**181a**) in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$]

following the *general procedure H*. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.



185c

Mp: 197-198 °C

Yield: 95 %

IR (KBr) ν_{max} cm^{-1}: 3036, 2972, 1612, 1487, 821, 700

^{1}H NMR (400 MHz) δ: 8.38 (1H, d, *J* = 7.8 Hz); 8.23 (2H, d, *J* = 8.0 Hz); 7.95-7.98 (2H, m); 7.64-7.66 (2H, m); 7.49-7.56 (3H, m); 7.45 (1H, d, *J* = 7.6 Hz); 7.40 (2H, d, *J* = 7.7 Hz); 7.30 (1H, t, *J* = 7.8 Hz); 6.73 (1H, t, *J* = 8.1 Hz); 6.15 (1H, d, *J* = 7.8 Hz); 4.53 (2H, q, *J* = 7.9 Hz, N-$C\underline{H}_2CH_3$); 2.50 (3H, s, ArC-$C\underline{H}_3$); 1.54 (3H, t, *J* = 7.9 Hz, N-$CH_2C\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 152.9, 146.6, 146.5, 142.9, 138.9, 138.8, 138.5, 136.9, 129.6, 129.5, 129.4, 129.2, 128.2, 127.2, 125.1, 123.8, 123.4, 122.4, 121.1, 118.6, 114.6, 114.1, 108.4 (aromatic C), 37.7, 21.4, 14.3 (aliphatic C)

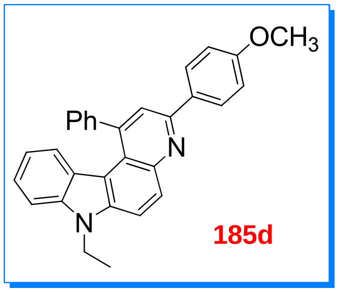
LCMS (m/z): 413 (M+H)$^+$

Anal. Calcd. for $C_{30}H_{24}N_2$: C, 87.35; H, 5.86; N, 6.79 %

Found: C, 87.25; H, 5.91; N, 6.92 %

7-Ethyl-3-(4-methoxylphenyl)-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185d)

The molecule was obtained as a white coloured solid by the reaction of **158c** with **165e** and phenylacetylene in [Bmim][BF_4] following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes.



185d

Mp: 184-185 °C

Yield: 91 %

IR (KBr) ν_{max} cm^{-1}: 3049, 2924, 1608, 1489, 835, 524

^{1}H NMR (400 MHz) δ: 8.34 (1H, d, *J* = 8.2 Hz); 8.29 (2H, d, *J* = 7.6 Hz); 7.93-7.96 (2H, m); 7.64-7.66 (2H, m); 7.52-7.54 (3H, m); 7.44 (1H, d, *J* = 7.8 Hz); 7.31 (1H, t, *J* = 8.0 Hz); 7.12 (2H, d, *J* = 7.9 Hz); 6.74 (1H, t, *J* = 7.8 Hz); 6.15 (1H, d, *J* = 7.9 Hz); 4.51 (2H, q, *J* = 7.6 Hz, N-C$\underline{H_2}$CH$_3$); 3.93 (3H, s, ArC-OC$\underline{H_3}$); 1.53 (3H, t, *J* = 7.7 Hz, N-CH$_2$C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 160.5, 152.6, 146.6, 146.5, 143.0, 139.0, 138.4, 132.4, 129.6, 129.4, 129.2, 128.6, 128.2, 125.1, 123.8, 123.4, 122.1, 120.8, 118.6, 114.6, 114.2, 114.0, 108.4 (aromatic C), 55.4, 37.7, 14.3 (aliphatic C)

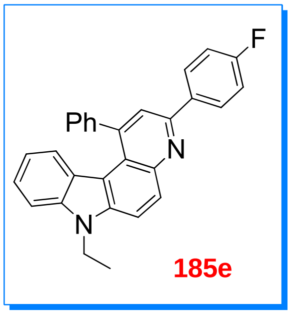
LCMS (m/z): 429 (M+H)$^+$

Anal. Calcd. for $C_{30}H_{24}N_2O$: C, 84.08; H, 5.65; N, 6.54 %

Found: C, 84.15; H, 5.58; N, 6.67 %

7-Ethyl-3-(4-fluorophenyl)-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185e)

The compound was obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with **165g** and **181a** in [Bmim][BF$_4$] following the *general procedure H*. The crude product was purified through silica gel column chromatography with 5 % ethyl acetate in hexanes.



185e

Mp: 160 °C

Yield: 86 %

IR (KBr) ν_{max} cm^{-1}: 3045, 2978, 1554, 1489, 796, 696

^{1}H NMR (400 MHz) δ: 8.33 (1H, d, *J* = 7.9 Hz); 8.26-8.30 (2H, m); 7.90-7.95 (2H, m); 7.60-7.63 (2H, m); 7.43-7.53 (4H, m); 7.23-7.32 (3H, m); 6.72 (1H, t, *J* = 7.6 Hz); 6.13 (1H, d, *J* = 8.0 Hz); 4.51 (2H, q, *J* = 7.7 Hz, N-C$\underline{H_2}$CH$_3$); 1.52 (3H, t, *J* = 8.0 Hz, N-CH$_2$C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 164.7, 162.4, 154.5, 151.8, 146.8, 146.4, 142.8, 138.9, 138.5, 135.8, 135.7, 129.6, 129.4, 129.3, 129.2, 129.1, 128.3, 125.1, 123.9, 123.3, 122.4, 120.9, 118.7, 117.9, 115.8, 115.6, 115.5, 115.3, 114.5, 114.3, 108.4 (aromatic C), 37.7, 14.3 (aliphatic C)

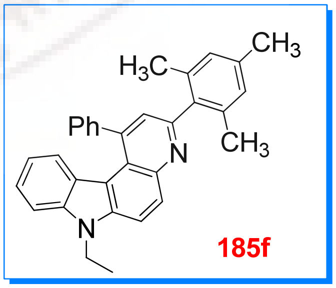
LCMS (m/z): 417 (M+H)$^+$

Anal. Calcd. for $C_{29}H_{21}N_2F$: C, 83.63; H, 5.08; N, 6.73 %

Found: C, 83.55; H, 5.12; N, 6.81 %

7-Ethyl-3-mesityl-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185f)

The compound was obtained by the reaction of **158c** with **165h** and **181a** in [Bmim][BF$_4$] following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5 % ethyl acetate in hexanes.



185f

Mp: 226-227 °C

Yield: 96 %

IR (KBr) ν_{max} cm^{-1}: 3043, 2970, 1610, 1556, 1508, 742, 601

^{1}H NMR (400 MHz) δ: 8.38 (1H, d, *J* = 8.0 Hz); 8.01 (1H, d, *J* = 7.8 Hz); 7.63-7.65 (2H, m); 7.48-7.53 (5H, m); 7.31-7.34 (1H, m); 7.05 (2H, s); 6.75 (1H, t, *J* = 7.9 Hz); 6.20 (1H, d, *J* = 7.6 Hz); 4.58 (2H, q, *J* = 7.8 Hz, N-C$\underline{H_2}$CH$_3$);

2.41 (3H, s, ArC-C$\underline{H}_3$); 2.20 (6H, s, ArC-C$\underline{H}_3$); 1.56 (3H, t, J = 8.1 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 155.9, 146.4, 146.1, 142.5, 139.0, 138.6, 137.8, 137.5, 136.1, 129.6, 129.3, 129.2, 128.5, 128.2, 125.1, 124.9, 123.9, 123.4, 121.9, 118.6, 114.6, 114.0, 108.4 (aromatic C), 37.7, 21.2, 20.4, 14.3 (aliphatic C)

LCMS (m/z): 441 (M+H)$^+$

Anal. Calcd. for $C_{32}H_{28}N_2$: C, 87.24; H, 6.41; N, 6.36 %

Found: C, 87.15; H, 6.45; N, 6.42 %

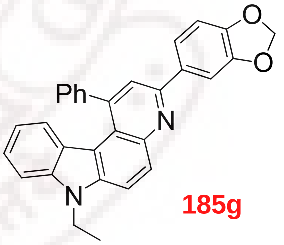
3-Benzo[d][1,3]dioxol-4-yl-7-ethyl-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185g)

Obtained **185g** by treating with **158c**, **181a** and piperonal (**165i**) in [Bmim][BF$_4$] in the presence of 10 mol % La(OTf)$_3$ and CuI (10 mol %) following the *general procedure H*. The crude product was purified by silica gel column chromatography with 4 % ethyl acetate in hexanes.

Mp: 188 °C

Yield: 82 %

IR (KBr) ν_{max} cm^{-1}: 3057, 2970, 1610, 1485, 804, 702



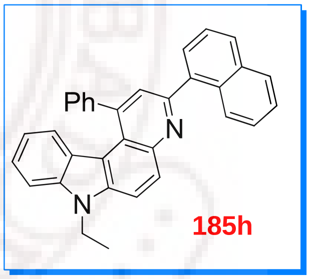
185g

^{1}H NMR (400 MHz) δ: 8.28 (1H, d, J = 8.0 Hz); 7.91 (1H, d, J = 7.9 Hz); 7.71-7.83 (3H, m); 7.58 (2H, d, J = 8.0 Hz); 7.46-7.48 (3H, m); 7.40 (1H, d, J = 7.8 Hz); 7.25 (1H, t, J = 8.1 Hz); 6.95 (1H, d, J = 7.6 Hz); 6.66 (1H, t, J = 7.8 Hz); 6.07 (1H, d, J = 7.9 Hz); 6.03 (2H, s, OC$\underline{H}_2$O); 4.50 (2H, q, J = 7.6 Hz, N-C$\underline{H}_2$CH$_3$); 1.50 (3H, t, J = 8.0 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ:	152.3, 148.4, 148.3, 146.6, 146.3, 142.9, 139.0, 138.4, 134.2, 129.5, 129.4, 129.2, 128.2, 125.0, 123.8, 123.3, 122.2, 121.3, 120.9, 118.6, 114.5, 114.1, 108.5, 108.3, 107.7 (aromatic C), 101.3, 37.7, 14.3 (aliphatic C)
LCMS (m/z):	443 $(M+H)^+$
Anal. Calcd. for $C_{30}H_{22}N_2O_2$:	C, 81.43; H, 5.01; N, 6.33 %
Found:	C, 81.38; H, 5.06; N, 6.45 %

7-Ethyl-3-(1-naphthyl)-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185h)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with napthaldehyde and phenylacetylene in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a white solid. Pure product was obtained through silica gel column chromatography with 4 % ethyl acetate in hexanes.



185h

Mp:	216 °C
Yield:	80 %
IR (KBr) ν_{max} cm^{-1}:	3042, 1556, 1244, 833, 698
^{1}H NMR (400 MHz) δ:	8.39 (1H, d, *J* = 8.0 Hz); 8.32 (1H, d, *J* = 7.8 Hz); 7.89-8.01 (5H, m); 7.65-7.69 (3H, m); 7.49-7.58 (6H, m); 7.34 (1H, t, *J* = 8.0 Hz); 6.78 (1H, t, *J* = 7.9 Hz); 6.23 (1H, d, *J* = 7.9 Hz); 4.58 (2H, q, *J* = 8.2 Hz, N-C*H*$_2$CH$_3$); 1.57 (3H, t, *J* = 8.0 Hz, N-CH$_2$C*H*$_3$)
^{13}C NMR (100 MHz) δ:	154.9, 146.4, 146.2, 142.6, 139.8, 139.7, 139.0, 134.2, 131.6, 129.6, 129.4, 129.2, 128.9, 128.4, 128.3, 127.8, 126.5, 126.0. 125.9, 125.5, 125.4, 125.3, 125.2, 124.0, 123.5, 122.3, 118.73, 114.6, 114.3, 108.5 (aromatic C), 37.7, 14.3 (aliphatic C)

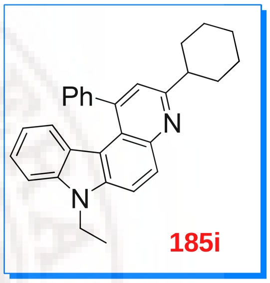
LCMS (m/z): 449 $(M+H)^+$

Anal. Calcd. for $C_{34}H_{24}N_2$: C, 88.36; H, 5.39; N, 6.25 %

Found: C, 88.25; H, 5.43; N, 6.32 %

3-Cyclohexyl-7-ethyl-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185i)

The pyridocarbazole derivative (**185i**) was obtained by the reaction of **158c** with cyclohexanal (**165k**) in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$] following the *general procedure H*. The crude product was purified through silica gel column chromatography with 4 % ethyl acetate in hexanes.



185i

Mp: 140 °C

Yield: 92 %

IR (KBr) ν_{max} cm^{-1}: 3045, 1564, 1246, 746, 696

^{1}H NMR (400 MHz) δ: 8.25 (1H, d, *J* = 7.6 Hz); 7.91 (1H, d, *J* = 7.9 Hz); 7.57 (2H, d, *J* = 8.0 Hz); 7.43-7.49 (5H, m); 7.27 (1H, t, *J* = 7.7 Hz); 6.68 (1H, t, *J* = 7.9 Hz); 6.10 (1H, d, *J* = 7.8 Hz); 4.50 (2H, q, *J* = 8.2 Hz, N-C$\underline{H}_2$CH$_3$); 3.00-3.07 (1H, m); 2.16 (2H, d, *J* = 7.7 Hz); 1.93-1.97 (2H, m); 1.69-1.79 (2H, m); 1.53-1.59 (2H, m); 1.49 (3H, t, *J* = 7.6 Hz, N-CH$_2$C$\underline{H}_3$); 1.37-1.44 (2H, m)

^{13}C NMR (100 MHz) δ: 162.3, 146.3, 145.9, 143.0, 138.9, 138.2, 129.6, 129.1, 128.8, 128.1, 125.0, 123.7, 123.3, 122.0, 121.7, 118.4, 114.6, 113.7, 108.3 (aromatic C), 47.1, 37.6, 33.2, 26.7, 26.3, 14.2 (aliphatic C)

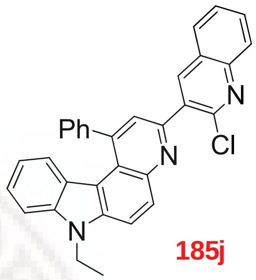
LCMS (m/z): 405 $(M+H)^+$

Anal. Calcd. for $C_{29}H_{28}N_2$: C, 86.10; H, 6.98; N, 6.92 %

Found: C, 86.15; H, 6.94; N, 7.04 %

3-(2-Chloro-3-quinolyl)-7-ethyl-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (185j)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with 2-chloro-3-quinolinecarboxyaldehyde (**165l**) in [Bmim][BF$_4$] following the *general procedure H* provided the title compound. Pure product was obtained through silica gel column chromatography with 6 % ethyl acetate in hexanes.

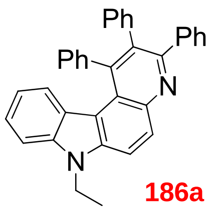


185j

Mp:	229 °C
Yield:	65 %
IR (KBr) ν_{max} cm^{-1}:	3057, 1585, 1321, 744, 698
^{1}H NMR (400 MHz) δ:	8.70 (1H, s); 8.35 (1H, s); 8.12 (1H, d, *J* = 7.8 Hz); 7.81-7.96 (3H, m); 7.79 (1H, t, *J* = 8.0 Hz); 7.60-7.64 (3H, m); 7.46-7.50 (4H, m); 7.29 (1H, t, *J* = 7.6 Hz); 6.72 (1H, t, *J* = 7.8 Hz); 6.15 (1H, d, *J* = 7.5 Hz); 4.55 (2H, q, *J* = 8.0 Hz, N-C$\underline{H_2}$CH$_3$); 1.54 (3H, t, *J* = 7.7 Hz, N-CH$_2$C$\underline{H_3}$)
^{13}C NMR (100 MHz) δ:	150.8, 149.0, 147.5, 146.3, 145.9, 142.3, 140.3, 139.1, 138.9, 133.8, 130.9, 129.6, 129.3, 129.2, 128.5, 128.4, 128.1, 127.4, 127.3, 125.2, 124.9, 124.1, 123.4, 122.7, 118.9, 114.6, 114.5, 108.5 (aromatic C), 37.8, 14.3 (aliphatic C)
LCMS (m/z):	484 (M+H)$^+$
Anal. Calcd. for $C_{32}H_{22}N_2Cl$:	C, 79.41; H, 4.58; N, 8.68 %
Found:	C, 79.45; H, 4.55; N, 8.72 %

7-Ethyl-1,2,3-triphenyl-7*H*-pyrido[2,3-*c*]carbazole (186a)

Obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with diphenylacetylene (**181b**) and benzaldehyde (**165a**) in [Bmim][BF$_4$] following the *general procedure H*. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.



186a

Mp: 205 °C

Yield: 75 %

IR (KBr) ν_{max} cm^{-1}: 3048, 2980, 1483, 1317, 1143, 696

^{1}H NMR (400 MHz) δ: 8.41 (1H, d, *J* = 7.7 Hz); 8.00 (1H, d, *J* = 8.0 Hz); 7.43 (1H, d, *J* = 7.6 Hz); 7.23-7.34 (11H, m); 7.06 (3H, d, *J* = 7.7 Hz); 6.91 (2H, d, *J* = 7.6 Hz); 6.61 (1H, t, *J* = 7.8 Hz); 5.84 (1H, d, *J* = 8.0 Hz); 4.54 (2H, q, *J* = 7.6 Hz, N-$C\underline{H}_2CH_3$); 1.53 (3H, t, *J* = 7.6 Hz, N-$CH_2C\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 154.8, 145.5, 144.7, 141.6, 140.8, 139.0, 138.8, 138.7, 134.0, 132.1, 131.8, 129.9, 129.7, 128.3, 127.6, 127.4, 127.1, 126.1, 125.1, 123.9, 123.8, 123.7, 118.7, 114.7, 114.2, 108.2 (aromatic C), 37.7, 14.2 (aliphatic C)

LCMS (m/z): 475 $(M+H)^+$

Anal. Calcd. for $C_{35}H_{26}N_2$: C, 88.58; H, 5.52; N, 5.90 %

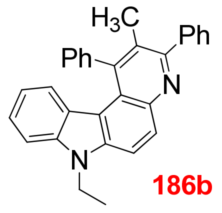
Found: C, 88.67; H, 5.57; N, 5.85 %

7-Ethyl-2-methyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (186b)

Obtained **186b** by treating with **158c**, **181c** and **165a** in [Bmim][BF_4] in the presence of 10 mol % CuI/La$(OTf)_3$ following the *general procedure H*. Pure product was obtained by silica gel column chromatography with 3 % ethyl acetate in hexanes.

Mp: 161 °C

Yield: 90 %



186b

IR (KBr) ν_{max} cm^{-1}: 3047, 2972, 1485, 1313, 1141, 700

^{1}H NMR (400 MHz) δ: 8.32 (1H, d, *J* = 7.6 Hz); 7.90 (1H, d, *J* = 7.8 Hz); 7.81 (2H, d, *J* = 8.0 Hz); 7.41-7.54 (9H, m); 7.27 (1H, t, *J* = 7.6 Hz); 6.68 (1H, t, *J* = 7.5 Hz); 5.94 (1H, d, *J* = 7.7 Hz); 4.50 (2H, q, *J* = 7.5 Hz, N-C$\underline{H}_2$CH$_3$); 2.31 (3H, s, ArC-C$\underline{H}_3$); 1.50 (3H, t, *J* = 7.3 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 156.7, 145.3, 144.0, 141.9, 141.7, 138.8, 138.7, 131.3, 129.7, 129.4, 129.2, 128.4, 128.1, 128.0, 127.2, 124.6, 123.9, 123.8, 123.6, 118.6, 114.3, 113.3, 108.2 (aromatic C), 37.6, 20.2, 14.2 (aliphatic C)

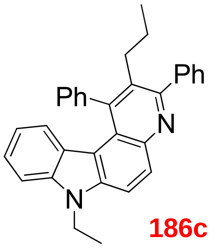
LCMS (m/z): 413 (M+H)$^+$

Anal. Calcd. for $C_{30}H_{24}N_2$: C, 87.35; H, 5.86; N, 6.79 %

Found: C, 87.25; H, 5.82; N, 6.83 %

7-Ethyl-1,3-diphenyl-2-propyl-7*H*-pyrido[2,3-*c*]carbazole (186c)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with **165a** and **181d** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a white solid. The crude product was purified through silica gel column chromatography with 6 % ethyl acetate in hexanes.



186c

Mp: 138 °C

Yield: 91 %

IR (KBr) ν_{max} cm^{-1}: 3051, 2970, 1462, 1315, 1140, 703

^{1}H NMR (400 MHz) δ: 8.31 (1H, d, *J* = 7.4 Hz); 7.91 (1H, d, *J* = 7.7 Hz); 7.70 (2H, d, *J* = 7.7 Hz); 7.41-7.55 (9H, m); 7.27 (1H, t, *J* = 7.8 Hz); 6.66 (1H, t, *J* = 7.6 Hz); 5.87 (1H, d, *J* = 7.8 Hz); 4.51 (2H, q, *J* = 7.7 Hz, N-C$\underline{H_2}$CH$_3$); 2.78 (2H, t, *J* = 7.5 Hz, ArC-C$\underline{H_2}$CH$_2$CH$_3$); 1.49 (3H, t, *J* = 7.8 Hz, N-CH$_2$C$\underline{H_3}$); 1.10 (2H, q, *J* = 7.2 Hz, ArC-CH$_2$C$\underline{H_2}$CH$_3$); 0.46 (3H, t, *J* = 7.1 Hz, ArC-CH$_2$CH$_2$C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 157.1, 145.0, 143.8, 142.2, 141.3, 138.7, 138.6, 132.3, 131.5, 129.7, 129.2, 129.0, 128.3, 128.1, 127.7, 124.8, 124.4, 123.9, 123.6, 118.6, 114.5, 113.4, 108.1 (aromatic C), 37.6, 32.5, 23.7, 20.2, 14.2, 14.1 (aliphatic C)

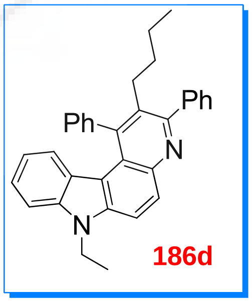
LCMS (m/z): 441 (M+H)$^+$

Anal. Calcd. for $C_{32}H_{28}N_2$: C, 87.24; H, 6.41; N, 6.36 %

Found: C, 87.15; H, 6.45; N, 6.30 %

2-Butyl-7-ethyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (186d)

The pyridocarbazole derivative (**186d**) was obtained by the reaction of **158c** with benzaldehyde (**165a**) and **181e** in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$] following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 4 % ethyl acetate in hexanes.



186d

Mp: 142 °C

Yield: 94 %

IR (KBr) ν_{max} cm^{-1}: 3057, 2953, 1483, 1315, 1136, 746

^{1}H NMR (400 MHz) δ: 8.31 (1H, d, *J* = 7.5 Hz); 7.92 (1H, bs); 7.42-7.72 (11H, m); 7.28 (1H, d, *J* = 8.0 Hz); 6.67 (1H, t, *J* = 7.9 Hz); 5.87 (1H, d, *J* = 7.7 Hz); 4.51 (2H, q, *J* = 7.3

Hz, N-C*H*$_2$CH$_3$); 2.84 (2H, bs, ArC-C*H*$_2$CH$_2$CH$_2$CH$_3$); 1.49 (3H, bs, N-CH$_2$C*H*$_3$); 1.05 (2H, bs, ArC-CH$_2$C*H*$_2$CH$_2$CH$_3$); 0.85 (2H, bs, ArC-CH$_2$CH$_2$C*H*$_2$CH$_3$); 0.48 (3H, bs, ArC-CH$_2$CH$_2$CH$_2$C*H*$_3$)

^{13}C NMR (100 MHz) δ: 157.1, 145.0, 143.7, 142.0, 141.2, 138.7, 138.6, 132.5, 131.5, 129.6, 129.2, 129.0, 128.2, 128.1, 127.7, 124.8, 124.5, 123.9, 123.6, 118.6, 113.5, 113.4, 108.1 (aromatic C), 37.6, 32.3, 29.9, 22.5, 14.2, 13,2 (aliphatic C)

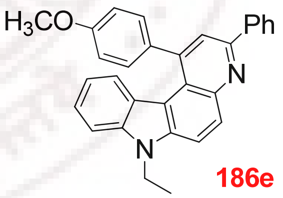
LCMS (m/z): 455 (M+H)$^+$

Anal. Calcd. for $C_{33}H_{30}N_2$: C, 87.19; H, 6.65; N, 6.16 %

Found: C, 87.11; H, 6.59; N, 6.22 %

7-Ethyl-1-(4-methoxyphenyl)-3-phenyl-7*H*-pyrido[2,3-*c*]carbazole (186e)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with **165a** and **181f** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a product. The crude product was purified through silica gel column chromatography with 6 % ethyl acetate in hexanes.



186e

Mp: 158 ^{o}C

Yield: 95 %

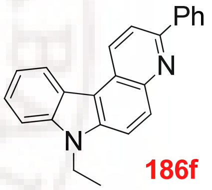
IR (KBr) ν_{max} cm^{-1}: 3045, 2962, 1552, 1493, 777, 696

^{1}H NMR (400 MHz) δ: 8.32-8.40 (3H, m); 7.91-7.98 (2H, m); 7.34-7.62 (7H, m); 7.05 (2H, d, *J* = 7.7 Hz); 6.82 (1H, t, *J* = 7.6 Hz); 6.30 (1H, d, *J* = 7.2 Hz); 4.48 (2H, q, *J* = 7.5 Hz, N-C*H*$_2$CH$_3$); 3.90 (3H, s, ArC-OC*H*$_3$); 1.51 (3H, t, *J* = 7.6 Hz, N-CH$_2$C*H*$_3$)

^{13}C NMR (100 MHz) δ:	159.9, 152.9, 146.5, 146.4, 139.8, 139.0, 138.5, 135.4, 130.7, 129.5, 128.9, 127.4, 125.4, 123.8, 123.4, 122.7, 121.1, 118.7, 114.7, 114.1, 108.4 (aromatic C), 55.6, 37.7, 14.3 (aliphatic C)
LCMS (m/z):	429 $(M+H)^+$
Anal. Calcd. for $C_{30}H_{24}N_2O$:	C, 84.08; H, 5.65; N, 6.54 %
Found:	C, 84.15; H, 5.51; N, 6.62 %

7-Ethyl-3-phenyl-7*H*-pyrido[2,3-*c*] carbazole (186f)

The pyridocarbazole derivative (**186f**) was obtained by the reaction of **158c** with trimethylsilyl acetylene (**181g**) and **165a** in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$] following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 7 % ethyl acetate in hexanes.

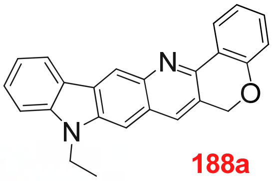


186f

Mp:	176 °C
Yield:	72 %
IR (KBr) ν_{max} cm^{-1}:	3059, 2924, 1572, 1450, 1317
^{1}H NMR (400 MHz) δ:	9.13 (1H, d, *J* = 7.5 Hz); 8.54 (1H, d, *J* = 7.6 Hz); 8.22-8.27 (3H, m); 8.06 (1H, d, *J* = 7.5 Hz); 7.90 (1H, d, *J* = 7.7 Hz); 7.40-7.65 (6H, m); 4.54 (2H, q, *J* = 7.4 Hz, N-C$\underline{H}_2$CH$_3$); 1.52 (3H, t, *J* = 7.7 Hz, N-CH$_2$C$\underline{H}_3$)
^{13}C NMR (100 MHz) δ:	153.7, 144.7, 139.2, 137.1, 131.8, 130.1, 128.9, 128.8, 128.6, 127.3, 124.6, 123.9, 123.5, 121.9, 120.0, 119.1, 114.4, 114.0, 109.5 (aromatic C), 37.8, 14.5 (aliphatic C)
LCMS (m/z):	323 $(M+H)^+$
Anal. Calcd. for $C_{23}H_{18}N_2$:	C, 85.68; H, 5.63; N, 8.69 %
Found:	C, 85.56; H, 5.66; N, 8.75 %

9-Ethyl-6,9-dihydrochromeno[3',4':5,6]pyrido[3,2-*b*]carbazole **(188a)**

The interesting second position cyclized product was prepared by the reaction of **158c** in the presence of CuI/La(OTf)$_3$ with **187a** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a product. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.


188a

Mp: 202 ^{o}C

Yield: 95 %

IR (KBr) ν_{max} cm^{-1}: 3045, 1602, 1224, 819, 738, 480

^{1}H NMR (400 MHz) δ: 8.87 (1H, s); 8.58 (1H, d, *J* = 8.0 Hz); 8.29 (1H, d, *J* = 7.2 Hz); 7.93 (1H, s); 7.53-7.61 (2H, m); 7.33-7.40 (2H, m); 7.30 (1H, t, *J* = 7.8 Hz); 7.23 (1H, t, *J* = 7.6 Hz); 7.07 (1H, d, *J* = 7.8 Hz); 5.40 (2H, s, OC$\underline{H_2}$); 4.37 (2H, q, *J* = 8.0 Hz, N-C$\underline{H_2}$CH$_3$); 1.49 (3H, t, *J* = 7.8 Hz, N-CH$_2$C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 157.2, 146.1, 142.8, 142.7, 139.7, 131.2, 129.9, 128.2, 127.8, 126.5, 125.2, 124.4, 123.8, 122.7, 122.5, 121.6, 120.0, 119.2, 117.3, 108.3, 102.3 (aromatic C), 68.8, 37.7, 13.3 (aliphatic C)

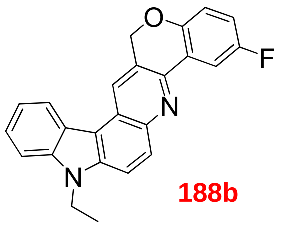
LCMS (m/z): 351 (M+H)$^{+}$

Anal. Calcd. for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99 %

Found: C, 82.35; H, 5.13; N, 8.11 %

8-Ethyl-3-fluoro-5a,6,12c,14-tetrahydrochromeno[3',4':5,6]pyrido[3,2-*c*]carbazole **(188b)**

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ **187b** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound as a white solid. Pure product was obtained through silica gel column chromatography with 6 % ethyl acetate in hexanes.



188b

Mp: 215 °C

Yield: 85 %

IR (KBr) ν_{max} cm^{-1}: 3128, 1514, 1240, 879, 736

^{1}H NMR (400 MHz) δ: 8.57 (1H, s); 8.37 (1H, d, *J* = 7.6 Hz); 8.09-8.15 (2H, m); 7.77 (1H, d, *J* = 7.8 Hz); 7.49-7.53 (2H, m); 7.37 (1H, t, *J* = 7.7 Hz); 6.96-7.06 (2H, m); 5.41 (2H, s, $OC\underline{H_2}$); 4.42 (2H, q, *J* = 8.0 Hz, $N\text{-}C\underline{H_2}CH_3$); 1.48 (3H, t, *J* = 8.0 Hz, $N\text{-}CH_2C\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 159.6, 157.3, 152.8, 144.5, 144.3, 139.1, 137.1, 128.2, 125.9, 125.0, 124.9, 124.6, 124.4, 123.3, 121.7, 120.0, 118.4, 118.3, 117.7, 117.5, 114.3, 113.9, 111.0, 110.8, 109.5 (aromatic C), 68.9, 37.7, 14.4 (aliphatic C)

LCMS (m/z): 368 $(M+H)^+$

Anal. Calcd. for $C_{24}H_{17}N_2FO$: C, 78.24; H, 4.65; N, 7.60 %

Found: C, 78.15; H, 4.70; N, 7.66 %

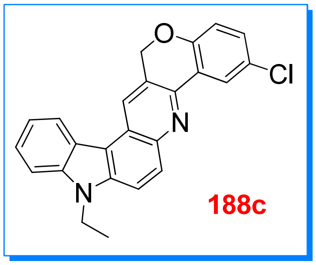
3-Chloro-8-ethyl-5a,6,12c,14-tetrahydrochromeno[3',4':5,6]pyrido[3,2-*c*]carbazole (188c)

Obtained by the reaction of 9-ethyl-3-aminocarbazole (**158c**) with **187c** in [Bmim][BF_4] following the *general procedure H*. The crude product was purified through silica gel column chromatography with 3 % ethyl acetate in hexanes.

Mp: 181-182 °C

Yield: 84 %

IR (KBr) ν_{max} cm^{-1}: 3055, 1510, 1249, 814, 734



188c

^{1}H NMR (400 MHz) δ: 8.99 (1H, s); 8.61 (1H, d, *J* = 7.7 Hz); 8.29 (1H, d, *J* = 7.2 Hz); 8.02-8.10 (2H, m); 7.67 (1H, d, *J* = 7.4 Hz); 7.48 (1H, t. *J* = 7.5 Hz); 7.28-7.35 (2H, m); 7.00 (1H, d, *J* = 7.6 Hz); 5.56 (2H, s, $OC\underline{H_2}$); 4.57 (2H, q, *J* = 8.1 Hz, $N\text{-}C\underline{H_2}CH_3$); 1.42 (3H, t, *J* = 7.7 Hz, $N\text{-}CH_2C\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 155.6, 144.3, 143.5, 139.2, 137.3, 130.8, 128.2, 127.1, 126.9, 125.4, 125.1, 125.0, 124.4, 124.2, 123.0, 122.2, 120.3, 119.3, 115.1, 114.2, 110.2 (aromatic C), 68.5, 37.8, 14.7 (aliphatic C)

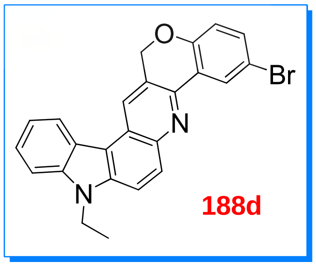
LCMS (m/z): 385 $(M+H)^+$

Anal. Calcd. for $C_{24}H_{17}N_2ClO$: C, 74.90; H, 4.45; N, 7.28 %

Found: C, 74.81; H, 4.41; N, 7.35

3-Bromo-8-ethyl-5a,6,12c,14-tetrahydrochromeno[3',4':5,6]pyrido [3,2-*c*]carbazole (188d)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with **187d** in ionic liquid following the *general procedure H* provided the title compound. Pure product was obtained through silica gel column chromatography with 2 % ethyl acetate in hexanes.



188d

Mp: 160 °C

Yield: 80 %

IR (KBr) ν_{max} cm^{-1}: 3055, 2966, 1514, 1317, 887, 592

^{1}H NMR (400 MHz) δ: 8.76 (1H, s); 8.43-8.45 (2H, m); 8.06 (1H, d, *J* = 7.4 Hz); 7.86 (1H, d, *J* = 7.6 Hz); 7.55 (1H, d. *J* = 7.5

Hz); 7.44 (1H, t, *J* = 7.8 Hz); 7.30-7.35 (2H, m); 6.86 (1H, d, *J* = 7.2 Hz); 5.47 (2H, s, OC$\underline{H}_2$); 4.48 (2H, q, *J* = 8.0 Hz, N-C$\underline{H}_2$CH$_3$); 1.42 (3H, t, *J* = 7.6 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 155.9, 144.5, 143.6, 139.2, 137.2, 133.5, 128.2, 127.3, 126.5, 125.5, 125.0, 124.9, 124.4, 123.1, 121.9, 120.2, 119.4, 114.7, 114.5, 114.2, 119.8 (aromatic C), 68.6, 37.8, 14.5 (aliphatic C)

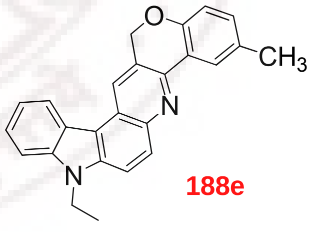
LCMS (m/z): 429 $(M+H)^+$, 431 $(M+2+H)^+$

Anal. Calcd. for $C_{24}H_{17}N_2BrO$: C, 67.14; H, 3.99; N, 6.53 %

Found: C, 67.25; H, 3.93; N, 6.45 %

8-Ethyl-3-methyl-5a,6,12c,14-tetrahydrochromeno[3',4':5,6]pyrido[3,2-*c*]carbazole (188e)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with **187e** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound. The crude product was purified through silica gel column chromatography with 2 % ethyl acetate in hexanes.



188e

Mp: 198 °C

Yield: 96 %

IR (KBr) ν_{max} cm^{-1}: 3053, 2968, 1514, 1373, 812, 549

^{1}H NMR (400 MHz) δ: 8.49 (1H, s); 8.32-8.35 (2H, m); 8.13 (1H, d, *J* = 7.3 Hz); 7.72 (1H, d, *J* = 7.5 Hz); 7.50 (2H, s); 7.36-7.39 (1H, m); 7.20 (1H, d, *J* = 7.7 Hz); 6.99 (1H, d, *J* = 7.3 Hz); 5.40 (2H, s, OC$\underline{H}_2$); 4.35 (2H, q, *J* = 7.8 Hz, N-C$\underline{H}_2$CH$_3$); 2.49 (3H, s, ArC-C$\underline{H}_3$); 1.45 (3H, t, *J* = 7.7 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 154.9, 145.3, 144.5, 139.1, 136.9, 131.8, 128.1, 125.9, 125.4, 125.0, 124.5, 124.1, 123.4, 123.3, 121.7, 119.8, 117.0, 114.3, 113.6, 109.4 (aromatic C), 68.9, 37.8, 20.9, 14.4 (aliphatic C)

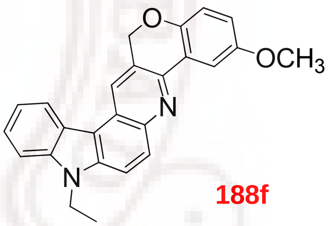
LCMS (m/z): 365 $(M+H)^+$

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69 %

Found: C, 82.25; H, 5.58; N, 7.75 %

8-Ethyl-3-methoxy-5a,6,12c,14-tetrahydrochromeno[3',4':5,6]pyrido[3,2-*c*]carbazole (188f)

Reaction of **158c** in the presence of 10 mol % of CuI and La(OTf)$_3$ (10 mol %) **187f** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound. Pure product was obtained through silica gel column chromatography with 3 % ethyl acetate in hexanes.



188f

Mp: 181-182 °C

Yield: 93 %

IR (KBr) ν_{max} cm^{-1}: 3063, 2970, 1591, 881, 596

^{1}H NMR (400 MHz) δ: 8.58 (1H, s); 8.37 (1H, d, *J* = 7.6 Hz); 8.13 (1H, d, *J* = 7.4 Hz); 8.00 (1H, d, *J* = 7.6 Hz); 7.75 (1H, d, *J* = 7.7 Hz); 7.49-7.50 (2H, m); 7.36 (1H, t, *J* = 7.8 Hz); 6.93-6.98 (2H, m); 5.38 (2H, s, OC$\underline{H}_2$); 4.40 (2H, q, *J* = 7.7 Hz, N-C$\underline{H}_2$CH$_3$); 3.95 (3H, s, ArC-OC$\underline{H}_3$); 1.45 (3H, t, *J* = 7.4 Hz, N-CH$_2$C$\underline{H}_3$)

^{13}C NMR (100 MHz) δ: 155.1, 151.1, 145.3, 144.5, 139.1, 137.0, 128.2, 126.0, 125.5, 124.6, 124.3, 124.1, 123.3, 121.7, 119.9, 119.5, 118.2, 114.4, 113.7, 109.9, 107.8 (aromatic C), 68.9, 56.0, 37.7, 14.4 (aliphatic C)

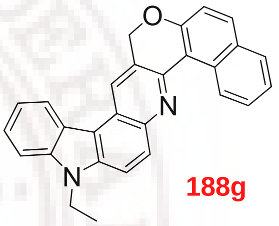
LCMS (m/z): 381 $(M+H)^+$

Anal. Calcd. for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36 %

Found: C, 78.85; H, 5.35; N, 7.45 %

10-Ethyl-7a,10,14c,16-tetrahydrobenzo[5',6']chromeno[3',4':5,6]pyrido[3,2-*c*]carbazole (188g)

Reaction of **158c** in the presence of CuI/La(OTf)$_3$ with **187g** in [Bmim][BF$_4$] following the *general procedure H* provided the title compound. The crude product was purified through silica gel column chromatography with 4 % ethyl acetate in hexanes.



188g

Mp: 222 °C

Yield: 84 %

IR (KBr) ν_{max} cm^{-1}: 3055, 2970, 1581, 879, 596

^{1}H NMR (400 MHz) δ: 10.12 (1H, d, *J* = 7.8 Hz); 8.70 (1H, s); 8.46 (1H, d, *J* = 7.6 Hz); 8.27 (1H, d, *J* = 7.5 Hz); 7.87-7.90 (2H, m); 7.75-7.80 (2H, m); 7.52-7.57 (3H, m); 7.42-7.44 (1H, m); 7.30 (1H, d, *J* = 7.6 Hz); 5.42 (2H, s, OC$\underline{H_2}$); 4.43 (2H, q, *J* = 7.6 Hz, N-C$\underline{H_2}$CH$_3$); 1.49 (3H, t, *J* = 7.3 Hz, N-CH$_2$C$\underline{H_3}$)

^{13}C NMR (100 MHz) δ: 157.0, 147.1, 144.3, 139.2, 137.1, 132.2, 131.3, 130.8, 128.4, 127.7, 127.3, 126.7, 126.0, 124.6, 124.4, 123.4, 123.3, 121.8, 119.9, 118.4, 116.6, 114.3, 113.5, 109.5 (aromatic C), 69.3, 37.7, 14.4 (aliphatic C)

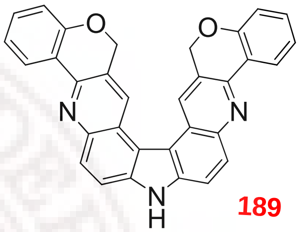
LCMS (m/z): 401 $(M+H)^+$

Anal. Calcd. for $C_{28}H_{20}N_2O$: C, 83.98; H, 5.03; N, 7.00 %

Found: C, 83.91; H, 5.09; N, 7.18 %

11,20-Dihydro-2*H*-dichromeno[3',4':5,6]pyrido[2,3-*c*:3,2-*g*]carbazole (189)

This *bis*-intramolecular imino Diels-Alder product (**189**) was prepared by the reaction of **158j** with **187a** in [Bmim][BF_4] following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 10 % ethyl acetate in hexanes.



189

Mp: 179 °C

Yield: 76 %

IR (KBr) ν_{max} cm^{-1}: 3414, 3054, 2930, 1564, 628

^{1}H NMR (400 MHz) δ: 12.68 (1H, s, N<u>*H*</u>); 9.16 (2H, s); 8.39 (2H, d, *J* = 7.9 Hz); 8.09 (3H, s); 7.42 (3H, t, *J* = 7.6 Hz); 7.20 (2H, t, *J* = 8.1 Hz); 7.09 (2H, d, *J* = 7.8 Hz); 5.65 (4H, s, OC<u>*H*</u>$_2$)

^{13}C NMR (100 MHz) δ: 157.2, 145.3, 145.0, 137.3, 131.9, 128.4, 128.1, 124.9, 124.5, 123.5, 123.4, 122.7, 117.8, 117.7, 116.6 (Aromatic C), 68.4 (aliphatic C) (Due to limited solubility and steric hindrance of the molecule, we could not get the some of carbon δ values)

LCMS (m/z): 476 (M-H)$^+$

Anal. Calcd. for $C_{32}H_{19}N_3O_2$: C, 80.49; H, 4.01; N, 8.80 %

Found: C, 80.25; H, 4.08; N, 8.89 %

Table 53. Crystal data and structure refinement for 182c

Empirical formula	$C_{29}H_{22}N_2$	
Formula weight	398.49	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.9474(16) Å	α = 90°
	b = 5.8428(8) Å	β = 99.327(2)°
	c = 32.421(5) Å	γ = 90°
Volume	2046.3(5) $Å^3$	
Z	4	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F (000)	840	
Crystal size	0.58 x 0.42 x 0.18 mm^3	
Theta range for data collection	1.27 to 25.00°	
Index ranges	-13<=h<=13, -6<=k<=6, -38<=l<=38	
Reflections collected	18586	
Independent reflections	3583 [R(int) = 0.0417]	
Completeness to theta = 26.04°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9865 and 0.9575	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3583 / 0 / 281	
Goodness-of-fit on F^2	1.164	
Final R indices [I>2sigma (I)]	R1 = 0.0562, wR2 = 0.1155	
R indices (all data)	R1 = 0.0712, wR2 = 0.1216	
Largest diff. peak and hole	0.157 and -0.171 e.$Å^{-3}$	
CCDC number	749234	

Table 54. Crystal data and structure refinement for 183

Empirical formula	: $C_{21}H_{20}N_2$	
Formula weight	: 300.39	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Triclinic	
Space group	: P-1	
Unit cell dimensions	: a = 5.907(6) Å	α = 89.811(17)°
	: b = 14.858(14) Å	β = 89.828(18)°
	: c = 18.889(18) Å	γ = 89.901(18)°
Volume	: 1658(3) Å^3	
Z	: 4	
Density (calculated)	: 1.204 Mg/m^3	
Absorption coefficient	: 0.071 mm^{-1}	
F (000)	: 640	
Crystal size	: 0.18 x 0.10 x 0.02 mm^3	
Theta range for data collection	: 1.08 to 25.00°	
Index ranges	: -7<=h<=7, -17<=k<=17, -22<=l<=22	
Reflections collected	: 14128	
Independent reflections	: 5781 [R(int) = 0.0606]	
Completeness to theta = 26.04°	: 99.4 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9986 and 0.9874	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 5781 / 0 / 400	
Goodness-of-fit on F^2	: 1.006	
Final R indices [I>2sigma (I)]	: R1 = 0.0612, wR2 = 0.1469	
R indices (all data)	: R1 = 0.1244, wR2 = 0.1732	
Largest diff. peak and hole	: 0.163 and -0.231 e.Å^{-3}	
CCDC number	: 749235	

Table 55. Crystal data and structure refinement for 184

Empirical formula	: $C_{86}H_{56}Cl_6N_6$	
Formula weight	: 1386.07	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/n	
Unit cell dimensions	: a = 44.357(7) Å	α = 90°
	: b = 11.885(2) Å	β = 96.214(3)°
	: c = 13.819(2) Å	γ = 90°
Volume	: 7242(2) $Å^3$	
Z	: 4	
Density (calculated)	: 1.271 Mg/m^3	
Absorption coefficient	: 0.288 mm^{-1}	
F (000)	: 2864	
Crystal size	: 0.50 x 0.22 x 0.10 mm^3	
Theta range for data collection	: 1.39 to 25.00°	
Index ranges	: -52<=h<=52, -14<=k<=14, -16<=l<=16	
Reflections collected	: 66841	
Independent reflections	: 12740 [R(int) = 0.1058]	
Completeness to theta = 26.04°	: 99.8 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9718 and 0.8695	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 12740 / 0 / 883	
Goodness-of-fit on F^2	: 2.035	
Final R indices [I>2sigma (I)]	: R1 = 0.2167, wR2 = 0.5392	
R indices (all data)	: R1 = 0.2532, wR2 = 0.5514	
Largest diff. peak and hole	: 0.960 and -0.755 e.$Å^{-3}$	
CCDC number	: 749242	

Table 56. Crystal data and structure refinement for 185f

Empirical formula	: $C_{32}H_{28}N_2$
Formula weight	: 440.56
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: C2/c
Unit cell dimensions	: a = 26.918(7) Å α = 90°
	: b = 7.655(2) Å β = 116.110(4)°
	: c = 25.490(7) Å γ = 90°
Volume	: 4716(2) $Å^3$
Z	: 8
Density (calculated)	: 1.241 Mg/m^3
Absorption coefficient	: 0.072 mm^{-1}
F (000)	: 1872
Crystal size	: 0.42 x 0.40 x 0.30 mm^3
Theta range for data collection	: 1.68 to 25.00°
Index ranges	: -32<=h<=32, -9<=k<=9, -30<=l<=30
Reflections collected	: 21774
Independent reflections	: 4155 [R(int) = 0.0276]
Completeness to theta = 26.04°	: 100.0 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9787 and 0.9704
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 4155 / 0 / 311
Goodness-of-fit on F^2	: 1.063
Final R indices [I>2sigma (I)]	: R1 = 0.0442, wR2 = 0.1152
R indices (all data)	: R1 = 0.0503, wR2 = 0.1198
Largest diff. peak and hole	: 0.220 and -0.219 e.$Å^{-3}$
CCDC number	: 749232

Table 57. Crystal data and structure refinement for 186a

Empirical formula	: $C_{35}H_{26}N_2$
Formula weight	: 474.58
Temperature	: 100(2) K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P-1
Unit cell dimensions	: a = 10.0337(12) Å α = 71.197(2)° : b = 10.2181(12) Å β = 69.694(2)° : c = 13.8949(16) Å γ = 72.316(2)°
Volume	: 1234.8(3) Å^3
Z	: 2
Density (calculated)	: 1.276 Mg/m^3
Absorption coefficient	: 0.074 mm^{-1}
F (000)	: 500
Crystal size	: 0.60 x 0.42 x 0.40 mm^3
Theta range for data collection	: 1.61 to 25.00°
Index ranges	: -11<=h<=11, -12<=k<=12, -16<=l<=16
Reflections collected	: 11874
Independent reflections	: 4338 [R(int) = 0.0197]
Completeness to theta = 26.04°	: 99.8 %
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9709 and 0.9569
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 4338 / 0 / 335
Goodness-of-fit on F^2	: 1.076
Final R indices [I>2sigma (I)]	: R1 = 0.0414, wR2 = 0.1021
R indices (all data)	: R1 = 0.0429, wR2 = 0.1037
Largest diff. peak and hole	: 0.212 and -0.462 e.Å^{-3}
CCDC number	: 749237

Table 58. Crystal data and structure refinement for 186c

Empirical formula : $C_{32}H_{28}N_2$

Formula weight : 440.56

Temperature : 100(2) K

Wavelength : 0.71073 Å

Crystal system : Monoclinic

Space group : P2(1)/n

Unit cell dimensions : a = 7.7325(6) Å α = 90°

: b = 19.1682(15) Å β = 101.84(10)°

: c = 16.3176(13) Å γ = 90°

Volume : 2367.1(3) $Å^3$

Z : 4

Density (calculated) : 1.236 Mg/m^3

Absorption coefficient : 0.072 mm^{-1}

F (000) : 936

Crystal size : 0.40 x 0.40 x 0.20 mm^3

Theta range for data collection : 1.66 to 25.00°

Index ranges : -9<=h<=9, -22<=k<=22, -19<=l<=19

Reflections collected : 21555

Independent reflections : 4165 [R(int) = 0.0312]

Completeness to theta = 26.04° : 100.0 %

Absorption correction : Semi-empirical from equivalents

Max. and min. transmission : 0.9858 and 0.9719

Refinement method : Full-matrix least-squares on F^2

Data / restraints / parameters : 4165 / 0 / 309

Goodness-of-fit on F^2 : 1.093

Final R indices [I>2sigma (I)] : R1 = 0.0488, wR2 = 0.1128

R indices (all data) : R1 = 0.0562, wR2 = 0.1170

Largest diff. peak and hole : 0.140 and -0.194 $e.Å^{-3}$

CCDC number : 749239

Table 59. Crystal data and structure refinement for 186d

Empirical formula	: $C_{33}H_{30}N_2$	
Formula weight	: 454.59	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Orthorhombic	
Space group	: P2(1)2(1)2(1)	
Unit cell dimensions	: a = 9.7135(8) Å	α = 90°
	: b = 15.8117(13) Å	β = 90°
	: c = 16.3277(14) Å	γ = 90°
Volume	: 2507.7(4) $Å^3$	
Z	: 4	
Density (calculated)	: 1.204 Mg/m^3	
Absorption coefficient	: 0.070 mm^{-1}	
F (000)	: 968	
Crystal size	: 0.40 x 0.18 x 0.08 mm^3	
Theta range for data collection	: 1.79 to 25.00°	
Index ranges	: -11<=h<=11, -18<=k<=18, -19<=l<=19	
Reflections collected	: 24276	
Independent reflections	: 2514 [R(int) = 0.1013]	
Completeness to theta = 26.04°	: 100.0 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9944 and 0.9726	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2514 / 0 / 318	
Goodness-of-fit on F^2	: 1.314	
Final R indices [I>2sigma (I)]	: R1 = 0.0865, wR2 = 0.1520	
R indices (all data)	: R1 = 0.1032, wR2 = 0.1574	
Largest diff. peak and hole	: 0.157 and -0.185 e.$Å^{-3}$	
CCDC number	: 749240	

Table 60. Crystal data and structure refinement for 186e

Empirical formula	: $C_{30}H_{24}N_2O$	
Formula weight	: 428.51	
Temperature	: 100(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Orthorhombic	
Space group	: P2(1)2(1)2(1)	
Unit cell dimensions	: a = 9.1039(6) Å	α = 90°
	: b = 9.6255(7) Å	β = 90°
	: c = 25.0902(18) Å	γ = 90°
Volume	: 2198.6(3) $Å^3$	
Z	: 4	
Density (calculated)	: 1.295 Mg/m^3	
Absorption coefficient	: 0.079 mm^{-1}	
F (000)	: 904	
Crystal size	: 0.58 x 0.48 x 0.20 mm^3	
Theta range for data collection	: 1.62 to 24.98°	
Index ranges	: -10<=h<=10, -11<=k<=11, -29<=l<=29	
Reflections collected	: 21173	
Independent reflections	: 2234 [R(int) = 0.0291]	
Completeness to theta = 26.04°	: 100.0 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9845 and 0.9559	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2234 / 0 / 300	
Goodness-of-fit on F^2	: 1.077	
Final R indices [I>2sigma (I)]	: R1 = 0.0284, wR2 = 0.0715	
R indices (all data)	: R1 = 0.0290, wR2 = 0.0719	
Largest diff. peak and hole	: 0.138 and -0.186 e.$Å^{-3}$	
CCDC number	: 749241	

Table 61. Crystal data and structure refinement for 188a

Empirical formula	$C_{24}H_{18}N_2O$	
Formula weight	350.40	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbcn	
Unit cell dimensions	a = 25.766(2) Å	$\alpha = 90°$
	b = 7.7528(6) Å	$\beta = 90°$
	c = 17.5998(14) Å	$\gamma = 90°$
Volume	3515.8(5) $Å^3$	
Z	8	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F (000)	1472	
Crystal size	0.60 x 0.42 x 0.32 mm^3	
Theta range for data collection	1.58 to 25.00°	
Index ranges	$-30<=h<=30$, $-9<=k<=9$, $-20<=l<=20$	
Reflections collected	31563	
Independent reflections	3102 [R(int) = 0.0369]	
Completeness to theta = 26.04°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9743 and 0.9526	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3102 / 0 / 245	
Goodness-of-fit on F^2	1.176	
Final R indices [I>2sigma (I)]	R1 = 0.0520, wR2 = 0.1184	
R indices (all data)	R1 = 0.0567, wR2 = 0.1212	
Largest diff. peak and hole	0.150 and -0.208 e.$Å^{-3}$	
CCDC number	749233	

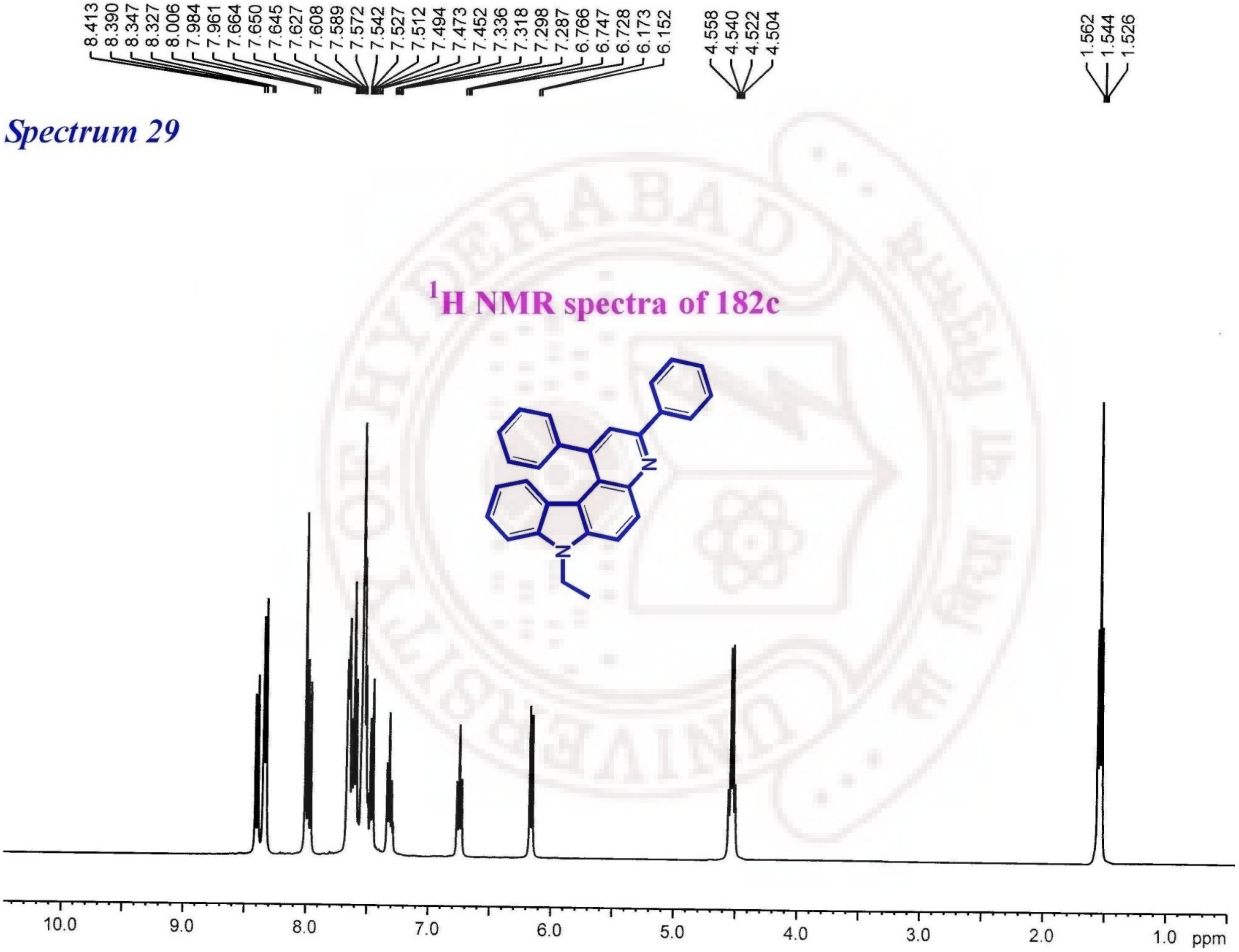
Table 62. Crystal data and structure refinement for 188b

Empirical formula	$C_{24}H_{17}FN_2O$	
Formula weight	368.40	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 32.272(3) Å	α = 90°
	b = 5.8561(5) Å	β = 111.706(2)°
	c = 19.5413(16) Å	γ = 90°
Volume	3431.3(5) $Å^3$	
Z	8	
Density (calculated)	1.426 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F (000)	1536	
Crystal size	0.40 x 0.30 x 0.22 mm^3	
Theta range for data collection	1.36 to 25.00°	
Index ranges	-38<=h<=38, -6<=k<=6, -23<=l<=22	
Reflections collected	15575	
Independent reflections	3010 [R(int) = 0.0269]	
Completeness to theta = 26.04°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9793 and 0.9628	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3010 / 0 / 254	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma (I)]	R1 = 0.0400, wR2 = 0.1017	
R indices (all data)	R1 = 0.0413, wR2 = 0.1031	
Largest diff. peak and hole	0.205 and -0.276 e.$Å^{-3}$	
CCDC number	749238	

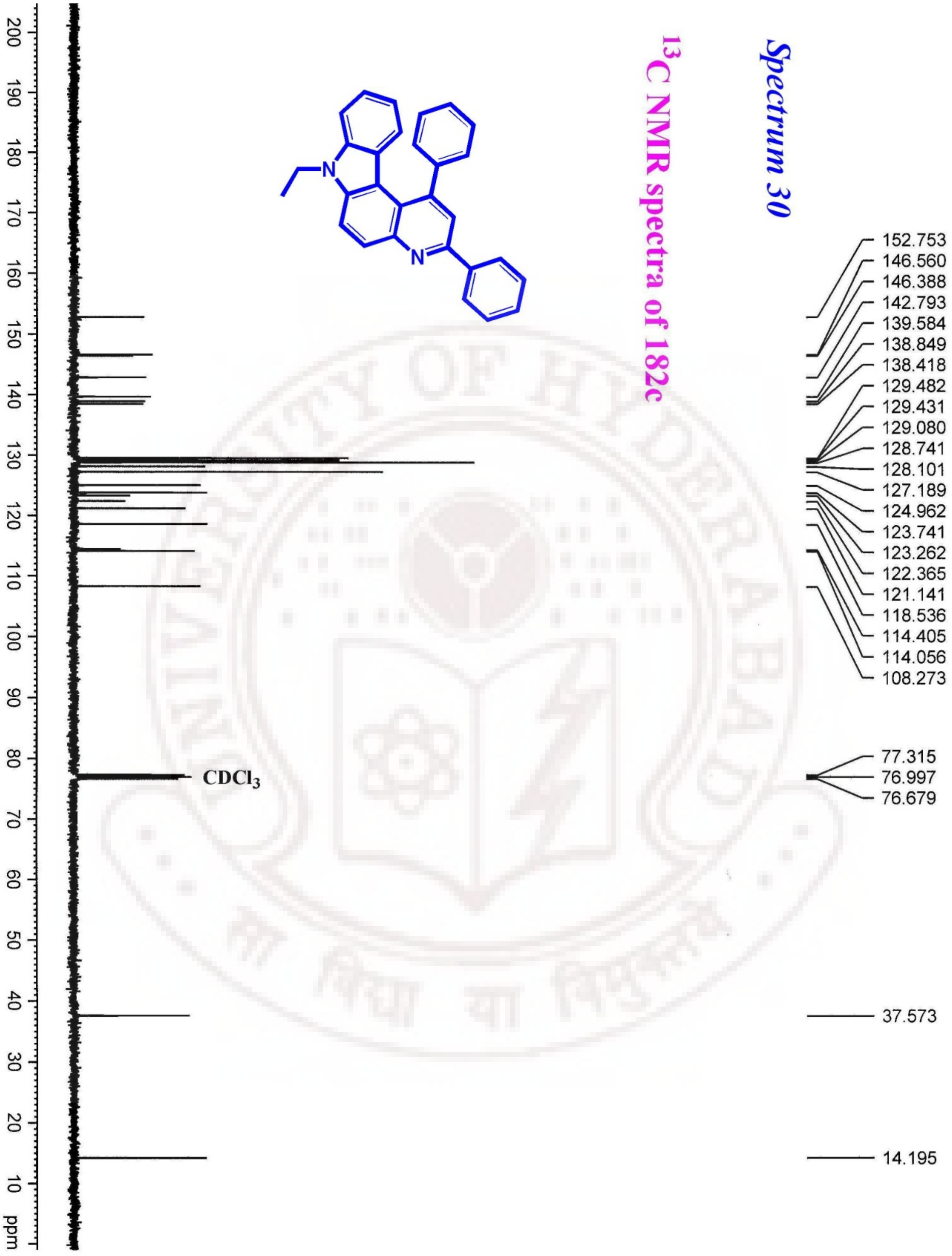
Table 63. Crystal data and structure refinement for 188g

Empirical formula	: $C_{28}H_{20}N_2O$	
Formula weight	: 400.46	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Orthorhombic	
Space group	: Pca2(1)	
Unit cell dimensions	: a = 23.639(12) Å	α = 90°
	: b = 5.241(3) Å	β = 90°
	: c = 16.110(8) Å	γ = 90°
Volume	: 1995.9(18) $Å^3$	
Z	: 4	
Density (calculated)	: 1.333 Mg/m^3	
Absorption coefficient	: 0.081 mm^{-1}	
F (000)	: 840	
Crystal size	: 0.48 x 0.32 x 0.22 mm^3	
Theta range for data collection	: 1.72 to 25.00°	
Index ranges	: -28<=h<=28, -6<=k<=6, -19<=l<=19	
Reflections collected	: 17665	
Independent reflections	: 1828 [R(int) = 0.0916]	
Completeness to theta = 26.04°	: 100.0 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9823 and 0.9620	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 1828 / 1 / 281	
Goodness-of-fit on F^2	: 1.243	
Final R indices [I>2sigma (I)]	: R1 = 0.0752, wR2 = 0.1748	
R indices (all data)	: R1 = 0.0811, wR2 = 0.1784	
Largest diff. peak and hole	: 0.250 and -0.209 e.$Å^{-3}$	
CCDC number	: 749236	

Spectrum 29

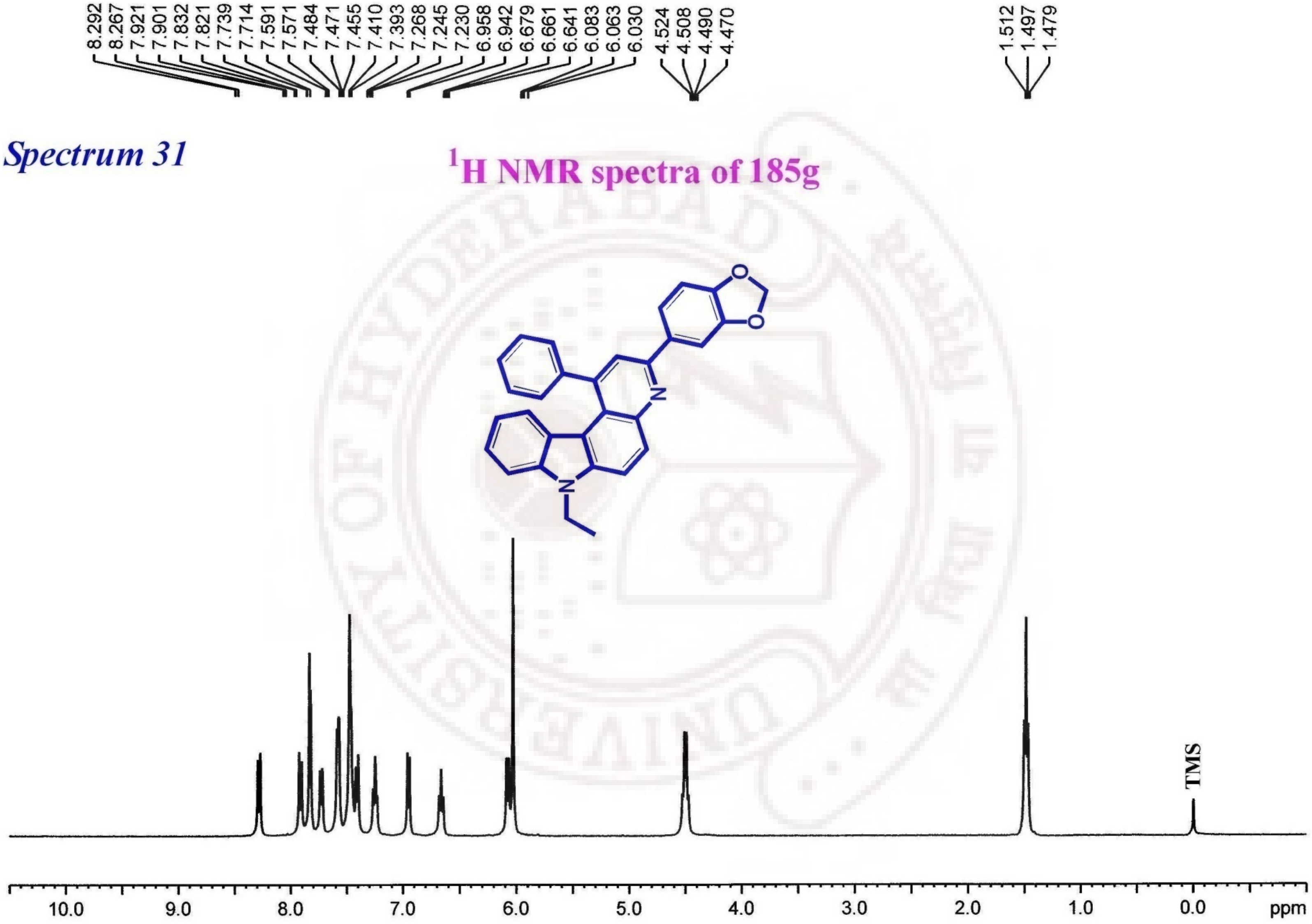


^{1}H NMR spectra of 182c



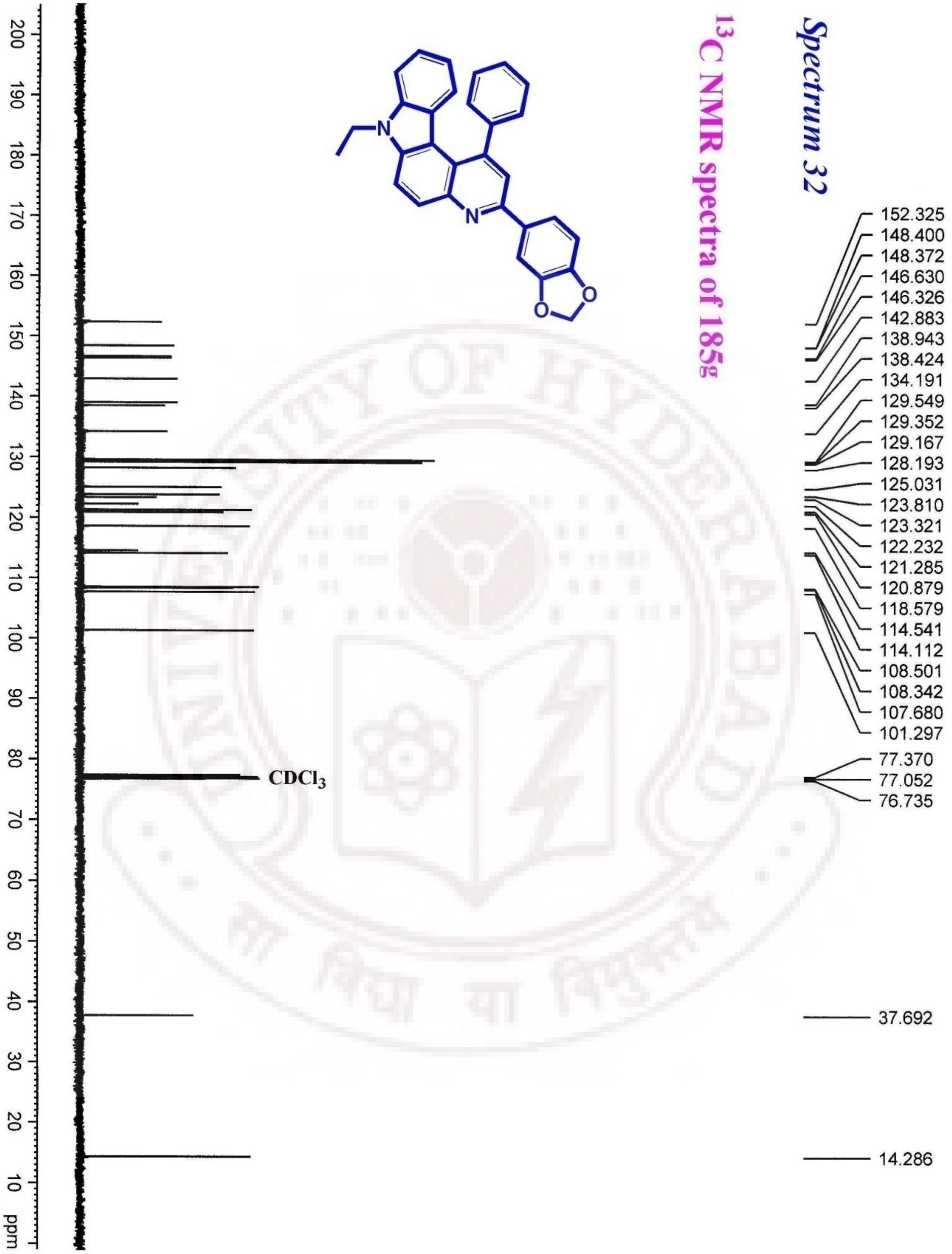
Spectrum 30

^{13}C NMR spectra of 182c



Spectrum 31

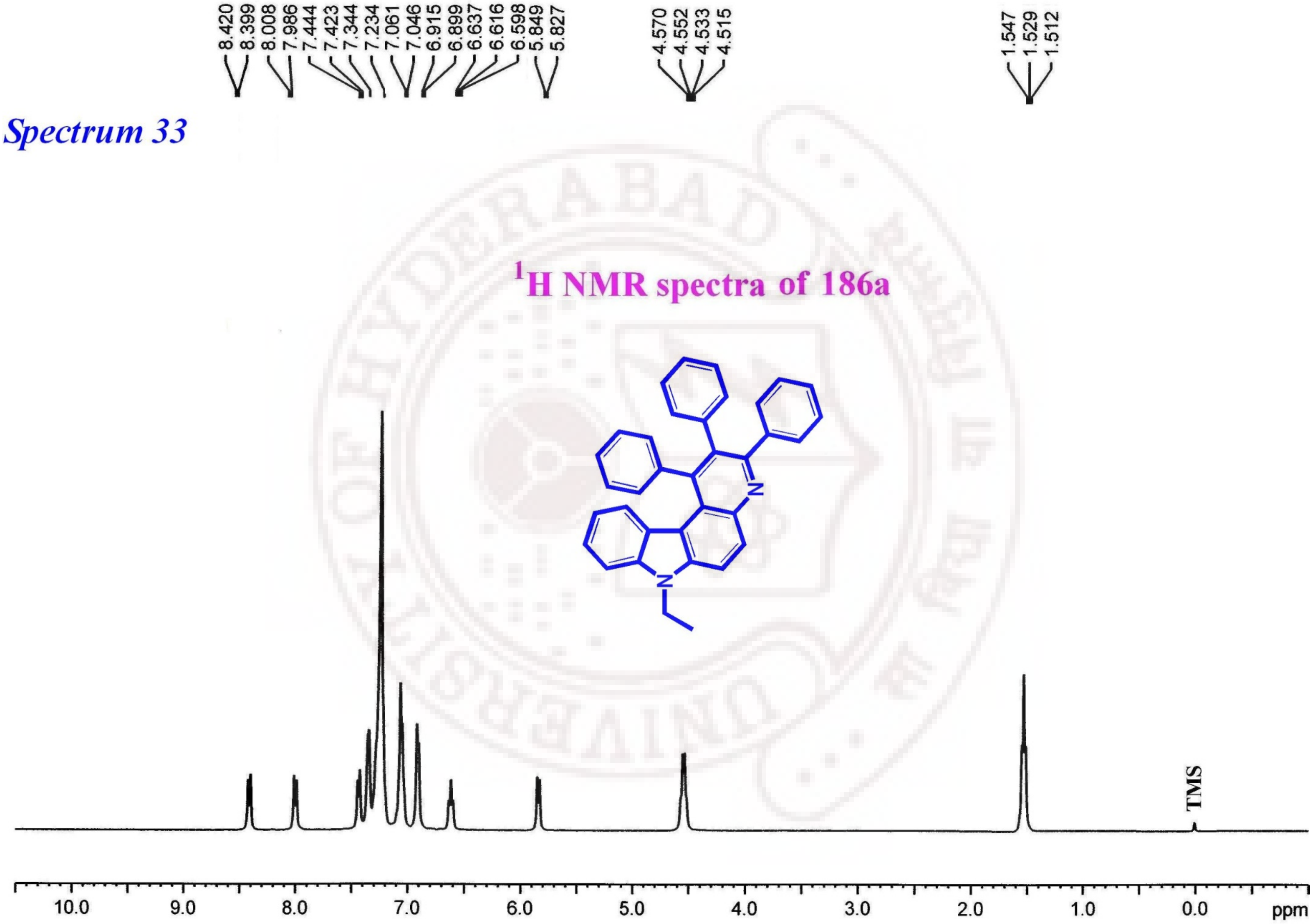
^{1}H NMR spectra of 185g



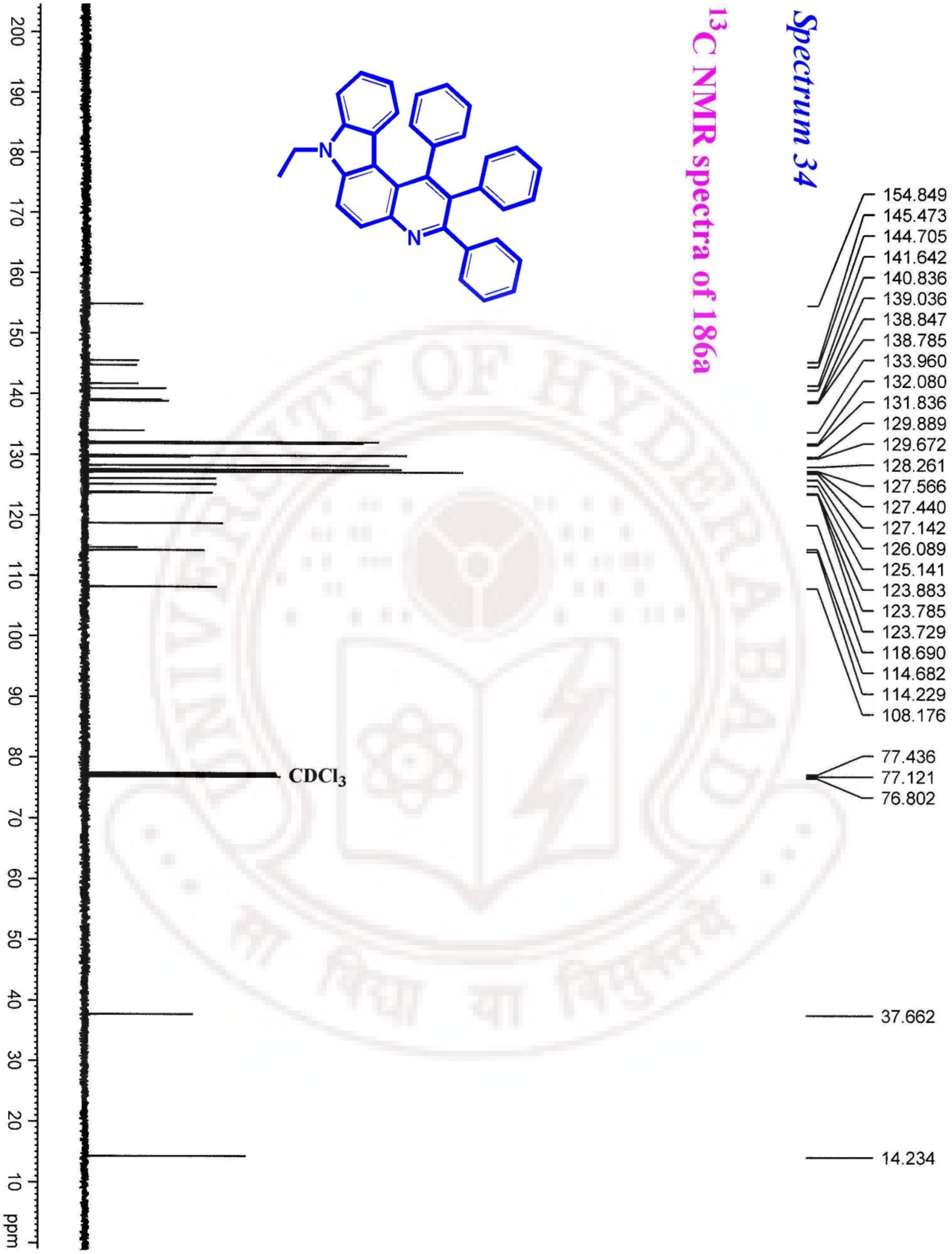
Spectrum 32

^{13}C NMR spectra of 185g

Spectrum 33



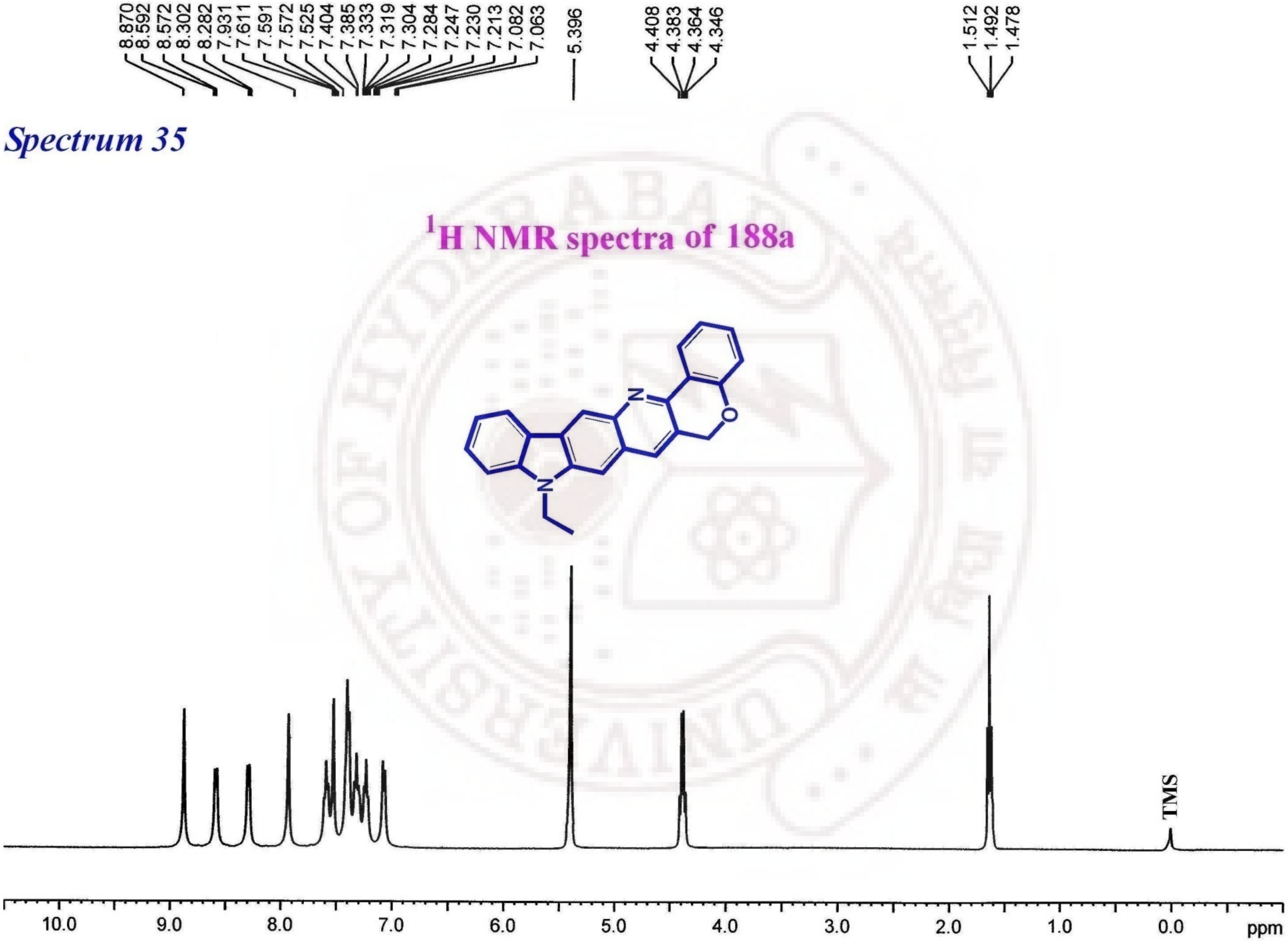
^{1}H NMR spectra of 186a



Spectrum 34

^{13}C NMR spectra of 186a

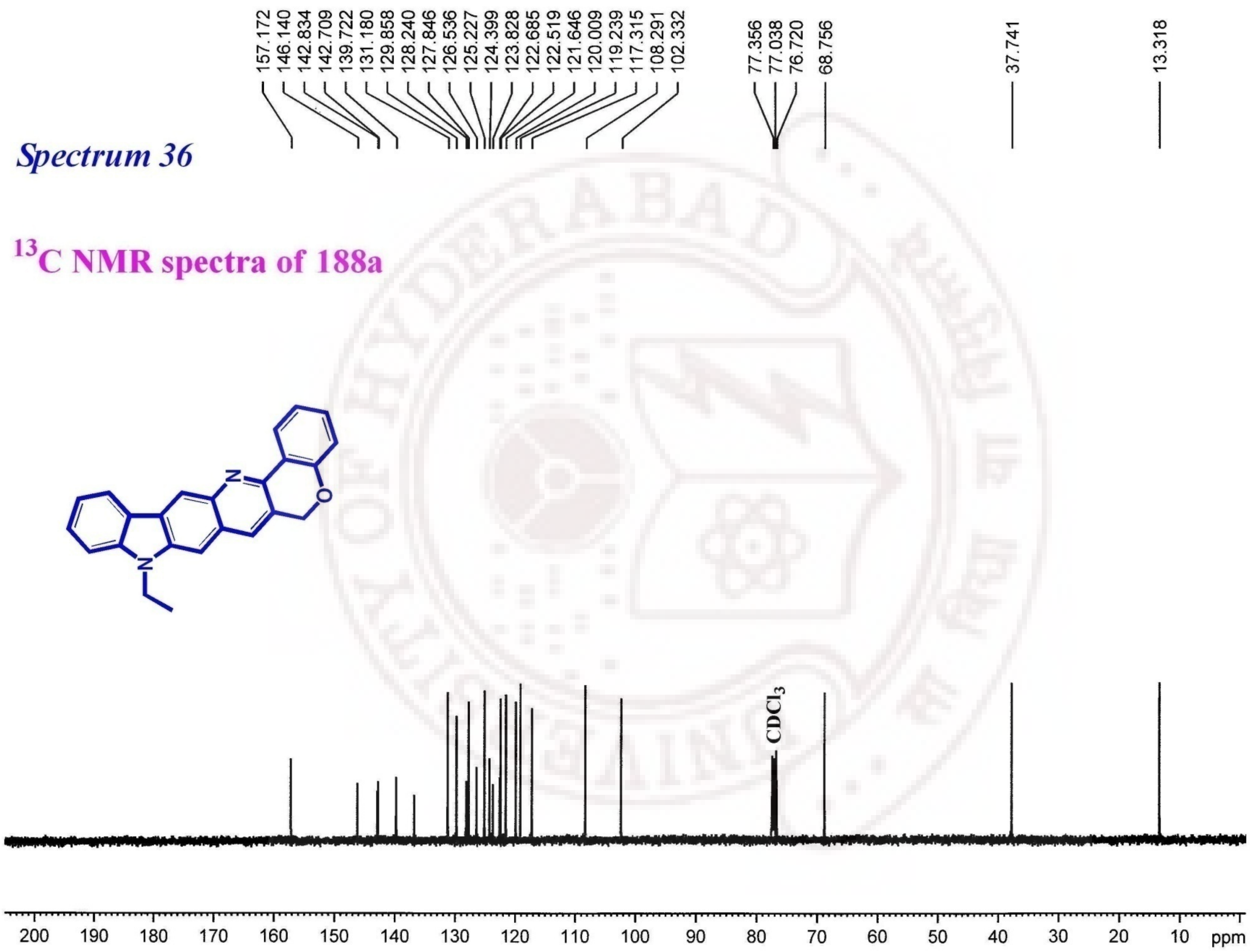
Spectrum 35

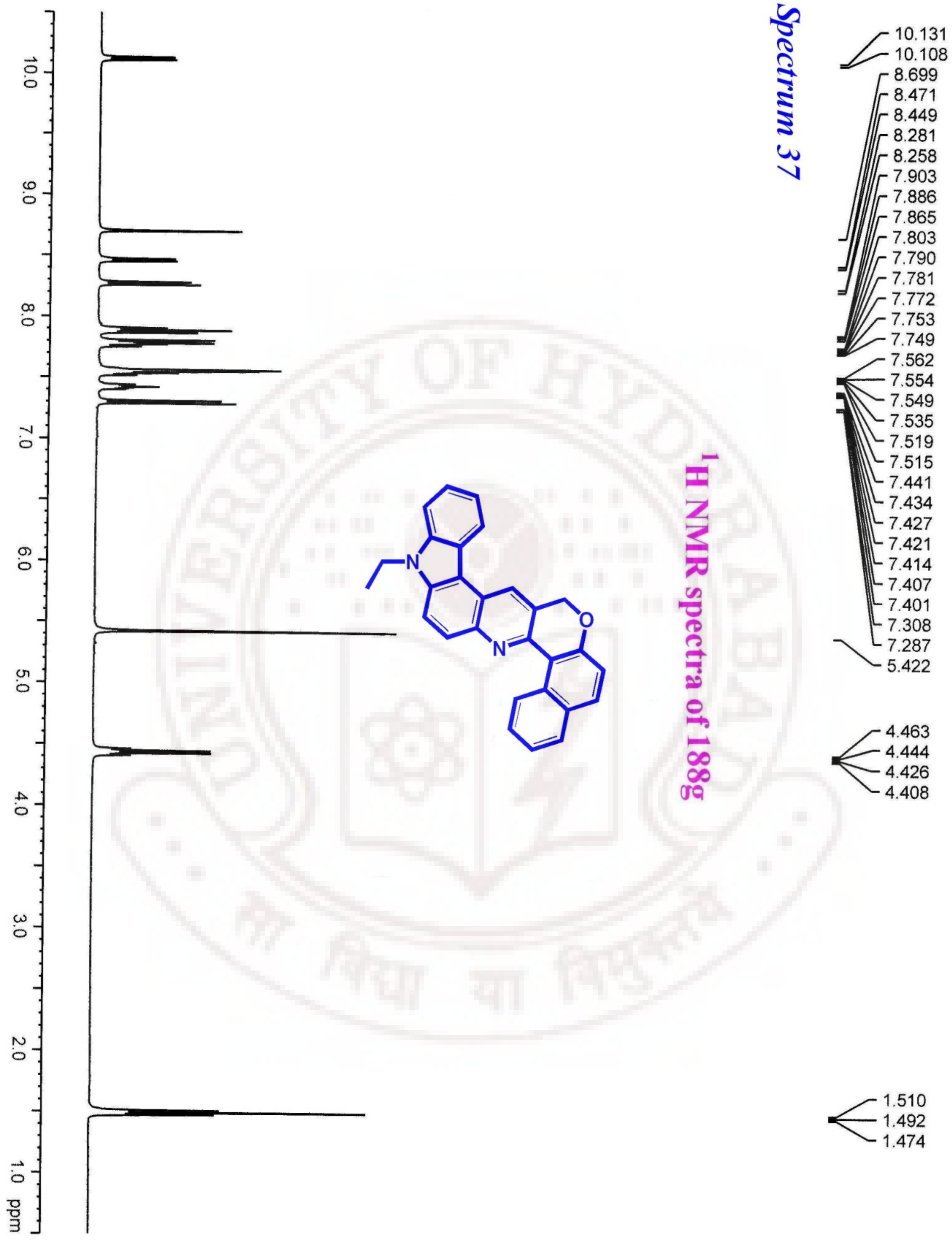


^{1}H NMR spectra of 188a

Spectrum 36

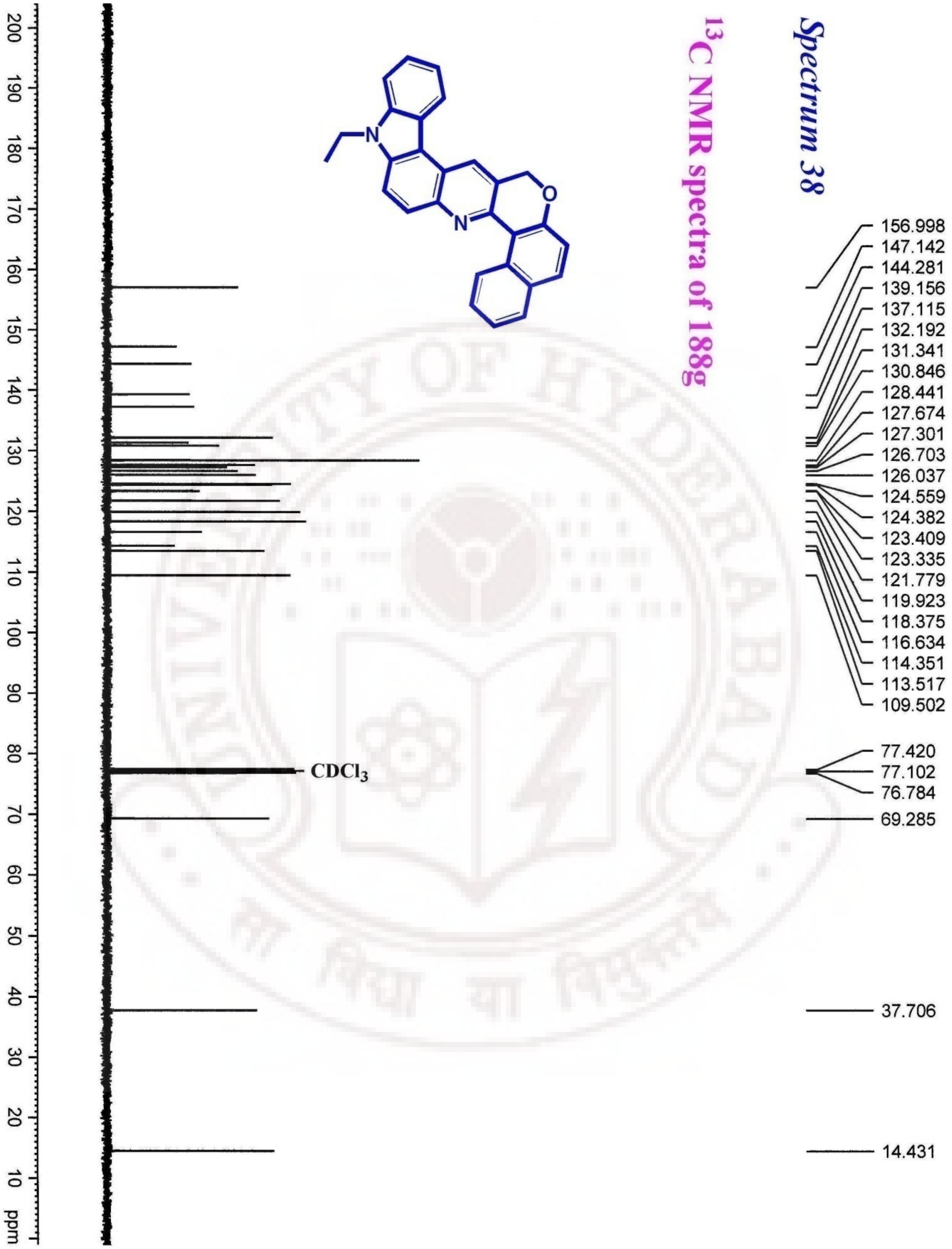
^{13}C NMR spectra of 188a





Spectrum 37

^{1}H NMR spectra of 188g



Spectrum 38

^{13}C NMR spectra of 188g

4.5. References

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Conclusions

We have made significant progress and achieved considerable success in our objectives on the synthesis of polycyclic aminoanthraquinone, indole and pyridocarbazole derivatives through inter and intramolecular hetero Diels-Alder reaction.

- We have developed a convenient, one-pot procedure for the synthesis of *cis*-fused pyrano and furanochromenylaminoanthraquinones (**96a-e**, **98a-e** and **100a-e**) by using hetero Diels-Alder reaction. In addition to its simplicity and mild reaction conditions, this procedure has advantages of high yields, easy availability and flexibility of starting materials, short reaction times, and useful diastereoselectivity. We have synthesized new mono and *bis*-naptho[2,3-*c*]acridines (**101-103**). We have also synthesized mono and bis chromanoquinolo naphthaquinones (**105a-g** and **106a-g**). We have presented the novel observation which originates from the reaction of aminoanthraquinones with salicylaldehydes. The nature of the substituents in the salicylaldehyde primarily determines the mechanistic pathway from the normal Diels-Alder to ene-type cyclization or unexpected reaction pathway. This unusual observation is novel and we have also explained the observation through the possible mechanism. The reactions are rapid and the products were obtained in moderate to excellent yields.

- We have described a novel, highly efficient and highly diastereoselective method for the synthesis of polycyclic indole derivatives (**130a-f**) through intramolecular imino Diels-Alder reaction. This method is very simple and straightforward starting from easily accessible starting materials. We have successfully synthesized indolopyrroloquinolines (**131a-e** and **135a-b**) *via* intramolecular imino Diels-Alder [4+2] cycloaddition. This method provides synthetically useful indole annulated pyrroloquinolines in good yields.

- We have described a useful method for the preparation of various polycyclic isomeric ellipticine derivatives or isomeric ellipticine derivatives fused with biologically important pyrroloindole or chromene moiety through intra (**159a-j**, **160**, **161a-e**, **162** and **164**) and intermolecular imino Diels-Alder reaction (**166a-j**, **167** and **168**) along with minor reductive amination products (**169a-d**).

- We have described a novel synthesis of pyridocarbazole derivatives with inter (**182a-i**, **183**, **184**, **185a-j** and **186a-f**) and intramolecular imino Diels-Alder reaction (**188a-g** and **189**) catalyzed by Cu/La(OTf)$_3$. Different substituents may be introduced to different positions of pyridocarbazole by just installing these substituents on any of the three components.