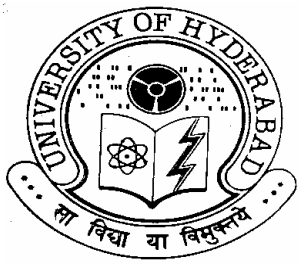
SYNTHESIS OF PYRROLO, PYRIDO, QUINO, INDOLO CARBAZOLE DERIVATIVES AND BOUCHARDATINE ALKALOID

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

MAYAVAN VIJI



SCHOOL OF CHEMISTRY

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INDIA

December 2012

STATEMENT

I hereby declare that the matter embodied in this thesis entitled "SYNTHESIS OF PYRROLO, PYRIDO, QUINO, INDOLO CARBAZOLE DERIVATIVES AND BOUCHARDATINE ALKALOID" 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:

Hyderabad **(MAYAVAN VIJI)**

CERTIFICATE

This is to certify that the work described in this thesis entitled "SYNTHESIS OF PYRROLO, PYRIDO, QUINO, INDOLO CARBAZOLE DERIVATIVES AND BOUCHARDATINE ALKALOID" has been carried out by MAYAVAN VIJI under my supervision and that the same has not been submitted elsewhere for any degree.

Dr. R. NAGARAJAN

(Thesis Supervisor)

Dean
School of Chemistry
University of Hyderabad

LIST OF PUBLICATIONS

1. CAN-Catalyzed Regioselective Synthesis of Pyrido[2,3-*c*]carbazoles by the Povarov Reaction **Mayavan Viji** and Rajagopal Nagarajan *Synthesis* **2012**, *44*, 253–258
2. $RuCl_3/SnCl_2$ mediated synthesis of pyrrolo[2,3-*c*]carbazoles and consequent preparation of indolo[2,3-*c*]carbazoles **Mayavan Viji** and Rajagopal Nagarajan *Tetrahedron* **2012***, 68*, 2453-2458
3. Zinc triflate catalyzed regioselective synthesis of pyrrolo[2,3-c]carbazoles via heteroannulation **Mayavan Viji** and Rajagopal Nagarajan *RSC Advances*, **2012**, *2*, 10544–10549
4. Palladium catalyzed C-H activation route to the synthesis of quino[2,3-*a*]carbazoles and indolo[2,3-*a*]carbazoles **Mayavan Viji** and Rajagopal Nagarajan (manuscript under preparation)
5. Synthesis of Bouchardatine alkaloids **Mayavan Viji** and Rajagopal Nagarajan (manuscript under preparation)

Posters and Presentations

1. Participated and gave an oral and poster presentation on "**Synthesis of Pyrrolocarbazoles *via* Heteroannulation"** at 8th "***CHEMFEST 2012***" (In-house symposium), School of Chemistry, University of Hyderabad, Hyderabad.
2. Participated and presented poster on "**CAN-Catalyzed Regioselective Synthesis of Pyrido[2,3-*c*]carbazoles by the Povarov Reaction**" at "***CRSI Zonal Meet*"** Pondicherry University, Puducherry during December 16-17, 2011.
3. Participated and presented poster on "**$RuCl_3/SnCl_2$ mediated synthesis of pyrrolo[2,3-*c*]carbazoles and consequent preparation of indolo[2,3-*c*]carbazoles"** in "**International Symposium on Recent Trends in Spectroscopy and Dynamics of Chemical Systems"** Organized by School of Chemistry, University of Hyderabad, Hyderabad during December 7-8, 2011.
4. Participated and gave poster presentation on "**$RuCl_3/SnCl_2$ mediated synthesis of pyrrolo[2,3-*c*]carbazoles"** at 7th "***CHEMFEST 2011***" (In-house symposium), School of Chemistry, University of Hyderabad, Hyderabad.
5. Participated and gave poster presentation on "**$RuCl_3/SnCl_2$ mediated synthesis of pyrrolo[2,3-*c*]carbazoles"** In "***Chennai Chemistry Conference"*** Organized by IIT Madras, Chennai during February 11-13, 2011.

Acknowledgements

With high regards and profound respect, I wish to express my deep sense of gratitude to **Dr. R. Nagarajan** for his inspiring guidance and constant encouragement throughout my research work and introducing me to this fascinating field of research. He has been a source of inspiration throughout with provoking discussions.

I thank, Dean **Prof. M. V. Rajasekharan**, School of Chemistry, former Deans **Prof. M. Periasamy** and **Prof. D. Basavaiah** for providing facilities to carry out my research work during my stay here. I also thank all the faculty members for their inspiration.

I would like to express my special thanks to Dr. H. Vignesh Babu, Dr. M. Nagarjuna Reddy, Dr.Y. Vijendar Reddy, Dr. K. Ramesh, Dr. A. Sateesh Kumar, for their helpful discussions and also for fighting during my research. I would like to thank my lab seniors Dr. G. Vikram, Dr. M. Ramu, Dr. T. K. Chaitanya, Dr. D. K. Sreenivas who teach me the lab culture. I thank Miss. P.V. Amulya Rao, Mr. N. Ram Kumar, Mr. S. Ramesh in lab and making the lab atmosphere to good. I acknowledge the help rendered by labmates Mr. J. Ramaraju, Mr. K. S. Prakash. Mr. Suman Kr. Ghosh. I also thank project students aniyathi C. S. Soniya, and Nanazi, Kumaraswamy, Sreenivas and Sundar.

My stay on this school of chemistry has been very pleasant with the association of each and every person. I thank S. Soumya, and P. Thamizharasi and M. Santhana Raj prabhu for their small comedies. I would like to express my thanks to Jeeva & Archana, Antony, RajKumar and B. ganesh kumar for their understanding and make my stay happy.

I gratefully acknowledge the help provided by the technical and office staff of the School of Chemistry. I thank Mr. Bhaskara Rao, Ms. Asia Parwez, Mr. Satyanarayana, and Smt. Vijaya Laxmi for their help in recording NMR spectra and P. Raghavaiah, Ramana for their help in X-ray crystallography. I also thank Mr. Prasad, Mr. Sambhasiva Rao, Mr. M. Shetty, Mr. Sudhakar, Mr. Santhosh, Mr. Anand, Mr. A. R. Shetty, Mr. Joseph, Mr. Sai, Mr. Sharma and Mr. Jayaram for their cooperation. I specially thank Mr. M. Venkateswara rao for his immense help in recording my NMR at regular times.

I am lucky enough to have the support of many School of Chemistry friends and colleagues Laxman, Guru, Suresh, Obul, Shanmuga raja, Dr.T. Manasai, Dr. Naga Raju, Dr. Mallesh, Dr. Sanjeev, Dr. Shekar reddy, Satpal, Lingaiyah, Chandrasekhar, Cyana, Malligarjun, Harathi, Dr. Anjaneyalu, Dr. Rama Suresh, Dr. Venu Srinivas, Dr. Sajna, Gangadhar, Sreenivas, Prasad, Leela, Dr. Ravi, P. Kishore, Anand, Kalyan, Arjun, Amala, Dr. Jagadeesh, Praveen, Shekhar Reddy, Sanyasi, Dr. Arindham, Dr. Sandeep, Sudhansu, Malkappa, Soura, Nagaraju, Swamy, Balawardhan, Satish, Krishna charry, Dr. Sreenivas, Mahaboob, Vikranth, Obaya, Satish, Sandeep, Tridib, Sreenivas, Ganesh, Ravidhra Babu, Vanaja, Naveen, Manoj, Ramana, Sakthivel, Thamizharasan, Chandrasekhar, Ajay, Narayana, Pramiti, Gupta, Hari, Ramu Yadav, Bhanu, Mallesh, Nagaraju, Nayan, Raja, sanathan, Ramakrishna Shesu, Venu, Suresh, Madhu, Anish, Malakappa, Naba, Suryanarayana, Rajesh, Sudalai, Santhosh, Dinesh, Ashok, Chandu, Dr. Rajesh, Tirupathi Reddy, Pavan, Sudeer, Yaseen, Gangadhar, Srinu, Santosh, Dr. Sivaranjan Reddy, Rajgopal Sr., Rajgopal Jr., Naga Prasad, Shugato, Rudra, Dr. Kishore, Dr. Ramkumar, Narayana, MadhavaCharry, Bharani, Shivaprasad, Srinivas Reddy, Bharath, Aarthi, Kishore, Dr. GDP, Krishna, Dr. Tanmay, Sasi Kanth, Paloumi, Sudharani, Venukumar exceptionally generous in helping me at various occasions.

My stay on this campus has been pleasant with the association of many friends. In this context, I would like to thank **All the scholars of School of chemsitry** for their help and support.

I would like to acknowledge Dr. Uma Maheswari akka IICT who helped me in several occasion and Dr. Vel Kannan IITM, and special thanks to Dr. R. Murali Shankar CLRI who treated me like his own brother. I Thank NRS hostel mates and my sweet seniors Dr. S. Selva Ganesan, Dr. T. S. Venkadesan, Dr. E. Balaraman, Dr. Prakash Prabhu, Dr. Vaira Prakash, Dr. P. Devaraj, Dr. D. Vijayan (Kabaali Khan), "Thaats" Dr. S. Vijayan, Dr. T. Arumuganadhan, Dr. M. Gnanavel, Dr. Arun Babu, Mr. M. Santhana raj Prabhu, Dr. Senthil for making the hostel life more memorable.I also thank my Tamil juniors B. Prabhu, Pram Ram, Rajakumar, Aiyappan, Justin, Muruganandham, Nelson, Deepanjan, Kishore, Master Sabur Ali. I extend my thank to Dr. Suresh and Dr. Rajendnra. Dr. Venkaiyah, Dr. Sandeep, Dr. Dinesh, Dr. Jimmu, Dr. Saneesh, Meera@Sura at gops.

I also thank my MKU friends Dr. P. Prasanna, Dr. E. Gnanamani, Dr. S. Purushothaman, Dr. P. Elumalai, Dr. P. Muthukumar, Dr. B. Natarajan, Dr. Ragu Kumar, Dr. S. Manivannan. I would like to thank my village friends K. Saravanan, P. Elango, M. Karthik, Dr. A. Babu karthik, R. Sasidharan, E. Sheela Devi, E. Sudhagar, E. Surandar, M. Senthil, A. Ayyanar

I am grateful to Council of Scientific and Industrial Research (CSIR, New Delhi) for providing fellowship support. I thank Department of Science and Technology (DST, New Delhi) for providing single crystal X-ray diffractometer facility and UPE programme of UGC for infrastructure facilities.

First and foremost, I would like to thank my parents, K. Mayavan and M. Ambika, and my dear brother M. Kumar and my beloved sister M. Mageswari for always being with me. My Uncle P. Apparaj and Gunasekhar. My aunties Amirdhavalli and Indhira. Chiththappa's K. Sadaiyandi, K. Arjunan, K. Kaliyappan. And my cousin sister Parameswari and her child G. Abirami and G. Gogul Raj. The unconditional love of my parents and their blessings made me what I am today and I wove everything to them. Dedicating thesis to them is a minor recognition for their relentless support and love.

Mayavan Viji

Dedicated to my parents ….

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Introduction

Chapter 1: Synthesis of Pyrrolocarbazoles *via* Heteroannulation

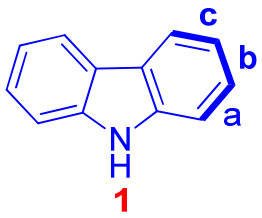
Chapter 2: Palladium catalyzed C-H activation route to the synthesis of quino[2,3-*a*]carbazoles and indolo[2,3-*a*]carbazoles

List of Abbreviations

Ac	**Acetyl**
aq.	**Aqueous**
Bn	**Benzyl**
EVE	**Ethylvinylether**
DCM	**Dichloromethane**
DMF	***N,N'*-dimethylformamide**
DMSO	**Dimethyl sulfoxide**
Et	**Ethyl**
Eq.	**Equation**
***i*-Pr**	***iso*-propyl**
LDA	**Lithium diisopropylamide**
***m*-CPBA**	***meta*-chloroperbenzoic acid**
Me	**Methyl**
Mp	**Melting point**
Ph	**Phenyl**
Bu	**Butyl**
***p*-TSA**	***para*-Toluenesulfonic acid**
rt	**Room temperature**
TBS	***tert*-butyldimethylsilyl**
***t*-Bu**	***tert*-butyl**
TFA	**Trifluoroacetic acid**
THF	**Tetrahydrofuran**
TMS	**Trimethylsilyl**
TPPT	**Triphenylphosphonium triflate**
DME	**Dimethoxyethane**
Tf	**Triflate**
Phen	**1,2-Phenylenediamine**
Equiv.	**Equivalent**

INTRODUCTION

Heterocyclic compounds are worth attention for many reasons; chief among them are their biological activities, and also because many drugs are heterocycles. Among the various classes of heterocyclic compounds, nitrogen heterocycles have attracted huge attention because of their widespread occurrence as natural and non-natural products displaying a broad spectrum of biological activities which comprise around 60% of all drug substances. Carbazole alkaloids are important class of heterocyclic compounds and there has been a tremendous development in this field in past few decades.[1] Because carbazole alkaloids are very useful heterocycles in organic synthesis, many groups are currently working on carbazole chemistry. New synthetic methodologies have been developed; existing methodologies have been improved and novel natural products have been isolated. In 1872, more than 100 years ago, Graebe and Glaser were the first to describe the parent compound 9*H*-carbazole (Fig 1), which was obtained from the anthracene fraction of coal tar distillate.[2] Ninety years later, the disclosure of the antimicrobial properties of murrayanine (3-formyl-1-methoxycarbazole), isolated from the plant *Murraya koenigii* Spreng,[3] initiated a strong interest in chemists and biologists. Since then, carbazoles represent a flourishing area in organic synthesis, as documented by the enormous number of monographs, accounts, and reviews that have appeared in the last 30 years.[4]



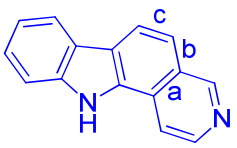
1

9*H*-Carbazole

a, b and c phases

Fig.1

Heteroarylcarbazoles



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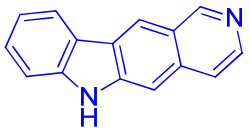
Pyrido[4,3-*a*]carbazole



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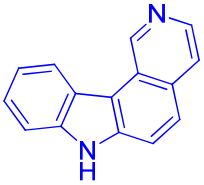
Pyrido[4,3-*b*]carbazole



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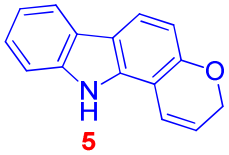
Pyrido[4,3-*c*]carbazole



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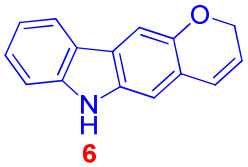
Pyrano[3,2-*a*]carbazole



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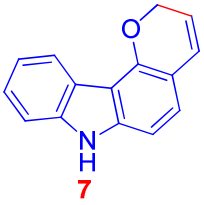
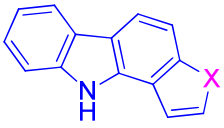
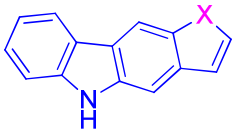
Pyrano[3,2-*b*]carbazole

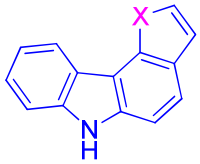


7

Pyrano[3,2-*c*]carbazole



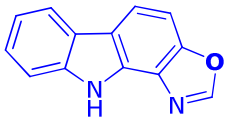




X = O Furo[3,2-*a*]carbazole, 8
X = N Pyrrolo[3,2-*a*]carbazole, 9
X = S Thieno[3,2-*a*]carbazole, 10

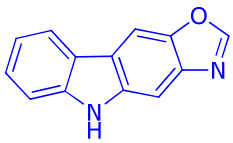
Furo[3,2-*b*]carbazole, 11
Pyrrolo[3,2-*b*]carbazole, 12
Thieno[3,2-*b*]carbazole, 13

Furo[3,2-*c*]carbazole, 14
Pyrrolo[3,2-*c*]carbazole, 15
Thieno[3,2-*c*]carbazole, 16



17

Oxazolo[4,5-*a*] carbazole



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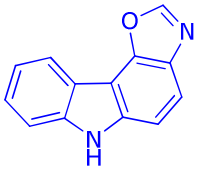
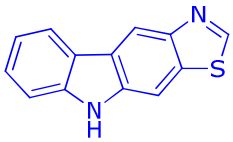
Oxazolo[4,5-*b*] carbazole



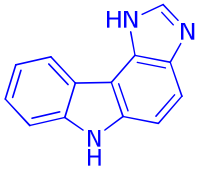
19

Oxazolo[4,5-*c*] carbazole



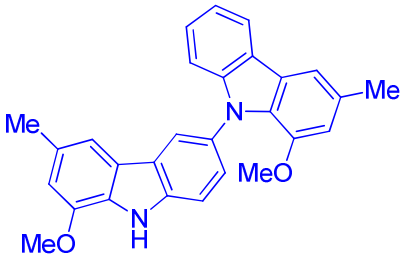
20

Thiazolo[5,4-*b*] carbazole



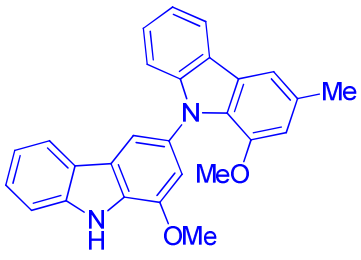
21

Imidazo[4,5-*c*] carbazole



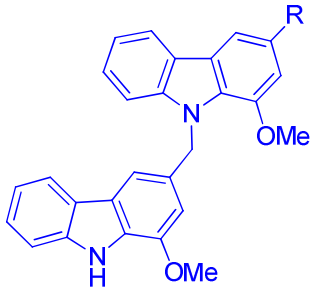
22

Murrastifoline-A



23

Murrastifoline-B



R = CH_2OH, Bismurrayafolinol, 24
R = Me, Bismurrayafoline-A, 25

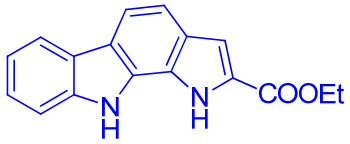
Fig 2

Over the last few decades numerous efforts have been invested in developing aryl-and heteroaryl-annulated carbazoles, which are reported and comprehensively reviewed.[1-4] To provide an overview on the heteroaryl-annulated carbazole derivatives, these compounds are classified into [*a*]-annulated, [*b*]-annulated, and [*c*]-annulated pyrido-, pyrano-, furo-, pyrrolo-, thieno-, oxazolo-, imidazolo-, indolo-, quino-, carbazolo carbazoles *etc*. This classification is solely based on the position at which the heteroaromatic ring is fused to the carbazole nucleus, either at phase a, b, or c as in fig 1. Moreover, the mode of fusion of the annulated heteroaromatic ring itself can vary; which leads to an even broader variety of heterocyclic ring systems. These have attracted growing attention since they are distributed in numerous natural products with diverse useful bioactivities.[5] Among them, many efforts have been devoted to the design and synthesis of annulated carbazoles such as pyridocarbazoles, indolocarbazoles, pyrrolocarbazoles, and quinocarbaozoles which seem to be the most intriguing; and thus have proven to be very important in medicinal chemistry.[10]

Pyrrolocarbazole alkaloids

Isolation from natural sources

Pyrrolocarbazoles are an important class of heterocycles; many efforts have been devoted to the design and synthesis of pyrrolocarbazoles. However, for a decade pyrrolocarbazoles have been solely of synthetic origin. Pyrrolocarbazoles, seem to be the most intriguing, and thus have proven to be very important in medicinal chemistry with a wide range of pharmacological and biological activities, such as anticancer, antidiabetic, neurotropic activities.[6] Moreover, the pyrrolo[2,3-*a*] and [3,4-*c*]carbazoles have great importance due to their inhibiting properties towards pim kinase inhibitors[7] and Chk1 inhibitors[8] respectively. Granulatimide and isogranulatimide, two naturally occurring alkaloids isolated from the marine ascidian *Didemnum granulatum*, were shown to be potent and selective inhibitors of Chk1.[9]



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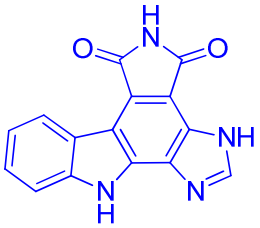
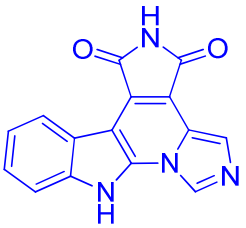
Potential Cyclin Dependent Kinase 1 (CDK1) Inhibitors



27

Granulatimide



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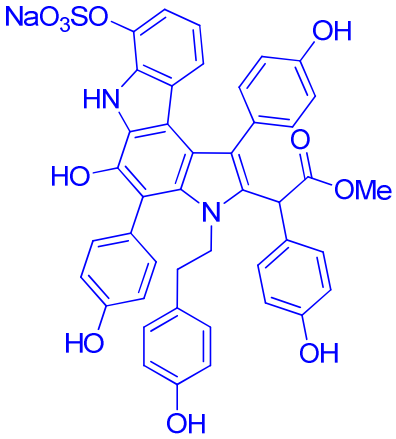
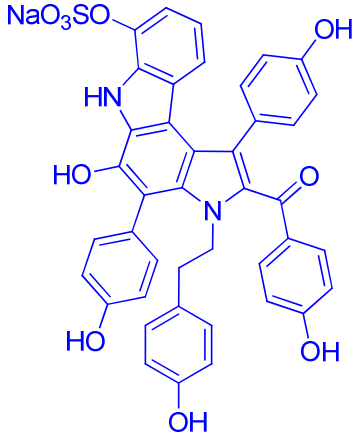
Isogranulatimide

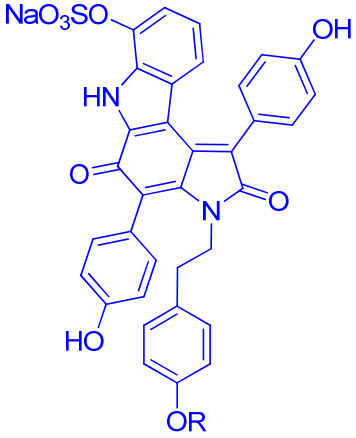
Fig. 3



29 Dictyodendrin A

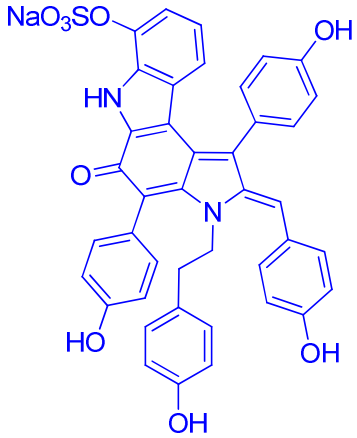


30 Dictyodendrin B



31, R = H, Dictyodendrin C

32, R = SO_3Na, Dictyodendrin D



33 Dictyodendrin E

Fig. 4

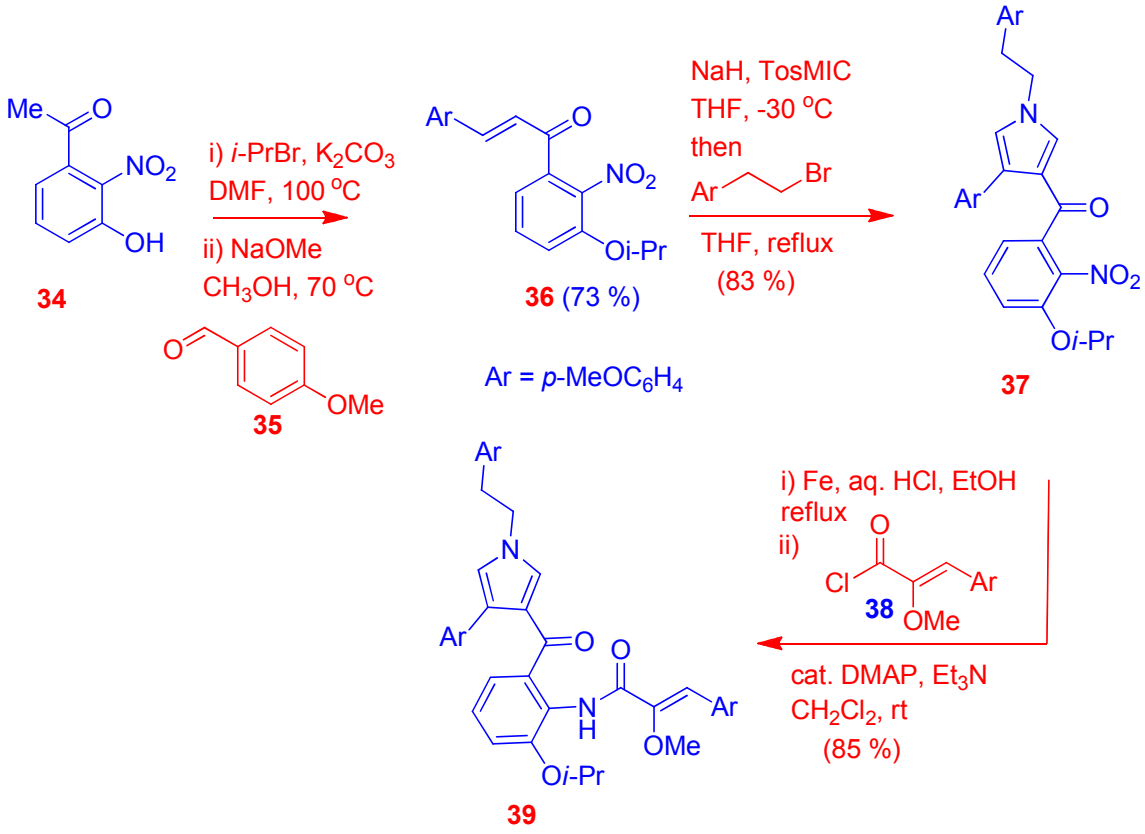
The marine environment has been explored in the search for new bioactive compounds over the last 50 years, becoming a highly important and rich source of potent molecules and drug leads reported to possess a wide scope of activities. Marine invertebrates have proven to be an outstanding source of active molecules, one of the most promising being carbazole alkaloids. A growing number of carbazole alkaloids are being reported from various marine organisms. Of these the dictyodendrins are fascinating marine products which could be used as excellent candidates for cancer chemotherapy. The potent anti-tumour activity and structural features of dictyodendrins A–E render these marine natural products attractive targets for total syntheses.

Dictyodendrins A-E (**29-33**) a pyrrolo[2,3-*c*]carbazole alkaloid,[10] (Fig. 4) were isolated from *dictyodendrilla verongiformis*, collected in southern Japan, the first marine natural products with telomerase inhibitory properties showing 100% inhibition at 50 μg/mL. Consequently, a number of non-natural pyrrolo[2,3-*c*]carbazoles have been prepared for structure−activity relationship studies.[11] Two years after the isolation, Fürstner *et al*. reported the first total synthesis of dictyodendrin B (**30**), C (**31**), and E (**33**) in the form of their ammonium salts from the common pyrrolocarbazole precursor **42** using a McMurry coupling and a 6π-electrocyclization as key steps. The synthesis of the relay compound **42** starts from the readily available 3-hydroxy-2-nitroacetophenone **34**.[12]

34 was transformed into the corresponding isopropyl ether by base-induced aldol condensation with *p*-methoxybenzaldehyde (**35**) to the chalcone **36** was followed by pyrrole-annulation with *p*-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of sodium hydride at low temperature and *in situ N*-alkylation with 4-methoxyphenethyl bromide to the substituted *N*-alkyl pyrrole **37**. The nitro group in **37** with reduced with iron under acidic conditions led almost quantitatively to the corresponding aniline and followed by treatment with the acid chloride **38** provided the amide **39** (**Eq. 1**). Intramolecular McMurry coupling of the ketoamide using low-valent titanium on graphite, prepared from titanium (III) chloride and 2 equiv. of potassium-graphite (KC_8), in 1,2- dimethoxyethane (DME) at reflux provided the indole **41** in up to 93% yield.

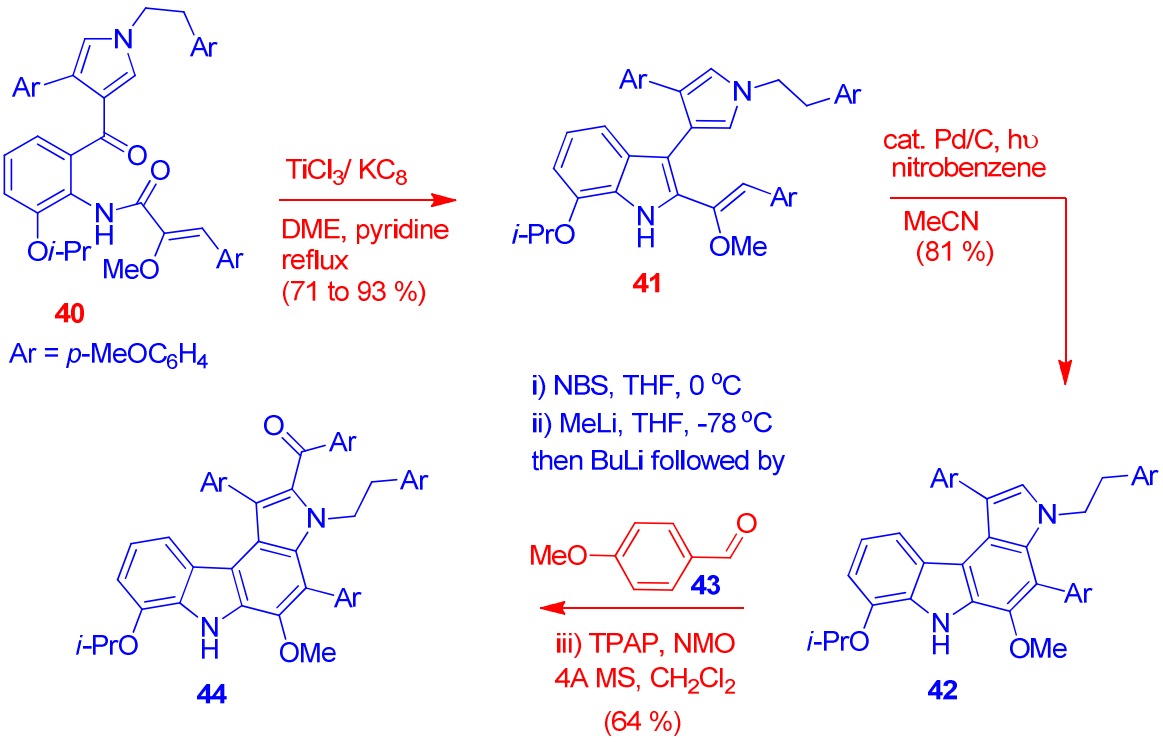
Synthesis of Pyrrolocarbazole alkaloids

Eq. 1



Irradiation of **41** with UV light in acetonitrile and nitrobenzene in the presence of palladium on activated carbon induced a 6π-electrocyclization followed by aromatization to give the pyrrolo[2,3-*c*]carbazole **42**. Then **42** was used as a relay compound for the synthesis of the dictyodendrins B (**30**), C (**31**), and E (**33**). For the synthesis of dictyodendrin B **30**, the pyrrolocarbazole **42** was subjected to regioselective bromination at C-2 with NBS to afford an unstable 2-bromopyrrolo[2,3-*c*]carbazole. Deprotonation of the carbazole nitrogen atom, halogen−metal exchange with butyllithium, and subsequent quenching of the intermediate lithio species with p-methoxybenzaldehyde (**43**) led to a secondary alcohol that was oxidized to the ketone **44** using catalytic amounts of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant (**Eq. 2**).

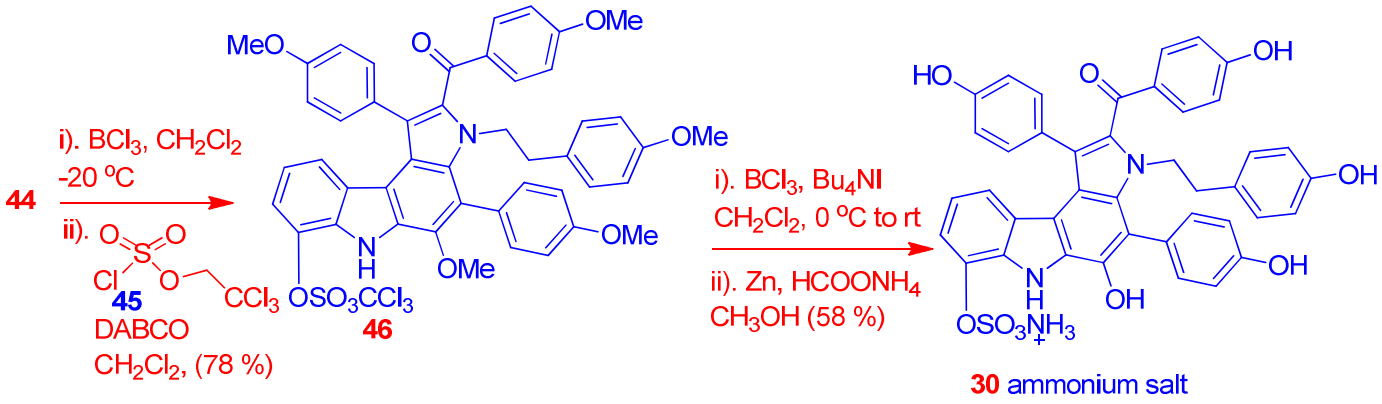
Eq. 2



The more direct approach, Friedel–Crafts acylation at C-2 of **42** with 4-methoxybenzoyl chloride using either titanium(IV) chloride, tin(IV) chloride, or boron trifluoride as the Lewis acid, had failed. Chemoselective cleavage of the isopropyl ether in **44** with BCl_3 and reaction of the resulting pyrrolo[2,3-*c*]carbazol-7-ol with 2,2,2-trichloroethyl chlorosulfonate afforded the aryl sulfate **46** in 78% yield. The exhaustive demethylation of **46** was achieved with BCl_3 and sub-stoichiometric amounts of tetrabutylammonium iodide (TBAI). Subsequent reductive cleavage of the trichloroethyl ester with zinc and ammonium formate led to the ammonium salt of dictyodendrin B (**30**) (**Eq. 3**). For the total synthesis of dictyodendrin C (**31**), the isopropyl ether in the relay compound **39** was first cleaved chemoselectively with boron trichloride.

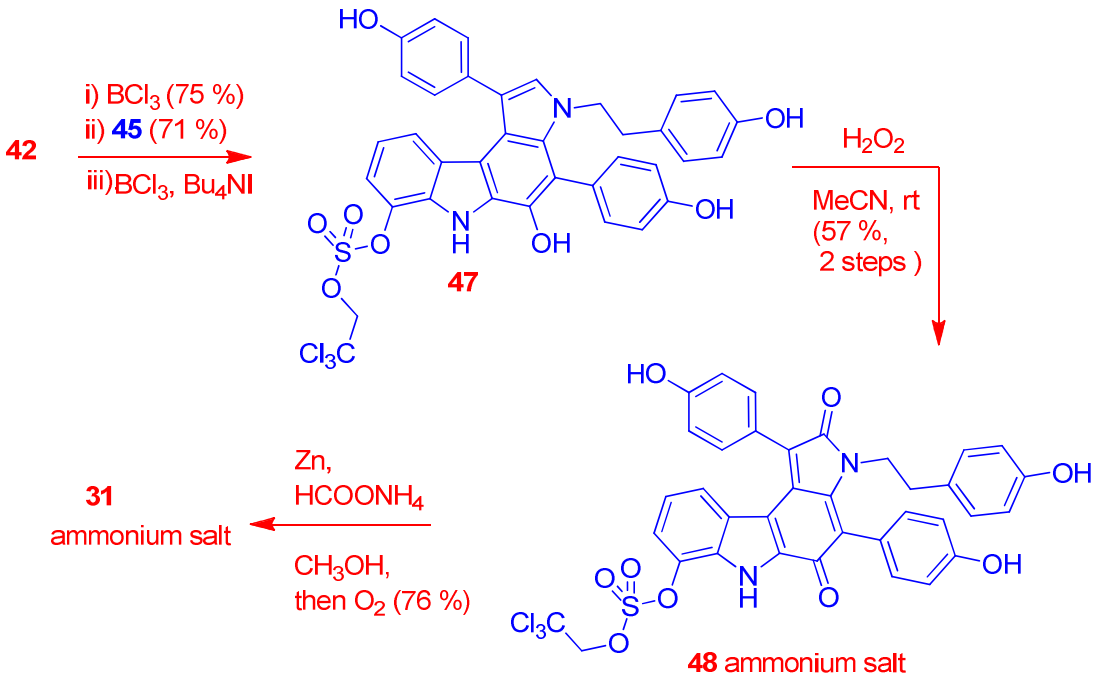
Esterification of the free hydroxy group at C-7 with 2,2,2-trichloroethyl chlorosulfonate (**45**) and followed by the cleavage of all methyl ethers using boron trichloride in the presence of tetrabutylammonium iodide provided the **47**.

Eq. 3.



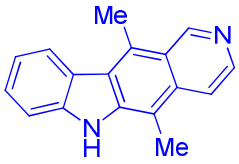
Treatment with hydrogen peroxide in acetonitrile effected a chemoselective oxidation of the pyrrolo[2,3-*c*]carbazol-5-ol core of **47** to the pyrrolo[2,3-*c*]carbazole-2,5-dione **48**. Finally, reductive cleavage of the trichloroethyl ester with an excess of zinc dust and ammonium formate in methanol followed by stirring the reaction mixture under an oxygen atmosphere afforded the ammonium salt of dictyodendrin C (**31**) in 76% yield (**Eq. 4**).[16]

Eq. 4

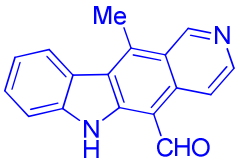


Pyridocarbazole alkaloids

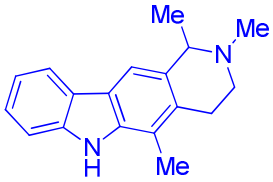
Isolation from natural sources



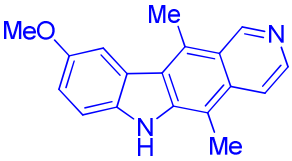
49 Ellipticine



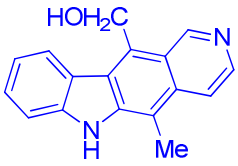
50 17-Oxoellipticine



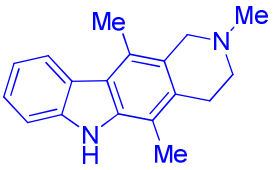
51 Guatambuine
(u-Alkaloid C)



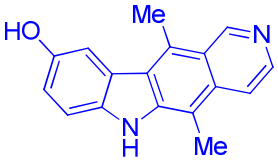
52 9-Methoxyellipticine



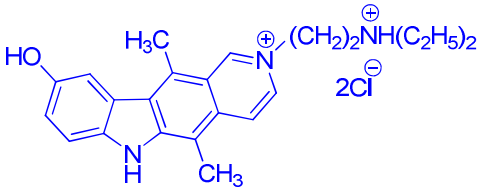
53 18-Hydroxyellipticine



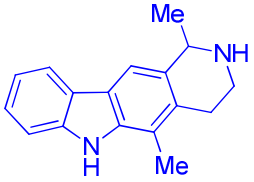
54 *N*-Methyltetrahydroellipticine



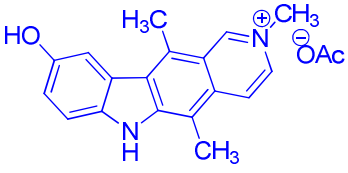
55 10-Hydroxyellipticine



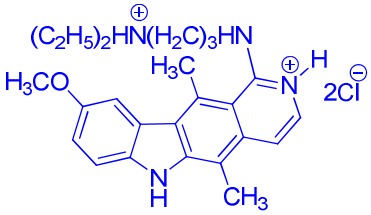
56
Datelliptium



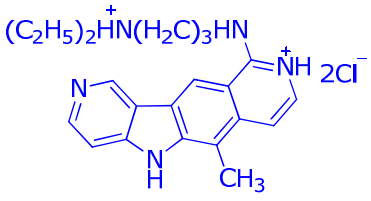
57 Janetine



58
Elliptinium acetate



59
Retellipticine (BD-84)



60
Pazellipticine (BD-40)

Fig. 5

It is well-established that the pyridocarbazole ring system is an appropriate skeleton to design DNA intercalating drugs.[13] For this reason, there has been a strong synthetic activity in this area. A wide variety of novel pyridocarbazole–based natural products, some of which showed interesting biological activities, and naturally occurring active compounds have been known for more than 40 years. They showed activity against treatment of breast cancer,[14] intercalation into the DNA double helix,[15] inhibition of topoisomerase II,[16] and anti-HIV agent.[17] Moreover, it has been demonstrated *in vitro* and *in vivo* that ellipticine binds covalently to DNA after being enzymatically activated by cytochrome P450 or peroxidase[18] which led to the commercialization of some ellipticine derivatives and their clinical use for treatment of myeloblastic leukemia, advanced breast cancer, and other solid tumors.[19]
There are several review articles and books covering different or limited aspects of the pyridocarbazole. In 1959, Goodwin *et al*. reported the isolation of ellipticine **49** and 9-methoxyellipticine fully aromatized pyrido[4,3-*b*]carbazole alkaloids, from the leaves of *Ochrosia elliptica* Labill and *Ochrosia sandwicensis* A.DC. of the Apocynaceae family.[20] In the following years, several groups reported the isolation of the same alkaloids from different plants of the Apocynaceae family, *Aspidosperma subincanum* Mart.[21] *Ochrosia maculata* Jacq. (*Ochrosia borbonica* Gmel.),[22] *Bleekeria vitiensis*,[23] *Ochrosia moorei*,[24] *Ochrosia acuminata*,[25] as well as from the Loganiaceae family, *Strychnos dinklagei* Gilg.[26]

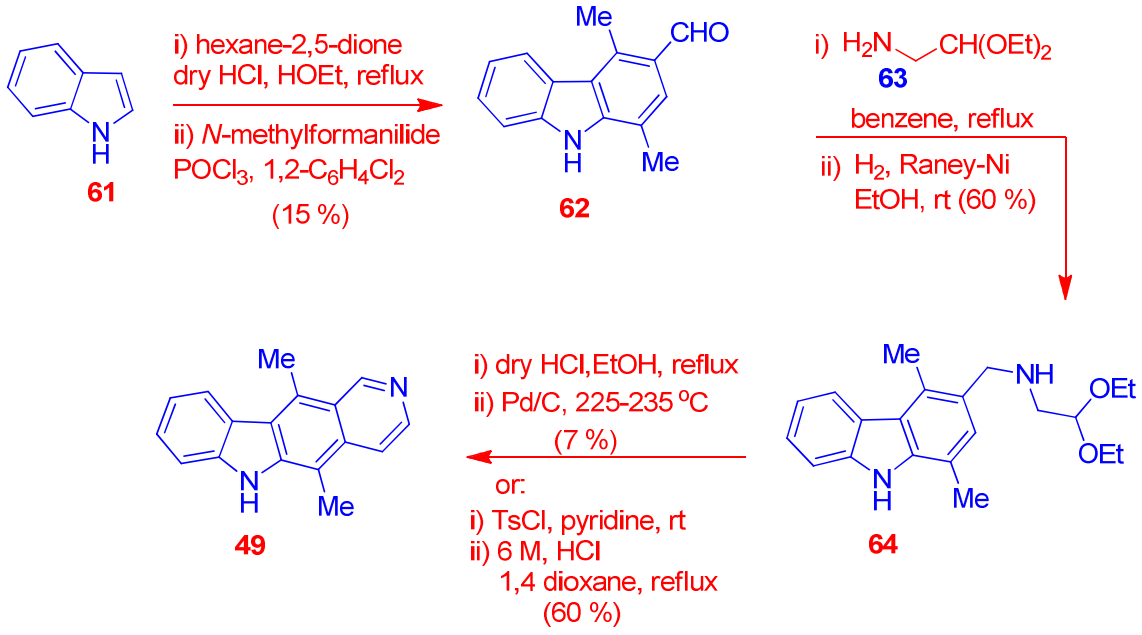
Synthesis of pyrido[4,3-*b*]carbazoles

The chemistry and biology of pyridocarbazoles underwent a tremendous development. This is emphasized by several comprehensive reviews covering the synthesis and biological activity of ellipticines. With the disclosure of the antitumor activity of ellipticine (**49**) and 9-methoxyellipticine (**52**) in several animal and human tumor systems, the pyrido[4,3-*b*]carbazole alkaloids became promising targets for many synthetic groups.[27]

In 1962, Cranwell and Saxton described a straightforward synthesis of ellipticine using a Pomeranz−Fritsch cyclization as key step.[28] Condensation of indole (**61**) with hexane-2,5-dione in the presence of gaseous HCl in ethanol followed by Vilsmeier formylation led to 3-formyl-1,4-dimethylcarbazole (**62**). Imine formation by reaction with **63** and hydrogenation of the resulting imine led to the secondary amine **64**. Acid-catalyzed cyclization of the amine **64** followed by solvent-free dehydrogenation with palladium on activated carbon led to ellipticine (**49**) in low yield. All attempts to directly induce cyclization of the imine, which was obtained from condensation of 3-formyl-1,4-dimethylcarbazole (**62**) and 2,2-

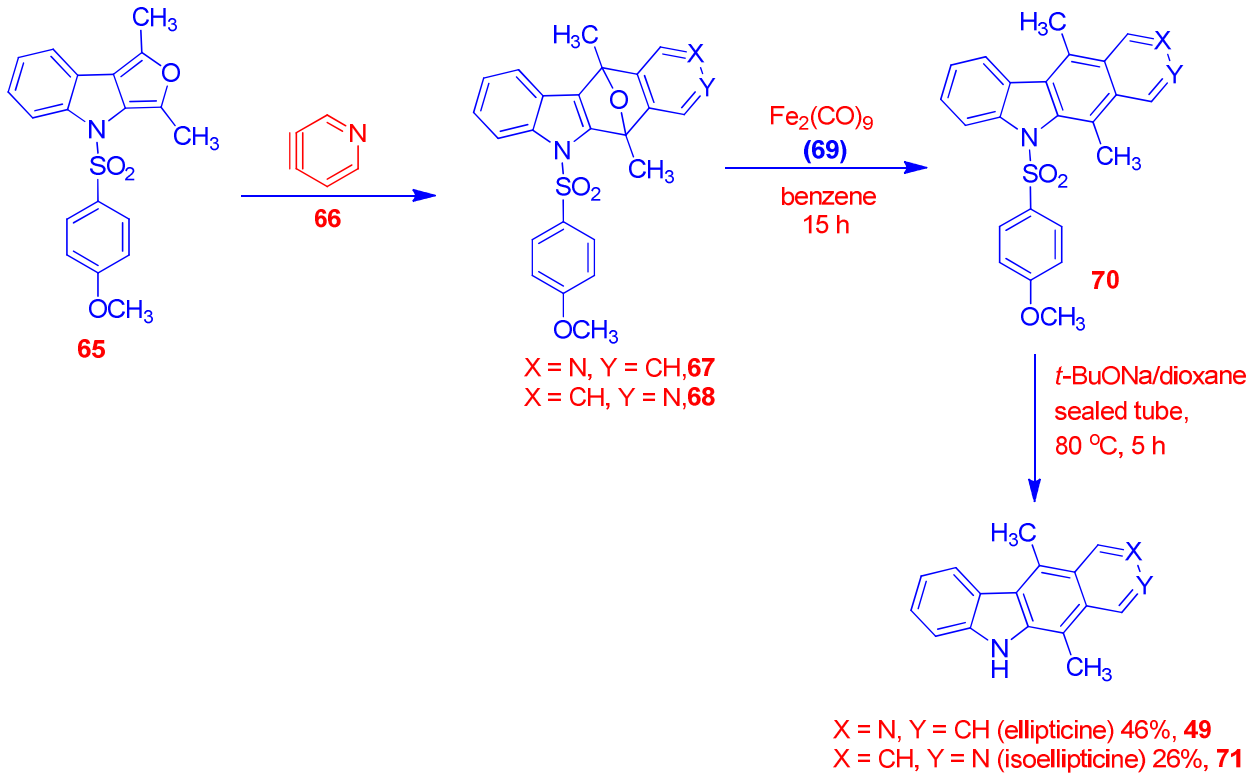
diethoxyethylamine (**63**), had failed. In 1974, Jackson and co-workers improved the efficiency of that approach by application of an improved procedure for the Pomeranz–Fritsch cyclization.[29] Tosylation of the secondary amine in **64** followed by heating of the tosylamide in a mixture of hydrochloric acid and 1,4-dioxane provided ellipticine (**49**) in 60% yield based on the amine **64**.

Eq. 5



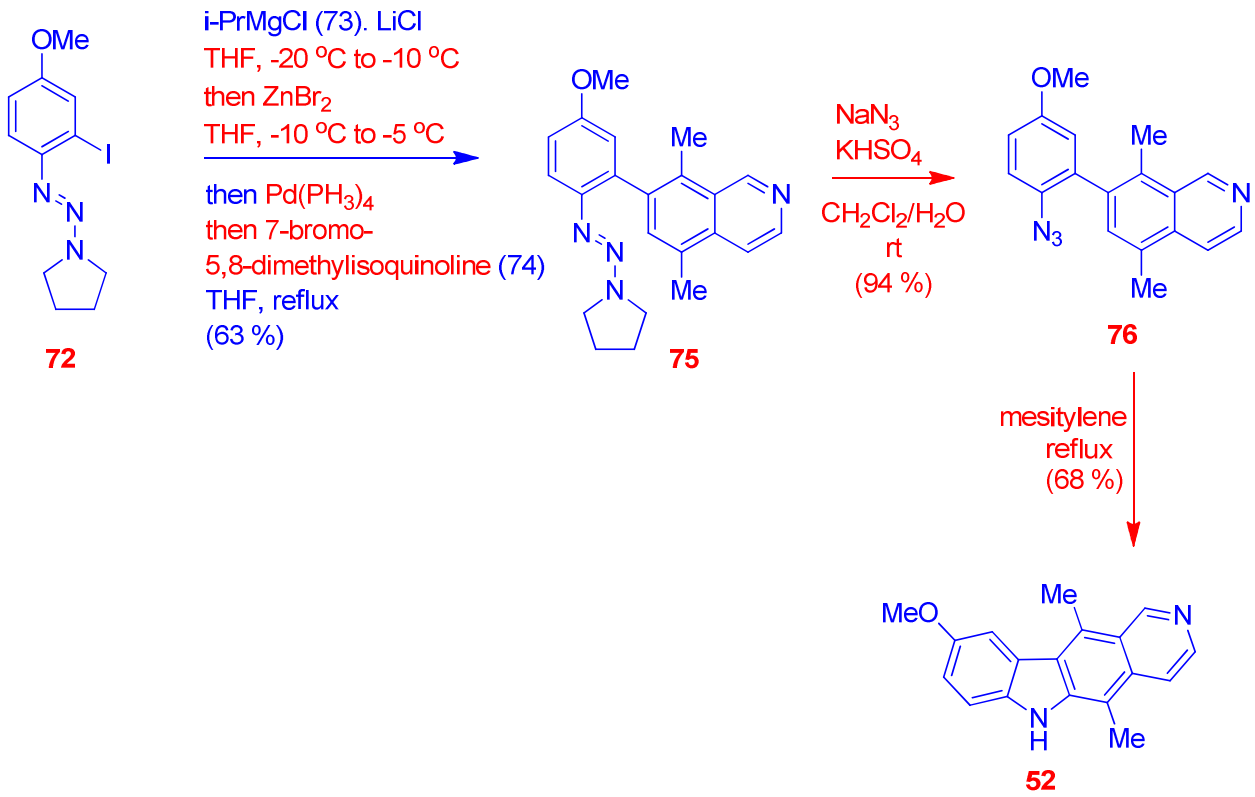
Pujol, *et al*. reported the synthesis of ellipticine by treating the diene **65** was successfully converted to the mixture of isomeric Diels-Alder adducts **67** and **68** by cycloaddition with **66**, 4-pyridyne as the dienophile, obtained from 3-bromopyridine. These adducts were deoxygenated with $Fe_2(CO)_9$ (**69**) without any further purification to obtain **70**. The last step, basic desulfonylation using *t*-BuONa in dioxane in a sealed tube, afforded the ellipticine **49** in 46% overall yield and the regioisomer isoellipticine **71** was obtained in 26% yield (Eq. 6).[30]

Eq. 6



For the synthesis of 9-methoxyellipticine (**52**), halogen–metal exchange of 1-(4-methoxy-2-iodophenylazo)-pyrrolidine (**72**) led to a Grignard reagent (**73**) that was transmetalated with zinc(II)bromide to afford the corresponding zinc intermediate, which on Negishi cross-coupling with the 7-bromoisoquinoline (**74**) led to the polyfunctionalized aryl triazene **75**. Addition of boron trifluoride-diethyl ether complex and trifluoroacetic acid in dichloromethane in the presence of sodium azide to **75** afforded the corresponding aryl azide **76**. Thermal cyclization in mesitylene at reflux afforded 9-methoxyellipticine (**52**) by loss of dinitrogen and C-H insertion of the intermediate nitrene.[31]

Eq. 7



Indolo[2,3-*a*]carbazole alkaloids

Isolation from natural sources

The indole ring system, in particular, is a very common structural motif and is found in numerous biologically active natural products and alkaloids. Because of the significance of these scaffolds in drug discovery and medicinal chemistry the development of new methodologies for the synthesis of indole alkaloids derivatives continues to be a very active field of research, as evidenced by the appearance of vast number of articles in the area in the last several decades. Compounds from the indolocarbazole family are interesting owing to the wide range of biological activites such as inhibition of protein kinase C, cytotoxic, antihypertensive, antibacterial, antiedema, hypotensive, antiallergic, cell cytotoxic activities and anti-inflammatory activities as well as inhibition of platelet aggregation.[32]

Several indolo[2,3-*a*]carbazoles, such as 6-cyano-5-methoxy-12-methylindolo-[2,3-*a*]carbazole and the tjipanazoles, have been obtained from *algae*, some of the Indolo[3,2-*a*]carbazoles have been synthesized.

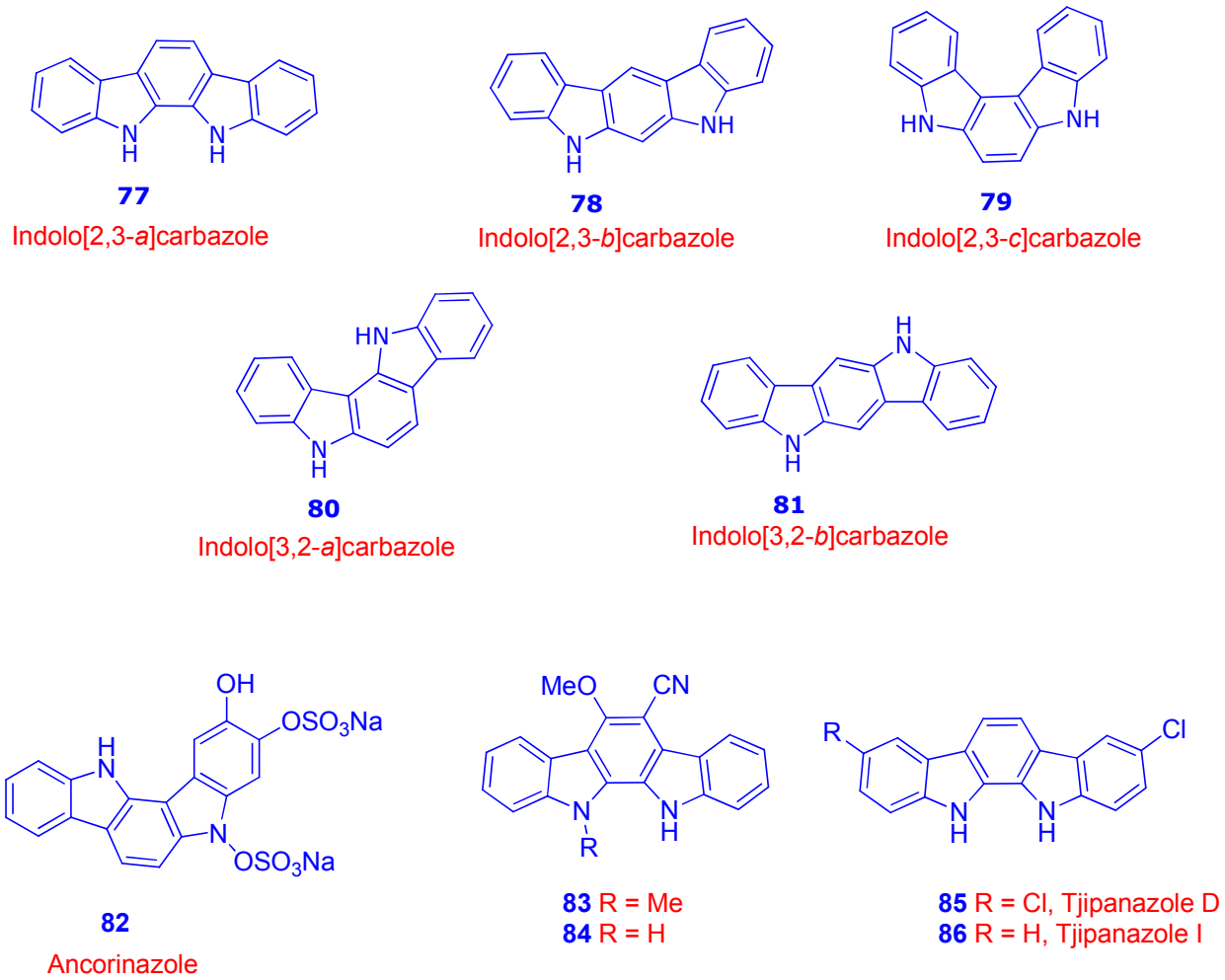
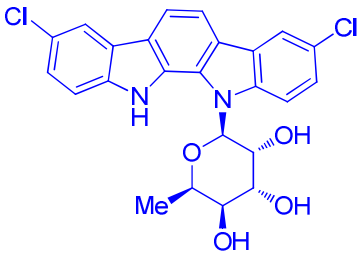
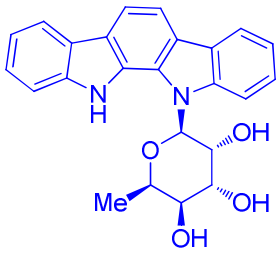


Fig. 6

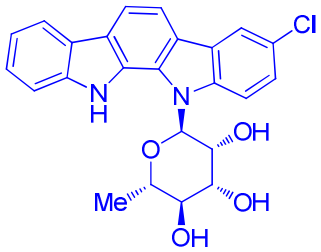
Tjipanazole A1 (**87**) and A2 (**91**) exhibited a selective fungicidal activity against rice blast and leaf rust wheat infections.[33] Tjipanazole D (**85**) was also isolated from a different terrestrial blue–green algae, Fischerella ambigua.[34] The bisindole ancorinazole **82** is the first



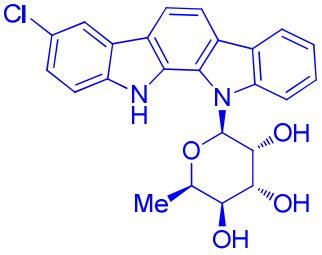
87 Tjipanazole A1



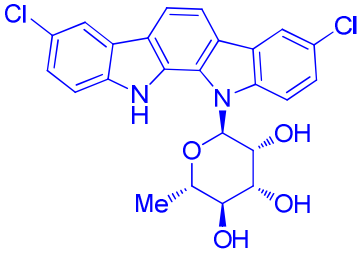
88 Tjipanazole G1



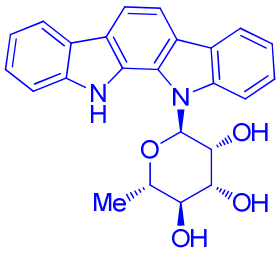
89 Tjipanazole C4



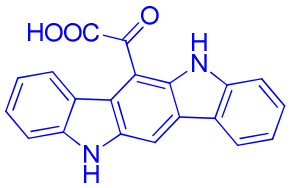
90 Tjipanazole C_1



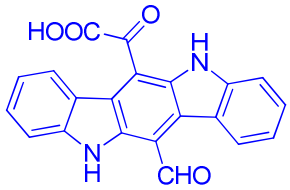
91 Tjipanazole A_2



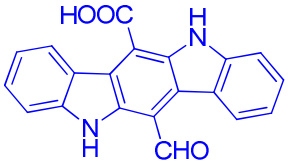
92 Tjipanazole G_2



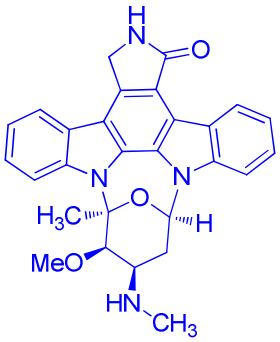
93 Malasseziasole A



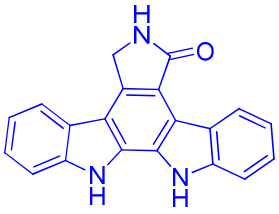
94 Malasseziasole B



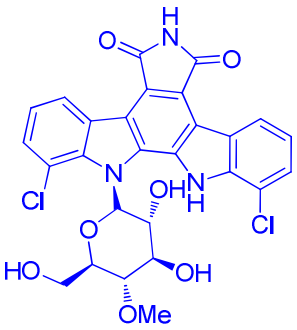
95 Malasseziasole C



96 (+) Staurosporinone (Am 2282)



97 (+) Staurosporinone K 252c, staurosporinone aglycone



98 Rebaccamycin

Fig. 7

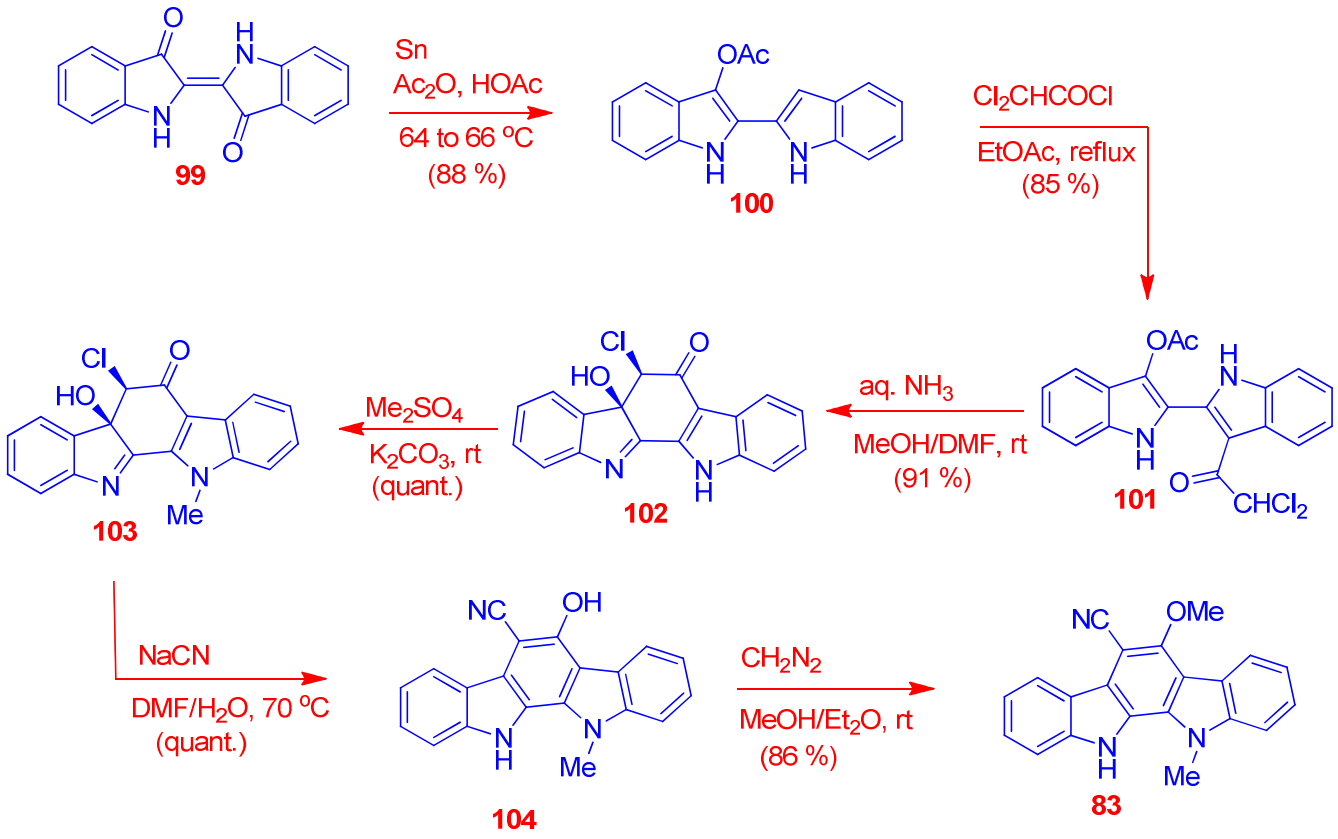
indolo[3,2-*a*]carbazole isolated from natural sources from methanolic extract of sponge *Ancorina* sp. collected in New Zealand, by Boyd and co-workers.[35] Modifications in the

indolocarbazole system leads to another class of carbazole alkaloids as indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole endowed with potent antitumor, antiviral, and antimicrobial activities. This family has raised considerable attention because of the central role of these molecules in the regulation of cell cycle progression and specific enzyme inhibition.[36] The indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole framework is found in the antitumor active alkaloids staurosporine, K-252a, and rebeccamycin, which are interesting due to their pharmacological importance and became attractive targets for total synthesis. Structure-activity relationships (SAR) in the indolocarbazole series have been extensively studied in the context of topoisomerase I inhibition and tumor cell killing. Compounds bearing a pyrroloindolocarbazole and equipped with one *N*-glycosidic bond, such as the antibiotic rebeccamycin, generally function as DNA topoisomerase I inhibitors. A few analogues, such as NB-506 and J-107088 (also known asedotecarin), have entered clinical trials for cancer treatment.[37]

Synthesis of Indolo[2,3-*a*]carbazole alkaloids

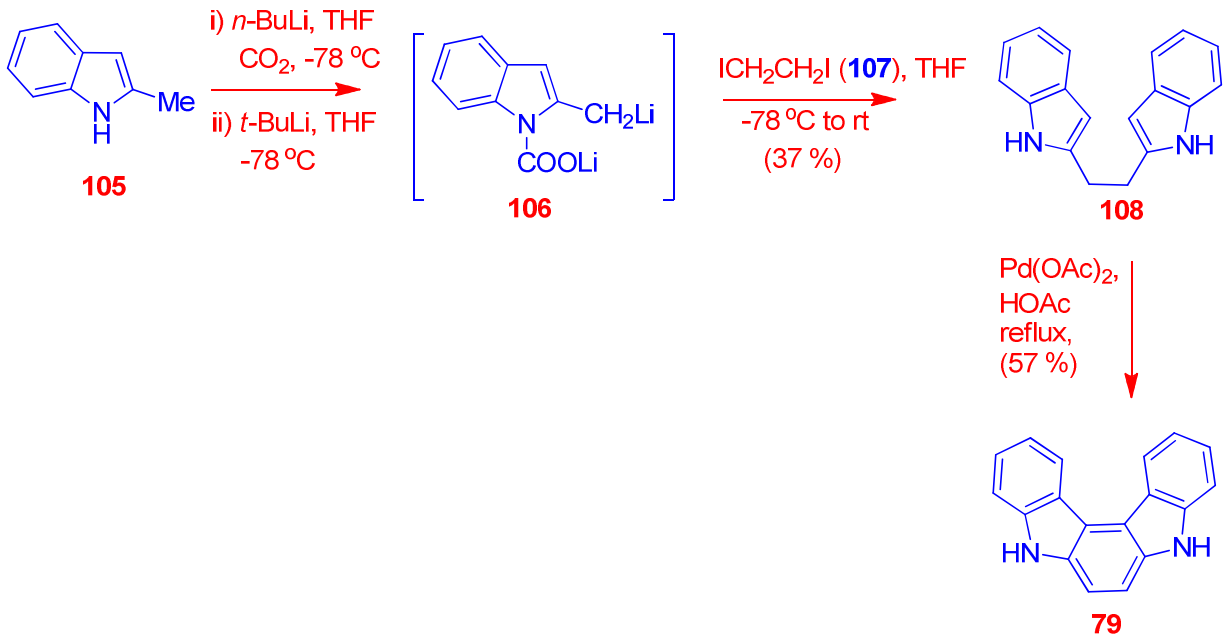
In 1997, Somei and coworkers reported the synthesis of 5-cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole (**83**) starting from indigo (**99**).[38] Reduction of **99** with tin in acetic acid/acetic anhydride afforded 3-acetoxy-2,2′-biindole (**100**) in 88 % yield. Heating of compound **100** with dichloroacetyl chloride in ethyl acetate at reflux provided 3-acetoxy-3′-dichloroacetyl-2,2′-biindole (**101**) in 85% yield. Treatment of **101** with aqueous ammonia in methanol/DMF at room temperature led to the indolo[2,3-*a*]carbazole derivative **102**. After *N*-methylation of **102**, the corresponding *N*-methyl derivative **103** was subjected to reductive cyanation to afford 5-cyano-6-hydroxy-11-methylindolo[2,3-*a*]carbazole (**104**). Finally, *O*-methylation of **104** with diazomethane afforded 5-cyano-6-methoxy-11-methylindolo-[2,3-*a*]carbazole (**83**) in 86% yield. On the basis of this approach, the same group subsequently reported the synthesis of a range of analogous compounds for bioactivity tests.[39]

Eq. 8



Using Katritzky's method, 2-methylindole **105** was transformed to the 2-lithiomethylindole derivative **106**,[40] which on reaction with 1,2-diiodoethane (**107**) afforded compound **108** in 37% yield.[41] The oxidative cyclization of 1,2-bis(1*H*-indol-2-yl)ethane **108** with $Pd(OAc)_2$ in refluxing acetic acid provided indolo[2,3-*c*]carbazole **79** in 57% yield. Alternatively, indolo[2,3-*c*]carbazole **79** was prepared by a double Fischer indolization of the *N*,*N*′-diphenylbishydrazone of cyclohexan-1,4-dione, albeit in low yield (8%).[42]

Eq. 9

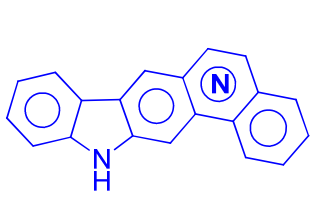


Quino[4,3-*b*]Carbazole alkaloids

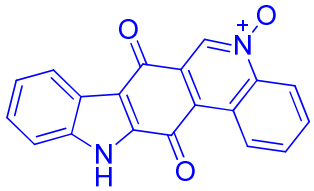
Isolation from natural sources

Quinocarbazoles constitute an important class of heterocycles that are known for their potent antitumor, antibacterial, antiinflammatory, psychotropic, and antihistamine properties. Also the structurally related heteroaryl annulated carbazoles have received considerable synthetic attention,[43] and these congeners showed a superior pharmacological profile.[44] One of the possible approaches to new ellipticine fused analogs was the modification for the pyridine part (ring D) of the tetracyclic skeleton, which seems to be a sensitive substructure in terms of a modulation of the molecule's antineoplastic properties. Thus, the position of the pyridine nitrogen atom has been systematically varied.[45]

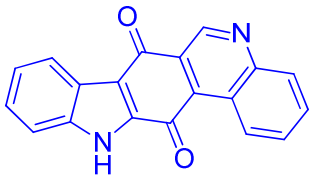
According to the Hantzsch–Widman nomenclature, the quino[4,3-*b*]carbazole framework should preferably be named as indolo[3,2-j]phenanthridine. Calothrixin A (**110**) and its *N*-deoxy derivative, calothrixin B (**111**), are the only quino[4,3-*b*]carbazole alkaloids known so far.



109 Quinocarbazole



110 Calothrixin A



111 Calothrixin B

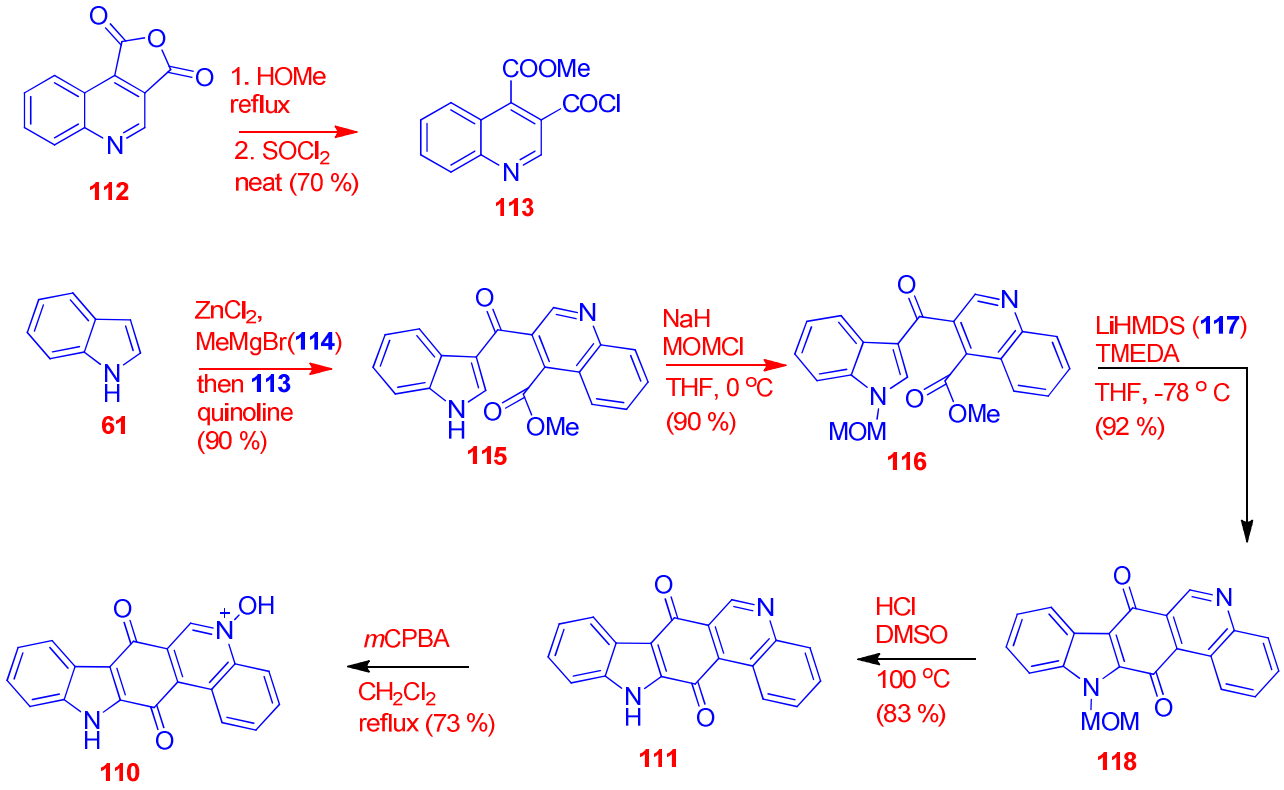
Fig. 8

Both have been obtained in 1999 by Rickards, Smith, and co-workers from a bioassay guided fractionation of photoautotrophic cultures of two strains of *calothrix cyanobacteria* (a blue-green algae). The quino[4,3-*b*]carbazole-1,4-quinones calothrixin A (**110**) and B (**111**) inhibit the growth of a chloroquineresistant strain of the malaria parasite Plasmodium falciparum and human HeLa cancer cells.[46]

synthesis of Quino[4,3-*b*]Carbazole alkaloids

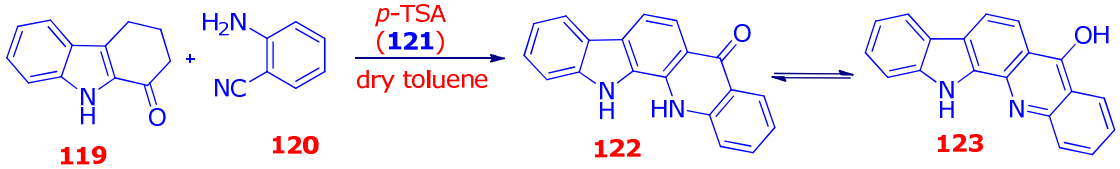
In 2002, Chai and co-workers reported a simple and concise route to calothrixin B (**111**) starting from indole (**61**) and the readily available quinoline-3,4-dicarboxylic anhydride (**112**).[47] Anhydride **112** was first transformed into the acid chloride **113**, which was then used for a Friedel−Crafts acylation. The diarylketone **115** was obtained in 90% yield by deprotonation of indole (**61**) with methylmagnesium bromide (**114**) in the presence of zinc chloride followed by addition of the acid chloride **113**. After protection of the indole nitrogen atom, the corresponding *N*-MOM derivative **116** was subjected to lithiation with lithium hexamethyldisilazide (**117**) (LiHMDS) in the presence of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine followed by intramolecular nucleophilic substitution of the ester to afford *N*-MOM-calothrixin B (**118**). Cleavage of the *N*-MOM group by dissolving **118** in DMSO under acidic conditions, afforded calothrixin B (**111**). Transformation of calothrixin B (**111**) to calothrixin A (**110**) was achieved by using *m*-CPBA as oxidant following a procedure reported by Kelly et al.[48]

Eq. 10



As shown in **Eq. 11**, Rajendra Prasad *et al*. reported the synthesis of quino[2,3-*a*]carbazole **123** by acid-catalysed condensation of 1-oxo-1,2,3,4-tetrahydrocarbazole **119** with *o*-aminobenzonitrile **120**.[49]

Eq. 11



Carbazolocarbazoles

Carbazolocarbazoles one of the heteroarylcarbazoles in which one carbazole fused with another carbazole skeleton at various positions. To the carbazolocarbazole family belong the five different isomeric ring systems namely carbazolo[2,3-*a*]carbazole **124**, carbazolo[2,3-*b*]carbazole **125**, carbazolo[2,3-*c*]carbazole **126**, carbazolo[3,2-*a*]carbazole **127** and carbazolo[3,2-*b*]carbazole **128** (Figure 9). carbazolo[2,3-*a*]carbazoles **124 is** the most interesting structural class amongst the above. The carbazolo[2,3-*a*]carbazole framework **124** is found in many natural products with a wide range of potent biological activities, e.g. antifungal, antimicrobial, antitumor, and antihypertensive activity.[50] Their activity as potent inhibitors of protein kinase C (PKC)[51] has received special attention and was the focus of several investigations. There are very less reports for the other class of derivatives such as carbazolo[2,3-*b*]carbazole **125**, carbazolo[2,3-*c*]carbazole **126**, carbazolo[3,2-*a*]carbazole **127**, carbazolo-[3,2-*b*]carbazole **128**.

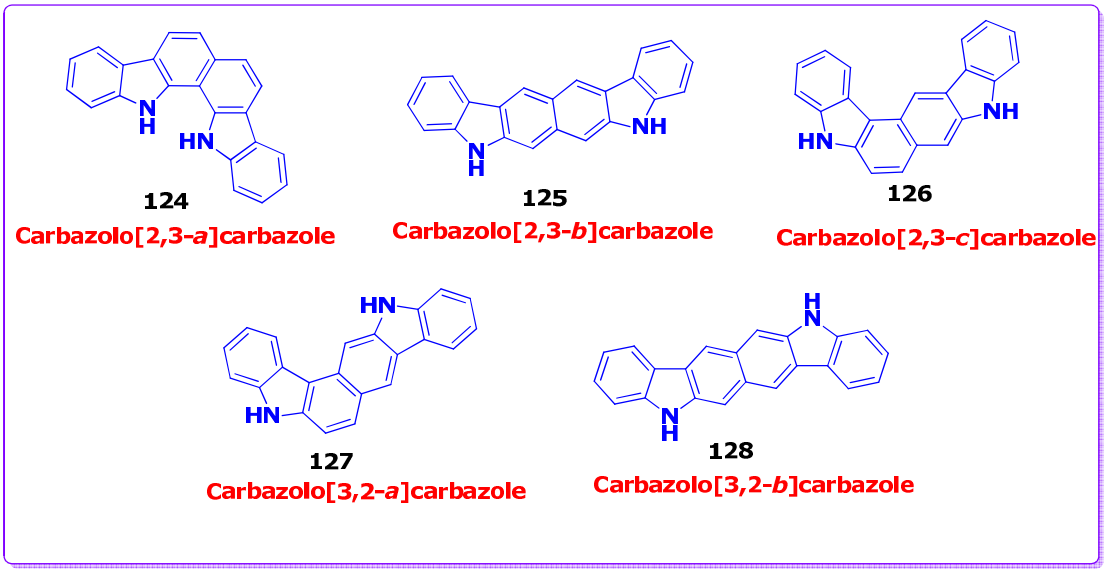
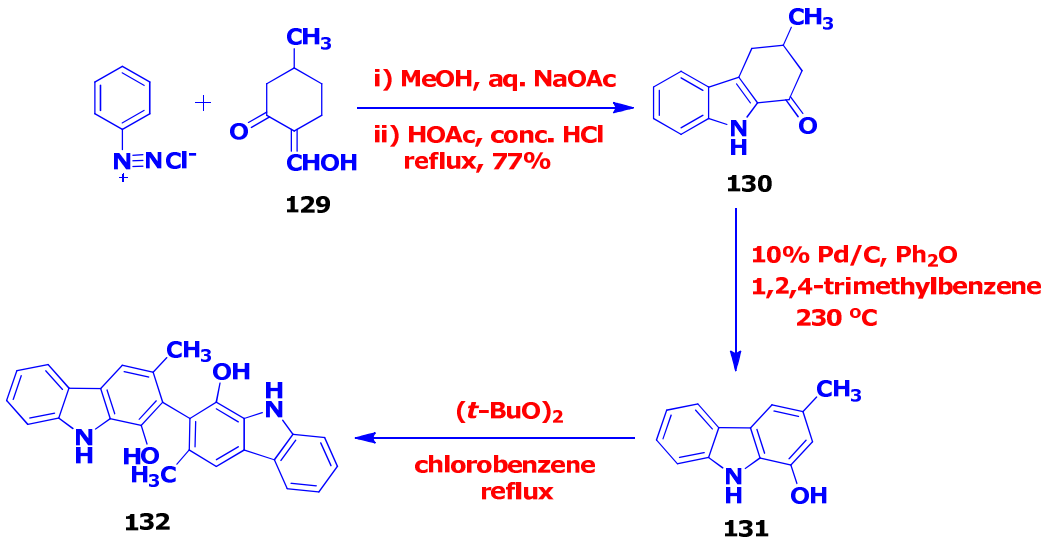


Fig. 9

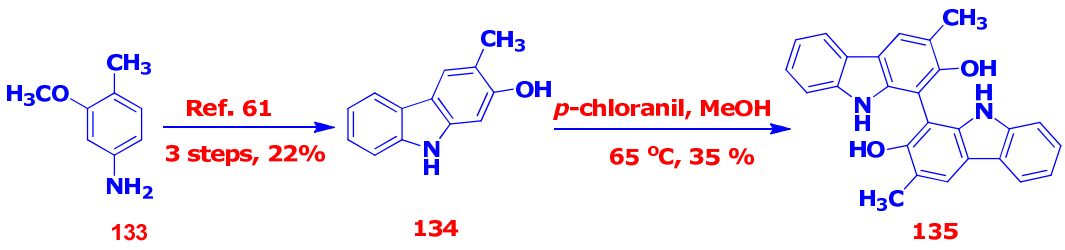
Bringmann *et al.* reported a biomimetic oxidative dimerization of the monomer[52,53] **131** with di-*tert*-butyl peroxide $(t\text{-BuO})_2$ afforded the 2,2′-linked bis(*O*-demethylmurrayafoline-A) **132** in 81% yield (**Eq. 12**).[54]

Eq. 12



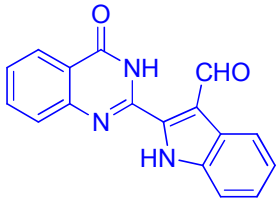
Knölker and co-workers described the first total synthesis of 1,1′-bis(2-hydroxy-3-methylcarbazole) **135** *via* molybdenum-mediated construction of the carbazole framework.[55] The required, 2-hydroxy-3-methylcarbazole monomer **134**, was obtained in three steps and 22% overall yield starting from dicarbonyl(4-cyclohexa-1,3-diene)(5-cyclopentadienyl)molybdenum hexafluorophosphate[56] and 3-methoxy-4-methylaniline as synthetic precursors. Oxidative coupling of the monomer **134** using *p*-chloranil provided 1,1′-*bis*(2-hydroxy-3-methylcarbazole) **135** in 38% yield (**Eq. 13**).[57]

Eq. 13



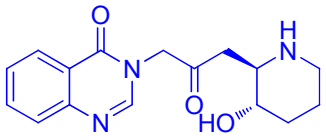
Quinazolinone Alkaloids

In the community of fused heterocycles, 2,3-dihydroquinazolin-4(1*H*)-one and 2-spiroquinazolinone are omnipresent and have been referred to as "core structures" in drug discovery. It is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, animals and microorganisms. These quinazolinones displayed wide range of biological activities as antitumor, antidefibrillatory, antidepressant, analgesic, diuretic, antihistamine, vasodilating agent, antihypertensive, CNS stimulant, tranquilizer and antianxietic.[58] Moreover these quinazolinones also have plant growth regulator abilities. The chemistry of the quinazolinone alkaloids is well documented in a number of comprehensive reviews and monographs and is continuously updated in Natural Product Reports.[59] A number of synthetic methods to prepare these compounds have been described in the past few years.

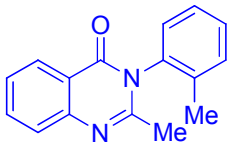


Bouchardatine
136

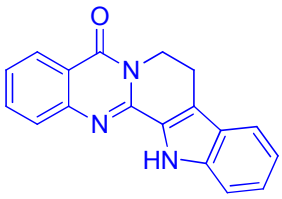
2-cyanoquinazolinone
137



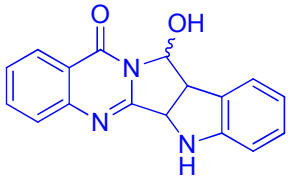
febrifugine
138



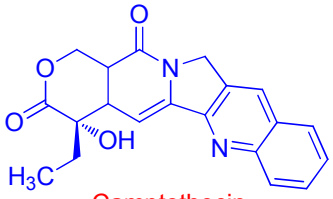
methaqualone
139



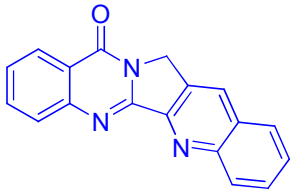
Rutaecarpine, **73**
140



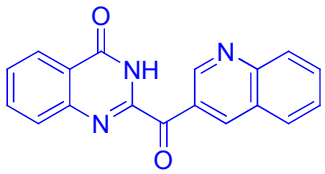
7-hydroxy-8-norruttaecarpine
141



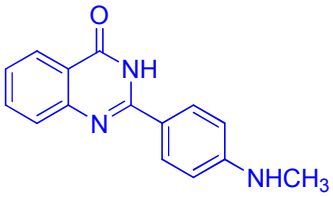
Camptothecin
142



Luotonin A
143



Luotonin F
144



Firefly Luciferase Inhibitor
145

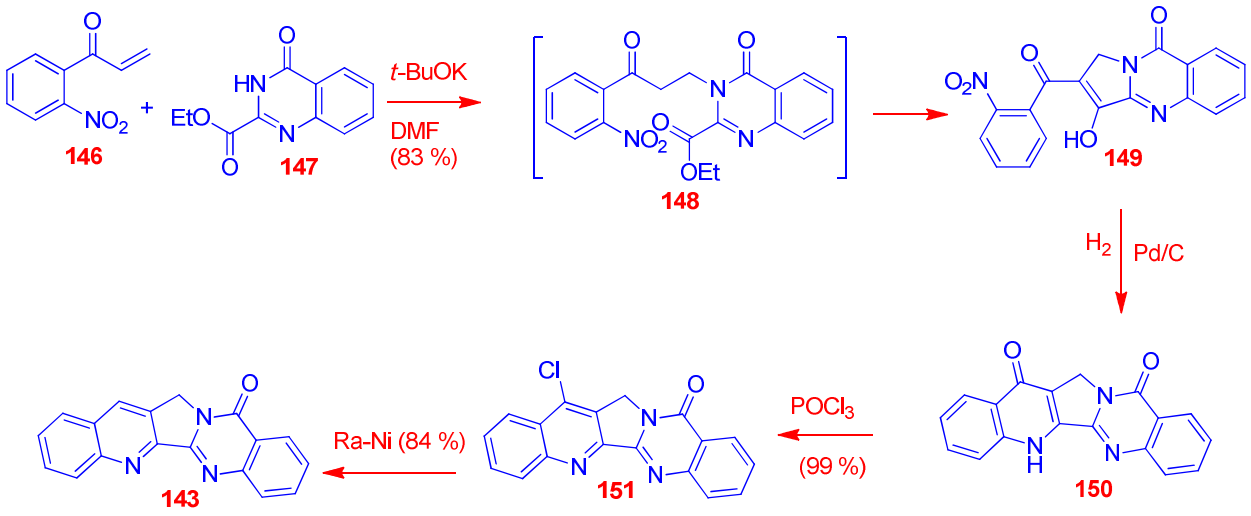
Fig. 10

Rutaecarpine (**140**) is the major quinazolinocarboline alkaloid isolated from *Evodia rutaecarpa* is the component of a Chinese herbal drug, Wu-Chu-Yu, used extensively as a remedy for headache, cholera, and dysentery.[60] Rutaecarpine type alkaloids constitute an important class of indolopyridoquinazolinone heterocycles, which belong to the subgroup of quinazoline-type alkaloids and their extracts have long been used as important remedies in the treatment of various diseases.[61] Rutaecarpine shows a variety of pharmacological activities including antithrombotic, vasorelaxant and cyclooxygenase (COX-2) inhibitory effects.[62]

Luotonine A (**143**) was isolated from a Chinese plant named Luo-Tuo-Hao and showed cytotoxicity toward the murine leukemia P388 cell line (IC50 = 1.8 μg/mL), and Luotonins A and B, are recently isolated members of a new alkaloid family extracted from the aerial parts of *Peganum nigellastrum* which contain a pyrroloquinazolinoquinoline skeleton.[63] Luotonin A seems to be very promising as a camptothecin like antitumour agent selectively inhibiting human DNA topoisomerase I.[64] In the past decade, luotonin A has become an important synthetic target and a large number of preparative methods have been published.[65] The plant extracts are used in traditional Chinese medicine and are reported to exhibit activity against a range of ailments including rheumatism, inflammation, influenza, hepatitis and leukaemia.[65a] The structural similarity between rutaecarpine and luotonins is remarkable and both alkaloids exhibit topoisomerase inhibitory activity. An obvious difference between the two compounds is the flexibility of the six-membered C-ring of rutaecarpine compared to the rigidity of the five-membered C ring of luotonin, which was postulated to be essential for biological activity.[66]

In 2006 Mason *et al.*[67] reported the synthesis of luotonin A. Michael addition of ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate (**147**) to 1-(2-nitrophenyl)propenone (**146**) gave an 83% yield of compound **148**, which undergoes a spontaneous intramolecular Claisen condensation to afford enolizable 1,3-diketone **149**. Catalytic hydrogenation of **149** in the presence of Pd/C afforded the 4(1*H*)-quinolinone derivative **150**, which was then chlorinated using $POCl_3$ to yield 14-chloro luotonin A. Hydrogenolysis of **151** with activated Raney Ni gave luotonin A **143**.

Eq. 14



Heteroannulations

Heteroannulation reactions have made a great contribution to the recent growth of organic synthesis, these have been proven to be valuable methods and vast numbers of heterocyclic molecules have been synthesized. Accordingly, it is not surprising that several reports are there in literature for the synthesis of heterocyclic compounds using heteroannulation reaction.[68] And a variety of synthetic methods have been reported using mainly Lewis acids and group VIII transition metal complexes in stoichiometric or catalytic amounts.[69] Recently, many powerful methodologies have been developed for the synthesis of the annulated compounds, such as intramolecular Diels–Alder reactions, ring-closing metathesis, Pd-catalyzed cross-coupling reactions, cyclo-addition cascade reactions, etc.[70,71]

Transition metal catalysts in organic synthesis

The efficient formation of carbon-carbon, carbon-nitrogen bonds are the fundamental transformations of organic synthesis. The development of efficient and sustainable synthetic methods to achieve the variety of organic transformation with good yield with full conversion is an important and challenging task in synthetic organic chemistry. In this aspect, transition metal catalyzed bond-forming reactions have proven to be a valuable synthetic method and found wide applications in organic synthesis, and moreover transition-

metal catalyzed reactions have proven highly selective and atom economical. The synthesis of complex molecules from relatively simple precursors has long been a goal for many organic chemists. The ability to selectively functionalize a molecule with minimal pre-activation can streamline syntheses and expand the opportunities to explore the utility of complex molecules in areas ranging from the pharmaceutical industry to materials science. Indeed, the issue of selectivity is paramount in the true test of the utility of a synthetic method is in its application to the synthesis of natural products or complex molecules. Several groups have demonstrated the applicability of C-H bond functionalization reactions toward complex molecule synthesis.[72]

Target-oriented synthesis provides a platform to test the effectiveness of a method in unique chemical and steric environments. In this respect, Pd-catalyzed methods for C-H bond functionalization stand out, with several syntheses being described in the literature that utilize C-H bond functionalization in a key step, and improvement of reaction conditions have enabled the synthesis of a wide variety of heterocyclic compounds in a highly efficient and environmentally friendly manner. Development of all C-H bond functionalization methods, several groups have developed elegant approaches toward achieving selectivity in molecules that possess many sterically and electronically similar C-H bonds.[73]

An important feature in the modern heterocyclic synthesis with transition-metal catalyzed reactions are becoming very popular and attracting keen interest of a wide range of organic chemists, since a transition-metal catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions. The transition-metal catalyzed synthesis of heterocyclic compounds has been summarized in several excellent reviews and they were cited extensively.[72-74] It is characteristic that this methodology is highly useful for the synthesis of medium and large-size heterocyclic compounds. It should be also noted that, in most sections, the very popular and modern reactions in the field of transition-metal-catalyzed chemistry are utilized for the synthesis of heterocycles.[74]

Palladium catalyzed reactions

Development of selective and efficient C-C bond forming reactions is of paramount importance for organic chemistry. Recently, transition-metal catalyzed C-H bond activation with subsequent C-C bond formation has gained great attention.[72] Palladium catalysis has achieved the status of an indispensable tool for both common and state-of-the art organic synthesis. In the last 40 years or so, however, palladium-catalyzed reactions, generally tolerant of a wide range of functionalities and therefore applicable to complex molecules, have achieved an important place in the arsenal of the practicing organic chemist. Palladium complexes are particularly attractive catalysts for such transformations for several reasons. First, ligand-directed C-H functionalization at Pd centers can be used to install many different types of bonds, including carbon-oxygen, carbon-halogen, carbon-nitrogen, carbon-sulfur, and carbon-carbon linkages. Such methodologies are invaluable tools in the synthesis of potential pharmaceuticals natural products and organic materials.[75] A fascinating myriad of adventurous and unique Pd-catalyzed transformations are routinely found as key steps in target-oriented syntheses, affording complex natural products, functional advanced materials, fluorescent compounds, pharmaceutical lead compounds, and other high-value commercial products. Almost every area of the organic synthesis has been deeply influenced by the profound potential of this versatile transition metal, modifying the way organic chemists design and realize synthetic processes.[73]

Innovative Pd catalyst design, the identification of new synthetic methodologies, and the acquirement of detailed mechanistic insight, spanning both homogeneous and heterogeneous fields, underpin the numerous developments seen in this area over the past few decades. Palladium-catalyzed reactions are in fact strongly dependent on a number of factors such as the nature of stabilizing ligands (as well as their presence or absence), bases, additives, combination of them, solvents, and temperature. All of these factors combine to afford a toolbox of tunable reaction conditions that make palladium chemistry so flexible and, to some extent, unpredictable, leaving room for an uninterrupted discovery of new, exciting chemistry despite the vast amount of studies developed so far.

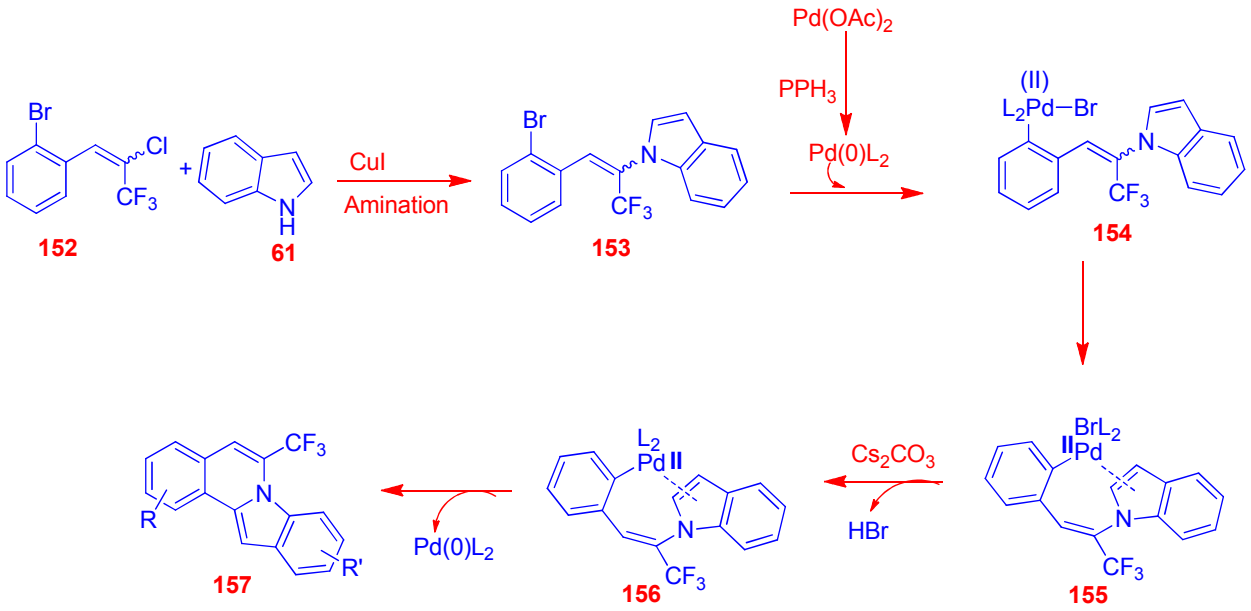
Finally, the vast majority of Pd-catalyzed directed C-H functionalization reactions can be performed in the presence of ambient air and moisture, making them exceptionally practical for applications in organic synthesis. Because of its catalytic nature, palladium-catalyzed

synthesis can provide access to fine chemicals, agrochemical and pharmaceutical intermediates, and active ingredients in fewer steps and with less waste than classical methods. Heterocyclic chemistry is no exception to this trend, and a great deal of studies have been directed toward the use of palladium catalysis in the synthesis and functionalization of heterocycles.[74]

Eq. 15

In 2012, Zhang[76] *et al* reported synthesis of pyrroloisoquinoline by using palladium acetate catalyst in good yield. A possible mechanism was proposed as outlined in **Eq. 16**.

Eq. 16



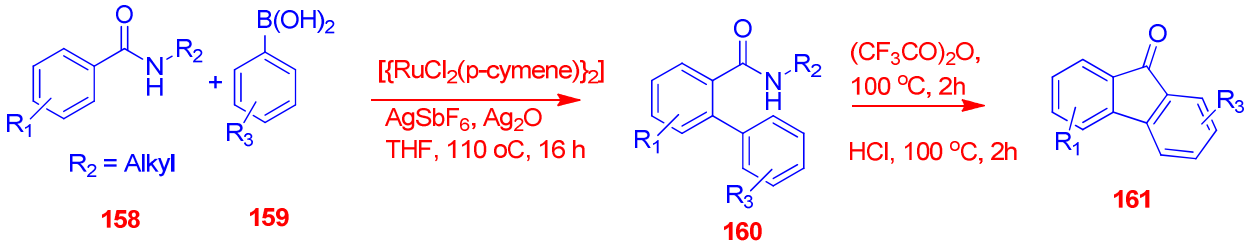
After copper-catalyzed amination of substrate **152**, the compound **153** is obtained which undergoes an oxidative addition process with Pd(0) to afford intermediate **154**. The intramolecular coordination of Pd(II) with indole moiety might provide palladium complex **155**, and the subsequent elimination of HBr in the presence of Cs_2CO_3 gives intermediate **156**. Finally, reductive elimination of **156** affords product **157** and regenerated Pd(0) species.

Ruthenium catalyzed reactions

Metal-catalyzed reactions have made a great contribution to the recent growth of organic synthesis, and a variety of synthetic methods have been reported using mainly group VIII transition metal complexes in stoichiometric or catalytic amounts. However, outside of ruthenium-catalyzed ring closing metathesis, the application of ruthenium catalysis to the formation of carbon-carbon bonds is a relatively unexplored and new field. Recent developments of the carbon-carbon bond forming reactions and C-H activation reactions in synthetic chemistry, ruthenium complexes have emerged as particularly attractive tools for C-H bond functionalizations with inexpensive easily accessible arylating reagents.[77] Since ruthenium has $4d^7 5s^1$ electron configuration, it has the widest scope of oxidation states (from -2 valent in $Ru(CO)_4^{2-}$ to octavalent in RuO_4) of all elements of the periodic table, and various coordination geometries in each electron configuration, which is in contrast to the narrow scope of oxidation states and simple square planar structure of palladium. The majority of the ruthenium complexes used herein is in the +2 to +4 oxidation state. For instance, in the principal lower oxidation states of 0, II, and III, ruthenium complexes normally prefer trigonal-bipyramidal and octahedral structures, respectively. Such a variety of ruthenium complexes has great potential for the exploitation of novel catalytic reactions and synthetic methods however, as a consequence of the difficulties of matching the catalysts and substrates; ruthenium chemistry has lagged behind that of palladium by almost a quarter century. $RuCl_3.nH_2O$ is frequently used as starting material for the preparation of most of these ruthenium complexes, and many ruthenium complexes are derived from it under ambient conditions. The great influence of ruthenium chemistry on organic synthesis in recent years has now elevated its importance to the same level as palladium. In addition to that, there is a larger availability of reactive ruthenium complexes which have proven to serve as highly efficient reagents and catalysts for a variety of organic transformations.[78]

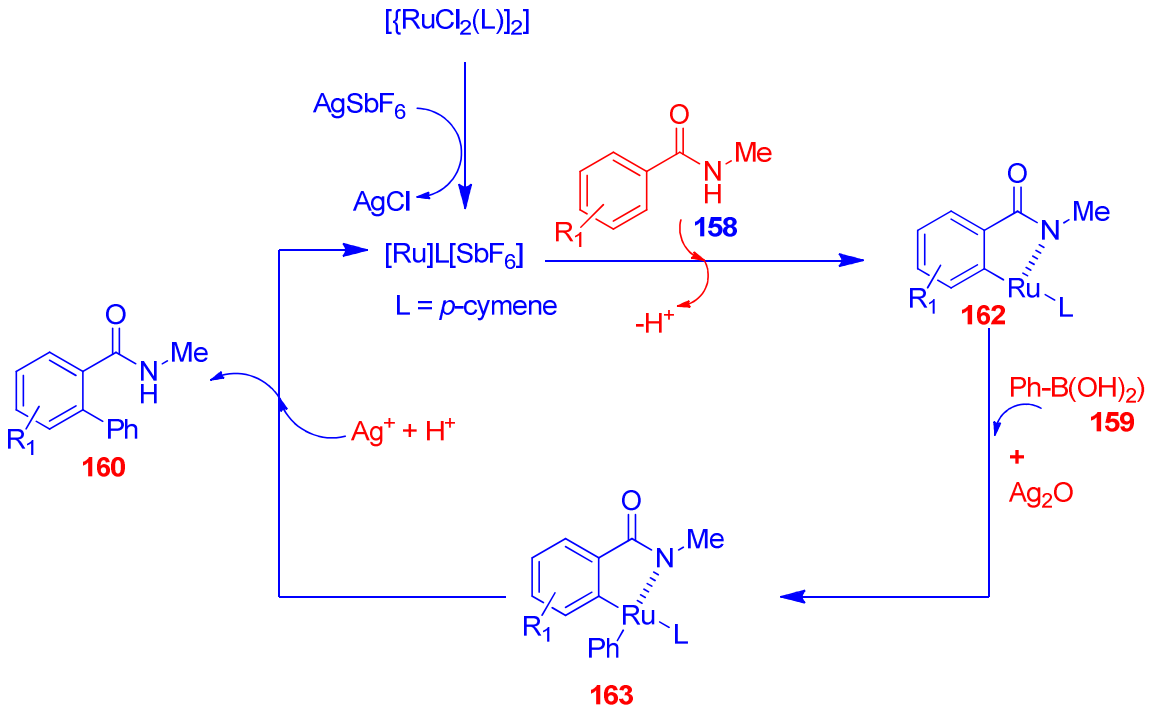
Recently, the [{$RuCl_2$(p-cymene)}$_2$] complex has been widely used as a catalyst in various C-H bond activation reactions due to remarkable reactivity, compatibility, and the low cost of the complex.[79] In 2012 Masilamani[80] *et al.* reported a ruthenium-catalyzed highly regioselective *ortho*-arylation of substituted *N*-alkylbenzamides with substituted aromatic and heteroaromatic boronic acids in the presence of $AgSbF_6$ and Ag_2O. Later, the observed coupling products were further converted into fluorenones in the presence of trifluoroacetic anhydride and HCl.

Eq. 17



On the basis of known metal-catalyzed C-H bond activations, a possible reaction mechanism is proposed to account for the present *ortho*-arylation reaction (equation 17). The first step involves removal of the chloride ligand from the ruthenium complex by $AgSbF_6$ providing the cationic ruthenium complex. Coordination of the carbonyl oxygen of benzamide **158** to the cationic ruthenium species followed by *ortho*-metalation gives ruthenacycle intermediate **162**.[81] Transmetalation of boronic acid **159** into intermediate **162** in the presence of Ag_2O provides intermediate **163**. Subsequent reductive elimination of intermediate **163** in the presence of Ag_2O affords product **160** and regenerates the active ruthenium species for the next catalytic cycle.

Eq. 18



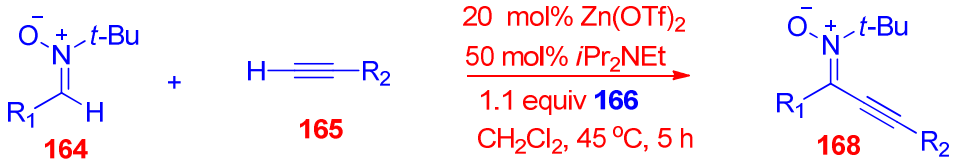
Zinc catalyzed reactions

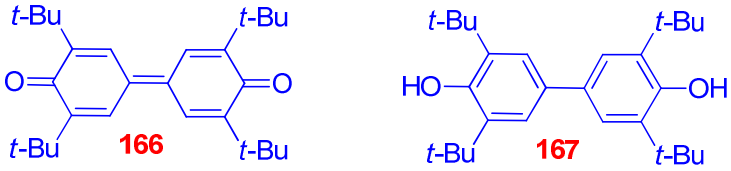
Transition metal-catalyzed synthesis of heteroaromatic compounds has received considerable attention. Lewis acids are versatile catalysts in organic synthesis. A wide range of carbocycles and heterocycles have been prepared by different kinds of reactions by Lewis acid-catalyzed annulations. It has been well-documented that Lewis acid catalyst synthesis is a field of great importance in its practical usefulness as well as its scientific interest. This is useful tools for the C-C, C-N bonding formation and construction of cyclic compounds. Since the rate of the reactions is directly dependent on the amount of catalyst employed, one of the most efficient strategies to achieve higher reaction rates is the use of a high amount of the catalyst, coupled with an efficient separation.[82]

Zinc mediated Lewis acid catalysts reactions have attracted particular attention because of the high reactivity, low catalyst loading and as it is inexpensive and easy to handle. In recent years, zinc-triflates complexes have emerged as powerful homogeneous catalysts for inducing a wide variety of transformation reactions.[83] In the past decade, these devices have attracted increasing research interest from the viewpoint of their many applications.

The possibility of catalyzing the reactions with Zn^{2+} ion exchanged zeolites has been demonstrated for the addition of methylamine to propyne (solid–gas system) and for the cyclization of 6-aminohex-1-yne (solid–liquid system).[84]

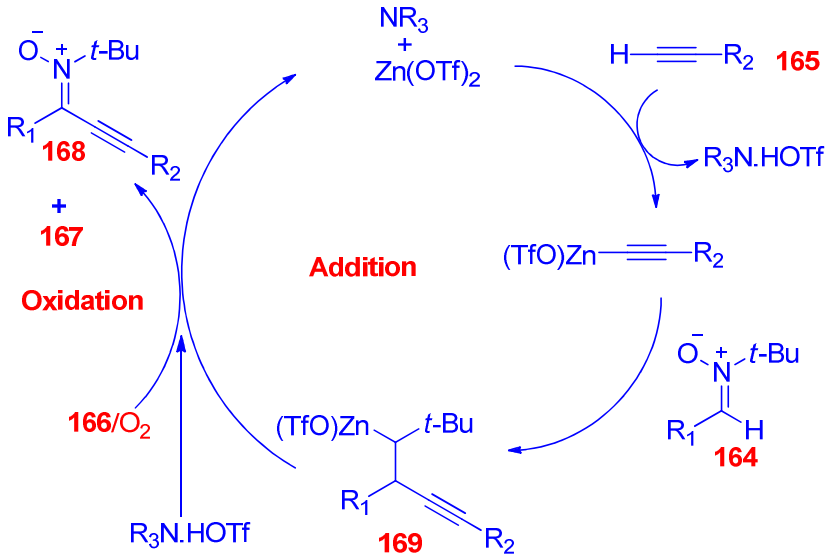
Eq. 19





In 2011 Armido *et al.* prepared nitrone from alkynes by zinc triflate catalyzed aerobic cross dehydrogenative reaction in good yield. Their envisioned oxidizing propargyl *N*-hydroxylamine intermediates of type **169** to the R-alkynylated nitrones **168**, while avoiding oxidative homocoupling of the metalated alkyne.[85] They proposed cascade comprises a $Zn(OTf)_2/NR_3$ catalyzed nucleophilic addition of a terminal alkyne to an *N*-*t*Bu nitrone to **169**, followed by mild oxidation of **169** to the cross-dehydrogenatively coupled R-alkynylated nitrone **168** (**Eq. 20**).

Eq. 20


NR3
+
Zn(OTf)2
H—≡—R2
165
R3N.HOTf
(TfO)Zn—≡—R2
Addition
O
N
t-Bu
R1
H
164
(TfO)Zn
t-Bu
R1
R2
169
R3N.HOTf
166/O2
Oxidation
168
+
167

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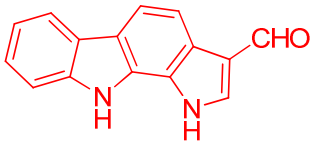
Synthesis of Pyrrolocarbazoles *via* Heteroannulation

CHAPTER 1

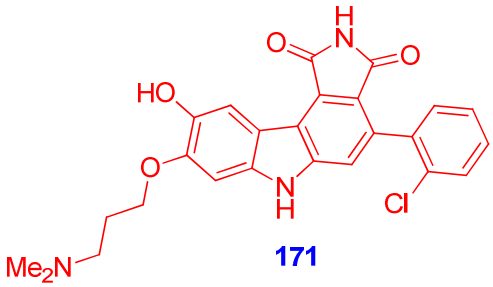
1.1 Introduction

Carbazole and its fused heteroaryl derivatives are abundantly found in numerous natural products, play an important role in pharmaceuticals and synthetic chemistry.[86,87] Recently, significant research effort has been focused on the preparation of pyrrolocarbazole scaffolds due to their promising biological activities, including antidepressant, anticancer, and antibacterial activity.[88] For example, the pyrrolo[2,3-*a*], [3,4-*c*] and [2,3-*c*]carbazoles have great importance due to their inhibiting properties towards pim kinase inhibitors as well as for their *in vitro* antiproliferative activities toward human fibroblast primary culture[89] and Chk1 inhibitors[90] telomerase inhibitors[14] respectively. Moreover pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione derivative (**Fig. 11**) exhibited potent Chk1 and Wee1 inhibitory activity.[91]



170

pyrrolo[2,3-*a*]carbazole



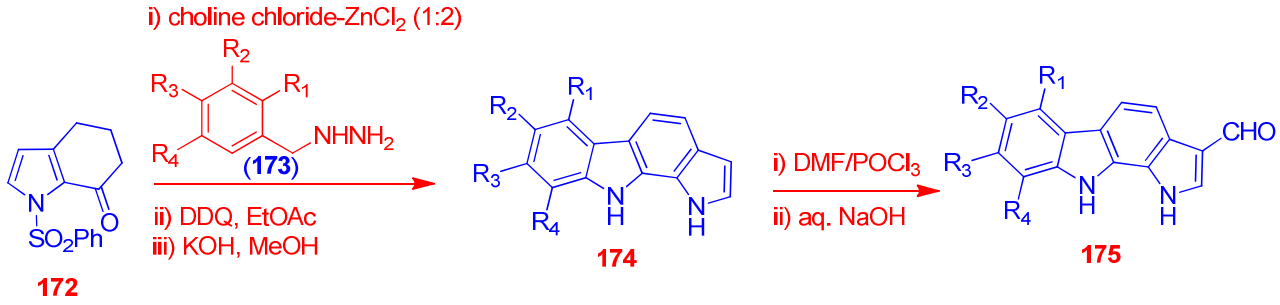
171

pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione

Fig. 11

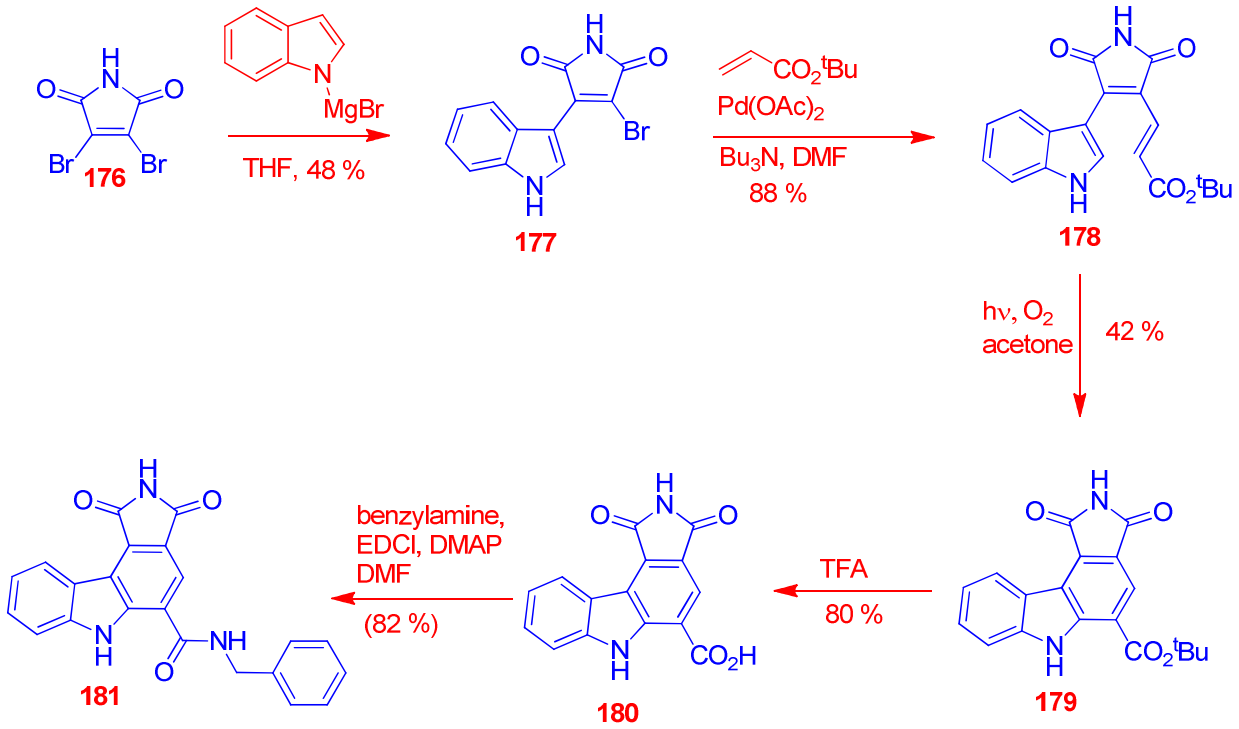
Gédu[92] *et al.* synthesized pyrrolo[2,3-*a*]carbazole efficiently by starting from phenylhydrazine derivatives. Compound **172** was heated in the presence of diversely substituted phenylhydrazines **173** in the readily accessible choline chloride/zinc chloride (1:2) ionic liquid. Subsequent oxidation with DDQ and deprotection in the presence of KOH in methanol led to substituted pyrrolo[2,3-*a*]carbazole **174**. Finally, formylation of compounds **174** in Vilsmeier conditions using DMF/$POCl_3$ gave the products **175** (**Eq. 21**).

Eq. 21



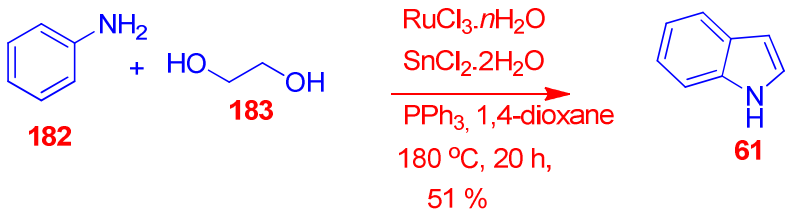
Matsuda[93] *et al.* reported the synthesis of pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione starting from bromoindolylmaleimide **177**, which was obtained from dibromomaleimide (**176**) and the magnesium salt of indole, was cross-coupled with *t*-butyl acrylate by the Heck reaction to give **178** in 88% yield. Photochemical electrocyclization followed by oxidative aromatization gave the desired pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione **179** in 42% yield. Deprotection of the *t*-Bu group afforded the carboxylic acid **180**. Condensation of **180** with benzylamine using EDCI and DMAP in DMF gave **181** in 82% yield (**Eq. 22**).

Eq. 22



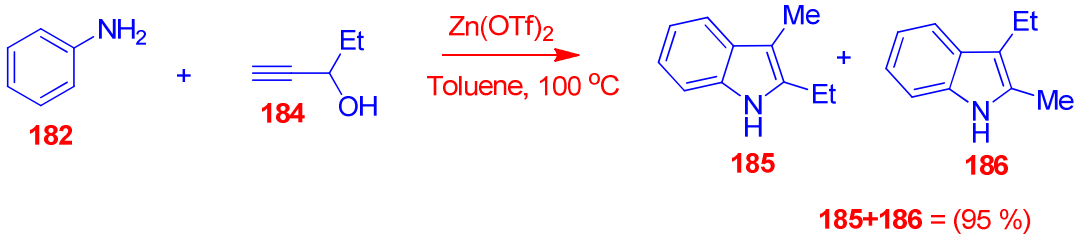
Shim *et al.* reported[94] synthesis of indole **61** starting from aniline, a mixture of **182** and **183** was subjected to heteroannulation reaction, in the presence of $RuCl_3 \cdot nH_2O$ and $SnCl_2 \cdot 2H_2O$; the product indole **61** was obtained (**Eq. 23**).

Eq. 23



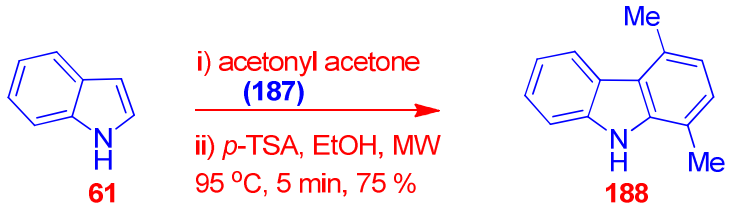
In 2006, Liu *et al.* synthesized[95] various substituted indoles by starting from aniline with propargyl alcohol derivatives. Treatment of aniline **182,** and propargyl alcohol derivative **184** with catalytic amounts of a $Zn(OTf)_2$, in toluene gave a mixture of indole regioisomers **185** and **186** (**Eq. 24**). The reaction When conducted in benzene and toluene as solvents in a sealed tube gave only indole **185** according to NMR analysis.

Eq. 24



Chern *et al*. reported[96] the synthesis of 1,4-dimethylcarbazole from indole. A treatment of indole (**61**) with acetonylacetone in the presence of *p*-toluenesulfonic acid (*P*-TSA) in ethanol at 100 °C for 5 min under MW irradiation afforded 1,4-dimethylcarbazole (**188**) in 75% yield (**Eq. 25**).

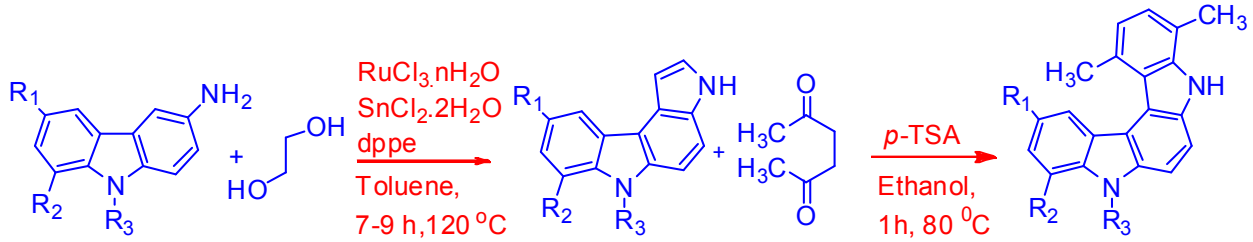
Eq. 25



1.2. $RuCl_3/SnCl_2$ mediated synthesis of pyrrolo[2,3-*c*]carbazoles and consequent preparation of indolo[2,3-*c*]carbazoles

Here, we describe a regioselective and good yielding procedure for the synthesis of pyrrolo[2,3-*c*]carbazoles *via* heteroannulation of *N*-alkylated-3-aminocarbazoles with ethylene glycol, mediated by $RuCl_3/SnCl_2$ system in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand. This method provides a route for the construction of a variety of substituted pyrrolo[2,3-*c*]carbazole derivatives as shown in scheme 1. Moreover, we wish to report an annulation of this pyrrolo[2,3-*c*]carbazoles into indolo[2,3-*c*]carbazoles by the reaction with acetonylacetone using *p*-TSA as a catalyst.

Scheme 1. The schematic representation of present work



3-aminocarbazole derivatives can be easily prepared based using literature procedures.[97] In the initial experiment, 9-ethyl-3-aminocarbazole **189a** was reacted with ethylene glycol **183** in the presence of $RuCl_3$, $SnCl_2.2H_2O$ and dppe in acetonitrile. The desired heteroannulated product **190a** was isolated in low yield. We have chosen **189a** and **183** as model substrates, and the representative results are summarized in Tables 1 & 2. With the preliminary result in hand, we investigated various reaction parameters. On the basis of the aforementioned line of reasoning, an array of solvents was undertaken, such as toluene, $CHCl_3$, THF, acetonitrile, DMA, acetone, and dioxane. Interestingly, $CHCl_3$, DMA, dioxane:H_2O, and acetonitrile gave the desired product in lower yields, whereas no product was detected with THF and acetone as shown in Table 1. The best yields were obtained when the reactions were carried out in toluene.

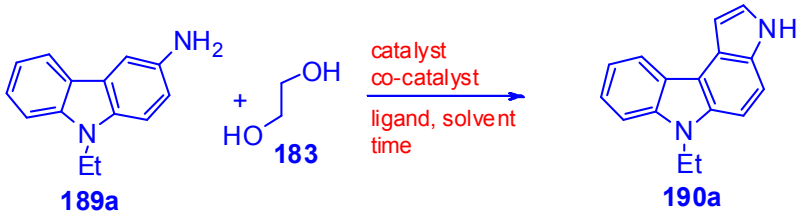


Table 1. Optimization condition for the conversion of **189a** to **190a**[a]

s. no	catalyst	co-catalyst	solvent	temp/°C time/h	yield[e]
1[b]	$PdCl_2(PPh_3)_2$	$SnCl_2.2H_2O$	Toluene	120, 12	-
2[b]	$RuCl_3$	$SnCl_2.2H_2O$	Toluene	120, 12	30
3[b]	$RhCl(PPh_3)_3$	$SnCl_2.2H_2O$	Toluene	120, 12	16
4	$RuCl_3$	$InCl_3$	Toluene	120, 12	-
5	$RuCl_3$	$SbCl_3$	Toluene	120, 12	12
6	$RuCl_3$	$CeCl_3.7H_2O$	Toluene	120, 12	30
7	$RuCl_3$	$AlCl_3$	Toluene	120, 12	25
8	$RuCl_3$	$ZnCl_2$	Toluene	120, 12	28
9	$RuCl_3$	$Bi(NO_2)_3.5H_2O$	Toluene	120, 12	-
10	$RuCl_3$	$FeCl_3.6H_2O$	Toluene	120, 12	-
11[c]	$RuCl_3$	$SnCl_2.2H_2O$	Dioxane:H_2O	120, 12	35
12	$RuCl_3$	$SnCl_2.2H_2O$	Toluene	120, 4	42
13	**$RuCl_3$**	**$SnCl_2.2H_2O$**	**Toluene**	**120, 12**	**73**
14[d]	$RuCl_3$	$SnCl_2.2H_2O$	Toluene	140, 12	73
15	$RuCl_3$	$SnCl_2.2H_2O$	THF	120, 12	-
16	$RuCl_3$	$SnCl_2.2H_2O$	$CHCl_3$	120, 12	18
17	$RuCl_3$	$SnCl_2.2H_2O$	DMA	140, 12	15
18	$RuCl_3$	$SnCl_2.2H_2O$	Acetone	120, 12	-
19	$RuCl_3$	$SnCl_2.2H_2O$	Acetonitrile	120, 12	26
20	$RuCl_3$	-	Toluene	140, 12	-

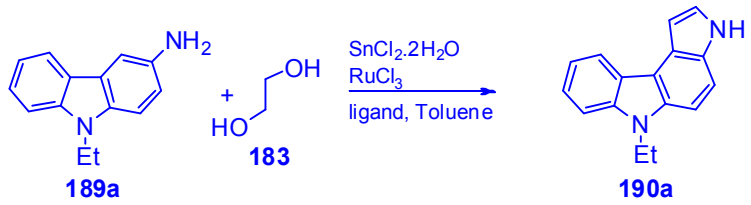
[a] Unless otherwise stated, all the reactions were carried out in a pressure tube using 5.0 mL solvent, 18 mol% catalyst, 15 mol% of dppe, 1.0 equiv. 9-ethyl-3-aminocarbazole **189a**, 2.0 equiv. ethylene glycol **183**, 3.0 equiv. co catalyst. [b] 6 mol% catalyst, 5 mol% dppe and 3.0 equiv. co catalyst were used. [c] Dioxane:H_2O in the ratio 9:1. [d] 24 mol% Catalyst, 20 mol% dppe were used. [e] isolated yields.

When **189a** and **183** were treated with $RuCl_3$ (6 mol%) and dppe (5 mol%) in the presence of $SnCl_2$ (3.0 equiv.) for 12 h at 120 °C, compound **190a** was obtained in 30% yield (Table 1, entry 2). It is intriguing to note that without the addition of $SnCl_2$,

heteroannulation reaction could not be promoted (Table 1, entry 20), while in the presence of $SnCl_2$ (3.0 equiv.), compound **190a** was obtained in 73% yield. We screened other co-catalysts, such as $SbCl_3$, $CeCl_3.7H_2O$, $AlCl_3$, $ZnCl_2$ which took longer reaction times (12 h) and gave lower yields of **190a** (Table 1, entries 5-8). No product formation was observed by using $InCl_3$, $Bi(NO_2)_3.5H_2O$, $FeCl_3.6H_2O$ (Table 1, entries 4, 9, 10).

$RuCl_3$ was found to be an efficient catalyst in this reaction compared with other catalysts such as $PdCl_2(PPh_3)_2$ and $RhCl(PPh_3)_3$. The best result was achieved by using 18 mol% $RuCl_3$, 15 mol% dppe, and 3.0 equiv. of $SnCl_2$ in 5 mL of toluene at 120 °C for 8 h. Further increase in temperature did not show any significant improvement in yield (Table 1, entry14). Attempts to reduce the catalyst loading were only partly successful as lesser amount of pyrrolo[2,3-*c*]carbazole **190a** was formed, when 6 mol% catalyst was employed. On the other hand, using 18 mol% catalyst loading gave good conversion, and identical yields were obtained with 24 mol% catalyst loading, although the reaction time was slightly prolonged as shown in Table 1.

Table 2. Ligand effect on heteroannulation of **189a**[a]



entry	ligand	temp/ °C time (h)	yield[b]
1	dppe	120, 4	42
2	dppe	120, 8	73
3	-	140, 24	14
4	$P(OEt)_3$	140, 12	36
5	PCy_3	140, 12	35
6	BINAP	140, 12	21
7	PPh_3	140, 12	42
8	dppp	140, 24	21
9	dppf	140, 24	28

[a] All the reactions were carried out in a pressure tube using 5.0 mL toluene, 18 mol% $RuCl_3$, 15 mol% ligand, 1.0 equiv. 9-ethyl-3-aminocarbazole, 2.0 equiv. ethylene glycol, 3.0 equiv. $SnCl_2.2H_2O$. [b] isolated yields.

Subsequently, the effect of ligands were further investigated under the above optimized solvent, catalyst and co-catalyst, it indicated that ligands played an important role in this

heteroannulation reaction. All the results are listed in Table 2. When heteroannulation of **189a** was carried out in the absence of ligand, the corresponding product **190a** was obtained in 16% yield (Table 2, entry 3) while in the presence of ligand the product **190a** was obtained with improved yield, which confirms the key role of ligand in this heteroannulation reaction. We were delighted to find that dppe was the most effective ligand for this reaction. In the presence of dppe the cyclization of **189a** afforded **190a** in 73% yield under the optimized condition (Table 2, entry 2).

Scheme 2. Synthesis of various pyrrolo[2,3-*c*]carbazole derivatives

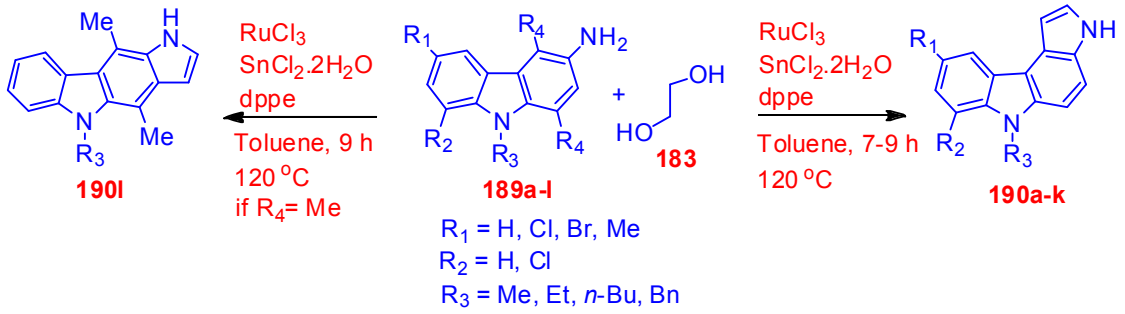
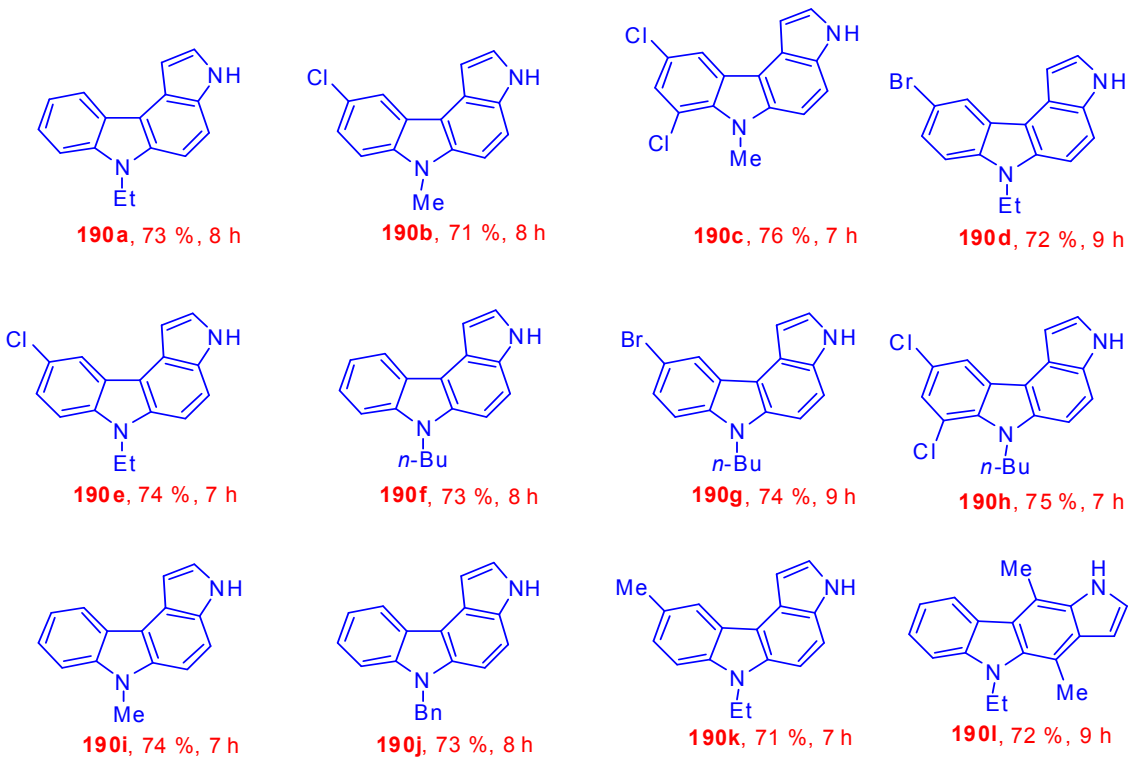


Table 3. $RuCl_3/SnCl_2$ catalyzed heteroannulation of various *N*-alkylated-3-aminocarbazoles[a]



[a] All the reactions were carried out in a pressure tube using 5.0 mL toluene, 1.0 equiv. 3-aminocarbazoles **189a-l**, 2.0 equiv. ethylene glycol **183**, 3.0 equiv. $SnCl_2.2H_2O$, 18 mol% $RuCl_3$, 15 mol% dppe, 120 °C.

With optimized conditions in our hand, we explored the scope of this method with respect to an array of *N*-alkylated-3-aminocarbazoles **189a-k** as summarized in Table 3. Various derivatives of **189a-k** smoothly underwent heteroannulation reaction to afford the desired pyrrolo[3,2-*c*]carbazole **190a-k** in good yields. When R_4 was substituted with methyl group pyrrolo[3,2-*b*]carbazole **190l** was obtained in good yield. The structure of product **190c** was also confirmed by single crystal X-ray analysis [98](**Fig. 12**).

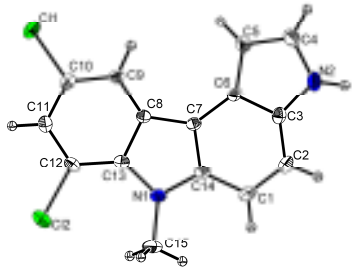


Fig. 12. ORTEP diagram of **190c**

Carbazole is obtained by the reaction of acetonylacetone with indole in the presence of Lewis acid.[96] We wish to apply this methodology for pyrrolo[2,3-*c*]carbazole into indolo[2,3-*c*]carbazoles. The desired indolo[2,3-*c*]carbazoles were successfully synthesized in good yields by the reaction of acetonylacetone (1.0 equiv.) with various pyrrolo[2,3-*c*]carbazoles (1.0 equiv.) and using p-toluenesulfonic acid (p-TSA, 0.5 equiv.) as a catalyst. The yield of the product was slightly lower when toluene was used a solvent instead of ethanol. Reaction of pyrrolocarbazoles (**190j, 190k, 190l)** with acetonylacetone works well, however the products are not identifiable from the spectroscopic data.

Scheme 3. Synthesis of indolo[2,3-*c*]carbazoles

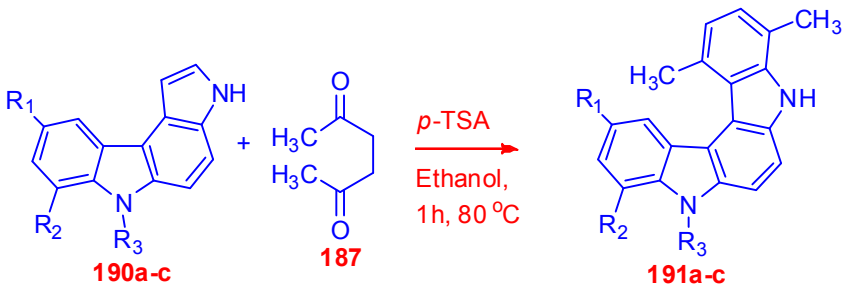
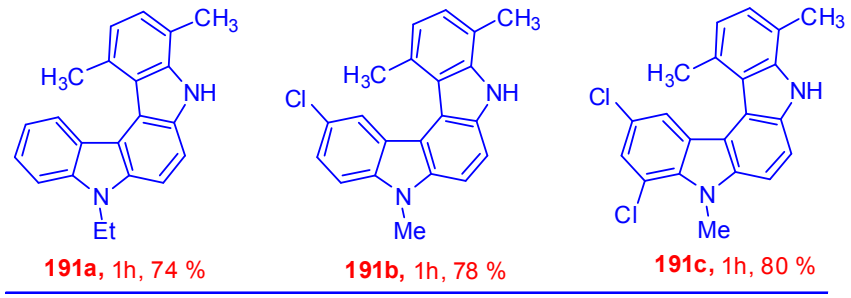


Table 4. Preparation of indolo[2,3-*c*]carbazoles form pyrrolo[2,3-*c*]carbazoles[a]



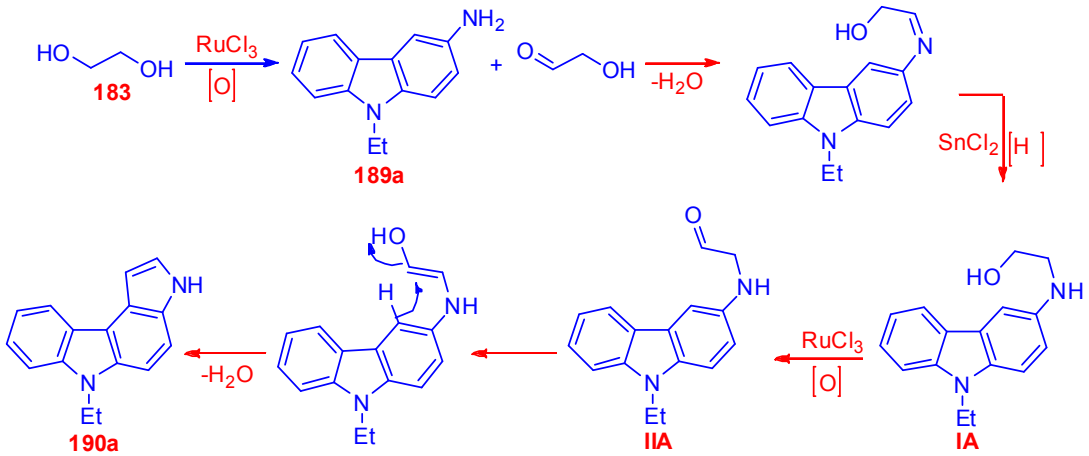
[a] All the reactions were carried out in a pressure tube using 5.0 mL ethanol, 1.0 equiv. pyrrolocarbazole, 1.0 equiv. acetonylacetone, 0.5 equiv. *p*-TSA stirred at 80 °C for 1 h.

Scheme 4. Possible mechanism for synthesis of **190a**

Based on the mechanism proposed for the synthesis of indole from aniline,[99] the possible reaction pathways for the synthesis of pyrrolocarbazole are shown in scheme 4 with path *a* and path *b*. In the first step $RuCl_3$ oxidizes the ethylene glycol (**183)** forming the imine intermediate, and then $SnCl_2$ reduces this imine into **IA**, this **IA** is again oxidized by $RuCl_3$ and gives rise to the **IIA.**

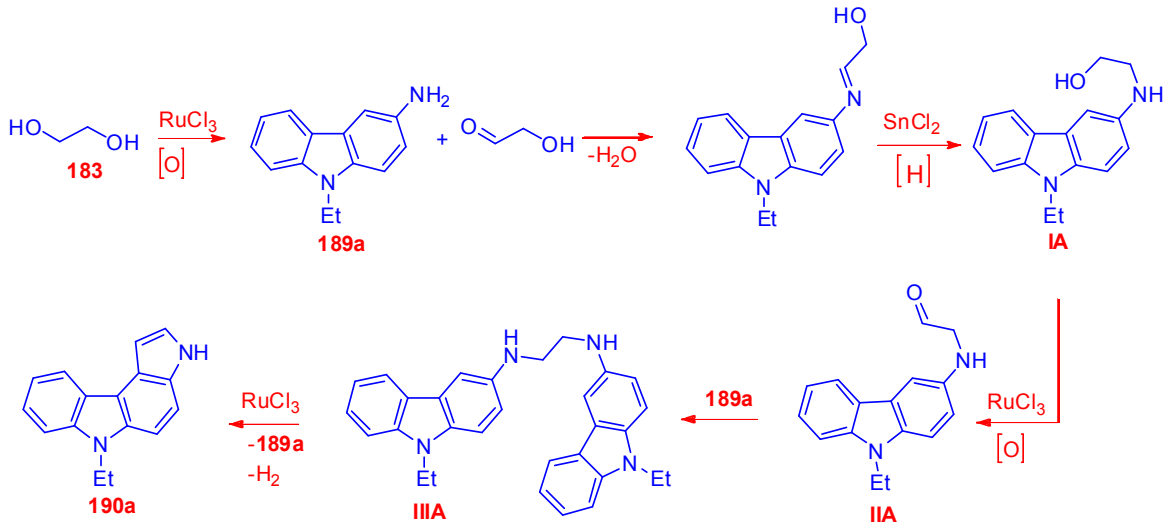
Then in path *a*, formation of **IIA** is followed by proton exchange producing **IIIA**. Elimination of water molecule gives rise to final product **190a**.

Path *a*:



In path *b*, after the formation of **IIA**, one more 3-aminocarbazole molecule (**189a)** reacts with **IIA** and gives rise to the **IIIA**, in final step removal of **189a** produce the desired product **190a**.

Path *b*:



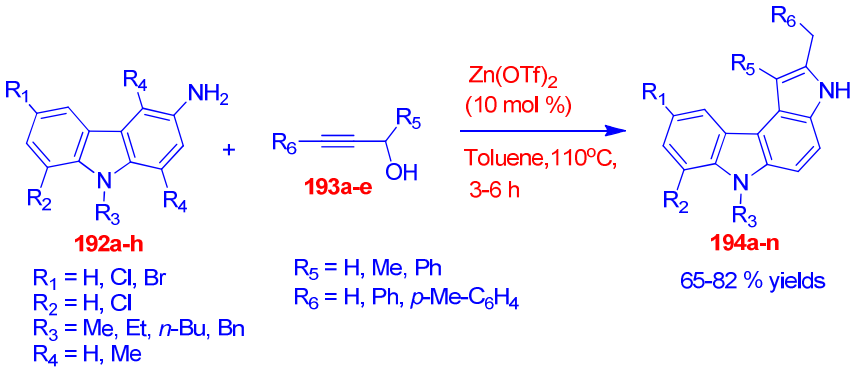
1.3 Conclusions

In summary, we have developed a direct approach for the construction of pyrrolo[2,3-*c*]carbazole and pyrrolo[3,2-*b*]carbazole in good yields using $RuCl_3/SnCl_2$ mediated system. The synthesized pyrrolo[2,3-*c*]carbazoles easily converted into indolo[2,3-*c*]carbazoles by the reaction with acetonylacetone in good yields.

1.4 Zinc triflate catalyzed regioselective synthesis of pyrrolo[2,3-*c*]carbazoles *via* heteroannulation

Herein, we report an efficient method for regioselective synthesis of pyrrolo[2,3-*c*]carbazole scaffolds via heteroannulation reaction was catalyzed by 10 mol % $Zn(OTf)_2$.

Scheme 5: Schematic representation of present work



Substituted 3-aminocarbazoles[97] as well as propargyl alcohol[100] derivatives was prepared based on the reported literature. 9-ethyl-3-aminocarbazole (**192a**) with propargyl alcohol (**193a**) was selected to optimize the experimental conditions for the heteroannulation reaction and the results are summarized in Table 1. The reaction afforded the desired product pyrrolo[2,3-*c*]carbazole **194a** with 35 % yield when using dioxane as the solvent, 5 mol% of $Zn(OTf)_2$ as the catalyst, and conventional heating at 110 °C (Table 5, entry 1). Encouraged by this result in our initial study we systematically evaluated a broad range of reaction conditions, namely, the effects of altering catalyst, ligand, solvent, temperature, and reaction time on the synthesis of **194a** and the results are summarized in Table 1. The two parameters we found to have the most significant impact on the cyclization were choice of solvent and catalyst and the results are presented in Table 5.

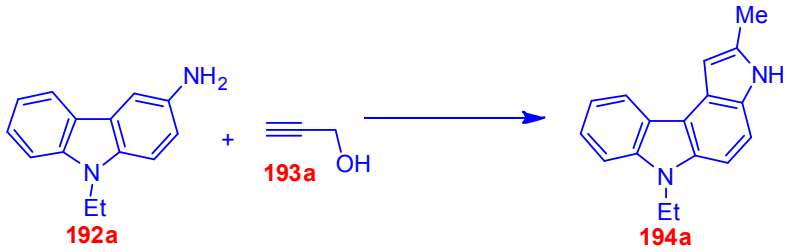


Table 5. Optimization condition for the $Zn(OTf)_2$ heteroannulation[a]

s.no	catalyst	solvent	time (h)	temp (^oC)	yield(%)[g]
1[b]	$Zn(OTf)_2$	Dioxane	6	110	35
2	$La(OTf)_3$	Toluene	24	110	25
3	$In(OTf)_3$	Toluene	8	110	71
4	$InCl_3$	Toluene	20	110	61
5[c]	$InCl_3$	Toluene	8	130	30
6	$La(OTf)_3$	Toluene	8	110	21
7[c]	$Zn(OTf)_2$	CH3CN	8	100	15
8	$Zn(OTf)_2$	CH3CN	8	100	62
9[d]	$Zn(OTf)_2$	Toluene	4	110	45
10	**$Zn(OTf)_2$**	**Toluene**	**4**	**110**	**75**
11[e]	$Zn(OTf)_2$	Toluene	10	120	75
12	$Zn(OTf)_2$	Toluene	10	70	32
13	CAN	Toluene	12	110	8
14	$InCl_3$	Dioxane	12	110	43
15	$InCl_3$	THF	10	80	-
16	$Cu(OTf)_2$	Solventf	24	110	-
17	AgOTf	Solventf	24	110	-
18	$Sc(OTf)_3$	Toluene	10	110	35
19	$Zn(OAc)_2$	Toluene	8	110	12
20	$ZnCl_2$	Toluene	8	110	47
21	$Zn(NO_3)_2.6H_2O$	Toluene	8	110	-
22	$ZnBr_2$	Toluene	8	110	26
23	$ZnCO_3$	Toluene	12	110	-
24	$Zn(OTf)_2$	THF	12	80	47
25	$La(OTf)_3$	DMA	8	120	-
26	*p*-TSA	Toluene	8	110	16
27	$Zn(OTf)_2$	DMF	8	110	-
28	-	Toluene	24	120	-

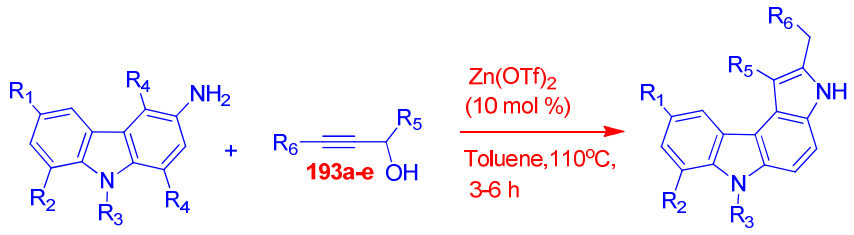
[a] Unless otherwise mentioned, all the reactions were conducted in a RB using 9-ethyl-3-aminocarbazole **192a** (1 equiv.), propargyl alcohol **193a** (1.5 equiv.) catalyst (10 mol%), 10 mL solvent. [b] 5 mol% of catalyst used. [c] reaction conducted in pressure tube, solvent 3 mL. [d] 1.0 equiv. of **193a** was used. [e] 15 mol% of catalyst used. [f] toluene or dioxane. [g] isolated yields.

We first examined the influence of triflates. Different triflate sources were examined and 10 mol% of $Zn(OTf)_2$ showed the highest activity followed by $In(OTf)_3$ (10 mol%) (Table 5, entries 11, 14). However, catalysts like $La(OTf)_3$ and $Sc(OTf)_3$ did not facilitate good conversion and relatively low yields were obtained (Table 1, entries 2, 6 and 17). Whereas catalysts such as Cu(OTf) and Ag(OTf) did not affect the above mentioned transformation. When the reaction was conducted at a moderate temperature of 70 °C with 10 mol% zinc triflate as catalyst, it proceeded with a lower yield, whereas when it was conducted at higher reaction temperature of 120 °C the yield did not increase beyond 75 %. (entries 12-13, Table 5).

The screening experiments also showed that increasing the amount of $Zn(OTf)_2$ did not enhance the yield and even prolonged the reaction time to 10 h. Among the other catalysts $InCl_3$ promoted the desired annulated product **194a** in moderate yield (entry 4). Of the various zinc salts that were tested in this reaction, zinc triflate gave the best yield compared to the others when the reaction where conducted in toluene (Table 5, entries 10 and 19-23). A relatively lower yield was obtained when the reaction was carried out by the use of $ZnCl_2$ as the catalyst (Table 5, entry 20). Control experiments showed that omitting the catalyst did not afford the product (entry 28). After a comprehensive screening, we found that zinc triflate was superior among the all other catalysts that were examined in this reaction, with a high level of regioselectivity. $In(OTf)_3$, and $InCl_3$ gave good yields but zinc triflate gave somewhat better yield than the above catalysts. And moreover zinc triflate is a commercially cheaper catalyst, and easier to handle than indium catalysts which needs inert atmosphere for this heteroannulation reaction.

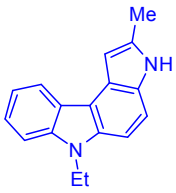
Further inspection of the reaction conditions reveals that the reaction proceeded efficiently in solvents such as CH_3CN, THF, and 1,4-dioxane, although they were less efficient compared with toluene. We also checked the feasibility of ligands towards the reaction yield, it did not play any significance role in this reaction. Various ligands such as, dppe, PPh_3, dppf, $P(OEt)_3$, PCy_3 were all unimpressive. The use of 1.5 equiv. of **193a** rather than 1.0 equiv. of **193a** improves the yield of the reaction (entry 9, Table 5). The best result was obtained when the reaction was conducted by mixing **192a, 193a** and catalyst zinc triflate (10 mol %) successively in toluene at 110 °C for 4 h to give the desired product **194a** in 75% yield (entry 10).

Table 6. Synthesis of pyrrolo[2,3-*c*]carbazole derivatives[a]

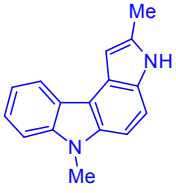


R_1 = H, Cl, Br
R_2 = H, Cl
R_3 = Me, Et, *n*-Bu, Bn
R_4 = H, Me

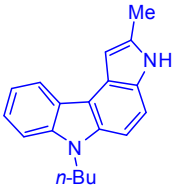
R_5 = H, Me, Ph
R_6 = H, Ph, PhMe



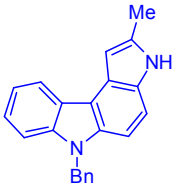
194a, 4h, 75 %



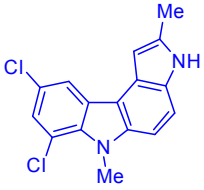
194b, 6h, 70 %



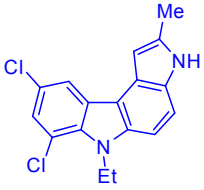
194c, 4h, 72 %



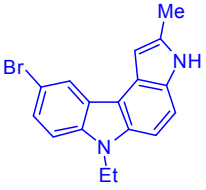
194, 3h, 79 %



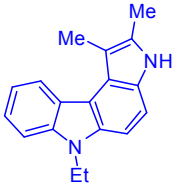
194e, 4h, 74 %.



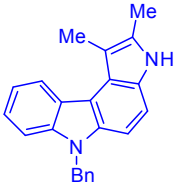
194f, 3h, 80 %



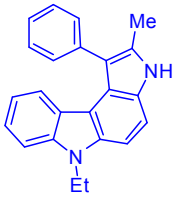
194g, 4h, 72 %



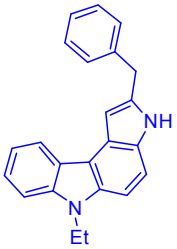
194h, 5h, 70 %



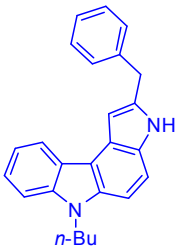
194i, 3h, 65 %



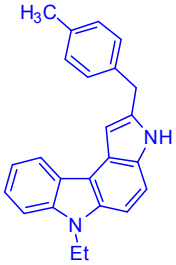
194j, 5.5 h, 78 %



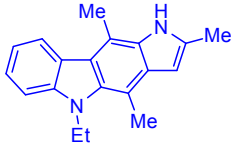
194k, 4.5 h, 82 %



194l, 5h, 74 %



194m, 6h, 71 %



194n, 6h, 67 %

[a]All the reactions were conducted in a RB using 3-aminocarbazole **192a-n** (1 equiv.), propargyl alcohol **193a-e** (1.5 equiv.), zinc triflate (10 mol%), 20 mL of toluene at 110 °C.

Having identified these optimal conditions, we sought to examine the scope and the generality of the method by applying it to a range of substituted 3-aminocarbazoles and propargyl alcohols, and the results are shown in Table 6. The products **194a-n** were generated from **192a-h**, **193a-e** in moderate to good yields. All the products displayed spectroscopic data in agreement with the expected pyrrolocarbazoles, and the structures **194f** and **194k** were further confirmed by X-ray data.[101] From the ORTEP we conclude that the methyl group in product comes from R_5 position of propargyl alcohol. If R_5 = H the products have a methyl group at the C_2 position (which is near to nitrogen atom), if R_5 = Ph the products have benzyl group at C_2 position. The pure products were simply obtained by column chromatography over alumina.

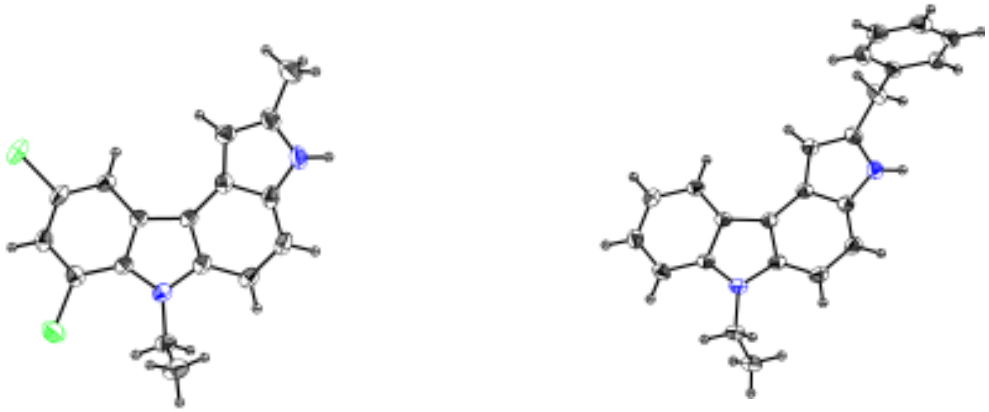
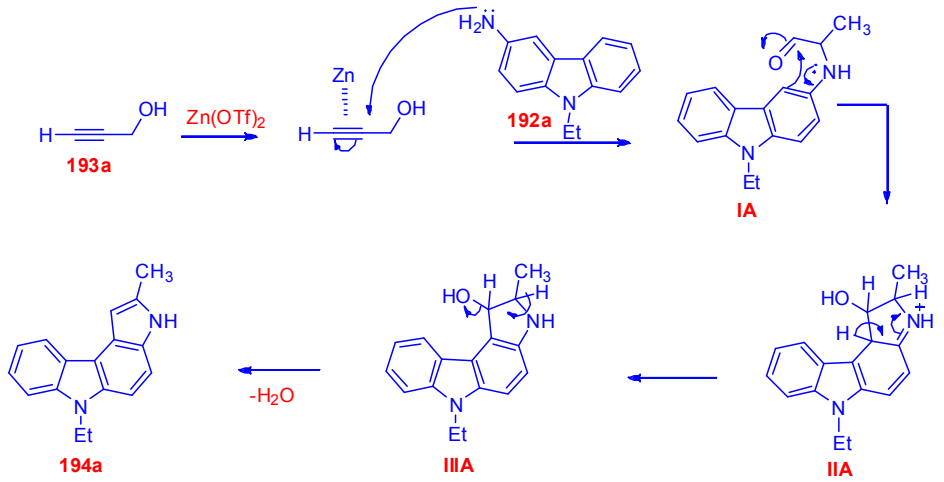


Fig 13 ORTEP of **194f** and **194k**

Scheme 6. Possible mechanism of the present reaction

This reaction mechanism was proposed on the basis of a literature report of the conversion of aniline to indole.[95] The reaction mechanism consists of the following steps, in the first step hydroamination of the C–C triple bond of propargyl alcohol takes place. Zinc triflate makes the alkyne carbon electron deficient, thereby facilitating the attack of nitrogen lone pair onto the alkyne carbon, followed by the hydrogen migration gives rise to the aminoketone structure **IA**. The migration of nitrogen lone pair gives rise to structure **IIA** and then rearomatization takes place in the carbazole ring which gives the structure **IIIA**. Finally, removal of water molecule gave the desired product **194a**.



1.5 Conclusion

In conclusion, we have established a general method for the preparation of fused pyrrolo[2,3-*c*]&[2,3-*b*]carbazole derivatives from 3-aminocarbazoles and propargyl alcohol derivatives *via* zinc triflate catalyzed heteroannulation reaction.

1.6. Experimental section

General Information

All ^{1}H, ^{13}C NMR spectra were recorded on AV-400 spectrometer operating at 400 and 100 MHz respectively. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Multiplicities was indicated as follows (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and coupling constants (Hz). Chemical shifts of common trace ^{1}H NMR impurities ($CDCl_3$, ppm): H_2O, 1.56; EtOAc, 1.26, 2.05, 4.12; CH_2Cl_2, 5.30; $CDCl_3$, 7.26. IR spectra were recorded on FT/IR-5300 spectrometer; absorptions are reported in cm^{-1}. Mass spectra were recorded on either using EI technique or LCMS-2010A mass spectrometer. Elemental analyses (C, H, and N) were recorded on EA 1112 analyzer in School of Chemistry, University of Hyderabad. Routine monitoring of the reactions was performed by TLC silica gel plates 60 F254 were used. Compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine. Column chromatography was carried out employing neutral alumina. Commercially available reagents and solvents were used without further purification and were purchased. Melting points were measured in open capillary tubes and are uncorrected.

General procedure A

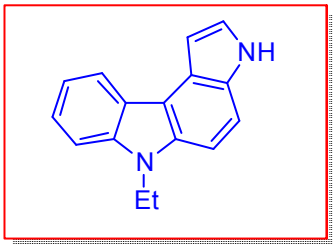
An oven dried 25 mL Ace pressure tube was charged with $RuCl_3$ (18 mol %), dppe (15 mol %) toluene (5 mL) along with *N*-alkylated-3-aminocarbazole **189a-l** (1.0 equiv.), $SnCl_2$ (3.0 equiv) and ethylene glycol **183** (2.0 equiv), and then capped with a teflon screw cap and the mixture was heated to 120 °C and stirred for 8 h, After completion of the reaction, followed by thin layer chromatography (TLC), the mixture was cooled to room temperature, the solvent was evaporated and dissolved in EtOAc. The resulting solution was directly filtered through a pad of celite and washed with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography on neutral alumina using EtOAc/hexanes as the eluent. The solvent was evaporated to dryness to get the pure product **190a-l**.

6-Ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190a):

The product **190a** was obtained as brown colored viscous liquid from **189a** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.

Yield: 73 %

IR (KBr) ν_{max} cm^{-1}: 3408, 3051, 2968, 2928, 2858, 1707, 1587, 1477, 1450, 1375, 1331, 1228, 1180, 1151, 1087, 1020, 889, 781, 748



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35-8.33 (m, 2H), 7.52-7.50 (m, 3H), 7.34-7.32 (m, 3H), 7.13 (s, 1H), 4.46 (q, 2H, *J* = 5.76 Hz), 1.46 (t, 3H, *J* = 6.64 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 134.9, 130.5, 124.2, 123.8, 123.1, 121.4, 121.3, 118.3, 113.6, 109.9, 108.3, 104.2, 100.8, 37.7, 14.3

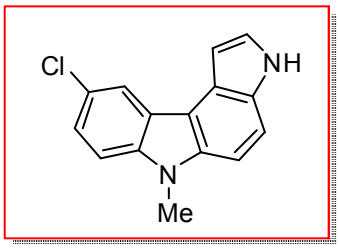
LC-MS (m/z): 235 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.98 %

Found: C, 82.15; H, 6.38; N, 11.86 %

9-Chloro-6-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190b)

The product **190b** was obtained as colorless solid from **189b** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 71%

Mp: 116 °C

IR (KBr) ν_{max} cm^{-1}: 3427, 2924, 2854, 1714, 1456, 1361, 1290, 1062, 1014, 868, 788

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.21-8.20 (m, 1H), 7.53-7.51 (m, 1H), 7.39-7.31 (m, 3H), 7.26-7.24 (m, 1H), 7.05 (s, 1H), 3.86 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 136.7, 130.6, 124.5, 123.95, 123.91, 123.8, 121.2, 120.6, 112.7, 110.6, 109.2, 104.3, 100.8, 29.5

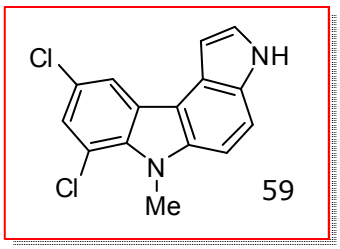
LC-MS (m/z): 256 $(M+H)^+$, 257 (M+1) positive mode

Anal. Calcd. for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35; N, 11.00 %

Found: C, 70.81; H, 4.26; N, 10.85 %.

7,9-Dichloro-6-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190c)

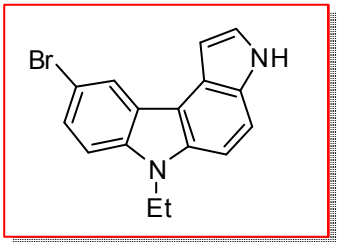
The product **190c** was obtained as colorless solid from **189c** through column chromatography using a mixture of 10% ethyl acetate and hexanes according to procedure A.



Yield:	76 %
Mp:	142 °C
IR (KBr) ν_{max} cm^{-1}:	3441, 3406, 2922, 1657, 1550, 1456, 1367, 1284, 1107, 844, 775, 731, 706
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.40 (s, 1H), 8.066-8.061 (m, 1H), 7.54-7.52 (m, 1H), 7.37-7.36 (m, 1H), 7.33-7.32 (m, 1H), 7.24-7.22 (m, 1H), 7.00-6.99 (m, 1H), 4.21 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 137.7, 133.8, 130.8, 126.5, 125.2, 124.7, 123.5, 120.8, 119.3, 116.1, 112.6, 111.4, 104.5, 100.8, 32.3
LC-MS (m/z):	287 $(M-H)^-$, 289 (M+2) negative mode
Anal. Calcd. for $C_{15}H_{10}N_2Cl_2$:	C, 62.03; H, 3.49; N, 9.69 %
Found:	C, 62.10; H, 3.46; N, 9.65 %

9-Bromo-6-ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190d)

The product **190d** was obtained as brown colored viscous liquid from **189d** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure A.



Yield:	72 %
IR (KBr) ν_{max} cm^{-1}:	3414, 2959, 2926, 2856, 2058, 1996, 1712, 1616, 1462, 1367, 1302, 1091, 794, 742
^{1}H NMR (400 MHz, $CDCl_3$):	δ 8.45 (s, 1H), 8.375-8.370 (m, 1H), 7.57-7.48 (m, 2H), 7.40 (s, 1H), 7.37-7.28 (m, 2H), 7.07 (s, 1H), 4.43 (q, 2H, J = 7.28 Hz), 1.43 (t, 3H, J = 7.24 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 135.4, 130.6, 126.4, 124.7, 124.4, 123.7, 121.3, 112.8, 111.1, 110.6, 109.7, 104.3, 100.9, 37.9, 14.0

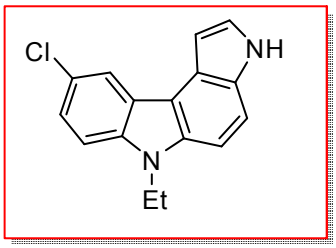
LC-MS (m/z): 315 $(M+H)^+$, 317 (M+2), positive mode

Anal. Calcd. for $C_{16}H_{13}N_2Br$: C, 61.36; H, 4.18; N, 8.94 %

Found: C, 61.28; H, 4.21; N, 8.86 %

9-Chloro-6-ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190e)

The product **190e** was obtained as brown colored viscous liquid from **189e** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 74 %

IR (KBr) ν_{max} cm^{-1}: 3393, 2924, 2858, 1736, 1622, 1462, 1302, 1259, 1099, 794

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.23 (s, 1H), 7.57-7.55 (m, 1H), 7.40-7.38 (m, 3H), 7.31-7.29 (m, 1H), 7.08 (s, 1H), 4.43 (q, 2H, J = 7.2 Hz), 1.44 (t, 3H, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 135.5, 131.8, 131.1, 130.5, 128.8, 124.4, 123.8, 121.3, 120.7, 110.6, 109.2, 104.3, 100.8, 37.9, 14.0

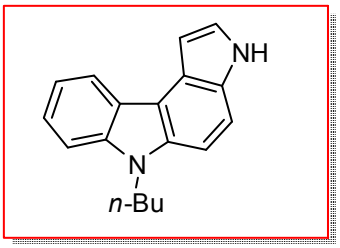
LC-MS (m/z): 269 $(M+H)^+$, 270 (M+1) positive mode

Anal. Calcd. for $C_{16}H_{13}N_2Cl$: C, 71.51; H, 4.88; N, 10.42 %

Found: C, 71.65; H, 4.79; N, 10.36 %

6-Butyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190f)

The product **190f** was obtained as light brown solid from **189f** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure A.



Yield: 73 %

IR (KBr) ν_{max} cm^{-1}: 3402, 3051, 2959, 2928, 2872, 1689, 1583, 1481, 1456, 1367, 1329, 1151, 1084, 1020, 881, 781, 748

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.31 (d, 1H, *J* = 7.64 Hz), 7.54-7.43 (m, 3H), 7.39-7.37 (m, 1H), 7.34-7.29 (m, 2H), 7.13 (s, 1H), 4.40 (t, 2H, *J* = 7.08 Hz), 1.93-1.88 (m, 2H), 1.47-1.39 (m, 2H), 0.95 (t, 3H, *J* = 7.28 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5, 135.4, 130.5, 124.1, 123.8, 123.7, 122.9, 121.4, 121.2, 118.2, 109.7, 108.5, 104.6, 101.0, 43.1, 31.4, 20.6, 13.9

LC-MS (m/z): 263 $(M+H)^+$, positive mode

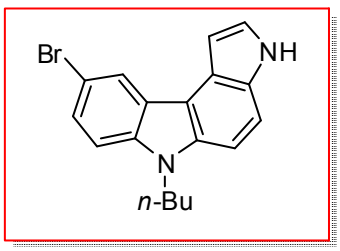
Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.41 ; H, 6.92; N, 10.68 %

Found: C, 82.55; H, 6.81; N, 10.56 %

9-Bromo-6-butyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190g)

The product **190g** was obtained as greenish colored viscous liquid from **189g** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure A.

Yield: 86 %



IR (KBr) ν_{max} cm^{-1}: 3400, 2957, 2926, 2856, 1720, 1606, 1454, 1375, 1329, 1099, 1016, 794

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.22-8.18 (m, 2H), 7.52-7.49 (m, 3H), 7.45-7.43 (m, 1H), 7.31-7.27 (m, 1H), 4.36 (t, 2H, *J* = 7.12 Hz), 1.98-1.89 (m, 2H), 1.47-1.41 (m, 2H), 0.97 (t, 3H, *J* = 7.32 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 135.8, 130.5, 126.4, 124.5, 124.4, 123.6, 121.2, 112.6, 110.9, 110.5, 109.9, 104.5, 100.8, 43.2, 31.3, 20.5, 13.8

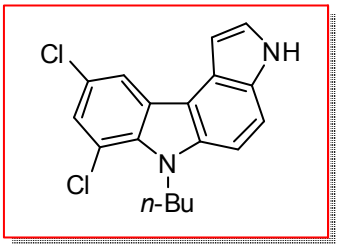
LC-MS (m/z): 341 $(M+H)^+$, 343 (M+2), positive mode

Anal. Calcd. for $C_{18}H_{17}N_2Br$: C, 63.35; H, 5.02; N, 8.21 %

Found: C, 63.48; H, 4.91; N, 8.15 %

6-Butyl-7,9-dichloro-3,6-dihydropyrrolo[2,3-*c*]carbazole (190h)

The product **190h** was obtained as colorless solid from **189h** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 86 %

Mp: 138 °C

IR (KBr) ν_{max} cm^{-1}: 3389, 2961, 2926, 2856, 1620, 1554, 1469, 1371, 1296, 1109, 777, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.129-8.125 (m, 1H), 7.56 (d, 1H, *J* = 8.84 Hz), 7.39-7.38 (m, 2H), 7.30-7.26 (m, 1H), 7.04 (s, 1H), 4.73 (t, 2H, *J* = 7.52 Hz), 1.91-1.83 (m, 2H), 1.47-1.40 (m, 2H), 0.96 (t, 3H, *J* = 7.32 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 133.1, 130.7, 126.8, 125.3, 124.7, 123.5, 120.9, 119.3, 115.9, 112.7, 111.4, 104.8, 100.8, 44.6, 33.0, 20.1, 13.9

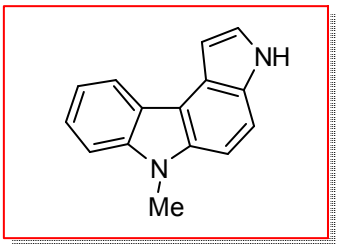
LC-MS (m/z): 331 $(M+H)^+$, 333 (M+2), positive mode

Anal. Calcd. for $C_{18}H_{16}N_2Cl_2$: C, 65.27; H, 4.87; N, 8.46 %

Found: C, 65.32; H, 4.90; N, 8.38 %

6-Methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190i)

The product **190i** was obtained as pale black colored viscous liquid from **189i** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 74 %

IR (KBr) ν_{max} cm^{-1}: 3393, 2920, 2851, 1699, 1647, 1539, 1450, 1242, 1018, 966

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.28 (d, 1H, J = 7.72 Hz), 7.50-7,48 (m, 1H), 7.45-7.44 (m, 2H), 7.34 (s, 1H), 7.29-7.27 (m, 2H), 7.09 (s, 1H), 3.90 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 136.0, 130.6, 124.2, 123.9, 122.9, 121.4, 121.2, 118.4, 113.5, 109.8, 108.3, 104.3, 100.9, 29.4

LC-MS (m/z): 221 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72 %

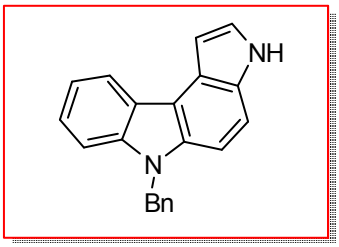
Found: C, 81.68; H, 5.56; N, 12.65 %

6-Benzyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190j)

The product **190j** was obtained as black colored viscous liquid from **189** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure A.

Yield: 73 %

IR (KBr) ν_{max} cm^{-1}: 3354, 3061, 2916, 2858, 1959, 1907, 1819, 1685, 1614, 1579, 1494, 1448, 1359, 1263, 1205, 1165, 1120, 1076, 1018, 908, 823, 752, 700



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.34 (d, 1H, J = 7.72 Hz), 7.48-7.46 (m, 1H), 7.44-7.43 (m, 2H), 7.40-7.39 (m, 1H), 7.26 (s, 1H), 7.24-7.22 (m, 3H), 7.15-7.12 (m, 4H), 5.62 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 137.7, 135.6, 130.7, 128.79, 128.70, 127.2, 126.3, 124.3, 124.2, 123.2, 121.4, 121.3, 118.8, 110.0, 108.7, 104.7, 101.0, 46.7

LC-MS (m/z): 297 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45 %

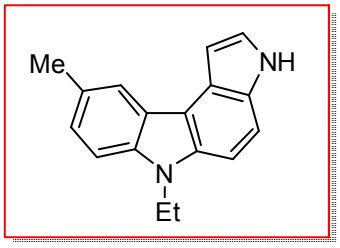
Found: C, 85.06; H, 5.48; N, 9.56 %

6-Ethyl-9-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190k)

The product **190k** was obtained as Pale white colored solid from **189k** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure A.

Yield: 71 %

Mp: 48 ^oC



IR (KBr) ν_{max} cm^{-1}: 3443, 2924, 2856, 1651, 1456, 1371, 1294, 1244, 1143, 1018

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.06 (s, 1H), 7.45-7.42 (m, 1H), 7.35-7.33 (m, 1H), 7.30-7.24 (m, 3H), 7.09-7.08 (m, 1H), 4.39 (q, 2H, *J* = 7.2 Hz), 2.59 (s, 3H), 1.39 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 135.1, 130.4, 127.5, 125.3, 124.0, 123.3, 121.5, 121.3, 113.4, 109.6, 108.0, 104.3, 100.9, 37.8, 21.5, 14.1

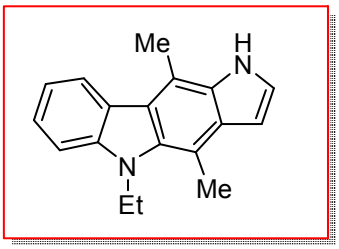
LC-MS (m/z): 247 $(M-H)^-$, negative mode

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28 %

Found: C, 82.13; H, 6.51; N, 11.36 %

5-Ethyl-4,10-dimethyl-1,5-dihydropyrrolo[3,2-*b*]carbazole (190l)

The product **190l** was obtained as pale black colored viscous liquid from **189l** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure A.



Yield: 72 %

IR (KBr) ν_{max} cm^{-1}: 3400, 2922, 2852, 2368, 1712, 1647, 1458, 1093, 1016

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 7.8 Hz), 8.12 (s, 1H), 7.44-7,42 (m, 1H), 7.39-7.37 (m, 1H), 7.34 (t, 1H, *J* = 2.64 Hz), 7.21-7.17 (m, 1H), 6.719-6.715 (m, 1H), 4.63 (q, 2H, *J* = 7.12 Hz), 2.98 (s, 3H), 2.97 (s, 3H), 1.42 (t, 3H, *J* = 7 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 134.9, 131.1, 128.6, 124.8, 124.58, 124.50, 122.2, 120.1, 117.8, 111.3, 107.8, 106.0, 100.9, 39.6, 15.2, 15.0, 14.5

LC-MS (m/z): 263 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68 %

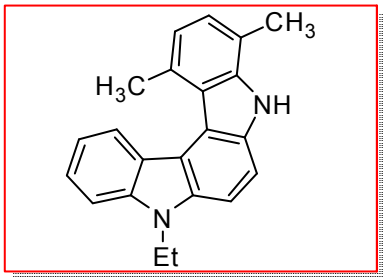
Found: C, 82.31; H, 6.81; N, 10.75 %

General procedure B

An oven dried 25 mL Ace pressure tube was charged with pyrrolocarbazole **190a-c** (1.0 equiv.), acetonylacetone **187** (1.0 equiv.), *p*-toluenesulphonic acid (0.5 equiv.) along with 5 mL of ethanol then capped with a teflon screw cap and the mixture was strried at 80 °C for 1 h. After completion of the reaction, followed by thin layer chromatography (TLC), the mixture was cooled to room temperature; the solvent was evaporated and dissolved in EtOAc. The resulting organic layer were washed with water, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography on neutral alumina using EtOAc/hexanes as the eluent. The solvent was evaporated to dryness to get the pure product **191a-c**.

8-Ethyl-1,4-dimethyl-5,8-dihydroindolo[2,3-*c*]carbazole (191a)

The product **191a** was obtained as yellow colored solid from **190a** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure B.



Yield: 74 %

Mp: 78 °C

IR (KBr) ν_{max} cm^{-1}: 3416, 2926, 2849, 1651, 1275, 1103, 1022, 750

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, J = 8.04 Hz), 8.14 (s, 1H), 7.62-7.60 (m, 1H), 7.56-7.54 (m, 1H), 7.51-7.45 (m, 2H), 7.25-7.21

(m, 2H), 7.04 (d, 1H, *J* = 6.9 Hz), 4.51 (q, 2H, *J* = 6.4 Hz), 3.00 (s, 3H), 2.61 (s, 3H), 1.51 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.6, 139.5, 135.9, 135.0, 131.0, 125.7, 125.0, 124.4, 123.4, 123.2, 121.5, 117.1, 116.5, 116.1, 116.0, 109.3, 108.0, 107.3, 37.8, 23.4, 16.6, 13.9

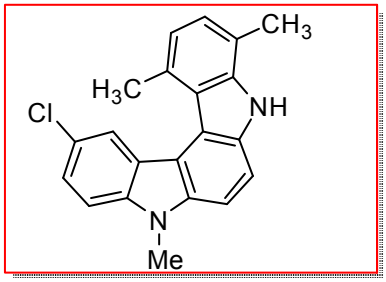
LC-MS (m/z): 313 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97 %

Found: C, 84.46; H, 6.41; N, 9.07 %

11-Chloro-1,4,8-trimethyl-5,8-dihydroindolo[2,3-*c*]carbazole (191b)

The product **191b** was obtained as yellow colored solid from **190b** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 78 %

Mp: 98 °C

IR (KBr) ν_{max} cm^{-1}: 3402, 2926, 2852, 1728, 1668, 1454, 1317, 1257, 1149, 1089, 1022, 794

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.38 (d, 1H, *J* = 1.72 Hz), 8.16 (s, 1H), 7.63-7.61 (m, 1H), 7.51-7.49 (m, 1H), 7.42-7.36 (m, 2H), 7.23 (d, 1H, *J* = 7.28 Hz), 7.11-7.09 (m, 1H), 3.93 (s, 3H), 2.98 (s, 3H), 2.60 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.9, 138.9, 137.4, 135.9, 129.2, 126.0, 124.3, 123.7, 123.0, 122.1, 121.9, 121.3, 117.3, 114.6, 113.9, 111.8, 110.8, 108.7, 29.9, 23.4, 17.1

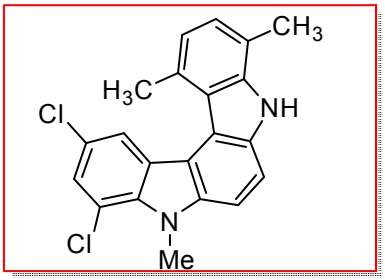
LC-MS (m/z): 333 $(M+H)^+$, 335 (M+2) positive mode

Anal. Calcd. for $C_{21}H_{17}N_2Cl$: C, 75.78; H, 5.15; N, 8.42 %

Found: C, 75.86; H, 5.09; N, 8.37 %

9,11-Dichloro-1,4,8-trimethyl-5,8-dihydroindolo[2,3-*c*]carbazole (191c)

The product **191c** was obtained as Yellow colored solid from **190c** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure B.



Yield: 80 %

Mp: 132 °C

IR (KBr) ν_{max} cm^{-1}: 3433, 2924, 2854, 1722, 1651, 1456, 1315, 1261, 1105, 1074, 1028

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.24 (s, 1H), 8.20 (s, 1H), 7.67-7.65 (m, 1H), 7.54-7.52 (m, 1H), 7.38 (s, 1H), 7.23 (s, 1H), 7.10 (d, 1H, *J* = 7.4 Hz), 4.34 (s, 3H), 2.88 (s, 3H), 2.60 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.6, 138.5, 135.3, 134.4, 130.5, 126.8, 126.2, 125.8, 122.8, 122.7, 122.3, 122.0, 116.3, 115.8, 115.7, 115.0, 110.9, 107.7, 32.5, 23.4, 16.6

LC-MS (m/z): 365 $(M-H)^-$, 367 (M+2) negative mode

Anal. Calcd. for $C_{21}H_{16}N_2Cl_2$: C, 68.68; H, 4.39; N, 7.63 %

Found: C, 68.56; H, 4.45; N, 7.58 %

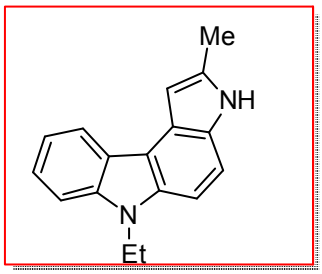
General procedure C

To a stirred solution of 9-ethyl-3-aminocarbazole **192a** (1 equiv.) and propargyl alcohol **193a** (1.5 equiv.) in toluene (20 mL), added zinc triflate (10 mol %) and stirred the reaction mixture at 110 °C for 4 h. After completion of the reaction, as indicated by TLC, reaction mixture was filtered through short celite bed, after the solvent was evaporated, the organic layer extracted with dichloromethane (3 x 10 mL) and washed with water, dried over anhydrous Na_2SO_4 and evaporated to furnish crude product, which was separated by

neutral alumina column chromatography eluting with a hexanes-ethyl acetate (95/5, v/v) mixture. The solvent was evaporated to dryness to get the pure product **194a**. The same procedure was followed for the preparation of other products (**194b-n**).

6-Ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194a)

The product **194a** was obtained as Pale white color solid from **192a** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.



Yield: 75 %

Mp: 42 °C

IR (KBr) ν_{max} cm^{-1}: 3402, 2974, 2916, 1728, 1662, 1595, 1481, 14229, 1329, 1228, 1018, 781, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, 1H, *J* = 7.6 Hz), 8.02 (s, 1H), 7.49-7.41 (m, 3H), 7.30-7.28 (m, 1H), 7.23-7.21 (m, 1H), 6.80 (s, 1H), 4.44 (q, 2H, *J* = 7.2 Hz), 2.57 (s, 3H), 1.45 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 135.1, 135.0, 130.5, 123.7, 123.2, 122.6, 121.3, 118.1, 113.2, 109.1, 108.1, 102.8, 99.2, 37.7, 14.06, 14.01

LC-MS (m/z): 249 $(M+H)^+$, positive mode

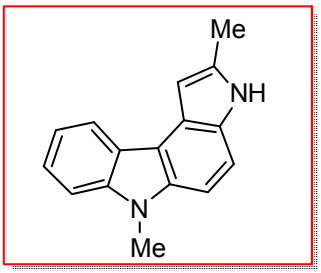
Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28 %

Found: C, 82.36; H, 6.55; N, 11.15 %

2,6-Dimethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194b)

The product **194b** was obtained as Brown color semi solid from **192b** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.

Yield: 70%



IR (KBr) ν_{max} cm^{-1}: 3449, 2924, 1626, 1547, 1448, 1271, 852, 817, 750, 626, 432

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, 1H, J = 7.6 Hz), 8.06 (s, 1H), 7.44-7.41 (m, 3H), 7.28-7.26 (m, 1H), 7.20-7.18 (m, 1H), 6.78 (s, 1H), 3.90 (s, 3H), 2.56 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 136.1, 135.2, 130.5, 123.7, 123.0, 122.4, 121.1, 118.2, 113.0, 109.1, 108.1, 102.7, 99.1, 29.4, 14.0

LC-MS (m/z): 235 $(M+H)^+$, positive mode

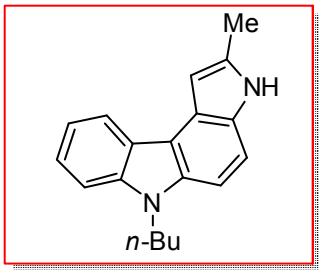
Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96 %

Found: C, 81.92 H, 6.12; N, 11.78 %

6-Butyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194c)

The product **194c** was obtained as Pale red color semisolid from **192c** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure C.

Yield: 72 %



IR (KBr) ν_{max} cm^{-1}: 3398, 3051, 2957, 2930, 2872, 1593, 1547, 1477, 1429, 1367, 1329, 1284, 102, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, 1H, J = 7.6 Hz), 8.00 (s, 1H), 7.42-7.36 (m, 3H), 7.24-7.23 (m, 1H), 7.19-7.17 (m, 1H), 6.77(s, 1H), 4.34 (t, 2H, J = 7.2 Hz), 2.52 (s, 3H), 1.87-1.83 (m, 2H), 1.41-1.36 (m, 2H), 0.92 (t, 3H, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 135.5, 135.2, 130.4, 123.7, 123.1, 122.5, 121.2, 118.1, 113.0, 109.0, 108.4, 103.0, 99.1, 43.0, 31.4, 20.6, 14.0, 13.9

LC-MS (m/z): 277 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14 %

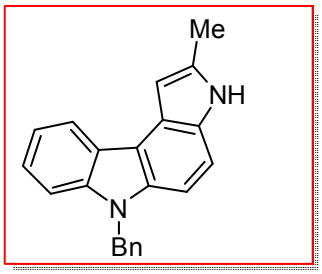
Found: C, 82.45; H, 7.23; N, 10.25 %

6-Benzyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194d)

The product **194d** was obtained as pale red color solid from **192d** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.

Yield: 79 %

Mp: 82 °C



IR (KBr) ν_{max} cm^{-1}: 3393, 2924, 2854, 1712, 1599, 1427, 1361, 1259, 1159, 1024, 736

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, J = 7.6 Hz), 8.05 (s, 1H), 7.39-7.37 (m, 2H), 7.35 (d, 1H, J = 8.4 Hz), 7.27-7.18 (m, 4H), 7.13-7.10 (m, 3H), 6.81 (s, 1H), 5.57 (s, 2H), 2.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 137.8, 135.7, 135.4, 130.7, 128.6, 127.2, 126.3, 124.0, 123.3, 122.5, 121.2, 118.6, 113.3, 109.3, 108.6, 103.2, 99.1, 46.7, 14.0

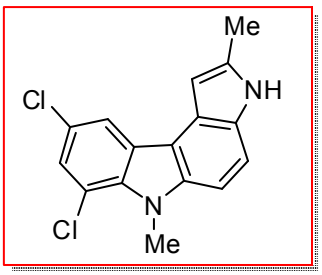
LC-MS (m/z): 311 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03

Found: C, 84.91; H, 5.79; N, 9.12 %

7,9-Dichloro-2,6-dimethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194e)

The product **194e** was obtained as colorless solid from **192e** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure C.



Yield: 74 %

Mp: 184 °C

IR (KBr) ν_{max} cm^{-1}: 3449, 2924, 1626, 1547, 1448, 1271, 852, 817, 750, 626, 432

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.01 (d, 1H, *J* = 1.6 Hz), 7.44 (d, 1H, *J* = 8.4 Hz), 7.31 (d, 1H, *J* = 2.0 Hz), 7.13 (d, 1H, *J* = 8.8 Hz), 6.69 (s, 1H), 4.21 (s, 3H), 2.55 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 135.9, 133.8, 130.7, 126.6, 125.0, 123.3, 121.9, 119.2, 115.9, 112.0, 110.7, 102.9, 99.0, 32.2, 14.0

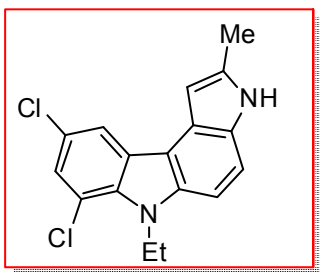
LC-MS (m/z): 301 $(M-H)^-$, 303 $(M+2H)^-$ negative mode

Anal. Calcd. for $C_{16}H_{12}N_2Cl_2$: C, 63.38; H, 3.99; N, 9.24 %

Found: C, 63.45; H, 3.91; N, 9.15 %

7,9-Dichloro-6-ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194f)

The product **194f** was obtained as colorless solid from **192f** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 118 °C

IR (KBr) v_{max} cm^{-1}: 3406, 2976, 2930, 1620, 1599, 1548, 1462, 1373, 1300, 1280, 1195, 1105

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1H, *J* = 1.64 Hz), 7.93 (s, 1H), 7.35-7.33 (m, 1H), 7.32 (d, 1H, *J* = 1.68 Hz), 7.12 (d, 1H, *J* = 8.8 Hz), 6.65 (s, 1H), 4.72 (q, 2H, *J* = 6.8 Hz), 2.46 (s, 3H), 1.40 (t, 3H, *J* = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 135.9, 133.0, 130.7, 127.0, 125.0, 123.3, 122.0, 119.2, 115.2, 112.3, 110.8, 102.9, 99.0, 39.5, 15.8, 13.9

LC-MS (m/z): 317 $(M+H)^+$, 318 $(M+2H)^+$ positive mode

Anal. Calcd. for $C_{17}H_{14}N_2Cl_2$: C, 64.37; H, 4.45; N, 8.83 %

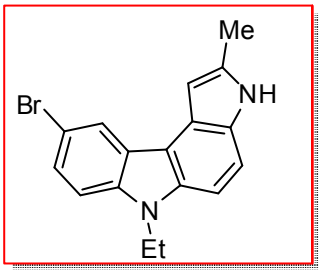
Found: C, 64.21; H, 4.51; N, 8.96 %

9-Bromo-6-ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194g)

The product **194g** was obtained as brown color semisolid from **192g** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.

Yield: 72 %

IR (KBr) v_{max} cm^{-1}: 3406, 2894, 1606, 1536, 1452, 1301, 858, 827, 750, 620



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 1H, *J* = 1.6 Hz), 8.08 (s, 1H), 7.49-7.47 (m, 1H), 7.45-7.42 (m, 1H), 7.31-7.29 (m, 1H), 7.18-7.16 (m, 1H), 6.74 (s, 1H), 4.39 (q, 2H, *J* = 7.2 Hz), 2.56 (s, 3H), 1.41 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 135.58, 135.52, 130.5, 126.3, 124.9, 123.7, 122.4, 112.3, 110.9, 109.9, 109.5, 102.7, 99.1, 37.9, 13.9

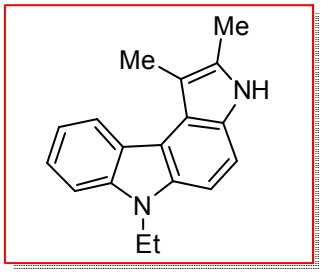
LC-MS (m/z): 325 $(M-H)^-$, 327 $(M+2H)^-$ negative mode

Anal. Calcd. for $C_{17}H_{15}N_2Br$: C, 62.40; H, 4.62; N, 8.56 %

Found: C, 62.21; H, 4.71; N, 8.45 %

6-Ethyl-1,2-dimethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194h)

The product **194h** was obtained as brown color semisolid from **192a** through from column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure C.



Yield: 70 %

IR (KBr) ν_{max} cm^{-1}: 3362, 3065, 2968, 2928, 1732, 1682, 1541, 1469, 1325, 1226, 804, 746

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.85-7.82 (m, 2H), 7.49 (d, 1H, J = 8.0 Hz), 7.44-7.40 (m, 2H), 7.23-7.22 (m, 1H), 4.35 (q, 2H, J = 7.2 Hz), 2.75 (s, 3H), 2.18 (s, 3H), 1.41 (t, 3H, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.3, 169.4, 140.5, 137.6, 128.6, 126.3, 125.0, 123.1, 122.3, 120.8, 119.3, 118.2, 110.6, 109.0, 37.6, 31.8, 24.1, 13.8

LC-MS (m/z): 263 $(M+H)^+$, positive mode

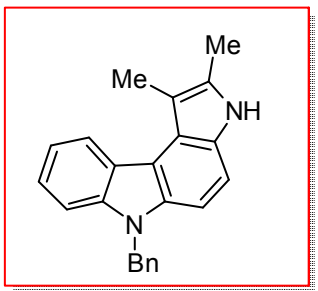
Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68 %

Found: C, 82.25; H, 6.98; N, 10.58 %

6-Benzyl-1,2-dimethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194i)

The product **194** was obtained as brown color semisolid from **192d** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.

Yield: 65 %



IR (KBr) ν_{max} cm^{-1}: 3398, 2918, 1636, 1607, 1438, 1263, 848, 817, 755, 626, 434

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1H, J = 7.6 Hz), 7.95 (s, 1H), 7.68 (s, 1H), 7.38-7.33 (m, 2H), 7.26-7.27 (m, 1H), 7.43-7.16 (m, 6H), 5.55 (s, 2H), 2.42 (s, 3H), 2.25 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 132.5, 131.4, 129.9, 129.2, 128.9, 128.8, 128.6, 127.1, 126.4, 126.3, 124.8, 123.6, 119.5, 118.0, 108.1, 100.4, 95.5, 46.6, 11.9, 8.7

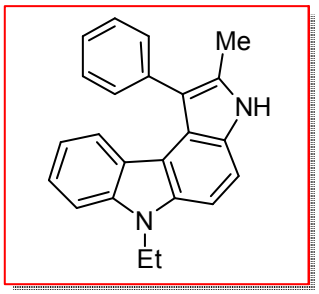
LC-MS (m/z): 325 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63 %

Found: C, 85.02; H, 6.28; N, 8.56 %

6-Ethyl-2-methyl-1-phenyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194j)

The product **194j** was obtained as brown color semisolid from **192a** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure C.



Yield: 78 %

IR (KBr) ν_{max} cm^{-1}: 3456, 2992, 1613, 1587, 1458, 1280, 842, 813, 750, 686, 430

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 8.30 (d, 1H, J = 8.8 Hz), 7.97-7.95 (m, 2H), 7.90-7.88 (m, 1H), 7.58-7.47 (m, 6H), 7.24-7.22 (m, 1H), 4.42 (q, 2H, J = 7.2 Hz), 2.80 (s, 3H), 1.46 (t, 3H, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 165.9, 140.9, 137.4, 134.4, 131.9, 128.8, 127.2, 126.9, 126.3, 126.1, 122.7, 122.1, 120.9, 119.3, 118.7, 111.3, 109.1, 37.7, 31.9, 13.8

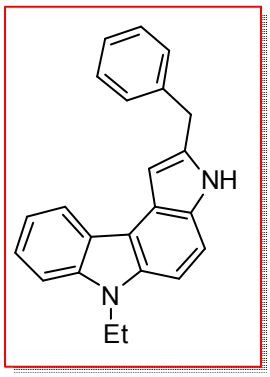
LC-MS (m/z): 325 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63 %

Found: C, 85.26; H, 6.51; N, 8.81 %

2-Benzyl-6-ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194k)

The product **194k** was obtained as yellow color solid from **192a** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.



Yield: 82 %

Mp: 132 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3402, 2974, 1604, m1483, 1431, 1381, 1332, 1230, 1151, 814, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, *J* = 7.6 Hz), 7.92 (s, 1H), 7.43-7.42 (m, 2H), 7.35-7.22 (m, 7H), 7.20-7.18 (m, 1H), 6.88 (s, 1H), 4.40 (q, 2H, *J* = 7.2 Hz), 4.23 (s, 2H), 1.41 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 138.8, 137.9, 135.0, 130.8, 128.9, 128.7, 126.7, 123.8, 123.2, 122.2, 121.3, 118.2, 113.3, 109.3, 108.2, 103.3, 99.8, 37.7, 34.9, 14.0

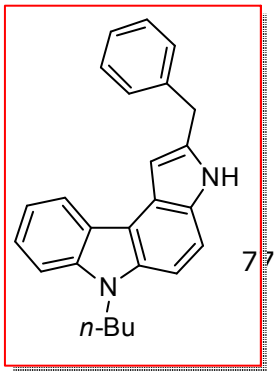
LC-MS (m/z): 325 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63 %

Found: C, 85.26; H, 6.15; N, 8.71 %

2-Benzyl-6-butyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194l)

The product **194l** was obtained as brown color semisolid from **192c** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure C.



Yield: 74 %

IR (KBr) v_{max} cm^{-1}: 3359, 2834, 1665, 1568, 1452, 1295, 859, 827, 762, 626, 458

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1H, *J* = 7.6 Hz), 7.87 (s, 1H), 7.37-7.33 (3H, m), 7.27-7.21 (m, 4H), 7.16-7.11 (3H, m), 6.81 (s, 1H), 4.27 (t, 2H, *J* = 7.2 Hz), 4.17 (s, 2H), 1.78 (pent, 2H, *J* = 7.2 Hz), 1.34-1.28 (m, 2H), 0.84 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.8, 137.9, 135.5, 130.7, 128.9, 128.7, 128.5, 128.3, 126.7, 123.7, 122.2, 121.2, 118.1, 109.2, 108.4, 103.5, 99.8, 43.0, 35.0, 31.4, 20.5, 13.9

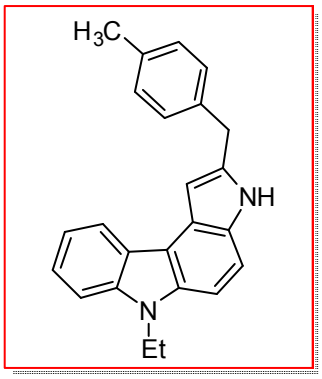
LC-MS (m/z): 353 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95 %

Found: C, 85.21; H, 6.83; N, 7.76 %

6-Ethyl-2-(4-methylbenzyl)-3,6-dihydropyrrolo[2,3-*c*]carbazole (194m)

The product **194m** was obtained as brown color semisolid from **192a** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 71 %

IR (KBr) v_{max} cm^{-1}: 3400, 3294, 2974, 2924, 2858, 1666, 1606, 1514, 1479, 1433, 1020, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, 1H, *J* = 8.0 Hz), 7.88 (s, 1H), 7.41 (d, 2H, *J* = 4 Hz), 7.28-7.24 (m, 2H), 7.16-7.09 (m, 5H), 6.84 (s, 1H), 4.36 (q, 2H, *J* = 7.2 Hz), 4.12 (s, 2H), 2.31 (s, 3H), 1.37 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 138.3, 136.2, 135.8, 135.0, 130.8, 129.4, 128.8, 123.8, 123.2, 122.3, 121.4, 118.2, 113.3, 109.4, 108.2, 103.2, 99.6, 37.7, 34.5, 21.1, 14.1

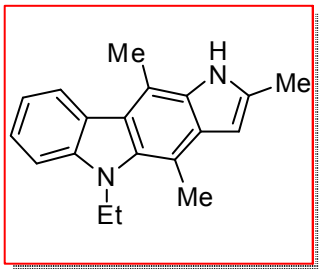
LC-MS (m/z): 339 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28 %

Found: C, 85.31; H, 6.45; N, 8.21 %

5-Ethyl-2,4,10-trimethyl-1,5-dihydropyrrolo[3,2-b]carbazole (194n)

The product **194n** was obtained as Brown color semisolid from **192h** through column chromatography using a mixture of 45% ethyl acetate and hexanes as described in procedure C.



Yield: 67 %

IR (KBr) v_{max} cm^{-1}: 3408, 2974, 1660, 1553, 1452, 1280, 858, 821, 758, 632, 435

^{1}H NMR (400 MHz, $CDCl_3$): δ 8 04 (s, 1H), 7.43-7.41 (m, 1H), 7.25-7.23 (m, 1H), 7.06 (s, 1H), 7.03 (d, 1H, *J* = 7.2 Hz), 6.88-6.86 (m, 1H), 4.68 (q, 2H, *J* = 7.08 Hz), 3.21 (s, 3H), 2.84 (s, 3H), 2.53 (s, 3H), 1.43 (t, 3H, *J* = 7.12 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 136.0, 133.5, 131.4, 129.8, 127.5, 123.8, 122.5, 120.4, 117.1, 114.5, 109.4, 103.3, 102.7, 39.4, 24.7, 20.7, 15.6, 13.8

LC-MS (m/z): 277 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14 %

Found: C, 82.68; H, 7.21; N, 10.21 %

1.7 References:

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97. (a) Stover, J.-S.; Shi, J.; Jin, W.; Vogt, P.-K.; Boger, D.-L. *J. Am. Chem. Soc.* **2009**, *131*, 3342–3348. (b) Mudadu, M. S.; Singh, A. S.; Thummel, R. P. *J. Org. Chem.* **2008**, *73*, 6513–6520. (c) Chabane, H.; Lamazzi, C.; Thiéry, V.; Guillaumet, G.; Besson, T. *Tetrahedron Lett*. **2002**, *43*, 2483–2486. (d) Estrada, L.-A.; Neckers, D.-C. *Org. Lett.* **2011**, 13, 3304–3307.
98. The CCDC deposition number for compound **190c** is 841557; molecular formula: $C_{15}H_{10}Cl_2N_2$. chemical formula weight is 289.15; monoclinic; unit cell parameters: a = 9.274(2) Å, b = 5.6445(9) Å, c = 24.572(4) Å, α. = 90°, β = 95.794(17)°, γ = 90°. space group P21/n.
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101. The CCDC deposition number for compound **194f** is 893524; molecular formula: $C_{17}H_{17}N_2Cl_2$. Chemical formula weight is 317.21; orthorhombic; unit cell parameters: a = 6.0170 (5) Å, b = 8.9910 (8) Å, c = 27.632 (3) Å, Space group P212121. The CCDC deposition number for compound **194k** is 893523; molecular formula: $C_{23}H_{20}N_2$. Chemical formula weight is 324.16; orthorhombic; unit cell parameters: a = 15.7399 (15) Å, b = 8.8045 (8) Å, c = 24.485 (2) Å, Space group Pbca.

Table 7. Crystal data and structure refinement for 190c

Empirical formula	: $C_{15}H_{10}Cl_2N_2$	
Formula weight	: 289.15	
Temperature	: 298 K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P 21/n	
Unit cell dimensions	: a=9.274(2)	α = 90°
	: b = 5.6445(9)	β = 95.794(17)
	: c = 24.572(4)	γ = 90°
Volume	: 1279.7(4)A^3	
Z	: 4	
Density (calculated)	: 1.501Mg/m^3	
Absorption coefficient	: 0.492 mm^{-1}	
F(000)	: 592	
Crystal size	: 0.36 x 0.28 x 0.18mm^3	
Theta range for data collection	: 3.16 to 26.37 °.	
Index ranges	: -11<=h<=11, -7<=k<=5, -30<=l<=24	
Reflections collected / unique	:4809 / 2608 [R(int) = 0.0211]	
Completeness to theta = 24.71°	: 99.7 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9167 and 0.8428	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2608 / 0 / 173	
Goodness-of-fit on F^2	: 1.026	
Final R indices [I>2sigma(I)]	: R1 = 0.0424, wR2 = 0.1027	
R indices (all data)	: R1 = 0.0567, wR2 = 0.1135	
Largest diff. peak and hole	: 0.258 and -0.265 e.Å-3	

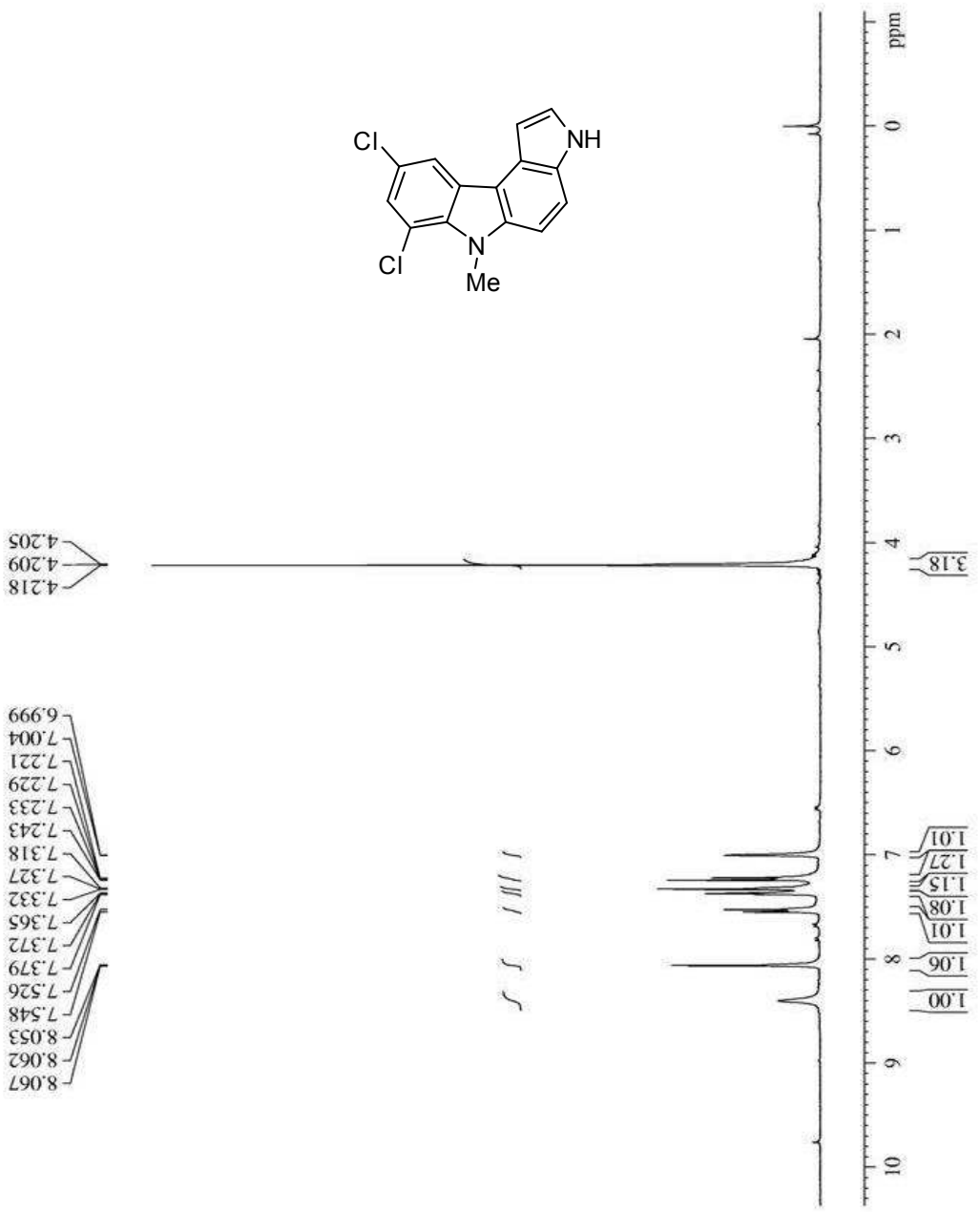
Table 8. Crystal data and structure refinement for 194f

Empirical formula	: $C_{17}H_{14}Cl_2N_2$	
Formula weight	: 317.20	
Temperature	: 298 K	
Wavelength	: 0.71073 Å	
Crystal system	: orthorhombic	
Space group	: P212121	
Unit cell dimensions	: a = 6.0170(5)	α = 90°
	: b = 8.9910(8)	β = 90°
	: c = 27.632(3)	γ = 90°
Volume	:1494.9(2)A^3	
Z	:24	
Density (calculated)	:1.409 Mg/m^3	
Absorption coefficient	: 0.428 mm^{-1}	
F(000)	:656	
Crystal size	: 0.22 x 0.18 x 0.16mm^3	
Theta range for data collection	: 1.47 to 24.99°.	
Index ranges	:-7<=h<=7, -10<=k<=10, -32<=l<=32	
Reflections collected / unique	: 14324 / 2632 [R(int) = 0.0296]	
Completeness to theta = 24.71°	:100.0 %	
Absorption correction	: empirical	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 2632 / 0 / 192	
Goodness-of-fit on F^2	: 1.219	
Final R indices [I>2sigma(I)]	: R1 = 0.0601, wR2 = 0.1599	
R indices (all data)	: R1 = 0.0621, wR2 = 0.1612	
Largest diff. peak and hole	: 0.351 and -0.391e.Å-3	

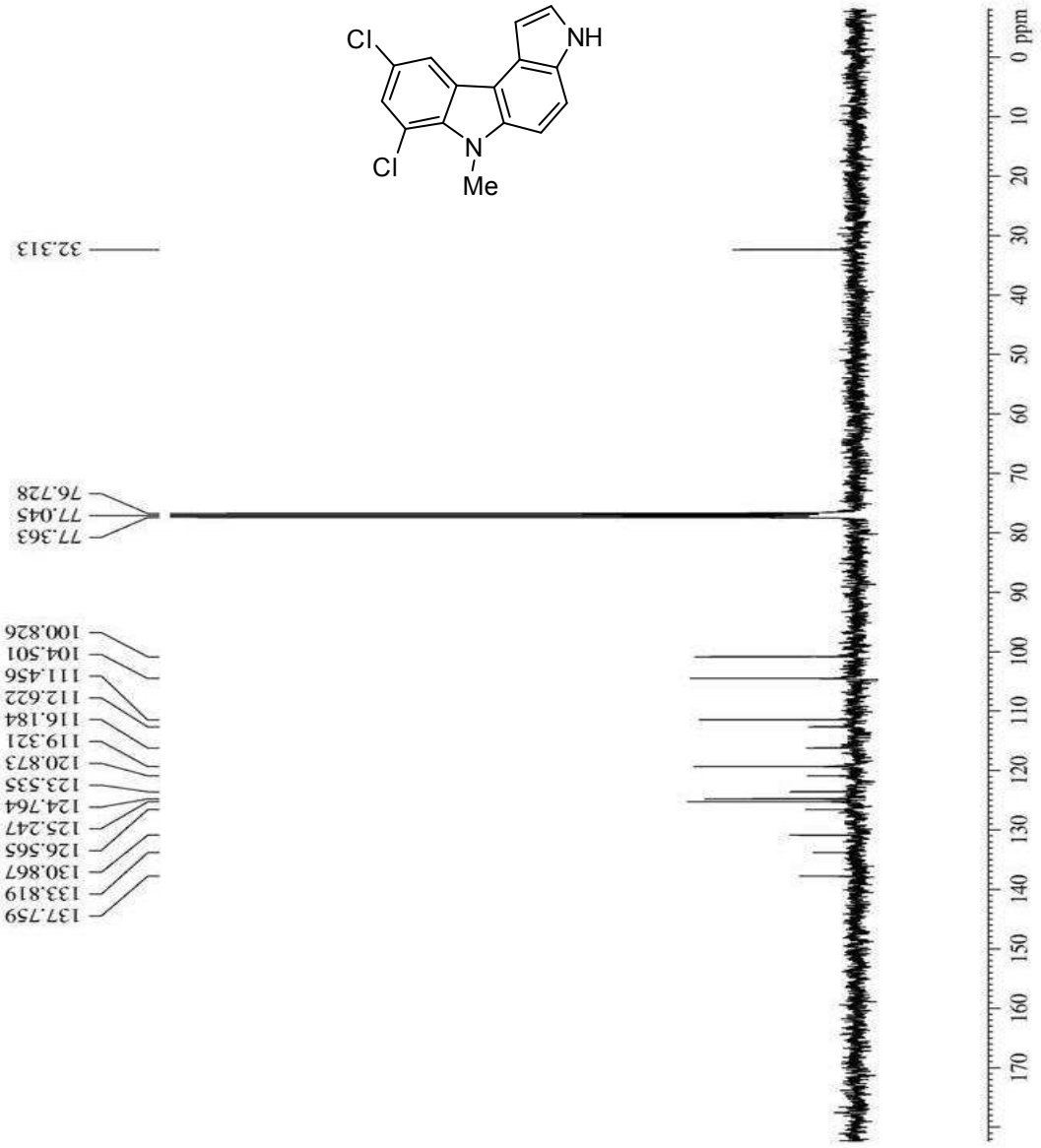
Table 9. Crystal data and structure refinement for 194k

Empirical formula	: $C_{23}H_{20}N_2$	
Formula weight	: 324.41	
Temperature	: 298 K	
Wavelength	: 0.71073 Å	
Crystal system	: orthorhombic	
Space group	: Pbca	
Unit cell dimensions	: a = 15.7399(15)	α = 90°
	: b = 8.8045(8)	β = 90°
	: c = 24.485(2)	γ = 90°
Volume	: 3393.2(6) A^3	
Z	: 100	
Density (calculated)	: 1.323 Mg/m^3	
Absorption coefficient	: 0.093 mm^{-1}	
F(000)	: 1400	
Crystal size	: 0.20 x 0.16x 0.10mm^3	
Theta range for data collection	: 1.66 to 25.98 °.	
Index ranges	:-19<=h<=19, -10<=k<=10, -30<=l<=30	
Reflections collected / unique	: 32906 / 3328 [R(int) = 0.0543]	
Completeness to theta = 24.71°	:100.0 %	
Absorption correction	: empirical	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 3328 / 0 / 227	
Goodness-of-fit on F^2	: 1.160	
Final R indices [I>2sigma(I)]	: R1 = 0.0596, wR2 = 0.1236	
R indices (all data)	: R1 = 0.0702, wR2 = 0.1288	
Largest diff. peak and hole	: 0.194 and -0.194.Å-3	

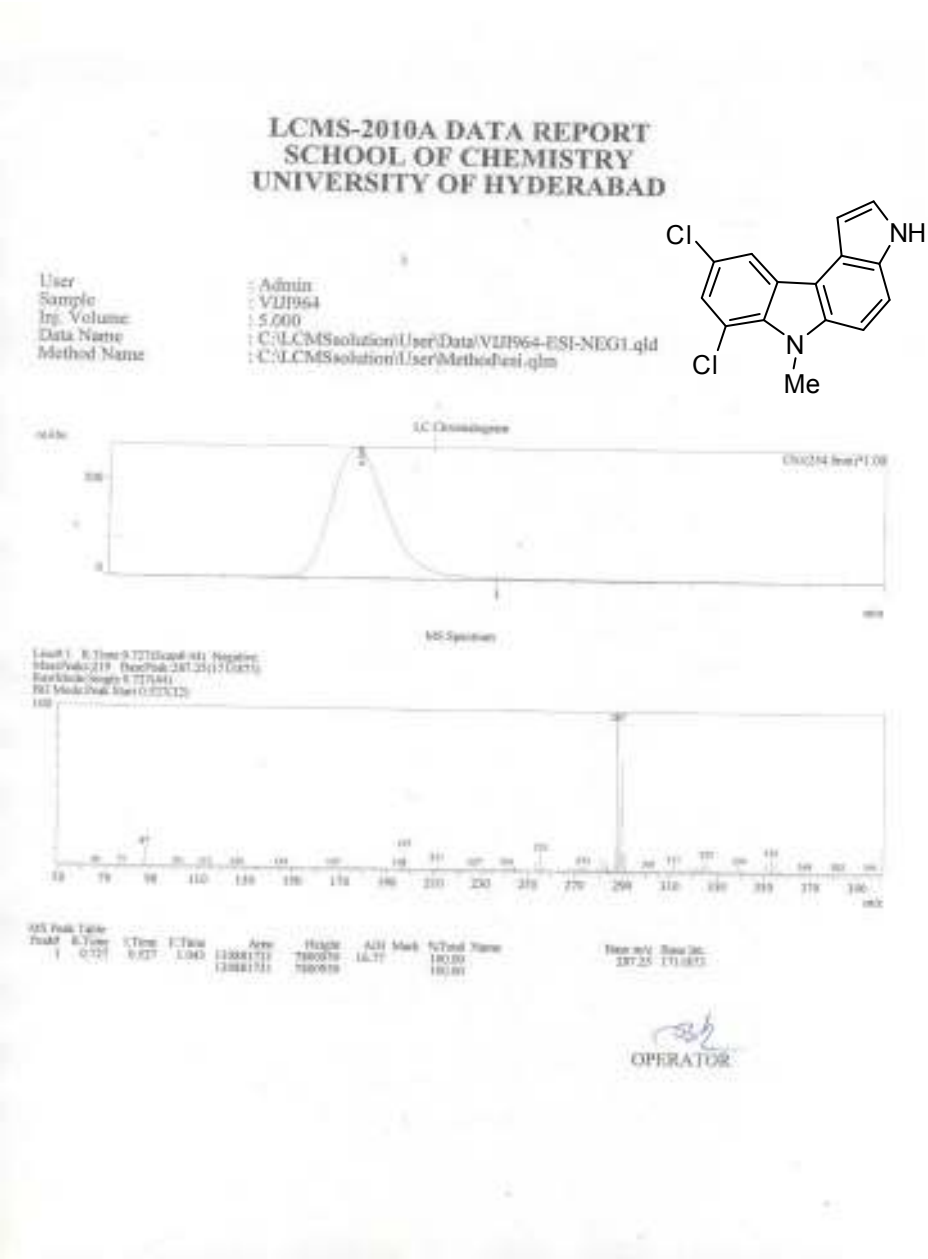
^{1}H NMR of 7,9-dichloro-6-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190c)



^{13}C NMR of 7,9-dichloro-6-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190c)



LC-MS of 7,9-dichloro-6-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190c)



Elemental analysis of 7,9-dichloro-6-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (190c)

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UNIVERSITY OF HYDERABAD

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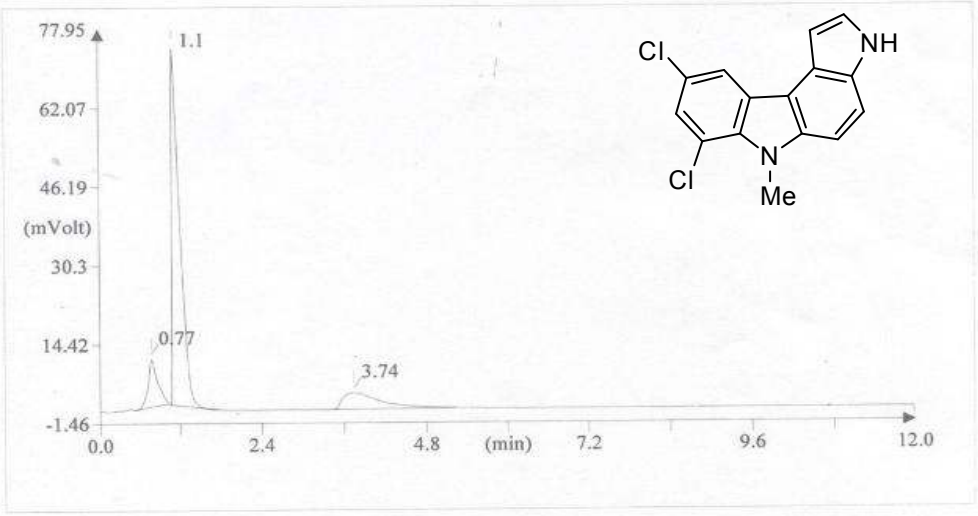
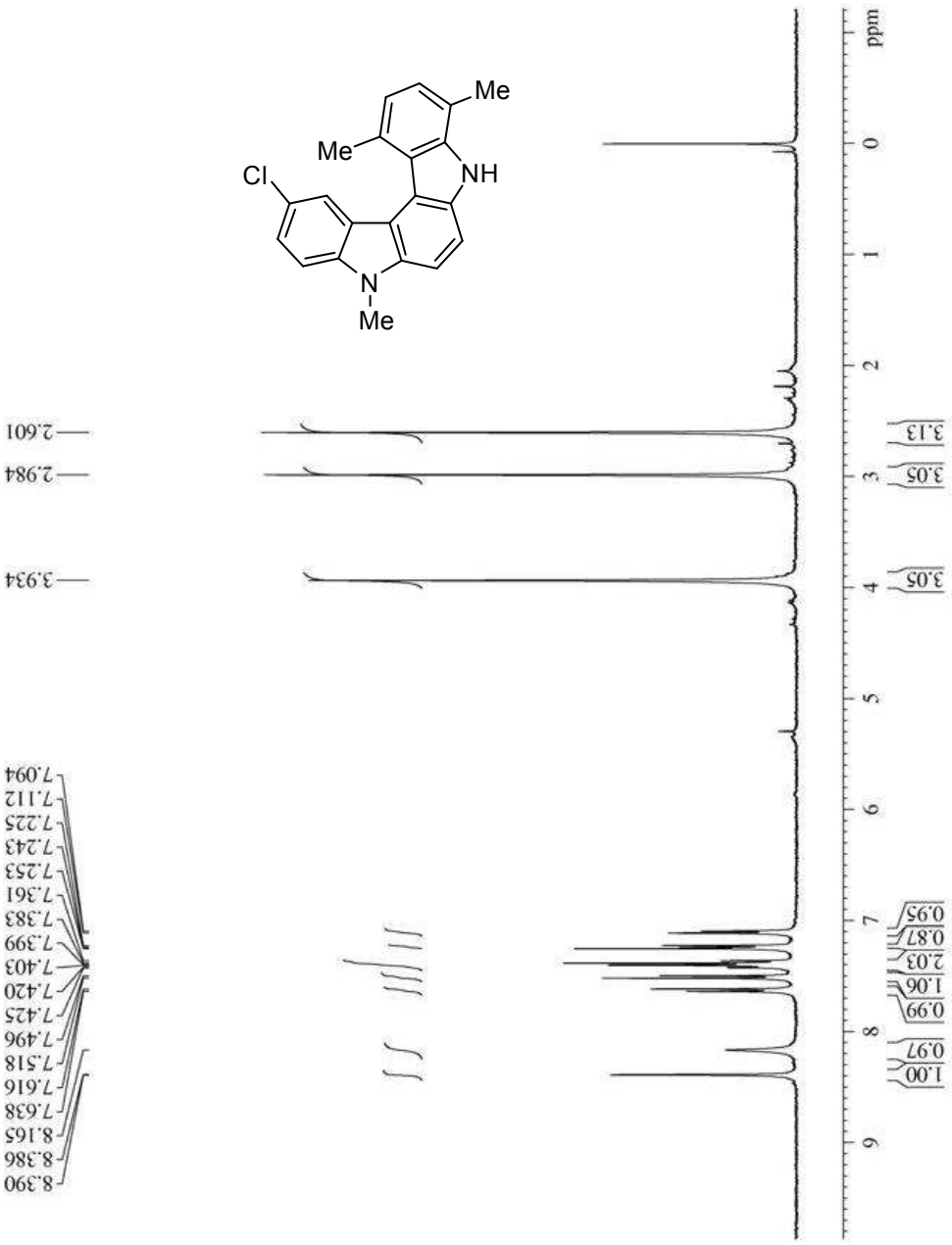
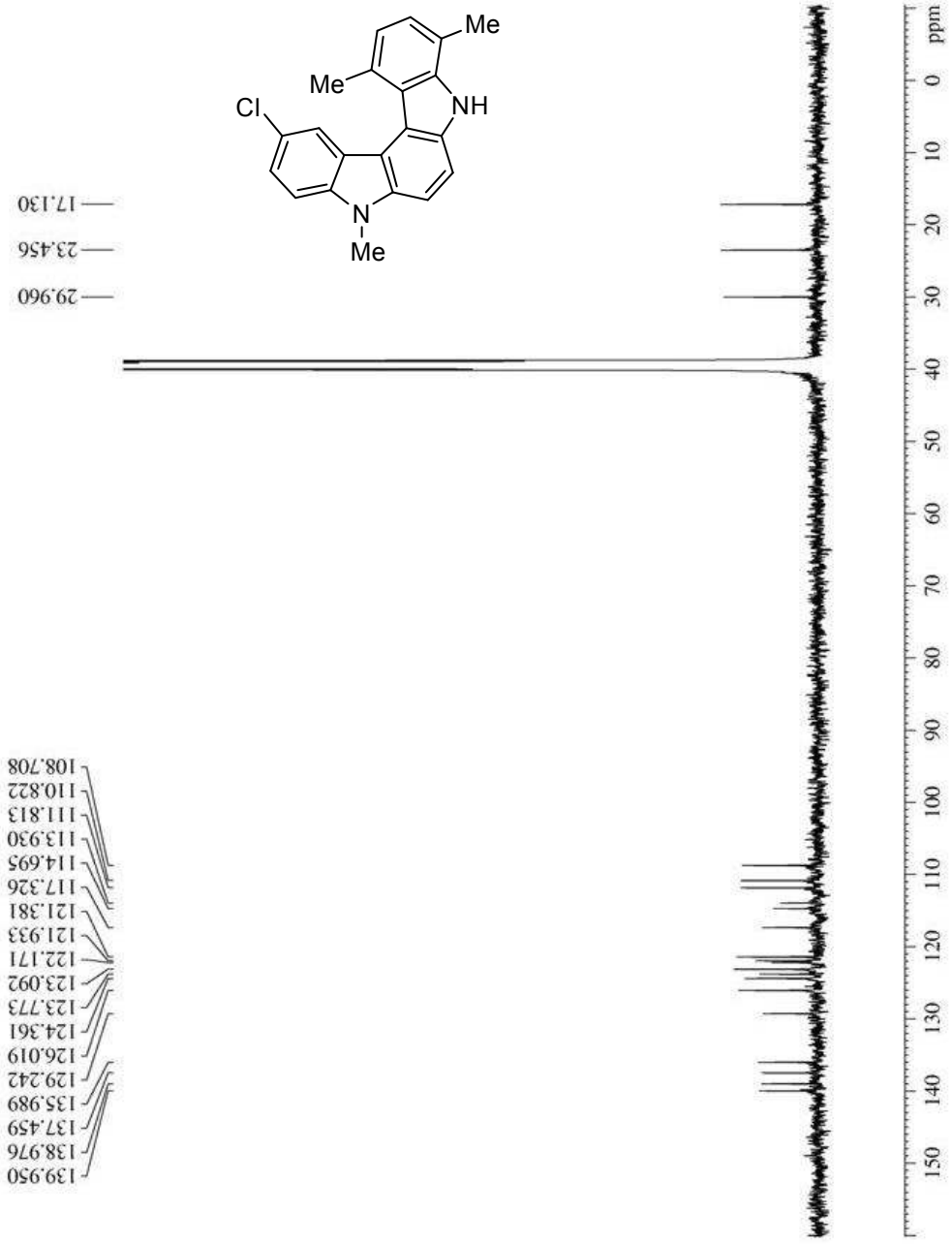


Element Name	Element %	Ret. Time
Nitrogen	8. 51	0. 77
Carbon	64. 76	1. 10
Hydrogen	5. 38	3. 74

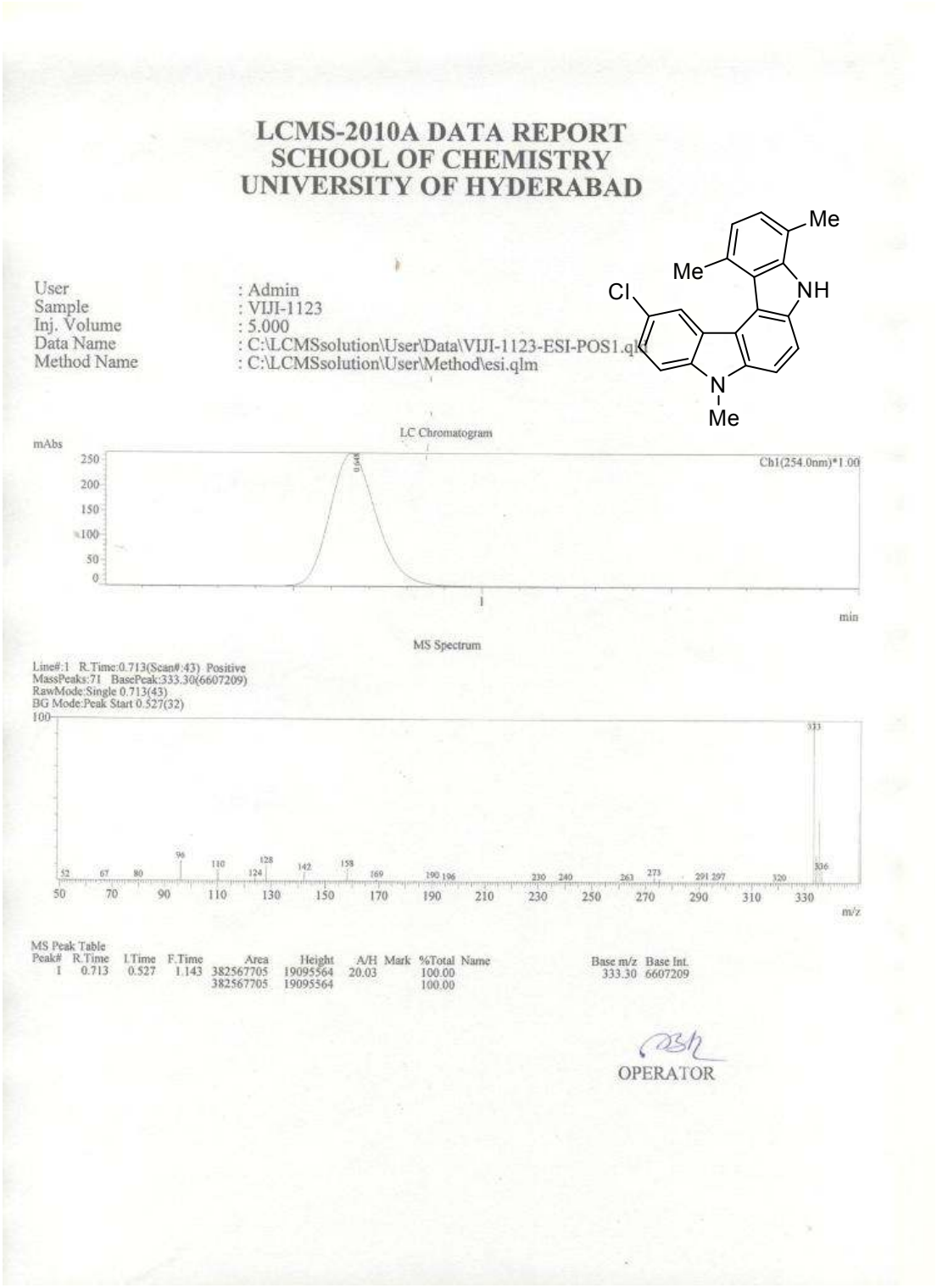
[1]H NMR of 11-chloro-1,4,8-trimethyl-5,8-dihydroindolo[2,3-*c*]carbazole (191b)



^{13}C NMR of 11-chloro-1,4,8-trimethyl-5,8-dihydroindolo[2,3-*c*]carbazole (191b)



LC-MS of 11-chloro-1,4,8-trimethyl-5,8-dihydroindolo[2,3-*c*]carbazole (191b)



LCMS-2010A DATA REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

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Inj. Volume : 5.000
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Method Name : C:\LCMSsolution\User\Method\esi.qlm

LC Chromatogram

MS Spectrum

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RawMode:Single 0.713(43)
BG Mode:Peak Start 0.527(32)

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				382567705	19095564			100.00			

OPERATOR

Elemental analysis of 11-chloro-1,4,8-trimethyl-5,8-dihydroindolo[2,3-*c*]carbazole (191b)

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Method filename:	C:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
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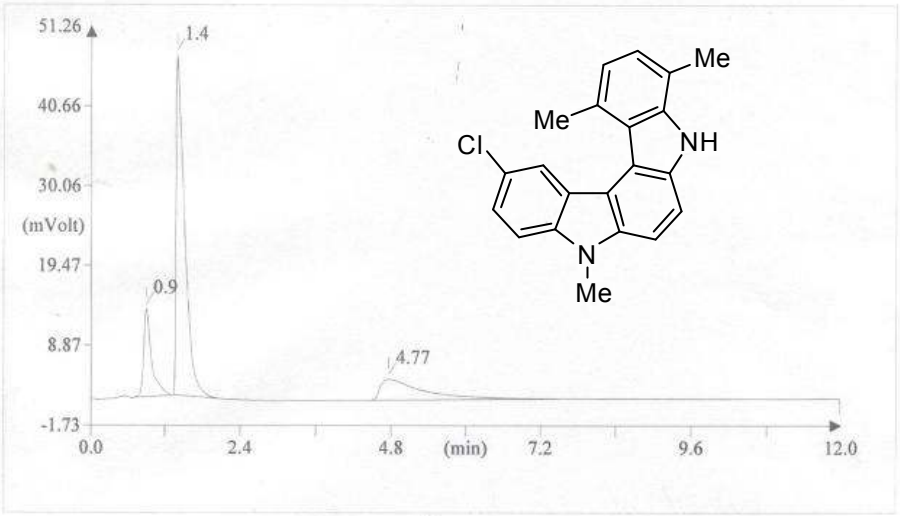
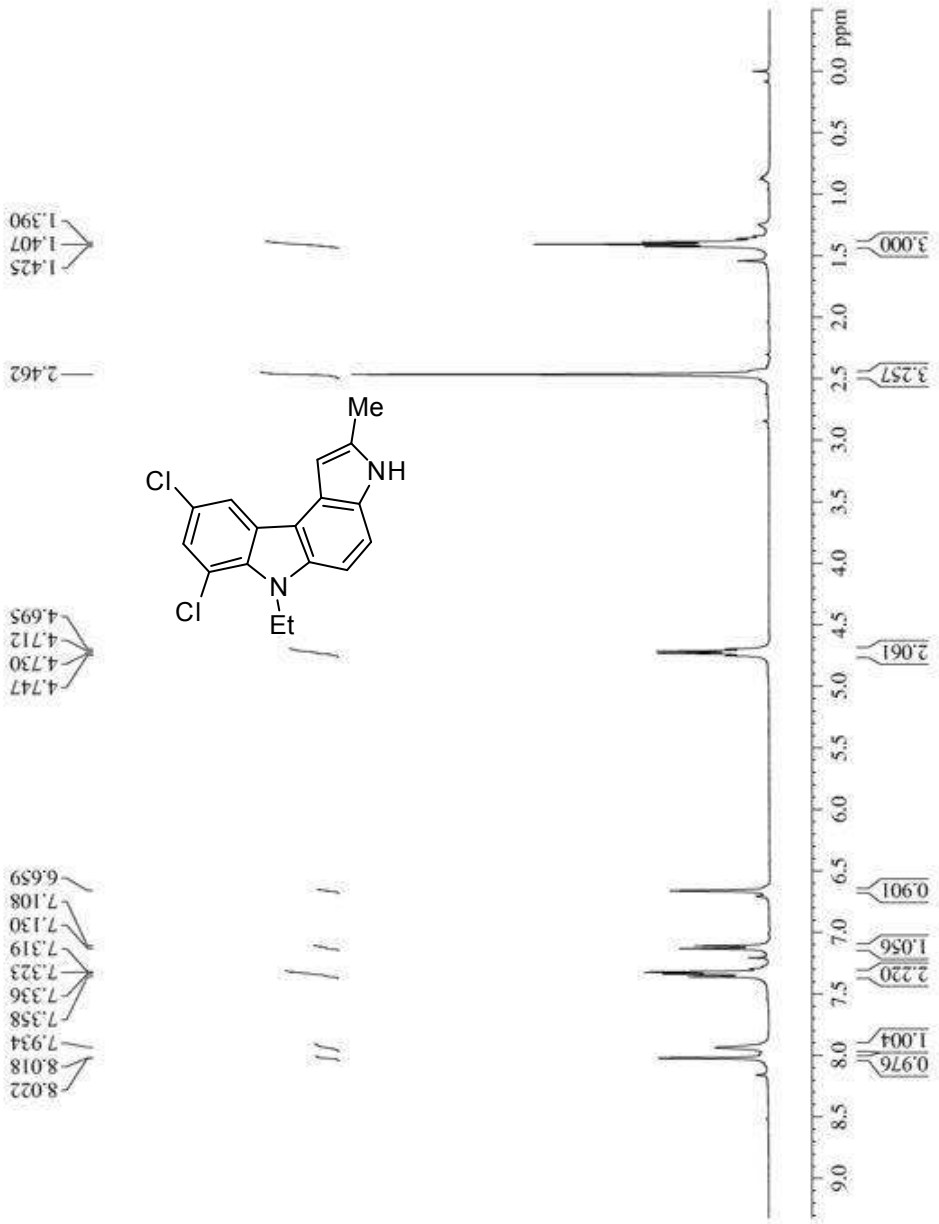
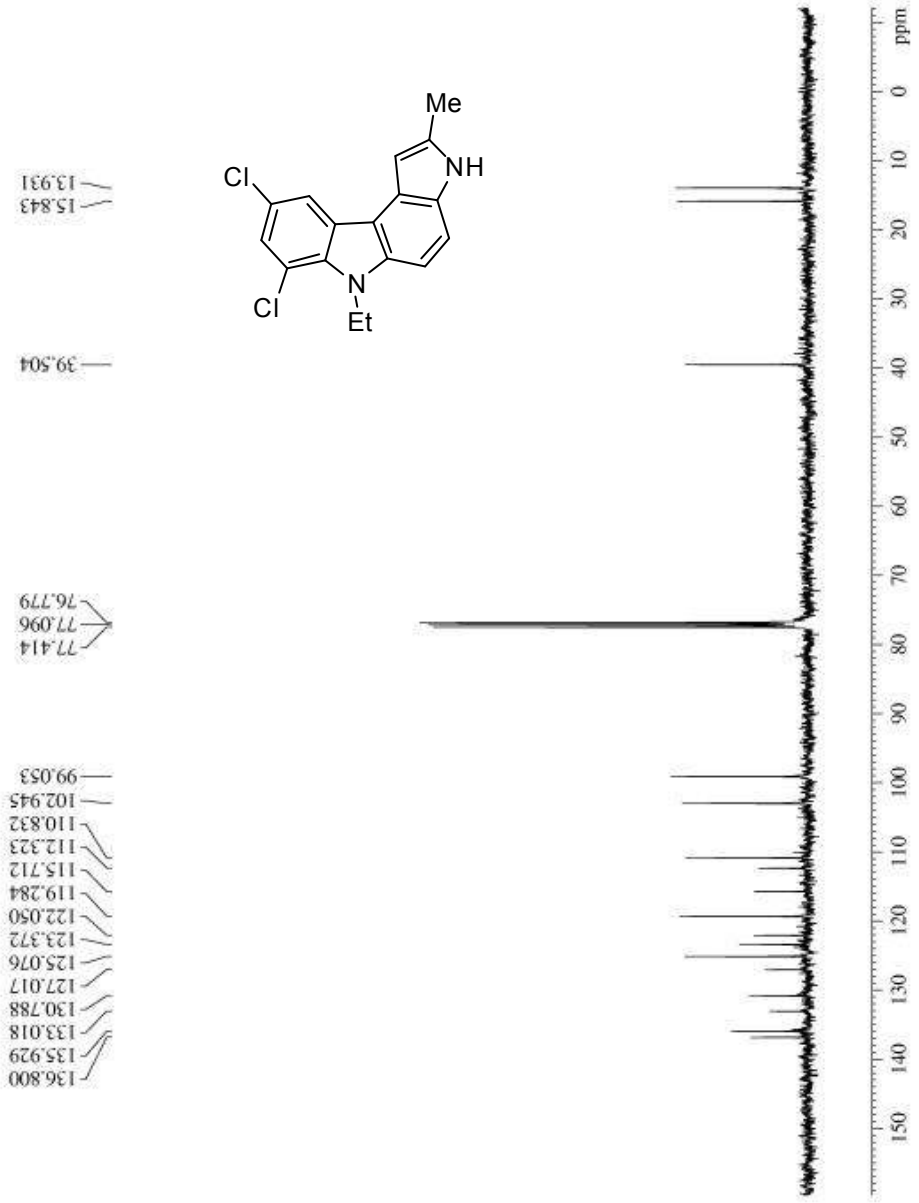


Element Name	Element %	Ret. Time
Nitrogen	8. 37	0. 90
Carbon	75. 86	1. 40
Hydrogen	5. 09	4. 77

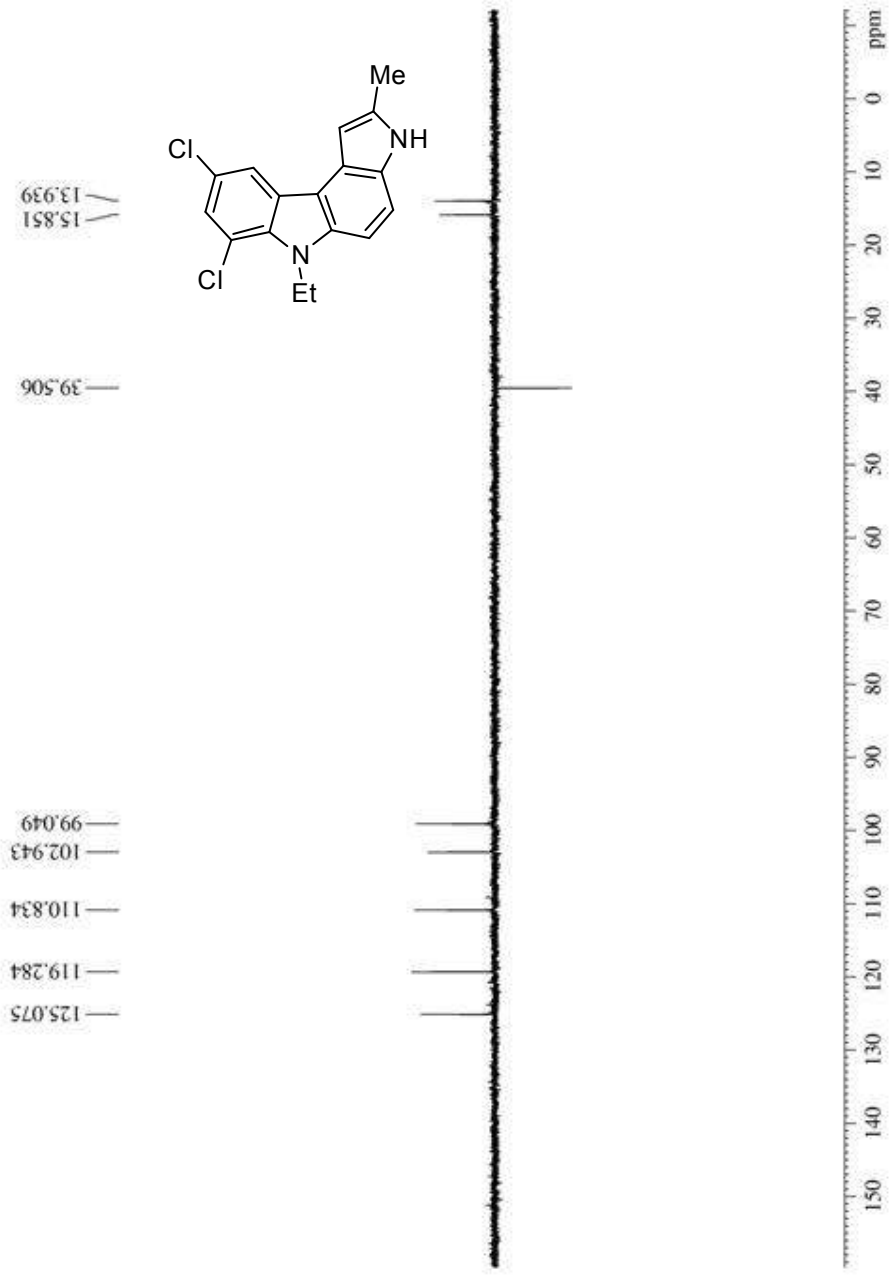
^{1}H NMR of 7,9-Dichloro-6-ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194f)



^{13}C NMR of 7,9-Dichloro-6-ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194f)



DEPT of 7,9-Dichloro-6-ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194f)



LC-MS of 7,9-Dichloro-6-ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194f)

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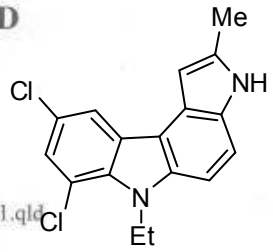

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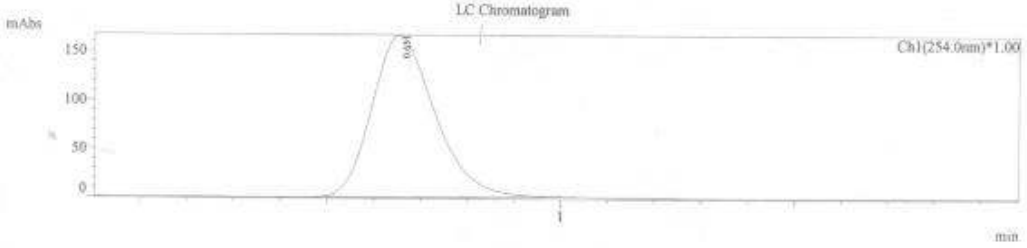

MS Spectrum

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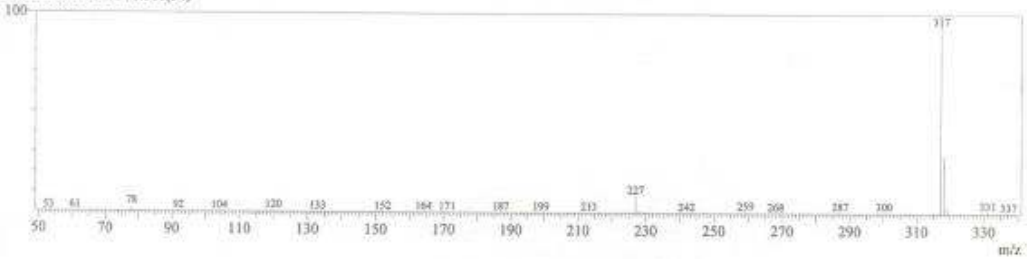
BG Mode:Peak Start 0.560(34)



MS Peak Table

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				147118259	12972574			100.00			

OPERATOR

Elemental analysis of 7,9-Dichloro-6-ethyl-2-methyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194f)

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Method filename:	E:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
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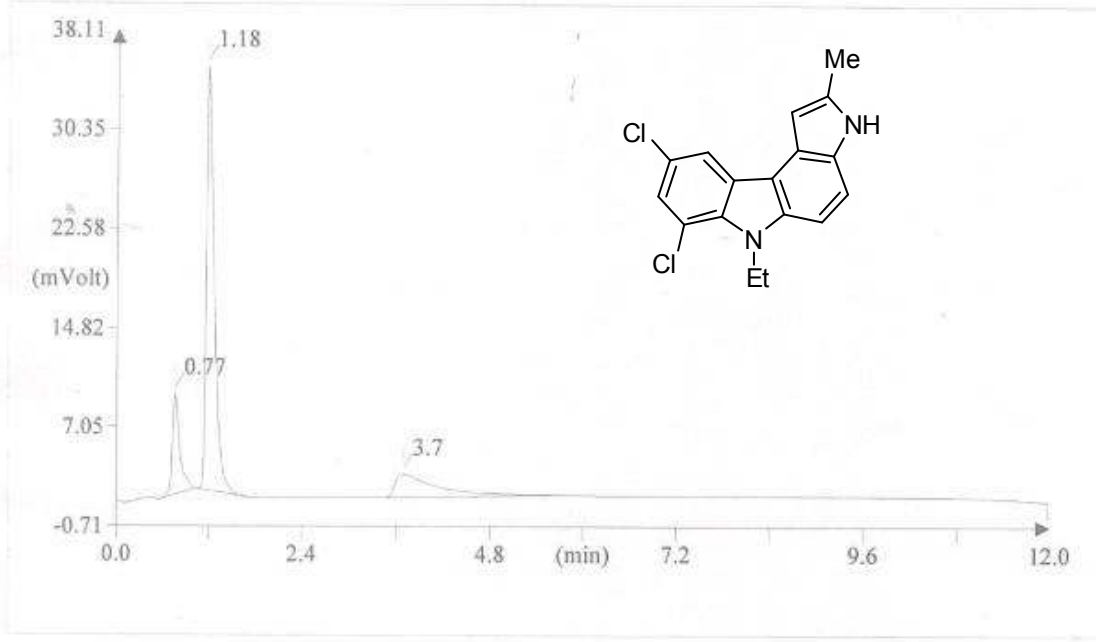
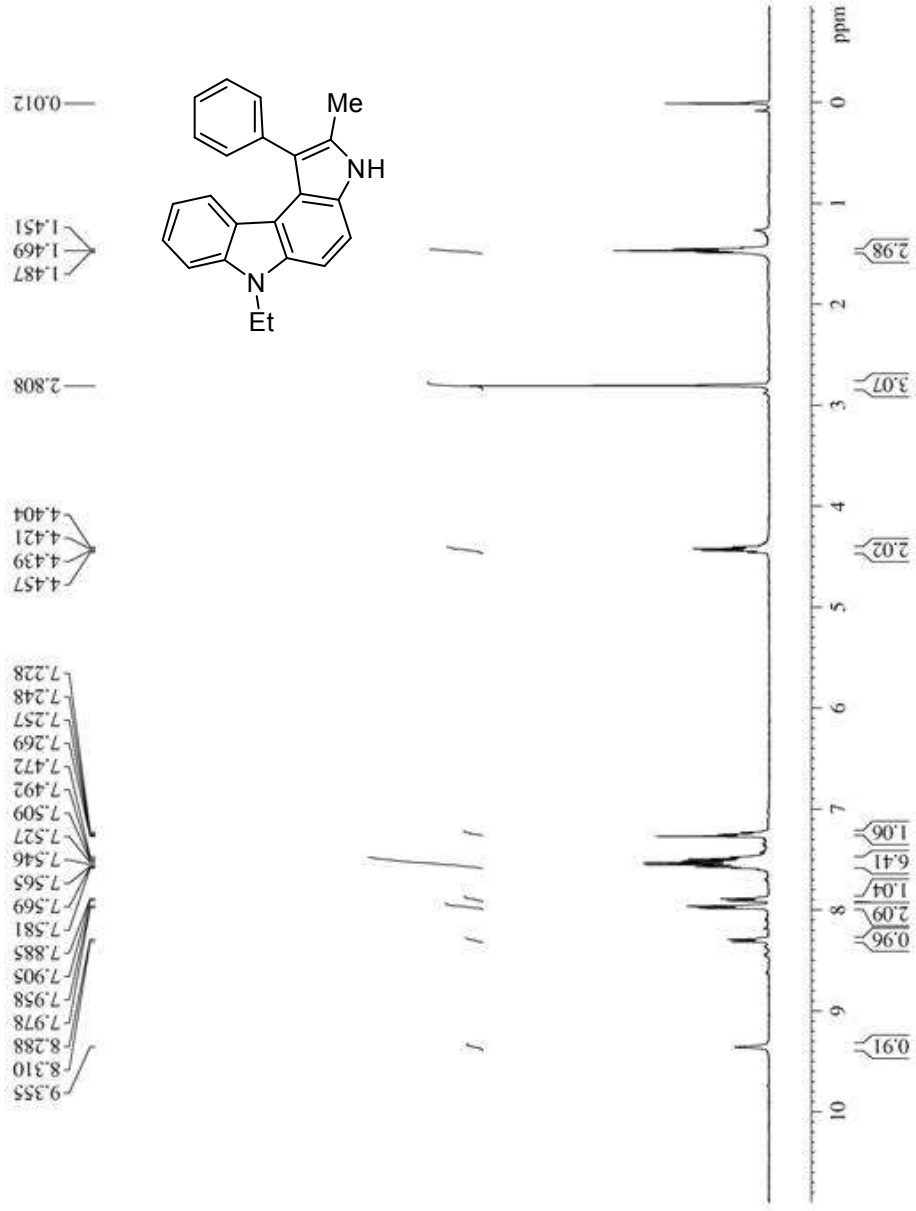
Sample weight:	1.127

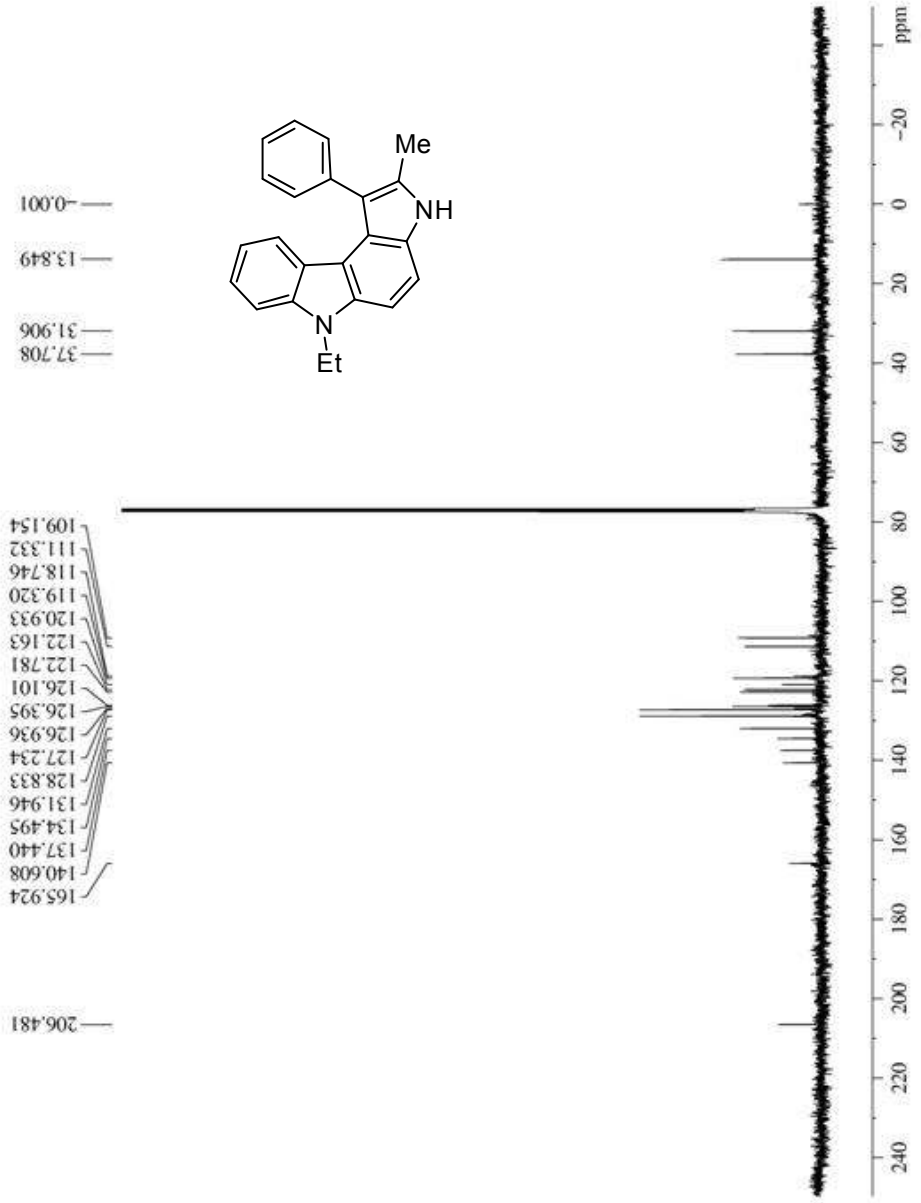


Element Name	Element %	Ret. Time
Nitrogen	8. 96	0. 77
Carbon	64. 21	1. 18
Hydrogen	4. 51	3. 70

^{1}H NMR of 6-Ethyl-2-methyl-1-phenyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194j)



^{13}C NMR of 6-Ethyl-2-methyl-1-phenyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194j)



LC-MS of 6-Ethyl-2-methyl-1-phenyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194j)

LCMS-2010A DATA REPORT
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Inj. Volume : 5.000
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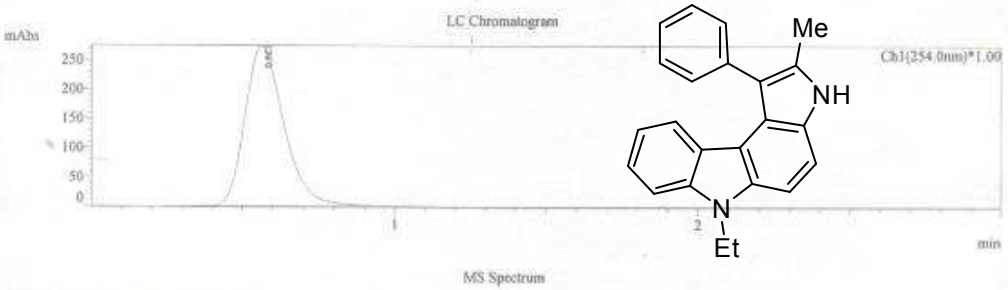

MS Spectrum

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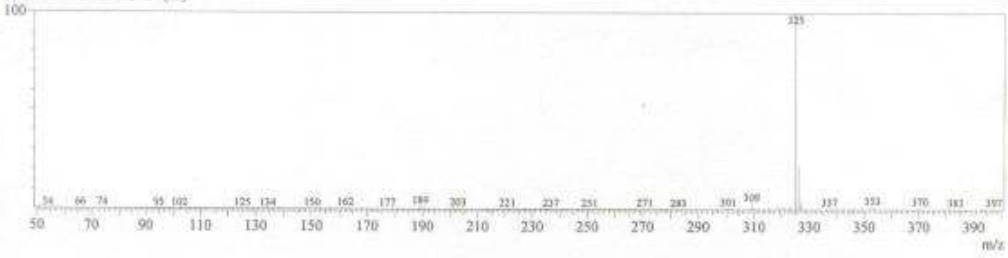
MassPeaks:183 BasePeak:325.00(823915)
RawMode:Single 0.644(39)
BG Mode:Peak Start 0.477(29)



MS Peak Table

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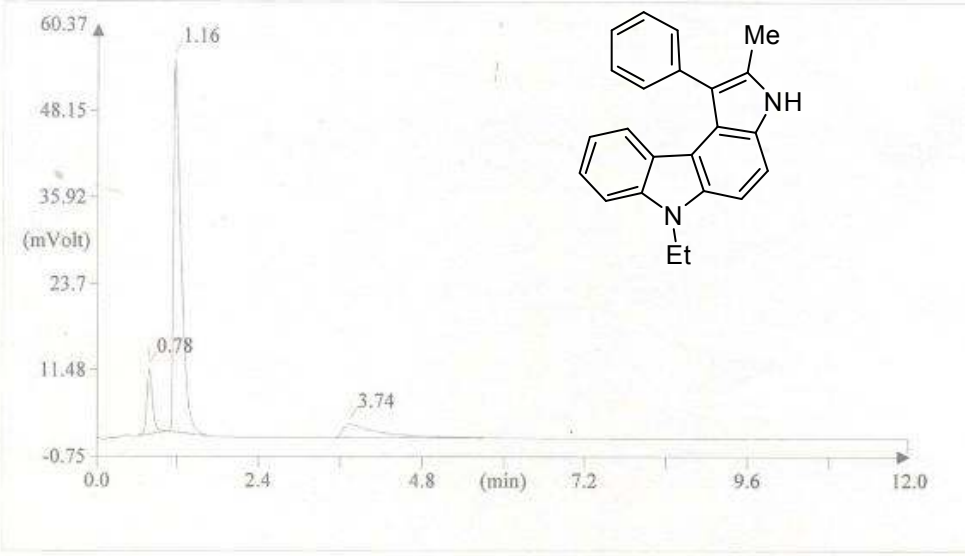
				12236511	1171759			100.00			

OPERATOR

Elemental Analysis of 6-Ethyl-2-methyl-1-phenyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194j)

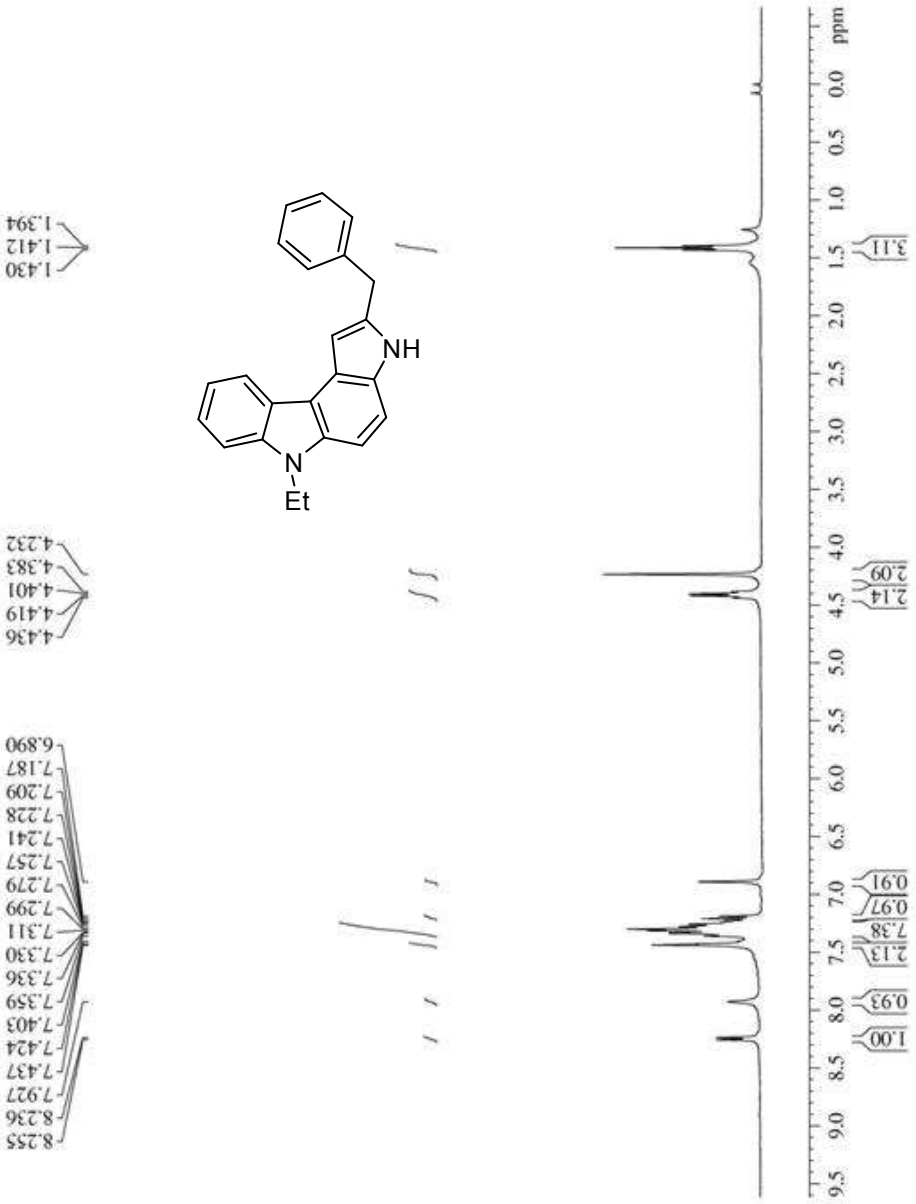
FLASH EA 1112 SERIES CHN REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

Method filename:	E:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID:	VIJI-1222 (# 5)
Analysis type:	UnkNown
Chromatogram filename:	UNK-11072012-5.dat
Sample weight:	1.263

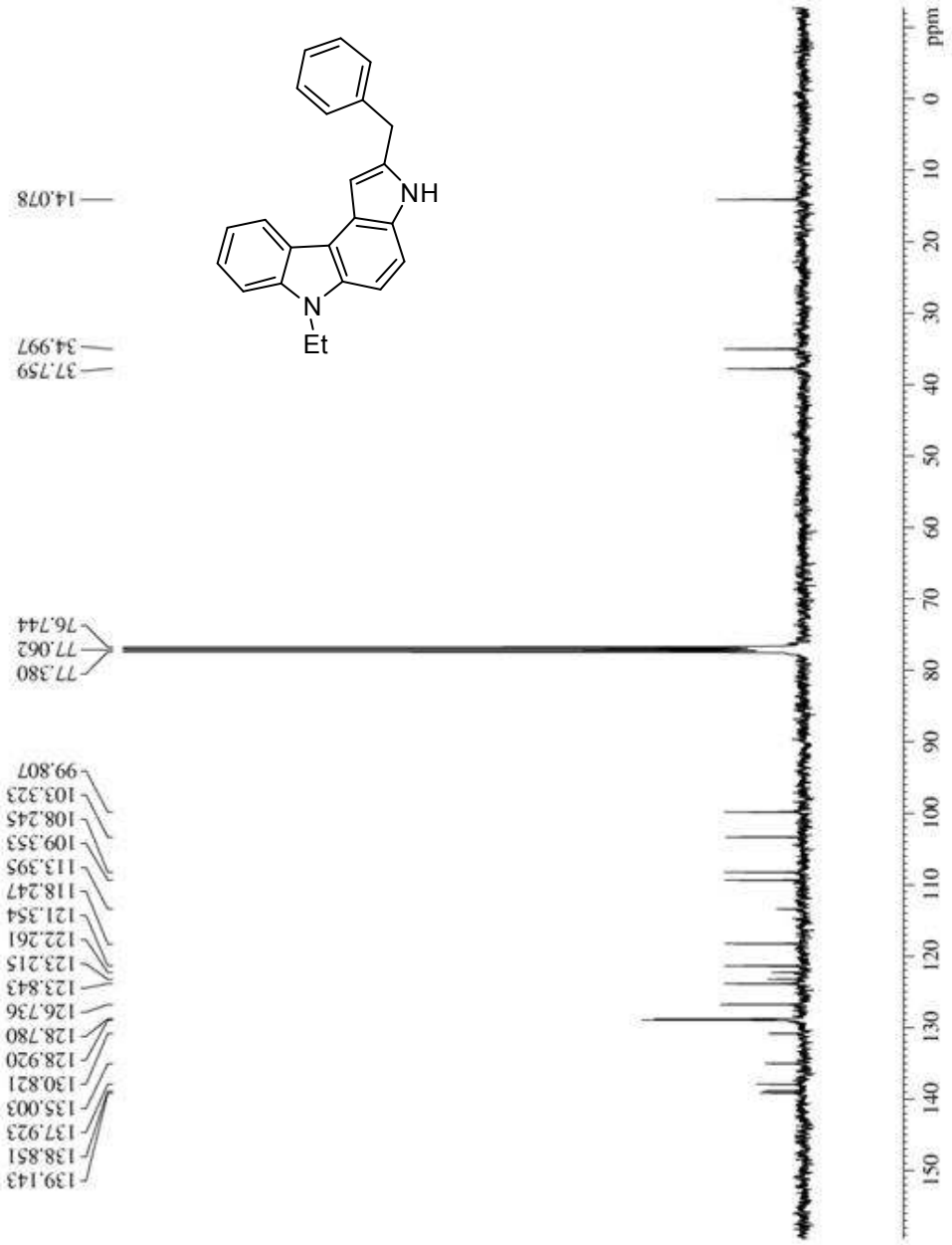


Element Name	Element %	Ret. Time
Nitrogen	8. 81	0. 78
Carbon	85. 26	1. 16
Hydrogen	6. 15	3. 74

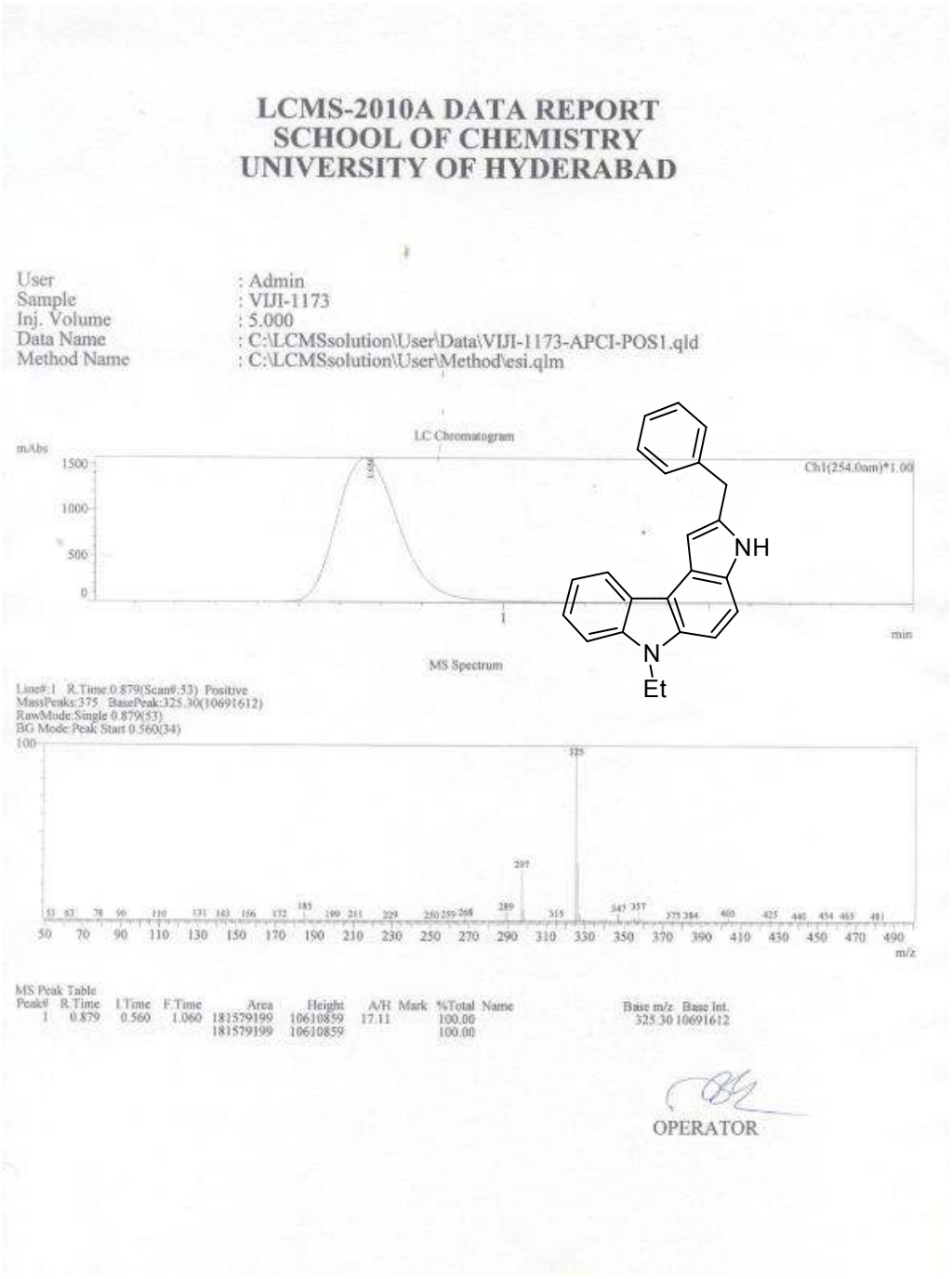
^{1}H NMR of 2-Benzyl-6-ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194k)



^{13}C NMR of 2-Benzyl-6-ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194k)



LC-MS of 2-Benzyl-6-ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194k)



LCMS-2010A DATA REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

User : Admin
Sample : VIJI-1173
Inj. Volume : 5.000
Data Name : C:\LCMSsolution\User\Data\VIJI-1173-APCI-POS1.qld
Method Name : C:\LCMSsolution\User\Method\esi.qlm

MS Spectrum

Line#:1 R.Time:0.879(Scan#:53) Positive
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RawMode:Single 0.879(53)
BG Mode:Peak Start 0.560(34)

MS Peak Table

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				181579199	10610859			100.00	

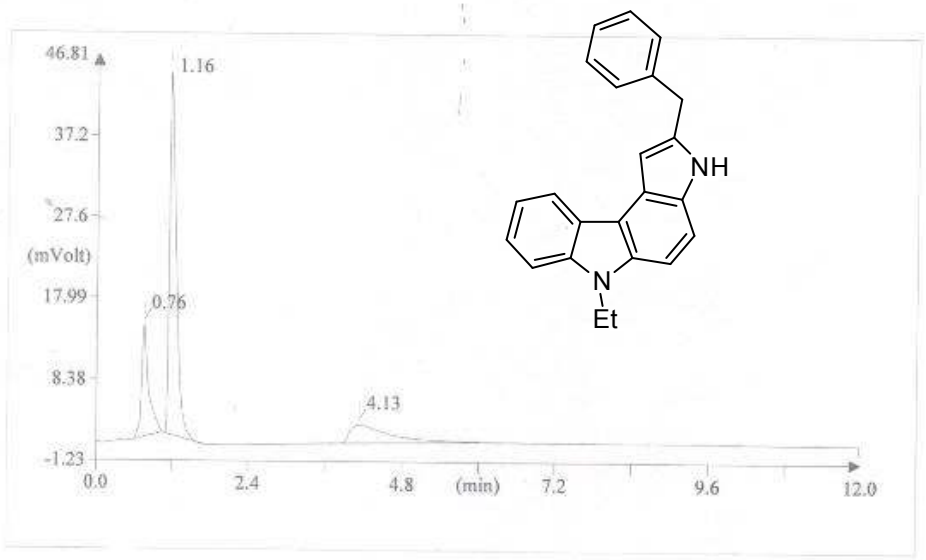
Base m/z Base Int.
325.30 10691612

OPERATOR

Elemental analysis of 2-Benzyl-6-ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (194k)

FLASH EA 1112 SERIES CHN REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

Method filename:	E:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID:	VIJI-1173 (# 17)
Analysis type:	UnkNown
Chromatogram filename:	UNK-11072012-17.dat
Sample weight:	1.119



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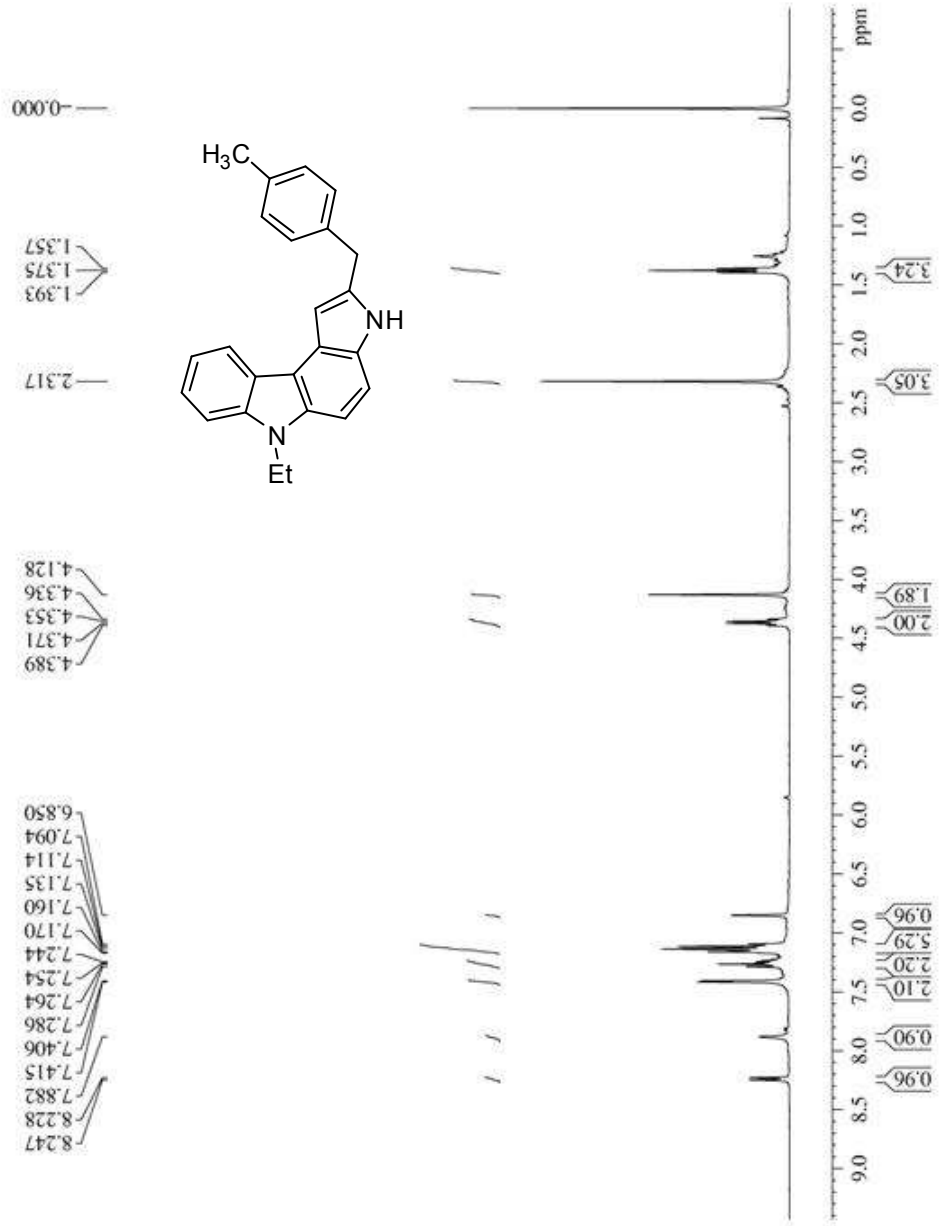
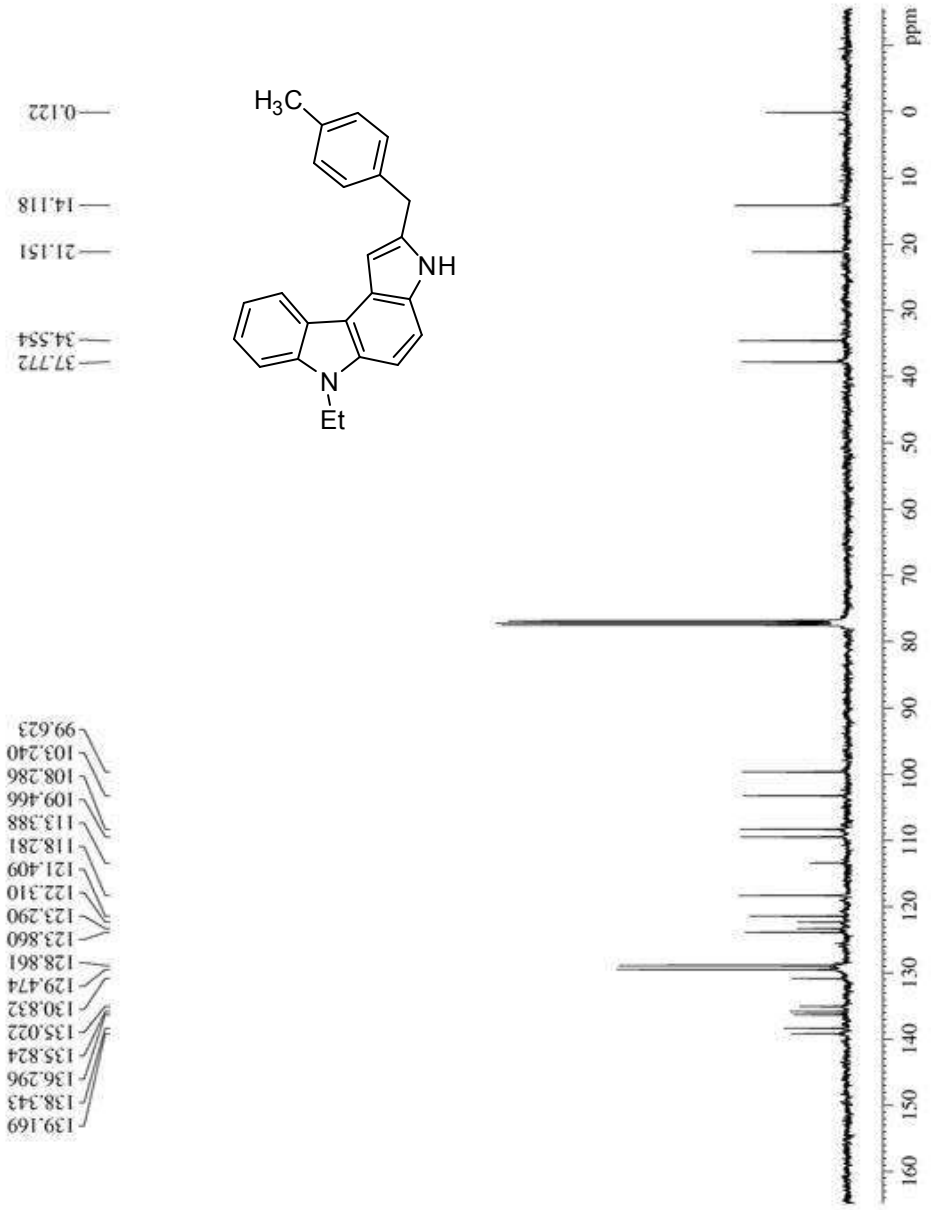
Carbon	85. 26	1. 16
Hydrogen	6. 15	4. 13

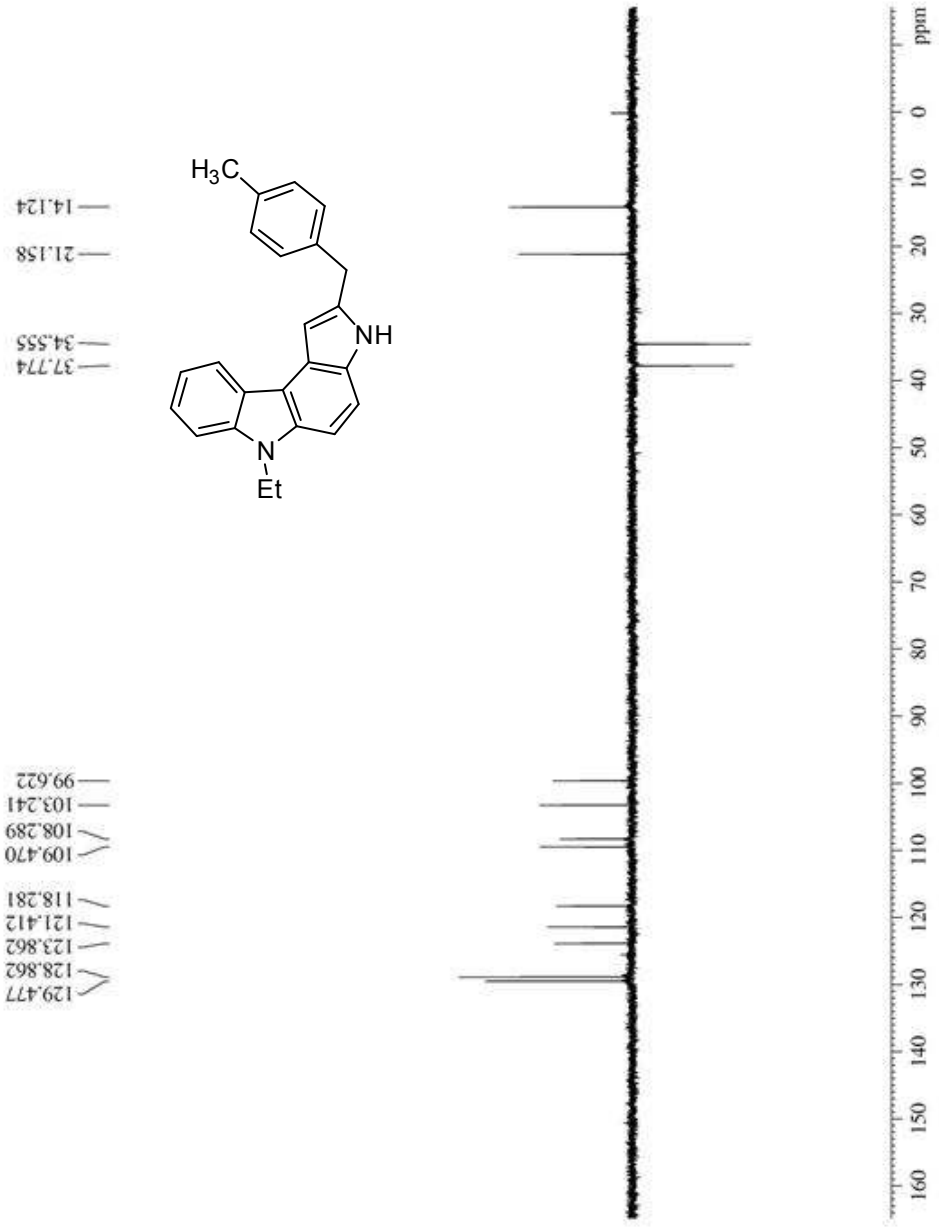
^{1}H NMR of 6-Ethyl-2-(4-methylbenzyl)-3,6-dihydropyrrolo[2,3-*c*]carbazole (194m)



^{13}C NMR of 6-Ethyl-2-(4-methylbenzyl)-3,6-dihydropyrrolo[2,3-*c*]carbazole (194m)

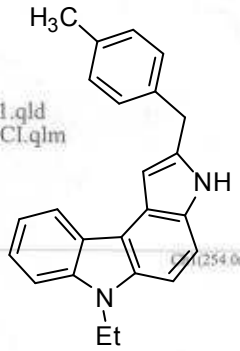


DEPT of 6-Ethyl-2-(4-methylbenzyl)-3,6-dihydropyrrolo[2,3-*c*]carbazole (194m)



LC-MS of 6-Ethyl-2-(4-methylbenzyl)-3,6-dihydropyrrolo[2,3-*c*]carbazole (194m)

LCMS-2010A DATA REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD



User : Admin
Sample : VIJI-1221
Inj. Volume : 5.000
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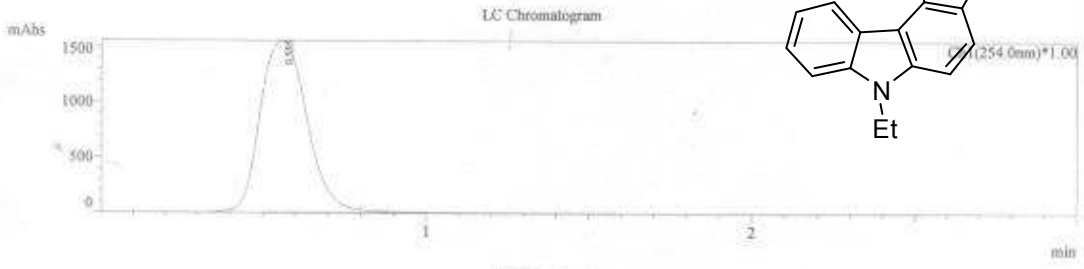
Method Name : C:\LCMSsolution\User\Method\Copy of JAY-4-APCI.qlm



MS Spectrum

Line#:1 R.Time:0.628(Scan#:38) Positive
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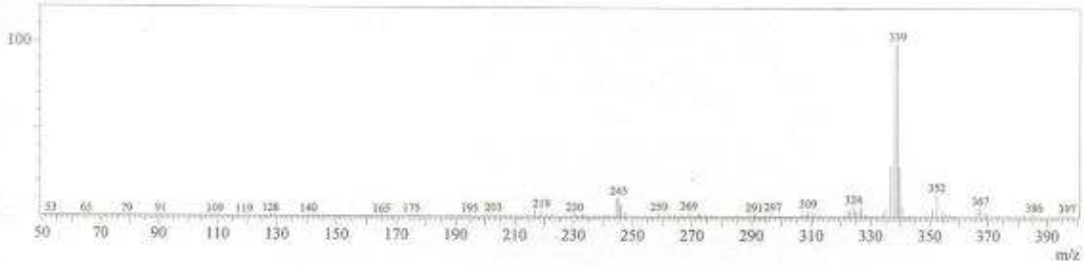
RawMode:Single 0.628(38)
BG Mode:Peak Start 0.443(27)



MS Peak Table

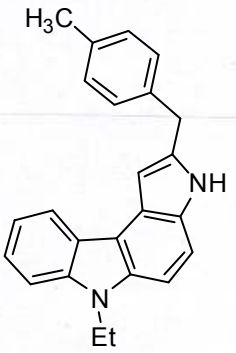
Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.628	0.443	0.843	94780062	8495166	11.15		100.00		339.05	1262006
				94780062	8495166			100.00			

OPERATOR

Elemental Analysis of 6-Ethyl-2-(4-methylbenzyl)-3,6-dihydropyrrolo[2,3-*c*]carbazole (194m)

FLASH EA 1112 SERIES CHN REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

Method filename: E:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID: VIJI-1221 (# 7)
Analysis type: UnkNown
Chromatogram filename: UNK-11072012-7.dat
Sample weight: 1.237



Element Name	Element %	Ret. Time
Nitrogen	8. 21	0. 87
Carbon	85. 31	1. 35
Hydrogen	6. 45	4. 68

CHAPTER 2

Palladium catalyzed C-H activation route to the synthesis of quino[2,3-*a*]carbazoles and indolo[2,3-*a*]carbazoles

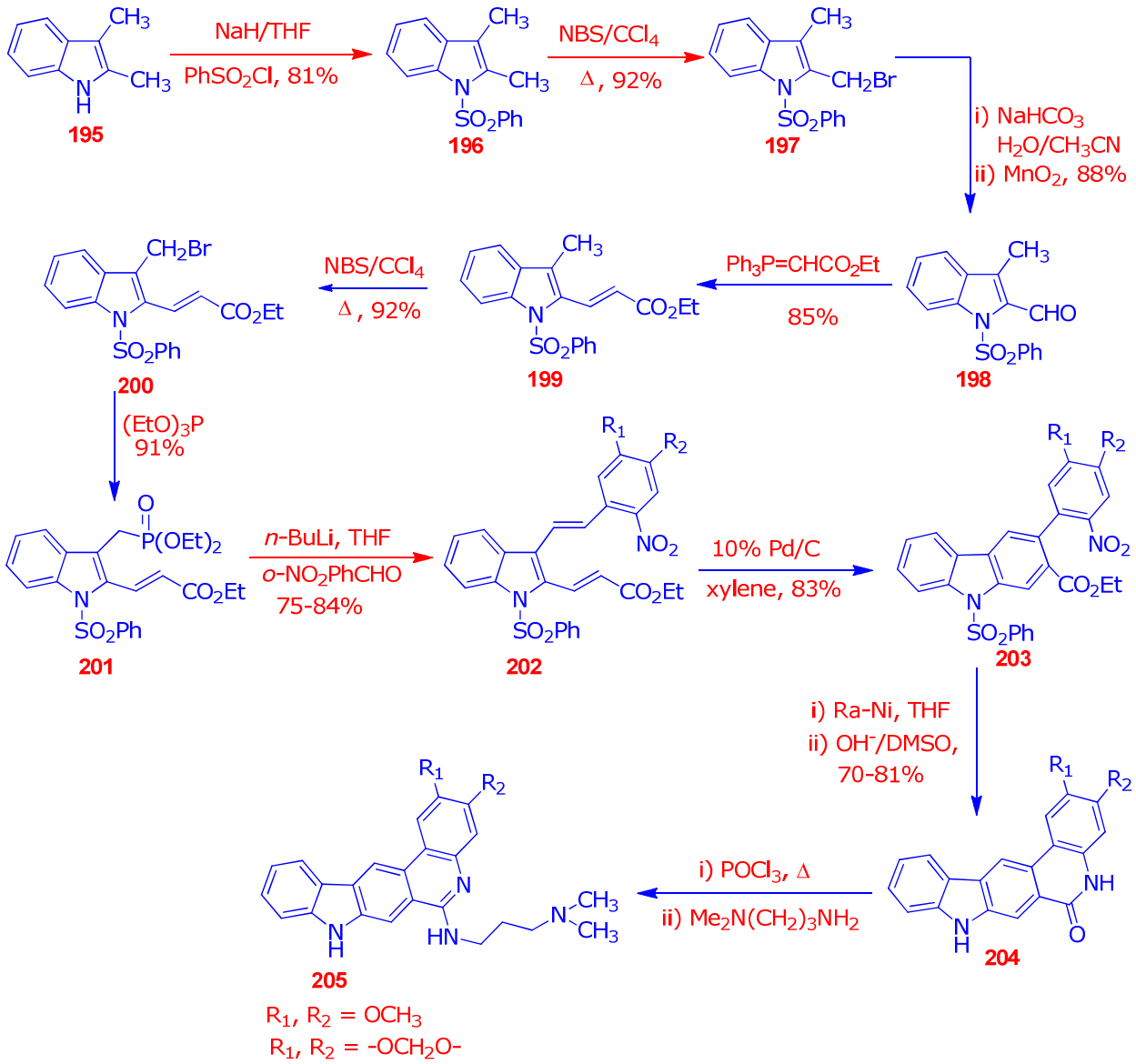
2.1 Introduction

Heteroannulated carbazoles play an important role in different areas of organic chemistry and biochemistry.[1-10, 86-87] In addition; indolocarbazoles[32] and quinolocarbazoles[43-44] are very important and versatile compounds in organic synthesis, and natural product chemistry, due to their biological and pharmacological relevance. Therefore, the preparation of the structurally complex and diverse heteroannulated compounds has received much attention in synthetic organic chemistry. As a result, over the decades organic chemists have sought to develop more efficient methods to prepare these compounds. A number of synthetic methods using transition-metal catalysts have been reported.[72-74]

2.2 Quinocarbazoles

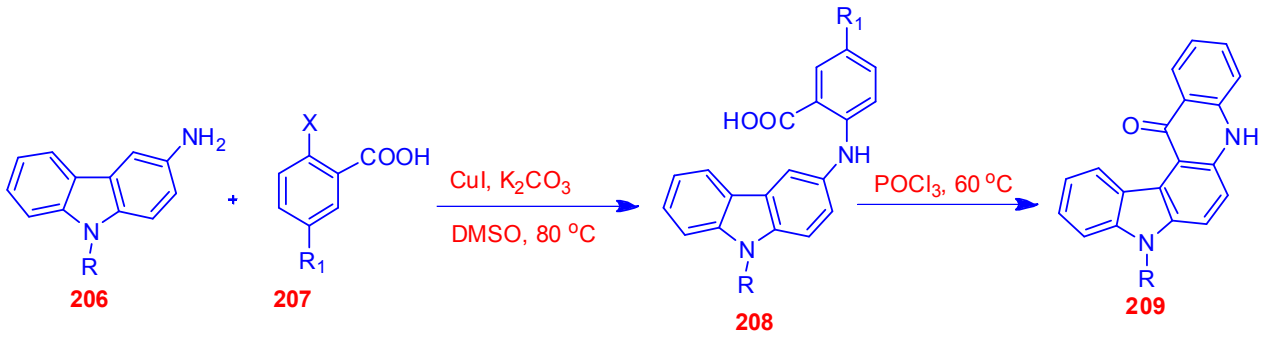
In 1995 Srinivasan *et al*. reported[102] a new synthetic route (Eq. 26) for the construction of quino[3,4-*b*]carbazole analogues. 2,3-Dimethylindole **195** was phenylsulfonylated by treatment with NaH and phenylsulfonyl chloride in THF to give **196**. Bromination of **196** gave the compound **197** in almost quantitative yield. The solvolysis of **197** using $NaHCO_3$ in CH_3CN followed by oxidation with MnO_2 gave **198** in 88% yields. The Wittig reaction of **198** with (carbethoxymethylene)triphenylphosphorane in THF gave **199** in 85% yield. The bromination of **199** followed by subsequent Arbuzov reaction gave the phosphonate ester **201** which underwent Wittig-Horner reaction with 2-nitrobenzaldehyde to give **202**. Boiling xylene solution of **202** in the presence of 10% Pd/C gave the expected carbazole **203** as a single product. The reductive cyclization of the carbazole **203** with Ra-Ni in boiling THF followed by cleavage of the phenylsulfonyl group gave the expected amide **204**. The quinocarbazole analogue **204** was converted to the corresponding [(dimethylamino)propyl]amino derivative **205** by treatment with $POCl_3$ and [(dimethylamino)propyl]amine (**Eq. 26**).

Eq. 26



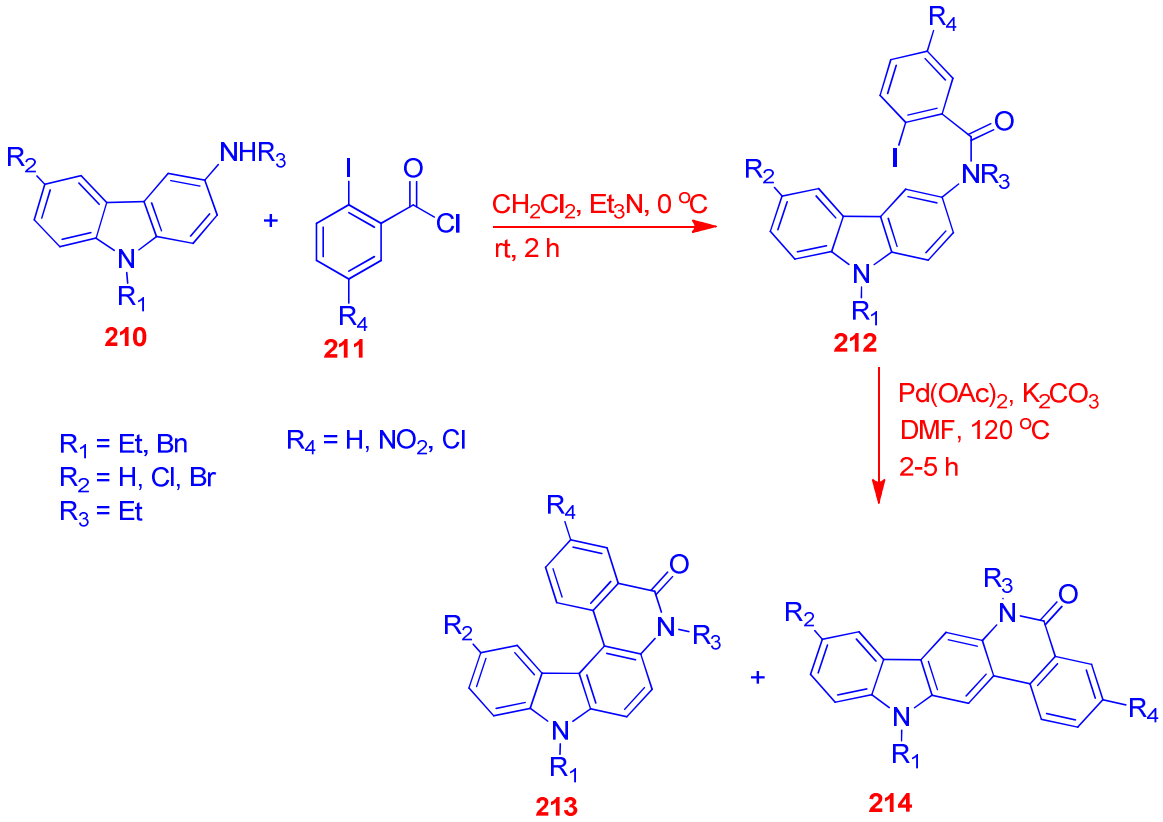
Nagarajan *et al*. have reported[103] the synthesis of quinocarbazoles carried out by the condensation of 3-amino-9-ethylcarbazole **206** with various *o*-iodobenzoic acids **207** in the presence of CuI (0.10 equiv.) and K_2CO_3 (2.0 equiv.) in DMSO at 80 °C obtaining the Ullmann coupled product in good yields. The condensed products underwent cyclization with phosphorous oxychloride at 60 °C furnishing the corresponding quinocarbazoles **209** in good yields (**Eq. 27**).

Eq. 27



In 2010, an efficient route for the construction of quino[2,3-*c*]-, [3,2-*b*]carbazole derivatives via palladium-catalyzed intramolecular *ortho* arylation has been reported.[104] The amide **212** formed from the reaction of **210** with **211** underwent Pd-catalyzed ortho-arylation which gave rise to the structure quinocarbazoles **213** as major product along with and **214** (**Eq. 28**).

Eq. 28



2.3 Indolocarbazoles

The indolocarbazole alkaloids constitute an important class of natural products, which have been isolated from actinomycetes, cyanobacteria, fungi, slime moulds and marine invertebrates.[105] After the isolation of the first indolocarbazole in 1977, this family of compounds has attracted the attention of many researchers from different disciplines because of the variety of chemical structures and the interesting biological activities showed by this family of compounds.

UCN-01 (**215**), a member of the indolocarbazole family,[106] generated considerable interest in the laboratory when it was found to be a potent inhibitor of DNA damage-induced S and G2 cell cycle checkpoints, which led to increased killing of tumor cells (Fig. 14).[107] Although UCN-01 is well recognized as a protein kinase C inhibitor,[108] this checkpoint inhibition was attributed to its ability to inhibit Chk1.[109] Unfortunately, UCN-01 binds avidly to human serum proteins thereby compromising its potential therapeutic activity.[110]

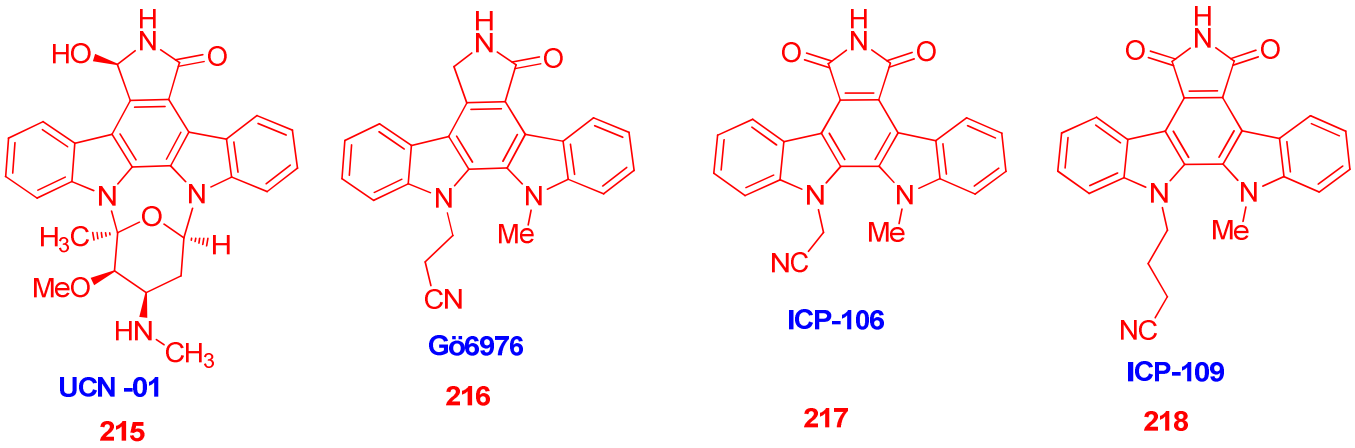


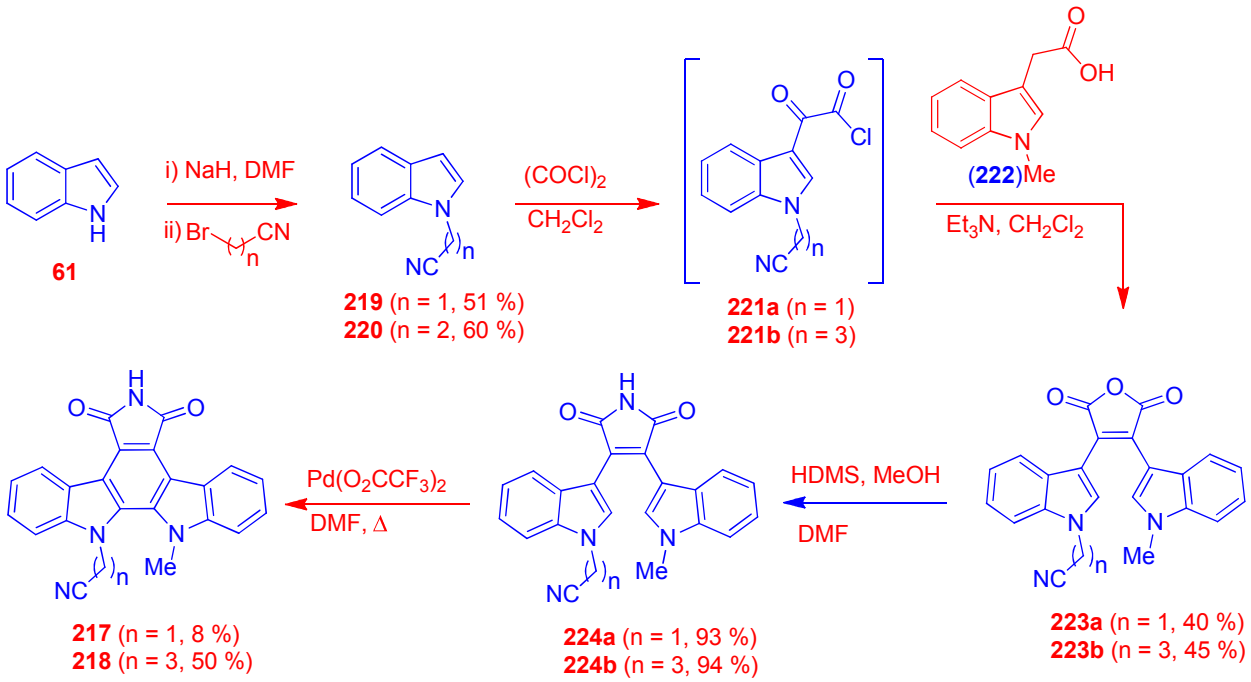
Fig. 14

More recently, Eastman *et al.* found that Gö6976 (**216**) is a very potent checkpoint inhibitor even in the presence of human serum,[111] and this has also been attributed to the inhibition of Chk1 (Fig. 14).[112]

In 2006, W. Gribble *et al.* reported substituted bioactive indolocarbazoles related to Gö6976.[113] Indole-1-acetonitrile **219** was treated with oxalyl chloride in dichloromethane to furnish the glyoxylyl chloride **221a**, which was immediately treated with 1-methylindole-3-

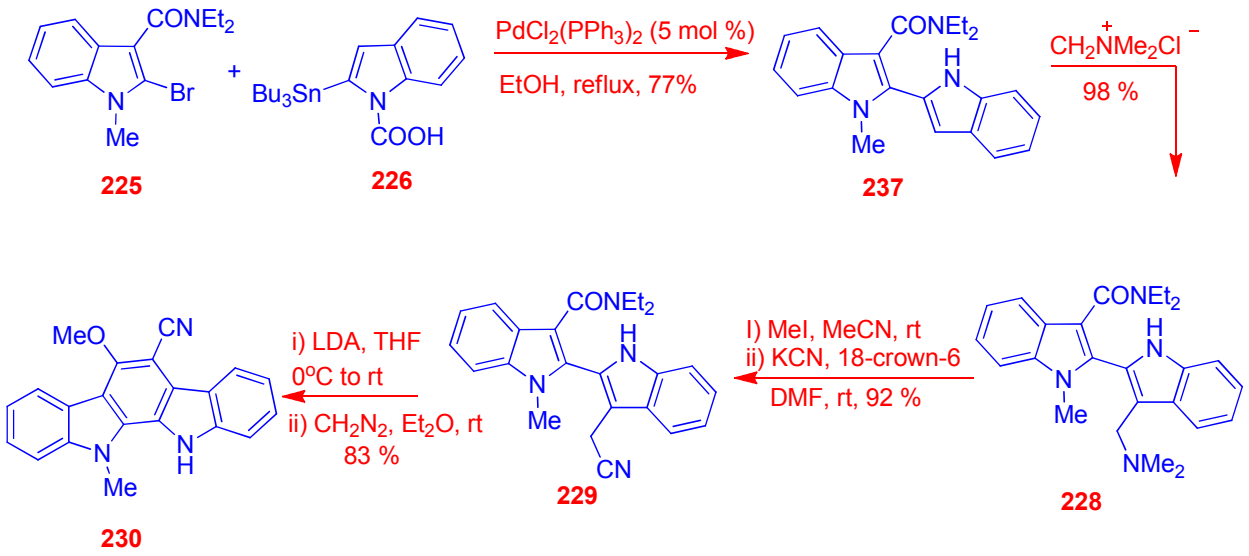
acetic acid **222** in the presence of triethylamine to produce anhydride **223a** in 40% yield in two steps from **219**.[114] Similarly, indole-1-butanenitrile **220** furnished **223b** in 45% yield via the intermediate glyoxylyl chloride **221b**. Due to the potentially labile nitrile functionality, ammonia was generated *insitu* from HMDS which was used to convert anhydrides **223a** and **223b** to imides **224a** and **224b**, respectively.[115] Heating bisindolylmaleimide **224a** and **224b** in DMF in the presence of palladium(II) trifluoroacetate gave the target compounds **217** and **218** in 8% and 50% yields, respectively. The lower yield of **217** may be a consequence of the strong inductive electron withdrawing effect of the cyano group that retards the oxidative addition of Pd(II) to bisindolylmaleimide **224a** (**Eq. 29**).

Eq. 29



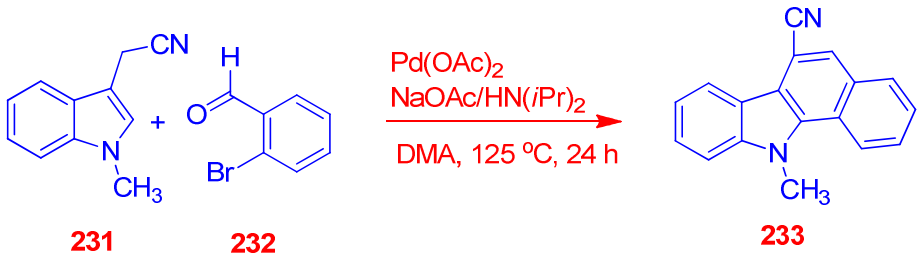
In 2010 Snieckus *et al.* reported[116] synthesis of indolocarbazole via cross-coupling strategies. Stille cross-coupling of the two indolic fragments **225** and **226** gave the 2,20-biindolyl **227**, which was treated with Eschenmoser's salt, giving the gramine derivative **228**. Quaternization of the amine functionality, followed by nucleophilic displacement using cyanide, yielded the molecule **229**, which could finally be annulated and O-methylated, thus completing a new total synthesis of the indolo[2,3-*a*]carbazole alkaloid **230** (**Eq. 30**).

Eq. 30



Ghanbari *et al.* reported[117] a one-pot synthesis of a wide range of benzo[*a*]carbazoles. (1-Methyl-1*H*-indol-3-yl)acetonitrile (**231**) and 2-bromobenzaldehyde (**232**), in the presence of sodium acetate, diisopropylamine, and $Pd(OAc)_2$ (10 mol %) in *N*,*N*-dimethylacetamide (DMA) at 125 °C for 24 h under an argon atmosphere. This led to the formation of **233** in 44% yield (**Eq. 31**).

Eq. 31



2.4 Synthesis of quino, indolocarbazole derivatives

Although a variety of transition metals have been used for the formation of aryl-aryl bonds, in past few years much effort has gone into developing palladium-catalyzed cross-coupling reactions which is an extremely important class of carbon–carbon and carbon–heteroatom bond-forming processes.[72,73] Here, we wish to report a Pd-catalyzed C-H activation reaction to synthesis heteroannulated carbazoles. Various quinoline and indolochloroaldehydes were cleanly converted by treatment with 10 mol % of $Pd(OAc)_2$, 30 mol%. of PPh_3, 2.5 equiv of K_2CO_3, and with active methylene indole derivatives in DMF, with conventional heating at 120 °C, conversions of 68-76 % could be attained after 18-24 h. In this process, one carbon-carbon bond can be formed, and polycyclic aromatic rings can also be constructed in a one-pot manner.

2.5 Synthesis of quinocarbazole derivatives

Scheme 7. Schematic representation of the present work

To performing the C-H activation reaction, the first objective was to prepare the required *N*-substituted indole-3-acetonitrile which in turn were prepared following the reported procedure.[118] The original impetus for this research came from an earlier observation that quinocarbazole **236a** could be obtained in 26% yield when indoloacetonitrile **234a** reacted with chloro aldehydes **235a** in DMA at 130 °C in the presence of 10 mol % of $Pd(OAc)_2$. To achieve suitable conditions for the synthesis of **236a**, we tested the reaction under various conditions, like changing Pd catalysts, ligands, bases, solvents, ligands and the results are shown in Table 10. The efficiency of $Pd(OAc)_2$ catalyst in the cyclization of compound **234a** in various solvents also shown in table 10. This Pd catalyst (10 mol %) is active in several solvents including DMA (32%), DMF (72%), and NMP (20%) but less active or inactive in toluene, DMSO, and dioxane. After examination of the reaction conditions, we were pleased to find that the reaction proceeded smoothly and provided a 72% yield of the

Table 10. Optimization conditions for the synthesis of the quinocarbazole[a]

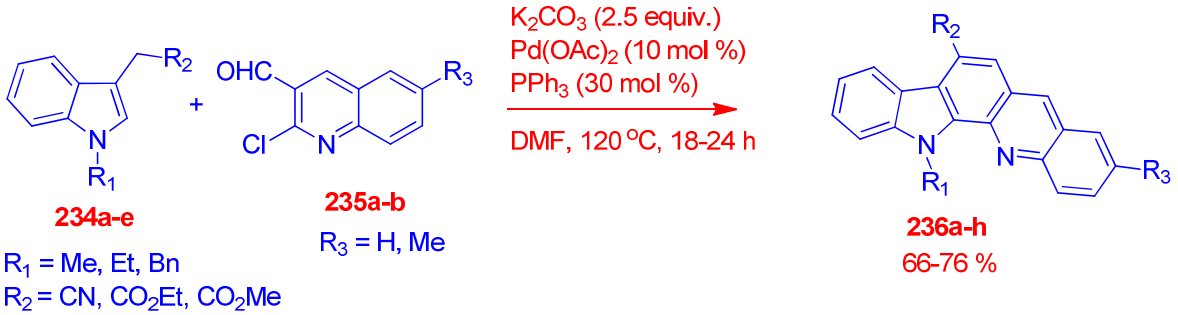
s.no	catalyst	ligand	base	solvent	temp °C	time (h)	yield[e] (%)
1	$Pd(OAc)_2$	PPh_3	KOAc	DMA	130	24	26
2	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMA	130	20	25
3	$Pd(OAc)_2$	PPh_3	K_2CO_3	solvents[d]	130	36	nr
4	$Pd(OAc)_2$	DIPA	NaOAc	DMA	120	24	nr
5	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	DMF	140	24	31
6	$Pd(PPh_3)_4$	PPh_3	K_2CO_3	DMF	120	12	26
7	$Pd(PPh_3)_2Cl_2$	PPh_3	K_2CO_3	DMF	120	36	16
8	$Pd(OAc)_2$	PCy_3	NaOAc	DMF	130	36	nr
9	$PdCl_2$	PPh_3	K_2CO_3	DMF	120	24	15
10	$RuCl_3$	PPh_3	K_2CO_3	DMF	120	36	nr
11	$RhCl(PPh_3)_3$	PPh_3	K_2CO_3	DMF	120	36	nr
12	$Pd(OAc)_2$	-	Cs_2CO_3	DMF	120	18	51
13	-	PPh_3	K_2CO_3	DMF	130	24	nr
14[b]	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	120	24	48
15	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	120	18	72
16	$Pd(OAc)_2$	dppe	K_2CO_3	DMF	130	18	37
17[c]	$Pd(OAc)_2$	-	KOAc	DMF	140	12	32
18	$Pd(OTf)_2$	PPh_3	K_2CO_3	NMP	120	24	20

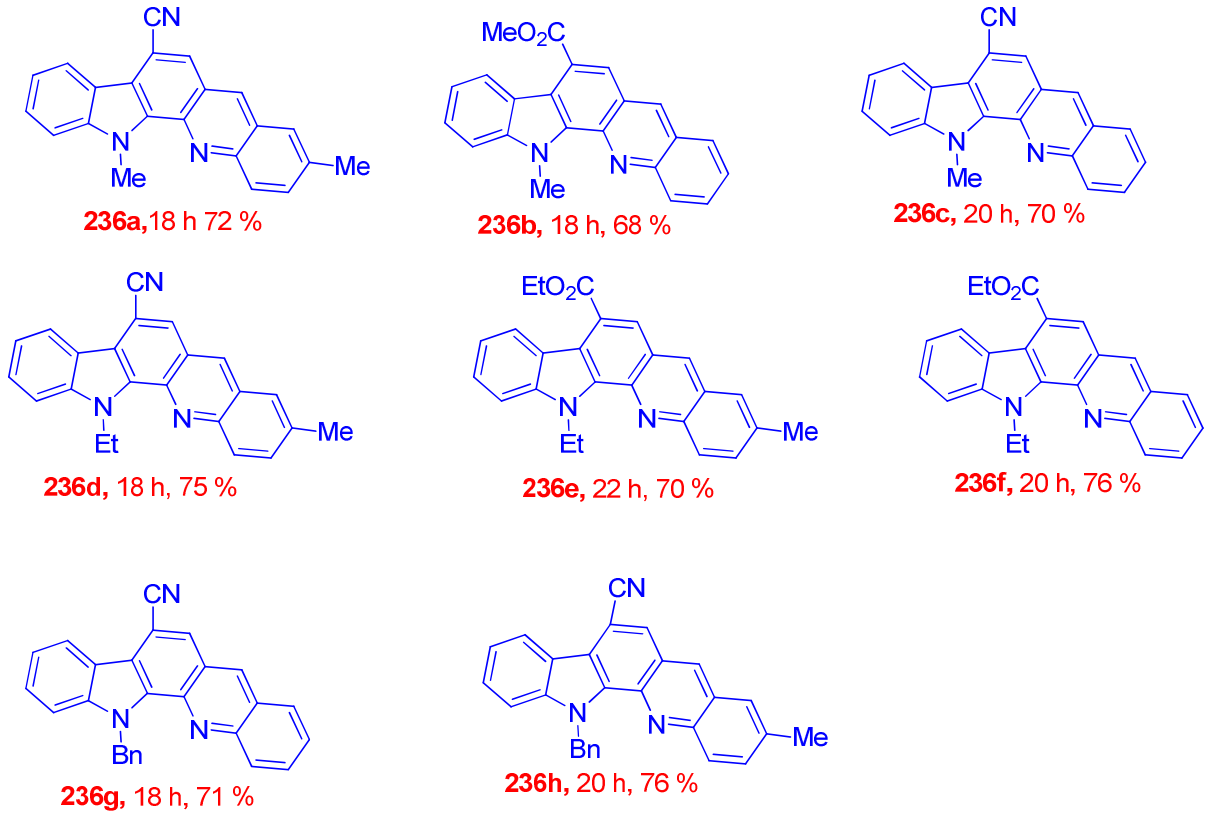
[a] Unless otherwise mentioned, all the reactions were conducted in Schlenk tube using n-methyl-3-acetonitrile indole **234a** (1 equiv.), 6-methyl-2-chloro-3-formyl-quinoline **235a** (1.0 equiv.) base (2.5 equiv.), catalyst (10 mol%), ligand (30 mol%) 3 mL solvent. [b] 5 mol% of catalyst used. [c] 15 mol% of catalyst used. [d] toluene, DMSO, dioxane. [e] isolated yields.

quinocarbazole **236a** at 120 °C in the presence of 10 mol % of $Pd(OAc)_2$ with 30 mol% of PPh_3. When the reaction of **234a** was carried out at lower temperatures, such as room temperature or 70 °C, the reaction doesn't occurred. When $Pd(OAc)_2$ alone was used as a catalyst, only a small amount of the anticipated **236a** was observed (table 10. entries 12, 17). The efficiency of this catalyst appears superior to that of other palladium catalysts including $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(OTf)_2$, which requires at least 20 mol % catalyst and longer reaction time to attain the product. We have also tested several other metal catalysts such as $RuCl_3$, $RhCl(PPh_3)_3$, but none of them gave the desired product. No reaction occurred in the absence of a palladium catalyst. A 30 mol% of PPh_3 as ligand is sufficient for

the reaction, but its absence or a change to other ligands provided either no product or low yields.

Table 11. Synthesis of quino[2,3-*a*]carbazole derivatives.[a]





All the reactions were conducted in Schlenk tube using **234a-e** (1 equiv.), 6-methyl-2-chloro-3-formyl-quinoline **235a-b** (1.0 equiv.) K_2CO_3 (2.5 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%), 3 mL DMF at 120 °C. Yields are isolated yield.

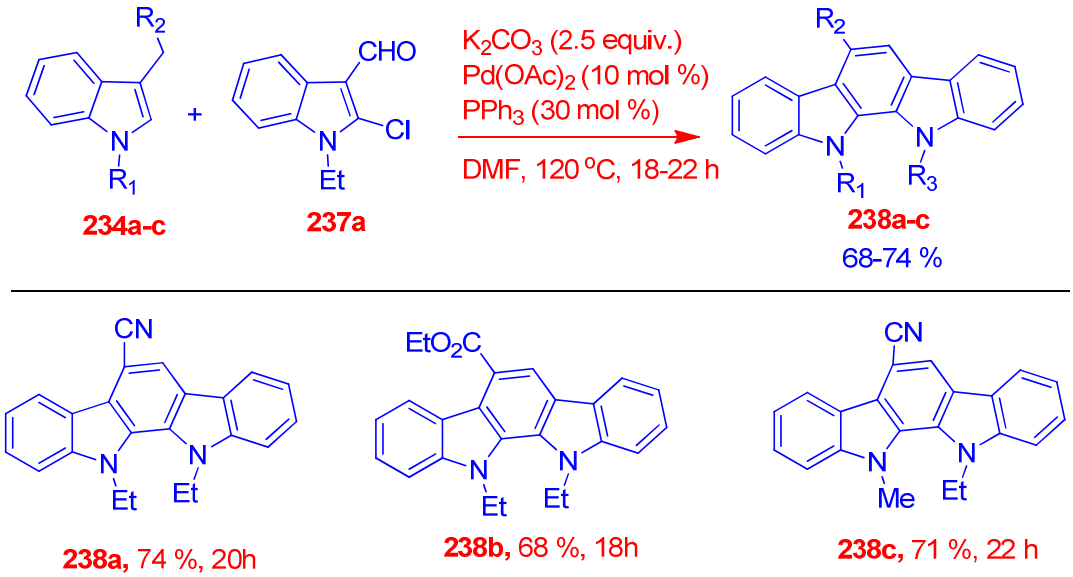
Difference among the bases was observed, KOAc and Cs_2CO_3 giving the moderate results, whereas NaOAc did not result in any product formation at all (table 10, entry 4). KOAc gave a moderate result with a conversion of 32% (entry 2). Cs_2CO_3 worked efficiently to promote the desired reaction to furnish the quinocarbazoles in moderate yield (table 10, entry 12). Further, we found that the Lewis acids were unsuccessful in executing the reaction.

To explore the scope of the above reaction, seven additional examples were also tested, and delightfully, all yielded analogous products in yields ranging from 68% to 78% (table 11). We proceeded with the preparation of different starting materials **234a-e** and **235a-c** and reacted in the presence of $Pd(OAc)_2$ and K_2CO_3 in DMF to afford respective products **236a-h** in good yields. The observed result clearly demonstrates that the method developed is useful for the conversion of **236a-h** in one pot under optimized reaction conditions which accordingly may find a wide range of application.

2.6. Synthesis of indolocarbazoles

Indolocarbazoles are widely utilized in organic synthesis, medicinal chemistry because of the wide spectrum of biological activity displayed by this class of compounds. Therefore, facile and selective derivatization of indolocarbazoles is highly important and desirable. In this regard, we describe herein a new entry of the C-H activation of indolocarbazoles with the use of $Pd(OAc)_2$. We extended the C-H activation strategy to 3-formyl-2-chloroindole **237a** with a view to synthesizing indolo[2,3-*a*]carbazole frameworks **238a-c** as shown in Table 12. Thus, we obtained the regiospecifically substituted indolo[2,3-*a*]carbazoles **238a-c** in good yields from the corresponding indole precursors **237a** under the optimized reaction conditions.

Table 12. Synthesis of indolo[2,3-*a*]carbazole derivatives.[a]



2.7 Conclusions

In conclusion, we have developed a novel palladium catalyzed C-H activation reaction of indole-3-acetonitrile with quinoline chloroaldehyde, which afforded a simple and efficient route to quinocarbazole derivatives. This methodology also extended to the synthesis of indolocarbazoles starting from indolochloroaldehydes. A range of functionalized heteroannulated carbazole were obtained.

2.8 Experimental Section

General Information

All ^{1}H, ^{13}C NMR spectra were recorded on AV-400 spectrometer operating at 400 and 100 MHz respectively. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Multiplicities was indicated as follows (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and coupling constants (Hz). Chemical shifts of common trace ^{1}H NMR impurities ($CDCl_3$, ppm): H_2O, 1.56; EtOAc, 1.26, 2.05, 4.12; CH_2Cl_2, 5.30; $CDCl_3$, 7.26. IR spectra were recorded on FT/IR-5300 spectrometer; absorptions are reported in cm^{-1}. Mass spectra were recorded on either using EI technique or LCMS-2010A mass spectrometer. Elemental analyses (C, H, and N) were recorded on EA

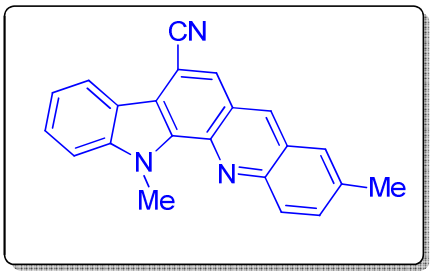
1112 analyzer in School of Chemistry, University of Hyderabad. Routine monitoring of the reactions was performed by TLC silica gel plates 60 F254 were used. Compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine. Column chromatography was carried out employing neutral alumina. Commercially available reagents and solvents were used without further purification and were purchased. Melting points were measured in open capillary tubes and are uncorrected. LCMS system, whereas MS (EI) were recorded with a JEOL JMS600H mass spectrometer. HRMS (ESI) were recorded in Bruker Maxis spectrometer.

General procedure D:

N-methyl-indole-3-acetonitrile **234a** (1 equiv.), 6-methyl-2-chloro-3-formyl quinoline **235a** (1 equiv.), K_2CO_3 (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%) were transferred into an oven-dried 25 mL Schlenk tube. The tube was evacuated and refilled with N_2, which was repeated for three times. After addition of 2 mL of DMF under a positive pressure of N_2 via syringe, the Schlenk tube was placed in a 120°C oil bath and stirred for 18 h. Upon completion of the reaction as monitored by TLC, and poured into water (25 mL) the contents were extracted with ethyl acetate (2 x 20 mL). Then the pooled organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a crude product **236a**. The crude product was purified by silica gel column chromatography using (hexanes/EtOAc, 95:05) to afford **236a**.

9,13-Dimethyl-13*H*-indolo[3,2-*c*]acridine-5-carbonitrile 236a:

The product **236a** was obtained as yellow colored solid from **234a** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.



Yield: 72 %

Mp: 68 °C

IR (KBr) ν_{max} cm^{-1}: 3408, 2912, 1701, 1587, 1477, 1338, 1331, 1252, 1180, 1087, 1020, 992, 781

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, 1H, *J* = 8 Hz), 8.56 (s, 1H), 8.09 (d, 1H, *J* = 8.8 Hz), 7.90 (s, 1H), 7.66 (s, 1H), 7.63-7.61 (m, 1H), 7.59-7.57 (m, 2H), 7.42-7.38 (m, 1H), 4.78 (s, 3H), 2.58 (s, 3H)

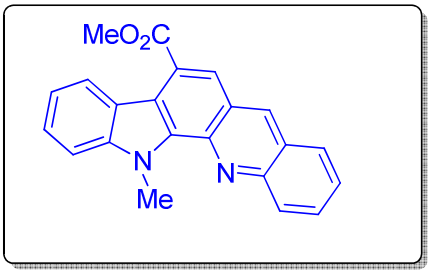
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 140.6, 140.4, 136.2, 135.7, 133.8, 133.5, 129.0, 127.1, 126.3, 125.8, 125.6, 124.6, 121.1, 120.7, 120.5, 118.8, 116.0, 109.7, 104.0, 33.3, 21.8

HRMS. Calcd. for $C_{22}H_{15}N_3$: 322.1345 (M+H)

Found: 322.1345

Methyl 13-methyl-13*H*-indolo[3,2-*c*]acridine-5-carboxylate 236b:

The product **236b** was obtained as yellow colored solid from **234b** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.



Yield: 68 %

Mp: 78 °C

IR (KBr) ν_{max} cm^{-1}: 3477, 2959, 2928, 2851, 1727, 1635, 1587, 1477, 1450, 1228, 1180, 1151, 1087, 1008, 915

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.69 (d, 1H, *J* = 8.2 Hz), 8.31 (d, 1H, J = 8.6 Hz), 8.28 (s, 1H), 8.04 (d, 1H, *J* = 8.4 Hz), 7.84 (t, 1H, *J* = 7.6 Hz), 7.66-7.64 (m, 1H), 7.58 (q, 2H, *J* = 7 Hz), 7.37 (t, 1H, *J* = 8 Hz), 4.94 (s, 3H), 4.15 (s, 3H)

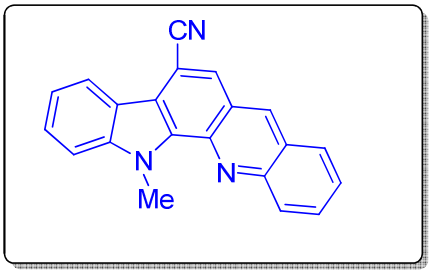
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 148.0, 142.1, 141.0, 137.1, 134.3, 130.3, 129.6, 128.2, 125.7, 125.5, 125.3, 124.7, 124.0, 123.8, 121.7, 120.1, 116.6, 109.5, 52.4, 33.6

HRMS. Calcd. for $C_{22}H_{16}N_2O_2$: 341.1291 (M+H)

Found: 341.1293

13-Methyl-13*H*-indolo[3,2-*c*]acridine-5-carbonitrile136c:

The product **236b** was obtained as orange colored solid from **234a** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.



Yield: 70 %

Mp: 240 °C

IR (KBr) ν_{max} cm^{-1}: 3398, 2928, 2818, 1707, 1450, 1375, 1331, 1128, 1111, 1047, 1020, 889, 702.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.71 (d, 1H, *J* = 8 Hz), 8.31 (d, 1H, *J* = 8.4 Hz), 8.09 (s, 1H), 8.05 (d, 1H, *J* = 8.4 Hz), 7.88 (t, 1H, *J* = 8 Hz), 7.68-7.60 (m, 2H), 7.44 (t, 2H, *J* = 7.6 Hz), 4.90 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 141.3, 140.3, 136.2, 135.2, 133.6, 133.4, 128.4, 127.5, 126.2, 125.4, 125.2, 124.8, 122.2, 121.0, 120.6, 119.0, 116.8, 110.3, 104.8, 33.6

LC-MS (m/z): 308 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{21}H_{13}N_3$: C, 82.06 H, 4.26; N, 13.67 %

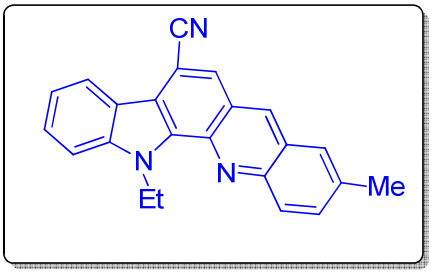
Found: C, 82.15; H, 4.22; N, 13.63 %

13-Ethyl-9-methyl-13*H*-indolo[3,2-*c*]acridine-5-carbonitrile 236d:

The product **236d** was obtained as yellow colored solid from **234c** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.

Yield: 75 %

Mp: 98 °C



IR (KBr) ν_{max} cm^{-1}: 3238, 2968, 2918, 2538, 1707, 1450, 1365, 1341, 1258, 1151, 1087, 1020, 989, 785

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, 1H, J = 8.2 Hz), 8.77 (s, 1H), 8.72 (d, 1H, J = 7.8 Hz), 8.20 (d, 1H, J = 8.6 Hz), 8.11 (s, 1H), 7.81 (s, 1H), 7.71 (d, 2H, J = 8.2 Hz), 7.55-7.52 (m, 1H), 4.89 (q, 2H, J = 7.2 Hz), 2.63 (s, 3H), 1.65 (t, 3H, J = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 136.3, 135.9, 133.8, 129.3, 128.4, 127.2, 127.1, 126.4, 125.97, 125.92, 124.9, 124.3, 122.2, 121.5, 120.8, 120.7, 120.5, 109.7, 108.9, 38.7, 21.8, 14.9

LC-MS (m/z): 336 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53 %

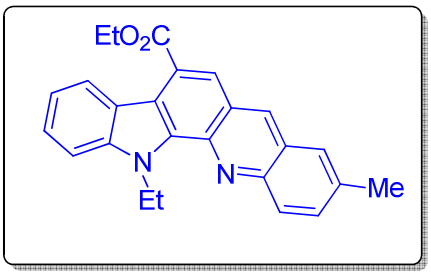
Found: C, 82.25; H, 5.06; N, 12.69 %

Ethyl 13-ethyl-9-methyl-13*H*-indolo[3,2-*c*]acridine-5-carboxylate 236e:

The product **236e** was obtained as yellow colored solid from **234d** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.

Yield: 70 %

Mp: 184 °C



IR (KBr) ν_{max} cm^{-1}: 3352, 3011, 2928, 2818, 1707, 1525, 1477, 1355, 1331,

1228, 1110, 1087, 1020, 880, 781,

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.70 (d, 1H, *J* = 8 Hz), 8.29 (s, 1H), 8.22 (d, 1H, *J* = 8.8 Hz), 7.81 (s, 1H), 7.69 (t, 2H, *J* = 8.2 Hz), 7.57-7.54 (m, 1H), 7.37-7.33 (m, 1H), 5.60 (q, 2H, *J* = 7.2 Hz), 4.63 (q, 2H, *J* = 7.2 Hz), 2.63 (s, 3H), 1.68-1.64 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 149.3, 141.8, 140.2, 139.2, 137.2, 134.0, 131.1, 130.7, 129.0, 126.8, 125.9, 125.0, 124.7, 123.9, 122.3, 120.5, 117.2, 114.9, 110.2, 62.3, 42.1, 21.9, 15.0, 14.3

LC-MS (m/z): 383 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32 %

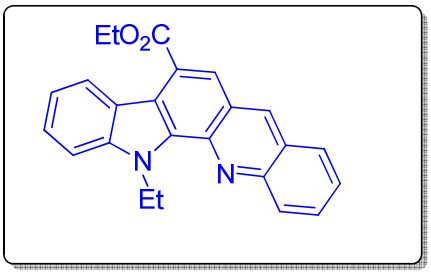
Found: C, 78.59; H, 5.83; N, 7.21 %

Ethyl 13-ethyl-13*H*-indolo[3,2-*c*]acridine-5-carboxylate 236f:

The product **236f** was obtained as orange colored solid from **234d** through column chromatography using a mixture of 6% ethyl acetate and hexanes as described in procedure D.

Yield: 76 %

Mp: 136 °C



IR (KBr) ν_{max} cm^{-1}: 3412, 3151, 2458, 1717, 1532, 1477, 1370, 1321, 1228, 1140, 1101, 1087, 889, 781, 728

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.70 (d, 1H, *J* = 8 Hz), 8.32-8.30 (m, 2H), 8.06 (d, 1H, *J* = 8.4 Hz), 7.86-7.82 (m, 1H), 7.72-7.70 (m, 1H), 7.62-7.55(m, 2H), 7.36 (t, 1H, *J* = 7.2 Hz), 5.60 (q, 2H, *J* = 7 Hz), 4.64 (q, 2H, *J* = 7.2 Hz), 1.66 (t, 3H, *J* = 7 Hz), 1.56 (t, 3H, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 148.3, 141.7, 139.9, 139.3, 136.9, 130.2, 129.7, 128.1, 126.1, 125.7, 125.2, 124.8, 124.1, 123.5, 121.9, 120.0, 116.7, 114.0, 109.4, 61.4, 40.8, 15.3, 14.4

HRMS. Calcd. for $C_{24}H_{20}N_2O_2$: 391.1423 (M+Na)

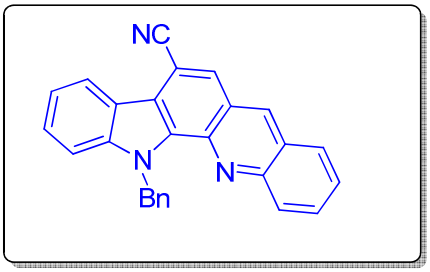
Found: 391.1423

13-Benzyl-13*H*-indolo[3,2-*c*]acridine-5-carbonitrile 236g:

The product **236g** was obtained as yellow color solid from **234e** through column chromatography using a mixture of 4% ethyl acetate and hexanes as described in procedure D.

Yield: 71 %

Mp: 180 ^{o}C



IR (KBr) ν_{max} cm^{-1}: 3412, 3001, 2868, 2858, 1707, 1687, 1450, 1365, 1331, 1228, 1180, 1151, 1087, 1020, 889, 721

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.71 (d, 1H, *J* = 8 Hz), 8.17 (d, 1H, *J* = 8.6 Hz), 8.05 (s, 1H), 7.98 (d, 1H, *J* = 8.4 Hz), 7.83-7.79 (m, 1H), 7.63-7.61 (m, 1H), 7.59-7.53 (m, 2H), 7.45-7.42 (m, 1H), 7.31-7.29 (m, 2H), 7.23-7.15 (m, 3H), 6.77 (s, 2H)

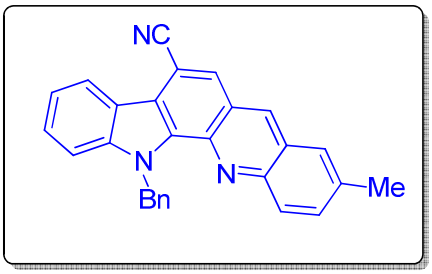
^{13}C NMR (500 MHz, $CDCl_3$): δ 148.4, 141.0, 140.4, 138.6, 137.0, 133.1, 131.0, 129.5, 128.55, 128.50, 128.2, 127.7, 127.0, 126.8, 126.3, 125.7, 124.7, 121.5, 121.2, 120.8, 118.6, 116.9, 110.5, 104.5, 49.3

HRMS. Calcd. for $C_{27}H_{17}N_3$: 384.1501 (M+H)

Found: 384.1500

13-Benzyl-9-methyl-13*H*-indolo[3,2-*c*]acridine-5-carbonitrile 236h:

The product **236h** was obtained as yellow colored solid from **234e** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.



Yield: 76 %

Mp: 212 °C

IR (KBr) ν_{max} cm^{-1}: 3451, 1637, 1262, 1221, 1019, 1008, 920, 889, 781, 729

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.70 (d, 1H, *J* = 8.0 Hz), 8.60 (s, 1H), 8.05 (d, 1H, *J* = 8.8 Hz), 8.00 (s, 1H), 7.67 (s, 1H), 7.63-7.61 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 1H), 7.29-7.28 (m, 1H), 7.24-7.16 (m, 4H), 6.77 (s, 2H), 2.56 (s, 3H)

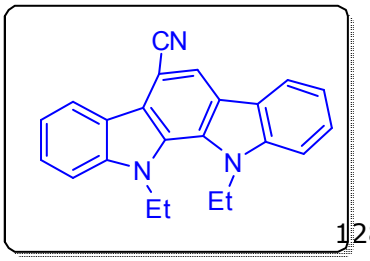
^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.2, 140.4, 140.2, 138.7, 136.3, 135.9, 133.9, 133.2, 129.1, 128.5, 127.7, 127.1, 126.9, 126.3, 126.1, 125.8, 124.7, 121.5, 121.1, 120.7, 118.7, 116.5, 110.5, 104.1, 49.2, 21.8

HRMS. Calcd. for $C_{28}H_{19}N_3$: 398.1658 (M+H)

Found: 397.9282

11,12-Diethyl-11,12-dihydroindolo[2,3-*a*]carbazole-5-carbonitrile 238a:

The product **238a** was obtained as orange color solid from **234c** through column chromatography using a mixture of 6% ethyl acetate and hexanes as described in procedure D.



Yield: 74 %

Mp: 204 °C

IR (KBr) ν_{max} cm^{-1}: 3477, 3051, 2960, 2928, 2868, 1607, 1477, 1450, 1375, 1351, 1228, 1151, 1087, 1008, 920

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, 1H, J = 8 Hz), 8.22 (s, 1H), 8.19 (d, 1H, J = 7.6 Hz), 7.59-7.54 (m, 2H), 7.47-7.44 (m, 2H), 7.34-7.30 (m, 2H), 4.80 (q, 2H, J = 7.2 Hz), 4.48 (q, 2H, J = 7.2 Hz), 1.58 (t, 3H, J = 7.2 Hz), 1.49 (t, 3H, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 141.2, 135.8, 134.2, 127.1, 126.8, 123.6, 123.0, 122.1, 122.0, 121.0, 120.1, 119.5, 119.0, 118.5, 108.97, 108.4, 104.5, 82.8, 38.5, 37.7, 14.8, 13.9

LC-MS (m/z) 338 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45 %

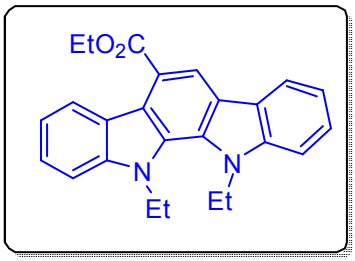
Found: C, 81.76; H, 5.61; N, 12.36 %

Ethyl 11,12-diethyl-11,12-dihydroindolo[2,3-*a*]carbazole-5-carboxylate 238b:

The product **238b** was obtained as orange color solid from **234d** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.

Yield: 68 %

Mp: 186 °C



IR (KBr) ν_{max} cm^{-1}: 3462, 3041, 2963, 2912, 2858, 1587, 1467, 1375, 1311, 1248, 1180, 1151, 1087, 1020, 891

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81-8.79 (m, 2H), 8.50 (s, 1H), 8.30-8.28 (m, 2H), 7.60-7.58 (m, 1H), 7.53-7.49 (m, 1H), 7.40-7.33 (m, 2H), 4.94 (q, 2H, J = 7.2 Hz), 4.61 (q, 2H, J = 7.2 Hz),

4.47 (q, 2H, *J* = 7.2 Hz), 1.80 (t, 3H, *J* = 7.2 Hz), 1.58-1.53 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.5, 142.5, 141.1, 140.5, 135.4, 126.5, 125.8, 125.0, 124.6, 124.2, 124.1, 122.6, 121.7, 121.5, 119.6, 117.4, 108.5, 107.7, 98.1, 61.0, 40.8, 37.7, 15.3, 14.5, 13.4

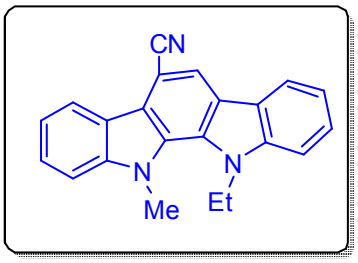
LC-MS (m/z): 385 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29 %

Found: C, 78.14; H, 6.32; N, 7.22 %

11-Ethyl-12-methyl-11,12-dihydroindolo[2,3-*a*]carbazole-5-carbonitrile 238c:

The product **238c** was obtained as yellow colored solid from **234a** through column chromatography using a mixture of 5% ethyl acetate and hexanes as described in procedure D.



Yield: 71 %

Mp: 192 °C

IR (KBr) ν_{max} cm^{-1}: 3968, 3063, 2968, 2852, 1687, 1477, 1331, 1328, 1180, 1082, 889, 748

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.73 (d, 1H, *J* = 8.2 Hz), 8.13 (s, 1H), 8.07 (d, 1H, *J* = 7.8 Hz), 7.52-7.49 (m, 2H), 7.47-7.45 (m, 2H), 7.31-7.29 (m, 2H), 4.9 (s, 3H), 4.52 (q, 2H, *J* = 7.4 Hz), 1.47 (t, 3H, *J* = 7.4 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 142.3, 141.0, 136.8, 134.7, 128.0, 126.7, 124.1, 123.2, 122.2, 122.0, 121.1, 120.8, 120.4, 120.0, 119.2, 109.5, 108.7, 104.8, 84.2, 37.7, 33.3, 14.0

LC-MS (m/z): 324 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 12.99 %

Found: C, 81.76; H, 5.28; N, 12.96 %

2.6 References:

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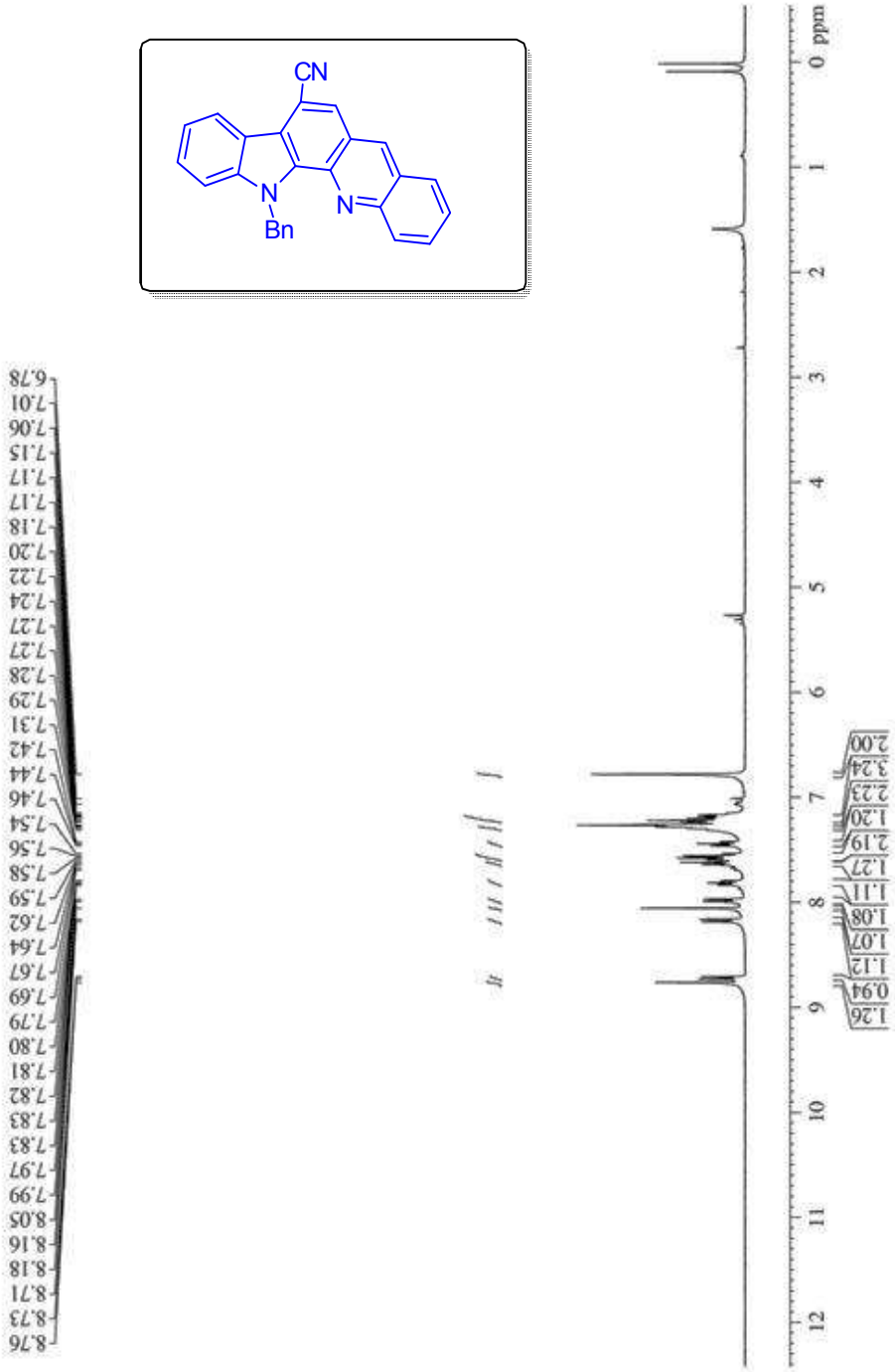
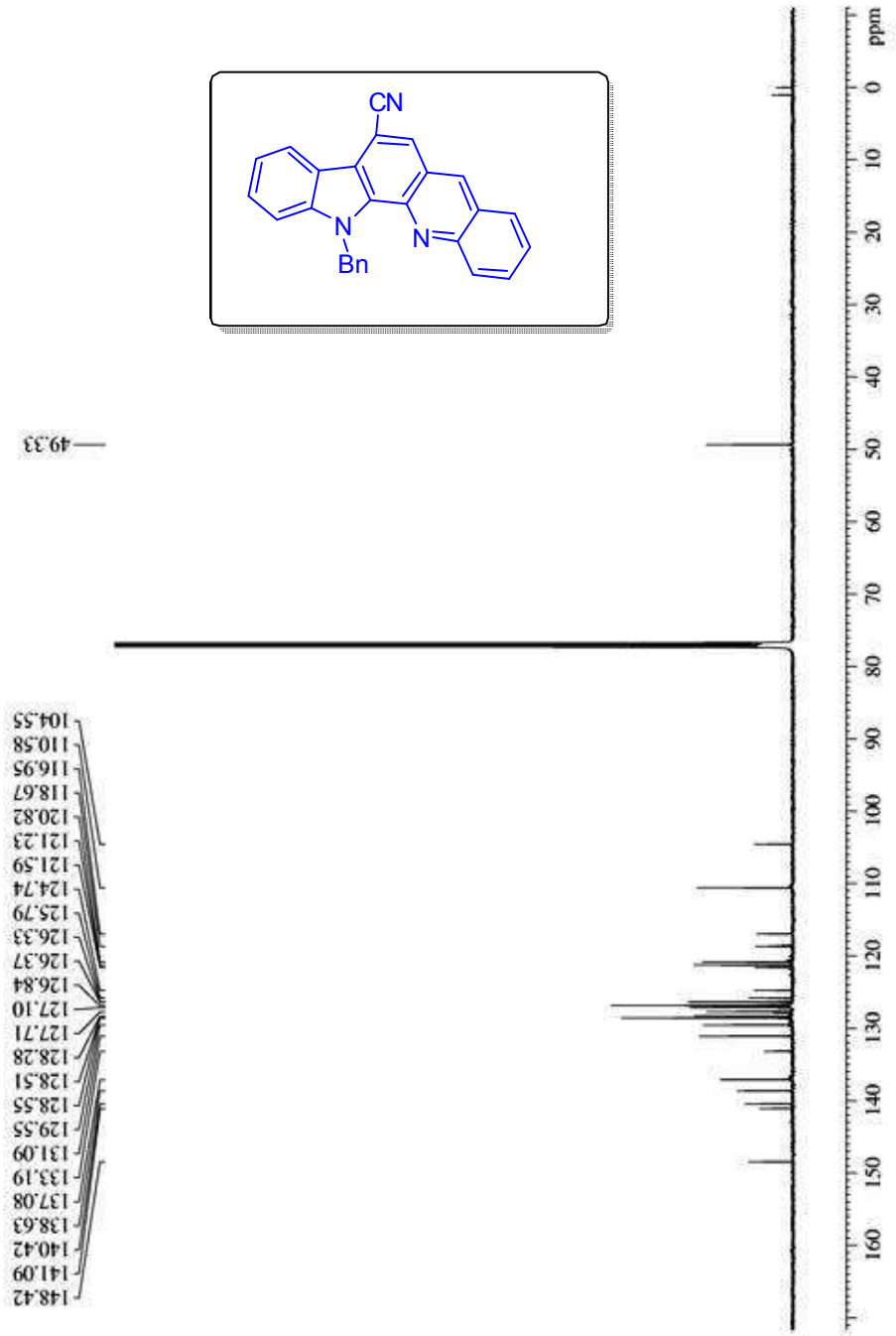
^{1}H NMR of 13-Benzyl-13*H*-indolo[3,2-*c*]acridine-5-carbonitrile 236g



^{13}C NMR of 13-Benzyl-13*H*-indolo[3,2-*c*]acridine-5-carbonitrile 236g



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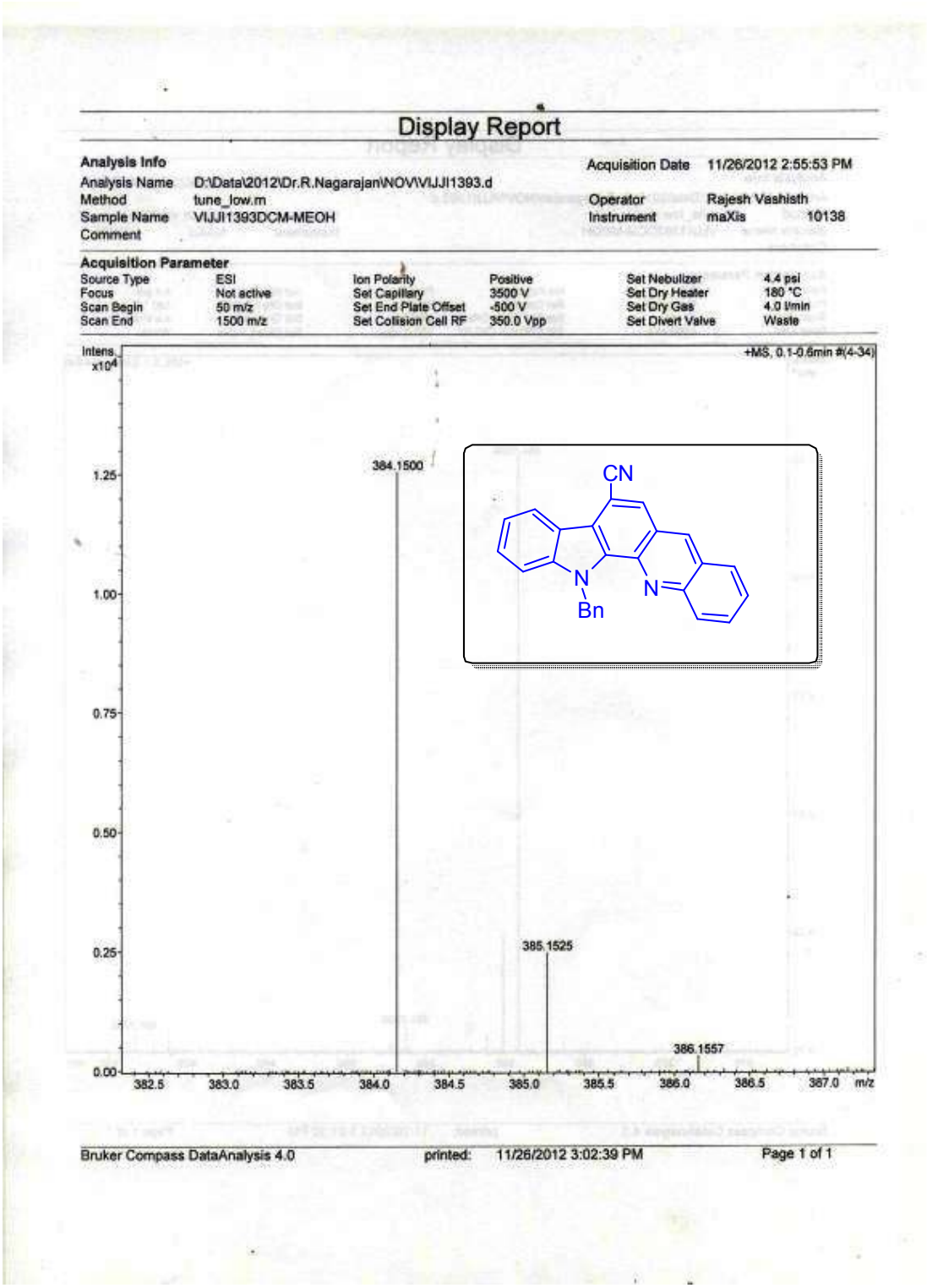
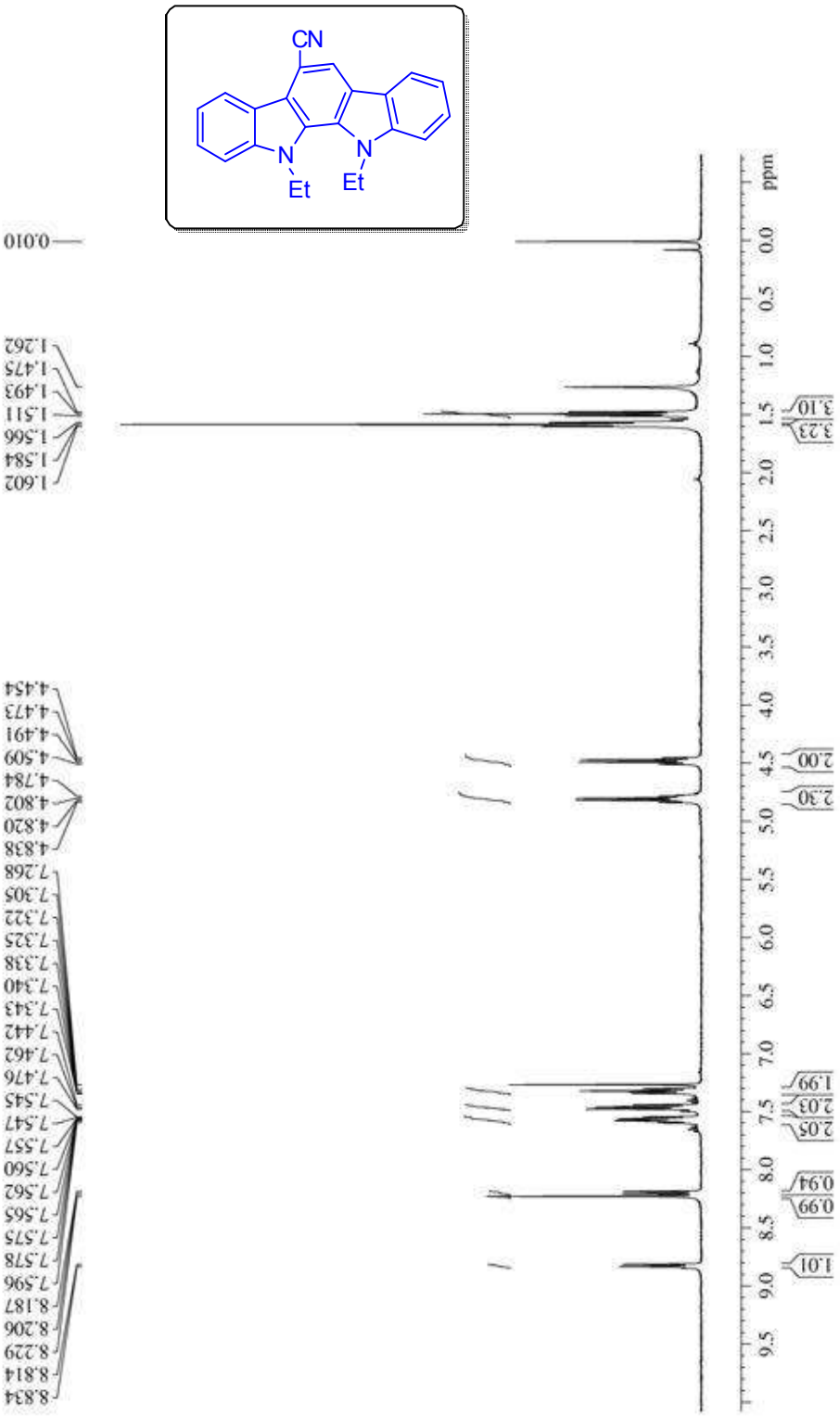


[1]H NMR 11,12-diethyl-11,12-Dihydroindolo[2,3-*a*]carbazole-5-carbonitrile 238a



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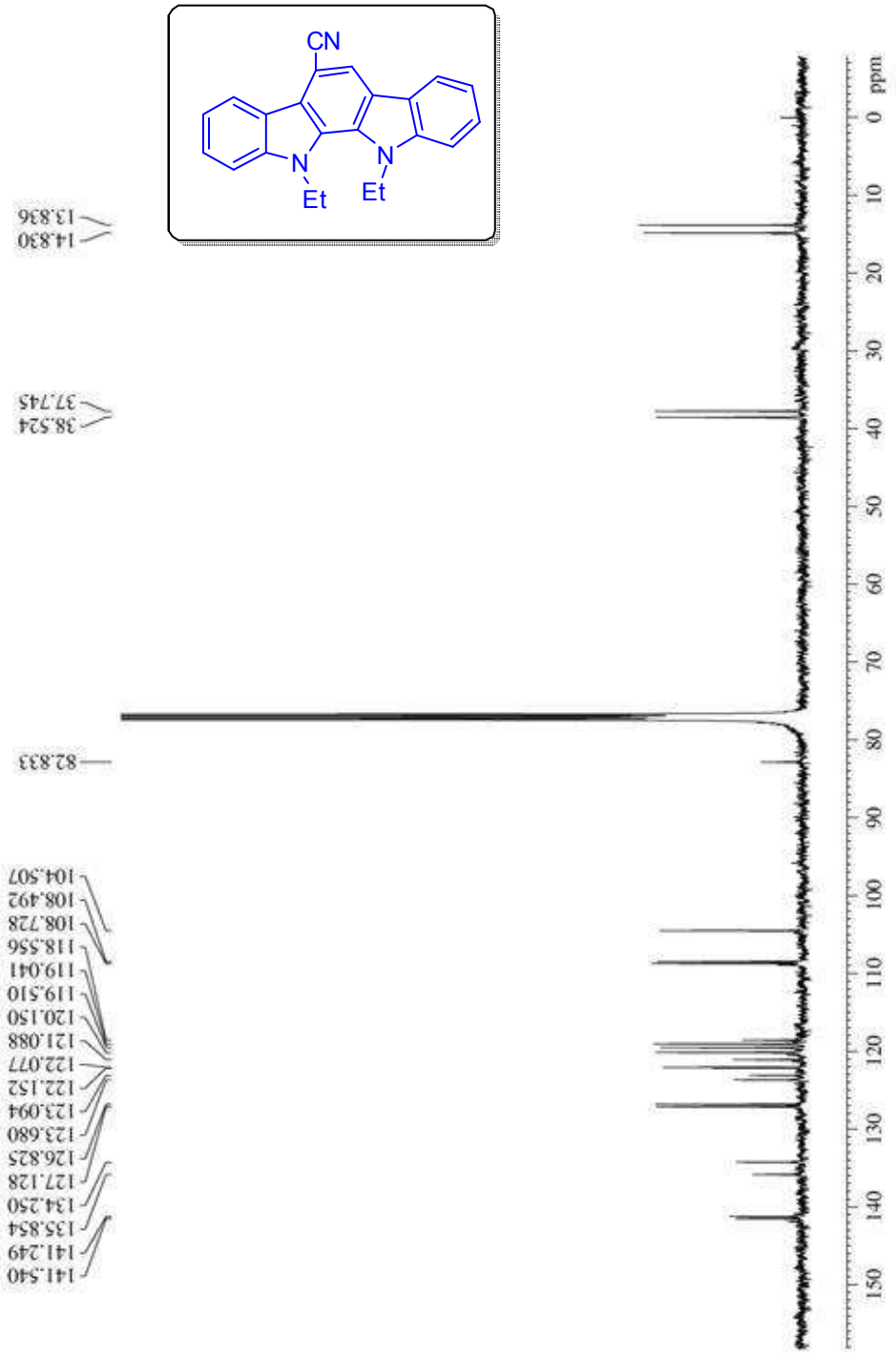
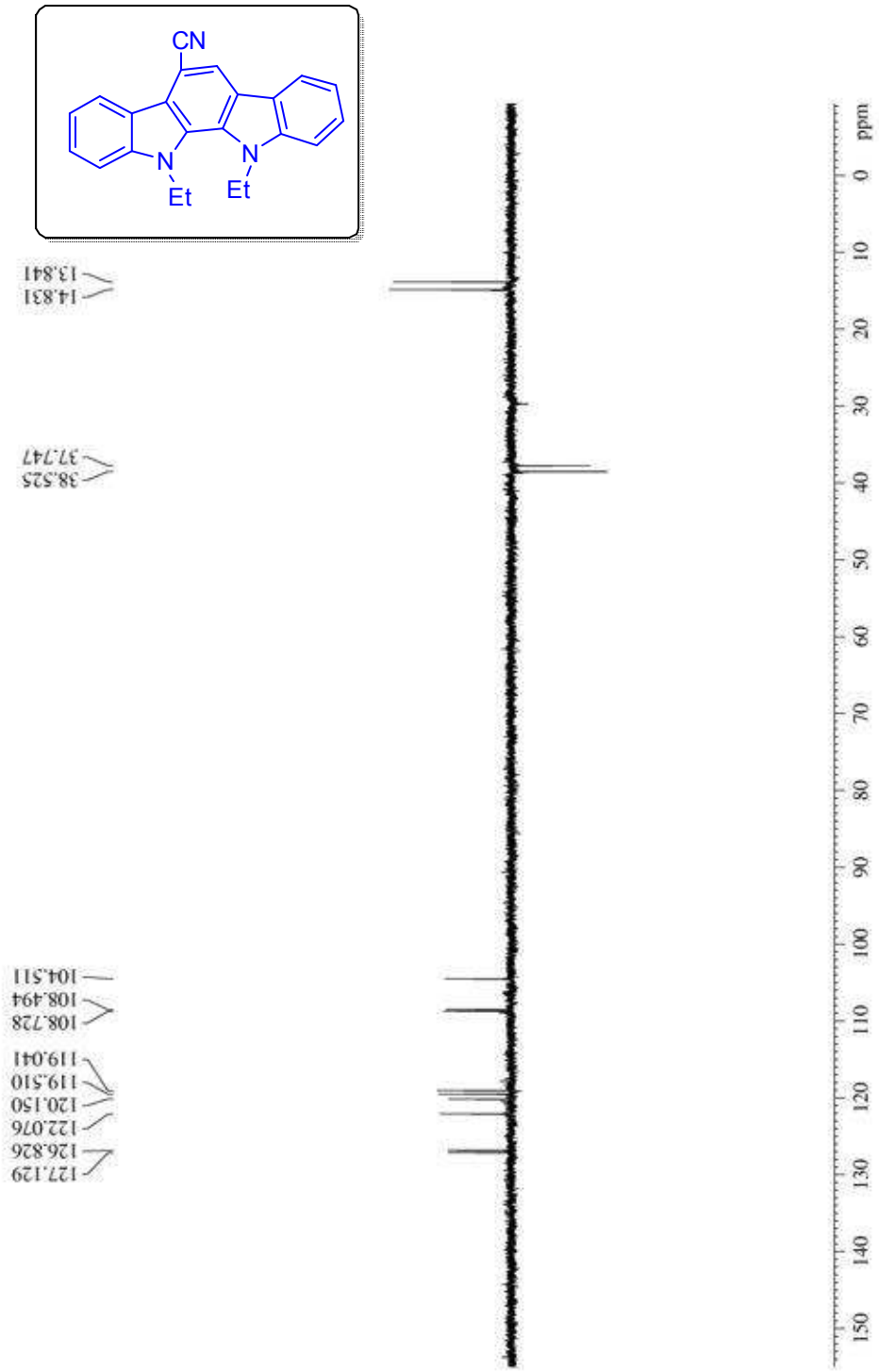


DEPT of 11,12-diethyl-11,12-Dihydroindolo[2,3-*a*]carbazole-5-carbonitrile 238a



LC-MS of 11,12-diethyl-11,12-Dihydroindolo[2,3-*a*]carbazole-5-carbonitrile 238a

LCMS-2010A DATA REPORT
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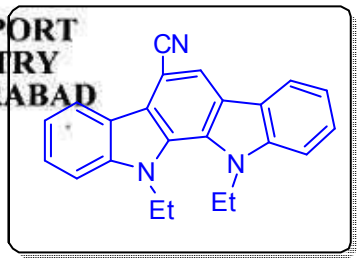

User : Admin
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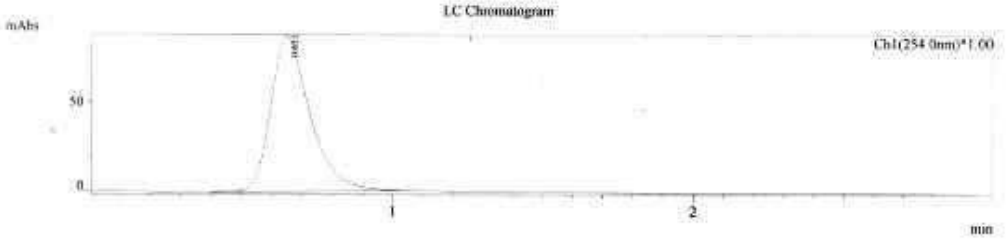
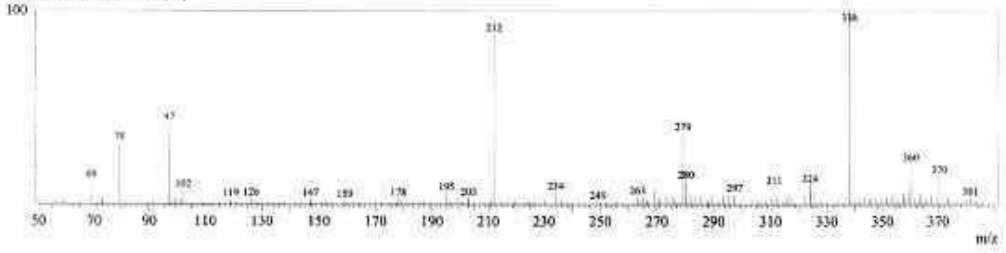
Inj. Volume : 5.000
Data Name : C:\LCMSsolution\User\Data\VIJI-1511-APCI-POS1.qld
Method Name : C:\LCMSsolution\User\Method\esi.qlm

LC Chromatogram



MS Spectrum

Line#:1 R.Time:0.777(Scan#:47) Positive
MassPeaks:246 BasePeak:338.10(220542)
RawMode:Single 0.777(47)
BG Mode:Peak Start 0.560(34)



MS Peak Table

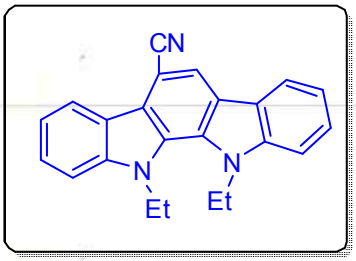
Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.777	0.560	1.060	29133753	1735894	16.78		100.00		338.10	220542
				29133753	1735894			100.00			

OPERATOR

Elemental analysis of 11,12-Diethyl-11,12-dihydroindolo[2,3-*a*]carbazole-5-carbonitrile 238a

FLASH EA 1112 SERIES CHN REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

Method filename: C:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID: VIJI-1511 (# 11)
Analysis type: UnkNown
Chromatogram filename: UNK-09112012-11.dat
Sample weight: .865



Element Name	Element %	Ret. Time
Nitrogen	12. 36	0. 90
Carbon	81. 76	1. 41
Hydrogen	5. 61	4. 77

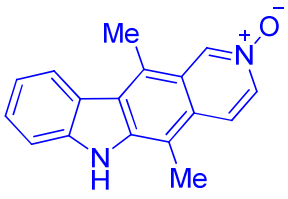
Synthesis of Pyridocarbazoles *via* Povarov reaction

CHAPTER 3

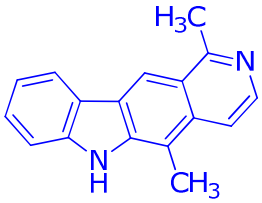
3.1 Introduction

Pyridocarbazoles are important constituents of the heteroannulated carbazoles for example, ellipticine, olivacine, strellidimine, and janetine belong to the group of pyrido[4,3-*b*]carbazole alkaloids which show potential biological activities[118] (Fig. 15). Among them, ellipticine is one of the simplest naturally occurring alkaloids which occupies a pivotal position in the field of medicinal chemistry because of its promising antitumor activity. [119] Its derivatives exhibit promising results in the treatment of osteolytic breast cancer metastasis, kidney sarcoma, brain tumours and myeloblastic leukemia. [119d-e]

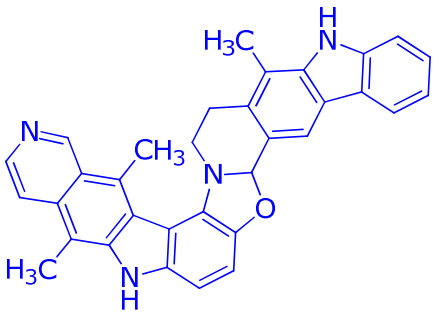
Numerous methods have been reported to synthesize ellipticine and its structurally modified derivatives.[120] However, much less attention has been paid to the synthesis of its isomeric pyridocarbazoles.[121] Several methods for the synthesis of isomeric ellipticine are known, however there have been continuous efforts to develop isomeric ellipticine using mild reaction conditions.



239 *N*-Oxyellipticine



240 Olivacine



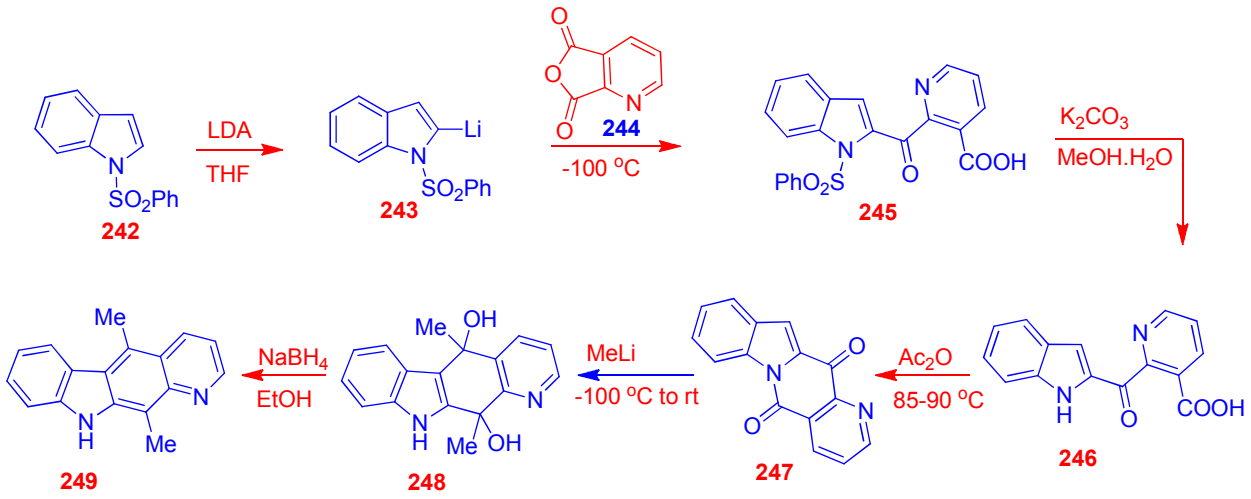
241 Sterillidimine

Fig: 15

Gribble *et al*. reported[121g] the synthesis of isomeric ellipticine derivatives in good yield starting from indole. Regiospecific C-2-lithiation of **242** with LDA (THF, -70 to 20 °C, 3 h) followed by the rapid addition at -100 °C of 2,3-pyridinedicarboxylic anhydride (**244**) gave keto acid **245** in 83% yield. Cleavage of the benzenesulfonyl protecting group in **245** was achieved with potassium carbonate (MeOH-H_2O, 3:1, reflux, 5 h) to give keto acid **246** in

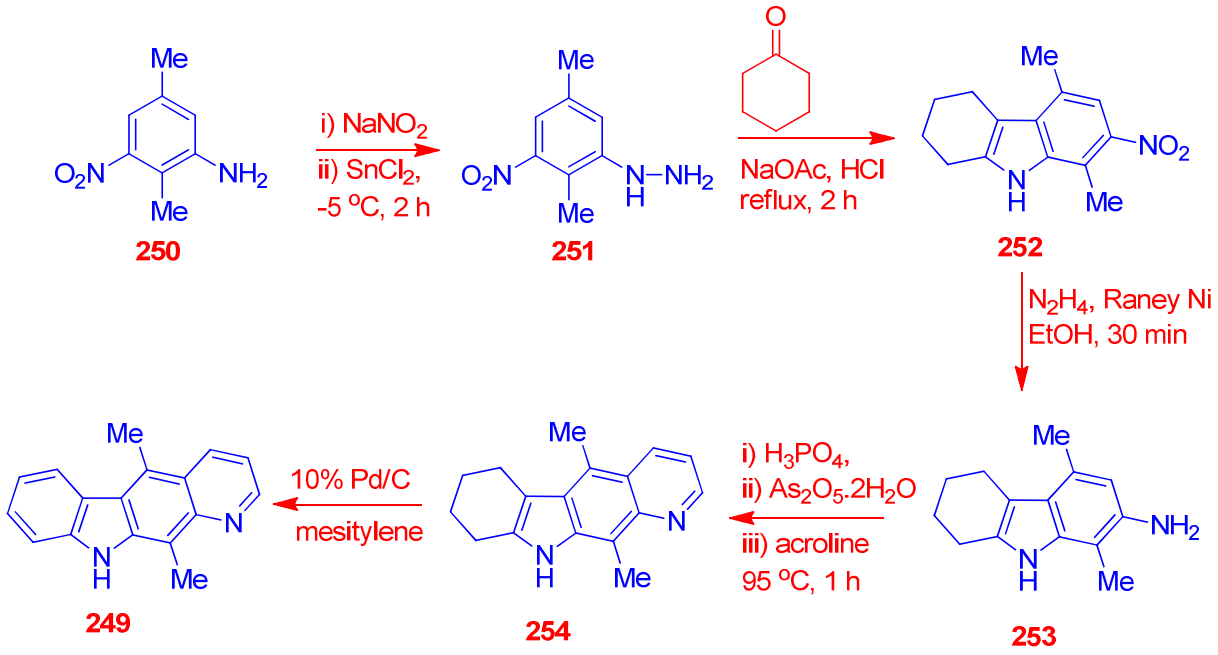
essentially quantitative yield. This was treated with hot acetic anhydride (85-90 °C, 21 h) to effect cyclization to the keto lactam **247**, isolated as greenish golden crystals in 84% yield. Then, keto lactam **247** was treated with methyllithium (2 equiv, -100 °C, THF) to afford a mixture of diols **248**, which, without purification, was treated with sodium borohydride (EtOH, reflux, 25 h) to afford 5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole (**249**) in 96% yield from **247** (**Eq. 32**).

Eq. 32



Lescot *et al.* have reported the synthesis of isomeric ellipticine a 10*H*-pyrido[2,3-*b*]carbazole isomer.[122] Diazotization was carried out in the usual manner of **250** by adding portion wise, and stirring a cold solution of sodium nitrite gives the **251**. Then 2-hydrazino-6-nitro-*p*-xylene **251** with cyclohexanone on reflux for 2 h gave the dimethyltetrahydronitrocarbazoles **252**. **252** was reduced to the corresponding tetrahydroaminocarbaoles by raney nickel to produce **253**. A Skraup reaction with **253** afforded **255** after aromatization of **254** with 10% palladium on activated carbon in boiling mesitylene (**Eq. 33**).

Eq. 33

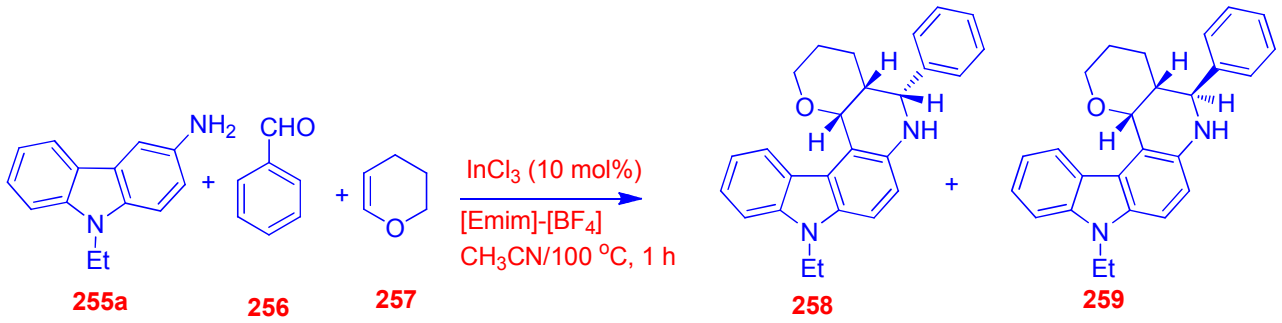


3.2 Hetero Diels-Alder reaction

Hetero Diels-Alder reaction has been recognized as one of the most fascinating areas of current research.[123] This method has been used as an efficient approach for the synthesis of biologically active natural and unnatural compounds.[124] Povarov reaction[125] has been proven to be a powerful tool for synthesis of functionalized carbocyclic and heterocyclic compounds[126] and various Lewis acid catalysts were extensively used to study this reaction.[127]

Nagarajan *et al*. reported the synthesis of isomeric ellipticine by imino Diles-Alder reaction.[121i] The cycloaddition of imine derived from 9-ethyl-3-aminocarbazole **255a** and benzaldehyde **256** in [Emim]-[BF_4] at 100 °C underwent an intermolecular [4+2] cycloaddition reaction with 3,4-dihydro-2*H*-pyran **257** in the presence of Lewis acid to yield 9-ethyl-5-phenyl-2,3,4,4a,5,6,9,13d-octahydropyrano[2′,3′:4,5]pyrido[2,3-*c*]carbazole **258** and **259** as a mixture of diastereomers, where the cis isomer **258** is the major product (**Eq. 34**).

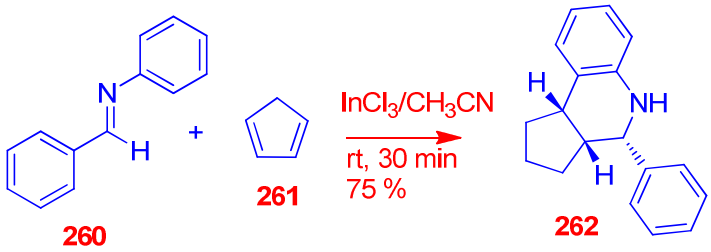
Eq. 34



255a 256 257 258 259

In 1997 Perumal *et al*. reported[127c] imino Diels-Alder reaction catalyzed by $InCl_3$. In the presence of 20 mol% anhydrous indium trichloride ($InCl_3$), *N*-benzilideneaniline (**260**) was treated with cyclopentadiene (**261**) in aeetonitrile at room temperature. The imine acted as a heterodiene and the reaction proceeded smoothly to give the corresponding tetrahydroquinoline derivative **262** in 30 min (**Eq. 35**).

Eq. 35

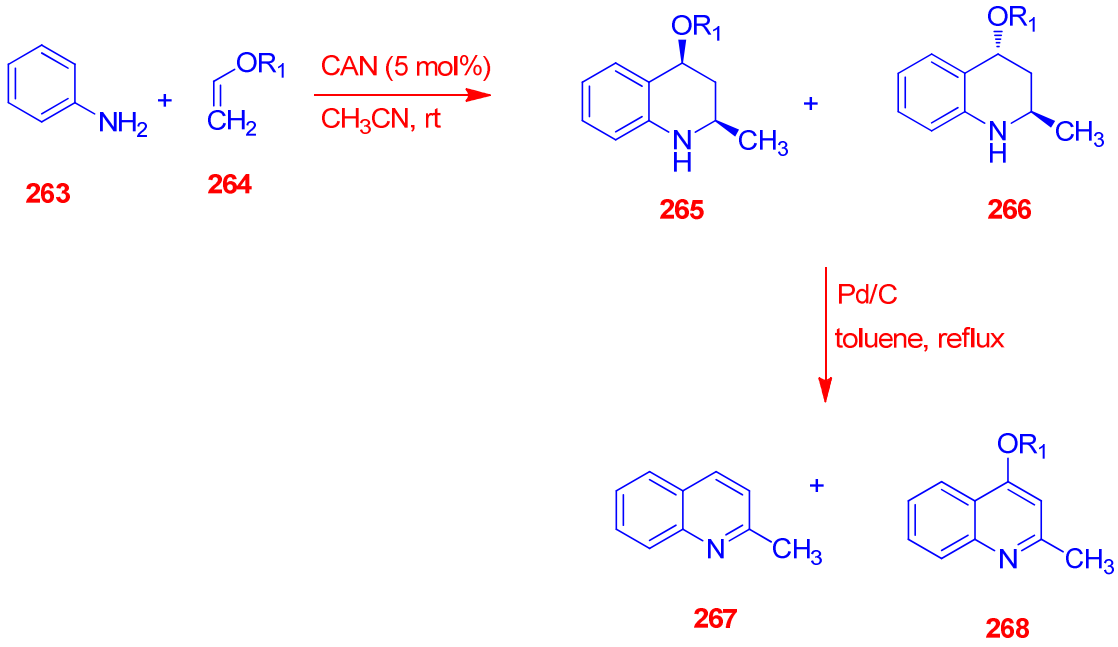


260 261 262

CAN has proved to be very useful to synthetic organic chemists for over four decades. The reasons for its, the large reduction potential value of 1.61 V (vs NHE) endowed in Ce^{+4} makes Ce(IV) reagents superior oxidizing agents compared to other metal ions and low toxicity, ease of handling, experimental simplicity, and solubility in a number of organic solvents, inexpensiveness, and eco-friendly nature. The enormous growth in the use of this reagent is evidenced by the publication of a large number of research papers and several reviews concerning CAN-mediated reactions.[128]

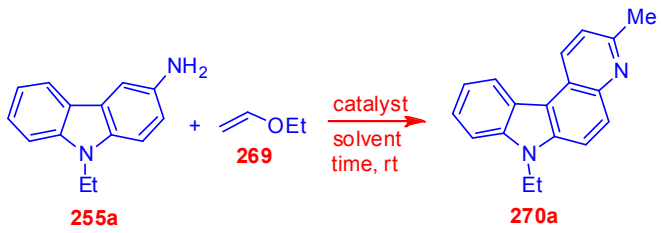
Menéndez *et al*. reported the synthesis of 2-methylquinoline derivatives by CAN mediated imino-Diels-Alder reaction.[128l] Aniline **263** and alkyl vinyl ether **264** in acetonitrile was added CAN to give a mixture of tetrahydroquinoline derivatives **265** and **266**. 2-Methylquinoline derivatives **267**, **268** were efficiently prepared from 4-alkoxy-2-methyl-1,2,3,4-tetrahydroquinolines by Pd/C-promoted dehydrogenation. Compound **267** formed majorly along with small amounts of the 4-alkoxy-2-methylquinolines **268** (**Eq. 36**).

Eq. 36



3.3 CAN catalyzed regioselective synthesis of pyrido[2,3-*c*]carbazoles through Povarov reaction

Scheme 8. Preparation of pyrido[2,3-*c*]carbazole



The synthetic strategy adopted for title compound pyrido[2,3-*c*]carbazole has been outlined in Scheme 8. At the outset of our studies, 9-ethyl-3-aminocarbazole **255a** was used as the model substrate to optimize reaction conditions with ethylvinylether (EVE) **269**. We probed the effect of representative catalysts, catalytic concentration, and solvents on this Povarov reaction and the results are summarized in Table 13. Our preliminary investigations revealed that the $Zn(OTf)_2$ was able to catalyze this transformation but generated the product pyridocarbazole **270a** in low yield, as a result we searched for alternative Lewis acid catalysts that proved to efficiently work with Povarov reaction.

CAN was found to be more effective than various catalysts that were examined for the reaction. It catalyzes this Povarov reaction smoothly and furnishes aromatized pyridocarbazoles in good yields. Trace amounts of product was formed when $Cu(OTf)_2$ and Ag(OTf) were employed as catalysts in the above reaction (Table 13, entries 20, 22). On the other hand, the reaction proceeded smoothly and gave the desired product **270a** in good yields when $In(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, and $Sc(OTf)_3$ were used as the catalysts (Table 13, entries 12, 13, 14, 19). The reaction did not proceed when ethanol, benzene, CCl_4, and DMSO were used as solvents (Table 13, entry 25). Further screening revealed that acetonitrile was the best choice (78% yield, Table 13, entry 6). Other solvents such as chloroform, DCM, and toluene provided reasonable yields in this Povarov reaction (Table 13, entries 1, 2, 4). No expected product was obtained even on prolonged reaction time when a blank experiment without the addition of CAN was conducted, which indicated the essential role of cerium(IV) in this transformation (Table 13, entry 26).

Table 13. Optimization conditions for the preparation of **270a**[a]

s. no	catalyst	solvent	time (h)	yield[f] (%)
1	CAN	$CHCl_3$	8	53
2	CAN	DCM	6	56
3	CAN	Dioxane	12	28
4	CAN	Toluene	7	61
5	CAN[b]	CH_3CN	6	51
6	**CAN**	**CH_3CN**	**6**	**78**
7	CAN[c]	CH_3CN	8	78
8	CAN	THF	12	32
9	$InCl_3$	Toluene	12	25
10	$InCl_3$	CH_3CN	12	61
11	Iodine	CH_3CN	8	32
12	$In(OTf)_3$	CH_3CN	8	72
13	$Yb(OTf)_3$	CH_3CN	8	68
14	$La(OTf)_3$	CH_3CN	8	68
15	Montmorillonite	CH_3CN	8	42
16	$AlCl_3$	CH_3CN	12	30
17	$ZnCl_2$	CH_3CN	12	33
18	p-TSA	CH_3CN	12	46
19	$Sc(OTf)_3$	CH_3CN	8	71
20	$Cu(OTf)_2$	CH_3CN	8	22
21	$La(OTf)_3$	Toluene	8	16
22	Ag(OTf)	CH_3CN	8	22
23	$Zn(OTf)_2$	CH_3CN	12	15
24	CAN	DMF	12	32
25	CAN	Solvents[d]	24	-
26	-	Solvents[d+e]	24	-

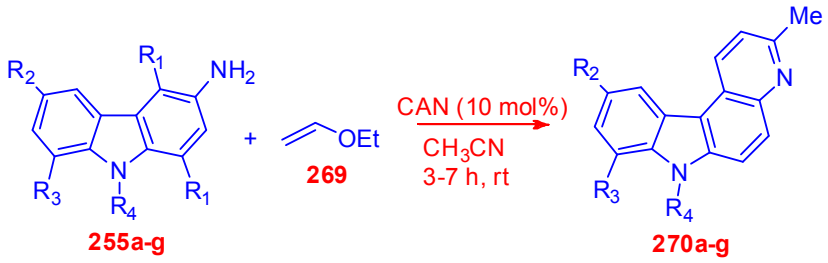
[a] Unless otherwise mentioned, all the reactions were conducted in a RB using 9-ethyl-3-aminocarbazole **255a** (1 equiv.), ethylvinylether **269** (2.5 equiv.) catalyst (10 mol%), 10 mL solvent stirred at room temperature. [b] 5 mol% of catalyst used. [c] 15 mol% of catalyst used. [d] ethanol, benzene, chloroform, DMSO, [e] toluene, CH_3CN, dioxane, DCM, CCl_4, THF. [f] isolated yield.

When the amount of EVE was decreased to 2.0 equiv. a slightly lower yield was obtained. No improvement was observed when the amount of EVE was increased to 4.0 equiv. The use of PPh_3 or dppe as a ligand along with reaction condition could not improve yield of the reaction. A lower concentration of catalyst could also be used with comparable success. For instance, 5 mol % catalyst resulted in a 51% yield of the product in 6 h (Table 13, entry 5). However, no improvement in the yield of the product was observed when the catalyst

loading was increased to 15 mol % (Table 13, entry 7). After careful screening, the optimal reaction condition was found to be 1.0 equiv. of aminocarbazoles (**255a-j)** 2.5 equiv. of EVE (**269)**, and 10 mol % of CAN in 10 ml of CH_3CN at room temperature.

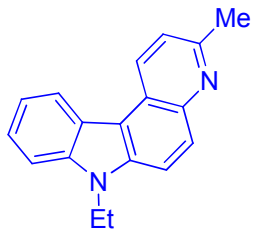
To demonstrate the generality of this transformation, the optimized conditions were applied to a variety of aminocarbazoles. Table 14 and scheme 10 summarize the results for the Povarov reaction of a series of aminocarbazoles **255a-j** with EVE produced the corresponding pyridocarbazoles **270a-j** in good yields. When R_1 was substituted with methyl group, pyrido[2,3-*b*]carbazole (**270h-i**) was obtained as product (Scheme 10). This optimized condition was examined for unprotected carbazoles and it afforded the pyridocarbzoles in good yields. For example, pyrido[2,3-*a*]carbazole **270j** was obtained as product when 1-aminocarbazole was subjected to Povarov reaction. Products of **270a-j** were confirmed by NMR analysis. Additionally, the structure of **270g** is confirmed by X-ray crystallographic analysis. The ORTEP diagram of **270g** is shown in Fig 16.[129]

Scheme 9. Preparation of pyrido[2,3-*c*]carbazoles from various 3-aminocarbazoles

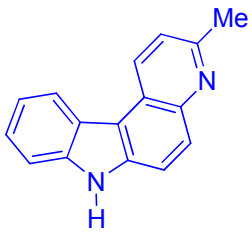


R_1 = H
R_2 = H, Cl, Br
R_3 = H, Cl
R_4 = H, Me, Et, *n*-Bu, Bn

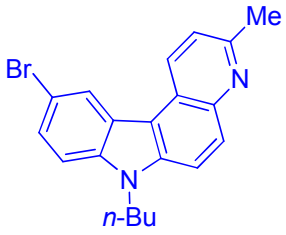
Table 14. Synthesis of pyrido[2,3-*c*]carbazoles from various 3-amino-carbazoles by Povarov reaction[a]



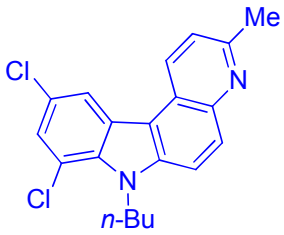
270a, 6 h, 78%



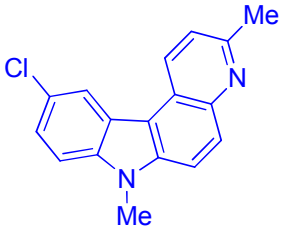
270b, 6 h, 79 %



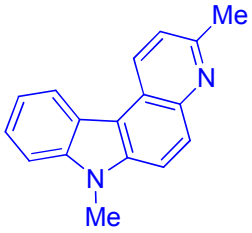
270c, 4 h, 80 %



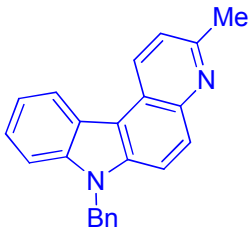
270d, 6 h, 75 %



270e, 3 h, 79 %

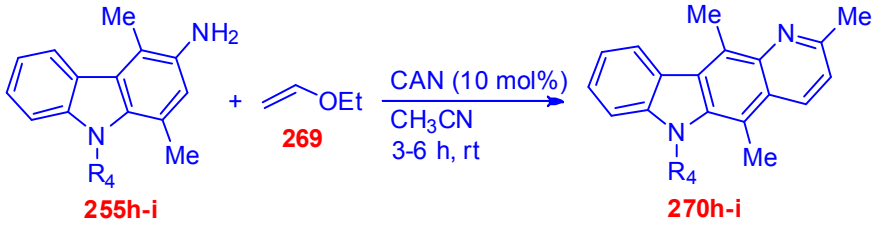


270f, 7 h, 76 %

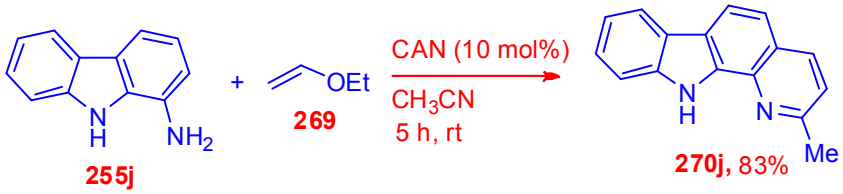


270g, 7 h, 76 %

Scheme 10. Preparation of pyrido[2,3-*b*] and pyrido[2,3-*a*]carbazoles[a]



if R_4 = H, yield = 82 % (3 h)
if R_4 = Et, yield = 80 % (6 h)



[a] All the reactions were conducted in a RB using 3-aminocarbazole **255a-j** (1.0 equiv.), ethylvinylether **269** (2.5 equiv.), CAN (10 mol%) CH_3CN (10 mL) stirred at room temperature. Yields are isolated yields.

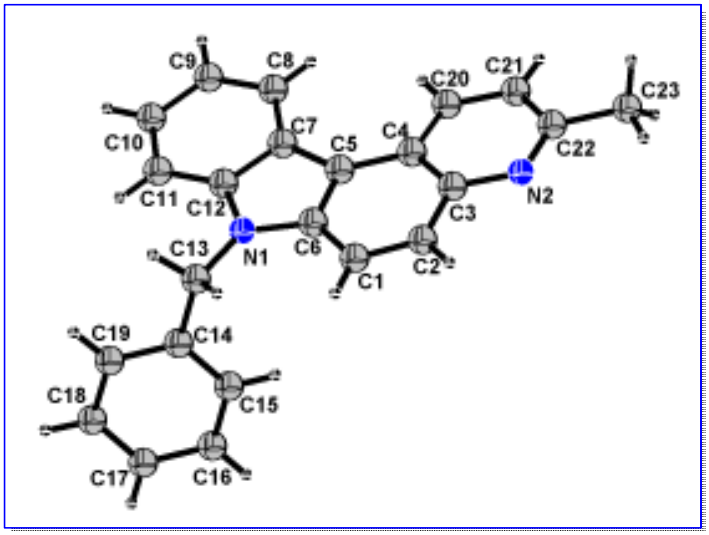
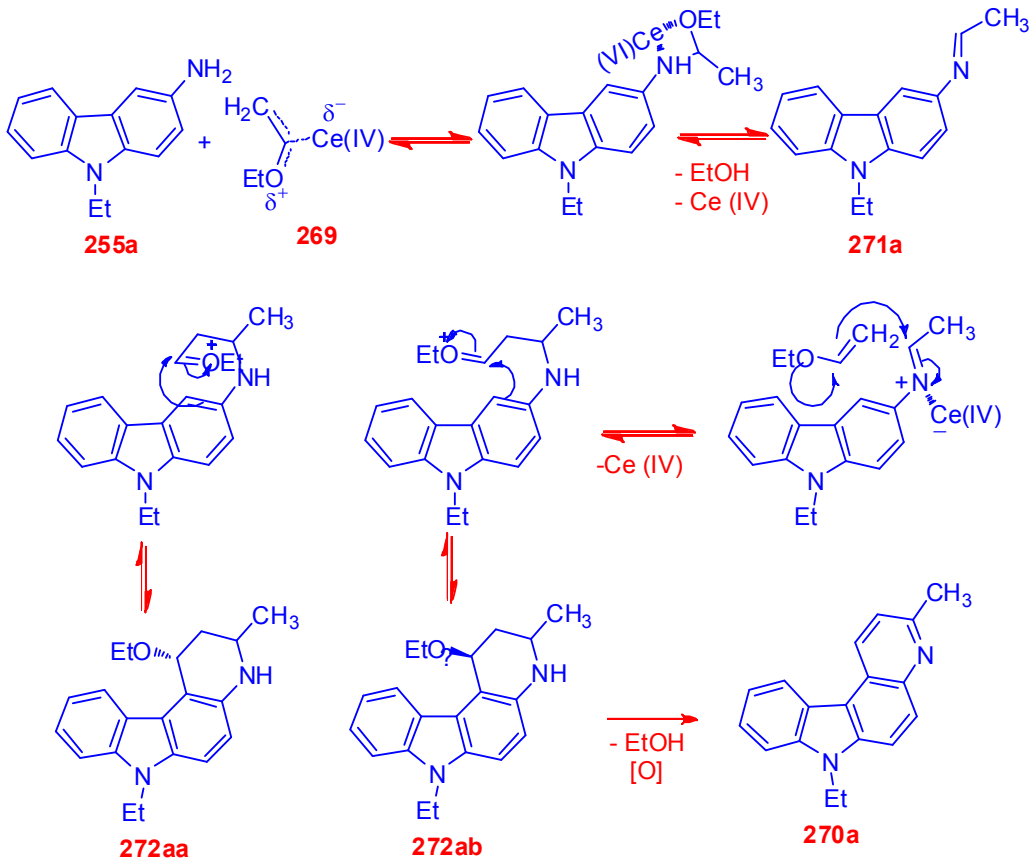


Fig 16. ORTEP diagram of **270g**

Scheme 11. Possible mechanism for synthesis of pyridocarbazoles **270a-j**

Extremely simple reagents and conditions were used in this Povarov reaction. A mixture of **255a** and **269** in acetonitrile containing a catalytic amount of CAN (10 mol %) was stirred at room temperature which afforded the imine intermediate (**271a**). Subsequently, intermolecular Povarov reaction of **271a** with electron rich EVE which act as dienophile would afford compounds **272aa** and **272ab**, which then undergo subsequent aromatization to furnish 3-methyl-7*H*-pyrido[2,3-*c*]carbazole **270a** in good yield. This mechanism was proposed based on the literature.[128l]



3.4 Conclusion

In conclusion, we have described an efficient route for the construction of potentially active pyridocarbazole framework via CAN-mediated Povarov reaction. This transformation proceeds with high regioselectively through Povarov reaction, and subsequent aromatization. It is noteworthy that this is the first example to the best of our knowledge of constructing pyrido[2,3-*c*], [2,3-*b*], [2,3-*a*]carbazoles under such mild conditions.

3.5 Experimental Section

General Information

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: ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER AVANCE-400 spectrometer. ^{1}H NMR (400 MHz) spectra of the some samples were measured in $CDCl_3$ (δ = 7.26 ppm) or in DMSO-d_6 (δ = 2.50 ppm) or in the mixture of $CDCl_3$/DMSO-d_6 with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 MHz) spectra of some samples were measured in chloroform-*d* (δ = 77.10 ppm, with its middle peak of the triplet 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.

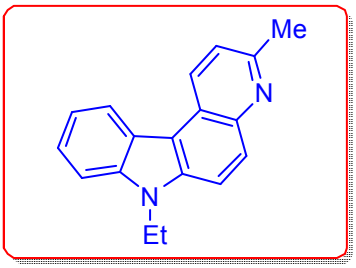
General procedures for the synthesis of 3-methyl-7*H*-pyrido[2,3-*c*]carbazole 270a:

Procedure E:

An oven dried 50 mL round bottom flask equipped with a mechanical stirrer and charged with CAN (10 mol %), and 9-ethyl-3-aminocarbzole **255a** (1.0 equiv.), CH_3CN (10 mL) along with ethylvinylether **270** (2.5 equiv.), and it was stirred at rt for 6 h, After completion of the reaction, followed by thin layer chromatography (TLC), the solvent was evaporated and dissolved in EtOAc. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography on neutral alumina using Hexane/EtOAc as the eluent. The solvent was evaporated to dryness to get the pure product **270a**. The same procedure was followed for other substrates **(270b-j)** also. All the compounds were purified by column chromatography.

7-Ethyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270a):

The product **270a** was obtained as Yellow colored solid from **255a** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure E.



Yield: 78 %

Mp: 48 °C

IR (KBr) ν_{max} cm^{-1}: 2920, 1649, 1537, 1466, 1020, 752

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (d, 1H, *J* = 8.0 Hz), 8.49 (d, 1H, *J* = 8.0 Hz), 8.10 (d, 1H, *J* = 9.2 Hz), 7.87-7.84 (m, 1H), 7.59-7.57 (m, 1H), 7.54-7.50 (m, 1H), 7.47 (d, 1H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 7.0 Hz), 4.52 (q, 2H, *J* = 7.0 Hz), 2.81 (s, 3H), 1.50 (t, 3H, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 144.2, 139.1, 136.7, 131.3, 127.4, 124.5, 123.3, 123.0, 122.0, 121.8, 119.7, 114.4, 113.6, 109.4, 37.7, 25.1, 14.4

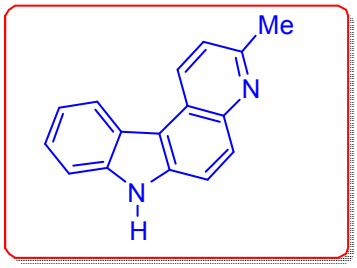
LC-MS (m/z): 261 $(M+H)^+$. positive mode

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76 %

Found: C, 83.15; H, 6.08; N, 10.65 %

3-Methyl-7*H*-pyrido[2,3-*c*]carbazole (270b):

The product **270b** was obtained as Yellow colored solid from **255b** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure E.



Yield: 79 %

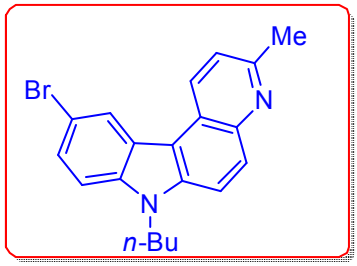
Mp: 78 °C

IR (KBr) ν_{max} cm^{-1}: 3404, 2924, 2858, 1722, 1655, 1601, 1529, 1431,

	1379, 1329, 1240, 1124, 837, 746
^{1}H NMR (400 MHz, $CDCl_3$):	δ 11.01 (s, 1H), 8.18 (d, 1H, *J* = 8.3 Hz), 8.13-8.09 (m, 2H), 7.52 (d, 1H, *J* = 8.4 Hz), 7.34-7.32 (m, 2H), 7.25-7.23 (m, 2H), 2.76 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 157.4, 139.0, 136.99, 136.95, 135.1, 125.3, 125.1, 123.8, 121.3, 120.1, 119.6, 119.4, 118.4, 111.3, 24.9.
LC-MS (m/z):	233 $(M+H)^+$. positive mode
Anal. Calcd. for $C_{16}H_{12}N_2$:	C, 82.73; H, 5.21; N, 12.06 %
Found:	C, 82.59; H, 5.21; N, 12.11 %

10-Bromo-7-butyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270c):

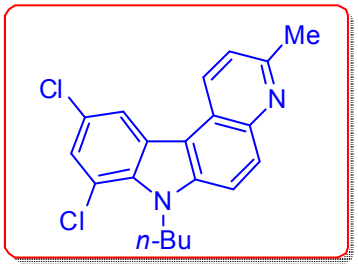
The product **270c** was obtained as Yellow colored solid from **255c** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure E.



Yield:	80 %
Mp:	62 °C
IR (KBr) ν_{max} cm^{-1}:	2964, 2924, 2858, 1612, 1579, 1518, 1467, 1375, 1317, 1153, 810, 734, 688, 434
^{1}H NMR (400 MHz, $CDCl_3$):	δ 8.94 (d, 1H, *J* = 8.4 Hz), 8.46 (d, 1H, *J* = 7.9 Hz), 8.08 (d, 1H, *J* = 9.1 Hz), 7.83-7.80 (m, 1H), 7.55-7.53 (m, 1H), 7.44 (d, 1H, *J* = 8.4 Hz), 7.37-7.35 (m, 1H), 4.40 (t, 2H, *J* = 7.1 Hz), 2.79 (s, 3H), 1.91-1.84 (m, 2H), 1.44-1.37 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 154.9, 144.1, 139.6, 137.2, 131.3, 127.3, 124.4, 123.2, 123.0, 122.0, 121.7, 199.7, 114.3, 113.9, 109.6, 42.9, 31.6, 25.0, 20.5, 13.8
LC-MS (m/z):	*m/z* = 368 $(M+H)^+$, 369 (M+1)), positive mode
Anal. Calcd. for $C_{20}H_{19}N_2Br$:	C, 65.40; H, 5.21; N, 7.63 %
Found:	C, 65.26; H, 5.21; N, 7.56 %

7-Butyl-8,10-dichloro-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270d):

The product **270d** was obtained as Yellow colored solid from **255c** through column chromatography using a mixture of 12% ethyl acetate and hexanes as described in procedure E.



Yield: 75 %

Mp: 132 °C

IR (KBr) ν_{max} cm^{-1}: 3447, 2959, 2928, 2868, 1739, 1647, 1583, 1545, 1520, 1456, 1367, 1300, 1211, 1080, 1014, 841, 810

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, 1H, *J* = 8.5 Hz), 8.18 (d, 1H, *J* = 1.8 Hz), 8.07-8.05 (m, 1H), 7.73-7.70 (m, 1H), 7.40 (d, 1H, *J* = 8.4 Hz), 7.38 (d, 1H, *J* = 1.8 Hz), 4.67 (t, 2H, *J* = 7.7 Hz), 2.79 (s, 3H), 1.88-1.80 (m, 2H), 1.46-1.37 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 144.4, 138.8, 133.2, 130.6, 129.0, 126.6, 125.9, 124.9, 122.4, 122.3, 119.7, 116.9, 113.8, 113.2, 44.5, 33.2, 25.0, 20.0, 13.8

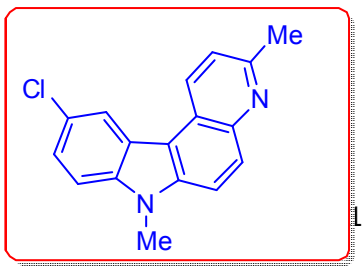
LC-MS (m/z): 357 $(M+H)^+$, 359 (M+2), positive mode

Anal. Calcd. for $C_{20}H_{18}N_2Cl_2$: C, 67.23; H, 5.08; N, 7.84 %

Found: C, 67.32; H, 5.08; N, 7.79 %

10-Chloro-3,7-dimethyl-7*H*-pyrido[2,3-*c*]carbazole (270e):

The product **270e** was obtained as Yellow colored solid from **255d** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure E.



Yield: 79 %

Mp: 52 °C

IR (KBr) ν_{max} cm^{-1}: 3360, 2961, 1633, 1606, 1483, 1323

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, 1H, *J* = 8.4 Hz), 7.79 (d, 1H, *J* = 9.0 Hz), 7.74 (s, 1H), 7.29 (d, 1H, *J* = 9.0 Hz), 7.20-7.18 (m, 1H), 7.12 (d, 1H, *J* = 8.4 Hz), 7.01-6.99 (m, 1H), 3.45 (s, 3H), 2.70 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 143.7, 137.8, 137.5, 130.4, 127.6, 124.7, 124.0, 123.3, 122.0, 121.8, 120.5, 112.9, 112.8, 109.7, 28.8, 20.0

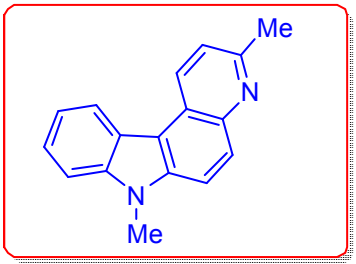
LC-MS (m/z): 281 $(M+H)^+$, 282 (M+1), positive mode

Anal. Calcd. for $C_{17}H_{13}N_2Cl$: C, 72.73; H, 4.67; N, 9.98 %

Found: C, 72.65; H, 4.58; N, 9.88 %

3,7-Dimethyl-7*H*-pyrido[2,3-*c*]carbazole (270f):

The product **270f** was obtained as Yellow colored solid from **255d** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure E.



Yield: 76 %

Mp: 118 °C

IR (KBr) ν_{max} cm^{-1}: 2918, 2856, 1645, 1527, 1113, 1020

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (d, 1H, *J* = 8.3 Hz), 8.47 (d, 1H, *J* = 7.9 Hz), 8.15 (d, 1H, *J* = 8.7 Hz), 7.87-7.84 (m, 1H), 7.58-7.54 (m, 2H), 7.49 (d, 1H, *J* = 8.0 Hz), 7.41-7.37 (m, 1H), 4.01 (s, 3H), 2.83 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 140.2, 137.7, 131.9, 126.98, 126.90, 124.7, 123.0, 122.9, 122.1, 121.6, 119.9, 114.3, 114.0, 109.5, 29.3, 24.7

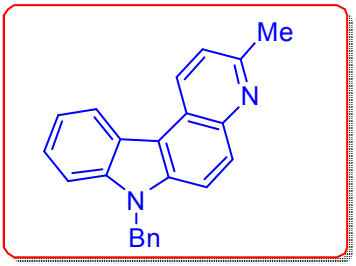
LC-MS (m/z): 247 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37 %

Found: C, 82.79; H, 5.61; N, 11.25 %

7-Benzyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270g):

The product **270g** was obtained as Yellow colored solid from **255e** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure E.



Yield: 76 %

Mp: 156 °C

IR (KBr) ν_{max} cm^{-1}: 2922, 2852, 1647, 1464, 1311, 1126, 1018, 744

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, 1H, J = 8.4 Hz), 8.46 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 9.0 Hz), 7.74-7.72 (m, 1H), 7.46-7.41 (m, 3H), 7.37-7.31 (m, 1H), 7.22-7.21 (m, 3H), 7.08-7.06 (m, 2H), 5.57 (s, 2H), 2.78 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 144.4, 139.9, 137.3, 136.9, 131.3, 128.8, 127.7, 127.6, 126.2, 124.7, 123.4, 122.9, 122.1, 121.8, 120.2, 114.7, 113.9, 109.8, 46.5, 25.1

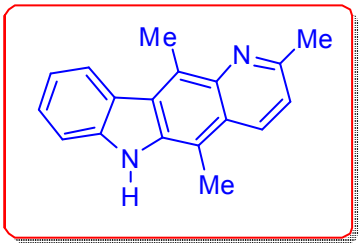
LC-MS (m/z): 323 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69 %

Found: C, 85.66; H, 5.51; N, 8.59 %

2,5,11-Trimethyl-6*H*-pyrido[3,2-*b*]carbazole (270h):

The product **270h** was obtained as Yellow colored solid from **255f** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure E.



Yield: 82 %

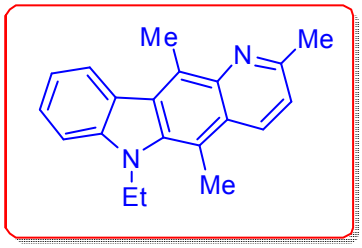
Mp: 84 °C

IR (KBr) ν_{max} cm^{-1}: 3443, 2970, 2926, 2856, 1741, 1635,

	1456, 1201, 1113
^{1}H NMR (400 MHz, $CDCl_3$):	δ 8.40 (d, 1H, J = 7.0 Hz), 8.33 (d, 1H, J = 8.8 Hz), 7.93 (s, 1H), 7.52-7.46 (m, 2H), 7.32-7.27 (m, 2H), 3.39 (s, 3H), 2.81 (s, 3H), 2.78 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 154.1, 142.1, 141.5, 137.1, 131.4, 128.4, 126.8, 125.5, 124.8, 124.3, 124.0, 120.2, 119.4, 110.1, 108.2, 25.5, 13.9, 12.1
LC-MS (m/z):	261 $(M+H)^+$, positive mode
Anal. Calcd. for $C_{18}H_{16}N_2$:	C, 83.04; H, 6.19; N, 10.76 %
Found:	C, 83.15; H, 6.23; N, 10.68 %

6-Ethyl-2,5,11-trimethyl-6*H*-pyrido[3,2-*b*]carbazole (270i):

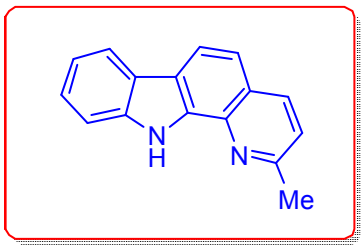
The product **270i** was obtained as Yellow colored solid from **255g** through column chromatography using a mixture of 12% ethyl acetate and hexanes as described in procedure E.



Yield:	80 %
Mp:	72 °C
IR (KBr) ν_{max} cm^{-1}:	3466, 2970, 2926, 1599, 1479, 1224, 744
^{1}H NMR (400 MHz, $CDCl_3$):	δ 8.37 (d, 1H, J = 7.7 Hz), 8.28 (d, 1H, J = 8.8 Hz), 7.51-7.47 (m, 1H), 7.32-7.30 (m, 1H), 7.26-7.22 (m, 1H), 7.20 (d, 1H, J = 8.8 Hz), 4.43 (q, 2H, J = 7.16 Hz), 3.35 (s, 3H), 2.88 (s, 3H), 2.76 (s, 3H), 1.40 (t, 3H, J = 7.12 Hz)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 154.0, 144.3, 141.2, 137.7, 131.5, 128.5, 126.8, 126.5, 124.9, 124.4, 124.3, 120.2, 119.1, 108.9, 108.2, 40.4, 25.4, 15.2, 14.1, 13.5
LC-MS (m/z):	289 $(M+H)^+$, positive mode
Anal. Calcd. for $C_{20}H_{20}N_2$:	C, 83.30; H, 6.99; N, 9.71 %
Found:	C, 83.21; H, 7.05; N, 9.65 %

2-Methyl-11*H*-pyrido[2,3-*a*]carbazole (270j):

The product **270j** was obtained as Yellow colored solid from **255h** through column chromatography using a mixture of 8% ethyl acetate and hexanes as described in procedure E.



Yield:	83 %
Mp:	136 °C
IR (KBr) ν_{max} cm^{-1}:	3186, 2916, 1601, 1527, 1431, 1379, 1327, 1246, 839, 742, 445
^{1}H NMR (400 MHz, $CDCl_3$):	δ 11.22 (s, 1H), 8.19 (d, 1H, *J* = 8.3 Hz), 8.11 (t, 2H, *J* = 8.6 Hz), 7.52 (d, 1H, *J* = 8.4 Hz), 7.34-7.31 (m, 2H), 7.25-7.19 (m, 2H), 2.76 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 157.5, 139.0, 137.0, 136.9, 135.2, 125.3, 125.1, 123.8, 121.3, 120.1, 119.6, 119.4, 118.4, 111.3, 24.9
LC-MS (m/z):	233 $(M+H)^+$, positive mode
Anal. Calcd. for $C_{16}H_{12}N_2$:	C, 82.73; H, 5.21; N, 12.06 %
Found:	C, 82.58; H, 5.21; N, 12.15 %

Table 15. Crystal data and structure refinement for 270g

Empirical formula	: $C_{23}H_{18}N_2$	
Formula weight	: 322.14	
Temperature	: 293 K	
Wavelength	: 0.71073 Å	
Crystal system	: orthorhombic	
Space group	: Pbca	
Unit cell dimensions	: a= 6.6020 (8)	α = 90°
	: b = 18.933 (3)	β = 90°
	: c = 27.575 (4)	γ = 90°
Volume	: 3446.7 (11)A^3	
Z	: 7	
Density (calculated)	: 1.246Mg/m^3	
Absorption coefficient	: 0. 0.073 mm^{-1}	
F(000)	: 1368	
Crystal size	: 0.40 x 0.32 x 0.18mm^3	
Theta range for data collection	: 2.95 to 26.37°.	
Index ranges	: -8<=h<=7, -23<=k<=23, -34<=l<=34	
Reflections collected / unique	: 12217 / 3519 [R(int) = 0.1450]	
Completeness to theta = 24.71°	: 99.9 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9167 and 0.8428	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 3519 / 0 / 228	
Goodness-of-fit on F^2	: 0.819	
Final R indices [I>2sigma(I)]	: R1 = 0.0782, wR2 = 0.2137	
R indices (all data)	: R1 = 0.2699, wR2 = 0.3842	
Largest diff. peak and hole	: 0.165 and -0.153 e.Å-3	

3.6. References

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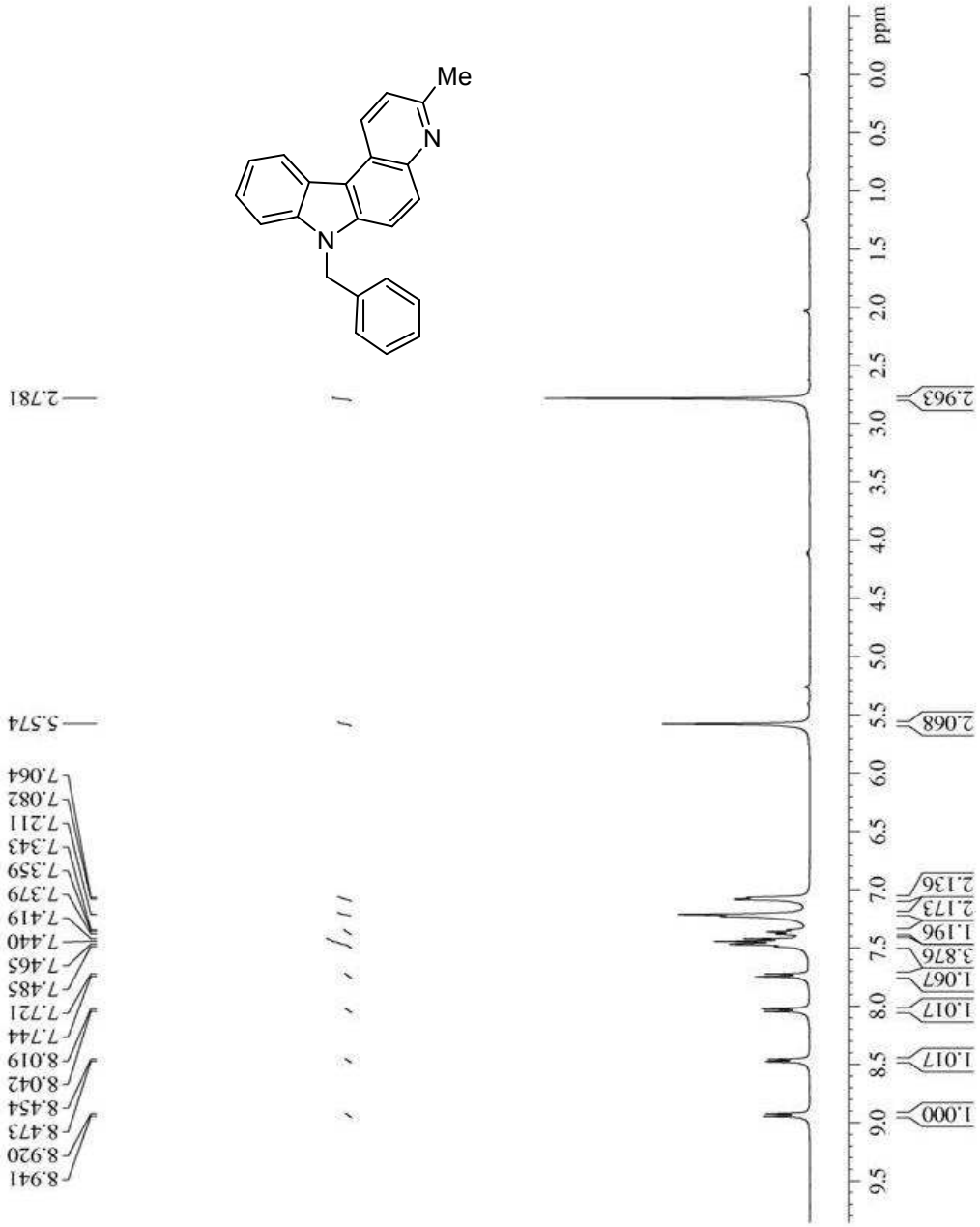
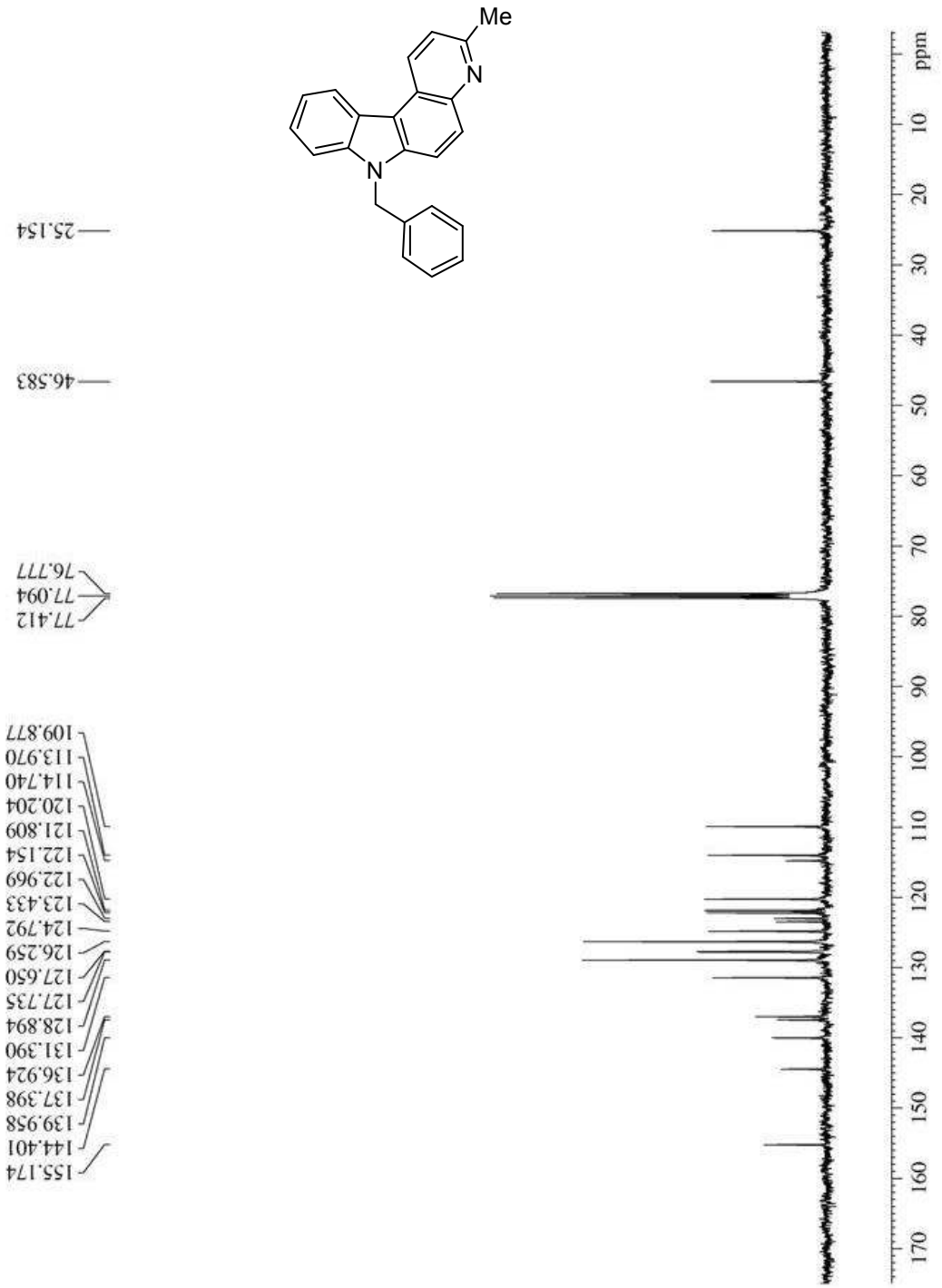
129. The CCDC deposition number for compound **4g** is 845183; molecular formula: $C_{23}H_{18}N_2$. Chemical formula weight is 322.39; orthorhombic; unit cell parameters: a = 6.6003(8) Å, b = 18.947(3) Å, c = 27.539(4) Å, α. = 90°, β = 90°, γ = 90°. Space group Pbca.

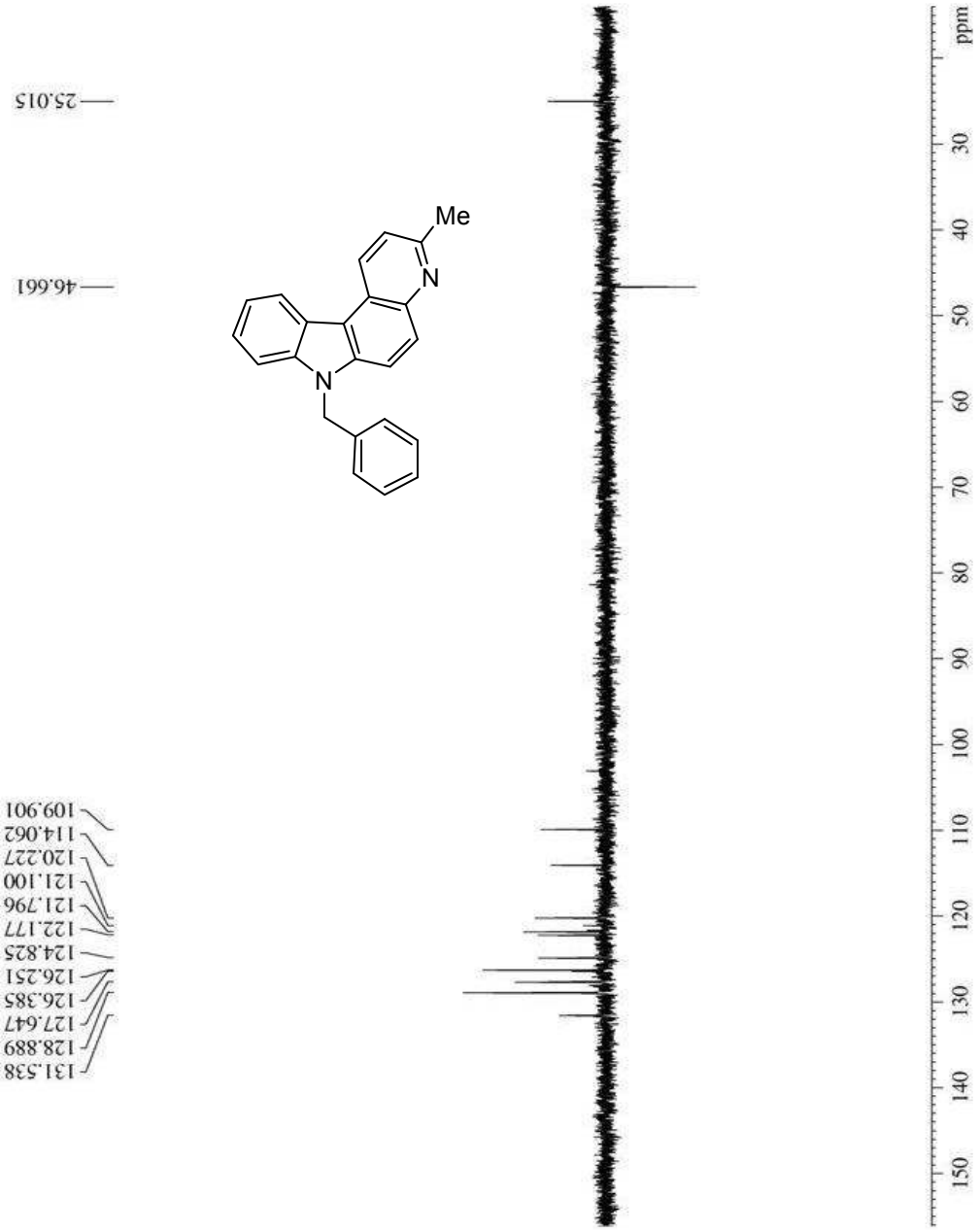
^{1}H NMR of 7-benzyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270g)



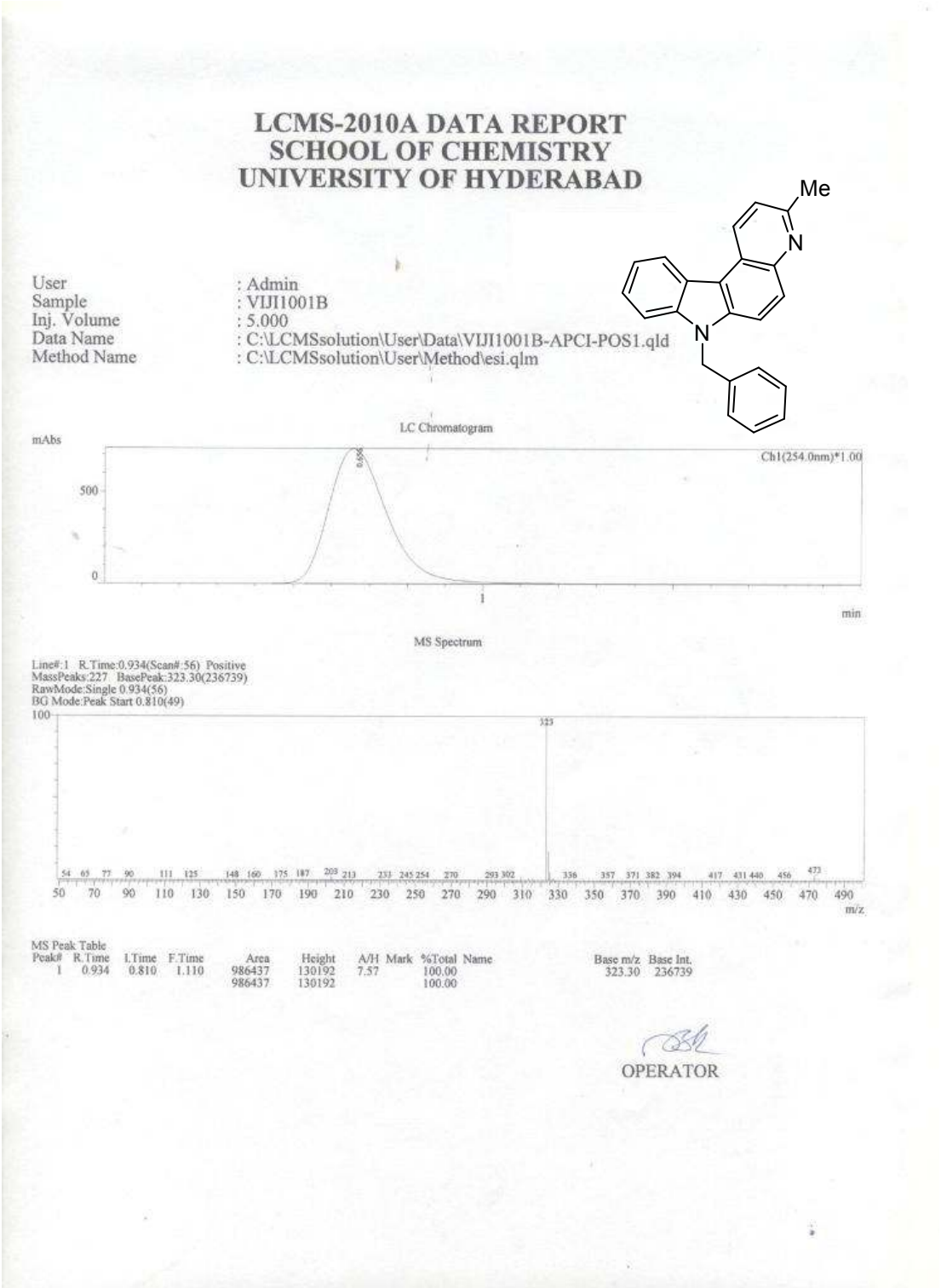
^{13}C NMR of 7-benzyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270g)



DEPT of 7-benzyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270g)



LC-MS of 7-benzyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270g)



Elemental analysis of 7-benzyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (270g)

FLASH EA 1112 SERIES CHN REPORT
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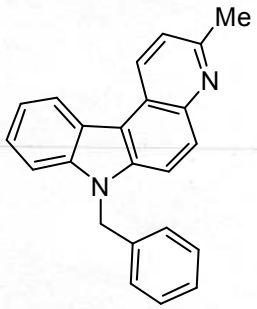
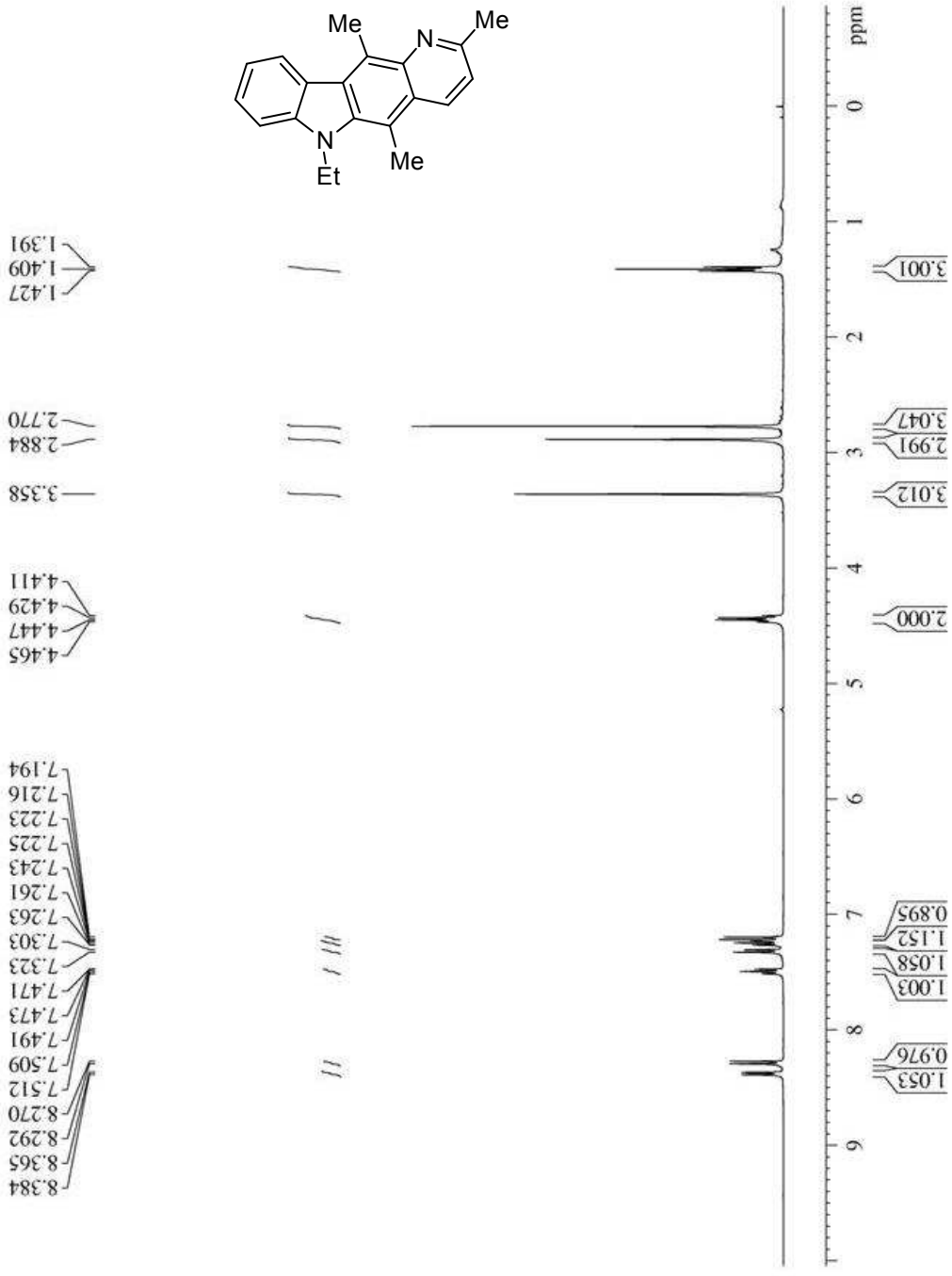


Element Name	Element %	Ret. Time
Nitrogen	8. 59	0. 87
Carbon	85. 66	1. 35
Hydrogen	5. 51	4. 49

^{1}H NMR of 6-ethyl-2,5,11-trimethyl-6*H*-pyrido[3,2-*b*]carbazole (270i)



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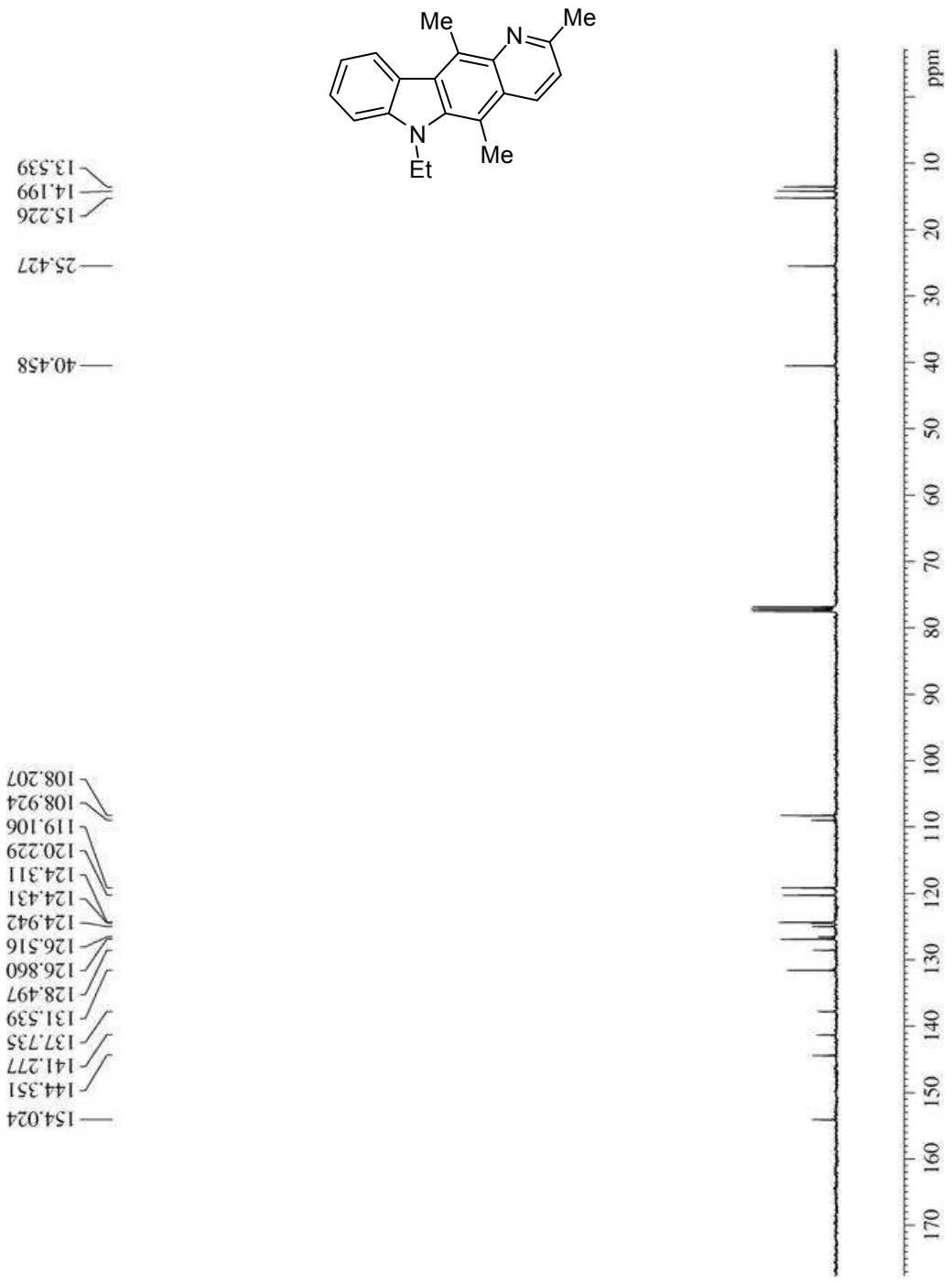

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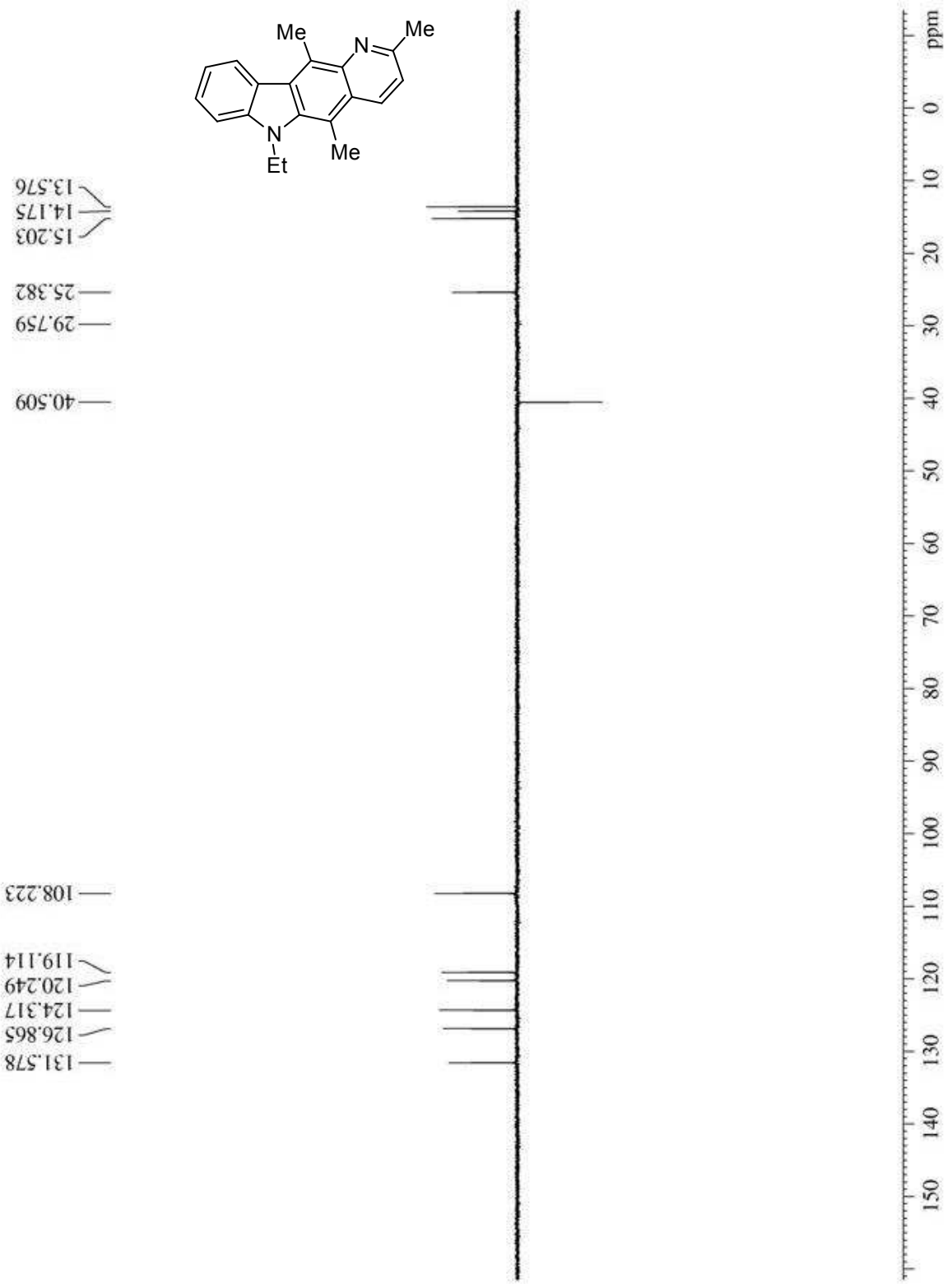

LC-MS of 6-ethyl-2,5,11-trimethyl-6*H*-pyrido[3,2-*b*]carbazole (270i)

LCMS-2010A DATA REPORT
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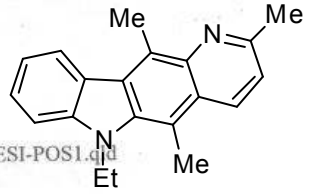

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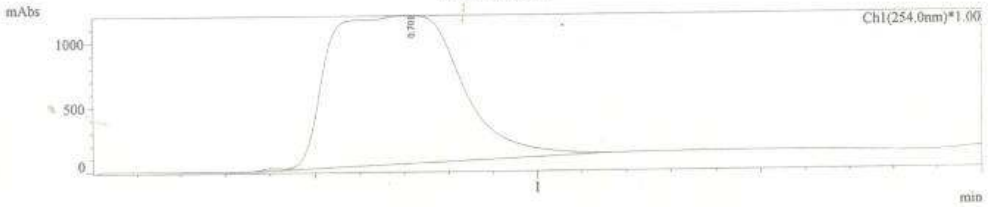
LC Chromatogram



MS Spectrum

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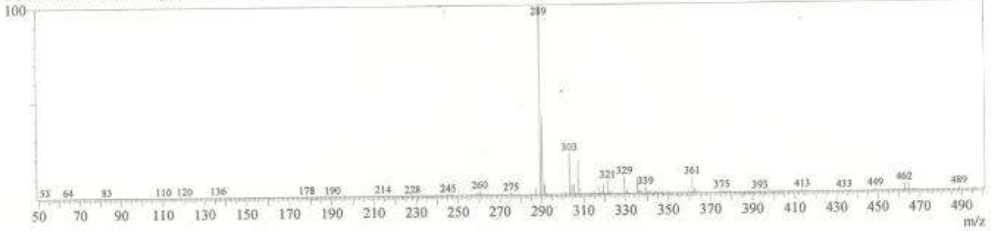
RawMode:Single 0.735(44)
BG Mode:Peak Start 0.527(32)



MS Peak Table

Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.735	0.527	1.043	720414267	47019975	15.32		100.00		289.30	7605628
				720414267	47019975			100.00			

OPERATOR

Elemental analysis of 6-ethyl-2,5,11-trimethyl-6*H*-pyrido[3,2-*b*]carbazole (270i)

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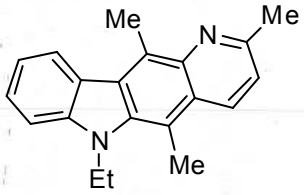
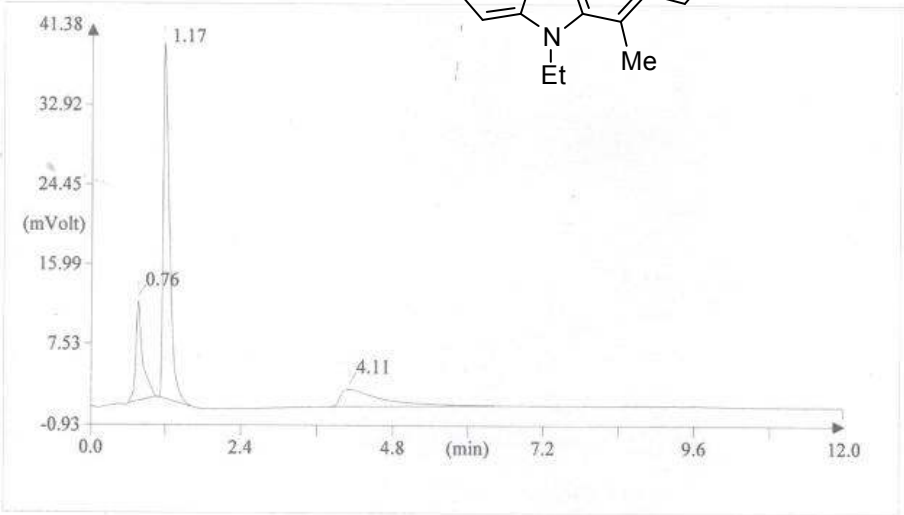
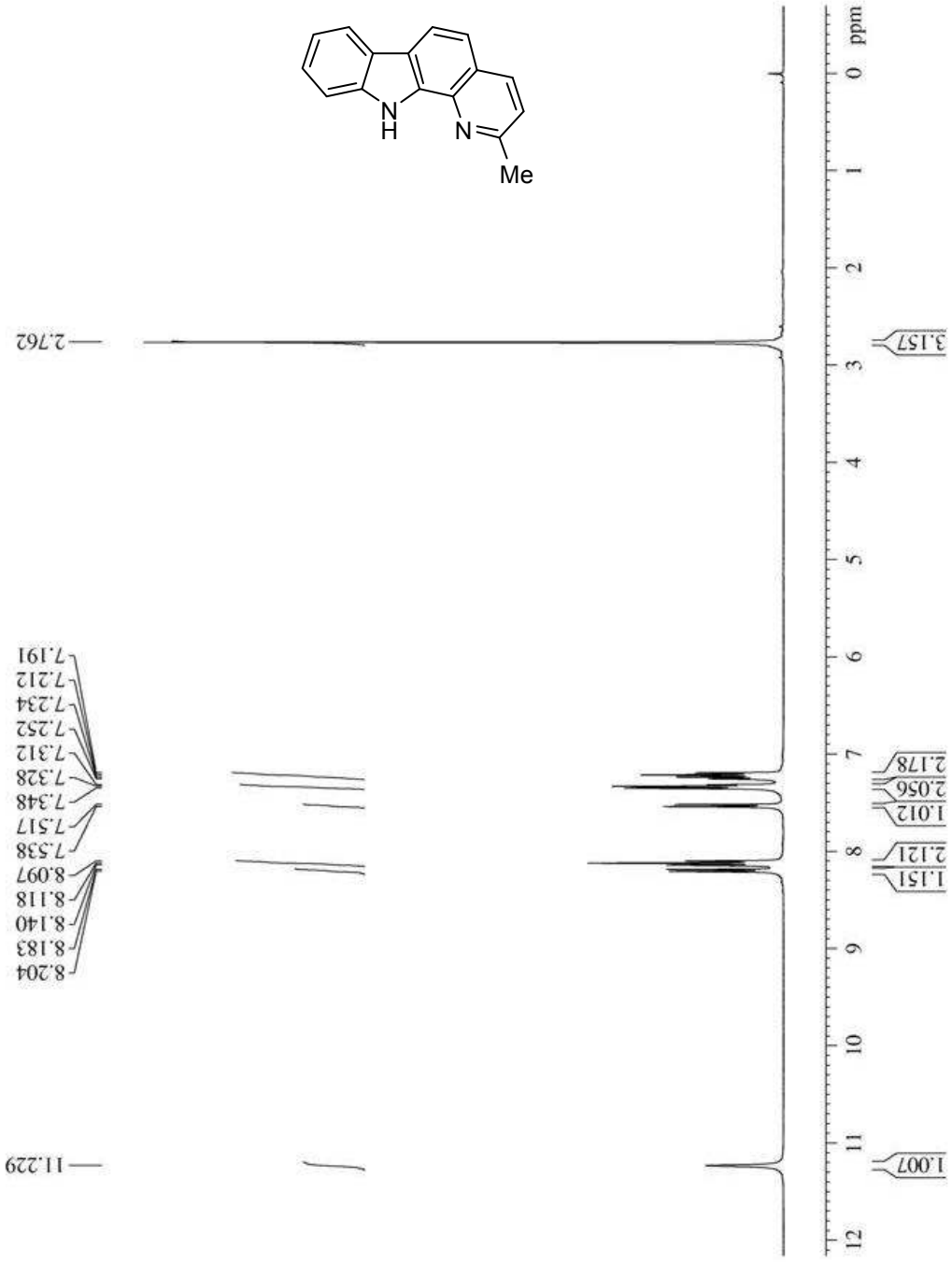


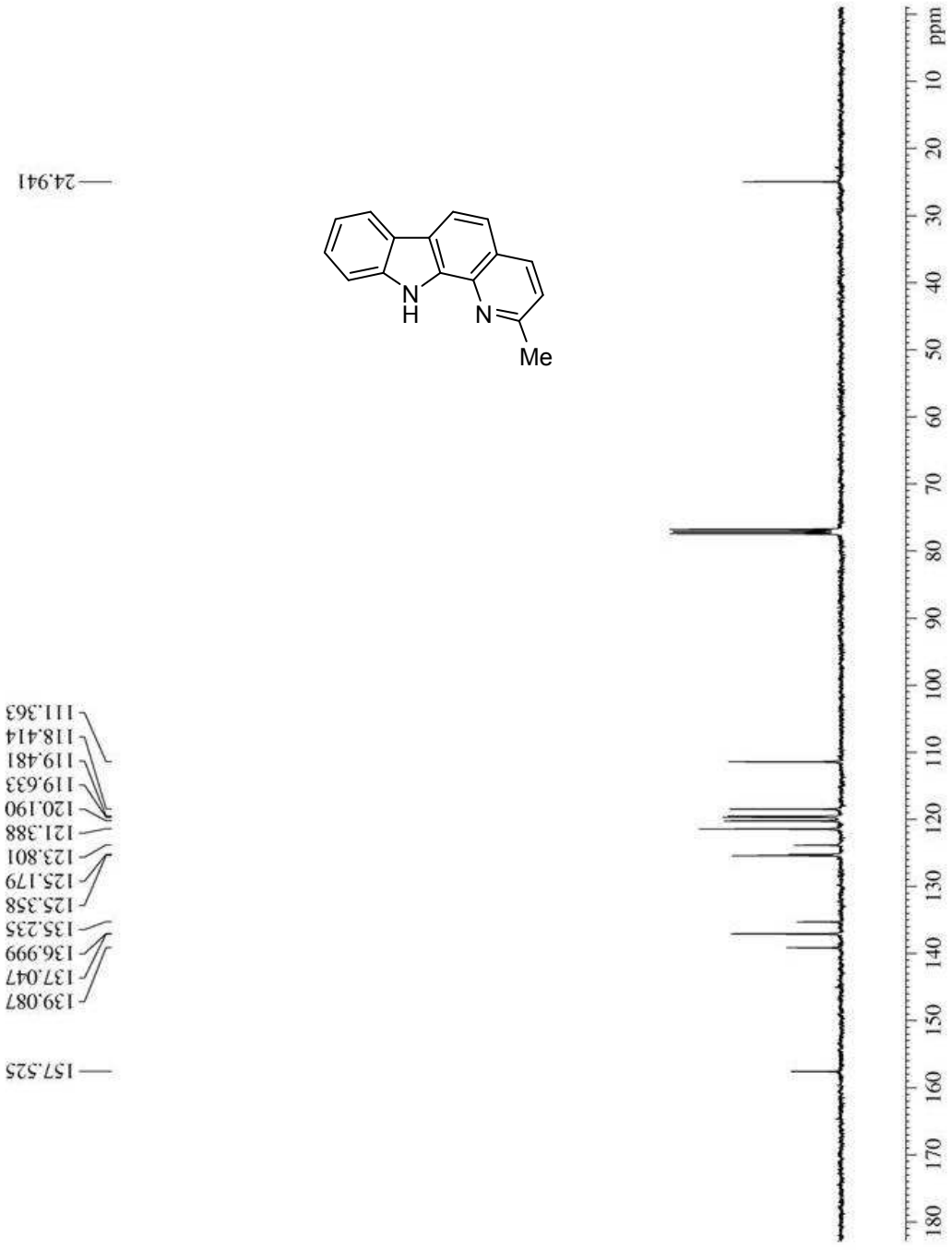


Element Name	Element %	Ret. Time
Nitrogen	9. 65	0. 76
Carbon	83. 21	1. 17
Hydrogen	7. 05	4. 11

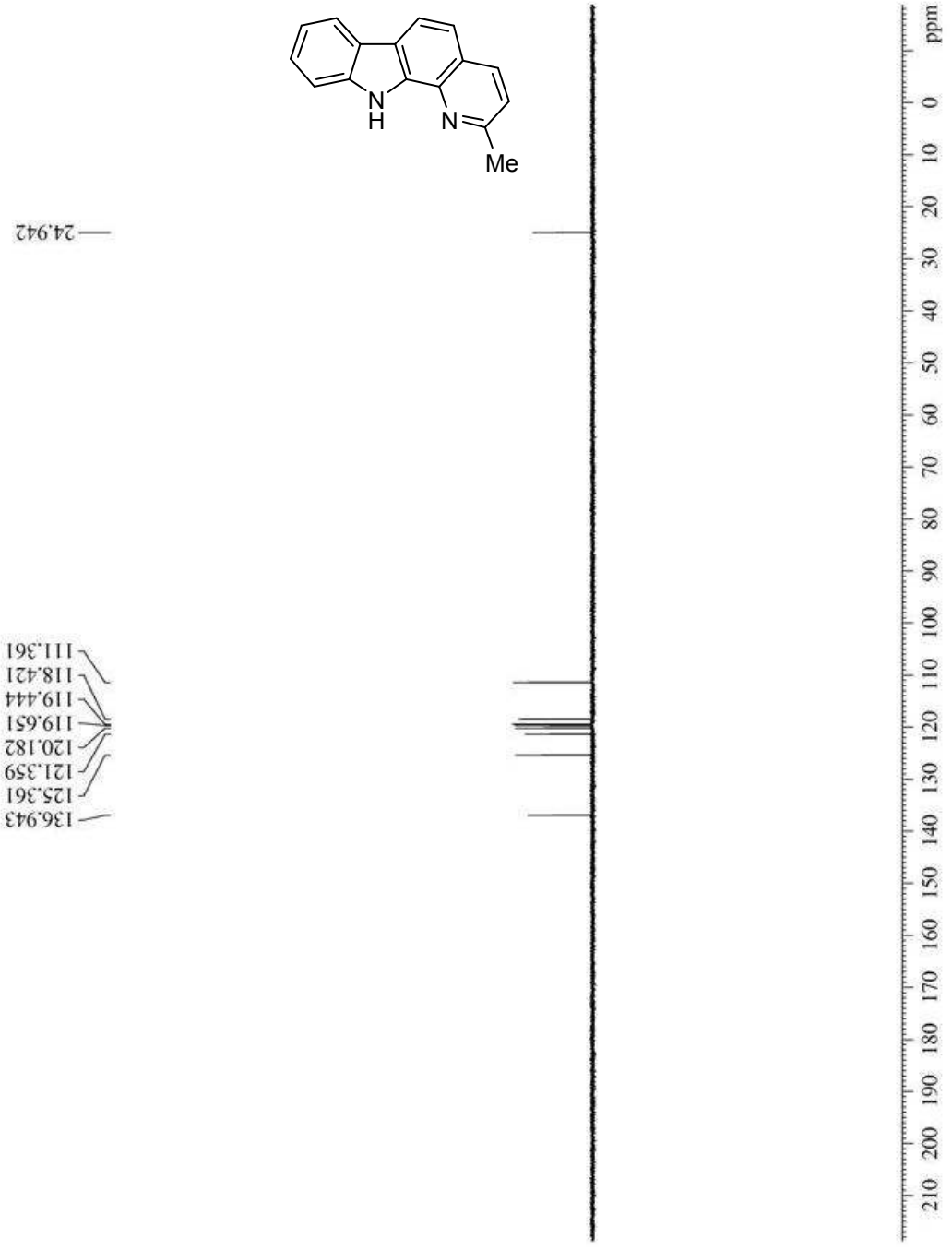
^{1}H NMR of 2-methyl-11*H*-pyrido[2,3-*a*]carbazole (270j)



^{13}C NMR of 2-methyl-11*H*-pyrido[2,3-*a*]carbazole (270j)



DEPT of 2-methyl-11*H*-pyrido[2,3-*a*]carbazole (270j)



LC-MS of 2-methyl-11*H*-pyrido[2,3-*a*]carbazole (270j)

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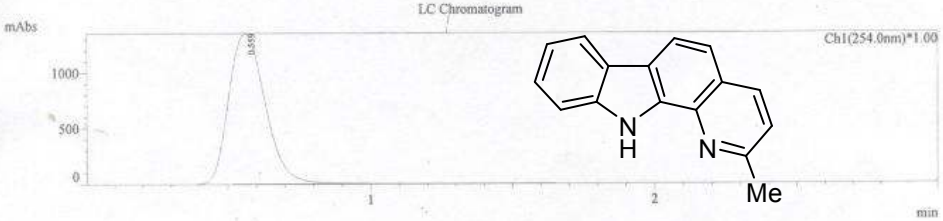
LC Chromatogram



MS Spectrum

Line#:1 R.Time:0.668(Scan#:40) Positive
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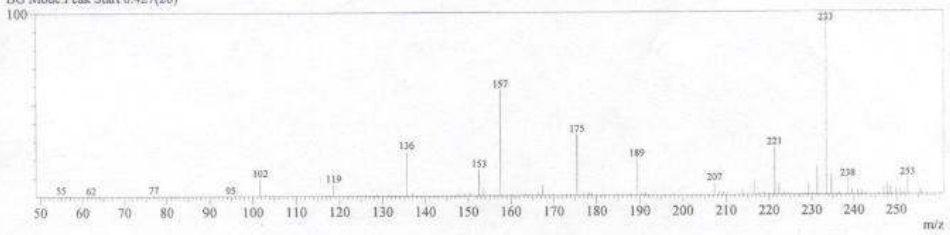
RawMode:Single 0.668(40)
BG Mode:Peak Start 0.427(26)



MS Peak Table

Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.668	0.427	0.843	1560613674	109145012	14.29	E	100.00		233.45	1412077
				1560613674	109145012			100.00			

OPERATOR

Elemental analysis of 2-methyl-11*H*-pyrido[2,3-*a*]carbazole (270j)

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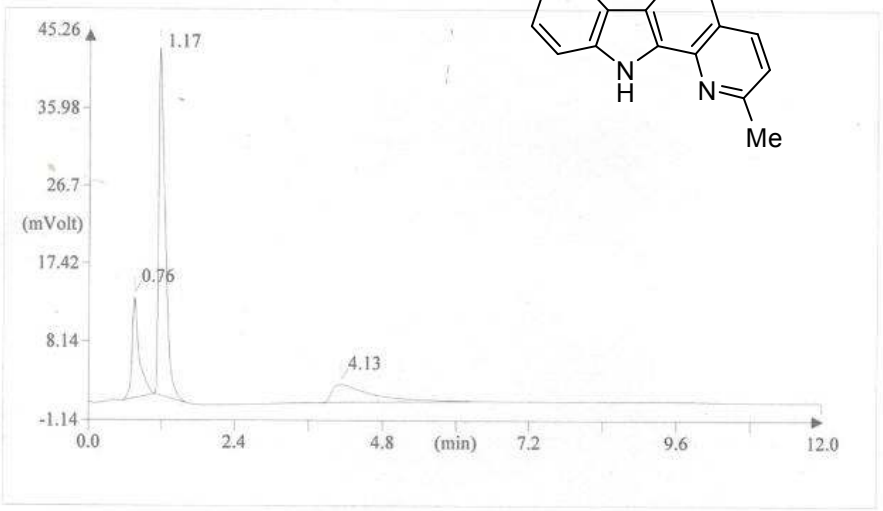
Sample weight: 1.151



Element Name	Element %	Ret. Time
Nitrogen	12. 15	0. 76
Carbon	82. 58	1. 17
Hydrogen	5. 21	4. 13

Synthesis of Bouchardatine alkaloid

CHAPTER 4

4.1 Introduction

Quinazolinone is an important pharmacophore and several new quinazolinone natural products have been isolated and synthesized during the past two decades. The chemistry of quinazolinone alkaloids is published in a broad range of scientific journals. A literature survey has revealed that there are about 75 new quinazolinone-based natural products isolated. Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of a quinazolinone alkaloid, 3-[b-keto-g-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone [febrifugine[130] (**137, 138**), Fig. 17], from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumor, anti-malarial biofungicide, diuretic properties and several others.[131]

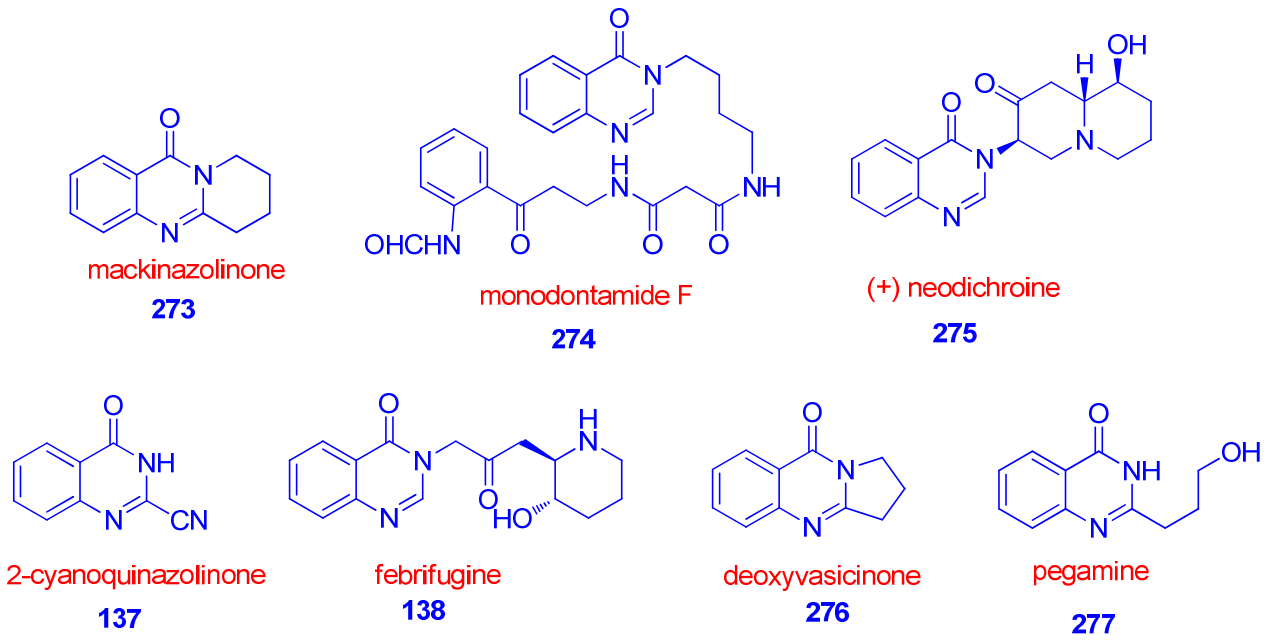


Fig. 17

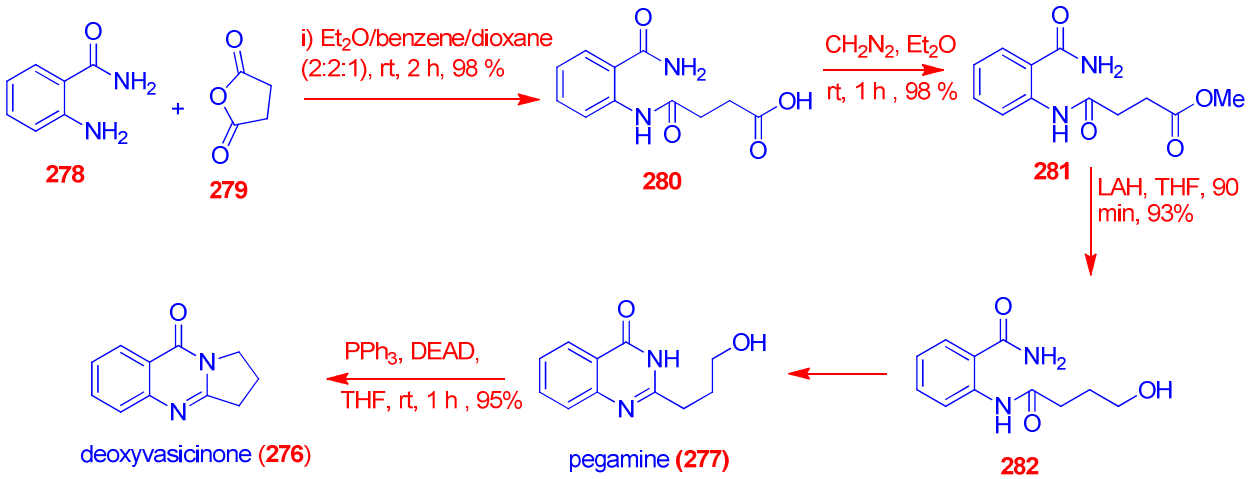
In view of the importance of quinazolinones and their derivatives, many classical methods for their synthesis have been reported in the literature.[58H,132] The main synthetic routes to quinazolinone compounds utilize 2-aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-carbomethoxyphenyl isocyanate, *N*-arylnitrilium salts, and 4*H*-3,1-benzoxazinones as suitable precursors. In the solid-phase synthesis field, lithium reagents and transition metals have been used for the preparation of these compounds.[131j]

4.2. Quinazolinones fused with a pyrrole ring system

There are nine naturally occurring quinazolinone alkaloids having quinazolinone ring fused with a pyrrole ring system. They all are analogs or derivatives of deoxyvasicinone **276** or vasicinone isolated from various species. **276** has been isolated from *Adhatoda vasica*[133] and possesses anti-microbial, anti-inflammatory and anti-depressant acitivities.[134] Several synthetic routes **276** are known in the literature.[135]

Argade *et al*. have developed[136] a new route to **276** with 85% overall yield via the acylation of anthranilamide **278** with succinic anhydride **279**, followed by diazomethane esterification of the formed succinanilic acid **280**, chemoselective LAH-reduction of ester **281**, *in situ* LiOH catalyzed dehydrative cyclization and an intramolecular Mitsunobu ring-closure reaction pathway (**Eq. 37**).

Eq. 37



4.3 Quinazolinones fused with a pyrroloquinoline ring system

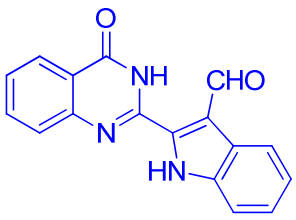
The species from the plant kingdom *Peganum nigellastrum* Bunge (Zygophyllaceae) is found all over Asia and is more common in the northwestern region of China. The same plant with the Chinese name Luo-Tuo-Hao has been used in Chinese traditional medicine as a remedy for rheumatism, abscesses, and inflammation.[137] Recently, Nomura and co-workers from Japan in their collaborative work with scientists from China have isolated six new alkaloids,[138] luotonin A–F, from the aerial parts of *P. nigellastrum*.

4.4. Quinazolinones fused with a piperidine ring system

Ten new quinazolinones fused with a piperidine ring system have been isolated from various species.[139] Actually, nine of them possess the indolopiperidine moiety. Rutaecarpine **73**, its analogs and auranthine are derivatives of mackinazolinone **273**, the simplest quinazolinone alkaloid having a quinazolinone ring fused with a piperidine ring system, which was isolated[140] from *Mackinalaya* species for which several syntheses[140-141] are known.

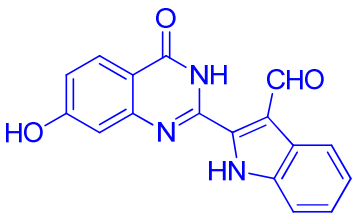
4.5. Indolylquinazolinone alkaloids

Bouchardatia Baill (Rutaceae) is a monotypic genus in the Tribe *Zanthoxyleae*, subfamily Rutoideae of the Rutaceae. The single species *B. neurococca* (F. Muell.) Baill forms a small tree up to 15 m tall and is endemic to the subtropical dry rain forests of the coastal areas of northeastern New South Wales[142] and southeastern Queensland, Australia.[143] Previously, an analysis of essential oil from the leaves of B. neurococca by GC/MS found that the major constituents were the sesquiterpenes β-caryophyllene, caryophyllene oxide, α-humulene and bicyclogermacrene.[144]



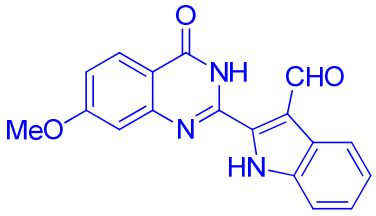
Bouchardatine

136



Orirenierine A

283



Orirenierine B

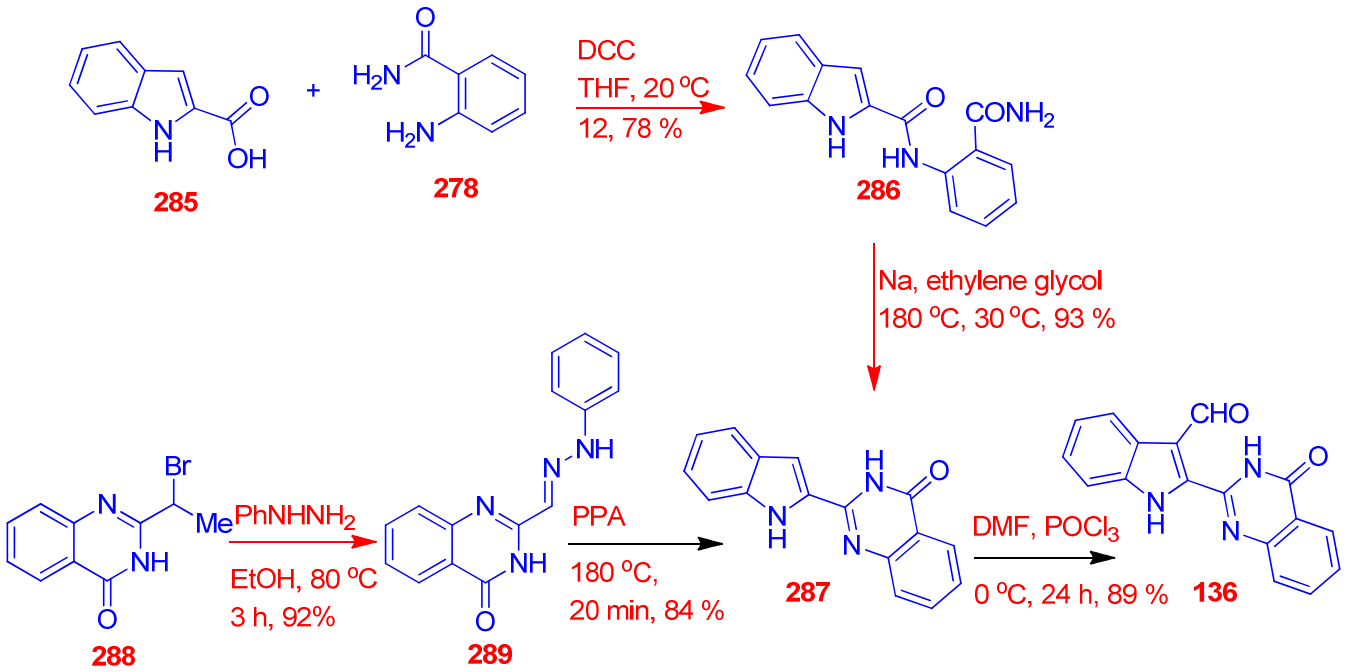
284

Fig. 18

In a continuing search for bioactive molecules from Cameroonian medicinal plants, *Oricia renieri* Gilbert (Rutaceae) is used traditionally by Cameroonian healers as purgative and for the treatment of infections and various cancers.[145] Rwandan healers value the aptitude of the trunk of the plant to cure female disorders like inflammation of mammary glands (mastitis) and crannied acromastia (**Fig. 18**).[146]

Bubenyák *et al*. synthesized bouchardatine alkaloids starting from indole-2-carboxylic acid **285**.[147] Condensation of **278** with **285** using DCC in tetrahydrofuran solution and subsequent base-catalyzed cyclocondensation gave the indolylquinazolone derivative **286**. The product **286** was also available by reaction of 2-bromoethylquinazolone **288** with 3 phenylhydrazine and indolization of the obtained phenylhydrazone **289** in polyphosphoric acid at 180 °C. Vilsmeier–Haack formylation of **287** using a slight excess of phosphoryl chloride in DMF under mild conditions (0 °C, 24 h) provided the 3-formylindole derivative **136** in almost quantitative yield (**Eq. 38**). The prepared compound **136** is identical with bouchardatine, the recently isolated natural alkaloid, from the aerial parts of *Bouchardatia neurococca* (Rutaceae).[148]

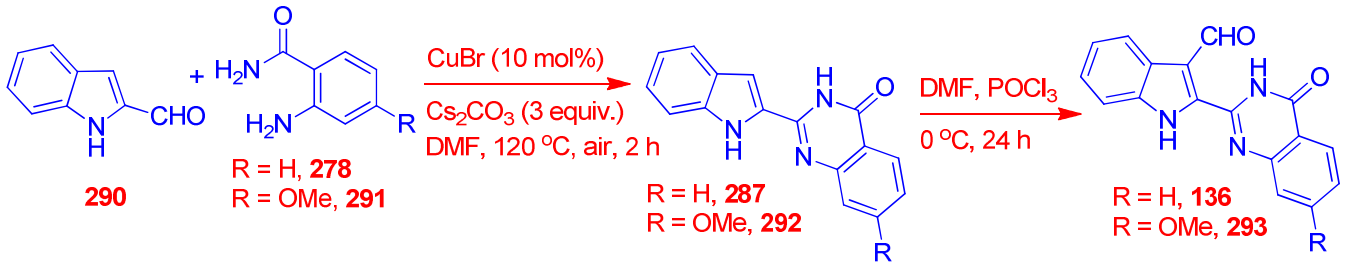
Eq. 38



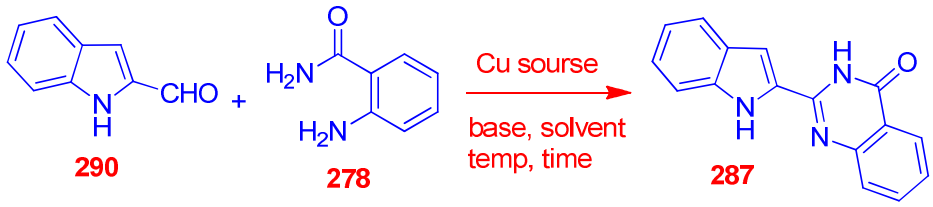
4.6. Synthesis of Bouchardatine alkaloid

Considering pharmalogical as well as biological properties, as we have seen in the above literature reports, a careful analysis of literature disclosed that very few number of reports were available for the synthesis of the bouchardatine alkaloid.[146-148] Therefore, we explored the synthetic methodology for the synthesis of bouchardatine alkaloids. Herein, we wish to report the synthesis of bouchardatine derivative starting with 2-formylindole through copper mediated condensation followed by aerobic oxidative reaction as shown in Scheme 12.

Scheme.12 Schematic representation of the present work



Scheme 13. Synthesis of of Bouchardatine alkaloid **287**



2-Formylindole **290** and anthranilamide **278** were used as model substrates for optimizing the reaction conditions. The influence of catalyst, ligand, base, solvent, and temperature in the reaction outcome were examined as shown in Table 16. In the initial screenings, different bases such as Cs_2CO_3, Na_2CO_3, KOAc, and K_2CO_3 were tested in the reaction; it was found that Cs_2CO_3 was superior to the other bases. Furthermore, DMF was found to be an efficient media in which various solvents were tested for the reaction.

Table 16. Optimization condition for the synthesis of indolylquinazolinone**287**[a]

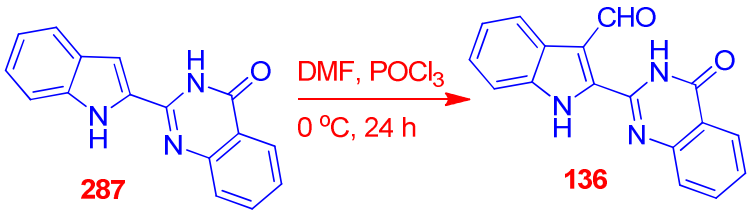
s. no	catalyst	base	solvent	time (h)	yield[c] (%)
1	CuBr	K_2CO_3	DMF	2	74
2	CuBr	KOAc	DMF	6	48
3	CuI	Cs_2CO_3	DMF	4	85
4	CuBr	Cs_2CO_3	NMP	8	10
5	$Cu(OAc)_2$	Cs_2CO_3	DMF	6	84
6[b]	**CuBr**	**Cs_2CO_3**	**DMF**	**2**	**94**
7	CuI	Cs_2CO_3	DMSO	8	20
8	CuBr	Na_2CO_3	DMF	12	72
9	CuCl	Cs_2CO_3	DMSO	12	35
10	CuBr	Cs_2CO_3	Toluene	12	22
11	CuI	K_2CO_3	DMF	4	72

[a] Unless otherwise mentioned, all the reactions were conducted in a RB using 2-formylindole **290** (1.0 equiv.), Anthranilamide **278** (1.0 equiv.) catalyst (10 mol%), base (2.0 equiv.) 3 mL solvent stirred at 120 °C in open air. [b] 3 equiv. of base used. [c] isolated yields

Without ligand and additive the reaction proceeded well within 2 h. No reaction occurred at or below 70 °C. By changing the catalyst loading below 5 mol %, the reaction took more time to reach completion. Based on above findings, we concluded that the optimal condition for this reaction involve 1.0 equiv of **290**, 1.0 equiv of **278** and 3.0 equiv of Cs_2CO_3 in DMF with 10 mol % of CuBr at 120 °C in open air. By using the optimized condition the product **287** was obtained in good yield (94%) within 2 h.

We prepared methoxy substituted indolylquinazolinone using the above mentioned optimized condition and we got almost 92% of the product **292**.

Scheme 14. Synthesis of bouchardatine alkaloid **136**



We prepared the bouchardatine alkaloids by using the reported procedure[147] by using DMF/$POCl_3$ at 0 °C for 24 h gave the **136** in 89% yield.

4.7 Conclusion

In conclusion, an efficient synthesis of substituted and unsubstituted indoloquinazolinone derivatives by using copper bromide catalyzed condensation followed by cyclization reaction. The reaction proceeds well under relatively mild conditions with shorter reaction times. We also prepared bouchardatine alkaloids in good yield, and synthesis of orirenierine A and B is under progress.

4.8 Experimental Section

General Information

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: ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER AVANCE-400 spectrometer. ^{1}H NMR (400, 500 MHz) spectra of the some samples were measured in $CDCl_3$ (δ = 7.26 ppm) or in DMSO-d_6 (δ = 2.50 ppm) or in the mixture of $CDCl_3$/DMSO-d_6 with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100, 125 MHz) spectra of some

samples were measured in chloroform-*d* (δ = 77.10 ppm, with its middle peak of the triplet 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.

General procedure for the synthesis of 3-methyl-7*H*-pyrido[2,3-*c*]carbazole 270a:

Procedure E:

An oven dried 25 mL round bottom flask charged with a magnetic pellet and CuBr (10 mol %), and 2-formylindole **290** (1.0 equiv.), DMF (3 mL) along with anthranilamide **278** (1.0 equiv.), Cs_2CO_3 (3.0 equiv.) and it was stirred at 120 °C for 2 h in open air. After completion of the reaction, followed by thin layer chromatography (TLC), The reaction mixture poured into water and extract with EtOAc (3×10 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography on neutral alumina using Hexane/EtOAc as the eluent. The solvent was evaporated to dryness to get the pure product **287**. The same procedure was followed for substrate **292** also.

General procedures for the synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde (136):

Procedure G:

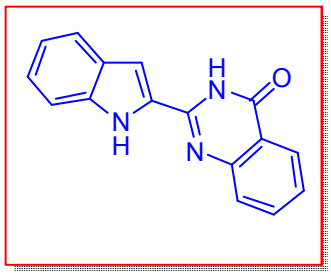
Phosphoryl chloride (9.0 equiv.) was dissolved in 3 mL of anhydrous DMF stirred at 0 °C. Then 1.0 equiv. of **287** was dissolved in 4 mL of DMF added dropwise to the reaction mixture. The mixture was stirred at 0 °C for 24 h, then the solution was added dropwise to 7 mL of saturated sodium bicarbonate solution. 10 mL of 10% sodium hydroxide solution were poured onto the mixture, and the precipitated solid was filtered off and washed with water. Recrystallization from hot ethanol provided a pale yellow colored solid **136** in 89% yield.

2-(1*H*-Indol-2-yl)quinazolin-4(3*H*)-one (287):

The product **287** was obtained as white colored solid from **290** through column chromatography using a mixture of 7% ethyl acetate and hexanes as described in procedure F.

Yield: 94 %

Mp: 270 °C



IR (KBr) ν_{max} cm^{-1}: 3424, 2964, 2926, 2849, 1676, 1594, 1336, 1309, 865, 777

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.62 (s, 1H), 11.81 (s, 1H), 8.14 (d, 1H, *J* = 7.8 Hz), 7.74-7.72 (m, 1H), 7.65 (s, 1H), 7.63 (d, 1H, *J* = 8 Hz), 7.53-7.49 (m, 2H), 7.22 (t, 1H, *J* = 7.0 Hz), 7.05 (t, 1H, *J* = 7.2 Hz)

^{13}C NMR (125 MHz, DMSO-d_6): δ 162.2, 149.2, 147.0, 138.1, 135.1, 130.5, 127.9, 127.4, 126.7, 126.5, 124.5, 122.0, 121.6, 120.4, 112.8, 105.4

LC-MS (m/z): 262 $(M+H)^+$ positive mode

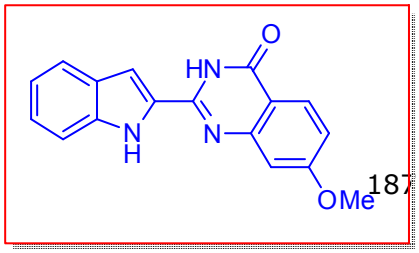
Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.18 %

Found: C, 73.31; H, 4.31; N, 16.12 %

2-(1*H*-Indol-2-yl)-7-methoxyquinazolin-4(3*H*)-one (292):

The product **292** was obtained as white colored solid from **290** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure F.

Yield: 92 %



Mp: 266°C

IR (KBr) v_{max} cm^{-1}: 3412, 2923, 2892, 2835, 1676, 1594, 1468, 1336, 1260, 861, 753

^{1}H NMR (400 MHz, DMSO-d_6): *δ* 12.50 (s, 1H), 11.80 (s, 1H), 8.04 (d, 1H, *J* = 8.4 Hz), 7.63-7.61 (m, 2H), 7.51 (d, 1H, *J* = 8.4 Hz), 7.21 (t, 1H, *J* = 7.6 Hz), 7.12 (s, 1H), 7.09-7.03 (m, 2H), 3.91 (s, 3H)

^{13}C NMR (125 MHz, DMSO-d_6): *δ* 169.3, 167.1, 156.2, 151.8, 142.2, 134.9, 132.8, 129.1, 126.6, 125.0, 120.5, 119.6, 116.7, 112.9, 110.4, 110.3, 60.3

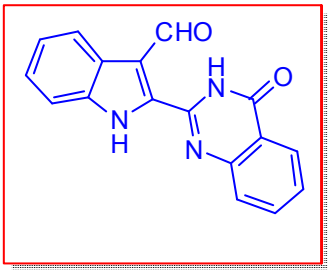
LC-MS (m/z): 290 $(M-H)^-$, negative mode

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42 %

Found: C, 70.15; H, 4.45; N, 14.56 %

2-(4-Oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde (136):

The product **136** was obtained as pale yellow colored solid from **287** through recrystalization from ethanol using procedure G.



Yield: 89 %

Mp: > 280 °C

IR (KBr) v_{max} cm^{-1}: 3462, 2986, 2875, 2821, 1718, 1693, 1562,1432, 1317, 1223, 865, 750

^{1}H NMR (400 MHz, DMSo-d_6): *δ* 13.65 (s, 1H), 13.13 (s, 1H), 10.4 (s, 1H), 8.26 (d, 1H, *J* = 8 Hz), 8.20 (d, 1H, J = 8 Hz), 7.92-7.89 (m, 1H), 7.85-7.83 (m, 1H), 7.68 (d, 1H, *J* = 8 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 7.41 (t, 1H, *J* = 7.2 Hz), 7.36-7.32 (m, 1H)

^{13}C NMR (125 MHz, DMSO-d_6):	δ 188.0, 161.6, 148.8, 145.7, 136.3, 136.2, 135.4, 128.1, 128.0, 127.9, 126.5, 125.8, 123.7, 122.2, 120.6, 115.5, 113.7
LC-MS (m/z):	290 $(M+H)^+$, positive mode
Anal. Calcd. for $C_{17}H_{119}N_3O_2$:	C, 70.58; H, 3.83; N, 14.53 %
Found:	C, 70.45; H, 3.78; N, 14.43 %

4.9. References

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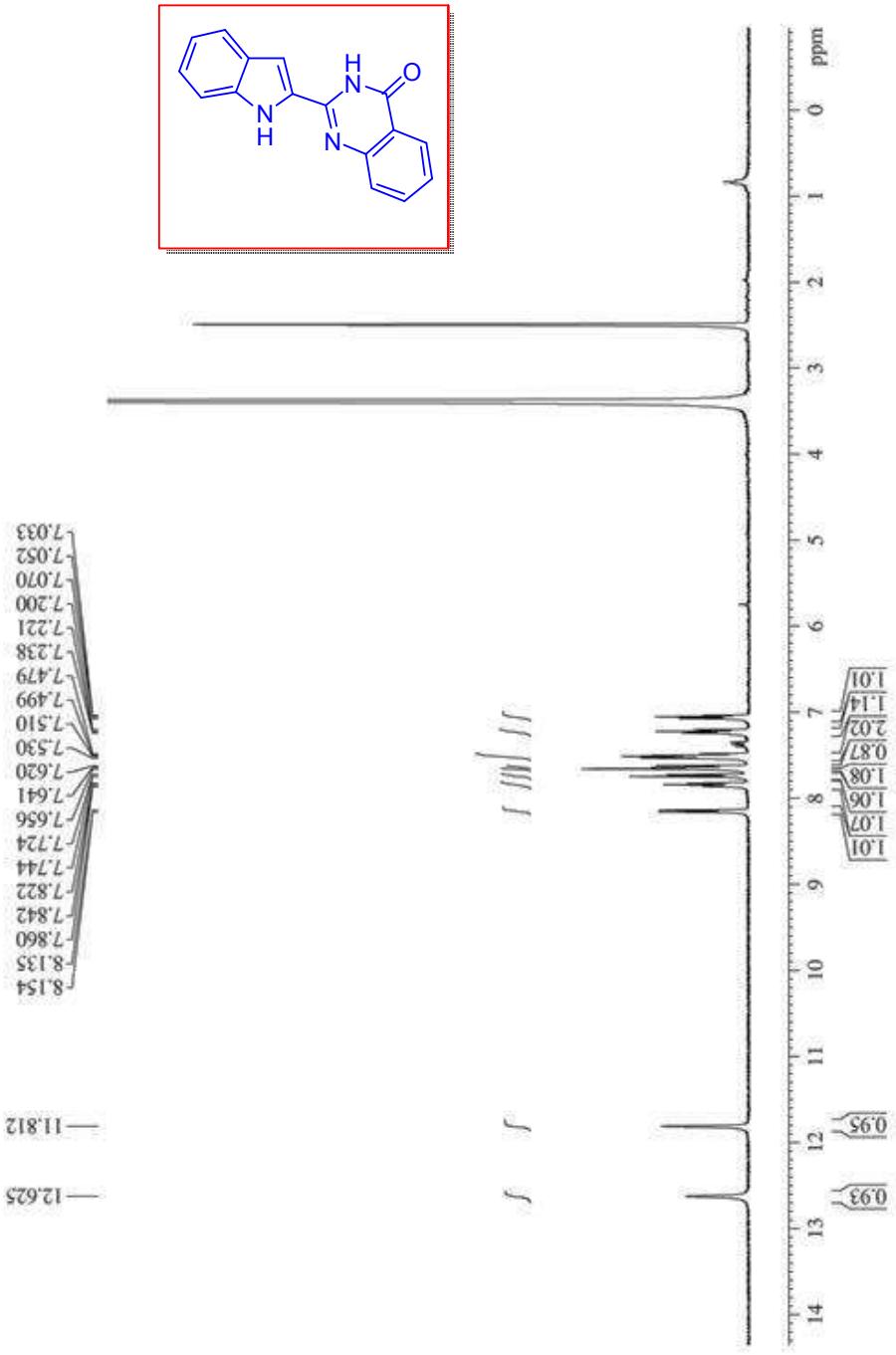
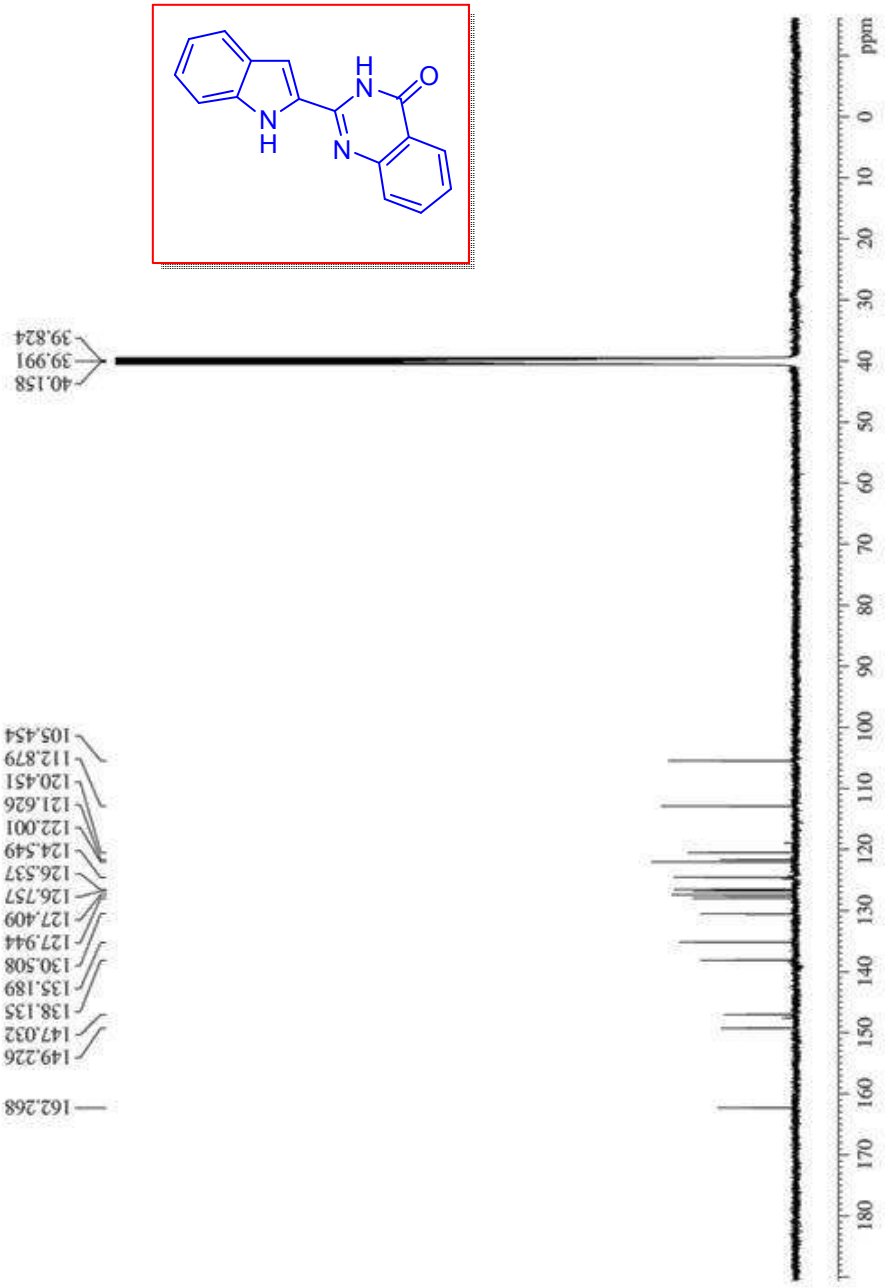
^{1}H NMR of 2-(1*H*-indol-2-yl)quinazolin-4(3*H*)-one (287):



^{13}C NMR of 2-(1*H*-indol-2-yl)quinazolin-4(3*H*)-one (287):



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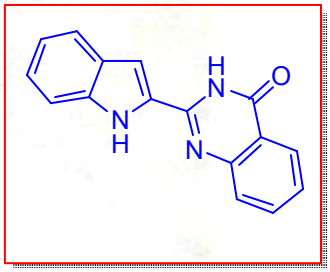
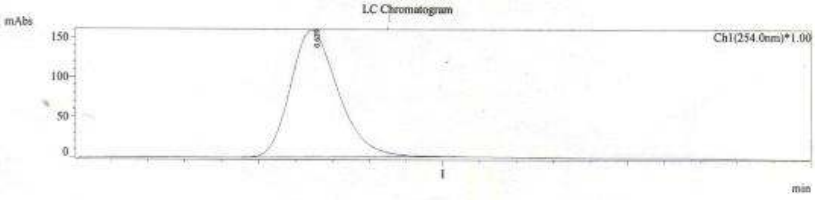


LCMS-2010A DATA REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

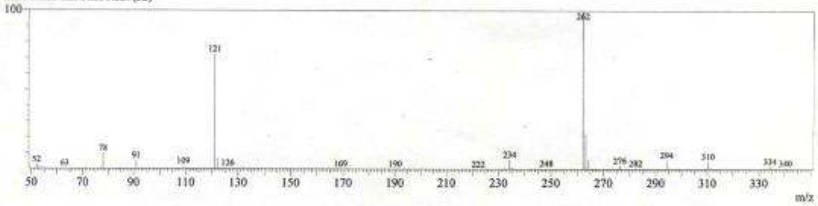
User : Admin
Sample : VIJI-1553
Inj. Volume : 5.000
Data Name : J:\LCMS DATA 20102011\VIJI-1553-APCI-POS1.qld
Method Name : C:\LCMSsolution\User\Method\esi.qlm

LC Chromatogram



MS Spectrum

Line#:1 R.Time:0.714(Scan#:43) Positive
MassPeaks:82 BasePeak:262.25(9404572)
RawMode:Single 0.714(43)
BG Mode:Peak Start 0.527(32)



MS Peak Table

Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.714	0.527	1.143	634658653	32532699	19.50		100.00		262.25	9404572
				634658653	32532699			100.00			

OPERATOR

Elemental analysis of 2-(1*H*-indol-2-yl)quinazolin-4(3*H*)-one (287):

FLASH EA 1112 SERIES CHN REPORT
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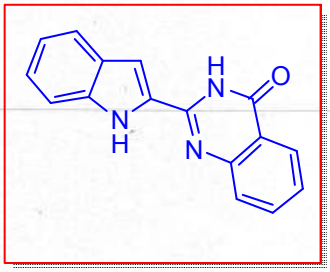
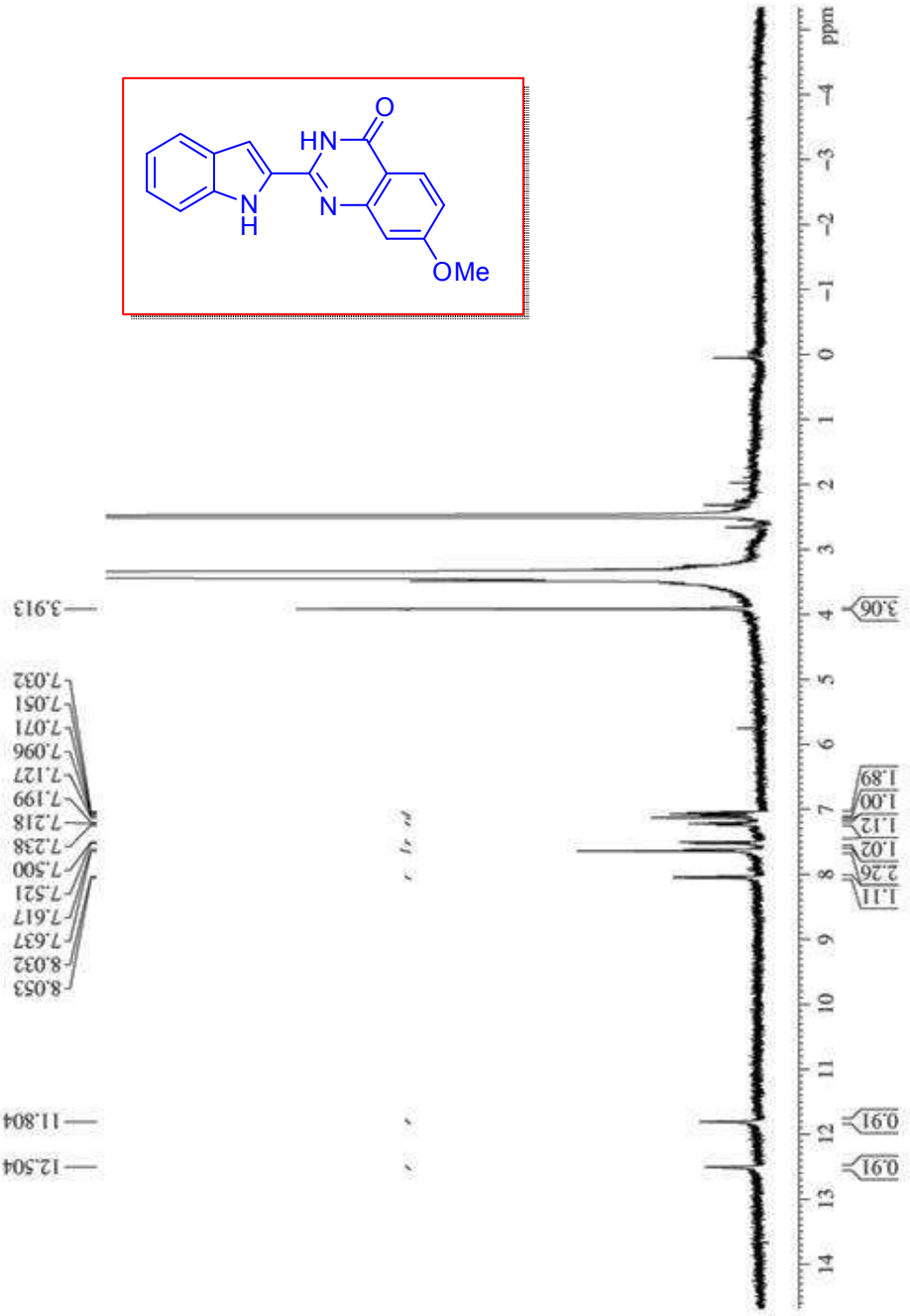
Method filename: C:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID: VIJI-1553 (# 74)
Analysis type: UnkNown
Chromatogram filename: UNK-03122012-24.dat
Sample weight: 1.226

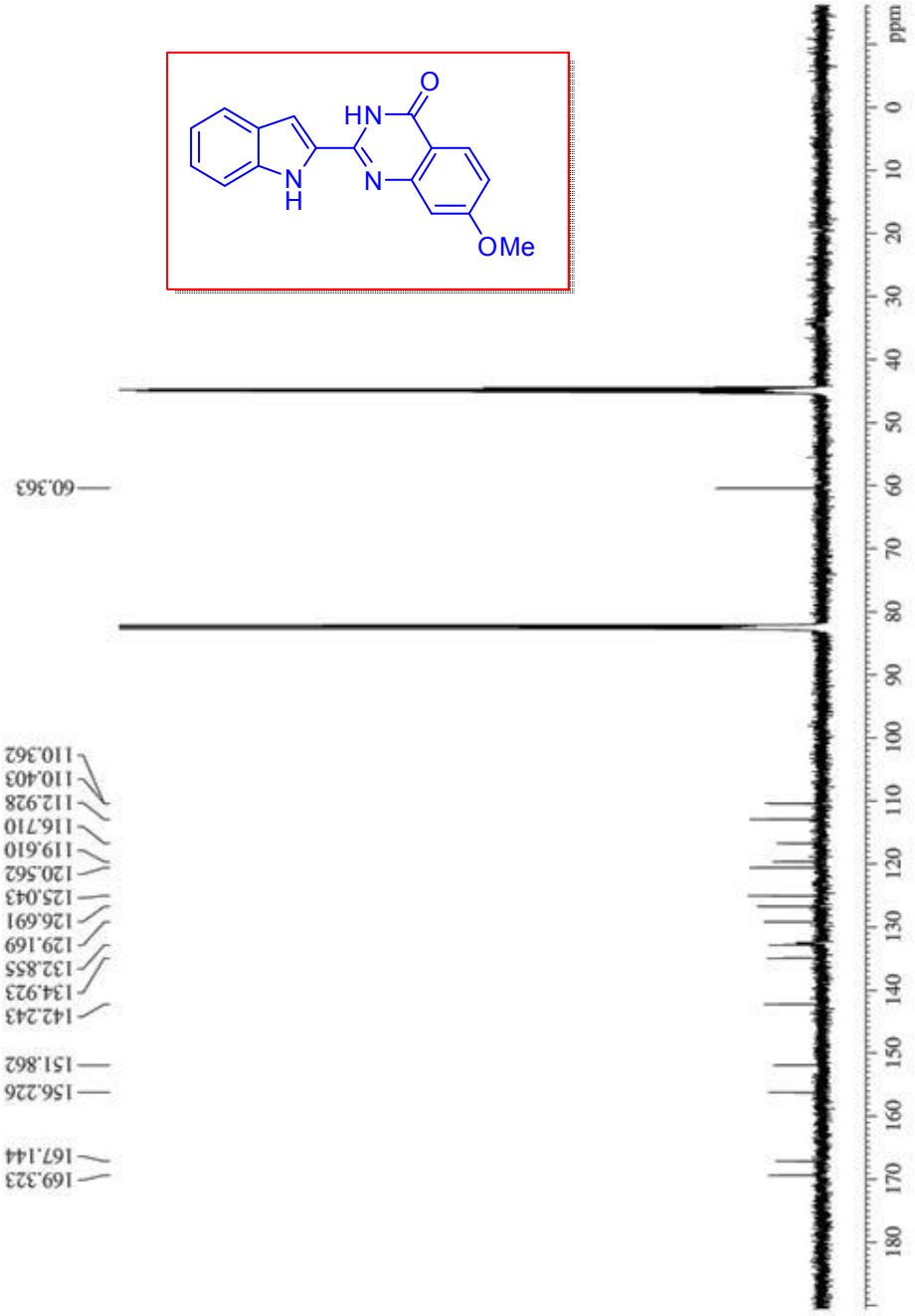


Element Name	Element %	Ret. Time
Nitrogen	16. 12	0. 75
Carbon	73. 31	1. 14
Hydrogen	4. 31	4. 15

^{1}H NMR of 2-(1*H*-indol-2-yl)-7-methoxyquinazolin-4(3*H*)-one (292):



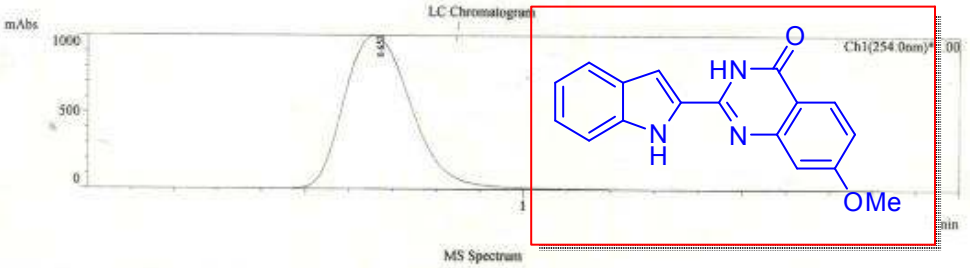
^{13}C NMR of 2-(1*H*-indol-2-yl)-7-methoxyquinazolin-4(3*H*)-one (292):



LC-MS of 2-(1*H*-indol-2-yl)-7-methoxyquinazolin-4(3*H*)-one (292):

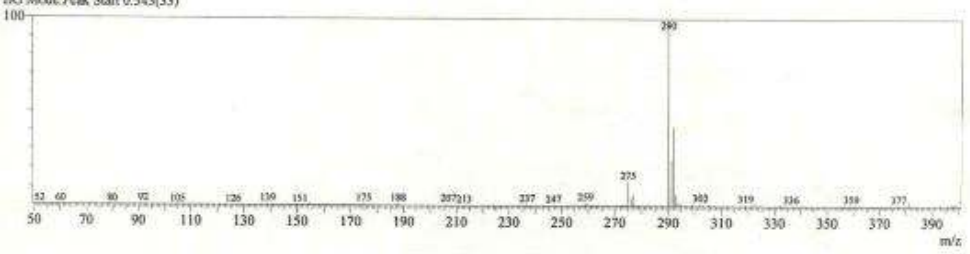
LCMS-2010A DATA REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

User : Admin
Sample : VIJI-1567-A
Inj. Volume : 5.000
Data Name : J:\LCMS DATA 20102011\VIJI-1567-A-APCI-NEG1.qld
Method Name : C:\LCMSsolution\User\Method\esi.qlm



MS Spectrum

Line#:1 R.Time:0.779(Scan#:47) Negative
MassPeaks:226 BasePeak:289.95(485238)
RawMode:Single 0.779(47)
BG Mode:Peak Start 0.543(33)



MS Peak Table

Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.779	0.543	1.043	21289132	1813376	11.74		100.00		289.95	485238
				21289132	1813376			100.00			

OPERATOR

Elemental analysis of 2-(1*H*-indol-2-yl)-7-methoxyquinazolin-4(3*H*)-one (292):

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SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

Method filename:	C:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID:	VIJI-1567-A (# 73)
Analysis type:	UnkNown
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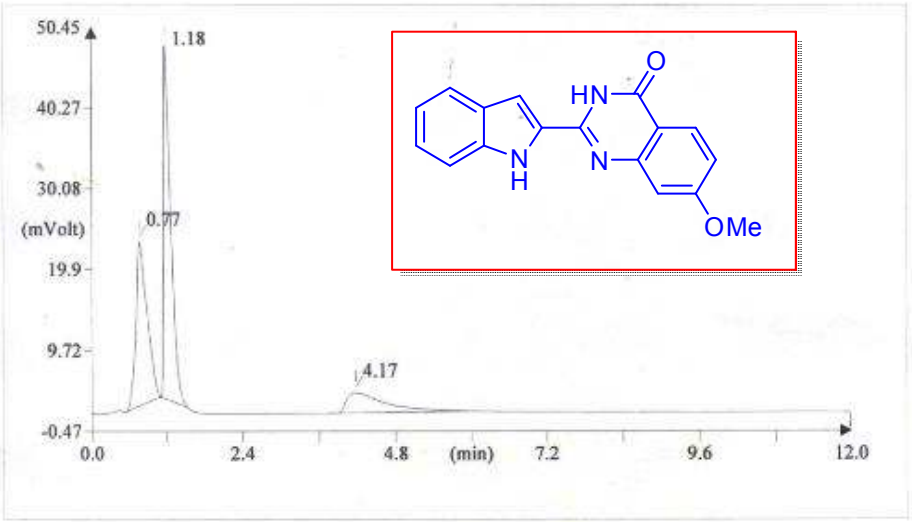
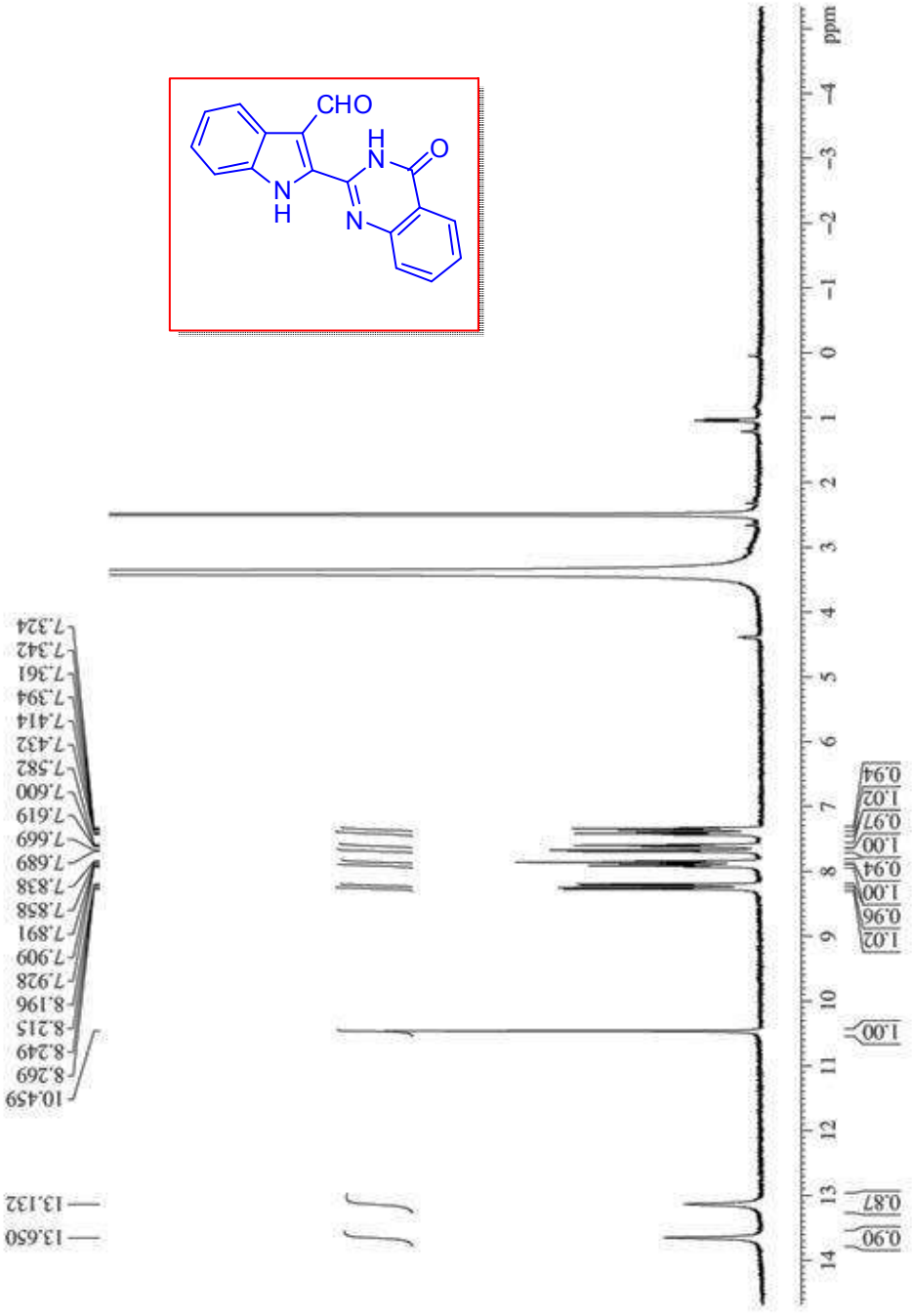
Sample weight:	1.218

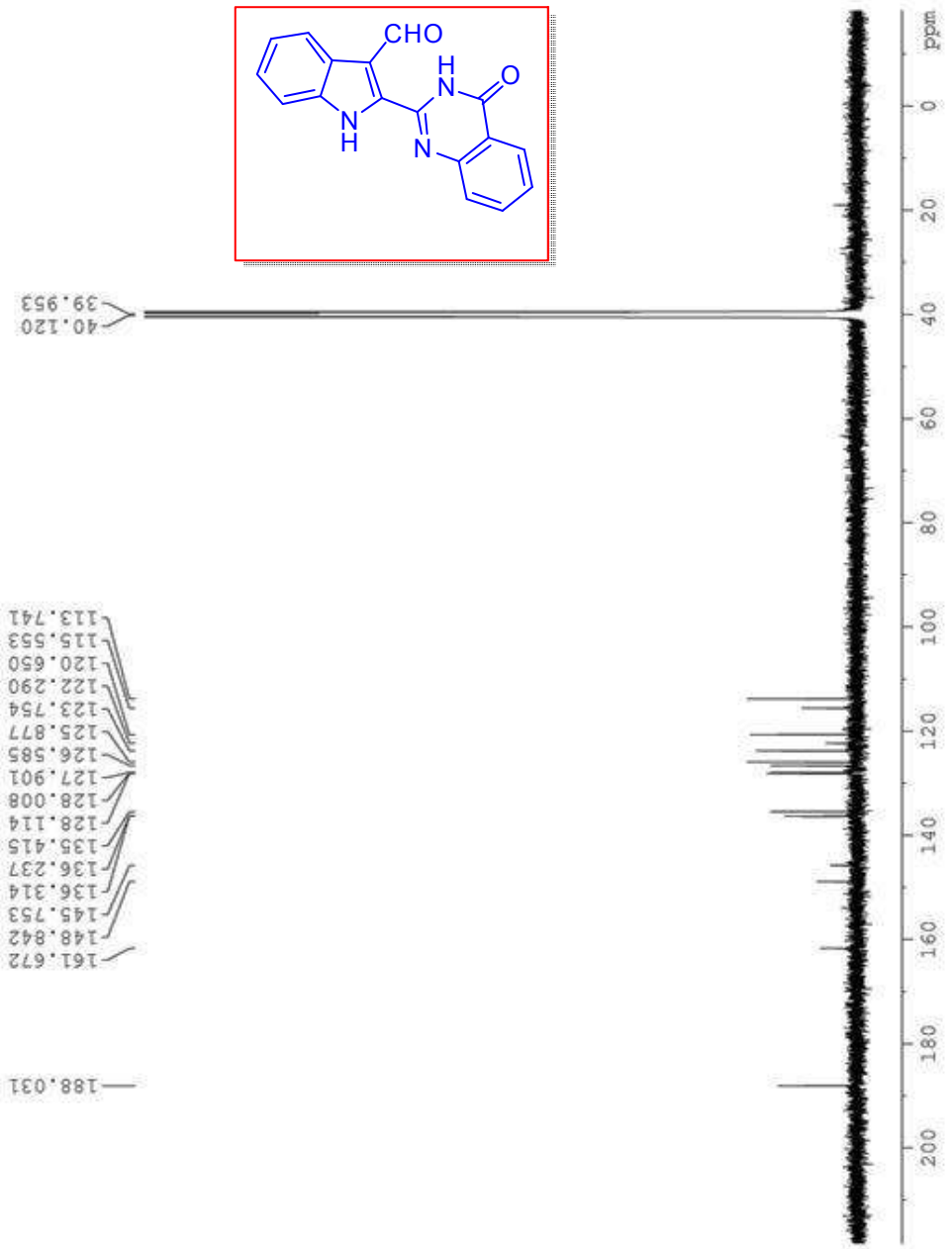


Element Name	Element %	Ret. Time
Nitrogen	14. 56	0. 77
Carbon	70. 15	1. 18
Hydrogen	4. 45	4. 17

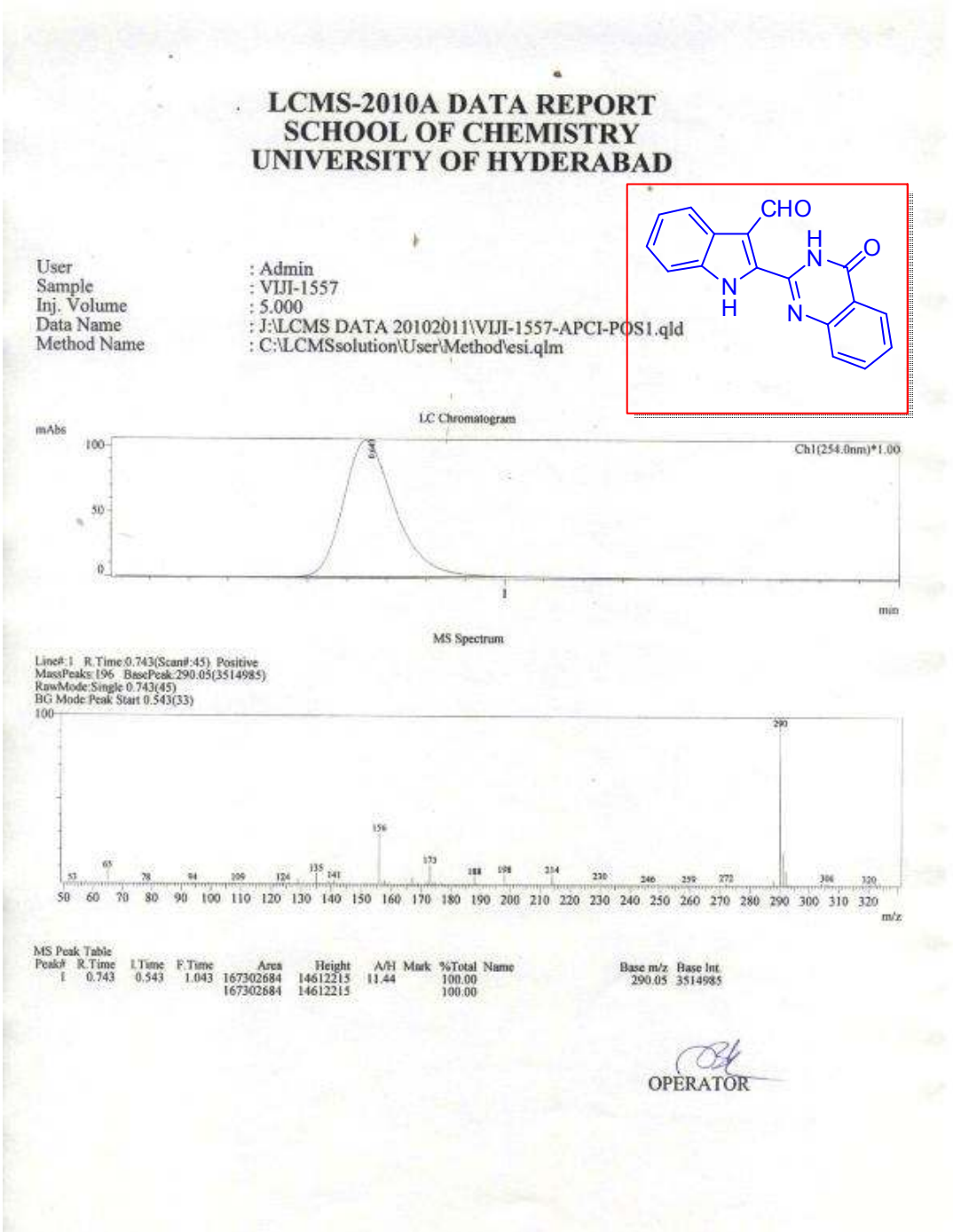
^{1}H NMR of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde (136):



^{13}C NMR of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde (136):



LC-MS of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde (136):



LCMS-2010A DATA REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

User : Admin
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Inj. Volume : 5.000
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Method Name : C:\LCMSsolution\User\Method\esi.qlm

LC Chromatogram

mAbs

Ch1(254.0nm)*1.00

min

MS Spectrum

Line#:1 R.Time:0.743(Scan#:45) Positive
MassPeaks:196 BasePeak:290.05(3514985)
RawMode:Single 0.743(45)
BG Mode:Peak Start 0.543(33)

m/z

MS Peak Table

Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.743	0.543	1.043	167302684	14612215	11.44		100.00		290.05	3514985
				167302684	14612215			100.00			

OPERATOR

Elemental analysis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1*H*-indole-3-carbaldehyde (136):

FLASH EA 1112 SERIES CHN REPORT
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

Method filename:	C:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
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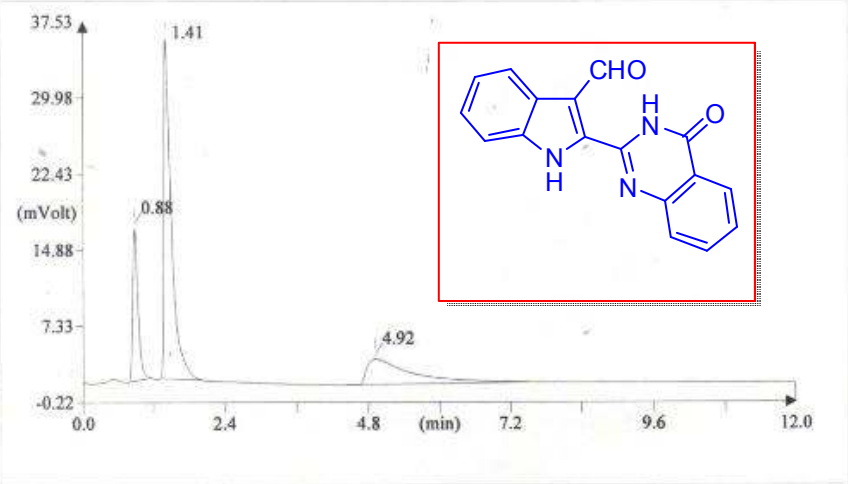


Element Name	Element %	Ret. Time
Nitrogen	14. 43	0. 88
Carbon	70. 45	1. 41
Hydrogen	3. 78	4. 92

Conclusions

We have made significant progress and achieved considerable success in our objectives on the synthesis of various heteroarylcarbazoles, which are known to be biologically active.

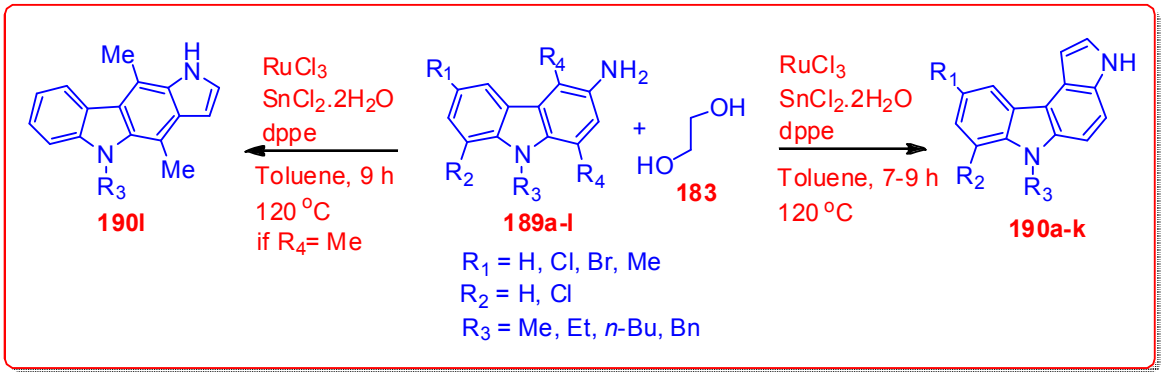
- In summary, we have developed a direct approach for the construction of pyrrolo[2,3-*c*]carbazole **189a-k** and pyrrolo[3,2-*b*]carbazole **189l** in good yields using $RuCl_3/SnCl_2$ mediated system. The synthesized pyrrolo[2,3-*c*]carbazoles easily converted into indolo[2,3-*c*]carbazoles **191a-c** by the reaction with acetonylacetone in good yields.

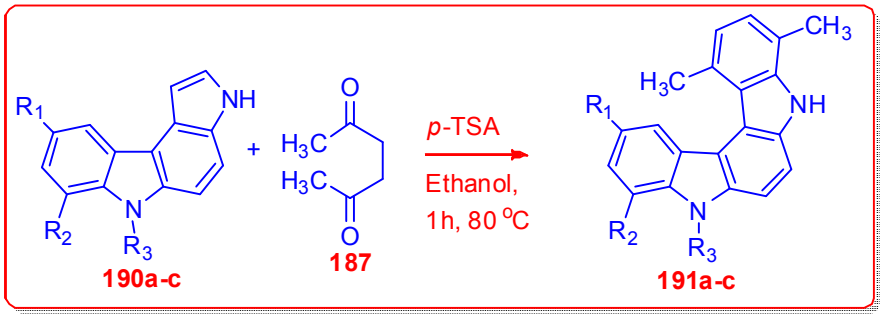
- In conclusion, we have established a general method for the preparation of fused pyrrolo[2,3-*c*]&[2,3-*b*]carbazole **194a-n** derivatives from 3-aminocarbazoles and propargyl alcohol derivatives *via* zinc triflate catalyzed heteroannulation reaction.
- In conclusion, we have developed a novel palladium catalyzed C-H activation reaction of indole-3-acetonitrile with quinoline chloroaldehyde, which afforded a simple and efficient route to quinocarbazole **236a-h** derivatives. This methodology also extended to the synthesis of indolocarbazoles **238a-c** starting from indolochloroaldehydes. A range of functionalized heteroannulatedcarbazole was obtained.
- In conclusion, we have described an efficient route for the construction of potentially active pyridocarbazole (**270a-j**) framework via CAN-mediated Povarov reaction. This transformation proceeds with high regioselectively through Povarov reaction, and subsequent aromatization. It is noteworthy that this is the first example to the best of our knowledge of constructing pyrido[2,3-*c*], [2,3-*b*], [2,3-*a*]carbazoles under such mild conditions.

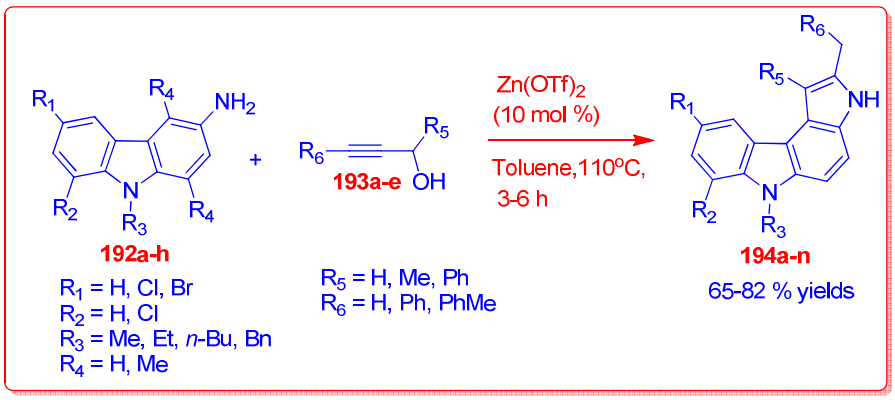
- In conclusion, an efficient synthesis of substituted and unsubstituted indoloquinazolinone (**287, 292**) derivatives by using copper bromide catalyzed condensation followed by cyclization reaction. The reaction proceeds well under relatively mild conditions with shorter reaction times. We also prepared bouchardatine alkaloid (**136**) in good yield, and synthesis of orirenierine A and B is under progress.

GRAPHICAL ABSTRACTS

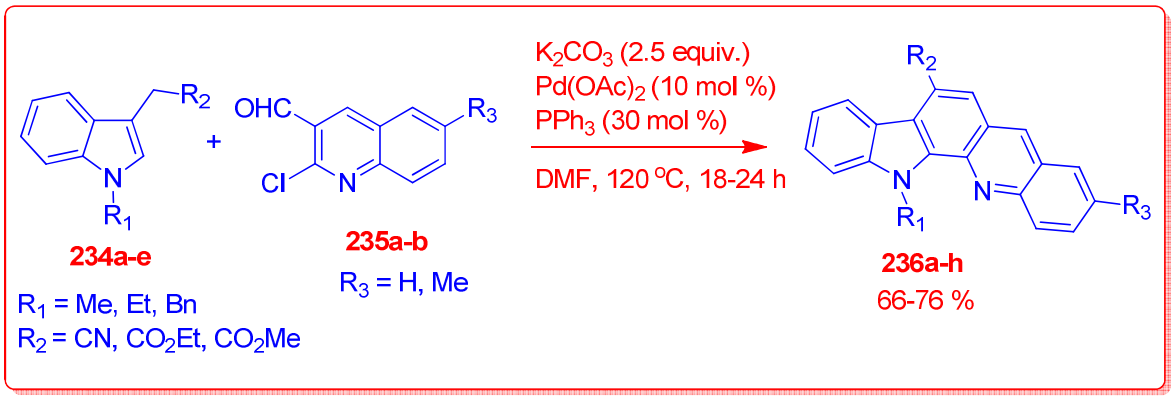
Chapter 1: Synthesis of Pyrrolocarbazoles *via* Heteroannulation

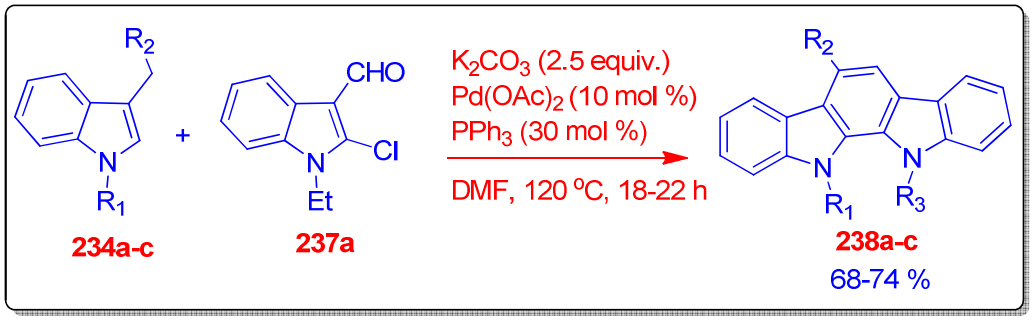




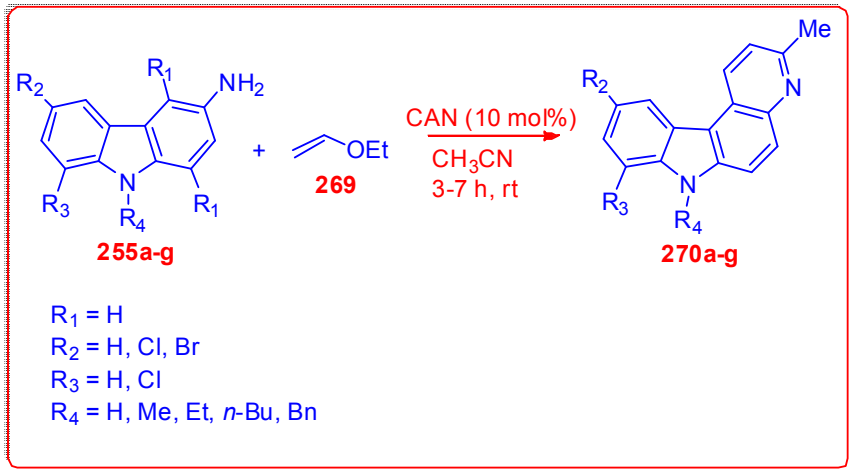


Chapter 2: Palladium catalyzed C-H activation route to the synthesis of quino[2,3-*a*]carbazoles and indolo[2,3-*a*]carbazoles

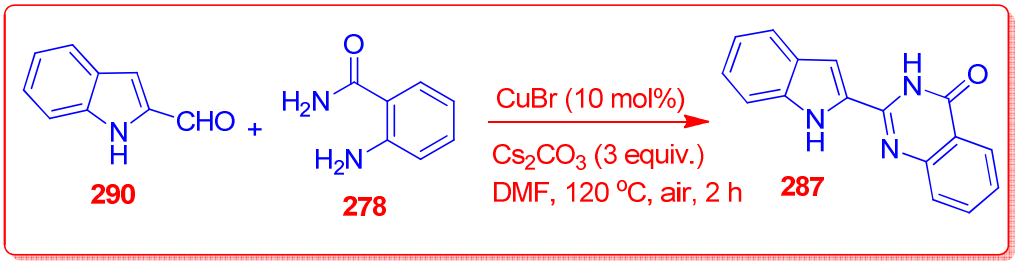


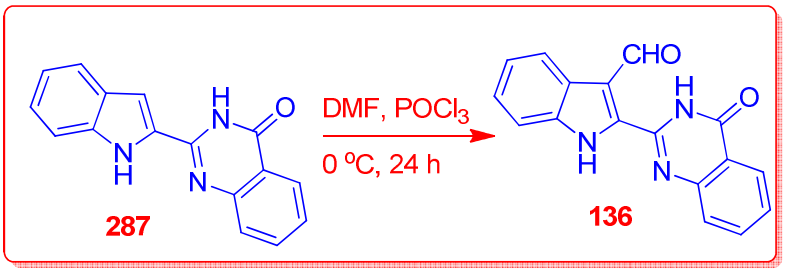


Chapter 3: Synthesis of Pyridocarbazoles *via* Povarov reaction



Chapter 4: Synthesis of Bouchardatine alkaloid





SYNOPSIS OF THE THESIS ENTITLED

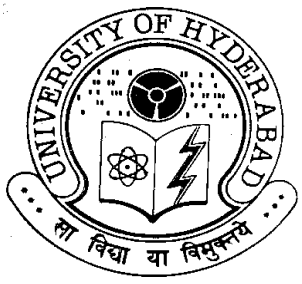
SYNTHESIS OF PYRROLO, PYRIDO, QUINO, INDOLO CARBAZOLE DERIVATIVES AND BOUCHARDATINE ALKALOID

TO BE SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

MAYAVAN VIJI



SCHOOL OF CHEMISTRY

UNIVERSITY OF HYDERABAD

HYDERABAD-500 046

INDIA

Synopsis

We synthesised various derivatives of heteroarylcarbazoles such as pyrrolocarbazoles, pyridocarbazoles, indolocarbazoles and quinocarbazoles *etc.* Moreover we synthesized bouchardatine alkaloids which are known to be biologically active anticancer or antitumour agents is the main emphasis in this thesis. Thesis comprises (i) Introduction, (ii) Chapter 1, (iii) Chapter 2, (iv) Chapter 3 and (v) Chapter 4.

Carbazole alkaloids are important class of heterocyclic compounds and there has been a tremendous development in this field in past few decades.[1] Because carbazole alkaloids are very useful heterocycles in organic synthesis, many groups are currently working on carbazole chemistry. New synthetic methodologies have been developed; existing methodologies have been improved and novel natural products have been isolated.

Over the last few decades numerous efforts have been invested in developing aryl-and heteroaryl-annulated carbazoles, which are reported and comprehensively reviewed.[1-4] To provide an overview on the heteroaryl-annulated carbazole derivatives, these compounds are classified into [*a*]-annulated, [*b*]-annulated, and [*c*]-annulated pyrido-, pyrano-, furo-, pyrrolo-, thieno-, oxazolo-, imidazolo-, pyrrolo-, pyrido-, indolo-, quino-, carbazolo carbazoles *etc*. And so, the synthesis and further applications of heteroarylcarbazoles has gained significant interest from synthetic chemists, which is main objective of this thesis work.

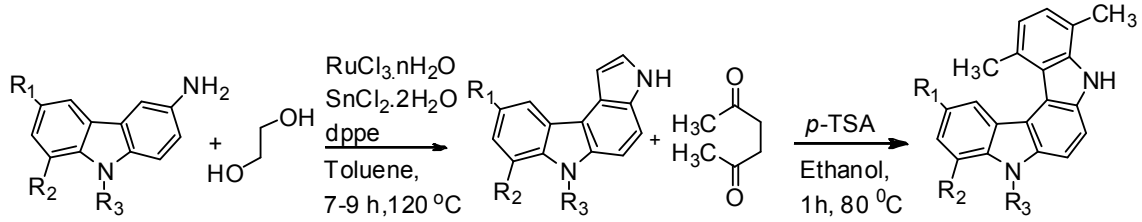
Chapter 1. Synthesis of Pyrrolocarbazoles *via* Heteroannulation

Recently, significant research effort has been focused on the preparation of pyrrolocarbazole scaffolds due to their promising biological activities, including antidepressant, anticancer, and antibacterial activity.[5] For example, the pyrrolo[2,3-*a*], [3,4-*c*] and [2,3-*c*]carbazoles have great importance due to their inhibiting properties towards pim kinase inhibitors as well as for their *in vitro* antiproliferative activities toward a human fibroblast primary culture[6] and Chk1 inhibitors[7] telomerase inhibitors[8] respectively. Moreover pyrrolo[3,4-

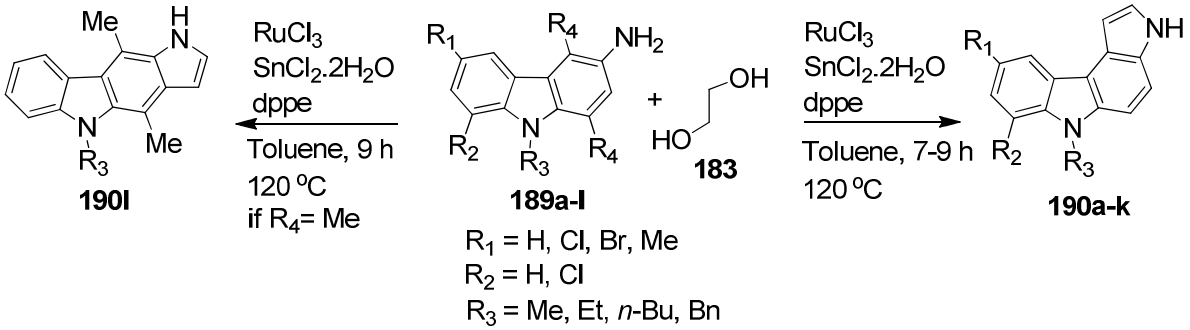
c]carbazole-1,3(2*H*,6*H*)-dione derivative exhibited potent Chk1 and Wee1 inhibitory activity.[9]

Chapter-1 comprises an efficient route to the synthesis of various functionalized pyrrole[2,3-*c*]carbazoles and indolo[2,3-*c*]carbazole derivatives.

Scheme 1. Outline of synthetic plan

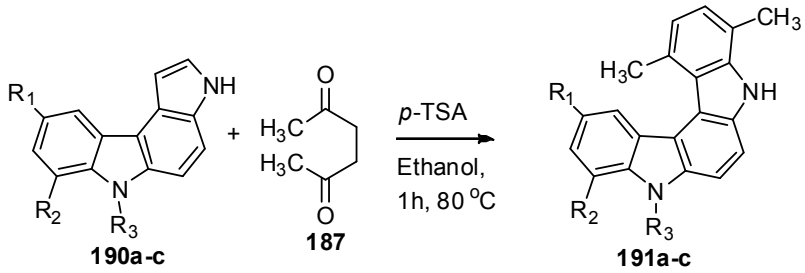


Scheme 2. Synthesis of pyrrole[2,3-*c*]carbazoles



$RuCl_3$ (18 mol %), dppe (15 mol %) toluene (5 mL) along with *N*-alkylated-3-aminocarbazole **189a** (1.0 equiv.), $SnCl_2$ (3.0 equiv) and ethylene glycol **183** (2.0 equiv), and then was heated to 120 °C in pressure tube for 8 h gave the pyrrolo[2,3-*c*]carbazole derivatives. We explored the scope of this method with respect to an array of *N*-alkylated-3-aminocarbazoles **189a-k** smoothly underwent heteroannulation reaction to afford the desired pyrrolo[3,2-*c*]carbazole **190a-k** in good yields. When R_4 was substituted with methyl group pyrrolo[3,2-*b*]carbazole

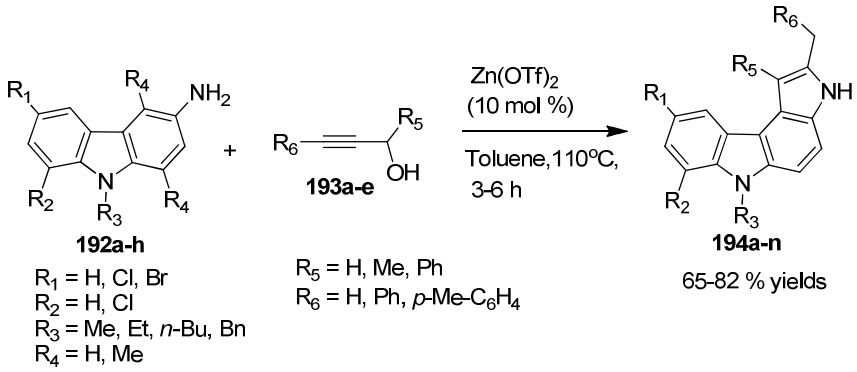
Scheme 3. Synthesis of indolo[2,3-*c*]carbazoles



The desired indolo[2,3-*c*]carbazoles were successfully synthesized in good yields by the reaction of acetonylacetone (1.0 equiv.) with various pyrrolo[2,3-*c*]carbazoles (1.0 equiv.) and using p-toluenesulfonic acid (p-TSA, 0.5 equiv.) as a catalyst along with 5 mL of ethanol then the mixture was strried at 80 °C for 1 h.

Scheme 4. Synthesis of pyrrolo[2,3-*c*]carbazoles catalyzed by zinctriflate

Lewis acid catalyzed annulations processes have received much attention for the facile construction of the heterocyclic skeletons. In recent years zinc triflate has been employed as catalyst in wide range of organic synthesis.[10]



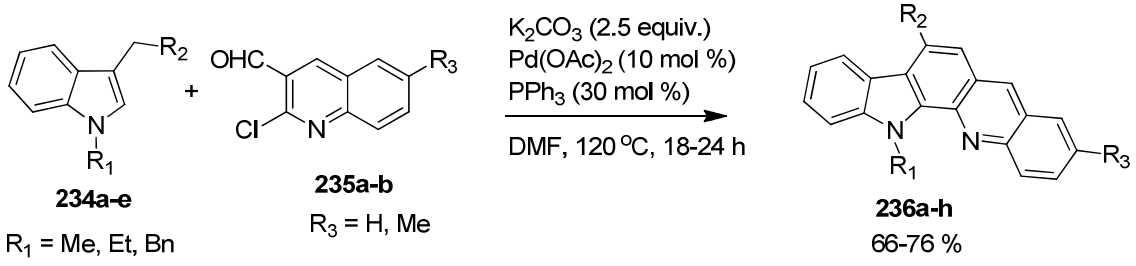
To a stirred solution of 9-ethyl-3-aminocarbazole **192a** (1 equiv.) and propargyl alcohol **193a** (1.5 equiv.) in toluene (20 mL), added zinc triflate (10 mol %) and stirred the reaction mixture at 110 °C for 4 hHaving identified these optimal conditions, we sought to examine the scope and the generality of the method by applying it to a range of substituted 3-aminocarbazoles and propargyl alcohols, and the results are shown in Table 6. The products **194a-n** was generated from **192a-h**, **193a-e** in moderate to good yields. All the products displayed spectroscopic data in agreement with the expected

Chapter 2. Palladium catalyzed C-H activation route to the synthesis of quino[2,3-*a*]carbazoles and indolo[2,3-*a*]carbazoles

In continuation of our efforts in the synthesis of various heteroarylcarbazole derivatives from easily accessible precursors, we report here, a simple and facile synthesis of new quino and indolocarbazole derivatives employing C-H activation.

Indolocarbazoles[11] and quinolocarbazoles[12] are very important and versatile compounds in organic synthesis, and natural product chemistry, due to their biological and pharmacological relevance. Therefore, the preparation of the structural complex and diverse heteroannulated compounds has received much attention in synthetic organic chemistry. As a result, over the decades organic chemists have sought to develop and more efficient methods to prepare these compounds. A number of synthetic methods using transition-metal catalysts have been reported.[13]

Scheme 5. Synthesis of quino[2,3-*a*]carbazoles



234a-e

R_1 = Me, Et, Bn

R_2 = CN, CO_2Et, CO_2Me

235a-b

R_3 = H, Me

236a-h

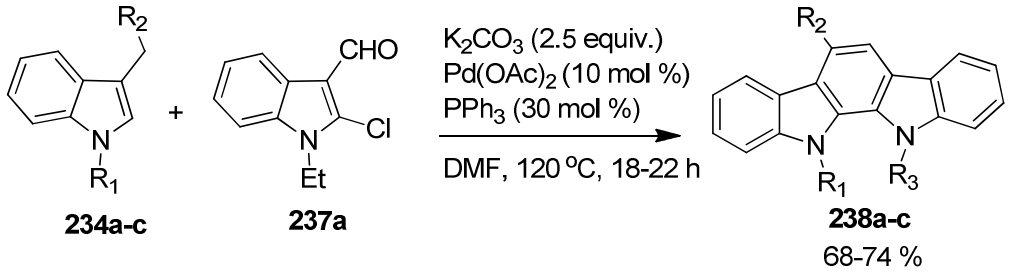
66-76 %

N-methyl-indole-3-acetonitrile **234a** (1 equiv.), 6-methyl-2-chloro-3-formyl quinoline **235a** (1 equiv.), K_2CO_3 (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%), After addition of 2 mL of DMF placed in a 120°C oil bath and stirred for 18 h gives rise to the product **236a**.

To explore the scope of the above reaction, seven additional examples were also tested, and delightfully, all yielded analogous products in yields ranging from 68% to 78%. We proceeded with the preparation of different starting materials **234a-e** and **235a-c** and reacted in the presence of $Pd(OAc)_2$ and K_2CO_3 in DMF to afford respective products **236a-h** in good yields.

Scheme 6. Synthesis of indolo[2,3-*a*]carbazoles

Indolocarbazoles are widely utilized in organic synthesis, medicinal chemistry because of the wide spectrum of biological activity displayed by this class of compounds. Therefore, facile and selective derivatization of indolocarbazoles is highly important and desirable. . We extended the C-H activation strategy to 3-formyl-2-chloroindole **237a** with a view to synthesizing indolo[2,3-*a*]carbazole frameworks **238a-c**. Thus, we obtained the regiospecifically substituted indolo[2,3-*a*]carbazoles **238a-c** in good yields from the corresponding indole precursors **237a** under the above optimized reaction conditions.

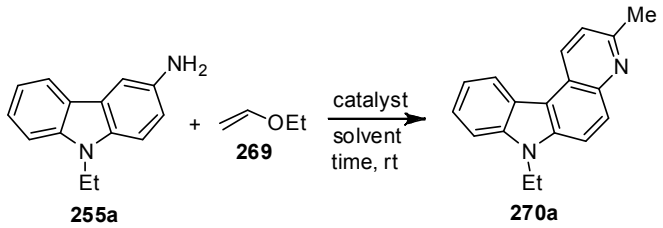


Chapter 3. Synthesis of Pyridocarbazoles *via* Povarov reaction

Pyridocarbazoles are important constituents of the heteroannulated carbazoles for example, ellipticine, olivacine, strellidimine, and janetine belong to the group of pyrido[4,3-*b*]carbazole alkaloids which show potential biological activities.[14] Among them, ellipticine is one of the simplest naturally occurring alkaloids which occupies a pivotal position in the field of medicinal chemistry because of its promising antitumor activity. Its derivative exhibit promising results in the treatment of osteolytic breast cancer metastasis, kidney sarcoma, brain tumours and myeloblastic leukemia.[15]

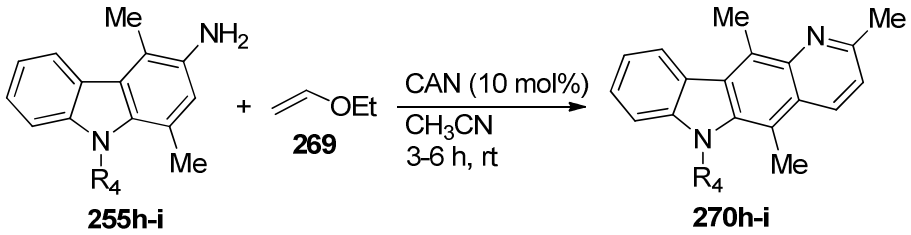
An oven dried 50 mL round bottom flask equipped with a mechanical stirrer and charged with CAN (10 mol %), and 9-ethyl-3-aminocarbzole **255a** (1.0 equiv.), CH_3CN (10 mL) along with ethylvinylether **270** (2.5 equiv.), and it was stirred at rt for 6 h gives rise to the products in good yield.

Scheme 7. Preparation of pyrido[2,3-*c*]carbazole



To demonstrate the generality of this transformation, the optimized conditions were applied to a variety of aminocarbazoles. Table 14 and scheme 10 summarize the results for the Povarov reaction of a series of aminocarbazoles **255a-j** with EVE to produce the corresponding pyridocarbazoles **270a-j** in good yields. When R_1 was substituted with methyl group, pyrido[2,3-*b*]carbazole (**270h-i**) was obtained as product (Scheme 10). This optimized condition was examined for unprotected carbazoles and it afforded the pyridocarbzoles in good yields.

Scheme 8. Preparation of pyrido[2,3-*b*]carbazole

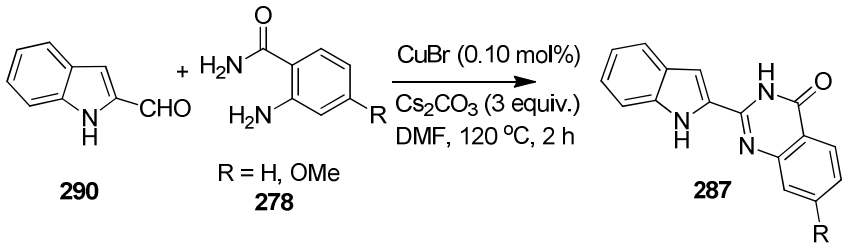


Chapter 4. Synthesis of Bouchardatine alkaloid

In the community of fused heterocycles, 2,3-dihydroquinazolin-4(1*H*)-one and 2-spiroquinazolinone are omnipresent and have been referred to as "core structures" in drug discovery. It is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, animals and microorganisms. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumor, anti-malarial activity, biofungicide, and diuretic properties and several others.[16]

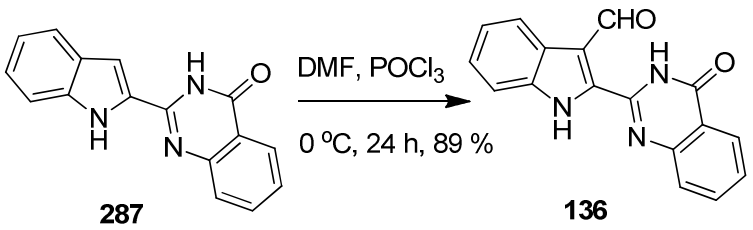
CuBr (10 mol %), and 2-formylindole **290** (1.0 equiv.), DMF (3 mL) along with anthranilamide **278** (1.0 equiv.), Cs_2CO_3 (3.0 equiv.) and it was stirred at 120 °C for 2 h in open air gave the indolylquinazolinone in good yields .

Scheme 9. Synthesis of indolylquinazolinone



Phosphoryl chloride (9.0 equiv.) was dissolved in 3 mL of anhydrous DMF stirred at 0 °C. Then 1.0 equiv. of **287** was dissolved in 4 mL of DMF stirred at 0 °C for 24 h ethanol provided a pale yellow colored solid **136** in 89% yield.

Scheme 10. Synthesis of bouchardatine



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