SYNTHESIS OF PYRROLO, PYRIDOCARBAZOLE DERIVATIVES AND ARSINDOLINE ALKALOIDS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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HYDERABAD-500 046

INDIA

February 2016

STATEMENT

I hereby declare that thesis entitled **"SYNTHESIS OF PYRROLO, PYRIDOCARBAZOLE DERIVATIVES AND ARSINDOLINE ALKALOIDS"** submitted by me under the guidance and supervision of **Dr. R. NAGARAJAN** is a bonafide research work which is also free from plagiarism. I also declare that it has not been submitted previously in part or in full to this University or any other Universities or Institution for the award of any degree or diploma. I hereby agree that my thesis can be deposited in Shodganga/INFLIBNET.

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Dean **(Dr. R. NAGARAJAN)**

School of Chemistry Supervisor

University of Hyderabad

LIST OF PUBLICATIONS

1. A Simple and Regioselective Synthesis of Dihydropyrido[2,3-*c*]carbazoles via Iodocyclization **Rama Raju Jella** and Rajagopal Nagarajan *Synlett* **2011**, *4*, 529

2. Synthesis of Indole Alkaloids Arsindoline A, Arsindoline B and their analogues in Low Melting Mixture **Rama Raju Jella** and Rajagopal Nagarajan *Tetrahedron* **2013**, *69*, 10249

3. Synthesis of Pyrrolo[3,2-*b*]carbazoles via Palladium Catalyzed C-H Activation **Rama Raju Jella** and Rajagopal Nagarajan *Synthesis* **2014**, *46*, 1211

Posters and Presentations

1. Participated and gave an oral and poster presentation on "**Total Synthesis of Indole Alkaloids Arsindolines"** at "***CHEMFEST 2014***" (In-house symposium), School of Chemistry, University of Hyderabad, Hyderabad.

2. Participated and presented poster on "**Synthesis of Pyrrolocarbazoles via Pd-catalyzed C-H activation**" at "***CHEMFEST 2013***" (In-house symposium), School of Chemistry, University of Hyderabad, Hyderabad.

3. Participated and presented poster on "**Synthesis of Pyridocarbazoles via Iodocyclization"** at "***CHEMFEST 2011***" (In-house symposium), School of Chemistry, University of Hyderabad, Hyderabad.

4. Participated and presented poster on "**Synthesis of Pyridocarbazoles via Iodocyclization"** in "***CHENNAI CHEMISTRY CONFERENCE 2011***" IIT Chennai.

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Ramakrishna, Dr. Sheshadri, Dr. Venu, Dr. Madhu, Dr. Santhosh, Dinesh, Dr. Ashok, Chandu, Dr. Tirupathi Reddy, Dr. Pavan, Sudeer, Dr. Yaseen, Dr. Santosh, Dr. T. Rajgopal, Dr. Kishore, Dr. Narayana, Dr. MadhavaCharry, Dr. Bharani, Dr. Shivaprasad, Dr. Srinivas Reddy, Murali, Sasi Kanth, Dr. Rama Krishna, Dr. Sudharani exceptionally generous in helping me at various occasions.

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Rama Raju Jella

Dedicated to my parents ….

Table of Contents

Chapter 3: Synthesis of Arsindoline A, Arsindoline B and their analogues in Low Melting mixture

List of Abbreviations

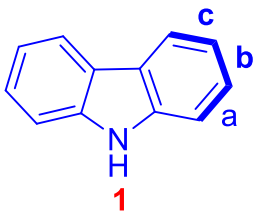
Ac	Acetyl
aq.	Aqueous
Anal. Calcd	Analytically calculated
Ar	Aryl
Bn	Benzyl
BIM	Bis(indolyl)methane
br	Broad (spectral)
Bu	Butyl
t-Bu	*tert*-butyl
^{o}C	Degree Celsius
Calcd	Calculated
CAN	Cerium Ammonium Nitrate
cm^{-1}	Wavenumber(s)
concd	Concentrated
m-CPBA	*meta*-chloroperbenzoic acid
d	Doublet (spectral)
DCM	Dichloromethane
dil.	Dilute
DMA	*N,N'*-dimethyacetamide
DMF	*N,N'*-dimethylformamide
DMSO	Dimethyl sulfoxide
DMU	*N,N'*-dimethylurea
Et	Ethyl
Eq.	Equation

Equiv.	Equivalent
g	Gram(s)
h	Hour(s)
Hex	Hexyl
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i-Pr	*iso*-propyl
IR	Infrared
J	Coupling constant (in NMR Spectroscopy)
LDA	Lithium diisopropylamide
m	meta
M	Molar (solution concentration)
m	multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
mg	Milligram(s)
min	minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
MeOH	Methanol
Mp	Melting point
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
ppm	Parts per million
p-TSA	*para*-Toluenesulfonic acid
q	Quartet (spectral)
rt	Room temperature

s	Singlet (spectral)
t	Triplet (spectral)
TBS	*tert*-butyldimethylsilyl
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl

INTRODUCTION

The isolation and synthesis of different heterocyclic compounds has attracted much attention because of their promising biological and pharmacological activities. Among various classes of heterocyclic compounds, nitrogen atom containing heterocyclic compounds are important molecules found in various natural products which are having broad spectrum of biological activities.[1] During past few decades there has been a remarkable growth in the area of isolation and development of new synthetic methods for carbazole alkaloids. Many research groups all over world are currently working on carbazole chemistry due to their wide occurrence in natural products which shows potential biological activities. Novel synthetic methodologies have been developed; available methods have been enhanced and new natural products have been isolated. In 1872, initially Graebe and Glaser illustrated the parent compound 9*H*-carbazole (Fig 1), which was obtained from the anthracene fraction of coal tar distillate.[2] After ninety years, the discovery of the antimicrobial properties of murrayanine, which was isolated from *Murraya koenigii* Spreng plant, attracted much attention among various research groups.[3] Subsequently, carbazoles correspond to a flourishing area in organic synthesis, as documented in the vast quantity of monographs, reviews and accounts that have appeared in the last 30 years.[4]



1

9*H*-Carbazole

a, b and c phases

Fig.1

Heteroarylcarbazoles

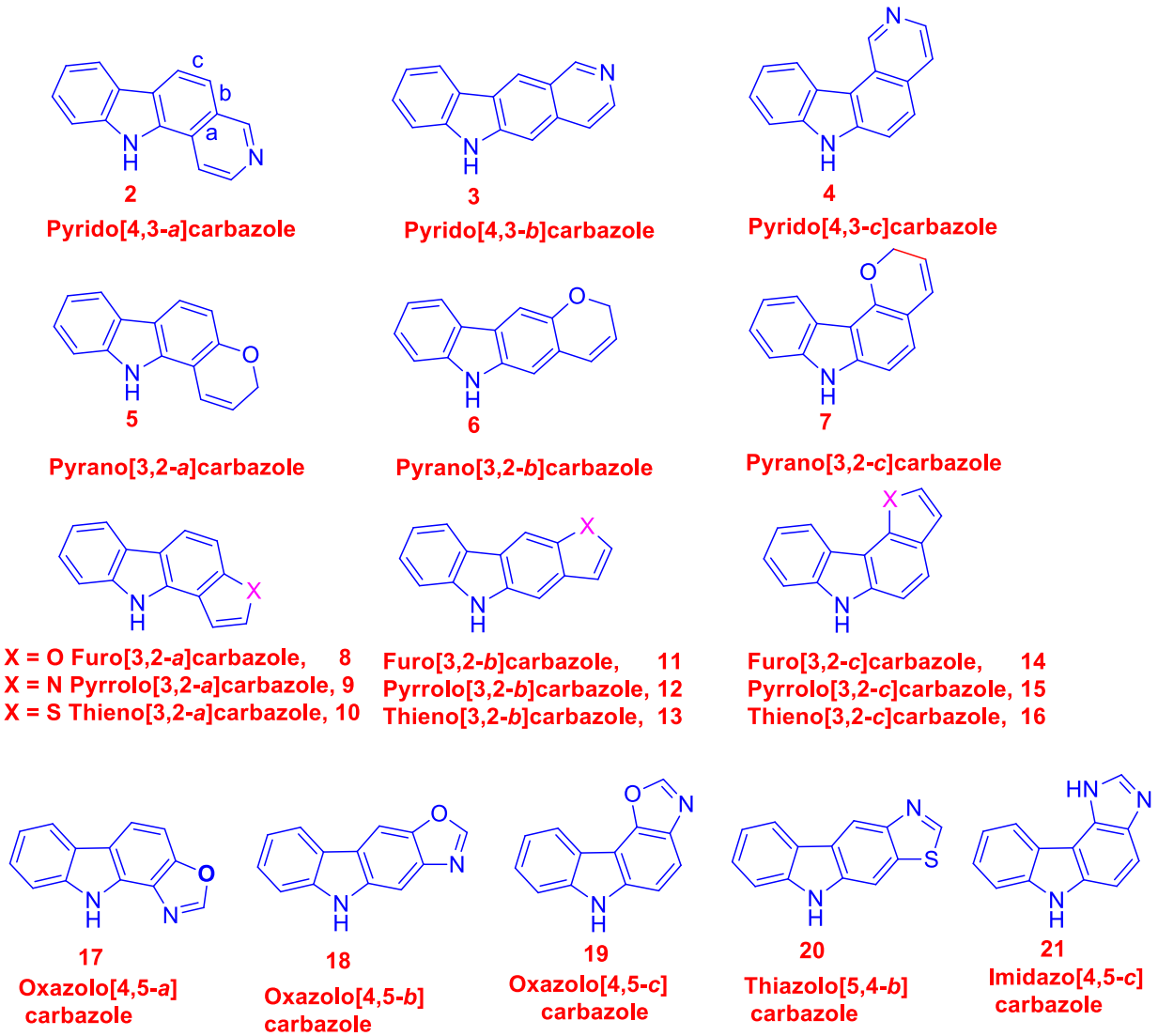


Fig. 2

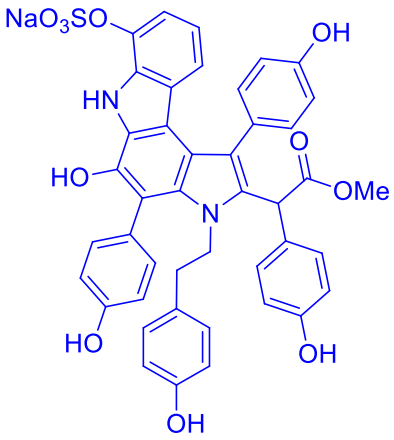
Over last few decades several efforts have been devoted for the development of aryl-and hetero-aryl annulated carbazoles, which are reported and broadly reviewed.[1-4] To give an overview on the heteroaryl-substituted carbazole derivatives, these compounds are divided into [*a*]-annulated, [*b*]-annulated, and [*c*]-annulated pyrido-, pyrano-, furo-, pyrrolo-, thieno-, oxazolo-, imidazolo-, indolo-, quino-, carbazolo carbazoles *etc* as shown in fig2. This categorization is exclusively based on the position where the heteroaromatic ring is fused to the carbazole core structure, depending upon the phase it is named as a, b, or c as

in fig 1. In addition, the way the annulated heteroaromatic ring joins itself may differ; which directed to larger array of heterocyclic ring systems. These have attracted much attention due to their occurrence in several natural products with different valuable biological activities.[5] Numerous efforts have been dedicated for the aim and synthesis of different carbazoles such as pyridocarbazoles and pyrrolocarbazoles, which appear to be the more interesting; and thus have established to be extremely crucial in medicinal chemistry.

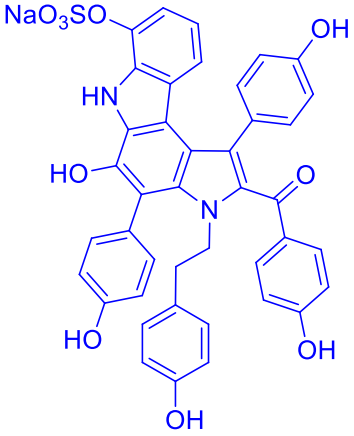
Pyrrolocarbazole alkaloids

Isolation from natural sources

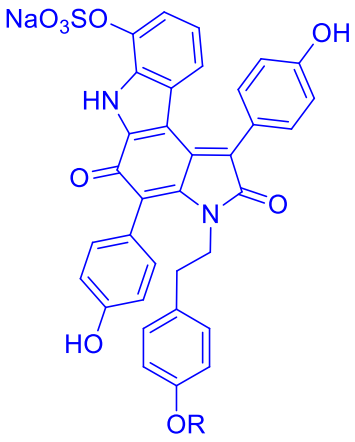
Pyrrolocarbazoles are an important class of heterocycles; numerous attempts have been devoted to the plan and synthesis of pyrrolocarbazoles. But, for many years pyrrolocarbazoles comprise exclusively of synthetic origin. Pyrrolocarbazoles, were the more interesting, and therefore have established to be exceptionally significant in medicinal chemistry with a broad range of pharmacological and biological activities like neurotropic, anticancer and antidiabetic, activities.[6] In addition, the pyrrolo[2,3-*a*] and [3,4-*c*]carbazoles comprise larger significance owing to their inhibiting properties towards pim kinase[7] inhibitors and Chk1 inhibitors[8,9] correspondingly.



22, Dictyodendrin A

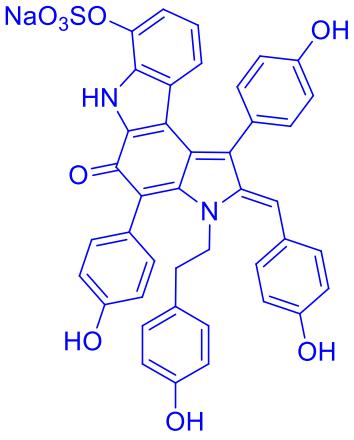


23, Dictyodendrin B



24, R = H, Dictyodendrin C

25, R = SO_3Na, Dictyodendrin D



26, Dictyodendrin E

Fig. 3

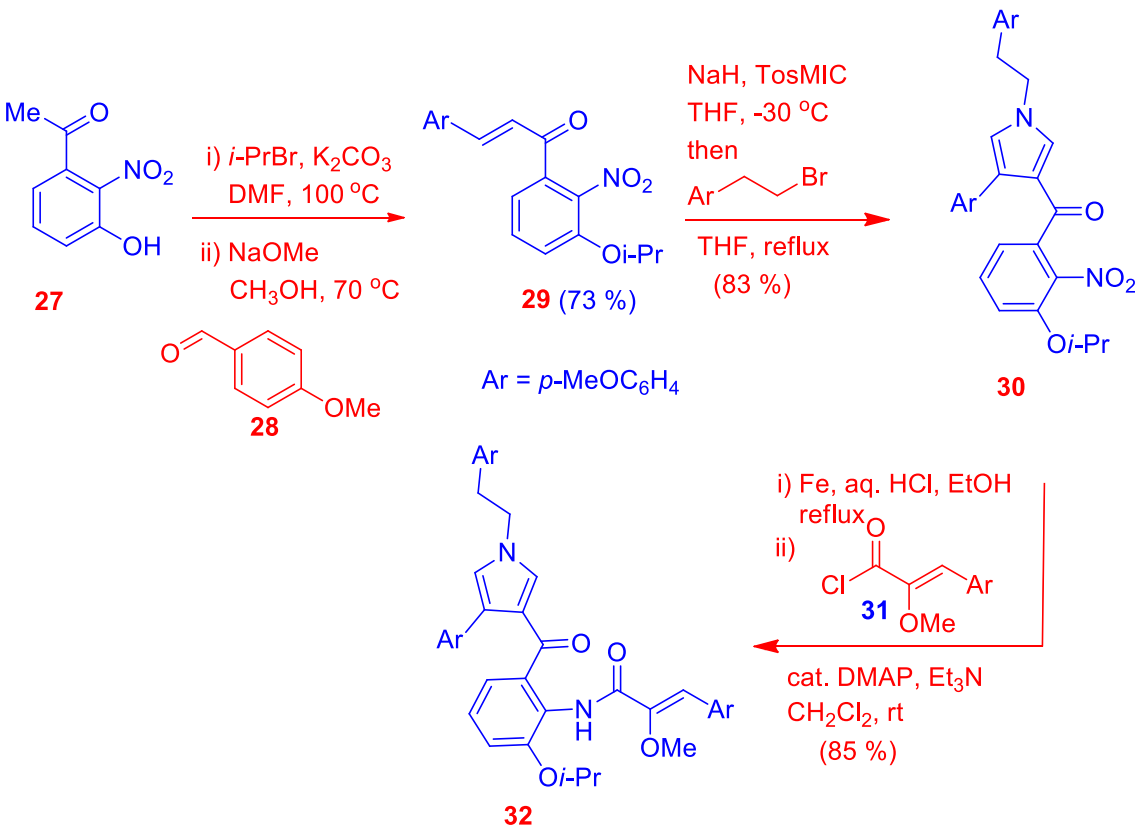
Over the previous 50 years, the marine surroundings have been investigated for novel bioactive compounds, flattering a greatly significant and affluent basis of potent compounds and drug leads accounted to acquire a broad range of activities. Marine surroundings have verified as an excellent resource of bioactive molecules, one of the most capable being carbazole alkaloids. An increasing number of carbazole alkaloids are seperated from diverse marine organisms. The dictyodendrins are interesting marine products which could be used as tremendous candidates for cancer chemotherapy. The strong anti-tumour activity and structural features of dictyodendrins A-E deliver these marine natural products attractive goals for total syntheses.

Dictyodendrins A-E (**22-26**) pyrrolo[2,3-*c*]carbazole alkaloids,[10] (Fig. **3**) were isolated from *dictyodendrilla verongiformis*, gathered in southern Japan, the aquatic natural products having telomerase inhibitory properties providing 100% inhibition by 50 µg/mL. Accordingly, several synthetic pyrrolo[2,3-*c*]carbazoles have been prepared for structure-activity relationship studies.[11] The first total synthesis of dictyodendrin B (**23**), C (**24**), and E (**26**) were reported by Fürstner *et al*. in their ammonium salts form starting from the familiar pyrrolocarbazole **34** using a McMurry coupling and a 6π-electrocyclization pathway. The synthesis of the relay compound **34** initiated from the readily available 3-hydroxy-2-nitroacetophenone **27**.[12]

First, **27** was treated with isopropyl bromide to obtain the required isopropyl ether, which was then treated with p-methoxy benzaldehyde (**28**) to give the chalcone (**29**). Reaction of chalcone (**29**) with *p*-toulenesulfonylmethyl isocyanide (TosMIC) in the presence of sodium hydride at -30°C and in situ *N*-alkylation with 4-methoxyphenethyl bromide to give pyrrole derivative **30**. Reduction of nitro group in **30** with iron in acidic conditions led to the corresponding aniline. Subsequent treatment with the acid chloride **31** gave the compound **32** (**Eq. 1**). Intramolecular McMurry coupling of the ketoamide **32** using low-valent titanium on graphite, prepared from titanium(III) chloride and two equiv. of potassium-graphite (KC_8), in 1,2- dimethoxyethane (DME) under reflux gave the indole **33** up to 93% yield.

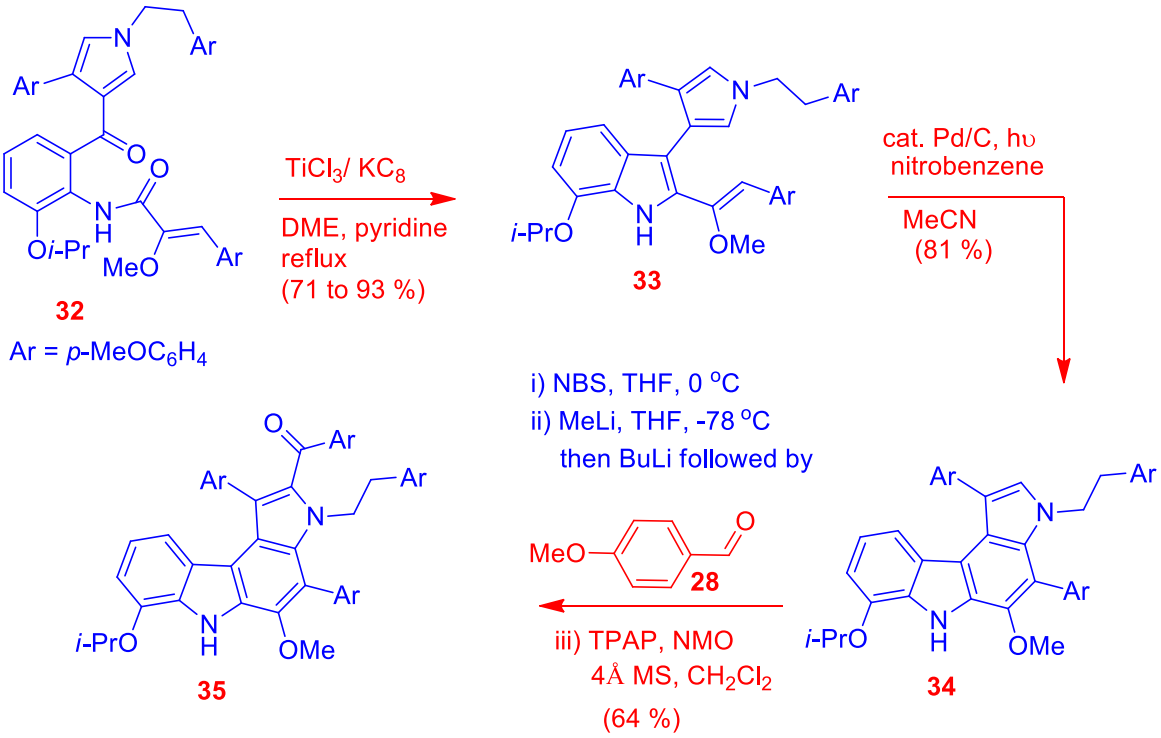
Synthesis of Pyrrolocarbazole alkaloids

Eq. 1



Irradiation of **33** using UV light in nitrobenzene and acetonitrile in the presence of palladium on activated carbon persuaded a 6π-electrocyclization followed by aromatization to provide the pyrrolo[2,3-*c*]carbazole **34**. Then obtained compound **34** was utilized for the synthesis of the dictyodendrins B (**30**), C (**31**), and E (**33**). For the synthesis of dictyodendrin B **23**, the pyrrolocarbazole **34** was subjected to regioselective bromination at C-2 using NBS to give an unstable 2-bromopyrrolo[2,3-*c*]carbazole. Deprotonation of the carbazole nitrogen atom, halogen-metal replaced with butyllithium and subsequent quenching of the intermediate lithio species with p-methoxybenzaldehyde (**28**) led to secondary alcohol which was then oxidized to the ketone **35** using catalytic amounts of tetrapropylammonium perruthenate (TPAP) and also *N*-methylmorpholine *N*-oxide (NMO) as the oxidant (**Eq. 2**).

Eq. 2

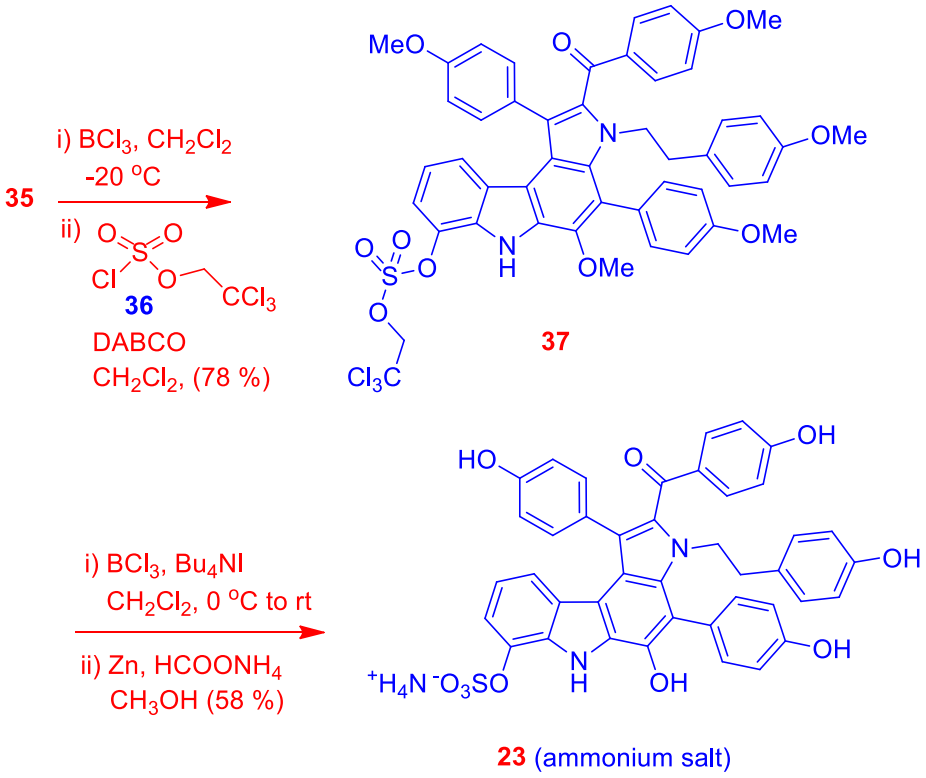


The Chemoselective cleavage of the isopropyl ether in **35** using BCl_3 and treatment of the resultant pyrrolo[2,3-*c*]carbazol-7-ol by 2,2,2-trichloroethyl chlorosulfonate gave the aryl sulfate **37** up to 78% yield. The exhaustive demethylation of **37** was achieved with BCl_3 and sub-stoichiometric amounts of tetrabutylammonium iodide (TBAI). Later reductive cleavage

of the trichloroethyl ester using zinc and ammonium formate gives the dictyodendrin B (**23**) as ammonium salt (**Eq. 3**).

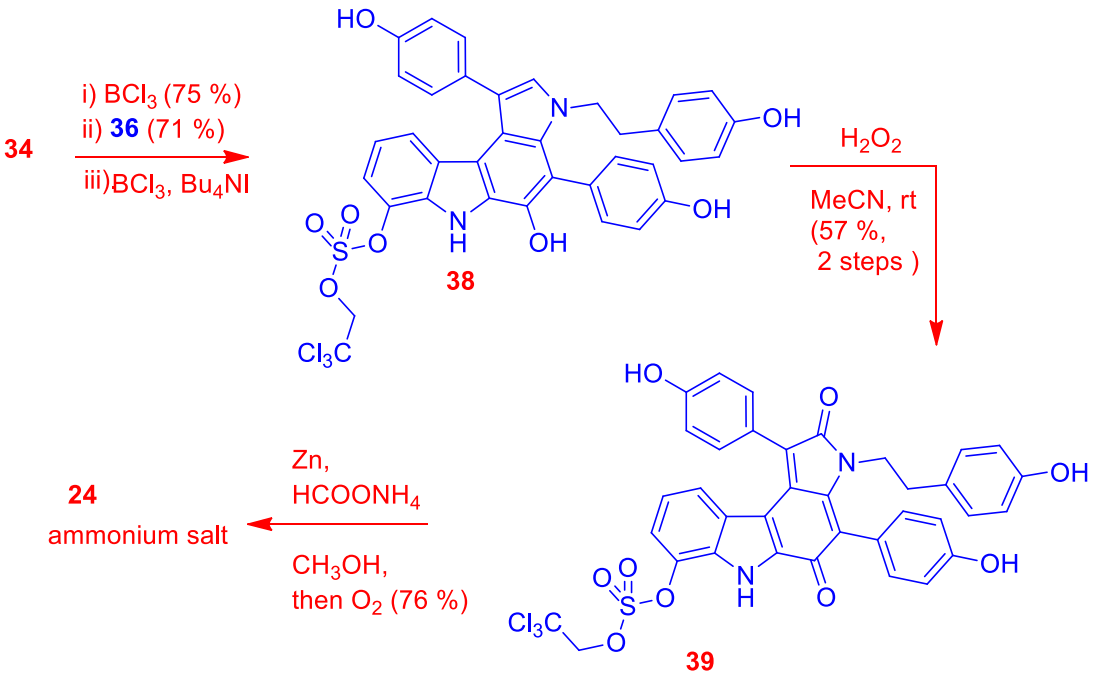
Esterification reaction of the hydroxy group at C-7 using 2,2,2-trichloroethyl chlorosulfonate (**36**) and followed by the cleavage of all methyl ethers using boron trichloride in the presnece of tetrabutylammonium iodide gave the compound **38**.

Eq. 3.



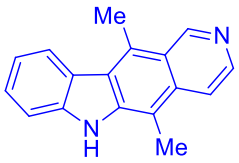
The reaction of pyrrolo[2,3-*c*]carbazol-5-ol core of **38** using hydrogen peroxide in acetonitrile solvent resulted to the pyrrolo[2,3-*c*]carbazole-2,5-dione **39**. Finally, the reductive cleavage of trichloroethyl ester with excess of zinc dust and ammonium formate in methanol followed by stirring the reaction mixture under an oxygen atmosphere gave the dictyodendrin C (**24**) as ammonium salt up to 76% yield (**Eq. 4**).[16]

Eq. 4

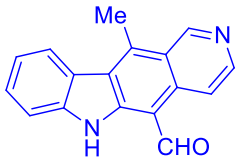

34
i) BCl3 (75 %)
ii) 36 (71 %)
iii) BCl3, Bu4NI
38
H2O2
MeCN, rt
(57 %,
2 steps)
39
Zn,
HCOONH4
CH3OH,
then O2 (76 %)
24
ammonium salt

Pyridocarbazole alkaloids

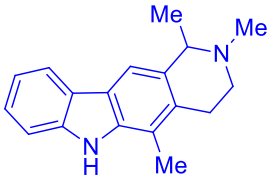
Isolation from natural sources



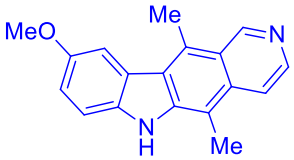
40, Ellipticine



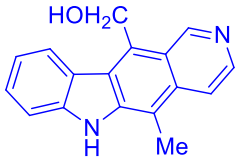
41, 17-Oxoellipticine



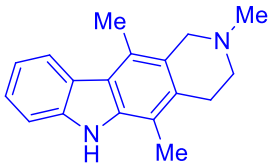
42, Guatambuine
(u-Alkaloid C)



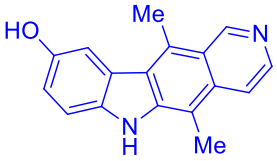
43, 9-Methoxyellipticine



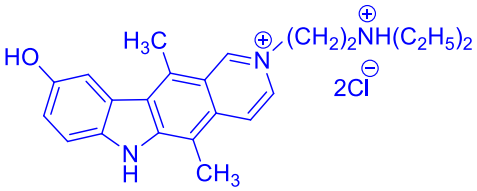
44, 18-Hydroxyellipticine



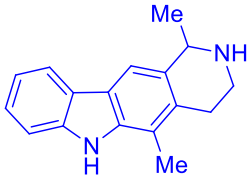
45, *N*-Methyltetrahydroellipticine



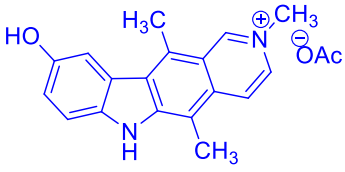
46, 10-Hydroxyellipticine



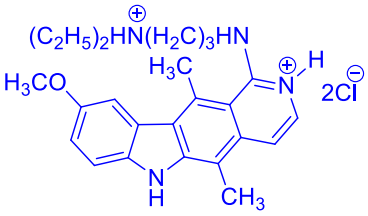
47, Datelliptium



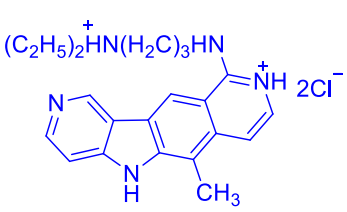
48, Janetine



49, Elliptinium acetate



50, Retellipticine (BD-84)



51, Pazellipticine (BD-40)

Fig. 4

It is well known that pyridocarbazole ring system is suitable framework to develop DNA intercalating drugs[13], hence there has been a strong synthetic activity in this area. A large variety of novel pyridocarbazole-based natural products (fig 4), some of which showed attractive biological activities, and naturally available bioactive molecules have been recognized for many years. They exhibit activity against treatment of breast cancer[14], intercalation into the DNA double helix[15], inhibition of topoisomerase II[16], and anti-HIV agent[17]. Furthermore it was verified *in vitro* and *in vivo* that ellipticine binds to DNA covalently and was driven by cytochrome P450 or peroxidase[18] enzyme which led to the development of several ellipticine derivatives and their clinical use for treatment of advanced breast cancer, myeloblastic leukemia and other tumors[19]. There are numerous review articles and books covering diverse or limited aspects of the pyridocarbazole. In 1959, Goodwin *et al*. reported the isolation of ellipticine **40** and 9-methoxyellipticine **43**, two 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 subsequent years, several groups reported the separation of the similar alkaloids from various 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] in addition to the Loganiaceae family, *Strychnos dinklagei* Gilg.[26]

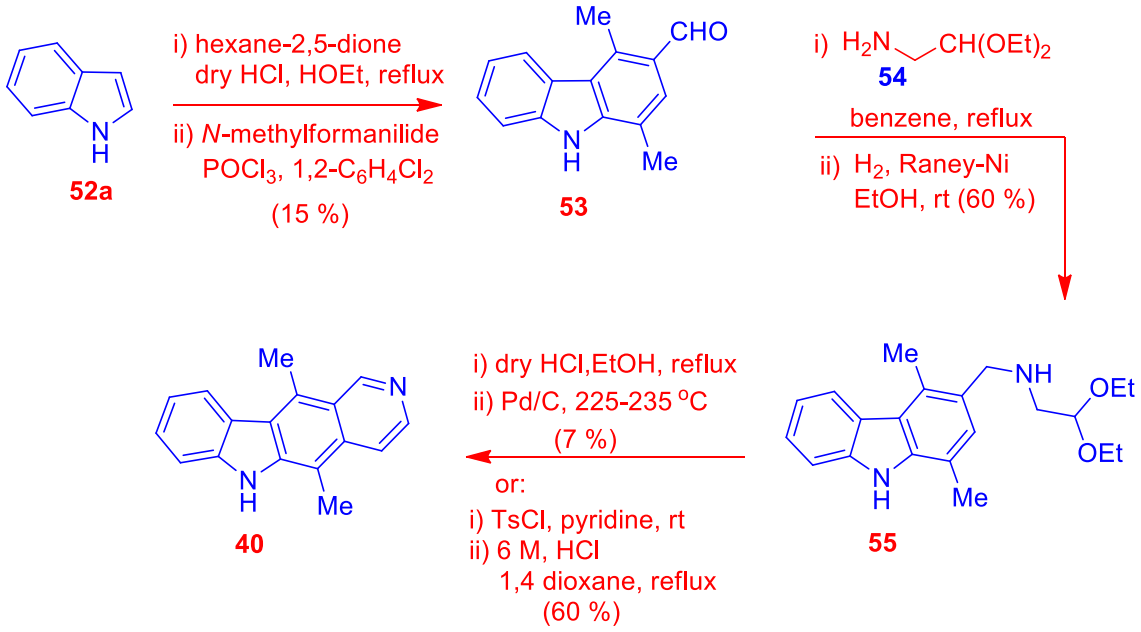
Synthesis of pyrido[4,3-*b*]carbazoles

The isolation and synthesis of different pyridocarbazole derivatives experienced a remarkable growth. This is highlighted in several reviews describing the synthesis and activity studies of ellipticines. Because of the discovery of the anticancer activity of ellipticine (**40**) and 9-methoxyellipticine (**43**) in numerous human and animal tumor systems, the pyrido[4,3-*b*]carbazole alkaloids became promising targets for various synthetic groups.[27]

In 1962, Cranwell and Saxton described a straightforward synthesis of ellipticine using a Pomeranz–Fritsch cyclization as key step.[28] Reaction of indole (**52a**) and hexane-2,5-dione in the presence of gaseous HCl in ethanol followed by Vilsmeier formylation led to 3-formyl-1,4-dimethylcarbazole (**53**). Imine formation by reaction with **54** and reduction of the resultant imine led to secondary amine **55**. Acid-catalyzed cyclization of the amine **55**

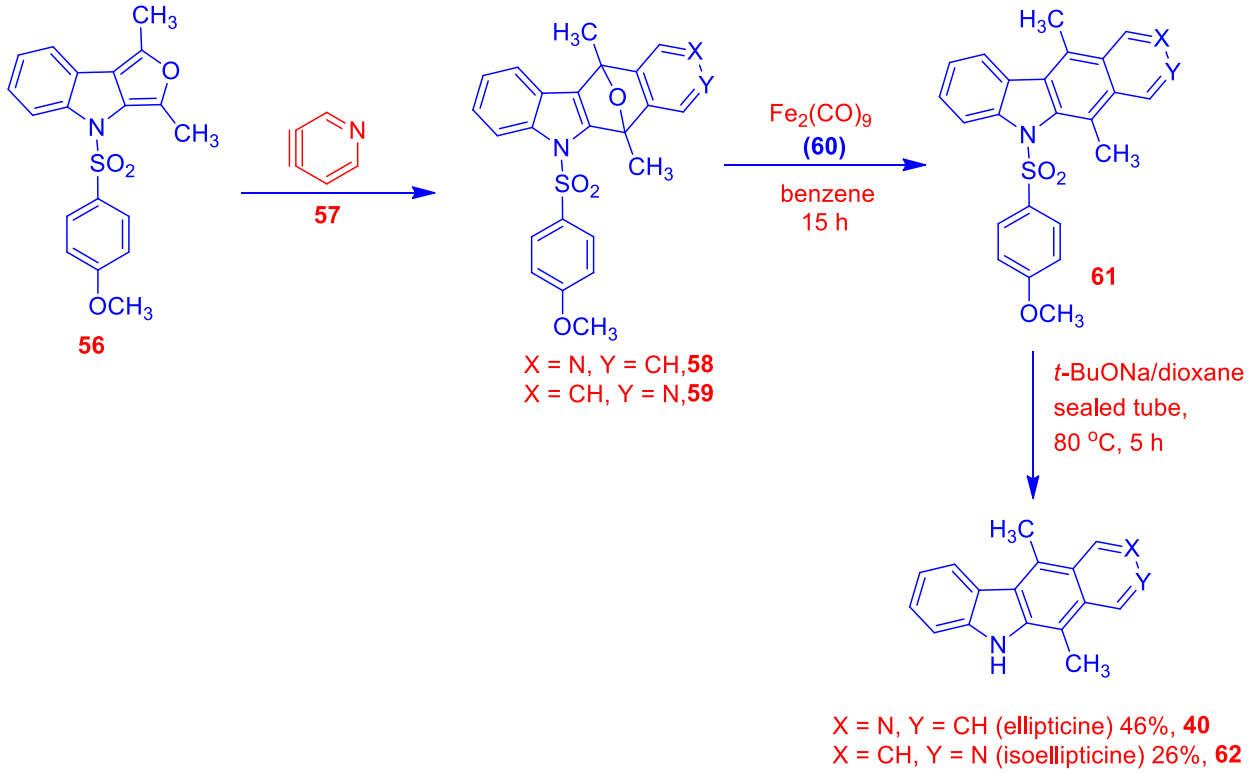
followed by solvent-free dehydrogenation with palladium on activated carbon led to ellipticine (**40**) with 7% yield. Jackson and co-workers developed the better method for the Pomeranz–Fritsch cyclization.[29] Tosylation of the secondary amine in **55** followed by heating of the tosylamide in a mixture of hydrochloric acid and 1,4-dioxane provided ellipticine (**40**) in 60% yield (**Eq. 5**).

Eq. 5



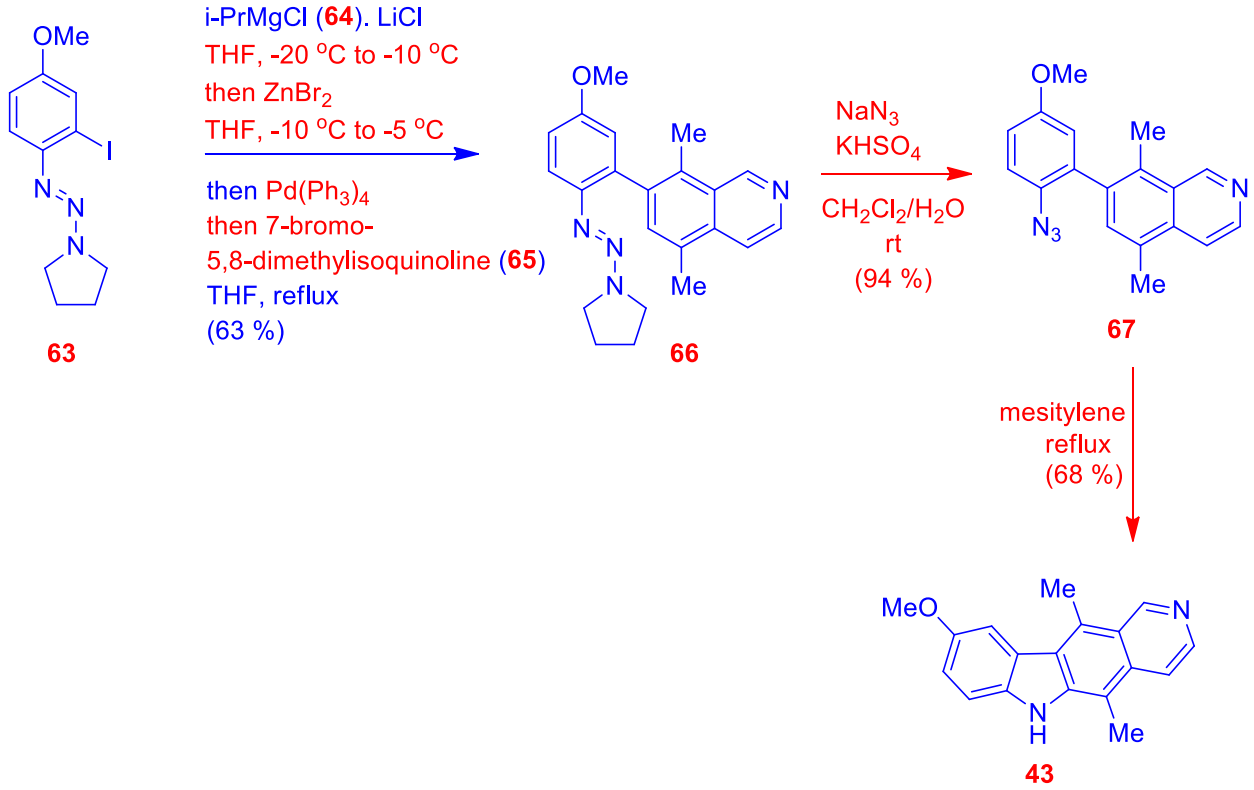
Pujol, *et al*. reported the synthesis of ellipticine by the reaction of diene **56** which was successfully converted into the mixture of isomeric Diels-Alder adducts **58** and **59** by cycloaddition with **57**, 4-pyridyne as the dienophile, obtained from 3-bromopyridine. These adducts were deoxygenated with $Fe_2(CO)_9$ (**60**) without any additional purification to get **61**. The last step, basic desulfonylation using *t*-BuONa in dioxane in a sealed tube, gave the ellipticine **40** in 46% overall yield and the regioisomer isoellipticine **62** was obtained in 26% yield (**Eq. 6**).[30]

Eq. 6



For the synthesis of 9-methoxyellipticine (**43**) (**Eq 7**), initially halogen−metal exchange of 1-(4-methoxy-2-iodophenylazo)-pyrrolidine (**63**) led to Grignard reagent (**64**) that was transmetalated with zinc(II)bromide to afford the corresponding zinc intermediate, which on Negishi cross-coupling with the 7-bromoisoquinoline (**65**) led to aryl triazene **66**. Addition of $KHSO_4$ in dichloromethane in the presence of sodium azide to **66** gave the resultant aryl azide **67**. Thermal cyclization in mesitylene at reflux afforded 9-methoxyellipticine (**43**) by loss of dinitrogen and C-H insertion of the intermediate nitrene.[31]

Eq. 7



Transition metal catalysts in organic synthesis

The fundamental renovation in organic synthesis is the creation of well-organized carbon-carbon and carbon-nitrogen bonds. The improvement of capable synthetic methods to accomplish multiple organic transformations in excellent yield through complete conversion is an essential and demanding task in synthetic organic chemistry. In this portion, transition metal catalyzed reactions have established to be helpful synthetic methods with broad applications in organic synthesis and in addition, transition metal catalyzed reactions have confirmed to be extremely selective and atom economical. The preparation of multifarious molecules starting from rather easy precursors has extended to be an ambition for many research groups. The capabilities to selectively functionalize a molecule through nominal pre-activation preserve rationalize syntheses and develop the opportunities to investigate the effectiveness of complex molecules in the pharmaceutical industry to materials science.

Certainly, the topic of selectivity is dominant in the true test of the effectiveness of a synthetic method is in its relevance to the preparation of natural products or complex molecules. A number of groups have established the applicability of C-H bond functionalization reactions to complex molecule synthesis.[32]

Target-oriented synthesis provides a platform to analyze the usefulness of a method in distinctive chemical and steric environments. In this esteem, Pd-catalyzed methods for C-H bond functionalization stand out, with several synthetic methods being illustrated in the literature that exploit C-H bond functionalization in a key step, and enhancement of reaction conditions have facilitated the synthesis of a broad range of heterocyclic compounds in an extremely resourceful and environmentally friendly manner. Improvement of all C-H bond functionalization methods, a number of groups have developed well-designed approaches to accomplish selectivity in molecules that possess many sterically and electronically similar C-H bonds.[33]

The main aspect in the contemporary heterocyclic synthesis with transition-metal catalyzed reactions are becoming very popular and attracting keen interest of a wide range of organic chemists, in view of the fact that a transition-metal catalyzed reaction can straightforwardly construct complicated molecules from readily available starting materials under mild conditions. The transition-metal catalyzed synthesis of heterocyclic compounds has been summarized in numerous outstanding reviews and they were cited comprehensively. It is distinctive that this methodology is extremely helpful 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.[34]

Palladium catalyzed reactions

Improvement of selective and well-organized C-C bond forming reactions is of dominant significance for organic chemistry. In recent times, transition-metal catalyzed C-H bond activation through consequent C-C bond construction has achieved enormous interest.[32] Palladium catalysis has attained the position of an essential tool for both familiar and state-of-the art organic synthesis. In the previous 40 years or so, yet, palladium-catalyzed reactions, usually tolerant of a broad variety of functionalities and therefore applicable to complex molecules, have achieved an important place in the arsenal of the practicing organic chemist. Palladium complexes are predominantly attractive catalysts for such

transformations for a number of reasons. Initially, ligand-directed C-H functionalization at Pd centers can be utilized to establish various special types of bonds, as well as carbon-oxygen, carbon-halogen, carbon-nitrogen, carbon-sulfur, and carbon-carbon linkages. Such methodologies are important tools in the preparation of possible pharmaceuticals, natural products and organic materials.[35] An interesting myriad of adventurous and exceptional Pd-catalyzed transformations are regularly originated as key steps in target-oriented syntheses, affording complex natural products, fluorescent compounds, functional advanced materials, pharmaceutical lead compounds, and additional high-value commercial products. Nearly each part of the organic synthesis has been profoundly inclined by the thoughtful potential of this transition metal, changing the way organic chemists plan and realize synthetic processes.[33]

Novel Pd catalyst design, the discovery of innovative synthetic methodologies, and the achievement of complete mechanistic approaching, across both homogeneous and heterogeneous fields, strengthen the several improvements seen in this area over the past few decades. Palladium-catalyzed reactions are in fact sturdily reliant on many factors such as the environment of stabilizing ligands (as well as their presence or absence), bases, and additives, combination of them, solvents, and temperature. Every part of of these factors unite to give a toolbox of tunable reaction conditions that formulate palladium chemistry so flexible and, to various extent, random, leaving room for a continuous invention of novel, exciting chemistry even with the huge amount of studies developed so far.

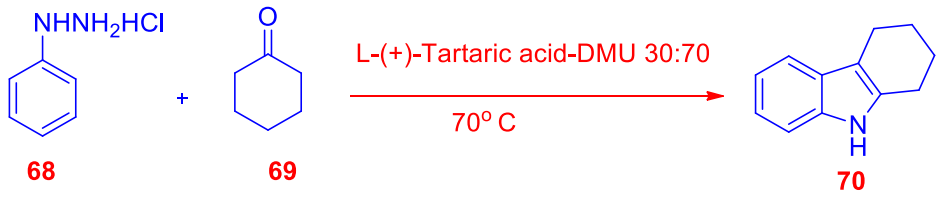
Finally, the enormous majority of Pd-catalyzed C-H functionalization reactions can be performed in the presence of ambient air and moisture, making them exceptionally practical for applications in organic synthesis. Owing to its catalytic nature, palladium-catalyzed synthesis can provide access to agrochemical, fine chemicals and pharmaceutical intermediates, and active ingredients in lesser steps and with less waste than traditional methods. Heterocyclic chemistry is no exemption to this development, and a great deal of studies has been directed toward the use of palladium catalysis in the synthesis and functionalization of heterocycles. [34]

Low melting mixtures in organic synthesis

In recent years the key force to increase the effectiveness of organic transformations is to decrease the quantity of waste materials. Solvent plays a crucial role in these attempts and solvents are frequently the major sources of wastes in organic synthesis. Reducing the utilization of solvents can significantly decrease the quantity of waste formed in the reaction. Modern attempts have paying attention on restraining the use of organic solvents and restore them through fresh environmentally benign conditions. Over last decade, ionic liquids at room temperature have attracted significant attention as a new reaction medium. From all their outstanding properties like thermal stability, tremendous salvation ability and low flammability made them as good reaction medium. But, On the other hand their toxicity to the environment is still in question to consider them as green reaction medium. In the year 2003, Abott and coworkers developed a low melting mixture at room temperature constitutes urea and ChCl, named as deep eutectic solvents which are attractive alternatives to ionic liquids.[36,37] These eutectic mixtures are nontoxic, biodegradable, less expensive and easily prepared. The synthesis of low meting mixture is very easy, which involves the mixing of components under heating to obtain a homogeneous clear liquid. The obtained liquid utilized as reaction medium.

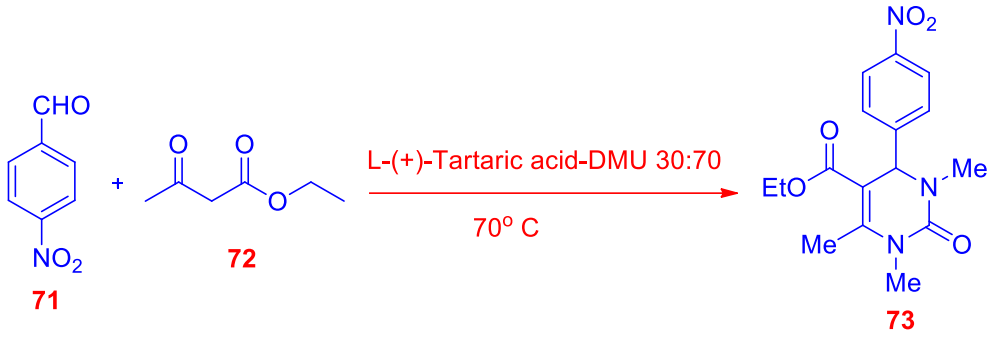
Baskaran *et al*. reported Fisher indole synthesis in low melting mixture. They have prepared corresponding indole derivative **70** by the reaction of phenylhydrazine **68** and cyclohexanone **69** in low melting L-(+) tartaric acid-dimethyl urea mixture.[38]

Eq. 8



Baskaran *et al*. have also synthesized 3,4-dihydropyrimidin-2-ones **73** by the reaction of 4-nitrobenzaldehyde **71**, ethylacetoacetate **72** and DMU in low melting L-(+) tartaric acid-dimethyl urea mixture.[39]

Eq. 9



Bis(indolyl)methanes (BIMs)

Several natural products, agrochemiacals and other important compounds generally contain indole ring system. The indole ring is fundamental unit for bis(indolyl)methanes (BIMs). Several important BIMs were separated from different aquatic natural sources. These BIMs displays many significant biological activities.[40] These BIMs were frequently used in treatment of various types of cancers and these are also utilized to reduce bladder cancer growth and mammary tumor growth, repectively. These BIMs displays antifungal, antibiotic, antitumorigenic and anti-inflammatory activities.[41] These BIMs provided as inhibitors of the platelet-derived growth factor receptor kinase, induce apoptosis in prostate cancer used as cytodifferentiating agents, antiangiogenic agents, have inhibitory effects on Phenobarbital-induced hepatic CYP mRNA expression, have radical scavenging activity, growth promoting activity and also used as glass-forming high-triplet-energy materials. Several forms of BIMs used in the preparation of dyes and calorimetric sensors.[42] In literature, different methodologies have been reported for the preparation of BIMs because of their enormous biological activities and medicinal applications. These BIMs were utilized as ligand for the development of complex molecules and various properties of those molecules have been discovered. Some of BIMs can also be used as chemotherapeutic agents against several cancers.[43]

Initially in the year 1886 Fischer prepared BIMs. The general method for the preparation of BIMs is Friedel-Crafts reaction among indoles and carbonyl compounds in the existence of acid or base. The traditional methods for the prepartion of BIMs also includes the utilization

of protic acids, such as H_2SO_4, HCl, $KHSO_4$, CH_3COOH and Lewis acids like $In(OTf)_3$, $Ln(OTf)_3$, some other catalysts CAN, ionic liquids, I_2, molten salts and eutectic salts.[43] The common method for the preparation of BIMs invoves the reaction of indoles with aliphatic or aromatic aldyhydes or ketones in the existence of acid to give azafulven **74** which can react with another indole molecule to generate BIMs as shown in figure **5**.

The mechanism of BIM formation

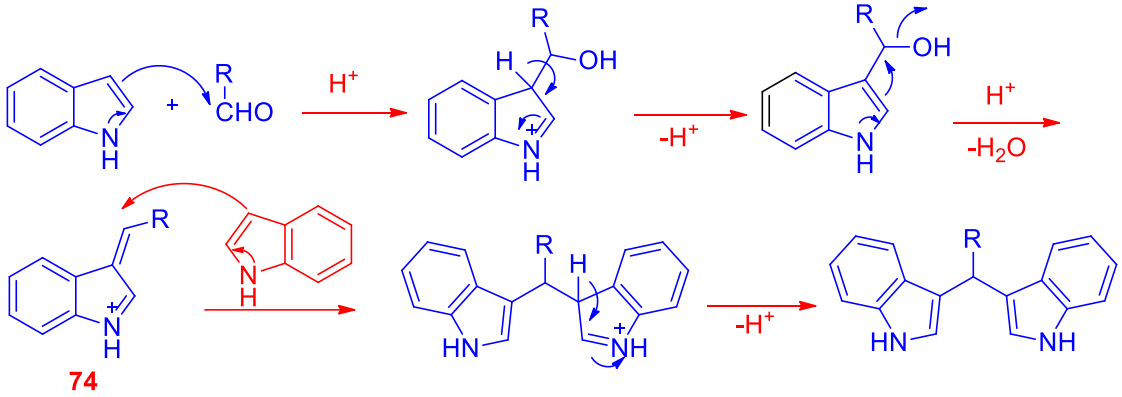
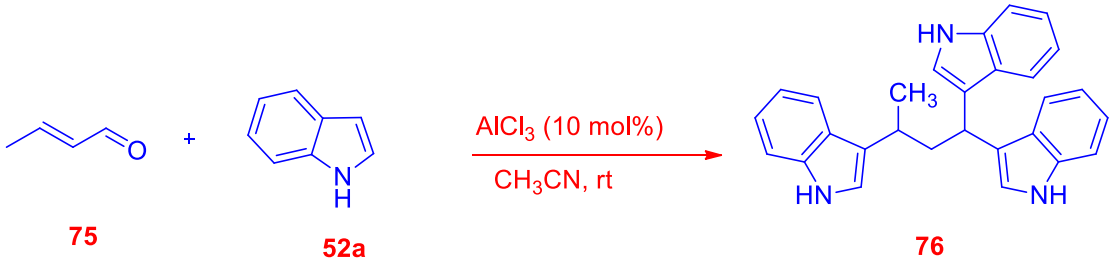


Fig. 5

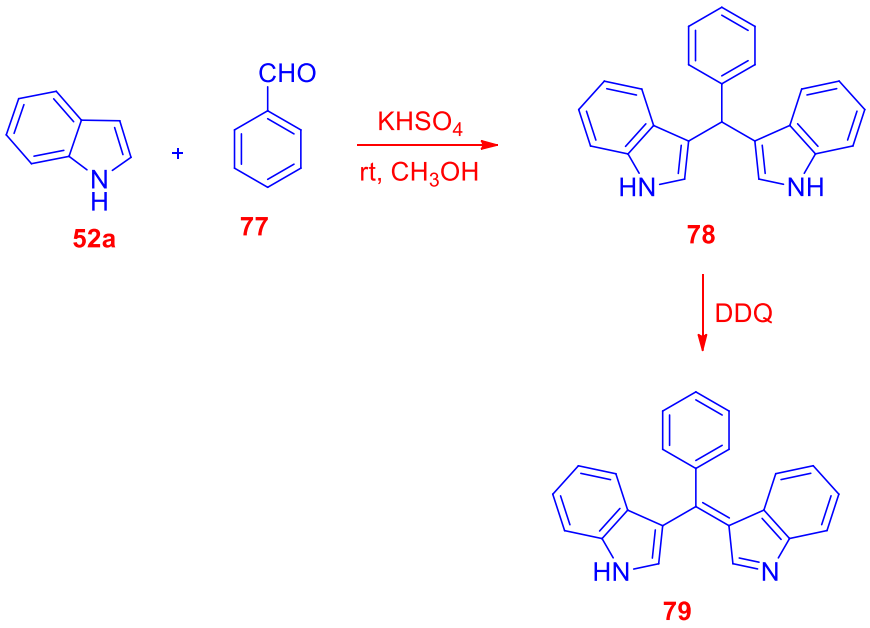
The reaction of crotonaldehyde **75** and indole **52** in presence of $AlCl_3$ in acetonitrile solvent gave a new model of BIMs, 1,1,3-tri(1*H*-indol-3-yl)butane **76** as shown in **Eq. 10**.[45]

Eq. 10



Shao *et al*. synthesized[46] oxidized bis(indolyl)methane **79** by the reaction of bis(indolyl)methane with DDQ. The required bis(indolyl)methane was prepared by the treatment of indole **52a** and benzaldehyde **77** using $KHSO_4$ in methanol solvent at room teperature as shown in **Eq 11**.

Eq. 11



52a **77** **78** **79**

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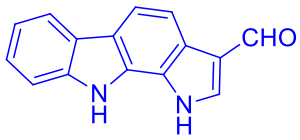
Synthesis of Pyrrolo[3,2-*b*]carbazoles *via* Pd-Catalyzed C-H Activation

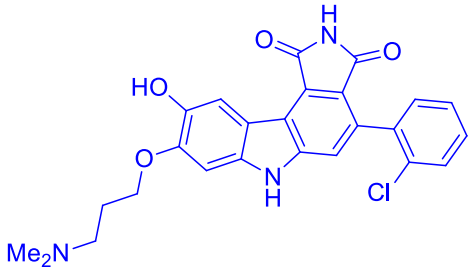
CHAPTER 1

1.1 Introduction

The synthesis of different heteroaryl-condensed carbazoles has emerged as a major research area due to their promising biological properties.[47,48] Their derivatives also show promising electronic and optical properties.[49] Pyrrolocarbazole, a pyrrole ring fused carbazole skeleton frequently occurs in several marine alkaloids[50] such as Dictyodendrins A-E. These compounds have broad spectrum of bioactivities such as anticancer, antidiabetic, neutrotropic and and protein kinase C(PKC) inhibitory properties.[51] Pyrrolo[3,2-*b*]carbazoles have been found to exhibit high anti-tumour activity with low toxicity against normal cell lines. In literature, the synthesis of pyrrolo[3,2-*b*]carbazoles are less explored compared to other analogues of pyrrolocarbazoles.[52] (Fig 6A)



80, Pyrrolo[2,3-*a*]carbazole

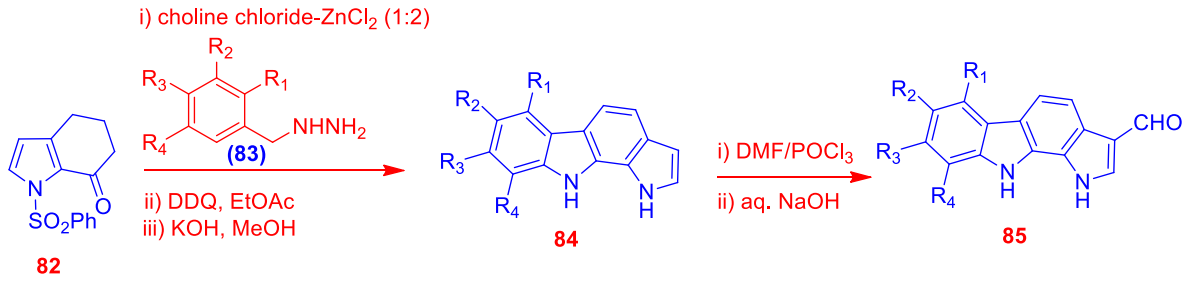


81, pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione

Fig. 6A

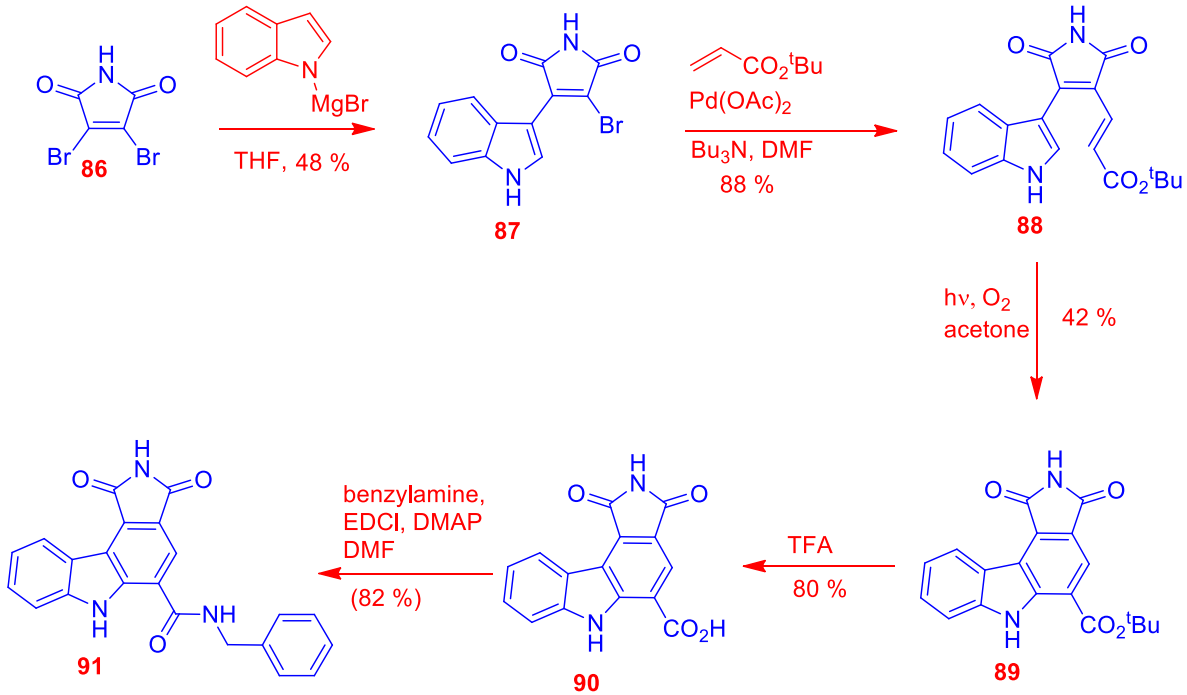
Gédu[53] *et al.* reported the synthesis of pyrrolo[2,3-*a*]carbazole **85** by using phenylhydrazine derivatives. Compound **82** was heated in the presence of substituted benzylhydrazines **83** in the readily available choline chloride/zinc chloride (1:2) ionic liquid. Consequent oxidation with DDQ and deprotection in the presence of KOH in methanol led to substituted pyrrolo[2,3-*a*]carbazoles **84**. Finally, Vilsmeier formylation of compounds **84** in DMF/$POCl_3$ gave the products **85** (**Eq. 12**).

Eq. 12



Matsuda[54] *et al.* reported the synthesis of pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione using bromoindolylmaleimide **87**, which was obtained from dibromomaleimide (**86**) and the magnesium salt of indole. The obtained product **87** undergoes cross-coupling Heck reaction with *t*-butyl acrylate afforded **88** in 88% yield. Photochemical electrocyclization followed by oxidative aromatization gave the desired pyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione **89** in 42% yield. Deprotection of the *t*-Bu group gave the carboxylic acid **90**. Condensation of **90** with benzylamine using EDCI and DMAP in DMF gave **91** in 82% yield (**Eq. 13**).

Eq. 13



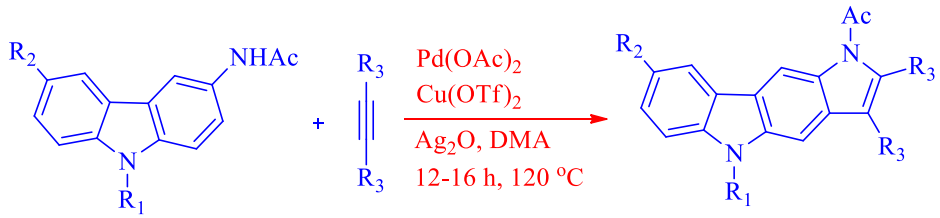
Lu *et al.* reported[55] the synthesis of *N*-acetyl indole **94** via palladium catalyzed C-H activation of *N*-aryl amide **92** with diphenyl acetylene **93a** in the presence of $Pd(OAc)_2$ catalyst, $Cu(OTf)_2$ oxidant and Ag_2O as additive as shown in (**Eq. 14**).

Eq. 14

1.2 Pd-Catalyzed synthesis of pyrrolo[3,2-*b*]carbazoles

Here, we describe a regioselective synthesis of pyrrolo[3,2-*b*]carbazoles via Pd-catalyzed C-H activation of different substituted 3-(acetylamino)carbazoles with various aryl alkynes using $Pd(OAc)_2$ as catalyst, $Cu(OTf)_2$ as oxidant, Ag_2O as additive in DMA solvent. This method provides a simple route for the preparation of variety of substituted pyrrolo[3,2-*b*]carbazole derivatives as shown in scheme 1.

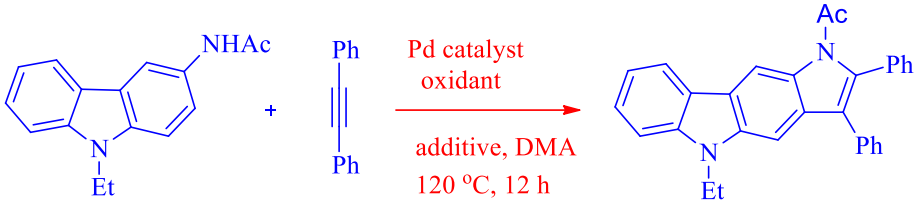
Scheme 1. The schematic representation of present work



3-(Acetylamino)carbazole derivatives can be easily prepared using literature procedures[56]. Initially we started with the reaction of *N*-acetyl-3-aminocarbazole **95a** and diphenylacetylene **93a** with 10 mol % of $Pd(OAc)_2$ using $Cu(OAc)_2$ as oxidant, we obtained the product as single regioisomer but in trace yield. While using $CuCl_2$ as oxidant, yield was significantly improved with some complex mixture of byproducts were observed. Meanwhile we used $Cu(OTf)_2$ as oxidant, the product was obtained without any byproducts but with low yield. We continued optimization by using different additives such as Ag_2CO_3, Ag(OAc), Ag_2O

and found that Ag_2O was giving moderate yield when used as additive. We also screened different Pd sources like $Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ was found to be the best catalyst. DMA was proven to be the best solvent, based on better solubility of starting material. Finally the best optimized condition was *N*-acetyl-3-aminocarbazole (1.0 equiv.), alkyne (1.2 equiv.), $Pd(OAc)_2$ (10 mol %), $Cu(OTf)_2$ (1 equiv.), Ag_2O (1 equiv.) in DMA at 120 °C under N_2 (Table 1).

Table 1 Optimization of reaction conditions[a]



95a **93a** **96a**

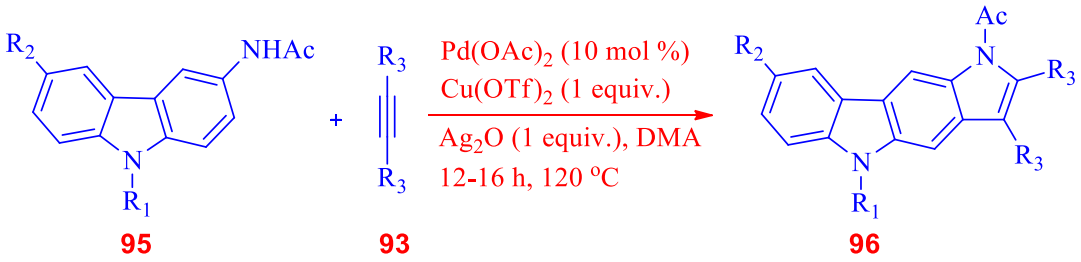
Entry	Catalyst (10 mol %)	Oxidant (equiv)	Additive (equiv)	Yield (%)[b]
1	$Pd(OAc)_2$	Air	_	_
2	$Pd(OAc)_2$	$Cu(OAc)_2$ (2.0)	_	trace
3	$Pd(OAc)_2$	$CuCl_2$ (2.0)	_	30
4	$Pd(OAc)_2$	$CuCl_2$ (2.0)	Ag_2CO_3(1.0)	24
5	$Pd(OAc)_2$	$Cu(OTf)_2$ (2.0)	_	35
6	**$Pd(OAc)_2$**	**$Cu(OTf)_2$ (1.0)**	**Ag_2O (1.0)**	**64**
7	$Pd(OAc)_2$	$Cu(OTf)_2$ (1.0)	Ag_2CO_3(1.0)	20
8	$Pd(OAc)_2$	$Cu(OTf)_2$ (1.0)	AgOAc (1.0)	12
9	$Pd(OAc)_2$	$Cu(OTf)_2$ (0.5)	Ag_2O (1.0)	30
10	$PdCl_2$	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	25
11	$PdCl_2(PPh_3)_2$	$Cu(OTf)_2$ (1.0)	Ag_2O (1.0)	10

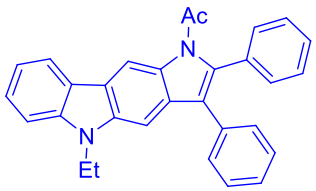
[a]Reaction conditions: **95a** (0.4 mmol), **93a** (0.6 mmol), Pd catalyst (10 mol %) in DMA (3.0 mL) at 120 °C under N_2. [b]Isolated yields

With this optimized condition, we examined the scope of reaction by taking different *N*-substituted and substituted 3-aminocarbazoles. A variety of internal alkynes having both electron donating and electron withdrawing groups were also employed in this reaction. The reaction went smoothly with 6-methyl substituted 3-aminocarbazole, gave the product **96f** in 70% yield whereas 6-bromo substituted 3-aminocarbazole gave the product **96e** in 54% yield. The diarylacetylenes bearing electron donating groups gave better yields compared to the alkynes having electron withdrawing groups (Scheme 2). The products **96a**, **96e** and **96i** were further confirmed by single crystal X-ray analysis[57] as shown in figure **6**. We also investigated the reaction with unsymmetrically disubstituted alkynes, but ended up with inseparable mixture of products in low yields.

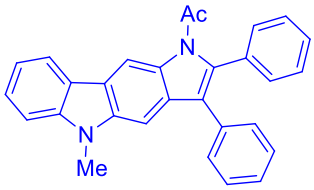
Based on the literature report[55], the mechanism for C-H activation reaction involves a six membered palladacycle generated by the acetamino group that gives vinylic palladium(II) intermediate by the insertion of alkyne **93**. The intramoleular amide attack and subsequent deprotonation gives palladium amide intermediate, which on reductive elimination affords the corresponding pyrrolocarbazole product **96**. $Cu(OTf)_2$ and Ag_2O are utilized for the reoxidation of Pd(0) complex to Pd(II) species in the reaction.

Table 2 Synthesis of various pyrrolo[3,2-*b*]carbazole derivatives

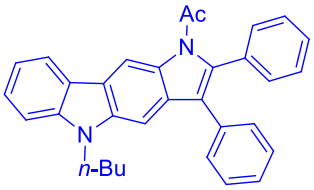




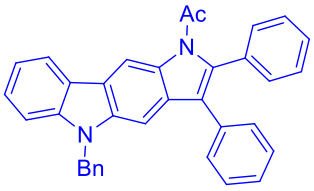
96a, 12 h, **64%**



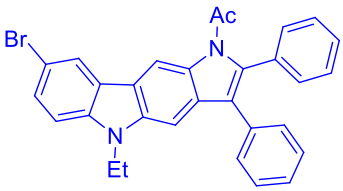
96b, 12 h, **62%**



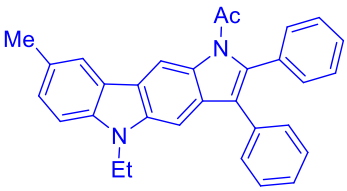
96c, 12 h, **64%**



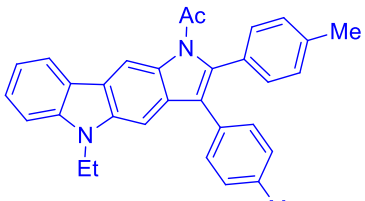
96d, 12 h, **58%**



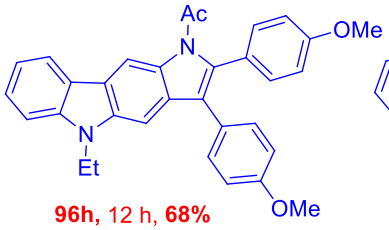
96e, 16 h, **54%**



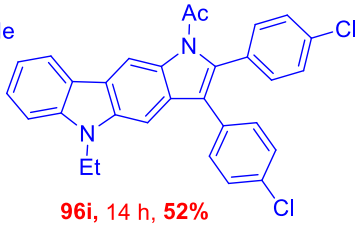
96f, 12 h, **70%**



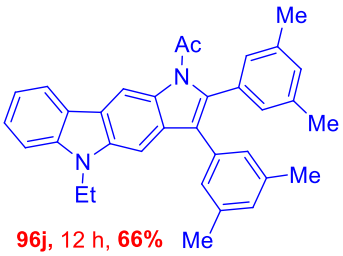
96g, 12 h, **68%**



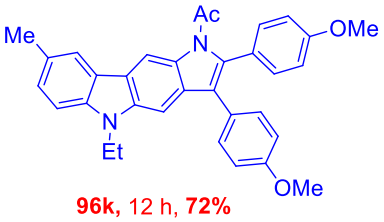
96h, 12 h, **68%**



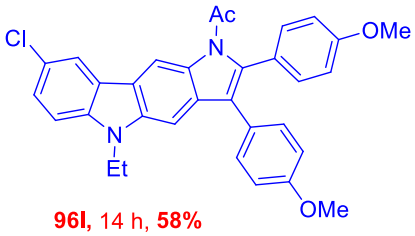
96i, 14 h, **52%**



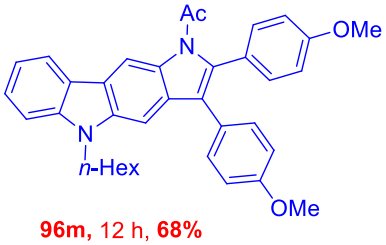
96j, 12 h, **66%**



96k, 12 h, **72%**



96l, 14 h, **58%**



96m, 12 h, **68%**

Scheme 2. Possible mechanism for synthesis of **96**

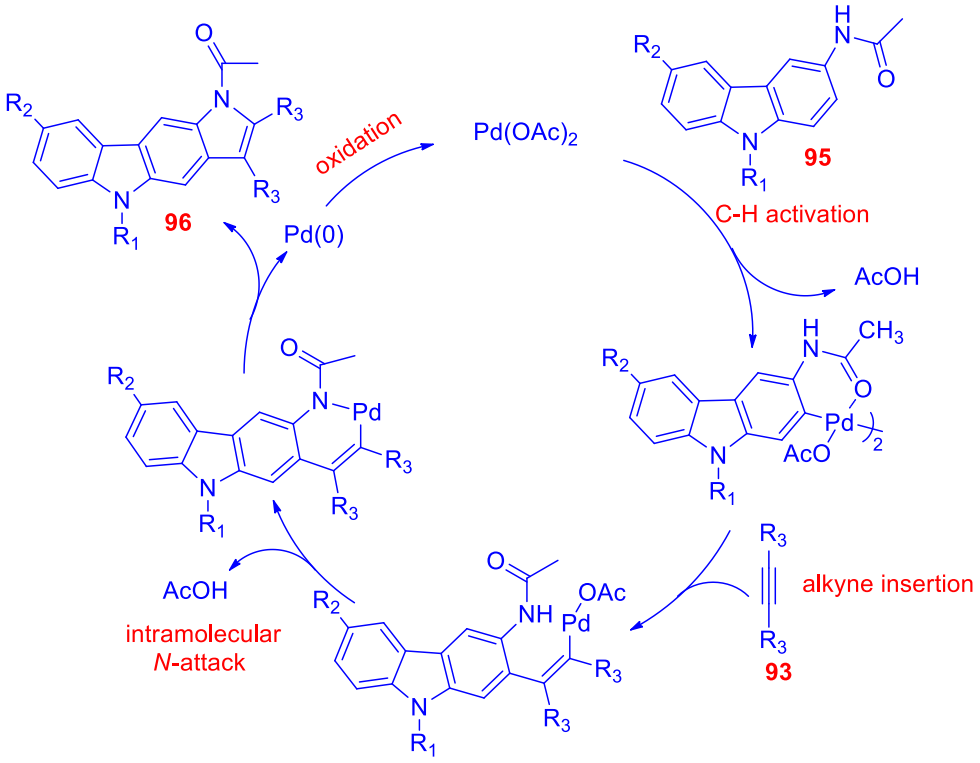
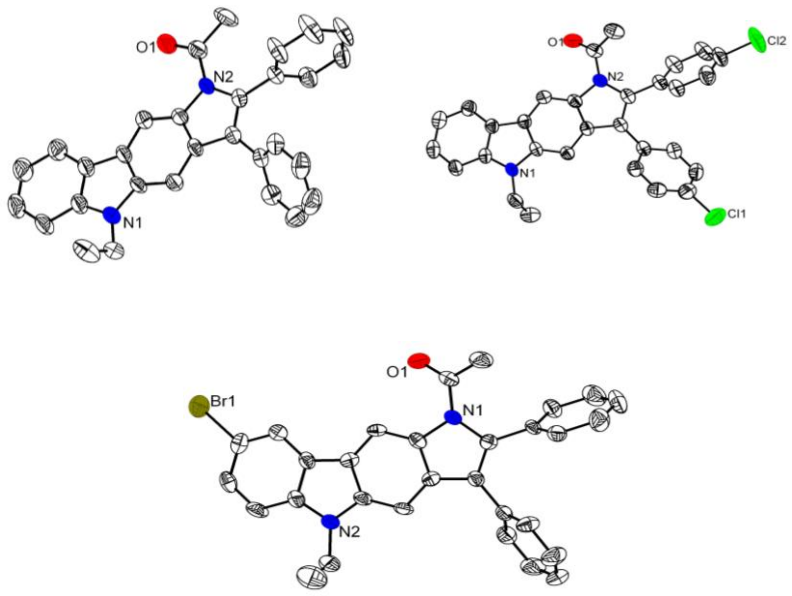


Figure 6B X-ray crystal structures of **96a**, **96e** and **96i**



1.3 Conclusions

In summary we have developed a simple method with easily prepared starting materials for the synthesis of different pyrrolo[3,2-*b*]carbazoles in moderate to good yields via Pd-catalyzed C-H activation. The reaction occur regioselectively giving exclusively one regioisomer. The reaction works well with various disubstituted aryl alkynes bearing both electron donating as well as electron withdrawing substituents.

1.4. Experimental section

General Information

All ^{1}H, ^{13}C NMR spectra were recorded on 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 were 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. High resolution mass spectra (HRMS) were performed using a mass spectrometer BRUKER-MAXIS with ESI-QTOF-II method. Routine monitoring of the reactions was performed by silica gel 60 F254 TLC plates. 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.

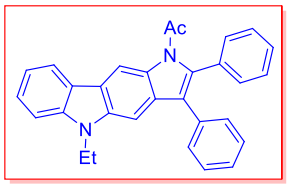
General procedure A

To a Schlenk tube, **95a** (0.4 mmol), **93a** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2O (1.0 equiv.), $Cu(OTf)_2$ (1.0 equiv.) and DMA (3.0 mL) were added successively under N_2. The mixture was stirred at room temperature for a few min. Then the tube was placed in pre-heated (120 °C) oil bath and stirred as monitored by TLC. After the completion of reaction, the solution was then cooled to rt, diluted with ethyl acetate (30 mL), washed with H_2O (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The

residue was purified by column chromatography (eluent:hexanes/ethyl acetate) to afford the product **96a**.

1-(5-Ethyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96a) :

The product **96a** was obtained as brown colored solid from **95a** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 64 %

Mp: 162-164 °C

IR (KBr) ν_{max} cm^{-1}: 2964, 1689, 1601, 1473, 1439, 1394, 1300, 1261, 1099, 800, 744

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (1H, s), 8.26 (1H, d, J = 8.0 Hz), 7.51-7.47 (1H, m), 7.41-7.32 (12H, m), 7.28-7.24 (1H, m), 4.35 (2H, q, J = 7.2 Hz), 2.06 (3H, s), 1.40 (3H, t, J = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 141.1, 138.1, 135.9, 133.6, 133.3, 131.8, 130.8, 130.2, 129.0, 128.5, 128.3, 126.9, 125.7, 123.9, 123.6, 122.5, 120.6, 118.5, 108.1, 108.0, 97.1, 37.5, 28.1, 13.5.

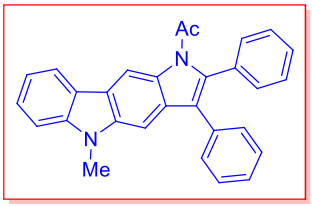
LC-MS (m/z): 429 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{24}N_2O$: C, 84.08; H, 5.65; N, 6.54 %

Found: C, 84.22; H, 5.58 ; N, 6.65 %

1-(5-Methyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone(96b) :

The product **96b** was obtained as colorless solid from **95b** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 62 %

Mp: 130-132 °C

IR (KBr) ν_{max} cm^{-1}: 3379, 3055, 2928, 1682, 1599, 1422, 1365, 1298, 1091, 802, 744

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (1H, s), 8.27 (1H, d, *J* = 7.6 Hz), 7.53-7.19 (14H, m), 3.84 (3H, s), 2.08 (3H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 142.2, 139.3, 135.8, 133.5, 133.3, 131.8, 130.8, 130.2, 129.1, 128.5, 128.3, 126.9, 125.7, 123.9, 123.4, 122.3, 120.5, 118.5, 108.1, 107.9, 97.2, 29.2, 28.1.

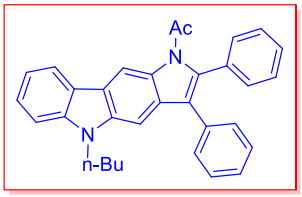
LC-MS (m/z): 415 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{29}H_{22}N_2O$: C, 84.03; H, 5.35; N, 6.76 %

Found: C, 84.12; H, 5.32 ; N, 6.81 %

1-(5-Butyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96c) :

The product **96c** was obtained as brown colored solid from **95c** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 64 %

Mp: 194-196 °C

IR (KBr) ν_{max} cm^{-1}: 3387, 3055, 2953, 2860, 1691, 1602, 1466, 1394, 1296, 1126, 879

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (1H, s), 8.26 (1H, d, *J* = 7.6 Hz), 7.51-7.47 (1H, m), 7.40-7.33 (12H, m), 7.28-7.24 (1H, m), 4.30 (2H, t, *J* = 6.8 Hz), 2.06 (3H, s), 1.85 (2H, t, *J* = 7.4 Hz), 1.41-1.35 (2H, m), 0.93 (3H, t, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 141.6, 138.7, 135.9, 133.6, 133.3, 131.7, 130.8, 130.2, 129.0, 128.5, 128.3, 126.9, 125.6, 123.8, 123.5, 122.4, 120.5, 118.4, 108.4, 107.9, 97.3, 42.8, 30.9, 28.0, 20.5, 13.9

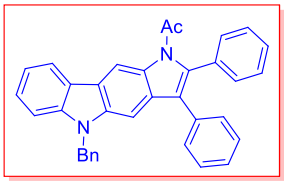
LC-MS (m/z): 456 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{32}H_{28}N_2O$: C, 84.18; H, 6.18 ; N, 6.14 %

Found: C, 83.75; H, 6.51; N, 6.23 %

1-(5-Benzyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone(96d) :

The product **96d** was obtained as colorless solid from **95d** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 58 %

Mp: 210-212 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 2922, 1684, 1601, 1437, 1369, 1178, 1024, 958, 877

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (1H, s), 8.28 (1H, d, J = 7.2 Hz), 7.43-7.38 (6H, m), 7.32-7.13 (13H, m), 5.51 (2H, s), 2.05 (3H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 141.7, 138.9, 137.2, 135.9, 133.3, 133.2, 132.0, 130.8, 130.1, 129.1, 128.7, 128.5, 128.3, 127.3, 126.9, 126.4, 125.9, 123.79, 123.73, 122.5, 120.6, 119.0, 108.7, 108.0, 97.7, 46.6, 28.0.

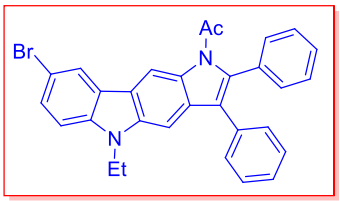
LC-MS (m/z): 490 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{35}H_{26}N_2O$: C, 85.69; H, 5.34 ; N, 5.71 %

Found: C, 85.51; H, 5.41; N, 5.65 %

1-(8-Bromo-5-ethyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96e):

The product **96e** was obtained as yellow colored solid from **95e** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 54 %

Mp: 202-204 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2974, 1685, 1458, 1392, 1302, 1186, 1109, 964, 860

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (1H, s), 8.36 (1H, *J* = 1.6 Hz, d), 7.57-7.55 (1H, m), 7.39-7.37 (8H, m), 7.34-7.25 (4H, m); 4.33 (2H, q, *J* = 7.2 Hz), 2.06 (3H, s), 1.40 (3H, t, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 139.7, 138.3, 136.4, 133.4, 133.1, 131.9, 130.7, 130.2, 129.7, 128.6, 128.5, 128.4, 128.2, 127.0, 125.4, 123.7, 123.3, 121.3, 111.2, 109.5, 108.2, 97.3, 37.7, 28.0, 13.4

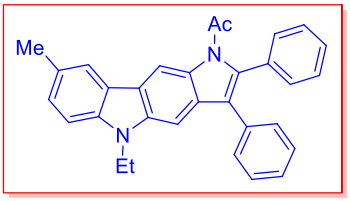
LC-MS (m/z): 506 $(M)^-$, negative mode

Anal. Calcd. for $C_{30}H_{23}BrN_2O$: C, 71.01; H, 4.57 ; N, 5.52 %

Found: C, 71.12; H, 4.52; N, 5.61 %

1-(5-Ethyl-8-methyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96f):

The product **96f** was obtained as brown colored solid from **95f** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 70 %

Mp: 104-106 °C

IR (KBr) ν_{max} cm^{-1}: 3443, 3055, 2922, 2854, 1682, 1483, 1367, 752, 698

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (1H, s), 8.07 (1H, s), 7.38-7.28 (13H, m), 4.33 (2H, q, *J* = 7.2 Hz), 2.58 (3H, s), 2.06 (3H, s), 1.38 (3H, t, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 139.4, 138.4, 135.8, 133.6, 133.3, 131.6, 130.8, 130.2, 128.9, 128.5, 128.3, 127.8, 126.9, 123.9,

123.7, 122.4, 120.7, 107.9, 107.8, 97.0, 37.5, 28.1, 21.4, 13.5

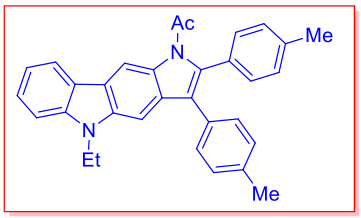
LC-MS (m/z): 441 (M-H), negative mode

Anal. Calcd. for $C_{31}H_{26}N_2O$: C, 84.13; H, 5.92; N, 6.33 %

Found: C, 84.31; H, 5.85 ; N, 6.29 %

1-(5-Ethyl-2,3-di-*p*-tolyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96g):

The product **96g** was obtained as brown colored solid from **95g** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 68 %

Mp: 220-222 °C

IR (KBr) ν_{max} cm^{-1}: 3412, 3028, 2974, 1687, 1602, 1469, 1394, 1302, 1184, 1018, 962, 881

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (1H, s), 8.26 (1H, d, *J* = 7.6 Hz), 7.49 (1H, t, *J* = 7.6 Hz); 7.39 (2H, d, *J* = 5.2 Hz), 7.28-7.23 (5H, m), 7.19 (4H, d, *J* = 8.0 Hz), 4.35 (2H, q, *J* = 7.2 Hz), 2.40 (6H, s), 2.06 (3H, s), 1.40 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 141.1, 138.4, 138.1, 136.4, 135.9, 131.7, 130.6, 130.4, 130.0, 129.2, 129.1, 125.5, 123.6, 123.5, 122.3, 120.6, 118.4, 108.1, 108.0, 97.1, 37.5, 28.0, 21.4, 21.3, 13.5

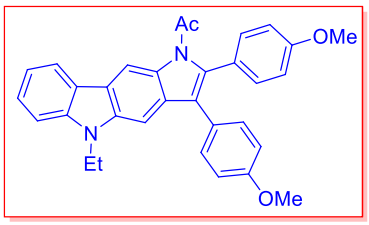
LC-MS (m/z): 457 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{32}H_{28}N_2O$: C, 84.18; H, 6.18; N, 6.14 %

Found: C, 84.07; H, 6.09; N, 6.19 %

1-(5-Ethyl-2,3-bis-(4-methoxyphenyl)-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96h):

The product **96h** was obtained as brown colored solid from **95h** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 68 %

Mp: 232-234 °C

IR (KBr) ν_{max} cm^{-1}: 3449, 2976, 2841, 1682, 1602, 1396, 1365, 1244, 1126, 1024, 962, 875

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (1H, s), 8.25 (1H, d, *J* = 7.6 Hz), 7.50-7.46 (1H, m), 7.40-7.36 (2H, m), 7.30-7.25 (5H, m), 6.93-6.90 (4H, m), 4.35 (2H, q, *J* = 7.2 Hz), 3.85 (6H, s), 2.07 (3H, s), 1.40 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 159.6, 158.4, 141.0, 138.1, 135.6, 132.0, 131.6, 131.2, 129.3, 125.9, 125.5, 123.6, 123.2, 122.3, 120.6, 118.4, 114.0, 113.8, 108.1, 97.0, 55.2, 55.0, 37.5, 28.0, 13.5

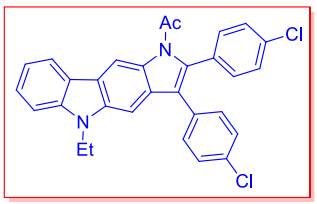
LC-MS (m/z): 489 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{32}H_{28}N_2O_3$: C, 78.67; H, 5.78; N, 5.73 %

Found: C, 78.56; H, 5.71 ; N, 5.66 %

1-(2,3-Bis-(4-chlorophenyl)-5-ethyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96i):

The product **96i** was obtained as brown colored solid from **95i** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 52 %

Mp: 202-204 °C

IR (KBr) ν_{max} cm^{-1}: 3437, 3055, 1682, 1604, 1477, 1392, 1128, 1086, 1012, 875, 821

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (1H, s), 8.24 (1H, d, *J* = 7.6 Hz), 7.52-7.48 (1H, m), 7.44-7.36 (5H, m), 7.31-7.28 (3H, m), 7.24-7.22 (3H, m), 4.35 (2H, q, *J* = 7.2 Hz), 2.10 (3H, s), 1.40 (3H, t, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 141.2, 138.1, 134.8, 134.6, 133.1, 131.9, 131.4, 129.0, 128.8, 128.6, 125.9, 123.4, 123.2, 122.8, 120.7, 118.6, 108.2, 108.0, 96.8, 37.5, 28.2, 13.5.

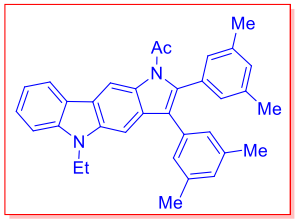
LC-MS (m/z): 498 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{22}Cl_2N_2O$: C, 72.44; H, 4.46; N, 5.63 %

Found: C, 72.59; H, 4.42 ; N, 5.71 %

1-(2,3-Bis-(3,5-dimethylphenyl)-5-ethyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96j) :

The product **96j** was obtained as brown colored solid from **95j** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 66 %

Mp: 106-108 °C

IR (KBr) ν_{max} cm^{-1}: 3449, 2918, 1693, 1601, 1466, 1442, 1304, 1157, 1033, 848, 742

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (1H, s), 8.25 (1H, d, *J* = 7.6 Hz), 7.50-7.46 (1H, m), 7.40-7.39 (2H, m), 7.27-7.23 (1H, m), 7.01-6.96 (6H, m), 4.36 (2H, q, *J* = 7.2 Hz), 2.31-2.30 (12H, m), 2.07 (3H, s), 1.40 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 141.1, 138.1, 137.8, 137.5, 136.2, 133.4, 133.1, 131.7, 130.0, 129.3, 128.5, 128.0, 125.5, 123.7, 122.3, 120.6, 118.4, 108.1, 107.9, 97.2, 37.5, 28.0, 21.4, 21.2, 13.5

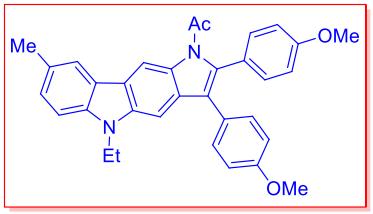
LC-MS (m/z): 485 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{34}H_{32}N_2O$: C, 84.26; H, 6.66; N, 5.78 %

Found: C, 84.15; H, 6.62; N, 5.71 %

1-(5-Ethyl-2,3-Bis-(4-methoxyphenyl)-8-methyl-1,5-dihydropyrrolo[3,2-*b*]-carbazol-1-yl)ethanone (96k):

The product **96k** was obtained as brown colored solid from **95k** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 72 %

Mp: 212-214 °C

IR (KBr) ν_{max} cm^{-1}: 3412, 2932, 1685, 1610, 1493, 1392, 1367, 1298, 1246, 1174, 1032, 962, 877

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (1H, s), 8.05 (1H, s), 7.33-7.24 (7H, m), 6.93-6.89 (4H, m), 4.32 (2H, q, J = 7.2 Hz), 3.84 (6H, s), 2.57 (3H, s), 2.06 (3H, s), 1.37 (3H, t, J = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 159.6, 158.4, 139.3, 138.3, 135.5, 133.0, 132.0, 131.5, 131.2, 129.2, 127.7, 126.8, 125.9, 125.6, 123.8, 123.2, 122.1, 120.6, 114.0, 113.8, 108.0, 107.8, 96.9, 55.26, 55.20, 37.5, 28.0, 21.4, 13.5.

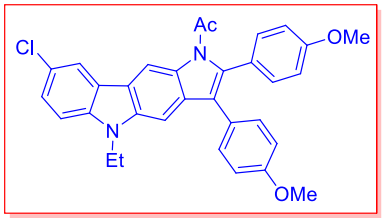
LC-MS (m/z): 503 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{33}H_{30}N_2O_3$: C, 78.86; H, 6.02; N, 5.57 %

Found: C, 78.69; H, 6.12 ; N, 5.65 %

1-(8-Chloro-5-ethyl-2,3-bis-(4-methoxyphenyl)-1,5-dihydropyrrolo[3,2-*b*]-carbazol-1-yl)ethanone (96l):

The product **96l** was obtained as brown colored solid from **95l** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 58 %

Mp: 196-198 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 2932, 1685, 1610, 1458, 1392, 1298

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (1H, s), 8.18 (1H, s), 7.42-7.23 (7H, m), 6.92-6.90 (4H, m), 4.31 (2H, q, J = 7.2 Hz), 3.84 (6H, s), 2.06 (3H, s), 1.38 (3H, t, J = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 159.7, 158.5, 139.3, 138.5, 136.1, 131.9, 131.2, 130.0, 128.1, 125.7, 125.4, 124.8, 123.9, 121.2, 120.2, 114.0, 113.9, 109.0, 108.2, 97.2, 55.27, 55.20, 37.7, 28.0, 13.5

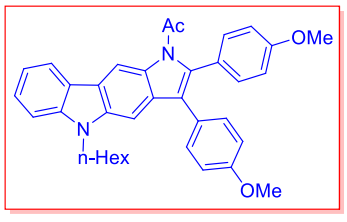
LC-MS (m/z): 524 $(M+2H)^+$, positive mode

Anal. Calcd. for $C_{32}H_{27}ClN_2O_3$: C, 73.49; H, 5.20; N, 5.36 %

Found: C, 73.32; H, 5.31; N, 5.15 %

1-(5-Hexyl-2,3-bis-(4-methoxyphenyl)-1,5-dihydropyrrolo[3,2-*b*]-carbazol-1-yl)-ethanone (96m) :

The product **96m** was obtained as brown colored solid from **95m** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 68 %

Mp: 204-206 °C

IR (KBr) ν_{max} cm^{-1}:	3441, 2928, 1691, 1604, 1583, 1439, 1363, 1244, 1174, 1026, 962, 829
^{1}H NMR (400 MHz, $CDCl_3$):	δ = 9.28 (1H, s), 8.25 (1H, d, J = 7.6 Hz), 7.48 (1H, t, J = 7.6 Hz), 7.41-7.38 (2H, m), 7.32-7.26 (5H, m), 6.94-6.92 (4H, m), 4.29 (2H, t, J = 7.0 Hz), 3.86 (6H, s), 2.08 (3H, s), 1.90-1.83 (2H, m), 1.38-1.30 (6H, m), 1.28 (3H, t, J = 6.8 Hz).
^{13}C NMR (100 MHz, $CDCl_3$):	δ 171.4, 159.6, 158.4, 141.5, 138.6, 135.6, 132.0, 131.6, 131.2, 129.3, 125.9, 125.5, 123.5, 123.2, 122.1, 120.5, 118.4, 114.0, 113.8, 108.3, 108.0, 97.2, 55.27, 55.20, 43.0, 31.5, 28.6, 28.0, 26.9, 22.5, 14.0.
LC-MS (m/z):	543 $(M+2H)^+$, positive mode
Anal. Calcd. for $C_{36}H_{36}N_2O_3$:	C, 79.38; H, 6.66; N, 5.14 %
Found:	C, 79.18; H, 6.61; N, 5.21 %

1.5 References:

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57. The CCDC deposition number for compound **96a** is 892569. Formula: $C_{30}H_{24}N_2O$. Unit cell parameters: *a* = 10.2471(14), *b* = 11.6921(11), *c* = 19.105(3), *α* = 90.00, *β* = 99.605(11), *γ* = 90.00, space group *P 21/c*. The CCDC deposition number for compound **96e** is 892570. Formula: $C_{30}H_{23}BrN_2O$. Unit cell parameters: *a* = 6.6599(13), *b* = 19.948(4), *c* = 17.974(3), *α* = 90.00, *β* = 98.107(18), *γ* = 90.00, space group *P 21/n*. The CCDC deposition number for compound **96i** is 892571. Formula: $C_{30}H_{22}Cl_2N_2O$. Unit cell parameters: *a* = 8.3466(18), *b* = 33.171(5), *c* = 10.746(3), *α* = 90.00, *β* = 126.096(16), *γ* = 90.00, space group *P 21/c*.

Table 2. Crystal data and structure refinement for 96a

Empirical formula	: $C_{30}H_{24}N_2O$	
Formula weight	: 428.51	
Temperature	: 298 K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P 21/c	
Unit cell dimensions	: a=10.2471(14)	α = 90°
	: b =11.6921(11)	β = 99.605(11)
	: c = 19.105(3)	γ = 90°
Volume	: 2256.9(5)A^3	
Z	: 4	
Density (calculated)	: 1.261g/cm^3	
Absorption coefficient	: 0.077 mm^{-1}	
F(000)	:904	
Crystal size	: 0.36 x 0.28 x 0.18mm^3	
Theta range for data collection	: 3.16 to 26.37 °.	
Index ranges	: -12<=h<=12, -13<=k<=13, -22<=l<=22	
Reflections collected	: 3971	
Completeness to theta = 24.71°	: 99.9 %	
Absorption correction	: Multi scan	
Max. and min. transmission	: 0.992 and 0.986	
Refinement method	: Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	: 0.995	
Final R indices [I>2sigma(I)]	: R1 = 0.0639, wR2 = 0.1689	

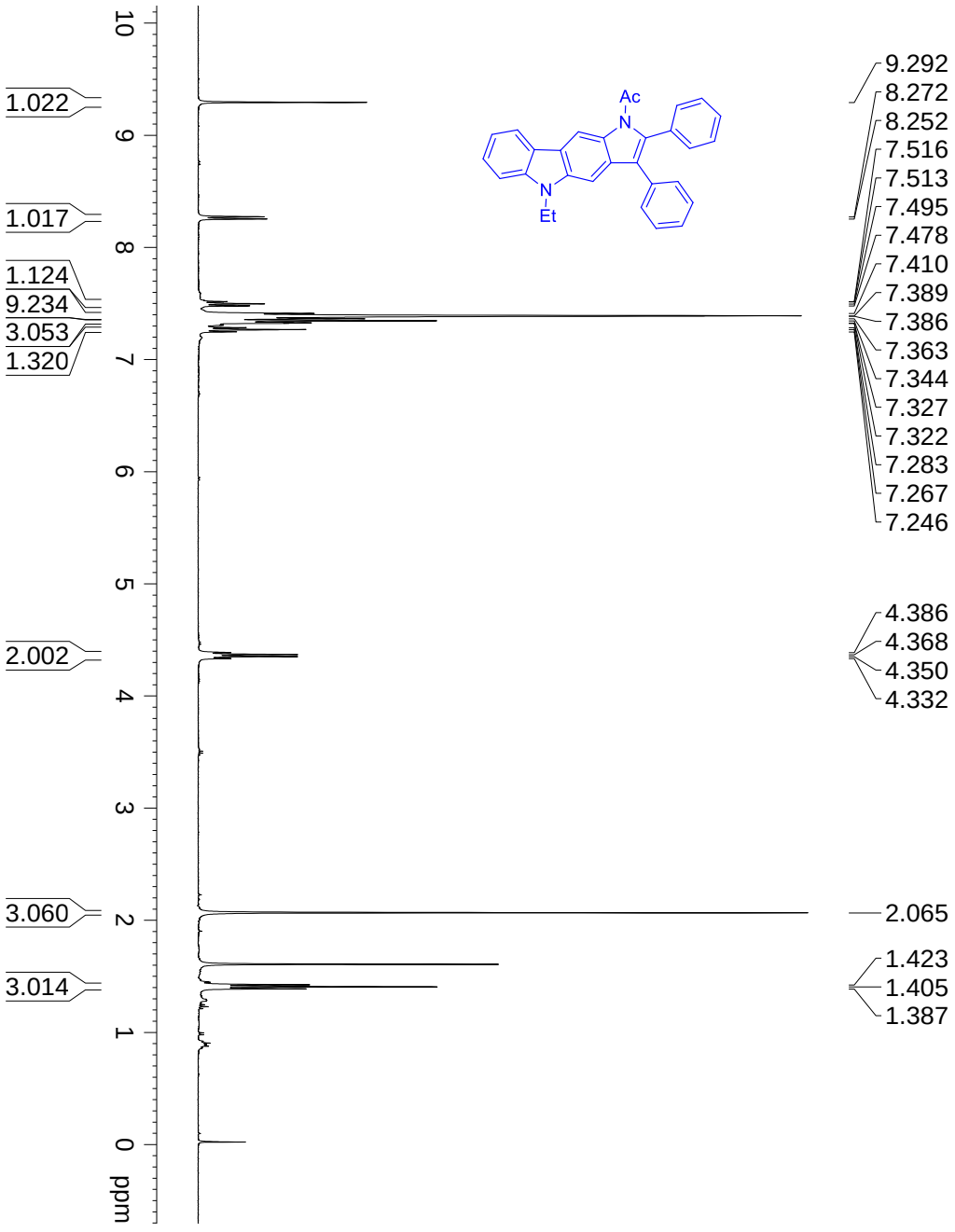
Table 3. Crystal data and structure refinement for 96e

Empirical formula	: $C_{30}H_{23}BrN_2O$	
Formula weight	: 507.4	
Temperature	: 298 K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P 21/n	
Unit cell dimensions	: a=6.6599(13)	α = 90°
	: b =19.948(4)	β = 98.107(18)
	: c = 17.974(3)	γ = 90°
Volume	: 2364.0(8)A^3	
Z	: 4	
Density (calculated)	: 1.426 g/cm^3	
Absorption coefficient	: 1.765 mm^{-1}	
F(000)	:1040	
Crystal size	: 0.32 x 0.24 x 0.16 `mm^3	
Theta range for data collection	: 3.16 to 26.37 °.	
Index ranges	: -7<=h<=7, -23<=k<=23, -21<=l<=21	
Reflections collected	: 4152	
Completeness to theta = 24.71°	: 99.9 %	
Absorption correction	: Multi scan	
Max. and min. transmission	: 0.838 and 0.661	
Refinement method	: Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	: 0.958	
Final R indices [I>2sigma(I)]	: R1 = 0.0787, wR2 = 0.1966	

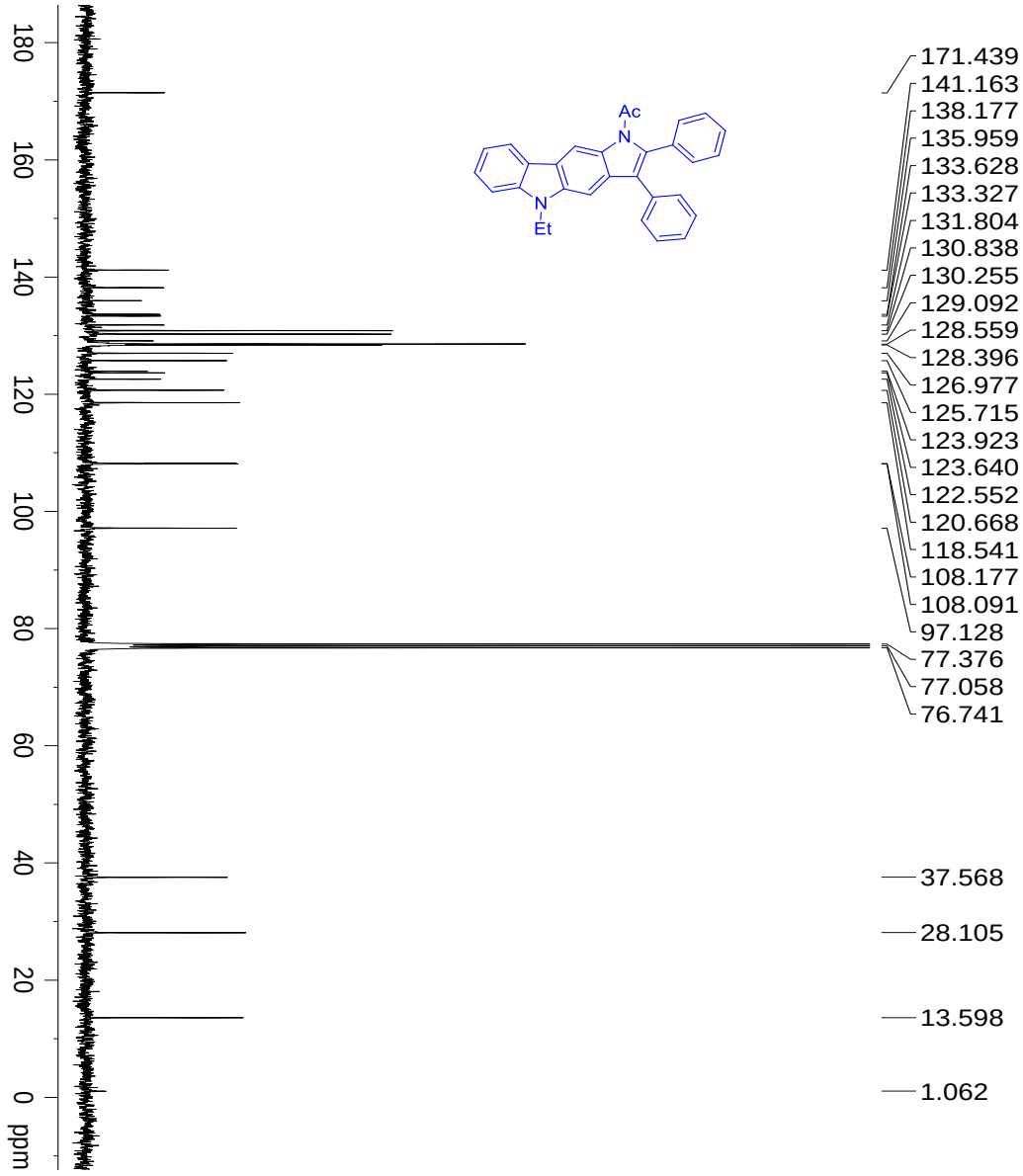
Table 4. Crystal data and structure refinement for 96i

Empirical formula	: $C_{30}H_{22}Cl_2N_2O$	
Formula weight	: 497.4	
Temperature	: 298 K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P 21/c	
Unit cell dimensions	: a=8.3466(18)	α = 90°
	: b =33.171(5)	β = 126.096(16)
	: c = 10.746(3)	γ = 90°
Volume	: 2404.1(10)A^3	
Z	: 4	
Density (calculated)	: 1.374 g/cm^3	
Absorption coefficient	: 0.297 mm^{-1}	
F(000)	:1032	
Crystal size	: 0.30 x 0.22 x 0.18 `mm^3	
Theta range for data collection	: 3.16 to 26.37 °.	
Index ranges	: -9<=h<=9, -39<=k<=39, -12<=l<=12	
Reflections collected	: 4236	
Completeness to theta = 24.71°	: 99.9 %	
Absorption correction	: Multi scan	
Max. and min. transmission	: 0.965 and 0.938	
Refinement method	: Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	: 1.029	
Final R indices [I>2sigma(I)]	: R1 = 0.0597, wR2 = 0.1397	

^{1}H NMR of 1-(5-ethyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96a)



^{13}C NMR of 1-(5-ethyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96a)



LC-MS of 1-(5-ethyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96a)

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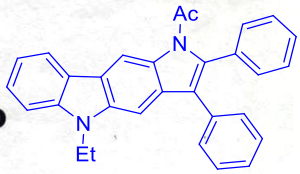

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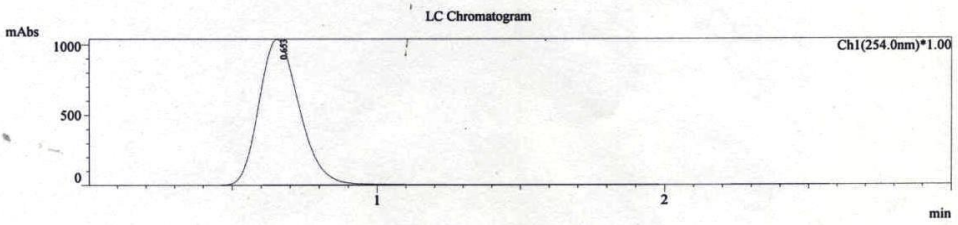
LC Chromatogram



MS Spectrum

Line#:1 R.Time:0.772(Scan#:47) Positive
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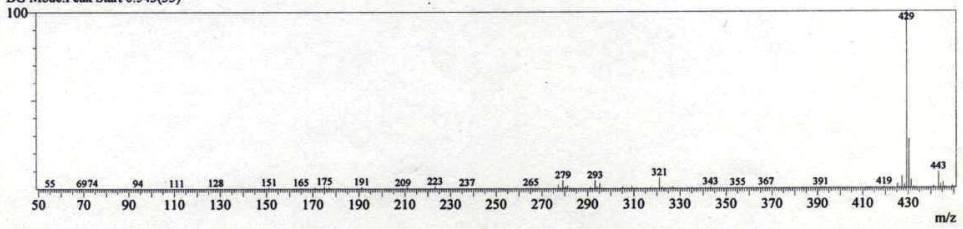
RawMode:Single 0.772(47)
BG Mode:Peak Start 0.543(33)



MS Peak Table

Peak#	R.Time	I.Time	F.Time	Area	Height	A/H	Mark	%Total	Name	Base m/z	Base Int.
1	0.772	0.543	1.043	150386009	11807080	12.73		100.00		429.35	3451942
				150386009	11807080			100.00			

OPERATOR

Elemental analysis of 1-(5-ethyl-2,3-diphenyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96a)

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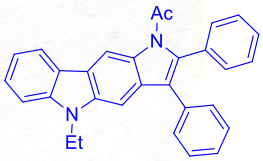

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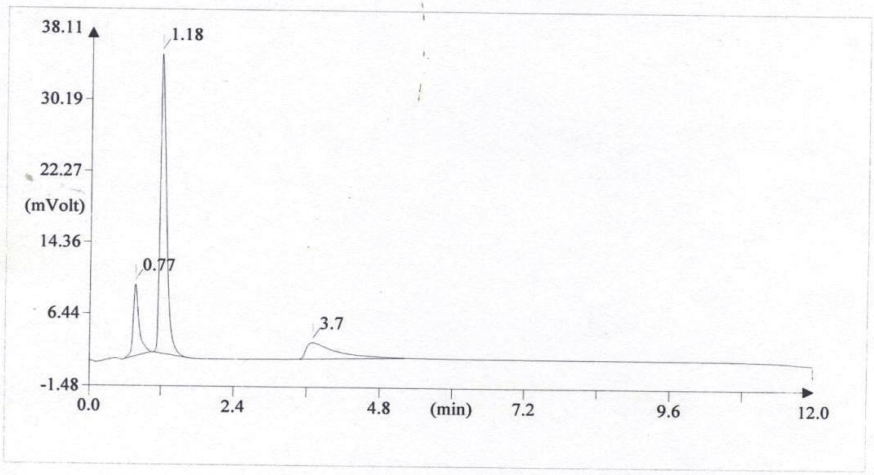
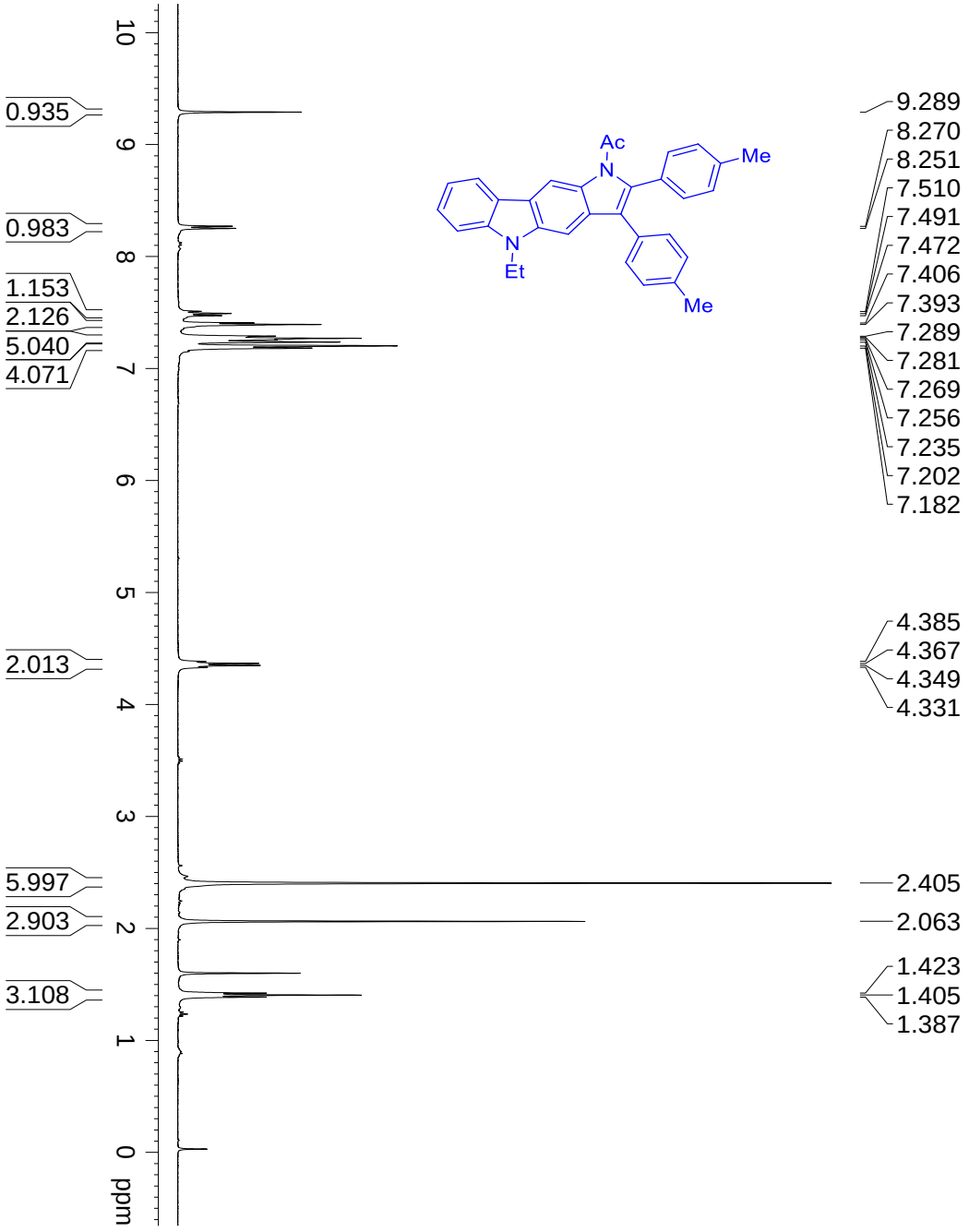
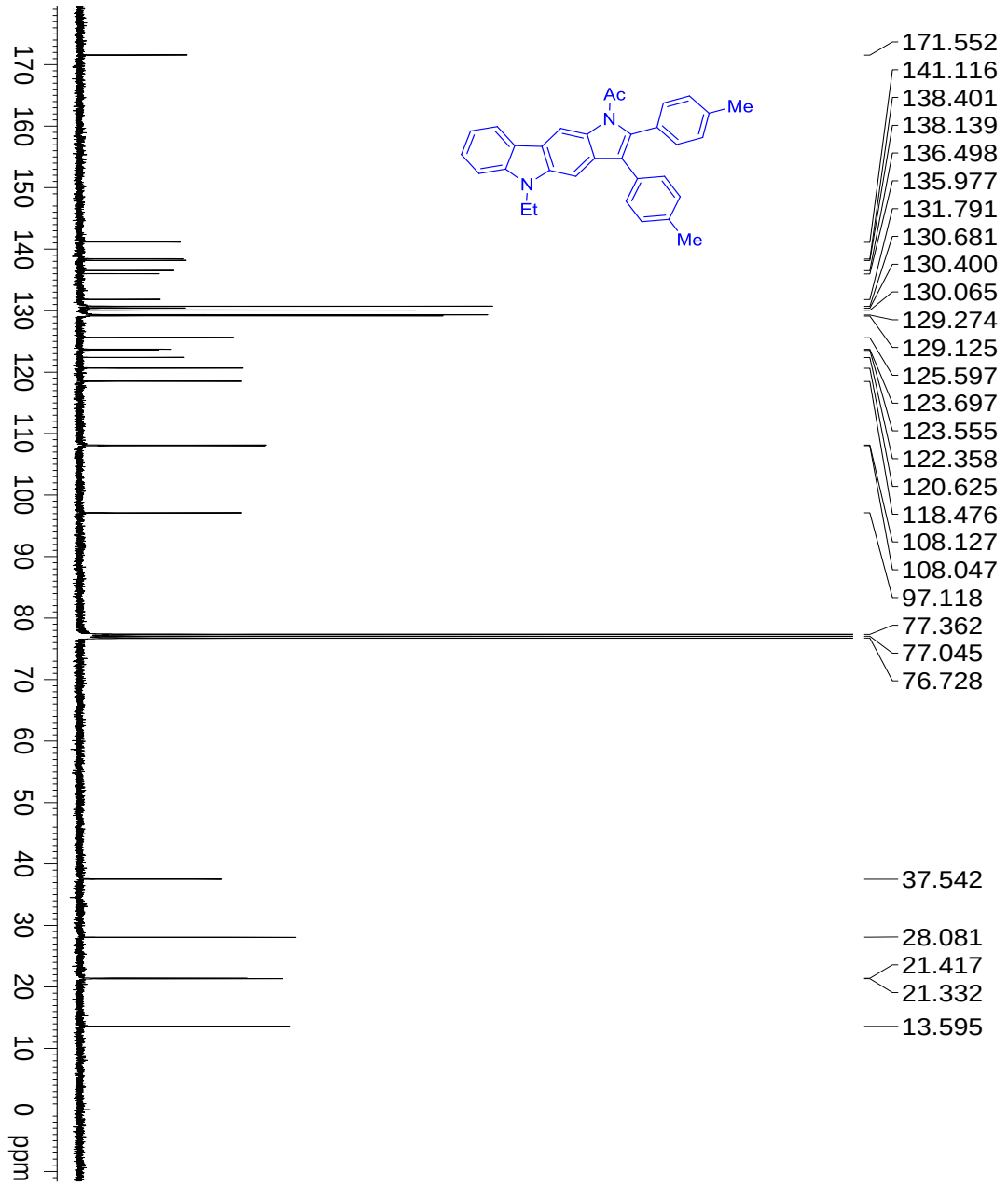


Element Name	Element %	Ret. Time
Nitrogen	6. 65	0. 77
Carbon	84. 22	1. 18
Hydrogen	5. 58	3. 70

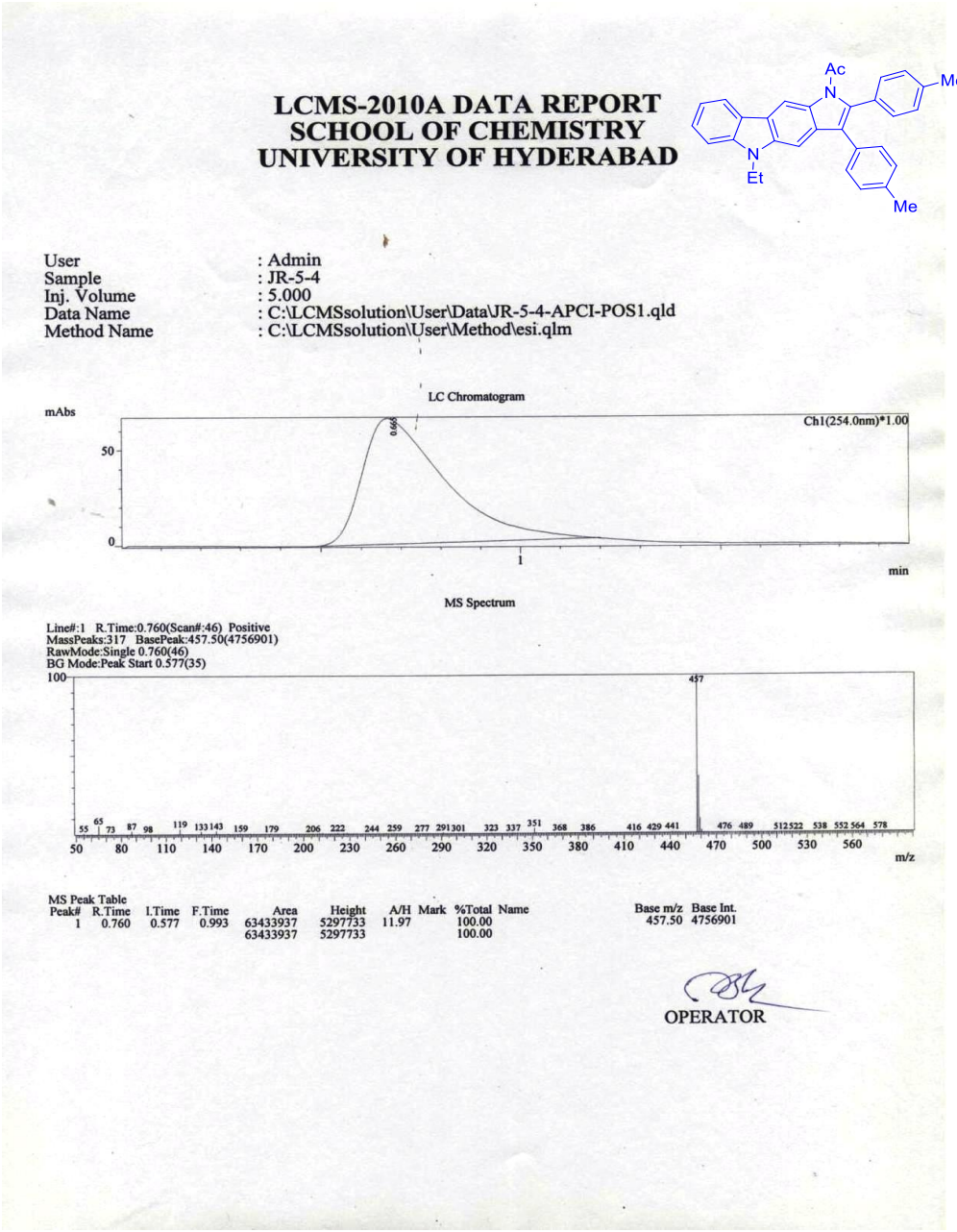
^{1}H NMR of 1-(5-ethyl-2,3-di-*p*-tolyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96g)



^{13}C NMR of 1-(5-ethyl-2,3-di-*p*-tolyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96g)



LC-MS of 1-(5-ethyl-2,3-di-*p*-tolyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96g)



Elemental analysis of 1-(5-ethyl-2,3-di-*p*-tolyl-1,5-dihydropyrrolo[3,2-*b*]carbazol-1-yl)ethanone (96g)

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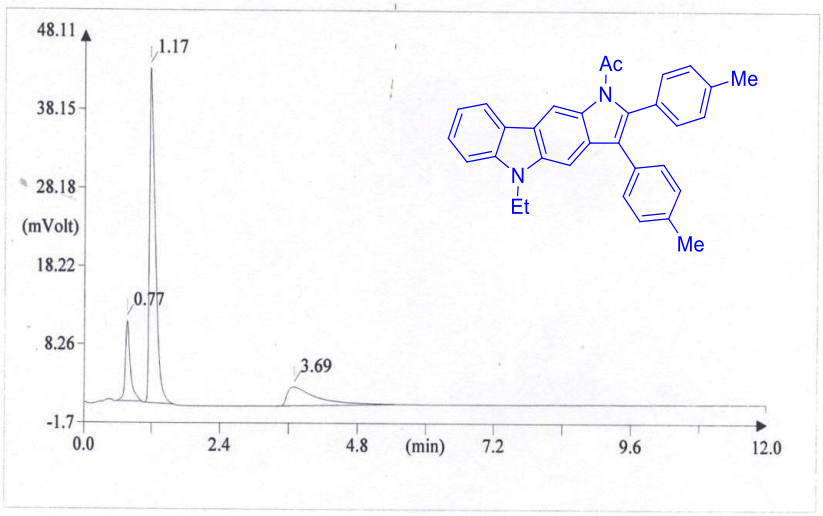
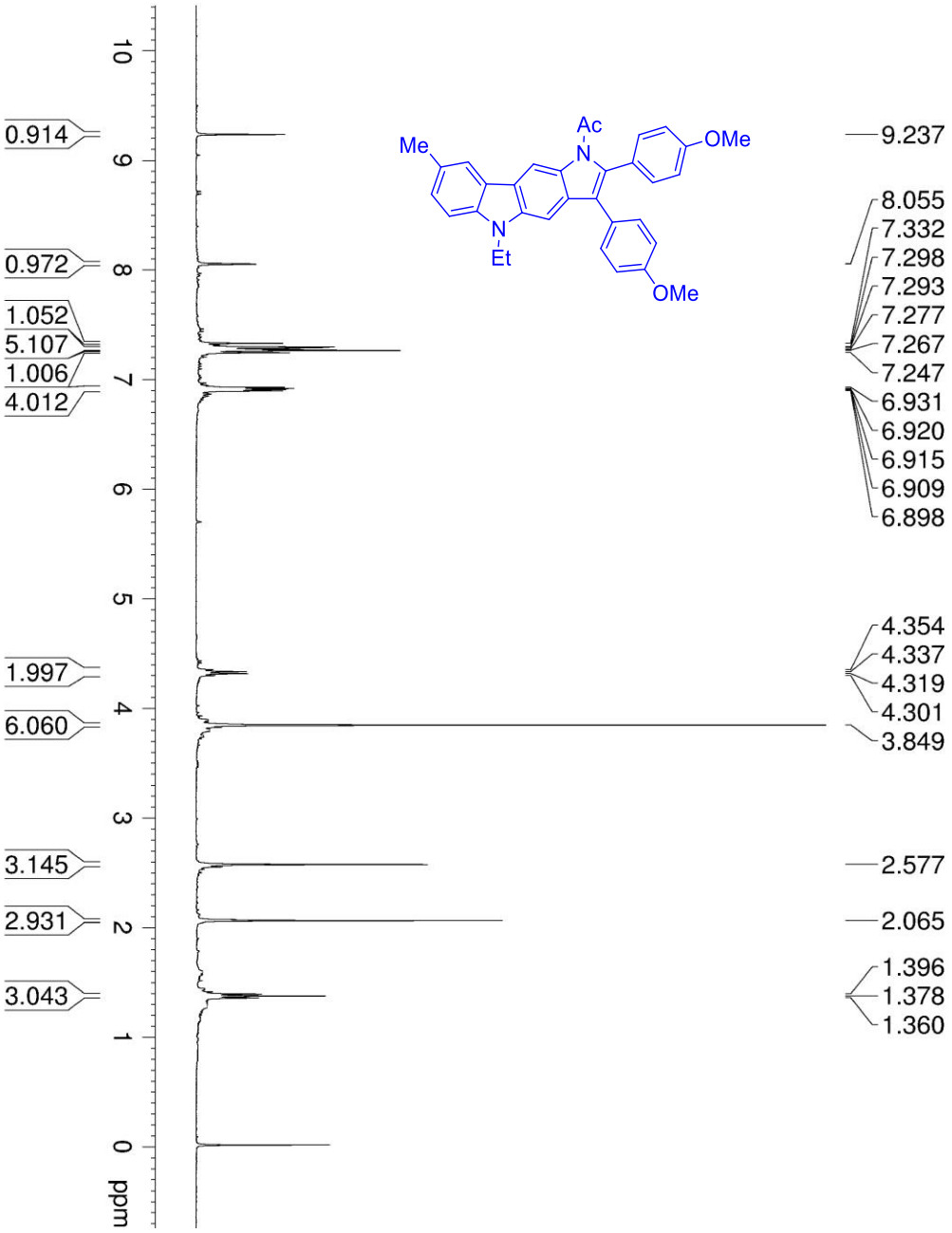
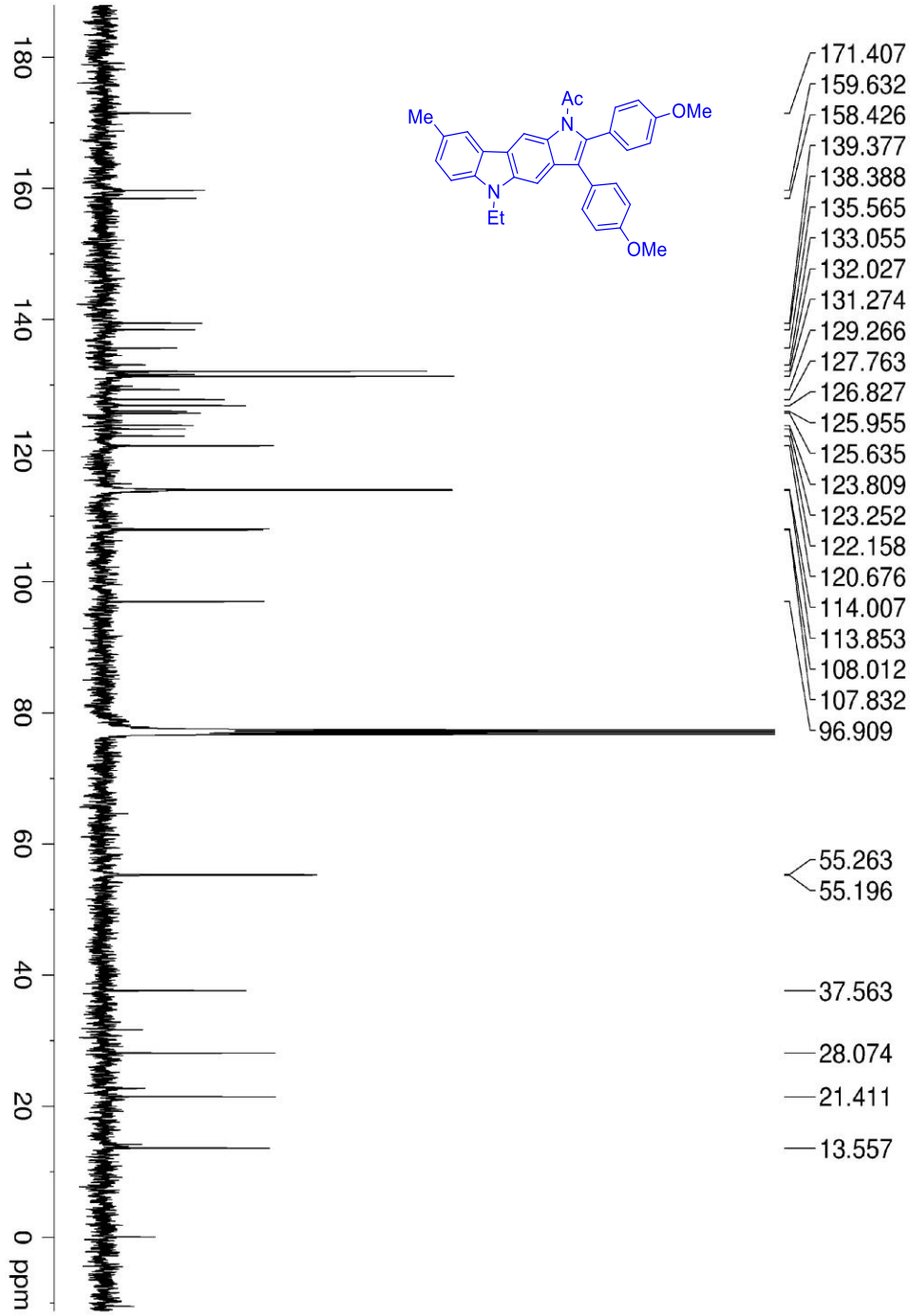


Element Name	Element %	Ret. Time
Nitrogen	6. 19	0. 77
Carbon	84. 07	1. 17
Hydrogen	6. 09	3. 69

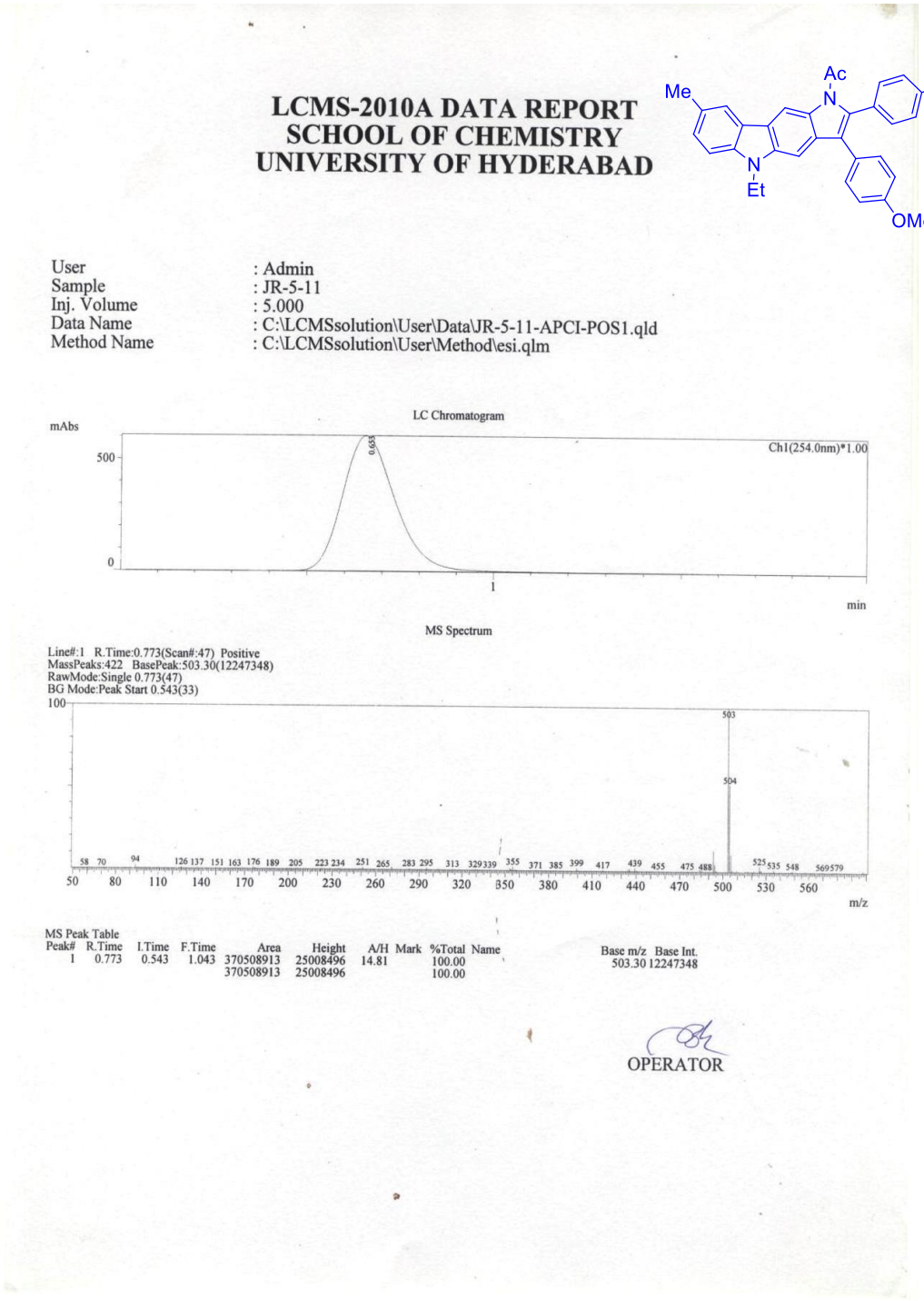
[1]H NMR of 1-(5-ethyl-2,3-bis-(4-methoxyphenyl)-8-methyl-1,5-dihydropyrrolo-[3,2-*b*]- carbazol-1-yl)ethanone (96k)



^{13}C NMR of 1-(5-ethyl-2,3-bis-(4-methoxyphenyl)-8-methyl-1,5-dihydropyrrolo-[3,2-*b*]- carbazol-1-yl)ethanone (96k)



LC-MS of 1-(5-ethyl-2,3-bis-(4-methoxyphenyl)-8-methyl-1,5-dihydropyrrolo-[3,2-*b*]- carbazol-1-yl)ethanone (96k)



Elemental analysis of 1-(5-ethyl-2,3-bis-(4-methoxyphenyl)-8-methyl-1,5-dihydropyrrolo- [3,2-*b*]- carbazol-1-yl)ethanone (96k)

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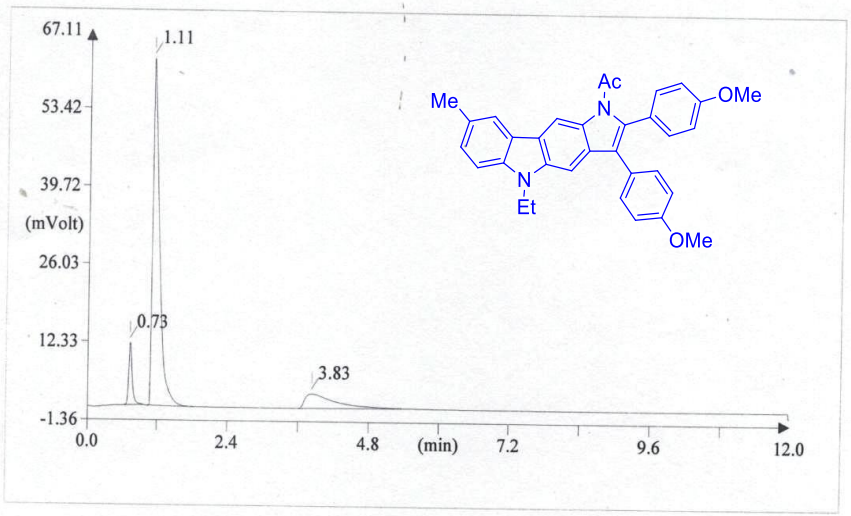


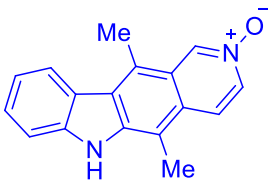
Element Name	Element %	Ret. Time
Nitrogen	5. 65	0. 73
Carbon	78. 69	1. 11
Hydrogen	6. 12	3. 83

Synthesis of Dihydropyrido[2,3-*c*] carbazoles *via* Iodocyclization

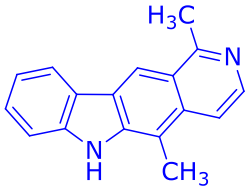
CHAPTER **2**

2.1 Introduction

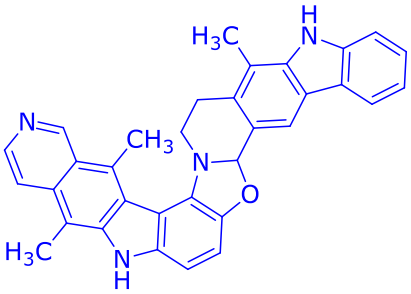
The synthesis of different heteroaryl carbazoles has attracted much attention due to their wide applications in medicinal chemistry.[58,59] Among them, pyridocarbazole derivatives (Fig 7) are extremely helpful in the improvement of numerous DNA intercalating drugs.[60] Ellipticine, a pyridocarbazole alkaloid shows anti cancer and anti-HIV activities because of its strong binding with DNA.[61] Its derivatives are widely used in the treatment of kidney sarcoma, osteolytic breast cancer metastases and myeloblastic leukemia. The limited toxic effects, high efficiency to act against several types of cancer and complete lack of hematological toxicity build additional attention in ellipticine and its derivatives for clinical purposes. Ellipticine exhibits antineoplastic property which depends upon its DNA intercalation and/or inhibition of topoisomerase II.[62]



97, *N*-Oxyellipticine



98, Olivacine



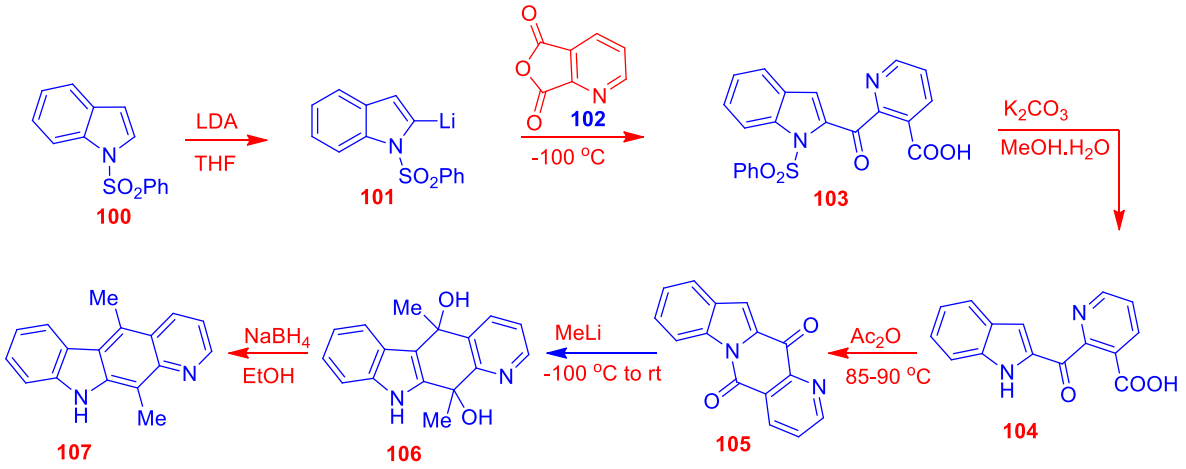
99, Sterillidimine

Fig: 7

Gribble *et al*. reported[63] the synthesis of various ellipticine derivatives in good yields using *N*-sulfonyl indole as starting material. They initiated with C-2-lithiation reaction of **100** using LDA in THF sovent at temperature -70 to 20 °C for 3 h which was then followed by the addition of 2,3-pyridinedicarboxylic anhydride (**102**) at -100 °C led to keto acid **103** upto 83% yield. Removal of the benzenesulfonyl protecting group in **103** was obtained using potassium carbonate in a mixture of MeOH-H_2O in 3:1 ratio under reflux for 5 h led to keto acid **104** in effectively quantitative yield. Treatment of obtained keto acid **104** with acetic anhydride at 85-90 °C for 21 h to undergo cyclization to the keto lactam **105**, separated in 84% yield. Subsequently reaction of keto lactam **105**

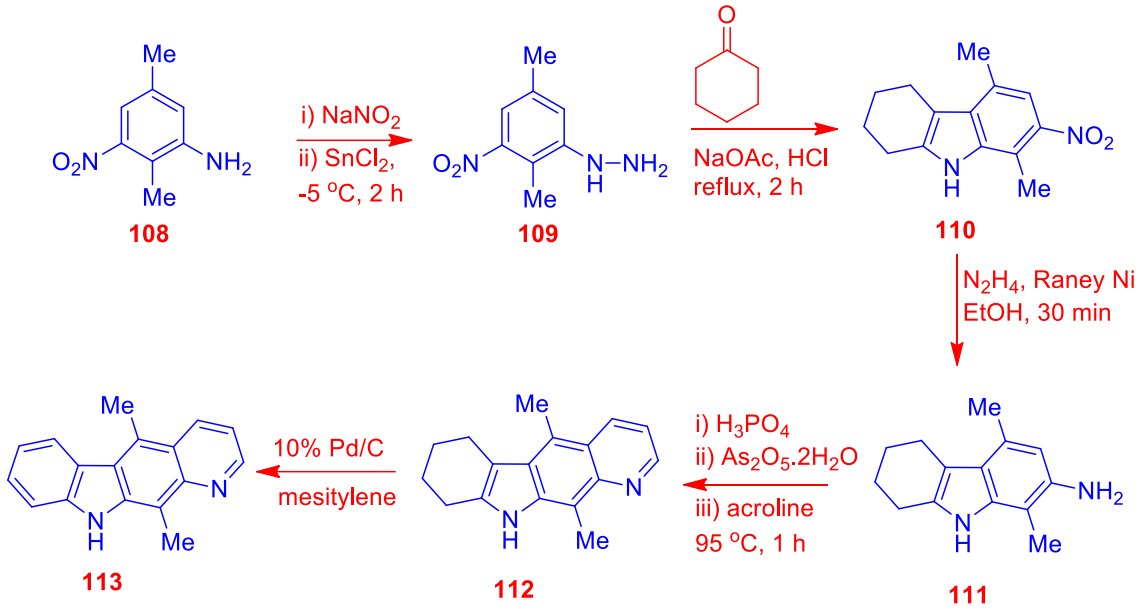
using two equivalents of methyllithium at -100 °C in THF to give a mixture of diols **106**, which, without further purification, was treated with sodium borohydride in EtOH under reflux for 25 h to give 5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole (**107**) upto 96% yield from **106** (**Eq. 15**).

Eq. 15



Lescot *et al.* have reported the synthesis of isomeric ellipticine 10*H*-pyrido[2,3-*b*]carbazole isomer.[64] Initially they started with diazotization of **108** by the addition of a cold solution of sodium nitrite affords the **109**. Then reaction of 2-hydrazino-6-nitro-*p*-xylene **109** using cyclohexanone under reflux for 2 h afforded the compound dimethyltetrahydronitrocarbazole **110**. Mean while reduction of **110** to the resultant tetrahydroaminocarbazole achieved by using raney nickel to generate **111**. The obtained **111** undergoes Skraup reaction to give **112** which was followed by aromatization of **112** using 10% palladium on activated carbon in mesitylene to give **113** (**Eq. 16**).

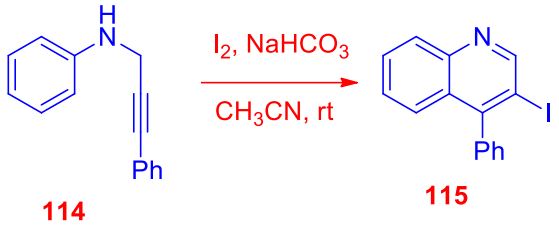
Eq. 16



In recent years, iodocyclization of alkynes has established significant attention due to efficient synthesis of a broad array of attractive carbocyclic and heterocyclic compounds.[65,66] These reactions involve iodine, which is inexpensive, non-toxic and readily available reagent. These reactions are also very efficient, clean and do not require harsh reaction conditions. Further, the iodosubstituted pyridocarbazole derivatives are important synthetic building blocks for the elaboration of molecular complexity, such as in the development of new C-C, C-N, or C-S bond forming reactions. Based on the iodocyclization reactions, Larock et al., reported[67-69] the synthesis of various heterocyclic compounds. Several methodologies have been developed by us for the synthesis of pyridocarbazole derivatives,[70] but herein we report a simple method for the synthesis of pyridocarabzole derivatives based on iodocyclization reaction. In this methodology, we utilized the well known Sonogashira coupling reaction to prepare different aryl containing propargylated aminocarbazoles which have undergone iodocyclization reaction.

Larock *et al.* reported[68c,69b] the synthesis of substituted quinoline by the treatment of propargylated aniline using iodine and $NaHCO_3$ in acetonitrile as shown in (**Eq. 17**).

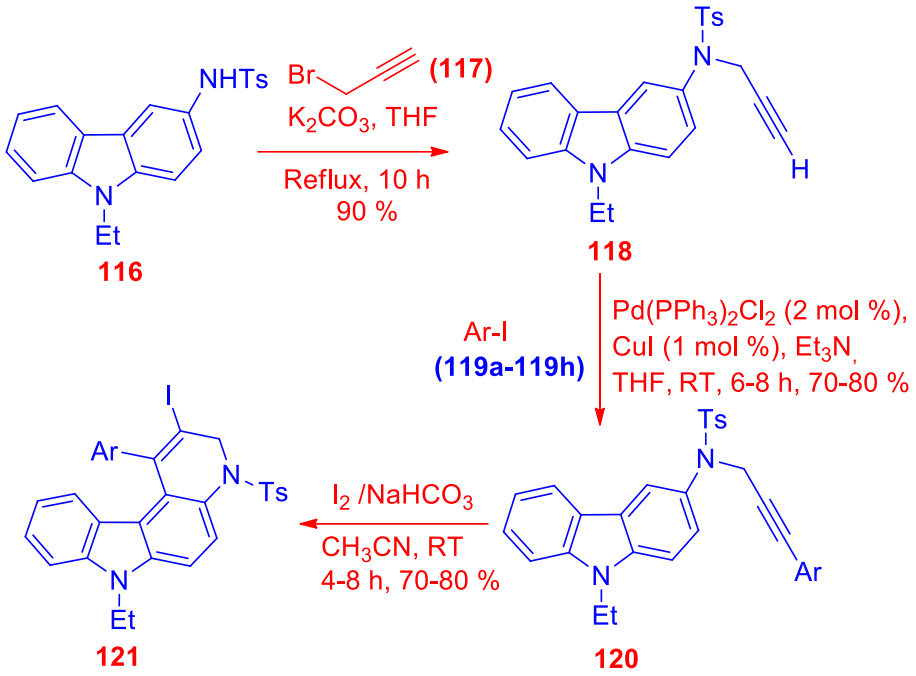
Eq. 17



114 **115**

2.2 Regioselective synthesis of dihydropyrido[2,3-c]carbazoles via Iodocyclization

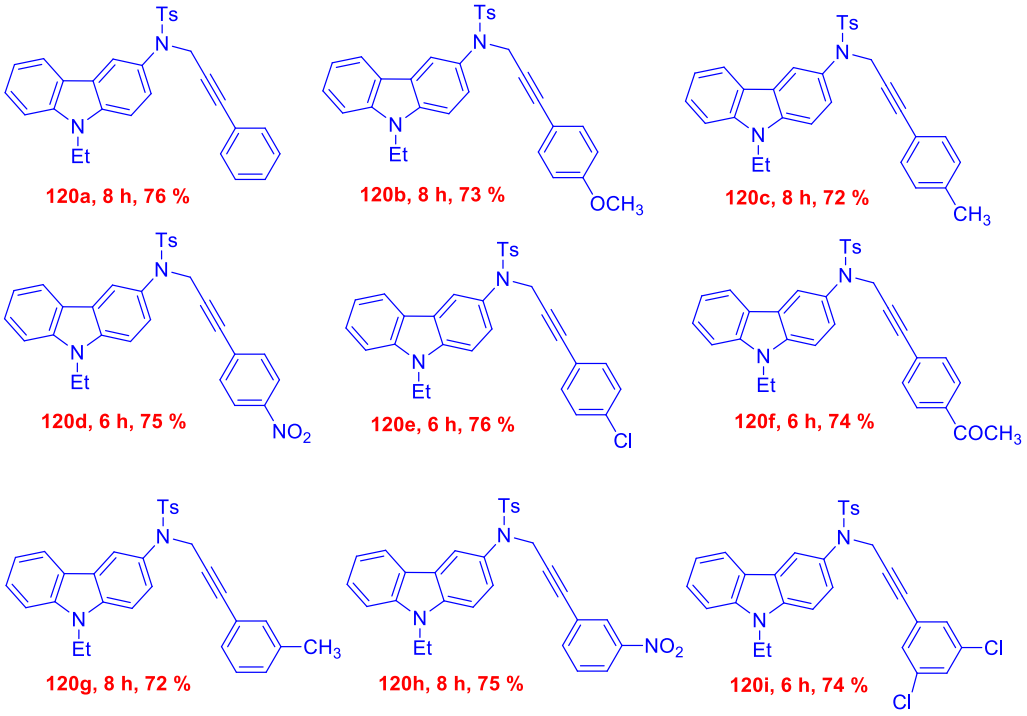
Scheme 5. Synthesis of dihydropyrido[2,3-*c*]carbazoles



Initially, we started with the synthesis of propargylated aminocarbazole **118** by the propargylation of *N*-tosylated aminocarbazole **116** with propargyl bromide **117** in the presence of K_2CO_3 in THF and the product was obtained with good yield. The obtained product **118** was subjected to Sonogashira coupling reaction with various aryl iodides (**119a**-**i**) under very mild conditions (25-35 °C, 8 h) in the presence of $Pd(PPh_3)_2Cl_2$ (2 mol %) as a catalyst and CuI (1 mol %) as a co-catalyst in THF solvent with triethyl

amine as a base. However, when triethylamine was used as both the solvent and base, we got very less yield due to incomplete solubility of starting material. DMF was also used under heating, but it led to unwanted byproducts. Best results were obtained using THF as a solvent. Using these reaction conditions C-arylation of terminal alkyne **118** took place yielding disubstituted alkynes **120a-h** in good yields (70-80 %) (Scheme **5** and Table **5**).

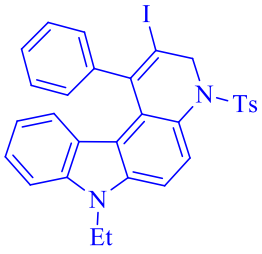
Table 5 Synthesis of 9-ethyl -3-[4-methylphenyl(3-phenylpropyl)sulfonamido]-9*H*-Carbazoles



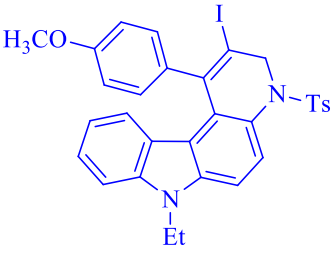
Then we attempted the reaction of phenyl substituted propargylated aminocarbazole **120a** with 3 equiv. of iodine, 2 equiv. of $NaHCO_3$ in acetonitrile at room temperature. The reaction went smoothly and produced the cyclized product **121a**. We screened the iodocyclization reaction with bases such as Et_3N and K_2CO_3 in different solvents by varying the amount of iodine in every case. Finally, we observed that the reaction was going smoothly with 3 equiv. of iodine and 2 equiv. of $NaHCO_3$ as a base in acetonitrile as a solvent with good Yields (70-80 %) (Scheme **5**, Table **6**). After the completion of

optimization, we examined the electronic effects of various substituents on the aryl moiety in this electrophilic cyclization. Both electron rich and electron poor aryl substituted alkynes reacted to form the corresponding products in moderate to good yields. The iodocyclization of both phenyl and methoxy phenyl substituted propargylic aminocarbazoles produced the corresponding iodo substituted pyridocarbazole derivatives in 80 and 72 % yields, respectively.

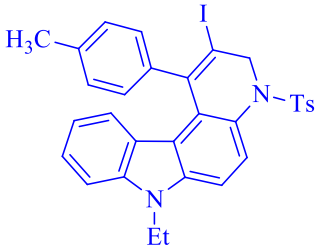
Table 6 Synthesis of 9-ethyl-3-[4-methylphenyl(3-phenylpropyl)sulfonamido]-9*H*-carbazoles



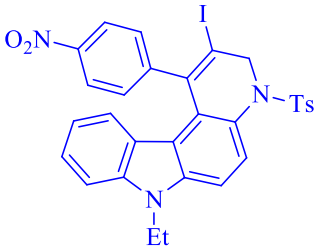
121a, 4 h, 80 %



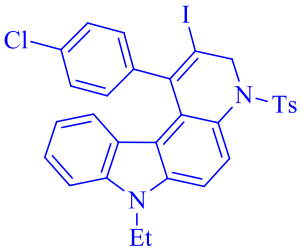
121b, 6 h, 72 %



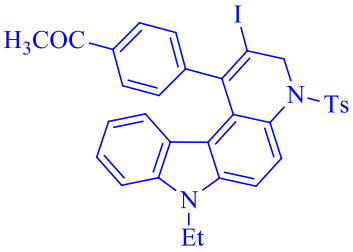
121c, 6 h, 74 %



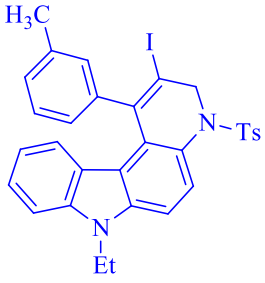
121d, 4 h, 71 %



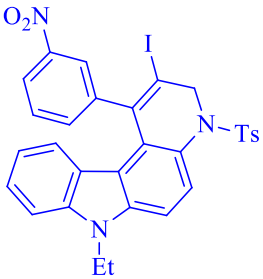
121e, 4 h, 76 %



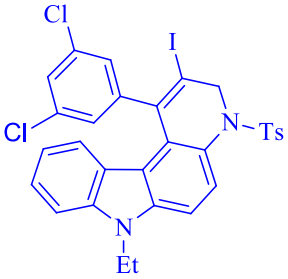
121f, 4 h, 71 %



121g, 6 h, 73 %



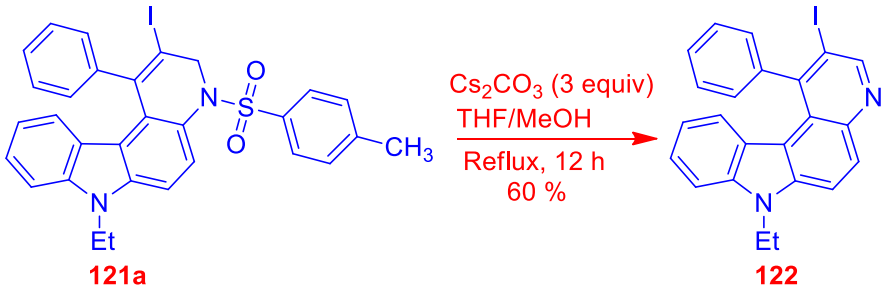
121h, 8 h, 70 %



121i, 6 h, 72 %

We performed the detosylation followed by aromatization of **121a** in the presence of cesium carbonate in the mixture of THF and MeOH at 50 °C, iodo substituted [2,3-*c*]pyridocarbazole **122** was obtained with moderate yield (scheme **6**). The detosylated product **122** was first confirmed by ^{1}H NMR in which a singlet was appeared at *δ* 9.27 ppm for the proton attached to the carbon adjacent to nitrogen atom and the broad singlet at *δ* 5 ppm in **121a** was disappeared. In addition, the structures of **121a** and **122** were confirmed by single crystal X-ray analysis[71] as shown in the figure **8**.

Scheme 6 Syntheis of 7-ethyl-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole



According to Larock's reports[68c,69b] on iodocyclization, we proposed the mechanism for this iodocyclization process (Scheme **7**).

Scheme 7 Proposed mechanism for the iodocyclization reaction.

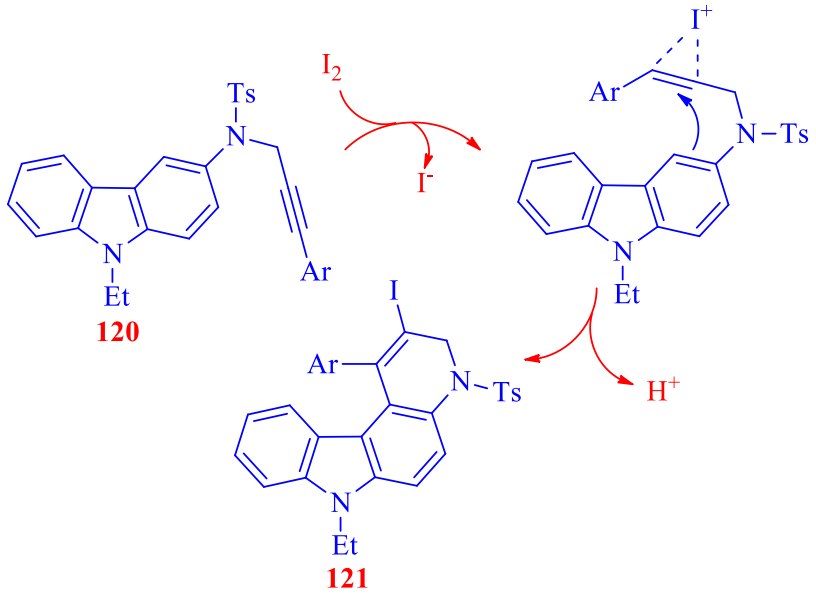
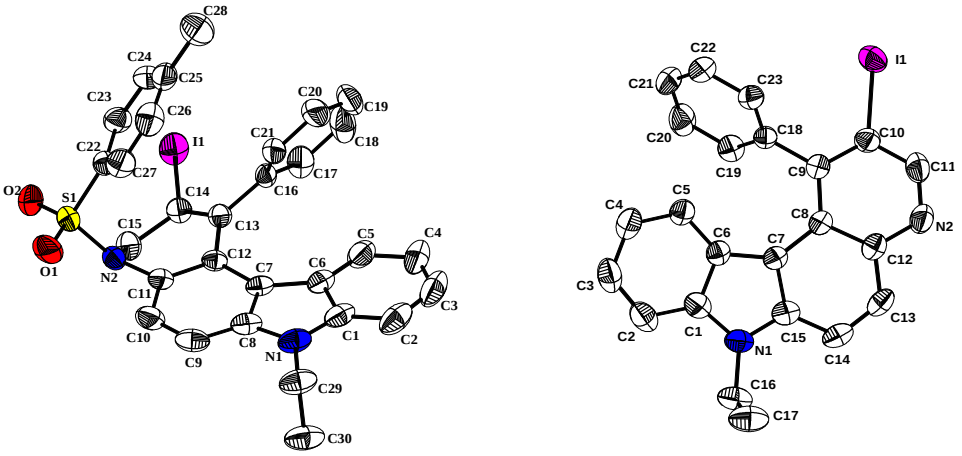


Figure 8 X-ray crystal structures of **121a**, **122**



2.3 Conclusions

In summary, we have developed a simple method for the synthesis of iodo substituted dihydropyridocarbazole derivatives using iodocyclization process. The reaction conditions are mild and the products are obtained in good yields. The iodine group present in the products is very useful for further functionalization and preparation of multisubstituted pyrido carbazole derivatives.

2.4 Experimental section

General procedure A

In a round bottom flask equipped with a magnetic stirring bar, 1.0 mmol of 9-ethyl-3-(4-methylphenylsulfonamido)-9*H*-carbazole **(116)** was stirred with 3.0 mmol of potassium carbonate at room temperature in 10mL of THF as solvent for 1h. Then 1.2 mmol of propargyl bromide **117** was added and the reaction mixture was heated under reflux for 10 h. After completion of the reaction, as indicated by the TLC, water (20 mL) was added to the crude reaction mass. Then aqueous layer was extracted with ethylacetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexane/ethylacetate) afforded **118**.

General procedure B

To a solution of THF (5 mL), Et_3N (3 mL), $PdCl_2(PPh_3)_2$ (2 mmol %), 2.5 mmol of 9-ethyl-3-[4methylphenyl(2-propynyl)sulfonamido]-9*H*-carbazole **118**, and 1.2 equiv. of aryl iodide **119** was added CuI (1 mol %). The reaction mixture was flushed with N2 and the flask was then sealed. The mixture was stirred at room temperature and was monitored by TLC to establish completion of the reaction. The resulting solution was filtered, washed with a satd. aq. NaCl solution, and extracted with ethylacetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent:hexane/ethylacetate) afforded **120a**.

General procedure C

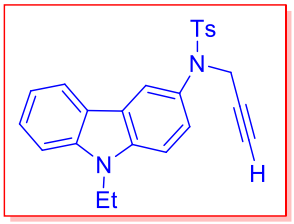
To a mixture of 9-ethyl-3-[4-methylphenyl(3-phenyl-propyl)sulfonamido]-9*H*-carbazole **120a** (0.5g, 1 mmol), iodine (0.8g, 3 mmol), and $NaHCO_3$ (0.36g, 2 mmol) was added 20 mL of acetonitrile at room temperature. The reaction mixture was stirred for 4h. The reaction mixture was then diluted with ethyl acetate, washed with 20 mL of saturated aq $Na_2S_2O_3$. The organic layer was seperated and aqueous was extracted with another 25 mL of ethyl acetate. The combined organic layers were dried over Na_2CO_3, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate) afforded (0.48 g, 80 %) (**121a**).

General procedure D

In a round bottom flask equipped with a magnetic stirring bar, 0.5 mmol of 7-ethyl-2-iodo-(4-methylphenylsulfonyl)-1-phenyl-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (**121a**) was dissolved in a mixture of THF (20 mL) and MeOH (10 mL) at room temperature. Cs_2CO_3 (1.5 mmol) was added to the clear solution. The resulting mixture was stirred at 50 ^{0}C and the progress of the reaction was monitered. When the reaction was complete (12 h), the mixture was evapourated under vacuum. To the residue was added water (20 mL) and the mixture was stirred at room temperature for 10 min. Then aqueous layer was extracted with dichloromethane (3 X 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate) afforded **122** (0.2 g, 60 %).

6-Ethyl-3-[4-methylphenyl(2-propynyl)sulfonamido]-9*H*-carbazole (118):

The product **118** was obtained as yellow colored solid from **116** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure A.



Yield: 73 %

Mp: 114-118 °C

IR (KBr) ν_{max} cm^{-1}: 3254, 3057, 2982, 1597, 1483, 1348, 1161, 1020, 866, 785

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (1H, d, J = 7.6 Hz); 7.88 (1H, s); 7.60 (2H, d, J = 8.0 Hz); 7.49 (1H, t, J = 7.2 Hz); 7.41 (1H, d, J = 8.0 Hz); 7.33-7.30 (2H, m); 7.28-7.21 (3H, m); 4.55 (2H, s); 4.36 (2H, q, J = 6.8 Hz); 2.43 (3H, s); 2.2 (1H, s); 1.44 (3H, t, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 140.4, 139.4, 135.9, 130.3, 129.2, 128.2, 126.6, 126.1, 123.0, 122.6, 121.2, 120.5, 119.1, 108.7, 108.5, 78.5, 73.7, 41.9, 37.7, 21.6, 13.8

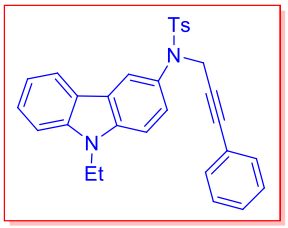
LC-MS (m/z): 403 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{24}H_{22}N_2O_2S$: C, 71.62; H, 5.51; N, 6.96 %

Found: C, 71.45; H, 5.58; N, 6.85 %

9-Ethyl-3-[4-methylphenyl(3-phenyl-2-propynyl)sulfonamido]-9*H*-carbazole (120a) :

The product **120a** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 154-158 °C

IR (KBr) ν_{max} cm^{-1}: 3049, 2980, 1597, 1344, 1232, 1165, 1089, 896, 814, 752

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, s); 7.95 (1H, d, *J* = 8.0 Hz); 7.66 (2H, d, *J* = 8.0 Hz); 7.49 (1H, t, *J* = 7.6 Hz); 7.41 (2H, d, *J* = 10.4 Hz); 7.35-7.19 (9H, m); 4.78 (2H, s); 4.36 (2H, q, *J* = 7.0 Hz); 2.39 (3H, s); 1.44 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 140.4, 139.4, 136.3, 131.5, 130.8, 129.2, 128.4, 128.3, 128.2, 126.8, 126.1, 123.0, 122.7, 122.5, 121.2, 120.5, 119.1, 108.7, 108.5, 85.6, 84.2, 42.9, 37.7, 21.5, 13.8

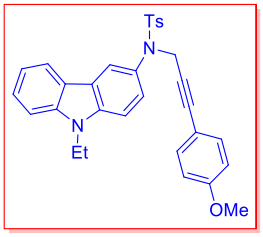
LC-MS (m/z): 480 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{26}N_2O_2S$: C, 75.29; H, 5.48; N, 5.85 %

Found: C, 75.12; H, 5.41; N, 5.91 %

9-Ethyl-3-[3-(4-methoxyphenyl)-2-propynyl(4-methylphenyl)sulfonamido]-9*H*-carbazole (120b) :

The product **120b** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 88-90 °C

IR (KBr) ν_{max} cm^{-1}: 3059, 2970, 2930, 1747, 1510, 1344, 1249, 1089, 866, 744

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (1H, s); 7.93 (1H, d, *J* = 7.6 Hz); 7.65 (2H, d, *J* = 8.0 Hz); 7.48 (1H, t, *J* = 7.4 Hz); 7.40 (2H, t, *J* = 7 Hz); 7.33 (1H, d, *J* = 8.8 Hz); 7.24-7.14 (5H, m); 6.79 (2H, d, *J* = 8.4 Hz); 4.75 (2H, s); 4.36

(2H, q, *J* = 6.8 Hz); 3.8 (3H, s); 2.39 (3H, s); 1.44 (3H, t, *J* = 7 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.6, 143.3, 140.4, 139.3, 136.3, 132.9, 130.9, 129.1, 128.3, 126.8, 126.1, 122.9, 122.7, 121.3, 120.5, 119.1, 114.6, 113.8, 108.7, 108.5, 85.5, 82.7, 55.3, 43.0, 37.7, 21.5, 13.8

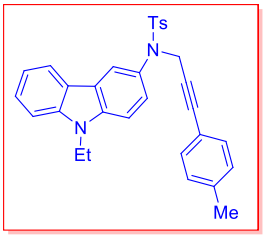
LC-MS (m/z): 509 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{31}H_{28}N_2O_3S$: C, 73.20; H, 5.55; N, 5.51 %

Found: C, 73.41; H, 5.62; N, 5.45 %

9-Ethyl-3-{4-methylphenyl[3-(4-methylphenyl)-2-propynyl]sulfonamide}-9*H*-carbazole (120c) :

The product **120c** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 96-98 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2964, 1626, 1508, 1346, 1269, 1188, 1089, 866, 744

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.01 (1H, s); 7.94 (1H, d, *J* = 7.2 Hz); 7.66 (2H, d, *J* = 7.6 Hz); 7.48 (1H, d, *J* = 7.2 Hz); 7.41 (2H, d, *J* = 8.4 Hz); 7.33 (1H, d, *J* = 8.8 Hz); 7.24-7.19 (3H, m); 7.11-7.09 (4H, m); 4.77 (2H, s); 4.35 (2H, q, *J* = 6.4 Hz); 2.39 (3H, s); 2.34 (3H, s); 1.44 (3H, t, *J* = 6.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.3, 140.4, 139.4, 138.5, 136.3, 131.4, 130.9, 129.2, 128.9, 128.3, 126.8, 126.1, 123.0, 122.7, 121.3, 120.5, 119.5, 119.1, 108.7, 108.5, 85.7, 83.5, 43.0, 37.7, 21.5, 21.4, 13.8

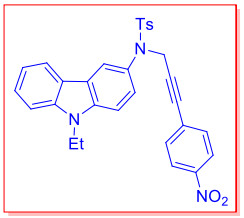
LC-MS (m/z): 493 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{31}H_{28}N_2O_2S$: C, 75.58; H, 5.73; N, 5.69 %

Found: C, 75.41; H, 5.68; N, 5.75 %

9-Ethyl-3-{4-methylphenyl[3-(4-nitrophenyl)-2-propynyl]sulfonamide}-9*H*-carbazole (120d) :

The product **120d** was obtained as brown colored viscous liquid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 148-150 °C

IR (KBr) ν_{max} cm^{-1}: 3049, 2976, 2916, 1626, 1512, 1464, 1338, 1161, 854, 748

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (2H, d, J = 8.4 Hz); 7.93 (2H, d, J = 6.8 Hz); 7.64 (2H, d, J = 8.0 Hz); 7.50 (1H, t, J = 7.6 Hz); 7.43 (1H, d, J = 8.0 Hz); 7.35-7.33 (4H, m); 7.25-7.22 (3H, m); 4.8 (2H, s); 4.36 (2H, q, J = 7.0 Hz); 2.41 (3H, s); 1.44 (3H, t, J = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 143.6, 140.4, 139.4, 136.1, 132.2, 130.5, 129.5, 129.3, 128.7, 128.2, 126.6, 126.3, 123.4, 123.1, 122.5, 121.1, 120.4, 119.3, 108.8, 108.6, 89.8, 83.7, 42.8, 37.7, 21.5, 13.8

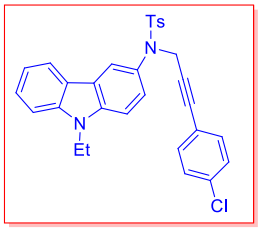
LC-MS (m/z): 524 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{25}N_3O_4S$: C, 68.82; H, 4.81; N, 8.03 %

Found: C, 68.75; H, 4.75 ; N, 7.91 %

3-[3-(4-Chlorophenyl)2-propynyl(4-methylphenyl)sulfonamido]-9-ethyl-9*H*-carbazole (120e):

The product **120e** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 136-138 °C

IR (KBr) ν_{max} cm^{-1}: 3045, 2978, 2932, 1624, 1483, 1304, 1238, 1161, 1089, 889

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, d, J = 8.4 Hz); 7.64 (2H, d, J = 8.0 Hz); 7.49 (1H, t, J = 7.6 Hz); 7.42 (1H, d, J = 8.4 Hz); 7.39-7.33 (2H, m); 7.26-7.20 (5H, m); 7.13 (2H, d, J = 8.4 Hz); 4.76 (2H, s); 4.36 (2H, q, J = 7.2 Hz); 2.4 (3H, s); 1.44 (3H, t, J = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 140.4, 139.4, 136.2, 134.4, 132.7, 130.7, 129.2, 128.5, 128.2, 126.7, 126.1, 123.0, 122.6, 121.2, 121.0, 120.4, 119.2, 108.7, 108.6, 85.3, 84.4, 42.9, 37.7, 21.5, 13.8

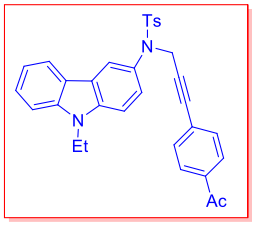
LC-MS (m/z): 513 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{25}ClN_2O_2S$: C, 70.23; H, 4.91; N, 5.46 %

Found: C, 70.45; H, 4.96; N, 5.38 %

3-[3-(4-Acetylphenyl)2-propynyl(4-methylphenyl)sulfonamido]-9-ethyl-9*H*-carbazole (120f):

The product **120f** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 132-134 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 3057, 2982, 1678, 1483, 1302, 1159, 1089, 960, 810

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.93 (2H, m); 7.85 (2H, d, *J* = 7.6 Hz); 7.65 (2H, d, *J* = 7.6 Hz); 7.49 (1H, t, *J* = 7.2 Hz); 7.43-7.34 (3H, m); 7.29 (2H, d, *J* = 7.6 Hz); 7.25-7.21 (3H, m); 4.79 (2H, s); 4.35 (2H, d, *J* = 6.8 Hz); 2.58 (3H, s); 2.40 (3H, s); 1.44 (3H, t, *J* = 6.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 143.5, 140.4, 139.4, 136.3, 136.2, 131.6, 130.6, 129.3, 128.2, 128.1, 127.3, 126.7, 126.2, 123.0, 122.6, 121.2, 120.4, 119.2, 108.8, 108.6, 87.7, 84.8, 42.9, 37.7, 26.6, 21.5, 13.8

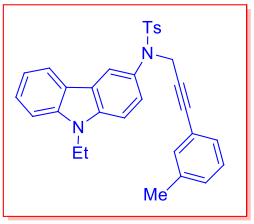
LC-MS (m/z): 521 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{32}H_{28}N_2O_3S$: C, 73.82; H, 5.42; N, 5.38 %

Found: C, 73.68; H, 5.47; N, 5.31 %

9-Ethyl-3-{4-methylphenyl[3-(3-phenylmethyl)-2-propynyl]sulfonamido}-9*H*-carbazole (120g) :

The product **120g** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 102-104 °C

IR (KBr) ν_{max} cm^{-1}: 3049, 2980, 2864, 1485, 1344, 1165, 1089, 898, 814, 787

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, s); 7.97 (1H, d, *J* = 7.6 Hz); 7.69 (2H, d, *J* = 7.6 Hz); 7.50 (1H, t, *J* = 7.4 Hz); 7.42 (2H, d, *J* = 6.8 Hz); 7.35 (1H, d, *J* = 8.4 Hz); 7.23-7.12 (5H, m); 7.05 (2H, s); 4.79 (2H, s); 4.35 (2H, q, *J* = 6.8 Hz); 2.41 (3H, s); 2.31 (3H, s); 1.45 (3H, t, *J* = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 140.4, 139.4, 137.9, 136.3, 132.1, 130.8, 129.3, 129.2, 128.5, 128.3, 128.1, 126.8, 126.1, 123.0, 122.7, 122.4, 121.3, 120.5, 119.1, 108.7, 108.6, 85.8, 83.9, 43.0, 37.7, 21.5, 21.2, 13.8

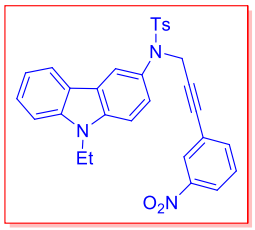
LC-MS (m/z): 493 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{31}H_{28}N_2O_2S$: C, 75.58; H, 5.73; N, 5.69 %

Found: C, 75.49; H, 5.68; N, 5.61 %

9-Ethyl-3-{4-methylphenyl[3-(3-nitrophenyl)-2-propynyl]sulfonamido}-9*H*-carbazole (120h) :

The product **120h** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 144-146 °C

IR (KBr) ν_{max} cm^{-1}: 3055, 2982, 2926, 2862, 1597, 1527, 1483, 1412, 1161, 869

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 8.0 Hz); 8.02 (1H, s); 7.95 (2H, d, *J* = 7.6 Hz); 7.66 (2H, d, *J* = 7.6 Hz); 7.54-7.42 (4H, m); 7.37 (2H, s); 7.27-7.21 (3H, m); 4.79 (2H, s); 4.37 (2H, q, *J* = 7.0 Hz); 2.42 (3H, s); 1.45 (3H, t, *J* = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 143.7, 140.5, 139.4, 137.1, 136.1, 130.6, 129.3, 128.2, 126.6, 126.2, 124.2, 123.1, 122.5, 121.2, 120.4, 119.2, 108.8, 108.7, 87.1, 83.1, 42.8, 37.7, 21.5, 13.8

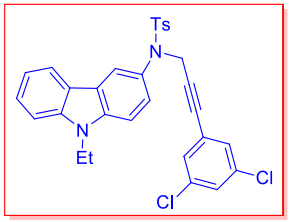
LC-MS (m/z): 524 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{25}N_3O_4S$: C, 68.82 ; H, 4.81; N, 8.03 %

Found: C, 68.75; H, 4.86; N, 8.12 %

3-[3-(3,5-Dichlorophenyl)-2-propynyl(4-methylphenyl)sulfonamido]-9-ethyl-9*H*-carbazole (120i) :

The product **120i** was obtained as brown colored solid from **118** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure B.



Yield: 73 %

Mp: 128-130 °C

IR (KBr) ν_{max} cm^{-1}: 3472, 3070, 2934, 1583, 1483, 1292, 1163, 1091, 896, 746

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (2H, d, J = 8.8 Hz); 7.65 (2H, d, J = 8.0 Hz); 7.50 (1H, t, J = 7.4 Hz); 7.42 (1H, d, J = 8.0 Hz); 7.37 (2H, s); 7.30 (1H, s); 7.24 (3H, t, J = 6.6 Hz); 7.05 (2H, d, J = 1.6 Hz); 4.76 (2H, s); 4.37 (2H, q, J = 7.2 Hz); 2.44 (3H, s); 1.45 (3H, t, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 140.4, 139.4, 136.3, 134.8, 130.7, 129.6, 129.3, 128.7, 128.3, 126.5, 126.2, 125.2, 123.0, 122.6, 121.1, 120.5, 119.3,108.8, 108.6, 86.9, 83.0, 42.8, 37.7, 21.6, 13.8

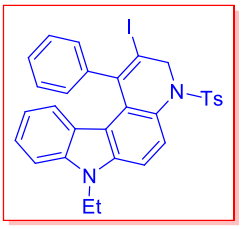
LC-MS (m/z): 547 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{24}Cl_2N_2O_2S$: C, 65.81 ; H, 4.42; N, 5.12 %

Found: C, 65.71; H, 4.48; N, 5.22 %

7-Ethyl-2-iodo-(4-methylphenylsulfonyl)-1-phenyl-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121a):

The product **121a** was obtained as colorless solid from **120a** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 172-174 °C

IR (KBr) ν_{max} cm^{-1}: 3043, 2976, 2926, 1608, 1593, 1440, 1346, 1163, 1087, 883

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (1H, d, J = 8.8 Hz); 7.55 (4H, d, J = 7.2 Hz); 7.26-7.16 (4H, m); 7.08 (2H, m); 6.95-6.93 (2H, m); 6.60-6.57 (2H,m); 5.00 (2H, br s); 4.4-4.3 (2H, m); 2.15 (3H, s); 1.44 (3H, t, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 141.0, 140.0, 139.8, 139.4, 135.6, 130.6, 129.9, 129.2, 128.1, 127.7, 127.1, 126.1, 125.2, 124.2, 124.0, 121.8, 118.4, 118.3, 109.2, 107.9, 91.7, 59.8, 37.5, 21.3, 13.6

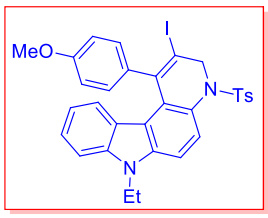
LC-MS (m/z): 604 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{25}IN_2O_2S$: C, 59.61; H, 4.17; N, 4.63 %

Found: C, 59.58; H, 4.10; N, 4.56 %

7-Ethyl-2-iodo-1-(4-methoxyphenyl)-4-(4-methylphenylsulfonyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121b) :

The product **121b** was obtained as colorless solid from **120b** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 162-164 °C

IR (KBr) ν_{max} cm^{-1}: 2926, 1747, 1604, 1506, 1381, 1246, 1161, 1033, 885, 738

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, d, *J* = 8.8 Hz); 7.52-7.48 (3H, m); 7.26-7.18 (3H, m); 6.93 (3H, d, *J* = 8.0 Hz); 6.59 (4H, d, *J* = 5.2 Hz); 4.98 (2H, br s); 4.37 (2H, q, *J* = 7.2 Hz); 3.75 (3H, s); 2.15 (3H, s); 1.43 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 143.4, 140.6, 139.9, 139.4, 135.5, 132.3, 131.8, 129.8, 129.1, 127.6, 126.3, 125.1, 124.4, 124.0, 121.8, 118.5, 118.4, 112.3, 109.1, 107.8, 90.7, 59.7, 55.2, 37.5, 21.4, 13.6

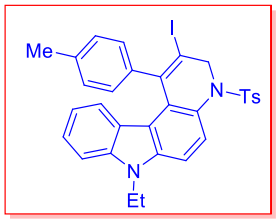
LC-MS (m/z): 636 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{31}H_{27}IN_2O_3S$: C, 58.68; H, 4.29; N, 4.41 %

Found: C, 58.61; H, 4.23; N, 4.51 %

7-Ethyl-2-iodo-1-(4-methylphenyl)-4-(4-methylphenylsulfonyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121c) :

The product **121c** was obtained as colorless solid from **120c** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 170-172 °C

IR (KBr) ν_{max} cm^{-1}: 3051, 2978, 1610, 1591, 1469, 1442, 1346, 1163, 1070, 887

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (1H, d, *J* = 8.8 Hz); 7.53-7.50 (4H, m); 7.24-7.18 (2H, m); 6.95-6.88 (5H, m); 6.60-6.54 (2H,

m); 4.99 (2H, br s); 4.37 (2H, q, *J* = 7.2 Hz); 2.27 (3H, s); 2.15 (3H, s); 1.43 (3H, q, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.4, 140.9, 139.9, 139.4, 137.9, 136.9, 135.6, 130.4, 129.8, 129.1, 127.7, 127.6, 126.3, 125.1, 124.4, 124.0, 121.8, 118.5, 118.2, 109.1, 107.8, 91.2, 59.7, 37.5, 21.3, 13.6

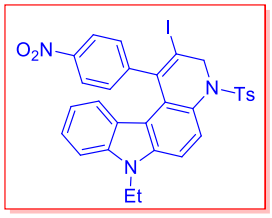
LC-MS (m/z): 619 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{31}H_{27}IN_2O_2S$: C, 60.20; H, 4.40; N, 4.53 %

Found: C, 60.31; H, 4.36; N, 4.45 %

7-Ethyl-2-iodo-4-(4-methylphenylsulfonyl)-1-(4-nitrophenyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121d) :

The product **121d** was obtained as colorless solid from **120d** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 180-182 °C

IR (KBr) ν_{max} cm^{-1}: 1595, 1520, 1471, 1440, 1346, 1161, 1068, 887, 856, 736

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.16 (1H, d, *J* = 8.8 Hz); 7.96-7.85 (2H, m); 7.57-7.51 (4H, m); 7.29-7.19 (3H, m); 6.94 (2H, d, *J* = 8.0 Hz); 6.59 (2H, d, *J* = 4.0 Hz); 5.02 (2H, br s); 4.39 (2H, q, *J* = 7.6 Hz); 2.15 (3H, s); 1.45 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.7, 146.2, 143.6, 140.1, 139.4, 139.2, 135.6, 131.3, 129.9, 129.5, 129.2, 128.6, 127.7, 125.6, 124.9, 123.8, 123.2, 122.2, 121.1, 118.4, 117.9, 109.8, 108.4, 93.7, 60.0, 37.6, 21.3, 13.6

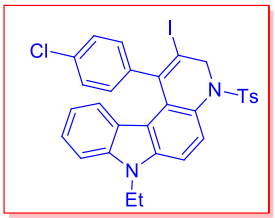
LC-MS (m/z): 650 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{24}IN_3O_4S$: C, 55.48; H, 3.72; N, 6.47 %

Found: C, 55.41; H, 3.65; N, 6.44 %

1-(4-Chlorophenyl)-7-ethyl-2-iodo-4-(4-methylphenylsulfonyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121e) :

The product **121e** was obtained as colorless solid from **120e** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 176-178 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3057, 2976, 2916, 1610, 1591, 1471, 1440 1346, 1086, 881

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (1H, d, J = 8.8 Hz); 7.53-7.50 (3H, m); 7.28 –7.21 (3H, m); 7.02–6.92 (4H, m); 6.66–6.58 (3H, m); 5.01 (2H, br s); 4.38 (2H, q, J = 7.2 Hz); 2.16 (3H, s); 1.43 (3H, t, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 140.0, 139.3, 138.1, 135.6, 133.8, 131.8, 129.9, 129.1, 127.6, 127.2, 125.6, 125.4, 123.9, 121.5, 118.4, 118.2, 109.4, 108.0, 92.0, 59.8, 37.5, 21.3, 13.6

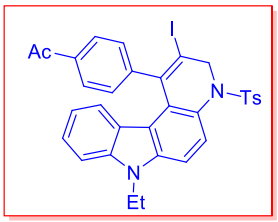
LC-MS (m/z): 639 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{24}ClIN_2O_2S$: C, 56.39; H, 3.79; N, 4.38 %

Found: C, 56.28; H, 3.83; N, 4.45 %

1-{4-[7-Ethyl-2-iodo-4-(4-methylphenylsulfonyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazol-1-yl]phenyl}-1-ethanone (121f) :

The product **121f** was obtained as colorless solid from **120f** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 172-174 °C

IR (KBr) ν_{max} cm^{-1}: 3059, 2976, 1597, 1558, 1437, 1261, 1068, 879, 740

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, J = 8.8 Hz); 7.65-7.51 (6H, m); 7.27-7.19 (3H, m); 6.93 (2H, d, J = 8.0 Hz); 6.60-6.54 (2H, m); 5.0 (2H, br s); 4.38 (2H, q, J = 7.2 Hz); 2.54 (3H, s); 2.15 (3H, s); 1.43 (3H, t, J = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 144.4, 143.5, 140.2, 140.0, 139.3, 136.0, 135.6, 130.6, 129.9, 129.2, 127.6, 127.0, 125.4, 125.4, 123.9, 123.7, 121.4, 118.3, 109.5, 108.1, 92.8, 59.9, 37.6, 26.6, 21.4, 13.6

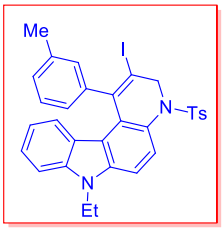
LC-MS (m/z): 647 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{32}H_{27}IN_2O_3S$: C, 59.45; H, 4.21; N, 4.33 %

Found: C, 59.62; H, 4.18; N, 4.28 %

7-Ethyl-2-iodo-1-(3-methylphenyl)-4-(4-methylphenylsulfonyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121g) :

The product **121g** was obtained as colorless solid from **120g** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 174-176 °C

IR (KBr) ν_{max} cm^{-1}: 3128, 3042, 2978, 1616, 1344, 1238, 1182, 1070, 939, 883

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (1H, d, *J* = 8.8 Hz); 7.54-7.5 (3H, m); 7.26-7.18 (3H, m); 6.99-6.90 (5H, m); 6.57-6.56 (2H, m); 4.99 (2H, br s); 4.37 (2H, q, *J* = 7.2 Hz); 2.22 (3H, s); 2.16 (3H, s); 1.43 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 141.1, 139.9, 136.5, 135.7, 131.3, 129.8, 129.1, 128.6, 127.6, 127.0, 126.2, 125.1, 124.4, 124.0, 121.8, 118.5, 118.1, 109.1, 107.1, 91.4, 59.6, 37.5, 21.4, 13.5

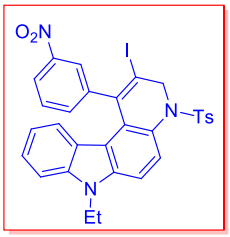
LC-MS (m/z): 620 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{31}H_{27}IN_2O_2S$: C, 60.20; H, 4.40; N, 4.53 %

Found: C, 60.31; H, 4.35; N, 4.65 %

7-Ethyl-2-iodo-4-(4-methylphenylsulfonyl)-1-(3-nitrophenyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121h) :

The product **121h** was obtained as colorless solid from **120h** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 176-178 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 2926, 1593, 1521, 1471, 1348, 1163, 1064, 887, 814

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (1H, d, *J* = 8.8 Hz); 8.01 (1H, d, *J* = 6.4 Hz); 7.58- 7.51 (4H, m); 7.43-7.17 (4H, m); 6.98 (2H, d, *J* = 7.6 Hz); 6.58-6.51 (2H, m); 5.05 (2H, br s); 4.38 (2H, q, *J* = 7.2 Hz); 2.05 (3H, s); 1.45 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 143.7, 141.2, 139.3, 139.0, 136.6, 135.5, 130.0, 129.2, 127.9, 127.5, 125.5, 124.9, 123.9, 123.2, 122.8, 121.0, 118.4, 117.8, 109.9, 108.4, 93.2, 59.7, 37.6, 29.7, 21.2, 13.6

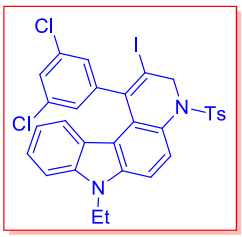
LC-MS (m/z): 650 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{24}IN_3O_4S$: C, 55.48; H, 3.72; N, 6.47 %

Found: C, 55.32; H, 3.80; N, 6.41 %

1-(3,5-Dichlorophenyl)-7-ethyl-2-iodo-4-(4-methylphenylsulfonyl)-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121i) :

The product **121i** was obtained as colorless solid from **120i** through column chromatography using a mixture of 15% ethyl acetate and hexanes as described in procedure C.



Yield: 80 %

Mp: 176-178 °C

IR (KBr) ν_{max} cm^{-1}: 3059, 2924, 2858, 1745, 1593, 1469, 1350, 1072, 885, 736

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (1H, d, *J* = 8.8 Hz); 7.56-7.50 (4H, m); 7.30-7.26 (3H, m); 7.15 (1H, s); 7.02 (2H, d, *J* = 8.0 Hz); 6.72-6.71 (2H, d, *J* = 3.2Hz); 4.99 (2H, br s); 4.40 (2H, q, *J* = 7.0 Hz); 2.22 (3H, s); 1.45 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.6, 140.1, 139.3, 138.8, 135.5, 133.6, 129.8, 129.3, 127.7, 127.5, 125.5, 124.9, 123.8, 121.2, 118.5, 117.9, 109.7, 108.3, 93.1, 59.7, 37.6, 21.5, 13.6

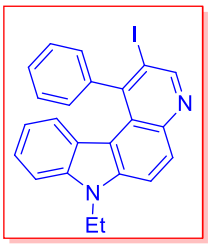
LC-MS (m/z): 673 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{30}H_{23}Cl_2IN_2O_2S$: C, 53.51; H, 3.44; N, 4.16 %

Found: C, 53.46; H, 3.41; N, 4.22 %

7-Ethyl-2-iodo-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (122) :

The product **122** was obtained as brown colored solid from **121a** through column chromatography using a mixture of 10% ethyl acetate and hexanes as described in procedure D.



Yield: 60 %

Mp: 178-180 °C

IR (KBr) ν_{max} cm^{-1}: 3126, 3055, 2972, 1614, 1591, 1504, 1444, 1379, 1253, 952

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (1H, s), 8.21 (1H, d, J = 8.0 Hz), 7.95 (1H, d, J = 8.0 Hz), 7.58-7.4 (6H, m), 7.27 (1H, t, J = 8.0 Hz), 6.64 (1H, t, J = 8.0 Hz), 5.78 (1H, d, J = 8.0 Hz), 4.50 (2H, q, J = 8.0 Hz), 1.48 (3H, t, J = 4.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 148.4, 145.5, 144.6, 138.8, 138.7, 131.2, 129.4, 129.0, 128.9, 125.8, 124.6, 124.1, 123.4, 118.9, 114.5, 114.1, 108.2, 100.1, 37.6, 14.1

LC-MS (m/z): 449 $(M+H)^+$, positive mode

Anal. Calcd. for $C_{23}H_{17}IN_2$: C, 61.62; H, 3.82; N, 6.25 %

Found: C, 61.31; H, 3.78; N, 6.31 %

2.4 References:

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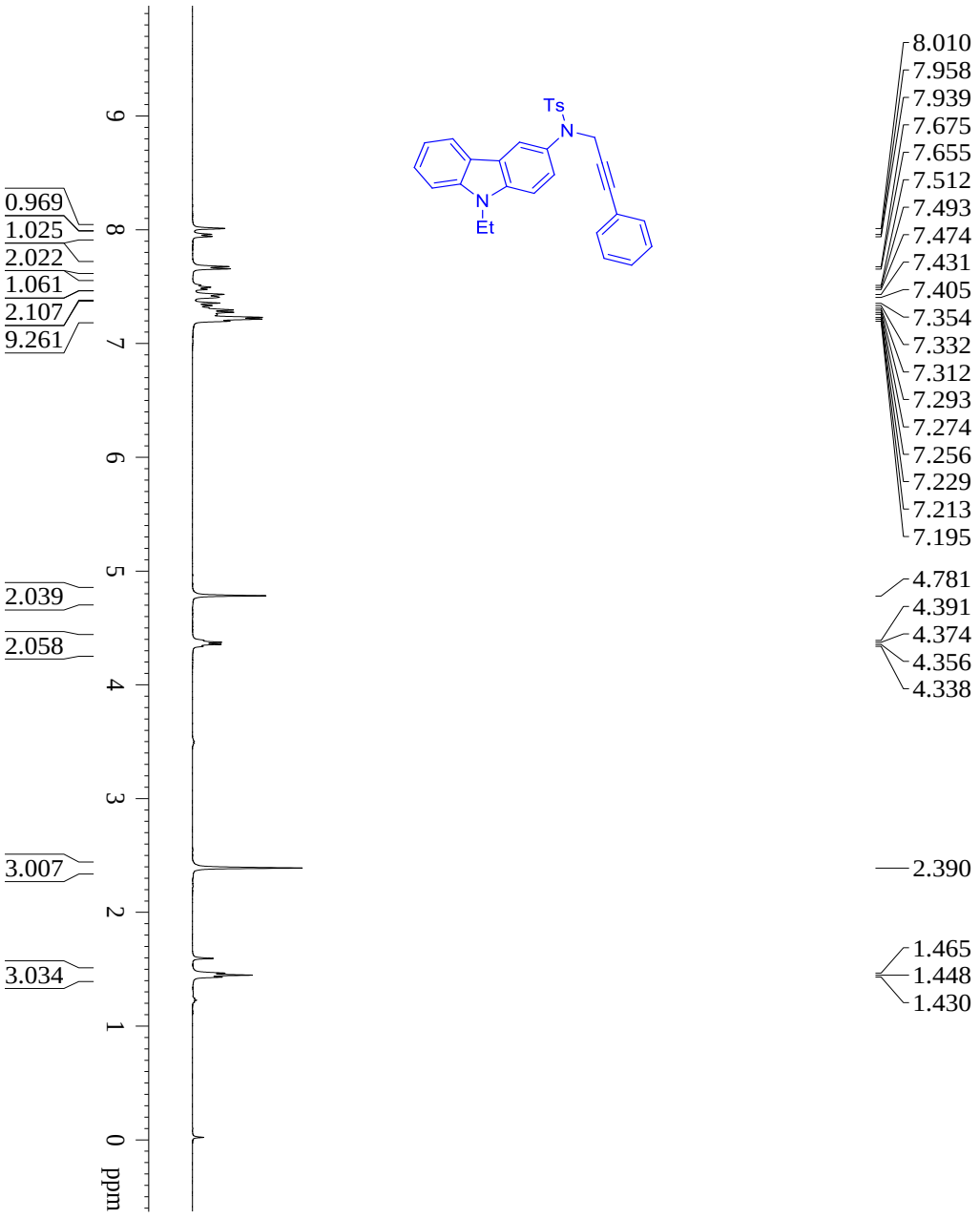
71. The CCDC deposition number for compound **121a** is 800159. Formula: $C_{30}H_{25}IN_2O_2S$. Unit cell parameters: *a* = 9.8829(15), *b* = 10.3179(13), *c* = 14.554(2), *α* = 80.103(11), *β* = 72.103(13), *γ* = 68.283(13), space group *P-1*. The CCDC deposition number for compound **122** is 800160. Formula: $C_{23}H_{17}IN_2$. Unit cell parameters: *a* = 11.4798(19), *b* = 10.4089(15), *c* = 15.3963(18), *α* = 90.00, *β* = 91.647(12), *γ* = 90.00, space group *P-1*.

^{1}H NMR of 9-Ethyl-3-[4-methylphenyl(3-phenyl-2-propynyl)sulfonamido]-9*H*-carbazole (120a)



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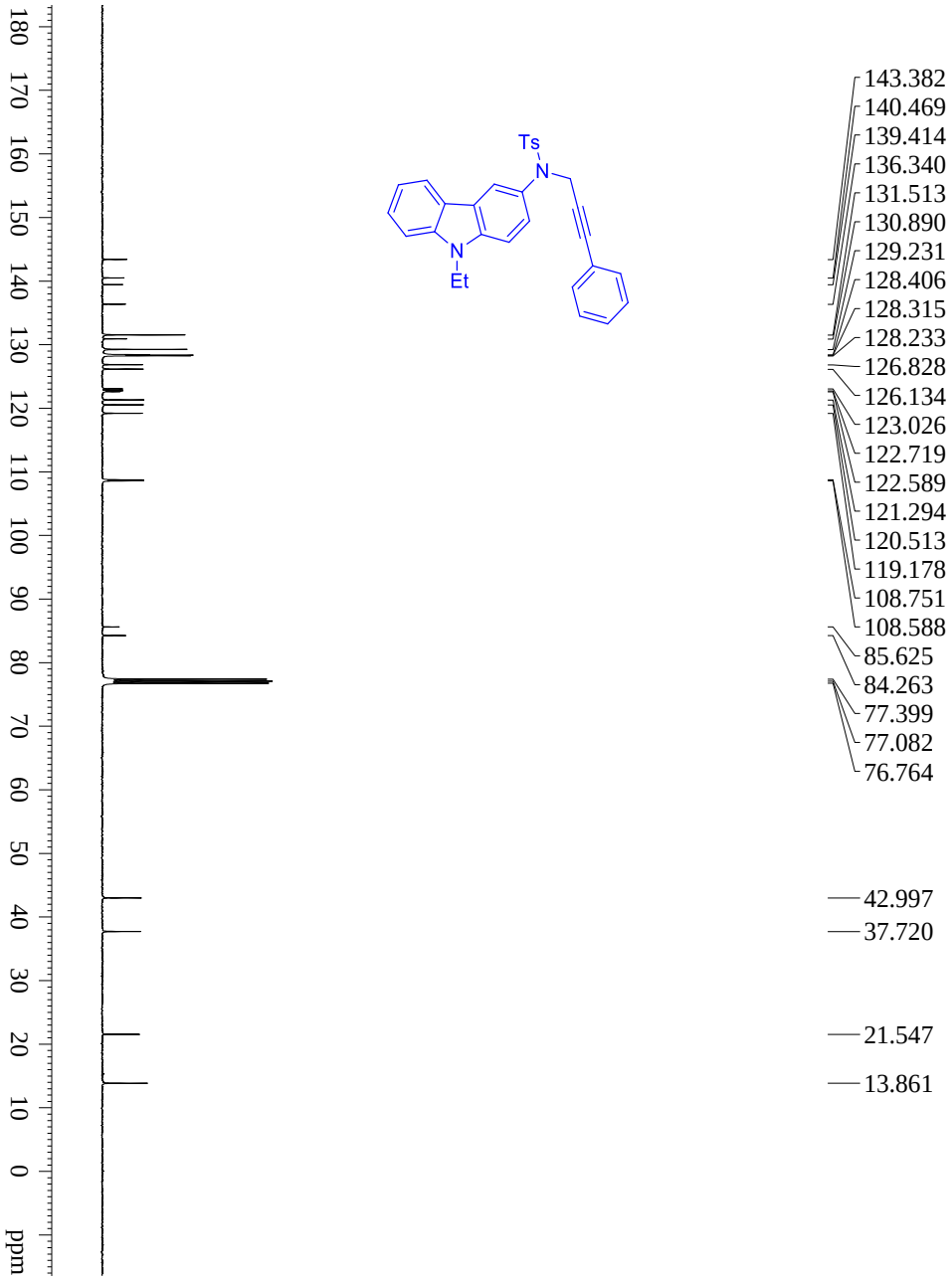

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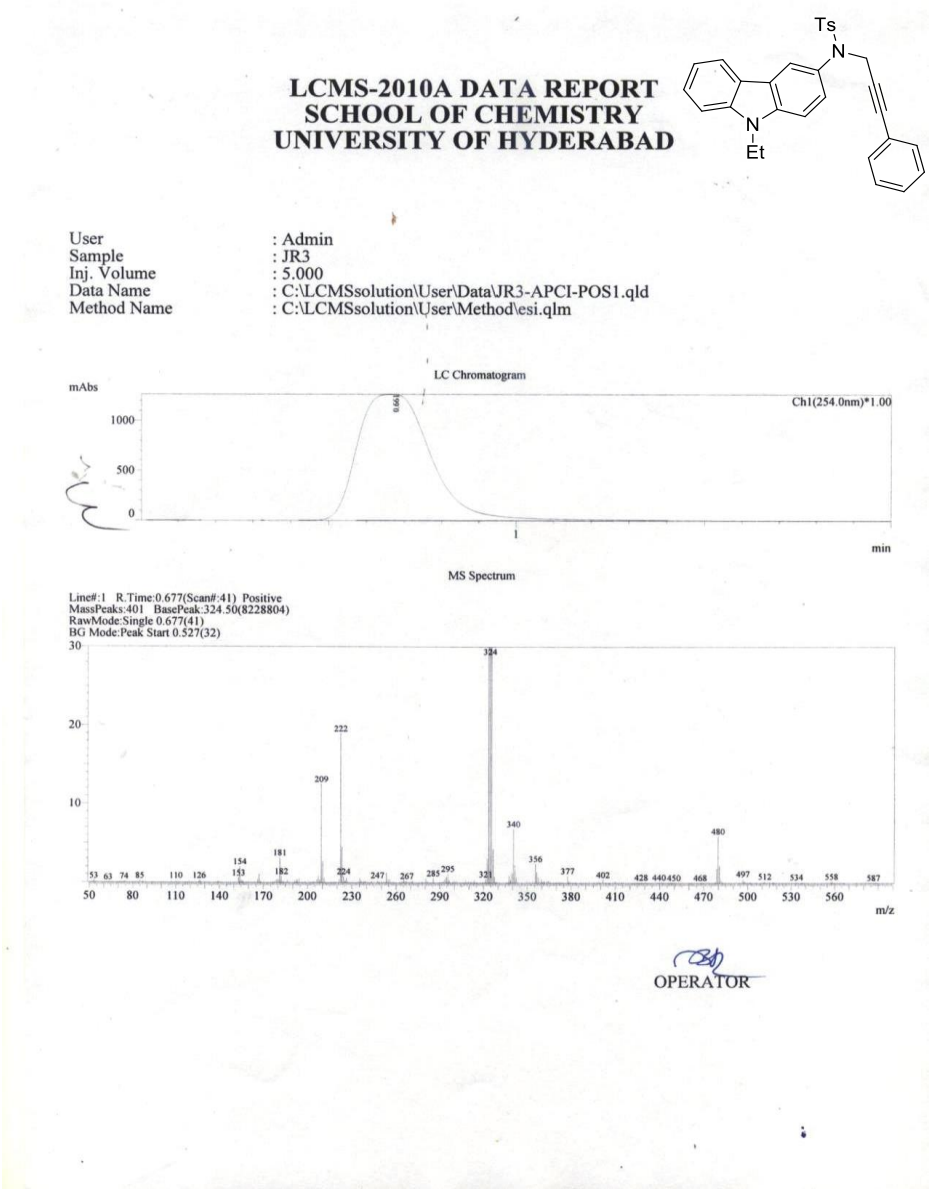

Elemental analysis of 9-Ethyl-3-[4-methylphenyl(3-phenyl-2-propynyl)sulfonamido]-9*H*-carbazole (120a)

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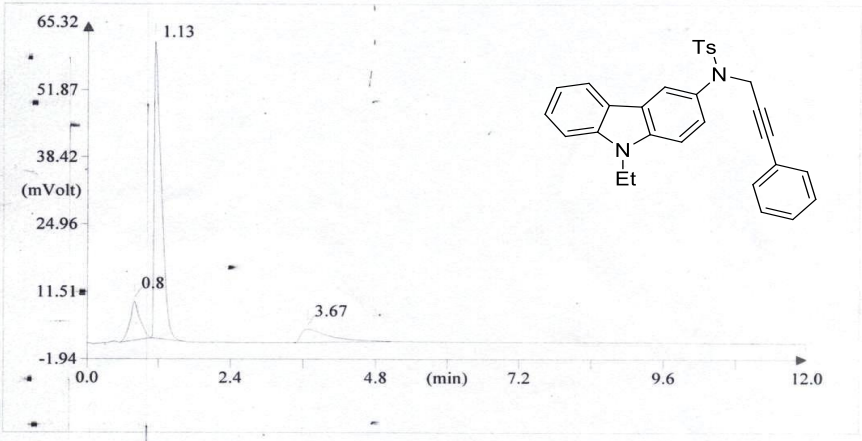
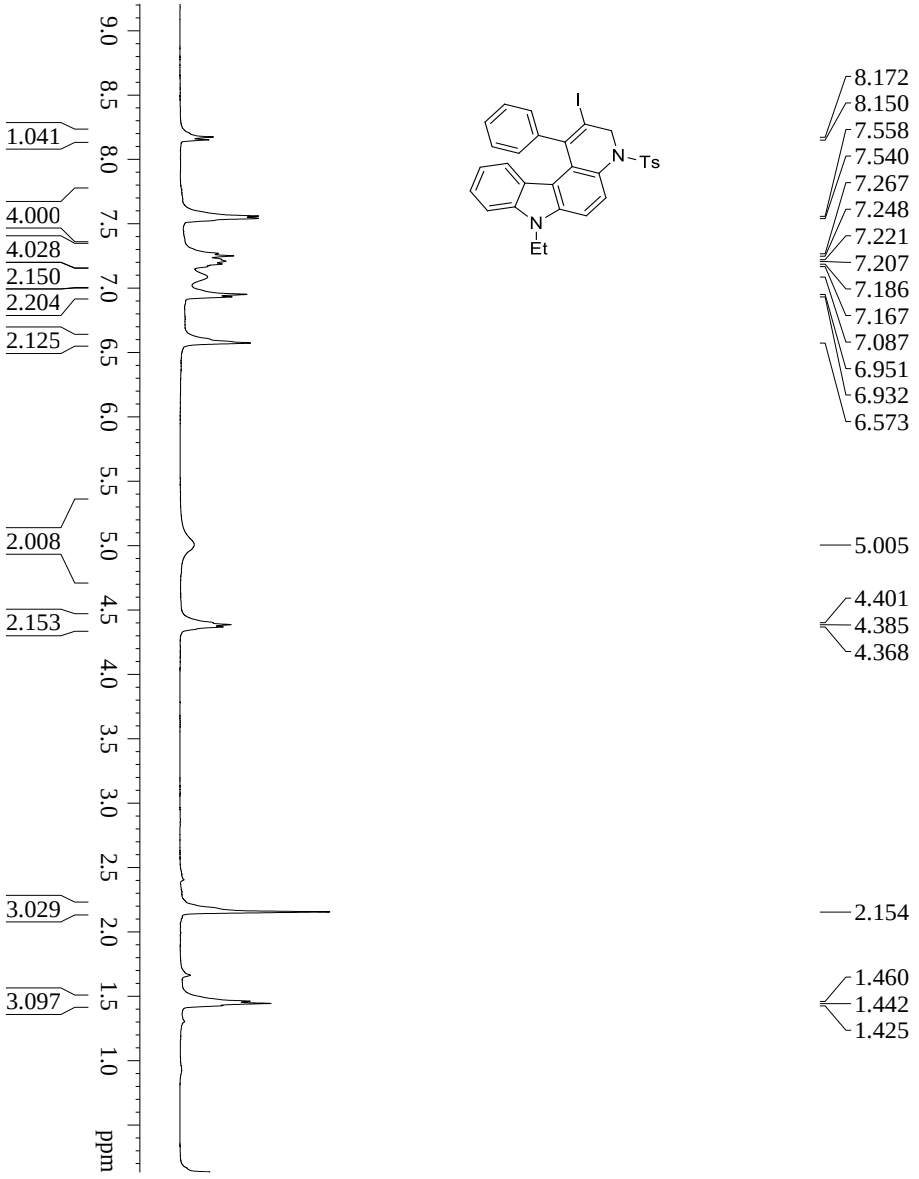


Element Name	Element %	Ret. Time
Nitrogen	5. 91	0. 80
Carbon	75. 12	1. 13
Hydrogen	5. 41	3. 67

^{1}H NMR of 7-Ethyl-2-iodo-(4-methylphenylsulfonyl)-1-phenyl-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121a)



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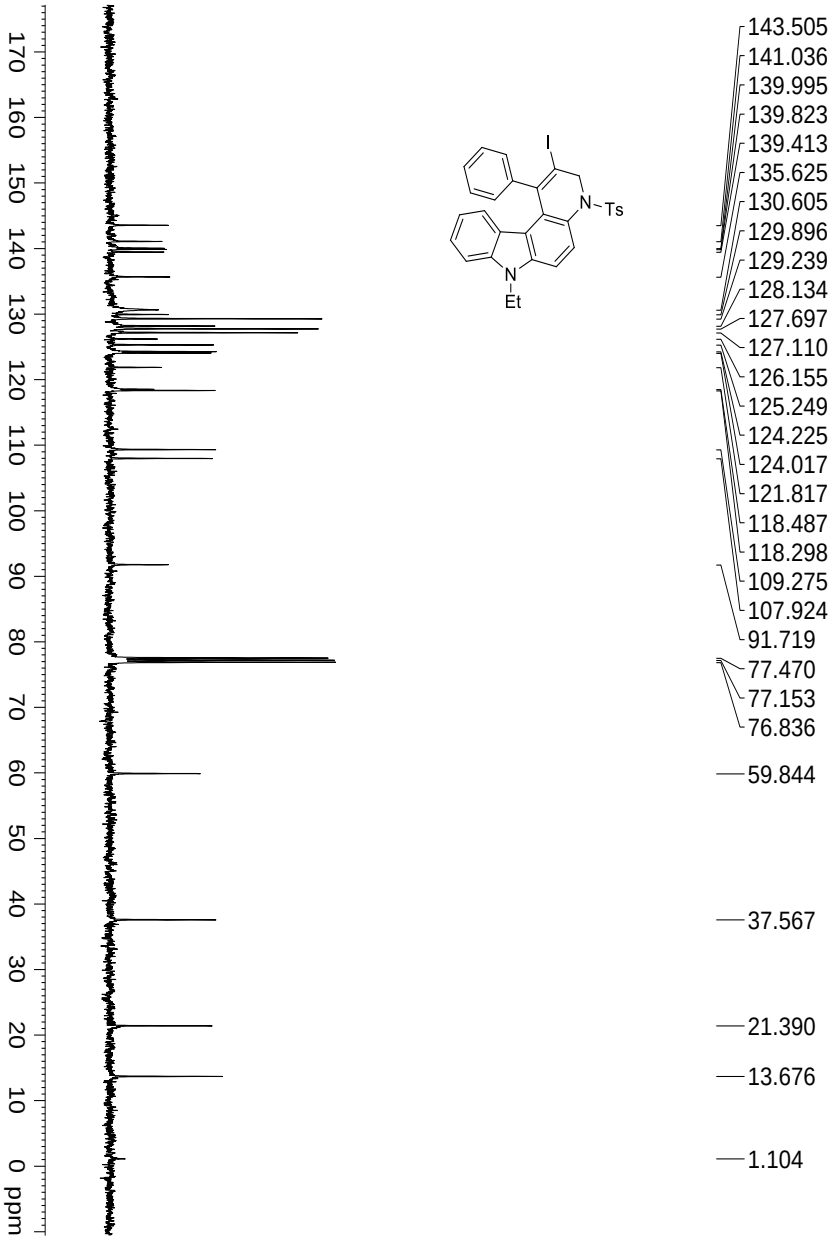
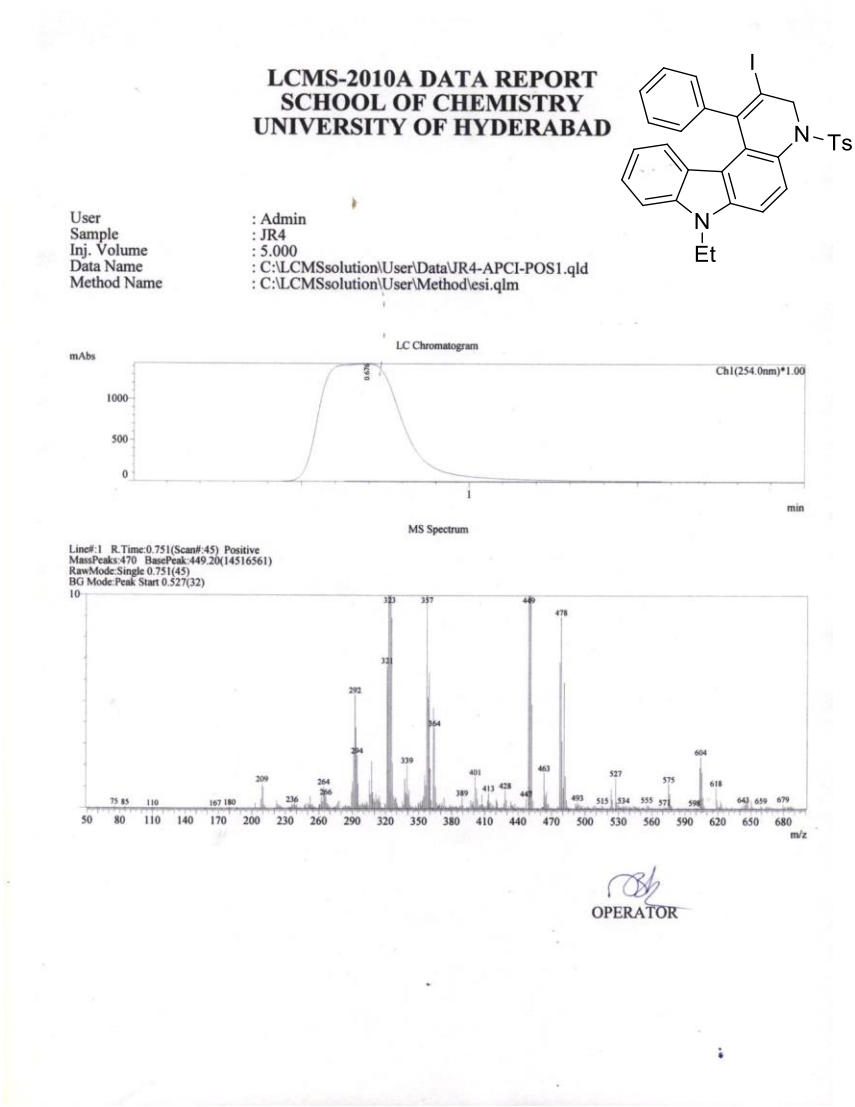


LC-MS of 7-Ethyl-2-iodo-(4-methylphenylsulfonyl)-1-phenyl-4,7-dihydro-3*H*-pyrido[2,3-*c*]carbazole (121a)



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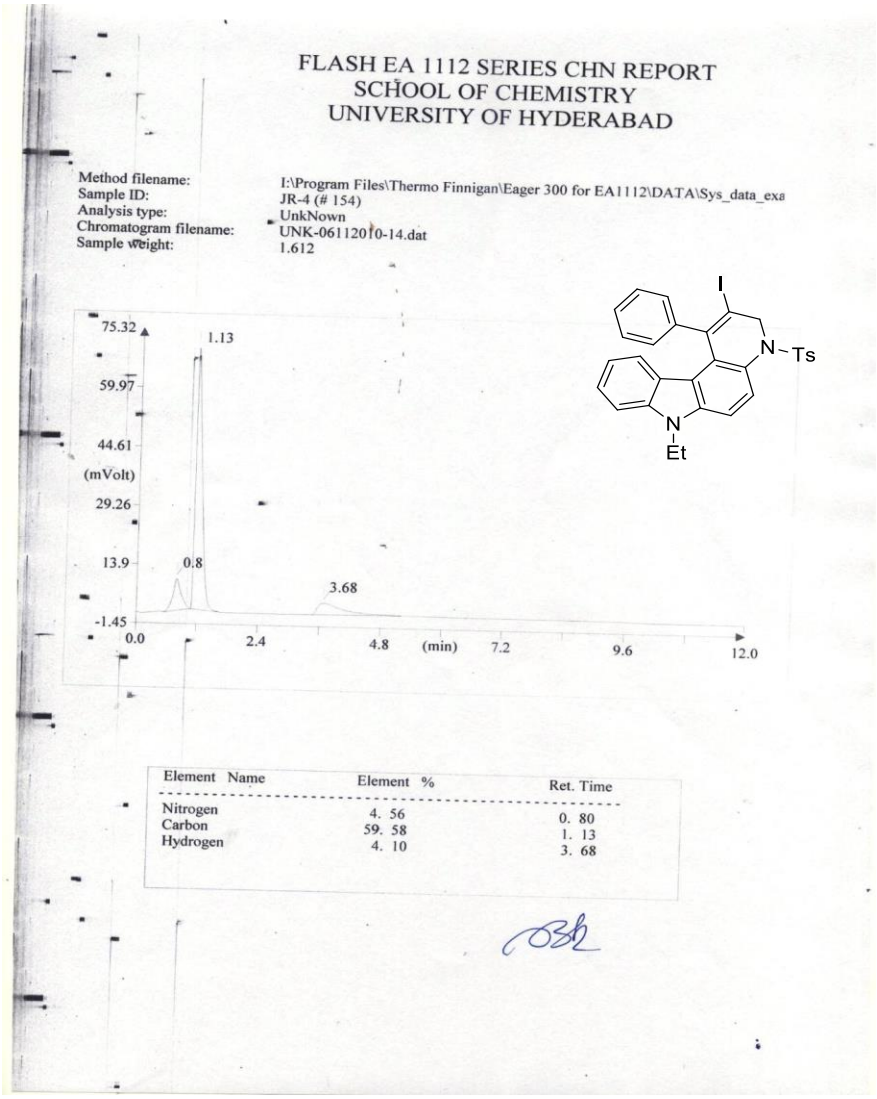

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Chromatogram filename: UNK-06112010-14.dat
Sample weight: 1.612

Element Name	Element %	Ret. Time
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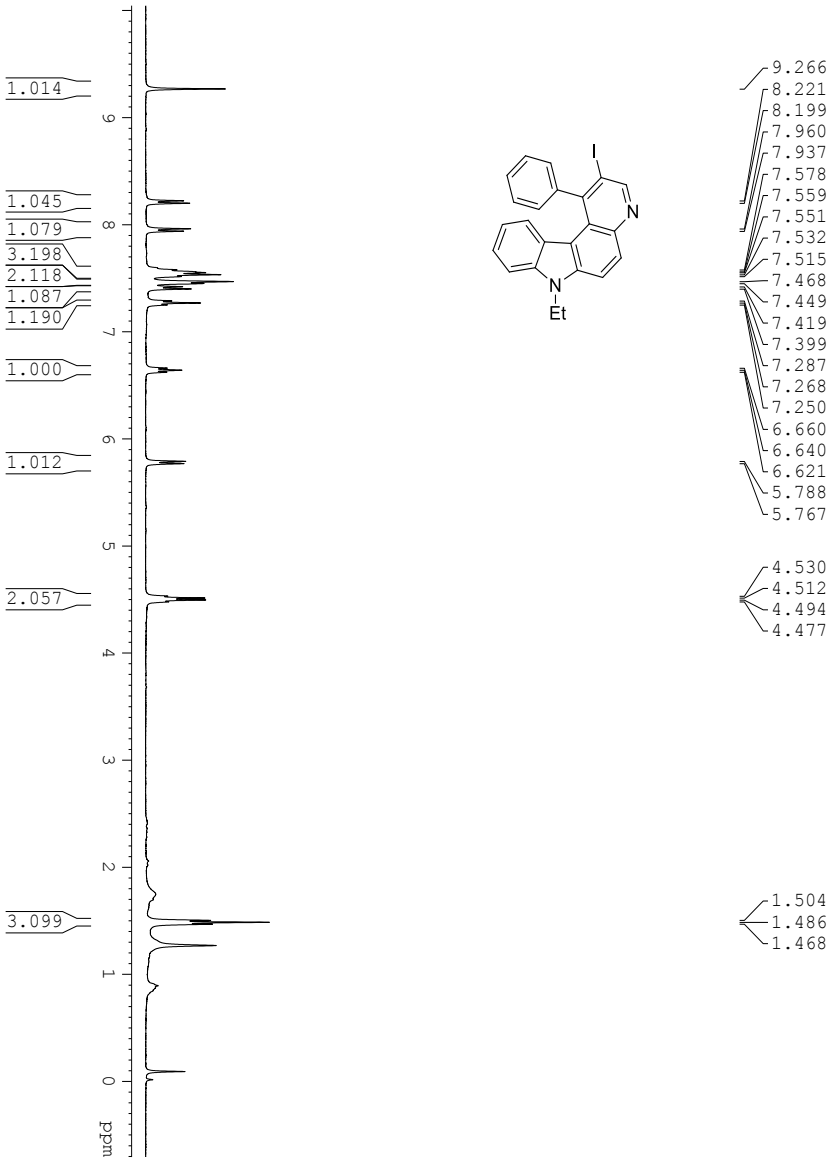
Carbon	59. 58	1. 13
Hydrogen	4. 10	3. 68

^{1}H NMR of 7-Ethyl-2-iodo-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (122)



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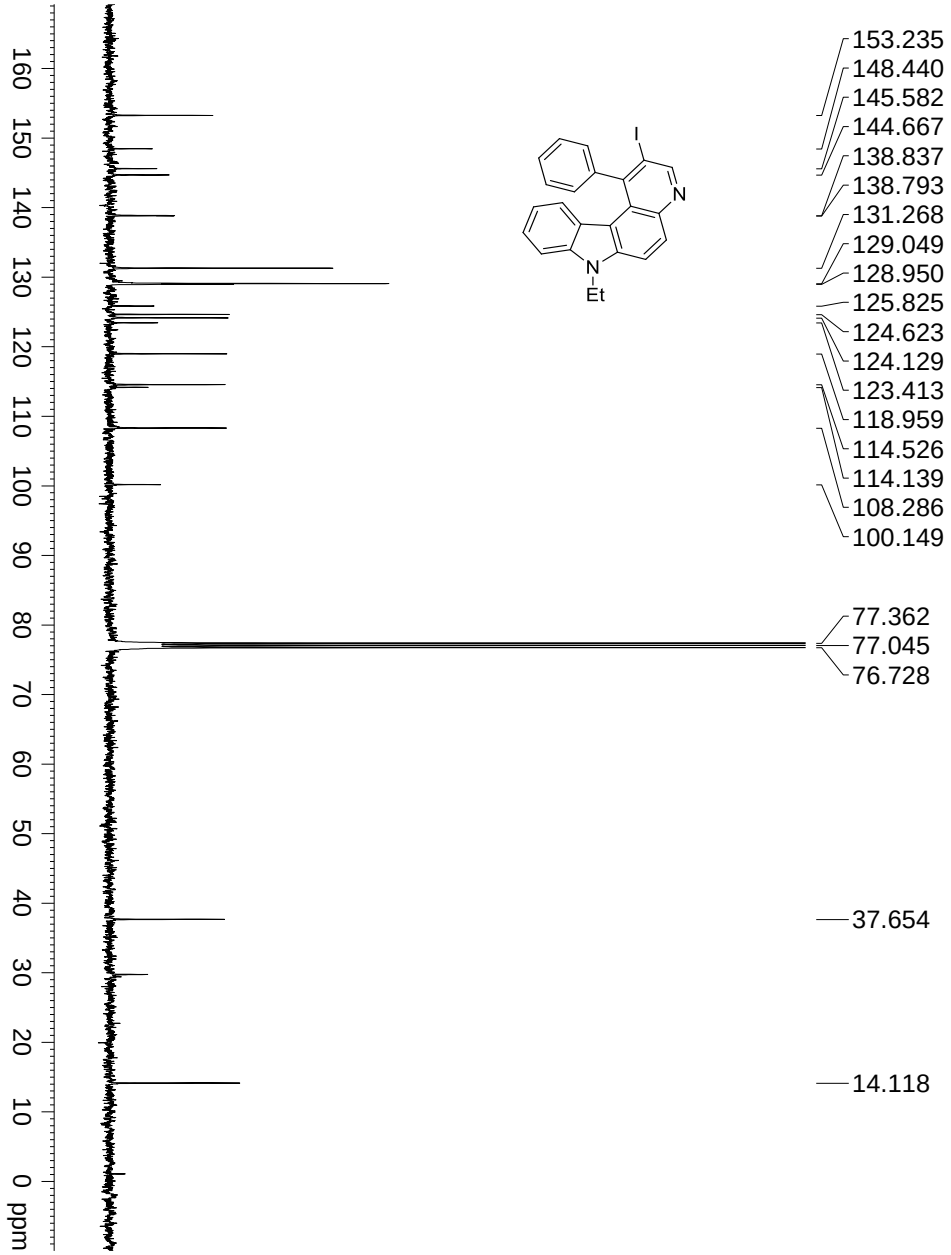

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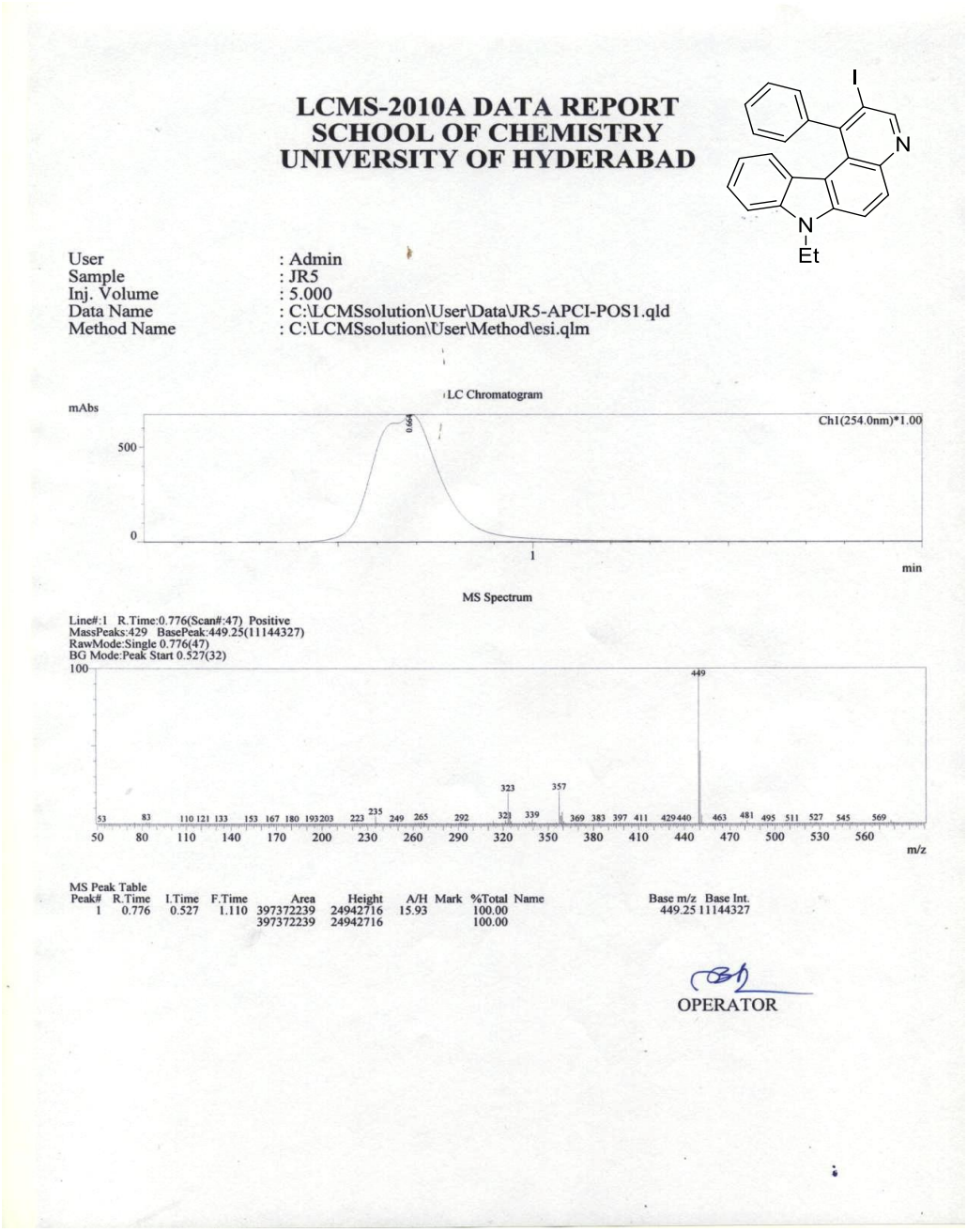

LCMS-2010A DATA REPORT
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Inj. Volume : 5.000
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LC Chromatogram

MS Spectrum

Line#:1 R.Time:0.776(Scan#:47) Positive
MassPeaks:429 BasePeak:449.25(11144327)
RawMode:Single 0.776(47)
BG Mode:Peak Start 0.527(32)

MS Peak Table

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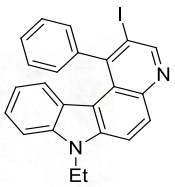
				397372239	24942716			100.00			

OPERATOR

Elemental analysis of 7-Ethyl-2-iodo-1-phenyl-7*H*-pyrido[2,3-*c*]carbazole (122)



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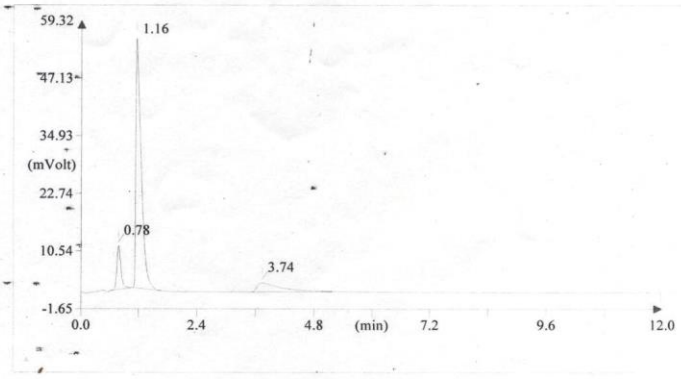


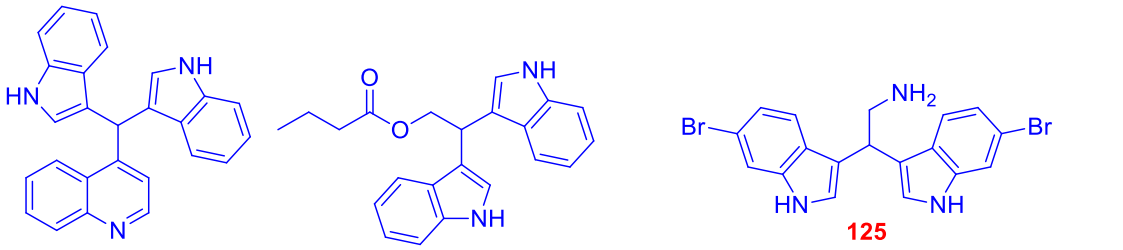
Element Name	Element %	Ret. Time
Nitrogen	6. 31	0. 78
Carbon	61. 52	1. 16
Hydrogen	3. 78	3. 74

Synthesis of Arsindoline A, Arsindoline B and their Analogues in Low Melting Mixture

CHAPTER 3

3.1 Introduction

Several bis(indolyl)methanes (BIMs) and their derivatives have been isolated and synthesized due to their wide applications in pharmaceuticals, agrochemicals and other areas of importance.[72,73] The most important BIMs were isolated from terrestrial and marine natural sorces.[74] These BIMs are utilized in cancer chemotherapy and inhibit bladder cancer growth, mammary tumor growth. These BIMs exhibits antibiotic, antifungal, antitumorigenic and anti-inflammatory activities.[75,76] These BIMs serve as inhibitors of the platelet-derived growth factor receptor kinase, induce apoptosis in prostate cancer, serve as cytodifferentiating agents, antiangiogenic agents, have inhibitory effects on Phenobarbital-induced hepatic CYP mRNA expression, have radical scavenging activity, growth promoting activity and also used as glass-forming high-triplet-energy materials. The oxidized form of BIMs utilized in dyes and calorimetric sensors.[77] Recently Gu and co-workers isolated two new indole alkaloids, arsindoline A and B (Fig 9) from a marine-derived bacterium strain CB101, identified as *Aeromonas sp*.[78] In literature, various methods have been reported for the synthesis of BIMs due to their vast biological activities and medicinal applications. The classical methods for the synthesis of BIMs includes the use of protic acids, such as HCl,[79a] H_2SO_4,[79b] $KHSO_4$,[79c] CH_3COOH[79d] and Lewis acids like $In(OTf)_3$,[80a] $Ln(OTf)_3$, some other catalysts CAN,[80b] I_2,[80c] as well as with ionic liquids[81], molten salts[82a] and eutectic salts[82b].



123, Arsindoline A

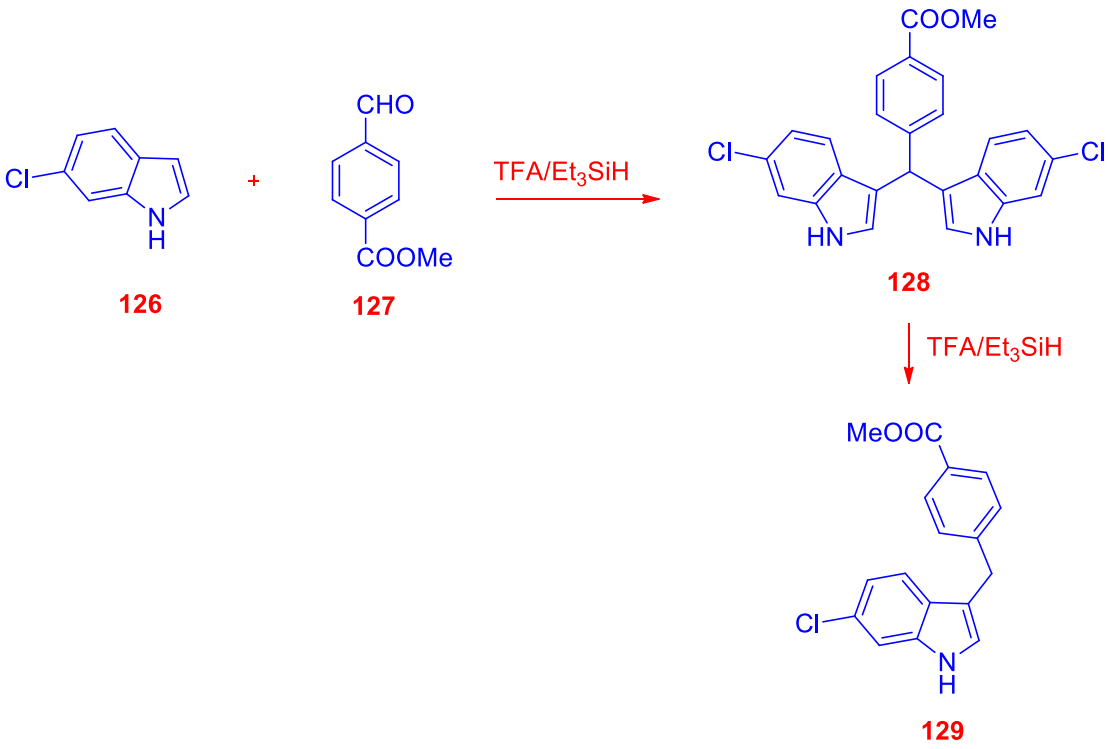
124, Arsindoline B

125
2,2-Bis(6-bromo-1*H*-indol-3-yl)ethanamine

Fig: 9

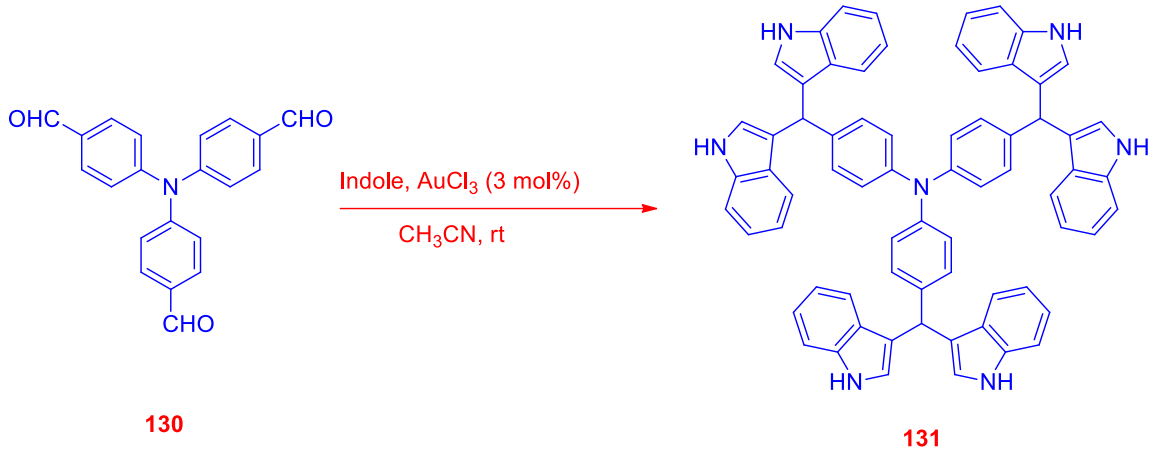
Mahadevan *et al*. have synthesized[83] bisindolylmethane **128** by the treatment of 6-chloroindole **126** with the corresponding aldehyde **127** in the presence of TFA/Et_3SiH. The obtained bisindolylmethane **128** was also reduced to product **129** in 60% yield under the similar reaction conditions as shown in **Eq. 18.**

Eq. 18



Nair *et al*. reported the synthesis of trimeric BIMs **131** by the reaction of tris[(4-formyl)phenyl]amine **130** with indole **52a** using $AuCl_3$ as catalyst in 35% yield (**Eq. 19**). This method is also sufficient for the condensation of other aldehydes and activated arenes such as 1,3,5-trimethoxybenzene, substituted indoles, 2-methyl thiophene, and 2-methylfurane.[84]

Eq. 19

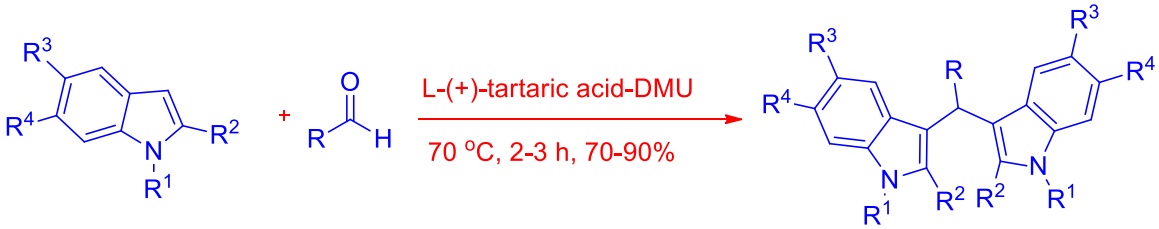


130 131

3.2 Synthesis of arsindoline A, arsindoline B and their analogues in low melting mixture

Considering pharmalogical as well as biological properties, as we have observed in the above literature reports, a careful analysis of literature disclosed that very less number of reports were available for the synthesis of these alkaloids. Therefore, we developed a synthetic methodology for the preparation of arsindoline alkaloids. Herein, we wish to report the synthesis of arsindoline derivatives starting with different substituted indoles in low melting mixture as shown in Scheme 8.

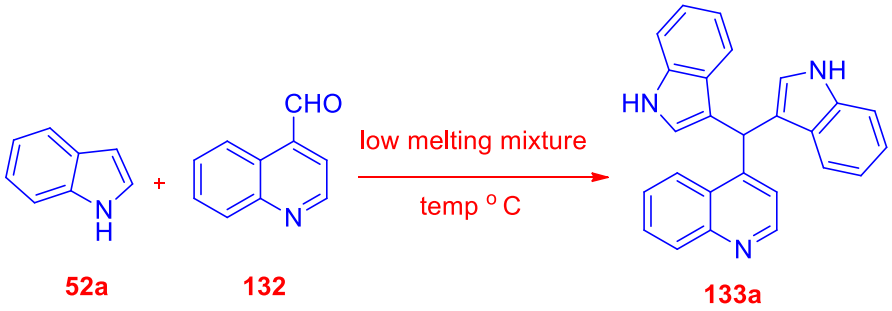
Scheme 8. Synthesis of arsindoline A, arsindoline B and its derivatives



R^1, R^2, R^3, R^4 = H, R = quinoline, Arsindoline A
R^1, R^2, R^3, R^4 = H, R = methyl butyrate, Arsindoline B

We initially examined the reaction of indole and quinoline-4-aldehyde in low melting mixture having organic acid as one of the melt components. We have chosen citric acid-dimethyl urea (DMU) (40:60) melt as reaction medium for the reaction of two equivalents of indole **52a** and one equivalent of quinoline-4-aldehyde **132**, obtained the product in good yield (entry 1, table 7). In order to optimize the reaction condition, we carried out the same reaction in various low melting mixtures and the results are summarized in table 7. We found that L-(+)-tartaric acid-dimethyl urea melt is the best reaction medium in terms of reaction time and yield (Scheme 9).

Table 7. Synthesis of arsindoline A in various melts[a]

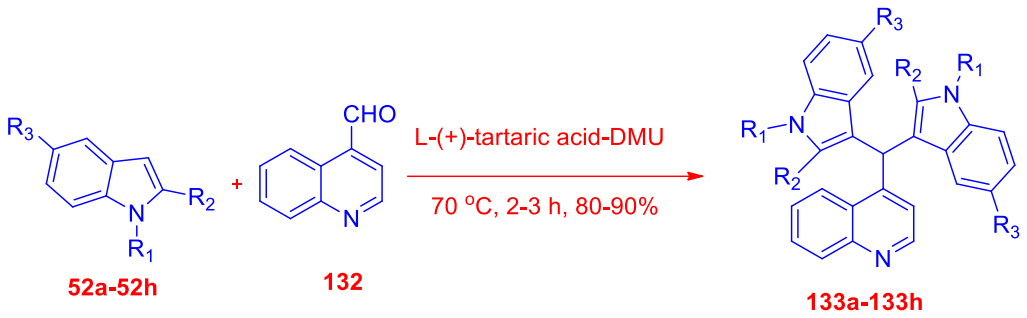


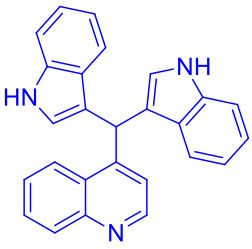
52a 132 133a

Entry	Melt	Temp (° C)	Time (h)	Yield (%)
1	Citric acid-DMU 40:60	65	3	78
2	**L-(+)-Tartaric acid-DMU 30:70**	**70**	**2**	**90**
3	L-(-)-Malic acid-DMU 30:70	80	3	72
4	L-Ascorbic acid-DMU 30:70	90	4	64

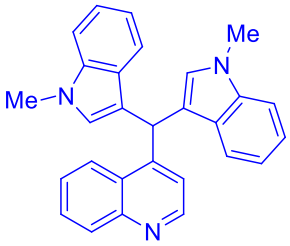
[a] Reaction conditions: indole (2 mmol), quinoline-4-aldehyde (1 mmol) in melt (1.5 g).

Scheme 9. Synthesis of arsindoline A and its derivatives

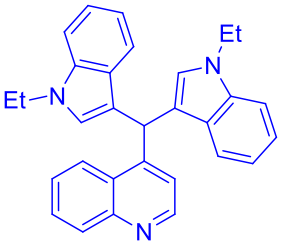




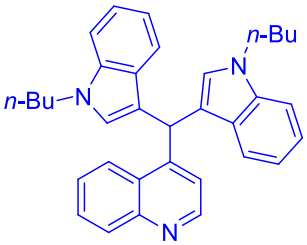
133a, 2 h, 90 %



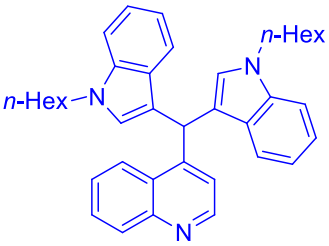
133b, 2 h, 88 %



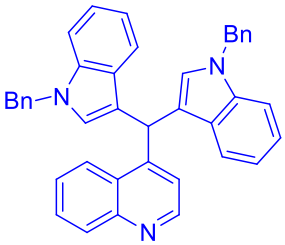
133c, 2 h, 86%



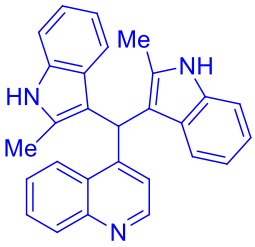
133d, 2 h, 86%



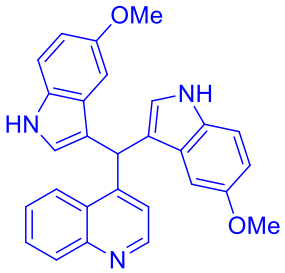
133e, 2 h, 85%



133f, 2 h, 80%



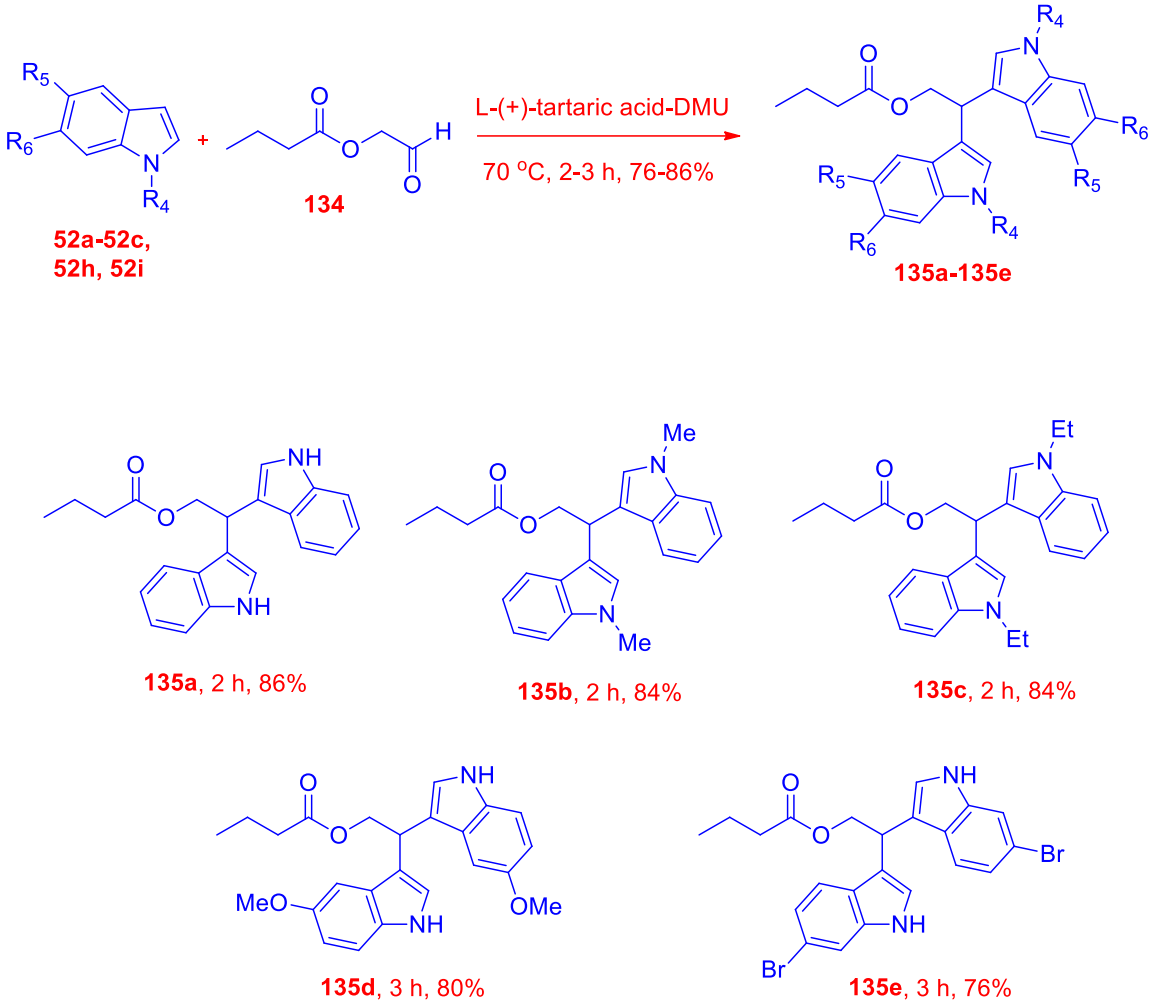
133g, 3 h, 82%



133h, 2 h, 85%

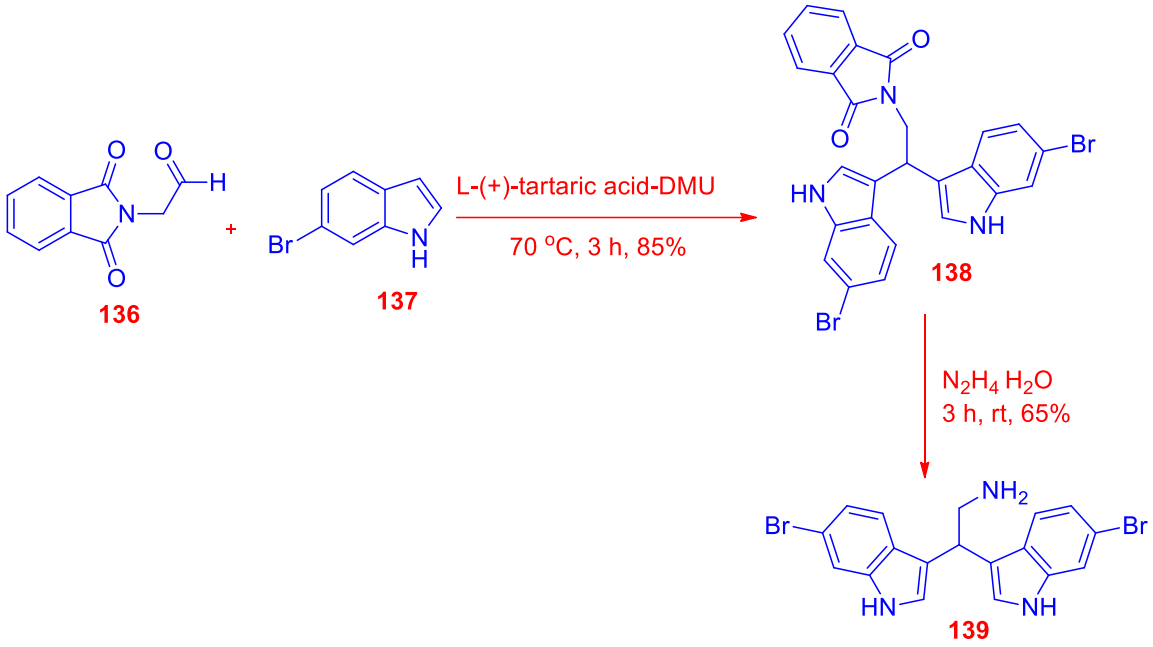
We then focused on the synthesis of arsindoline B using low melting mixture. The required aldehyde, 2-oxoethyl butyrate **134** was prepared using literature report.[85] With starting materials in hand, we initiated the synthesis of arsindoline B by taking two equivalents of indole **52a** and one equivalent of 2-oxoethyl butyrate **134** using L-(+)-tartaric acid-dimethyl urea melt as reaction medium. The reaction went smoothly and the product was obtained in good yield. We further prepared various analogues of arsindoline B by varying the different *N*-substituted indoles and substituted indoles as shown in scheme 10.

Scheme 10. Synthesis of arsindoline B and its derivatives



In continuation we have applied the low melting mixture reaction strategy for the synthesis of another alkaloid 2,2-di(6-bromo-3-indolyl)ethylamine in scheme 11. Following the literature report[86] we have prepared 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde **136** treated with 6-bromo indole **137** in L-(+)-tartaric acid-dimethyl urea melt at 70 °C, afforded product **138** in good yield. The deprotection step using reported procedure[86] afforded the final product **139** (Scheme 11).

Scheme 11. Synthesis of 2,2-di(6-bromo-3-indolyl)ethylamine



3.3 Conclusions

In summary we have developed a efficient method for the synthesis of arsindoline A, arsindoline B and 2,2-di(6-bromo-3-indolyl)ethylamine in low melting mixture. The reaction is simple, non-toxic and occurs in environmentally benign conditions with good yields. The melt medium acts as catalyst as well as solvent in the reaction.

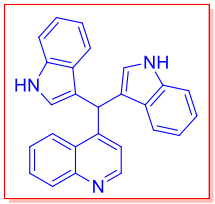
3.4 Experimental Section

General procedure for the synthesis of BIMs in low melting mixtures

In a typical experiment, 1.5 g of L-(+)-tartaric acid–DMU (30 : 70) was heated to 70 °C to obtain a clear melt. To this melt, 1.0 mmol of aldehyde and 2.0 mmol of indole were added at 70 °C. The reaction was monitored by thin layer chromatography. When the reaction was complete, water (10 mL) was added to quench the reaction and extracted with CH_2Cl_2 (30 mL). The combined organic layers were dried using anhydrous Na_2SO_4, filtered and the solvent evaporated. The crude products were purified by column chromatography and eluted with ethyl acetate and hexane mixture to afford the products.

4-(Di(1*H*-indol-3-yl)methyl)quinoline (133a) :

The product **133a** was obtained as colorless solid through column chromatography using a mixture of 50% ethyl acetate and hexanes as described in general procedure.



Yield: 90 %

Mp: 164-168 °C

IR (KBr) ν_{max} cm^{-1} : 3405, 3054, 2971, 1618, 1589, 1508, 1456, 1340, 1089, 738.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.74 (1H, d, J = 4.4 Hz); 8.23 (2H, br s); 8.16 (2H, d, J = 8.8 Hz); 7.67 (1H, t, J = 7.6 Hz); 7.45-7.36 (5H, m); 7.22-7.15 (3H, m); 7.03 (2H, t, J = 7.6 Hz); 6.66 (1H, s); 6.55 (2H, br s)

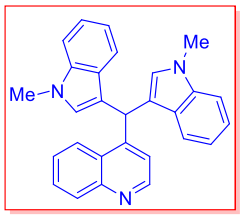
^{13}C NMR (100 MHz, $CDCl_3$) : δ 150.3, 149.8, 148.3, 136.7, 129.8, 129.0, 127.3, 126.7o, 126.5, 124.4, 124.2, 122.2, 121.0, 119.4, 117.5, 111.3, 35.5

HRMS (ESI-MS) of $C_{26}H_{19}N_3$: 374.1657 $(M+H)^+$ positive mode

Found: 374.1656

4-(Bis(1-methyl-1*H*-indol-3-yl)methyl)quinoline (133b) :

The product **133b** was obtained as colorless solid through column chromatography using a mixture of 20% ethyl acetate and hexanes as described in general procedure.



Yield: 88 %

Mp: 238-242 °C

IR (KBr) ν_{max} cm^{-1}: 3120, 3047, 2964, 1619, 1593, 1500, 1469, 1381, 1200, 755.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (1H, d, J = 4.8 Hz); 8.19 (2H, d, J = 8.8 Hz); 7.70 (1H, t, J = 7.6 Hz); 7.46 (1H, t, J = 7.8 Hz); 7.40-7.33 (4H, m); 7.27-7.24 (2H, m); 7.20 (1H, d, J = 4.8 Hz); 7.04 (2H, t, J = 7.6 Hz); 6.68 (1H, s); 6.48 (2H, s); 3.68 (6H, s)

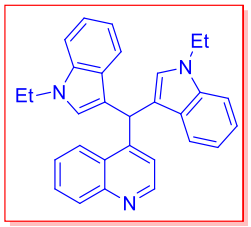
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 149.9, 148.5, 137.4, 130.1, 128.9, 127.3, 127.1, 126.5, 124.2, 121.7, 120.9, 119.6, 118.9, 116.2, 109.3, 35.3, 32.7

HRMS (ESI-MS) of $C_{28}H_{23}N_3$: 402.1970 $(M+H)^+$ positive mode

Found: 402.1970

4-(Bis(1-ethyl-1*H*-indol-3-yl)methyl)quinoline (133c) :

The product **133c** was obtained as colorless solid through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.



Yield: 86 %

Mp: 228-232 °C

IR (KBr) ν_{max} cm^{-1}: 3419, 3117, 2969, 2865, 1594, 1441, 1013, 1013, 756, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (1H, d, *J* = 4.8 Hz); 8.18 (2H, d, *J* = 8.4 Hz); 7.72-7.68 (1H, m); 7.47-7.43 (1H, m); 7.38-7.36 (4H, m); 7.25- 7.19 (3H, m); 7.04-7.0 (2H, m); 6.67 (1H, s); 6.53 (2H, s); 4.06 (4H, q, *J* = 7.2 Hz); 1.36 (6H, t, *J* = 7.2 Hz)

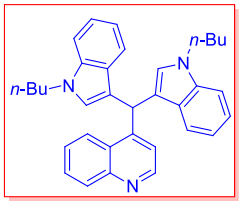
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 150.0, 148.5, 136.4, 130.0, 128.9, 127.4, 127.3, 126.4, 124.2, 121.5, 121.0, 119.8, 118.8, 116.2, 109.4, 40.9, 35.5, 15.5

HRMS (ESI-MS) of $C_{30}H_{27}N_3$: 430.2283 $(M+H)^+$ positive mode

Found: 430.2283

4-(Bis(1-butyl-1*H*-indol-3-yl)methyl)quinoline (133d) :

The product **133d** was obtained as colorless solid through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.



Yield: 86 %

Mp: 157-161 °C

IR (KBr) ν_{max} cm^{-1}: 3397, 3041, 2953, 2876, 1600, 1463, 1326, 1156, 1013, 767

^{1}H NMR (400 MHz, $CDCl_3$): 8.78 (1H, d, *J* = 4.0 Hz); 8.18-8.15 (2H, m); 7.71-7.67 (1H, m); 7.46-7.36 (5H, m); 7.27-7.18 (3H, m); 7.03-6.99 (2H, m); 6.66 (1H, s); 6.49 (2H, s); 4.00 (4H, t, *J* = 4.0 Hz); 1.72 (4H, quintet, *J* = 8.0 Hz); 1.23 (4H, sextet, *J* = 8.0 Hz); 0.87 (6H, t, *J* = 8.0 Hz)

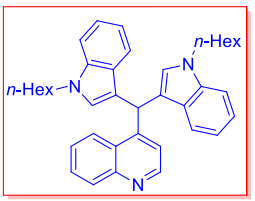
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 150.0, 148.4, 136.7, 130.0, 128.8, 128.1, 127.4, 127.2, 126.3, 124.3, 121.5, 121.0, 119.8, 118.8, 116.0, 109.5, 46.0, 35.6, 32.2, 20.0, 13.6

HRMS (ESI-MS) of $C_{34}H_{35}N_3$: 486.2909 $(M+H)^+$ positive mode

Found: 486.2908

4-(Bis(1-hexyl-1*H*-indol-3-yl)methyl)quinoline (133e) :

The product **133e** was obtained as colorless solid through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.



Yield: 85 %

Mp: 128-132 °C

IR (KBr) ν_{max} cm^{-1}: 3452, 3041, 2953, 2931, 1600, 1353, 1178, 1156, 739

^{1}H NMR (400 MHz, $CDCl_3$): 8.78 (1H, d, *J* = 4.0 Hz); 8.17 (2H, d, *J* = 8.0 Hz); 7.69 (1H, t, *J* = 8.0 Hz); 7.44 (1H, t, *J* = 8.0 Hz); 7.39-7.36 (4H, m); 7.27-7.18 (3H, m); 7.01 (2H, t, *J* = 6.0 Hz); 6.66 (1H, s); 6.50 (2H, s); 3.99 (4H, t, *J* = 6.0 Hz); 1.75-1.72 (4H, m); 1.22 (12H, br s); 0.84-0.83 (6H, m)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 150.5, 150.0, 148.5, 136.6, 130.0, 128.8, 128.0, 127.4, 127.2, 126.3, 124.3, 121.5, 120.9, 119.7, 118.8, 116.0, 109.5, 46.3, 35.5, 31.3, 30.0, 26.5, 14.0

HRMS (ESI-MS) of $C_{38}H_{43}N_3$: 542.3535 $(M+H)^+$ positive mode

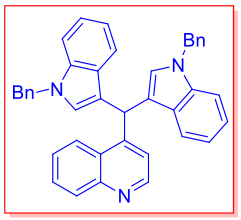
Found: 542.3539

4-(Bis(1-benzyl-1*H*-indol-3-yl)methyl)quinoline (133f) :

The product **133f** was obtained as colorless solid through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.

Yield: 80 %

Mp: 104-108 °C



IR (KBr) ν_{max} cm^{-1}: 3128, 3041, 2120, 1589, 1463, 1326, 1068, 887, 778, 745

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.79 (1H, d, *J* = 4.8 Hz); 8.18 (2H, t, *J* = 7.2 Hz); 7.73-7.69 (1H, m); 7.49-7.42 (3H, m); 7.28-7.26 (3H,

m); 7.25-7.16 (8H, m); 7.05-6.99 (6H, m); 6.71 (1H, br s); 6.61 (2H, s); 5.21 (4H, s)

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 149.5, 148.5, 137.6, 137.1, 130.1, 128.9, 128.7, 128.6, 127.4, 126.4, 124.3, 122.0, 121.0, 119.8, 119.3, 116.8, 109.9, 49.9, 35.7

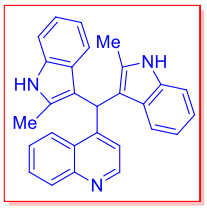
HRMS (ESI-MS) of $C_{40}H_{31}N_3$: 554.2596 $(M+H)^+$ positive mode

Found: 554.2595

4-(Bis(2-methyl-1*H*-indol-3-yl)methyl)quinoline (133g) :

The product **133g** was obtained as colorless solid through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.

Yield: 82 %



Mp: 228-232 °C

IR (KBr) ν_{max} cm^{-1}: 3397, 3057, 2969, 2876, 1594, 1419, 1150, 1013, 772, 745

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (1H, d, J = 4.0 Hz); 8.14 (1H, d, J = 8.0 Hz); 7.99 (1H, d, J = 8.0 Hz); 7.85 (2H, s); 7.67-7.63 (1H, m); 7.36 (1H, t, J = 6.0 Hz); 7.28-7.26 (2H, m); 7.19 (1H, d, J = 4.0 Hz); 7.08-7.04 (4H, m); 6.87 (2H, t, J = 8.0 Hz); 6.60 (1H, s); 1.94 (6H, s)

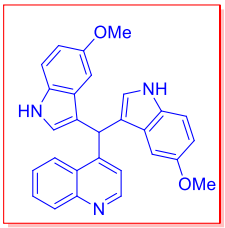
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 150.0, 147.9, 135.1, 132.5, 129.6, 128.7, 128.5, 127.7, 126.2, 124.2, 121.5, 120.2, 118.6, 118.2, 110.9, 110.3, 36.1, 12.1

HRMS (ESI-MS) of $C_{28}H_{23}N_3$: 402.1971 $(M+H)^+$ positive mode

Found: 402.1969

4-(Bis(5-methoxy-1*H*-indol-3-yl)methyl)quinoline (133h) :

The product **133h** was obtained as colorless solid through column chromatography using a mixture of 50% ethyl acetate and hexanes as described in general procedure.



Yield: 85 %

Mp: 132-136 °C

IR (KBr) ν_{max} cm^{-1}: 3452, 3041, 2953, 2854, 1600, 1468, 1355, 1178, 1156, 739

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75-8.74 (1H, m); 8.16-8.15 (4H, m); 7.68-7.64 (1H, m); 7.45-7.42 (1H, m); 7.27-7.24 (2H, m); 7.17-7.16 (1H, m); 6.88-6.85 (2H, m); 6.80 (2H, br s); 6.55-6.53 (3H, m); 3.68 (6H, d, J = 2.0 Hz)

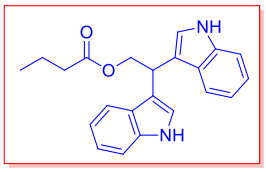
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 150.3, 149.5, 148.4, 131.9, 129.9, 128.9, 127.4, 127.1, 126.5, 125.2, 124.2, 120.9, 117.1, 112.0, 111.9, 101.5, 55.9, 35.6

HRMS (ESI-MS) of $C_{28}H_{23}N_3O_2$: 434.1869 $(M+H)^+$ positive mode

Found: 434.1871

2,2-Bis(1*H*-indol-3-yl)ethyl butyrate (135a) :

The product **135a** was obtained as colorless oil through column chromatography using a mixture of 20% ethyl acetate and hexanes as described in general procedure.



Yield: 86 %

IR (KBr) ν_{max} cm^{-1}: 3408, 3052, 2964,1720, 1616, 1452, 1342, 1183, 1095, 1008, 739

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, br s); 7.64 (2H, d, J = 8.0 Hz); 7.35 (2H, d, J = 8.4 Hz); 7.19 (2H, t, J = 7.4 Hz); 7.08 (2H, t, J = 7.6 Hz); 6.97 (2H, s); 4.96 (1H, t, J = 7.0 Hz); 4.76

(2H, d, *J* = 7.2 Hz); 2.23 (2H, t, *J* = 7.8 Hz); 1.59-1.54 (2H, m); 0.85 (3H, t, *J* = 7.4 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 173.9, 136.4, 127.0, 122.1, 122.0, 119.5, 119.3, 116.3, 111.1, 67.0, 36.2, 33.6, 18.3, 13.6

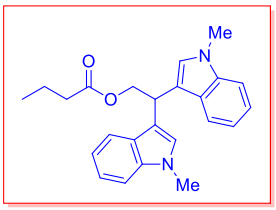
HRMS (ESI-MS) of $C_{22}H_{22}N_2O_2$: 369.1579 $(M+H)^+$ positive mode

Found: 369.1575

2,2-Bis(1*H*-indol-3-yl)ethyl butyrate (135b) :

The product **135b** was obtained as colorless oil through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.

Yield: 84 %



IR (KBr) ν_{max} cm^{-1}: 3046, 2964, 2871, 1731, 1610, 1550, 1331, 1090, 991, 739

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.70 (2H, d, *J* = 8.0 Hz); 7.34 (2H, d, *J* = 8.4 Hz); 7.27 (2H, t, *J* = 7.6 Hz); 7.12 (2H, t, *J* = 7.2 Hz); 6.91 (2H, s); 5.00 (1H, t, *J* = 7.2 Hz); 4.77 (2H, d, *J* = 7.2 Hz); 3.75 (6H, s); 2.27 (2H, t, *J* = 7.2 Hz); 1.67-1.57 (2H, m); 0.90 (3H, t, *J* = 7.4 Hz)

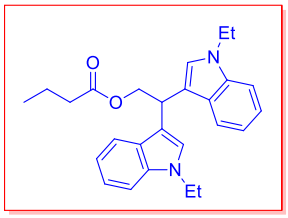
^{13}C NMR (100 MHz, $CDCl_3$): *δ* 173.9, 137.2, 127.5, 126.9, 121.5, 119.7, 118.8, 114.9, 109.2, 67.3, 36.2, 33.5, 32.7, 18.3, 13.6

HRMS (ESI-MS) of $C_{24}H_{26}N_2O_2$: 397.1892 $(M+H)^+$ positive mode

Found: 397.1892

2,2-Bis(1*H*-indol-3-yl)ethyl butyrate (135c) :

The product **135c** was obtained as colorless oil through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.



Yield: 84 %

IR (KBr) ν_{max} cm^{-1}: 3052, 2964, 2876, 1736, 1610, 1353, 1090, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (2H, d, *J* = 8.0 Hz); 7.40 (2H, d, *J* = 8.4 Hz); 7.28 (2H, t, *J* = 7.2 Hz); 7.14 (2H, t, *J* = 7.4 Hz); 7.02 (2H, s); 5.05 (1H, t, *J* = 7.0 Hz); 4.83 (2H, d, *J* = 7.2 Hz); 4.16 (4H, q, *J* = 7.2 Hz); 2.31 (2H, t, *J* = 7.4 Hz); 1.70-1.60 (2H, m); 1.48 (6H, t, *J* = 7.2 Hz); 0.93 (3H, t, *J* = 7.4 Hz)

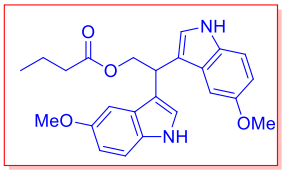
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 136.3, 127.7, 125.3, 121.4, 119.9, 118.7, 115.0, 109.3, 67.3, 40.9, 36.3, 33.7, 18.4, 15.5, 13.6

HRMS (ESI-MS) of $C_{26}H_{30}N_2O_2$: 403.2385 $(M+H)^+$ positive mode

Found: 403.2385

2,2-Bis(5-methoxy-1*H*-indol-3-yl)ethyl butyrate (135d) :

The product **135d** was obtained as colorless oil through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.



Yield: 80 %

IR (KBr) ν_{max} cm^{-1}: 3413, 2958, 2832, 1720, 1632, 1210, 1035, 800

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (2H, br s); 7.23 (2H, d, *J* = 8.8 Hz); 7.08 (2H, s); 6.95 (2H, s); 6.85-6.82 (2H, m); 4.84 (1H, t, *J* = 7.0 Hz); 4.72 (2H, d, *J* = 7.2 Hz); 3.78 (6H, s); 2.22 (2H, t, *J* = 7.4 Hz); 1.61-1.51 (2H, m); 0.84 (3H, t, *J* = 7.4 Hz)

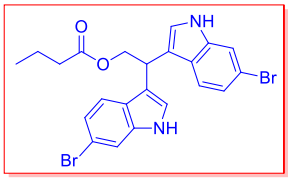
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 153.8, 131.6, 127.4, 123.0, 115.8, 112.0, 111.8, 101.4, 66.9, 55.9, 36.3, 33.6, 18.4, 13.5

HRMS (ESI-MS) of $C_{24}H_{26}N_2O_4$: 429.1791 $(M+H)^+$ positive mode

Found: 429.1792

2,2-Bis(6-bromo-1*H*-indol-3-yl)ethyl butyrate (135e) :

The product **135e** was obtained as colorless oil through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in general procedure.



Yield: 76 %

IR (KBr) ν_{max} cm^{-1}: 3419, 2958, 2876, 1715, 1621, 1545, 1260, 1095, 805, 734

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (2H, br s); 7.50 (2H, s); 7.41 (2H, d, *J* = 8.4 Hz); 7.15-7.13 (2H, m); 6.96 (2H, s); 4.86 (1H, t, *J* = 6.8 Hz); 4.69 (2H, d, *J* = 7.2 Hz); 2.22 (2H, t, *J* = 7.4 Hz); 1.60-1.52 (2H, m); 0.84 (3H, t, *J* = 7.4 Hz)

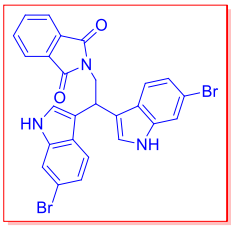
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 137.1, 125.8, 122.7, 122.6, 120.7, 116.2, 115.7, 114.1, 66.8, 36.2, 33.4, 18.3, 13.5

HRMS (ESI-MS) of $C_{22}H_{20}BrN_3O_2$: 524.9790 $(M+H)^+$ positive mode

Found: 524.9792

1-(2,2-Bis(6-bromo-1*H*-indol-3-yl)indoline-2,3-dione (138) :

The product **138** was obtained as yellow colored solid through column chromatography using a mixture of 30% ethyl acetate and hexanes as described in procedure F.



Yield: 85 %

Mp: 136-138 °C

IR (KBr) ν_{max} cm^{-1}: 2969, 2882, 1780, 1709, 1468, 1304, 1194, 1013, 876, 712, 531

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.99 (2H, s); 7.76 (4H, s); 7.46 (2H, s); 7.37 (2H, d, J = 8.4 Hz); 7.30 (2H, s); 6.97 (2H, d, J = 8.4 Hz); 4.94 (1H, t, J = 8.0 Hz); 4.27 (2H, d, J = 7.6 Hz)

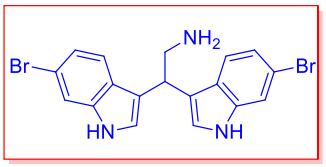
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 137.6, 134.9, 131.7, 126.0, 124.2, 123.4, 121.6, 115.6, 114.4, 114.2, 42.7, 32.5

HRMS (ESI-MS) of $C_{26}H_{17}Br_2N_3O_2$: 583.9586 $(M+H)^+$ positive mode

Found: 583.9584

1-(2,2-Bis(6-bromo-1*H*-indol-3-yl)indoline-2,3-dione (139) :

The product **287** was obtained as brown colored solid.



Yield: 65 %

Mp: 230-232 °C

IR (KBr) ν_{max} cm^{-1}: 3413, 2964, 2926, 2854, 1605, 1457, 1331, 1101, 887,586

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (2H, bs); 7.56 (2H, s); 7.32 (2H, d, J = 8.8 Hz); 7.19 (2H, d, J = 8.0 Hz); 7.12 (2H, s); 6.84 (2H, bs); 4.86 (1H, t, J = 7.6 Hz); 3.86 (2H, d, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 124.5, 123.6, 123.0, 119.7, 118.6, 116.7, 115.8, 114.7, 112.9, 110.1, 44.1, 32.9

HRMS (ESI-MS) of $C_{18}H_{15}Br_2N_3$: 430.9633

Found: 431.9706 $[M+H]^+$, 432.9729 $[M+2H]^+$

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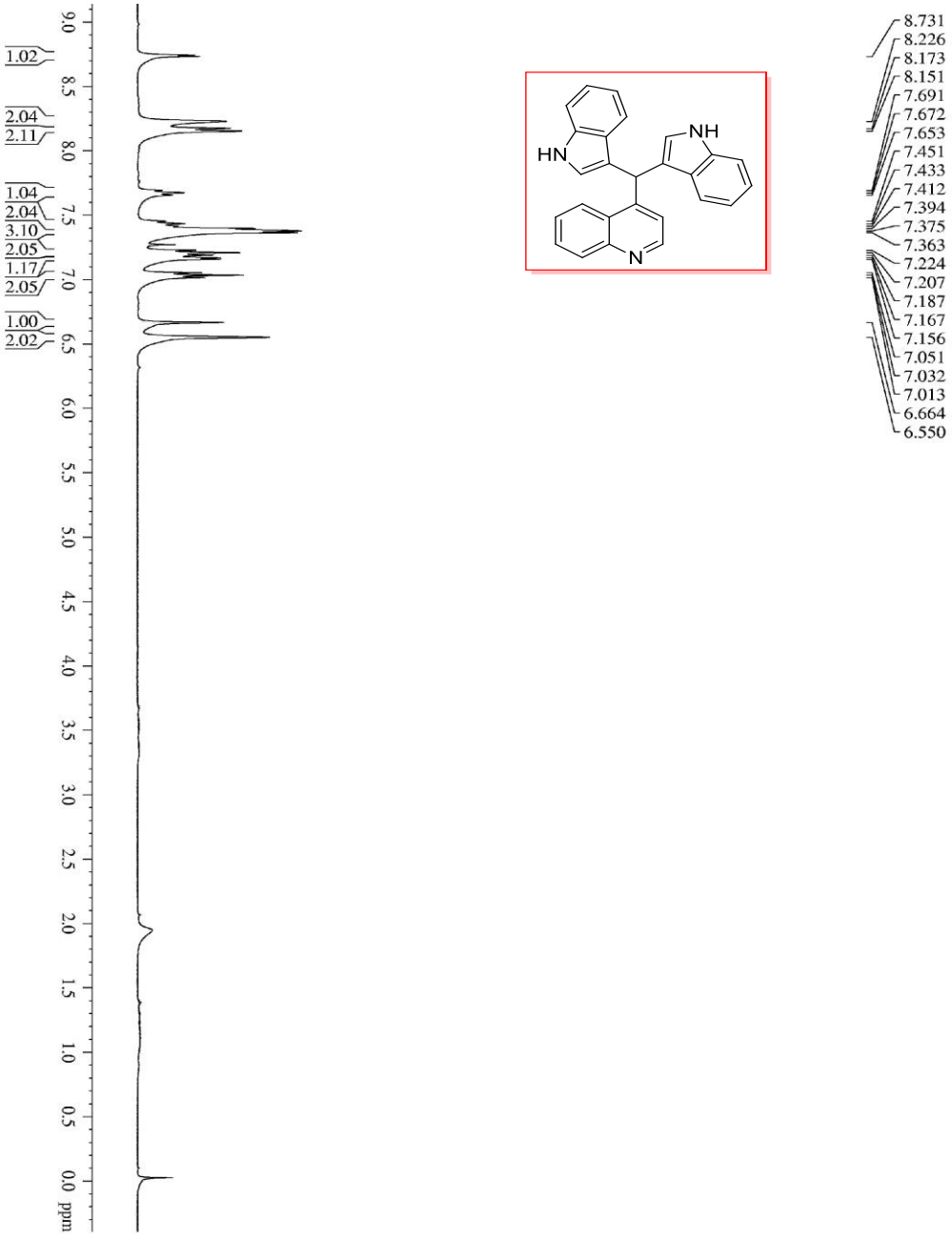
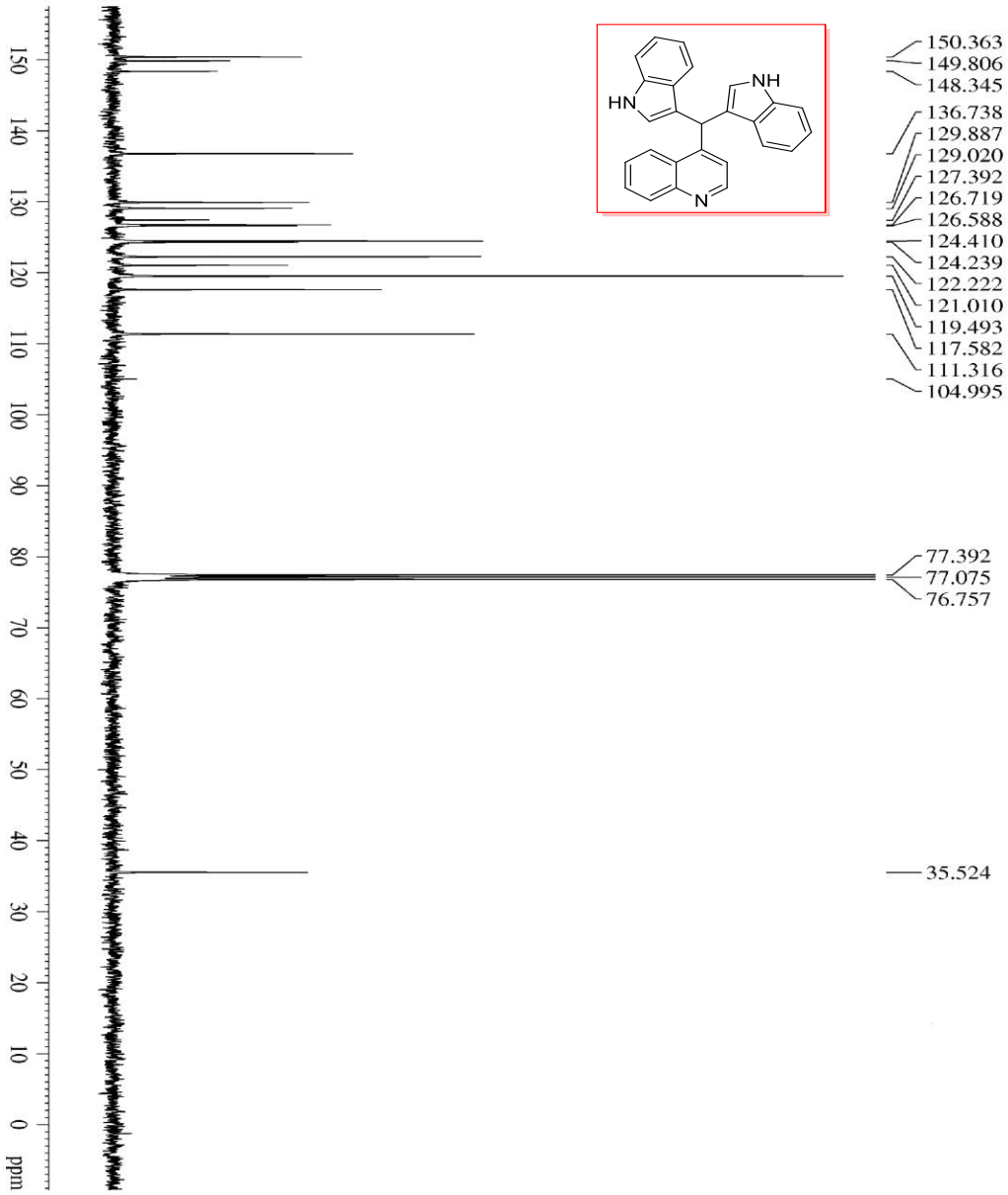
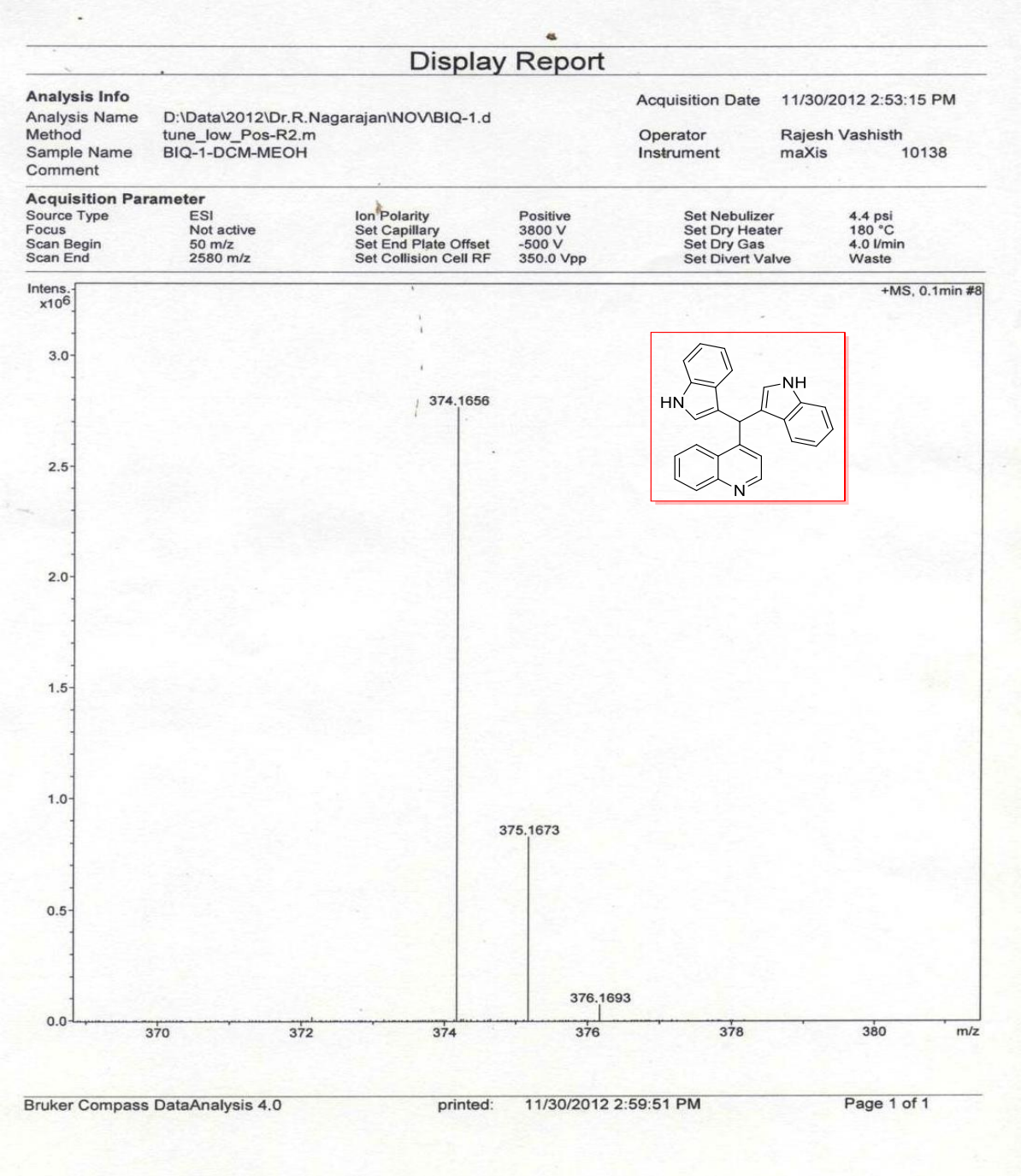
^{1}H NMR of 4-(di(1*H*-indol-3-yl)methyl)quinoline:



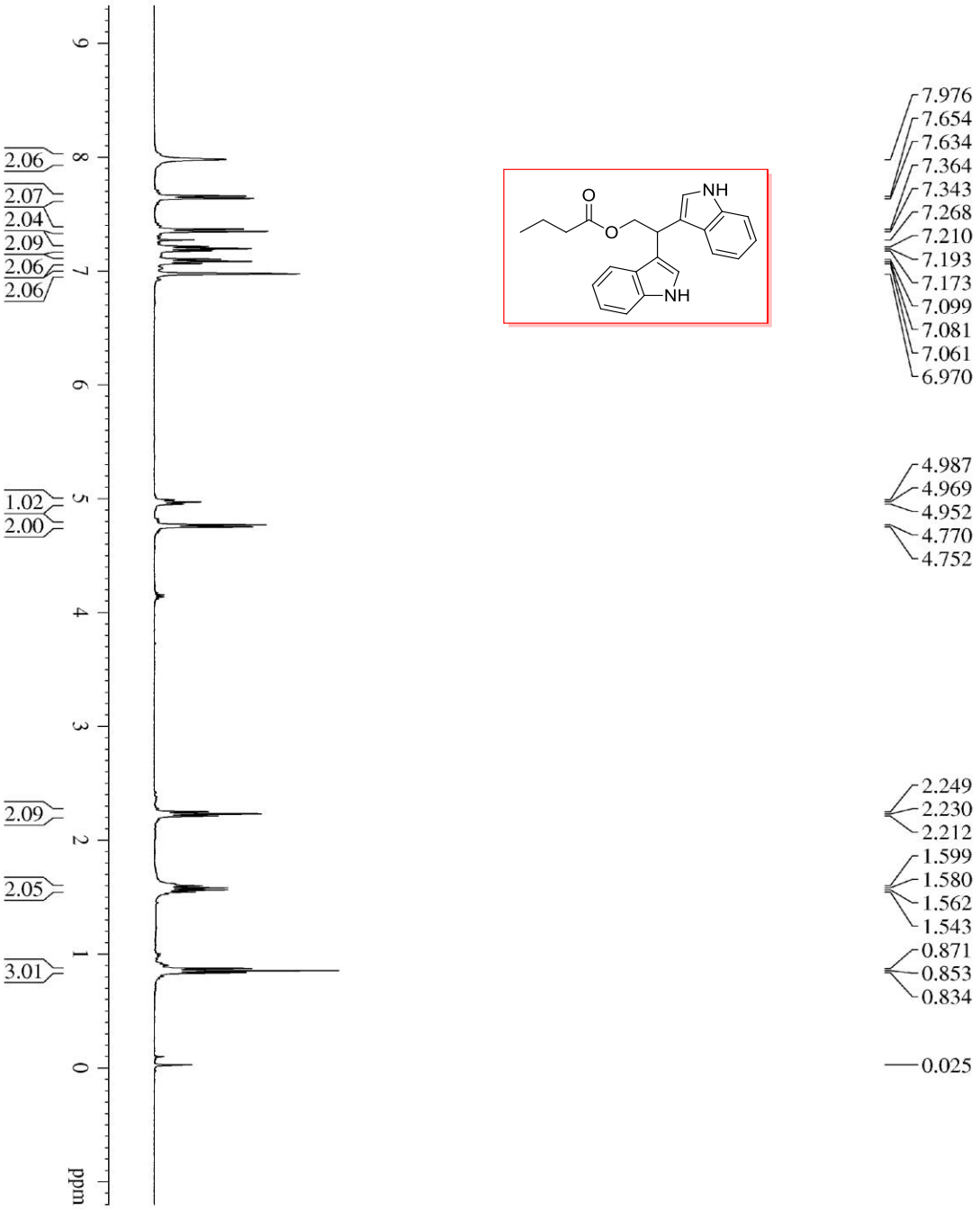
^{13}C NMR of 4-(di(1*H*-indol-3-yl)methyl)quinoline:



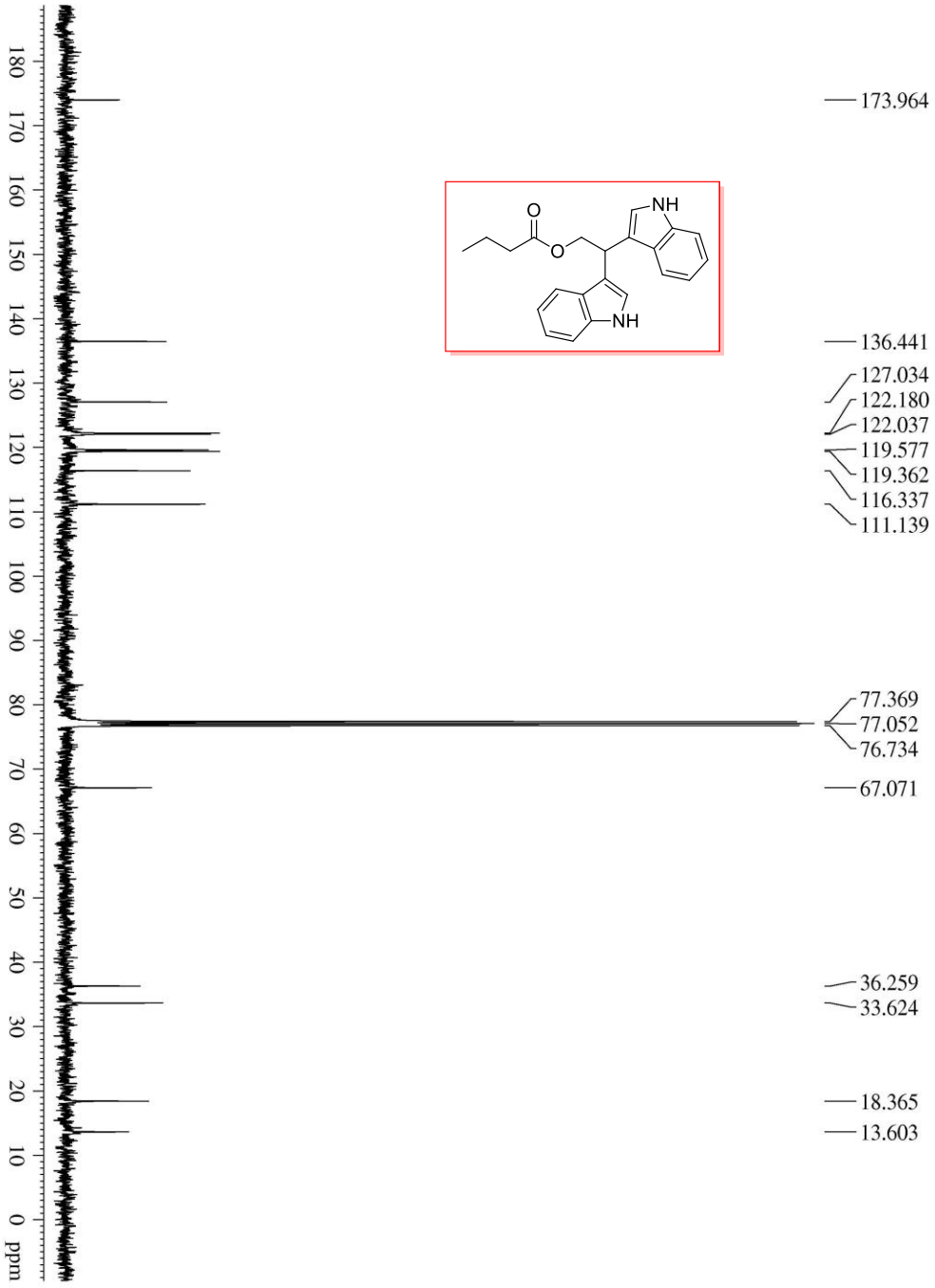
HRMS of 4-(di(1*H*-indol-3-yl)methyl)quinoline:



[1]H NMR of 2,2-bis(1*H*-indol-3-yl)ethylbutyrate:



^{13}C NMR of 2,2-bis(1*H*-indol-3-yl)ethylbutyrate:



HRMS of 2,2-bis(1*H*-indol-3-yl)ethylbutyrate:

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University of Hyderabad

Analysis Info

Analysis Name	D:\Data\2013\Dr.NAGARAJAN\APR\JR-ARS-BR.d	Acquisition Date	4/25/2013 3:22:00 PM
Method	tune_low_Pos.m	Operator	Ramu Sridhar
Sample Name	JR-ARS-B-DCM-MEOH	Instrument	maXis 10138
Comment			

Acquisition Parameter

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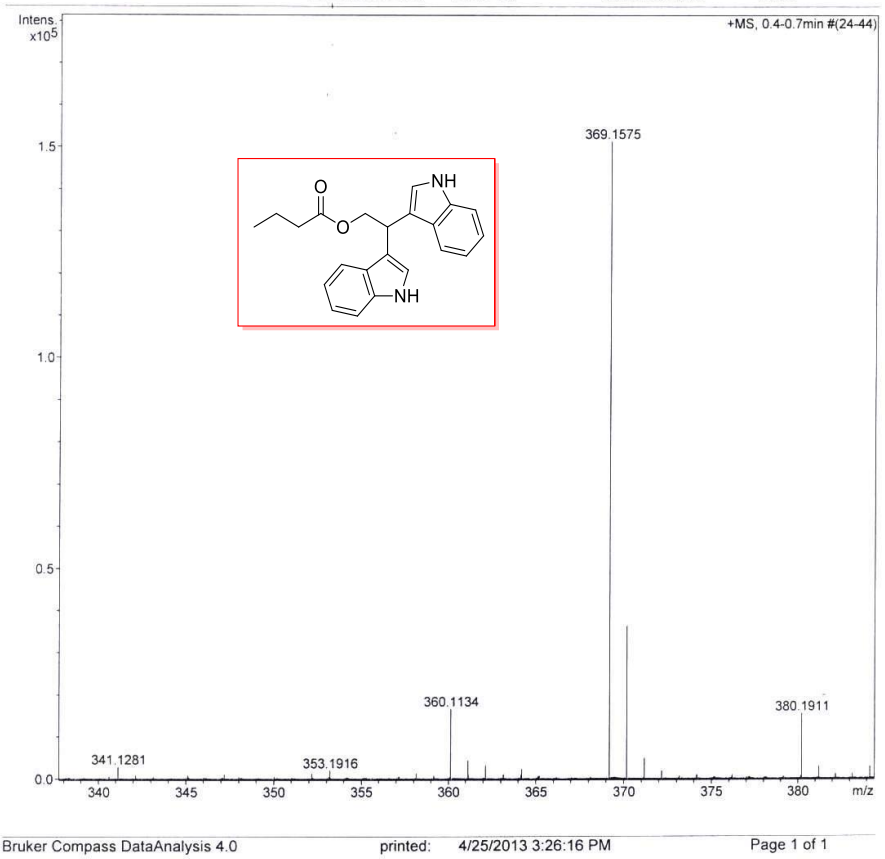
Scan End	1500 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste



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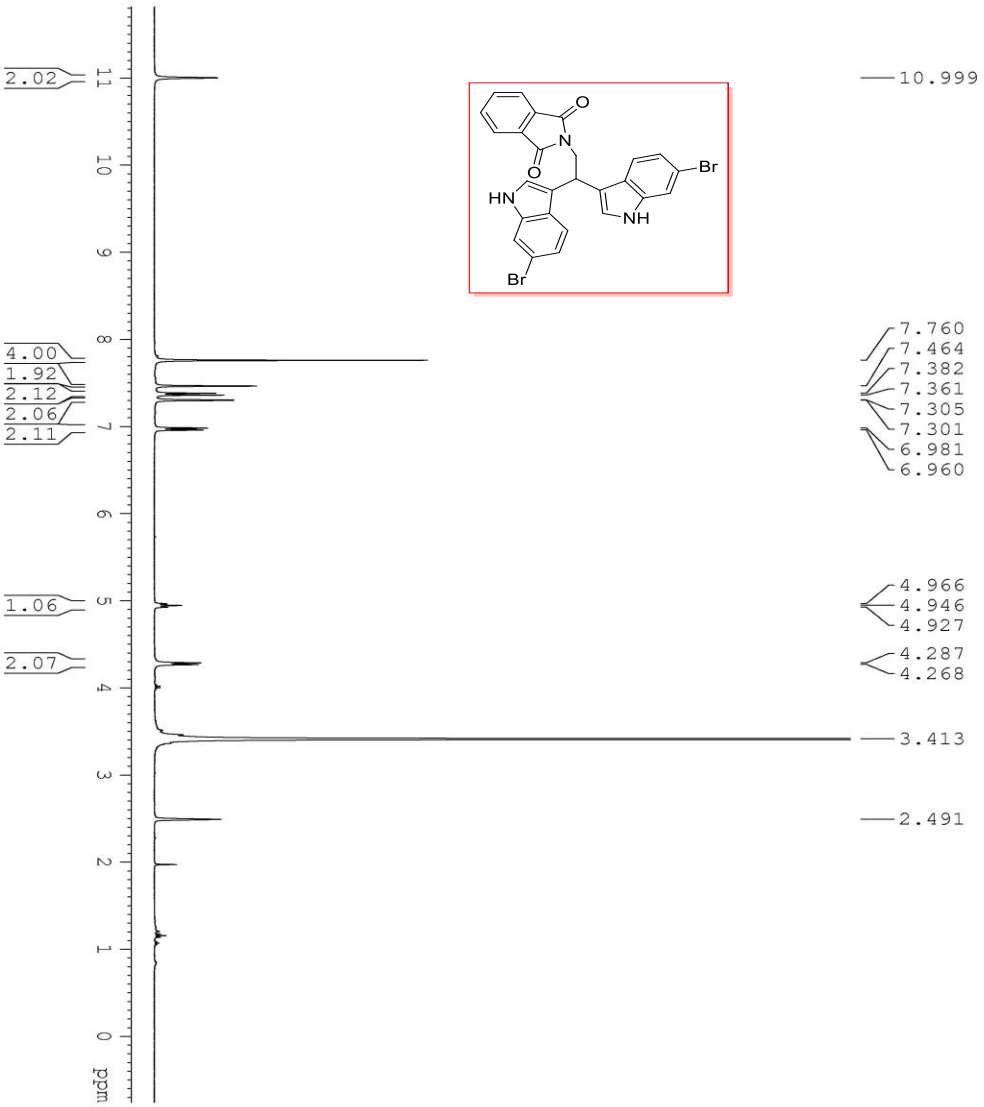
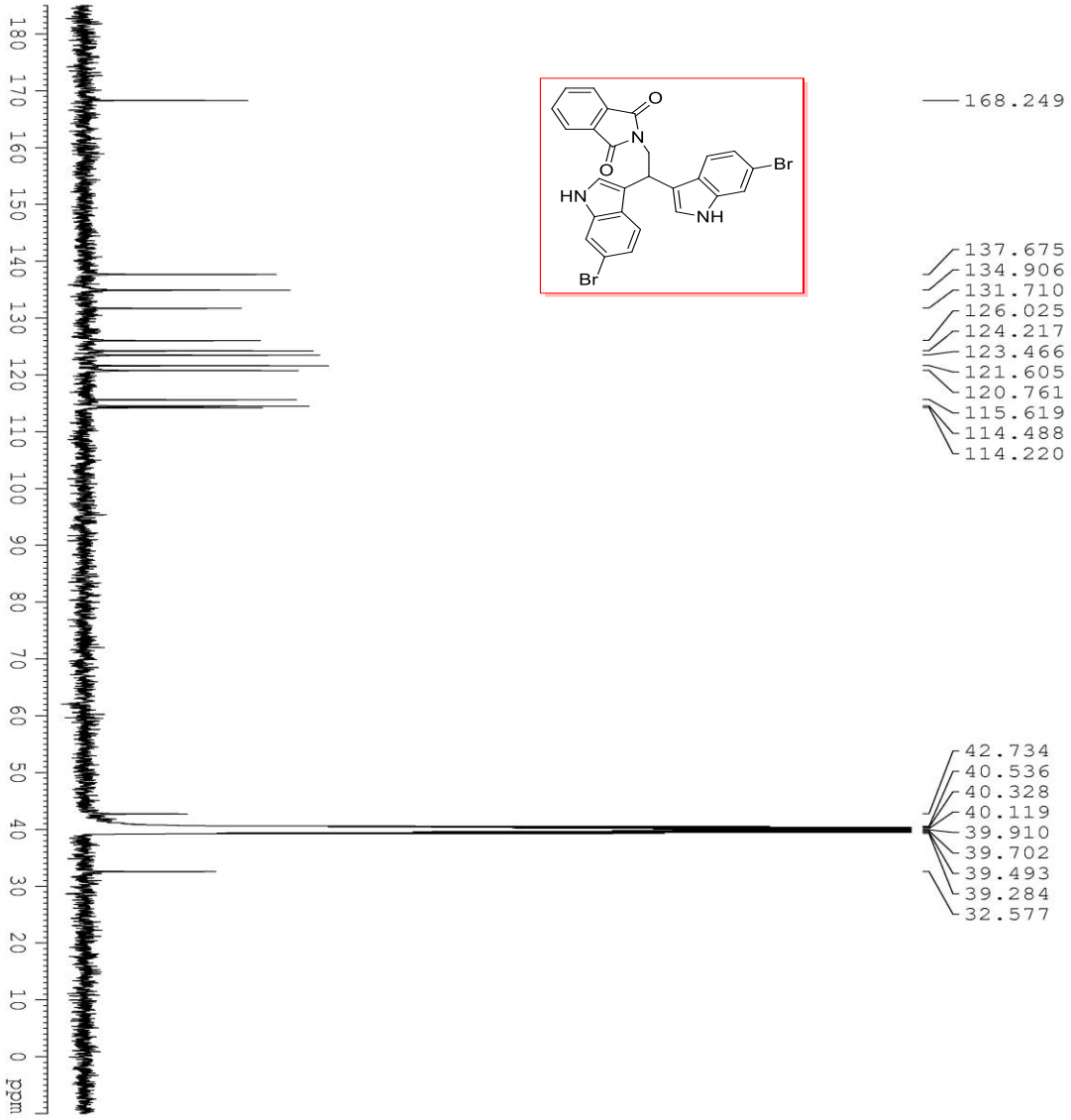
^{1}H NMR of 1-(2,2-bis(6-bromo-1*H*-indol-3-yl)indoline-2,3-dione:



^{13}C NMR of 1-(2,2-bis(6-bromo-1*H*-indol-3-yl)indoline-2,3-dione:



HRMS of 1-(2,2-bis(6-bromo-1*H*-indol-3-yl)indoline-2,3-dione:

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Analysis Info

Analysis Name	D:\Data\2013\Dr.NAGARAJAN\APR\JR-BIAP.d	Acquisition Date	4/25/2013 3:33:19 PM
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Sample Name	JR-BIAP-DCM-MEOH	Instrument	maXis 10138
Comment			

Acquisition Parameter

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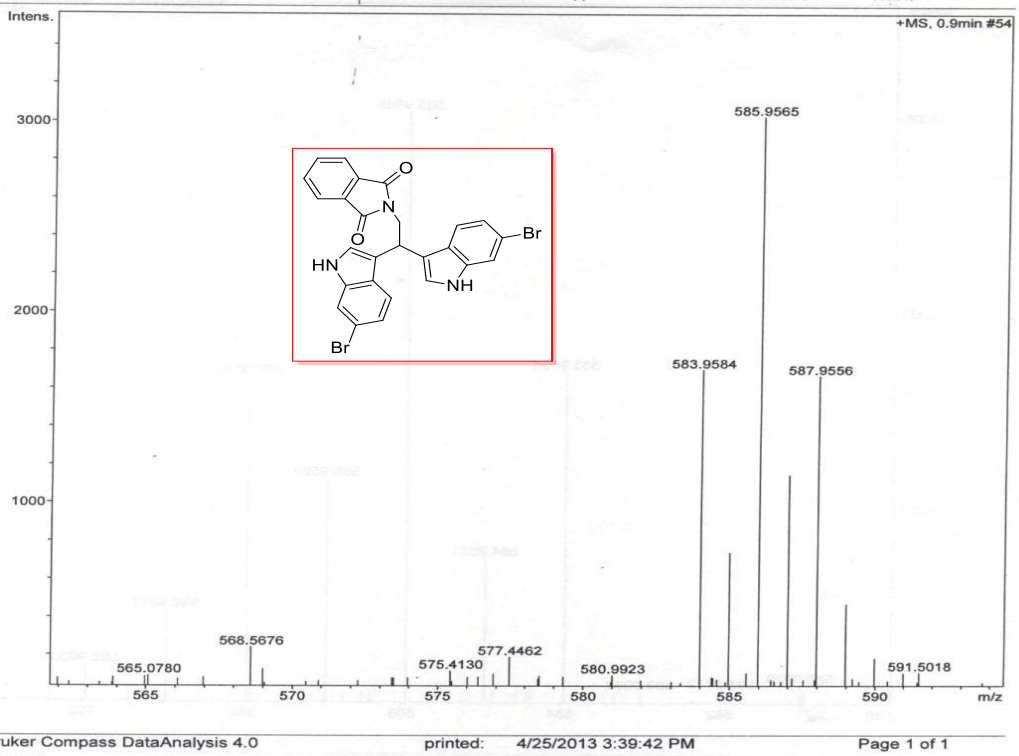
Scan End	1500 m/z	Set Collision Cell RF	350.0 Vpp	Set Divert Valve	Waste



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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.

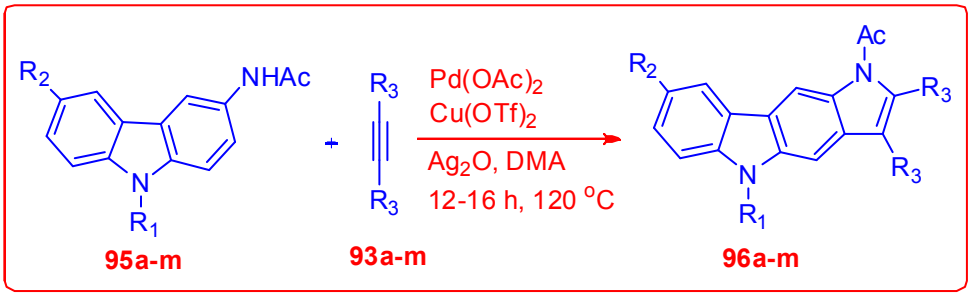
- In conclusion, we have developed a direct approach for the construction of different pyrrolo[3,2-*b*]carbazoles **96a-m** in moderate to good yields via Pd-catalyzed C-H activation. The reaction occur regioselectively giving exclusively single regioisomer. The reaction works well with various disubstituted aryl alkynes bearing both electron donating as well as electron withdrawing substituents.

- In conclusion, we have established a simple method for the synthesis of iodo substituted dihydropyridocarbazole derivatives **121a-i** using iodocyclization process. The reaction conditions are mild and the products are obtained in good yields. The iodine group present in the products is very useful for further functionalization and preparation of multisubstituted pyrido carbazole derivatives.

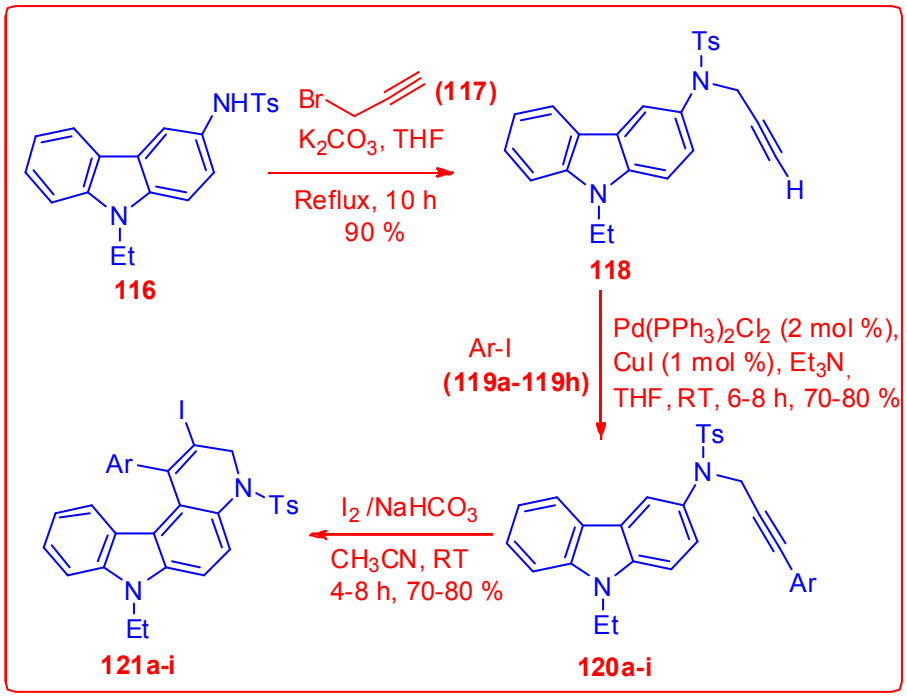
- In summary we have developed a efficient method for the synthesis of arsindoline A **133a**, arsindoline B **135a** and 2,2-di(6-bromo-3-indolyl)ethylamine **139** in low melting mixture. The reaction is simple, non-toxic and occurs in environmentally benign conditions with good yields. The melt medium acts as catalyst as well as solvent in the reaction.

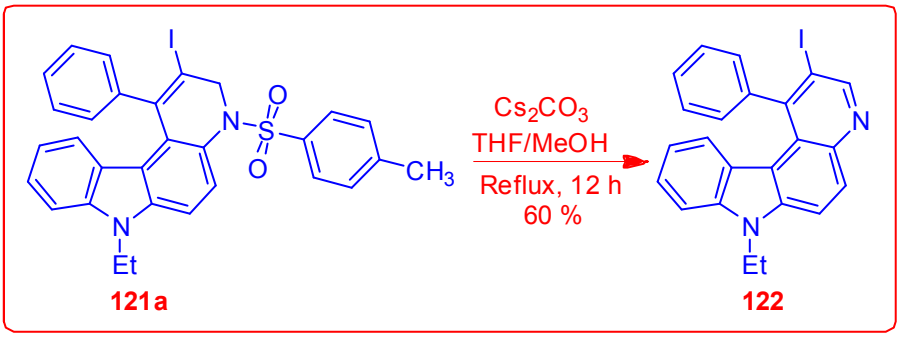
GRAPHICAL ABSTRACTS

Chapter 1: Synthesis of Pyrrolo[3,2-*b*]carbazoles *via* Pd-Catalyzed C-H activation



Chapter 2: Synthesis of Dihydropyrido[2,3-*c*]carbazoles via Iodocyclization





Chapter 3: Synthesis of Arsindoline A, Arsindoline B and their analogues in Eutectic mixture