Synthesis of Heteroarylcarbazoles: Ellipticine, Pyranocarbazole, Chromenylcarbazole and Carbazolocarbazole Derivatives

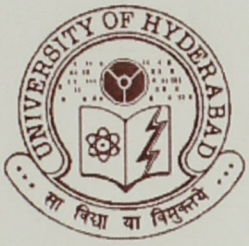
A Thesis

Submitted for the Degree of

Doctor of Philosophy

By

T. Krishna Chaitanya



School of Chemistry
University of Hyderabad
Hyderabad 500 046
India

June 2011

STATEMENT

I hereby declare that the matter embodied in this thesis entitled **"SYNTHESIS OF HETEROARYLCARBAZOLES: ELLIPTICINE, PYRANOCARBAZOLE, CHROMENYLCARBAZOLE AND CARBAZOLO CARBAZOLE DERIVATIVES"** is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad under the supervision of **Dr. R. NAGARAJAN**.

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

Date:
Hyderabad

(T. KRISHNA CHAITANYA)

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Hyderabad **(T. KRISHNA CHAITANYA)**

CERTIFICATE

This is to certify that the work described in this thesis entitled "**SYNTHESIS OF HETEROARYLCARBAZOLES: ELLIPTICINE, PYRANOCARBAZOLE, CHROMENYLCARBAZOLE AND CARBAZOLO CARBAZOLE DERIVATIVES**" has been carried out by Mr. **T. KRISHNA CHAITANYA** under my supervision and that the same has not been submitted elsewhere for any degree.

Dr. R. NAGARAJAN

(Thesis Supervisor)

Dean

School of Chemistry
University of Hyderabad

LIST OF PUBLICATIONS

1. An efficient solvent-free approach to heteroarylcarbazoles: synthesis of 3-chromenylcarbazoles, 3,6-bis-chromenylcarbazoles and 3-quinolylcarbazoles
   T. Krishna Chaitanya and R. Nagarajan, *Tetrahedron Lett*. **2007**, *48*, 2489-2492.

2. Synthesis of Functionalized Ellipticinium and Ellipticine Derivatives via Electrophilic Cyclization.
   T. Krishna Chaitanya and R. Nagarajan, *Org. Biomol. Chem.* **2011**, *9*, 4662-4670.

3. Metal-free synthesis of benzimidazo[2,1-*a*]ellipticines via tandem inter and intramolecular Cyclization**.**
   T. Krishna Chaitanya, K. S. Prakash and R. Nagarajan, *Tetrahedron* **2011** *(in press)*.

4. Synthesis of New Pyrano[2,3-*c*]carbazoles, Pyrano[3,2-*b*]carbazoles and Furo[3,2-*b*]carbazole derivatives via Iodocyclization.
   T. Krishna Chaitanya and R. Nagarajan, *(Communicated)*.

5. A Tandem Route to the Synthesis of Carbazolo[1,2-*b*]carbazoles
   T. Krishna Chaitanya and R. Nagarajan, (*Communicated*).

Posters and Oral Presentations

1. Participated and gave an oral presentation on "Synthesis of Functionalized Ellipticinium and Ellipticine Derivatives via Electrophilic Cyclization" at 7th in-house symposium "***CHEMFEST 2010***", conducted by School of Chemistry, University of Hyderabad, Hyderabad from 8-9th January 2010.

2. Participated and Gave Oral Presentation on "Total synthesis of ellipticine derivatives" at **5th J-NOST** National symposium conducted by IIT Kanpur from December 4-7th 2009.

3. Participated and presented poster on "A rapid and efficient entry to synthesis of quino and chromenocarbazoles via Ullmann-Goldberg condensation" in the **CRSI** sponsored 11th National Symposium in Chemistry organized by the NCL and IISER, Pune during February 6-9, 2009.

4. Participated and presented poster on "An efficient solvent-free approach to heteroarylcarbazoles: synthesis of 3-chromenylcarbazoles, 3,6-bis-chromenylcarbazoles and 3-quinolylcarbazoles". at 3rd in-house symposium "***CHEMFEST 2006***", conducted by School of Chemistry, University of Hyderabad, Hyderabad from March 9-10th 2007.

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కీ.శే. నాగభూషణం తాతయ్య, నాయనమ్మ, అమ్మమ్మ, తాతగారు: మీ ఆశీస్సులే నాకు రక్ష. మీకు సదా రుణపడి ఉంటాను. నా చెల్లెలు స్రవంతి-అంజి బావ; కోటిబావ, ప్రతిమక్క: మీ అభిమానం, ప్రోత్సాహం మరువలేనివి. రిషి, అనన్య, ఇషాన్.. మీ అల్లరి నాకు ఎనర్జీ.

నాకోసం అనుక్షణం తపనపడుతూ, నా జీవితపు ప్రతి అడుగు ఆనందంగా సాగాలని, నాకు ఏ కష్టం తెలియకుండా తోడుగా నిలిచిన అమ్మకి, నాన్నకి...

తాళ్ళూరి క్రిష్ణచైతన్య

అమ్మకి నాన్నకి...

ప్రేమతో అంకితం

Table of Contents

List of Abbreviations

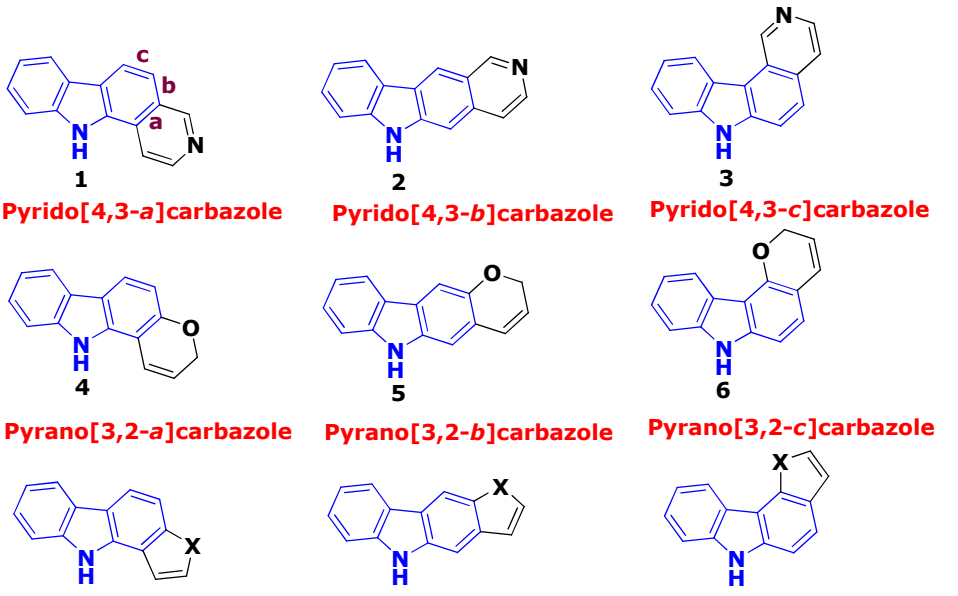
Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
DMA	*N,N'*-dimethylacetamide
DMF	*N,N'*-dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Eq.	Equation
i-Pr	*iso*-propyl
LDA	Lithium Diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
MOM	Methoxy methyl ether
Mp	Melting point
Ph	Phenyl
Bu	Butyl
p-TSA	*para*-Toluenesulfonic acid
rt	Room temperature
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TPPT	Triphenylphosphonium triflate
DME	Dimethoxyethane
Tf	Triflate
DBA	Dibenzilideneacetone
Phen	1,2-Phenylenediamine
Equiv.	Equivalent
PE	Petroleum ether
DNA	Deoxyribonucleic acid
Naph	Naphthyl

Introduction

• Heteroarylcarbazoles

Heteroarylcarbazoles are molecules with a heterocyclic moiety fused with carbazole skeleton. The rapidly growing class of heteroaryl-condensed carbazoles began to attract increasing synthetic interest because of their broad spectrum of useful biological activities.[1] To provide an overview on the heteroaryl-annulated carbazole derivatives, these compounds are classified into [*a*]-annulated, [*b*]-annulated, and [*c*]-annulated pyrido-, pyrano-, furo-, pyrrolo-, thienocarbazoles *etc*. This classification is solely based on the position at which the heteroaromatic ring is fused to the carbazole nucleus, either at bond *a*, *b*, or *c* (Figure 1). In Figure 1, only the structures with a [4,3]-annulated pyridine ring, [3,2]-annulated pyrano- and furan rings are shown, as these are more commonly existing in nature. Moreover, the mode of fusion of the annulated heteroaromatic ring itself can vary, which leads to an even broader variety of heterocyclic ring systems.

Figure 1

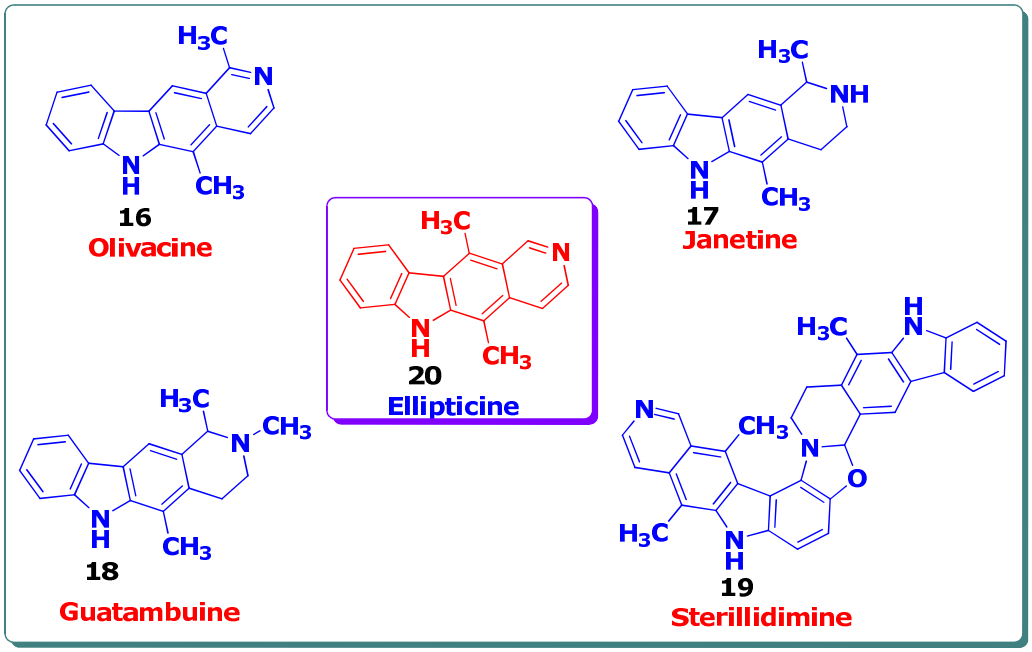


It is well established that the pyridocarbazole ring system is one of the appropriate skeletons to design DNA intercalating drugs.[2] For this reason, there has been a strong synthetic activity in this area. Examples of potential annulation modes are the pyrido[4,3-*a*]carbazoles **1**, the pyrido[4,3-*b*]carbazoles **2** and the pyrido[4,3-*c*]carbazoles **3**.

• Pyrido[4,3-*b*]carbazoles

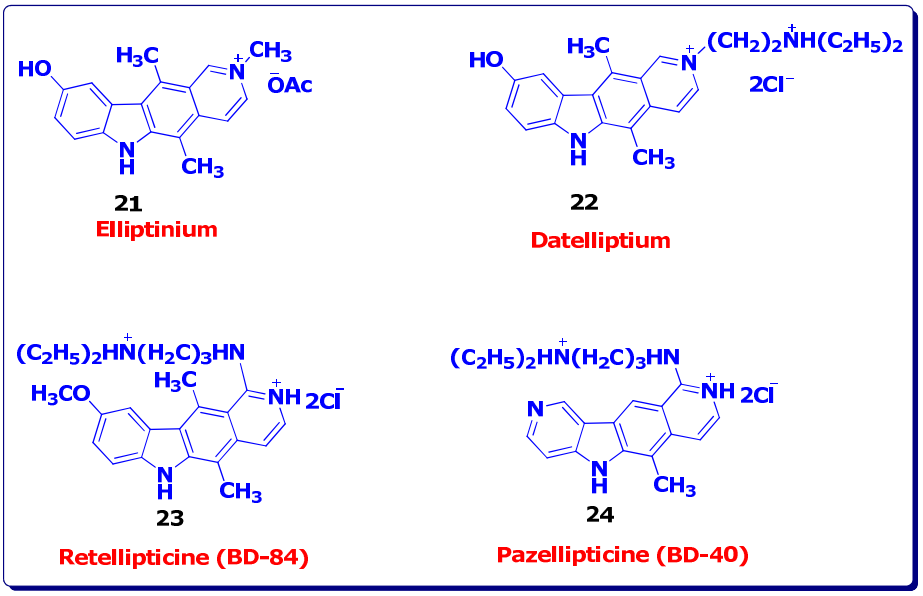
Among the different isomeric pyridocarbazole frameworks, the pyrido[4,3-*b*]carbazole **2** has attracted most of the interest because ellipticine and its 9-hydroxy and 9-methoxy derivatives show significant anticancer activity.[3] In 1959, Goodwin *et al.* isolated ellipticine **20**, a pyrido[4,3-*b*]carbazole, from the leaves of *Ochrosia elliptica* Labill.[4] In the same year Woodward *et al.* assigned this plant alkaloid as 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, confirmed by the first total synthesis.[5] In the following years, ellipticine **20** and its analogues **16-19** (Figure 2) were isolated from various other species of the genera *Aspidosperma*, *Tabernaemontana*, *Strychnos*, and *Peschiera buchtieni*.[6] In 1967, Australian scientists disclosed the antitumor activity of ellipticine and 9-methoxyellipticine toward various animal tumors.[7] This discovery stimulated a strong interest in the synthesis of ellipticine and its analogues.

Figure 2



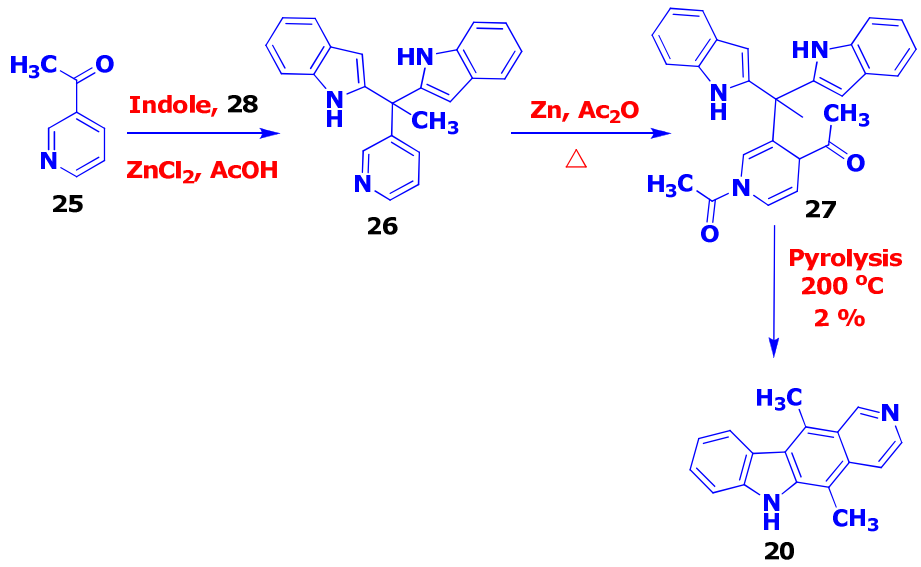
A derivative of 9-hydroxyellipticine, *N*-2-methyl-9-hydroxyellipticinium acetate **21** (elliptinium), was commercialized for clinical use in the treatment of myeloblastic leukemia, advanced breast cancer, and other solid tumors.[8] In the late 1980s, a second generation of ellipticine-derived antitumor agents was developed, including the new clinical candidates datelliptium **22**,[9] retellipticine (BD-84) **23**,[10] and pazellipticine (PZE or BD-40) **24**[11] (Figure 3). These findings initiated further extensive activities directed toward the synthesis of pyrido[4,3-*b*]carbazole derivatives for biological evaluation.

Figure 3



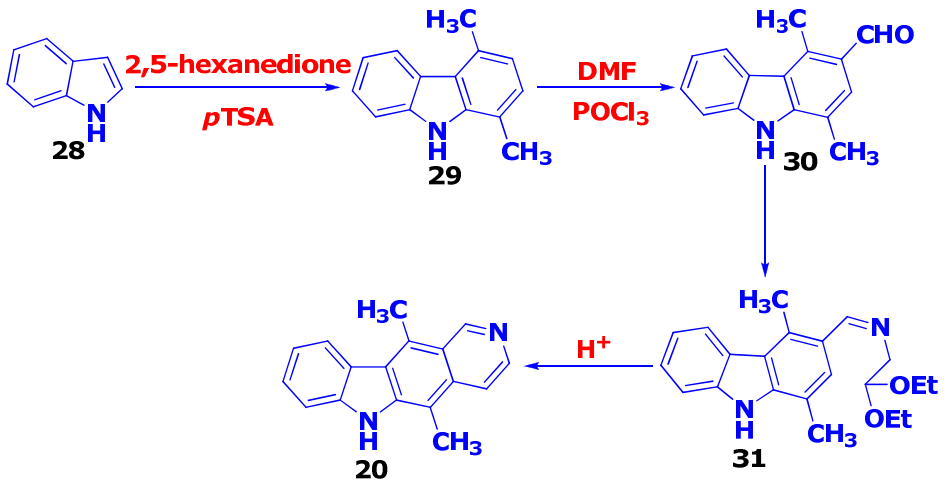
The first total synthesis of ellipticine was reported by R. B. Woodward and co-workers in 1959.[5] The bisindolyl derivative **26** of 3-acetylpyridine **25** upon reductive acetylation followed by pyrolysis at 200 °C provided ellipticine in just 2% yield (Eq. 1).

Eq. 1



Cranwell and Saxton reported an efficient and simple synthesis of ellipticine from Indole **28** (Eq. 2). Indole was converted to 1,4-dimethylcarbazole **29**.[12] Vilsmeier-Haack formylation followed by condensation and cyclization with diethyl glycinal provided ellipticine in good yields.

Eq. 2

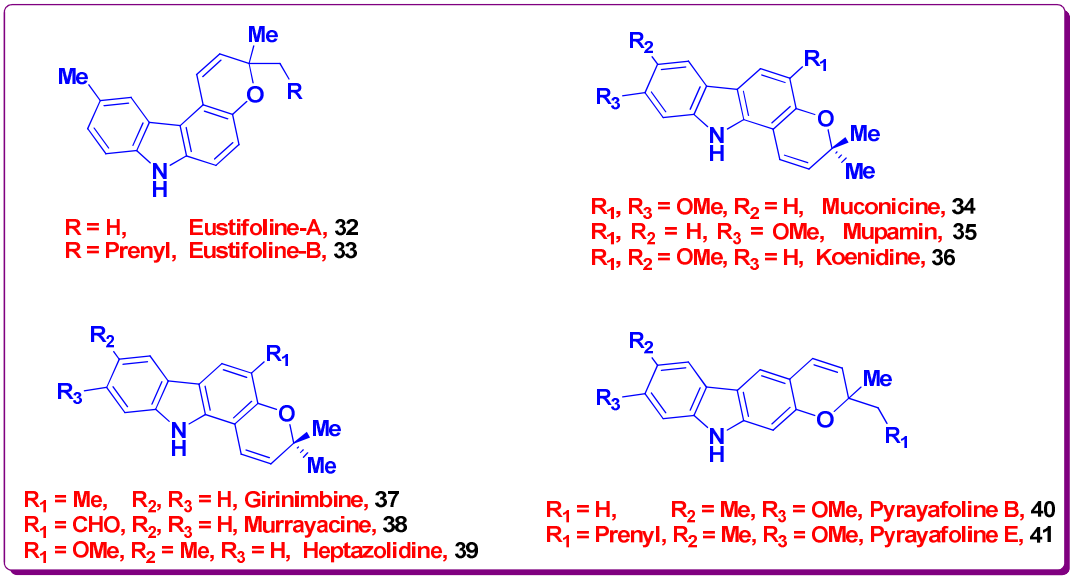


• Pyranocarbazoles

Another important class of heteroarylcarbazoles is pyranocarbazoles. Many molecules with pyranocarbazole skeleton were isolated from nature. Girinimbine **37**, the first member of the pyrano[3,2-*a*]carbazole alkaloids, was isolated from the stem bark of

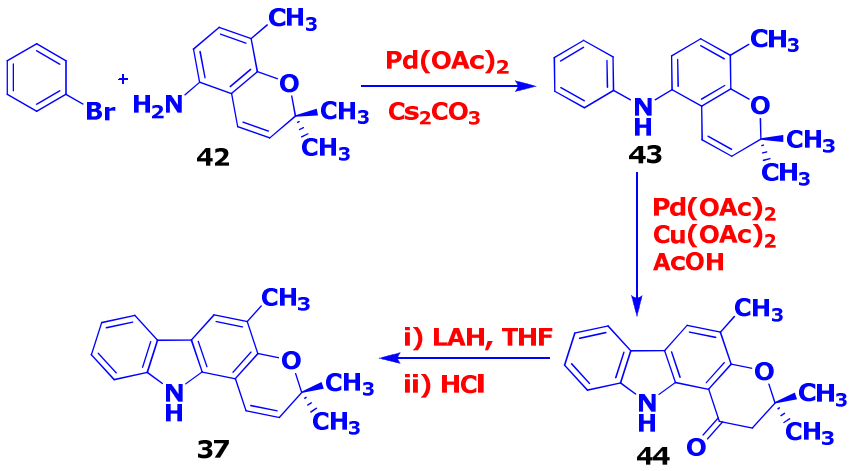
M. koenigii Spreng by Chakraborty *et al*.[13] On the basis of chemical degradation studies, Chakraborty *et al*. proposed that the pyran ring and the aromatic methyl group are attached to different benzene rings of the carbazole nucleus.[14] Later, Dutta and Quasim reassigned the structure of girinimbine on the basis of NMR studies and proposed that the pyran ring and the methyl group are at the same benzene ring.[15] Chakraborty *et al*. also reported the isolation of murrayacine **38**, a formyl analogue of girinimbine from two different natural sources, *M. koenigii*[16] and *C. heptaphylla*.[17] Furukawa *et al*. isolated in 1991 isolated the linear isomers, pyrayafoline B **40**[18] and E **41**.[19] In 1989, Reisch *et al.* isolated glycomaurin from *Glycosmis mauritiana*.[20] In the following year, Furukawa *et al*. isolated the same compound from a different natural source, *M. euchrestifolia Hayata*, and named it eustifoline-A.[21] Along with eustifoline-A **32**, they also reported the isolation of the corresponding prenyl analogue, eustifoline-B **33**.[21]

Figure 4



Knölker and Gruner reported the synthesis of Girinimbine **37** by employing a palladium(II)-catalyzed one-pot triple C–H bond activation as key step leading to the Wacker oxidation with concomitant intramolecular oxidative C–C bond formation (Eq. 3).[22] The diarylamine precursor is obtained by a palladium(0)-catalyzed Buchwald–Hartwig coupling of bromobenzene and aminochromene **42**. The aminochromene **42** has been prepared in three steps and 70% overall yield starting from 2-methyl-5-nitrophenol.[23]

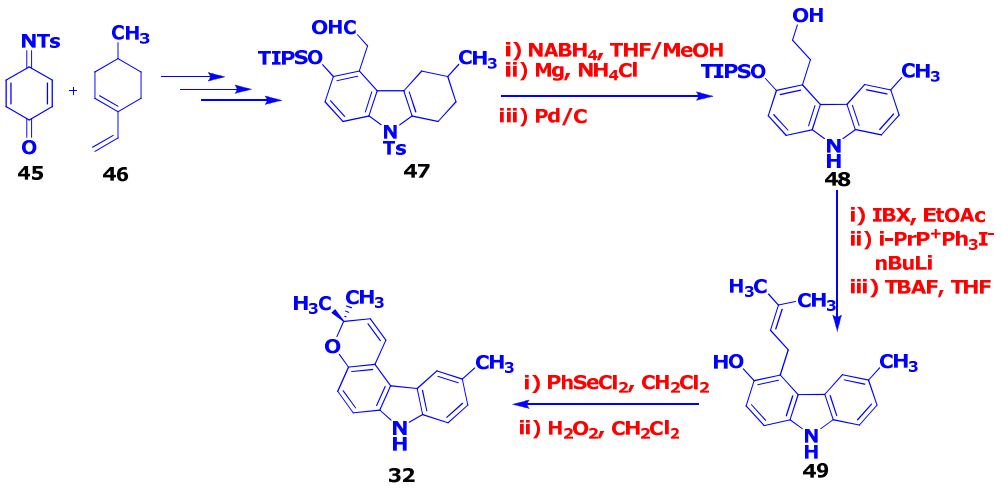
Eq. 3



The Diels-Alder reaction between a quinone mono-imine and cyclic diene allows for the construction of substituted carbazoles in a regiospecific manner. This methodology has successfully been employed by M. A. Kerr and T. P. Lebold in a divergent strategy, culminating in the synthesis of eustifolines A-D and glycomaurrol.[24]

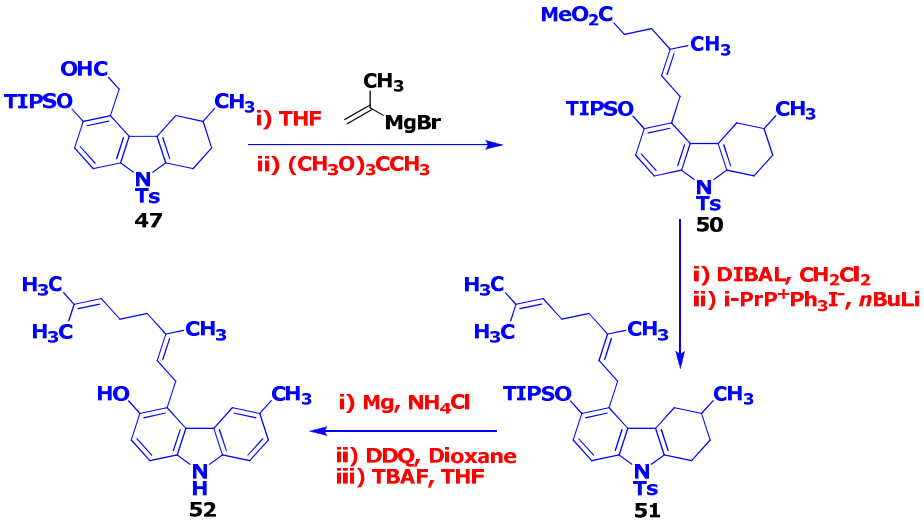
Readily available quinone imine **45** and diene **46** were converted to the tetrahydrocarbazole **47** via a Diels-Alder strategy followed by oxidative cleavage of the double bond (via the diol) followed by treatment of the resulting dicarbonyl with acid to afford the desired tetrahydrocarbazole in 61% yield over the four steps. Aldehyde reduction, tosyl removal, and dehydrogenation yielded carbazole **48** in 89% yield over the three steps. Tosyl removal was required to effect the dehydrogenation. Reduction of the aldehyde was found necessary to effect clean tosyl removal and dehydrogenation. The preparation of glycomaurrol as well as eustifolines D and A required reoxidation of **47** to the corresponding aldehyde (Eq. 4). Treatment with IBX in refluxing EtOAc afforded the desired aldehyde in excellent yield.[25] Olefination of the crude aldehyde with a triphenylphosphonium isopropyl ylide followed by desilylation with TBAF yielded glycomaurrol in 86% yield. Cyclization of glycomaurrol **49** with PhSeCl followed by oxidation with H_2O_2 afforded eustifoline A **32** in 50% yield over the two steps.

Eq. 4



Treatment of **47** with isopropenylmagnesium bromide followed by *in situ* generation of a ketene acetal *en route* to a Johnson-Claisen rearrangement led to the formation of ester **50** with the desired *E* geometry about the double bond in 86% overall yield (Eq. 5). Reduction to the aldehyde using DIBAL and olefination with triphenylphosphonium isopropyl ylide gave **51** bearing the requisite isopropylidine moiety in 78% overall yield. With the geranyl side chain installed, attention was turned to the dehydrogenative conversion of the tetrahydrocarbazole to the desired carbazole. *N*-Tosyl removal was effected with magnesium metal in methanolic aqueous ammonium chloride. The DDQ-mediated process which gave in 21% yield over the two steps. Desilylation gave eustifoline C **52** in 64% yield. Oxidative cyclization, using $Pd(OAc)_2$, generated eustifoline B **33** in 64% yield (Eq. 5).

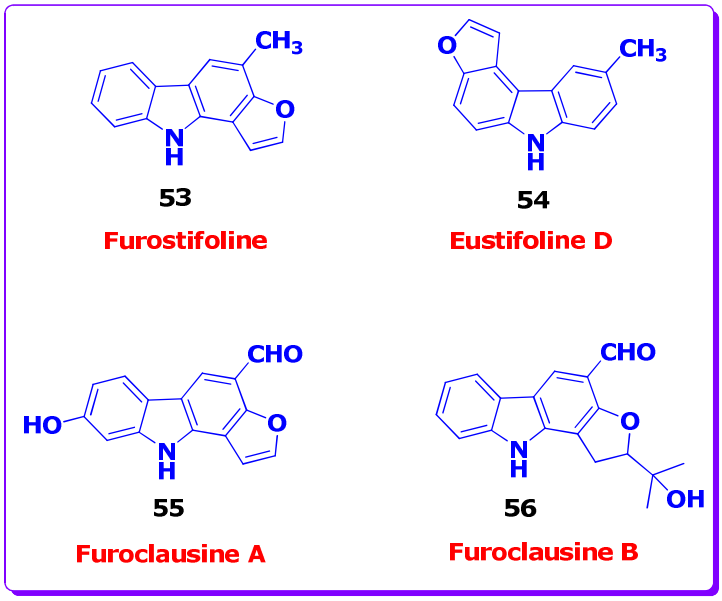
Eq. 5



• Furocarbazoles

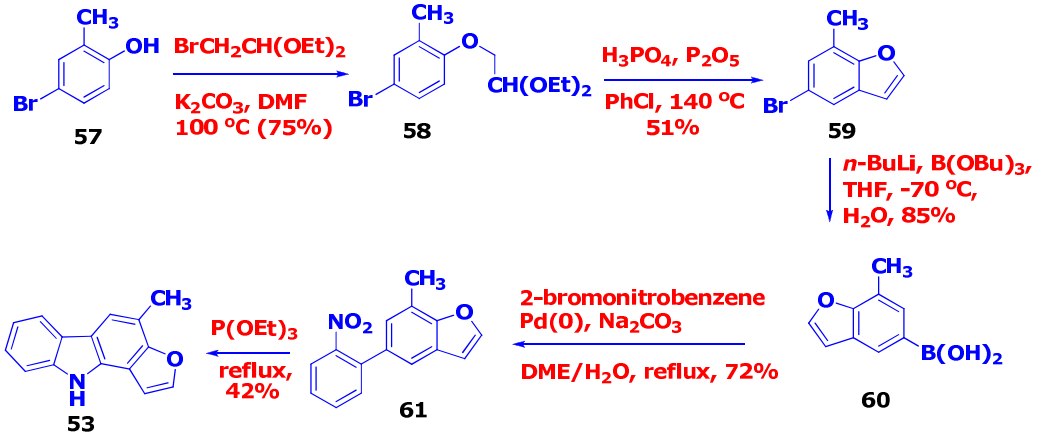
In 1990, Ito and Furukawa isolated two new members of tetracyclic carbazole alkaloids, furostifoline **53** and the isomeric eustifoline D **54** from *M. euchrestifolia* Hayata (Figure 4).[21] They were the first furocarbazole alkaloids obtained from natural sources. In the late 1990s, Wu *et al*. described the isolation and structural elucidation of two further furocarbazole alkaloids, furoclausine A **55** and B **56** from the root bark of *C. excavata* (Figure 4).[26]

Figure 5



In 1999, Timári *et al*. reported the total synthesis of furostifoline **53** from the bromocresol **57** (Eq. 6).[27] The key steps of their approach are the Suzuki coupling to generate *o*-nitrobiaryl compound **61** and the subsequent reductive cyclization via a nitrene intermediate. Annulation of the furan ring at the bromocresol **57** by reaction with bromoacetaldehyde diethyl acetal afforded 5-bromo-7-methylbenzofuran **59**. A halogen/metal exchange reaction of 5-bromo-7-methylbenzofuran **59** with *n*-butyllithium and subsequent treatment with tributyl borate gave the boronic acid derivative **60**. The palladium(0)-catalyzed cross-coupling of the boronic acid derivative **60** with 2-bromonitrobenzene provided the *o*-nitrobiaryl compound **61** in 72% yield. Using Cadogan's method, by reductive cyclization with triethyl phosphite,[28] the *o*-nitrobiaryl compound **61** was transformed to furostifoline **53** in 42% yield (Eq. 6). Thus, furostifoline **53** was made available in five steps and 10% overall yield based on compound **57**.

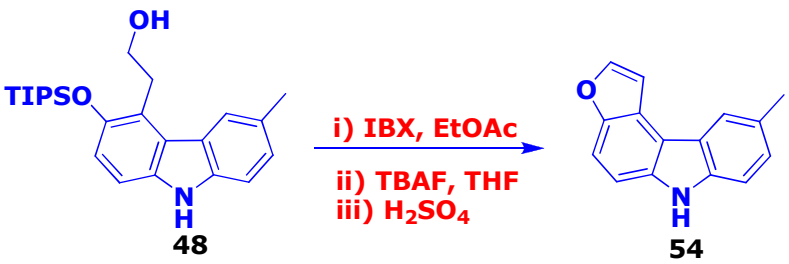
Eq. 6



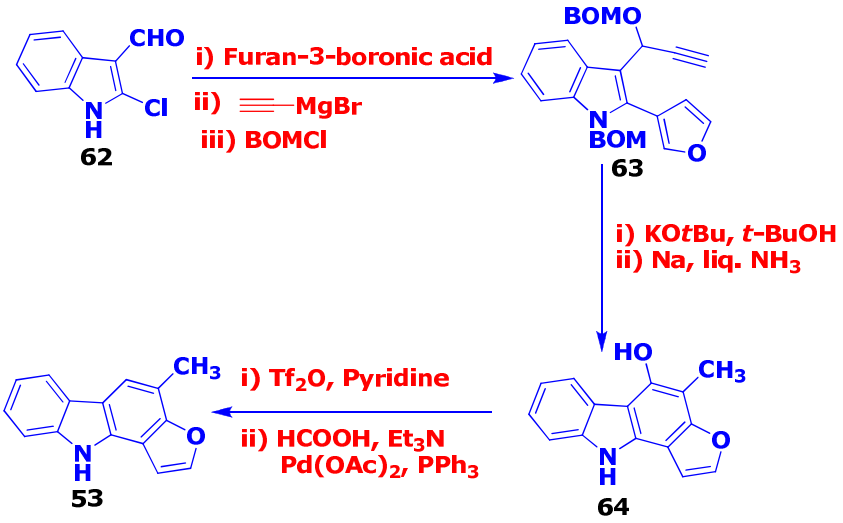
Eustifoline D **54** was prepared by oxidizing carbazole **48** and subjecting the resulting aldehyde to desilylation with TBAF followed by treatment with acid to effect benzofuran formation in 53% yield over the three steps (Eq.8).[24]

Hibino and co-workers described the total synthesis of furostifoline **53** from 2-chloro-3-formylindole **62** using the electrocyclic reaction of an intermediate allene with the 2,3-double bonds of indole and furan as the key step (Eq. 7). Suzuki cross-coupling of 2-chloro-3-formylindole **62** and furan-3-boronic acid,[29] protection as the benzyloxymethyl (BOM) ether, Grignard reaction of the *N*-BOM-protected 2-(fur-3-yl)indole-3-carbaldehyde with ethynylmagnesium bromide, and again BOM-protection of the propargylic alcohol provided in four steps the 2-(fur-3-yl)-3-propargylindole **63**. Using thermal reaction conditions the 2-(fur-3-yl)-3-propargylindole **63** was transformed to the 4-oxygenated furo[3,2-*a*]carbazole. Deprotection of compound under Birch conditions led to furo[3,2-*a*]carbazole **64** (51%). For the final transformation of the furocarbazole **64** to furostifoline **53**, the hydroxy group was removed via reductive elimination[30] of the intermediate triflate (Eq. 7).[31] This route affords furostifoline in nine steps and 43% overall yield.

Eq. 7



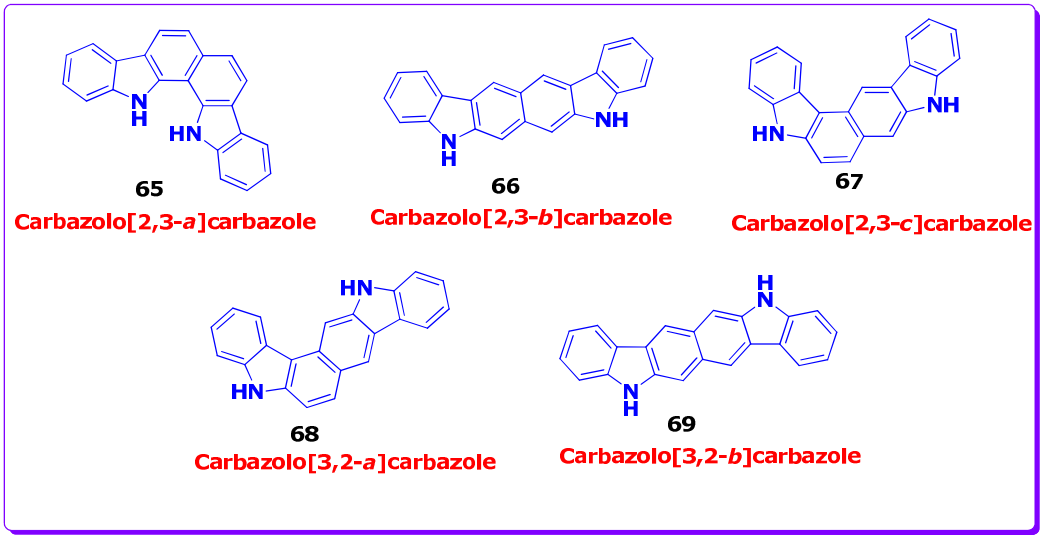
Eq. 8



- **Carbazolocarbazoles**

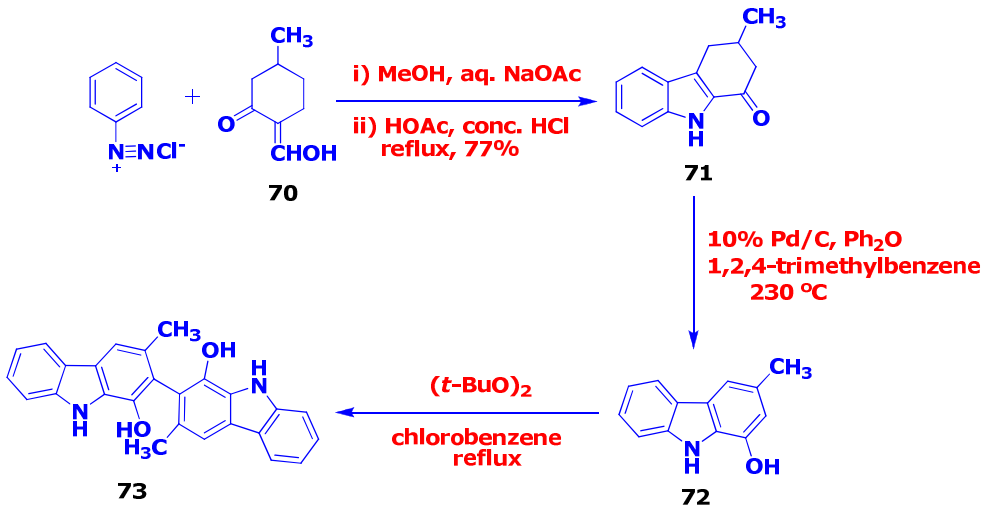
Carbazolocarbazoles constitute another versatile class of heteroarylcarbazoles. These are the molecules with one carbazole attached with another carbazole skeleton at various positions. To the carbazolocarbazole family belong the five different isomeric ring systems namely carbazolo[2,3-*a*]carbazole **65**, carbazolo[2,3-*b*]carbazole **66**, carbazolo[2,3-*c*]carbazole **67**, carbazolo[3,2-*a*]carbazole **68** and carbazolo[3,2-*b*]carbazole **69** (Figure 5). Among these, the most interesting structural class is the carbazolo[2,3-*a*]carbazoles **65**. The carbazolo[2,3-*a*]carbazole framework **65** is found in many natural products with a broad range of potent biological activities, e.g. antifungal, antimicrobial, antitumor, and antihypertensive activity.[32] Their activity as potent inhibitors of protein kinase C (PKC)[33] has received special attention and was the focus of several investigations. The carbazolo[2,3-*b*]carbazole **66**, carbazolo[2,3-*c*]carbazole **67**, carbazolo[3,2-*a*]carbazole **68**, carbazolo- [3,2-*b*]carbazole **69** and their derivatives have been studied in much less detail. This is explained by the fact that they are not present in natural products and there is a lack of knowledge of their biological activities. The diverse synthetic approaches to the isomeric carbazolocarbazole ring systems **65**-**69** were summarized in chapter 4.[34]

Figure 6



Bringmann *et al.* reported a biomimetic oxidative dimerization of the monomer[35,36] **72** with di-*tert*-butyl peroxide (*t*-BuO)$_2$ afforded the 2,2′-linked bis(*O*-demethylmurrayafoline-A) **73** in 81% yield.[37]

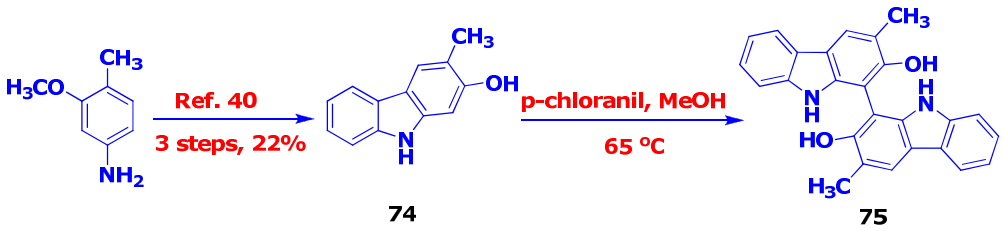
Eq. 9



Knölker and co-workers described the first total synthesis of 1,1′-bis(2-hydroxy-3-methylcarbazole) **75** *via* molybdenum-mediated construction of the carbazole framework.[38] The required monomer, 2-hydroxy-3-methylcarbazole **74**, was obtained in three steps and 22% overall yield starting from dicarbonyl(4-cyclohexa-1,3-diene)(5-cyclopentadienyl)molybdenum hexafluorophosphate[39] and 3-methoxy-4-methylaniline as synthetic precursors. Oxidative coupling of the monomer **74** using

p-chloranil provided 1,1′-*bis*(2-hydroxy-3-methylcarbazole) **75** in 38% yield (Eq. 10).[40]

Eq. 10



• Electrophilic cyclization

Alkynes are versatile building blocks in organic synthesis. A wide range of carbocycles and heterocycles have been prepared by the electrophilic cyclization of functionally substituted alkynes[41] and by transition metal-catalyzed annulations.[42] Recently, Larock and others have reported that the electrophilic cyclization of alkynes can be a very powerful tool for the preparation of a wide variety of interesting carbocyclic and heterocyclic compounds, including benzofurans,[43] furans,[44] benzothiophenes, [45] thiophenes,[46] benzopyrans,[47] benzoselenophenes,[48] selenophenes,[49] naphthols,[50] indoles,[51] quinolines,[52] isoquinolines,[53] *R*-pyrones,[54] isocoumarins,[54] isochromenes,[55] isoindolinones,[56] naphthalenes[57] and polycyclic aromatics,[58] isoxazoles,[59] chromones,[60] bicyclic-lactams,[61] cyclic carbonates,[62] pyrroles,[63] furopyridines,[64] spiro[4.5]trienones,[65] coumestrol and coumestans,[66] furanones,[67] benzothiazine-1,1-dioxides,[68] *etc*.[69] In general, these electrophilic cyclization reactions are very efficient, afford clean reactions, proceed under very mild reaction conditions in short reaction times, and tolerate almost all important functional groups. Furthermore, the iodine-containing products can be further elaborated to a wide range of functionally substituted derivatives using subsequent palladium-catalyzed processes. These reactions are generally believed to proceed by a stepwise mechanism involving electrophilic activation of the alkyne carbon-carbon triple bond, intramolecular nucleophilic attack on the cationic intermediate and subsequent de-alkylation.

This electrophilic cyclization methodology has been applied to a variety of unsymmetrical functionally substituted diarylalkynes and the resulting products characterized in order to determine the relative reactivities of various functional groups toward electrophilic cyclization. The required diarylalkynes are readily

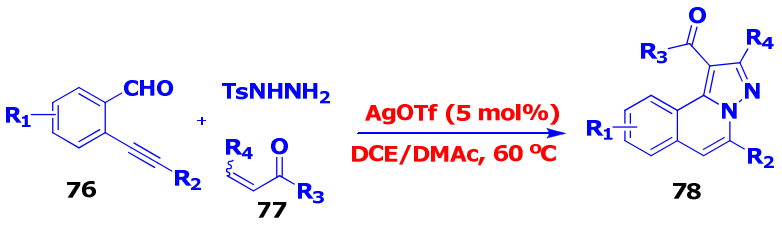
prepared by consecutive Sonogashira reactions[70] of appropriately substituted aryl halides. Thus, Sonogashira substitution with trimethylsilyl acetylene, removal of the TMS group, followed by a second Sonogashira reaction, generally affords moderate to excellent yields of the desired diarylalkynes. A number of factors affect the cyclization. These include electronic (relative nucleophilicity of the functional groups, polarization of the carbon-carbon triple bond, and the cationic nature of the intermediate) and steric factors (hindrance and geometrical alignment of the functional groups), as well as the nature of the electrophile.

Three kinds of results have been observed for these competitive cyclizations. (1) Only one of the two possible products has been obtained. This is most common, indicating that there is a hierarchy of functional group reactivity toward the electrophilic cyclizations. Assuming that the various factors mentioned above may affect the cyclization, the dominance of one functional group over another can be attributed to any one or a combination of two or more factors operating in favor of the one functional group over the other. (2) A mixture of both possible products has been observed. This occurs less commonly, but even in these cases, one product is often obtained in a significantly higher yield than the other, indicating that one group is usually significantly more reactive toward cyclization. (3) A complex reaction mixture is obtained. Although this does not provide any substantial information about the relative reactivity, it points to the fact that either the more reactive functional group is not compatible with the particular reaction conditions or neither of the two functional groups involved has a dominant reactivity, thus resulting in a complex reaction mixture. It also should be noted that since these reactions are very fast in general, and may involve multiple steps and intermediates, it is quite difficult to strictly assign the reactivity of any particular functional group to any one factor mentioned above. Indeed in some cases one or more factors are operating in opposition to each other, resulting in a mixture of products.

Jie Wu *et al* reported a highly efficient silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated carbonyl compound which affords *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylates in good yield (Eq. 11).[71] They explained that after condensation of 2-alkynylbenzaldehyde **76** with sulfonohydrazide, *N*'-(2-alkynylbenzylidene)hydrazide would be obtained. In the presence of AgOTf, the triple bond would be activated and then the 6-*endo*-cyclization occurred to afford the isoquinolinium-2-yl amide. Subsequently, acrylate **77** would be involved in the [3+2] cycloaddition process to generate the intermediate. After

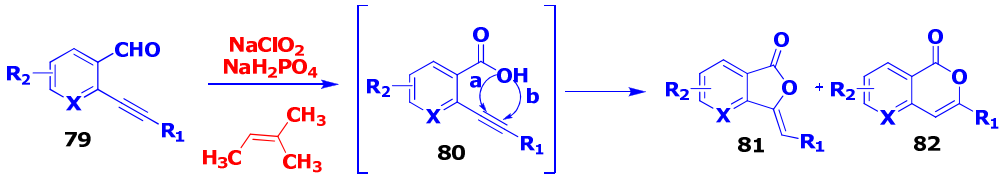
release of tosyl group and aromatization, *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylate **78** was then afforded.

Eq. 11



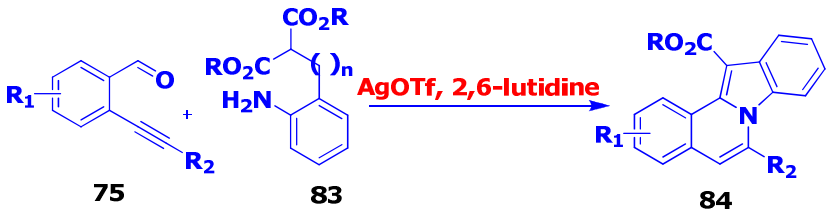
Jim Li and coworkers described a one-pot synthesis of phthalides via an intramolecular 5-*exo*-dig cyclization of *ortho*-alkynylbenzaldehydes under mild $NaClO_2$ oxidation conditions.[72] The alkynylarylaldehyde **79** was oxidized to acid **80**, which further cyclizes by the activation of triple bond to the products **81** and **82** (Eq. 12).

Eq. 12



Waldmann *et al.* reported silver catalyzed and microwave assisted one-pot cascade synthesis which provides efficient access to diverse alkaloid-inspired scaffold classes (Eq. 13) and a concise and efficient total synthesis of homofascaplysin C and fascaplysin.[73]

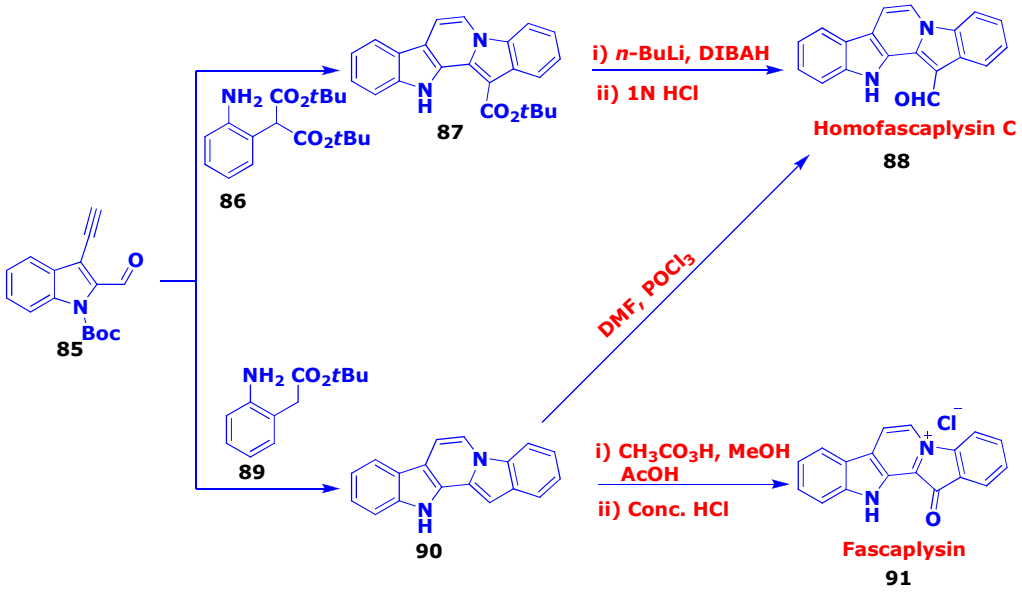
Eq. 13



Boc-protected 3-ethynyl-indole-2-carbaldehyde **85** was employed as a common precursor for the natural product targets fascaplysin **91** and homofascaplysin C **88**. The microwave assisted silver catalyzed cascade cyclization of **85** with aniline **86** yielded the pentacyclic core **87** in high yield after acidic work-up. Partial reduction of the *tert*-butyl ester (60% conversion) by means of *in situ* generated lithium

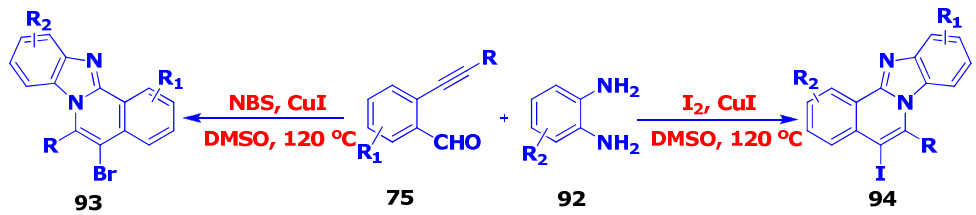
diisobutylpiperidinohydroaluminate provided the natural product homofascaplysin C **88** in 48% overall yield over four steps from **85** (Eq. 14). To overcome the difficult reduction of the *tert*-butyl ester **87** to final product **88**, aniline **89** was employed in the cascade synthesis of pentacyclic core **90** which was obtained in 61% yield. Formylation of **90** with $POCl_3$ cleanly provided homofascaplysin C **88** with an overall yield of 53%. In addition, the pentacyclic core **90** was efficiently transformed to the natural product fascaplysin **91** by oxidation with peracetic acid, followed by salt formation in 52% overall yield (Eq. 14).[74]

Eq. 14



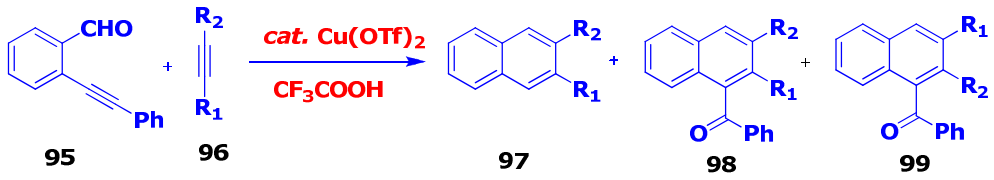
J.-H. Li and co-workers have developed an efficient tandem route to the synthesis of iodoisoquinoline-fused benzimidazole derivatives including an iodocyclization strategy (Eq. 15).[75] In the presence of CuI, a variety of 2-ethynylbenzaldehydes **75** underwent the tandem reaction with benzenediamines **92** and iodine to afford the corresponding iodoisoquinoline-fused benzimidazoles **94** and bromoisoquinoline fused benzimidazoles **93** in moderate to good yields.

Eq. 15



Y. Yamamoto *et al.* reported the reaction of *o*-alkynyl(oxo)benzenes **95** with alkynes **96** in the presence of a catalytic amount of $AuCl_3$ in $(CH_2Cl)_2$ at 80 °C which gave the [4+2] benzannulation products, naphthyl ketone derivatives **98** and **99** in high yields (Eq. 16).[76] When the reaction was carried out using $AuBr_3$ instead of $AuCl_3$, the reaction speed was enhanced and the chemical yield was increased. On the other hand, when the reaction was carried out in the presence of a catalytic amount of $Cu(OTf)_2$ and 1 equiv. of a Brønsted acid, such as CF_3CO_2H, in $(CH_2Cl)_2$ at 100 °C, the decarbonylated naphthalene products **97** were obtained in high yields.

Eq. 16



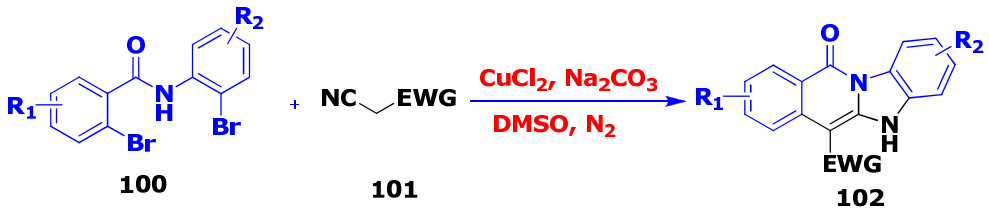
• Tandem Reactions

The future of organic synthesis lies in efficient methodology and the discovery of new processes for building up complex chemical architecture using simple techniques. Brevity in organic synthesis is of paramount importance for industry and over the past few years there were dramatic improvements in this subject and the development of novel catalysts for achieving tandem reactions. Such processes will minimize waste and costs will be kept to a minimum thus increasing efficiency. Transition metal catalyzed tandem reactions have emerged as a useful tool for the synthesis of multi-ring heterocyclic compounds because of the intriguing selectivity, atom economy,[77] and exceptional ability to activate π systems, especially alkynes, towards intermolecular and intramolecular nucleophilic attack.[78] Among the transition-metal-catalyzed reactions, palladium is extensively used because of its tolerance of many functional groups and its low toxicity.[79] However, in recent years copper-catalyzed reactions have received considerable attention because of their efficiency and low costs.[80] The reported annulation chemistry for the synthesis of heterocycles from alkynes proceeds through π complexation of the alkyne and subsequent attack of the resulting metal complex onto the appropriate adjacent functionalized arene.[81] Metal-free approach to tandem reactions attracts the chemists due to economical and environmental factors.

Fu *et al.* have developed a simple and efficient copper-catalyzed one-pot tandem method for synthesis of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives

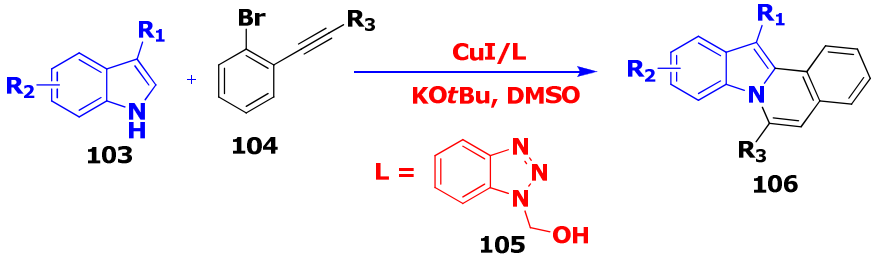
102 via reactions of substituted 2-halo-*N*-(2-halophenyl)benzamides **100** with alkyl 2-cyanoacetates **101** or malononitrile under mild conditions (Eq. 17).[82]

Eq. 17



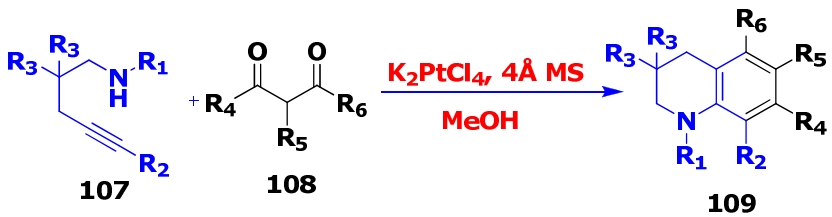
A facile and direct synthesis of diversely-substituted, medicinally-useful indolo- and pyrrolo[2,1-*a*]isoquinolines **106** in good yields with excellent regioselectivity was reported by A. K. Verma and co-workers (Eq. 18).[83]

Eq. 18



Che and Liu have described[84] a new, efficient platinum(II) catalyzed tandem cyclization reaction from simple, readily available starting materials to furnish multiply substituted indolines **109** in excellent yields with high regioselectivity under mild reaction conditions (Eq. 19). The procedure is easy to perform and allows for a straightforward, diversity-oriented and regioselective synthesis of indoline derivatives with a broad substrate scope, thus rendering the method a valuable addition to alternative indoline syntheses.

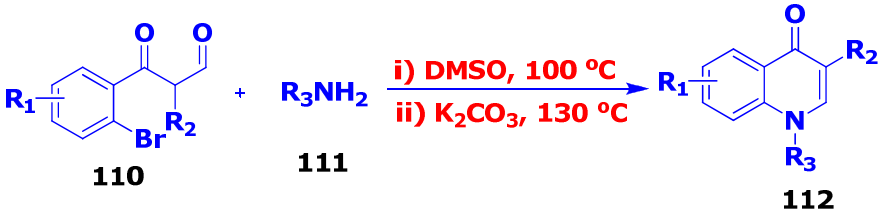
Eq. 19



• Metal-free tandem reactions

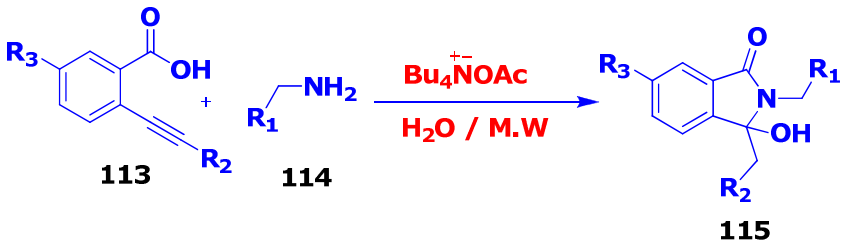
A copper-free tandem strategy using easily obtained β-ketoarylaldehydes **110** and amines **111** as starting material for the synthesis of 3-substituted 4-quinolones **112** is reported by Zhu *et al* (Eq. 20). The strategy gives 3-substituted quinolones **112** in up to 97.5% yield without isolation of intermediates, and is tolerant of a wide range of functional groups and applicable to library synthesis.[85]

Eq. 20



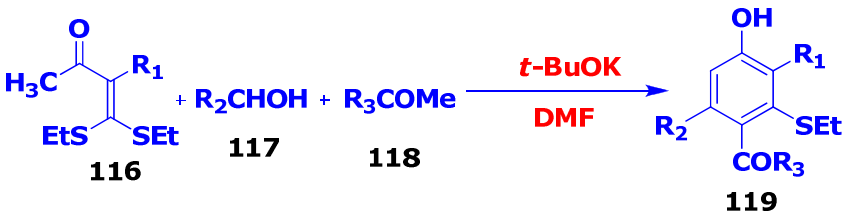
Liu and co-workers have developed[86] a mild and effective method for the construction of 3-hydroxyisoindolin-1-ones **115** *via* a metal-free tandem transformation using a phase transfer catalyst in good yields with excellent regioselectivity (Eq. 21). Significantly, the strategy presents an atom-economical and environmentally friendly transformation, and has a high functional group tolerance.

Eq. 21



Wang and Liu reported a facile multi-component synthesis of highly substituted phenols **119** has been developed starting from readily available acyclic precursors under mild conditions (Eq. 21).[87] In the first stage, the [4 + 1 + 1] annulation of an aldehyde **117** and two different methyl ketones **116** and **118** involving an aldol condensation/intermolecular Michael addition/intramolecular Michael addition/elimination of ethanethiol sequence, is highly chemo and regioselective since the two ketones show different reactivities.

Eq. 22



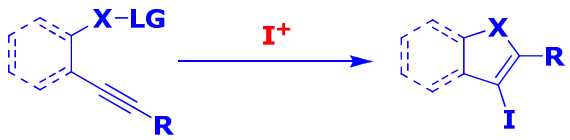
- **Iodocyclization**

The iodocyclization of alkynes has emerged as an efficient tool for the synthesis of important heterocycles and carbocycles. In general, iodocyclization is a very efficient reaction, proceeds under very mild reaction conditions and exhibits a very broad scope in terms of the functional group/substituent compatibility.[88] As iodine is known to be an excellent handle for further elaboration through transition-metal catalyzed cross-couplings, especially palladium-catalyzed transformations,[89] the iodocyclization products are ideal substrates for further functionalization and a rapid increase in molecular diversity. Polyheterocyclic compounds (PHCs) of this type have found applications in biological as well as materials chemistry. [90,91] The general strategies employed for poly-heterocycle synthesis involves the Sonogashira coupling of a functionally substituted haloarene with a functionalized alkyne. The alkyne is then subjected to iodocyclization, and the resulting 3-iodoheterocycle is generally isolated in good to excellent yields. The resulting iodine-containing heterocycle can be used as the starting material for further iterative cycles of Sonogashira coupling and iodocyclization to generate the desired polyheterocyclic molecule.

In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available reagent to effect iodocyclization and cyclodehydroiodination reactions of tethered heteroatom-containing alkenyl or alkynyl systems to afford heterocyclic compounds with many synthetic and biological applications. Although halogen molecules on their own are nonpolar, they are easily polarized by the π electrons of the C-C multiple bond to become electrophilic. The electrophilic properties of iodine have been exploited over the years to effect cyclization of heteroatom-containing alkenyl and alkynyl derivatives. Halocyclization is a reaction whereby the intramolecular nucleophilic group attacks the carbon–carbon double or triple bond activated by electrophilic halogenating reagent to give cyclic compounds (Eq. 23). The outcome of this cyclization strategy is rationalized in terms of the rules previously developed by Baldwin for predicting the relative ease of organic ring-forming reactions. The physical bases for these three rules are the

stereochemistry requirements of the transition states for various tetrahedral, trigonal, and digonal systems in nucleophilic, homolytic, and cationic ring closure processes.[92] Iodocyclization of tethered heteroatom-containing alkenyl or alkynyl derivatives as well as iodocyclization of 2-allyl-1,3-dicarbonyl derivatives take advantage of the electrophilic nature of iodine.

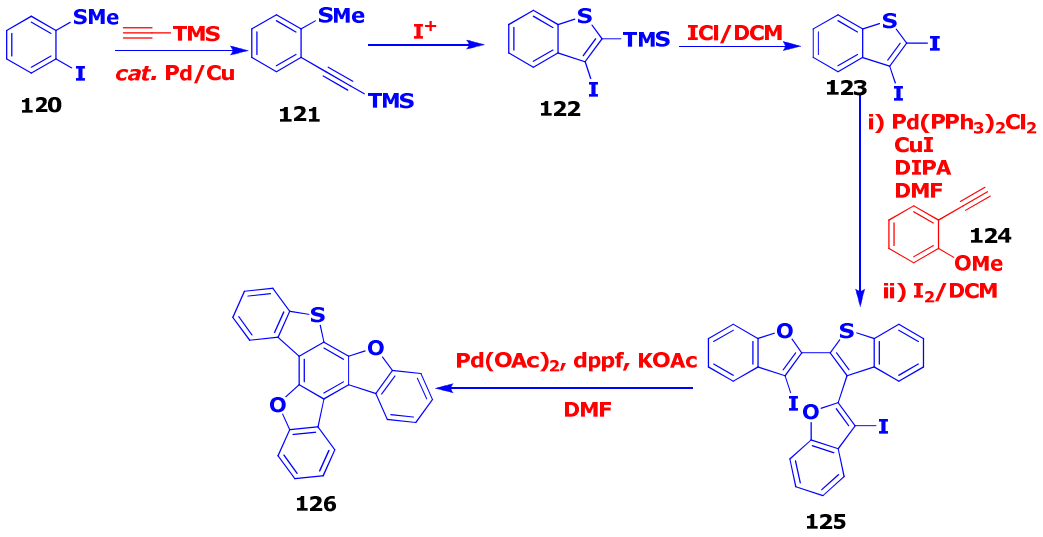
Eq. 23



LG = Leaving Group
X = O, S, NMe *etc*
R = Alkyl, Aryl, Vinylic, TMS

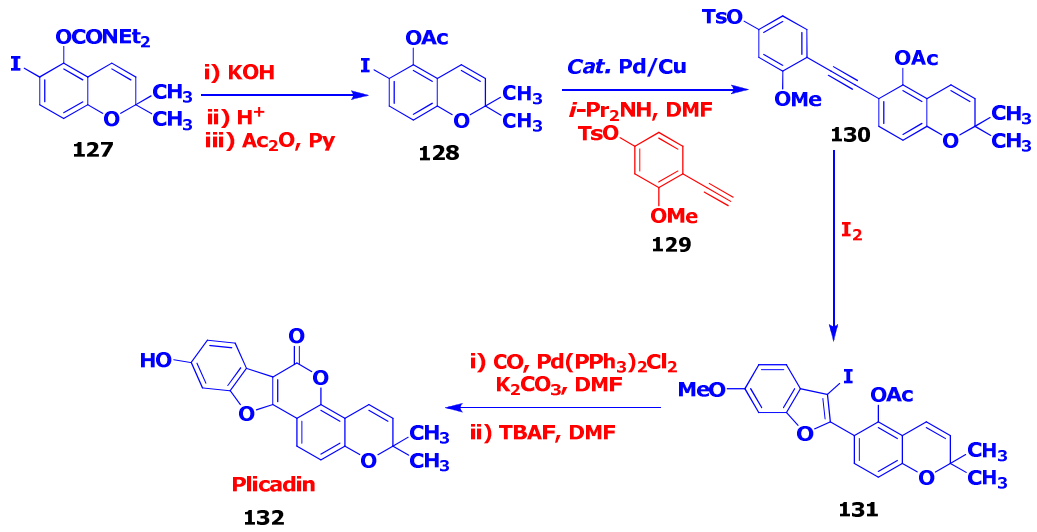
Larock *et al.* reported a simple strategy for the synthesis of polyheterocyclic compounds. After successful implementation of this general strategy for the efficient synthesis of PHCs, several variations in the approach have been explored that further highlight the versatility and scope of this methodology. First, iodocyclization can be carried out quite selectively affording a variety of intermediates, which should prove quite versatile for further elaboration. A variety of heterocyclic units are readily accessible by this iodocyclization strategy. This approach can be combined with other efficient transformations to broaden the scope of the methodology and allow easy access to heterocycles that are not presently accessible by iodocyclization. For example, in an effort to synthesize fused polyheterocyclic compounds, the benzothiophene derivative **122** was subjected to silyl-iodine exchange (Eq. 24). The resulting 2,3-diiodobenzothiophene **123** on double Sonogashira coupling with an appropriate *o*-functionalized terminal alkyne **124**, followed by double cyclization, quickly leads to a compound **125**, having three linked heterocyclic units and two iodine handles. The diiodo compound **125** was then subjected to a palladium-catalyzed Ullmann reaction leading to the formation of fused heterocycle **126** (Eq. 24).[93] Similar fused heterocyclic systems have been shown to exhibit interesting electronic and luminescent properties.[94] This approach can be conveniently extended to the synthesis of symmetrical fused heterocycles as well. PHCs such as these should prove useful as ligands in coordination and organometallic chemistry.

Eq. 24



Plicadin **132** was synthesized by Larock and co-workers employing iodocyclization methodology (Eq. 25). Hydrolysis of the known chromene carbamate **127**,[95] followed by protection of the resulting OH group as an acetoxy group, afforded chromene **128** in a 51% overall yield (Eq. 25). Sonogashira coupling of **128** with **129** under our previous optimized conditions led to alkyne **130** in a moderate yield. Iodocyclization of **130** afforded 3-iodobenzofuran **131** in a good yield (Eq. 25). Under optimal conditions for the Pd-catalyzed lactonization, benzofuran **131** is converted to the proposed plicadin tosylate in a 61% yield, which was nearly quantitatively converted to plicadin **132** by deprotection with TBAF.

Eq. 25

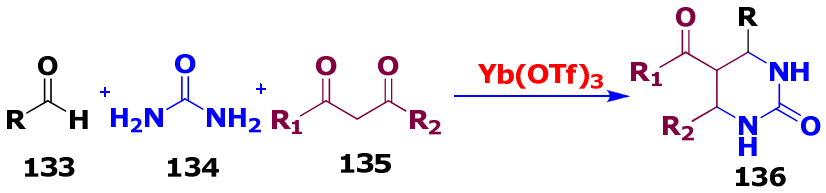


• Solvent-free reactions

Chemists still carry out their reactions in solution, even when a special reason for the use of solvent cannot be found. Many reactions proceed efficiently in the solid state.[96] Indeed, in many cases, solid-state organic reaction occurs more efficiently and more selectively than does its solution counterpart, since molecules in a crystal are arranged tightly and regularly. Furthermore, the solid-state reaction (or solvent-free reaction) has many advantages: reduced pollution, low costs, and simplicity in process and handling. Solvent-free thermal reactions are important for practical synthetic processes in industry. The occurrence of efficient solid-state reactions shows that the molecules reacting are able to move freely in the solid state.

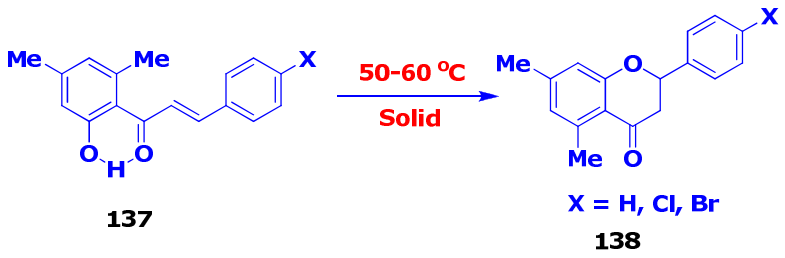
A new and simple modification of the Biginelli dihydropyrimidinones **136** from aldehydes **133**, urea **134** and 1,3-dicarbonyls **135** by using $Yb(OTf)_3$ as a catalyst and under solvent-free reaction conditions was reported by Quin and co-workers (Eq. 26).[97]

Eq. 26



As reported by Desiraju and co-workers,[98] several substituted 2′-hydroxy-4′,6′-dimethylchalcones **137** undergo a solid-state intramolecular Michael-type addition reaction to yield the corresponding flavanones **138**, at temperatures below their melting points. Conversions of the chalcones **137** to flavanones **138** could be followed by the orange to pale yellow color change (Eq. 27). X-ray studies of the reactant and product indicate that these reactions proceed in a non-topochemical fashion.

Eq. 27



However, not all organic synthesis can be carried out in the absence of solvent. Some organic reactions proceed explosively in the solid state. In such cases, solvent is useful in order to mediate the reaction rate. Finally, it is always important

to choose the best conditions for organic synthesis. For reactions that proceed moderately in the absence of solvent or in a water suspension, then solid-state reaction would be the better choice. For reactions that proceed vigorously in the solid state, then solution reaction in a nontoxic solvent would be better.

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Synthesis of Functionalized Ellipticinium, Ellipticine and Benzimidazo[2,1-*a*] ellipticine Derivatives

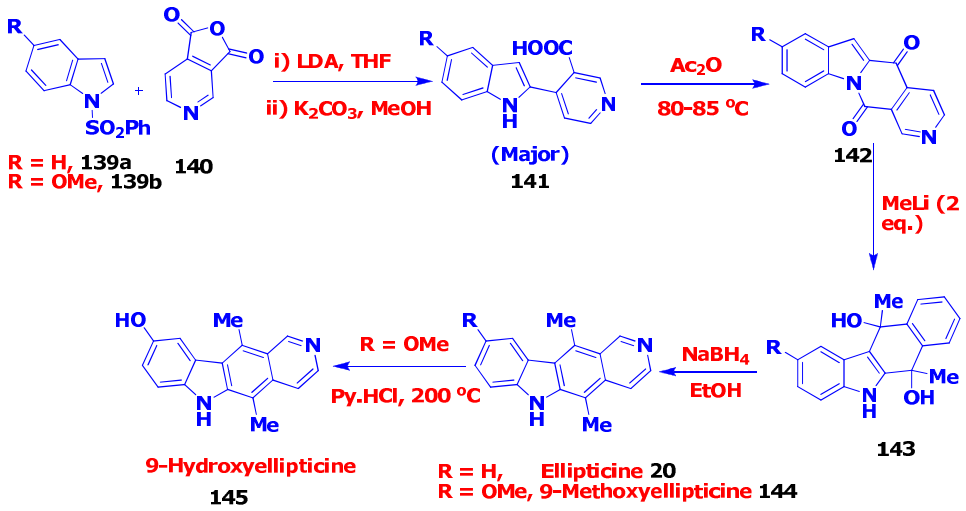
CHAPTER 1

1.1. Introduction

The plant alkaloids ellipticine, 9-methoxyellipticine, 9-hydroxyellipticine and olivacine are potent antitumor agents and elliptinium is used clinically as a drug to treat advanced breast cancer, myeloblastic leukemia and some solid tumors. In recent years many second generation ellipticine-derived antitumor agents like datelliptium and retellipticine have been developed. The molecular basis for their antitumor activity stems from their ability to intercalate between the base pairs in DNA.[99] 9-Hydroxyellipticine exhibits enhanced antitumor activity relative to ellipticine, since the presence of the 9-hydroxyl group could stabilize the intercalating complex by hydrogen bonding with the phosphate groups or base pairs present in the DNA.[100] Further, 9-hydroxyellipticine undergoes oxidation *in vivo* resulting in the formation of electrophilic quinine imines. This type of quinone imines could covalently bind to biomolecules such as proteins and nucleic acids.[101] The promising anticancer activity of ellipticine and its analogues prompted chemists to develop simple synthetic routes to access ellipticine nucleus and to synthesize a number of analogues for pharmacological evaluation.[102]

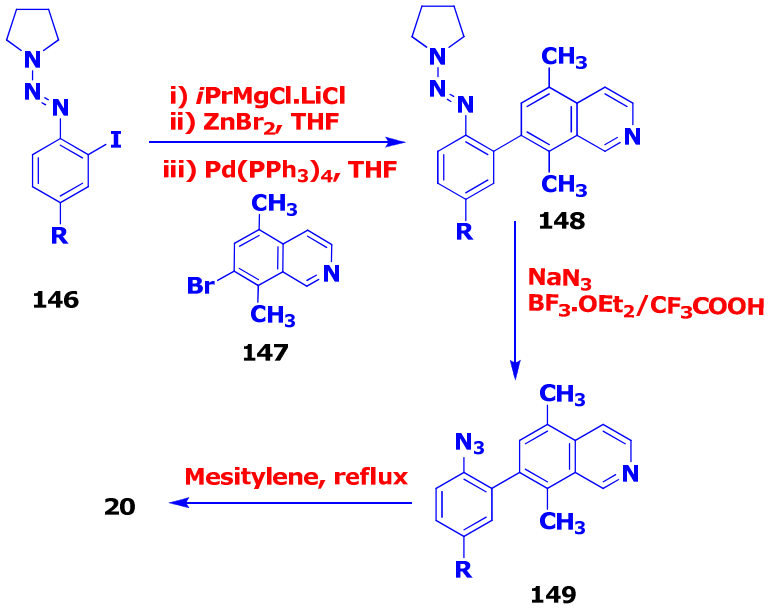
A general and efficient synthesis of the 6*H*-pyrido[4,3-*b*]carbazole ring system was described by Gribble and co-workers,[103] in which the key steps were (1) regioselective acylation of a 1-(phenylsulfonyl)indole **139** with 3,4-pyridinedicarboxylic acid anhydride **140**, (2) cyclization of the deprotected keto acid **141** to keto lactam **142** with acetic anhydride, and (3) the addition of methyllithium to give, after reduction of the intermediate diol **143** with sodium borohydride, the target ring system (Eq. 28). In this fashion, ellipticine **20**, 9-methoxyellipticine **144**, and 9-hydroxyellipticine **145** were synthesized in excellent overall yields from indole.

Eq. 28



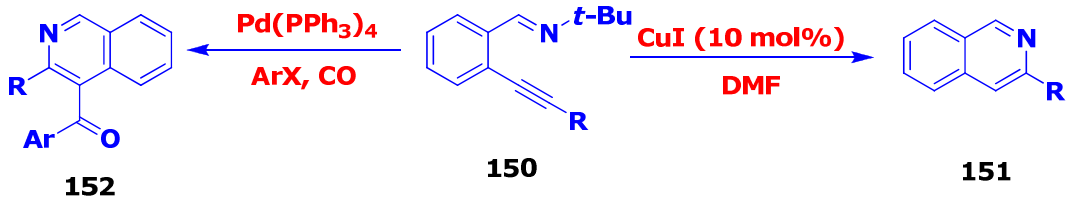
Knochel and co-workers have accomplished ellipticine synthesis[104] by starting with the triazene **146**. After I/Mg exchange with *i*PrMgCl.LiCl (-40 °C, 1 h) and transmetalation with $ZnBr_2$, the resulting zinc intermediate was submitted to a Negishi cross-coupling[105] with 7-bromo-5,8-dimethylisoquinoline **147** leading to the poly-functional aryl triazene **148** (75%). This compound was readily converted to the corresponding aryl azide **149** (78%) by the addition of BF_3OEt_2/TFA in CH_2Cl_2 in the presence of NaN_3. Thermal decomposition of azide **149** in refluxing mesitylene (6 h) gave ellipticine **20** in 57% yield (Eq. 29). The same approach was used for preparing 9-methoxyellipticine.

Eq. 29



Larock *et al.* have developed an efficient palladium- and copper-catalyzed synthesis of isoquinolines **151** and pyridines (Eq. 30).[106] A wide variety of functionalized terminal acetylenes participate in this palladium-catalyzed coupling and copper catalyzed cyclization process to afford the desired nitrogen heterocycles in moderate to excellent yields. Employing the same precursors Larock and co-workers had also developed an efficient synthetic approach for the carbonylative cyclization of *N*-*tert*-butyl-*o*-(1-alkynyl)benzaldimines **150** to the corresponding 3-substituted 4-aroylisoquinolines **152**.[107]

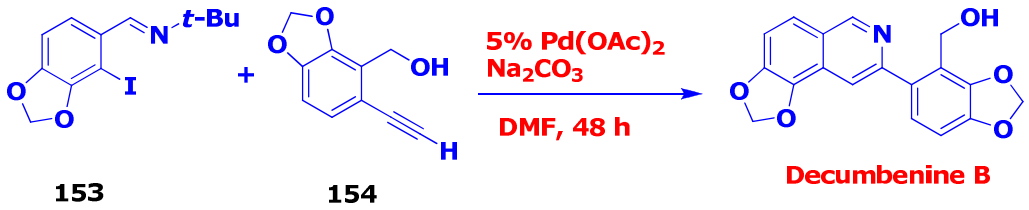
Eq. 30



To demonstrate the versatility of this annulation methodology, they have applied this coupling/cyclization process to the synthesis of the naturally occurring isoquinoline alkaloid decumbenine B **155**. Employing the palladium-catalyzed coupling/cyclization of imine **153** and alkyne **154**, since the alkyne contains alcohol

functionality, decumbenine B was synthesized in seven steps and 20% overall yield (Eq. 31).

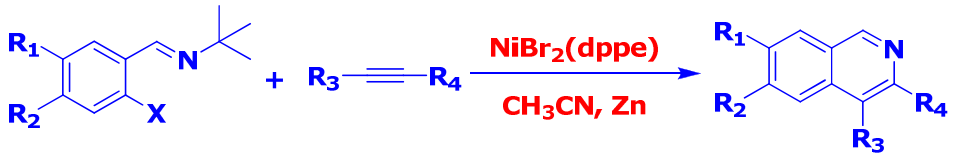
Eq. 31



153 **154** **Decumbenine B** **155**

Cheng and Korivi have demonstrated[108] a very convenient and highly regioselective synthetic approach for the preparation of substituted isoquinolines **158** (Eq. 32). This nickel-catalyzed annulation was much more efficient than the known palladium catalyzed reaction in terms of the catalytic reaction rate and the scope of the alkyne substrates. The method tolerates a wide variety of functional groups and utilizes non-expensive catalysts like nickel salts.

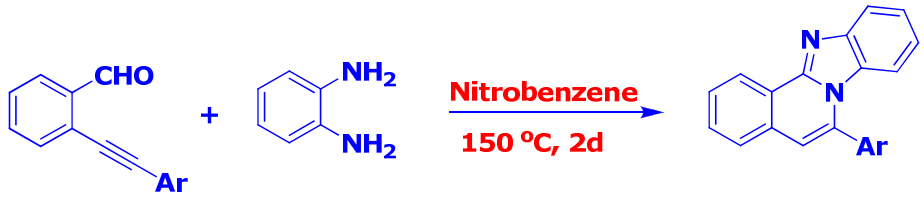
Eq. 32



156 **157** **158**

Dyker *et al*. have reported a domino process for the synthesis of benzimidazo[2,1-*a*]isoquinolines **161** from 2-alkynylbenzaldehydes **159** and 1,2-aryldiamines **160** upon refluxing in nitrobenzene for 2 days. The products were obtained in poor yields (Eq. 33).[109]

Eq. 33

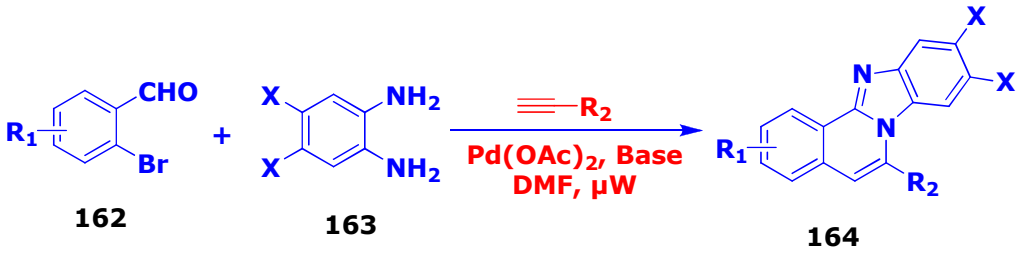


159 **160** **161**

Yanada and co-workers have demonstrated a new and concise method for one-pot construction of benzimidazo[2,1-*a*]isoquinolines **164** starting from 2-bromoarylaldehydes **162**, terminal alkynes, and 1,2-phenylenediamines **163** by a

microwave-promoted tandem process that involves imine formation, copper-ligand-free Sonogashira reaction, 5-*endo-trig* cyclization, oxidative aromatization, and 6-*endo-dig* cyclization reaction (Eq. 34).[110]

Eq. 34



162 **163** **164**

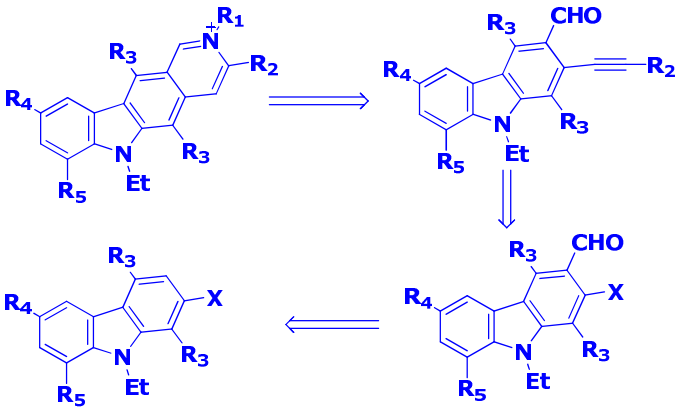
1.2. Synthesis of Ellipticinium derivatives

In most of the earlier reports, these compounds were derivatized directly from ellipticine, leaving a limited scope to prepare more number of diverse candidates for clinical trials. Further there are very few reports available in literature for the synthesis of these diverse and functionalized ellipticinium and ellipticine derivatives. In this context, development of a useful methodology for the synthesis of various functionalized ellipticinium and ellipticine derivatives is important. In continuation of our research in the development of efficient methodologies for the synthesis of heteroarylcarbazoles, we started working on the development of a simple and facile methodology for the synthesis of isomeric ellipticine derivatives.[111]

Recently, there has been an immense synthetic interest in the application of 2-alkynylarylaldehydes towards the synthesis of isoquinolines, benzofurans, benzopyrans, benzimidazoles and their derivatives.[112] 2-Alkynylarylaldehydes on reacting with amines in presence of various Lewis acidic metal salts undergo a facile electrophilic cyclization to furnish isoquinolines and their derivatives in excellent yields. We envisaged that 2-alkynyl-3-formylcarbazoles are excellent precursors for the synthesis of ellipticine derivatives. These 2-alkynyl-3-formylcarbazoles on reacting with various amines can be successfully converted to the corresponding ellipticine derivatives efficiently. Further this methodology can be of broad scope in terms of functionalizing the basic ellipticine motif at more positions and so significant in the synthesis of more derivatives of ellipticines and ellipticiniums.

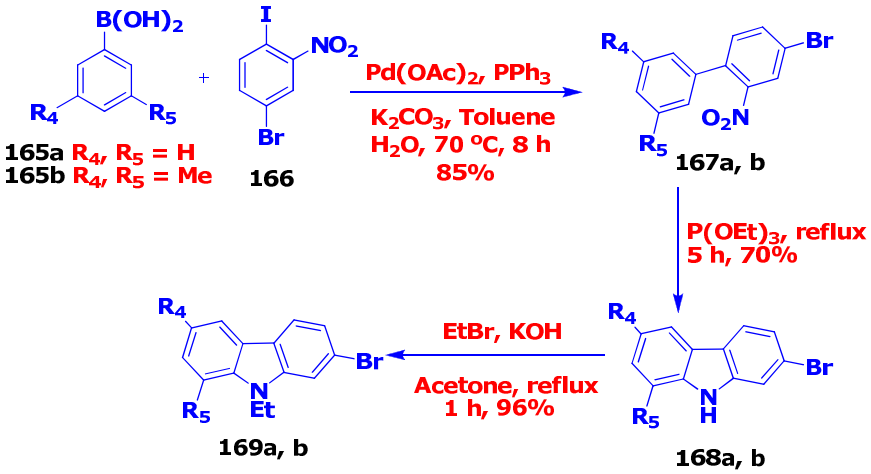
As outlined in Scheme 1, these precursor molecules can be prepared from the corresponding 2-bromoformyl carbazoles, which can be further obtained from the corresponding 2-bromocarbazoles.

Scheme 1. Outline of synthetic plan



The syntheses of 2-bromo-9-ethylcarbazoles **169a** and **169b** are depicted in Scheme 2. The arylboronic acids **165a** and **165b** on subjecting to Suzuki coupling with 4-bromo-2-nitroiodobenzene **166** in presence of palladium acetate and PPh_3 provided 4-bromo-2-nitrobiaryls **167a** and **167b** in 85% yields. **167a** and **167b** were subjected to reductive cyclization using triethylphosphite under reflux to give the corresponding bromocarbazoles **168a** and **168b** in 70% yield which upon *N*-alkylation using ethyl bromide and potassium hydroxide as base in acetone provided 2-bromo-9-ethylcarbazoles **169a** and **169b** in 96% yield.

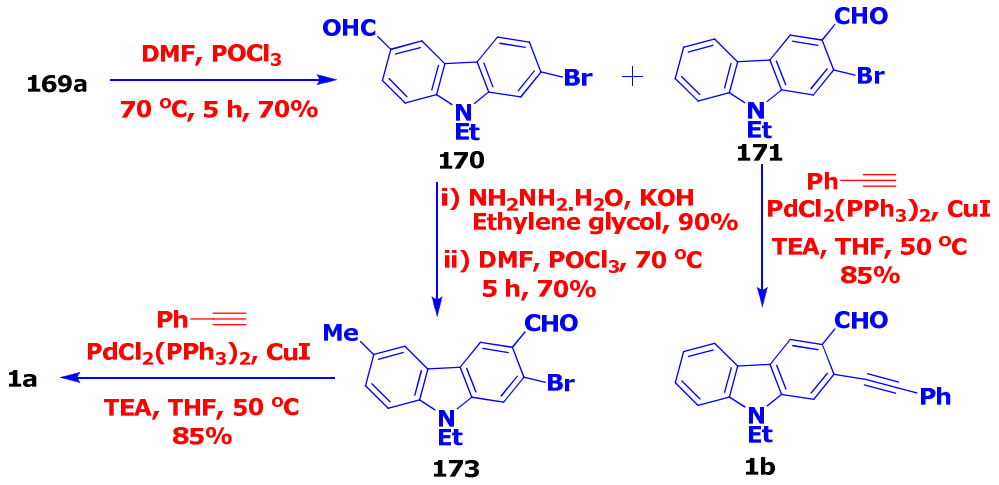
Scheme 2. Synthesis of 2-bromocarbazoles



As shown in Scheme 3, upon Vilsmeier-Haack formylation of **169a**, the desired 3-formyl regioisomer **171** was obtained in very low yield, where as the 6-formyl derivative **170** was formed as a major isomer. When we attempted the formylation of

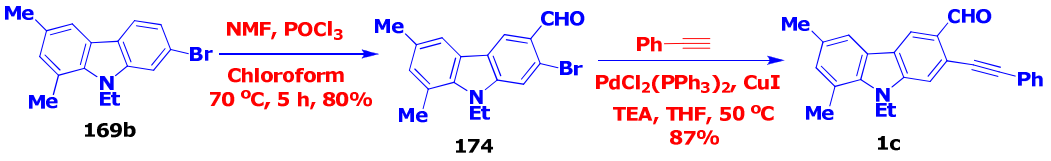
169a using *N*-methylformanilide as formylating agent, **170** was obtained exclusively. These observations led us to conclude that it may be due to the bulkiness and deactivating effect of bromo group the formylation is directed towards 6th position. The Wolff-Kishner reduction of 6-formyl derivative **170** provided the 2-bromo-9-ethyl-6-methyl-9*H*-carbazole in excellent yield. Vilsmeier-Haack formylation of 6-methyl derivative provided the 2-bromo-3-formyl-6-methyl derivative **173** in 70% yield. **173** on Sonogashira coupling with phenylacetylene employing *bis*(triphenylphospine)palladium dichloride, copper(I) iodide and triethylamine as a base afforded the precursor **1a** in 85% yield. Employing similar conditions, the precursor **1b** was obtained from **171** in 85% yield.

Scheme 3. Synthesis of precursors 1a and 1b



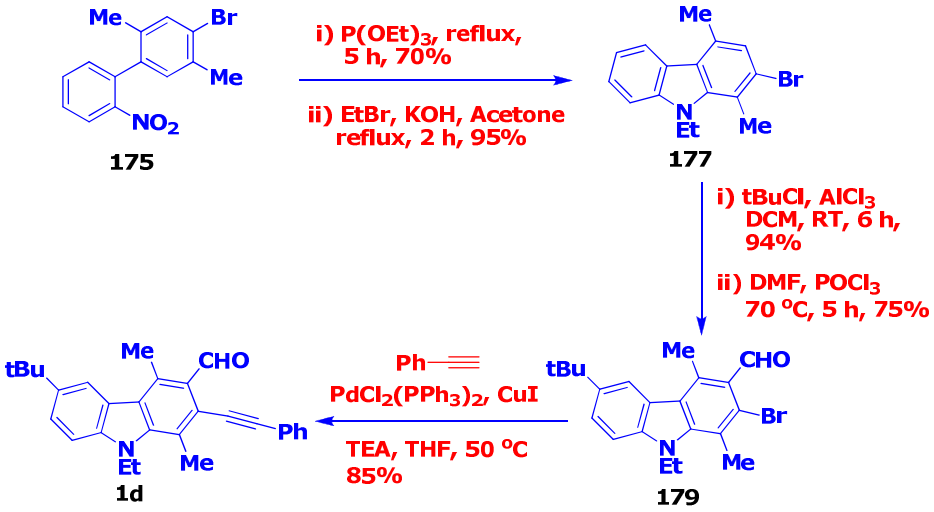
The synthesis of precursor molecule 6,8-dimethyl-3-formyl-2-phenylethynylcarbazole **1c** starting from 2-bromo-6,8-dimethyl-9-ethylcarbazole **169b** is outlined in Scheme 4. Vilsmeier-Haack formylation of **169b** using DMF and $POCl_3$ at 70 °C for 5 h provided the 2-bromo-6,8-dimethyl-3-formyl derivative **174** in 40% yield along with 7-formyl derivative in 20% yield. As expected, when *N*-methylformanilide was employed as formylating agent instead of DMF, exclusively **174** was obtained in 80% yield. Because of the bulkiness of the Vilsmeier salt formed from *N*-methylformanilide, formylation at 7th position was hindered. **174** on coupling with phenylacetylene under Sonogashira conditions afforded the precursor **1c** in 87% yield.

Scheme 4. Synthesis of precursor 1c



The synthesis of precursor 6-*tert*-butyl-3-formyl-2-phenylethynylcarbazole **1d** starting from 4-bromo-2,5-dimethyl-2′-nitrobiphenyl **175** is outlined in Scheme 5. The biphenyl **175** was prepared by Suzuki coupling of the 4-bromo-2,5-dimethylphenylboronic acid with 2-iodonitrobenzene using $Pd(OAc)_2$ and PPh_3. Reductive cyclization of **175** in triethylphosphite under reflux followed by *N*-alkylation with ethyl bromide using potassium hydroxide as base afforded 2-bromo-1,4-dimethyl-9-ethylcarbazole **177** in 65% overall yield. Upon Friedel-Craft's alkylation of **177** using *tert*-butyl chloride and aluminium chloride, 2-bromo-6-*tert*-butyl-9-ethyl-1,4-dimethyl-9*H*-carbazole was obtained regioselectively in 94% yield. The formation of other possible 3-*tert*-butyl regioisomer was not observed probably due to bulkier bromo substituent at 2nd position. The 2-bromo-1,4-dimethyl-3-formyl derivative **179** was obtained in 75% yield by Vilsmeier-Haack formylation of 6-*tert*-butyl derivative. A Sonogashira reaction of **179** with phenylacetylene using $Pd(PPh_3)_2Cl_2$ afforded precursor **1d** in 85% yield.

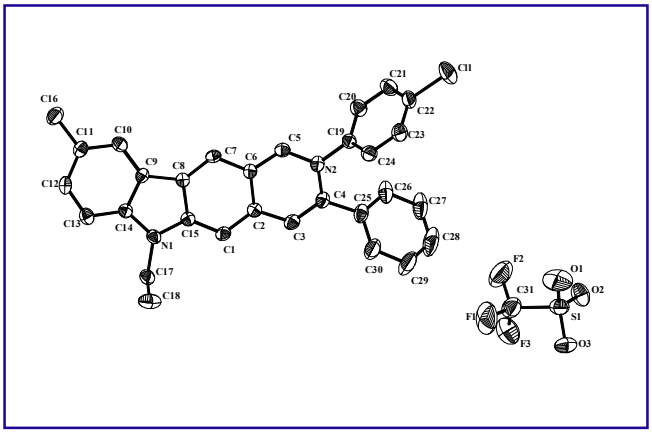
Scheme 5. Synthesis of precursor 1d



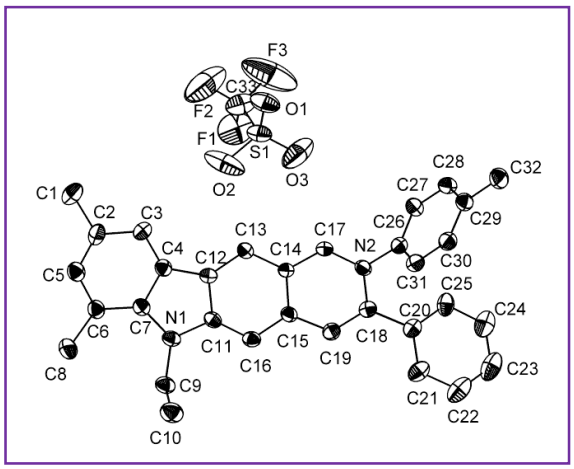
Then we carried out the electrophilic cyclization of **1a** with *p*-toluidine employing AgOTf (Table 1). When the reaction was carried out in one-pot involving both Schiff's base formation and cyclization using 4Å molecular sieves in ethanol, the

corresponding ellipticinium triflate **181** was obtained in 70% yield. But to our delight, when we carried out the cyclization of isolated aldimines employing AgOTf in CH_2Cl_2, the ellipticinium triflate **181** was obtained in almost quantitative yield. The precursor molecules **1a-1d** were subjected to electrophilic cyclization with various aliphatic and aromatic amines under the optimized conditions to provide highly functionalized ellipticinium derivatives in excellent yields. The results are summarized in Table 1. The structure of compounds **180** and **184** were also determined unambiguously by X-ray crystallography.[15] The ORTEP diagrams of **179** and 184 are shown in Figure 7. It is worth noting that various amines with diverse functionalities were employed and all the ellipticiniums were obtained in excellent yields.

Figure 7. ORTEP diagram of 180. Hydrogen atoms are omitted for clarity.

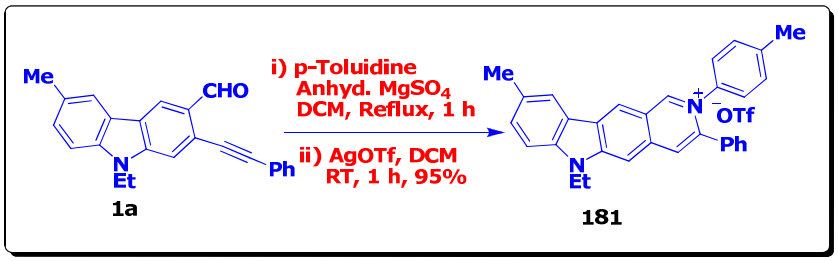


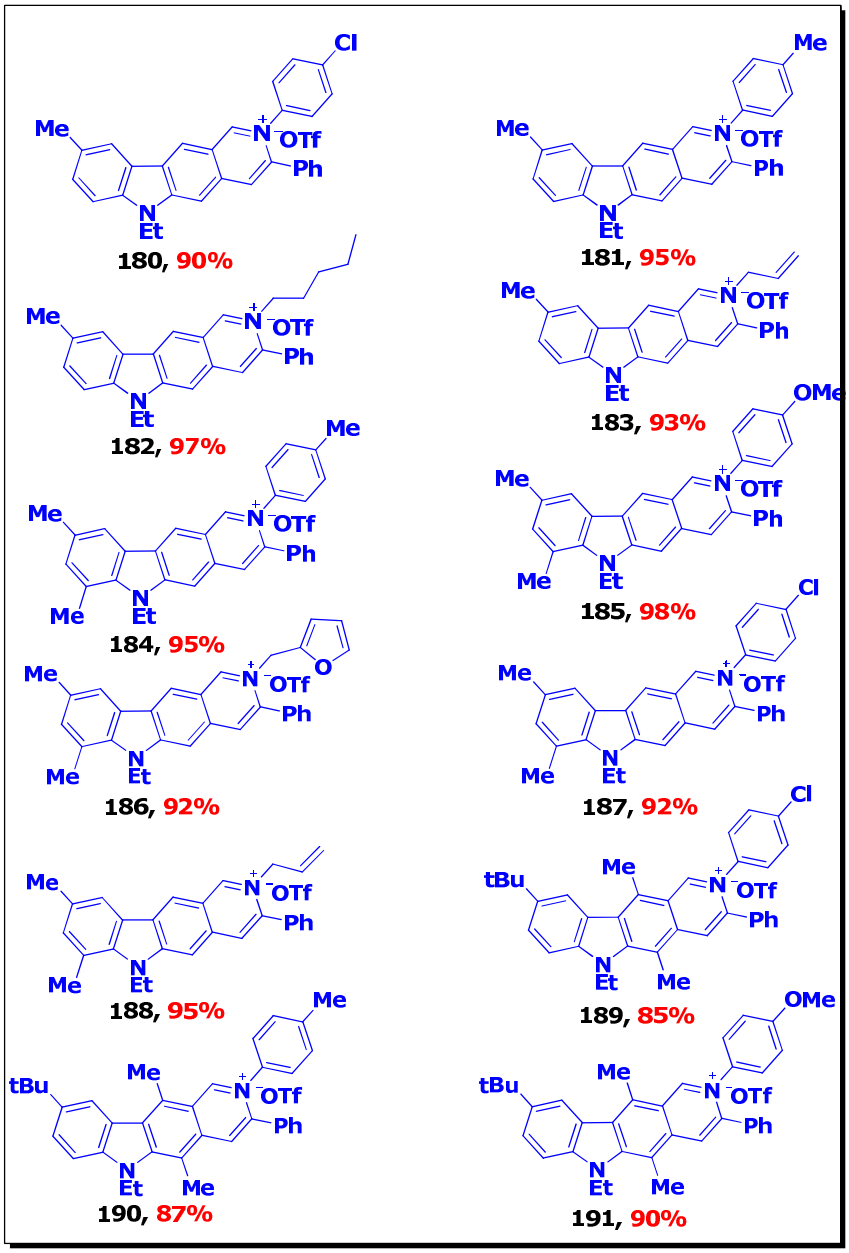
180



184

Table 1. Ellipticinium derivatives

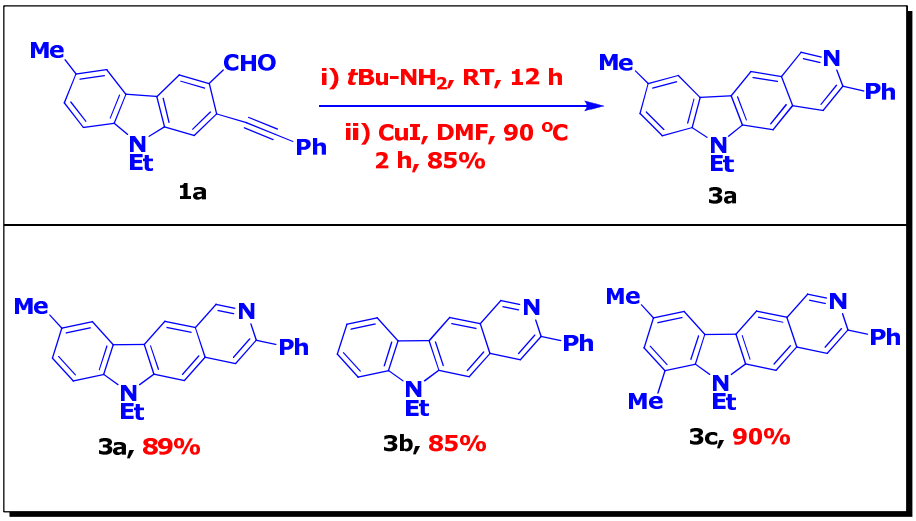




1.3. Synthesis of Ellipticine derivatives

Then we turned our attention towards the synthesis of ellipticine derivatives from the same precursor molecules. By employing the optimized conditions, we successfully prepared ellipticine derivatives in good yields. **1a**, **1b** and **1c** on reaction with *tert*-butylamine followed by CuI induced cyclization in DMF provided the corresponding ellipticines **3a**, **3b** and **3c** in 85-90% yields. The products are listed in Table 2. The precursor **1d** failed to form an imine with *tert*-butylamine probably due to steric hinderance between *tert*-butyl group of amine and methyl group at the 4th position of carbazole.

Table 2. Ellipticine derivatives



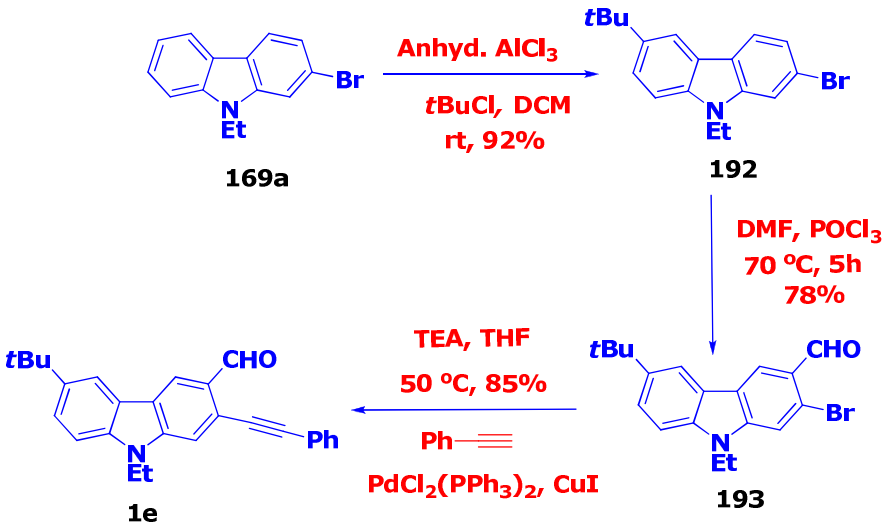
1.4. Synthesis of Benzimidazoellipticine derivatives

Compounds containing benzimidazole core systems have attracted considerable attention in recent years because of their promising antitumour activity and their fused heterocyclic variants have attracted considerable attention from medicinal and synthetic organic chemists because of their wide range of biological activities such as anxiolytic, antibacterial/antifungal, antineoplastic, anticancer, DNA intercalator etc.[113] Brana *et al*. and Hranjec *et al*. reported cyano- and amidino-substituted derivatives of styryl-2-benzimidazoles, benzimidazo[1,2-*a*]quinolines, benzimidazo[1,2-*c*]quinazolines and showed that these compounds have excellent DNA intercalation properties.[114] Considering the importance of benzimidazole fused heterocyclic moieties, synthesis of benzimidazo[2,1-*a*]ellipticine derivatives is desirable.

Tandem cyclization using metal catalysts has become one of the most powerful tools for the synthesis molecules containing ring systems.[115] One of the most efficient methodologies involves direct formation of the benzimidazole ring from 2-alkynylarylaldehyde derivatives.[116] In the process of synthesizing ellipticine derivatives from 2-alkynyl-3-formylcarbaldimines by reacting with various amines, when we carried out the reaction with *o*-phenylenediamine in DMF using AgOTf, to our surprise we observed the formation of benzimidazoellipticine instead of the anticipated ellipticinium derivative. This interesting observation prompted us to investigate this tandem process.

9-Ethyl-2-bromocarbazole **169a** was selectively alkylated at 6th position using *tert*-butyl chloride and *anhyd.* aluminium chloride in dichloromethane to give **192** in 92% yield (Scheme 6). **192** on Vilsmeier-Haack formylation furnished the 3-formyl derivative **193** in 78% yield. **193** was coupled with phenylacetylene under Sonogashira conditions to provide the corresponding precursor **1e** in excellent yield. **1f** and **1g** were also prepared in similar manner.

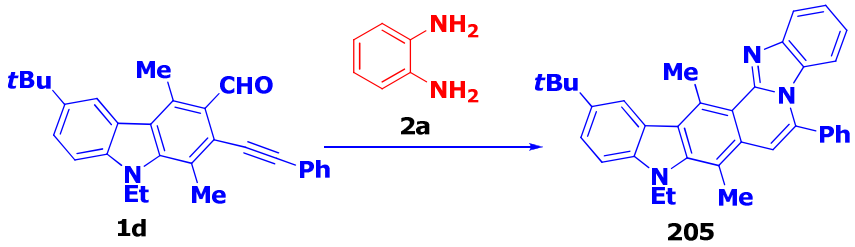
Scheme 6. Synthesis of precursor 1e



Upon heating the mixture of compounds **1d** and **2a** in nitrobenzene at 140 °C for 48h, we were able to obtain the desired product **205** but in poor yield; The prolonged reaction time and poor yield prompted us to optimize the reaction conditions (Table 3). When the reaction was carried out in water, a complex mixture of spots was observed in TLC and the desired product was not observed. Upon heating the reactants at 150 °C without solvent, no reaction was observed and starting materials were intact. When we employed comparatively low boiling solvents like

tetrahydrofuran and dioxane, we observed less conversion of starting materials with yields ranging from 25-40%, but when toluene was employed, we got 70% isolated yield of the product. From Table 3, we can conclude that DMF is the optimal choice for this tandem cyclization. A mixture of DMF and water had resulted in a complex mixture of products with 15% yield of product being isolated.

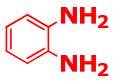
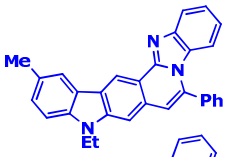
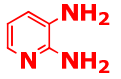
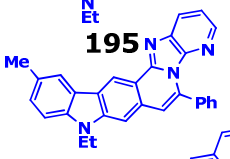
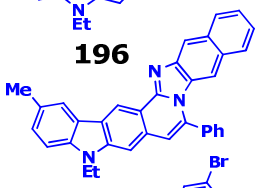
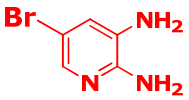
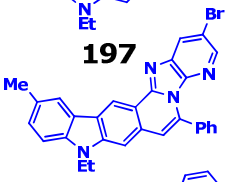
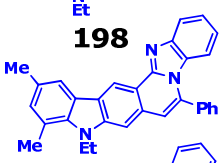
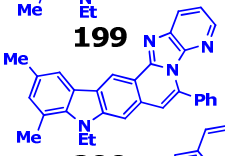
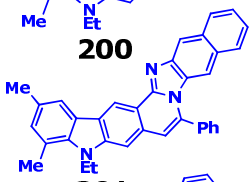
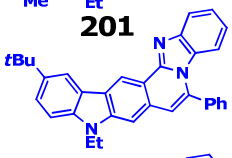
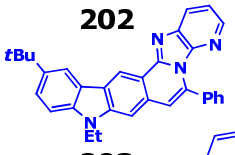
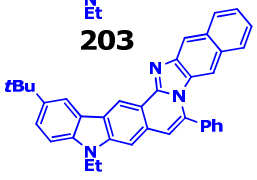
Table 3. Optimization chart



Run	Solvent	T °C	Time in hrs	Yield %
1	$PhNO_2$	140	24	56
2	DMSO	140	8	60
3	DMF	120	2	84
4	DMF+H_2O (1:1)	100	6	15
5	H_2O	reflux	8	–
6	THF	reflux	8	25
7	Dioxane	reflux	8	40
8	Toluene	reflux	4	70
9	Neat	150	2	–

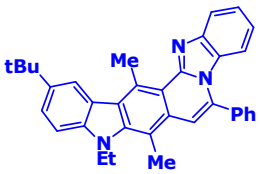
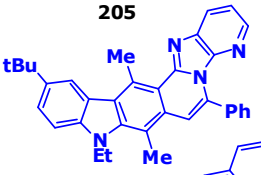
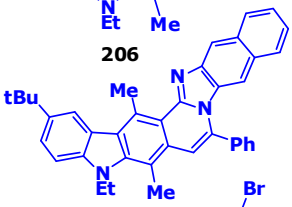
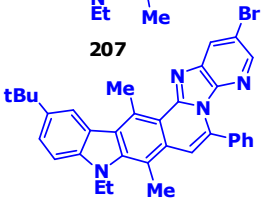
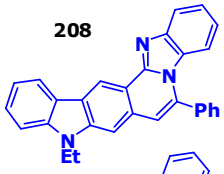
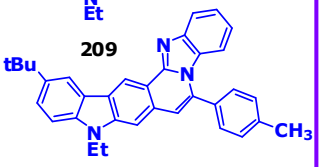
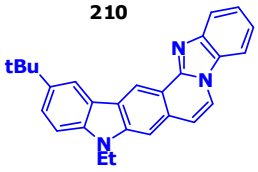
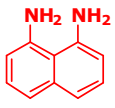
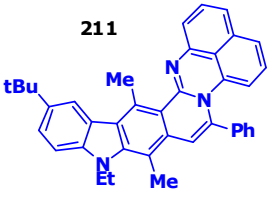
Having optimized the conditions, we carried out the reaction with different kinds of aryldiamines like naphthyl, pyridyl, 5-bromopyridyl etc. All precursors (**1a-1g**) on reacting with various aryldiamines (**2a-2d**) under optimized conditions, provided the corresponding benzimidazo[2,1-*a*]ellipticine derivatives in excellent yields (Table 4). Reaction with diamine **2e** has yielded no product indicating that the formation of six membered pyrimidine intermediate after the 5-*endo* cyclization may not be favoured. The electron withdrawing substituents on diamines have negatively affected the formation of products probably because of the decreased nucleophilicity

Table 4. Benzimidazoellipticine derivatives

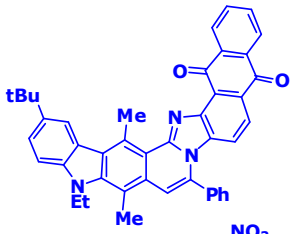
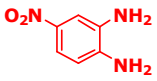
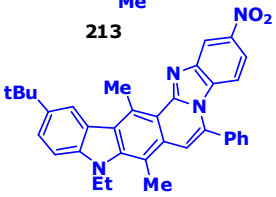
entry	precursor	Diamine	yield (%)	Product
1	1a	 2a	82	 195
2	1a	 2b	73	 196
3	1a	 2c	78	 197
4	1a	 2d	84	 198
5	1c	2a	81	 199
6	1c	2b	74	 200
7	1c	2c	80	 201
8	1e	2a	81	 202
9	1e	2b	76	 203
10	1e	2c	78	 204

of amino groups. So, we didn't observe any products in case of aryl diamines **2f** and **2g** (Table 4).

Contd...

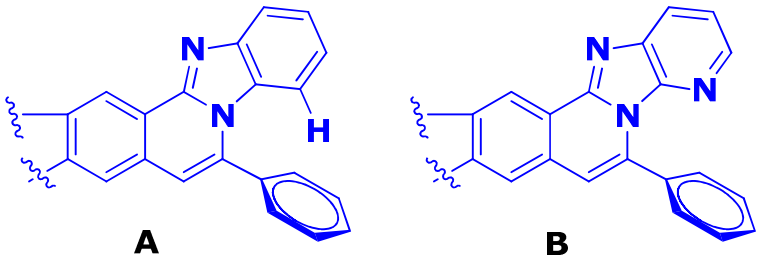
11	1d	2a	84	 205
12	1d	2b	72	 206
13	1d	2c	81	 207
14	1d	2d	85	 208
15	1b	2a	82	 209
16	1f	2a	79	 210
17	1g	2a	77	 211
18	1d	 2e	0	 212

Contd...

19	1d	 2f	0	 213
20	1d	 2g	trace	 214

Surprisingly when diaminopyridines **2b** and **2d** were employed, we obtained exclusively one regioisomer. The regioisomer was characterized by careful observation of ^{1}H NMR spectra.

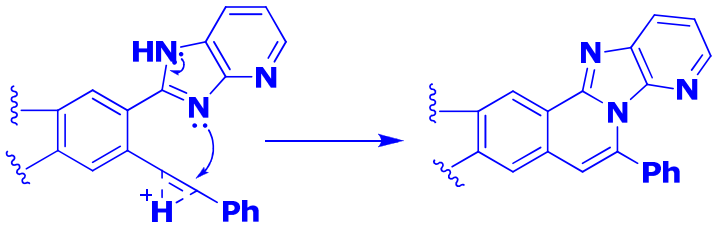
Figure 8. Electronic interactions between the proton and aryl ring (A). In pyridine case it is absent (B).



When we compared the ^{1}H NMR spectra of both phenyl and pyridyl diamines derived products, we observed that the up field aromatic proton peak around δ 6.5-6.2 in phenylenediamine cases was absent in pyridyldiamine spectra. This peak may correspond to the proton of phenylenediamine group that faces the phenyl substituent of alkynyl group. As shown in Figure 2, probably, because of the spatial electronic clouding of phenyl group (A), the proton signal was moved to up field. The perpendicular conformation of the phenyl ring (Figure 8) is the reason for this anisotropic effect. Where as in case of pyridyl, the regioisomer formed was the one with nitrogen facing the phenyl group (B); so the corresponding proton signal was

absent. This observation was further confirmed by X-ray crystallographic analysis in case of compound **196**.

Scheme 7. Possible mechanism

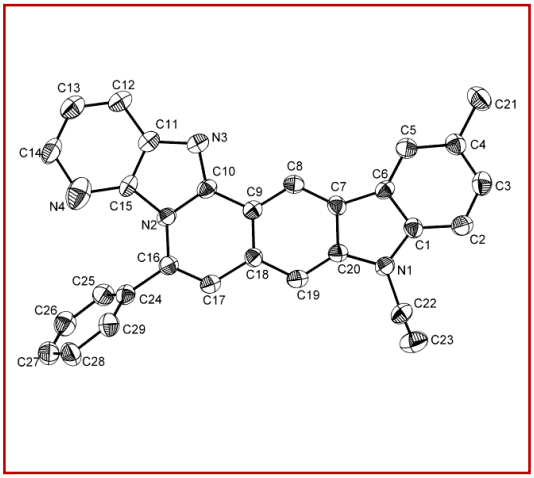


I **II**

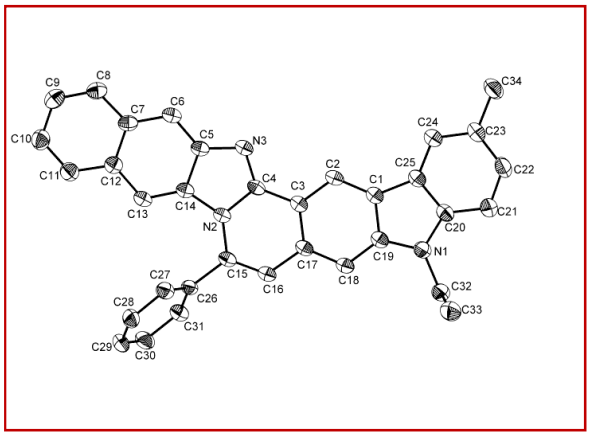
The formation of single regioisomer in case of diaminopyridines led us to draw some logical conclusions about how this tandem process may be happening (Scheme 7). In case of pyridyl, the benzimidazole intermediate **I** is the exclusive regioisomer that will form after 5-*endo* cyclization[117] because of the different nucleophilicities of amino groups and then the nitrogen lone pair attack on the triple bond results in the formation of product **II**. This observation is a clear evidence for the sequence of reactions in this tandem process; 5-*endo* cyclization, oxidative aromatization followed by 6-*endo* cyclization.

Absence of aldehydic proton peak at δ 10-11 and excess aromatic protons for corresponding diamine in ^{1}H NMR spectra indicate the formation of oxidized products. Compounds **196** and **197** were also confirmed by X-ray crystallographic analysis. The ORTEP diagrams are shown in Figure 9.

Figure 9. ORTEP diagrams of 196 and 197. Hydrogen atoms are omitted for clarity



196



197

1.5. Conclusion

In conclusion, we have developed a novel and efficient methodology for the synthesis of diverse and highly functionalized ellipticinium and ellipticine derivatives in excellent yields. Many carbazole intermediates with potential synthetic scope are synthesized for the first time. An efficient, metal-free synthesis of benzimidazo[2,1-*a*]ellipticine derivatives via a tandem inter- and intramolecular cyclization; 5-*endo* cyclization, oxidative aromatization followed by 6-*endo* cyclization in good yields is established. We successfully characterized and analyzed the formation of a single regioisomer in case of diaminopyridines.

The scope of this synthetic route is general and all the products are obtained in excellent yields. The overall modularity of this process is noteworthy. It is anticipated that this methodology can be extremely valuable for the development of selective anti-cancer agents with pyrido[4,3-*b*]carbazole skeleton. Studies toward this end will be the focus of future work from our laboratory.

1.6. Experimental Section

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

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

NMR Spectra: ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER AVANCE-400 spectrometer. ^{1}H NMR (400 MHz) spectra of the some samples were measured in chloroform-*d* (δ = 7.26 ppm) or in DMSO-d_6 (δ = 2.50 ppm) or in the mixture of $CDCl_3$/DMSO-d_6 with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (100 MHz) spectra of some samples were measured in chloroform-*d* (δ = 77.10 ppm, with its middle peak of the triplet as an internal standard) or in DMSO-d_6 (δ = 39.70 ppm its middle peak of the septet) or in the mixture of $CDCl_3$/DMSO-d_6.

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

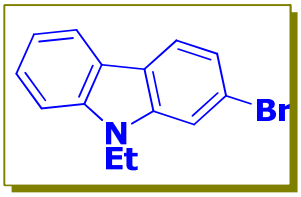
Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

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

2-Bromo-9-ethyl-9*H*-carbazole (169a):

A oven dried 250 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 10 g (0.04 mol) of 2-bromocarbazole and 100 mL of acetone under stirring. 6.8 g (0.12 mol) of potassium hydroxide is added and refluxed for 30 minutes. 5.8 mL (0.08 mol) of ethyl bromide was added slowly and reflux continued for 1 h, after which time TLC (90:10 hexanes:ethyl acetate) indicated complete conversion. Reaction was allowed to room temperature and acetone is removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with 2% dil. hydrochloric acid, water and brine. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to give white solid. The crude material was used further without purification.

Yield: 96%



Mp: 77-79 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2970, 1591, 1489, 1473, 1448, 1323, 1230, 1153, 1122, 1053, 900, 830, 806, 746, 717, 428

^{1}H NMR (400 MHz) δ: 8.10 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 7.53 (t, *J* = 6.8 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 6.8 , 1.6 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 4.28 (q, *J* = 8.0 Hz, 2H), 1.45 (t, *J* = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 140.8, 140.1, 126.1, 122.4, 121.9, 121.9, 121.5, 120.4, 119.4, 119.3, 115.6, 108.7, 37.7, 13.8

LCMS (m/z): 274 (M), 276 (M+2)

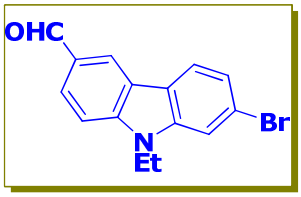
Anal. Calcd. for $C_{14}H_{12}BrN$: C, 61.33; H, 4.41; N, 5.11%

Found: C, 61.23; H, 4.48; N, 5.15%

Formylation of 2-bromo-9-ethyl-9*H*-carbazole (170 and 171):

A oven dried 250 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 10 g (0.036 mol) of 2-bromo-9-ethylcarbazole (**169a**) and 80 mL of dimethylformamide under stirring and cooled to 0 °C. 10 mL (0.11 mol) of phosphoryl chloride was added dropwise for 15 minutes. Reaction was allowed to room temperature and heated at 70 °C for 5 h, after which time TLC (90:10 hexanes:ethyl acetate) indicated complete conversion. Reaction was allowed to room temperature and quenched with ice. The reaction mass was poured into crushed ice slowly, neutralized with 5% aq. sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent is removed under reduced pressure. The crude material was purified by column chromatography (eluent: 5-10% ethyl acetate in hexane). 3-Formyl derivative was eluted in 5% eluent as minor isomer and 6-formyl derivative is eluted in 10% eluent as major isomer. Overall yield: 70%

7-Bromo-9-ethyl-9*H*-carbazole-3-carbaldehyde (170):



Yield: 65%

Mp: 129-131 °C

IR (KBr) ν_{max} cm^{-1}: 2974, 2814, 2723, 1582, 1622, 1585, 1485, 1431, 1234, 1170, 1143, 908, 804, 742, 549

^{1}H NMR (400 MHz) δ: 10.12 (s, 1H), 8.52 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.40 – 7.43 (m, 2H), 4.30 (q, 2H), 1.43 (t, *J* = 7.6 Hz, 3H)

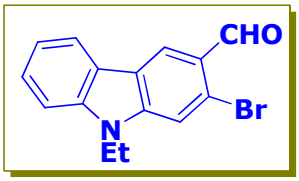
^{13}C NMR (100 MHz) δ: 191.6, 143.6, 141.4, 129.0, 127.5, 123.8, 123.5, 122.6, 121.9, 121.9, 120.4, 112.3, 108.9, 38.1, 13.8

LC–MS (m/z): 302 (M), 304 (M+2)

Anal. Calcd. for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; N, 4.64 %

Found: C, 59.72; H, 4.08; N, 4.55 %

2-Bromo-9-ethyl-9*H*-carbazole-3-carbaldehyde (171):



Yield: 5%

Mp: 125-127 °C

IR (KBr) ν_{max} cm^{-1}: 2974, 2852, 1680, 1589, 1469, 1425, 1346, 1317, 1236, 912, 838, 792, 742, 430

^{1}H NMR (400 MHz) δ: 10.42 (s, 1H), 8.63 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.57 (m, 2H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 4.28 (q, *J* = 7.6 Hz, 2H), 1.45 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 191.7, 143.7, 140.8, 127.2, 124.8, 124.1, 122.8, 122.7, 122.5, 121.0, 120.8, 112.7, 109.3, 37.8, 13.8

LC–MS (m/z): 302 (M), 304 (M+2)

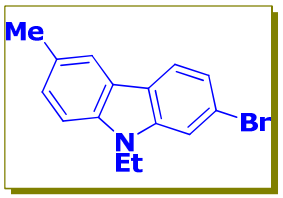
Anal. Calcd. for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; N, 4.64 %

Found: C, 59.48; H, 4.12; N, 4.71 %

2-Bromo-9-ethyl-6-methyl-9*H*-carbazole (172):

A oven dried 250 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 5 g (0.016 mol) of 7-bromo-9-ethyl-9*H*-carbazole-3-carbaldehyde (**170**) and 100 mL of ethylene glycol under stirring. 1.85 g (0.033 mol) of potassium hydroxide and 1.65 mL (0.033 mol) of hydrazine hydrate were added under stirring. The reaction mixture was refluxed at 200 °C for 3 h, after which time TLC (90:10 hexanes:ethyl acetate) indicated complete conversion. Reaction was allowed to room temperature and quenched with ice. The reaction mass was poured into crushed ice slowly, neutralized with 2% dil. hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to give the 2-bromo-9-ethyl-6-methyl-9*H*-carbazole as pure white solid in almost quantitative yield. The product was used without further purification.

Yield: 95%



Mp: 78-80 °C

IR (KBr) ν_{max} cm^{-1}: 2974, 2922, 1682, 1628, 1593, 1483, 1442, 1228, 1084, 1060, 842, 798, 592, 416

^{1}H NMR (400 MHz) δ: 7.91 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.54 (s, 1H), 7.31 – 7.33 (m, 3H), 4.29 (q, J = 8.0 Hz, 2H), 2.56 (s, 3H), 1.42 (t, J = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 141.0, 138.4, 128.7, 127.4, 122.6, 121.7, 121.6, 121.5, 120.4, 119.1, 111.5, 108.4, 37.7, 21.4, 13.7

LC–MS (m/z): 288 (M), 300 (M+2)

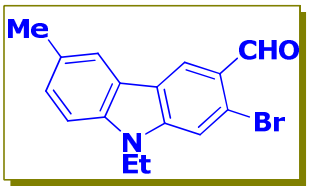
Anal. Calcd. for $C_{15}H_{14}BrN$: C, 62.52; H, 4.90; N, 4.86 %

Found: C, 62.45; H, 4.95; N, 4.81 %

2-Bromo-9-ethyl-6-methyl-9*H*-carbazole-3-carbaldehyde (173):

Procedure for the preparation of **171** was followed to give 2-bromo-9-ethyl-6-methyl-9*H*-carbazole-3-carbaldehyde **173** as a white solid after column chromatography with 10% hexanes in ethyl acetate.

Yield: 70%



Mp: 148-150 °C

IR (KBr) ν_{max} cm^{-1}: 2916, 2843, 1670, 1595, 1479, 1350, 1302, 1224, 1145, 856, 790, 761, 694, 464, 420

^{1}H NMR (400 MHz) δ: 10.39 (s, 1H), 8.57 (s, 1H), 7.84 (s, 1H), 7.48 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 4.24 (q, J = 7.6 Hz, 2H), 2.53 (s, 3H), 1.42 (t, J = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 191.7, 143.8, 139.6, 130.3, 128.5, 124.5, 123.9, 123.0, 122.5, 122.5, 121.0, 112.5, 108.9, 38.0, 21.4, 13.8

LC–MS (m/z): 316 (M), 318 (M+2)

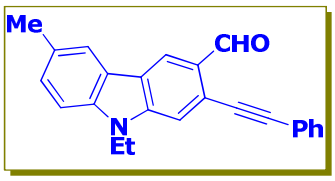
Anal. Calcd. for $C_{16}H_{14}BrNO$: C, 60.78; H, 4.46; N, 4.43 %

Found: C, 60.58; H, 4.40; N, 4.51 %

9-Ethyl-6-methyl-2-(phenylethynyl)-9*H*-carbazole-3-carbaldehyde (1a):

An oven dried 50 mL schlenk tube equipped with a teflon coated magnetic stirring bar was charged with 1 g (3 mmol) of **173**, 1 g of molecular sieves and 0.42 mL (3.8 mmol) of phenyl acetylene. The tube was evacuated and filled with nitrogen. To it, 10 mL of dry THF and 5 mL of freshly distilled triethylamine are added under nitrogen and the reaction was stirred for 10 minutes at room temperature. 42 mg of $Pd(PPh_3)_2Cl_2$ (2 mol%) and 6 mg of CuI (1 mol%) were added under nitrogen and the schlenk tube was heated at 60 °C for 4 h, after which time TLC (85:15 hexanes:ethyl acetate) indicated complete conversion. Reaction was allowed to room temperature and filtered. The filterate was poured into crushed ice slowly and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent is removed under reduced pressure. The crude material was purified by column chromatography (eluent: 8-15% ethyl acetate in hexane). The product was eluted in 12% eluent as a pale yellow solid.

Yield: 85%



Mp: 137-139 °C

IR (KBr) ν_{max} cm^{-1}: 2916, 2843, 1670, 1595, 1479, 1350, 1302, 1224, 1145, 856, 790, 761, 694, 464, 420

^{1}H NMR (400 MHz) δ: 10.72 (s, 1H), 8.68 (s 1H), 7.91 (s, 1H), 7.63 7.65 (m, 2H), 7.55 (s, 1H), 7.31 – 7.43 (m, 5H), 4.33 (q, J = 8.0 Hz, 2H), 2.56 (s, 3H), 1.47 (t, J = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 191.4, 142.8, 139.6, 131.6, 130.1, 128.8, 128.6, 128.5, 127.7, 123.7, 123.3, 123.1, 122.8, 121.1, 120.6, 112.3, 108.8, 95.1, 86.7, 37.9, 21.4, 13.8

LC–MS (m/z): 338 (M+H)

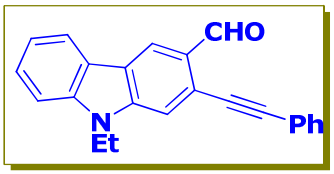
Anal. Calcd. for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15 %

Found: C, 85.21; H, 5.72; N, 4.22 %

9-Ethyl-2-(phenylethynyl)-9*H*-carbazole-3-carbaldehyde (1b):

Employing similar procedure for the synthesis of **1a**, **1b** was obtained as an yellow solid after column chromatography with 7% hexanes in ethyl acetate.

Yield: 85%



Mp: 110-112 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2970, 2843, 1672, 1620, 1589, 1494, 1469, 1452, 1359, 1329, 1232, 1159, 1126, 1103, 923, 898, 852, 760, 738, 719, 696, 665, 528, 468

^{1}H NMR (400 MHz) δ: 10.74 (s, 1H), 8.74 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.65 (m, 4H), 7.41 – 7.46 (m, 4H), 7.34 (t, *J* = 7.6 Hz, 1H), 4.38 (q, *J* = 7.6 Hz, 2H), 1.49 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 191.5, 142.7, 141.3, 131.6, 128.8, 128.5, 127.9, 127.3, 123.9, 123.3, 123.1, 122.7, 121.2, 120.7, 120.6, 112.4, 109.1, 95.2, 86.5, 38.0, 13.8

LC–MS (m/z): 324 (M+H)

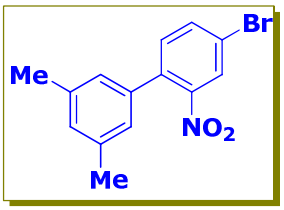
Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33 %

Found: C, 85.31; H, 5.41; N, 4.41 %

4-Bromo-3',5'-dimethyl-2-nitrobiphenyl (167b):

Employing similar procedure for the synthesis of **167a**, **167b** was obtained as yellow liquid which solidified gradually. The crude product was used without further purification.

Yield: 85%



Mp: 53-55 °C

IR (KBr) ν_{max} cm^{-1}: 3086, 2914, 1601, 1523, 1346, 1271, 1205, 1151, 1018, 883, 852, 831, 709, 688, 551, 432

^{1}H NMR (400 MHz) δ: 8.02 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 6.92 (s, 2H), 2.37 (s, 6H)

^{13}C NMR (100 MHz) δ: 149.6, 138.5, 136.2, 135.5, 135.2, 133.2, 130.3, 126.9, 125.5, 121.0, 21.3

LC–MS (m/z): 307 (M), 309 (M+2)

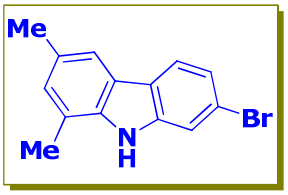
Anal. Calcd. for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.51 %

Found: C, 54.85; H, 3.92; N, 4.51 %

7-Bromo-1,3-dimethyl-9*H*-carbazole (168b):

Employing similar procedure for the synthesis of **168a**, **168b** was obtained as a white crystalline solid after column chromatography with 10% hexanes in ethyl acetate.

Yield: 70%



Mp: 123-125 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 3074, 2918, 2860, 1882, 1599, 1429, 1331, 1302, 1226, 1051, 1033, 850, 814, 584, 432, 414

^{1}H NMR (400 MHz) δ: 8.41 (bs, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.69 (s, 1H), 7.59 (s, 1H), 7.30 – 7.33 (m, 1H), 7.10 (s, 1H), 2.52 – 2.55 (t, 6H)

^{13}C NMR (100 MHz) δ: 140.6, 137.3, 129.3, 128.3, 122.6, 122.4, 122.2, 121.4, 119.7, 118.7, 117.6, 113.8, 21.4, 16.2

LC–MS (m/z): 274 (M), 276 (M+2)

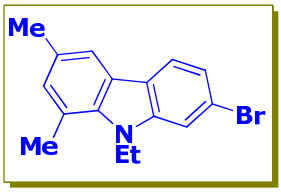
Anal. Calcd. for $C_{14}H_{12}BrN$: C, 61.33; H, 4.41; N, 5.11 %

Found: C, 61.24; H, 4.52; N, 5.31 %

7-Bromo-9-ethyl-1,3-dimethyl-9*H*-carbazole (169b):

169b was obtained by employing similar procedure for the synthesis of **169a** as a white solid. The crude product was used further without purification.

Yield: 95%



Mp: 123-125 °C

IR (KBr) ν_{max} cm^{-1}: 3468, 2922, 2864, 1593, 1471, 1439, 1331, 1219, 1055, 889, 842, 804, 582

^{1}H NMR (400 MHz) δ: 7.88 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.53 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 4.49 (q, *J* = 7.6 Hz, 2H), 2.78 (s, 3H), 2.52 (s, 3H), 1.41 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 141.7, 137.1, 130.9, 128.9, 123.5, 122.1, 121.8, 121.2, 119.9, 119.1, 118.1, 111.6, 39.5, 21.1, 19.8, 15.5

LC–MS (m/z): 302 (M), 304 (M+2)

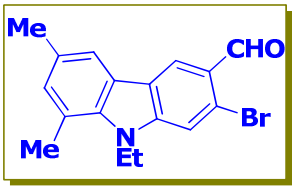
Anal. Calcd. for $C_{16}H_{16}BrN$: C, 63.59; H, 5.34; N, 4.63 %

Found: C, 63.52; H, 5.41; N, 4.55 %

2-Bromo-9-ethyl-6,8-dimethyl-9*H*-carbazole-3-carbaldehyde (174):

A oven dried 50 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 2 g (6.6 mmol) of **169b**, 10 mL of chloroform and 3 mL of *N*-methylformanilide. The reaction mixture was cooled in an ice bath at 0 °C–5 °C for 15 minutes. 2 mL of $POCl_3$ was added to the reaction mixture dropwise under stirring. Reaction mixture was allowed to room temperature and refluxed for 6 h, after which time TLC (90:10 hexanes:ethyl acetate) indicated complete conversion. Reaction was allowed to room temperature and quenched with ice. The reaction mass was poured into crushed ice slowly, neutralized with a ice cold solution of aq. 5% sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude material was purified by column chromatography (eluent: 10% ethyl acetate in hexane) and the product was obtained as white solid.

Yield: 80%



Mp: 139-141 °C

IR (KBr) ν_{max} cm^{-1}: 3013, 2878, 2916, 2852, 1668, 1593, 1469, 1442, 1342, 1309, 1222, 1155, 1005, 848, 704, 569, 416

^{1}H NMR (400 MHz) δ: 10.42 (s, 1H), 8.59 (s, 1H), 7.74 (s, 1H), 7.51 (s, 1H), 7.09 (s, 1H), 4.48 (q, J = 7.6 Hz, 2H), 2.76 (s, 3H), 2.42 (s, 3H), 1.45 (t, J = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 191.7, 144.5, 137.7, 132.0, 130.4, 124.7, 123.9, 123.8, 122.8, 122.2, 120.4, 118.7, 112.7, 39.8, 21.0, 19.6, 15.5

LC–MS (m/z): 330 (M), 332 (M+2)

Anal. Calcd. for $C_{17}H_{16}BrNO$: C, 61.83; H, 4.88; N, 4.24 %

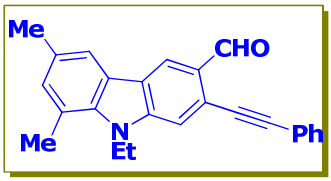
Found: C, 61.75; H, 4.81; N, 4.36 %

9-Ethyl-6,8-dimethyl-2-(phenylethynyl)-9*H*-carbazole-3-carbaldehyde (1c):

General procedure for the synthesis of **1a** and **1b** was employed. The product was obtained as a pale yellow solid after column chromatography with 10% hexanes in ethyl acetate.

Yield: 87%

Mp: 157-159 °C



IR (KBr) ν_{max} cm^{-1}: 3009, 2964, 2916, 2843, 1670, 1595, 1496, 1466, 1309, 1217, 842, 763, 690, 578

^{1}H NMR (400 MHz) δ: 10.73 (s, 1H), 8.68 (s, 1H), 7.80 (s, 1H), 7.63 – 7.65 (m, 2H), 7.57 (s, 1H), 7.41 – 7.44 (m, 3H), 7.11 (s, 1H), 4.58 (q, *J* = 7.0 Hz, 2H), 2.86 (s, 3H), 2.79 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 191.4, 143.5, 138.3, 132.1, 131.6, 130.2, 128.7, 128.5, 128.0, 124.3, 123.6, 123.5, 122.8, 120.4, 120.3, 118.9, 112.5, 94.9, 86.7, 39.8, 21.0, 19.7, 15.6

LC–MS (m/z): 352 (M+H)

Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99 %

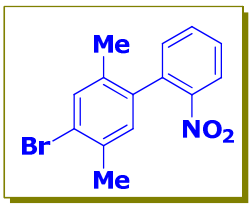
Found: C, 85.32; H, 6.11; N, 3.89 %

4-Bromo-2,5-dimethyl-2'-nitrobiphenyl (175):

Procedure for the synthesis of **167a** and **167b** was employed. Starting from 2-iodonitrobenzene and 4-bromo-2,5-dimethylphenylboronic acid, the biphenyl **175** was obtained as a yellow liquid. The crude product was used further without purification.

Yield: 85%

Mp: 56-58 °C



IR (KBr) ν_{max} cm^{-1}: 3088, 2924, 1600, 1527, 1346, 1270, 1204, 1153, 1018, 851, 831, 708

^{1}H NMR (400 MHz) δ: 8.04 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.47 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 2.38 (s, 3H), 2.06 (s, 3H)

^{13}C NMR (100 MHz) δ: 148.9, 136.7, 135.6, 135.1, 135.0, 133.5, 132.7, 132.1, 130.3, 128.5, 124.5, 124.2, 22.3, 19.1

LC–MS (m/z): 306 (M), 308 (M+2)

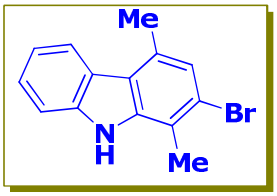
Anal. Calcd. for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.57 %

Found: C, 54.85; H, 4.03; N, 4.51 %

2-Bromo-1,4-dimethyl-9*H*-carbazole (176):

General procedure for the synthesis of **168a** was applied. Starting from **175**, the bromocarbazole was obtained in 70% yield. The crude product was used further without purification.

Yield: 70%



Mp: 86-88 °C

IR (KBr) ν_{max} cm^{-1}: 3412, 3040, 2916, 2856, 1593, 1579, 1454, 1377, 1319, 1288, 1014, 773, 750, 731, 441

^{1}H NMR (400 MHz) δ: 8.14 (d, *J* = 8.0 Hz, 1H), 7.5 (bs, 1H), 7.46 – 7.48 (m, 2H), 7.28 – 7.33 (m, 1H), 7.24 (s, 1H), 2.81 (s, 3H), 2.57 (s, 3H)

^{13}C NMR (100 MHz) δ: 139.4, 139.1, 132.0, 125.4, 124.7, 124.1, 122.5, 121.2, 120.6, 119.9, 116.8, 110.7, 20.1, 16.6

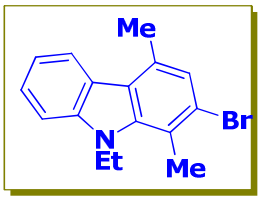
LC–MS (m/z): 274 (M); 276 (M+2)

Anal. Calcd. for $C_{14}H_{12}BrN$: C, 61.33; H, 4.41; N, 5.11 %

Found: C, 61.23; H, 4.46; N, 5.19 %

2-Bromo-9-ethyl-1,4-dimethyl-9*H*-carbazole (177):

General procedure for the synthesis of **169a** was applied. Starting from **176**, the *N*-ethyl-bromocarbazole (**177**) was obtained as a white solid. The crude product was used further without purification.



Yield: 95%

Mp: 110-112 °C

IR (KBr) ν_{max} cm^{-1}: 2966, 2920, 1608, 1560, 1456, 1346, 1302, 1157, 1113, 1005, 868, 781, 744, 723, 545

^{1}H NMR (400 MHz) δ: 8.19 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.32 (m, 2H), 4.60 (q, *J* = 7.6 Hz, 2H), 2.93 (s, 3H), 2.83 (s, 3H), 1.48 (t, *J* = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 141.2, 139.5, 132.1, 125.3, 125.2, 123.7, 123.4, 122.5, 121.8, 119.5, 117.1, 108.8, 39.9, 20.5, 18.9, 15.5

LC–MS (m/z): 302 (M), 304 (M+2)

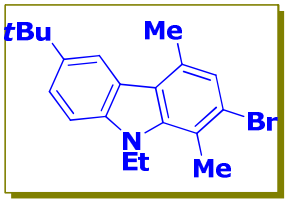
Anal. Calcd. for $C_{16}H_{16}BrN$: C, 63.59; H, 5.34; N, 4.63 %

Found: C, 63.48; H, 5.43; N, 4.55 %

2-Bromo-6-*tert*-butyl-9-ethyl-1,4-dimethyl-9*H*-carbazole (178):

A oven dried 100 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 2 g (6.6 mmol) of **177**, 40 mL of

dichloromethane and 0.9 g (6.6 mmol) of anhydrous aluminium chloride under stirring. To it, 2 mL of *tert*-butyl chloride was added slowly and the reaction mixture is stirred at room temperature for 6 h, after which time TLC (98:02 hexanes:ethyl acetate) indicated complete conversion. Reaction mass was poured into crushed ice slowly, neutralized with a solution of aq. 5% sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to give **178** as a white solid.



Yield: 94%

Mp: 82-84 °C

IR (KBr) ν_{max} cm^{-1}: 2962, 2862, 1566, 1462, 1375, 1309, 1236, 1172, 1120, 1020, 949, 879, 833, 802, 640, 561, 443

^{1}H NMR (400 MHz) δ: 8.18 (d, *J* = 1.6 Hz, 1H), 7.6 (dd, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 4.60 (q, *J* = 7.6 Hz, 2H), 2.92 (s, 3H), 2.84 (s, 3H), 1.50 (s, 12H)

^{13}C NMR (100 MHz) δ: 142.3, 139.8, 139.3, 131.8, 125.3, 123.6, 123.3, 123.1, 122.0, 118.6, 117.0, 108.3, 39.0, 34.6, 32.0, 20.6, 19.1, 15.6

LC–MS (m/z): 358 (M); 360 (M+2)

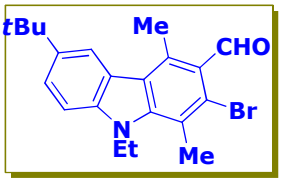
Anal. Calcd. for $C_{20}H_{24}BrN$: C, 67.04; H, 6.75; N, 3.91 %

Found: C, 67.12; H, 6.63; N, 3.85 %

2-Bromo-6-*tert*-butyl-9-ethyl-1,4-dimethyl-9*H*-carbazole-3-carbaldehyde (179):

General procedure for Vilsmeier-Haack formylation for **171** was used. Starting from **178**, the formylated product was obtained as a white solid after column purification (eluent: 5 - 10% ethyl acetate in hexane). The product was eluted in 7% eluent as white solid.

Yield: 75%



Mp: 126-128 °C

IR (KBr) ν_{max} cm^{-1}: 2964, 2916, 2856, 1672, 1593, 1440, 1340, 1309, 1222, 1155, 898, 846, 704, 569

^{1}H NMR (400 MHz) δ: 10.66 (s, 1H), 8.31 (s, 1H), 7.65 (dd, *J* = 1.6 Hz, 8.4 Hz, 1H), 7.41 (d, *J* = 1.2 Hz, 1H), 4.56 (q, *J* = 7.6 Hz, 2H), 3.1 (s, 3H), 2.9 (s, 3H), 1.5 (s, 12H)

^{13}C NMR (100 MHz) δ: 195.8, 143.5, 141.5, 139.9, 135.7, 128.4, 125.5, 124.2, 123.6, 122.7, 119.7, 118.0, 108.8, 40.3, 34.8, 32.0, 19.0, 17.1, 15.6

LC–MS (m/z): 386 (M), 388 (M+2); 330, 332 for fragment without *t*-butyl group

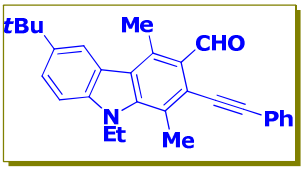
Anal. Calcd. for $C_{21}H_{24}BrNO$: C, 65.29; H, 6.26; N, 3.63 %

Found: C, 65.41; H, 6.23; N, 3.56 %

6-*tert*-Butyl-9-ethyl-1,4-dimethyl-2-(phenylethynyl)-9*H*-carbazole-3-carbaldehyde (1d):

General Sonogashira reaction conditions were employed as in the cases of **1a** – **1c**. **1d** was obtained as light yellow solid after column chromatography with 10% hexanes in ethyl acetate.

Yield: 85%



Mp: 130-132 °C

IR (KBr) ν_{max} cm^{-1}:	2957, 1674, 1556, 1487, 1342, 1307, 1228, 802, 754, 688, 526
^{1}H NMR (400 MHz) *δ*:	11.06 (s, 1H), 8.37 (s, 1H), 7.62 – 7.65 (m, 3H), 7.42 – 7.43 (m, 4H), 4.60 (q, *J* = 7.6 Hz, 2H), 3.24 (s, 3H), 3.05 (s, 3H), 1.51 (s, 12H)
^{13}C NMR (100 MHz) *δ*:	195.4, 143.4, 141.1, 140.2, 135.7, 131.4, 128.6, 128.5, 126.6, 125.9, 124.3, 123.9, 123.3, 123.2, 120.2, 119.9, 108.7, 101.0, 86.3, 39.9, 34.8, 32.0, 17.0, 16.99, 15.7
LC–MS (m/z):	408 (M+H); 330, 332 for fragment without *t*-butyl group
Anal. Calcd. for $C_{29}H_{29}NO$:	C, 85.47; H, 7.17; N, 3.44 %
Found:	C, 85.32; H, 7.21; N, 3.51 %

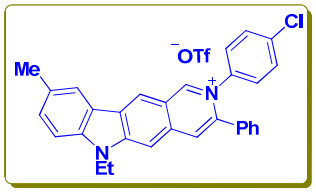
General procedure A for the synthesis of ellipticinium triflates:

A oven dried 10 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 0.3 mmol of 3-formyl-2-phenylethynylcarbazole, 0.3 mmol of amine, 0.5 g of anhydrous magnesium sulphate and 5 mL of dichloromethane. The reaction mixture was refluxed for 1 – 2 h under stirring. The yellow solution was filtered and the filterate is concentrated under vacuum. The compound was freshly dissolved in 5 mL of dichloromethane under stirring. To it, 0.3 mmol silver triflate was added and stirred at room temperature for 1 h. The reaction mass was diluted with dichloromethane, filtered and the solvent was removed under reduced pressure. The crude product was recrystallized from ethanol as dark yellow crystalline solid.

2-(4-Chlorophenyl)-6-ethyl-9-methyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (180):

180 was synthesized from alkynylaldehyde **1a** and *p*-chloroaniline according to general procedure A. The product was obtained as an orange coloured crystalline solid after re-crystallization from ethanol.

Yield: 90%



Mp: 189-191 °C

IR (KBr) ν_{max} cm^{-1}: 3488, 2959, 1622, 1454, 1412, 1257, 1035, 837, 765, 632

^{1}H NMR (400 MHz) δ: 10.23 (s, 1H), 9.33 (s, 1H), 8.54 (s, 1H), 8.41 (s, 1H), 8.32 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.73 (d, 2H), 7.61 – 7.64 (m, 3H), 7.43 (s, 5H), 4.63 (d, *J* = 7.6 Hz, 2H), 2.57 (s, 3H), 1.44 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 152.0, 146.4, 143.1, 141.4, 141.3, 136.1, 135.2, 133.5, 131.6, 131.4, 130.6, 130.1, 129.8, 129.6, 129.1, 128.9, 124.7, 123.9, 122.7, 121.7, 120.2, 112.2, 110.7, 38.5, 21.3, 13.6

LC–MS (m/z): 447 (M), 449 (M+2)

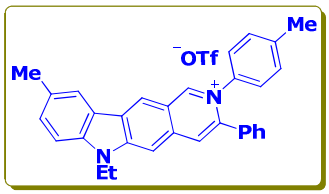
Anal. Calcd. for $C_{30}H_{24}ClN_2$: C, 80.43; H, 5.40; N, 6.25 %

Found: C, 80.25; H, 5.48; N, 6.17 %

6-Ethyl-9-methyl-3-phenyl-2-p-tolyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (181):

181 was synthesized from alkynylaldehyde **1a** and *p*-toluidine according to general procedure A. The product was obtained as an yellow coloured crystalline solid after recrystallization from ethanol.

Yield: 95%



Mp: 212-214 °C

IR (KBr) ν_{max} cm^{-1}: 3028, 2924, 1608, 1564, 1494, 1435, 1259, 1028, 763, 698, 638, 516

^{1}H NMR (400 MHz) δ: 10.15 (s, 1H), 9.31 (s, 1H), 8.52 (s, 1H), 8.38 (s, 1H), 8.27 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.39 (m, 7H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.6 (q, *J* = 8.0 Hz, 2H), 2.56 (s, 3H), 2.31 (s, 3H), 1.43 (t, *J* = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 151.8, 146.3, 143.2, 141.4, 140.3, 140.2, 136.0, 133.7, 131.5, 131.4, 130.5, 130.2, 129.9, 129.0, 128.8, 127.3, 124.9, 123.8, 122.6, 121.7, 120.2, 110.6, 103.2, 38.0, 21.3, 21.1, 13.6

LC–MS (m/z): 428 (M+H)

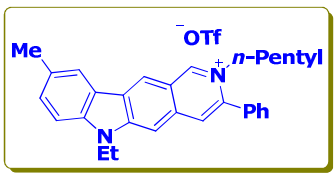
Anal. Calcd. for $C_{31}H_{27}N_2$: C, 87.06; H, 6.37; N, 6.55 %

Found: C, 87.15; H, 6.34; N, 6.68 %

6-Ethyl-9-methyl-2-pentyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (182):

182 was synthesized from alkynylaldehyde **1a** and amyl amine according to general procedure A. The product was obtained as an yellow crystalline solid after re-crystallization from ethanol.

Yield: 97%



Mp: 193-195 °C

IR (KBr) ν_{max} cm^{-1}: 3419, 2916, 2862, 2259, 2112, 1653, 1477, 1440, 1019, 1076, 826, 759

^{1}H NMR (400 MHz) δ: 10.08 (s, 1H), 9.18 (s, 1H), 8.28-8.21 (m, 3H), 7.73-7.67 (m, 6H), 7.50 (m, 1H), 4.52 (m, 4H),

2.56 (s, 3H), 1.70 (m, 2H), 1.37 (t, *J* = 7.6 Hz, 3H), 1.08 (m, 4H), 0.71 (m, 3H).

^{13}C NMR (100 MHz) *δ*: 150.5, 145.9, 142.9, 141.3, 135.2, 133.2, 131.3, 131.0, 130.8, 130.3, 129.5, 128.8, 125.5, 123.0, 122.6, 121.6, 120.5, 110.3, 103.0, 57.6, 38.3, 30.1, 28.0, 21.6, 21.4, 14.0, 13.6

LC–MS (m/z): 408 (M+H)

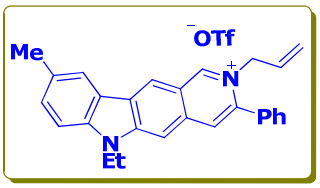
Anal. Calcd. for $C_{29}H_{31}N_2$: C, 85.46; H, 7.67; N, 6.87 %

Found: C, 85.23; H, 7.76; N, 6.75 %

2-Allyl-6-ethyl-9-methyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (183):

183 was synthesized from alkynylaldehyde **1a** and allyl amine according to general procedure A. The product was obtained as an orange coloured crystalline solid after recrystallization from ethanol.

Yield: 93%



Mp: 185-187 °C

IR (KBr) ν_{max} cm^{-1}: 3418, 2872, 2254, 2127, 1651, 1487, 1439, 1028, 1006, 825, 763

^{1}H NMR (400 MHz) *δ*: 10.06 (s, 1H), 9.34 (s, 1H), 8.37 (s, 1H), 8.32 (d, 2H), 7.59 – 7.76 (m, 7H), 6.0 (m, *J* = 5.2 Hz, 1H), 5.28 (d, *J* = 10.2 Hz, 1H), 5.18 (d, *J* = 5.2 Hz, 2H), 4.95 (d, *J* = 1.7 Hz, 1H), 4.58 (q, *J* = 7.6 Hz, 2H), 2.57 (s, 3H), 1.4 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) *δ*: 150.8, 146.1, 143.2, 141.4, 135.5, 133.07, 132.6, 131.4, 131.2, 130.8, 130.3, 129.3, 129.0, 125.5,

123.3, 122.7, 121.7, 120.6, 120.3, 110.5, 103.16, 59.6, 38.4, 21.4, 13.6

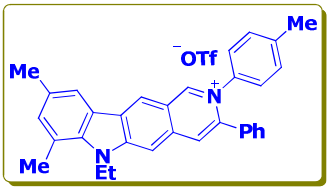
LC–MS (m/z): 376 (M-H)

Anal. Calcd. for $C_{27}H_{25}N_2$: C, 85.90; H, 6.68; N, 7.42 %

Found: C, 85.96; H, 6.61; N, 7.32 %

6-Ethyl-7,9-dimethyl-3-phenyl-2-p-tolyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (184):

184 was synthesized from alkynylaldehyde **1c** and *p*-toluidine according to general procedure A. The product was obtained as a red coloured crystalline solid after re-crystallization from ethanol.



Yield: 95%

Mp: 211-213 °C

IR (KBr) ν_{max} cm^{-1}: 3418, 2916, 2253, 2125, 166, 1651, 1271, 1224, 1159, 1024, 823, 760

^{1}H NMR (400 MHz) δ: 10.16 (s, 1H), 9.29 (s, 1H), 8.5 (s, 1H), 8.4 (s, 1H), 8.11 (s, 1H), 7.31 – 7.51 (m, 10H), 4.76 (s, 2H), 2.83 (s, 3H), 2.55 (s, 3H), 2.33 (s, 3H), 1.45 (s, 3H)

^{13}C NMR (100 MHz) δ: 160.3, 152.0, 147.0, 143.4, 139.7, 136.0, 135.5, 134.8, 133.8, 131.4, 130.5, 129.9, 129.2, 128.9, 128.8, 124.9, 123.2, 122.7, 121.6, 120.4, 120.3, 114.7, 103.3, 56.1, 40.4, 21.0, 19.4, 15.2

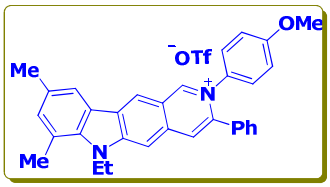
LC–MS (m/z): 442 (M+H)

Anal. Calcd. for $C_{32}H_{29}N_2$: C, 87.04; H, 6.62; N, 6.34 %

Found: C, 87.12; H, 6.59; N, 6.45 %

6-Ethyl-2-(4-methoxyphenyl)-7,9-dimethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate(185):

185 was synthesized from alkynylaldehyde **1c** and *p*-anisidine according to general procedure A. The product was obtained as a red coloured crystalline solid after re-crystallization from ethanol.



Yield: 98%

Mp: 204-206 °C

IR (KBr) ν_{max} cm^{-1}: 2916, 2856, 1606, 1493, 1439, 1265, 1145, 1028, 634, 516

^{1}H NMR (400 MHz) δ: 10.13 (s, 1H), 9.27 (s, 1H), 8.49 (s, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.4 – 7.57 (m, 5H), 7.34 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.74 (q, *J* = 8.0 Hz, 2H), 3.77 (s, 3H), 2.82 (s, 3H), 2.33 (s, 3H), 1.43 (t, *J* = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 160.3, 152.0, 147.0, 143.4, 139.7, 136.0, 135.5, 134.8, 133.8, 131.4, 130.5, 129.9, 129.2, 128.9, 128.8, 124.9, 123.2, 122.7, 121.6, 120.4, 120.3, 114.7, 103.3, 56.1, 40.4, 21.0, 19.4, 15.2

LC–MS (m/z): 458 (M+H)

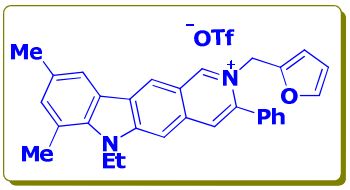
Anal. Calcd. for $C_{32}H_{29}N_2O$: C, 83.99; H, 6.39; N, 6.12 %

Found: C, 83.85; H, 6.41; N, 6.32 %

6-Ethyl-2-(furan-2-ylmethyl)-7,9-dimethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (186):

186 was synthesized from alkynylaldehyde **1c** and furfuryl amine according to general procedure A. The product was obtained as an orange coloured crystalline solid after re-crystallization from ethanol.

Yield: 92%



Mp: 219-221 °C

IR (KBr) ν_{max} cm^{-1}: 2947, 2872, 1647, 1518, 1269, 1161, 1028, 825

^{1}H NMR (400 MHz) δ: 10.14 (s, 1H), 9.29 (s, 1H), 8.33 (s, 1H), 8.26 (s, 1H), 8.13 (s, 1H), 7.64 – 7.68 (m, 6H), 7.29 (s, 1H), 6.42 (q, *J* = 1.2 Hz, 1H), 6.14 (d, *J* = 3.6 Hz, 1H), 5.86 (s, 2H), 4.68 (d, 2H), 2.78 (s, 3H), 2.5 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 150.7, 147.3, 146.9, 144.8, 142.7, 139.7, 135.6, 134.7, 132.9, 131.2, 130.8, 130.3, 129.4, 129.2, 125.7, 123.0, 122.7, 121.5, 120.6, 120.5, 111.5, 111.4, 103.3, 54.0, 39.0, 21.0, 19.3, 15.2

LC–MS (m/z): 432 (M+H)

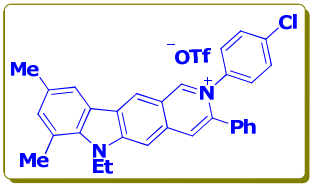
Anal. Calcd. for $C_{30}H_{27}N_2O$: C, 83.50; H, 6.31; N, 6.49 %

Found: C, 83.39; H, 6.28; N, 6.53 %

2-(4-Chlorophenyl)-6-ethyl-7,9-dimethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (187):

187 was synthesized from alkynylaldehyde **1c** and *p*-chloroaniline according to general procedure A. The product was obtained as an orange coloured crystalline solid after re-crystallization from ethanol.

Yield: 92%



Mp: 197-199 °C

IR (KBr) ν_{max} cm^{-1}: 3485, 2957, 1626, 1458, 1410, 1257, 1032, 833, 763, 638

^{1}H NMR (400 MHz) δ: 10.17 (s, 1H), 9.28 (s, 1H), 8.51 (s, 1H), 8.39 (s, 1H), 8.13 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.41 (bs, 5H), 7.35 (s, 1H), 4.75 (q, *J* = 7.2 Hz, 2H), 3.40 (s, 3H), 2.82 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 151.8, 147.2, 142.9, 141.3, 139.8, 136.1, 135.2, 134.9, 133.4, 131.5, 130.6, 130.1, 129.8, 129.6, 129.3, 128.9, 124.9, 123.5, 122.7, 121.7, 120.4, 120.3, 103.4, 40.1, 21.0, 19.4, 15.2

LC–MS (m/z): 461 (M) 463 (M+2)

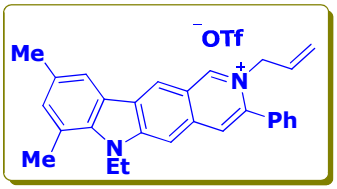
Anal. Calcd. for $C_{31}H_{26}ClN_2$: C, 80.59, H, 5.67, N, 6.06 %

Found: C, 80.45, H, 5.71, N, 6.12 %

2-Allyl-6-ethyl-7,9-dimethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (188):

188 was synthesized from alkynylaldehyde **1c** and allylamine according to general procedure A. The product was obtained as red coloured crystalline solid after re-crystallization from ethanol.

Yield: 95%



Mp: 157-159 °C

IR (KBr) ν_{max} cm^{-1}: 3417, 2869, 2248, 2129, 1660, 1488, 1440, 1029, 1011, 825, 762

^{1}H NMR (400 MHz) δ: 9.98 (s, 1H), 9.22 (s, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 8.10 (s, 1H), 7.61- 7.70 (m, 5H), 7.28 (s,

1H), 6.00 (m, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.17 (d, *J* = 4.4 Hz, 2H), 4.95 (d, *J* = 17.2 Hz, 1H), 4.67 (d, *J* = 8.0 Hz, 2H), 2.78 (s, 3H), 2.48 (s, 3H), 1.41 (t, *J* = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) *δ*: 150.6, 146.7, 143.0, 139.7, 135.5, 134.7, 133.1, 132.5, 131.2, 130.8, 130.3, 129.9, 129.3, 129.1, 125.5, 122.7, 122.6, 122.0, 121.4, 120.7, 120.4, 103.2, 59.6, 21.0, 19.4, 15.3

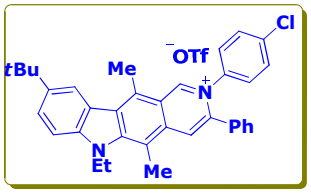
LC–MS (m/z): 392 (M+H)

Anal. Calcd. for $C_{28}H_{27}N_2$: C, 85.89, H, 6.95, N, 7.15 %

Found: C, 85.76, H, 6.91, N, 7.07 %

9-*tert*-Butyl-2-(4-chlorophenyl)-6-ethyl-5,11-dimethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (189):

189 was synthesized from alkynylaldehyde **1d** and *p*-chloroaniline according to general procedure A. The product was obtained as a red coloured crystalline solid after re-crystallization from ethanol.



Yield: 85%

Mp: 193-195 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2957, 1732, 1624, 1587, 1510, 1458, 1410, 1280, 1255, 1141, 1030, 763, 636, 515

^{1}H NMR (400 MHz) *δ*: 10.18 (s, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 7.84 (d, *J* = 2.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.48 - 7.46 (m, 2H), 7.41 - 7.40 (m, 3H), 4.84 (q, *J* = 6.4 Hz, 2H), 3.40 (s, 3H), 3.16 (s, 3H), 1.46 (s, 12H)

^{13}C NMR (100 MHz) δ: 149.0, 145.2, 144.9, 142.4, 141.3, 135.3, 135.1, 135.0, 133.7, 130.9, 129.9, 129.6, 128.8, 128.1, 127.5, 122.7, 122.2, 121.8, 121.2, 120.2, 119.2, 111.3, 110.5, 40.1, 35.1, 32.1, 15.9, 15.7, 13.9

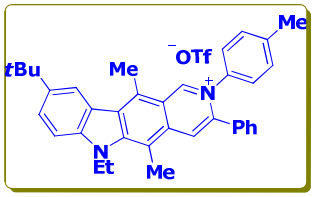
LC–MS (m/z): 517 (M), 519 (M+2)

Anal. Calcd. for $C_{35}H_{34}ClN_2$: C, 81.14; H, 6.61; N, 5.41 %

Found: C, 81.32; H, 6.57; N, 5.45 %

9-*tert*-Butyl-6-ethyl-5,11-dimethyl-3-phenyl-2-p-tolyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (190):

190 was synthesized from alkynylaldehyde **1d** and *p*-toluidine according to general procedure A. The product was obtained as a red coloured crystalline solid after re-crystallization from ethanol.



Yield: 87%

Mp: 183-185 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2916, 1626, 1601, 1521, 1452, 1275, 1221, 852, 763, 740

^{1}H NMR (400 MHz) δ: 10.11 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 7.86 (t, *J* = 1.2 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.47 (m, 2H), 7.42 – 7.40 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.83 (q, *J* = 7.6 Hz, 2H), 3.41 (s, 3H), 3.17 (s, 3H), 2.35 (s, 3H), 1.48 (s, 12H)

^{13}C NMR (100 MHz) δ: 148.9, 145.1, 144.8, 142.6, 142.4, 140.3, 140.1, 135.2, 134.8, 134.0, 130.8, 130.0, 129.8, 128.7, 127.6, 127.4, 122.7, 122.3, 121.9, 121.1, 120.2, 111.2, 110.5, 35.1, 32.1, 21.2, 15.9, 15.7, 14.5, 13.9

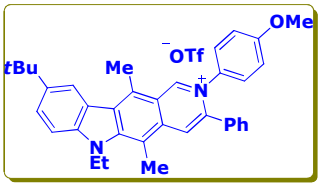
LC–MS (m/z): 498 (M+H)

Anal. Calcd. for $C_{36}H_{37}N_2$: C, 86.88; H, 7.49; N, 5.63 %

Found: C, 86.73; H, 7.55; N, 5.71 %

9-*tert*-Butyl-6-ethyl-2-(4-methoxyphenyl)-5,11-dimethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazol-2-ium triflate (191):

191 was synthesized from alkynylaldehyde **1d** and *p*-anisidine according to general procedure A. The product was obtained as red coloured crystalline solid after re-crystallization from ethanol.



Yield: 90%

Mp: 251-253°C

IR (KBr) ν_{max} cm^{-1}: 3466, 2916, 2852, 1606, 1494, 1435, 1332, 1263, 1032, 763, 698, 516

^{1}H NMR (400 MHz) δ: 10.09 (s, 1H), 8.59 (s, 1H), 8.45 (s, 1H), 7.83 (t, *J* = 6.8 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.1 – 7.46 (m, 5H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.82 (s, 2H), 3.96 (s, 3H), 3.69 (s, 3H), 3.15 (s, 3H), 1.46 (s, 12H)

^{13}C NMR (100 MHz) δ: 160.3, 149.1, 145.0, 144.8, 142.8, 142.4, 135.6, 135.2, 134.7, 134.0, 130.8, 129.7, 129.2, 128.7, 128.0, 127.4, 122.0, 121.8, 121.1, 120.2, 114.6, 111.2, 110.5, 56.1, 40.1, 35.1, 32.1, 15.9, 15.7, 14.4

LC–MS (m/z): 514 (M+H)

Anal. Calcd. for $C_{36}H_{37}N_2O$: C, 84.17; H, 7.26; N, 5.45 %

Found: C, 84.07; H, 7.31; N, 5.56 %

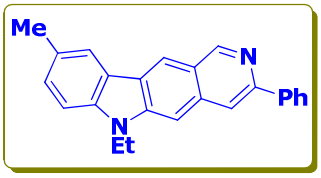
General procedure B for the synthesis of ellipticines:

An oven dried 10 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 0.3 mmol of 3-formyl-2-phenylethynylcarbazole and 1 mL of *tert*-butylamine. The reaction mixture was stirred at room temperature for 12 h and excess *tert*-butylamine was removed under vacuum. The residue was dissolved in 3 mL of DMF, CuI (0.03 mmol) was added and heated at 90 °C for 2 h. Reaction was allowed to room temperature, poured into ice and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude material was purified by column chromatography (eluent: 10% ethyl acetate in hexane). The product was eluted in 10% eluent as light yellow solid.

6-Ethyl-9-methyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazole (3a):

3a was synthesized from alkynylaldehyde **1a** according to general procedure B. The product was obtained as an yellow coloured solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 89%



Mp: 176-178 °C

IR (KBr) ν_{max} cm^{-1}: 3433, 3057, 2976, 2868, 1876, 1697, 1612, 1412, 1300, 1221, 1016, 935, 696, 464

^{1}H NMR (400 MHz) δ: 9.47 (s, 1H), 8.60 (s, 1H), 8.22 – 8.20 (m, 2H), 8.16 (s, 1H), 8.03 (s, 1H), 7.58 – 7.54 (m, 3H), 7.47 – 7.40 (m, 2H), 7.31 (s, 1H), 4.35 (q, J = 7.6 Hz, 2H), 2.6 (s, 3H), 1.48 (t, J = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 153.0, 149.5, 142.7, 140.8, 140.2, 135.2, 129.0, 129.0, 128.7, 128.1, 127.0, 126.2, 122.8, 122.6, 121.4, 119.0, 115.8, 108.1, 101.4, 37.7, 21.4, 13.2

LC–MS (m/z): 337 (M+H)

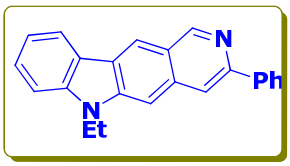
Anal. Calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33 %

Found: C, 85.51; H, 5.91; N, 8.45 %

6-Ethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazole (3b):

3b was synthesized from alkynylaldehyde **1b** according to general procedure B. The product was obtained as a yellow coloured solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 85%



Mp: 170-172 °C

IR (KBr) ν_{max} cm^{-1}: 2966, 2924, 1630, 1601, 1466, 1261, 1097, 1018, 800, 690, 468

^{1}H NMR (400 MHz) δ: 9.48 (s, 1H), 8.65 (s, 1H), 8.24 – 8.17 (m, 4H), 7.62 (s, 1H), 7.60 – 7.52 (m, 3H), 7.44 – 7.40 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 153.0, 149.6, 142.7, 142.6, 140.1, 135.3, 128.8, 128.2, 127.9, 127.0, 126.3, 122.7, 122.6, 121.3, 119.7, 119.2, 115.9, 108.4, 101.6, 37.8, 13.3

LC–MS (m/z): 323 (M+H)

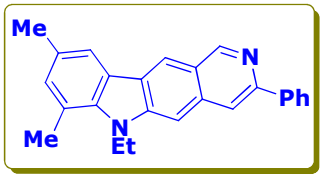
Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69 %

Found: C, 85.49; H, 5.71; N, 8.61 %

6-Ethyl-7,9-dimethyl-3-phenyl-6*H*-pyrido[4,3-*b*]carbazole (3c):

3c was synthesized from alkynylaldehyde **1c** according to general procedure B. The product was obtained as a yellow coloured solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 90%



Mp: 183-185 °C

IR (KBr) ν_{max} cm^{-1}: 3435, 3052, 2971, 2866, 1873, 1692, 1612, 1409, 1302, 1223, 1016, 690

^{1}H NMR (400 MHz) δ: 9.45 (s, 1H), 8.58 (s, 1H), 8.18 (d, *J* = 1.6 Hz, 2H), 8.15 (s, 1H), 7.88 (s, 1H), 7.57 (s, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.12 (s, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 2.78 (s, 3H), 2.53 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 152.9, 149.4, 143.6, 140.2, 139.4, 135.2, 132.6, 129.2, 128.7, 128.1, 127.0, 126.5, 123.7, 122.7, 119.7, 119.1, 118.6, 115.1, 101.7, 39.7, 29.0, 19.8, 15.0

LC–MS (m/z): 351 (M+H)

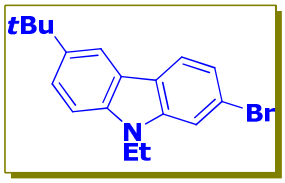
Anal. Calcd. for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99 %

Found: C, 85.51; H, 6.39; N, 7.86 %

2-Bromo-6-*tert*-butyl-9-ethyl-9*H*-carbazole (192):

A oven dried 100 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 2 g (6.6 mmol) of 2-bromocarbazole, 40 mL of dichloromethane and 0.9 g (6.6 mmol) of anhydrous aluminium chloride under stirring. To it, 2 mL of *tert*-butyl chloride was added slowly and the reaction mixture was stirred at room temperature for 6 h, after which time TLC (98:02 hexanes:ethyl acetate) indicated complete conversion. Reaction mass was poured into crushed ice slowly, neutralized with a solution of aq. 5% sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to give **192** as a white solid.

Yield: 94%



Mp: 78-80 °C

IR (KBr) ν_{max} cm^{-1}: 2955, 1652, 1634, 1475, 1341, 1310, 1257, 1229, 929, 798, 642

^{1}H NMR (400 MHz) δ: 8.12 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.57 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 1.50 (s, 9H), 1.45 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 142.5, 141.1, 138.3, 124.1, 122.2, 121.7, 121.4, 120.0, 116.5, 111.5, 108.2, 105.0 (aromatic C), 37.7, 34.7, 32.0, 13.8 (aliphatic C)

LC–MS (m/z): 331 (M+H), 333 (M+2)

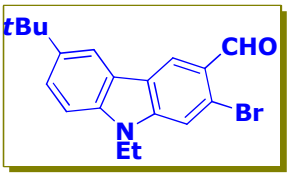
Anal. Calcd. for $C_{18}H_{20}BrN$: C, 65.46; H, 6.10; N, 4.24%

Found: C, 65.36; H, 6.21; N, 4.32%

2-Bromo-6-*tert*-butyl-9-ethyl-9*H*-carbazole-3-carbaldehyde (193):

A oven dried 50 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 2 g (0.036 mol) of 6-*tert*-butyl-2-bromo-9-ethylcarbazole and 15 mL of dimethylformamide under stirring and cooled to 0 °C. 2 mL (0.11 mol) of phosphoryl chloride was added dropwise for 5 minutes. Reaction was allowed to room temperature and heated at 70 °C for 5 h, after which time TLC (95:5 hexanes:ethyl acetate) indicated complete conversion. Reaction was allowed to room temperature and quenched with ice. The reaction mass was poured into crushed ice slowly, neutralized with 5% aq. sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure; purified by column chromatography (96:4 hexanes and ethyl acetate) to give **193** as a white solid.

Yield: 72%



Mp: 150-152 °C

IR (KBr) ν_{max} cm^{-1}: 2951, 2858, 1672, 1628, 1483, 1344, 1300, 1255, 1236, 926, 833, 800, 638

^{1}H NMR (400 MHz) δ: 10.45 (s, 1H), 8.72 (s, 1H), 8.16 (d, *J* = 3.0 Hz, 1H), 7.64 (dd, *J* = 8.5 Hz , 3.0 Hz, 1H), 7.56 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 1.47 (s, 12H)

^{13}C NMR (100 MHz) δ: 191.8, 144.2, 144.1, 139.0, 125.2, 124.7, 123.9, 123.1, 122.7, 122.5, 117.3, 112.6, 108.8 (aromatic C), 38.1, 34.8, 31.9, 13.8 (aliphatic C)

LC–MS (m/z): 358 (M), 360 (M+2)

Anal. Calcd. for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91%

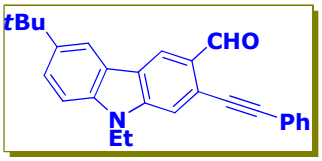
Found: C, 63.85; H, 5.68; N, 3.85%

6-*tert*-Butyl-9-ethyl-2-(phenylethynyl)-9*H*-carbazole-3-carbaldehyde (1e):

A oven dried 50 mL schlenk tube equipped with a teflon coated magnetic stirring bar was charged with 1 g (3 mmol) of **193**, 1 g of molecular sieves (4 Å) and 0.42 mL (3.8 mmol) of phenyl acetylene. The tube was evacuated and filled with nitrogen. To it, 10 mL of dry THF and 5 mL of freshly distilled triethylamine are added under nitrogen and the reaction was stirred for 10 minutes at room temperature. 42 mg of $Pd(PPh_3)_2Cl_2$ (2 mol%) and 6 mg of CuI (1 mol%) were added under nitrogen and the schlenk tube was heated at 60 ^oC for 4 h, after which time TLC (85:15 hexanes:ethyl acetate) indicated complete conversion. Reaction was allowed to room temperature and filtered. The filterate was poured into crushed ice slowly and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced

pressure. The crude material was purified by column chromatography (eluent: 8-15% ethyl acetate in hexane). The product was eluted in 12% eluent as a pale yellow solid.

Yield: 85%



Mp: 104-106 °C

IR (KBr) ν_{max} cm^{-1}: 3061, 2961, 1668, 1626, 1587, 1485, 1367, 1304, 848, 794, 686

^{1}H NMR (400 MHz) δ: 10.74 (s, 1H), 8.77 (s, 1H), 8.18 (s, 1H), 7.59 - 7.62 (m, 4H), 7.39 (m, 4H), 4.37 (s, 2H), 1.46 (s, 12H)

^{13}C NMR (100 MHz) δ: 191.5, 143.9, 143.0, 139.6, 131.6, 128.8, 128.5, 127.8, 125.3, 123.7, 123.6, 123.0, 122.8, 120.6, 117.4, 112.4, 108.7 (aromatic C), 95.1, 86.7 (alkyne C), 38.0, 34.8, 31.9, 13.9 (aliphatic C)

LC–MS (m/z): 380 (M+H)

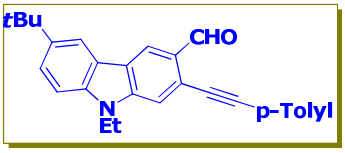
Anal. Calcd. for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69%

Found: C, 85.31; H, 6.58; N, 3.75%

6-*tert*-Butyl-9-ethyl-2-(*p*-tolylethynyl)-9*H*-carbazole-3-carbaldehyde (1f):

General Sonogashira reaction conditions were employed as in the cases of **1e**. **1f** was obtained as light yellow solid after column chromatography with 10% hexanes in ethyl acetate.

Yield: 84%



Mp: 104-106 °C

IR (KBr) ν_{max} cm^{-1}: 3075, 2963, 2120, 1671, 1646, 1586, 1445, 1327, 1301, 854, 790

^{1}H NMR (400 MHz) δ: 10.76 (s, 1H), 8.78 (s, 1H), 8.19 (s, 1H), 7.22-7.64 (m, 7H), 4.38 (q, *J* = 6.0 Hz, 2H), 2.42 (s, 3H), 1.48 (s, 12H)

^{13}C NMR (100 MHz) δ: 191.6, 143.9, 143.0, 139.6, 139.0, 131.5, 129.3, 127.8, 125.2, 124.0, 123.5, 123.0, 120.5, 119.7, 117.4, 112.2, 108.7, 95.4, 86.0 (aromatic C), 38.0, 34.8, 31.9, 21.6, 13.9 (aliphatic C)

LC–MS (m/z): 394 (M+H)

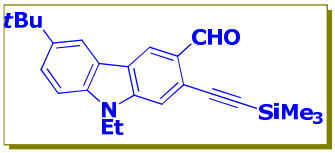
Anal. Calcd. for $C_{28}H_{27}NO$: C, 85.46; H, 6.92; N, 3.56%

Found: C, 85.32; H, 6.88; N, 3.51%

6-*tert*-Butyl-9-ethyl-2-((trimethylsilyl)ethynyl)-9*H*-carbazole-3-carbaldehyde (194):

Compound **194** was prepared by coupling trimethyl silyl acetylene with 2-bromo-6-*tert*-butyl-9-ethyl-9*H*-carbazole-3-carbaldehyde employing general Sonogashira reaction conditions.

Yield: 90%



Mp: 98-100 °C

IR (KBr) ν_{max} cm^{-1}: 3051, 2961, 2047, 1661, 1616, 1585, 1483, 1347, 1300, 842

^{1}H NMR (400 MHz) δ: 10.68 (s, 1H), 8.74 (s, 1H), 8.18 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 4.32 (q, *J* = 6.0 Hz, 2H), 1.47 (s, 12H), 0.37 (s, 9H)

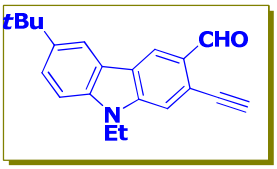
^{13}C NMR (100 MHz) δ: 191.6, 143.9, 142.8, 139.6, 128.1, 125.3, 123.8, 123.5, 122.9, 120.2, 117.4, 112.7, 108.7, 102.0,

	100.7 (aromatic C), 37.9, 34.8, 31.9, 13.9, 0.1 (aliphatic C)
LC–MS (m/z):	376 (M+H)
Anal. Calcd. for $C_{24}H_{29}NOSi$:	C, 76.75; H, 7.76; N, 3.73 %
Found:	C, 76.85; H, 7.71; N, 3.65 %

6-*tert*-Butyl-9-ethyl-2-(ethynyl)-9*H*-carbazole-3-carbaldehyde (1g):

Compound **1g** was prepared by desilylation of **194** in MeOH using K_2CO_3.

Yield:	87%



Mp:	102-104 °C
IR (KBr) ν_{max} cm^{-1}:	3318, 3061, 2962, 1667, 1616, 1577, 1485, 1367, 1314, 852, 785, 689
^{1}H NMR (400 MHz) δ:	10.62 (s, 1H), 8.75 (s, 1H), 8.18 (s, 1H), 7.38 - 7.62 (m, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.49 (s, 1H), 1.46 (s, 12H)
^{13}C NMR (100 MHz) δ:	191.2, 144.0, 142.7, 139.6, 128.3, 124.0, 122.2, 120.6, 118.9, 117.5, 113.2, 108.8, 105.5, 82.8, 80.9 (aromatic C), 38.0, 34.8, 31.9, 13.9 (aliphatic C)
LC–MS (m/z):	304 (M+H)
Anal. Calcd. for $C_{21}H_{21}NO$:	C, 83.13; H, 6.98; N, 4.62 %
Found:	C, 83.21; H, 6.91; N, 4.71 %

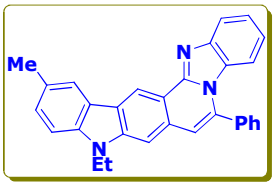
General procedure C for the preparation of benzimidazo[2,1-*a*]ellipticine derivatives:

A oven dried 10 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with 0.5 mmol of 3-formyl-2-phenylethynylcarbazole (**1a–1g**), 1,2-aryldiamine (0.5 mmol) (**2a-2f**) and 5 mL of dimethylformamide. The reaction mixture was heated at 120 °C for 2 h under stirring until complete consumption of starting material as monitored by TLC. After the reaction was completed, the reaction mixture was extracted with ethyl acetate, dried over anhydrous sodium sulphate, and evaporated in vacuum. The residue was adsorbed on silica gel and purified by column chromatography using silica gel (94:6 hexanes:ethyl acetate) to afford the desired product.

Compound (195):

Compound **195** was synthesized from 2-alkynylaldehyde **1a** and phenylenediamine **2a** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 15% hexanes in ethyl acetate.

Yield: 82%



Mp: 198-200 °C

IR (KBr) ν_{max} cm^{-1}: 1635, 1610, 1529, 1467, 1302, 1230, 734, 700

^{1}H NMR (400 MHz) δ: 9.62 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 7.64 – 7.34 (s, 5H), 7.34 – 7.32 (m, 4H), 6.52 (s, 2H), 6.50 (s, 1H), 4.41 (s, 2H), 2.62 (s, 3H), 1.48 (s, 3H)

^{13}C NMR (100 MHz) δ: 149.7, 144.3, 141.9, 139.9, 136.3, 135.0, 131.0, 130.0, 129.7, 129.5, 129.2, 129.0, 128.3, 124.6, 123.8, 123.1, 121.4, 120.6, 119.1, 117.4, 115.2, 113.8, 113.4, 108.3, 103.8 (aromatic C), 37.8, 21.5, 13.6 (aliphatic C)

LC–MS (m/z): 426 (M+H)

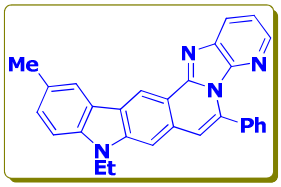
Anal. Calcd. for $C_{30}H_{23}N_3$: C, 84.68; H, 5.45; N, 9.87 %

Found: C, 84.51; H, 5.41; N, 9.93 %

Compound (196):

Compound **196** was synthesized from 2-alkynylaldehyde **1a** and phenylenediamine **2b** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 15% hexanes in ethyl acetate.

Yield: 73%



Mp: 197-199 °C

IR (KBr) ν_{max} cm^{-1}: 1628, 1610, 1529, 1467, 1230, 1014, 869, 792, 734, 700, 570

^{1}H NMR (400 MHz) δ: 9.61 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 3.6 Hz, 1H), 8.14 (s, 1H), 7.74 (d, *J* = 6.0 Hz, 2H), 7.62 – 7.56 (m, 4H), 7.41 – 7.35 (m, 3H), 7.12 (s, 1H), 4.60 (q, *J* = 8.0 Hz, 2H), 2.61 (s, 3H), 1.51 (s, 3H)

^{13}C NMR (100 MHz) δ: 150.3, 145.0, 142.3, 141.5, 140.0, 136.4, 136.3, 134.7, 130.6, 129.7, 129.4, 129.0, 128.5, 127.7, 126.0, 124.8, 123.0, 121.5, 119.7, 117.2, 115.2, 114.9, 108.4, 104.1 (aromatic C), 37.9, 21.5, 13.6 (aliphatic C)

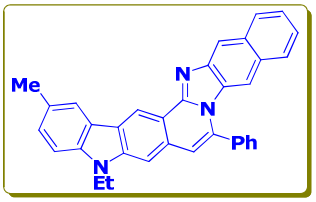
LC–MS (m/z): 427 (M+H)

Anal. Calcd. for $C_{29}H_{22}N_4$: C, 81.66; H, 5.20; N, 13.14 %

Found: C, 81.52; H, 5.23; N, 13.07 %

Compound (197):

Compound **197** was synthesized from 2-alkynylaldehyde **1a** and phenylenediamine **2c** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 15% hexanes in ethyl acetate.



Yield: 78%

Mp: 217-219 °C

IR (KBr) ν_{max} cm^{-1}: 2926, 2856, 1734, 1670, 1579, 1535, 1458, 1377, 1305, 1234, 1022, 852, 760

^{1}H NMR (400 MHz) δ: 9.67 (s, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H); 7.74 – 7.68 (m, 5H), 7.58 (s, 1H), 7.57 (s, 1H), 7.43 – 7.39 (m, 4H), 7.03 (s, 1H), 6.87 (s, 1H), 4.45 (q, *J* = 8.0 Hz, 2H), 2.63 (s, 3H), 1.52 (t, *J* = 8.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: Due to poor solubility, ^{13}C NMR couldn't be recorded.

LC–MS (m/z): 476 (M+H)

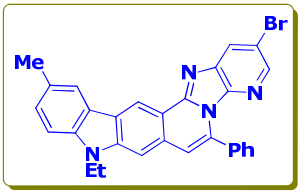
Anal. Calcd. for $C_{34}H_{25}N_3$: C, 85.87; H, 5.30; N, 8.84 %

Found: C, 85.48; H, 5.36; N, 8.79 %

Compound (198):

Compound **198** was synthesized from 2-alkynylaldehyde **1a** and phenylenediamine **2d** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 15% hexanes in ethyl acetate.

Yield: 84%



Mp: 223-225 °C

IR (KBr) ν_{max} cm^{-1}: 3040, 2968, 2914, 1631, 1608, 1512, 1477, 1412, 1126, 864, 706

^{1}H NMR (400 MHz) δ: 9.46 (s, 1H), 8.50 (s, 1H), 7.98 (s, 1H), 7.55 - 7.46 (m, 6H), 7.30 (m, 2H), 7.02 (s, 1H), 6.64 (s, 1H), 4.30 (s, 2H), 2.53 (s, merged with DMSO Peak, 3H), 1.37 (3H, s)

^{13}C NMR (100 MHz) δ: 162.4, 154.8, 151.9, 146.6, 142.2, 139.8, 135.4, 133.6, 130.3, 129.9, 129.4, 129.2, 128.7, 124.8, 124.0, 123.5, 122.7, 121.2, 118.1, 115.4, 114.3, 110.7, 108.4, 104.1 (aromatic C), 37.8, 21.4, 13.5 (aliphatic C)

LC–MS (m/z): 505 (M+H)

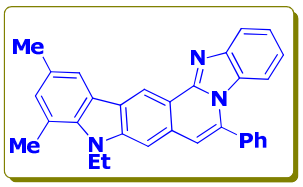
Anal. Calcd. for $C_{29}H_{21}BrN_4$: C, 68.92; H, 4.19; N, 11.09 %

Found: C, 68.85; H, 4.12; N, 11.15 %

Compound (199):

Compound **199** was synthesized from 2-alkynylaldehyde **1c** and phenylenediamine **2a** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 12% hexanes in ethyl acetate.

Yield: 81%



Mp: 236-238 °C

IR (KBr) ν_{max} cm^{-1}: 3474, 3425, 2922, 1526, 1458, 1254, 1024, 405

^{1}H NMR (400 MHz) δ: 9.23 (s, 1H), 7.63 (s, 2H), 7.32 – 7.28 (bs, 6H), 7.06 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.67 (s, 1H), 6.14 (d, *J* = 8.0 Hz, 1H), 4.33 (s, 2H), 2.78 (s, merged with DMSO peak, 3H), 2.48 (s, 3H), 1.15 (s, 3H)

^{13}C NMR (100 MHz) δ: 168.9, 167.7, 148.3, 142.6, 138.3, 135.6, 134.1, 132.0, 130.1, 129.9, 129.7, 129.67, 129.2, 129.1, 128.8, 124.8, 124.1, 123.3, 121.0, 119.8, 118.8, 117.8, 116.6, 114.0, 113.8, 104.1 (aromatic C), 20.9, 19.5, 15.1 (aliphatic C)

LC–MS (m/z): 440 (M+H)

Anal. Calcd. for $C_{31}H_{25}N_3$: C, 84.71; H, 5.73; N, 9.56 %

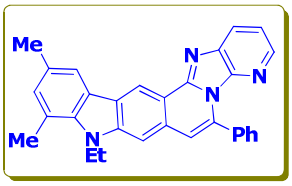
Found: C, 84.62; H, 5.65; N, 9.45 %

Compound (200):

Compound **200** was synthesized from 2-alkynylaldehyde **1c** and phenylenediamine **2b** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 15% hexanes in ethyl acetate.

Yield: 74%

Mp: 231-233 °C



IR (KBr) ν_{max} cm^{-1}: 3545, 1647, 1481, 1423, 1263, 1091, 1018, 883, 798, 692

^{1}H NMR (400 MHz) δ: 9.60 (s, 1H), 8.60 (s, 1H), 7.98 (s, 1H), 7.66 – 7.58 (bs, 5H), 7.50 (s, 1H), 7.08 (d, 2H), 6.87 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.59 (s, 2H), 2.78 (s, 3H), 2.54 (s, 3H), 1.46 (s, 3H)

^{13}C NMR (100 MHz) δ: 145.7, 143.1, 138.6, 138.2, 135.6, 134.3, 132.2, 130.1, 130.0, 129.7, 129.4, 129.2, 125.3, 123.9, 123.7, 121.5, 119.8, 119.4, 118.3, 117.8, 115.5, 114.6, 114.3, 104.1 (aromatic C), 39.8, 21.1, 19.8, 15.3 (aliphatic C)

LC–MS (m/z): 441 (M+H)

Anal. Calcd. for $C_{30}H_{24}N_4$: C, 81.79; H, 5.49; N, 12.72 %

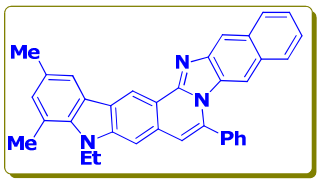
Found: C, 81.68; H, 5.43; N, 12.62 %

Compound (201):

Compound **201** was synthesized from 2-alkynylaldehyde **1c** and phenylenediamine **2c** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 80%

Mp: 241-243 °C



IR (KBr) ν_{max} cm^{-1}: 3057, 2920, 2181, 1610, 1527, 1440, 1396, 1267, 1221, 864, 733

^{1}H NMR (400 MHz) δ: 9.61 (s, 1H), 8.41 (s, 1H), 8.04 (d, *J* = 6.5 Hz, 1H), 8.02 (s, 1H), 7.73 – 7.67 (m, 5H), 7.43 (t, *J* = 6.5 Hz, 2H), 7.33 (t, *J* = 6.5 Hz, 1H), 7.28 (s, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 6.86 (s, 1H), 4.64 (q, *J* = 7.0 Hz, 2H), 2.82 (s, 3H), 2.56 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 153.0, 144.3, 143.1, 138.5, 136.7, 135.0, 131.9, 131.0, 130.9, 129.7, 129.6, 129.57, 128.9, 128.7, 128.2, 127.7, 127.5, 124.9, 124.1, 123.4, 123.2, 119.8, 119.2, 117.8, 115.0, 114.9, 112.7, 110.7,

104.1, (aromatic C), 39.8, 21.1, 19.8, 15.3 (aliphatic C)

LC–MS (m/z): 490 (M+H)

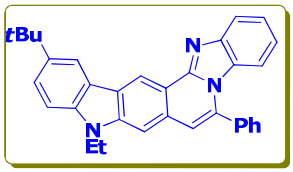
Anal. Calcd. for $C_{35}H_{27}N_3$: C, 85.86; H, 5.56; N, 8.58 %

Found: C, 85.92; H, 5.51; N, 8.48 %

Compound (202):

Compound **202** was synthesized from 2-alkynylaldehyde **1e** and phenylenediamine **2a** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 12% hexanes in ethyl acetate.

Yield: 81%



Mp: 219-221 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2968, 2926, 1730, 1637, 1608, 1529, 1450, 1261, 1103, 1022, 802, 698

^{1}H NMR (400 MHz) δ: 9.68 (s, 1H), 8.43 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.68-7.64 (m, 6H), 7.59 (s, 1H), 7.43 (m, 2H), 7.05 (s, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 4.44 (q, *J* = 7.6 Hz, 2H), 1.52 (s, 12H)

^{13}C NMR (100 MHz) δ: 149.8, 144.4, 143.0, 142.1, 139.8, 136.3, 135.1, 131.0, 130.0, 129.7, 129.5, 128.9, 125.1, 125.0, 123.8, 122.7, 120.6, 119.2, 117.7, 117.3, 115.4, 113.8, 113.3, 108.1, 103.8 (aromatic C), 37.9, 34.8, 32.0, 13.7 (aliphatic C)

LC–MS (m/z): 468 (M+H)

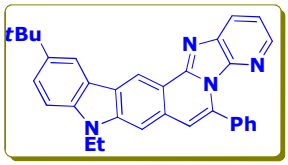
Anal. Calcd. for $C_{33}H_{29}N_3$: C, 84.76; H, 6.25; N, 8.99 %

Found: C, 84.65; H, 6.32; N, 8.89 %

Compound (203):

Compound **203** was synthesized from 2-alkynylaldehyde **1e** and phenylenediamine **2b** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 15% hexanes in ethyl acetate.

Yield: 76%



Mp: 220-222 °C

IR (KBr) ν_{max} cm^{-1}: 2922, 2855, 1639, 1572, 1468, 1381, 1248, 1025, 789

^{1}H NMR (400 MHz) δ: 9.66 (s, 1H), 8.42 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 3.2 Hz, 1H), 7.76-7.69 (m, 7H), 7.45 (s, 1H), 7.37-7.35 (m, 1H), 7.13 (s, 1H), 4.48 (q, *J* = 8.0 Hz, 2H), 1.51 (s, 12H)

^{13}C NMR (100 MHz) δ: 150.4, 145.0, 143.1, 142.4, 141.5, 139.9, 136.4, 136.3, 134.7, 130.5, 129.7, 129.0, 127.7, 125.9, 125.7, 125.2, 122.6, 119.7, 117.7, 117.1, 115.1, 114.9, 108.2, 104.1 (aromatic C), 38.0, 34.8, 32.0, 13.7 (aliphatic C)

LC–MS (m/z): 469 (M+H)

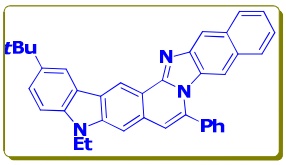
Anal. Calcd. for $C_{32}H_{28}N_4$: C, 82.02; H, 6.02; N, 11.96 %

Found: C, 82.15; H, 6.12; N, 11.79 %

Compound (204):

Compound **204** was synthesized from 2-alkynylaldehyde **1e** and phenylenediamine **2c** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 12% hexanes in ethyl acetate.

Yield: 78%



Mp: 227-229 °C

IR (KBr) ν_{max} cm^{-1}: 2927, 2849, 1751, 1665, 1544, 1472, 1271, 1167, 1024

^{1}H NMR (400 MHz) δ: 9.75 (s, 1H), 8.45 (s, 2H), 8.05 (d, *J* = 6.6 Hz, 1H), 7.74 - 7.73 (m, 3H), 7.30 - 7.04 (m, 3H), 7.68 (d, *J* = 6.6 Hz, 1H), 7.67 (m, 1H), 7.43 (m, 2H), 7.41 (m, 1H), 7.07 (s, 1H), 6.86 (s, 1H), 4.45 (q, *J* = 8.0 Hz, 2H), 1.52 (s, 12H)

^{13}C NMR (100 MHz) δ: 143.3, 142.7, 139.8, 136.7, 134.8, 131.7, 131.1, 130.9, 129.9, 129.6, 129.0, 128.7, 128.2, 128.1, 127.8, 127.7, 125.2, 124.6, 124.3, 123.6, 122.7, 118.3, 117.9, 114.7, 113.0, 110.9, 108.5, 108.2, 103.9 (aromatic C), 37.9, 34.8, 32.0, 13.7 (aliphatic C)

LC–MS (m/z): 518 (M+H)

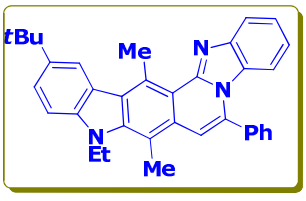
Anal. Calcd. for $C_{37}H_{31}N_3$: C, 85.85; H, 6.04; N, 8.12 %

Found: C, 85.76; H, 6.12; N, 8.19 %

Compound (205):

Compound **205** was synthesized from 2-alkynylaldehyde **1d** and phenylenediamine **2a** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 80%



Mp: 209-211 °C

IR (KBr) ν_{max} cm^{-1}: 3746, 3373, 2939, 1641, 1577, 1489, 1456, 1375, 1302, 1016, 798, 721

^{1}H NMR (400 MHz) δ: 8.61 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.02 – 7.54 (m, 6H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 4.64 (q, *J* = 8.0 Hz, 2H), 4.09 (s, 3H), 3.02 (s, 3H), 1.50 (s, 12H)

^{13}C NMR (100 MHz) δ: 150.6, 144.0, 142.6, 141.3, 140.6, 135.7, 135.5, 132.9, 130.2, 129.7, 129.5, 128.9, 129.5, 125.0, 124.1, 124.0, 123.4, 120.6, 120.5, 119.4, 115.3, 113.6, 111.1, 110.2, 108.1 (aromatic C), 37.5, 34.8, 32.0, 20.1, 15.5, 14.9 (aliphatic C)

LC–MS (m/z): 496 (M+H)

Anal. Calcd. for $C_{35}H_{33}N_3$: C, 84.81; H, 6.71; N, 8.48 %

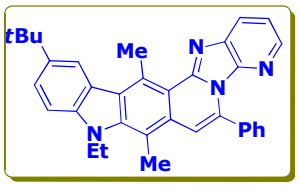
Found: C, 84.71; H, 6.75; N, 8.55 %

Compound (206):

Compound **206** was synthesized from 2-alkynylaldehyde **1d** and phenylenediamine **2b** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 15% hexanes in ethyl acetate.

Yield: 72%

Mp: 213-215 °C



IR (KBr) ν_{max} cm^{-1}: 2916, 2854, 1643, 1570, 1466, 1381, 1253, 1020, 785

^{1}H NMR (400 MHz) δ: 8.58 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H), 7.73 – 7.72 (m, 3H), 7.57 (bs, 3H), 7.46 (d,

J = 8.0 Hz, 1H), 7.29 – 7.27 (m, 2H), 4.65 (s, 2H), 4.02 (s, 3H), 3.03 (s, 3H), 1.56 (s, 12H)

^{13}C NMR (100 MHz) *δ*: 151.2, 143.9, 142.8, 141.6, 141.3, 140.9, 135.9, 135.5, 135.2, 133.2, 130.7, 129.5, 128.8, 127.8, 126.2, 125.2, 124.1, 124.0, 120.5, 119.3, 114.8, 112.0, 111.6, 108.2, (aromatic C), 40.7, 34.8, 32.0, 20.1, 15.6, 15.0 (aliphatic C)

LC–MS (m/z): 497 (M+H)

Anal. Calcd. for $C_{34}H_{32}N_4$: C, 82.22; H, 6.49; N, 11.28 %

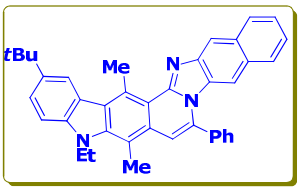
Found: C, 82.36; H, 6.41; N, 11.15 %

Compound (207):

Compound **207** was synthesized from 2-alkynylaldehyde **1d** and phenylenediamine **2c** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 81%

Mp: 225-227 °C



IR (KBr) ν_{max} cm^{-1}: 2924, 2852, 1747, 1660, 1541, 1473, 1269, 1165, 1022

^{1}H NMR (400 MHz) *δ*: 8.60 (s, 1H), 8.42 (s, 1H), 7.72 (d, *J* = 6.0 Hz, 1H), 7.67 – 7.66 (m, 6H), 7.60 (s, 1H), 7.52 (m, 2H), 7.43 (s, 1H), 7.19 (s, 1H), 6.83 (s, 1H), 4.62 (s, 2H), 4.08 (s, 3H), 3.0 (s, 3H), 1.57 (s, 12H)

^{13}C NMR (100 MHz) *δ*: 153.9, 144.0, 142.8, 141.3, 141.0, 136.0, 135.6, 133.9, 131.1, 130.8, 130.7, 129.6, 129.56, 129.0, 128.7, 128.2, 127.7, 125.0, 124.1, 124.0, 123.9, 123.3, 120.5, 115.2, 114.9, 111.3, 110.4, 109.5,

108.2 (aromatic C), 34.8, 32.1, 29.7, 20.3, 15.6, 15.0 (aliphatic C)

LC–MS (m/z): 546 (M+H)

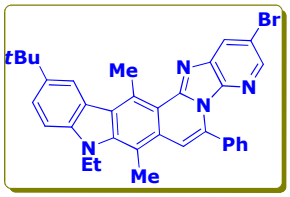
Anal. Calcd. for $C_{39}H_{35}N_3$: C, 85.84; H, 6.46; N, 7.70 %

Found: C, 85.71; H, 6.41; N, 7.78 %

Compound (208):

Compound **208** was synthesized from 2-alkynylaldehyde **1d** and phenylenediamine **2d** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 12% hexanes in ethyl acetate.

Yield: 85%



Mp: 231-233 °C

IR (KBr) ν_{max} cm^{-1}: 3042, 2957, 2918, 1782, 1722, 1631, 1514, 1469, 1078, 796, 640

^{1}H NMR (400 MHz) δ: 8.64 (s, 1H), 8.59 (s, 1H), 7.70 - 7.67 (m, 5H), 7.46 (d, J = 8.8 Hz, 2H), 7.45 (s, 1H), 7.34 (s, 1H), 6.75 (s, 1H), 4.63 (d, J = 8.0 Hz, 2H), 4.03 (s, 2H), 3.02 (s, 3H), 1.56 (s, 12H)

^{13}C NMR (100 MHz) δ: 154.6, 152.8, 146.6, 143.1, 141.3, 141.2, 134.6, 134.5, 134.4, 130.2, 129.7, 129.4, 125.5, 124.3, 123.9, 123.5, 122.8, 122.1, 120.6, 114.4, 111.5, 111.1, 110.9, 108.3 (aromatic C), 40.7, 34.8, 32.1, 20.1, 15.5, 14.9 (aliphatic C)

LC–MS (m/z): 574 (M), 576 (M+2)

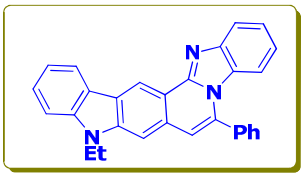
Anal. Calcd. for $C_{34}H_{31}BrN_4$: C, 70.95; H, 5.43; N, 9.73 %

Found: C, 70.85; H, 5.51; N, 9.65 %

Compound (209):

Compound **209** was synthesized from 2-alkynylaldehyde **1b** and phenylenediamine **2a** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 85%



Mp: 214-216 °C

IR (KBr) ν_{max} cm^{-1}: 2969, 2930, 1732, 1635, 1618, 1520, 1265, 1022, 800, 787

^{1}H NMR (400 MHz) δ: 9.67 (s, 1H), 8.35 (d, *J* = 6.0 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.67–7.57 (m, 7H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.42 (m, 2H), 7.05 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.50 (d, *J* = 6.8 Hz, 1H), 4.65 (q, *J* = 7.5 Hz, 2H), 1.52 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (100 MHz) δ: 149.6, 141.8, 141.7, 137.3, 138.5, 135.0, 131.0, 130.7, 130.2, 129.7, 129.5, 128.9, 127.1, 124.8, 123.8, 123.0, 121.4, 120.7, 119.8, 119.2, 117.5, 113.8, 113.3, 108.5, 103.9 (aromatic C), 37.9, 13.6 (aliphatic C)

LC–MS (m/z): 412 (M+H)

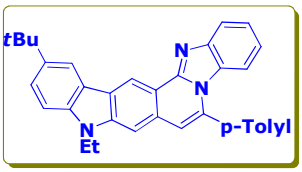
Anal. Calcd. for $C_{29}H_{21}N_3$: C, 84.64; H, 5.14; N, 10.21 %

Found: C, 84.51; H, 5.21; N, 10.35 %

Compound (210):

Compound **210** was synthesized from 2-alkynylaldehyde **1f** and phenylenediamine **2a** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 85%



Mp: 208-210 °C

IR (KBr) ν_{max} cm^{-1}: 3042, 2960, 2924, 1635, 1508, 1510, 1476, 1420, 1120, 854, 708

^{1}H NMR (400 MHz) δ: 9.70 (s, 1H), 8.44 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.65 (m, 1H), 7.50-7.33 (m, 7H), 6.97-6.55 (m, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 1.51 (s, 12H)

^{13}C NMR (100 MHz) δ: 149.7, 144.1, 142.9, 142.0, 139.8, 139.7, 136.3, 132.1, 131.2, 130.9, 129.6, 129.4, 125.0, 124.9, 123.8, 122.7, 120.6, 119.0, 117.8, 117.4, 115.1, 114.0, 113.5, 108.1, 103.7 (aromatic C), 37.8, 34.8, 32.0, 21.6, 13.7 (aliphatic C)

LC–MS (m/z): 483 (M+H)

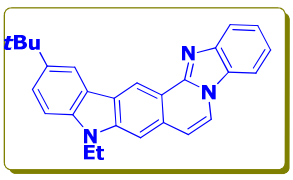
Anal. Calcd. for $C_{34}H_{31}N_3$: C, 84.79; H, 6.49; N, 8.72 %

Found: C, 84.71; H, 6.53; N, 8.65 %

Compound (211):

Compound **211** was synthesized from 2-alkynylaldehyde **1g** and phenylenediamine **2a** according to general procedure C. The product was obtained as light yellow solid after column chromatography using 10% hexanes in ethyl acetate.

Yield: 85%



Mp: 200-202 °C

IR (KBr) ν_{max} cm^{-1}: 3059, 2970, 2930, 1732, 1632, 1529, 1452, 1266, 1105, 1027, 805, 700

^{1}H NMR (400 MHz) δ: 9.54 (s, 1H), 8.37 (s, 1H), 8.03-8.01 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.48 (m, 1H), 7.35 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.48 (12H, s)

^{13}C NMR (100 MHz) δ: 148.7, 143.8, 142.9, 141.7, 139.7, 130.3, 129.8, 125.0, 124.2, 123.2, 122.5, 121.1, 120.0, 119.2, 117.6, 117.0, 115.7, 111.9, 109.4, 108.1, 104.2 (aromatic C), 37.7, 34.7, 32.0, 13.7 (aliphatic C)

LC–MS (m/z): 392 (M+H)

Anal. Calcd. for $C_{27}H_{25}N_3$: C, 82.83; H, 6.44; N, 10.73 %

Found: C, 82.71; H, 6.49; N, 10.65 %

Table 5. Crystal data and structure refinement for 180

Empirical formula	: $C_{31}H_{24}ClF_3N_2O_3S$	
Formula weight	: 597.03	
Temperature	: 293(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Triclinic	
Space group	: P-1	
Unit cell dimensions	: a = 8.1010(16) Å	α = 100.23(3)°.
	: b = 11.081(2) Å	β = 99.20(3)°.
	: c = 16.926(3) Å	γ = 104.73(3)°.
Volume	: 1412.1(5) $Å^3$	
Z	: 2	
Density (calculated)	: 1.404 Mg/m^3	
Absorption coefficient	: 0.265 mm^{-1}	
F(000)	: 616	
Crystal size	: 0.40 x 0.20 x 0.10 mm^3	
Theta range for data collection	: 1.95 to 25.00°.	
Index ranges	: -9<=h<=9, -13<=k<=13, -19<=l<=20	
Reflections collected	: 9776	
Independent reflections	: 4948 [R(int) = 0.0497]	
Completeness to theta = 25.00°	: 99.3 %	
Absorption correction	: Empirical	
Max. and min. transmission	: 0.9740 and 0.9013	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 4948 / 0 / 372	
Goodness-of-fit on F^2	: 1.033	
Final R indices [I>2sigma(I)]	: R1 = 0.0954, wR2 = 0.1895	
R indices (all data)	: R1 = 0.1654, wR2 = 0.2240	
Largest diff. peak and hole	: 0.413 and -0.254 $e.Å^{-3}$	
CCDC number	: 804670	

Table 6. Crystal data and structure refinement for 184

Empirical formula	: $C_{33}H_{29}F_3N_2O_3S$	
Formula weight	: 590.64	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Orthorhombic	
Space group	: P n a 21	
Unit cell dimensions	: a = 8.1925(3) Å	α= 90°.
	: b = 16.7763(8) Å	β= 90°.
	: c = 21.6041(10) Å	γ = 90°.
Volume	: 2969.3(2) $Å^3$	
Z	: 4	
Density (calculated)	: 1.321 Mg/m^3	
Absorption coefficient	: 0.164 mm^{-1}	
F(000)	: 1232	
Crystal size	: 0.24 x 0.18 x 0.12 mm^3	
Theta range for data collection	: 2.77 to 29.01°.	
Index ranges	: -7<=h<=10, -17<=k<=21, -22<=l<=27	
Reflections collected	: 9034	
Independent reflections	: 5089 [R(int) = 0.0292]	
Completeness to theta = 29.01°	: 87.8 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9805 and 0.9616	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 5089 / 1 / 384	
Goodness-of-fit on F^2	: 1.029	
Final R indices [I>2sigma(I)]	: R1 = 0.0607, wR2 = 0.1390	
R indices (all data)	: R1 = 0.0962, wR2 = 0.1622	
Absolute structure parameter	: -0.22(13)	
Extinction coefficient	: 0.0024(8)	
Largest diff. peak and hole	: 0.293 and -0.279 e.$Å^{-3}$	
CCDC number	: 805312	

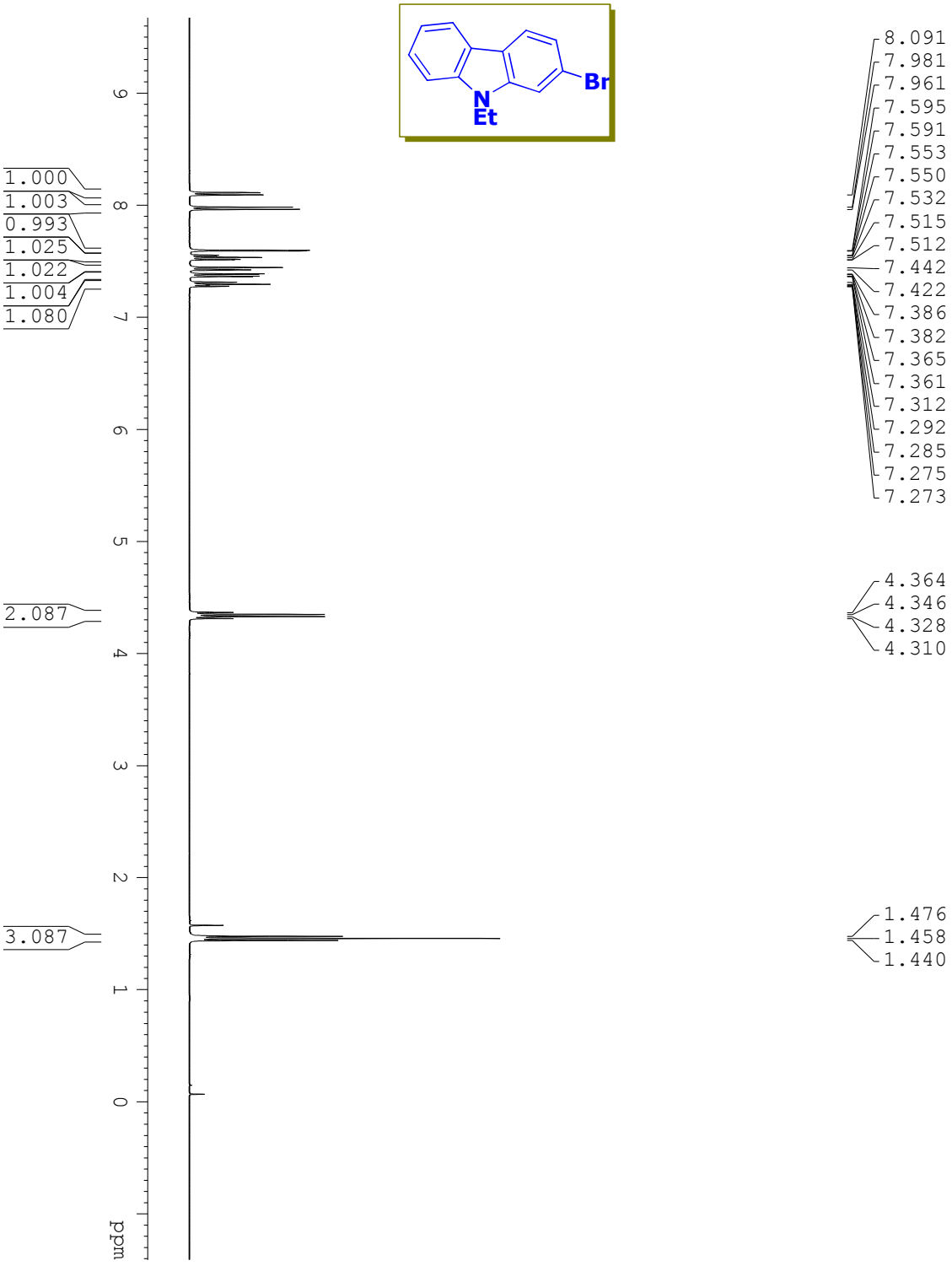
Table 7. Crystal data and structure refinement for 196

Empirical formula	: $C_{29}H_{22}N_4$	
Formula weight	: 426.51	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: monoclinic	
Space group	: P 1 21/n 1	
Unit cell dimensions	: a = 9.3186(15) Å	α= 90°.
	: b = 18.272(2) Å	β= 99.788(12)°.
	: c = 13.1361(18) Å	γ = 90°.
Volume	: 2204.2(5) $Å^3$	
Z	: 4	
Density (calculated)	: 1.285 Mg/m^3	
Absorption coefficient	: 0.077 mm^{-1}	
F(000)	: 896	
Crystal size	: 0.24 x 0.18 x 0.12 mm^3	
Theta range for data collection	: 2.73 to 28.89°.	
Index ranges	: -11<=h<=11, -13<=k<=23, -9<=l<=17	
Reflections collected	: 9209	
Independent reflections	: 5018 [R(int) = 0.0949]	
Completeness to theta = 28.89°	: 86.5 %	
Absorption correction	: Semi-empirical from equivalents	
Max. and min. transmission	: 0.9908 and 0.9817	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 5018 / 0 / 301	
Goodness-of-fit on F^2	: 0.925	
Final R indices [I>2sigma(I)]	: R1 = 0.0774, wR2 = 0.1086	
R indices (all data)	: R1 = 0.2826, wR2 = 0.1825	
Extinction coefficient	: 0.0020(3)	
Largest diff. peak and hole	: 0.217 and -0.248 e.$Å^{-3}$	
CCDC number	: 814066	

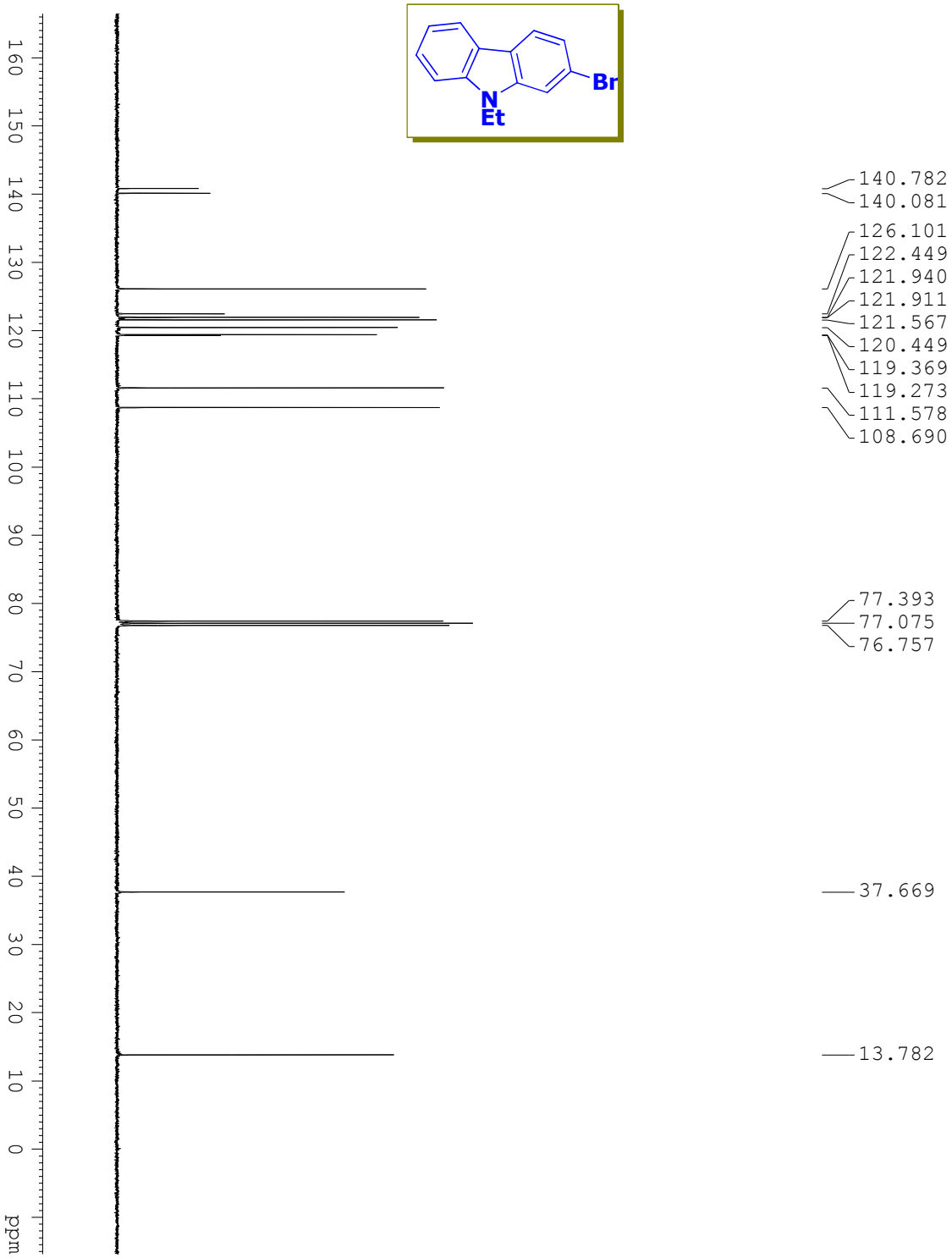
Table 8. Crystal data and structure refinement for 197

Empirical formula	: $C_{34}H_{27}N_3O$	
Formula weight	: 493.59	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Trigonal	
Space group	: P-3c1	
Unit cell dimensions	: a = 18.3228(9) Å	α= 90°.
	: b = 18.3228(9) Å	β= 90°.
	: c = 26.723(3) Å	γ = 120°.
Volume	: 7769.7(9) $Å^3$	
Z	: 12	
Density (calculated)	: 1.266 Mg/m^3	
Absorption coefficient	: 0.077 mm^{-1}	
F(000)	: 3120	
Crystal size	: 0.26 x 0.20 x 0.16 mm^3	
Theta range for data collection	: 1.28 to 24.98°.	
Index ranges	:-21<=h<=21, -21<=k<=21, -31<=l<=31	
Reflections collected	: 71600	
Independent reflections	: 4577 [R(int) = 0.0650]	
Completeness to theta = 24.98°	: 100.0 %	
Absorption correction	: Empirical	
Max. and min. transmission	: 0.9878 and 0.9802	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 4577 / 0 / 346	
Goodness-of-fit on F^2	: 1.078	
Final R indices [I>2sigma(I)]	: R1 = 0.0664, wR2 = 0.1626	
R indices (all data)	: R1 = 0.0819, wR2 = 0.1732	
Extinction coefficient	: 0.00026(13)	
Largest diff. peak and hole	:0.458 and -0.659 e.$Å^{-3}$	
CCDC number	: 814065	

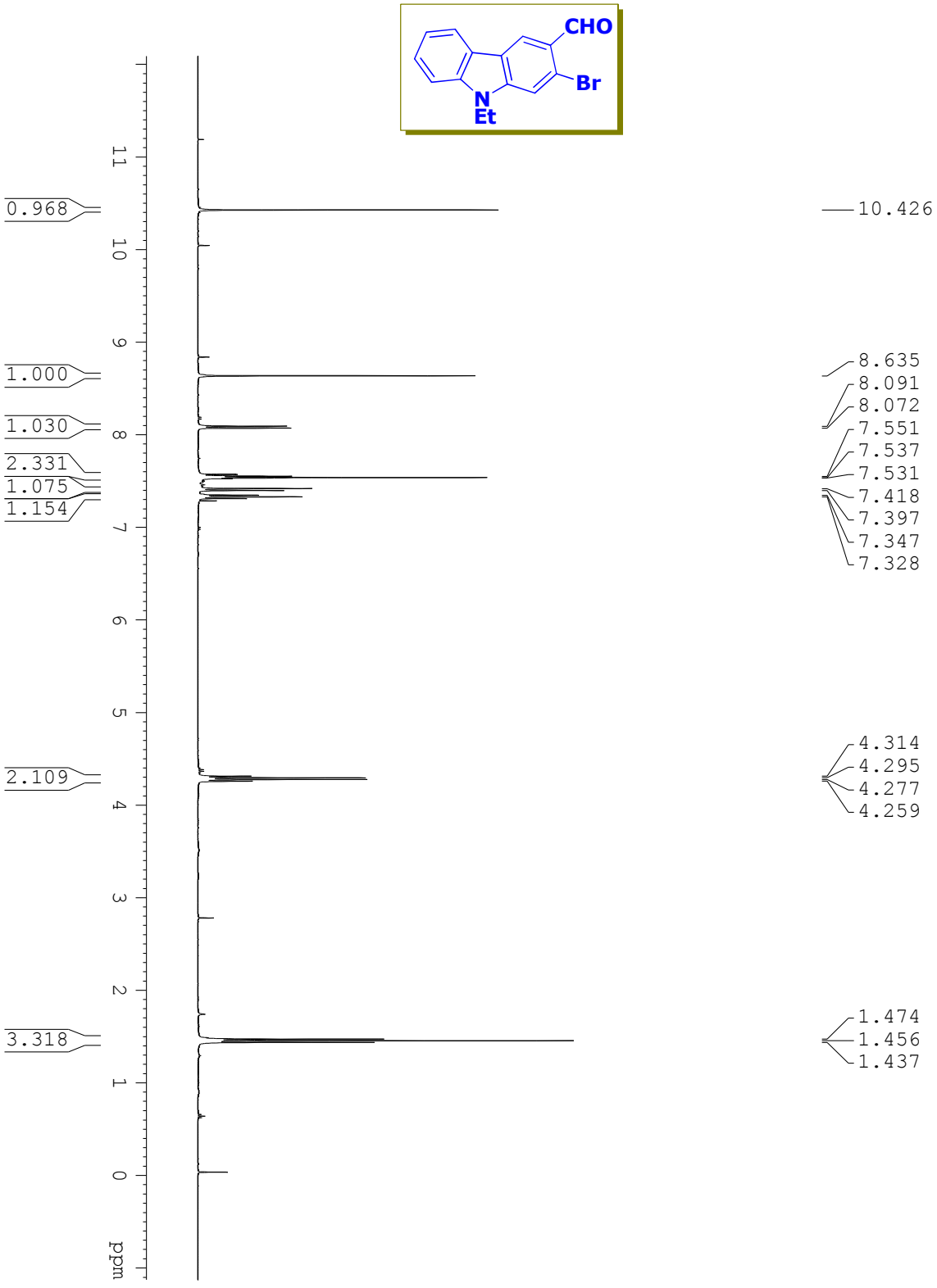
Spectrum No: 1, ^{1}H NMR of 169a



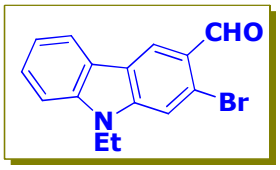
Spectrum No: 2, ^{13}C NMR of 169a



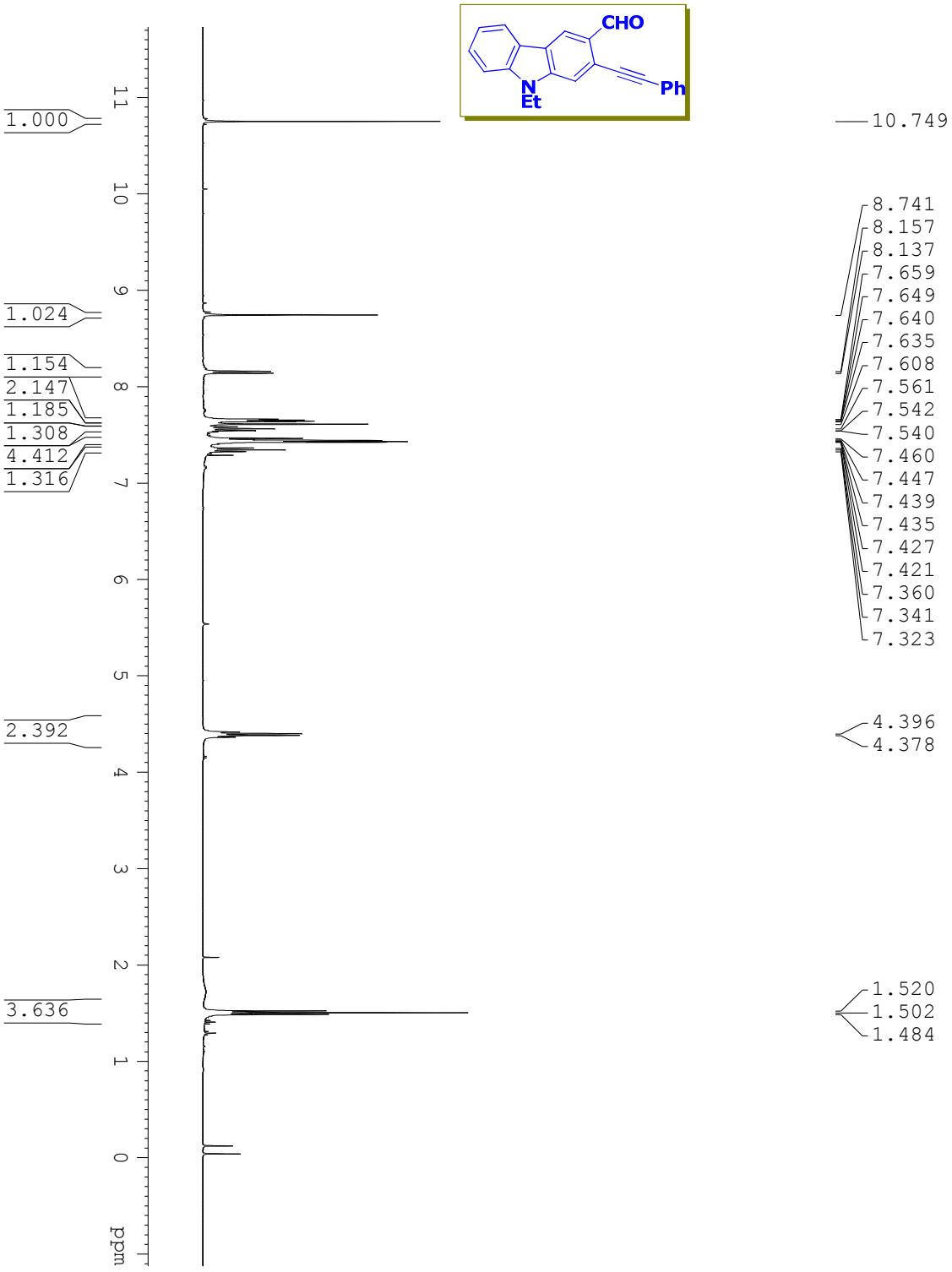
Spectrum No: 3, ^{1}H NMR of 171



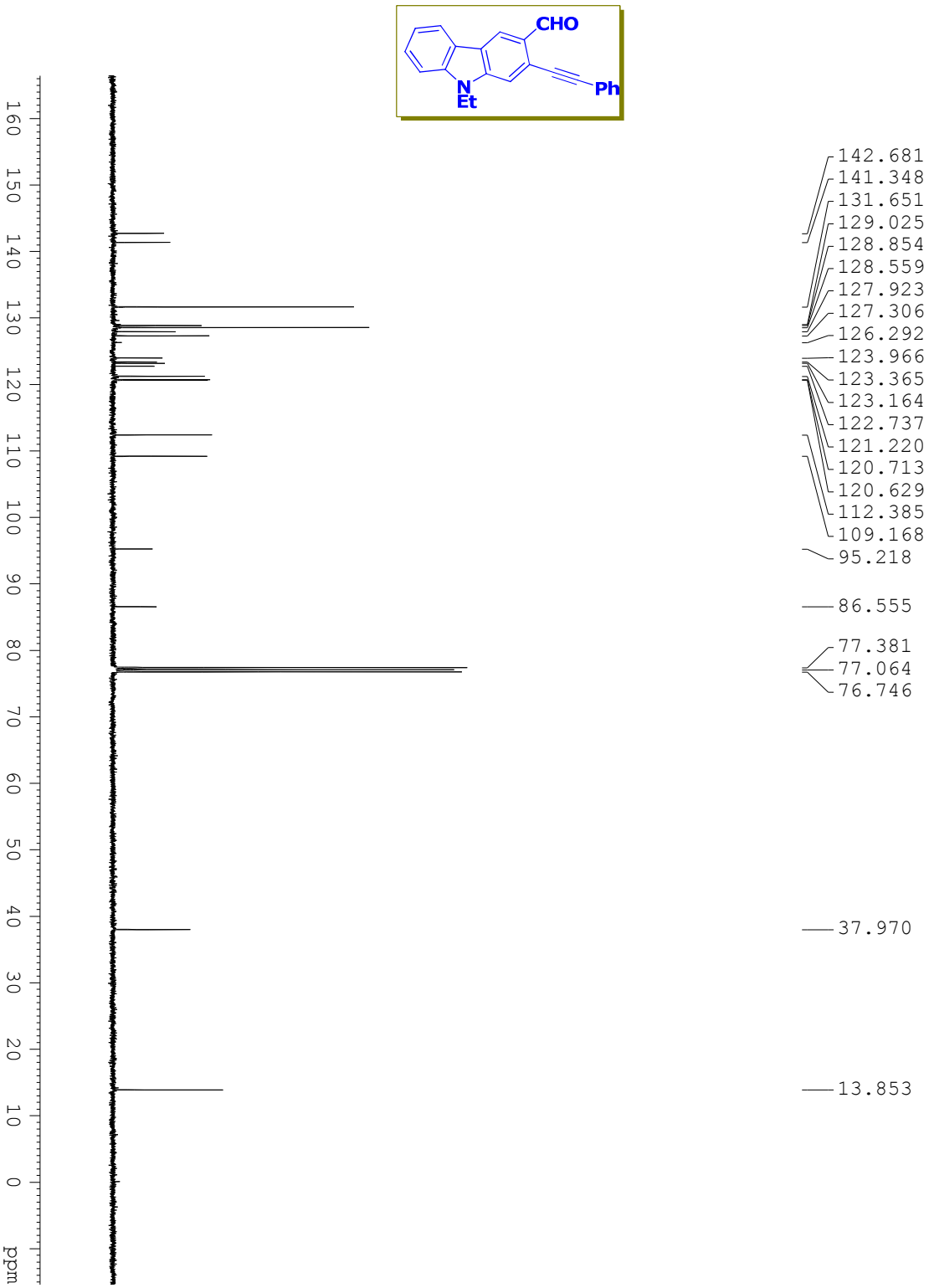
Spectrum No: 4, ^{13}C NMR of 171



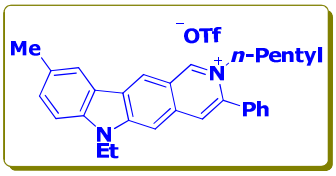
Spectrum No: 5, ^{1}H NMR of 1b



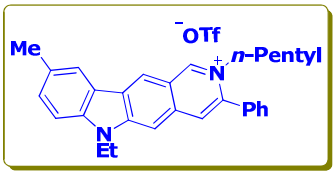
Spectrum No: 6, ^{13}C NMR of 1b



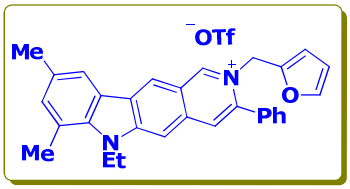
Spectrum No: 7, ^{1}H NMR of 182

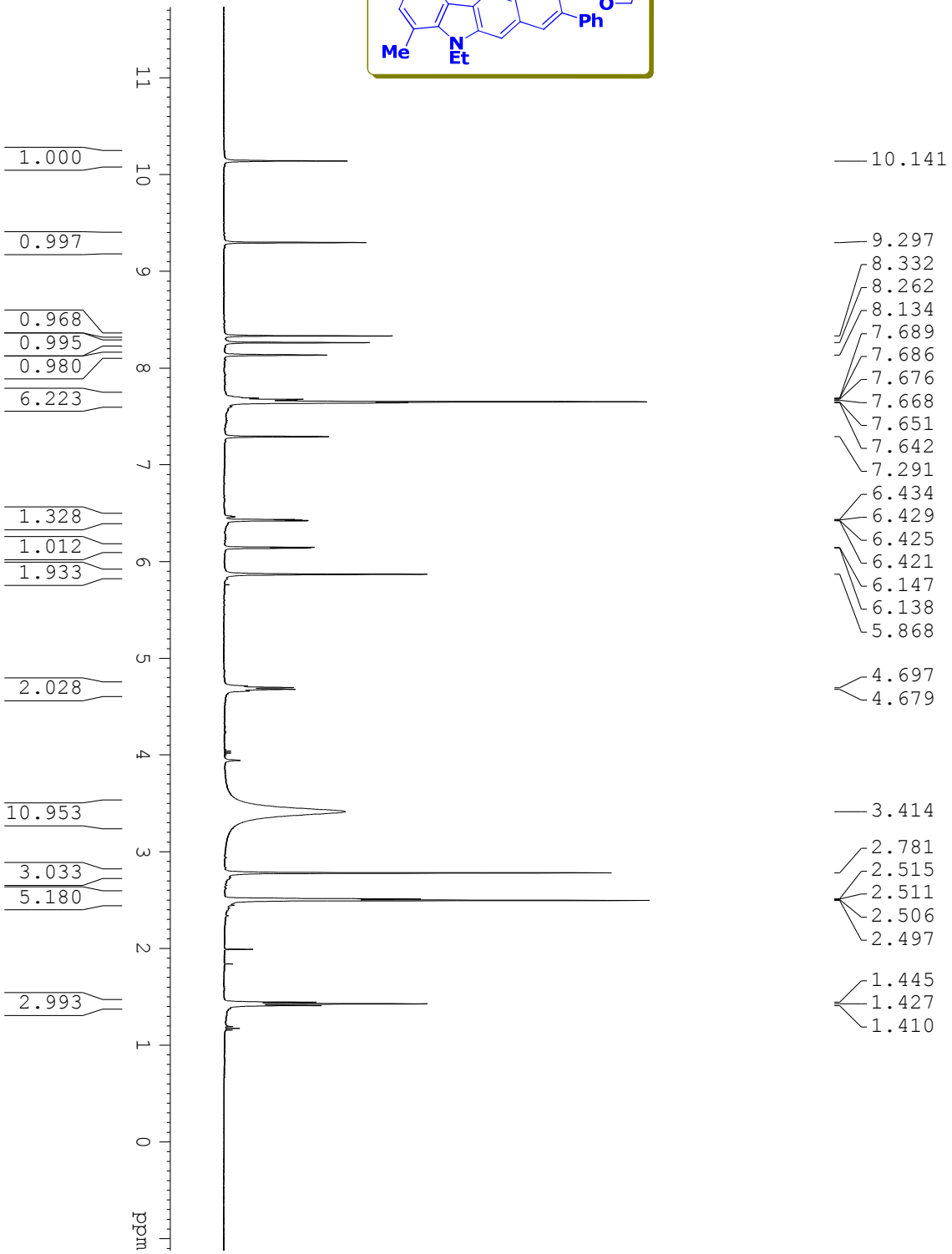


Spectrum No: 8, ^{13}C NMR of 182

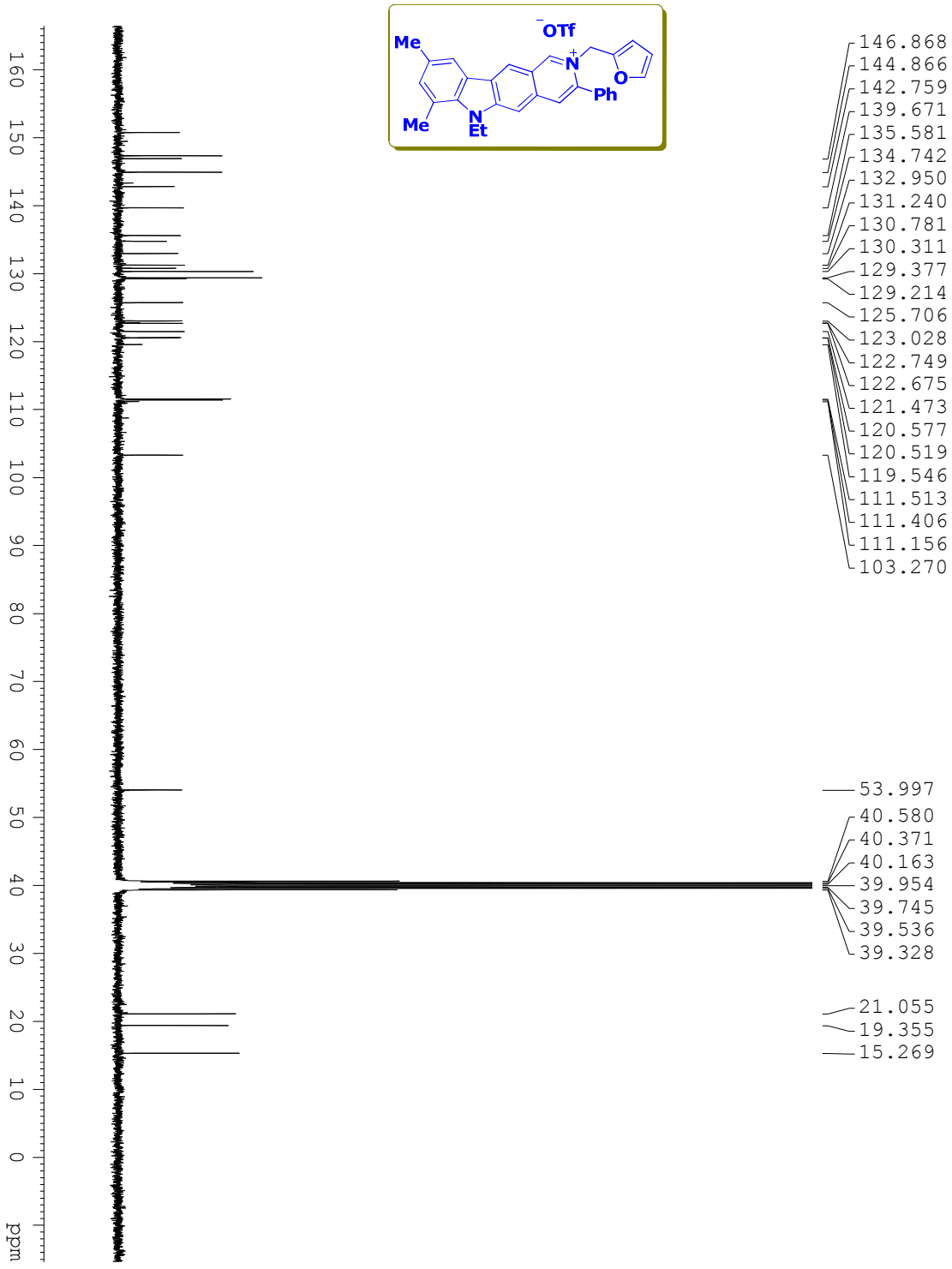


Spectrum No: 9, ^{1}H NMR of 186

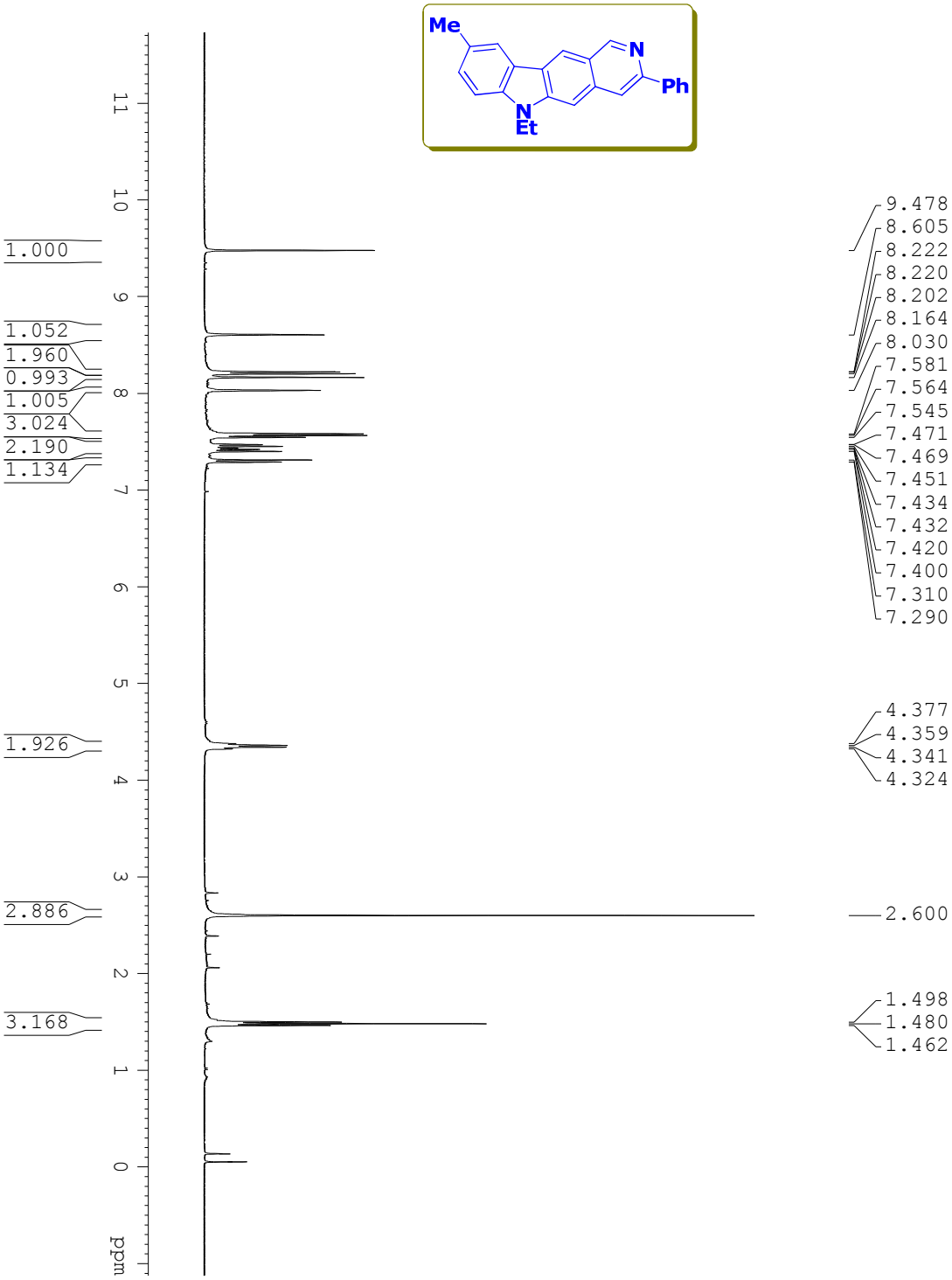




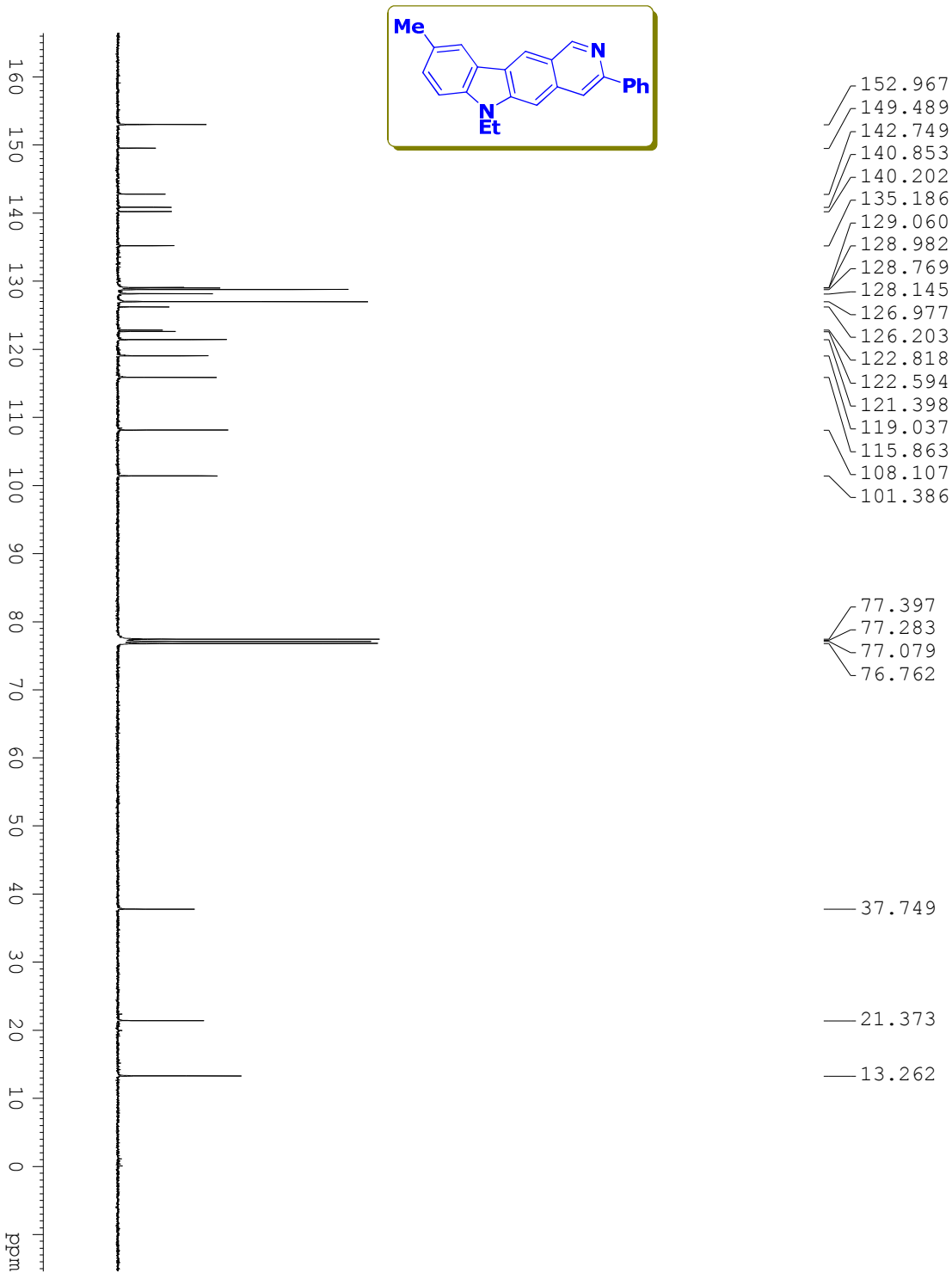
Spectrum No: 10, ^{13}C NMR of 186



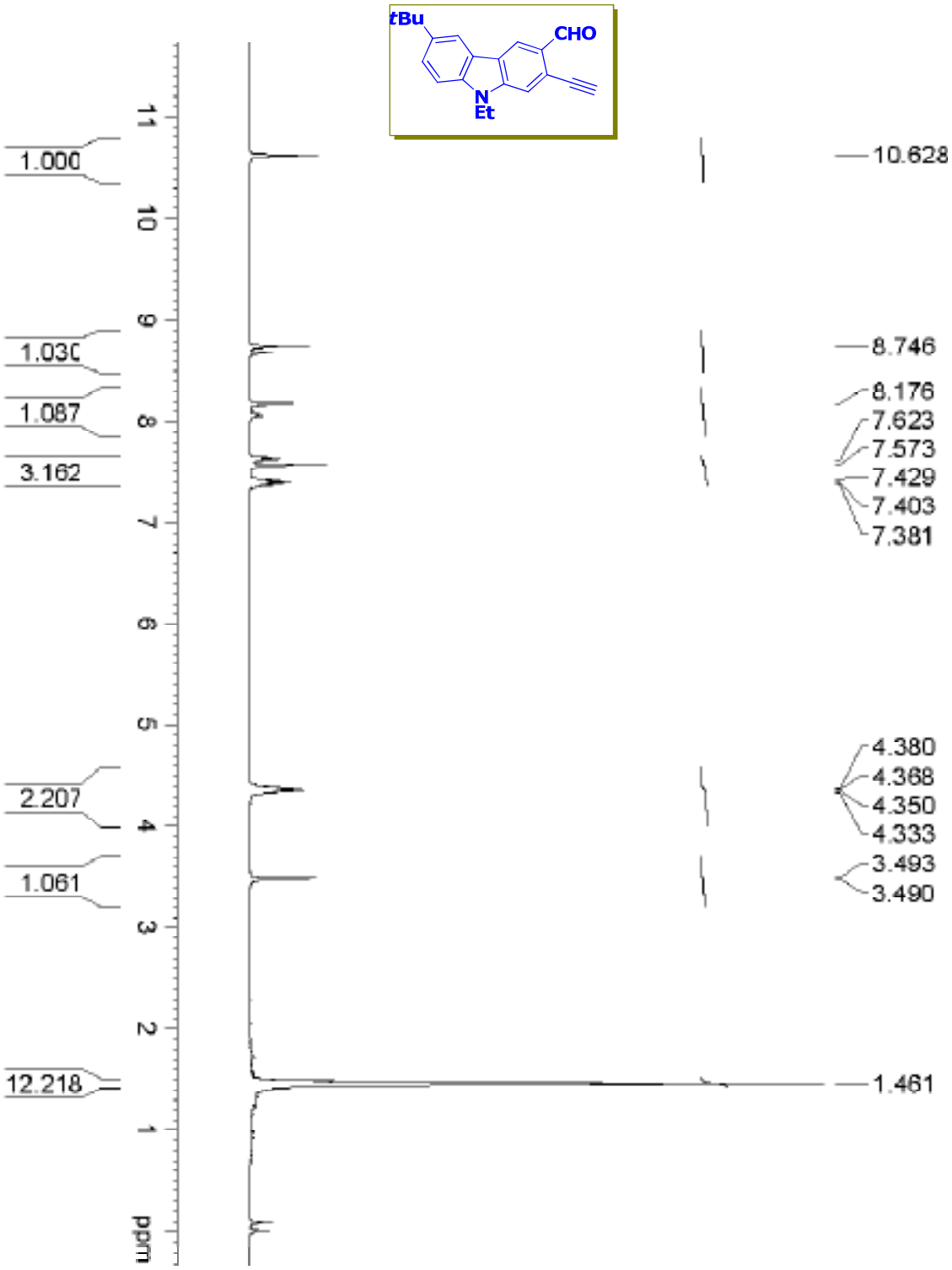
Spectrum No: 11, ^{1}H NMR of 3a



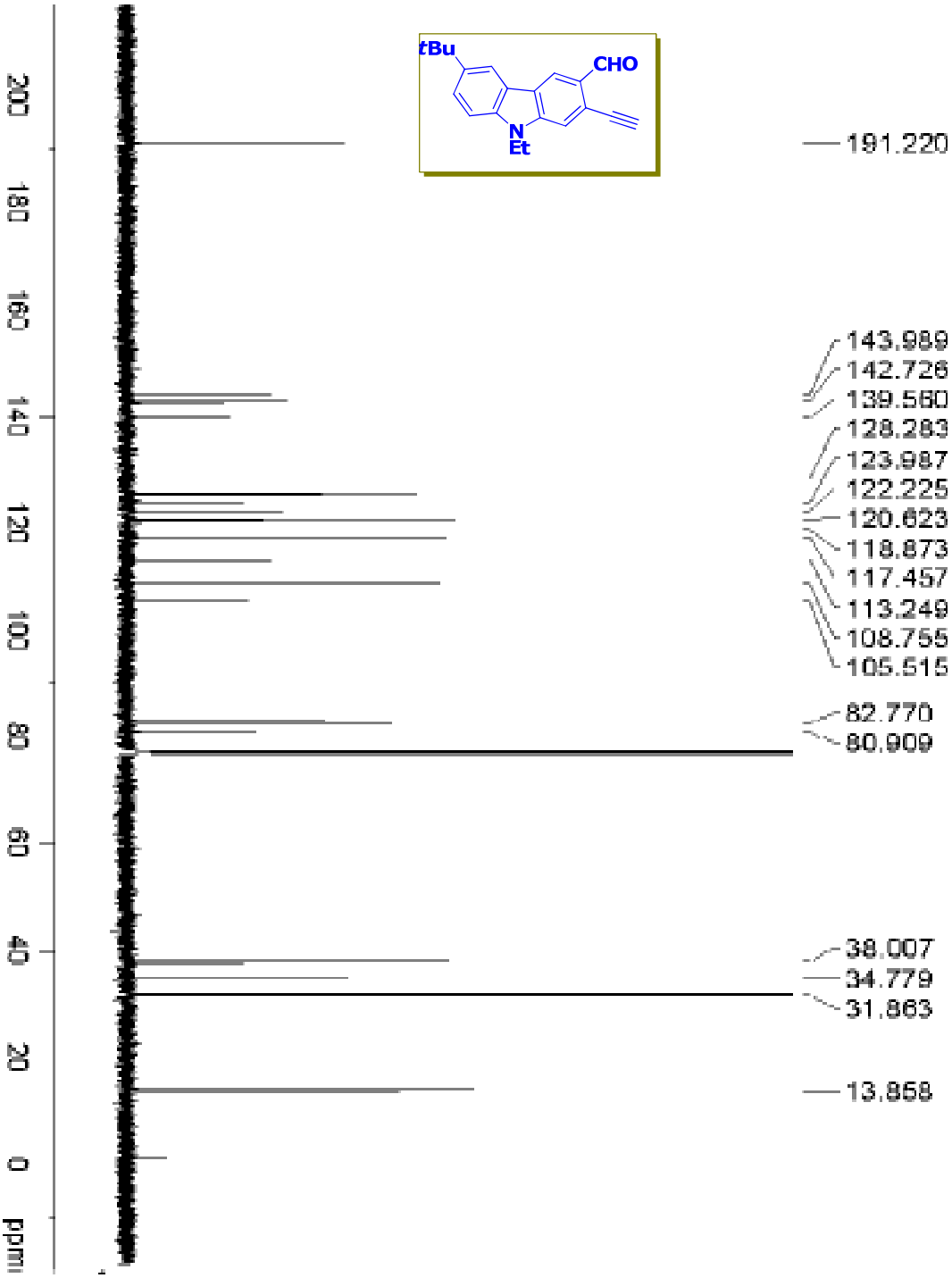
Spectrum No: 12, ^{13}C NMR of 3a



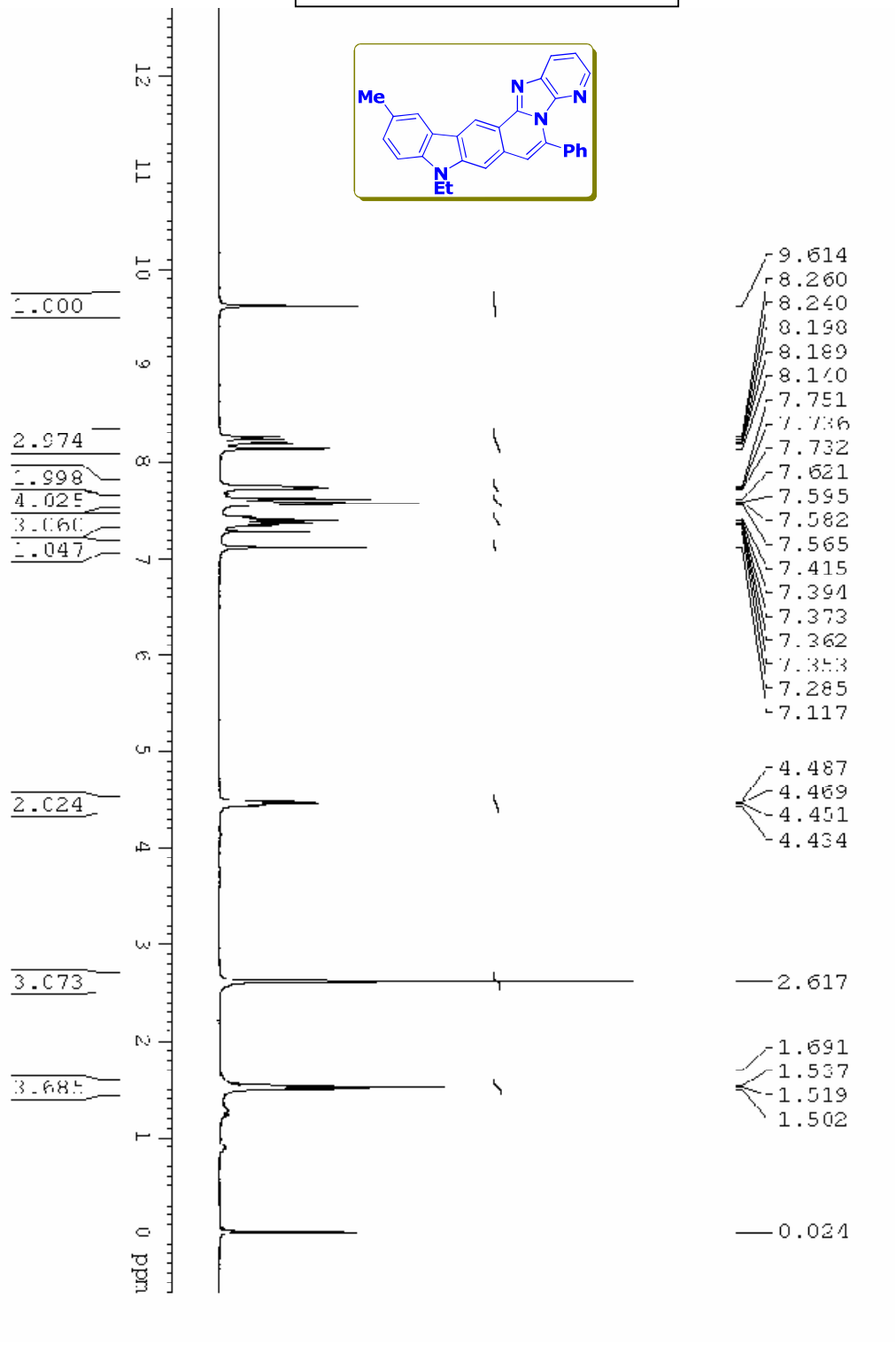
Spectrum No: 13, ^{1}H NMR of 1g



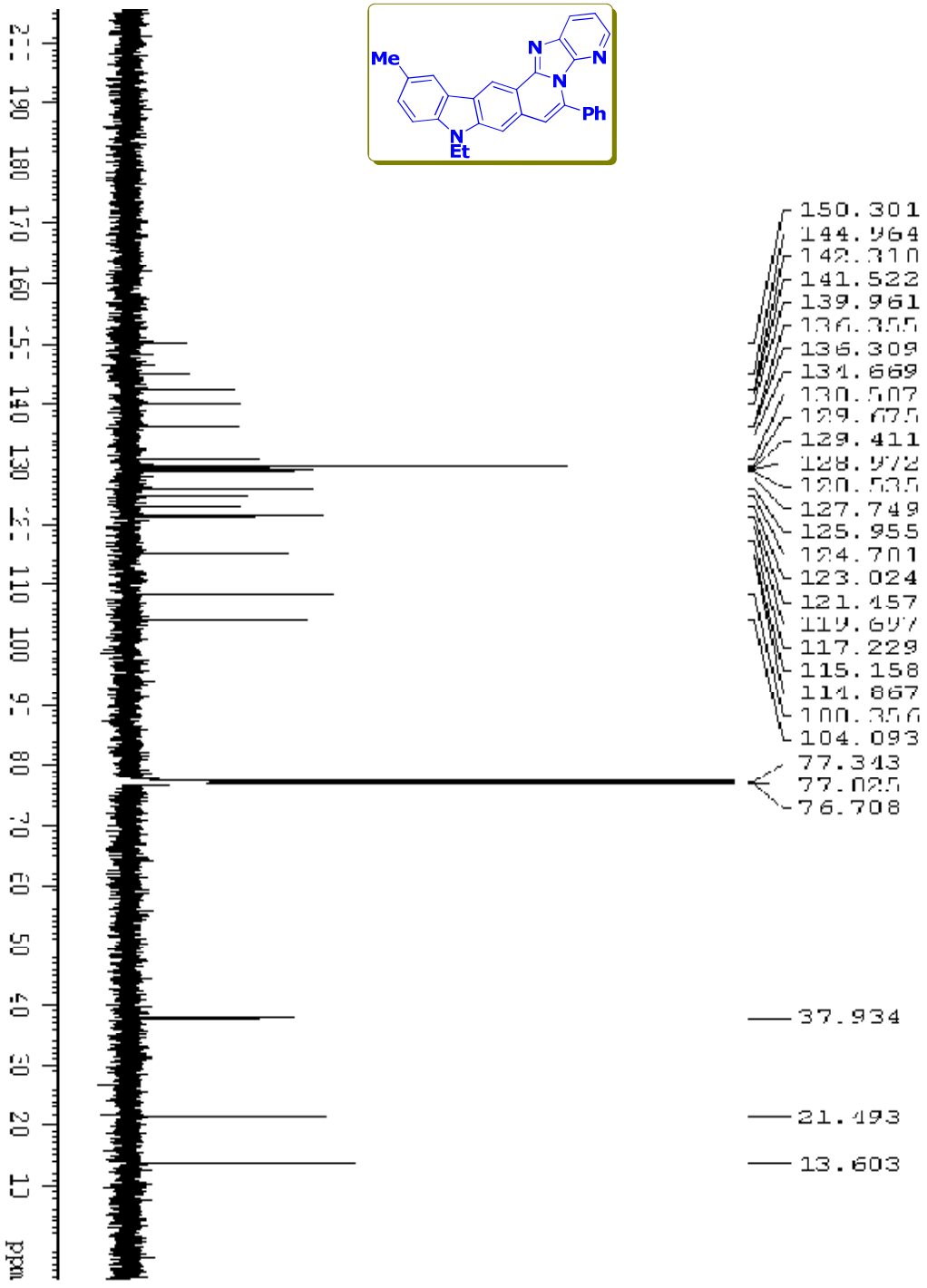
Spectrum No: 14, ^{13}C NMR of 1g



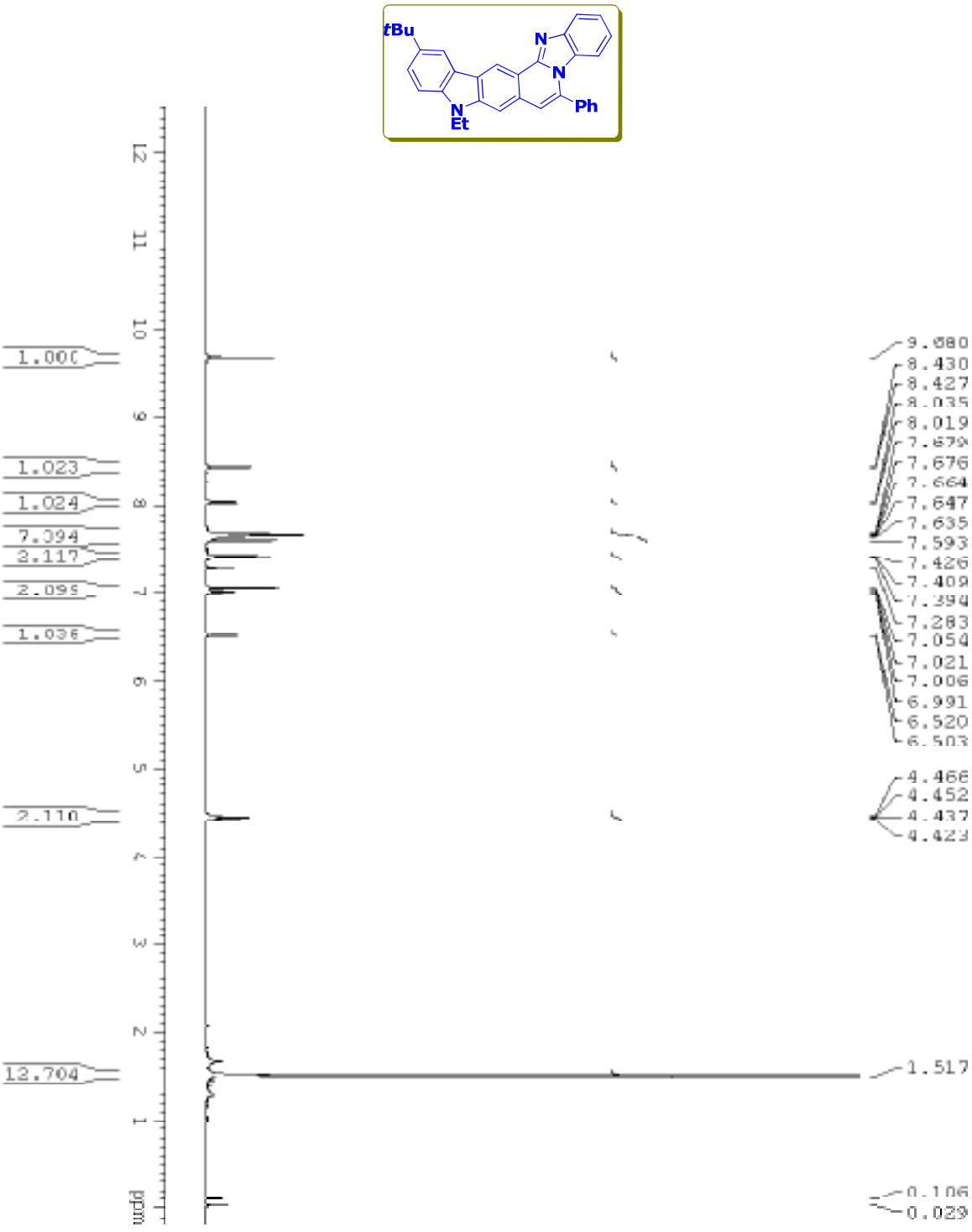
Spectrum No: 15, ^{1}H NMR of 196



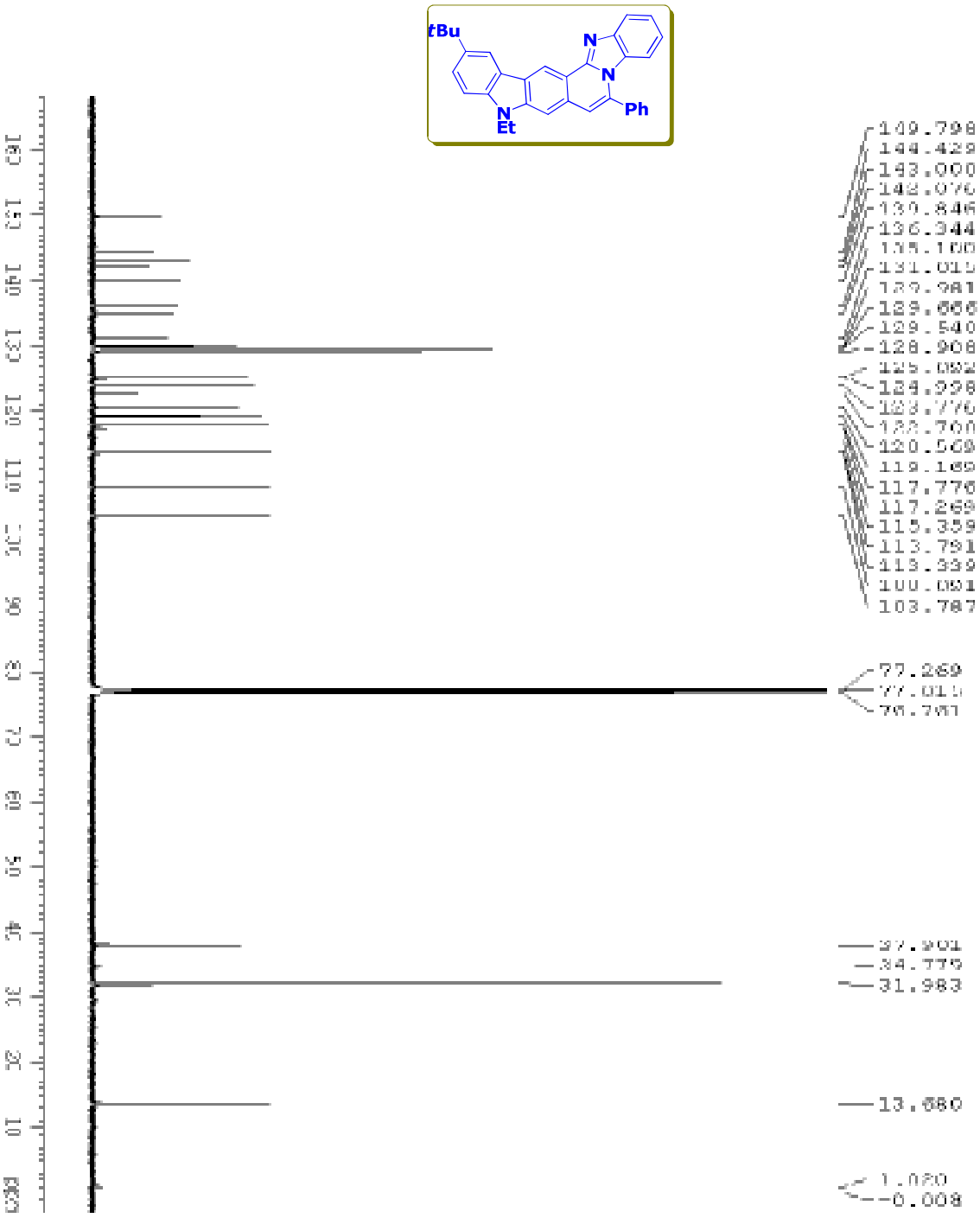
Spectrum No: 16, ^{13}C NMR of 196



Spectrum No: 17, ^{1}H NMR of 202



Spectrum No: 18, ^{13}C NMR of 202



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Synthesis of Pyrano[2,3-*c*]carbazoles, Pyrano[3,2-*b*]carbazoles and Furo[3,2-*b*]carbazole Derivatives via Iodocyclization

CHAPTER 2

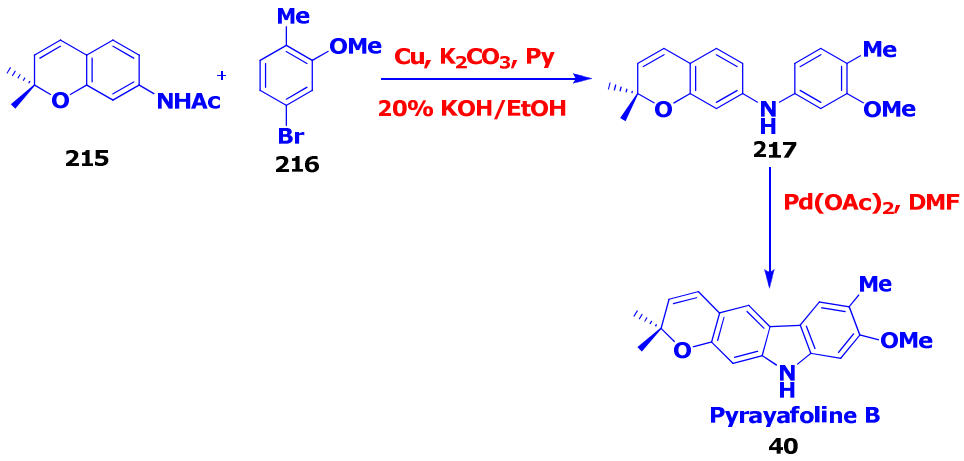
2.1. Introduction

Carbazole alkaloids have immensely attracted synthetic chemists due to their easily accessible structural features and promising biological applications.[118] Among these, pyranocarbazole alkaloids form a prominent group due to their wide isolation from various plant sources and also their intriguing structural features.[2] Pyrayafolines, eustifolines, clausamines, clausevatines *etc.* are some of the important pyranocarbazole alkaloids that have been synthesized in recent times.[119] Clausamines have been reported to inhibit EBV activation in Raji cells.[120] Diaryl pyranocarbazole derivatives were reported to show photochromic properties.[121]

Synthesis of benzopyran and quinoline derivatives from the corresponding propargyl derivatives has attracted synthetic chemists in recent times.[122-3] Larock *et al.* reported a simple methodology for the synthesis of benzopyrans through iodocyclization.[124] These reactions involve readily available reagents like iodine and simple bases which are inexpensive and eco-friendly. These reactions are also very efficient, clean and do not require harsh reaction conditions. Further, these products can be useful building blocks for the synthesis of fused heterocycles. In this context, an efficient methodology for the synthesis of these pyranocarbazole derivatives is desirable.

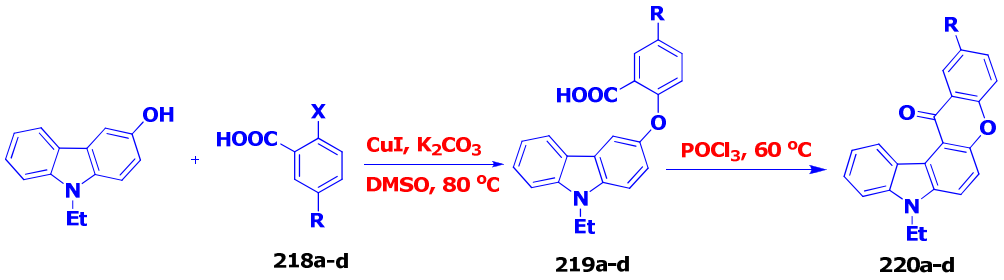
Coupling of 7-acetylamino-2,2-dimethylchromene **215**[125] with 5-bromo-2-methylanisole **216** and hydrolysis to the diarylamine **217** followed by oxidative cyclization with palladium(II) acetate in DMF provided *O*-methylpyrayafoline B **40** (Eq. 35) as reported by Ito and Furokawa.[126]

Eq. 35



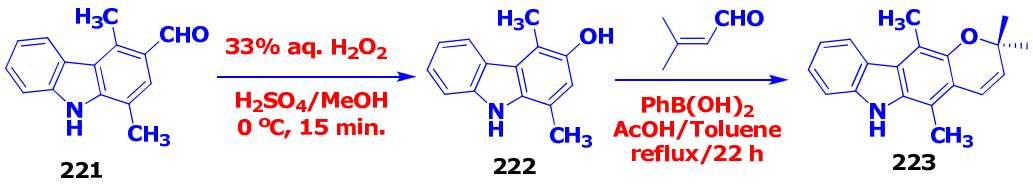
Our group has reported the synthesis of chromenocarbazoles. 3-Hydroxy-9-ethylcarbazole **158** was condensed with *o*-halobenzoic acids **218a-d** to provide the corresponding products **219a–d** in good yield. The condensed products **219a–d** underwent the cyclization to the corresponding chromenocarbazoles **220a-d** in good yields on treatment with excess of $POCl_3$ (Eq. 36). In this case, only one regioisomer was formed at 60 °C.[127]

Eq. 36



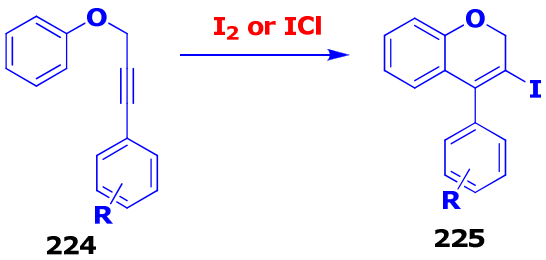
Dufat and co-workers reported construction of the fused dimethylpyran ring was ensured by condensation of **222** with 3-methylbut-2-enal (senecioaldehyde) in the presence of phenylboronic acid as Lewis acid catalyst which gave the target compound **223** (Eq. 37). The same reaction sequence, applied to 6-methoxy-1,4-dimethyl-9*H*-carbazole-3-carbaldehyde furnished successively 6-methoxy-1,4-dimethyl-9*H*-carbazol-3-ol and 9-methoxy-2,2,5,11-tetramethyl-2,6-dihydropyrano [3,2-*b*]carbazole.[128]

Eq. 37



Larock *et al*. reported a novel iodocyclization strategy for the synthesis of benzopyrans (Eq. 38). Cyclizations were carried out using our optimized conditions for I_2 or ICl. 3,4-Disubstituted 2*H*-benzopyrans **225** were obtained in good yields using when the substituent on the propargylic alkyne was either a simple phenyl or an alkenyl group. The introduction of substituents on the aryl groups has a considerable effect on the yield of the reaction. Substituents were first introduced onto the aromatic ring attached to the alkyne. Electron-donating groups, like Me and OMe in the *para* or *ortho* positions, gave good yields, while an electron-withdrawing group, like a NO_2 group, gave relatively poor yields of 59% with I_2 and 53% with ICl. Electron donating groups, like Me, *t*-Bu, and OMe, on the phenyl ring *para* to the oxygen gave better yields with I_2 as the electrophile.[129]

Eq. 38



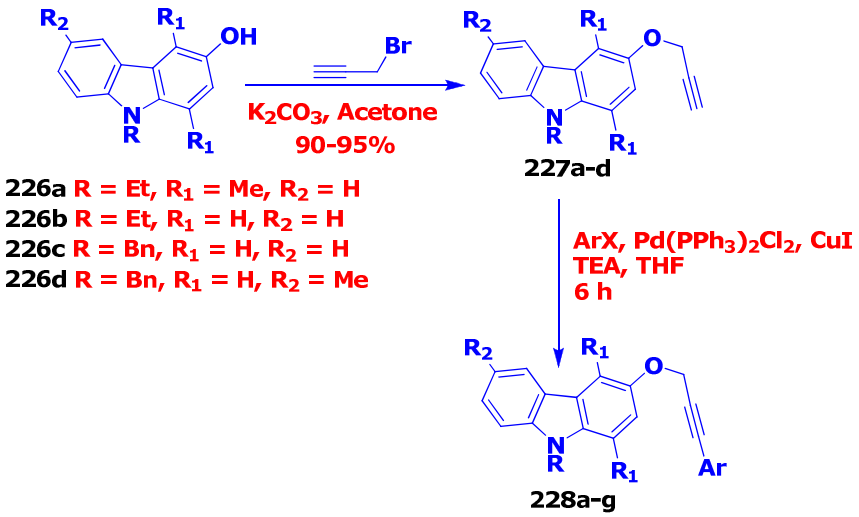
2.2. Synthesis of pyranocarbazole derivatives

In continuation of our efforts in the synthesis of various heteroarylcarbazole derivatives from easily accessible precursors,[130] we report here, a simple and facile synthesis of new pyranocarbazole derivatives employing iodocyclization.

The synthesis of aryl-*O*-propargylated precursors is demonstrated in Scheme 8. 3-Hydroxycarbazoles (**226a**-**d**) were synthesized employing methods reported in

literature.[131] These 3-hydroxycarbazoles were *O*-alkylated using propargyl bromide, K_2CO_3 in THF. The *O*-propargyl derivatives (**227a**-**d**) were subjected to Sonogashira coupling with various aryl iodides employing $Pd(PPh_3)_2Cl_2$, CuI and triethylamine as base in THF (Scheme 8). The various Sonogashira products (**228a**-**g**) and their yields are summarized in Table 9. All the products were obtained in good yields.

Scheme 8. Synthesis of *O*-propargylcarbazoles



Then we carried out the cyclization reaction of phenyl-*O*-propargyl derivative **228a** in various solvents like THF, dioxane, DMF *etc* and we found the condition using nitromethane as solvent, 2.5 eq. iodine and 2 eq. sodium bicarbonate was giving better yields. Employing these optimized conditions, we successfully synthesized various pyranocarbazole derivatives in good yields. Products are summarized in Table 10. Substituent effect is observed in the reaction. Electron withdrawing substituents on the aryl group increased the yields. Electron donating substituents resulted in a complex mixture of products. Various carbazoles were employed, the 1,4-dimethyl derivative **228g** provided linear product, which are of particular interest in biological applications.

Table 9. Aryl-*O*-propargylated Carbazoles derivatives

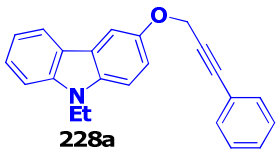
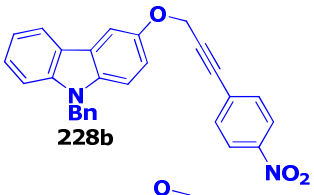
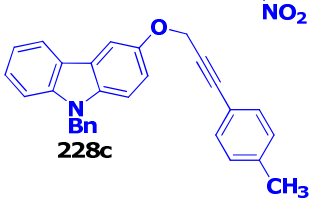
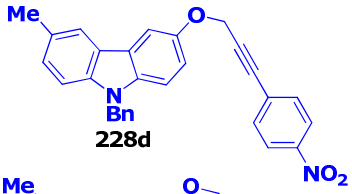
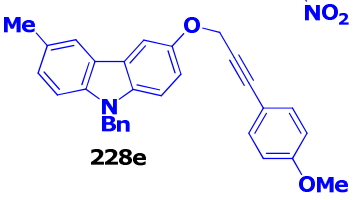
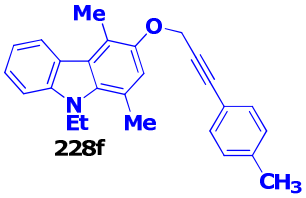
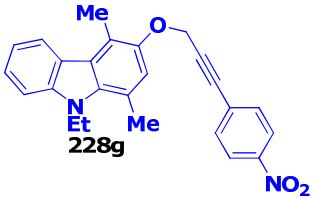
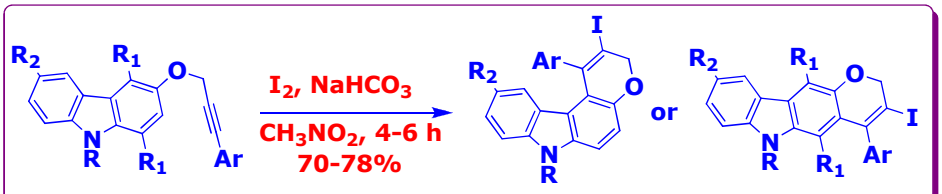
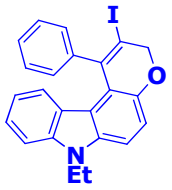
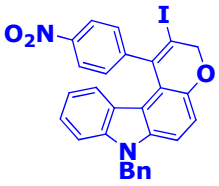
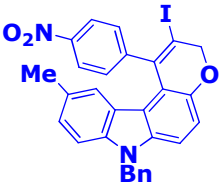
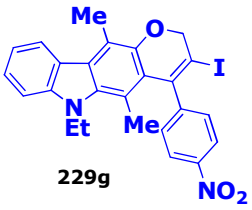
Entry	Reactant	HydroxyCarb.	Coupled Product	Time (h)	Yield (%)
1	C_6H_5	227b	 228a	8	85
2	4-O_2N-C_6H_4	227c	 228b	8	82
3	4-Me-C_6H_4	227c	 228c	8	81
4	4-O_2N-C_6H_4	227d	 228d	6	85
5	4-MeO-C_6H_4	227d	 228e	6	86
6	4-Me-C_6H_4	227a	 228f	6	84
7	4-O_2N-C_6H_4	227a	 228g	8	78

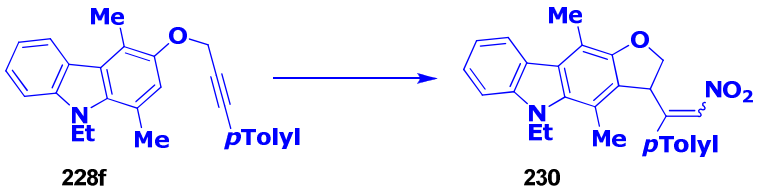
Table 10. Pyranocarbazole derivatives



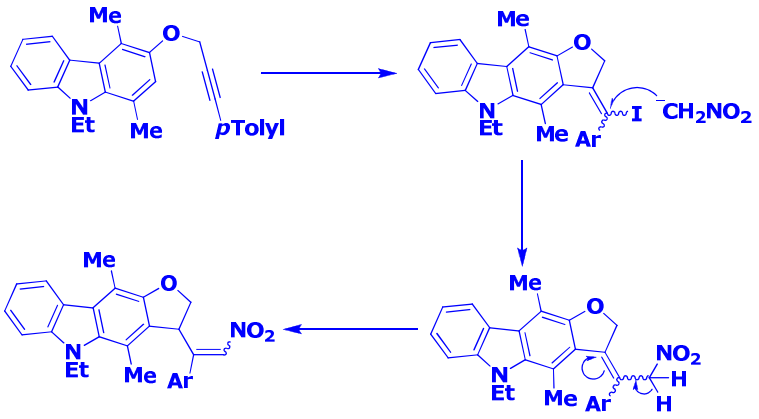
Entry	Reactant	Cyclized product	Time (h)	Yield (%)
1	228a	 229a	4	70
2	228b	 229b	6	72
3	228c	 229c	6	74
4	228g	 229g	4	78

To our surprise, when we carried out the reaction with 9-ethyl-1,4-dimethyl-3-(3-(4-*p*-tolyl-prop-2-ynyloxy)-9*H*-carbazole **228f,** we obtained a completely different product **230** (Scheme 9). A furocarbazole derivative formation was observed. Formation of a five membered ring followed by the replacement of iodine by nitromethyl anion resulted in the furocarbazole derivative. The proposed mechanism for this observation is shown in Scheme 10.

Scheme 9. Furocarbazole derivative formation

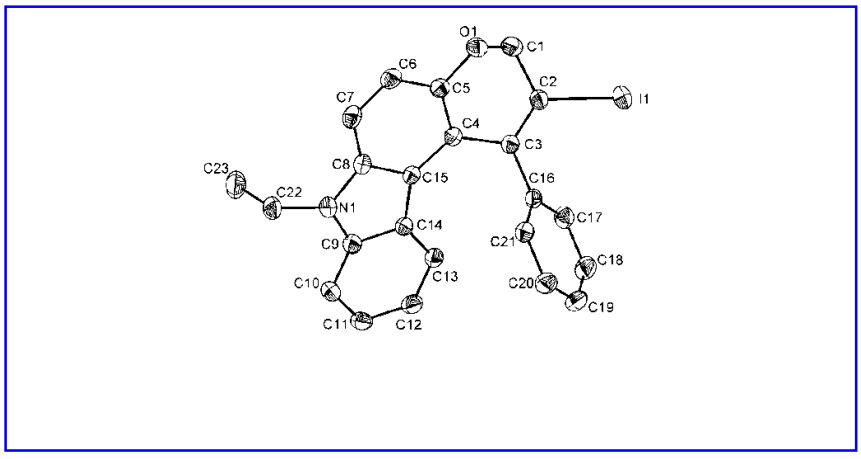


Scheme 10. Plausible mechanism for the synthesis of 230

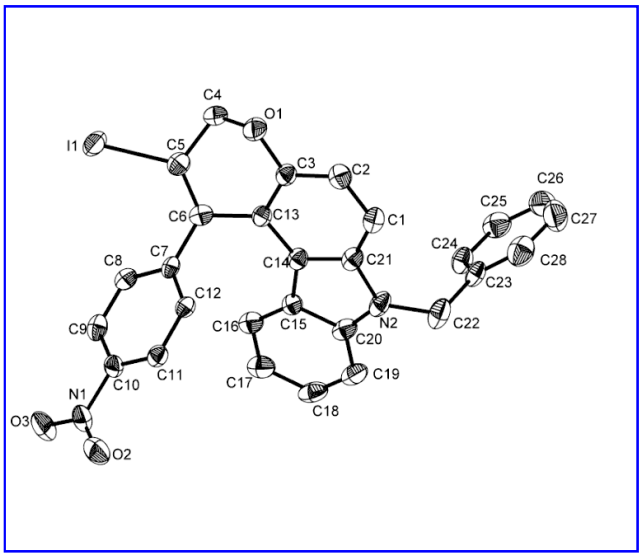


The compounds **229a** and **229b** were also characterized by X-ray crystallographic analysis. The ORTEP diagrams are shown in Figure 10.

Figure 10. ORTEP diagrams of 229a and 229b. Hydrogen atoms are omitted for clarity



229a



229b

2.3. Conclusion

In conclusion, we reported a simple and facile synthesis of new pyranocarbazole derivatives from easily accessible *O*-propargylated carbazoles employing iodocyclization in good yields. An interesting product with nitromethyl group insertion is observed.

2.4. Experimental Section

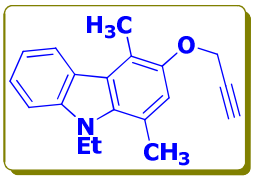
General procedure D

A oven dried 10 mL round bottom flask equipped with a Teflon coated magnetic stirring bar was charged with hydroxycarbazole (5 mmol), K_2CO_3 (15 mmol) in 15 mL of acetone under stirring. After stirring for 30 minutes, propargyl bromide (6 mmol) was added slowly and reaction mass was stirred at room temperature for 6 h. Reaction mass is poured into water, neutralized with 0.1 M HCl, extracted with ethyl acetate, washed twice with water (50 mL x 2), dried over anhyd. sodium sulphate and solvent was removed under vacuum to furnish the corresponding *O*-propargylated carbazole as a low melting solid.

9-Ethyl-1,4-dimethyl-3-(prop-2-ynyloxy)-9*H*-carbazole (227a):

227a was synthesized from hydroxycarbazole **226a** and propargyl bromide according to general procedure D. The product was obtained as a low melting solid.

Yield: 95%



Mp: 72-74 °C

IR (KBr) ν_{max} cm^{-1}: 3273, 2968, 2920, 2870, 2125, 1581, 1512, 1464, 1371, 1302, 1261, 1197, 1140, 1070, 1026, 792, 744, 540, 432

^{1}H NMR (400 MHz) δ: 8.24 (d, *J* = 8.0 Hz, 1H), 7.46-7.40 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 4.72 (s, 2H), 4.58 (q, *J* = 6.8 Hz, 2H), 2.81 (s, 6H), 2.51 (s, 1H), 1.41 (t, *J* = 6.8 Hz, 3H)

^{13}C NMR (100 MHz) δ: 148.7, 141.5, 125.1, 124.1, 123.3, 122.9, 120.8, 120.4, 118.6, 118.4, 117.4, 108.4, 79.7, 74.9, 59.5, 39.3, 20.0, 15.4, 12.9

LC–MS (m/z): 277 (M+H)

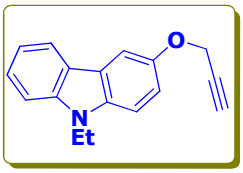
Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05 %

Found: C, 82.11; H, 6.85; N, 5.12 %

9-Ethyl-3-(prop-2-ynyloxy)-9*H*-carbazole (227b):

227b was synthesized from hydroxycarbazole **226b** and propargyl bromide according to general procedure D. The product was obtained as a low melting solid.

Yield: 92%



Mp: 66-68 °C

IR (KBr) ν_{max} cm^{-1}: 3287, 3051, 2976, 2932, 2121, 1622, 1579, 1485, 1323, 1292, 1230, 1180, 1086, 1060, 1024, 923, 856, 802, 746

^{1}H NMR (400 MHz) *δ*: 8.15 (d, *J* = 7.6 Hz, 1H), 7.78 (s, 1H), 7.52 (t, *J* = 6.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.27 - 7.24 (m, 2H), 4.86 (s, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 2.61 (s, 1H), 1.44 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) *δ*: 151.5, 140.6, 135.7, 125.8, 123.2, 122.7, 120.5, 118.5, 115.7, 109.2, 108.7, 105.8, 79.4, 75.4, 57.3, 37.6, 13.9

LC–MS (m/z): 250 (M+H)

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62 %

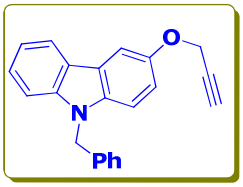
Found: C, 81.85; H, 6.12; N, 5.56 %

9-Benzyl-3-(prop-2-ynyloxy)-9*H*-carbazole (227c)

227c was synthesized from hydroxycarbazole **226c** and propargyl bromide according to general procedure D. The product was obtained as a low melting solid.

Yield: 95%

Mp: 102-104 °C



IR (KBr) ν_{max} cm^{-1}: 3283, 3065, 3024, 2912, 2852, 2127, 1626, 1597, 1489, 1448, 1381, 1354, 1325, 1188, 1057, 966, 933, 893, 848, 802

^{1}H NMR (400 MHz) *δ*: 8.10 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.26 - 7.22 (m, 5H), 7.15 - 7.13 (m, 3H), 5.5 (s, 2H), 4.8 (s, 2H), 2.55 (d, *J* = 2.0 Hz, 1H)

^{13}C NMR (100 MHz) *δ*: 151.7, 141.3, 137.2, 136.3, 128.8, 127.5, 126.4, 126.0, 123.3, 122.8, 120.4, 118.9, 115.8, 109.6, 109.0, 105.6, 79.2, 75.3, 57.2, 46.7

LC–MS (m/z): 312 (M+H)

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50 %

Found: C, 84.95; H, 5.56; N, 4.39 %

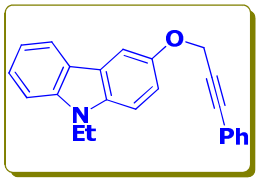
General procedure E

A oven dried 50 mL Schlenk tube equipped with a teflon coated magnetic stirring bar was charged with *O*-propargylated carbazole (2 mmol), 1 g of molecular sieves and aryl iodide (2.2 mmol). The tube was evacuated and filled with nitrogen. To it, 10 mL of dry THF and 5 mL of freshly distilled triethylamine were added under nitrogen and the reaction is stirred for 10 minutes at room temperature. $Pd(PPh_3)_2Cl_2$ (2 mol%) and CuI (1 mol%) were added under nitrogen and the the reaction mixture was stirred at room temperature for 4 h, after which time TLC (95:05 hexanes:ethyl acetate) indicated complete conversion. Reaction mass was filtered through celite. The filterate was poured into crushed ice slowly and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude material was purified by column chromatography (eluent: 5-15% ethyl acetate in hexanes).

9-Ethyl-3-(3-phenylprop-2-ynyloxy)-9*H*-carbazole (228a):

228a was synthesized from hydroxycarbazole **227b** and iodobenzene according to general procedure E. The product was obtained as a pure white solid after column chromatography with 5% ethyl acetate in hexanes.

Yield: 85%



Mp: 120-122 °C

IR (KBr) ν_{max} cm^{-1}: 3043, 2974, 2854, 1626, 1595, 1483, 1471, 1444, 1371, 1321, 1288, 1230, 1190, 1151, 1008, 844, 800, 748, 690, 420

^{1}H NMR (400 MHz) δ: 8.11 (d, *J* = 7.6 Hz, 1H), 7.80 (s, 1H), 7.50 (m, 3H), 7.42 - 7.22 (m, 7H), 5.05 (s, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) *δ*: 151.8, 140.6, 135.6, 131.9, 128.3, 125.7, 123.3, 122.8, 122.6, 120.5, 119.1, 118.5, 115.8, 109.1, 108.6, 105.9, 87.1, 84.7, 58.2, 37.6, 13.9

LC–MS (m/z): 326 (M+H)

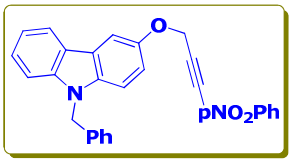
Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30 %

Found: C, 84.66; H, 5.81; N, 4.28 %

9-Benzyl-3-(3-(4-nitrophenyl)prop-2-ynyloxy)-9*H*-carbazole (228b):

228b was synthesized from hydroxycarbazole **227c** and 4-iodonitrobenzene according to general procedure E. The product was obtained as a light yellow solid after column chromatography with 5% ethyl acetate in hexanes.

Yield: 81%



Mp: 154-156 °C

IR (KBr) ν_{max} cm^{-1}: 3088, 3024, 2924, 2856, 1626, 1591, 1487, 1467, 1448, 1379, 1344, 1286, 1238, 1215, 1184, 1059, 895, 817, 723, 607, 424

^{1}H NMR (400 MHz) *δ*: 8.17 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 2 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.45 (t, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.30 - 7.26 (m, 5H), 7.22 - 7.16 (m, 3H), 5.50 (s, 2H), 5.07 (s, 2H)

^{13}C NMR (100 MHz) *δ*: 151.8, 147.3, 141.3, 137.2, 136.4, 132.5, 129.2, 128.8, 127.5, 126.4, 126.1, 123.5, 123.4, 122.7, 120.4, 119.0, 115.8, 109.7, 109.1, 105.8, 90.0, 85.2, 57.9, 46.7

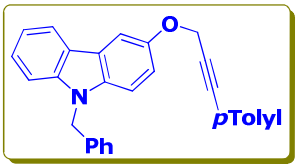
LC–MS (m/z): 433 (M+H)

Anal. Calcd. for $C_{28}H_{20}N_2O_3$: C, 77.76; H, 4.66; N, 6.48 %

Found: C, 77.62; H, 4.61; N, 6.56 %

9-Benzyl-3-(3-p-tolylprop-2-ynyloxy)-9*H*-carbazole (228c):

228c was synthesized from hydroxycarbazole **227c** and 4-iodotoluene according to general procedure E. The product was obtained as a pure white solid after column chromatography with 5% ethyl acetate in hexanes.



Yield: 82%

Mp: 140-142 °C

IR (KBr) ν_{max} cm^{-1}: 3028, 2916, 2229, 1604, 1510, 1493, 1475, 1356, 1323, 1246, 1222, 1174, 1055, 1026, 909

^{1}H NMR (400 MHz) *δ*: 8.15 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.42 - 7.37 (m, 3H), 7.31 - 7.26 (m, 5H), 7.23 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.18 - 7.14 (m, 4H), 5.50 (s, 2H), 5.05 (s, 2H), 2.38 (s, 3H)

^{13}C NMR (100 MHz) *δ*: 152.1, 141.3, 138.8, 137.3, 136.3, 131.8, 129.1, 128.8, 127.5, 126.4, 126.0, 123.4, 122.9, 120.5, 119.5, 118.9, 116.0, 109.6, 109.0, 105.8, 87.3, 83.9, 58.2, 46.7, 21.5

LC–MS (m/z): 402 (M+H)

Anal. Calcd. for $C_{29}H_{23}NO$: C, 86.75; H, 5.77; N, 3.49 %

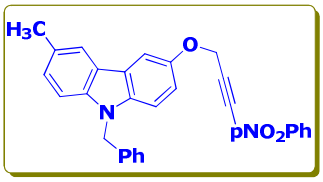
Found: C, 86.67; H, 5.72; N, 3.41 %

9-Benzyl-3-methyl-6-(3-(4-nitrophenyl)prop-2-ynyloxy)-9*H*-carbazole (228d):

228d was synthesized from hydroxycarbazole **227d** and 4-iodonitrobenzene according to general procedure E. The product was obtained as a pale yellow solid after column chromatography with 5% ethyl acetate in hexanes.

Yield: 84%

Mp: 170-172 °C



IR (KBr) ν_{max} cm^{-1}: 2922, 2858, 1732, 1593, 1493, 1452, 1340, 1199, 1026, 850, 796

^{1}H NMR (400 MHz) *δ*: 8.16 (d, *J* = 8.8 Hz, 2H), 7.90 (s, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.28 - 7.26 (m, 6H), 7.17 - 7.12 (m, 3H), 5.46 (s, 2H), 5.04 (s, 2H), 2.5 (s, 3H)

^{13}C NMR (100 MHz) *δ*: 151.5, 147.3, 139.6, 137.3, 136.6, 132.6, 129.3, 128.8, 128.3, 127.5, 127.5, 126.4, 123.5, 123.2, 122.8, 120.3, 115.6, 109.6, 108.8, 105.7, 90.1, 85.1, 57.9, 46.7, 21.4

LC–MS (m/z): 447 (M+H)

Anal. Calcd. for $C_{29}H_{22}N_2O_3$: C, 78.01; H, 4.97; N, 6.27 %

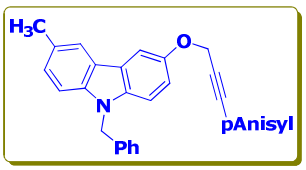
Found: C, 78.21; H, 5.06; N, 6.35 %

9-Benzyl-3-(3-(4-methoxyphenyl)prop-2-ynyloxy)-6-methyl-9*H*-carbazole (228e):

228e was synthesized from hydroxycarbazole **227d** and 4-iodoanisole according to general procedure E. The product was obtained as a pure white solid after column chromatography with 5% ethyl acetate in hexanes.

Yield: 85%

Mp: 134-136 °C



IR (KBr) ν_{max} cm^{-1}: 3020, 2916, 2228, 1600, 1510, 1475, 1355, 1322, 1240, 1222, 1174, 1050, 1026, 908

^{1}H NMR (400 MHz) δ: 7.92 (s, 1H), 7.77 (s, 1H), 7.43 (d, 2H), 7.24-7.42 (m, 4H), 7.19 - 7.13 (m, 3H), 6.85 (d, *J* = 6.8 Hz, 2H), 5.48 (s, 2H), 5.03 (s, 2H), 3.82 (s, 3H), 2.56 (s, 3H)

^{13}C NMR (100 MHz) δ: 159.8, 151.9, 139.6, 137.4, 136.5, 133.4, 128.7, 128.1, 127.4, 126.4, 123.1, 123.0, 120.3, 115.8, 114.6, 113.9, 109.5, 108.7, 105.7, 87.0, 83.2, 58.2, 55.3, 46.7, 21.4

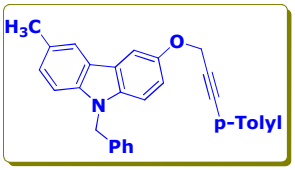
LC–MS (m/z): 418 (M+H)

Anal. Calcd. for $C_{29}H_{23}NO_2$: C, 83.43; H, 5.55; N, 3.35 %

Found: C, 83.28; H, 5.51; N, 3.41 %

9-Benzyl-3-methyl-6-(3-*p*-tolylprop-2-ynyloxy)-9*H*-carbazole (228f):

228f was synthesized from hydroxycarbazole **227d** and 4-iodotoluene according to general procedure E. The product was obtained as a pure white solid after column chromatography with 5% ethyl acetate in hexanes.



Yield: 86%

Mp: 128-130 °C

IR (KBr) ν_{max} cm^{-1}: 3026, 2915, 2227, 1601, 1491, 1475, 1356, 1243, 1226, 1171, 1055, 1021, 911

^{1}H NMR (400 MHz) δ: 7.93 (s, 1H), 7.78 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.28 - 7.13 (m, 11H), 5.48 (s, 2H), 5.03 (s, 2H), 2.57 (s, 3H), 2.37 (s, 3H)

^{13}C NMR (100 MHz) δ: 151.9, 139.6, 138.7, 137.4, 136.5, 131.8, 129.1, 128.8, 128.2, 127.4, 127.3, 126.4, 123.1, 123.0,

120.4, 119.4, 115.8, 109.5, 108.7, 105.7, 87.2, 83.9, 58.2, 46.7, 21.5, 21.4

LC–MS (m/z): 416 (M+H)

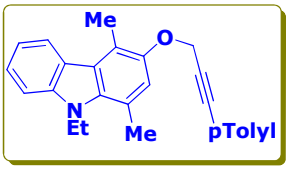
Anal. Calcd. for $C_{30}H_{25}NO$: C, 86.71; H, 6.06; N, 3.37 %

Found: C, 86.85; H, 6.12; N, 3.36 %

9-Ethyl-1,4-dimethyl-3-(3-*p*-tolyl prop-2-ynyloxy)-9*H*-carbazole (228g):

228g was synthesized from hydroxycarbazole **227a** and 4-iodotoluene according to general procedure E. The product was obtained as a pure white solid after column chromatography with 5% ethyl acetate in hexanes.

Yield: 78%



Mp: 148-150 °C

IR (KBr) ν_{max} cm^{-1}: 3020, 2925, 2230, 1600, 1475, 1355, 1240, 1225, 1170, 1056, 1021, 911

^{1}H NMR (400 MHz) δ: 8.36 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.41 - 7.39 (m, 2H), 7.30 - 7.25 (m, 1H), 7.16 - 7.12 (m, 2H), 4.90 (s, 2H), 4.60 (q, *J* = 7.0 Hz, 2H), 2.90 (s, 3H), 2.89 (s, 3H), 2.39 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 149.1, 141.5, 138.6, 137.3, 134.9, 131.7, 129.1, 125.1, 124.2, 122.9, 121.1, 119.1, 118.6, 117.4, 114.6, 108.4, 86.9, 84.6, 60.7, 39.3, 21.5, 20.2, 15.4, 13.0

LC–MS (m/z): 368 (M+H)

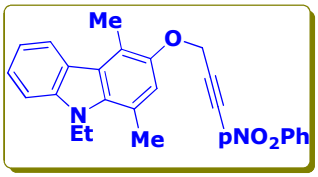
Anal. Calcd. for $C_{26}H_{25}NO$: C, 84.98; H, 6.86; N, 3.81 %

Found: C, 84.85; H, 6.72; N, 3.76 %

9-Ethyl-1,4-dimethyl-3-(3-(4-nitrophenyl)prop-2-ynyloxy)-9*H*-carbazole (228h):

228h was synthesized from hydroxycarbazole **227a** and 4-iodonitrobenzene according to general procedure E. The product was obtained as a yellow solid after column chromatography with 5% ethyl acetate in hexanes.

Yield: 85%



Mp: 166-168 °C

IR (KBr) ν_{max} cm^{-1}: 2918, 2854, 1743, 1610, 1554, 1508, 1332, 1261, 1205, 1182, 1091, 1016, 883, 869, 812, 752

^{1}H NMR (400 MHz) δ: 8.31 (d, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.38 (m, 1H), 7.06 (s, 1H), 5.08 (s, 2H), 4.61 (q, *J* = 7.2 Hz, 2H), 2.86 (s, 3H), 2.84 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 148.7, 141.4, 135.0, 132.5, 132.4, 129.5, 125.2, 123.5, 122.8, 121.0, 120.4, 118.8, 118.7, 117.5, 114.5, 108.5, 90.7, 84.9, 60.4, 39.3, 20.2, 15.5, 13.0

LC–MS (m/z): 399 (M+H)

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03 %

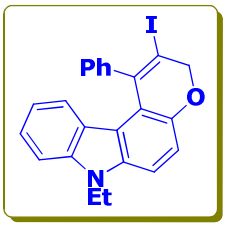
Found: C, 75.48; H, 5.51; N, 7.12 %

General procedure F

A oven dried 10 mL round bottom flask equipped with a teflon coated magnetic stirring bar was charged with aryl-*O*-propargyl carbazole (0.2 mmol), sodium bicarbonate (0.4 mmol) and iodine (0.6 mmol) in nitromethane (20 mL) and reaction mixture was stirred at room temperature for 4-6 h, after which time TLC (95:05 hexanes:ethyl acetate) indicated complete conversion. The reaction mixture was quenched with 5% solution of sodium thiosulphate, extracted with dichloromethane, dried over anhyd. sodium sulphate, adsorbed on silica and purified by column chromatography (5-10% ethyl acetate in hexanes).

7-Ethyl-2-iodo-1-phenyl-3,7-dihydropyrano[2,3-*c*]carbazole (229a)

229a was synthesized from aryl-*O*-propargylcarbazole **228a** according to general procedure F. The product was obtained as a fluffy yellow solid after column chromatography with 3% ethyl acetate in hexanes.



Yield: 70%

Mp: 146-148 °C

IR (KBr) ν_{max} cm^{-1}: 3051, 2912, 2858, 1592, 1513, 1454, 1425, 1194, 1090, 1005, 889, 733

^{1}H NMR (400 MHz) δ: 7.45 - 7.43 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.34 - 7.23 (m, 6H), 6.60 (m, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.08 (s, 2H), 4.36 (q, *J* = 7.6 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR (100 MHz) δ: 150.8, 141.1, 140.4, 140.1, 136.3, 130.8, 128.3, 128.0, 124.9, 124.1, 121.9, 119.1, 118.6, 117.8, 114.4, 110.2, 107.8, 86.7, 77.1, 37.4, 13.8

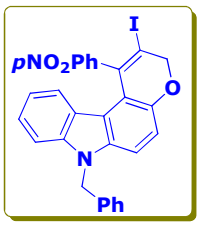
LC–MS (m/z): 452 (M), 454 (M+2)

Anal. Calcd. for $C_{23}H_{18}INO$: C, 61.21; H, 4.02; N, 3.10 %

Found: C, 61.25; H, 4.04; N, 3.06 %

7-Benzyl-2-iodo-1-(4-nitrophenyl)-3,7-dihydropyrano[2,3-*c*]carbazole (229b):

229b was synthesized from aryl-*O*-propargylcarbazole **228b** according to general procedure F. The product was obtained as a fluffy yellow solid after column chromatography with 7% ethyl acetate in hexanes.



Yield: 72%

Mp: 188-190 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2922, 2858, 1595, 1514, 1454, 1425, 1194, 1091, 1005, 889, 848, 733

^{1}H NMR (400 MHz) δ: 8.17 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.30 - 7.27 (m, 4H), 7.23 - 7.20 (m, 2H), 7.12 (d, *J* = 6.8 Hz, 2H), 6.66 - 6.63 (m, 2H), 5.52 (s, 2H), 5.10 (s, 2H)

^{13}C NMR (100 MHz) δ: 151.7, 147.1, 146.9, 141.1, 139.6, 136.9, 136.8, 131.6, 128.9, 127.6, 126.3, 125.6, 123.3, 123.1, 121.4, 118.5, 118.3, 118.0, 114.7, 111.5, 108.7, 88.8, 77.2, 46.5

LC–MS (m/z): 558 (M), 560 (M+2)

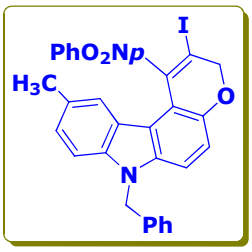
Anal. Calcd. for $C_{28}H_{19}IN_2O_3$: C, 60.23; H, 3.43; N, 5.02 %

Found: C, 60.45; H, 3.38; N, 5.12 %

7-Benzyl-2-iodo-10-methyl-1-(4-nitrophenyl)-3,7-dihydropyrano[2,3-*c*]carbazole (229c):

229c was synthesized from aryl-*O*-propargylcarbazole **228f** according to general procedure F. The product was obtained as a fluffy yellow solid after column chromatography with 7% ethyl acetate in hexanes.

Yield: 74%



Mp: 194-196 °C

IR (KBr) ν_{max} cm^{-1}: 3207, 3069, 3032, 2916, 2852, 1730, 1595, 1518, 1452, 1305, 1211, 1147, 1066, 1014, 848, 800, 721

^{1}H NMR (400 MHz) δ: 8.18 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.37 - 7.02 (m, 9H), 6.35 (s, 1H), 5.47 (s, 2H), 5.09 (s, 2H), 2.06 (s, 3H)

^{13}C NMR (100 MHz) δ: 151.0, 147.2, 147.1, 139.6, 139.4, 137.2, 137.0, 131.9, 128.9, 127.6, 127.6, 127.1, 126.3, 123.2, 123.1, 122.5, 121.5, 118.0, 114.6, 111.4, 108.3, 88.7, 76.0, 46.5, 20.8

LC–MS (m/z): 573 (M), 575 (M+2)

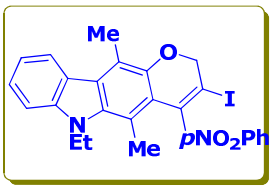
Anal. Calcd. for $C_{29}H_{21}IN_2O_3$: C, 60.85; H, 3.70; N, 4.89 %

Found: C, 60.75; H, 3.75; N, 4.76 %

6-Ethyl-3-iodo-5,11-dimethyl-4-(4-nitrophenyl)-2,6-dihydropyrano[3,2-*b*]carbazole (229h):

229d was synthesized from aryl-*O*-propargylcarbazole **228h** according to general procedure F. The product was obtained as a fluffy yellow solid after column chromatography with 8% ethyl acetate in hexanes.

Yield: 78%



Mp: 180-182 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 2961, 2914, 2843, 1595, 1510, 1454, 1346, 1176, 1078, 1006, 860, 736

^{1}H NMR (400 MHz) δ: 8.24-8.26 (m, 3H), 7.50 - 7.48 (m, 3H), 7.38 (m, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 4.99 (s, 2H), 4.35 (d, *J* = 6.4 Hz, 2H), 2.8 (s, 3H), 2.02 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR (100 MHz) δ: 150.0, 147.6, 146.8, 143.2, 141.5, 136.1, 130.8, 127.5, 126.1, 124.5, 124.5, 124.1, 123.4, 123.2, 119.3, 117.1, 114.8, 109.1, 91.2, 40.4, 19.8, 15.1, 12.9

LC–MS (m/z): 525 (M+H)

Anal. Calcd. for $C_{25}H_{21}IN_2O_3$: C, 57.26; H, 4.04; N, 5.34 %

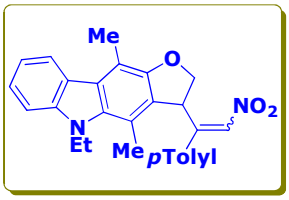
Found: C, 57.36; H, 4.08; N, 5.23 %

5-Ethyl-4,10-dimethyl-3-(2-nitro-1-*p*-tolylvinyl)-3,5-dihydro-2*H*-furo[3,2-*b*]carbazole (230):

230 was synthesized from aryl-*O*-propargylcarbazole **228g** according to general procedure F. The product was obtained as a fluffy yellow solid after column chromatography with 10% ethyl acetate in hexanes.

Yield: 70%

Mp: 140-142 °C



IR (KBr) ν_{max} cm^{-1}: 3210, 3059, 3032, 2852, 1731, 1595, 1519, 1451, 1305, 1213, 1146, 1068, 1014, 848, 721

^{1}H NMR (400 MHz) δ: 8.25 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.26 - 7.19 (m, 5H), 5.93 (d, *J* = 5.2 Hz, 1H), 5.50 (m, 1H), 4.84 (dd, *J* = 9.6 Hz, *J* = 9.6 Hz, 1H), 4.54 (dd, *J* = 3.6 Hz, *J* = 3.6 Hz, 1H), 4.46 (q, *J* = 7.6 Hz, 2H), 2.76 (s, 3H), 2.42 (s, 3H), 2.21 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) *δ*:	144.6, 142.9, 141.8, 138.7, 137.5, 136.6, 129.4, 126.9, 125.8, 124.2, 123.2, 122.3, 119.8, 119.1, 118.4, 115.9, 108.9, 76.7, 75.6, 70.8, 40.3, 21.2, 20.3, 15.0, 12.7
LC–MS (m/z):	427 (M+H)
Anal. Calcd. for $C_{27}H_{26}N_2O_3$:	C, 76.03; H, 6.14; N, 6.57 %
Found:	C, 76.31; H, 6.41; N, 6.53 %

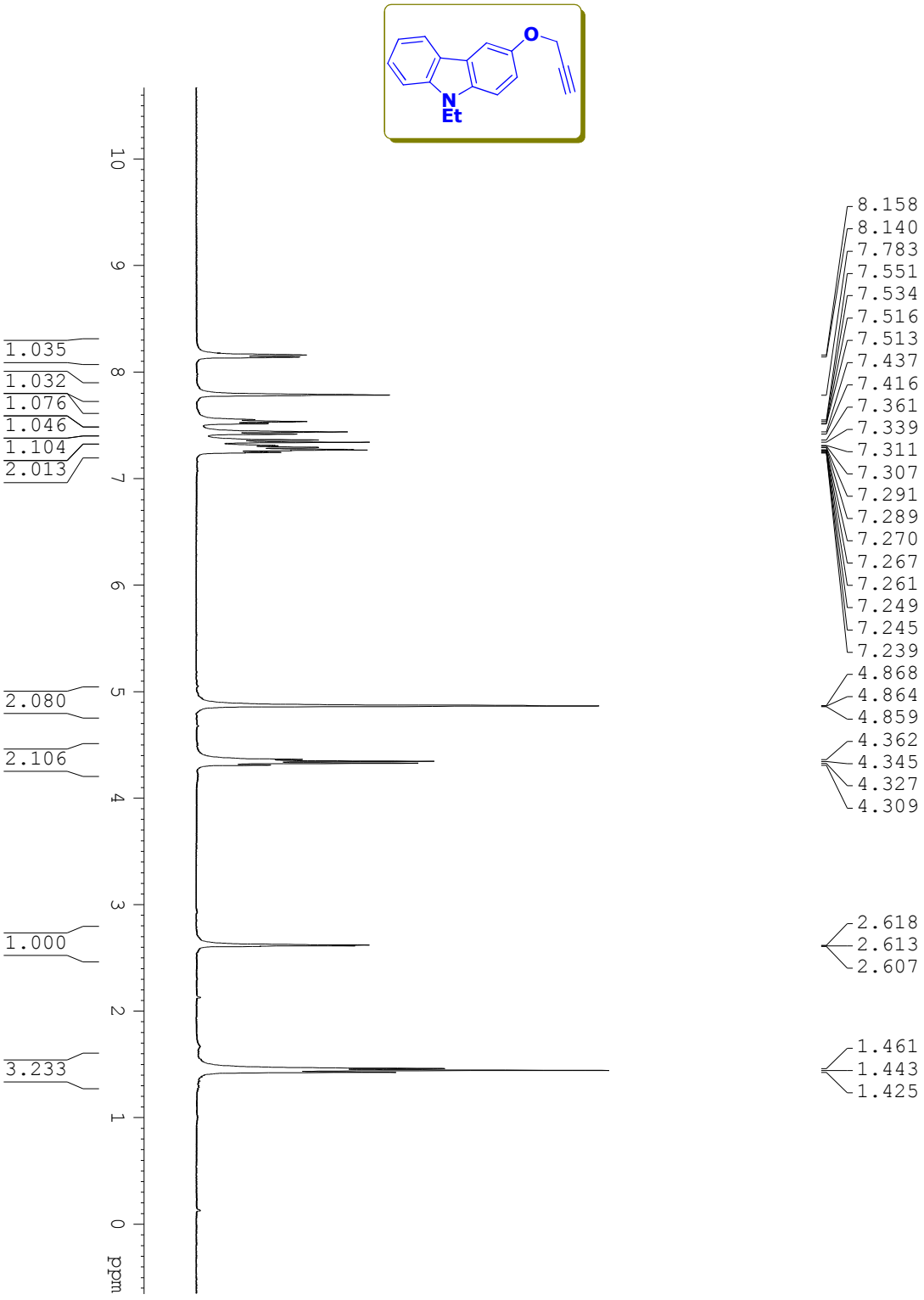
Table 11. Crystal data and structure refinement for 229a

Empirical formula	: $C_{23}H_{18}INO$	
Formula weight	: 451.28	
Temperature	: 298(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Monoclinic	
Space group	: P2(1)/c	
Unit cell dimensions	: a = 6.4622(14) Å	α= 90°.
	: b = 13.492(3) Å	β= 98.668(3)°.
	: c = 21.416(5) Å	γ = 90°.
Volume	: 1845.9(7) $Å^3$	
Z	: 4	
Density (calculated)	: 1.624 Mg/m^3	
Absorption coefficient	: 1.746 mm^{-1}	
F(000)	: 896	
Crystal size	: 0.24 x 0.18 x 0.12 mm^3	
Theta range for data collection	: 1.79 to 24.99°.	
Index ranges	: -7<=h<=7, -16<=k<=16, -25<=l<=25	
Reflections collected	: 17273	
Independent reflections	: 3245 [R(int) = 0.0244]	
Completeness to theta = 24.99°	: 100.0 %	
Absorption correction	: Empirical	
Max. and min. transmission	: 0.8178 and 0.6793	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 3245 / 0 / 236	
Goodness-of-fit on F^2	: 1.109	
Final R indices [I>2sigma(I)]	: R1 = 0.0257, wR2 = 0.0663	
R indices (all data)	: R1 = 0.0274, wR2 = 0.0674	
Largest diff. peak and hole	: 0.257 and -0.765 $e.Å^{-3}$	
CCDC number	: 818251	

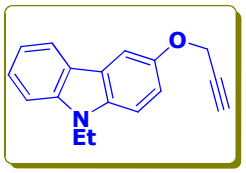
Table 12. Crystal data and structure refinement for 229b

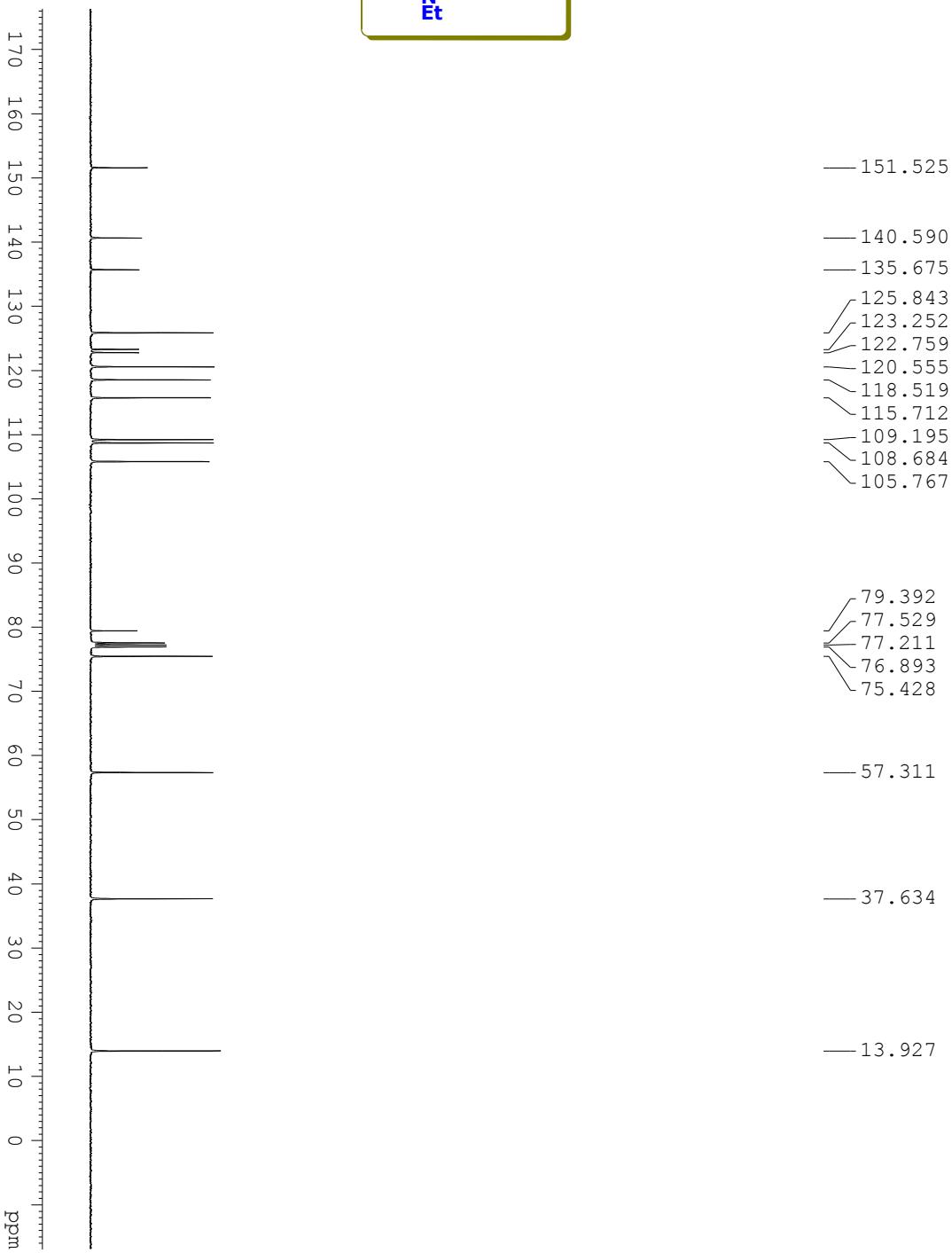
Empirical formula	: $C_{28}H_{19}IN_2O_3$	
Formula weight	: 539.20	
Temperature	: 293(2) K	
Wavelength	: 0.71073 Å	
Crystal system	: Orthorombic	
Space group	: Pna21	
Unit cell dimensions	: a = 17.9078(18) Å	α= 90°.
	: b = 12.4689(15) Å	β= 90°.
	: c = 20.656(2) Å	γ = 90°.
Volume	: 4612.2(9) $Å^3$	
Z	: 8	
Density (calculated)	: 1.553 Mg/m^3	
Absorption coefficient	: 1.420 mm^{-1}	
F(000)	: 2072	
Crystal size	: 0.20 x 0.18 x 0.10 mm^3	
Theta range for data collection	: 2.80 to 29.18°.	
Index ranges	:-22<=h<=22, -15<=k<=15, -25<=l<=27	
Reflections collected	: 24628	
Independent reflections	: 10382 [R(int) = 0.0389]	
Completeness to theta = 29.18°	: 88.5 %	
Refinement method	: Full-matrix least-squares on F^2	
Data / restraints / parameters	: 10382 / 1 / 613	
Goodness-of-fit on F^2	: 1.007	
Final R indices [I>2sigma(I)]	: R1 = 0.0494, wR2 = 0.0895	
R indices (all data)	: R1 = 0.0882, wR2 = 0.1033	
Absolute structure parameter	: 0.407(18)	
Largest diff. peak and hole	: 0.500 and -0.411 $e.Å^{-3}$	
CCDC number	: 818250	

Spectrum No: 19, ^{1}H NMR of 227b

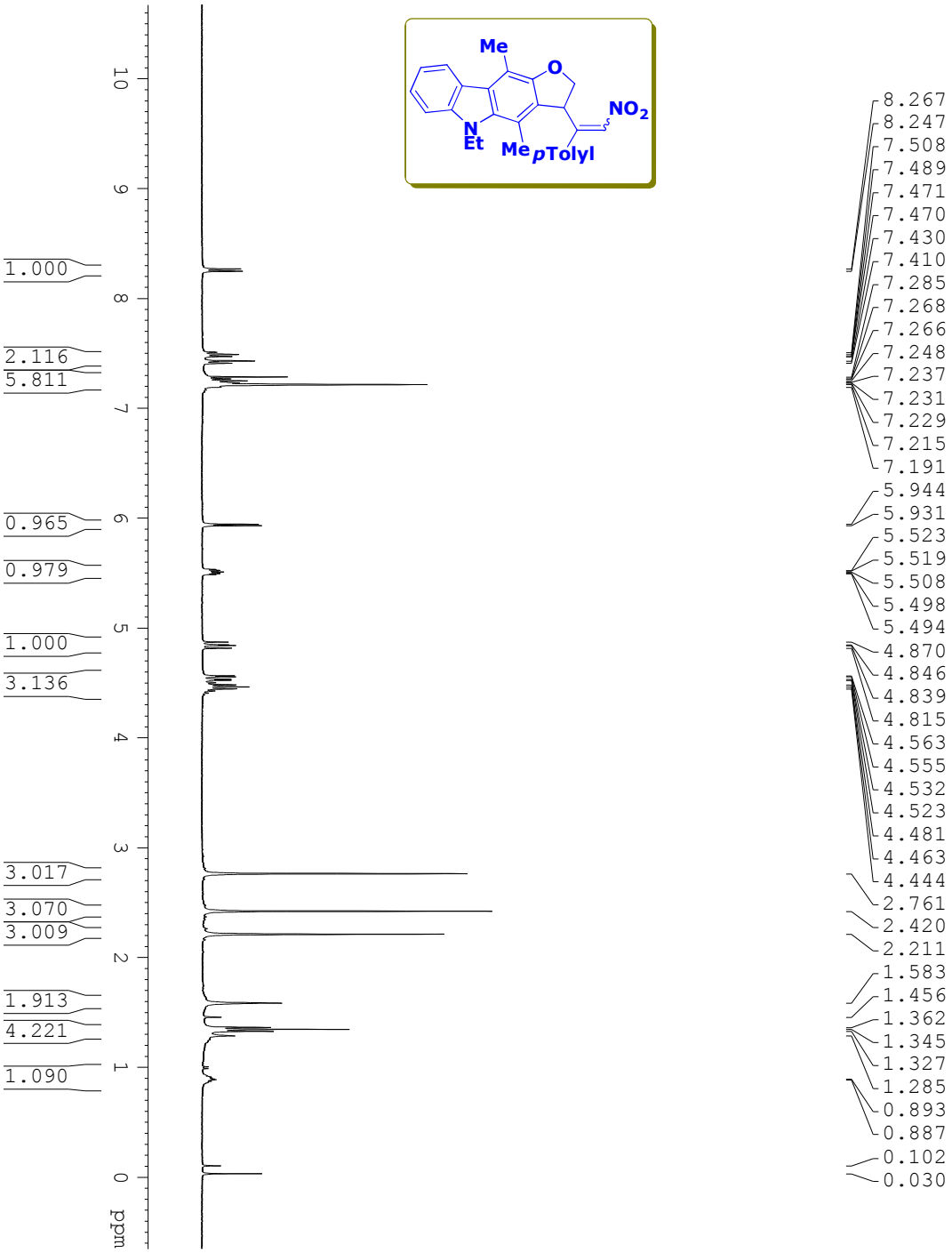


Spectrum No: 20, ^{13}C NMR of 227b

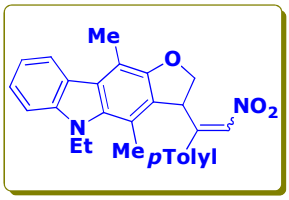




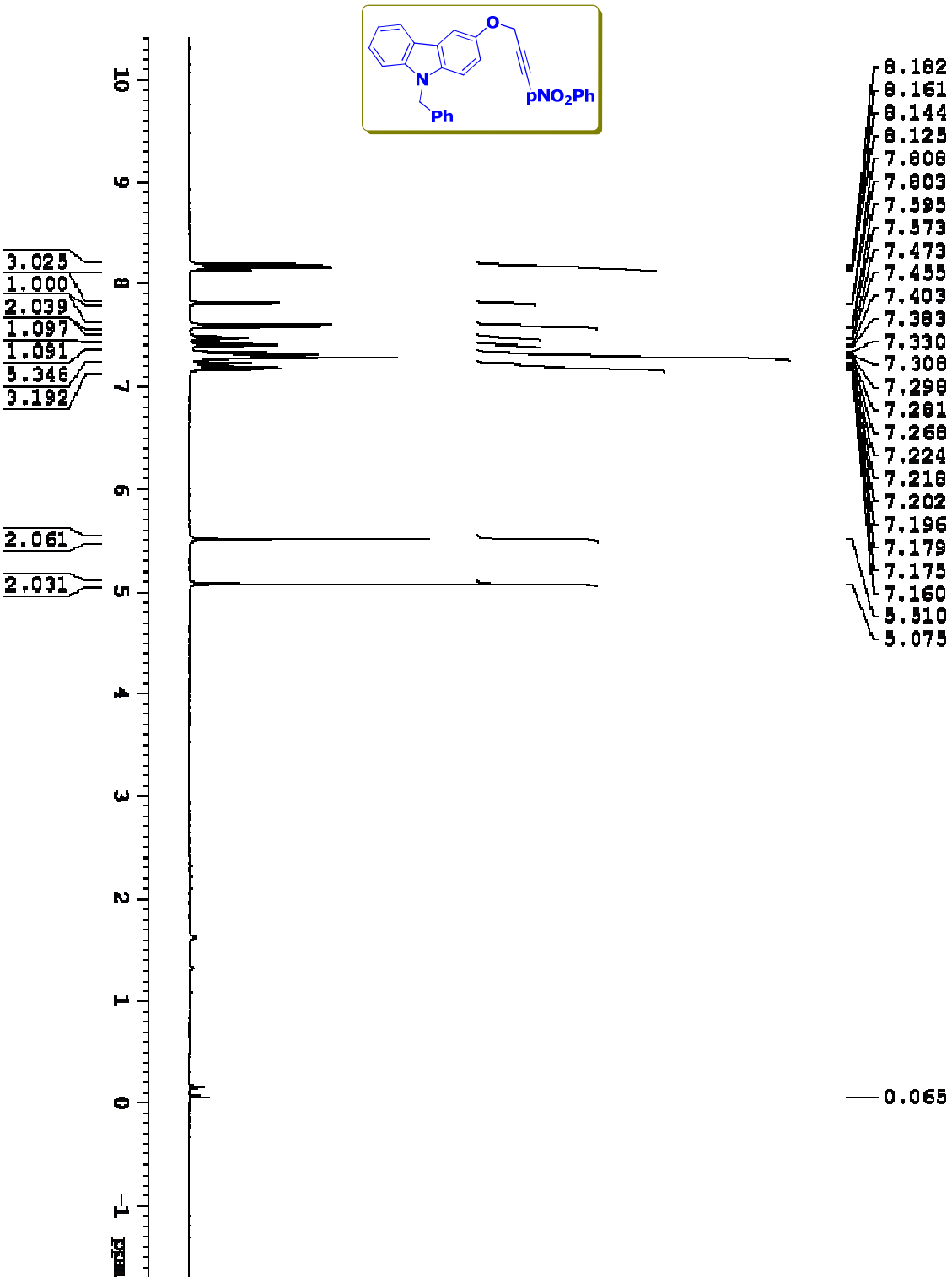
Spectrum No: 21, ^{1}H NMR of 230



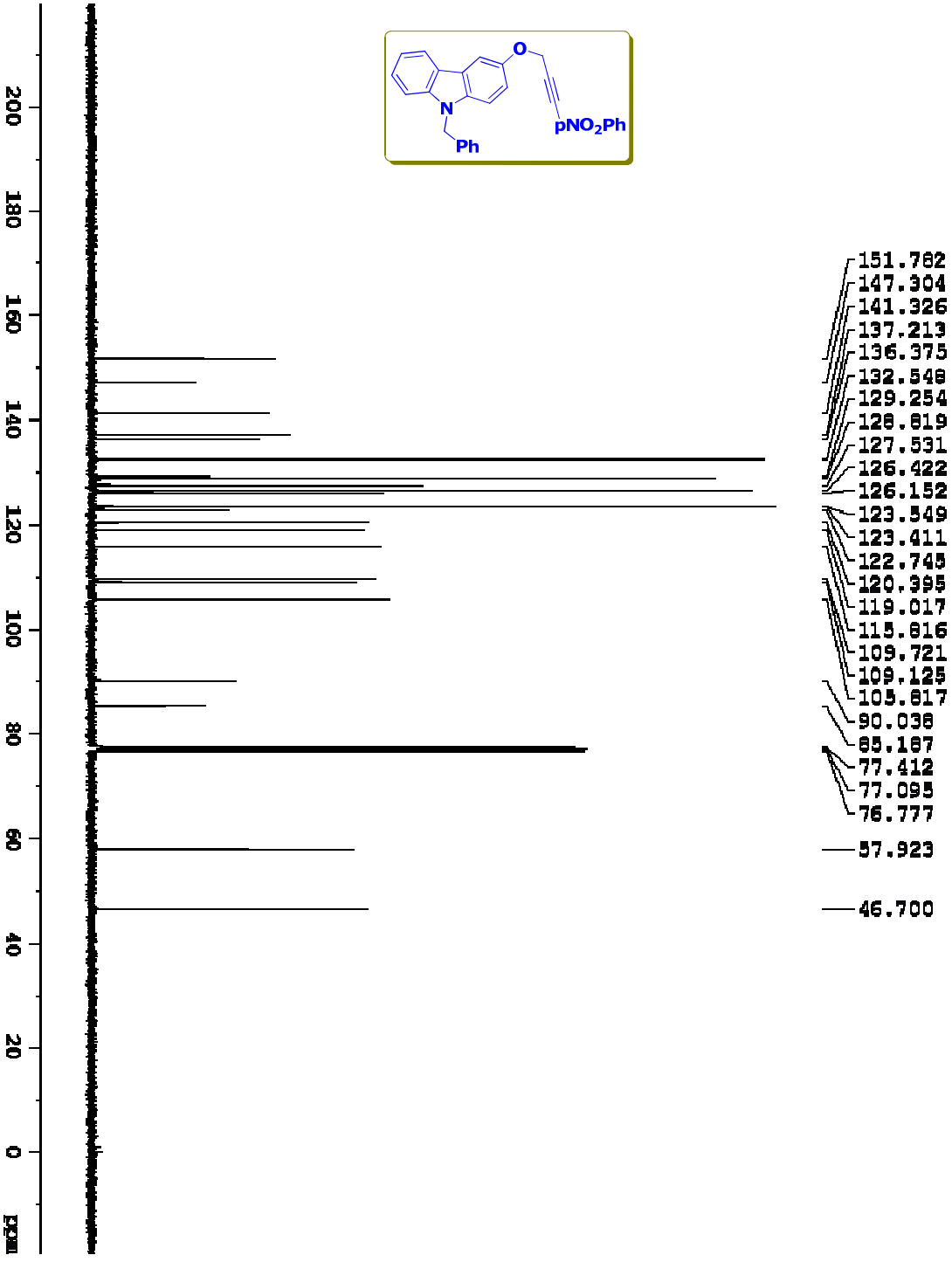
Spectrum No: 22, ^{13}C NMR of 230



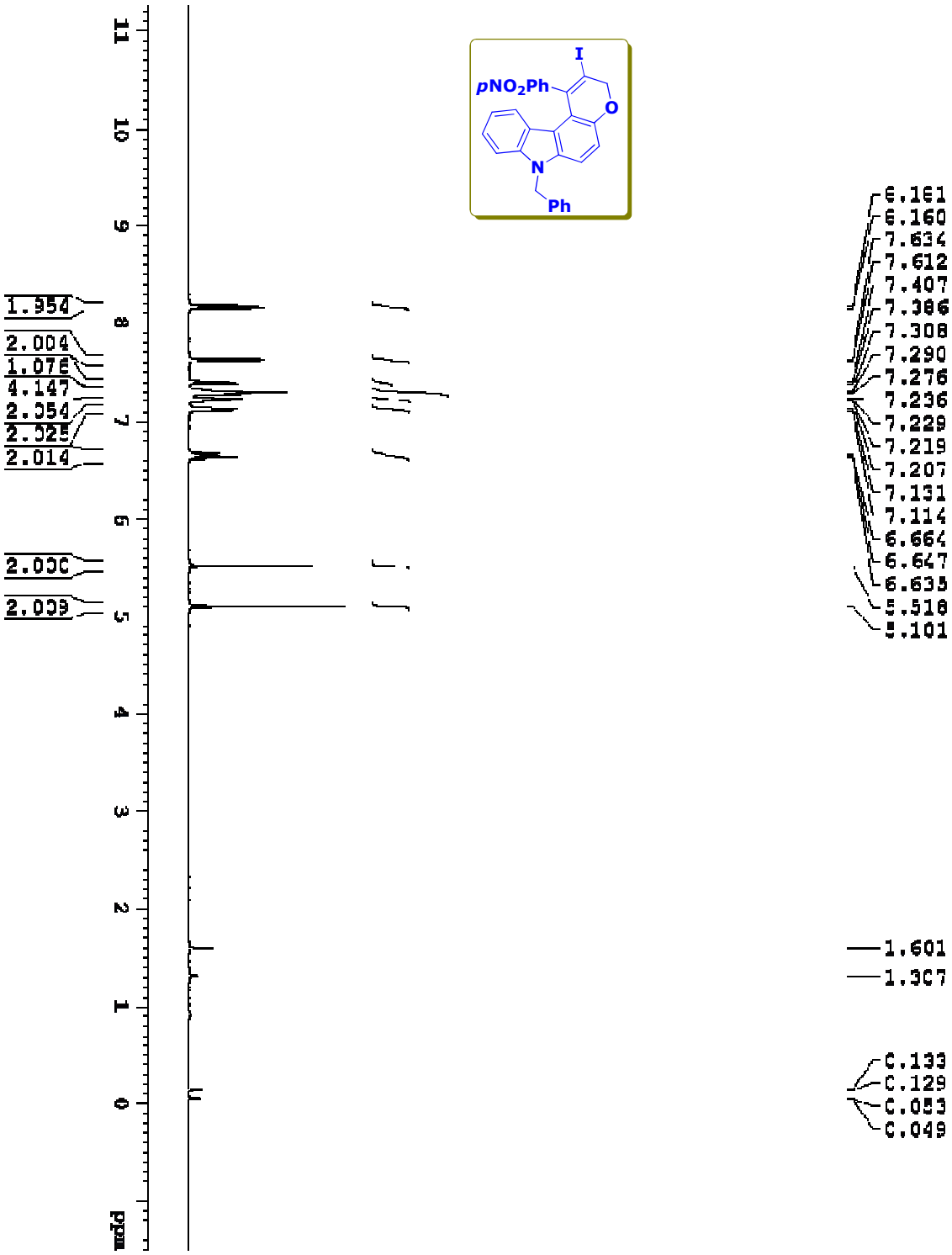
Spectrum No: 23, ^{1}H NMR of 228b



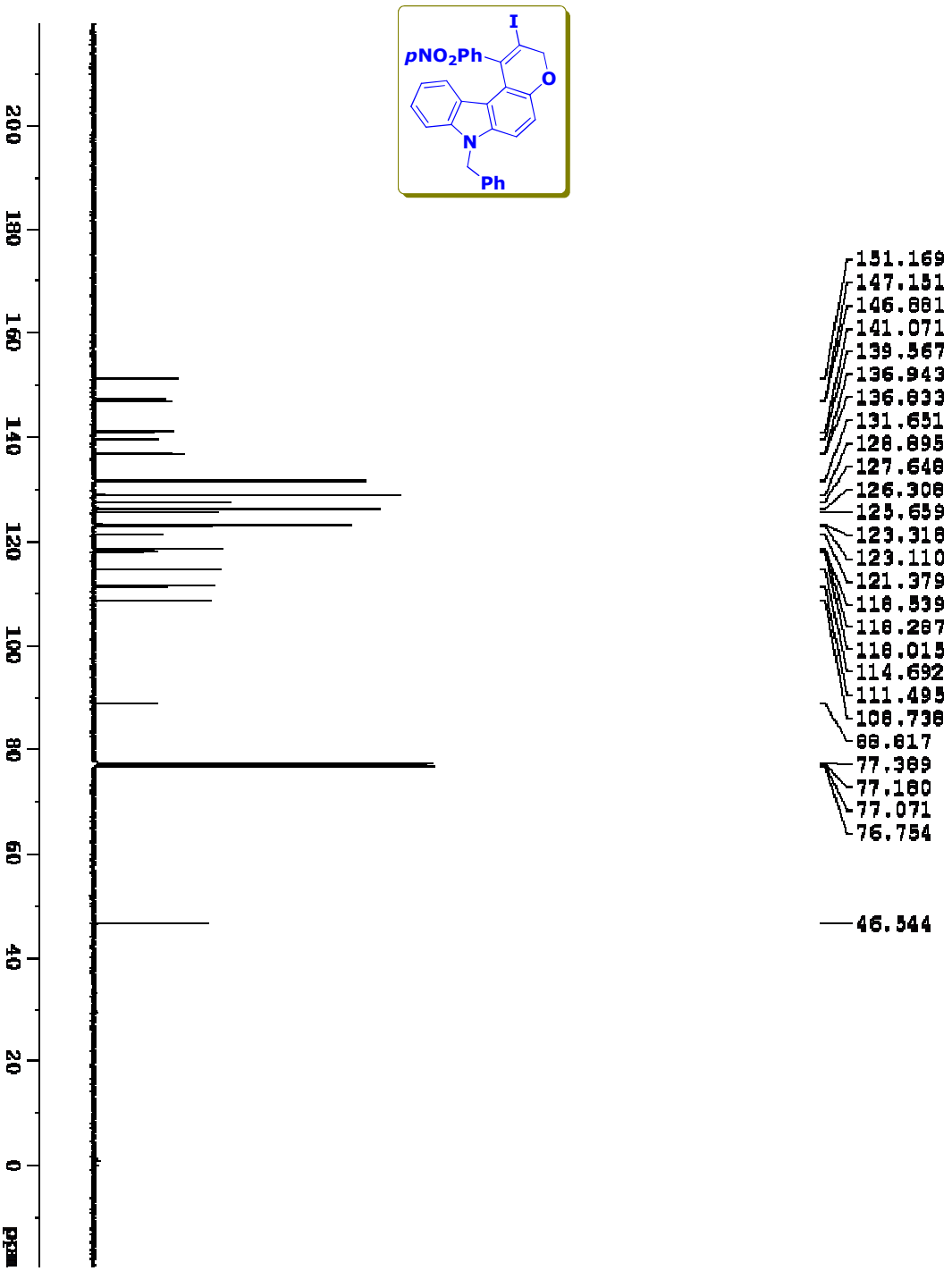
Spectrum No: 24, ^{13}C NMR of 228b



Spectrum No: 25, ^{1}H NMR of 229b



Spectrum No: 26, ^{13}C NMR of 229b



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Synthesis of 3-chromenylcarbazoles, 3,6-*bis*-(chromenyl)carbazoles and 3-quinolyl carbazoles

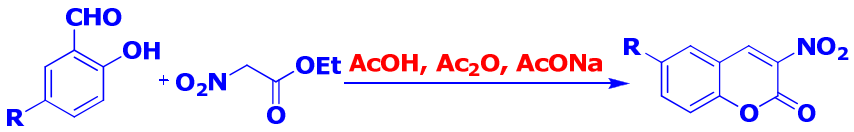
CHAPTER 3

3.1. Introduction

The synthesis[132] and biological activity[133] of 3-nitrochromenes have attracted considerable synthetic interest because of their potential as precursors to a variety of medically important 2*H*-benzopyran derivatives such as flavonols,[134] amines,[135] *etc*. It also has been reported that chromenes containing electron-withdrawing substituents at the 3-position possess radio-protecting properties[136] and 3-nitrochromenes with appropriate substituents are potential candidates for non-linear optical applications.[137]

Coumarins having a nitrogen-containing substituent in the 3[rd] position are known to exhibit biological activity. For example, 3-nitrocoumarin inhibits phospholipase C in pathogenic yeasts *Candida albicans*.[138] Suboch *et al*. reported the synthesis of 3-nitrocoumarins **233a-b** from salicylaldehydes **231a-b** and ethyl nitroacetate **232** (Eq. 39).[139]

Eq. 39



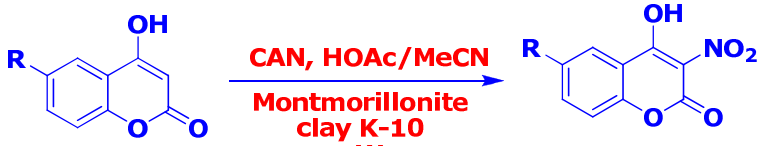
R = H, Br
231a, b

232

233a, b

Ganguly *et al.* reported nitration of 6-hydroxycoumarins **234** and their *O*-methyl ethers employing CAN in solution phase and solvent free condition on montmorillonite K-10 clay support under microwave irradiation (Eq. 40).[140]

Eq. 40

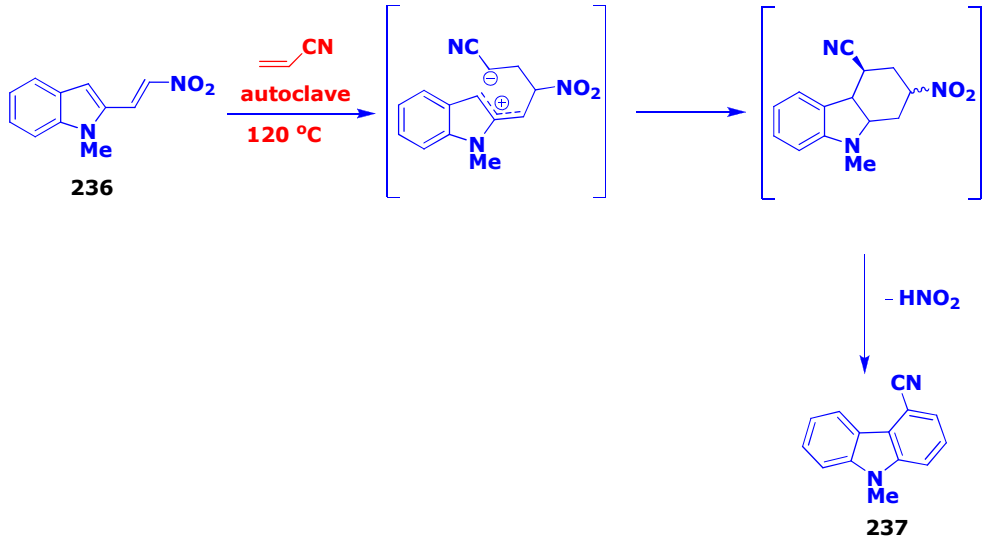


234

235

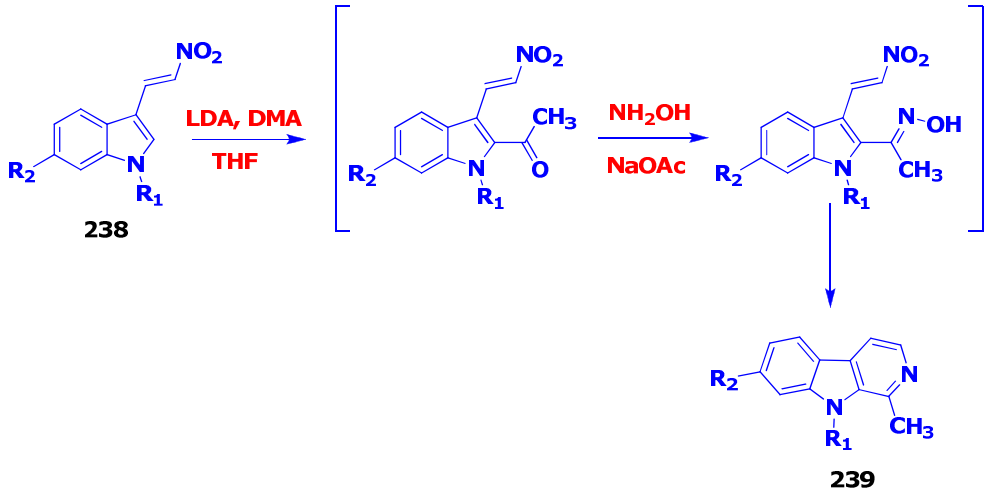
Pindur *et al.* reported the synthesis of carbazoles **237** from Diels-Alder reaction of (E)-1-methyl-2-(2-nitrovinyl)-1*H*-indole **236** with acrylonitrile at 120 °C (Eq. 41).[141]

Eq. 41



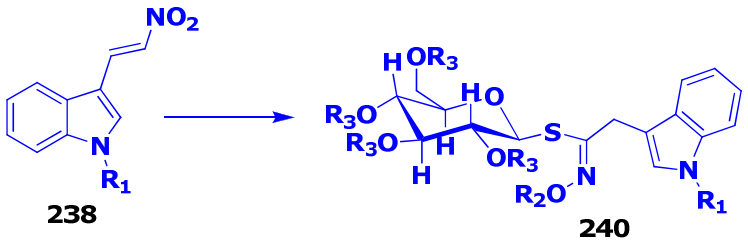
Kusurkar *et al.* described the synthesis of harman **239**, derivatives of harman and 1-aryl-β-carbolines using electrocyclisation reaction, of monoazahexatriene system as a key step (Eq. 42).[142]

Eq. 42



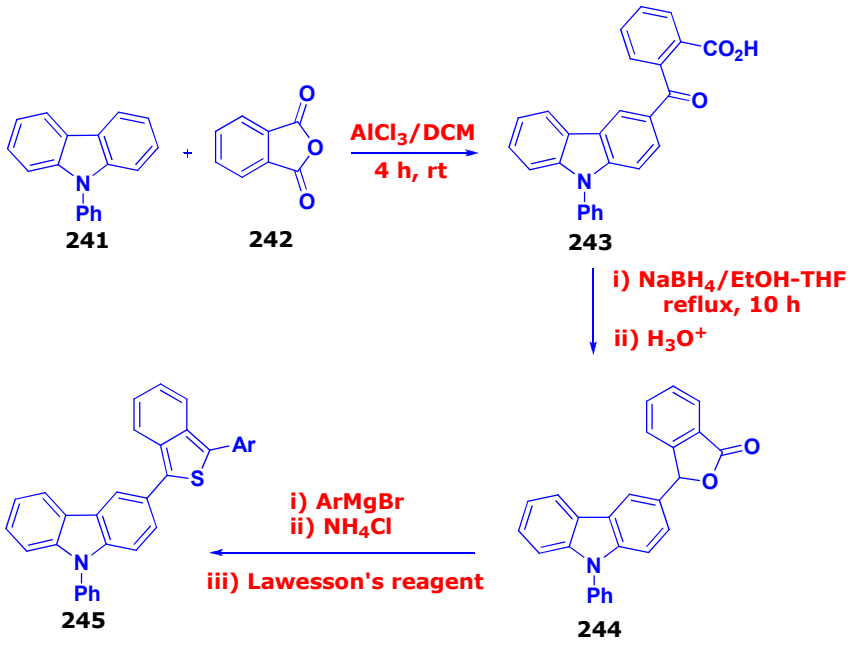
Rollin *et al.* reported an efficient methodology for the synthesis of arylalkyl and indolylmethyl glucosinolates (GSLs) **240** from indolyl nitrostyrenes **238** through oxime formation (Eq. 43).[143]

Eq. 43



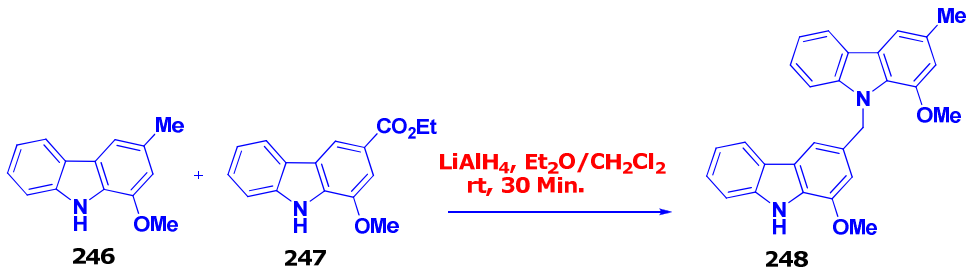
Mohanakrishnan *et al*. reported[144] the synthesis of 3-(benzo[*c*]thiophen-1-yl)-9-phenyl-9*H*-carbazoles **245** from 9-phenylcarbazole **241** and phthalic anhydride **242**. Friedel-Crafts phthaloylation of 9-phenylcarbazole **241** afforded keto acid **243**. Selective reduction of the ketone carbonyl function of the keto acid **243** and acid catalyzed cyclization furnished the required lactone **244**. Ring opening of the lactone **244** using freshly prepared arylmagnesium bromide followed by quenching with aq. NH_4Cl led to the formation of keto alcohol. The dichloromethane solution of keto alcohol on thionation using of Lawesson's reagent afforded **245** as shown in Eq. 44.

Eq. 44



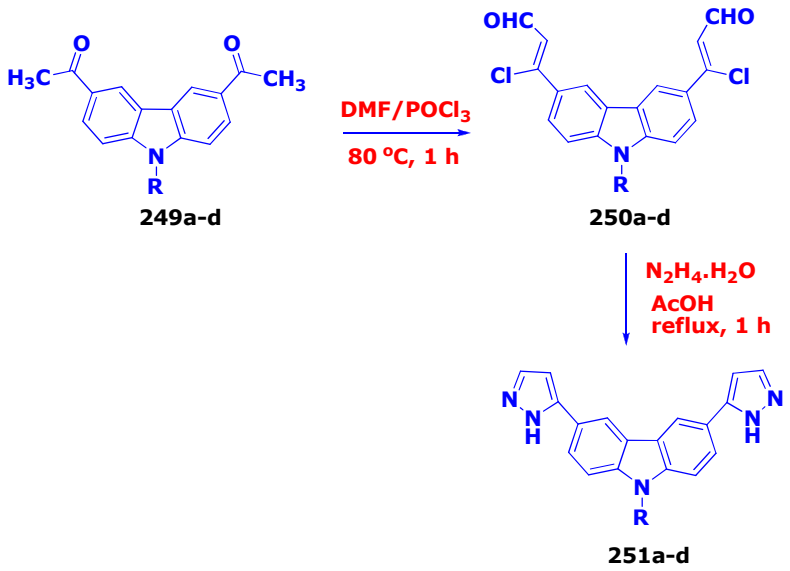
Bringmann *et al*. reported[145] the first synthesis of the methylene-bridged binary carbazole alkaloid bismurrayafoline-A **248** by treating murrayafoline-A **246** and ethyl-1-methoxy-9*H*-carbazol-3-carboxylate **247** (Eq. 45).

Eq. 45



Our group has reported the synthesis of bispyrazolylcarbazoles **251a-d** from the corresponding acryl aldehyde derivatives **250a-d**, which were further obtained from the corresponding acetyl derivatives **249a-d** (Eq. 46).[146]

Eq. 46

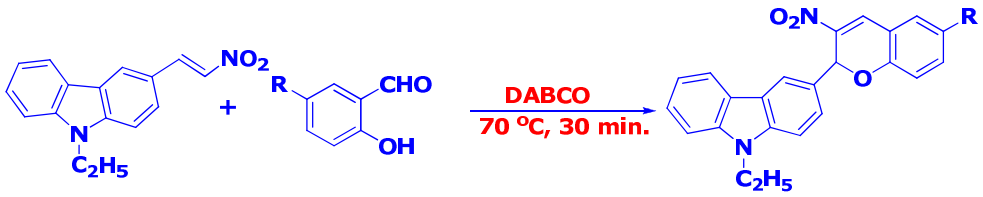


3.2. Synthesis of 3-chromenylcarbazoles

Most heteroarylcarbazoles reported in the literature contain a heteroaryl moiety fused with a carbazole; however, there are a few reports where the heteroaryl moiety is substituted with a carbazole unit. Hence, a practical method for the preparation of such compounds is desirable. In our continued interest on the synthesis of heteroaryl and diheteroarylcarbazoles of biological importance, we developed a new route to the synthesis of 3-chromenylcarbazoles, 3,6-*bis*-(chromenyl)carbazoles.

The reaction of β-nitrovinylcarbazole[147] **252a** with 2-hydroxybenzaldehydes **253a-e** with DABCO (50 mol%) was heated at 70°C for 30 minutes furnished the chromenylcarbazoles **254a-e** in good yields (scheme 11). The reaction proceeds via Michael addition of 2-hydroxybenzaldehyde to β-nitrovinylcarbazole followed by aldol condensation. The intermediate 4-hydroxyflavone was not observed, indicating its immediate dehydration to the corresponding 3-nitrochromenylcarbazoles. We have carried out the same reaction using different bases like sodium methoxide, triethylamine, piperidine etc., but observed faster and cleaner reactions only with DABCO.

Scheme 11. Synthesis of 3-(3-nitrochromenyl)carbazoles

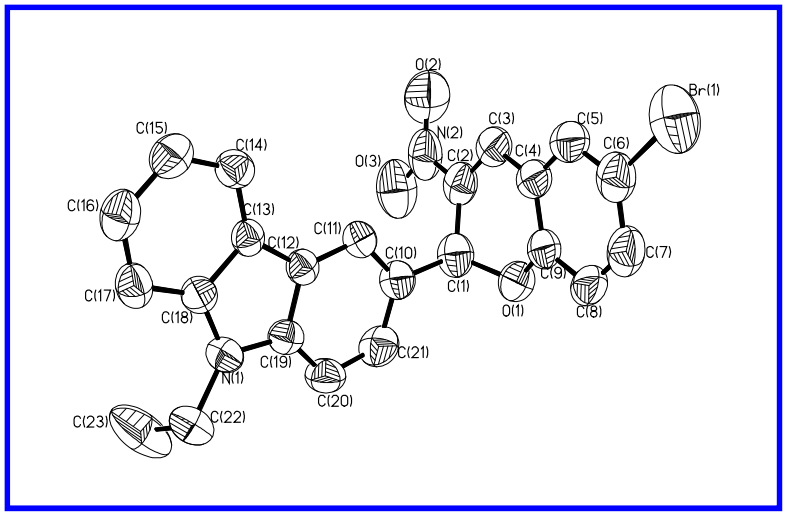


252 **253a-e** **254a-e**

253a, R = H
253b, R = OCH_3
253c, R = CH_3
253d, R = Br
253e, R = Cl

254a, R = H, 95%
254b, R = OCH_3, >99%
254c, R = CH_3, 85%
254d, R = Br, 79%
254e, R = Cl, 75%

Figure 11. ORTEP diagram of 9-ethyl-3-(6-bromo-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole 254d. Hydrogen atoms are omitted for clarity.



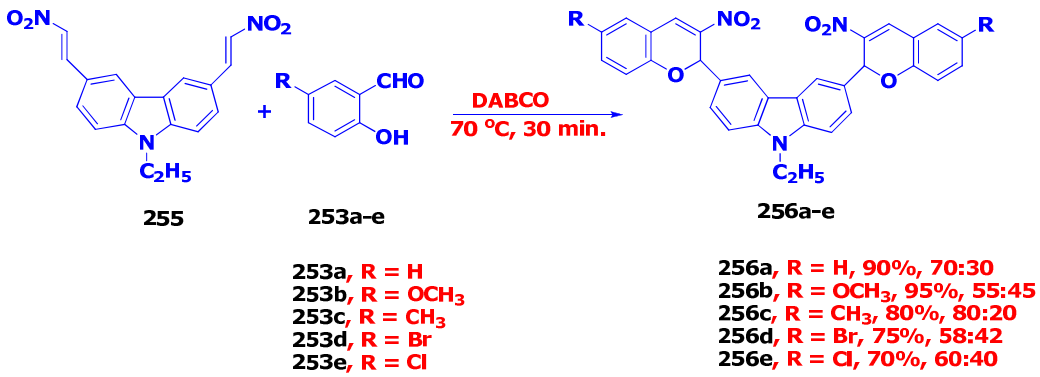
254d

The chromene formation was characterized by ^{1}H and ^{13}C spectra. In the ^{1}H NMR spectrum, the chromenyl 2-*H* proton was observed as a sharp singlet at δ 6.7 and 4-*H* proton appeared as a singlet at δ 8.1, down field. The ^{13}C NMR spectrum show chromenyl C-2 at 150 ppm indicating that it is attached to the electronegative oxygen atom. The structure of the product **254d** was also confirmed by single crystal X-ray analysis (figure 11).

3.2. Synthesis of 3,6-*bis*-(chromenyl)carbazoles

Extending the methodology, we have synthesized the *bis*-(3-nitrochromenyl)carbazoles **256a-e** by the reaction of salicylaldehydes **253a-e** with *bis*-(β-nitrovinyl)carbazole **255** using DABCO. *Bis*-(chromenyl)carbazole derivatives **256a-e** were obtained as a mixture of two diastereomers in good yields (scheme 12). The structure was confirmed by ^{1}H spectra and ^{13}C spectra. In the ^{1}H NMR, 2*H* and 4*H* protons were observed at δ 6.7 and δ 8.1, similar to monochromenyl derivatives **254a-e**. The diastereomeric ratio was calculated from ^{1}H NMR spectra. At higher temperatures decomposition of 3,6-*bis*-β-nitrovinylcarbazole was observed.

Scheme 12. Synthesis of 3,6-*bis*-(3-nitrochromenyl)carbazoles



255 **253a-e** **256a-e**

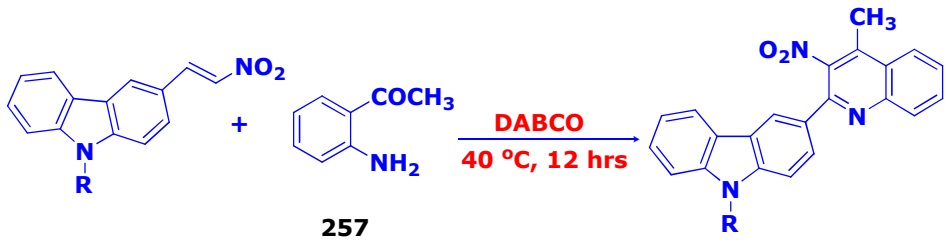
253a, R = H
253b, R = OCH_3
253c, R = CH_3
253d, R = Br
253e, R = Cl

256a, R = H, 90%, 70:30
256b, R = OCH_3, 95%, 55:45
256c, R = CH_3, 80%, 80:20
256d, R = Br, 75%, 58:42
256e, R = Cl, 70%, 60:40

3.3. Synthesis of 3-(3-nitroquinolyl)carbazoles

Quinolines are important and widely used heterocyclic compounds in organic chemistry, and a variety of methods for the preparation of nitroquinolines have been reported. Direct nitration of quinolines leds to several regioisomers. We have synthesized carbazole substituted with 3-nitroquinoline moiety by using our methodology.

Scheme 13. Synthesis of 3-(3-nitroquinolyl)carbazoles



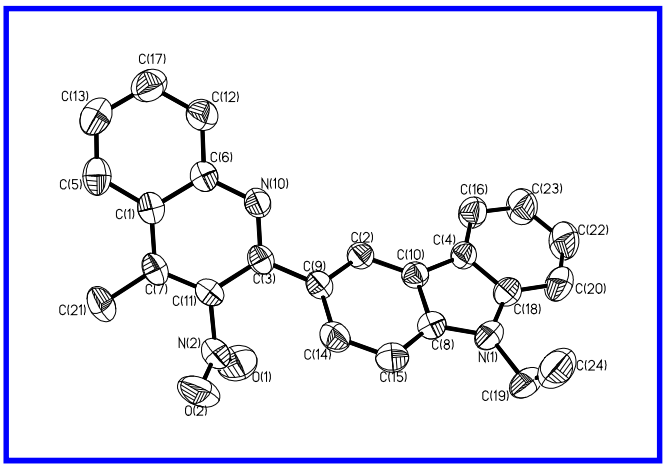
257

252a, R = C_2H_5
252b, R = CH_2Ph

258a-b

258a, R = C_2H_5, 55%
258b, R = CH_2Ph, 50%

Figure 12. ORTEP diagram of 9-ethyl-3-(4-methyl-3-nitroquinolin-2-yl)-9*H*-carbazole 258a. Hydrogen atoms are omitted for clarity.



258a

3-(3-nitroquinolyl)carbazoles **258a-b** were synthesized in good yields under ecofriendly condition in one pot way by the reaction of *β*-nitrovinylcarbazole **252a-b** with 2-aminoacetophenone **257** at 40°C (scheme 13). The dihydroquinoline was not observed, and this indicates immediate aromatization to quinolines. At higher temperatures (>50°C) resulted in the lower yield due to the self condensation of 2-aminoacetophenone and partial decomposition of nitrovinylcarbazole. In ^{1}H NMR, the methyl group at the 4th carbon of quinoline was observed as a sharp singlet at δ 2.73. The carbazole C_4-*H* proton was observed as a singlet far downfield at δ 8.4 because of $-NO_2$ space effect. The absence of –N*H* and C_2-*H* proton peaks of quinoline indicated the complete aromatization of quinoline. The structure was also confirmed by single crystal X-ray analysis (Figure 12). Attempts to synthesize *bis*-quinolyl derivatives were failed due to the decomposition of *bis*-β-nitrovinylcarbazole.

3.4. Conclusion

In conclusion, we herein report a new, easy and efficient synthesis of 3-(3-nitrochromenyl)carbazoles, 3,6-*bis*-(3-nitrochromenyl)carbazoles and 3-(3-nitroquinolyl)carbazoles under solvent free conditions in moderate to quantitative yields. The procedure evidences from several advantages such as short reaction time, no need for organic solvents and a series of reactions has been performed in one-pot way. Thus, our method has advantages from both environmental and economic point of view for the synthesis of biologically important derivatives of carbazole, quinolines and chromenes.

3.5. Experimental Section

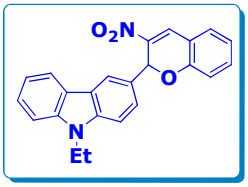
General Procedure G

9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **1** (1 mmol), salicylaldehydes **2a-e** (3 mmol) and DABCO (0.5 mmol) were mixed under stirring and heated at 70 °C for 30 minutes. After the reaction was over, the residue was diluted with dichloromethane, adsorbed on silicagel and subjected to column chromatography to obtain the chromenes in good yields.

9-Ethyl-3-(3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (254a):

The compound **254a** was prepared from 9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **252a** and **253a** by following the general procedure G. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 95%



Mp: 161-163 °C

IR (KBr) ν_{max} cm^{-1}: 3057, 2968, 1641, 1601, 1566, 1387, 1323, 1221, 1157, 964

^{1}H NMR (400 MHz) δ: 8.16 (s, 1H), 8.06 (d, *J* = 7.3 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.41 - 7.28 (m, 5H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.80 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 153.7, 141.7, 140.4, 134.2, 131.1, 130.3, 129.1, 127.3, 126.1, 125.0, 123.1, 122.7, 122.3, 120.6, 119.5, 119.2, 118.2, 117.4, 108.8, 108.7, 75.2, 37.6, 13.8

LC-MS (m/z): 370 (M^+)

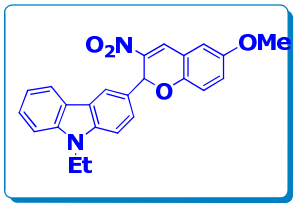
Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56 %

Found: C, 74.56; H, 4.90; N, 7.58 %

9-Ethyl-3-(6-methoxy-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (254b):

The compound **254b** was prepared from 9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **252a** and **253b** by following the general procedure G. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: >99%



Mp: 164-166 °C

IR (KBr) ν_{max} cm^{-1}: 3070, 2961, 1651, 1601, 1323, 1259, 1207, 1132, 976, 883

^{1}H NMR (400 MHz) δ: 8.12 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.51 - 7.46 (m, 2H), 7.4 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.28 (s, 1H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.90 (s, 1H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 4.34 (q, *J* = 7.32 Hz, 2H), 3.81 (s, 3H), 1.41 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz) δ: 154.8, 147.7, 142.4, 140.4, 129.1, 127.1, 126.1, 124.9, 123.5, 123.1, 122.7, 120.6, 119.5, 119.2, 118.7, 118.2, 116.1, 113.8, 108.67, 108.7, 75.3, 55.3, 37.6, 13.8

LC-MS (m/z): 401 (M+H)

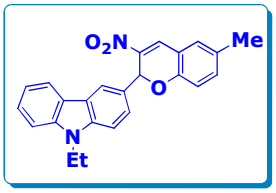
Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00 %

Found: C, 71.86; H, 5.01; N, 6.97 %

9-Ethyl-3-(6-methyl-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (254c):

The compound **254c** was prepared from 9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **252a** and **253c** by following the general procedure G. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 85%



Mp: 168-170 °C

IR (KBr) ν_{max} cm^{-1}: 3073, 2964, 1655, 1600, 1261, 1217, 1134, 1066, 979, 889

^{1}H NMR (400 MHz) δ: 8.13 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.51 - 7.47 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.23 (t, *J* = 7.0 Hz, 1H), 7.27 (s, 1H), 6.89 (s, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.74 (s, 1H), 4.31 (q, *J* = 7.42 Hz, 2H), 2.23 (s, 3H), 1.42 (t, *J* = 7.41 Hz, 3H)

^{13}C NMR (100 MHz) δ: 154.7, 147.5, 142.4, 140.4, 129.1, 127.0, 126.0, 124.9, 123.0, 122.8, 121.1, 120.5, 119.5, 119.2, 118.6, 118.2, 116.0, 113.8, 108.7, 108.6, 73.3, 37.6, 33.0, 13.8

LC-MS (m/z): 385 (M+H)

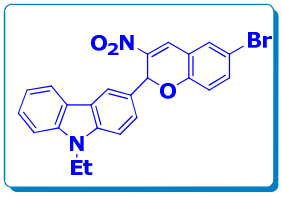
Anal. Calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29 %

Found: C, 74.91; H, 5.21; N, 7.17 %

9-Ethyl-3-(6-bromo-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (254d):

The compound **254d** was prepared from 9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **252a** and **253d** by following the general procedure G. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 79%



Mp: 182-184 °C

IR (KBr) ν_{max} cm^{-1}: 3074, 2972, 1645, 1251, 1234, 1195, 1165, 1128, 1060, 954 cm^{-1}

^{1}H NMR (400 MHz) δ: 8.03 (s, 2H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.46 (d, *J* = 1.2 Hz, 1H), 7.44 – 7.42 (m, 2H), 7.39 (s, 1H), 7.36 (t, *J* = 2.2 Hz, 1H), 7.25 (s, 1H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.76 (s, 1H), 6.72 (d, *J* = 8.9 Hz, 1H), 4.32 (q, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.05 Hz, 3H)

^{13}C NMR (100 MHz) δ: 152.5, 142.4, 140.6, 140.3, 136.5, 132.2, 127.6, 126.5, 126.2, 124.8, 123.1, 122.6, 120.6, 119.9, 119.5, 119.3, 119.2, 114.0, 108.9, 108.7, 75.3, 37.6, 13.8

LC-MS (m/z): 448 (M), 450 (M+2)

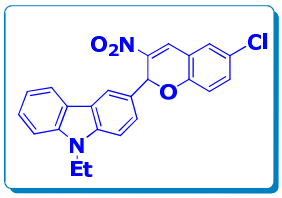
Anal. Calcd. for $C_{23}H_{17}BrN_2O_3$: C, 61.48; H, 3.81; N, 6.23 %

Found: C, 61.40; H, 3.83; N, 6.26 %

9-Ethyl-3-(6-chloro-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (254e):

The compound **254e** was prepared from 9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **252a** and **253e** by following the general procedure G. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 75%



Mp: 190-192 °C

IR (KBr) ν_{max} cm^{-1}: 3076, 2976, 1646, 1601, 1236, 1194, 1168, 1128, 1063, 959

^{1}H NMR (400 MHz) δ: 8.16 (s, 1H), 8.06 (d, *J* = 7.34 Hz, 1H), 7.56 - 7.46 (m, 3H), 7.41 - 7.28 (m, 4H), 7.24 (t, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.90 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 153.7, 141.7, 140.5, 134.2, 130.3, 129.2, 127.3, 126.2, 124.9, 123.1, 122.7, 122.3, 122.1, 120.6, 119.6, 119.2, 118.2, 117.3, 108.8, 107.6, 75.2, 37.6, 13.8,

LC-MS (m/z): 404 (M), 406 (M+2)

Anal. Calcd. for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23; N, 6.92 %

Found: C, 68.20; H, 4.13; N, 6.86 %

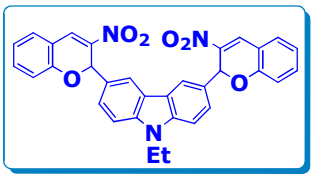
General Procedure H

9-Ethyl-3,6-bis-[(*E*)-2-nitrovinyl]-9*H*-carbazole (1mmol), salicylaldehyde (5 mmol) and DABCO (1 mmol) were mixed under stirring and heated at 70°C for 30 minutes. The reaction mass was dissolved with CH_2Cl_2, adsorbed on silicagel and subjected to column chromatography to obtain the 3,6-*bis*-(3-nitro-chromen-2-yl)carbazoles in good yields.

9-Ethyl-3,6-bis-(3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (256a):

The compound **256a** was prepared from 9-ethyl-3,6-bis-[(*E*)-2-nitrovinyl]-9*H*-carbazole **255** and **253a** by following the general procedure H. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 90%



Mp: 224-226 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 3063, 2974, 2359, 1647, 1602, 1219, 1151, 1118, 1064, 945

^{1}H NMR (400 MHz) δ: 8.16 (s, 2H), 8.02 (s, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.42 - 7.39 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 1.8 Hz, 2H), 4.26 (q, *J* = 7.4 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (100 MHz) δ: 158.0, 146.0, 145.5, 139.4, 136.2, 135.2, 132.6, 130.3, 127.5, 127.1, 125.1, 123.5, 121.9, 114.8, 79.3, 42.4, 18.8

LC-MS (m/z): 546 $(M+H)^+$

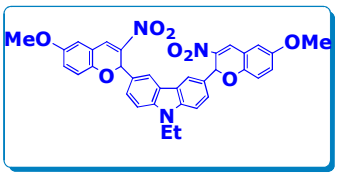
Anal. Calcd. for $C_{32}H_{23}N_3O_6$: C, 70.45; H, 4.25; N, 7.70 %

Found: C, 70.36; H, 4.24; N, 7.80 %

9-Ethyl-3,6-bis-(6-methoxy-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (256b):

The compound **256b** was prepared from 9-ethyl-3,6-bis-[(*E*)-2-nitrovinyl]-9*H*-carbazole **255** and **253b** by following the general procedure H. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 95%



Mp: 228-230 °C

IR (KBr) ν_{max} cm^{-1}: 3059, 2959, 2829, 1874, 1730, 1643, 1244, 1201, 1157, 1068, 1030, 968

^{1}H NMR (400 MHz) δ: 8.13 (s, 2H), 8.01 (d, *J* = 5.2 Hz, 2H), 7.47 - 7.44 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.91 - 6.88 (m, 4H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.72 (s, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz) δ: 154.6, 147.1, 141.8, 140.7, 130.7, 127.7, 125.4, 122.3, 120.9, 120.4, 119.3, 118.1, 115.0, 110.1, 74.3, 56.0, 37.5, 14.1

LC-MS (m/z): 606 ($M+H^+$)

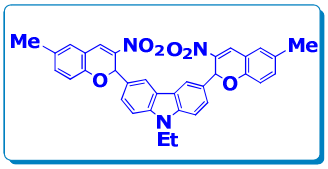
Anal. Calcd. for $C_{34}H_{27}N_3O_8$: C, 67.43; H, 4.49; N, 6.94%

Found: C, 67.59; H, 4.48; N, 6.92%

9-Ethyl-3,6-bis-(6-methyl-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (256c):

The compound **256c** was prepared from 9-ethyl-3,6-bis-[(*E*)-2-nitrovinyl]-9*H*-carbazole **255** and **253c** by following the general procedure H. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 80%



Mp: 240-244 °C

IR (KBr) ν_{max} cm^{-1}: 3061, 2964, 2863, 1879, 1740, 1641, 1613, 1579, 1245, 1069, 969

^{1}H NMR (400 MHz) δ: 8.14 (s, 2H), 8.02 (d, *J* = 5.2 Hz, 2H), 7.47 - 7.44 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.90 - 6.86 (m, 4H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.62 (s, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 2.21 (s, 6H), 1.34 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz) δ: 158.1, 146.5, 145.5, 139.5, 136.2, 135.2, 132.6, 130.4, 129.7, 127.6, 127.1, 125.1, 123.4, 121.9, 114.8, 79.3, 42.4, 18.7

LC-MS (m/z): 606 $(M+H)^+$

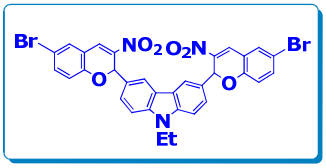
Anal. Calcd. for $C_{34}H_{27}N_3O_6$: C, 71.19; H, 4.74; N, 7.33 %

Found: C, 71.14; H, 4.68; N, 7.52 %

9-Ethyl-3,6-bis-(6-bromo-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (256d):

The compound **256d** was prepared from 9-ethyl-3,6-bis-[(*E*)-2-nitrovinyl]-9*H*-carbazole **255** and **253d** by following the general procedure H. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 75%



Mp: 260-262 °C

IR (KBr) ν_{max} cm^{-1}: 3067, 2968, 2867, 1881, 1751, 1647, 1249, 1211, 1161, 1065, 1031, 957

^{1}H NMR (400 MHz) δ: 8.07 (s, 2H), 8.02 (d, *J* = 4.2 Hz, 2H), 7.53 (d, *J* = 1.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.76 (s, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz) δ: 158.0, 146.0, 145.5, 139.4, 136.3, 135.2, 132.6, 130.4, 127.5, 127.1, 125.1, 123.5, 121.9, 114.8, 79.5, 42.4, 18.8

LC-MS (m/z): 703 (M), 705 (M+2)

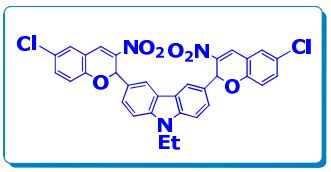
Anal. Calcd. for $C_{32}H_{21}Br_2N_3O_6$: C, 54.65; H, 3.01; N, 5.97 %

Found: C, 54.67; H, 2.98; N, 5.92 %

9-Ethyl-3,6-bis-(6-chloro-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole (256e):

The compound **256e** was prepared from 9-ethyl-3,6-bis-[(*E*)-2-nitrovinyl]-9*H*-carbazole **256** and **253e** by following the general procedure H. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 70%



Mp: 268-272 °C

IR (KBr) ν_{max} cm^{-1}: 3062, 2967, 2873, 1878, 1748, 1647, 1616, 1247, 1213, 1161, 1069, 1032, 969

^{1}H NMR (400 MHz) δ: 8.07 (s, 2H), 8.01 (d, *J* = 3.0 Hz, 2H), 7.51 (s, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.74 (s, 2H), 6.74 (d, *J* = 8.9 Hz, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 1.36 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz) δ: 158.2, 146.3, 145.5, 139.5, 136.2, 135.2, 132.6, 130.0, 127.5, 127.3, 125.1, 123.6, 121.9, 114.8, 79.5, 42.4, 18.8

LC-MS (m/z): 614 (M), 616 (M+2)

Anal. Calcd. for $C_{32}H_{21}Cl_2N_3O_6$: C, 62.55; H, 3.44; N, 6.84 %

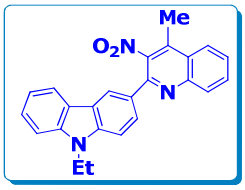
Found: C, 62.51; H, 3.47; N, 6.82 %

General Procedure I

9-Alkyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole (1 mmol), 2'-aminoacetophenone (5 mmol) and DABCO (0.5 mmol) were mixed under stirring and heated at 40 °C for 12 hours. The residue was diluted with CH_2Cl_2, adsorbed on silicagel and subjected to column chromatography to obtain the nitroquinolines in good yields.

9-Ethyl-3-(4-methyl-3-nitroquinolin-2-yl)-9*H*-carbazole (258a):

The compound **258a** was prepared from 9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **252a** and **257** by following the general procedure I. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 55%

Mp: 186-188 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 3057, 1728, 1589, 1520, 1471, 1344, 1232, 1153, 1120, 848

^{1}H NMR (400 MHz) δ: 8.47 (d, *J* = 1.5 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 8.85 - 7.79 (m, 2H), 7.70 - 7.63 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.27 - 7.23 (m, 1H), 4.39 (q, *J* = 7.3 Hz, 2H), 2.73 (s, 3H), 1.45 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz) δ: 151.1, 147.1, 146.0, 140.8, 136.5, 134.4, 132.0, 131.2, 130.4, 127.7, 126.1, 125.5, 124.6, 123.4, 120.7, 119.3, 118.4, 117.2, 115.7, 108.7, 56.7, 37.7, 27.8, 13.8

LC-MS (m/z): 380 ($M-H^+$), negative mode

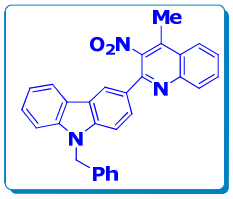
Anal. Calcd. for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02 %

Found: C, 75.54; H, 5.04; N, 11.04 %

9-Benzyl-3-(4-methyl-3-nitroquinolin-2-yl)-9*H*-carbazole (258b):

The compound **258b** was prepared from 9-ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **252b** and **257** by following the general procedure I. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 50%



Mp: 192-194 °C

IR (KBr) ν_{max} cm^{-1}: 3416, 3059, 1729, 1591, 1522, 1474, 1348, 1236, 1158, 1128, 845 cm^{-1}

^{1}H NMR (400 MHz) δ: 8.50 (d, *J* = 1.5 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 7.4 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.86 - 7.80 (m, 2H), 7.67 - 7.64 (m, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.37 - 7.23 (m, 6H), 3.61 (s, 2H), 2.73 (s, 3H)

^{13}C NMR (100 MHz) δ: 151.1, 147.1, 146.0, 140.7, 136.5, 134.3, 132.0, 131.2, 130.4, 127.7, 127.3, 126.1, 125.5, 124.6, 123.4, 120.7, 119.3, 118.4, 117.2, 115.8, 110.1, 109.2, 109.1, 108.7, 56.7, 39.6, 33.1

LC-MS (m/z): 444 $(M+H)^+$

Anal. Calcd. for $C_{29}H_{21}N_3O_2$: C, 78.54; H, 4.77; N, 9.47 %

Found: C, 78.51; H, 4.77; N, 9.46 %

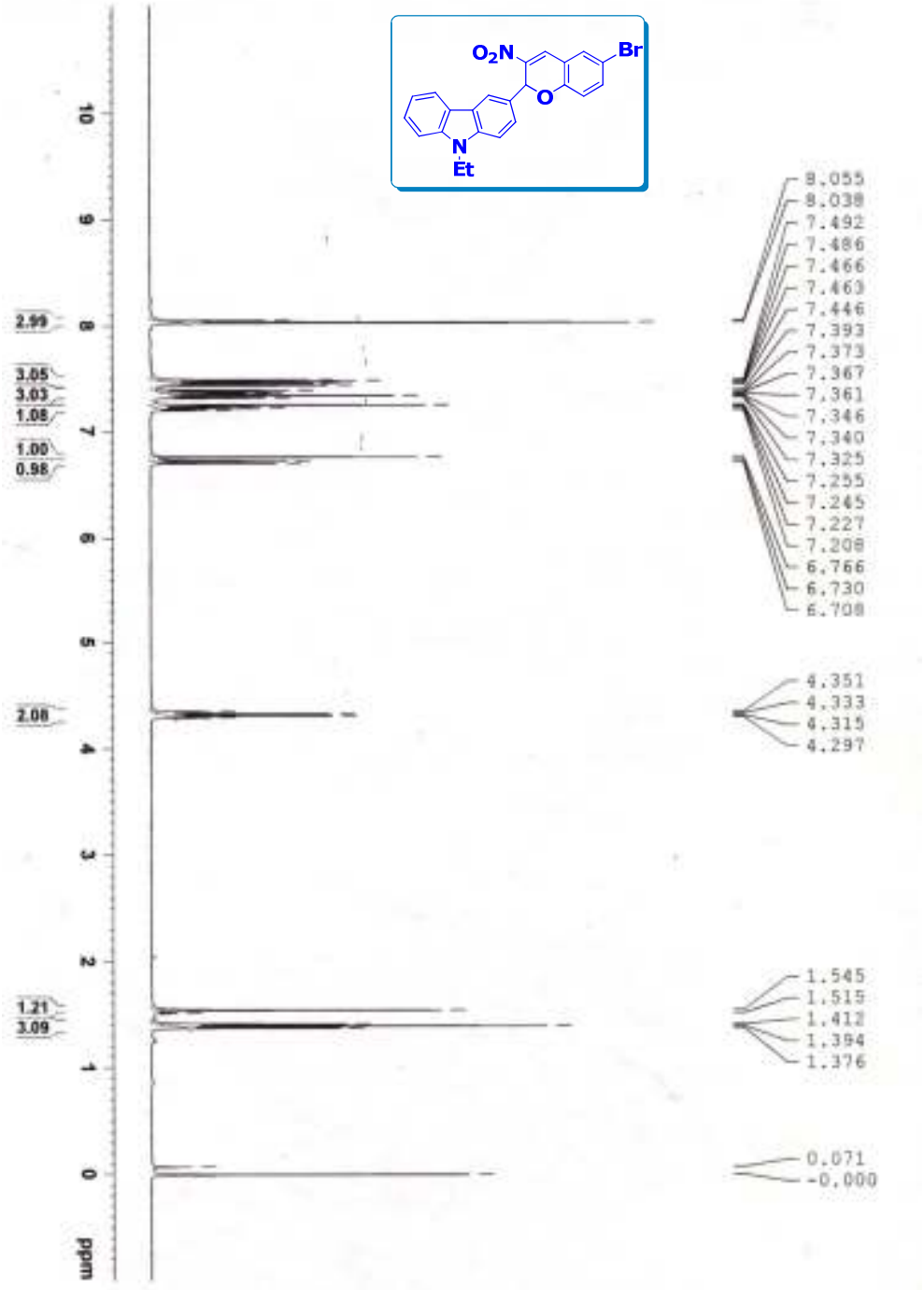
Table 13. Crystal data and structure refinement for 254d

Empirical formula	: $C_{23}H_{17}BrN_2O_3$
Formula weight	: 449.30
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 15.154(4) Å, α = 90°
	: b = 12.088(3) Å, β = 107.604°
	: c = 11.316(3) Å, γ = 90°
Volume	: 1975.7(8) $Å^3$
Z	: 4
Density (calculated)	: 1.510 Mg/m^3
Absorption coefficient	: 2.108 mm^{-1}
F (000)	: 912
Crystal size	: 0.44 x 0.32 x 0.18 mm
Theta range for data collection	: 2.20to 25.39°
Index ranges	: -18<=h<=18, -14<=k<=14,
	-14<=l<=14
Reflections collected	: 13876
Completeness to theta = 25.97	: 97.3%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9964 and 0.9805
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2858 / 0 / 218
Goodness-of-fit on F^2	: 1.219
Final R indices [I>2sigma(I)]	: R1 = 0.1086, wR2 = 0.1841
R indices (all data)	: R1 = 0.1520, wR2 = 0.2036
Largest diff. peak and hole	: 0.206 and -0.198 $e.Å^{-3}$
CCDC number	: 627871

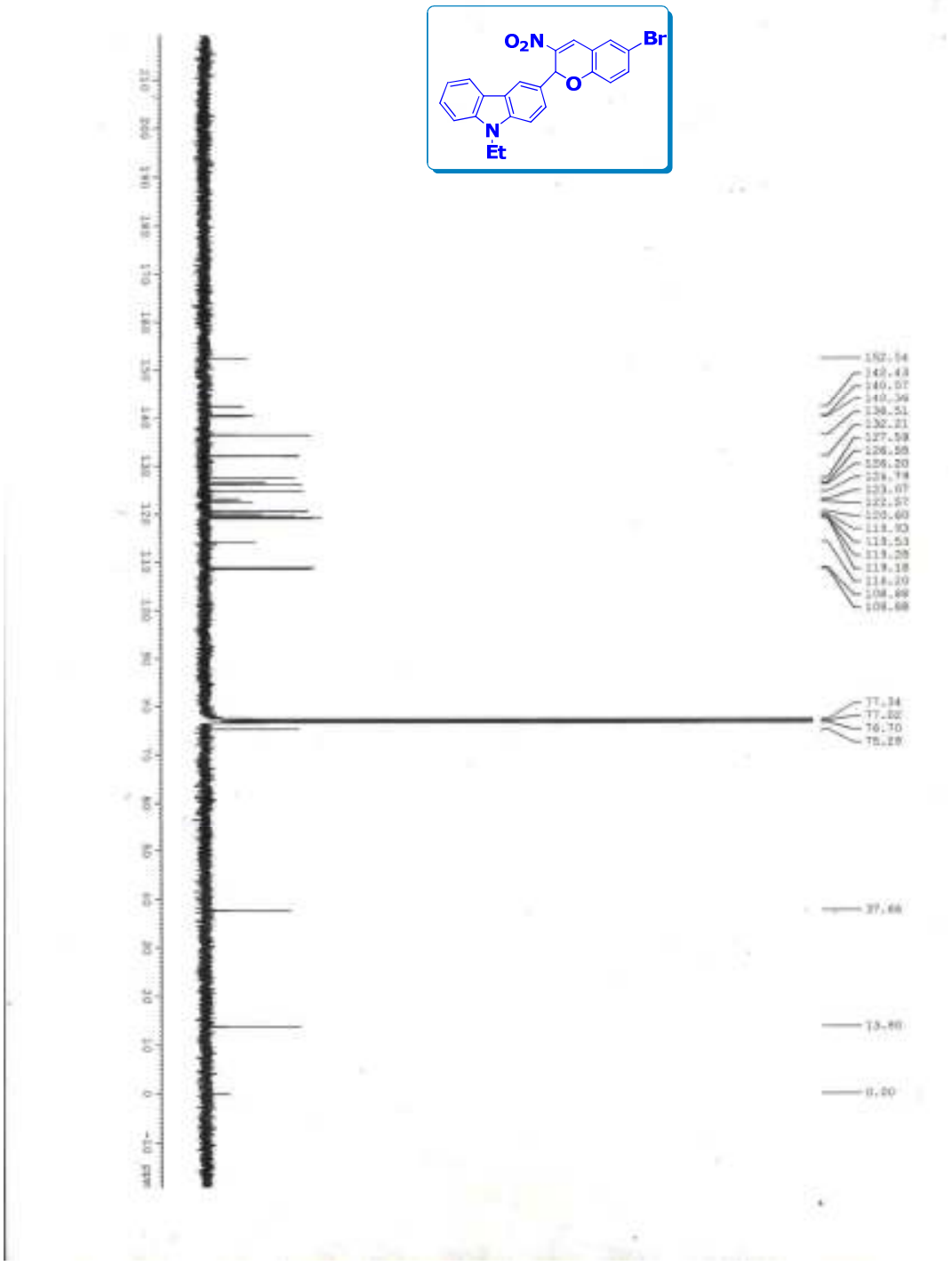
Table 14. Crystal data and structure refinement for 258a

Empirical formula	: $C_{24}H_{19}N_3O_2$
Formula weight	: 381.42
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: C2/c
Unit cell dimensions	: a = 26.834(3) Å, α = 90°
	: b = 9.3498(11)Å, β = 97.956(2)°
	: c = 15.3302(18) Å, γ = 90°
Volume	: 3809.2(8) $Å^3$
Z	: 8
Density (calculated)	: 1.330 Mg/m^3
Absorption coefficient	: 0.086 mm^{-1}
F (000)	: 1600
Crystal size	: 0.34 x 0.20 x 0.10mm
Theta range for data collection	: 1.53 to 26.05°
Index ranges	: -32<=h<=33, -11<=k<=10,
	-18<=l<=18
Reflections collected	: 10063
Completeness to theta = 25.97	: 99.7 %
Absorption correction	: None
Max. and min. transmission	: 0.9914 and 0.9712
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3757 / 0 / 273
Goodness-of-fit on F^2	: 1.024
Final R indices [I>2sigma(I)]	: R1 =0.0541, wR2 = 0.1841
R indices (all data)	: R1 =0.0861, wR2 = 0.1341
Largest diff. peak and hole	: 0.160 and -0.168 $e.Å^{-3}$
CCDC number	: 627870

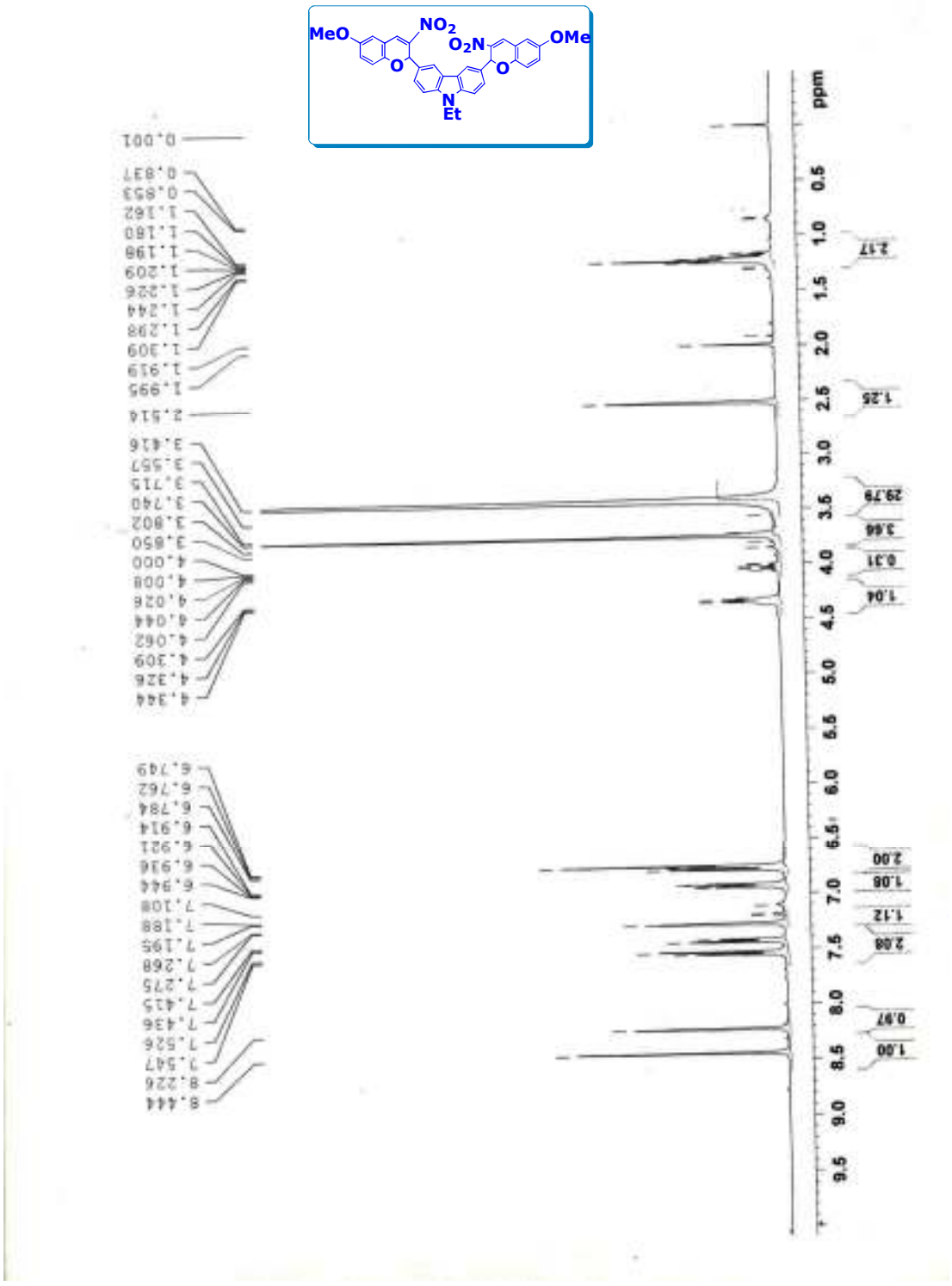
Spectrum No: 27, ^{1}H NMR of 254d



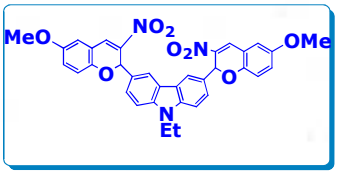
Spectrum No: 28, ^{13}C NMR of 254d

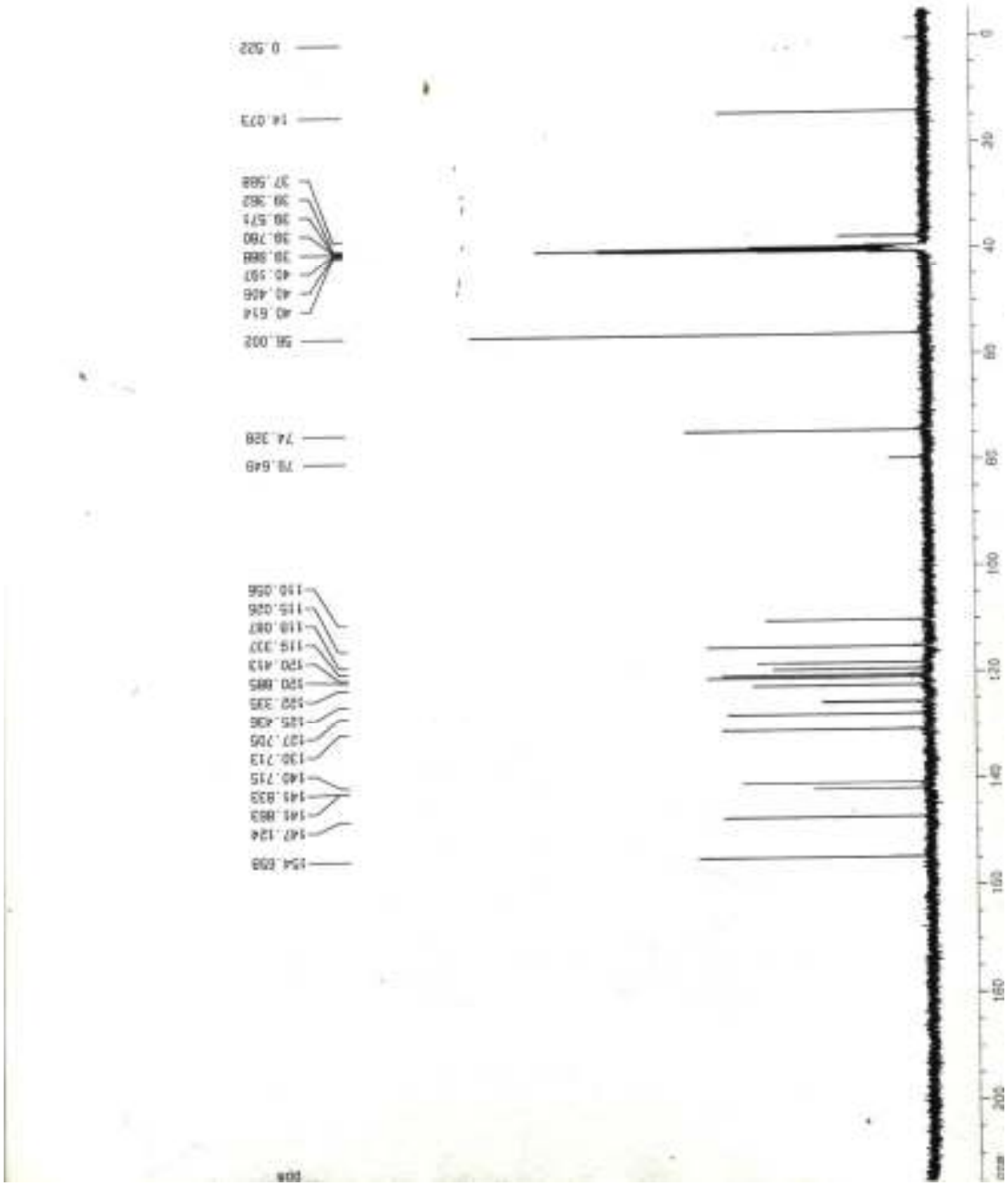


Spectrum No: 29, ^{1}H NMR of 256b

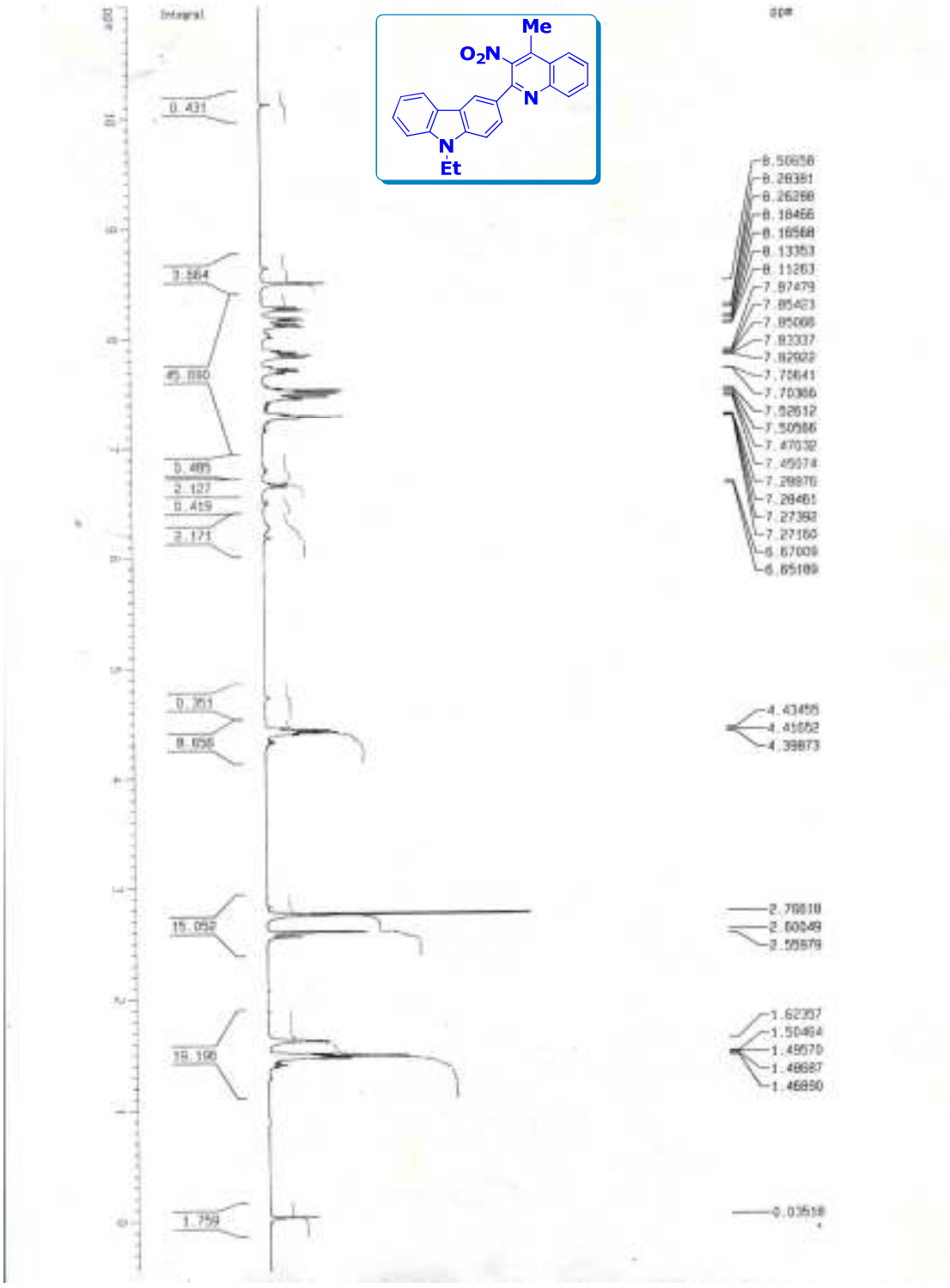


Spectrum No: 30, ^{13}C NMR of 256b

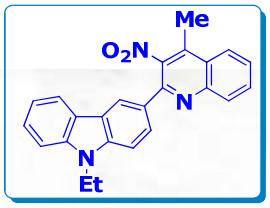




Spectrum No: 31, ^{1}H NMR of 258a



Spectrum No: 32, ^{13}C NMR of 258a



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A Tandem Route to the Synthesis of Carbazolo[1,2-*b*]carbazoles

CHAPTER 4

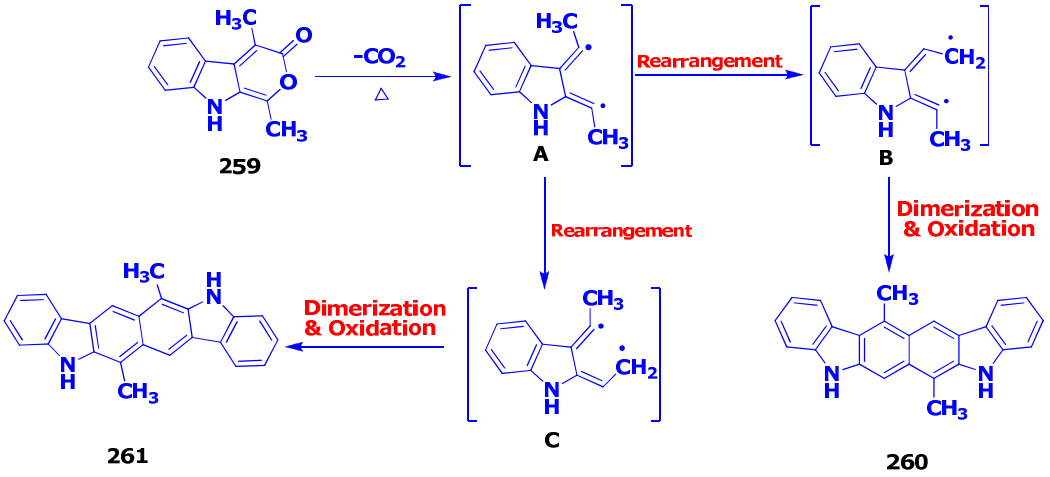
4.1. Introduction

A broad range of carbazole alkaloids with interesting structural motifs and useful biological applications such as pyridocarbazoles,[148-9] pyranocarbazoles,[150] furocarbazoles,[151] indolocarbazoles *etc.*,[152] which have a heteroarylcarbazole skeleton have been isolated from diverse natural sources. This initiated the development of many novel and efficient synthetic methods for these heteroarylcarbazole derivatives.

Carbazolocarbazoles are a new class of heteroarylcarbazoles where a carbazole is fused with another carbazole at various positions. These molecules are little explored and very few reports are available in literature, though they are reported to form stronger *π*-donor complexes. Carbazolo[3,4-*c*]carbazole and tetranitroflourenone are reported to form a strong electron donor-acceptor complex (EDA complex).[153]

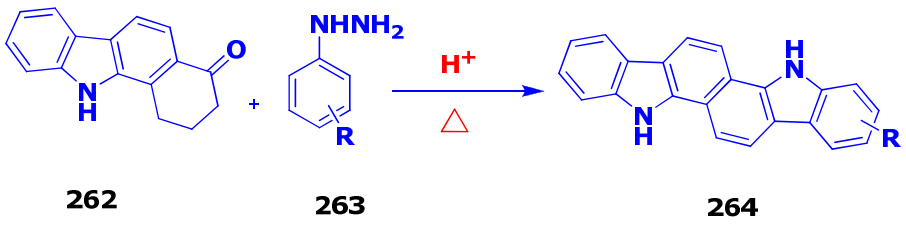
Haider *et al.* found that 1,4-disubstituted pyrano[3,4-*b*]indol-3(9*H*)-one **259** undergoes side reactions to some extent under the conditions employed, and they were able to isolate two interesting final products of such a process. These hexacyclic compounds **260** and **261**, both featuring a carbazolocarbazole skeleton, were obtained in 14% and 19% yields, respectively. A possible mechanism for the formation of **260** and **261** could involve thermally induced extrusion of carbon dioxide from **259**, affording a highly reactive species (**A**) with a diradicalic or zwitterionic structure. Rearrangement of this intermediate, followed by a sequence of dimerization (**B**+**B** for **260**, **B**+**C** for **261**) and oxidation/dehydrogenation finally might lead to the formation of the two isomeric polycycles (Eq. 47).[154]

Eq. 47



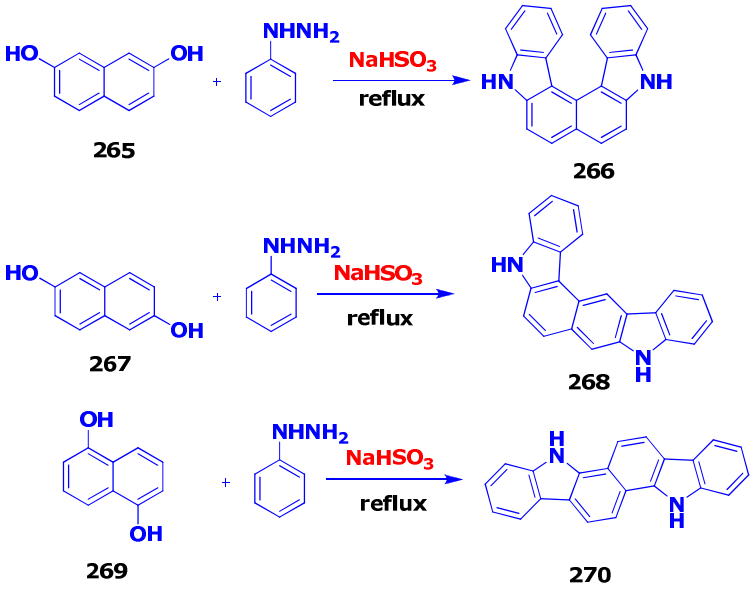
Kirsch and Dufour reported the synthesis of a series of carbazolo[2,1-*a*]carbazoles **264** from 4-oxo-1,2,3,4-tetrahydrobenzo[*a*]carbazole derivatives **262** (Eq. 48). The synthesis involved Fischer indole synthesis of 4-oxo-1,2,3,4-tetrahydrobenzo[*a*]carbazole derivatives **262** with aryl hydrazines **263** as the key step.[155]

Eq. 48



Zander *et al*. reported that when 2,7-Dihydroxynaphthalene **265** refluxed with $PhNHNH_2$ and $NaHSO_3$, gave 5,10-dihydrocarbazolo[3,4-*c*]carbazole **266**. Similarly were prepared 5,12-dihydrocarbazolo[2,1-*a*]-carbazole **270**, 4-hydroxy-11*H*-benzo [*a*]carbazole, 5,8-dihydrocarbazolo[3,4-*a*]carbazole **268**, 3-hydroxy-11*H*-benzo[*a*]carbazole and 4-hydroxy-7*H*-benzo[*c*]carbazole (Eq. 49).[156]

Eq. 49

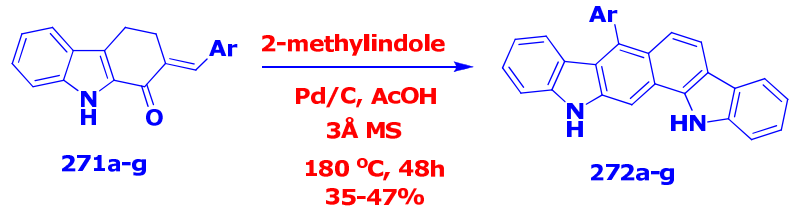


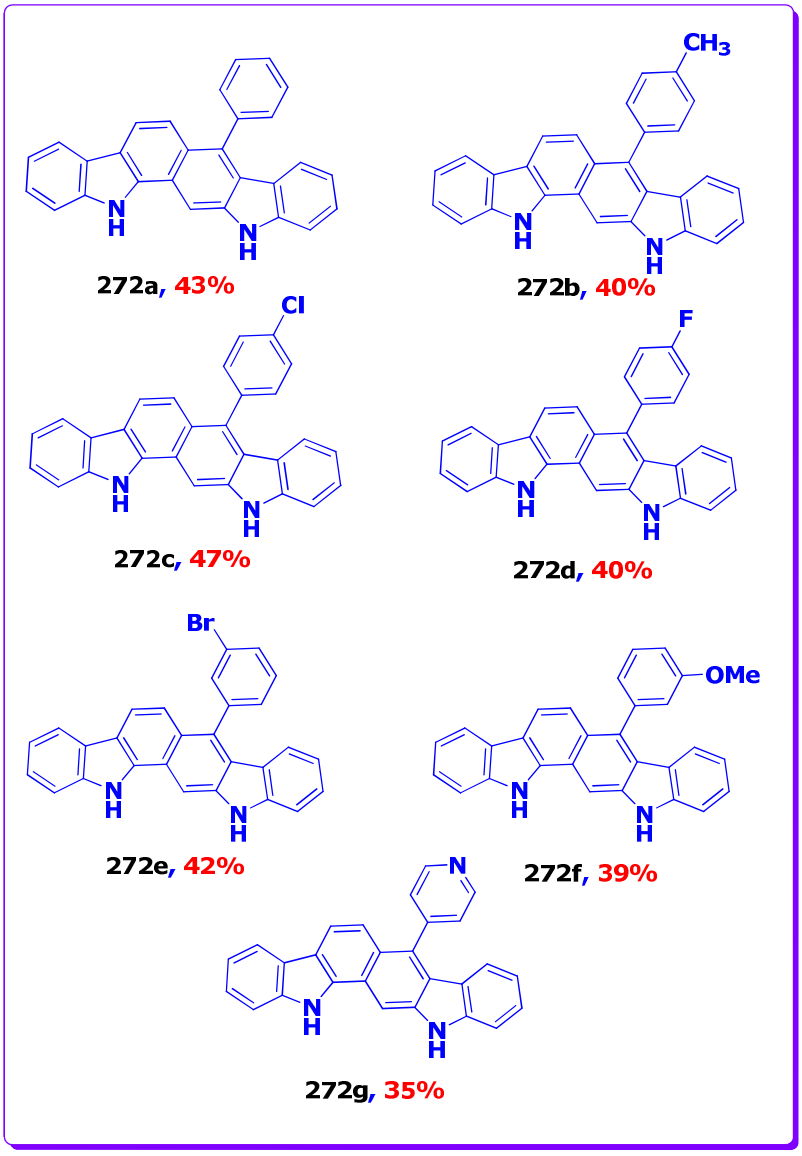
4.2. Synthesis of Carbazolocarbazoles

Synthesis of heterocycles employing tandem reactions is one of the most economical and desirable synthetic strategies.[157] Tandem processes are well explored in literature and development of new tandem processes is of continuous synthetic interest. In continuation of development of efficient methodologies[158] for new heteroarylcarbazole derivatives, we report here a simple and efficient route for the synthesis of carbazolo[1,2-*b*]carbazole derivatives.

We envisioned that 2-alkylindole on condensation with the chalcones of 1-ketotetrahydrocarbazole followed by aromatization can provide the desired products. We employed various solvent systems like Water, DMF, DMSO; but we found negligible conversion of starting materials. When we conducted the reaction in acetic acid, we were successful in obtaining the products in moderate yields (Scheme 1). Aryl chalcones of 1-ketotetrahydrocarbazole **271a-g** on reacting with 2-methylindole in presence of palladium charcoal in acetic acid upon heating at 180 ^{o}C in hydrothermal oven provided the carbazolo[1,2-*b*]carbazole derivatives **272a-g** in moderate yields. When we carried out the reaction without Pd/C and in the presence of oxygen, we didn't observe any product formation. Addition of molecular sieves to the reaction had slightly increased the yields up to 5%. Aryl chalcones were prepared from 1-ketotetrahydrocarbazole and the corresponding aryl aldehydes.[159]

Scheme 14. Synthesis of carbazolo[1,2-*b*]carbazoles



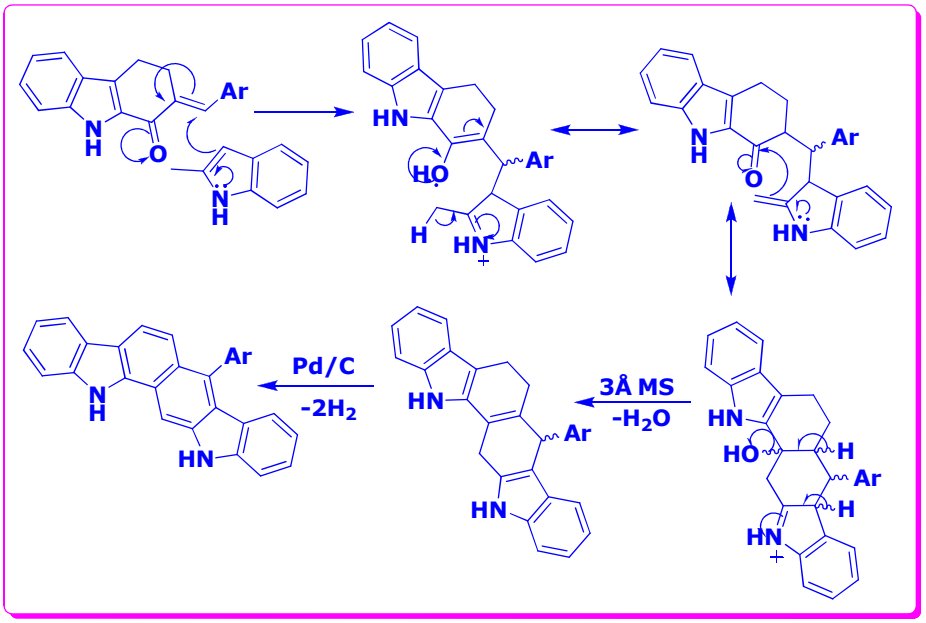


Products were obtained in moderate yields. The unreacted starting materials were recovered from the reaction mixture. The products were well characterized by

NMR spectroscopy. In the ^{1}H NMR spectra, absence of peaks in aliphatic region and two singlets around δ 12 and δ 11 correspond to the two N*H* protons clearly indicated the formation of desired products. A sharp singlet at δ 8.5 corresponds to the C*H* at 1st position, indicating the complete aromatization of the product. When we carried out the reactions with 4-cyano and 4-nitro aldehydes, we obtained a complex mixture of products. We also attempted reaction using 2-benzylindole under similar conditions, but reaction didn't proceed, probably due to steric factors.

The possible mechanism for this tandem process is explained in Scheme 2. 2-Methylindole attacks in Michael fashion on chalcone to give addition product. In presence of acid, the iminium intermediate of indole results in generation of anion at the methyl position, which attacks on the carbonyl centre. Elimination of a water molecule gives the tetrahydrocarbazole derivative, which undergoes aromatization in presence of Pd/C to furnish the desired carbazolo[1,2-*b*]carbazole.

Scheme 15. Proposed mechanism for carbazolocarbazoles



4.3. Conclusion

In conclusion, we report here a simple and facile synthesis of carbazolo[1,2-*b*]carbazole derivatives via Michael addition of 2-methylindole, condensation of methyl group with the carbonyl, dehydration followed by aromatization. This tandem process

is noteworthy as it involves easily accessible starting materials and provides carbazolocarbazoles in moderate yields.

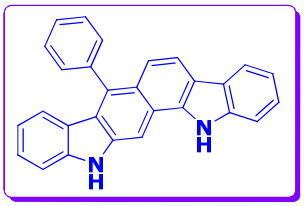
4.4. Experimental Section

General Procedure J

A mixture of 2-methylindole (1 mmol), chalcone (1 mmol), 3 Å molecular sieves (0.2 g), Pd/C (15 mg, 10%) and acetic acid (10 mL) were stirred at room temperature for 30 minutes and then transferred to autoclave under nitrogen atmosphere. The autoclave was heated at 180 ^{o}C for 48 h. After allowing to room temperature, the reaction mixture was diluted with ethyl acetate and filtered through celite. The organic layer was washed with water and concentrated *in vacuo*. The residue was purified by column chromatography using 15% hexanes in ethyl acetate as eluent to provide the desired carbazolocarbazoles. Unreacted starting materials were recovered as non-polar fractions.

9-Phenyl-2,14-dihydrocarbazolo[1,2-*b*]carbazole (272a):

The compound **272a** was prepared from **271a** and 2-methylindole by following the general procedure J. The product was obtained as a gummy solid by silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 43%

Mp: 176-178 °C

IR (KBr) ν_{max} cm^{-1}: 3412, 1602, 1466, 1317, 740, 694

^{1}H NMR (400 MHz) δ: 11.66 (s, 1H), 10.82 (s, 1H), 8.50 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.56-7.64 (m, 4H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.27-7.42 (m, 4H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.76-6.83 (m, 2H)

^{13}C NMR (100 MHz) δ: 142.8, 139.2, 139.1, 138.6, 135.6, 133.2, 133.0, 132.2, 129.7, 127.2, 125.2, 124.6, 123.9, 122.6,

122.2, 122.1, 121.2, 120.0, 119.5, 118.9, 117.5, 116.7, 116.4, 111.8, 111.1, 100.6

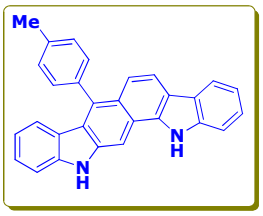
LC–MS (m/z): 382 $(M+H)^+$

Anal. Calcd. for $C_{28}H_{18}N_2$: C, 87.93; H, 4.74; N, 7.32 %

Found: C, 87.85; H, 4.81; N, 7.26 %

9-*p*-Toluyl-2,14-dihydrocarbazolo[1,2-*b*]carbazole (272b):

The compound **272b** was prepared from **271b** and 2-methylindole by following the general procedure J. The product was obtained as a gummy solid by silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 40%

Mp: 184-186 °C

IR (KBr) ν_{max} cm^{-1}: 3410, 1605, 1466, 1318, 741, 693

^{1}H NMR (400 MHz) δ: 12.30 (s, 1H), 11.58 (s, 1H), 8.56 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 3H), 7.36-7.41 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.89 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 2.55 (s, 3H)

^{13}C NMR (100 MHz) δ: 142.8, 139.2, 137.4, 136.8, 135.6, 134.6, 130.1, 130.1, 127.0, 125.6, 124.5, 124.0, 122.9, 122.4, 122.3, 121.3, 120.0, 119.4, 118.6, 117.9, 116.3, 116.3, 111.7, 110.9, 100.2, 21.5

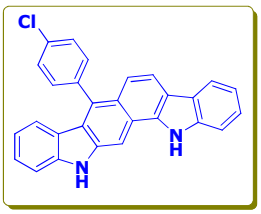
LC–MS (m/z): 397 $(M+H)^+$

Anal. Calcd. for $C_{29}H_{20}N_2$: C, 87.85; H, 5.08; N 7.07 %

Found: C, 87.69; H, 5.14; N, 7.15 %

9-*p*-Chlorophenyl-2,14-dihydrocarbazolo[1,2-*b*]carbazole (272c):

The compound **272c** was prepared from **271c** and 2-methylindole by following the general procedure J. The product was obtained as a gummy solid by silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 47%

Mp: 200-202 °C

IR (KBr) ν_{max} cm^{-1}: 3416, 1604, 1491, 1390, 1317, 1240, 1086, 1014, 802, 744

^{1}H NMR (400 MHz) δ: 12.29 (s, 1H), 11.58 (s, 1H), 8.55 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.18-7.52 (m, 7H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H)

^{13}C NMR (100 MHz) δ: 142.8, 139.2, 139.1, 138.6, 135.5, 133.2, 133.0, 132.2, 129.7, 127.2, 125.2, 124.7, 123.9, 122.5, 122.1, 121.2, 120.0, 119.5, 118.9, 117.5, 116.7, 116.4, 111.8, 111.1, 100.6

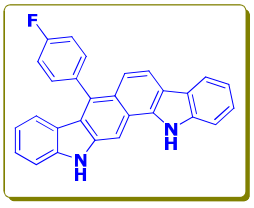
LC–MS (m/z): 417 (M+H)

Anal. Calcd. for $C_{28}H_{17}ClN_2$: C, 80.67; H, 4.11; N, 6.72 %

Found: C, 80.75; H, 4.16; N, 6.65 %

9-*p*-Fluorophenyl-2,14-dihydrocarbazolo[1,2-*b*]carbazole (272d):

The compound **272d** was prepared from **271d** and 2-methylindole by following the general procedure J. The product was obtained as a gummy solid by silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 40%

Mp: 154-156 °C

IR (KBr) v_{max} cm^{-1}: 3414, 1600, 1492, 1387, 1316, 1241, 1084

^{1}H NMR (400 MHz) δ: 12.30 (s, 1H), 11.60 (s, 1H), 8.56 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.56-7.54 (m, 4H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.41-7.38 (m, 2H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H)

^{13}C NMR (100 MHz) δ: 142.8, 139.2, 139.1, 138.6, 135.6, 133.2, 133.0, 132.2, 129.7, 127.2, 125.2, 124.6, 123.9, 122.5, 122.2, 121.2, 120.0, 119.5, 118.8, 117.5, 116.7, 116.4, 111.8, 111.0, 100.6

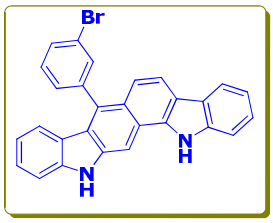
LC–MS (m/z): 401 (M+H)

Anal. Calcd. for $C_{28}H_{17}FN_2$: C, 83.98; H, 4.28; N, 7.00 %

Found: C, 83.84; H, 4.37; N, 6.96 %

9-(3-Bromophenyl)-2,14-dihydrocarbazolo[1,2-*b*]carbazole (272e):

The compound **272e** was prepared from **271e** and 2-methylindole by following the general procedure J. The product was obtained as a gummy solid by silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 42%

Mp: 146-148 °C

IR (KBr) v_{max} cm^{-1}: 3416, 1604, 1491, 1390, 1317, 1240, 1086, 1014, 802, 744

^{1}H NMR (400 MHz) δ: 12.33 (s, 1H), 11.65 (s, 1H), 8.60 (s, 1H), 8. 10 (d, *J* = 5.6 Hz, 1H), 7.97 (d, *J* = 6.4 Hz, 1H), 7.73-7.68 (m, 3H), 7.57-7.53 (m, 2H), 7.40 (m,

2H), 7.26 (d, *J* = 6.8 Hz, 1H), 7.21 (m, 2H), 6.93 (m, 1H), 6.76 (d, *J* = 6.0 Hz, 1H)

^{13}C NMR (100 MHz) δ: 142.9, 142.3, 139.2, 139.1, 135.6, 132.9, 132.6, 131.7, 131.6, 131.3, 129.5, 127.2, 125.1, 124.6, 124.0, 122.7, 122.5, 122.1, 121.3, 120.0, 119.5, 118.8, 117.4, 116.7, 116.4, 111.8, 111.1, 100.9

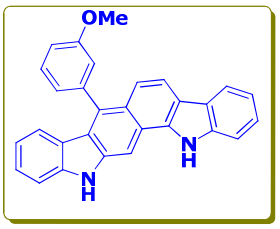
LC–MS (m/z): 461 (M), 463 (M+2)

Anal. Calcd. for $C_{28}H_{17}BrN_2$: C, 72.89; H, 3.71; N, 6.07 %

Found: C, 72.75; H, 3.76; N, 6.05 %

9-(3-Methoxyphenyl)-2,14-dihydrocarbazolo[1,2-*b*]carbazole (272f):

The compound **272f** was prepared from **271f** and 2-methylindole by following the general procedure J. The product was obtained as a gummy solid by silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 39%

Mp: 130-132 °C

IR (KBr) ν_{max} cm^{-1}: 3416, 1604, 1491, 1390, 1317, 1240, 1086, 1014, 802, 744

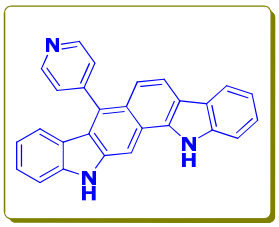
^{1}H NMR (400 MHz) δ: 12.29 (s, 1H), 11.58 (s, 1H), 8.56 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.67 (t, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H) 7.41-7.33 (m, 3H), 7.24-7.21 (m, 2H), 7.10-7.06 (m, 2H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 3.83 (s, 3H)

^{13}C NMR (100 MHz) δ: 142.8, 141.2, 139.2, 139.17 (merged), 135.6, 134.3, 130.7, 127.0, 125.2, 124.5, 124.0, 122.8, 122.5, 122.4, 122.1, 121.3, 120.0, 119.4, 118.7,

	117.9, 116.4, 116.3, 115.6, 113.9, 111.7, 110.9, 100.3, 55.7
LC–MS (m/z):	413 (M+H)
Anal. Calcd. for $C_{29}H_{20}N_2O$:	C, 84.44; H, 4.89; N, 6.79 %
Found:	C, 84.45; H, 4.66; N, 6.65 %

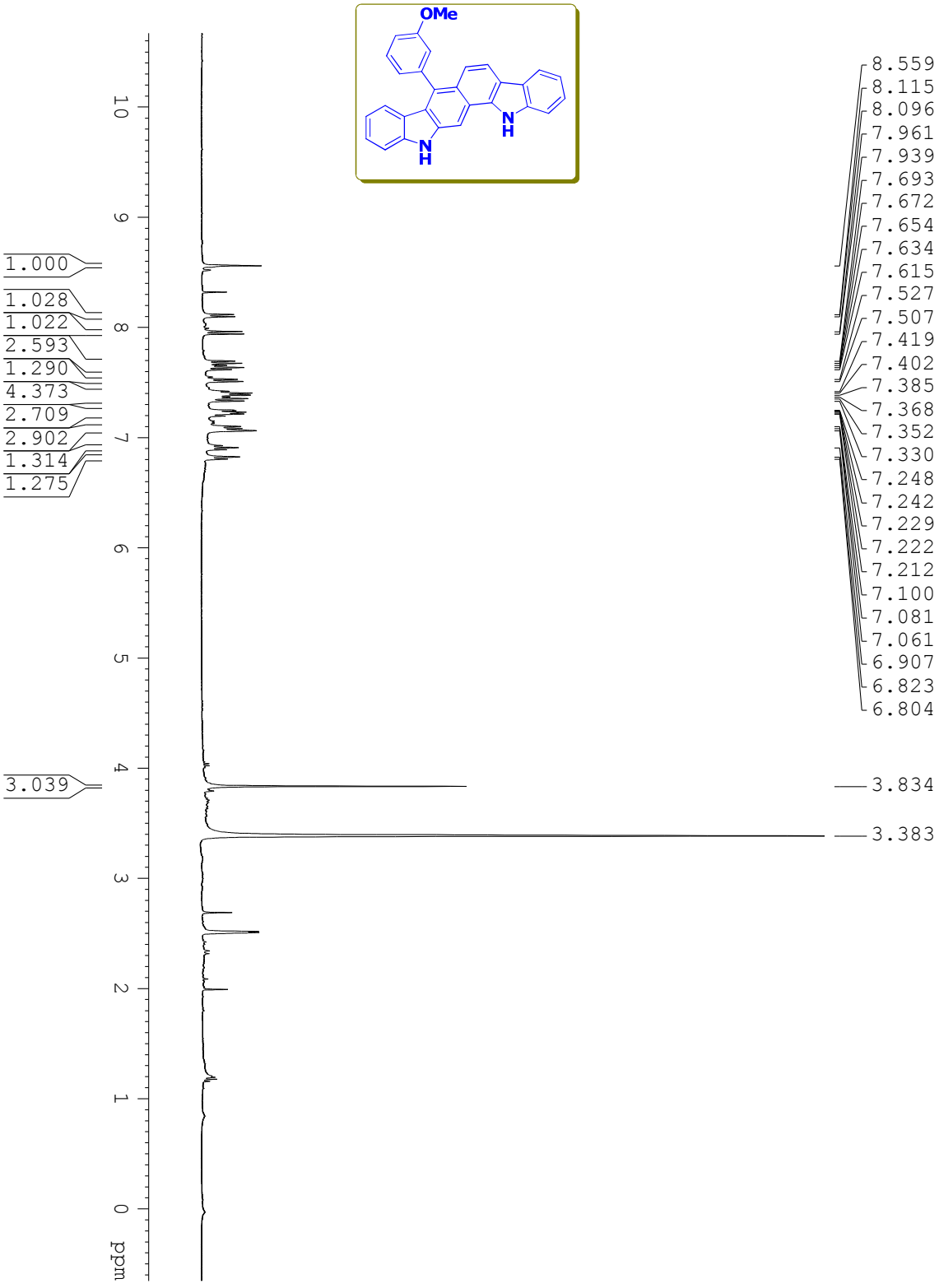
9-(4-Pyridyl)-2,14-dihydrocarbazolo[1,2-*b*]carbazole (272g):

The compound **272g** was prepared from **271g** and 2-methylindole by following the general procedure J. The product was obtained as a gummy solid by silica gel column chromatography with 15% ethyl acetate in hexanes.

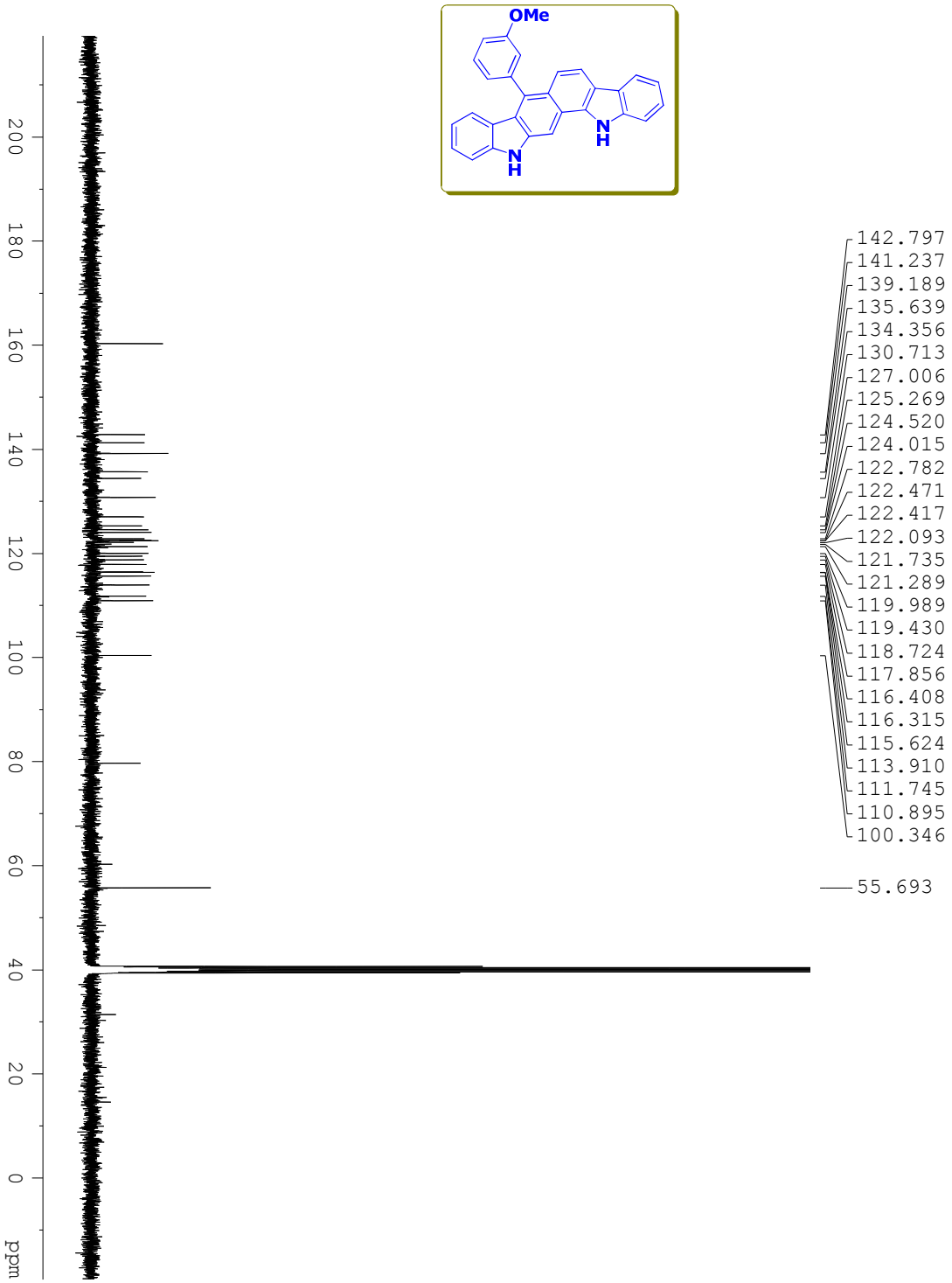


Yield:	35%
Mp:	146-148 °C
IR (KBr) ν_{max} cm^{-1}:	3416, 1604, 1491, 1390, 1317, 1240, 1086, 1014, 802, 744
^{1}H NMR (400 MHz) δ:	12.30 (s, 1H), 11.60 (s, 1H), 8.56 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.56-7.50 (m, 5H), 7.42-7.37 (m, 2H), 7.26 (d, J = 9.2 Hz, 1H), 7.23-7.19 (m, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H)
^{13}C NMR (100 MHz) δ:	142.8, 139.2, 139.1, 135.6, 132.4, 132.3, 127.1, 125.5, 124.5, 124.0, 122.7, 122.3, 122.3, 121.2, 120.0, 119.4, 118.8, 117.6, 116.6, 116.5, 116.4, 116.3, 111.7, 111.0, 100.5
LC–MS (m/z):	384 (M+H)
Anal. Calcd. for $C_{27}H_{17}N_3$:	C, 84.57; H, 4.47; N, 10.96 %
Found:	C, 84.75; H, 4.36; N, 10.75 %

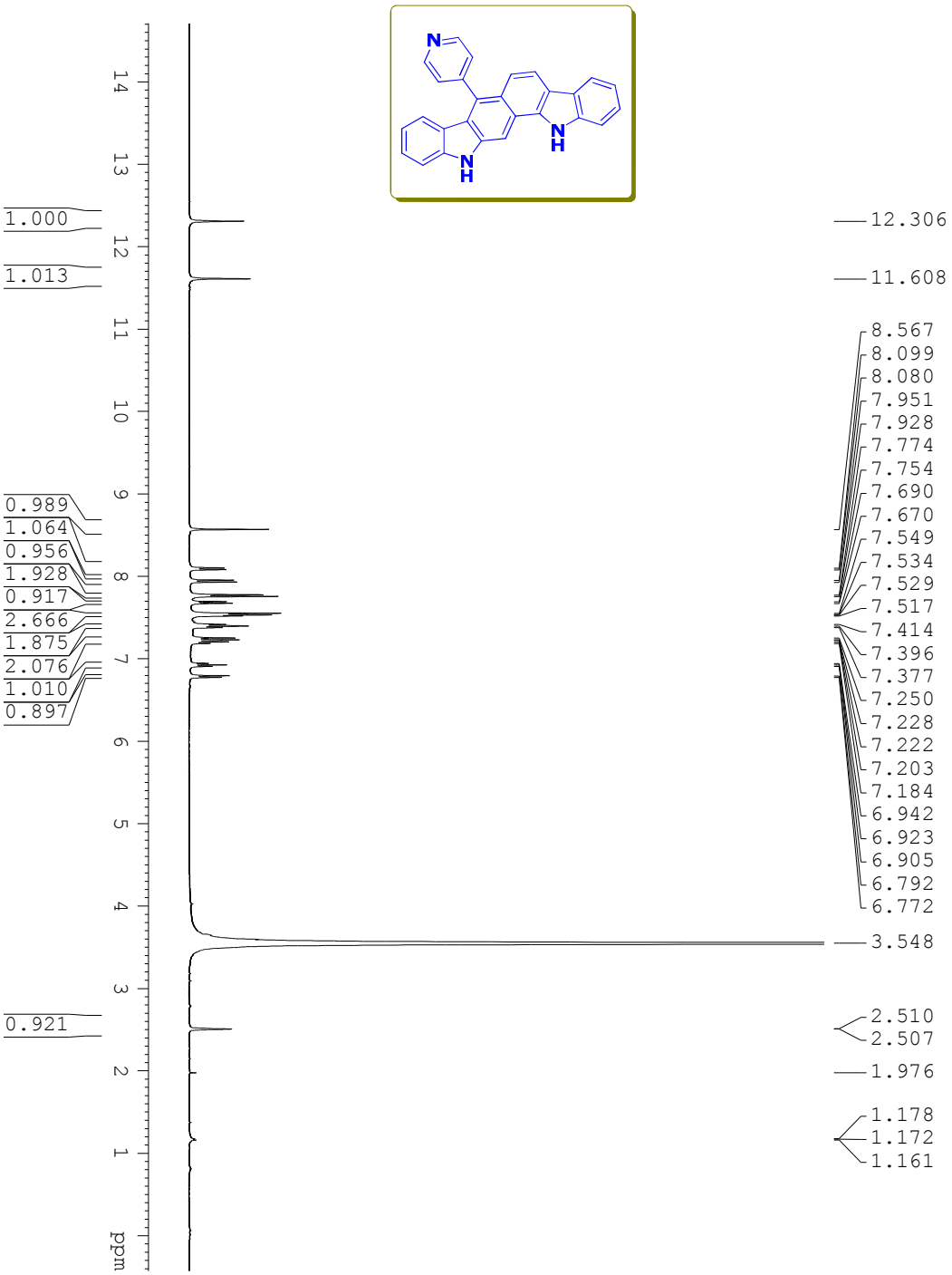
Spectrum No: 33, ^{1}H NMR of 272f



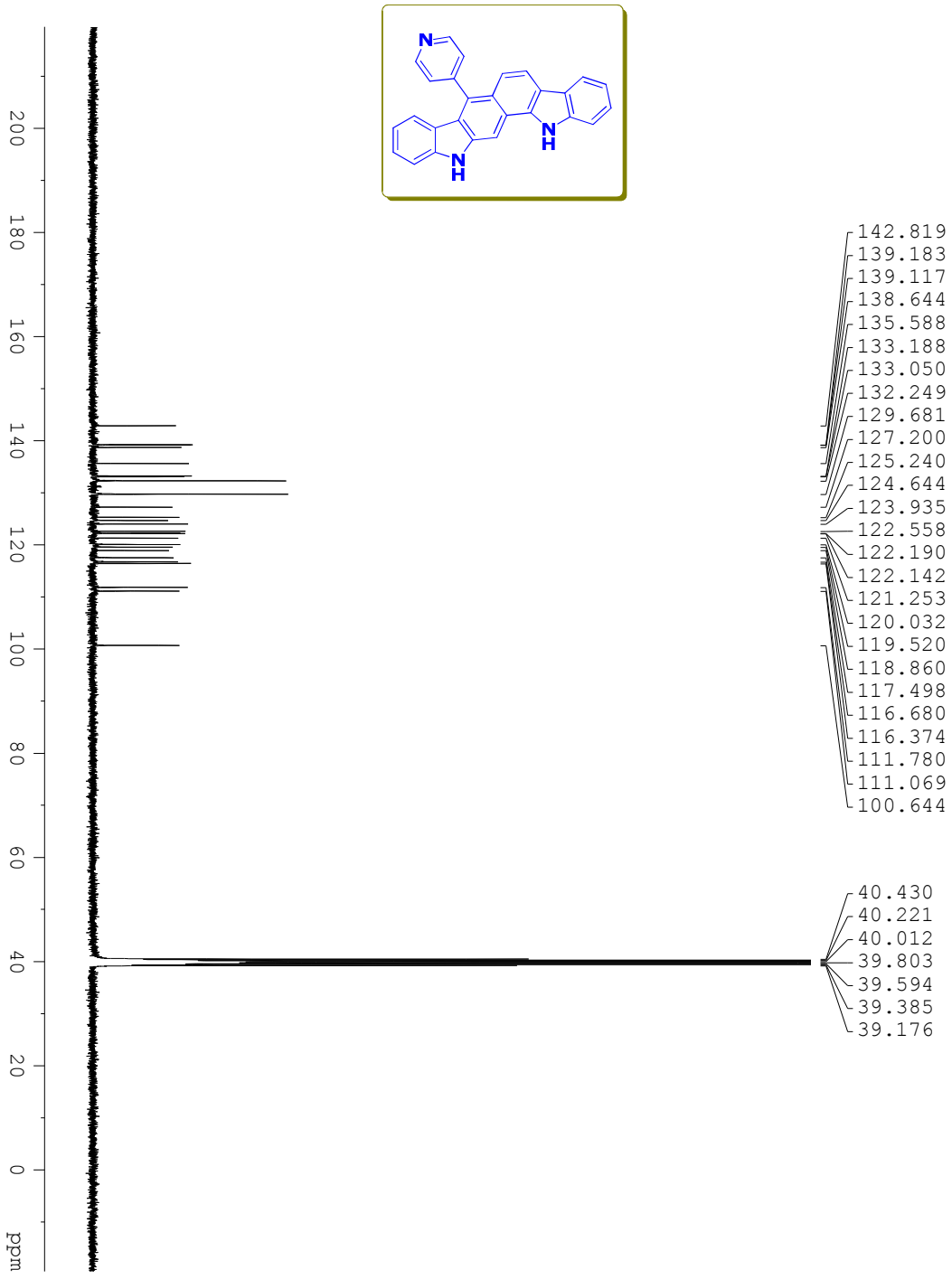
Spectrum No: 34, ^{13}C NMR of 272f



Spectrum No: 35, ^{1}H NMR of 272g



Spectrum No: 36, ^{13}C NMR of 272g



4.5. References

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Conclusions

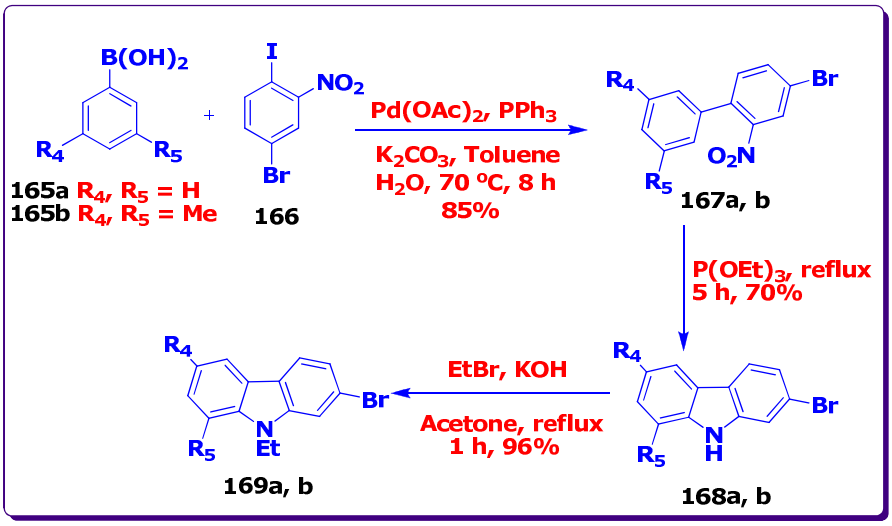
We have made significant contribution to the synthesis of various heteroarylcarbazole derivatives, which are known to be biologically active. We successfully synthesized some important carbazole molecules, which can be useful as good building blocks for the synthesis of derivatives of carbazoles. We achieved considerable success in our objectives on the synthesis of various heteroarylcarbazole derivatives.

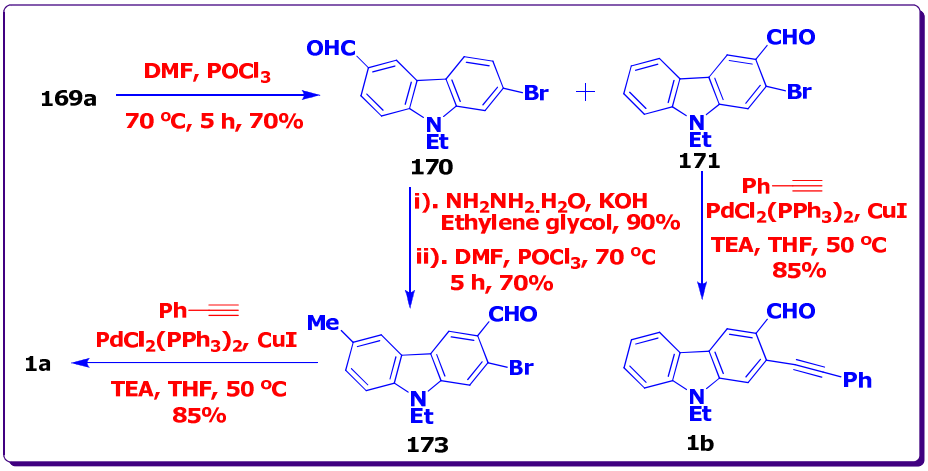
- We have developed a novel and efficient methodology for the synthesis of diverse and highly functionalized ellipticinium and ellipticine derivatives in excellent yields. Many carbazole intermediates with potential synthetic scope are synthesized for the first time. An efficient, metal-free synthesis of benzimidazo[2,1-*a*]ellipticine derivatives via a tandem inter- and intramolecular cyclization; 5-*endo* cyclization, oxidative aromatization followed by 6-*endo* cyclization in good yields is established. We successfully characterized and analyzed the formation of a single regioisomer in case of diaminopyridines. The scope of this synthetic route is general and all the products are obtained in excellent yields. The overall modularity of this process is noteworthy. It is anticipated that this methodology can contribute for the development of selective anti-cancer agents with pyrido[4,3-*b*]carbazole skeleton.
- We have achieved a simple and facile synthesis of new pyranocarbazole derivatives from easily accessible *O*-propargylated carbazoles employing iodocyclization in good yields. This process is eco-friendly and the iodo-products obtained can be used as further building blocks. An interesting product with nitromethyl group insertion is observed.
- We developed a new, easy and efficient synthesis of 3-(3-nitrochromenyl)carbazoles, 3,6-*bis*-(3-nitrochromenyl)carbazoles and 3-(3-nitroquinolyl)carbazoles under solvent free conditions in moderate to quantitative yields. The procedure evidences from several advantages such as short reaction time, no need for organic solvents and a series of reactions has been performed in one-pot way. Thus, our method has advantages from both environmental and economic point of view for the synthesis of biologically important derivatives of carbazole, quinolines and chromenes.

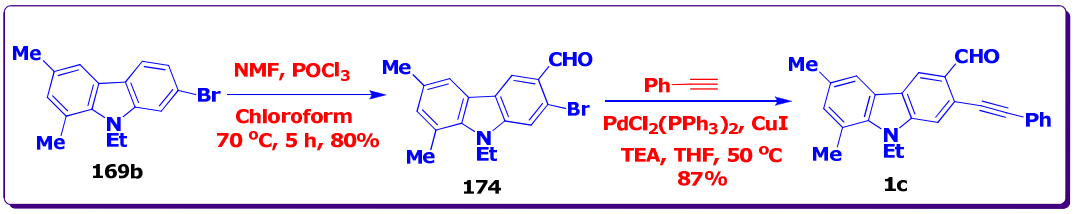
- We established a simple and facile synthesis of carbazolo[1,2-*b*]carbazole derivatives via Michael addition of 2-methylindole, condensation of methyl group with the carbonyl, elimination of water molecule followed by aromatization. This tandem process is noteworthy as it involves easily accessible starting materials and provides carbazolocarbazoles in moderate yields.

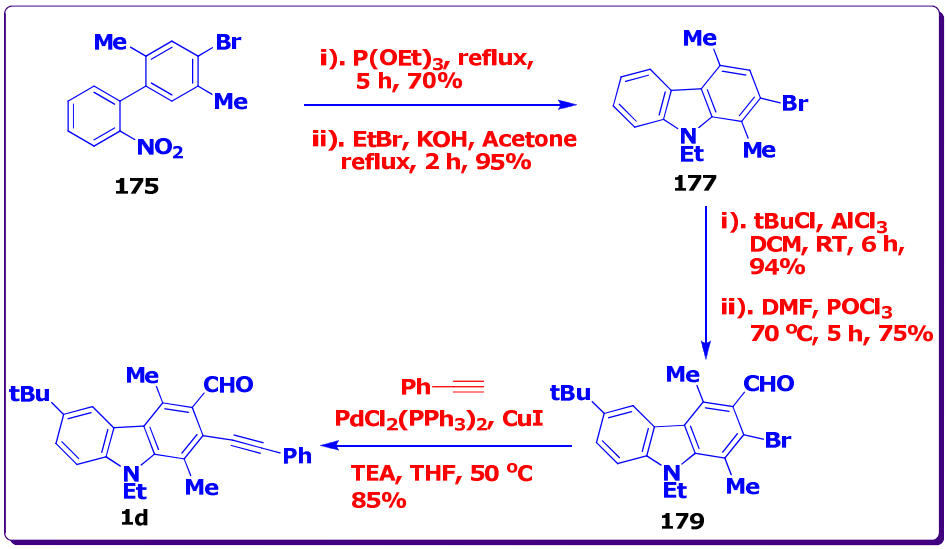
Graphical Abstracts

Chapter 1: Synthesis of Functionalized Ellipticinium, Ellipticine and Benzimidazo[2,1-*a*] ellipticine Derivatives





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Br
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NO2
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5 h, 70%
ii). EtBr, KOH, Acetone
reflux, 2 h, 95%
Me
Br
N
Et
Me
177
i). tBuCl, AlCl3
DCM, RT, 6 h,
94%
ii). DMF, POCl3
70 °C, 5 h, 75%
tBu
Me
CHO
Br
N
Et
Me
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Ph
PdCl2(PPh3)2, CuI
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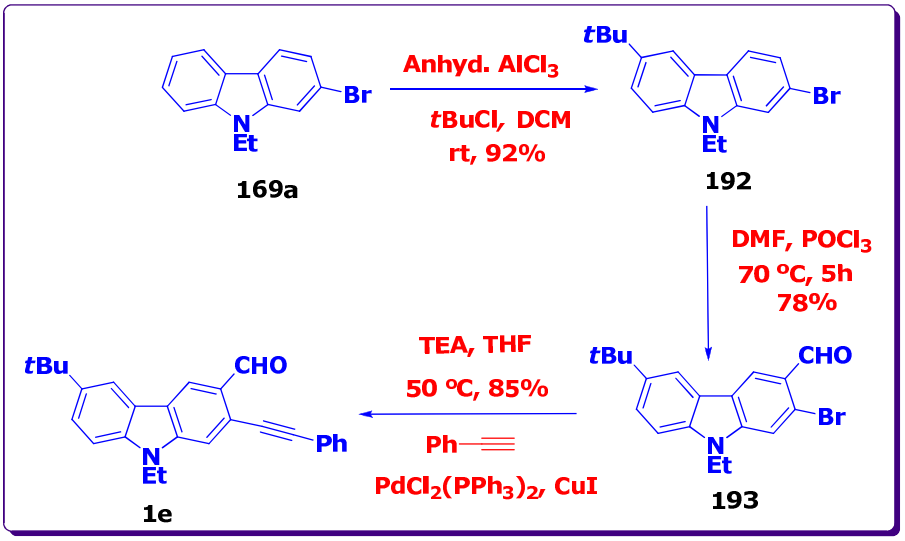
tBu
Me
CHO
Ph
N
Et
Me
1d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Et
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Anhyd. AlCl3
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rt, 92%
tBu
Br
N
Et
192
DMF, POCl3
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78%
TEA, THF
50 °C, 85%
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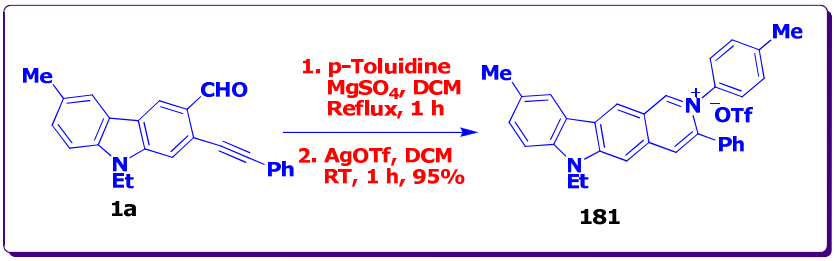
CHO
Br
N
Et
193
tBu
CHO
Ph
N
Et
1e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Me
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OTf
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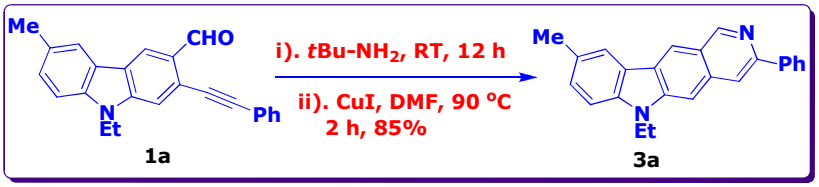
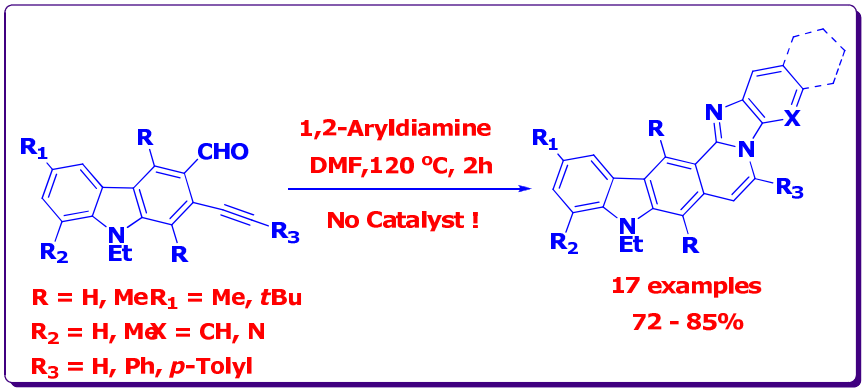
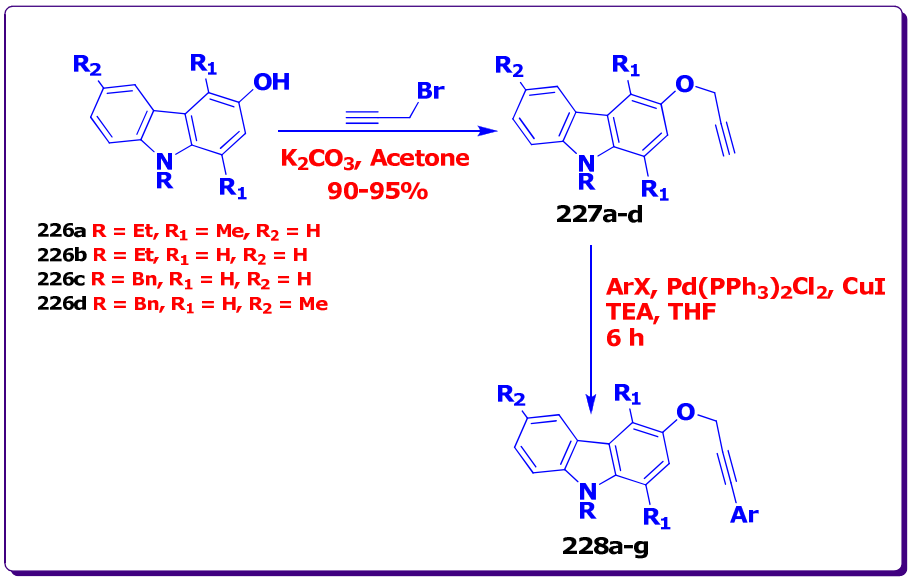
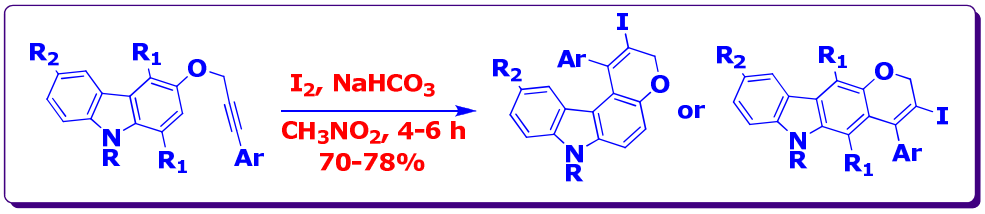
N
Et
181

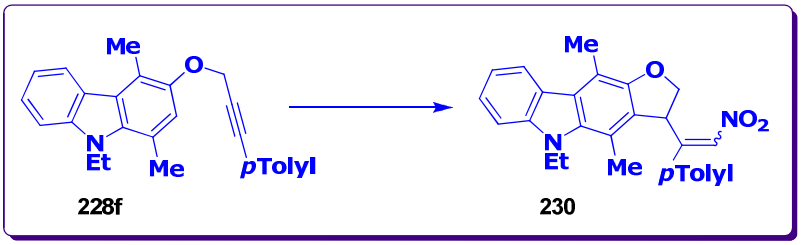




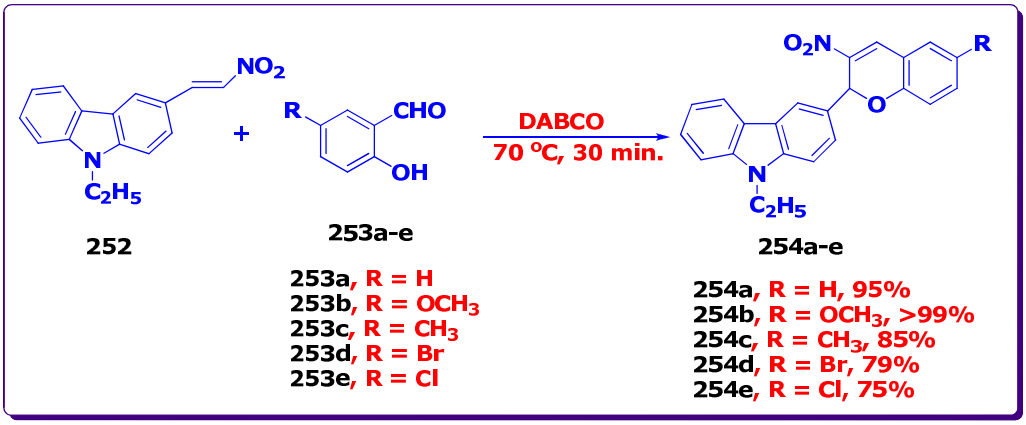
Chapter 2: Synthesis of Pyrano[2,3-*c*]carbazoles, Pyrano[3,2-*b*]carbazoles and Furo[3,2-*b*]carbazole Derivatives via Iodocyclization

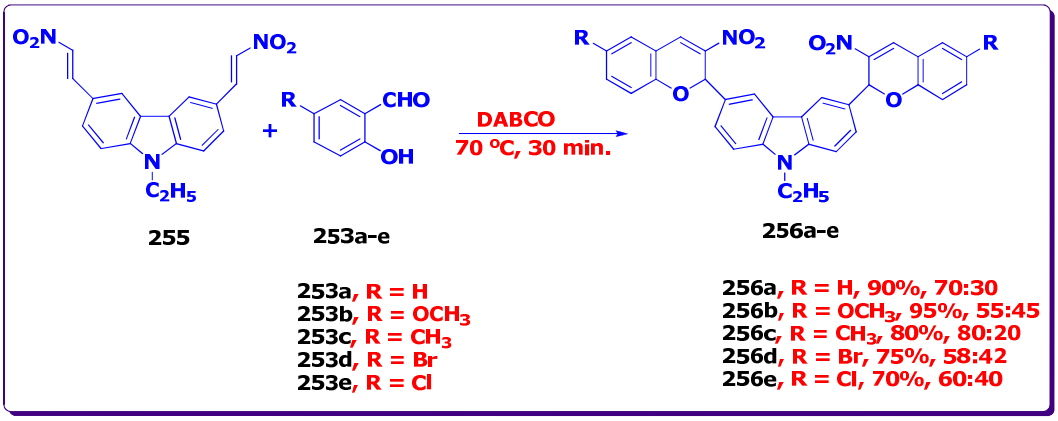


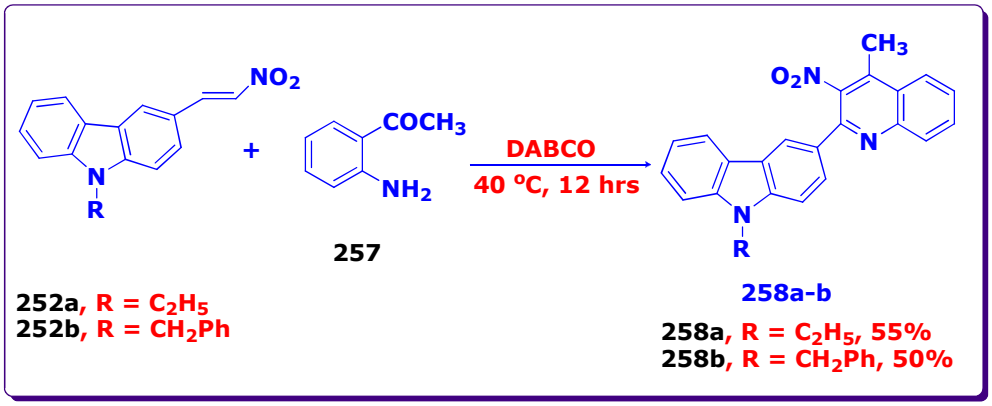




Chapter 3: Synthesis of 3-chromenylcarbazoles, 3,6-*bis*-(chromenyl)carbazoles and 3-quinolylcarbazoles







Chapter 4: A Tandem Route to the Synthesis of Carbazolo[1,2-*b*]carbazoles