SYNTHESIS OF HETEROARYL-ANNULATED CARBAZOLES AND INDOLES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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JUNE 2010

STATEMENT

I hereby declare that the matter embodied in this thesis entitled "**SYNTHESIS OF HETEROARYL-ANNULATED CARBAZOLES AND INDOLES**" 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

(RAMU MEESALA)

CERTIFICATE

This is to certify that the work described in this thesis entitled "**SYNTHESIS OF HETEROARYL-ANNULATED CARBAZOLES AND INDOLES**" has been carried out by **RAMU MEESALA** 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. Synthesis of new diheteroarylcarbazoles: a facile and simple route of 3,6-di(pyrazol-4-yl)carbazoles
   Ramu Meesala and Rajagopal Nagarajan, ***Tetrahedron Lett***. **2006**, *47*, 7557.

2. A rapid intramolecular imino Diels-Alder reaction of aminoanthraquinones with citronellal or prenylated salicylaldehydes: substituent effect on changing the reaction pathway from Diels–Alder to ene-type cyclization
   Vikram Gaddam, **Ramu Meesala** and Rajagopal Nagarajan, ***Synthesis*** **2007**, 2503.

3. Synthesis of new heteroaryldi(diindolyl)methanes: colorimetric detection of DNA by di(diindolylmethyl)carbazoles
   Ramu Meesala and Rajagopal Nagarajan, ***J. Chem. Sci*****. 2009**, *121*, 183.

4. A rapid and efficient entry to synthesis of quino and chromenocarbazoles via Ullmann-Goldberg condensation
   Ramu Meesala and Rajagopal Nagarajan, ***Tetrahedron*** **2009**, *65*, 6050.

5. A short route to the synthesis of pyrroloacridines via Ullmann-Goldberg condensation
   Ramu Meesala and Rajagopal Nagarajan, ***Tetrahedron Lett*****. 2010**, *51*, 422.

6. Cu-catalyzed aerobic oxidative coupling of aminocarbazoles and aminoindoles: unexpected synthesis of diindolophenazines and dipyrrolophenazines
   Ramu Meesala and Rajagopal Nagarajan (*Communicated*).

Posters and Presentations

1. Presented a poster entitled "Synthesis of di(diindolylmethyl)carbazole derivatives" in the CRSI sponsored "***9th National Symposium in Chemistry***" organized by the Department of Chemistry, University of Delhi, during February 1-4, 2007.

2. Presented a poster entitled "Synthesis of new diheteroarylcarbazoles: a facile and simple route of 3,6-di(pyrazol-4-yl)carbazoles" in 3rd in-house symposium "***Chemfest-2006***" held at University of Hyderabad, Hyderabad, India on March 4, 2006.

3. Presented a poster on "Synthesis of new heteroaryldi(diindolyl)methanes: colorimetric detection of DNA by di(diindolylmethyl)carbazoles" in "***5th Singapore-India collaborative and cooperative chemistry symposium***", held at University of Hyderabad, Hyderabad, India on February 20-21, 2009.

4. Given a flash oral presentation on "A rapid and efficient entry to synthesis of quino and chromenocarbazoles via Ullmann-Goldberg condensation" in 6th in-house symposium "***Chemfest-2009***" held at University of Hyderabad, Hyderabad, India, on March 7-9, 2009.

5. Presented a poster on "Cu-catalyzed aerobic oxidative coupling of aminocarbazoles and aminoindoles: a new and unexpected synthesis of diindolophenazines and dipyrrolophenazines" in 7th in-house symposium "***Chemfest-2010***" held at University of Hyderabad, Hyderabad, India on January 8-9, 2010.

Acknowledgements

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

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

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

I gratefully acknowledge the help provided by the technical and office staff of the School of Chemistry. I thank Mr. Bhaskara Rao, Mr. Satyanarayana, and Smt. Vijaya Laxmi for their help in recording NMR spectra. I also thank Mr. Prasad, Mr. Sambhasiva Rao, Mr. M. Shetty, Mr. Sudhakar, Mr. Santhosh, Mr. Anand, Mr. A. R. Shetty, Mr. Joseph, Mr. Sai, Mr. Sharma and Mr. Jayaram for their cooperation.

I also take this opportunity in thanking all my childhood teachers, Mrs. Bharati, Mr. Satyam, Mr. Ramurthy, Dr. Seeta Rama Raju, Mr. Kodandaram, Mr. Nabhikhan.

I would like to express my special thanks to my labmate Chaitanya for his helpful discussions during my research. I would also wish to thank my friendly and cooperative labmates Vikram, Sreenivas, Satish, Viji, Ramesh and Rama Raju for their help on various aspects.

My stay on this campus has been pleasant with the association of many friends. In this context, I would like to thank my M.Sc. classmates Sekhar, Satish, Ramakumar, Phanipavan, Venu, DS, Nagaraju, Venket, Sreedhar, Naresh and Koti. I am also thankful to Dr. Narahari, Dr. Ramesh Reddy, Dr. Bipul, Kishore, Venket Narayana, Anji, Ramesh, Ramasuresh, Vijay, Venky, Ramesh, Nagarjuna, Tanmay,

Ranjit, GDP, Rambabu, Sanjeev, Mallesh, Kishore, Bharat, Sreenu, Ganesh, Ravi, Gupta, Hariprasad, Vanajakshi, Anand, Kishore and Nagarjuna.

I would like to express my thanks to Subbu anna who helped and encouraged me during my graduation at A. P. Residential Degree College, Nagarjuna Sagar.

The unconditional love of my Amma & Nanna and their blessings made me what I am today and I owe everthing to them. I would like to thank all my family members Lakshmi akka, Padmakka, Pedda akka, Annayya, late Ramu Naidu uncle, Ramanamma aunty, Lakshman mama, Parvathi pinny, Kala chelli, Jaya akka, Ramesh Naidu and Venky anna. I am also thankful to my best friends Thaviti and Ramesh Naidu.

I would like to express my special thanks to my beloved Srinu mama and Sunny mama for their support during my study career.

.....Ramu

.....Dedicated to Amma and Nanna

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List of Abbreviations

Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
DCM	Dichloromethane
DMF	*N,N'*-dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Eq.	Equation
i-Pr	*iso*-propyl
LDA	Lithium Diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
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

Heteroaryl-annulated carbazoles

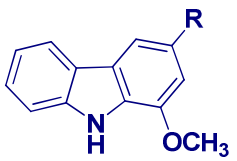
Carbazole was isolated first from coal tar in 1872 by Graebe and Glazer.[1] In 1965, Chakraborty *et al*. described the isolation and antibiotic properties of murrayanine from *Murraya koenigii* Spreng.[2] In India, the leaves of this small tree (known as currypatta or curry-leaf tree) are used in the preparation of an Indian food curry. The isolation of murrayanine was the first report of a naturally occurring carbazole alkaloid. Since then there has been a strong interest in this area among chemists and biologists due to the intriguing structural features and promising biological activities exhibited by many carbazole alkaloids. The explosive growth of carbazole chemistry is emphasized by a large number of monographs, accounts and reviews.[3-4]

Most carbazole alkaloids have been isolated from the taxonomically related higher plants of the genus *Murraya*, *Glycosmis* and *Clausena* from the family Rutaceae. The genus *Murraya* represents the richest source of carbazole alkaloids from terrestrial plants. The lower plants from which carbazole alkaloids have been isolated include several different *Streptomyces* species. Further natural sources for carbazole alkaloids are, for example, the blue-green algae *Hyellacaespitosa*, *Aspergillus* species*, Actinomadura* species and the ascidian *Didemnum granulatum*.

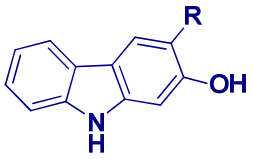
The isolation of several 3-methylcarbazole derivatives from higher plants and of carbazole from *Glycosmis pentaphylla* shows that the aromatic methyl group can be eliminated oxidatively from the key intermediate 3-methylcarbazole via -CH_2OH, -CHO and -COOH functionalities in biosynthetic pathway.[5] The isolation of 3-methylcarbazole from the genus *Clausena*, the co-occurrence of murrayafoline A **1**, koenoline **2**, murrayanine **3** and mukoeic acid **4** in *M. koenigii*, as well as the subsequent isolation of mukonine **5** and mukonidine **8** and the discovery of 2-hydroxy-3-methylcarbazole **6** and mukonal **7** in *M. koenigii* support the hypothesis of biomimetic hydroxylation of 3-methylcarbazole.[6] Congeners that differ in the oxidation state of the C-3 methyl group, i.e. -CH_2OH, -CHO, -COOH and -COOMe, were found for various alkaloids, a fact which indicates an *in vivo* oxidation of carbazole alkaloids (Figure 1).

The occurrence of heptaphylline[7] **9** and murrayacine[8] **10** in *Clausena heptaphylla* is circumstantial evidence for the origin of the pyran ring from the prenylated congener. This explains the formation of pyranocarbazoles from 2-hydroxy-3-methylcarbazole as shown by Popli and Kapil. The co-occurrence of 2-hydroxy-3-methylcarbazole[9] **6**, mukonal[10] **7**, and mukonidine[11] **8** provides clear evidence for the *in vivo* oxidation of the methyl group in 2-hydroxy-3-methylcarbazole **6**. All these findings strongly suggest 3-methylcarbazole as the key precursor for the carbazoles isolated from higher plants.

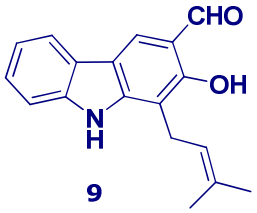
Figure 1



1 R = CH_3, Murrayafoline A
2 R = CH_2OH, Koenoline
3 R = CHO, Murrayanine
4 R = COOH, Mukoeic acid
5 R = $COOCH_3$, Mukonine

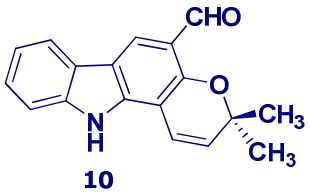


6 R = CH_3, 2-Hydroxy-3-methylcarbazole
7 R = CHO, Mukonal
8 R = $COOCH_3$, Mukonidine



9

Heptaphylline

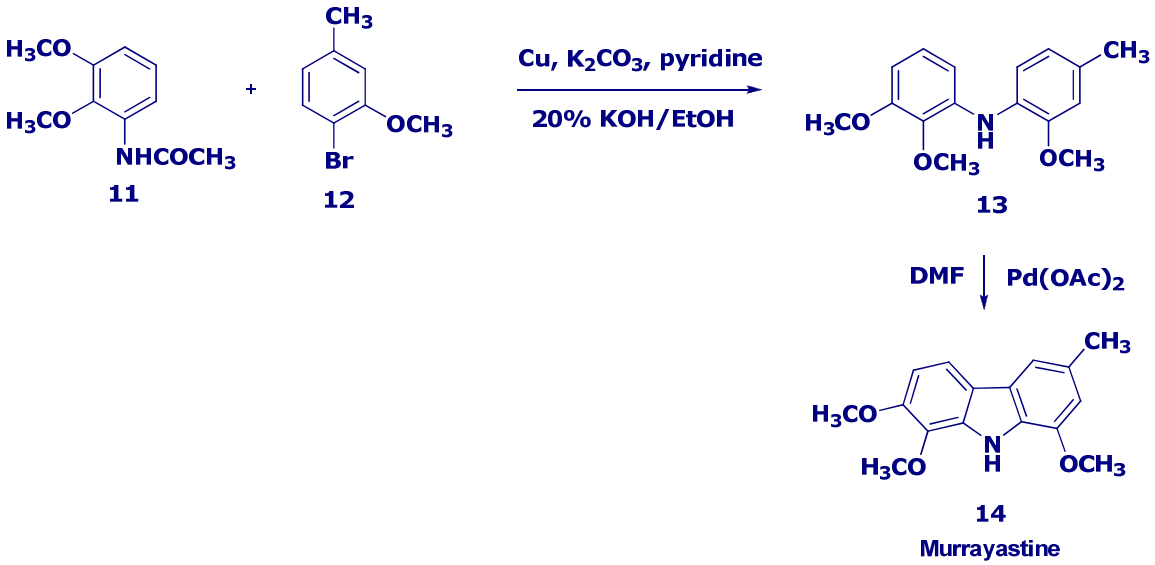


10

Murrayacine

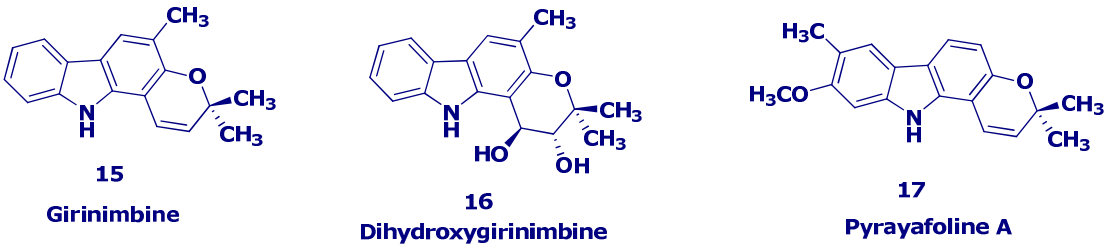
Ullmann-Goldberg coupling of *N*-acetyl-2,3-dimethoxyaniline **11** and 2-bromo-5-methylanisole **12** with Cu and K_2CO_3 in pyridine followed by hydrolysis with 20% KOH/EtOH provided the diarylamine **13**. The cyclization of **13** with palladium(II) acetate in DMF afforded murrayastine **14** as shown in Eq. 1.[12]

Eq. 1



The pyranocarbazole alkaloids were all obtained from terrestrial plants (Figure 2). Girinimbine **15** has a pyrano[3,2-*a*]carbazole framework and was isolated first from the stem bark of *Murraya koenigii*.[13] Subsequently, girinimbine was obtained from the roots of *Clausena heptaphylla*.[14] Dihydroxygirinimbine[15] **16** and pyrayafoline A[16] **17** were obtained from *Murraya euchrestifolia*. The pyran ring of dihydroxygirinimbine **16** contains a *trans*-1,2-diol moiety. However, the absolute configuration is not known.

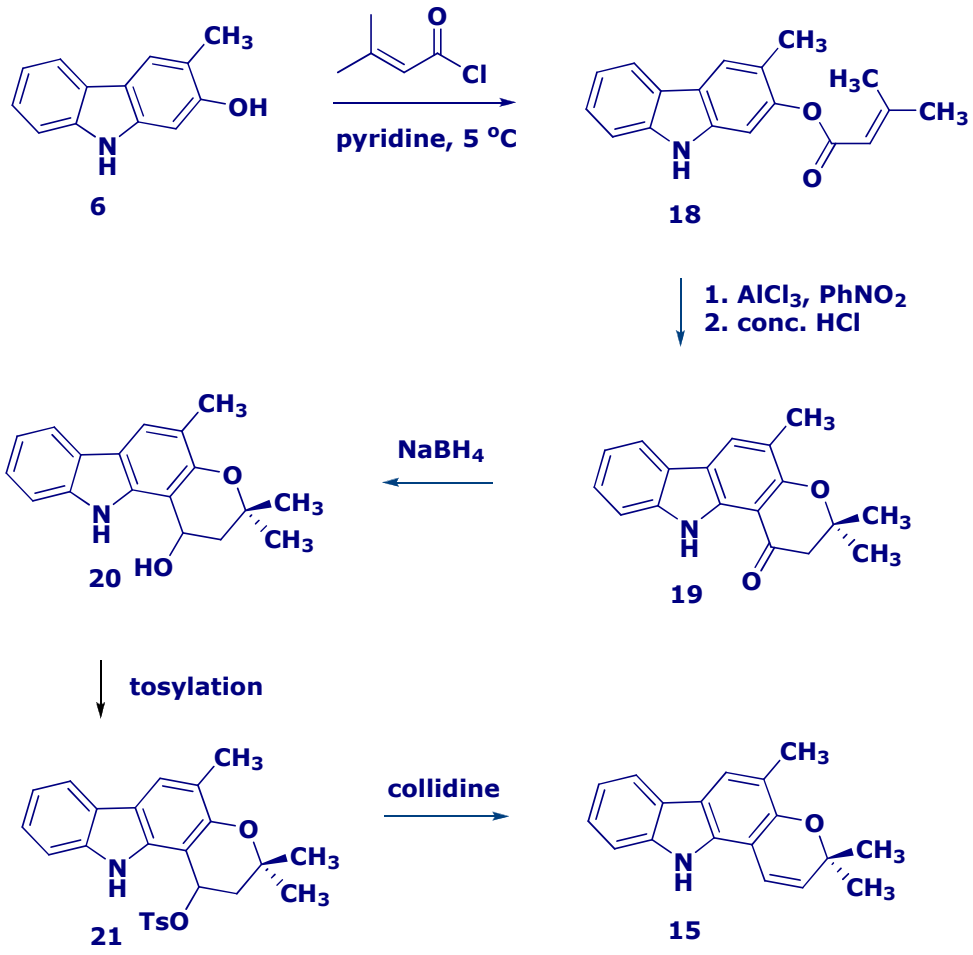
Figure 2



In 1971, Chakraborty and Islam reported the synthesis of girinimbine **15** from 2-hydroxy-3-methylcarbazole[17] **6** by annulation of a 2,2-dimethyl-Δ^3-pyran ring. The acylation of 2-hydroxy-3-methylcarbazole **6** with *β*,*β*′-dimethylacryloyl

chloride afforded the acyl derivative **18**. A Fries rearrangement of compound **18** led to the indolochromanone **19**. Twenty-five years later, Wu *et al*. isolated compound **19** from nature and named it euchrestifoline. Finally, the indolochromanone **19** was transformed to girinimbine **15** by the sequence reduction, tosylation and elimination as shown in Eq. 2.[18]

Eq. 2

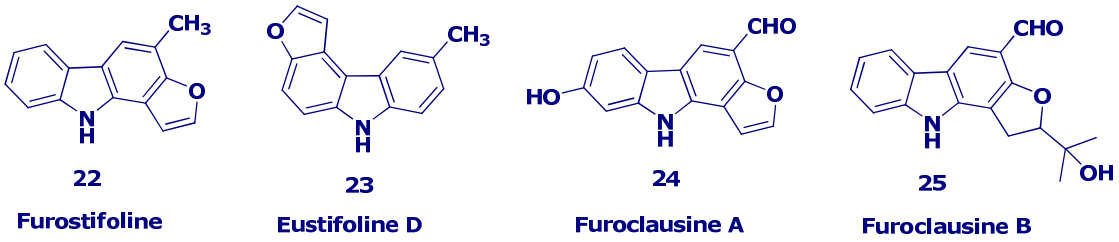


Over the past years, the rapidly growing class of heteroaryl-condensed carbazoles began to attract increasing interest because of their broad spectrum of useful biological activities.[19] To provide an overview on the heteroaryl-annulated carbazole derivatives, these compounds can be classified into [*a*]-annulated, [*b*]-annulated and [*c*]-annulated furo-, thieno- and pyrrolocarbazoles respectively. 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.

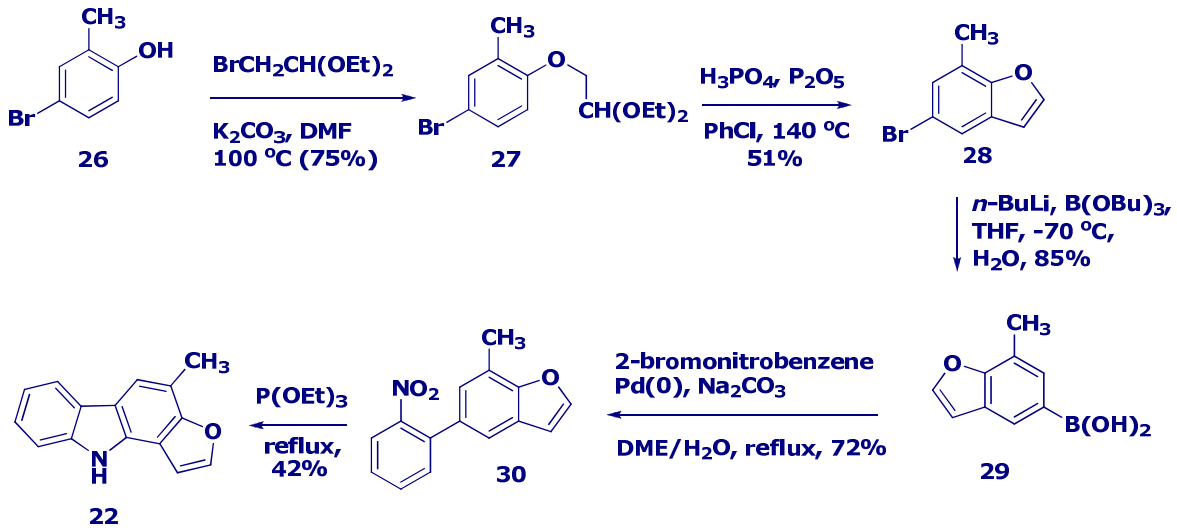
In 1990, Ito and Furukawa isolated two new members of tetracyclic carbazole alkaloids, furostifoline **22** and the isomeric eustifoline D **23** from *M. euchrestifolia* Hayata (Figure 3).[20] They were the first furocarbazole alkaloids obtained from natural sources. In the late 1990s, Wu *et al*. described the isolation and structural elucidation of two further furocarbazole alkaloids, furoclausine A **24** and B **25** from the root bark of *C. excavata* (Figure 3).[21]

Figure 3



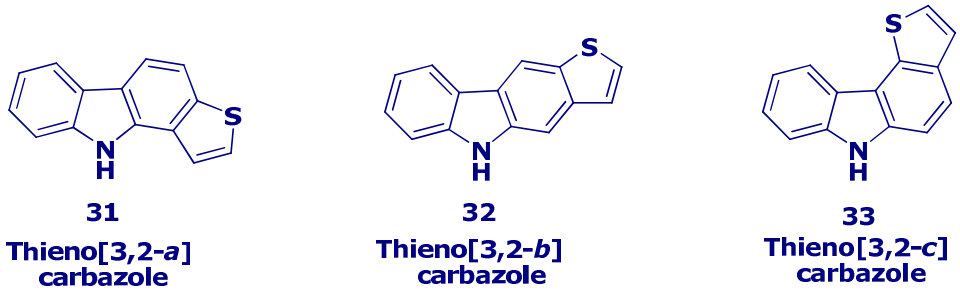
In 1999, Timári *et al*. reported the total synthesis of furostifoline **22** from the bromocresol **26**. The key steps of their approach are the Suzuki coupling to generate *o*-nitrobiaryl compound **30** and the subsequent reductive cyclization via a nitrene intermediate. Annulation of the furan ring at the bromocresol **26** by reaction with bromoacetaldehyde diethyl acetal afforded 5-bromo-7-methylbenzofuran **28**. A halogen/metal exchange reaction of 5-bromo-7-methylbenzofuran **28** with *n*-butyllithium and subsequent treatment with tributyl borate gave the boronic acid derivative **29**. The palladium(0)-catalyzed cross-coupling of the boronic acid derivative **29** with 2-bromonitrobenzene provided the *o*-nitrobiaryl compound **30** in 72% yield. Using Cadogan's method, by reductive cyclization with triethyl phosphite,[22] the *o*-nitrobiaryl compound **30** was transformed to furostifoline **22** in 42% yield (Eq. 3).[23] Thus, furostifoline **22** was made available in five steps and 10% overall yield based on compound **26**.

Eq. 3



Although there are no reports of natural products with a thienocarbazole framework, the synthesis of isomeric thieno[*a*]-, -[*b*]-, and -[*c*]carbazoles **31**-**33** (Figure 4) was reported by various groups in the 1990's.[24] These syntheses were mostly developed to study the biological activities of the thieno-fused carbazoles.[25]

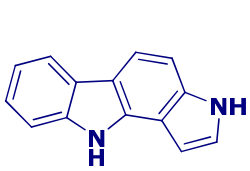
Figure 4



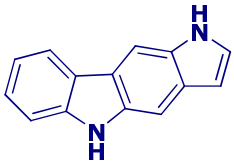
Since the early 1980s, the pyrrolocarbazoles **34**-**40** (Figure 5) have received attention due to their pharmacological activities,[26] e.g. anticancer, antidiabetic, neurotropic, and inhibitory properties against protein kinase C. Only the pyrrolo[2,3-*c*]carbazole skeleton **37** has been found in nature so far. All other different isomeric pyrrolocarbazoles are of synthetic origin. The pyrrolo[2,3-*c*]carbazole alkaloids were isolated from the marine sponge *Dictyodendrilla* sp. They show a potent aldose

reductase inhibitory activity. Various synthetic methodologies led to the generation of broad structural variety of different isomeric pyrrolocarbazoles.[27]

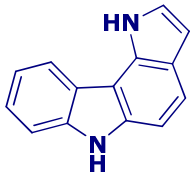
Figure 5



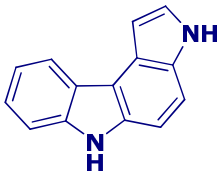
34
Pyrrolo[3,2-*a*] carbazole



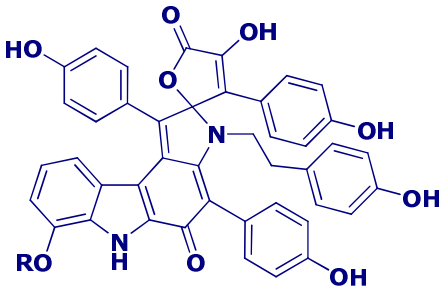
35
Pyrrolo[3,2-*b*] carbazole



36
Pyrrolo[3,2-*c*] carbazole

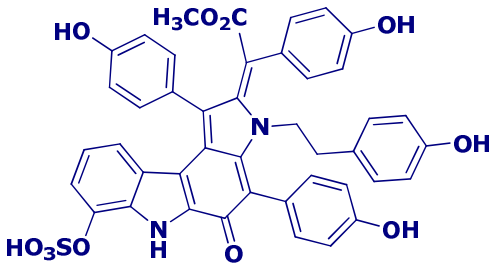


37
Pyrrolo[2,3-*c*] carbazole



38 R = SO_3Na
39 R = SO_3H

Pyrrolo[2,3-*c*] carbazole alkaloid



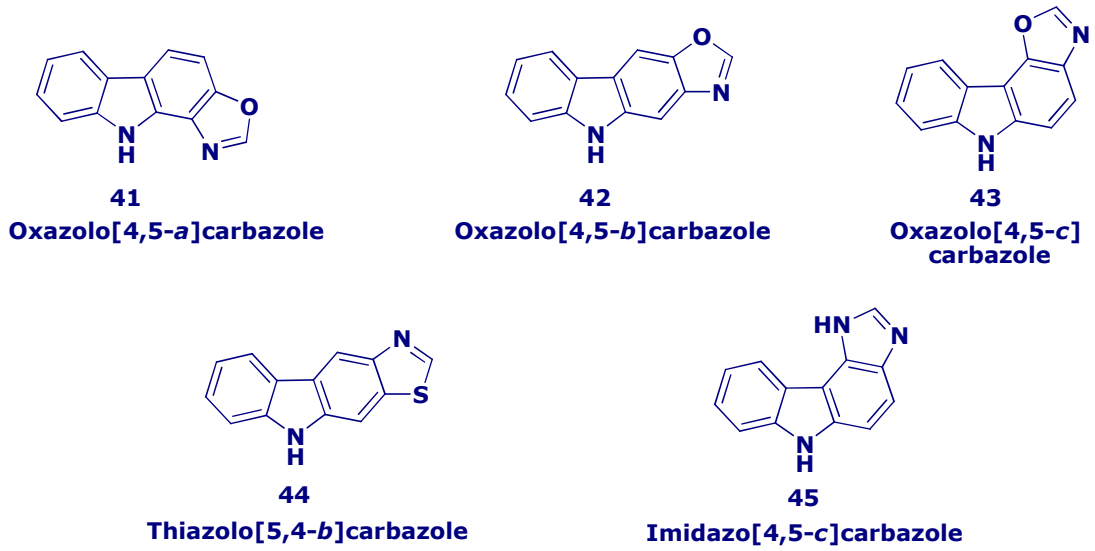
40

(*E*)-methyl 2-(3-(4-hydroxyphenethyl)-1,4-bis(4-hydroxyphenyl)-5-oxo-7-(sulfoxy)pyrrolo[2,3-*c*]carbazol-2(3*H*,5*H*,6*H*)-ylidene)-2-(4-hydroxyphenyl)acetate

So far there are no reports of natural products containing an oxazolocarbazole **41-45** or an isoxazolo carbazole framework (Figure 6). In 1985, Das and co-workers reported the synthesis of oxazolo[5,4-*c*]carbazole derivatives to study the *in vivo* mechanism of action and the structure-activity relationship of *N*-2-methyl-9-

hydroxyelliptinium acetate (elliptinium).[28] Elliptinium, a derivative of the pyrido[4,3-*b*]carbazole alkaloid ellipticine, is used for the treatment of osteolytic metastases of breast cancer. In an investigation of the antioxidant carazostatin, Moody *et al*. prepared an oxazolo[5,4-*c*]carbazole from indole-3-ylacetic acid.[29] Hibino *et al*. reported the synthesis of oxazolo[4,5-*c*]carbazole **43** and oxazolo[5,4-*c*]carbazole by electrocyclization of the corresponding 3-oxazolyl-2-propargylindoles.[30] In 1999, Shanmugasundaram and Prasad reported the synthesis of isoxazolo[3,4-*a*]carbazoles.[31] Besson and co-workers described a simple synthesis of thiazolo[5,4-*b*]carbazole **44** from the corresponding 3-aminocarbazoles.[32a] Achab *et al*. obtained imidazo[4,5-*c*]carbazole **45** by electrocyclization of an appropriate 3-(imidazol-5-yl)-2-vinylindole.[32b]

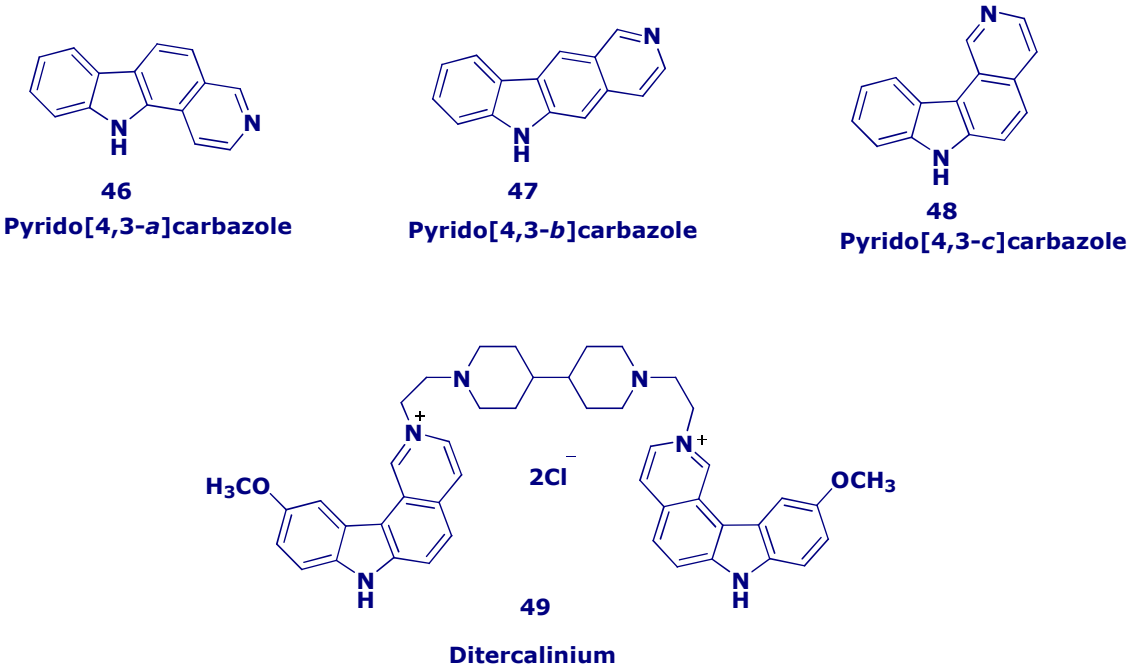
Figure 6



It is well-established that the pyridocarbazole ring system is an appropriate skeleton to design DNA intercalating drugs.[33] For this reason, there has been a strong synthetic activity in this area. Examples of potential annulation modes are the compounds with pyrido[4,3-*a*]carbazole **46**, the pyrido[4,3-*b*]carbazole **47** and the pyrido[4,3-*c*]carbazole **48** (Figure 7) skeleton. Among the different isomeric pyridocarbazole frameworks, the pyrido[4,3-*b*]carbazoles **47** has attracted most of the interest because ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and its 9-hydroxy and 9-methoxy derivatives show significant anticancer activity.[34] Therefore,

various methods have been developed for the synthesis of the pyrido[4,3-*b*]carbazoles.[35] Ditercalinium **49**, a dimeric pyrido[4,3-*c*]carbazole, is under clinical trial for the treatment of cancer (Figure 7).[36] Compared to the synthetic efforts and structure activity studies focused on the pyrido[4,3-*b*]carbazole **47**, little attention has been directed toward the isomeric pyridocarbazoles. A few methods were available in literature for the synthesis of various isomeric pyrido[*a*]carbazoles and pyrido[*c*]carbazoles.[37]

Figure 7

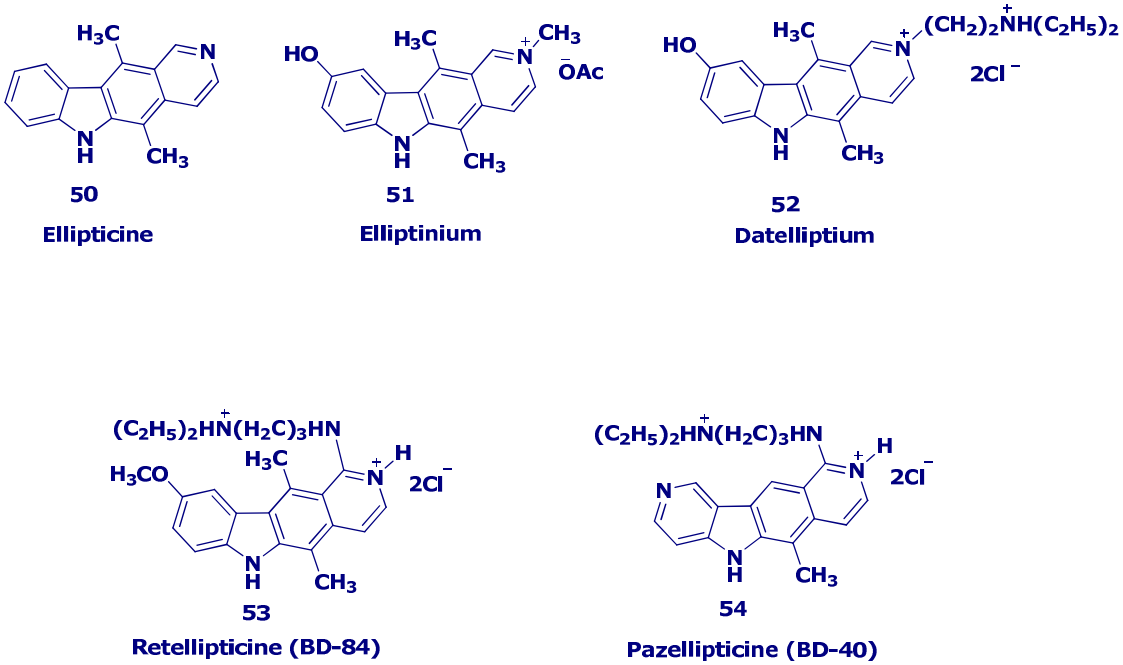


Pyrido[4,3-*b*]carbazole Alkaloids

In 1959, Goodwin *et al*. isolated ellipticine **50**, a pyrido[4,3-*b*]carbazole, from the leaves of *Ochrosia elliptica* Labill.[38] 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.[39] In the following years, ellipticine **50** and its derivatives were isolated from the various other species of the genera *Aspidosperma*, *Tabernaemontana*, *Strychnos* and *Peschiera Buchtieni*. In 1967, Australian scientists disclosed the antitumor activity of ellipticine **50** and 9-methoxyellipticine toward various animal tumors.[40] This discovery stimulated a strong interest in the synthesis of ellipticine and its analogues. A derivative of 9-hydroxyellipticine, *N*-methyl-9-

hydroxyellipticinium acetate **51** (elliptinium), was commercialized for clinical use in the treatment of myeloblastic leukemia, advanced breast cancer and other solid tumors.[41] In the late 1980s, a second generation of ellipticine-derived antitumor agents were developed, including the new clinical candidates datelliptium **52**, retellipticine (BD-84) **53** and pazellipticine (PZE or BD-40) **54** (Figure 8). These findings initiated further extensive activities directed toward the synthesis of pyrido[4,3-*b*]carbazole derivatives for the biological evaluation. Recently, Knölker *et al*. provided an overview on isolation and synthesis of biologically active carbazole alkaloids.[4b]

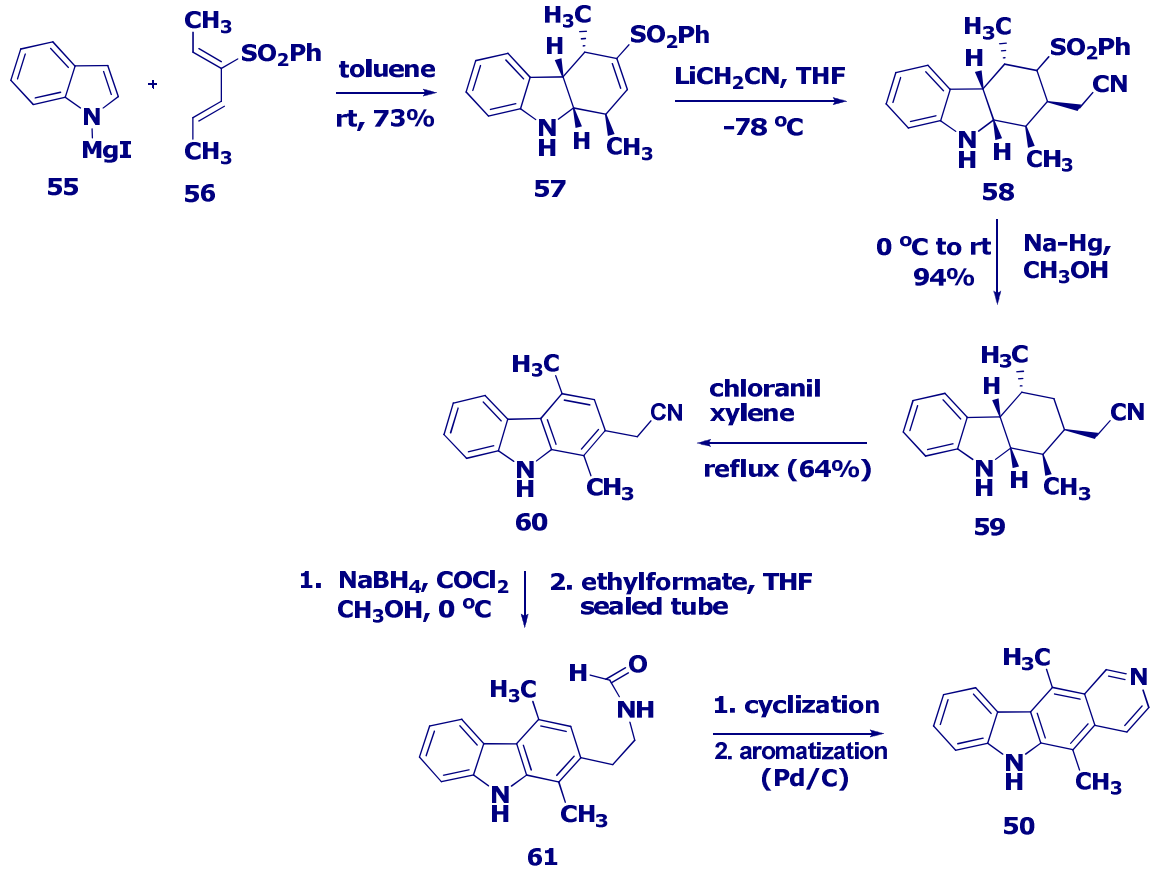
Figure 8



Bäckvall and Plobeck reported a formal synthesis of ellipticine **50** starting from indole. The [4+2] cycloaddition of 1-indolylmagnesium iodide[42] **55** with 3-(phenylsulfonyl)-2,4-hexadiene[43] **56** afforded the tetrahydrocarbazole **57** as the major diastereoisomer. Michael addition of lithio acetonitrile to the tetrahydrocarbazole **57** gave the hexahydrocarbazole **58**. Reductive desulfonation of **58** with sodium amalgam in buffered methanol to **59** followed by aromatization with chloranil provided the carbazole **60**. Reduction of compound **60** using $COCl_2/NaBH_4$ to the amine and subsequent formylation with ethylformate led to the formamide **61**.

The known formamide[44] **61** was previously reported to provide ellipticine **50** in 77% overall yield by Bischler-Napieralski cyclization to dihydroellipticine and subsequent aromatization as shown in Eq. 4.[45]

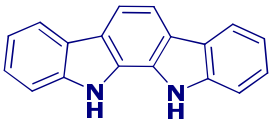
Eq. 4



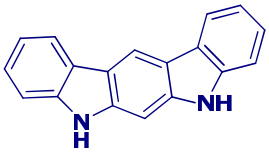
To the indolocarbazole family belong the five different isomeric ring systems namely indolo[2,3-*a*]carbazole **62**, indolo[2,3-*b*]carbazole **63**, indolo[2,3-*c*]carbazole **64**, indolo[3,2-*a*]carbazole **65** and indolo[3,2-*b*]carbazole **66** (Figure 9). Among these, the most interesting structural class is the indolo[2,3-*a*]carbazoles **62**. The indolo[2,3-*a*]carbazole framework **62** is found in many natural products with a broad range of potent biological activities, e.g. antifungal, antimicrobial, antitumor, and antihypertensive activity.[46] Their activity as potent inhibitors of protein kinase C (PKC)622 has received special attention and was the focus of several investigations. The indolo[2,3-*b*]carbazole **63**, indolo[2,3-*c*]carbazole **64**, indolo[3,2-*a*]carbazole

65, indolo[3,2-*b*]carbazole **66** 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 indolocarbazole ring systems **62**-**66** were summarized by Bergman and co-workers.[47]

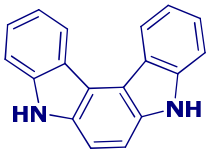
Figure 9



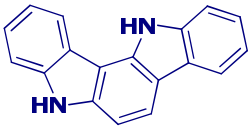
62
Indolo[2,3-*a*]carbazole



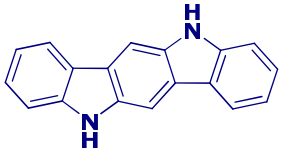
63
Indolo[2,3-*b*]carbazole



64
Indolo[2,3-*c*]carbazole



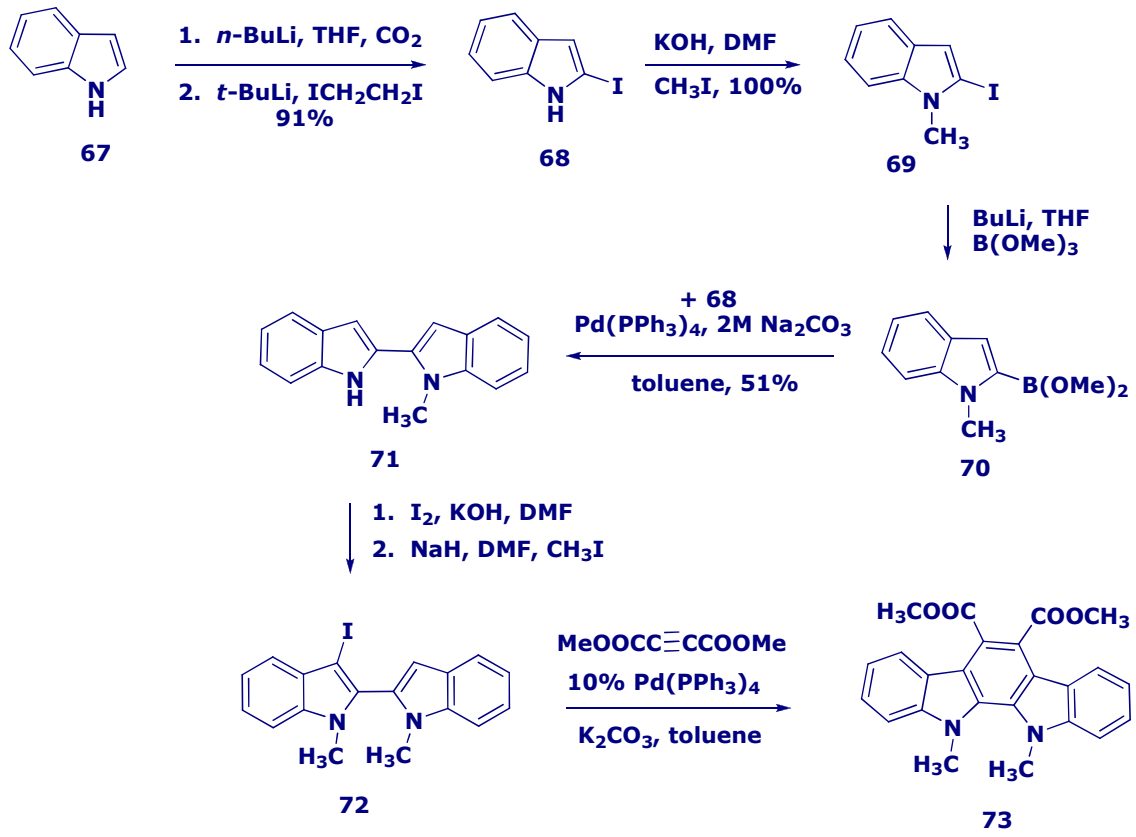
65
Indolo[3,2-*a*]carbazole



66
Indolo[3,2-*b*]carbazole

In 1997, Merlic and McInnes reported the synthesis indolo[2,3-*a*]carbazole derivatives from indole **67** using sequential palladium-catalyzed cross-coupling reactions. Indole **67** was iodinated at the 2-position to **68** using the procedure of Bergman and then *N*-methylated to give 2-iodo-1-methylindole **69**. A Suzuki cross-coupling reaction of **69** with the *in situ* generated boronic ester **70** provided the unsymmetrical 1-methyl-2,2′-bisindolyl **71**. Iodination at the 3′-position using the procedure of Bocchi and Palla[48] followed by *N*′-methylation afforded 3-iodo-1,1′-dimethyl-2,2′-bisindolyl **72**. The palladium-catalyzed benzannulation of compound **72** with acetylene esters afforded the indolo[2,3-*a*]carbazole **73** as shown in Eq. 5.[49]

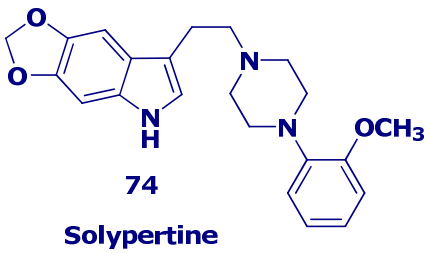
Eq. 5



Heteroaryl-annulated indoles

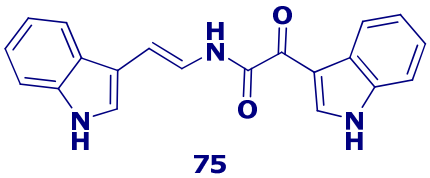
The indole ring system is probably the most ubiquitous heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents.[50] Substituted indoles have been referred to as "privileged structures" since they are capable of binding to many receptors with high affinity.[51] For well over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists and numerous methods for the preparation of indoles have been developed.[52] A few examples of indole alkaloids are shown in Figure 10.

Figure 10



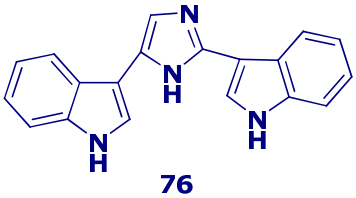
74

Solypertine



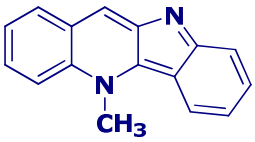
75

Coscinamide B



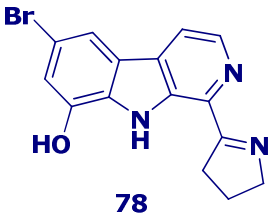
76

Nortopsentin D



77

Cryptolepine

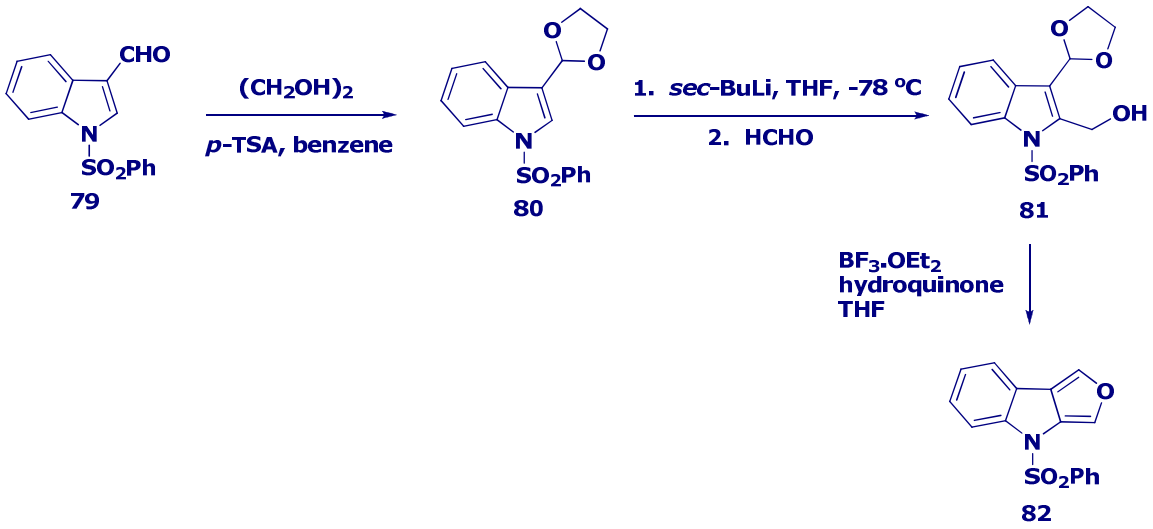


78

Eudistomidine A

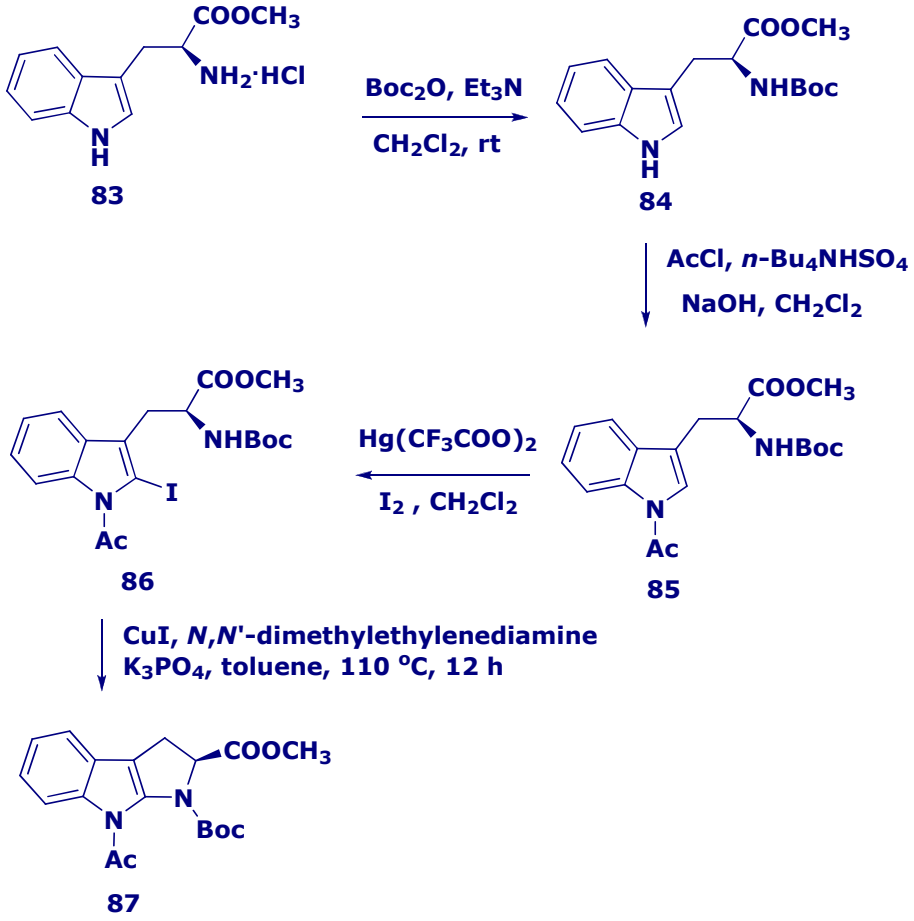
The furoindole ring system is a structural unit in natural products.[53] Due to its inherent biological activity and the use as synthetic target of numerous natural compounds, there is a demand for general synthetic methods for this ring system.[54] Gribble *et al*. reported[55] the synthesis of furo[3,4-*b*]indole from indole-3-carbaldehyde. Indole-3-carbaldehyde was protected using a phase transfer method to give the *N*-phenylsulfonyl derivative **79**. Acetalization under typical conditions gave acetal **80**. Lithiation of **80** at C-2 with *sec*-BuLi followed by treatment with gaseous formaldehyde gave hydroxyl acetal **81** (not isolated). The reaction mixture was treated with $BF_3.OEt_2$ and hydroquinone to afford furoindole **82** in 52% yield from acetal **80** as shown in Eq. 6.

Eq. 6



The pyrroloindole skeleton is a key structural motif[56] that appears in the core structure of an impressive number of biologically active alkaloids which exhibit interesting biological properties such as the potent vasodilator,[57a] the insecticidal[57b] and the anticancer.[57c] Due to the biological importance of the pyrroloindoles, a lot of synthetic methods have been developed[58] to synthesize these compounds. Recently Evano *et al*. reported[58d] the synthesis of tetrahydropyrrolo[2,3-*b*]indoles by the intramolecular copper-catalyzed coupling of 2-iodotryptophan as shown in Eq. 7. L-Tyrptophan methyl ester **83** was protected using Boc_2O to give **84**, then indole NH was protected by acetyl chloride to provide **85** which was iodinated regio-selectively at C-2 to prepare 2-iodotryptophan **86** which was subsequently subjected to intramolecular cyclization in presence of copper(I) iodide as a catalyst, diamine as a ligand and K_3PO_4 as base in toluene at 110 °C to give tetrahydropyrrolo[2,3-*b*]indole **87** (Eq. 7).

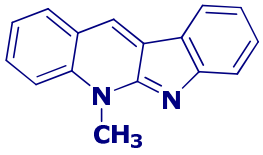
Eq. 7



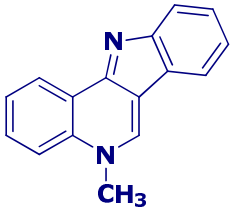
Indoloquinoline alkaloids are receiving a prominent attention in recent years as they are known to act as DNA intercalating agents[59] and exhibit antimalarial properties.[60] The World Health Organization placed malaria besides tuberculosis and AIDS as a major infectious disease. The roots of the West African plant Cryptolepis sanguinolenta,[61] a rich source of indoloquinoline alkaloids, have been used by Ghanaian healers to treat a variety of health disorders including malaria. Since 1974, a decoction of this plant has been used in the clinical therapy of rheumatism, urinary tract infections, malaria, and other diseases.[62] The linear indoloquinoline alkaloids cryptolepine **77** (5-methyl-5*H*-indolo[3,2-*b*]quinoline, Figure 10), cryptotackieine **88** (neocryptolepine, 5-methyl-5*H*-indolo[2,3-*b*]quinoline) and an angularly-fused alkaloid cryptosanguinolentine **89** (isocryptolepine, 5-methyl-5*H*-indolo[3,2-*c*]quinoline) are three of the characterized alkaloids (Figure 11), which behave as

DNA intercalating agents, inhibiting DNA replication and transcription. These compounds also exhibit strong antiplasmodial activity. Cryptolepine binds 10-folds more tightly to DNA than other alkaloids and proves to be much more cytotoxic toward B16 melanoma cells.[63] It has been reported that some methyl-substituted indoloquinolines act as cytotoxic agents, liposomally-formulated anticancer agents and DNA-Topoisomerase II inhibitors.[64]

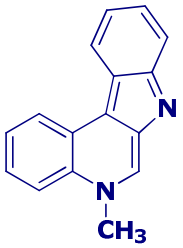
Figure 11



88
Neocryptolepine



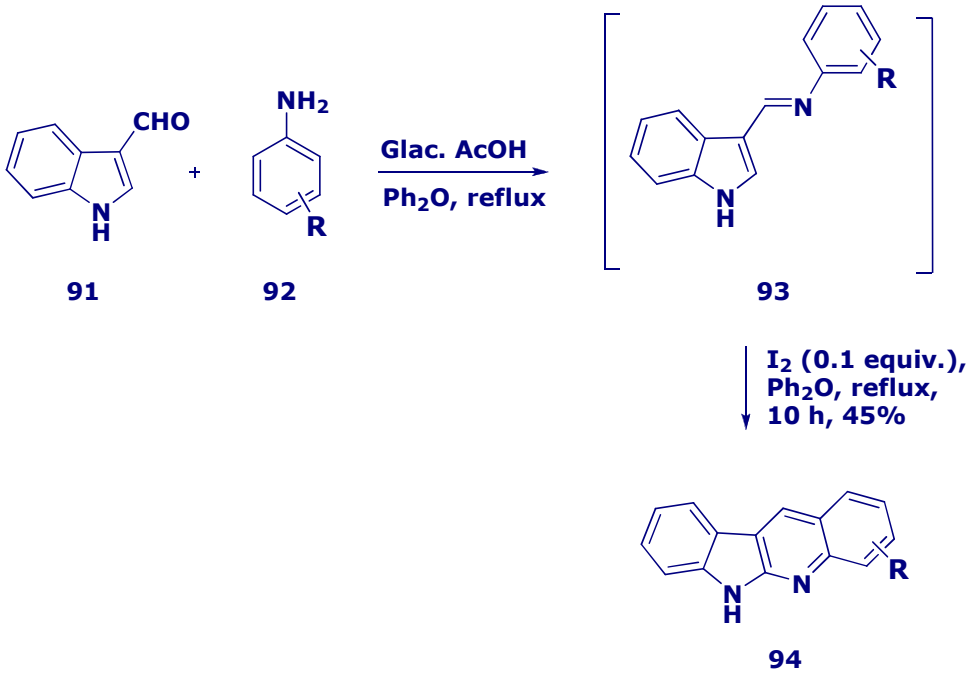
89
Isocryptolepine



90
Isoneocryptolepine

The interesting biological activity of indoloquinolines has generated an interest in developing new synthetic pathways for the synthesis of indoloquinolines.[65] More recently, Tilve *et al*. reported a new and simple method for the preparation of 6*H*-indolo[2,3-*b*]quinolines. The method involves the reaction of indole-3-carboxaldehyde **91** with aniline **92** in the presence of a catalytic amount of iodine in diphenyl ether to yield indolo[2,3-*b*]quinoline **94** in one-pot as shown in Eq. 8.[65e]

Eq. 8



91 **92** **93** **94**

Organocopper chemistry

Until the beginning of the 21st century, this was certainly not the case for copper-mediated C-N, C-O, and C-C bond formation reactions, first reported a hundred years ago in the pioneering and remarkable work of Ullmann and Goldberg.[67,68,69] Even if these conceptual publications clearly are the basis of today's developments of copper-mediated reactions, and even if they found numerous industrial and academic applications, harsh reaction conditions and low substrate scope hampered their use in the natural product synthesis. Using such reactions on complex substrates was a strategic decision that bore way too much risk and even seemed somewhat counterintuitive: palladium-catalyzed transformations were prefered in most cases and only smart adaptations of the classical reaction conditions or activation of the aryl halide were reported from time to time for the synthesis of complex targets. This situation has come to an end with the development, in the past 10 years or so, of highly efficient catalytic systems that allow reactions to be conducted in milder conditions and with dramatically enhanced yields compared to classical procedures. The keys to the success of these improved conditions were the observation that simple organic derivatives could speed up cross-couplings and the introduction of new reaction partners such as organoboranes. This has allowed for the use of a wide range of substrates and mild reaction conditions together with the

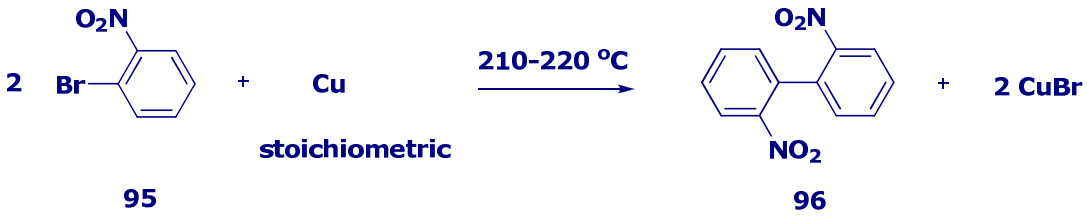
extension of these coupling reactions to the introduction of vinyl and alkyne functional groups. The synthetic potential of these transformations is now quite obvious, even if the golden age of copper-mediated cross-coupling reactions is probably just beginning. Their application in natural product synthesis has flourished recently: an array of copper-mediated procedures has been successfully employed to assemble many complex targets with new and efficient bond disconnections.[66]

Background: Copper-Mediated Coupling Reactions

Ullmann, Goldberg, and Hurtley Coupling Reactions

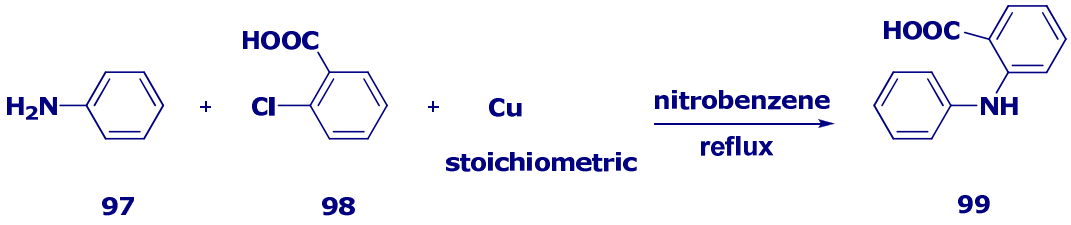
The foundations of modern copper-mediated chemistry lie in the pioneering and remarkable work of Fritz Ullmann and Irma Goldberg. It all started in 1901 when Ullmann reported[67] that if one heats *o*-bromonitrobenzene with fine spreaded Cu powder, one recognizes that the latter one is loooze its shine and turns into a mattegray mass. After purification of the reaction products, it appears that copper has turned into copper bromide and that the bromonitrobenzene **95** has turned into a bromo-free substance, which, on a closer look, turns out to be identical with the 2,2'-dinitrobiphenyl **96** synthesized in a different way by Taubeŕ. Two molecules of *o*-bromonitrobenzene could be coupled in the presence of metallic copper to give the corresponding biaryl: the Ullmann reaction was born (Eq. 9).

Eq. 9

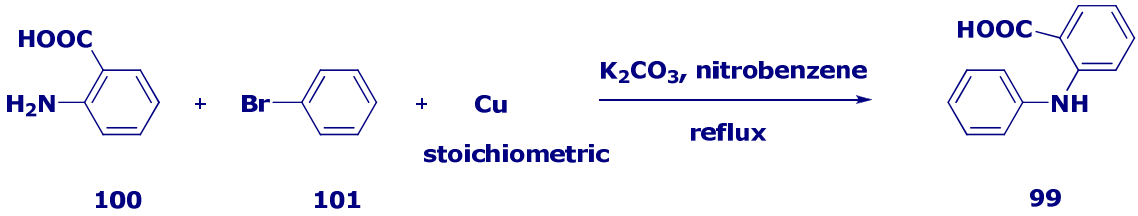


Two years later, Ullmann reported that aniline **97** reacted with 2-chlorobenzoic acid **98** in the presence of 1 equiv. of copper to give 2-phenylaminobenzoic acid **99**,[68] a reaction that was shown to be catalytic by Goldberg in 1906 starting from the potassium salt of 2-aminobenzoic acid **100** (Eq. 10 & 11).[69] It is quite amazing to note, a century later, that the *ortho*-effect that still has a deep impact on copper-mediated transformations was already touched upon.

Eq. 10

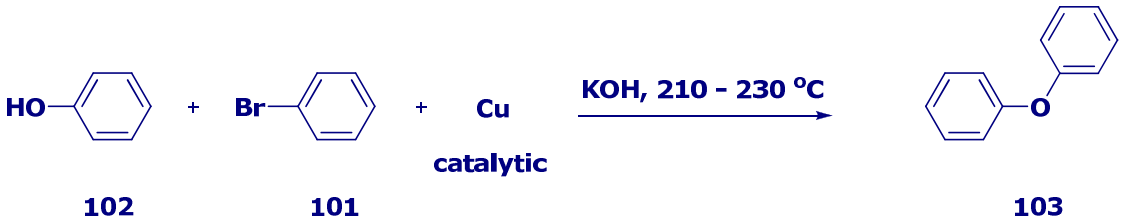


Eq. 11



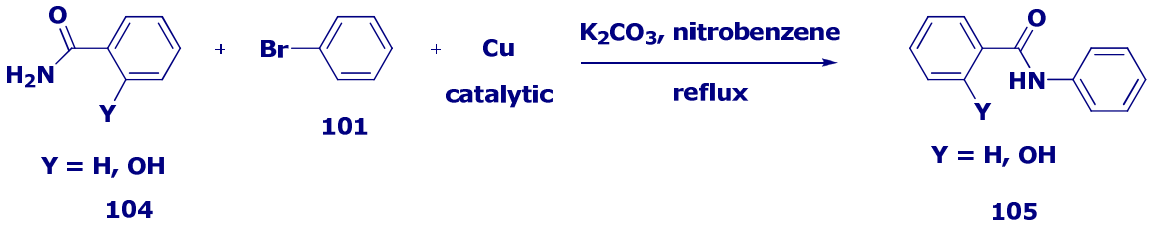
Ullmann next extended the reaction to the preparation of diphenyl ether **103** by the reaction of potassium salt of phenol **102** and bromobenzene **101** and demonstrated the considerable effect of catalytic amounts of copper on the rate of the reaction (Eq. 12).[70]

Eq. 12



A year later, the first copper-catalyzed arylation of amides **105** was successfully reported by Goldberg, who managed to condense bromobenzene **101** with benzamide **104** (Eq. 13).[69]

Eq. 13



Twenty years later, another exceptional contribution was reported by William R. H. Hurtley: under the catalytic influence of copper-bronze or copper acetate, the halogen atom in *o*-bromobenzoic acid **107** is easily substituted by sodium salts of diketones **106** and malonates to synthesize the corresponding benzoic acid derivative **108** (Eq. 14).[71] Here again, the *ortho*-effect had a dramatic influence because "the halogen atom in *o*-bromobenzoic acid is much more reactive".

Eq. 14

These pioneering contributions clearly paved the way for the development of copper-mediated coupling reactions and are the basis of today's developments. Since the early work of Ullmann, Goldberg and Hurtley, an array of copper sources, ligands and preformed catalysts have been introduced and used for the development of milder and general procedures. Some useful copper sources (Figure 12) and ligands (Figure 13) are shown below.

Figure 12

Copper Sources

Cu Cu bronze

CuI CuBr $CuBr.SMe_2$ CuCl CuCN Cu_2O

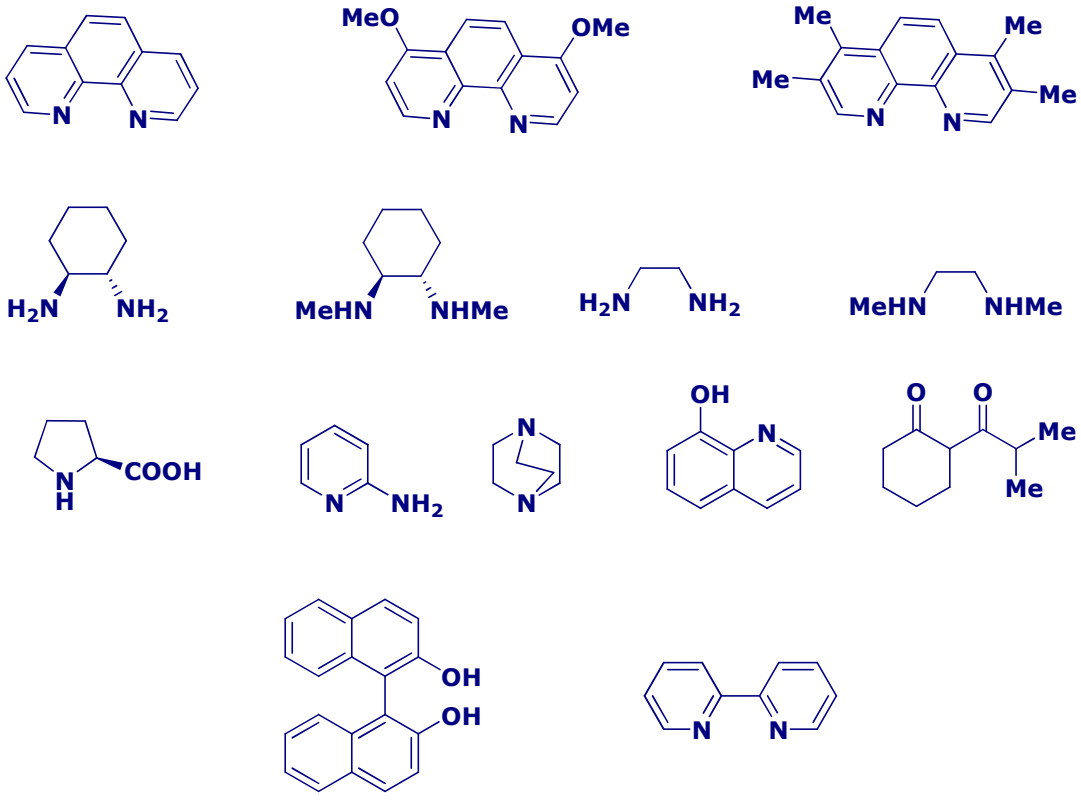
$Cu(CH_3CN)_4PF_6$ $(CuOTf)_2.PhH$ $(CuOTf)_2.PhMe$

$Cu(NO_3)_2$ $Cu(OAc)_2$ $Cu(OAc)_2.H_2O$ $Cu(acac)_2$

$CuCl_2$ $Cu(BF_4)_2$ $CuSO_4$

Figure 13

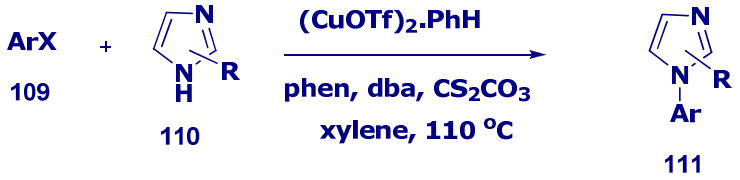
Ligands



C-N Bond Formation

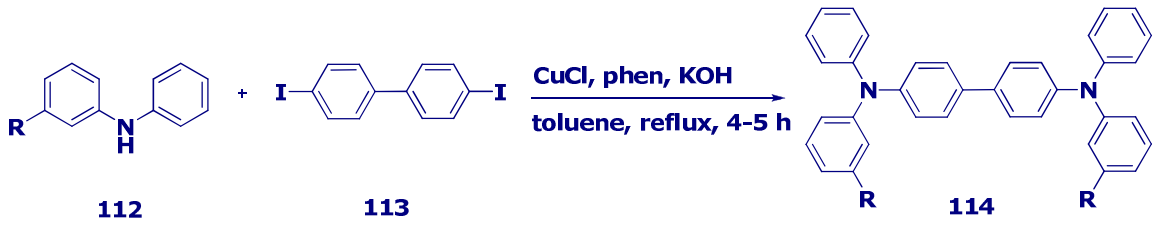
Functionalized aromatic and heteroaromatic amines are key building blocks for the synthesis of pharmaceuticals, polymers, or materials. In recognition of their widespread importance, many synthetic methods have emerged over the years for the formation of C-N bonds. Classic Ullmann and Goldberg protocols typically require harsh reaction conditions such as high temperatures, extended reaction time, in some cases stoichiometric amounts of copper and lower yields. To circumvent these problems, chemists have referred to the more recently developed palladium-catalyzed C-N bond forming reactions as a means to generate a diverse array of arylated amines.[66] However, the palladium-catalyzed *N*-arylation also encounters some limitations. For example, substrates with functional groups containing free N-H moieties[72] as well as amides[73] and heterocycles[72a,b] remain problematic. The employment of chelating ligands has provided the major driving force behind the evolution of Cu-catalyzed C-N bond forming processes. The first report concerning the intentional use of exogenous ligands focused on 1,10-phenanthroline. For example, for *N*-arylation of imidazoles **110** and synthesis of arylamines, catalyst systems based on 1,10-phenanthroline allowed for lower temperatures, shorter reaction times, and reaction in nonpolar solvents, in comparison to the classic Ullmann conditions (Eq. 15).[74]

Eq. 15



Also, during the synthesis of triarylamines, the 1,10-phenanthroline/CuCl catalyst system was found to be the most effective, thus allowing the reactions to occur at much lower temperatures than those previously used (Eq. 16).[75]

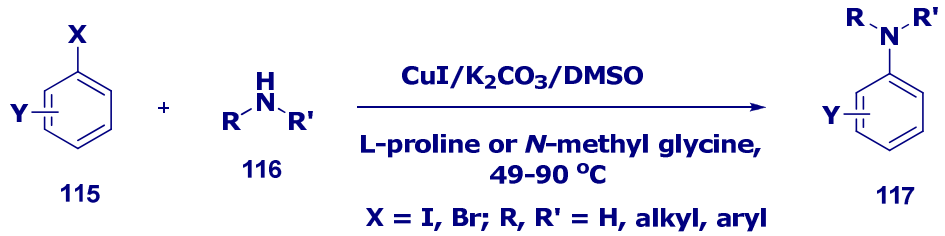
Eq. 16



112 113 114

Moreover, soluble complexes of Cu(I) and 1,10-phenanthroline, i.e., $LCu(PPh_3)Br$ and its derivatives based on neocuproine and 2,2′-bipyridine, have been exploited in the synthesis of aryl amines.[76] Other chelating ligands such as ethylene glycol,[77] L-proline,[78] *N*-methyl glycine,[78] and diethylsalicylamide[79] have also proven to be quite effective in the *N*-arylation of both aliphatic and aryl amines. Eq. 17 represents coupling reaction of aryl halides with amines under the catalysis of CuI and L-Proline.[78]

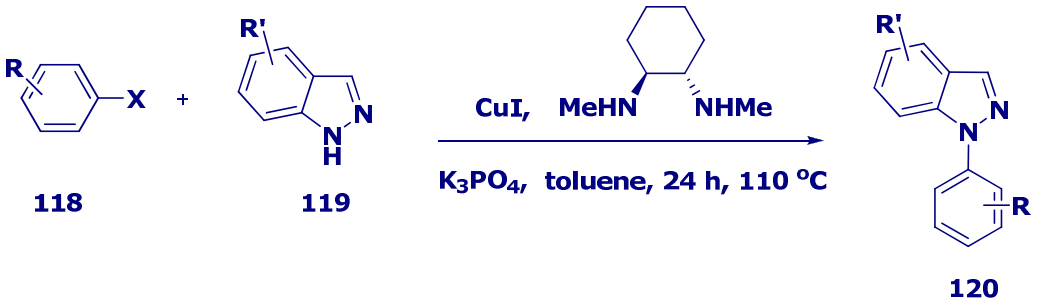
Eq. 17



115 116 117

One of the most general catalyst systems based on a chelating ligand, which is used in the *N*-arylation of amides and heterocycles as well as cyanation and halide exchange reactions, is that derived from inexpensive 1,2-diamines (Eq. 18).[80] This catalyst system allows for the efficient coupling of a wide variety of substrates, specifically, those containing free N-H and O-H as well as heterocycles.

Eq. 18



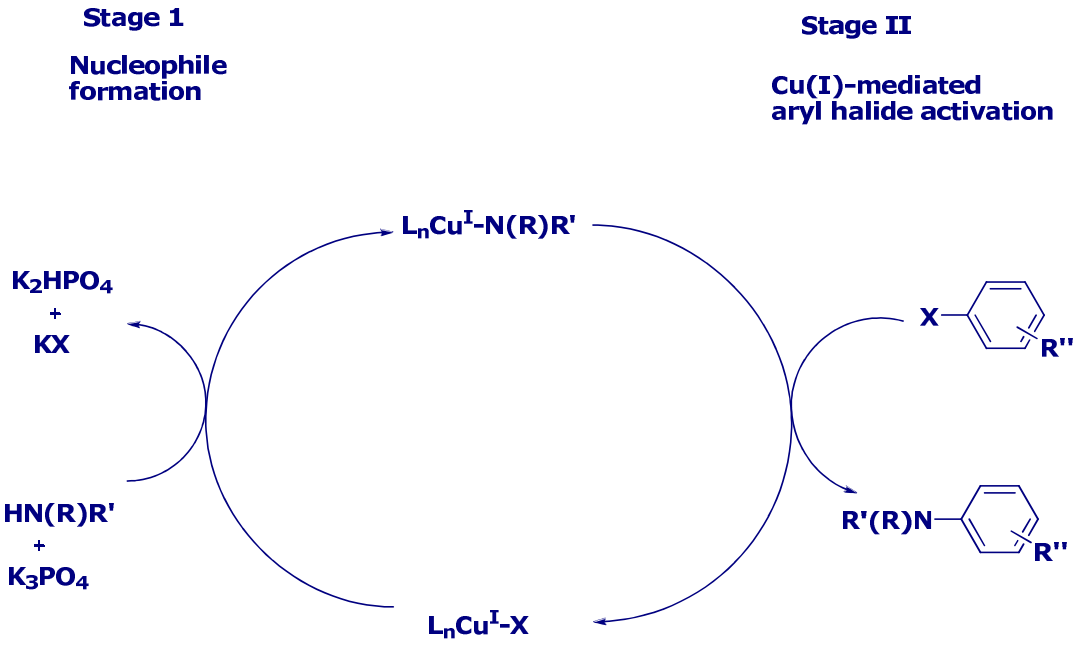
Despite these achievements, most of the copper-based catalyst systems have yet to achieve the high turnover numbers that are typically obtained in the complementary palladium chemistry. Moreover, reactions of less active substrates such as aryl chlorides and aryl sulfonates have thus far been relatively unsuccessful, especially in the latter case. Attempts to understand similar deficiencies in the related palladium chemistry have been investigated through a significant amount of mechanistic work; however, analogous studies on copper-catalyzed reactions are relatively scarce.[66]

Of the few mechanistic studies that have been performed on Cu-catalyzed C-N and C-O bond-forming reactions, the major emphasis has been on the empirical observations pertaining to which catalyst system, i.e., Cu(0), Cu(I) or Cu(II), provides the fastest reaction rate. Since the earliest work by both Ullmann and Goldberg and later Adkins, several different copper sources were found to be effective for the transformation, e.g., $CuBr_2$, $CuCl_2$, $Cu(OAc)_2$, CuI, CuBr, CuCl, and even Cu(0). Copper sources from three different oxidation states provided nearly identical reaction rates in both *N*- and *O*-arylations, with Cu(I) salts providing slightly higher rates compared to those of Cu(0) and Cu (II). The initial hypothesis for this behavior was that a single catalytic species results from each of these precursors and the active oxidation state is Cu(I).[81] Investigations by electron paramagnetic resonance (EPR) showed that indeed the Cu(II) species decays over time while in the presence of the amine, thereby producing Cu(I).[82] This process was proposed to occur through oxidation of the ligand bound to Cu(II), either the alkoxide, phenolate, or amide. The only direct evidence for ligand oxidation occurred when tetraphenylhydrazine was isolated from the *N*-arylation of diphenylamine using $CuBr_2$ or $Cu(acac)_2$ as the precatalyst.[83] With regard to the use of Cu(0) as a precatalyst,

Paine has found through SEM imaging that the surface of Cu(0) is covered with a thin layer of Cu_2O, which then possibly leaches into solution upon amine coordination.[83a] Taken together, these results do indeed support the primary role of Cu(I) in facilitating Ullmann-type reactions. Several stoichiometric studies have been performed to remedy the cryptic nature of the active Cu(I) species. Initial experiments have implied that a simple metathesis reaction occurs between either the CuX_2 or CuX salt and the metal alkoxide or amide, thus providing an explanation for the nearly identical reaction rates obtained with different copper salts. With regard to the copper-catalyzed C-O bond-forming reaction, an additional equivalent of alkoxide is then required to form the catalytically active species, which is cuprate-like, i.e., $M[Cu(OR)_2]$, where M is Na.[83b]

Catalytic Mechanism: Recently, Buchwald *et al*. have reported[84] mechanistic studies on the copper-catalyzed *N*-arylation of amides. The Cu(I)-catalyzed C-N bond-forming reaction between *N*-nucleophiles and aryl halides proceeds by a Cu(I)-mediated nucleophilic aromatic substitution type mechanism in which the aryl halide activation and the nucleophile formation occur in two independent, sequential stages as shown in Figure 14.

Figure 14

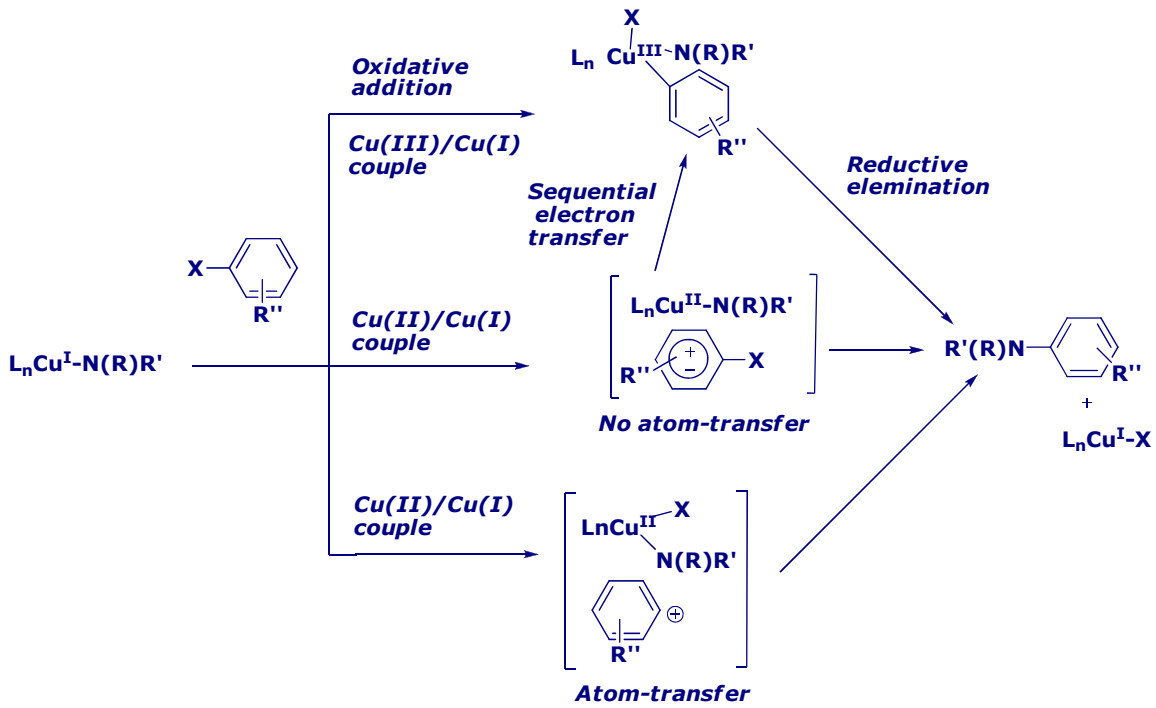


Consistent with this proposal, Cu(I) amidates promote the kinetically competent stoichiometric *N*-arylation. Kinetic studies on the catalytic *N*-arylation of amides using the Cu(I)/1,2-diamine catalyst system reveal a positive-order rate dependence on aryl iodide concentration under conditions where the rate dependences on [amide] and [1,2-diamine] are changing, i.e., the studies carried out at high and low [1,2-diamine]. These results suggest that the Cu(I)-mediated aryl halide activation step (Stage II, Figure 14), under all circumstances, is the rate determining step. The linear Hammett plot obtained under the changing dependencies on [amide] and [1,2-diamine] further substantiates this proposal. Evidence pinpointing a single mechanism for the Cu(I)-mediated aryl halide activation step (Stage II, Figure 14) is relatively scarce. Previous research concerning the mechanism of the Ullmann C-N bond-forming reaction has suggested that the aryl halide activation step occurs through an oxidative addition process where the redox chemistry takes place between either a Cu(III)/Cu(I) couple or a sequential electron-transfer process involving all three oxidation states of copper, i.e., Cu(I), Cu(II), and Cu(II) (Figure 15). Additionally, there are two plausible mechanisms for the "inner-sphere" electron transfer involving the Cu(II)/Cu(I) couple. The first involves a radical anion intermediate which forms without atom-transfer to Cu(II) prior to C-N bond formation, i.e., a SRN1-type mechanism, while the second involves an aryl radical which forms upon oxidation of Cu(I) to Cu(II) with concurrent atom-transfer (Figure 15). All of these postulates originate from the pioneering work of Kochi, Whitesides, Johnson, and Cohen through their mechanistic investigations on alkyl radical additions to Cu(II), Ullmann C-C coupling, halogen-exchange and organocuprate nucleophilic substitutions. There are two contrasting views for aryl halide activation during C-N bond-forming reaction. While studying the Ullmann condensation reaction of haloanthraquinone derivatives with 2-aminoethanol, Hida observed the oxidation of initial Cu(I) species to a Cu(II) species with the concomitant formation of a 1-bromoanthraquinone radical anion via EPR spectroscopy.[85a]

This result supports an aryl halide activation process involving a Cu(II)/Cu(I) redox couple but unfortunately due to the rate of subsequent steps, the intermediacy of a Cu(III) species could not be established. In contrast, both Bethell[85b] and Hartwig[85c] have suggested that a Cu(III) intermediate is formed during the coupling reaction between aryl halides and amines/amides. In support of this, Huffman and Stahl have provided evidence for a pathway involving a Cu(III)/Cu(I) couple by

demonstrating that C-N bond-forming reductive elimination occurs rapidly from well-defined Cu(III)-aryl species.[86]

Figure 15



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CHAPTER

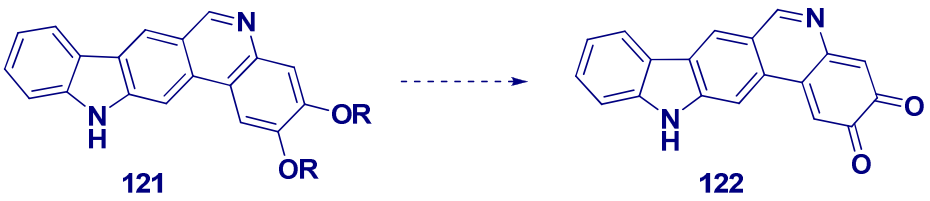
1

Synthesis of Quino, Chromenocarbazoles and Pyrroloacridines via Ullmann-Goldberg Condensation

1.1. Introduction

The plant alkaloid 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 retelliptine have been developed. The molecular basis for their antitumor activity stems from their ability to intercalate between the base pairs in DNA. 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.[87] 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.[88] It was conceived that quinolino carbazole **121** having adjacent methoxy groups at the E ring may undergo similar *in vivo* oxidation to give quinone derivatives **122** (Figure 16) which in turn may covalently bind to DNA or proteins.

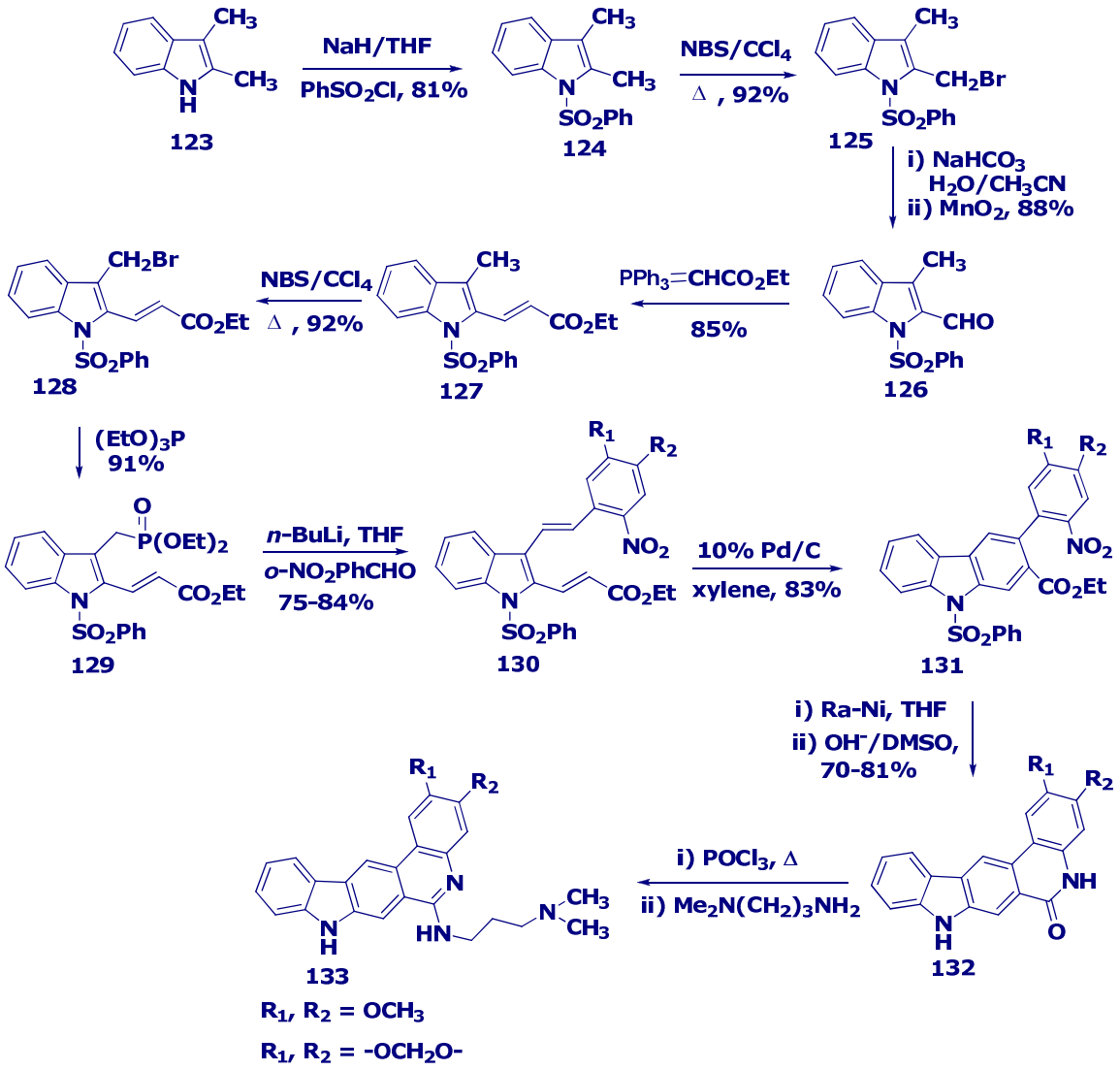
Figure 16



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.[89]

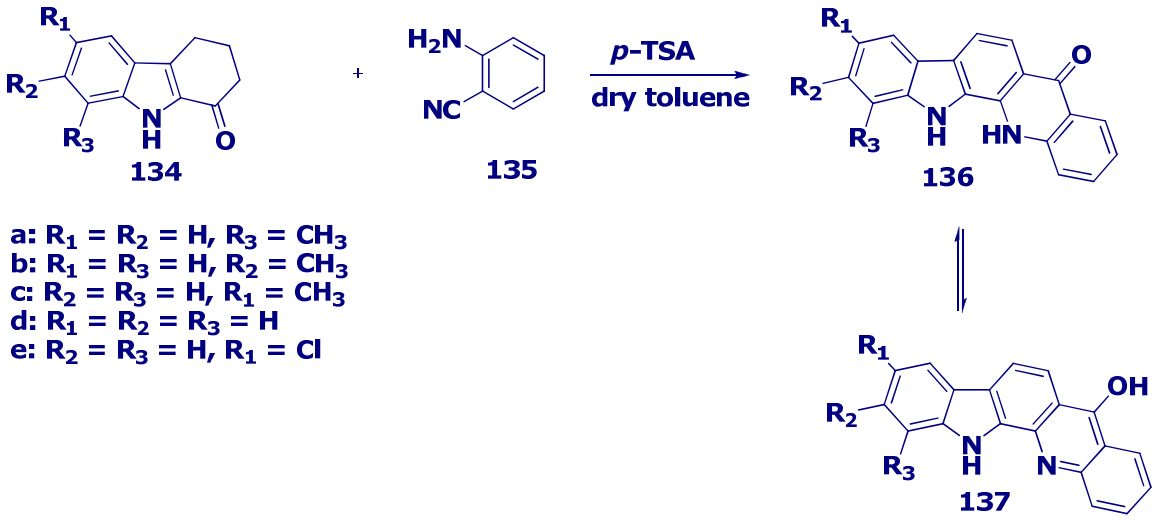
Srinivasan *et al*. reported[90] a new synthetic route (Eq. 19) for the construction of quino[3,4-*b*]carbazole analogues, oxygenated in A, D and E rings as potential DNA binders. 2,3-dimethylindole **123** was phenylsulfonylated by treatment with NaH and phenylsulfonyl chloride in THF to give **124**. Bromination of **124** with 1 equiv. of NBS in boiling CCl_4 gave the monobromo compound **125** in almost quantitative yield. The subsequent solvolysis of **125** using $NaHCO_3$ in CH_3CN followed by oxidation with MnO_2 in boiling 1,2-dichloroethane gave the known 1-(phenylsulfonyl)-3-methylindole-2-carboxaldehyde **126** in 88% yield. The Wittig reaction of **126** with (carbethoxymethylene)triphenylphosphorane in THF gave **127** in 85% yield. The bromination of **127** to give **128** followed by subsequent Arbuzov reaction with triethyl phosphate gave the phosphonate ester **129** which underwent Wittig-Horner reaction with 2-nitrobenzaldehyde in *n*-BuLi/THF condition to give **130**. Boiling a xylene solution of **130** in the presence of 10% Pd/C gave the expected carbazole **131** as a single product. The reductive cyclization of the carbazole **131** with Ra-Ni in boiling THF followed by cleavage of the phenylsulfonyl group gave the expected amide **132**. The quinocarbazole analogue **132** was converted to the corresponding [(dimethylamino)propyl]amino derivative **133** by treatment with $POCl_3$ and [(dimethylamino)propyl]amine.

Eq. 19



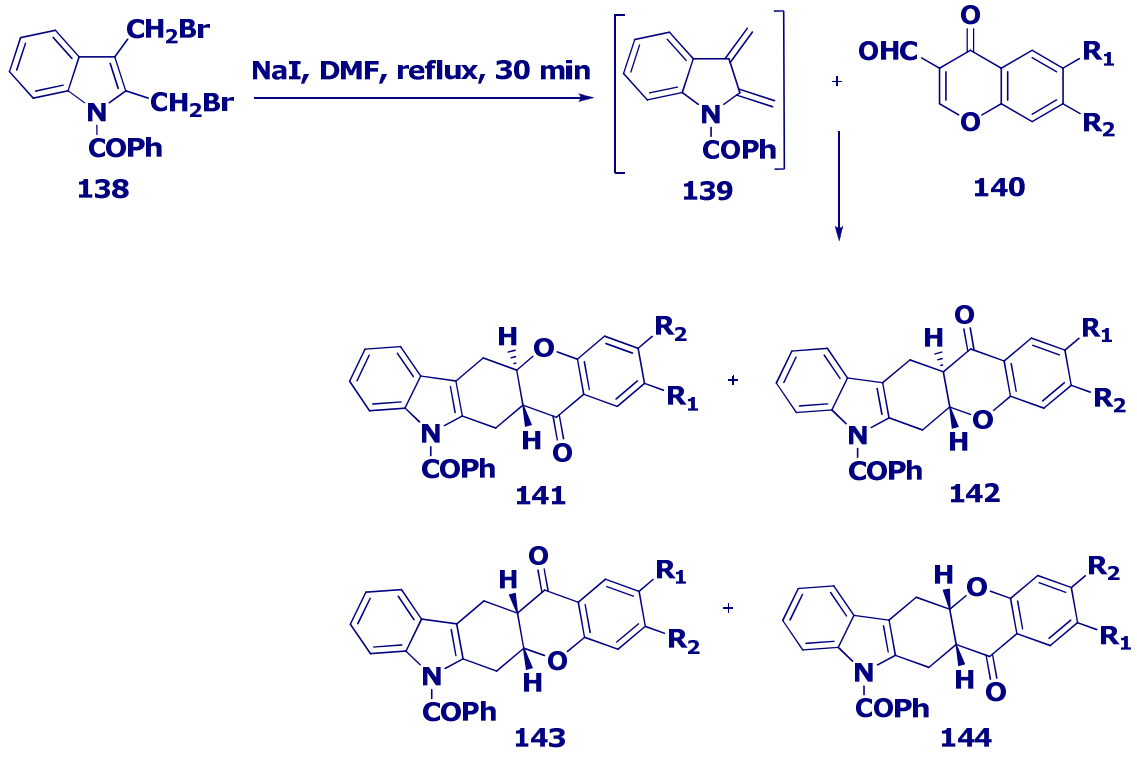
As shown in Eq. 20, Rajendra Prasad *et al*. reported[91] the synthesis of quino[2,3-*a*]carbazole **137** by acid-catalysed condensation of 1-oxo-1,2,3,4-tetrahydrocarbazoles **134** with *o*-aminobenzonitrile **135**.

Eq. 20



Stephanidou-Stephanatou *et al*. developed[92] a synthetic route for the synthesis of a new class of indole derivatives, tetrahydrochromeno[2,3-*b*]carbazoles **141**-**144**. The cycloaddition reactions of chromone-3-carboxaldehydes **140** with indole-*o*-quinodimethane **139** which was synthesized from (2,3-bis(bromomethyl)-1*H*-indol-1-yl)(phenyl)methanone **138** gave a diastereomeric mixture of Diels–Alder cycloadducts in good yields after *in situ* deformylation as shown in Eq. 21.

Eq. 21



1.2. Synthesis of Quinocarbazoles

As a result of their significant potential as therapeutics, interest has grown in the development of methods for the efficient and rapid synthesis of the derivatives of pyrido and pyranocarbazoles especially because the current methods, which involve multi-step reactions, lower yields, longer reaction times and high cost of palladium,[93] are unsatisfactory. Herein, therefore, we described a simple, economical and effective two-step procedure for the synthesis of quino and chromenocarbazoles based on C–N and C–O bond formation through Ullmann–Goldberg condensation[94] followed by intramolecular Friedel–Crafts[95] cyclization with $POCl_3$. Since the starting materials *o*-halobenzoic acids can be readily prepared[96] by diazotization of anthranilic acid derivatives and the reagents CuI and $POCl_3$ are relatively cheap, our synthetic methodology for the preparation of quino and chromenocarbazoles is simple and efficient.

As shown in Scheme 1, we carried out the condensation of 3-amino-9-ethylcarbazole **145b** with various *o*-iodobenzoic acids **146a–e** in presence of CuI (0.1 equiv.) and K_2CO_3 (2.0 equiv.) without any ligand in DMSO at 80 °C. The

reaction also works with 3-aminocarbazole **145a** and the corresponding product **147a** is obtained in 73% yield. Facile reaction without any ligand is due to the activation of halogens with the *ortho*-carboxylic acid group.[97] In the absence of CuI, no condensation was observed. Outcome of the substituents **147a-e** are presented in Table 1. In some cases, *NH* and *OH* protons could not be observed in ^{1}H NMR spectrum due to the deuterium exchange of DMSO. The structure of **147b** was also confirmed by the single crystal X-ray analysis and the Figure 17 shows the ORTEP diagram of **147b**. Due to the activation of the strong electron-withdrawing nitro group, the time required for the formation of **147e** was comparatively reduced to half than that required for the other iodobenzoic acids. Since the order for ease of halogen displacement follows as I>Br>Cl, 2-bromobenzoic acid required longer reaction time.

Scheme 1. Synthesis of condensed products

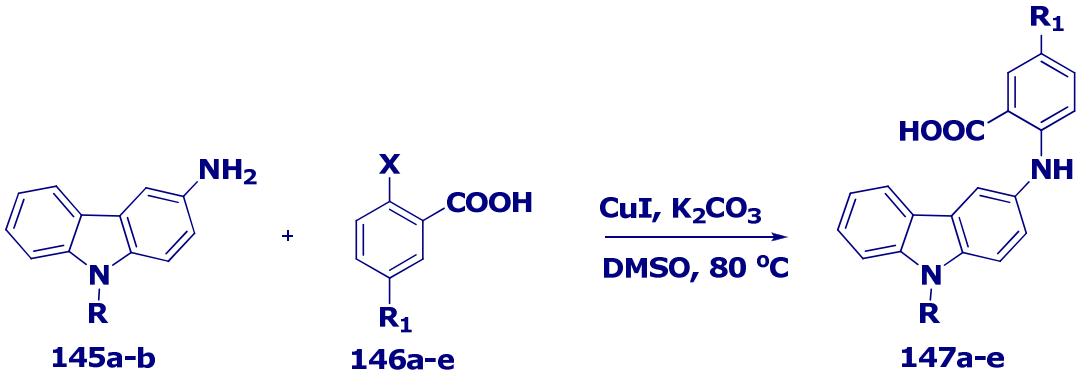


Figure 17. ORTEP diagram of 147b

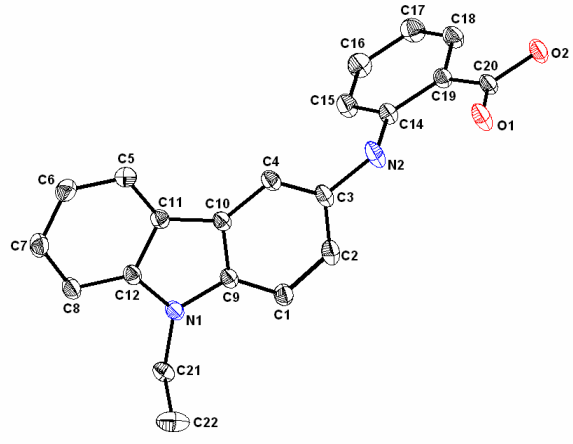


Table 1. Synthesis of condensed products

S. No.	R	R_1	X	Condensed product	Time (h)	Yield (%)
1	H	H	I	**147a**	1.0	73
2	Et	H	I	**147b**	1.0	73
3	Et	Cl	I	**147c**	1.0	72
4	Et	Br	I	**147d**	1.0	70
5	Et	NO_2	I	**147e**	0.5	74
6	Et	H	Br	**147a**	3.0	64

Interestingly, diazocarbazole was obtained as a by-product (<5%) during the coupling between 3-amino-9-ethylcarbazole and *o*-halobenzoic acids. The aerobic oxidation of CuI produces the active Cu(II) species, which oxidizes the aminocarbazole to the corresponding diazocarbazole.[98]

The products **147a–e** were subjected to cyclization with $POCl_3$ as shown in Scheme 2. At 60 °C, **147a** undergoes facile cyclization to give the corresponding product **148a** in good yield. The reaction works for other condensation products **147b-e** (Scheme 2 and Table 2) as well. The structure of **148c** was also confirmed by the single crystal X-ray analysis (Figure 18). When the same reaction was performed at 120 °C, two regioisomeric quinocarbazoles were formed. Compounds **149a–e** were formed as major products along with minor products **150a–e** (Scheme 2). These two isomers have been identified from ^{1}H NMR spectrum. The presence of two singlets at δ 8.85 and 7.96 ppm differentiate the regioisomer **150c** from the other regioisomer **149c** in which two doublets are present in the same region. The structures of these two isomers were also confirmed by the single crystal X-ray analysis (Figure 19).

Scheme 2. Synthesis of Quinocarbazoles

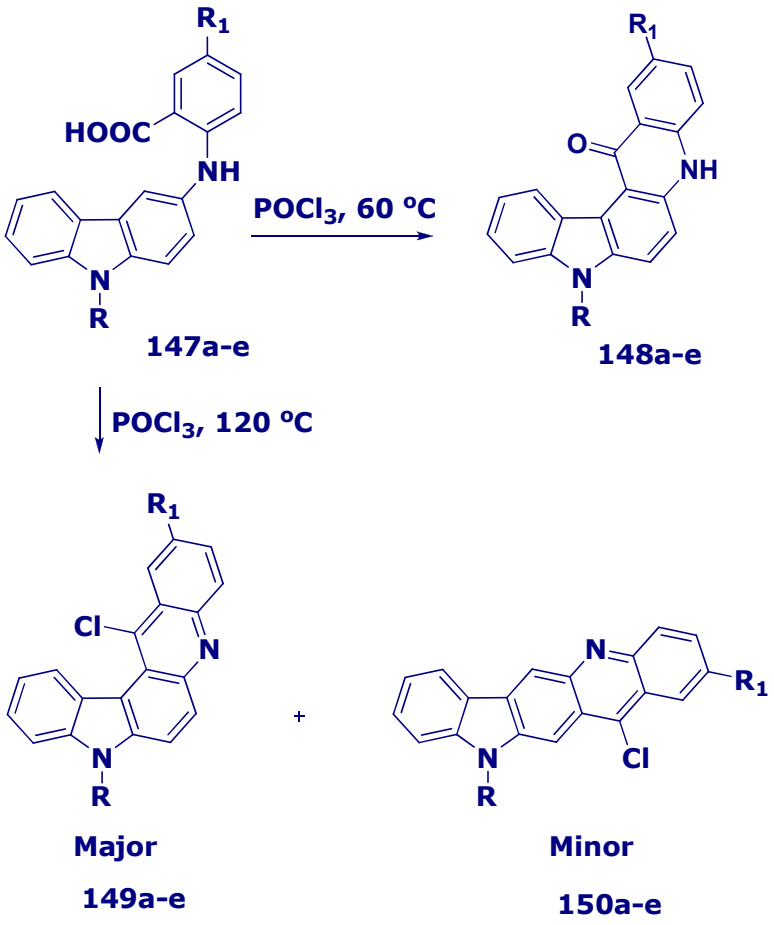


Figure 18. ORTEP diagram of 148c

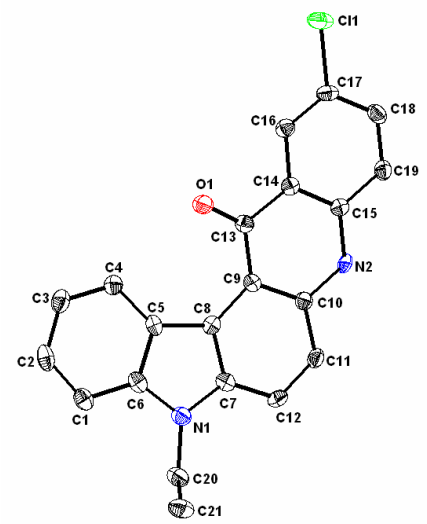
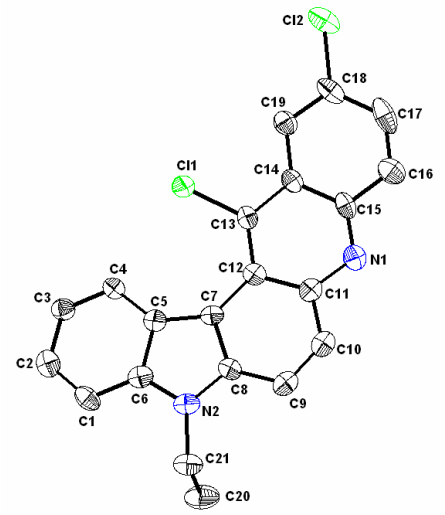


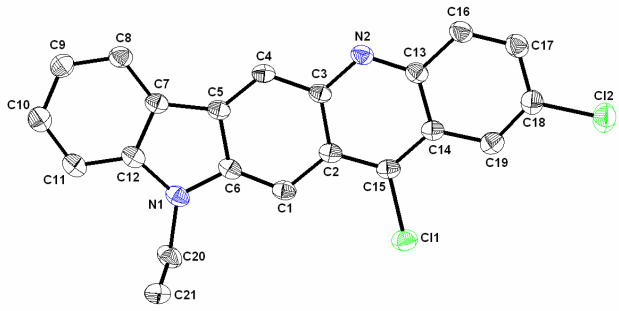
Table 2. Synthesis of quinocarbazoles

S. No.	Condensed product	Cyclized product	Time (h)	Yield (%)
1	**147a**	**148a**	1	71
		149a	1	73
		150a	1	10
2	**147b**	**148b**	1	76
		149b	1	78
		150b	1	12
3	**147c**	**148c**	1	73
		149c	1	74
		150c	1	14
4	**147d**	**148d**	1	72
		149d	1	75
		150d	1	13
5	**147e**	**148e**	1	75
		149e	1	75
		150e	1	12

Figure 19. ORTEP diagrams of 149c and 150c



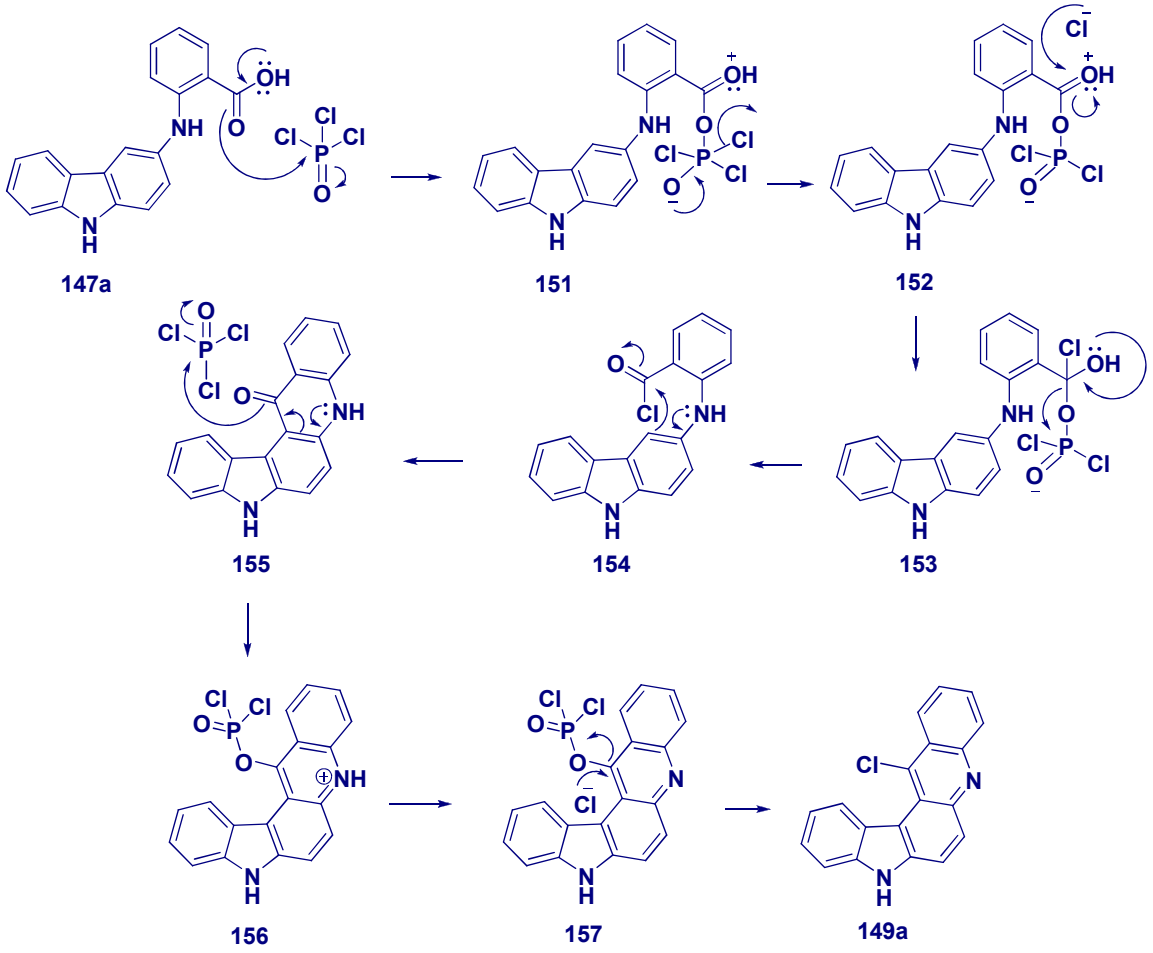
149c



150c

A possible mechanism for the formation of **149a** from **147a** was presented in Scheme 3. Initially, the carboxlic acid **147a** converted into acyl chloride **154** followed by intramolecular Friedel-Craft's acylation results in **155**. **155** reacts with $POCl_3$ to provide the intermediate iminium ion **156** which finally converted into **149a** as shown in Scheme 3.

Scheme 3. Representative mechanism for the formation 149a from 147a



1.3. Synthesis of chromenocarbazoles

The same method was successfully extended to 3-hydroxy-9-ethylcarbazole **158** as shown in Scheme 4. 3-Hydroxy-9-ethylcarbazole **158** condensed with *o*-halobenzoic acids **146a-d** to provide the corresponding products **159a–d** in good yield and the results are summarized in Table 3.

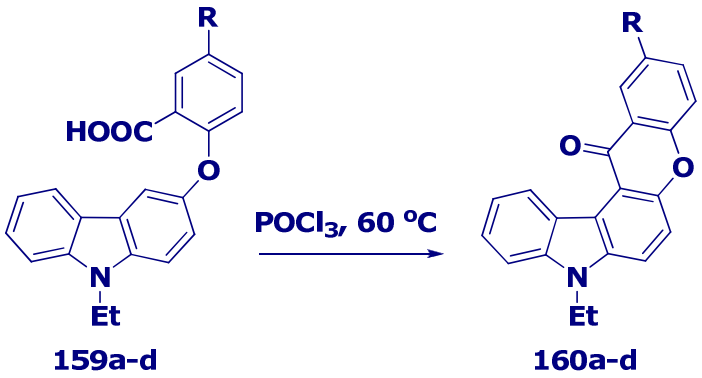
Scheme 4. Synthesis of condensed products

Table 3. Synthesis of condensed products

S. No.	R	X	Condensed product	Time (h)	Yield (%)
1	H	I	**159a**	8	73
2	Cl	I	**159b**	8	75
3	Br	I	**159c**	8	73
4	NO_2	I	**159d**	6	71
5	H	Br	**159a**	10	73

As shown in Scheme 5, the condensed products **159a–d** underwent the cyclization to the corresponding chromenocarbazoles **160a-d** in good yields (Table 4) on treatment with excess of $POCl_3$. In this case, only one regioisomer was formed at 60 °C. The structure of **160a** was also confirmed by the single crystal X-ray analysis (Figure 20).

Scheme 5. Synthesis of chromenocarbazoles

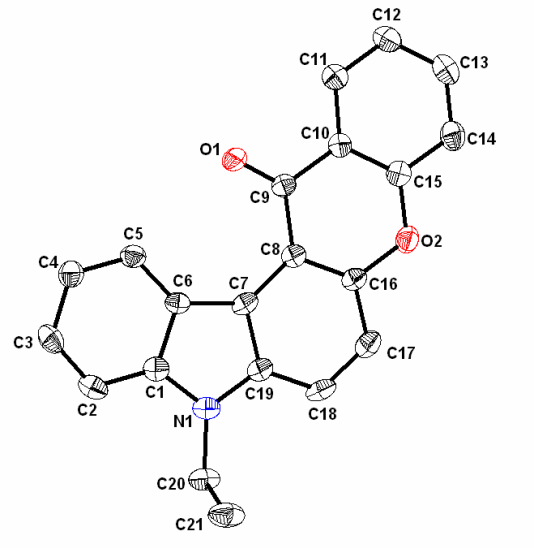


159a-d 160a-d

Table 4. Synthesis of chromenocarbazoles

S. No.	Condensed product	Cyclized product	Time (h)	Yield (%)
1	**159a**	**160a**	2	73
2	**159b**	**160b**	2	75
3	**159c**	**160c**	2	73
4	**159d**	**160d**	2	71

Figure 20. ORTEP diagram of 160a

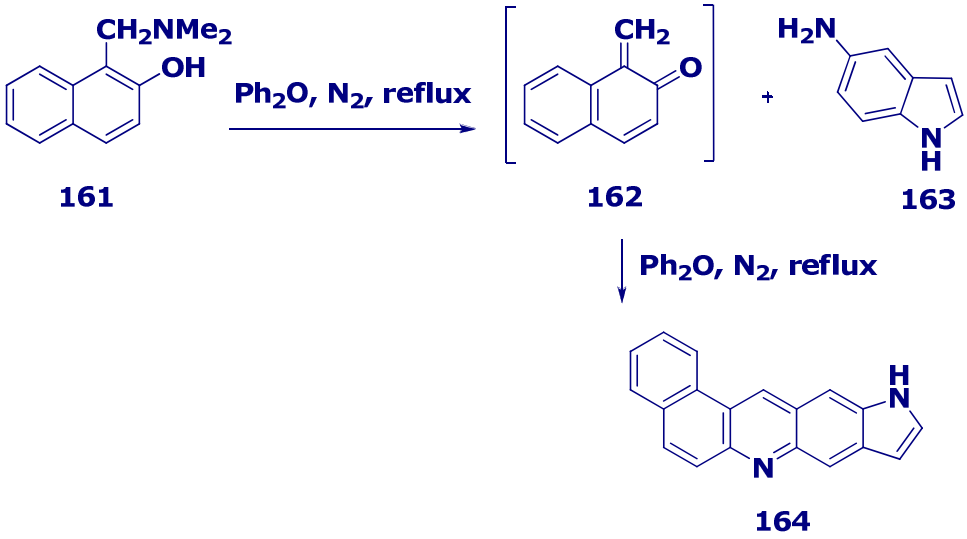


1.4. Synthesis of pyrroloacridones and pyrroloacridines

Pyrroloacridines and pyrroloacridones are of particular interest because they have a variety of interesting biological activities. Significantly, members of this family are active in assays for antihelmintic,[99] antitumor,[99,100] antifungal,[101] and DNA binding.[102-104] These abilities are specifically important in inhibiting the growth of cancerous cells, making these compounds ideal for developing novel anticancer drugs. To date, the only pyrroloacridines that have been published from marine sources are plakinidines A–E and alpkinidine.[99,105–108] Only a few reports[109] are available for the synthesis of pyrroloacridines.

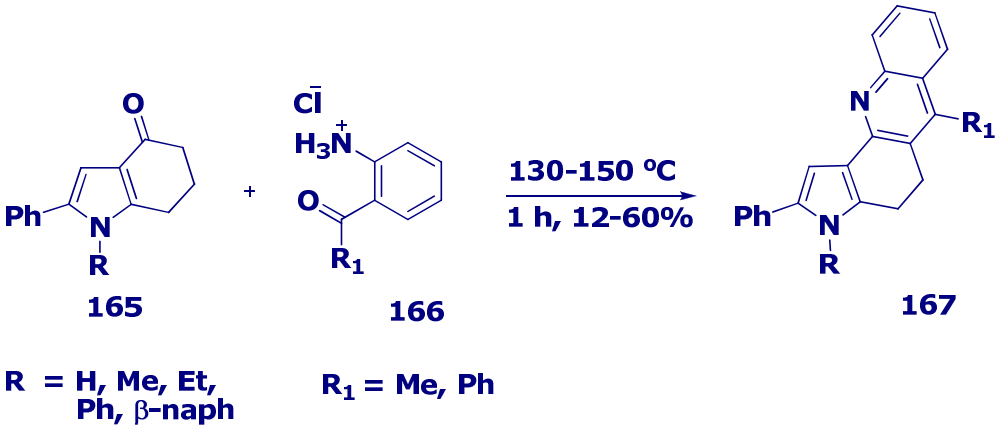
Bilgic and Young have reported[110] the formation of the benzopyrrolo[2,3-*b*]acridine **164** in a reaction between 1-(*N*,*N*-dimethylaminomethyl)naphth-2-ol **161** and 5-aminoindole **163**. A quinone methide **162** is believed to be involved as an intermediate (Eq. 22).

Eq. 22



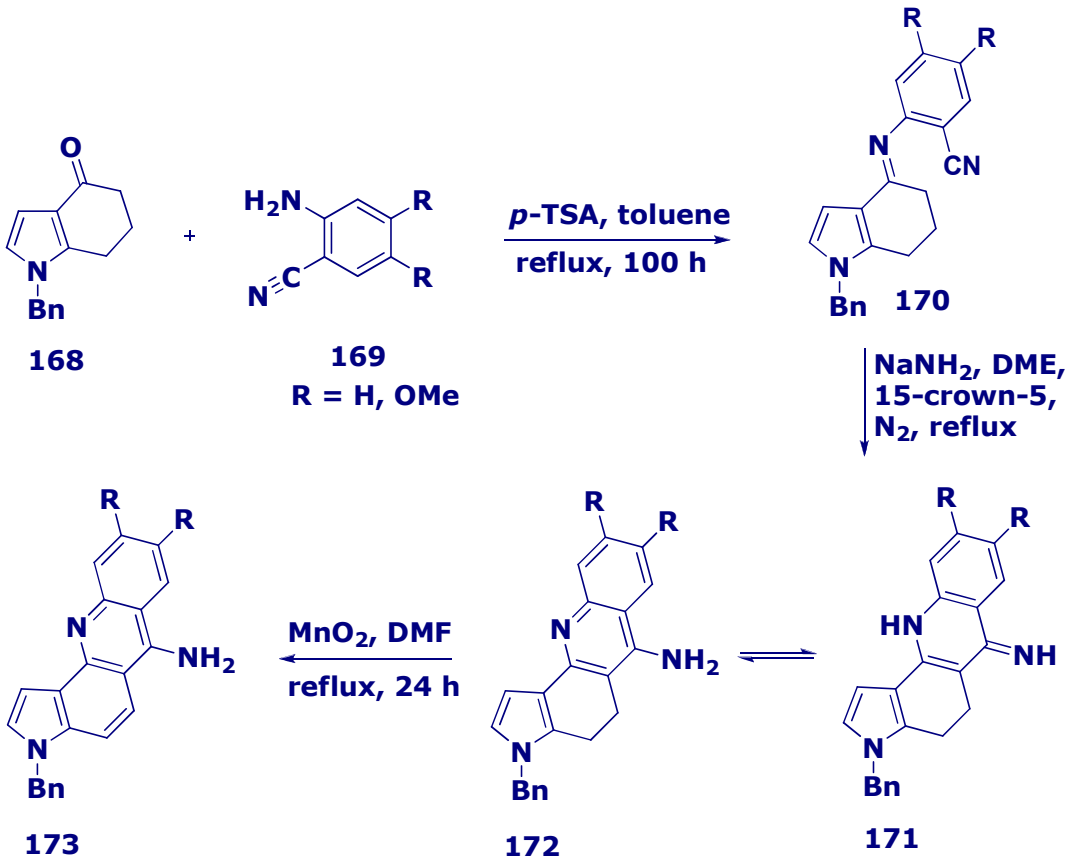
As shown in Eq. 23, Takagi *et al*. have synthesized[111] a number of 4,5-dihydropyrrolo[2,3-*c*]acridines **167** from 4-oxo-4,5,6,7-tetrahydroindoles **165** and **166**.

Eq. 23



Munawar *et al*. reported[112] the synthesis of 6-amino-3-benzylpyrroloacridine **173** from *N*-benzyl-4,5,6,7-tetrahydroindol-4-one **168** and anthranilonitriles **169** via imine **170** formation followed by cyclization into **171** which is in equilibration with **172** and subsequent aromatization (Eq. 24).

Eq. 24



As a result of their significant potential as therapeutics, a considerable synthetic attention has been directed at the development of efficient methods toward the construction of pyrroloacridine moiety. So, we became interested in synthesizing pyrroloacridines which are isomeric analogues of bioactive pyrroloacridines. Our method is based on CuI mediated *N*-arylation of 5-amino-2-methylindole with *o*-halobenzoic acids by Ullmann-Goldberg condensation followed by intramolecular Friedel-Crafts cyclization with $POCl_3$.

As shown in Scheme 6, 5-amino-2-methylindole **174a** was subjected to Ullmann–Goldberg condensation with 2-iodobenzoic acid **146a** in the presence of CuI (10 mol%) and K_2CO_3 (1.0 equiv.) at 80 °C in DMSO to give the condensation product **175a**. Due to the activation of halogens by the ortho-substituted carboxylic group, a facile condensation occurred. The results, presented in Table 5, indicate the condensation products are obtained in good yields. 2-Bromo and 2-chloro benzoic acids required relatively longer reaction time than their iodo analogue due to the order of halogen displacement I > Br > Cl.

Scheme 6. Synthesis of condensed products

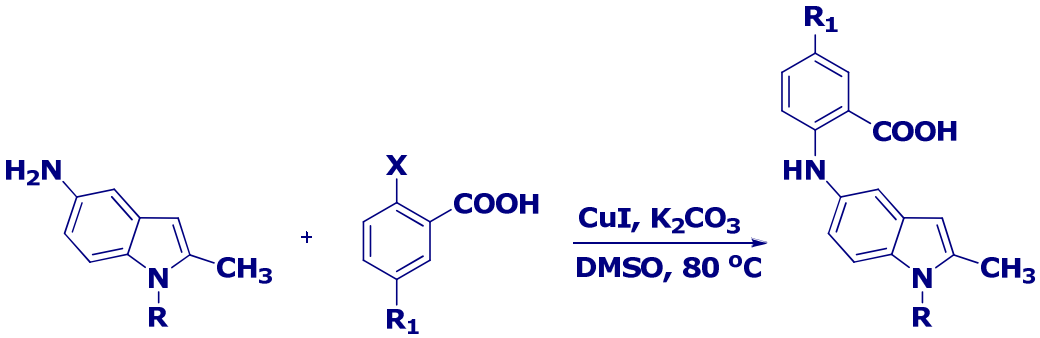


Table 5. Synthesis of condensed products

S. No.	R	R_1	X	Condensed product	Time (h)	Yield (%)
1	H	H	I	**175a**	0.5	86
2	H	H	Br	**175a**	2.0	80
3	Me	OMe	Br	**175b**	2.0	81
4	Me	H	I	**175c**	0.5	91
5	Me	H	Br	**175c**	2.0	82
6	Me	Cl	I	**175d**	0.5	87
7	Me	Br	I	**175e**	0.5	79
8	Me	NO_2	I	**175f**	0.25	84
9	SO_2Ph	H	I	**175g**	0.5	71
10	SO_2Ph	H	Br	**175g**	2.0	68
11	SO_2Ph	H	Cl	**175g**	3.0	65
12	SO_2Ph	Cl	I	**175h**	0.5	75
13	SO_2Ph	Br	I	**175i**	0.5	77

The condensation products **175a–i** were subjected to cyclization with $POCl_3$ which resulted in the corresponding pyrroloacridones and pyrroloacridines depending on the reaction temperature. As shown in Scheme 7, the condensation products **175a–f** have produced the corresponding pyrroloacridones **176a–f** after being treated with an excess of $POCl_3$ in good yield at 60 °C. The results are summarized in Table 6. The condensation products **175g–i** could not give the corresponding pyrroloacridones at 60 °C. This may be due to the strong electron-withdrawing nature of phenylsulphonyl group. When the reaction was performed at 120 °C, the condensation products **175a–i** gave the corresponding pyrroloacridines **177a–i**. The absence of two singlets (due to 4^{th} and 7^{th} position protons of indole) in the aromatic region of ^1H NMR spectrum, clearly reveals the exclusive formation of regioisomeric pyrroloacridines **177a–i**. This is further confirmed by the characterization of the structure of **177g** by the single crystal X-ray analysis. The ORTEP diagram of **177g** is shown in Figure 21.

Scheme 7. Synthesis of pyrrolo[3,2-*a*]acridones and pyrrolo[3,2-*a*]acridines

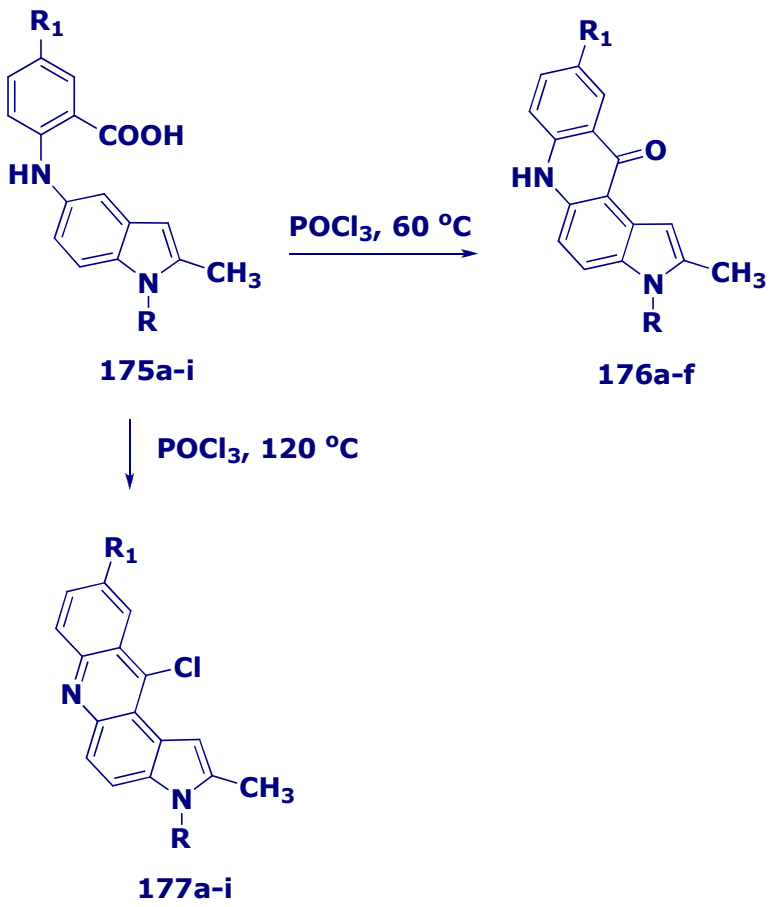


Figure 21. ORTEP diagram of 177g

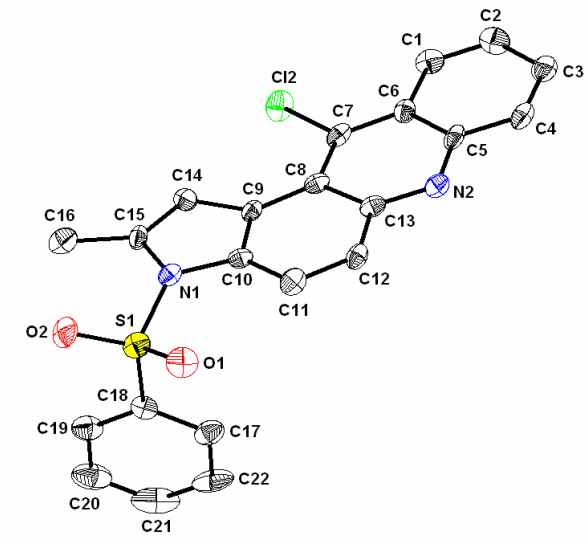


Table 6. Synthesis of pyrrolo[3,2-*a*]acridones and pyrrolo[3,2-*a*]acridines

S. No.	Condensed product	Cyclized product	Time (h)	Yield (%)
1	**175a**	**176a**	0.5	75
		177a	3.0	76
2	**175b**	**176b**	0.5	74
		177b	3.0	71
3	**175c**	**176c**	0.5	72
		177c	3.0	75
4	**175d**	**176d**	0.5	77
		177d	3.0	77
5	**175e**	**176e**	0.5	76
		177e	3.0	73
6	**175f**	**176f**	0.5	79
		177f	3.0	82
7	**175g**	**177g**	3.0	73
	175h	**177h**	3.0	72
8	**175i**	**177i**	3.0	75

1.5. Conclusion

In conclusion, we have developed a new, fast and efficient route to synthesize of chromenocarbazoles and pyrroloacridines via Ullmann-Goldberg condensation followed by intramolecular Friedel-Crafts cyclization with $POCl_3$.

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.

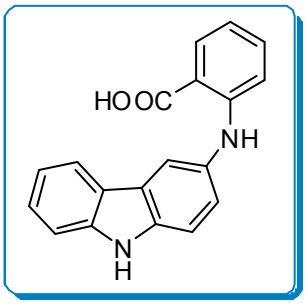
General procedure A

A mixture of 3-aminocarbazoles **145a-b** (1.0 mmol), 2-iodobenzoic acids **146a-e** (1.0 mmol), CuI (0.1 mmol) and K_2CO_3 (2.0 mmol) in DMSO was heated at 80 ^{o}C for required time. After the completion of the reaction, as indicated by TLC, the reaction mixture was poured over water and extracted with ethyl acetate (3 X 30 mL). The organic layer was dried over anhyd. Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude materials were purified by column chromatography (silica gel, 100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to afford the pure products.

2-(9*H*-Carbazolylamino)benzoic acid (147a):

The condensation product **147a** was obtained by the reaction of 3-amino-9*H*-carbazole **145a** (0.18g, 1.0 mmol) and 2-iodobenzoic acid **146a** (0.25g, 1.0 mmol) by following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 73%



Mp: 163 – 164 °C

IR (KBr) ν_{max} cm^{-1}: 3387, 1649, 1575, 1493, 1238, 1126, 748

^{1}H NMR (400 MHz) δ: 8.86 (1H, s), 8.19 (1H, d, *J* = 4.0 Hz), 8.13 (1H, d, *J* = 8.0 Hz), 8.01 (1H, d, *J* = 8.0 Hz), 7.78 (1H, t, *J* = 6.0 Hz), 7.64 (1H, t, *J* = 8.0 Hz), 7.48 (1H, d, *J* = 8.0 Hz), 7.37 (1H, t, *J* = 8.0 Hz), 7.27–7.24 (2H, m), 7.06 (1H, d, *J* = 8.0 Hz), 6.99 (1H, d, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 168.8, 144.6, 142.9, 141.1, 135.9, 134.3, 132.8, 130.9, 130.2, 129.5, 128.8, 127.5, 123.0, 121.7, 120.8, 119.9, 117.1, 110.2, 109.1

LCMS (m/z): 303 ($M+H^+$)

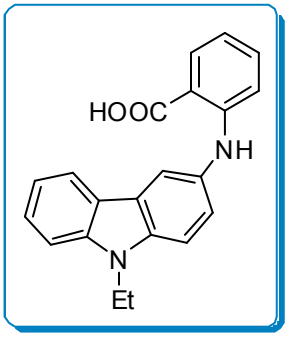
Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27%

Found: C, 75.52; H, 4.61; N, 9.32%

2-(9-Ethyl-9*H*-carbazolylamino)benzoic acid (147b):

The product **147b** was obtained by the reaction of 3-amino-9-ethylcarbazole **145b** (0.21g, 1.0 mmol) and 2-iodobenzoic acid **146a** (0.25g, 1.0 mmol) by following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 73%



Mp: 173–174 °C

IR (KBr): ν_{max} cm^{-1}: 3343, 2986, 1666, 1580, 1447, 1242, 1159, 735

^{1}H NMR (400 MHz) δ: 9.63 (1H, s), 8.13 (1H, d, *J* = 7.6 Hz), 8.04 (1H, s), 7.87 (1H, d, *J* = 8.0 Hz), 7.62–7.57 (2H, m), 7.43 (1H, t, *J* = 7.6 Hz), 7.35–7.27 (2H, m), 7.15 (1H, t, *J* = 7.6 Hz), 6.94 (1H, d, *J* = 8.4 Hz), 6.66 (1H, t, *J* = 7.6 Hz), 4.43 (2H, q, *J* = 7.2 Hz), 1.31 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz) δ: 170.7, 150.2, 140.5, 137.5, 134.7, 132.2, 132.0, 126.3, 123.8, 123.4, 122.4, 121.1, 119.0, 116.7, 116.4, 113.2, 111.4, 110.2, 109.5, 37.5, 14.1

LC–MS (m/z): 331 ($M+H^+$)

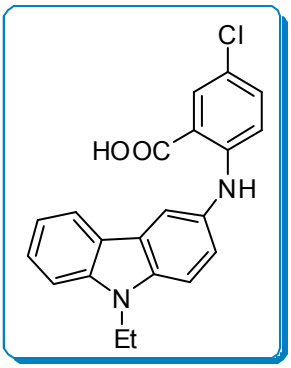
Anal. Calcd. For $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48%

Found: C, 76.18; H, 5.45; N, 8.37%

5-Chloro-2-(9-ethyl-9*H*-carbazolylamino)benzoic acid (147c):

The condensation product **147c** was obtained by the reaction of 3-amino-9-ethylcarbazole **145b** (0.21g, 1.0 mmol) and 5-chloro-2-iodobenzoic acid **146b** (0.28g, 1.0 mmol) by following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 72%



Mp: 227–229 °C

IR (KBr) ν_{max} cm^{-1}: 3341, 2967, 1668, 1572, 1435, 1227, 1140, 816 717

^{1}H NMR (400 MHz) δ: 9.27 (1H, s), 7.62 (1H, d, *J* = 7.6 Hz), 7.55–7.53 (2H, m), 7.08–7.02 (3H, m), 6.94–6.92 (1H, m), 6.81–6.75 (2H, m), 6.57 (1H, d, *J* = 9.2 Hz), 3.96 (2H, q, *J* = 7.2 Hz), 1.02 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz) δ: 172.0, 151.3, 142.6, 139.8, 136.0, 134.4, 133.8, 133.4, 128.3, 126.0, 125.7, 124.6, 122.7, 121.1, 119.0, 117.0, 114.4, 111.6, 111.0, 39.8, 16.1

LC–MS (m/z): 364.5 (M), 366.5 (M+2)

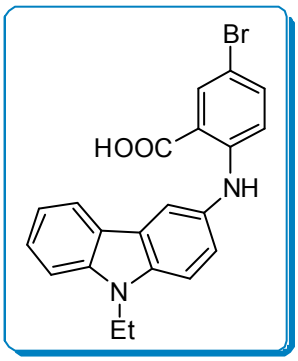
Anal. Calcd. for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68%
Found: C, 69.14; H, 4.72; N, 7.93%

5-Bromo-2-(9-ethyl-9*H*-carbazolylamino)benzoic acid (147d):

The condensation product **147d** was obtained by the reaction of 3-amino-9-ethylcarbazole **145b** (0.21g, 1.0 mmol) and 5-bromo-2-iodobenzoic acid **146c** (0.32g, 1.0 mmol) by following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 70%

Mp: 181–183 °C



IR (KBr) ν_{max} cm^{-1}: 3343, 2920, 1667, 1611, 1568, 1493, 1377, 1229, 814, 744

^{1}H NMR (400 MHz) δ: 8.09 (1H, s), 7.99 (1H, s), 7.55 (2H, d, *J* = 5.2 Hz), 7.42 (2H, s), 7.28 (2H, s), 7.13 (2H, s), 7.01 (2H, s), 4.40 (2H, s), 1.29 (3H, m)

^{13}C NMR (100 MHz) δ: 169.9, 149.1, 140.3, 137.6, 133.7, 131.6, 131.2, 125.9, 123.8, 123.5, 122.4, 120.4, 119.9, 118.7, 116.9, 114.6, 112.0, 109.1, 108.6, 37.6, 13.8

LC-MS (m/z): 408 (M), 410 (M+2)

Anal. Calcd. for $C_{21}H_{17}BrN_2O_2$: C, 61.63; H, 4.19; N, 6.84%
Found: C, 61.67; H, 4.18; N, 6.82%

5-Nitro-2-(9-ethyl-9*H*-carbazolylamino)benzoic acid (147e)

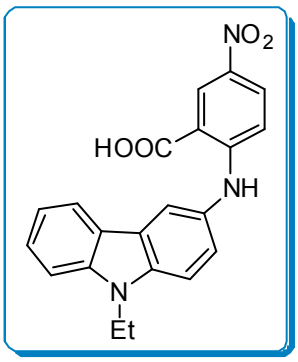
The condensation product **147e** was obtained by the reaction of 3-amino-9-ethylcarbazole (0.21g, 1.0 mmol) **145b** and 5-nitro-2-iodobenzoic acid **146d** (0.29g, 1.0 mmol) by following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 18% ethyl acetate in hexanes.

Yield: 74%

Mp: 177–178 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3478, 2974, 2924, 1717, 1589, 1522, 1492, 1319, 1231, 1146, 928, 802

^{1}H NMR (400 MHz) δ: 10.45 (1H, s), 8.77 (1H, s), 7.98–7.94 (4H, m), 7.49 (1H, d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 7.14 (2H, s), 6.89 (1H, d, *J* = 8.0 Hz), 4.36 (2H, q, *J* = 6.0 Hz), 1.37 (3H, s)



^{13}C NMR (100 MHz) δ: 169.5, 148.8, 140.1, 137.3, 133.5, 131.4, 130.9, 125.8, 123.5, 123.2, 122.1, 120.2, 119.5, 118.6, 116.5, 114.5, 111.9, 109.1, 108.6, 37.3, 13.6

LC–MS (m/z): 376 ($M+H^+$)

Anal. Calcd. for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19%
Found: C, 67.21; H, 4.52; N, 11.32%

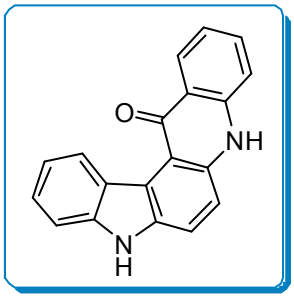
General Procedure B

The condensation products **147a-e** (1.0 mmol) in $POCl_3$ (5 mL) were heated for 1 h at 60 °C. Then the reaction mixture was poured onto the crushed ice and then neutralized with 10% aq. NaOH solution. Then it was extracted with dichloromethane (3 × 30 mL) and the organic layer was dried over anhyd. Na_2SO_4. The solvent was evaporated under reduced pressure and the crude materials were chromatographed over silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products of indoloacridinones. When the reaction was performed at 120 °C, indolo[3,2-*a*]acridines **149a-e** and indolo[2,3-*b*]acridines **150a-e** were obtained in major and minor quantities, respectively.

8,13-Dihydro-5*H*-indolo[3,2-*a*]acridin-13-one (148a):

The compound **148a** was prepared from the condensation product **147a** (0.32g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 71%



Mp: 296–298 °C

IR (KBr) ν_{max} cm^{-1}: 3395, 2067, 1747, 1581, 1469, 1261, 1099, 804

^{1}H NMR (400 MHz) δ: 11.81 (1H, s), 11.71 (1H, s), 9.81 (1H, d, *J* = 8.0 Hz), 8.38 (1H, d, *J* = 8.0 Hz), 8.00 (1H, d, *J* = 8.0 Hz), 7.69–7.63 (2H, m), 7.58–7.51 (2H, m), 7.38 (1H, t, *J* = 6.0 Hz), 7.25 (1H, t, *J* = 6.0 Hz), 7.15 (1H, t, *J* = 6.0 Hz)

^{13}C NMR (100 MHz) δ: 177.7, 140.4, 139.9, 137.9, 135.2, 132.6, 128.6, 126.6, 125.6, 123.6, 121.8, 120.9, 119.6, 118.2, 117.9, 117.2, 117.1, 116.6, 111.1

LC–MS (m/z): 285 ($M+H^+$)

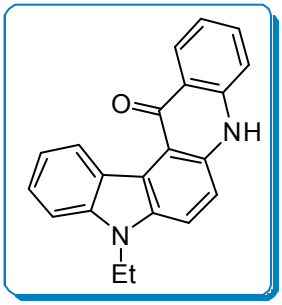
Anal. Calcd. for $C_{19}H_{12}N_2O$: C, 80.27; H, 4.25; N, 9.85%

Found: C, 80.15; H, 4.29; N, 9.96%

8-Ethyl-8,13-dihydro-5*H*-indolo[3,2-*a*]acridin-13-one (148b):

The compound **148b** was prepared from the condensation product **147b** (0.33g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 76%



Mp: 277–278 °C

IR (KBr) ν_{max} cm^{-1}: 3266, 2930, 2072, 1738, 1584, 1474, 1150, 804

^{1}H NMR (400 MHz) δ: 12.15 (1H, s), 9.89 (1H, d, J = 8.0 Hz), 8.38 (1H, d, J = 8.0 Hz), 8.18 (1H, d, J = 9.2 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.65–7.61 (2H, m), 7.46 (1H, t, J = 7.3 Hz), 7.26 (1H, t, J = 8.0 Hz), 7.19 (1H, t, J = 8.0 Hz), 4.56 (2H, q, J = 8.0 Hz), 1.32 (3H, t, J = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 180.1, 142.6, 142.5, 140.6, 137.4, 135.4, 131.5, 129.1, 128.4, 125.8, 124.3, 123.6, 120.9, 120.4, 120.2, 119.8, 119.6, 119.4, 111.7, 39.9, 17.0

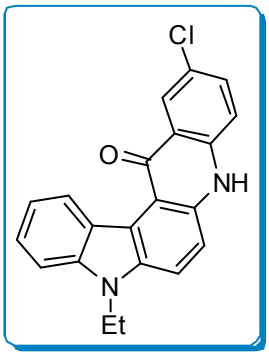
LC–MS (m/z): 313 ($M+H^+$)

Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97%

Found: C, 80.61; H, 5.14; N, 9.00%

2-Chloro-8-ethyl-8,13-dihydro-5*H*-indolo[3,2-*a*]acridin-13-one (148c):

The compound **148c** was prepared from the condensation product **147c** (0.36g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 73%

Mp: 315–317 °C

IR (KBr) ν_{max} cm^{-1}: 3439, 2971, 2928, 1632, 1557, 1474, 1321, 1024, 812

^{1}H NMR (400 MHz) δ: 12.35 (1H, s), 9.84 (1H, d, *J* = 8.4 Hz), 8.30 (1H, s), 8.20 (1H, d, *J* = 9.2 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.72–7.63 (3H, m), 7.46 (1H, t, *J* = 8.0 Hz), 7.20 (1H, t, *J* = 8.0 Hz), 4.56 (2H, q, *J* = 8.0 Hz), 1.31 (3H, t, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 176.4, 140.0, 138.5, 137.9, 135.0, 132.8, 128.8, 126.0, 125.4, 125.3, 124.1, 123.1, 122.4, 119.8, 118.5, 117.9, 117.6, 116.9, 109.2, 37.4, 14.5

LC–MS (m/z): 346.5 (M), 348.5 (M+2)

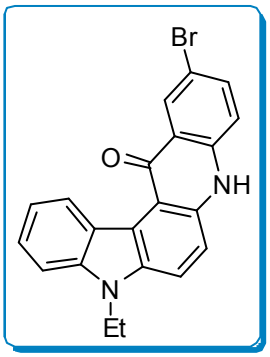
Anal. Calcd. for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08%

Found: C, 72.69; H, 4.40; N, 8.10%

2-Bromo-8-ethyl-8,13-dihydro-5*H*-indolo[3,2-*a*]acridin-13-one (148d):

The compound **148d** was prepared from the condensation product **147d** (0.41g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 72%



Mp: 301–302 °C

IR (KBr) ν_{max} cm^{-1}: 3271, 2967, 2924, 2864, 1628, 1578, 1557, 1022, 812

^{1}H NMR (400 MHz) δ: 12.35 (1H, s), 9.84 (1H, d, *J* = 8.4 Hz), 8.45 (1H, d, *J* = 2.4 Hz), 8.19 (1H, d, *J* = 8.8 Hz), 7.82–7.75 (2H, m), 7.64–7.61 (2H, m), 7.46 (1H, t, *J* = 8.0 Hz), 7.20 (1H, t, *J* = 7.8 Hz), 4.55 (2H, q, *J* = 7.2 Hz), 1.31 (3H, t, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 178.9, 142.6, 141.3, 140.5, 137.9, 137.6, 131.3, 131.1, 128.6, 125.6, 125.5, 122.5, 121.1, 120.5, 120.3, 119.6, 119.0, 115.7, 111.8, 39.9, 17.0

LC–MS (m/z): 390 (M), 392 (M+2)

Anal. Calcd. for $C_{21}H_{15}BrN_2O$: C, 64.46; H, 3.86; N, 7.16%
Found: C, 64.41; H, 3.84; N, 7.20%

2-Nitro-8-ethyl-8,13-dihydro-5*H*-indolo[3,2-*a*]acridin-13-one (148e):

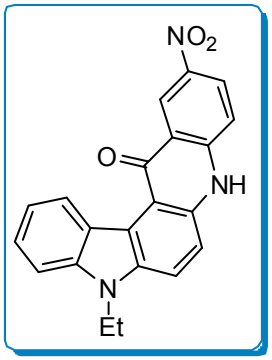
The compound **148e** was prepared from the condensation product **147e** (0.37g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 33% ethyl acetate in hexanes.

Yield: 75%

Mp: 320–322 °C

IR (KBr) ν_{max} cm^{-1}: 3418, 2924, 2857, 1616, 1555, 1516, 1460, 1331, 723

^{1}H NMR (400 MHz) δ: 12.61 (1H, s), 9.79 (1H, d, *J* = 12.0 Hz), 9.12 (1H, s), 8.38 (1H, d, *J* = 8.0 Hz), 8.24 (1H, d, *J* = 8.0 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.71–7.66 (2H, m), 7.50 (1H, t, *J* = 4.0 Hz), 7.23 (1H, t, *J* = 4.0 Hz), 4.57 (2H, q, *J* = 8.0 Hz), 1.33 (3H, t, *J* = 8.0 Hz)



^{13}C NMR (100 MHz) δ: 179.8, 145.9, 143.4, 142.9, 140.0, 138.4, 131.2, 129.3, 126.6, 125.4, 122.8, 121.3, 120.8, 120.5, 119.6, 119.0, 117.3, 114.7, 111.9, 40.0, 17.0

LC–MS (m/z): 356 ($M-H^+$)

Anal. Calcd. for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76%
Found: C, 70.60; H, 4.21; N, 11.73%

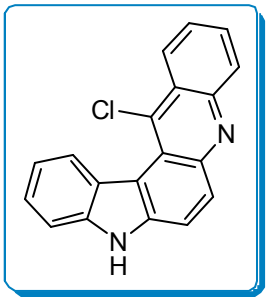
13-Chloro-8*H*-indolo[3,2-*a*]acridine (149a):

The compound **149a** was prepared from the condensation product **147a** (0.3g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 73%

Mp: 207–208 °C

IR (KBr) ν_{max} cm^{-1}: 2067, 1732, 1604, 1024, 1473, 1375, 1148, 1028, 817, 640, 551



^{1}H NMR (400 MHz) δ: 12.12 (1H, s), 8.90 (1H, s), 8.63 (1H, d, *J* = 8.0 Hz), 8.45 (1H, d, *J* = 4.0 Hz), 8.15 (2H, d, *J* = 13.0 Hz), 8.07 (1H, d, *J* = 8.0 Hz), 7.59 (2H, d, *J* = 4.0 Hz), 7.54–7.53 (1H, d, *J* = 4.0 Hz), 7.37 (1H, t, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 145.9, 142.3, 137.8, 135.2, 133.7, 131.0, 130.6, 130.0, 128.6, 125.8, 125.6, 123.0, 122.7, 120.8, 120.6, 118.5, 115.5, 111.6, 110.3

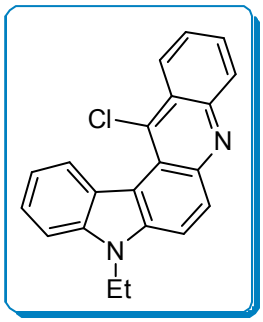
LC–MS (m/z): 302.5 (M), 304.5 (M+2)

Anal. Calcd. for $C_{19}H_{11}ClN_2$: C, 75.38; H, 3.66; N, 9.25%
Found: C, 75.45; H, 3.68; N, 9.19%

13-Chloro-8-ethyl-8*H*-indolo[3,2-*a*]acridine (149b):

The compound **149b** was prepared from the condensation product **147b** (0.33g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 78%



Mp: 219–220 °C

IR (KBr) ν_{max} cm^{-1}: 2924, 1740, 1634, 1584, 1477, 1366, 1150, 1022, 804, 631, 557

^{1}H NMR (400 MHz) δ: 8.89 (1H, d, *J* = 8.3 Hz), 8.65 (1H, d, *J* = 8.8 Hz), 8.48–8.44 (2H, m), 8.08 (1H, d, *J* = 9.2 Hz), 7.88 (1H, t, *J* = 7.0 Hz), 7.76 (1H, t, *J* = 7.2 Hz), 7.63 (1H, d, *J* = 8.2 Hz), 7.53 (1H, t, *J* = 7.2 Hz), 7.39 (1H, t, *J* = 7.8 Hz), 4.62 (2H, q, *J* = 6.9 Hz), 1.56 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz) δ: 145.4, 143.5, 138.8, 137.5, 130.3, 129.5, 127.4, 127.0, 126.9, 126.5, 124.9, 124.6, 123.4, 122.7, 119.7, 118.6, 111.7, 109.4, 107.7, 38.0, 14.6

LC–MS (m/z): 330.5 (M), 332.5 (M+2)

Anal. Calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; N, 8.47%

Found: C, 76.20; H, 4.55; N, 8.50%

2,13-Dichloro-8-ethyl-8*H*-indolo[3,2-*a*]acridine (149c):

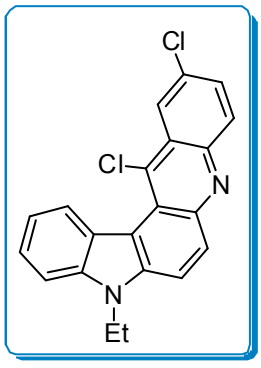
The compound **149c** was prepared from the condensation product **147c** (0.36g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 74%

Mp: 223–224 °C

IR (KBr) ν_{max} cm^{-1}: 2963, 1707, 1584, 1435, 1337, 1244, 1078, 814, 636, 550

^{1}H NMR (400 MHz) δ: 8.87 (1H, d, *J* = 8.0 Hz), 8.60 (1H, d, *J* = 2.0 Hz), 8.20 (2H, d, *J* = 8.0 Hz), 8.01 (1H, d, *J* = 9.2 Hz), 7.72 (1H, d, *J* = 7.2 Hz), 7.61 (1H, d, *J* = 8.0 Hz), 7.52 (1H, t, *J* = 6.8 Hz), 7.39 (1H, t, *J* = 8.0 Hz), 4.60 (2H, q, *J* = 7.2 Hz), 1.56 (3H, t, *J* = 7.2 Hz)



^{13}C NMR (100 MHz) δ: 150.1, 146.5, 141.3, 140.5, 136.9, 135.6, 133.2, 132.7, 131.4, 129.4, 128.0, 126.2, 125.7, 125.6, 123.1, 122.2, 120.1, 114.2, 111.9, 40.5, 17.2

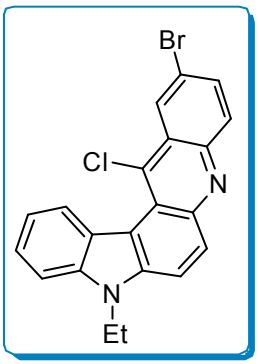
LC–MS (m/z): 364 (M), 366 (M+2), 368 (M+4)

Anal. Calcd. for $C_{21}H_{14}Cl_2N_2$: C, 69.05; H, 3.86; N, 7.67%
Found: C, 69.03; H, 3.82; N, 7.70%

2-Bromo-13-chloro-8-ethyl-8*H*-indolo[3,2-*a*]acridine (149d):

The compound **149d** was prepared from the condensation product **147d** (0.41g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 75%



Mp: 266–267 °C

IR (KBr) ν_{max} cm^{-1}: 2965, 1584, 1460, 1323, 1142, 1071, 953, 814, 781, 654

^{1}H NMR (400 MHz) δ: 8.85 (1H, d, *J* = 8.4 Hz), 8.75 (1H, d, *J* = 1.6 Hz), 8.16–8.12 (2H, m), 7.98 (1H, d, *J* = 9.2 Hz), 7.82 (1H, d, *J* = 9.2 Hz), 7.59 (1H, d, *J* = 8.0 Hz), 7.51 (1H, t, *J* = 7.6 Hz), 7.38 (1H, t, *J* = 7.2 Hz), 4.56 (2H, q, *J* = 8.0 Hz), 1.54 (3H, t, *J* = 7.2 Hz)

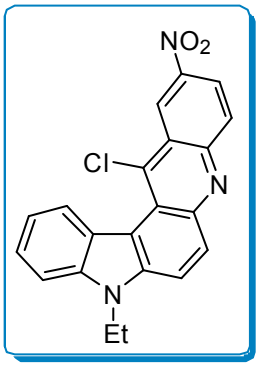
^{13}C NMR (100 MHz) δ: 147.8, 145.2, 143.6, 138.8, 137.9, 132.6, 130.7, 128.9, 126.8, 126.6, 125.9, 124.3, 123.7, 123.0, 121.3, 119.7, 117.6, 111.7, 109.4, 37.9, 14.6

LC–MS (m/z): 408.5 (M), 410.5 (M+2), 412.5 (M+4)

Anal. Calcd for $C_{21}H_{14}BrClN_2$: C, 61.56; H, 3.44; N, 6.84%
Found: C, 60.63; H, 3.10; N, 6.24%

2-Nitro-13-chloro-8-ethyl-8*H*-indolo[3,2-*a*]acridine (149e):

The compound **149e** was prepared from the condensation product **147e** (0.37g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 8% ethyl acetate in hexanes.



Yield: 75%

Mp: 255–257 °C

IR (KBr) ν_{max} cm^{-1}: 2962, 1708, 1575, 1421, 1337, 1256, 1069, 826, 647, 551

^{1}H NMR (400 MHz) δ: 9.44 (1H, s), 8.79 (1H, d, *J* = 8.28 Hz), 8.38 (1H, d, *J* = 7.6 Hz), 8.24 (1H, d, *J* = 8.0 Hz), 8.09 (1H, d, *J* = 8.0 Hz), 8.03 (1H, d, *J* = 7.8 Hz), 7.57 (1H, d, *J* = 7.3 Hz), 7.50 (1H, t, *J* = 7.7 Hz), 7.38 (1H, t, *J* = 8.0 Hz) 4.55 (2H, q, *J* = 7.1 Hz), 1.52 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (100 MHz) δ: 152.3, 149.1, 148.0, 141.4, 140.4, 140.2, 133.5, 131.4, 129.3, 127.2, 126.0, 125.9, 124.9, 124.3, 122.5, 121.8, 114.1, 112.1, 108.3, 40.6, 17.2

LC–MS (m/z): 375.5 (M), 377.5 (M+2)

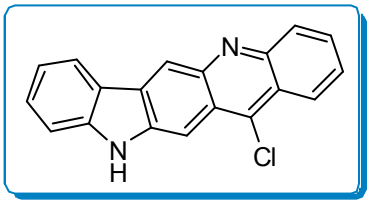
Anal. Calcd. for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18%

Found: C, 67.15; H, 3.77; N, 11.15%

13-Chloro-11*H*-indolo[2,3-*b*]acridine (150a):

The compound **150a** was prepared from the condensation product **147a** (0.32g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 10%



Mp: 167–169 °C

IR (KBr) ν_{max} cm^{-1}: 2057, 1789, 1601, 1452, 1022, 1160, 1022, 806

^{1}H NMR (400 MHz) δ: 11.95 (1H, s), 8.96 (1H, s), 8.72 (1H, d, *J* = 8.0 Hz), 8.53 (1H, s), 8.28–8.16 (3H, m), 7.67–7.61 (2H, m), 7.40 (2H, d, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 146.0, 142.2, 137.6, 135.4, 133.7, 131.0, 130.5, 129.8, 128.5, 125.7, 125.5, 122.8, 122.5, 120.8, 120.5, 117.5, 115.3, 111.6, 110.2

LC–MS (m/z): 302.5 (M), 304.5 (M+2)

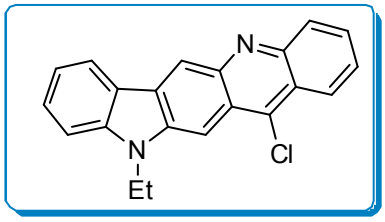
Anal. Calcd. for $C_{19}H_{11}ClN_2$: C, 75.38; H, 3.66; N, 9.25%

Found: C, 75.45; H, 3.62; N, 9.32%

13-Chloro-11-ethyl-11*H*-indolo[2,3-*b*]acridine (150b):

The compound **150b** was prepared from the condensation product **147b** (0.33g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 12%



Mp: 129–130 °C

IR (KBr) ν_{max} cm^{-1}: 2926, 1740, 1637, 1564, 1477, 1366, 1148, 1020, 804, 634, 557

^{1}H NMR (400 MHz) δ: 9.08 (1H, s), 8.46 (1H, d, *J* = 8.0 Hz), 8.42 (1H, d, *J* = 8.0 Hz), 8.23 (1H, s), 8.20 (1H, d, *J* = 4.0 Hz), 7.86 (1H, t, *J* = 8.0 Hz), 7.74 (1H, t, *J* = 8.0

Hz), 7.64 (2H, t, *J* = 4.0 Hz), 7.32–7.28 (1H, m), 4.54 (2H, q, *J* = 8.0 Hz), 1.40 (3H, t, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) *δ*: 145.5, 144.3, 139.0, 137.6, 130.4, 129.6, 127.5, 127.1, 127.0, 126.6, 125.0, 124.7, 123.5, 122.8, 119.8, 118.7, 111.8, 109.5, 107.8, 38.1, 14.8

LC–MS (m/z): 330.5 (M), 332.5 (M+2)

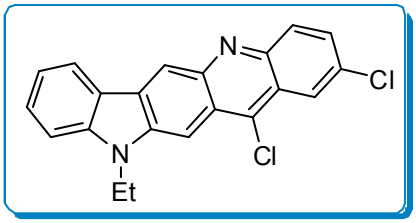
Anal. Calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; N, 8.47%
Found: C, 76.18; H, 4.60; N, 8.58%

2,13-Dichloro-11-ethyl-11*H*-indolo[2,3-*b*]acridine (150c):

The compound **150c** was prepared from the condensation product **147c** (0.36g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 14%

Mp: 140–141 °C



IR (KBr) ν_{max} cm^{-1}: 2963, 1701, 1584, 1435, 1333, 1240, 1080, 814, 646, 550

^{1}H NMR (400 MHz) *δ*: 8.85 (1H, s), 8.36 (1H, d, *J* = 1.9 Hz), 8.25 (1H, d, *J* = 8.5 Hz), 8.17 (1H, d, *J* = 9.1 Hz), 7.96 (1H, s), 7.64–7.59 (2H, m), 7.35–7.29 (2H, m), 4.38 (2H, q, *J* = 7.2 Hz), 1.52 (3H, t, *J* = 7.1 Hz)

^{13}C NMR (100 MHz) *δ*: 147.4, 146.5, 143.7, 139.2, 135.0, 134.9, 132.6, 132.0, 130.0, 129.4, 126.3, 125.1, 125.0, 124.6, 122.5, 122.3, 120.1, 111.0, 110.0, 40.3, 16.6

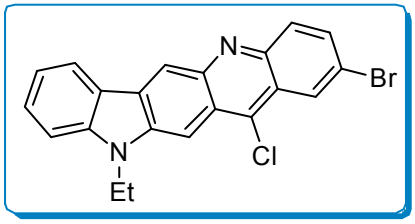
LC–MS (m/z): 364 (M), 366 (M+2), 368 (M+4)

Anal. Calcd for $C_{21}H_{14}Cl_2N_2$: C, 69.05; H, 3.86; N, 7.67%
Found: C, 69.12; H, 3.81; N, 7.71%

2-Bromo-13-chloro-11-ethyl-11*H*-indolo[2,3-*b*]acridine (150d):

The compound **150d** was prepared from the condensation product **147d** (0.41g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 13%



Mp: 151–152 °C

IR (KBr) ν_{max} cm^{-1}: 2968, 1576, 1460, 1323, 1139, 1065, 953, 814, 778, 654

^{1}H NMR (400 MHz) δ: 8.87 (1H, s), 8.39 (1H, s), 8.25 (1H, d, *J* = 8.0 Hz), 8.18 (1H, d, *J* = 8.0 Hz), 7.90 (1H, s), 7.64–7.60 (2H, m), 7.37–7.30 (2H, m), 4.41 (2H, q, *J* = 4.0 Hz), 1.55 (3H, t, *J* = 10.0 Hz)

^{13}C NMR (100 MHz) δ: 147.8, 145.2, 143.6, 138.8, 137.9, 132.6, 130.7, 128.9, 126.8, 126.6, 125.9, 124.3, 123.7, 123.0, 121.3, 119.7, 117.6, 111.7, 109.4, 37.9, 14.6

LC–MS (m/z): 408.5 (M), 410.5 (M+2), 412.5 (M+4)

Anal. Calcd. for $C_{21}H_{14}BrClN_2$: C, 61.56; H, 3.44; N, 6.84%
Found: C, 61.60; H, 3.46; N, 6.87%

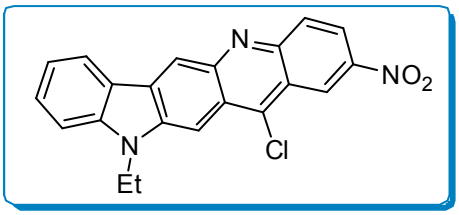
2-Nitro-13-chloro-11-ethyl-11*H*-indolo[2,3-*b*]acridine (150e):

The compound **150e** was prepared from the condensation product **147e** (0.37g, 1.0 mmol) by following the *general procedure B.* The crude product was purified by silica gel column chromatography with 8% ethyl acetate in hexanes.

Yield: 12%

Mp: 172–173 °C

IR (KBr) ν_{max} cm^{-1}: 2962, 1708, 1573, 1419, 1330, 1252, 1069, 826, 644



^{1}H NMR (400 MHz) δ: 9.62 (1H, s), 8.87 (1H, d, *J* = 8.0 Hz), 8.52 (1H, d, *J* = 8.0 Hz), 8.38 (1H, d, *J* = 8.0 Hz), 8.22 (1H, d, *J* = 8.0 Hz), 8.15 (1H, s), 7.66 (1H, d, *J* = 8.0 Hz), 7.57 (1H, t, *J* = 8.0 Hz), 7.44 (1H, t, *J* = 8.0 Hz), 4.51 (2H, q, *J* = 7.6 Hz), 1.55 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (100 MHz) δ: 150.0, 147.1, 146.7, 140.1, 139.0, 138.0, 137.9, 131.1, 129.0, 127.0, 125.0, 123.6, 122.5, 121.8, 120.1, 119.4, 116.3, 114.1, 109.7, 38.1, 14.7

LC–MS (m/z): 375.5 (M), 377.5 (M+2)

Anal. Calcd. for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18%

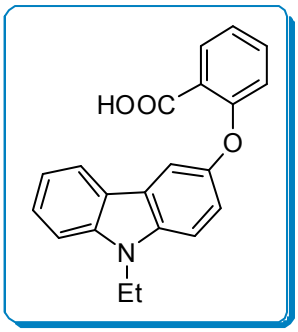
Found: C, 67.22; H, 3.72; N, 11.25%

General Procedure C

A mixture of 9-ethyl-3-hydroxycarbazole **158** (1.0 mmol), 2-iodobenzoic acids **146a-d** (1.0 mmol), CuI (0.1 mmol) and K_2CO_3 (2.0 mmol) in DMSO was heated at 80 °C for required time. Then the reaction mixture was poured in water and extracted with ethyl acetate (3 X 30 mL). The organic layer was dried over anhyd. Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude materials were purified by column chromatography (silica gel, 100-200 mesh size) and eluted ethyl acetate/hexanes mixture to afford the pure products.

2-(9-Ethyl-9*H*-carbazolyloxy)benzoic acid (159a):

The condensation product **159a** was obtained by the reaction of 9-ethyl-3-hydroxycarbazole **158** (0.21g, 1.0 mmol) and 2-iodobenzoic acid **146a** (0.25g, 1.0 mmol) by following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 73%

Mp: 187–186 °C

IR (KBr) ν_{max} cm^{-1}: 3445, 2972, 2924, 1736, 1697, 1488, 1321, 1256, 1219, 1149, 789

^{1}H NMR (400 MHz) δ: 8.18 (1H, d, *J* = 8.0 Hz), 8.03 (1H, d, *J* = 7.8 Hz), 7.87 (1H, d, *J* = 4.0 Hz), 7.53–7.49 (2H, m), 7.46–7.41 (2H, m), 7.27–7.24 (2H, m), 7.18–7.15 (1H, m), 6.83 (1H, d, *J* = 8.0 Hz), 4.47 (2H, q, *J* = 8.0 Hz), 1.41 (3H, t, *J* = 4.0 Hz)

^{13}C NMR (100 MHz) δ: 172.3, 163.1, 156.6, 153.9, 145.3, 141.5, 138.0, 136.6, 130.9, 128.2, 127.1, 126.9, 125.3, 123.5, 123.4, 122.9, 116.1, 114.2, 113.6, 42.3, 18.6

LC–MS (m/z): 330 ($M\text{-}H^{+}$)

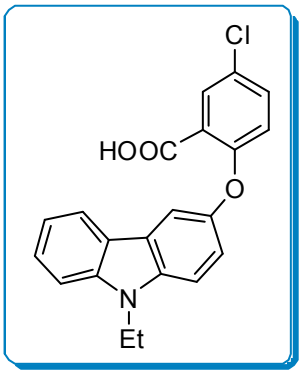
Anal. Calcd. for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23%

Found: C, 76.17; H, 5.13; N, 4.19%

5-Chloro-2-(9-ethyl-9*H*-carbazolyloxy)benzoic acid (159b):

The condensation product **159b** was obtained by the reaction of 9-ethyl-3-hydroxycarbazole **158** (0.21g, 1.0 mmol) and 5-choloro-2-iodobenzoic acid **146b** (0.28g, 1.0 mmol) by following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 75%



Mp: 171–172 °C

IR (KBr) ν_{max} cm^{-1}: 3046, 2972, 2876, 1736, 1626, 1458, 1379, 1256, 1148, 745

^{1}H NMR (400 MHz) δ: 8.20 (1H, d, *J* = 2.8 Hz), 8.05 (1H, d, *J* = 8.0 Hz), 7.85 (1H, d, *J* = 2.0 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.45–7.42 (2H, m), 7.35 (2H, d, *J* = 6.4 Hz), 7.27–7.24 (2H, m), 6.77 (1H, d, *J* = 9.2 Hz), 4.39 (2H, q, *J* = 7.2 Hz), 1.46 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz) δ: 165.0, 157.5, 146.4, 140.7, 137.7, 134.5, 132.8, 128.2, 126.6, 123.9, 122.2, 120.7, 119.9, 119.2, 118.6, 117.9, 112.5, 109.7, 108.9, 37.8, 13.8

LC–MS (m/z): 365.5 (M), 367.5 (M+2)

Anal. Calcd. for $C_{21}H_{16}ClNO_3$: C, 68.95; H, 4.41; N, 3.83%
Found: C, 68.89; H, 4.47; N, 3.85%

5-Bromo-2-(9-ethyl-9*H*-carbazolyloxy)benzoic acid (159c):

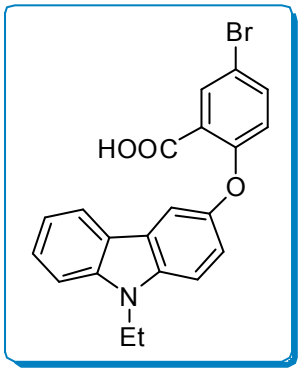
The condensation product **159c** was obtained by the reaction of 9-ethyl-3-hydroxycarbazole **158** (0.21g, 1.0 mmol) and 5-bromo-2-iodobenzoic acid **146c** (0.32g, 1.0 mmol) by following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 73%

Mp: 179–180 °C

IR (KBr) ν_{max} cm^{-1}: 3039, 2967, 2776, 1726, 1646, 1459, 1369, 1255, 1132, 749

^{1}H NMR (400 MHz) δ: 8.23 (1H, s), 8.03 (1H, s), 7.86 (1H, s), 7.52 (1H, d, *J* = 8.0 Hz), 7.51–7.42 (2H, m), 7.40–7.34 (3H, m), 6.78 (1H, s), 4.41 (2H, q, *J* = 8.0 Hz), 1.47 (3H, t, *J* = 8.0 Hz)



^{13}C NMR (100 MHz) δ: 177.9, 155.2, 152.5, 140.7, 135.9, 133.8, 128.5, 126.7, 126.5, 123.4, 122.9, 122.5, 119.0, 118.7, 117.7, 117.4, 115.9, 115.8, 108.1, 37.4, 13.9

LC–MS (m/z): 410 (M), 412 (M+2)

Anal. Calcd. for $C_{21}H_{16}BrNO_3$: C, 61.48; H, 3.93; N, 3.41%

Found: C, 61.50; H, 3.84; N, 3.29%

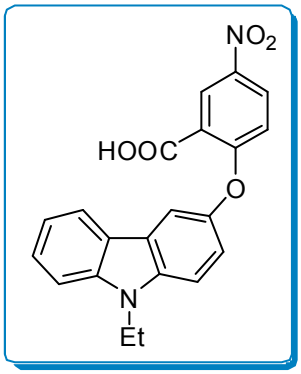
5-Nitro-2-(9-ethyl-9*H*-carbazolyloxy)benzoic acid (159d):

The condensation product **159d** was obtained by the reaction of 9-ethyl-3-hydroxycarbazole **158** (0.21g, 1.0 mmol) and 5-nitro-2-iodobenzoic acid **146d** (0.29g, 1.0 mmol) by following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 18% ethyl acetate in hexanes.

Yield: 71%

Mp: 167–168 °C

IR (KBr) ν_{max} cm^{-1}: 3468, 2969, 2361, 1709, 1613, 1516, 1472, 1379, 1259, 1149, 1070, 922, 837



^{1}H NMR (400 MHz) δ: 8.67 (1H, d, J = 4.0 Hz), 7.99 (1H, d, J = 8.0 Hz), 7.86 (1H, d, J = 4.0 Hz), 7.68 (1H, d, J = 4.0 Hz), 7.35–7.30 (3H, m), 7.07 (2H, d, J = 4.0 Hz), 6.72 (1H, t, J = 4.0 Hz), 4.26 (2H, q, J = 4.0 Hz), 1.30 (3H, t, J = 4.0 Hz)

^{13}C NMR (100 MHz) δ: 165.7, 163.8, 147.0, 141.2, 140.5, 139.6, 137.4, 127.9, 126.3, 123.6, 122.1, 122.0, 120.5, 118.9, 118.8, 116.7, 112.4, 109.6, 108.8, 37.6, 13.7

LC–MS (m/z): 376 (M)

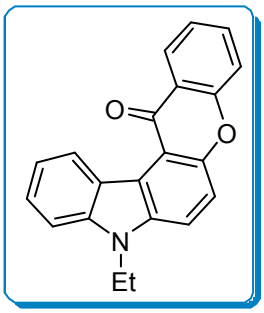
Anal. Calcd. for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.28; N, 7.44%
Found: C, 66.95; H, 4.24; N, 7.42%

General Procedure D

The condensation products **160a-d** (1.0 mmol) in $POCl_3$ (5 mL) were heated for 2 h at 60 °C. Then the reaction mixture was poured onto the crushed ice and then neutralized with 10% aq. NaOH solution. Then it was extracted with dichloromethane (3 × 30 mL) and the organic layer was dried over anhyd. Na_2SO_4. The solvent was evaporated under reduced pressure and the crude materials were chromatographed over silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products of chromenocarbazoles.

8-Ethyl-8,13-dihydrochromeno[2,3-*c*]carbazol-13-one (160a):

The compound **160a** was prepared from the condensation product **159a** (0.33g, 1.0 mmol) by following the *general procedure D.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 73%

Mp: 187–189 °C

IR (KBr) ν_{max} cm^{-1}: 2963, 2926, 1719, 1645,

1611, 1578, 1443, 1323, 1149, 1022, 891, 748, 619

^{1}H NMR (400 MHz) δ: 9.84 (1H, d, *J* = 8.4 Hz), 8.48 (1H, d, *J* = 6.8 Hz), 7.79 (1H, d, *J* = 8.8 Hz), 7.73–7.68 (1H, m), 7.59–7.34 (6H, m), 4.42 (2H, q, *J* = 7.2 Hz), 1.42 (3H, t, *J* = 7.2 Hz)

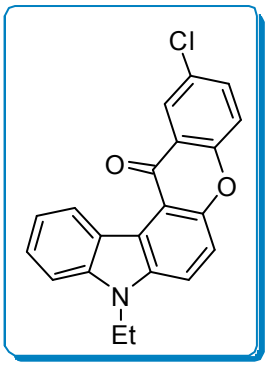
^{13}C NMR (100 MHz) δ: 177.9, 155.2, 152.5, 140.7, 135.9, 133.8, 128.5, 126.7, 126.5, 123.4, 122.9, 122.5, 119.0, 118.7, 117.7, 117.4, 115.9, 115.8, 108.1, 37.4, 13.9

LC–MS (m/z): 314 ($M+H^+$)

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47%
Found: C, 80.53; H, 4.79; N, 4.45%

2-Chloro-8-ethyl-8,13-dihydrochromeno[2,3-*c*]carbazol-13-one (160b):

The compound **160b** was prepared from the condensation product **159b** (0.36g, 1.0 mmol) by following the *general procedure D.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 75%

Mp: 158–159 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 2922, 2857, 1713, 1634, 1312, 1020, 806, 741, 621

^{1}H NMR (400 MHz) δ: 9.75 (1H, d, *J* = 7.4 Hz), 8.39 (1H, s), 7.78 (1H, d, *J* = 9.2 Hz), 7.60–7.53 (3H, m), 7.45–7.35 (3H, m), 4.42 (2H, q, *J* = 8.0 Hz), 1.43 (3H, t, *J* = 4.0 Hz)

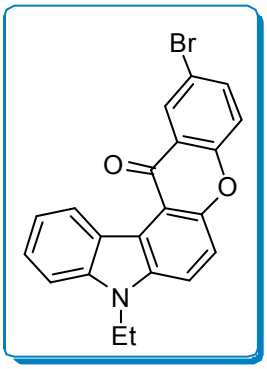
^{13}C NMR (100 MHz) δ: 176.6, 155.4, 155.1, 140.7, 135.9, 133.8, 128.5, 126.7, 125.9, 123.2, 122.7, 119.4, 119.0, 118.6, 117.2, 116.1, 115.6, 108.9, 108.1, 37.4, 14.0

LC–MS (m/z): 347.5 (M), 349.5 (M+2)

Anal. Calcd. for $C_{21}H_{14}ClNO_2$: C, 72.52; H, 4.06; N, 4.03%
Found: C, 72.74; H, 3.93; N, 4.09%

2-Bromo-8-ethyl-8,13-dihydrochromeno[2,3-*c*]carbazol-13-one (160c):

The compound **160c** was prepared from the condensation product **159c** (0.41g, 1.0 mmol) by following the *general procedure D.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 73%

Mp: 177–178 °C

IR (KBr) cm^{-1}: 3419, 2915, 2868, 1711, 1619, 1322, 1016, 809, 768, 617

^{1}H NMR (400 MHz) δ: 9.74 (1H, s), 8.54 (1H, s), 7.73–7.70 (2H, m), 7.57–7.52 (2H, m), 7.35–7.32 (3H, m), 4.40 (2H, q, J = 8.0 Hz), 1.48 (3H, s)

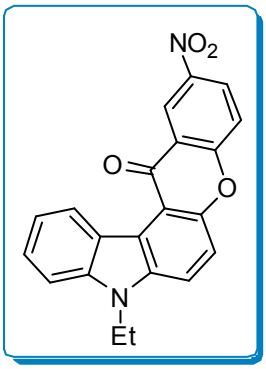
^{13}C NMR (100 MHz) δ: 176.4, 155.2, 153.9, 140.8, 137.1, 136.6, 129.0, 128.4, 126.8, 123.1, 121.9, 121.3, 119.4, 119.2, 117.4, 116.5, 115.7, 108.9, 108.2, 37.5, 14.0

LC–MS (m/z): 393 (M), 395 (M+2)

Anal. Calcd. for $C_{21}H_{14}BrNO_2$: C, 64.30; H, 3.60; N, 3.57%
Found: C, 64.31; H, 3.67; N, 3.56%

2-Nitro-8-ethyl-8,13-dihydrochromeno[2,3-*c*]carbazol-13-one (160d):

The compound **160d** was prepared from the condensation product **159d** (0.37g, 1.0 mmol) by following the *general procedure D.* The crude product was purified by silica gel column chromatography with 33% ethyl acetate in hexanes.



Yield: 71%

Mp: 167–168 °C

IR (KBr) ν_{max} cm^{-1}: 3298, 2930, 2863, 1657, 1462, 1343, 1261, 1099, 804, 746

^{1}H NMR (400 MHz) δ: 9.64 (1H, d, *J* = 8.0 Hz), 9.13 (1H, s), 8.33 (1H, d, *J* = 8.0 Hz), 7.88 (1H, d, *J* = 8.0 Hz), 7.66–7.57 (2H, m), 7.46–7.44 (2H, m), 7.34 (1H, m), 4.43 (2H, q, *J* = 7.6 Hz), 1.46 (3H, t, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 176.2, 167.6, 158.3, 150.2, 143.2, 140.5, 135.5, 128.2, 127.8, 127.2, 123.5, 122.3, 121.7, 119.4, 118.8, 116.6, 115.6, 108.3, 106.5, 37.5, 14.0

LC–MS (m/z): 358 (M)

Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.39; H, 3.94; N, 7.82%

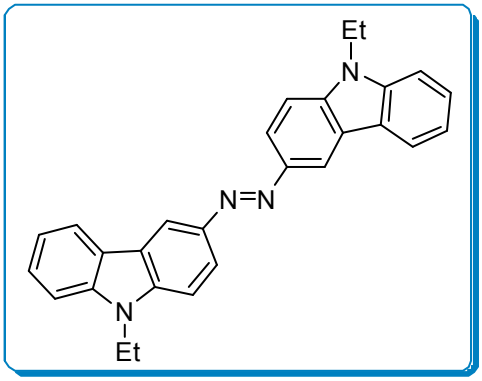
Found: C, 70.54; H, 3.95; N, 8.09%

(9-Ethyl-9*H*-3-carbazolyl)-9-ethyl-9*H*-azocarbazole:

The title compound was obtained as a side product during the condensation of 3-amino-9-ethylcarbazole **145b** (0.21g, 1.0 mmol) and 5-nitro-2-iodobenzoic acid **146d** (0.29g, 1.0 mmol) by following the *general procedure A.* It was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 5%

Mp: 202–203 °C



IR (KBr) ν_{max} cm^{-1}: 2984, 2926, 1525, 1522, 1472, 1323, 1231, 1135, 933, 802

^{1}H NMR (400 MHz) δ: 8.78 (2H, s), 8.23 (4H, s), 7.51–7.46 (6H, m), 7.32 (2H, s), 4.40 (4H, s), 1.49 (6H, s)

^{13}C NMR (100 MHz) δ: 149.1, 143.8, 143.3, 128.7, 126.2, 125.9, 123.4, 123.3, 122.1, 118.6, 111.5, 111.2, 40.4, 16.4

LC–MS (m/z): 417 ($M+H^+$)

Anal. Calcd. for $C_{28}H_{24}N_4$: C, 80.74; H, 5.81; N, 13.45%

Found: C, 80.52; H, 5.88; N, 13.52%

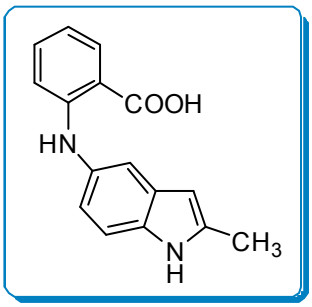
General Procedure E

A mixture of 5-amino-2-methylindoles **174a-c** (1.0 mmol), 2-iodobenzoic acids **146a-i** (1.0 mmol), CuI (0.1 mmol) and K_2CO_3 (1.0 mmol) in DMSO was heated at 80 °C for required time. After the completion of the reaction, as indicated by TLC, the reaction mixture was poured to water contained in a beaker and extracted with ethyl acetate (3 X 30 mL). The organic layer was dried over anhyd. Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude materials were purified by column chromatography (silica gel, 100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to get the pure products.

2-(2-Methyl-1*H*-5-indolylamino)benzoic acid (175a):

The title compound **175a** was obtained by the condensation of 5-amino-2-methylindole **174a** (0.14g, 1.0 mmol) and 2-iodobenzoic acid **146a** (0.25g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 86%



Mp: 217-218 °C

IR (KBr) ν_{max} cm^{-1}: 3414, 2997, 1716, 1666, 1581, 1437, 1313, 1024, 952

^{1}H NMR (400 MHz) δ: 9.45 (1H, bs), 7.91 (1H, d, J = 8.0 Hz), 7.31 (1H, d, J = 2.0 Hz), 7.18 - 7.11 (2H, m), 6.97 (1H, dd, J_1 = 1.6 Hz, J_2 = 2.0 Hz), 6.89 (1H, d, J = 8.0 Hz), 6.54 (2H, t, J = 8.0 Hz), 6.14 (1H, s), 2.36 (3H, s)

^{13}C NMR (100 MHz) δ: 171.0, 150.7, 137.6, 135.0, 133.9, 132.4, 132.0, 128.4, 118.9, 115.9, 115.3, 113.1, 110.6, 109.2, 99.4, 12.7

LC-MS (m/z): 267 ($M+H^+$)

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52%
Found: C, 72.12; H, 5.27; N, 10.48%

5-Methoxy-2-(2-methyl-1*H*-5-indolylamino)benzoic acid (175b):

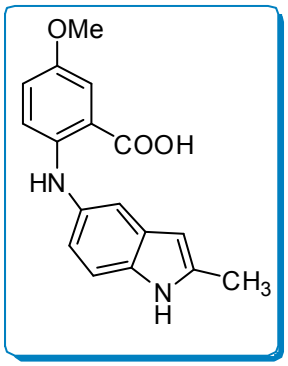
The title compound **175b** was obtained by the condensation of 5-amino-2-methylindole **174a** (0.14g, 1.0 mmol) and 5-methoxy-2-iodobenzoic acid **146f** (0.28g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 81%

Mp: 217-218 °C

IR (KBr) ν_{max} cm^{-1}: 3393, 3367, 2959, 2914, 1647, 1516, 1481, 1259, 1045, 812

^{1}H NMR (400 MHz) δ: 9.70 (1H, s), 7.20 (1H, s), 6.99 (2H, d, J = 8.0 Hz), 6.71 (1H, d, J = 12.0 Hz), 6.61 (2H, s), 5.81 (1H, s), 3.48 (3H, s), 2.15 (3H, s)



^{13}C NMR (100 MHz) δ: 175.3, 154.6, 150.1, 141.4, 140.3, 138.5, 137.8, 134.4, 127.2, 122.9, 119.9, 119.2, 119.1, 115.9, 104.1, 60.6, 18.5

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

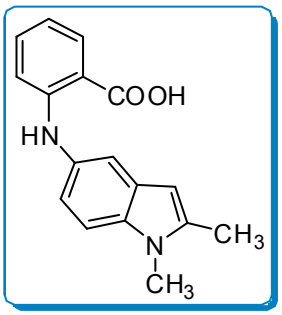
Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45%
Found: C, 68.85; H, 5.41; N, 9.61%

2-(1,2-Dimethyl-1*H*-5-indolylamino)benzoic acid (175c):

The title compound **175c** was obtained by the condensation of 5-amino-1,2-dimethylindole **174b** (0.16g, 1.0 mmol) and 2-iodobenzoic acid **146a** (0.25g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 91%

Mp: 208-209 °C



IR (KBr) ν_{max} cm^{-1}: 3369, 2916, 2733, 1643, 1498, 1392, 1242, 1163, 871

^{1}H NMR (400 MHz) δ: 9.51 (1H, bs), 7.83 (1H, s), 7.36 (1H, d, *J* = 8.0 Hz), 7.26-7.23 (2H, m), 6.92 (2H, d, *J* = 7.2 Hz), 6.61 (1H, s), 6.15 (1H, s), 3.63 (3H, s), 2.37 (3H, s)

^{13}C NMR (100 MHz) δ: 173.4, 151.5, 137.8, 135.4, 135.0, 132.3, 131.9, 130.9, 129.5, 120.4, 119.3, 116.5, 115.6, 109.3, 99.6, 31.7, 12.8

LC-MS (m/z): 281 ($M+H^+$)

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99%
Found: C, 72.81; H, 5.80; N, 10.03%

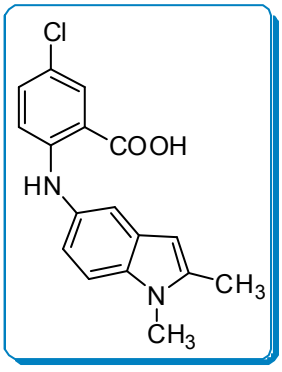
5-Chloro-2-(1,2-dimethyl-1*H*-5-indolylamino)benzoic acid (175d):

The title compound **175d** was obtained by the condensation of 5-amino-1,2-dimethylindole **174b** (0.16g, 1.0 mmol) and 5-choloro-2-iodobenzoic acid **146b** (0.28g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 87%

Mp: 223–224 °C

IR (KBr) ν_{max} cm^{-1}: 3350, 2916, 2550, 1657, 1502, 1440, 1332, 1280, 1161, 812, 738, 657



^{1}H NMR (400 MHz) δ: 9.5 (1H, s), 7.76 (1H, s), 7.37 (1H, d, *J* = 7.6 Hz), 7.26 (2H, s), 6.91 (2H, d, *J* = 6.4 Hz), 6.16 (1H, s), 3.64 (3H, s), 2.37 (3H, s)

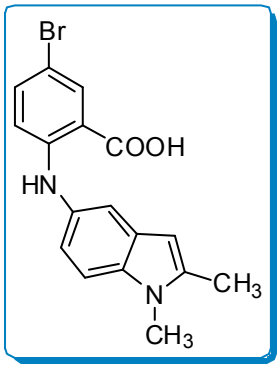
^{13}C NMR (100 MHz) δ: 175.2, 142.8, 140.0, 138.4, 136.5, 133.2, 130.6, 129.3, 123.2, 120.3, 119.8, 116.3, 115.1, 114.4, 104.3, 34.3, 17.5

LC–MS (m/z): 314.5 (M), 316.5 (M+2)

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90%
Found: C, 64.81; H, 4.85; N, 8.98 %

5-Bromo-2-(1,2-dimethyl-1*H*-5-indolylamino)benzoic acid (175e):

The title compound **175e** was obtained by the condensation of 5-amino-1,2-dimethylindole **174b** (0.16g, 1.0 mmol) and 5-bromo-2-iodobenzoic acid **146c** (0.32g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 15% ethyl acetate in hexanes.



Yield: 79%

Mp: 237-238 °C

IR (KBr) ν_{max} cm^{-1}: 2912, 1606, 1570, 1491, 1373, 1263, 812, 605, 520

^{1}H NMR (400 MHz) δ: 9.46 (1H, s), 7.88 (1H, d, *J* = 8.0 Hz), 7.27 (1H, s), 7.17-7.10 (1H, m), 6.94-6.88 (2H, m), 6.53 (1H, t, *J* = 8.0 Hz), 6.11 (1H, s), 3.58 (3H, s), 2.34 (3H, s)

^{13}C NMR (100 MHz) δ: 172.4, 155.4, 142.5, 139.8, 138.6, 137.0, 133.2, 130.3, 129.1, 123.4, 120.4, 120.2, 117.8, 114.1, 104.1, 34.3, 17.5

LC-MS (m/z): 314.5 (M), 316.5 (M+2)

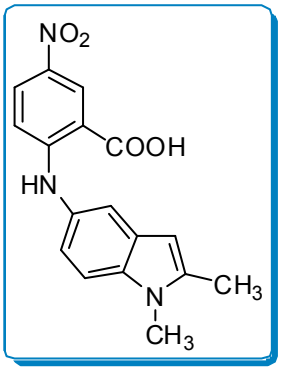
Anal. Calcd. for $C_{17}H_{15}N_2BrO_2$: C, 56.84; H, 4.21; N, 7.80%
Found: C, 56.91, H, 4.25; N, 7.92%

5-Nitro-2-(1,2-dimethyl-1*H*-5-indolylamino)benzoic acid (175f):

The title compound **175f** was obtained by the condensation of 5-amino-1,2-dimethylindole **174b** (0.16g, 1.0 mmol) and 5-nitro-2-iodobenzoic acid **146c** (0.29g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 18% ethyl acetate in hexanes.

Yield: 84%

Mp: 257-258 °C



IR (KBr) ν_{max} cm^{-1}: 2922, 2343, 1653, 1587, 1487, 1323, 1251, 1130, 1082, 1052, 911

^{1}H NMR (400 MHz) δ: 10.35 (1H, s), 8.90 (1H, s), 7.99 (1H, d, *J* = 8.0 Hz), 7.36 (1H, s), 7.30 (1H, d, *J* = 8.0 Hz), 6.99 (1H, d, *J* =8.0 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 6.24 (1H, s), 3.70 (3H, s), 2.45 (3H, s)

^{13}C NMR (100 MHz) δ: 169.2, 154.3, 141.9, 137.9, 135.5, 133.8, 129.4, 129.0, 128.3, 127.9, 118.0, 115.9, 112.2, 109.2, 99.2, 29.0, 12.2

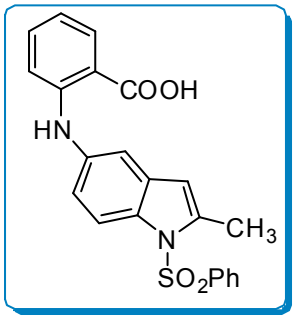
LC-MS (m/z): 326 ($M+H^+$)

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 62.76; H, 4.65; N, 12.92%
Found: C, 62.65; H, 4.62; N, 13.02%

2-(2-Methyl-1-phenylsulfony-1*H*-5-indolylamino)benzoic acid (175g):

The title compound **175g** was obtained by the condensation of 5-amino-2-methyl-1-phenylsulphonylindole **174c** (0.28g, 1.0 mmol) and 2-iodobenzoic acid **146a** (0.25g,

1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 18% ethyl acetate in hexanes.



Yield: 71%

Mp: 182-183 °C

IR (KBr) ν_{max} cm^{-1}: 3348, 2920, 1651, 1581, 1444, 1363, 1168, 1130, 1091, 906, 734

^{1}H NMR (400 MHz) δ: 9.30 (1H, bs), 8.14 (1H, d, J = 8.0 Hz), 8.02 (1H, d, J = 8.0 Hz), 7.80 (2H, d, J = 8.0 Hz), 7.56 (1H, t, J = 6.0 Hz), 7.46 (2H, t, J = 8.0 Hz), 7.32 (2H, t, J = 6.0 Hz), 7.17 (1H, dd, J_1 = 2.0 Hz, J_2 = 4.0 Hz), 7.10 (1H, d, J = 8.0 Hz), 6.72 (1H, t, J = 8.0 Hz), 6.32 (1H, s), 2.60 (3H, s)

^{13}C NMR (100 MHz) δ: 173.4, 149.8, 139.2, 138.3, 136.1, 135.2, 134.2, 133.7, 132.5, 130.7, 130.1, 129.3, 126.3, 120.8, 119.8, 116.7, 115.3, 115.0, 113.8, 109.8, 109.6, 15.7

LC-MS (m/z): 407 ($M+H^+$)

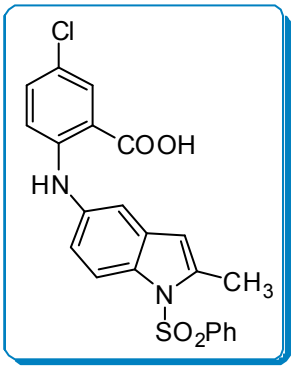
Anal. Calcd. for $C_{22}H_{18}N_2O_4S$: C, 65.01; H, 4.46; N, 6.89%

Found: C, 65.12; H, 4.41; N, 6.95%

5-Chloro-2-(2-methyl-1-phenylsulfony-1*H*-5-indolylamino)benzoic acid (175h):

The title compound **175h** was obtained by the condensation of 5-amino-2-methyl-1-phenylsulphonylindole **174c** (0.28g, 1.0 mmol) and 5-chloro-2-iodobenzoic acid **146b** (0.28g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 18% ethyl acetate in hexanes.

Yield: 75%



Mp: 143-144 °C

IR (KBr) ν_{max} cm^{-1}: 3396, 3314, 2922, 1610, 1575, 1446, 1367, 1221, 1170, 1091, 885

^{1}H NMR (400 MHz) δ: 9.25 (1H, bs), 8.17 (1H, d, J = 8.0 Hz), 7.90 (1H, d, J = 4.0 Hz), 7.82 (2H, d, J = 8.0 Hz), 7.59 (1H, t, J = 8.0 Hz), 7.48 (2H, t, J = 8.0 Hz), 7.28-7.24 (2H, m), 7.15 (1H, dd, J_1 = 2.0 Hz, J_2 = 2.0 Hz), 7.04 (1H, d, J = 8.0 Hz), 6.34 (1H, s), 2.63 (3H, s)

^{13}C NMR (100 MHz) δ: 172.6, 148.4, 139.1, 138.5, 135.6, 135.1, 134.4, 133.8, 131.5, 130.7, 129.3, 129.1, 128.5, 126.3, 126.2, 121.1, 120.7, 115.4, 115.2, 110.7, 109.5, 15.7

LC-MS (m/z): 440 (M), 442 (M+2)

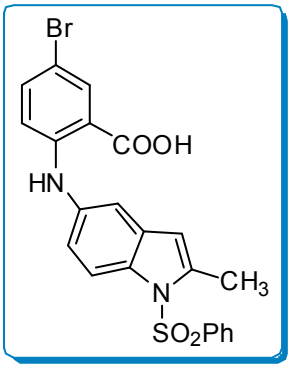
Anal. Calcd. for $C_{22}H_{17}ClN_2O_4S$: C, 59.93; H, 3.89; N, 6.35%
Found: C, 59.86; H, 3.93; N, 6.31%

5-Bromo-2-(2-methyl-1-phenylsulfony-1*H*-5-indolylamino)benzoic acid (175i):

The title compound **175i** was obtained by the condensation of 5-amino-2-methyl-1-phenylsulphonylindole **174c** (0.28g, 1.0 mmol) and 5-bromo-2-iodobenzoic acid **146c** (0.32g, 1.0 mmol) by following the *general procedure E*. The crude product was purified by silica gel column chromatography with 18% ethyl acetate in hexanes.

Yield: 77%

Mp: 234-235 °C



IR (KBr) ν_{max} cm^{-1}: 3427, 3306, 2924, 1606, 1572, 1500, 1221, 1170, 1091, 810

^{1}H NMR (400 MHz) δ: 9.33 (1H, bs), 8.17 (1H, d, J = 8.0 Hz), 7.98 (1H, d, J = 4.0 Hz), 7.82 (2H, d, J = 8.0 Hz), 7.59 (2H, t, J = 8.0 Hz), 7.28 (2H, s), 7.14 (1H, dd, J_1 = 4.0 Hz, J_2 = 4.0 Hz), 7.12 (1H, d, J = 8.0 Hz), 7.04 (1H, d, J = 8.0 Hz), 6.34 (1H, s), 2.63 (3H, s)

^{13}C NMR (100 MHz) δ: 172.4, 148.5, 139.1, 138.5, 135.6, 135.1, 134.4, 133.8, 132.5, 131.5, 130.7, 130.2, 129.3, 128.5, 126.3, 121.1, 120.8, 115.4, 115.3, 110.7, 109.5, 15.7.

LC-MS (m/z): 485 (M), 487 (M+2)

Anal. Calcd. for $C_{22}H_{17}BrN_2O_4S$: C, 54.44; H, 3.53; N, 5.77%

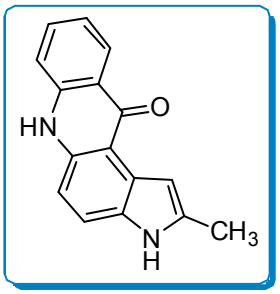
Found: C, 54.51; H, 3.49; N, 5.71%

General Procedure F

The condensation products **175a-i** (1.0 mmol) in $POCl_3$ (5 mL) were heated for 0.5 h at 60 °C. Then the reaction mixture was poured onto the crushed ice and then neutralized with 10% aq. NaOH solution. Then it was extracted with dichloromethane (3 × 30 mL) and the organic layer was dried over anhyd. Na_2SO_4. The solvent was evaporated under reduced pressure and the crude materials were chromatographed over silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products of pyrroloacridones. The reaction was carried out at 120 °C for 3 h to give the corresponding pyrroloacridines.

2-Methyl-6,11-dihydro-3*H*-pyrrolo[3,2-*a*]acridin-11-one (176a)

The compound **176a** was prepared from the condensation product **175a** (0.26g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 75%

Mp: 237-238 °C

IR (KBr) ν_{max} cm^{-1}: 3427, 3265, 2930, 1660, 1473, 1359, 1207, 1153, 1026, 823, 761

^{1}H NMR (400 MHz) δ: 11.64 (1H, s), 11.35 (1H, s), 8.27 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.66 (1H, t, *J* = 8.0 Hz), 7.54 (1H, d, *J* = 12.0 Hz), 7.32 (1H, s), 7.31-7.18 (2H, m), 2.48 (3H, s)

^{13}C NMR (100 MHz) δ: 177.5, 140.3, 137.5, 137.0, 132.3, 130.6, 126.1, 125.0, 121.5, 120.5, 118.8, 117.3, 113.1, 109.8, 103.2, 14.0

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

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28%

Found: C, 77.47; H, 3.83; N, 10.71%

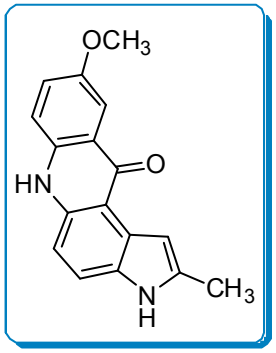
9-Methoxy-2-methyl-6,11-dihydro-3*H*-pyrrolo[3,2-*a*]acridin-11-one (176b):

The compound **176b** was prepared from the condensation product **175b** (0.29g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 74%

Mp: 223-224 °C

IR (KBr) ν_{max} cm^{-1}: 3393, 2924, 1614, 1493, 1369, 1228, 1168, 1026, 815



^{1}H NMR (400 MHz) δ: 10.91 (1H, s), 10.06 (1H, s), 7.74 (1H, s), 7.47 (1H, d, *J* = 12.0 Hz), 7.35 (1H, s), 7.08 (2H, d, *J* = 8.0 Hz), 7.02 (1H, d, *J* = 8.0 Hz), 3.74 (3H, s), 2.38 (3H, s)

^{13}C NMR (100 MHz) δ: 177.8, 153.9, 137.2, 136.4, 134.9, 128.7, 122.5, 121.8, 118.6, 118.1, 115.1, 114.6, 112.6, 109.6, 104.6, 55.5, 13.8

LC-MS (m/z): 279 ($M+H^+$)

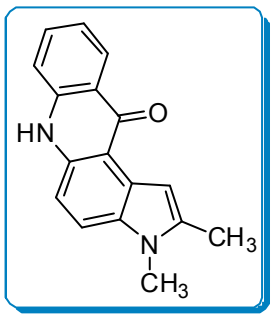
Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07%
Found: C, 73.25; H, 5.12; N, 10.21%

2,3-Dimethyl-6,11-dihydro-3*H*-pyrrolo[3,2-*a*]acridin-11-one (176c):

The compound **176c** was prepared from the condensation product **175c** (0.28g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 72%

Mp: 212-213 °C



IR (KBr) cm^{-1}: 2966, 2922, 1726, 1635, 1599, 1477.0, 1359, 1261, 1097, 802

^{1}H NMR (400 MHz) δ: 11.61 (1H, s), 8.26-8.21 (1H, m), 7.85 (1H, d, *J* = 8.0 Hz), 7.64 (1H, t, *J* = 8.0 Hz), 7.54 (1H, d,

J = 8.0 Hz), 7.37 (1H, s), 7.21 (2H, q, *J* = 8.0 Hz), 3.76 (3H, s), 2.47 (3H, s)

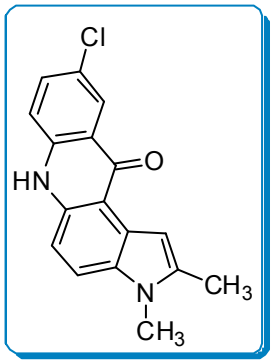
^{13}C NMR (100 MHz) *δ*: 177.4, 140.3, 138.5, 137.6, 132.4, 131.7, 130.3, 126.0, 123.9, 121.5, 120.6, 117.4, 112.9, 109.8, 103.0, 29.9, 13.0

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

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68%
Found: C, 77.77; H, 5.30; N, 10.68%

9-Chloro-2,3-dimethyl-6,11-dihydro-3*H*-pyrrolo[3,2-*a*]acridin-11-one (176d):

The compound **176d** was prepared from the condensation product **175d** (0.31g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 77%

Mp: 147–148 °C

IR (KBr) ν_{max} cm^{-1}: 3477, 1635, 1560, 1475, 1415, 1016, 655

^{1}H NMR (400 MHz): 11.4 (1H, s), 8.37 (1H, d, *J* = 4.0 Hz), 7.61 (1H, t, *J* = 8.0 Hz), 7.53–7.45 (3H, m), 7.22 (1H, d, *J* = 8.0 Hz), 3.76 (3H, s), 2.50 (3H, s)

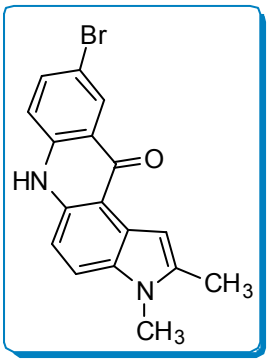
^{13}C NMR (100 MHz): 181.9, 143.2, 143.0, 142.3, 136.7, 136.4, 130.3, 129.9, 128.7, 127.0, 123.7, 121.3, 117.8, 114.5, 108.0, 34.5, 17.9

LC–MS (m/z): 296.5 (M), 298.5 (M+2)

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44%
Found: C, 68.75; H, 4.49; N, 9.68%

9-Bromo-2,3-dimethyl-6,11-dihydro-3*H*-pyrrolo[3,2-*a*]acridin-11-one (176e):

The compound **176e** was prepared from the condensation product **175e** (0.36g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 76%

Mp: 167-168 °C

IR (KBr) ν_{max} cm^{-1}: 2922, 1718, 1631, 1593, 1473, 1356, 1149, 815, 638, 576

^{1}H NMR (400 MHz) δ: 11.4 (1H, s), 8.56 (1H, d, *J* = 8 Hz), 7.72-7.65 (2H, m), 7.52-7.45 (2H, t, *J* = 8 Hz), 7.24 (1H, d, *J* = 8 Hz), 3.64 (3H, s), 2.5 (3H, s)

^{13}C NMR (100 MHz) δ: 181.8, 143.6, 143.1, 142.3, 139.2, 136.4, 133.1, 128.7, 127.5, 124.0, 121.3, 118.0, 117.8, 114.5, 108.0, 34.5, 17.6

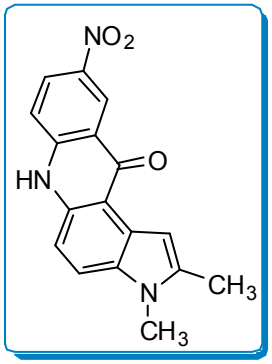
LC-MS (m/z): 341 (M), 343 (M+2)

Anal. Calcd. for $C_{17}H_{13}N_2ClO$: C, 59.84; H, 3.84; N, 8.21%
Found: C, 59.96; H, 3.89; N, 8.32%

9-Nitro-2,3-dimethyl-6,11-dihydro-3*H*-pyrrolo[3,2-*a*]acridin-11-one (176f):

The compound **176f** was prepared from the condensation product **175f** (0.32g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 79%



Mp: 155-156 °C

IR (KBr) ν_{max} cm^{-1}: 3476, 1665, 1520, 1485, 1412, 1016, 865, 777, 556

^{1}H NMR (400 MHz) δ: 11.40 (1H, s), 8.37 (1H, d, *J* = 4.0 Hz), 7.61 (1H, t, *J* = 8.0 Hz), 7.53-7.45 (3H, m), 7.22 (1H, d, *J* = 8.0 Hz), 3.76 (3H, s), 2.50 (3H, s)

^{13}C NMR (100 MHz) δ: 177.4, 140.3, 138.5, 137.6, 132.4, 131.7, 130.3, 126.0, 123.9, 121.5, 120.6, 117.4, 112.9, 109.8, 103.0, 29.9, 13.0

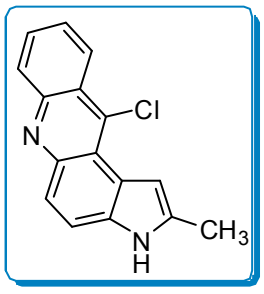
LC-MS (m/z): 308 ($M+H^+$)

Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67%
Found: C, 66.52; H, 4.16; N, 13.63%

11-Chloro-2-methyl-3*H*-pyrrolo[3,2-*a*]acridine (177a):

The compound **177a** was prepared from the condensation product **175a** (0.26g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 76%



Mp: 217-218 °C

IR (KBr) ν_{max} cm^{-1}: 3408, 2928, 1631, 1566, 1433, 1026, 823, 761, 688

^{1}H NMR (400 MHz) δ: 12.05 (1H, s), 8.44 (1H, d, *J* = 8.0 Hz), 8.18 (1H, d, *J* = 8.0 Hz), 7.95 (1H, d, *J* = 12.0 Hz), 7.77-7.71 (3H, m), 7.47 (1H, s), 2.53 (3H, s)

^{13}C NMR (100 MHz) δ: 148.2, 145.8, 136.2, 134.0, 132.0, 129.6, 129.4, 127.2, 124.0, 123.9, 122.5, 120.8, 120.2, 119.2, 106.1, 13.7

LC-MS (m/z): 266 (M), 268 (M+2)

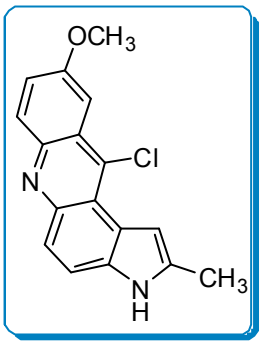
Anal. Calcd. for $C_{16}H_{11}N_2Cl$: C, 72.05; H, 4.16; N, 10.50%
Found: C, 72.13; H, 3.97; N, 10.47%

9-Methoxy-11-chloro-2-methyl-3*H*-pyrrolo[3,2-*a*]acridine (177b):

The compound **177b** was prepared from the condensation product **175b** (0.29g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 71%

Mp: 197-198 ^{o}C



IR (KBr) ν_{max} cm^{-1}: 3369, 2922, 1626, 1575, 1471, 1427, 1228, 1028, 817

^{1}H NMR (400 MHz) δ: 10.67 (1H, s), 7.95 (1H, d, *J* = 5.2 Hz), 7.66 (1H, d, *J* = 8.0 Hz), 7.54 (1H, s), 7.42 (1H, s), 7.29-7.24 (2H, m), 3.92 (3H, s), 2.45 (3H, s)

^{13}C NMR (100 MHz) δ: 157.7, 146.2, 142.5, 133.1, 132.1, 130.8, 128.4, 125.3, 127.4, 123.2, 122.5, 119.3, 118.7, 105.8, 100.1, 55.5, 13.5

LC-MS (m/z): 296.5 (M), 298.5 (M+2)

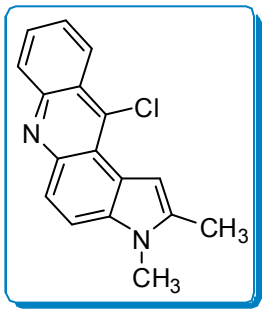
Anal. Calcd. for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44%
Found: C, 68.91; H, 4.46; N, 9.38%

11-Chloro-2,3-dimethyl-3*H*-pyrrolo[3,2-*a*]acridine (177c):

The compound **177c** was prepared from the condensation product **175c** (0.28g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 75%

Mp: 180-181 °C



IR (KBr) ν_{max} cm^{-1}: 2929, 1639, 1572, 1421, 1317, 1275, 1234, 1039, 750, 594

^{1}H NMR (400 MHz) δ: 8.53 (1H, d, *J* = 8.0 Hz), 8.32 (1H, d, *J* = 12.0 Hz), 7.96 (1H, d, *J* = 12.0 Hz), 7.84 (1H, d, *J* = 8.0 Hz), 7.80-7.76 (1H, m), 7.67-7.63 (1H, m), 7.60 (1H, s), 3.84 (3H, s), 2.54 (3H, s)

^{13}C NMR (100 MHz) δ: 148.3, 146.1, 138.1, 134.4, 132.5, 129.3, 128.8, 126.2, 124.6, 124.1, 122.8, 120.3, 119.1, 117.6, 106.2, 29.9, 12.7

LC-MS (m/z): 280 (M), 282.5 (M+2)

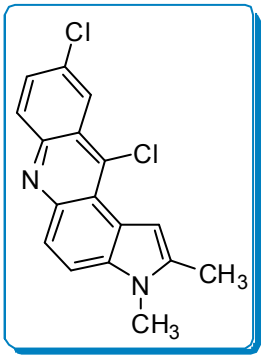
Anal. Calcd. for $C_{17}H_{13}ClN_2$: C, 72.73; H, 4.67; N, 9.98%
Found: C, 72.68; H, 4.63; N, 10.07%

9,11-Dichloro-2,3-dimethyl-3*H*-pyrrolo[3,2-*a*]acridine (177d):

The compound **177d** was prepared from the condensation product **175d** (0.31g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 77%

Mp: 202–203 °C



IR (KBr) ν_{max} cm^{-1}: 2924, 1628, 1520, 1415, 1261, 1080, 866, 802, 767, 663, 601

^{1}H NMR (400 MHz) δ: 8.45 (1H, s), 8.31 (1H, d, *J* = 8.4 Hz), 7.96 (1H, d, *J* = 8.8 Hz), 7.83 (1H, d, *J* = 9.2 Hz), 7.69 (1H, d, *J* = 8.8 Hz), 7.50 (1H, s), 3.8 (3H, s), 2.54 (3H, s)

^{13}C NMR (100 MHz) δ: 138.5, 136.1, 134.0, 133.6, 132.1, 132.0, 127.4, 126.6, 123.7, 121.8, 121.7, 120.2, 119.3, 116.2, 107.5, 31.2, 14.0

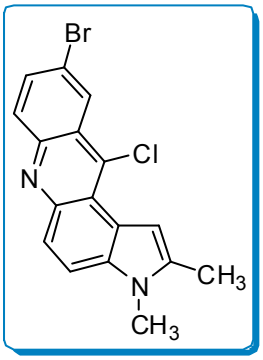
LC–MS (m/z): 315 (M), 317 (M+2)

Anal. Calcd for $C_{17}H_{12}N_2Cl_2$: C, 64.78; H, 3.84; N, 8.89%

Found: C, 64.81; H, 3.88; N, 8.93%

9-Bromo-11-chloro-2,3-dimethyl-3*H*-pyrrolo[3,2-*a*]acridine (177e):

The compound **177e** was prepared from the condensation product **175e** (0.36g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 73%

Mp: 177-178 °C

IR (KBr) ν_{max} cm^{-1}: 2916, 1682, 1520, 1471, 1271, 1194, 1060, 941,

869, 655, 601

^{1}H NMR (400 MHz) δ: 8.66 (1H, d, *J* = 2 Hz), 8.08 (1H, d, *J* = 8.0 Hz), 7.87-7.76 (3H, m), 7.58 (1H, s), 3.83 (3H, s), 2.54 (3H, s)

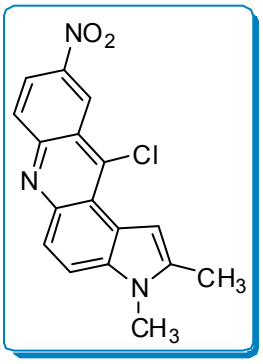
^{13}C NMR (100 MHz) δ: 143.2, 138.5, 136.1, 134.0, 133.6, 132.0, 127.4, 126.6, 123.7, 121.8, 121.7, 120.2, 119.3, 117.2, 107.5, 31.2, 14.0

LC-MS (m/z): 358 (M), 360 (M+2), 362 (M+4)

Anal. Calcd. for $C_{17}H_{12}N_2ClBr$: C, 56.77; H, 3.36; N, 7.79%
Found: C, 56.65; H, 3.41; N, 7.82%

11-Chloro-2,3-dimethyl-9-nitro-3*H*-pyrrolo[3,2-*a*]acridine (177f):

The compound **177f** was prepared from the condensation product **175f** (0.32g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 82%

Mp: 213-214 °C

IR (KBr) ν_{max} cm^{-1}: 2926, 2843, 1672, 1525, 1421, 1371, 1164, 1050, 951, 872

^{1}H NMR (400 MHz) δ: 9.39 (1H, s), 8.39 (1H, d, *J* = 8.0 Hz), 8.25 (1H, d, *J* = 8.0 Hz), 7.95-7.86 (2H, m), 7.58 (1H, s), 3.87 (3H, s), 2.58 (3H, s)

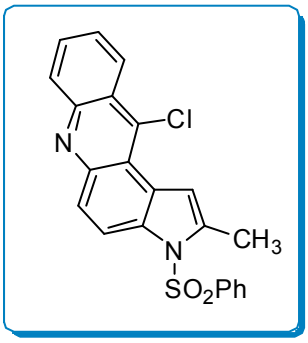
^{13}C NMR (100 MHz) δ: 166.9, 147.7, 142.8, 138.5, 132.5, 129.3, 128.8, 127.7, 126.5, 124.5, 122.8, 120.7, 119.3, 117.9, 104.0, 29.4, 13.0

LC-MS (m/z): 325 (M), 327 (M+2)

Anal. Calcd. for $C_{17}H_{12}ClN_3O_2$: C, 62.68; H, 3.71; N, 12.90%
Found: C, 63.72; H, 3.69; N, 12.87%

11-Chloro-2-methyl-3-phenylsulfonyl-3H-pyrrolo[3,2-*a*]acridine (177g):

The compound **177g** was prepared from the condensation product **175g** (0.40g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 73%

Mp: 193-194 °C

IR (KBr) ν_{max} cm^{-1}: 2920, 1624, 1419, 1367, 1222, 1174, 906, 804, 733, 688

^{1}H NMR (400 MHz) δ: 8.73 (1H, d, *J* = 8.0 Hz), 8.44 (1H, d, *J* = 8.0 Hz), 8.25 (1H, d, *J* = 8.0 Hz), 8.07 (1H, d, *J* = 12.0 Hz), 7.83 - 7.72 (4H, m), 7.63 (1H, t, *J* = 8.0 Hz), 7.55 (1H, t, *J* = 8.0 Hz), 7.45 (2H, t, *J* = 8.0 Hz), 2.74 (3H, s)

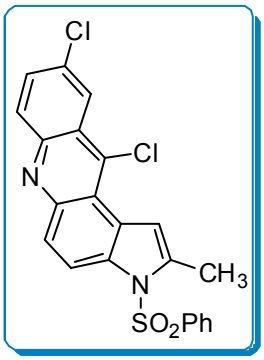
^{13}C NMR (100 MHz) δ: 147.4, 146.5, 139.0, 136.1, 135.2, 134.1, 133.4, 130.4, 129.7, 128.8, 128.5, 127.1, 126.9, 126.3, 126.1, 125.4, 124.2, 122.7, 120.6, 119.0, 112.8, 15.8

LC-MS (m/z): 406 (M), 408 (M+2)

Anal. Calcd. for $C_{22}H_{15}ClN_2O_2S$: C, 64.94; H, 3.72; N, 6.88%
Found: C, 64.89; H, 3.76; N, 6.83%

9,11-Dichloro-2-methyl-3-phenylsulfonyl-3*H*-pyrrolo[3,2-*a*]acridine (177h):

The compound **177h** was prepared from the condensation product **175h** (0.44g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 72%

Mp: 187-188 °C

IR (KBr) ν_{max} cm-^{1}: 2924, 1739, 1595, 1466, 1373, 1261, 1170, 1091, 806

^{1}H NMR (400 MHz) δ: 8.77 (1H, d, *J* = 8.0 Hz), 8.66 (1H, s), 8.11 (1H, d, *J* = 8.0 Hz), 8.04 (1H, d, *J* = 8.0 Hz), 7.85 (3H, t, *J* = 4.0 Hz), 7.78 (1H, s), 7.47 (3H, t, *J* = 8.0 Hz), 2.78 (3H, s)

^{13}C NMR (100 MHz) δ: 139.0, 136.2, 134.9, 134.3, 133.8, 133.5, 131.8, 130.1, 129.7, 129.4, 128.9, 128.5, 126.4, 126.3, 126.0, 125.1, 123.0, 122.6, 121.2, 120.1, 112.8, 15.4

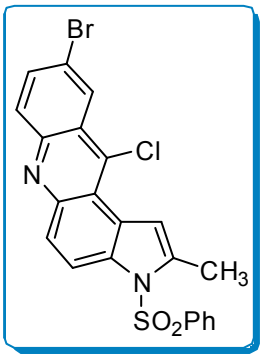
LC-MS (m/z): 440 (M), 442 (M+2), 444 (M+4)

Anal. Calcd. for $C_{22}H_{14}Cl_2N_2O_2S$: C, 59.87; H, 3.20; N, 6.35%
Found: C, 59.75; H, 3.24; N, 6.42%

9-Bromo-11-chloro-2-methyl-3-phenylsulfonyl-3*H*-pyrrolo[3,2-*a*]acridine (177i):

The compound **177i** was prepared from the condensation product **175i** (0.48g, 1.0 mmol) by following the *general procedure F.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 75%



Mp: 219-220 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 2918, 1739, 1601, 1554, 1444, 1371, 1259, 1170, 1089, 1039, 933, 862

^{1}H NMR (400 MHz) δ: 8.77 (1H, d, *J* = 8.0 Hz), 8.66 (1H, s), 8.11 (1H, d, *J* = 8.0 Hz), 8.04 (1H, d, *J* = 8.0 Hz), 7.85 (3H, t, *J* = 4.0 Hz), 7.78 (1H, s), 7.47 (3H, t, *J* = 8.0 Hz), 2.78 (3H, s)

^{13}C NMR (100 MHz) δ: 147.8, 145.4, 139.0, 137.9, 136.2, 134.2, 133.8, 131.0, 129.6, 129.5, 126.5, 126.3, 125.5, 123.9, 122.5, 122.1, 120.6, 119.2, 112.7, 109.6, 107.7, 15.8

LC-MS (m/z): 485.5 (M), 487.5 (M+2), 489.5 (M+4)

Anal. Calcd. for $C_{22}H_{14}BrClN_2O_2S$: C, 54.39; H, 2.90; N, 5.77%

Found: C, 54.43; H, 2.87; N, 5.85%

Table 7. Crystal data and structure refinement for 147b

Empirical formula	: $C_{21}H_{18}N_2O_2$
Formula weight	: 330.37
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P-1
Unit cell dimensions	: a = 8.332(3) Å, α = 82.401(5)°
	: b = 8.399(3) Å, β = 71.671(5)°
	: c = 12.655(4) Å, γ = 83.297(5)°
Volume	: 830.7(5) $Å^3$
Z	: 2
Density (calculated)	: 1.321 Mg/m^3
Absorption coefficient	: 0.086 mm^{-1}
F (000)	: 348
Crystal size	: 0.3 x 0.28 x 0.08 mm
Theta range for data collection	: 1.70 to 25.98°
Index ranges	: -10<=h<=10, -10<=k<=10,
	-15<=l<=15
Reflections collected	: 8550
Completeness to theta = 25.98	: 98.3%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.993 and 0.975
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3214 / 0 / 228
Goodness-of-fit on F^2	: 1.051
Final R indices [I>2sigma(I)]	: R1 = 0.0448, wR2 = 0.1178
R indices (all data)	: R1 = 0.0519, wR2 = 0.1231
Largest diff. peak and hole	: 0.178 and -0.303 $e.Å^{-3}$
CCDC number	: 705915

Table 8. Crystal data and structure refinement for 148c

Empirical formula	: $C_{21}H_{17}ClN_2O_2$
Formula weight	: 364.82
Temperature	: 298(2) K
Wavelength	: 0.71073 A
Crystal system space group	: Monoclinic
Space group	: P2(1)/n
Unit cell dimensions	: a = 9.2880(7) Å, α = 90°
	: b = 8.5941(7) Å, β = 93.1790(10)°
	: c = 20.8861(16) Å, γ = 90°
Volume	: 1664.6(2) $Å^3$
Z	: 4
Density (calculated)	: 1.456 Mg/m^3
Absorption coefficient	: 0.249 mm^{-1}
F (000)	: 760
Crystal size	: 0.32 x 0.18 x 0.14 mm
Theta range for data collection	: 1.95 to 26.04°
Index ranges	: -11<=h<=11, -10<=k<=10, -25<=l<=25
Reflections collected	: 16221
Completeness to theta = 26.04	: 98.3%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9660 and 0.9247
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3241 / 0 / 252
Goodness-of-fit on F^2	: 1.387
Final R indices [I>2sigma(I)]	: R1 = 0.1155, wR2 = 0.2102
R indices (all data)	: R1 = 0.1223, wR2 = 0.2132
Largest diff. peak and hole	: 0.491 and -0.387 $e.Å^{-3}$
CCDC number	: 705696

Table 9. Crystal data and structure refinement for 149c

Empirical formula	: $C_{21}H_{14}Cl_2N_2$
Formula weight	: 365.24
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Tetragonal
Space group	: I-4
Unit cell dimensions	: a = 27.0331(12) Å, α = 90°
	: b = 27.0331(12) Å, β = 90°
	: c = 4.8457(4) Å, γ = 90°
Volume	: 3541.2(4) $Å^3$
Z	: 8
Density (calculated)	: 1.370 Mg/m^3
Absorption coefficient	: 0.372 mm^{-1}
F (000)	: 1504
Crystal size	: 0.28 x 0.08 x 0.06 mm
Theta range for data collection	: 1.07 to 26.01°
Index ranges	: -33<=h<=33, -33<=k<=33, -5<=l<=5
Reflections collected	: 16554
Completeness to theta = 26.01	: 93.8%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.978 and 0.965
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3270 / 0 / 227
Goodness-of-fit on F^2	: 0.886
Final R indices [I>2sigma(I)]	: R1 = 0.0667, wR2 = 0.1931
R indices (all data)	: R1 = 0.1735, wR2 = 0.2405
Absolute structure parameter	: 0.1(2)
Largest diff. peak and hole	: 0.823 and -0.218 e. $Å^3$
CCDC number	: 705697

Table 10. Crystal data and structure refinement for 150c

Empirical formula	: $C_{21}H_{14}Cl_2N_2$
Formula weight	: 365.24
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 9.847(5) Å, α = 90°
	: b = 17.712(9) Å, β = 96.447(9)°
	: c = 9.711(5) Å, γ = 90°
Volume	: 1683.0(15) $Å^3$
Z	: 4
Density (calculated)	: 1.441 Mg/m^3
Absorption coefficient	: 0.391 mm^{-1}
F (000)	: 752
Crystal size	: 0.24 x 0.10 x 0.06 mm
Theta range for data collection	: 2.08 to 25.00°
Index ranges	: -11<=h<=11, -21<=k<=21, -11<=l<=11
Reflections collected	: 14120
Completeness to theta = 25.00	: 99.2%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9769 and 0.9120
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 2941 / 0 / 227
Goodness-of-fit on F^2	: 1.051
Final R indices [I>2sigma(I)]	: R1 = 0.0480, wR2 = 0.1159
R indices (all data)	: R1 = 0.0637, wR2 = 0.1251
Largest diff. peak and hole	: 0.249 and -0.253 $e.Å^{-3}$
CCDC number	: 705698

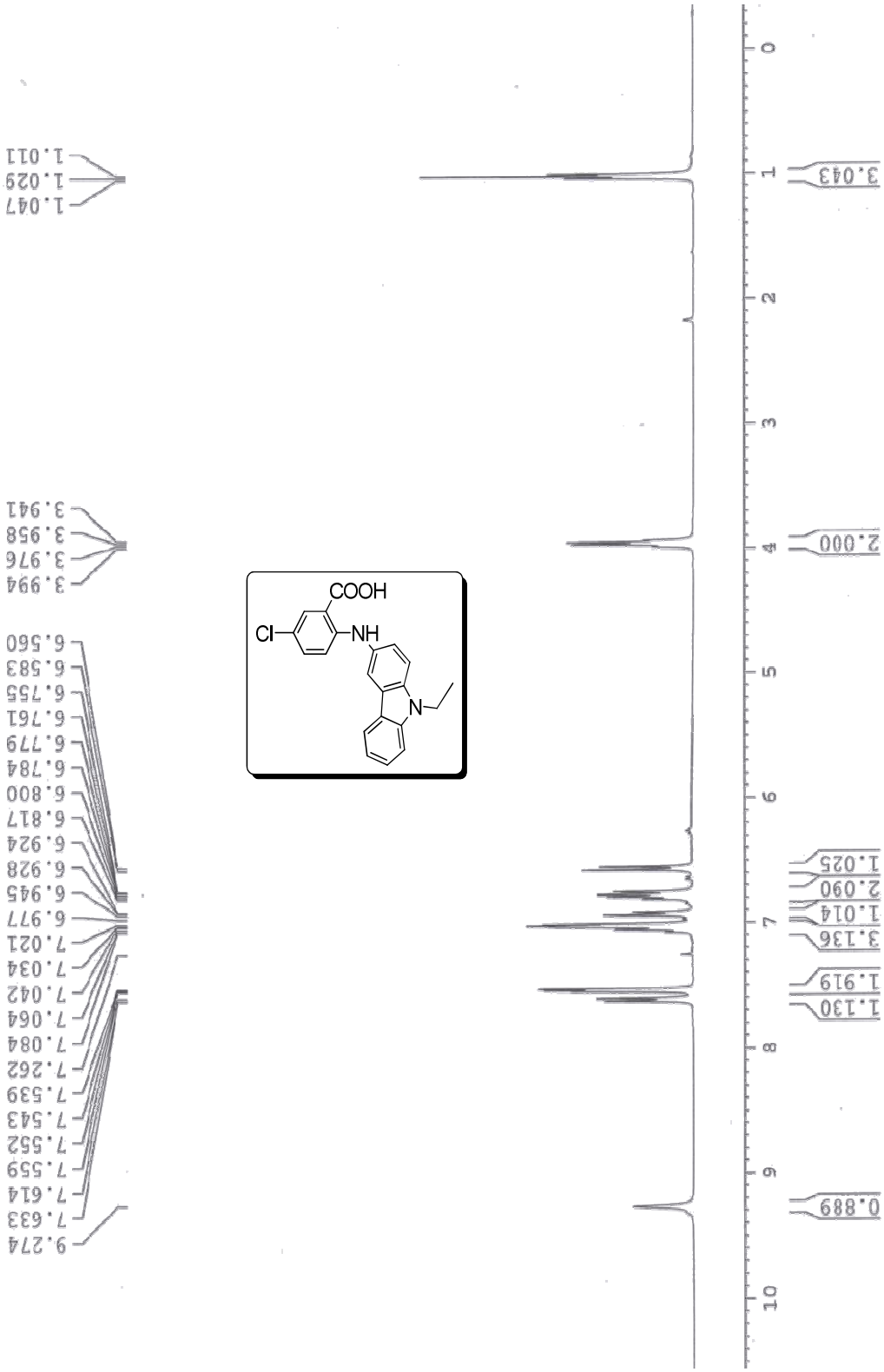
Table 11. Crystal data and structure refinement for 160a

Empirical formula	: $C_{21}H_{15}NO_2$
Formula weight	: 313.34
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/c
Unit cell dimensions	: a = 8.780(2) Å, α = 90°
	: b = 20.842(5) Å, β = 110.036 (5)°
	: c = 8.698(2) Å, γ = 90°
Volume	: 1495.2(6) $Å^3$
Z	: 4
Density (calculated)	: 1.392 Mg/m^3
Absorption coefficient	: 0.090 mm^{-1}
F (000)	: 656
Crystal size	: 0.22 x 0.08 x 0.04 mm
Theta range for data collection	: 1.95 to 25.97°
Index ranges	: -10<=h<=10, -25<=k<=25, -10<=l<=10
Reflections collected	: 14976
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	: 705699

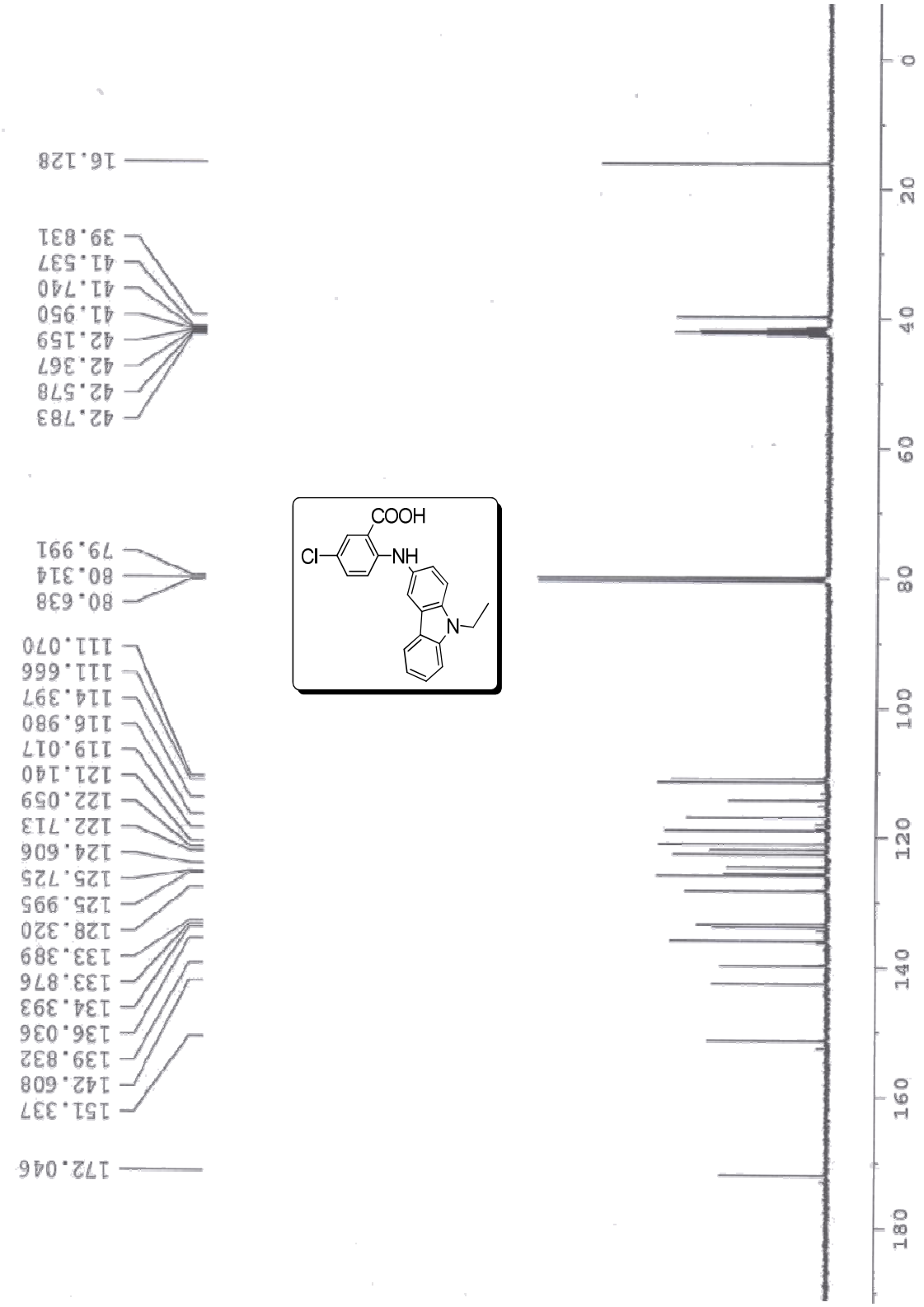
Table 12. Crystal data and structure refinement for 177g

Empirical formula	: $C_{22}H_{15}ClN_2O_2S$
Formula weight	: 406.88
Temperature	: 273(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/n
Unit cell dimensions	: a = 12.867(8) Å, α = 90°
	: b = 8.145(5) Å, β = 96.404(12)°
	: c = 17.143(11) Å, γ = 90°
Volume	: 1785.4(19) $Å^3$
Z	: 4
Density (calculated)	: 1.514 Mg/m^3
Absorption coefficient	: 0.353 mm^{-1}
F (000)	: 210
Crystal size	: 0.4 x 0.06 x 0.05 mm
Theta range for data collection	: 1.88 to 24.88°
Index ranges	: -15<=h<=15, -9<=k<=9,
	-20<=l<=20
Reflections collected	: 15668
Completeness to theta = 24.88	: 99.8%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.996 and 0.994
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3094 / 0 / 254
Goodness-of-fit on F^2	: 0.776
Final R indices [I>2sigma(I)]	: R1 = 0.0753, wR2 = 0.1087
R indices (all data)	: R1 = 0.2564, wR2 = 0.1414
Largest diff. peak and hole	: 0.259 and -0.252 $e.Å^{-3}$
CCDC number	: 737672

Spectrum 1. ^{1}H NMR of 147c

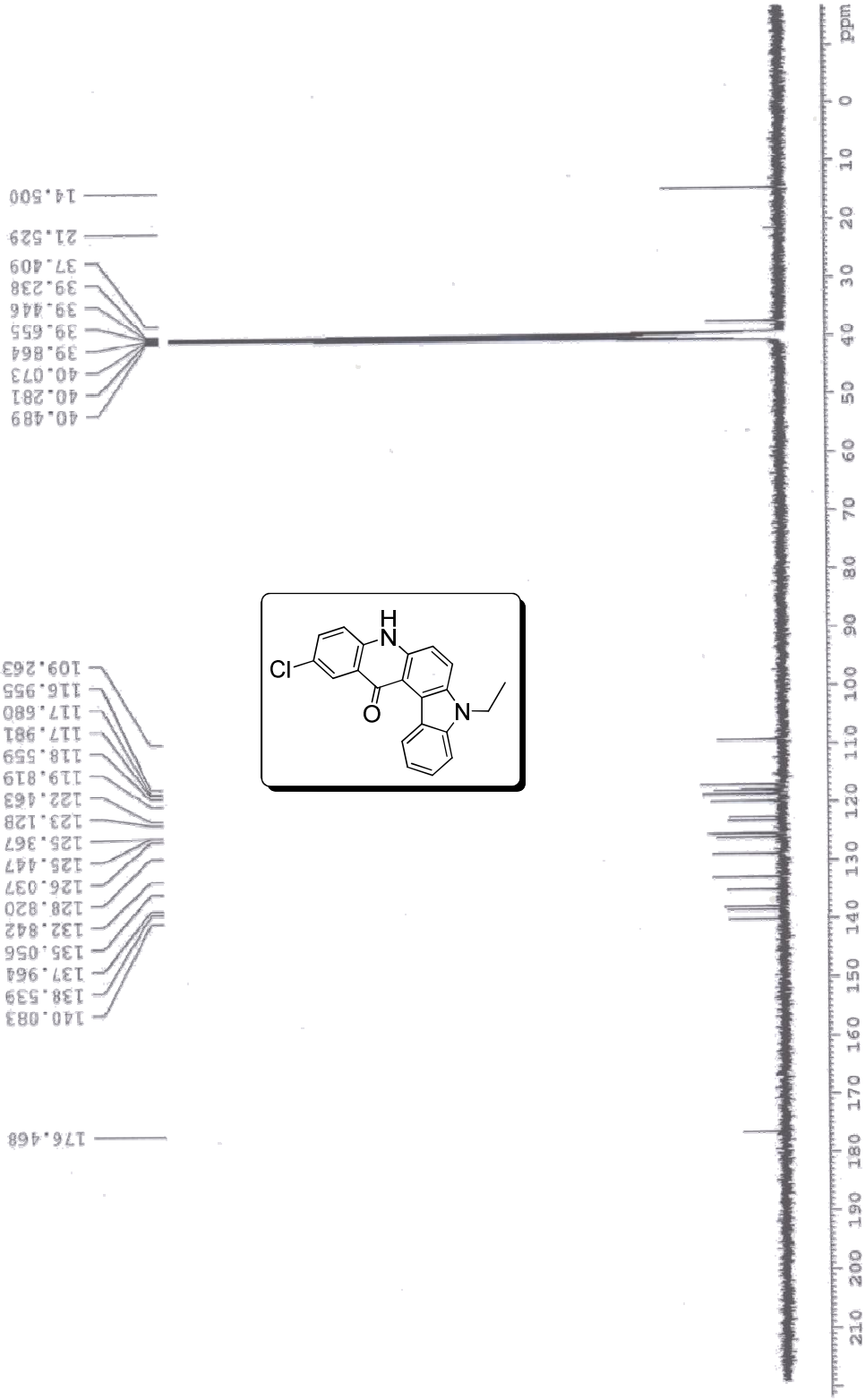


Spectrum 2. ^{13}C NMR of 147c

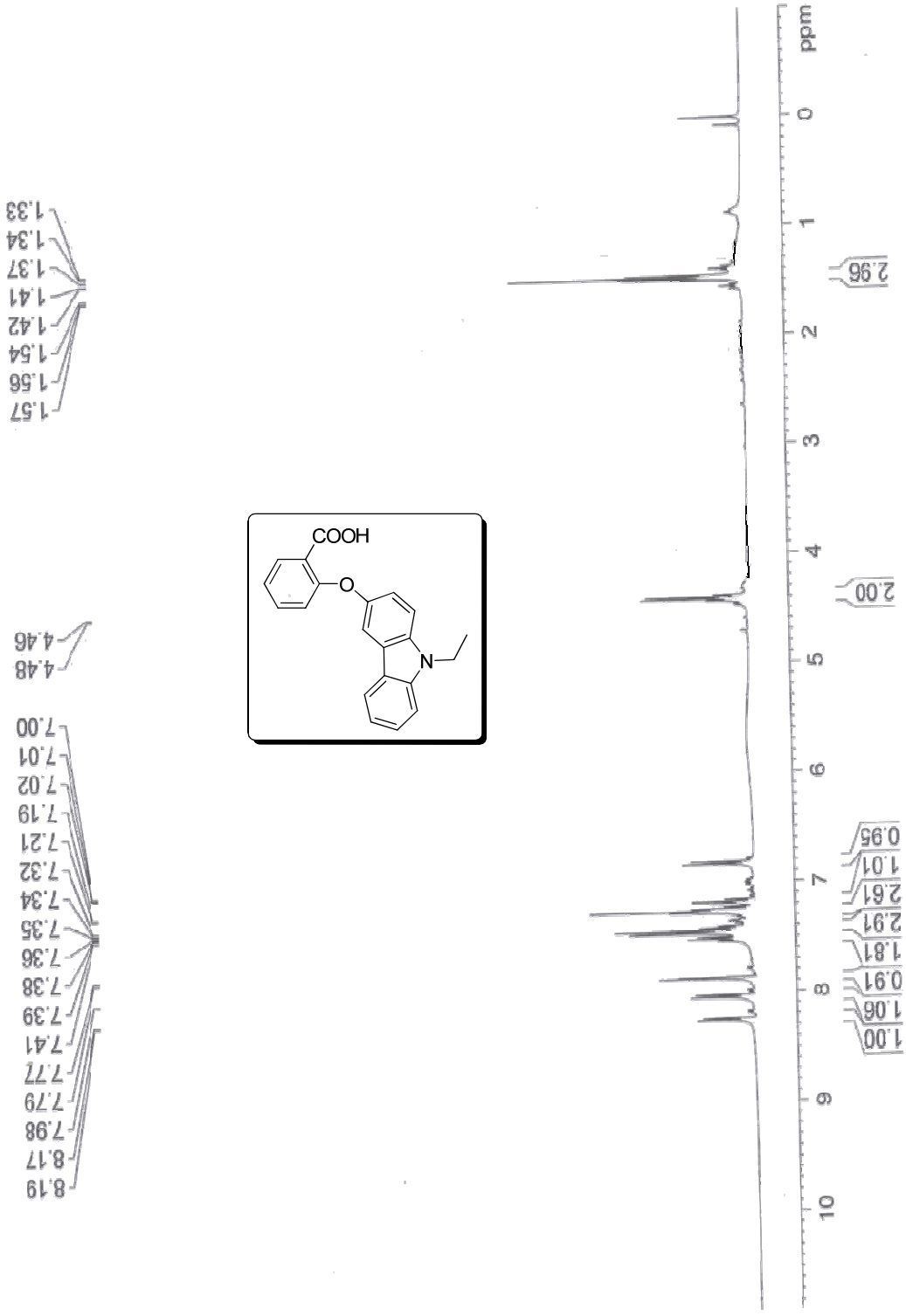


Spectrum 3. ^{1}H NMR of 148c

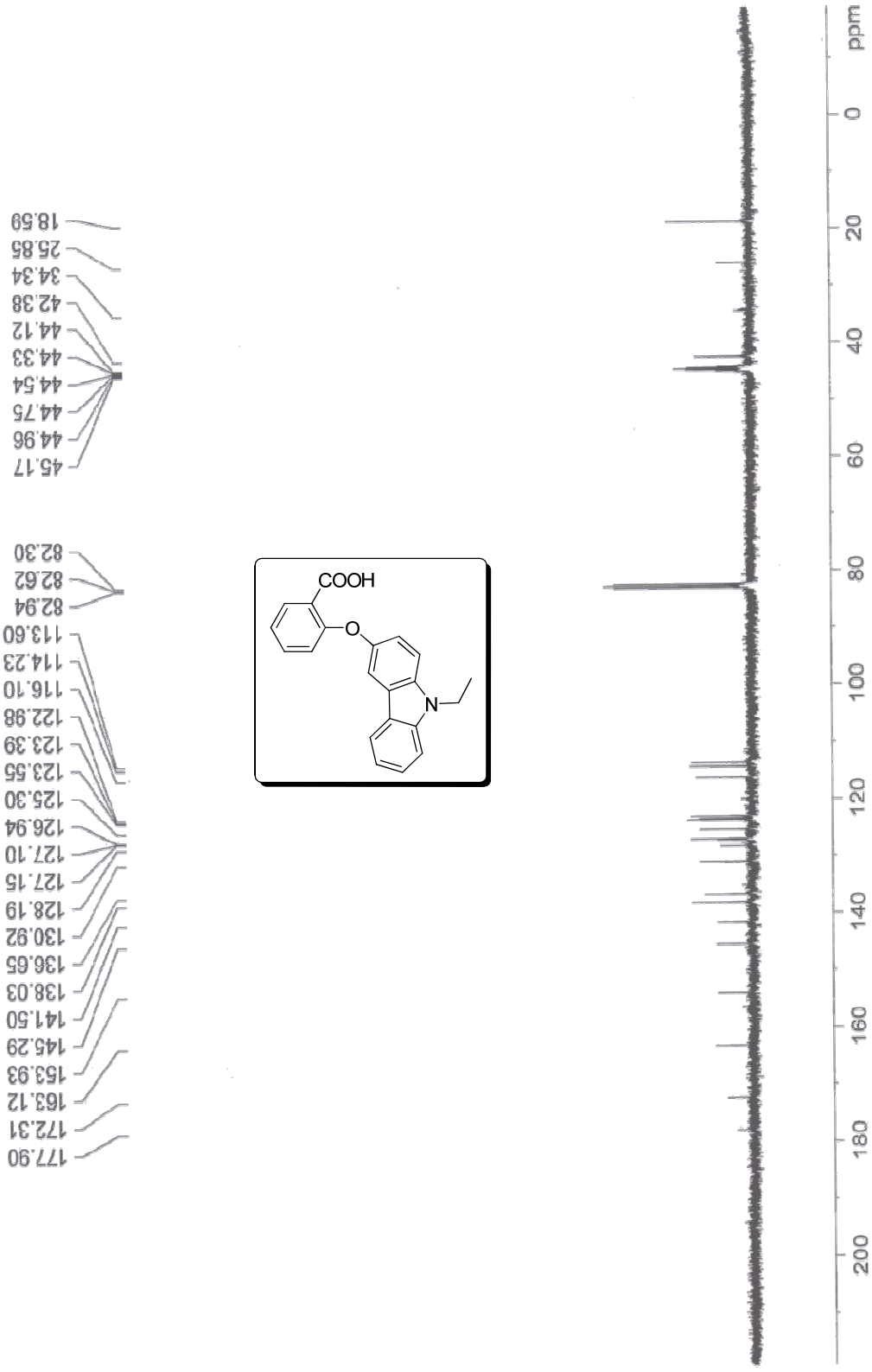
Spectrum 4. ^{13}C NMR of 148c



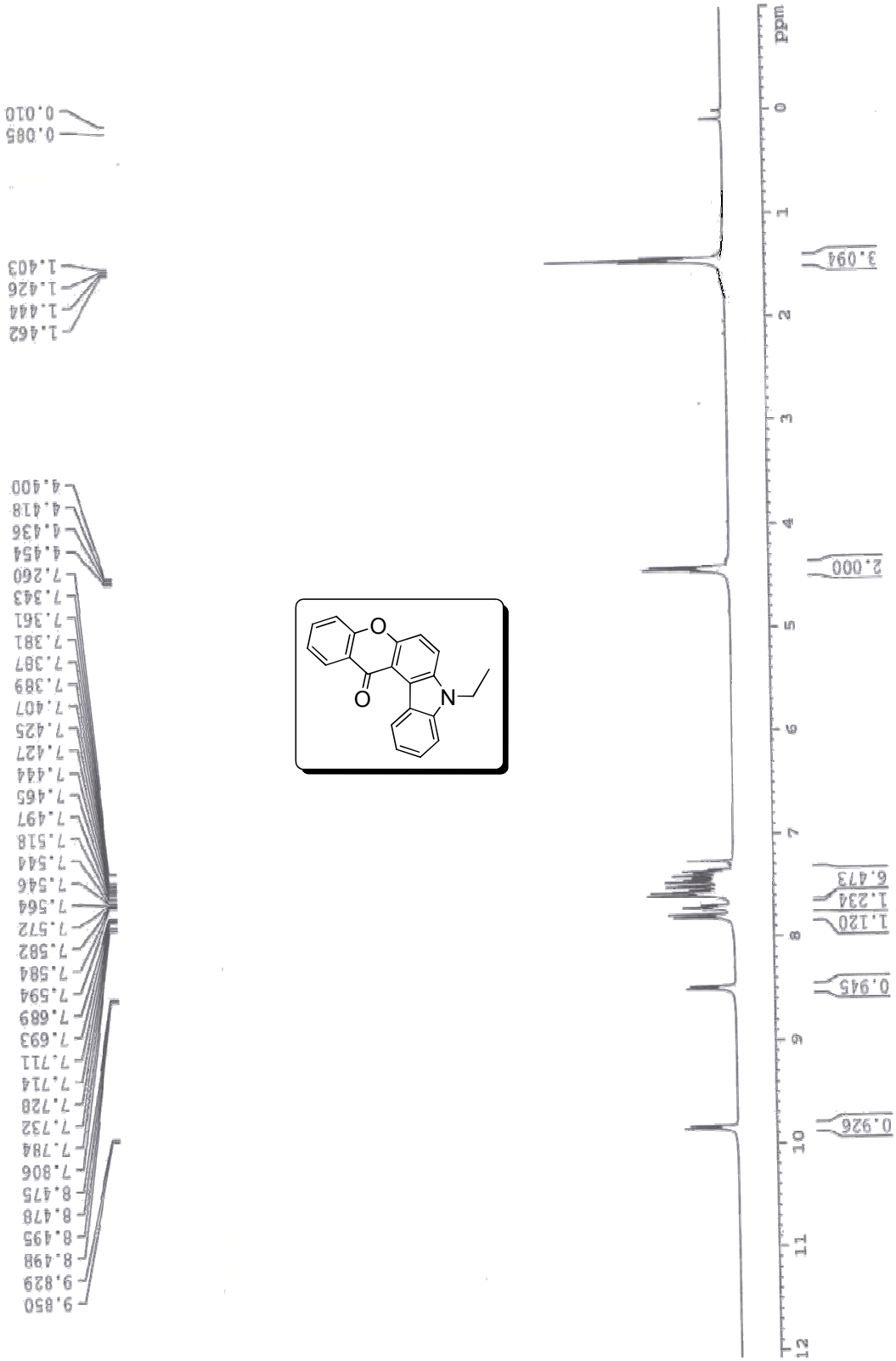
Spectrum 5. ^{1}H NMR of 159a



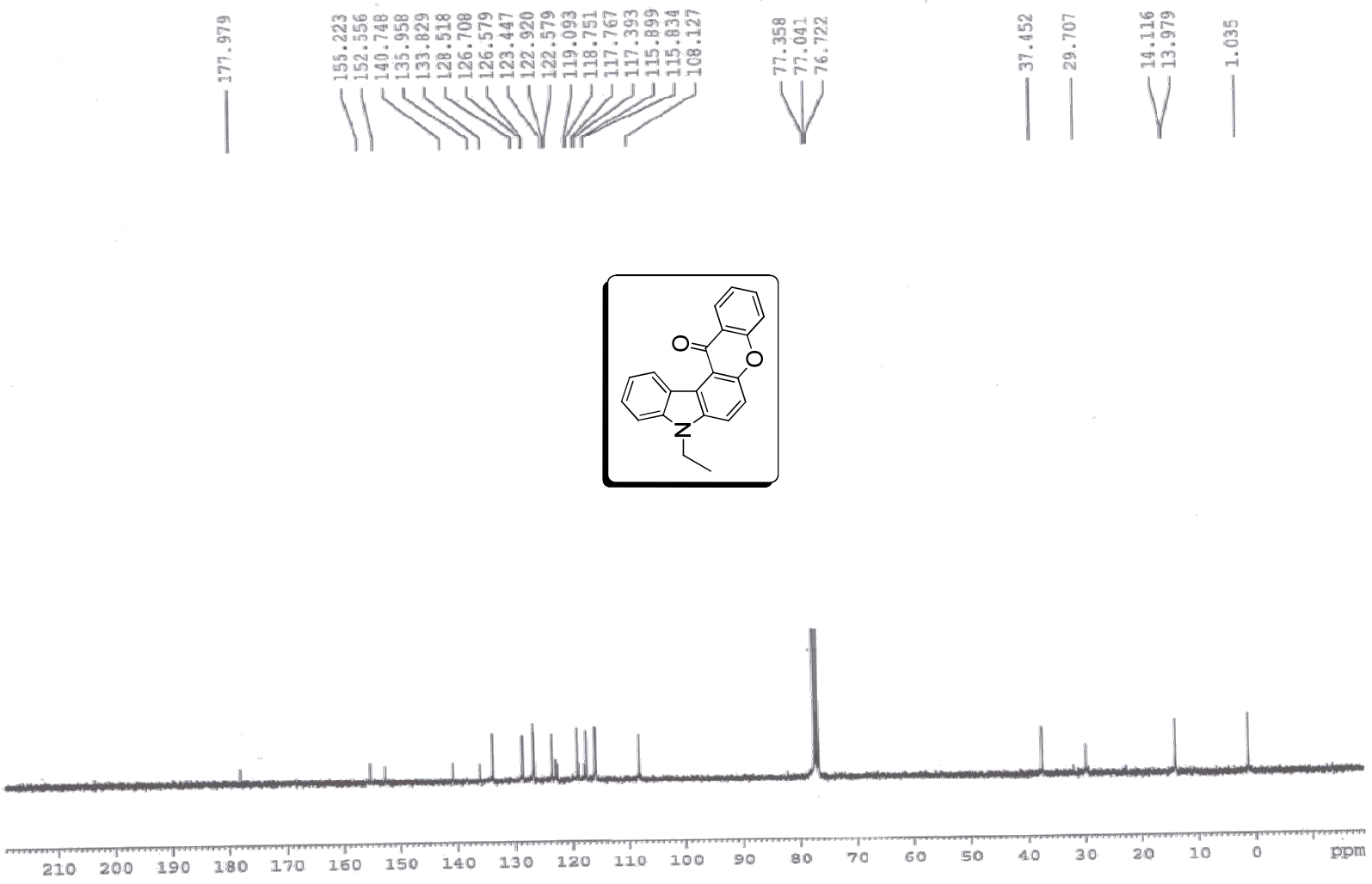
Spectrum 6. ^{13}C NMR of 159a



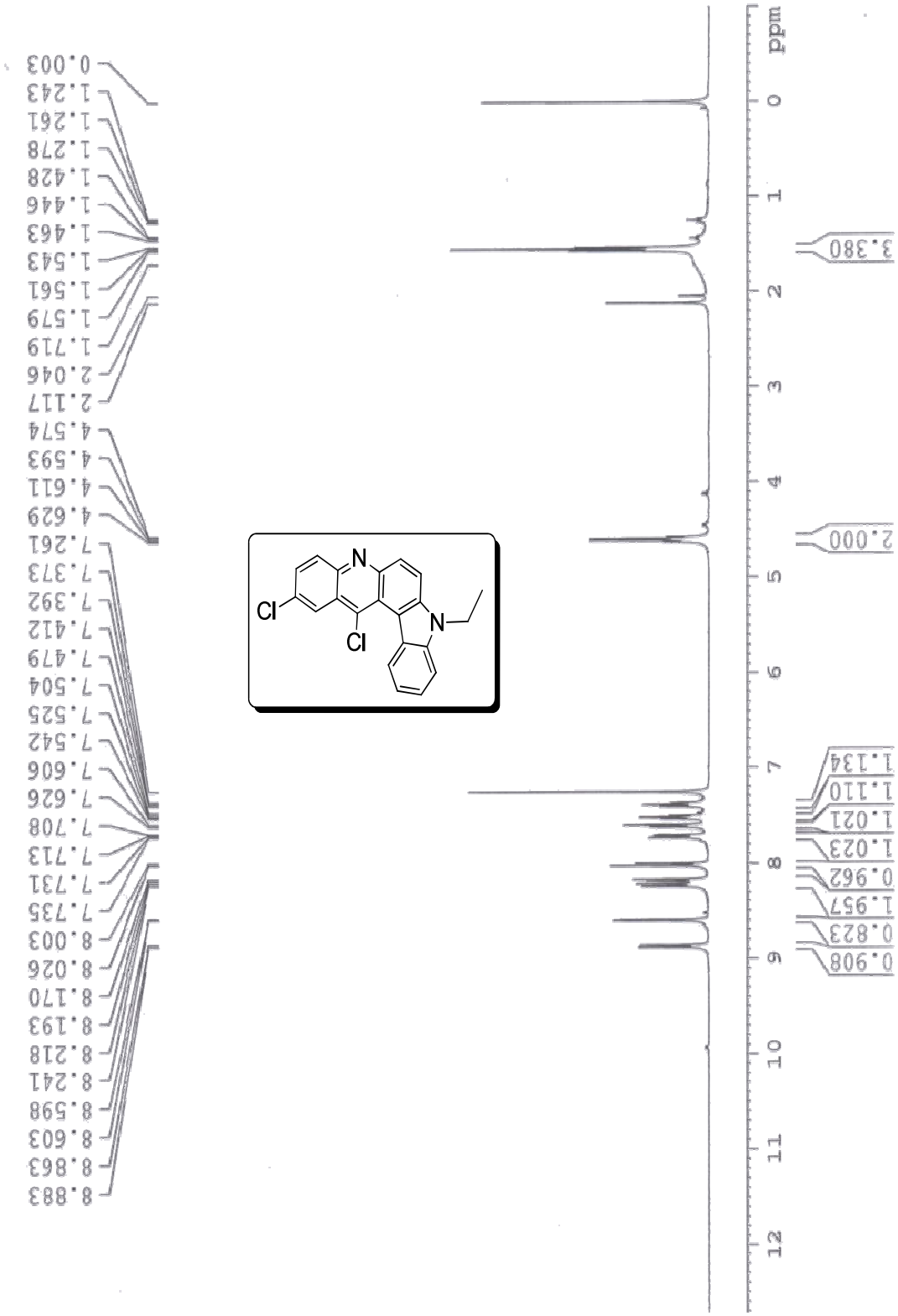
Spectrum 7. ^{1}H NMR of 160a



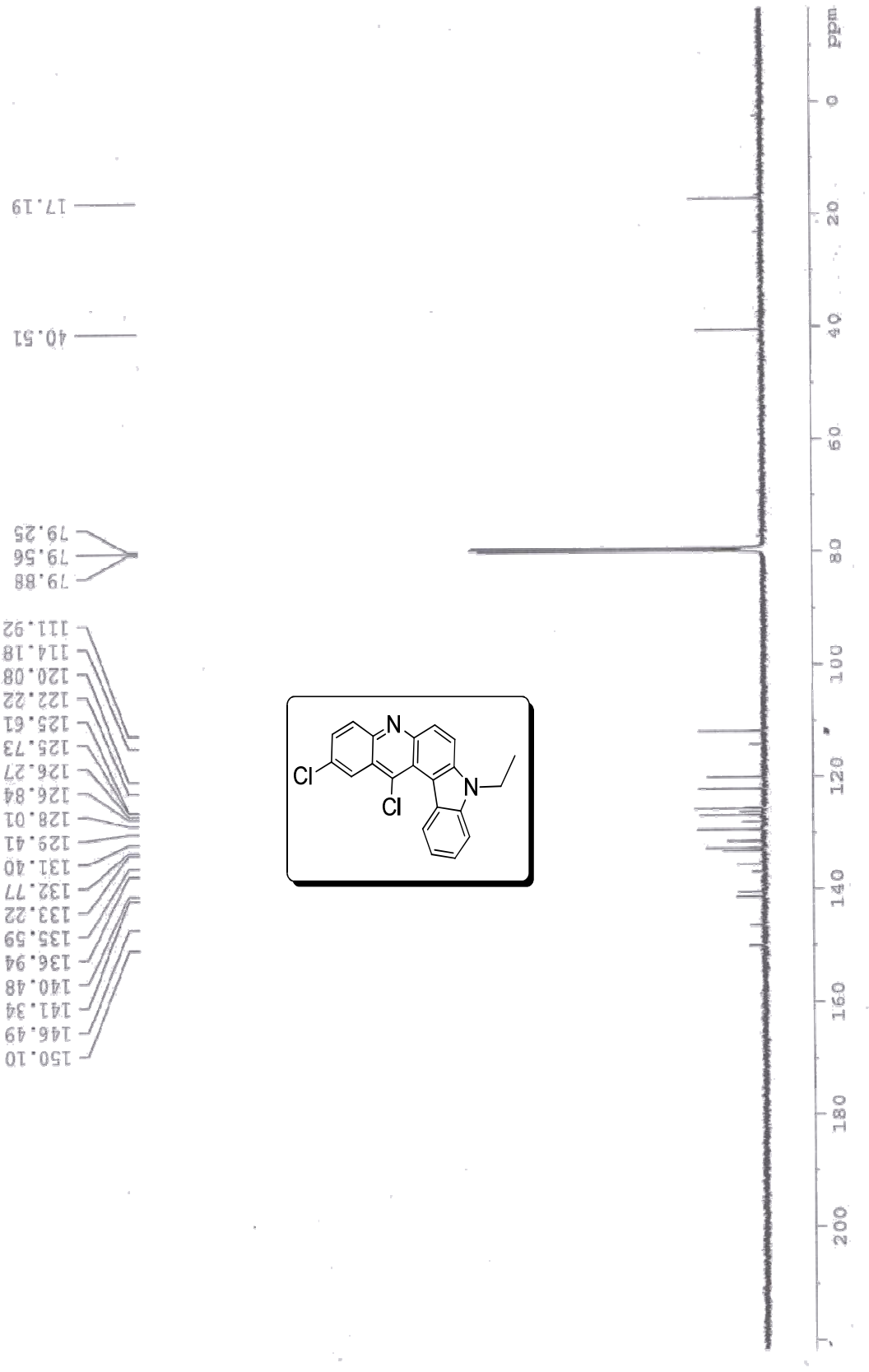
Spectrum 8. ^{13}C NMR of 160a



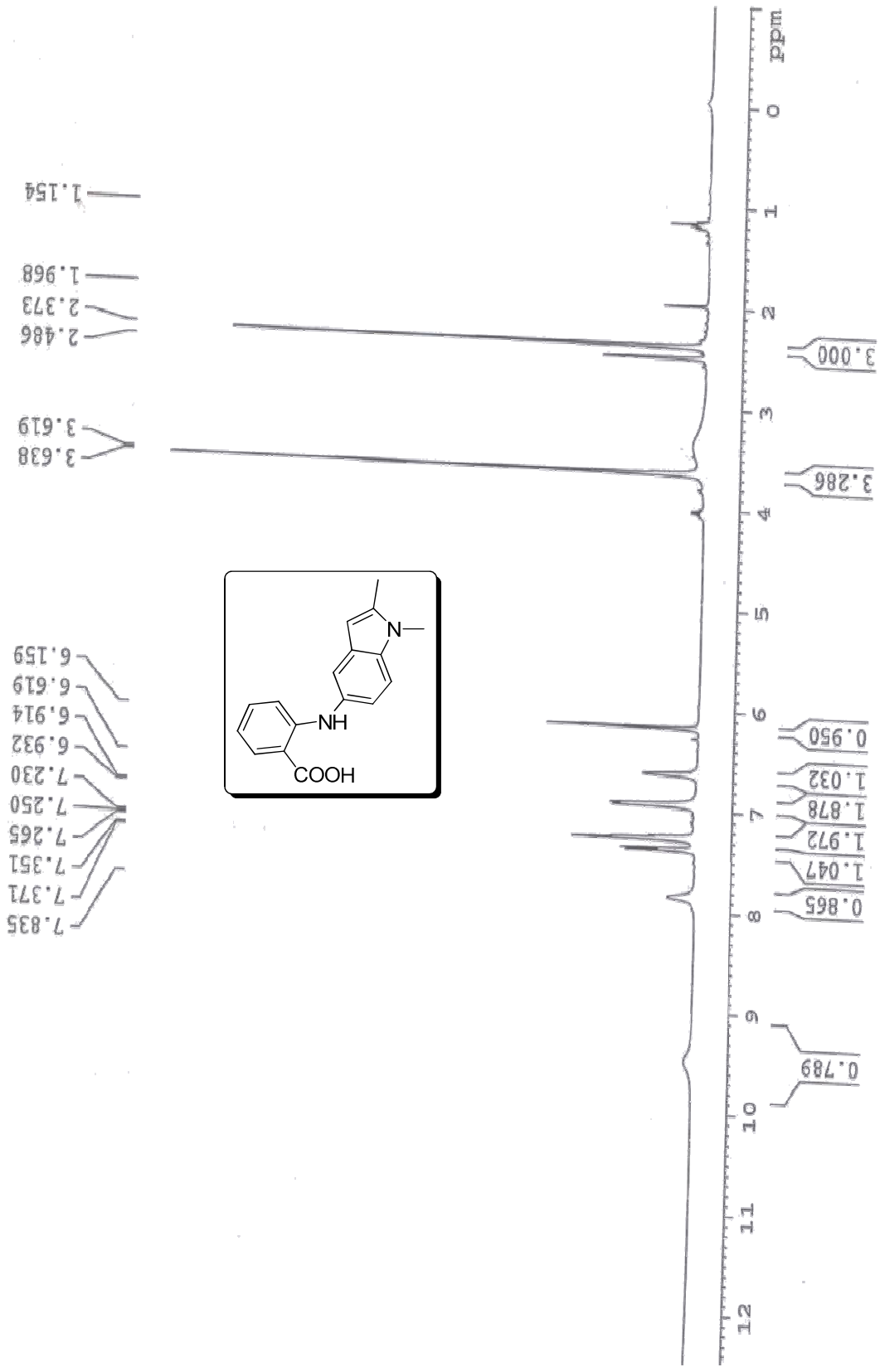
Spectrum 9. ^{1}H NMR of 149c



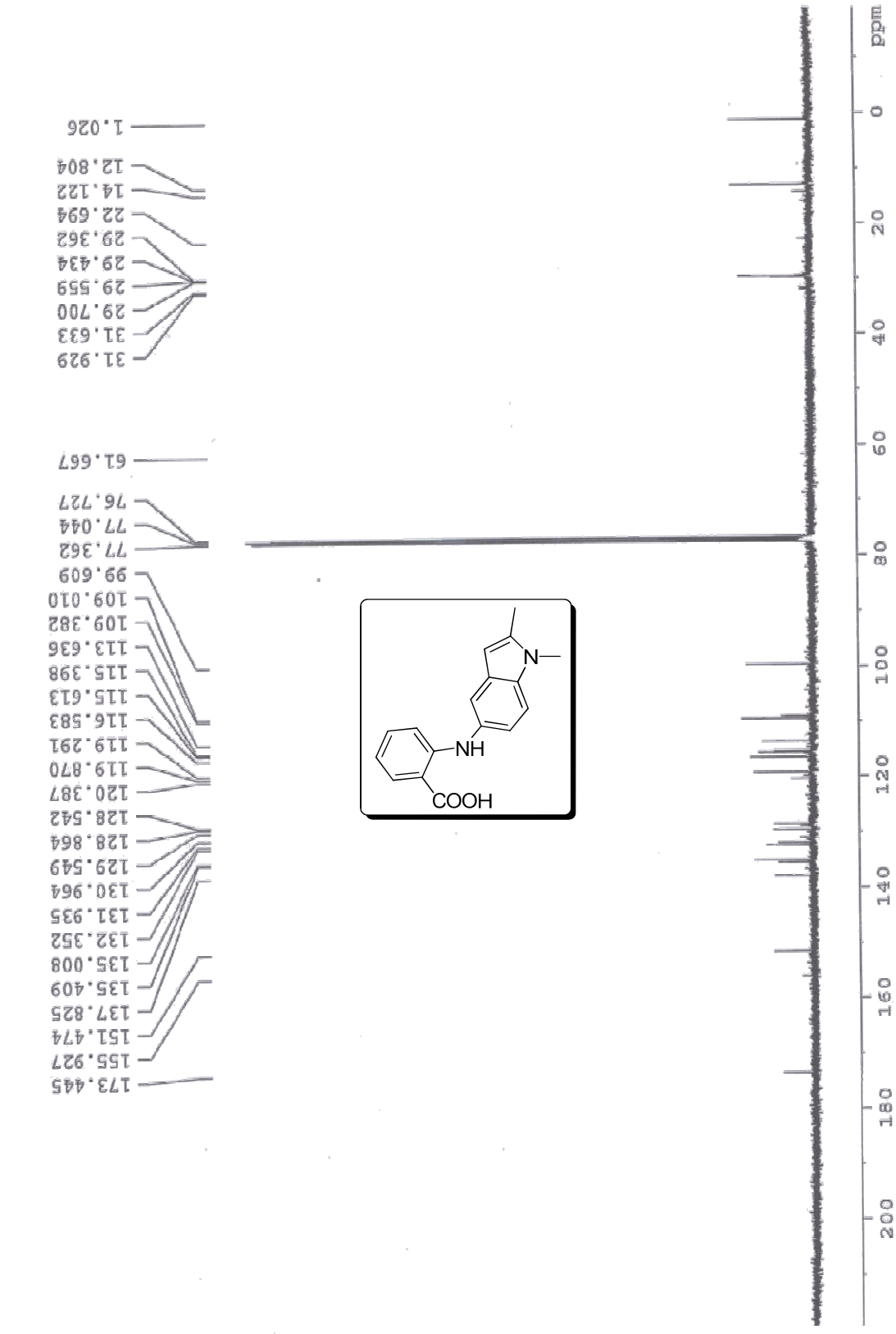
Spectrum 10. ^{13}C NMR of 149c



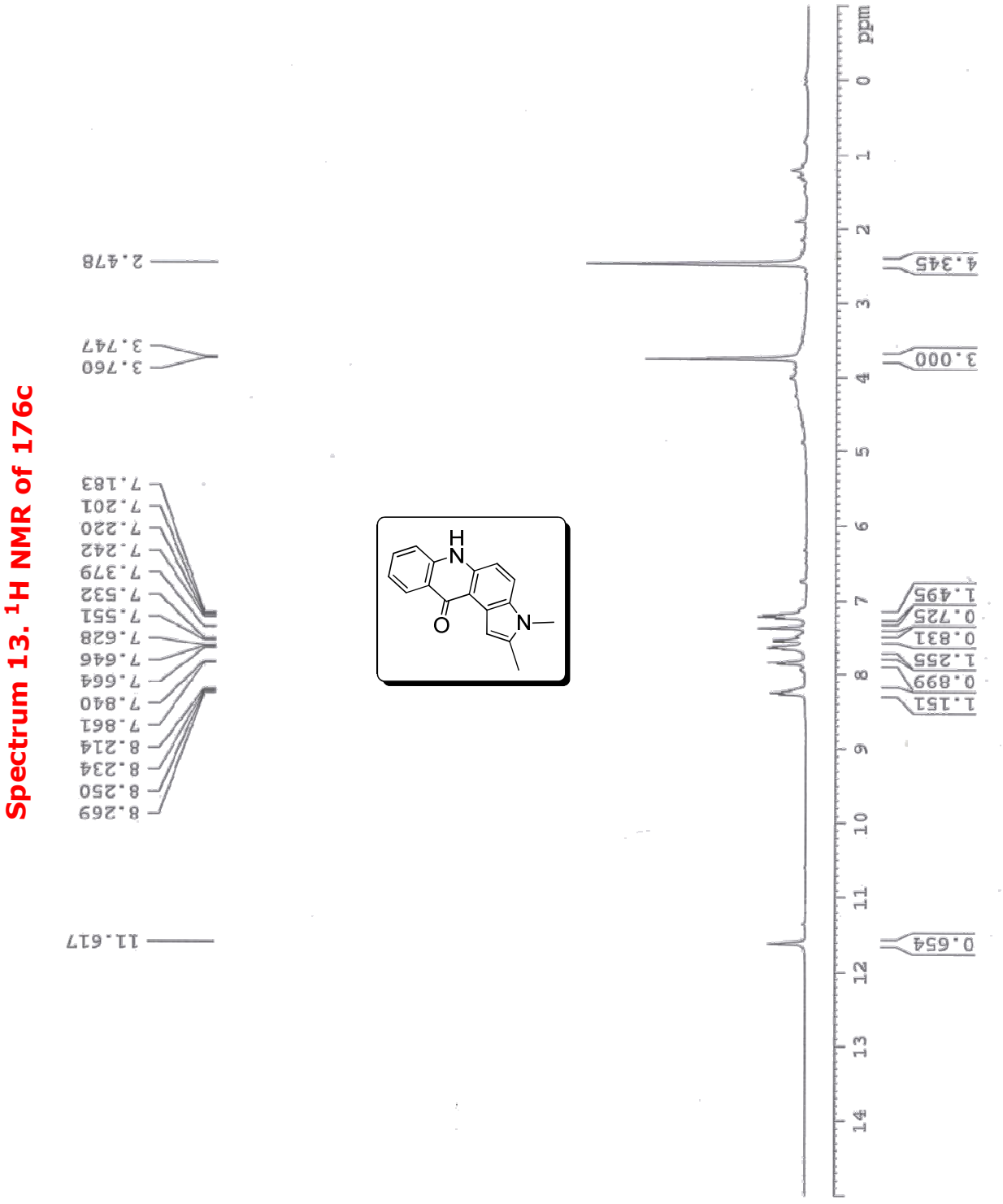
Spectrum 11. ^{1}H NMR of 175c



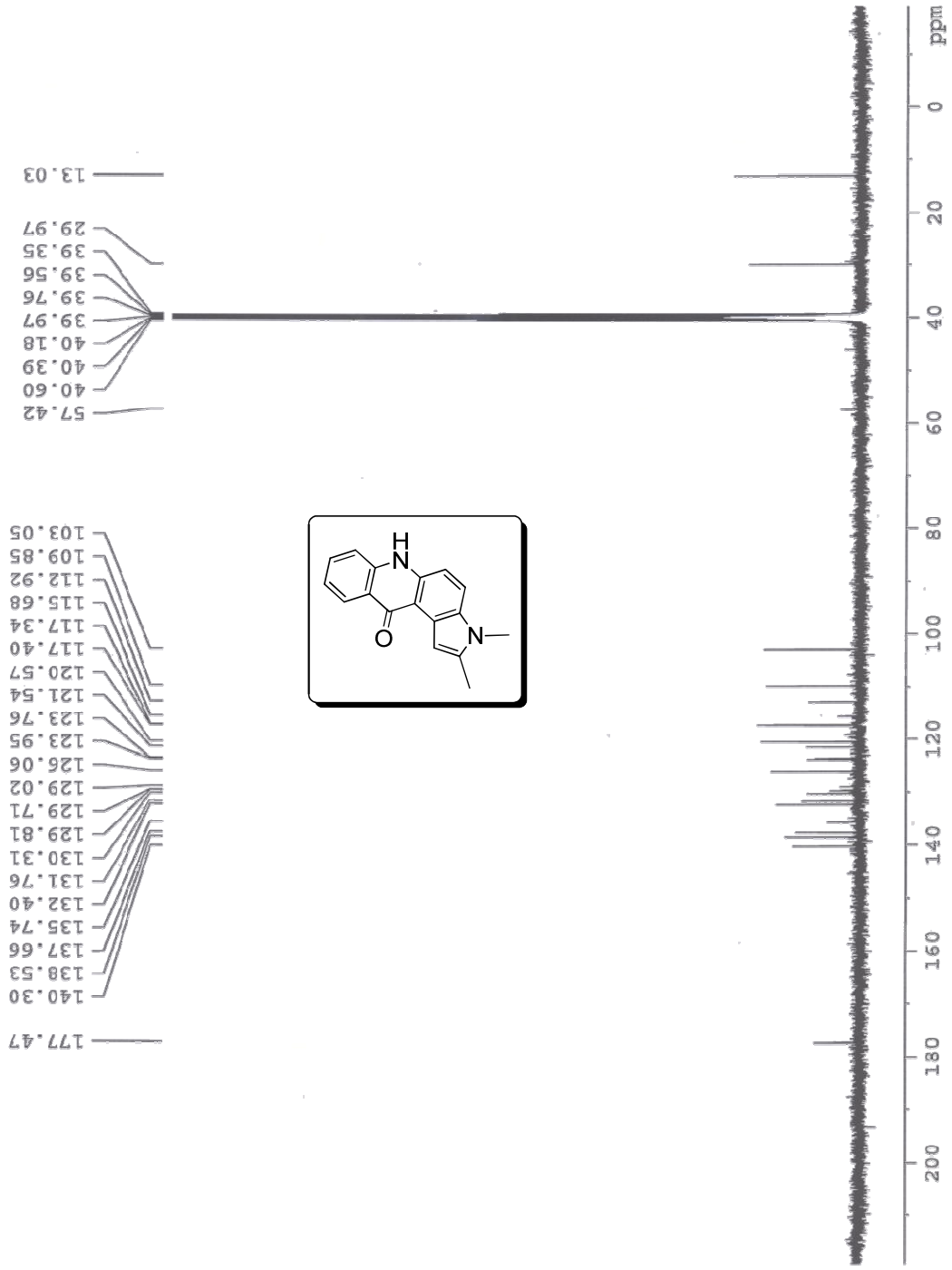
Spectrum 12. ^{13}C NMR of 175c



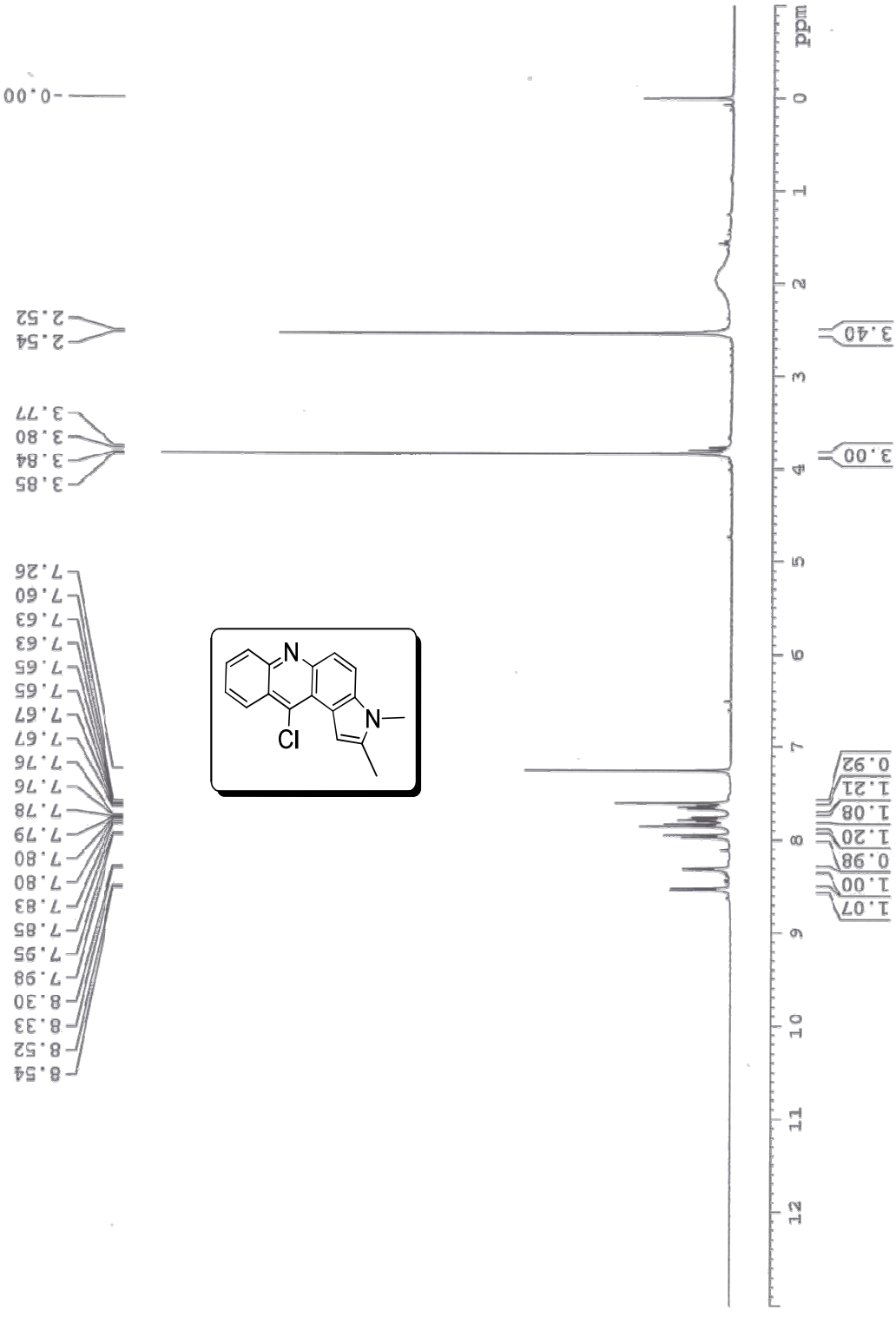
Spectrum 13. ^{1}H NMR of 176c



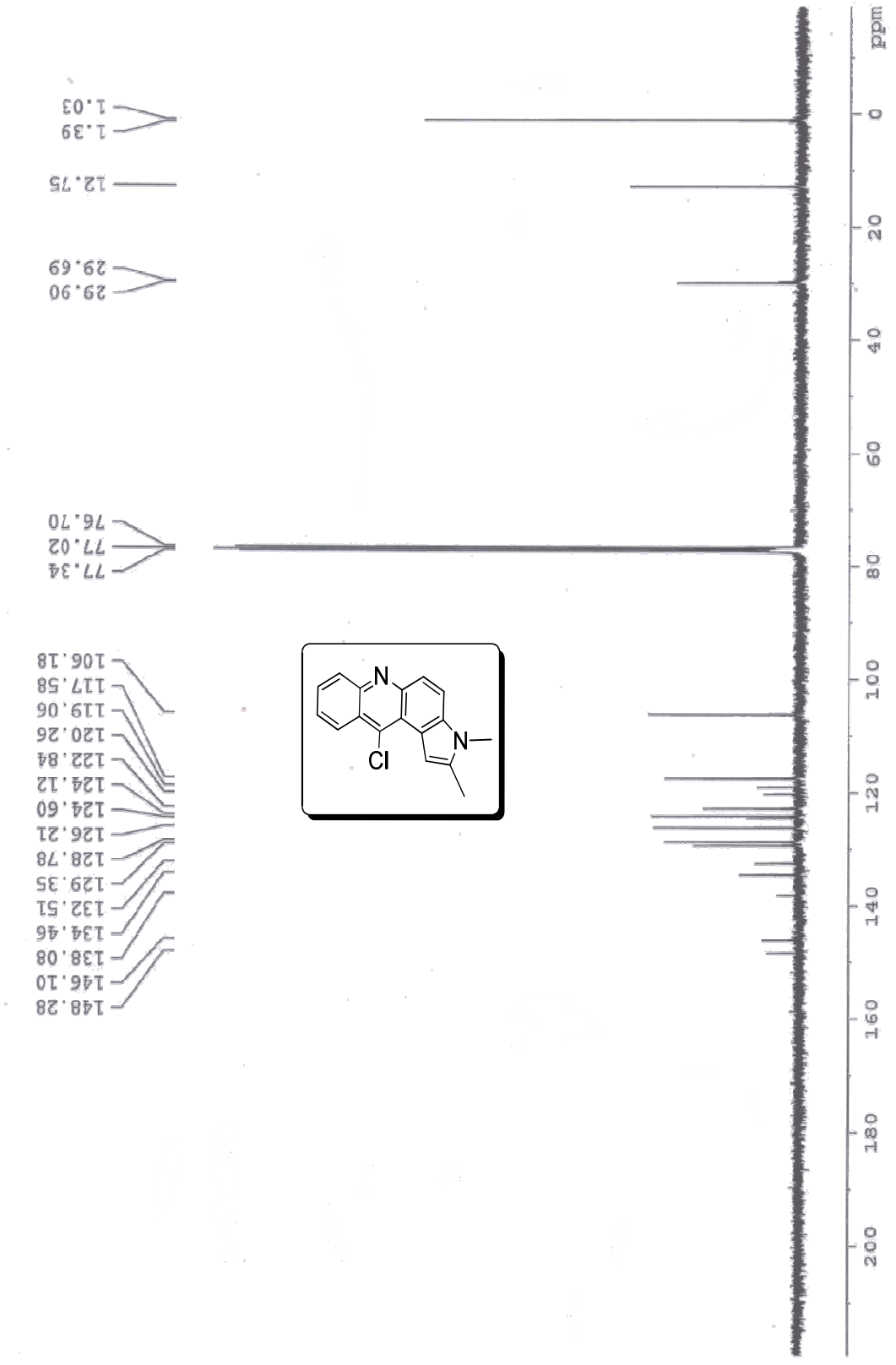
Spectrum 14. ^{13}C NMR of 176c



Spectrum 15. ^{1}H NMR of 177c



Spectrum 16. ^{13}C NMR of 177c



1.7. References

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CHAPTER

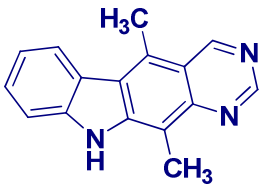
2

Synthesis of Diindolophenazines and Dipyrrolophenazines

2.1. Introduction

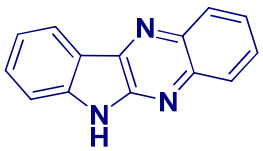
Indolo[2,3-*b*]quinoxalines are important DNA intercalating agents with antiviral and cytotoxic activities.[113] 6*H*-Indolo[2,3-*b*]quinoxaline **179** can be seen as an aza analogue of ellipticine **178** (Figure 22).

Figure 22



178

5,11-Dimethyl-10*H*-pyrimido [4,5-*b*]carbazole



179

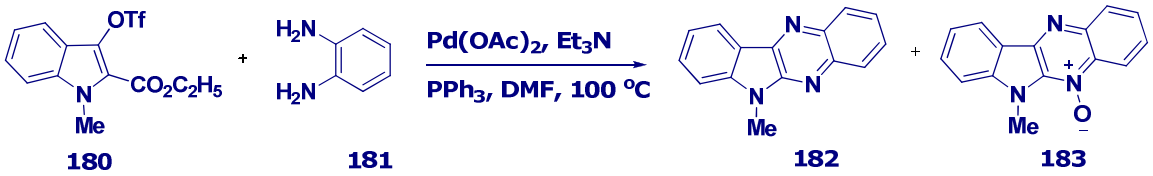
6*H*-Indolo[2,3-*b*]quinoxaline

It is a well-examined and well-described compound, primarily by Bergman and co-workers.[114–116] It has nitrogen atoms in the third ring instead of the 5,11-methyl groups in ellipticine. Several analogues of 6*H*-indolo[2,3-*b*]quinoxaline have been synthesized, e.g., B-220 (2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]quinoxaline), which have shown high antiviral activity.[117,118] The replacement of the methyl groups in positions 5 and 11 by nitrogen atoms gave little or no cytotoxicity against most cancer models except for Burkitt's lymphoma, a cancer type that is closely related to viral activity.[119] This information resulted in the development of 2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo-[2,3-*b*]quinoxalin-e (B-220*a*)[120] and further studies revealed that it exhibited good antiviral activity

against herpes simplex virus type 1 (HSV-1), cytomegalovirus (CMV) and varicella-zoster virus (VZV). It has been reported that the mechanism of the antiviral action against HSV-1 appears to involve binding by intercalation into the DNA helix and, thus, disturbing the processes that are vital for viral uncoating.[117,121] Further development of a new series of indoloquinoxaline derivatives related to B-220 have shown to have a significant effect against autoimmune inflammatory diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), and other diseases.[122]

Indolo[2,3-*b*]quinoxalines have been synthesized[123] either by condensation of an isatin with a 1,2-phenylenediamine or by alkylation of an indoloquinoxaline. Mérour *et al*. developed a method[124] by treating the triflate **180** with *o*-phenylenediamine **181** in the presence of palladium acetate, triphenyl phosphine and triethylamine in DMF at 100 °C to obtain the 6-methyl-6*H*-indolo[2,3-*b*]quinoxaline **182** in 60% yield along with the corresponding *N*-oxide product **183** in 27% yield as shown in Eq. 25.

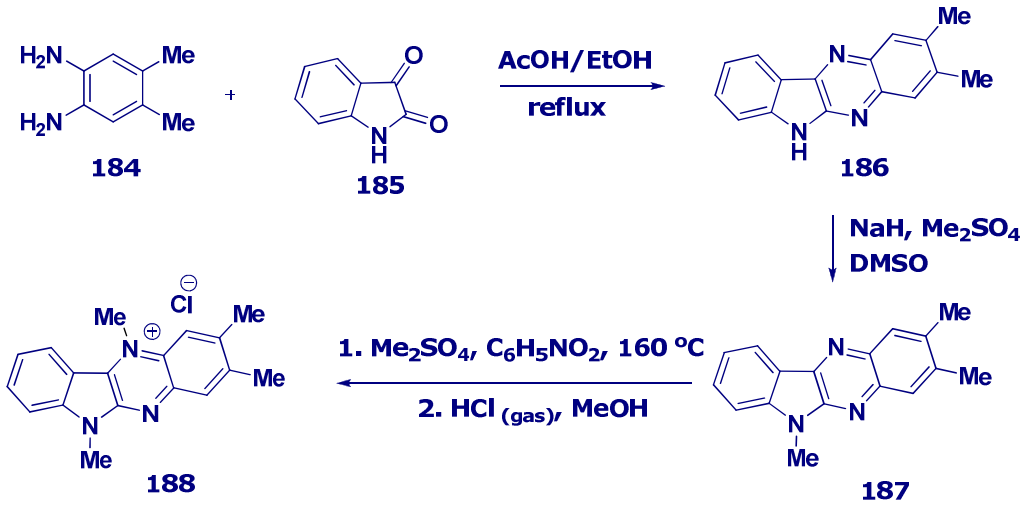
Eq. 25



180 **181** **182** **183**

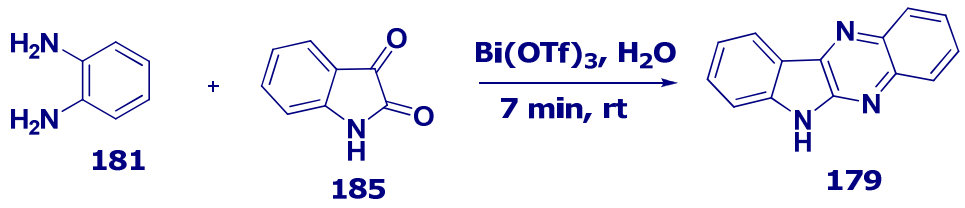
Sylviane *et al*. reported[125] 2,3,6,11-tetramethylindolo[2,3-*b*]quinoxalinium chloride **188** by treating with diamine **184** and isatin **185** which provides indolo[2,3-*b*]quinoxaline **186** and then subjecting the successive methylation of **186** (Eq. 26).

Eq. 26



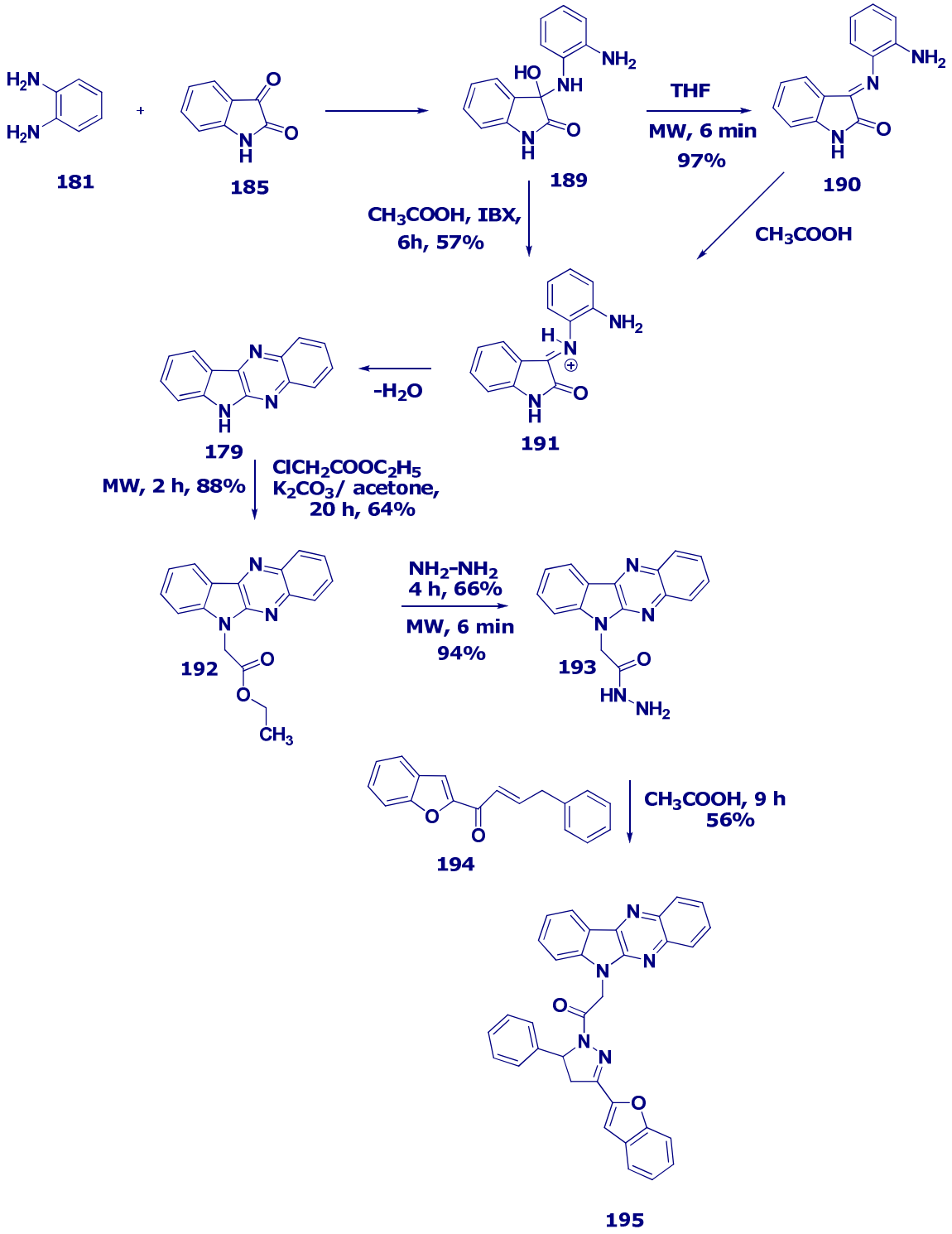
As shown in Eq. 27, Yadav group reported[126] the synthesis of indoloquinoxaline **179** in high yields under mild conditions by cyclocondensation of aromatic 1,2-diamine **181** with 1,2-dicarbonyl **185** using a catalytic amount of $Bi(OTf)_3$.

Eq. 27



2-[1-(5,8-Dihydroquinoxalino[2,3-*b*]indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl]phenyl **195** derivatives were synthesized[127] by Manna *et al*. from 2-(5,8-dihydroquinoxalino[2,3-*b*]indol-5-yl)acetohydrazide **193** and (2*E*)-1-(1-benzofuran-2-yl)-4-phenylbut-2-en-1-one **194** derivatives using microwave-assisted synthesis as shown in Eq. 28.

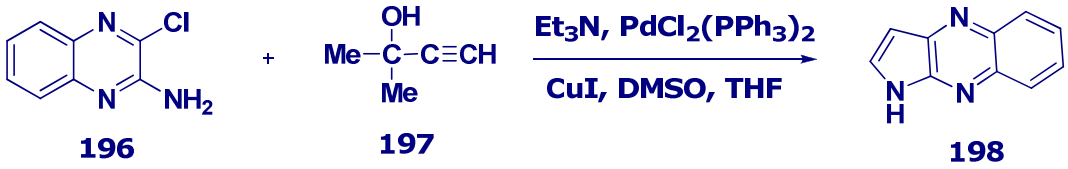
Eq. 28



Ames *et al*. reported[128] the synthesis of pyrrolo[2,3-*b*]quinoxaline **198** by treating of 3-chloro-2-aminoquinoxaline **196** with terminal alkynes HC≡CCMe$_2$OH

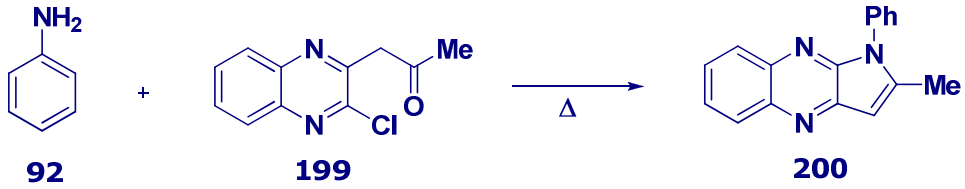
197 in the presence of Pd(II), Cu(I) and triethylamine in DMSO/THF as shown in Eq. 29.

Eq. 29



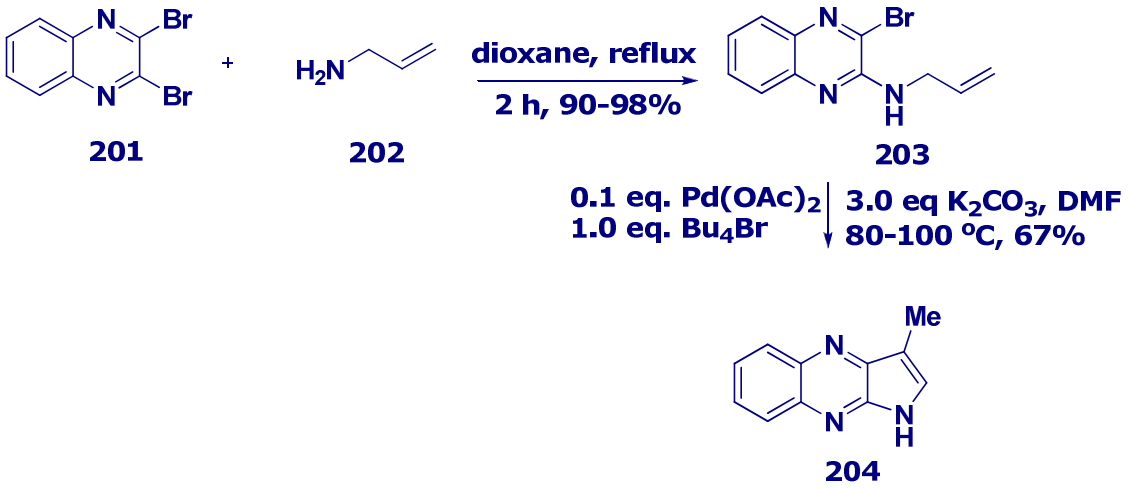
As shown in Eq. 30, Chihoko *et al*. obtained[129] 2-methyl-1-phenylpyrrolo[2,3-*b*]quinoxalines **200** by heating with aniline **92** and 1-(3-chloro-2-quinoxalinyl)-2-alkanones **199**.

Eq. 30



Treatment of 2,3-dibromoquinoxalines **201** with allylamines **202** in 1,4-dioxane furnished allyl(3-haloquinoxalin-2-yl)amine **203** which provides 3-methyl-pyrrolo[2,3-*b*]quinoxaline **204** under classic Heck conditions as shown in Eq. 31.[130]

Eq. 31



2.2. Synthesis of diindolophenazines

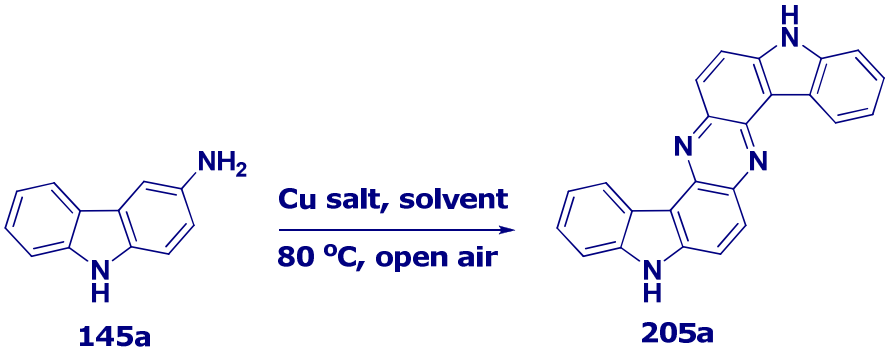
As a part of our research programme on the synthesis of nitrogen-based heterocycles, we have developed a new and novel method for the synthesis of diindolophenazine derivatives by the aerobic oxidative coupling of 3-aminocarbazole derivatives in presence of the catalytic CuBr (10 mol%) in DMSO at 80 °C. Aerobic oxidation under mild conditions is one of the current challenges in view of environmental and economical point of view.[131] However, aerobic oxidative transformations of amines are limited to a few reactions, which include the ruthenium-catalyzed oxidative cyanation of tertiary amines,[132] transition metal-catalyzed oxidation of secondary amines to imines,[133] primary amines to nitriles[134] and flavin-catalyzed oxidation of secondary amines to nitrones.[135]

In general,[136] phenazine moiety can be constructed through the cyclization of suitably substituted diphenylamines. The literature reports, among others, both the reductive cyclization of *o*,*o'*-dinitrodiphenylamines with Raney nickel,[137d] of *o*-nitrodiphenylamines with $NaBH_4$/NaOMe or FeC_2O_4/Pb[137e] and of *o*-nitro-*o'*-fluorodiphenylamines with $NaBH_4$/NaOEt[137f] as well as the oxidative cyclization of *o*,*o'*-diaminodiphenylamines with $FeCl_3$/HCl.[137g] The substituted diphenylamines required are traditionally synthesized via nucleophilic aromatic substitution[137h] and Ullmann coupling.[137i-j] In general, these methods require harsh reaction conditions and have problems ranging from different substitution pattern of the substrates obtained and lower yields. Here, we report a new and novel method for the construction of phenazine moiety from 3-aminocarbazoles and 5-aminoindoles.

In continuation of our research on Ullmann-Goldberg condensation, we are interested to synthesize diindoloquinolines by the coupling of 3-aminocarbazole with 3-iodoindol-2-carboxylic acid in the presence of CuBr and K_2CO_3 in DMSO followed by cyclization with $POCl_3$. However the expected coupling product was not observed. After careful analysis, we identified the product as diindolophenazine. The present results represent a new method for the synthesis of diindolophenazine and dipyrrolophenazine derivatives by copper(I) bromide (10 mol%) catalyzed aerobic oxidation of 3-aminocarbazole and 5-aminoindole derivatives in DMSO at 80 ^{o}C.

We initiated our studies by examining the reaction of 3-aminocarbazole in presence of catalytic copper salts (10 mol%) in different solvents in open air at 80 ^{o}C (Table 13). After screening a variety of solvents and catalysts, the best result was obtained when the reaction was carried out in DMSO at 80 ^{o}C for 6 h using copper(I) bromide as the catalyst (entry 1). CuI and CuCl were found to catalyze the same reaction giving comparable yields but with extended reaction time (entry 5 & 6). An attempt to lower the amount of CuBr to 5 mol% resulted in the incomplete consumption of amine, in spite of extended reaction time (entry 13). By increasing the mol% of CuBr, there was no variation of yield but it was found that the reaction time was reduced (entry 14, 15 &16). Cu(II) salts can also perform the reaction with less efficiency (enytry 8, 9, 10 and 11). This is due to the Cu(II) species generated from Cu(I)/air is more active than the Cu(II) salts. We have also performed the reaction under nitrogen atmosphere and found that only the trace amount of the product (entry 17) which indicates that the air is necessary for the oxidation.

Table 13. Screening of reaction conditions



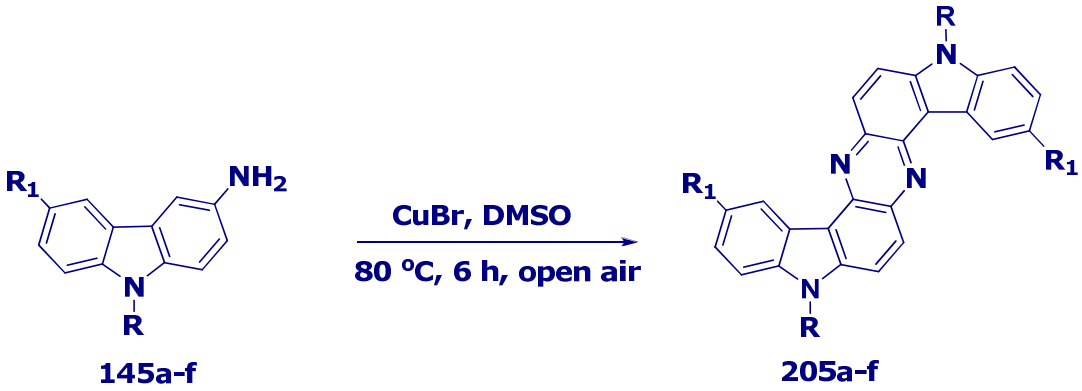
145a 205a

Entry	Catalyst	Mole (%)	Solvent	Time (h)	Yield[a] (%)
1	CuBr	10	DMSO	6	82
2	CuBr	10	DMF	18	71
3	CuBr	10	Toluene	24	0
4	CuBr	10	Xylene	24	0
5	CuI	10	DMSO	7	79
6	CuCl	10	DMSO	7	80
7	CuO	10	DMSO	12	0
8	$Cu(OAc)_2$	10	DMSO	15	67
9	$Cu(OTf)_2$	10	DMSO	24	65
10	$CuCl_2$	10	DMSO	12	47
11	$CuBr_2$	10	DMSO	12	55
12	$CuSO_4$	10	DMSO	12	0
13	CuBr	5	DMSO	12	50
14	CuBr	20	DMSO	4	81
15	CuBr	30	DMSO	4	81
16	CuBr	50	DMSO	3.5	82
17	CuBr	10	DMSO	15	trace[b]

[a] Isolated yield, [b] Reaction was performed under N_2 atmosphere

Using the optimized conditions, the cyclization of a variety of 3-aminocarbazole derivatives are subjected to explore the scope and generality of the reaction (Scheme 8). As shown in Table 14, a variety of substituents such as Me, OMe, Cl, Br are tolerated well on the 3-aminocarbazole. In case of **145b** and **145f**, the corresponding diazocarbazoles were also obtained as side products. The structure of **205b** was also confirmed by the single crystal X-ray analysis (Figure 23).

Scheme 8. Synthesis of diindolophenazines



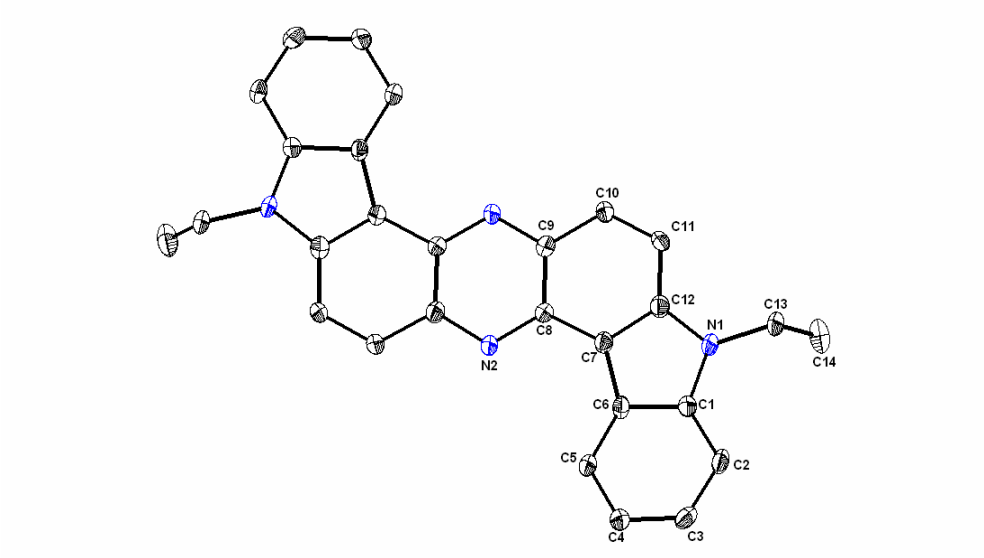
145a-f **205a-f**

Table 14. Synthesis of diindolophenazines

Entry	R	R_1	Product	Yield[a] (%)
1	H	H	**205a**	82
2	Et	H	**205b**	76
3	H	Cl	**205c**	86
4	H	Br	**205d**	85
5	Me	Me	**205e**	78
6	Me	OMe	**205f**	70

[a] Isolated yield

Figure 23. ORTEP diagram of 205b



2.3. Synthesis of dipyrrolophenazines

The same protocol was also successfully extended to 5-aminoindole derivatives as shown in Scheme 9. 5-Aminoindole derivatives **206a-c** were also cyclized smoothly to give the corresponding products **207a-c**. The outcome of the reaction are presented in Table 15. Simple aromatic amines provide diazobenzenes under the same reaction conditions.

Scheme 9. Synthesis of dipyrrolophenazines

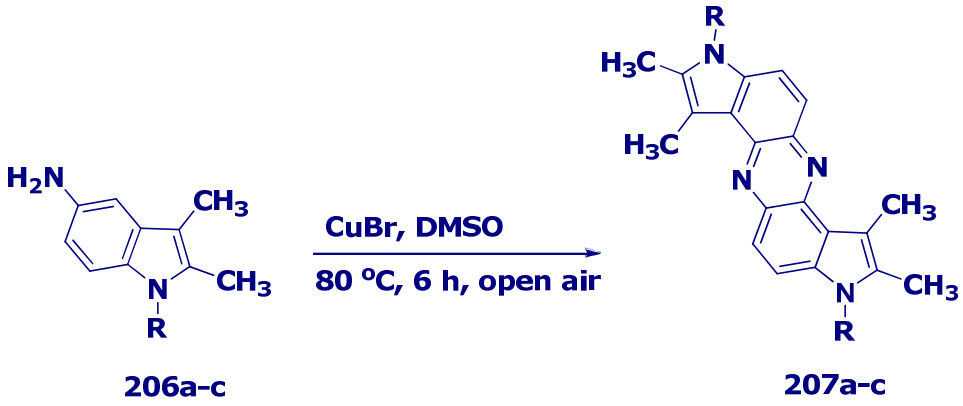


Table 15. Synthesis of dipyrrolophenazines

Entry	R	Product	Yield[a] (%)
1	H	**207a**	78
2	Me	**207b**	81
3	Et	**207c**	76

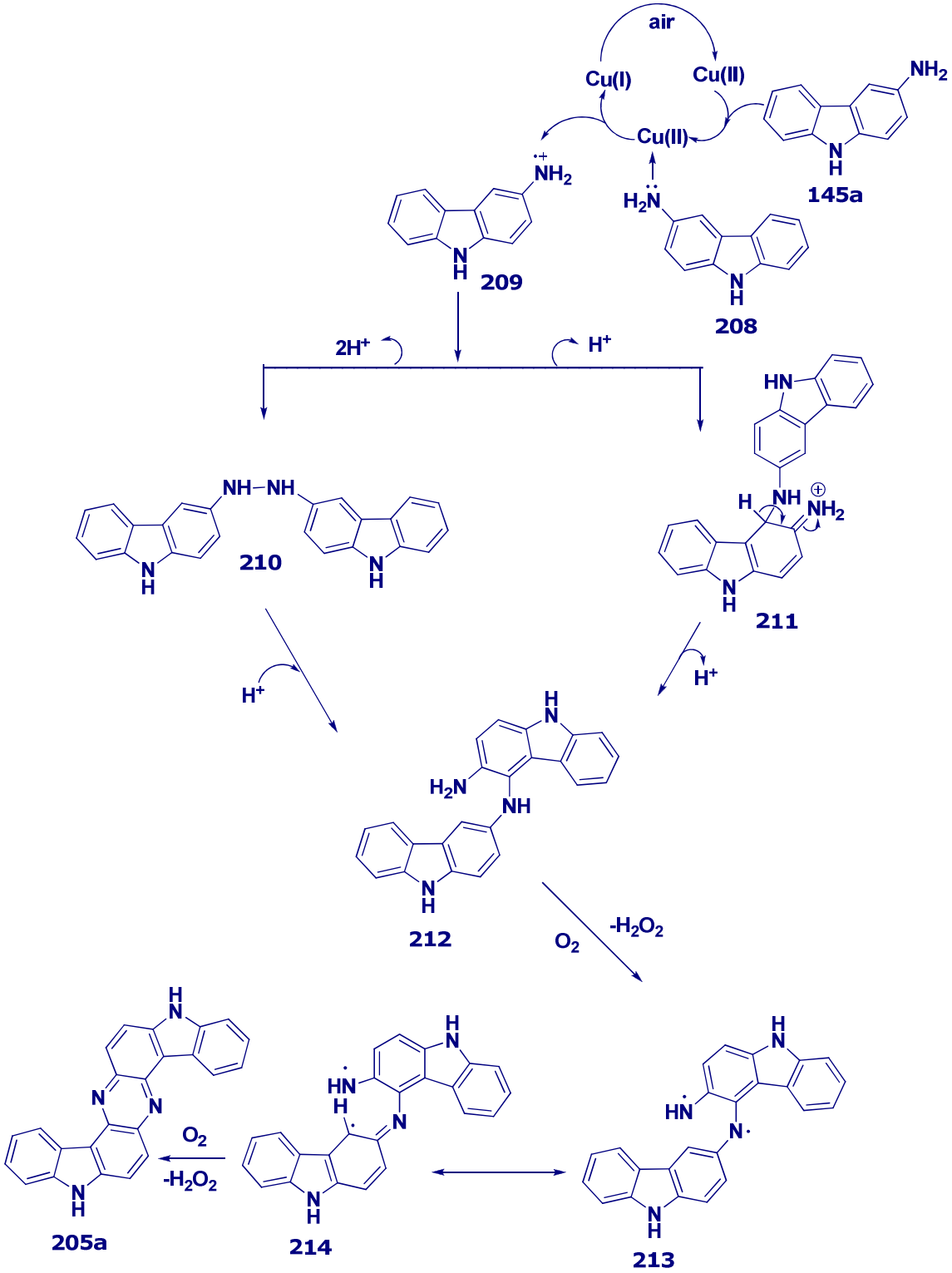
[a] Isolated yield

The reaction can be rationalized by assuming two mechanistic path ways "a" and "b" as shown in Scheme 10. This synthetically interesting oxidation process starts with atmospheric oxygen as the cheapest and most abundant ultimate "electron scavenger". As shown in Scheme 1a, initially Cu(I) salt was oxidized by air to give more active Cu(II) precursor, which coordinated with amine leading to **208**. **208** gives the aminium radical **209** by loosing one electron to Cu(II). This radical dimerized via head-to-head to give hydrazocarbazole **210.** On the other hand, the radical **209** couples with its resonance form where the single electron lies at 4th position of the carbazole to give **211**. **210** and **211** gives an intermediate **212** as shown in Scheme 10a. The oxidative coupling of the intermediate **212** could produce the amine radical[136b] **213** which in turn underwent the second oxidative coupling to provide the final product **205a**.

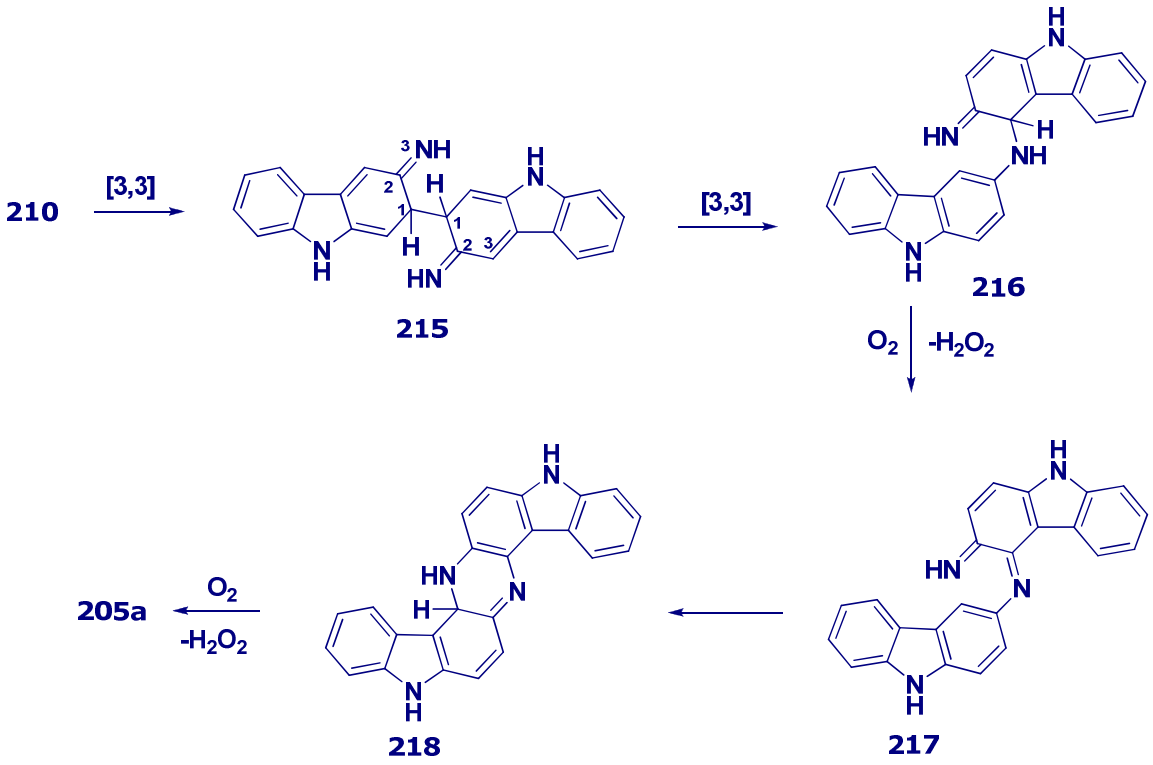
As shown in Scheme 10b[136c], [3,3] sigmatropic shift transforms hydrazocarbazole **210** into **215**, which has an analogous structure to the ortho-benzidine precursor. Consecutive [3,3] shift provides another intermediate **216**, which has a counterpart in the benzidine rearrangement. The oxidative coupling of the intermediate **216** produced another intermediate **217** which in turn underwent the second oxidative coupling to provide the final product **205a**.

Scheme 10. Plausible mechanism

a)



b)



2.4. Conclusion

In conclusion, we have found that a novel and an efficient aerobic oxidative transformation of 3-aminocarbazole and 5-aminoindole derivatives to the corresponding diindolophenazines **205a-f** and dipyrrolophenazines **207a-c** respectively in the presence of the catalyst CuBr.

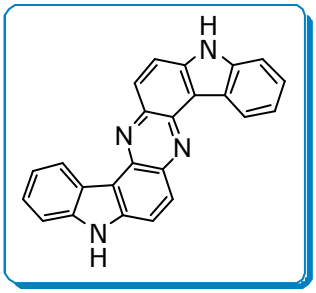
2.5. Experimental Section

General procedure G

A mixture of 3-aminocarbazoles **145a-f** (1.0 mmol) and copper(I) bromide (10 mol%) in DMSO was heated at 80 °C in open air for 6 h. Then the reaction mixture was poured on to water and extracted with ethyl acetate (3 x 30 mL). The solvent was dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude products were purified by column chromatography using silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products of diindolophenazines.

1,9-Dihydrodiindolo[3,2-*a*:3,2-*h*]phenazine (205a):

The title compound **205a** was prepared from 3-aminocarbazole **145a** (0.18g, 1.0 mmol) by following the *general procedure G.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 82%

Mp: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 3393, 3053, 2926, 2854, 1726, 1601, 1462, 1379, 1265, 1074, 895, 742

^{1}H NMR (400 MHz) δ: 12.18 (2H, s), 9.06 (2H, d, *J* = 7.6 Hz), 8.30 (2H, d, *J* = 9.2 Hz), 8.23 (2H, d, *J* = 8.8 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.49 (2H, t, *J* = 7.2 Hz), 7.43 (2H, t, *J* = 7.6 Hz)

^{13}C NMR (100 MHz) δ: 139.9, 139.0, 138.9, 138.5, 127.5, 125.2, 123.8, 123.2, 121.0, 120.3, 114.3, 112.4

LC-MS (m/z): 359 ($M+H^+$)

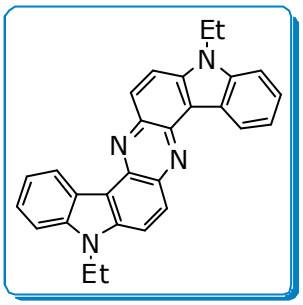
Anal. Calcd. for $C_{24}H_{14}N_4$: C, 80.43; H, 3.94; N, 15.63%

Found: C, 80.25; H, 3.89; N, 15.77%

1,9-Diethyl-1,9-dihydrodiindolo[3,2-*a*:3,2-*h*]phenazine (205b):

The title compound **205b** was prepared from 3-amino-9-ethylcarbazole **145b** (0.21g, 1.0 mmol) by following the *general procedure G.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 76%



Mp: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 2966, 2916, 1593, 1537, 1471, 1313, 1232, 1118, 889, 748

^{1}H NMR (400 MHz) δ: 9.14 (2H, d, *J* = 8.0 Hz), 8.47 (2H, d, *J* = 8.8 Hz), 8.37 (2H, d, *J* = 9.2 Hz), 7.87 (2H, d, *J* = 8.0 Hz), 7.56 (2H, t, *J* = 8.0 Hz), 7.47 (2H, t, *J* = 8.0 Hz), 4.74 (4H, q, *J* = 7.5 Hz), 1.45 (6H, t, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 140.3, 139.5, 138.7, 138.0, 127.8, 125.2, 124.6, 124.1, 123.9, 120.7, 116.3, 109.2, 38.1, 14.9

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

Anal. Calcd. for $C_{28}H_{22}N_4$: C, 81.13; H, 5.35; N, 13.52%

Found: C, 81.22; H, 5.32; N, 13.61%

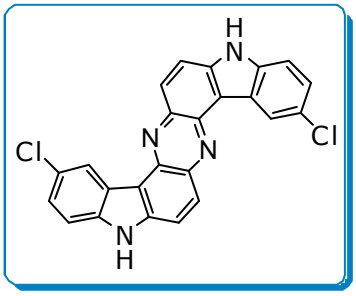
4,12-Dichloro-1,9-dihydrodiindolo[3,2-*a*:3,2-*h*]phenazine (205c):

The title compound **205c** was prepared from 6-chloro-3-aminocarbazole **145c** (0.21g, 1.0 mmol) by following the *general procedure G.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 86%

Mp: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 3337, 2928, 2856, 1547, 1464, 1292, 1209, 1126, 1018, 949



^{1}H NMR (400 MHz) δ: 12.37 (2H, s), 8.99 (2H, s), 8.36 (2H, d, *J* = 8.8 Hz), 8.22 (2H, d, *J* = 9.2 Hz), 7.75 (2H, d, *J* = 8.4 Hz), 7.49 (2H, t, *J* = 8.4 Hz)

^{13}C NMR (100 MHz) δ: 139.9, 139.6, 139.0, 137.5, 128.4, 125.2, 124.9, 124.8, 122.0, 120.4, 114.1, 113.6

LC-MS (m/z): 427 (M), 429 (M+2), 431 (M+4)

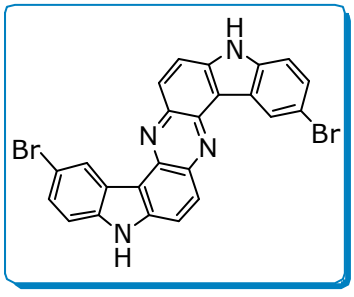
Anal. Calcd. for $C_{24}H_{12}Cl_2N_4$: C, 67.46; H, 2.83; N, 13.11%

Found: C, 67.31; H, 2.81; N, 13.26%

4,12-Dibromo-1,9-dihydrodiindolo[3,2-*a*:3,2-*h*]phenazine (205d):

The title compound **205d** was prepared from 6-bromo-3-aminocarbazole **145d** (0.26g, 1.0 mmol) 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: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 3425, 1292, 1151, 1026, 1001, 825, 765

^{1}H NMR (400 MHz) δ: 12.41 (2H, s), 9.16 (2H, s), 8.38 (2H, d, *J* = 9.2 Hz), 8.24 (2H, d, *J* = 9.2 Hz), 7.73 (2H, d, *J* = 8.4 Hz), 7.62 (2H, d, *J* = 8.8 Hz)

^{13}C NMR (100 MHz) δ: 140.0, 139.4, 139.0, 137.7, 128.5, 127.5, 125.5, 125.0, 120.4, 114.6, 113.4, 113.2

LC-MS (m/z): 516 (M), 518 (M+2), 520 (M+4)

Anal. Calcd. for $C_{24}H_{12}Br_2N_4$: C, 55.84; H, 2.34; N, 10.85%
Found: C, 55.76; H, 2.32; N, 10.91%

1,4,9,12-Tetramethyl-1,9-dihydrodiindolo[3,2-*a*:3,2-*h*]phenazine (205e):

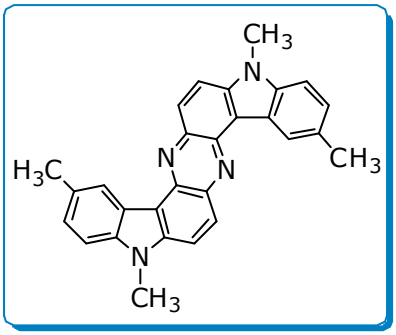
The title compound **205e** was prepared from 6,9-dimethyl-3-aminocarbazole **145e** (0.21g, 1.0 mmol) by following the *general procedure G.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 78%

Mp: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 2256, 2127, 1024, 995, 827, 767

^{1}H NMR (400 MHz) δ: 9.10 (2H, s), 8.44 (2H, d, *J* = 8.0 Hz), 8.07 (2H, d, *J* = 8.0 Hz), 7.51 (2H, d, *J* = 8.0 Hz), 7.40 (2H, d, *J* = 8.0 Hz), 4.10 (6H, s), 2.72 (6H, s)



^{13}C NMR (100 MHz) δ: 150.8, 147.3, 145, 133.7, 132.9, 127.9, 127.4, 125.7, 124.8, 121.3, 114.8, 114.7, 34.5, 26.3

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

Anal. Calcd. for $C_{28}H_{22}N_4$: C, 81.13; H, 5.35; N, 13.52%

Found: C, 81.22; H, 5.38; N, 13.65%

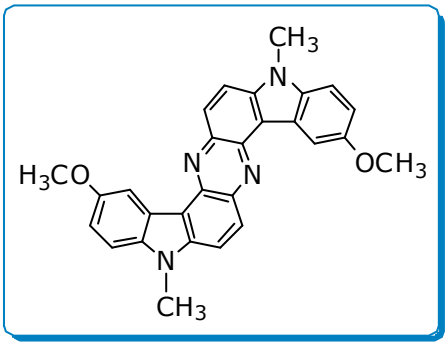
4,12-Dimethoxy-1,9-dimethyl-1,9-dihydrodiindolo[3,2-*a*:3,2-*h*]phenazine (205f):

The title compound **205f** was prepared from 6-methoxy-9-methyl-3-aminocarbazole **145f** (0.22g, 1.0 mmol) by following the *general procedure G.* The crude product was purified by silica gel column chromatography with 13% ethyl acetate in hexanes.

Yield: 70%

Mp: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 2236, 2121, 1556, 1432, 1074, 975, 817, 761

^{1}H NMR (400 MHz) *δ*: 

8.82 (2H, s), 8.37 (2H, d, *J* = 8.0 Hz), 8.04 (2H, d, *J* = 9.2 Hz), 7.52 (2H, d, *J* = 8.8 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 4.14 (6H, s), 4.09 (6H, s)

^{13}C NMR (100 MHz) *δ*: 154.3, 145.8, 142.7, 136.8, 123.5, 122.7, 120.1, 116.7, 115.9, 110.9, 110.1, 104.0, 56.1, 29.8

LC-MS (m/z): 447 ($M+H^+$)

Anal. Calcd. for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55%

Found: C, 75.25; H, 5.02; N, 12.67%

General procedure H

A mixture of 2,3-dimethyl-5-aminoindoles **206a-c** (1.0 mmol) and copper(I) bromide (10 mol%) in DMSO was heated at 80 °C in open air for 6 h. Then the reaction mixture was poured on to water and extracted with ethyl acetate (3 x 20 mL). The solvent was dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude materials were purified by column chromatography using silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products of dipyrrolophenazines.

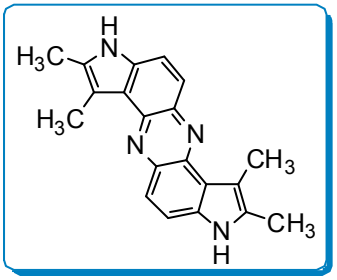
1,2,7,8-Tetramethyl-3,9-dihydrodipyrrolo[3,2-*a*:3,2-*h*]phenazine (207a):

The compound **207a** was prepared from 2,3-dimethyl-5-aminoindole **206a** (0.14g, 1.0 mmol) by following the *general procedure H.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 78%

Mp: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 3371, 2920, 2854, 1651, 1585, 1506, 1423, 1292, 1107, 806



^{1}H NMR (400 MHz) *δ*: 11.52 (2H, s), 7.80 (2H, d, *J* = 8.8 Hz), 7.65 (2H, d, *J* = 8.8 Hz), 2.77 (6H, s), 2.42 (6H, s)

^{13}C NMR (100 MHz) *δ*: 139.4, 138.5, 131.9, 130.8, 121.0, 120.8, 118.6, 111.6, 11.7, 11.5

LC-MS (m/z): 315 ($M+H^+$)

Anal. Calcd. for $C_{20}H_{18}N_4$: C, 76.41; H, 5.77; N, 17.82%

Found: C, 76.32; H, 5.71; N, 17.91%

1,2,3,7,8,9-Hexamethyl-3,9-dihydrodipyrrolo[3,2-*a*:3,2-*h*]phenazine (207b):

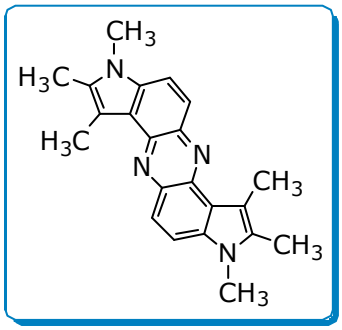
The compound **207b** was prepared from 1,2,3-trimethyl-5-aminoindole **206b** (0.16g, 1.0 mmol) by following the *general procedure H.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 81%

Mp: 206-207 °C

IR (KBr) ν_{max} cm^{-1}: 2918, 2852, 1739, 1610, 1458, 1109, 1020, 800

^{1}H NMR (400 MHz) δ: 7.89 (2H, d, *J* = 8.8 Hz), 7.77 (2H, d, *J* = 8.6 Hz), 3.85 (6H, s), 2.95 (6H, s), 2.48 (6H, s)



^{13}C NMR (100 MHz) δ: 139.6, 138.7, 131.7, 130.6, 121.4, 120.4, 115.4, 112.3, 38.2, 16.0, 11.5

LC-MS (m/z): 343 ($M+H^+$)

Anal. Calcd. for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36%

Found: C, 77.23; H, 6.42; N, 16.41%

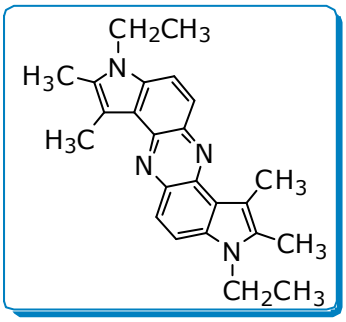
3,9-Diethyl-1,2,7,8-tetramethyl-3,9-dihydrodipyrrolo[3,2-*a*:3,2-*h*]phenazine (207c):

The compound **207c** was prepared from 2,3-dimethyl-1-ethyl-5-aminoindole **206c** (0.17g, 1.0 mmol) by following the *general procedure H.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 76%

Mp: > 340 °C

IR (KBr) ν_{max} cm^{-1}: 2964, 2926, 2854, 1732, 1604, 1437, 1309, 1107, 1024, 802



^{1}H NMR (400 MHz) δ: 7.67 (2H, d, *J* = 8.8 Hz), 7.61 (2H, d, *J* = 9.2 Hz), 4.14 (4H, q, *J* = 7.2 Hz), 2.76 (6H, s), 2.31 (6H, s), 1.26 (6H, t, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 139.6, 138.6, 131.7, 130.6, 121.4, 120.4, 115.4, 112.3, 38.2, 16.0, 11.5, 9.7

LC-MS (m/z): 371 ($M+H^{+}$)

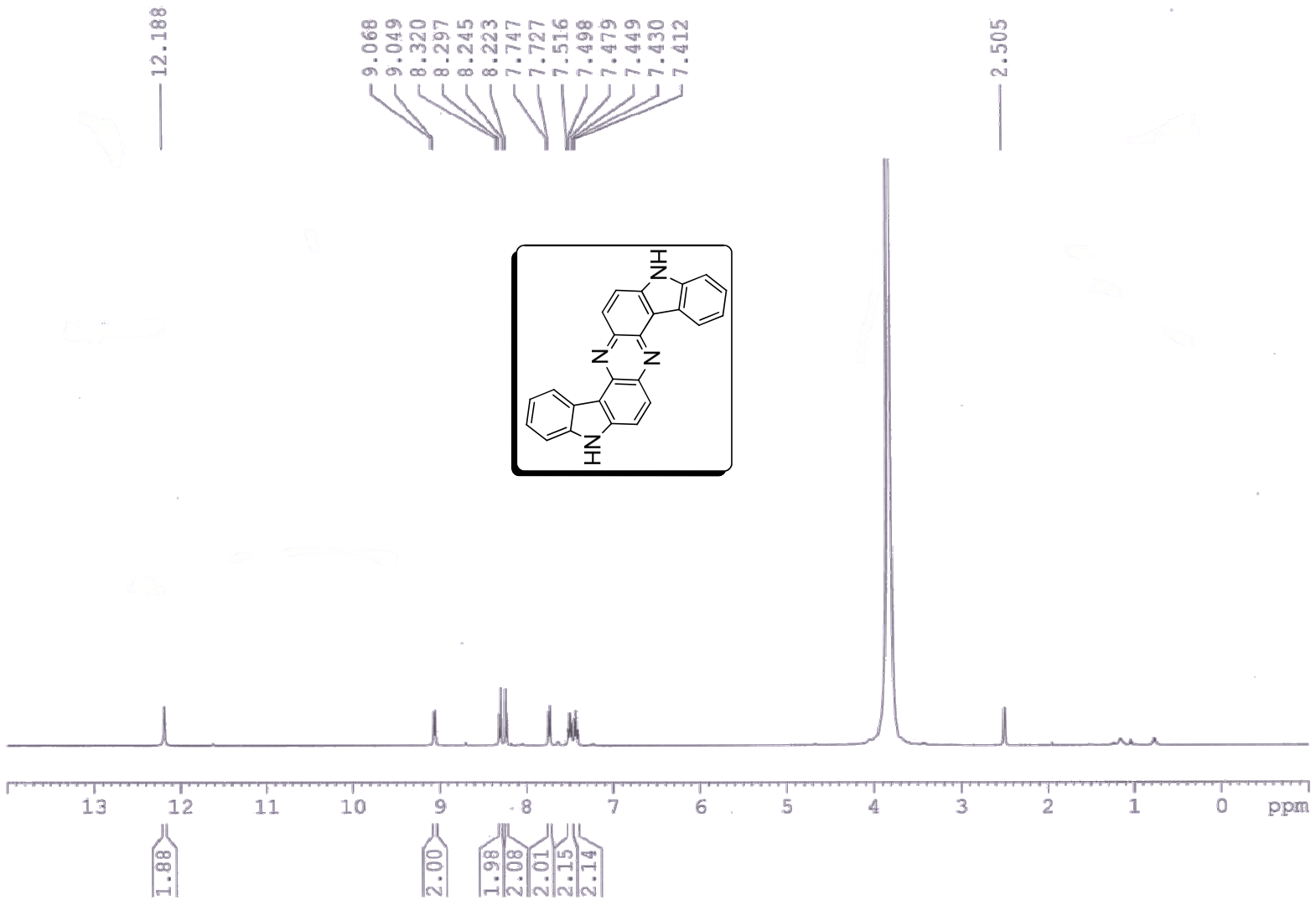
Anal. Calcd. for $C_{24}H_{26}N_4$: C, 77.80; H, 7.07; N, 15.12%

Found: C, 77.91; H, 7.15; N, 15.32%

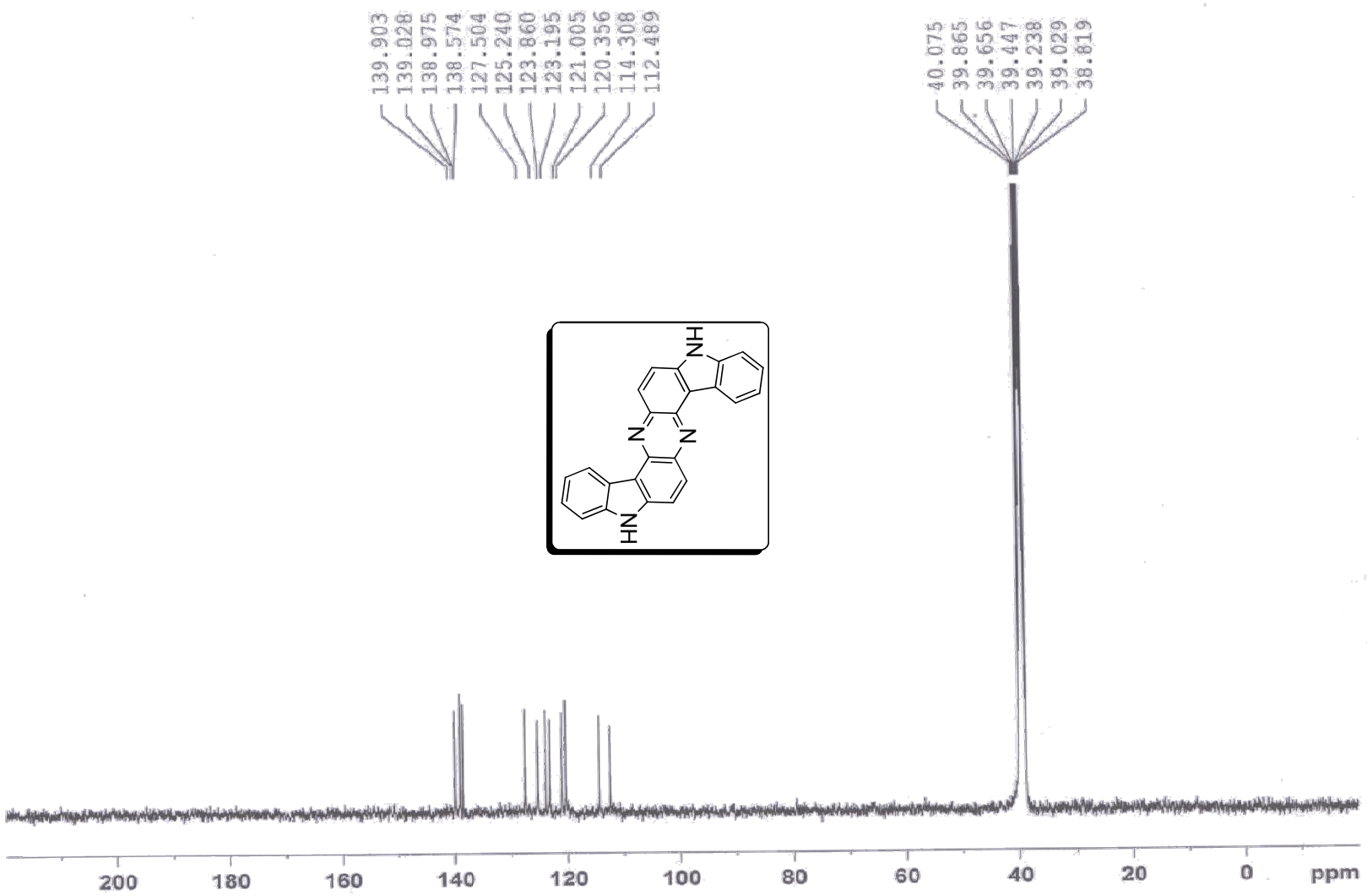
Table 16. Crystal data and structure refinement for 205b

Empirical formula	: $C_{28}H_{22}N_4$
Formula weight	: 414.50
Temperature	: 293(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: C2/c
Unit cell dimensions	: a = 16.704(18) Å, α = 90°
	: b = 7.614(8) Å, β = 108.19(2)°
	: c = 17.163(19) Å, γ = 90°
Volume	: 2074(4) $Å^3$
Z	: 4
Density (calculated)	: 1.328 Mg/m^3
Absorption coefficient	: 0.080 mm^{-1}
F (000)	: 872
Crystal size	: 0.16 x 0.12 x 0.10 mm
Theta range for data collection	: 2.50 to 25.89°
Index ranges	: -20<=h<=20, -9<=k<=9,
	: -20<=l<=20
Reflections collected	: 9474
Completeness to theta = 25.89	: 96.6%
Absorption correction	: Empirical
Max. and min. transmission	: 0.9921 and 0.9873
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 1950 / 0 / 146
Goodness-of-fit on F^2	: 1.047
Final R indices [I>2sigma(I)]	: R1 = 0.0942, wR2 = 0.1736
R indices (all data)	: R1 = 0.1573, wR2 = 0.2034
Largest diff. peak and hole	: 0.217 and -0.235 e. $Å^{-3}$
CCDC number	: 760485

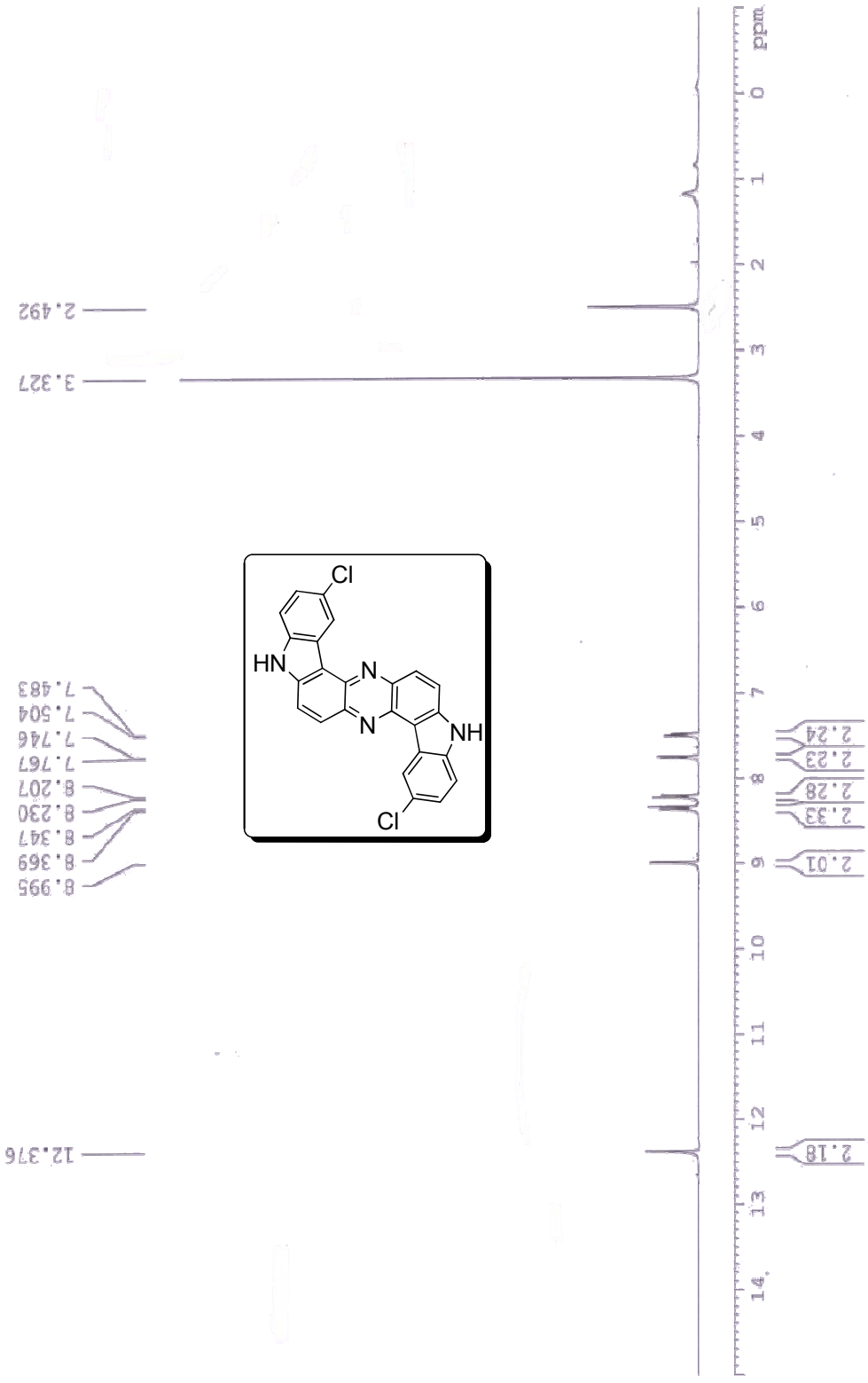
Spectrum 17. ^{1}H NMR of 205a



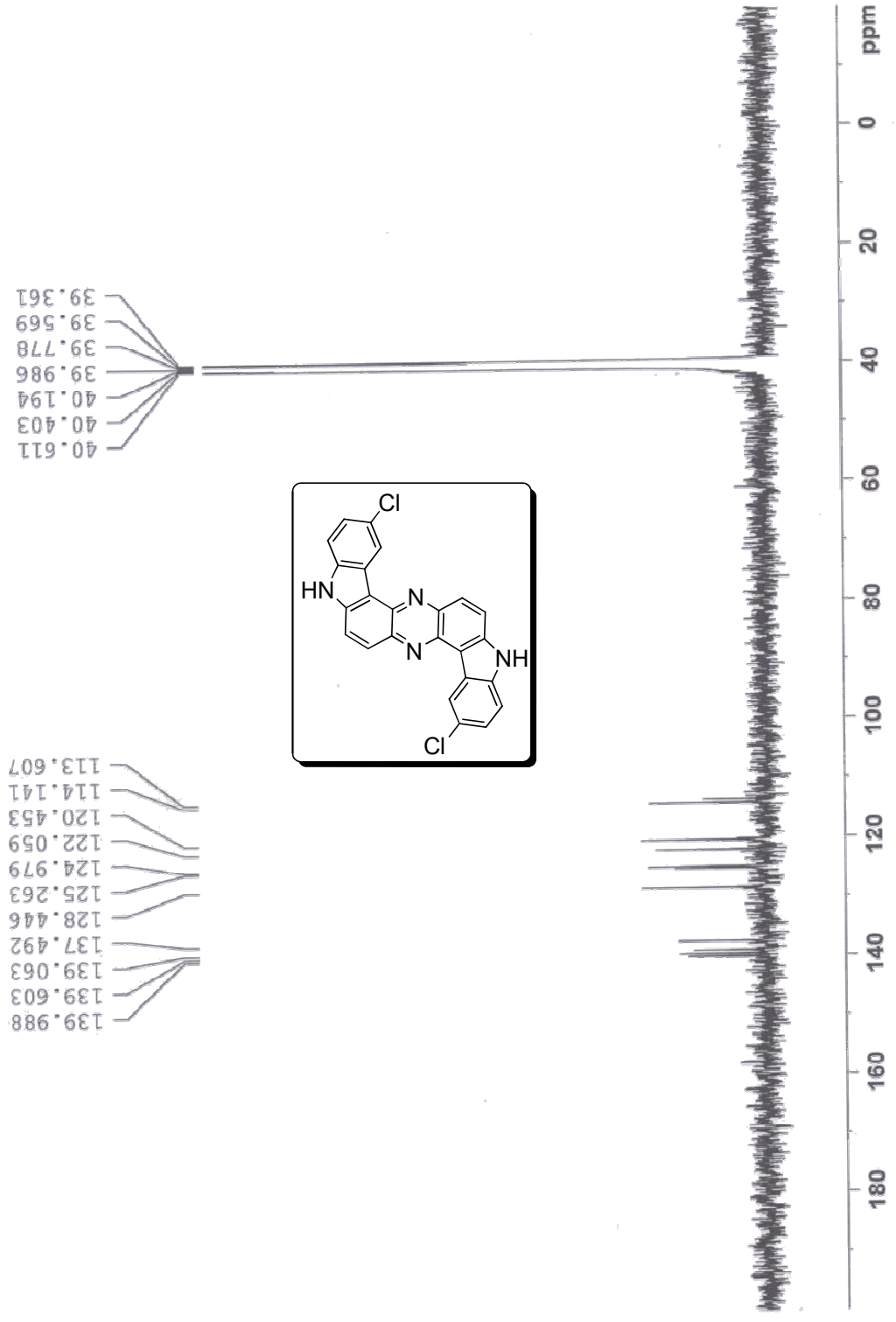
Spectrum 18. ^{13}C NMR of 205a



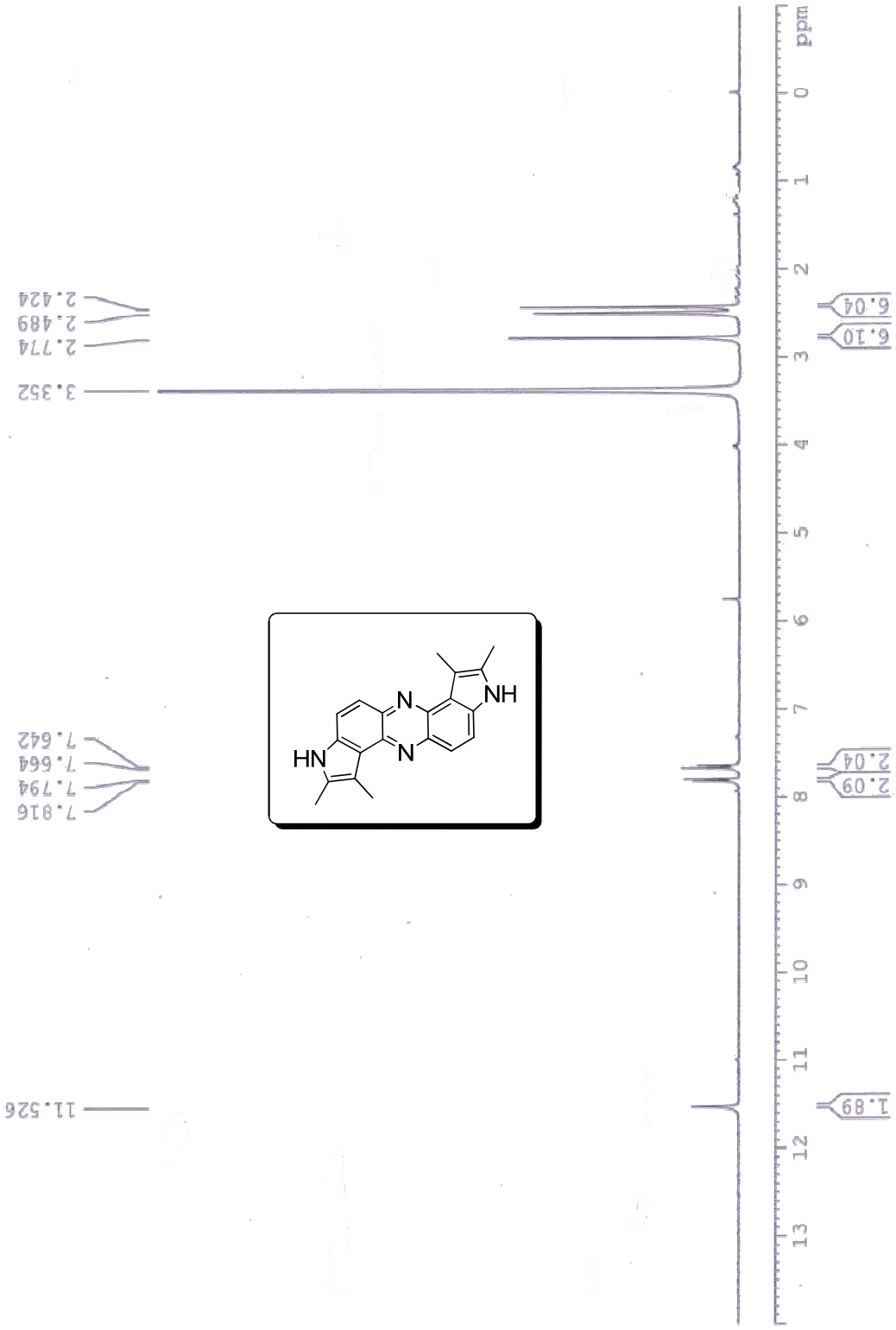
Spectrum 19. ^{1}H NMR of 205c



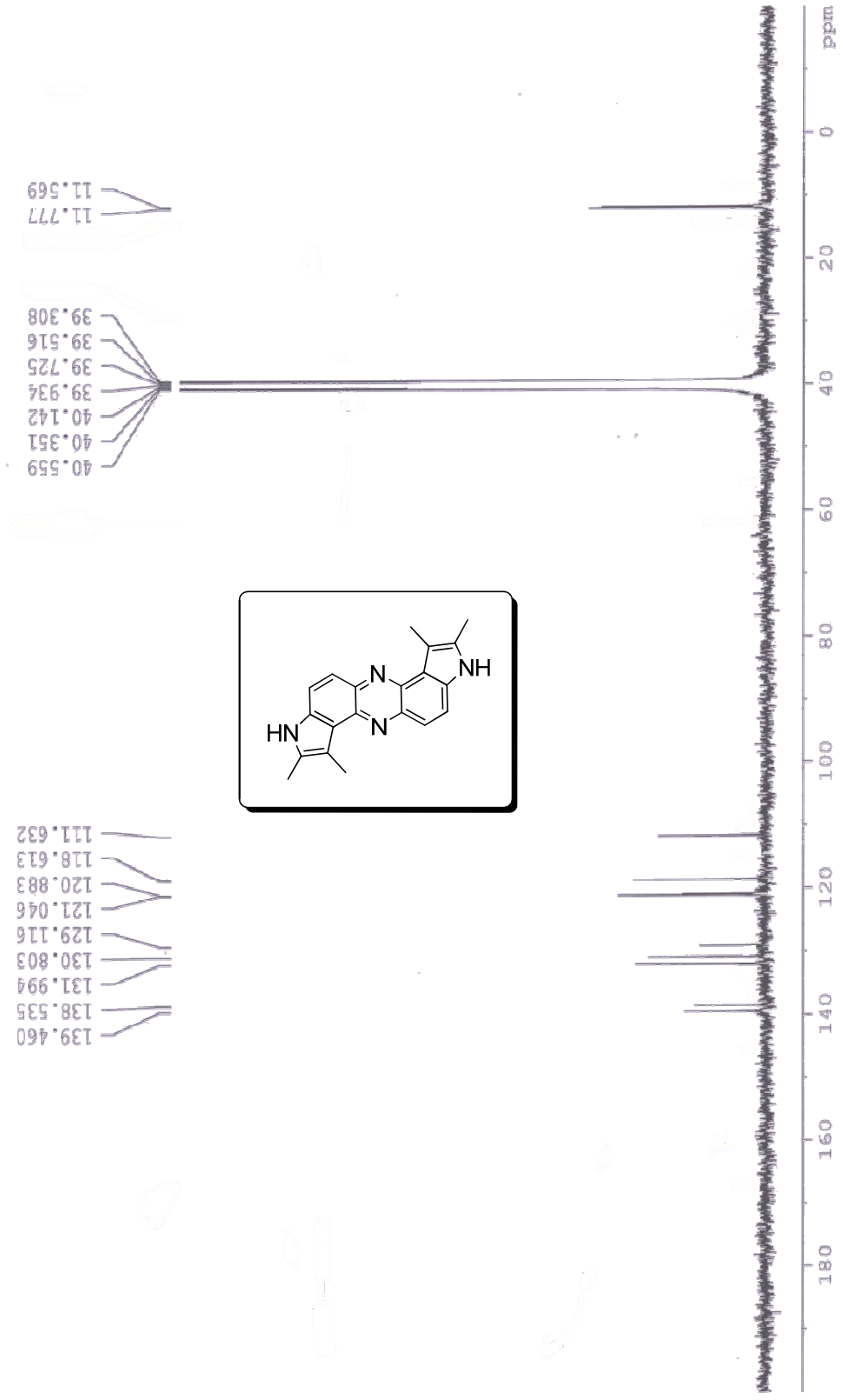
Spectrum 20. ^{13}C NMR of 205c



Spectrum 21. ^{1}H NMR of 207a



Spectrum 22. ^{13}C NMR of 207a



2.6. References

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CHAPTER

3

Synthesis of 3,6-Di(pyrazol-4-yl)carbazoles

3.1. Introduction

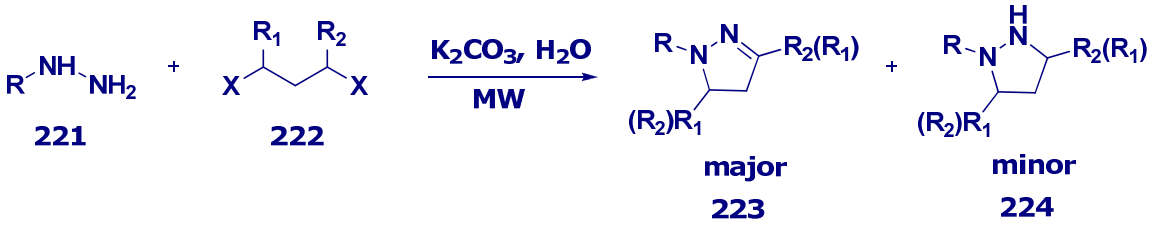
Pyrazole derivatives have become increasingly important in the past few years because they have proven to be extremely useful intermediates for the preparation of new biological materials. Pyrazole nucleus has pronounced pharmacological applications as anti-anxiety,[138,139] antipyretic, analgesic and anti-inflammatory drugs.[140-142] Certain alkyl pyrazoles show significant bacteriostatic, bactericidal and fungicidal activities.[143] The pyrazole ring is present in numerous pharmacologically and agrochemically important compounds, including those used as inhibitors of HIV-1 reverse transcriptase,[144] sodium hydrogen ion exchanger NHE-1,[145] and dipeptidyl peptidase IV (DPP-IV).[146] Several compounds of this type act as antagonists of the $\alpha_v\beta_3$ receptor, which is present on the surface of many tumor cells,[147] whereas others constitute important agrochemicals used, for instance, as insecticides.[148] Of particular importance as a pharmacophore, the *N*-methylpyrazole unit forms part of several drugs such as the antidepressant Zometapine,[149] the inhibitor of type 5 cGMP phosphodiesterase Sildenafil[150] and the antibacterial agent FR21818.[151] Good examples of the usefulness of this same unit in the preparation of insecticides and acaricides include the pesticides Tebufenpyrad,[152] Tolfenpyrad,[153] Cyanopyrafen[154] and Fenpyroximate.[155]

The main methods for the construction of pyrazole ring consist of the reaction between hydrazines and β-difunctional compounds[156] or 1,3-dipolar cycloadditions of diazo compounds onto triple bonds.[157] Perumal *et al*. have synthesized[158] a few 1*H*-pyrazolecarboxylates **220** related microbicides from 2,4-dinitrophenyl hydrazones of *β*-ketoesters **219** upon treatment with Vilsmeier reagent DMF/$POCl_3$ (Eq. 32).

Eq. 32

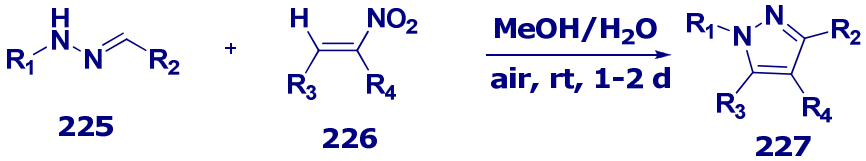
The direct synthesis of 4,5-dihydropyrazole derivatives **223**, **224** via double alkylation of hydrazine derivatives **221** by alkyl dihalides **222** in aqueous media under microwave irradiation were demonstrated[159] by Varma and co-workers as shown in Eq. 33.

Eq. 33



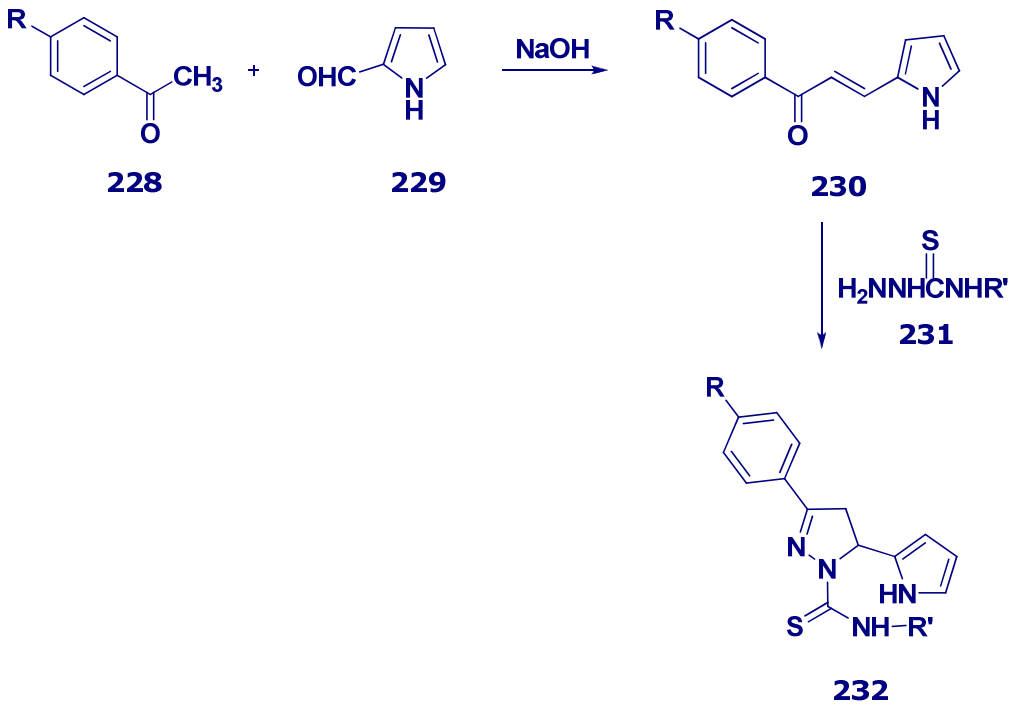
A novel regioselective synthesis of substituted pyrazoles **227** from *N*-monosubstituted hydrazones **225** and nitroolefins **226** is described[160] by Deng and co-workers (Eq. 34).

Eq. 34



As shown in Eq. 35, Gökhan-Kelekçi *et al*. have developed[161] 1-(*N*-substituted thiocarbamoyl)-3-phenyl-5-(pyrrol-2-yl)-4,5-dihydro-(1*H*)-pyrazole **232** by treating 1-phenyl-3-(pyrrol-2-yl)-2-propen-1-one **230** which can be synthesized by the reaction of 4-substituted thiosemicarbazides **231** with the condensation product of pyrrol-2-carboxaldehyde **229** and 4-substituted acetophenone derivatives **228**.

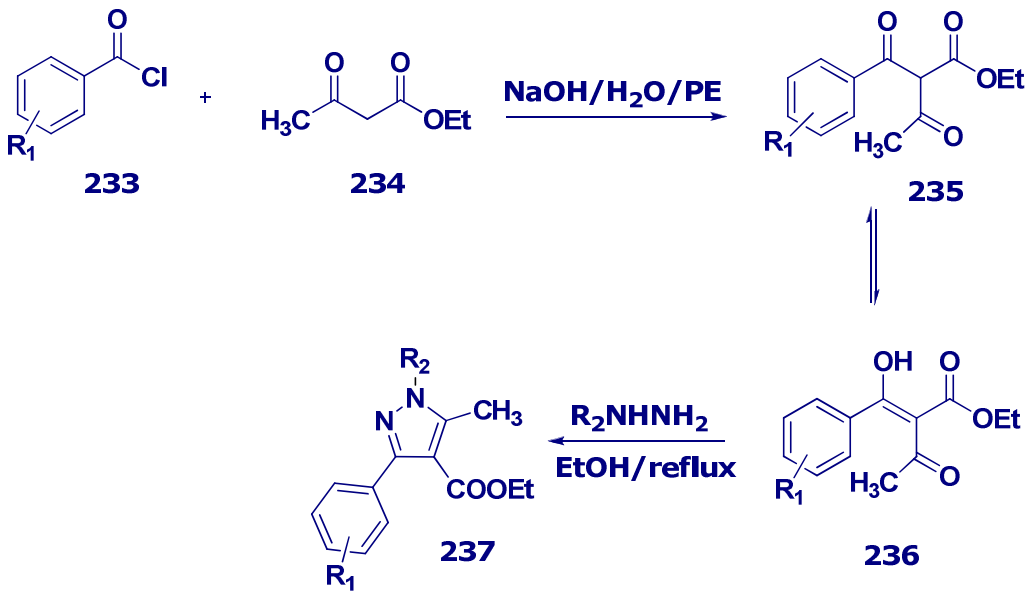
Eq. 35



228 **229** **230** **231** **232**

Zhao *et al*. synthesized[162] multi-substituted pyrazole derivatives **237** as outlined in Eq. 36. The precursors **236** were easily synthesized by the treatment of ethyl acetoacetate **234** with the appropriate aryl acid chlorides **233** in the mixture of aqueous solution of sodium hydroxide and petroleum ether. The desired pyrazole derivatives **237** were obtained by the reaction of **236** with hydrazine hydrate and phenylhydrazine in ethanol at refluxing condition.

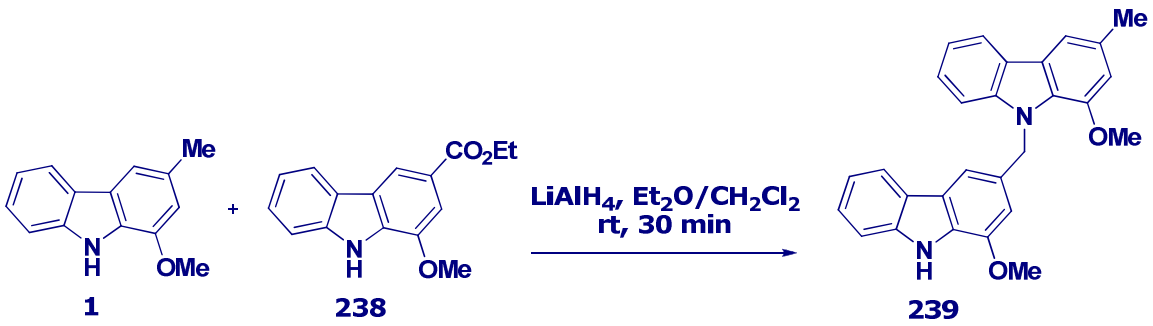
Eq. 36



3.1.1. Heteroarylcarbazoles

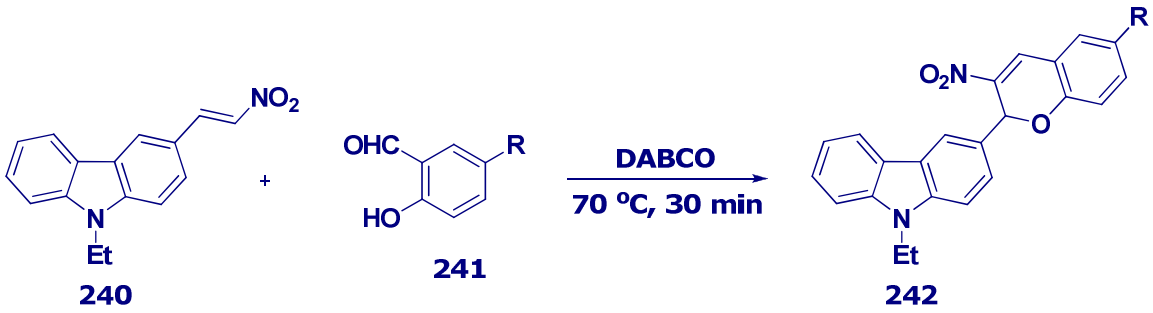
Bringmann *et al*. reported[163] the first synthesis of the methylene-bridged binary carbazole alkaloid bismurrayafoline-A **239** by treating murrayafoline-A **1** and ethyl-1-methoxy-9*H*-carbazol-3-carboxylate **238** (Eq. 37).

Eq. 37



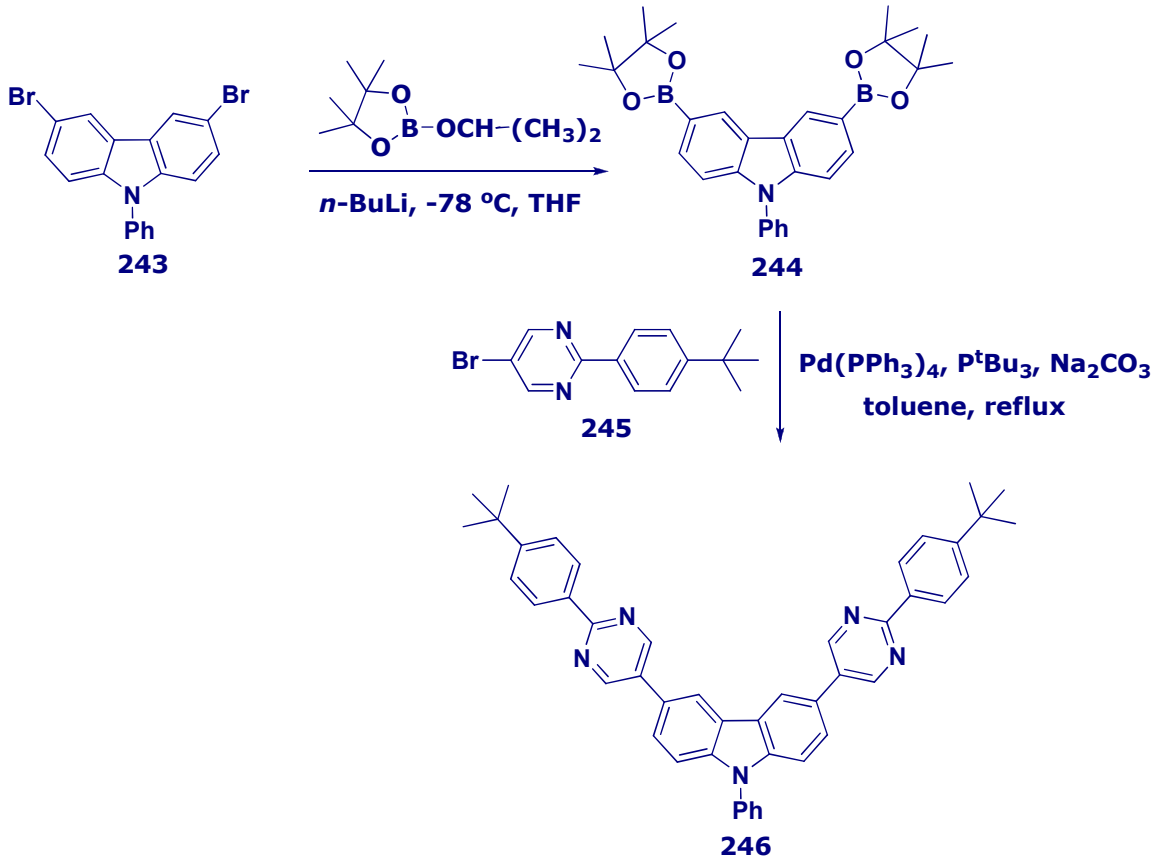
Chromenylcarbazoles **242** have been synthesized in good yields under solvent free conditions from *β*-nitrovinylcarbazole **240** and 2-hydroxybenzaldehydes **241** by Nagarajan *et al*. as shown in Eq. 38.[164]

Eq. 38



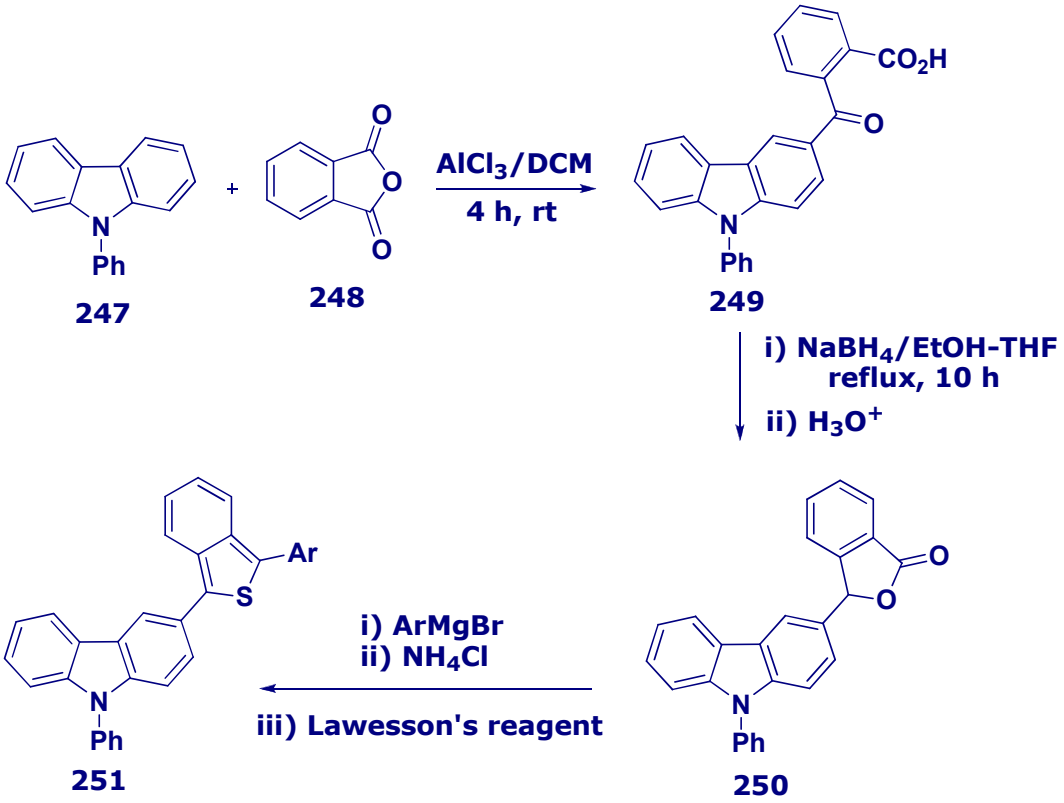
As shown in Eq. 39, Wong *et al*. reported[165] the synthesis of 3,6-bis(2-(4-*tert*-butylphenyl)pyrimidin-5-yl)-9*H*-carbazole **246** by Suzuki coupling of 2-(4-*tert*-butylphenyl)-5-bromopyrimidine **245** and diboronic ester **244** which was prepared from 5,8-dibromo-1-phenylcarbazole **243**.

Eq. 39



Mohanakrishnan *et al*. reported[166] the synthesis of 3-(benzo[*c*]thiophen-1-yl)-9-phenyl-9*H*-carbazoles **251** from 9-phenylcarbazole **247** and phthalic anhydride **248**. Friedel-Crafts phthaloylation of 9-phenylcarbazole **247** afforded keto acid **249**. Selective reduction of the ketone carbonyl function of the keto acid **249** and acid catalyzed cyclization furnished the required lactone **250**. Ring opening of the lactone **250** 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 **251** as shown in Eq. 40.

Eq. 40



3.2. Synthesis of 3,6-di(pyrazol-4-yl)carbazoles

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. The promising biological activities of pyrazole moiety prompted us to introduce pyrazoles in the 3,6-positions of 9-alkylcarbazoles. Biologically active 3-substituted and 3,6-disubstituted carbazoles have been reported in the literature.[167] We herein report a short synthesis of 3,6-di(pyrazol-4-yl)carbazoles from 3,6-diacetylcarbazoles.

The carbazolyl-*β*-chlorovinylaldehydes were readily prepared from 9-alkyl-3,6-diacetylcarbazoles[168] using the Vilsmeier reagent; for example, the reaction of 9-methyl-3,6-diacetylcarbazole **252a** with $DMF/POCl_3$ gave carbazolyl-*β*-chlorovinylaldehyde **253a** in 72% yield. Condensation followed by cyclization with hydrazine hydrate in acetic acid at reflux for 1 h gave dipyrazolylcarbazole **254a** in 76% yield (Scheme 11). The structure of the product **253c** was also confirmed by

the single crystal X-ray analysis and the ORTEP diagram was shown in Figure 24. The reaction also worked well for other 9-alkylcarbazoles as shown in Scheme 11 and Table 17.

Scheme 11. Synthesis of 3,6-di(pyrazol-4-yl)carbazoles

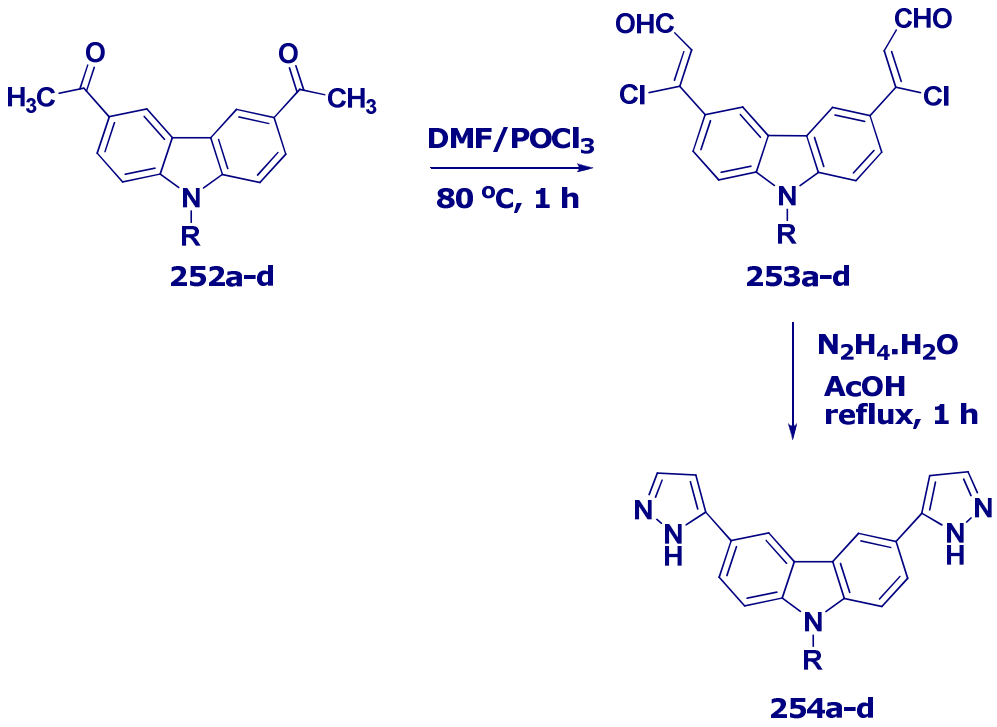
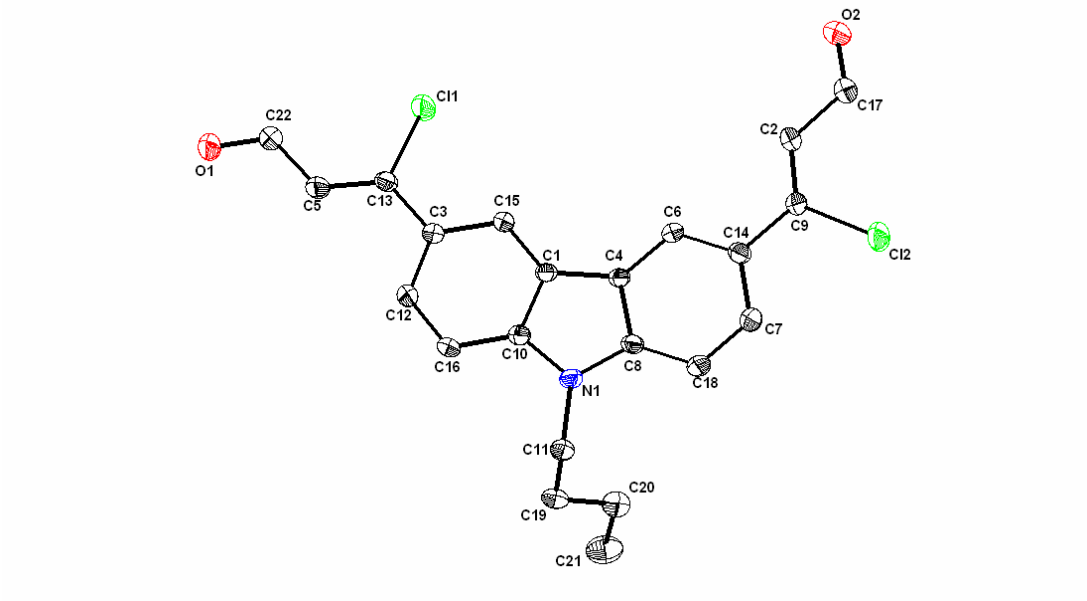


Table 17. Synthesis of 3,6-di(pyrazol-4-yl)carbazoles

Entry	R	Acraldehyde	Yield (%)	product	Yield[a] (%)
1	Me	**253a**	72	**254a**	76
2	Et	**253b**	77	**254b**	79
3	*n*-Bu	**253c**	73	**254c**	82
4	Bn	**253d**	74	**254d**	72

[a] Isolated yield

Figure 24. ORTEP diagram of 253c



3.3. Synthesis of 3,6-di(4-formyl-1-phenyl-1*H*-3-pyrazolyl) carbazoles

The cyclization of iminium species under Vilsmeier conditions is an important synthetic tool in organic chemistry which provides an entry in to a large number of heterocyclic systems. The classical Vilsmeier–Haack reaction involves electrophilic substitution of an activated aromatic ring with a halomethyleneiminium salt to yield the corresponding iminium species.[169] However, the scope of this reagent is not restricted to aromatic formylation and a wide variety of alkene derivatives,[170] activated methyl and methylene groups,[171] oxygen and nitrogen nucleophiles[172] react with the Vilsmeier reagent to yield the corresponding iminium salts. In connection with this, we describe the cyclization of phenylhydrazones of *N*-alkyl-3,6-diacetylcarbazoles under Vilsmeier–Haack reaction conditions. As shown in Scheme 12, the hydrazones were easily prepared from the corresponding diacetylcarbazoles by the reaction with phenylhydrazine in acetic acid at room temperature. Hydrazone **255a** of 9-methyl-3,6-diacetylcarbazole **252a** on reaction with an excess of Vilsmeier reagent resulted in the formation of pyrazole dicarboxaldehyde **256a** in 89% yield (Table 18). The reaction was also carried out with other 9-alkyl substituents and the products were obtained in good yields as shown in Table 18. The structure of the product **256d** was also confirmed by the single crystal X-ray analysis and the ORTEP diagram was shown in Figure 25.

Scheme 12. Synthesis of 3,6-di(4-formyl-1-phenyl-1*H*-3-pyrazolyl) carbazoles

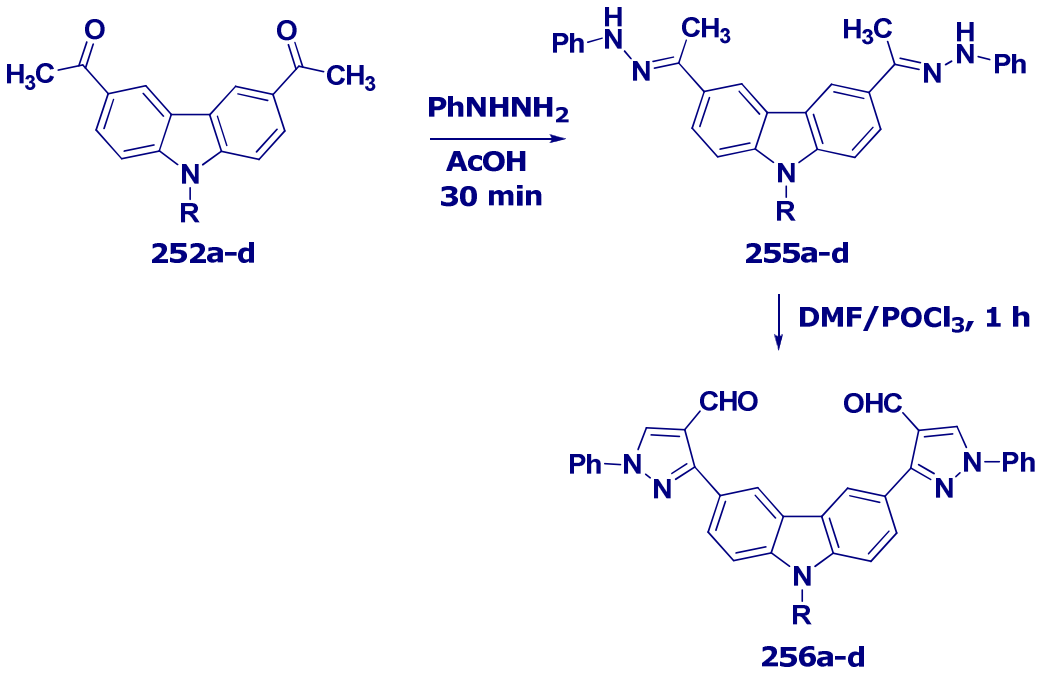
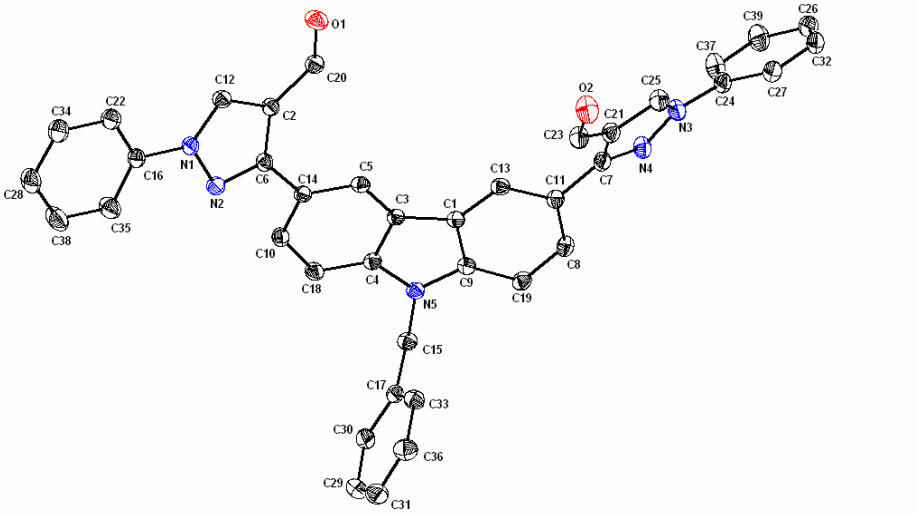


Table 18. Synthesis of 3,6-di(4-formyl-1-phenyl-1*H*-3-pyrazolyl)carbazoles

Entry	R	product	Yield[a] (%)
1	Me	**256a**	89
2	Et	**256b**	88
3	*n*-Bu	**256c**	87
4	Bn	**256d**	85

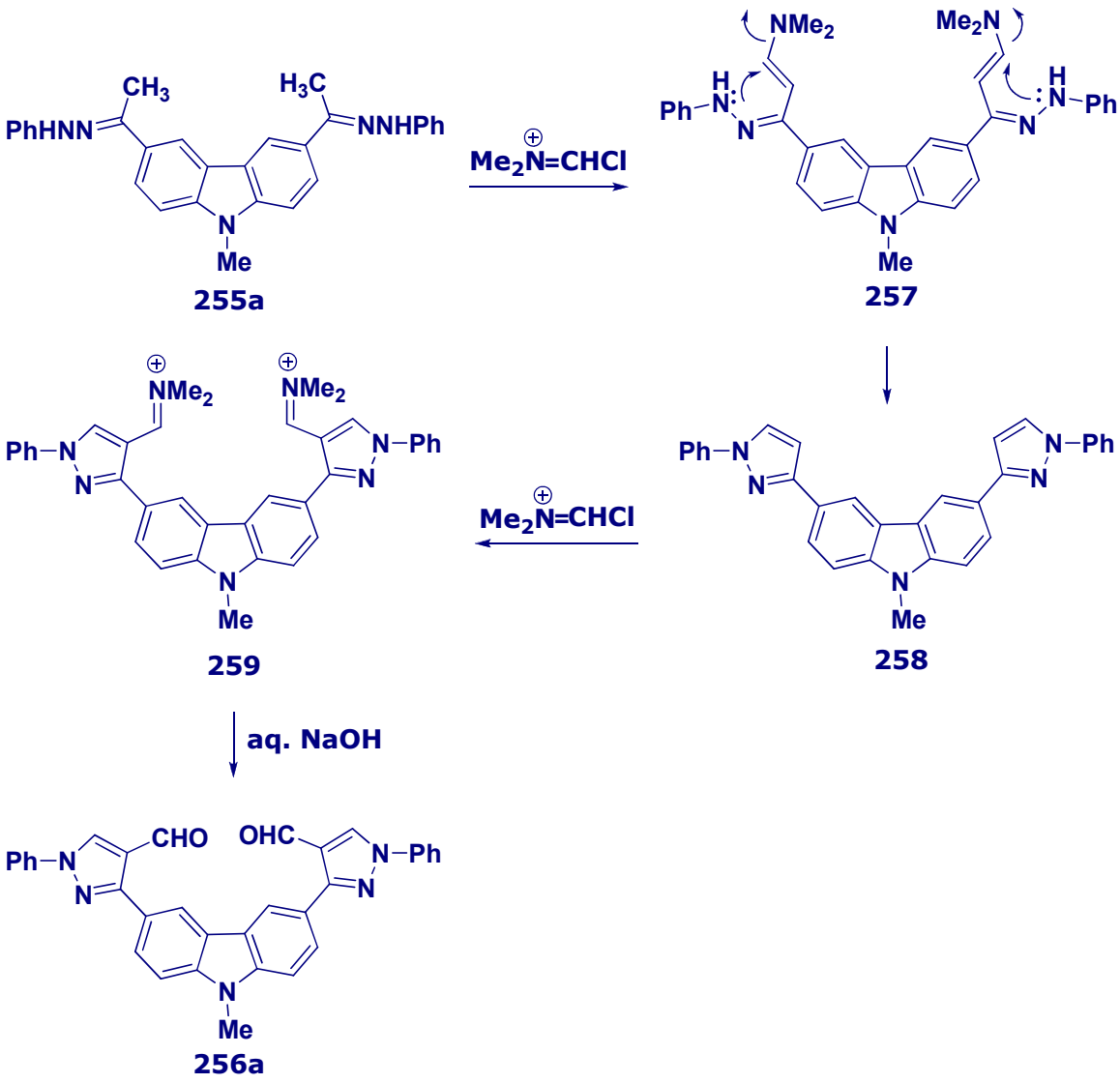
[a] Isolated yield

Figure 25. ORTEP diagram of 256d



A possible mechanism for the formation of the compound **256a** is given in Scheme 13. The methyl group of phenylhydrazone **255a** reacts with the *in situ* generated halomethyleneiminium salt to form the intermediate **257** which loses a molecule of dimethylamine to yield pyrazole **258**. This further reacts with the halomethyleneiminium salt to afford iminium salt **259**, which is hydrolyzed to pyrazole dicarboxyaldehyde **256a**.

Scheme 13. Tentative mechanism for the formation 256a



3.4. Conclusion

In summary, we have prepared an interesting class of heterocyclic compounds namely 3,6-di(pyrazol-4-yl)carbazoles from easily available starting materials via a simple synthetic procedure. The methods are simple and straightforward starting from easily accessible starting materials.

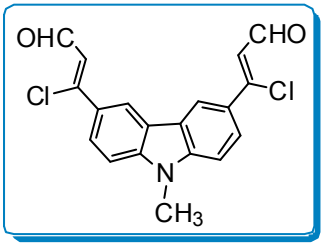
3.5. Experimental Section

General Procedure I

9-Alkyl-3,6-diacetylcarbazoles **252a-d** (2 mmol) were dissolved in DMF (15 mL) at room temperature and then $POCl_3$ (12 mmol) was added dropwise at 0 °C. After the complete addition of $POCl_3$, the reaction mixture was warmed to room temperature and then heated at 80 °C for 1 h. The reaction mixture was poured onto crushed ice and then neutralized with a 10% aqueous NaOH solution. The products were extracted with DCM (3 x 30 mL) and the organic layer was washed with water (5–6 times) to remove excess of DMF, dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude materials were purified by column chromatography using silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products.

3-Chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-methyl-9*H*-carbazol-3-yl]propenal (253a):

The compound **253a** was prepared from 9-methyl-3,6-diacetylcarbazole **252a** (0.53g, 2.0 mmol) by following the *general procedure I.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 72%

Mp: 213 °C

IR (KBr) ν_{max} cm^{-1}: 2962, 1662, 1575, 1457, 1382, 1234, 1158, 843, 792, 689

^{1}H NMR (400 MHz) δ: 10.11 (2H, d, J = 7.2 Hz), 8.50 (2H, s), 7.91 (2H, dd, J_1 = 1.6 Hz, J_2 = 1.7 Hz), 7.37 (2H, d, J = 8.8 Hz), 6.68 (2H, d, J = 6.8 Hz), 3.80 (3H, s)

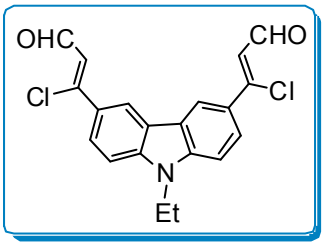
^{13}C NMR (100 MHz) δ: 191.5, 152.9, 142.6, 129.2, 127.3, 125.5, 122.9, 120.6, 109.2, 29.7

LC-MS (m/z): 358 (M), 360 (M+2), 362 (M+4)

Anal. Calcd. for $C_{19}H_{13}Cl_2NO_2$: C, 63.71; H, 3.66; N, 3.91%
Found: C, 63.82; H, 3.59; N, 3.83%

3-Chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-ethyl-9*H*-carbazol-3-yl]propenal (253b):

The compound **253b** was prepared from 9-ethyl-3,6-diacetylcarbazole **252b** (0.56g, 2.0 mmol) by following the *general procedure I.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 77%

Mp: 195 °C

IR (KBr) ν_{max} cm^{-1}: 2862, 1658, 1581, 1487, 1383, 1238, 1163, 841, 796, 694

^{1}H NMR (400 MHz) δ: 10.26 (2H, d, J = 6.8 Hz), 8.61 (2H, s), 7.91 (2H, dd, J_1= 1.6 Hz, J_2 = 1.8 Hz), 7.48 (2H, d, J = 8.8 Hz), 6.80 (2H, d, J = 6.8 Hz), 4.42 (2H, q, J = 7.2 Hz), 1.49 (3H, t, J = 7.2 Hz)

^{13}C NMR (100M Hz) δ: 191.5, 152.9, 142.6, 129.3, 127.4, 125.8, 123.0, 120.6, 109.3, 29.7, 13.9

LC-MS (m/z): 372 (M), 374 (M+2), 376 (M+4)

Anal. Calcd. for $C_{20}H_{15}Cl_2NO_2$: C, 64.53; H, 4.06; N, 3.76%
Found: C, 64.69; H, 3.93; N, 3.94%

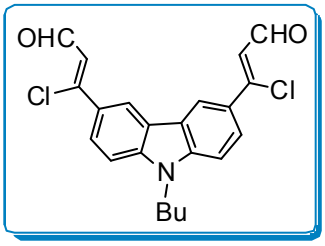
3-Chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-*n*-butyl-9*H*-carbazol-3-yl]propenal (253c):

The compound **253c** was prepared from 9-butyl-3,6-diacetylcarbazole **252c** (0.61g, 2.0 mmol) by following the *general procedure I.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 73%

Mp: 168 °C

IR (KBr) ν_{max} cm^{-1}: 2959, 1660, 1586, 1482, 1389, 1241, 1167, 845, 791, 696



^{1}H NMR (400 MHz) δ: 10.26 (2H, d, J = 6.8 Hz), 8.6 (2H, s), 7.91 (2H, dd, J_1 = 1.8 Hz, J_2 = 1.6 Hz), 7.47 (2H, d, J = 8.8 Hz), 6.79 (2H, d, J = 6.8 Hz), 4.35 (2H, t, J = 7.2 Hz), 1.92-1.85 (2H, m), 1.45-1.36 (2H, m), 0.96 (3H, t, J = 5.7 Hz)

^{13}C NMR (100 MHz) δ: 191.5, 152.9, 143.0, 129.3, 127.3, 125.7, 123.1, 120.7, 109.6, 43.5, 31.0, 20.5, 13.8

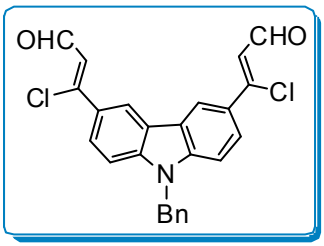
LC-MS (m/z): 400 (M), 402 (M+2), 404 (M+4)

Anal. Calcd. for $C_{22}H_{19}Cl_2NO_2$: C, 66.01; H, 4.78; N, 3.50%

Found: C, 65.85; H, 4.69; N, 3.63%

3-Chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-benzyl-9*H*-carbazol-3-yl]propenal (253d):

The compound **253d** was prepared from 9-benzyl-3,6-diacetylcarbazole **252d** (0.68g, 2.0 mmol) by following the *general procedure I.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 74%

Mp: 78-79 °C

IR (KBr) ν_{max} cm^{-1}: 1663, 1543, 1483, 1383, 1134, 897, 800, 698, 611

^{1}H NMR (400 MHz) δ: 10.26 (2H, d, *J* = 6.8 Hz), 8.6 (2H, s), 7.88 (2H, d, *J* = 8.7 Hz), 7.45 (2H, d, *J* = 8.7 Hz), 7.29–7.31 (3H, m), 7.12 (2H, d, *J* = 7.1 Hz), 6.79 (2H, d, *J* = 6.8 Hz), 5.57 (2H, s)

^{13}C NMR (100 MHz) δ: 191.4, 152.8, 142.7, 135.5, 129.4, 129.1, 128.2, 126.3, 126.0, 123.2, 122.8, 120.6, 109.30, 47.2

LC-MS (m/z): 434 (M), 436 (M+2), 438 (M+4)

Anal. Calcd. for $C_{25}H_{17}Cl_2NO_2$: C, 69.14; H, 3.95; N, 3.23%
Found: C, 68.97; H, 4.12; N, 3.31%

General procedure J

The chlorovinyl aldehydes **253a-d** (1.0 mmol) were dissolved in AcOH (20 mL) under reflux. The reaction mixture was cooled to room temperature and hydrazine hydrate (7.5 mmol) was added slowly after which the reaction mixture was refluxed for 1 h. The reaction mixture was poured onto water and then neutralized with 10% aq $NaHCO_3$ solution. The compounds were extracted with dichloromethane (3 x 30 mL), the organic layer was dried over anhyd. Na_2SO_4 and the solvent was removed under reduced pressure. The crude products were purified by column chromatography by using silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products.

9-Methyl-3,6-di(1*H*-5-pyrazolyl)-9*H*-carbazole (254a):

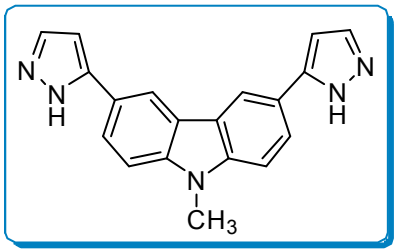
The title compound **254a** was prepared from 3-chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-methyl-9*H*-carbazol-3-yl]propenal **253a** (0.36g, 1.0 mmol) by following the *general procedure J.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 76%

Mp: 152 °C

IR (KBr) ν_{max} cm^{-1}: 3180, 2962, 1713, 1603, 1444, 1338, 1261, 868, 798, 659

^{1}H NMR (400 MHz) δ: 12.93 (2H, bs), 8.64 (2H, s, *J* = 7.6 Hz), 7.95 (2H, d, *J* = 8.4 Hz), 7.72 (2H, s), 7.63 (2H, d, *J* = 8.6 Hz), 6.78 (2H, d, *J* = 1.8 Hz), 3.91 (3H, s)



^{13}C NMR (100 MHz) δ: 148.5, 140.9, 133.7, 124.1, 123.7, 122.9, 117.4, 109.1, 101.5, 29.4

LC-MS (m/z): 312 (M-H^{+})

Anal. Calcd. for $C_{19}H_{15}N_5$: C, 72.83; H, 4.82; N, 22.35%

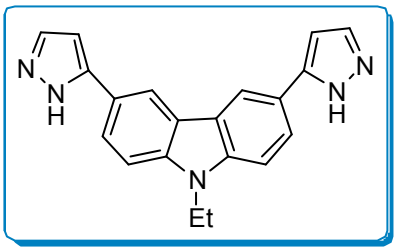
Found: C, 72.94; H, 4.74; N, 22.25%

9-Ethyl-3,6-di(1*H*-5-pyrazolyl)-9*H*-carbazole (254b):

The title compound **254b** was prepared from 3-chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-ethyl-9*H*-carbazol-3-yl]propenal **253b** (0.37g, 1.0 mmol) by following the *general procedure J.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 79%

Mp: 113 °C



IR (KBr) ν_{max} cm^{-1}: 3169, 2964, 1865, 1705, 1655, 1589, 1444, 1261, 1097, 931, 877, 659

^{1}H NMR (400 MHz) δ: 12.92 (2H, bs), 8.64 (2H, s), 7.94 (2H, d, *J* = 8.0 Hz), 7.73 (2H, s), 7.64 (2H, d, *J* = 8.0 Hz), 6.78 (2H, s), 4.45 (2H, q, *J* = 4.0 Hz), 1.34 (3H, t, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 148.3, 139.5, 133.5, 123.7, 123.3, 122.7, 117.2, 108.6, 101.2, 37.3, 13.6

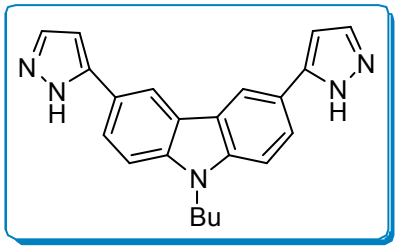
LC-MS (m/z): 326 ($M-H^+$)

Anal. Calcd. for $C_{20}H_{17}N_5$: C, 73.37; H, 5.23; N, 21.39%

Found: C, 73.29; H, 5.17; N, 21.28%

9-*n*-Butyl-3,6-di(1*H*-5-pyrazolyl)-9*H*-carbazole (254c):

The title compound **254c** was prepared from 3-chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-*n*-butyl-9*H*-carbazol-3-yl]propenal **253c** (0.40g, 1.0 mmol) by following the *general procedure J.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 82%

Mp: 105 °C

IR (KBr) ν_{max} cm^{-1}: 3167, 2959, 1718, 1606, 1439, 1261, 1087, 931, 879, 802, 659

^{1}H NMR: (400 MHz) δ: 12.92 (2H, bs), 8.63 (2H, s), 7.93 (2H, d, *J* = 8.3 Hz), 7.71 (2H, s), 7.63 (2H, d, *J* = 8.6 Hz), 6.77 (2H, s), 4.41 (2H, t, *J* = 6.8 Hz), 1.82–1.74 (2H, m), 1.36–1.27 (2H, m), 0.89 (3H, t, *J* = 7.2 Hz)

^{13}C NMR (100 MHz) δ: 149.0, 140.3, 134.8, 124.1, 122.8, 122.6, 118.2, 108.3, 102.1, 42.8, 31.2, 20.5, 13.8

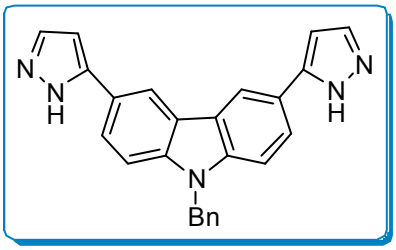
LC-MS (m/z): 356 ($M+H^+$)

Anal. Calcd. for $C_{22}H_{21}N_5$: C, 74.34; H, 5.96; N, 19.70%

Found: C, 74.41; H, 6.11; N, 19.82%

9-Benzyl-3,6-di(1*H*-5-pyrazolyl)-9*H*-carbazole (254d):

The title compound **254d** was prepared from 3-chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-benzyl-9*H*-carbazol-3-yl]propenal **253d** (0.43g, 1.0 mmol) by following the *general procedure J.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 72%

Mp: 65-67 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 2966, 1649, 1595, 1385, 1261, 1093, 1022, 800

^{1}H NMR (400 MHz) δ: 11.82 (2H, bs), 8.65 (2H, s), 7.91 (2H, d, *J* = 7.6 Hz), 7.71 (2H, s), 7.66 (2H, d, *J* = 8.4 Hz), 7.28–7.20 (5H, m), 6.77 (2H, s), 5.68 (2H, s)

^{13}C NMR (100 MHz) δ: 148.6, 140.6, 134.6, 129.6, 128.9, 127.5, 123.4, 123.3, 122.9, 119.7, 118.0, 109.4, 102.2, 53.5

LC-MS (m/z): 390 ($M+H^+$)

Anal. Calcd. for $C_{25}H_{19}N_5$: C, 77.10; H, 4.92; N, 17.98%

Found: C, 76.93; H, 4.83; N, 18.09%

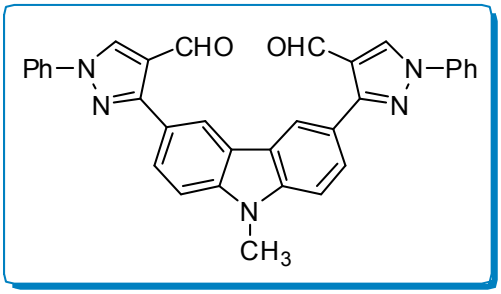
General procedure K

The phenylhydrazones **255a-d** (1.0 mmol) were dissolved in DMF (15 mL) and then $POCl_3$ (6.0 mmol) was added slowly dropwise at 0 °C. After a complete addition of $POCl_3$, the reaction mixture was heated at 90 °C for 1 h. After completition of the reaction, the reaction mixture was poured onto crushed ice and then neutralized with 10% aq. NaOH solution. The products were extracted with DCM (3 x 30 mL) and the organic layer was washed with water (5–6 times) to remove excess of DMF. The DCM

layer was dried over anhyd. Na_2SO_4 and evaporated. The crude products were purified by column chromatography by using silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products.

3-[6-(4-Formyl-1-phenyl-1*H*-3-pyrazolyl)-9-methyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarbaldehyde (256a):

The title compound **256a** was prepared from 9-methyl-3,6-bis((*E*)-1-(2-phenylhydrazono)ethyl)-9*H*-carbazole **255a** (0.44g, 1.0 mmol) by following the *general procedure K.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 89%

Mp: 132-133 °C

IR (KBr) ν_{max} cm^{-1}: 3113, 3052, 2976, 1733, 1674, 1537, 1384, 1130, 1025, 809

^{1}H NMR (400 MHz) δ: 10.18 (2H, s), 8.66 (2H, d, *J* = 1.2 Hz), 8.60 (2H, s), 8.03 (1H, d, *J* = 1.6 Hz), 8.01 (1H, d, *J* = 1.60 Hz), 7.89 (2H, s), 7.87 (2H, s), 7.58–7.53 (6H, m), 7.44 (2H, t, *J* = 7.4 Hz), 3.98 (3H, s)

^{13}C NMR (100 MHz) δ: 185.5, 155.0, 141.9, 139.1, 131.2, 129.6, 127.7, 127.2, 123.1, 122.6, 122.4, 121.2, 119.6, 108.8, 29.3

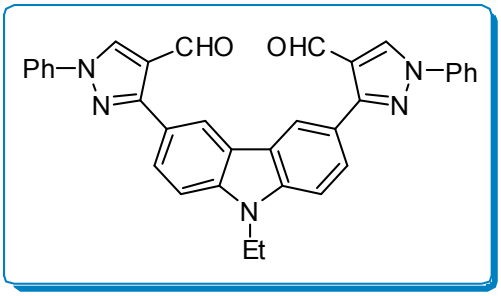
LC-MS (m/z): 522 ($M+H^+$)

Anal. Calcd. for $C_{33}H_{23}N_5O_2$: C, 75.99; H, 4.44; N, 13.43%

Found: C, 76.10; H, 4.36; N, 13.49%

3-[6-(4-Formyl-1-phenyl-1*H*-3-pyrazolyl)-9-ethyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarbaldehyde (256b):

The title compound **256b** was prepared from 9-ethyl-3,6-bis((*E*)-1-(2-phenylhydrazono)ethyl)-9*H*-carbazole **255b** (0.46g, 1.0 mmol) by following the *general procedure K.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 88%

Mp: 65-66 ºC

IR (KBr) ν_{max} cm^{-1}: 3113, 3057, 2974, 1732, 1672, 1525, 1396, 1128, 1028, 810

^{1}H NMR (400 MHz) δ: 10.19 (2H, s), 8.67 (2H, d, *J* = 1.2 Hz), 8.60 (2H, s), 8.03 (1H, d, *J* = 1.6 Hz), 8.01 (1H, d, *J* = 1.60 Hz), 7.89 (2H, s), 7.87 (2H, s), 7.59–7.53 (6H, m), 7.42 (2H, t, *J* = 8.0 Hz), 4.48 (2H, q, *J* = 4.0 Hz), 1.53 (3H, t, *J* = 8.0 Hz)

^{13}C NMR (100 MHz) δ: 185.5, 155.4, 140.9, 139.1, 131.3, 129.6, 127.7, 127.2, 123.3, 122.6, 122.5, 121.4, 119.6, 108.9, 37.9, 13.9

LC-MS (m/z): 536 ($M+H^+$)

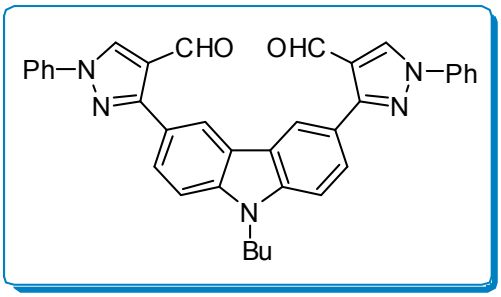
Anal. Calcd. for $C_{34}H_{25}N_5O_2$: C, 76.24; H, 4.70; N, 13.08%

Found: C, 76.07; H, 4.59; N, 13.20%

3-[6-(4-Formyl-1-phenyl-1*H*-3-pyrazolyl)-9-*n*-butyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarbaldehyde (256c):

The title compound **256c** was prepared from 9-butyl-3,6-bis((*E*)-1-(2-phenylhydrazono)ethyl)-9*H*-carbazole **255c** (0.49g, 1.0 mmol) by following the

general procedure K. The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.



Yield: 87%

Mp: 82 ºC

IR (KBr) ν_{max} cm^{-1}: 3113, 3057, 2955, 2862, 1672, 1597, 1442, 1286, 1153, 887

^{1}H NMR (400 MHz) δ: 10.19 (2H, s), 8.66 (2H, d, *J* = 1.0 Hz), 8.61 (2H, s), 8.01 (1H, d, *J* = 1.5 Hz), 7.99 (1H, d, *J* = 1.48 Hz), 7.89 (2H, s), 7.87 (2H, s), 7.59–7.53 (6H, m), 7.42 (2H, t, *J* = 7.4 Hz), 4.43 (2H, t, *J* = 7.0 Hz), 1.98–1.92 (2H, m), 1.49–1.43 (2H, m), 1.00 (3H, t, *J* = 7.28 Hz)

^{13}C NMR (100 MHz) δ: 185.5, 155.4, 141.4, 139.0, 131.2, 129.6, 127.7, 127.1, 123.2, 122.5, 122.4, 121.3, 119.6, 109.1, 43.1, 31.1, 20.5, 13.9

LC-MS (m/z): 564 ($M+H^+$)

Anal. Calcd. for $C_{36}H_{29}N_5O_2$: C, 76.71; H, 5.19; N, 12.43%
Found: C, 76.84; H, 5.08; N, 12.31%

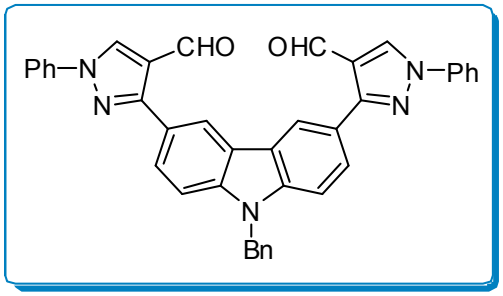
3-[6-(4-Formyl-1-phenyl-1*H*-3-pyrazolyl)-9-benzyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarbaldehyde (256d):

The title compound **256d** was prepared from 9-benzyl-3,6-bis((*E*)-1-(2-phenylhydrazono)ethyl)-9*H*-carbazole **255d** (0.52g, 1.0 mmol) by following the *general procedure K.* The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexanes.

Yield: 85%

Mp: 187 ºC

IR (KBr) ν_{max} cm^{-1}: 2963, 1663, 1599, 1451, 1396, 1211, 1096, 1022, 905

^{1}H NMR (400 MHz) δ: 

10.18 (2H, s), 8.70 (2H, s), 8.60 (2H, s), 7.97 (2H, d, *J* = 8.0 Hz), 7.88 (2H, s), 7.86 (2H, s), 7.56–7.52 (6H, m), 7.41 (2H, t, *J* = 8.0 Hz), 7.33–7.20 (3H, m), 7.19 (2H, d, *J* = 4.0 Hz), 5.62 (2H, s)

^{13}C NMR (100 MHz) δ: 190.0, 159.8, 146.2, 143.7, 141.3, 136.5, 134.4, 133.6, 132.5, 132.4, 132.1, 128.0, 127.7, 127.1, 126.0, 124.3, 114.2, 51.2

LC-MS (m/z): 598 ($M+H^+$)

Anal. Calcd. for $C_{39}H_{27}N_5O_2$: C, 78.37; H, 4.55; N, 11.72%

Found: C, 78.49; H, 4.61; N, 11.68%

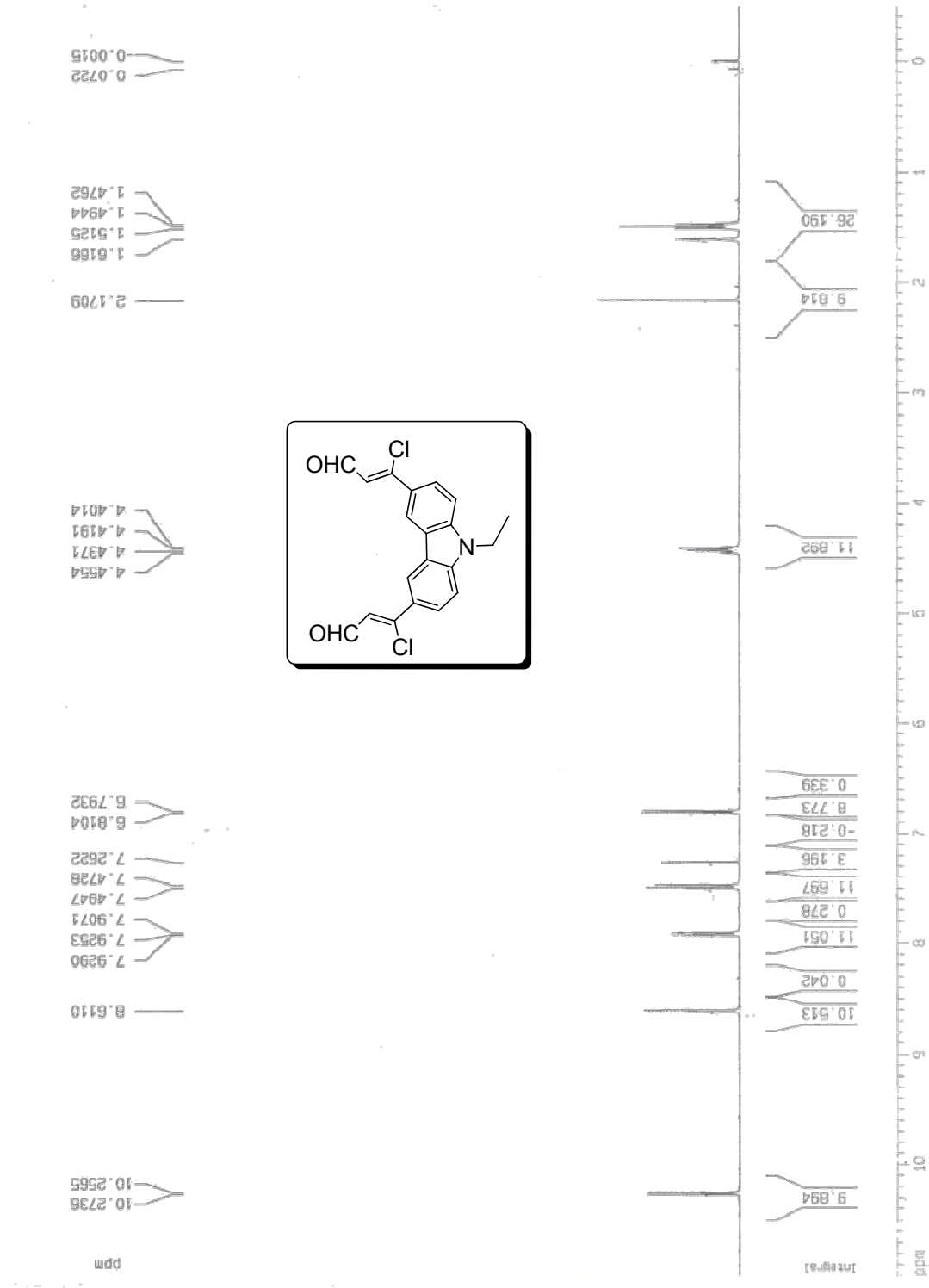
Table 19. Crystal data and structure refinement for 253c

Empirical formula	: $C_{22}H_{19}Cl_2NO_2$
Formula weight	: 400.28
Temperature	: 273(2) K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P-1
Unit cell dimensions	: a = 5.520(3) Å, α = 88.390(6)°
	: b = 12.497(6) Å, β = 78.77°
	: c = 14.171(6) Å, γ = 81.705(9)°
Volume	: 948.7(8) $Å^3$
Z	: 2
Density (calculated)	: 1.401 Mg/m^3
Absorption coefficient	: 0.360 mm^{-1}
F (000)	: 416
Crystal size	: 0.42 x 0.36 x 0.28 mm
Theta range for data collection	: 1.47 to 25.00°
Index ranges	: -6<=h<=6, -14<=k<=14,
	-16<=l<=16
Reflections collected	: 9055
Completeness to theta = 25.00	: 99.3%
Absorption correction	: Empirical
Max. and min. transmission	: 0.904 and 0.860
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 3334 / 0 / 245
Goodness-of-fit on F^2	: 0.960
Final R indices [I>2sigma(I)]	: R1 = 0.0648, wR2 = 0.1344
R indices (all data)	: R1 = 0.1465, wR2 = 0.1596
Largest diff. peak and hole	: 0.366 and -0.254 $e.Å^{-3}$
CCDC number	: 612979

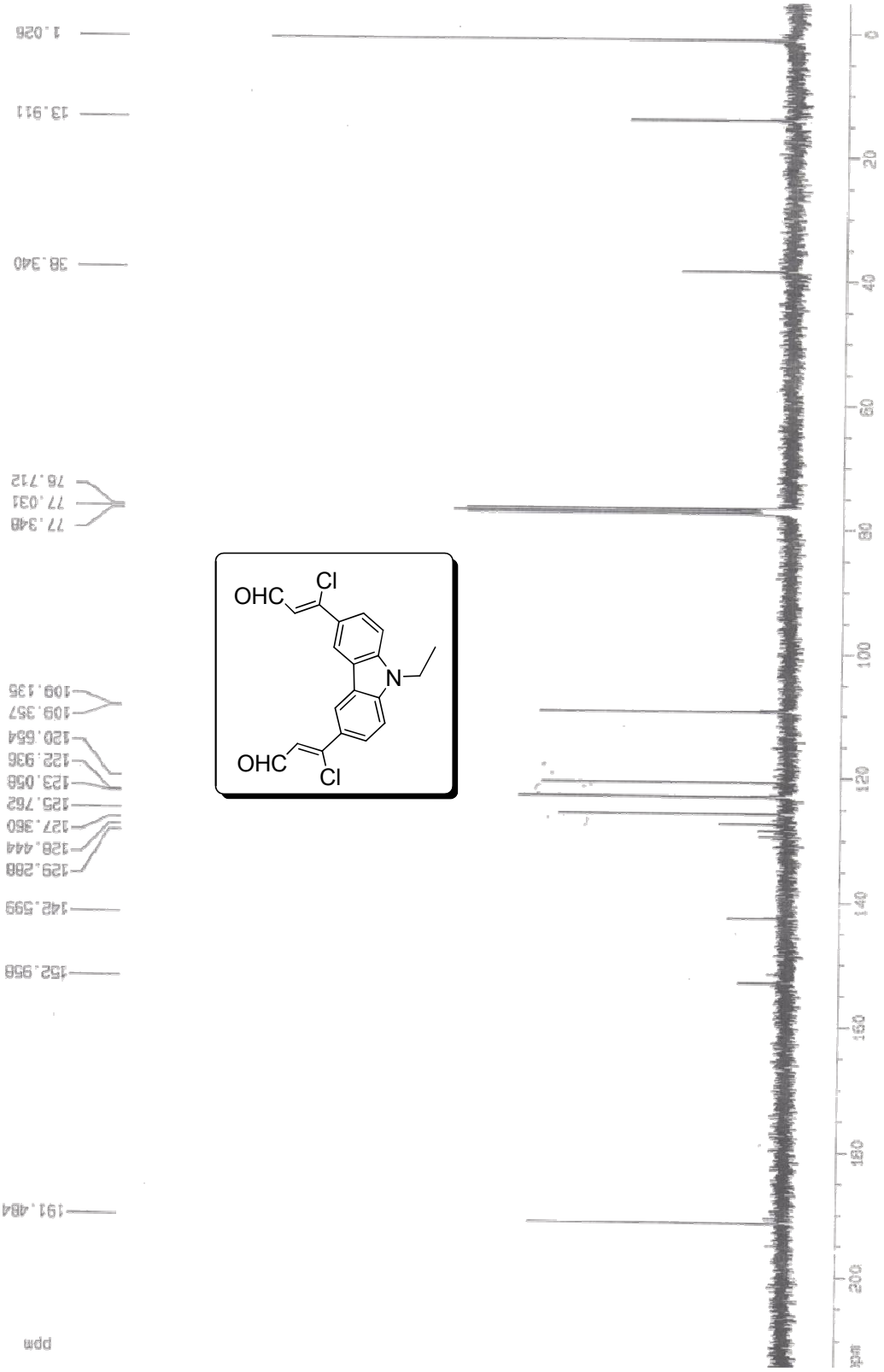
Table 20. Crystal data and structure refinement for 256d

Empirical formula	: $C_{39}H_{27}N_5O_2$
Formula weight	: 597.66
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Triclinic
Space group	: P-1
Unit cell dimensions	: a = 10.5420(11) Å,
	α = 80.861(2)°
	: b = 11.7232(13) Å,
	β = 75.235(2)°
	: c = 12.8321(14) Å,
	γ = 77.600(2)°
Volume	: 1488.6(3) $Å^3$
Z	: 2
Density (calculated)	: 1.333 Mg/m^3
Absorption coefficient	: 0.084 mm^{-1}
F (000)	: 624
Crystal size	: 0.28 x 0.06 x 0.05 mm
Theta range for data collection	: 1.65 to 25.93°
Index ranges	: -12<=h<=12, -14<=k<=14,
	-15<=l<=15
Reflections collected	: 15512
Completeness to theta = 25.93	: 99.3%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9958 and 0.9767
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 5774 / 0 / 415
Goodness-of-fit on F^2	: 1.011
Final R indices [I>2sigma(I)]	: R1 = 0.0486, wR2 = 0.1093
R indices (all data)	: R1 = 0.0863, wR2 = 0.1244
Largest diff. peak and hole	: 0.168 and -0.156 e.$Å^{-3}$
CCDC number	: 612978

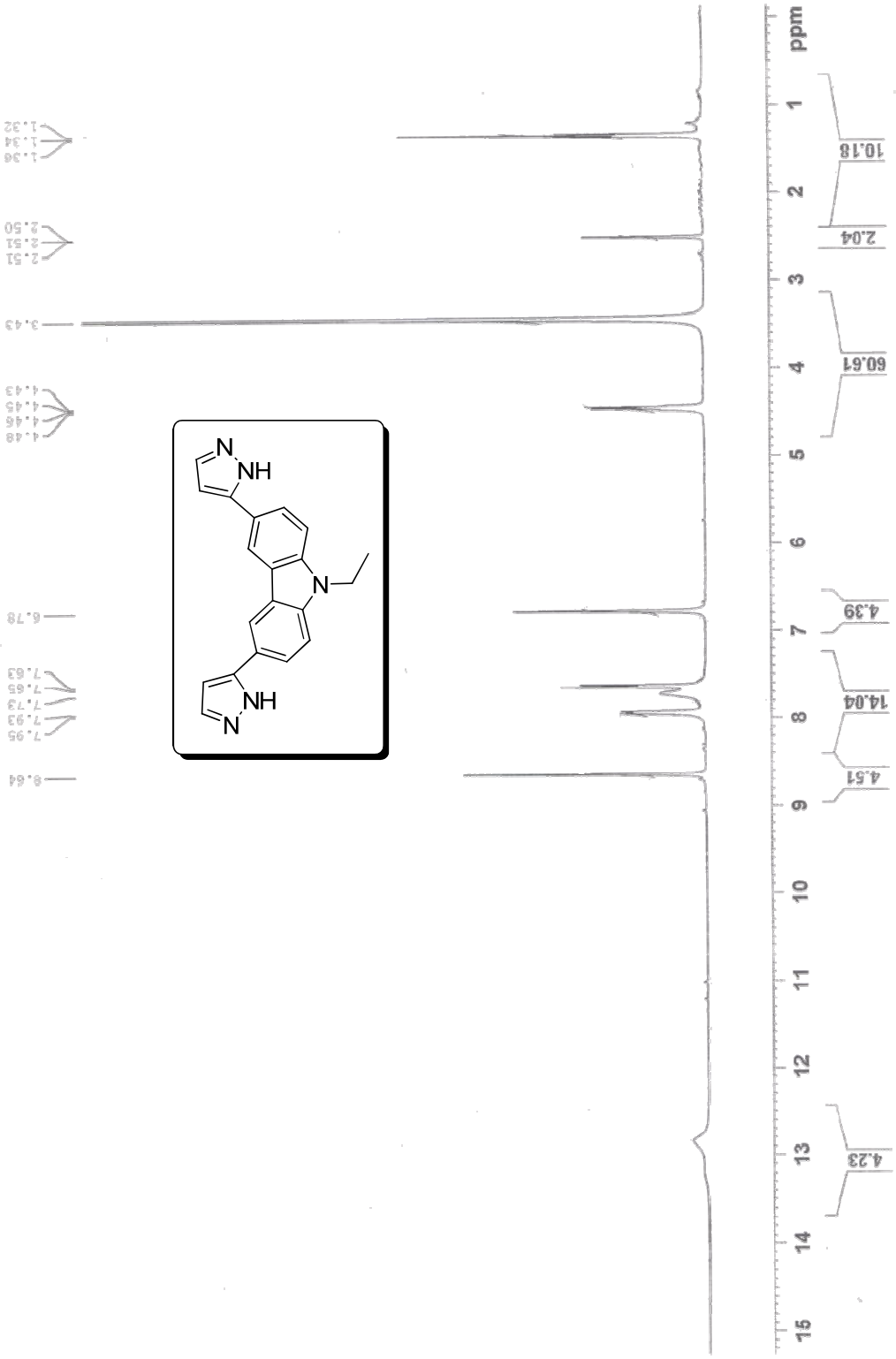
Spectrum 23. ^{1}H NMR of 253b



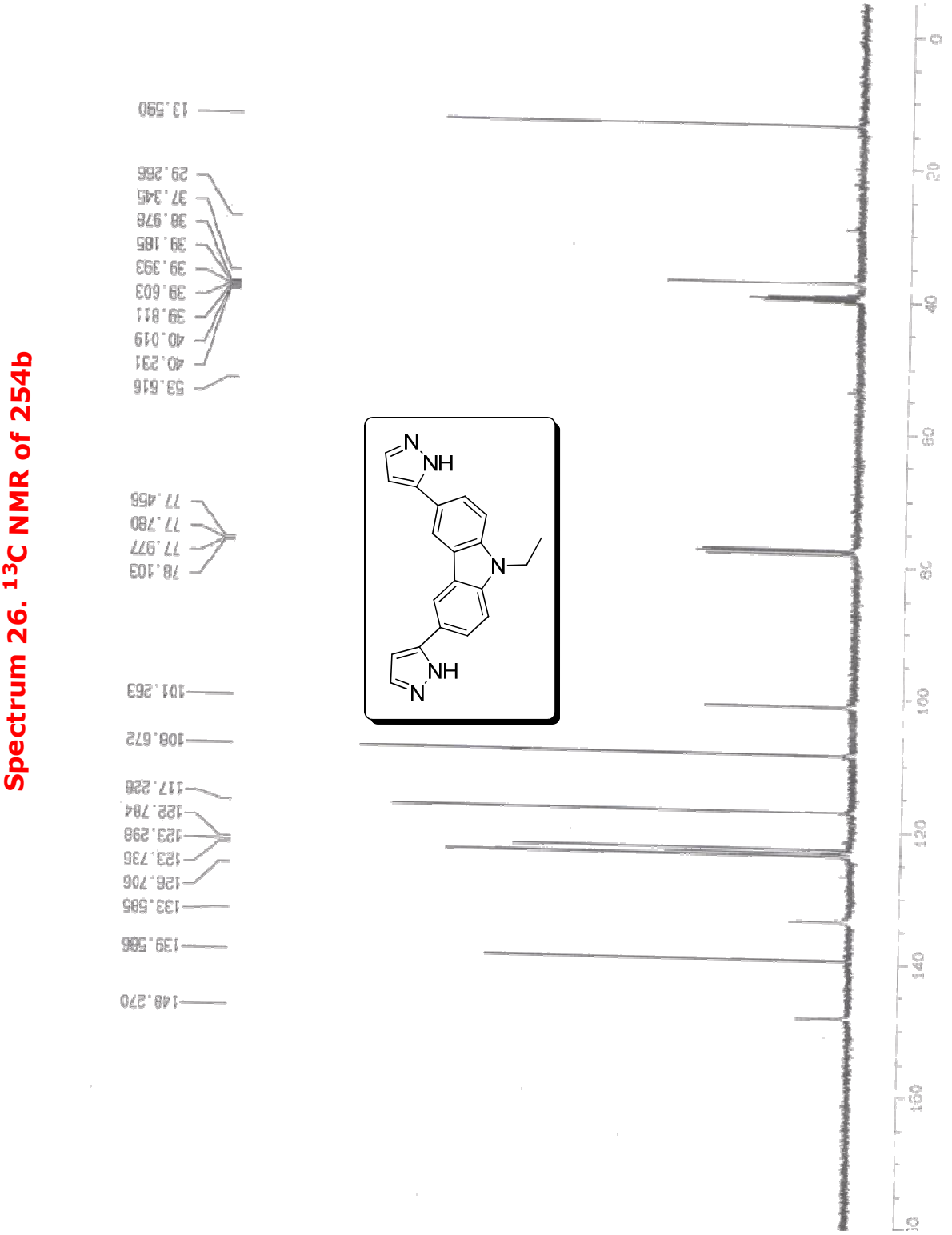
Spectrum 24. ^{13}C NMR of 253b



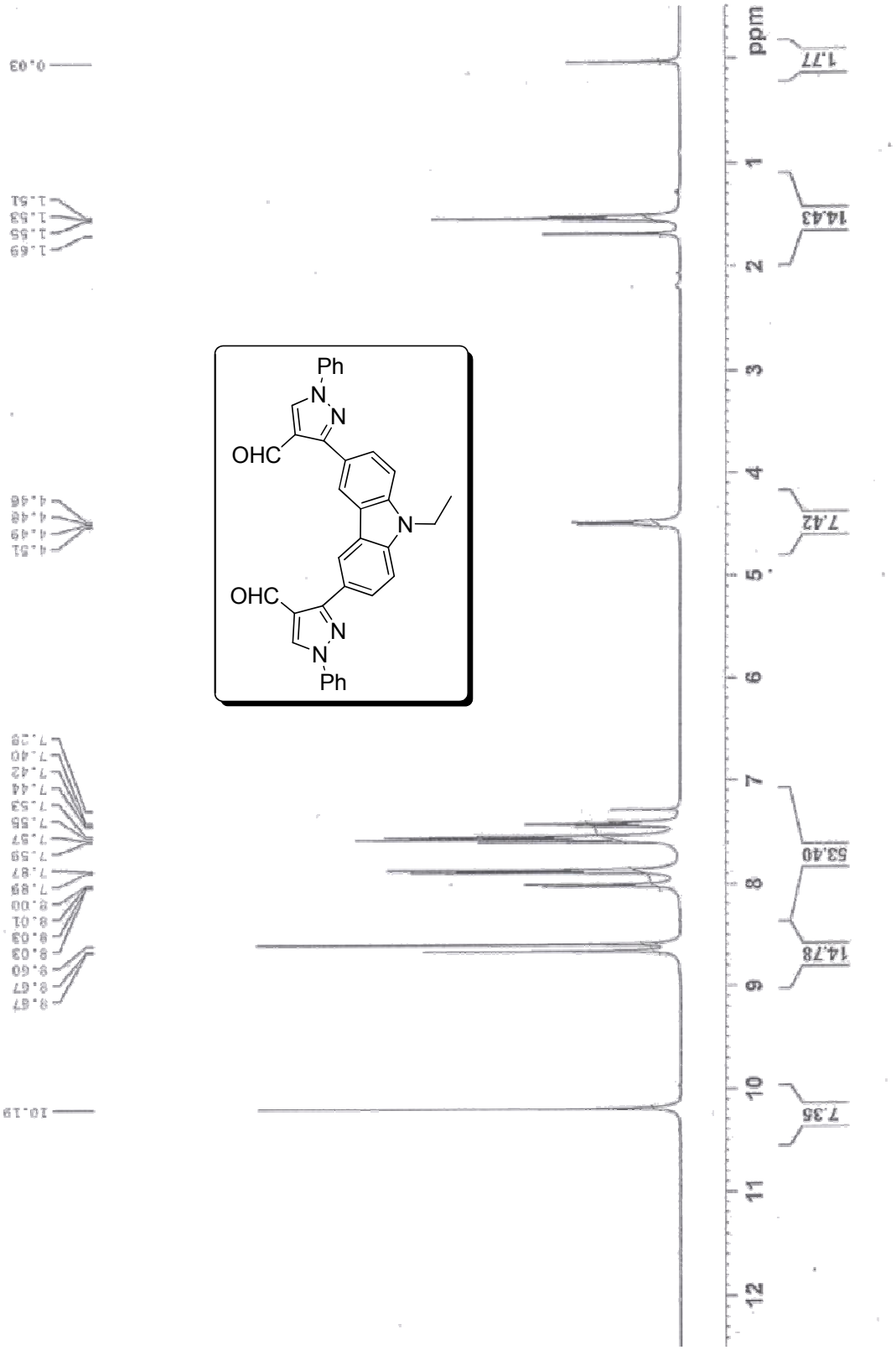
Spectrum 25. ^{1}H NMR of 254b



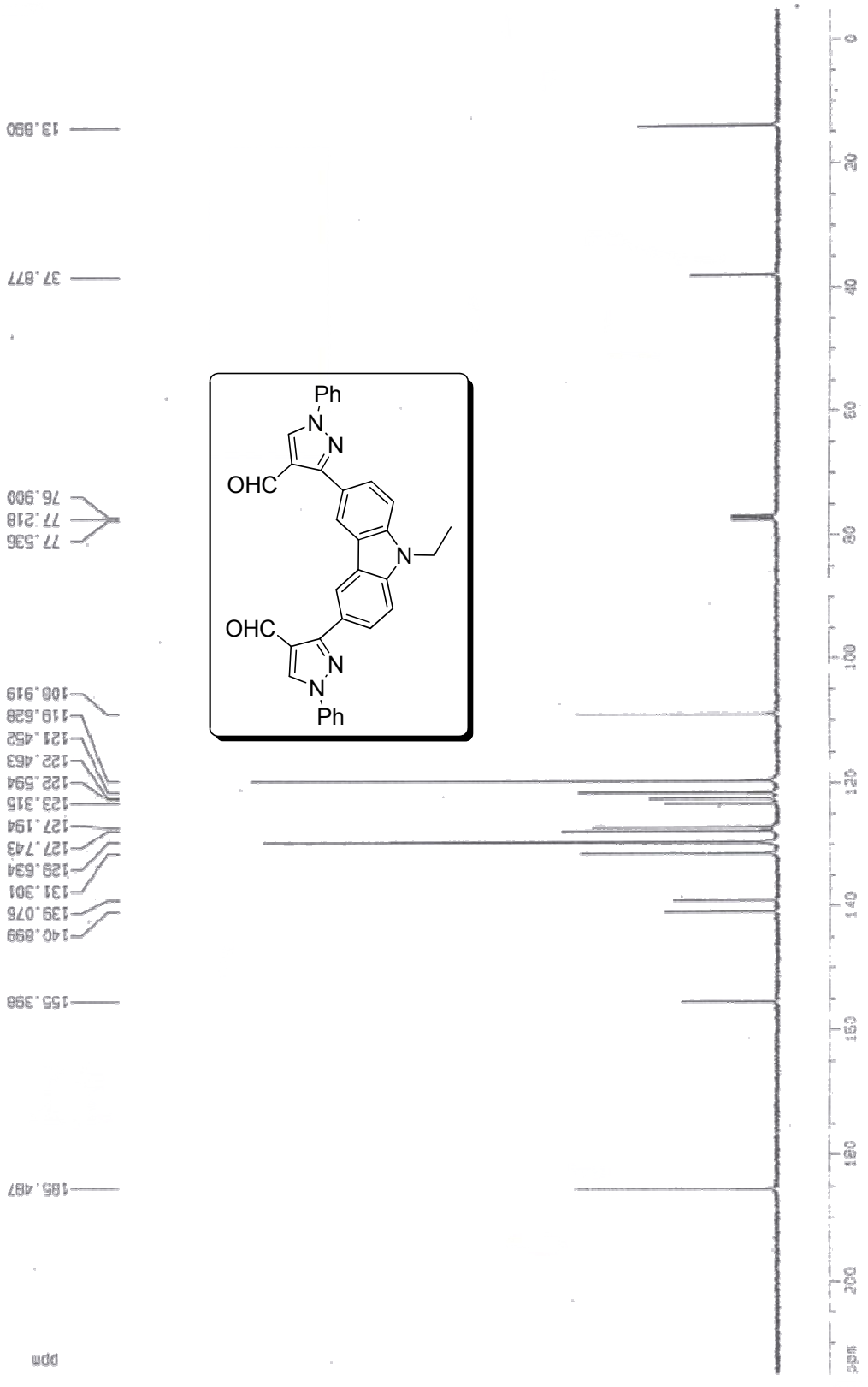
Spectrum 26. ^{13}C NMR of 254b



Spectrum 27. ^{1}H NMR of 256b



Spectrum 28. ^{13}C NMR of 256b



3.6. References

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CHAPTER

4

Synthesis of New Di(diindolylmethyl)carbazoles and Di(diindolylmethyl)pyrroles

4.1. Introduction

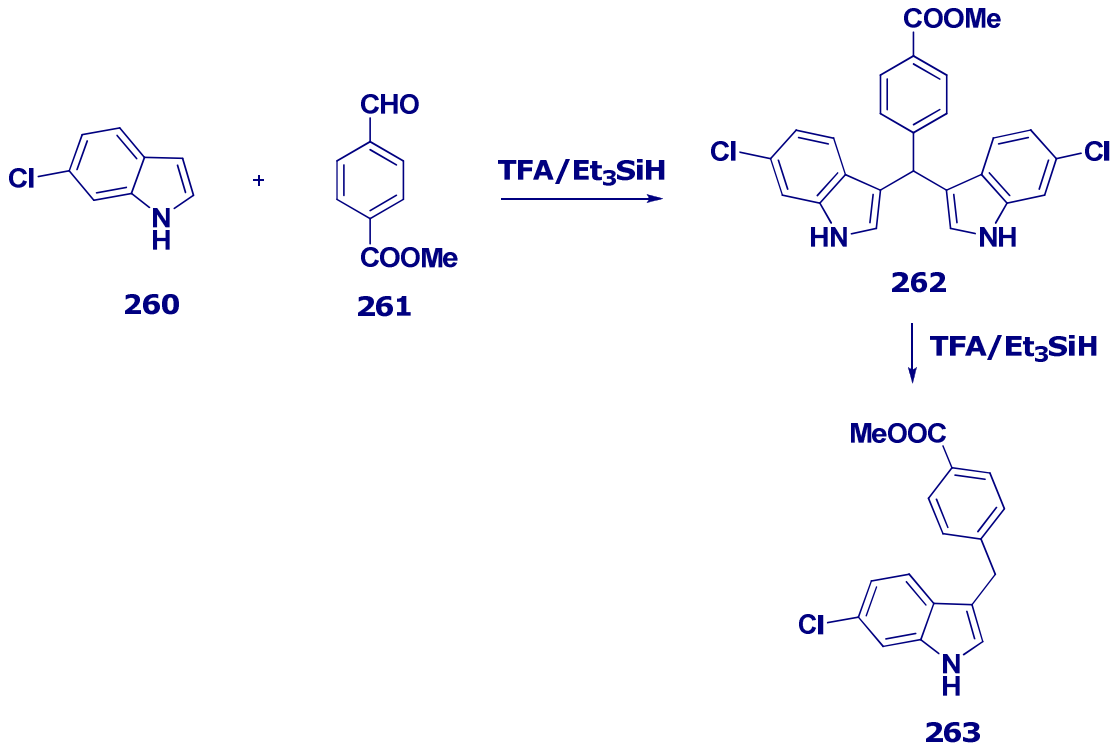
Many of the important bisindolylmethanes (BIMs) were widely isolated from various terrestrial and marine natural sources. These natural products have novel structures and exhibit a range of important biological activities.[173] Cancer chemotherapy with bis(3-indolyl)methane was recently reviewed and numerous activities have been reported.[174] 3,3′-Diindolylmethane and derivatives are also used as dietary supplements for humans.[175] BIMs inhibit bladder cancer growth,[176] inhibit renal cell carcinoma growth,[177] have growth inhibitory activity on lung cancer cells,[178] are active against colon cancer,[179] inhibit mammary tumor growth,[180] induce apoptosis in prostate cancer,[181] inhibit the proliferation process in breast tumor cells,[182] have growth inhibitory activity on prostate cancer cell lines,[183] have antitumorigenic activity,[184] serve as topoisomerase IIR catalytic inhibitors,[185] serve as inhibitors of the platelet-derived growth factor receptor kinase,[186] exhibit antimicrobial and antifungal activities,[187] exhibit antibiotic activity and antibacterial activity,[188] have inhibitory effects on phenobarbital-induced hepatic CYP mRNA expression,[189] serve as cytodifferentiating agents,[190] are antiangiogenic and cytotoxic agents,[191] have radical scavenging activity,[192] growth promoting activity,[193] and analgesic and anti-inflammatory activities.[194] The oxidized form of BIMs are utilized as dyes,[195] as well as colorimetric sensors.[196]

A patent[197] disclosed the synthetic method of chromogenic 3,3′-bisindolyl-4-azaphthalides and their uses as color formers in pressure- and heat-sensitive recording materials. A recent patent describes the synthesis of BIMs forming complexes with radioactive metal ions (Gd^{3+}), which are useful contrast agents for

radio-imaging and visualization of various tissues and organs.[198] Recently Maciejewska *et al*.[199] used DNA-based electrochemical biosensors to demonstrate that bis(5-methoxyindol-3-yl)methane, considerably reduces the growth of cancer cell lines such as HOP-92 (lung), A498 (renal), and MDAMB-231/1TCC (breast). Their results also indicate that BIMs could potentially be applied as chemotherapeutic agents against tumors.[199,200] Ghaedi *et al*.[201] have used BIMs coated on an alumina-sodium dodecyl sulfate (SDS) surface for preconcentration and determination of Cu(II), Zn(II), Pb(II) and Fe(III) ions by flame atomic absorption spectrometry. It is therefore clear that there are various attractive reasons why researchers want to synthesize various derivatives of BIMs. Due to the versatile application possibilities of BIMs there is a continuous quest for more efficient methods for indole derivative synthesis.[202]

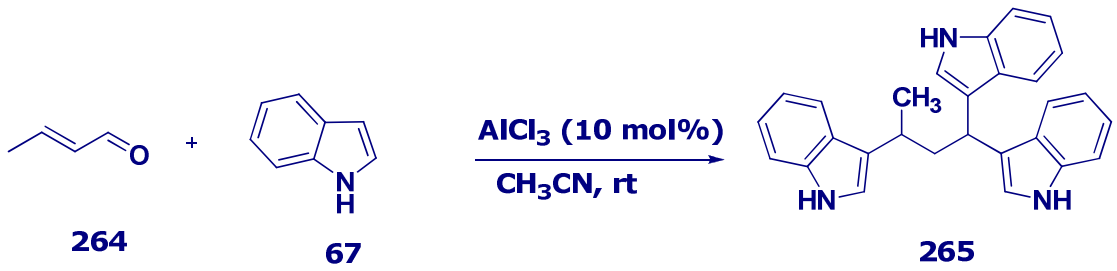
The indole ring is more reactive at the 3-carbon atom. The majority of BIM's found in literature are therefore 3,3'-BIMs. 3,3'-BIMs were prepared by Fischer in 1886 for the first time.[203] The standard method for the synthesis of 3,3'-BIMs is the Friedel-Crafts reaction between indoles and carbonyl compounds in the presence of acid or base. Mahadevan *et al*. have synthesized[204] bisindolylmethane **262** by treating 6-chloroindole **260** with the corresponding aldehyde **261** in the presence of TFA/Et_3SiH. The bisindolylmethane **262** is also reduced to the product **263** in 60% yield under the same reaction conditions as shown in Eq. 41.

Eq. 41



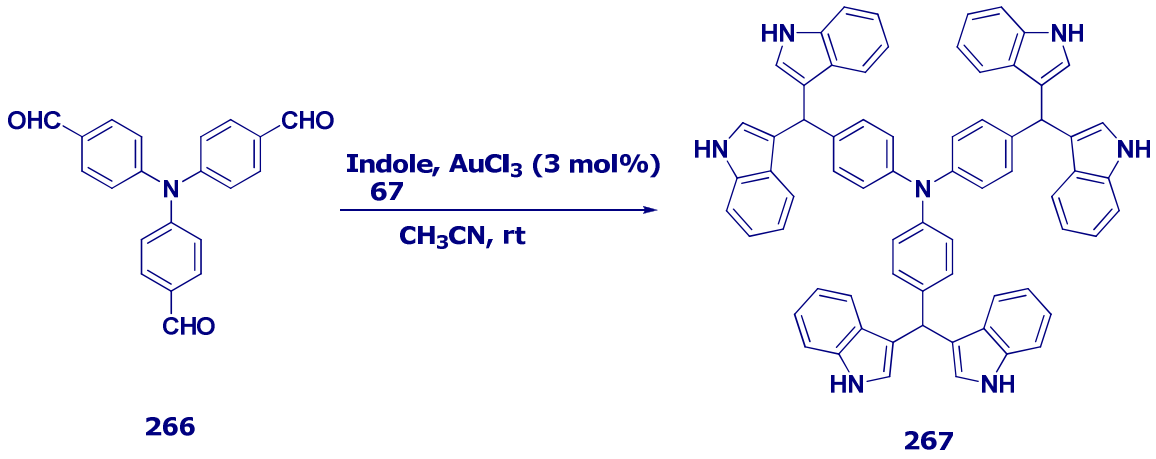
The reaction of crotonaldehyde **264** and indole **67** in the presence of $AlCl_3$ in acetonitrile gave a new model of BIMs, 1,1,3-tri(1*H*-indol-3-yl)butane **265** as shown in Eq. 42.[205]

Eq. 42



Nair *et al*. reported the synthesis of trimeric BIMs **267** by the reaction of tris[(4-formyl)phenyl]amine **266** and indole **67** catalyzed by $AuCl_3$ in 35% yield (Eq. 43). This method is also sufficient for the condensation of other aldehydes and activated arenes such as 1,3,5-trimethoxybenzene, substituted indoles, 2-methyl thiophene and 2-methylfurane.[206]

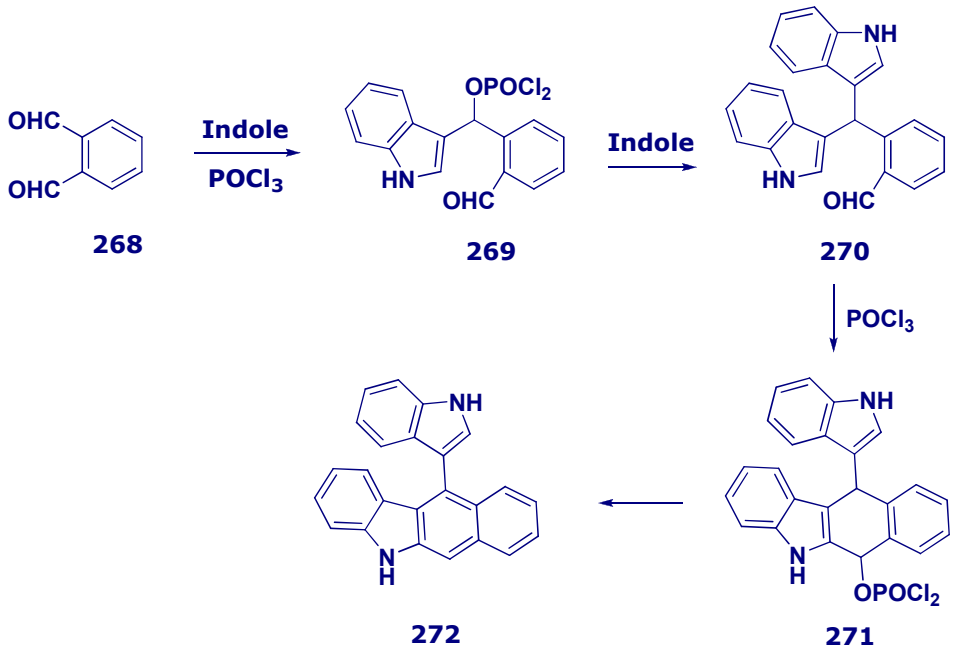
Eq. 43



266 **267**

In a noncyclic synthetic attempt, indole **67** was reacted with *o*-phthaldialdehyde **268** (in a 2:1 ratio) in anhydrous chloroform and in the presence of phosphoryl chloride. The reaction completed after 1 h and afforded the 11-(3-indolyl)benzo[*b*]carbazole **272** in 58% yield. The suggested mechanism involves the formation of a 3,3′-BIM **270**, which undergoes cyclization to **271** and aromatization to give the benzocarbazole **272** as shown in Eq. 44.[207]

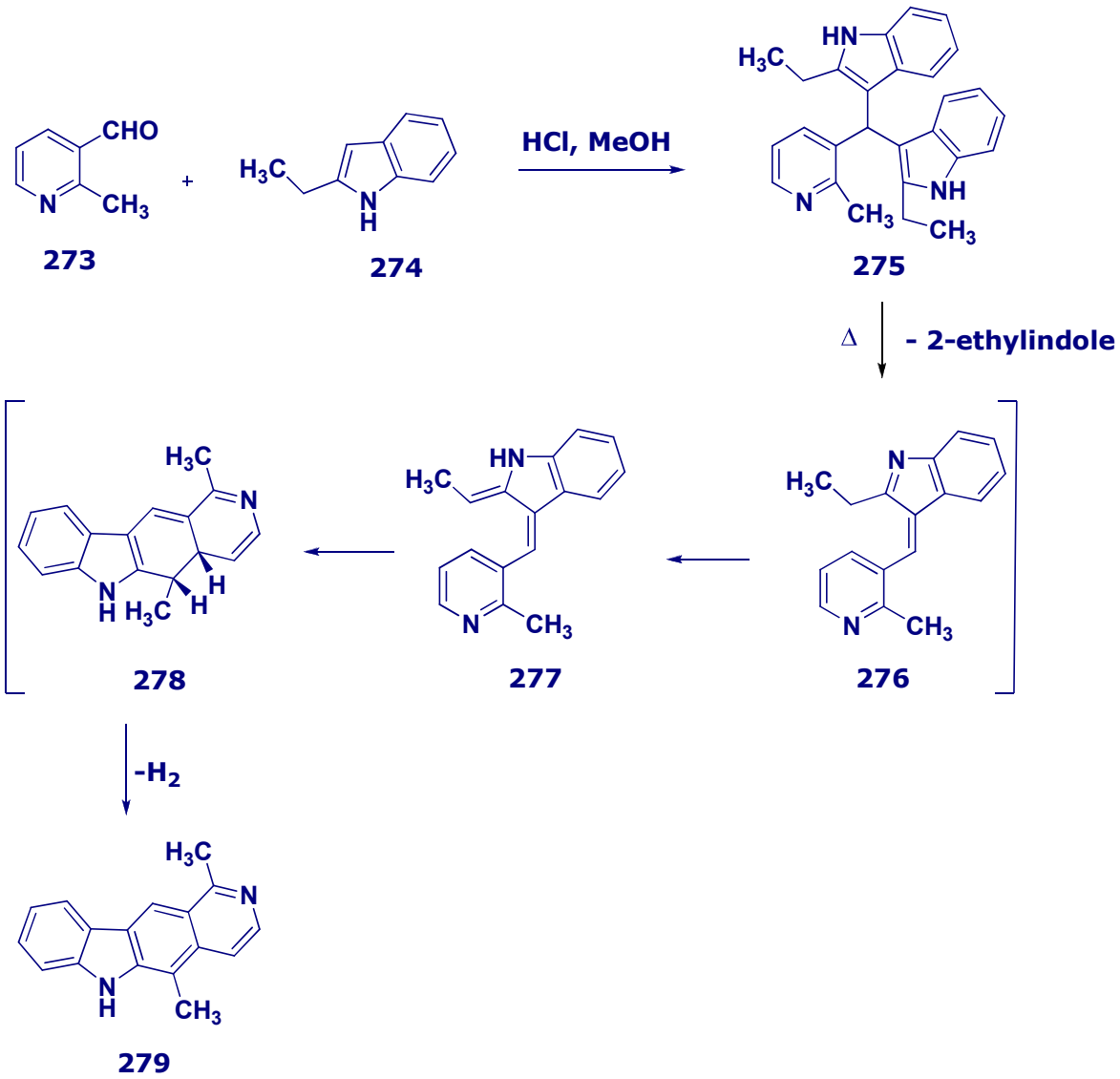
Eq. 44



268 **269** **270** **271** **272**

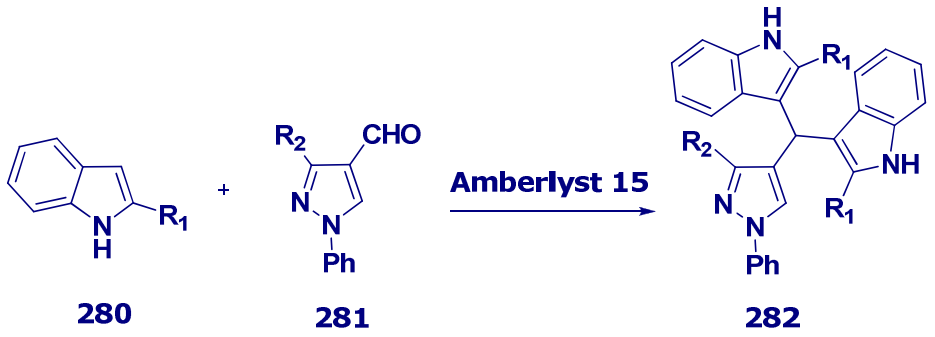
2-Methyl-3-formylpyridine **273** reacts with 2-ethylindole **274** to yield BIM **275**, which under thermolytic and low-pressure conditions decomposes to form 2-ethylindole and olivacine **279** as proposed in Eq. 45.[208]

Eq. 45



An efficient synthesis of (pyrazolyl)bisindolylmethanes **282** was developed using an Amberlyst 15 catalyzed condensation of 1,3-diaryl-4-formyl pyrazoles **281** with indoles **280** in 77-96% yields (Eq. 46).[209]

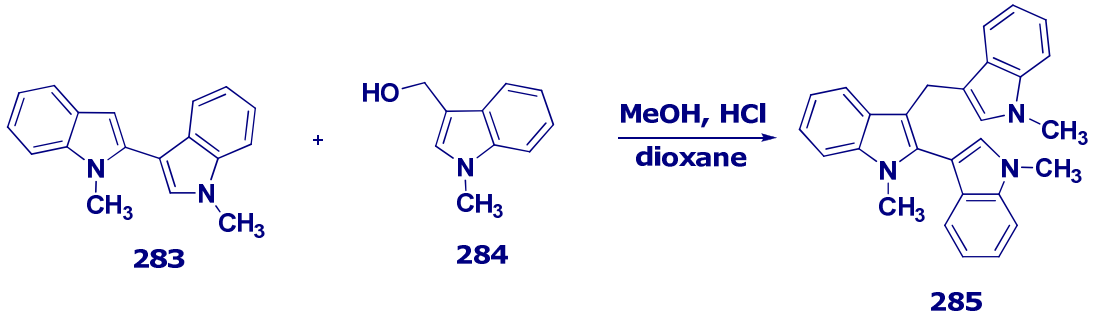
Eq. 46



280 281 282

Usually nucleophilic substitution of the alcohols, amines or related compounds with indoles leads to alkylation of indoles. Using this strategy, Bergman synthesized the BIM **285** from biindole **283** and *N*-methylindole-3-carbinol **284** in a solution of methanolic hydrochloric acid in 80% yield (Eq. 47).[210]

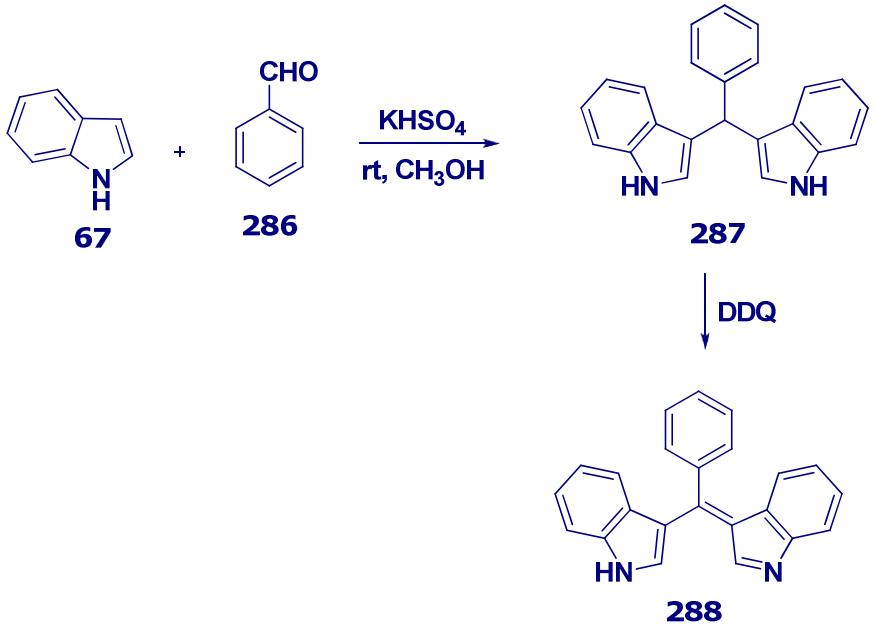
Eq. 47



283 284 285

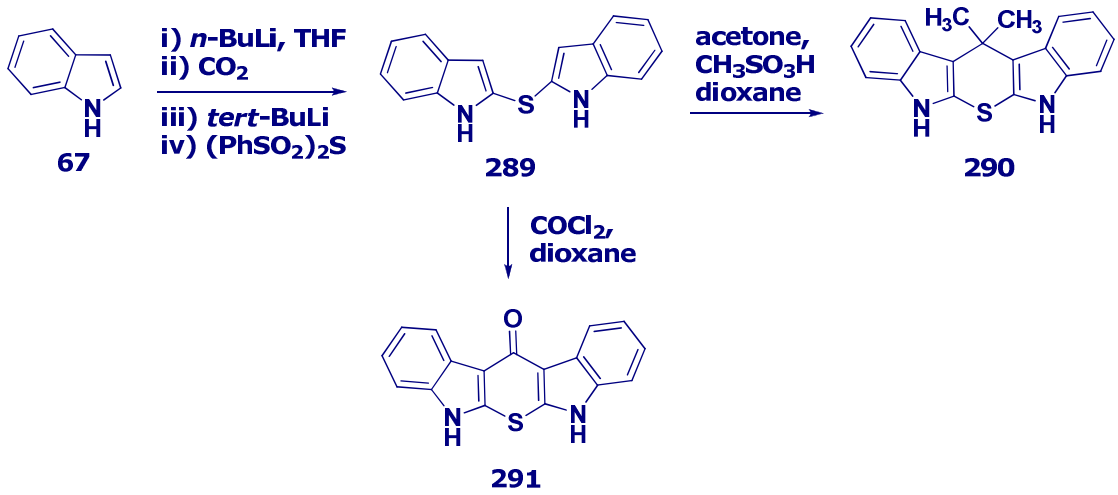
Shao *et al*. synthesized[211] oxidized form of bis(indolyl)methane **287** by the oxidation of bis(indolyl)methane **287** which was synthesized by the reaction of indole **67** and benzaldehyde **286** as shown in Eq 48. They explored **288** as a selective colorimetric sensor either for F^- in aprotic solvent or for HSO_4^- and weak acidic species in water-containing medium.

Eq. 48



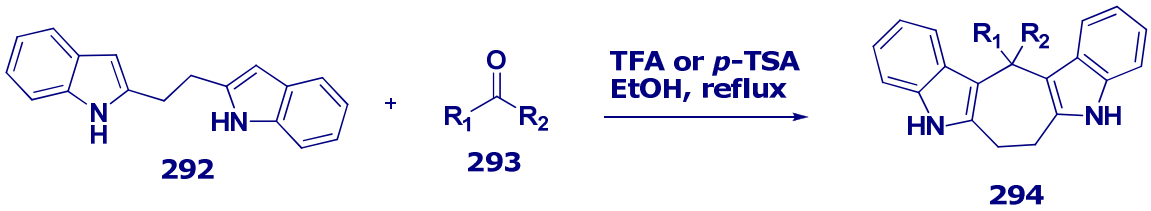
Bergman and his group synthesized bisindolyl sulfide **285** through lithiation of indole **67** followed by treatment with bis(phenylsulfonyl)sulfide. The sulfide **289** gives the alternative BIM **290** upon treatment with acetone under acidic conditions, whereas the reaction of **289** with phosgene affords the keto derivative **291** in reasonable yield.[212]

Eq. 49



Bergman *et al*. synthesized pentacyclic compounds **294** from 1,2-bis(1*H*-indol-2-yl)ethane **292** and carbonyl compounds **293** under acidic conditions as shown in Eq. 50.[213]

Eq. 50



4.2. Synthesis of di(diindolylmethyl)carbazoles

Biosensor technologies that focus on the direct detection of nucleic acids are currently an area of interest as they play a major role in clinical, forensic and pharmaceutical applications.[214] The molecular probes that cause an increase in both absorbance and emission intensity by association with the host biomacromolecules (e.g. DNA, RNA, and proteins) are very useful photoluminescent markers in genomics and proteomics.[215] These simple and straightforward spectroscopic methods are especially advantageous because small organic dyes absorb and emit at wavelengths that do not interfere with the absorption of the DNA bases (λ_{max} ~ 260 nm). Indeed, spectrophotometric and spectrofluorimetric titrations are direct methodologies that indicate the association of a specific dye with DNA.[216] The design of new small molecular organic fluorophores is not a simple task.[217]

Although the extensive work has been done on the simple alkyl and aryl diindolylmethanes,[202] the reports on the synthesis of heteroaryl diindolylmethanes are very rare. In particular there were no reports on the synthesis of pyrrolyl diindolylmethanes to the best of our knowledge. Earlier attempt to the synthesis of diindolyl(pyrrolyl)methane by the reaction of pyrrol-2-carboxaldehyde with indole in presence of M.K-10 clay catalyst leads to triindolylmethane instead of diindolylmethane.[218]

The electrophilic substitution reaction of indoles with carbonyl compounds to produce bis(indolyl)alkane is an acid catalyzed reaction and both protic[219] as well as Lewis acids[220] are known to promote this reaction. However, many Lewis acids are

prone to undergo decomposition in the presence of nitrogen containing reactants and this necessitates the use of excess and sometimes stoichiometric amount of Lewis acid catalyst.[221] To overcome such problems, Montmorillonite K-10,[222] triphenylphosphonium perchlorate, lithium perchlorate,[223,224] iodine,[225] zeolites,[226] triflate of lanthanides[227] and cyanuric chloride[228] have been reported to catalyze this reaction. However, many of these reagents are expensive, need longer reaction time and are not environmental friendly which warrants the development of a new, practical, economical and environmental friendly protocol for the synthesis of bis(indolyl)methanes.

We report here the synthesis of di(diindolylmethyl)carbazole derivatives catalysed by a new catalyst $PPh_3.CF_3SO_3H$ (20 mol%). Di(diindolylmethyl)carbazoles **297a–p** were synthesized in good yields by the reaction of 9-alkylcarbazol-3,6-dicarboxaldehydes **295a–d** with indole derivatives **296a-d** in the presence of a catalytic amount (20 mol%) of $PPh_3.CF_3SO_3H$ in $CHCl_3$ at room temperature (Scheme 14). The results are summarized in Table 21 which clearly indicates the scope and generality of the reaction. Longer reaction times were observed in the case of 2-phenylindole derivatives. This may be due to the steric hindrance and the electron withdrawing nature of the phenyl ring which lowers the nucleophilicity of the indole.

Scheme 14. Synthesis of di(diindolylmethyl)carbazoles

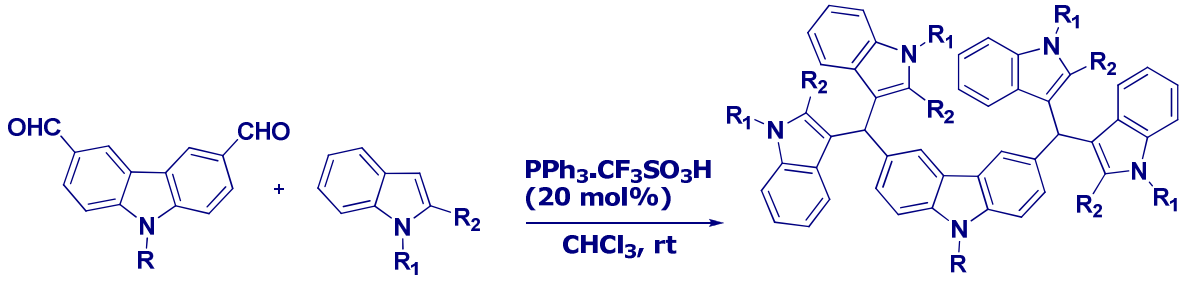


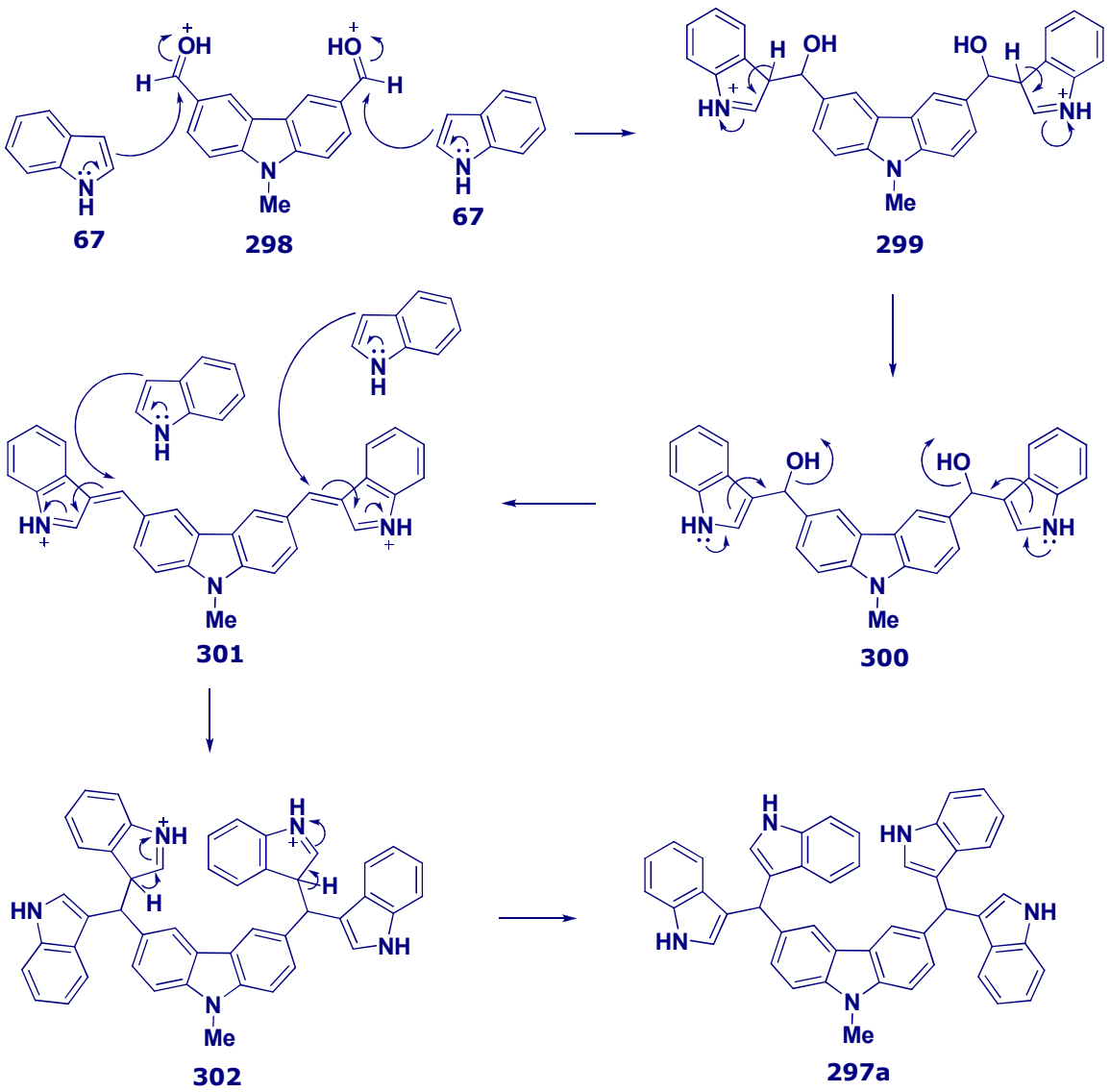
Table 21. Synthesis of di(diindolylmethyl)carbazoles

Entry	R	R_1	R_2	Product	Time (h)	Yield[a] (%)
1	Me	H	H	**297a**	1	75
2	Et	H	H	**297b**	1	71
3	*n*-Bu	H	H	**297c**	1	77
4	Bn	H	H	**297d**	1	70
5	Me	Me	H	**297e**	1	78
6	Et	Me	H	**297f**	1	80
7	*n*-Bu	Me	H	**297g**	1	81
8	Bn	Me	H	**297h**	1	79
9	Me	H	Me	**297i**	3	76
10	Et	H	Me	**297j**	3	71
11	*n*-Bu	H	Me	**297k**	3	73
12	Bn	H	Me	**297l**	3	69
13	Me	H	Ph	**297m**	12	64
14	Et	H	Ph	**297n**	12	61
15	*n*-Bu	H	Ph	**297o**	12	60
16	Bn	H	Ph	**297p**	12	62

[a] Isolated yield

Scheme 15 illustrates the general mechanism for the acid-catalyzed formation of bis(indolyl)methanes. Initially indole attacks protonated form of 9-methylcarbazol-3,6-dicarboxaldehyde **298** which results the formation of the intermediate **299**. Aromatization of **299** gives **300** which undergoes facile dehydration to **301**. Finally attack of indole on the intermediate **301** followed by aromatization gives di(diindolylmethyl)carbazole **297a**.

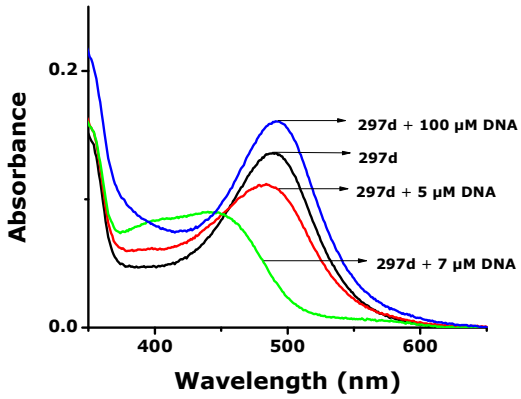
Scheme 15. Mechanism for the formation of di(diindolylmethyl)carbazole



4.2.1. DNA binding studies

The interaction of the compound **297d** in DMSO (40 μM) was investigated by titrating with CT-DNA in Tris-buffer. As shown in Figure 26, on addition of 7 μM of DNA, the absorption band centered at 489 nm disappeared and a new band at higher energy was observed at 447 nm. The binding constant was deduced to be $1{\cdot}4 \times 10^5$ M^{-1} using nonlinear least-squares treatment of UV/Vis titrations. As can be expected from UV/vis data (Figure 26), colour change occurs from orange to pale yellow colour of the dye **297d** by the addition of 10 μM of DNA (Figure 27). Further addition of DNA (100 μM) caused the colour change of the solution from pale yellow to light reddish brown (Figure 27) while in the UV/Visible spectrum (Figure 26), the band at 447 nm disappears and a new band appeares at 491 nm. This optical response may be due to the non-covalent interactions between DNA and di(diindolylmethyl)carbazole moiety.

Figure 26. Family of UV-Vis spectra taken in the course of the titration of DMSO solution of 297d (40 μM) with CT-DNA in Tris buffer



Other di(diindolylmethyl)carbazole derivatives were also found to exibit similar behaviour like **297d**. On the addition of DNA aliquots to **297i** (40 μM), the peak at 514 nm disappears and a new peak at 407 nm appears in the UV-Vis spectrum (Figure 28) which results the colour change of the dye from pink to pale yellow (Figure 29). Further addition of DNA (100 μM), the peak at 407 nm disappears and a new peak at 512 nm evolved (Figure 28). Again the colour changes from pale yellow to intensive pink colour (Figure 29).

Figure 27. Color changes upon addition of CT-DNA to the DMSO solution of 297d (50 μM) from left to right: a) 297d b) 297d + 10 μM of DNA c) 297d + 100 μM of DNA.

Figure 28. Spectophotometric titration of a DMSO solution of 297i (40 μM) by Calf-Thymus DNA in 5 mM Tris, 50 mM NaCl (pH = 7.0): (a) after the addition of 0, 2.5, 5.0, 7.5, 9.5 μM CT-DNA (b) after the addition of 10, 15, 20, 25, 30, 40, 50, 100 μM of CT-DNA.

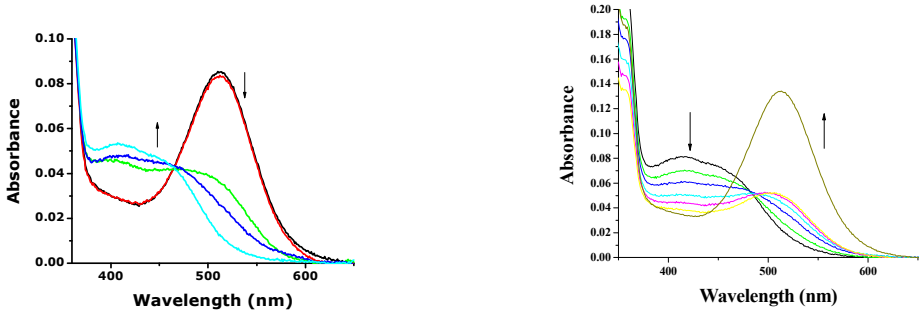


Figure 29. Color changes upon addition of CT-DNA to the DMSO solution of 297i (50 μM) from left to right: (a) 297i (b) 297i + 10 μM of DNA (c) 297i + 100 μM of DNA

We have also carried out ^{1}H and ^{31}P NMR titrations of **297i** with DNA. All the protons of di(diindolylmethyl)carbazole moiety were moving to the upfield (Figure 30) which indicates that the absence of hydrogen bonding and the presence of non-covalent interactions. In ^{31}P the singlet was splitted into four new peaks (Figure 31).

Figure 30. Partial ^{1}H NMR spectra for the titration of 297i in DMSO with CT-DNA in Tris buffer. Bottom: 297i, top: 297i + CT-DNA.

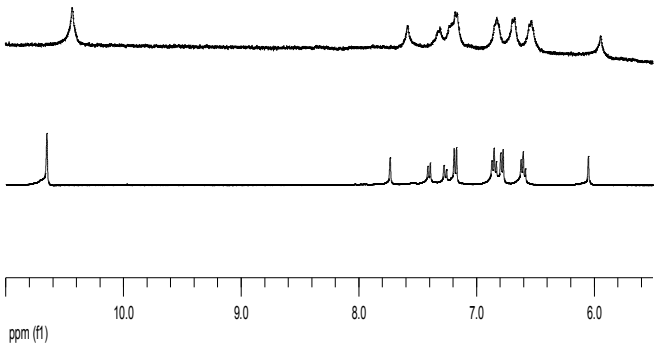
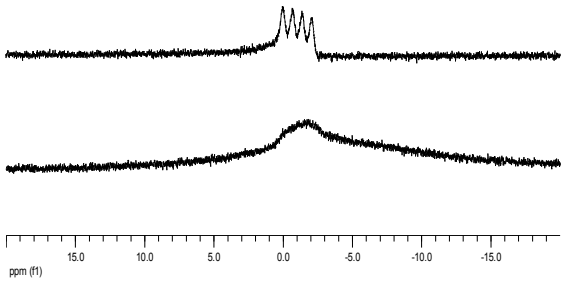


Figure 31. ^{31}P NMR spectra for the titration of CT-DNA in Tris-HCl buffer with 297i. Bottom: CT-DNA, top: CT-DNA + 297i.



As shown in Figure 33, the colour of **297p** changes from violet to pale yellow corresponding to the disappearance of the peak at 551 nm and the appearance of a new peak at 440 nm upon the addition of DNA aliquots (Figure 32). Again the colour changes from pale yellow to violet after addition of 100 μM DNA (Figure 33) and the peak at 440 nm disappeared and a new peak at 548 nm appeared (Figure 32).

But di[di(1-methylindolylmethyl)]carbazole derivatives did not give any colour change after the addition of excess of DNA also. Absorbance of the peak at 498 nm decreased but no new peak was observed (Figure 34). This clearly indicates that the

NH protons were playing a major role for the optical response of the other di(diindolylmethyl)carbazoles

Figure 32. Family of UV/vis spectra taken in the course of the titration of a DMSO solution in the receptor 297p (40 μM) with CT-DNA in Tris buffer

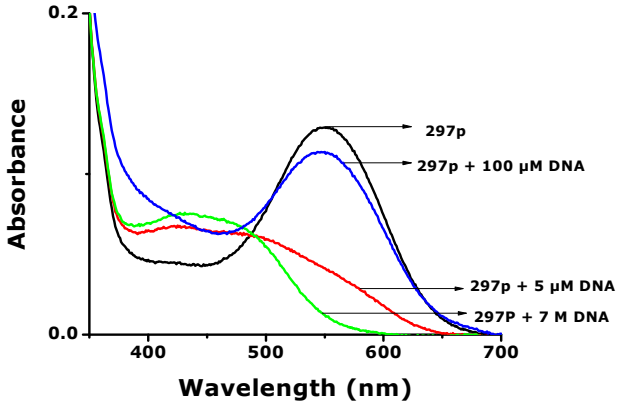


Figure 33. Color changes upon addition CT-DNA to the DMSO solution of 297p (50 μM). From left to right: (a) 297p (b) 297p + 10 μM of DNA (c) 297p + 100 μM of DNA

All di(diindolylmethyl)carbazole derivatives are fluorescent. The fluorescent intensity of all derivatives was going to quench after the addition of DNA. As shown in Figure 35, the intensity of characteristic emission maximum at 372 nm and 389 nm gradually decreases upon the incremental addition of DNA upon exciting at 280 nm.

Figure 34. Family of UV/vis spectra taken in the course of the titration of a DMSO solution in 297f (40 μM) with CT-DNA in Tris buffer. DNA concetrations: 0, 2.5, 5, 7.5, 10, 15, 20 μM.

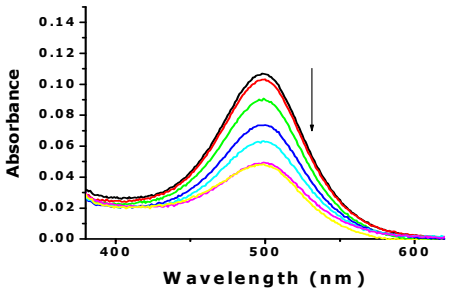
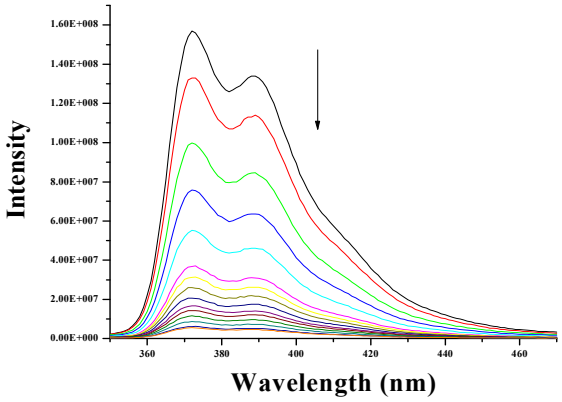


Figure 35. Fluorescent titration curves for 297d upon incremental additions of CT-DNA. DNA concentrations: 0, 2.5, 5, 7, 9.5, 15, 20, 25, 30, 40, 50 μM.



4.3. Synthesis of di(diindolylmethyl)pyrroles

As shown in Scheme 16, di(diindolylmethyl)pyrrole derivatives were formed by treating with 3,5-dichloro-2,4-pyrroledicarboxaldehydes **303a-b** with various indole derivatives **296a-h**. The results are summarized in Table 22. The formation of triindolylmethane (~ 20%) was observed with indole only. There was no formation of the corresponding triindolylmethane with other indole derivatives. The formation of triindolylmethane may be considered to proceed through the successive formation of the expected diindolylmethane and indoleninium species. The structure of **304e** was also confirmed further by the single crystal X-ray analysis (Figure 36).

Di(diindolylmethyl)pyrroles could not exhibit any optical properties even after adding the excess of DNA also.

Scheme 16. Synthesis of di(diindolylmethyl)pyrroles

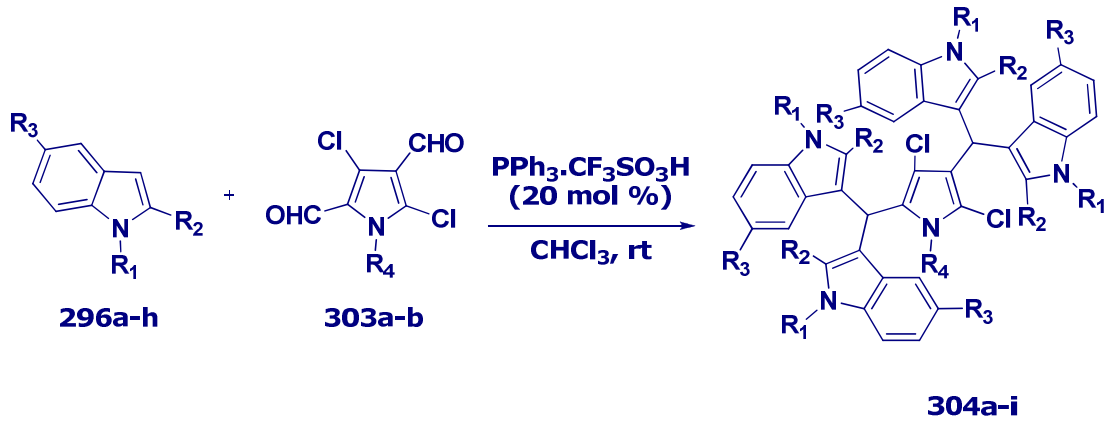


Figure 36. ORTEP diagram of 304e

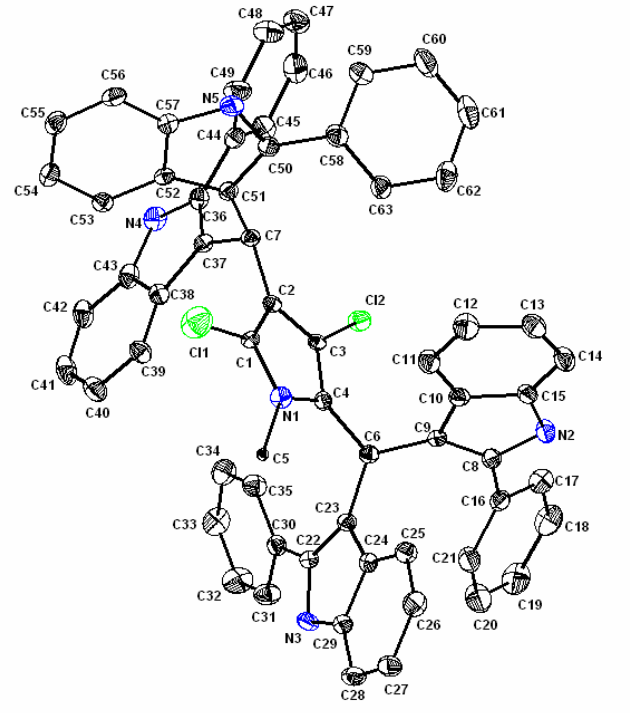


Table 22. Synthesis of di(diindolylmethyl)pyrroles

Entry	R_1	R_2	R_3	R_4	Product	Time (h)	Yield[b] (%)
1	H	H	H	H	**304a**	2	74
2	Me	H	H	H	**304b**	2	72
3	H	Me	H	H	**304c**	3	70
4	H	Ph	H	H	**304d**	12	59
5	H	Ph	H	Me	**304e**	12	56
6	H	(4-Br)Ph	H	H	**304f**	12	61
7	H	(4-OMe)Ph	H	H	**304g**	12	58
8	Bn	H	H	H	**304h**	2	59
9	H	H	Br	H	**304i**	2	63

[b] Isolated yield

4.4. Conclusion

In conclusion, we have synthesized di(diindolylmethyl)carbazoles and pyrroles by employing a new catalyst $PPh_3.CF_3SO_3H$ and also demonstrated the utility of the di(diindolylmethyl)carbazole derivatives for the colourimetric and fluorometric detection of DNA.

4.5. Experimental Section

4.5.1. General Information

CT-DNA was purched from Aldrich and it was sonicated to dissolve completely in 5 mM Tris, 50 mM NaCl, pH = 7.1. Di(diindolylmethyl)carbazoles were dissolved in DMSO and used for DNA binding studies. The absorption of the DNA bases observed at λ_{max} ~ 260 nm.

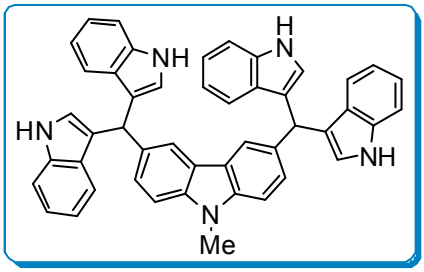
General Procedure L

A mixture of 9-alkyl-3,6-carbazoledicarboxaldehydes **295a-d** (1·0 mmol), indoles **296a-d** (4·0 mmol) and TPP triflate (20 mol%) in chloroform (15 mL) was stirred at room temperature for required time. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude materials were subjected to

column chromatography by using silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products.

3,6-Di(di-1*H*-3-indolylmethyl)-9-methyl-9*H*-carbazole (297a):

The title compound **297a** was prepared from 9-methylcarbazol-3,6-dicarboxaldehyde **295a** (0.24g, 1.0 mmol) and indole **296a** (0.47g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 75%

Mp: 115–116 °C

IR (KBr) ν_{max} cm^{-1}: 3404, 3043, 1607, 1485, 1413, 1228, 1083, 1158, 845, 790, 787, 683

^{1}H NMR (400 MHz) *δ*: 10·56 (4H, s), 8·06 (2H, s), 7·48 (4H, s), 7·27–7·34 (8H, m), 6·99–7·05 (4H, m), 6·78–6·92 (8H, m), 3·64 (3H, s), 5·97 (2H, s)

^{13}C NMR (100 MHz) *δ*: 138.9, 137.2, 135.9, 128.5, 127.3, 126.8, 122.8, 122.5, 121.3, 120.4, 119.9, 118.7, 111.9, 108.9, 65·4, 37·5

LC-MS (m/z): 668 ($M–H^+$)

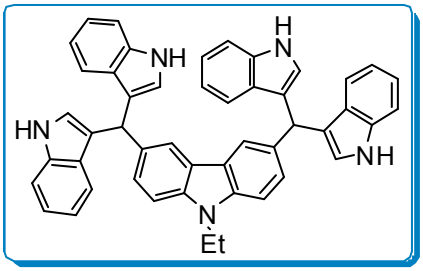
Anal. Calcd. for $C_{47}H_{35}N_5$: C, 84·28; H, 5·27; N, 10·46%

Found: C, 84·41; H, 5·35; N, 10·22%

3,6-Di(di-1*H*-3-indolylmethyl)-9-ethyl-9*H*-carbazole (297b):

The title compound **297b** was prepared from 9-ethylcarbazol-3,6-dicarboxaldehyde **295b** (0.25g, 1.0 mmol) and indole **296a** (0.47g, 4.0 mmol) by following the

general procedure L. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 71%

Mp: 119-120 °C

IR (KBr) ν_{max} cm^{-1}: 3406, 3047, 1602, 1483, 1413, 1232, 1089, 787, 1158, 843, 792, 689

^{1}H NMR (400 MHz) δ: 10.75 (4H, s), 8.03 (2H, s), 7.42 (4H, s), 7.29-7.35 (8H, m), 7.02 (4H, t, *J* = 7.3 Hz), 6.85-6.80 (8H, m), 5.97 (2H, s), 4.33 (2H, q, *J* = 6.8 Hz), 1.09 (3H, t, *J* = 6.9 Hz)

^{13}C NMR (100 MHz) δ: 138.9, 137.2, 135.9, 128.6, 127.2, 126.1, 122.8, 122.5, 121.3, 120.5, 119.9, 118.7, 111.9, 108.9, 65.4, 37.4, 14.2

LC-MS (m/z): 682 ($M-H^+$)

Anal. Calcd. for $C_{48}H_{37}N_5$: C, 84.31; H, 5.45; N, 10.24%
Found: C, 84.64; H, 5.23; N, 10.31%

3,6-Di(di-1*H*-3-indolylmethyl)-9-*n*-butyl-9*H*-carbazole (297c):

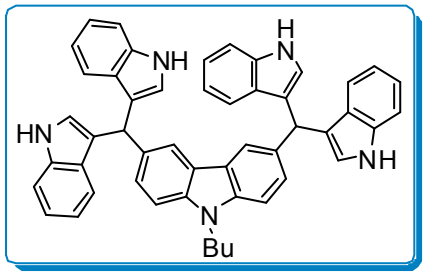
The title compound **297c** was prepared from 9-butylcarbazol-3,6-dicarboxaldehyde **295c** (0.28g, 1.0 mmol) and indole **296a** (0.47g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 77%

Mp: 117-118 °C

IR (KBr) ν_{max} cm^{-1}: 3406, 3057, 2957, 2860, 1873, 1664, 1485, 1211, 1122, 1089, 785

^{1}H NMR (400 MHz) δ: 10.76 (4H, s), 8.03 (2H, s), 7.42 (4H, s), 7.30-7.35 (8H, m), 7.02 (4H, t, *J* = 7.3 Hz), 6.82-6.85 (8H, m), 5.98 (2H, s), 4.27 (2H, t, *J* = 6.6 Hz), 1.68-1.72 (2H, m), 1.26-1.32 (2H, m), 0.85 (3H, t, *J* = 7.24 Hz)



^{13}C NMR (100 MHz) δ: 139.4, 137.1, 135.9, 129.2, 127.2, 126.7, 124.1, 122.4, 121.3, 119.7, 119.5, 118.6, 111.9, 109.1, 60.3, 31.3, 21.2, 20.4, 14.2

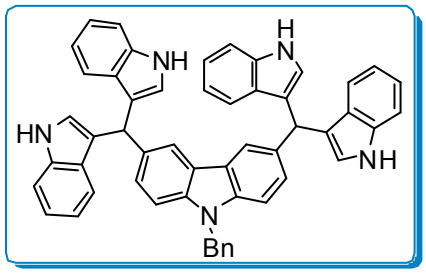
LC-MS (m/z): 710 ($M-H^+$)

Anal. Calcd. for $C_{50}H_{41}N_5$: C, 84.36; H, 5.81; N, 9.84%

Found: C, 84.13; H, 6.11; N, 9.97%

3,6-Di(di-1*H*-3-indolylmethyl)-9-benzyl-9*H*-carbazole (297d):

The title compound **297d** was prepared from 9-benzylcarbazol-3,6-dicarboxaldehyde **295d** (0.31g, 1.0 mmol) and indole **296a** (0.47g, 4.0 mmol) by following the *general procedure L*. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 70%

Mp: 110-111 °C

IR (KBr) ν_{max} cm^{-1}: 3398, 3047, 1653, 1489, 1415, 1244, 1211, 1149, 1122, 1089, 785

^{1}H NMR (400 MHz) δ: 10.76 (4H, s), 8.05 (2H, s), 7.51-7.65 (5H, m), 7.45 (4H, s), 7.29-7.34 (8H, m), 7.01 (4H, t, *J* = 7.3 Hz), 6.81-6.85 (8H, m), 5.96 (2H, s), 5.57 (2H, s)

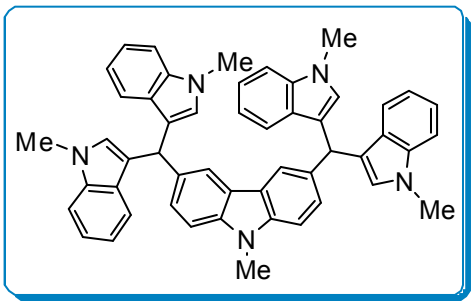
^{13}C NMR (100 MHz) δ: 139.6, 139.5, 138.4, 138.38, 137.2, 136.4, 129.2, 127.7, 127.4, 126.9, 124.1, 122.6, 121.4, 120.0, 119.8, 119.6, 118.9, 118.7, 111.9, 109.4, 65.4, 46.3

LC-MS (m/z): 744 ($M-H^+$)

Anal. Calcd. for $C_{53}H_{39}N_5$: C, 85.34; H, 5.27; N, 9.39%
Found: C, 85.25; H, 5.50; N, 9.34%

3,6-Di[di(1-methyl-1*H*-3-indolyl)methyl]-9-methyl-9*H*-carbazole (297e):

The title compound **297e** was prepared from 9-methylcarbazol-3,6-dicarboxaldehyde **295a** (0.24g, 1.0 mmol) and 1-methylindole **296b** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 78%

Mp: 120-121 °C

IR (KBr) ν_{max} cm^{-1}: 3435, 3052, 2931, 1866, 1610, 1478, 1367, 1230, 1012, 892

^{1}H NMR (400 MHz) δ: 7.92 (2H, s), 7.38 (6H, t, *J* = 8.2 Hz), 7.20-7.24 (6H, m), 7.13 (4H, t, *J* = 7.28 Hz), 6.92 (4H, t, *J* = 7.3 Hz), 6.45 (4H, s), 6.00 (2H, s), 3.75 (3H, s), 3.60 (12H, s)

^{13}C NMR (100 MHz) δ: 140.2, 137.6, 132.6, 128.6, 127.6, 126.6, 122.9, 121.6, 121.4, 120.4, 119.2, 118.8, 109.3, 108.1, 60.5, 40.2, 32.7

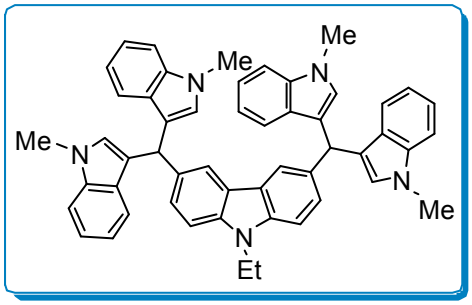
LC-MS (m/z): 724 ($M-H^+$)

Anal. Calcd. for $C_{51}H_{43}N_5$: C, 84.38; H, 5.97; N, 9.65%
Found: C, 84.31; H, 6.02; N, 10.11%

3,6-Di[di(1-methyl-1*H*-3-indolyl)methyl]-9-ethyl-9*H*-carbazole (297f):

The title compound **297f** was prepared from 9-ethylcarbazol-3,6-dicarboxaldehyde **295b** (0.25g, 1.0 mmol) and 1-methylindole **296b** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 80%



Mp: 127-128 °C

IR (KBr) ν_{max} cm^{-1}: 3435, 3053, 2930, 2878, 1867, 1543, 1423, 1151, 1010, 798

^{1}H NMR (400 MHz) δ: 7.95 (2H, s), 7.40 (6H, t, *J* = 7.9 Hz), 7.27-7.25 (6H, m), 7.16 (4H, t, *J* = 7.2 Hz), 6.95 (4H, t, *J* = 7.2 Hz), 6.50 (4H, s), 6.02 (2H, s), 4.30 (2H, q, *J* = 7.2 Hz), 3.67 (12H, s), 1.41 (3H, t, *J* = 6.8 Hz)

^{13}C NMR (100 MHz) δ: 140.2, 137.6, 135.0, 128.6, 127.7, 126.6, 123.0, 121.4, 120.5, 120.3, 119.3, 118.6, 109.1, 108.1, 60.5, 40.2, 32.7, 14.1

LC-MS (m/z): 738 ($M-H^+$)

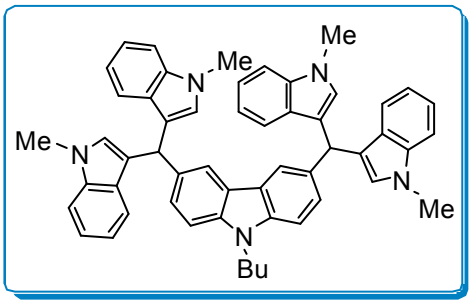
Anal. Calcd. for $C_{52}H_{45}N_5$: C, 84.41; H, 6.13; N, 9.46%

Found: C, 84.71; H, 5.93; N, 9.36%

3,6-Di[di(1-methyl-1*H*-3-indolyl)methyl]-9-*n*-butyl-9*H*-carbazole (297g):

The title compound **297g** was prepared from 9-butylcarbazol-3,6-dicarboxaldehyde **295c** (0.28g, 1.0 mmol) and 1-methylindole **296b** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 81%



Mp: 123-124 °C

IR (KBr) ν_{max} cm^{-1}: 3438, 3049, 2928, 2870, 1608, 1543, 1421, 1369, 1244, 1116, 794

^{1}H NMR (400 MHz) δ: 7.95 (2H, s), 7.39 (6H, d, *J* = 8.0 Hz), 7.27-7.33 (6H, m), 7.22 (4H, t, *J* = 7.4 Hz), 7.00 (4H, t, *J* = 7.1 Hz), 6.49 (4H, s), 6.02 (2H, s), 4.21 (2H, t, *J* = 6.4 Hz), 3.61 (12H, s), 1.79-1.83 (2H, m), 1.24-1.32 (2H, m), 0.91 (3H, t, *J* = 6.7 Hz)

^{13}C NMR (100 MHz) δ: 139.8, 137.7, 135.1, 128.7, 127.8, 126.7, 123.1, 121.5, 120.7, 120.4, 119.4, 118.8, 109.2, 108.4, 60.6, 40.3, 32.7, 31.5, 20.9, 14.1

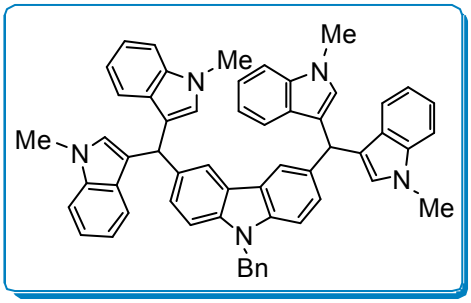
LC-MS (m/z): 766 ($M-H^+$)

Anal. Calcd. for $C_{54}H_{49}N_5$: C, 84.45; H, 6.43; N, 9.12%

Found: C, 84.44; H, 6.43; N, 9.12%

3,6-Di[di(1-methyl-1*H*-3-indolyl)methyl]-9-benzyl-9*H*-carbazole (297h):

The title compound **297h** was prepared from 9-benzylcarbazol-3,6-dicarboxaldehyde **295d** (0.31g, 1.0 mmol) and 1-methylindole **296b** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 79%

Mp: 118-129 °C

IR (KBr) ν_{max} cm^{-1}: 3436, 3047, 2930, 1610, 1473, 1369, 1230, 1116, 1010, 889, 798

^{1}H NMR (400 MHz) δ: 8.01 (2H, s), 7.39-7.45 (8H, m), 7.18-7.54 (13H, m), 6.99 (4H, t, *J* = 7.4 Hz), 6.53 (4H, s), 6.06 (2H, s), 5.45 (2H, s), 3.67 (12H, s)

^{13}C NMR (100 MHz) δ: 139.9, 137.7, 137.5, 135.5, 128.7, 128.6, 127.6, 127.5, 126.8, 126.7, 123.2, 121.4, 120.4, 120.3, 119.2, 118.7, 109.1, 108.5, 60.5, 46.8, 32.7

LC-MS (m/z): 800 ($M-H^+$)

Anal. Calcd. for $C_{57}H_{47}N_5$: C, 85.36; H, 5.91; N, 8.73%

Found: C, 84.461; H, 5.91; N, 8.63%

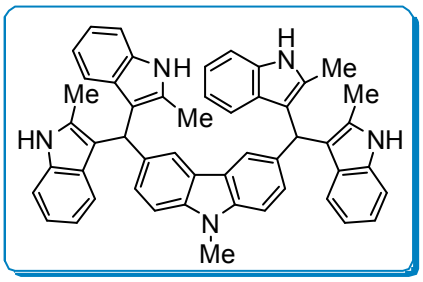
3,6-Di[di(2-methyl-1*H*-3-indolyl)methyl]-9-methyl-9*H*-carbazole (297i):

The title compound **297i** was prepared from 9-methylcarbazol-3,6-dicarboxaldehyde **295a** (0.24g, 1.0 mmol) and 2-methylindole **296c** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 76%

Mp: 217-218 °C

IR (KBr) ν_{max} cm^{-1}: 3396, 3049, 2914, 1618, 1460, 1338, 1246, 1151, 1012, 740



^{1}H NMR (400 MHz) δ: 10.66 (4H, s), 7.75 (2H, s), 7.41 (2H, d, *J* = 8.5 Hz), 7.28 (2H, d, *J* = 8.5 Hz), 7.19 (4H, d, *J* = 7.9 Hz), 6.79-6.88 (8H, m), 6.61 (4H, t, *J* = 7.3 Hz), 6.07 (2H, s), 3.82 (3H, s), 2.02 (12H, s)

^{13}C NMR (100 MHz) δ: 140.1, 135.6, 135.2, 132.0, 128.9, 127.2, 122.3, 120.1, 119.9, 119.1, 118.4, 113.6, 110.8, 108.7, 65.4, 29.4, 14.5

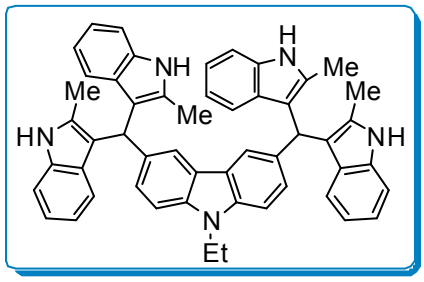
LC-MS (m/z): 726 ($M+H^+$)

Anal. Calcd. for $C_{51}H_{43}N_5$: C, 84.38; H, 5.97; N, 9.65%

Found: C, 84.55; H, 5.89; N, 9.61%

3,6-Di[di(2-methyl-1*H*-3-indolyl)methyl]-9-ethyl-9*H*-carbazole (297j):

The title compound **297j** was prepared from 9-ethylcarbazol-3,6-dicarboxaldehyde **295a** (0.25g, 1.0 mmol) and 2-methylindole **296c** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 71%

Mp: 227-228 °C

IR (KBr) ν_{max} cm^{-1}: 3395, 3057, 1878, 1614, 1298, 1230, 1118, 1012, 804, 740

^{1}H NMR (400 MHz) δ: 10.66 (4H, s), 7.75 (2H, s), 7.42 (2H, d, *J* = 8.5 Hz), 7.27 (2H, d, *J* = 8.5 Hz), 7.19 (4H, d, *J* = 8.0 Hz), 6.80-6.88 (8H, m), 6.62 (4H, t, *J* = 7.9 Hz), 6.06 (2H, s), 4.36 (2H, q, *J* = 7.04 Hz), 2.02 (12H, s), 1.30 (3H, t, *J* = 6.8 Hz)

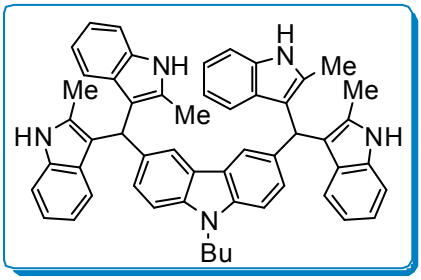
^{13}C NMR (100 MHz) δ: 139.0, 135.5, 135.2, 131.9, 128.9, 127.2, 122.5, 120.2, 119.9, 119.0, 118.4, 113.6, 110.8, 108.7, 65.4, 37.5, 14.2, 12.5

LC-MS (m/z): 738 ($M-H^+$)

Anal. Calcd. for $C_{52}H_{45}N_5$: C, 84.41; H, 6.13; N, 9.46%
Found: C, 84.46; H, 5.99; N, 9.44%

3,6-Di[di(2-methyl-1*H*-3-indolyl)methyl]-9-*n*-butyl-9*H*-carbazole (297k):

The title compound **297k** was prepared from 9-butylcarbazol-3,6-dicarboxaldehyde **295c** (0.28g, 1.0 mmol) and 2-methylindole **296c** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 73%

Mp: 233-234 °C

IR (KBr) ν_{max} cm^{-1}: 3406, 3051, 2922, 1664, 1614, 1487, 1460, 1213, 1014, 800

^{1}H NMR (400 MHz) δ: 10.66 (4H, s), 7.74 (2H, s), 7.42 (2H, d, *J* = 8.5 Hz), 7.27 (2H, d, *J* = 8.5 Hz), 7.19 (4H, d, *J* = 7.9 Hz), 6.79-6.88 (8H, m), 6.61 (4H, t, *J* = 7.3

Hz), 6.06 (2H, s), 4.32 (2H, t, *J* = 6.4 Hz), 2.02 (12H, s), 1.71-1.75 (2H, m), 1.25-1.30 (2H, m), 0.85 (3H, t, *J* = 7.2 Hz)

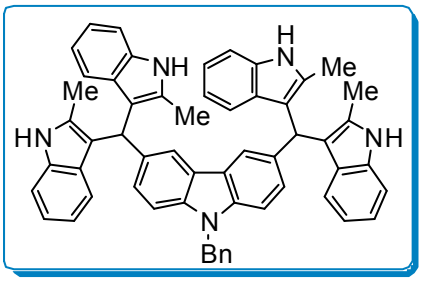
^{13}C NMR (100 MHz) *δ*: 142.1, 138.0, 134.9, 132.4, 131.4, 129.6, 126.2, 124.9, 122.4, 121.5, 120.8, 116.1, 113.3, 111.5, 65.1, 45.1, 33.7, 22.8, 16.7, 14.9

LC-MS (m/z): 766 ($M-H^+$)

Anal. Calcd. for $C_{54}H_{49}N_5$: C, 84.45; H, 6.43; N, 9.12%
Found: C, 84.39; H, 6.41; N, 9.35%

3,6-Di[di(2-methyl-1*H*-3-indolyl)methyl]-9-benzyl-9*H*-carbazole (297l):

The title compound **297l** was prepared from 9-benzylcarbazol-3,6-dicarboxaldehyde **295d** (0.31g, 1.0 mmol) and 2-methylindole **296c** (0.52g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 69%

Mp: 252-253 °C

IR (KBr) ν_{max} cm^{-1}: 3393, 3049, 1604, 1554, 1489, 1456, 1302, 1209, 1014, 925

^{1}H NMR (400 MHz) *δ*: 10.66 (4H, s), 7.77 (2H, s), 7.48 (2H, d, *J* = 8.5 Hz), 7.15-7.27 (11H, m), 6.77-6.88 (8H, m), 6.61 (4H, t, *J* = 7.3 Hz), 6.06 (2H, s), 5.59 (2H, s), 2.02 (12H, s)

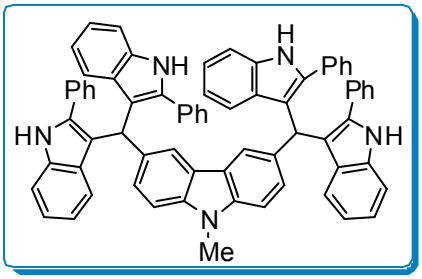
^{13}C NMR (100 MHz) *δ*: 139.5, 138.1, 135.3, 133.2, 132.1, 128.7, 127.2, 127.1, 122.4, 119.9, 119.7, 118.8, 118.1, 113.4, 110.5, 109.0, 79.3, 46.1, 12.2

LC-MS (m/z): 802 ($M+H^+$)

Anal. Calcd. for $C_{57}H_{47}N_5$: C, 85.36; H, 5.91; N, 8.73%
Found: C, 85.41; H, 5.79; N, 8.79%

3,6-Di[di(2-phenyl-1*H*-3-indolyl)methyl]-9-methyl-9*H*-carbazole (297m):

The title compound **297m** was prepared from 9-methylcarbazol-3,6-dicarboxaldehyde **295a** (0.24g, 1.0 mmol) and 2-phenylindole **296d** (0.77g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 64%

Mp: 148-149 °C

IR (KBr) ν_{max} cm^{-1}: 3353, 3059, 1664, 1591, 1487, 1361, 1091, 807, 742

^{1}H NMR (400 MHz) δ: 11.52 (4H, s), 8.01 (2H, s), 7.44 (2H, d, *J* = 8.3 Hz), 7.49 – 7.62 (14H, m), 7.41 (12H, m), 6.98 (4H, t, *J* = 7.3 Hz), 6.88 (4H, d, *J* = 7.4 Hz), 6.62 (4H, t, *J* = 7.2 Hz), 6.19 (2H, s), 3.93 (3H, s)

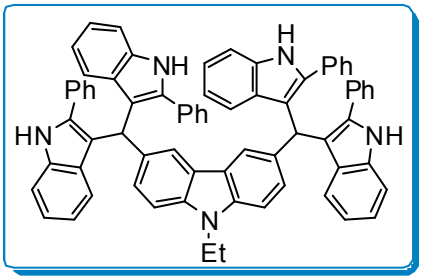
^{13}C NMR (100 MHz) δ: 140.5, 136.8, 133.9, 132.0, 131.9, 129.1, 128.8, 128.7, 128.6, 127.7, 121.4, 121.3, 119.0, 115.3, 111.9, 110.9, 79.6, 36.3

LC-MS (m/z): 972 ($M-H^+$)

Anal. Calcd. for $C_{71}H_{51}N_5$: C, 87.53; H, 5.28; N, 7.19%
Found: C, 87.46; H, 5.13; N, 7.30%

3,6-Di[di(2-phenyl-1*H*-3-indolyl)methyl]-9-ethyl-9*H*-carbazole (297n):

The title compound **297n** was prepared from 9-ethylcarbazol-3,6-dicarboxaldehyde **295b** (0.25g, 1.0 mmol) and 2-phenylindole **296d** (0.77g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 61%

Mp: 173-174 °C

IR (KBr) ν_{max} cm^{-1}: 3350, 3055, 1616, 1593, 1450, 1304, 1249, 1097, 808

^{1}H NMR (400 MHz) δ: 11.28 (4H, s), 8.02 (2H, s), 7.76 (2H, d, *J* = 8.4 Hz), 7.35 – 7.51 (14H, m), 7.21 (12H, s), 7.03 (4H, d, *J* = 7.6 Hz), 6.96 (4H, t, *J* = 7.2 Hz), 6.67 (4H, t, *J* = 7.4 Hz), 6.21 (2H, s), 4.36 (2H, q, *J* = 5.6 Hz), 1.42 (3H, t, *J* = 6.7 Hz)

^{13}C NMR (100 MHz) δ: 141.7, 139.2, 138.7, 138.0, 135.9, 131.4, 131.3, 131.1, 130.0, 129.6, 125.4, 123.8, 123.3, 121.4, 118.2, 114.2, 79.3, 38.8, 16.9

LC-MS (m/z): 986 ($M-H^+$)

Anal. Calcd. for $C_{72}H_{53}N_5$: C, 87.51; H, 5.41; N, 7.09%

Found: C, 87.27; H, 5.63; N, 7.23%

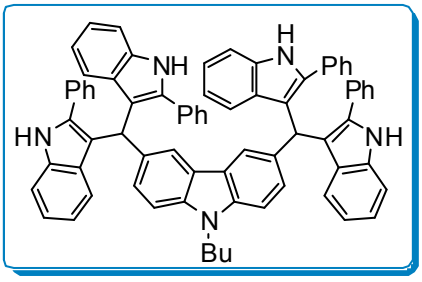
3,6-Di[di(2-phenyl-1*H*-3-indolyl)methyl]-9-*n*-butyl-9*H*-carbazole (297o):

The title compound **297o** was prepared from 9-butylcarbazol-3,6-dicarboxaldehyde **295c** (0.28g, 1.0 mmol) and 2-phenylindole **296d** (0.77g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 60%

Mp: 152-153 °C

IR (KBr) ν_{max} cm^{-1}: 3395, 3055, 2957, 2870, 1670, 1599, 1452, 1211, 1099, 922, 742

^{1}H NMR (400 MHz) δ: 

11.20 (4H, s), 7.67 (2H, s), 7.43 (2H, d, *J* = 8.4 Hz), 7.27 –7.33 (14H, m), 7.14 (12H, s), 6.96 (4H, t, *J* = 7.3 Hz), 6.86 (4H, d, *J* = 7.6 Hz), 6.59 (4H, t, *J* = 7.2 Hz), 6.13 (2H, s), 4.31 (2H, t, *J* = 7.2 Hz), 1.74-1.79 (2H, m), 1.31-1.38 (2H, m), 0.89 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (100 MHz) δ: 139.4, 136.4, 133.9, 135.2, 133.2, 128.7, 128.3, 127.2, 126.9, 122.5, 121.0, 120.4, 118.6, 115.5, 111.5, 108.7, 79.6, 42.5, 31.02, 20.1, 13.9

LC-MS (m/z): 1014 ($M-H^+$)

Anal. Calcd. for $C_{74}H_{57}N_5$: C, 87.46; H, 5.65; N, 6.89%

Found: C, 87.49; H, 5.68; N, 6.82%

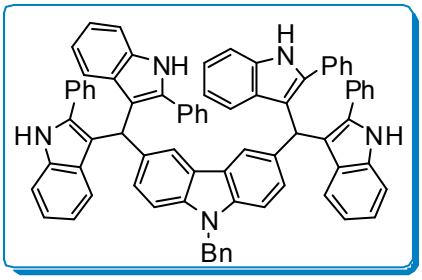
3,6-Di[di(2-phenyl-1*H*-3-indolyl)methyl]-9-benzyl-9*H*-carbazole (297p):

The title compound **297p** was prepared from 9-benzylcarbazol-3,6-dicarboxaldehyde **295d** (0.31g, 1.0 mmol) and 2-phenylindole **296d** (0.77g, 4.0 mmol) by following the *general procedure L.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 62%

Mp: 215-216 °C

IR (KBr) ν_{max} cm^{-1}: 3393, 3053, 2957, 1670, 1483, 1300, 1230, 1072, 798, 742



^{1}H NMR (400 MHz) δ: 11.21 (4H, s), 7.7 (2H, s), 7.52 (2H, d, *J* = 8.4 Hz), 7.27–7.33 (19H, m), 7.13 - 7.14 (12H, s), 6.96 (4H, t, *J* = 7.6 Hz), 6.84 (4H, d, *J* = 8.0 Hz), 6.60 (4H, t, *J* = 7.2 Hz), 6.15 (2H, s), 5.58 (2H, s)

^{13}C NMR (100 MHz) δ: 139.9, 138.4, 136.7, 136.5, 135.5, 133.5, 129.0, 128.9, 128.6, 127.8, 127.7, 127.5, 127.3, 123.0, 121.3, 120.9, 118.9, 115.7, 111.7, 109.3, 79.7, 46.4

LC-MS (m/z): 1049 ($M-H^+$)

Anal. Calcd. for $C_{77}H_{55}N_5$: C, 88.05; H, 5.28; N, 6.67%

Found: C, 88.10; H, 5.27; N, 6.90%

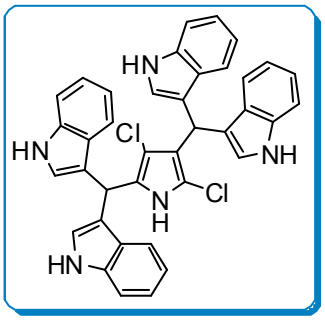
General procedure M

A mixture of 3,5-dichloro-pyrrol-2,4-dicarboxaldehydes **303a-b** (1·0 mmol), indoles **296a-h** (4·0 mmol) and TPP triflate (20 mol%) in chloroform (15 mL) was stirred at room temperature for required time. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude materials were subjected to column chromatography by using silica gel (100-200 mesh size) and eluted with ethyl acetate/hexanes mixture to obtain the pure products.

3-[3,5-Dichloro-4-di(1*H*-indolyl)methyl-1*H*-2-pyrrol(di(1*H*-3-indolyl)methyl]-1*H*-indole (304a):

The compound **304a** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and indole **296a** (0.47g, 4.0 mmol) by following the

general procedure M. The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 74%

Mp: 127-128 °C

IR (KBr) ν_{max} cm^{-1}: 3402, 1655, 1554, 1456, 1336, 1217, 1093, 740, 582, 449, 420

^{1}H NMR (400 MHz) δ: 11.35 (1H, s), 10.87 (2H, s), 10.76 (2H, s), 7.37-7.29 (8H, m), 7.06 (4H, q, *J* = 7.6 Hz), 6.95 – 6.85 (8H, m), 5.90 (1H, s), 5.80 (1H, s)

^{13}C NMR (100 MHz) δ: 136.6, 135.4, 131.9, 127.2, 126.7, 124.0, 123.8, 121.6, 119.9, 119.6, 119.4, 119.1, 118.9, 118.7, 118.3, 116.8, 116.2, 111.4, 110.6, 106.9, 65.8

LC-MS (m/z): 624 (M), 626 (M+2), 628 (M+4)

Anal. Calcd for $C_{38}H_{27}N_5Cl_2$: C, 73.08; H, 4.36; N, 11.21%

Found: C, 73.00; H, 4.37; N, 11.42%

3-[3,5-Dichloro-4-di(1-methyl-1*H*-indolyl)methyl-1*H*-2-pyrrol(di(1-methyl-1*H*-3-indolyl)methyl]-1-methyl-1*H*-indole (304b):

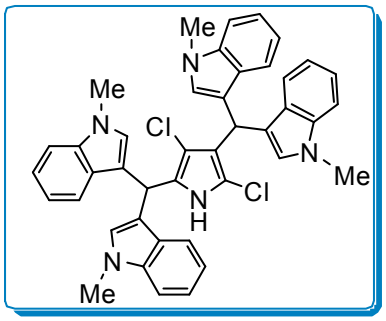
The compound **304b** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and 1-methylindole **296b** (0.52g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 72%

Mp: 132-133 °C

IR (KBr) ν_{max} cm^{-1}: 3425, 2926, 1736, 1660, 1612, 1467, 1369, 1327, 1226, 1118, 1012, 802

^{1}H NMR (400 MHz) δ: 11.36 (1H, s), 7.40 – 7.30 (8H, m), 7.14 (4H, q, *J* = 7.5 Hz), 6.95 – 6.85 (8H, m), 5.89 (1H, s), 5.80 (1H, s), 3.70 (12H, d, *J* = 5.2 Hz)



^{13}C NMR (100 MHz) δ: 137.25, 137.20, 129.8, 128.5, 127.5, 127.2, 126.6, 122.2, 121.6, 121.4, 119.3, 119.1, 119.0, 117.7, 115.7, 115.6, 115.1, 113.5, 110.1, 110.0, 67.3, 32.84, 32.80

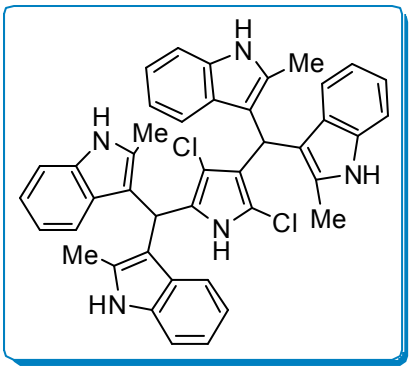
LC-MS (m/z): 680 (M), 682 (M+2), 684 (M+4)

Anal. Calcd. for $C_{42}H_{35}N_5Cl_2$: C, 74.11; H, 5.18; N, 10.29%

Found: C, 74.27; H, 5.13; N, 10.29%

3-[3,5-Dichloro-4-di(2-methyl-1*H*-indolyl)methyl-1*H*-2-pyrrol(di(2-methyl-1*H*-3-indolyl)methyl]-2-methyl-1*H*-indole (304c):

The compound **304c** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and 2-methylindole **296c** (0.52g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 70%

Mp: 149-150 ^oC

IR (KBr) ν_{max} cm^{-1}: 3402, 3053, 2968, 2852, 1699, 1618, 1558, 1487, 1460, 1338, 1219, 738

^{1}H NMR (400 MHz) δ: 10.13 (2H, s), 9.93 (2H, s), 9.46 (1H, s), 7.24 – 7.21 (4H, m), 7.04 (2H, d, *J* = 8.0 Hz), 6.94 –

6.89 (6H, m), 6.76 (4H, t, *J* = 7.6 Hz), 5.94 (1H, s), 5.92 (1H, s), 1.97 (12H, d, *J* = 2.0 Hz)

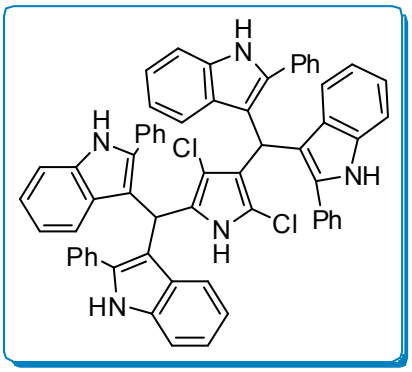
^{13}C NMR (100 MHz) *δ*: 136.2, 133.6, 130.1, 129.5, 128.4, 127.3, 127.1, 126.6, 126.3, 122.2, 121.7, 120.9, 120.5, 119.6, 119.4, 119.2, 119.1, 119.0, 111.7, 110.2, 66.5, 13.0, 12.8

LC-MS (m/z): 680 (M), 682 (M+2), 684 (M+4)

Anal. Calcd. for $C_{42}H_{35}N_5Cl_2$: C, 74.11; H, 5.18; N, 10.29%
Found: C, 74.28; H, 5.17; N. 10.38%

3-[3,5-Dichloro-4-di(2-phenyl-1*H*-indolyl)methyl-1*H*-2-pyrrol(di(2-phenyl-1*H*-3-indolyl)methyl]-2-phenyl-1*H*-indole (304d):

The compound **304d** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and 2-phenylindole **296d** (0.77g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 59%

Mp: 167-168 °C

IR (KBr) ν_{max} cm^{-1}: 3398, 3055, 1707, 1602, 1487, 1452, 1371, 1305, 1251, 1041, 844, 738

^{1}H NMR (400 MHz) *δ*: 11.35 (1H, s), 11.20 (1H, s), 11.10 (1H, s), 11.07 (2H, d, *J* = 8.4 Hz), 7.43 – 7.41 (4H, m), 7.33 – 7.05 (10H, m), 7.21 – 6.88 (20H, m), 6.64 – 6.59 (2H, m), 5.73 (2H, s)

^{13}C NMR (100 MHz) *δ*: 136.5, 136.4, 135.9, 135.7, 135.2, 133.6, 133.3, 130.6, 129.8, 129.6, 129.0, 128.7, 128.5, 128.2,

127.4, 127.1, 121.8, 121.1, 120.9, 120.2, 119.3, 119.0, 118.6, 114.3, 113.9, 112.6, 111.6, 110.4, 67.2

LC-MS (m/z): 928 (M), 930 (M+2), 932 (M+2)

Anal. Calcd. for $C_{62}H_{43}N_5Cl_2$: C, 80.16; H, 4.67; N, 7.54%
Found: C, 80.22; H, 4.65; N, 7.81%

3-[3,5-Dichloro-4-di(2-phenyl-1*H*-indolyl)methyl-1-methyl-1*H*-2-pyrrol(di(2-phenyl-1*H*-3-indolyl)methyl]-2-phenyl-1*H*-indole (304e):

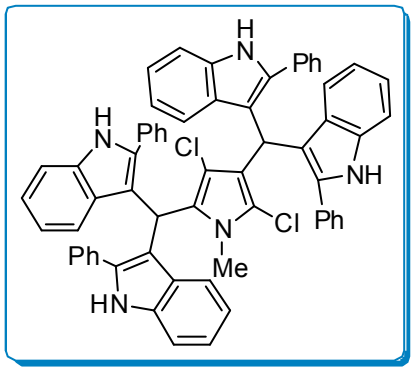
The compound **304e** was prepared from 3,5-dichloro-pyrrol-1-methyl-2,4-dicarboxaldehyde **303b** (0.20g, 1.0 mmol) and 2-phenylindole **296d** (0.77g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 56%

Mp: 143-144 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3402, 3051, 2922, 1716, 1602, 1550, 1454, 1305, 1242, 1014, 740

^{1}H NMR (400 MHz) δ: 11.30-11.23 (4H, m), 7.43 (3H, s), 7.41 – 7.28 (15H, m), 7.17 – 6.95 (16H, m), 6.57 – 6.38 (2H, m), 5.85 (1H, s), 5.72 (1H, s), 2.89 (3H, d, *J* = 12.9 Hz)



^{13}C NMR (100 MHz) δ: 136.5, 136.4, 135.9, 135.7, 135.2, 133.6, 133.2, 130.6, 129.5, 129.0, 128.9, 128.8, 128.77,

128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 121.1, 120.1, 118.6, 114.5, 113.5, 111.7, 110.9, 67.5, 34.3

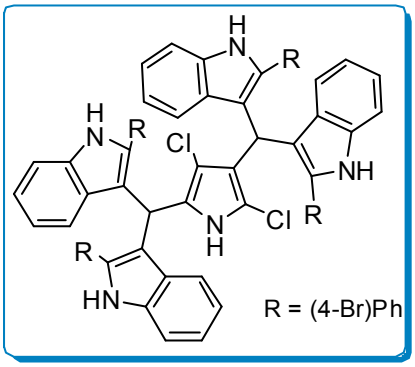
LC-MS (m/z): 942 (M), 944 (M+2), 946 (M+4)

Anal. Calcd. for $C_{63}H_{45}N_5Cl_2$: C, 80.24; H, 4.81; N, 7.43%

Found: C, 80.22; H, 4.82; N, 7.37%

3-[3,5-Dichloro-4-di(2-(4-bromophenyl)-1*H*-indolyl)methyl-1*H*-2-pyrrol(di(2-(4-bromophenyl)-1*H*-3-indolyl)methyl]-2-(4-bromophenyl)-1*H*-indole (304f):

The compound **304f** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and 2-(4-bromophenyl)indole **296e** (1.1g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 61%

Mp: 173-174 °C

IR (KBr) ν_{max} cm^{-1}: 3431, 3393, 3053, 2953, 1890, 1575, 1483, 1454, 1429, 1388, 1242, 744

^{1}H NMR (400 MHz) δ: 11.32 (1H, s), 11.20 (1H, s), 11.10 (1H, s), 11.04 (2H, s), 7.45 – 7.40 (16H, m), 7.21 – 7.04 (5H, m), 6.93 – 6.88 (4H, m), 6.73 – 6.69 (7H, m), 5.55 (2H, s)

^{13}C NMR (100 MHz) δ: 139.6, 139.1, 137.4, 136.5, 135.1, 134.8, 134.1, 133.8, 133.0, 132.6, 132.0, 131.8, 131.5, 126.2, 124.2, 124.0, 123.9, 123.2, 122.8, 122.0, 121.7, 121.4, 116.9, 115.8, 115.0, 114.4, 113.0, 111.0, 62.8

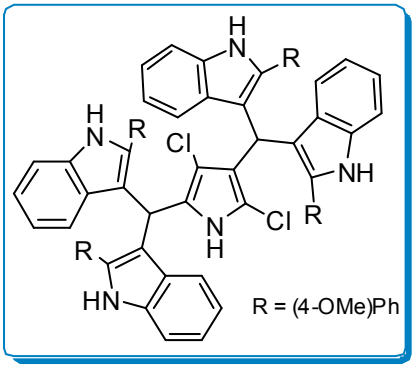
LC-MS (m/z): 1244 (M), 1246 (M+2), 1248 (M+4)

Anal. Calcd. for $C_{62}H_{39}N_5Cl_2Br_4$: C, 59.83; H, 3.16; N, 5.63%

Found: C, 59.99; H, 3.12; N. 5.56%

3-[3,5-Dichloro-4-di(2-(4-methoxyphenyl)-1*H*-indolyl)methyl-1*H*-2-pyrrol(di(2-(4-methoxyphenyl)-1*H*-3-indolyl)methyl]-2-(4-methoxyphenyl)-1*H*-indole (304g):

The compound **304g** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and 2-(4-methoxyphenyl)indole **296f** (0.89g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 58%

Mp: 163-162 °C

IR (KBr) ν_{max} cm^{-1}: 3398, 3051, 1702, 1607, 1477, 1439, 1370, 1319, 1251, 1061, 842, 738

^{1}H NMR (400 MHz) δ: 11.32 (1H, s), 11.20 (1H, s), 11.10 (1H, s), 11.04 (2H, s), 7.43 – 7.39 (16H, m), 7.19 – 7.01 (5H, m), 6.99 – 6.89 (4H, m), 6.71 – 6.50 (7H, m), 5.55 (2H, s), 3.66 (6H, s), 3.63 (6H, s)

^{13}C NMR (100 MHz) δ: 142.5, 138.8, 138.2, 134.6, 132.5, 132.0, 128.1, 126.7, 124.2, 123.3, 122.6, 121.8, 121.3, 120.1, 119.3, 118.8, 117.6, 116.7, 116.5, 116.1, 115.7, 115.0, 114.3, 114.1, 113.9, 113.0, 113.7, 111.0, 67.4, 58.4, 58.0

LC-MS (m/z): 1049 (M), 1051 (M+2), 1053 (M+4)

Anal. Calcd. for $C_{66}H_{51}N_5Cl_2O_4$: C, 75.56; H, 4.90; N, 6.68%

Found: C, 75.64; H, 4.99; N, 6.541%

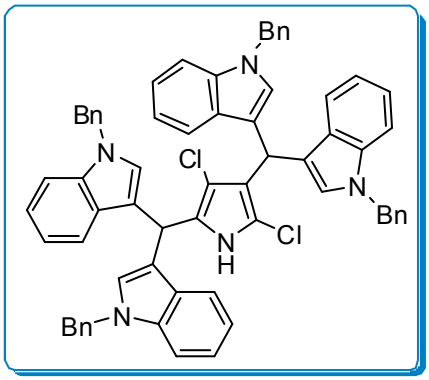
3-[3,5-Dichloro-4-di(1-benzyl-1*H*-indolyl)methyl-1*H*-2-pyrrol(di(1-benzyl-1*H*-3-indolyl)methyl]-1-benzyl-1*H*-indole (304h):

The compound **304h** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and 1-benzylindole **296g** (0.83g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 59%

Mp: 139-140 ^{o}C

IR (KBr) ν_{max} cm^{-1}: 3734, 3055, 2957, 2860, 1651, 1572, 1452, 1331, 1172, 1014, 881, 787



^{1}H NMR (400 MHz) δ: 7.52 (2H, d, J = 7.76 Hz), 7.37 (2H, d, J = 8.04 Hz), 7.23-6.89 (32H, m), 6.94–6.95 (5H, m), 6.03 (2H, s), 5.21 (4H, d, J = 5.16 Hz), 5.17 (4H, d, J = 2.36 Hz)

^{13}C NMR (100 MHz) δ: 138.9, 138.8, 137.6, 136.7, 129.4, 128.9, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.3, 127.1, 121.7, 121.5, 119.6, 119.5, 119.2, 119.0, 117.5, 116.0, 115.6, 113.2, 110.6, 110.5, 110.2, 107.7, 68.2, 49.5, 49.4

LC-MS (m/z): 985 (M), 987 (M+2), 989 (M+4)

Anal. Calcd. for $C_{66}H_{51}N_5Cl_2$: C, 80.47; H, 5.22; N, 7.11%

Found: C, 80.56; H, 5.19; N. 7.41%

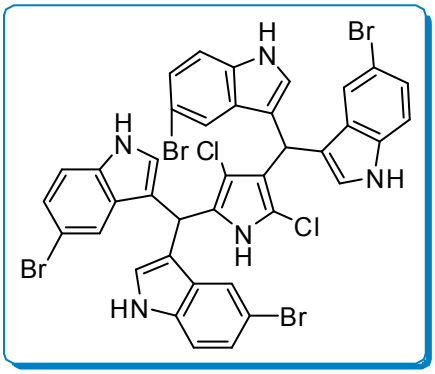
3-[3,5-Dichloro-4-di(5-bromo-1*H*-indolyl)methyl-1*H*-2-pyrrol(di(5-bromo-1*H*-3-indolyl)methyl]-5-bromo-1*H*-indole (304i):

The compound **304i** was prepared from 3,5-dichloro-pyrrol-2,4-dicarboxaldehyde **303a** (0.19g, 1.0 mmol) and 5-bromoindole **296h** (0.78g, 4.0 mmol) by following the *general procedure M.* The crude product was purified by silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 63%

Mp: 152-153 °C

IR (KBr) ν_{max} cm^{-1}: 3407, 1645, 1544, 1453, 1376, 1212, 1097, 760, 586, 439, 415



^{1}H NMR (400 MHz) δ: 11.33 (1H, s), 10.86 (2H, s), 10.78 (2H, s), 7.35-7.26 (8H, m), , 7.08 (4H, m), 6.95 – 6.85 (4H, m), 5.88 (1H, s), 5.82 (1H, s)

^{13}C NMR (100 MHz) δ: 136.4, 135.7, 131.7, 127.2, 126.3, 124.1, 123.9, 121.4, 120.1, 119.6, 119.3, 119.1, 118.6, 118.7, 118.3, 117.0, 116.2, 111.7, 110.6, 107.4, 65.7

LC-MS (m/z): 940 (M), 942 (M+2), 944 (M+4)

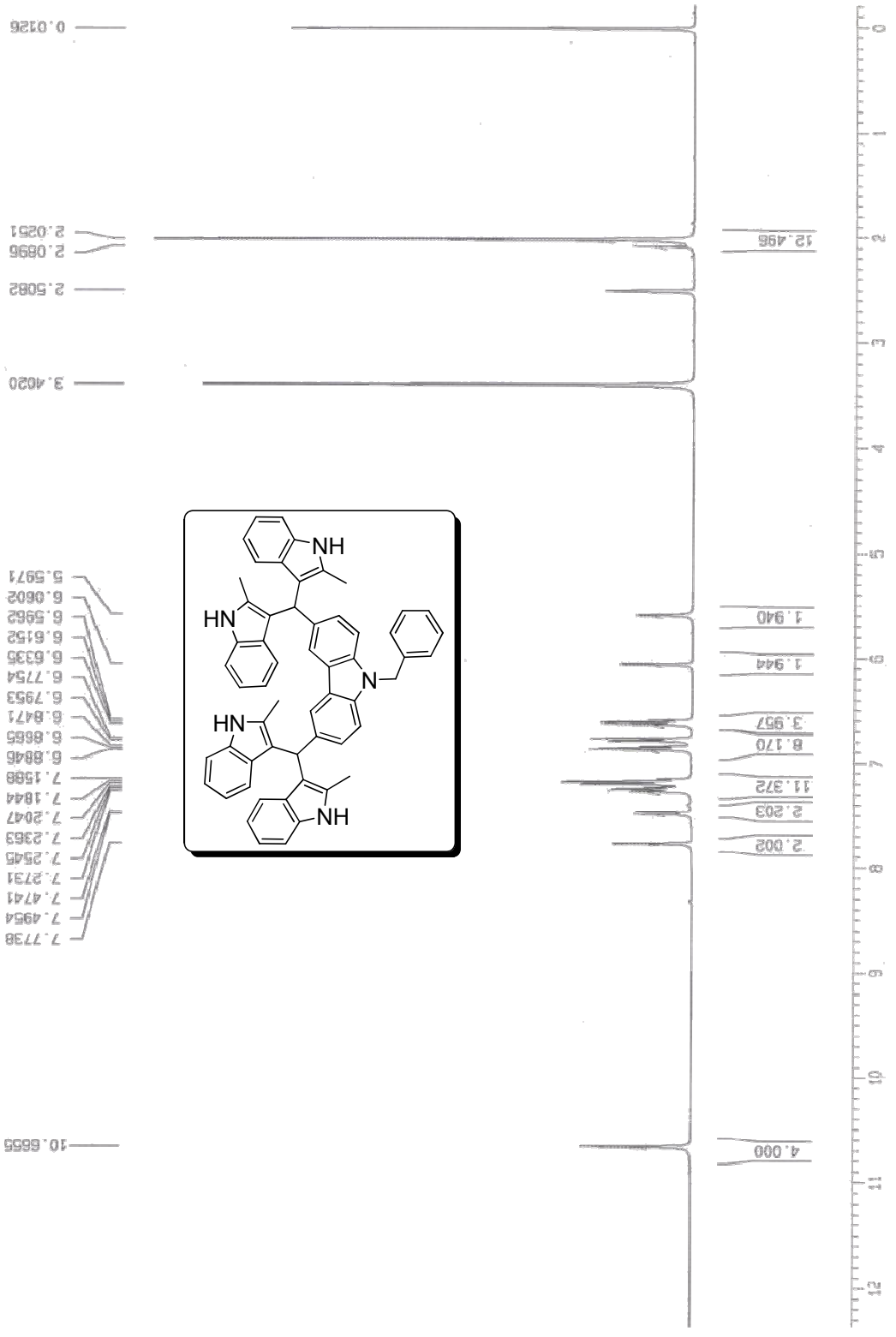
Anal. Calcd. for $C_{38}H_{23}N_5Br_4Cl_2$: C, 48.55; H, 2.47; N, 7.45%

Found: C, 48.31; H, 2.52; N, 7.40%

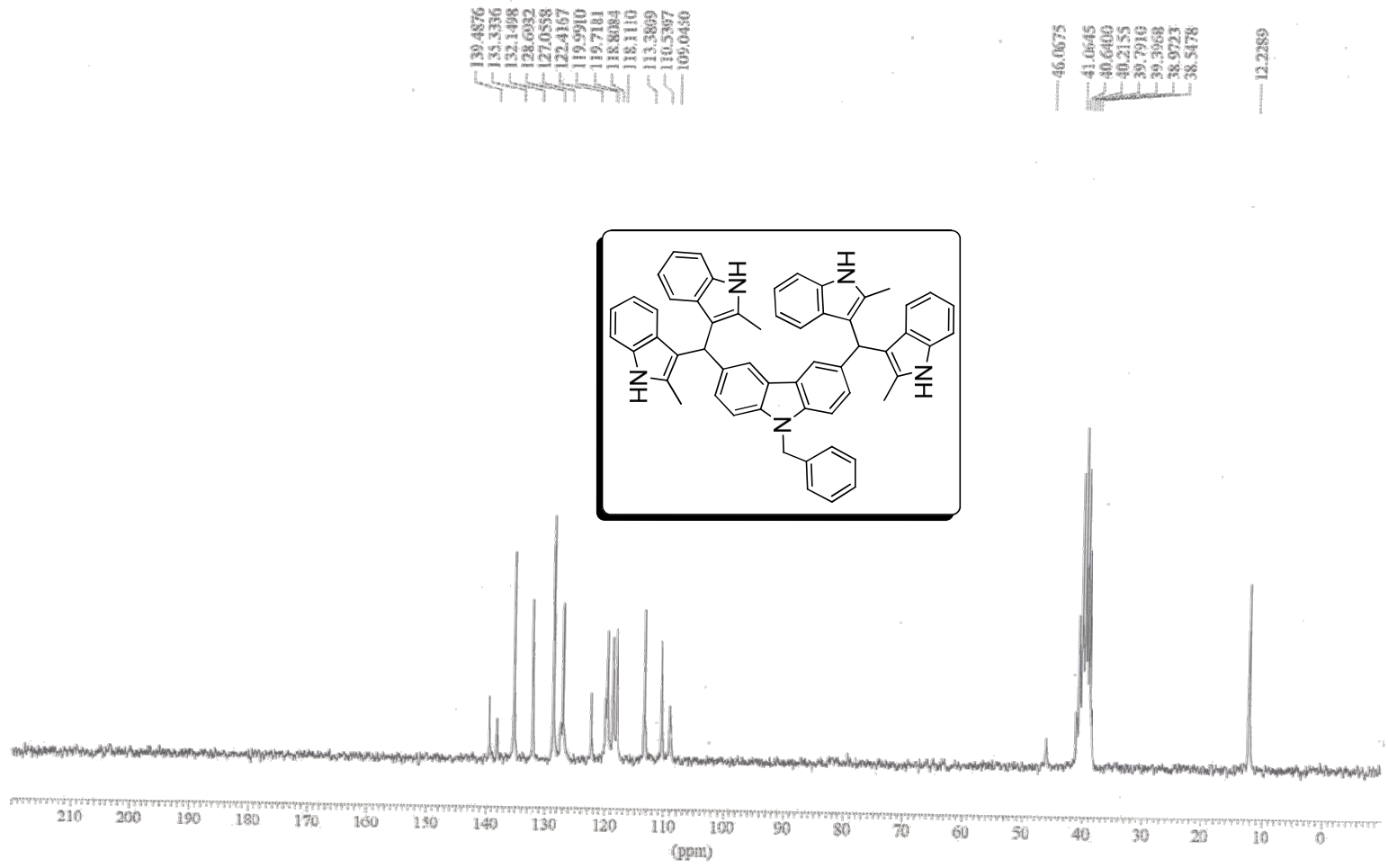
Table 23. Crystal data and structure refinement for 304e

Empirical formula	: $C_{71}H_{61}Cl_2N_5O_4$
Formula weight	: 1119.15
Temperature	: 298(2) K
Wavelength	: 0.71073 Å
Crystal system	: Monoclinic
Space group	: P2(1)/n
Unit cell dimensions	: a = 16.6198(10) Å, α = 90°
	: b = 21.5543(13) Å,
	β = 110.6790(10)°
	: c = 17.8697(10) Å, γ = 90°
Volume	: 5989.0(6) $Å^3$
Z	: 4
Density (calculated)	: 1.241 Mg/m^3
Absorption coefficient	: 0.163 mm^{-1}
F (000)	: 2352
Crystal size	: 0.26 x 0.22 x 0.10 mm
Theta range for data collection	: 1.54 to 25.00°
Index ranges	: -19<=h<=19, -25<=k<=25,
	-21<=l<=21
Reflections collected	: 51500
Completeness to theta = 25.00	: 100.0%
Absorption correction	: Semi-empirical from equivalents
Max. and min. transmission	: 0.9839 and 0.9589
Refinement method	: Full-matrix least-squares on F^2
Data / restraints / parameters	: 10557 / 0 / 739
Goodness-of-fit on F^2	: 1.041
Final R indices [I>2sigma(I)]	: R1 = 0.1061, wR2 = 0.2995
R indices (all data)	: R1 = 0.1856, wR2 = 0.3522
Largest diff. peak and hole	: 1.329 and -1.010 e. $Å^{-3}$
CCDC number	: 653448

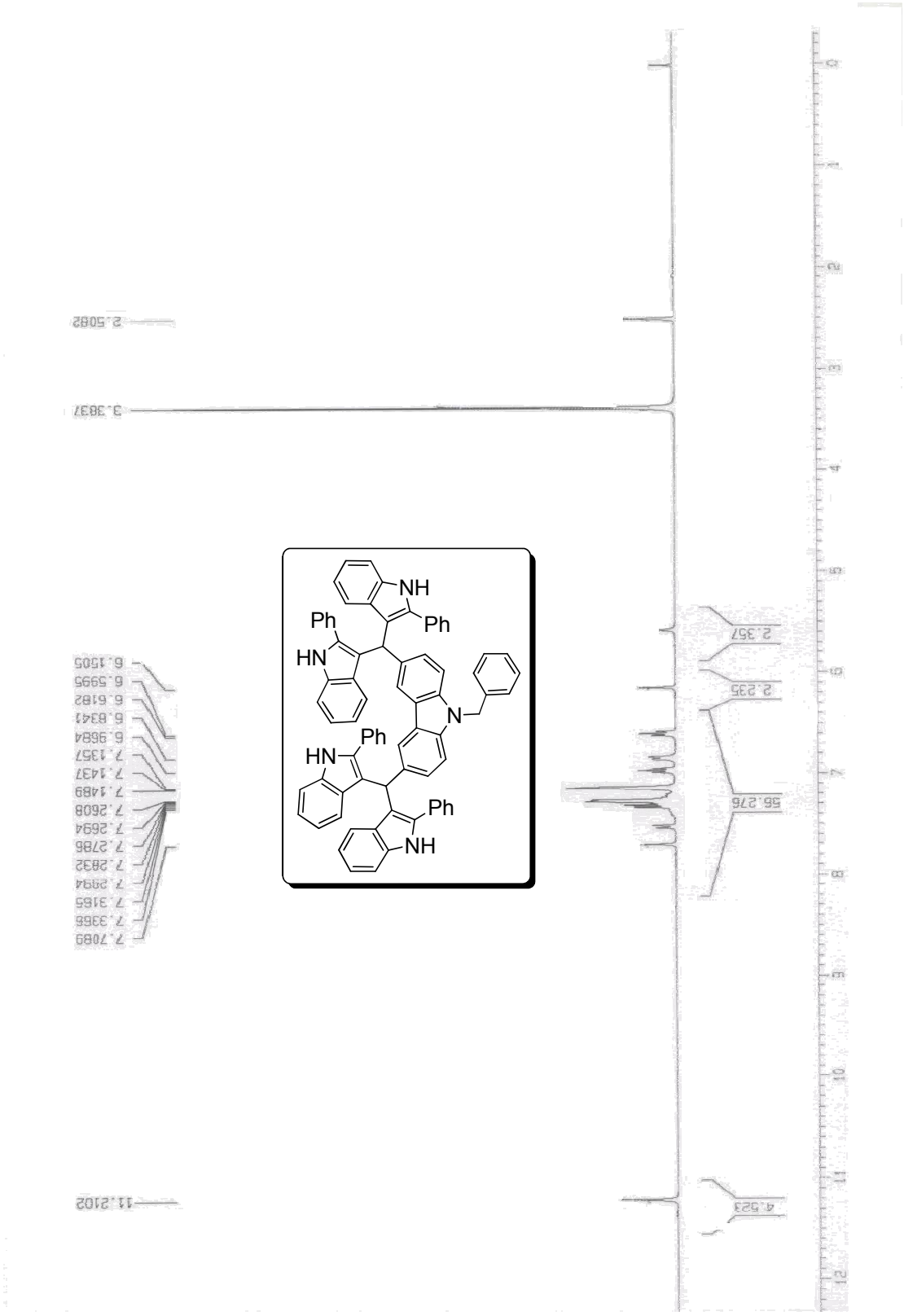
Spectrum 29. ^{1}H NMR of 297l



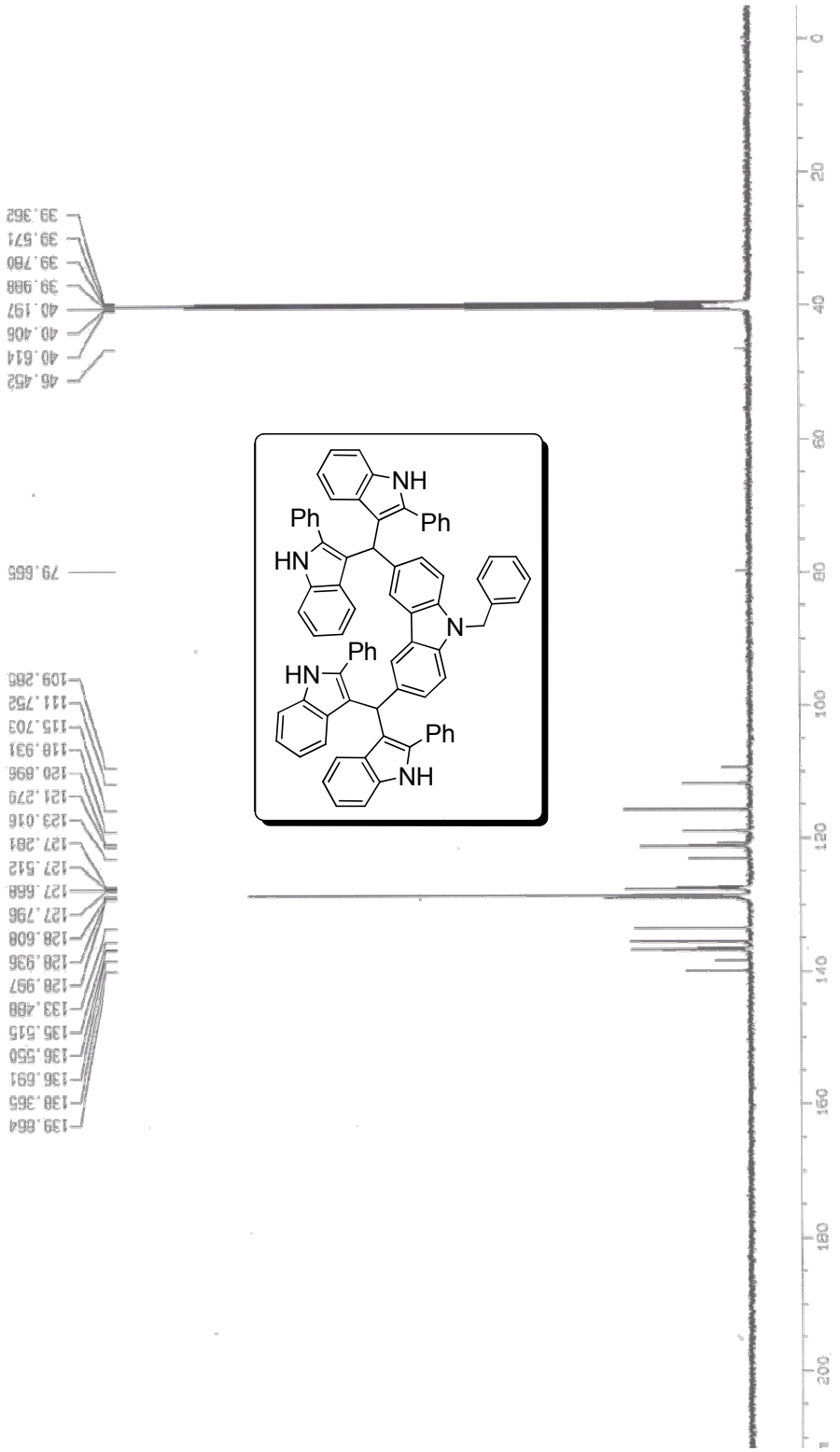
Spectrum 30. ^{13}C NMR of 297l



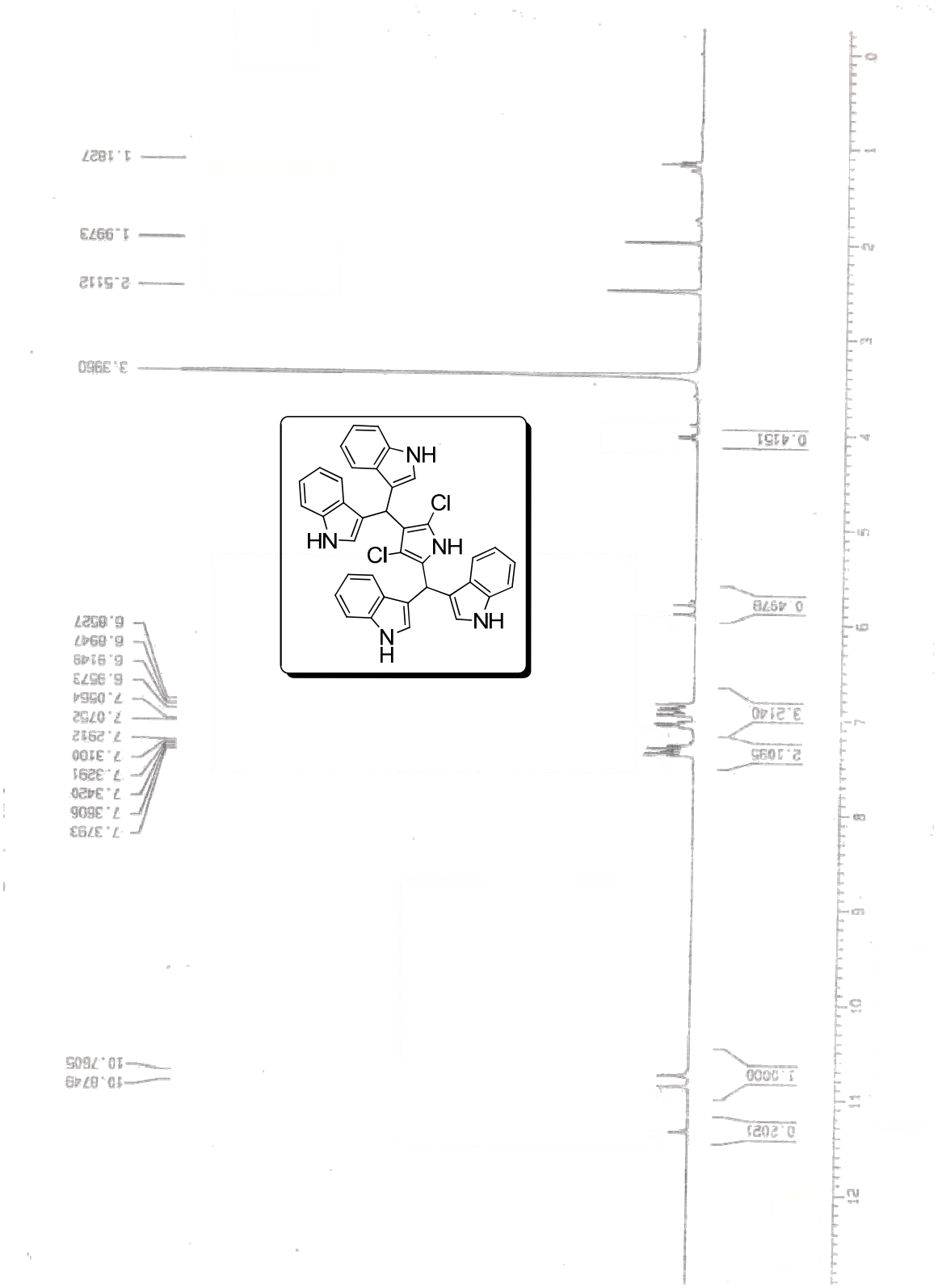
Spectrum 31. ^{1}H NMR of 297p



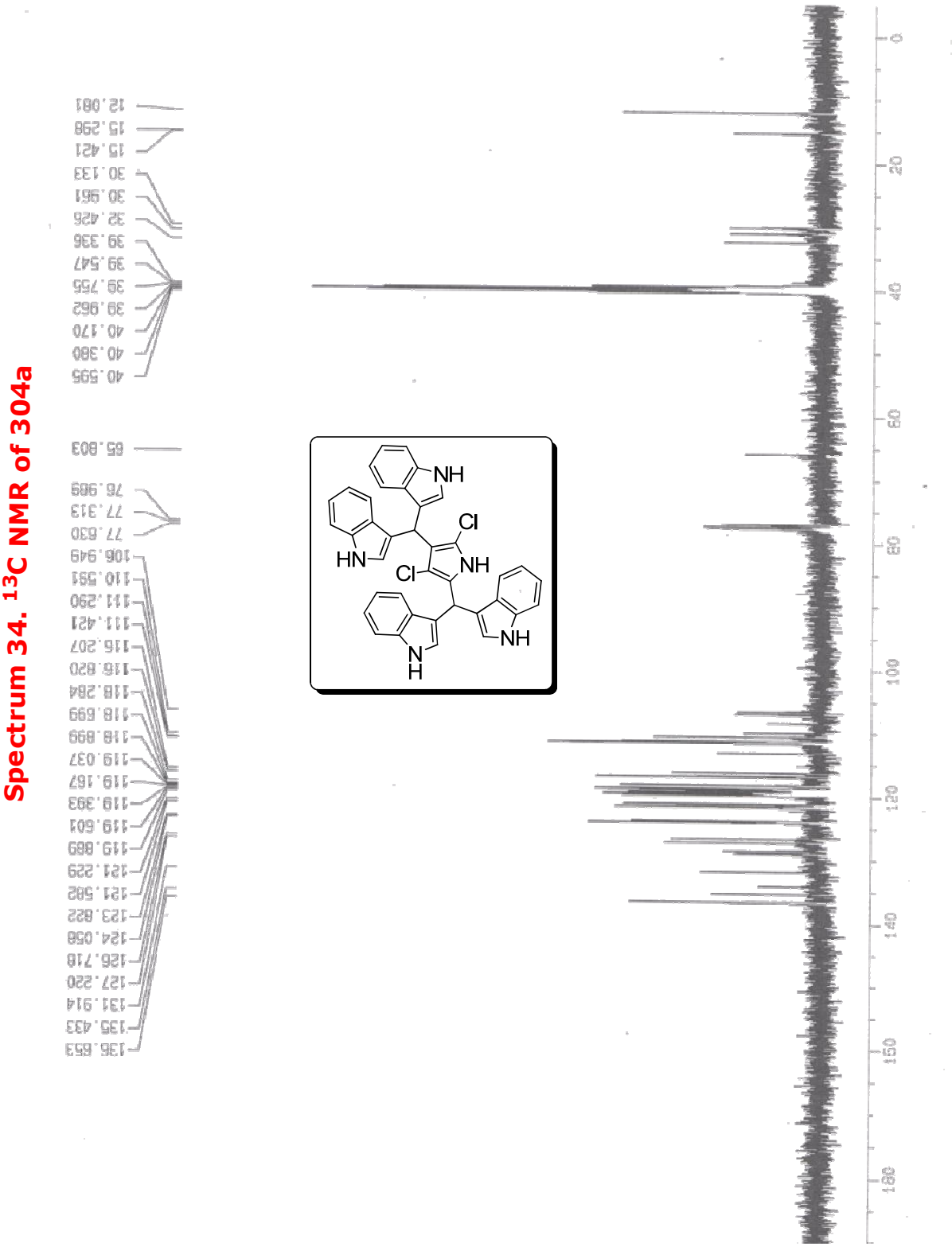
Spectrum 32. ^{13}C NMR of 297p



Spectrum 33. ^{1}H NMR of 304a



Spectrum 34. ^{13}C NMR of 304a



4.6. References

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Conclusions

We have made significant progress and achieved considerable success in our objectives on the synthesis of various heteroaryl-annulated carbazole and indole derivatives.

- We have synthesized biologically important compounds quinocarbazoles (**148a-e**, **149a-e**, **150a-e**) which are analogues to anti-cancer drug ellipticine via Ullmann-Goldberg condensation. We have also prepared chromenocarbazoles (**160a-d**) via this methodology . The same method also successfully extended to indole moiety. Thus, We have synthesized biologically important pyrroloacridones (**176a-f**) and pyrroloacridines (**177a-i**).

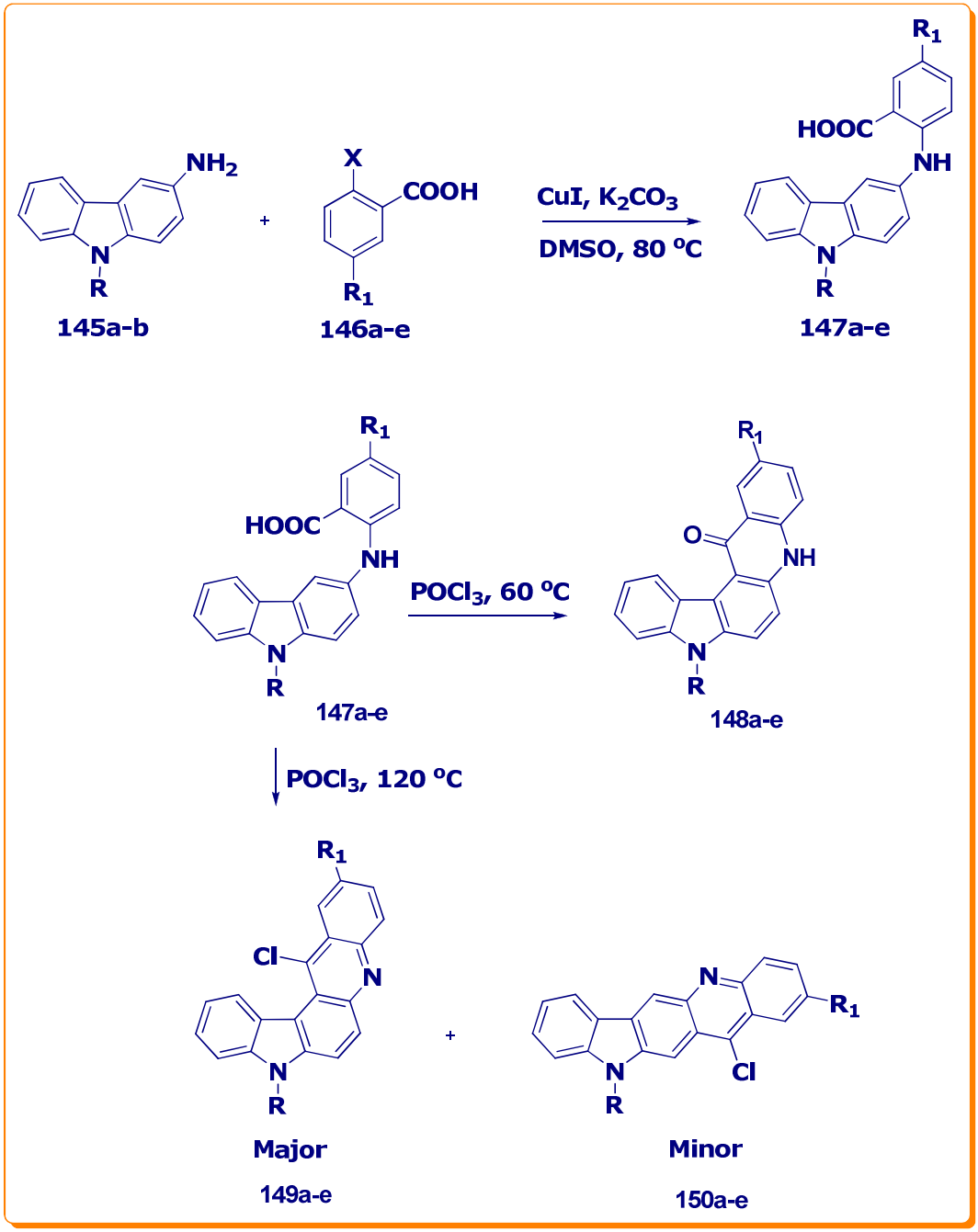
- We have developed a new and simple method for the synthesis of diindolophenazines (**205a-f**) by Cu(I)-catalyzed aerobic oxidative coupling of 3-aminocarbazoles. We have also synthesized dipyrrolophenazines (**207a-c**) by applying the same method to 5-aminoindole derivatives. These compounds may have significant biological properties. This type of compounds can also be used as the potential candidates for the Organic Light-Emitting Diods (OLEDs).

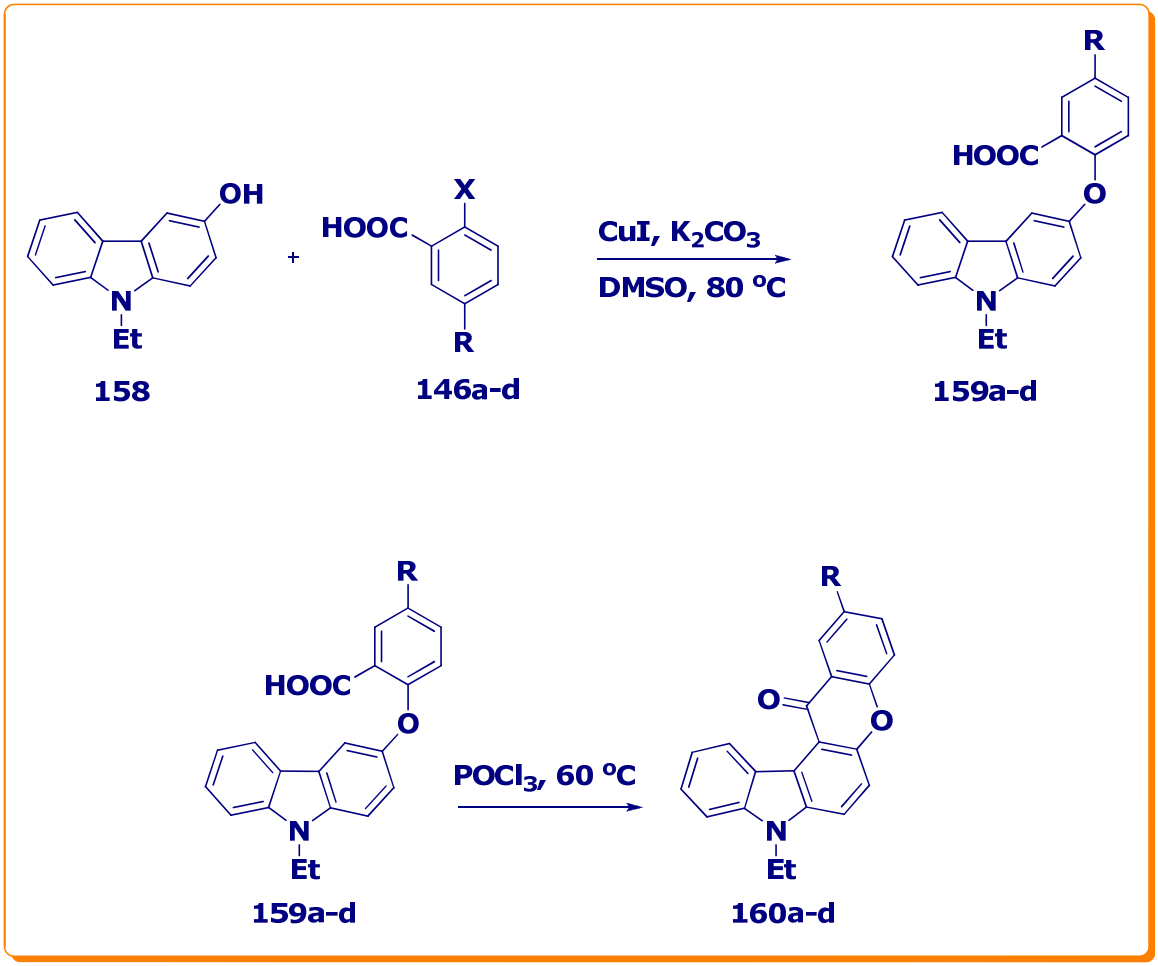
- We have prepared an interesting class of heteroaryl carbazoles namely 3,6-di(pyrazol-4-yl)carbazoles (**250a-d**) and 3,6-di(4-formyl-1-phenyl-1*H*-3-pyrazolyl)carbazoles (**252a-d**) compounds from easily available starting materials via a simple procedure. The methods are simple and straightforward starting from easily accessible starting materials.

- We have also prepared di(diindolylmethyl)carbazoles (**293a-p**) and di(diindolylmethyl)pyrroles (**300a-i**) in good yields. These compounds may contain significant biological properties. We have also explored the utility of di(diindolylmethyl)carbazole derivatives for the colorimetric and fluorometric detection of DNA.

Graphical Abstracts

Chapter 1. Synthesis of Quino, Chromenocarbazoles and Pyrroloacridines via Ullmann-Goldberg Condensation

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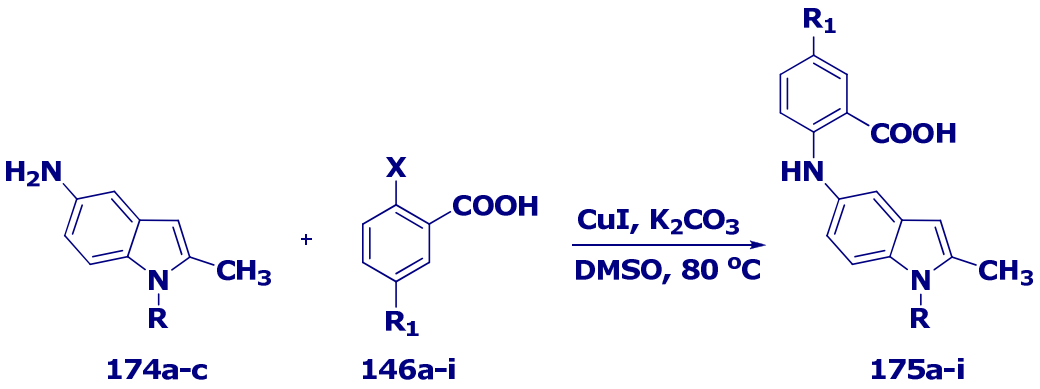
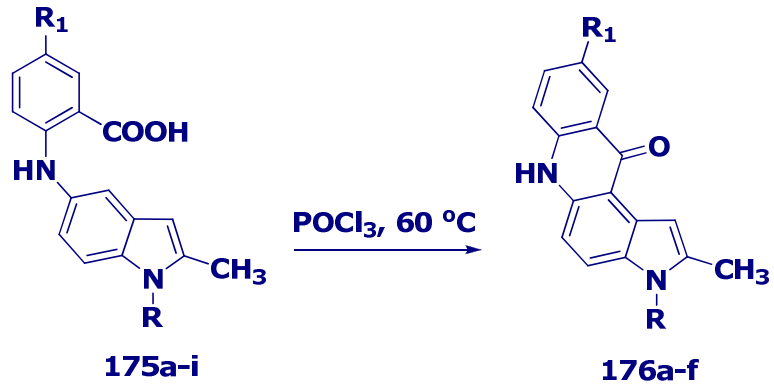
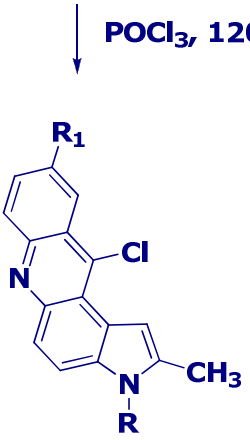
O
N
Et
160a-d



174a-c 146a-i 175a-i

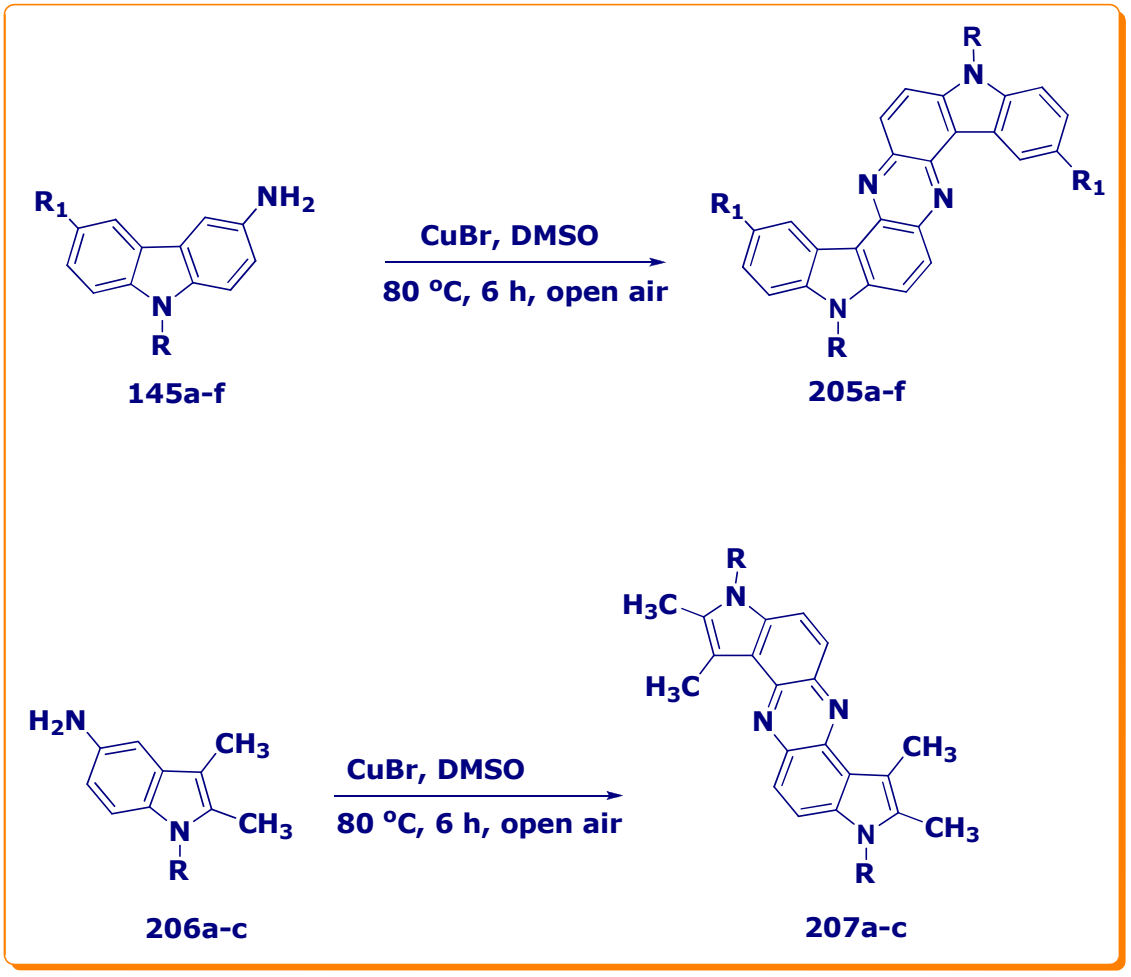


175a-i 176a-f

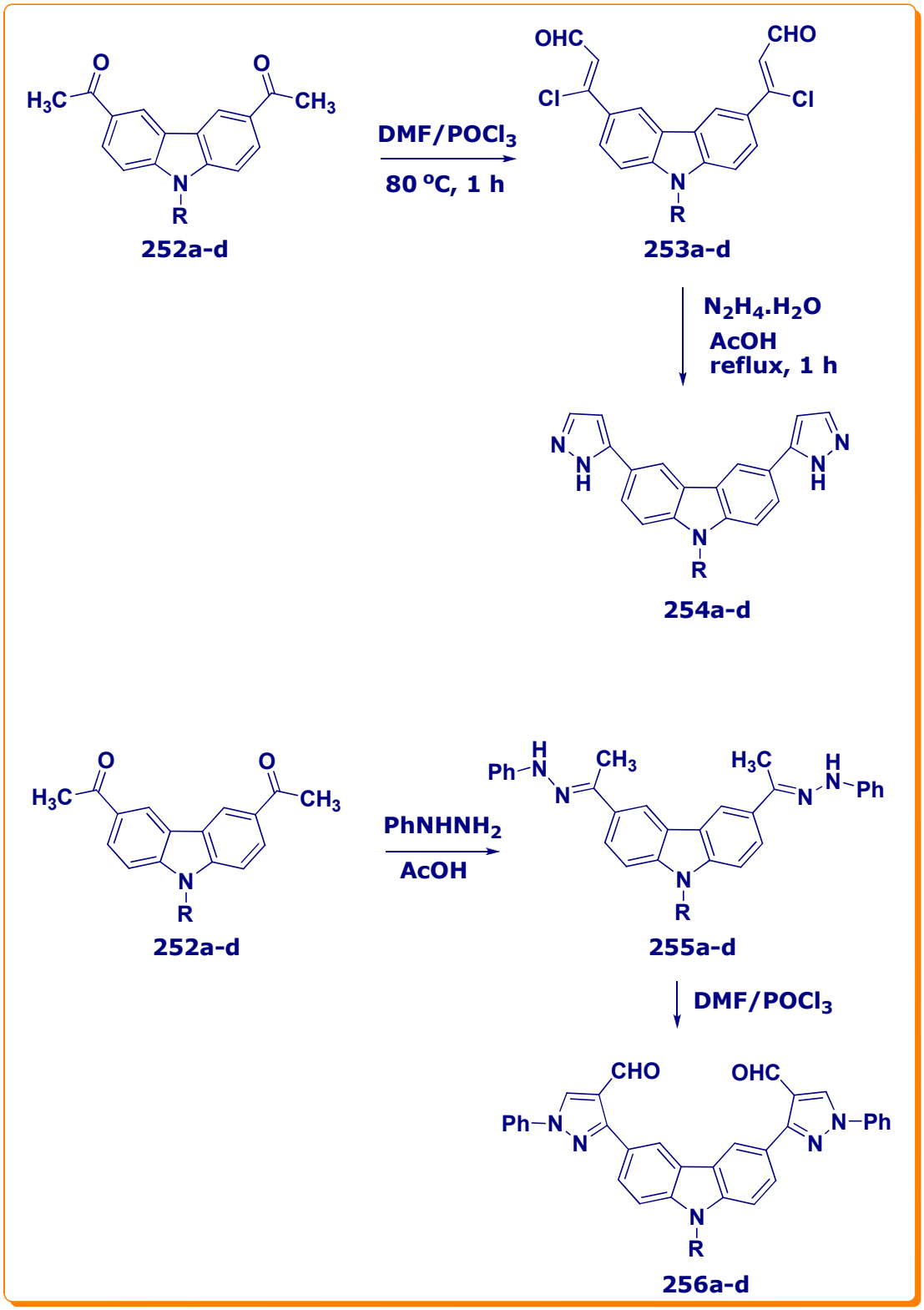


177a-i

Chapter 2. Synthesis of Diindolophenazines and Dipyrrolophenazines



Chapter 3. Synthesis of 3,6-Di(pyrazol-4-yl)carbazoles



Chapter 4.

Synthesis of New Di(diindolylmethyl)carbazoles and Di(diindolylmethyl)pyrroles