# SYNTHESIS OF HETEROARYL QUINOLINE, CARBOLINE AND BENZIMIDAZOLOPYRAZINE DERIVATIVES VIA CYCLIZATION REACTIONS WITH ALKYNE OR ALKENE

A Thesis
Submitted for the Degree of
Doctor of Philosophy

By

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## STATEMENT

I hereby declare that the matter embodied in this thesis entitled "**SYNTHESIS OF HETEROARYL QUINOLINE, CARBOLINE AND BENZIMIDAZOLOPYRAZINE DERIVATIVES VIA CYCLIZATION REACTIONS WITH ALKYNE OR ALKENE**" 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: **(S. RAMESH)**

Hyderabad

## CERTIFICATE

Certified that the work "**SYNTHESIS OF HETEROARYL QUINOLINE, CARBOLINE AND BENZIMIDAZOLOPYRAZINE DERIVATIVES VIA CYCLIZATION REACTIONS WITH ALKYNE OR ALKENE**" has been carried out by **S. RAMESH** under my supervision and that the same has not been submitted elsewhere for a degree.

**DEAN**

School of Chemistry
University of Hyderabad

**(Dr. R. NAGARAJAN)**

Thesis Supervisor

## LIST OF PUBLICATIONS

**1.** A Flexible Approach to the Chromenoquinoline Derivatives under Copper/Lewis acid Catalysis
**S. Ramesh**, V. Gaddam and R. Nagarajan, *Synlett* **2010**, 757.

**2.** CuI/La(OTf)$_3$ catalyzed, one-pot synthesis of isomeric ellipticine derivatives in ionic liquid
V. Gaddam, **S. Ramesh** and R. Nagarajan, *Tetrahedron* **2010**, *66*, 4218.

**3.** Efficient One-Pot Multicomponent Synthesis of Carbazolylamino)furan-2(5*H*)-one and Carbazolyltetrahydropyrimidine Derivatives
**S. Ramesh** and R. Nagarajan, *Synthesis* **2011**, 3307.

**4.** Synthesis of dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolines via intramolecular aza Diels–Alder reaction
**S. Ramesh** and R. Nagarajan, *Tetrahedron Lett.* **2011,** *52***,** 4857.

**5.** One-Pot Synthesis of Pyrrolo[3,2-*f*]- and Pyrrolo[2,3-*h*]quinoline Derivatives: Observation of an Unexpected Mechanistic Pathway
**S. Ramesh** and R. Nagarajan, *Synlett* **2012**, 717.

**6.** A Formal Synthesis of Lavendamycin Methyl Ester, Nitramarine, and their Analogues: A Povarov Approach
**S. Ramesh** and R. Nagarajan, *J. Org. Chem.* **2013**, *78*, 545.

**7.** A novel route to synthesize lavendamycin analogues through an $A^3$ coupling reaction
**S. Ramesh** and R. Nagarajan, *Tetrahedron* **2013**, *69*, 4890.

**8.** Copper catalyzed synthesis of fused benzimidazolopyrazine derivatives via tandem benzimidazole formation/annulation of δ-alkynyl aldehyde
**S. Ramesh**, S. K. Ghosh and R. Nagarajan, *Org. Biomol. Chem.* **2013**, *11*, 7712.

**9.** Synthesis of dihydroquinolino[2',3':4,5]pyrano[2,3-*b*]carbazole via intramolecular aza-Diels-Alder reaction
**S. Ramesh** and R. Nagarajan, **2013** (to be communicated).

**10.** Copper catalyzed cyclization route to the synthesis of fascaplysin, rutaecarpine and granulatimide analogues
**S. Ramesh** and R. Nagarajan, (under preparation).

## Posters and Presentations

1. Presented a poster entitled "A Flexible Approach to the Chromenoquinolines under Copper/Lewis Acid Catalysis " in 7th in-house symposium "***Chemfest-2010***" held at University of Hyderabad, India on January 8-9, 2010.

2. Presented a poster entitled "Efficient One-Pot Multicomponent Synthesis of (Carbazolylamino)furan-2(5*H*)-one and Carbazolyltetrahydropyrimidine Derivatives" in National Conference on "***Recent Trends in Organic Synthesis - 2011***" organized by School of Chemistry, Bharathidasan University, Tiruchirappalli, India on February 24-26, 2011.

3. Presented a poster entitled "Formal Total Synthesis of Lavendamycin Methyl Ester, Nitramarine and their Analogues through a Povarov Reaction" in "***7th J-NOST conference"*** held at IISER Mohali, on December 15-18, 2011.

4. Presented an oral entitled "Formal Total Synthesis of Lavendamycin Methyl Ester, Nitramarine and their Analogues through a Povarov Reaction" *in* "***Chennai Chemistry Conference – 2013"*** held at CSIR-CLRI, Chennai on February 8-10, 2013.

5. Presented an oral entitled "Formal Total Synthesis of Lavendamycin Methyl Ester, Nitramarine and their Analogues through a Povarov Reaction" in "***Chemfest-2013"*** in house symposium, on February 15-16, 2013.

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**...S. Ramesh**

This thesis is dedicated to

# My family

# TABLE OF CONTENTS

# List of Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| Bmim | 1-Butyl-3-methylimidazolium |
| Boc | tert butyl oxycarbonyl |
| CAN | Ceric ammonium nitrate |
| DBTMP | 2,9-Di-n-butyl-3,4,7,8-tetramethyl-1,10-phenanthroline |
| DEAD | Diethyl azodicarboxylate |
| DIB | Diacetoxyiodo benzene |
| DMAP | 4-Dimethylaminopyridine |
| Emim | 1-Ethyl-3-methylimidazolium |
| Eq. | Equation |
| Et | Ethyl |
| Fig. | Figure |
| HMDS | Bis(trimethylsilyl)amine |
| IBX | 2-Iodoxybenzoic acid |
| Me | Methyl |
| MIC | Minimum Inhibitory Concentration |
| MOM | Methoxy methyl ether |
| Mp | Melting point |
| ORTEP | Oak Ridge Thermal Ellipsoid Plot |
| Ph | Phenyl |
| PMB | *p*-Methoxybenzyl ether |
| RCM | Ring Closing Metathesis |
| t-Bu | tert-butyl |
| TEMPO | 2,2,6,6-Tetramethylpiperidinyloxy |
| TFA | Trifluoroacetic acid |
| TSA | Toluenesulphonic Acid |

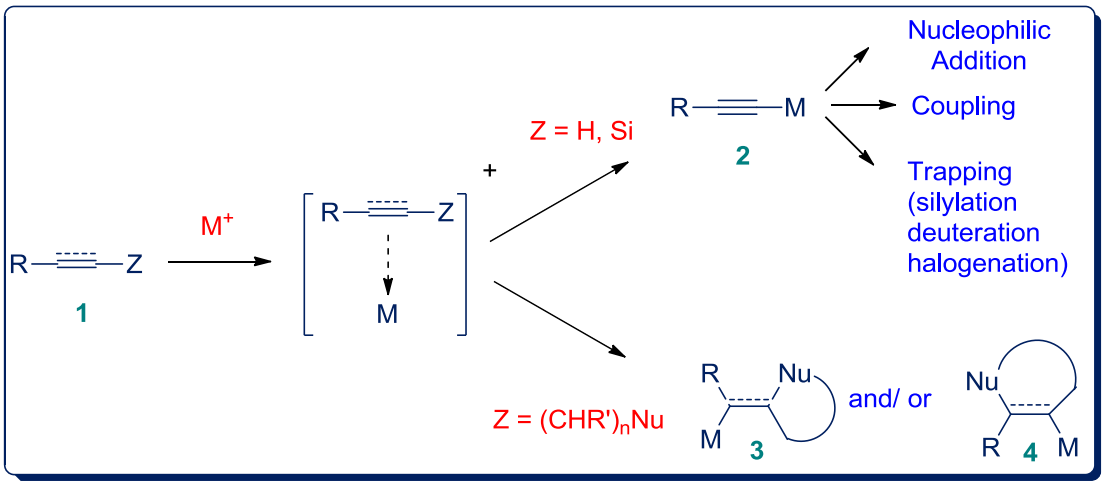
# Introduction

## General background

Interest in the organic reactions with C–C multiple bonds has undergone a marked increase, that opened access to a great chemical diversity through direct and selective $\pi$-electrophilic activations. Electrophilic activation of the well-recognized $\pi$-electron-containing compounds (e.g. alkenes, alkynes, allenes) has rapidly revolutionized and expanded the synthetic portfolio for the decoration of aromatic compounds. In addition, using electrocylization, five-, six-, seven- and even eight-membered rings can be readily accessible in a highly regiochemical fashion.

Alkyne is one of the basic functional groups played an important role as building block or versatile intermediate for the synthesis of a vast array of carbocycles and heterocycles. Upon coordination of transition metal, $\pi-$system with internal nucleophile becomes prone to nucleophilic attack. Hence, cyclization reaction is expected (**3** and/ or **4**). In case of a terminal or a silylated alkyne, the $\pi-$system would favor for acetylide **2** formation. Thus, it becomes an organometallic compound and can act as a nucleophile (**Fig. 1**).[1a]

**Fig. 1**



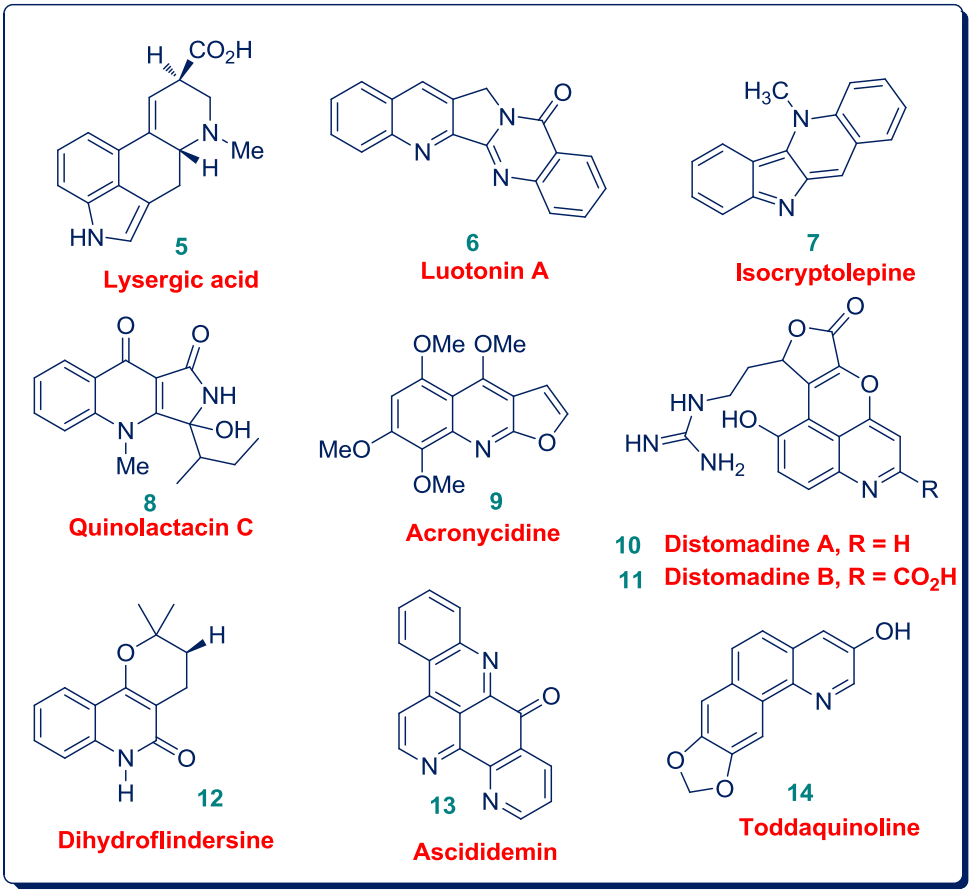

Nitrogen heterocycles are worth, in particular, for their biological activities. They have been assigned as privileged structures in drug discovery. Designing and testing new heterocyclic derivatives have often contributed significant advances in medicinal chemistry. Moreover, most of the pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products which are in significant need of human life. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, as are countless additives and modifiers used in industries as varied as cosmetics, reprography,

information storage, antioxidants, and vulcanization accelerators. Hence, organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations.[1b] Considering the growing environmental awareness and the negative environmental impacts of organic volatile solvents, synthesis of organic compounds with environmentally more benign and alternatives to the traditional organic volatile solvents is an important concern over academic as well as industrial oriented synthesis. The introductory part of the thesis demonstrates the significance of synthesis of quinolines, $\beta$-carboline derivatives, important methodologies (Povarov reaction, electrocyclization and MCR), ionic liquids (IL), trivalent lanthanides, and copper catalysis with functionally substituted alkynes or alkenes.

## Heteroaryl quinolines

Quinolines have been widely found as the most prevalent heterocyclic compounds in natural products with potential biological activities.[1c-d] They have been broadly used in medicinal chemistry, drug synthesis[2] and functional compound materials as building blocks.[3]

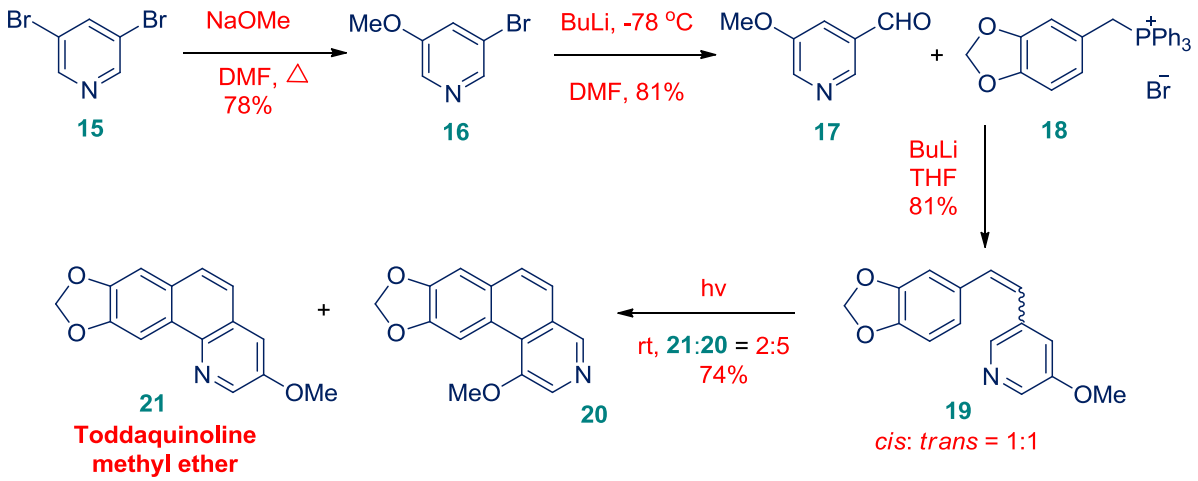
**Fig. 2: Some of important polyheteroarylquinoline alkaloids**



The known methods for synthesizing quinolines and related polyheterocyclic quinolines are the Skraup reaction, Combes, Friedlander and Conrad-Limpach-Knorr reactions.[4] Some of important polyheteroaryl quinoline alkaloids are shown in **Fig. 2**. The tetracyclic toddaquinoline alkaloid was isolated from the root bark of Formosan *Toddalia asiatica*,[5] a constituent of many asian folk medicines.[6]

Harrowven *et al*. described a strategy which involved photocyclization of an azastilbene **19**. It is noteworthy that the specific geometry of alkene was not required for the convergent cycloaddition. However, the mode of cyclization was not explained clearly. The straightforward synthesis of azastilbene (**Eq. 1**) was commenced with 3,5-dibromopyridine **15**.

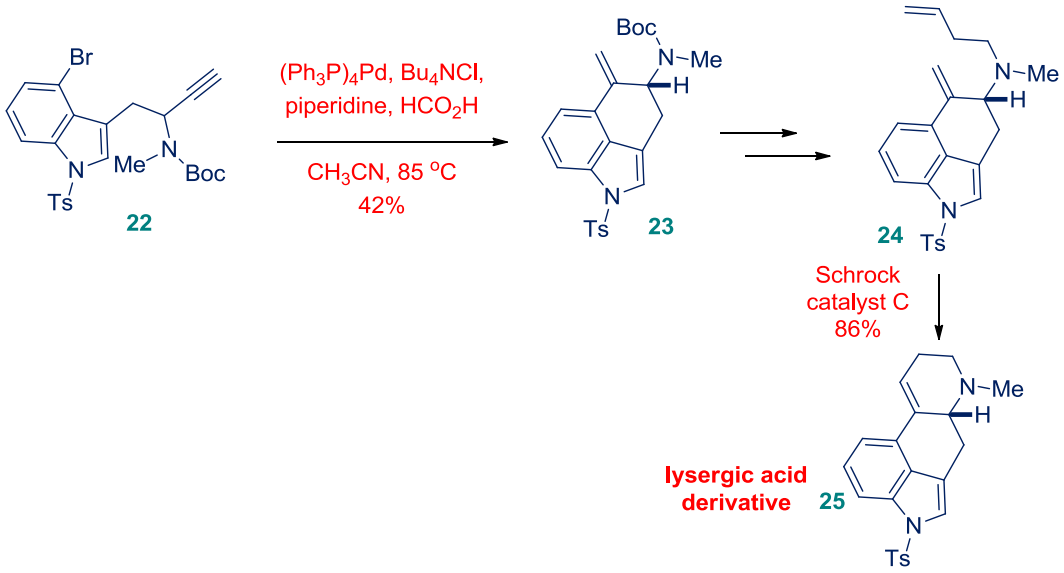
**Eq. 1**




The sequence involved aromatic substitution of one of the aryl halides **15** with methoxide, followed by treatment of butyllithium and quenching with DMF. The aldehyde **17** underwent Wittig coupling reaction with ylide **18** to give *cis*- and *trans*-azastilbenes **19**. The irradiation of azastilbenes using a medium pressure lamp facilitated cyclization between C-4 of the pyridine and C-6 of the benzodioxide to give compound **20** as major. Whereas, toddaquinoline methyl ether (**21**) was isolated as a minor compound.[7]

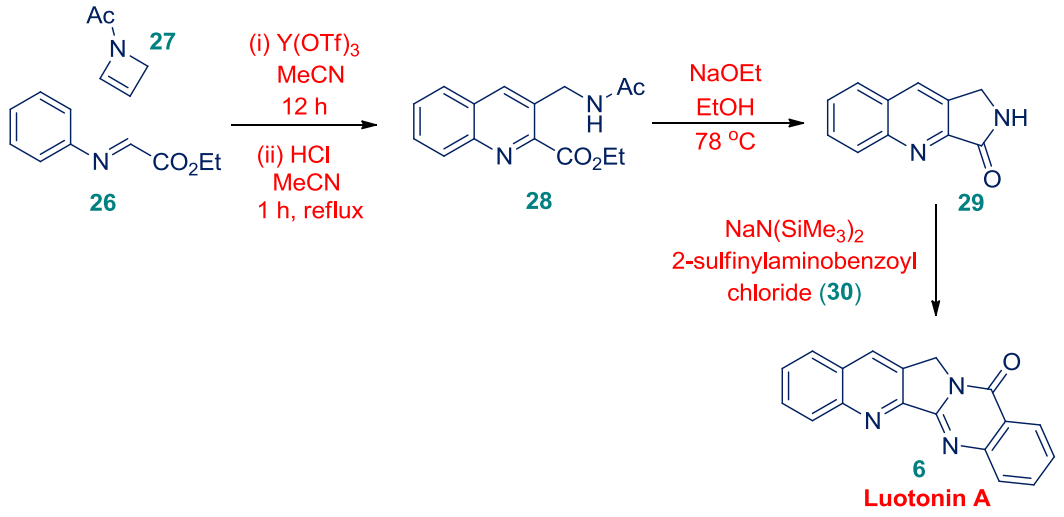
Martin *et al*.[8] reported a RCM based (**Eq. 2**) novel synthesis of tetracyclic ring system **25**, found in the *Ergot* alkaloid lysergic acid (**5**).[9] They applied the Heck cyclization on **22** to obtain the key tricyclic intermediate **23**. The compound **22** was prepared in seven steps from 4-bromoindole. Boc group deprotection of **23**, followed by *N*-alkylation gave the compound **24**. The compound **24** was cyclized in the presence of reactive Schrock catalyst C to give **25**. This cyclization is noteworthy, because there are relatively few examples of RCM reactions involving exocyclic olefins.

**Eq. 2**

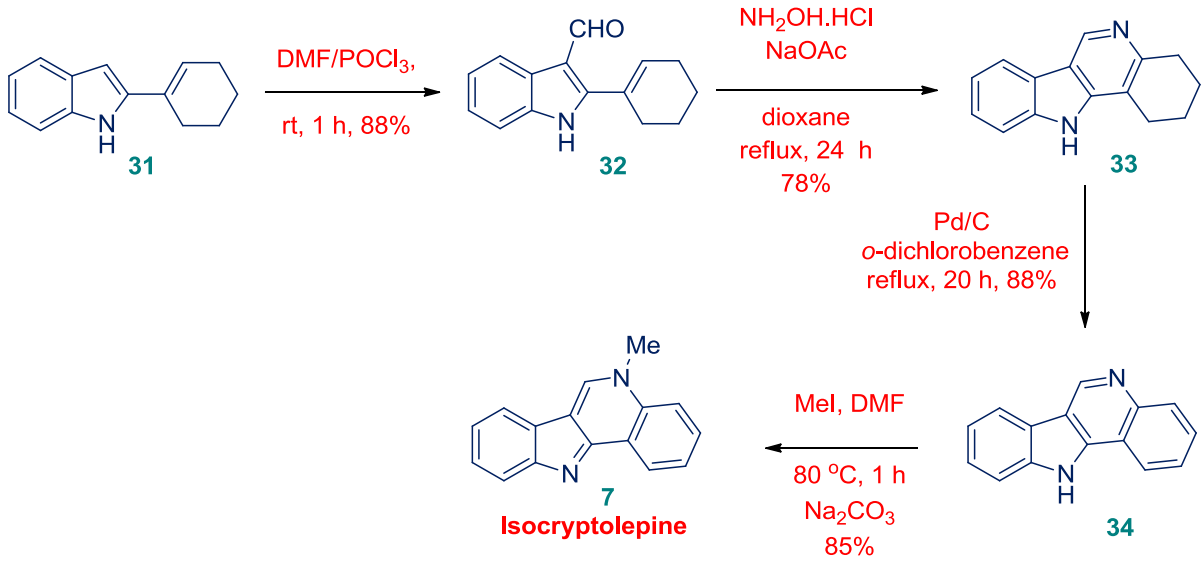



In 1997, Ma *et al*. isolated luotonin A, a cytotoxic alkaloid from the plant *Peganum nigellastrum*. This plant has been used in Chinese medicine for the treatment of rheumatism and inflammantion.[10] Stevenson *et al*.[11] investigated [4+2] cycloaddition (**Eq. 3**) and fragmentation reaction between *N*-acetyl-2-azetine (**27**) and imine **26** derived from aniline to afford 2,3-disubstituted tetrahydroquinoline in the presence of catalytic amount of $Y(OTf)_3$. In acidic condition, tetrahydroquinoline can be converted into aromatic quinoline **28**, which was treated with sodium ethoxide in ethanol resulted in formation of the compound **29**. The lactam **29** was reacted with 2-sulfinylaminobenzoyl chloride (**30**) to convert into luotonin A (**6**).

**Eq. 3**



**Eq. 4**

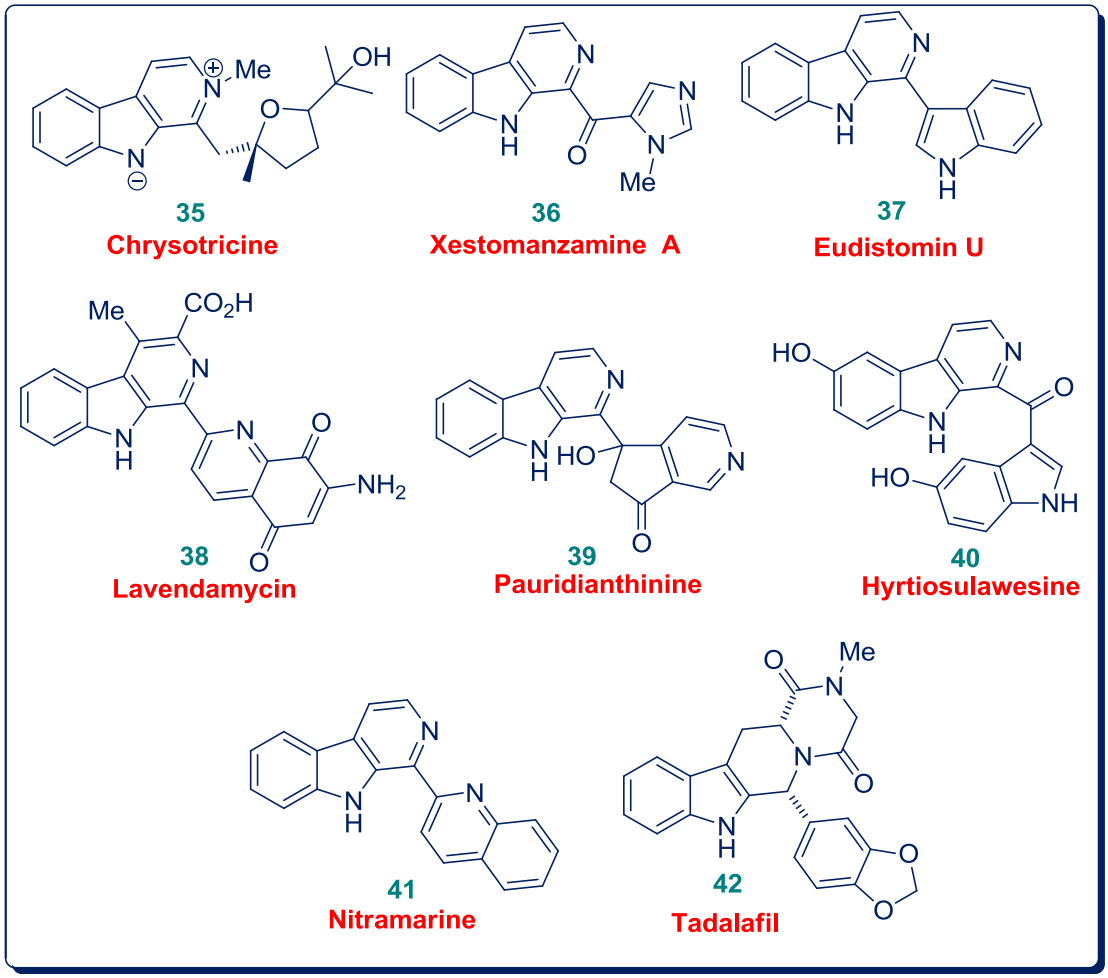



In 1995, an important indolo[3,2-*c*]quinoline alkaloid, isocryptolepine (**7**) was isolated from *Cryptolepis sanguinolenta*, and used in folk medicine as an antimalarial agent.[12,13] Kusurkar *et al*.[14] established an efficient and short route to synthesize of naturally occurring antiplasmodial isocryptolepine. The thermal electrocyclization reaction between the compound **32** and hydroxylamine hydrochloride furnished the compound **33**. Further dehydrogenation and treatment of **34** with methyl iodide afforded isocryptolepine (**7**) in the overall yield of 37%. In 1988, Kobayashi *et al*.[15] isolated ascididemin, a pyridoacridine alkaloid from the okinawan tunicate *Didemnum* sp. Ascididemin (**13**) and their derivatives showed significant *in vitro* and *in vivo* cytotoxic activities against several tumor cell lines[16] and antimicrobial, antiviral, antiparasitic and fungicidal properties.[17,18]

## Heteroaryl-$\beta$-carbolines

Compounds containing $\beta$-carboline core are worth our attention for many reasons; chief among them is their biological activities which include anticonvulsant, hypnotic, antimalarial, antimicrobial, anxiolytic and antiviral.[19] The Pictet-Spengler and the Bischler-Napieralski reactions[20] are by far the most commonly utilized among the methods available for preparation of $\beta$-carbolines. These derivatives or alkaloids can be classified into two main categories namely substituted $\beta$-carbolines and fused $\beta$-carbolines.

**Fig. 3: Some of $\alpha$-heteroaryl substituted $\beta$-carboline alkaloids**

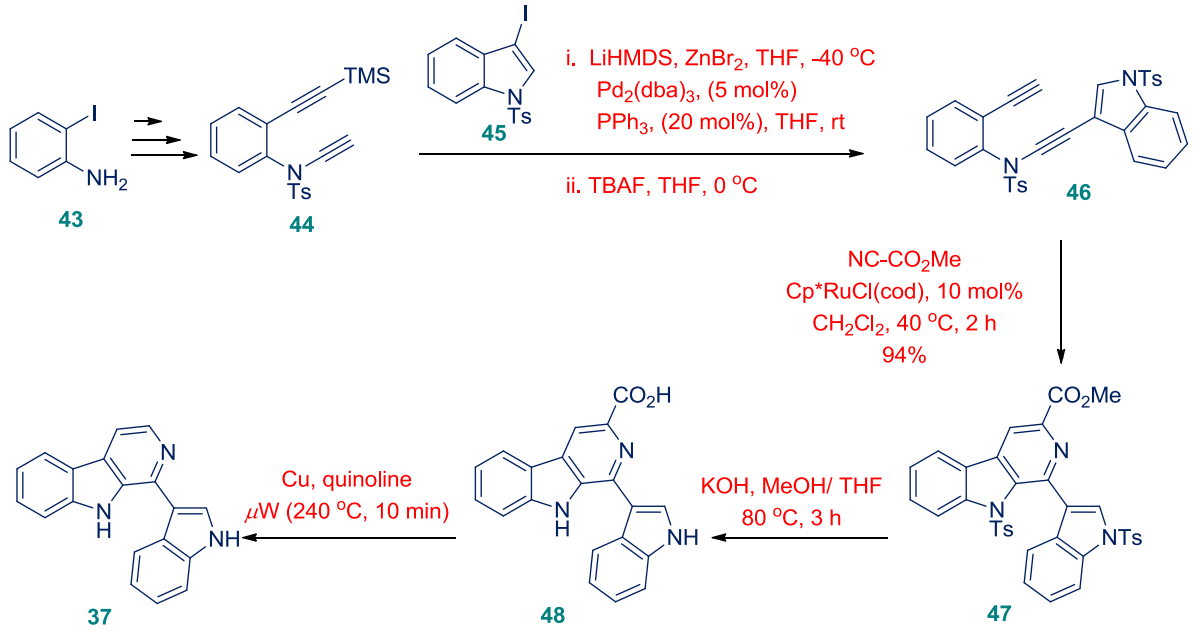



Among the different substituted $\beta$-carbolines, many molecules with $\alpha$-heteroaryl substituted $\beta$-carboline derivatives (**Fig. 3**) were isolated from the nature. Chrysotricine **35**, a *trans*-tri-substituted tetrahydrofuran attached $\beta$-carboline, was first isolated from chinese herb medicine *Hedyotis chrysoticha* which shows an inhibitory activity against the growth of HL-60 cells in *vitro*.[21] In 1981, Doyle and co-workers from Bristol Laboratories reported the isolation of naturally occurring antitumour-antibiotic lavendamycin (**38**) from the fermentation broth of *streptomyces lavendulae* strain C22030 as a dark red solid.[22]

Subsequently, its structure was elucidated as a pentacyclic quinone by Balitz and co-workers by means of analytical and spectroscopic studies.[22] In 1984, the first total synthesis of lavendamycin methyl ester was achieved by Kende's *et al*. via Bischler-Napieralski reaction.[23] In 1994, Badre *et al*. reported the isolation of 3-indolyl substituted carboline alkaloid eudistomin U (**37**), from de Caribbean *ascidiam Lissoclinum* fragile of Ilet Pingeon in Guadeloupe. The alkaloid and its derivatives showed binding affinity with DNA and exhibited strong antibacterial activity.[24] Nitramarine (**41**) is an $\alpha$-quinolinyl-$\beta$-carboline alkaloid which was isolated from *nitraria komarovii* plant by

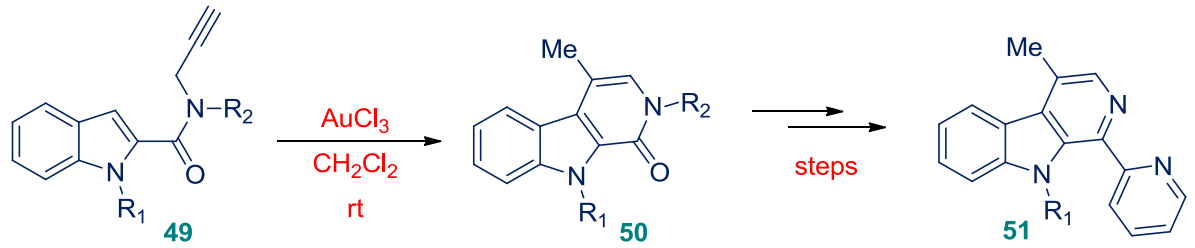
Tulyaganov *et al*. in 1984.[25] It exhibits sleeping time prolonging effect,[26a] hypotensive and spasmolytic activities.[26b] In 1995, Kitagawa *et al*. isolated cytotoxic constituents xestomanzamine A (**36**), an imidazoloyl substituted $\beta$-carboline alkaloid, from an okinawan marine sponge *Xestopongia sp*.[27] Pousset *et al*. (in 1971)[28] and Mostafa *et al*. (in 2002),[29] isolated pauridianthinine (**39**) and hyrtiosulawesine (**40**) respectively.

**Eq. 5**




Recently, Nissen *et al*. described the total synthesis of both eudistomin U (**37**)[30] and lavendamycin (**38**)[31] based on ruthenium or rhodium catalyzed [2+2+2] cycloaddition reactions. This route afforded the marine alkaloid **37** in 8 steps with 49% overall yield starting from commercially available 2-iodoaniline (**43**) (**Eq. 5**).

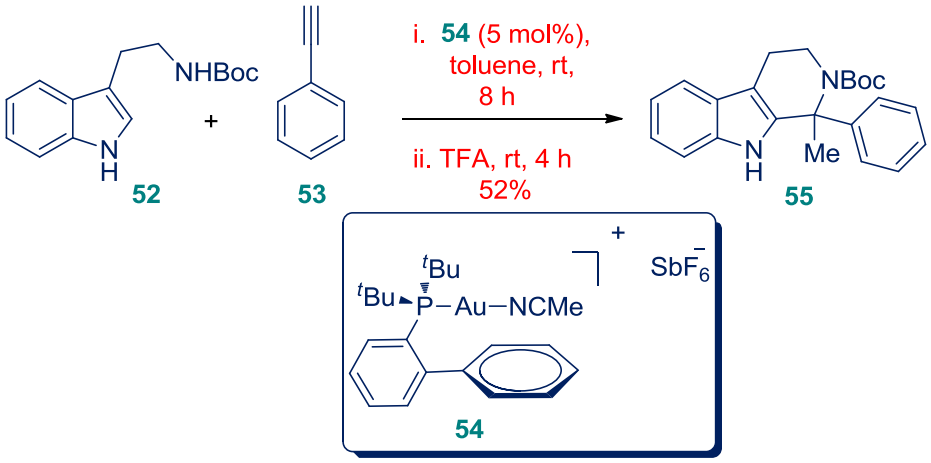
**Eq. 6**




Patwa, *et al*.[32] found an $AuCl_3$ catalyzed cycloisomerization of *N*-propargylindole-2-carboxamides **49** to afford $\beta$-carbolines **50**. The powerful soft Lewis acidic nature of gold salts is known for activating C-C triple bonds towards nucleophilic attack. The process involves *6-exo-dig* cyclization by attack of the $C_3$-position of the indole ring, followed by protodemetalation and isomerization (**Eq. 6**).

Echavarren, *et al*.[33] reported intermolecular cyclization reaction of indole **52** with alkyne **53** catalyzed by gold salt **54**. The Pictet-Spengler process of tryptamine and acetylene afforded $\alpha$-substituted tetrahydro-$\beta$-carboline **55** (**Eq. 7**).

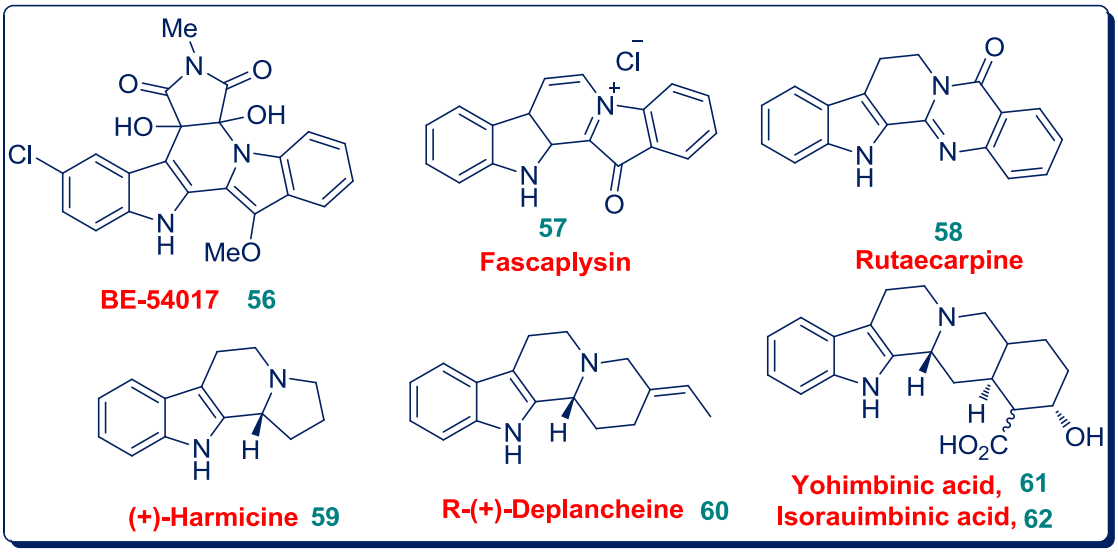
**Eq. 7**




## Heteroannulated-$\beta$-carbolines

Among the annulated $\beta$-carbolines, the most interesting structural class is the $\alpha$-fused pyrido[3,4-*b*]indole framework. The $\alpha$-fused pyrido[3,4-*b*]indole framework is found in many natural products (**Fig. 4**) with a broad range of potent biological activities, e.g. antifungal, antimicrobial, antitumor, and antihypertensive activities.

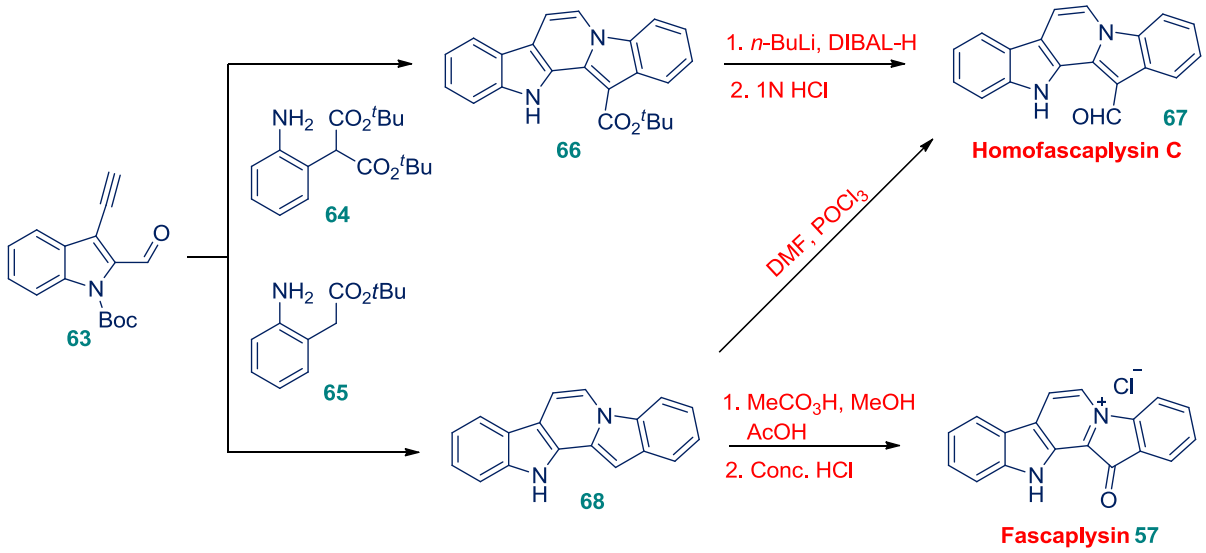
**Fig. 4: Some of heteroannulated-$\beta$-carboline alkaloids**




In 1988, fascaplysin (**57**) was isolated from the marine sponge *fascaplysinopsis Bergquist* sp., collected in the south pacific near the Fiji islands. It exhibits anti-microbial and cytotoxic activities.[34] Gribble *et al*. reported the first total synthesis of fascaplysin

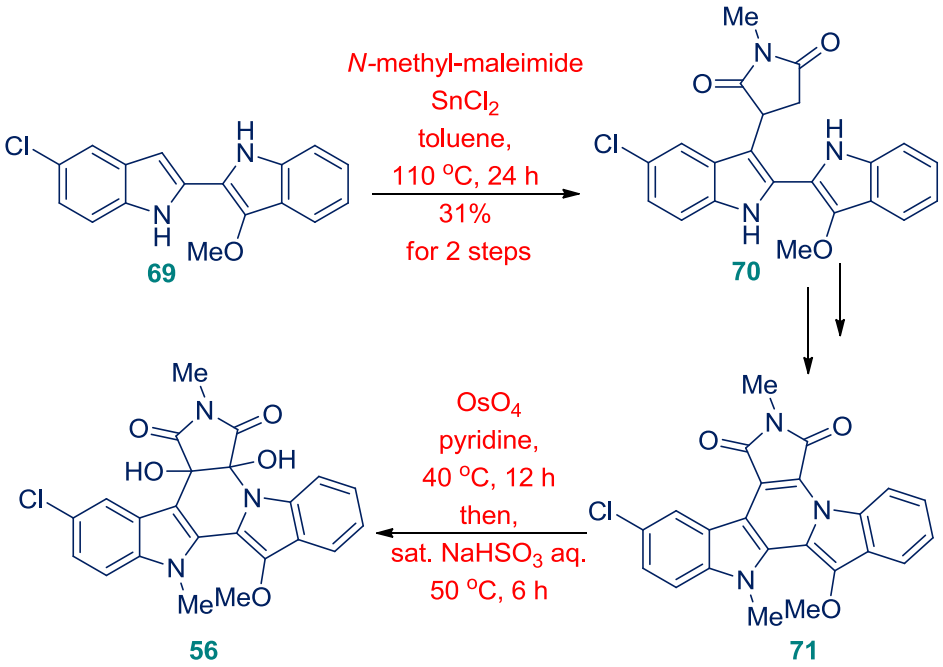
and homofascaplysin B and C.[35] Waldmann *et al*. employed Boc-protected 3-ethynyl-indole-2-carbaldehyde **63** as a common precursor for the natural products fascaplysin and homofascaplysin C (**67**) (**Eq. 8**). The synthesis for pentacyclic core was obtained in 61% from the cascade reaction between aniline **64** or **65** and aldehyde **63**.

**Eq. 8**



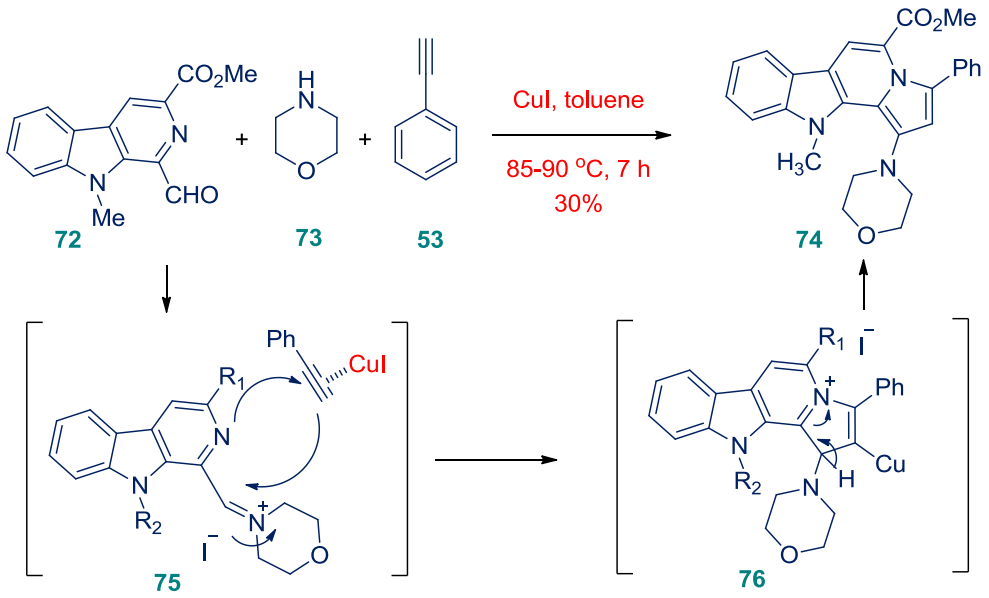

The homofascaplysin C (**67**) was obtained from by formylation of the compound **68** using $POCl_3$. In addition, the pentacyclic core was efficiently transformed to the natural product fascaplylsin by oxidation with peracetic acid, followed by salt formation in 52% overall yield.[36]

**Eq. 9**



Recently, Watanabe *et al*. reported synthesis and assignment of the absolute configuration of indenotryptoline bisindole alkaloid BE-54017 (**56**). The alkaloid synthesis was accomplished using osmium-promoted cis-dihydroxylation of maleimide as a key step (**Eq. 9**).[37a]

**Eq. 10**

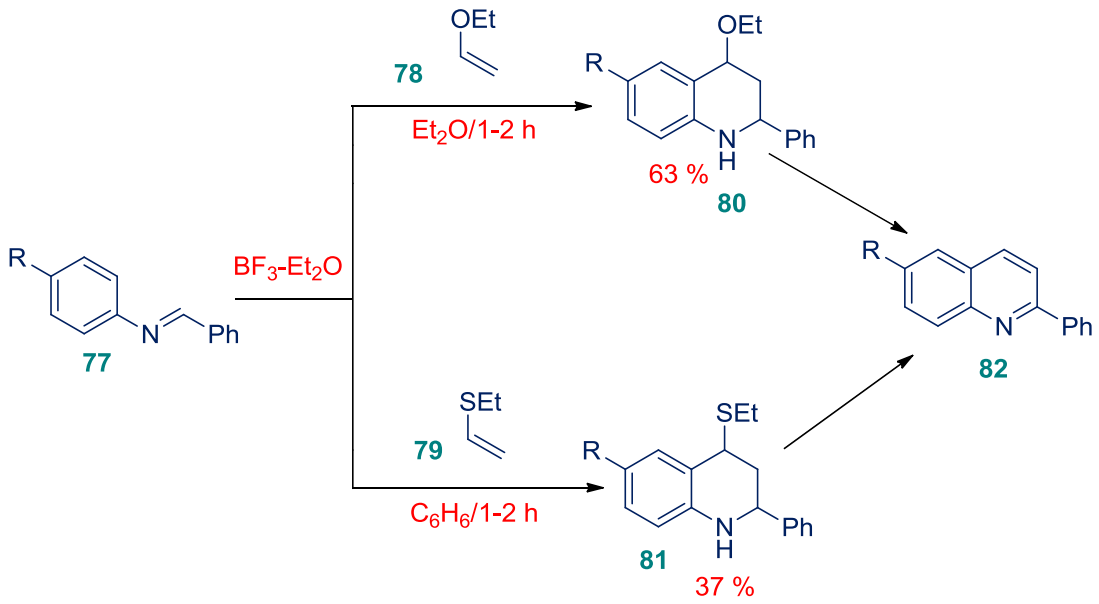



Batra *et al*.[37b] synthesized harmicine derivatives **74** using three component coupling/cycloisomerization reaction between $\alpha$-formyl-$\beta$-carbolines **72**, secondary amines **73**, and substituted alkynes **53** in the presence of CuI (**Eq. 10**). The proposed reaction pathway is following the initial formation of iminium ion **75** by condensation reaction between secondary amine **73** and aldehyde **72**, followed by a nucleophilic attack of pyridyl nitrogen on a Cu-coordinated alkynyl bond.

## Povarov reaction (Hetero Diels-Alder)

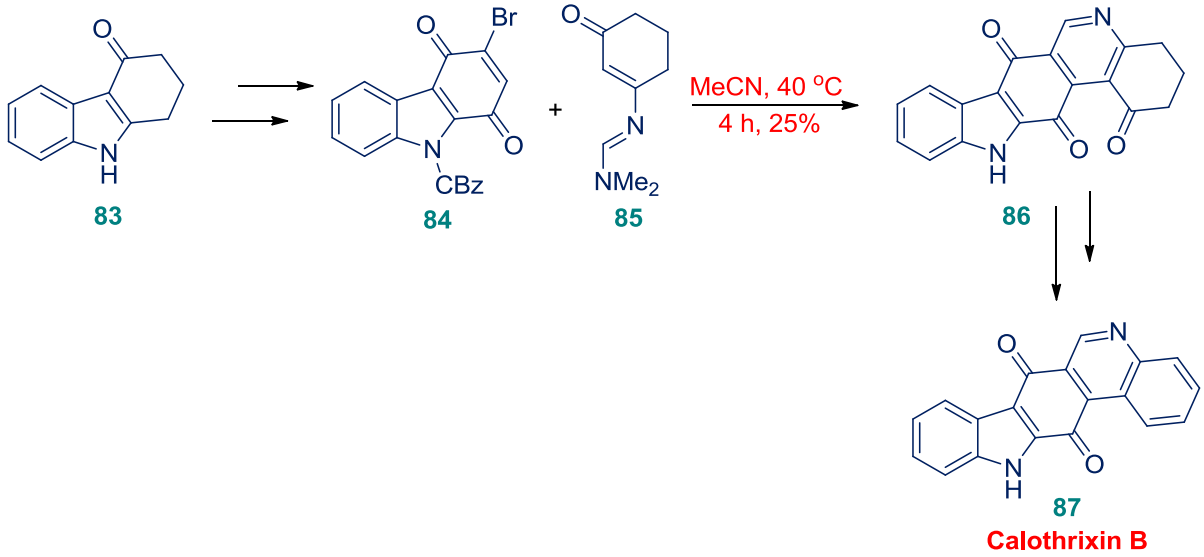
Recently, much attention has been paid to the synthesis of quinoline and tetrahydroquinoline containing natural products, which exhibit interesting biological activities. The reaction between electron deficient Schiff bases and electron-rich alkenes or alkynes called as Povarov reaction,[38] has recently experienced a renaissance in the chemical literature. The first report of Povarov[38d] described reactions of ethyl vinyl ether (**78**) or ethyl vinyl sulfide (**79**) with *N*-arylaldimine **77** under $BF_3$-$OEt_2$ to obtain 2,4-substituted tetrahydroquinolines **80** or **81** which were converted into corresponding quinoline product **82** (**Eq. 11**). Depending on the reaction conditions the tetrahydroquinolines or quinolines, are main products of the Povarov reaction. This part of the introduction focuses on the synthetic application of Povarov reaction for few important polycyclic *N*-containing natural products.

**Eq. 11**



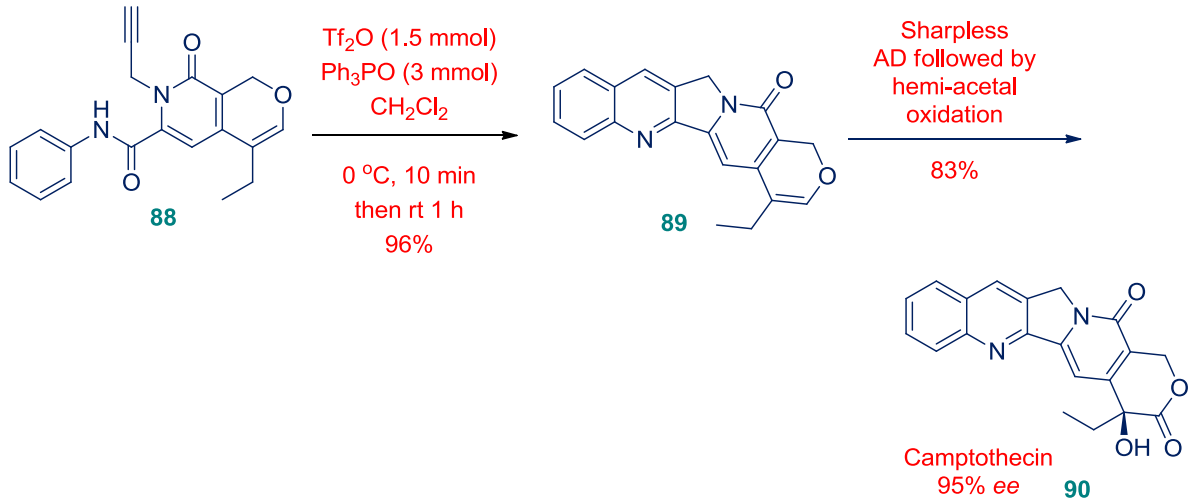

Calothrixin B (**87**), a carbazole alkaloid was isolated from cyanobacterial *Calothrix* species. Guingant and co-workers[39] have studied the use of Povarov reaction to assemble the core structure of calothrixin B in a regioselective manner. The synthesis of dienophile **84** was accomplished in a four step sequence, started with commercially available tetrahydrocarbazolone (**83**).[39] Transformation of dienophile **84** towards adduct **86** was effected with a slight excess of diene **85** in MeCN at 40 °C for 4 h. The total synthesis of calothrixin B is shown in **Eq. 12.**

**Eq. 12**



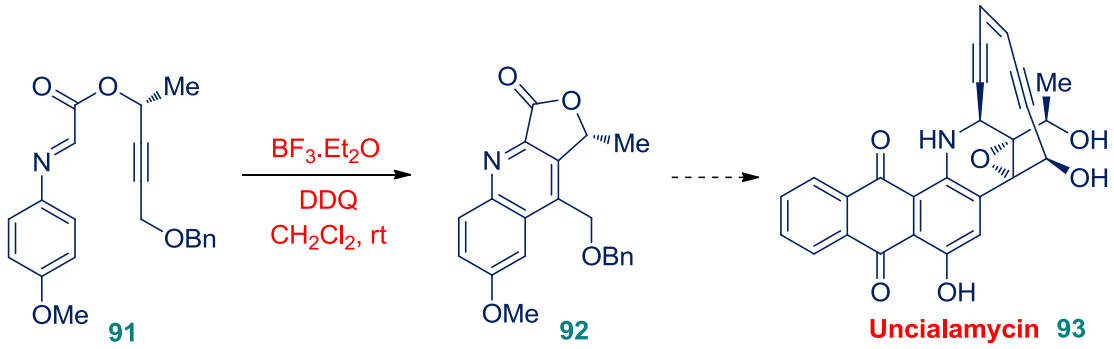
Camptothecin (**90**), a tetracyclic quinoline alkaloid was isolated from the chinese plant *Camptotheca acuminata* in 1966 by Wani and Wall.[40] Yao *et al*. reported a concise total synthesis of camptothecin using intramolecular Povarov reaction as a key step.[41] Here, the cascade reaction is between an alkyne as dienophile and *N*-arylimidate **88** as diene triggered by *in-situ* formation of bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate. $Tf_2O$-$2Ph_3PO$ is an amide activator which is converting the amide into corresponding imidate under mild conditions and is to promote the subsequent Povarov reaction (**Eq. 13**).

**Eq. 13**



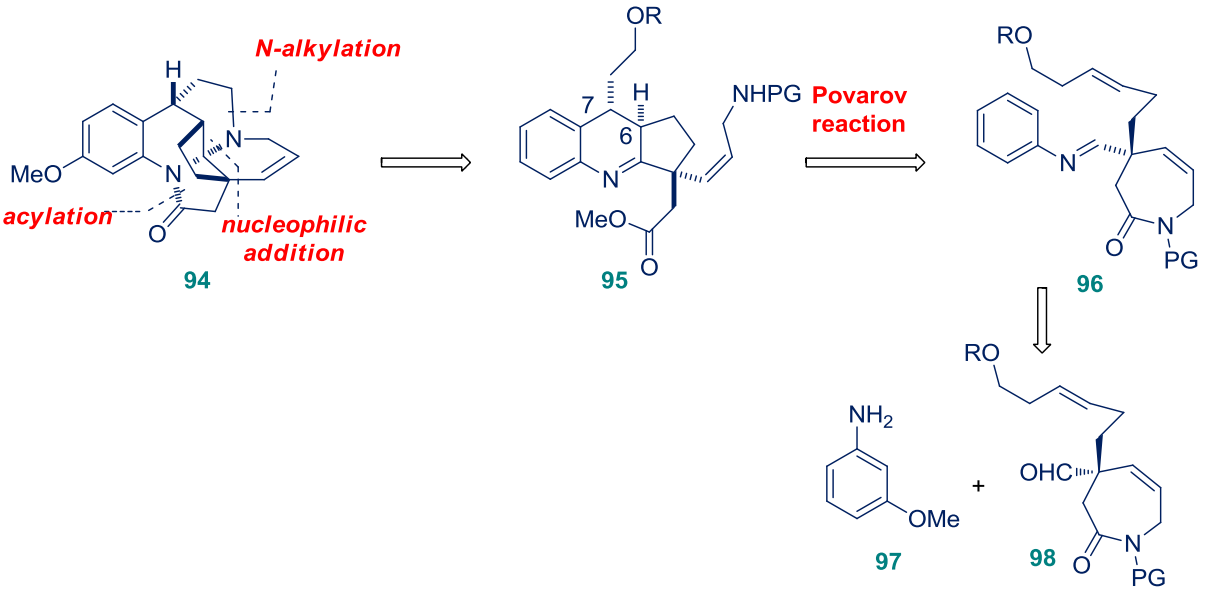

Weghe *et al*. described the synthesis of chiral quinoline moiety **92** of uncialamycin (**93**), an enediyne natural product.[42] They accomplished the quinoline **92** using intramaolecular povarov reaction in the presence of $BF_3.Et_2O$ as catalyst and DDQ as oxidant. Without the yield of cycloaddition being affected, they prepared the quinoline ring using an alkene or an alkyne as dienophile (**Eq. 14**).

**Eq. 14**



Magomedov reported construction of cyclopenta[*b*]quinoline core of isoschizozygane (**94**) alkaloids *via* intramolecular formal Povarov reaction.[43] Their synthetic strategy in the assemblage of isoschizogaline is illustrated in **Eq. 15**. They devised a retrosynthetic analysis whereby the compound **94** could be generated from the compound **95** by a sequence of reactions. The tetrahydroquinoline **95** ring with *trans* substituent at C-6 and C-7 could be generated by a Povaraov reaction with imine **96**, which in turn could be formed from corresponding aldehyde **98** and *m*-anisidine **97**.

**Eq. 15**

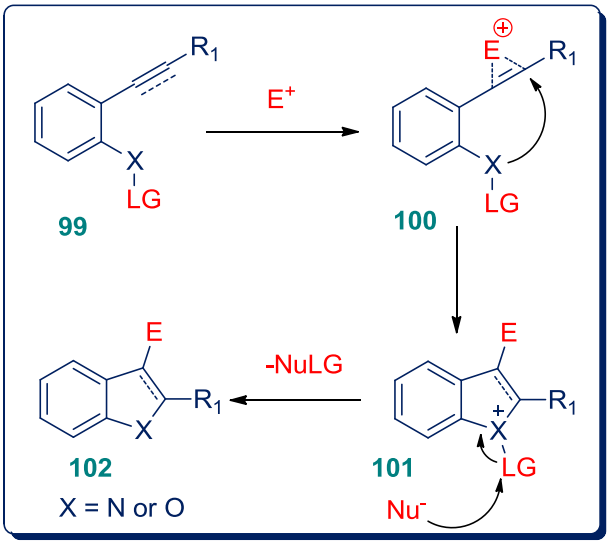



Some of the other heterocyclic alkaloids, such as (±)-Alantrypinone,[44] (±)-Eburnamonine,[45] (±)-Lapatin B,[46] Luotonin A,[47] Mappicine,[48] Nothapodytine B,[48] Martinelline[49] and Martinellic acid[49] have also been prepared by the versatile Povarov reaction.

## Electrophilic cyclization

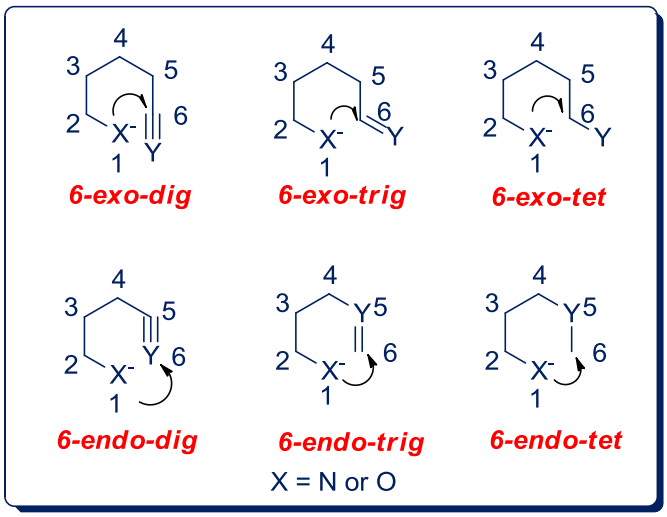
There has been a growing interest for finding a simple, and an efficient methodology to construct heterocyclic compounds particularly polycyclic nitrogen containing compounds. The electrocyclization reactions have been proved their efficiency for constructing heterocycles. Among them, transition metal catalyzed cyclization reactions are one of the most attractive ways to directly construct complex heterocycles under mild conditions.[50]

**Eq. 16**




In general, an electrophilic cyclization reaction involves a course of process that is (i) addition of electrophilic sources into a C-C multiple bonds (alkynes, alkenes, allenes and conjucated dienes), so that C-C bond is activated for nucleophilic attack. (ii) nucleophilic attack on the activated alkyne or alkene to make an annulated ring. (iii) removal of the group attached with the nucleophile via $S_N2$ displacement by the nucleophilic present in the reaction mixture (**Eq. 16**).

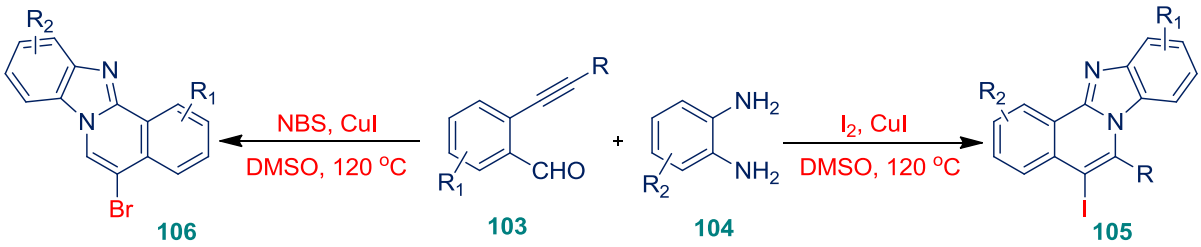
**Fig. 5**




Larock and co-workers demonstrated the factors affecting this cyclization. These include (i) relative nucleophilicity of the functional group, (ii) polarization of the C-C bond, (iii) steric factor, and (iv) nature of the electrophilic source.[51] The cyclization reactions involve *endo* or *exo* modes for annulations. The way of mode is depending upon the chain length, substitution pattern on the chain, and the electrophile employed. In 1970, Baldwin made a rule which describes the relative ease of ring formation. The three features of the rule are (i) the size of the ring being formed, (ii) the hybridization

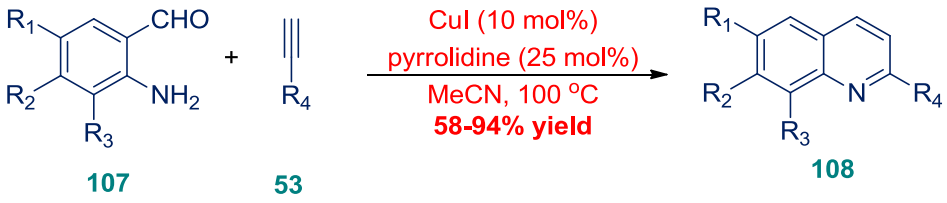
of carbon involves in the ring closing reaction, (iii) the cyclization mode which depends on newly formed bond either internal or external to the broken bond (**Fig. 5**).[52] Li and co-workers have developed an efficient tandem route to the synthesis of iodoisoquinoline-fused benzimidazole derivatives including an iodocyclization strategy (**Eq. 17**).[53] In the presence of CuI, a variety of 2-ethynylbenzaldehydes **103** underwent the tandem reaction with benzenediamines **104** and iodine/NBS to afford the corresponding iodoisoquinoline-fused benzimidazoles **105**/bromoisoquinoline fused benzimidazoles **106** respectively in moderate to good yields.

**Eq. 17**



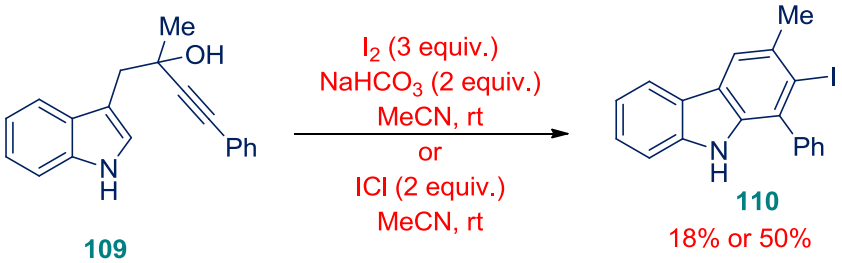

Patil and Raut reported a highly efficient pyrrolidine and CuI catalyzed two component reactions of 2-aminobenzaldehyde (**107**) and terminal alkynes **53** through an addition cycoisomerization cascade which affords 2-substituted quinolines **108** (**Eq. 18**).[54]

**Eq. 18**



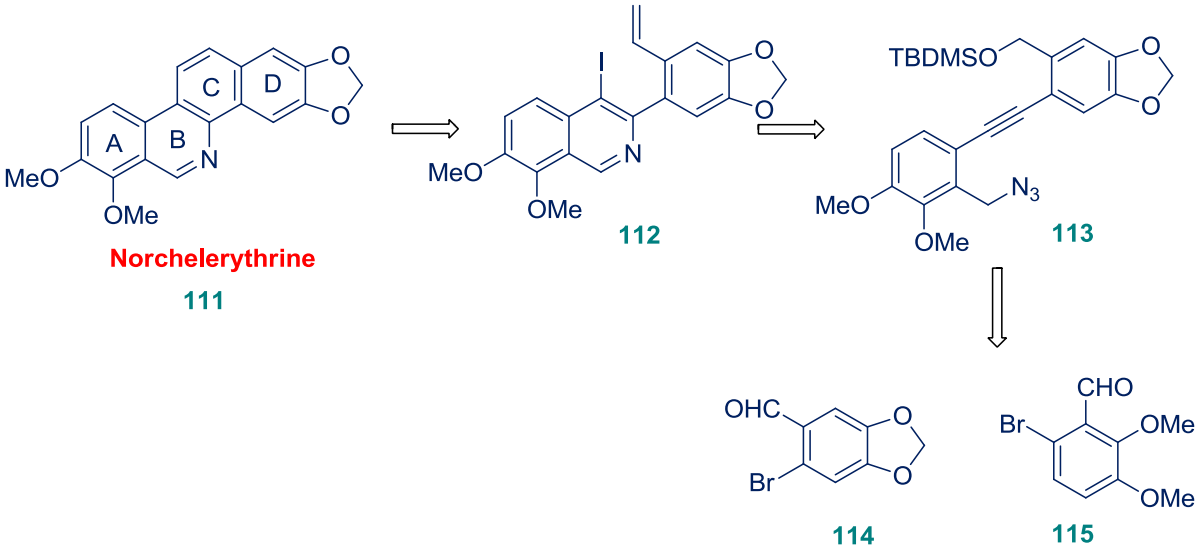

Larock *et al.* described highly regiocontrolled synthesis of iodocarbazole **110** using electrophilic cyclization in which they used an important electon-rich indole ring **109**. They obtained the iodocarbazole **110** in only an 18% yield in $I_2$, however, they could improve the yield up to 50% when ICl was used as the electrophile (**Eq. 19**).[55]

**Eq. 19**



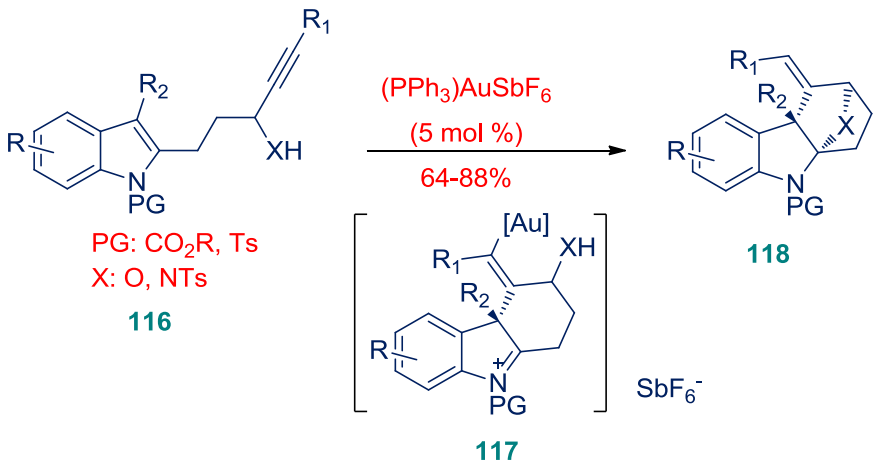
Yamamoto *et al*.[56] reported the total synthesis of norchelerythrine **111** based on iodine mediated electrophilic cyclization of 2-alkynyl-1-methylene azide aromatics **113**. Their retrosynthetic analysis is shown in **Eq. 20** which involved the construction of a key fragment containing a 3,4-disubstituted isoquinoline **112**. The compound **111** showed potent pharmacological activities such as antitumor and antiviral activities.[57]

**Eq. 20**




Wang and co-workers[58] accomplished a diversity oriented synthesis of diastereomerically pure tetracyclic indolines **118** by means of gold catalyzed (**117**) hydroarylation of alkynes **116** (indole $C_3$ attack to the C-C triple bond). The reaction involves a tandem cyclization of indolyl-propargylic alcohols/amines **118** under mild conditions (**Eq. 21**).

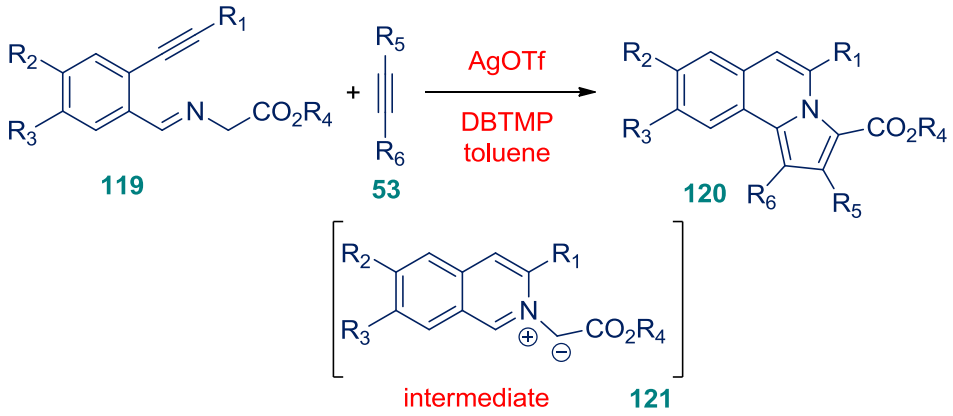
**Eq. 21**




Porco *et al*. reported an interesting domino cycloisomerization/ dipolar [3+2] cycloaddition using alkynes **53** as dienophiles. Pyrroloisoquinolines **120** are structurally related to the lamellarin family of natural products which have been synthesized using

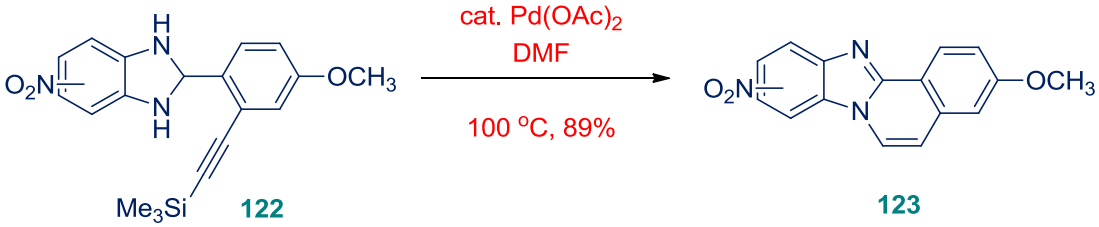
the reaction between an alkynyl *N*-benzylidene glycinate **119** with an alkyne **53** in the presence of AgOTf (**Eq. 22**).[59]

**Eq. 22**



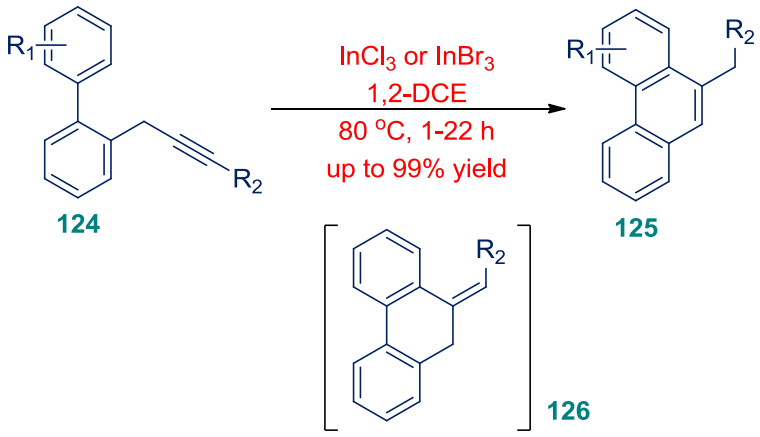

Sun *et al*. demonstrated the $Pd(OAc)_2$ catalyzed synthesis of benzimidazole **123** in refluxing DMF to afford a 1:2 mixture of two isomeric isoquinolines in an 89% yield (**Eq. 23**).[60]

**Eq. 23**



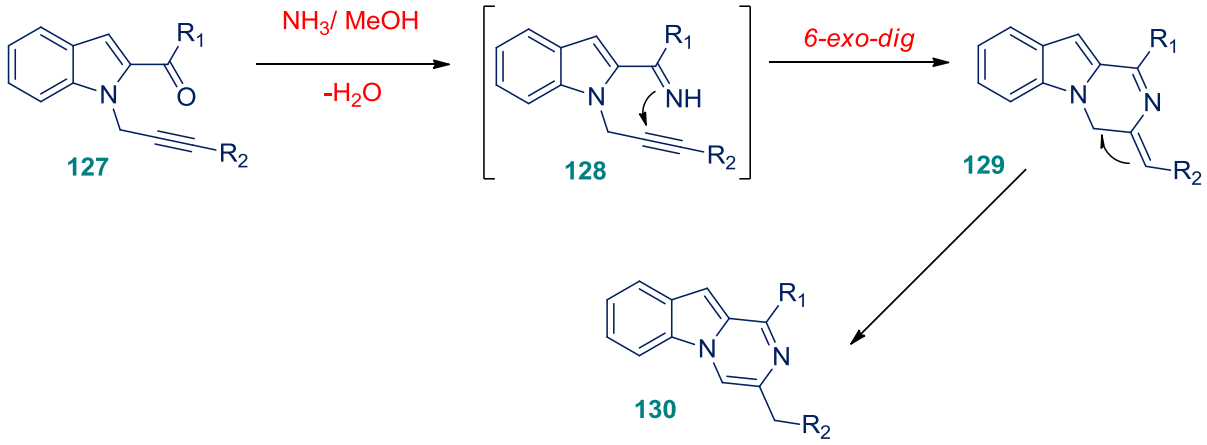

Kim *et al*. investigated the first electrophile-promoted nucleophilic cyclization of *o*-propargylbiaryls **124** for synthesizing phenanthrenes **125** in the presence of In(III)-catalyst. The six membered functionalized phenanthrenes have been synthesized in a regioselective manner through *6-exo-dig* hydroarylation followed by double bond migration (**Eq. 24**).[61]

**Eq. 24**



Abbiati *et al.* reported the synthesis of pyrazino[1,2-*a*]indoles (**130**) in the presence of ammonia through an intramolecular cyclization of several 2-carbonyl-1-propargylindoles **127** under heating (**Eq. 25**). They have also demonstrated the reaction under microwave heating, where they could reduce the reaction time and improve overall yields. They explained the utility of $TiCl_4$ for the synthesis of pyrazinoindoles from 1-alkynyl-2-acetylindoles.[62]

**Eq. 25**




## Ionic liquids (IL)

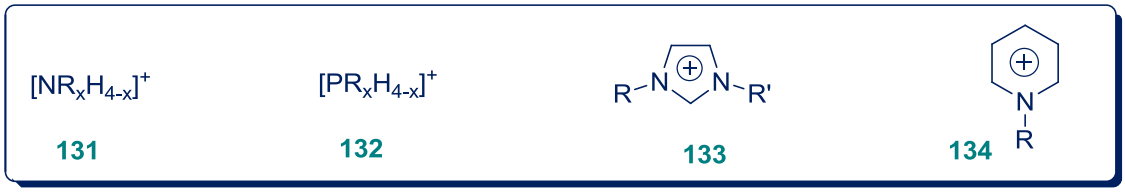
The introduction of environment friendly solvent and catalyst technologies has drawn attention throughout both industry and academia. Conventional solvents are high on the list of damaging ecology due to their excess utility and they are usually volatile liquids that are difficult to contain. Therefore the replacement of most damaging solvents has become a high priority. In the context of green organic synthesis, room temperature ionic liquids based on 1-alkyl-3-methylimidazolium salts were first reported in 1982 by Wiles *et al*. (1st generation).[63] Low melting fused salts are generally called as ionic liquids which contain normally large organic cations, like imidazolium[64], pyridinium[64], pyrrolidinium[65], quaternary ammonium[66] or phosphonium ions.[67] Whereas, anions are often $Cl^-$, $Br^-$ (for hydrophilic ionic liquids) and $BF_4^-$, $PF_6^-$ (for hydrophobic ionic liquids).

Because of their unique properties such as non-flammability, non-volatility, thermal stability, recycling and controlled miscibility, they are much safer to work with in the lab than the conventional organic solvents. Ionic liquids can be considered as "designer solvents" because of their dissolving ability for metal salts, polarity, viscosity and density can be tuned by an appropriate choice of the anion and the cation.

Higher rates and better selectivity has been observed in selected ionic liquids in a number of reactions, which include the Baylis–Hillman reaction, Knoevenagel condensation, Claisen–Schmidt condensation, Horner–Wadsworth–Emmons reaction,

Heck reaction, Suzuki coupling, Stille coupling, Sonogashira reaction, nitration, elimination reactions, hydrogenations, alkene dimerizations, Diels–Alder and Friedel–Crafts reactions.[68]

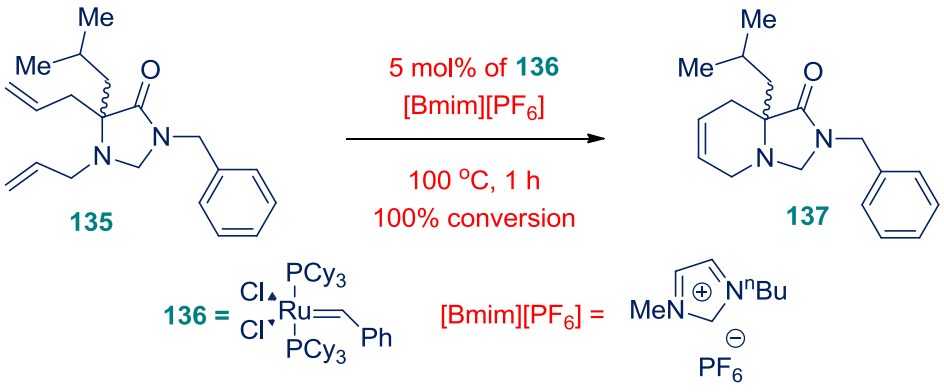
**Fig. 6: Alkylammonium (131), alkylphosphonium (132), *N,N'*-dialkylimidazolium (133) and *N*-alkylpyridinium cations (134)**




There are many applications of the ionic liquids in different areas, in particular their use in heterocyclic synthesis. They have been a significant tool to improve product yields, reaction times and have been a good solvent for both inorganic and organic materials. These highly polar, non-coordinating IL can provide single phase with unusual combination of reagents. They are able to act as a catalyst, catalyst activator, and co-catalyst for an organic reaction. In the following discussion, C-C multiple bonds involved, IL catalyzed or mediated synthesis of few carbocycles and heterocycles will be described.

Ring-closing metathesis is known for creating heterocycles and complex natural products. Buijsman *et al*.[69] described a ring-closing metathesis (RCM) using Grubbs catalysts in the presence of [Bmim][$PF_6$] as an effective medium. They have proved that the ionic liquid is an excellent medium for high conversions, broad substrate tolerance and recycling (**Eq. 26**).

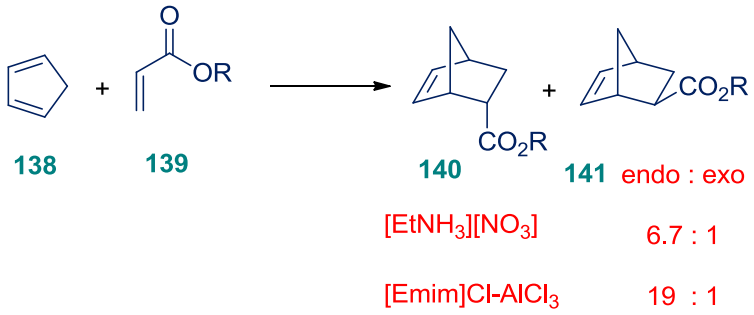
**Eq. 26**




The outcome of Diels-Alder reactions have been influenced by high polarizability, dipolarity and good hydrogen bond donor ability.[70] The first Diels-Alder reaction between cyclopentadiene (**138**) and alkyl acrylates **139** in ethylammonium nitrate gave high regioselective *endo* and *exo* products (**140** and **141**) in a ratio of 6.7:1.[71]

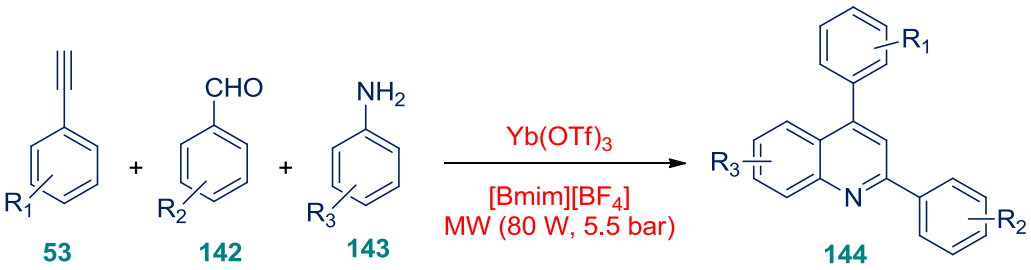
The same DA with [Emim][Cl]-$AlCl_3$ (51% $AlCl_3$) provided the rate of reaction 10, 175, and 560 times faster than in water, ethyl ammonium nitrate and 1-chlorobutane, respectively (**Eq. 27**) and afforded higher regioselectivity.

**Eq. 27**



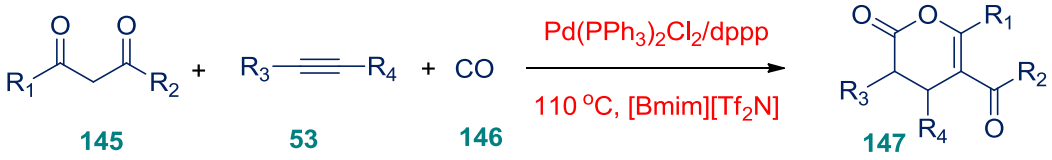

The quinoline nucleus is a privileged heterocyclic ring system because they are present in many natural compounds and medicinally active substances with a broad range of biological activity.[72] The conventional method for synthesis of quinolines and their derivatives is the Friedlander quinoline synthesis[73] which involves harsh reaction conditions, such as strong acids or bases, and higher reaction temperatures.

**Eq. 28**




Microwave-assisted, a straightforward and efficient three-component reaction of aldehydes **142**, alkynes **53**, and amines **143** for the synthesis of substituted quinolines **144** has been developed by Kumar, *et al*.[74] using Yb(OTf)$_3$ in [Bmim][$BF_4$]. It is noteworthy to mention that the IL was recycled and reused four times with good yields 90%, 88%, 85%, and 86% respectively (**Eq. 28**).

**Eq. 29**



Alper *et al*.[75] developed a procedure for the regioselective synthesis of highly substituted endocyclic enol lactones through the three component coupling reactions of alkynes **53**, 1,3-diketones **145** and CO **146** in ionic liquid. It is noteworthy to mention that the desired carbonylation product **147** was detected only in trace amount in organic solvents, whereas ionic liquid [Bmim][$Tf_2N$] could be able to give more than 60% product yield. They observed moderate loss of catalytic activity of $Pd(PPh_3)_2Cl_2$ and dppp even after five runs, because of their good solubility nature in the ionic liquid (**Eq. 29**).

## Trivalent Lanthanides

The trivalent lanthanide salts are mostly used in the organic transformations. The choice of $La^{3+}$ salt for many organic syntheses is mainly due to its broad solvent tolerance including water, the scope for asymmetric catalysis and the reactivity of them can be tuned by suitable lanthanides and choice of counter anion. The catalytic activity of $Ln^{3+}$ is because of their hard nature. It has strong affinity towards hard base such as oxygen donor ligands. According to Pearson's HSAB principle, the interaction between hard acids and hard bases is ionic, whereas bonding between soft acids and soft bases is covalent in character.[76]

From tandem mass spectrometry, based on competitive ligand dissociation from complexes, it has been proven that the Lewis acidity increases within the lanthanide series, in which Yb(III) and Sc(III) have extraordinary Lewis acidity due their smaller ionic radii.[77] The scandium salts are somewhat expensive, owing to the difficulties with isolation and separation from the ores. The drawback with yetterbium is that anhydrous conditions are required, though they are cheaper, more readily available and can catalyze many reactions.[78] The aspects of lanthanide mediated organic synthesis have been recognized by a number of excellent review articles.[79] These trivalent lanthanides are efficient for many chemo- and stereoselective synthesis, including Diels-Alder reactions, aldol condensations, olefine polymerization, and bromination of aromatic compounds.[79] Luche reported chemoselective reduction of ketone in the presence of aldehyde and unsaturated ketone in the presence of non-conjugated ketone with sodium borohydride in combination with $CeCl_3$. Recently, Taylor *et al.* demonstrated the utility of Luche reduction for their total synthesis of the indole alkaloid, Spirobacillene A.[80] Among trivalent lanthanide salts, $Ln(OTf)_3$ have been mostly contributing for organic transformations. These triflates can be prepared by reaction of the corresponding metal oxide or chloride with aqueous trifluoromethanesulfonic acid.[81]

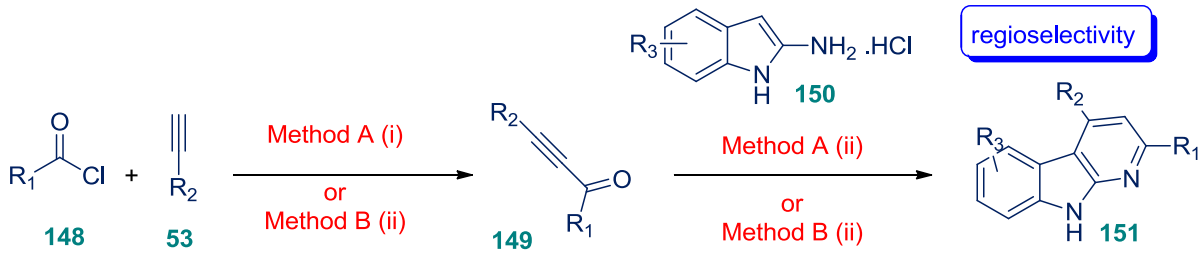
## Copper catalysis

The copper based organic synthesis is extremely enormous because its accessibility towards different oxidation states such as $Cu^0$, $Cu^I$, $Cu^{II}$ and $Cu^{III}$ as well, so that, it can allow one-electron or two electron processes. As a result both radical pathways and two electron bonding interaction are feasible with Cu salts like organometallic intermediate as like Pd chemistry. The copper salts are mostly inexpensive, nontoxic catalyst, insensitive to air in comparison with other transition metal salts such as Pd, Pt, and Au. Therefore, copper catalyzed organic syntheses with C-C multiple bonds have been accepted as convenient tool to make many carbocyclic as well as heterocyclic compounds.

The route to modern copper-mediated chemistry was commenced with the pioneering and inimitable work of Fritz Ullmann and Irma Goldberg. Ullmann reported the nucleophilic reaction between aniline and 2-chlorobenzoic acid in the presence of 1 equiv. of copper to afford 2-phenylaminobenzoic acid.[82] Goldberg reported the first copper-catalyzed arylation of amides using bromobenzene and benzamide.[83]

Their pioneering discoveries have undoubtedly paved the way for the development of copper-mediated reactions. In modern era, the forefront of coupling reactions is the Buchwald's mild transition-metal-catalyzed C-N bond forming reactions.[84] They developed a catalytic copper/diamine-ligand-based system for a broad range of aryl and alkyl amides to aryl and heteroaryl halides, whereas Ullmann's amination and Goldberg's amidation reactions suffered from harsh conditions, in particular due to higher reaction temperatures.

**Eq. 30**



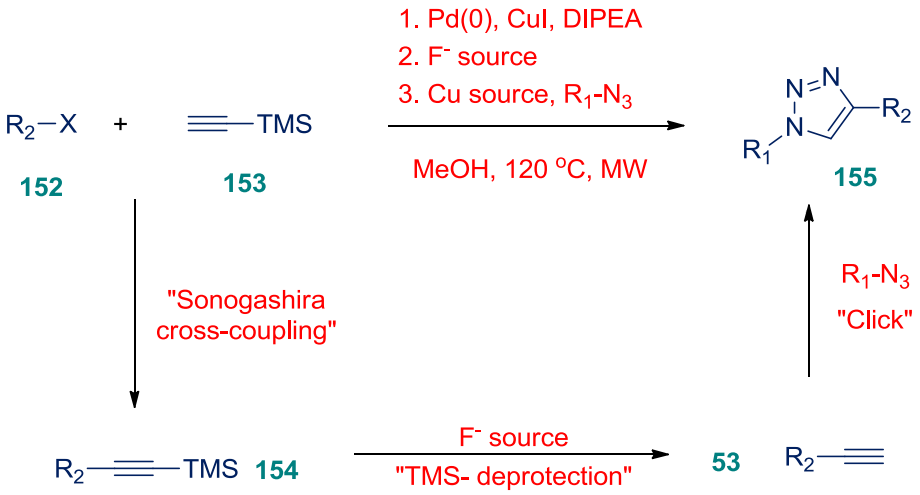

Method A: (i) $PdCl_2(PPh_3)_2$/ CuI, $K_2CO_3$, SDS, $H_2O$ (1 mL), 3 h, 0-65 $^oC$
(ii) KOH (4 equiv.), DMSO (1 mL), 2 h
Method B: (i) $PdCl_2(PPh_3)_2$/ CuI, TEA, rt, 1 h
(ii) KOH (4 equiv.), DMSO-$H_2O$, rt, 15 min

Kundu *et al*.[85] have developed an efficient, three-component tandem reaction for the synthesis of highly substituted naturally occurring $\alpha$-carbolines derivatives (**Eq. 30**).

The strategy involves condensation of acid chlorides **148** with terminal alkynes **53** under Sonogashira conditions both in aqueous and non-aqueous medium followed by in *situ* cyclocondensation of the resulting alkynones **149** with 2-aminoindole **150** hydrochlorides in the presence of KOH in DMSO or DMSO–$H_2O$ (**Eq. 30**).

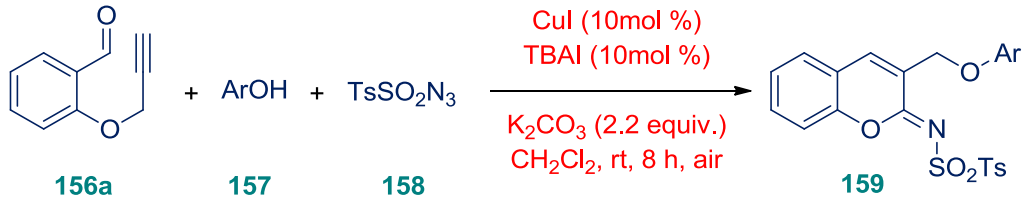
Cu(I)-catalyzed 1,3-dipolar cycloadditions of azides with terminal alkynes to give 1,4-disubtituted triazoles **155**. Triazoles are used in agrochemicals and have industrial applications such as dyes and corrosion inhibitors, and have been regarded as an interesting unit in terms of biological activity.[86] Huisgen's 1,3-dipolar cycloaddition is the earliest known method for the synthesis of 1,2,3-triazoles.[86] Recently, Boons *et al*. reported one-pot three step synthesis of 1,2,3-triazoles by copper-catalyzed cycloaddition of azides with alkynes formed by a Sonogashira cross-coupling and desilylation (**Eq. 31**).[87]

**Eq. 31**



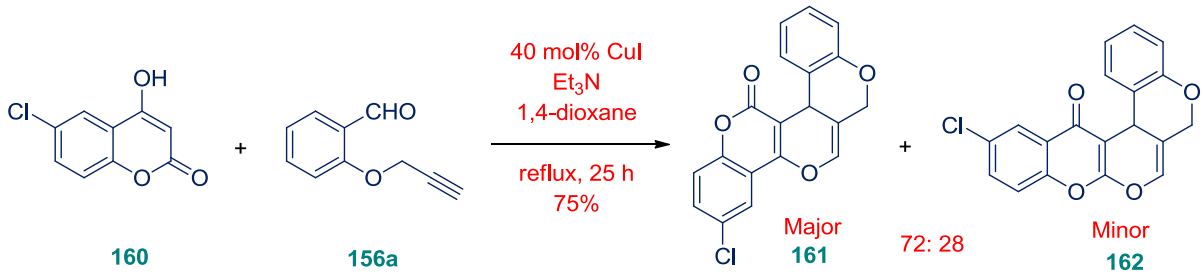

Punniyamurthy *et al*.[88] synthesized iminocoumarin aryl methyl ethers **159** via novel copper-catalyzed multicomponent cascade synthesis (**Eq. 32**). The formation of the product involves a cascade [3+2]-cycloaddition, 1,3-pseudopericyclic ketenimine rearrangement, 1,4-conjugate addition, and aldol-type condensation though copper catalysis.

**Eq. 32**



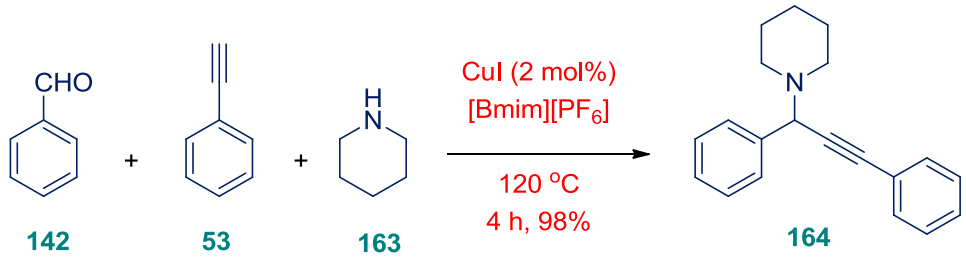
Balalaie *et al*. explained the domino Knoevenagel hetero-Diels-Alder reaction of the *O*-propargylated salicylaldehyde **156a** and 4-hydroxycoumarin **160** leading to pyranocoumarin **161** and **162** in high yield in the presence of CuI as a Lewis acid. In all cases, the reaction was shown to exhibit high regioselectivity and gave **161** as main product (**Eq. 33**).[89]

**Eq. 33**




Alper *et al*. developed an efficient synthesis of propargylamines through three-component coupling of aldehydes **142**, amines **163** and alkynes **53** *via* C-H activation by a copper catalyst in the ionic liquid (**Eq. 34**).[90]

**Eq. 34**

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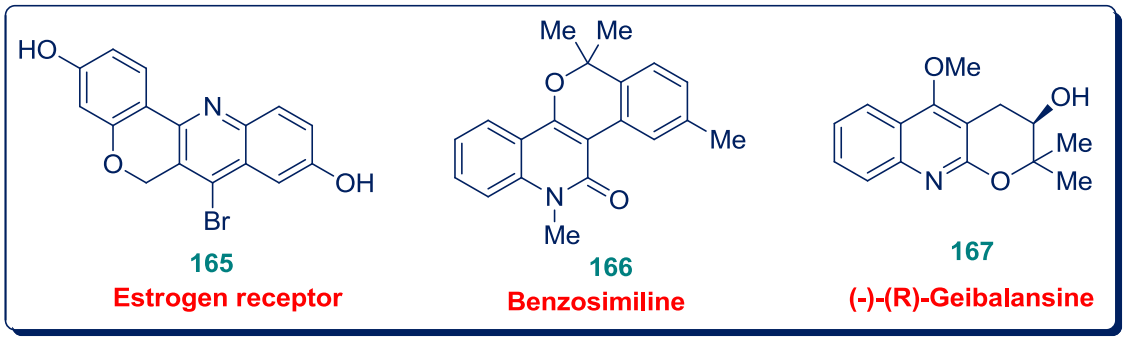
# CHAPTER 1

# Synthesis of chromenoquinolines via intramolecular aza-Diels-Alder reaction

## 1.1. Introduction

Chromenes are an important class of heterocyclic compounds which have attracted considerable attention, due to their diverse biological activites.[91] Their derivatives produce remarkable effects as pharmaceuticals, including antifungal,[91] antimicrobial,[92a] progestational,[92b] antibiotic rhodomyrtone,[92c] antiallergic,[92d] and antiulcer agents.[92e] As a member of this family, chromenoquinoline derivatives have attracted much attention recently due to the biological and pharmacological activities, (**Fig. 7**) such as selective progesterone receptor modulators,[93a] transcriptional activity,[93b] and glucocorticoid modulators.[93c]

**Fig. 7**



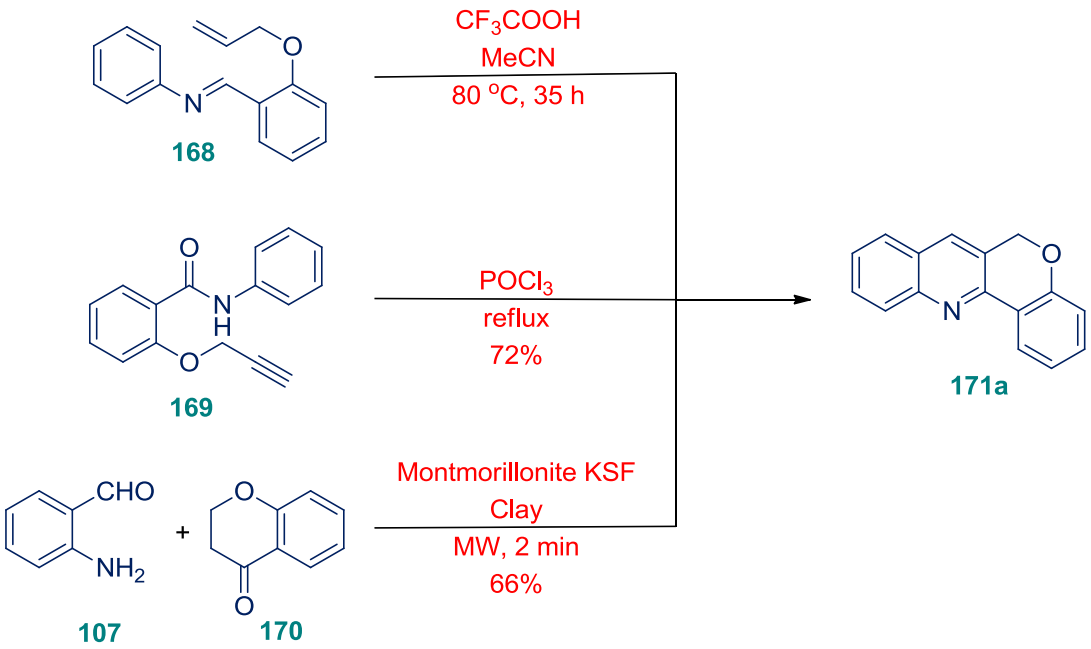

165
Estrogen receptor

166
Benzosimiline

167
(-)-(R)-Geibalansine

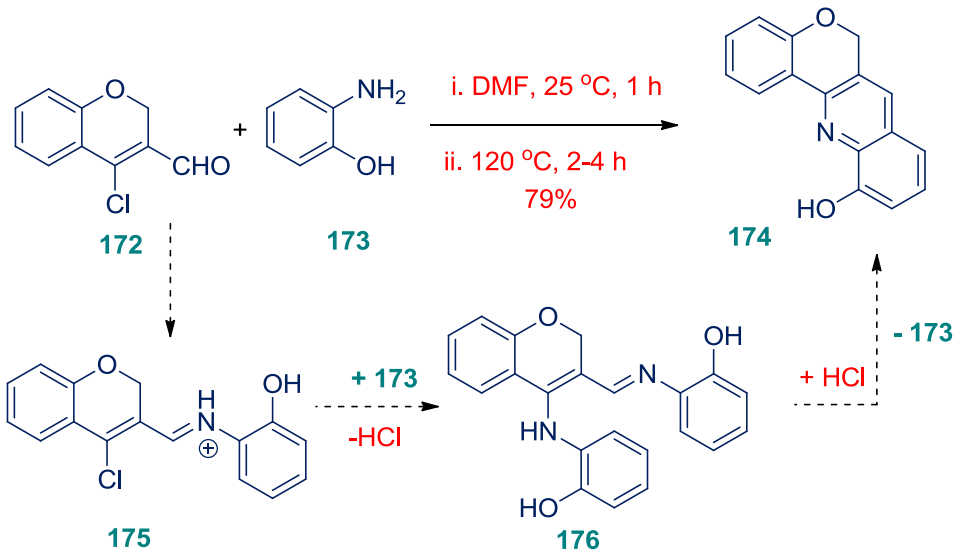
However, only a few reports are available in the literature for the synthesis of chromenoquinolines. Tomashevskaya *et al*. demonstrated the intramolecular aza Diels-Alder reaction of Schiff base **168** generated from aniline and 2-allyloxybenzaldehyde (**Eq. 35**).[94] They also reported the synthesis of chromenoquinoline through $POCl_3$ mediated cyclization of *o*-alkoxyamide **169** (**Eq. 35**).[94] Sabitha *et al*. reported microwave assisted Friedlander condensation catalyzed by clay (**Eq. 35**).[95]

**Eq. 35**



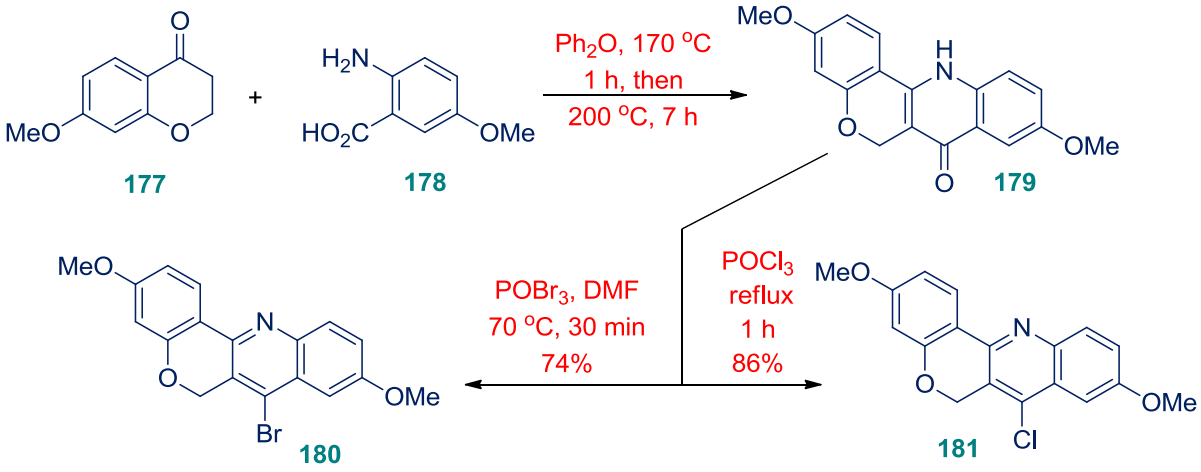

Pal, *et al*. synthesized the chromenoquinoline by reaction of chloroacrolein (**172**) with 2-aminophenol (**173**) (**Eq. 36**). The reaction proceeded via protonated imine intermediate which further reacts with another molecule of 2-aminophenol, followed by C-N bond formation from elimination of HCl. The *β*-amino imine **176** underwent ring closing mechanism in acidic medium to provide the quinoline **174**.[96]

**Eq. 36**




Vu and co-workers prepared Cl- and Br- based estrogen receptor *β*-selective chromenoquinoline ligands. They carried out Niementowski modified Freidlander synthesis of the quinolines. Thus, condensation of chromanone **177** and anthranilic acid derivative **178** gave compound **179**. Subsequent reaction with $POCl_3$ and $POBr_3$ afforded chloro and bromo chromenoquinolines **180** and **181** respectively (**Eq. 37**).[97]

**Eq. 37**



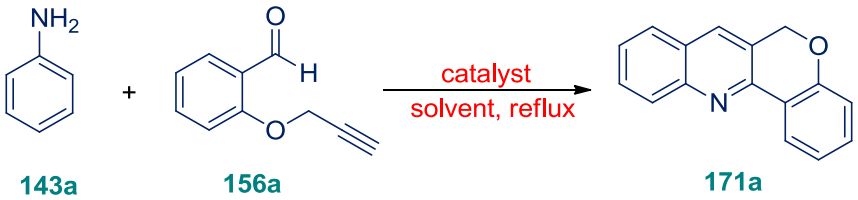

In these reports longer reaction time was required, lower product yields were obtained, and harsh conditions were needed. Activation of a terminal alkyne C–H bond by transition-metal catalysts is one of the fundamental interests in organic synthesis. It has been reported that transition-metal catalysts such as Cu(I),[98] Au(I), Au(III), silver, and ruthenium can activate terminal alkynes.[99] We chose copper catalyst[100] compared to other transition-metal catalysts since most of copper compounds are readily available, inexpensive, nontoxic catalyst, insensitive to air, and much cheaper than silver,[101] gold,[102] ruthenium, or other metals.[103]

Imino Diels–Alder reaction is the one of the most powerful synthetic tools for biologically interesting heterocycles and natural product synthesis.[38] Herein we demonstrate facile one-pot copper catalyzed aza-Diels–Alder type reaction between various amines and propargylated salicylaldehydes to afford different chromenoquinoline derivatives in moderate to good yields.

## 1.2. Synthesis of 6*H*-chromenoquinolines

Herein, we delineate the synthesis of 6*H*-chromeno[4,3-*b*]quinolines **171a-i, 172b-f** and **174** using the mixture of copper(I) iodide and lanthanum triflate as efficient catalysts.

**Scheme 1**



Initially, we examined the reaction between aniline **143a** and *O*-propargylated salicylaldehyde **156a** as starting materials using different catalysts to optimize the reaction conditions (**Scheme 1**). It was found that 10 mol% of $BF_3{\cdot}Et_2O$ as a Lewis acid was not much useful to obtain the desired product and only 20% yield was obtained (**Table 1**, entry 1).

**Table 1: Optimization of the reaction conditions**

| Entry | Catalyst | Solvent | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | $BF_3.Et_2O$ (10 mol%) | MeCN | 10 | 20 |
| 2 | $La(OTf)_3$ (10 mol%) | MeCN | 7 | 45 |
| 3 | $InCl_3$ (10 mol%) | MeCN | 8 | 40 |
| 4 | CuBr (10 mol%) | MeCN | 11 | 60 |
| 5 | CuCl (10 mol%) | MeCN | 7 | 65 |
| 6 | CuI (10 mol%) | MeCN | 5.5 | 70 |
| 7 | CuBr/$La(OTf)_3$ (10 mol%) | MeCN | 5.5 | 72 |
| 8 | CuCl/$La(OTf)_3$ (10 mol%) | MeCN | 6 | 75 |
| 9 | CuI/$InCl_3$ (10 mol%) | MeCN | 6 | 75 |
| 10 | CuI/AgOTf (10 mol%) | MeCN | 6 | 76 |
| 11 | CuI/$CF_3COOH$ (10 mol%) | MeCN | 8 | 60 |
| 12 | CuI/$Sc(OTf)_3$ (10 mol%) | MeCN | 6 | 81 |
| 13 | CuI/$Yb(OTf)_3$ (10 mol%) | MeCN | 6 | 83 |
| **14** | **CuI/$La(OTf)_3$ (10 mol%)** | **MeCN** | **4** | **90** |
| 15 | CuI/$La(OTf)_3$ (10 mol%) | THF | 7 | 78 |
| 16 | CuI/$La(OTf)_3$ (10 mol%) | DMF | 8 | 82 |
| 17 | CuI/$La(OTf)_3$(10 mol%) | DMSO | 8 | 74 |
| 18 | CuI/$La(OTf)_3$ (10 mol%) | EtOH | 10 | 67 |
| 19 | CuI/$La(OTf)_3$ (20 mol%) | MeCN | 4.5 | 89 |
| 20 | CuI/$La(OTf)_3$ (5 mol%) | MeCN | 4.5 | 80 |

Then we turned our attention to the use of other Lewis acids like $La(OTf)_3$, $InCl_3$ (entries 2 and 3) as catalysts for the synthesis of 6*H*-chromeno[4,3-*b*]quinoline because they are more reactive than $BF_3{\cdot}Et_2O$ in acetonitrile as solvent. Further optimization was performed to improve the yield of the product. All Cu(I) species (entries 4–6) showed better catalytic properties. We could find out that catalytic property was excellent when we use combination of Cu(I) species/ Lewis acids or Brønsted acids (entries 7–14). When we employed AgOTf (entry 10) in combination with CuI, 76% of yield was obtained. On

the other hand, only 60% of yield was obtained when we use $CF_3COOH$ (entry 11) as a Brønsted acid. Transition-metal triflates such as scandium triflate, ytterbium triflate, and lanthanum triflate catalysts also furnished the reaction with good yields (entry 12–14). These three triflates have similar reactivity in terms of reaction yield. But we chose $La(OTf)_3$ for the further optimization of the reaction due to its low cost and stability under moisture. In particular, the combination of 10 mol% of each CuI and $La(OTf)_3$ (entry 14) gave the highest yield. We changed the percentage loading of the catalysts by 5 mol%, 10 mol%, and 20 mol% (entries 17 and 18).

The use of 5 mol% of CuI/$La(OTf)_3$ gave 80% of yield which is lower than the reaction with 10 mol% of CuI/$La(OTf)_3$. But 20 mol% of the catalyst did not change any considerable yield difference (entry 19). Our further study has revealed that this cyclization reaction can be accelerated at an elevated temperature.

**Scheme 2**

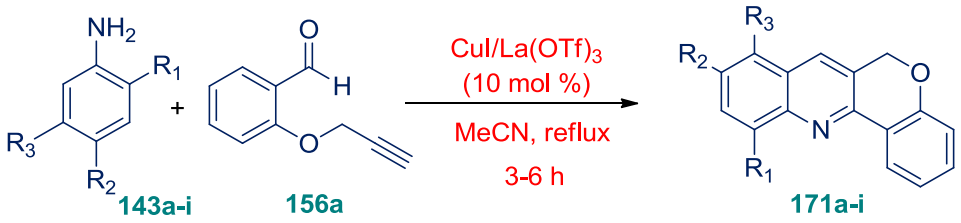



**Table 2: Synthesis of chromenoquinolines (171a-i) with different armomatic amines (143a-i)**

| Entry | $R_2$ | $R_1$ | $R_3$ | Amine | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | H | H | H | **143a** | **171a** | 4.5 | 90 |
| 2 | Me | H | H | **143b** | **171b** | 3 | 92 |
| 3 | OMe | H | H | **143c** | **171c** | 3.5 | 93 |
| 4 | H | OMe | H | **143d** | **171d** | 4 | 91 |
| 5 | F | H | H | **143e** | **171e** | 4 | 85 |
| 6 | Cl | H | H | **143f** | **171f** | 4 | 83 |
| 7 | Br | H | H | **143g** | **171g** | 4.5 | 81 |
| 8 | H | OMe | Cl | **143h** | **171h** | 5.5 | 85 |
| 9 | 1-Aminonaphthalene | | | **143i** | **171i** | 6 | 80 |

When the reaction is run at reflux temperature of acetonitrile, 90% yield (entry 12) of desired product was obtained. Yield was less than 90% when other solvents like

THF, DMF, DMSO, and EtOH (entry 13–16) were used. Finally, we found that synthesis of 6*H*-chromeno[4,3-*b*]quinoline in the presence of CuI/La(OTf)$_3$ (10 mol%) at reflux temperature of MeCN was good.

Having optimized the reaction conditions, a variety of amines **143a**–**i** were employed in this reaction and a range of 6*H*-chromeno[4,3-*b*]quinoline derivatives **171a**–**i** were synthesized (**Scheme 2**) in good yields. As evident from **Table 2**, all the amines with ring-activating groups in the *ortho*, *para*, and *meta* positions participated in this reaction smoothly, and the yields of the products were remarkably similar. The single-crystal X-ray analysis of compound **171c** was also achieved in order to confirm their molecular structure (**Fig. 8**).

Naphthalen-1-yl-amine **143i** gave 80% yield of the desired chromenoquinoline product **171i**. ORTEP diagram of the compounds **171b** and **171f** are shown in **Fig. 8**. A series of *O*-propargylated salicylaldehydes **156b–f** were subjected to react with aniline (**143a**) by carrying out the reaction in the optimized conditions (**Scheme 3**). As shown in the **Table 3**, for most of the substrates the reaction provided good yields of chromenoquinoline derivatives (**172b-f**). It was noted that the substituents $R_4$ did not significantly affect the reaction.

**Scheme 3**

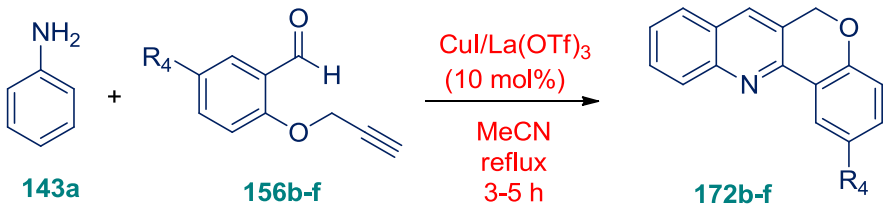
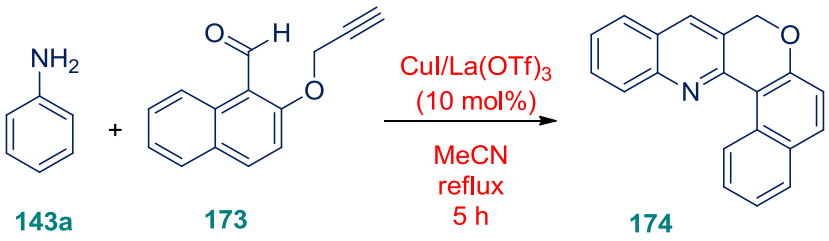



**Table 3: Synthesis of chromenoquinolines (171b-f) with different aldehydes (156b-f)**

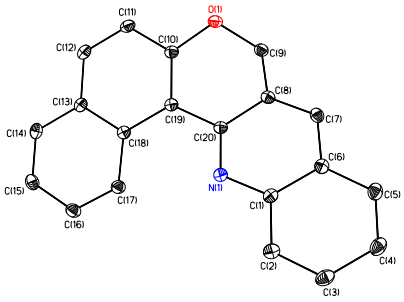
| Entry | $R_4$ | Aldehyde | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Me | **156b** | **172b** | 3.5 | 92 |
| 2 | OMe | **156c** | **172c** | 3 | 93 |
| 3 | F | **156d** | **172d** | 4 | 91 |
| 4 | Cl | **156e** | **172e** | 4 | 88 |
| 5 | Br | **156f** | **172f** | 5 | 86 |

**Scheme 4**

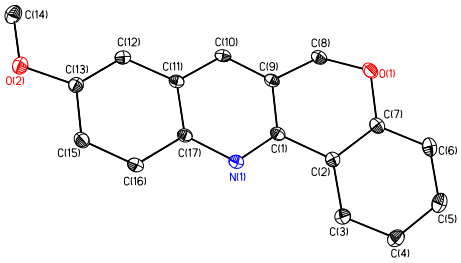



To check the generality of this reaction, we used 2-*O*-propargyl-1-naphthaldehyde **173** in this reaction (**Scheme 4**). The reaction proceeded well, and the product **174** was obtained in 78% yield. ORTEP diagram of **174** is shown in **Fig. 8.**

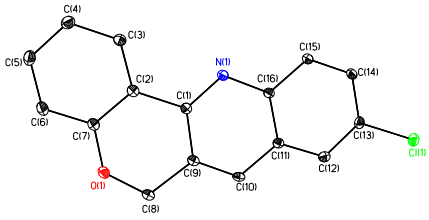
**Fig. 8: ORTEP of 174, 171b, 171c and 171f**



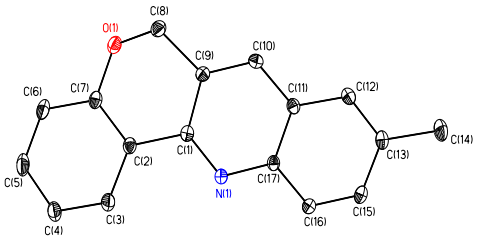
**174**



**171c**



**171f**

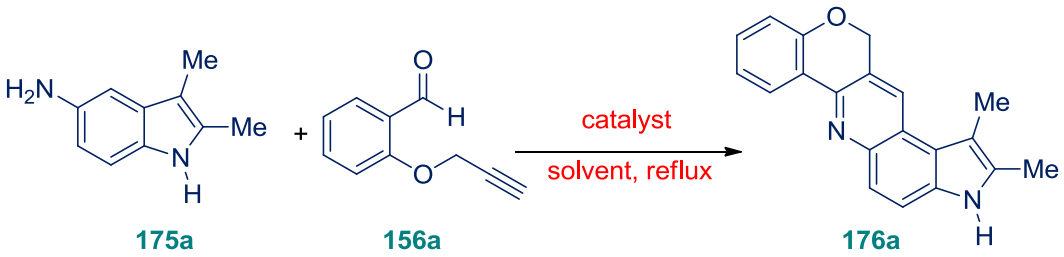


**171b**

## 1.3. Synthesis of chromenopyrroloquinoline derivatives

Pyrroloquinolines form the basic skeleton of numerous alkaloids and biologically active compounds.[104] It is envisioned that chromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolines, which contain both pyrroloquinoline and chromene moieties may exhibit unique biological activities and we paid attention to develop a methodology for their preparation. Herein we demonstrate a facile one-pot copper catalyzed aza-Diels–Alder type reaction between 5-aminoindoles and *O*-propargyl salicylaldehydes to afford dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline derivatives in moderate to good yields.

**Scheme 5**



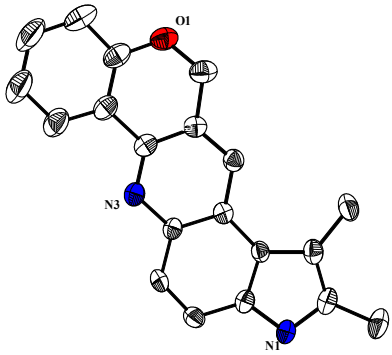

175a 156a 176a

**Table 4: Optimization of the reaction conditions**

| Entry | Catalyst | Solvent | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | CuBr (10 mol%) | MeCN | 5 | 40 |
| 2 | CuCl (10 mol%) | MeCN | 5 | 55 |
| 3 | $InCl_3$ (10 mol%) | MeCN | 20 | - |
| 4 | $La(OTf)_3$ (10 mol%) | MeCN | 20 | - |
| 5 | CuI (10 mol%) | MeCN | 5 | 68 |
| 6 | AgOTf (10 mol%) | MeCN | 6 | 50 |
| 7 | $Cu(OTf)_2$ (10 mol%) | MeCN | 8 | 60 |
| 8 | $PdCl_2$ (10 mol%) | MeCN | 15 | 25 |
| 9 | $Pd(OAc)_2$ (10 mol%) | MeCN | 10 | Trace |
| 10 | CuI (10 mol%) | THF | 8 | 60 |
| 11 | CuI (10 mol%) | DMF | 6 | 68 |
| 12 | CuI (10 mol%) | Toluene | 10 | 70 |
| 13 | CuI (10 mol%) | Ethanol | 12 | 65 |
| **14** | **CuI (10 mol%)** | **[Bmim][$BF_4$]** | **2** | **85** |
| 15 | CuI (10 mol%) | [Bmim][$PF_6$] | 2 | 75 |
| 16 | CuI (10 mol%) | [Bmim][Cl] | 2 | 75 |
| 17 | CuI/ $La(OTf)_3$ (10 mol%) | [Bmim][$BF_4$] | 10 | 85 |
| 18 | CuI (10 mol%) | DMSO | 24 | 60 |
| 19 | CuI (10 mol%) | Xylene | 24 | 65 |
| 20 | CuI (30 mol%) | [Bmim][$BF_4$] | 5 | 85 |
| 21 | CuI (10 mol%) | [Bmim][$BF_4$] | 48 | 85 |
| 22[b] | CuI (10 mol%) | MeCN | 24 | 70 |

For the entries 1-9 reflux temperature of MeCN was maintained. For the entries 10-13 reflux temperature of the corresponding solvents were maintained. Temperature was maintained 90-95 °C for entries (14-21). In all entries, catalyst mol% was calculated relative to 5-aminoindole. [a] Yield refers to column purified product. [b] Reaction was performed with MeCN as solvent at 120 °C in a sealed tube.

**Fig. 9: ORTEP of compound 176a**




Initially, a mixture of 2,3-dimethyl-1*H*-5-indolamine (**175a**) and *O*-propargylsalicylaldehyde (**156a**) in MeCN as solvent was stirred at reflux temperature to optimize the reaction conditions (**Table 4**). When the reaction was catalyzed by CuBr (10 mol%), we observed the formation of the expected product **176a** in 40% yield (**Table 4**, entry 1). The structure of **176a** was also confirmed by single crystal X-ray crystallography (**Fig. 9**). No desired product was obtained when the reaction was carried out with $InCl_3$ and $La(OTf)_3$ for 20 h (entries 3 and 4). Other metal salts, such as CuI, AgOTf, $Cu(OTf)_2$, $PdCl_2$, $Pd(OAc)_2$ were also tested in the aza-Diels–Alder reaction (entries 5–9), and CuI was found to be the best choice (entry 5). To improve the yield, we examined various solvents in the presence of CuI as catalyst (entries 10–19). The best result was obtained when ionic liquid [Bmim][$BF_4$] was used. The yield of the product was not improved when mixed catalytic system was used (entry 17). 70% yield of **176a** was obtained, when the reaction was conducted in a sealed tube using MeCN solvent at 120 °C (entry 22). The reaction times were exceedingly long, when the reaction was conducted at temperatures lower than 90 °C. At temperatures above 100 °C, several unidentified minor side products were formed.

With the optimized conditions in hand, that is, CuI as the suitable catalyst and [Bmim][$BF_4$], we next evaluated the substrate scope of this reaction. Different 5-aminoindoles (**175a–i**) were successfully employed with *O*-propargyl salicylaldehyde (**156a**) to produce the corresponding dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline derivatives (**176a–i**) (**Scheme 6**).

**Scheme 6**

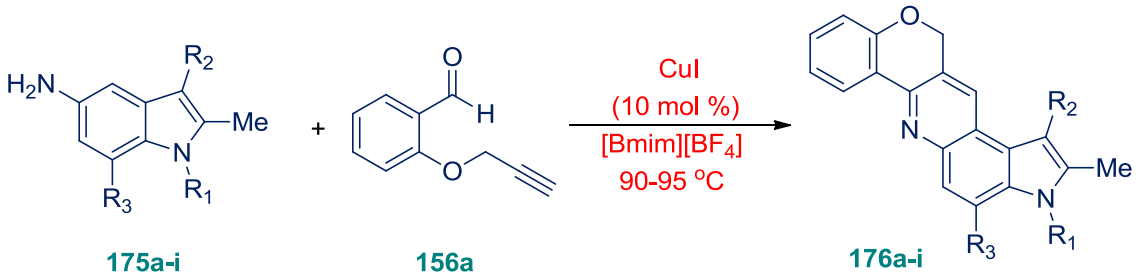
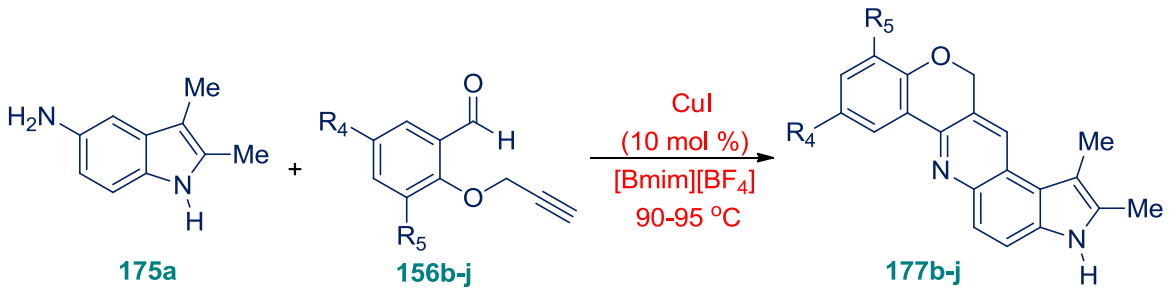


**Table 5: Synthesis of chromenopyrroloquinoline derivatives (176a-i) with different indoloamines (175a-i)**

| Entry | $R_1$ | $R_2$ | $R_3$ | Amine | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | H | Me | H | **175a** | **176a** | 2 | 85 |
| 2 | $C_2H_5$ | Me | H | **175b** | **176b** | 2 | 85 |
| 3 | $CH_2Ph$ | Me | H | **175c** | **176c** | 2 | 85 |
| 4 | H | H | H | **175d** | **176d** | 3 | 75 |
| 5 | *n*-Bu | H | H | **175e** | **176e** | 3 | 80 |
| 6 | Me | H | H | **175f** | **176f** | 3 | 80 |
| 7 | Me | Me | H | **175g** | **176g** | 3 | 83 |
| 8 | $SO_2Ph$ | H | H | **175h** | **176h** | 3 | 65 |
| 9 | H | Me | Cl | **175i** | **176i** | 3 | 83 |

Various substitution patterns at 1, 2, 3 positions as well as 7-Cl of 5-aminoindoles well tolerated the reaction (**Table 5**, entries 1–7, 9). This aza-Diels–Alder reaction was slightly affected by the electron withdrawing group (–$SO_2Ph$) and led to moderate yield (entry 8).

**Scheme 7**




We next turned our attention to vary the *O*-propargyl salicylaldehydes (**156b–i** and **173**) of the one-pot reaction with 5-aminoindole (**175a**) (**Scheme 7**). *O*-Propargyl salicylaldehydes with electron donating and electron withdrawing substituents did not show any significant change in the yields (**Table 6**, entries 1–9). The ORTEP of compound **177c** is shown in **Fig. 10**.

**Fig. 10: ORTEP of compound 177c**

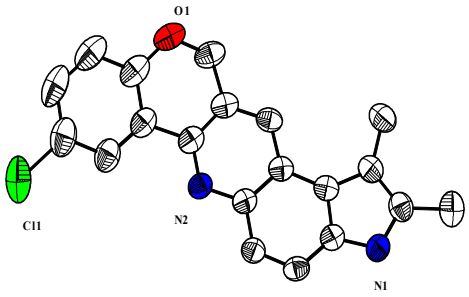


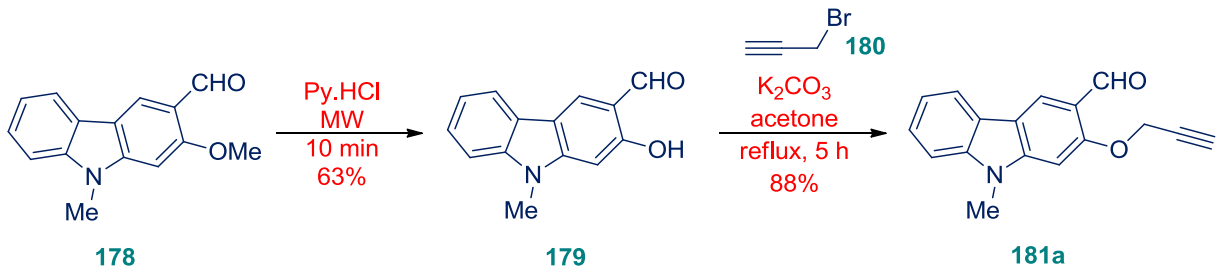

**Table 6: Synthesis of chromenopyrroloquinoline derivatives (177b-j) with different aldehydes (156b-i and 173)**

| Entry | $R_4$ | $R_5$ | Aldehyde | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Me | H | **156b** | **177b** | 2 | 85 |
| 2 | OMe | H | **156c** | **177c** | 3 | 80 |
| 3 | F | H | **156d** | **177d** | 1 | 88 |
| 4 | Cl | H | **156e** | **177e** | 2 | 80 |
| 5 | Br | H | **156f** | **177f** | 3 | 85 |
| 6 | Napthyl derivative | | **173** | **177g** | 3 | 85 |
| 7 | H | OMe | **156g** | **177h** | 2 | 81 |
| 8 | Cl | Cl | **156h** | **177i** | 3 | 80 |
| 9 | H | F | **156i** | **177j** | 3 | 84 |

## 1.4. Synthesis of pyrano[2,3-*b*]carbazole derivatives

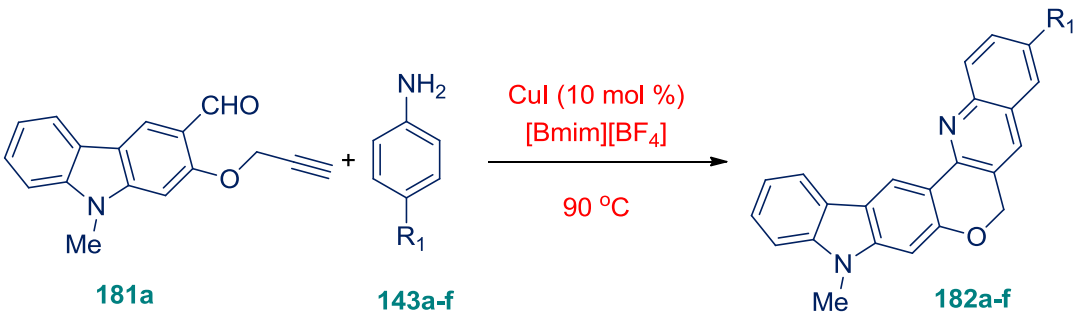
Carbazole alkaloids have immensely attracted synthetic chemists due to their easily accessible structural features and promising biological applications.[105] Among these, pyranocarbazole alkaloids form a prominent group due to their wide isolation from various plant sources and also their intriguing structural features.[106]

**Scheme 8**



Pyrayafolines, Eustifolines, Clausamines, Clausevatines *etc.* are some of the important pyranocarbazole alkaloids that have been synthesized in recent times.[106] Clausamines have been reported to inhibit EBV activation in Raji cells.[107] Diaryl pyranocarbazole derivatives were reported to show photochromic properties.[108] In continuation of our synthesis of chromenoquinolines via aza-Diels-Alder reaction, we report here, a simple and facile synthesis of new pyranocarbazole derivatives. The synthesis of *O*-propargylaldehyde precursor is shown in **Scheme 8**.

**Scheme 9**




181a 143a-f 182a-f

**Table 7: Synthesis of pyrano[2,3-*b*]carbazole derivatives (182a-f) with different anilines (143a-g)**

| Entry | $R_1$ | Aniline | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | H | **143a** | **182a** | 2.5 | 78 |
| 2 | Me | **143b** | **182b** | 2 | 81 |
| 3 | OMe | **143c** | **182c** | 2 | 83 |
| 4 | F | **143e** | **182d** | 5 | 76 |
| 5 | Cl | **143f** | **182e** | 4.5 | 75 |
| 6 | Br | **143g** | **182f** | 5 | 72 |

Then we carried out the cyclization reaction of *O*-propargyl derivative **181a** with aniline **143a** in the presence of CuI (**Scheme 9**) as it showed better activity in the synthesis of chrominoquinoline **171a-i** and **172b-f**, pyrroloquinoline derivatives **176a-i** and **177b-j**. We screened various solvents like THF, dioxane, DMSO, [Bmim][$BF_4$] *etc*. We found the condition using [Bmim][$BF_4$] as solvent, 10 mol% of CuI at 90 °C is giving better yield. Employing these optimized conditions, we successfully synthesized various pyranocarbazole derivatives **182a-f** in good yields (**Table 7**).

## 1.5. 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 spectrums were recorded on BRUKER-AVANCE-400/ 500 spectrometers. $^{1}H$ NMR (400 or 500 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned ($\delta$ = 2.50 ppm for $^{1}H$ NMR in the case of DMSO-$d_6$), with TMS ($\delta$ = 0 ppm) as an internal standard. $^{13}C$ NMR (100 or 125MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-$d_6$, $\delta$ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet ($\delta$ = 77.10 ppm) as an internal standard.

**Mass Spectral Analysis:** Shimadzu LCMS 2010A mass spectrometer. All the cases DCM or MeOH were used to dissolve the compounds. The TOF and quadrupole mass analyzer types are used for the HRMS measurements. Mass spectral data were obtained from HRMS (ESI).

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

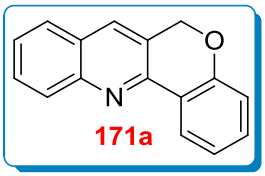
**X-ray Crystallography:** The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-$K_\alpha$ fine-focus sealed tube ($\lambda$ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). The detector was placed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

***General procedure A:***

In a round bottom flask equipped with a magnetic stirring bar, 1.0 mmol of aniline, 1.0 mmol of *O*-propargylated salicylaldehyde in 20 mL of acetonitrile, was added 10 mol% of $La(OTf)_3$ and 10 mol% of CuI. After completion of the reaction, as indicated by the TLC, acetonitrile was evaporated; water (20 mL) was then added to the crude reaction mass. Then aqueous layer was extracted with dichloromethane (3 x 20 mL) and

the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel eluted using ethyl acetate and hexanes.

**6*H*-chromeno[4,3-*b*]quinoline (171a):** Compound **171a** was synthesized from salicylaldehyde (**156a**) and aniline **143a** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



171a

Yield: 90%

Mp: 126 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3051, 2295, 1649, 1033, 740

$^1H$ NMR (500 MHz) δ: 8.48 (1H, d, *J* = 8.0 Hz), 8.11 (1H, d, *J* = 8.0 Hz), 7.81 (1H, s), 7.72 (1H, d, *J* = 7.5 Hz), 7.67 (1H, t, *J* = 7.5 Hz), 7.46 (1H, t, *J* = 6.5 Hz); 7.36 (1H, t, *J* = 7.5 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 7.01 (1H, d, *J* = 7.5 Hz); 5.32 (2H, s)

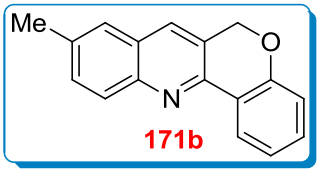
$^{13}C$ NMR (125 MHz) δ: 157.4, 149.0, 148.3, 131.8, 130.9, 129.5, 129.4, 127.5, 127.4, 126.2, 125.5, 125.2, 123.2, 122.5, 117.3 (aromatic C), 68.4 (aliphatic C)

LCMS (m/z): 234 $(M+H)^+$

Anal. calcd. for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00%

Found: C, 82.25; H, 4.80; N, 6.12%

**9-Methyl-6*H*-chromeno[4,3-*b*]quinoline (171b):** Compound **171b** was synthesized from salicylaldehyde (**156a**) and aniline **143b** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.



171b

Yield: 92%

Mp: 118-120 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2918, 1604, 1464, 1035

$^1H$ NMR (400 MHz) δ: 8.43-8.46 (1H, m), 8.00 (1H, d, *J* = 7.9 Hz), 7.76 (1H, s), 7.56-7.46 (1H, m), 7.45 (1H, s), 7.33 (1H, t, *J* = 7.7 Hz),

7.12 (1H, t, *J* = 7.9 Hz), 6.99 (1H, t, *J* = 8.1 Hz), 5.26 (2H, s), 2.47 (3H, s)

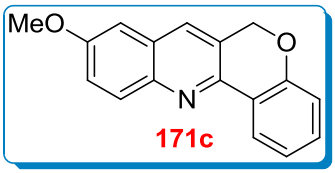
$^{13}$C NMR (100 MHz) δ: 157.3, 148.2, 146.9, 136.2, 131.8, 131.6, 130.3, 129.1, 127.6, 126.4, 125.4, 125.1, 123.4, 122.5, 117.3 (aromatic C), 68.5, 21.6 (aliphatic C)

LCMS (m/z): 248 $(M+H)^+$

Anal. calcd. for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66%

Found: C, 82.68; H, 5.21; N, 5.78%

**9-Methoxy-6*H*-chromeno[4,3-*b*]quinoline (171c):** Compound **171c** was synthesized from salicylaldehyde (**156a**) and aniline **143c** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.




Yield: 93%

Mp: 125 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2924, 1804, 1494, 1163, 621

$^1$H NMR (400 MHz) δ: 8.46 (1H, d, *J* = 7.5 Hz), 8.03 (1H, d, *J* = 7.9 Hz), 7.63 (1H, s), 7.36 (2H, s), 7.18 (1H, t, *J* = 7.8 Hz), 7.01 (1H, d, *J* = 8.2 Hz), 6.96 (1H, s), 5.28 (2H, s), 3.89 (3H, s)

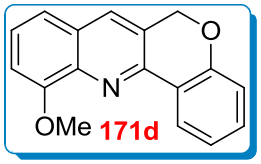
$^{13}$C NMR (100 MHz) δ: 157.7, 157.0, 146.7, 144.4, 131.3, 130.8, 129.7, 128.6, 125.5, 125.2, 123.5, 122.5, 121.1, 117.3, 105.2 (aromatic C), 68.4, 55.5 (aliphatic C)

LCMS (m/z): 264 $(M+H)^+$

Anal. calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32%

Found: C, 77.63; H, 4.89 N, 5.40%

**11-Methoxy-6*H*-chromeno[4,3-*b*]quinoline (171d):** Compound **171d** was synthesized from salicylaldehyde (**156a**) and aniline **143d** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 91%

Mp: 121 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2926, 1728, 1342, 1026, 738

$^{1}H$ NMR (400 MHz) δ: 8.55 (1H, d, *J* = 7.5 Hz); 7.82 (1H, s); 7.34-7.40 (3H, m); 7.16-7.18 (1H, m); 7.00-7.05 (2H, m); 5.34 (2H, s), 4.10 (3H, s)

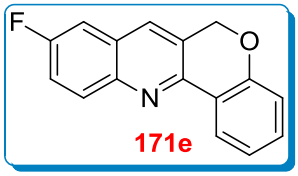
$^{13}C$ NMR (100 MHz) δ: 157.3, 155.4, 148.0, 140.2, 131.8, 131.1, 128.8, 126.5, 126.0, 125.7, 123.3, 122.6, 119.4, 117.2, 108.1 (aromatic C), 68.3, 56.2 (aliphatic C)

LCMS (m/z): 264 $(M+H)^{+}$

Anal. calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32%

Found: C, 77.40; H, 4.90; N, 5.37%

**9-Fluoro-6*H*-chromeno[4,3-*b*]quinoline (171e):** Compound **171e** was synthesized from salicylaldehyde **156a** and aniline **143e** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 4% ethyl acetate in hexanes.



171e

Yield: 85%

Mp: 99-101 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2944, 2100, 1602, 1462, 758

$^{1}H$ NMR (400 MHz) δ: 8.41 (1H, d, *J* = 7.9 Hz), 8.05-8.08 (1H, m), 7.71 (1H, s), 7.42 (1H, t, *J* = 8.1 Hz), 7.31-7.35 (2H, m), 7.14 (1H, t, *J* = 7.7 Hz), 6.99 (1H, d, *J* = 7.8 Hz), 5.28 (2H, s)

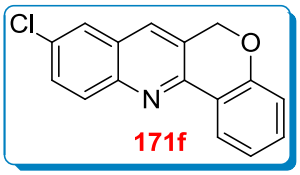
$^{13}C$ NMR (100 MHz) δ: 161.5, 159.1, 157.3, 148.4, 145.4, 131.9, 131.7, 130.2, 130.1, 128.1, 128.0, 126.0, 125.4, 123.0, 122.6, 119.7, 119.4, 117.3, 110.6, 110.4 (aromatic C), 68.2 (aliphatic C)

LCMS (m/z): 252 $(M+H)^{+}$

Anal. calcd. for $C_{16}H_{10}FNO$: C, 76.48; H, 4.01; N, 5.57%

Found: C, 76.54; H, 4.07; N, 5.64%

**9-Chloro-6*H*-chromeno[4,3-*b*]quinoline (171f):** Compound **171f** was synthesized from salicylaldehyde **156a** and aniline **143f** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



171f

Yield: 83%

Mp: 128-130 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3012, 2429, 1604, 1485, 572

$^{1}H$ NMR (400 MHz) δ: 8.41 (1H, d, *J* = 8.1 Hz), 8.00 (1H, d, *J* = 7.9 Hz), 7.66 (2H, s), 7.58 (1H, d, *J* = 7.6 Hz), 7.34-7.38 (1H, m), 7.00-7.14 (1H, m), 6.99 (1H, d, *J* = 7.9 Hz), 5.28 (2H, s)

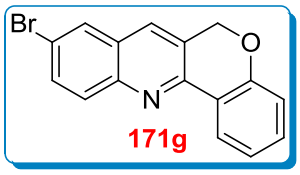
$^{13}C$ NMR (100 MHz) δ: 157.4, 149.3, 146.7, 132.2, 131.9, 131.0, 130.4, 130.0, 128.1, 126.1, 125.6, 122.9, 122.6, 117.4 (aromatic C), 68.2 (aliphatic C)

LCMS (m/z): 268 $(M+H)^{+}$

Anal. calcd. for $C_{16}H_{10}ClNO$: C, 71.78; H, 3.77; N, 5.23%

Found: C, 71.85; H, 3.70; N, 5.30%

**9-Bromo-6*H*-chromeno[4,3-*b*]quinoline (171g):** Compound **171g** was synthesized from salicylaldehyde (**156a**) and aniline **143g** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



171g

Yield: 81%

Mp: 138 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3043, 2854, 1458, 1107, 603

$^{1}H$ NMR (400 MHz) δ: 8.43 (1H, d, *J* = 7.8 Hz), 7.96 (1H, d, *J* = 8.1 Hz), 7.86 (1H, s), 7.72 (1H, d, *J* = 8.5 Hz), 7.68 (1H, s), 7.39 (1H, t, *J* = 7.9 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 7.02 (1H, d, *J* = 8.3 Hz), 5.30 (2H, s)

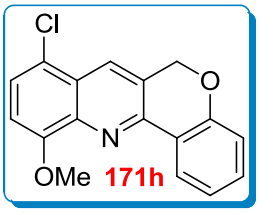
$^{13}C$ NMR (100 MHz) δ: 157.4, 149.3, 146.8, 132.9, 132.1, 131.0, 129.7, 129.4, 128.6, 126.1, 125.6, 122.8, 122.3, 120.0, 117.4 (aromatic C), 68.2 (aliphatic C)

LCMS (m/z): 313 $(M+2)^+$

Anal. calcd. for $C_{16}H_{10}BrNO$: C, 61.56; H, 3.23; N, 4.49%

Found: C, 61.50; H, 3.29; N, 4.53%

**8-Chloro-11-methoxy-6*H*-chromeno[4,3-*b*]quinoline (171h):** Compound **171h** was synthesized from salicylaldehyde (**156a**) and aniline **143h** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



171h

Yield: 85%

Mp: 130 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3067, 3015, 1602, 1030, 536

$^1H$ NMR (400 MHz) δ: 8.51 (1H, d, *J* = 7.9 Hz), 8.21 (1H, s), 7.45 (1H, d, *J* = 8.2 Hz), 7.35-7.39 (1H, m), 7.16 (1H, t, *J* = 7.7 Hz), 7.01 (1H, d, *J* = 8.0 Hz), 6.94 (1H, d, *J* = 8.1 Hz), 5.40 (2H, s), 4.08 (3H, s)

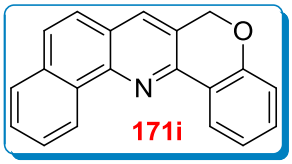
$^{13}C$ NMR (100 MHz) δ: 157.4, 154.7, 148.6, 140.6, 132.2, 128.2, 126.5, 126.3, 126.1, 126.0, 122.8, 122.6, 122.1, 117.3, 108.0 (aromatic C), 68.3, 56.4 (aliphatic C)

LCMS (m/z): 298 $(M+H)^+$

Anal. calcd. for $C_{17}H_{12}ClNO_2$: C, 68.58; H, 4.06; N, 4.70%

Found: C, 68.62; H, 4.10; N, 4.77%

**6*H*-benzo[h]chromeno[4,3-*b*]quinoline (171i):** Compound **171i** was synthesized from salicylaldehyde (**156a**) and aniline **143i** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.



171i

Yield: 80%

Mp: 130 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3043, 1599, 1404, 1107, 526

$^1H$ NMR (400 MHz) δ: 9.46 (1H, d, *J* = 7.9 Hz), 8.67 (1H, d, *J* = 8.2 Hz), 7.89 (1H, d, *J* = 7.6 Hz), 7.81 (1H, s), 7.70-7.78 (3H, m), 7.61 (1H,

d, *J* = 7.9 Hz), 7.40 (1H, t, *J* = 7.8 Hz), 7.22 (1H, t, *J* = 7.9 Hz), 7.05 (1H, d, *J* = 8.0 Hz), 5.39 (2H, s)

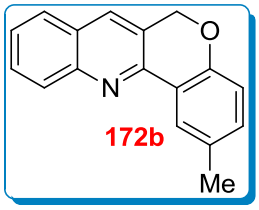
$^{13}$C NMR (100 MHz) δ: 157.1, 147.4, 146.3, 133.7, 131.6, 130.9, 128.2, 127.8, 127.5, 126.9, 125.6, 125.5, 125.2, 125.0, 124.7, 123.7, 122.5, 117.2 (aromatic C), 68.3 (aliphatic C)

LCMS (m/z): 284 $(M+H)^+$

Anal. calcd. for $C_{20}H_{13}NO$: C, 84.78; H, 4.62; N, 4.94%

Found: C, 84.70; H, 4.68; N, 4.88%

**2-Methyl-6*H*-chromeno[4,3-*b*]quinoline (172b):** Compound **172b** was synthesized from salicylaldehyde **156b** and aniline **143a** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.




Yield: 92%

Mp: 117 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3043, 2922, 1739, 1024, 746

$^1$H NMR (400 MHz) δ: 8.29 (1H, s), 8.14 (1H, d, *J* = 7.8 Hz), 7.71-7.77 (1H, m), 7.67 (2H, d, *J* = 7.7 Hz), 7.45-7.49 (1H, m), 7.18 (1H, d, *J* = 7.6 Hz), 6.93 (1H, d, *J* = 7.9 Hz), 5.27 (2H, s), 2.42 (3H, s)

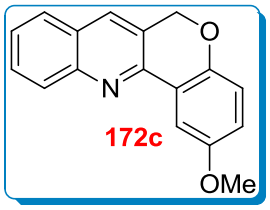
$^{13}$C NMR (100 MHz) δ: 155.4, 149.3, 148.3, 132.7, 132.0, 130.9, 129.5, 129.4, 128.8, 127.6, 127.5, 126.2, 125.5, 122.9, 117.1 (aromatic C), 68.4, 20.8 (aliphatic C)

LCMS (m/z): 248 $(M+H)^+$

Anal. calcd. for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66%

Found: C, 82.45; H, 5.28; N, 5.71%

**2-Methoxy-6*H*-chromeno[4,3-*b*]quinoline (172c):** Compound **172c** was synthesized from salicylaldehyde **156b** and aniline **143a** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 93%

Mp: 126-128 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3051, 2835, 1282, 1041, 694

$^{1}H$ NMR (400 MHz) δ: 8.14 (1H, d, *J* = 8.4 Hz), 8.0 (1H, s), 7.86 (1H, s), 7.77 (1H, d, *J* = 7.9 Hz), 7.70 (1H, t, *J* = 6.8 Hz), 7.50-7.54 (1H, m), 6.97 (2H, s), 5.31 (2H, s), 3.95 (3H, s)

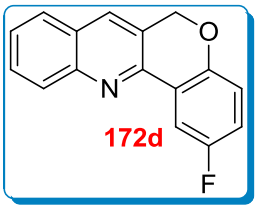
$^{13}C$ NMR (100 MHz) δ: 155.2, 151.7, 148.3, 131.0, 129.5, 129.4, 128.8, 127.7, 127.6, 126.4, 125.6, 123.7, 119.6, 118.4, 108.0 (aromatic C), 68.5, 55.9 (aliphatic C)

LCMS (m/z): 264 $(M+H)^{+}$

Anal. calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32%

Found: C, 77.61; H, 4.92; N, 5.41%

**2-Fluoro-6*H*-chromeno[4,3-*b*]quinoline (172d):** Compound **172d** was synthesized from salicylaldehyde **156d** and aniline **143a** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 91%

Mp: 122 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3045, 2843, 1608, 1116, 736

$^{1}H$ NMR (400 MHz) δ: 8.10-8.16 (2H, m), 7.81 (1H, s), 7.68-7.75 (2H, m), 7.48-7.52 (1H, m), 7.03-7.08 (1H, m), 6.95-6.98 (1H, m), 5.30 (2H, s)

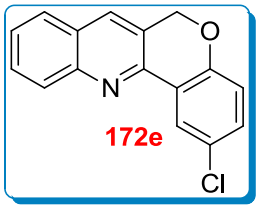
$^{13}C$ NMR (100 MHz) δ: 159.6, 157.2, 153.4, 148.3, 148.1, 131.0, 129.7, 129.5, 127.8, 127.5, 126.6, 125.0, 124.4, 124.3, 118.7, 118.6, 118.5, 118.4, 111.5, 111.3 (aromatic C), 68.5 (aliphatic C)

LCMS (m/z): 252 $(M+H)^{+}$

Anal. calcd. for $C_{16}H_{10}FNO$: C, 76.48; H, 4.01; N, 5.57%

Found: C, 76.54; H, 4.08; N, 5.60%

**2-Chloro-6*H*-chromeno[4,3-*b*]quinoline (172e):** Compound **172e** was synthesized from salicylaldehyde **156e** and aniline **143a** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 88%

Mp: 121 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3040, 2843, 1481, 1010, 733

$^{1}H$ NMR (400 MHz) δ: 8.47 (1H, d, *J* = 7.8 Hz), 8.13 (1H, d, *J* = 8.1 Hz), 7.89 (1H, s), 7.79 (1H, d, *J* = 8.0 Hz), 7.72 (1H, t, *J* = 8.0 Hz), 7.53 (1H, t, *J* = 7.6 Hz), 7.30-7.33 (1H, m), 6.97 (1H, d, *J* = 8.1 Hz), 5.37 (2H, s)

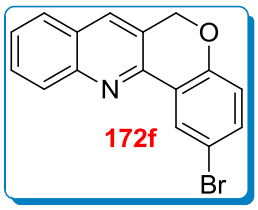
$^{13}C$ NMR (100 MHz) δ: 155.9, 148.3, 147.8, 131.6, 131.1, 129.8, 129.6, 128.8, 127.8, 127.5, 126.7, 125.2, 120.9, 120.6, 118.9 (aromatic C), 68.4 (aliphatic C)

LCMS (m/z): 268 $(M+H)^{+}$

Anal. calcd. for $C_{16}H_{10}ClNO$: C, 71.78; H, 3.77; N, 5.23%

Found: C, 71.82; H, 3.83; N, 5.30%

**2-Bromo-6*H*-chromeno[4,3-*b*]quinoline (172f):** Compound **172f** was synthesized from salicylaldehyde **156f** and aniline **143a** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 86%

Mp: 131 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3067, 2852, 1479, 1001, 522

$^{1}H$ NMR (400 MHz) δ: 8.58 (1H, d, *J* = 4.0 Hz), 8.11 (1H, d, *J* = 7.9 Hz), 7.82 (1H, s), 7.68-7.76 (2H, m), 7.49-7.52 (1H, m), 7.42-7.44 (1H, m), 6.88 (1H, d, *J* = 8.0 Hz), 5.32 (2H, s)

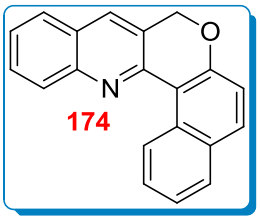
$^{13}C$ NMR (100 MHz) δ: 156.3, 148.3, 147.6, 134.4, 131.1, 129.8, 129.5, 128.1, 127.7, 127.5, 126.7, 125.0, 124.7, 119.2, 115.2 (aromatic C), 68.4 (aliphatic C)

LCMS (m/z): 313 $(M+2)^+$

Anal. calcd. for $C_{16}H_{10}BrNO$: C, 61.56; H, 3.23; N, 4.49%

Found: C, 61.51; H, 3.30; N, 5.43%

**8*H*-benzo[5,6]chromeno[4,3-*b*]quinoline (174):** Compound **174** was synthesized from salicylaldehyde **173** and aniline **143a** following the *general procedure A*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 78%

Mp: 128 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3051, 2852, 1305, 1010, 819

$^1H$ NMR (400 MHz) δ: 9.97 (1H, d, *J* = 8.0 Hz), 8.25 (1H, d, *J* = 7.9 Hz), 7.95 (1H, s), 7.80-7.88 (3H, m), 7.71-7.73 (2H, m), 7.49-7.55 (2H, m), 7.24 (1H, d, *J* = 7.5 Hz), 5.32 (2H, s)

$^{13}C$ NMR (100 MHz) δ: 157.8, 150.8, 148.1, 133.1, 131.4, 130.8, 129.7, 129.4, 128.4, 127.9, 127.3, 127.2, 126.7, 126.3, 124.5, 118.3, 116.2 (aromatic C), 68.9 (aliphatic C)

LCMS (m/z): 284 $(M+H)^+$

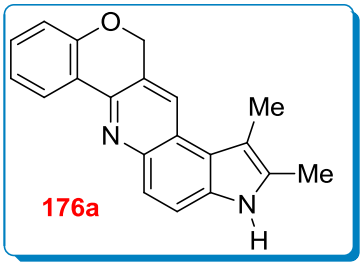
Anal. calcd. for $C_{20}H_{13}NO$: C, 84.78; H, 4.62; N, 4.94%

Found: C, 84.72; H, 4.67; N, 4.89%

***General procedure B:***

In a round bottom flask equipped with a magnetic stirring bar, 1.0 mmol of 5-indoamine and 1.0 mmol of *O*-propargyl salicylaldehyde in 5 mL of ionic liquid [Bmim][$BF_4$] as solvent, was added 10 mol% of CuI. Reaction mixture was stirred at 90–95 °C. After completion of the reaction, as indicated by the TLC, water (20 mL) was added to the crude reaction mass. Then aqueous layer was extracted with dichloromethane (3 X 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel eluted with ethyl acetate and hexanes.

**1,2-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (176a):** Compound **176a** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography (10% of ethylacetate in hexanes).




Yield: 85%

Mp: 243 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3366, 2852, 1388, 1298, 898, 580

$^1$H NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ: 9.79 (1H, s), 8.34-8.36 (2H, m), 7.67 (1H, d, *J* = 8.6 Hz), 7.58 (1H, d, *J* = 8.8 Hz), 7.22 (1H, t, *J* = 7.2 Hz), 7.04 (1H, t, *J* = 7.2 Hz), 6.9 (1H, d, *J* = 8.2 Hz), 5.33 (2H, s), 2.45 (3H, s), 2.36 (3H, s)

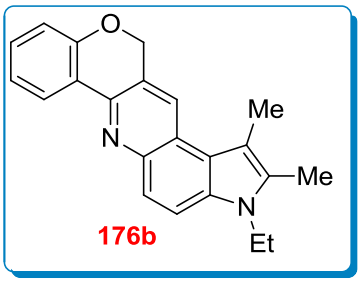
$^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ: 156.7, 145.5, 144.4, 131.3, 130.9, 130.7, 126.3, 124.7, 123.9, 123.4, 123.2, 122.3, 122.1, 120.9, 117.0, 116.2, 109.5 (aromatic C), 68.9, 12.2, 11.4 (aliphatic C)

LCMS (m/z): 301 $(M+H)^+$

Anal. calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33%

Found: C, 79.85; H, 5.41; N, 9.45%

**3-Ethyl-1,2-dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (176b):** Compound **176b** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175b** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 6% ethyl acetate in hexanes.




Yield: 85%

Mp: 217-219 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3061, 2920, 1365, 650

$^1$H NMR (400 MHz) δ: 8.50 (1H, d, *J* = 7.6 Hz), 8.43 (1H, s), 7.86 (1H, d, *J* = 8.9 Hz), 7.68 (1H, d, *J* = 9.0 Hz), 7.34 (1H, d, *J* = 7.1 Hz), 7.17 (1H, t, *J* = 7.2 Hz), 7.03 (1H, d, *J* = 8.0 Hz), 5.4 (2H, s), 4.23 (2H, q, *J* = 7.2 Hz), 2.6 (3H, s), 2.4 (3H, s), 1.38 (3H, t, *J* = 7.2 Hz)

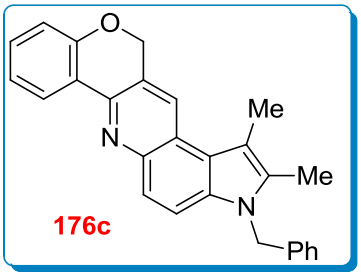
$^{13}$C NMR (100 MHz) δ: 156.8, 145.6, 144.7, 131.4, 130.7, 126.3, 124.9, 124.1, 123.6, 123.4, 122.5, 122.4, 120.5, 117.1, 113.9, 109.6 (aromatic C), 38.2, 15.9, 12.6, 9.8 (aliphatic C)

LCMS (m/z): 329 $(M+H)^+$

Anal. calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53%

Found: C, 80.55; H, 6.20; N, 8.39%

**3-Benzyl-1,2-dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (176c):** Compound **176c** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175c** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.



176c

Yield: 85%

Mp: 195-197 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3028, 2852, 1105, 817

$^1$H NMR (400 MHz) δ: 8.47-8.50 (2H, m), 7.83 (1H, d, *J* = 9.0 Hz), 7.62 (1H, d, *J* = 9.0 Hz), 7.24-7.36 (4H, m), 7.17 (1H, t, *J* = 7.4 Hz), 7.04 (1H, d, *J* = 8.1 Hz), 6.96 (2H, d, *J* = 7.0 Hz), 5.42 (2H, s), 5.41 (2H, s), 2.64 (3H, s), 2.30 (3H, s)

$^{13}$C NMR (100 MHz) δ: 156.9, 145.7, 144.9, 137.7, 132.5, 132.2, 130.8, 128.9, 127.4, 126.3, 125.9, 124.9, 124.0, 123.8, 123.3, 122.9, 122.4, 120.7, 117.1, 114.3, 110.2 (aromatic C), 69.0, 46.8, 12.7, 10.1 (aliphatic C)

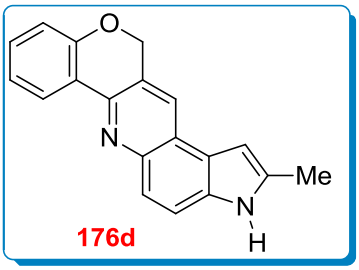
LCMS (m/z): 391 $(M+H)^+$

Anal. calcd. for $C_{27}H_{22}N_2O$: C, 83.05; H, 5.68; N, 7.17%

Found: C, 82.91; H, 5.73; N, 7.08%

**2-Methyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (176d):** Compound **176d** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175d** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 4% ethyl acetate in hexanes.

Yield: 75%




Mp: 190-192 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3423, 1575, 1032, 750

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.50 (1H, s), 8.42 (1H, s), 8.31 (1H, d, *J* = 7.4 Hz), 7.60-7.71 (2H, m), 7.35 (1H, t, *J* = 6.9 Hz), 7.14 (1H, t, *J* = 7.4 Hz), 7.02 (1H, d, *J* = 8.0 Hz), 6.76 (1H, s), 5.44 (2H, s), 2.47 (3H, s)

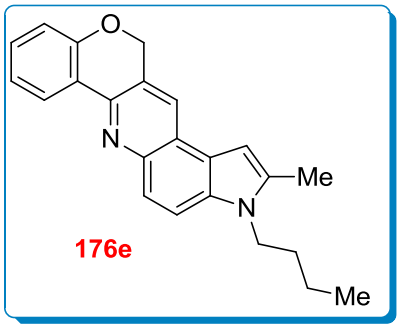
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 156.9, 144.7, 135.5, 132.3, 131.4, 127.3, 124.9, 124.3, 123.9, 123.2, 122.6, 121.9, 121.8, 117.6, 116.9, 99.9 (aromatic C), 68.3, 13.9 (aliphatic C)

LCMS (m/z): 287 $(M+H)^+$

Anal. calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78%

Found: C, 79.58; H, 4.90; N, 9.65%

**3-Butyl-2-methyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (176e):** Compound **176e** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175e** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 4% ethyl acetate in hexanes.




Yield: 80%

Mp: 141-143 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 2922, 1400, 1033, 644

$^1$H NMR (400 MHz) δ: 8.50 (1H, d, *J* = 6.9 Hz), 8.16 (1H, s), 7.85 (1H, d, *J* = 8.8 Hz), 7.66 (1H, d, *J* = 8.8 Hz), 7.34 (1H, t, *J* = 6.6 Hz), 7.17 (1H, t, *J* = 6.9 Hz), 7.03 (1H, d, *J* = 7.8 Hz), 6.73 (1H, s), 5.4 (2H, s), 4.16 (2H, t, *J* = 6.9 Hz), 2.50 (3H, s), 1.79 (2H, d, *J* = 6.9 Hz), 1.41 (2H, q, *J* = 6.9 Hz), 0.98 (3H, t, *J* = 6.9 Hz)

$^{13}$C NMR (100 MHz) δ: 156.9, 145.6, 145.2, 135.6, 132.6, 130.8, 126.2, 125.0, 124.1, 122.4, 122.3, 122.2, 121.8, 117.1, 114.4, 99.6

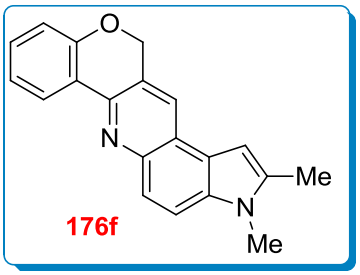
(aromatic C), 68.8, 43.4, 32.8, 20.3, 13.9, 12.9 (aliphatic C)

LCMS (m/z): 343 $(M+H)^+$

Anal. calcd. for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18%

Found: C, 80.45; H, 6.41; N, 8.25%

**2,3-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (176f):** Compound **176f** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175f** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 80%

Mp: 175-177 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2962, 1599, 1099, 815

$^1H$ NMR (400 MHz) δ: 8.49 (1H, d, *J* = 7.3 Hz), 8.15 (1H, s), 7.85 (1H, d, *J* = 9.0 Hz), 7.65 (1H, d, *J* = 9.0 Hz), 7.34 (1H, t, *J* = 7.0 Hz), 7.17 (1H, t, *J* = 7.4 Hz), 7.02 (1H, d, *J* = 8.0 Hz), 6.73 (1H, s), 5.4 (2H, s), 3.76 (3H, s), 2.50 (3H, s)

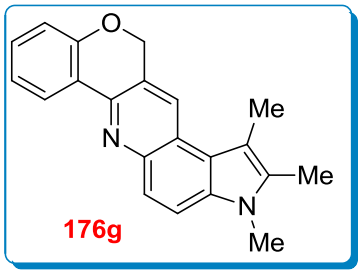
$^{13}C$ NMR (100 MHz) δ: 156.9, 145.6, 145.2, 136.1, 133.2, 130.9, 126.3, 125.0, 124.9, 124.1, 122.4, 122.1, 121.7, 117.1, 114.1, 99.4, 99.3 (aromatic C), 68.8, 29.9, 12.9 (aliphatic C)

LCMS (m/z): 301 $(M+H)^+$

Anal. calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33%

Found: C, 79.85; H, 5.31; N, 9.45%

**3-Methyl-1,2-dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (176g):** Compound **176g** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175g** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 83%

Mp: 200-201 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2918, 1483, 1005, 761

$^1H$ NMR (400 MHz) δ: 8.48-8.54 (1H, m), 8.36 (1H, s), 7.84 (1H, d, *J* = 8.4 Hz), 7.63 (1H, d, *J* = 8.9 Hz), 7.32-7.38 (1H, m), 7.18 (1H, d, *J* = 7.2 Hz), 7.01-7.03 (1H, m), 5.38 (2H, s), 3.72 (3H, s), 2.38 (3H, s), 2.56 (3H, s)

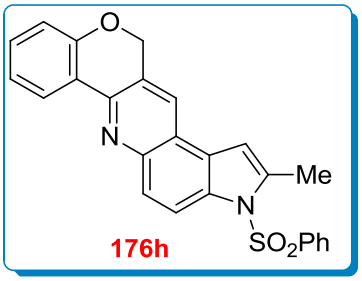
$^{13}C$ NMR (100 MHz) δ: 156.8, 145.5, 144.6, 132.4, 130.7, 126.3, 124.9, 124.0, 123.6, 123.2, 122.4, 120.3, 117.1, 113.9, 109.4, 102.9 (aromatic C), 68.9, 29.9, 12.6, 10.0 (aliphatic C)

LCMS (m/z): 315 $(M+H)^+$

Anal. calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91%

Found: C, 80.15; H, 5.71; N, 9.12%

**2-Methyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolin-3-yl-phenyl-sulfon (176h):** Compound **176h** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175h** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.



176h

Yield: 65%

Mp: 201-203 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 1602, 1508, 945, 582, 565

$^1H$ NMR (400 MHz, DMSO-$d_6$+$CDCl_3$) δ: 8.46-8.54 (2H, m), 7.96-8.03 (2H, m), 7.8-7.89 (2H, m), 7.26-7,53 (4H, m), 7.00-7.16 (2H, m), 6.8 (1H, s), 5.35 (2H, s), 2.68 (3H, s)

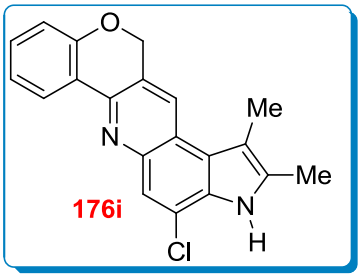
$^{13}C$ NMR (100 MHz, DMSO-$d_6$+$CDCl_3$) δ: 162.0, 152.2, 150.4, 143.4, 142.2, 139.3, 137.8, 136.6, 134.7, 132.4, 131.8, 130.7, 130.0, 127.9, 127.2, 125.7, 122.5, 122.2, 113.3, 99.9 (aromatic C), 72.9, 20.7 (aliphatic C)

LCMS (m/z): 427 $(M+H)^+$

Anal. calcd. for $C_{25}H_{18}N_2O_3S$: C, 70.40; H, 4.25; N, 6.57%

Found: C, 70.55; H, 4.21; N, 6.48%

**1,2-Methyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolin-3-yl-chloride (176i):** Compound **176i** was synthesized from salicylaldehyde (**156a**) and 5-aminoindole **175i** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 83%

Mp: 220-222 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 1502, 1411, 655, 565

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.61 (1H, s), 8.50 (1H, s), 8.28 (1H, d, *J* = 8.0 Hz), 7.65 (1H, s), 7.36 (1H, t, *J* = 7.28 Hz), 7.14 (1H, t, *J* = 7.24 Hz), 7.01 (1H, d, *J* = 8.0 Hz), 5.43 (2H, s), 2.48 (3H, s), 2.40 (3H, s)

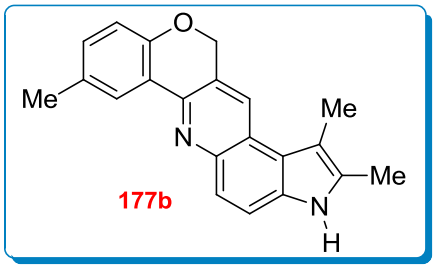
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 157.0, 145.1, 148.8, 133.5, 131.6, 128.3, 126.9, 124.9, 124.2, 123.6, 122.6, 122.1, 121.2, 119.9, 117.6, 110.6 (aromatic C), 68.3, 12.1, 13.4 (aliphatic C)

LCMS (m/z): 335 $(M+H)^+$, 337 $(M+2)^+$

Anal. calcd. for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; N, 8.37%

Found: C, 71.65; H, 4.55; N, 8.29%

**1,2,8-Trimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (177b):** Compound **177b** was synthesized from salicylaldehyde **156b** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 85%

Mp: 199-201 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3219, 2858, 1547, 1126, 821

$^{1}$H NMR (400 MHz, DMSO-$d_6$) δ: 11.32 (1H, s), 8.49 (1H, s), 8.17 (1H, d, *J* = 8.2 Hz), 7.59-7.67 (2H, m), 7.09-7.13 (1H, m), 6.85-6.89 (1H, m), 5.36 (2H, s), 2.47 (3H, s), 2.30 (6H, s)

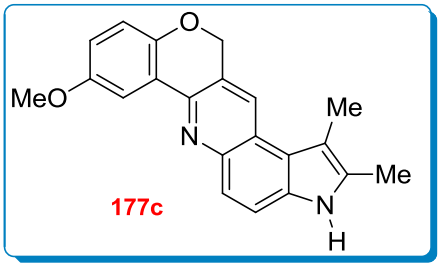
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 159.7, 149.9, 148.9, 136.7, 136.4, 136.2, 131.6, 129.6, 128.8, 128.4, 127.9, 126.6, 125.7, 122.1, 121.6, 114.1 (aromatic C), 73.2, 25.7, 17.0, 16.3 (aliphatic C)

LCMS (m/z): 315 $(M+H)^+$

Anal. calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91%

Found: C, 80.32; H, 5.65; N, 8.75%

**1,2-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolin-8-yl-methylether (177c):** Compound **177c** was synthesized from salicylaldehyde **156c** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



177c

Yield: 80%

Mp: 193-195 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3406, 1595, 1194, 831, 542

$^{1}$H NMR (400 MHz, DMSO-$d_6$) δ: 10.38 (1H, s); 8.47 (1H, s); 7.97 (1H, d, *J* = 2.8 Hz); 7.73 (2H, dd, *J* = 8.8 Hz); 6.87-6.95 (2H, m); 5.37 (2H, s); 3.93 (3H, s) 2.59 (3H, s); 2.46 (3H, s)

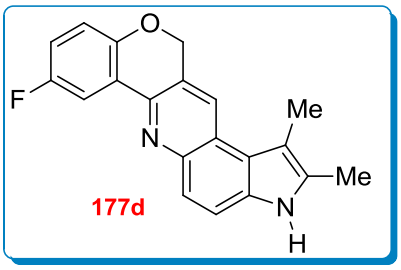
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 154.8, 150.8, 145.2, 144.2, 131.3, 131.1, 126.2, 124.3, 123.5, 123.1, 121.8, 120.8, 117.9, 117.7, 116.2, 109.3, 107.6 (aromatic C), 68.8, 55.7, 12.1, 11.3 (aliphatic C)

LCMS (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, 76.25; H, 5.53; N, 8.55%

**1,2-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolin-8-yl-fluoride (177d):** Compound **177d** was synthesized from salicylaldehyde **156d** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



177d

Yield: 88%

Mp: 153-155 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3175, 2924, 1547, 1028, 869

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.38 (1H, s), 8.48 (1H, s), 7.95 (1H, d, *J* = 7.6 Hz), 7.60-7.71 (2H, m), 7.04-7.18 (2H, m), 5.40 (2H, s), 2.46 (3H, s), 2.36 (3H, s)

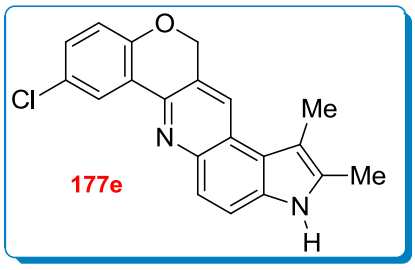
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 159.2, 156.8, 153.1, 145.1, 142.9, 131.9, 131.6, 126.9, 125.3, 123.7, 123.5, 121.8, 120.9, 119.2, 117.9, 117.7, 117.1, 110.4, 110.2, 109.4 (aromatic C), 68.5, 12.2, 11.5 (aliphatic C)

LCMS (m/z): 319 $(M+H)^+$

Anal. calcd. for $C_{20}H_{15}FN_2O$: C, 75.46; H, 4.75; N, 8.80%

Found: C, 75.31; H, 4.81; N, 8.92%

**1,2-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolin-8-yl-chloride (177e):** Compound **177e** was synthesized from salicylaldehyde **156e** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.



177e

Yield: 80%

Mp: 214-216 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3151, 2918, 1292, 945, 547

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.37 (1H, s), 8.20-8.42 (2H, m), 7.62-7.69 (2H, m), 7.34 (1H, s), 7.02 (1H, s), 5.41 (2H, s), 2.44 (3H, s), 2.36 (3H, s)

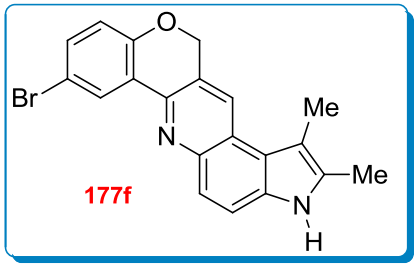
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 155.6, 145.1, 142.5, 131.8, 131.6, 130.7, 127.0, 126.6, 125.5, 125.4, 123.9, 123.5, 121.8, 120.9, 119.6, 117.2, 109.4 (aromatic C), 68.6, 12.2, 11.5 (aliphatic C)

LCMS (m/z): 335 $(M+H)^+$

Anal. calcd. for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; N, 8.37%

Found: C, 71.65; H, 4.61; N, 8.51%

**1,2-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolin-8-yl-bromide (177f):** Compound **177f** was synthesized from salicylaldehyde **156f** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.



177f

Yield: 85%

Mp: 182-184 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3178, 2916, 1520, 1008, 603

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.39 (1H, s), 8.35-8.47 (2H, m), 7.63-7.71 (2H, m), 7.47 (1H, d, $J$ = 7.5 Hz), 6.97 (1H, d, $J$ = 7.2 Hz), 5.44 (2H, s), 2.48 (3H, s), 2.37 (3H, s)

$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 156.0, 145.1, 142.3, 133.5, 131.8, 131.6, 127.0, 126.8, 125.1, 123.5, 123.45, 121.8, 120.9, 119.9, 117.2, 114.3, 109.4 (aromatic C), 68.5, 12.2, 11.5 (aliphatic C)

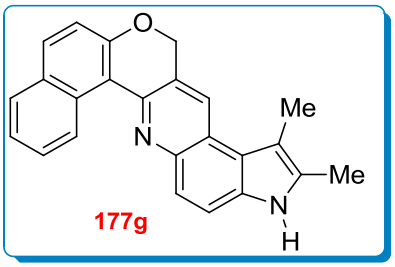
LCMS (m/z): 380 $(M+2)^+$

Anal. calcd. for $C_{20}H_{15}BrN_2O$: C, 63.34; H, 3.99; N, 7.39%

Found: C, 63.41; H, 4.12; N, 7.25%

**10,11-Dimethyl-8,12-dihydrobenzo[5,6]chromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (177g):** Compound **177g** was synthesized from salicylaldehyde **173** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 85%



177g

Mp: 244-246 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3269, 2849, 1450, 1003, 896

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.39 (1H, s), 10.02 (1H, d, *J* = 8.5 Hz), 8.67 (1H, s), 7.93 (2H, t, *J* = 8.9 Hz), 7.65-7.72 (3H, m), 7.46 (1H, t, *J* = 7.5 Hz), 7.29 (1H, d, *J* = 8.8 Hz), 5.46 (2H, s), 2.57 (3H, s), 2.42 (3H, s)

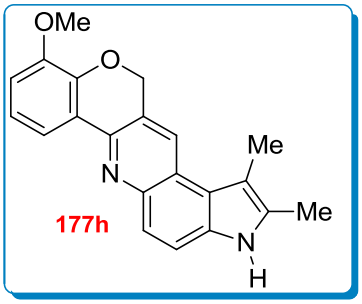
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 156.9, 146.1, 144.8, 132.4, 131.7, 131.6, 131.2, 130.7, 128.9, 127.8, 127.5, 126.9, 125.5, 124.6, 122.3, 122.0, 120.9, 118.9, 116.8, 116.5, 109.3 (aromatic C), 68.9, 12.3, 11.6 (aliphatic C)

LCMS (m/z): 351 $(M+H)^+$

Anal. calcd.for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99%

Found: C, 82.15; H, 5.23; N, 8.22%

**1,2-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinolin-10-yl-methyl ether (177h):** Compound **177h** was synthesized from salicylaldehyde **156g** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



177h

Yield: 81%

Mp: 230-232 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3431, 2253, 1269, 823, 761

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.49 (1H, s), 8.70 (1H, s), 8.03-8.06 (1H, m), 7.83 (1H, d, *J* = 8.84 Hz), 7.76 (1H, d, *J* = 8.88 Hz), 7.17-7.22 (2H, m), 5.59 (2H, s), 3.95 (3H, s), 2.66 (3H, s), 2.53 (3H, s)

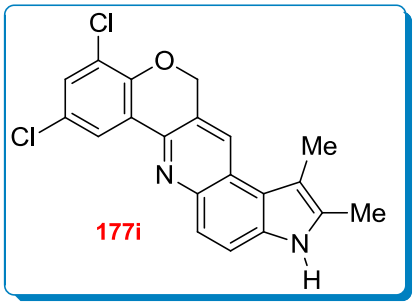
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 149.1, 146.5, 145.2, 144.1, 131.7, 131.5, 126.8, 124.7, 123.9, 123.2, 122.1, 121.9, 121.0, 116.9, 116.5, 113.9, 109.3 (aromatic C), 68.5, 56.2, 12.3, 11.5 (aliphatic C)

LCMS (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, 76.27; H, 5.53; N, 8.55%

**8,10-Dichloro-1,2-dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline (177i):** Compound **177i** was synthesized from salicylaldehyde **156h** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 80%

Mp: 175-177 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3404, 2253, 1645, 1026, 760

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.40 (1H, s), 8.57 (1H, s), 8.19 (1H,s), 7.73 (1H, d, *J* = 8.84 Hz), 7.62-7.64 (2H, m), 5.61 (2H, s), 2.49 (3H, s), 2.39 (3H, s)

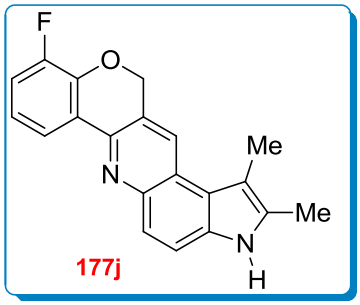
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 151.4, 145.2, 141.6, 132.0, 131.8, 130.3, 127.2, 126.7, 126.4, 123.7, 123.1, 122.8, 121.9, 120.9, 117.5, 109.6 (aromatic C), 69.2, 12.2, 11.6 (aliphatic C)

LCMS (m/z): 369 $(M+H)^+$, 370 $(M+2)^+$

Anal. calcd. for $C_{20}H_{14}Cl_2N_2O$: C, 65.06; H, 3.82; N, 7.59%

Found: C, 65.18; H, 3.85; N, 7.51%

**1,2-Dimethyl-3,12-dihydrochromeno[4,3-*b*]pyrrolo[3,2-*f*]quinoline-10-yl fluoride (177j):** Compound **177j** was synthesized from salicylaldehyde **156i** and 5-aminoindole **175a** following the *general procedure B*. Pure product was obtained through silica gel column chromatography with 6% ethyl acetate in hexanes.




Yield: 84%

Mp: 222-224 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3455, 2366, 1451, 1058, 845

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 11.37 (1H, s), 8.57 (1H, s),

8.12 (1H, d, *J* = 7.6 Hz), 7.71 (1H, d, *J* = 8.84 Hz), 7.63 (1H, d, *J* = 9.8 Hz), 7.29 (1H, t, *J* = 8.7 Hz), 7.08-7.14 (1H, m), 5.55 (2H, s), 2.52 (3H, s), 2.39 (3H, s)

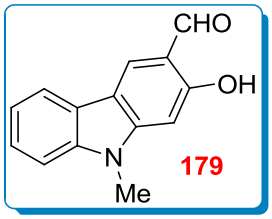
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 152.9, 150.4, 145.1, 144.7, 142.9, 131.9, 131.6, 127.1, 126.5, 123.6, 123.4, 122.3, 121.9, 120.9, 120.2, 117.7, 117.5, 117.2, 109.4 (aromatic C), 68.9, 12.2, 11.6 (aliphatic C)

LCMS (m/z): 319 $(M+H)^+$, 320 $(M+2)^+$

Anal. calcd. for $C_{20}H_{15}FN_2O$: C, 75.46; H, 4.75; N, 8.80%

Found: C, 75.32; H, 4.80; N, 8.75%

**2-Hydroxy-9-methyl-9*H*-carbazole-3-carbaldehyde (179):** Compound **179** was synthesized by a reaction of aldehyde (**178**) (1 mmol) with pyridine HCl salt (10 equiv.) under microwave condition for 10 min. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.




Yield: 63%

Mp: 165-167 °C

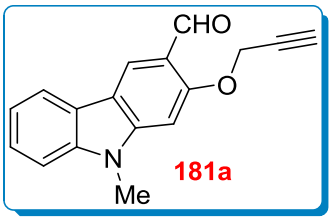
IR (KBr) $\nu_{max}$ $cm^{-1}$: 3357, 1936, 1147, 665

$^1$H NMR (400 MHz) δ: 11.53 (1H, s), 9.9 (1H, s), 8.13 (1H, s), 7.99 (1H, d, *J* = 7.6 Hz), 7.47 (1H, t, *J* = 7.2 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 7.29 (1H, t, *J* = 7.6 Hz), 6.79 (1H, s), 3.77 (3H, s)

$^{13}$C NMR (100 MHz) δ: 195.0, 161.3, 146.9, 142.1, 127.1, 126.0, 123.1, 120.7, 119.7, 117.2, 115.0, 108.9, 94.9 (aromatic C), 29.4 (aliphatic C)

LCMS (m/z) ($C_{14}H_{11}NO_2$): 226 $(M+H)^+$

**9-Methyl-2-(prop-2-yn-1-yloxy)-9*H*-carbazole-3-carbaldehyde (181a):** Compound **181a** was synthesized from salicylaldehyde (**179**) (1 mmol) and propargyl bromide (**180**) (1.5 mmol) under the condition of $K_2CO_3$ (5 equiv.)/ acetone (10 mL) at reflux temperature. Pure product was obtained through silica gel column chromatography with 2% ethyl acetate in hexanes.



Yield: 88%

Mp: 124-126 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3457, 2829, 1697, 1147, 645

$^1$H NMR (400 MHz) δ: 10.49 (1H, s), 8.65 (1H, s), 8.01 (1H, d, *J* = 7.6 Hz), 7.45 (1H, t, *J* = 6.8 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.26-7.29 (1H, m), 6.86 (1H, s), 4.91 (2H, s), 3.78 (3H, s), 2.62 (1H, s)

$^{13}$C NMR (100 MHz) δ: 189.2, 159.4, 145.7, 141.8, 125.9, 123.2, 121.5, 120.5, 120.2, 118.9, 117.6, 108.8, 92.1 (aromatic C), 77.9, 76.6, 56.9, 29.4 (aliphatic C)

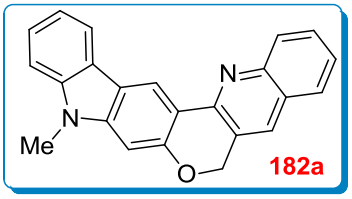
LCMS (m/z) ($C_{17}H_{13}NO_2$): 264 $(M+H)^+$

***General procedure C*:**

In a round bottom flask equipped with a magnetic stirring bar, 1.0 mmol of aniline and 1.0 mmol of *O*-propargyl salicylaldehyde in 5 mL of ionic liquid [Bmim][$BF_4$] as solvent, was added 10 mol% of CuI. Reaction mixture was stirred at 90–95 °C. After completion of the reaction, as indicated by the TLC, water (20 mL) was added to the crude reaction mass. Then aqueous layer was extracted with dichloromethane (3 X 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate).

**9-Methyl-6,9-dihydroquinolino[2',3':4,5]pyrano[2,3-*b*]carbazole (182a):**

Compound **182a** was synthesized from salicylaldehyde **181a** and aniline **143a** following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.




Yield: 78%

Mp: 198-200 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3024, 2841, 1174, 1059, 634

$^1$H NMR (500 MHz) δ: 9.21 (1H, s), 8.21 (2H, d, *J* = 8.0 Hz), 7.88 (1H, s), 7.78 (1H, d, *J* = 8.0 Hz), 7.31 (1H, dt, *J*1 = 1.5 Hz and *J*2 = 7.0 Hz), 7.46-7.52 (2H, m), 7.38 (1H, d, *J* = 8.0 Hz), 7.30 (1H, d, *J* = 7.5 Hz), 6.99 (1H, s), 5.41 (2H, s), 3.82 (3H, s)

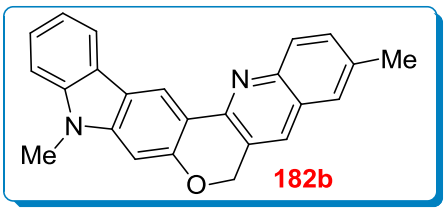
$^{13}$C NMR (125 MHz) δ: 156.9, 150.4, 148.6, 144.0, 141.9, 130.7, 129.5, 129.1, 127.4, 127.2, 125.7, 125.3, 125.2, 123.5, 120.4, 119.7, 119.2, 117.8, 116.0, 108.4, 96.0 (aromatic C), 68.9, 29.2 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{23}H_{16}N_2O$: 337.1341 (M+H)

Found: 337.1344

**3,9-Dimethyl-6,9-dihydroquinolino[2',3':4,5]pyrano[2,3-*b*]carbazole (182b):**
Compound **182b** was synthesized from salicylaldehyde **181a** and aniline **143b** following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



182b

Yield: 81%

Mp: 254-256 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3187, 2829, 1148, 1025, 659

$^{1}$H NMR (400 MHz) δ: 9.16 (1H, s), 8.19 (1H, d, *J* = 8.0 Hz), 8.09 (1H, d, *J* = 8.4 Hz), 7.76 (1H, s), 7.53-7.57 (2H, m), 7.47 (1H, t, *J* = 7.6 Hz), 7.37 (1H, d, *J* = 8.0 Hz), 7.27-7.31 (1H, m), 6.97 (1H, s), 5.38 (2H, s), 3.80 (3H, s), 2.56 (3H, s)

$^{13}$C NMR (100 MHz) δ: 156.7, 149.6, 147.1, 143.8, 141.8, 135.5, 131.8, 130.2, 128.7, 127.2, 126.4, 125.3, 125.2, 123.5, 120.4, 119.6, 119.0, 117.6, 116.1, 108.4, 96.1 (aromatic C), 69.0, 29.3, 21.6 (aliphatic C)

HRMS (ESI-MS)

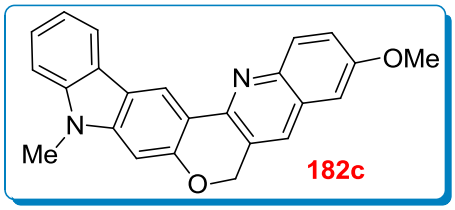
Calcd for: $C_{24}H_{18}N_2O$: 351.1497 (M+H)

Found: 351.1499

**3-Methoxy-9-methyl-6,9-dihydroquinolino[2',3':4,5]pyrano[2,3-*b*]carbazole (182c):** Compound **182c** was synthesized from salicylaldehyde **181a** and aniline **143c** following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.

Yield: 83%

Mp: 228-230 °C




IR (KBr) $\nu_{max}$ $cm^{-1}$: 3149, 2837, 1249, 1164, 618

$^1$H NMR (400 MHz) δ: 9.09 (1H, s), 8.17 (1H, d, *J* = 7.6 Hz), 8.08 (1H, d), *J* = 9.2 Hz), 7.72 (1H, s), 7.44 (1H, d, *J* = 7.2 Hz), 7.34-7.38 (2H, m), 7.25-7.28 (1H, m), 7.01 (1H, d, *J* = 2.4), 6.93 (1H, s), 5.36 (2H, s), 3.93 (3H, s), 3.77 (3H, s)

$^{13}$C NMR (100 MHz) δ: 157.3, 156.5, 148.1, 144.5, 143.6, 141.8, 130.5, 129.6, 128.1, 125.5, 125.2, 123.5, 121.8, 120.4, 119.6, 117.3, 116.1, 108.3, 105.4, 96.0 (aromatic C), 68.9, 55.5, 29.2 (aliphatic C)

HRMS (ESI-MS)

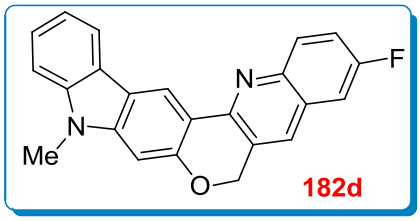
Calcd for: $C_{24}H_{18}N_2O_2$: 367.1446 (M+H)

Found: 367.1451

**3-Fluoro-9-methyl-6,9-dihydroquinolino[2',3':4,5]pyrano[2,3-*b*]carbazole (182d):** Compound **182d** was synthesized from salicylaldehyde **181a** and aniline **143e** following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 76%

Mp: 241-243 °C




IR (KBr) $\nu_{max}$ $cm^{-1}$: 3125, 2835, 1451, 1179, 632

$^1$H NMR (500 MHz) δ: 9.08 (1H, s), 8.16-8.18 (2H, m), 7.69 (1H, s), 7.45-7.47 (2H, m), 7.28-7.35 (3H, m), 6.91 (1H, s), 5.34 (2H, s), 3.74 (3H, s)

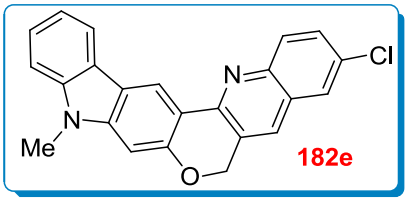
$^{13}$C NMR (125 MHz) δ: 161.0, 159.0, 156.7, 149.8, 145.5, 143.9, 141.8, 131.4, 131.3, 129.91, 129.9, 127.7, 127.6, 126.0, 125.3, 123.4, 120.7, 120.3, 119.7, 119.5, 119.3, 119.1, 117.5, 115.7, 110.6, 110.5, 108.8, 108.4, 96.0, 94.9 (aromatic C), 68.7, 29.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{23}H_{15}FN_2O$: 355.1246 (M+H)

Found: 355.1246

**3-Chloro-9-methyl-6,9-dihydroquinolino[2',3':4,5]pyrano[2,3-b]carbazole (182e):** Compound **182e** was synthesized from salicylaldehyde **181a** and aniline **143f** following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 75%

Mp: 212-214 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3032, 2857, 1364, 1157, 629

$^1H$ NMR (500 MHz, DMSO-$d_6$) δ: 9.05 (1H, s), 8.23 (1H, d, *J* = 7.5 Hz), 8.19 (1H, s), 8.15 (1H, s), 8.01 (1H, d, *J* = 8.5 Hz), 7.85 (1H, d, *J* = 8.5 Hz), 7.56 (1H, d, *J* = 8.0 Hz), 7.46 (1H, t, *J* = 7.0 Hz), 7.21-7.26 (2H, m), 5.45 (2H, s), 3.84 (3H, s)

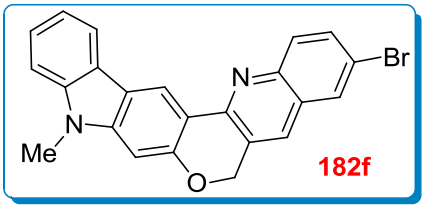
$^{13}C$ NMR (125 MHz) δ: 157.1, 150.6, 146.9, 144.3, 142.1, 133.1, 131.1, 130.9, 130.2, 128.7, 126.7, 126.0, 123.0, 120.5, 120.1, 118.9, 118.6, 117.6, 115.6, 109.7, 97.2 (aromatic C), 68.4, 29.7 (aliphatic C)

HRMS (ESI-MS)

Calcd for: $C_{23}H_{15}ClN_2O$: 371.0951 (M+H)

Found: 371.0953

**3-Bromo-9-methyl-6,9-dihydroquinolino[2',3':4,5]pyrano[2,3-*b*]carbazole (182f):** Compound **182f** was synthesized from salicylaldehyde **181a** and aniline **143g** following the *general procedure C*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 72%

Mp: 223-225 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3048, 2874, 1483, 1148, 625

| | |
|---|---|
| $^{1}$H NMR (400 MHz) δ: | 9.06 (1H, s), 8.15 (1H, d, *J* = 7.2 Hz), 8.00 (1H, d, *J* = 8.8 Hz), 7.82 (1H, s), 7.74 (1H, dd, *J*1 = 7.2 Hz, *J*2 = 2.0 Hz), 7.65 (1H, s), 7.46 (1H, t, *J* = 7.6 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 7.26-7.29 (1H, m), 6.89 (1H, s), 5.35 (2H, s), 3.74 (3H, s) |
| $^{13}$C NMR (100 MHz) δ: | 156.7, 150.7, 147.0, 144.0, 141.8, 132.8, 130.6, 129.6, 129.4, 128.2, 126.1, 125.4, 123.4, 120.4, 119.7, 119.2, 119.1, 117.7, 115.5, 108.4, 96.0 (aromatic C), 68.7, 29.2 (aliphatic C) |
| HRMS (ESI-MS) | |
| Calcd for $C_{23}H_{15}BrN_2O$: | 415.0446 (M+H) |
| Found: | 415.0446 |

**Table 8. Crystal data and structure refinement for 174**

| | |
|---|---|
| Empirical formula | : $C_{20}H_{13}NO$ |
| Formula weight | : 283.31 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P2(1)/c |
| Unit cell dimensions | : a = 8.6729(14) Å $\alpha$= 90° |
| | : b = 15.418(3) Å $\beta$= 106.891(2)° |
| | : c = 10.8031(18) Å $\gamma$ = 90° |
| Volume | : 1382.3(4) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.361 $Mg/m^3$ |
| Absorption coefficient | : 0.090 $mm^{-1}$ |
| F (000) | : 592 |
| Crystal size | : 0.42 x 0.31 x 0.27 $mm^3$ |
| Theta range for data collection | : 2.37 to 25.00° |
| Index ranges | : -10<=h<=10, -18<=k<=18, -12<=l<=12 |
| Reflections collected | : 13041 |
| Independent reflections | : 2433 [R(int) = 0.0321] |
| Completeness to theta = 26.04° | : 100.0% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9777 and 0.9656 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 2433 / 0 / 199 |
| Goodness-of-fit on $F^2$ | : 1.085 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0425, wR2 = 0.1009 |
| R indices (all data) | : R1 = 0.0496, wR2 = 0.1051 |
| Largest diff. peak and hole | : 0.124 and -0.155 $e.Å^{-3}$ |
| CCDC number | : 753401 |

**Table 9. Crystal data and structure refinement for 171b**

| | |
|---|---|
| Empirical formula | : $C_{34}H_{26}N_2O_2$ |
| Formula weight | : 494.57 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P2(1)/c |
| Unit cell dimensions | : a = 12.9795(11) Å $\alpha$= 90° |
| | : b = 23.1902(19) Å $\beta$= 95.2790(10) |
| | : c = 8.4440(7) Å $\gamma$ = 90° |
| Volume | : 2530.8(4) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.298 $Mg/m^3$ |
| Absorption coefficient | : 0.081 $mm^{-1}$ |
| F (000) | : 1040 |
| Crystal size | : 0.44 x 0.40 x 0.36 $mm^3$ |
| Theta range for data collection | : 1.58 to 25.00° |
| Index ranges | : -15<=h<=15, -27<=k<=27, -10<=l<=10 |
| Reflections collected | : 23986 |
| Independent reflections | : 4453 [R(int) = 0.0448] |
| Completeness to theta = 26.04° | : 100.0% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9715 and 0.9653 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 4453 / 0 / 345 |
| Goodness-of-fit on $F^2$ | : 1.233 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0763, wR2 = 0.1525 |
| R indices (all data) | : R1 = 0.0971, wR2 = 0.1611 |
| Largest diff. peak and hole | : 0.203 and -0.151 $e.Å^{-3}$ |
| CCDC number | : 753402 |

**Table 10. Crystal data and structure refinement for 171c**

| | |
|---|---|
| Empirical formula | : $C_{17}H_{13}NO_2$ |
| Formula weight | : 263.28 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P2(1)/c |
| Unit cell dimensions | : a = 13.037(8) Å $\alpha$= 90° |
| | : b = 7.587(4) Å $\beta$= 97.576(9)° |
| | : c = 13.158(8) Å $\gamma$ = 90° |
| Volume | : 1290.2(13) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.355 $Mg/m^3$ |
| Absorption coefficient | : 0.089 $mm^{-1}$ |
| F (000) | : 552 |
| Crystal size | : 0.45 x 0.36 x 0.35 $mm^3$ |
| Theta range for data collection | : 1.58 to 25.00° |
| Index ranges | : -15<=h<=15, -9<=k<=9, -15<=l<=15 |
| Reflections collected | : 11753 |
| Independent reflections | : 2266 [R(int) = 0.0260] |
| Completeness to theta = 26.04° | : 100.0% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9694 and 0.9609 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 2266 / 0 / 183 |
| Goodness-of-fit on $F^2$ | : 1.057 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0377, wR2 = 0.1035 |
| R indices (all data) | : R1 = 0.0426, wR2 = 0.1082 |
| Largest diff. peak and hole | : 0.121 and -0.153 $e.Å^{-3}$ |
| CCDC number | : 753403 |

**Table 11. Crystal data and structure refinement for 171f**

| | |
|---|---|
| Empirical formula | : $C_{16}H_{10}ClNO$ |
| Formula weight | : 267.71 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : c2/c |
| Unit cell dimensions | : a = 31.333(3) Å $\alpha$= 90° |
| | : b = 3.8586(4) Å $\beta$= 102.334(4)° |
| | : c = 40.188(5) Å $\gamma$ = 90° |
| Volume | : 4746.6(9) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.504 $Mg/m^3$ |
| Absorption coefficient | : 0.310 $mm^{-1}$ |
| F (000) | : 2224 |
| Crystal size | : 0.64 x 0.53 x 0.43 $mm^3$ |
| Theta range for data collection | : 1.04 to 25.00° |
| Index ranges | : -36<=h<=36, -4<=k<=4, -47<=l<=47 |
| Reflections collected | : 20942 |
| Independent reflections | : 4186 [R(int) = 0.0505] |
| Completeness to theta = 26.04° | : 99.8% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.8781 and 0.8261 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 4186 / 0 / 343 |
| Goodness-of-fit on $F^2$ | : 1.160 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0658, wR2 = 0.1169 |
| R indices (all data) | : R1 = 0.0861, wR2 = 0.1249 |
| Largest diff. peak and hole | : 0.252 and -0.222 $e.Å^{-3}$ |
| CCDC number | : 753404 |

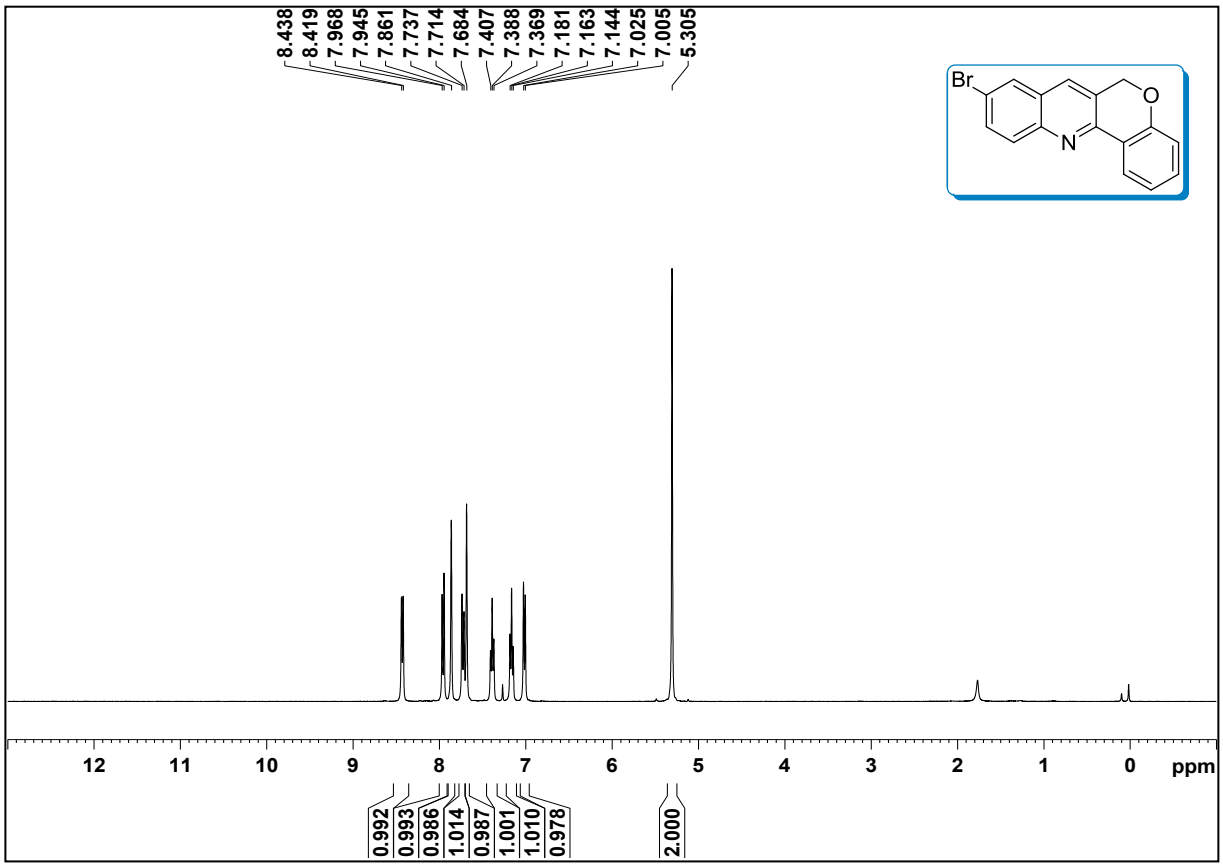
**Table 12. Crystal data and structure refinement for 176a**

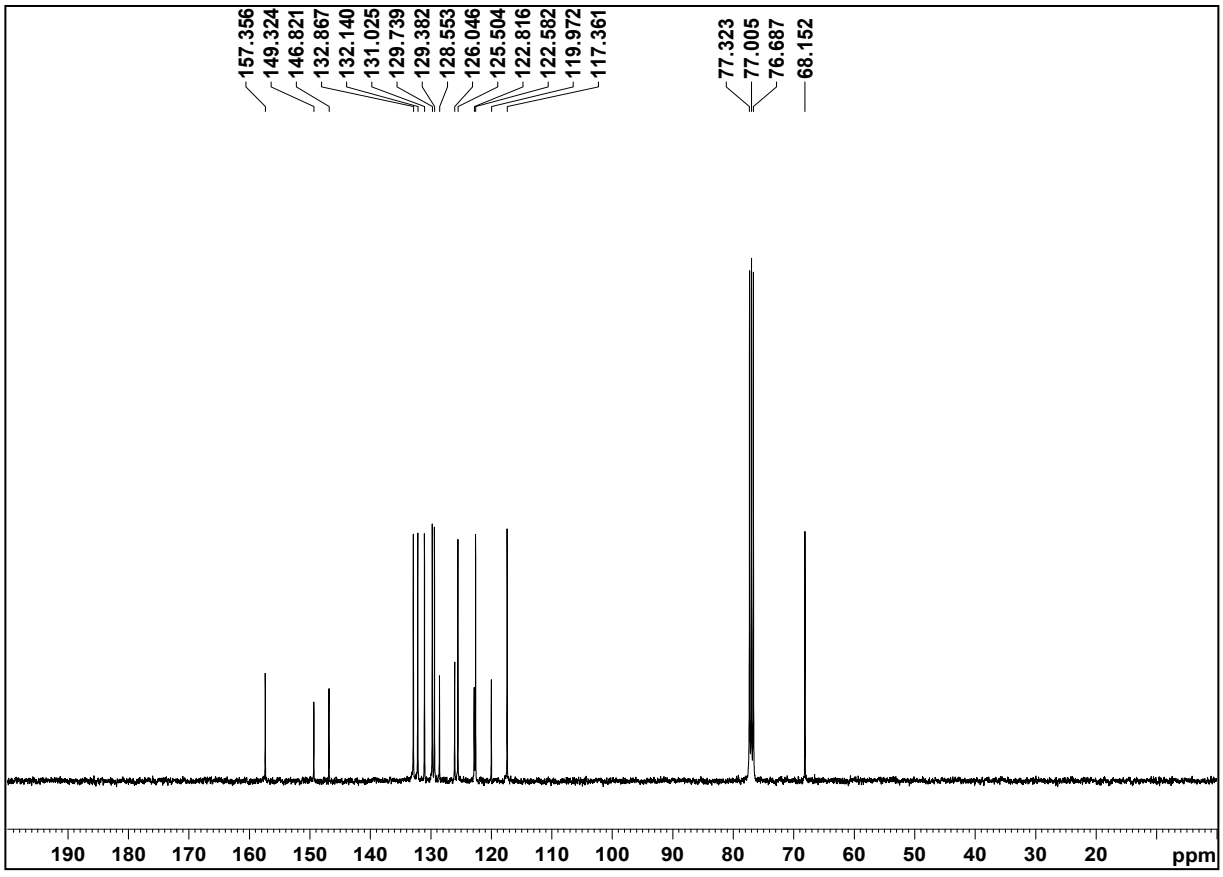
| | |
|---|---|
| Empirical formula | : $C_{20}H_{16}N_2O$ |
| Formula weight | : 300.35 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Orthorhombic |
| Space group | : P b n b |
| Unit cell dimensions | : a = 9.3913(6) Å $\alpha$= 90° |
| | : b = 25.0587(18) Å $\beta$= 90° |
| | : c = 16.0101(11) Å $\gamma$ = 90° |
| Volume | : 3767.7(4) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.059 $Mg/m^3$ |
| Absorption coefficient | : 0.066 $mm^{-1}$ |
| F (000) | : 1264 |
| Crystal size | : 0.24 x 0.16 x 0.12 $mm^3$ |
| Theta range for data collection | : 3.26 to 34.73° |
| Index ranges | : -14<=h<=14, -34<=k<=38, -22<=l<=25 |
| Reflections collected | : 19655 |
| Independent reflections | : 7627 [R(int) = 0.0788] |
| Completeness to theta = 26.04° | : 99.8% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9921 and 0.9843 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 7627 / 0 / 212 |
| Goodness-of-fit on $F^2$ | : 1.280 |
| Final R indices [I>2sigma (I)] | : R1 = 0.1554, wR2 = 0.4261 |
| R indices (all data) | : R1 = 0.2869, wR2 = 0.4828 |
| Largest diff. peak and hole | : 1.889 and -0.636 $e.Å^{-3}$ |
| CCDC number | : 796986 |

**Table 13. Crystal data and structure refinement for 177e**

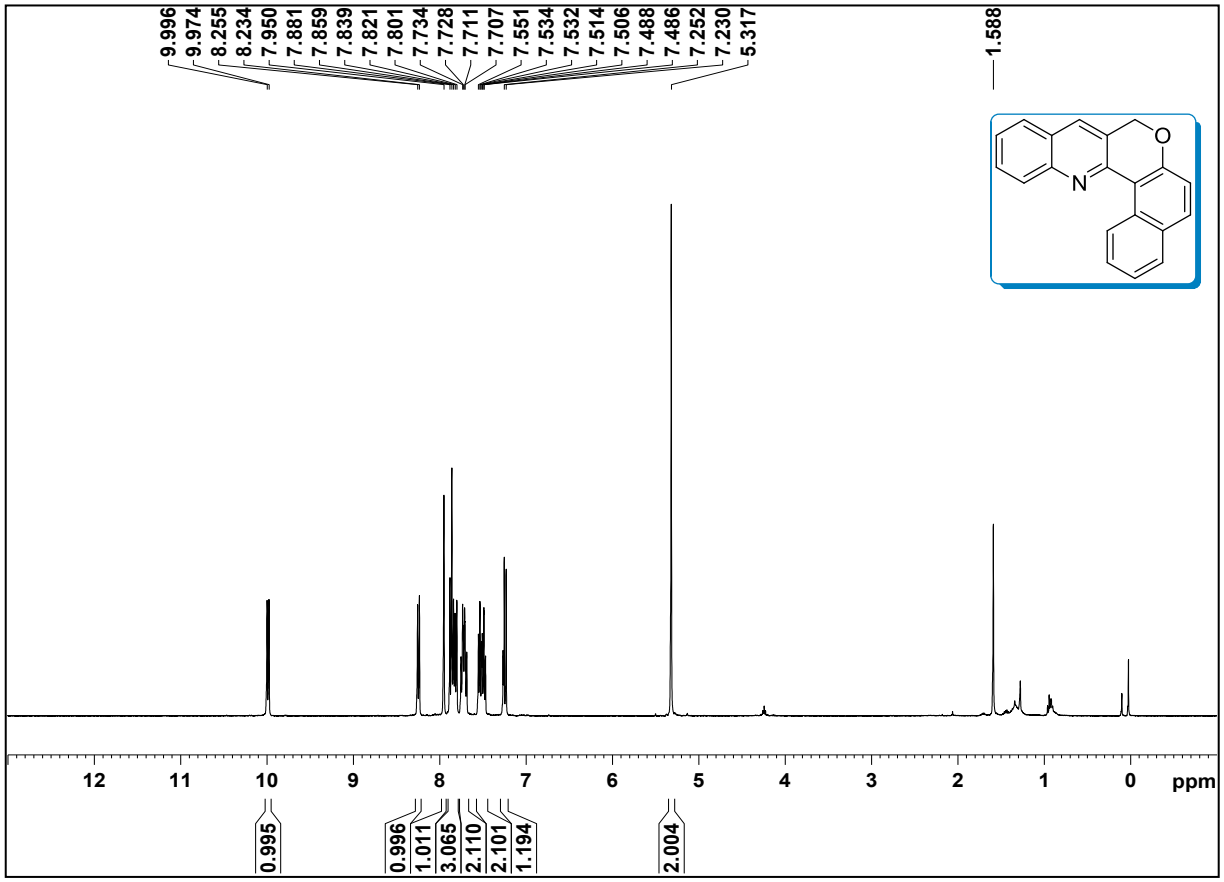
| | |
|---|---|
| Empirical formula | : $C_{22}H_{15}ClN_2O_2S$ |
| Formula weight | : 406.87 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P2(1)/c |
| Unit cell dimensions | : a = 15.9100(12) Å $\alpha$= 90° |
| | : b = 9.0681(7) Å $\beta$= 117.7960(10)° |
| | : c = 16.2656(18) Å $\gamma$ = 90° |
| Volume | : 2075.9(3) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.302 $Mg/m^3$ |
| Absorption coefficient | : 0.304 $mm^{-1}$ |
| F (000) | : 840 |
| Crystal size | : 0.32 x 0.30 x 0.12 $mm^3$ |
| Theta range for data collection | : 1.45 to 25.92° |
| Index ranges | : -19<=h<=19, -11<=k<=11, -19<=l<=19 |
| Reflections collected | : 20457 |
| Independent reflections | : 4014 [R(int) = 0.0542] |
| Completeness to theta = 26.04° | : 99.3% |
| Absorption correction | : Empirical |
| Max. and min. transmission | : 0.9645 and 0.9090 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 4014 / 0 / 277 |
| Goodness-of-fit on $F^2$ | : 1.115 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0774, wR2 = 0.1871 |
| R indices (all data) | : R1 = 0.1151, wR2 = 0.2105 |
| Largest diff. peak and hole | : 0.334 and -0.173 e.$Å^{-3}$ |
| CCDC number | : 796987 |

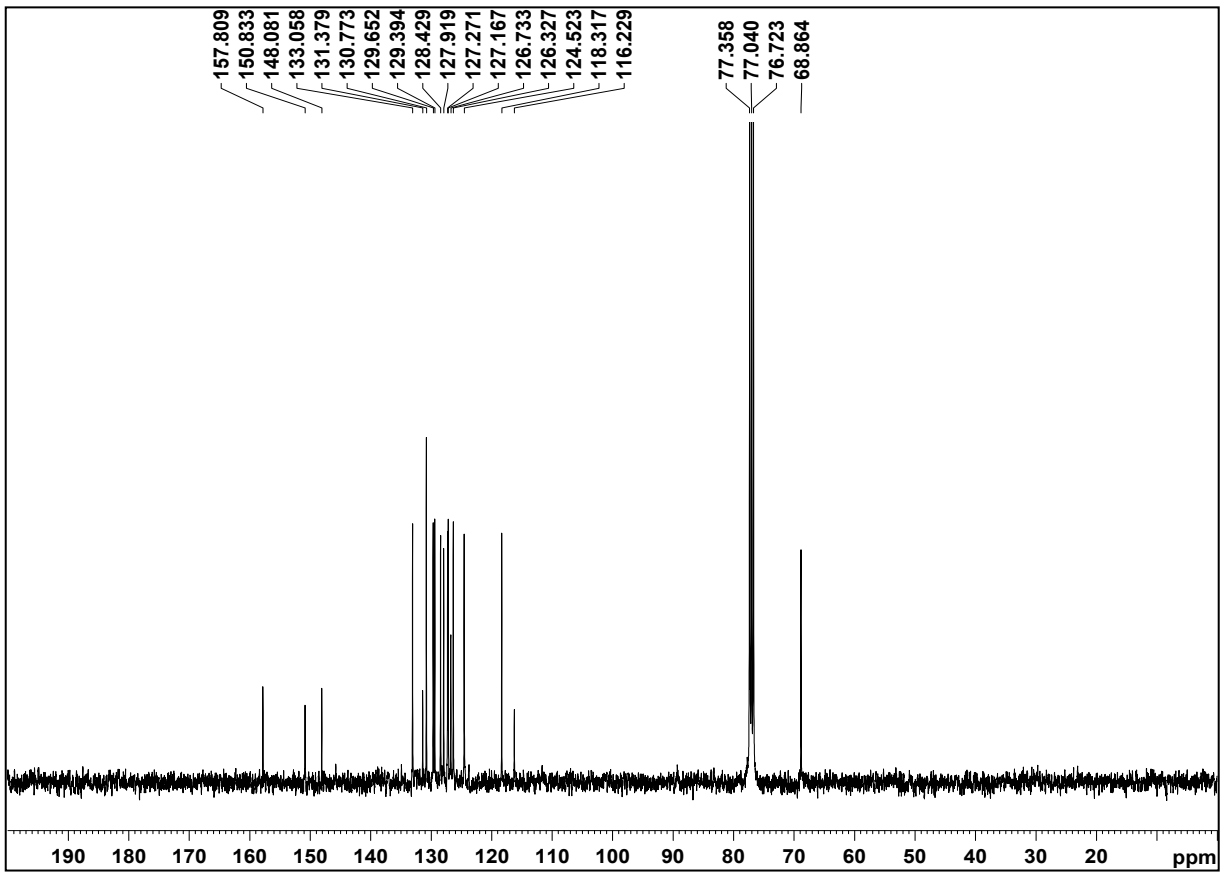
## Spectra No. 1: $^{1}H$ and $^{13}C$ spectra of compound 171g



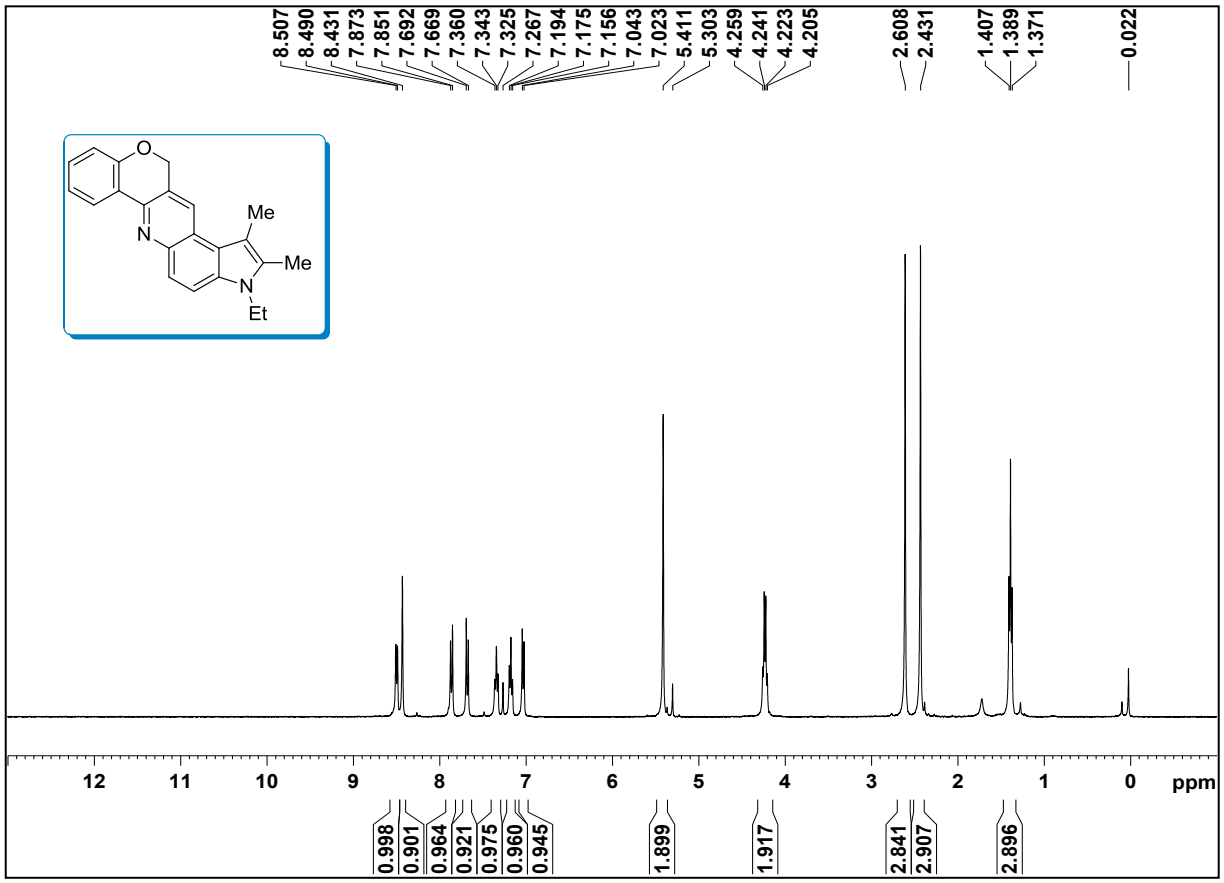



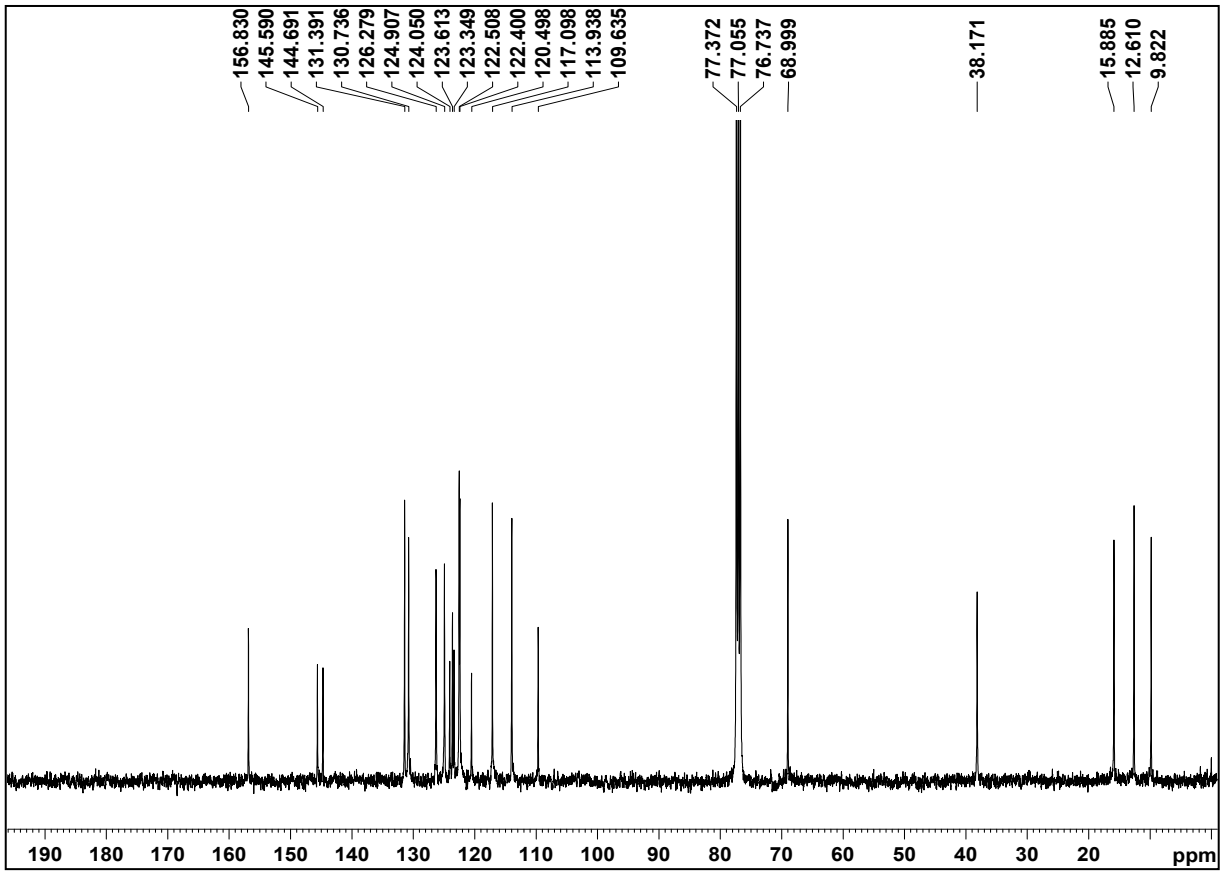
## Spectra No. 2: $^{1}H$ and $^{13}C$ spectra of compound 174



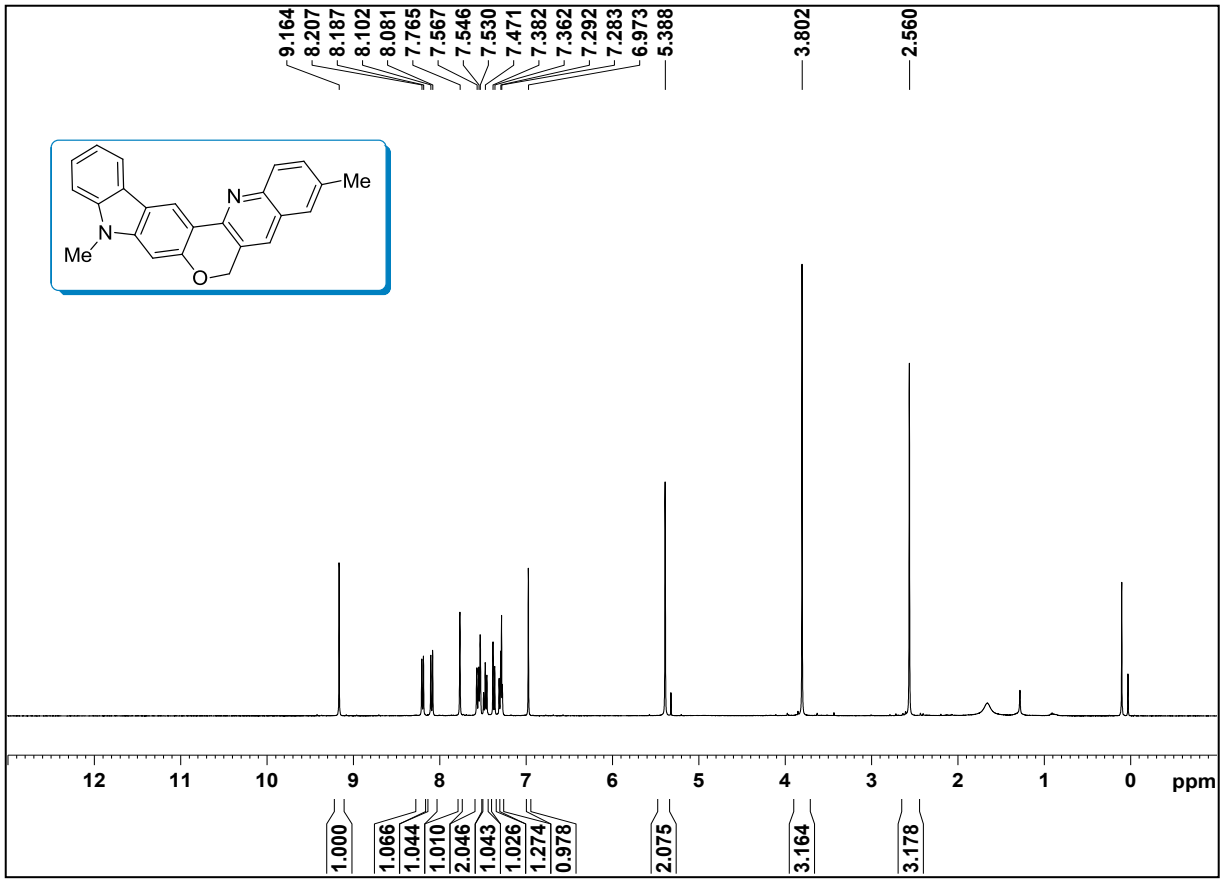



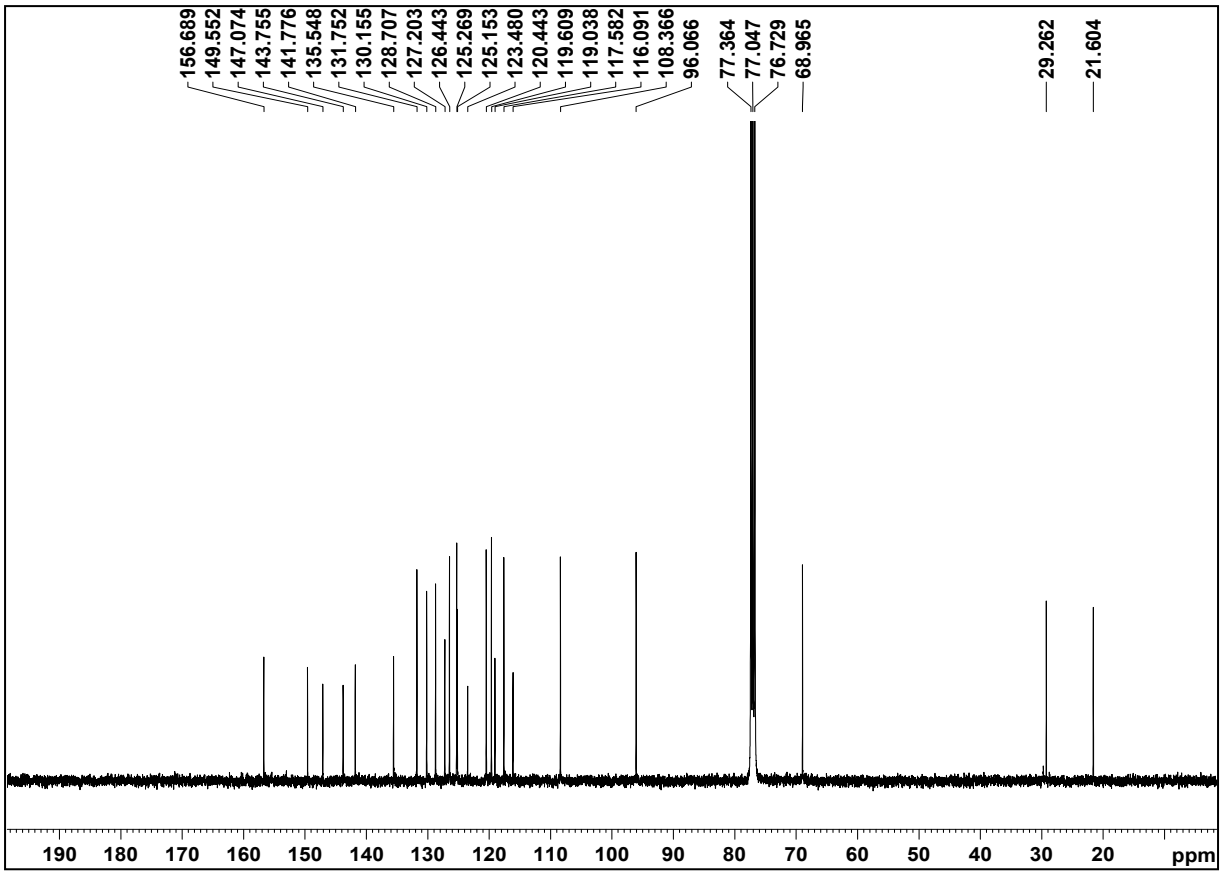
## Spectra No. 3: $^{1}H$ and $^{13}C$ spectra of compound 176b



## Spectra No. 4: $^{1}H$ and $^{13}C$ spectra of compound 182b



## 1.6. Conclusions

- The intramolecular aza Diels-Alder synthetic methodology using *O*-propargylsalicylaldehyde and aromatic amine catalyzed by CuI is reported for the synthesis of chromenoquinoline derivatives.
- An efficient method has been adopted with its potential for the synthesis of other important novel pyrroloquinoline and pyranocarbazole derivatives.
- In addition to its simplicity, this procedure has the advantage of high yields; lesser time has been devised from the readily available starting materials.

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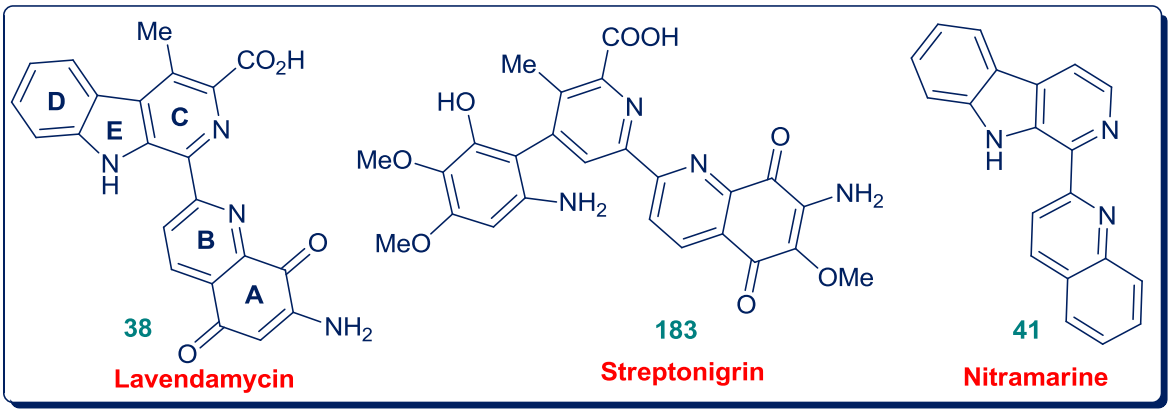
# CHAPTER 2

# Formal synthesis of lavendamycin methyl ester, nitramarine alkaloids and their derivatives

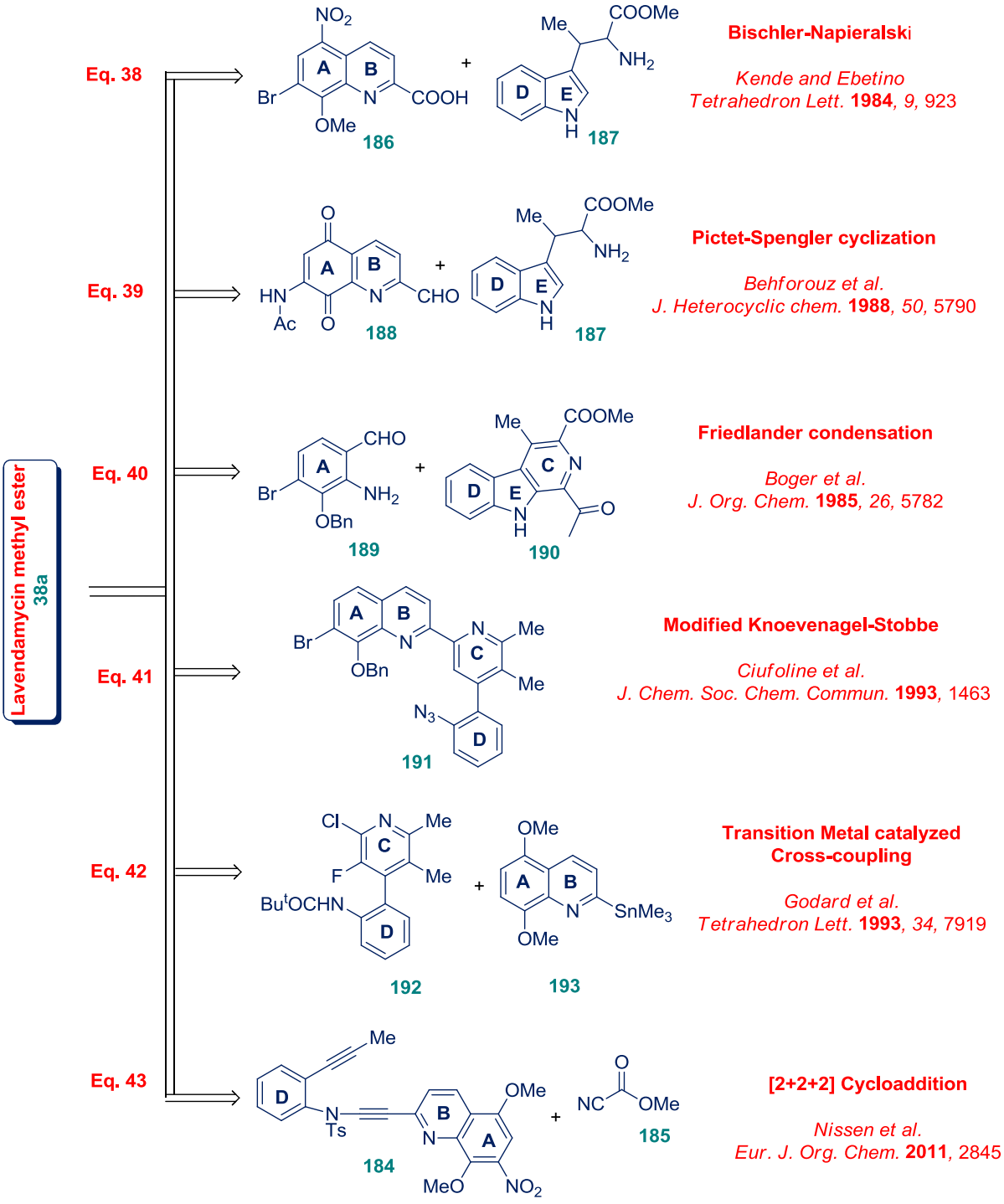
## 2.1. Introduction

In 1981, Doyle and co-workers from Bristol Laboratories reported the isolation of naturally occurring antitumor/antibiotic lavendamycin (**38**, **Fig. 11**) from the fermentation broth of Streptomyces lavendulae strain C22030 as a dark red solid.[22] Subsequently, its structure was elucidated as a pentacyclic quinone by Balitz and co-workers by means of analytical and spectroscopic studies.[22]

**Fig. 11**




In 1984, the first total synthesis of lavendamycin was achieved by Kende *et al*. via Bischler–Napieralski reaction (**Eq. 39**).[23] Structurally and biosynthetically, lavendamycin is related to well-known antitumor antibiotic streptonigrin alkaloid (**183**) (**Fig. 11**).[109] Lavendamycin and its analogues exhibit promising biological properties such as inhibition of HIV reverse transcriptase,[110a,b] MKN45 gastric carcinoma and WiDr colon carcinoma cells[110c] as well as antiproliferative[110c] and cytotoxic[111a] activities. Lavendamycin exhibits antitumor activity against topoisomerase I cell with a minimum inhibitory concentration (MIC) of 0.1 μg/mL.[111b,c] Produced in a challenging atmosphere and importantly for its biological significance, lavendamycin and its analogues have stimulated the interest of synthetic community.



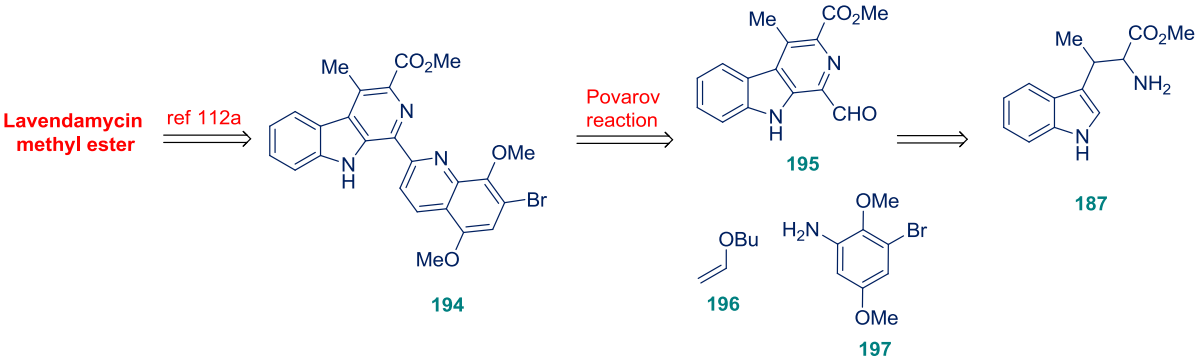

They have been the target of various groups with extensive synthetic efforts.[23,112] Some of the other basic methods for the synthesis of lavendamycin methyl ester include Bischler–Napieralski reaction (**Eq. 38**),[110,112a] Pictet–Spengler cyclization (**Eq. 39**),[112b-e] Friedlander condensation (**Eq. 40**),[112f] aza-Wittig/electrocyclic ring closure,[112g] modified Knoevenagel–Stobbe condensation (**Eq. 41**)[112h] and transition metal catalyzed cross-coupling (**Eq. 42**).[112i-l] The most recent synthetic study by Nissen *et al*.[113] is ruthenium-catalyzed [2+2+2] cycloaddition of an electron-deficient nitrile to an alkynylynamide (**Eq. 43**).

Continuing with our ongoing interest in alkyne chemistry,[114] we have chosen povarov reaction and $A^3$ coupling reaction to generate lavendamycin and its analogues with diverse substitution patterns.

## 2.2. Synthesis of lavendamycin methyl ester and their analogues through Povarov reaction

For the past several years, Povarov reaction (imino Diels–Alder reaction) has played a central and crucial role to produce quinoline and tetrahydroquinoline molecules.[38, 115-116] These nitrogen containing heterocycles have significantly attracted the synthetic community because of their prevalence in many natural products[116] and synthetic compounds with a wide spectrum of biological activities.[117]

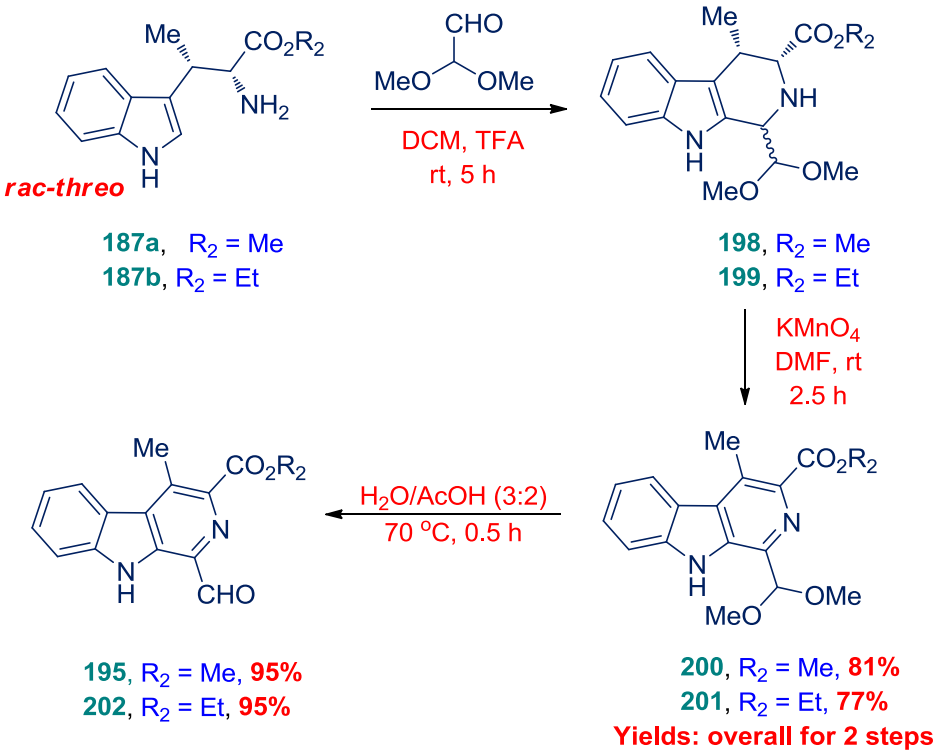
**Scheme 10**



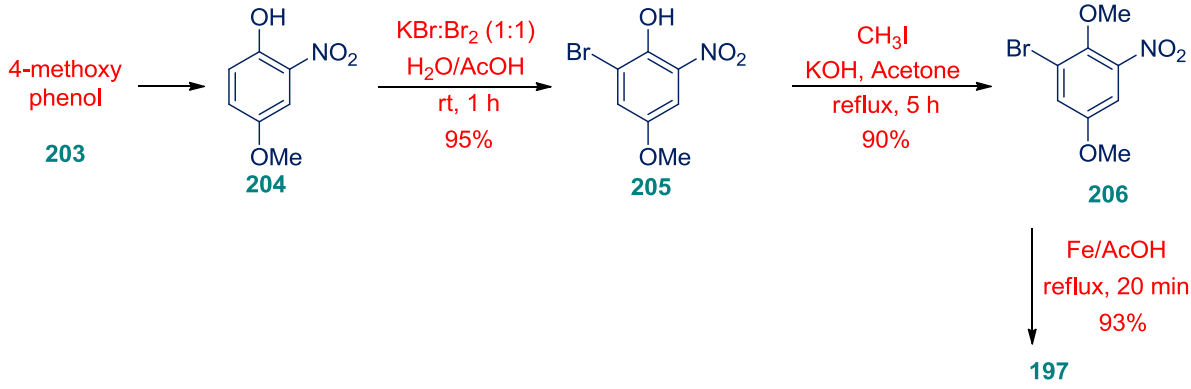

Our prime target molecule would be a substituted $\alpha$-quinolinyl-$\beta$-carboline **194** as mentioned in **Scheme 10**, because compound **194** had already been converted into lavendamycin methyl ester.[112a] We envisioned that the compound **194** would be derived from $\alpha$-formyl-$\beta$-carboline **195** (CDE ring) and aniline **197** (A ring) via Povarov reaction with *n*-butylvinyl ether (**196**) to construct ring B.

The compounds **195** and **202** (CDE ring) were prepared from *rac-threo*-$\beta$-methyltryptophan esters (**187a** and **187b**) (**Scheme 11**) that, in turn, is known to be derived from indole in a three steps sequence.[118] Pictet–Spengler cyclization of tryptophan esters **187a** and **187b** with dimethoxy acetaledehyde in DCM/TFA (rt, 5 h) led to the desired diasteromeric mixtures **198** and **199**. Without further purification, when the diastereomeric mixtures were subjected to $KMnO_4$ oxidation (DMF, rt), $\alpha$-dimethoxymethyl-$\beta$-carbolines (**200** and **201**) were obtained in good yields and then deprotection of **200** and **201** afforded $\alpha$-formyl-$\beta$-carbolines (**195** and **202**) in excellent yields. The requisite aniline **197** was prepared in a four steps sequence, which commenced with commercially available 4-methoxyphenol (**203**) (**Scheme 12**).

**Scheme 11**




**Scheme 12**




We started the preliminary investigation using $\alpha$-formyl-$\beta$-carboline (**207**),[119] anline (**143a**) and *n*-butylvinyl ether (**196**) so as to test the feasibility of this approach (**Table 14**). The first experiment was performed in refluxing ethanol and in presence of $BF_3{\cdot}Et_2O$ affording the desired product **208** in trace amount (entry 1). We suspected that the formation of water during shiff base formation would be deleterious to the reaction.

**Scheme 13**

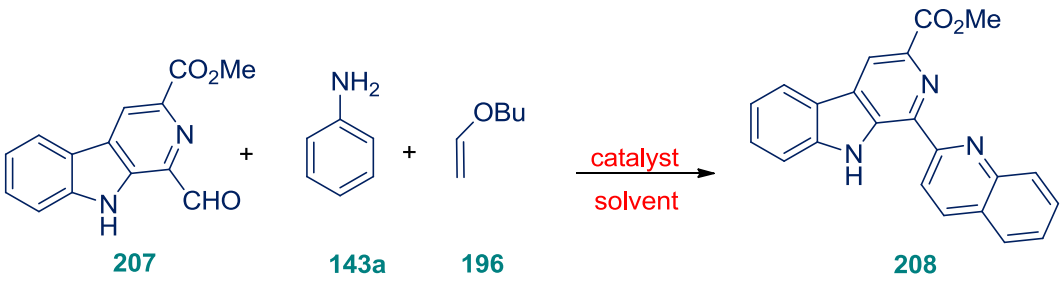



**Table 14: Optimization of the reaction conditions**

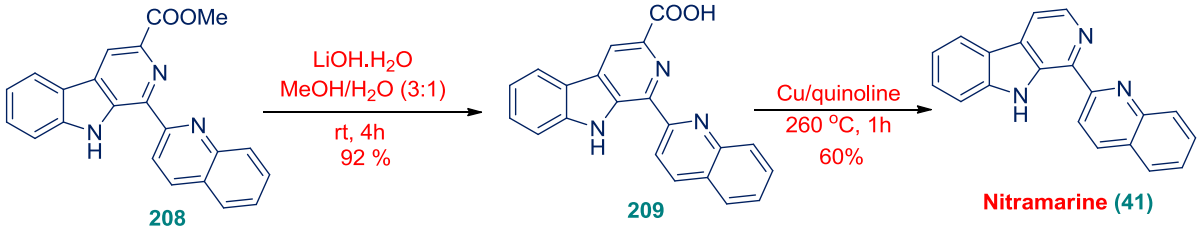
| Entry | Condition | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | $BF_3.Et_2O$ (10 mol%)/ethanol | 24 | Trace |
| 2 | $BF_3.Et_2O$ (10 mol%)/ethanol | 24 | 28 |
| 3 | $Cu(OTf)_2$ (10 mol%)/MeCN | 24 | 22 |
| 4 | AgOTf (10 mol%)/MeCN | 24 | 12 |
| 5 | $La(OTf)_3$ (10 mol%)/MeCN | 20 | 72 |
| 6 | $La(OTf)_3$ (10 mol%)/dioxane | 20 | 65 |
| 7 | $La(OTf)_3$ (10 mol%)/toluene | 32 | 68 |
| 8 | $Sc(OTf)_3$ (10 mol%)/MeCN | 20 | 55 |
| 9 | $Yb(OTf)_3$ (10 mol%)/MeCN | 18 | 51 |
| 10 | $I_2$ (10 mol%)/MeCN | 12 | 75 |
| 11 | $I_2$ (10 mol%)/MeOH | 15 | 61 |
| 12 | $I_2$ (10 mol%)/toluene | 20 | 45 |
| 13 | $I_2$ (10 mol%)/THF | 8 | 89 |
| 14 | $I_2$ (20 mol%)/THF | 24 | 89 |
| 15 | $I_2$ (5 mol%)/THF | 24 | 82 |

General conditions: Aldehyde (**207**) 0.25 mmol, aniline (**143a**) 0.25 mmol and vinyl ether (**196**) (0.30 mmol ). Yield refers to column purified product. For entry 1, the Povarov reaction between aldehyde (**207**), aniline (**143a**) and vinyl ether (**196**) was performed. For entry 2-15, the Povarov reaction between isolated aldimine and vinyl ether (**196**) was performed. The aldimine was prepared by refluxing the aniline and aldehyde in DCM solvent in the presence of $MgSO_4$ for 1 h. For all entries, reflux temperature of corresponding solvents was maintained.

As anticipated, the reaction between isolated aldimine and *n*-butylvinyl ether (**196**) in the same above-mentioned conditions (entry 2), afforded the desired product in better yield. Consequently, we decided to optimize the reaction conditions only with aldimine and vinyl ether.Soft metal triflates such as $Cu(OTf)_2$ and AgOTf triggered the reaction with poor yields (entries 3 and 4). In addition, lanthanide triflates such as $La(OTf)_3$, $Sc(OTf)_3$ and $Yb(OTf)_3$ also catalyzed the reaction with moderate yields (entries 5–9). A satisfactory result was

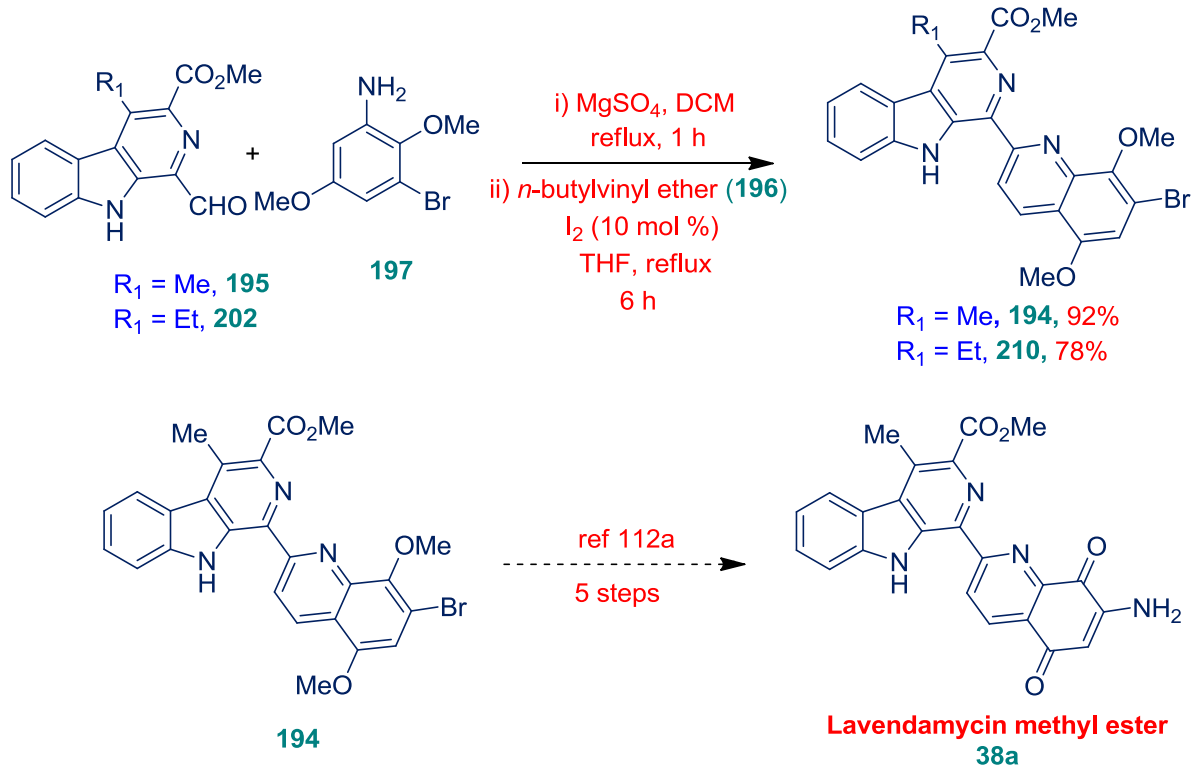
obtained with 10 mol% of $I_2$ in refluxing MeCN (entry 10). With molecular iodine as a good catalyst, we next proceeded with solvents screening and catalytic loading (entries 11–15). As shown in the **Table 14**, the best result was obtained using THF as a solvent and 10 mol% of $I_2$ as a catalyst (entry 13).

**Scheme 14**



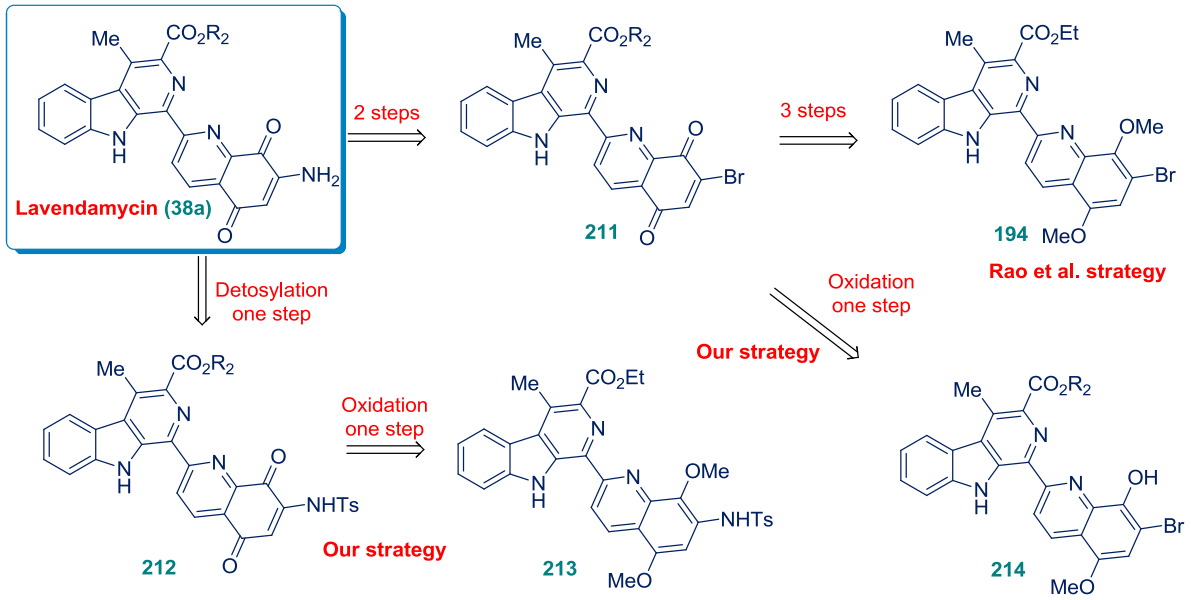

Nitramarine (**41**) (**Fig. 11**) is a $\alpha$-quinolinyl-$\beta$-carboline alkaloid, which was isolated from *Nitraria komarovii* plant by Tulyaganov *et al*. in 1984.[25] It exhibits sleeping time pronging effect,[26a] hypotensive and spasmolytic activities.[26b] However, only few literature reports were available for the synthesis of nitramarine.[26a,120a–c] The compound **208** was de-esterified using LiOH in MeOH/$H_2O$ (3:1) at room temperature to furnish a 92% yield of compound **209**, which was de-carboxylated using the reported procedure[120b] in moderate yield (**Scheme 14**). The spectroscopic data of synthetic **41** ($^1$H and $^{13}$C NMR, LC–MS, CHN analysis) were in full accordance with those reported.[120c]

**Scheme 15**



With the optimized conditions in hand, $\alpha$-formyl-$\beta$-carbolines **195** and **202** were subjected to the Povarov reaction with *n*-butylvinyl ether (**196**) and aniline **197** to give the corresponding compounds **194** and **210** in excellent yields (**Scheme 15**). The compound **194** is identical to the Rao's intermediate, which would be converted into lavendamycin methyl ester from their literature report.[112a] However, the conversion of the compound **194** to lavendamycin methyl ester was tedious and not in good yields.

## Scheme 16

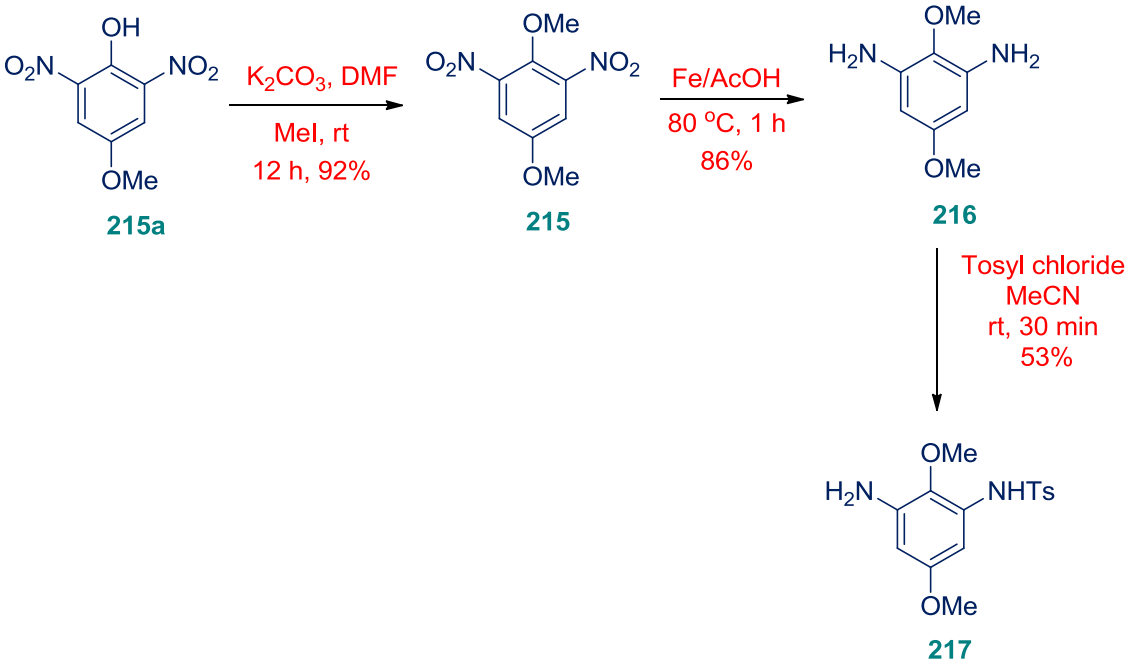



At this juncture, our endeavour was to modify the synthetic route attempted in the literature[112a] (**Scheme 16**). We envisioned that replacing the Br group at C-7 position of compound **194** with amino group (**Scheme 16**) could perhaps favour the oxidation step. Such a strategy, if successful, would be able to provide an intermediate **212**, which in turn, could easily be converted into lavendamycin ester (**38a**), thereby reducing the 3 steps[112a] (**Scheme 16**). Intermediate **213** was envisaged to be derived from $\alpha$-formyl-$\beta$-carboline **195** or **202** and 3-amino-2,5-dimethoxy-1-(4-methylphenylsulfonamido)benzene (**217**).

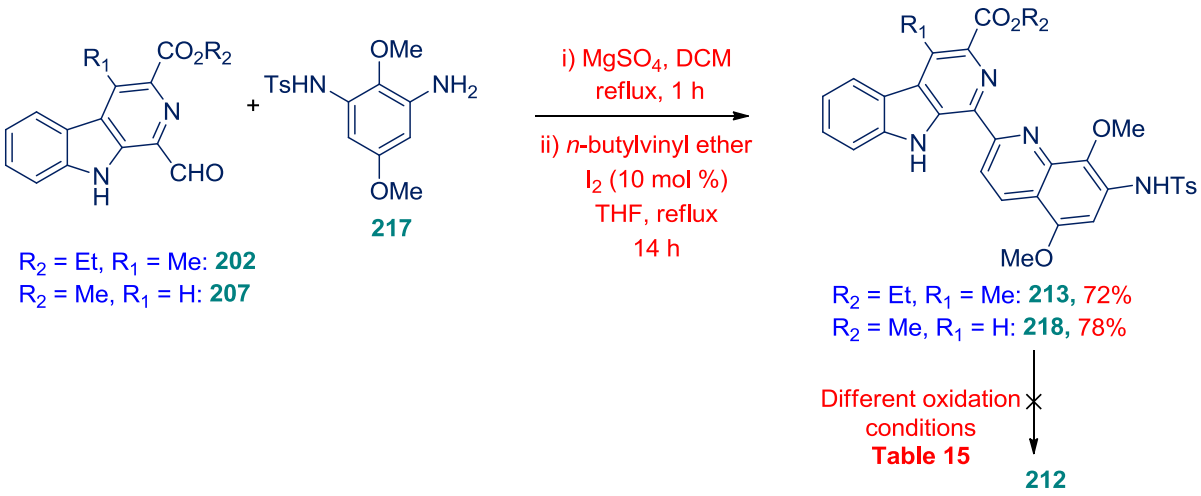
To examine this hypothesis, attempts were initiated to synthesize the aniline **217**, which was constructed via a three steps sequence starting with 4-methoxy-2,6-dinitrophenol (**Scheme 17**). With the requisite aniline **217** in hand, we next attempted the Povarov reactions with $\alpha$-formyl-$\beta$-carboline aldehyde **202** and **207** to afford compounds **213** and **218** in good yields (**Scheme 18**). Our attempts to oxidize the compound **213** under the conditions as in **Table 15** failed to deliver the desired compound **212.** However, the compound **213** remained unaffected in some of conditions (**Table 15**, entries 1, 5–10) and recovered from the reaction mixture. Oxidation conditions such as a higher equivalent of CAN (more than 5 equiv.), higher temperature (entry 3) and the presence of acid (entries 2 and

4) led to an unidentified complex reaction mixture. On the other hand, the Povarov reaction of aldehyde **195** and 2-amino-4-methoxy-6-bromo phenol **219** did not yield the expected intermediate **214**.

**Scheme 17**

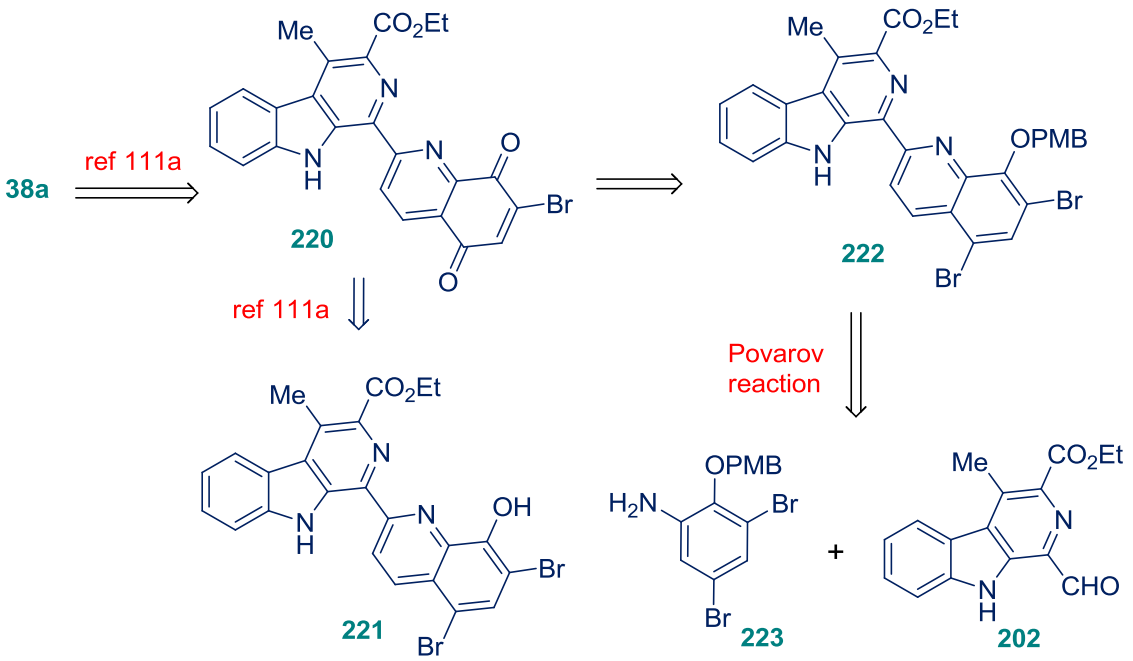



**Scheme 18**



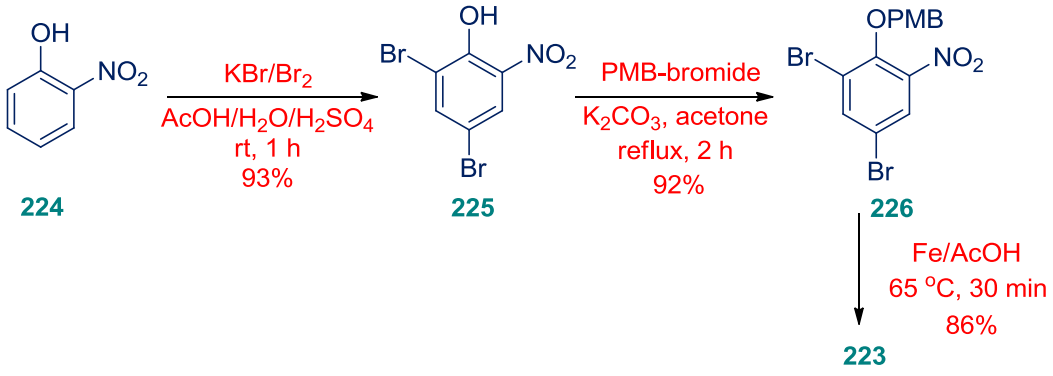

Next, we directed a revised retrosynthetic analysis, as delineated in **Scheme 19** according to the literature report.[111a] We endeavoured to attain the intermediate **222** for two reasons: (i) the Povarov reaction is not working without protection of aminophenol and (ii) the quinolyl carboline, particularly protected with PMB ether **222**, could be easily deprotected as well as oxidized by CAN in a single step to generate compound **220**.

**Scheme 19**




The route to synthesize the compound **222** commenced with the preparation of *p*-methoxybenzyl (PMB)-protected aniline **223**, which in turn could be accessed from 2-nitrophenol (**224**) in a short sequence (**Scheme 20**). With the aniline derivative **223** in hand, we explored the Povarov reaction of aldehydes **202** and **207** with aniline **223**, gave the compounds **222** and **227** respectively (**Scheme 21**).

**Scheme 20**




But unfortunately, all our efforts to oxidize the compound **222** were abortive under various conditions with CAN and DDQ (**Table 15**, entry 1, 3, 5–8). Under these conditions, the PMB-protected compound **222** was stable and could be recovered from the reaction mixture. We failed to obtain the quinolinedione **220**, despite our extensive efforts in troubleshooting the oxidation process.

**Scheme 21**

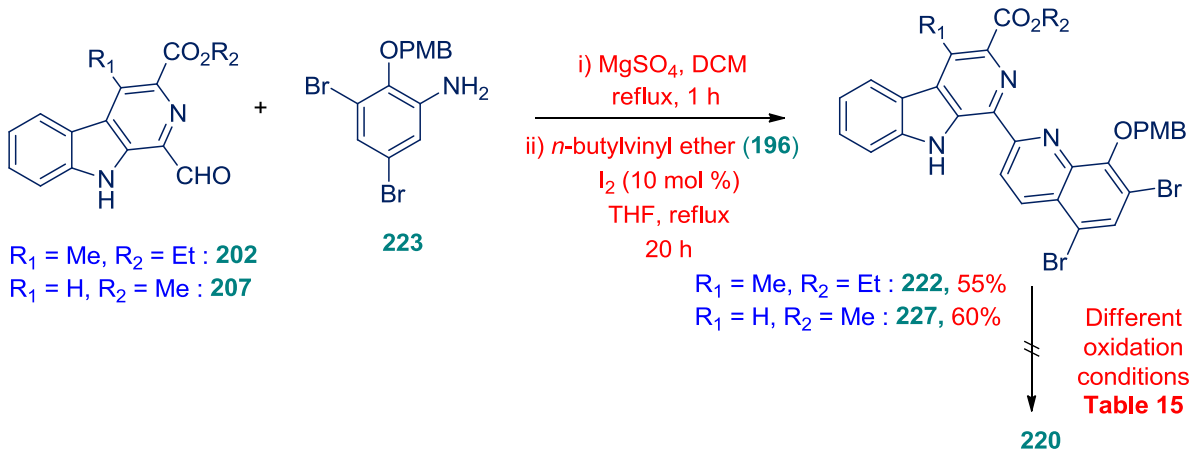
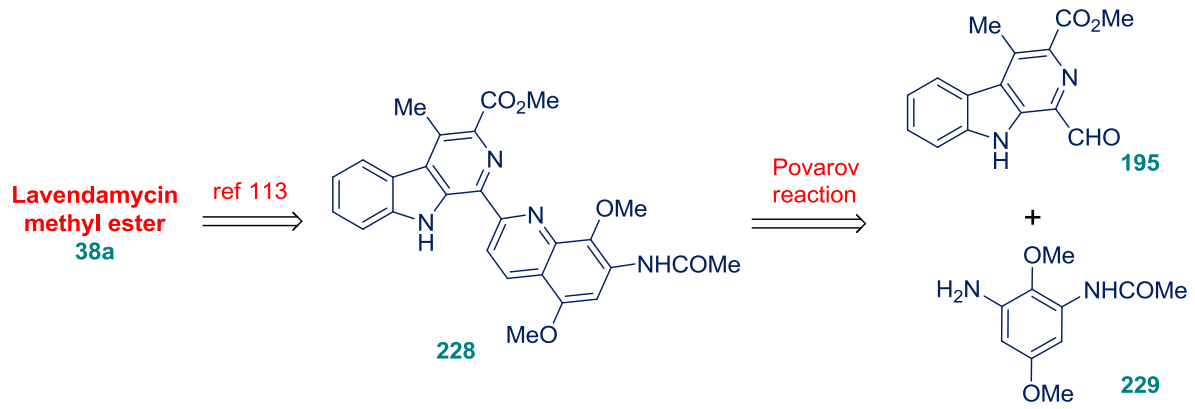



**Table 15: Attempted oxidative conditions**

| Entry | Condition |
|---|---|
| 1 | CAN (2.5 equiv.)/ MeCN-$H_2O$ (1:1) / 0 °C to rt, 24 h |
| 2 | AcOH / $K_2Cr_2O_7$ / DCM-H2O / rt, 1 h |
| 3 | CAN (2.5 equiv.)/ MeCN-$H_2O$ (1:1) / 80 °C, 1 h |
| 4 | $H_2SO_4$-70% aq. $HNO_3$ (3:1) / 0 °C-rt, 1h |
| 5 | CAN (2.5 equiv.)/ THF-$H_2O$ (1:1) / 0 °C to rt, 24 h |
| 6 | CAN (2.5 equiv.)/ DCM-$H_2O$ (1:1) / 0 °C to rt, 24 h |
| 7 | CAN (5 equiv.)/ DCM-$H_2O$ (1:1) / 0 °C to rt, 24 h |
| 8 | DDQ (1.2 equiv.)/ DCM-$H_2O$ (1:0.5) / 0 °C to rt, 24 h |
| 9 | IBX (4 equiv.)/ MeCN-$H_2O$ (1:1) / rt, 24 h |
| 10 | DIB (4 equiv.)/ MeCN-$H_2O$-MeOH (1:1:0.1) / rt, 24 h |

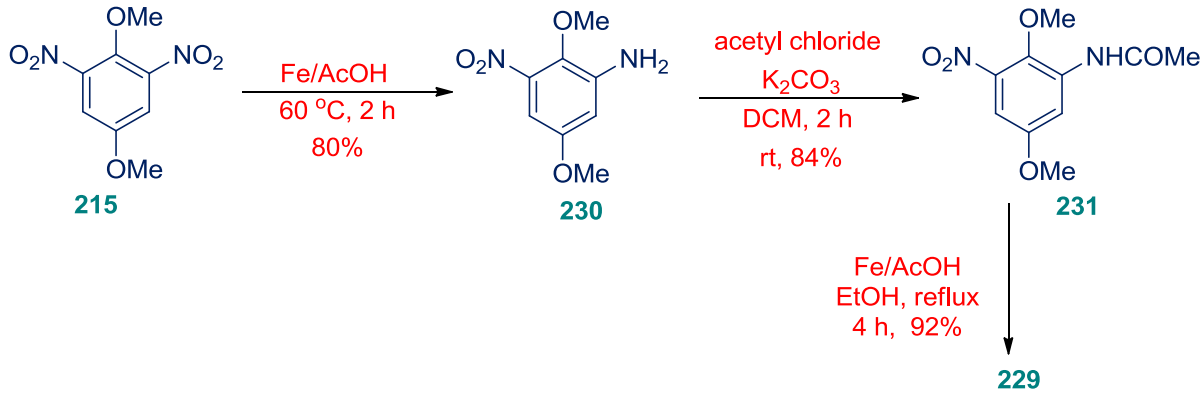
**Scheme 22**




Hence, we resolved to synthesize an acylated quinolyl carboline, which had been accounted by Nissen *et al*. in their recent total synthesis of lavendamycin methyl ester.[113] As

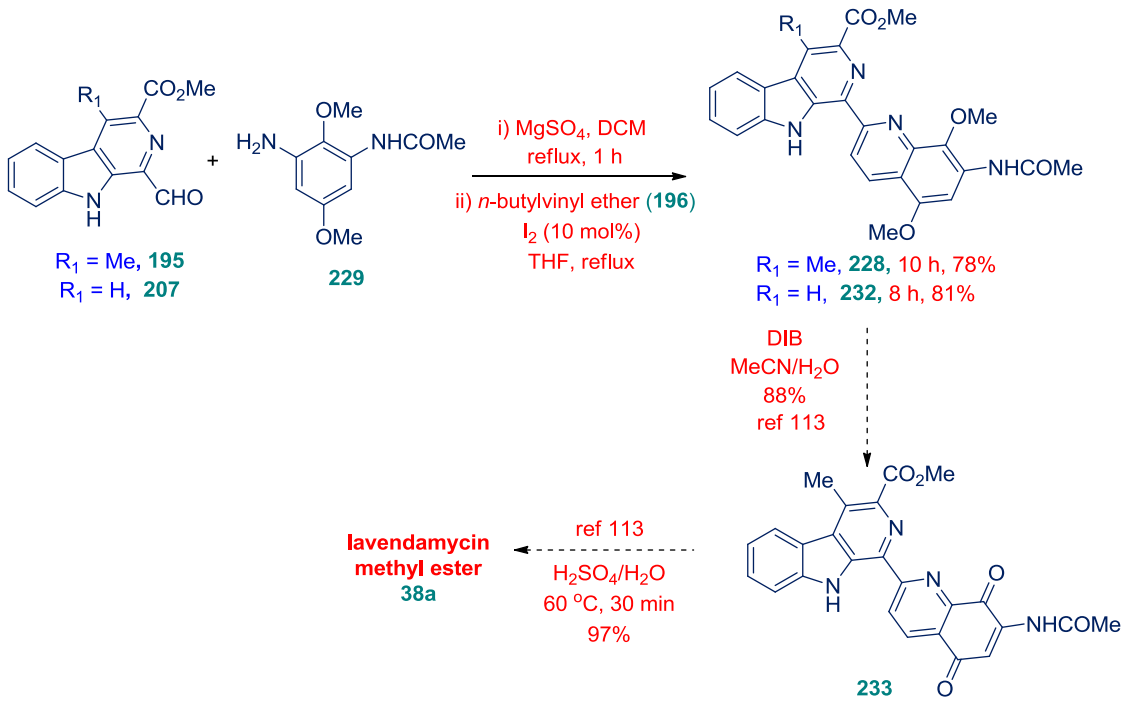
indicated in the revised retrosynthetic analysis (**Scheme 22**), for the construction of the intermediate **228**, *N*1-(3-amino-2,5-dimethoxyphenyl)acetamide (**229**) had to be prepared.

**Scheme 23**

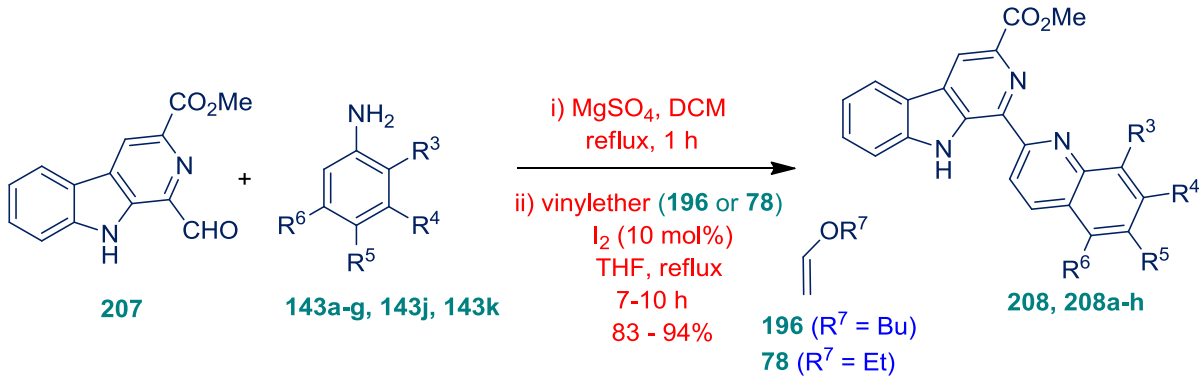



Upon preparation of the requisite aniline derivative **229** (**Scheme 23**), we proceeded next to the Povarov reaction between aldehydes (**195** and **207**) and the aniline **229** (**Scheme 24**), which afforded the expected *β*-carbolines **228** and **232** in good yields, thereby completing the formal synthesis of lavendamycin methyl ester, as the compound **228** could easily be converted into lavendamycin methyl ester in a two-step sequence with excellent yields. The overall yield for our synthetic sequence toward the compound **228** is **60%** with respect to methyltryptophan ester **187a**. Upon completion of the two reported steps, our synthetic strategy would be able to provide lavendamycin methyl ester in **51%** overall yield.

**Scheme 24**



**Scheme 25**




Considering the biological importance of lavendamycin analogues and scope of this methodology, we extended this reaction to different anilines (**143a-g**, **143j**, **143k**) and alkylvinyl ethers (**196** and **78**), resulting in high yields of corresponding lavendamycin methyl ester derivatives (**208**, **208a–h**) (**Table 16**). Aromatic amines contain both electron-donating (entries 5–7, 9) as well as electron-withdrawing (entries 2–4, 8) groups, which tolerated the reaction and corresponding products, were obtained in excellent yields.

**Table 16: Synthesis of various lavendamycin analogues (208, 208a-h)**

| Entry | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Amine | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | **143a** | **208** | 8 | 89 |
| 2 | H | H | F | H | **143e** | **208a** | 10 | 87 |
| 3 | H | H | Cl | H | **143f** | **208b** | 10 | 85 |
| 4 | H | H | Br | H | **143g** | **208c** | 10 | 85 |
| 5 | H | H | Me | H | **143b** | **208d** | 7 | 92 |
| 6 | H | H | OMe | H | **143c** | **208e** | 8 | 94 |
| 7 | OMe | H | H | H | **143d** | **208f** | 8 | 90 |
| 8 | H | Cl | H | Cl | **143j** | **208g** | 10 | 86 |
| 9 | H | OMe | H | H | **143k** | **208h** | 7 | 85 |
| 10 | H | H | H | H | **143a** | **208** | 10 | 83 |

Yield refers to column purified product. For entry 1-9, *n*-butylvinyl ether (**196**) was used. For entry 10, ethylvinyl ether (**78**) was used.

The compound **208** was also synthesized in good yield (83%, entry 10) using this synthetic approach via ethylvinyl ether (**78**) instead of *n*-butylvinyl ether (**196**). The structure of compound **208c** (**Fig. 12**) was unambiguously confirmed by X-ray single crystal analysis. The proposed reaction mechanism is shown in **Scheme 26**.

**Scheme 26**

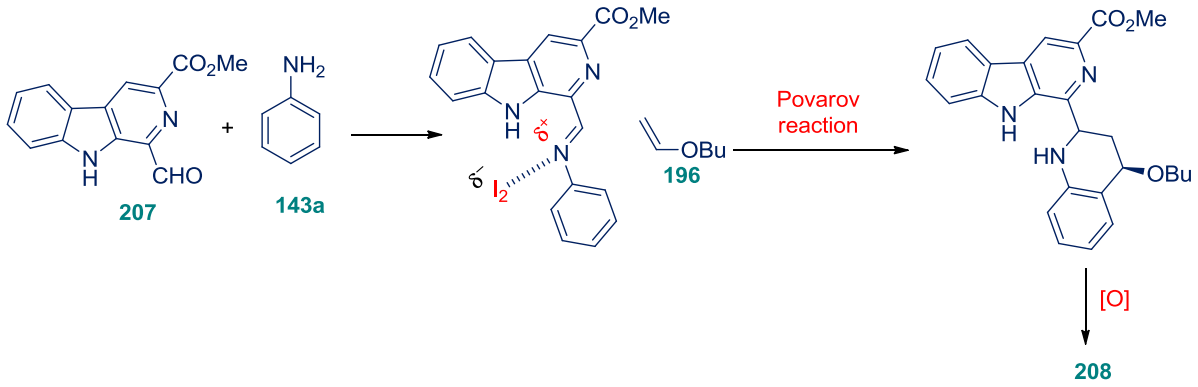
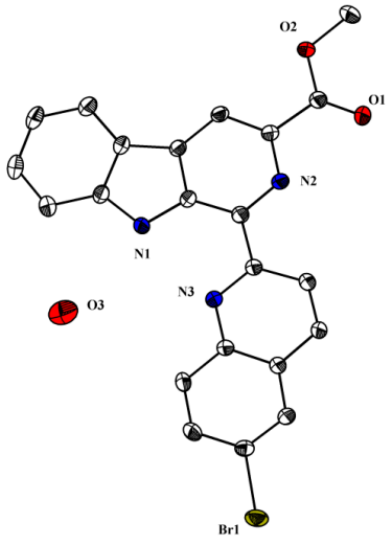



**Fig. 12: ORTEP of the compound 208c**

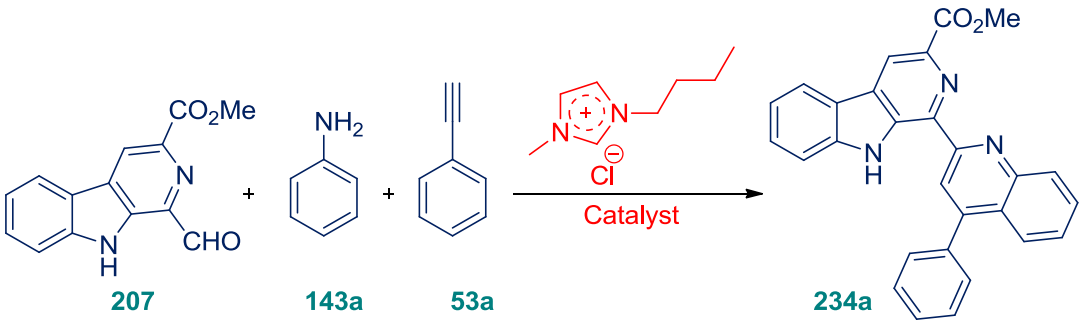


## 2.3. Synthesis of lavendamycin analogues through an $A^3$ coupling reaction

The three component reactions between amines, aldehydes, and terminal acetylenes ($A^3$ coupling) have been continuously witnessed as a versatile method to construct quinoline ring systems.[128] The important biological profile of these compounds and the broad scope of the $A^3$ coupling reactions promoted us to synthesize a new variety of lavendamycin analogues with diverse substitution pattern. Despite being an antibiotic, lavendamycin showed toxicity on human cells and hence the preclinical use of this alkaloid has been precluded. It has been partly believed that the presence of quinolone present in the lavendamycin structure could perhaps be the cause for this toxicity.[129]

Hence, synthesis of lavendamycin analogues is the major concern for the synthetic community compared to lavendamycin itself. Lavendamycin analogues are associated with remarkable attributes. In continuation of our work on $A^3$ coupling reactions,[128e] we wish to report here a methodology for the synthesis of lavendamycin analogues. Considering the growing environmental awareness and the negative environmental impacts of organic volatile solvents, we decided to optimize the reaction condition with environmentally more benign and alternatives to the traditional organic volatile solvents, i.e., ionic liquids (so called green solvent) as a solvent medium. Some of the physical properties, such as (i) nonvolatility, (ii) greater effective surface area, (iii) potential activity of a liquid phase and the catalytic nature and (iv) recycling make them an interesting solvent for a synthesis.

**Scheme 27**




In the first attempt, the reaction between aldehyde (**207**)[119] aniline (**143a**), and phenylacetylene (**53a**) in [Bmim][Cl] at room temperature without catalyst failed to give the desired product **234a** (**Table 17**, entry 1). However, heating the reaction around 95-100 °C provided the compound (**234a**) in poor yield (entry 2). Further investigation with various ionic liquids (entries 3-8) like [Bmim][Br], [Bmim][Tfa], [Emim][Tfa], [Bmim][Tsa], [Bmim][$PF_6$], and [Bmim][$BF_4$] revealed that [Bmim][$BF_4$] was superior to other ionic liquids and provided **234a** in 34% yield (entry 8). We envisaged that addition of Lewis acids along with ionic liquid could further enhance the reaction yield (entries 9-15). To our delight,

addition of $La(OTf)_3$ (10 mol%) to the reaction mixture significantly increased the yield of the product **234a** (entry 14). Lowering the catalytic loading to 5 mol% resulted in the incomplete conversion of **234a** (entry 16). On the other hand, the yield remained unaffected on addition of 20 mol% of $La(OTf)_3$ (entry 17).

**Table 17: Optimization of the reaction conditions**

| Entry | IL / catalyst | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | [Bmim][Cl] | 48 | - |
| 2 | [Bmim][Cl] | 24 | 14 |
| 3 | [Bmim][Br] | 24 | Trace |
| 4 | [Bmim][Tfa] | 24 | 20 |
| 5 | [Emim][Tfa] | 24 | 22 |
| 6 | [Bmim][Tsa] | 48 | Trace |
| 7 | [Bmim][$PF_6$] | 24 | 15 |
| 8 | [Bmim][$BF_4$] | 24 | 34 |
| 9 | [Bmim][$BF_4$]/$I_2$ (10 mol%) | 12 | 47 |
| 10 | [Bmim][$BF_4$]/$Zn(OTf)_2$ (10 mol%) | 10 | Trace |
| 11 | [Bmim][$BF_4$]/CuI (10 mol%) | 20 | - |
| 12 | [Bmim][$BF_4$]/$Pd(OAc)_2$ (10 mol%) | 20 | - |
| 13 | [Bmim][$BF_4$]/$Cu(OTf)_2$ (10 mol%) | 8 | 56 |
| 14 | [Bmim][$BF_4$]/$La(OTf)_3$ (10 mol%) | 4 | 78 |
| 15 | [Bmim][$BF_4$]/$Yb(OTf)_3$ (10 mol%) | 3 | 70 |
| 16 | [Bmim][$BF_4$]/$La(OTf)_3$ (5 mol%) | 4 | 72 |
| 17 | [Bmim][$BF_4$]/$La(OTf)_3$ (20 mol%) | 4 | 76 |

General conditions: Aldehyde (**207**) 0.3 mmol, aniline (**143a**) 0.3 mmol and phenylacetylene (**53a**) 0.35 mmol. aYield refers to column purified product. For entry 1, room temperature was maintained. For entry 2-17, 95-100 °C temperature were maintained. Tfa = $CF_3COO$, Tsa = *p*-toluenesulphonic acid. Emim = 1-ethyl-3-methylimidazole, Bmim = 1-butyl-3-methylimidazole.

**Scheme 28**

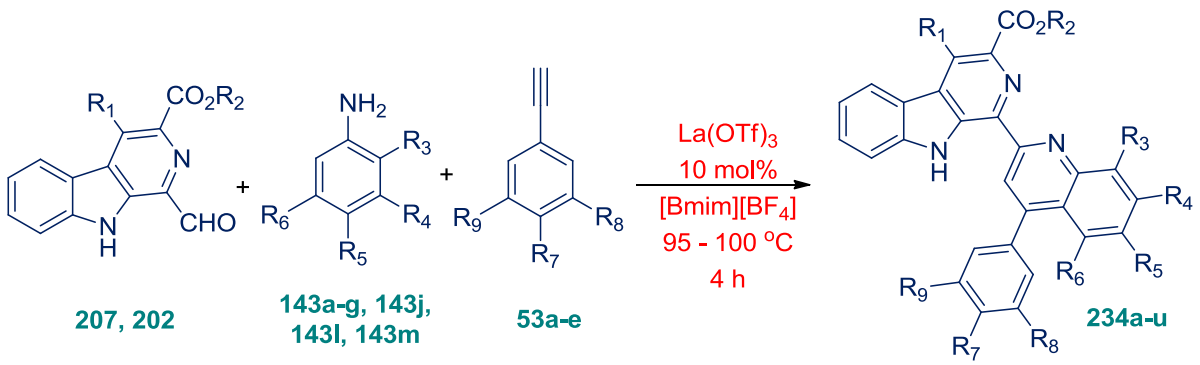


**Table 18: Synthesis of various lavaendamycin analogues (234a-u)**

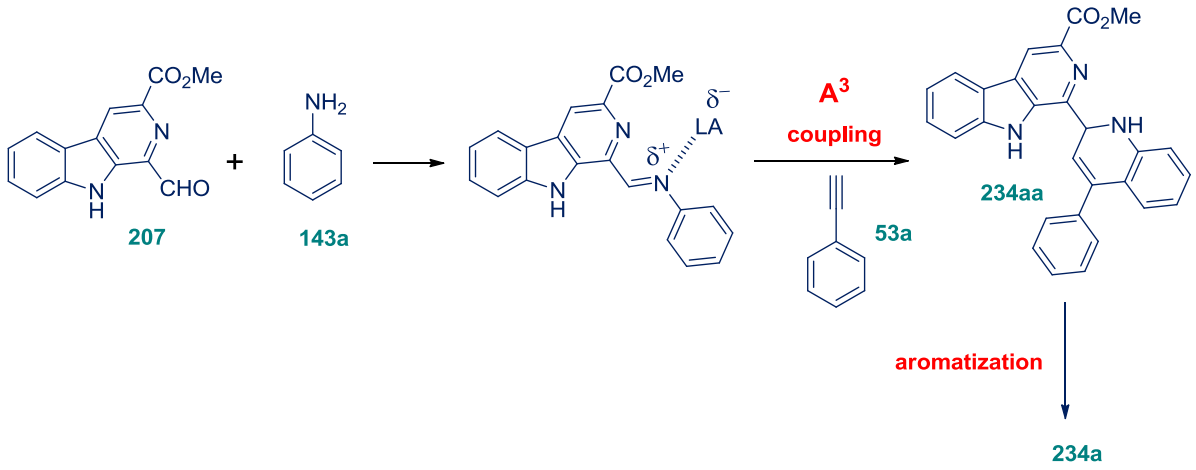
| Entry | Substitutents | Amine | Acetylene | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | $R_2$ = Me; $R_1$, $R_{3-9}$ = H | **143a** | **53a** | **234a** | 78 |
| 2 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_{6-9}$=H; $R_5$ = Me | **143b** | **53a** | **234b** | 85 |
| 3 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_{6-9}$=H; $R_5$ = OMe | **143c** | **53a** | **234c** | 83 |
| 4 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_{6-9}$=H; $R_5$ = F | **143e** | **53a** | **234d** | 77 |
| 5 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_{6-9}$=H; $R_5$ = Cl | **143f** | **53a** | **234e** | 80 |
| 6 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_{6-9}$=H; $R_5$ = Br | **143g** | **53a** | **234f** | 75 |
| 7 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_{6-9}$=H; $R_3$ = OMe | **143d** | **53a** | **234g** | 79 |
| 8 | Amine = *N*-Et-3-aminocarbazole | **143l** | **53a** | **234h** | 72 |
| 9 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_{6-9}$=H; $R_5$ = $NO_2$ | **143m** | **53a** | **234i** | 68 |
| 10 | $R_2$ = Me; $R_1$, $R_3$, $R_5$, $R_{7-9}$=H; $R_4$, $R_6$ = Cl | **143j** | **53a** | **234j** | 75 |
| 11 | $R_2$ = Me; $R_1$, $R_{3-6}$, $R_{8-9}$ = H; $R_7$ = Me | **143a** | **53b** | **234k** | 85 |
| 12 | $R_2$ = Me; $R_1$, $R_{3-6}$, $R_{8-9}$ = H; $R_7$ = F | **143a** | **53c** | **234l** | 81 |
| 13 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_6$, $R_{8-9}$ = H; $R_5$ = Cl; $R_7$ = Me | **143f** | **53b** | **234m** | 84 |
| 14 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_6$, $R_{8-9}$ = H; $R_5$ = Br; $R_7$ = Me | **143g** | **53b** | **234n** | 80 |
| 15 | $R_2$ = Me; $R_1$, $R_{3-7}$ = H; $R_{8-9}$ = Me | **143a** | **53d** | **234o** | 79 |
| 16 | $R_2$ = Me; $R_1$, $R_5$, $R_{7-9}$ = H; $R_3$, $R_6$ = OMe; $R_4$ = Br | **143n** | **53a** | **234p** | 74 |
| 17 | $R_2$ = Et, $R_1$ = Me; $R_{3-9}$ = H | **143a** | **53a** | **234q** | 73 |
| 18 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_6$, $R_{8-9}$ = H; $R_5$ = Me; $R_7$ = Cl | **143b** | **53e** | **234r** | 80 |
| 19 | $R_2$ = Me; $R_1$, $R_{3-4}$, $R_6$, $R_{8-9}$ = H; $R_5$ = OMe; $R_7$ = Cl | **143c** | **53e** | **234s** | 82 |
| 20 | $R_2$ = Me; $R_1$, $R_{4-9}$ = H; $R_3$ = Br | **143o** | **53a** | **234t** | 73 |
| 21 | $R_2$ = Me; $R_1$, $R_{4-9}$ = H; $R_3$ = Cl | **143p** | **53a** | **234u** | 77 |

With these optimized condition in hand, next we examined the scope of the reaction with variety of amines (**143a-g, 143j, 143l** & **143m**), acetylenes (**53a-e**), and aldehydes (**207**, **202**) to generate the lavendamycin analogues (**234a-u**) (**Scheme 28**).

As indicated in **Table 18**, anilines with electron donating substituents (-Me, -OMe) (entries 2, 3, 7, 16, 18, and 19) and with electron withdrawing substituents (-F, -Cl, -Br, -$NO_2$) (entries 4-6, 9, 10, 13, 14, 20, and 21) in *ortho*-, *para*-, and *meta*-positions well tolerated the reaction with good yields. Carbazole nucleus represents an important heterocyclic scaffold found in many natural products, which possess interesting biological properties[105] and in view of introducing a carbazole unit in the $\beta$-carboline core, we tested the reactivity of 3-amino-9-ethylcarbazole (**143l**) as an amine precursor in this reaction (entry 8). As anticipated, the reaction afforded the pyridocarbazole derivative (**234h**) in good yield.

**Fig. 13: ORTEP of compound 234g**

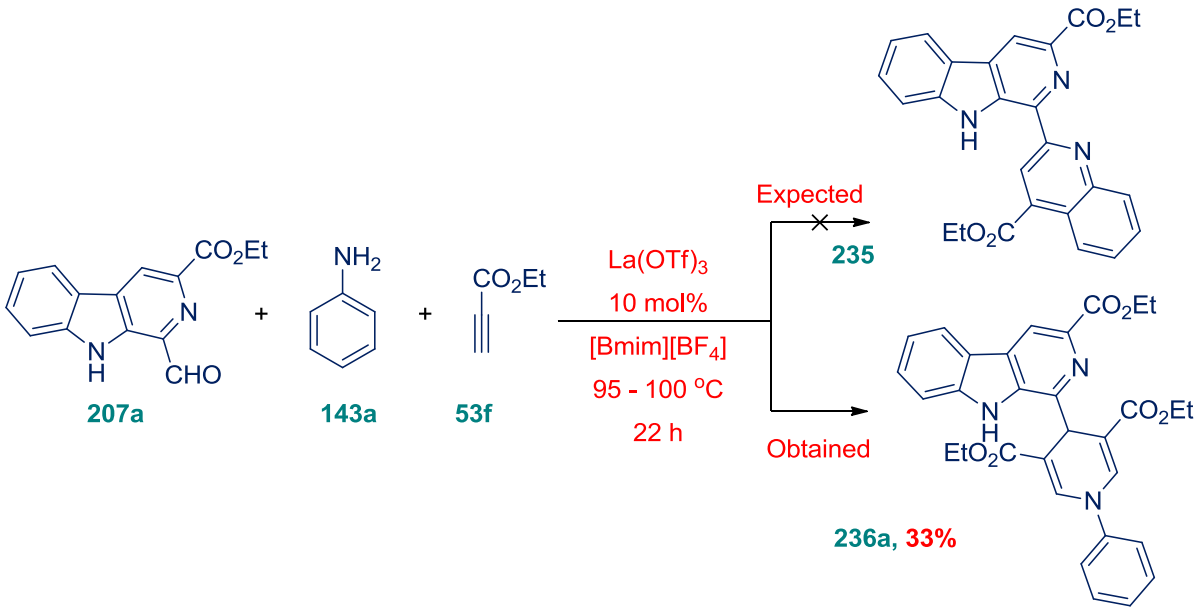

**Scheme 29**




The reaction with substituted phenylacetylenes (**53b-e**) also efficiently proceeded to afford the desired lavendamycin analogues (entries 11, 12, 15, and 18) in good yields. The structure of compound **234g** is confirmed by X-ray diffraction analysis (**Fig. 13**). According

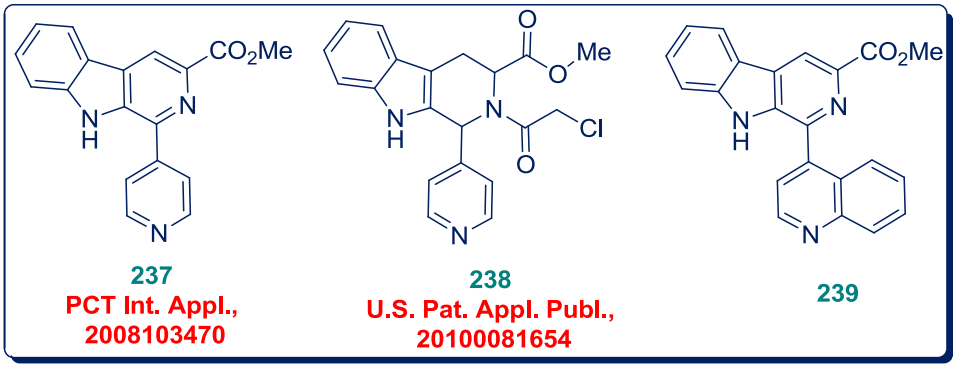
to the literature,[128] the proposed mechanism is shown in **Scheme 29**. Aldimine formed from aldehyde (**207**) and aniline (**143a**), followed by Lewis acid catalyzed coupling reaction with phenylacetylene (**53a**) gave **234aa**. Subsequent aromatization of **234aa** affords **234a**. After the successful synthesis of analogues **234a-u**, this sequence was extended from phenylacetylene (**53a-e**) to ethylpropiolate (**53f**) but, to our surprise the reaction (**Scheme 30**) failed to provide the expected $\alpha$-quinolo-$\beta$-carboline (**235**).

**Scheme 30**

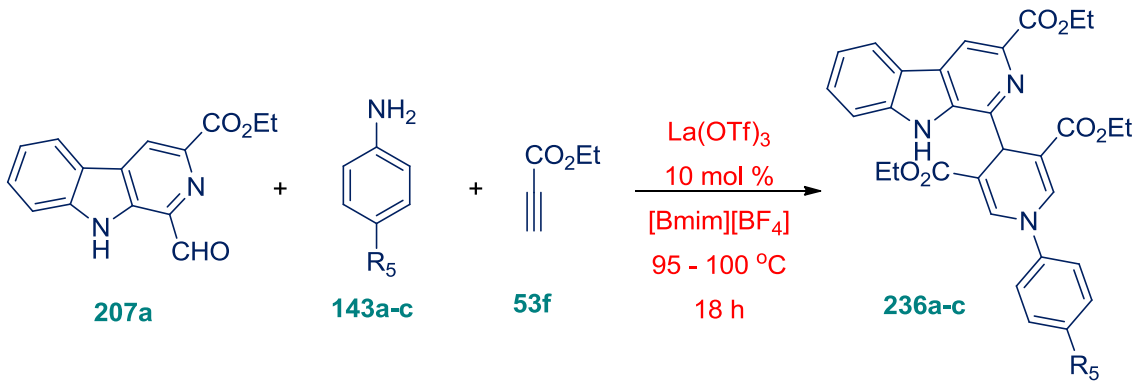



However, according to literature reports[130] and with the help of NMR spectroscopy, the structure of the obtained compound **236a** was confirmed as a dihydropyrido-$\beta$-carboline. It is noteworthy that $\alpha$-pyrido-$\beta$-carboline and their derivatives (**Fig. 14**) also have drawn attention from synthetic chemists due to their antitumor properties and hence, a few syntheses of these analogues have been reported.[131]

**Fig. 14**



**Scheme 31**

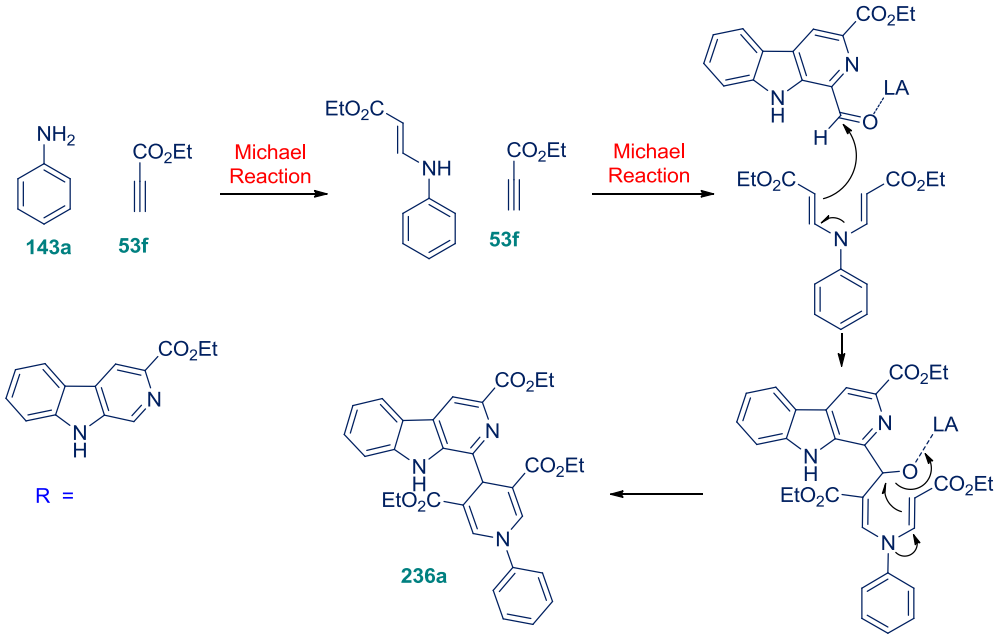



The compound **236a** was incorporated with two units of ethylpropiolate (**53f**) and hence increasing the equivalents of **53f** could perhaps enhance the yield of the product. As expected, when we used 3 equiv. of **53f** along with 1 equiv. of each aldehyde (**207a**) and anilines (**143a**, **143b**, **143c**), the dihydropyrido-$\beta$-carbolines (**236a-c**) were obtained in good yields (**Scheme 31**).

**Table 19: Synthesis of $\alpha$-pyrido-$\beta$-carboline analouges (236a-c)**

| Entry | $R_5$ | Amine | Product | Yield (%) |
|---|---|---|---|---|
| 1 | H | **143a** | **236a** | 72 |
| 2 | Me | **143b** | **236b** | 76 |
| 3 | OMe | **143c** | **236c** | 75 |

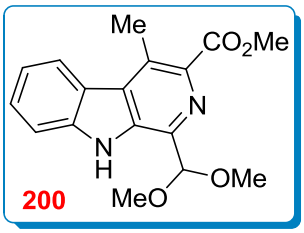
**Scheme 32**



The observed differences in reactivity between phenylacetylene (**53a**) and ethylpropiolate (**53f**) are explained in the proposed mechanism (**Scheme 32**). First, aniline **143a** undergoes Michael reaction with ethylpropiolate instead of forming imine with aldehyde **207a** as in the case of **Scheme 27**, followed by second Michael reaction and reaction with aldehyde afford dihydropyrido compound **236a**.

## 2.4. Experimental Section

**Methyl 1-dimethoxymethyl-4-methyl-9*H*-$\beta$-carboline-3-carboxylate (200):** To a solution of $\beta$-methyltryptophan ester (**187a**) (2.15 mmol) in dichloromethane (25 mL) were added 60% wt. solution in water of dimethoxyacetaldehyde (3 mmol) and 98% of TFA (3 mmol). The reaction mixture was allowed to stir at room temperature for a period of 5 h. The reaction mixture was concentrated in vacuum and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$, concentrated in vacuum and carried forward to the next step without further purification. To the crude diastereomeric mixture (**198**, 2.1 mmol) in DMF (20 mL) was added $KMnO_4$ (3.1 mmol). The reaction mixture was stirred over a period of 2.5 h at room temperature. The reaction mixture was filtered using Celite-545 bed. The filterate was concentrated and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromotography (silica gel: hexanes/ethyl acetate = 10:4) to give the desired product **200** as a viscous liquid in 81% yield (overall two steps).




IR (KBr) $\nu_{max}$ $cm^{-1}$: 3366, 3059, 1716, 1215, 798, 746

$^1$H NMR (400 MHz) δ: 9.50 (1H, s), 8.26 (1H, d, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 3.2 Hz), 7.28-7.33 (1H, m), 5.71 (1H, s), 3.99 (3H, s), 3.48 (6H, s), 3.11 (3H, s)

$^{13}$C NMR (100 MHz) δ: 167.7, 140.4, 137.7, 136.5, 133.8, 131.5, 129.5, 128.1, 123.8, 121.9, 120.5, 111.9, 106.8 (aromatic C), 54.7, 52.5, 16.6 (aliphatic C)

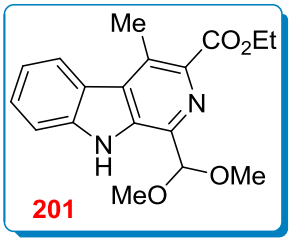
HRMS (ESI-MS). Calcd: 315.1345 (M+H)

Found: 315.1349

Anal. calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91%

Found: C, 64.79; H, 5.85; N, 8.96%

**Ethyl 1-dimethoxymethyl-4-methyl-9*H*-$\beta$-carboline-3-carboxylate (201):** To a solution of $\beta$-methyltryptophan ester (**187b**) (2.0 mmol) in dichloromethane (25 mL) were added 60% wt. solution in water of dimethoxyacetaldehyde (3 mmol) and 98% of TFA (3 mmol). The reaction mixture was allowed to stir at room temperature for a period of 5 h. The reaction mixture was concentrated in vacuum and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$, concentrated in vacuum and carried forward to the next step without further purification. To the crude diastereomeric mixture (**199,** 1.83 mmol) in DMF (20 mL) was added $KMnO_4$ (3.0 mmol). The reaction mixture was stirred over a period of 2.5 h at room temperature. The reaction mixture was filtered using Celite-545 bed. The filterate was concentrated and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The residue was purified by column chromotography (silica gel: hexanes/ethyl acetate = 10:4) to give the desired product **201** as a viscous liquid in 77% yield (overall two steps).



201

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3360, 2935, 1712, 1213, 1070, 746

$^1$H NMR (400 MHz) δ: 9.81 (1H, s), 8.16 (1H, d, *J* = 8.0 Hz), 7.37-7.51 (2H, m), 7.21 (1H, t, *J* = 6.8 Hz), 5.62 (1H, s), 4.44 (2H, q, *J* = 6.8 Hz), 3.37 (6H, s), 3.06 (3H, s), 1.35 (3H, t, *J* = 7.2 Hz)

$^{13}$C NMR (100 MHz) δ: 167.5, 140.5, 137.8, 137.1, 133.6, 130.6, 129.3, 127.9, 123.5, 121.8, 120.3, 112.0, 106.8 (aromatic C), 61.3, 54.7, 16.6, 14.3 (aliphatic C)

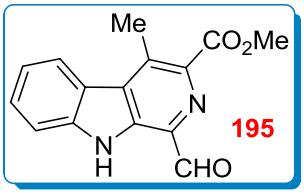
HRMS (ESI-MS). Calcd: 329.1501 (M+H)

Found: 329.1501

Anal. calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53%

Found: C, 65.73; H, 6.19 ; N, 8.45%

**Methyl 1-formyl-4-methyl-9*H*-$\beta$-carboline-3-carboxylate (195):** In a 150 mL round bottom flask equipped with a magnetic bar, the compound **200** (1.2 mmol) was dissolved in $H_2O$/AcOH (40 mL/32 mL) solvent mixture then the solution was heated at 70 $^oC$ over a period of 30 min. The hot solution was cooled down to room temperature and concentrated under reduced pressure. The residue was extracted with EtOAc, dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The title compound **195** was isolated as a pale yellow solid which was carried forward to further reactions without further purifications. (Yield: 95%).




Mp: 160 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3364, 2920, 1720, 1441, 1073, 739

$^{1}H$ NMR (400 MHz) δ: 10.34 (1H, s), 10.32 (1H, s), 8.29 (1H, d, *J* = 8.0 Hz), 7.63-7.64 (2H, m), 7.38-7.42 (1H, m), 4.07 (3H, s), 3.17 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 194.9, 166.9, 141.3, 138.5, 136.2, 135.2, 132.9, 131.1, 129.2, 124.1, 121.8, 121.4, 112.4 (aromatic C), 52.9, 17.2 (aliphatic C)

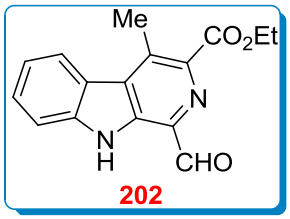
HRMS (ESI-MS). Calcd: 269.0926 (M+H)

Found: 269.0927

Anal. calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44%

Found: C, 67.25; H, 4.61; N, 10.31%

**Ethyl 1-formyl-4-methyl-9*H*-β-carboline-3-carboxylate (202):** In a 150 mL round bottom flask equipped with a magnetic bar, the compound **201** (1.2 mmol) was dissolved in $H_2O$/ AcOH (40 mL/ 32 mL) solvent mixture then the solution was heated at 70 °C over a period of 30 min. The hot solution was cooled down to room temperature and concentrated under reduced pressure. The residue was extracted with EtOAc, dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The title compound **202** was isolated as a pale yellow solid which was carried forward to further reactions without further purifications. (Yield: 95%).




Mp: 148 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3360, 2986, 170 7, 1331, 1280, 927, 742

$^{1}H$ NMR (400 MHz) δ: 10.34 (1H, s), 10.30 (1H, s), 8.30 (1H, d, *J* = 8.0 Hz), 7.64-7.65 (2H, m), 7.39-7.43 (1H, m), 4.56 (2H, q, *J* = 7.2 Hz), 3.16 (3H, s), 1.51 (3H, t, *J* = 7.2 Hz)

$^{13}C$ NMR (100 MHz) δ: 195.2, 166.7, 141.3, 139.3, 135.6, 135.2, 133.0, 131.0, 129.2, 124.1, 121.8, 121.5, 112.4 (aromatic C), 61.9, 17.3, 14.4 (aliphatic C)

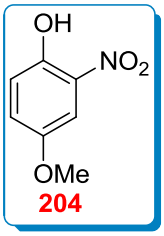
HRMS (ESI-MS). Calcd: 283.1082 (M+H)

Found: 283.1084

Anal. calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92%

Found: C, 68.15; H, 5.12; N, 9.85%

**Procedure for the synthesis of 4-methoxy-2-nitrophenol (204):** A round bottom flask equipped with magnetic stir bar, was charged with 4-methoxy-nitrophenol (**2.24**) (500 mg, 4 mmol) and glacial AcOH (25 mL), then 67% nitric acid was added dropwise and maintaining the internal temperature of the flask below 20 °C. Upon completion of acid addition, the reaction mixture was stirred at room temperature for a period of 1 h. The reaction mixture was quenched by saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The title compound **204** was purified by column chromotography (silica gel: hexanes/EtOAc = 10:0.5) (476 mg, yield. 70%). The spectroscopic data of the compound **204** were in full accordance with those reported.[121a,121b]




Mp: 80 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3321, 2831, 1675, 765

$^1H$ NMR (400 MHz) δ: 10.31 (1H, s), 7.48 (1H, d, *J* = 3.2 Hz), 7.20 (1H, dd, *J* = 3.2 & 9.2 Hz), 7.07 (1H, d, *J* = 9.2 Hz), 3.81 (3H, s)

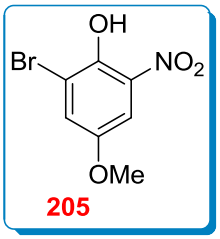
$^{13}C$ NMR (100 MHz) δ: 152.6, 150.0, 132.9, 127.3, 120.9, 105.6 (aromatic C), 55.9 (aliphatic C)

LCMS (m/z): 170 $(M+H)^+$

Anal. calcd. for $C_7H_7NO_4$: C, 49.71; H, 4.17; N, 8.28%

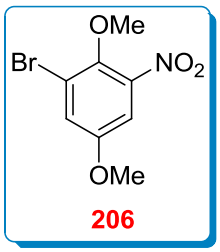
Found: C, 49.65; H, 4.06; N, 8.35%

**Procedure for the synthesis of 2-bromo-4-methoxy-6-nitrophenol (205):** To a solution of 4-methoxy-2-nitrophenol (**204**) (400 mg, 2.3 mmol), KBr (1 equiv.) in $H_2O$ (5 mL) and AcOH (15 mL), was added bromine (1 equiv.) in dropwise. After completion of the addition, the reaction mixture was agitated at room temperature for a period of 1 h. Then, the reaction was quenched with saturated solution of $Na_2S_2O_3.5H_2O$ and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under vacuum. The residue was obtained (557 mg, 95%) as a yellow solid and carried forward to the next step without purification. The spectroscopic data of the compound **205** were in full accordance with those reported.[122a,122b]




| | |
|---|---|
| Mp: | 116 °C |
| IR (KBr) $\nu_{max}$ $cm^{-1}$: | 3244, 3101, 2845, 17 11, 1244, 1138, 677 |
| $^1$H NMR (400 MHz) δ: | 10.79 (1H, s), 7.50-7.53 (2H, m), 3.82 (3H, s) |
| $^{13}$C NMR (100 MHz) δ: | 152.2, 147.1, 133.6, 129.8, 113.8, 106.3 (aromatic C), 56.2 (aliphatic C) |
| LCMS (m/z): | 246 $(M-H)^+$ |
| Anal. calcd. for $C_7H_6BrNO_4$: | C, 33.90; H, 2.44; N, 5.65% |
| Found: | C, 33.85; H, 2.39; N, 5.57% |

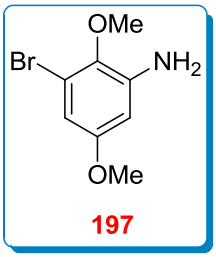
**Procedure for the synthesis of 1-bromo-2,5-dimethoxy-3-nitrobenzene (206):** To the solution of compound **205** (500 mg, 2 mmol), KOH (3 equiv.) in acetone (20 mL) was added MeI (1.5 equiv.) dropwise. The reaction mixture was heated at reflux temperature of acetone. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. The reaction mass was concentrated under vacuum and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The compound **206** (475 mg, 90%) was isolated as a yellow solid and carried forward to the next step without purification. The spectroscopic data of the compound **206** were in full accordance with those reported.[122b,123]




| | |
|---|---|
| Mp: | 106 °C |
| IR (KBr) $\nu_{max}$ $cm^{-1}$: | 2854, 1544, 1012, 756 |
| $^1$H NMR (500 MHz) δ: | 7.35 (1H, d, *J* = 3.0 Hz), 7.29 (1H, d, *J* = 3.0 Hz), 3.97 (3H, s), 3.84 (3H, s) |
| $^{13}$C NMR (125 MHz) δ: | 155.5, 145.0, 144.5, 123.9, 120.2, 109.2 (aromatic C), 62.7, 56.3 (aliphatic C) |
| LCMS (m/z): | 261 $(M^+)$, 262 $(M+H)^+$, 263 $(M+2)^+$ |
| Anal. calcd. for $C_8H_8BrNO_4$: | C, 36.67; H, 3.08; N, 5.34% |
| Found: | C, 36.51; H, 3.13; N, 5.28% |

**Procedure for the synthesis of 3-bromo-2,5-dimethoxyaniline (197):** To the compound **206** (400 mg, 1.5 mmol) in AcOH (20 mL) was added Fe powder (3 equiv.). The reaction mixture was heated at 80 °C for a period of 20 min. then cooled to room

temperature. The mixture was filtered to remove iron powder using Celite-545 bed. The filtrate was concentrated and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuum. The compound 3-bromo-2,5-dimethoxyaniline (**197**) was obtained as a brown viscous oil in 93% yield and used for further reactions without any purification. The spectroscopic data of the compound **197** were in full accordance with those reported.[122b,123,124a,124b]



**197**

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3463, 3369, 2832, 1616, 1227, 997, 838

$^1H$ NMR (400 MHz) δ: 6.31 (1H, d, *J* = 2.4 Hz), 6.08 (1H, d, *J* = 2.8 Hz), 3.88 (2H, s), 3.63 (3H, s), 3.54 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 156.8, 141.5, 138.6, 116.9, 106.9, 101.2 (aromatic C), 59.8, 55.6 (aliphatic C)

LCMS (m/z): 231 $(M^+)$, 232 $(M+H)^+$, 233 $(M+2)^+$

Anal. calcd. for $C_8H_{10}BrNO_2$: C, 41.40; H, 4.34; N, 6.04%

Found: C, 41.52; H, 4.31; N, 6.15%

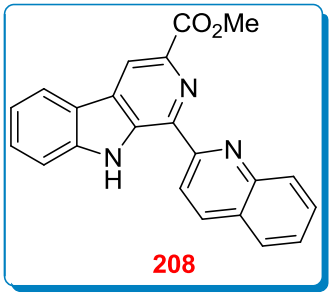
***General procedure D:***

In a round bottom flask equipped with a magnetic stirring bar, mixture of 0.3 mmol of α-formyl-β-carboline, 0.3 mmol of aniline and 0.5 mmol of anhydrous $MgSO_4$ in 10 mL of dichloromethane was refluxed for 1 h under stirring. The yellow solution was filtered and the filtrate was concentrated under vacuum. Without purification, to the isolated imine in 10 mL of THF solvent was added butylvinyl ether and 10 mol% of $I_2$. After completion of the reaction, as indicated by the TLC, the reaction mixture was quenched by saturated solution of $Na_2S_2O_3.5H_2O$, extracted with ethyl acetate and dried over anhydrous $Na_2SO_4$. The solvent was concentrated under the reduced pressure.

**Methyl 1-(quinolin-2-yl)-9*H*-β-carboline-3-carboxylate (208):** Compound **208** was synthesized from α-formyl-β-carboline (**207**) and aniline **143a** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 89%

Mp: 202-204 °C



**208**

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3364, 3061, 2854, 1712, 1564, 1259, 750

$^1H$ NMR (400 MHz) δ: 11.96 (1H, s), 9.04 (1H, d, *J* = 8.8 Hz), 8.98 (1H, s), 8.38 (1H, d, *J* = 8.8 Hz), 8.31 (1H, d, *J* = 8.4 Hz), 8.26 (1H, d, *J* = 8.0 Hz), 7.92 (1H, d, *J* = 8.0 Hz), 7.83 (1H, t, *J* = 8.0 Hz), 7.75 (1H, d, *J* = 8.4 Hz), 7.63-7.69 (2H, m), 7.40 (1H, t, *J* = 7.6 Hz), 4.13 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 166.8, 157.5, 147.2, 141.0, 137.5, 136.9, 136.7, 130.7, 129.8, 129.2, 129.1, 128.1, 128.0, 127.1, 122.0, 121.6, 121.0, 119.7, 118.7, 112.4 (aromatic C), 52.7 (aliphatic C)

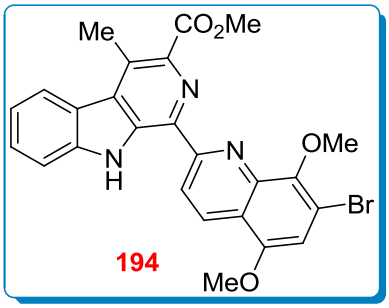
HRMS (ESI-MS). Calcd: 354.1242 (M+H)

Found: 354.1242

Anal. calcd. for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89%

Found: C, 74.65; H, 4.21; N, 12.07%

**Methyl-1-(7-bromo-5,8-dimethoxy-2-quinolyl)-4-methyl-9*H*-β-carboline-3-carboxylate (194):** Compound **194** was synthesized from α-formyl-β-carboline **195** and aniline **197** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.



**194**

Yield: 92%

Mp: 284-286 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3346, 1714, 1456, 1082, 1016

$^1H$ NMR (500 MHz) δ: 12.42 (1H, s), 8.90 (1H, d, *J* = 9.0 Hz), 8.67 (1H, d, *J* = 9.0 Hz), 8.40 (1H, d, *J* = 8.0 Hz), 7.74 (1H, d, *J* = 8.5 Hz), 7.66 (1H, dt, $J_1$ = 0.5 Hz, $J_2$ = 7.5 Hz), 7.41 (1H, dt, $J_1$ = 0.5 Hz, $J_2$ = 8.0 Hz), 7.01 (1H, s), 4.27 (3H, s), 4.11 (3H, s), 4.05 (3H, s), 3.24 (3H, s)

$^{13}C$ NMR (125 MHz) δ: 167.9, 157.8, 151.8, 146.7, 142.0, 141.0, 137.0, 135.9, 134.8, 132.6, 132.1, 130.1, 128.2, 124.1, 122.3, 120.7, 120.5, 118.7, 116.6, 112.2, 108.7 (aromatic C), 61.5, 56.1, 52.5, 16.9 (aliphatic C)

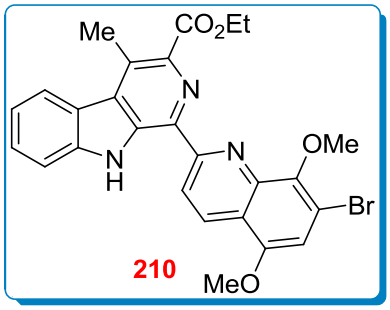
HRMS (ESI-MS). Calcd: 506.0715 (M+H)

Found: 506.0716

Anal. calcd. for $C_{25}H_{20}BrN_3O_4$: C, 59.30; H, 3.98; N, 8.30%

Found: C, 59.42; H, 3.93; N, 8.45%

**Ethyl-1-(7-bromo-5,8-dimethoxy-2-quinolyl)-4-methyl-9*H*-$\beta$-carboline-3-carboxylate (210):** Compound **210** by the reaction of $\alpha$-formyl-$\beta$-carboline **202** and aniline **197** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.



**210**

Yield: 78%

Mp: 276-278 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3342, 2843, 1764, 1034, 754

$^1$H NMR (400 MHz) δ: 12.34 (1H, s), 8.86 (1H, d, *J* = 8.8 Hz), 8.63 (1H, d, *J* = 8.8 Hz), 8.36 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.63 (1H, t, *J* = 7.2 Hz), 7.38 (1H, t, *J* = 7.2 Hz), 6.97 (1H, s), 4.57 (2H, q, *J* = 7.2 Hz), 4.25 (3H, s), 4.02 (3H, s), 3.20 (3H, s), 1.56 (3H, t, *J* = 7.2 Hz)

$^{13}$C NMR (100 MHz) δ: 167.6, 157.8, 151.8, 146.6, 141.9, 141.0, 137.6, 135.8, 134.7, 132.0, 130.0, 128.2, 124.0, 122.3, 120.6, 120.5, 118.6, 116.6, 112.2, 108.6 (aromatic C), 61.5, 61.4, 56.1, 16.9, 14.5 (aliphatic C)

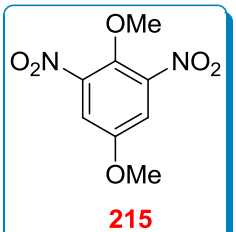
HRMS (ESI-MS). Calcd: 520.0872 (M+H)

Found: 520.0870

Anal. calcd. for $C_{26}H_{22}BrN_3O_4$: C, 60.01; H, 4.26; N, 8.07%

Found: C, 60.15; H, 4.21; N, 7.96%

**Procedure for the synthesis of 1,4-dimethoxy-3,5-dinitrobenzene (215):** To a solution of 4-methoxy-2,6-dinitrophenol[125] (1.00 g, 4.6 mmol) in DMF (20 mL) were added methyliodide (0.99 g, 6.99 mmol), and $K_2CO_3$ (1.49 g, 14.03 mmol). The resultant mixture was stirred at room temperature for 12 h. The reaction mixture was poured into ice-cooled water. The solid precipitate was filtered off and dissolved in EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$ and

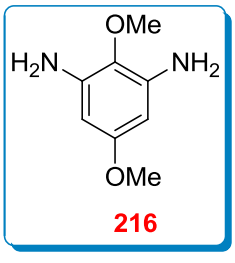


**215**

concentrated under reduced pressure. The compound **215** was obtained as a colorless solid in 92% yield (0.965 g) and used for further reactions without any purification. The spectroscopic data of the compound **215** were in full accordance with those reported.[125,113]

| | |
|---|---|
| Mp: | 111-113 °C |
| IR (KBr) $\nu_{max}$ $cm^{-1}$: | 3094, 1416, 1037, 787 |
| $^{1}H$ NMR (400 MHz) δ: | 7.57 (2H, s), 4.02 (3H, s), 3.92 (3H, s) |
| $^{13}C$ NMR (100 MHz) δ: | 154.7, 145.7, 141.0, 114.7 (aromatic C), 65.0, 56.7 (aliphatic C) |
| HRMS (ESI-MS). Calcd: | 251.0280 (M+Na) |
| Found: | 251.0280 |
| Anal. calcd. for $C_8H_8N_2O_6$: | C, 42.11; H, 3.53; N, 12.28% |
| Found: | C, 41.25; H, 3.43; N, 12.15% |

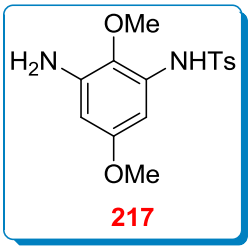
**Procedure for the synthesis of 2,5-dimethoxy-1,3-benzenediamine (216):** The dimethoxynitro compound **215** (0.5 g, 2.19 mmol) was dissolved in AcOH (15 mL) and heated to 80 °C. After 10 min stirring, Fe powder (0.611 g, 10.95 mmol) was added in the reaction mixture. The reaction mixture was then allowed to 80 °C over 1 h with stirring. After disappearance of starting material monitored by TLC, the residue was filtered off and extracted with EtOAc. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 10:3) to give the desired product **216** as a viscous liquid in 86% yield (0.965 g). The spectroscopic data of the compound **216** were in full accordance with those reported.[126]



**216**

| | |
|---|---|
| IR (KBr) $\nu_{max}$ $cm^{-1}$: | 3345, 2876, 1675, 1544, 776 |
| $^{1}H$ NMR (400 MHz) δ: | 5.77 (2H, s), 3.73 (3H, s), 3.69 (3H, s) |
| $^{13}C$ NMR (100 MHz) δ: | 157.0, 140.4, 129.1, 92.1 (aromatic C), 58.8, 55.2 (aliphatic C) |
| LCMS (m/z): | 169.10 (M+H) |
| Anal. calcd.for $C_8H_{12}N_2O_2$: | C, 57.13; H, 7.19; N, 16.66% |
| Found: | C, 57.26; H, 7.23; N, 16.43% |

**Procedure for the synthesis of 3-amino-2,5-dimethoxy-1-(4-methylphenylsulfonamido)benzene (217):** To a solution of compound **216** (0.2 g, 1.19 mmol) in MeCN was added tosyl chloride (0.181 g, 0.951 mmol). The reaction mixture was stirred at room temperature for 30 min and then quenched with water. The aqueous layer was extracted with EtOAc and dried over anhydrous $Na_2SO_4$. The organic layer was concentrated *in vacuo* and was purified by column chromatography (silica gel, hexanes/EtOAc = 10:3) to give the desired compound **217** (0.203 g, 53%) as a viscous liquid.



**217**

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3211, 2425, 1433, 1221, 1024, 744

$^1$H NMR (400 MHz) δ: 7.74 (2H, d, *J* = 7.5 Hz), 7.21 (2H, d, *J* = 7.3 Hz), 6.56 (1H, s), 5.98 (1H, s), 3.76 (2H, s), 3.69 (3H, s), 3.42 (3H, s), 2.35 (3H, s)

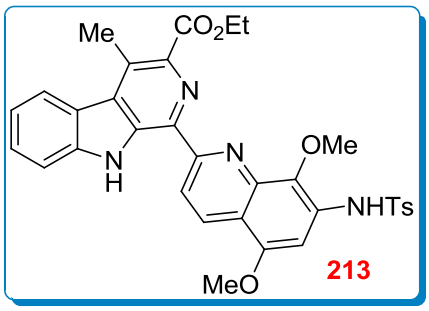
$^{13}$C NMR (100 MHz) δ: 156.8, 143.9, 140.3, 136.4, 130.9, 130.8, 129.6, 127.2, 97.6, 94.7 (aromatic C), 59.7, 55.4, 21.5 (aliphatic C)

LCMS (m/z): 323.20 $(M+H)^+$

Anal. calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69%

Found: C, 55.68; H, 5.59; N, 8.81%

**Ethyl 1-[5,8-dimethoxy-7-(4-methylphenylsulfonamido)-2-quinolyl]-4-methyl-9*H*-β-carboline-3-carboxylate (213):** Compound **213** was synthesized from α-formyl-β-carboline **202** and aniline **217** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**213**

Yield: 72%

Mp: 267-269 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3423, 3034, 2834, 2234, 1897, 1327, 867

$^1$H NMR (400 MHz) δ: 12.08 (1H, s), 8.76 (1H, d, *J* = 8.8 Hz), 8.59 (1H, d, *J* = 8.8 Hz), 8.34 (1H, d, *J* = 7.9 Hz), 7.80 (2H, d, *J* = 8.1 Hz), 7.62-7.64 (2H, m), 7.52 (1H, s), 7.34-7.39 (2H, m), 7.24-7.27 (1H, m), 4.56 (2H, q, *J* = 7.0 Hz), 4.05 (3H, s), 3.86 (3H, s), 3.17 (3H, s), 2.30 (3H, s), 1.55 (3H, t, *J* = 7.1 Hz)

$^{13}$C NMR (100 MHz) δ: 167.6, 157.7, 152.1, 144.4, 141.1, 140.8, 137.7, 136.9, 136.2, 135.6, 134.7, 131.9, 131.8, 130.3, 129.97, 129.9, 128.1, 127.2, 124.0, 122.3, 120.7, 118.1, 117.6, 111.9, 98.1 (aromatic C), 61.9, 61.4, 56.1, 21.5, 16.8, 14.5 (aliphatic C)

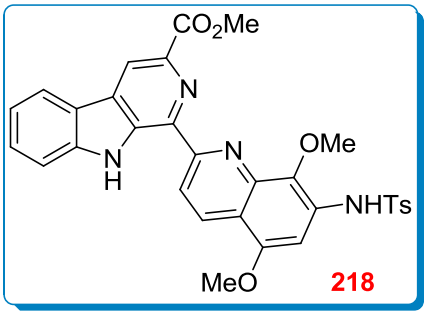
HRMS (ESI-MS). Calcd: 633.1784 (M+Na)

Found: 633.1786

Anal. calcd. for $C_{33}H_{30}N_4O_6S$: C, 64.90; H, 4.95; N, 9.17%

Found: C, 64.71; H, 4.86; N, 9.25%

**Ethyl 1-[5,8-dimethoxy-7-(4-methylphenylsulfonamido)-2-quinolyl]-9*H*-*β*-carboline-3-carboxylate (218):** Compound **218** was synthesized from *α*-formyl-*β*-carboline **207** and aniline **217** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 78%

Mp: 284-286 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3423, 2639, 1123, 1102, 732

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 12.11 (1H, s), 10.29 (1H, s), 9.06 (1H, s), 8.65 (2H, s), 8.50 (1H, d, *J* = 7.7 Hz), 7.80-7.82 (3H, m), 7.69 (1H, t, *J* = 7.5 Hz), 7.36-7.42 (3H, m), 7.21 (1H, s), 3.97 (3H, s), 3.94 (3H, s), 3.86 (3H, s), 2.29 (3H, s)

$^{13}$C NMR (100 MHz) δ: Due to limited solubitity of the compound **218** both in $CDCl_3$ as well as in DMSO-$d_6$, we were unable to record $^{13}$C NMR spectrum.

HRMS (ESI-MS). Calcd: 583.1651 (M+H)

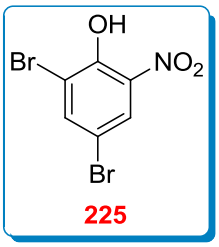
Found: 583.1656

Anal. calcd. for $C_{31}H_{26}N_4O_6S$: C, 63.91; H, 4.50; N, 9.62%

Found: C, 63.85; H, 4.45; N, 9.56%

**Procedure for the synthesis of 2,4-dibromo-6-nitrophenol (225):** A mixture of *o*-nitrophenol (**224**) (1.0 g, 7.18 mmol), KBr (0.846 g, 7.18 mmol) in acetic acid/water

(10 mL/ 5 mL) was stirred for 10 min and cooled on ice. Then, 1 mL of con. $H_2SO_4$ was added dropwise over a period of 10 min. Into the ice cooled solution, was added bromine (1.133 g, 7.18 mmol) dropwise. After the addition, the reaction was left stirring at room temperature for a further 1 h. After completion of the reaction as indicated by TLC, the reaction was then quenched with saturated solution of $Na_2S_2O_3.5H_2O$ and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* to yield the desired compound **225** (1.97 g, 93%) as a bright yellow solid. The spectroscopic data of the compound **225** were in full accordance with those reported.[127a,127b]



**225**

Mp: 108-110 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3387, 3088, 1704, 1453, 1022, 675

$^1H$ NMR (400 MHz) δ: 11.05 (1H, s), 8.25 (1H, d, *J* = 2.2 Hz), 7.99 (1H, d, *J* = 2.1 Hz)

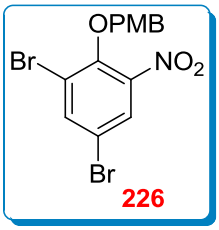
$^{13}C$ NMR (100 MHz) δ: 151.4, 142.9, 134.4, 126.8, 114.5, 111.5 (aromatic C)

LCMS (m/z): $296.05\ (M+2)^+$

Anal. calcd. for $C_6H_3Br_2NO_3$: C, 24.27; H, 1.02; N, 4.72%

Found: C, 24.36; H, 1.12; N, 4.85%

**Procedure for the synthesis of 1,5-dibromo-2-(4-methoxybenzyloxy)-3-nitrobenzene (226):** A solution of compound **225** (1.0 g, 3.39 mmol) and $K_2CO_3$ (1.41 g, 10.17 mmol) in 20 mL of acetone was vigorously stirred whilst adding *p*-methoxybenzyl bromide (0.812 g, 4.06 mmol). The reaction mixture was heated at reflux temperature of acetone. Upon completion (disappearance of starting materials as indicated by TLC), the mixture was quenched with water and extracted with EtOAc. The combined organic layers were concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/ethyl acetate = 10:1) to give the desired product **226** as a colorless solid (1.48 g, 92%).



**226**

Mp: 105-107 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3299, 3 099, 1654, 1455, 1287, 876, 653

$^1H$ NMR (400 MHz) δ: 7.90-7.96 (2H, m), 7.45 (2H, d, *J* = 7.9 Hz), 6.93 (2H, d, *J* = 7.9 Hz), 5.11 (2H, s), 3.83 (3H, s)

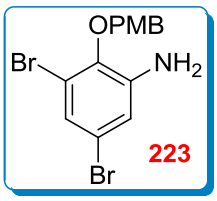
$^{13}$C NMR (100 MHz) δ: 160.2, 148.5, 145.9, 140.1, 130.8, 127.4, 127.1, 121.3, 116.9, 114.0 (aromatic C), 76.7, 55.3 (aliphatic C)

LCMS (m/z): 415.25 $(M+H)^+$

Anal. calcd. for $C_{14}H_{11}Br_2NO_4$: C, 40.32; H, 2.66; N, 3.36%

Found: C, 40.38; H, 2.62; N, 3.31%

**Procedure for the synthesis of 3,5-dibromo-2-(4-methoxybenzyloxy)aniline (223):** Into a solution of compound **226** (1.0 g, 2.41 mmol) in 20 mL of acetic acid was added Fe powder (0.672 g, 12.05 mmol) and heated around 65-70 °C. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered off. The filtrate was quenched with water and extracted with EtOAc. The combined organic layer was concentrated under reduced pressure and purified using column chromatography (silica gel: hexanes/EtOAc = 10:3) as a colourless solid **223** (0.798 g, 86%).




Mp: 88-90 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3455, 2976, 1527, 1235, 987

$^1$H NMR (400 MHz) δ: 7.42 (2H, d, 8.6 Hz), 7.06 (1H, d, *J* = 2.2 Hz), 6.93 (2H, d, *J* = 8.6 Hz), 6.79 (1H, d, *J* = 2.2 Hz), 4.89 (2H, s), 3.83-3.85 (5H, m)

$^{13}$C NMR (100 MHz) δ: 159.9, 142.8, 142.3, 130.2, 128.8, 124.3, 118.0, 117.6, 114.1 (aromatic C), 74.1, 55.3 (aliphatic C)

LCMS (m/z): 385.35 $(M^+)$

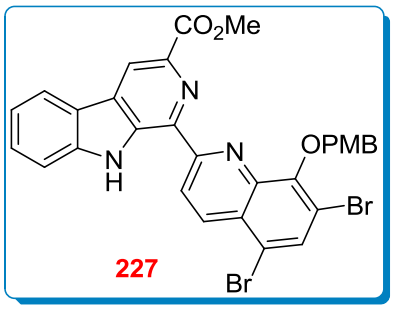
Anal. calcd. for $C_{14}H_{13}Br_2NO_2$: C, 43.44; H, 3.39; N, 3.62%

Found: C, 43.52; H, 3.32; N, 3.51%

**Methyl 1-[5,7-dibromo-8(4-methoxybenzyloxy)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (227):** Compound **227** was synthesized from α-formyl-β-carboline **207** and aniline **223** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 60%

Mp: 320-322 °C



227

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3432, 3133, 2298, 1723, 1673, 739

$^1$H NMR (400 MHz) δ: 11.64 (1H, s), 8.96 (1H, d, *J* = 8.5 Hz), 8.89 (1H, s), 8.54 (1H, d, *J* = 8.5 Hz), 8.14 (1H, d, *J* = 7.3 Hz), 8.00 (1H, s), 7.49 (2H, d, *J* = 7.6 Hz), 7.40 (1H, t, *J* = 6.96 Hz), 7.29-7.31 (1H, m), 6.86 (2H, d, *J* = 7.8 Hz), 6.55 (1H, d, *J* = 7.8 Hz), 5.20 (2H, s), 4.11 (3H, s), 3.81 (3H, s)

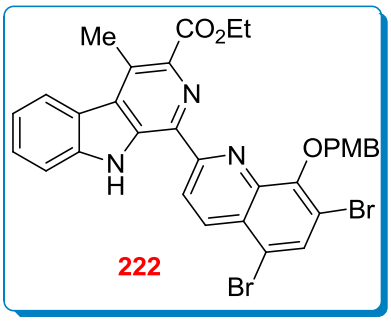
$^{13}$C NMR (100 MHz) δ: 166.5, 159.9, 157.9, 151.8, 142.8, 140.9, 136.8, 136.5, 136.4, 133.7, 130.9, 129.8, 128.7, 128.6, 127.5, 121.5, 121.2, 120.9, 119.0, 117.3, 114.2, 113.1 (aromatic C), 75.9, 55.4, 52.7 (aliphatic C)

LCMS (m/z): 647.30 $(M+2)^+$

Anal. calcd. for $C_{30}H_{21}Br_2N_3O_4$: C, 55.66; H, 3.27; N, 6.49%

Found: C, 55.76; H, 3.21; N, 6.43%

**Ethyl 1-[5,7-dibromo-8(4-methoxybenzyloxy)-2-quinolyl]-4-methyl-9*H*-β-carboline-3-carboxylate (222):** Compound **222** was synthesized from α-formyl-β-carboline **202** and aniline **223** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 8% ethyl cetate in hexanes.



222

Yield: 55%

Mp: 298-300 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3011, 2109, 1543, 1109, 621

$^1$H NMR (500 MHz) δ: 11.75 (1H, s), 8.97 (1H, d, *J* = 8.9 Hz), 8.59 (1H, d, *J* = 8.9 Hz), 8.30 (1H, d, *J* = 7.9 Hz), 8.03 (1H, s), 7.52 (2H, d, *J* = 8.7 Hz), 7.40 (1H, dt, $J_1$ = 1.0 Hz, $J_2$ = 7.2 Hz), 7.32 (1H, dt, $J_1$ = 1.0 Hz, $J_2$ = 7.2 Hz), 6.86-6.89 (2H, m), 6.62 (1H, d, *J* = 8.2 Hz), 5.24 (2H, s), 4.59 (2H, q, *J* = 7.1 Hz), 3.83 (3H, s), 3.20 (3H, s), 1.58 (3H, t, *J* = 7.1 Hz)

$^{13}$C NMR (125 MHz) δ: 167.5, 159.9, 158.2, 151.8, 142.9, 140.7, 137.7, 136.4, 135.6, 133.9, 133.5, 132.3, 130.2, 129.9, 128.7, 127.7, 127.5, 123.6, 122.0, 120.9, 120.6, 117.3, 117.2, 114.2, 112.9 (aromatic C), 75.9, 61.4, 55.4, 16.9, 14.5 (aliphatic C)

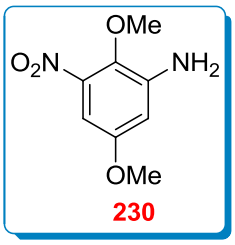
HRMS (ESI-MS). Calcd: 674.0290 (M+H)

Found: 674.0290

Anal. calcd. for $C_{32}H_{25}Br_2N_3O_4$: C,56.91; H, 3.73; N, 6.22%

Found: C, 56.85; H, 3.68; N, 6.15%

**Procedure for the synthesis of 2,5-dimethoxy-3-nitroaniline (230):** To a solution of dinitro compound **215** (0.5 g, 2.19 mmol) in AcOH (20 mL) was added Fe powder (0.367 g, 6.58 mmol). After stirring for 2 h at 60 °C, water was added and the reaction mixture was filtered off. The residue was extracted with EtOAc. The combined organic layer were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The crude was purified using column chromatography (silica gel: hexanes/EtOAc = 10:2) to give compound **230** as a red color solid (80%, 0.347 g). The spectroscopic data of the compound **230** were in full accordance with that reported.[113]




Mp: 85-87 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3456, 2876, 1498, 1231, 765

$^1$H NMR (400 MHz) δ: 6.71 (1H, d, *J* = 3.2 Hz), 6.49 (1H, d, *J* = 3.2 Hz), 4.13 (2H, s), 3.84 (3H, s), 3.76 (3H, s)

$^{13}$C NMR (100 MHz) δ: 155.7, 143.9, 142.9, 134.9, 106.1, 98.3 (aromatic C), 61.2, 55.7 (aliphatic C)

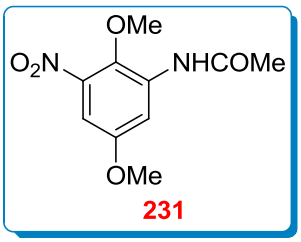
LCMS (m/z): 199.10 $(M+H)^+$

Anal. calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14%

Found: C, 48.37; H, 5.15; N, 14.06%

**Procedure for the synthesis of *N*1-(2,5-dimethoxy-3-nitrophenyl)acetamide (231):** The mixture of mononitro compound **230** (0.3 g, 1.51 mmol), acetylchloride (0.177 g, 2.27 mmol) and $K_2CO_3$ (0.631 g, 4.54 mmol) was stirred in $CH_2Cl_2$ at room temperature for 2 h. The mixture was directly concentrated under reduced pressure and

the residue was purified by column chromatography (silica gel: hexanes/EtOAc = 10:2) to afford the compound **231** as a light brownish color solid (0.304 g, 84%). The spectroscopic data of the compound **231** were in full accordance with that reported.[126]




Mp: 140-142 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 332 1, 2987, 1548, 1290, 1092, 947

$^1$H NMR (500 MHz) δ: 8.29 (1H, d, *J* = 2.8 Hz), 7.85 (1H, s), 7.09 (1H, d, *J* = 3.2 Hz), 3.87 (3H, s), 2.99 (3H, s), 2.25 (3H, s)

$^{13}$C NMR (125 MHz) δ: 168.7, 155.6, 134.2, 111.3, 104.3 (aromatic C), 62.6, 56.0, 25.0 (aliphatic C)

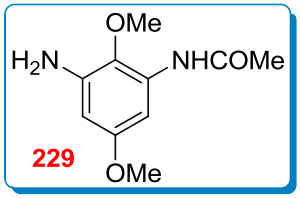
HRMS (ESI-MS). Calcd: 241.0824 (M+H)

Found: 241.0825

Anal. calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66%

Found: C, 50.12; H, 5.12; N, 11.43%

**Procedure for the synthesis of *N*1-(3-amino-2,5-dimethoxyphenyl)acetamide (229):** To a solution of **231** (0.250 g, 1.04 mmol) in AcOH (5 mL)/ ethanol (10 mL) mixture was added Fe powder (0.174 g, 3.12 mmol). The reaction mixture was heated to 85 °C. After completion of the reaction as indicated by TLC (disappearance of starting material), water was added and extracted with EtOAc. The combined organic layer were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: hexanes/EtOAc = 10:3) to afford the compound **229** as a viscous liquid (92%, 0.201 g). The spectroscopic data of the compound **229** were in full accordance with those reported.[125,126]




IR (KBr) $\nu_{max}$ $cm^{-1}$: 3321, 2987, 1548, 1290, 1092, 947

$^1$H NMR (400 MHz) δ: 7.75 (1H, s), 7.34 (1H, d, *J* = 2.6 Hz), 6.02 (1H, d, *J* = 2.8 Hz), 3.88 (2H, s), 3.67 (3H, s), 3.66 (3H, s), 2.16 (3H, s)

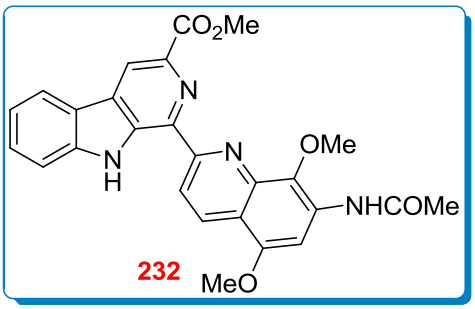
$^{13}$C NMR (100 MHz) δ: 168.5, 156.6, 139.8, 131.9, 130.3, 97.5, 95.8 (aromatic C), 59.7, 55.4, 24.9 (aliphatic C)

LCMS (m/z): 211.15 $(M+H)^+$

Anal. calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33%

Found: C, 57.23; H, 6.75; N, 13.43%

**Methyl 1-(5,8-dimethoxy-7-methylcarboxamido-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (232):** Compound **232** was synthesized from $\alpha$-formyl-$\beta$-carboline **207** and aniline **229** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



232

Yield: 81%

Mp: 323-325 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3438, 3056, 2987, 1223, 1098, 864

$^1$H NMR (400 MHz) δ: 12.25 (1H, s), 8.95 (1H, s), 8.83 (1H, d, *J* = 8.8 Hz), 8.64 (1H, d, *J* = 8.8 Hz), 8.24 (1H, d, *J* = 8.0 Hz), 8.16 (1H, s), 8.13 (1H, s), 7.63-7.68 (2H, m), 7.37-7.41 (1H, m), 4.22 (3H, s), 4.12 (3H, s), 4.04 (3H, s), 2.36 (3H, s)

$^{13}$C NMR (100 MHz) δ: 168.8, 166.8, 157.2, 151.9, 141.1, 140.8, 137.6, 136.8, 135.4, 132.1, 132.0, 130.6, 129.0, 122.1, 121.6, 120.9, 118.7, 117.7, 117.3, 112.0, 99.0 (aromatic C), 61.7, 56.0, 52.7, 25.3 (aliphatic C)

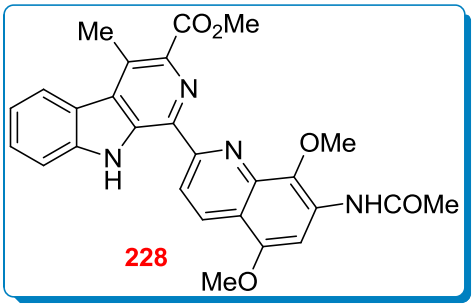
HRMS (ESI-MS). Calcd: 471.1668 (M+H)

Found: 471.1668

Anal. calcd. for $C_{26}H_{22}N_4O_5$: C, 66.37; H, 4.71; N, 11.91%

Found: C, 66.25; H, 4.65; N, 11.85%

**Methyl 1-(5,8-dimethoxy-7-methylcarboxamido-2-quinolyl)-4-methyl-9*H*-$\beta$-carboline-3-carboxylate (228):** Compound **228** was synthesized from $\alpha$-formyl-$\beta$-carboline **195** and aniline **229** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



228

Yield: 78%

Mp: 336-338 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3432, 3083, 2234, 1876, 1276, 865

$^1$H NMR (500 MHz) δ: 12.24 (1H, s), 8.72 (1H, d, *J* = 8.5 Hz), 8.57 (1H, d, *J* = 8.5 Hz), 8.35 (1H, d, *J* = 8.0 Hz), 8.15 (1H, s), 8.11 (1H, s), 7.63-7.65 (2H, m), 7.39 (1H, t, *J* = 7.0 Hz), 4.20 (3H, s), 4.11 (3H, s), 4.03 (3H, s), 3.19 (3H, s), 2.37 (3H, s)

$^{13}$C NMR (125 MHz) δ: 168.8, 168.0, 157.3, 151.8, 140.8, 140.7, 137.0, 135.7, 135.5, 135.0, 132.2, 131.8, 130.0, 128.0, 124.0, 122.3, 120.6, 117.4, 117.0, 112.0, 99.0 (aromatic C), 61.6, 56.0, 52.4, 25.2, 16.8 (aliphatic C)

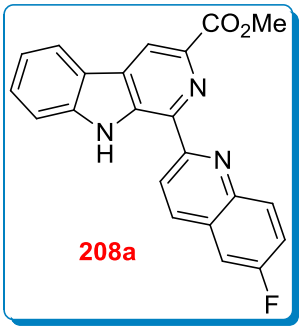
HRMS (ESI-MS). Calcd: 485.1825 (M+H)

Found: 485.1825

Anal. calcd. for $C_{27}H_{24}N_4O_5$: C, 66.93; H, 4.99; N, 11.56%

Found: C, 67.06; H, 4.89; N, 11.43%

**Methyl-1-(6-fluoro-2-quinolyl)-9*H*-β-carboline-3-carboxylate (208a):** Compound **208a** was synthesized from α-formyl-β-carboline (**207**) and aniline (**143e**) following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



**208a**

Yield: 87%

Mp: 204-206 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3386, 3046, 1742, 1254, 1227, 734

$^1$H NMR (400 MHz) δ: 11.59 (1H, s), 8.93 (1H, d, *J* = 8.4 Hz), 8.84 (1H, s), 8.16-8.20 (3H, m), 7.60-7.63 (2H, m), 7.52 (1H, t, *J* = 6.0 Hz), 7.44 (1H, d, *J* = 8.4 Hz), 7.36 (1H, t, *J* = 6.0 Hz), 4.09 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.6, 161.9, 159.5, 156.9, 144.1, 140.8, 137.0, 136.8, 136.3, 136.0, 131.5, 131.4, 130.6, 128.9, 128.7, 128.6, 121.9, 121.5, 120.9, 120.3, 119.9, 119.7, 118.5, 112.3, 111.2, 110.9 (aromatic C), 52.6 (aliphatic C)

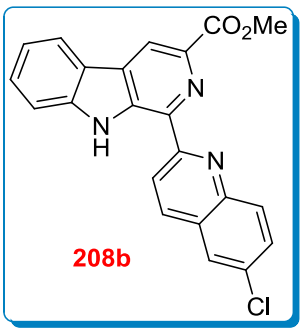
HRMS (ESI-MS). Calcd: 372.1147 (M+H)

Found: 372.1148

Anal. calcd. for $C_{22}H_{14}FN_3O_2$: C, 71.15; H, 3.80; N, 11.32%

Found: C, 71.28; H, 3.73; N, 11.22%

**Methyl-1-(6-chloro-2-quinolyl)-9*H*-β-carboline-3-carboxylate (208b):** Compound **208b** was synthesized from α-formyl-β-carboline **207** and aniline **143f** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



208b

Yield: 85%

Mp: 230-232 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3348, 2922, 1749, 1431, 889, 625

$^1$H NMR (500 MHz) δ: 11.70 (1H, s), 9.02 (1H, d, *J* = 8.5 Hz), 8.94 (1H, s), 8.24 (2H, d, *J* = 8.0 Hz), 8.19 (1H, d, *J* = 9.0 Hz), 7.86 (1H, d, *J* = 2.0 Hz), 7.71-7.74 (2H, m), 7.67 (1H, t, *J* = 7.5 Hz), 7.41 (1H, t, *J* = 7.0 Hz), 4.13 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.6, 157.7, 145.5, 140.9, 136.9, 136.8, 136.5, 135.8, 132.7, 130.8, 130.7, 130.6, 129.1, 128.6, 126.7, 121.9, 121.5, 121.1, 120.5, 118.7, 112.3 (aromatic C), 52.7 (aliphatic C)

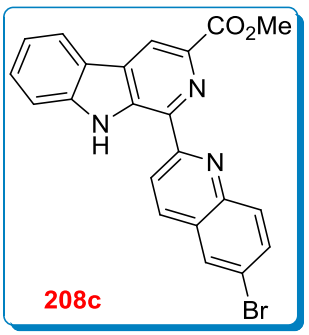
HRMS (ESI-MS). Calcd: 388.0853 (M+H)

Found: 388.0853

Anal. calcd. for $C_{22}H_{14}ClN_3O_2$: C, 68.13; H, 3.64; N, 10.83%

Found: C, 68.06; H, 3.75; N, 10.75%

**Methyl-1-(6-bromo-2-quinolyl)-9*H*-β-carboline-3-carboxylate (208c):** Compound **208c** was synthesized from α-formyl-β-carboline **207** and aniline **143g** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



208c

Yield: 85%

Mp: 270-271 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3465, 2976, 1765, 1288, 1043, 654

$^1H$ NMR (400 MHz) δ: 11.72 (1H, s), 9.01 (1H, d, *J* = 8.8 Hz), 8.96 (1H, s), 8.24 (2H, d, *J* = 8.4 Hz), 8.14 (1H, d, *J* = 8.8 Hz), 8.05 (1H, s), 7.85-7.88 (1H, m), 7.71-7,73 (1H, m), 7.67 (1H, t, *J* = 7.2 Hz), 7.41 (1H, t, *J* = 7.2 Hz), 4.12 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 166.6, 157.9, 145.8, 140.9, 136.9, 136.6, 135.8, 133.2, 130.8, 130.7, 130.1, 129.2, 129.1, 122.0, 121.5, 121.1, 120.9, 120.6, 118.8, 112.3 (aromatic C), 52.7 (aliphatic C)

HRMS (ESI-MS). Calcd: 432.0347 (M+H)

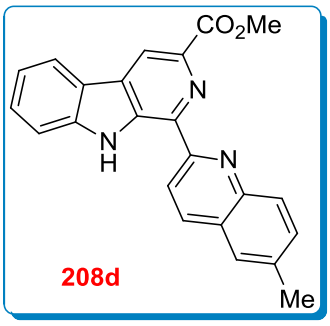
Found: 432.0349

Anal. calcd. for $C_{22}H_{14}BrN_3O_2$:C, 61.13; H, 3.26; N, 9.72%

Found: C, 61.05; H, 3.21; N, 9.85%

**Methyl-1-(6-methyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (208d):**

Compound **208d** was synthesized from α-formyl-β-carboline **207** and aniline **143b** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



**208d**

Yield: 92%

Mp: 218-220 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3358, 2854, 1709, 1103, 601

$^1H$ NMR (400 MHz) δ: 11.89 (1H, s), 8.96 (1H, d, *J* = 8.8 Hz), 8.93 (1H, s), 8.22-8.25 (2H, m), 8.14 (1H, d, *J* = 8.4 Hz), 7.69-7.71 (1H, m), 7.60-7.66 (3H, m), 7.38 (1H, t, *J* = 7.6 Hz), 4.11 (3H, s), 2.58 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 166.8, 156.6, 145.7, 140.9, 137.7, 137.1, 136.8, 136.6, 136.1, 132.0, 130.5, 128.9, 128.8, 128.1, 126.9, 121.9, 121.6, 120.9, 119.6, 118.4, 112.3 (aromatic C), 52.6, 21.7 (aliphatic C)

HRMS (ESI-MS). Calcd: 368.1399 (M+H)

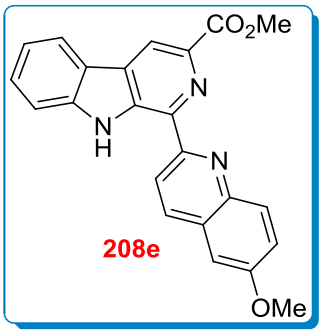
Found: 368.1399

Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44%

Found: C, 75.36; H, 4.61; N, 11.32%

**Methyl-1-(6-methoxy-2-quinolyl)-9*H*-β-carboline-3-carboxylate (208e):**

Compound **208e** was synthesized from α-formyl-β-carboline **207** and aniline **143c** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



208e

Yield: 94%

Mp: 195-197 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3366, 2854, 1707, 1500, 1261, 746

$^1$H NMR (500 MHz) δ: 11.79 (1H, s), 8.93 (1H, d, *J* = 9.0 Hz), 8.89 (1H, s), 8.19-8.22 (2H, m), 8.12 (1H, d, *J* = 9.0 Hz), 7.69 (1H, d, *J* = 8.0 Hz), 7.64 (1H, t, *J* = 7.5 Hz), 7.42 (1H, dd, $J_1$ = 2.0 Hz, $J_2$ = 9.0 Hz), 7.38 (1H, t, *J* = 7.5 Hz), 7.12 (1H, d, *J* = 2.5 Hz), 4.12 (3H, s), 3.98 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.8, 158.2, 155.1, 143.1, 140.9, 137.7, 136.7, 136.3, 135.5, 130.5, 130.4, 129.1, 128.9, 122.5, 121.9, 121.6, 120.8, 119.9, 118.2, 112.3, 105.4 (aromatic C), 55.6, 52.6 (aliphatic C)

HRMS (ESI-MS). Calcd: 384.1348 (M+H)

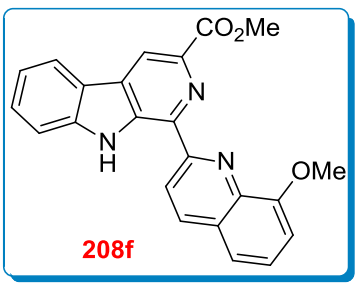
Found: 384.1348

Anal. calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96%

Found: C, 72.15; H, 4.41; N, 10.86%

**Methyl-1-(8-methoxy-2-quinolyl)-9*H*-β-carboline-3-carboxylate (208f):**

Compound **208f** was synthesized from α-formyl-β-carboline **207** and aniline **143d** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



208f

Yield: 90%

Mp: 206-208 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3456, 2962, 1711, 1504, 1018

$^1H$ NMR (500 MHz) δ: 12.49 (1H, s), 8.92-8.94 (2H, m), 8.30 (1H, d, *J* = 8.5 Hz), 8.23 (1H, d, *J* = 7.5 Hz), 7.64 (2H, d, *J* = 3.5 Hz), 7.51 (1H, t, *J* = 8.0 Hz), 7.45 (1H, d, *J* = 8.0 Hz), 7.35-7.40 (1H, m), 7.11 (1H, d, *J* = 7.0 Hz), 4.24 (3H, s), 4.14 (3H, s)

$^{13}C$ NMR (125 MHz) δ: 166.8, 155.5, 155.1, 141.3, 138.7, 137.8, 136.8, 136.5, 136.4, 130.4, 128.8, 128.7, 127.2, 121.9, 121.6, 120.7, 119.5, 119.4, 118.6, 112.4, 107.7 (aromatic C), 56.2, 52.6 (aliphatic C)

HRMS (ESI-MS). Calcd: 384.1348 (M+H)

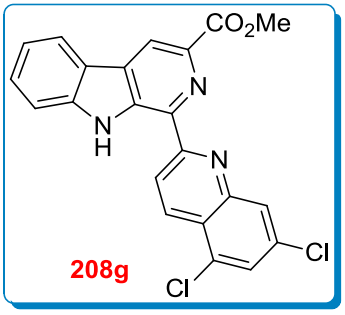
Found: 384.1356

Anal. calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96%

Found: C, 72.15; H, 4.41; N, 10.85%

**Methyl-1-(5,7-dichloro-2-quinolyl)-9*H*-β-carboline-3-carboxylate (208g):**

Compound **208g** was synthesized from α-formyl-β-carboline **207** and aniline **143j** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



208g

Yield: 86%

Mp: 254-256 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3365, 2928, 1593, 1259, 764

$^1H$ NMR (500 MHz) δ: 11.56 (1H, s), 9.09 (1H, d, *J* = 9.0 Hz), 8.96 (1H, s), 8.67 (1H, d, *J* = 9.0 Hz), 8.25 (1H, d, *J* = 8.0 Hz), 8.19 (1H, d, *J* = 1.0 Hz), 7.75-7.76 (1H, m), 7.69-7.71 (1H, m), 7.67 (1H, d, *J* = 1.0 Hz), 7.43 (1H, t, *J* = 7.5 Hz), 4.14 (3H, s)

$^{13}C$ NMR (125 MHz) δ: 166.5, 159.1, 147.9, 140.9, 137.1, 136.6, 136.3, 135.0, 133.5, 132.7, 131.1, 129.3, 127.6, 127.2, 124.6, 122.0, 121.4, 121.2, 120.7, 119.0, 112.4 (aromatic C), 52.7 (aliphatic C)

HRMS (ESI-MS). Calcd: 422.0463 (M+H)

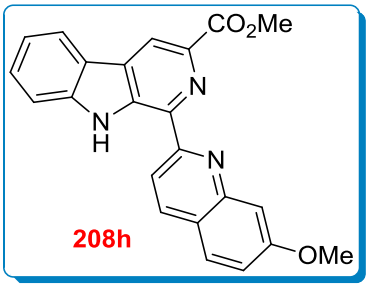
Found: 422.0463

Anal. calcd. for $C_{22}H_{13}Cl_2N_3O_2$: C, 62.58; H, 3.10; N, 9.95%

Found: C, 62.45; H, 3.17; N, 9.88%

**Methyl-1-(7-methoxy-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (208h):**

Compound **208h** was synthesized from $\alpha$-formyl-$\beta$-carboline **207** and aniline **143k** following the *general procedure D*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



208h

Yield: 85%

Mp: 178-180 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3433, 2920, 1726, 1585, 1022

$^1$H NMR (500 MHz) δ: 11.72 (1H, s), 8.86 (1H, s), 8.80 (1H, d, *J* = 8.5 Hz), 8.17-8.19 (2H, m), 7.68-7.70 (2H, m), 7.62 (1H, t, *J* = 7.5 Hz), 7.42 (1H, s), 7.37 (1H, t, *J* = 6.0 Hz), 7.21 (1H, dd, $J_1$ = 2.0 Hz, $J_2$ = 8.5 Hz), 4.11 (3H, s), 4.05 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.7, 160.9, 157.6, 148.8, 140.9, 137.5, 136.8, 136.5, 136.3, 130.5, 128.83, 128.82, 123.3, 121.9, 121.5, 120.8, 119.8, 118.3, 117.5, 112.3, 107.3 (aromatic C), 55.7, 52.6 (aliphatic C)

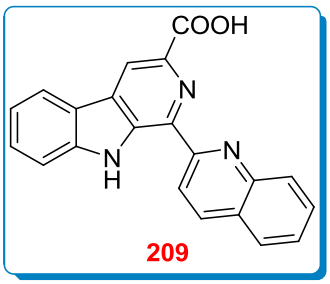
HRMS (ESI-MS). Calcd: 384.1348 (M+H)

Found: 384.1344

Anal. calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96%

Found: C, 71.89; H, 4.56; N, 10.86%

**1-(2-Quinolyl)-9*H*-$\beta$-carboline-3-carboxylic acid (209)**: In to the reaction mixture of 1 mmol of ester **208** in MeOH/$H_2O$ (3:1) was added 10 mmol of LiOH.$H_2O$. The reaction mixture was stirred at room temperature for 4h. Then, it was neutralized with diluted HCl. The compound was extracted with EtOAc, and dried over anhydrous $Na_2SO_4$. Without further purification, we proceed for further reactions.



209

Yield: 92%

Mp: 276-278 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3478, 3054, 2876, 1785, 1022, 739

$^{1}H$ NMR (400 MHz) δ: 12.89 (1H, br), 12.37 (1H, s), 9.08 (1H, s), 9.04 (1H, d, *J* = 8.8 Hz), 8.77 (1H, d, *J* = 8.4 Hz), 8.60 (1H, d, *J* = 8.8 Hz), 8.48 (1H, d, *J* = 7.6 Hz), 8.05-8.08 (2H, m), 7.91 (1H, t, *J* = 7.6 Hz), 7.67-7.71 (2H, m), 7.37 (1H, t, *J* = 7.2 Hz)

$^{13}C$ NMR (100 MHz) δ: 167.1, 157.0, 147.6, 142.0, 137.5, 137.1, 135.8, 131.1, 130.3, 130.2, 129.5, 128.3, 128.1, 127.8, 122.6, 121.3, 121.2, 119.8, 118.7, 114.0 (aromatic C)

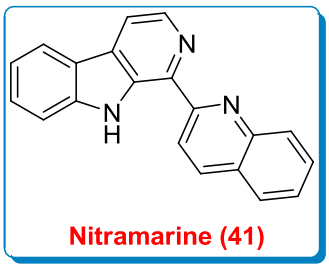
HRMS (ESI-MS). Calcd: 362.0906 (M+Na)

Found: 362.0906

Anal. calcd. for $C_{21}H_{13}N_3O_2$: C, 74.33; H, 3.86; N, 12.38%

Found: C, 74.26; H, 3.94; N, 12.25%

**1-(2-Quinolyl)-9*H*-β-carboline (41)**:



Nitramarine (41)

Yield: 60%

Mp: 176-178 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3360, 3049, 2851, 1626, 1502, 1284

$^{1}H$ NMR (500 MHz) δ: 11.72 (1H, s), 8.93 (1H, d, *J* = 8.5 Hz), 8.64 (1H, d, *J* = 5.0 Hz), 8.37 (1H, d, *J* = 8.5 Hz), 8.33 (1H, d, *J* = 8.5 Hz), 8.23 (1H, d, *J* = 8.0 Hz), 8.10 (1H, d, *J* = 5.0 Hz), 7.92 (1H, dd, *J* = 1.0 & 8.0 Hz), 7.82-7.85 (1H, m), 7.72-7.74 (1H, m), 7.61-7.66 (2H, m), 7.34-7.37 (1H, m)

$^{13}C$ NMR (125 MHz) δ: 158.3, 147.4, 140.7, 138.3, 138.0, 136.7, 135.3, 130.6, 129.7, 129.2, 128.6, 127.9, 127.8, 126.8, 121.8, 121.3, 120.0, 119.3, 115.9, 112.0 (aromatic C)

HRMS (ESI-MS). Calcd: 296.1187 (M+H)

Found: 296.1188

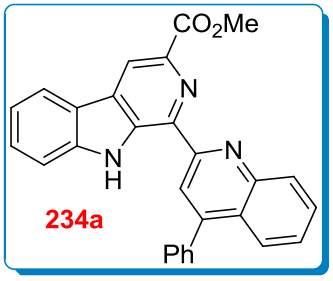
Anal. calcd. for $C_{20}H_{13}N_3$: C, 81.34; H, 4.44; N, 14.23%

Found: C, 81.25; H, 4.51; N, 14.12%

***General procedure E:***

In a round bottom flask equipped with a magnetic stirring bar, 0.3 mmol of $\alpha$-formyl-$\beta$-carboline and 0.3 mmol of aniline in 4 mL of [Bmim][$BF_4$] was stirred for 12 min. Into this reaction mixture were added 0.35 mmol of phenylacetylene and 10 mol% of La(OTf)$_3$ and then heated around 95-100 $^oC$. After completion of the reaction, as indicated by the TLC, water was added and extracted with ethyl acetate. The organic layer was dried over anhydrous $Na_2SO_4$. The solvent was concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate).

**Methyl 1-(4-phenyl-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (234a):** Compound **234a** was synthesized from $\alpha$-formyl-$\beta$-carboline **207**, aniline (**143a**) and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



234a

Yield: 78%

Mp: 298-300 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3383, 2924, 1732, 1032, 700

$^1$H NMR (400 MHz) δ: 12.01 (1H, s), 8.98 (1H, s), 8.95 (1H, s), 8.36 (1H, d, *J* = 8.4 Hz), 8.26 (1H, d, *J* = 8.0 Hz), 7.99 (1H, d, *J* = 8.4 Hz). 7.83 (1H, t, *J* = 7.2 Hz), 7.76 (1H, d, *J* = 8.4 Hz), 7.65-7.69 (3H, m), 7.56-7.62 (4H, m), 7.41 (1H, t, *J* = 7.4 Hz), 4.09 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.7, 156.9, 149.5, 147.7, 140.9, 138.2, 137.6, 136.9, 136.8, 130.7, 129.7, 129.68, 129.5, 129.1, 128.5, 128.4, 127.1, 126.8, 126.2, 121.9, 121.6, 120.9, 119.6, 118.7, 112.4 (aromatic C), 52.6 (aliphatic C)

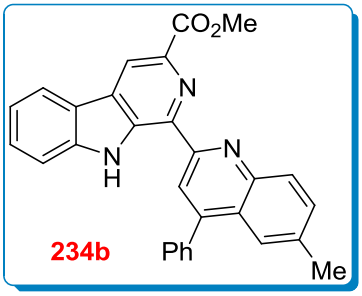
HRMS (ESI-MS). Calcd: 452.1375 (M+Na)

Found: 452.1375

Anal. calcd. for $C_{28}H_{19}N_3O_2$: C, 78.31; H, 4.46; N, 9.78%

Found: C, 78.45; H, 4.41; N, 9.68%

**Methyl 1-(6-methyl-4-phenyl-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (234b):** Compound **234b** was synthesized from $\alpha$-formyl-$\beta$-carboline **207**, aniline **143b** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 85%

Mp: 277-279 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3348, 2965, 1458, 1039, 758, 700

$^1$H NMR (400 MHz) δ: 11.98 (1H, s), 8.95 (1H, s), 8.88 (1H, s), 8.23 (2H, t, *J* = 8.0 Hz), 7.71-7.75 (2H, m), 7.55-7.68 (7H, m), 7.39 (1H, t, *J* = 7.2 Hz), 4.08 (3H, s), 2.53 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.8, 156.0, 148.7, 146.2, 140.9, 138.4, 137.7, 137.2, 136.8, 136.7, 131.8, 130.6, 129.7, 129.2, 128.9, 128.5, 128.3, 126.7, 124.9, 121.9, 121.6, 120.9, 119.7, 118.5, 112.4 (aromatic C), 52.6, 21.9 (aliphatic C)

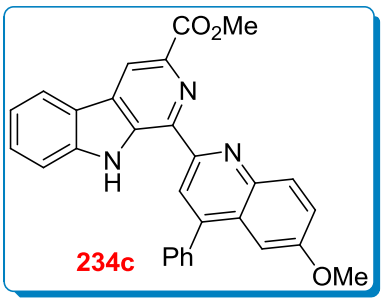
HRMS (ESI-MS). Calcd: 466.1532 (M+Na)

Found: 466.1532

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

Found: C, 78.47; H, 4.71; N, 9.36%

**Methyl 1-(6-methoxy-4-phenyl-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (234c):** Compound **234c** was synthesized from $\alpha$-formyl-$\beta$-carboline **207**, aniline **143c** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 83%

Mp: 319-321 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3354, 2945, 1457, 1028, 705

$^1$H NMR (400 MHz) δ: 11.94 (1H, s), 8.95 (1H, s), 8.88 (1H, s), 8.23-8.26 (2H, m), 7.73-7.75 (1H, m), 7.66-7.69 (3H, m), 7.53-7.62 (3H, m), 7.47 (1H, dd, $J_1$ = 2.8 Hz

& *J2* = 9.2 Hz), 7.40 (1H, t, *J* = 7.6 Hz), 7.25 (1H, d, *J* = 2.4 Hz), 4.08 (3H, s), 3.84 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.8, 158.4, 154.7, 148.1, 143.7, 140.9, 138.5, 137.9, 136.8, 136.6, 130.9, 130.5, 129.5, 128.9, 128.6, 128.4, 127.8, 122.0, 121.9, 121.6, 120.9, 119.9, 118.3, 112.3, 104.2 (aromatic C), 55.5, 52.6 (aliphatic C)

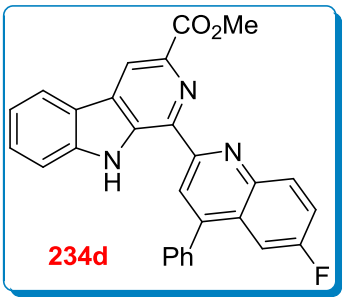
HRMS (ESI-MS). Calcd: 482.1481 (M+Na)

Found: 482.1481

Anal. calcd. for $C_{29}H_{21}N_3O_3$: C, 75.80; H, 4.61; N, 9.14%

Found: C, 75,91; H, 4.55; N, 9.21%

**Methyl 1-(6-fluoro-4-phenyl-2-quinolyl)-9*H*-*β*-carboline-3-carboxylate (234d):** Compound **234d** was synthesized from *α*-formyl-*β*-carboline **207**, aniline **143e** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 77%

Mp: 255-257 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3353, 2969, 1720, 1019, 701

$^{1}$H NMR (400 MHz) δ: 11.79 (1H, s), 8.93 (2H, s), 8.29-8.33 (1H, m), 8.23 (1H, d, *J* = 7.8 Hz), 7.70-7.72 (1H, m), 7.65-7.67 (1H, m), 7.54-7.63 (7H, m), 7.39 (1H, t, *J* = 7.4 Hz), 4.06 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.7, 156.5, 149.0, 144.8, 140.9, 137.7, 137.4, 136.9, 136.7, 131.9, 131.8, 130.8, 129.5, 129.1, 128.8, 127.7, 122.0, 121.6, 121.0, 120.2, 119.9, 119.7, 118.7, 112.4, 109.9, 109.7 (aromatic C), 52.7 (aliphatic C)

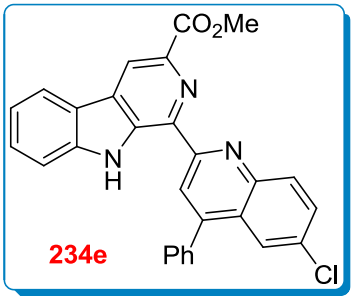
HRMS (ESI-MS). Calcd: 470.1281 (M+Na)

Found: 470.1281

Anal. calcd. for $C_{28}H_{18}FN_3O_2$: C, 75.16; H, 4.05; N, 9.39%

Found: C, 75.26; H, 4.15; N, 9.28%

**Methyl 1-(6-chloro-4-phenyl-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (234e):** Compound **234e** was synthesized from $\alpha$-formyl-$\beta$-carboline (**207**), aniline **143f** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



234e

Yield: 80%

Mp: 241-243 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3354, 2965, 1547, 1046, 725

$^1$H NMR (400 MHz) δ: 11.78 (1H, s), 8.93 (2H, s), 8.24 (2H, d, *J* = 8.4 Hz), 7.92 (1H, d, *J* = 2.4 Hz), 7.71-7.75 (2H, m), 7.60 (1H, t, *J* = 7.6 Hz), 7.58-7.62 (5H, m), 7.41 (1H, t, *J* = 7.2 Hz), 4.07 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.6, 157.1, 148.6, 146.1, 140.9, 137.5, 137.1, 136.9, 136.7, 132.9, 130.9, 130.8, 130.5, 129.6, 129.1, 128.8, 127.4, 125.1, 121.9, 121.5, 121.0, 120.4, 118.8, 112.3 (aromatic C), 52.6 (aliphatic C)

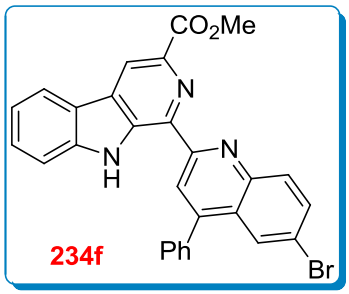
HRMS (ESI-MS). Calcd: 486.0986 (M+Na)

Found: 486.0986

Anal. calcd. for $C_{28}H_{18}ClN_3O_2$: C, 72.49; H, 3.91; N, 9.06%

Found: C, 72.29; H, 3.86; N, 9.15%

**Methyl 1-(6-bromo-4-phenyl-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (234f):** Compound **234f** was synthesized from $\alpha$-formyl-$\beta$-carboline **207**, aniline **143g** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



234f

Yield: 75%

Mp: 314-316 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3424, 1736, 1649, 1424, 1019, 767

$^1$H NMR (400 MHz) δ: 11.81 (1H, s), 8.95 (1H, s), 8.93 (1H, s), 8.25 (1H, d, *J* = 7.9 Hz), 8.19 (1H, d, *J* = 8.9 Hz), 8.09 (1H, s), 8.97 (1H, d, *J* = 8.7 Hz), 7,73 (1H, d, *J* = 8.2 Hz), 7.67 (1H, t, *J* = 7.3

Hz), 7.57-7.61 (5H, m), 7.40 (1H, t, *J* = 7.4 Hz), 4.07 (3H, s)

$^{13}$C NMR (100 MHz, $CDCl_3$+DMSO-$d_6$) δ: 166.6, 157.2, 148.6, 146.3, 140.9, 137.4, 137.1, 136.9, 136.7, 133.1, 131.2, 130.8, 129.6, 129.2, 128.8, 128.3, 127.9, 121.9, 121.4, 121.2, 121.1, 120.4, 118.8, 112.5 (aromatic C), 52.6 (aliphatic C)

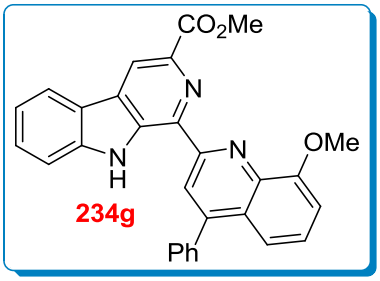
HRMS (ESI-MS). Calcd: 532.0460 (M+Na)

Found: 532.0460

Anal. calcd. for $C_{28}H_{18}BrN_4O_2$: C, 66.15; H, 3.57; N, 8.27%

Found: C, 66.25; H, 3.65; N, 8.19%

**Methyl 1-(8-methoxy-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (234g):** Compound **234g** was synthesized from α-formyl-β-carboline **207**, aniline **143d** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



234g

Yield: 79%

Mp: 269-271 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3354, 1736, 1432, 1087, 754

$^1$H NMR (400 MHz) δ: 12.69 (1H, s), 8.99 (1H, s), 8.88 (1H, s), 8.27 (1H, d, *J* = 7.6 Hz), 7.64-7.72 (4H, m), 7.53-7.59 (4H, m), 7.48 (1H, t, *J* = 8.0 Hz), 7.39 (1H, t, *J* = 6.8 Hz), 7.17 (1H, d, *J* = 7.2 Hz), 4.29 (3H, s), 4.08 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.9, 155.4, 155.0, 149.3, 141.4, 139.4, 138.5, 138.1, 137.1, 136.6, 130.6, 129.7, 128.8, 128.5, 128.4, 127.6, 127.0, 122.0, 121.1, 120.7, 119.5, 118.7, 117.9, 112.4, 107.7 (aromatic C), 56.4, 52.6 (aliphatic C)

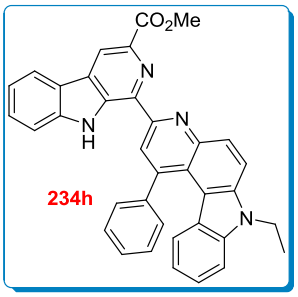
HRMS (ESI-MS). Calcd: 482.1481 (M+Na)

Found: 482.1494

Anal. calcd. for $C_{29}H_{21}N_3O_3$: C, 75.80; H, 4.61; N, 9.14%

Found: C, 75.86; H, 4.56; N, 9.21%

**Methyl 1-(7-ethyl-1-phenyl-7*H*-pyrido[2,3-c]carbazole-3-yl)- 9*H*-$\beta$-carboline-3-carboxylate (234h):** Compound **234h** was synthesized from $\alpha$-formyl-$\beta$-carboline **207**, aniline **143l** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 72%

Mp: 264-266 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3021, 2835, 1544, 1428, 1054

$^1$H NMR (400 MHz, DMSO-$d_6$) δ: 12.39 (1H, s), 9.06 (1H, s), 8.99 (1H, d, *J* = 9.1 Hz), 8.81 (1H, s), 8.49 (1H, d, *J* = 7.9 Hz), 8.44 (1H, d, *J* = 9.0 Hz), 8.12 (1H, d , *J* = 7.9 Hz), 7.59-7.71 (7H, m), 7.39 (1H, t, *J* = 6.6 Hz), 7.28 (1H, t, *J* = 7.3 Hz), 6.62 (1H, t, *J* = 7.4 Hz), 5.98 (1H, d, *J* = 7.9 Hz), 4.69 (2H, q, *J* = 6.1 Hz), 3.97 (3H, s), 1.42 (3H, t, *J* = 6.6 Hz)

$^{13}$C NMR (100 MHz) δ: Due to limited solubility of compound **234h** in both $CDCl_3$ as well as in DMSO-$d_6$, we were unable to record the $^{13}$C NMR spetra

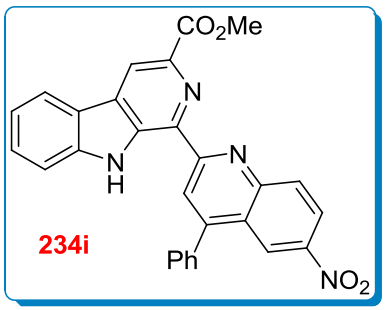
HRMS (ESI-MS). Calcd: 547.2134 (M+Na)

Found: 547.2134

Anal. calcd. for $C_{36}H_{26}N_4O_2$: C, 79.10; H, 4.79; N, 10.25%

Found: C, 79.25; H, 4.71; N, 10.18%

**Methyl 1-(6-nitro-4-phenyl-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (234i):** Compound **234i** was synthesized from $\alpha$-formyl-$\beta$-carboline **207**, aniline **143m** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 68%

Mp: 283-285 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3364, 1544, 1467, 1027, 705

$^1$H NMR (400 MHz) δ: 11.76 (1H, s), 9.12 (1H, s),

9.03 (1H, s), 8.93 (1H, d, *J* = 2.3 Hz), 8.58-8.61 (1H, m), 8.48-8.50 (1H, m), 8.29 (1H, d, *J* = 7.9 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.62-7.75 (6H, m), 7.44 (1H, t, *J* = 7.6 Hz), 4.09 (3H, s)

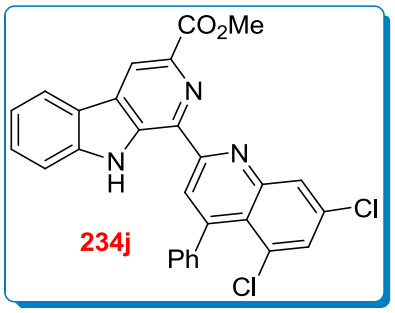
$^{13}$C NMR (100 MHz) δ: Due to limited solubility of compound **234i** in both $CDCl_3$ as well as in DMSO-$d_6$, we were unable to record the $^{13}$C NMR spetra

LCMS (m/z): 475.25 $(M+H)^+$

Anal. calcd. for $C_{28}H_{18}N_4O_4$: C, 70.88; H, 3.82; N, 11.81%

Found: C, 70.72; H, 3.93; N, 11.68%

**Methyl 1-(5,7-dichloro-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (234j):** Compound **234j** was synthesized from α-formyl-β-carboline **207**, aniline **143j** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 75%

Mp: 255-257 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3369, 1738, 1054, 709, 654

$^1$H NMR (400 MHz) δ: 11.64 (1H, s), 8.98 (1H, s), 8.84 (1H, s), 8.26-8.29 (2H, m), 7.78-7.80 (1H, m), 7.71 (1H, t, *J* = 8.0 Hz), 7.61 (1H, d, *J* = 2.0 Hz), 7.42-7.49 (6H, m), 4.07 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.5, 157.5, 149.4, 149.3, 140.9, 140.3, 137.1, 136.9, 136.3, 134.7, 132.5, 131.1, 130.3, 129.4, 129.1, 128.1, 128.0, 127.8, 123.2, 123.0, 122.1, 121.5, 121.3, 119.1, 112.4 (aromatic C), 52.7(aliphatic C)

HRMS (ESI-MS). Calcd: 520.0596 (M+Na)

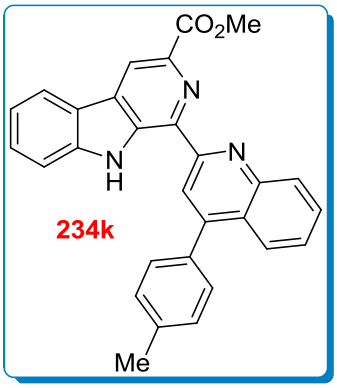
Found: 520.0596

HRMS (ESI-MS): $(M+Na)^+$

Anal. calcd. for $C_{28}H_{17}Cl_2N_3O_2$: C, 67.48; H, 3.44; N, 8.43%

Found: C, 67.38; H, 3.41; N, 8.56%

**Methyl 1-[4-(4-methylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (234k):** Compound **234k** was synthesized from α-formyl-β-carboline **207**, aniline (**143a**) and acetylene **53b** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 85%

Mp: 248-250 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3352, 3055, 1589, 1003, 744

$^1$H NMR (400 MHz) δ: 12.04 (1H, s), 8.99 (1H, s), 8.94 (1H, s), 8.37 (1H, d, *J* = 8.3 Hz), 8.27 (1H, d, *J* = 7.8 Hz), 8.01 (1H, d, *J* = 8.4 Hz), 7.82 (1H, t, *J* = 7.8 Hz), 7.75-7.77 (1H, m), 7.68 (1H, t, *J* = 7.4 Hz), 7.54-7.58 (3H, m), 7.39-7.42 (3H, m), 4.08 (3H, s), 2.50 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.8, 156.9, 149.6, 147.8, 141.0, 138.4, 137.7, 136.9, 135.2, 130.7, 129.7, 129.5, 129.3, 129.1, 127.0, 126.9, 126.3, 122.0, 121.6, 120.9, 119.6, 118.7, 112.4 (aromatic C), 52.7, 21.4 (aliphatic C)

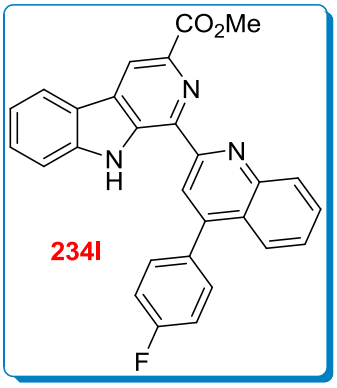
HRMS (ESI-MS). Calcd: 466.1532 (M+Na)

Found: 466.1532

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

Found: C, 78.42; H, 4.71; N, 9.36%

**Methyl 1-[4-(4-fluorophenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (234l):** Compound **234l** was synthesized from α-formyl-β-carboline **207**, aniline (**143a**) and acetylene **53c** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 81%

Mp: 247-248 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3362, 2951, 1498, 1157, 1024, 767

$^{1}$H NMR (500 MHz) δ: 12.01 (1H, s), 9.00 (1H, s), 8.93 (1H, s), 8.39 (1H, d, *J* = 8.3 Hz), 8.28 (1H, d, *J* = 7.8 Hz), 7.95 (1H, d, *J* = 8.3 Hz), 7.86 (1H, t, *J* = 7.4 Hz), 7.77-7.89 (1H, m), 7.69 (1H, t, *J* = 7.4 Hz), 7.58-7.65 (3H, m), 7.43 (1H, t, *J* = 7.4 Hz), 7.29-7.31 (2H, m), 4.09 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.7, 164.0, 161.9, 156.9, 148.4, 147.8, 141.0, 136.8, 131.5, 131.4, 130.8, 129.8, 129.6, 129.1, 127.2, 125.9, 122.0, 121.6, 121.0, 119.7, 118.8, 115.7, 115.5, 112.4 (aromatic C), 52.8 (aliphatic C)

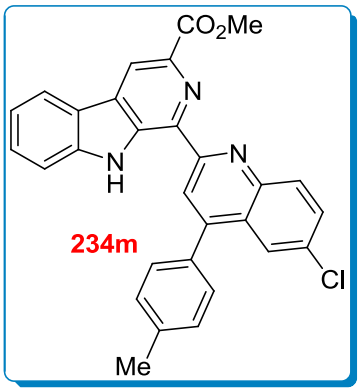
HRMS (ESI-MS). Calcd: 448.1461 (M+Na)

Found: 448.1461

Anal. calcd. for $C_{28}H_{18}FN_3O_2$: C, 75.16; H, 4.05; N, 9.39%

Found: C, 74.98; H, 4.12; N, 9.26%

**Methyl 1-[6-chloro-4-(4-methylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (234m):** Compound **234m** was synthesized from α-formyl-β-carboline **207**, aniline **143f** and acetylene **53b** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 84%

Mp: 297-299 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3362, 2932, 1493, 1020, 744

$^{1}$H NMR (400 MHz) δ: 11.83 (1H, s), 8.97 (1H, s), 8.95 (1H, s), 8.25-8.28 (2H, m), 7.97 (1H, d, *J* = 2.0 Hz), 7.73-7.75 (2H, m), 7.68 (1H, t, *J* = 7.4 Hz), 7.52-7.54 (2H, m), 7.41-7.43 (3H, m), 4.08 (3H, s), 2.54 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.7, 157.2, 148.8, 146.1, 140.9, 138.7, 137.2, 136.9, 136.7, 134.6, 132.9, 130.9, 130.8, 130.5, 129.5, 129.4, 129.1, 127.6, 125.2, 121.9, 121.0, 120.4, 118.7, 112.3 (aromatic C), 52.6, 21.4 (aliphatic C)

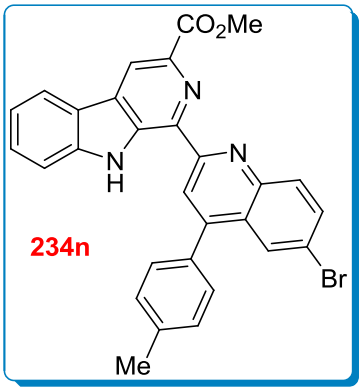
HRMS (ESI-MS). Calcd: 500.1142 (M+Na)

Found: 500.1142

Anal. calcd. for $C_{29}H_{20}ClN_3O_2$: C,72.88; H, 4.22; N, 8.79%

Found: C, 72.96; H, 4.32; N, 8.61%

**Methyl 1-[6-bromo-4-(4-methylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (234n):** Compound **234n** was synthesized from α-formyl-β-carboline **207**, aniline **143g** and acetylene **53b** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 80%

Mp: 319-321°C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3055, 1732, 1215, 1145, 603

$^1$H NMR (400 MHz) δ: 11.81 (1H, s), 8.96 (1H, s), 8.93 (1H, s), 8.25 (1H, d, *J* = 7.8 Hz), 8.18 (1H, d, *J* = 8.9 Hz), 8.13 (1H, s), 8.86 (1H, d, *J* = 8.4 Hz), 7.72-7.74 (1H, m), 7.67 (1H, t, *J* = 7.1 Hz), 7.51-7.53 (2H, m), 7.39-7.43 (3H, m), 4.08 (3H, s), 2.54 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.6, 157.3, 148.7, 146.3, 140.9, 138.7, 137.1, 136.9, 136.7, 134.5, 133.1, 131.1, 130.8, 129.5, 129.4, 129.1, 128.4, 128.1, 121.9, 121.5, 121.1, 121.0, 120.4, 118.8, 112.3 (aromatic C), 52.6, 21.4 (aliphatic C)

HRMS (ESI-MS). Calcd: 544.0637 (M+Na)

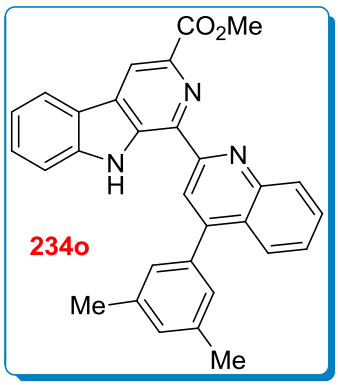
Found: 544.0637

Anal. calcd. for $C_{29}H_{20}BrN_3O_2$: C, 66.68; H, 3.86; N, 8.04%

Found: C, 66.52; H, 3.75; N, 8.16%

**Methyl 1-[4-(3,5-dimethylphenyl)-2-quinolyl]-9*H*-β-carboline-3-carboxylate (234o):** Compound **234o** was synthesized from α-formyl-β-carboline **207**, aniline (**143a**) and acetylene **53d** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.

Yield: 79%




Mp: 309-311 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3369, 1724, 1358, 1107, 761

$^1$H NMR (400 MHz) δ: 12.06 (1H, s), 8.99 (1H, s), 8.93 (1H, s), 8.36 (1H, d, *J* = 8.3 Hz), 8.28 (1H, d, *J* = 7.5 Hz), 8.00 (1H, d, *J* = 8.0 Hz), 7.83 (1H, t, *J* = 7.3 Hz), 7.76-7.78 (1H, m), 7.68 (1H, t, *J* = 7.6 Hz), 7.57 (1H, t, *J* = 7.7 Hz), 7.41 (1H, t, *J* = 7.4 Hz), 7.26-7.27 (2H, m), 7.18 (1H, s), 4,08 (3H, s), 2.46 (6H, s)

$^{13}$C NMR (100 MHz) δ: 166.8, 156.9, 149.9, 147.7, 141.0, 138.1, 137.7, 136.9, 130.7, 130.0, 129.6, 129.4, 129.1, 127.5, 126.9, 126.5, 122.0, 121.6, 120.9, 119.5, 118.7, 112.4 (aromatic C), 52.6, 21.4 (aliphatic C)

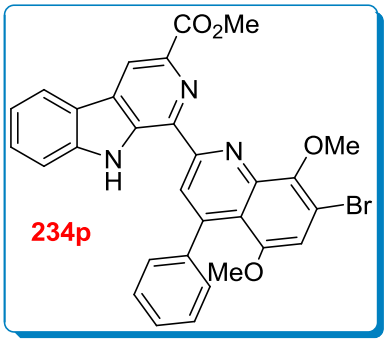
HRMS (ESI-MS). Calcd: 480.1688 (M+Na)

Found: 480.1688

Anal. calcd. for $C_{30}H_{23}N_3O_2$: C,78.75; H, 5.07; N,9.18%

Found: C, 78.62; H, 5.15; N, 9.07%

**Methyl 1-(7-bromo-5,8-dimethoxy-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (234p):** Compound **234p** was synthesized from α-formyl-β-carboline **207**, aniline **143n** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 74%

Mp: 277-279 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3356, 2939, 2841, 1107, 744

$^1$H NMR (400 MHz) δ: 12.51 (1H, s), 9.01 (1H, s), 8.77 (1H, s), 8.28 (1H, d, *J* = 7.7 Hz), 7.76-7.78 (1H, m), 7.69 (1H, t, *J* = 7.4 Hz), 7.40-7.45 (6H, m), 6.99 (1H, s), 4.31 (3H, s), 4.08 (3H, s), 3.56 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.7, 156.3, 153.2, 149.7, 147.2, 143.3, 141.9, 141.3, 137.3, 137.2, 136.9, 130.8, 129.2, 128.3, 127.2, 127.1, 122.1, 121.6, 121.3, 120.9, 119.0, 118.9, 116.7, 112.3, 110.3 (aromatic C), 61.6, 55.7, 52.6 (aliphatic C)

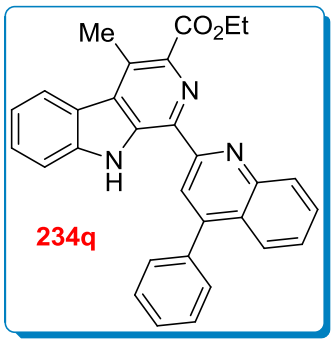
HRMS (ESI-MS). Calcd: 590.0692 (M+Na)

Found: 590.0692

Anal. calcd. for $C_{30}H_{22}BrN_3O_4$: C,63.39; H, 3.90; N, 7.39%

Found: C, 63.25; H, 3.98; N, 7.21%

**Ethyl 4-methyl-1-(4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (234q):** Compound **234q** was synthesized from α-formyl-β-carboline **202**, aniline (**143a**) and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



234q

Yield: 73%

Mp: 238-240 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3350, 2962, 1728, 700

$^1$H NMR (400 MHz) δ: 12.08 (1H, s), 8.89 (1H, s), 8.36-8.40 (2H, m), 7.98 (1H, d, *J* = 8.3 Hz), 7.77-7.84 (2H, m), 7.63-7.68 (3H, m), 7.53-7.59 (4H, m), 7.40 (1H, t, *J* = 7.6 Hz), 4.53 (2H, q, *J* = 7.1 Hz), 3.20 (3H, s), 1.49 (3H, t, *J* = 7.1 Hz)

$^{13}$C NMR (100 MHz) δ: 167.8, 157.2, 149.2, 147.8, 140.8, 138.3, 135.7, 135.1, 131.4, 129.9, 129.7, 129.6, 129.5, 128.5, 128.4, 128.1, 126.8, 126.6, 126.2, 124.0, 122.3, 120.7, 119.6, 112.3 (aromatic C), 61.4, 16.8, 14.5 (aliphatic C)

HRMS (ESI-MS). Calcd: 480.1688 (M+Na)

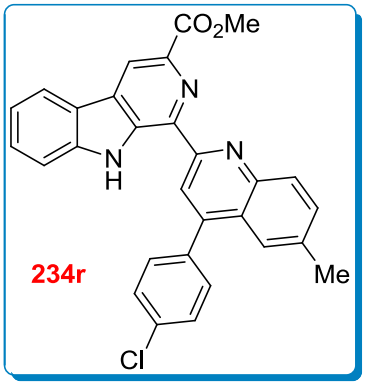
Found: 480.1688

Anal. calcd. for $C_{30}H_{23}N_3O_2$: C, 78.75; H, 5.07; N, 9.18%

Found: C, 78.62; H, 5.13; N, 9.25%

**Methyl 1-[4-(4-chlorophenyl)-6-methyl-2-quinolyl]-9*H*-β-carboline-3-carboxylate (234r):** Compound **234r** was synthesized from α-formyl-β-carboline **207**,

aniline **143b** and acetylene **53e** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 80%

Mp: 288-290 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3337, 2945, 1003, 605

$^1$H NMR (500 MHz) δ: 11.97 (1H, s), 8.98 (1H, s), 8.86 (1H, s), 8.26 (2H, t, *J* = 8.3 Hz), 7.75-7.77 (1H, m), 7.66-7.70 (3H, m), 7.57-7.59 (4H, m), 7.42 (1H, t, *J* = 7.2 Hz), 4.09 (3H, s), 2.54 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.7, 156.1, 147.4, 146.3, 141.0, 137.6, 137.5, 136.9, 136.8, 136.7, 134.6, 132.0, 131.0, 130.7, 129.4, 129.0, 128.8, 126.5, 124.7, 121.9, 121.6, 120.9, 119.6, 118.6, 112.4 (aromatic C), 52.6, 21.9 (aliphatic C)

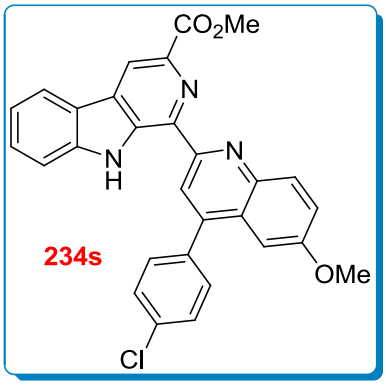
HRMS (ESI-MS). Calcd: 500.1142 (M+Na)

Found: 500.1142

Anal. calcd. for $C_{29}H_{20}ClN_3O_2$: C, 72.88; H, 4.22; N, 8.79%

Found: C, 72.96; H, 4.12; N, 8.91%

**Methyl 1-[4-(4-chlorophenyl)-6-methoxy-2-quinolyl]-9*H*-β-carboline-3-carboxylate (234s):** Compound **234s** was synthesized from α-formyl-β-carboline **207**, aniline **143c** and acetylene **53e** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 82%

Mp: 265-267 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3402, 2924, 1728, 1358, 746

$^1$H NMR (500 MHz) δ: 11.88 (1H, s), 8.94 (1H, s), 8.80 (1H, s), 8.21-8.26 (2H, m), 7.73-7.74 (1H, m), 7.67

(1H, t, $J$ = 7.4 Hz), 7.56-7.61 (4H, m), 7.47 (1H, dd, $J_1$ = 2.2 Hz, $J_2$ = 9.1 Hz), 7.41 (1H, t, $J$ = 7.4 Hz), 7.16 (1H, d, $J$ = 2.4 Hz), 4.08 (3H, s), 3.85 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.7, 158.6, 154.6, 146.7, 143.7, 140.9, 137.7, 136.9, 136.8, 136.5, 134.6, 131.1, 130.8, 130.5, 128.98, 128.9, 127.5, 122.2, 121.9, 121.6, 120.9, 119.9, 118.4, 112.3, 103.8 (aromatic C), 55.6, 52.6 (aliphatic C)

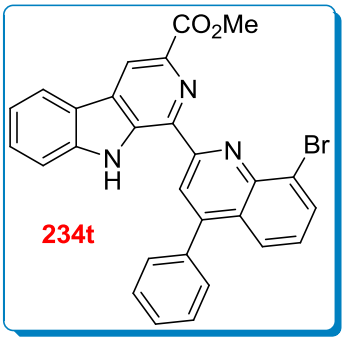
HRMS (ESI-MS). Calcd: 516.1091 (M+Na)

Found: 516.1091

Anal. calcd. for $C_{29}H_{20}ClN_3O_3$:C, 70.52; H, 4.08; N, 8.51%

Found: C, 70.65; H, 4.12; N, 8.71%

**Methyl 1-(8-bromo-4-phenyl-2-quinolyl)-9*H*-β-carboline-3-carboxylate (234t):** Compound **234t** was synthesized from α-formyl-β-carboline **207**, aniline **143o** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 73%

Mp: 245-247 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3354, 2781, 1327, 782

$^1$H NMR (500 MHz) δ: 12.57 (1H, s), 9.01 (1H, s), 9.00 (1H, s), 8.27 (1H, d, $J$ = 7.9 Hz), 8.16 (1H, dd, $J_1$ = 0.9 Hz, $J_2$ = 7.5 Hz), 7.96 (1H, dd, $J_1$ = 0.8 Hz, $J_2$ = 8.3 Hz), 7.74-7.76 (1H, m), 7.56-7.69 (6H, m), 7.39-7.44 (2H, m), 4.09 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.7, 157.1, 150.2, 144.6, 141.5, 137.8, 137.0, 136.8, 136.7, 133.1, 130.9, 129.7, 129.1, 128.7, 128.6, 128.3, 127.2, 126.2, 125.3, 121.9, 121.5, 120.9, 120.2, 119.1, 112.4 (aromatic C), 52.6 (aliphatic C)

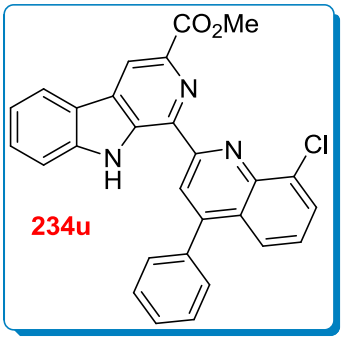
HRMS (ESI-MS). Calcd: 530.0460 (M+Na)

Found: 530.0480

Anal. calcd. for $C_{28}H_{18}BrN_3O_2$:C, 66.15; H, 3.57; N, 8.27%

Found: C, 66.38; H, 3.51; N, 8.35%

**Methyl 1-(8-chloro-4-phenyl-2-quinolyl)-9*H*-$\beta$-carboline-3-carboxylate (234u):** Compound **234u** was synthesized from $\alpha$-formyl-$\beta$-carboline **207**, aniline **143p** and acetylene **53a** following the *general procedure E*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



**234u**

Yield: 77%

Mp: 267-269 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3329, 2922, 1711, 1016, 671

$^1$H NMR (500 MHz) δ: 12.49 (1H, s), 9.00 (1H, s), 8.99 (1H, s), 8.27 (1H, d, *J* = 7.8 Hz), 7.96 (1H, d, *J* = 7.4 Hz), 7.91 (1H, dd, $J_1$ = 0.7 Hz, $J_2$ = 8.3 Hz), 7.74-7.75 (1H, m), 7.56-7.69 (6H, m), 7.48 (1H, t, *J* = 8.1 Hz), 7.41 (1H, t, *J* = 7.3 Hz), 4.09 (3H, s)

$^{13}$C NMR (125 MHz) δ: 166.7, 156.8, 150.1, 143.8, 141.4, 137.8, 137.1, 136.9, 136.8, 133.5, 130.9, 129.7, 129.5, 129.1, 128.7, 128.6, 128.1, 126.6, 125.4, 121.9, 121.5, 120.9, 120.1, 119.0, 112.5 (aromatic C), 52.6 (aliphatic C)

HRMS (ESI-MS). Calcd: 486.0986 (M+Na)

Found: 486.0986

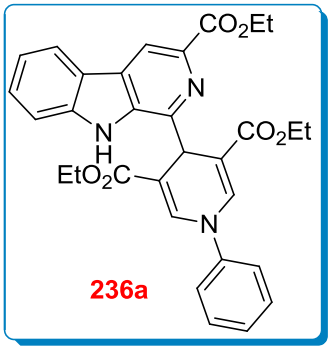
Anal. calcd. for $C_{28}H_{18}ClN_3O_2$: C, 72.49; H, 3.91; N, 9.06%

Found: C, 72.31; H, 3.85; N, 9.18%

***General procedure F:***

In a round bottom flask equipped with a magnetic stirring bar, 0.3 mmol of $\alpha$-formyl-$\beta$-carboline, 0.3 mmol of aniline and 0.9 mmol of **53f** in 4 mL of [Bmim][$BF_4$] was stirred for 12 min. Into this reaction mixture were added 0.35 mmol of phenylacetylene and 10 mol% of La(OTf)$_3$ and then heated around 95-100 °C. After completion of the reaction, as indicated by the TLC, water was added and extracted with ethyl acetate, The organic layer was dried over anhydrous $Na_2SO_4$. The solvent was concentrated under the reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate).

**Diethyl 4-(3-ethyloxycarbonyl-9*H*-β-carbolin-1-yl)-1-phenyl-1,4-dihydro-3,5-pyridinedicarboxylate (236a):** Compound **236a** was synthesized from α-formyl-β-carboline **207a**, aniline (**143a**) and acetylene **53f** following the *general procedure F*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 72%

Mp: 166-168 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3344, 2955, 1012, 742

$^1$H NMR (400 MHz) δ: 9.84 (1H, s), 8.72 (1H, s), 8.14 (1H, d, *J* = 7.4 Hz), 7.81 (2H, s), 7.59-7.62 (1H, m), 7.53-7.57 (1H, m), 7.46-7.52 (4H, m), 7.27-7.34 (2H, m), 5.58 (1H, s), 4.40 (2H, q, *J* = 6.9 Hz), 3.99-4.13 (4H, m), 1.38 (3H, q, *J* = 7.0 Hz), 1.11 (6H, t, *J* = 7.0 Hz)

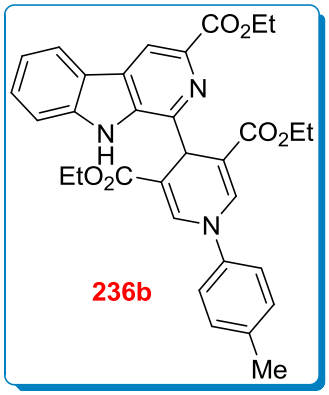
$^{13}$C NMR (100 MHz) δ: 167.3, 166.5, 146.9, 143.5, 141.1, 138.1, 137.9, 134.9, 129.8, 128.0, 128.3, 126.8, 122.3, 121.9, 121.7, 120.4, 116.7, 112.4, 107.8 (aromatic C), 60.9, 60.4, 35.1, 14.4, 14.2 (aliphatic C)

LCMS (m/z): 540.21 $(M+H)^+$

Anal. calcd. for $C_{31}H_{29}N_3O_6$: C, 69.00; H, 5.42; N, 7.79%

Found: C, 69.21; H, 5.53; N, 7.65%

**Diethyl 4-(3-ethyloxycarbonyl-9*H*-β-carbolin-1-yl)-1-(4-methylphenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (236b):** Compound **236b** was synthesized from α-formyl-β-carboline **207a**, aniline **143b** and acetylene **53f** following the *general procedure F*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 76%

Mp: 175-177 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3365, 2903, 1025, 700

$^1$H NMR (500 MHz) δ: 9.88 (1H, s), 8.73 (1H, s), 8.14 (1H, d, *J* = 7.8 Hz), 7.78 (2H, s),

7.58-7.61 (1H, m), 7.54-7.57 (1H, m), 7.38-7.39 (2H, m), 7.29-7.32 (3H, m), 5.59 (1H, s), 4.43 (2H, q, *J* = 7.2 Hz), 4.08-4.15 (2H, m), 3.99-4.06 (2H, m), 2.43 (3H, s), 1.41 (3H, t, *J* = 7.1 Hz), 1.12 (6H, t, *J* = 7.2 Hz)

$^{13}$C NMR (125 MHz) δ: 167.4, 166.5, 147.1, 141.2, 141.1, 138.2, 138.1, 136.7, 134.9, 130.3, 128.9, 128.3, 122.3, 122.1, 121.6, 120.4, 116.6, 112.3, 107.4 (aromatic C), 60.8, 60.4, 35.1, 20.9, 14.4, 14.2 (aliphatic C)

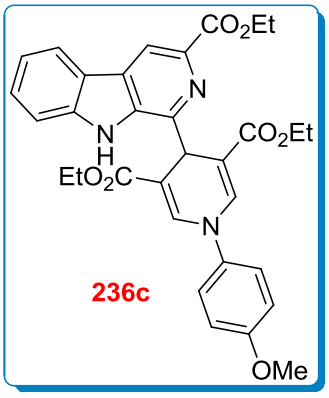
HRMS (ESI-MS). Calcd: 576.2111 (M+Na)

Found: 576.2111

Anal. calcd. for $C_{32}H_{31}N_3O_6$: C, 69.43; H, 5.64; N, 7.59%

Found: C, 69.28; H, 5.58; N, 7.71%

**Diethyl 4-(3-ethyloxycarbonyl-9*H*-β-carbolin-1-yl)-1-(4-methoxyphenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (236c):** Compound **236c** was synthesized from α-formyl-β-carboline **207a**, aniline **143c** and acetylene **53f** following the *general procedure F*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



236c

Yield: 75%

Mp: 165-167 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3387, 2980, 1672, 1197, 798

$^{1}$H NMR (400 MHz) δ: 9.86 (1H, s), 8.71 (1H, s), 8.13 (1H, d, *J* = 7.6 Hz), 7.69 (2H, s), 7.52-7.59 (2H, m), 7.43 (2H, d, *J* = 8.3 Hz), 7.27-7.31 (1H, m), 6.99-7.01 (2H, m), 5.57 (1H, s), 4.42 (2H, q, *J* = 7.1 Hz), 3.99-4.12 (4H, m), 3.86 (3H, s), 1.42 (3H, t, *J* = 6.9 Hz), 1.10 (6H, t, *J* = 6.8 Hz)

$^{13}$C NMR (100 MHz) δ: 167.4, 166.5, 158.6, 147.1, 141.1, 138.6, 138.1, 137.0, 134.9, 128.9, 128.3, 124.2, 122.3, 121.6, 120.4, 116.6, 114.9, 112.3, 107.1 (aromatic C), 60.8, 60.3, 55.6, 34.9, 14.5, 14.2 (aliphatic C)

HRMS (ESI-MS). Calcd: 592.2060 (M+Na)

Found: 592.2060

Anal. calcd. for $C_{32}H_{31}N_3O_7$: C, 67.48; H, 5.49; N, 7.38%

Found: C, 67.59; H, 5.42; N, 7.51%

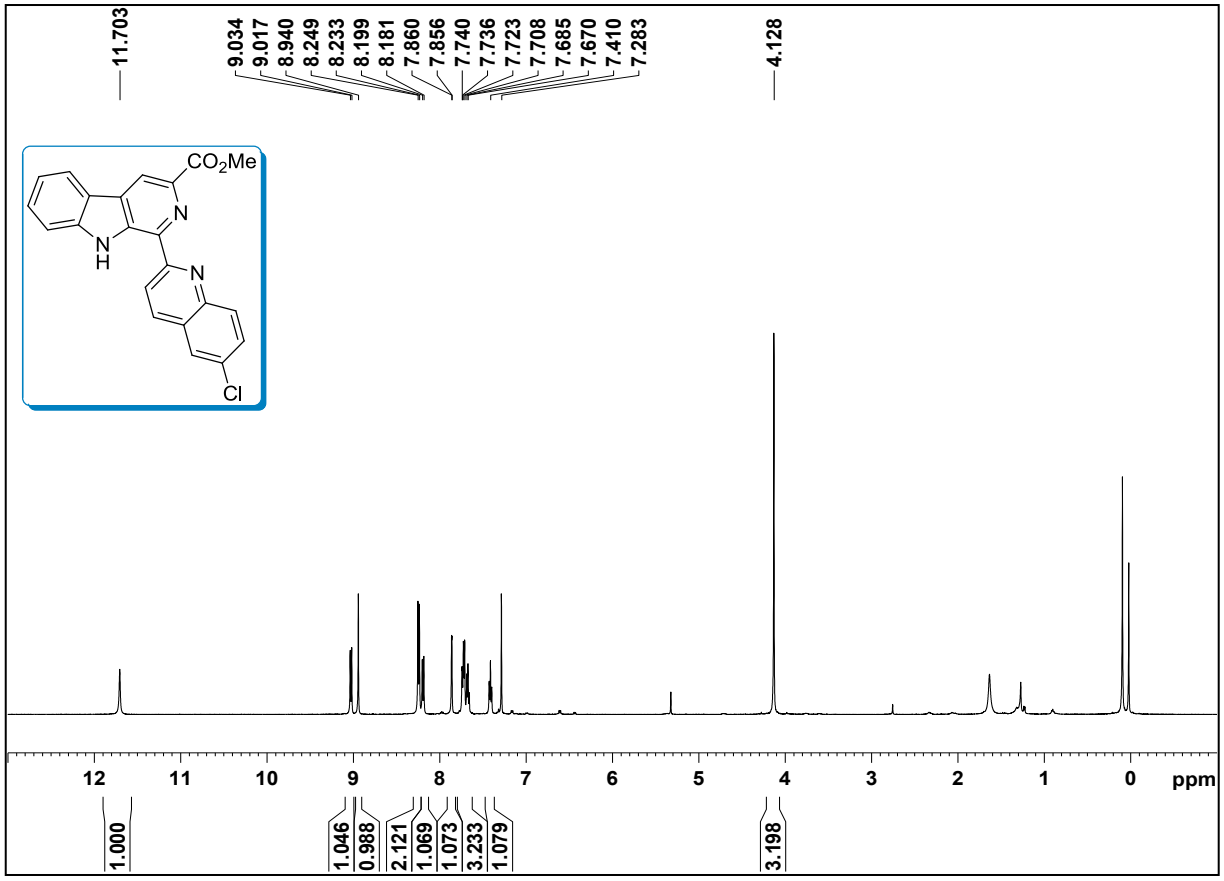
**Table 20. Crystal data and structure refinement for 208c**

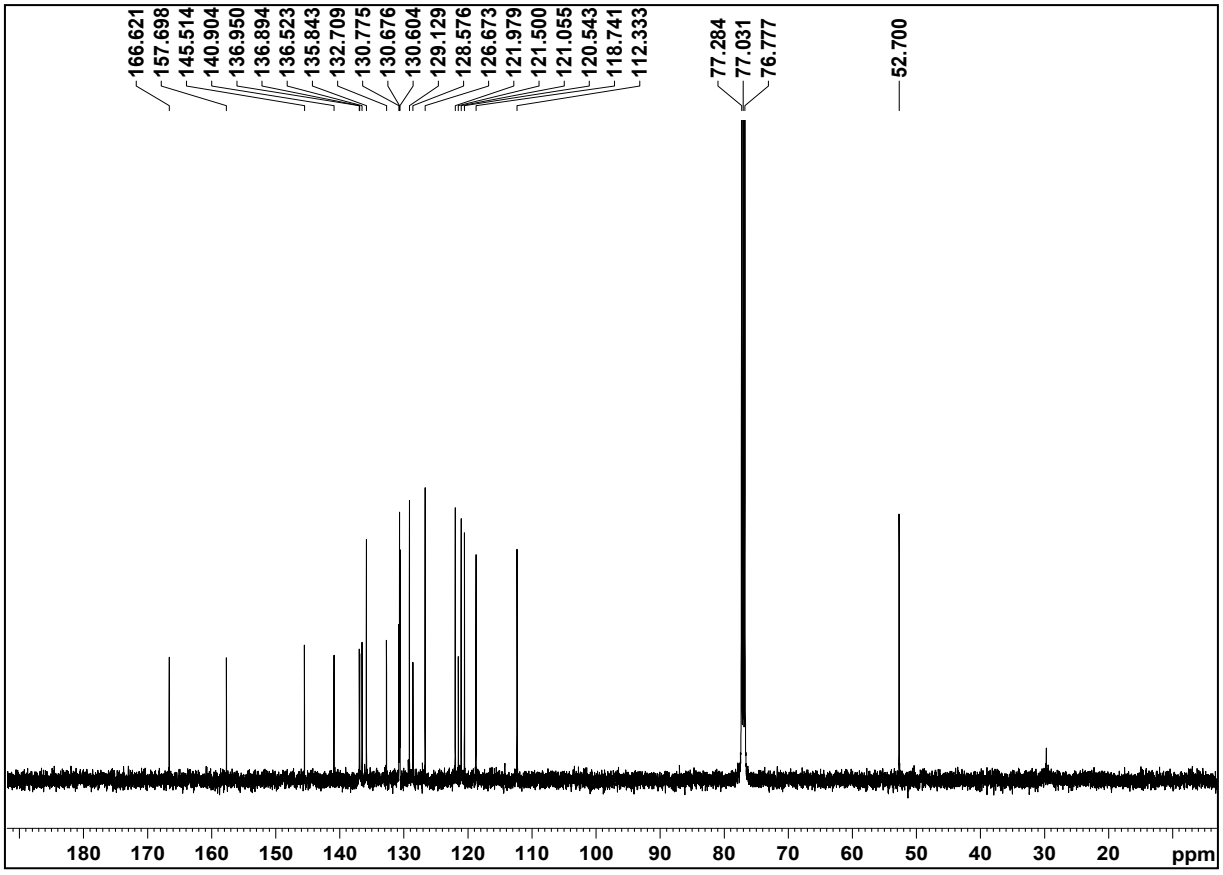
| | |
|---|---|
| Empirical formula | : $C_{22}H_{16}BrN_3O_3$ |
| Formula weight | : 450.29 |
| Temperature | : 298(2) K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Triclinic |
| Space group | : P -1 |
| Unit cell dimensions | : a = 7.3928(6) Å α= 87.961(7)°. |
| | : b = 9.1829(8) Å β= 86.302(7)° |
| | : c = 14.4452(13) Å γ = 71.408(8)° |
| Volume | : 927.42(14) $Å^3$ |
| Z | : 2 |
| Density (calculated) | : 1.612 $Mg/m^3$ |
| Absorption coefficient | : 2.247 $mm^{-1}$ |
| F (000) | : 456 |
| Crystal size | : 0.20 x 0.16 x 0.12 $mm^3$ |
| Theta range for data collection | : 2.71 to 24.71° |
| Index ranges | : -8<=h<=8, -10<=k<=10, -16<=l<=15 |
| Reflections collected | : 5953 |
| Independent reflections | : 3162 [R(int) = 0.0228] |
| Completeness to theta = 26.04° | : 99.9% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.7743 and 0.6621 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 3162 / 0 / 263 |
| Goodness-of-fit on $F^2$ | : 1.028 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0353, wR2 = 0.0779 |
| R indices (all data) | : R1 = 0.0476, wR2 = 0.0831 |
| Largest diff. peak and hole | : 0.368 and -0.320 $e.Å^{-3}$ |
| CCDC number | : 856967 |

**Table 21. Crystal data and structure refinement for 234g**

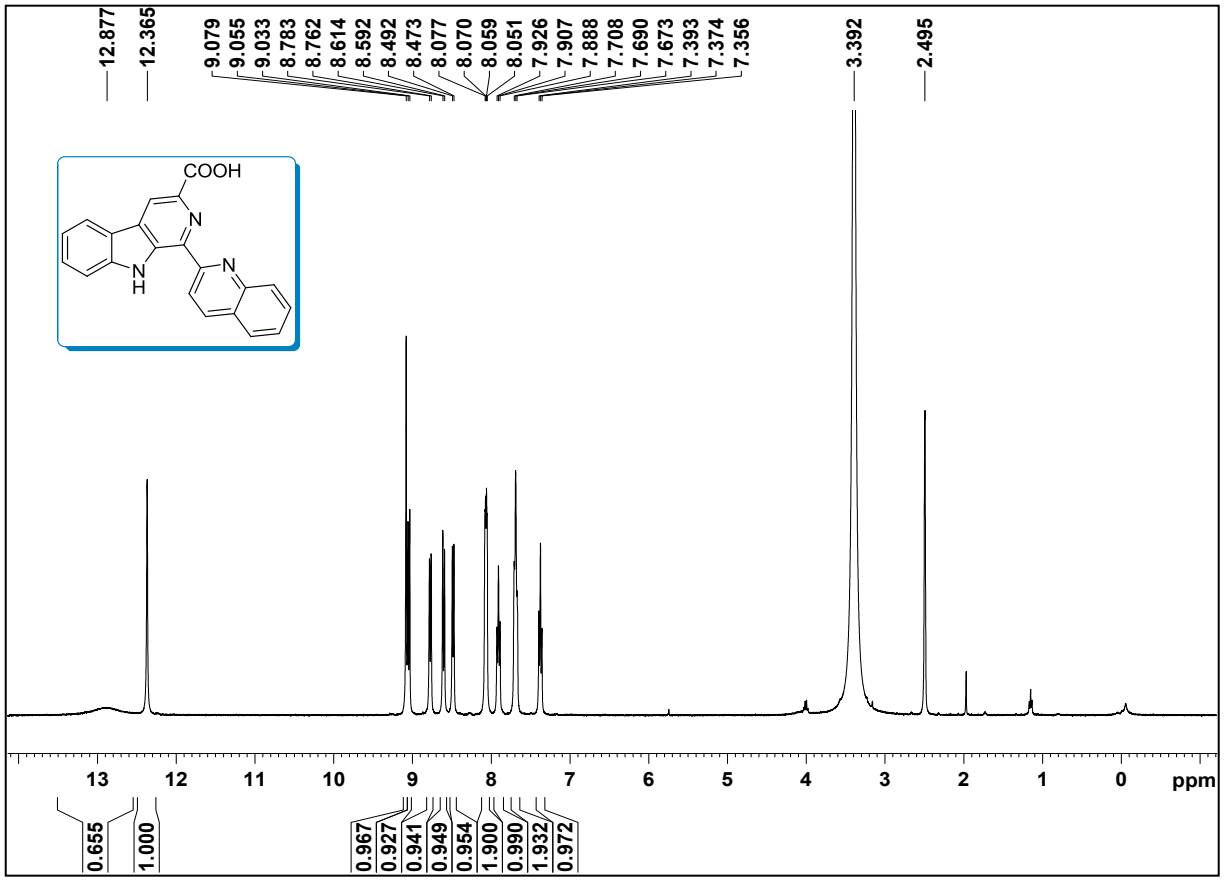
| | |
|---|---|
| Empirical formula | : $C_{29}H_{21}N_3O_3$ |
| Formula weight | : 459.49 |
| Temperature | : 298(2) K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P2(1)/c |
| Unit cell dimensions | : a = 11.7620(15) Å $\alpha$= 90° |
| | : b = 10.3613(13) Å $\beta$= 100.041(3)° |
| | : c = 18.295(2) Å $\gamma$ = 90° |
| Volume | : 2195.5(5) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.390 $Mg/m^3$ |
| Absorption coefficient | : 0.092 $mm^{-1}$ |
| F (000) | : 960 |
| Crystal size | : 0.22 x 0.20 x 0.18 $mm^3$ |
| Theta range for data collection | : 1.76 to 25.00° |
| Index ranges | : -13<=h<=13, -12<=k<=12, -21<=l<=21 |
| Reflections collected | : 20614 |
| Independent reflections | : 3868 [R(int) = 0.0478] |
| Completeness to theta = 26.04° | : 99.9% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9837 and 0.9801 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 3868 / 0 / 318 |
| Goodness-of-fit on $F^2$ | : 1.109 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0559, wR2 = 0.1140 |
| R indices (all data) | : R1 = 0.0715, wR2 = 0.1212 |
| Largest diff. peak and hole | : 0.167 and -0.150 $e.Å^{-3}$ |
| CCDC number | : 903601 |

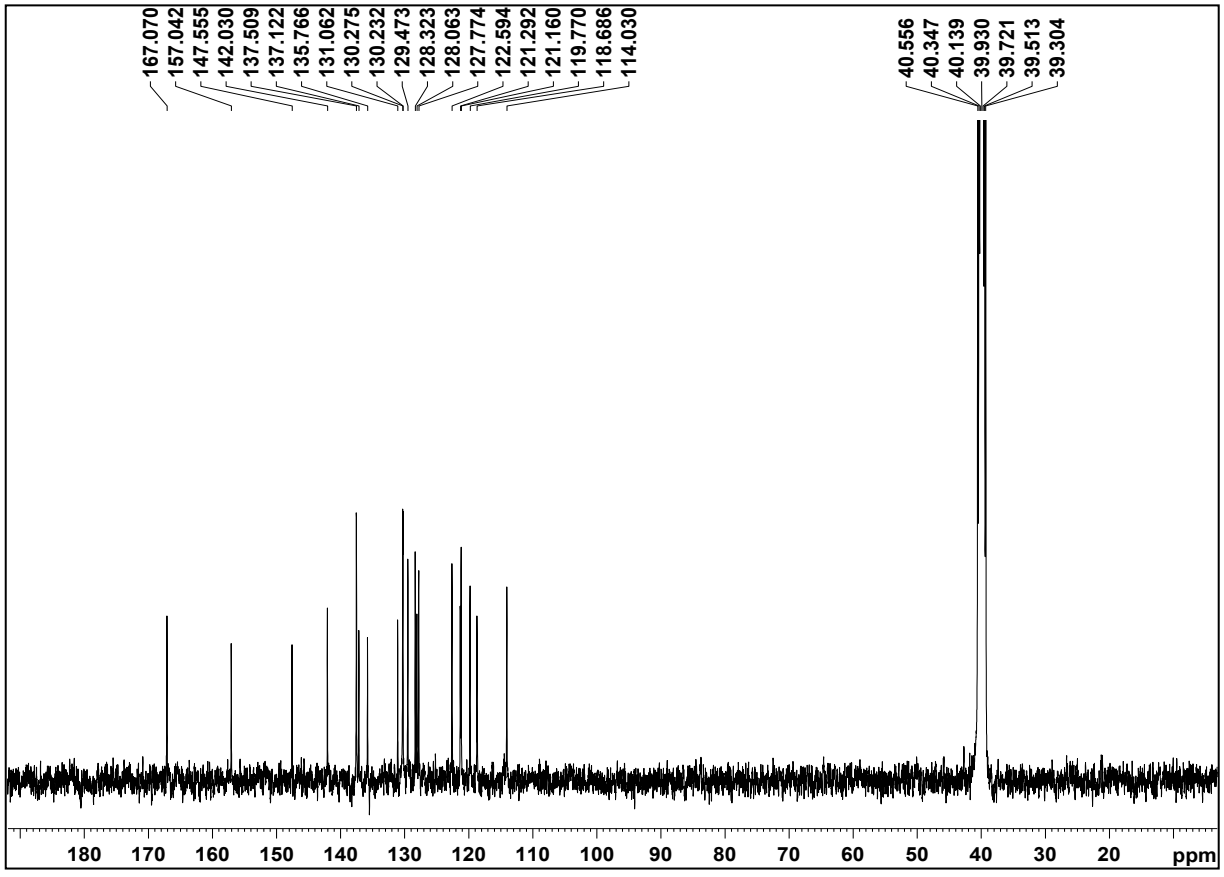
## Spectra No. 5: $^{1}H$ and $^{13}C$ spectra of compound 208b



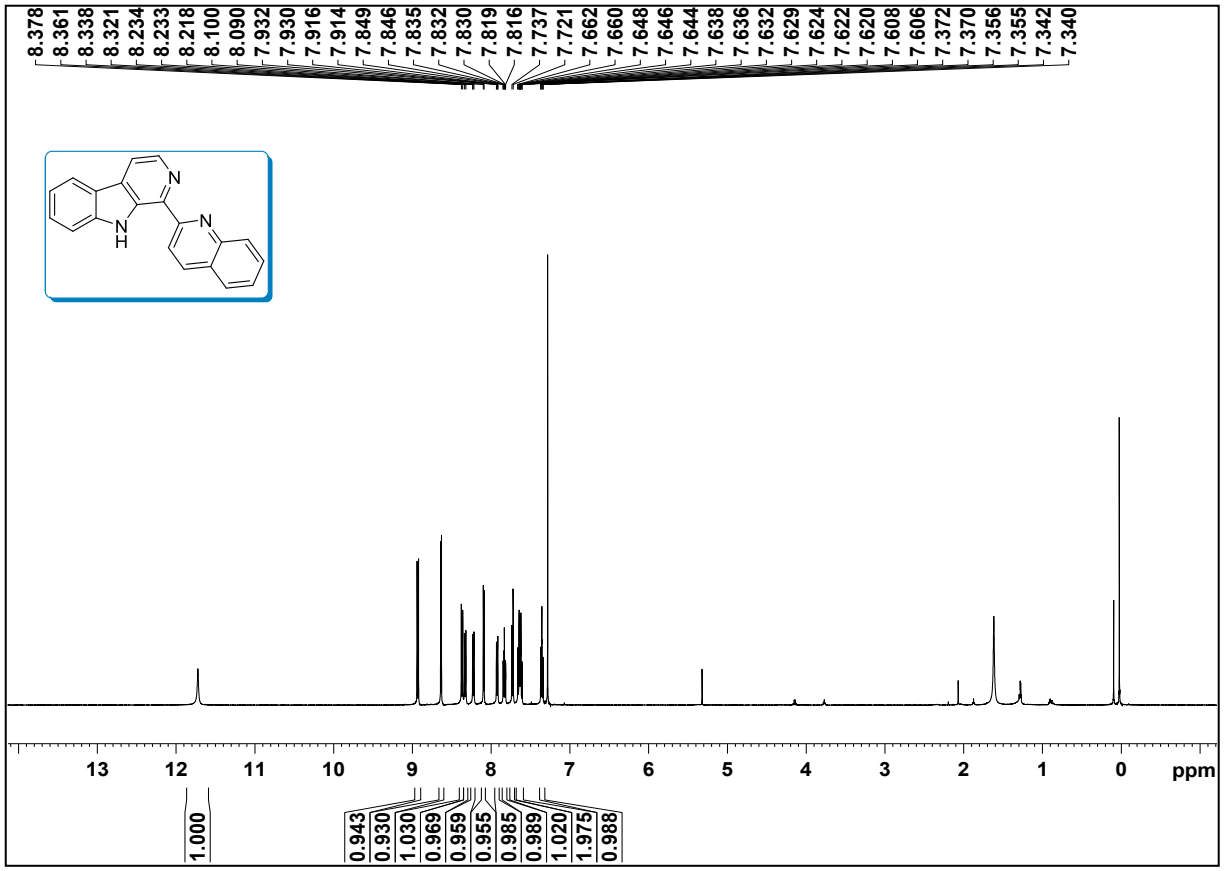



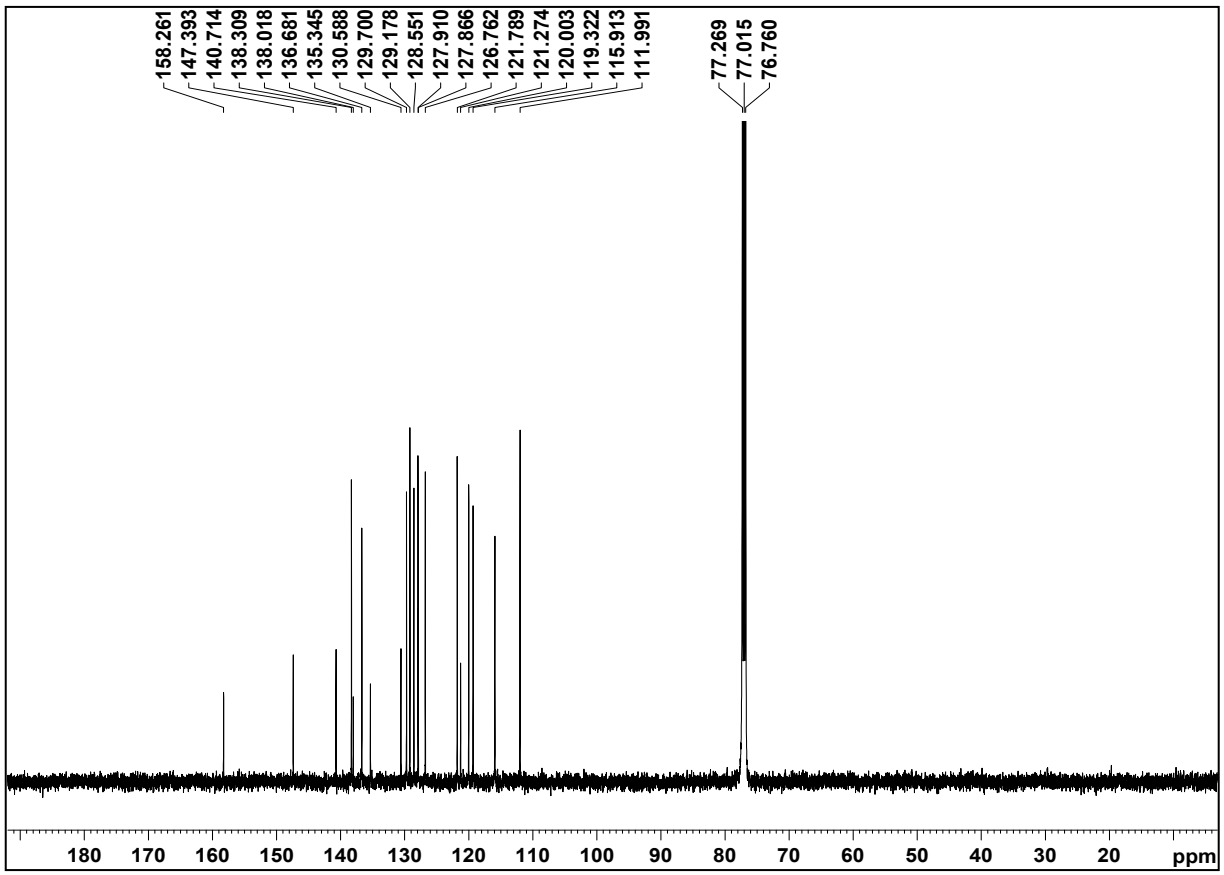
## Spectra No. 6: $^{1}H$ and $^{13}C$ spectra of compound 209



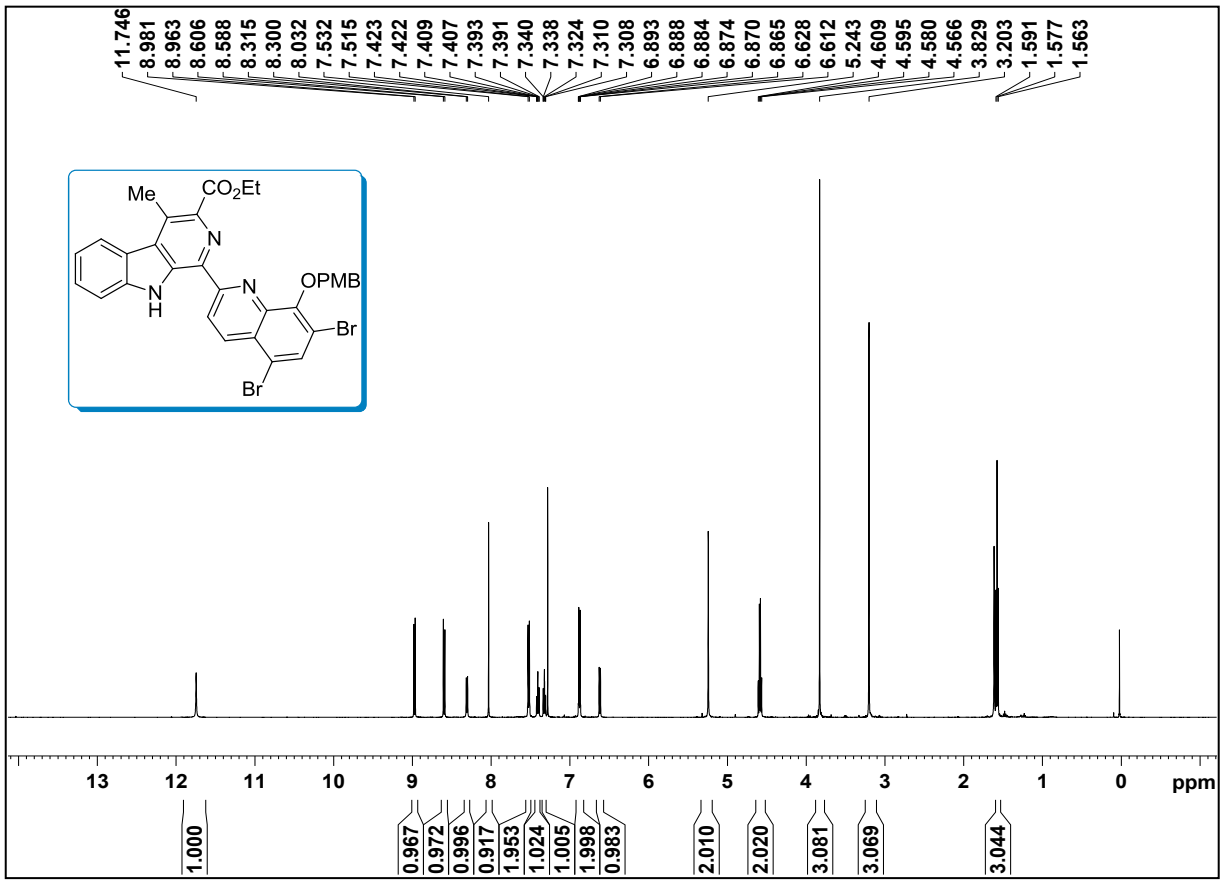



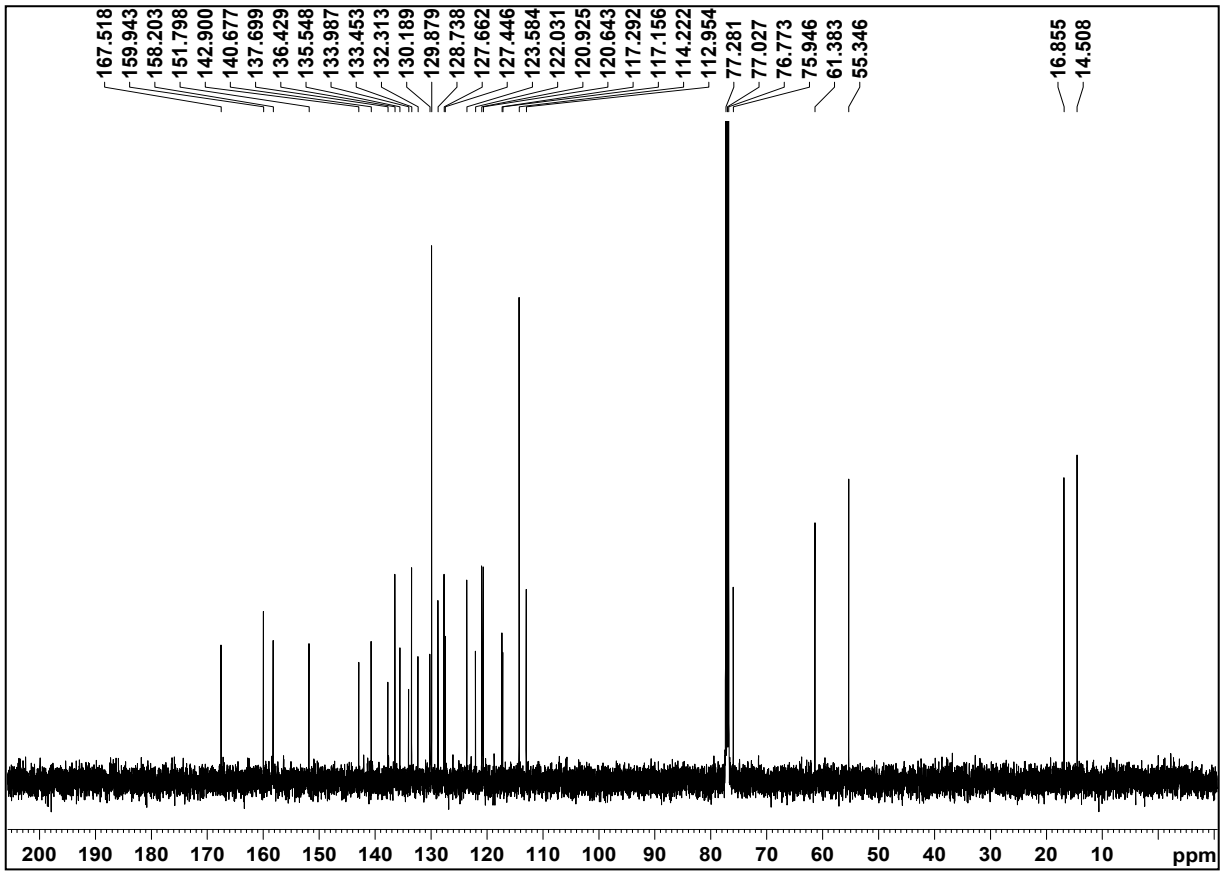
## Spectra No. 7: $^{1}H$ and $^{13}C$ spectra of Nitramarine (41)



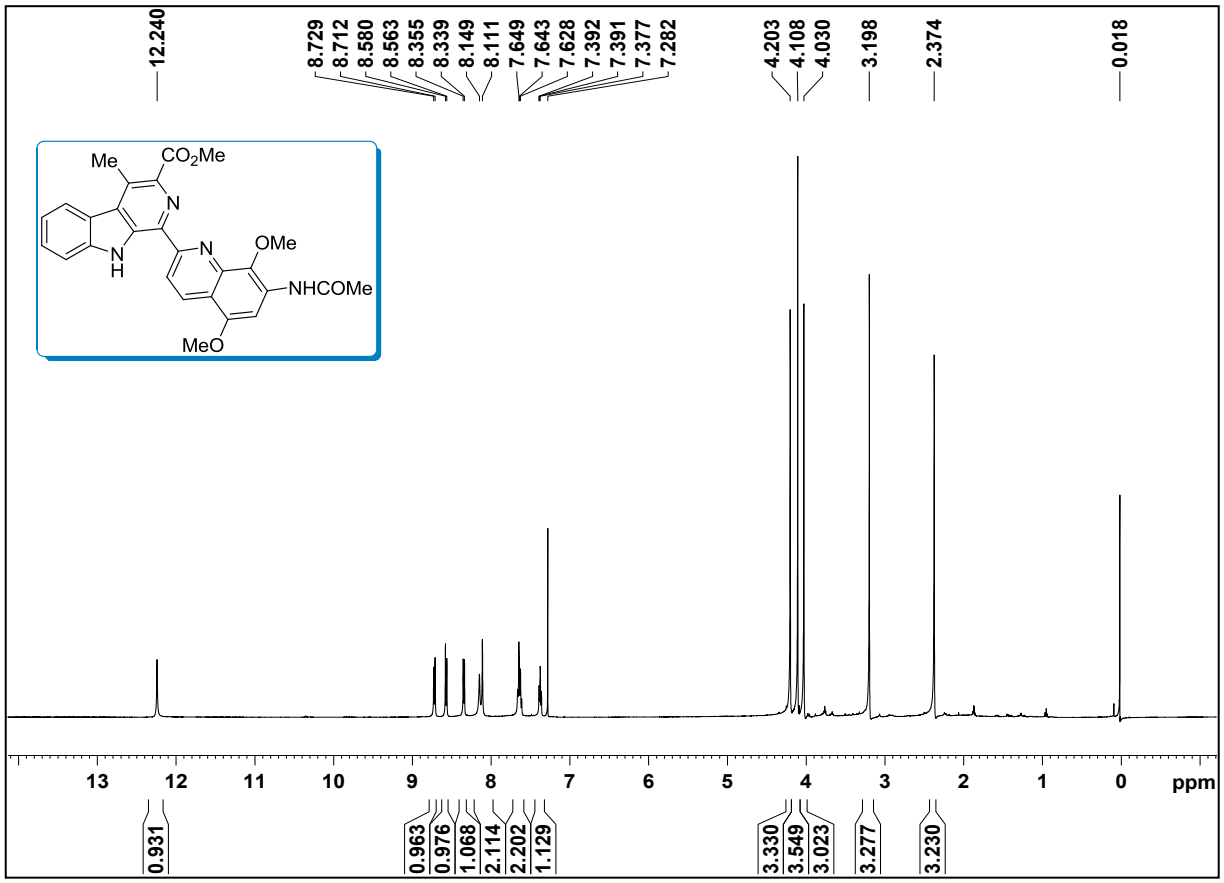



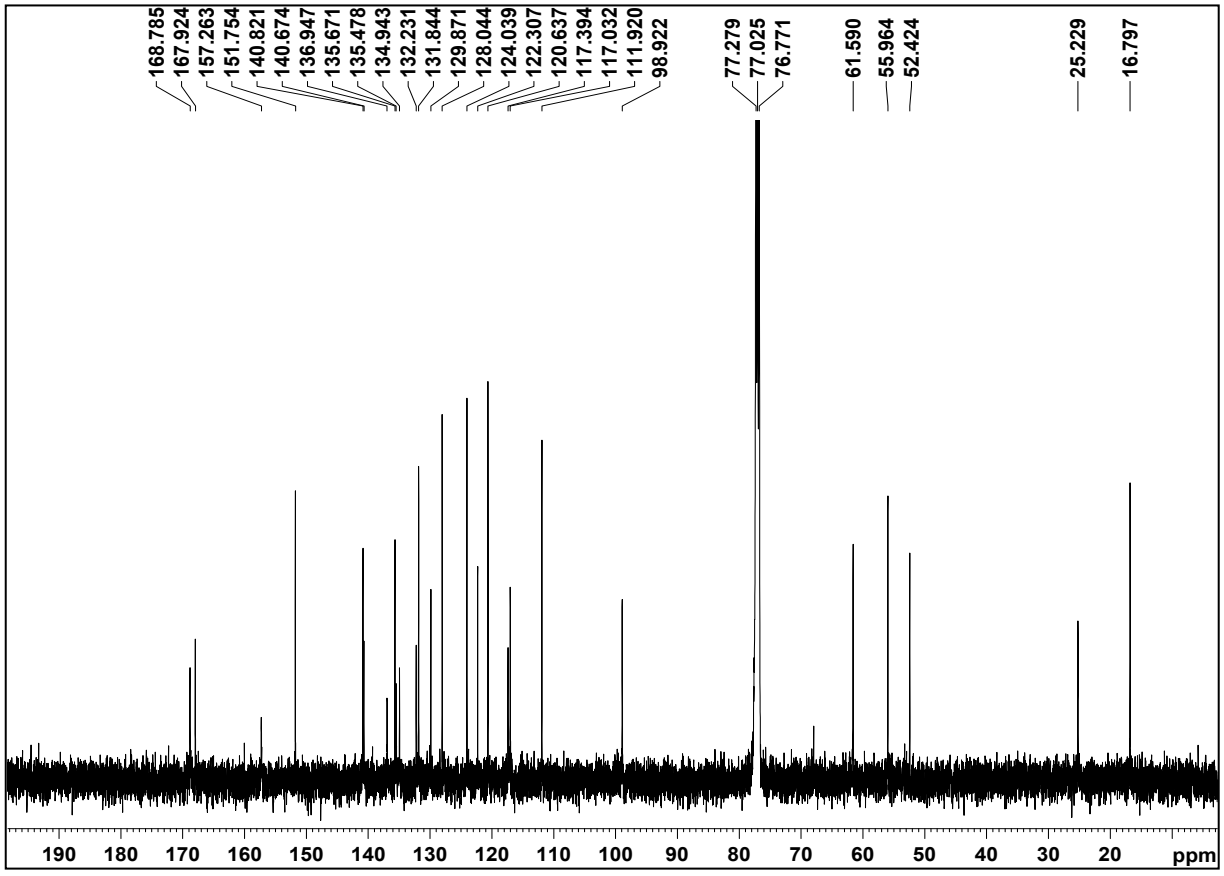
## Spectra No. 8: $^{1}H$ and $^{13}C$ spectra of compound 222



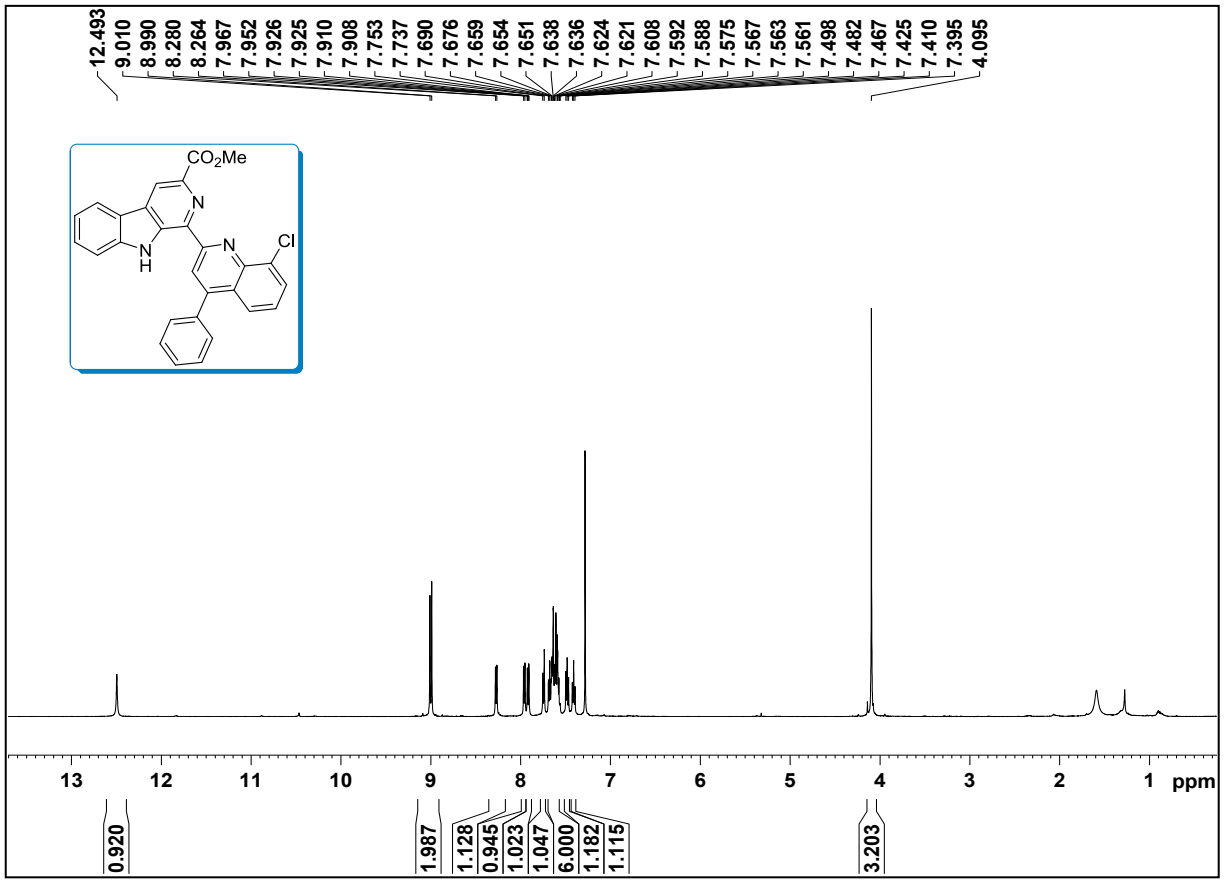



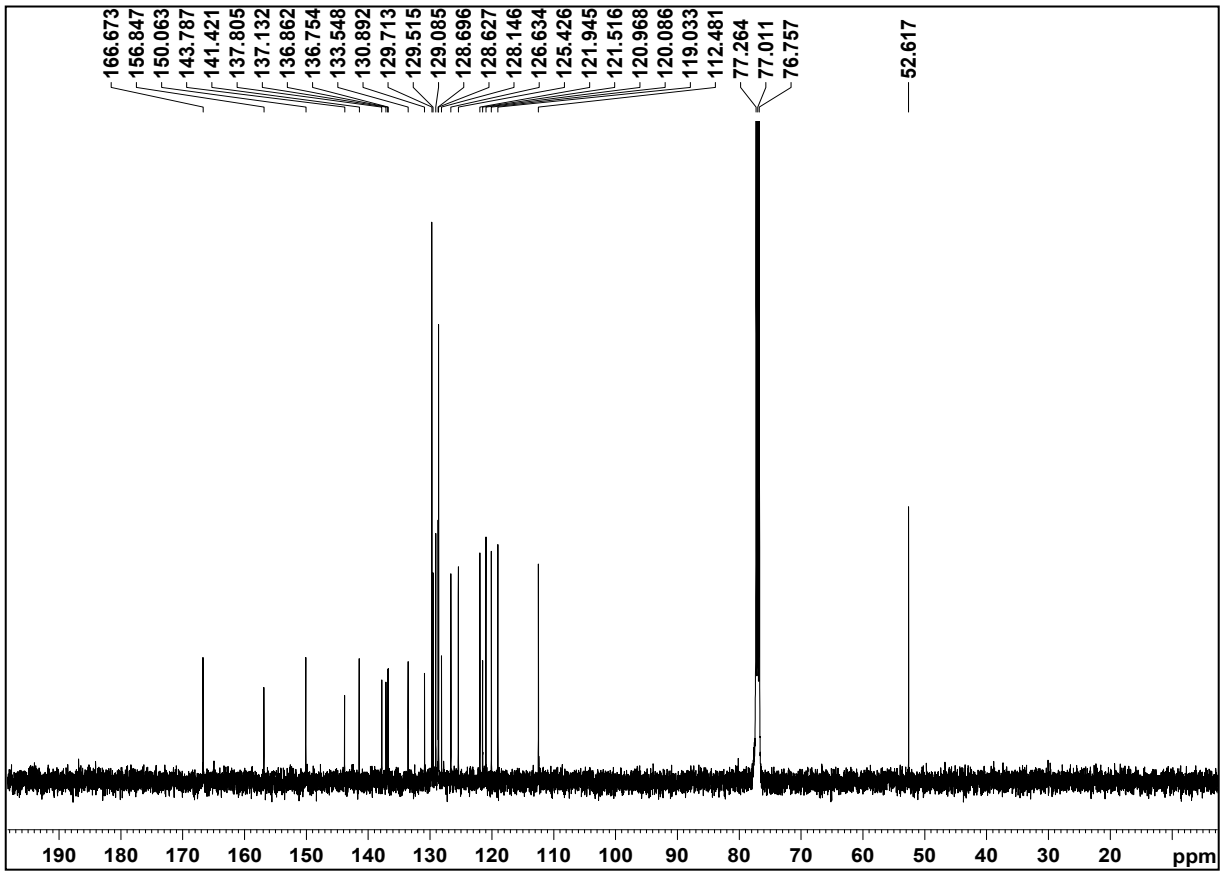
## Spectra No. 9: $^{1}H$ and $^{13}C$ spectra of compound 228



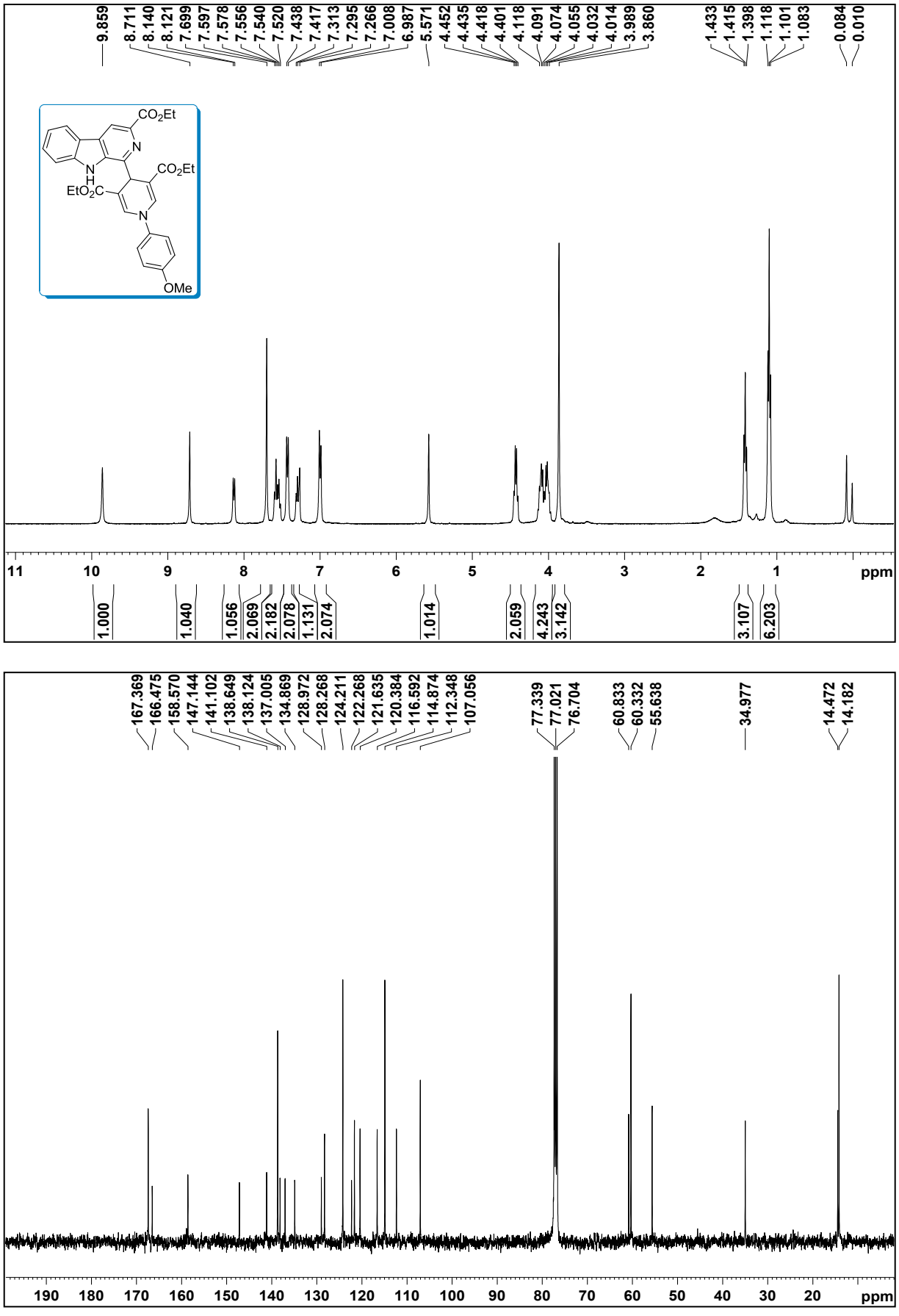



## Spectra No. 10: $^{1}H$ and $^{13}C$ spectra of compound 234u



## Spectra No. 11: $^{1}H$ and $^{13}C$ spectra of compound 236c



## 2.5. Conclusions

- It is noteworthy that all the synthetic steps of this sequence, involved readily available inexpensive materials to start with and gave good to excellent yields. The formal synthesis of lavendamycin methyl ester was accomplished using a Povarov approach that featured inexpensive catalyst with an overall yield of 51% to produce the lavenamycin methyl ester. We have also demonstrated the versatility of this approach toward the synthesis of lavendamycin analogues (**208, 208a-h**). The synthesized lavendamycin analogue (**208**) was transformed into **209**, thereby completing the formal synthesis of nitramarine (**41**).

- We have demonstrated a simple, novel and efficient method to generate a range of lavendamycin analogues (**234a-u**) via an $A^3$ coupling protocol in good yields. This methodology can be exploited to construct new analogues of lavendamycin which are of great interest in the synthetic community due to their remarkable pharmaceutical and biological properties. Moreover, we delineated here the importance of ionic liquids and their applications. New analogues of 1,4-dihydro-3,5-pyridinedicarboxylate also have been efficiently synthesized.

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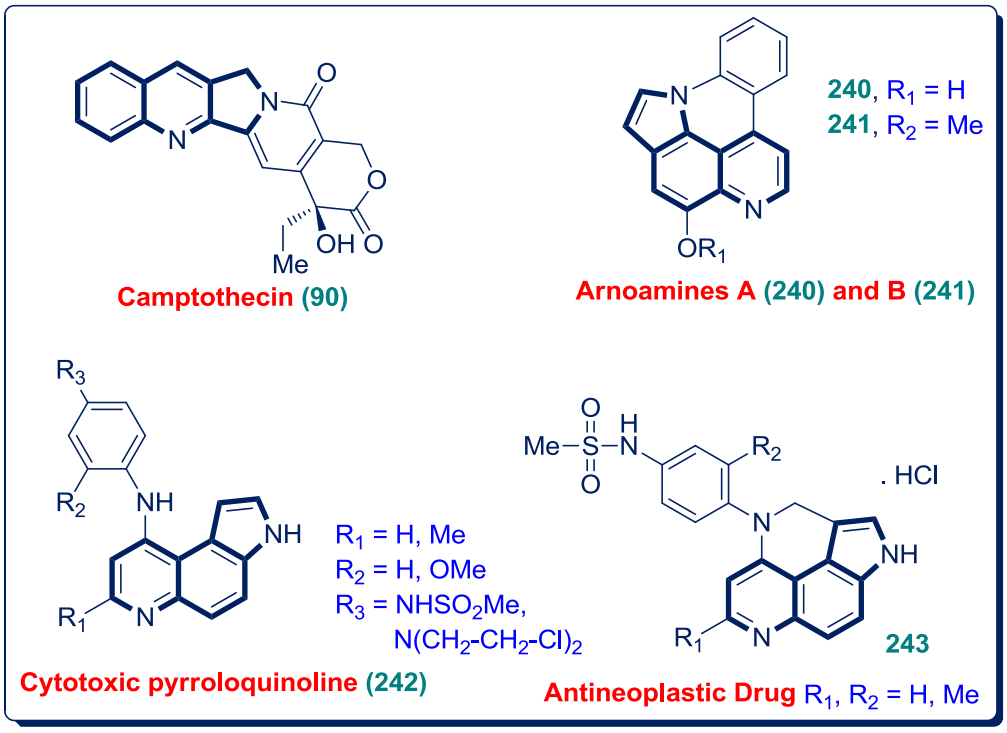
# CHAPTER 3

# Synthesis of pyrrolo[3,2-*f*]- and pyrrolo[2,3-*h*]quinoline derivatives

## 3.1. Introduction

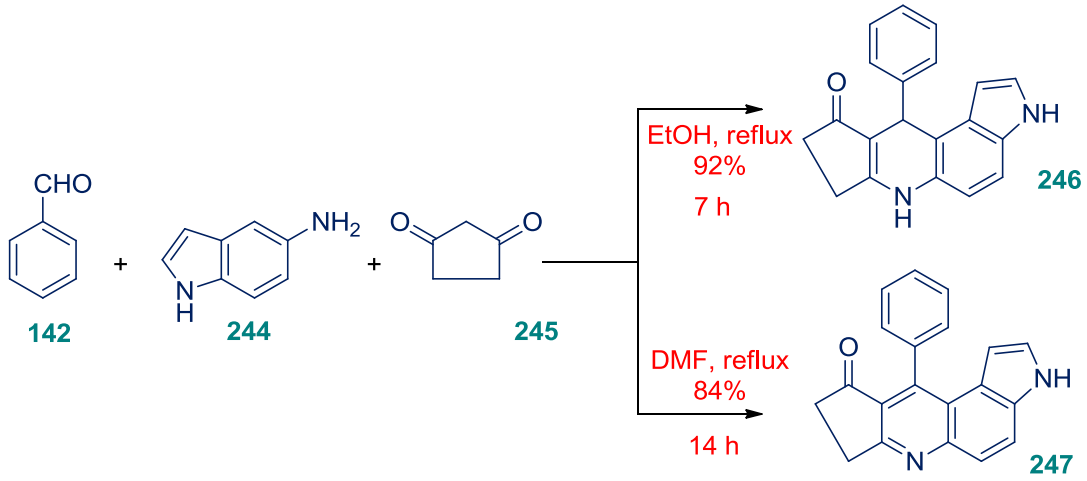
Recently, great interest has arisen in the synthesis of compounds containing a quinoline or indole moiety.[132] Pyrroloquinolines are nitrogen containing heterocyclic compounds having fused structures of pyrrole and quinoline. These important heterocyclic compounds are commonly found in natural products and biologically active compounds such as (±)-martinellic acid,[133a] ammosamides,[133b] batzelline D,[133c] mycenarubins,[133d,e] arnoamine A.[133f]

**Fig. 15**



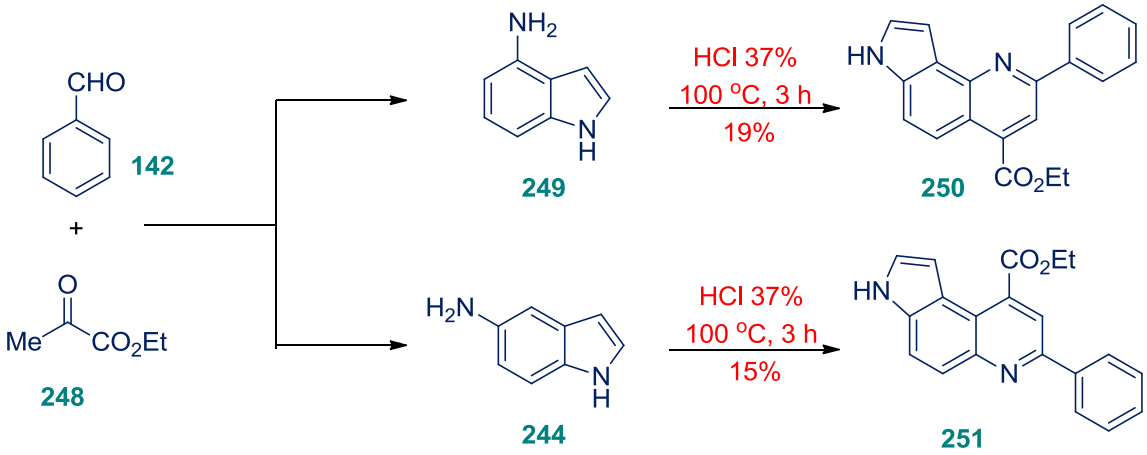

These polycyclic heterocyclic compounds exhibit pharmacological effects due to their angular aromatic tricyclic or tetracyclic system which are suitable for binding with biological targets.[133h] Particularly, we are focusing on pyrrolo[3,2-*f*]- and pyrrolo[2,3-*h*]quinoline derivatives. These pyrroloquinoles (**Fig. 15**) have a wide range of biological applications

**Eq. 44**



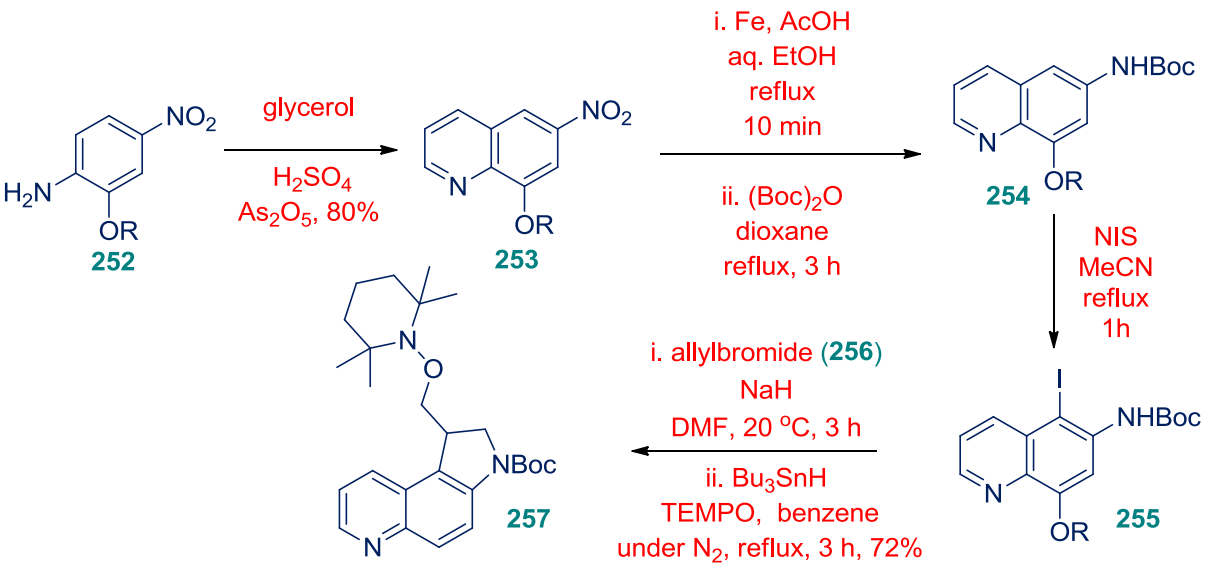

including antitopoisomerase- II,[134a] antiproliferative[134a] antineoplastic,[134b] cytotoxic, [134c] antimitotic,[134d] and vasco-relaxing[134e] activities. Wang *et al*.[135a] reported a combinatorial synthesis of pyrroloquinoline derivatives (**246** & **247**) via a three-component reaction of aromatic aldehyde **142**, indol-5-amine **244**, and 1,3-dicarbonyl **245** compounds under catalyst free conditions (**Eq. 44**).

**Eq. 45**



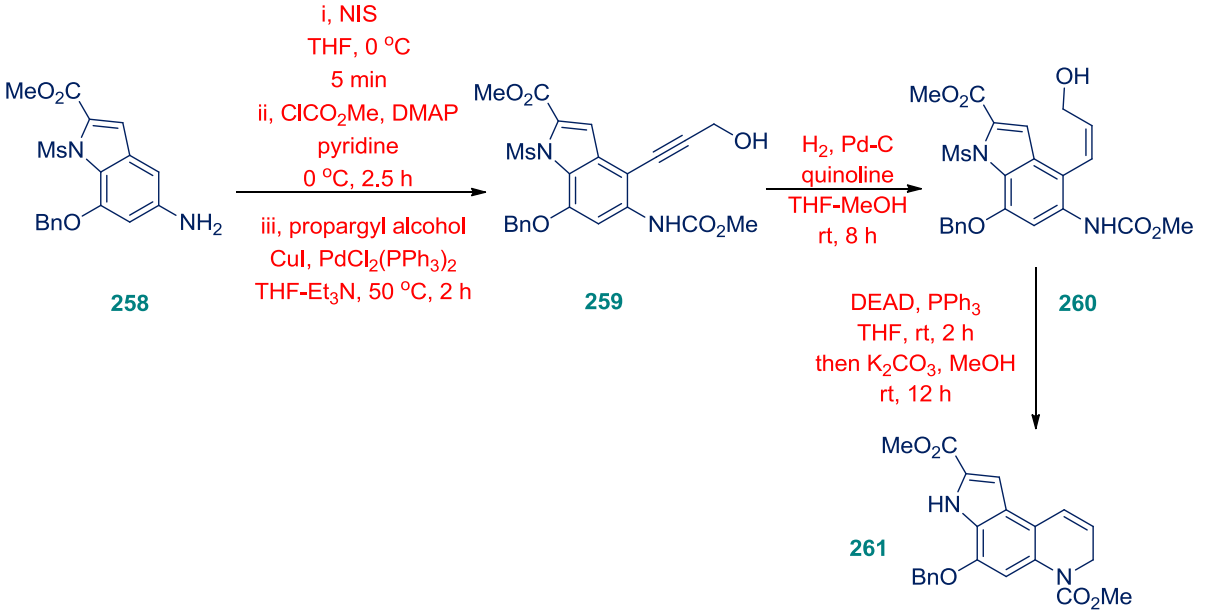

Ferlin *et al*.[135b] synthesized both pyrrolo[2,3-*h*] and [3,2-*f*] quinoline derivatives as nonsteroidal CYP19 aromatase inhibitors. They applied one pot Doebner-Miller reaction of 4-aminoindole (**249**) and 5-aminoindole (**250**) with aromatic aldehyde and ethylpyruvate in refluxing acidic ethanol to afford both pyrrolo[2,3-*h*] and pyrrolo[3,2-*f*]quinolines (**250** & **251**) in 19% and 15% yield respectively (**Eq. 45**).

**Eq. 46**




Deny *et al*.[135c] prepared dihydro-pyrrolo[3,2-*f*]quinoline (**257**) as hypoxia selective cytotoxins. They utilized Skraup reaction for the conversion of nitroaniline **252** to nitroquinoline **253**. The compound **253** was reduced into amine followed by -Boc protection afforded **254**. The compound **255** could be allylated and the allyl derivative cyclized in the presence of $Bu_3SnH$ and TEMPO to give the pyrroloquinoline **257** (**Eq. 46**).

**Eq. 47**



Hiroya *et al*.[135d] investigated the synthesis of pyrroloquinoline **261** and showed their application to the total synthesis of Duocarmycin SA, an alkaloid. The 5-aminoindole **258** substrate was iodinated at 4$^{th}$ position regioselectively, followed by carbamate protection and Sonogashira reaction with propargyl alcohol gave **259**. The acetylene was reduced to *Z*-olefin by Pd-C. Finally, the intramolecular Mitsunobu reaction using DEAD and $PPh_3$ to afford the dihydropyrroloquinoline **261** (**Eq. 47**).

Yamashkin and Yurovskaya[135e] followed the Fisher indole method, Palumbo and co-workers[135f] utilized Conrad-Limpach for the synthesis of the pyrroloquinolines. Developing a new methodology to synthesize pyrroloquinolines in a simple one-pot fashion is desirable because most of the methods for synthesizing these pyrroloquinoline derivatives require several steps and give products in poor yields. Despite several other methods to synthesize these compounds, the synthesis of these types of pyrroloquinolines from aminoindoles in a one-pot approach using typical Lewis acid is unknown at present.

## 3.2. Synthesis of pyrroloquinoline derivatives: Observation of an unexpected mechanistic pathway

Initially, our studies commenced with the reaction of 1,2,3-trimethyl-1*H*-5-indolamine (**175g**), benzaldehyde (**142a**), and phenylacetylene (**53a**) as the model substrates to optimize the reaction conditions at the reflux temperature of MeCN (**Scheme 33**). In the absence of catalyst, no desired product was observed (**Table 22**, entry 1). However, switching to La(OTf)$_3$ as the catalyst resulted in 1,2,3-trimethyl-7,9-diphenyl-3*H*-pyrrolo[3,2-*f*]quinoline (**262a**) and 7,8,9-trimethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (**263a**) in 53% overall yield (entry 2).

**Scheme 33**

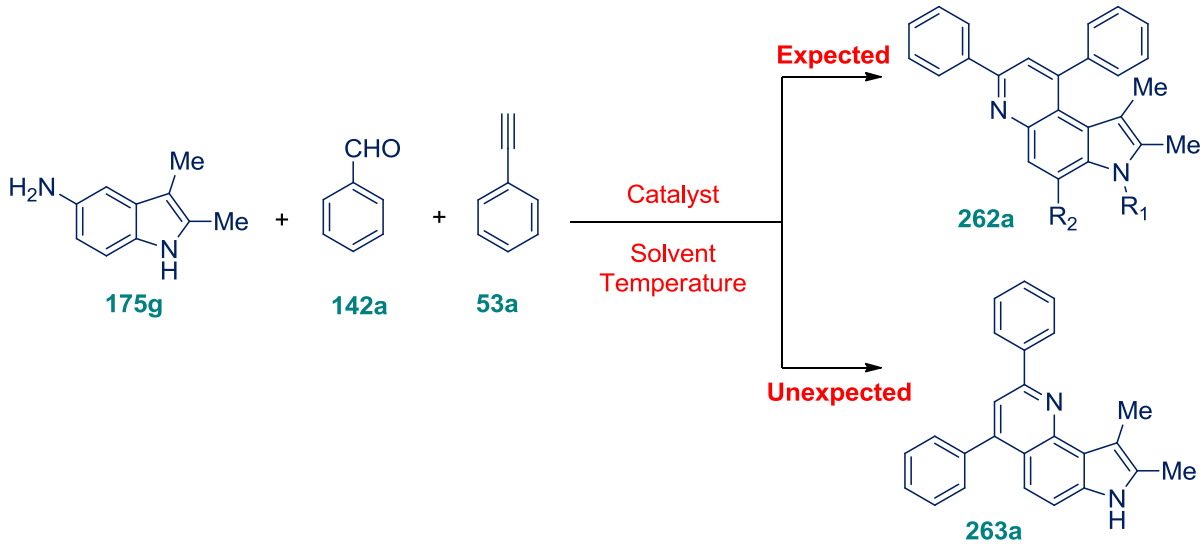


**Table 22: Optimization of the reaction conditions**

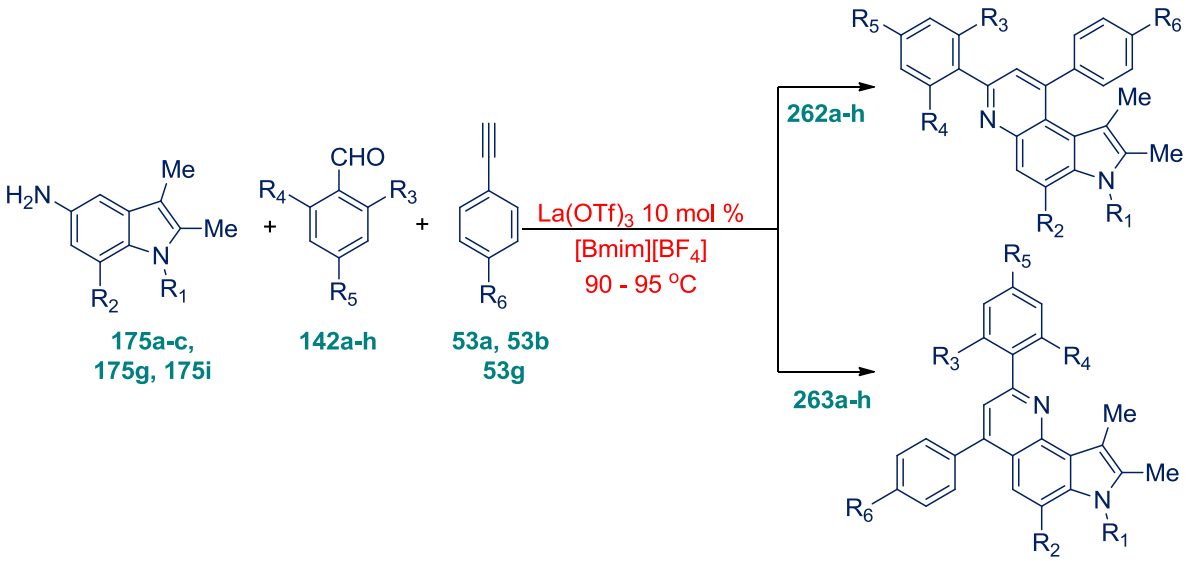
| Entry | Catalyst | Solvent | Time (h) | Yield (%) 262a/263a |
|---|---|---|---|---|
| 1 | - | MeCN | 48 | - |
| 2 | $La(OTf)_3$ | MeCN | 3 | 35/18 |
| 3 | $PdCl_2$ | MeCN | 24 | - |
| 4 | $Pd(OAc)_2$ | MeCN | 24 | - |
| 5 | CuI | MeCN | 24 | - |
| 6 | AgOTf | MeCN | 24 | - |
| 7 | $Ag_2CO_3$ | MeCN | 24 | - |
| 8 | $InCl_3$ | MeCN | 20 | 20/7 |
| 9 | $In(OTf)_3$ | MeCN | 22 | 15/8 |
| 10 | $Cu(OTf)_2$ | MeCN | 24 | - |
| 11 | TEMPO | MeCN | 24 | - |
| 12 | AIBN | MeCN | 24 | - |
| 13 | $La(OTf)_3$ | Ethanol | 10 | 28/17 |
| 14 | $La(OTf)_3$ | THF | 15 | 32/15 |
| 15 | $La(OTf)_3$ | $CH_2Cl_2$ | 10 | 29/10 |
| 16 | $La(OTf)_3$ | [Bmim][Cl] | 4 | 44/22 |
| **17** | **$La(OTf)_3$** | **[Bmim][$BF_4$]** | **3** | **46/27** |
| 18 | $La(OTf)_3$ | [Bmim][$PF_6$] | 3 | 43/20 |
| 19 | $La(OTf)_3$ | DMF | 8 | 44/20 |
| 20 | $La(OTf)_3$ | DMSO | 10 | 33/19 |
| 21 | $La(OTf)_3$ | [Bmim][$BF_4$] | 5 | 46/27 |

General conditions: aminoindole **175g** (1.0 mmol), aldehyde **142a** (1.0 mmol) and acetylene **53a** (1.0 mmol). Yield refers to column purified product. For the entries 1-12 reflux temperature of MeCN was maintained. For the entries 13-15, 19 reflux temperatures of the corresponding solvents were maintained. Temperature was maintained 90-95 °C for all the ionic liquids (entry 16-18, 21) (1.0 mL). In all entries, catalyst 10 mol% was calculated relative to the aminoindole (**175g**). For entry 21, catalyst 20 mol% was calculated.

Typical soft metal salts, such as $PdCl_2$, $Pd(OAc)_2$, AgOTf, $Ag_2CO_3$, CuI, and $Cu(OTf)_2$ were ineffective for the synthesis of these compounds (entries 3–7, and 10). Interestingly, the use of indium salts, such as $InCl_3$ and $In(OTf)_3$ moderately enhanced the yields of the products (entries 8 and 9). Radical generators such as TEMPO and AIBN were not be able to afford the desired products (entries 11 and 12). On the other hand, the use of various solvents such as EtOH, $CH_2Cl_2$, THF, DMF, and DMSO led to the formation of **262a** and **263a**

in moderate yields (entries 13–15, 19, and 20). In toluene or under neat conditions, no reaction was observed. Ionic liquids such as [Bmim][Cl], [Bmim][$BF_4$], and [Bmim][$PF_6$] were also tested (entries 16–18); the best result was obtained when [Bmim][$BF_4$] was used as solvent (entry 17). The yield of the reaction could not be increased by raising the catalytic amount of La(OTf)$_3$ from 10 mol% to 20 mol% (entry 21). When lower or higher temperatures were chosen, the product yields decreased; so that at 90–95 °C an optimum was determined. The scope of the reaction was investigated with various aromatic aldehydes **142a**–**h**, 5-aminoindoles **175a-c, 175g, 175i**, and phenylacetylenes **53a, 53b** & **53g** under the optimized reaction conditions (**Table 23**).

**Scheme 34**




For benzaldehydes **142a**–**h**, the presence of electron-donating groups (Me, OMe, (2,4,6-trimethyl)), entries 5–7, **Table 23**) and electron-withdrawing groups (F, Cl, Br, Table 2, entries 2–4, and 8) did not show significant effects on the yield of the products. However, substitution pattern on first, second, and third positions in 5-aminoindole significantly changed the reaction yield. As expected, different 1-alkyl and benzyl 2, 3-dimethyl-5-aminoindoles (entries 9 and 10) were tolerated by the reaction under the optimized conditions.

However, the electron-withdrawing group $SO_2Ph$ was not suitable for this reaction. No desired products were observed when 5-aminoindoles such as, 2,3-dimethyl-1-(phenylsulfonyl)-1*H*-indol-5-amine (**175h**), 1,2-dimethyl-1*H*-indol-5-amine (**175f**), 1*H*-indol-5-amine (**244**) and 2-methyl-1*H*-indol-5-amine (**175d**) were employed in the reaction with **142a** and **53a**. We reasoned that the absence of a methyl group at the third position of 5-aminoindoles **175h, 175f, 244** & **175d** might not facilitate the possible delocalization as

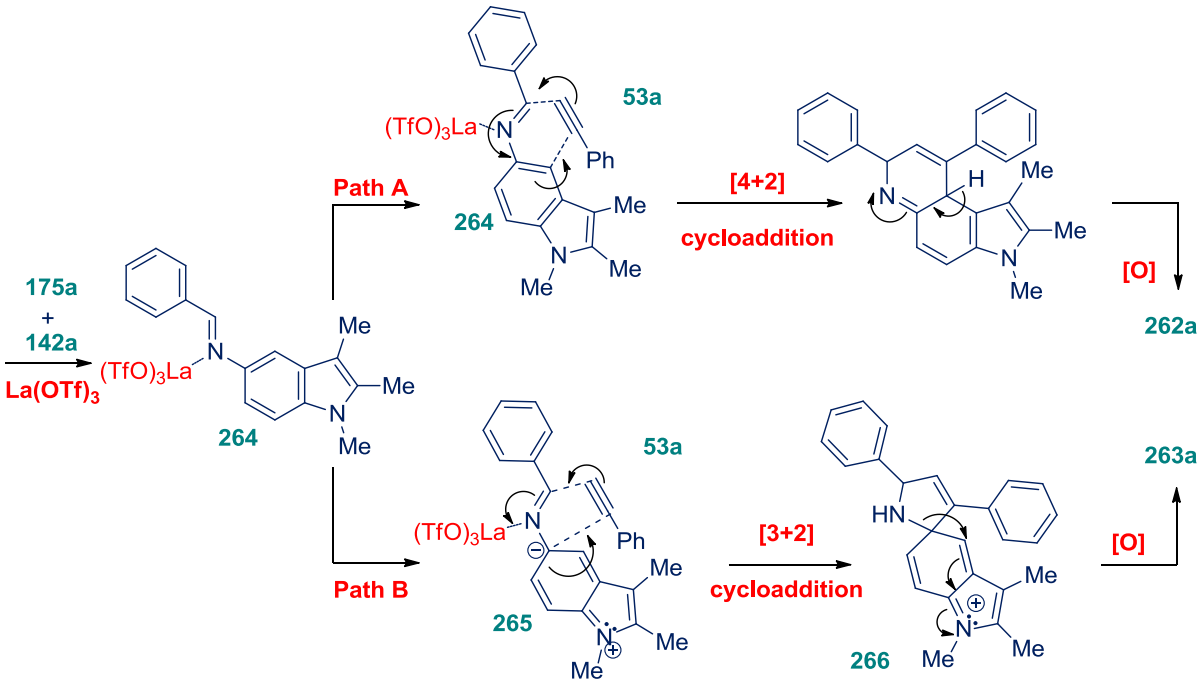
shown in **Scheme 35**. Under the optimized conditions, the scope of this reaction was examined with different acetylenes **53a, 53b, 53g**. Results are shown in **Table 23**.

**Table 23: Synthesis of various pyrroloquinoline derivatives (262a-h/263a-h)**

| Entry | Substituent | Amine | CHO | Alkyne | Time (h) | Product/ Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $R_1$ = Me; $R_{2-6}$ = H | **175g** | **142a** | **53a** | 3 | **262a/263a** (46/27) |
| 2 | $R_1$ = Me; $R_{2-4}$, $R_6$ = H; $R_5$ = F | **175g** | **142b** | **53a** | 3 | **262b/263b** (50/25) |
| 3 | $R_1$ = Me; $R_{2-4}$, $R_6$ = H; $R_5$ = Cl | **175g** | **142c** | **53a** | 3 | **262c/263c** (47/25) |
| 4 | $R_1$ = Me; $R_{2-4}$, $R_6$ = H; $R_5$ = Br | **175g** | **142d** | **53a** | 3.5 | **262d/263d** (49/23) |
| 5 | $R_1$ = Me; $R_{2-4}$, $R_6$ = H; $R_5$ = Me | **175g** | **142e** | **53a** | 4 | **262e/263e** (46/28) |
| 6 | $R_1$ = Me; $R_{2-4}$, $R_6$ = H; $R_5$ = OMe | **175g** | **142f** | **53a** | 3 | **262f/263f** (48/25) |
| 7 | $R_1$, $R_{3-5}$ = Me; $R_2$, $R_6$ = H | **175g** | **142g** | **53a** | 4 | **262g/263g** (46/24) |
| 8 | $R_3$ = Cl; $R_{1-2}$, $R_{4-6}$ = H | **175a** | **142h** | **53a** | 4 | **262h/263h** (42/23) |
| 9 | $R_1$ = $C_2H_5$; $R_{2-6}$ = H | **175b** | **142a** | **53a** | 3 | **262i/263i** (50/26) |
| 10 | $R_1$ = $CH_2Ph$; $R_{2-6}$ = H | **175c** | **142a** | **53a** | 3.5 | **262j/263j** (46/24) |
| 11 | $R_{1-6}$ = H | **175a** | **142a** | **53a** | 4.5 | **262k/263k** (42/22) |
| 12 | $R_2$ = Cl; $R_1$, $R_{3-6}$ = H | **175i** | **142a** | **53a** | 4 | **262l/263l** (45/27) |
| 13 | $R_1$ = Me; $R_{2-5}$ = H; $R_6$ = OMe | **175g** | **142a** | **53g** | 3 | **262m/263m** (50/26) |
| 14 | $R_{1-5}$ = H; $R_6$ = Me | **175a** | **142a** | **53b** | 3 | **262n/263n** (52/27) |

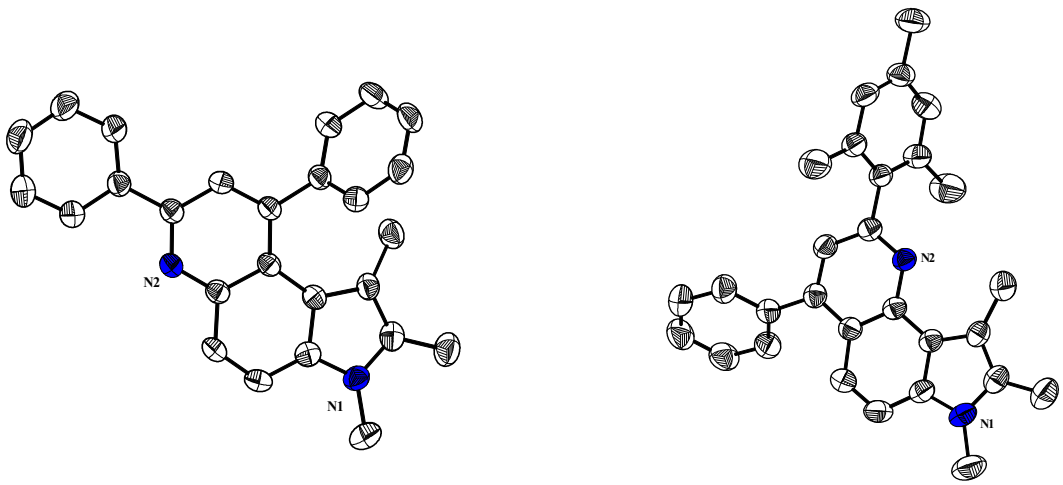
Satisfactory yields were obtained from phenylacetylenes bearing electron-donating groups [4-OMe (**53g**), 4-Me (**53b**), entries 13 and 14]. But the reaction with *o*-nitrophenylacetylene **53h**, diphenylacetylene **53i**, and alkylacetylene **53j** did not afford the corresponding pyrroloquinoline derivatives. The structure of the products **262a** and **263g** were ascertained by single crystal X-ray analysis (**Fig. 16**). According to the above experimental results, a possible reaction mechanism that accounts for the formation of **262a** and **263a** is shown in **Scheme 35**.

**Scheme 35**




Thus condensation of 5-aminoindole **175g** with benzaldehyde **142a** gives the imine **264**. Then [4+2] cycloaddition between phenylacetylene **53a** and azadiene **264** provides **262a** as major product (**path A**). Since other amines (3-aminocarbazole, aniline, and 2-naphthylamine) did not afford the unexpected product like **263a** under Lewis acid catalysis,[136] we assume that the presence of the indole moiety in the intermediate **264** would be a key role for [3+2] cycloaddition which affords the unexpected product **263a**. The formation of **263a** can be considered as a result of the five-membered intermediate **266**[137] in path B as depicted in **Scheme 35**.

**Fig. 16: ORTEP of compounds 262a and 263g**




**262a** **263g**

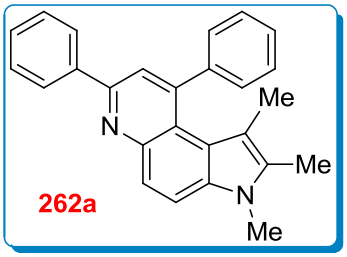
## 3.3. Experimental Section

***General procedure G:***

In a round bottom flask equipped with a magnetic stirring bar, to 1.0 mmol of 1,2,3-trimethyl-1*H*-indol-5-ylamine, 1.0 mmol of benzaldehyde, 1.0 mmol of phenylacetylene in 5 mL of ionicliquid [Bmim][$BF_4$] as solvent, was added 10 mol% of La(OTf)$_3$. Reaction mixture was stirred at 90–95 °C for 4 h. After completion of the reaction, as indicated by the TLC, water (20 mL) was added to the crude reaction mass. Then the crude was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated under the reduced pressure. Product was purified by column chromatography on silica gel.

**1,2,3-Trimethyl 7,9 diphenyl 3*H*- pyrrolo[3,2-*f*]quinoline (262a) and 7,8,9-trim ethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263a):** Compounds **262a** and **263a** were synthesized from 5-indoloamine **175g**, benzaledyde (**142a**) and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.

**Compound 262a:**




Yield: 46%

Mp: 138-140 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3055, 1556, 1026, 688

$^1$H NMR (400 MHz) δ: 8.20 (2H, d, *J* = 8.0 Hz), 7.94 (1H, d, *J* = 8.0 Hz), 7.72 (1H, s), 7.67 (1H, d, *J* = 8.0 Hz), 7.52-7.54 (2H, m), 7.46-7.50 (2H, m), 7.38 (4H, m), 3.60 (3H, s), 2.19 (3H, s), 1.20 (3H, s)

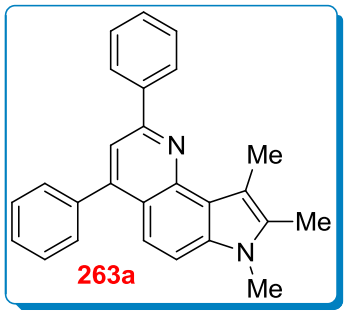
$^{13}$C NMR (100 MHz) δ: 152.7, 147.4, 147.1, 144.2, 139.9, 134.1, 132.8, 130.1, 129.3, 128.8, 128.3, 127.6, 127.4, 121.0, 120.7, 120.0, 114.5, 111.2 (aromatic C), 30.1, 12.0, 10.5 (aliphatic C)

LCMS (m/z): 363 $(M+H)^+$

Anal. calcd. for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73%

Found: C, 86.21; H, 6.18; N, 7.65%

**Compound 263a:**




Yield: 27%

Mp: 200-202 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3042, 1558, 767, 692

$^{1}H$ NMR (400 MHz) δ: 8.38 (2H, d, *J* = 7.6 Hz), 7.78 (1H, s), 7.59-7.61 (3H, m), 7.50-7.56 (5H, m), 7.40-7.46 (2H, m), 3.78 (3H, s), 2.9 (3H, s), 2.48 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 153.8, 148.9, 145.7, 140.5, 140.3, 135.2, 131.8, 129.8, 128.8, 128.7, 128.4, 127.9, 127.3, 122.4, 120.9, 117.8, 115.5, 111.2, 111.1 (aromatic C), 29.4, 12.4, 10.1 (aliphatic C)

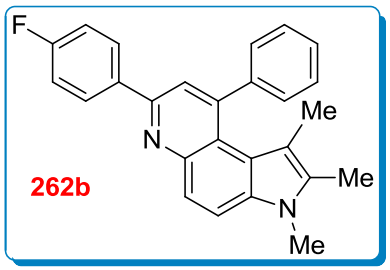
LCMS (m/z): 363 $(M+H)^{+}$

Anal. calcd. for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73%

Found: C, 86.05; H, 6.18; N, 7.68%

**4-(1,2,3-Trimethyl-9-phenyl-3*H*-pyrrolo[3,2-*f*]quinolin 7-yl)phenyl fluoride (262b) and 2-(4-fluorophenyl)-7,8,9-trimethyl-4-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263b):** Compounds **262b** and **263b** were synthesized from 5-indoloamine **175g**, benzaledyde **142b** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.

**Compound 262b:**




Yield: 50%

Mp: 197-199 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3061, 1599, 1228, 590

$^{1}H$ NMR (400 MHz) δ: 8.23 (2H, t, *J* = 8 Hz), 7.93 (1H, d, *J* = 8.9 Hz), 7.75-7.71 (2H, m), 7.57 (2H, d, *J* = 6.6 Hz), 7.42-7.46 (3H, m), 7.21 (2H, t, *J* = 8.6 Hz), 3.76(3H, s), 2.27 (3H, s), 1.26 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 163.4, 151.6, 147.4, 147.0, 144.1, 136.16, 134.0, 132.8, 129.2, 129.0, 128.9, 128.7, 127.6, 122.9, 120.8, 120.69,

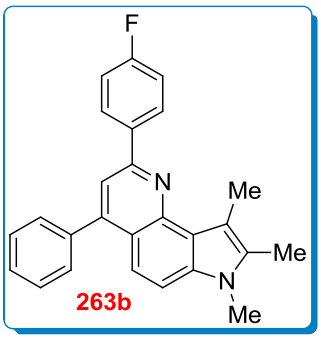
119.5, 115.6, 115.4, 114.5, 111.1 (aromatic C), 30.0, 11.9, 10.4 (aliphatic C)

LCMS (m/z): 381 $(M+H)^+$

Anal. calcd. for $C_{26}H_{21}FN_2$: C, 82.08; H, 5.56; N, 7.36%

Found: C, 81.91; H, 5.62; N, 7.25%

**Compound 263b:**




Yield: 25%

Mp: 209-211 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 1560, 1095, 704, 503

$^1H$ NMR (400 MHz) δ: 8.30 (2H, t, *J* = 7.3 Hz), 7.67 (1H, s), 7.46-7.55 (6H, m), 7.33 (1H, d, *J* = 8.9 Hz), 7.17 (2H, t, *J* = 8.6 Hz), 3.68 (3H, s), 2.91 (3H, s), 2.40 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 163.5, 152.8, 148.9, 145.6, 140.2, 136.6, 135.2, 131.9, 129.7, 129.0, 128.9, 128.4, 127.9, 122.3, 120.7, 117.8, 115.6, 115.4, 115.1, 111.1 (aromatic C), 29.3, 12.4, 10.1 (aliphatic C)

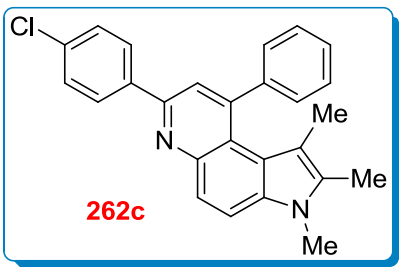
LCMS (m/z): 381 $(M+H)^+$

Anal. calcd. for $C_{26}H_{21}FN_2$: C, 82.08; H, 5.56; N, 7.36%

Found: C, 82.21; H, 5.49; N, 7.45%

**4 (1,2,3- Trimethyl 9 phenyl 3*H* -pyrrolo[3,2-*f*]quinolin 7-yl)phenyl chloride (262c) and 2-(4-chlorophenyl)-7,8,9-trimethyl-4-phenyl-7*H*-pyrrolo[2,3-h]quinoline (263c):** Compounds **262c** and **263c** were synthesized from 5-indoloamine **175g**, benzaledyde **142c** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.

**Compound 262c:**




Yield: 47%

Mp: 177-179 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3055, 1591, 835, 617

$^1H$ NMR (400 MHz) δ: 8.18 (2H, d, *J* = 7.8 Hz), 7.92 (1H, d, *J* = 8.8 Hz), 7.70-7.74 (2H, m), 7.56 (2H, d, *J* = 6.1 Hz), 7.44-7.49 (5H, m), 3.77(3H, s), 2.27 (3H, s), 1.25 (3H, s)

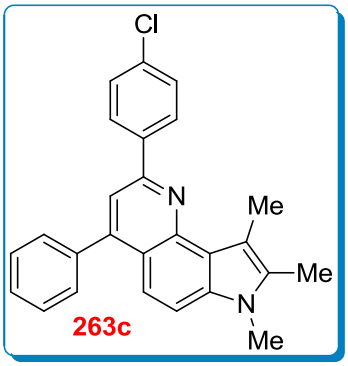
$^{13}C$ NMR (100 MHz) δ: 151.3, 147.4, 147.1, 144.1, 138.4, 134.6, 134.1, 132.8, 129.2, 128.9, 128.5, 127.7, 122.9, 121.1, 120.7, 119.5, 114.7, 111.2 (aromatic C), 30.10, 11.96, 10.49 (aliphatic C)

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

Anal. calcd. for $C_{26}H_{21}ClN_2$: C, 78.68; H, 5.33; N, 7.06%

Found: C, 78.55; H, 5.41; N, 6.95%

**Compound 263c:**




Yield: 25%

Mp: 140-142 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2922, 1562, 1087, 702

$^1H$ NMR (400 MHz) δ: 8.31 (2H, t, *J* = 8.2 Hz), 7.71 (1H, s), 7.48-7.59 (8H, m), 7.42 (1H, d, *J* = 9.0 Hz), 3.79 (3H, s), 2.94 (3H, s), 2.48 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 152.6, 149.0, 145.6, 140.1, 138.9, 135.2, 134.7, 131.9, 129.7, 128.8, 128.5, 128.4, 127.9, 122.3, 120.9, 117.8, 115.2, 111.2, 111.1 (aromatic C), 30.0, 12.3, 10.2 (aliphatic C)

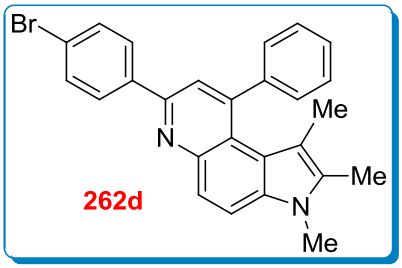
LCMS (m/z): 397 $(M+H)^+$

Anal. calcd. for $C_{26}H_{21}ClN_2$: C, 78.68; H, 5.33; N, 7.06%

Found: C, 78.51; H, 5.26; N, 7.18%

**4-(1,2,3-Trimethyl-9-phenyl-3*H*-pyrrolo[3,2-*f*]quinolin-7-yl)phenyl bromide (262d) and 2-(4-bromophenyl)-7,8,9-trimethyl-4-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263d):** Compounds **262d** and **263d** were synthesized from 5-indoloamine **175g**, benzaledyde **142d** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.

**Compound 262d:**




Yield: 49%

Mp: 180-182 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3049, 1585, 1074, 785

$^1$H NMR (400 MHz) δ: 8.12 (2H, d, *J* = 8.5 Hz), 7.91 (1H, d, *J* = 9 Hz), 7.70-7.74 (2H, m), 7.63 (2H, d, *J* = 8.5 Hz), 7.55-7.57 (2H, m), 7.41-7.47 (3H, m), 3.77(3H, s), 2.27 (3H, s), 1.24 (3H, s)

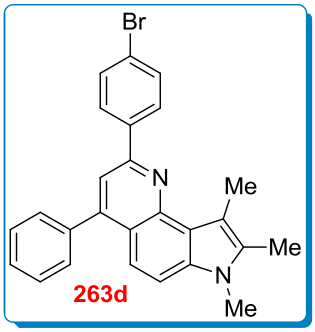
$^{13}$C NMR (100 MHz) δ: 151.3, 147.4, 147.1, 144.1, 138.9, 134.2, 132.9, 131.8, 129.2, 128.8, 127.7, 123.0, 121.1, 120.7, 119.4, 114.6, 111.2 (aromatic C), 30.1, 11.9, 10.5 (aliphatic C)

LCMS (m/z): 441 $(M+H)^+$, 442 $(M+2)^+$

Anal. calcd. for $C_{26}H_{21}BrN_2$: C, 70.75; H, 4.80; N, 6.35%

Found: C, 70.65; H, 4.76; N, 6.25%

**Compound 263d:**




Yield: 23%

Mp: 110-112 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2918, 1736, 1464, 491

$^1$H NMR (400 MHz) δ: 8.24 (2H, d, *J* = 8.4 Hz), 7.72 (1H, s); 7.66 (2H, d, *J* = 10.7 Hz), 7.52-7.60 (6H, m), 7.41(1H, d, *J* = 9 Hz), 3.75 (3H, s), 2.96 (3H, s), 2.47 (3H, s)

$^{13}$C NMR (100 MHz) δ: 152.6, 149.0, 145.6, 140.1, 139.3, 138.1, 135.2, 132.2, 131.9, 131.8, 129.9, 129.7, 128.8, 128.4, 127.9, 123.1, 122.3, 120.9, 117.7, 115.1, 111.3, 111.1 (aromatic C), 29.9, 12.4, 10.1 (aliphatic C)

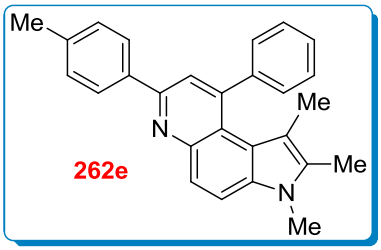
LCMS (m/z): 441 $(M+H)^+$, 442 $(M+2)^+$

Anal. calcd. for $C_{26}H_{21}BrN_2$: C, 70.75; H, 4.80; N, 6.35%

Found: C, 70.62; H, 4.86; N, 6.28%

**1,2,3-Trimethyl-7-(4-methylphenyl)-9-phenyl-3*H*-pyrrolo[3,2-*f*]quinoline (262e) and 7,8.9-trimethyl-2-(4-methylphenyl)-4-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263e):** Compounds **262e** and **263e** were synthesized from 5-indoloamine **175g**, benzaledyde **142e** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 4% ethyl acetate in hexanes.

**Compound 262e:**




Yield: 46%

Mp: 147-149 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3040, 1591, 1182, 787

$^1$H NMR (400 MHz) δ: 8.14 (2H, d, *J* = 8.0 Hz), 7.94 (1H, d, *J* = 9 Hz), 7.72-7.74 (2H, m), 7.57-7.59 (2H, m), 7.41-7.47 (3H, m), 7.34 (2H, d, *J* = 9.7 Hz), 3.77(3H, s), 2.44 (3H, s), 2.28 (3H, s), 1.25 (3H, s)

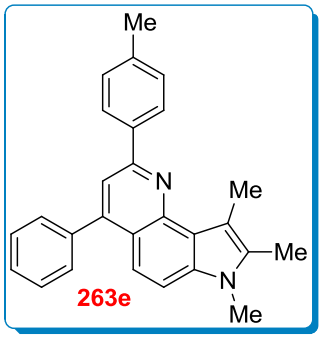
$^{13}$C NMR (100 MHz) δ: 152.7, 147.4, 146.8, 144.3, 138.5, 137.2, 134.0, 132.7, 129.5, 129.2, 128.7, 127.5, 127.1, 123.1, 120.8, 120.7, 119.7, 114.3, 111.1 (aromatic C), 30.1, 21.4, 11.9, 10.5 (aliphatic C)

LCMS (m/z): 377 $(M+H)^+$

Anal. calcd. for $C_{27}H_{24}N_2$: C, 86.13; H, 6.43; N, 7.44%

Found: C, 86.21; H, 6.55; N, 7.38%

**Compound 263e:**




Yield: 28%

Mp: 109-112 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 2912, 1176

$^1$H NMR (400 MHz) δ: 8.28 (2H, d, *J* = 8.0 Hz), 7.75 (1H, s), 7.60 (2H, d, *J* = 6.8 Hz), 7.50-7.57 (4H, m), 7.34-7.41 (3H, m), 3.78 (3H, s), 2.98 (3H, s), 2.48 (3H, s), 2.46(3H, s)

$^{13}$C NMR (100 MHz) δ: 153.9, 148.7, 145.7, 140.3, 138.7, 137.7, 135.2, 131.7, 129.7, 129.4, 128.4, 127.8, 127.2, 122.4, 120.7, 117.8, 115.4, 111.1, 110.8 (aromatic C), 29.9, 21.4, 12.3, 10.1 (aliphatic C)

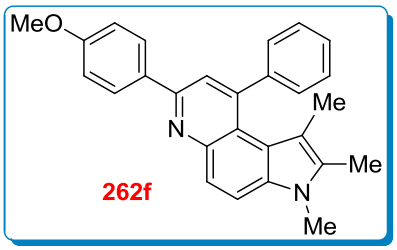
LCMS (m/z): 377 $(M+H)^+$

Anal. calcd. for $C_{27}H_{24}N_2$: C, 86.13; H, 6.43; N, 7.44%

Found: C, 86.05; H, 6.37; N, 7.56%

**7-(4-Methoxyphenyl)-1,2,3-trimethyl-9-phenyl-3*H*-pyrrolo[3,2-*f*]quinoline (262f) and 2-(4-methoxyphenyl)-7,8,9-trimethyl-4-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263f):** Compounds **262f** and **263f** were synthesized from 5-indoloamine **175g**, benzaledyde **142f** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 4% ethyl acetate in hexanes.

**Compound 262f:**




Yield: 48%

Mp: 140-142 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3047, 2835, 1174, 787, 597

$^1$H NMR (400 MHz) δ: 8.18 (2H, d, *J* = 7.7 Hz), 7.92 (1H, d, *J* = 8.8 Hz), 7.69-7.73 (2H, m), 7.57 (2H, d, *J* = 7.4 Hz), 7.40-7.46 (3H, m), 7.02 (2H, d, *J* = 7.7 Hz), 3.88(3H, s), 3.77 (3H, s), 2.27 (3H, s), 1.24 (3H, s)

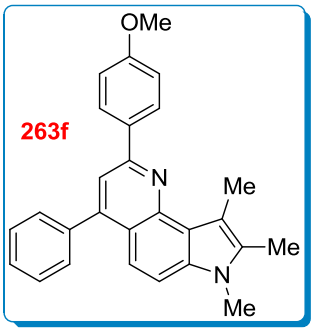
$^{13}$C NMR (100 MHz) δ: 160.2, 152.4, 147.3, 146.8, 144.2, 133.9, 132.6, 129.2, 128.6, 128.4, 127.4, 122.9, 120.7, 120.5, 119.4, 114.2, 114.0, 113.3, 110.9 (aromatic C), 55.3, 29.9, 11.9, 10.4 (aliphatic C)

LCMS (m/z): 393 $(M+H)^+$

Anal. calcd. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%

Found: C, 82.71; H, 6.08; N, 7.07%

**Compound 263f:**




Yield: 25%

Mp: 109-112 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 2916, 1400, 702

$^1$H NMR (400 MHz) δ: 8.34 (2H, d, *J* = 8.2 Hz), 7.72 (1H, s), 7.50-7.60 (6H, m), 7.38 (1H, d, *J* = 8.8 Hz), 7.08 (2H, d, *J* = 8.2 Hz), 3.91 (3H, s), 3.77 (3H, s), 2.98 (3H, s), 2.47(3H, s)

$^{13}$C NMR (100 MHz) δ: 160.4, 153.6, 148.7, 145.7, 140.4, 135.2, 133.2, 131.6, 129.7, 128.5, 128.4, 127.8, 122.3, 120.4, 117.8, 115.0, 114.1, 111.1, 110.6 (aromatic C), 55.4, 29.9, 12.4, 12.4, 10.1 (aliphatic C)

LCMS (m/z): 393 $(M+H)^+$

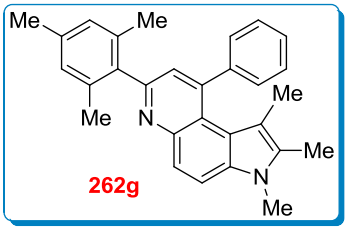
Anal. calcd. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%

Found: C, 82.56; H, 6.21; N, 7.22%

**7-(Mesityl)-1,2,3-trimethyl-9-phenyl-3*H*-pyrrolo[3,2-*f*]quinoline (262g) and 2-mesityl-7,8,9-trimethyl-4-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263g):**

Compounds **262g** and **263g** were synthesized from 5-indoloamine **175g**, benzaledyde **142g** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.

**Compound 262g:**




Yield: 46%

Mp: 190-192 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3030, 2918, 1342, 1174, 692

$^1$H NMR (400 MHz) δ: 7.91 (1H, d, *J* = 8.8 Hz), 7.74 (1H, d, *J* = 15.6 Hz), 7.55 (2H, d, *J* = 6.7 Hz), 7.40-7.42 (3H, m), 7.28 (1H, s), 6.97 (2H, s), 3.8 (3H, s), 2.35 (3H, s), 2.29 (3H, s), 2.12 (6H, s), 1.2 (3H, s)

$^{13}$C NMR (100 MHz) δ: 155.4, 147.1, 146.1, 143.7, 137.9, 137.1, 135.9, 133.9, 132.7, 129.0, 128.5, 128.2, 127.4, 123.2, 122.6, 120.5,

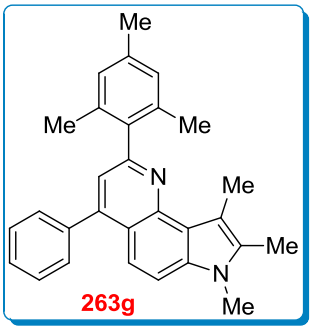
120.1, 113.9, 110.9 (aromatic C), 29.9, 21.0, 20.2, 11.8, 10.3 (aliphatic C)

LCMS (m/z): 405 $(M+H)^+$

Anal. calcd. for $C_{29}H_{28}N_2$: C, 86.10; H, 6.98; N, 6.92%

Found: C, 85.92; H, 6.94; N, 7.05%

**Compound 263g:**




Yield: 24%

Mp: 179-181 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2914, 1770, 1195, 628

$^1H$ NMR (400 MHz) δ: 7.66-7.72 (3H, m), 7.57-7.61 (2H, m), 7.50-7.55 (2H, m), 7.29 (1H, s), 7.09 (2H, s), 3.82 (3H, s), 2.85 (3H, s), 2.49 (3H, s), 2.46 (3H, s), 2.3 (6H, s)

$^{13}C$ NMR (100 MHz) δ: 157.2, 147.7, 145.7, 140.0, 139.3, 136.9, 136.3, 135.1, 131.7, 129.9, 128.44, 128.40, 127.9, 122.3, 120.3, 119.9, 117.9, 111.3, 110.9 (aromatic C), 29.9, 21.3, 20.7, 12.1, 10.1 (aliphatic C)

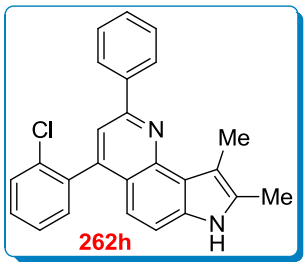
LCMS (m/z): 393 $(M+H)^+$

Anal. calcd. for $C_{29}H_{28}N_2$: C, 86.10; H, 6.98; N, 6.92%

Found: C, 86.85; H, 7.12; N, 6.85%

**2-(1,2-Dimethyl-9-phenyl-3*H*-pyrrolo[3,2-*f*]quinolin-7yl)phenyl chloride (262h) and 2-(2-chlorophenyl)-8,9-dimethyl-4-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263h):** Compounds **262h** and **263h** were synthesized from 5-indoloamine **175a**, benzaledyde **142h** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 6% ethyl acetate in hexanes.

**Compound 262h:**




Yield: 42%

Mp: 167-169 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2556, 1570, 1595, 748

$^1H$ NMR (400 MHz) δ: 10.88 (1H, s), 7.74 (1H, d, *J* = 7.5 Hz), 7.67-7.70 (2H, m), 7.51 (1H, s), 7.42-7.47 (3H, m), 7.27-7.38 (5H, m), 2.21 (3H, s), 1.12 (3H, s)

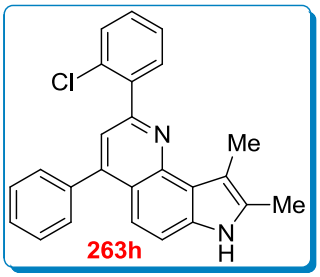
$^{13}C$ NMR (100 MHz) δ: 151.6, 147.0, 145.7, 143.6, 139.7, 133.4, 132.3, 131.9, 130.0, 129.6, 129.2, 128.8, 127.3, 127.2, 123.0, 122.1, 120.9, 120.8, 117.1, 111.0 (aromatic C), 11.9, 11.5 (aliphatic C)

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

Anal. calcd. for $C_{25}H_{19}ClN_2$: C, 78.42; H, 5.00; N, 7.32%

Found: C, 78.36; H, 4.93; N, 7.25%

**Compound 263h:**



263h

Yield: 23%

Mp: 189-191 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3123, 2343, 1765, 683

$^1H$ NMR (400 MHz) δ: 8.15 (1H, s), 7.97 (1H, dd, *J* = 1.4, 7.6 Hz), 7.71 (1H, s), 7.57-7.61 (2H, m), 7.51-7.55 (4H, m), 7.48 (1H, d, *J* = 7.16 Hz), 7.42-7.44 (2H, m), 7.36 (1H, dt, *J* = 1.6, 7.56 Hz), 2.81 (3H, s), 2.47 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 154.0, 147.7, 145.6, 140.3, 139.9, 133.8, 132.6, 130.3, 129.8, 129.7, 129.2, 128.6, 128.3, 128.0, 127.9, 126.9, 123.3, 120.8, 120.0, 118.2 (aromatic C), 11.59, 11.54 (aliphatic C)

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

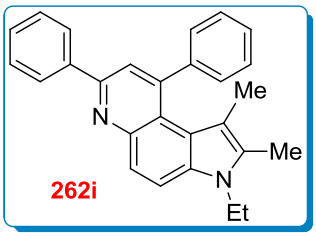
Anal. calcd. for $C_{25}H_{19}ClN_2$: C, 78.42; H, 5.00; N, 7.32%

Found: C, 78.56; H, 4.95; N, 7.41%

**3-Ethyl-1,2-dimethyl-7,9-diphenyl-3*H*-pyrrolo[3,2-*f*]quinoline (262i) and 3-ethyl-1,2-demethyl-7,9-diphenyl-3*H*-pyrrolo[3,2-*f*]quinoline (263i):** Compounds **262i** and **263i** were synthesized from 5-indoloamine **175b**, benzaledyde **142a** and

phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.

**Compound 262i:**



262i

Yield: 50%

Mp: 157-159 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2972, 1558, 1078, 785, 617

$^1$H NMR (400 MHz) δ: 8.27 (1H, d, *J* = 7.3 Hz), 7.99 (2H, d, *J* = 8 Hz), 7.75-7.79 (2H, m), 7.61 (2H, d, *J* = 6.8 Hz), 7.55 (2H, t, *J* = 7.1 Hz), 7.45-7.47 (4H, m), 4.23(2H, q, *J* = 7.0 Hz), 2.28(3H, s), 1.40 (3H, t, *J* = 7.0 Hz), 1.28(3H, s)

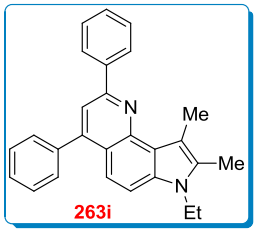
$^{13}$C NMR (100 MHz) δ: 152.7, 147.5, 146.9, 144.3, 140.1, 133.1, 131.9, 129.3, 128.8, 128.6, 127.6, 127.3, 123.1, 121.1, 120.9, 119.9, 114.4, 111.3 (aromatic C), 38.2, 15.8, 12.0, 10.3 (aliphatic C)

LCMS (m/z): 377 $(M+H)^+$

Anal. calcd. for $C_{27}H_{24}N_2$: C, 86.13; H, 6.43; N, 7.44%

Found: C, 86.33; H, 6.32; N, 7.32%

**Compound 263i:**



263i

Yield: 26%

Mp: 134-136 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2755, 1645, 1063, 765, 620

$^1$H NMR (400 MHz) δ: 8.23 (2H, d, *J* = 7.4 Hz), 7.60 (1H, s), 7.39-7.41 (2H, m), 7.22-7.36 (7H, m), 7.16 (1H, d, *J* = 9.0 Hz), 3.92 (2H, q, *J* = 7.1 Hz), 2.83 (3H, s), 2.22 (3H, s), 1.09 (3H, t, *J* = 7.1 Hz)

$^{13}$C NMR (100 MHz) δ: 152.9, 147.9, 145.0, 139.6, 139.4, 133.3, 129.9, 128.9, 127.8, 127.6, 127.0, 126.4, 121.9, 120.0, 116.9, 114.6, 110.6, 110.2 (aromatic C), 37.2, 15.0, 11.5, 9.0 (aliphatic C)

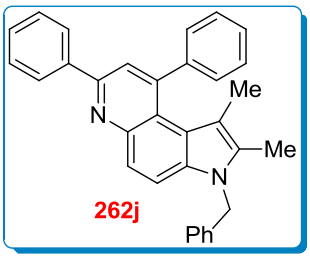
LCMS (m/z): 377 $(M+H)^+$

Anal. calcd. for $C_{27}H_{24}N_2$: C, 86.13; H, 6.43; N, 7.44%

Found: C, 86.28; H, 6.39; N, 7.35%

**3-Benzyl-1,2-dimethyl-7,9-diphenyl-3*H*-pyrrolo[3,2-*f*]quinoline (262j) and 7-benzyl-8,9-dimethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263j):** Compounds **262j** and **263j** were synthesized from 5-indoloamine **175c**, benzaledyde **142a** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 4% ethyl acetate in hexanes.

**Compound 262j:**



262j

Yield: 46%

Mp: 162-164 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3433, 3026, 2862, 1026, 557

$^1H$ NMR (400 MHz) δ: 8.24 (2H, d, *J* = 6.4 Hz), 7.93 (1H, d, *J* = 8.5 Hz), 7.79 (1H, s), 7.69 (1H, d, *J* = 8.6 Hz), 7.62 (2H, d, *J* = 5.4 Hz), 7.46-7.54 (6H, m), 7.28-7.30 (3H, m), 6.96-6.97 (2H, m), 5.44(2H, s), 2.22 (3H, s), 1.30 (3H, s)

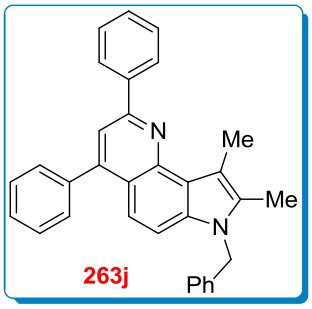
$^{13}C$ NMR (100 MHz) δ: 152.8, 147.5, 146.9, 144.2, 139.9, 137.6, 134.0, 132.5, 129.2, 129.8, 128.7, 129.5, 127.5, 127.3, 127.2, 125.9, 123.4, 120.9, 119.9, 114.7, 111.8 (aromatic C), 46.8, 12.0, 10.4 (aliphatic C)

LCMS (m/z): 439 $(M+H)^+$

Anal. calcd. for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39%

Found: C, 87.75; H, 5.88; N, 6.28%

**Compound 263j:**



263j

Yield: 24%

Mp: 177-179 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 2852, 1203, 1026

$^1H$ NMR (400 MHz) δ: 8.39 (2H, d, *J* = 4.8 Hz), 7.79 (1H, s), 7.49-7.57 (9H, m), 7.37 (1H, d, *J* = 7.1 Hz), 7.25 (3H, d, *J* = 6.8 Hz), 6.96 (2H, d, *J* = 5.4 Hz), 5.44 (2H, s), 3.02 (3H, s), 2.42 (3H, s)

$^{13}$C NMR (100 MHz) δ: 153.9, 148.9, 145.7, 140.4, 140.1, 138.0, 135.2, 131.7, 129.7, 128.7, 128.4, 127.9, 127.3, 125.9, 122.7, 121.0, 118.2, 115.7, 111.9, 111.3 (aromatic C), 46.9, 12.4, 10.1 (aliphatic C)

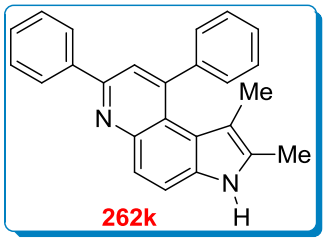
LCMS (m/z): 439 $(M+H)^+$

Anal. calcd. for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39%

Found: C, 87.45; H, 6.13; N, 6.32%

**8,9-Dimethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (262k) and 8,9-dimethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263k):** Compounds **262k** and **263k** were synthesized from 5-indoloamine **175a**, benzaledyde **142a** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 4% ethyl acetate in hexanes.

**Compound 262k:**




Yield: 42%

Mp: 189-201°C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3225, 2943, 1677, 1124, 654

$^1$H NMR (400 MHz, $CDCl_3$+DMSO-$d_6$) δ: 11.39 (1H, s), 8.26 (2H, d, *J* = 7.24 Hz), 7.68-7.77 (3H, m), 7.41-7.55 (8H, m), 2.23 (3H, s), 1.11 (3H, s)

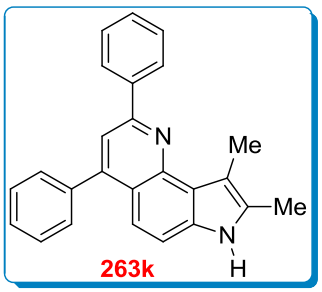
$^{13}$C NMR (100 MHz, $CDCl_3$+DMSO-$d_6$) δ: 151.3, 147.1, 146.9, 143.9, 139.4, 133.3, 132.1, 129.4, 129.1, 128.1, 127.2, 122.4, 121.0, 120.9, 119.1, 117.5, 110.6 (aromatic C), 11.9, 11.6 (aliphatic C)

LCMS (m/z): 349 $(M+H)^+$

Anal. calcd. for $C_{25}H_{20}N_2$: C, 86.17; H, 5.79; N, 8.04%

Found: C, 86.05; H, 5.72; N, 8.14%

**Compound 263k:**




Yield: 22%

Mp: 135-137 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3423, 3059, 1491, 1024, 700

$^1H$ NMR (400 MHz) δ: 8.38 (2H, d, *J* = 7.2 Hz), 8.10 (1H, s), 7.79 (1H, s), 7.45-7.58 (9H, m), 7.38 (1H, d, *J* = 8.5 Hz), 2.94 (3H, s), 2.48 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 153.9, 148.9, 145.6, 140.3, 140.1, 133.9, 129.7, 128.9, 128.8, 128.7, 128.4, 127.9, 127.2, 123.4, 121.1, 118.3, 115.7, 112.6, 111.8 (aromatic C), 12.0, 11.6 (aliphatic C)

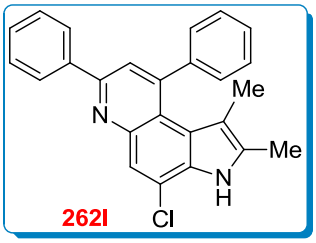
LCMS (m/z): 349 $(M+H)^+$

Anal. calcd. for $C_{25}H_{20}N_2$: C, 86.17; H, 5.79; N, 8.04%

Found: C, 86.25; H, 5.71; N, 8.12%

**1,2-Dimethyl-7,9-diphenyl-3*H*-pyrrolo[3,2-*f*]quinolin-4-yl chloride (262l) and 6-chloro-8,9-dimethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263l):** Compounds **262l** and **263l** were synthesized from 5-indoloamine **175i**, benzaledyde **142a** and phenylacetylene **53a** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.

**Compound 262l:**



262l

Yield: 45%

Mp: 200-202 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3213, 1322, 1212, 613

$^1H$ NMR (400 MHz) δ: 8.58 (1H, s), 8.22 (2H, d, *J* = 7.4 Hz), 7.99 (1H, s), 7.76 (1H, s), 7.52-7.57 (4H, m), 7.44-7.49 (4H, m), 2.31 (3H, s), 1.20 (3H, s)

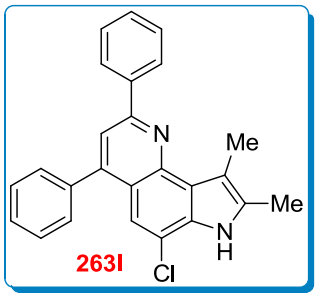
$^{13}C$ NMR (100 MHz) δ: 153.5, 147.7, 147.3, 143.7, 139.5, 131.7, 130.1, 129.3, 128.9, 128.8, 128.7, 127.9, 127.3, 122.8, 121.8, 121.5, 120.2, 120.1, 113.2 (aromatic C), 12.1, 11.5 (aliphatic C)

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

Anal. calcd. for $C_{25}H_{19}ClN_2$: C, 78.42; H, 5.00; N, 7.32%

Found: C, 78.29; H, 4.94; N, 7.45%

**Compound 263l:**




Yield: 27%

Mp: 164-166 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3332, 1609, 1321, 694

$^1$H NMR (400 MHz) δ: 8.36-8.38 (3H, m), 7.82 (1H, s), 7.52-7.59 (8H, m), 7.48 (1H, t, *J* = 7.2 Hz), 2.94 (3H, s), 2.53 (3H, s)

$^{13}$C NMR (100 MHz) δ: 154.1, 148.3, 144.5, 139.9, 139.6, 130.9, 130.6, 129.6, 128.9, 128.7, 128.6, 128.2, 127.2, 124.7, 121.8, 118.0, 116.6, 116.3, 113.1 (aromatic C), 11.8, 11.6 (aliphatic C)

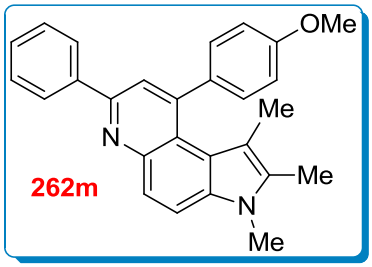
LCMS (m/z): 383 $(M+H)^+$

Anal. calcd. for $C_{25}H_{19}ClN_2$: C, 78.42; H, 5.00; N, 7.32%

Found: C, 78.59; H, 5.08; N, 7.25%

**9-(4-Methoxyphenyl)-1,2,3-trimethyl-7-phenyl-3*H*-pyrrolo[3,2-*f*]quinoline (262m) and 4 (4-methoxyphenyl)-7,8,9-trimethyl-2-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263m):** Compounds **262m** and **263m** were synthesized from 5-indoloamine **175g**, benzaledyde **142a** and phenylacetylene **53g** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.

**Compound 262m:**




Yield: 50%

Mp: 210-212 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3043, 1604, 1176, 613

$^1$H NMR (400 MHz) δ: 8.27 (2H, d, *J* = 5.7 Hz), 7.97 (1H, d, *J* = 8 Hz), 7.71-7.76 (2H, m), 7.45-7.55 (5H, m), 7.01 (2H, d, *J* = 6.5 Hz), 3.89 (3H, s), 3.74 (3H, s), 2.27 (3H, s), 1.36 (3H, s)

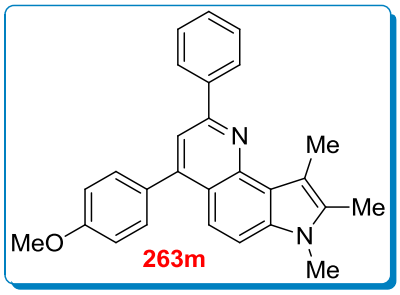
$^{13}$C NMR (100 MHz) δ: 159.1, 152.6, 147.3, 146.5, 139.9, 136.7, 133.9, 132.6, 130.1, 128.6, 128.4, 127.1, 122.9, 120.9, 120.7, 119.6, 114.2, 113.9, 110.9 (aromatic C), 55.2, 29.9, 12.1, 10.4 (aliphatic C)

LCMS (m/z): 393 $(M+H)^+$

Anal. calcd. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%

Found: C, 82.73; H, 6.13; N, 7.08%

**Compound 263m:**




Yield: 26%

Mp: 181-183 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3439, 1606, 1028, 690

$^1H$ NMR (400 MHz) δ: 8.41 (2H, d, *J* = 7.5 Hz), 7.78 (1H, s), 7.55-7.60 (5H, m), 7.47 (1H, t, *J* = 7.1 Hz), 7.40 (1H, d, *J* = 9.0 Hz), 7.10 (2H, d, *J* = 7.6 Hz), 3.93 (3H, s), 3.75 (3H, s), 3.01 (3H, s), 2.47 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 159.5, 153.8, 148.5, 145.8, 140.5, 135.2, 132.6, 131.7, 130.9, 128.7, 127.3, 122.4, 121.0, 117.8, 115.6, 113.9, 111.2, 110.9 (aromatic C), 55.4, 29.9, 12.3, 10.1 (aliphatic C)

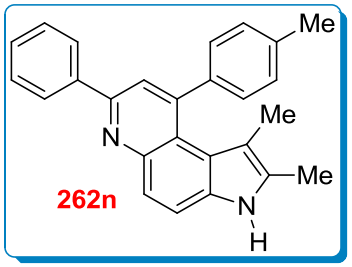
LCMS (m/z): 393 $(M+H)^+$

Anal. calcd. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14%

Found: C, 82.55; H, 6.10; N, 7.22%

**1,2-Dimethyl-9-(4-methylphenyl)-7-phenyl-3*H*-pyrrolo[3,2-*f*]quinoline (262n) and 8,9-dimethyl-4-(4-methylphenyl)-2-phenyl-7*H*-pyrrolo[2,3-*h*]quinoline (263n):** Compounds **262n** and **263n** were synthesized from 5-indoloamine **175a**, benzaledyde **142a** and phenylacetylene **53b** following the *general procedure G*. Pure products were obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.

**Compound 262n:**




Yield: 52%

Mp: 210-212 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3211, 1654, 1286, 698

$^{1}$H NMR (400 MHz) δ: 8.42 (1H, s), 8.21-8.24 (2H, s), 7.92 (1H, d, *J* = 8.8 Hz), 7.75 (1H, s), 7.63 (1H, d, *J* = 8.8 Hz), 7.53 (2H, t, *J* = 6.9 Hz), 7.43-7.49 (3H, m), 7.27-7.29 (2H, m), 2.47 (3H, s), 2.25 (3H, s), 1.25 (3H, s)

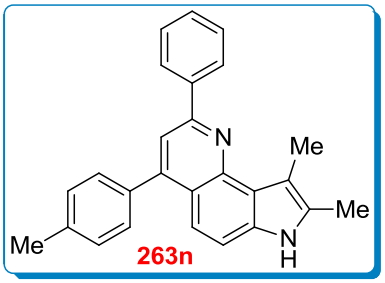
$^{13}$C NMR (100 MHz) δ: 152.9, 147.5, 147.3, 141.2, 139.9, 137.5, 132.9, 130.8, 129.4, 129.1, 128.7, 128.6, 127.3, 123.3, 121.7, 121.3, 119.9, 116.2, 111.9 (aromatic C), 21.3, 11.9, 11.7 (aliphatic C)

LCMS (m/z): 363 $(M+H)^+$

Anal. calcd. for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73%

Found: C, 86.05; H, 6.18; N, 7.65%

**Compound 263n:**



263n

Yield: 27%

Mp: 181-183 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3431, 1698, 1543, 689

$^{1}$H NMR (400 MHz) δ: 8.41 (2H, d, *J* = 7.3 Hz), 8.11 (1H, s), 7.80 (1H, s), 7.55-7.59 (2H, m), 7.49-7.54 (3H, m), 7.46-7.47 (1H, m), 7.34-7.39 (3H, m), 2.97 (3H, s), 2.52 (3H, s), 2.47 (3H, s)

$^{13}$C NMR (100 MHz) δ: 153.9, 148.9, 145.7, 140.4, 137.7, 137.2, 133.9, 129.6, 129.1, 128.8, 128.7, 127.3, 123.4, 121.2, 118.4, 115.8, 112.6, 111.8 (aromatic C), 21.3, 12.0, 11.5 (aliphatic C)

LCMS (m/z): 363 $(M+H)^+$

Anal. calcd. for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73%

Found: C, 86.23; H, 6.18; N, 7.64%

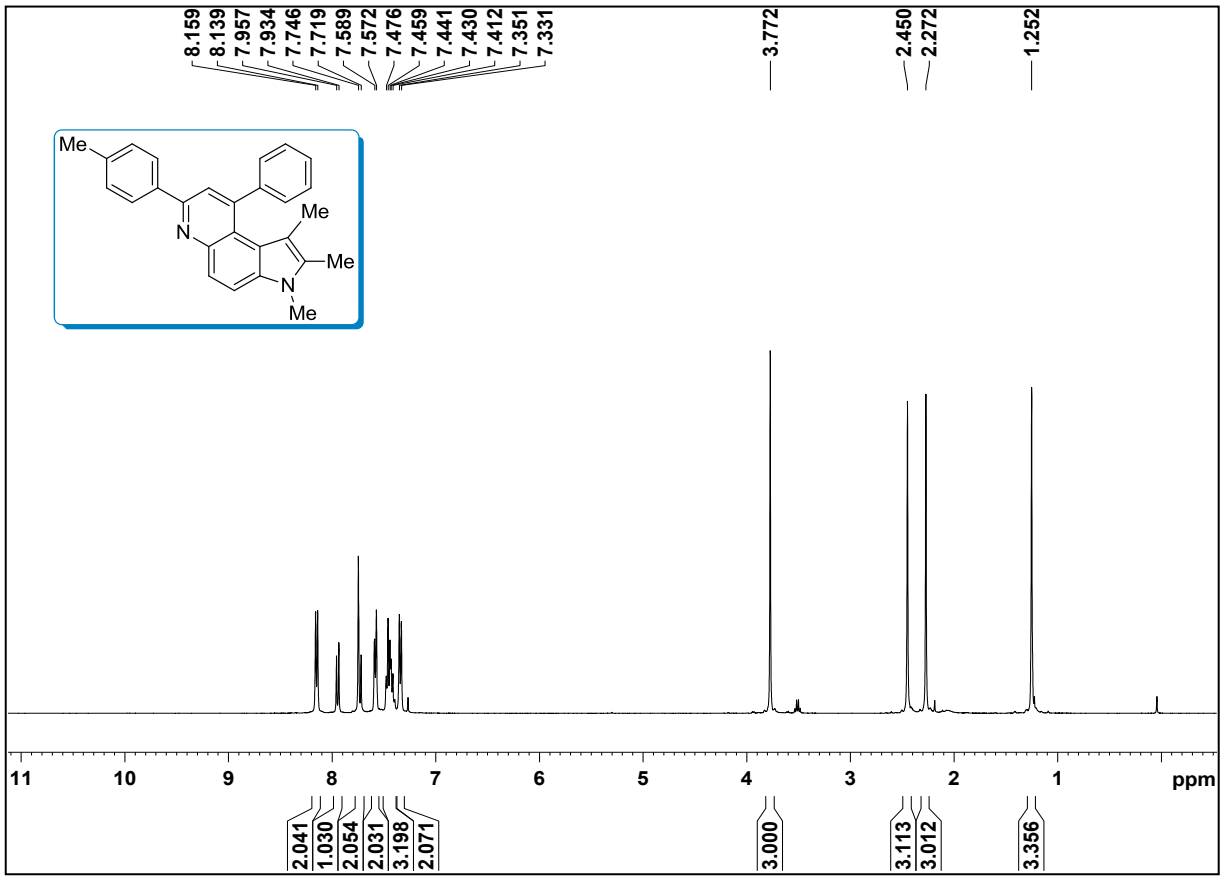
**Table 24. Crystal data and structure refinement for 262a**

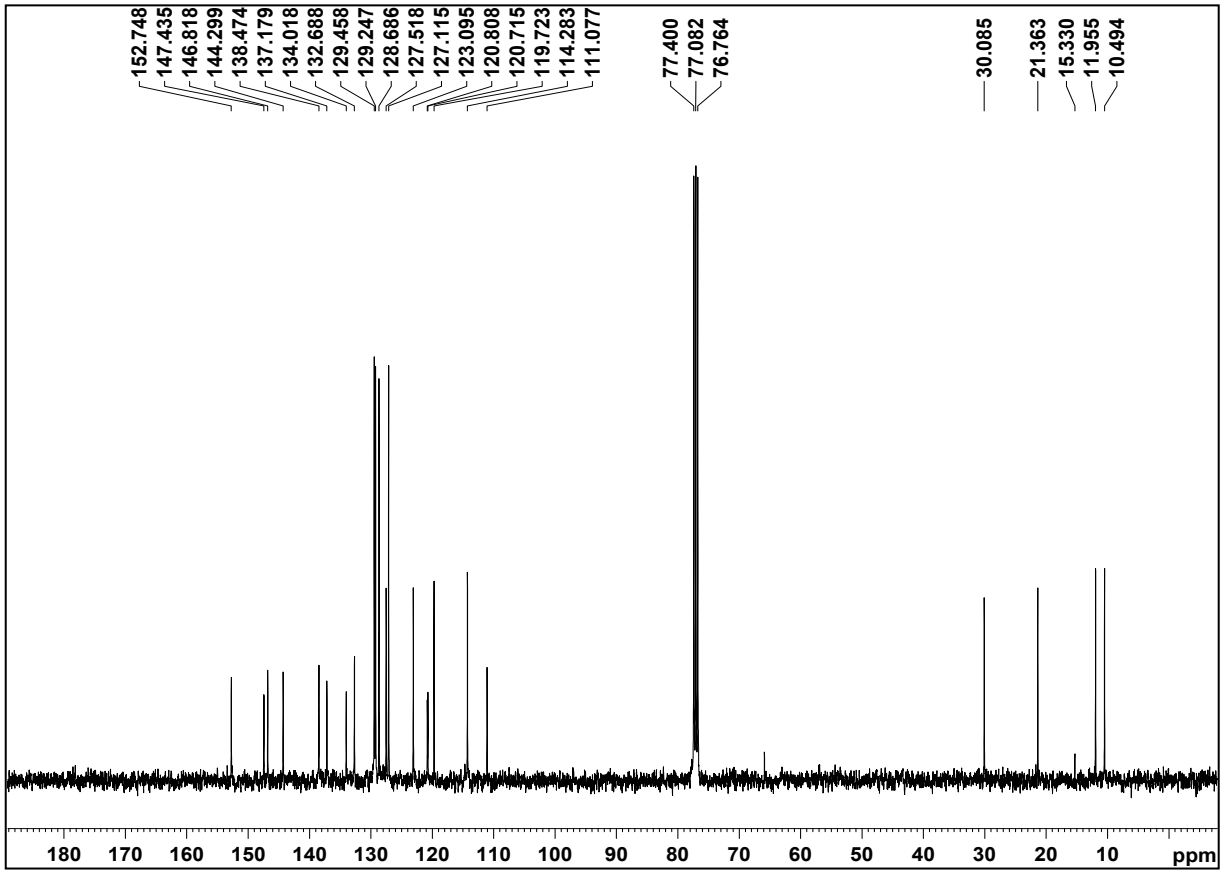
| | |
|---|---|
| Empirical formula | : $C_{26}H_{22}N_2$ |
| Formula weight | : 362.46 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Triclinic |
| Space group | : P -1 |
| Unit cell dimensions | : a = 7.3436(16) Å $\alpha$= 99.382(15)° |
| | : b = 11.1808(17) Å $\beta$= 102.495(19)° |
| | : c = 12.467(3) Å $\gamma$ = 94.742(15)° |
| Volume | : 978.6(3) $Å^3$ |
| Z | : 3 |
| Density (calculated) | : 1.845 $Mg/m^3$ |
| Absorption coefficient | : 0.108 $mm^{-1}$ |
| F (000) | : 576 |
| Crystal size | : 0.22 x 0.14 x 0.16 $mm^3$ |
| Theta range for data collection | : 2.75 to 26.37° |
| Index ranges | : -9<=h<=8, -12<=k<=13, -15<=l<=12 |
| Reflections collected | : 7484 |
| Independent reflections | : 4001 [R(int) = 0.0207] |
| Completeness to theta = 26.04° | : 99.9% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9837 and 0.9801 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 4001 / 0 / 256 |
| Goodness-of-fit on $F^2$ | : 0.966 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0441, wR2 = 0.1132 |
| R indices (all data) | : R1 = 0.0711, wR2 = 0.1219 |
| Largest diff. peak and hole | : 0.190 and -0.228 $e.Å^{-3}$ |
| CCDC number | : 796984 |

**Table 25. Crystal data and structure refinement for 263g**

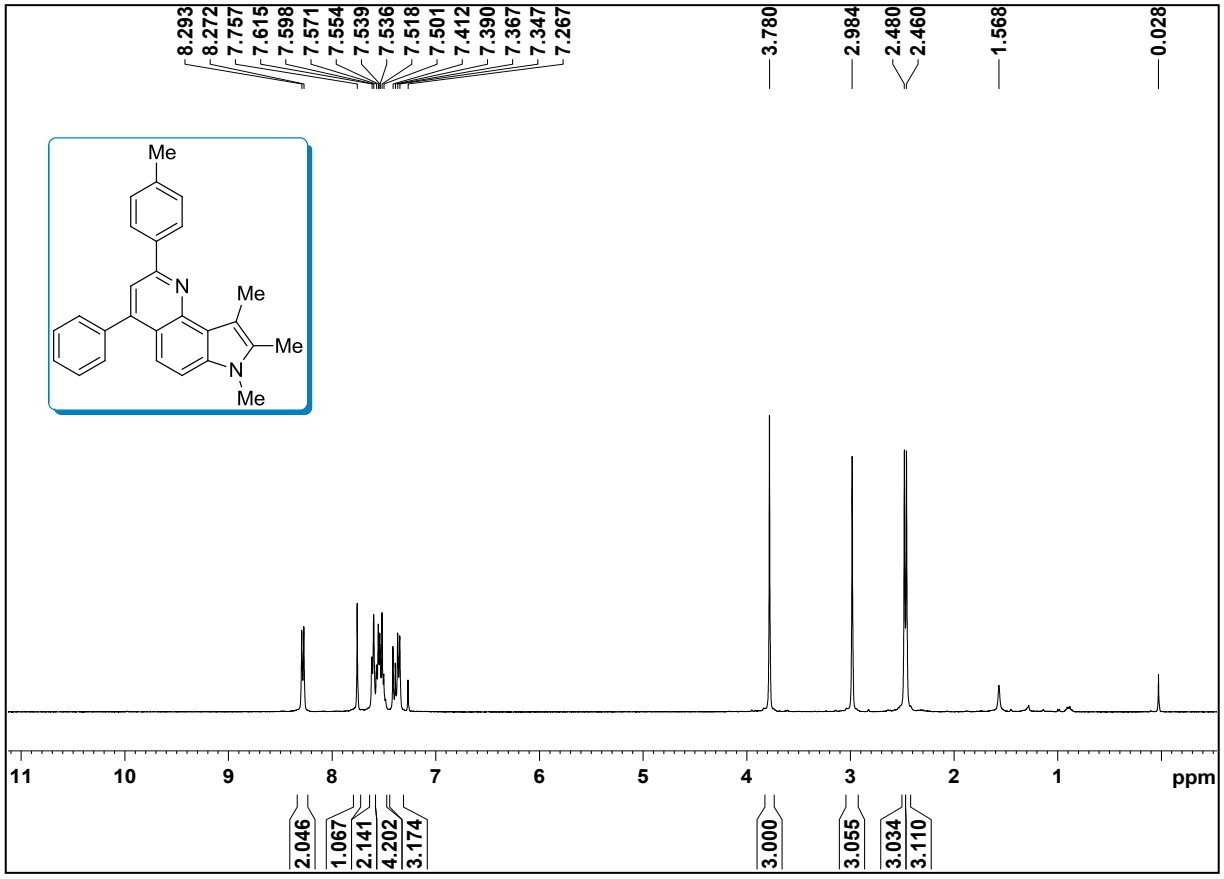
| | |
|---|---|
| Empirical formula | : $C_{58}H_{56}N_4$ |
| Formula weight | : 809.07 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Triclinic |
| Space group | : P -1 |
| Unit cell dimensions | : a = 8.3864(9) Å $\alpha$= 80.350(8)° |
| | : b = 13.2389(14) Å $\beta$= 82.567(8)° |
| | : c = 21.6848(19) Å $\gamma$ = 82.391(9)° |
| Volume | : 2338.4(4) $Å^3$ |
| Z | : 2 |
| Density (calculated) | : 1.149 $Mg/m^3$ |
| Absorption coefficient | : 0.067 $mm^{-1}$ |
| F (000) | : 864 |
| Crystal size | : 0.24 x 0.18 x 0.14 $mm^3$ |
| Theta range for data collection | : 2.88 to 29.07° |
| Index ranges | : -8<=h<=10, -16<=k<=17, -29<=l<=29 |
| Reflections collected | : 17902 |
| Independent reflections | : 10621 [R(int) = 0.0376] |
| Completeness to theta = 26.04° | : 99.9% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9907 and 0.9842 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 10621 / 0 / 571 |
| Goodness-of-fit on $F^2$ | : 0.836 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0552, wR2 = 0.1107 |
| R indices (all data) | : R1 = 0.1472, wR2 = 0.1332 |
| Largest diff. peak and hole | : 0.169 and -0.169 e.$Å^{-3}$ |
| CCDC number | : 796985 |

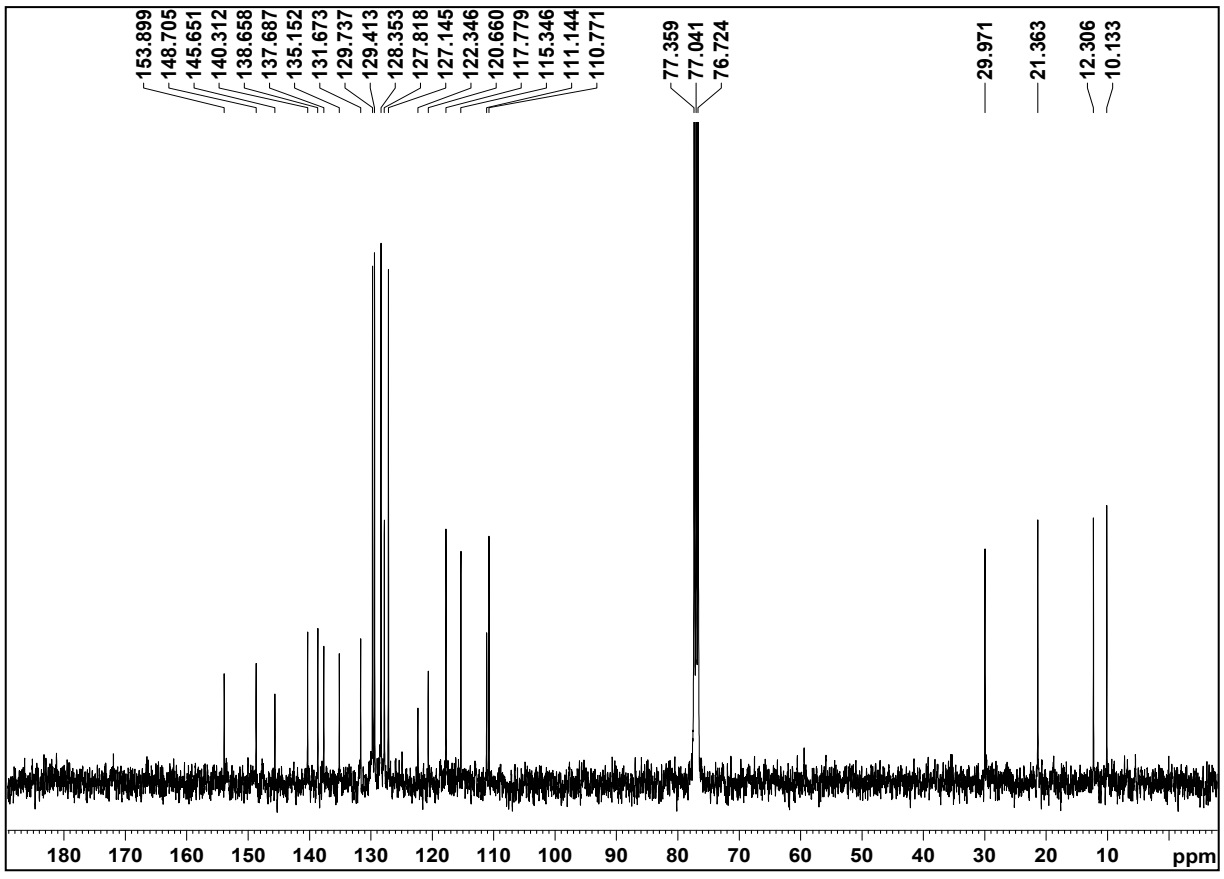
## Spectra No. 12: $^{1}H$ and $^{13}C$ spectra of compound 262e



## Spectra No. 13: $^{1}H$ and $^{13}C$ spectra of compound 263e



## 3.4. Conclusions

- In summary, we have developed an efficient, simple, and high-yielding strategy for the preparation of pyrrolo[3,2-*f*]quinoline and pyrrolo[2,3-*h*]quinoline derivatives exploiting a one-pot process using easily accessible starting materials such as indoloamines, benzaldehydes, and phenylacetylenes.
- To our best knowledge, this is the first report to make these two pyrroloquinolines in one step.
- We have also observed an interesting and unexpected mechanistic pathway in this reaction.

## 3.5. References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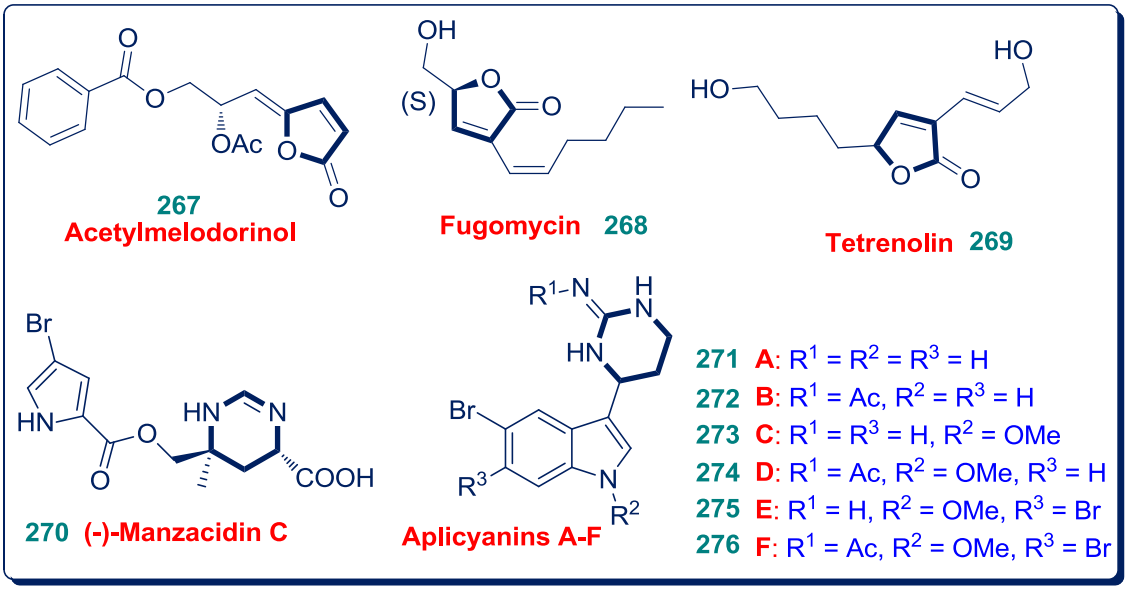
# CHAPTER 4

# Synthesis of furano and tetrahydropyrimido carbazole derivatives

## 4.1. Introduction

Multicomponent reactions (MCRs) are one of the current important areas of modern synthetic organic chemistry.[138] MCRs have been becoming a powerful tool for simple and convergent paths to synthesize structurally complex products from simple starting materials in a one-pot fashion. The MCR strategies demonstrate a broad scope of applications for the synthesis of a variety of natural products.[139] In recent years, furan-2(5*H*)-ones[140] have attracted considerable attention as they are found in a large number of biologically active natural products (**Fig. 17**).[141] These products exhibit diverse biological activities, such as antifungal,[142] antioxidant,[143] anti-inflammatory,[143] cytotoxic and antiproliferative activity (against colon cancer, pancreatic carcinoma, prostatic cancer and human lung cancer), and also some other activities.[144]

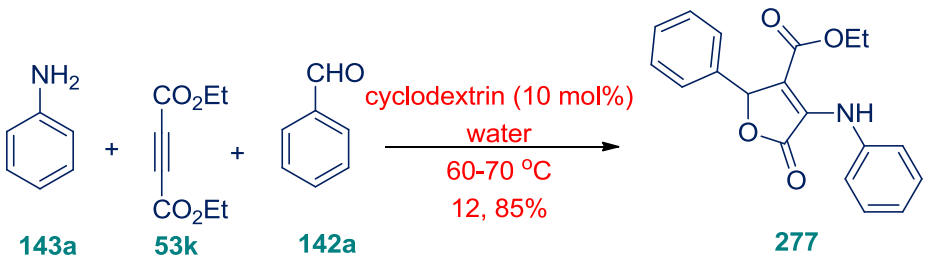
**Fig. 17**




Tetrahydropyrimidine[145] represents one of the most important classes of heterocycles that have gained attention due to their broad biological activities. Several

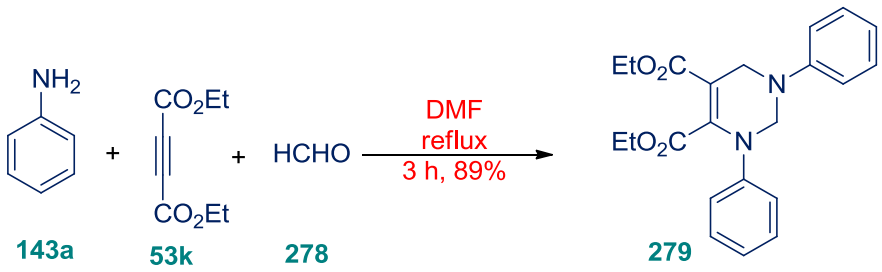
tetrahydropyrimidine derivatives exhibit muscarinic agonist activity.[145q,r] Biologically active heterocycles such as pyridone, iminopyridines and thiazolidinones incorporated with the tetrahydropyrimidine moiety have shown strong antimicrobial activity.[146] Aplicyanins A–F (**271-276**) (**Fig. 17**), a new family of tetrahydropyrimidine-based indole alkaloids, have cytotoxic, antiproliferative and antimitotic activities.[147]

**Eq. 48**




Numerous compounds with a carbazole nucleus have been shown to possess a wide range of pharmacological properties.[105] Considering the few reports on heteroarylsubstituted carbazoles, the development of new and simple synthetic methods for this kind of compound is an interesting challenge. 3,4,5-Substituted furanone derivative (**277**) were synthesized by Nageswar *et al*.[148] from aniline (**143a**), acetylenedicarboxylate **53k** and benzaldehyde (**142a**) using cyclodextrin as reusable catalyst (**Eq. 48**).

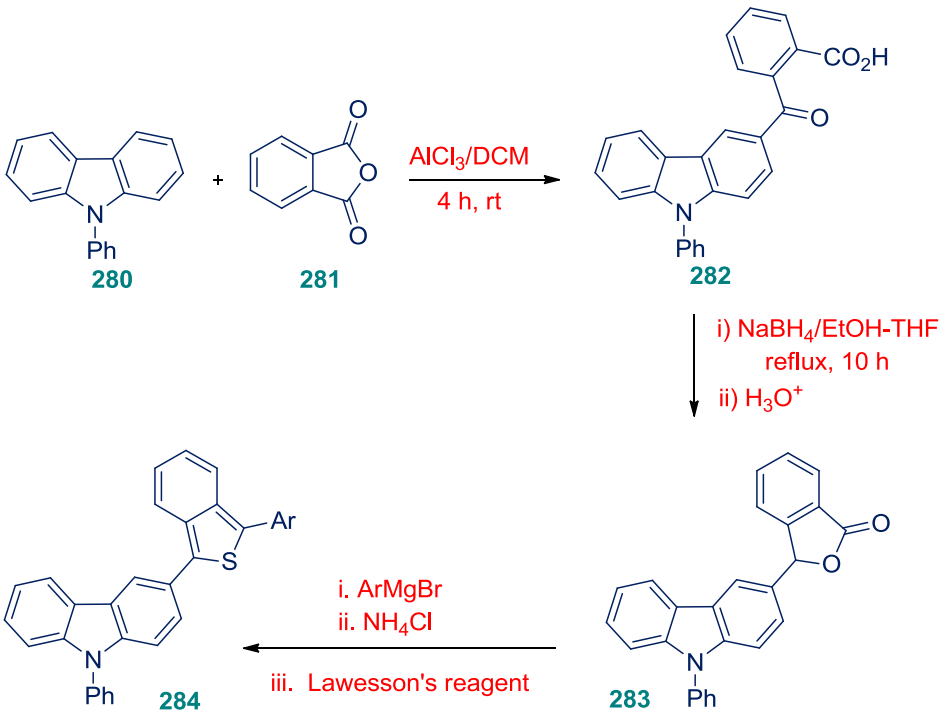
**Eq. 49**




Jiang *et al*.[149] synthesized multi-substituted tetrahydropyrimidines **279** via catalyst-free multicomponent reactions using aniline (**143a**), acetylenedicarboxylate **53k** and formaldehyde (**278**). Mohanakrishnan *et al*.[150] reported the synthesis of 3-(benzo[*c*]thiophen-1-yl)-9-phenyl-9*H*-carbazoles **284** from 9-phenylcarbazole **280** and phthalic anhydride **281**. Friedel-Crafts phthaloylation of 9-phenylcarbazole **280** afforded keto acid **282**. Selective reduction of the ketone carbonyl function of the keto acid **282** and acid catalyzed cyclization furnished the required lactone **283**. Ring opening of the lactone **283** using arylmagnesium bromide followed by quenching with aq. $NH_4Cl$ led to

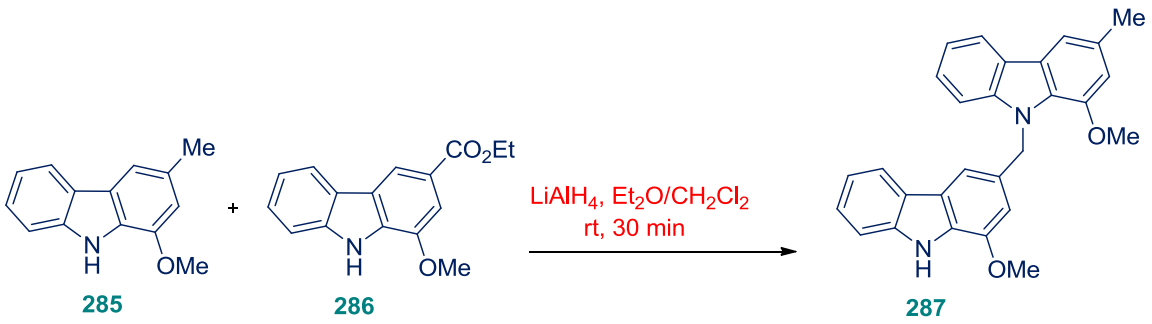
the formation of keto alcohol. The dichloromethane solution of keto alcohol on thionation using Lawesson's reagent afforded **284** as shown in **Eq. 50**.

**Eq. 50**




Bringmann *et al*. reported[151] the first synthesis of the methylene-bridged binary carbazole alkaloid bismurrayafoline-A **287** by treating murrayafoline-A **285** and ethyl-1-methoxy-9*H*-carbazol-3-carboxylate **286** (**Eq. 51**).

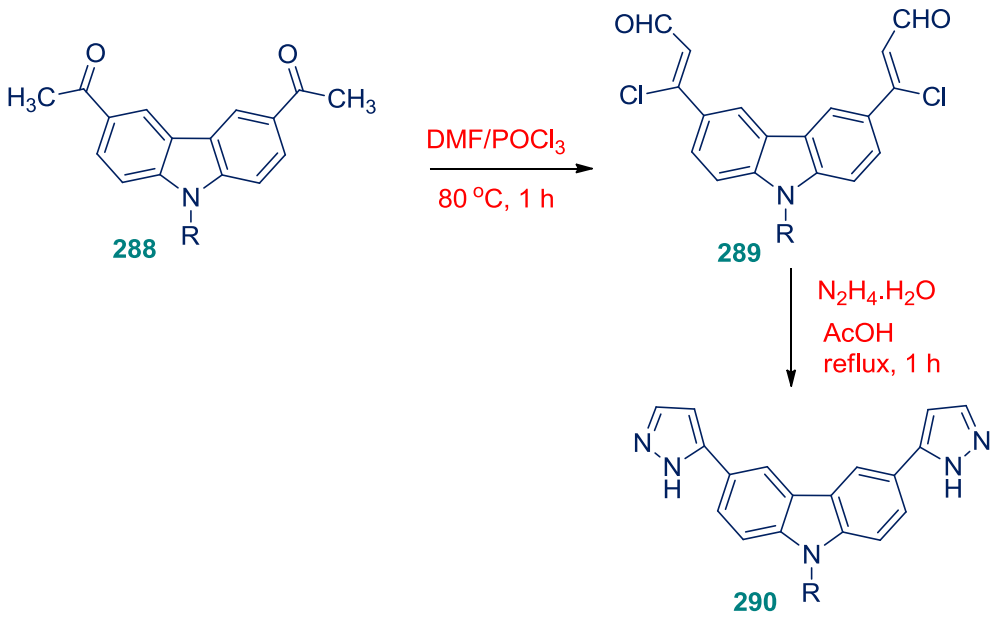
**Eq. 51**



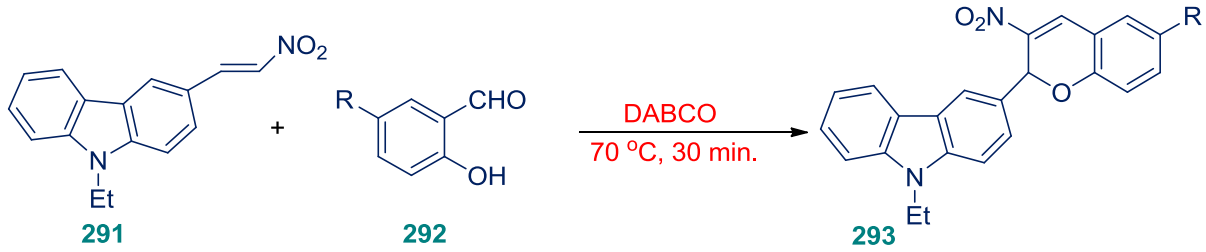

In our group, we have reported the synthesis of bispyrazolylcarbazole **290** from the corresponding acryl aldehyde **289**, which in turn could be prepared from the corresponding acetyl derivative **288** (**Eq. 52**).[152a] We also reported a new, easy and efficient synthesis of 3-(3-nitrochromenyl)carbazoles, 3,6-*bis*-(3-nitrochromenyl)carbazoles and 3-(3-nitroquinolyl)carbazoles under solvent free

conditions in moderate to quantitative yields (**Eq. 53**).[152b] In continuation of our work on the synthesis of heteroarylcarbazoles,[152] we have now extended our methodology to synthesize of new furanone- and tetrahydropyrimidine- substituted carbazole derivatives.

**Eq. 52**




**Eq. 53**



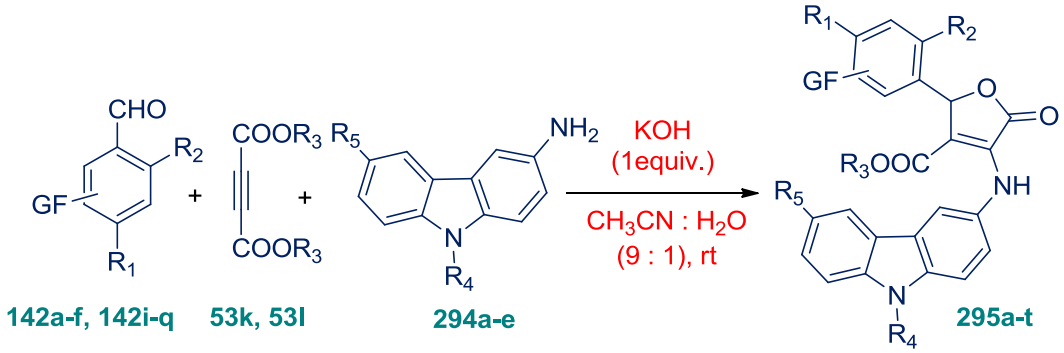

## 4.2. Synthesis of furano-2(5*H*)-one derivatives

Initially, *p*-nitrobenzaldehyde (**142i**), diethyl acetylenedicarboxylate (**53k**) and 9-ethyl-9*H*-carbazol-3-amine (**294a**) were stirred in acetonitrile as solvent at room temperature to establish the feasibility of the strategy, and we obtained ethyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-nitrophenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (**295a**) in a trace amount.

Encouraged by this result, we continued to focus on the optimization of the reaction conditions. The optimization for the reaction was performed on various parameters, such as temperature, base ($Et_3N$, $Na_2CO_3$, $K_2CO_3$, KOH), concentration of

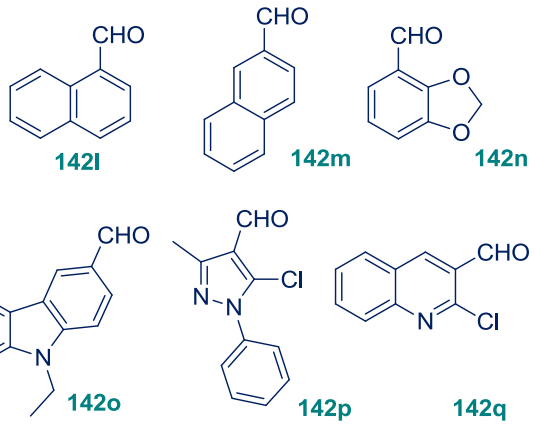
base and solvent. Among them, when a mixture of acetonitrile/water (9:1) and 1 equiv. of KOH at room temperature were used, 90% product yield was obtained. Under the optimized conditions, the scope of this three-component reaction was examined with a series of aldehydes **142a-f** & **142i-q** (aromatic, heterocyclic), acetylenedicarboxylates **53k**, **53l** and 9-alkyl-9*H*-carbazol-3-amines (**294a**–**e**) (**Table 26**).

**Scheme 36**




**Aldehydes**

**142i:** $R_1 = NO_2$, $R_2 = H$
**142b:** $R_1 = F$, $R_2 = H$
**142c:** $R_1 = Cl$, $R_2 = H$
**142d:** $R_1 = Br$, $R_2 = H$
**142a:** $R_1 = H$, $R_2 = H$
**142e:** $R_1 = Me$, $R_2 = H$
**142f:** $R_1 = OMe$, $R_2 = H$
**142j:** $R_1 = Cl$, $R_2 = Cl$
**142k:** $R_1 = H$, $R_2 = Br$




**Acetylenes**

**53k:** $R_3 = Et$
**53l:** $R_3 = Me$

**Aminocarbazoles**

**294a:** $R_4 = Et$, $R_5 = H$
**294b:** $R_4 = Me$, $R_5 = H$
**294c:** $R_4 = CH_2Ph$, $R_5 = H$
**294d:** $R_4 = Et$, $R_5 = Cl$
**294e:** $R_4 = Et$, $R_5 = Br$

The benzaldehydes with electron-withdrawing groups (such as F, Cl, Br, $NO_2$) or electron-donating groups (such as Me, OMe), as well as the heteroaromatic aldehydes (such as carbazole, quinoline and pyrazole derivatives) with similar substituent, gave the corresponding (carbazolylamino)furan-2(5*H*)-ones **295a**–**t** in good yields.

**Fig. 18: ORTEP of compound 295a**

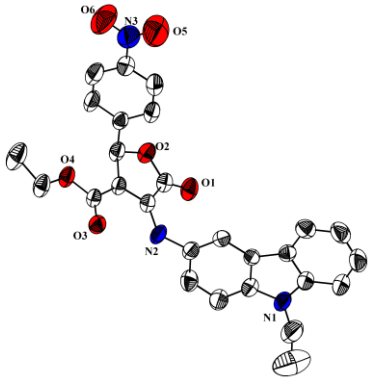
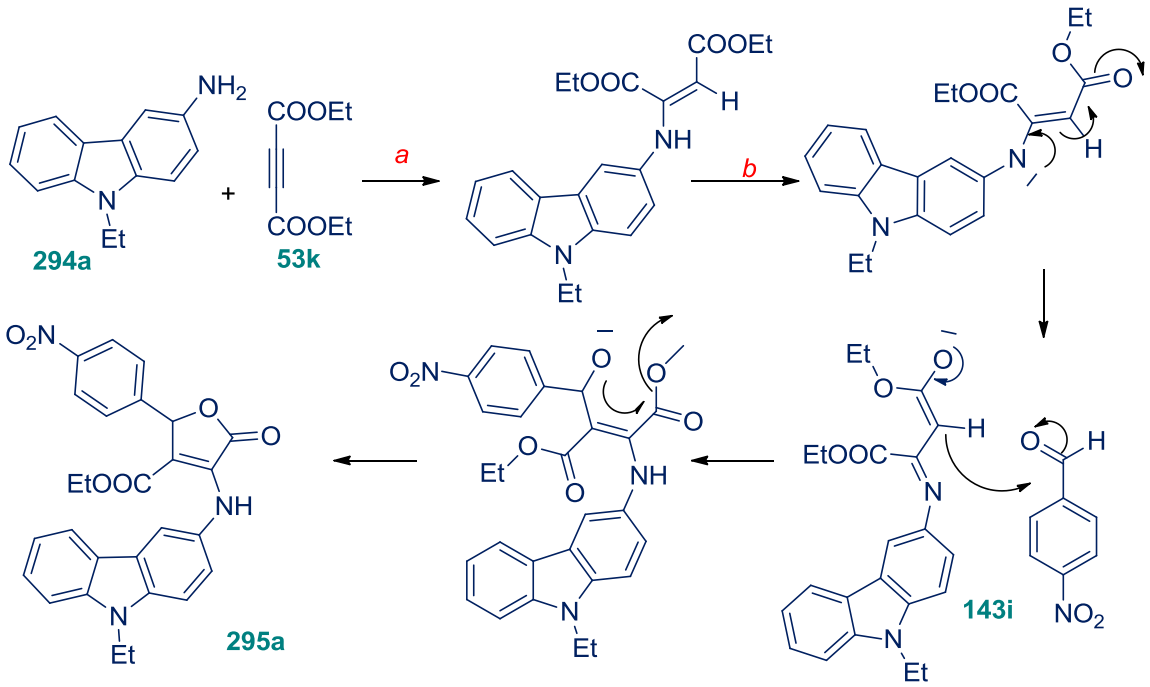


**Table 26: Synthesis of various furano- 2(5*H*)-one derivatives (295a-t)**

| Entry | Aldehydes | Amines | Products | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | **142i** | **294a** | **295a** | 0.5 | 90 |
| 2 | **142b** | **294a** | **295b** | 0.5 | 87 |
| 3 | **142c** | **294a** | **295c** | 0.5 | 85 |
| 4 | **142d** | **294a** | **295d** | 0.5 | 83 |
| 5 | **142a** | **294a** | **295e** | 1.0 | 72 |
| 6 | **142e** | **294a** | **295f** | 2.0 | 65 |
| 7 | **142f** | **294a** | **295g** | 2.0 | 60 |
| 8 | **142j** | **294a** | **295h** | 0.5 | 83 |
| 9 | **142k** | **294a** | **295i** | 0.5 | 85 |
| 10 | **142l** | **294a** | **295j** | 0.5 | 75 |
| 11 | **142m** | **294a** | **295k** | 0.5 | 72 |
| 12 | **142n** | **294a** | **295l** | 0.5 | 78 |
| 13 | **142o** | **294a** | **295m** | 0.5 | 85 |
| 14 | **142p** | **294a** | **295n** | 0.5 | 80 |
| 15 | **142q** | **294a** | **295o** | 0.5 | 70 |
| 16 | **142i with acetylene 53l** | **294a** | **295p** | 0.5 | 92 |
| 17 | **142i** | **294b** | **295q** | 0.5 | 90 |
| 18 | **142i** | **294c** | **295r** | 0.5 | 91 |
| 19 | **142i** | **294d** | **295s** | 0.5 | 90 |
| 20 | **142i** | **294e** | **295t** | 0.5 | 90 |

Unfortunately, aliphatic aldehydes (such as propanal and valeraldehyde) did not tolerate the reaction. This may be due to the lesser reactivity of aliphatic aldehydes. The X-ray crystal structure of **295a** is shown in **Fig. 18**. The proposed mechanism for the formation of **295a** is shown in **Scheme 37**.

**Scheme 37**




a = Hydroamination, b = KOH (1equiv.)

## 4.3. Synthesis of tetrahydropyrimidine derivatives

In our next experiment, the MCR strategy was focused on the synthesis of carbazolyltetrahydropyrimidine derivatives **296a–j** using 3-aminocarbazoles **294a–e**, acetylenes **53k, 53l** & **53f** and formaldehyde **278**. In order to synthesize the tetrahydropyrimidine attached to two carbazole units, we started the optimization with 2 equivalents of 9-ethyl-9*H*-carbazol-3-amine (**294a**), 1.2 equivalents of diethyl acetylenedicarboxylate (**53k**) and 6.0 equivalents of 37% formaldehyde solution (**278**) at room temperature with 1.0 equivalent of potassium hydroxide as base and acetonitrile as solvent. When the reaction was performed at 50 °C, 60 °C and 80 °C, the yield was 20%, 35% and 40%, respectively.

We observed that the temperature is an important parameter for this conversion. Thus, we focused on high-boiling solvents such as *N*,*N*-dimethylformamide, dimethyl sulfoxide, toluene and ionic liquids. The yield remained unaffected in the absence of added base. Prolonging the reaction time did not lead to an increased yield. From the optimization process, we found that the maximum yield (84%) of **296a** was obtained in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][$BF_4$], 3 mL) at 110 °C for 1 hour without any catalyst.

With the optimized conditions in hand, the scope of this three-component reaction was examined with a series of 3-aminocarbazoles **294a–e**, acetylenes **53k, 53l** & **53f** and formaldehyde (**278**) (**Table 27**). The proposed mechanism for the formation of **296a** is shown in **Scheme 39**. The single crystal X-ray structure of **296b** is shown in **Fig. 19**.

**Scheme 38**

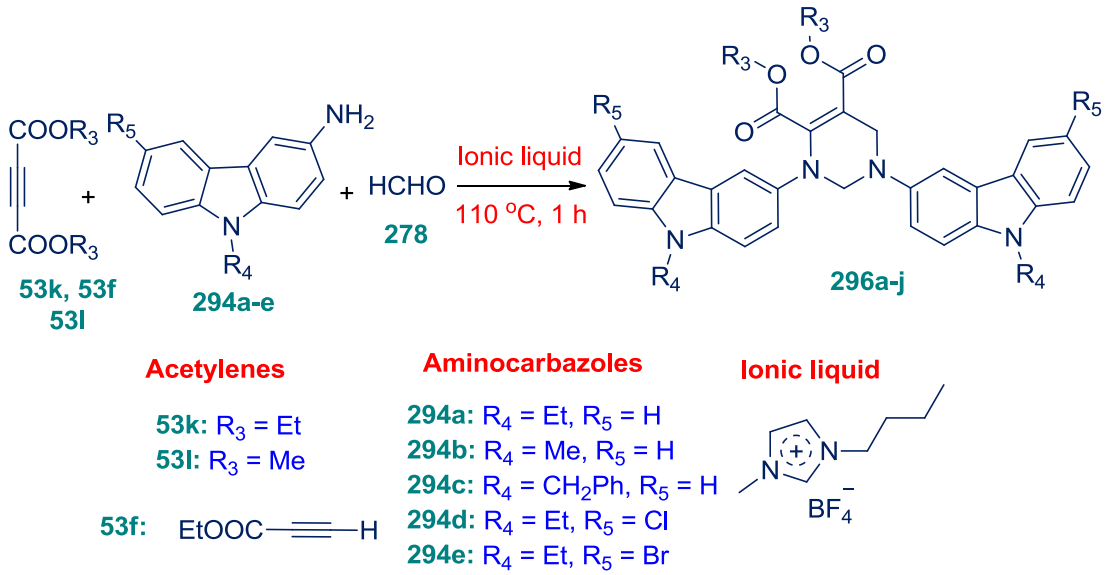
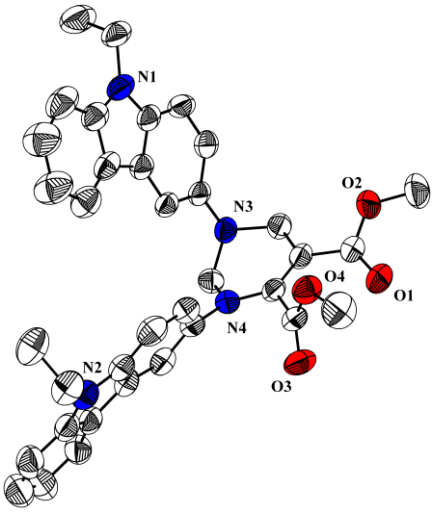


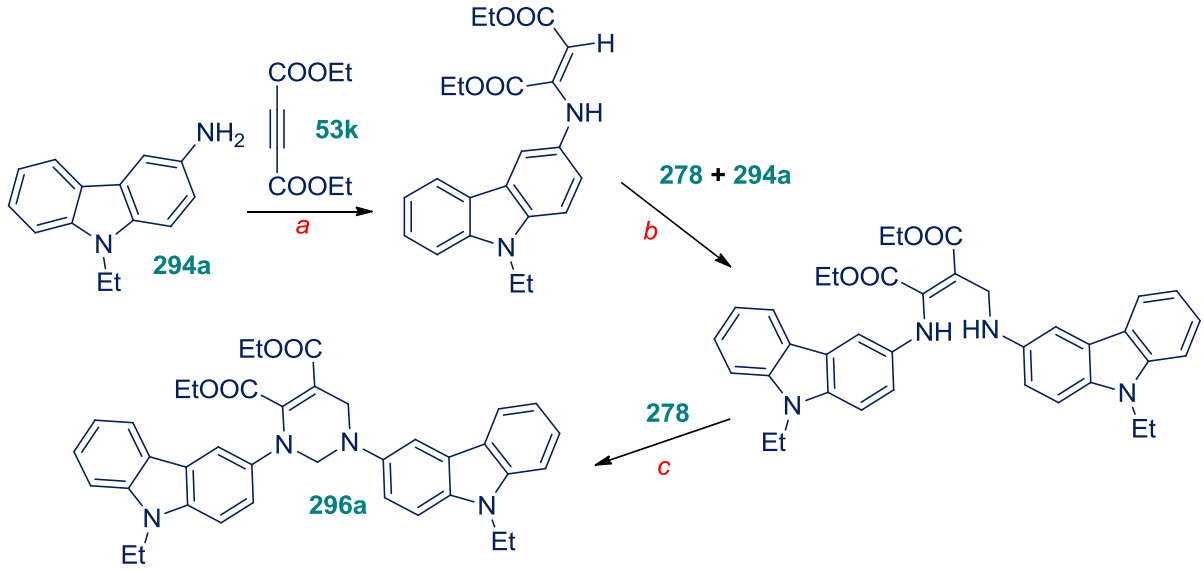

**Table 27: Synthesis of various tetrahydropyrimidines (296a-j)**

| Entry | Acetylene | Amine | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **53k** | **294a** | **296a** | 84 |
| 2 | **53l** | **294a** | **296b** | 88 |
| 3 | **53f** | **294a** | **296c** | 75 |
| 4 | **53k** | **294b** | **296d** | 85 |
| 5 | **53l** | **294b** | **296e** | 82 |
| 6 | **53k** | **294c** | **296f** | 80 |
| 7 | **53k** | **294d** | **296g** | 83 |
| 8 | **53l** | **294d** | **296h** | 85 |
| 9 | **53k** | **294e** | **296i** | 85 |
| 10 | **53l** | **294e** | **296j** | 82 |

**Fig. 19: ORTEP of compound 296b**




**Scheme 39**




a) Hydroamination, b) Mannich type reaction, c) Dehydration

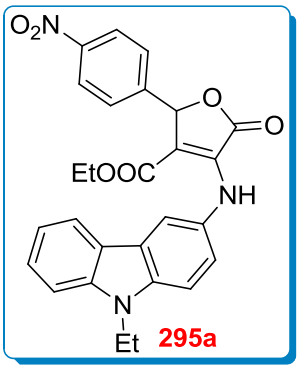
## 4.4. Experimental section

***Genereal procedure H:***

In a round-bottom flask equipped with a magnetic stirrer bar, and containing amine (1.0 mmol) and acetylenedicarboxylate (1.2 mmol) in MeCN (2.7 mL) and $H_2O$ (0.3 mL) as solvent, were added benzaldehyde (1 mmol) and KOH (1 mmol). The reaction mixture was stirred at r.t. After completion of the reaction, as indicated by TLC, $H_2O$ (10 mL) was added to the crude reaction mass. Then, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and

concentrated under reduced pressure. Purification of product by column chromatography on silica gel eluted with ethyl acetate in hexanes.

**Ethyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-nitrophenyl)-5- oxo-2,5-dihydro-3-furancarboxylate (295a):** Compound **295a** was synthesized from aminocarbazole **294a**, benzaldehyde **142i** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 3% of ethyl acetate in hexanes.



295a

Yield: 90%

MP: 199–201 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3314, 2978, 1784, 1672, 1234

$^{1}H$ NMR (400 MHz) δ: 8.41 (1H, s), 8.25 (2H, d, *J* = 8.0 Hz), 8.05 (1H, d, *J* = 7.4 Hz), 7.91 (1H, s), 7.55 (2H, d, *J* = 8.2 Hz, 2 H), 7.48 (1H, t, *J* = 8.4 Hz), 7.42–7.36 (2H, m), 7.31–7.29 (1H, m), 7.24–7.21 (1H, m), 6.13 (1H, s), 4.37 (2H, q, *J* = 6.0 Hz), 4.10 (2H, q, *J* = 6.9 Hz), 1.45 (3H, t, *J* = 6.9 Hz), 1.08 (3H, t, *J* = 7.1 Hz)

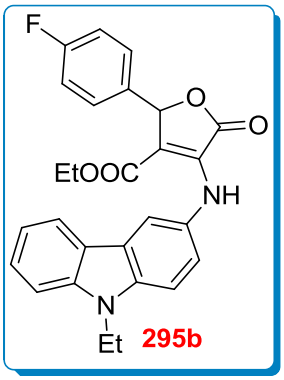
$^{13}C$ NMR (100 MHz) δ: 166.2, 163.9, 148.3, 143.6, 140.6, 139.3, 138.3, 128.7, 128.4, 126.1, 123.7, 122.9, 122.8, 122.5, 120.6, 119.0, 116.4, 111.3, 108.7, 108.3 (aromatic C), 79.0, 60.8, 37.7, 14.0, 13.9 (aliphatic C)

LCMS (m/z): 486 $(M+H)^{+}$

Anal. calcd. for $C_{27}H_{23}N_3O_6$: C, 66.80; H, 4.78; N, 8.66%

Found: C, 66.72; H, 4.85; N, 8.58%

**Ethyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-fluorophenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295b):** Compound **295b** was synthesized from aminocarbazole **294a**, benzaldehyde **142b** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.



295b

Yield: 87%

MP: 120–122 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3315, 2976, 1494, 1232, 1118

$^1$H NMR (400 MHz) δ: 8.41 (1H, s), 8.07 (1H, d, *J* = 6.4 Hz), 7.93 (1H, s), 7.50 (1H, t, *J* = 7.4 Hz), 7.42–7.31 (5H, m), 7.24 (1H, t, *J* = 7.8 Hz), 7.09 (2H, t, *J* = 8.2 Hz), 6.07 (1H, s), 4.36 (2H, q, *J* = 7.0 Hz), 4.10 (2H, q, *J* = 8.2 Hz), 1.45 (3H, t, *J* = 6.2 Hz), 1.07 (3H, t, *J* = 6.6 Hz)

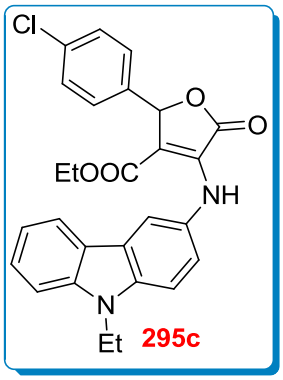
$^{13}$C NMR (100 MHz) δ: 166.6, 164.4, 164.2, 161.9, 140.6, 139.3, 138.2, 132.2, 129.4, 129.3, 129.1, 126.0, 122.9, 122.7, 122.6, 120.6, 118.9, 116.2, 115.7, 115.4, 112.2, 108.7, 108.3 (aromatic C), 79.9, 60.0, 37.7, 13.9, 13.8 (aliphatic C)

LCMS (m/z): 459 $(M+H)^+$

Anal. calcd. for $C_{27}H_{23}FN_2O_4$: C, 70.73; H, 5.06; N, 6.11%

Found: C, 70.65; H, 5.11; N, 6.21%

**Ethyl 2-(4-chlorophenyl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)-5-oxo-2,5-dihydro-3-furancarboxylate (295c):** Compound **295c** was synthesized from aminocarbazole **294a**, benzaldehyde **142c** and acetylenedicarboxylate **53f** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.



**295c**

Yield: 85%

MP: 135–137 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3431, 2976, 1780, 1120, 455

$^1$H NMR (400 MHz) δ: 8.39 (1H, s), 8.07 (1H, d, *J* = 7.7 Hz), 7.92 (1H, s), 7.49 (1H, t, *J* = 7.4 Hz), 7.42–7.36 (4H, m), 7.33–7.31 (3H, m), 7.26–7.22 (1H, m), 6.05 (1H, s), 4.37 (2H, q, *J* = 7.1 Hz), 4.10 (2H, q, *J* = 7.1 Hz), 1.45 (3H, t, *J* = 7.1 Hz), 1.08 (3H, t, *J* = 7.1 Hz)

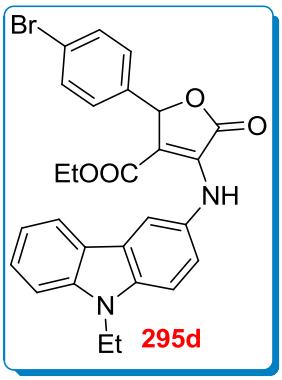
$^{13}$C NMR (100 MHz) δ: 166.5, 164.1, 140.6, 139.3, 138.2, 135.0, 129.1, 128.9, 128.8, 126.1, 122.9, 122.7, 120.6, 118.9, 116.2, 112.0, 108.7, 108.3 (aromatic C), 79.8, 60.0, 37.7, 14.0, 13.9 (aliphatic C)

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

Anal. calcd. for $C_{27}H_{23}ClN_2O_4$: C, 68.28; H, 4.88; N, 5.90%

Found: C, 68.11; H, 4.91; N, 5.85%

**Ethyl 2-(4-bromophenyl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)-5-oxo-2,5-dihydro-3-furancarboxylate (295d):** Compound **295d** was synthesized from aminocarbazole **294a**, benzaldehyde **142d** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 83%

MP: 143–145 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3310, 2930, 1672, 1120, 806

$^1H$ NMR (400 MHz) δ: 8.41 (1H, s), 8.08 (1H, d, *J* = 7.6 Hz), 7.93 (1H, s), 7.55–7.48 (3H, m), 7.42–7.40 (1H, m), 7.34 (2H, q, *J* = 8.5 Hz), 7.27–7.23 (3H, m), 6.03 (1H, s), 4.35 (2H, q, *J* = 6.8 Hz), 4.10 (2H, q, *J* = 6.9 Hz), 1.44 (3H, t, *J* = 7.0 Hz), 1.08 (3H, t, *J* = 7.0 Hz)

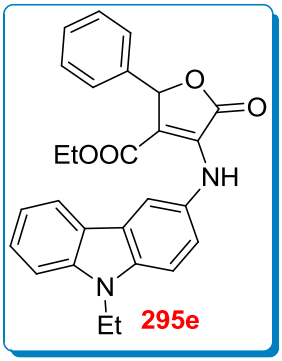
$^{13}C$ NMR (100 MHz) δ: 166.6, 164.1, 140.6, 139.2, 138.2, 135.6, 131.7, 129.2, 129.1, 126.1, 123.2, 122.9, 122.7, 122.6, 120.6, 118.9, 116.2, 112.0, 108.7, 108.3 (aromatic C), 79.9, 60.6, 37.7, 14.0, 13.9 (aliphatic C)

LCMS (m/z): 519 $(M+H)^+$

Anal. calcd. for $C_{27}H_{23}BrN_2O_4$: C, 62.44; H, 4.46; N, 5.39%

Found: C, 62.31; H, 4.52; N, 5.31%

**Ethyl 4-(9-ethyl 9*H*-carbazol-3-ylamino)-5-oxo-2-phenyl-2,5-dihydro-3-furancarboxylate (295e):** Compound **295e** was synthesized from aminocarbazole **294a**, benzaldehyde **295e** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.




Yield: 72%

MP: 145–147 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3314, 2287, 1263, 887

$^1$H NMR (400 MHz) δ: 8.40 (1H, s), 8.08 (1H, d, *J* = 7.7 Hz), 7.93 (1H, s), 7.51–7.47 (1H, m), 7.42–7.35 (7H, m), 7.34–7.32 (1H, m), 7.24 (1H, t, *J* = 7.2 Hz), 6.09 (1H, s), 4.36 (2H, q, *J* = 6.5 Hz), 4.10 (2H, q, *J* = 7.1 Hz), 1.45 (3H, t, *J* = 7.2 Hz), 1.06 (3H, t, *J* = 7.8 Hz)

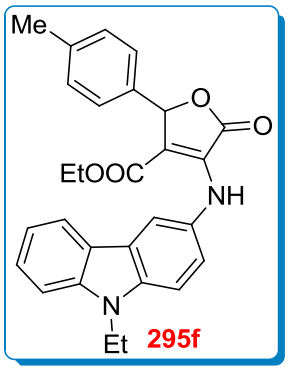
$^{13}$C NMR (100 MHz) δ: 166.8, 164.3, 140.6, 139.2, 138.1, 136.4, 129.3, 129.1, 128.5, 127.5, 126.0, 122.9, 122.7, 120.7, 118.9, 116.1, 112.7, 108.7, 108.3 (aromatic C), 80.7, 60.5, 37.7, 13.96, 13.90 (aliphatic C)

LCMS (m/z): 439 $(M-H)^+$

Anal. calcd. for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36%

Found: C, 73.48; H, 5.45; N, 6.41%

**Ethyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-methylphenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295f):** Compound **295f** was synthesized from aminocarbazole **294a**, benzaldehyde **142e** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.




Yield: 65%

MP: 118–122 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3439, 2924, 1232, 1039, 750

$^1$H NMR (400 MHz) δ: 8.35 (1H, s), 8.06 (1H, d, *J* = 7.7 Hz), 7.92 (1H, s), 7.48 (1H, t, *J* = 7.4 Hz), 7.42–7.40 (1H, m), 7.38–7.36 (1H, m), 7.33–7.31 (1H, m), 7.27–7.25 (2H, m), 7.21 (3H, t, *J* = 8.0 Hz), 6.06 (1H, s), 4.37 (2H, q, *J* = 7.2 Hz), 4.09 (2H, q, *J* = 6.8 Hz), 2.38 (3H, s), 1.45 (3H, t, *J* = 7.2 Hz), 1.07 (3H, t, *J* = 7.1 Hz)

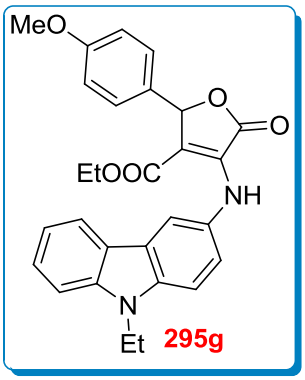
$^{13}$C NMR (100 MHz) δ: 166.9, 164.3, 140.6, 139.1, 139.0, 138.1, 133.4, 129.4, 129.2, 127.4, 125.9, 122.9, 122.7, 120.6, 118.9, 116.0, 112.7, 108.6, 108.2 (aromatic C), 80.6, 60.5, 37.7, 21.3, 13.9, 13.8 (aliphatic C)

LCMS (m/z): 455 $(M+H)^+$

Anal. calcd. for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16%

Found: C, 73.85; H, 5.71; N, 6.22%

**Ethyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295g):** Compound **295g** was synthesized from aminocarbazole **294a**, benzaldehyde **142f** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



**295g**

Yield: 60%

MP: 154–156 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3325, 1763, 1230, 1149, 462

$^1$H NMR (400 MHz) δ: 8.43 (1H, s), 8.04 (1H, d, *J* = 7.4 Hz), 7.89 (1H, s), 7.47–7.45 (1H, m), 7.42–7.36 (2H, m), 7.32–7.28 (3H, m), 7.21 (1H, t, *J* = 7.1 Hz), 6.91 (2H, d, *J* = 6.8 Hz), 6.05 (1H, s), 4.38 (2H, q, *J* = 6.4 Hz), 4.06 (2H, q, *J* = 6.5 Hz), 3.82 (3H, s), 1.44 (3H, t, *J* = 5.6 Hz), 1.03 (3H, t, *J* = 6.8 Hz)

$^{13}$C NMR (100 MHz) δ: 166.8, 163.9, 160.0, 140.3, 138.7, 137.8, 129.5, 128.7, 128.2, 125.9, 122.4, 120.4, 118.7, 115.7, 113.8, 112.5, 108.6, 108.1 (aromatic C), 80.4, 60.3, 55.2, 37.5, 13.8, 13.7 (aliphatic C)

LCMS (m/z): 471 $(M+H)^+$

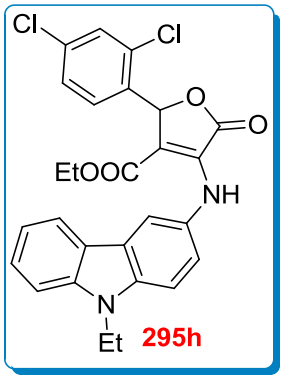
Anal. calcd. for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.95%

Found: C, 71.32; H, 5.62; N, 5.86%

**Ethyl 2-(2,4 dichlorophenyl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)-5-oxo-2,5-dihydro-3-furancarboxylate (295h):** Compound **295h** was synthesized from aminocarbazole **294a**, benzaledyde **142j** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.

Yield: 83%

MP: 120–122 °C




IR (KBr) $\nu_{max}$ $cm^{-1}$: 3352, 1782, 1155, 1005, 765

$^1$H NMR (400 MHz) δ: 8.47 (1H, s), 8.06 (1H, d, *J* = 7.6 Hz), 7.91 (1H, s), 7.51–7.47 (2H, m), 7.42–7.36 (2H, m), 7.32–7.21 (3H, m), 7.19–7.16 (1H, m), 6.55 (1H, s), 4.37 (2H, q, *J* = 7.0 Hz), 4.11 (2H, q, *J* = 6.2 Hz), 1.45 (3H, t, *J* = 7.0 Hz), 1.08 (3H, t, *J* = 6.6 Hz)

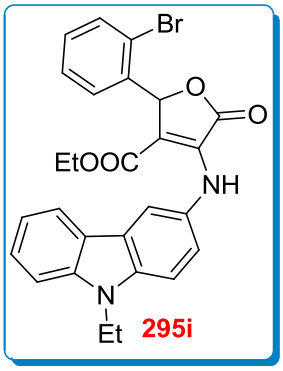
$^{13}$C NMR (100 MHz) δ: 166.3, 164.1, 140.6, 140.0, 138.2, 135.5, 135.4, 132.5, 129.8, 129.5, 128.5, 127.5, 126.1, 122.9, 122.7, 122.6, 120.6, 118.9, 116.2, 110.9, 108.7, 108.3 (aromatic C), 76.2, 60.7, 37.7, 13.96, 13.90 (aliphatic C)

LCMS (m/z): 509 $(M+H)^+$

Anal. calcd. for $C_{27}H_{22}Cl_2N_2O_4$: C, 63.66; H, 4.35; N, 5.50%

Found: C, 63.45; H, 4.31; N, 5.56%

**Ethyl 2-(2-bromophenyl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)-5-oxo-2,5-dihydro-3-furancarboxylate (295i):** Compound **295i** was synthesized from aminocarbazole **294a**, benzaldehyde **142k** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 3% ethyl acetate in hexanes.




Yield: 85%

MP: 130–135 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3356, 2968, 1684, 1249, 671

$^1$H NMR (400 MHz) δ: 8.50 (1H, s), 8.08 (1H, d, *J* = 7.9 Hz), 7.94 (1H, s), 7.64 (1H, d, *J* = 8.3 Hz), 7.50 (1H, t, *J* = 7.7 Hz), 7.42–7.40 (1H, m), 7.38–7.32 (3H, m), 7.26–7.22 (3H, m), 6.64 (1H, s), 4.35 (2H, q, *J* = 7.2 Hz), 4.10 (2H, q, *J* = 6.8 Hz), 1.44 (3H, t, *J* = 7.1 Hz), 1.06 (3H, t, *J* = 7.1 Hz)

$^{13}$C NMR (100 MHz) δ: 166.6, 164.2, 140.6, 140.0, 138.2, 135.3, 133.3, 130.6, 129.1, 128.7, 127.7, 126.0, 124.9, 122.9, 122.7, 122.6,

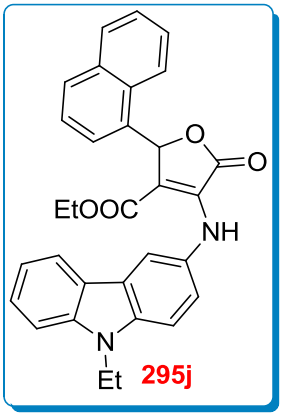
120.6, 118.9, 116.2, 111.7, 108.7, 108.3 (aromatic C), 79.2, 60.6, 37.7, 13.98, 13.91 (aliphatic C)

LCMS (m/z): 519 $(M+H)^+$

Anal. calcd. for $C_{27}H_{23}BrN_2O_4$: C, 62.44; H, 4.46; N, 5.39%

Found: C, 62.34; H, 4.39; N, 5.45%

**Ethyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(1-naphthyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295j):** Compound **295j** was synthesized from aminocarbazole **294a**, aldehyde **142l** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 75%

MP: 134–136 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3468, 2926, 1460, 1116, 748

$^1$H NMR (400 MHz) δ: 8.58 (1H, s), 8.32 (1H, d, *J* = 8.5 Hz), 8.06 (1H, d, *J* = 8.1 Hz), 7.95–7.89 (3H, m), 7.63 (1H, t, *J* = 7.2 Hz), 7.55 (1H, t, *J* = 7.5 Hz), 7.48 (2H, t, *J* = 7.4 Hz), 7.42–7.37 (4H, m), 7.23–7.21 (1H, m), 6.97 (1H, s), 4.37 (2H, q, *J* = 7.2 Hz), 4.07 (2H, q, *J* = 7.0 Hz), 1.45 (3H, t, *J* = 7.0 Hz), 0.92 (3H, t, *J* = 6.8 Hz)

$^{13}$C NMR (100 MHz) δ: 166.5, 164.7, 140.6, 140.2, 138.2, 133.9, 132.3, 132.1, 129.9, 129.3, 128.8, 128.1, 126.7, 125.9, 125.1, 123.4, 122.9, 122.7, 120.6, 118.9, 116.1, 111.6, 108.6, 108.3 (aromatic C), 76.7, 60.5, 37.7, 13.96, 13.90 (aliphatic C)

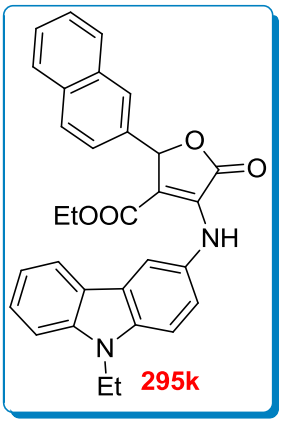
LCMS (m/z): 489 $(M-H)^+$

Anal. calcd. for $C_{31}H_{26}N_2O_4$: C, 75.90; H, 5.34; N, 5.71%

Found: C, 75.81; H, 5.29; N, 5.62%

**Ethyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(2-naphthyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295k):** Compound **295k** was synthesized from aminocarbazole **294a**, aldehyde **142m** and acetylenedicarboxylate **53k** following the *general procedure*

*H*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 72%

MP: 148–152 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3342, 2974, 1766, 1230, 748

$^1$H NMR (400 MHz) δ: 8.49 (1H, s), 8.11 (1H, d, *J* = 7.1 Hz), 7.99 (1H, s), 7.92–7.88 (4H, m), 7.56–7.50 (3H, m), 7.47– 7.41 (2H, m), 7.38 (2H, s), 7.27 (1H, t, *J* = 7.2 Hz), 6.28 (1H, s), 4.35 (2H, q, *J* = 7.0 Hz), 4.07 (2H, q, *J* = 7.9 Hz), 1.45 (3H, t, *J* = 7.0 Hz), 1.03 (3H, t, *J* = 7.0 Hz)

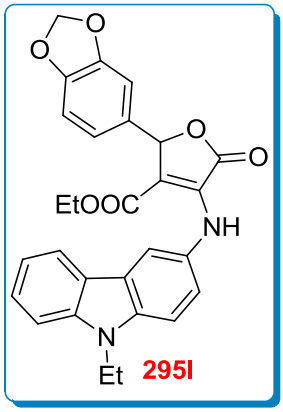
$^{13}$C NMR (100 MHz) δ: 166.9, 164.4, 140.6, 139.3, 138.2, 133.7, 133.1, 129.3, 128.5, 128.2, 127.8, 127.6, 126.7, 126.5, 126.0, 124.2, 122.9, 122.7, 120.7, 118.9, 116.1, 112.7, 108.7, 108.3 (aromatic C), 80.9, 60.6, 37.7, 13.99, 13.92 (aliphatic C)

LCMS (m/z): 491 $(M+H)^+$

Anal. calcd. for $C_{31}H_{26}N_2O_4$: C, 75.90; H, 5.34; N, 5.71%

Found: C, 75.81; H, 5.40; N, 5.76%

**Ethyl 2-(1,3-benzodioxol-5-yl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)-5-oxo-2,5-dihydro-3-furancarboxylate (295l):** Compound **295l** was synthesized from aminocarbazole **294a**, aldehyde **142n** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 78%

MP: 163–165 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3310, 2930, 1491, 1035, 636

$^1$H NMR (400 MHz) δ: 8.37 (1H, s), 8.08 (1H, d, *J* = 7.6 Hz), 7.92 (1H, s), 7.50 (1H, t, *J* = 7.4 Hz), 7.43–7.37 (2H, m), 7.34–7.32 (1H, m), 7.24 (1H, t, *J* = 7.3 Hz), 6.92 (1H, d, *J* = 7.6 Hz), 6.83 (2H, d, *J* = 9.2 Hz), 6.01 (3H, s), 4.39 (2H, q, *J* =

7.0 Hz), 4.13 (2H, q, *J* = 7.0 Hz), 1.47 (3H, t, *J* = 5.7 Hz), 1.10 (3H, t, *J* = 6.9 Hz)

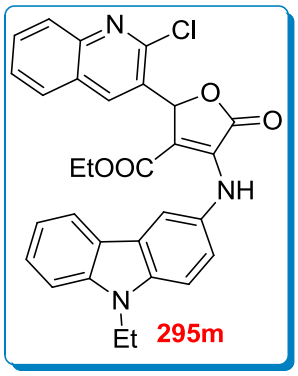
$^{13}$C NMR (100 MHz) δ: 166.7, 164.3, 148.3, 147.9, 140.6, 139.2, 138.1, 130.2, 129.3, 126.0, 122.9, 122.7, 121.9, 120.7, 118.9, 116.1, 112.3, 108.7, 108.3, 107.4 (aromatic C), 101.4, 80.6, 60.6, 37.7, 14.1, 13.9 (aliphatic C)

LCMS (m/z): 483 $(M-H)^+$

Anal. calcd. for $C_{28}H_{24}N_2O_6$: C, 69.41; H, 4.99; N, 5.78%

Found: C, 69.52; H, 4.91; N, 5.65%

**Ethyl 2-(2-chloro-3-quinolyl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)- 5-oxo-2,5-dihydro-3-furancarboxylate (295m):** Compound **295m** was synthesized from aminocarbazole **295a**, aldehyde **142o** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 85%

MP: 139–141 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3306, 2924, 1776, 1234, 750

$^1$H NMR (400 MHz) δ: 8.59 (1H, s), 8.07–8.05 (3H, m), 7.96 (1H, s), 7.83 (1H, d, *J* = 8.0 Hz), 7.78 (1H, t, *J* = 7.7 Hz), 7.58 (1H, t, *J* = 7.5 Hz), 7.49 (1H, t, *J* = 7.6 Hz), 7.42–7.37 (3H, m), 7.24 (1H, t, *J* = 7.8 Hz), 6.67 (1H, s), 4.35 (2H, q, *J* = 6.8 Hz), 4.13–4.03 (2H, m), 1.44 (3H, t, *J* = 7.0 Hz), 1.03 (3H, t, *J* = 7.0 Hz)

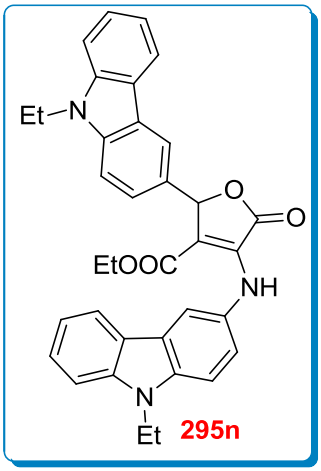
$^{13}$C NMR (100 MHz) δ: 166.2, 164.1, 150.1, 147.6, 140.6, 140.4, 138.3, 138.1, 131.4, 128.8, 128.4, 127.8, 127.6, 126.8, 126.1, 122.9, 122.8, 122.6, 120.6, 118.9, 116.3, 110.3, 108.7, 108.3 (aromatic C), 77.0, 60.8, 37.7, 14.0, 13.9 (aliphatic C)

LCMS (m/z): 527 $(M+2)^+$

Anal. calcd. for $C_{30}H_{24}ClN_3O_4$: C, 68.50; H, 4.60; N, 7.99%

Found: C, 68.45; H, 4.66; N, 8.12%

**Ethyl 2-(9-ethyl-9*H*-carbazol-3-yl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)-5-oxo-2,5-dihydro-3-furancarboxylate (295n):** Compound **295n** was synthesized from aminocarbazole **294a**, aldehyde **142p** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 7% ethyl acetate in hexanes.




Yield: 80%

MP: 158–160 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3369, 2924, 1693, 1012, 746

$^1$H NMR (400 MHz) δ: 8.40 (1H, s), 8.12–8.05 (3H, m), 7.94 (1H, s), 7.47–7.35 (8H, m), 7.26–7.19 (2H, m), 6.29 (1H, s), 4.33–4.32 (4H, m), 4.05–4.00 (2H, m), 1.42–1.40 (6H, m), 0.98 (3H, t, *J* = 6.7 Hz)

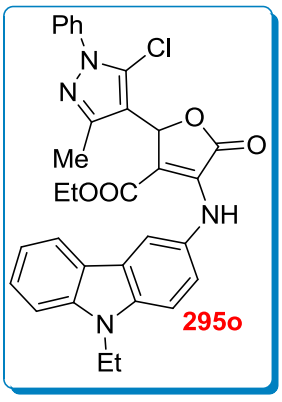
$^{13}$C NMR (100 MHz) δ: 167.1, 164.5, 140.6, 140.4, 139.2, 138.1, 129.6, 126.5, 125.9, 124.9, 123.0, 122.9, 122.8, 122.7, 122.6, 120.7, 120.6, 120.1, 119.2, 118.9, 115.9, 113.2, 108.7, 108.5, 108.3 (aromatic C), 81.7, 60.5, 37.7, 14.0, 13.9, 13.8 (aliphatic C)

LCMS (m/z): 559 $(M+2)^+$

Anal. calcd. for $C_{35}H_{31}N_3O_4$: C, 75.38; H, 5.60; N, 7.54%

Found: C, 75.42; H, 5.66; N, 7.45%

**Ethyl 2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4-(9-ethyl-9*H*-carbazol-3-ylamino)-5-oxo-2,5-dihydro-3-furancarboxylate (295o):** Compound **295o** was synthesized from aminocarbazole **294a**, aldehyde **142q** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 70%

MP: 175–177 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3431, 1668, 1275, 663

$^{1}$H NMR (400 MHz) δ: 8.45 (1H, s), 8.07 (1H, d, *J* = 7.7 Hz), 7.92 (1H, s), 7.62–7.48 (5H, m), 7.46–7.38 (3H, m), 7.33–7.31 (1H, m), 7.28–7.22 (1H, m), 6.21 (1H, s), 4.39 (2H, q, *J* = 7.8 Hz), 4.20 (2H, q, *J* = 6.8 Hz), 2.36 (3H, s), 1.46 (3H, t, *J* = 7.1 Hz), 1.18 (3H, t, *J* = 7.8 Hz)

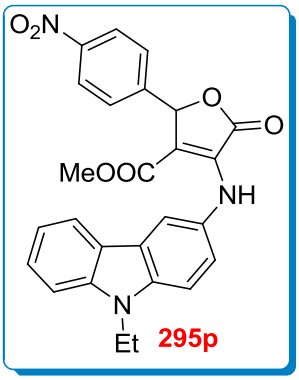
$^{13}$C NMR (100 MHz) δ: 166.5, 164.2, 148.7, 140.6, 139.8, 138.2, 137.9, 129.2, 129.1, 128.4, 127.0, 126.0, 125.1, 122.9, 122.7, 122.6, 120.6, 118.9, 116.1, 112.0, 110.1, 108.6, 108.3 (aromatic C), 72.5, 60.6, 37.7, 14.1, 13.9, 12.9 (aliphatic C)

LCMS (m/z): 556 $(M+2)^{+}$

Anal. calcd. for $C_{31}H_{27}ClN_4O_4$: C, 67.08; H, 4.90; N, 10.09%

Found: C, 67.18; H, 4.85; N, 10.21%

**Methyl 4-(9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-nitrophenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295p):** Compound **295p** was synthesized from aminocarbazole **294a**, aldehyde **142i** and acetylenedicarboxylate **53l** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 92%

MP: 186–188 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3300, 2916, 2843, 1770, 1454, 829

$^{1}$H NMR (400 MHz) δ: 8.44 (1H, s), 8.24 (2H, d, *J* = 8.7 Hz), 8.08 (1H, d, *J* = 7.7 Hz), 7.94 (1H, d, *J* = 1.6 Hz), 7.55 (2H, d, *J* = 8.7 Hz), 7.51 (1H, d, *J* = 7.3 Hz), 7.44–7.38 (2H, m), 7.34–7.32 (1H, m), 7.26 (1H, t, *J* = 7.4 Hz), 6.12 (1H, s), 4.37 (2H, q, *J* = 7.2 Hz), 3.64 (3H, s), 1.46 (3H, t, *J* = 7.2 Hz)

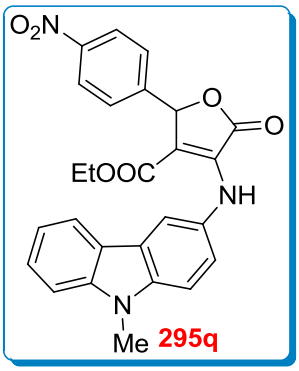
$^{13}$C NMR (100 MHz) δ: 166.1, 164.2, 148.3, 143.5, 140.6, 139.4, 138.3, 128.7, 128.4, 126.2, 123.8, 122.9, 122.8, 122.5, 120.6, 119.0, 116.5, 110.9, 108.8, 108.3 (aromatic C), 78.9, 51.7, 37.7, 13.9 (aliphatic C)

LCMS (m/z): 472 $(M+H)^{+}$

Anal. calcd. for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91%

Found: C, 66.35; H, 4.41; N, 8.79%

**Ethyl 4-(9-methyl-9*H*-carbazol-3-ylamino)-2-(4-nitrophenyl)- 5-oxo-2,5-dihydro-3-furancarboxylate (295q):** Compound **295q** was synthesized from aminocarbazole **294b**, aldehyde **142i** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 90%

MP: 170–172 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3308, 2978, 1647, 1116, 746

$^1$H NMR (400 MHz) δ: 8.43 (1H, s), 8.25 (2H, d, *J* = 7.9 Hz), 8.05 (1H, d, *J* = 7.5 Hz), 7.91 (1H, s), 7.57–7.48 (3H, m), 7.42–7.31 (3H, m), 7.26–7.22 (1H, m), 6.13 (1H, s), 4.12 (2H, q, *J* = 7.0 Hz), 3.86 (3H, s), 1.10 (3H, t, *J* = 6.1 Hz)

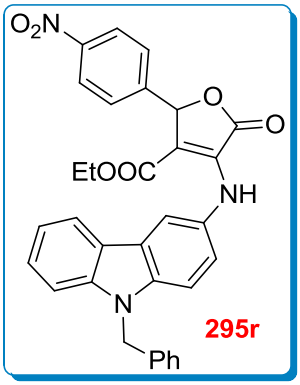
$^{13}$C NMR (100 MHz) δ: 166.0, 163.9, 143.6, 141.6, 139.4, 128.7, 128.4, 126.2, 123.7, 122.9, 122.4, 120.5, 119.1, 116.3, 111.3, 108.7, 108.3 (aromatic C), 79.0, 60.8, 29.3, 14.1 (aliphatic C)

LCMS (m/z): 472 $(M+H)^+$

Anal. calcd. for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91%

Found: C, 66.35; H, 4.41; N, 8.79%

**Ethyl 4-(9-Benzyl-9*H*-carbazol-3-ylamino)-2-(4-nitrophenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295r):** Compound **295r** was synthesized from aminocarbazole **294c**, aldehyde **142i** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 91%

MP: 159–161 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3294, 2976, 1514, 850

$^1$H NMR (400 MHz) δ: 8.41 (1H, s), 8.24 (2H, d, *J* = 8.5 Hz), 8.09 (1H, d, *J* = 7.6 Hz), 7.95

(1H, s), 7.55 (2H, d, *J* = 8.4 Hz), 7.46 (1H, t, *J* = 7.6 Hz), 7.38 (1H, d, *J* = 8.1 Hz), 7.33–7.26 (6H, m), 7.16–7.15 (2H, m), 6.13 (1H, s), 5.50 (2H, s), 4.09 (2H, q, *J* = 6.9 Hz), 1.07 (3H, t, *J* = 6.9 Hz)

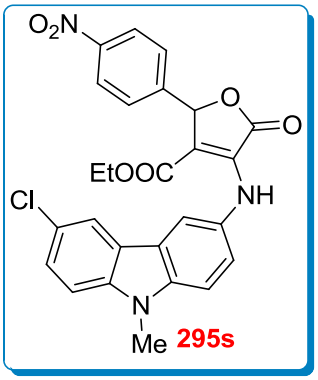
$^{13}$C NMR (100 MHz) δ: 166.3, 163.8, 148.3, 143.6, 141.3, 139.1, 138.9, 136.9, 129.2, 128.9, 128.4, 127.6, 126.4, 123.8, 123.1, 122.9, 122.7, 120.6, 119.5, 116.3, 111.5, 109.2, 108.9 (aromatic C), 79.1, 60.9, 46.7, 14.0 (aliphatic C)

LCMS (m/z): 548 $(M+H)^+$

Anal. calcd. for $C_{32}H_{25}N_3O_6$: C, 70.19; H, 4.60; N, 7.67%

Found: C, 70.09; H, 4.55; N, 7.72%

**Ethyl 4-(6-chloro-9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-nitrophenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295s):** Compound **295s** was synthesized from aminocarbazole **294d**, aldehyde **142i** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 90%

MP: 119–121 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3323, 2980, 1641, 1201, 736

$^1$H NMR (400 MHz) δ: 8.43 (1H, s), 8.25 (2H, d, *J* = 7.9 Hz), 7.99 (1H, s), 7.85 (1H, s), 7.55 (2H, d, *J* = 7.9 Hz), 7.42 (1H, d, *J* = 8.7 Hz), 7.38–7.30 (3H, m), 6.14 (1H, s), 4.33 (2H, q, *J* = 6.8 Hz), 4.12 (2H, q, *J* = 6.8 Hz), 1.43 (3H, t, *J* = 6.9 Hz), 1.10 (3H, t, *J* = 6.9 Hz)

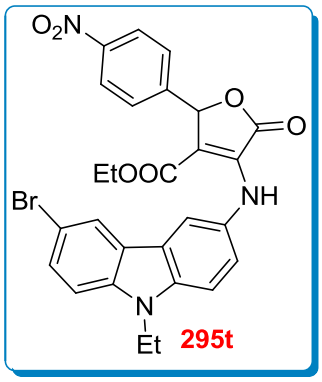
$^{13}$C NMR (100 MHz) δ: 166.1, 163.8, 148.3, 143.5, 139.3, 138.9, 138.7, 129.0, 128.4, 126.2, 124.5, 123.7, 123.6, 123.5, 122.0, 120.3, 116.5, 111.7, 109.7, 108.7 (aromatic C), 79.0, 60.9, 37.9, 14.0, 13.8 (aliphatic C)

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

Anal. calcd. for $C_{27}H_{22}ClN_3O_6$: C, 62.37; H, 4.26; N, 8.08%

Found: C, 62.28; H, 4.31; N, 8.15%

**Ethyl 4-(6-bromo-9-ethyl-9*H*-carbazol-3-ylamino)-2-(4-nitrophenyl)-5-oxo-2,5-dihydro-3-furancarboxylate (295t):** Compound **295t** was synthesized from aminocarbazole **294e**, aldehyde **142i** and acetylenedicarboxylate **53k** following the *general procedure H*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.



**295t**

Yield: 90%

MP: 145–147 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3314, 1682, 1232, 804

$^1$H NMR (400 MHz) δ: 8.43 (1H, s), 8.25 (2H, d, *J* = 8.2 Hz), 8.14 (1H, s), 7.84 (1H, s), 7.55 (3H, d, *J* = 8.1 Hz), 7.34 (2H, q, *J* = 8.5 Hz), 7.27 (1H, d, *J* = 8.4 Hz), 6.13 (1H, s), 4.32 (2H, q, *J* = 7.1 Hz), 4.12 (2H, q, *J* = 6.9 Hz), 1.43 (3H, t, *J* = 6.8 Hz), 1.10 (3H, t, *J* = 6.9 Hz)

$^{13}$C NMR (100 MHz) δ: 166.1, 163.9, 148.3, 143.5, 139.3, 139.2, 138.6, 129.1, 128.8, 128.4, 124.2, 123.8, 123.5, 123.3, 121.9, 116.5, 111.8, 111.7, 110.2, 108.6 (aromatic C), 79.0, 60.9, 37.9, 14.0, 13.8 (aliphatic C)

LCMS (m/z): 565 $(M+2)^+$

Anal. calcd. for $C_{27}H_{22}BrN_3O_6$: C, 57.46; H, 3.93; N, 7.45%

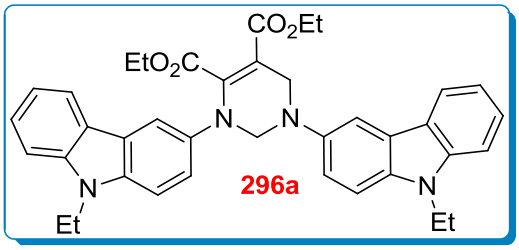
Found: C, 57.39; H, 3.85; N, 7.38%

***General procedure I:***

In a round-bottom flask equipped with a magnetic stirrer bar, and containing amine (2.0 mmol) and diethyl acetylenedicarboxylate (1.2 mmol) in [Bmim][$BF_4$] (3 mL) as solvent, was added 37% formaldehyde solution (**278,** 6 mmol). The reaction mixture was stirred at 110 °C for 1 h. After completion of the reaction, as indicated by TLC, $H_2O$ (10 mL) was added to the crude reaction mass. Then, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure.

**Diethyl 1,3-bis(9-ethyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedicarboxylate (296a):** Compound **296a** was synthesized from aminocarbazole **294a** and

acetylenedicarboxylate **53k** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.




Yield: 84%

MP: 120–122 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3051, 1738, 1693, 1230, 746

$^1$H NMR (400 MHz) δ: 7.96 (1H, d, *J* = 7.7 Hz), 7.81–7.80 (2H, m), 7.76 (1H, s), 7.48–7.42 (2H, m), 7.39–7.37 (2H, m), 7.29–7.25 (3H, m), 7.19–7.11 (3H, m), 5.04 (2H, s), 4.41 (2H, s), 4.34–4.29 (4H, m), 4.26–4.21 (2H, m), 3.95 (2H, q, *J* = 7.1 Hz), 1.42–1.36 (6H, m), 1.30 (3H, t, *J* = 7.1 Hz), 0.90 (3H, t, *J* = 7.2 Hz)

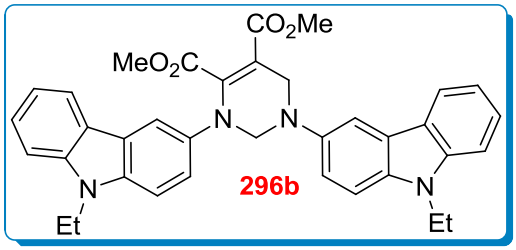
$^{13}$C NMR (100 MHz) δ: 166.1, 164.4, 148.1, 141.9, 140.5, 138.5, 136.0, 135.1, 126.1, 125.6, 124.5, 123.2, 122.9, 122.8, 122.5, 120.5, 120.4, 119.6, 119.1, 118.8, 118.5, 110.9, 109.1, 108.7, 108.5 (aromatic C), 97.7, 71.7, 61.4, 60.0, 49.1, 37.7, 37.6, 14.5, 13.9, 13.7 (aliphatic C)

LCMS (m/z): 615 $(M+H)^+$

Anal. calcd. for $C_{38}H_{38}N_4O_4$: C, 74.24; H, 6.23; N, 9.11%

Found: C, 74.32; H, 6.18; N, 9.15%

**Dimethyl 1,3-bis(9-ethyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedi carboxylate (296b):** Compound **296b** was synthesized from aminocarbazole **294a** and acetylenedicarboxylate **53l** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.




Yield: 88%

MP: 134–136 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3059, 1269, 1111, 746

$^1$H NMR (400 MHz) δ: 8.00 (1H, d, *J* = 7.7 Hz), 7.88– 7.84 (2H, m), 7.76 (1H, d, *J* = 1.4 Hz), 7.48 (2H, q, *J* = 7.5 Hz), 7.42–7.40 (2H, m), 7.34–7.32 (2H, m), 7.29–7.27 (1H, m), 7.22– 7.15 (3H, m),

5.09 (2H, s), 4.45 (2H, s), 4.34 (4H, q, *J* = 6.8 Hz), 3.82 (3H, s), 3.55 (3H, s), 1.45–1.39 (6H, m)

$^{13}$C NMR (100 MHz) δ: 166.6, 164.9, 148.2, 141.8, 140.5, 140.4, 138.5, 136.1, 134.9, 126.2, 125.6, 124.3, 123.3, 123.1, 122.8, 122.5, 120.6, 120.5, 119.5, 119.1, 118.5, 110.8, 109.1, 108.7, 108.5 (aromatic C), 97.3, 71.7, 52.4, 51.4, 48.9, 37.7, 37.6, 13.9 (aliphatic C)

LCMS (m/z): 587 $(M+H)^+$

Anal. calcd. for $C_{36}H_{34}N_4O_4$: C, 73.70; H, 5.84; N, 9.55%

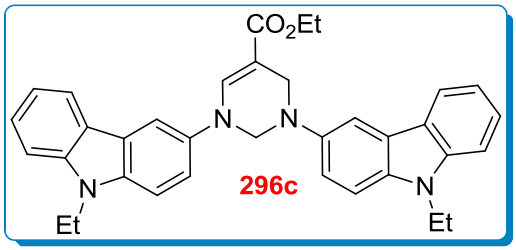
Found: C, 73.65; H, 5.91; N, 9.48%

**Ethyl 1,3-bis(9-ethyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4-pyrimidinecarboxylate (296c):** Compound **296c** was synthesized from aminocarbazole **294a** and acetylenedicarboxylate **53f** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 75%

MP: 141–143 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 1672, 1379, 1022, 723




$^1$H NMR (400 MHz) δ: 8.08 (1H, d, *J* = 7.8 Hz), 8.02 (1H, d, *J* = 2.4 Hz), 7.90 (1H, d, *J* = 6.0 Hz), 7.80–7.79 (2H, m), 7.52 (1H, t, *J* = 7.2 Hz), 7.43 (2H, t, *J* = 8.4 Hz), 7.37–7.30 (4H, m), 7.26 (1H, t, *J* = 8.2 Hz), 7.21–7.19 (1H, m), 7.15–7.11 (1H, m), 5.21 (2H, s), 4.44 (2H, s), 4.35–4.33 (2H, m), 4.32–4.30 (4H, m), 1.46 (3H, t, *J* = 7.2 Hz), 1.41–1.34 (6H, m)

$^{13}$C NMR (100 MHz) δ: 167.4, 142.4, 142.3, 140.6, 140.4, 137.5, 137.2, 135.9, 126.3, 125.6, 123.6, 123.2, 122.7, 122.5, 120.7, 120.3, 119.3, 118.9, 118.7, 118.4, 111.8, 110.6, 109.2, 109.0, 108.8, 108.5 (aromatic C), 98.0, 68.2, 59.4, 49.1, 37.7, 37.6, 14.7, 13.9 (aliphatic C)

LCMS (m/z): 543 $(M+H)^+$

Anal. calcd. for $C_{35}H_{34}N_4O_2$: C, 77.46; H, 6.32; N, 10.32%

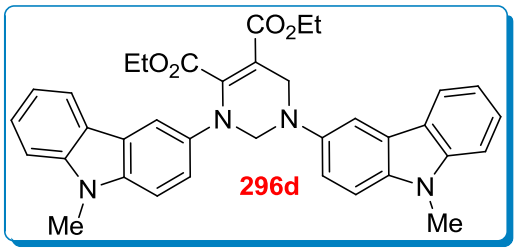
Found: C, 77.32; H, 6.41; N, 10.21%

**Diethyl 1,3-bis(9-methyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedicarboxylate (296d):** Compound **296d** was synthesized from aminocarbazole **294b** and acetylenedicarboxylate **53k** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 85%

MP: 110–112 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 2930, 1469, 1103, 632




$^{1}H$ NMR (400 MHz) δ: 7.99 (1H, d, *J* = 6.8 Hz), 7.85– 7.82 (2H, m), 7.75 (1H, s), 7.47 (2H, d, *J* = 6.7 Hz), 7.36 (2H, d, *J* = 7.5 Hz), 7.29–7.19 (6H, m), 5.05 (2H, s), 4.45 (2H, s), 4.28 (2H, q, *J* = 6.1 Hz), 3.97 (2H, q, *J* = 6.1 Hz), 3.83–3.72 (6H, m), 1.34 (3H, t, *J* = 7.1 Hz), 0.94 (3H, t, *J* = 7.1 Hz)

$^{13}C$ NMR (100 MHz) δ: 166.1, 164.4, 148.1, 141.9, 141.5, 139.5, 137.1, 135.2, 126.2, 125.7, 124.5, 123.1, 122.8, 122.6, 122.3, 120.4, 119.6, 119.2, 118.7, 118.5, 110.8, 109.1, 108.7, 108.5 (aromatic C), 97.8, 71.8, 61.4, 60.0, 49.1, 29.2, 14.5, 13.7 (aliphatic C)

LCMS (m/z): 587 $(M+H)^{+}$

Anal. calcd. for $C_{36}H_{34}N_4O_4$: C, 73.70; H, 5.84; N, 9.55%

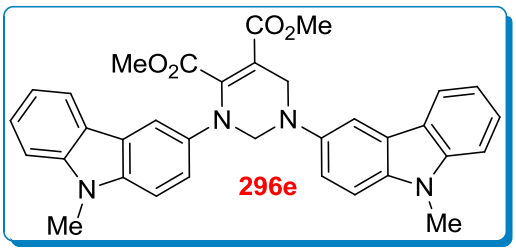
Found: C, 73.85; H, 5.81; N, 9.48%

**Diethyl 1,3-bis(9-methyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedicarboxylate (296e):** Compound **296e** was synthesized from aminocarbazole **294b** and acetylenedicarboxylate **53l** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 82%

MP: 184–186 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2926, 1745, 1467, 746



$^1$H NMR (400 MHz) δ: 7.97 (1H, d, *J* = 7.7 Hz), 7.83– 7.81 (2H, m), 7.71 (1H, d, *J* = 1.4 Hz), 7.48–7.46 (2H, m), 7.37 (2H, d, *J* = 8.1 Hz), 7.29–7.23 (3H, m), 7.18–7.13 (3H, m), 5.06 (2H, s), 4.44 (2H, s), 3.80 (6H, s), 3.79 (3H, s), 3.50 (3H, s)

$^{13}$C NMR (100 MHz) δ: 166.5, 164.9, 148.2, 141.9, 141.6, 141.5, 139.5, 137.2, 135.1, 126.2, 125.7, 124.3, 123.1, 122.9, 122.6, 122.3, 120.4, 120.3, 119.5, 119.2, 118.5, 118.4, 110.8, 109.1, 108.72, 108.66, 108.5 (aromatic C), 97.4, 71.8, 52.4, 51.4, 48.9, 29.2, 29.1 (aliphatic C)

LCMS (m/z): 559 $(M+H)^+$

Anal. calcd. for $C_{34}H_{30}N_4O_4$: C, 73.10; H, 5.41; N, 10.03%

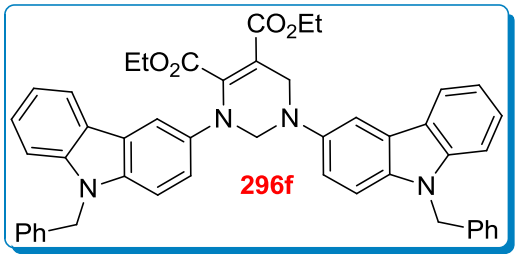
Found: C, 73.25; H, 5.36; N, 9.89.%

**Diethyl 1,3-bis(9-benzyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedi carboxylate (296f):** Compound **296f** was synthesized from aminocarbazole **294c** and acetylenedicarboxylate **53k** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.

Yield: 80%

MP: 166–168 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3055, 2926, 1491, 1327, 746




$^1$H NMR (400 MHz) δ: 8.00 (1H, d, *J* = 7.4 Hz), 7.87–7.82 (3H, m), 7.43–7.32 (4H, m), 7.24–7.10 (16H, m), 5.46 (4H, d, *J* = 7.4 Hz), 5.04 (2H, s), 4.40 (2H, s), 4.24 (2H, q, *J* = 6.9 Hz), 3.97 (2H, q, *J* = 6.8 Hz), 1.31 (3H, t, *J* = 6.6 Hz), 0.86 (3H, t, *J* = 6.6 Hz)

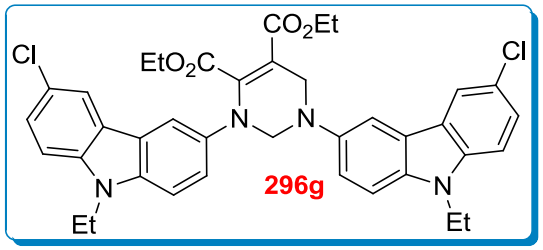
$^{13}$C NMR (100 MHz) δ: 166.0, 164.3, 147.9, 142.3, 141.3, 141.2, 139.2, 137.3, 136.8, 136.7, 135.4, 128.8, 128.7, 127.6, 127.4, 126.38, 126.35, 125.8, 124.7, 123.4, 123.1, 122.9, 122.6, 120.6, 120.4, 119.7, 119.6, 118.9, 118.8, 110.8, 109.6, 109.2, 108.9 (aromatic C), 97.8, 71.4, 61.4, 60.0, 49.2, 46.7, 46.6, 14.5, 13.6 (aliphatic C)

LCMS (m/z): 737 $(M-H)^+$

Anal. calcd. for $C_{48}H_{42}N_4O_4$: C, 78.03; H, 5.73; N, 7.58%

Found: C, 78.12; H, 5.65; N, 7.51%

**Diethyl 1,3-bis(6-chloro-9-ethyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedicarboxylate (296g):** Compound **296g** was synthesized from aminocarbazole **294d** and acetylenedicarboxylate **53k** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.




Yield: 80%

MP: 166–168 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2976, 1697, 1226, 655

$^{1}H$ NMR (400 MHz) δ: 7.87 (1H, s), 7.73 (1H, s), 7.68 (1H, s), 7.56 (1H, s), 7.40–7.37 (2H, m), 7.32–7.22 (6H, m), 5.04 (2H, s), 4.43 (2H, s), 4.28 (6H, q, *J* = 6.4 Hz), 4.00 (2H, q, *J* = 7.0 Hz), 1.41–1.32 (9H,m), 0.94 (3H, t, *J* = 7.1 Hz)

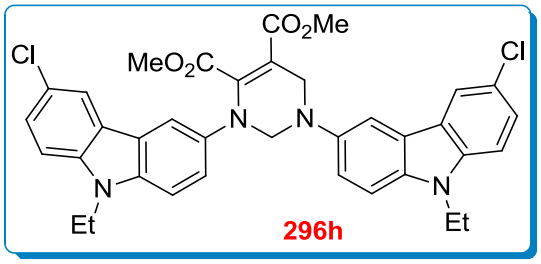
$^{13}C$ NMR (100 MHz) δ: 165.9, 164.3, 147.8, 142.1, 138.8, 138.7, 136.4, 130.5, 126.2, 125.6, 125.1, 124.6, 123.9, 123.8, 123.5, 122.3, 122.0, 120.3, 120.0, 119.9, 118.8, 110.8, 109.7, 109.6, 109.4, 108.9 (aromatic C), 98.5, 71.7, 61.5, 60.1, 49.1, 37.9, 37.8, 14.4, 13.8, 13.6 (aliphatic C)

LCMS (m/z): 684 $(M+2)^{+}$

Anal. calcd. for $C_{38}H_{36}Cl_2N_4O_4$: C, 66.76; H, 5.31; N, 8.20%

Found: C, 66.58; H, 5.36; N, 8.31%

**Dimethyl 1,3-bis(6-chloro-9-ethyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedicarboxylate (296h):** Compound **296h** was synthesized from aminocarbazole **294d** and acetylenedicarboxylate **53l** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.




Yield: 85%

MP: 195–197 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3063, 2943, 1294,

746

$^{1}$H NMR (400 MHz) δ: 7.85 (1H, s), 7.68 (2H, s), 7.52 (1H, s), 7.38–7.35 (2H, m), 7.28–7.24 (5H, m), 7.21–7.18 (1H, m), 5.03 (2H, s), 4.41 (2H, s), 4.29–4.26 (4H, m), 3.80 (3H, s), 3.54 (3H, s), 1.40–1.34 (6H, m)

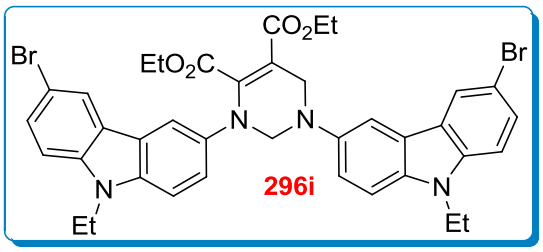
$^{13}$C NMR (100 MHz) δ: 166.4, 164.9, 147.9, 142.0, 138.83, 138.80, 138.7, 136.4, 135.4, 126.3, 125.7, 124.9, 124.6, 123.9, 123.7, 123.5, 122.3, 122.2, 120.2, 120.1, 119.9, 118.5, 110.7, 109.7, 109.6, 109.4, 109.0 (aromatic C), 98.1, 71.7, 62.5, 61.5, 48.9, 37.9, 37.8, 13.82, 13.79 (aliphatic C)

LCMS (m/z): 656 $(M+2)^{+}$

Anal. calcd. for $C_{36}H_{32}Cl_2N_4O_4$: C, 65.96; H, 4.92; N, 8.55%

Found: C, 65.88; H, 4.96; N, 8.65%

**Diethyl 1,3-bis(6-bromo-9-ethyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedicarboxylate (296i):** Compound **296i** was synthesized from aminocarbazole **294e** and acetylenedicarboxylate **53k** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.




Yield: 85%

MP: 95-97 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2970, 1736, 1481, 1226

$^{1}$H NMR (400 MHz) δ: 7.99 (1H, s), 7.83 (1H, s), 7.69 (1H, s), 7.55 (1H, s), 7.49 (2H, t, *J* = 7.8 Hz), 7.28–7.21 (6H, m), 5.02 (2H, s), 4.41 (2H, s), 4.26 (6H, q, *J* = 7.1 Hz), 3.98 (2H, q, *J* = 6.6 Hz), 1.38–1.28 (9H, m), 0.92 (3H, t, *J* = 6.9 Hz)

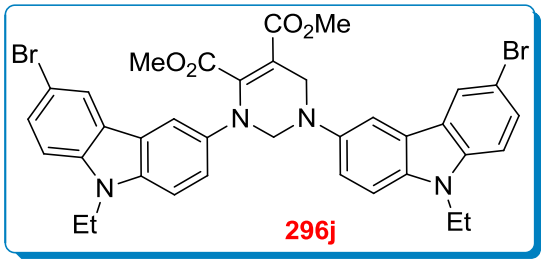
$^{13}$C NMR (100 MHz) δ: 165.9, 164.3, 147.8, 142.2, 139.1, 138.9, 138.6, 136.2, 135.6, 128.8, 128.2, 125.1, 124.4, 124.1, 123.1, 122.9, 122.2, 121.9, 120.3, 118.8, 111.9, 111.2, 110.8, 110.2, 110.1, 109.4, 108.9 (aromatic C), 98.6, 71.6, 61.5, 60.1, 49.1, 37.9, 37.8, 14.5, 13.8, 13.7 (aliphatic C)

LCMS (m/z): 772 $(M+2)^{+}$

Anal. calcd. for $C_{38}H_{36}Br_2N_4O_4$:C, 59.08; H, 4.70; N, 7.25%

Found: C, 59.15; H, 4.61; N, 7.36%

**Dimethyl 1,3-bis(6-bromo-9-ethyl-9*H*-carbazol-3-yl)-1,2,3,6-tetrahydro-4,5-pyrimidinedicarboxylate (296j):** Compound **296j** was synthesized from aminocarbazole **294e** and acetylenedicarboxylate **53l** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 15% ethyl acetate in hexanes.




Yield: 82%

MP: 110–112 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2943, 1697, 1228, 605

$^1$H NMR (500 MHz) δ: 7.89 (1H, d, *J* = 1.7 Hz), 7.73 (1H, d, *J* = 1.7 Hz), 7.56 (1H, s), 7.41–7.36 (3H, m), 7.17 (2H, d, *J* = 0.7 Hz), 7.15–7.07 (4H, m), 4.92 (2H, s), 4.29 (2H, s), 4.19–4.14 (4H, m), 3.68 (3H, s), 3.42 (3H, s), 1.29–1.23 (6H, m)

$^{13}$C NMR (125 MHz) δ: 166.4, 164.8, 147.8, 142.1, 139.1, 139.0, 138.7, 136.3, 135.5, 128.9, 128.3, 124.9, 124.4, 124.1, 123.1, 123.0, 122.3, 122.1, 120.1, 118.5, 111.9, 111.2, 110.7, 110.2, 110.1, 109.4, 108.9 (aromatic C), 98.2, 71.6, 52.5, 51.5, 48.9, 37.9, 37.8, 13.8, 13.7 (aliphatic C)

LCMS (m/z): 742 $(M^+)$, 744 $(M+2)^+$

Anal. calcd. for $C_{36}H_{32}Br_2N_4O_4$:C, 58.08; H, 4.33; N, 7.53%

Found: C, 58.16; H, 4.37; N, 7.45%

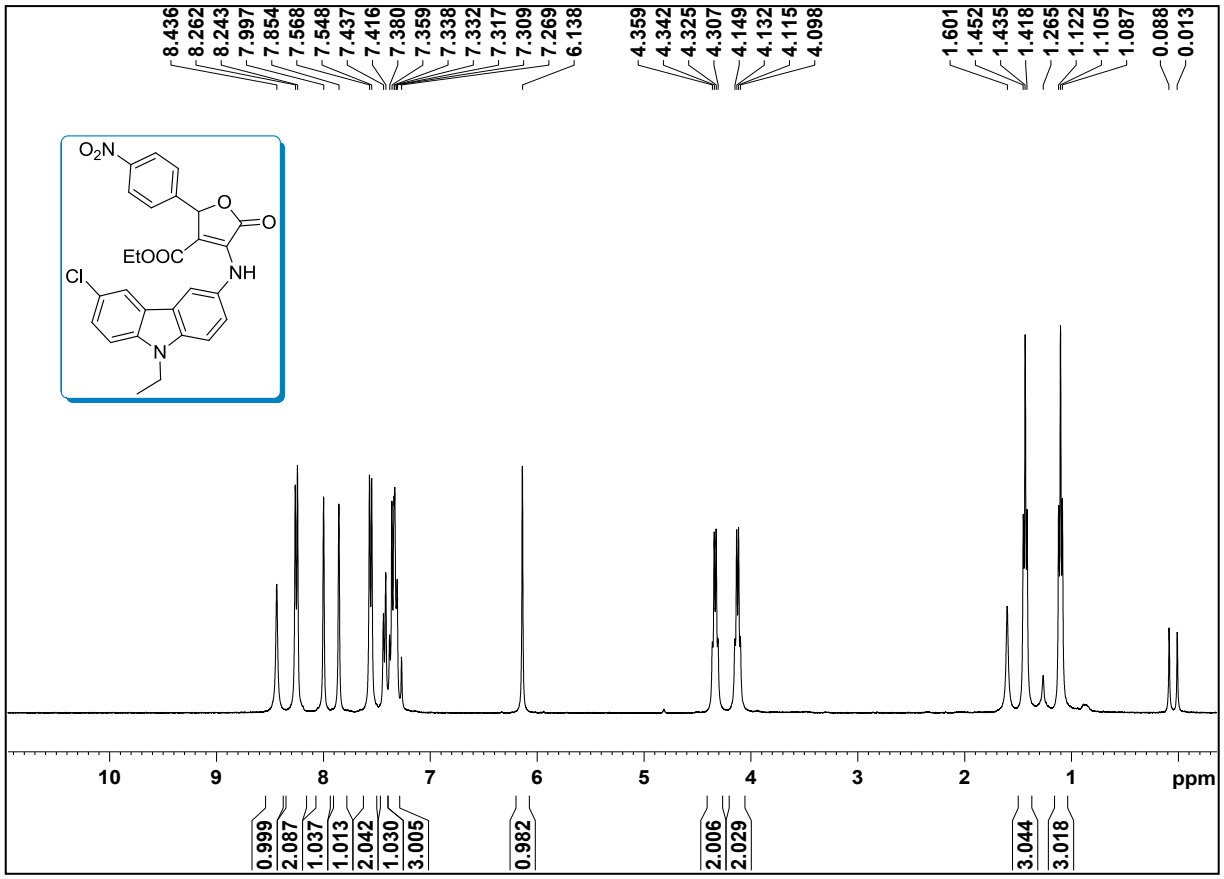
**Table 28. Crystal data and structure refinement for 295a**

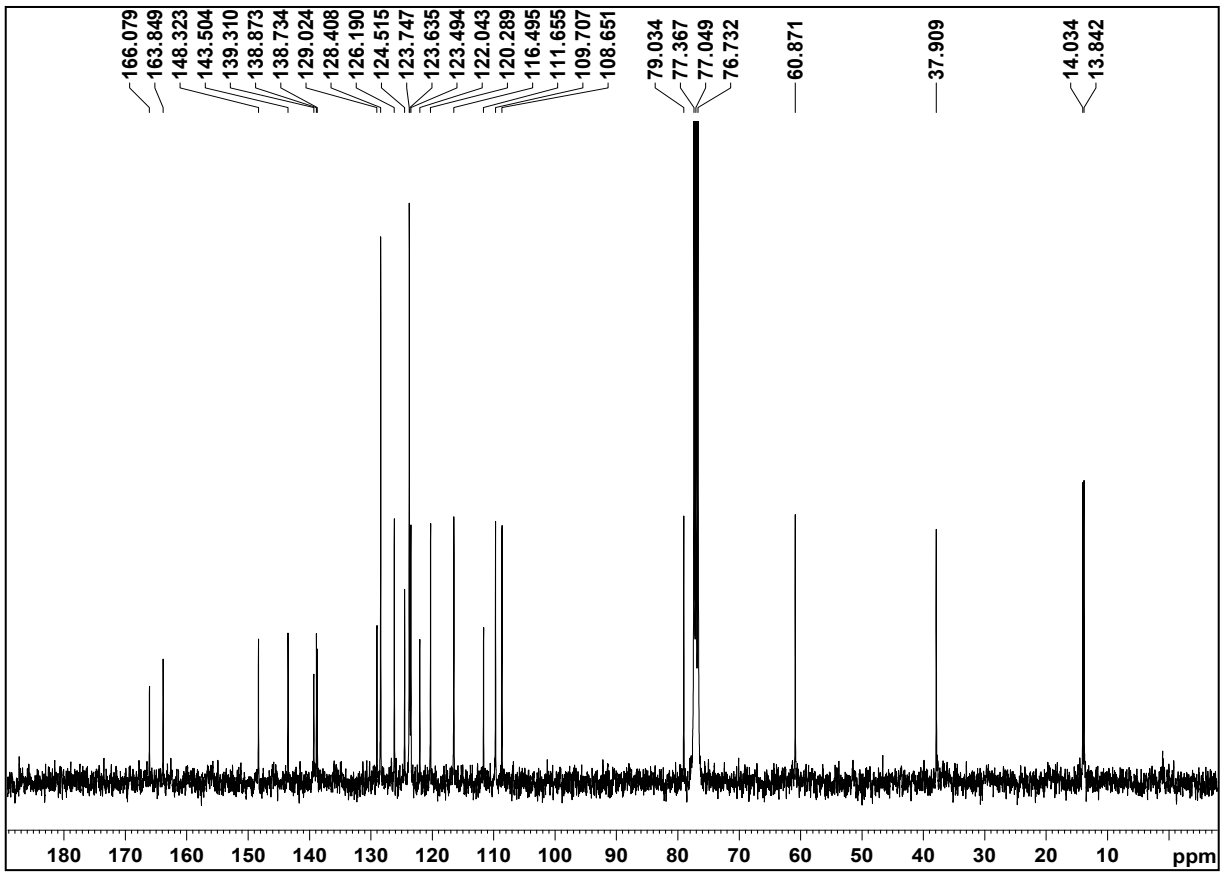
| | |
|---|---|
| Empirical formula | : $C_{27}H_{23}N_3O_6$ |
| Formula weight | : 485.48 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Triclinic |
| Space group | : P -1 |
| Unit cell dimensions | : a = 8.5722(18) Å $\alpha$= 73.836(16)° |
| | : b = 9.8231(18) Å $\beta$= 74.258(18)° |
| | : c = 15.607(3) Å $\gamma$ = 76.080(17)° |
| Volume | : 1195.4(4) $Å^3$ |
| Z | : 2 |
| Density (calculated) | : 1.349 $Mg/m^3$ |
| Absorption coefficient | : 0.097 $mm^{-1}$ |
| F (000) | : 508 |
| Crystal size | : 0.40 x 0.20 x 0.12 $mm^3$ |
| Theta range for data collection | : 2.79 to 24.71° |
| Index ranges | : -10<=h<=10, -11<=k<=9, -18<=l<=18 |
| Reflections collected | : 7470 |
| Independent reflections | : 4074 [R(int) = 0.0338] |
| Completeness to theta = 26.04° | : 99.9% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9885 and 0.9623 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 4074 / 0 / 331 |
| Goodness-of-fit on $F^2$ | : 0.883 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0534, wR2 = 0.1307 |
| R indices (all data) | : R1 = 0.1038, wR2 = 0.1490 |
| Largest diff. peak and hole | : 0.534 and -0.206 $e.Å^{-3}$ |
| CCDC number | : 808976 |

**Table 29. Crystal data and structure refinement for 296b**

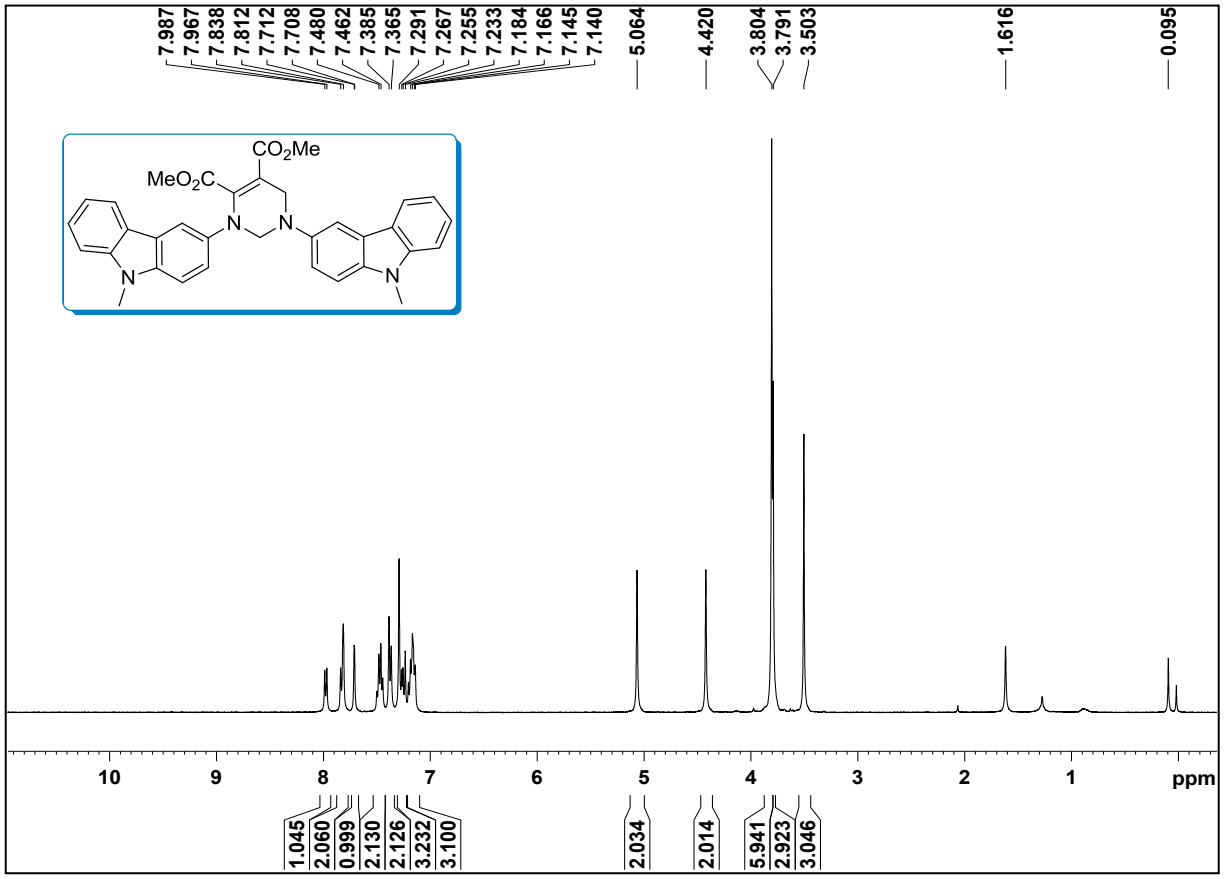
| | |
|---|---|
| Empirical formula | : $C_{36}H_{34}N_4O_4$ |
| Formula weight | : 586.67 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Triclinic |
| Space group | : P -1 |
| Unit cell dimensions | : a = 8.9790(6) Å $\alpha$= 85.908(5)° |
| | : b = 12.9073(8) Å $\beta$= 73.556(6)° |
| | : c = 15.8140(10) Å $\gamma$ = 76.731(6)° |
| Volume | : 1710.83(19) $Å^3$ |
| Z | : 2 |
| Density (calculated) | : 1.139 $Mg/m^3$ |
| Absorption coefficient | : 0.075 $mm^{-1}$ |
| F (000) | : 620 |
| Crystal size | : 0.36 x 0.18 x 0.10 $mm^3$ |
| Theta range for data collection | : 2.69 to 24.71° |
| Index ranges | : -10<=h<=7, -15<=k<=15, -18<=l<=18 |
| Reflections collected | : 12997 |
| Independent reflections | : 5836 [R(int) = 0.0550] |
| Completeness to theta = 26.04° | : 99.8% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9925 and 0.9734 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 5836 / 0 / 401 |
| Goodness-of-fit on $F^2$ | : 1.054 |
| Final R indices [I>2sigma (I)] | : R1 = 0.1000, wR2 = 0.2911 |
| R indices (all data) | : R1 = 0.1635, wR2 = 0.3515 |
| Largest diff. peak and hole | : 0.826 and -0.335 $e.Å^{-3}$ |
| CCDC number | : 808977 |

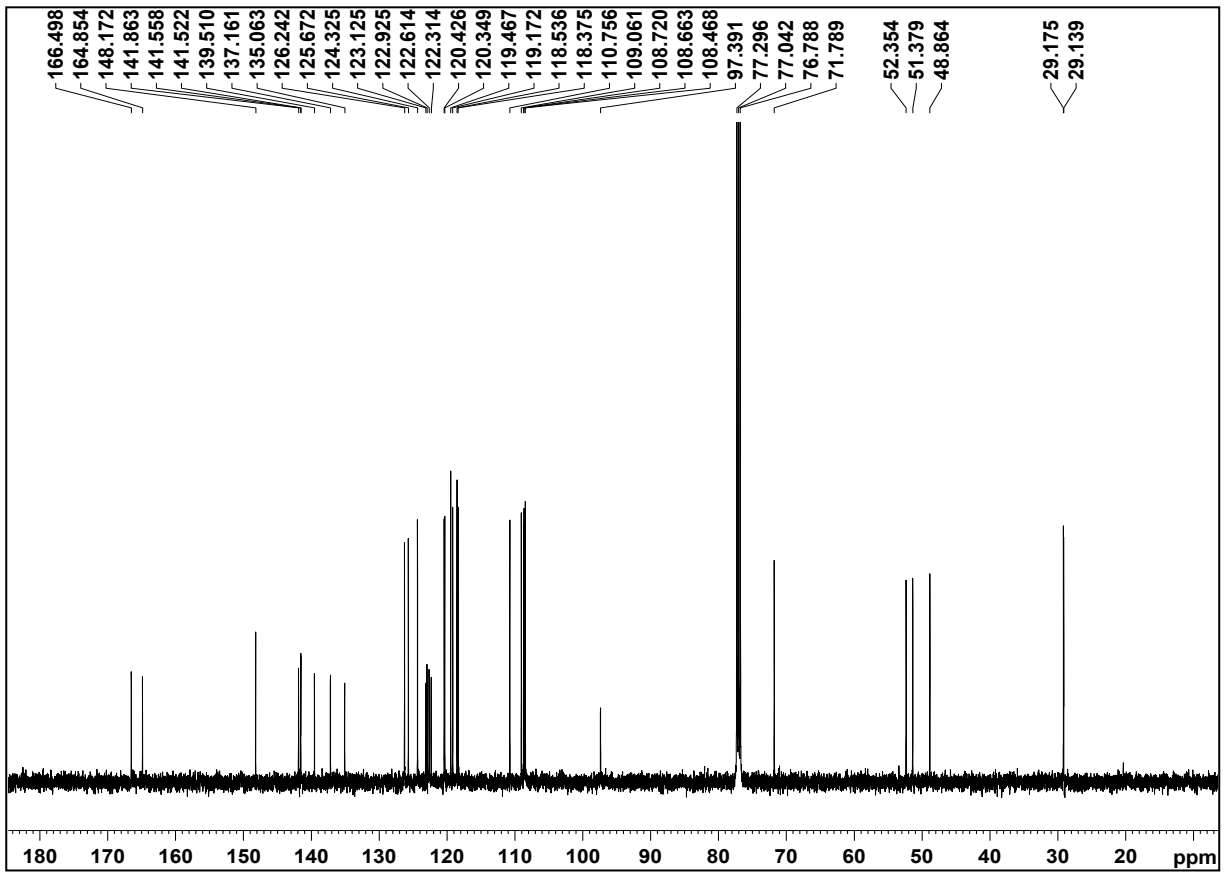
## Spectra No. 14: $^{1}H$ and $^{13}C$ spectra of compound 295s



## Spectra No. 15: $^{1}H$ and $^{13}C$ spectra of compound 296e



## 4.5. Conclusions

In summary, we have described a highly efficient three component synthesis of new carbazolyl furanones and carbazolyl tetrahydropyrimidines in good yields. The important features of this synthetic method are the mild reaction conditions, inexpensive starting materials, and avoiding expensive catalysts.

## 4.6. References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# CHAPTER 5

# Synthesis of benzimidazolopyrazine and fused β-carboline derivatives using *6-exo-dig* cylcization reactions

Recent years have witnessed a flurry of activity around the intramolecular addition of C- and heteroatom nucleophiles across the alkynes with carbophilic $\pi$-Lewis acids. Compared to the synthesis of oxygen containing heterocycles such as furan, pyran, benzopyran, and spiroketal skeletons, via C-O bond formation using electrocyclization, reports concerning the synthesis of nitrogen heterocycles through C-N or C-C bond formation are less. In recent years, transition metals evolved to be particularly useful in this respect because they allow attack of various *O*-, *N*-, or *C*-nucleophiles to the C-C triple bond under very mild conditions and in high efficiency. In this context, *6-exo-dig* cyclization using metal has been a powerful tool to synthesize indole fused heterocyclic derivatives.[153] Keeping all these points in view herein, we wish to report an unprecedented copper mediated protocol to synthesize fused benzimidazolopiperazine via C-N bond formation (**Part A**) and $\beta$-carboline derivatives via C-C bond formation (**Part B**) using 6-*exo-dig* cyclization reactions.

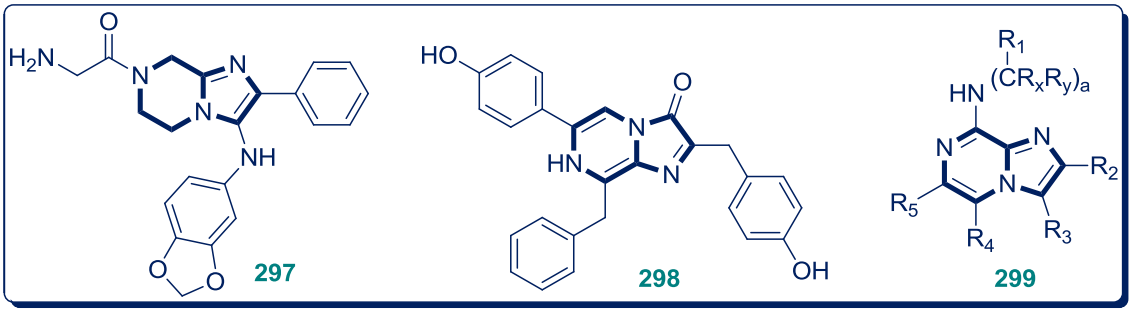
## Part A: Synthesis of fused benzimidazolopyrazine derivatives via tan dem imidazole formation/annulation of *δ*-alkynylaldehyde

### 5.1. Introduction

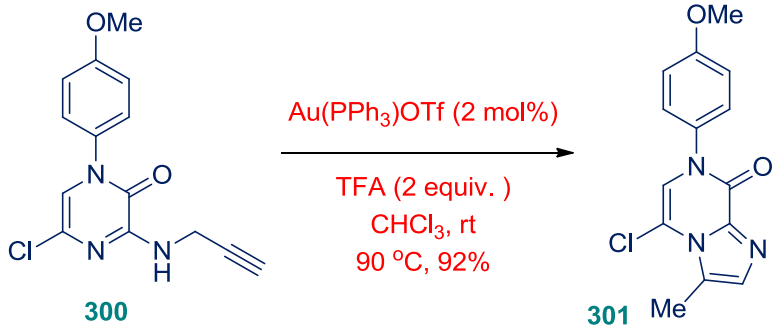
Fused heterocyclic compounds, particularly, imidazole,[154] benzimidazole[155] and pyrazine[156] derivatives show multifarious medicinal activities. Synthesis of these diverse heterocyclic derivatives, ignite a great interest on the chemical community in view of their wide spectrum of medicinal activities.[154-156] Imidazolopyrazines and imidazolopiperazines belong to the class of fused heterocycles, which are therapeutically effective. Imidazolopyrazine derivatives evince anti-inflammatory,[158] anti-arthritic,[158] antiviral activity[159] and also can inhibit MAPK-activated PK5.[158] Recent publications understandably delineated that imidazolopiperazine derivatives exhibit anti malarial activity,[157] and act as an effective CXCR3 antagonist along with pharmkaokinetic property,[160] and potent inhibitor of IGF-1R[161] as well. Polycyclic indole[162a-e] and pyrrole[162f-j] derivatives impart diverse biological activities.[162] An extensive survey of literature shows that imidazolopiperazine core itself is the

basic for antimalarial activity,[157] which may be enhanced through incorporation of indole or pyrrole moiety.

**Fig. 20**

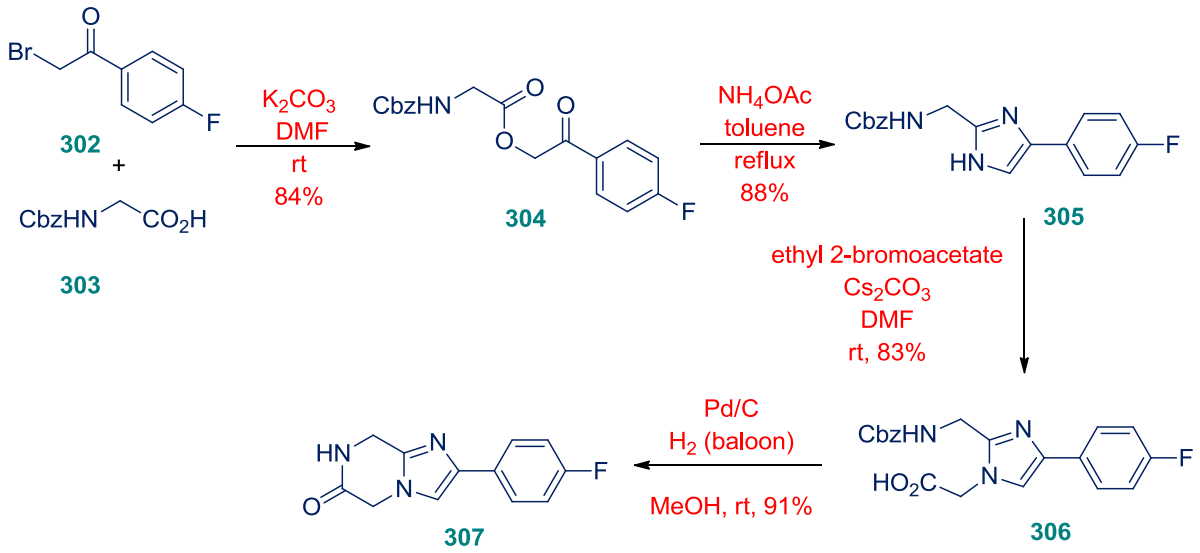



**Eq. 54**



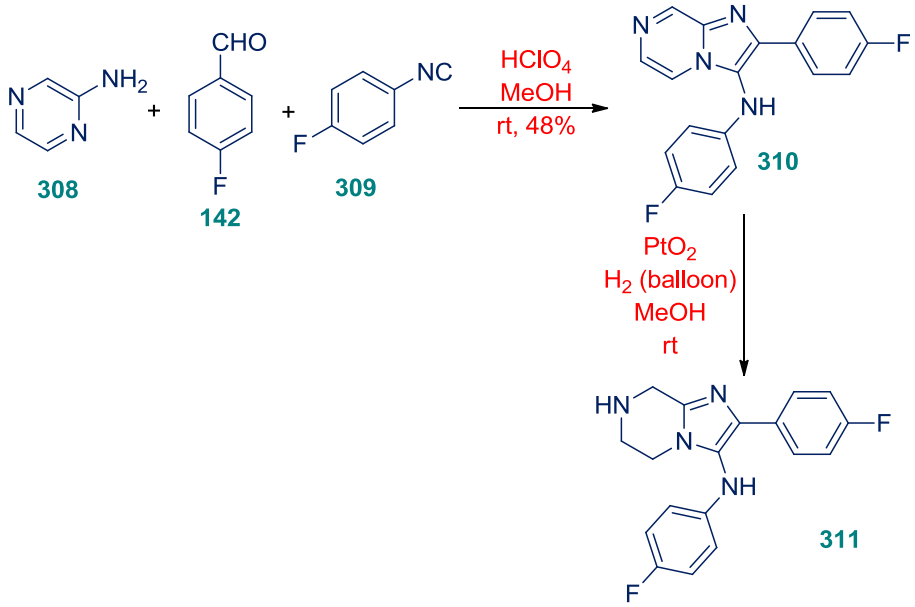

Benzimidazolopiperazine too has a considerable affinity towards $H_3$ and $H_4$-receptor for SK-N-MC cells.[163] Eycken *et al*. synthesized imidazo[1,2-*a*]pyrazinone via gold catalyzed regioselective heteroannulation of propynylaminopyrazinones (**Eq. 54**). The cationic gold-catalyzed 5-*exo-dig* heteroannulation involves nucleophilic attack of nitrogen on the activated alkyne followed by subsequent deprotonation and protodeauration. Finally, 1,3-proton shift led to product **301**.[164]

**Eq. 55**



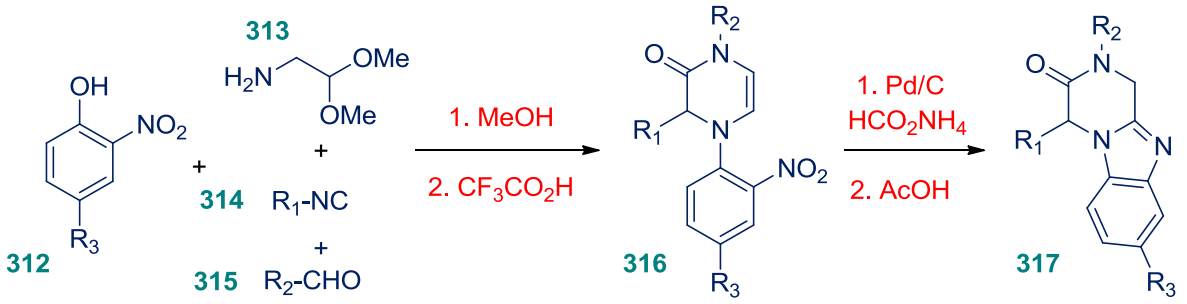
Distinct syntheses were designed and executed by Chatterjee *et al*. to obtain imidazolopiperazine core (**Eq. 55**). One of the sequences for the synthesis started with an alkylation reaction between Cbz-protected glycine derivative **303** and bromide **302**. The compound **304** was then refluxed with $NH_4OAc$ in toluene to give imidazole **305**. Regioselective *N*-alkylation with ethyl 2-bromoacetate followed by a one-pot deprotection/cyclization sequence furnished the imidazolopiperazine core **307** (**Eq. 56**). The same group reported Groebke-Blackburn three-component reaction of 2-aminopyrazine (**308**) with 4-fluorophenyl isocyanide (**309**) and 4-fluorobenzldehyde (**142**) followed by a $PtO_2$ mediated reduction of the pyrazine ring afforded the imidazolopiperazine core **311**. [157b-c]

**Eq. 56**




In addition to that, recently, a protocol for the synthesis of fused benzimidazolopiperazine derivatives **317** using Ugi-Smiles coupling has been reported (**Eq. 57**).[166] However, some shortcomings associated with the reported methodologies such as usage of toxic solvents, complex combination of starting materials and reagents may limit their applications. Inspite of such a vast applications, there is lack of new strategies to synthesize these biologically active scaffolds.

**Eq. 57**



## 5.2. Synthesis of benzimidazopyrazinoindoles

Our study commenced with the reaction between propargyl-1*H*-indole-2-carbaldehyde (**318a**) and *O*-phenylenediamine (**104a**) with copper salts. Trace amount of product **319a** was formed when CuI was used as the catalyst (**Table 30**, entry 1,) in MeCN and the reaction was not successful in the absence of catalyst (entry 2).

**Scheme 40**

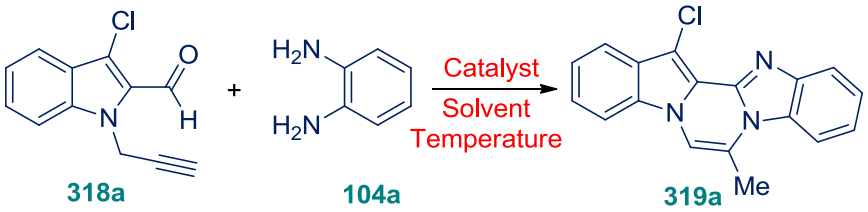



**Table 30: Optimization of the reaction conditions**

| Entry | Catalyst | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | CuI | MeCN | rt | 14 | trace |
| 2 | - | MeCN | rt | 14 | nd |
| 3 | CuI | MeCN | 90 | 14 | 20 |
| 4 | CuI | DMSO | 120 | 12 | trace |
| 5 | CuI | DMA | 90 | 2 | 30 |
| 6 | CuI | Dioxane | 90 | 7 | 35 |
| 7 | CuI | H2O | 90 | 24 | nd |
| 8 | CuI | MeCN/AcOH | 90 | 14 | 40 |
| 9 | CuI | AcOH | 90 | 15 | 50 |
| 10 | CuI | EtOH/AcOH | reflux | 15 | 62 |
| **11** | **CuI** | **$H_2O$/AcOH** | **90** | **14** | **68** |
| 12 | $Pd(OAc)_2$ | $H_2O$/AcOH | 90 | 15 | 40 |
| 13 | CuBr | $H_2O$/AcOH | 90 | 7 | 45 |
| 14 | $Cu(OTf)_2$ | $H_2O$/AcOH | 90 | 8 | trace |
| 15 | $PdCl_2$ | $H_2O$/AcOH | 90 | 24 | 20 |
| 16 | $I_2$ | $H_2O$/AcOH | 90 | 15 | trace |
| 17 | CuI | $H_2O$/HCl | 90 | 12 | 53 |
| 18 | CuI | $H_2O$/TfOH | rt | 24 | 20 |

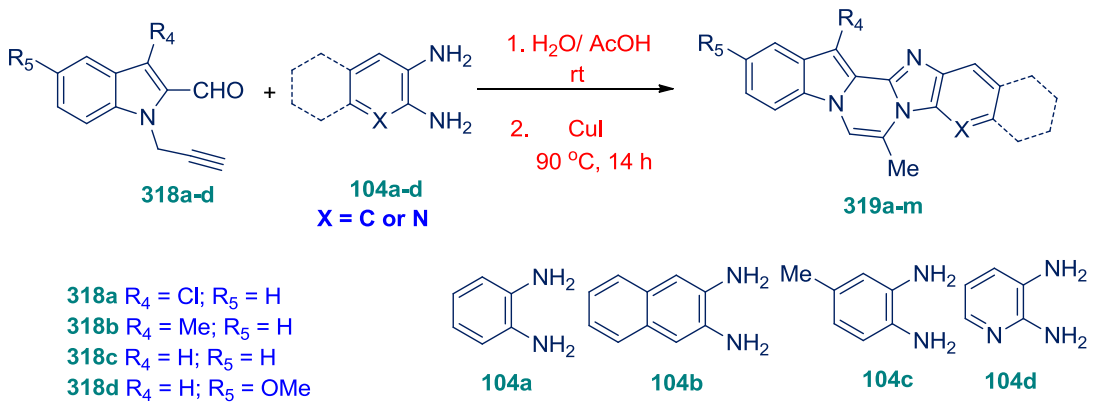
Isolated yield, reaction conditions: **318a** (1 mmol), **104a** (1.2 mmol), in solvent 5 ml at rt for 2-3 h, then catalyst in 10 mol% and heating up to 90 °C.

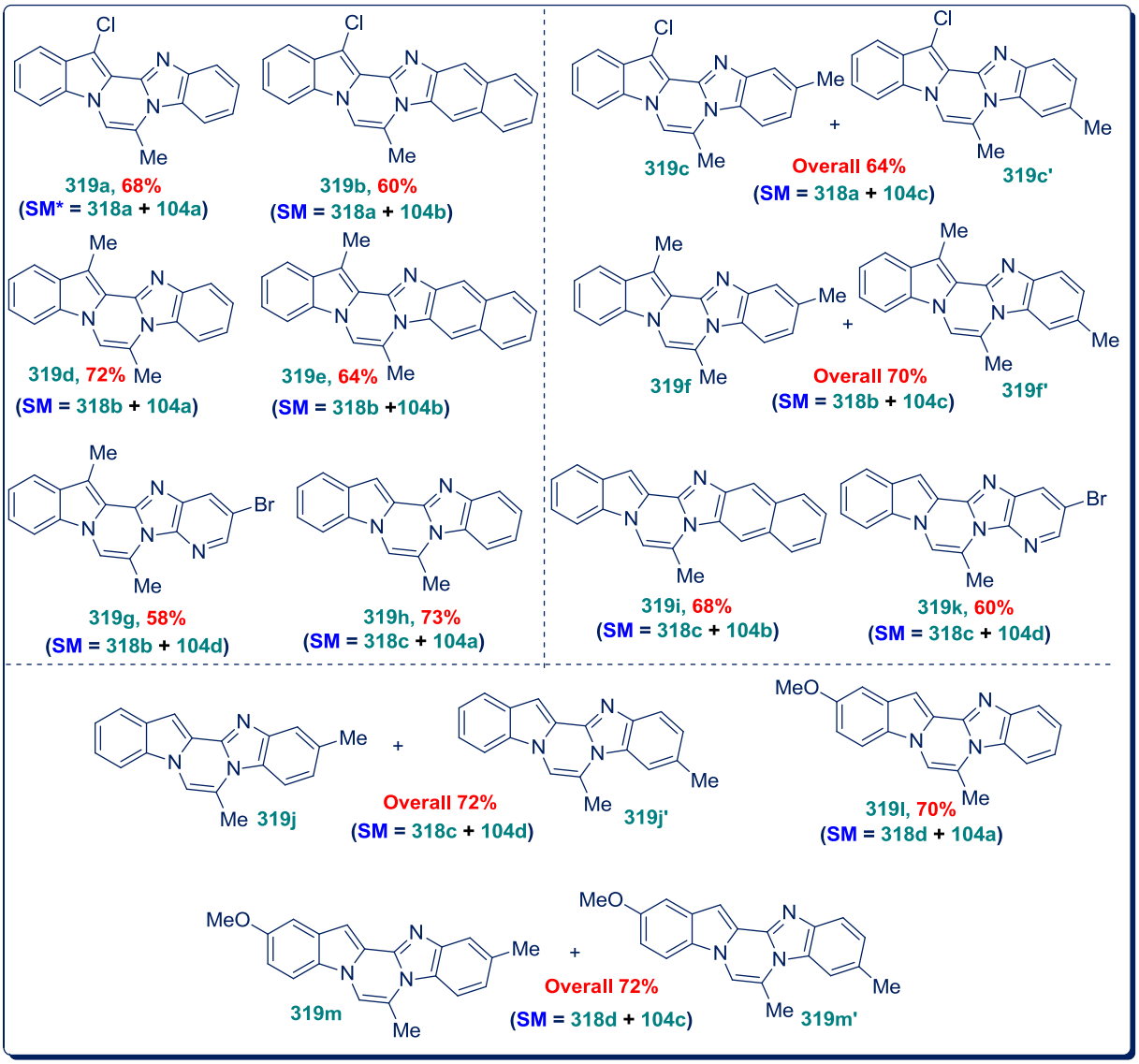
We obtained the product **319a** with 20% of yield while heating at 90 °C (entry 3). To access a better yield, we investigated some other solvents like DMSO, DMA, dioxane and $H_2O$ with CuI catalyst, but they also failed to give more than 35% yield (entries 4-7). We believe that faster formation of benzimidazole could promote this transformation which would be done by adding some protic acid. So, we used mixed solvents MeCN/AcOH in a ratio of 4:1, and CuI as the catalyst (entry 8). Interestingly, it increased the yield to 40%. Encouraged with this result, we screened some polar protic solvents along with AcOH. The reaction mixed solvents EtOH/ AcOH (4:1) with the same catalyst at reflux temperature for 14 h, afforded 62% yield (entry 10). To check the feasibility of the reaction in more polar solvents, we did the reaction in $H_2O$/ AcOH (4:1) condition (entry 11). As expected, yield of product **319a** was increased up to 68%.

We then surveyed the effect of different metal salts such as $Pd(OAc)_2$, CuBr, $Cu(OTf)_2$, and $PdCl_2$ (entry 12-15), but the results were unsatisfactory. Inspired by literature survey, to obtain an iodine incorporated product, via triple bond activation, we utilized $I_2$ as a catalyst, but it gave low efficiency (entry 16). To know the effect of acid strength, few protic acids such as TfOH, HCl were involved in the reaction instead of AcOH along with $H_2O$ (entry 17, 18). The other acids were not as good as AcOH.

With the support of the above results, reaction between aldehyde **318a** and diamine **104a** in a mixed solvent $H_2O$/AcOH (4:1) at room temperature for 2-3 h followed by CuI catalyzed cyclisation at 90 °C, was deemed to provide the optimum condition (entry 11) for the desired product **319a**. With this optimized condition in hand, we have explored the scope of this reaction with substituted 1-propargyl-1*H*-indole-2-carbaldehydes (**318a-d**) and various *O*-phenylenediamines (**104a-d**) as coupling partners. In the beginning, we investigated the reaction between 3-chloro-1-propargyl-1*H*-indole-2-carbaldehyde (**318a**) and various *o*-diamines (**Scheme 41**), in our optimized conditions.

**Scheme 41**

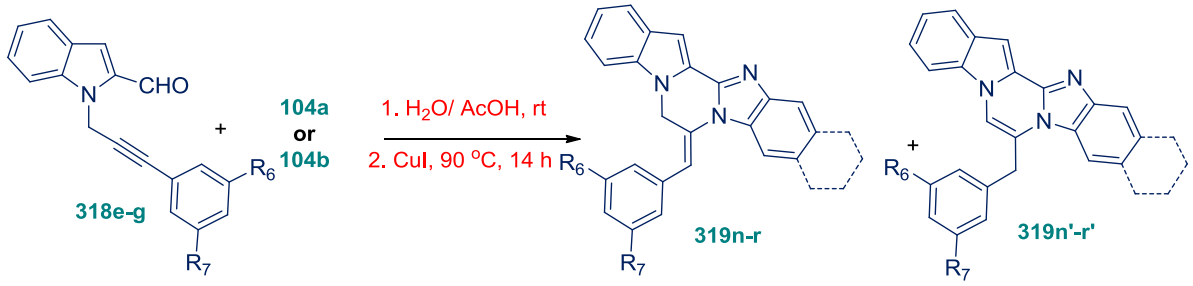




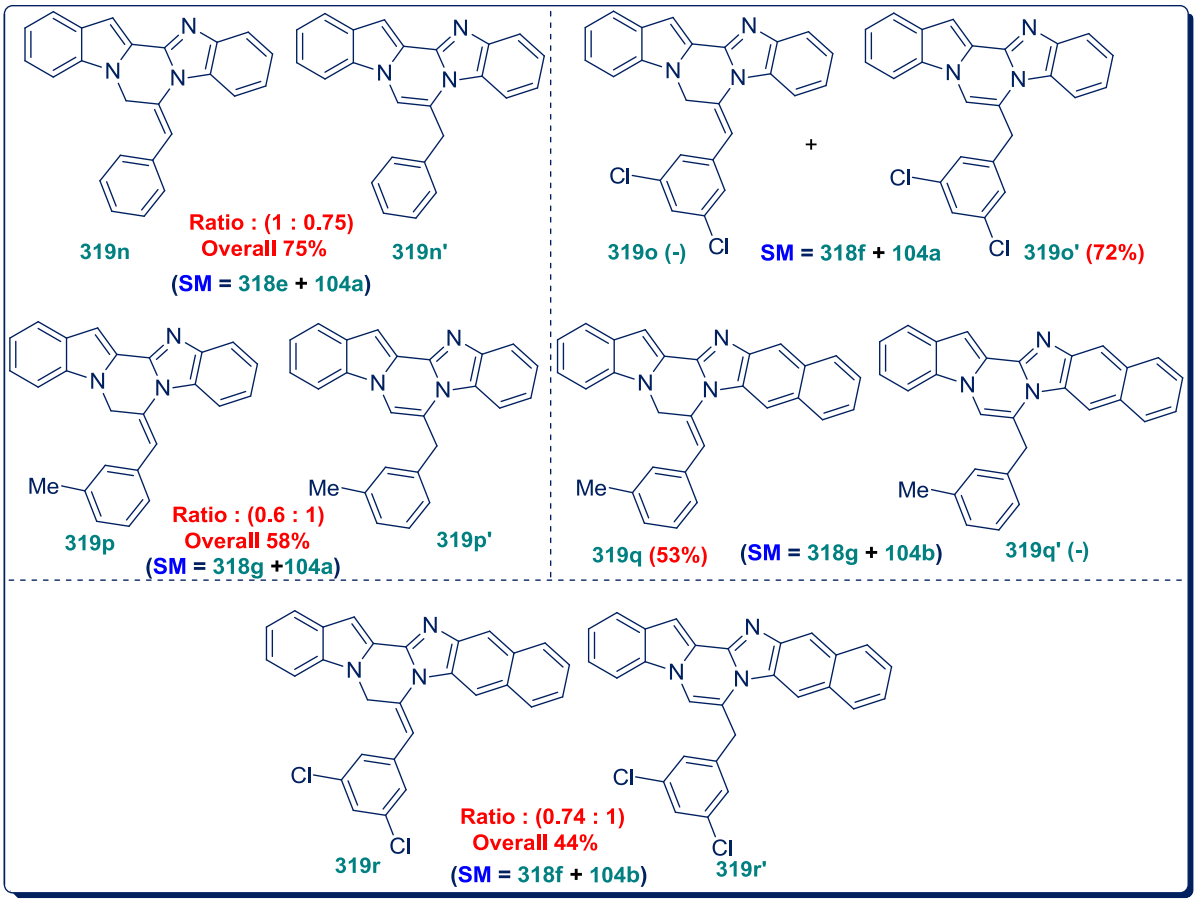

***SM = Starting materials**

The results showed moderate to good yields of the corresponding imidazolopyrazinoindole derivatives (**319a-c**). However, 4-methyl-*O*-phenylenediamine (**104c**) provided two inseparable regioisomers (**319c** & **319c'**) with almost 1.5:1 ratio.

## Scheme 42

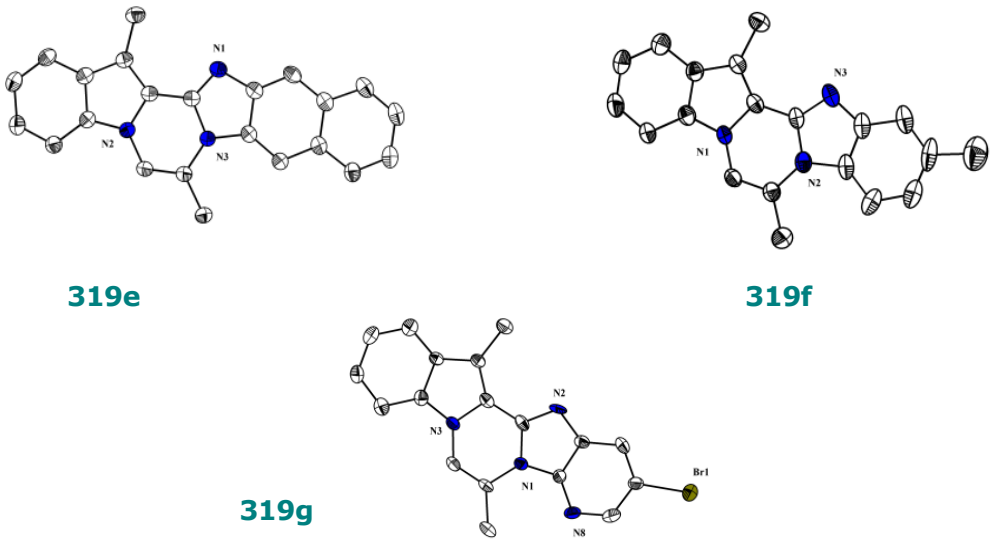



318e: $R_6$, $R_7$ = H, 318f: $R_6$, $R_7$ = Cl, 318g: $R_6$, $R_6$ = Me




To explore the effect on the yield of the benzimidazolopiperazine, we examined the reaction between different *o*-diamines (**104a-d**) and propargyl-1*H*-indole-2-carbaldehydes (**318b-d**). To our delight, the yields of the products **319d-j, 319l-m** were increased in comparison with chloro substituted imidazolopyrazinoindoles **319a-c**. Notably, the reaction of 2,3-diamino-5-bromopyridine (**104d**) with propargyl-1*H*-indole-2-carbaldehyde (**318b-c**) led to produce low yield of the products **319g** and **319k**.

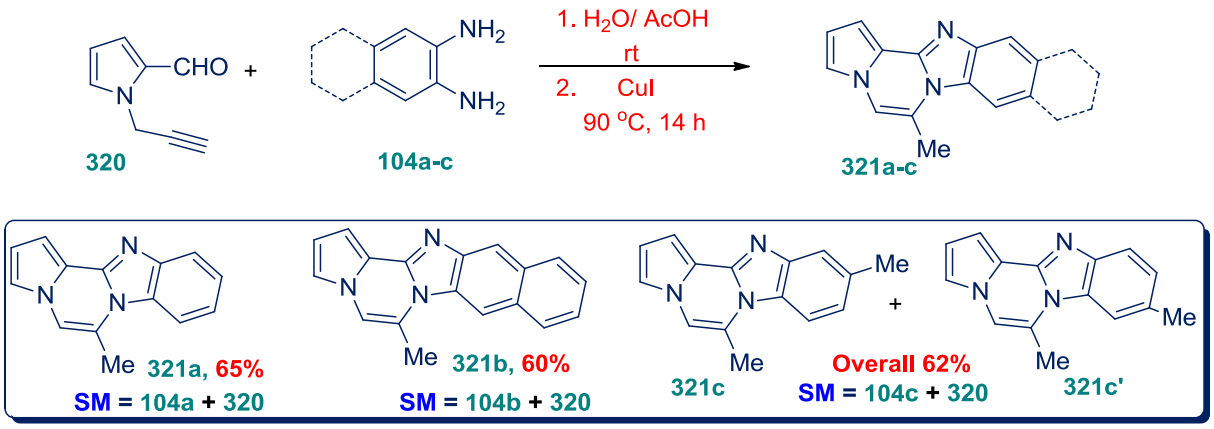
**Fig. 21: The ORTEP of compounds 319e, 319f and 319g**



The ORTEP of compounds **319e**, **319f** and **319g** are shown in **Fig. 21**. In order to assist the scope of the reaction, we next moved to the 6-*exo-dig* cyclisation with 1-propargylic indole derivatives (**318e-g**)[5.1e-f] which could afford kinetically (**319n-r**) and/or thermodynamically (**319n'-r'**) stable products. The yields of the products (**319n-r/319n'-r'**) vary with substituents on propargylic benzene as well as steric effect of diamine benzene moiety (**Scheme 42**).

## 5.3. Synthesis of benzoimidazopyrrolopyrazine derivatives

**Scheme 43**




With these optimized conditions, we were eager to examine the generality of the reaction. So we explored the condition with 1-propargyl-1*H*-pyrrole-2-carbaldehyde (**320**) and the diamines (**104a-c**) (**Scheme 43**). It was noteworthy that the desired products (**321a-c**) were furnished in moderate to good yield.

## 5.4. Synthesis of hydrobenzoimidazopyrazine derivatives

Inspired with the success of this transformation with indole and pyrrole moieties, we next concentrated on fused benzimidazolopiperazine without indole or pyrrole ring. We, first investigated reaction between 4-methyl-*N*-(2-oxo-ethyl)-*N*-prop-2-ynyl-benzenesulfonamide (**322**) and *O*-phenylenediamine (**104a**) with our optimized reaction condition (**Table 31**, entry 1) which gave disappointedly complex reaction mixture. Use of ethanol as solvent also failed to give product (entry 2). So we again enquired for an optimum reaction condition. The screening started with **322** and *O*-phenylenediamine **104a** in the presence of CuI (10 mol%) as catalyst, and acetonitrile solvent for overnight at room temperature. We obtained the desired product **323a** with 55% of yield with an undetected complex mixture (entry 3), whereas in reflux, the yield of the product was decreased (entry 4).

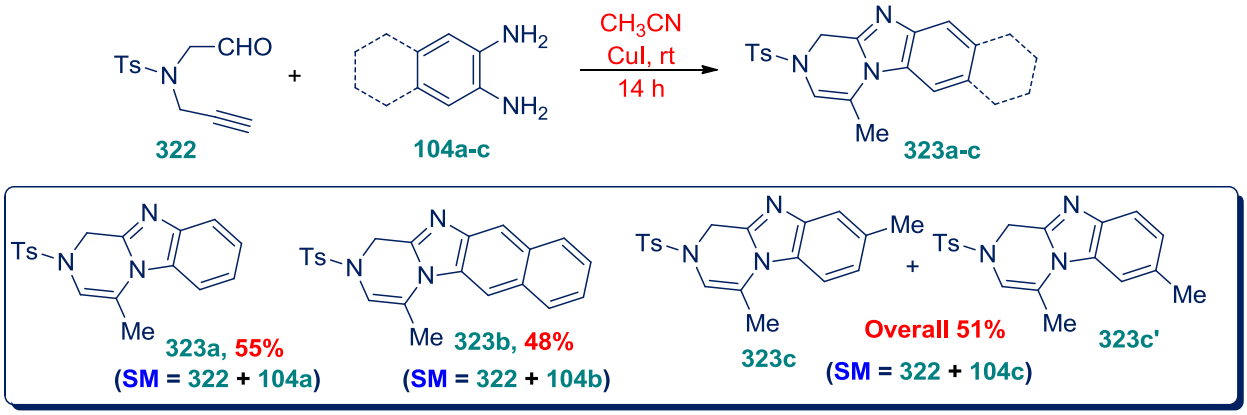
**Table 31: Optimization of the reaction condition**

| Entry | Catalyst 10 mol% | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | CuI | H2O/AcOH (4:1) | 80-90 °C | 14 | complex mixt. |
| 2 | CuI | EtOH/ AcOH | reflux | 14 | complex mixt. |
| **3** | **CuI** | **MeCN** | **rt** | **14** | **55** |
| 4 | CuI | MeCN | reflux | 14 | 40 |
| 5 | CuI | EtOH | rt | 14 | 38 |
| 6 | AgOTf | EtOH | rt | 14 | trace |
| 7 | AgOTf | EtOH/AcOH (4:1) | rt | 14 | complex mixt. |
| 8 | CuI | EtOH | rt | 6 | nd |
| 9 | CuI | DMA | rt | 48 | complex mixt. |
| 10 | CuI | Acetone | rt | 48 | decomposed |
| 11 | CuI | MeOH | rt | 4 | nd |
| 12 | CuI | Toluene | rt | 14 | nd |

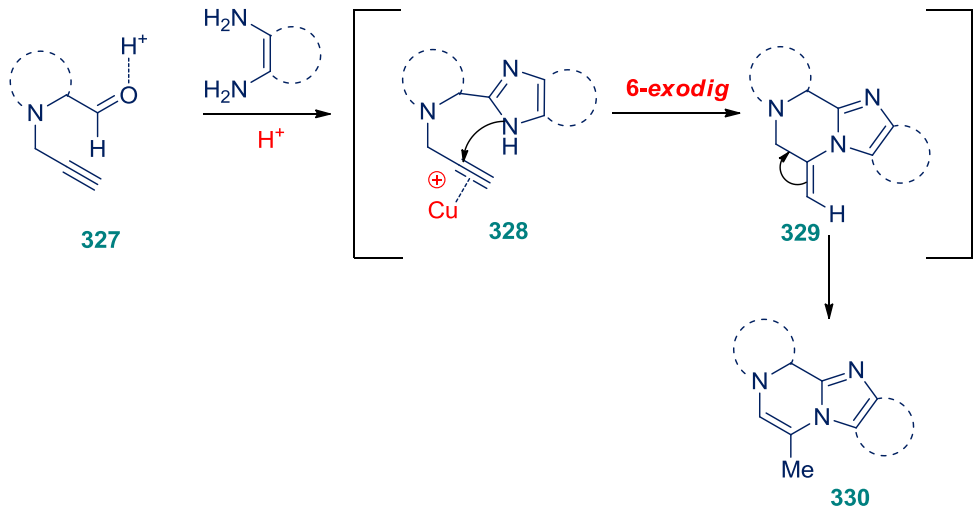
Reaction conditions: For entries 1,2 [**322** (1 mmol), **104a** (1.2 mmol), in solvents at rt for 2-3 h, then CuI (10 mol%) and heated at 90 °C.]. for entries 3, 5-12 [ **322** (1 mmol), **104a** (1.2 mmol), catalyst (10 mol%) stirred at rt overnight]

The reaction in more polar solvent ethanol at room temperature led to lower the yield (entry 5, table 2). With AgOTf as catalyst, a trace amount of product was obtained (entry 6).Unfortunately, the other solvents were not efficient to provide product **323a** (entries 8-12). Using these optimized conditions, different phenylendiamines (**104a-c**) were examined with *N*1-formylmethyl-*N*1-(2-propynyl)-4- methyl-1-benzenesulfonamide (**322**) in this tandem imidazole formation/ heteroannulation process. The expected products (**323a-c**, **Scheme 44**) were isolated with moderate yield.

**Scheme 44**



**Scheme 45**

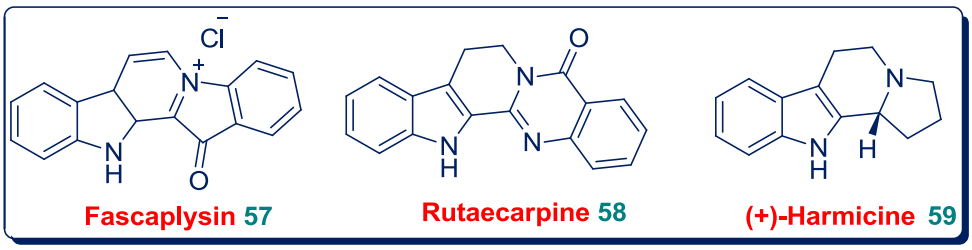



A plausible path of the reaction (**Scheme 45**) may follow activation of the carbonyl oxygen to furnish the benzimidazole as a key intermediate **328**, which immediately undergoes 6-*exo-dig* cyclization with the alkyne through intramolecular copper catalysis to furnish dihydroimidazopyrazino derivatives **329** rather than imidazolopyrazine derivatives **330**. As already reported that the dihydroimidazopyrazino intermediate (**329**) is kinetically stable, whereas the imidazolopyrazine **330** is a thermodynamically controlled product.

## Part B: Cu-catalyzed cyclization route to the synthesis of fascaplysin, rutacarpine and granulatimide analogues

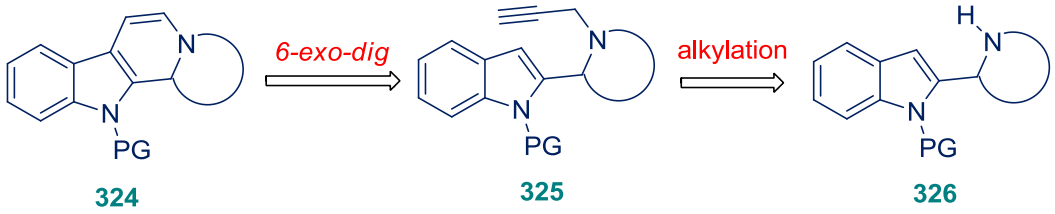
As we already discussed the biological applications and various synthetic approaches for the annulated $\beta$-carboline alkaloids and their derivatives in the introduction, we precede here an electocyclization approach for making few hetero annulated $\beta$-carboline analogues (**Fig. 22**).

**Fig. 22**




A retrosynthetic analysis is shown in **Scheme 46**. We envisaged that the compound **324** could easily be prepared from metal catalyzed *6-exo-dig* electrophilic cyclization reaction of N-propargylated indole derivative through C-C bond formation. The compound **325** can be prepared from routine *N*-propargylation of particular heteroaryl substituted indole derivative **326**.

**Scheme 46**




We turned our attention towards establishing various *N*-propargylated indole derivatives (**Scheme 47**). For this purpose, few of heteroaryl substituted protected indoles were identified as an appropriate chemical equivalent which in turn could easily be prepared from corresponding indole derivatives.

**Scheme 47**

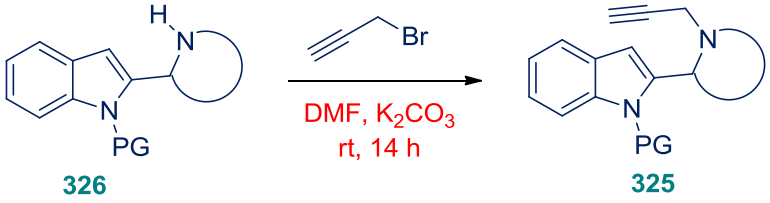
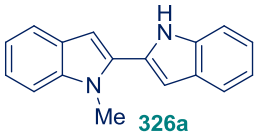
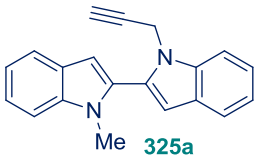
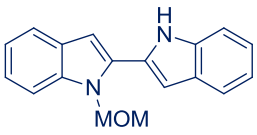
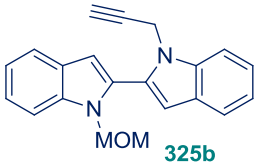
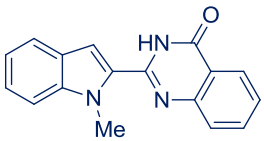
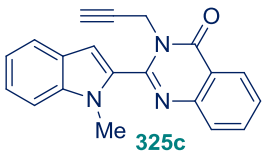
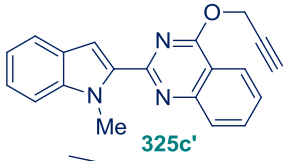
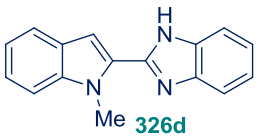
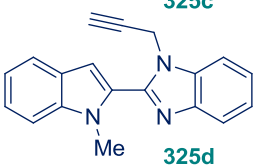
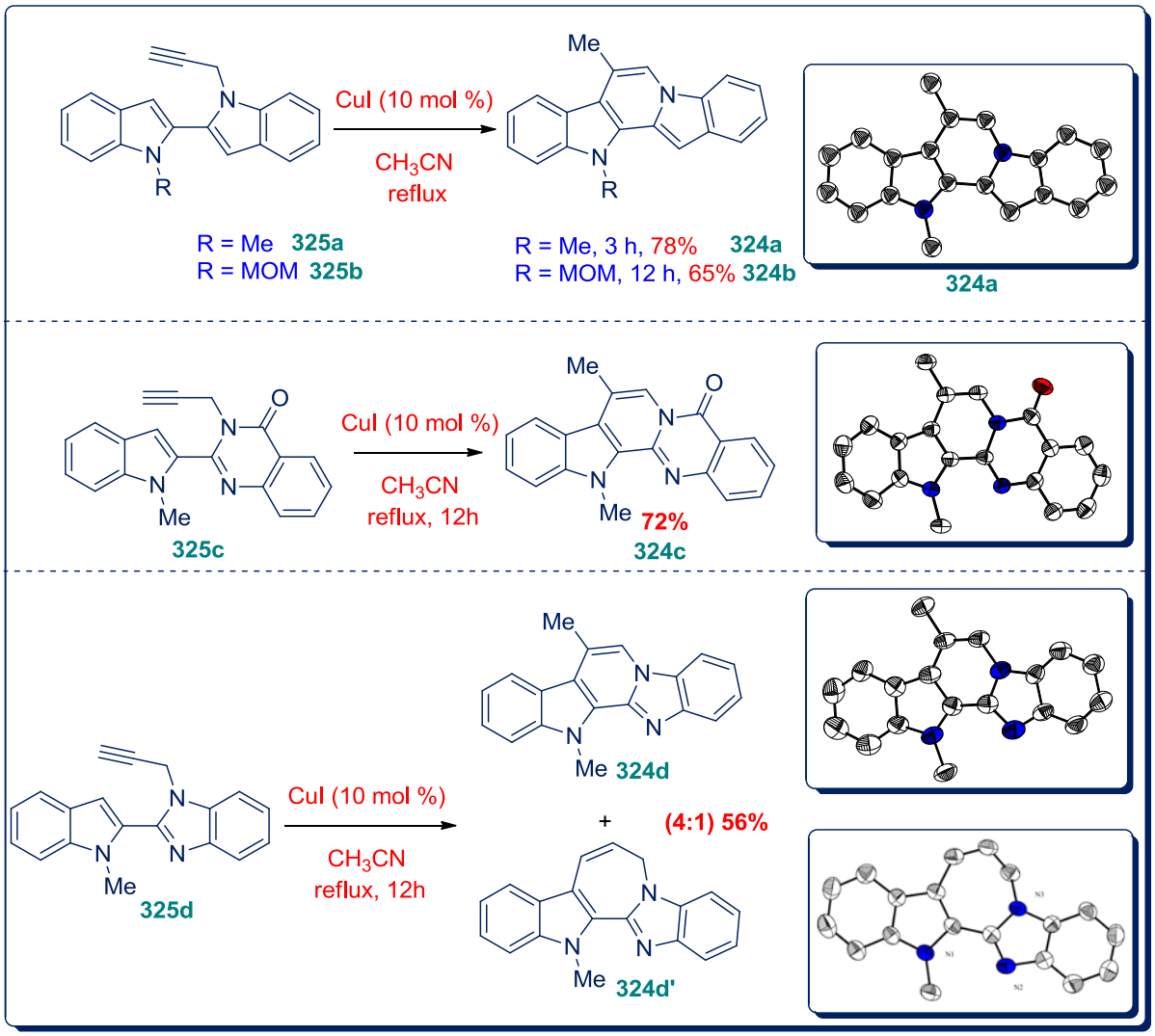



**Table 32**

| Indole dervative | Product | |
|---|---|---|
|  326a |  325a | 84% |
|  326b |  325b | 81% |
|  326c |  325c | 47% |
| |  325c' | 19% |
|  326d |  325d | 78% |

The *N*-alkylation of various indole derivatives **326** afforded *N*-propargyl indole derivatives **325** using propargyl bromide in DMF/$K_2CO_3$ at room temperature. The compound **326c** afforded two isomeric propargylated products **325c** and **325c'** in 47% and 19% yield respectively. The cyclization stage for the synthesis of *β*-carboline derivatives were implemented by following the earlier established CuI catalyzed protocol. Preliminary investigation with CuI (10 mol%) as catalyst and MeCN as solvent for the C-C bond forming electophilic cyclization of N-propargylated indole derivatives **325** afforded annulated *β*-carboline derivatives **324** in moderate to good yields. The compounds **325a**, **325b** and **325c** underwent *6-exo-dig* cyclization whereas the compound **325d** participated in the selective synthesis of *6-exo-dig* (major) and *7-endo*-dig (minor) products. The optimal condition for the electrophilic cyclization, generality of the reaction with various terminal as well as internal alkynes, applications toward total synthesis of alkaloids and reasons for the selectivity of *6-exo-dig/7-endo-dig* cyclizations are being processed.

**Scheme 48**

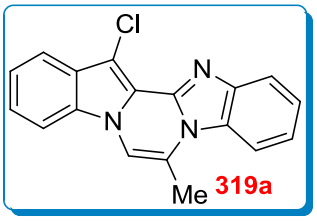


## 5.5. Experimental section

***General procedure J:***

Into the reaction mixture of 1-(2-propynyl)-1*H*-indole-2-carbaldehyde (1 mmol ) in a mixed solvent of $H_2O$/AcOH (4:1) 5 mL was added *o*-phenylenediamine (1.2 mmol) and stirred at room temperature for 2-3 h until a percentage of yellow benzimidazole formed. Then CuI (10 mol%) was added to the mixture and heated around 90 °C until the full conversion of the benzimidazole. Then the reaction mixture was extracted with EtOAc, dried over anhydrous $Na_2SO_4$ and evaporated in vacuum. The residue was purified by column chromatography on silica gel.

**7-Methylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319a):** Compound **319a** was synthesized from alkynyl aldehyde **318a** and diamine **104a** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 68%

Mp: 180 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3397, 3052, 2958, 1616, 1512, 1265, 800, 739

$^1$H NMR (400 MHz, DMSO-$d_6$ ) δ: 8.16 (1H, s), 8.08-8.12 (2H, m), 7.89 (1H, d, *J* = 8.0 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.35-7.49 (4H, m), 2.86 (3H, s)

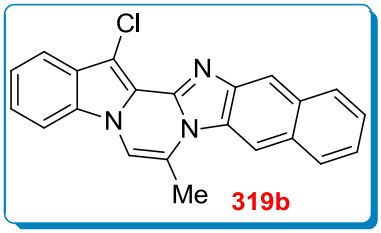
$^{13}$C NMR (100 MHz) δ: 144.4, 141.0, 131.1, 130.4, 125.7, 124.5, 124.4, 123.8, 123.6, 123.3, 120.24, 120.19, 118.6, 114.2, 111.8, 108.3, 100.7 (aromatic C), 17.5 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{18}H_{12}ClN_3$: 306.0798 (M+H)

Found: 306.0798

**16-Chloro-7-methylnaphtho[2'',3'':4',5']imidazo[2',1':3,4] pyrazino[1,2-*a*]indole (319b):** Compound **319b** was synthesized from alkynyl aldehyde **318a** and diamine **104b** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



Yield: 60%

Mp: 240 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3408, 2964, 2920, 2849, 1600, 1391, 1265, 800, 739, 723

$^1$H NMR (400 MHz, DMSO-$d_6$ ) δ: 8.60 (1H, s), 8.41 (1H, s), 8.06-8.13 (4H, m), 7.78 (1H, d, *J* = 8.0 Hz), 7.43-7.53 (4H, m), 3.00 (3H, s)

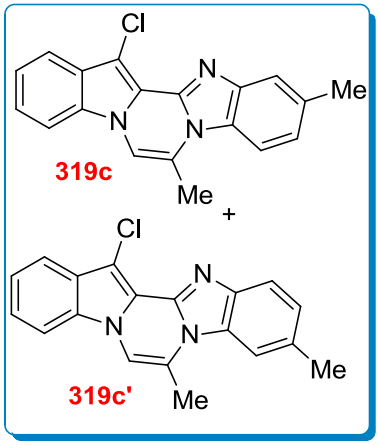
$^{13}$C NMR (100 MHz, DMSO-$d_6$ ) δ: Due to poor solubility of compound in $CDCl_3$ as well as in DMSO-$d_6$, we were unable to take $^{13}$C NMR

HRMS (ESI-MS)

Calcd for $C_{22}H_{14}ClN_3$: 356.0955 (M+H)

Found: 356.0955

**14-Chloro-7,10-dimethylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indole(319c), 14-chloro-7,11-dimethylbenzo[4',5']imidazo[2',1':3,4] pyrazino[1,2-*a*]indole (319c'):** Compounds **319c** and **319c'** (4-Me/5-Me = 1.5:1) were synthesized from alkynyl aldehyde **318a** and diamine **104c** following the *general procedure J*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 64%

Mp: 196 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3419, 3101, 2920, 1506, 1391, 1260, 805, 739, 723

$^1$H NMR (400 MHz, DMSO-$d_6$ ) δ: 8.09-8.10 (5.02H, d, *J* = 4.0 Hz), 7.64-7.90 (7.91H, m), 7.40-7.46 (5.29H, m), 7.11-7.17 (2.68H, m), 2.82 (7.55H, s), 2.42 (7.50H, s)

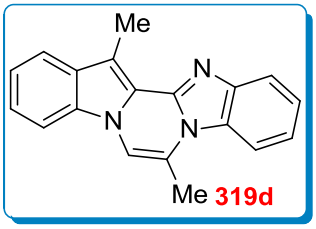
$^{13}$C NMR (100 MHz) δ: Due to poor solubility of compounds in $CDCl_3$ as well as in DMSO-$d_6$, we were unable to record $^{13}$C NMR

HRMS (ESI-MS)

Calcd for $C_{19}H_{14}ClN_3$: 320.0954 (M+H)

Found: 320.0955

**7,14-Dimethylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indole (319d):** Compound **319d** was synthesized from alkynyl aldehyde **318b** and diamine **104a** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**319d**

Yield: 72%

Mp: 184 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3057, 2920, 1610, 1523, 1435, 745, 723, 690

$^1$H NMR (400 MHz) δ: 7.93 (1H, d, *J* = 8.0 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.54 (1H, d, *J* = 8.0 Hz), 7.23-7.37 (4H, m), 7.08 (1H, s), 2.97 (3H, s), 2.71 (3H, s)

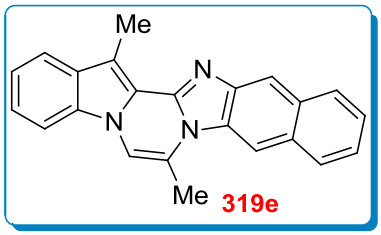
$^{13}$C NMR (100 MHz) δ: 144.6, 143.9, 131.1, 130.9, 128.8, 123.4, 122.9, 122.5, 121.6, 121.1, 120.1, 119.8, 117.7, 112.5, 110.3, 109.5, 107.4 (aromatic C), 17.9, 9.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{19}H_{15}N_3$: 286.1346 (M+H)

Found: 286.1346

**7,16-Dimethylnaphtho[2'',3'':4',5']imidazo[2',1':3,4] pyrazino[1,2-*a*]indole (319e):** Compound **319e** was synthesized from alkynyl aldehyde **318b** and diamine **104b** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**319e**

Yield: 64%

Mp: 206 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3052, 2915, 1600, 1528, 1408, 860, 739, 717

$^1$H NMR (400 MHz) δ: 8.30 (1H, s), 8.04 (1H, s), 7.94 (1H, d, *J* = 6.5 Hz), 7.74-7.80 (2H, m), 7.53 (1H, d, *J* = 7.2 Hz), 7.29-7.36 (4H, m), 6.99 (1H, s), 3.01 (3H, s), 2.78 (3H, s)

$^{13}$C NMR (100 MHz) δ: 147.0, 144.3, 131.6, 131.2, 130.6, 130.0, 128.6, 127.9, 127.8, 124.1, 124.0, 123.4, 121.5, 120.7, 120.0, 118.0,

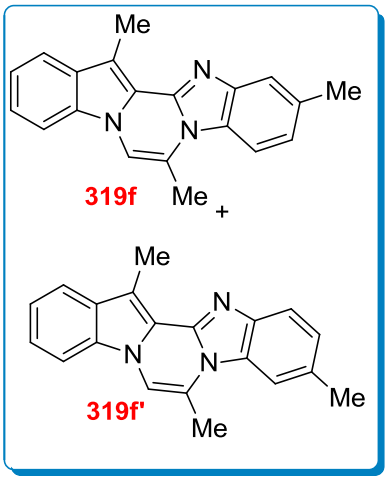
116.2, 112.1, 109.5, 108.6, 106.5 (aromatic C), 17.9, 10.0 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{23}H_{17}N_3$: 336.1500 (M+H)

Found: 336.1503

**7,10,14-Trimethylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indole (319f) and 7,11,14-trimethylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indole (319f'):** Compounds **319f** and **319f'** (4-Me/5-Me = 1.5:1) were synthesized from alkynyl aldehyde **318b** and diamine **104c** following the *general procedure J*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 70%

Mp: 150 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3386, 3101, 2914, 1523, 1468, 1375, 723

$^1$H NMR (400 MHz) δ: 7.77-7.83 (3.35H, m), 7.71-7.73 (3.14H, m), 7.59-7.64 (3.37H, m), 7.30-7.38 (5.12H, m), 7.18-7.20 (3.41H, m), 7.07-7.10 (1.58H, m), 2.99-3.00 (7.22H, m), 2.79-2.80 (7.21H, m), 2.50 (7.50H, s)

$^{13}$C NMR (100 MHz) δ: 144.9, 143.9, 143.6, 142.7, 133.3, 132.5, 131.3, 130.9, 129.1, 128.8, 125.0, 124.1, 122.8, 121.6, 121.5, 121.29, 121.26, 119.9, 119.5, 117.8, 112.5, 112.0, 110.1, 110.0, 109.5, 109.4, 107.4, 107.3 (aromatic C), 22.1, 21.5, 18.1, 17.9, 9.9 (aliphatic C)

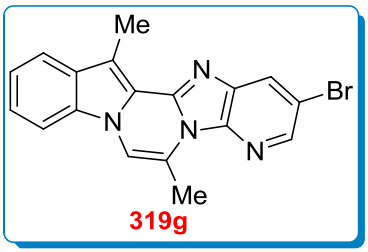
HRMS (ESI-MS)

Calcd for $C_{20}H_{17}N_3$: 300.1500 (M+H)

Found: 300.1500

**2-Bromo-6,13-dimethylpyrido[3'',2'':4',5']imidazo[2',1':3,4] pyrazino[1,2-*a*]indole (319g):** Compound **319g** was synthesized from alkynyl aldehyde **318b** and

diamine **104d** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**319g**

Yield: 58%

Mp: 178 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3420, 2923, 2871, 1603, 1505, 1412, 863

$^1$H NMR (400 MHz) δ: 8.38 (1H, s), 8.25 (1H, s), 7.81 (1H, d, *J* = 8.0 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.39-7.44 (1H, m), 7.32-7.36 (1H, m), 7.22-7.26 (1H, m), 2.97 (3H, s), 2.95 (3H, s)

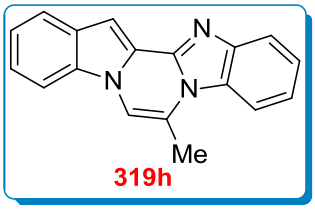
$^{13}$C NMR (100 MHz, $CDCl_3$ + DMSO-$d_6$) δ: 145.1, 143.7, 142.9, 137.3, 131.0, 128.1, 125.3, 124.5, 123.4, 121.5, 119.5, 117.4, 114.4, 111.2, 109.9, 108.4 (aromatic C), 16.5, 9.4 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{18}H_{13}BrN_4$: 365.0402 (M+H)

Found: 365.0401

**7-Methylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indole (319h):** Compound **319h** was synthesized from alkynyl aldehyde **318c** and diamine **104a** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**319h**

Yield: 73%

Mp: 182 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2958, 2920, 1720, 1616, 1446, 739

$^1$H NMR (500 MHz) δ: 7.92 (1H, d, *J* = 8.0 Hz), 7.84-7.87 (2H, m), 7.62-7.63 (1H, m), 7.51 (1H, s), 7.40 (1H, t, *J* = 7.5Hz), 7.32-7.35 (2H, m), 7.28-7.30 (1H, m), 7.25 (1H, s), 2.82 (3H, d, *J* = 0.5 Hz)

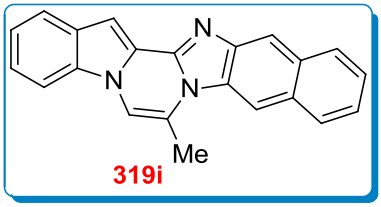
$^{13}$C NMR (125 MHz) δ: 144.3, 142.7, 131.8, 131.5, 128.4, 124.9, 123.9, 122.9, 122.8, 122.4, 121.8, 120.1, 118.6, 112.7, 109.7, 107.3, 98.4 (aromatic C), 17.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{18}H_{13}N_3$: 272.1187 (M+H)

Found: 272.1185

**8-Methylnaphtho[2'',3'':4',5']imidazo[2',1':3,4]pyrazino[1,2-*a*]indole 319i:** Compound **319i** was synthesized from alkynyl aldehyde **318c** and diamine **104b** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**319i**

Yield: 68%

Mp: 201 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3424, 2854, 2126, 1649, 1276, 1057, 1030, 821

$^1$H NMR (500 MHz) δ: 8.34-8.38 (2H, m), 7.90-8.06 (3H, m), 7.66-7.74 (2H, m), 7.44-7.46 (3H, m), 7.37 (2H, s), 3.06 (3H, s)

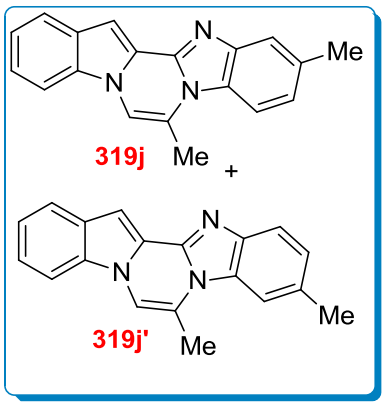
$^{13}$C NMR (125 MHz) δ: 145.9, 144.1, 132.3, 132.2, 130.9, 130.3, 128.4, 128.1, 127.9, 124.5, 124.4, 123.5, 122.2, 119.2, 116.5, 109.8, 109.2, 106.7, 100.1 (aromatic C), 18.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{22}H_{15}N_3$: 322.1344 (M+H)

Found: 322.1344

**8,13-Dimethylnaphtho[2'',3'':4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole and 8,12-dimethylnaphtho[2'',3'':4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319j and 319j'):** Compounds **319j** and **319j'** were synthesized from alkynyl aldehyde **318c** and diamine **104c** following the *general procedure J*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**319j** **319j'**

Yield: 72%

Mp: 165-167 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3408, 2257, 2126, 1654, 1057, 1030, 827

$^1$H NMR (500 MHz) δ: 7.85-7.87 (1.70H, m), 7.80-7.82 (0.66H, m), 7.76-7.77

(1H, m), 7.71 (1H, s), 7.66-7.68 (2.48H, m), 7.54-7.57 (1.68H, m), 7.32-7.38 (5.1H, m), 7.22-7.24 (0.71H, m), 7.11-7.13 (1H, m), 2.88 (1.85H, s), 2.86 (3H, s), 2.52 (5.42H, s)

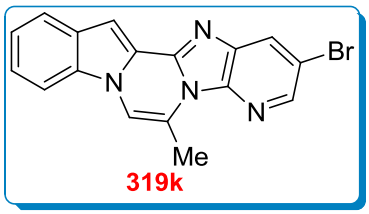
$^{13}$C NMR (125 MHz) δ: 144.5, 142.3, 133.6, 132.8, 132.0, 129.7, 128.2, 125.7, 124.9, 124.7, 123.1, 122.8, 121.8, 119.64, 119.56, 119.4, 113.8, 113.6, 111.4, 108.2, 97.6 (aromatic C), 22.1, 21.6, 17.6, 17.4 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{19}H_{15}N_3$: 286.1344 (M+H)

Found: 286.1344

**13-Bromo-8-methylindolo[2'',1'':3',4']pyrazino[1',2':1,2]imidazo[4,5-g]quinoline 319k:** Compound **319k** was synthesized from alkynyl aldehyde **318c** and diamine **104d** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**319k**

Yield: 60%

Mp: 210-212 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 3468, 2980, 2082, 1375, 1101, 1052, 942, 849

$^{1}$H NMR (400 MHz) δ: 8.43 (1H, s), 8.25 (1H, s), 7.87 (1H, d, *J* = 7.6), 7.71 (1H, d, *J* = 8.0), 7.57 (1H, s), 7.34-7.45 (3H, m), 3.02 (3H, s)

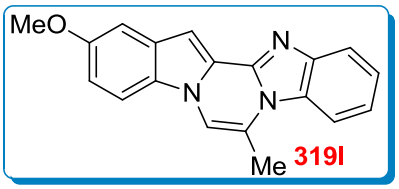
$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 144.5, 143.9, 137.7, 132.2, 129.1, 128.3, 124.1, 123.7, 122.7, 122.2, 118.9, 115.6, 109.9, 108.2, 99.7 (aromatic C), 17.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{17}H_{11}BrN_4$: 351.0245 (M+H)

Found: 351.0245

**2-Methoxy-7-methylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319l):** Compound **319l** was synthesized from alkynyl aldehyde **318d** and diamine **104a** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 70%

Mp: 145 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2958, 2841, 1075, 1553, 1189, 1064, 753

$^1$H NMR (400 MHz) δ: 7.91 (2H, t, *J* = 7.6 Hz), 7.55 (1H, d, *J* = 8.9 Hz), 7.40-7.43 (2H, m), 7.28-7.33 (2H, m), 7.21 (1H, s), 7.01 (1H, d, *J* = 8.0 Hz), 3.90 (3H, s), 2.85 (3H, s)

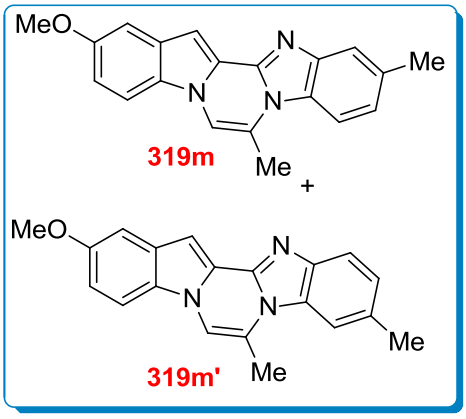
$^{13}$C NMR (100 MHz) δ: 155.9, 144.2, 142.7, 131.4, 129.1, 127.1, 125.1, 124.0, 122.8, 119.9, 118.5, 114.3, 112.8, 110.6, 107.5, 101.9, 98.0 (aromatic C), 55.7, 17. 9 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{19}H_{15}N_3O$: 302.1293 (M+H)

Found: 302.1293

**2-Methoxy-7,11-dimethylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319m) and 2-methoxy-7,10-dimethylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319m'):** Compounds **319m** and **319m'** (4-Me/5-Me = 1.9:1) were synthesized from alkynyl aldehyde **318d** and diamine **104c** following the *general procedure J*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 72%

Mp: 165 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2953, 2854, 1731, 1463, 1380, 1260, 1079, 1019, 805

$^1$H NMR (500 MHz) δ: 7.82 (0.5H, d, *J* = 8.3 Hz), 7.78 (1.2H, d, *J* = 8.5 Hz), 7.69 (1.6H, s), 7.55-7.58 (1.6H, m), 7.42-7.43 (1.5H, m), 7.27-7.29 (1.6H, m), 7.23-7.24 (1.7H, m), 7.12-7.14 (1.6H, m), 7.01-7.04 (1.6H, m), 3.92 (4.6H, s), 2.86-2.88 (4.5H, m), 2.53-2.54 (4.6H, m)

$^{13}$C NMR (125 MHz) δ: 156.0, 144.6, 142.6, 142.4, 133.9, 132.7, 129.5, 129.1, 127.1, 125.5, 125.3, 124.5, 124.3, 119.7, 119.5, 118.5,

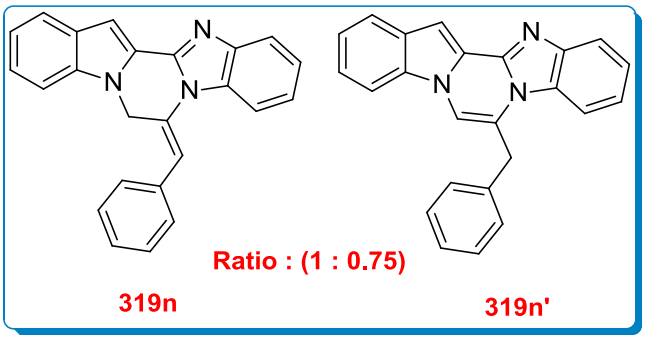
118.4, 114.13, 114.07, 112.7, 112.2, 110.6, 110.5, 107.3, 107.25, 102.0, 97.8, 97.76 (aromatic C), 55.7, 22.7, 21.6, 17.9, 17.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{20}H_{17}N_3O$: 316.1450 (M+H)

Found: 316.1448

**(E)-7-Benzylidene-6,7-dihydrobenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319n) and 7-benzylbenzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319n'):** Compounds **319n** and **319n'** were synthesized from alkynyl aldehyde **318e** with diamine **104a** following the *general procedure J*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 75%

Mp: 160 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2854, 1638, 1397, 1200, 865, 712

$^1H$ NMR (500 MHz) δ: 7.94-7.96 (0.77H, m), 7.87-7.90 (0.98H, m), 7.76-7.81 (2.81H, m), 7.56-7.62 (1.89H, m), 7.35-7.46 (10.63H, m), 7.15-7.27 (7.87H, m), 7.01 (2H, m), 6.86-6.90 (1H, m), 6.71 (1H, s), 6.39 (1H, d, *J* = 5.0 Hz), 5.08 (2H, s), 4.64 (1.50H, s)

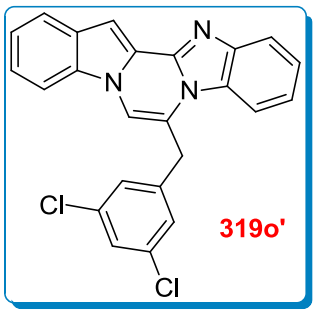
$^{13}C$ NMR (125 MHz) δ: 144.4, 144.3, 142.9, 136.6, 135.7, 133.8, 132.0, 130.9, 130.8, 129.2, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 127.5, 126.7, 125.9, 124.9, 123.98, 123.96, 123.2, 123.0, 122.9, 122.7, 122.6, 122.4, 121.9, 121.6, 121.0, 121.1, 119.7, 113.6, 113.2, 109.7, 109.3, 109.3, 102.5, 98.8 (aromatic C), 48.4, 36.7 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{24}H_{17}N_3$: 348.1500 (M+H)

Found: 348.1499

**7-(3,5-Dichlorobenzyl)benzo[4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319o'):** Compound **319o'** was synthesized from alkynyl aldehyde **318f** and diamine **104a** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 72%

Mp: 220 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2964, 2920, 2849, 1457, 1369, 745

$^1$H NMR (500 MHz) δ: 7.88-7.93 (2H, m), 7.56-7.61 (3H, m), 7.33-7.38 (4H, m), 7.21-7.27 (4H, m), 4.53 (2H, s)

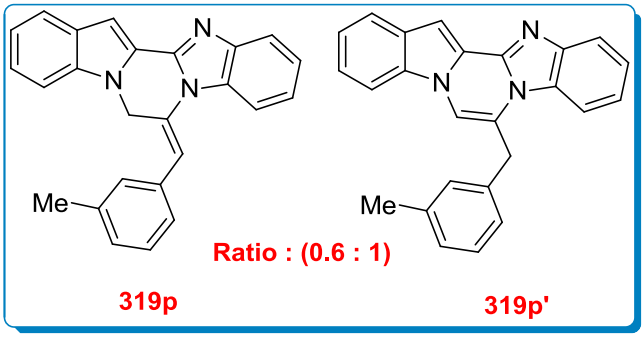
$^{13}$C NMR (125 MHz) δ: 144.2, 139.5, 135.8, 132.0, 130.5, 128.7, 127.9, 126.9, 124.7, 124.1, 123.3, 123.2, 122.9, 122.1, 120.2, 119.3, 112.7, 109.8, 99.3 (aromatic C), 35.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{24}H_{15}Cl_2N_3$: 416.0721 (M+H)

Found: 416.0720

**(E)-7-(3-Methylbenzylidene)-6,7-dihydrobenzo[4',5']imidazo[2',1':3,4]pyrazino [1,2-a]indole (319p) and 7-(3-methylbenzyl)benzo[4',5']imidazo[2',1':3,4]pyra zino[1,2-a]indole (319p'):** Compounds **319p** and **319p'** were synthesized from alkynyl aldehyde **318g** and diamine **104a** following the *general procedure J*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 58%

Mp: 156 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2854, 1754, 1065, 764, 564

$^1$H NMR (400 MHz) δ: 7.94 (1H, d, *J* = 8.0 Hz), 7.87-7.88 (1H, m), 7.75-7.80 (2H, m), 7.55-7.59 (2H, m), 7.46 (0.5H, s), 7.34-7.41 (4.5H, m), 7.29-7.31 (1H, m), 7.19-7.24 (2.5H, m), 7.15-7.16 (4H, m), 6.98-7.06 (1.8H, m), 6.89 (0.6H, t, *J* = 7.5 Hz), 6.78-6.79

(1H, m), 6.66 (0.5H, s), 6.37 (0.48H, d, *J* = 8.1 Hz), 5.06 (1.1H, s), 4.56 (2H, s), 2.36 (3H, s), 2.11 (1.7H, s)

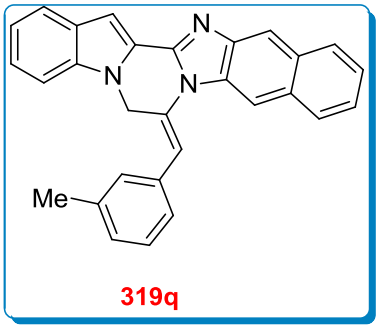
$^{13}$C NMR (100 MHz) δ: 144.2, 142.9, 138.9, 138.0, 135.6, 131.9, 130.9, 129.7, 129.3, 129.1, 128.9, 128.6, 128.5, 128.3, 128.2, 126.1, 125.8, 125.6, 124.9, 123.9, 123.2, 122.9, 122.6, 122.4, 121.9, 121.6, 120.9, 120.3, 119.9, 119.6, 113.8, 113.3, 109.8, 109.3, 109.27, 102.5, 98.8 (aromatic C), 48.4, 36.6, 21.5, 21.2 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{25}H_{19}N_3$: 362.1657 (M+H)

Found: 362.1656

**(E)-8-(3-Methylbenzylidene)-7,8-dihydronaphtho[2'',3'':4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319q):** Compound **319q** was synthesized from alkynyl aldehyde **318g** and diamine **104b** following the *general procedure J*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



319q

Yield: 53%

Mp: 210 °C

IR (KBr) $\nu_{max}$ cm$^{-1}$: 2812, 1564, 1212, 1074, 860, 782

$^{1}$H NMR (400 MHz) δ: 8.22 (1H, s), 7.95 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 7.56 (1H, s), 7.45-7.47 (1H, m), 7.29-7.40 (4H, m), 7.22-7.25 (1H, m), 6.97-6.98 (2H, m), 6.81-6.83 (2H, m), 6.73 (1H, s), 6.60 (1H, s), 5.14 (2H, s), 2.03 (3H, s)

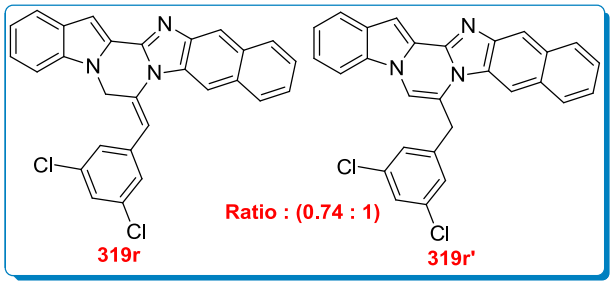
$^{13}$C NMR (100 MHz) δ: 147.55, 144.01, 137.8, 136.8, 133.8, 130.6, 130.2, 129.8, 128.9, 128.8, 128.4, 128.1, 127.8, 126.4, 126.2, 125.5, 124.4, 124.0, 122.6, 121.1, 119.5, 116.3, 110.8, 109.4, 103.7 (aromatic C), 48.5, 21.1 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{29}H_{21}N_3$: 412.1813 (M+H)

Found: 412.1811

**(E)-8-(3,5-Dichlorobenzylidene)-7,8-dihydronaphtho[2'',3'':4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319r) and 8-(3,5-dichlorobenzyl)naphtho[2'',3'':4',5']imidazo[2',1':3,4]pyrazino[1,2-a]indole (319r'):** Compounds **319r** and **319r'** were synthesized from alkynyl aldehyde **318f** and diamine **104b** following the *general procedure J*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.




Yield: 44%

Mp: 234 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 2958, 2849, 1704, 1660, 1556, 1452, 794, 569

$^1$H NMR (400 MHz) δ: 8.29 (1H, s), 8.23 (0.7H, s), 7.91-7.95 (3.4H, m), 7.86 (1H, d, *J* = 7.0 Hz), 7.79 (1H, d, *J* = 7.6 Hz), 7.74 (1H, d, *J* = 7.4 Hz), 7.65 (1.7H, s), 7.54-7.57 (2.2H, m), 7.39-7.45 (5H, m), 7.31-7.37 (5H, m), 7.15 (1H, s), 7.07 (1.7H, s), 6.87 (1.7H, s), 6.58 (1.7H, s), 5.12 (1.5H, s), 4.59 (2H, s)

$^{13}$C NMR (100 MHz) δ: Due to poor solubility of compounds both in $CDCl_3$ as well as in DMSO-$d_6$ we were not able to take $^{13}$C NMR spectra

HRMS (ESI-MS)

Calcd for $C_{28}H_{17}Cl_2N_3$: 466.0878 (M+H)

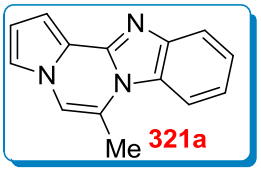
Found: 466.0876

***General procedure K*:**

Into the reaction mixture of propynyl-1*H*-pyrrole-2-carbaldehyde (1 mmol) in a mixed solvent of $H_2O$/AcOH (4:1) 5 mL was added *o*-phenylenediamine (1.2 mmol) and stirred at room temperature for 2-3 hrs until a percentage of yellow benzimidazole formed. Then CuI (10 mol%) was added to the mixture and heated around 90 °C until the full conversion of the benzimidazole. Then the reaction mixture was extracted with EtOAc, dried over anhydrous $Na_2SO_4$ and evaporated in vacuum. The residue was purified by column chromatography on silica gel (EtOAc/hexanes = 1:19) to afford the desired product.

**6-methyl-9,10,11,12-tetrahydronaphtho[2',3':4,5]imidazo[1,2-a]pyrrolo[2,1-c]pyrazine (321a):** Compound **321a** was synthesized from alkynyl aldehyde **320** and

diamine **104a** following the *general procedure K*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 65%

Mp: 158 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3369, 3210, 2915, 1616, 1501, 1227, 739

$^1$H NMR (500 MHz) δ: 7.81-7.84 (2H, m), 7.32-7.35 (1H, m), 7.20-7.23 (2H, m), 7.13-7.14 (1H, m), 7.03-7.04 (1H, m), 6.62 (1H, q, *J* = 2.7 Hz), 2.77 (3H, d, *J* = 0.85 Hz)

$^{13}$C NMR (125 MHz) δ: 144.3, 143.2, 131.2, 123.9, 122.0, 120.7, 120.5, 119.6, 117.1, 112.7, 112.6, 109.9, 106.1 (aromatic C), 17.8 (aliphatic C)

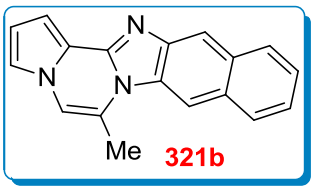
HRMS (ESI-MS)

Calcd for $C_{14}H_{11}N_3$: 222.1031 (M+H)

Found: 222.1033

**6-Methylnaphtho[2',3':4,5]imidazo[1,2-*a*]Pyrrolo[2,1-*c*]pyrazine (321b):**

Compound **321b** was synthesized from alkynyl aldehyde **320** and diamine **104b** following the *general procedure K*. Pure product was obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 60%

Mp: 210 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3441, 3095, 3046, 1682, 1600, 1506, 1336, 723

$^1$H NMR (400 MHz) δ: 8.26 (1H, s), 8.20 (1H, s), 7.99 (1H, d, *J* = 8 Hz), 7.89 (1H, d, *J* = 8.0 Hz), 7.38-7.46 (2H, m), 7.34-7.35 (1H, m), 7.19-7.20 (1H, d, *J* = 4.0 Hz), 7.01-7.00 (1H, d, *J* = 4.0 Hz), 6.69 (1H, s), 2.90 (3H, s)

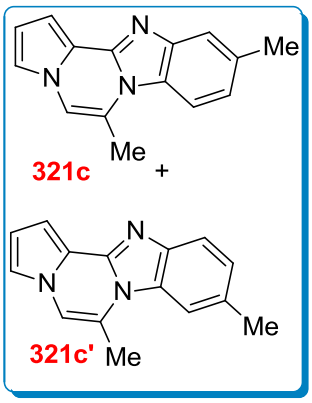
$^{13}$C NMR (100 MHz) δ: 144.2, 132.6, 132.1, 130.9, 129.8, 127.8, 124.9, 124.3, 124.1, 121.3, 120.1, 117.9, 112.8, 109.0, 107.6 (aromatic C), 17.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{18}H_{13}N_3$: 272.1187 (M+H)

Found: 272.1187

**6,9-Dimethylbenzo[4,5]imidazo[1,2-*a*]Pyrrolo[2,1-*c*]pyrazine (321c) and 6,10-dimethylbenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (321c'):** Compounds **321c** and **321c'** (4-Me/5-Me = 1.5:1) were synthesized from alkynyl aldehyde **320** and diamine **104c** following the *general procedure K*. Pure products were obtained through silica gel column chromatography with 8% ethyl acetate in hexanes.




Yield: 62%

Mp: 114 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3397, 3095, 2909, 1649, 1506, 1347, 723

$^1$H NMR (500 MHz) δ: 7.71-7.76 (2.37H, m), 7.64-7.65 (2.18H, m), 7.28-7.30 (3.06H, m), 7.17-7.22 (3.36H, m), 7.04-7.08 (3.75H, m), 6.67-6.68 (2.10H, m), 2.78-2.80 (7.52H, m), 2.51 (7.50H, s)

$^{13}$C NMR (125 MHz) δ: 133.9, 131.9, 131.2, 129.0, 125.4, 123.5, 120.7, 120.2, 119.1, 118.8, 117.1, 117.05, 112.7, 112.6, 112.1, 109.8, 106.1, 105.9 (aromatic C), 22.1, 22.6, 17.8, 17.7 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{15}H_{13}N_3$: 236.1187 (M+H)

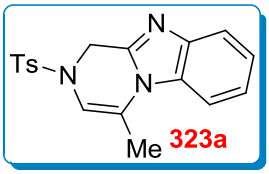
Found: 236.1186

***General procedure I*:**

Into the reaction mixture of propynylcarbaldehyde (1 mmol), in acetonitrile solvent was added *O*-phenylenediamine (1.2 mmol), and CuI (10 mol%), and stirred at room temperature for overnight. Reaction was monitored by TLC. After the product formation, the mixture was extracted with EtOAc, dried over anhydrous $Na_2SO_4$ and evaporated in vacuum. The residue was purified by column chromatography on silica gel.

**4-methyl-2-tosyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine (323a):** Compound **323a** was synthesized from alkynyl aldehyde **322** and diamine **104a** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 55%




Mp: 122 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3101, 3052, 2926, 1600, 1457, 1347, 1161, 739, 663

$^1$H NMR (400 MHz) δ: 7.66 (1H, d, *J* = 6.8 Hz), 7.62 (2H, d, *J* = 8.0 Hz), 7.46 (1H, d, *J* = 7.6 Hz), 7.20-7.25 (2H, m), 7.10 (2H, d, *J* = 8.0 Hz), 6.24 (1H, s), 4.84 (2H, s), 2.48 (3H, s), 2.19 (3H, s)

$^{13}$C NMR (100 MHz) δ: 144.7, 144.5, 143.1, 133.3, 129.5, 127.6, 127.0, 123.5, 123.2, 122.9, 120.3, 111.4, 110.5 (aromatic C), 44.0, 21.4, 16.7 (aliphatic C)

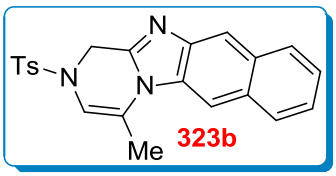
HRMS (ESI-MS)

Calcd for $C_{18}H_{17}N_3O_2S$: 340.1119 (M+H)

Found: 340.1119

**4-Methyl-2-(4-methylphenylsulfonyl)-1,2-dihydronaphtho [2',3':4,5]imidazo[1,2-*a*]pyrazine (323b):** Compound **323b** was synthesized from alkynyl aldehyde **322** and diamine **104b** following the *general procedure I*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: 48%




Mp: 128 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3391, 3046, 2915, 1506, 1167, 821, 756, 679

$^1$H NMR (400 MHz) δ: 8.10 (1H, s), 7.93-7.95 (1H, m), 7.85-7.87 (1H, m), 7.83 (1H, s), 7.63 (2H, d, *J* = 8.0 Hz), 7.41-7.46 (2H, m), 7.06 (2H, d, *J* = 7.8 Hz), 6.24 (1H, s), 4.88 (2H, s), 2.59 (3H, s), 2.01 (3H, s)

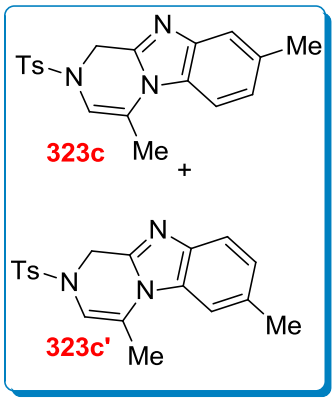
$^{13}$C NMR (100 MHz) δ: 148.6, 144.5, 142.9, 133.3, 131.7, 130.6, 130.1, 129.5, 128.2, 127.7, 127.0, 125.0, 124.3, 123.8, 117.3, 109.8, 107.7 (aromatic C), 44.2, 21.2, 16.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{22}H_{19}N_3O_2S$: 390.1276 (M+H)

Found: 390.1275

**4,7-Dimethyl-2-(4-methylphenylsulfonyl)-1,2-dihydrobenzo [4,5]imidazo[1,2-*a*]pyrazine (323c) and 4,8-dimethyl-2-(4-methylphenylsulfonyl)-1,2-dihydrobenzo [4,5]imidazo[1,2-*a*]pyrazine (323c'):** Compounds **323c** and **323c'** (4-Me/5-Me = 1.5:1) were synthesized from alkynyl aldehyde **322** and diamine **104c** following the *general procedure I*. Pure products were obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 51%

Mp: 125 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3090, 2926, 1616,1539, 1353, 816, 778, 673

$^1$H NMR (400 MHz) δ: 7.61 (5.02H, d, *J* = 8.0 Hz), 7.52 (1.07H, d, *J* = 8.0 Hz), 7.43 (1.49H, s), 7.32 (1.51H, d, *J* = 8.0 Hz), 7.24 (1.02H, s), 7.10 (5.07H, d, *J* = 8.0 Hz), 7.00-7.05 (2.45H, m), 6.21 (2.50H, s), 4.81 (5.13H, s), 2.45 (4.00H, s), 2.44 (6.82H, s), 2.43 (4.05H, s), 2.20 (7.53H, s)

$^{13}$C NMR (100 MHz) δ: 144.5, 144.4, 144.2, 143.5, 141.2, 133.5, 132.6, 131.7, 129.5, 127.0, 124.9, 124.3, 123.2, 123.1, 120.1, 119.7, 111.4, 110.9, 110.2, 110.1 (aromatic C), 44.0, 22.0, 21.4, 16.8, 16.7 (aliphatic C)

HRMS (ESI-MS)

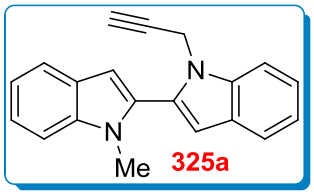
Calcd for $C_{19}H_{19}N_3O_2S$: 354.1276 (M+H)

Found: 354.1276

***General procedure M*:**

Into the reaction mixture of 2-hetero substituted indole derivative (1 mmol ) in DMF 5 mL was added $K_2CO_3$ (5 mmol) and propargyl bromide (1.5 mmol) stirred at room temperature for 14 h. Then the reaction mixture was added into water and extracted with EtOAc, dried over anhydrous $Na_2SO_4$ and evaporated in vacuum. The residue was purified by column chromatography on silica gel.

**1-methyl-1'-(prop-2-yn-1-yl)-1H,1'H-2,2'-biindole (325a):** Compound **325a** was synthesized from indole derivative **326a** and propargyl bromide following the *general procedure M*. Pure product was obtained through silica gel column chromatography with 2% ethyl acetate in hexanes.




Yield: 84%

Mp: 85 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3042, 2845, 1037, 678

$^1$H NMR (400 MHz) δ: 7.72-7.74 (2H, m), 7.59 (1H, d, *J* = 8.2 Hz), 7.45 (1H, d, *J* = 8.2 Hz), 7.33-7.39 (2H, m), 7.23-7.27 (2H, m), 6.82 (1H, s), 6.71 (1H, s), 4.88 (2H, d, *J* = 2.3 Hz), 3.78 (3H, s), 2.34 (1H, t, *J* = 2.2 Hz)

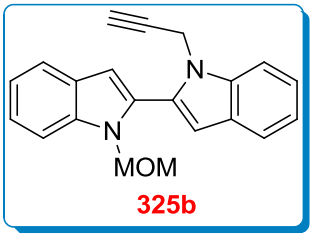
$^{13}$C NMR (100 MHz) δ: 138.1, 137.1, 130.8, 130.7, 128.0, 127.6, 122.8, 122.5, 121.0, 120.9, 120.7, 120.1, 110.3, 109.8, 105.3, 104.7 (aromatic C), 33.8, 30.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{20}H_{16}N_2$: 285.1391 (M+H)

Found: 285.1390

**1-(methoxymethyl)-1'-(prop-2-yn-1-yl)-1H,1'H-2,2'-biindole (325b):** Compound **325b** was synthesized from indole derivative **326b** and propargyl bromide following the *general procedure M*. Pure product was obtained through silica gel column chromatography with 2% ethyl acetate in hexanes as a viscous liquid.




Yield: 81%

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3028, 2853, 1064, 766

$^1$H NMR (400 MHz) δ: 7.76 (2H, d, *J* = 7.7 Hz), 7.62 (2H, m), 7.37-7.42 (2H, m), 7.26-7.30 (2H, m), 6.89 (1H, s), 6.87 (1H, s), 5.51 (2H, s), 4.90 (2H, d, *J* = 2.2 Hz), 3.30 (3H, s), 2.36 (1H, t, *J* = 2.2 Hz)

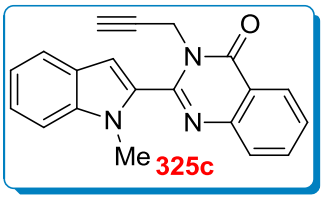
$^{13}$C NMR (100 MHz) δ: 137.9, 137.2, 130.7, 130.2, 128.1, 128.0, 123.2, 122.9, 122.5, 121.2, 121.1, 120.8, 110.6, 110.3, 106.4, 105.9 (aromatic C), 78.6, 74.9, 72.8, 56.0, 33.8 (aliphatic C)

LCMS (m/z) ($C_{20}H_{16}N_2$): 315 $(M+H)^+$

**2-(1-methyl-1H-indol-2-yl)-3-(prop-2-yn-1-yl)quinazolin-4(3H)-one (325c) and 2-(1-methyl-1H-indol-2-yl)-4-(prop-2-yn-1-yloxy)quinazoline (325c'):** Compound **325c** and **325c'** were synthesized from indole derivative **326c** and propargyl

bromide following the *general procedure M*. Pure products were obtained through silica gel column chromatography with 2% ethyl acetate in hexanes.

**Compound 325c**




Yield: 47%

Mp: 120-122 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3049, 2954, 1653, 1024, 651

$^1$H NMR (400 MHz) δ: 8.39 (1H, d, *J* = 7.9 Hz), 7.76-7.81 (2H, m), 7.72 (1H, d, *J* = 7.9 Hz), 7.57 (1H, t, *J* = 7.6 Hz), 7.45 (1H, d, *J* = 8.2 Hz), 7.37 (1H, *t*, *J* = 7.1 Hz), 7.22 (1H, *t*, *J* = 7.4 Hz), 7.14 (1H, s), 4.94 (2H, s), 3.89 (3H, s), 2.36 (1H, s)

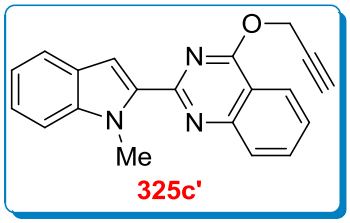
$^{13}$C NMR (100 MHz) δ: 161.6, 147.9, 146.8, 138.2, 134.8, 131.1, 127.7, 127.0, 126.9, 123.8, 121.8, 120.8, 120.7, 110.1, 105.3 (aromatic C), 78.4, 72.7, 36.2, 31.5 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{20}H_{15}N_3O$: 314.1293 (M+H)

Found: 314.1294

**Compound 325c'**




Yield: 19%

Mp: 154-156 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3014, 2830, 1057, 618

$^1$H NMR (400 MHz) δ: 8.20 (1H, d, *J* = 8.0 Hz), 7.97 (1H, d, *J* = 8.0 Hz), 7.83 (1H, *t*, J = 6.9 Hz), 7.72 (1H, d, *J* = 7.6 Hz), 7.61 (1H, s), 7.53 (1H, *t*, J = 7.0 Hz), 7.44 (1H, d, *J* = 8.1 Hz), 7.32 (1H, t, *J* = 6.8 Hz), 7.16 (1H, t, *J* = 7.2 Hz), 5.33 (2H, s), 4.38 (3H, s), 2.58 (1H, s)

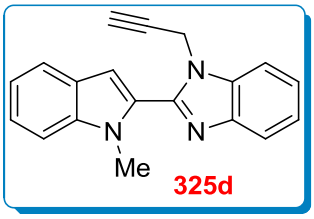
$^{13}$C NMR (100 MHz) δ: 151.8, 140.4, 136.9, 133.8, 127.8, 127.0, 126.6, 123.5, 121.7, 120.0, 114.7, 110.0, 108.3 (aromatic C), 78.2, 75.2, 54.3, 32.8 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{20}H_{15}N_3O$: 314.1293 (M+H)

Found: 314.1295

**2-(1-methyl-1H-indol-2-yl)-1-(prop-2-yn-1-yl)-1H-benzo[d]imidazole (325d):** Compound **325d** was synthesized from indole derivative **326d** and propargyl bromide following the *general procedure M*. Pure product was obtained through silica gel column chromatography with 2% ethyl acetate in hexanes.




Yield: 78%

Mp: 113-115 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3024, 2854, 1037, 752

$^{1}H$ NMR (400 MHz) δ: 7.91 (1H, t, *J* = 7.8 Hz), 7.76 (1H, t, *J* = 8.5 Hz), 7.61 (1H, t, *J* = 7.9 Hz), 7.35-7.50 (4H, m), 7.21-7.28 (1H, m), 7.08 (1H, s), 5.10 (2H, s), 4.06 (3H, s), 2.49 (1H, s)

$^{13}C$ NMR (100 MHz) δ: 145.6, 143.1, 138.3, 134.8, 127.4, 127.2, 123.6 ,123.1, 121.4, 120.4, 120.2, 110.2, 105.8 (aromatic C) Alkyne quaternary C merged with $CDCl_3$ peak, 73.9,34.7, 31.5 (aliphatic C)

HRMS (ESI-MS)

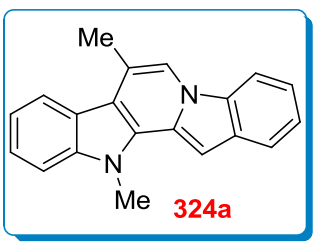
Calcd for $C_{19}H_{15}N_3$: 286.1344 (M+H)

Found: 286.1344

***General procedure N*:**

Into the reaction mixture of N-propargylated indole derivative (0.25 mmol) in MeCN 5 mL was added CuI (10 mol%) and stirred at reflux temperature. After completion of the reaction as indicated by TLC, was added into water and extracted with EtOAc, dried over anhydrous $Na_2SO_4$ and evaporated in vacuum. The residue was purified by column chromatography on silica gel.

**7,12-Dimethyl-12H-pyrido[1,2-a:3,4-b']diindole (324a):** Compound **324a** was synthesized from indole derivative **325a** and propargyl bromide following the *general procedure N*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.




Yield: 78%

Mp: 184-186 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3014, 2754, 1059, 650 °C

$^1$H NMR (400 MHz) δ: 8.14 (1H, d, *J* = 7.8 Hz), 7.90-7.92 (2H, m), 7.85 (1H, d, *J* = 7.6 Hz), 7.52 (1H, d, *J* = 7.9 Hz), 7.43 (1H, t, *J* = 6.8 Hz), 7.26-7.38 (3H, m), 7.09 (1H, s), 4.30 (3H, s), 2.80 (3H, s)

$^{13}$C NMR (100 MHz) δ: Due to poor solubility of compound in both $CDCl_3$ as well as DMSO-$d_6$, we were unable to take $^{13}$C NMR

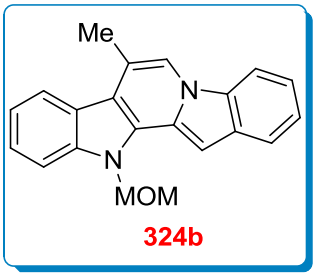
HRMS (ESI-MS)

Calcd for $C_{20}H_{16}N_2$: 285.1391 (M+H)

Found: 285.1390

**12-(Methoxymethyl)-7-methyl-12H-pyrido[1,2-a:3,4-b']diindole (324b):**

Compound **324b** was synthesized from indole derivative **325b** and propargyl bromide following the *general procedure N*. Pure product was obtained through silica gel column chromatography with 5% ethyl acetate in hexanes.



**324b**

Yield: 65%

Mp: 157-159 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3021, 2854, 1037, 687 °C

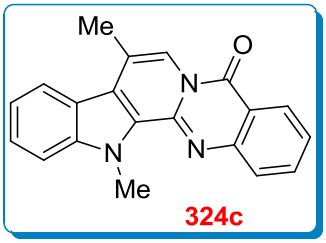
$^1$H NMR (400 MHz) δ: 8.12 (1H, d, *J* = 8.0 Hz), 7.84-7.91 (3H, m), 7.63 (1H, d, *J* = 8.2 Hz), 7.44 (1H, t, *J* = 7.4 Hz), 7.29-7.39 (3H, m), 7.04 (1H, s), 5.91 (2H, s), 3.40 (3H, s), 2.76 (3H, s)

$^{13}$C NMR (100 MHz) δ: 139.8, 130.1, 129.4, 128.9, 127.1, 124.3, 124.1, 122.3, 121.4, 120.9, 120.6, 119.9, 115.9, 114.2, 110.2, 109.7, 90.2 (aromatic C), 74.8, 55.9, 18.0 (aliphatic C)

LCMS(m/z) ($C_{21}H_{18}N_2O$): 315 $(M+H)^+$

**8,13-Dimethylindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(13H)-one (324c):**

Compound **324c** was synthesized from indole derivative **325c** and propargyl bromide following the *general procedure N*. Pure product was obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.



**324c**

Yield: 72%

Mp: 234-236 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3045, 2748, 1254, 634

$^1$H NMR (400 MHz) δ: 8.35-8.38 (2H, m), 8.03 (1H, d, *J* = 7.6 Hz), 7.71-7.73 (2H, m), 7.46-7.48 (2H, m), 7.36 (1H, t, *J* = 6.3 Hz), 7.26 (1H, s), 4.56 (3H, s), 2.68 (3H, s)

$^{13}$C NMR (100 MHz) δ: 158.9, 147.2, 141.5, 140.5, 133.9, 128.0, 127.2, 126.8, 126.3, 124.3, 122.2, 121.5, 121.3, 120.8, 119.4, 115.9, 115.8, 110.2 (aromatic C), 32.9, 17.9 (aliphatic C)

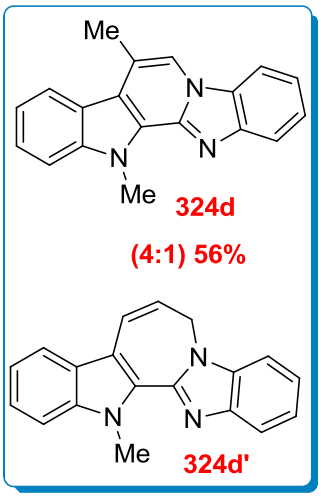
HRMS (ESI-MS)

Calcd for $C_{20}H_{15}N_3O$: 314.1293 (M+H)

Found: 314.1293

**7,12-Dimethyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (324d) and 13-methyl-6,13-dihydrobenzo[4',5']imidazo[1',2':1,2]azepino[3,4-b]indole (324d'):** Compounds **324d** and **324d'** were synthesized from indole derivative **325d** and propargyl bromide following the *general procedure N*. Pure products were obtained through silica gel column chromatography with 10% ethyl acetate in hexanes.

Yield: overall 56%




**Compound 324d**

Mp: 167-169 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3027, 2964, 1067, 674

$^1$H NMR (400 MHz) δ: 8.17 (1H, d, *J* = 8.0 Hz), 8.00 (1H, d, *J* = 8.2 Hz), 7.84-7.86 (2H, m), 7.49-7.53 (3H, m), 7.31-7.39 (2H, m), 4.56 (3H, s), 2.81 (3H, s)

$^{13}$C NMR (100 MHz) δ: 144.1, 140.9, 140.3, 129.1, 126.4, 125.2, 124.6, 123.1, 121.9, 120.8, 120.4, 119.5, 117.9, 117.4, 114.5, 110.2, 109.9 (aromatic C) 32.0, 17.9 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{19}H_{15}N_3$: 286.1344 (M+H)

Found: 286.1344

### Compound 324d'

Mp: 148-150 °C

IR (KBr) $\nu_{max}$ $cm^{-1}$: 3054, 2847, 1064, 653

$^{1}H$ NMR (400 MHz) δ: 7.86 (1H, d, *J* = 7.6 Hz), 7.76 (1H, d, *J* = 7.8 Hz), 7.50 (2H, *t*, *J* = 7.2 Hz), 7.42 (1H, *t*, *J* = 7.0 Hz), 7.31-7.37 (2H, m), 7.24-7.28 (1H, m), 7.21-7.24 (1H, m), 6.03-6.06 (1H, m), 4.68 (2H, d, *J* = 6.4 Hz), 4.36 (3H, s)

$^{13}C$ NMR (100 MHz) δ: 146.3, 144.0, 138.8, 133.7, 127.3, 125.7, 124.5, 122.7, 122.3, 120.7, 120.1, 119.8, 119.3, 115.7, 110.1, 109.2 (aromatic C), 41.0, 32.4 (aliphatic C)

HRMS (ESI-MS)

Calcd for $C_{19}H_{15}N_3$: 286.1344 (M+H)

Found: 286.1345

**Table 33. Crystal data and structure refinement for 319e**

| | |
|---|---|
| Empirical formula | : $C_{23}H_{17}N_3$ |
| Formula weight | : 335.40 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P2(1)/n |
| Unit cell dimensions | : a = 7.928(2) Å $\alpha$= 90° |
| | : b = 16.966(5) Å $\beta$= 93.429(5)° |
| | : c = 12.302(4) Å $\gamma$ = 90° |
| Volume | : 1651.8(9) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.349 $Mg/m^3$ |
| Absorption coefficient | : 0.081 $mm^{-1}$ |
| F (000) | : 704 |
| Crystal size | : 0.22 x 0.18 x 0.10 $mm^3$ |
| Theta range for data collection | : 2.05 to 26.12° |
| Index ranges | : -9<=h<=9, -20<=k<=20, -15<=l<=15 |
| Reflections collected | : 16856 |
| Independent reflections | : 3268 [R(int) = 0.0352] |
| Completeness to theta = 26.04° | : 99.5% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9920 and 0.9824 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 3268 / 0 / 237 |
| Goodness-of-fit on $F^2$ | : 1.044 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0441, wR2 = 0.1103 |
| R indices (all data) | : R1 = 0.0513, wR2 = 0.1168 |
| Largest diff. peak and hole | : 0.213 and -0.294 $e.Å^{-3}$ |
| CCDC number | : 921988 |

**Table 34. Crystal data and structure refinement for 319f**

| | |
|---|---|
| Empirical formula | : $C_{40}H_{34}N_6O$ |
| Formula weight | : 614.73 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : C2/c |
| Unit cell dimensions | : a = 18.482(3) Å $\alpha$ = 90° |
| | : b = 24.976(4) Å $\beta$ = 108.136(2)° |
| | : c = 14.268(2) Å $\gamma$ = 90° |
| Volume | : 6259.1(17) $Å^3$ |
| Z | : 8 |
| Density (calculated) | : 1.305 $Mg/m^3$ |
| Absorption coefficient | : 0.081 $mm^{-1}$ |
| F (000) | : 2592 |
| Crystal size | : 0.24 x 0.18 x 0.10 $mm^3$ |
| Theta range for data collection | : 1.42 to 26.04° |
| Index ranges | : -22<=h<=22, -30<=k<=30, -17<=l<=17 |
| Reflections collected | : 32322 |
| Independent reflections | : 6180 [R(int) = 0.0409] |
| Completeness to theta = 26.04° | : 99.8% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9920 and 0.9809 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 6180 / 0 / 430 |
| Goodness-of-fit on $F^2$ | : 1.301 |
| Final R indices [I>2sigma (I)] | : R1 = 0.1048, wR2 = 0.3198 |
| R indices (all data) | : R1 = 0.1411, wR2 = 0.3499 |
| Largest diff. peak and hole | : 1.417 and -0.610 $e.Å^{-3}$ |
| CCDC number | : 921989 |

**Table 35. Crystal data and structure refinement for 319g**

| | |
|---|---|
| Empirical formula | : $C_{18}H_{13}BrN_4$ |
| Formula weight | : 365.23 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P 1 21/c 1 |
| Unit cell dimensions | : a = 7.5297(8) Å $\alpha$ = 90° |
| | : b = 15.7552(16) Å $\beta$= 94.664(10)° |
| | : c = 12.3971(16) Å $\gamma$ = 90° |
| Volume | : 1465.8(3) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.655 $Mg/m^3$ |
| Absorption coefficient | : 2.809 $mm^{-1}$ |
| F (000) | : 736 |
| Crystal size | : 0.22 x 0.20 x 0.12 $mm^3$ |
| Theta range for data collection | : 3.01 to 26.37° |
| Index ranges | : -9<=h<=5, -7<=k<=19, -10<=l<=15 |
| Reflections collected | : 3007 |
| Independent reflections | : 2035 [R(int) = 0.0420] |
| Completeness to theta = 26.04° | : 99.6% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 1.00000 and 0.07869 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 2035 / 0 / 210 |
| Goodness-of-fit on $F^2$ | : 0.974 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0614, wR2 = 0.0654 |
| R indices (all data) | : R1 = 0.1224, wR2 = 0.0843 |
| Largest diff. peak and hole | : 0.396 and -0.327 $e.Å^{-3}$ |
| CCDC number | : 921987 |

**Table 36. Crystal data and structure refinement for 324d**

| | |
|---|---|
| Empirical formula | : $C_{19}H_{15}N_3$ |
| Formula weight | : 285.34 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : I 1 2/a 1 |
| Unit cell dimensions | : a = 14.543(3) Å $\alpha$ = 90° |
| | : b = 11.0849(19) Å $\beta$= 89.91(3)° |
| | : c = 17.240(4) Å $\gamma$ = 90° |
| Volume | : 2779.1(10) $Å^3$ |
| Z | : 8 |
| Density (calculated) | : 1.364 $Mg/m^3$ |
| Absorption coefficient | : 0.083 $mm^{-1}$ |
| F (000) | : 1200 |
| Crystal size | : 0.30 x 0.20 x 0.15 $mm^3$ |
| Theta range for data collection | : 2.80 to 26.37° |
| Index ranges | : -18<=h<=10, -12<=k<=13, -21<=l<=10 |
| Reflections collected | : 3784 |
| Independent reflections | : 2180 [R(int) = 0.0959] |
| Completeness to theta = 26.04° | : 99.6% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9877 and 0.9757 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 2180 / 0 / 202 |
| Goodness-of-fit on $F^2$ | : 1.014 |
| Final R indices [I>2sigma (I)] | : R1 = 0.1207, wR2 = 0.2839 |
| R indices (all data) | : R1 = 0.1807, wR2 = 0.3550 |
| Largest diff. peak and hole | : 0.416 and -0.350 $e.Å^{-3}$ |

**Table 37. Crystal data and structure refinement for 324d'**

| | |
|---|---|
| Empirical formula | : $C_{19}H_{15}N_3$ |
| Formula weight | : 285.34 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Orthorhombic |
| Space group | : P 21 21 21 |
| Unit cell dimensions | : a = 7.777(3) Å $\alpha$ = 90° |
| | : b = 9.866(3) Å $\beta$ = 90° |
| | : c = 18.442(6) Å $\gamma$ = 90° |
| Volume | : 1414.9(8) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.340 $Mg/m^3$ |
| Absorption coefficient | : 0.081 $mm^{-1}$ |
| F (000) | : 600 |
| Crystal size | : 0.30 x 0.20 x 0.15 $mm^3$ |
| Theta range for data collection | : 2.84 to 26.37° |
| Index ranges | : -9<=h<=4, -11<=k<=12, -14<=l<=23 |
| Reflections collected | : 4072 |
| Independent reflections | : 2539 [R(int) = 0.0402] |
| Completeness to theta = 26.04° | : 99.6% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9879 and 0.9761 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 2539 / 0 / 200 |
| Goodness-of-fit on $F^2$ | : 0.916 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0508, wR2 = 0.0774 |
| R indices (all data) | : R1 = 0.0861, wR2 = 0.0890 |
| Largest diff. peak and hole | : 0.159 and -0.148 $e.Å^{-3}$ |

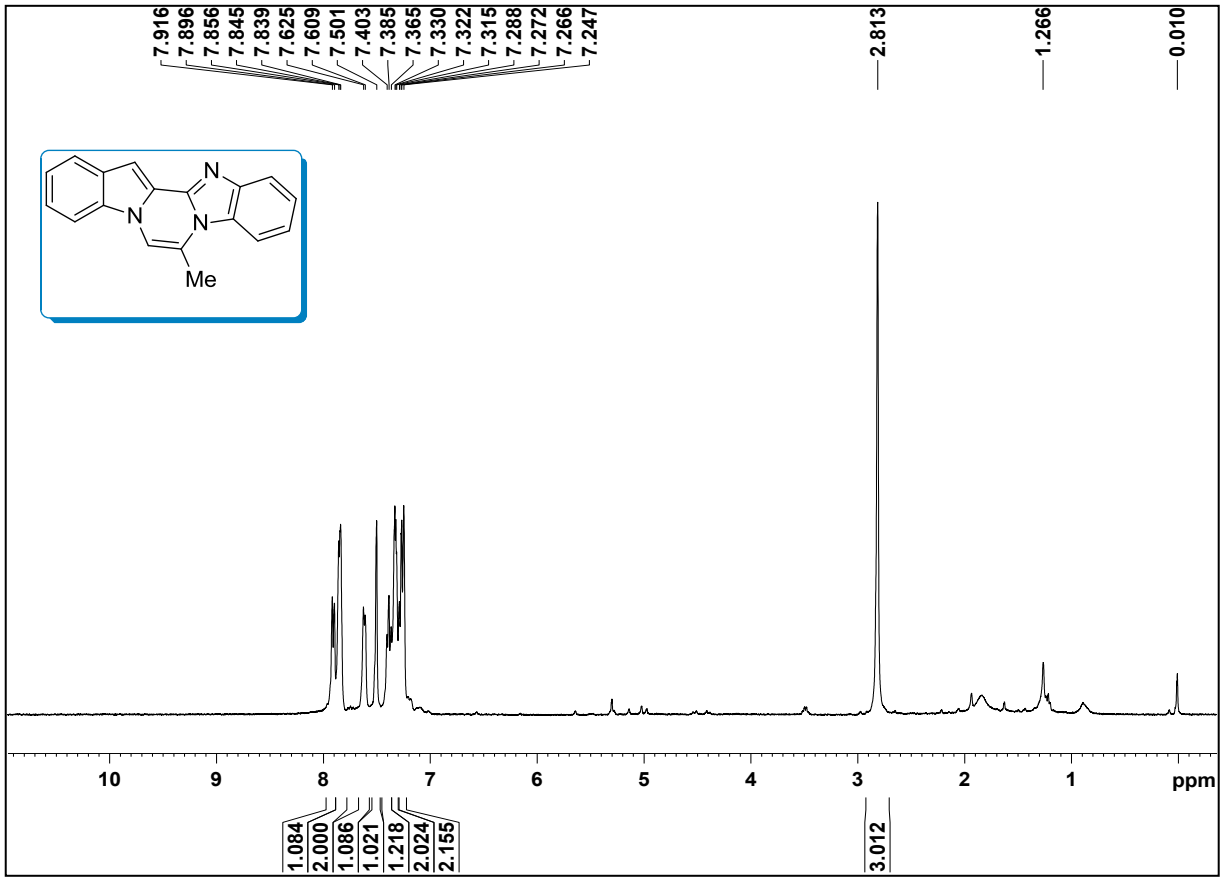
**Table 38. Crystal data and structure refinement for 324c**

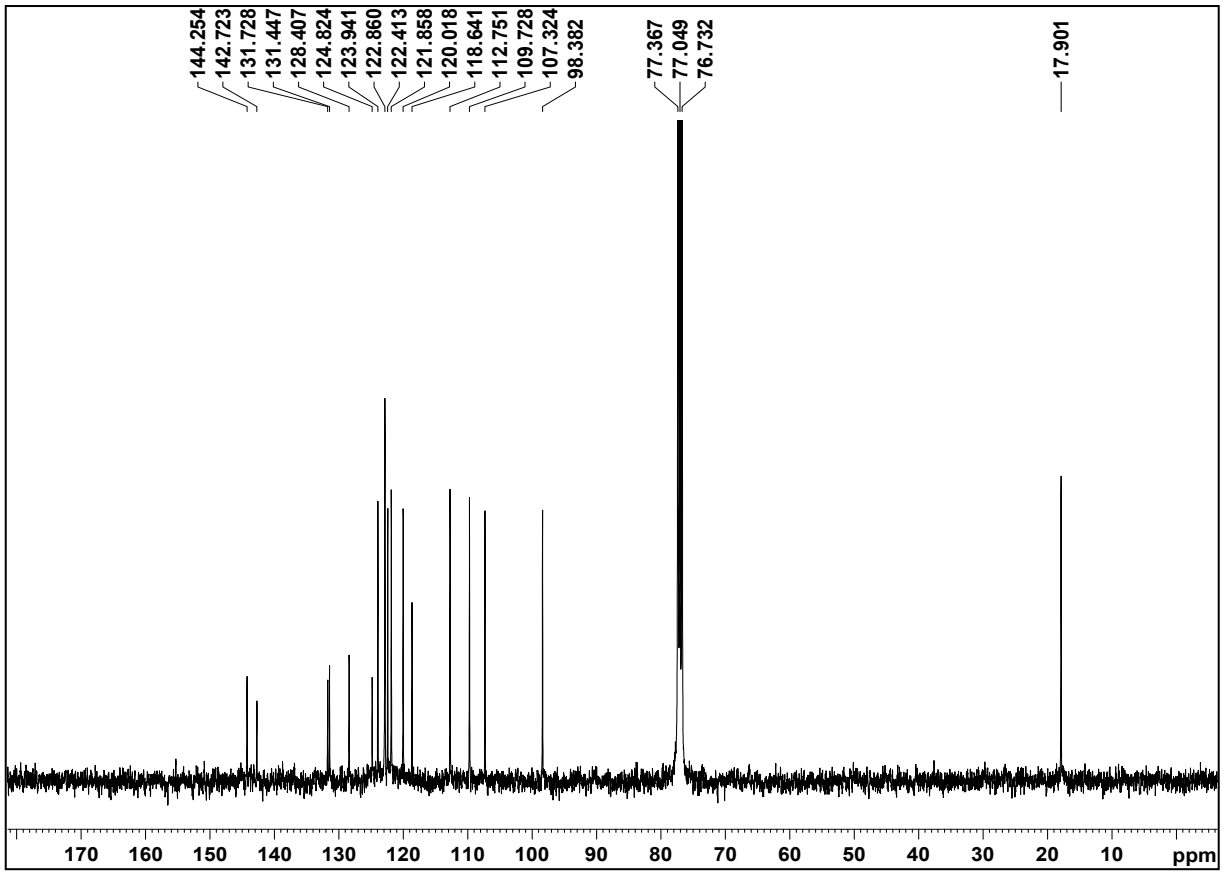
| | |
|---|---|
| Empirical formula | : $C_{20}H_{15}N_3O$ |
| Formula weight | : 313.35 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Triclinic |
| Space group | : P -1 |
| Unit cell dimensions | : a = 8.0050(14) Å $\alpha$ = 91.642(12)° |
| | : b = 8.9248(12) Å $\beta$ = 107.378(14)° |
| | : c = 11.6607(17) Å $\gamma$ = 108.731(14)° |
| Volume | : 745.8(2) $Å^3$ |
| Z | : 2 |
| Density (calculated) | : 1.395 $Mg/m^3$ |
| Absorption coefficient | : 0.089 $mm^{-1}$ |
| F (000) | : 328 |
| Crystal size | : 0.30 x 0.20 x 0.15 $mm^3$ |
| Theta range for data collection | : 2.84 to 26.37° |
| Index ranges | : -9<=h<=9, -10<=k<=11, -14<=l<=8 |
| Reflections collected | : 5106 |
| Independent reflections | : 3040 [R(int) = 0.0222] |
| Completeness to theta = 26.04° | : 99.9% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9868 and 0.9739 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 3040 / 0 / 219 |
| Goodness-of-fit on $F^2$ | : 1.008 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0557, wR2 = 0.1062 |
| R indices (all data) | : R1 = 0.1028, wR2 = 0.1344 |
| Largest diff. peak and hole | : 0.203 and -0.237 $e.Å^{-3}$ |

**Table 39. Crystal data and structure refinement for 324a**

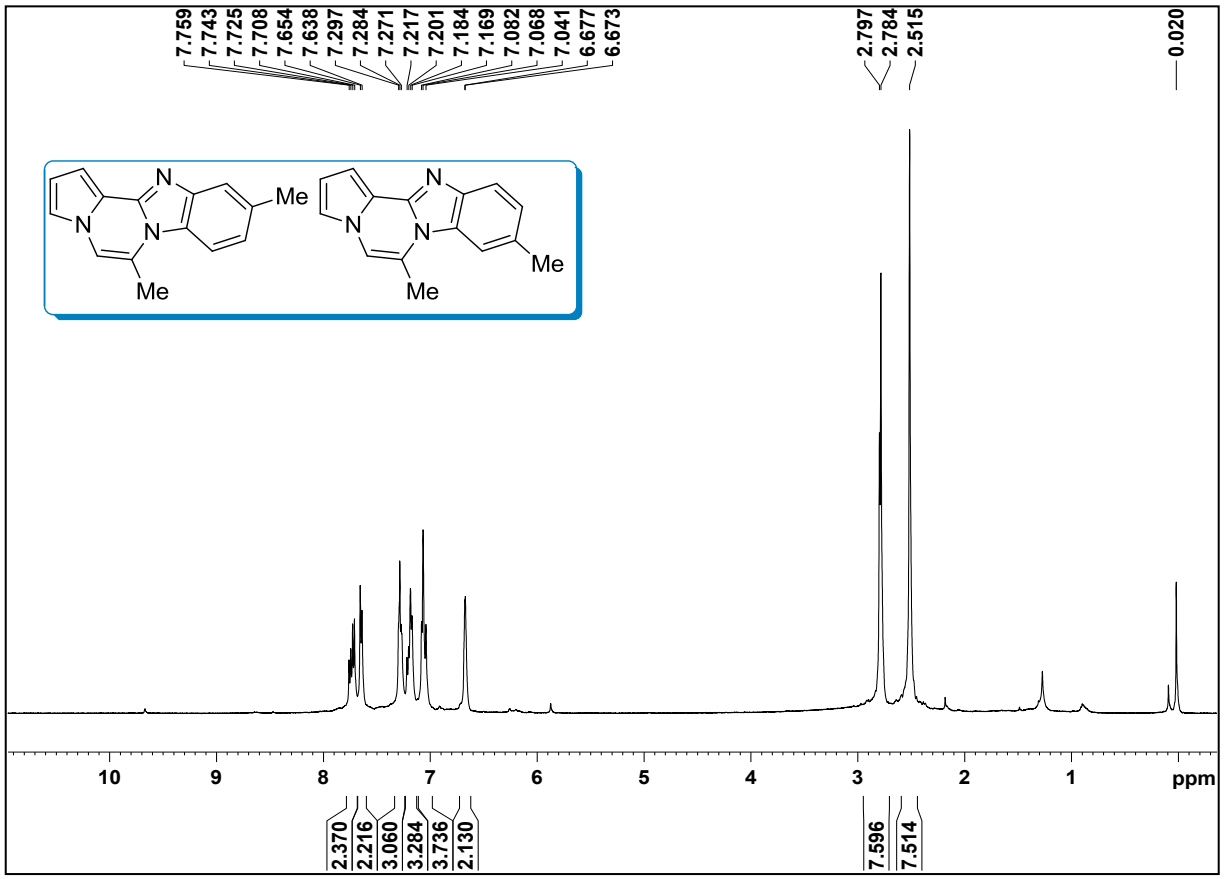
| | |
|---|---|
| Empirical formula | : $C_{20}H_{16}N_2$ |
| Formula weight | : 284.35 |
| Temperature | : 298 K |
| Wavelength | : 0.71073 Å |
| Crystal system | : Monoclinic |
| Space group | : P 1 21/n 1 |
| Unit cell dimensions | : a = 14.339(4) Å $\alpha$ = 90° |
| | : b = 5.5906(18) Å $\beta$= 106.95(3)° |
| | : c = 18.609(5) Å $\gamma$ = 90° |
| Volume | : 1427.0(7) $Å^3$ |
| Z | : 4 |
| Density (calculated) | : 1.324 $Mg/m^3$ |
| Absorption coefficient | : 0.078 $mm^{-1}$ |
| F (000) | : 600 |
| Crystal size | : 0.30 x 0.20 x 0.15 $mm^3$ |
| Theta range for data collection | : 2.97 to 26.37° |
| Index ranges | : -17<=h<=16, -6<=k<=6, -12<=l<=23 |
| Reflections collected | : 5131 |
| Independent reflections | : 2895 [R(int) = 0.0223] |
| Completeness to theta = 26.04° | : 99.8% |
| Absorption correction | : Semi-empirical from equivalents |
| Max. and min. transmission | : 0.9884 and 0.9769 |
| Refinement method | : Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | : 2895 / 0 / 201 |
| Goodness-of-fit on $F^2$ | : 1.021 |
| Final R indices [I>2sigma (I)] | : R1 = 0.0521, wR2 = 0.1183 |
| R indices (all data) | : R1 = 0.0906, wR2 = 0.1400 |
| Largest diff. peak and hole | : 0.214 and -0.142 $e.Å^{-3}$ |

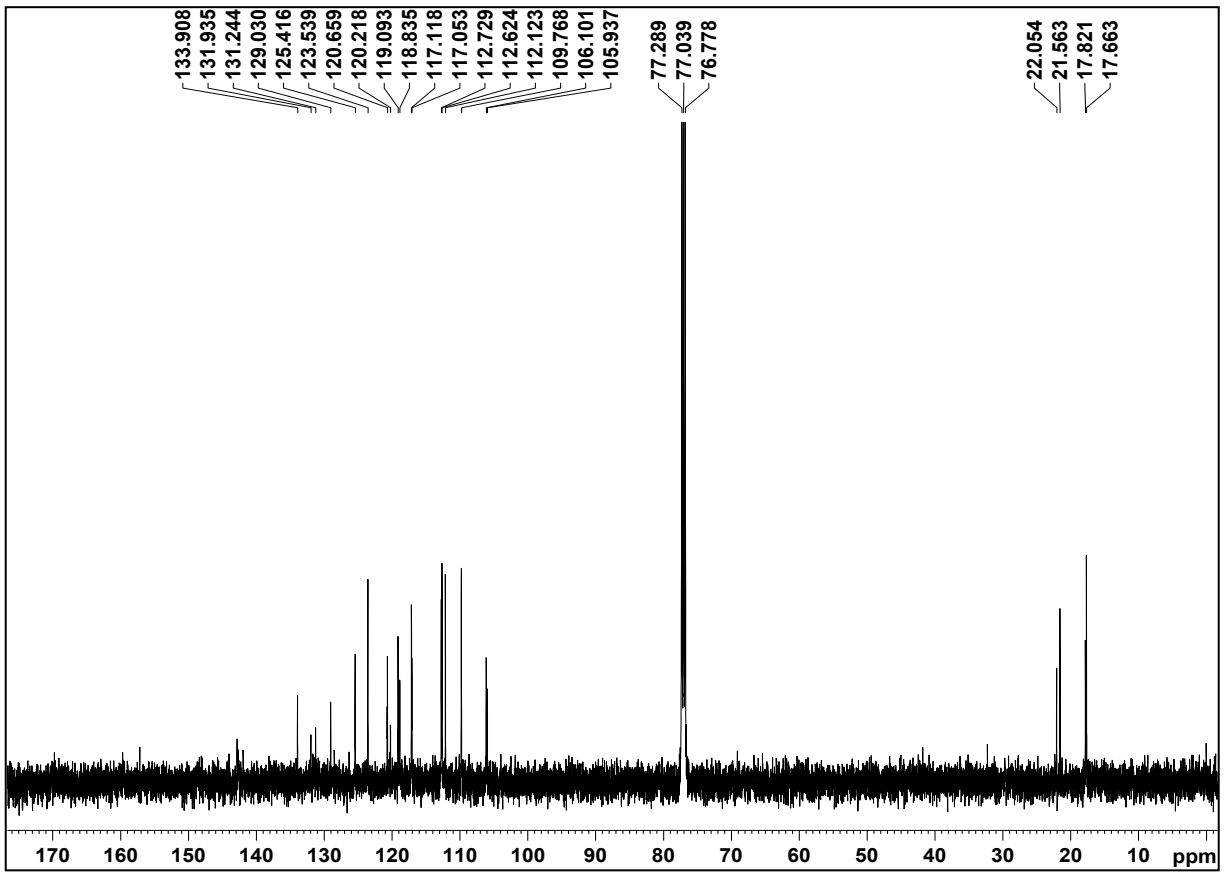
## Spectra No. 16: $^{1}H$ and $^{13}C$ spectra of compound 319h



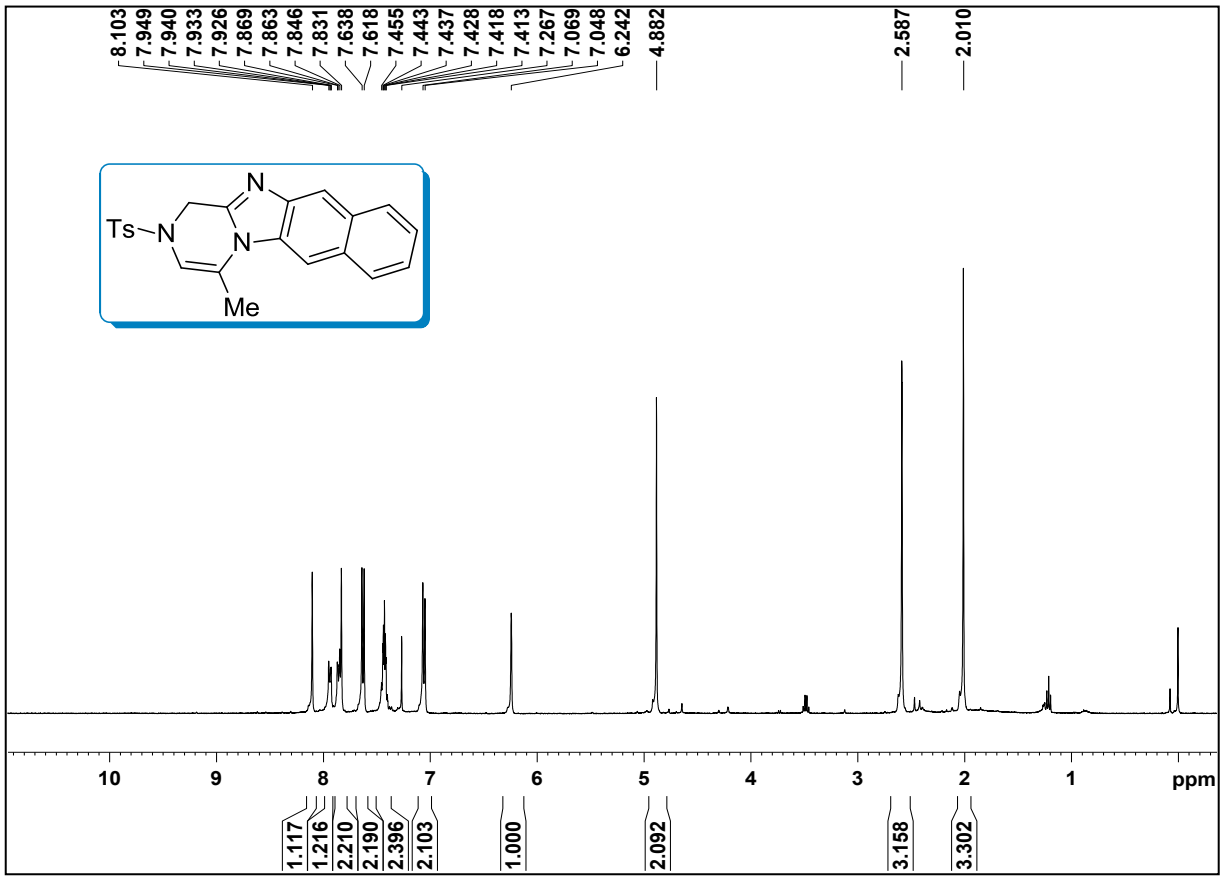



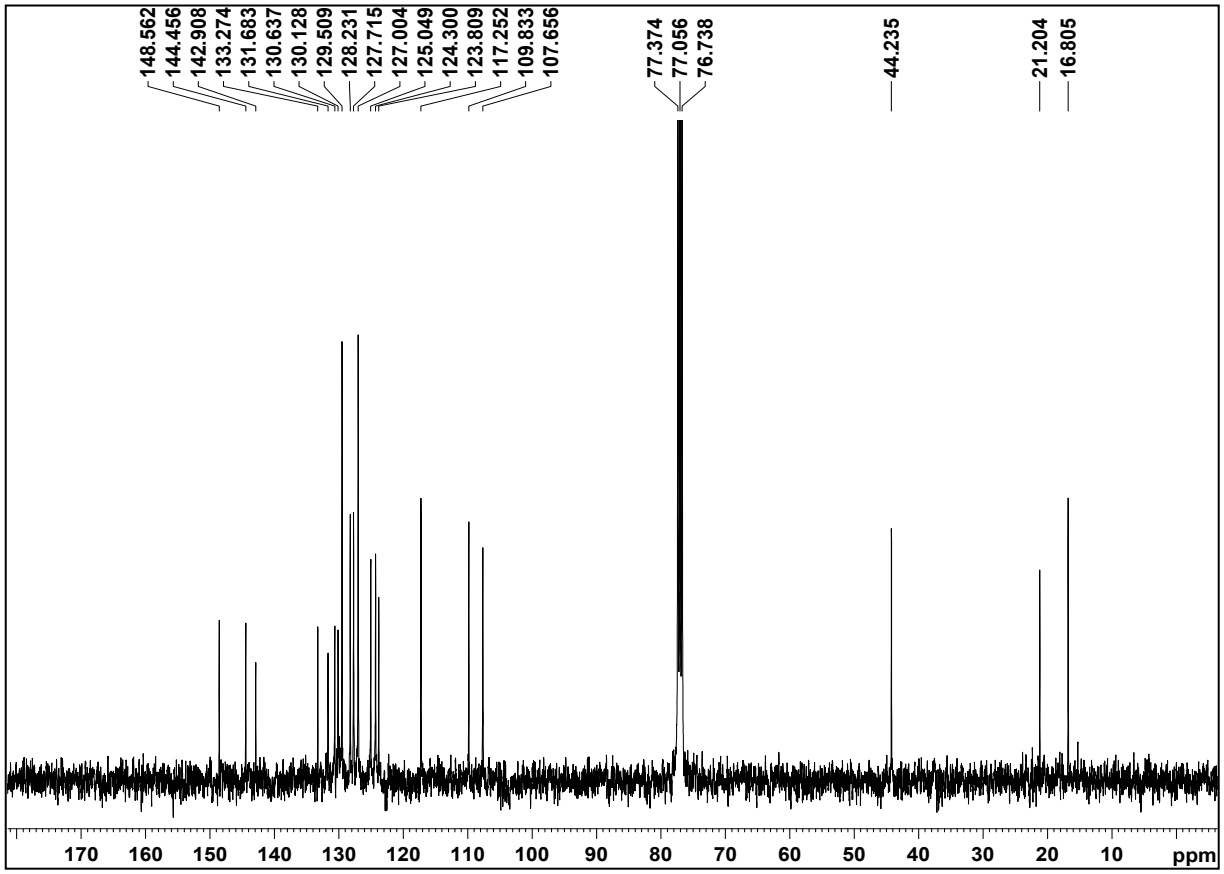
## Spectra No. 17: $^{1}H$ and $^{13}C$ spectra of compounds 321c and 321c'



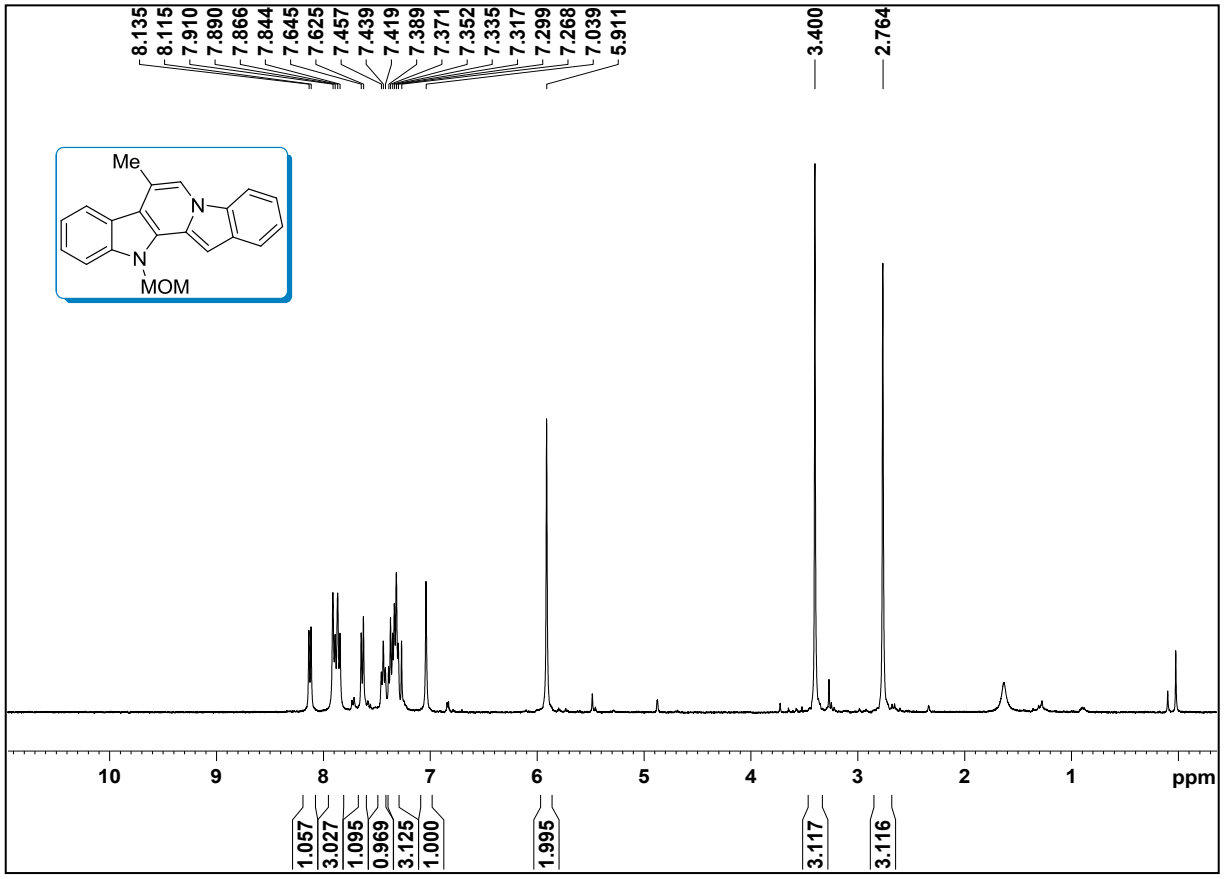



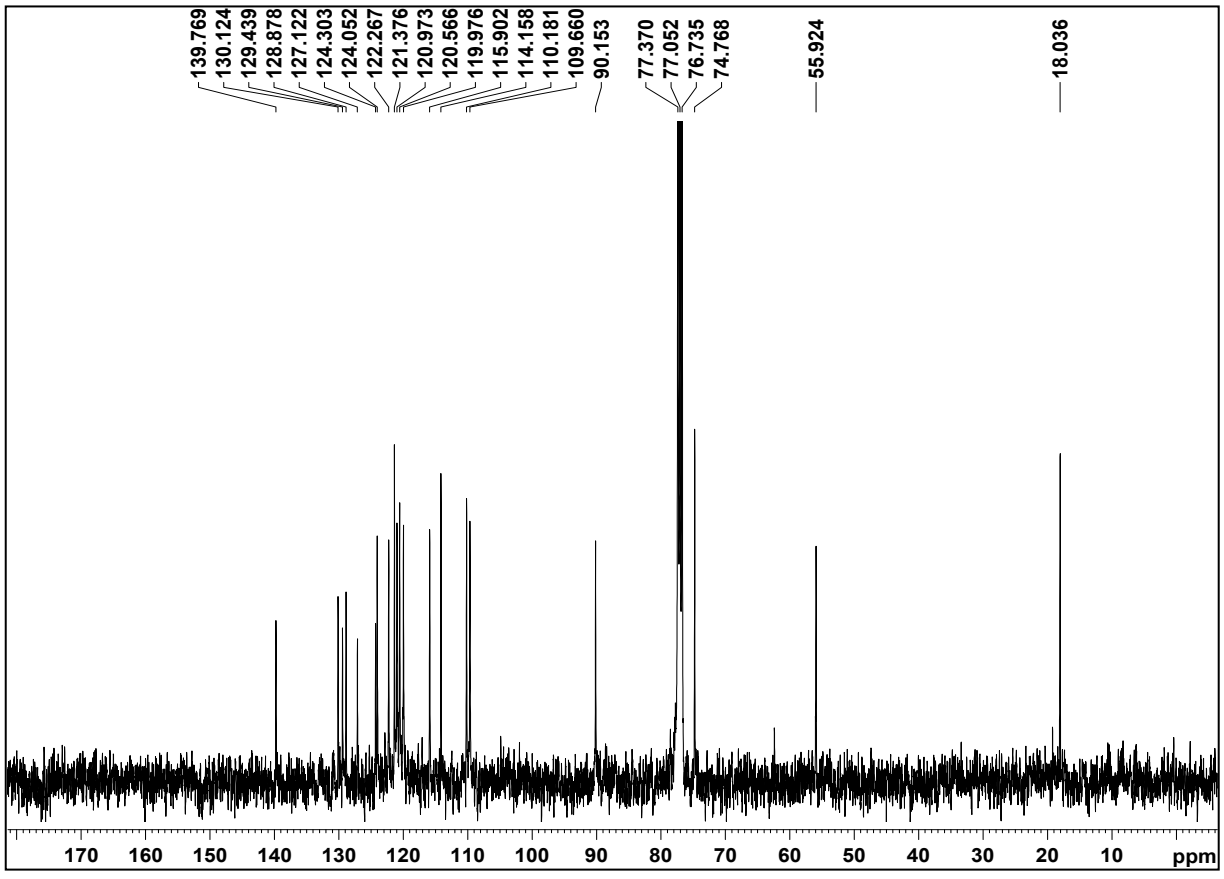
## Spectra No. 18: $^{1}H$ and $^{13}C$ spectra of compound 323b



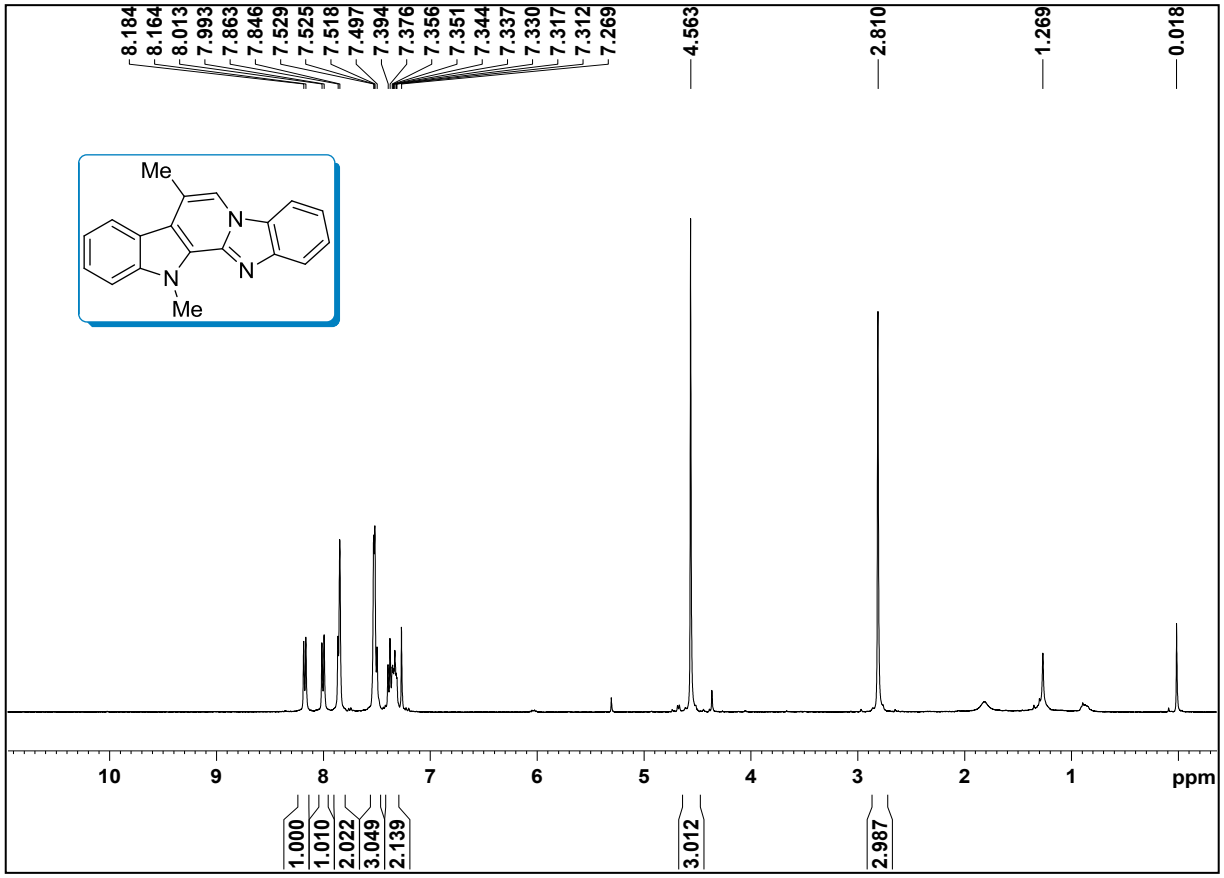



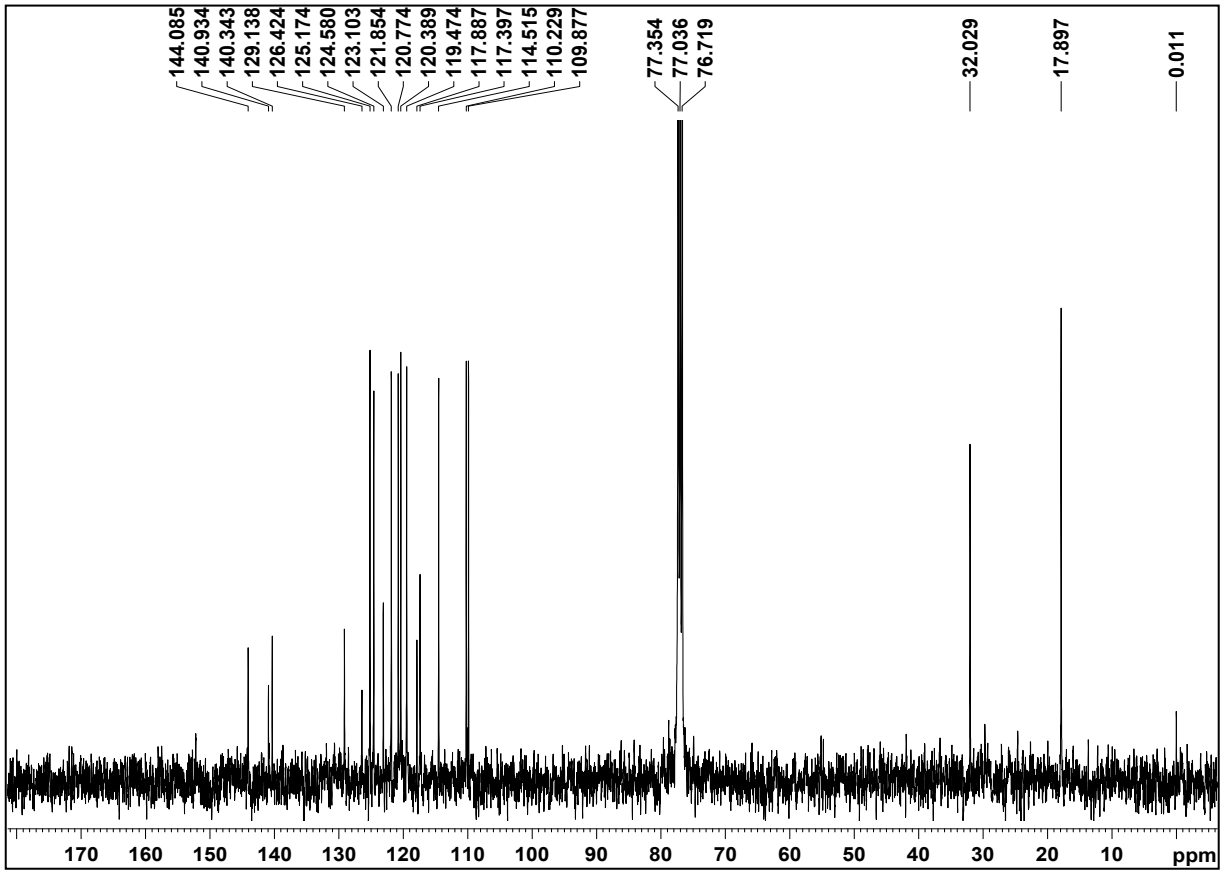
## Spectra No. 19: $^{1}H$ and $^{13}C$ spectra of compound 324b



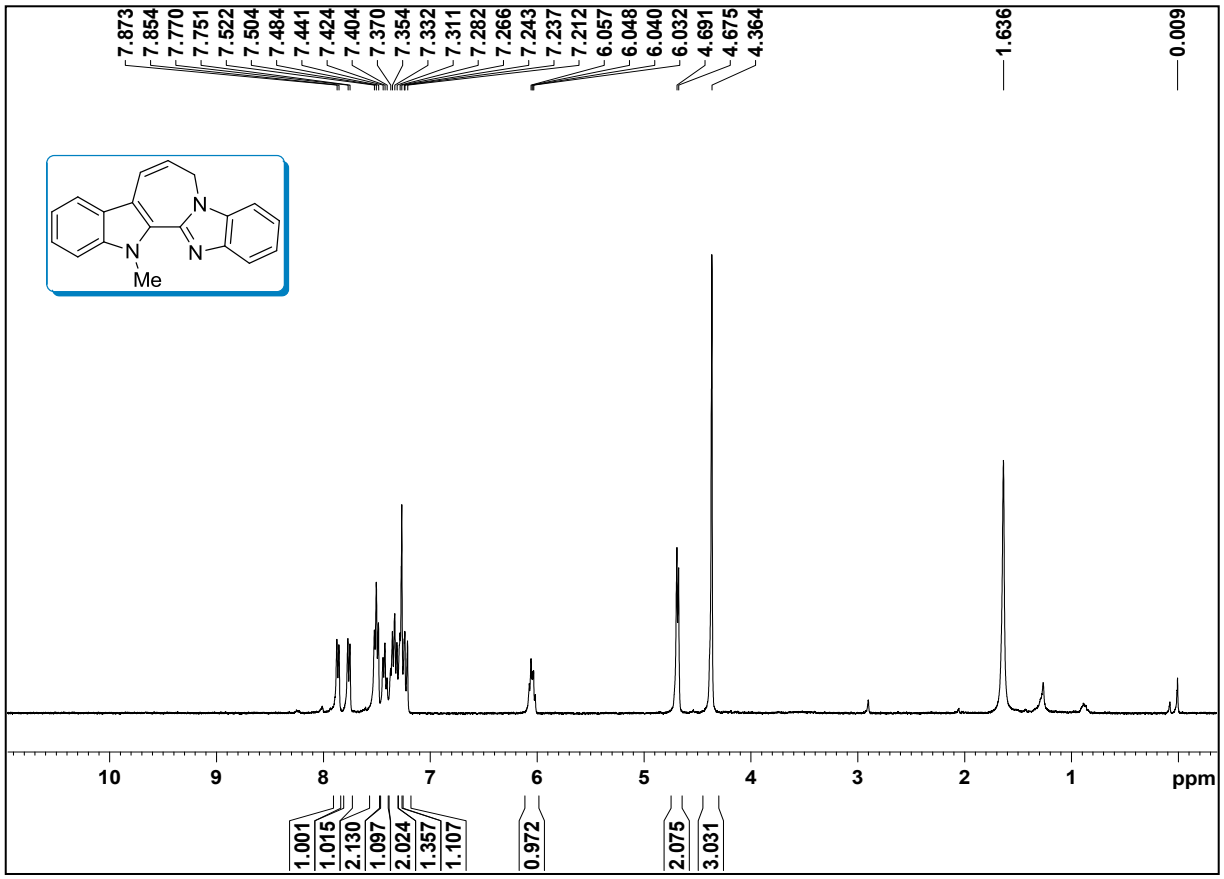



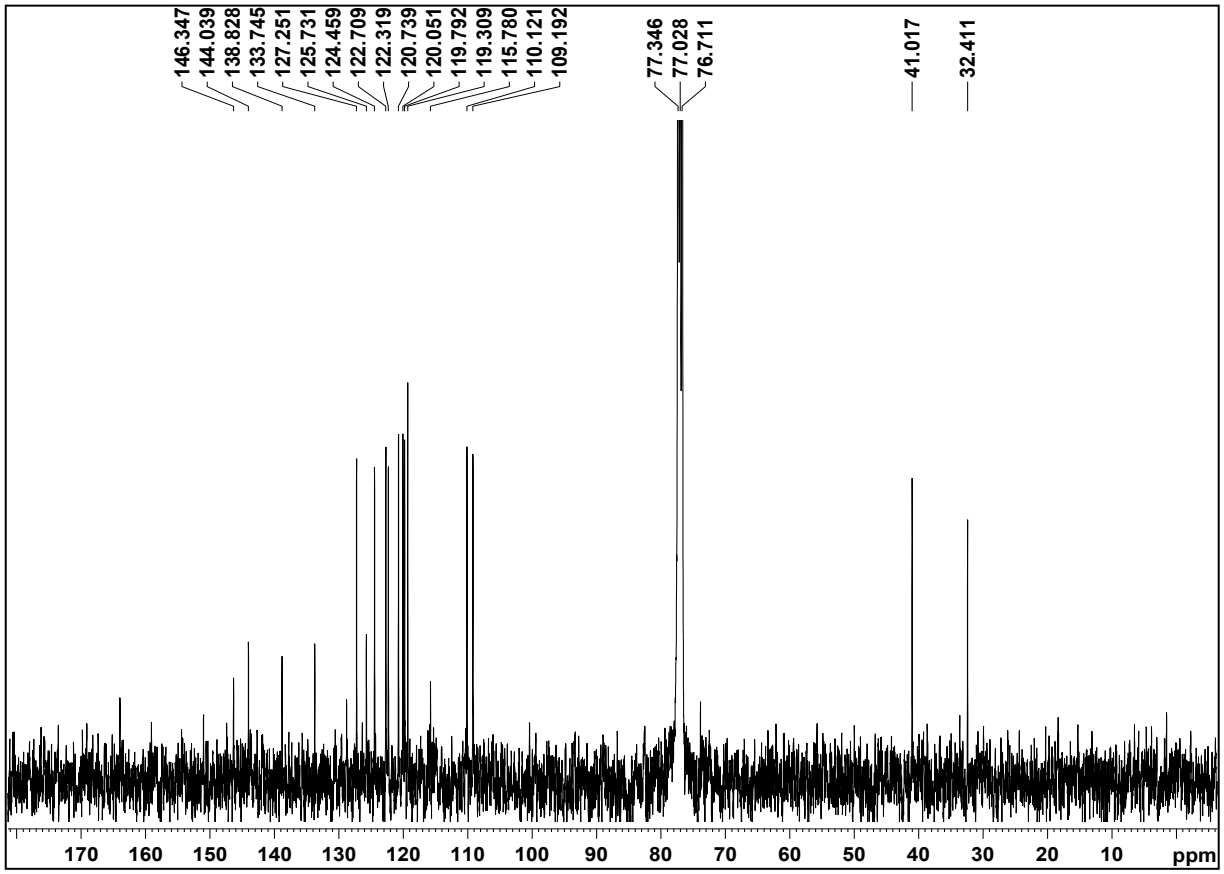
## Spectra No. 20: $^{1}H$ and $^{13}C$ spectra of compound 324d



## Spectra No. 21: $^{1}H$ and $^{13}C$ spectra of compound 324d'



## 5.6. Conclusions

A simple and efficient route has been demonstrated for synthesizing a variety of benzimidazolopyrazine derivatives. We have delineated this synthetic protocol in the biologically important indole and pyrrole systems as well as in the aliphatic system. We believe that these heterocyclic fused benzimidazolopyrazines would be important pharmacophores in pharmacology. Our synthetic protocol offers a one-pot procedure, environmentally benign solvents and copper catalyzed *6-exo-dig* cyclization in good yields.

## 5.7. References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# Conclusions

We have made noticeable progress and accomplished considerable success in our objectives on the synthesis of pivotal heteroaryl quinoline, carboline, imidazolopiperazine derivatives via alkyne and alkene chemistry.

.

- We have developed a novel intramolecular aza Diels-Alder approach for the synthesis of chromenoquinoline, pyrroloquinoline and pyranocarbazole derivat ives from *O*-propargylic aldehydes and aromatic amines catalyzed by CuI.

- We have successfully achieved the formal synthesis of lavendamycin methyl ester and nitramarine alkaloid using aza Diels-Alder reaction between aza diene and alkyl vinyl ether. We have disclosed the utility of aza Diels-Alder and $A^3$ coupling (between aldehyde, amine and phenylacetylene) reactions for synthesizing variety of lavendamycin analogues with diverse substitution pattern.

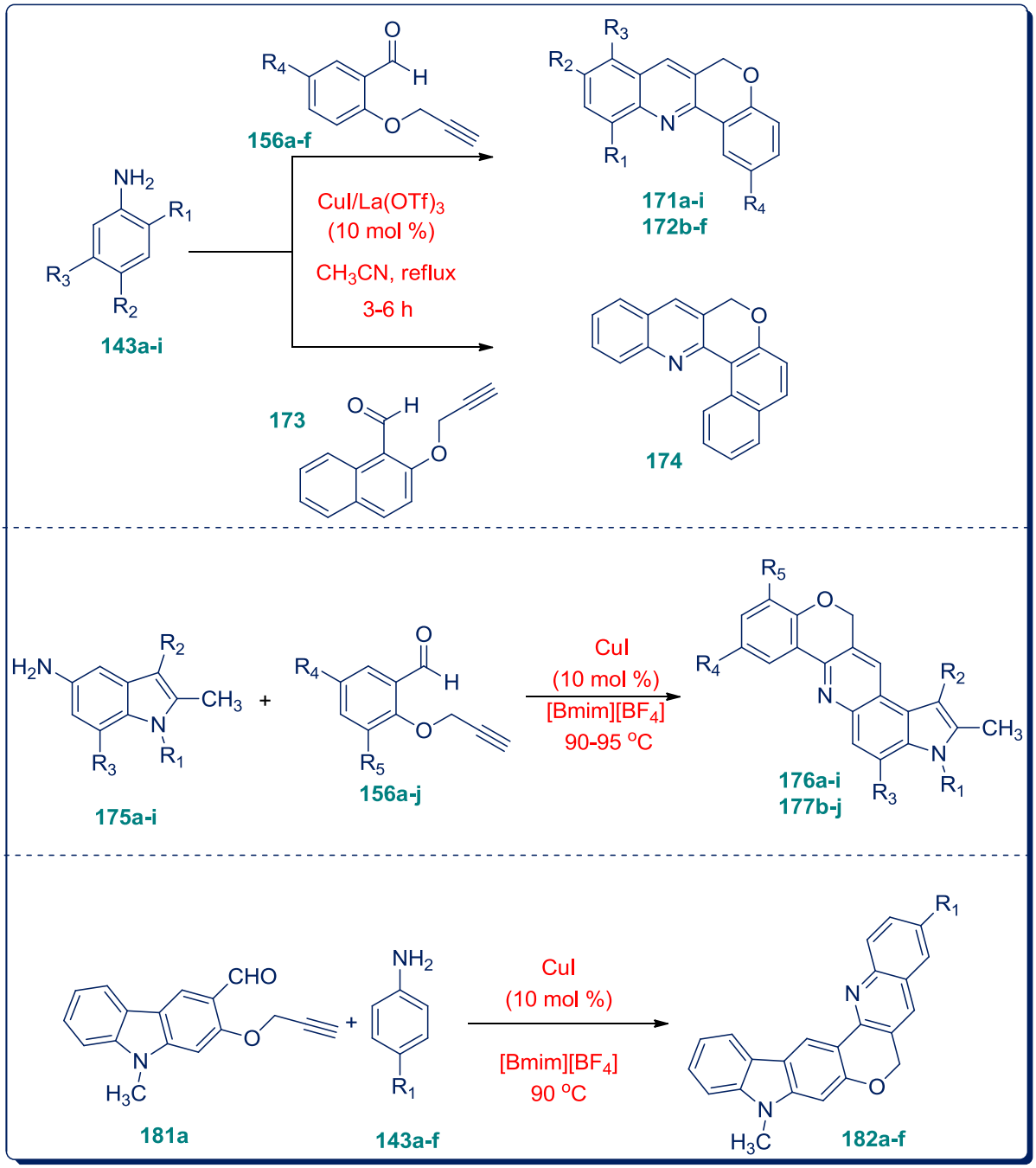
- We have demonstrated the first Lewis acid catalyzed [4+2] and [3+2] cycloaddition reactions using aldehyde, amine and phenylacetylene for the synthesis of pyrrolo[3,2-*f*]quinoline and pyrrolo[2,3-*h*]quinoline derivatives in one-pot.

- We have described a highly efficient three component (aminocarbazole, acetylene carboxylate and aldehyde/ formaldehyde) synthesis of new carbazolyl furanones and carbazolyl tetrahydropyrimidines in good yields.

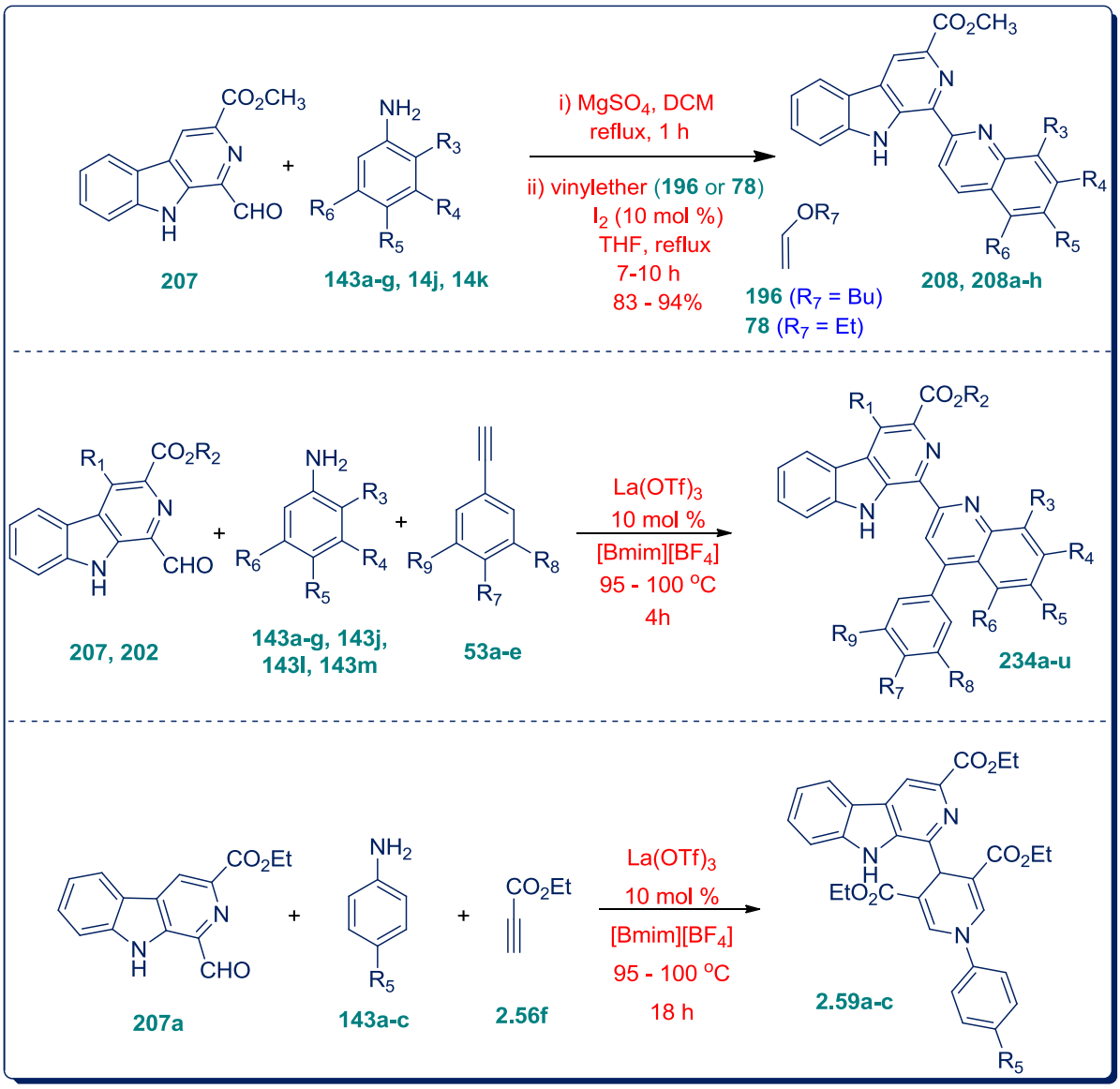
- The synthesis of benzimidazolopiperazine derivatives and annulated $\beta$-carboline derivatives explain the consequence of metal carbophilicity on *N*-propargyl group in intramolecular fashion through *6-exo-dig/7-endo-dig* cyclization.

# Graphical Abstracts

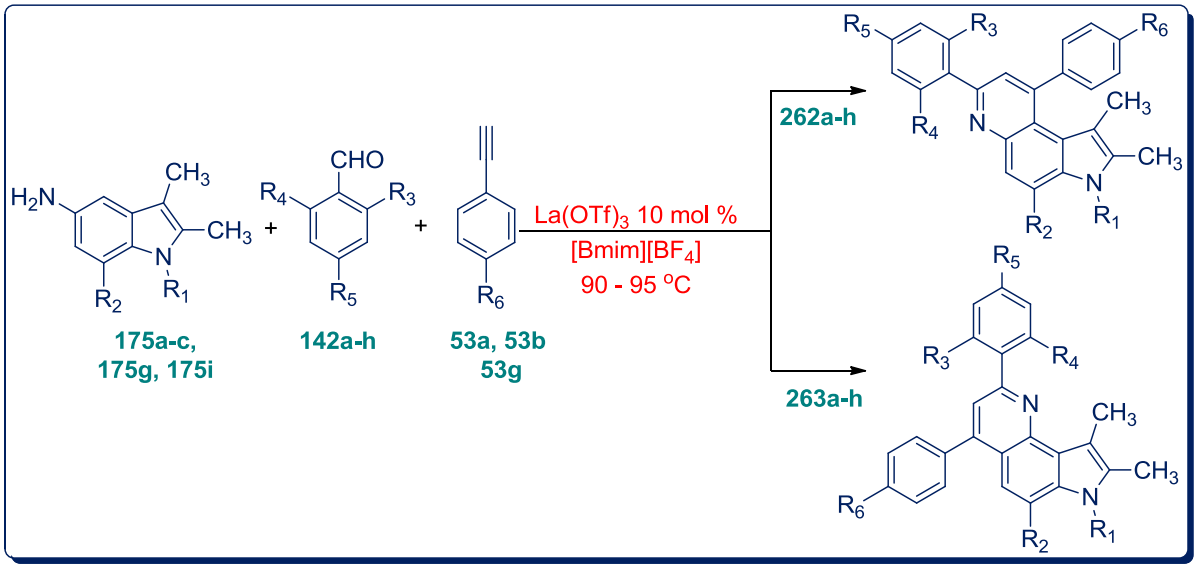
## CHAPTER 1: Synthesis of chromenoquinolines via intramolecular aza-Diels-Alder reaction



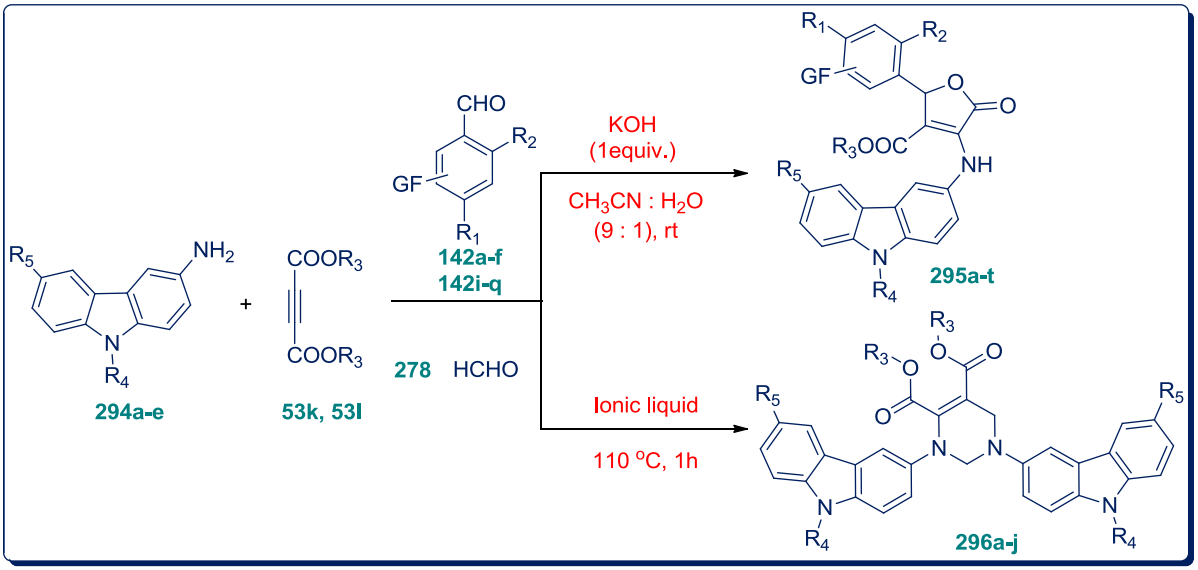
# Chapter 2: Formal synthesis of lavendamycin methyl ester, nitram arine alkaloids and their derivatives



## Chapter 3: Synthesis of pyrrolo[3,2-*f* ]- and pyrrolo[2,3-*h*]quinoline derivatives

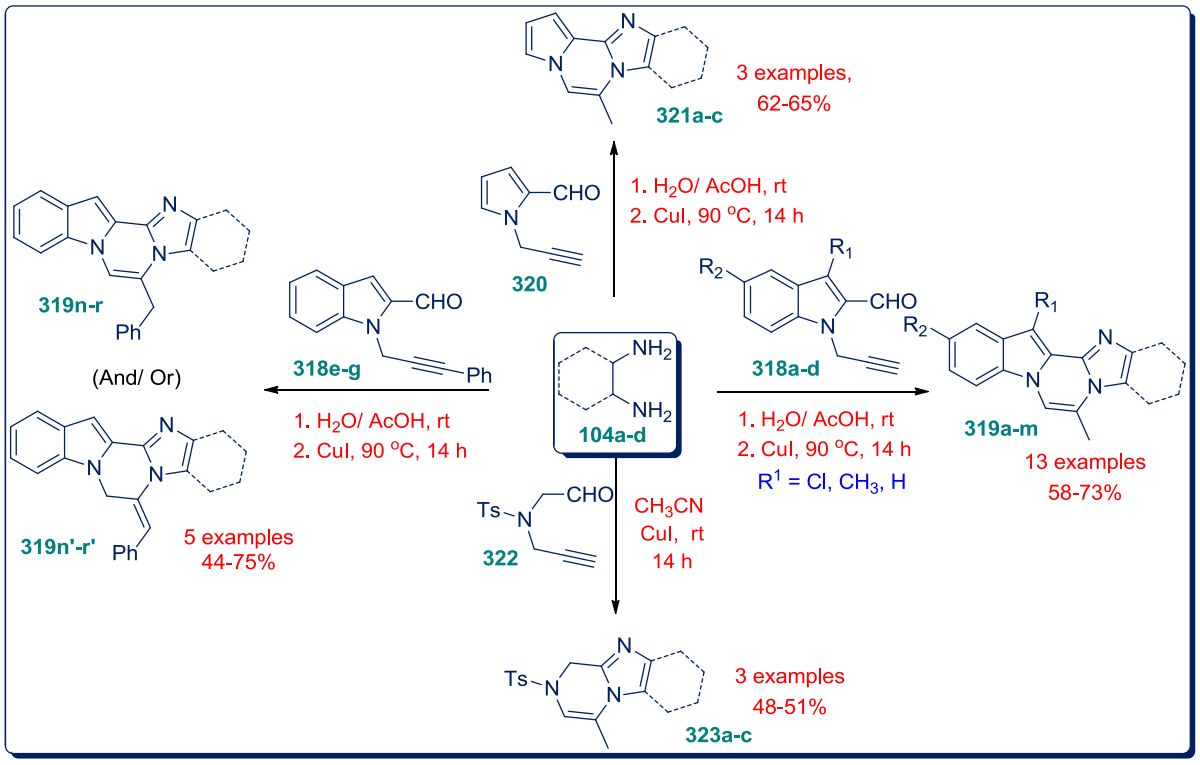



## Chapter 4: Synthesis of furano and tetrahydropyrimido carbazole derivatives



# Chapter 5: Synthesis of benzimidazolopyrazine and fused *β*-carboline derivatives using *6-exo-dig* cylcization reactions

## Part A: Synthesis of fused benzimidazolopyrazine derivatives via tandem benzimidazole formation/annulation of *δ*-alkynylaldehyde




## Part B: Cu-catalyzed electrocyclization reactions for the synthesis of fascaplysin, rutacarpine and granulatimide analogues