Metal-free Decarboxylative Method for the Synthesis of Indole Alkaloids and Synthesis of Canthinones via Knoevenagel Condensation

A Thesis
Submitted for the degree of
Doctor of Philosophy

By

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Reg. No. 17CHPH36

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July 2023

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DECLARATION

I hereby declare that the matter embodied in the thesis entitled ***"Metal-free Decarboxylative Method for the Synthesis of Indole Alkaloids and Synthesis of Canthinones via Knoevenagel Condensation"*** is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. R. Nagarajan**.

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CERTIFICATE

This is to certify that the thesis entitled ***"Metal-free Decarboxylative Method for the Synthesis of Indole Alkaloids and Synthesis of Canthinones via Knoevenagel Condensation"*** submitted by **V. Dinesh** bearing registration number **17CHPH36** in partial fulfillment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonafide work carried out by him under my supervision and guidance. This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma.

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A. Published in the following publication

1). Dinesh, V.; Nagarajan, R. *J. Org. Chem.*, **2022**, *87*, 10359–10365. (*Chapter-I (A)*)

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1). **ChemFest-2023** In House Symposium held at School of Chemistry, University of Hyderabad, Hyderabad, Telangana, India.

2). **ChemFest-2020** In House Symposium held at School of Chemistry, University of Hyderabad, Hyderabad, Telangana, India.

3). **MMT-2023** International conference on Molecules and Materials Technology held at NIT Kurukshetra, Kurukshetra, Haryana, India.

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List of Publications

- Dinesh, V.; Nagarajan, R. $(NH_4)_2S_2O_8$-Mediated Metal-Free Decarboxylative Formylation/Acylation of α-Oxo/Ketoacids and its Application to the Synthesis of Indole Alkaloids *J. Org. Chem.,* **2022**, *87*, 10359-10365
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Conference presentations

- Presented an Oral and Poster presentation on "A Metal free decarboxylative formylation of indoles and acylation of *β*-carbolines" in **ChemFest-2023** In House Symposium held at University of Hyderabad, Hyderabad, Telangana, India.
- Presented an Poster presentation on "Total synthesis of bio-active natural products: Canthinone and New canthinone alkaloid" in **ChemFest-2020** In House Symposium held at University of Hyderabad, Hyderabad, Telangana, India.
- Presented an Poster presentation on "A Metal free decarboxylative formylation of indoles and acylation of *β*-carbolines" International conference on Molecules and Materials Technology (**MMT-2023**) held at NIT Kurukshetra, Kurukshetra, Haryana, India.

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List of Abbreviations Used

Ac	Acetyl
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
br	Broad (spectral)
Bu	Butyl
t-Bu	*tert*-Butyl
BOC	*tert*-Butyloxycarbonyl
°C	Degree Celsius
Calcd	Calculated
Concd	Concentrated
C-C	Carbo-Carbon
C-X	Carbon-Heteroatom
CDC	Cross Dehydrogenative coupling
m-CPBA	meta-Chloroperbenzoic acid
δ	Chemical shift in parts per million
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d	Doublet (spectral)
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets (spectral)
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DMF	*N, N'*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DMP	Dess-Martin periodinane
Eq.	Equation

equiv	Equivalent(s)
EtOAc	Ethyl acetate
EtOH	Ethanol
EDG	Electron donating group
EWG	Electron withdrawing group
ESI	Electronspray ionization
g	Gram(s)
h	Hour(s)
Hz	Hertz
HRMS	High Resolution Mass Spectrometry
HMTA	Hexamethylenetetramine
IBX	2-Iodoxybenzoic acid
i-Pr	Isopropyl
J	Coupling constant
m	multiplet
M	Molar (solution concentration)
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
MOM	Methoxymethyl
MS	Molecular sieves
m.p	Melting point
MW	Microwave
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide

NMR	Nuclear Magnetic Resonance
N	Normal (solution concentration)
Ph	Phenyl
PG	Protecting group
ppm	Parts per million
py	Pyridine/pyridyl
PEG	Polyethylene glycol
p-TSA	para-Toluenesulfonic acid
PIDA	(Diacetoxy)iodobenzene
q	Quartet (spectral)
R_f	Retention factor
rt	Room temperature
SET	Single electron transfer
Sec	secondary
s	Singlet (spectral)
t	Triplet (spectral)
TMEDA	Tetramethylethylenediamine
TFA	Trifluoroacetic acid
tert	tertiary
TMS	Trimethylsilyl
TBAB	Tetra-n-butylammonium bromide
TBHP	*tert*-Butyl hydroperoxide
TLC	Thin layer chromatography
Ts	Tosyl
UV	Ultraviolet

SYNOPSIS

This thesis entitled as "***Metal-free decarboxylative method for the synthesis of indole alkaloids and synthesis of canthinones via Knoevenagel condensation***" consists of three chapters.

Introduction:

Indole alkaloids: Indole is a well-known privileged *N*-heterocyclic organic compound, it was a bicyclic aromatic compound contains benzene ring fused with pyrrole. Naturally available violet-blue dye named as indigo, which leads to the synthesis of indole in 1866 Adolf von Baeyer were first isolated, accomplished by zinc distillation with oxindole. Marine indole alkaloids which was produced from marine sources having much attention from both natural product chemists, and pharmacologists due to its abundance biological activities. These alkaloids shown anti-cancer, anti-microbial, anti-malarial, anti-fungal, anti-inflammatory, anti-plasmodial, anti-virus and anti-cholinesterase activities. Marine indole alkaloids (**Figure 1**) have several advantages due to its complex structures, important scaffold's these are tremendous potential leads to the drug discovery.

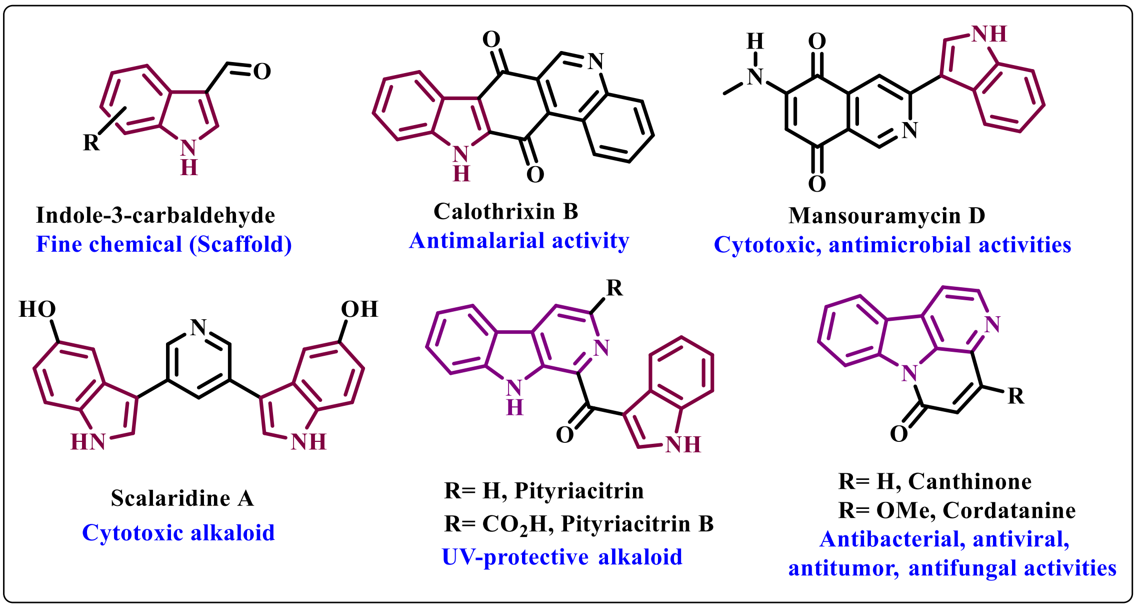


Figure 1. Representative examples of indole-based alkaloids

***β*-Carboline alkaloids:** Carbolines are most attractive and important heterocyclic natural products, with great structural diversity and promising biological activities. They are tricyclic, pyridine fused indole alkaloids. Based on the position of *N*-atom in pyridine ring classified as *α*-, *β*-, *γ*- and *δ*-carbolines. Among them *β*-carboline alkaloids (**Figure 1**) are existing natural occurrences over the large numbers including various plants, marine creatures, insects, mammals, human tissues, foodstuffs, and body fluids. The core unit of β-carboline scaffolds having in several natural products as well as pharmaceutical agents. These alkaloids exhibit various biological activities such as antitumor, antiviral, anxiolytic, hypnotic, anticonvulsant, antiparasitic, and antimicrobial, activities.

Carbon-Carbon bond forming coupling reactions: The developments for the formation of carbon-carbon bonds have long attracted attention to chemists. These Carbon-Carbon bond forming reactions are the key steps in organic synthesis towards design the carbon frame work in various organic molecules, especially in total synthesis C-C bond forming reactions are the crucial role to obtain the corresponding coupled product. Based on the coupling partners involved, cross-coupling reactions further classified as traditional cross-coupling, C-H activation, cross dehydrogenative coupling and decarboxylative cross-coupling.

Decarboxylative cross-coupling: Carboxylic acids are the versatile reactants for synthetic approach since they are readily available, non-toxic, affordable, easy to handle and typically stable at room temperature, air, and moisture. Furthermore, many of carboxylic acids may be produced entirely from natural sources, avoiding the need to use fossil fuels like oil or gas to prepare the compounds. Carboxylic acids generated from biomass exhibit a wide range of structural diversity such as amino acids, fatty acids, and sugars. Decarboxylative coupling reactions of carboxylic acids have drawn a lot of interest from chemists in recent years, and have emerged, attractive as one of the most effective methods for forming carbon-carbon (C-C) and carbon-heteroatom and (C-X; X = N, P, S) bond extrusion of CO_2.

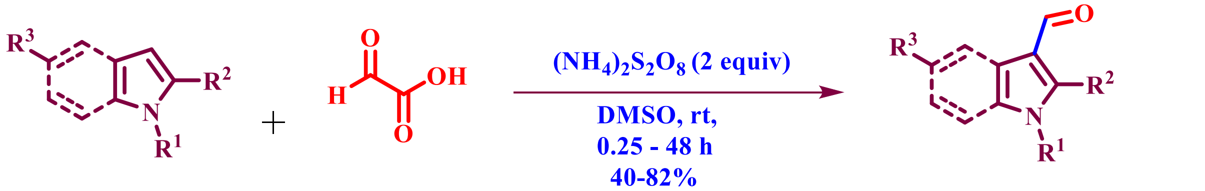
There are numerous decarboxylative coupling reactions available up to date, and the number of reactions is growing rapidly. In the modern organic synthesis decarboxylative oxidative cross-coupling have an important role, this approach is more cost-effective and environmentally favourable than other traditional ways. In this field different types of carboxylic acids involves, such as aromatic, aliphatic, unsaturated, and *oxo*carboxylic acids, can be decarboxylated to produce the corresponding alkylation, arylation, alkynylation, olefination, acylation, homocoupling, and cyclization products by reacting with different reactive partners. This thesis mainly focuses on the decarboxylative method with various reactive starting precursors.

CHAPTER-I (A)

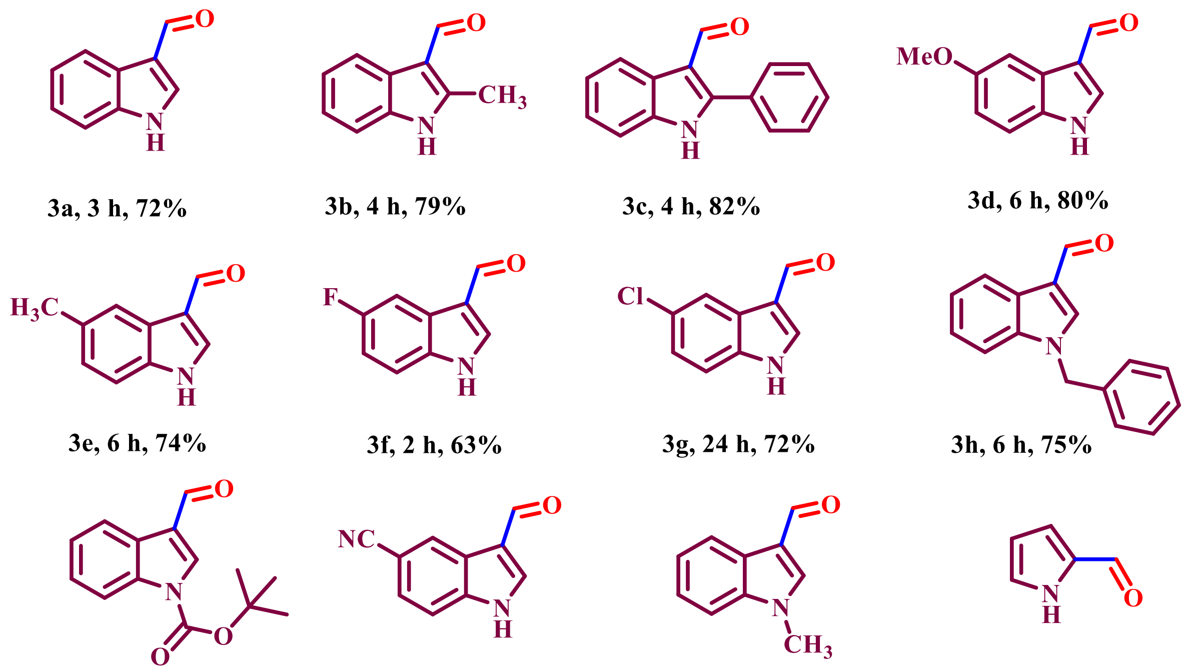
Metal-free decarboxylative formylation of indoles and acylation of *β*-carbolines: Application to the synthesis of indole alkaloids

Introduction: Formylation and acylation of *N*-heterocycles are important method for the preparation of fine chemicals and biologically important alkaloids. The conventional methods for the preparation of aromatic/hetero aromatic aldehydes were Vilsmeier-Haack, Reimer-Tiemann, Rieche, Duff and Friedel-Crafts reaction for acylation. Many of these methods suffers from several disadvantages such as corrosive, moisture sensitive, harsh reaction conditions, poor selectivity, waste bi-products and less functional group tolerance. However, several new approaches are found in the past years for the synthesis of indole-3-carbaldehde. A mild and general, operationally simple methods of 3-formylindoles are still of interest.

Scheme 1.1: Formylation of indoles with $(NH_4)_2S_2O_8$ [a]



1a-k, 1m + 2 → 3a-k, 3m



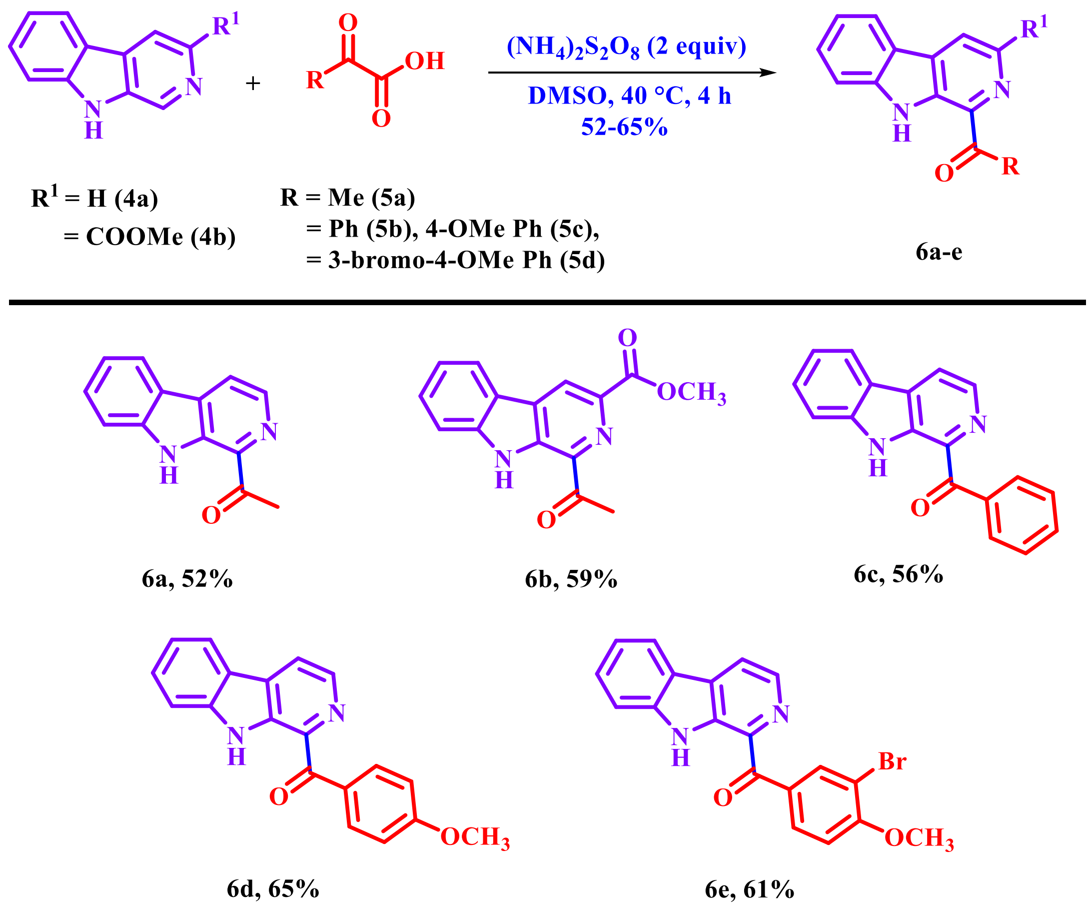
3a, 3 h, 72%; 3b, 4 h, 79%; 3c, 4 h, 82%; 3d, 6 h, 80%; 3e, 6 h, 74%; 3f, 2 h, 63%; 3g, 24 h, 72%; 3h, 6 h, 75%; 3i, 48 h, 00%; 3j, 24 h, 40%; 3k, 4 h, 76%; 3m, 0.25 h, 43%

[a] Reaction conditions: Indole and its substituents **1a-k**, pyrrole **1m** (0.85 mmol, 1.0 equiv), 50% aqueous glyoxylic acid solution **2** (1.70 mmol, 2 equiv), $(NH_4)_2S_2O_8$ (1.70 mmol, 2 equiv), DMSO (1.0 mL) at room temperature. Isolated yields after chromatography.

We have synthesized a metal-free decarboxylative formylation of indole and its substituents with *α*-oxo/keto acid 50% aqueous glyoxylic acid solution as a formyl equivalent using ammonium persulphate $(NH_4)_2S_2O_8$/ DMSO an oxidant with good yields (**Scheme 1.1**).

β-Carboline alkaloids are part of indole containing alkaloids it exhibits various biological activities and find more importance in medicinal chemistry. Though formylation of *β*-carboline leads to inseparable mixtures, acylation of *β*-carboline with pyruvic acid and phenyl glyoxylic acids under $(NH_4)_2S_2O_8$ mediated by employing decarboxylative acylation methodology to afforded 1-acyl-*β*-carbolines in moderate yields (**Scheme 1.2**). The conventional method of acylation of *β*-carboline involves a multistep sequence using protecting groups.

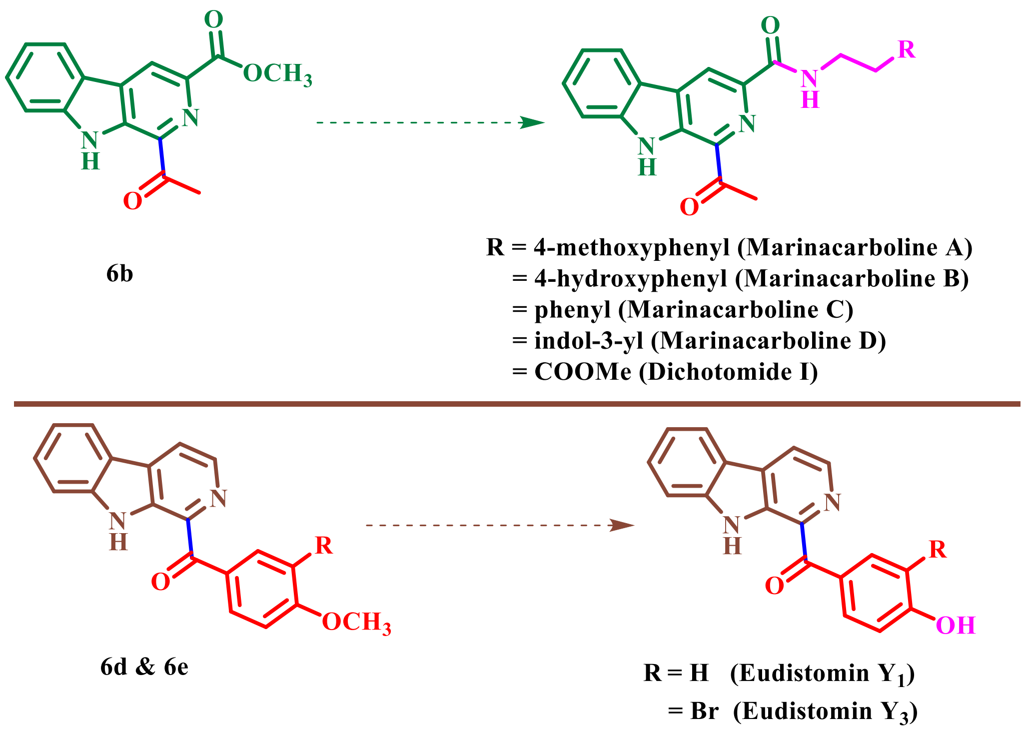
Scheme 1.2: Acylation of *β*-carbolines with $(NH_4)_2S_2O_8$ [a]



[a] Reaction conditions: β-carbolines **4a-b** (0.30 mmol, 1.0 equiv), α-ketoacids **5a-d** (1.5 equiv), $(NH_4)_2S_2O_8$ (0.59 mmol, 2 equiv), DMSO (1.5 mL), 40 °C, 4 h. Isolated yields after chromatography.

The same methodology was implemented for acylation of β-carboline and its substituents we afforded 1-acetyl β-carboline compounds **6a-e**, which are readily available for the synthesis of biologically active β-carboline alkaloids eudistomins Y_1, Y_3 and marinacarbolines A-D (**Figure 1.1**).

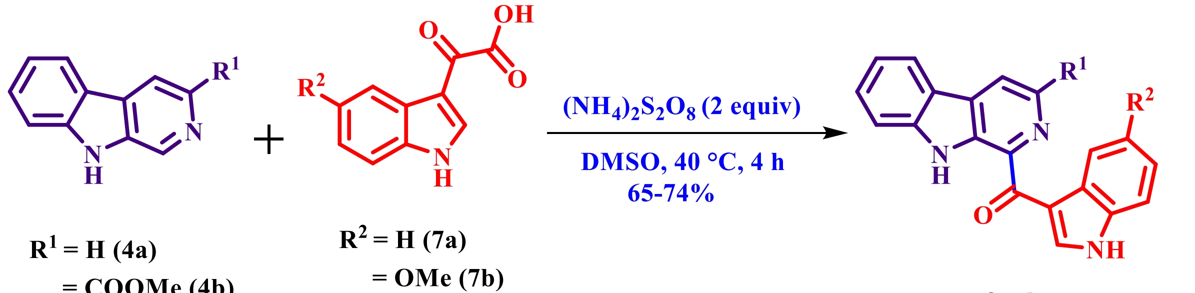
Figure 1.1 Possible alkaloids from 6b, 6d & 6e



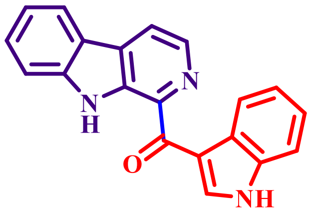
The marine β-carboline alkaloid pityriacitrin **8a** (1*H*-Indol-3-yl-9*H*-pyrido[3,4-*b*]indol-1-yl)methanone) was first isolated from marine bacterium of the genus *Paracoccus sp.,* from the human pathogenic yeast *Malassezia furfur* in 1999 and recently from the marine fungus *Dichotomomyces cejpii*.

We have extended our methodology for the total synthesis of pityriacitrin and its substituents. We accomplished a metal free decarboxylative cross coupling of β-carboline with indole-3-glyoxylicacid in 74% yield in single step without employing any protection deprotection strategy (Scheme **1.3**).

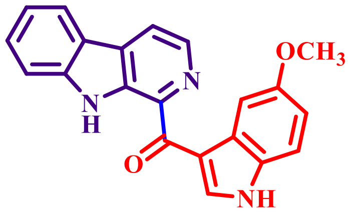
Scheme 1.3: Synthesis of *β*-carboline alkaloid Pityriacitrin with $(NH_4)_2S_2O_8$ [a]



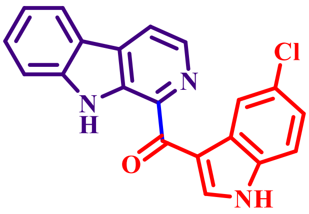
8a-d



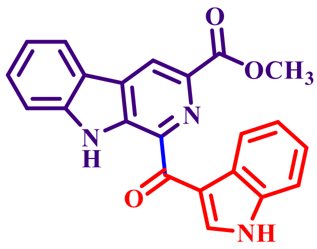
Pityriacitrin 8a, 74%



8b, 68%



8c, 65%



8d, 73%

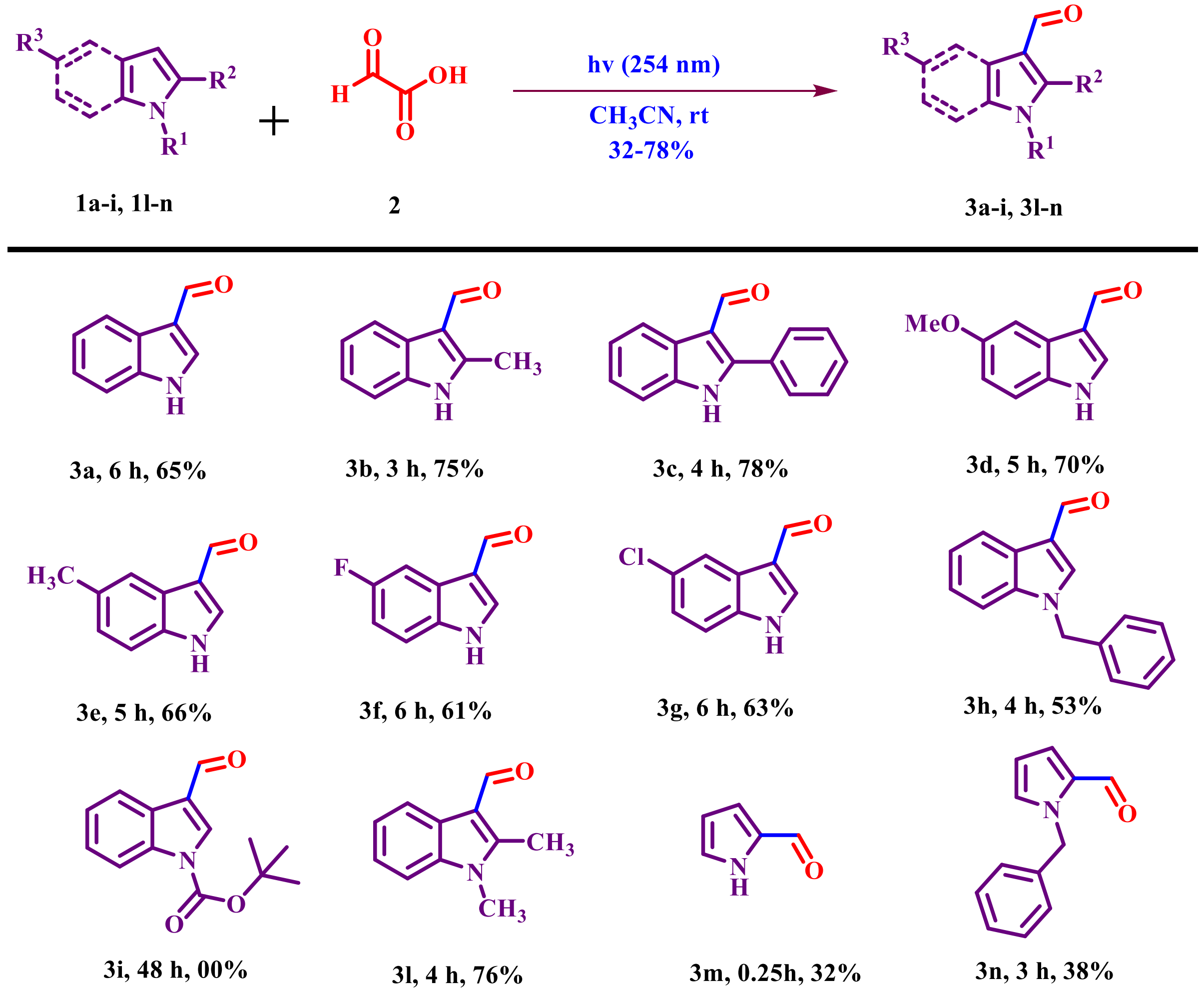
[a] Reaction conditions: *β*-carbolines **4a-b** (0.30 mmol, 1.0 equiv), indole-3-glyoxylic acid **7a-c** (1.5 equiv), $(NH_4)_2S_2O_8$ (0.59 mmol, 2 equiv), DMSO (1.5 mL), 40 °C, 4 h, Isolated yields after chromatography.

In summary, we developed a metal-free decarboxylative formylation of indoles and acylation of *β*-carbolines with $(NH_4)_2S_2O_8$/DMSO. The reactions were carried out from room temperature to 40 °C and does not require any special reaction conditions, and the products were obtained in good to moderate yields. This methodology was applied to the synthesis of biologically active natural product pityriacitrin with 74% yield in a single step and formal synthesis of eudistomins Y_1&Y_3, marinacarbolines A-D.

Photochemical decarboxylative formylation of indoles with aq. glyoxylic acid

Introduction: Aldehydes are ubiquitous organic functional group, and versatile intermediates, widely used in medicines, pesticides, chemical raw materials, and functional group interconversions. Indole-3-carboxaldehyde and its derivatives are the key structures for the preparation of biologically active molecules, and are important generic materials. Indole-3-carboxaldehyde usually synthesized by conventional methods having lack of drawbacks using non-ecofriendly reagents and harsh reaction conditions. Recently, metal-catalyzed, or photo-mediated decarboxylative coupling reactions have emerged and attracted field. Herein, we synthesized a transition-metal-free and oxidant-free photochemical decarboxylative formylation of indoles (**Scheme 1.4**) with aqueous glyoxylic acid as a formyl synthon.

Scheme 1.4. Light mediated synthesis of indole-3-carboxaldehyde



Reaction conditions: **1a-i, 1l-n** (1.0 equiv), 50% aqueous glyoxylic acid solution **2** (2 equiv), Acetonitrile (6.0 mL) using eight 8W 254 nm UV-lamps, room temperature, air.; [b] Isolated yields after chromatography.

In conclusion, we have developed a photochemical decarboxylative formylation of indoles and its substituents, pyrrole with aqueous glyoxylic acid as a formyl source. Advantages of this method include its commercially available inexpensive starting materials; no transition metals, additives, or oxidants; the ease of handling of the reagents; and good to moderate yields of the products.

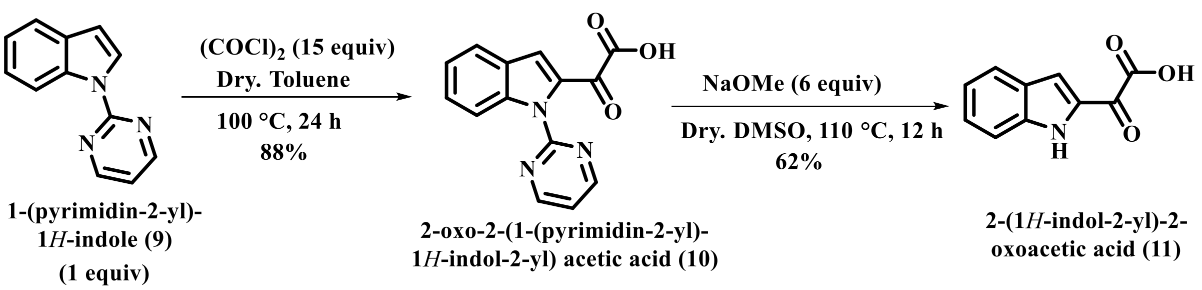
CHAPTER-II

Synthesis of isomeric Calothrixin B 7*H*-Indolo[2,3-*j*] phenanthridine-7,13(8*H*)-dione and *N*-Pyrimidyl Ellipticine quinone

Introduction: Calothrixin A and B are indolo[3,2-*j*]phenanthridine alkaloids, originally isolated from *Calothrix* cyanobacteria by Rickards *et al.* in 1999. These pentacyclic quinone based alkaloids exhibits human DNA topoisomerase I poisoning activity, and antiproliferative characteristics against many cancer cell lines are both displayed by chloroquinone-resistant variant of the malaria parasite Plasmodium falciparum.

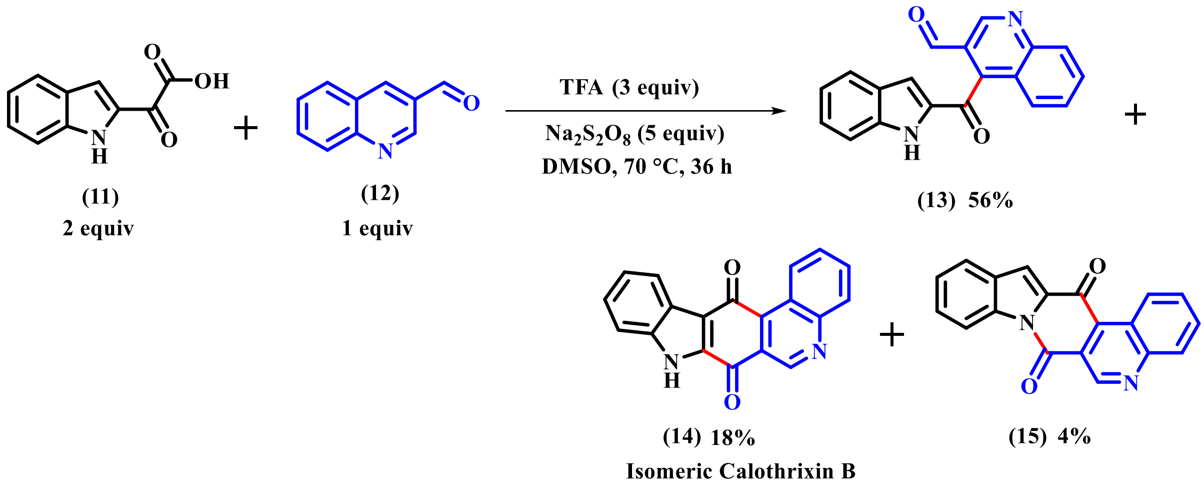
Owing to their biological properties and fascinating structural features we targeted to achieve the synthesis of calothrixins with novel methodology, although several reports available, during the synthesis of calothrixins we have identified an unprecedented indolo[2,3-*j*]phenanthridine frame work isomeric form of calothrioxin.

Scheme 2.1: Synthesis of starting precursor 2-(1*H*-indol-2-yl)-2-oxoacetic acid (11):



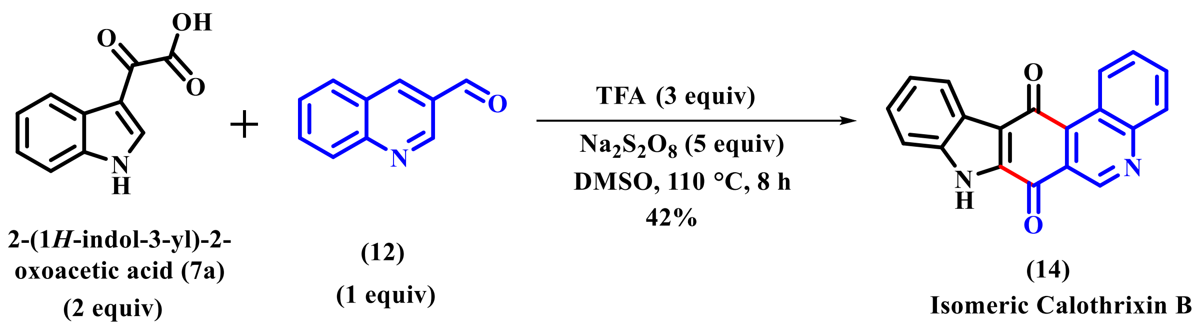
We have synthesized the starting precursor 2-(1*H*-indol-2-yl)-2-oxoacetic acid (**11**) from *N*-Pyrimidyl indole **9** treated with oxalyl chloride inducing the reflux with toluene solvent at 100 °C in 24 h to obtain the compound 2-oxo-2-(1-(pyrimidin-2-yl)-1*H*-indol-2-yl) acetic acid (**10**) further deprotection with NaOMe in Dry. DMSO at 110 °C to afford the compound indole-2-ketoacid (**11**) with good yields (**Scheme 2.1**).

Scheme 2.2: Synthesis of isomeric Calothrixin B



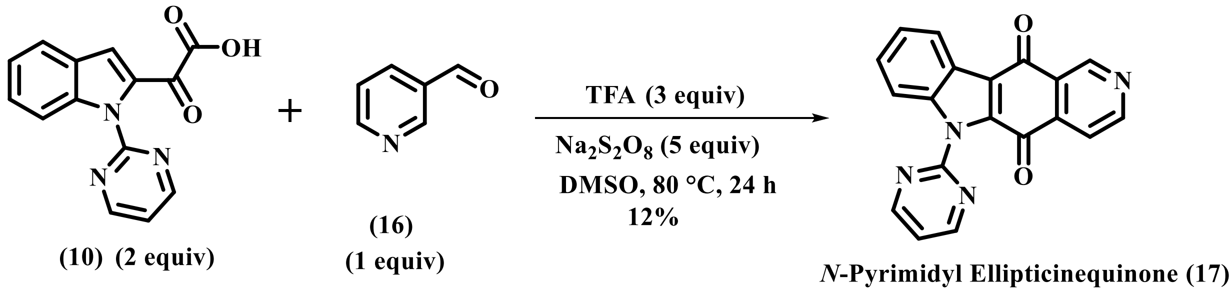
We attempted the reaction for the synthesis of calothrixin B from the prepared starting material 2-(1*H*-indol-2-yl)-2-oxoacetic acid (**11**) treated with commercially available quinoline-3-carbaldehyde (**12**) involving decarboxylative cross-coupling method in the presence of acid catalyzed, sodium persulfate as an oxidant with DMSO solvent at 70 °C in 36 hours, and exclusively observed the decarboxylative cross-coupled product, isomeric calothrixin B (**14**) in 18% and along with isomeric decarboxylated coupling products **13, 15,** 56%, 4% yields respectively (**Scheme 2.2**).

Scheme 2.3: Synthesis of isomeric Calothrixin B



Although we alter the starting material 2-(1*H*-indol-3-yl)-2-oxoacetic acid (**7a**) reacts with quinoline-3-carbaldehyde (**12**) involving decarboxylative cross-coupling strategy in the presence of acid catalyzed, sodium persulfate as an oxidant with DMSO solvent at 110 °C in 8 h reaction period we found that, exclusive product isomeric calothrixin B (**14**) with 42% yield (**Scheme 2.3**).

Scheme 2.4: Synthesis of *N*-Pyrimidyl Ellipticine quinone (17) alkaloid



We have also synthesized *N*-pyrimidyl ellipticine quinone alkaloid from the prepared compound **10** with commercially available starting material pyridine-3-carboxaldehyde (**16**) in the presence of acid-mediated sodium persulfate an oxidant with DMSO at 80 °C in 24 h undergoes metal free decarboxylative cross-coupling to afforded compound **17** with 12% yield (**Scheme 2.4**).

In summary, we have developed an efficient method for the constructing indolo[2,3-*j*] phenanthridine frame work involving transition metal-free decarboxylative cross-coupling methodology in a single step. We aimed to synthesize calothrixin B, unfortunately, we found that isomeric calothrixin B (**14**) in moderate yield. In addition, we have also synthesized *N*-Pyrimidyl ellipticine quinone (**17**) by using decarboxylative cross-coupling strategy with low yield.

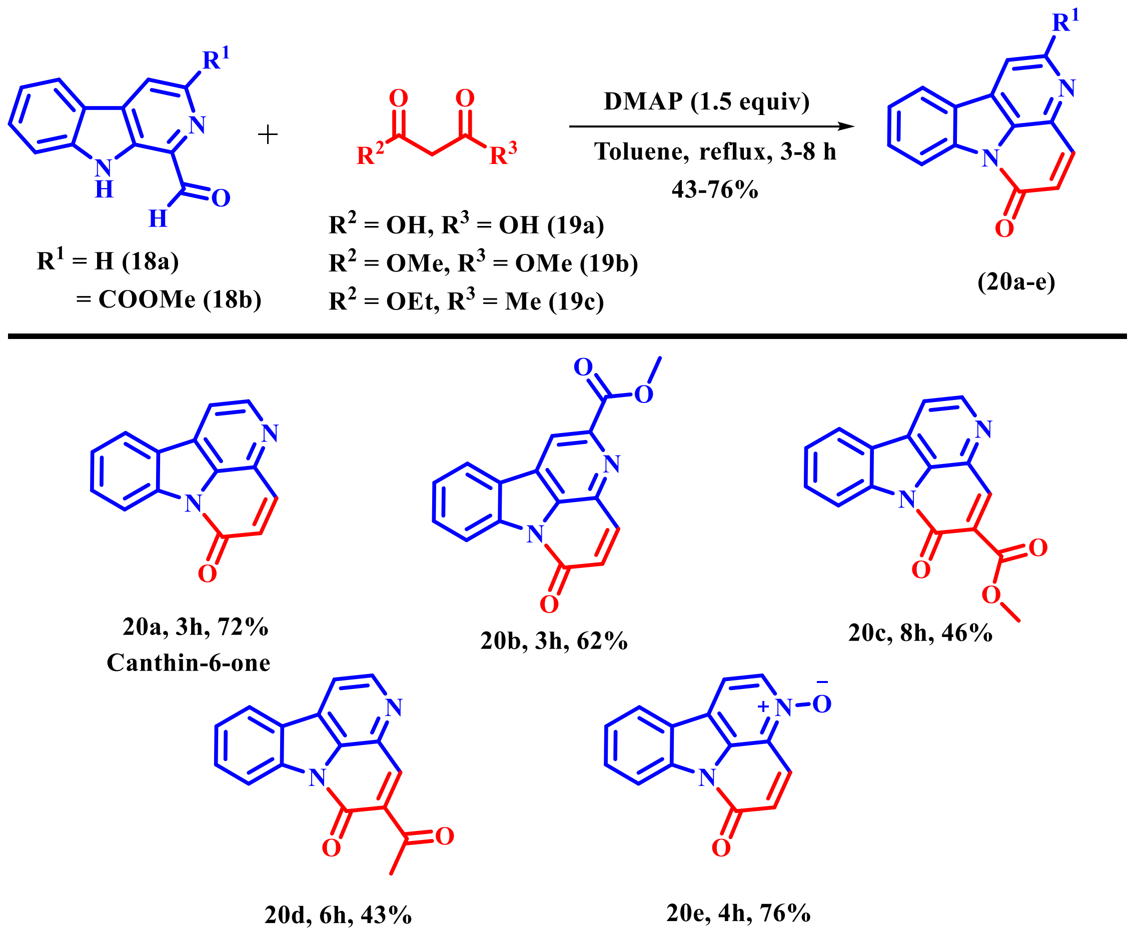
CHAPTER-III

Synthesis of bio-active natural product Canthinone and its analogues

Introduction: Canthin-6-one (6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one) was first isolated in 1952 by Haynes *et al*. from the Australian tree *Pentaceras australis*, also found from the various plants families those are *Rutaceae*, *Simaroubaceae*, *Malvaceae*, *Amaranthaceae*, *Caryophyllaceae* and *Zygophyllaceae* and recently from fungi (Boletus curtisii *Berk*), marine organisms. It is a sub class of *β*-carboline alkaloid with an additional D-ring. Canthinone and its analogues shows various biological activities such as antitumor, antiviral, antibacterial, antifungal, antiproliferative, anti-inflammatory, aphrodisiac, and antiparasitic agents, also uses in DNA screening, cancer chemoprevention, and so on.

The starting precursors *β*-carboline-1-carboxaldehydes (**18a-b**) are prepared as per the literature procedure. The reaction of *β*-carboline-1-carboxaldehyde (**18a**) and malonic acid (**19a**) with DMAP under refluxing with toluene undergoes condensation followed by cyclization to canthi-6-one **20a** with 72% yield in single step. This methodology was applied with the commercially available starting materials **19a-c** and afforded the the products (**20a-e**) with moderate yields (**Scheme 3.1**).

Scheme 3.1: Synthesis of Canthin-6-one and its analogues



[a] Reaction conditions: *β*-carbolines-1-carboxaldehydes **18a-b** (0.30 mmol, 1.0 equiv), **19a-c** (1.2 equiv), DMAP (0.764 mmol, 1.5 equiv), toluene, reflux, 3-8 h, Isolated yields after chromatography.

In conclusion, we have synthesized biologically active *β*-carboline alkaloid canthinone and its derivatives starting from kumujian C **18a-b** treatment with commercially available starting precursors **19a-c** under the base mediated involving condensation followed by cyclization to afforded in a single step with good to moderate yields.

INTRODUCTION

General background

The science of organic chemistry having a broad and diversity, in the past many scientists or investigators from different countries making the discoveries and developments that combined over the 200 years led to the field organic chemistry. Organic compounds were isolated from nature with the pure form in 16th century. Scientists are believed that organic compounds were obtained from natural resources with the special "vital force" theory; said that impossible to prepare the organic materials from laboratory.[1] Fortunately, in 1828 a German chemist Friedrich Wöhler were discovered urea, and invalidate the vital force theorem by synthesized from ammonium cyanate heating in the laboratory. His discovery proven that, organic compounds can be synthesize from laboratory, with this achievement the pathway for many scientists to synthesize the various organic compounds.[2]

In general, organic compounds was classified as acyclic/open chain and cyclic compounds based on structure and its properties. Both the cyclic and acyclic compounds further subdivided in each two categories. A class of cyclic compounds with heteroatom is called heterocyclic compounds.

Heterocycles

Heterocycles are classified under cyclic containing organic compounds which contains minimal single hetero atom present in entire cyclic system. In general, the heterocycle contains non-metallic elements like oxygen, nitrogen, and sulfur, etc. Heterocyclic compounds generally classified as alicyclic (saturated) and aromatic (unsaturated) systems based on their electronic structures. Heterocycles available in various ring sizes from three membered to nine membered.[3]

The alicyclic heterocyclic compounds contain at least one heteroatom with cyclic saturated compounds such as tetrahydrofuran, piperidine, dioxane, etc. Furthermore, unsaturated heterocyclic compounds include pyridine, pyrrole, furan, thiophene and benzo fused heterocycles such as indole, quinoline, isoquinoline and benzothiophene, etc. Many of the heterocycles have broad range of applications in various fields: pharmaceuticals, agro, food, dye chemistry, polymer, material, and medicinal chemistry.[3c]

Natural products

Natural products are a chemical substance produced by living organism exist in nature. It contains high structural diversity, complex chemical structures and outstanding biological or pharmaceutical properties.[4] Natural products are any organic materials was synthesized by living organisms induces primary and secondary metabolites. Primary metabolites have intrinsic functions, absolutely required for surviving these are generally produced from the essential organic molecules includes the building blocks amino acids, carbohydrates, proteins, vitamins, nucleic acids, lactic acid etc., on the other hand secondary metabolites have extrinsic functions, not essential for survival theses are belongs **alkaloids**, flavonoids, terpenoids, steroids, essential oils, etc. To fulfil the human being medicinal requirements, synthesizing natural products in the laboratory using semi synthesis or total synthesis were playing a crucial role in the field of synthetic organic chemistry. Furthermore, natural products on its efficient bioactive compounds from natural resources are highly inspired much attention for the developments of drug discovery in pharmaceutical industries (Figure **1**).[5]

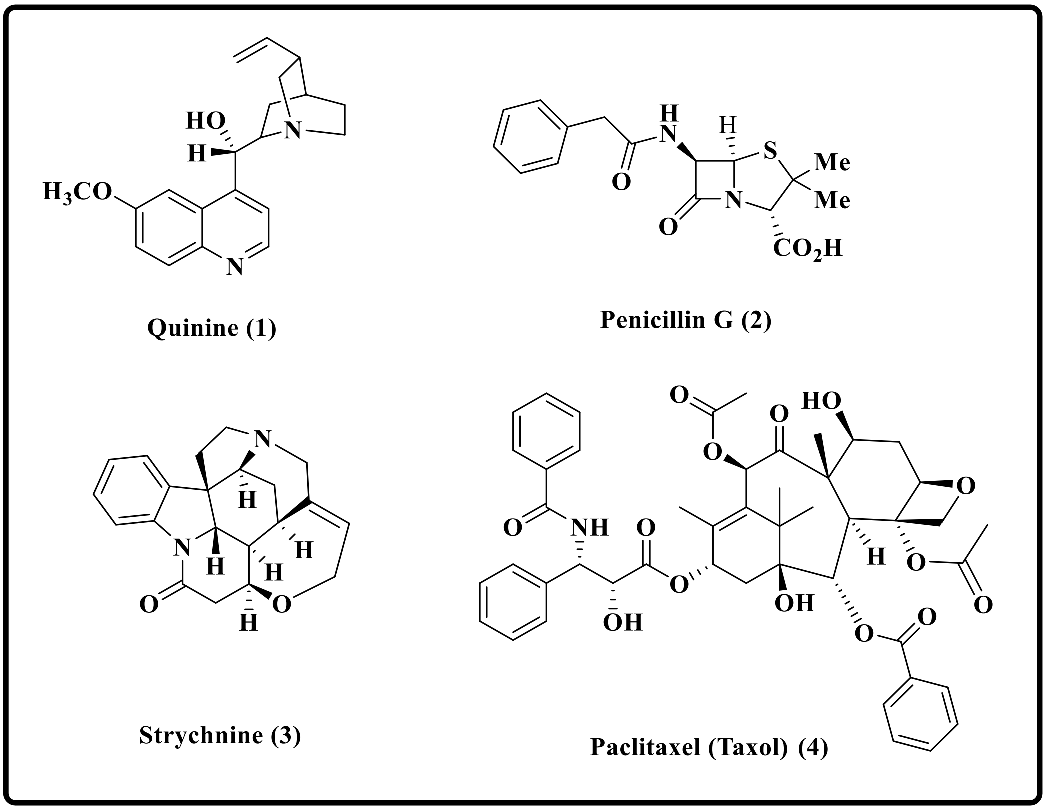


Figure 1. Few of milestone natural products

Alkaloids

The chemistry of alkaloids is one of the most important topic in organic and bioorganic field. The term "alkaloid" was first introduced in 1819 by Friedrich W. Meissner and naturally occurring organic compound it contains at least one nitrogen atom. Alkaloids are the best example of secondary metabolites, it produced by variety of organisms such as higher plants, fungi, bacteria, algae, plants and animals and other living organisms. Alkaloids are basic in nature, bitter in taste and it shows various biological activities. Based on biochemical precursors (tyrosine, tryptophan, lysine, etc.) or carbon skeleton of the molecule (indole, quinoline, isoquinoline, etc.) alkaloids are classified[6] as,

1). True alkaloids: It contains *N*-heterocycles, originally from amino acids. Ex: morphine, atropine, and nicotine

2). Pseudo alkaloids: These alkaloids are not coming from the amino acids, but likely to the alkaloids. Ex: steroid-like, terpene-like, and purine-like alkaloids

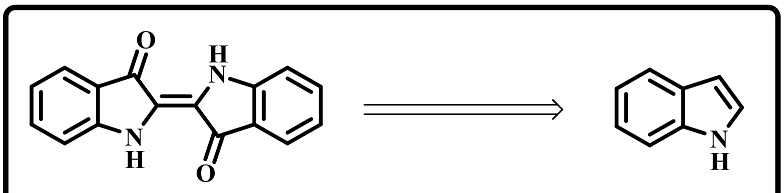
3). Proto alkaloids: It possess the nitrogen atom, which is not involving in heterocyclic system and originated from amino acids. Ex: adrenaline, mescaline, and ephedrine's.

4). Polyamines: Ex: spermidine, putrescine, and spermines

5). Cyclopeptide and Peptide alkaloids

Indole Alkaloids

Indole (**6**) is a well-known privileged *N*-heterocyclic organic compound and having widespread biological activities. It was a bicyclic aromatic compound, contain benzene ring fused with pyrrole. The extensive research growing on the mid of 19th century due to naturally available violet-blue dye named as indigo, which leads to the synthesis of indole in 1866 Adolf von Baeyer were first isolated, accomplished by zinc distillation with oxindole.[7]



Indigo dye (5) Indole (6)

Indole nucleus is planar molecule it consists 10π electrons around the nucleus, it is aromatic compound obeys Huckel [4n+2] rule. The indole C-3 position having highest electron density and more reactive towards electrophilic substitution reactions.

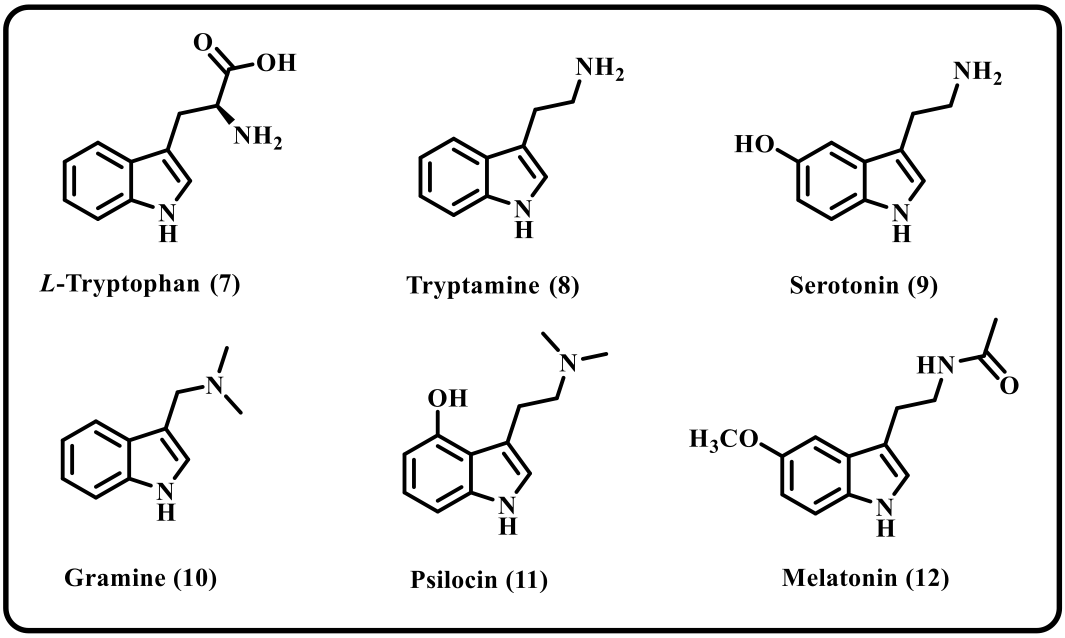


Figure 2. Examples of natural indole alkaloids

The indole scaffolds are pharmacologically active naturally existing alkaloids such as *L*-Tryptophan **7** is an essential amino acid, Serotonin **9** is a monoamine neurotransmitter and Gramine **10** acts as the agonist of the adiponectin receptor 1, Psilocin **11** acts as 5-HT_{1A} and 5-HT_{2A} and 5-HT_{2C} agonist receptors and Melatonin **12** as the important role in regulation of sleep-wake up process (Figure **2**).[8]

Indole and its derivatives having tremendous applications in various fields, there are several named reactions associated with the synthesis of indole alkaloids.[9]

Marine Indole Alkaloids

Marine indole alkaloids have shown much attention from both natural product chemists, and pharmacologists due to its abundance biological activities. Marine indole alkaloids have several advantages due to its complex structures, important scaffold's these are beneficial for the drug discovery, usually it possesses higher molecular weight and large number of carbons with heteroatoms. Isolated from marine environment under the high pressure, lower the temperature with various marine micro and macro-organisms includes bacteria, fungi, sponges, algae, bryozoans, and mangrove plants, etc.

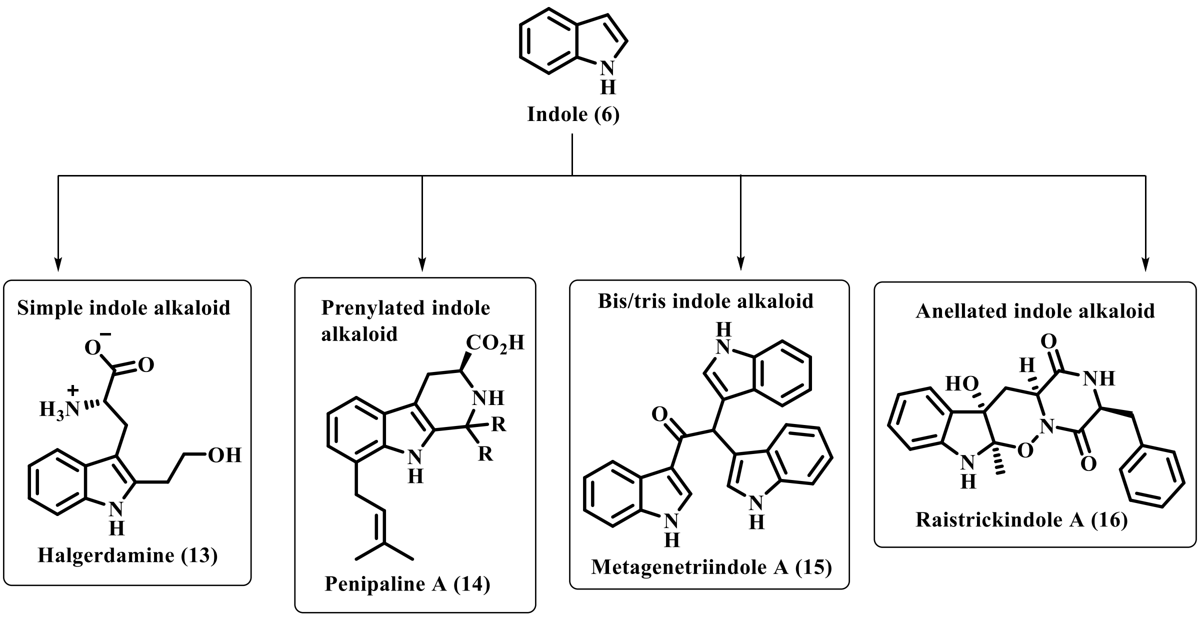


Figure 3. Classifications of indole alkaloids

These alkaloids show anti-malarial, anti-microbial, anti-fungal, anti-inflammatory, anti-plasmodial, anti-virus, anti-cholinesterase, and anti-cancer activities.[10a] Generally marine indole alkaloids can be classified in to four groups, those are simple, prenylated, anellated and bis/tris indole alkaloids (Figure **3**).[10b]

Simple indole alkaloids

Tryptophan or its precursors are the primary source of the simple indole alkaloids. In 2003 Kim and co-workers were isolated N_b-acetyl tryptamine (**17**) from alga *Gracilaria verrucosa's* surface.[11] Kondracki *et al.* was extracted indole alkaloids including 5-hydroxy indole-3-carboxaldehyde (**18**), methyl-5-hydroxy-indole-3-carboxylate (**19**), 3-formylindole (**20**), and 5-deoxyhyrtiosine A (**21**) from marine sponge *Hyrtios erectus* in 2006 (Figure **4**).[12]

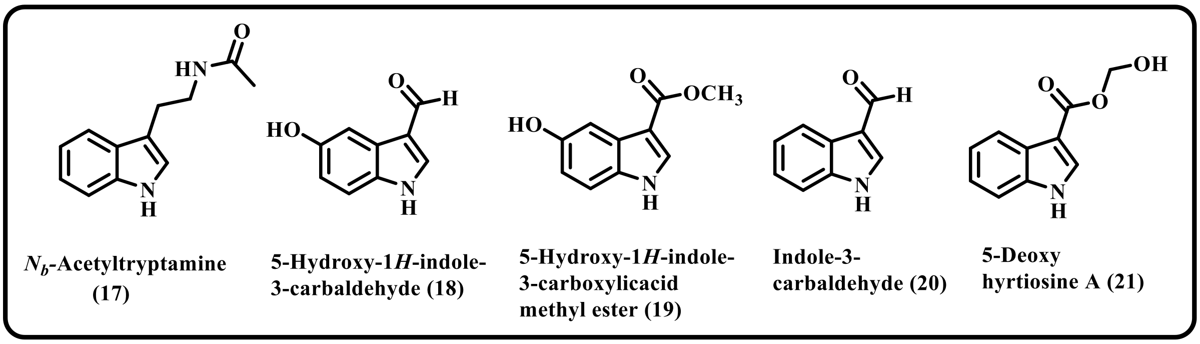
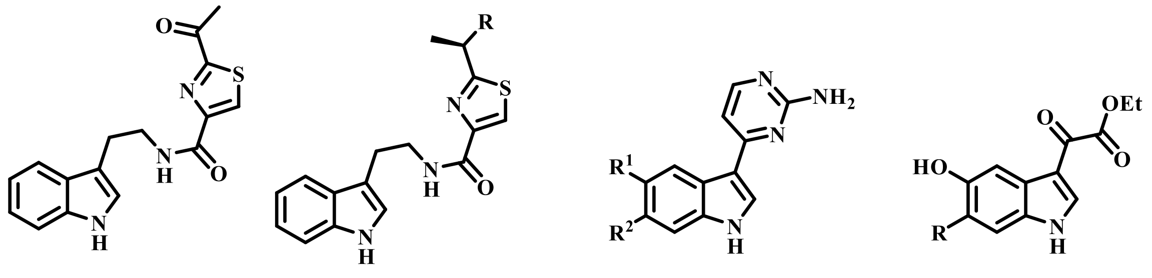


Figure 4. Examples of simple marine indole alkaloids

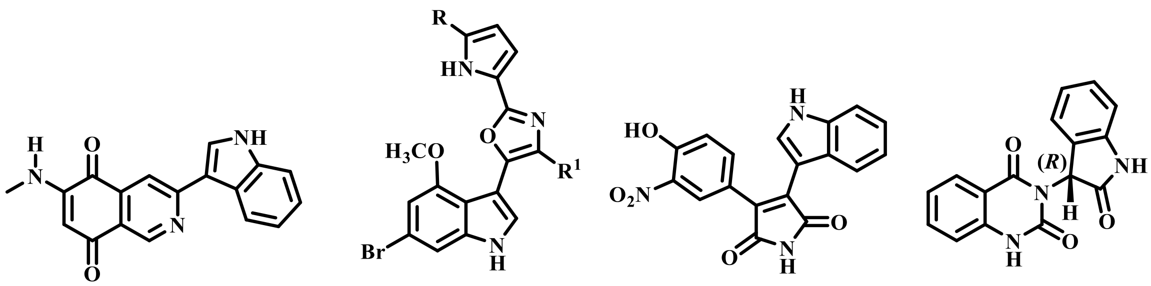
Bacillamide A (**22**) obtained[13a] by Murakami *et al.* in marine bacterium *Bacillus sp.* in 2003, it shows the algicidal activity. Simultaneously in the year of 2007 Rowley and co-workers[13b] found Bacillamide A-C (**22-24**) in *Bacillus endophyticus Species* (Figure **5**).



Bacillamide A (22) **R= OH, Bacillamide B (23)** **R= NHAc, Bacillamide C (24)** **R^1= R^2= Br, Meridianin F (25)** **R^1= R^2= H, Meridianin G (26)** **R= Br, (27)** **R= H, (28)**

Figure 5. Examples of simple marine indole alkaloids

In 2007 Palermo *et al.* were extracted[14] Meridianins F-G (**25-26**) from tunicate *Aplidiummeridianum*. Ethyl-2-(6-bromo-5-hydroxy-1*H*-indol-3-yl)-2-oxoacetate (**27**) isolated[15a] by Santalova *et al.* from the sea squirts *Syncarpa Oviformis* in 2008. Ethyl-2-(5-hydroxy-1*H*-indol-3-yl)-2-oxoacetate (**28**) isolated by Yamazaki and co-workers[15b] from marine sponge *Ircinia* species in 2015 (Figure **5**).

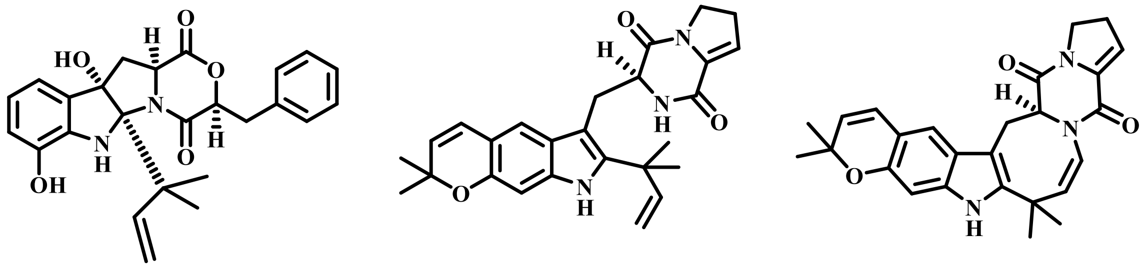


Mansouramycin D (29) **R= H, R^1= I, Breitfussin A (30)** **R= Br, R^1= H, Breitfussin B (31)** **Aqabamycin G (32)** **Shewanelline C (33)**

Figure 6. Representative simple marine indole alkaloids

Laatsch and co-workers[16] isolated mansouramycin D (**29**) from marine *streotomyces sp.* in 2009, it is a cytotoxic alkaloid contains indole and isoquinoline rings. Breitfussin A-B (**30-31**) isolated[17] from hydrozoan *Thuiria breitfussi* by Marcel Jaspars in 2012. Indole containing alkaloid Aqabamycin G (**32**) was extracted[18] of *Sinularia polydactyla* by W. A. Zereini *et al.* and Yao *et al.* in the year of 2010. Wang *et al.* were obtained[19] cytotoxic alkaloid Shewanelline C (**33**) from *Shewanella piezotolerans* in 2014 (Figure **6**).

Prenylated indole alkaloids



Shornephine A (34) Carneamide A (35) Carneamide B (36)

Figure 7. Examples of prenylated marine indole alkaloids

Prenylated indole alkaloids have large number of subgroups, it shows numerous biological activities. Shornephine A (**34**) was extracted[20] from marine derived *Aspergillus* sp. Carneamide A-B (**35-36**) are diketopiperazine alkaloids produced[21] from the marine fungus *Aspergillus carneus (Figure 7).*

Bis-and Tris-indole alkaloids

These alkaloids are derived from biosynthetic pathway that contains two or more indole fragments and it exhibits wide range of biological properties. Lee *et.al* was isolated[22] Scalaridine A (**37**) from sponge *Scalarispongia sp.* in 2013. In the year 2007 Kobayashi and co-workers[23] isolated bis-indole marine alkaloid Hyrtinadine A (**38**) from *Hyrtios species.* Gu *et al.*[24] was derived Arsindoline A (**39**) from marine bacterium *Aeromonas sp.* Deoxytopsentin (**40**) and Metagenetriindole (**15**) are cytotoxic bis- and tris-indole alkaloids obtained from Escherichia coli fermentation process by Qui and co-workers[25] in 2014. Pseudellone C (**41**) was isolated[26] by Lan and co-workers from *Pseudallescheria ellipsoidea* fungus in the year 2015. Liu *et al.* was isolated[27] Racemosin B (**42**) from *Caulerpa racemosa* in the year 2013 (Figure **8**).

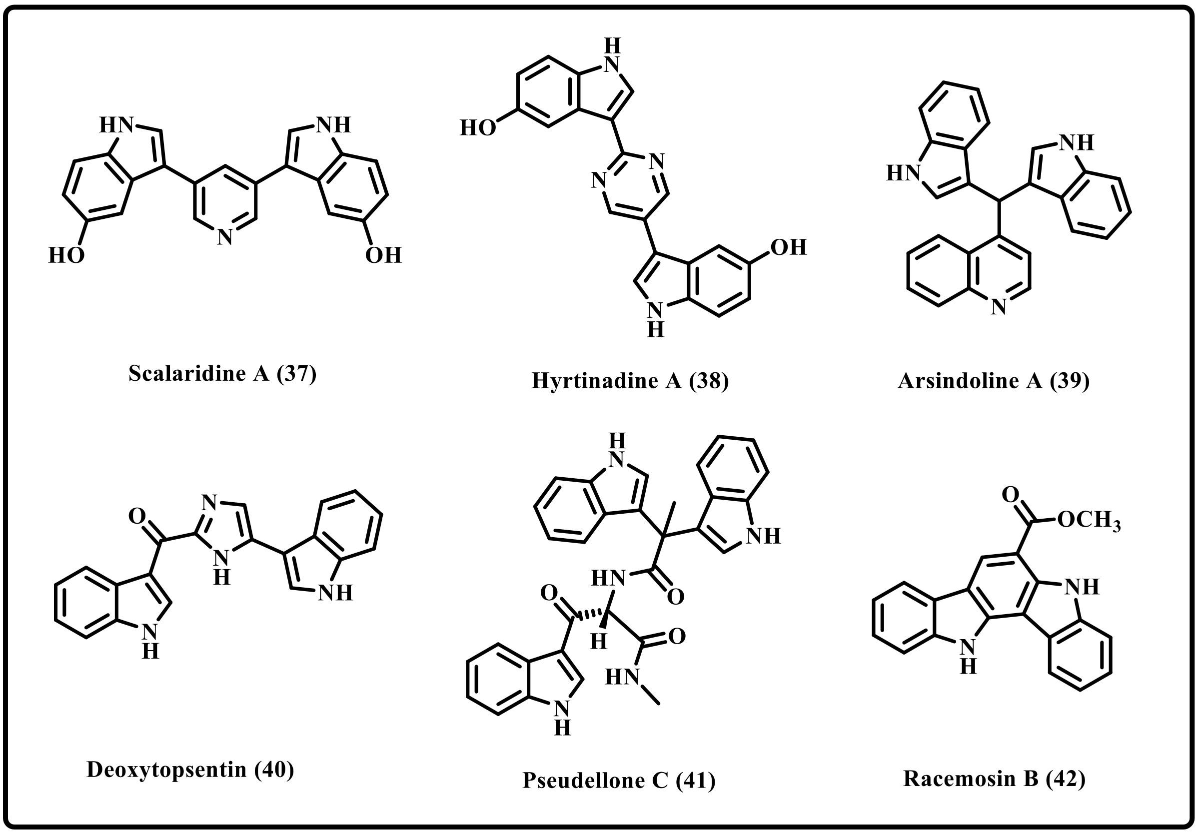


Figure 8. Examples of Bis and tris indole alkaloids

Anellated indole alkaloids

These types of alkaloids having atleast one indole ring annulated with other rings. Steglich and co-workers[28] isolated Pityriazole (**43**) marine indole alkaloid from yeast Malassezia furfur in the year 2005. In 2012 Br-related alkaloids **44** and **45** were isolated[29] by Stonick *et al.* from the sea sponge *Penares sp.* It shows moderate cytotoxic activities (Figure **9**).

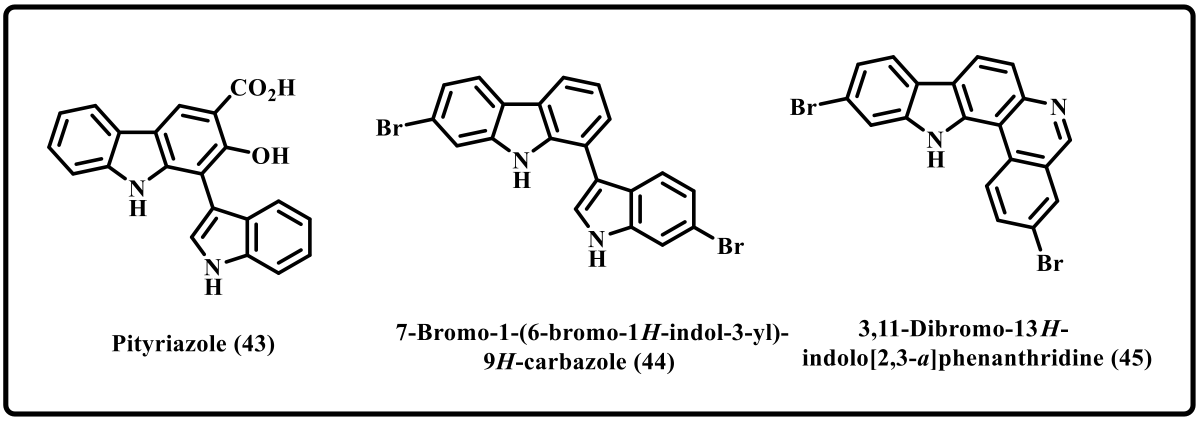
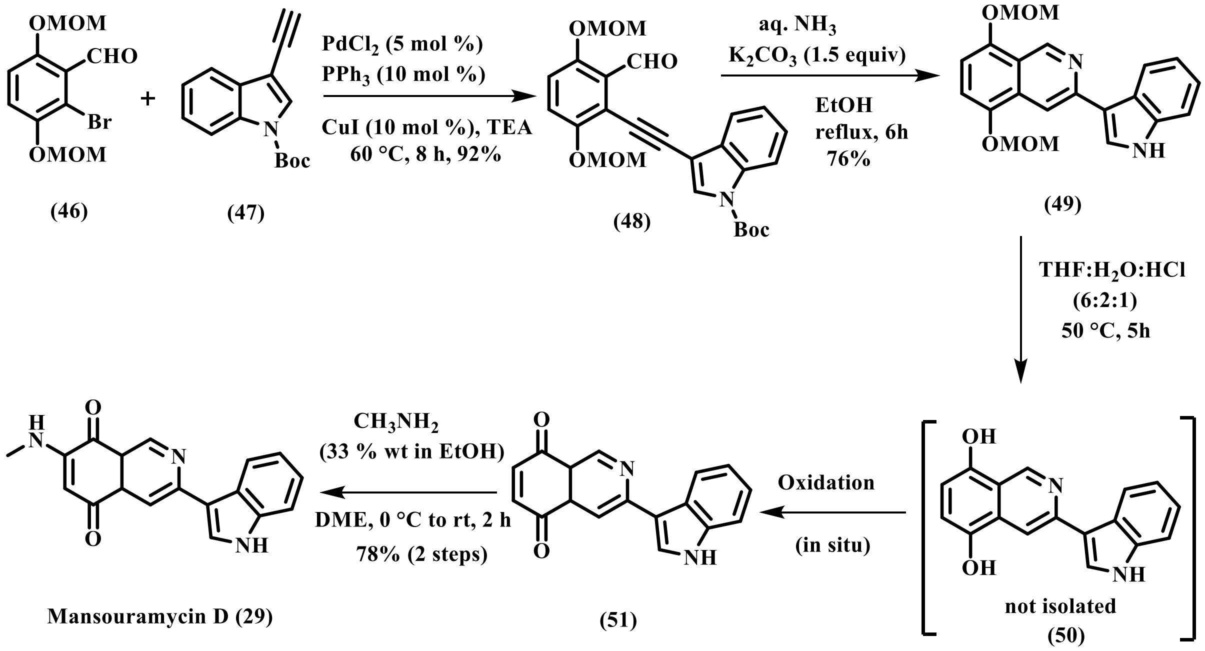


Figure 9. Examples of Anellated indole alkaloids

Selective synthesis of indole containing alkaloid

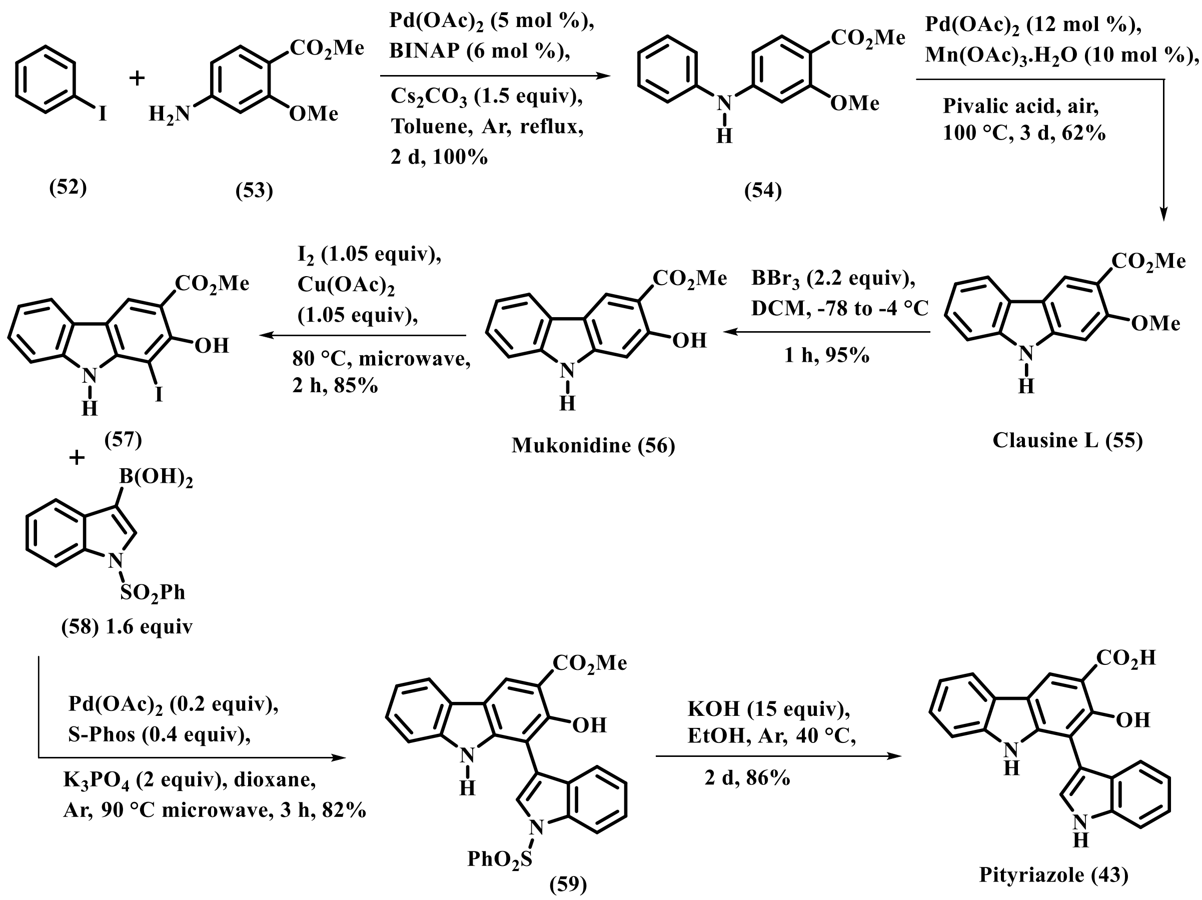
Eq. 1: Synthesis of Mansouramycin D



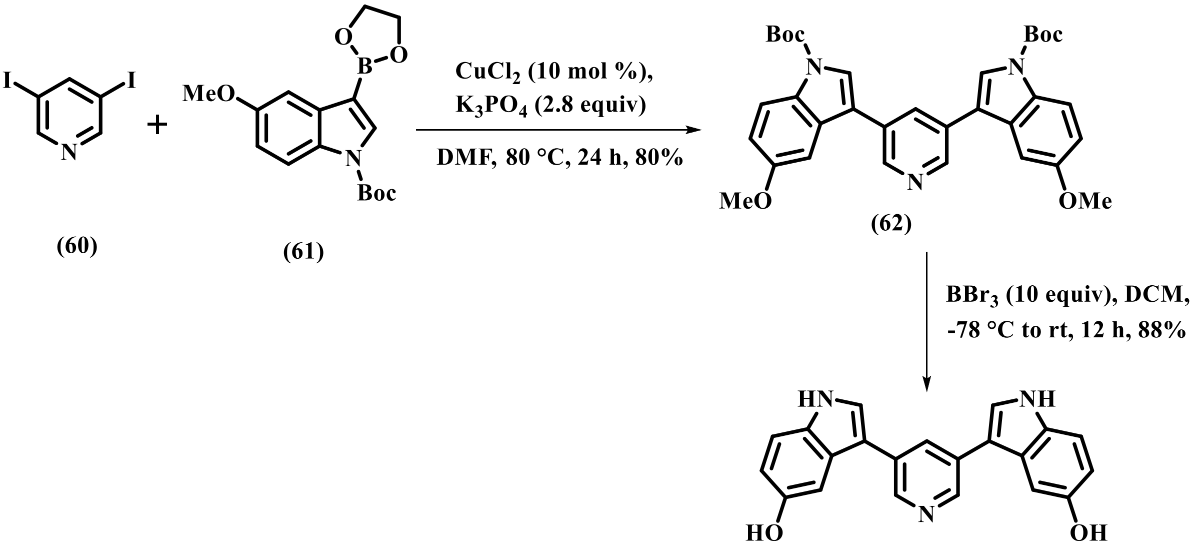
In 2013 Prakash *et al.* were described[30] first total synthesis Mansouramycin D (**29**). It is an cytotoxic alkaloid, which is involving Sonogashira coupling subsequently iminoannulation, oxidation then aminomethylation with the overall 54.5-60.9 % yield (**Eq. 1**).

Eq. 2: Synthesis of Pityriazole

Forke *et al.* was synthesized[31] first total synthesis of Pityriazole (**43**) via Pd-catalyzed construction of carbazole frame work involving Buchwald-Hartwig amination, subsequently Pd-catalyzed C-H activation to obtained Clausine L (**55**) compound further undergoes demethylation and halogenation to gave compound **57**. Then, compound **57** undergoes Suzuki-Miyaura coupling with compound **58** to afforded *N*-sulfonyl indol-3-yl carbazole skeleton **59**, further deprotection to provide the targeted compound Pityriazole (**43**) with overall 35% yield in 6-steps in 2008 (**Eq. 2**).



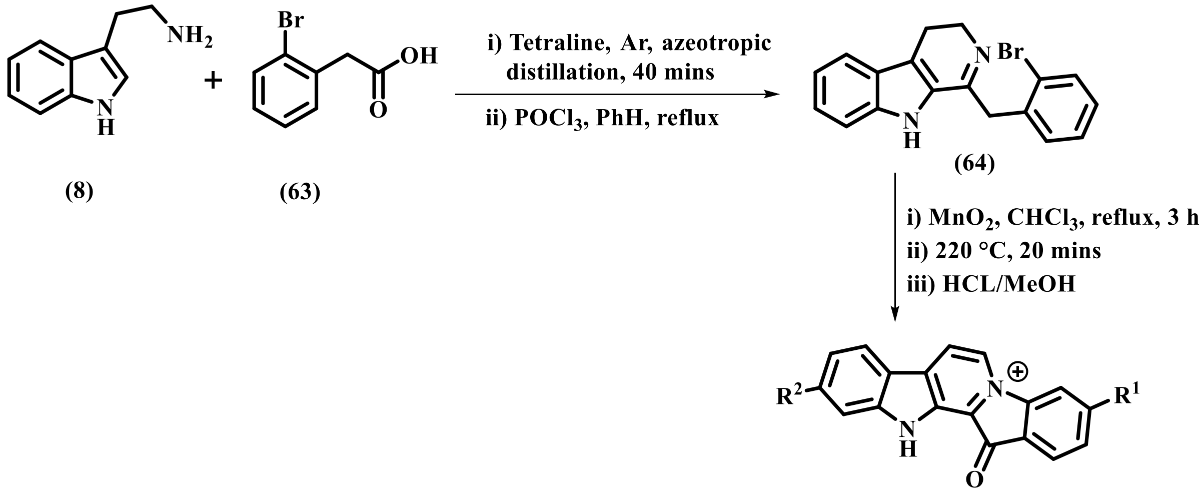
Eq. 3: Synthesis of Scalaridine A



Scalaridine A (37)

Ranjani *et al.* was synthesized bis-indole alkaloid Scalaridine A (**37**) from $CuCl_2$ in-situ generated nano-Cu_2O without using external ligands involving Suzuki-Miyaura coupling product and demethylation to obtained with 60% overall yield in the year 2017 (**Eq. 3**).[32]

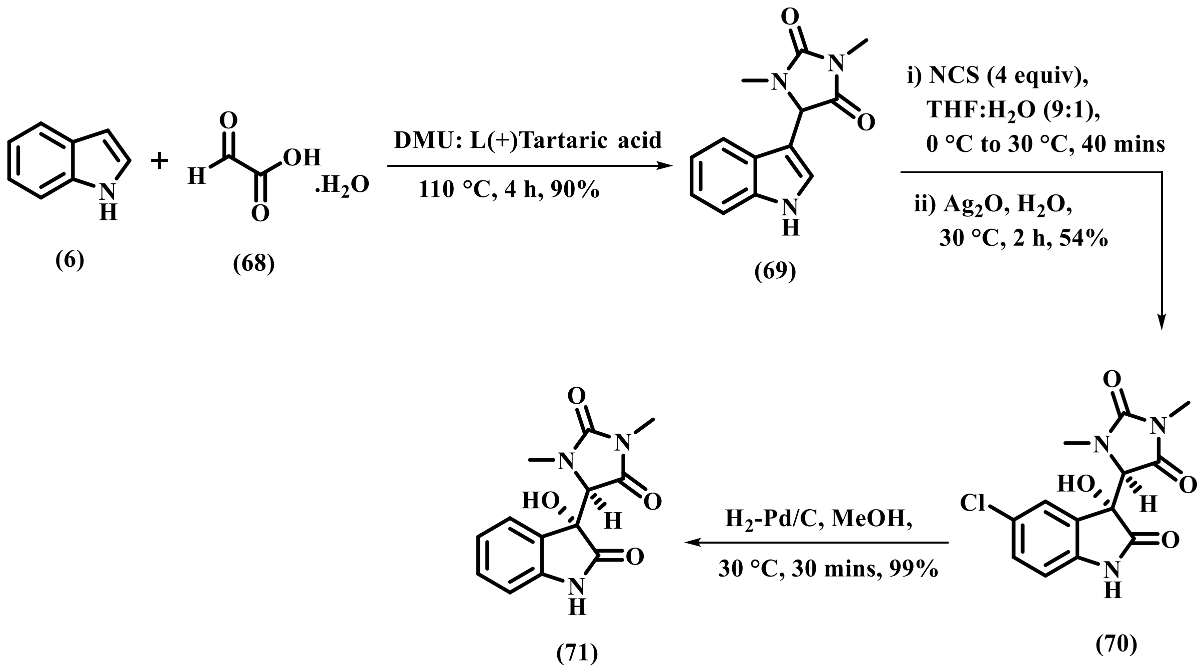
Eq. 4: Synthesis of Fascaplysins



R^1= Br, R^2= H 3-Bromofascaplysin (65)
R^1= H, R^2= Br 10-Bromofascaplysin (66)
R^1= Br, R^2= Br 3,10-Dibromofascaplysin (67)

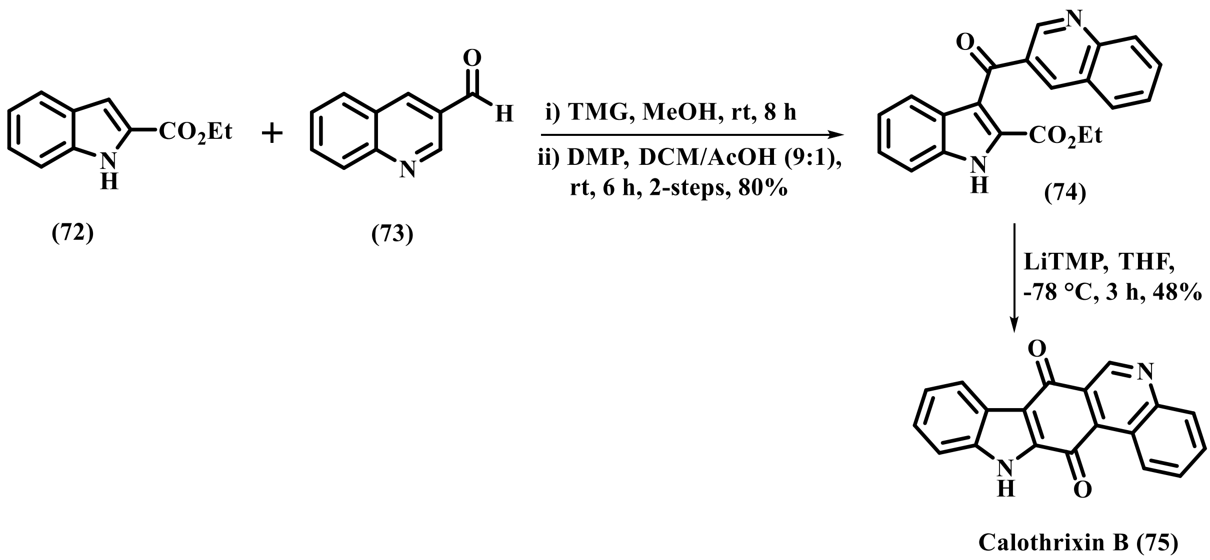
Radchenco *et al*. were described[33] first total synthesis of indole containing alkaloids substituted fascaplysins (**65-67**) from commercially available starting precursors with the overall 40-43% yield in the year 1997 (**Eq. 4**).

Eq. 5: Synthesis of (±)-Oxoaplysinopsin B



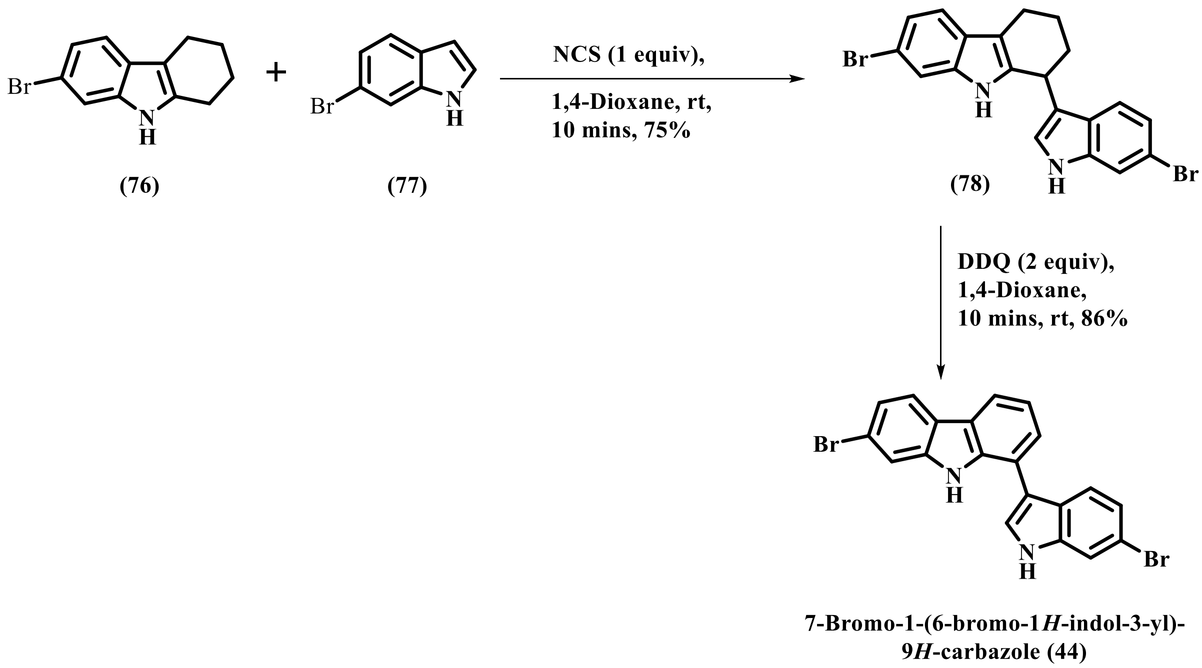
Nagarajan and co-workers first reported[34] total synthesis (±)-Oxoaplysinopsin B (**71**) in 2021. It is an indole alkaloid synthesized from commercially available starting precursors using deep eutectic solvents with an overall 48% yield (**Eq. 5**).

Eq. 6: Synthesis of Calothrixin B



In 2014 Ramkumar *et al.* were synthesized[35] indole fused alkaloid Calothrixin B (**75**), involving Friedel-Crafts hydroxy alkylation subsequently oxidation and direct ortho lithiated cyclization within 3-steps obtain the desired product overall 38% yield (**Eq. 6**).

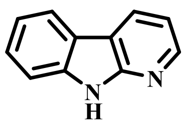
Eq. 7: Synthesis of 7-Bromo-1-(6-bromo-1*H*-indol-3-yl)-9*H*-carbazole



7-Bromo-1-(6-bromo-1*H*-indol-3-yl)-9*H*-carbazole (**44**) is a marine cytotoxic indole alkaloid. Nagarajan and co-workers[36] first reported total synthesis was developed an methodology operationally simple, and meta-free oxidative cross coupling of tetrahydro carbazole and its substituents with commercially available starting materials indole and its substituents to obtain the corresponding 1-indolyl tetrahydro carbazole (**78**) frame work followed by aromatization to gave the desired product **44** in two steps with an overall 64% yield in 2019 (**Eq. 7**).

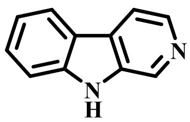
Carbolines

Carbolines are most attractive and important heterocyclic natural products, significant structural features, and promising biological properties. They are tricyclic, pyridine fused indole alkaloids. According to the degree of saturation carbolines are classified as saturated (tetrahydrocarbolines), partially saturated (dihydrocarbolines) and unsaturated (fully aromatized) carboline alkaloids. Based on the location of *N*-heteroatom in pyridine ring classified as *α*-, *β*-, *γ*- and *δ*- carbolines (Figure **10**). Among them *β*-carbolines alkaloids are existing natural occurrences over the large numbers which includes many different plants, marine creatures, foodstuffs, insects, mammals, human tissues, and also body fluids. And this family of alkaloids exhibits numerous biological activities such as antitumor, antiviral, anxiolytic, hypnotic, anticonvulsant, antiparasitic, and antimicrobial activities.[37]



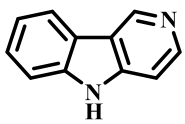
9*H*-pyrido[2,3-*b*]indole (79)

α- carboline



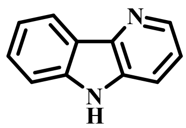
9*H*-pyrido[3,4-*b*]indole (80)

β- carboline



5*H*-pyrido[4,3-*b*]indole (81)

γ- carboline



5*H*-pyrido[3,2-*b*]indole (82)

δ- carboline

Figure 10. Classification of carbolines

The basic skeleton of *β*-carboline alkaloids found in various matrices, including marine organisms, insects, food products, plant extracts, and biological fluids and tissues. The core unit of *β*-carboline scaffolds are having in several natural products as well as pharmaceutical agents (Figure **11**).[38]

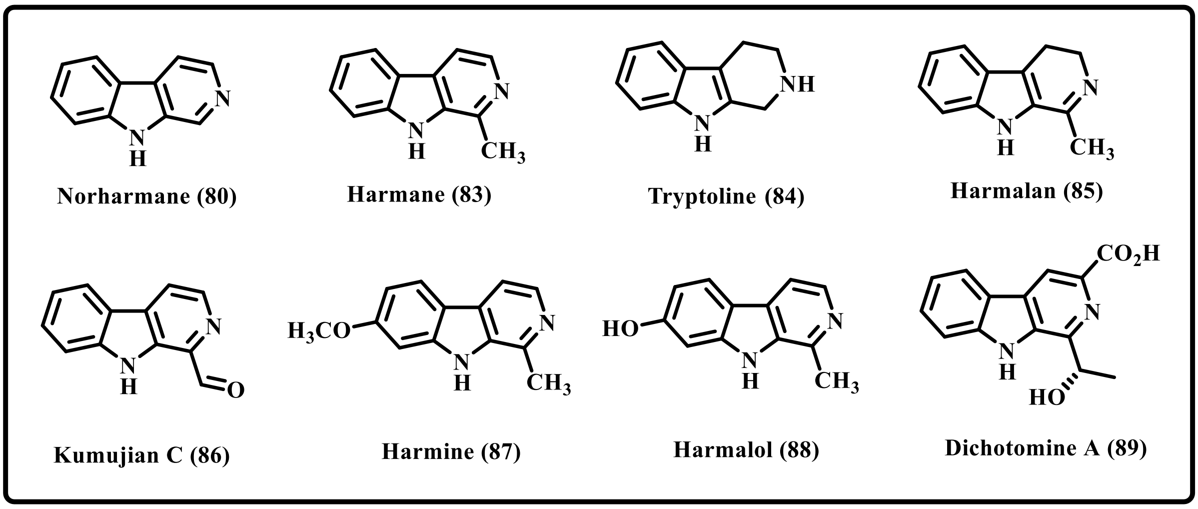


Figure 11. Examples of simple β-carboline alkaloids

In addition, other β-carboline containing alkaloids[37] Eudistomins Y_{1-3} (**90-92**) isolated from genus *Eudistoma*, Pityriacitrins (**93-94**) isolated from marine bacterium of genus *Paracoccus sp.,* Metatacarboline A (**95**) occurred from *Mycena metata*, and Canthinone (**96**), Cordatanine (**97**) was isolated from the family of *Caryophyllaceae*, moreover Eudistomin U (**98**) were isolated from marine ascidian *Lissoclinum fragile,* and Nitramarine (**99**), Nitraridine (**100**) found from *Nitraria Komarovii* plant. Those are mentioned few of *β*-carboline containing alkaloids exhibits variety of biological activities (Figure **12**).

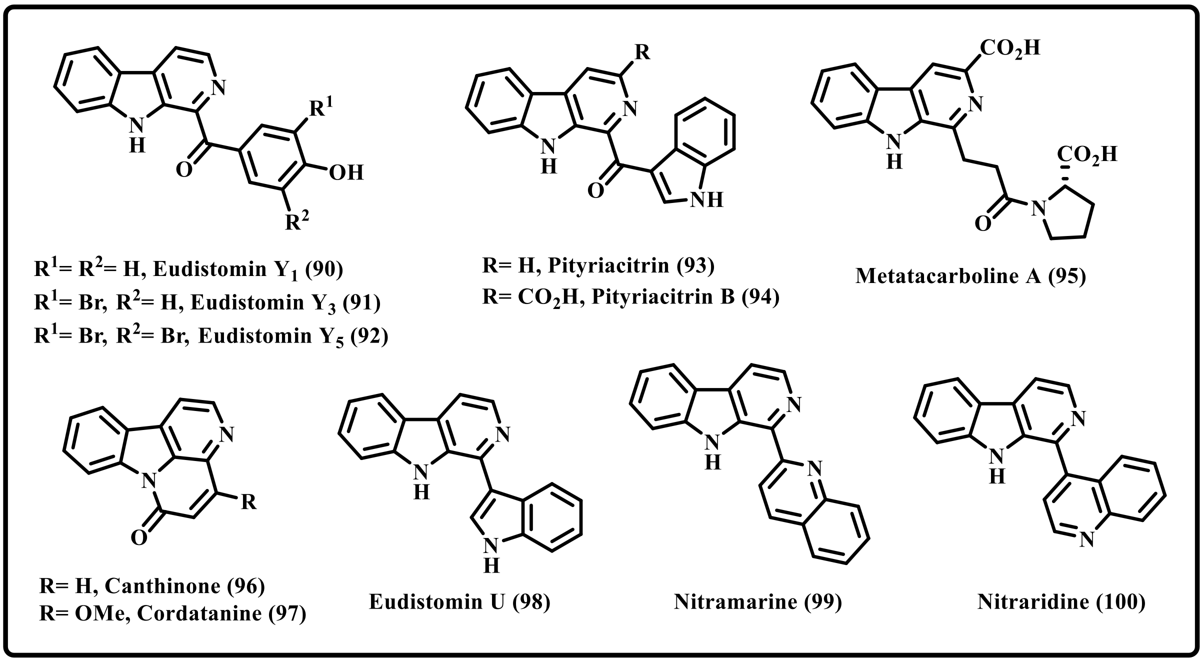
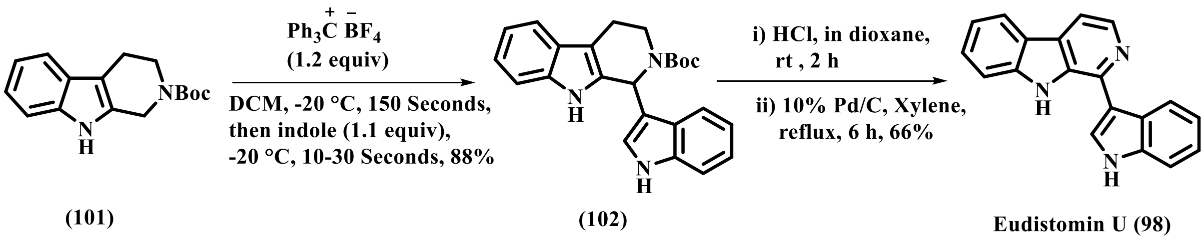


Figure 12. Examples of *β*-carboline containing alkaloids

Selective synthesis of *β*-carboline containing alkaloids

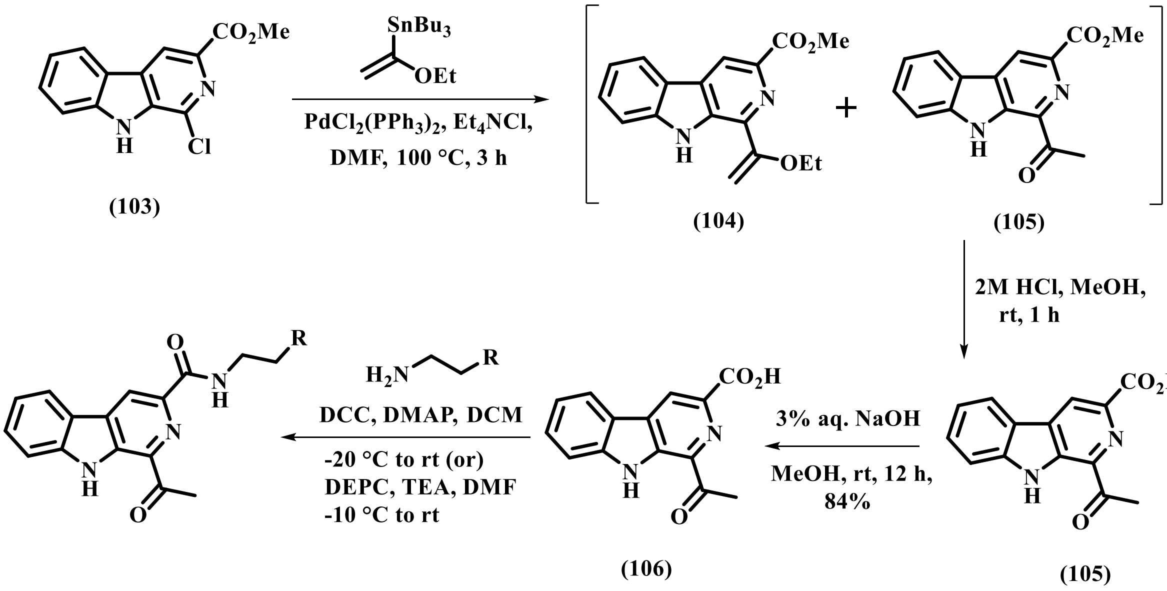
Eq. 8: Synthesis of Eudistomin U

In 2021 Nagarajan and co-workers[39] synthesized Eudistomin U (**98**), tetrahydro *β*-carboline (**101**) treated with indole (**6**) in the presence of trityl salt through metal-free cross dehydrogenative coupling to afford 1-indolyl tetrahydro *β*-carboline compound (**102**) followed by deprotection and aromatization to accomplished the compound **98** with the overall 3-steps in 58% yield (**Eq. 8**).



Eq. 9: Synthesis of Marinacarbolines (A-D)

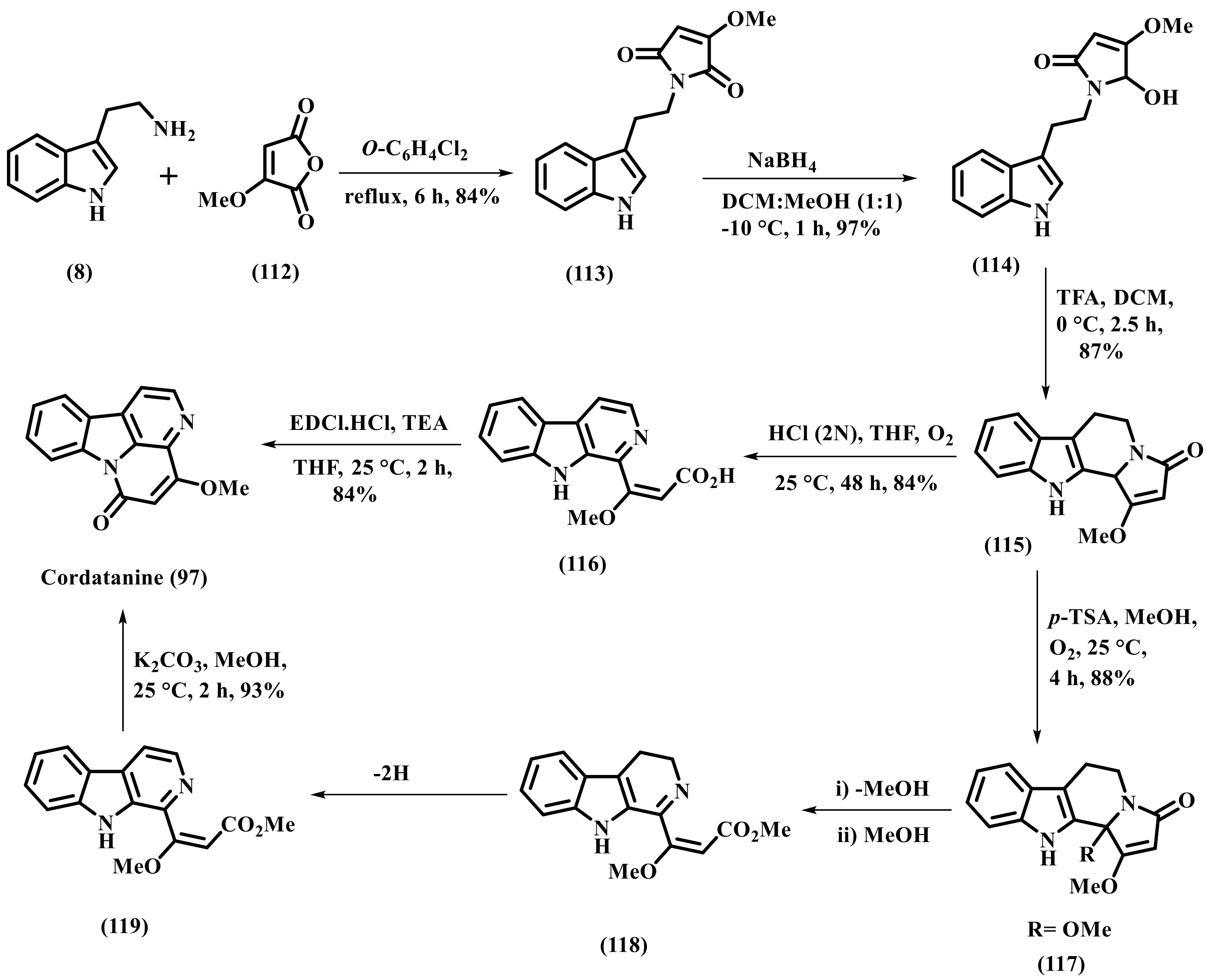
Tagawa *et al.* was described[40] first total synthesis of *β*-carboline alkaloid Marinacarbolines (A-D) (**107-110**) involving Stille cross coupling subsequently functional group modifications in the year 2013 (**Eq. 9**).



R = 4-methoxyphenyl (Marinacarboline A) (107), 98%
= 4-hydroxyphenyl (Marinacarboline B) (108), 97%
= phenyl (Marinacarboline C) (109), 99%
= indol-3-yl (Marinacarboline D) (110), 97%
= COOMe (Dichotomide I) (111)

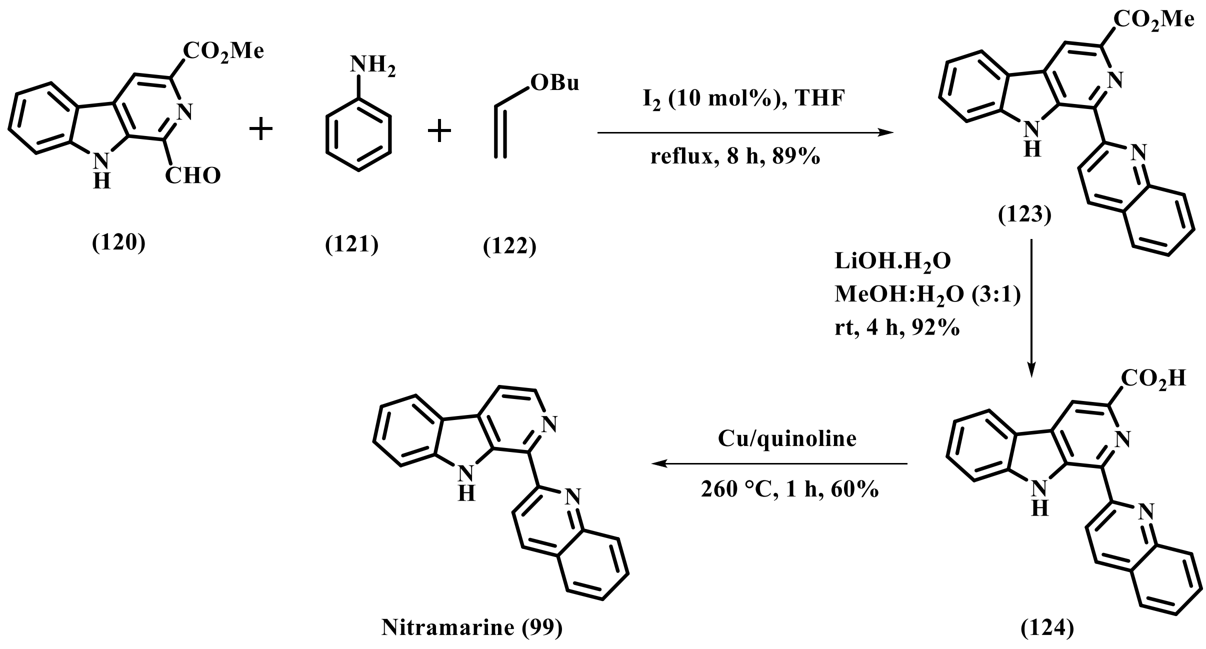
Eq. 10: Synthesis of Cordatanine

Argade and co-workers[41] were accomplished β-carboline alkaloid Cordatanine (**97**) starting from tryptamine (**8**) and methoxy maleic anhydride (**112**) by regioselective reduction and subsequently acid catalyzed intramolecular cyclization to furnished compound **115** followed by methanolysis of lactum ring or cleavage of lactum ring then cyclization to afforded the compound **97** with overall 58% yield in the year 2017 (**Eq. 10**).



Eq. 11: Synthesis of Nitramarine

In 2013 Ramesh *et al.* were reported[42] the three-components (**120-122**) synthesis of Nitramarine (**99**) through Povarov approach subsequently saponification, and decarboxylation with overall 49% yield (**Eq. 11**).



C-C bond forming coupling reactions

The developments for the formation of carbon-carbon bonds[43] have long attracted attention to chemists. C-C bond reactions are one of the most important processes in organic synthesis towards design the carbon frame works in various organic molecules, especially in total synthesis C-C bond forming reactions are the crucial role to obtain the corresponding coupled product. There are two types of coupling reactions: homocoupling and cross-coupling based on the coupling patterners involved in the reaction. Cross-coupling reactions are often categorised as seen in Figure **13**.

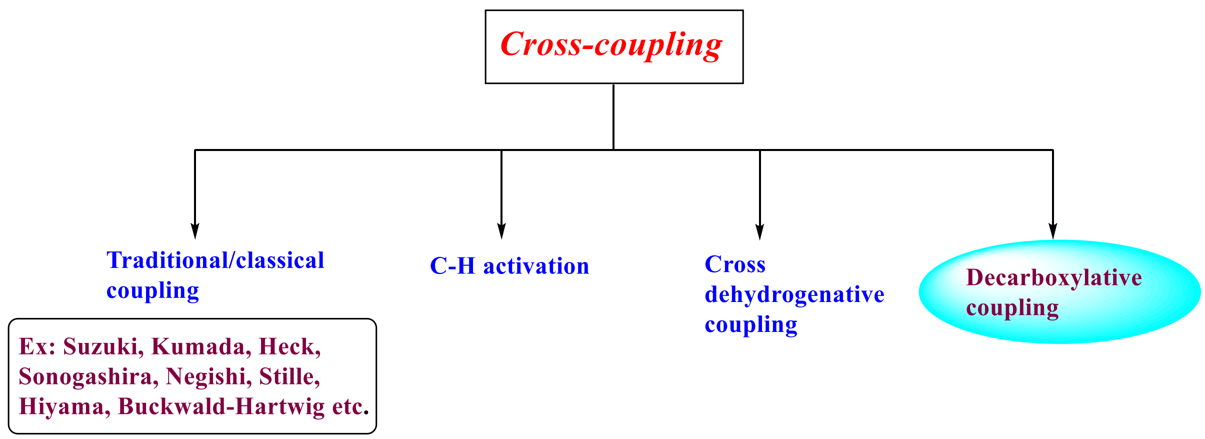


Figure 13. Classifications of cross-coupling reactions

Cross-coupling processes, which allow for the selective coupling of C-C bonds, have proven to be very helpful tools for organometallic as well as synthetic organic chemists. Cross-coupling reactions, discovered about 50 years ago, are now utilised extensively in industries and academics and many synthetic technologies. C-C bond-producing reactions are among the most difficult challenges in synthetic organic chemists. One of the greatest discoveries of the last century was transition metal-catalyzed cross-coupling.[44] It has been shown to be a strong tool for the formation of numerous chemical linkages. The recognised and well-known classical cross-coupling reactions include Suzuki, Heck, Negishi, Stille reactions, also Hiyama, Buchwald-Hartwig reaction, etc. In general, these type of coupling reactions are involving transition metal catalysts, typically modelled with an electrophile and a nucleophilic partner. On the other hand, C-H activation is a type of organic reaction, the process of cleavage C-H bond involving transition metal to generate the respective organometallic species to form C-C bond. The waste production will be high in conventional coupling reactions because of the halides and leaving groups, and additives.[45]

When the two distinct nucleophiles are combined directly without any pre-functionalization to produce a cross-coupled product, in such reactions are called as cross dehydrogenative coupling reactions[46] and only H_2 will be the by-product, with this approach the waste materials can be reduced and coupling can be more ecologically friendly approach. Generally, in this type of reactions they used oxidants like, peroxides, persulfates, O_2, benzoquinones, and hypervalent iodine compounds, etc. Although, oxidative coupling reactions are difficult due to likelihood of homocoupling, overoxidation, selectivity problems, and the direct reactivity of oxidants with nucleophiles. Decarboxylative oxidative cross-coupling[47] was a convenient and alternative method to generate the C-C/C-X bonds with the only CO_2 is sole by-product. The main topic of this thesis has decarboxylative cross-coupling with different reactive starting precursors.

Decarboxylative cross-coupling

Carboxylic acids are the versatile reactants for synthetic approach since they are readily available, nontoxic, affordable, easy to handle and typically stable at room temperature, air, and moisture. Furthermore, many of carboxylic acids may be produced entirely from natural sources, avoiding the need to use fossil fuels like oil or gas to prepare the compounds. Carboxylic acids generated from biomass exhibit a wide range of structural diversity such as amino acids, fatty acids, and sugars. Decarboxylative cross-coupling methods serve as economical and eco-friendly alternatives for instance, they have used in conventional cross-coupling processes, which involves costly organic halides, boronic acids, air and moisture sensitive organometallic reagents. Decarboxylative reactions of carboxylic acids drawn a lot of interest from synthetic chemists in recent years, and have emerged, attractive as one of the most effective methods for forming C-C and C-X (X = N, P, S) bond extrusion of CO_2. In this field various types of carboxylic acids involve like, aliphatic, aromatic, and unsaturated and *α*-oxo/keto carboxylic acids.[48]

There are numerous decarboxylative coupling reactions available up to date,[49] and the number of reactions is growing rapidly. The classical oldest decarboxylative reaction is the Kolbe electrolysis[50a] (Figure **14** (**A**)). Here radicals are electrochemically produced from carboxylic acids and dimerize both the radicals to form C-C bond in 1848. As a results cross-coupling products were obtained from electrolysis is quite difficult. Another classical method, Hunsdiecker demonstrated[50b-c] silver catalyzed oxidative decarboxylation to generate the respective alkyl radicals trapping by halides to give alkyl halides in 1861 (Figure **14** (**B**)). Barton decarboxylation method[50d] (Figure **14** (**D**)) undergoes decarboxylation in the presence of radical initiators to form the corresponding alkanes. Nilsson *et al.* were described the first decarboxylative reaction, known as the Ullman reaction[50e] in 1966, which contained two aromatic compounds (Figure **14** (**C**)).

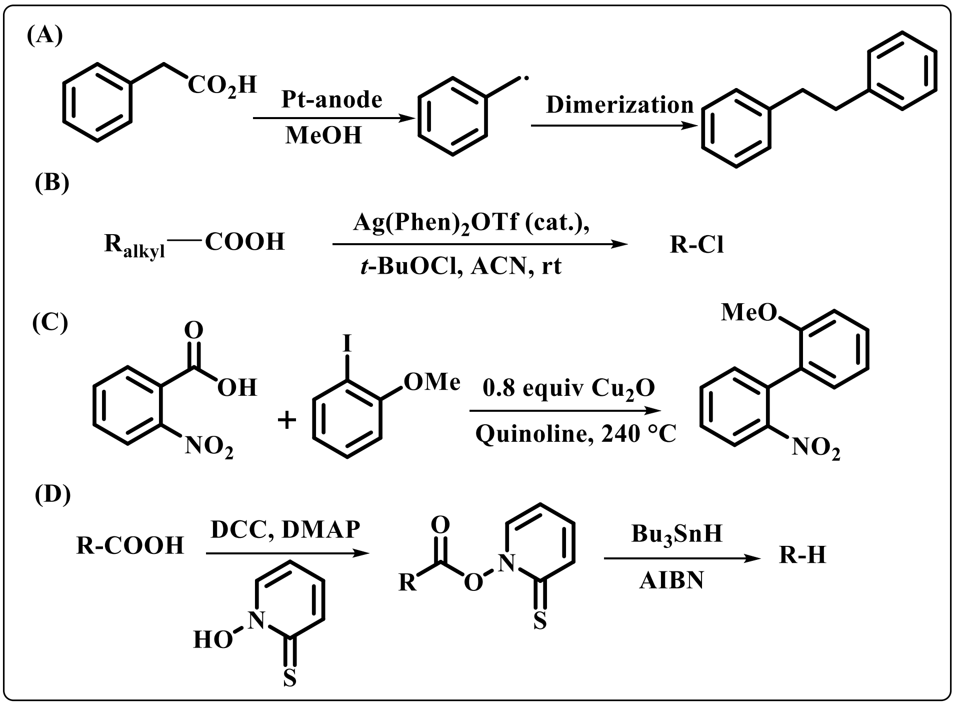


Figure 14. Classical decarboxylative coupling reactions

The above mentioned classical decarboxylative coupling reactions depicted in Figure **14**. (A) Kolbe electrolysis (B) Hunsdiecker reaction (C) Ullmann cross-coupling reaction and (D) Barton reaction

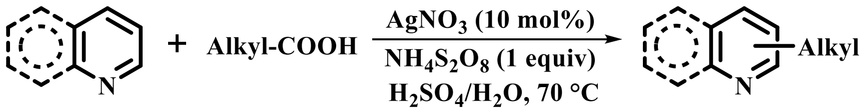
In the modern organic synthesis decarboxylative oxidative cross-coupling have an important role, this approach is more cost-effective and environmentally favourable than other traditional ways. Different types of carboxylic acids, such as aromatic, aliphatic, unsaturated, and oxocarboxylic acids, can be decarboxylated to produce the corresponding alkylation, arylation, alkynylation, olefination, acylation, homocoupling, and cyclization products by reacting with different reactive partners.[51]

Radical additions to aromatic/heteroaromatic systems have a long history in organic field that goes back to the early days. For instance, Gomberg-Bachmann reaction well-researched biphenyl synthesis from the early 1920s,[52a] involves aryl radical addition to the aromatic system (benzene). However, scientists had been looking into other analogue pyridine. When aryl radicals are added to heteroaromatic systems, pyridine reactions take place as early as the 1890s.[52b-c] There were other sources of phenyl radical discovered in the early 1960s, however the pyridine reaction's efficiency remained poor and the addition process created several regioisomers. However, significant progress was achieved, including regioisomeric ratio which undergoes radical addition throughout the 1960s period. Later, in 1961, demonstrated that pyridine-*N*-oxide reacting with phenyl radical to produced reactions with acceptable yields and improved regioselectivity.[52d] In 1964 Lynch *et al*. [53a-b] comparing the rate of phenyl radical addition to pyridinium and imidazolium ions to that of the neutral heteroaromatic base, suggested that in these heteroaromatic systems, ionic species might be dominant in the direction of radical substitution and depends on delocalization energies which was strongly favoured high reactivity towards 2nd position of pyridine. Furthermore, in 1965 Dou *et al*. discovered[53c-e] that protonation accelerated reaction times and improved positional selectivity for the addition of phenyl radicals to several heteroaromatic bases, including quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, benzothiazole, and *N*-methylbenzimidazole. These results prompted to draw the conclusion that, addition of radicals to the heteroaromatic compounds would be synthetically feasible modifications under acidic conditions.

Later, in 1971 Minisci also demonstrated[54a] that, addition of radicals to the heteroaromatic compounds are enhances positional selectivity and rate of reaction under the acidic conditions. Minisci and other synthetic chemists are developed and improved these reactions to the point of view, where they now comprise a powerful collection of unique transformations. This is the reason why "Minisci reactions" are occasionally used to describe radical additions to heteroaromatic bases. This reaction was an effective method for C-H functionalisation of heteroaromatic bases. This reaction most likely followed the Freidel-Crafts procedure, although the reactivity and selectivity were substantially different.[54b-d]

Selected example of decarboxylative alkylation

Eq. 12

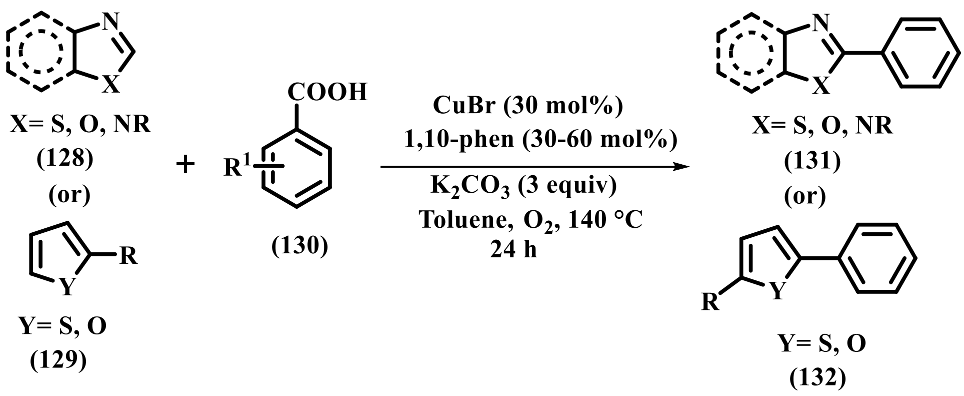


(125) (126) (127)

Minisci *et al.* were reported[54a] Ag-catalyzed decarboxylative alkylation of *N*-heteroarenes with simple carboxylic acids **126** by using ammonium persulfate as an oxidant to afford the cross-coupled product in the year 1971. This protocol was convenient and effective method for alkylation or arylation of electron deficient species (**Eq. 12**).

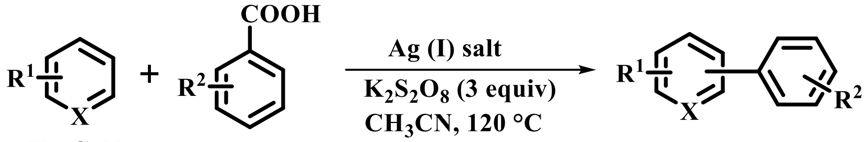
Selected examples of decarboxylative arylation

Eq. 13



In 2016 Maiti and co-workers[55a] reported Cu-catalyzed decarboxylative arylation of variety of five-membered heteroarenes **128-129** with one or two heteroatoms can easily couple together with benzoic acids and its substituents **130** using oxygen as the oxidant with good to moderate yields (**Eq. 13**).

Eq. 14



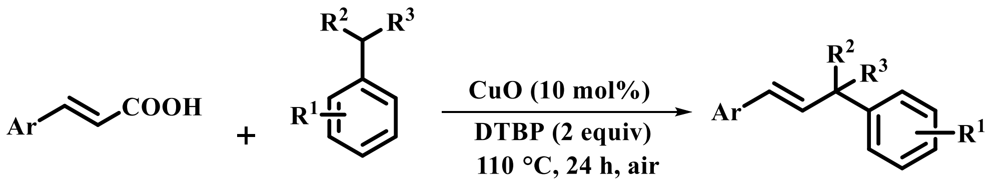
X= C, N
(133)
(130)
(134)

Ag(I) catalyzed decarboxylative arylation of aromatic and heteroaromatic systems with benzoic acids and its substituents **130** by using potassium persulfate as oxidant to obtained the cross-coupled products with good to moderate yields by Su and co-workers in the year 2015 (**Eq. 14**).[55b]

Selected examples of decarboxylative olefination

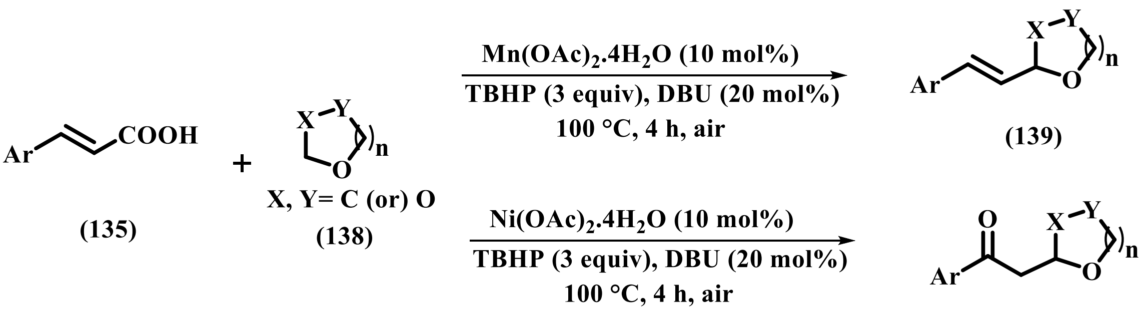
Eq. 15

Mao *et al.* were described[56a] a Cu-catalyzed decarboxylative cross-coupling method by the reaction between cinnamic acids **135** and benzylic substrates **136** with DTBP as oxidant to afforded the corresponding olefination products **137** in the year 2012. Later, the same group reported benzylic olefination products in the presence of Fe-catalyzed[56b] to obtain good yields (**Eq. 15**).



(135)
(136)
(137)

Eq. 16

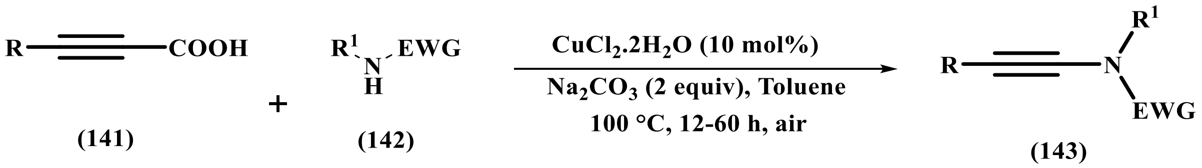


(135)
X, Y= C (or) O
(138)
(139)
(140)

In 2014 Zhang *et al.* were developed[56c] Mn-catalyzed decarboxylative method by the reaction between unsaturated carboxylic acids **135** and cyclic ethers like 1, 4-dioxane or tetrahydrofuran **138** with TBHP as an oxidant to obtain the corresponding alkenylation product **139**, in the presence of Ni-catalyst with the same oxidant afforded the oxyalkylation product **140** (**Eq. 16**).

Selected example of decarboxylative alkynylation

Eq. 17

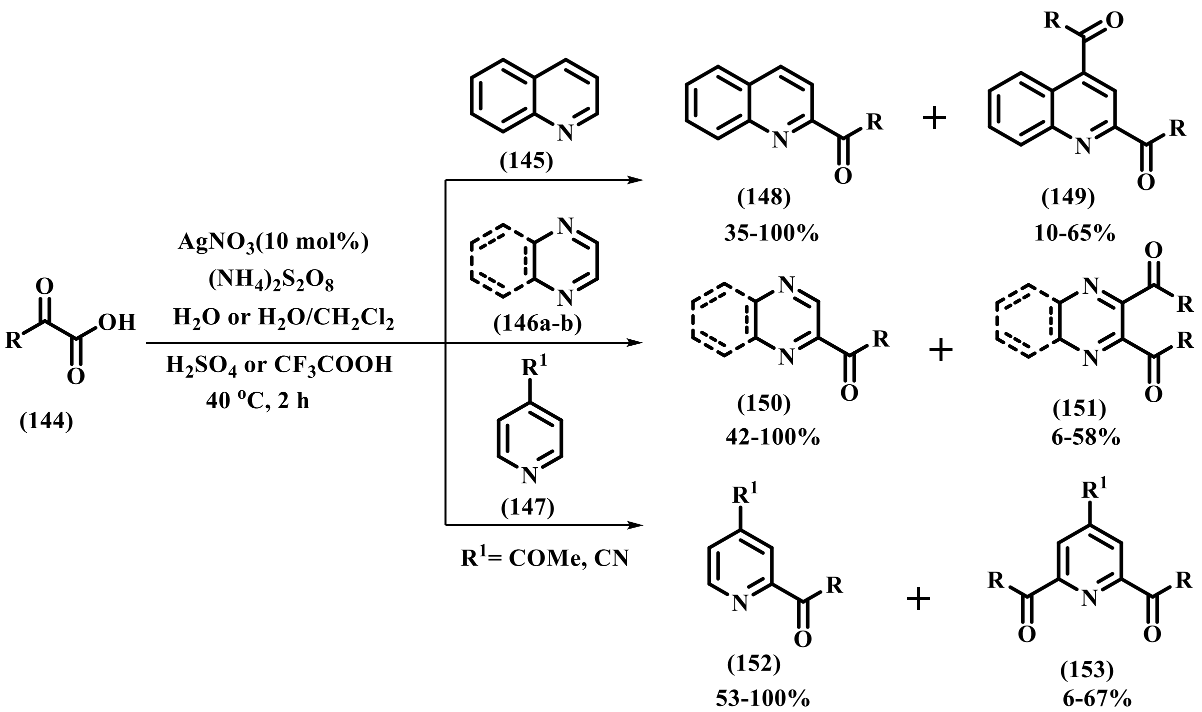


Jia *et al.* were described[57] an decarboxylative oxidative amidation **143** of alkynyl carboxylic acid **141** in the presence of Cu-mediated cross-coupled by using air as an oxidant in the year 2010 (**Eq. 17**).

Selected examples of decarboxylative acylation

Transition metal catalyzed acylation reactions

Eq. 18

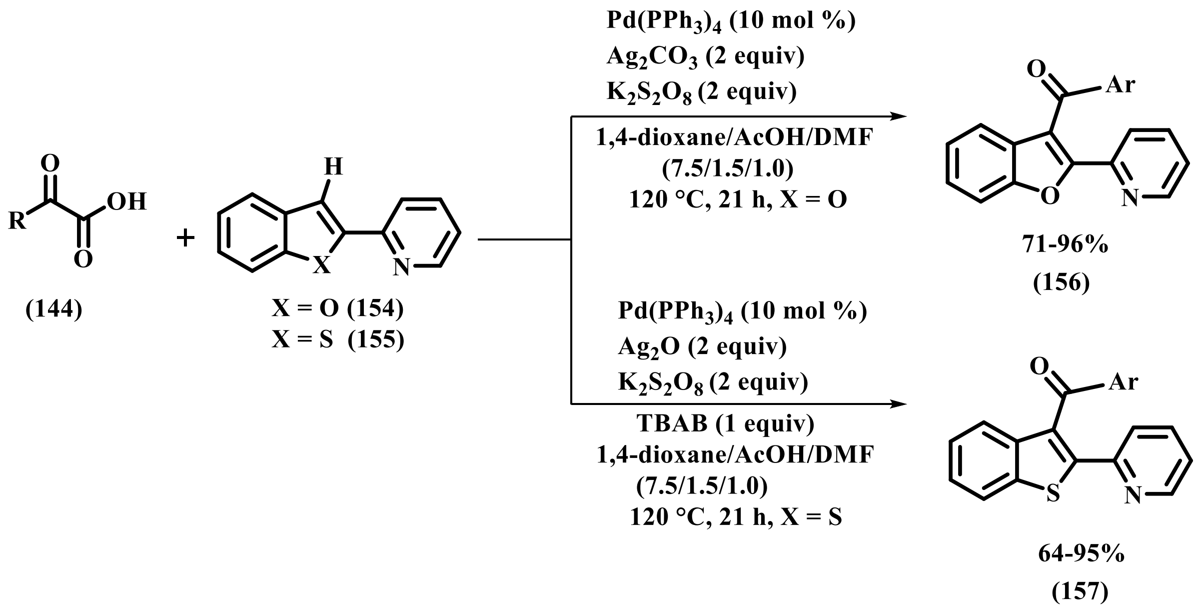


In 1991, Fontana *et al.* were first reported[58a] α-keto acids as the acylating agents for selected *N*-heteroarenes. Ag-catalyzed decarboxylative oxidative cross-coupling of *N*-

heteroarenes quinoline **145**, quinoxaline **146a**, pyrazine **146b**, pyridines **147** with α-keto acids **144** by using ammonium persulfate as an oxidant to afforded the corresponding mono or diacylated products. The generated acyl radicals from α-keto acids **144** are highly reactive towards *N*-heteroarenes. Decarboxylative coupling reactions of α-oxo/keto acids **144** have been popular in recent years for direct acylation method (**Eq. 18**).

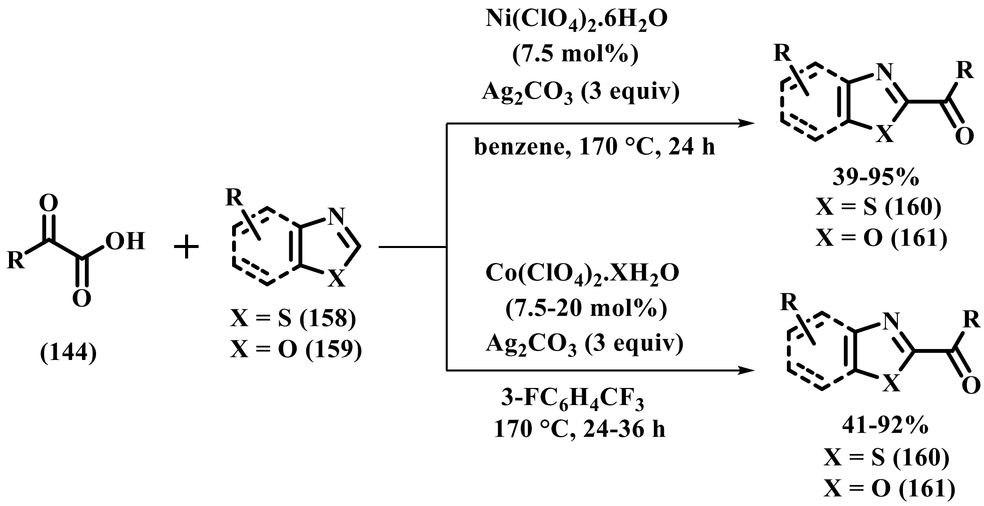
Eq. 19

In 2015 Lang and co-workers[58b] developed Pd and Ag-catalyzed decarboxylative C3-acylation of 2-pyridyl benzofuran **154** and 2-pyridyl benzothiophene **155** with α-keto acids **144** by using potassium persulfate as oxidant, combination of solvents 1,4-dioxane:AcOH:DMF (7.5:1.5:1.0) at 120 °C in 21 h time period obtained the corresponding C3-acylated products with good to moderate yields (**Eq. 19**).



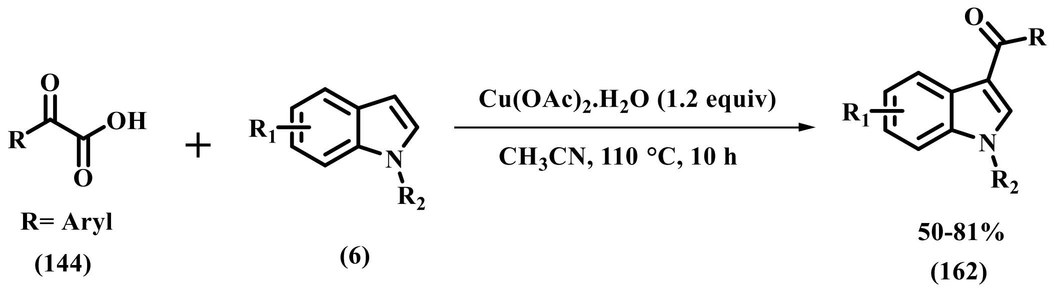
Eq. 20

Two groups are studies that combination of metals used in 2015 Lu, *et al.* Co(II)-catalyzed,[58c] in 2014 Ge and co-workers Ni(II)-catalyzed[58d] C-2 acylation of compound **158** thiazoles and compound **159** oxazoles involving decarboxylative method in the presence of Ag_2CO_3 oxidant at 170 °C in 24-36 h obtained the corresponding C2-acylated products with good to moderate yields (**Eq. 20**).



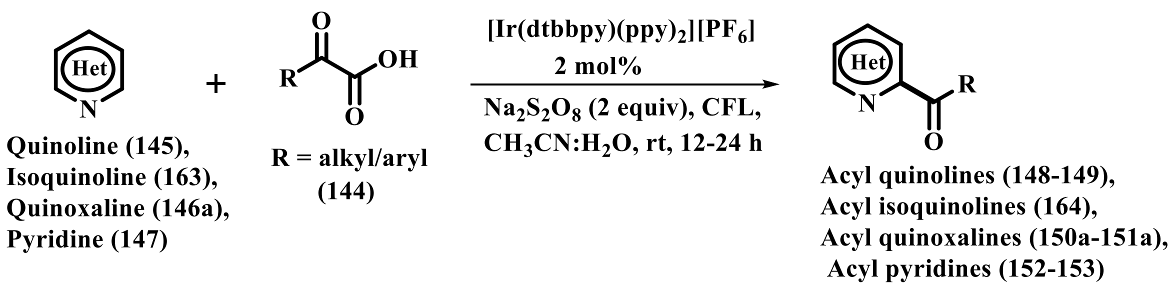
Eq. 21

In 2013 Wang group developed[58e] C3-acetylation of substituted indoles **6** with aryl glyoxylic acid and its substituents **144** undergoes decarboxylative method utilizing $Cu(OAc)_2.H_2O$ acts as catalyst as well as oxidant at 110 °C temperature in 10 h to afforded C3-acylated indoles **162** with good yields (**Eq. 21**).



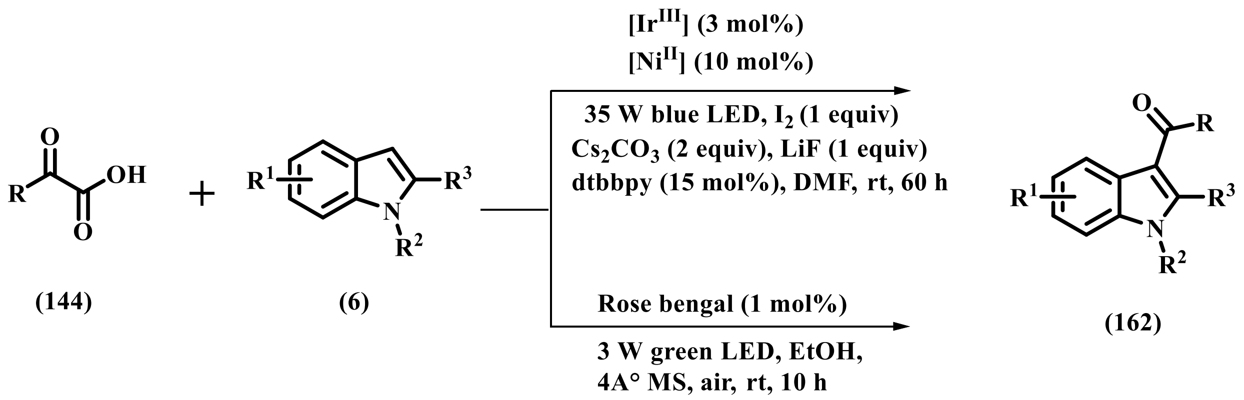
Visible-light mediated acylation reactions

Eq. 22



Prabhu *et al.* were developed[59a] Ir-photocatalyzed visible-light mediated direct decarboxylative acylation of *N*-heteroarenes with *α*-keto acids **144** by using sodium persulfate as an oxidant at room temperature to obtain the acylated products with decent yields in the year 2019 (**Eq. 22**).

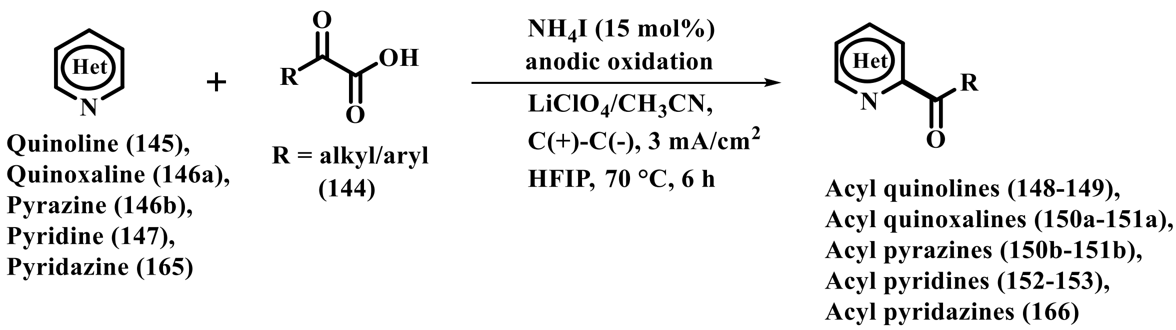
Eq. 23



Gu and co-workers[59b] reported combined catalysts Ir(III) and Ni(II) under visible-light mediated direct decarboxylative acylation of indoles using Cs_2CO_3, I_2 and LiF in DMF at room temperature to obtain decarboxylative cross-coupled product **162** in good to moderate yields (**Eq. 23**). Simultaneously Wang *et al.*[59c] were reported visible-light promoted direct decarboxylative acylation of indoles utilizing rose bengal as photo catalyst at room temperature under air to afford C3-acylated products **162** with decent yields in the year of 2016 (**Eq. 23**).

Electrochemical mediated acylation reaction

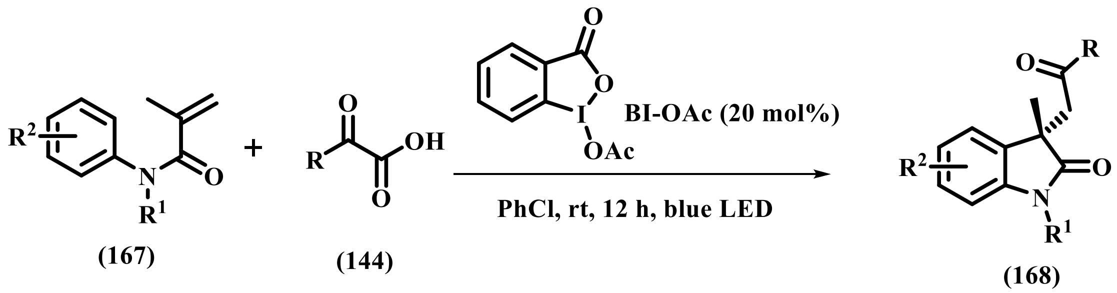
Eq. 24



In 2017 Zeng and co-workers[60] reported electrochemical mediated decarboxylative acylation of electron-deficient *N*-heteroarenes like quinoline **145**, quinoxaline **146a**, pyrazine **146b**, pyridazine **147**, and pyridine **147** with *α*-oxo/keto acids **144** using catalytic amount of NH_4I as redox catalyst at 70 °C in 6 h to afforded decarboxylative acylated products with decent yields (**Eq. 24**).

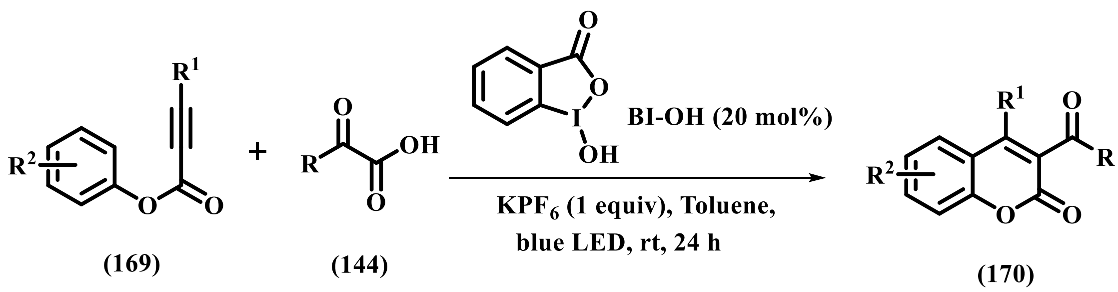
Hypervalent iodine (III) with photo mediated acylation reactions

Eq. 25



In 2016 Wang and co-workers[61a] developed hypervalent iodine reagent with visible light mediated direct decarboxylative acetylation of acrylamide compound **167** with acylating agent **144** under irradiation with blue LED at room temperature to obtain the acetylated oxindole product **168** in good yields. It was another method to that of Ag(I)/persulfate condition to generate the decarboxylative acyl radical from α-keto acids **144** (**Eq. 25**).

Eq. 26

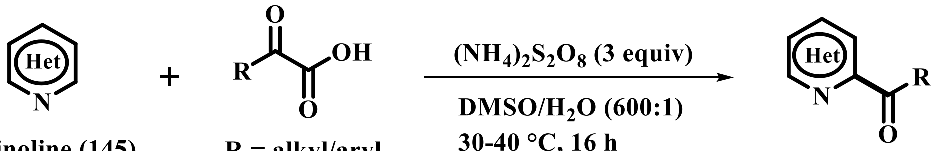


In 2017 Wang *et al.* was reported[61b] visible light promoted, hypervalent iodine mediated decarboxylative acylation of phenyl propiolate compound **169** with α-keto/oxo carboxylic acids **144** at room temperature to obtain direct C3-acylation of coumarins **170** in good to moderate yields (**Eq. 26**).

Metal-free acylation reactions

Eq. 27

Recently, Lee and his group[62a] were first developed direct decarboxylative acylation under metal-, light-, electrocatalyst-, and light-free synthesis in the presence of ammonium persulfate as sole oxidant at milder conditions to obtain the corresponding acylation product with good to moderate yields (**Eq. 27**).

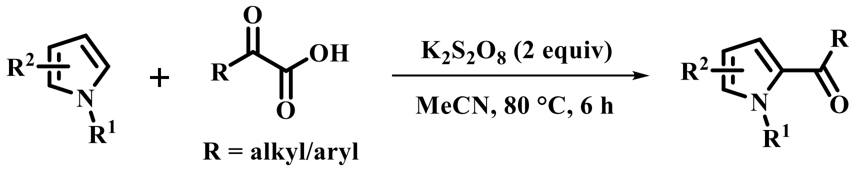


Quinoline (145), Isoquinoline (163) Pyridine (147), Quinoxaline (146a), Quinazoline (171) Benzoquinone (172)

R = alkyl/aryl (144)

Acyl quinoline (148-149), Acyl isoquinoline (164) Acyl pyridine (152-153), Acyl quinoxaline (150a), Acyl quinazoline (173) Acyl benzoquinone (174)

Eq. 28

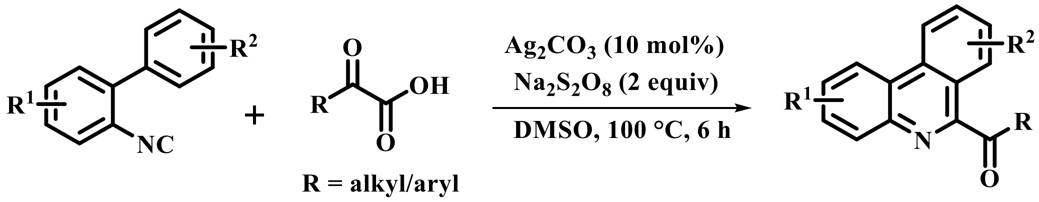


(175) **R = alkyl/aryl (144)** **(176)**

Laha *et al.* developed[62b] a transition metal-free direct decarboxylative acylation of electron rich arene pyrroles in the presence of potassium persulfate as an oxidant with acetonitrile at 80 °C in 6 h to afford the corresponding acylated product with good yields in the year 2020 (**Eq. 28**).

Selected example of decarboxylative cyclization

Eq. 29



(177) **R = alkyl/aryl (144)** **(178)**

In 2014 Lei *et al.* were reported[63] Ag-catalyzed decarboxylative cyclization of α-keto/oxo carboxylic acid **144** with substituted isonitriles **177** using sodium persulfate an oxidant and DMSO solvent at 100 °C in 6 h afforded decarboxylation followed by cyclized product 6-acyl phenanthridines **178** with good to moderate yields (**Eq. 29**).

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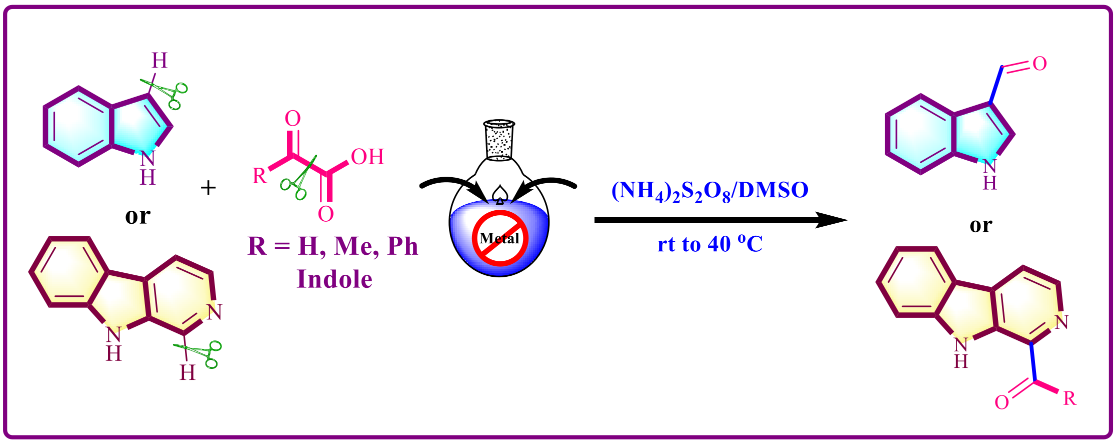
CHAPTER- *I (A)*

Metal-free decarboxylative formylation of indoles and acylation of *β*-carbolines: Application to the synthesis of indole alkaloids



Abstract:

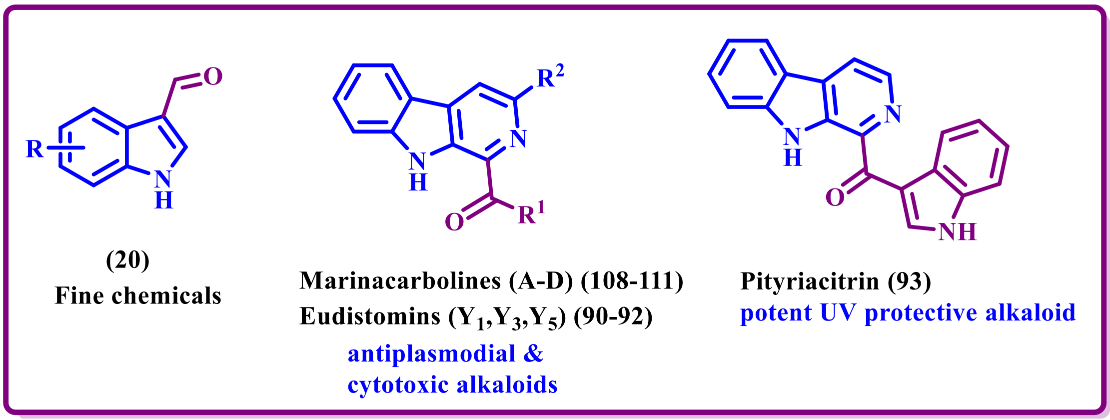
We have developed transition metal free direct decarboxylative cross coupling of *α*-oxo/ketoacids for formylation of indoles and acylation of *β*-carbolines with $(NH_4)_2S_2O_8$/DMSO. This reaction proceeds smoothly between ambient temperature and 40 °C under mild reaction conditions with commercially accessible starting precursors. This methodology was applied to the synthesis of biologically active natural product pityriacitrins and formal synthesis of eudistomins Y_1&Y_3, marinacarbolines A-D.

1.1. Introduction:

The development of an efficient method for C-C bond formation is essential in organic chemistry as well as in medicinal chemistry.[3c,44b] In this context, Minisci reaction[54] played a crucial role in the past several years to construct C-C bond via direct C-H functionalization via radical pathway.[43a, 46c, 47, 54b] Over the past few decades decarboxylative coupling reactions[48a, 51a] are emerged, attractive and alternative approach for the C-C bond formation. In this field various type of carboxylic acids will involves like aromatic, aliphatic, unsaturated carboxylic acids and α-oxo/keto carboxylic acids have been proven and investigated;[51b] among these, *α*-keto carboxylic acids and its acetals played an essential role in the direct formyl/acylation in the synthetic chemistry,[49] which are readily available, inexpensive, stable, and non-toxic. Moreover, α-keto carboxylic acids are attractive due to high reactivity. A decarboxylative coupling strategy is convenient, more environmentally friendly, and step-economic compared with other traditional methods.[64]

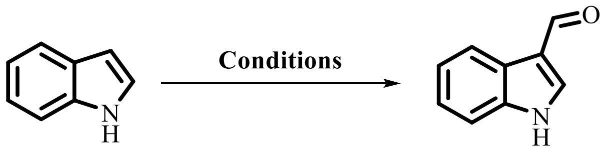
Formylation and acylation[62a] of *N*-heterocycles[65,66] are important method for the preparation of fine chemicals and biologically important alkaloids (**Figure 1.1**).

Figure 1.1 Examples of biologically important indole alkaloids



The conventional methods for the preparation of aromatic/hetero aromatic aldehydes (shown in **Table 1.1**) were Vilsmeier-Haack[67a], Reimer-Tiemann[67b], Rieche[67c], Duff[67d] and Friedel-Crafts reaction[67e] for acylation. Many of these methods suffers from several disadvantages such as corrosive, moisture sensitive, harsh reaction conditions, poor selectivity, waste bi-products and less functional group tolerance. However, several new approaches for formylation and acylation of indoles have been found in the past years, and general and operationally simple methods of 3-formylindoles are still of interest.

Table 1.1 Previous reports for the synthesis of indole-3-carboxaldehyde (20)



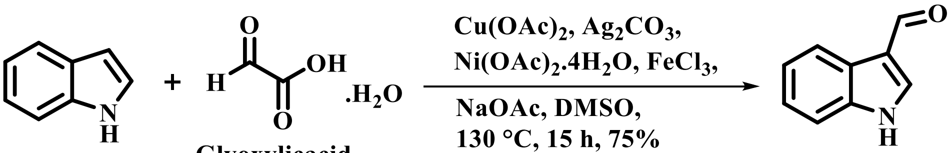
(6) (20)

Formyl Source	Classical methods	Metal mediated	Light mediated	Electrochemical
DMF/$POCl_3$	Vilsmeier-Haack			
$CHCl_3$/NaOH	Reimer-Tieman			
PhNH(CH_3)		$RuCl_3$/TBHP, PivOH, NMA		
TMEDA		$CuCl_2/O_2$, K_2CO_3, CH_3CN	1).Rose bengal, KI, O_2, visible-light, MeCN-H_2O, 60 °C 2).Eosin-Y, KI, air, Blue LED, MeCN-H_2O, rt	
HMTA	Duff reaction	$Ce(NH_4)_2(NO_3)_6$ -SiO_2, CH_3CN		
HCHO/NH_3		$FeCl_3$, DMF, 130 °C, air		
Glyoxylic acid		$Cu(OAc)_2$,Ag_2CO_3, $Ni(OAc)_2.4H_2O$,$FeCl_3$, NaOAc, DMSO,130 °C, 15 h	NaOAc, Purple LED, MeCN, rt, air, 24 h	$(CH_3)_2NH/PhNH_2$, $NaClO_4$, Pt-Pt foils

Recently, Minisci type formylation of *N*-heteroarenes was reported with trioxane and glyoxylic acid/acetal using as formyl radical synthons.[68]

Synthesis of indole-3-carboxaldehyde with glyoxylic acid

(A) Transition metal catalyzed reaction

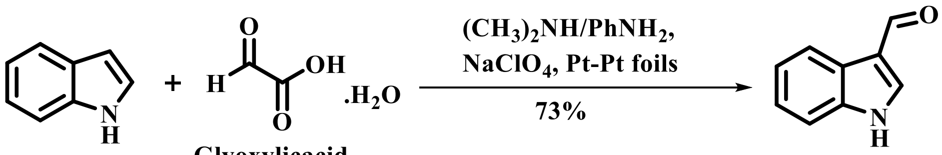


(6) **Glyoxylicacid. monohydrate (68)** **(20)**

Eq. 30. Wu *et al.* (2018)[69a]

In 2018 Wu and co-workers[69a] was reported a selective Ni-catalyzed decarboxylative cross coupling of indoles (**6**) with glyoxylic acid monohydrate **68** to obtain 3-formylindole **20** (**Eq. 30**).

(B) Electrochemical method

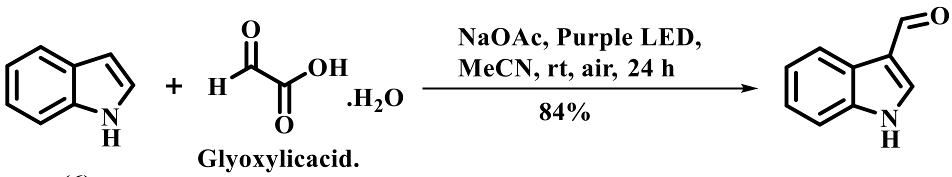


(6) Glyoxylicacid. monohydrate (68) (20)

Eq. 31. Huang *et al.* (2019)[69b]

In 2019 Huang's group also reported[69b] 3-formylindoles **20** from amine catalyzed electrochemical decarboxylation method using glyoxylic acid monohydrate **68** as formyl synthon (**Eq. 31**).

(C) Photochemical method



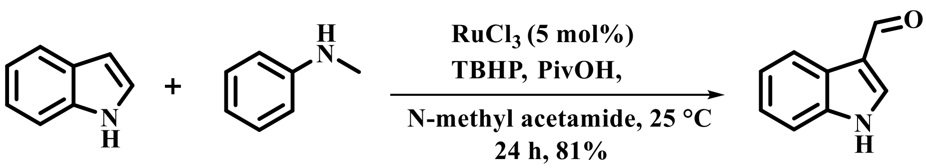
(6) Glyoxylicacid. monohydrate (68) (20)

Eq. 32. Wang *et al.* (2022)[69c]

Recently, in 2022 Wang and co-workers[69c] reported photoredox catalyzed decarboxylative cross coupling of indoles (**6**) with glyoxylic acid monohydrate **68** to obtain indole-3-carboxaldehyde **20** (**Eq. 32**).

Synthesis of indole-3-carboxaldehyde with *N*-methylaniline

(A) Transition metal catalyzed reaction

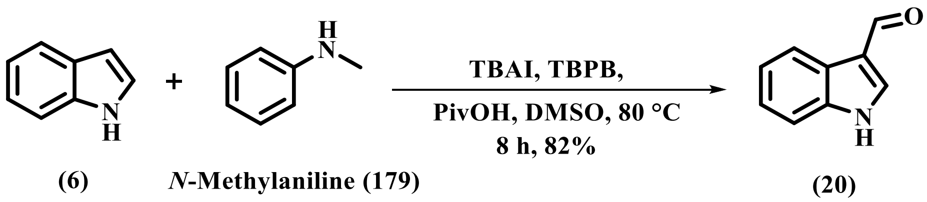


(6) *N*-Methylaniline (179) (20)

Eq. 33. Su *et al.* (2011)

In 2011 Su *et al.* was synthesized indole-3-carboxaldehyde **20** from Ru-catalyzed[70a] oxidative coupling of indole **6** with *N*-methylaniline **179** as the formyl equivalent (**Eq. 33**).

(B) Hypervalent Iodine catalyzed reaction

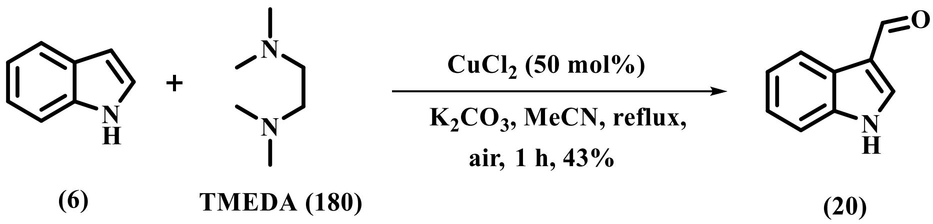


Eq. 34. Wang *et al.* (2012)

Wang and co-workers developed[70b] tetrabutylammonium iodide (TBAI) catalyzed C-3 formylation of indoles with the help of *N*-methylaniline **179** as formyl source in 2012 (**Eq. 34**).

Synthesis of indole-3-carboxaldehyde with TMEDA

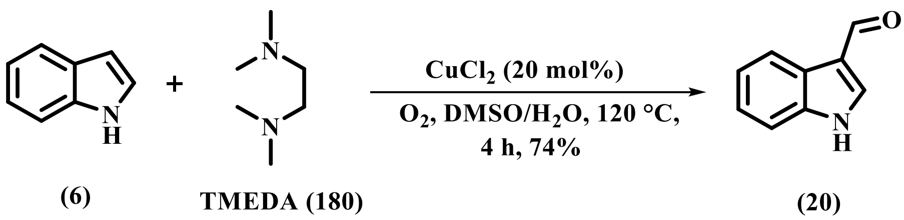
(A) Transition metal catalyzed reactions



Eq. 35. Zhang *et al.* (2012)

In 2012 Cheng and co-workers[71a] and Zhang *et al.* were reported[71b] Cu-catalyzed formylation of indoles using tetramethyl ethylenediamine **180** (TMEDA) as formyl synthetic equivalent by employing oxygen as the clean oxidant (**Eq. 35, 36**).

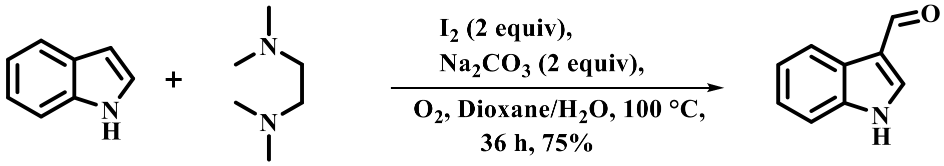
Eq. 36. Cheng *et al.* (2012)



(B) Hypervalent Iodine catalyzed reaction

Liu and co-workers were synthesized[71c] molecular I_2-promoted C3-formylation of indoles with tetramethyl ethylenediamine **180** (TMEDA) as the carbonyl source, molecular oxygen as oxidant in 2014 (**Eq. 37**).

Eq. 37. Liu and co-workers (2014)

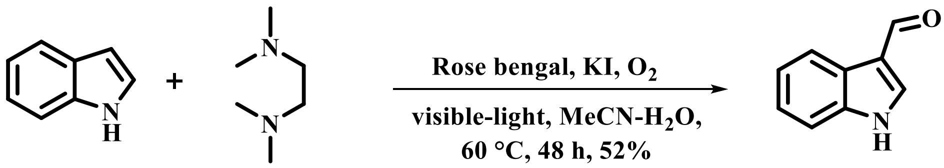


(6) **TMEDA (180)** **(20)**

(C) Photochemical method

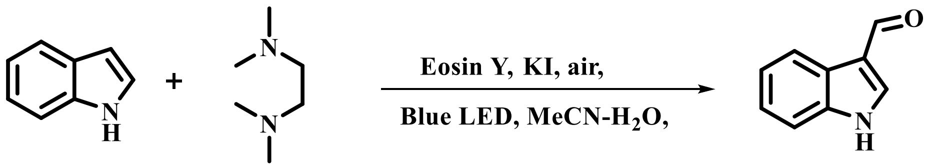
Li and co-workers[71d] demonstrated a metal-free visible-light mediated aerobic indole-3-carboxaldehyde reaction catalyzed by Rose Bengal, employs molecular oxygen as sole oxidant and tetramethyl ethylenediamine **180** (TMEDA) acts as formyl source used in 2014 (**Eq. 38**). Recently, Zhao *et al.* developed[71e] Eosin-Y catalyzed C3-formylation of indoles by using the same tetramethyl ethylenediamine **180** (TMEDA) as carbon source in 2022 (**Eq. 39**).

Eq. 38. Li and co-workers (2014)



(6) **TMEDA (180)** **(20)**

Eq. 39. Zhao *et al.* (2022)



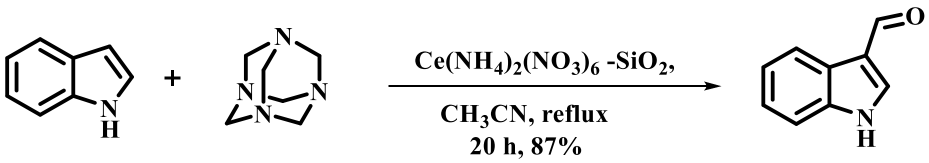
(6) **TMEDA (180)** **(20)**

Synthesis of indole-3-carboxaldehyde with HMTA

(A) Transition metal catalyzed reaction

In 2014, Sakee *et al.* were reported[72a] Ce-catalyzed silica supported C3-formylation of indoles achieved by using formyl synthon obtained from hexamethylenetetramine **181** (HMTA) (**Eq. 40**).

Eq. 40. Sakee *et al.* (2014)

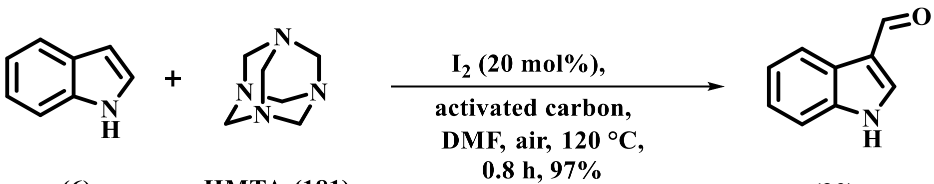


(6) HMTA (181) (20)

(B) Hypervalent Iodine catalyzed reaction

Zeng and co-workers developed[72b] iodine catalyzed formylation of indoles was synthesized, in this reaction hexamethylenetetramine **181** (HMTA) as source of formyl equivalent, and using activated carbon under the atmospheric oxygen in 2017 (**Eq. 41**).

Eq. 41. Zeng and co-workers (2017)

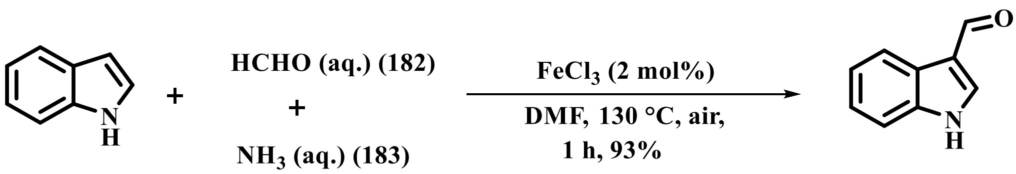


(6) HMTA (181) (20)

Miscellaneous reactions

In 2017 Wang *et al.* reported[73a] Fe-catalyzed chemo selective C3-formylation of indoles by employing aq. formaldehyde **182** and aqueous ammonia **183** under the atmospheric air as an oxidant (**Eq. 42**).

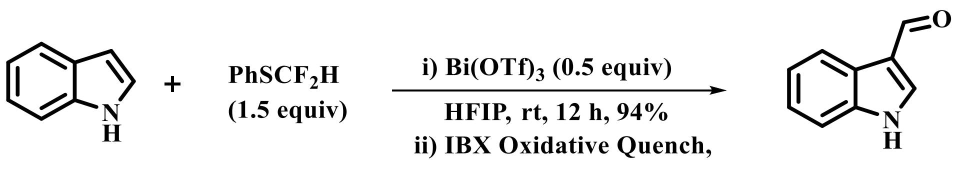
Eq. 42. Wang *et al.* (2017)



(6) (20)

In the year 2018, Kuhakarn and co-workers were reported[73b] Bi-catalyzed formylation of indoles utilizing difluoro(phenylsulfanyl)methane **184** as formyl equivalent in hexafluoro isopropanol (HFIP) as suitable solvent system (**Eq. 43**).

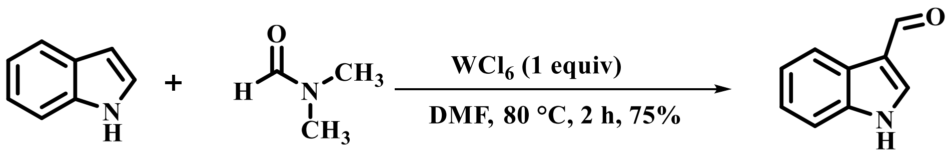
Eq. 43. Kuhakarn and co-workers (2018)



(6) (184) (20)

Iranpoor *et al.* was synthesized[73c] indole-3-carboxaldehyde **20** in the presence of W-catalyzed an efficient metal halide (WCl_6) with DMF **185** as new reagent system the source of formyl group introduced in 2014 (**Eq. 44**).

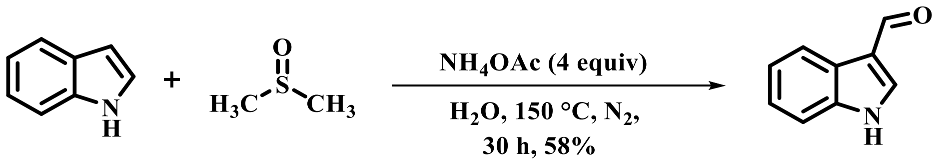
Eq. 44. Iranpoor *et al.* (2014)



(6) (185) (20)

In 2013 Cheng and co-workers developed[73d] DMSO **186** serves the carbon source for the formation of indole-3-carboxaldehyde **20**, by using suitable combination DMSO **186** with H_2O in the presence of NH_4OAc (**Eq. 45**).

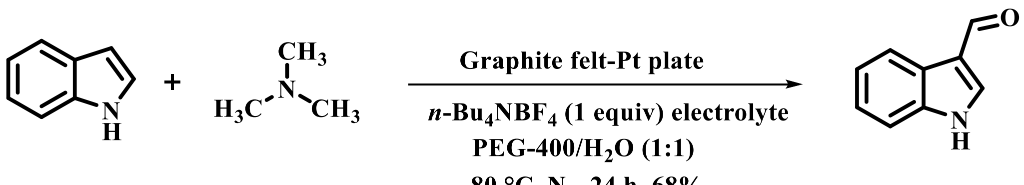
Eq. 45. Cheng and co-workers (2013)



(6) (186) (20)

Ling *et al*. was reported[73e] an electrochemical method for synthesis of 3-formyl indoles utilizing trimethylamine **187** (NMe_3) as the formylating agent under the recyclable and reusable aqueous biphasic system *n*-Bu_4NBF_4/PEG-400/H_2O in 2021 (**Eq. 46**).

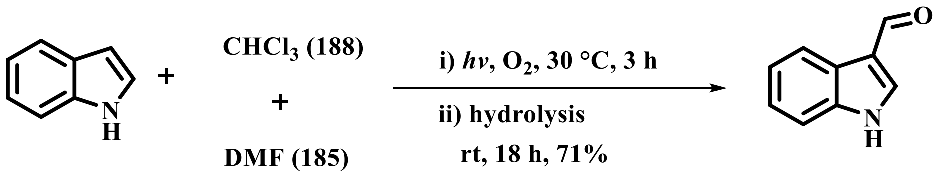
Eq. 46. Ling *et al.* (2021)



(6) (187) (20)

In 2021 Liang *et al.* were developed[73f] Photo-Demand synthesis of vilsmeier reagent, obtained from $CHCl_3$ (**188**) + DMF (**185**) solution on photo-irradiation under O_2 bubbling readily available for synthesis of indole-3-carboxaldehyde (**Eq. 47**).

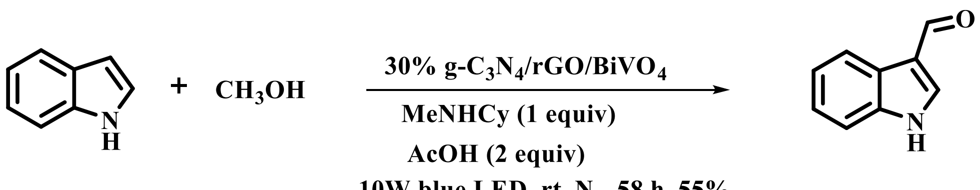
Eq. 47. Liang *et al.* (2021)



(6) (20)

Recently, in 2023 Lei *et al.* were developed[73g] a synthesis of 3-formyl indoles by using methanol **189** serves as the novel formylating reagent in the presence of recyclable photocatalyst 30% g-C_3N_4/rGO/$BiVO_4$ (**Eq. 48**).

Eq. 48. Lei *et al.* (2023)



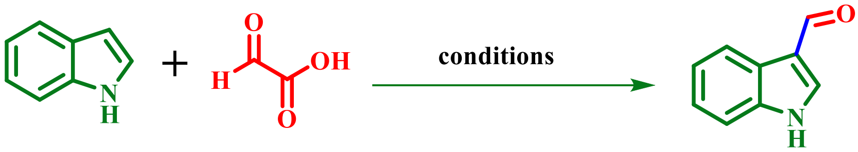
(6) (189) (20)

Many of the formylation methods is proceeded entirely with requiring expensive transition metals[74] like Ir, Ag and Pd[75], photocatalyst[76], electrocatalyst[77], light irradiation and expensive ligands, special equipment setup or difficult to handling some harmful reagents. Consideringly, to overcome these limitations and to address this problem we reported this protocol.

1.2. Results and discussion:

Herein, we report a direct C-H formylation/acylation of α-ketoacids (**144**) with indoles **6** or β-carboline **80** in a single step through metal-free decarboxylative cross-coupling mediated by ammonium persulfate (APS) [$(NH_4)_2S_2O_8$] in DMSO *via* in situ generated respective radical formyl/acyl synthon in good to moderate yields. This methodology was extended to synthesis of some indole alkaloids.

Table 2.1 Optimization of the reaction conditions (20) [a]



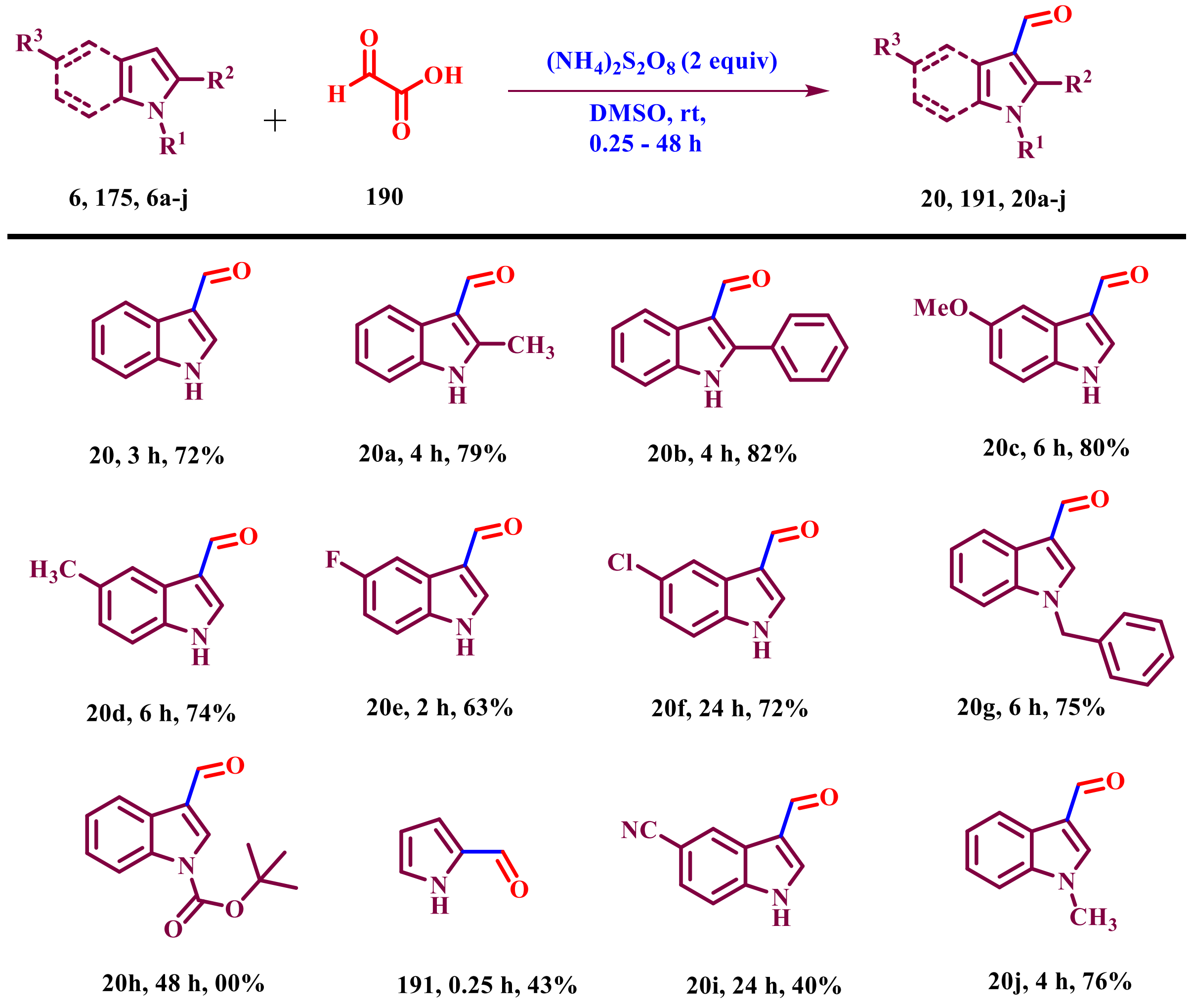
(6) (190) (20)

Entry	$(NH_4)_2S_2O_8$ (equiv)	aq. Glyoxylic acid (equiv)	Solvent	20 (%) [b]
1	1	2	CH_3CN	21
2	2	2	CH_3CN/H_2O (1:1)	42
3	2	2	Toluene	0
4	2	2	Acetone	0
5	2	2	DMSO	72
6	2.5	2.5	DMSO	72
7	0	2	DMSO	0
8	2	2	$DMSO/H_2O$ (1:1)	56
9	2	2	H_2O	45

[a] Reaction conditions: Indole (**6**) (0.85 mmol, 1.0 equiv), 50% aqueous glyoxylic acid solution **190** (1.70 mmol, 2 equiv), Oxidant $(NH_4)_2S_2O_8$ (APS) (1.70 mmol, 2 equiv), DMSO (1 mL), RT, 3h. [b] Isolated yields after chromatography.

The optimizations of reaction conditions with different solvents and different equivalents of APS were carried out (**Table 2.1**). From this, we identified 2 equiv. of APS and 2 equiv. of glyoxylic acid **190** was found to be better reaction condition (**entry 5**) based on isolated yields. Both $(NH_4)_2S_2O_8$ and DMSO are inexpensive, easily removed by washing with water, and all starting materials are commercially available. This direct methodology of formylation/acylation of indoles (**6**) and β-carbolines (**80**) is convenient, cost-effective and has several other advantages compared with traditional methods and other metal-catalyzed decarboxylative acylation: (i) proceeds smoothly under aqueous medium, (ii) commercially available, inexpensive, non-flammable, (iii) easy to handle reagents, (iv) formylations at room temperature, and (v) without an inert atmosphere and the products were obtained in good to moderate yields.

Scheme 2.1 Formylation of indoles with $(NH_4)_2S_2O_8$ [a]

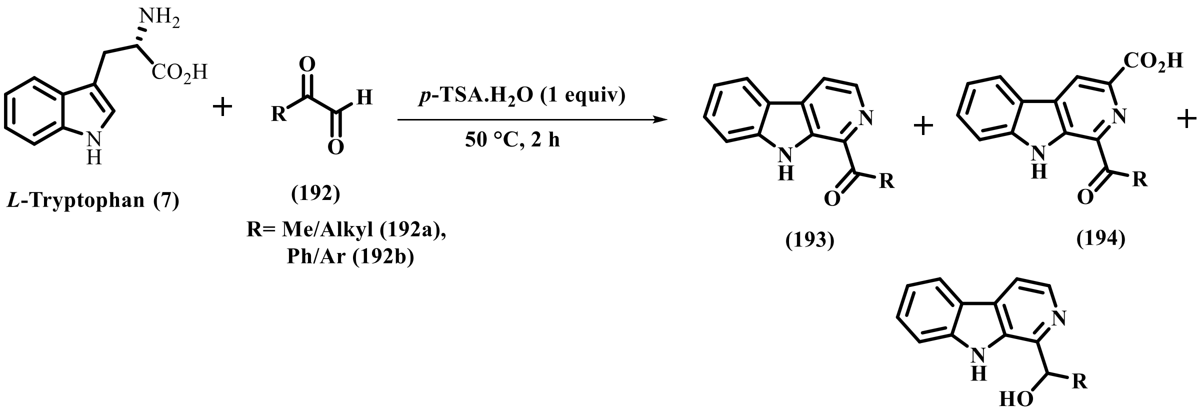


[a] Reaction conditions: Indole **6**, indole substituents **6a-j**, Pyrrole **175** (0.85 mmol, 1.0 equiv), 50% aqueous glyoxylic acid solution **190** (1.70 mmol, 2 equiv), $(NH_4)_2S_2O_8$ (1.70 mmol, 2 equiv), DMSO (1.0 mL) at room temperature. Isolated yields after chromatography.

After optimization of the reaction conditions, we carried out the reaction of substituted 3-formylindoles using 50% aqueous glyoxylic acid **190** with APS using optimized conditions and the products **20, 191, 20a-j** were obtained in 40-82 % yields (**Scheme 2.1**).

This formylation methodology was extended to pyrrole **175** and obtained pyrrole-2-carboxaldehyde **191** in 43 % yield. Quinolones **145** (quinoline, 2- and 4-methyl, 2-ethylester), isoquinoline **163**, pyridines **147** (pyridine, 2-hydroxy, 2,6-dibromo), pyrazine **146b**, *β*-carboline **80** imidazole, and 1,4-dimethoxybenzene, anisole and hydroquinone led to an inseparable mixture of products as well as decomposition products.

Previous reports on acylation of *β*-Carbolines:



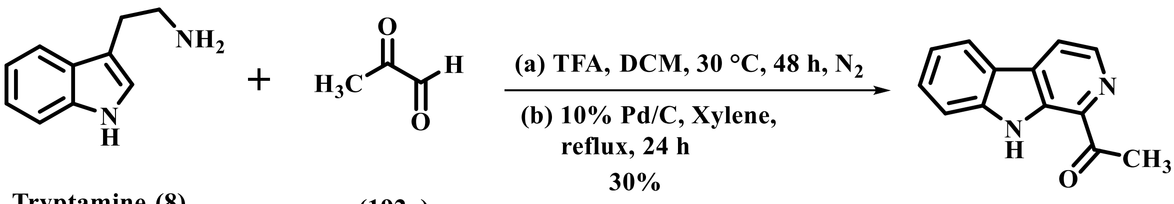
L-Tryptophan (7)

(192)
R= Me/Alkyl (192a), Ph/Ar (192b)

(193) (194) (195)

Eq. 49: Yang *et al.* (2006)

In 2006 Yang *et al.* were synthesized[78a] in single-step conversion of 1-substituted *β*-carbolines. *L*-tryptophan **7** treated with 1,2-dicarbonyl compounds **192** by using Pictet-Spengler methodology to afforded acylation of *β*-Carbolines with low yields (**Eq. 49**).



Tryptamine (8)

(192a)

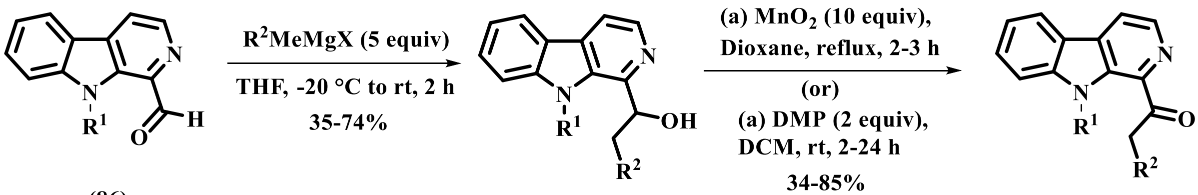
(196)

Eq. 50: Kumar and co-workers (2018)

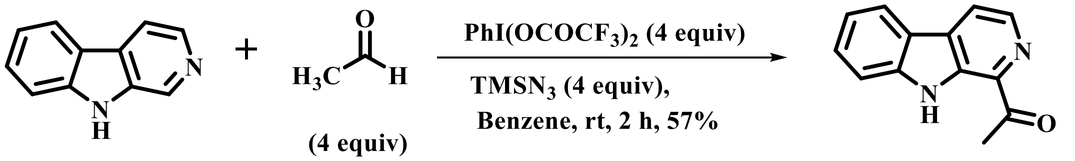
Tryptamine **8** reacts with pyruvaldehyde **192a** in the presence of trifluoroaceticacid catalyzed Pictet-Spengler cyclization, subsequently Pd/C mediated aromatisation to obtain the corresponding 1-acyl *β*-Carboline **196** with overall 30% yield by Kumar and co-workers[78b] in 2018 (**Eq. 50**).

Recently Balogh and co-workers reported[78c] 1-acetyl *β*-Carboline **196** starting from Kumujian C **86** treated with Grignard reagents transformed to 1-(ethyl-1-ol)-*β*-carbolines **197** followed by oxidation of alcohol **197** further transformed to corresponding ketones **193** in the presence of dess-martin periodinane (DMP) or activated manganese dioxide (MnO_2) with the overall good to moderate yields in the year 2021 (**Eq. 51**).

Eq. 51: Balogh and co-workers (2021)



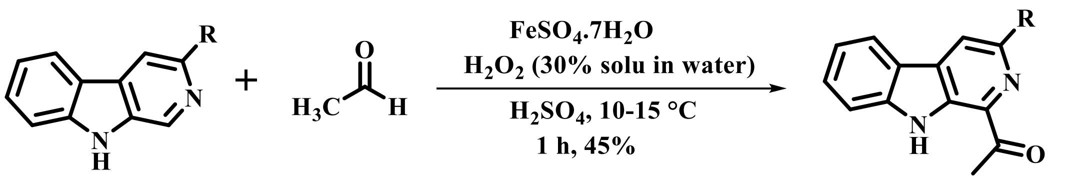
(86) (197) (193)



(80) (198) (196)

Eq. 52. Matcha *et al.* (2013)

In 2013 Matcha *et al.* was developed[78d] a cross-dehydrogenative coupling of β-carboline **86** with acetaldehyde **198** by using hypervalent iodine reagent [bis(trifluoro acetoxy)iodo]benzene $PhI(OCOCF_3)_2$ oxidant and sodium azide NaN_3 additive at room temperature to obtain the 1-acyl β-carboline **196** with 57% yield (**Eq. 52**).



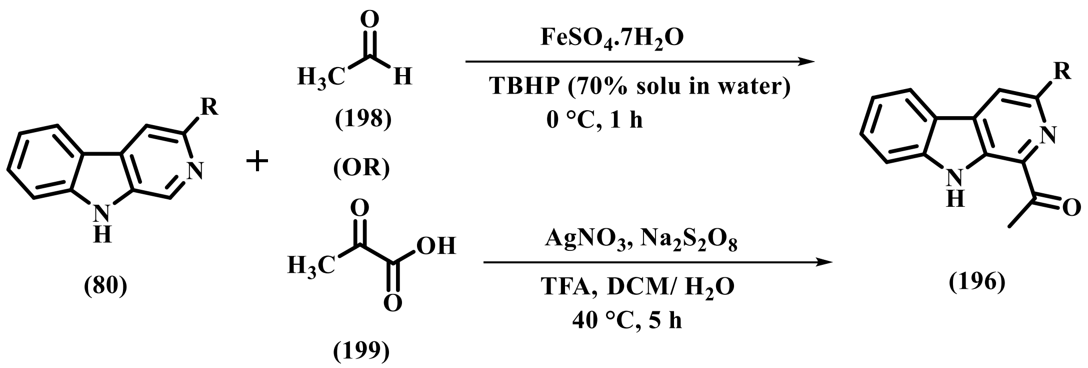
(80) (198) (196)

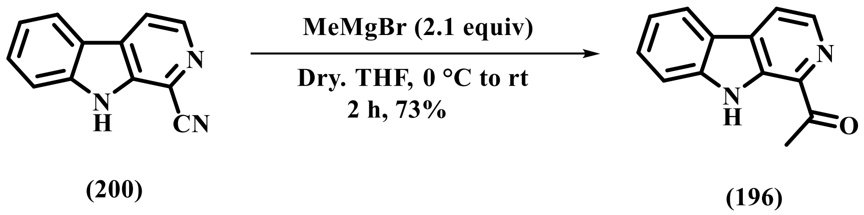
Eq. 53. Lin *et al.* (2011)

Lin *et al.* were reported[78e] Fe-catalyzed 1-substituted β-carboline involving minisci reaction from commercially available starting materials β-carboline **80** treated with acetaldehyde **198** by using H_2O_2 as oxidant maintain the temperature at 10-15 °C in 1 h to afforded the compound **196** with 45% yield (**Eq. 53**).

In 1995 Bracher *et al.* were reported[78f] acetylation of β-carbolines by using both acetaldehyde **198** and pyruvic acid **199** as the acetyl synthetic equivalents. In the case of acetaldehyde was an acetyl radical precursor with the combination of $FeSO_4$/TBHP redox system gave the 1-acetyl β-carboline **196** in 48% yield, if the amount of $FeSO_4$/TBHP redox system becomes twice, reaction time observed the yield enhances to 79%. Alternatively, they preferred another acetyl radical precursor pyruvic acid **199** in the presence of TFA mediated $AgNO_3$-catalyzed decarboxylative coupling with β-carboline **80** using sodium persulfate as an oxidant in two-phase system to obtain 1-acetyl β-carboline **196** in 33% yield, performing the same reaction with the combination $AgNO_3/Na_2S_2O_8$ with H_2SO_4 in homogeneous solution gave the compound 1-acetyl β-carboline **196** in trace amount (**Eq. 54**).

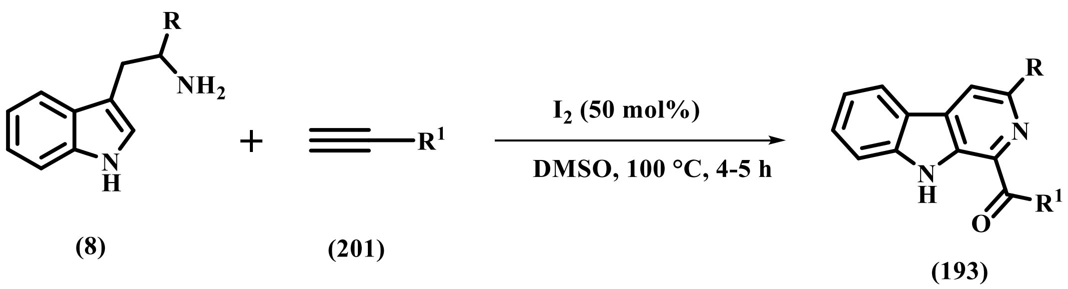
Eq. 54. Bracher *et al.* (1995)





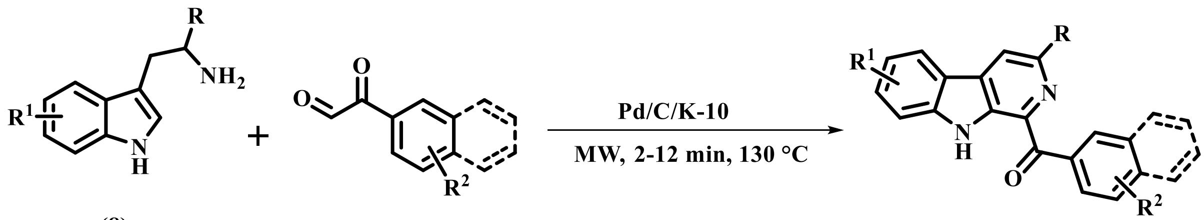
Eq. 55. Omar and co-workers (1997)

Omar and co-workers[79a] synthesized 1-acetyl β-carboline **196** by 1-cyano β-carboline **200** treated with Grignard reagent methyl magnesium bromide addition followed by hydrolysis to obtain the compound **196** with 73% yield (**Eq. 55**).



Eq. 56. Batra and co-workers (2017)

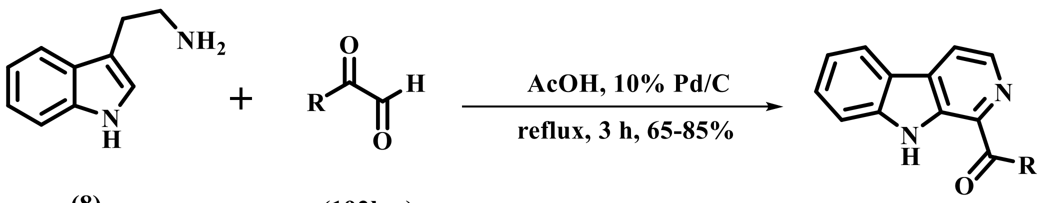
In 2017 Batra and co-workers reported[79b] 1-aroyl β-carbolines **193** by using terminal alkynes **201** as the precursor of 2-oxoaldehydes treated with tryptamine **8** and its substituents in the presence of iodine mediated oxidative Pictet-Spengler cyclization and followed by aromatisation to obtain the compound 1-substituted β-carbolines **193** with better yields (**Eq. 56**).



(8) (192b) (193)

Eq. 57. Kulkarni *et al.* (2009)

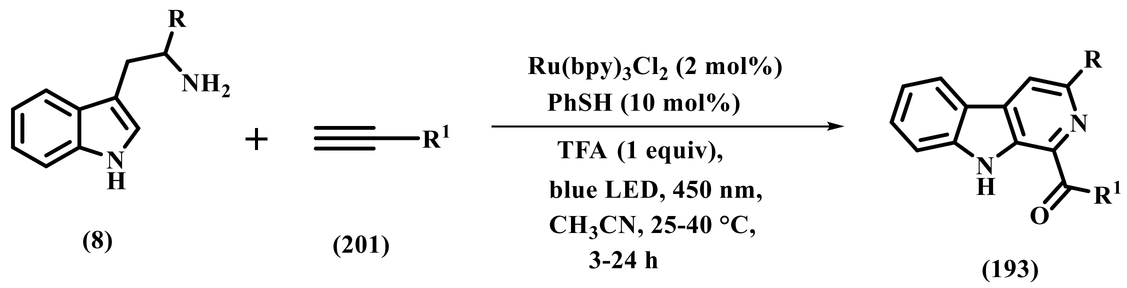
Kulkarni *et al.* were synthesized[79c] microwave-assisted 1-substituted (aroyl) β-carbolines **193** from tryptamine **8** and its substituents treated with arylglyoxals **192b** in the presence of bifunctional catalyst Pd/C/K-10 in three step domino reaction involving Pictet-Spengler cyclization subsequently aromatisation to afford the corresponding 1-substituted (aroyl) β-carbolines **193** in shorter reaction time with good to excellent yields (**Eq. 57**).



(8) (192b-c) (193)

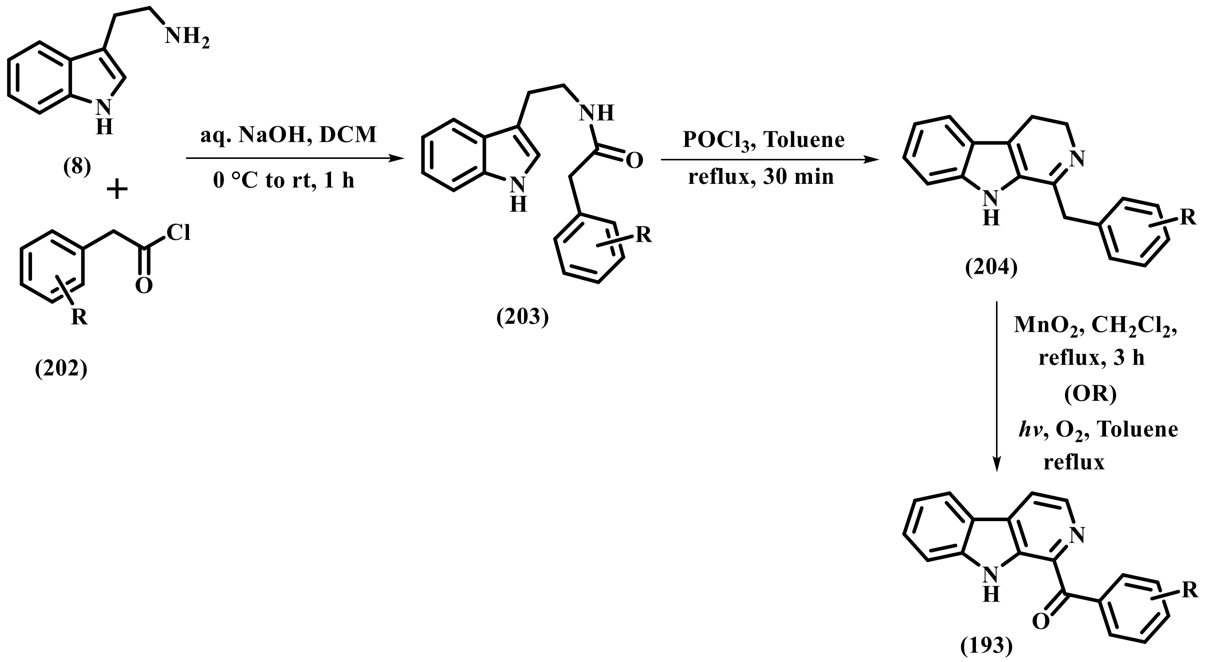
Eq. 58. Manda *et al.* (2016)

Manda *et al*. were reported[79d] 1-substituted β-carbolines **193** from tryptamine **8** reacts with arylglyoxals **192b-c** involving Pictet-Spengler cyclization the presence of glacial AcOH with Pd/C reflux in 3 h to obtain the cyclization and aromatized compound **193** with good to moderate yields (**Eq. 58**).



Eq. 59. Chalotra *et al.* (2018)

Chalotra *et al.* developed[79e] a Ru-photo redox catalyzed 1-substituted β-carbolines **193** by using alkynes **201** as the surrogates of 2-oxoaldehydes/1,2-diones. In the presence of visible light mediated aerobic oxidative conversion of alkyne to insitu generated 2-oxoaldehydes reacts with active nucleophile tryptamine **8** and its substituents to afforded 1-acetyl β-carbolines **193** with good to moderate yields in the year 2018 (**Eq. 59**).

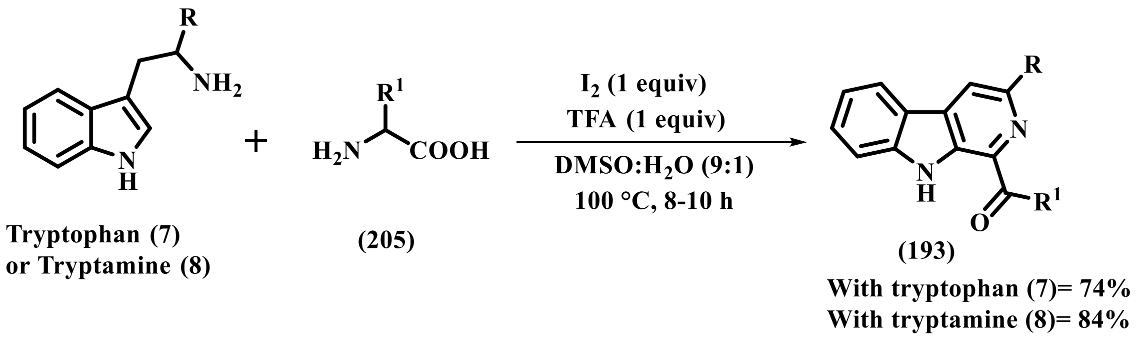


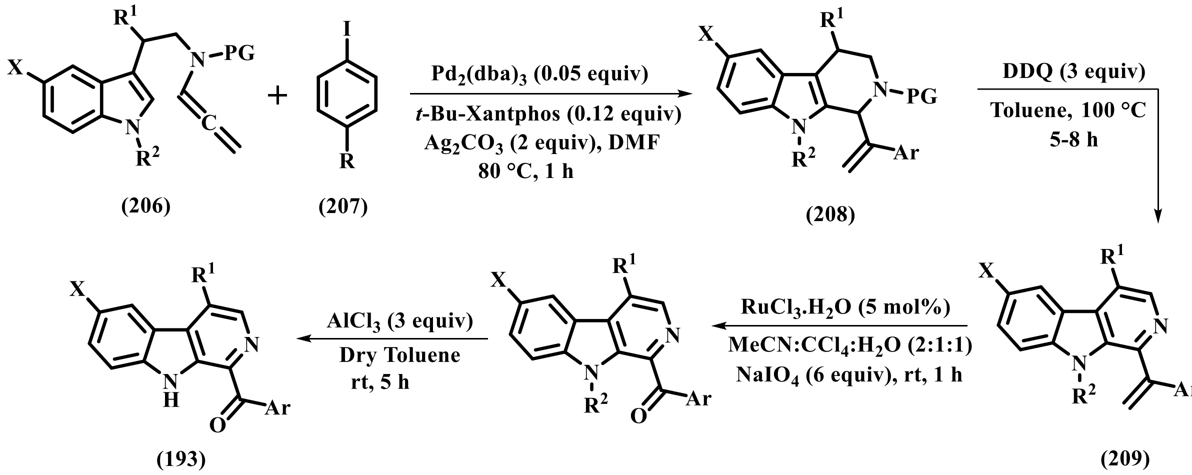
Eq. 60. Jenkins and co-workers (2006)

In 2006 Jenkins and co-workers[80a-b] described 1-aroyl β-carbolines **193** by tryptamine **8** treated with phenyl acetyl chloride **202** to gave the acetamide compound **203**, the acetamide derivative further undergoes Bischler-Napieralski reaction with $POCl_3$ in refluxing toluene to obtain the cyclized compound **204**, subsequently oxidized by MnO_2 in DCM refluxing method or another approach irradiation with 500 watts halogen lamp inducing reflux with toluene to produces the benzylic oxidation and fully aromatisation to form 1-aroyl β-carbolines **193** with good to moderate yields (**Eq. 60**).

Recently, in 2022 Samanta *et al.* reported[80c] one-pot tandem protocol for the synthesis of 1-aroyl *β*-carbolines **193** in in the presence of molecular iodine catalyzed, TFA mediated tryptophan (**7**)/tryptamine (**8**) with amino acid **205** in this process involves consecutive decarboxylation and oxidation followed by cyclization to afford the 1-substituted *β*-carbolines **193** with good yields (**Eq. 61**).

Eq. 61. Samanta *et al.* (2022)



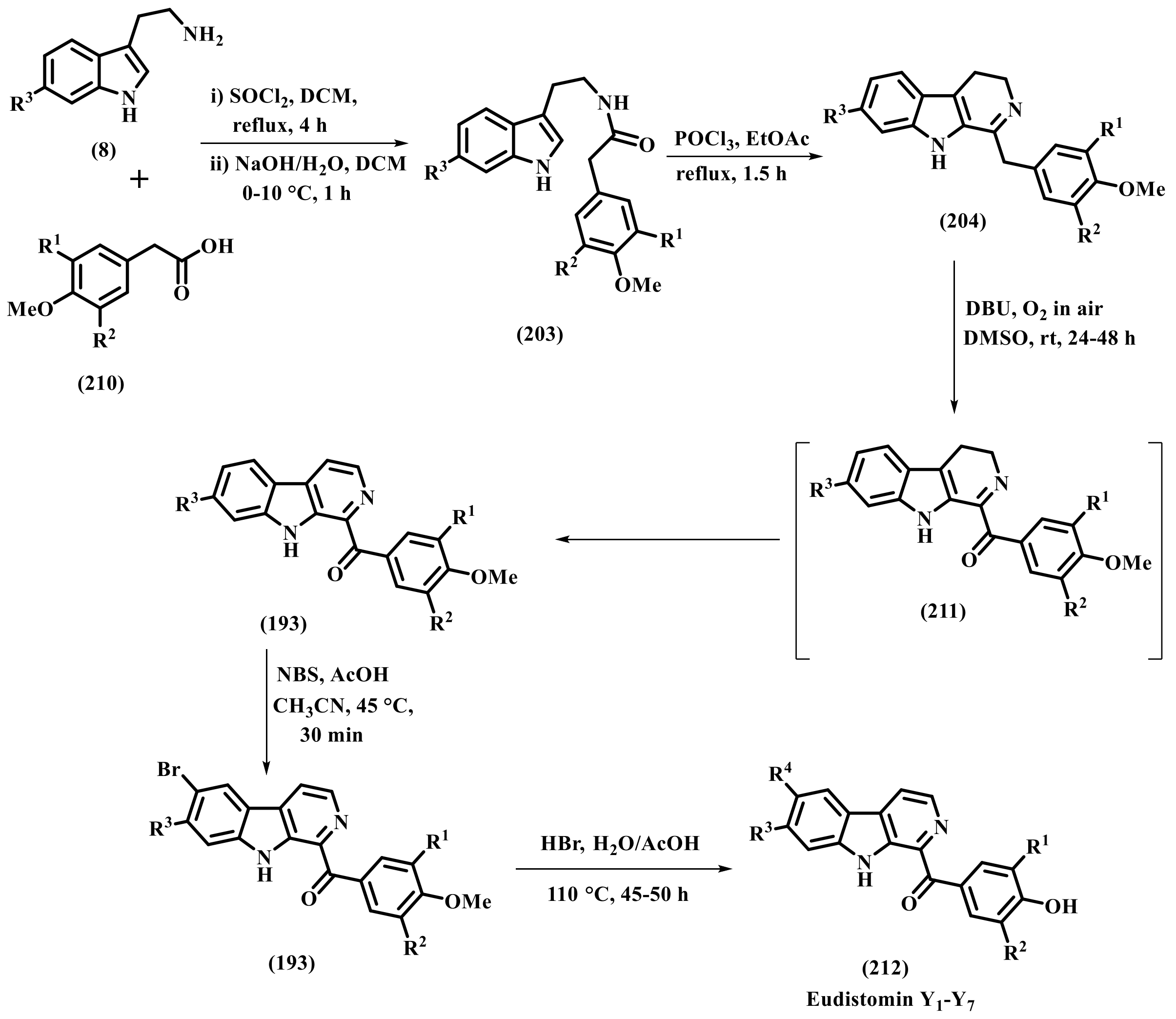


Eq. 62. Mondal *et al.* (2021)

In 2021 Mondal *et al.* were synthesized[80d] Pd-catalyzed 1-vinyltetrahydro *β*-carbolines **208** through cyclo condensation between *N*-allenyltryptamine **206** and aryl iodides **207** followed by DDQ-oxidation to obtain the corresponding *β*-carboline framework compound **209** and which are easily converted in to 1-aroyl *β*-carbolines **193** with moderate yields in pharmacological interesting biologically active *β*-carboline alkaloids (**Eq. 62**).

Trieu *et al.* were described[80e] for the synthesis of eudistomins Y_1-Y_7 by tryptamine **8** and its substituents reacts with substituted phenyl acetic acid **210** to gave the acetamide derivative **203** further involves Bischler-Napieralski reaction with $POCl_3$ in refluxing condition to obtain the cyclized compound **204**, subsequently tandem benzylic oxidation and aromatisation with DBU in DMSO under an atmospheric oxygen at room temperature to form benzylic oxidized product **211** and rapidly aromatisation to convert 1-aroyl *β*-carbolines **193** which was the precursor of *β*-carboline alkaloids eudistomin Y_1, Y_3, and Y_5. Upon the compound **193** treated with NBS in AcOH/CH_3CN preferably mono bromination at C-6 position occurred these brominated compounds are the precursors of *β*-carboline alkaloids eudistomin Y_2, Y_4, and Y_6. Further demethylation with aqueous HBr in AcOH to gave the desired products eudistomin Y_1-Y_7 (**212**) in the year 2013 (**Eq. 63**).

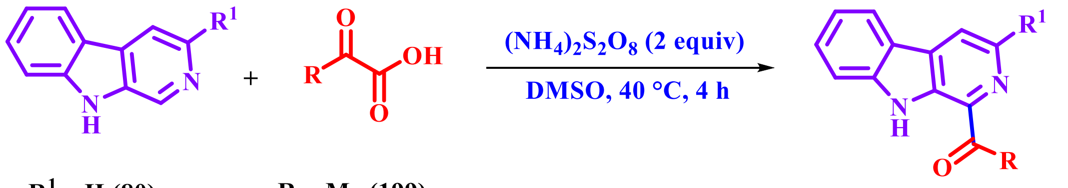
Eq. 63. Trieu *et al.* (2013)



β-Carboline **80** alkaloids are some indole **6** alkaloids that exhibits various biological activities and find more importance in medicinal chemistry.[81] Though formylation of *β*-carboline **80** leads to inseparable mixtures, acylation of β-carboline **80** with pyruvic acid **199** and phenyl glyoxylic acids **213** under APS-mediated methodology afforded 1-acyl-*β*-

carbolines **193** in moderate yields. The conventional method of acylation of β-carboline **80** involves a multistep sequence using protecting groups.[78c] β-Carboline **80** on reaction with pyruvic acid **199** and phenyl glyoxylic acid **213** by employing decarboxylative acylation were produced in 52-65 % yields (Scheme **2.2**).

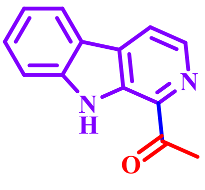
Scheme 2.2. Acylation of β-carbolines with $(NH_4)_2S_2O_8$ [a]



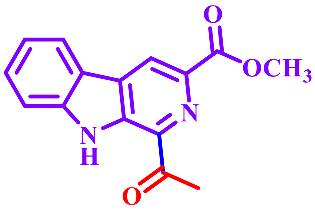
R^1 = H (80)
= COOMe (80a^1)

R = Me (199)
= Ph (213), 4-OMe Ph (213a),
= 3-bromo-4-OMe Ph (213b)

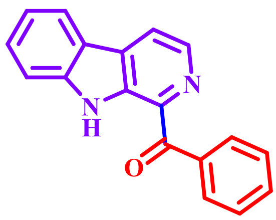
196, 105, 214, 214a-b



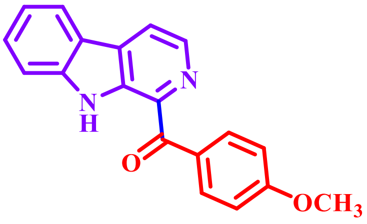
196, 52%



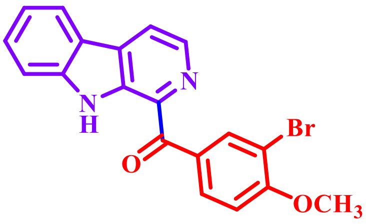
105, 59%



214, 56%



214a, 65%



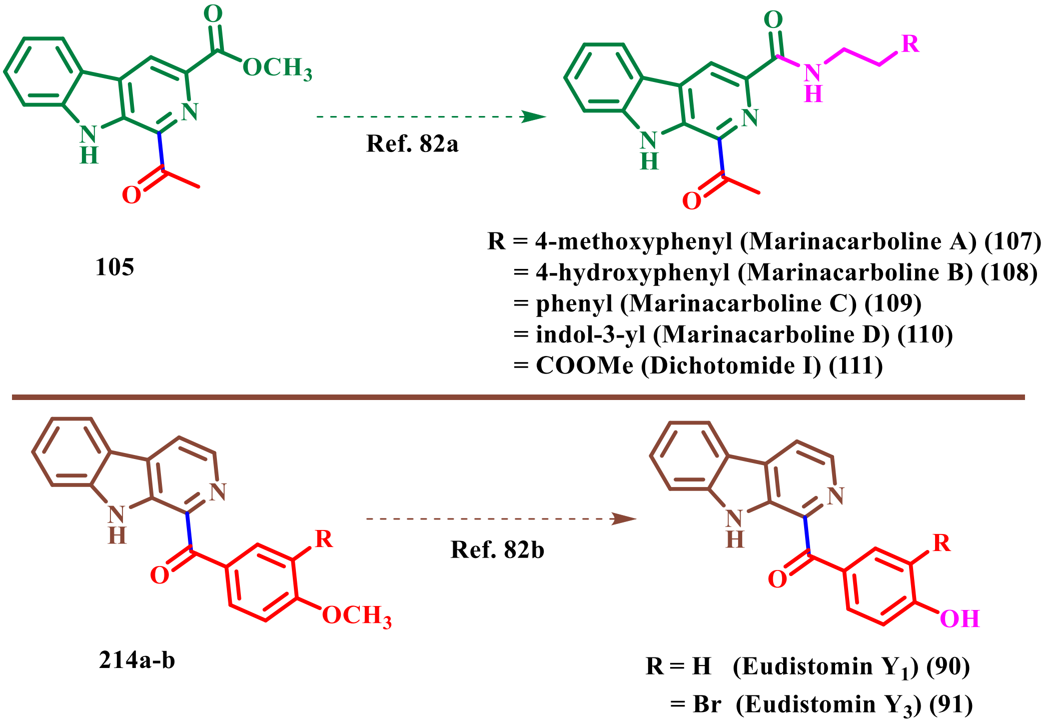
214b, 61%

[a] Reaction conditions: β-carbolines **80, 80a^1** (0.30 mmol, 1.0 equiv), α-ketoacids **199, 213, 213a-b** (1.5 equiv), APS (0.59 mmol, 2 equiv), DMSO (1.5 mL), 40 °C, 4 h. Isolated yields after chromatography.

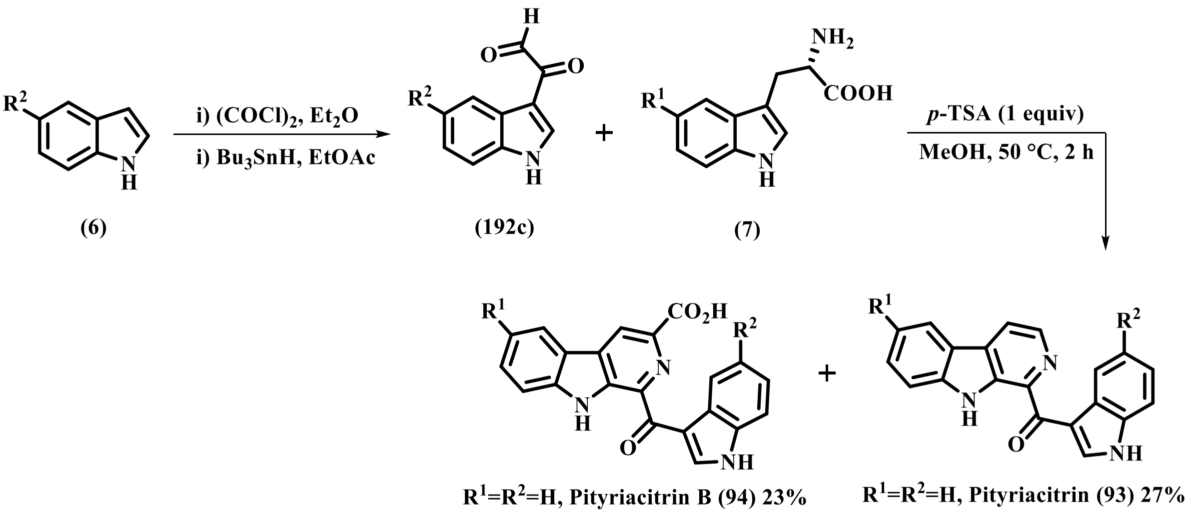
The starting materials **105, 214a-b** will be readily used for the synthesis of biologically active β-carboline alkaloids marinacarbolines (A-D) and eudistomins Y_1 and Y_3 as reported in the literature[82] (**Figure. 1.2**).

The marine β-carboline alkaloid pityriacitrin (1*H*-Indol-3-yl-9*H*-pyrido[3,4-*b*] indol-1-yl) methanone **93**) was first isolated from marine bacterium of the genus *Paracoccus sp.,*[83a] from the human pathogenic yeast *Malassezia furfur*[83b] in 1999 and recently from the marine fungus *Dichotomomyces cejpii*.[83c] Although only a few of reports are available, many of them involve multi-step sequence under harsh reaction conditions.

Figure 1.2 Possible alkaloids from 105 and 214a-b

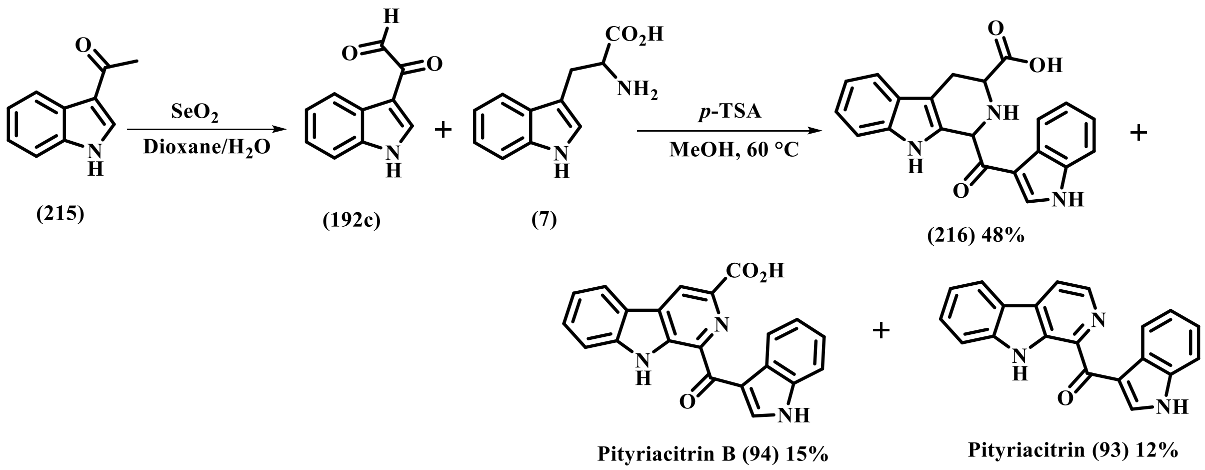


Previous reports on synthesis of *β*-carboline alkaloid Pityriacitrin:



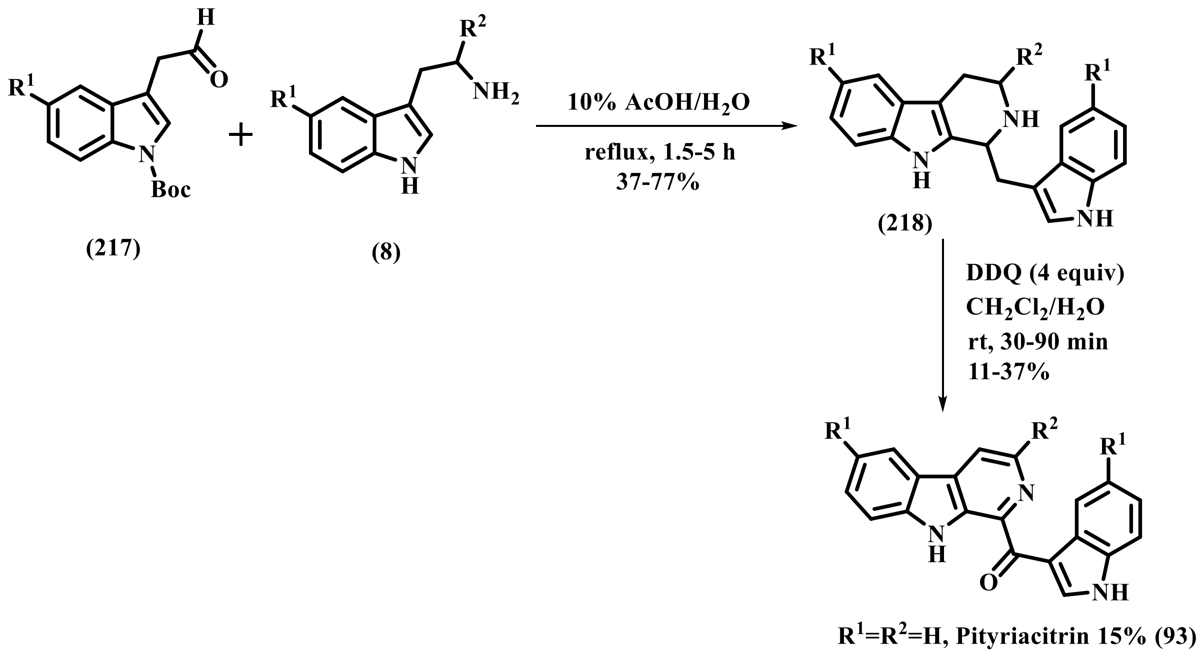
Eq. 64. Zhang *et al.* (2011)

Zhang *et al.* were reported[84a] acid-catalyzed Pictet-Spengler reaction by *L*-Tryptophan **7** and its substituents reacts with indole-3-glyoxal **192c** and its substituents in the presence of *p*-toluenesulfonicacid mediated Pictet-Spengler cyclization and aromatisation to obtain in single step *β*-carboline alkaloids pityriacitrin with 27% yield, and also synthesized pityriacitrin B with 23% yields and its derivatives with low yields in the year 2011 (**Eq. 64**).



Eq. 65. Xu *et al.* (2019)

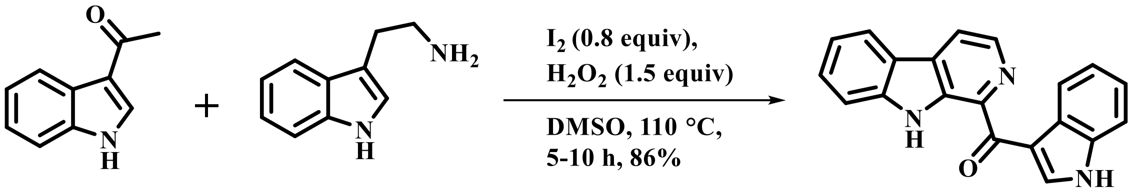
In 2019 Xu *et al.* synthesized[84b] β-carboline alkaloids by using Pictet-Spengler method with indole-3-glyoxal **192c** which was prepared from 3-acetyl indole **215** treated with tryptophan **7** in the presence of *p*-TSA mediated observed the mixture of compounds tetrahydro β-carboline **216** in 48%, pityriacitrin **93** in 12% and compound **94** pityriacitrin B with 15% yields (**Eq. 65**).



Eq. 66. Liew *et al.* (2014)

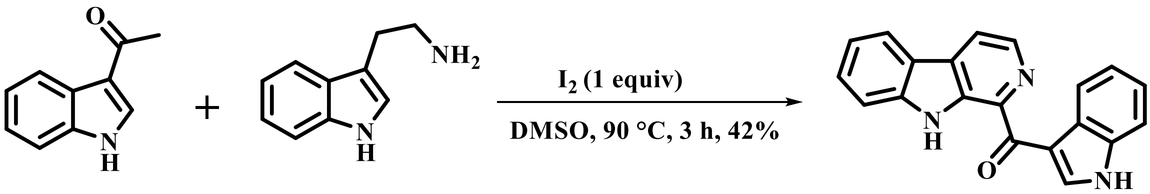
In 2014 Liew *et al.* were synthesized[84c] a series of 1-substituted β-carboline alkaloids from substituted indole-acetaldehydes **217** treated with substituted tryptamines **8** in the presence of 10% AcOH/H_2O under refluxing to gave the Pictet-Spengler cyclized compound

1-substituted tetrahydro *β*-carboline **218** followed by DDQ-mediated oxidation to afford the *β*-carboline alkaloid pityriacitrin with 15% yield (**Eq. 66**).



Eq. 67. Zhu *et al.* (2013)

Zhu *et al*. were developed[84d] cascade coupling protocol for the synthesis of *β*-carboline containing alkaloids pityriacitrin **93** and eudistomin Y_1-Y_6. Tryptamine **8** reacts with indole-3-glyoxal **192c** which is insitu generated from 3-acetyl indole **215** with the combination of I_2/DMSO (Kornblum oxidation) mediated, involving Pictet-Spengler condensation, and followed by aromatisation to obtain the *β*-carboline alkaloid pityriacitrin **93** with 86% yield (**Eq. 67**).

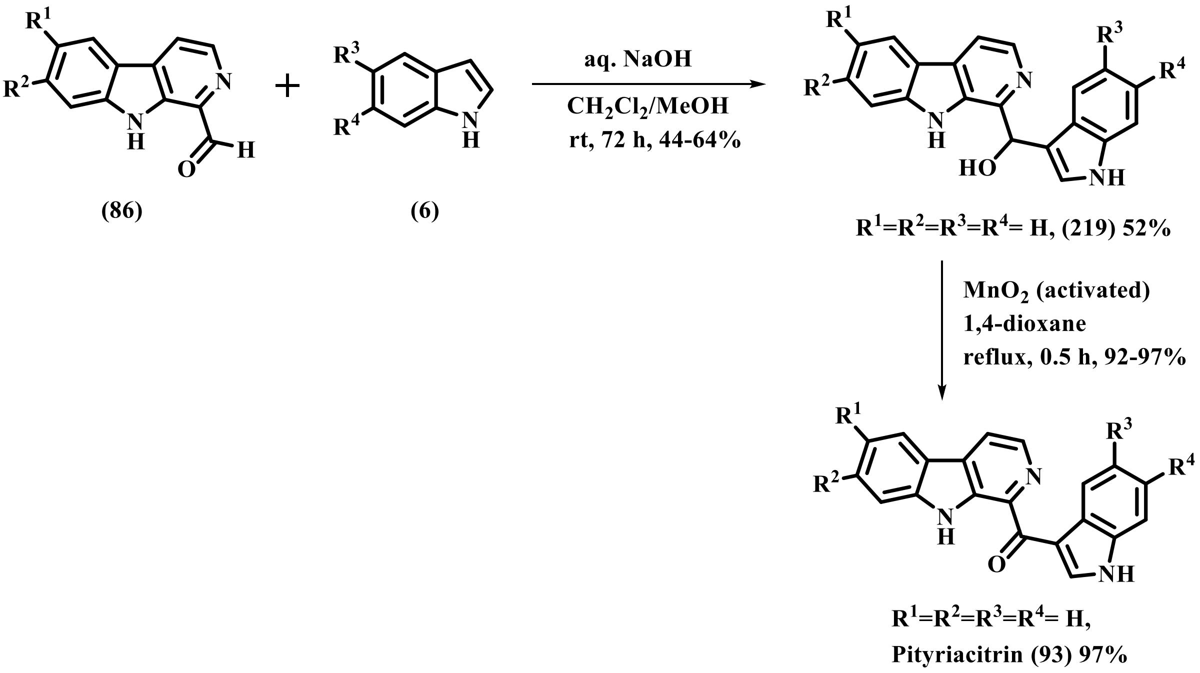


Eq. 68. Battini *et al.* (2014)

Battini *et al.* were developed[84e] iodine-mediated *β*-carboline containing alkaloids pityriacitrin **93** and pityriacitrin B **94**, marinacarbolines (A&B) **107-110**, eudistomin Y_1 **90** and fascaplysins. Tryptamine **8** treated with 3-acetyl indole **215** involving Pictet-Spengler methodology by using iodine/DMSO-mediated at 90 °C for 3 h to afford the desired product pityriacitrin **93** in a single-step with 42% yield (**Eq. 68**).

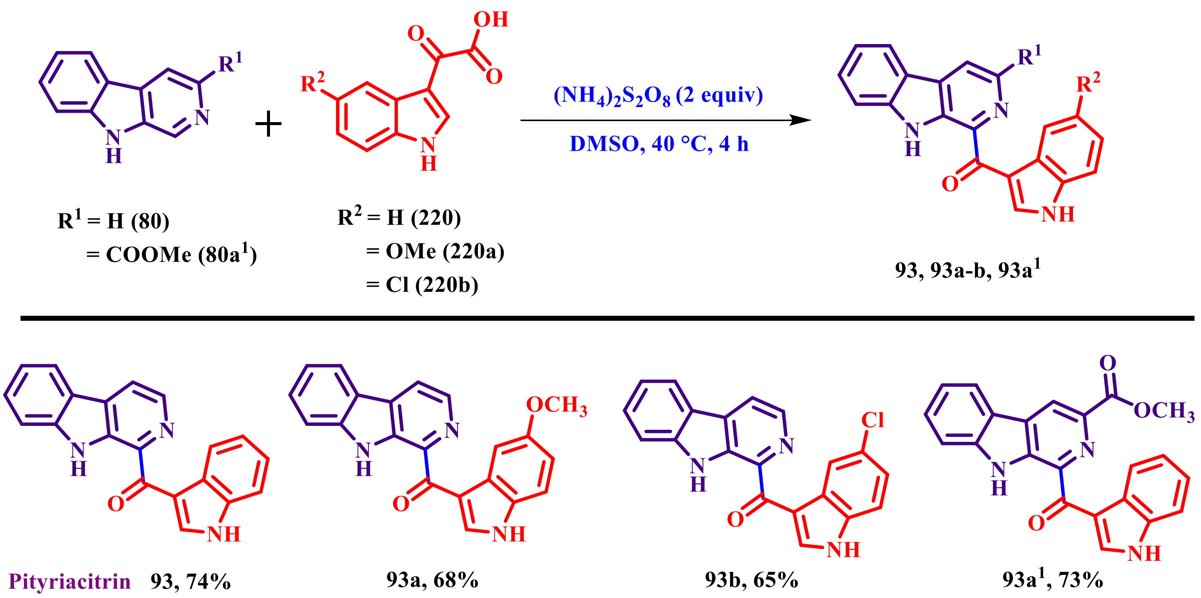
Milen and his group described[84f] for the synthesis of *β*-carboline based alkaloids pityriacitrin **93**, trigonostemines A-B, and hyrtiosulawesine. *β*-carboline-1-carboxaldehyde **86** and its substituents reacts with indole **6** and its substituents in the presence of aq. NaOH basic condition to obtain with the indole coupled product secondary alcoholic compound **219**, further this alcoholic compound **219** treated with activated MnO_2 inducing reflux condition to afford the *β*-carboline alkaloid pityriacitrin **93** with overall 50% yield (**Eq. 69**).

Eq. 69. Milen and group (2019)



Therefore, we have developed a methodology and extended for the total synthesis of pityriacitrin **93** by the reaction of *β*-carbolines **80** with indole-3-glyoxylic acid **220** in 74% yield in a single step without using any protecting groups (Scheme **2.3**).

Scheme 2.3. Reaction of *β*-carbolines with indole-3-glyoxylic acids using $(NH_4)_2S_2O_8$ [a]

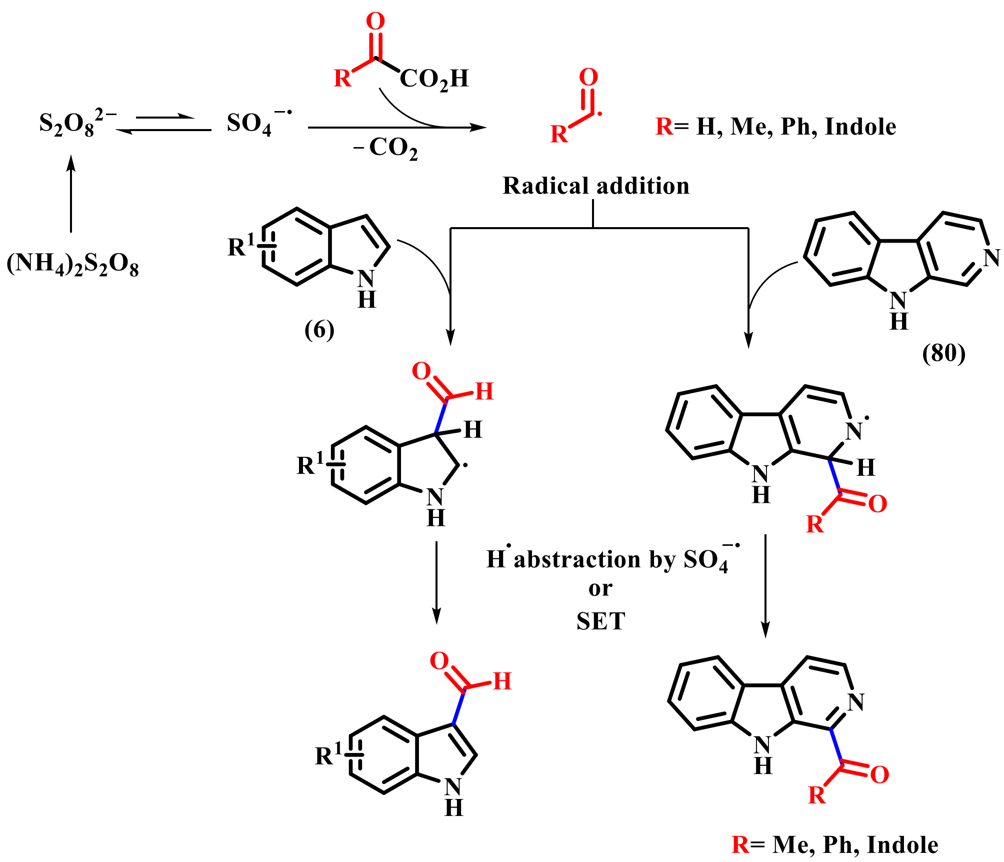


[a] Reaction conditions: *β*-carbolines **80, 80a[1]** (0.30 mmol, 1.0 equiv), indole-3-glyoxylic acid **220, 220a-b** (1.5 equiv), $(NH_4)_2S_2O_8$ (0.59 mmol, 2 equiv), DMSO (1.5 mL), 40 °C, 4 h, Isolated yields after chromatography.

The methodology was extended with substituted pityriacitrins **93, 93a-b, 93a[1]** in 65-74 % yields. Indole did not undergo acetylation or aroylation under our reaction conditions.

We postulated a mechanism based on the previous literature reports[62a] that of *α*-oxo/ketoacids with *N*-heterocycles. The sulfate radical anion formed from APS can readily abstracts hydrogen radical from available α-ketoacids to form the formyl or acyl radical with extrusion of CO_2. This generated radical species adds to *N*-heterocycles and subsequent, hydrogen radical abstraction by a sulfate radical anion or by a mechanism of single-electron transfer (SET) to the corresponding carbonyl products (Scheme **2.4**).

Scheme 2.4. Plausible mechanism



1.3. Conclusion:

We have developed a direct metal-free decarboxylative method for the formylation of indoles and acylation of β-carbolines using α-oxo/ketoacids **144** and $(NH_4)_2S_2O_8$ as oxidant. The reactions were carried out from room temperature to 40 °C and does not require any special reaction conditions, and the products were obtained in good to moderate yields. This methodology was extended to acylation of β-carbolines, and an alkaloid, pityriacitrin **93**, was prepared in 74% yield in a single step.

1.4. Experimental section:

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

NMR spectra: DMSO-d_6 and $CDCl_3$ are used as the NMR solvents to record ^1H and ^{13}C NMR spectra were recorded at BRUKER-ADVANCE NMR analyser at 400 and 100 MHz or at 500 and 125 MHz respectively. Chemical shifts values were assigned with respect to TMS ($\delta = 0$) for ^1H NMR, and relative to NMR solvent residual peaks in $CDCl_3$ resonance ($\delta = 77.12$) and DMSO-d_6 ($\delta = 39.52$) for ^{13}C NMR. Data are presented as follows: chemical shifts, multiplicity (br s = broad singlet, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz) and integration.

Mass spectral analysis: Shimadzu LCMS 2010A mass spectrometer was used. In all the cases EtOAc or DCM or MeOH were used to dissolve the compounds. HRMS were obtained from TOF and quadrupole mass analyzer types.

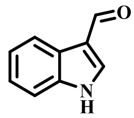
General procedure for formylation:

Indole **6** (0.853 mmol, 1 equiv) was dissolved in DMSO (1 mL) in an RB flask closed with a guard tube, and then a 50% aqueous glyoxylic acid solution **190** (1.70 mmol, 2 equiv) was added followed by $(NH_4)_2S_2O_8$ (1.70 mmol, 2 equiv). The resulting solution was stirred at room temperature for 0.25−48 h. After the reaction had reached completion as determined by using TLC, the reaction was quenched with water (10 mL), the mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated using a rotary evaporator. The crude product was further purified by column chromatography on silica gel with an ethyl acetate/hexane solvent mixture.

General procedure for acylation:

β-Carboline **80** (0.30 mmol, 1 equiv) was dissolved in DMSO (1.5 mL) in an RB flask closed with a guard tube, and then pyruvic acid **199**, phenyl glyoxylic acid **213**, or indole-3-glyoxylic acid **220** (0.445 mmol, 1.5 equiv) was added followed by $(NH_4)_2S_2O_8$ (0.59 mmol, 2 equiv). The resulting solution was stirred in a preheated oil bath at 40 °C for 4 h. After the reaction had reached completion as determined by using TLC, the reaction was quenched with water (10 mL), the mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated using a rotary evaporator. The crude product was further purified by column chromatography on silica gel with an ethyl acetate/hexane solvent mixture.

1*H*-Indole-3-carboxaldehyde (20)



20

R*f*: 0.5 EtOAc/hexane (1:1)

Physical state: yellow solid

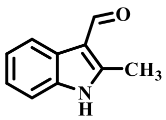
Yield: 89 mg (72 %)

M. P: 189-191 °C (Lit.[73a] 190-192 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.15 (1H, br s), 9.95 (1H, s), 8.28 (1H, s), 8.13 (1H, d, *J* = 7.4 Hz), 7.53 (1H, d, 7.85 Hz), 7.28-7.21 (2H, m).

^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ 185.4, 138.8, 137.5, 124.6, 123.9, 122.6, 121.3, 118.6, 112.8.

2-Methyl-1*H*-indole-3-carboxaldehyde (20a)



20a

R*f*: 0.42 EtOAc/hexane (1:1)

Physical state: orange solid

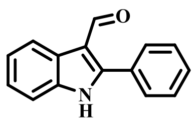
Yield: 96 mg (79 %)

M.P: 191-194 °C (Lit.[73h] 195-200 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 11.97 (1H, br s), 10.05 (1H, s), 8.06-8.04 (1H, m), 7.40-7.38 (1H, m), 7.19-7.13 (2H, m), 2.67 (3H, s).

^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$): δ 184.6, 149.0, 135.8, 126.0, 123.0, 122.3, 120.4, 114.1, 111.8, 11.9.

2-Phenyl-1*H*-indole-3-carboxaldehyde (20b)



20b

R_f: 0.57 EtOAc/hexane (4:6)

Physical state: yellow solid

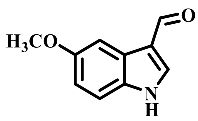
Yield: 94 mg (82 %)

M.P: 248-251 °C (Lit.[73a] 250-252 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.41 (1H, br s), 9.98 (1H, s), 8.23 (1H, d, J = 7.5 Hz), 7.78 (2H, d, J = 6.8 Hz), 7.59-7.56 (3H, m), 7.52 (1H, d, J = 7.8 Hz), 7.3-7.23 (2H, m).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 185.9, 149.5, 136.4, 130.3, 130.2, 129.4, 126.2, 124.1, 122.9, 121.5, 113.9, 112.4.

5-Methoxy-1*H*-indole-3-carboxaldehyde (20c)



20c

R_f: 0.33 EtOAc/hexane (1:1)

Physical state: orange solid

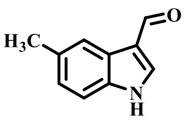
Yield: 95 mg (80 %)

M.P: 175-178 °C (Lit.[73a] 180-181 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.01 (1H, br s), 9.90 (1H, s), 8.21 (1H, d, J = 3.2 Hz), 7.60 (1H, d, J = 2.5 Hz), 7.41 (1H, dd, J = 8.7, 0.2 Hz), 6.90 (1H, dd, J = 8.8, 2.5 Hz), 3.79 (3H, s).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 185.3, 156.1, 138.8, 132.2, 125.3, 118.5, 113.7, 113.6, 103.0, 55.7.

5-Methyl-1*H*-indole-3-carboxaldehyde (20d)



20d

R_f: 0.42 EtOAc/hexane (1:1)

Physical state: orange solid

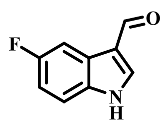
Yield: 90 mg (74 %)

M.P: 148-151 °C (Lit. [73a] 149-150 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.02 (1H, br s), 9.90 (1H, s), 8.21 (1H, d, J = 3.1 Hz), 7.91 (1H, d, J = 0.7 Hz), 7.40 (1H, d, J = 8.2 Hz), 7.08 (1H, dd, J = 8.3, 1.5 Hz), 2.40 (3H, s).

$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 185.3, 138.8, 135.8, 131.5, 125.3, 124.8, 121.0, 118.3, 112.4, 21.6.

5-Fluoro-1*H*-indole-3-carboxaldehyde (20e)



20e

R$_f$: 0.3 EtOAc/hexane (1:1)

Physical state: yellow solid

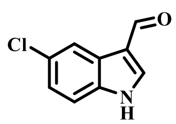
Yield: 75 mg (63 %)

M.P: 142-145 °C (Lit.[73a] 144-146 °C)

^1H NMR (500 MHz, DMSO-d_6): δ 12.23 (1H, br s), 9.92 (1H, s), 8.35 (1H, d, J = 2.8 Hz), 7.77 (1H, dd, J = 9.5, 2.6 Hz), 7.53 (1H, dd, J = 8.8, 4.5 Hz), 7.13-7.09 (1H, m).

$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 185.4, 160.1, 139.9, 134.0, 125.2, 118.6, 114.2, 112.1, 106.2.

5-Chloro-1*H*-indole-3-carboxaldehyde (20f)



20f

R$_f$: 0.3 EtOAc/hexane (1:1)

Physical state: yellow solid

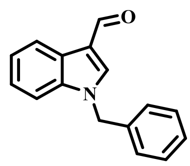
Yield: 85 mg (72 %)

M.P: 210-213 °C (Lit.[73a] 214-216 °C)

^1H NMR (500 MHz, DMSO-d_6): δ 12.29 (1H, br s), 9.93 (1H, s), 8.36 (1H, d, J = 3.1 Hz), 8.07 (1H, d, J = 2.0 Hz), 7.54 (1H, d, J = 8.6 Hz), 7.28 (1H, dd, J = 8.6, 2.1 Hz).

$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 185.5, 139.8, 135.9, 127.2, 125.7, 123.9, 120.3, 118.0, 114.5.

1-Benzyl-1*H*-indole-3-carboxaldehyde (20g)



20g

R$_f$: 0.66 EtOAc/hexane (1:1)

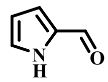
Physical state: yellow oil

Yield: 85 mg (75 %)

^1H NMR (500 MHz, $CDCl_3$): δ 9.97 (1H, s), 8.33-8.31 (1H, m), 7.68 (1H, s), 7.34-7.28 (6H, m), 7.17-7.15 (2H, m), 5.33 (2H, s).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 184.6, 138.5, 137.4, 135.3, 129.1, 128.4, 127.2, 125.5, 124.1, 123.0, 122.1, 118.5, 110.4, 50.9.

1*H*-Pyrrole-2-carboxaldehyde (191)



191

R*f*: 0.44 EtOAc/hexane (2:8)

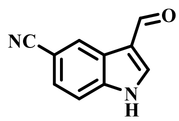
Physical state: viscous oil

Yield: 61 mg (43 %)

^1H NMR (500 MHz, $CDCl_3$): δ 10.41 (1H, br s), 9.52 (1H, br s), 7.196-7.195 (1H, m), 7.03-7.02 (1H, m), 6.38-6.36 (1H, m).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 179.5, 132.8, 127.1, 122.0, 111.3.

3-Formyl-1*H*-indole-5-carbonitrile (20i)



20i

R*f*: 0.38 EtOAc/hexane (7:3)

Physical state: yellow solid

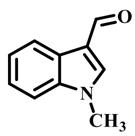
Yield: 47 mg (40 %)

M.P: 242-245 °C (Lit.[73i] 241-243 °C)

^1H NMR (500 MHz, DMSO-*d*$_6$): δ 12.57 (1H, br s), 9.99 (1H, s), 8.49 (1H, s), 8.45 (1H, d, J = 0.9 Hz), 7.70 (1H, dd, J = 8.4, 0.6 Hz), 7.63 (1H, dd, J = 8.4, 1.6 Hz).

$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-*d*$_6$): δ 185.8, 140.6, 139.2, 126.8, 126.1, 124.4, 120.3, 118.4, 114.4, 104.8.

1-Methyl-1*H*-indole-3-carboxaldehyde (20j)



20j

R*f*: 0.38 EtOAc/hexane (1:1)

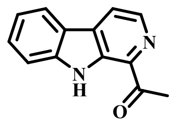
Physical state: yellow oil

Yield: 92 mg (76 %)

^1H NMR (500 MHz, $CDCl_3$): δ 9.95 (1H, s), 8.30-8.28 (1H, m), 7.63 (1H, s), 7.35-7.29 (3H, m), 3.83 (3H, s).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 184.4, 139.2, 137.8, 125.2, 124.0, 122.9, 122.0, 118.0, 109.8, 33.6.

1-(9*H*-pyrido[3,4-*b*]indol-1-yl)ethan-1-one (196)



196

R$_f$: 0.71 EtOAc/hexane (1:9)

Physical state: yellow solid

Yield: 32 mg (52 %)

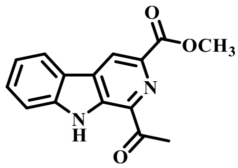
M.P: 205-208 °C (Lit.[78a] 207-209 °C)

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.31 (1H, br s), 8.53 (1H, d, J = 4.9 Hz), 8.14-8.13 (2H, m), 7.61-7.56 (2H, m), 7.34-7.31 (1H, m), 2.89 (3H, s).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 203.3, 141.1, 138.1, 136.0, 135.4, 131.5, 129.2, 121.8, 120.7, 120.5, 119.0, 111.9, 25.9.

HRMS (ESI-TOF) Calcd for $C_{13}H_{10}N_2O$ $[M+H]^+$ 211.0866, found: 211.0866.

Methyl-1-acetyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (105)



105

R$_f$: 0.69 EtOAc/hexane (1:9)

Physical state: yellow solid

Yield: 35 mg (59 %)

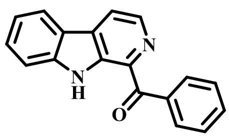
M.P: 221-224 °C (Lit.[84e] 222-224 °C)

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.43 (1H, br s), 8.92 (1H, d, J = 0.4 Hz), 8.10 (1H, dd, J = 7.9, 0.6 Hz), 7.57-7.52 (2H, m), 7.32-7.29 (1H, m), 4.00 (3H, s), 2.88 (3H, s).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 203.2, 166.0, 141.4, 136.8, 136.4, 135.2, 131.8, 129.7, 122.0, 121.6, 121.2, 120.9, 112.3, 52.7, 25.6.

HRMS (ESI-TOF) Calcd for $C_{15}H_{12}N_2O_3$ $[M+H]^+$ 269.0921, found: 269.0925.

Phenyl-(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (214)



214

R$_f$: 0.79 EtOAc/hexane (3:7)

Physical state: yellow solid

Yield: 45 mg (56 %)

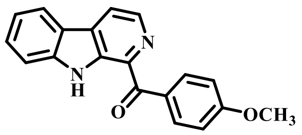
M.P: 137-140 °C (Lit.[80e] 139-139.5 °C)

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.49 (1H, br s), 8.63 (1H, d, J = 4.9 Hz), 8.36-8.34 (2H, m), 8.20-8.17 (2H, m), 7.65-7.60 (3H, m), 7.58-7.55 (2H, m), 7.38-7.35 (1H, m).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 195.5, 141.0, 138.0, 137.5, 137.3, 136.3, 132.3, 131.6, 131.2, 129.2, 128.0, 121.8, 120.8, 120.7, 118.5, 112.0.

HRMS (ESI-TOF) Calcd for $C_{18}H_{12}N_2O$ $[M+H]^+$ 273.1022, found: 273.1024.

(4-Methoxyphenyl) (9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (214a)



214a

R$_f$: 0.67 EtOAc/hexane (3:7)

Physical state: yellow solid

Yield: 58 mg (65 %)

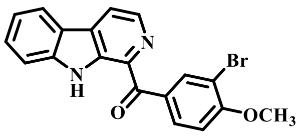
M.P: 181-184 °C (Lit.[80e] 184-185 °C)

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.49 (1H, br s), 8.62 (1H, d, J = 4.9 Hz), 8.49-8.46 (2H, m), 8.18 (1H, d, J = 7.8 Hz), 8.16 (1H, d, J = 4.9 Hz), 7.63-7.58 (2H, m), 7.36-7.33 (1H, m), 7.06-7.04 (2H, m), 3.92 (3H, s).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 193.4, 163.2, 141.0, 137.8, 137.2, 136.9, 133.8, 131.5, 130.2, 129.1, 121.7, 120.9, 120.6, 118.1, 113.4, 111.9, 55.4.

HRMS (ESI-TOF) Calcd for $C_{19}H_{14}N_2O_2$ $[M+H]^+$ 303.1128, Found: 303.1127.

(3-Bromo-4-methoxyphenyl) (9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (214b)



214b

R$_f$: 0.64 EtOAc/hexane (3:7)

Physical state: yellow solid

Yield: 69 mg (61 %)

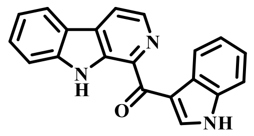
M.P: 196-199 °C (Lit.[80e] 196-196.5 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.01 (1H, br s), 8.56 (1H, d, J = 1.7 Hz), 8.53 (1H, d, J = 4.8 Hz), 8.42 (1H, d, J = 4.8 Hz), 8.36 (1H, dd, J = 8.6, 1.6 Hz), 8.30 (1H, d, J = 7.8 Hz), 7.81 (1H, d, J = 8.2 Hz), 7.60 (1H, t, J = 7.6 Hz), 7.31-7.26 (2H, m), 3.96 (3H, s).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 190.7, 159.1, 142.1, 137.5, 136.8, 136.3, 136.1, 133.3, 131.5, 131.3, 129.4, 122.2, 120.6, 120.5, 119.2, 113.4, 112.3, 110.5, 57.1.

HRMS (ESI-TOF) Calcd for $C_{19}H_{13}BrN_2O_2$ $[M+H]^+$ 381.0233, found: 381.0236.

(1*H*-Indol-3-yl) (9*H*-pyrido[3,4-*b*]indol-1-yl)methanone or Pityriacitrin (93)



93

R_f: 0.46 EtOAc/hexane (3:7)

Physical state: yellow solid

Yield: 68 mg (74 %)

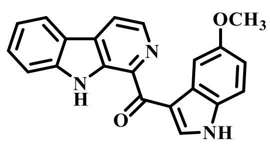
M.P: 236-239 °C (Lit.[84d] 237-239 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.13 (1H, br s), 12.01 (1H, br s), 9.27 (1H, d, J = 3.1 Hz), 8.59-8.56 (2H, m), 8.39 (1H, d, J = 4.9 Hz), 8.30 (1H, d, J = 7.8 Hz), 7.85 (1H, d, J = 8.1 Hz), 7.60-7.57 (2H, m), 7.30-7.27 (3H, m).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 187.8, 142.0, 138.9, 138.3, 137.4, 136.4, 135.5, 131.2, 129.1, 127.6, 123.3, 122.5, 122.13, 122.12, 120.5, 120.3, 118.3, 114.7, 113.4, 112.7.

HRMS (ESI-TOF) Calcd for $C_{20}H_{13}N_3O$ $[M+H]^+$ 312.1131, found: 312.1135.

(5-Methoxy-1*H*-indol-3-yl) (9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (93a)



93a

R_f: 0.38 EtOAc/hexane (3:7)

Physical state: yellow solid

Yield: 69 mg (68 %)

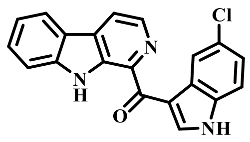
M.P: 240-243 °C (Lit.[84a] 214-216 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.02 (2H, br s), 9.24 (1H, d, J = 3.0 Hz), 8.56 (1H, d, J = 4.8 Hz), 8.39 (1H, d, J = 4.8 Hz), 8.30 (1H, d, J = 7.8 Hz), 8.12 (1H, d, J = 2.1 Hz), 7.86 (1H, d, J = 8.2 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.47 (1H, d, J = 8.7 Hz), 7.28 (1H, t, J = 7.4 Hz), 6.91 (1H, dd, J = 8.7, 2.3 Hz), 3.86 (3H, s).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 187.7, 156.1, 142.0, 138.9, 138.4, 137.3, 135.5, 131.22, 131.20, 129.1, 128.5, 122.1, 120.5, 120.2, 118.3, 114.6, 113.5, 113.4, 113.2, 103.9, 55.7.

HRMS (ESI-TOF) Calcd for $C_{21}H_{15}N_3O_2$ $[M+H]^+$ 342.1237, found: 342.1242.

(5-Chloro-1*H*-indol-3-yl) (9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (93b)



93b

R$_f$: 0.38 EtOAc/hexane (3:7)

Physical state: yellow solid

Yield: 67 mg (65 %)

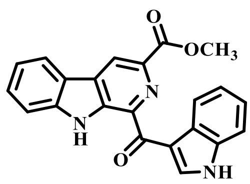
M.P: 279-282 °C

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.29 (1H, br s), 12.02 (1H, br s), 9.35 (1H, d, *J* = 3.1 Hz), 8.60 (1H, d, *J* = 2.1 Hz), 8.57 (1H, d, *J* = 4.9 Hz), 8.39 (1H, d, *J* = 4.9 Hz), 8.29 (1H, d, *J* = 7.8 Hz), 7.85 (1H, d, *J* = 8.2 Hz), 7.61-7.57 (2H, m), 7.31-7.26 (2H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$): δ 187.7, 142.1, 139.4, 138.5, 137.5, 135.6, 134.9, 131.3, 129.2, 128.9, 127.2, 123.3, 122.2, 121.4, 120.5, 120.4, 118.6, 114.4, 114.3, 113.5.

HRMS (ESI-TOF) Calcd for $C_{20}H_{12}ClN_3O$ $[M+H]^+$ 346.0742, found: 346.0742.

Methyl 1-(1*H*-indole-3-carbonyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (93a^1)



93a^1

R$_f$: 0.41 EtOAc/hexane (3:7)

Physical state: yellow solid

Yield: 59 mg (73 %)

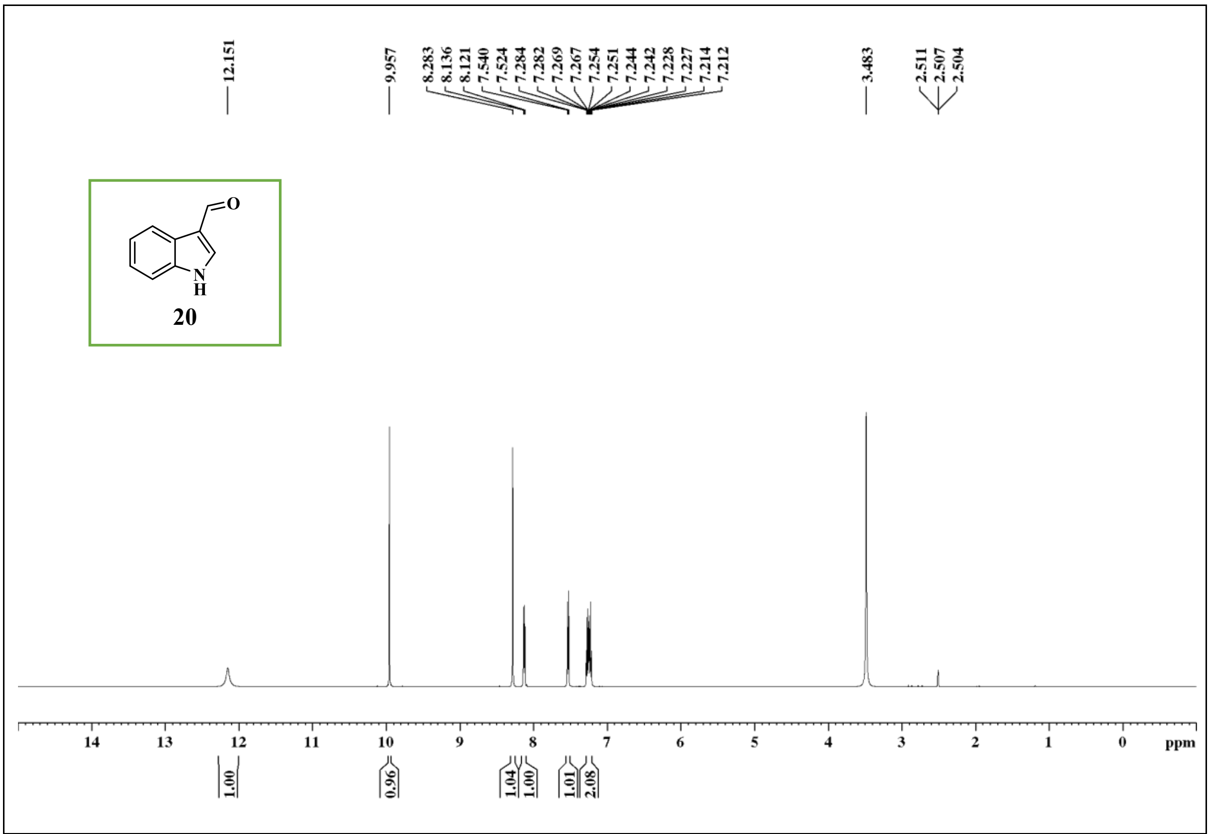
M.P: 258-261 °C (Lit.[84e] 254-256 °C)

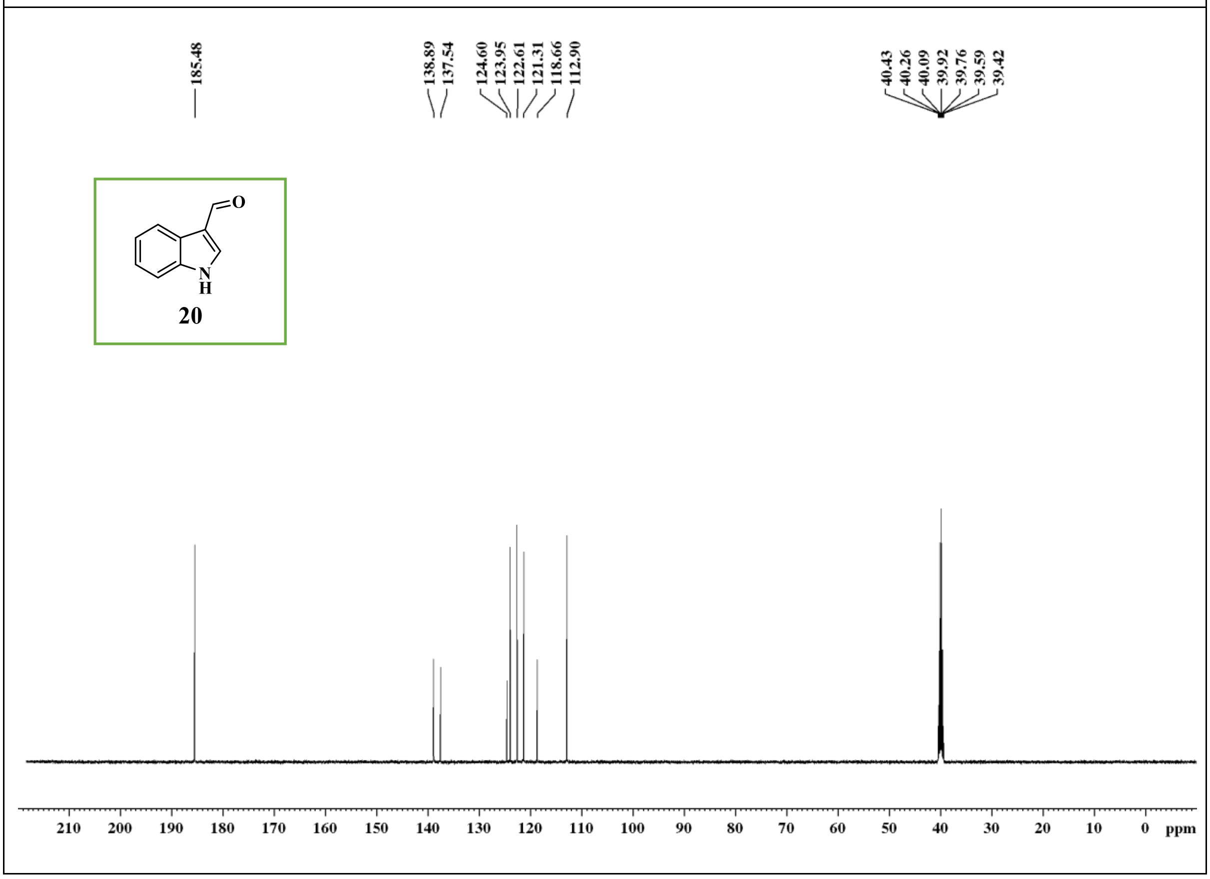
^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.42 (1H, br s), 12.26 (1H, br s), 9.67 (1H, d, *J* = 3.1 Hz), 9.11 (1H, s), 8.61-8.60 (1H, m), 8.44 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 8.2 Hz), 7.64-7.61 (1H, m), 7.59-7.57 (1H, m), 7.35-7.28 (3H, m), 4.02 (3H, s).

^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ 186.7, 166.0, 142.5, 138.8, 137.7, 136.4, 136.3, 135.2, 131.7, 129.6, 127.7, 123.4, 122.6, 122.5, 122.1, 121.2, 120.9, 120.2, 114.6, 113.9, 112.7, 52.8.

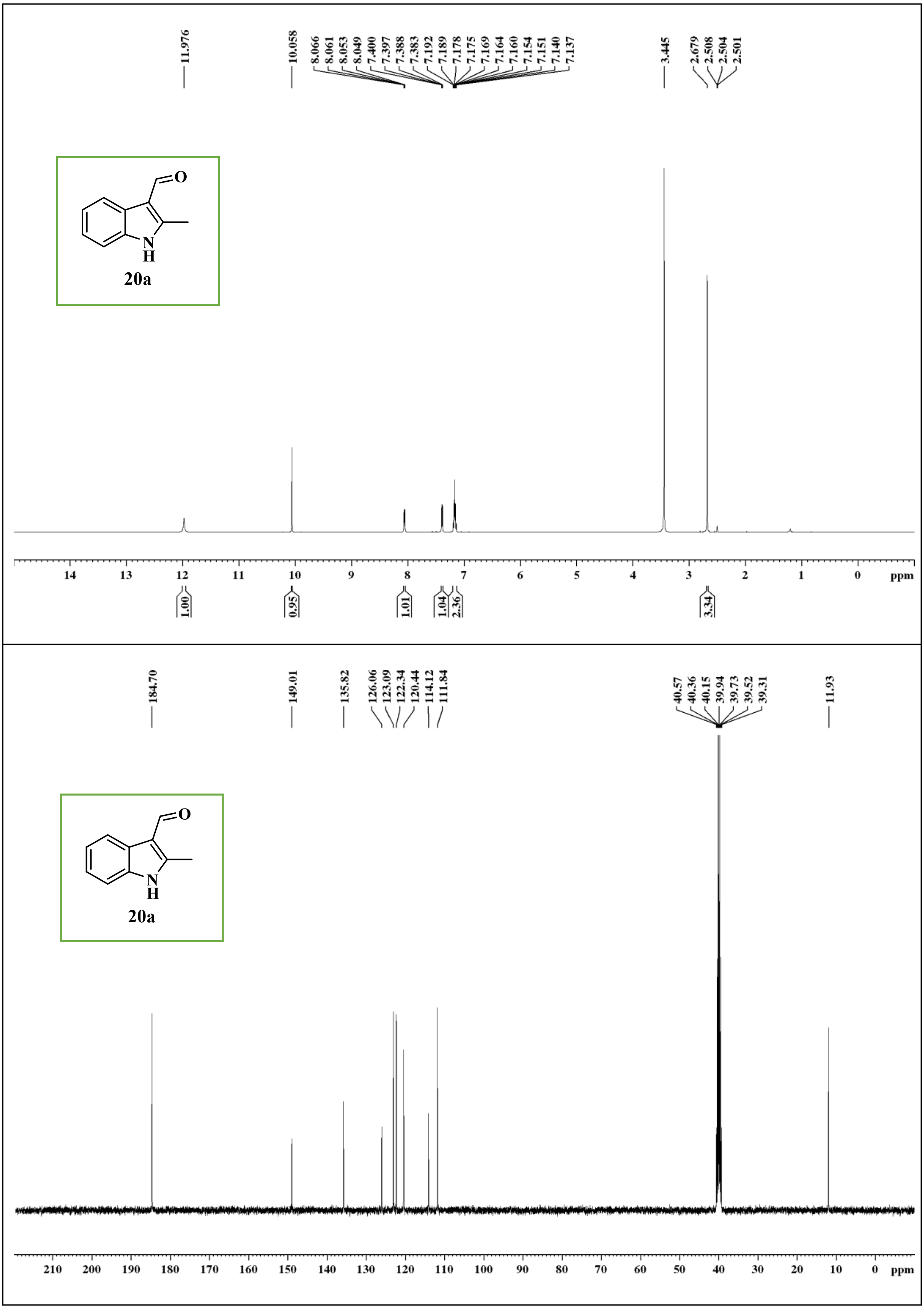
HRMS (ESI-TOF) Calcd for $C_{22}H_{15}N_3O_3$ $[M+H]^+$ 370.1186, found: 370.1185.

^{1}H and ^{13}C NMR Spectra of Compound **20**

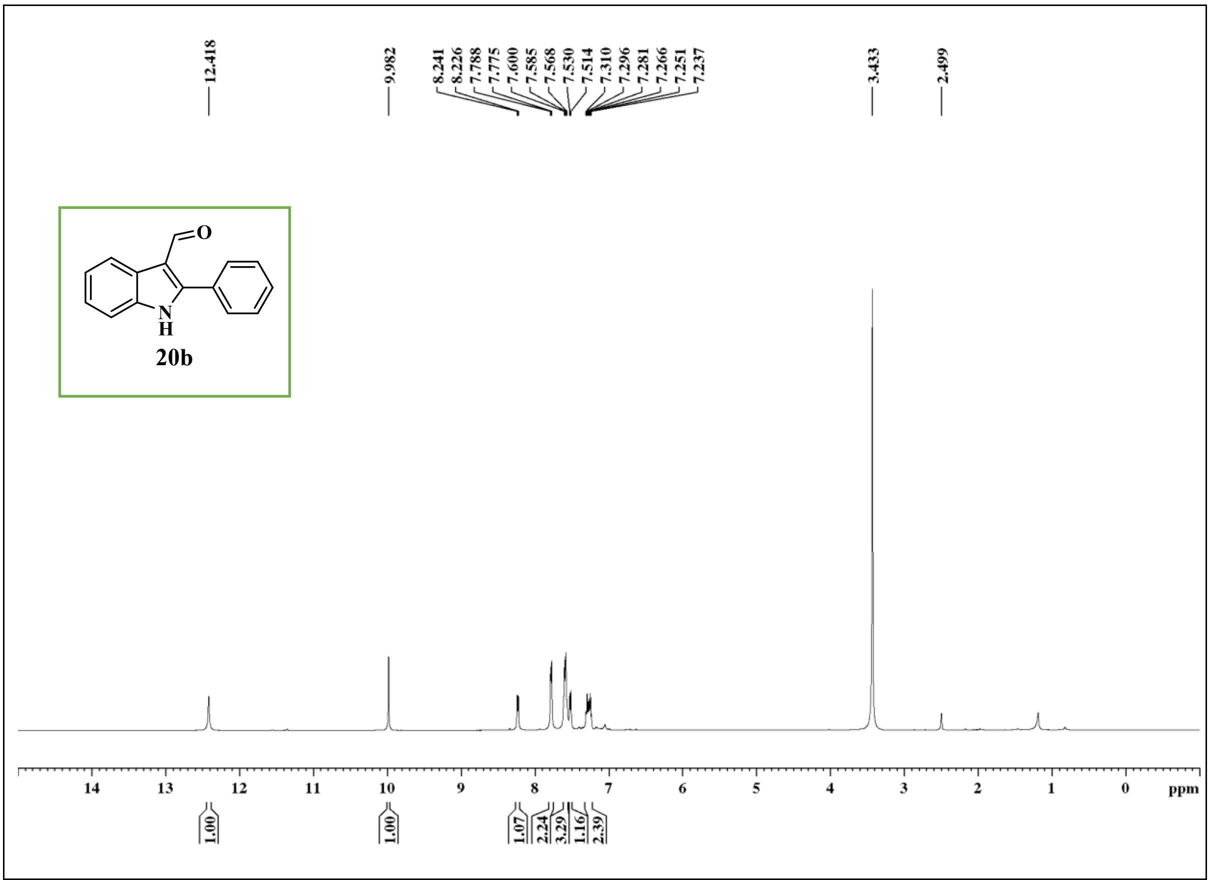


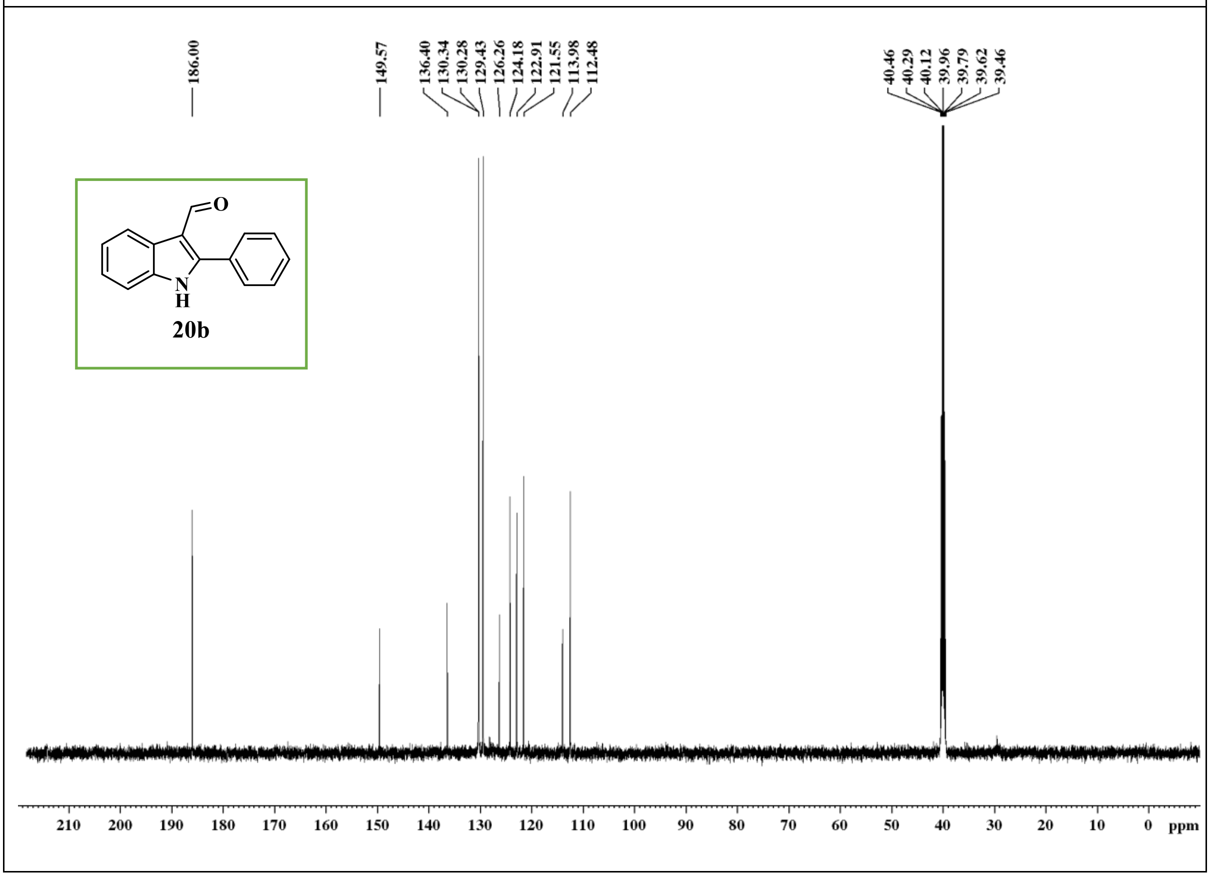


^{1}H and ^{13}C NMR Spectra of Compound **20a**

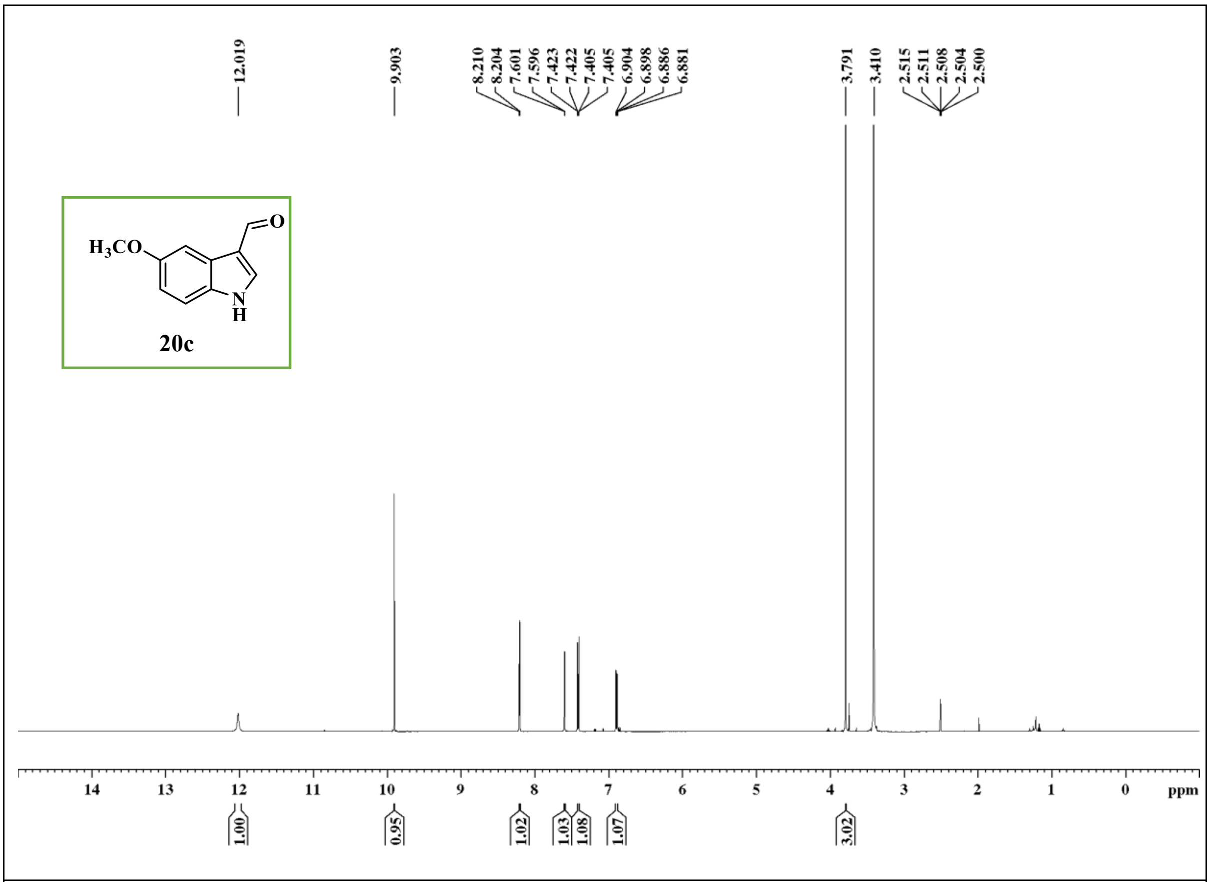


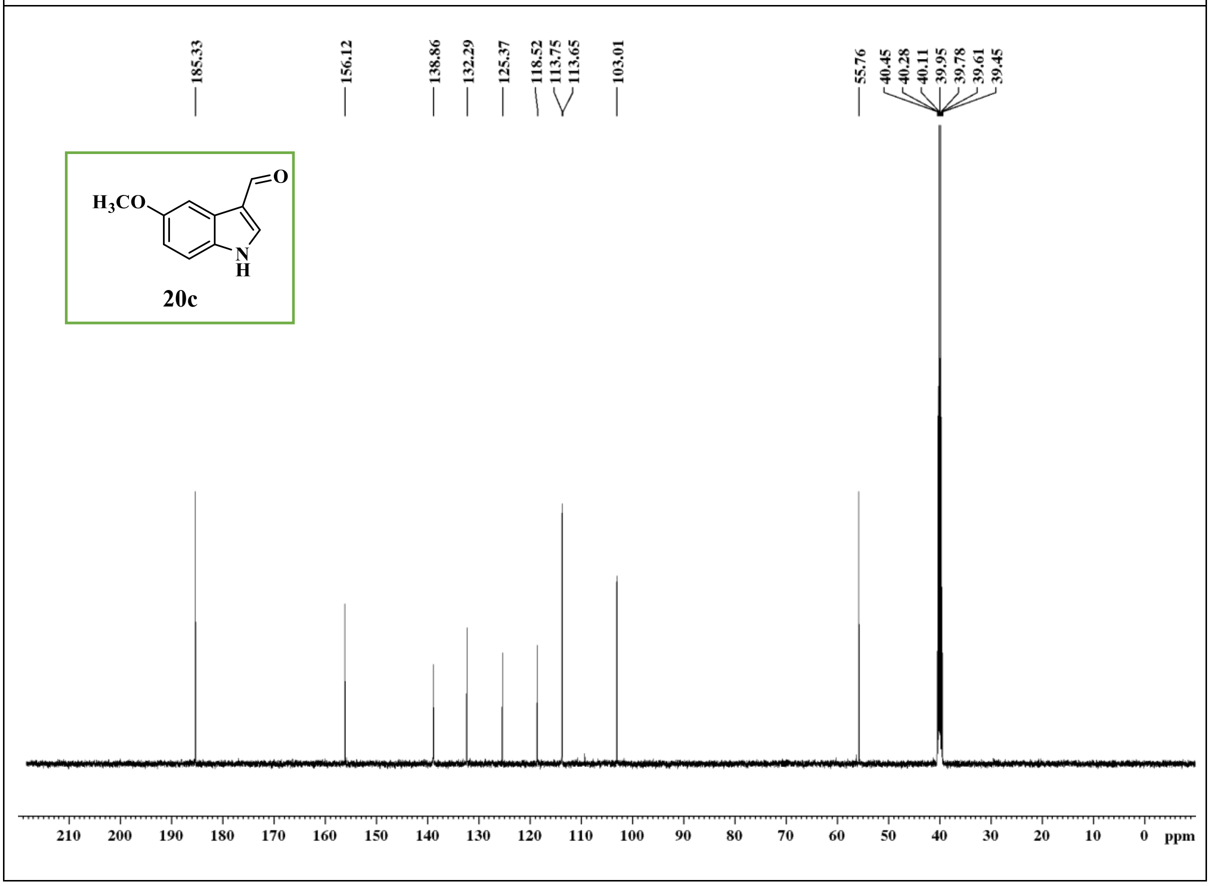
^{1}H and ^{13}C NMR Spectra of Compound **20b**



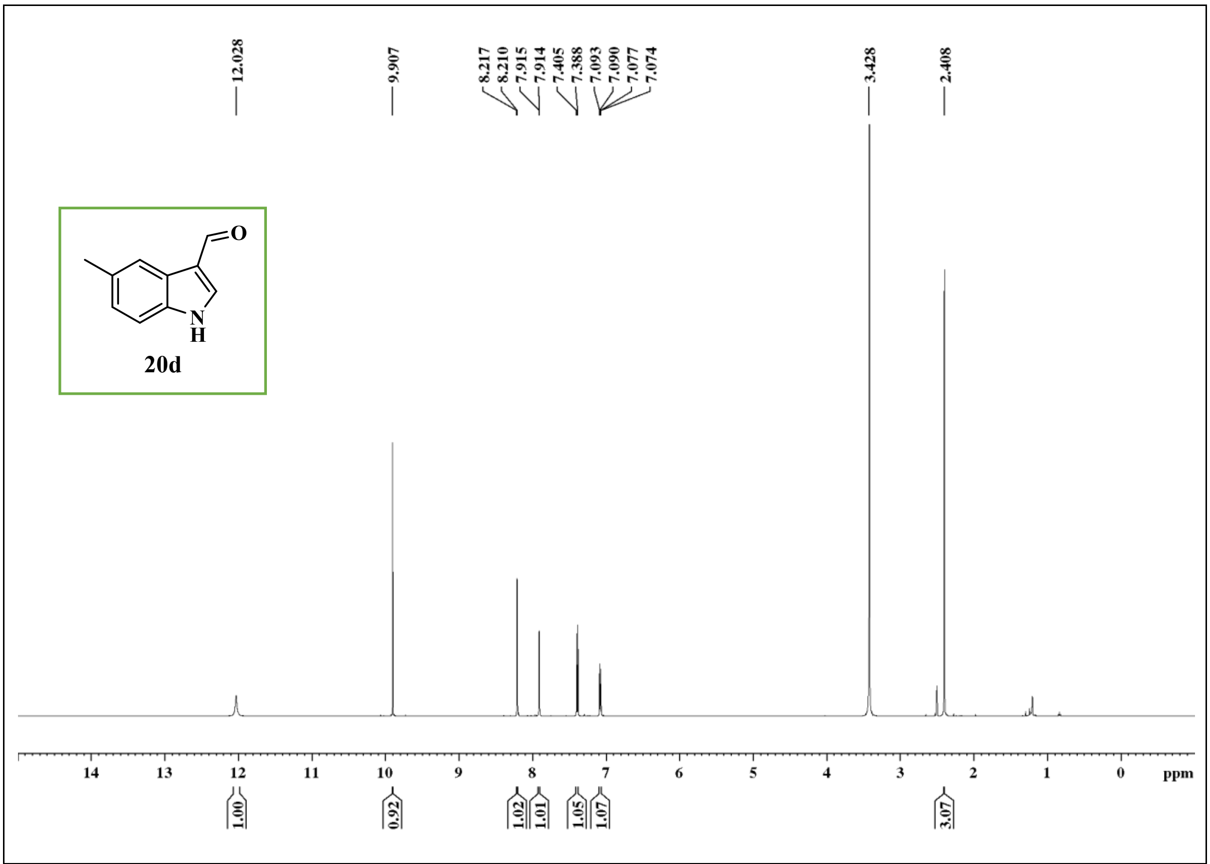


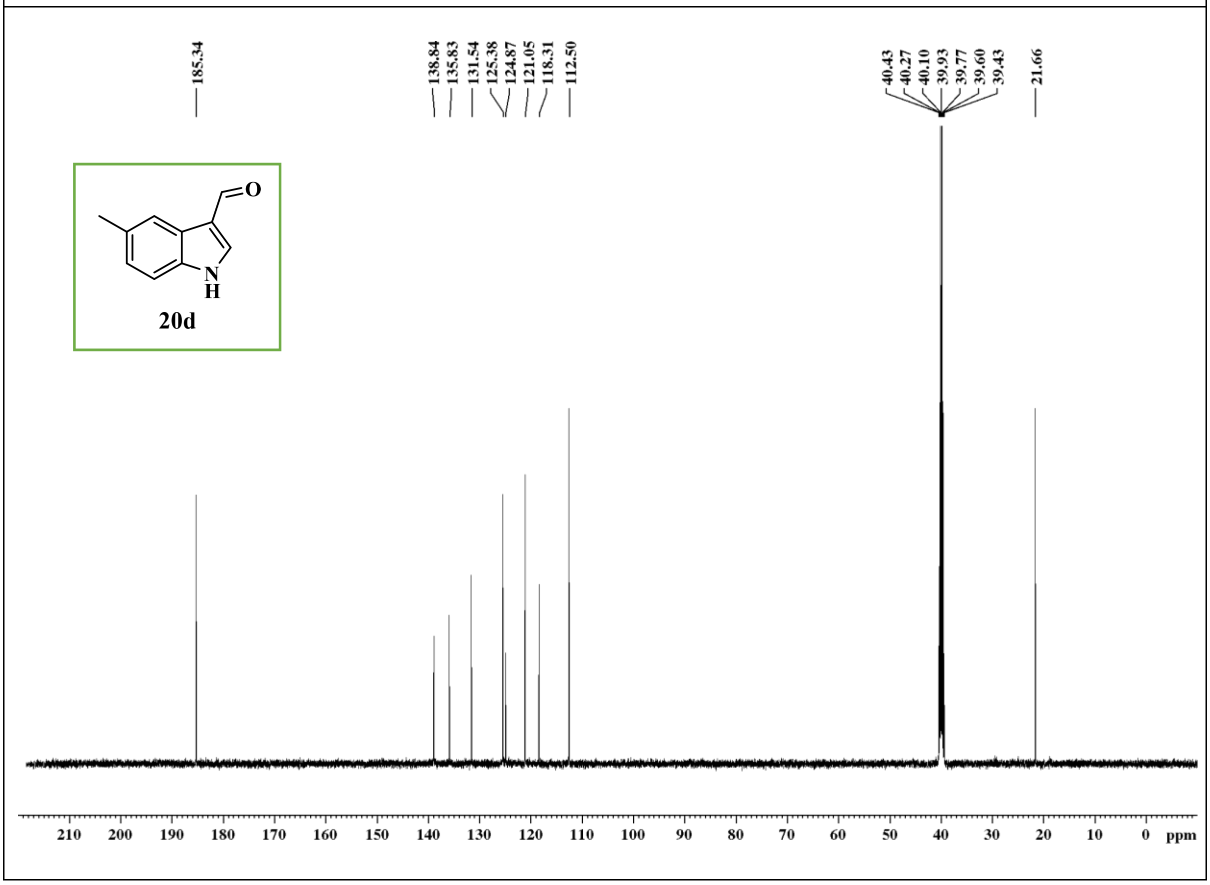
[1]H and [13]C NMR Spectra of Compound **20c**



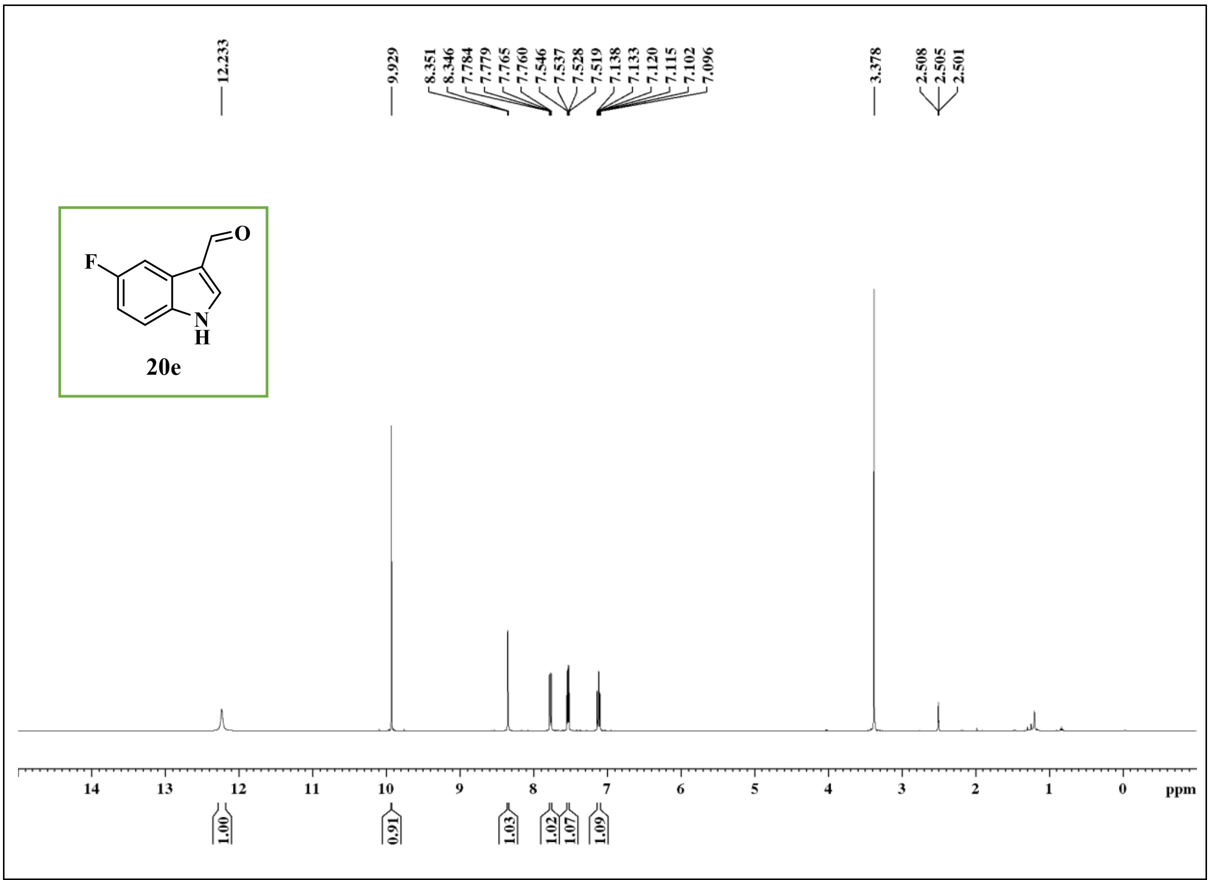


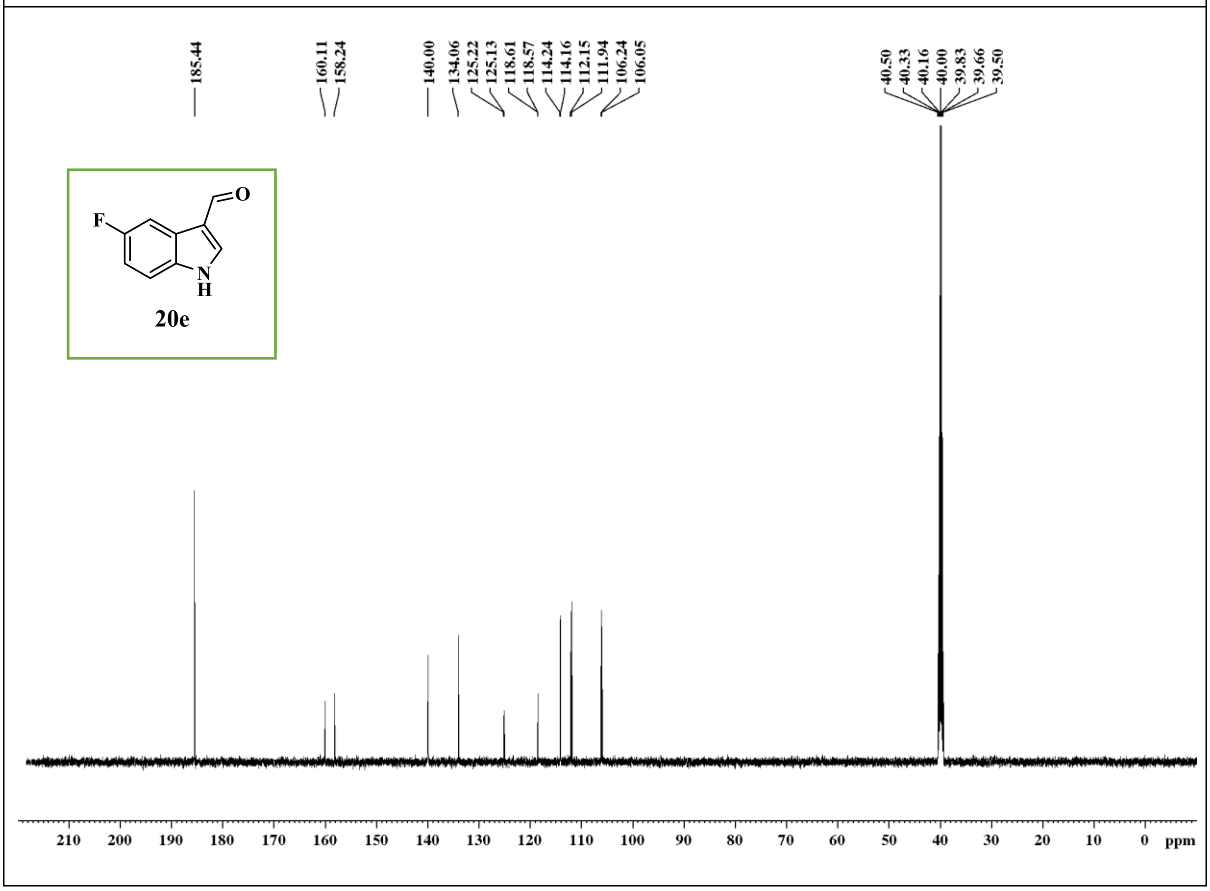
^{1}H and ^{13}C NMR Spectra of Compound **20d**



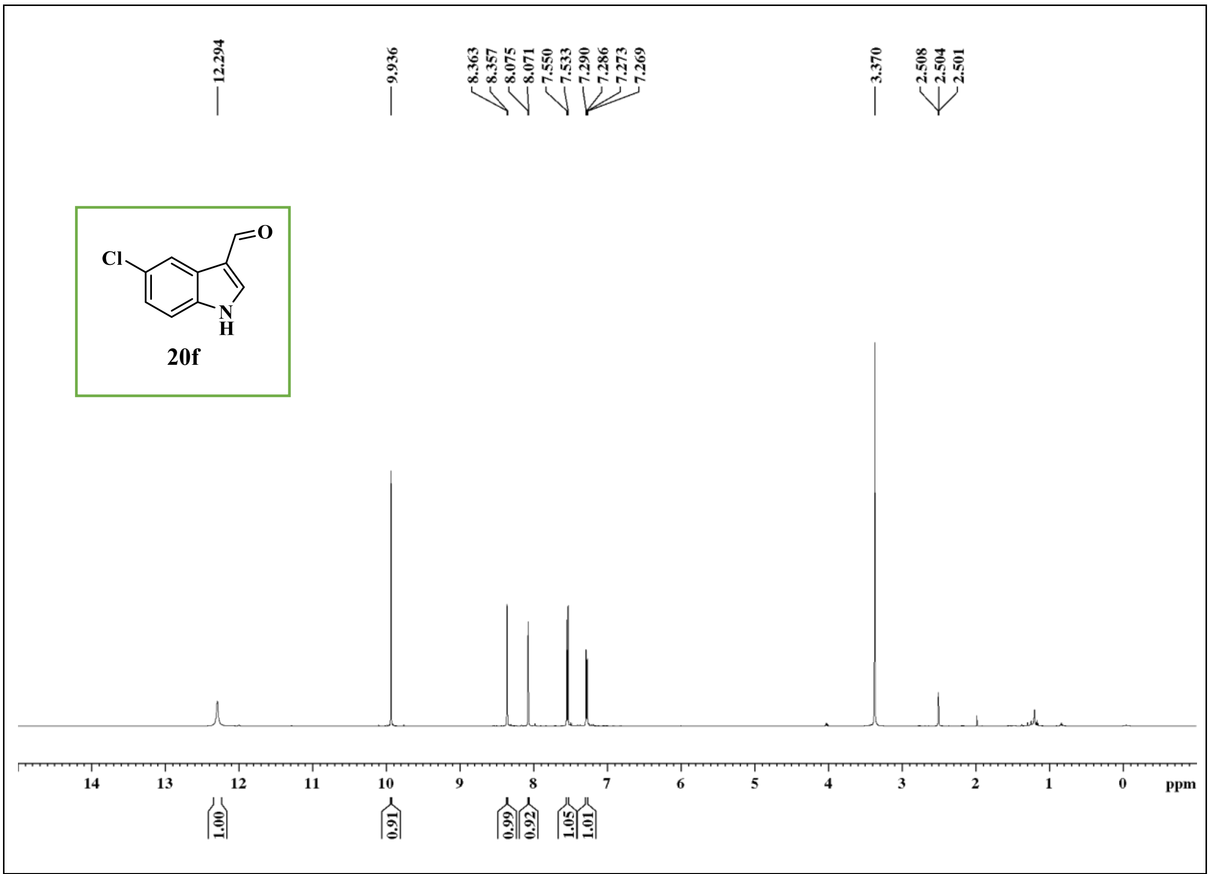


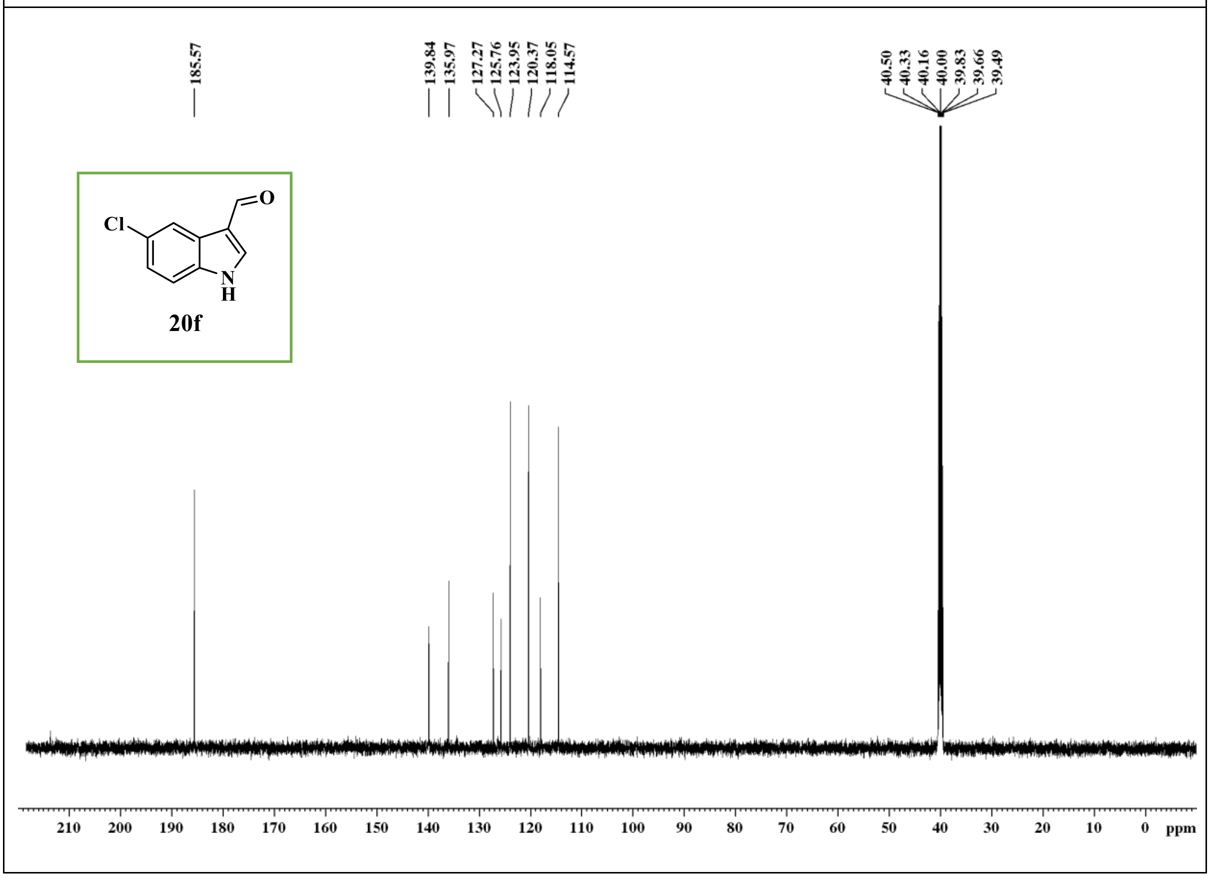
[1]H and [13]C NMR Spectra of Compound **20e**



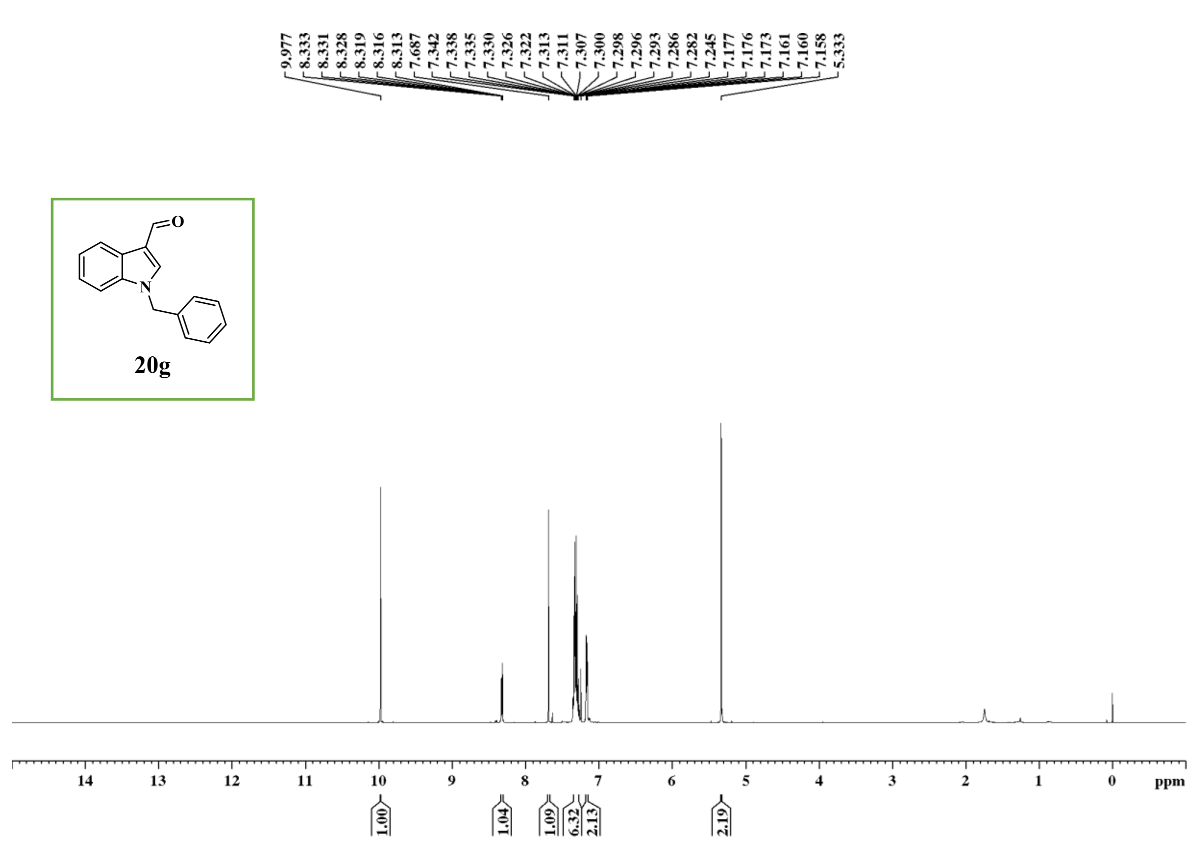


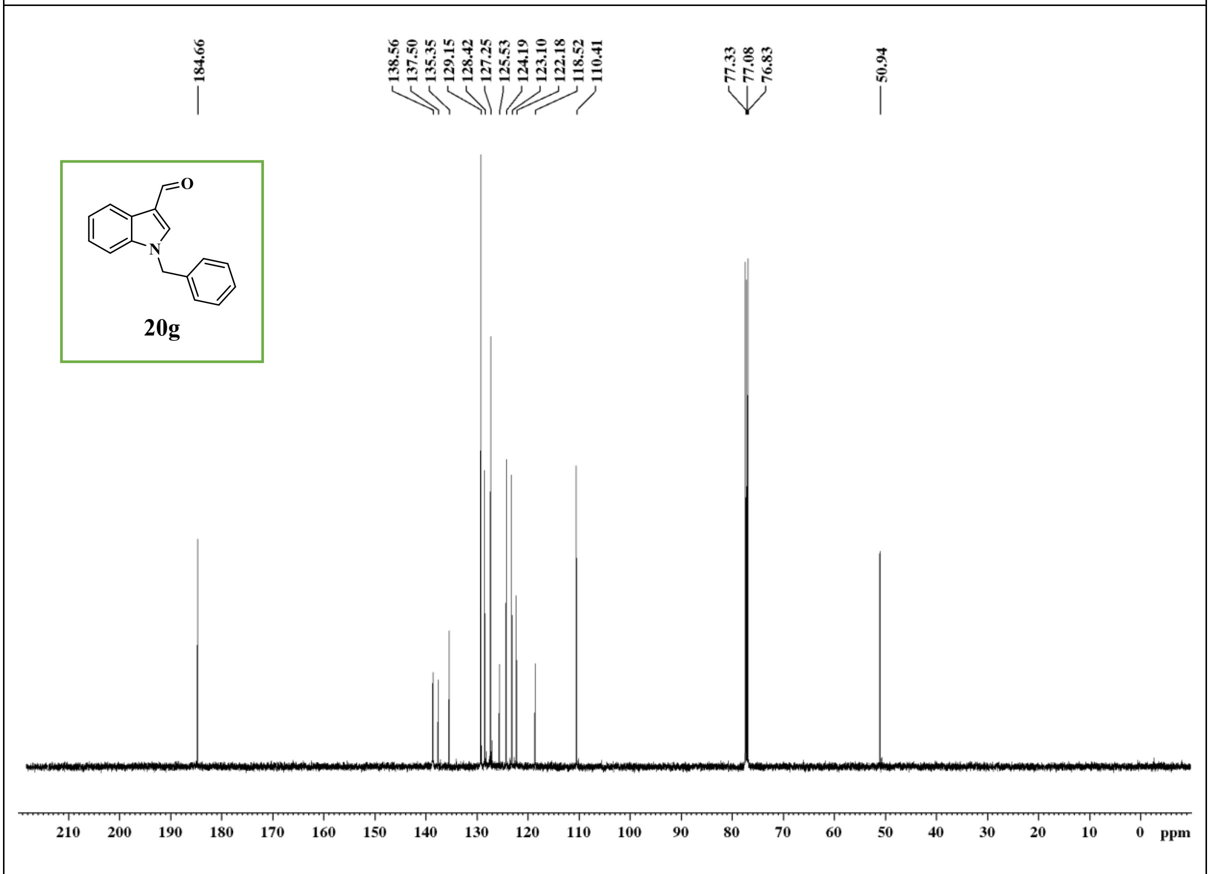
^{1}H and ^{13}C NMR Spectra of Compound **20f**



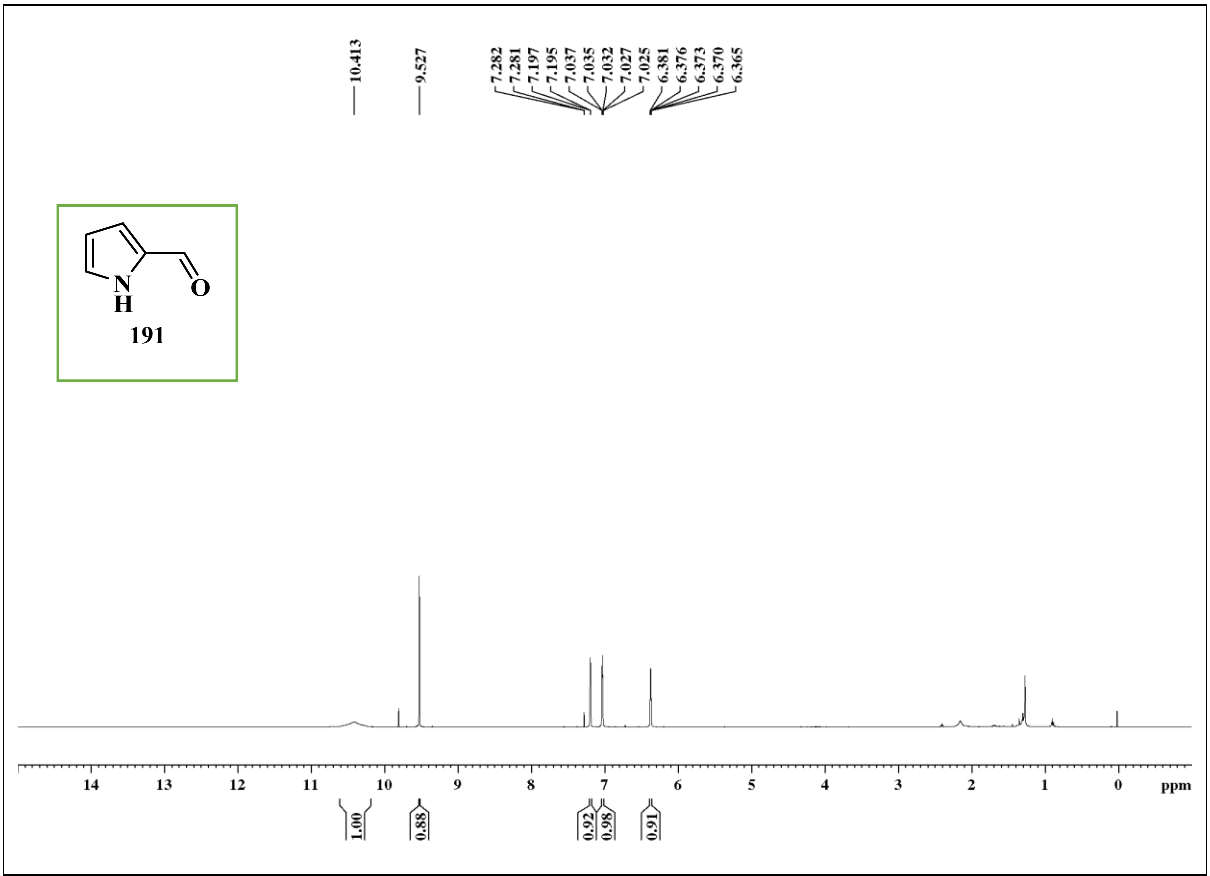


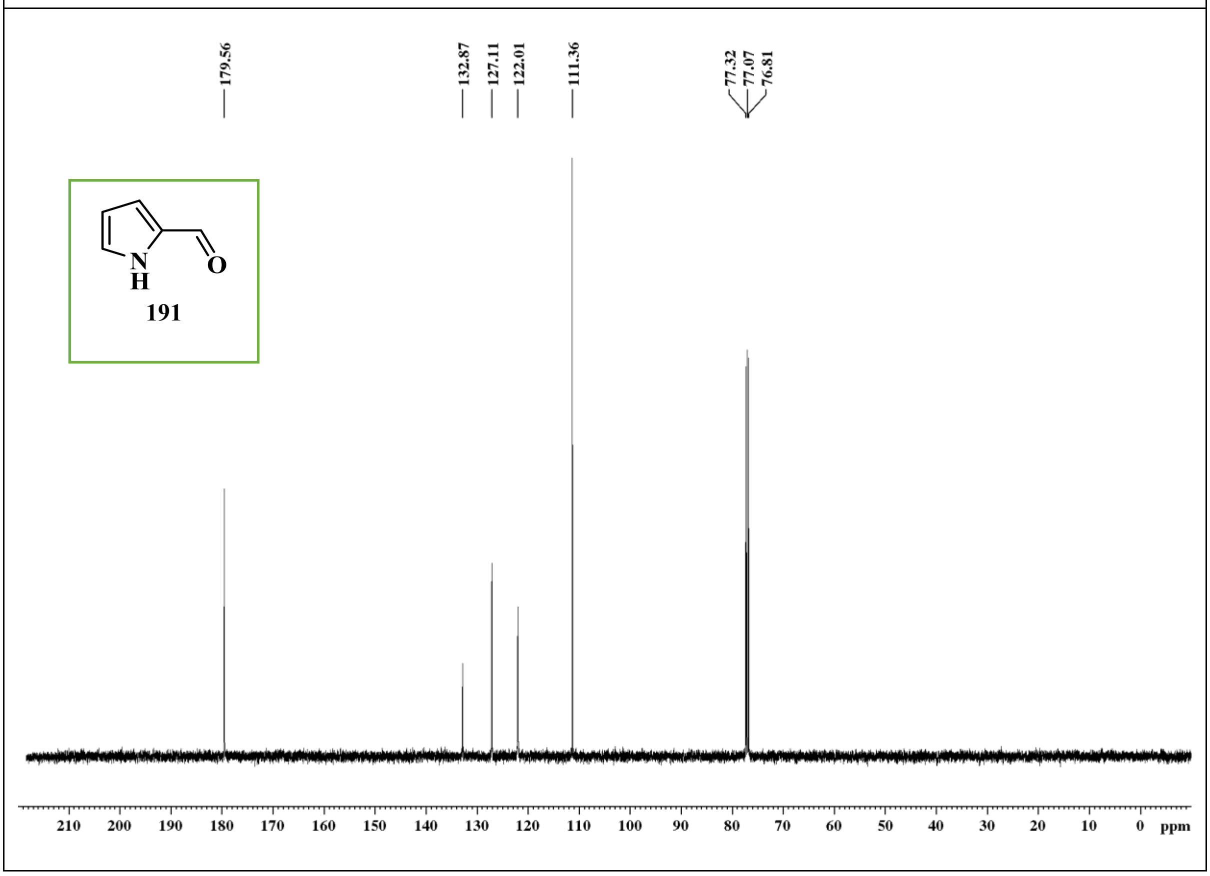
^{1}H and ^{13}C NMR Spectra of Compound **20g**



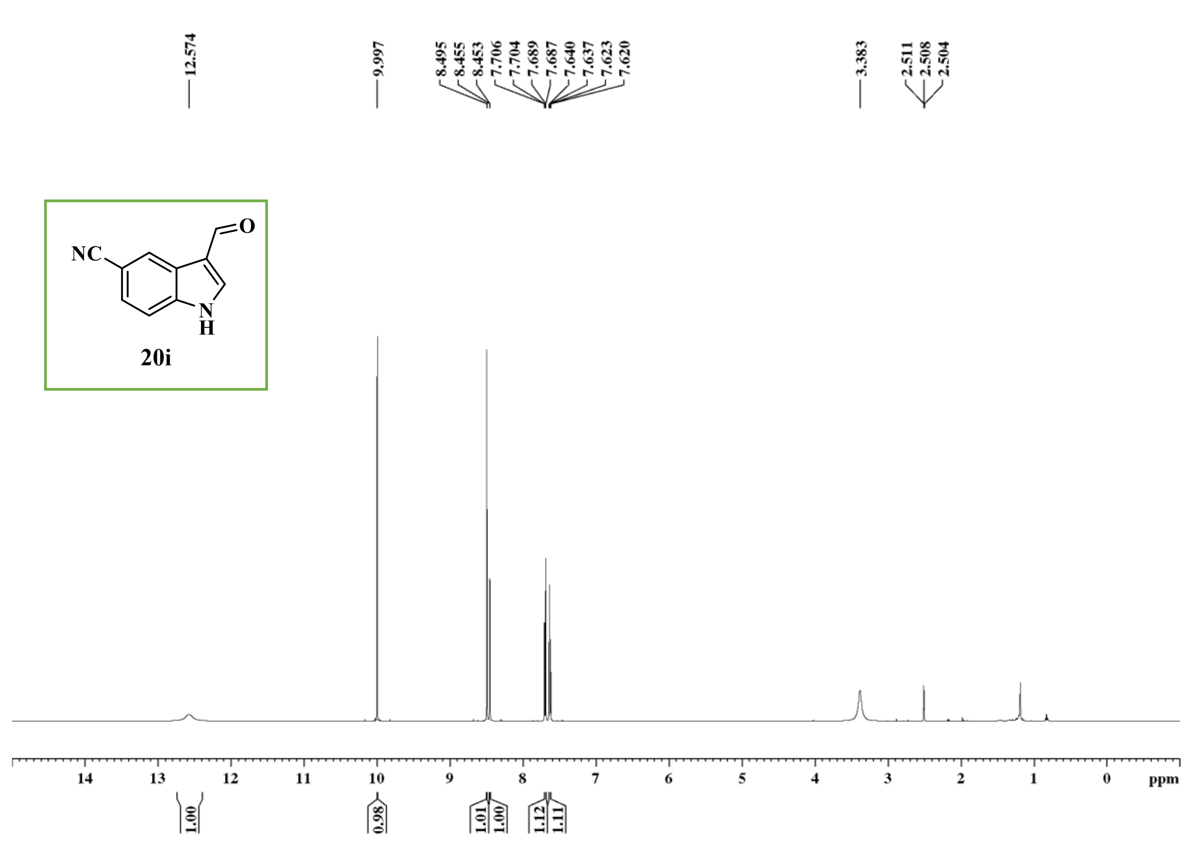


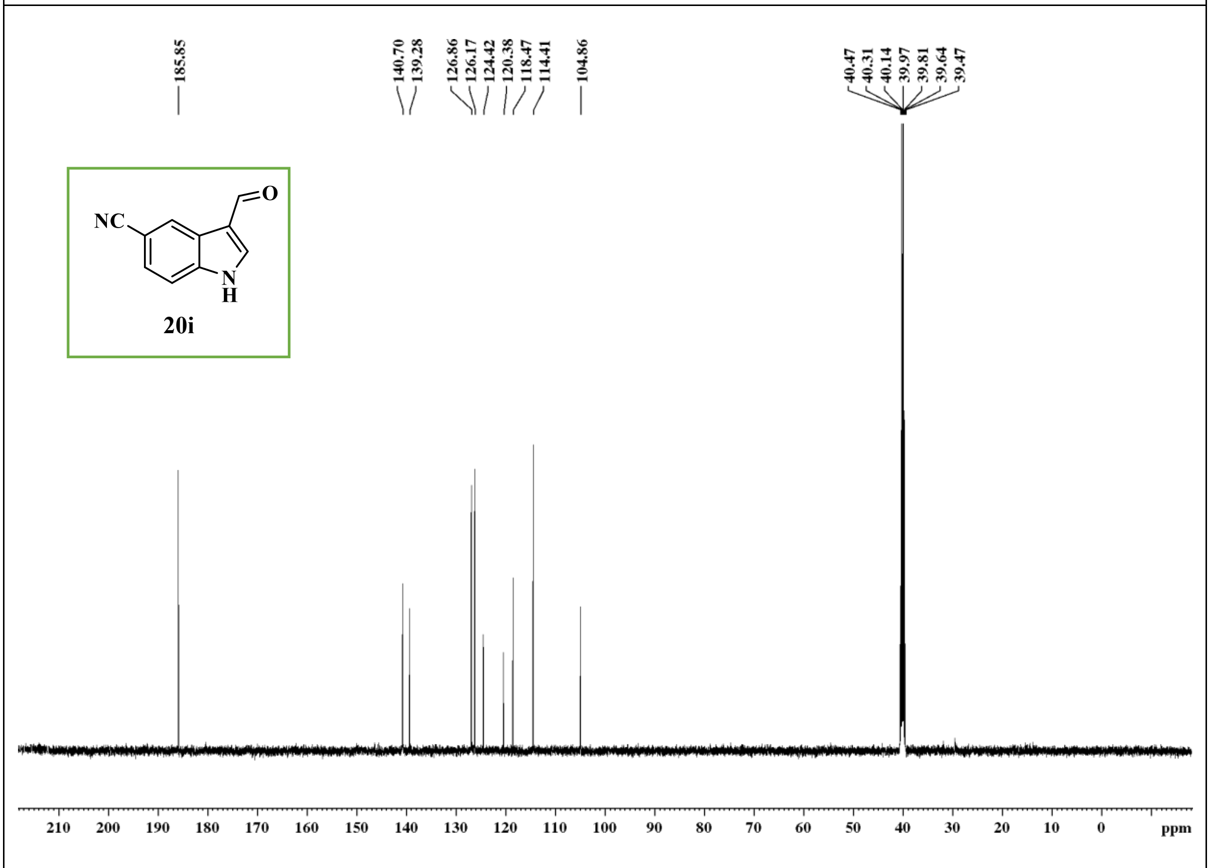
[1]H and [13]C NMR Spectra of Compound **191**



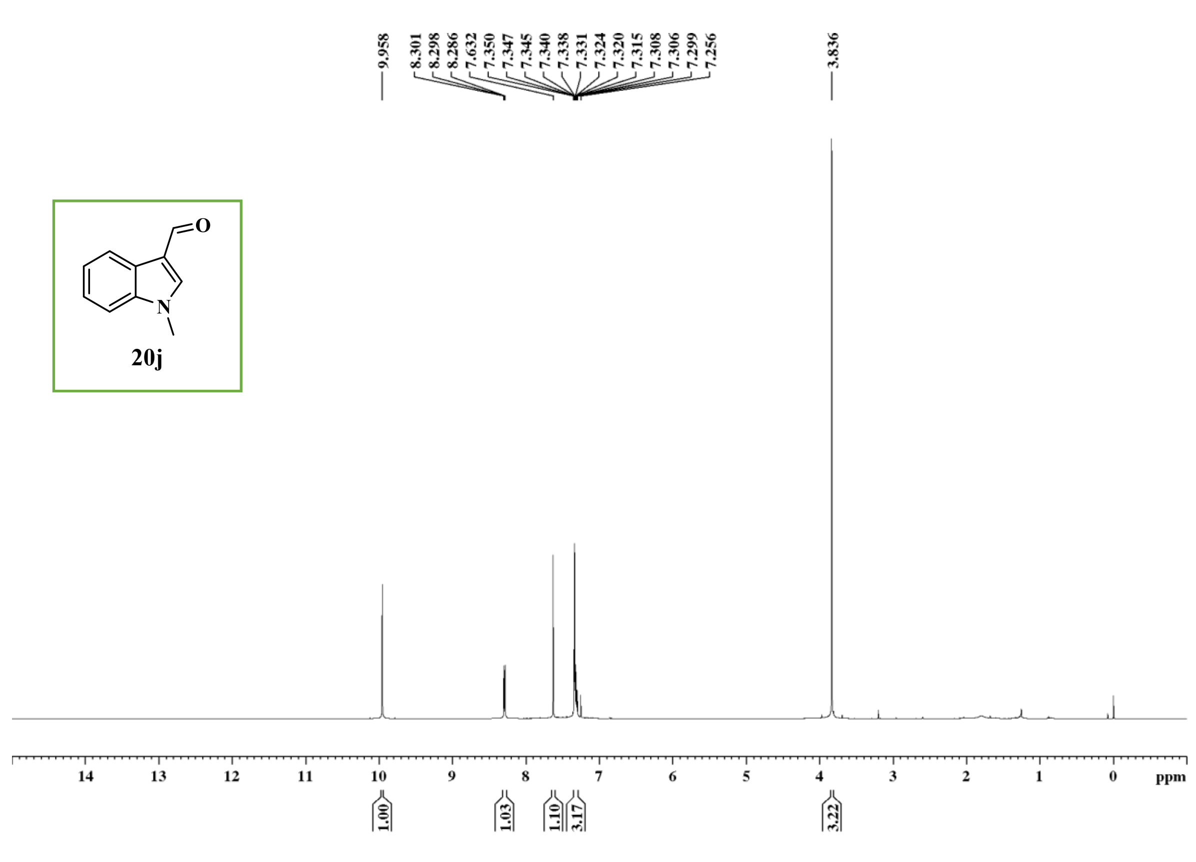


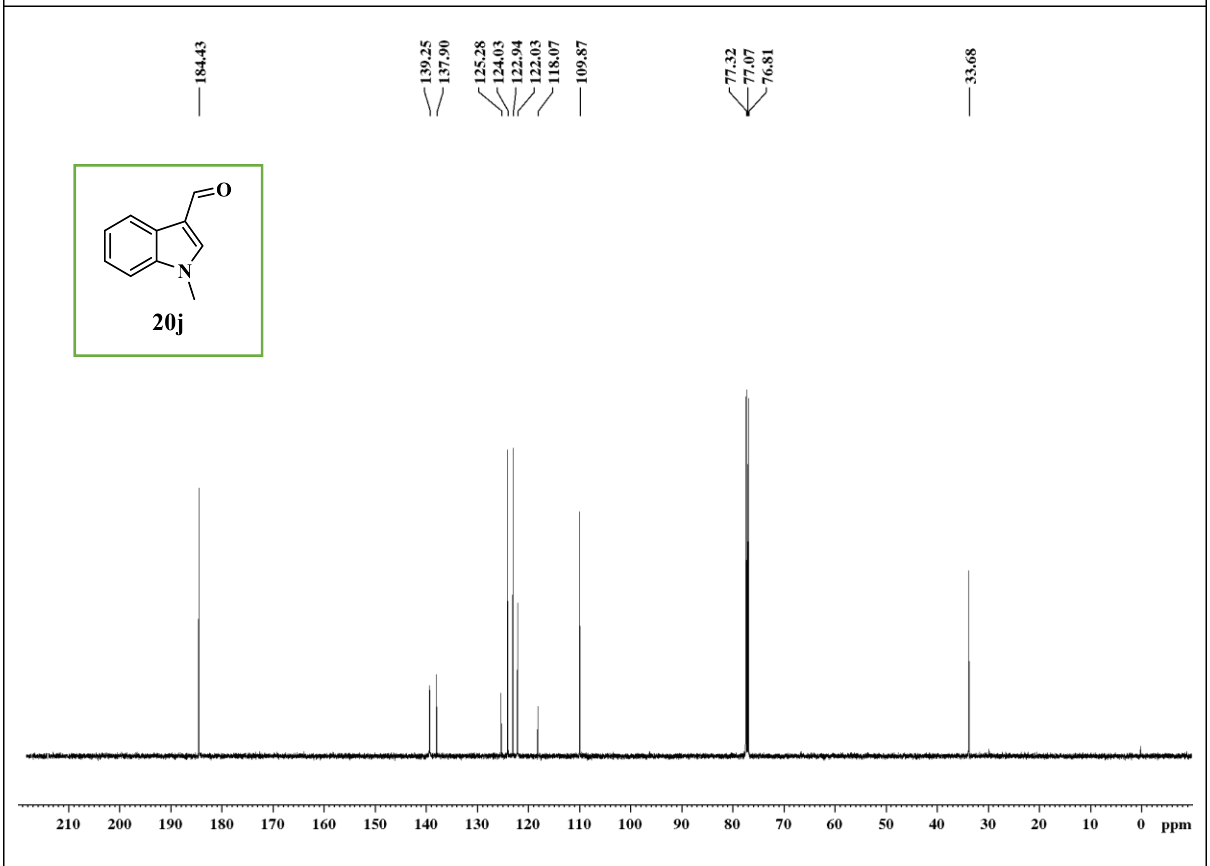
^{1}H and ^{13}C NMR Spectra of Compound **20i**



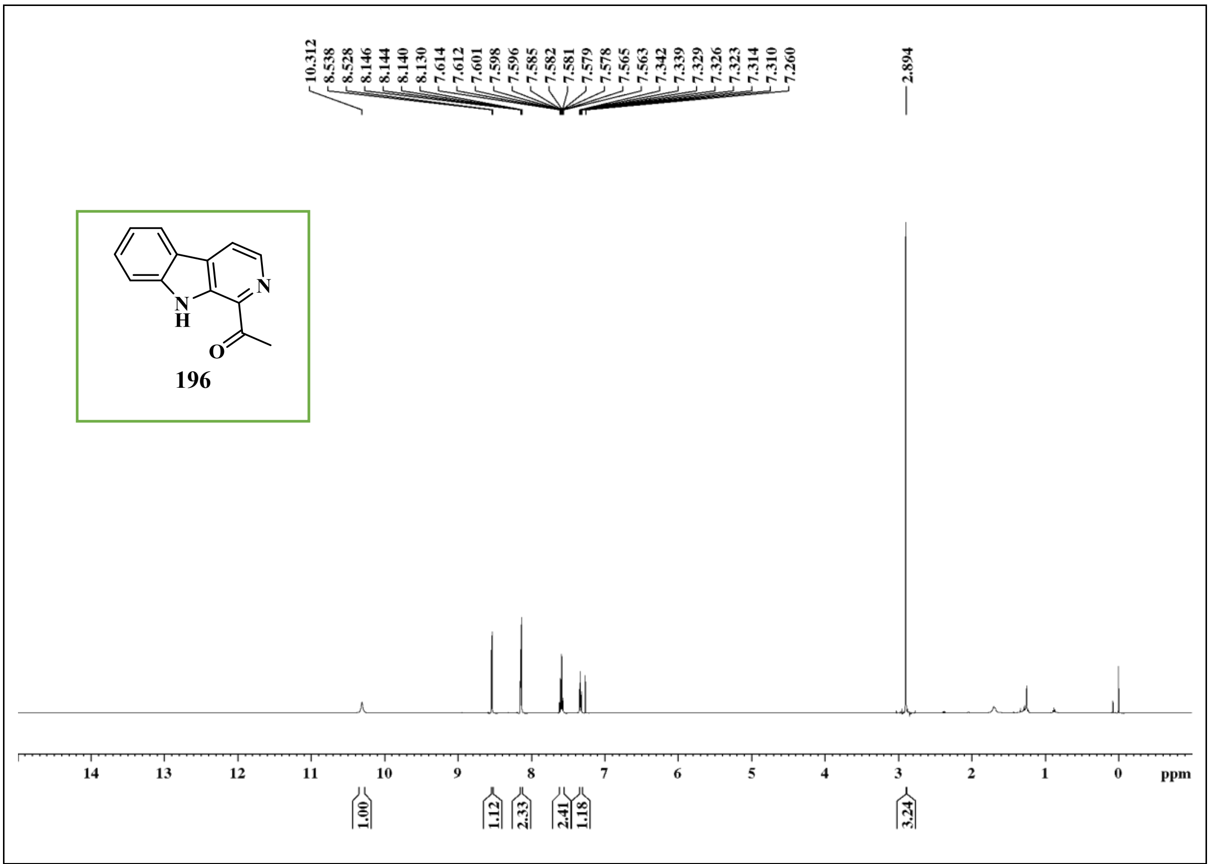


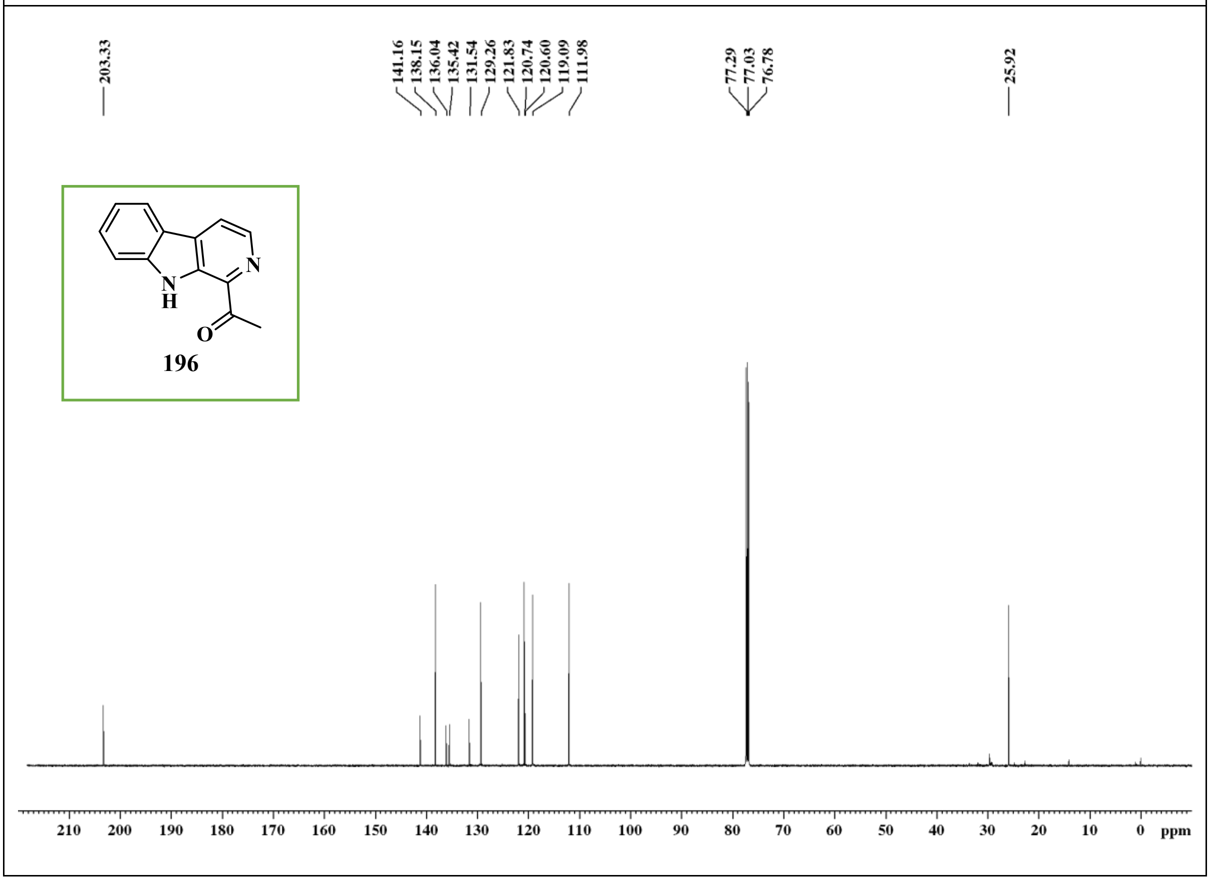
^1H and ^{13}C NMR Spectra of Compound **20j**





^{1}H and ^{13}C NMR Spectra of Compound **196**





HRMS of Compound 196

Display Report

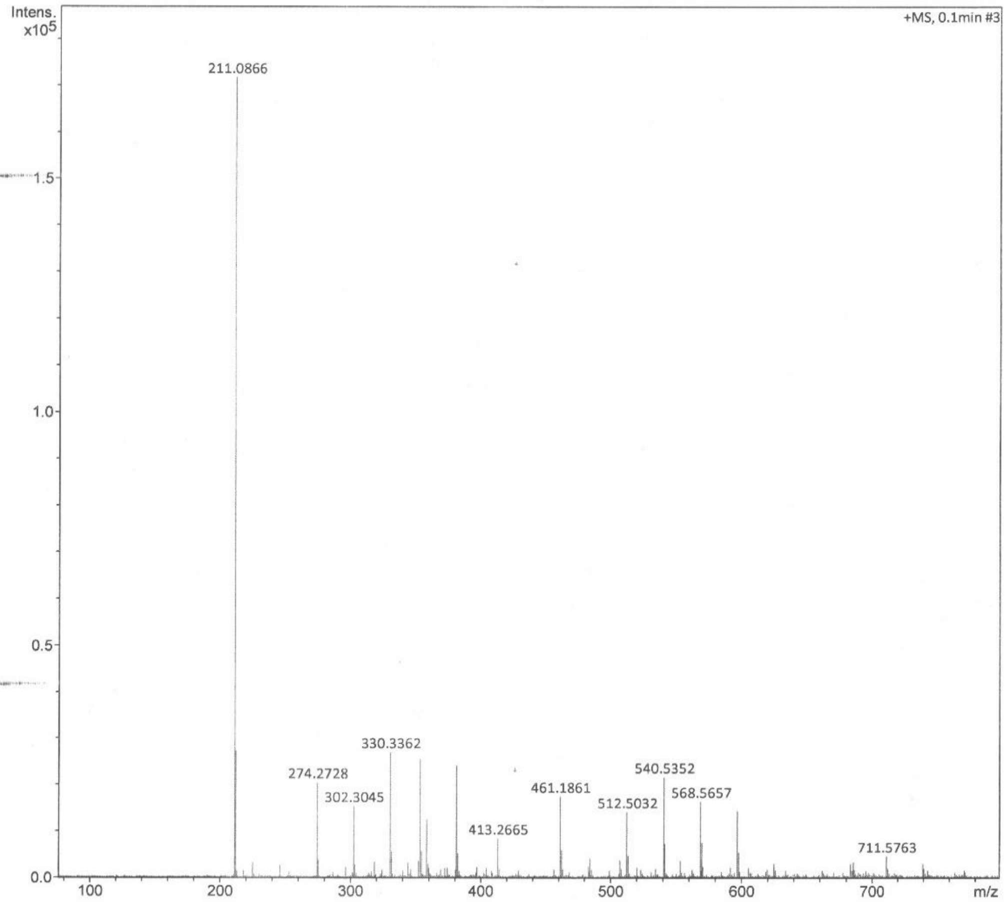
Analysis Info

Analysis Name D:\Data\2021-data\PROF.RN\NOV\12.d
Method tune_low_Pos-R2.m
Sample Name 12
Comment

Acquisition Date 11/22/2021 4:36:46 PM
Operator BDAL
Instrument maXis 255552.10138

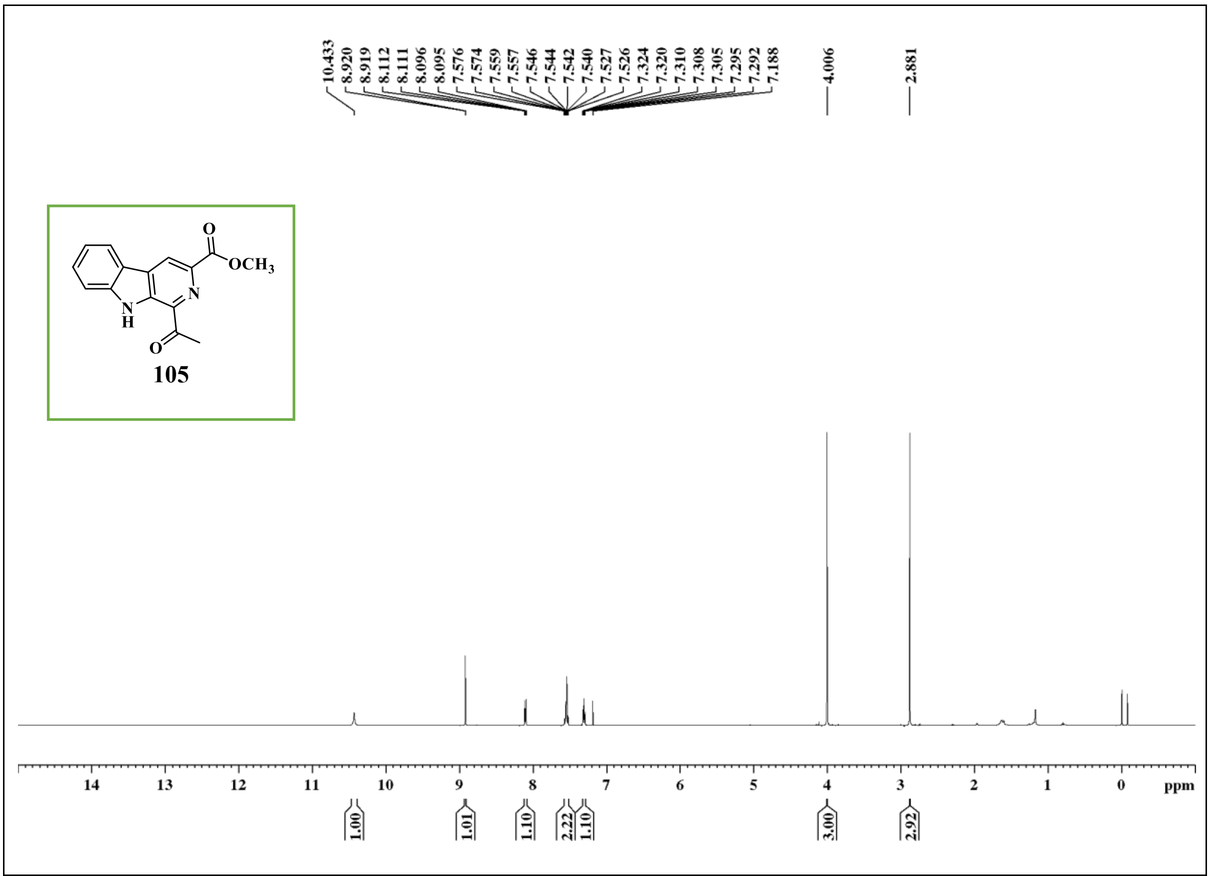
Acquisition Parameter

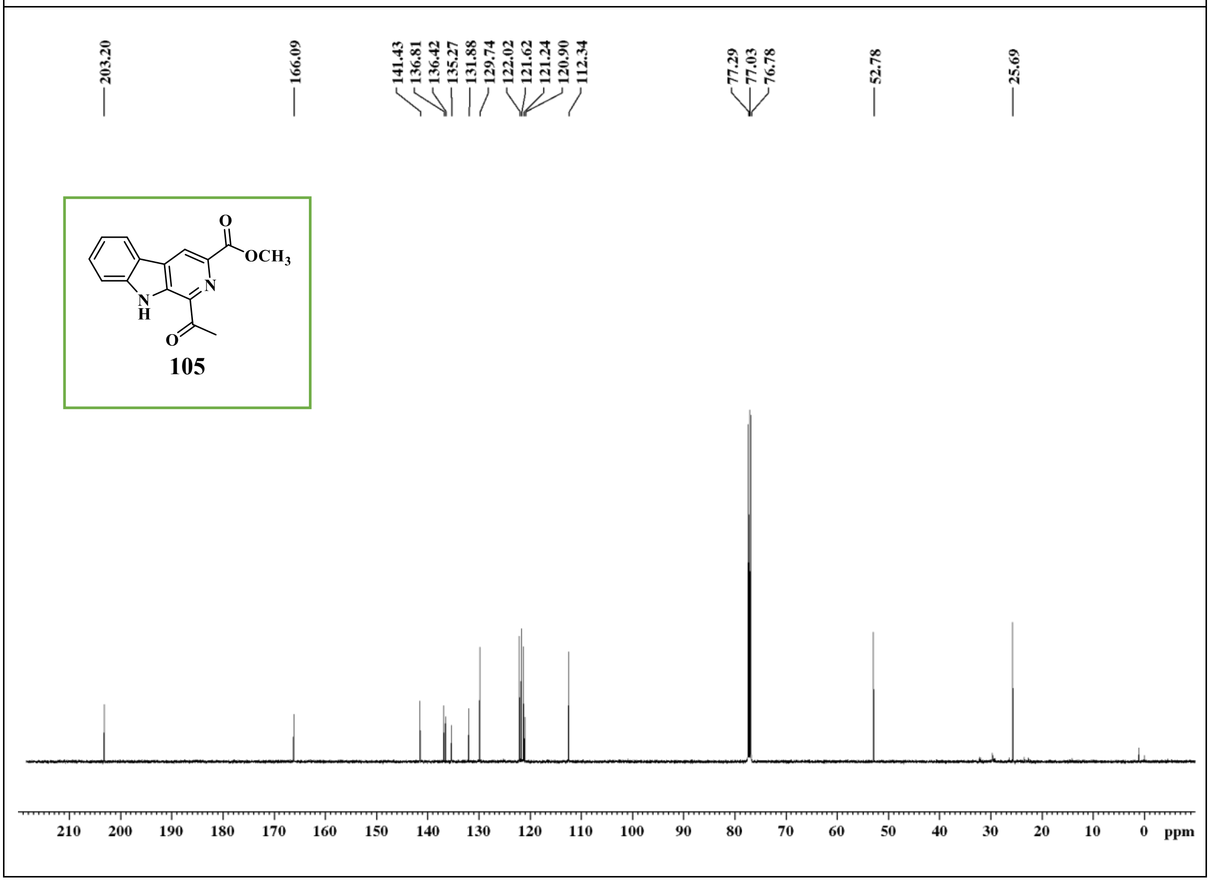
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	3500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2580 m/z	Set Charging Voltage	0 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



12.d
Bruker Compass DataAnalysis 4.2 printed: 11/22/2021 4:45:11 PM by: BDAL Page 1 of 1

^{1}H and ^{13}C NMR Spectra of Compound **105**





HRMS of Compound 105

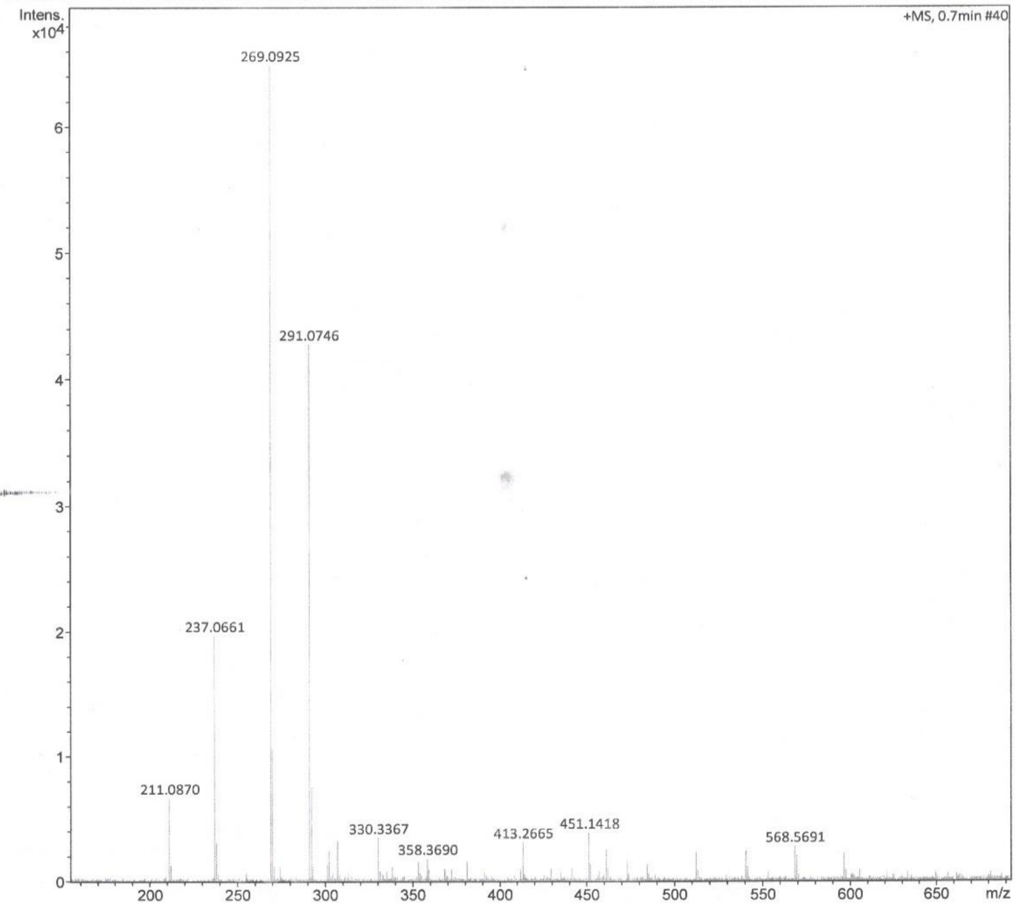
Display Report

Analysis Info

Analysis Name	D:\Data\2021-data\PROF.RN\NOV\13 .d	Acquisition Date	11/22/2021 4:48:03 PM
Method	tune_low.m	Operator	BDAL
Sample Name	13	Instrument	maXis 255552.10138
Comment			

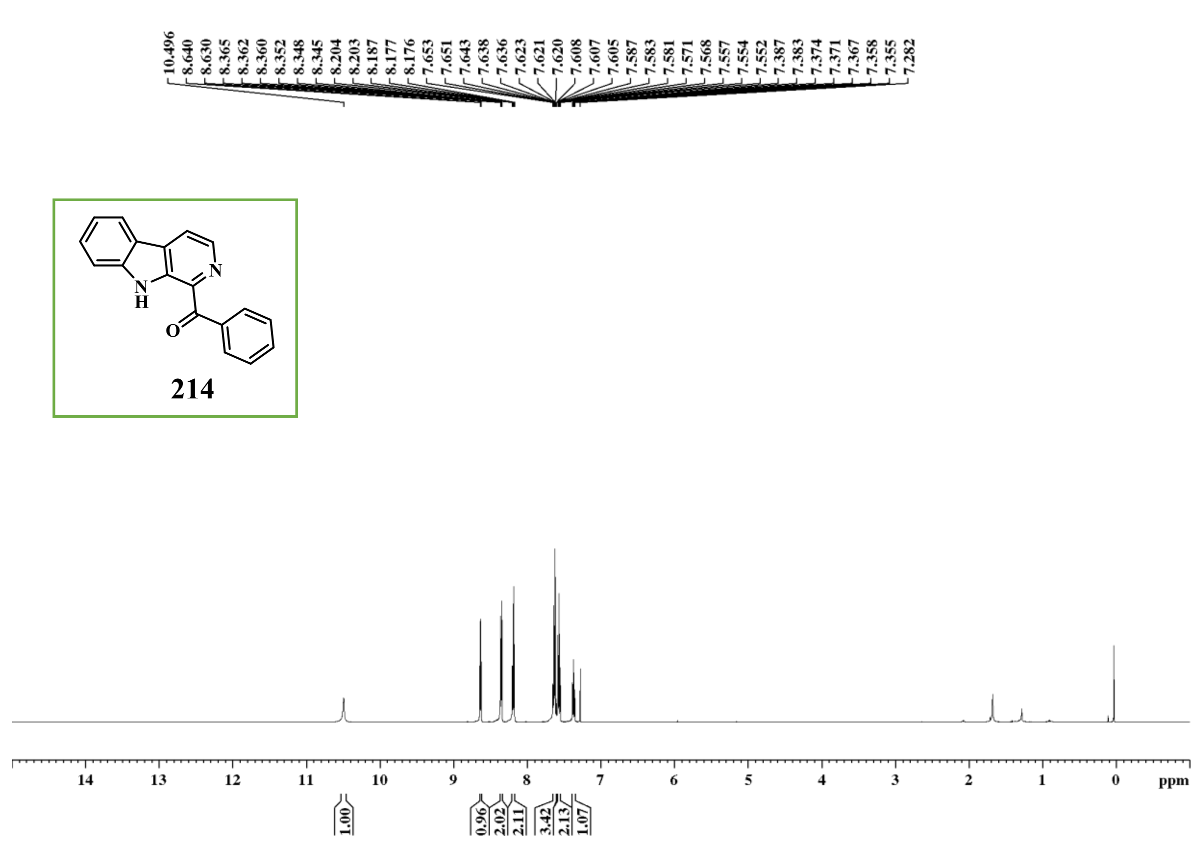
Acquisition Parameter

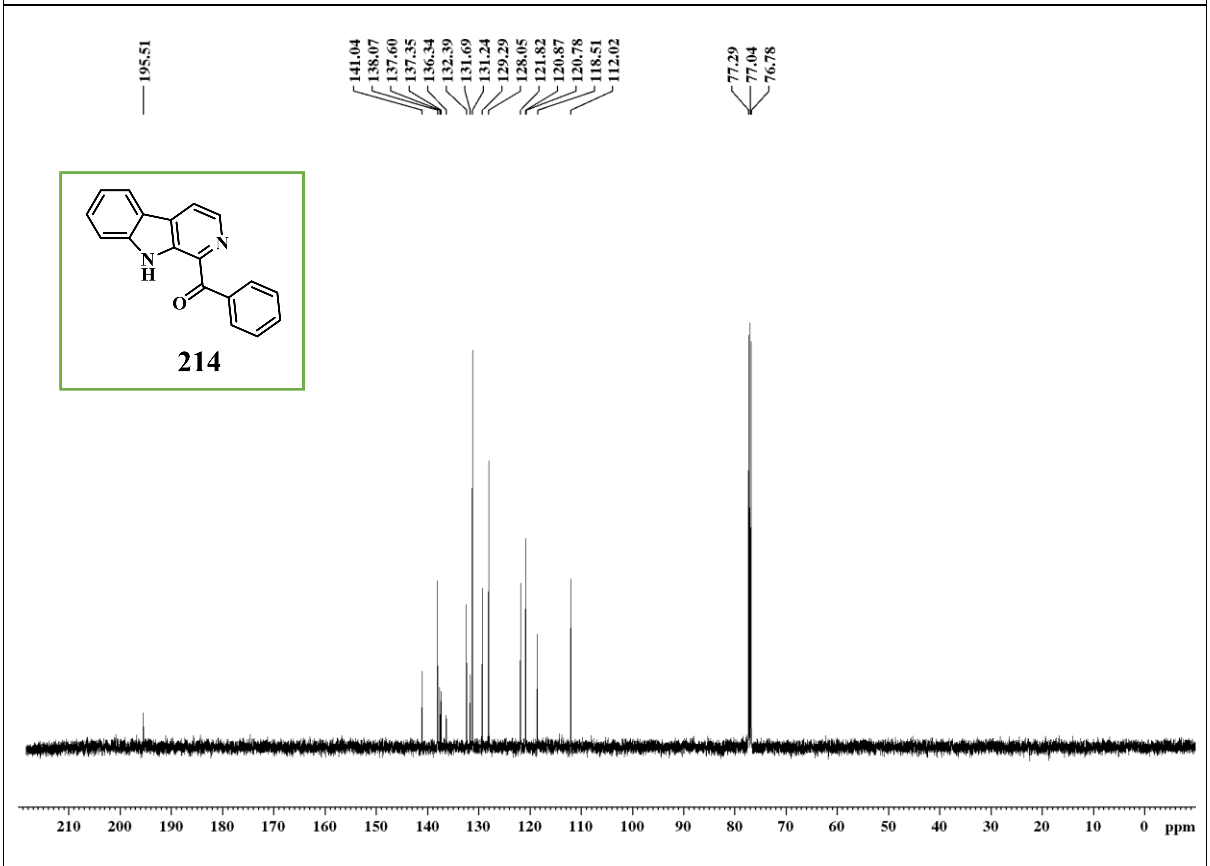
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



13 .d
Bruker Compass DataAnalysis 4.2 printed: 11/22/2021 5:05:41 PM by: BDAL Page 1 of 1

^{1}H and ^{13}C NMR Spectra of Compound **214**





HRMS of Compound 214

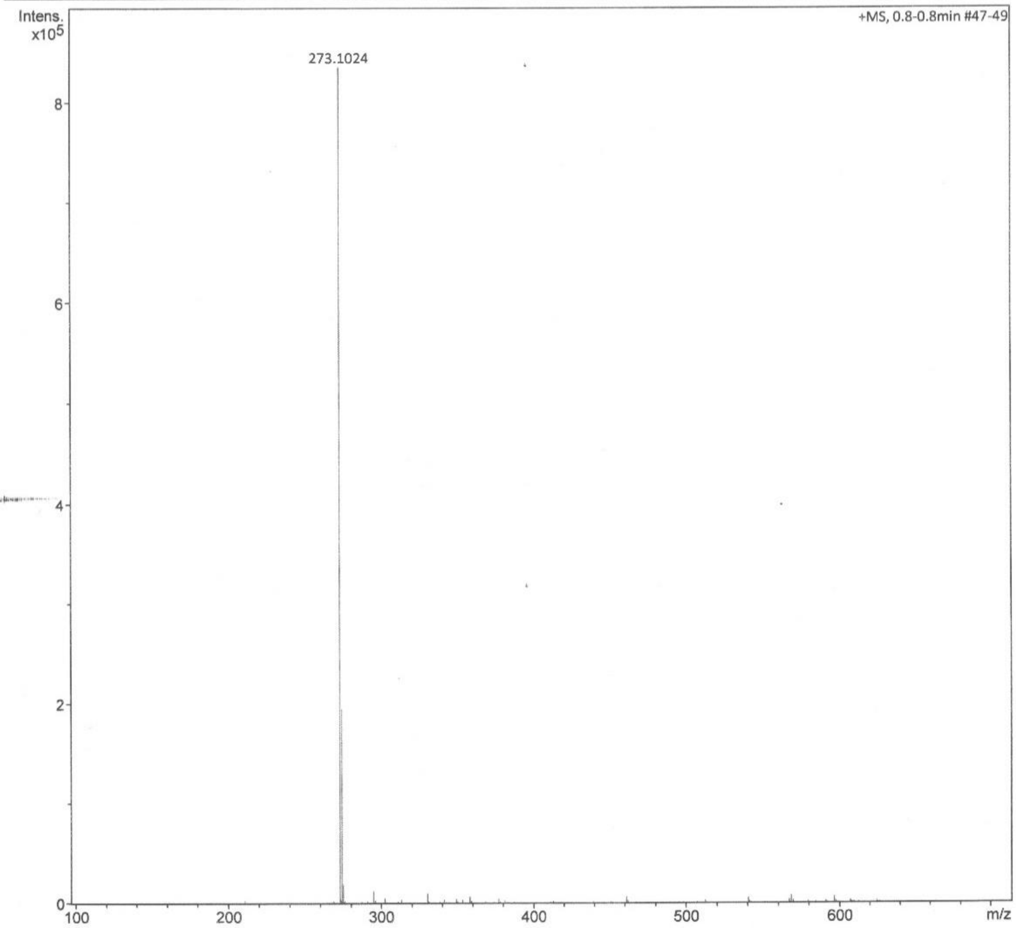
Display Report

Analysis Info

Analysis Name	D:\Data\2021-data\PROF.RN\NOV\14.d	Acquisition Date	11/22/2021 4:51:30 PM
Method	tune_low.m	Operator	BDAL
Sample Name	14	Instrument	maXis 255552.10138
Comment			

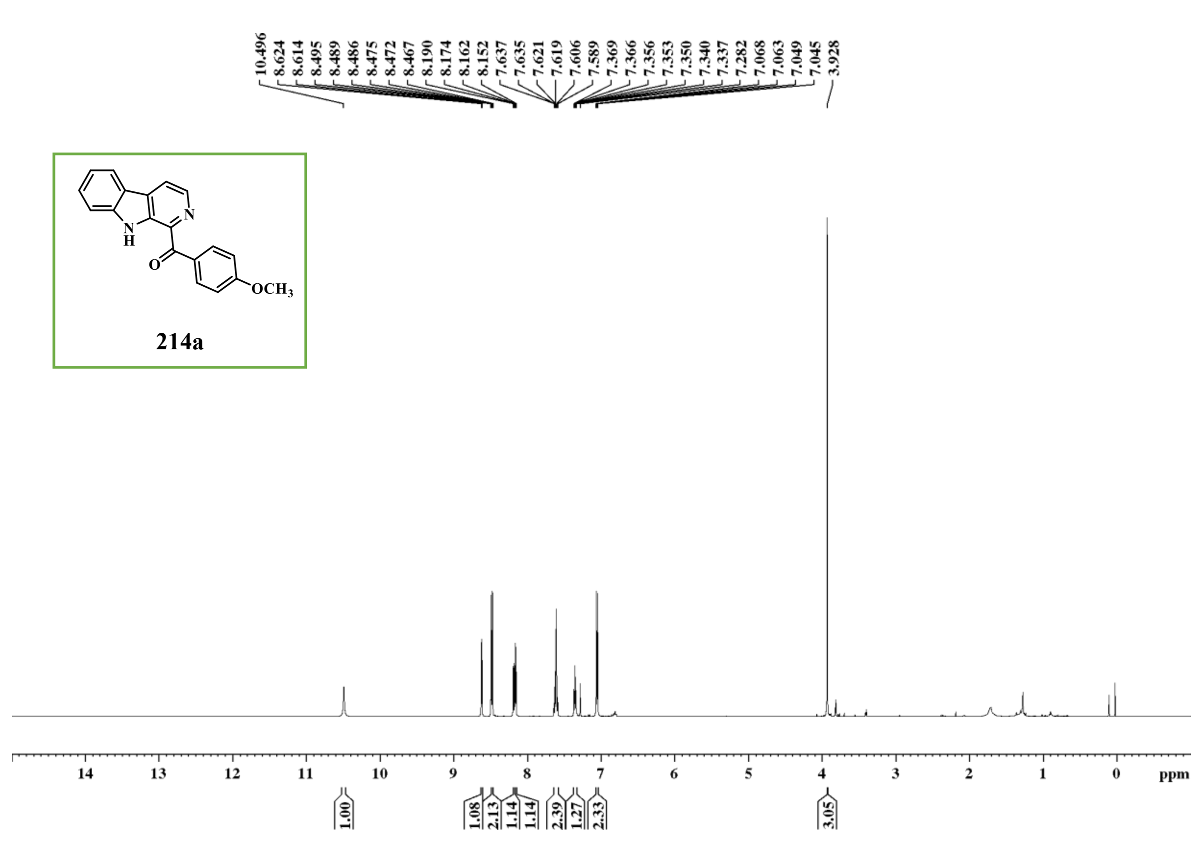
Acquisition Parameter

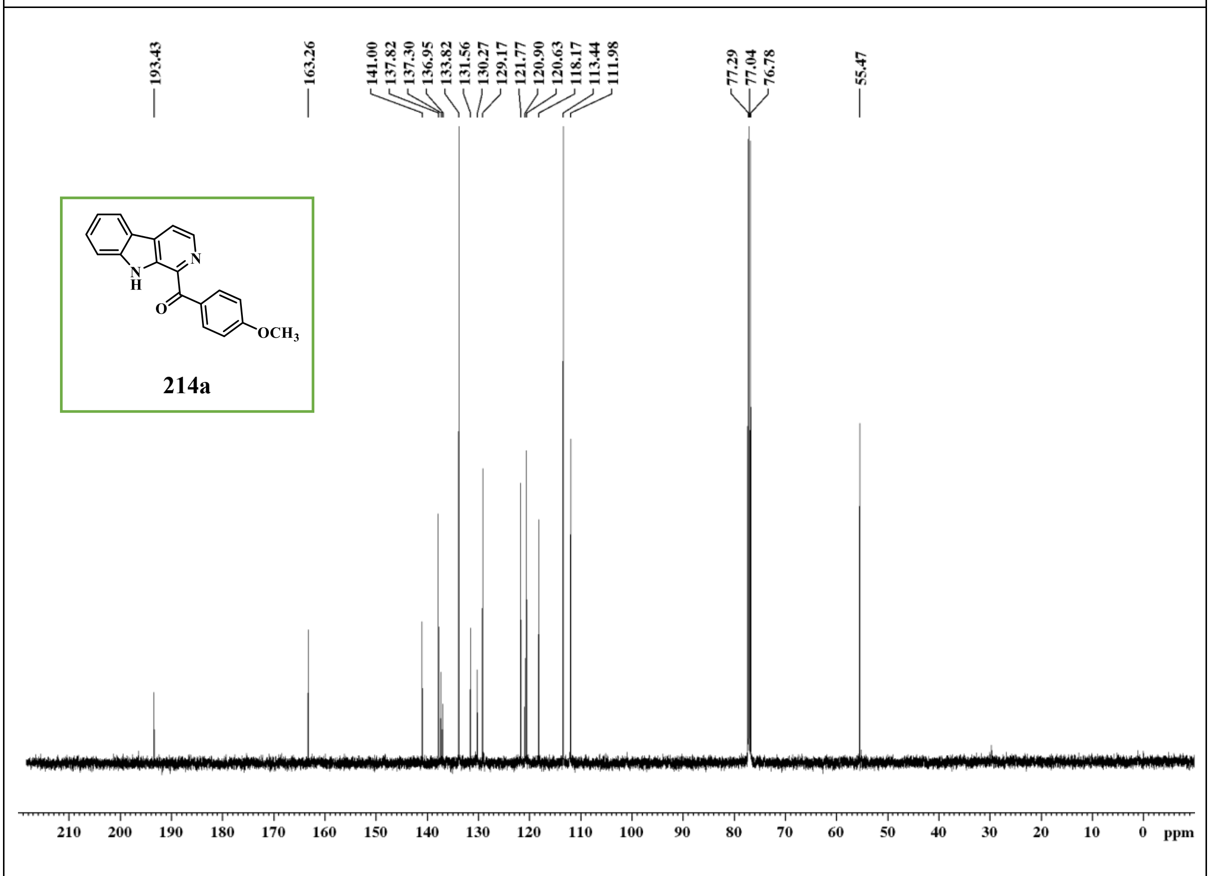
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



14.d
Bruker Compass DataAnalysis 4.2 printed: 11/22/2021 5:06:40 PM by: BDAL Page 1 of 1

^{1}H and ^{13}C NMR Spectra of Compound **214a**





HRMS of Compound 214a

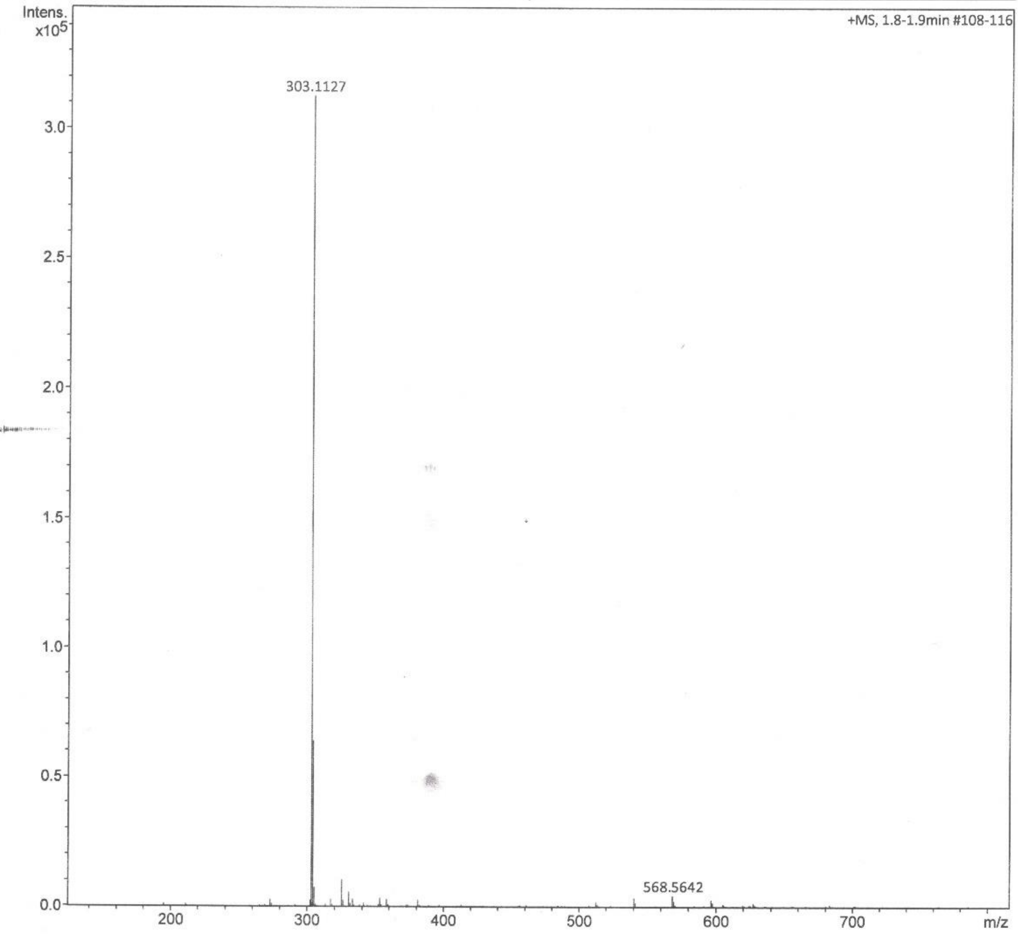
Display Report

Analysis Info

Analysis Name	D:\Data\2021-data\PROF.RN\NOV\15.d	Acquisition Date	11/22/2021 4:54:32 PM
Method	tune_low.m	Operator	BDAL
Sample Name	15	Instrument	maXis 255552.10138
Comment			

Acquisition Parameter

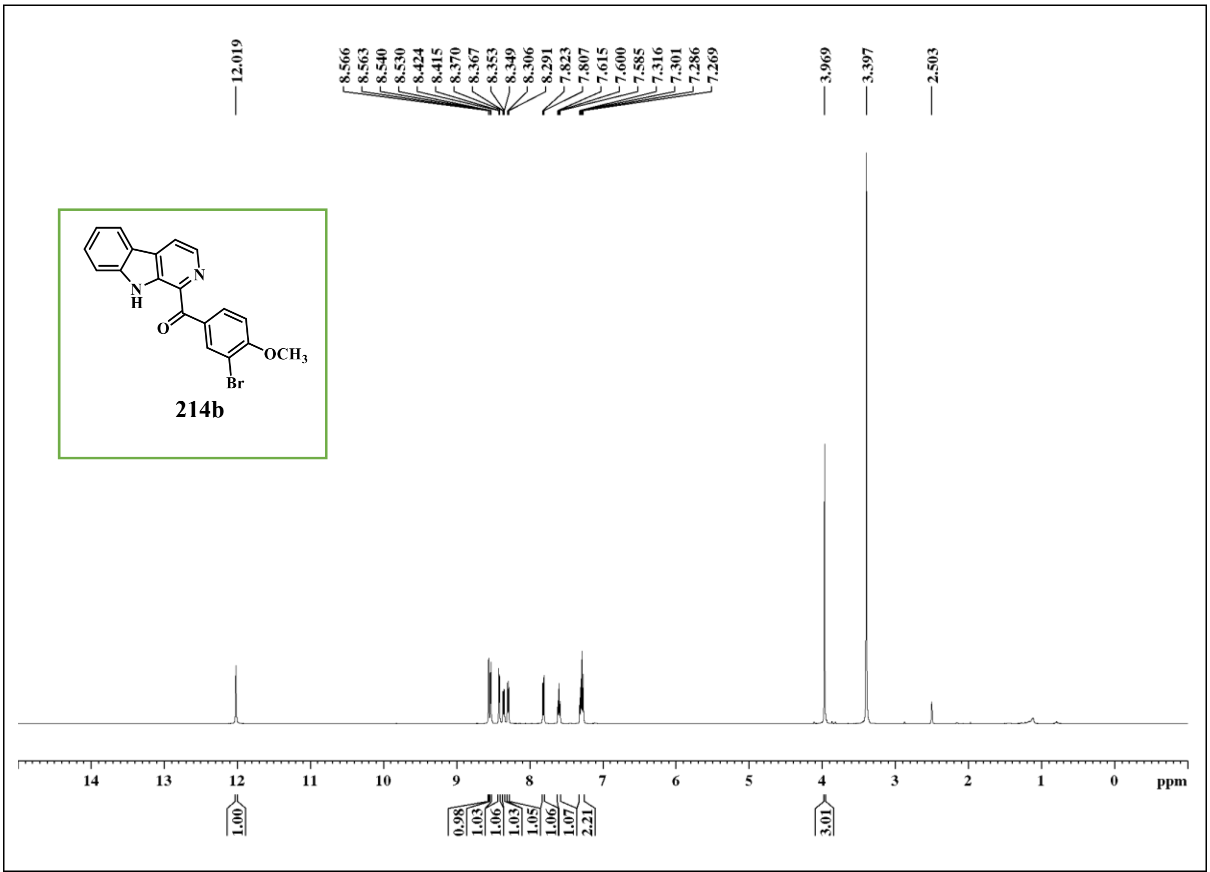
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C

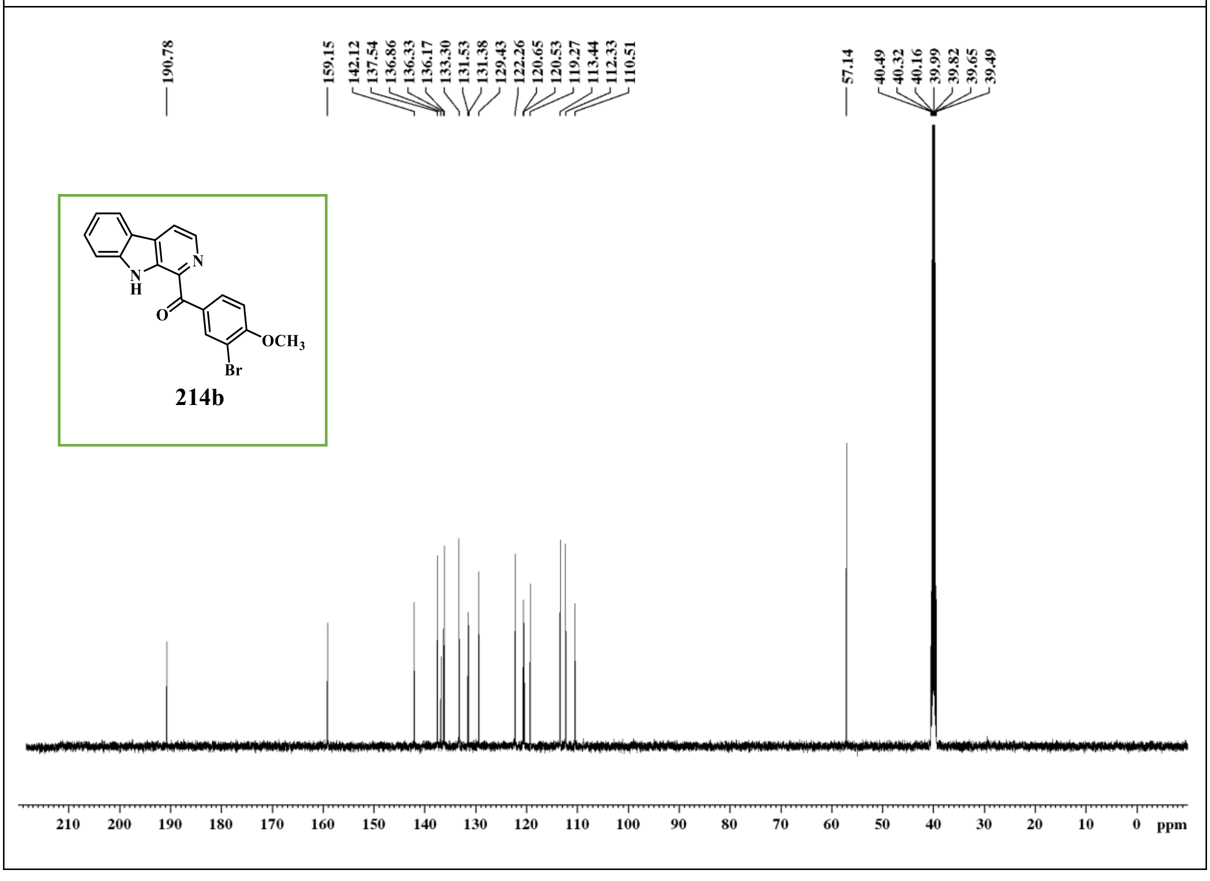


15.d

Bruker Compass DataAnalysis 4.2 printed: 11/22/2021 5:07:41 PM by: BDAL Page 1 of 1

^{1}H and ^{13}C NMR Spectra of Compound **214b**





HRMS of Compound 214b

Display Report

Analysis Info

Analysis Name D:\Data\2021-data\PROF.RN\NOV\16.d
Method tune_low.m
Sample Name 16
Comment

Acquisition Date 11/22/2021 4:59:15 PM
Operator BDAL
Instrument maXis 255552.10138

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Waste
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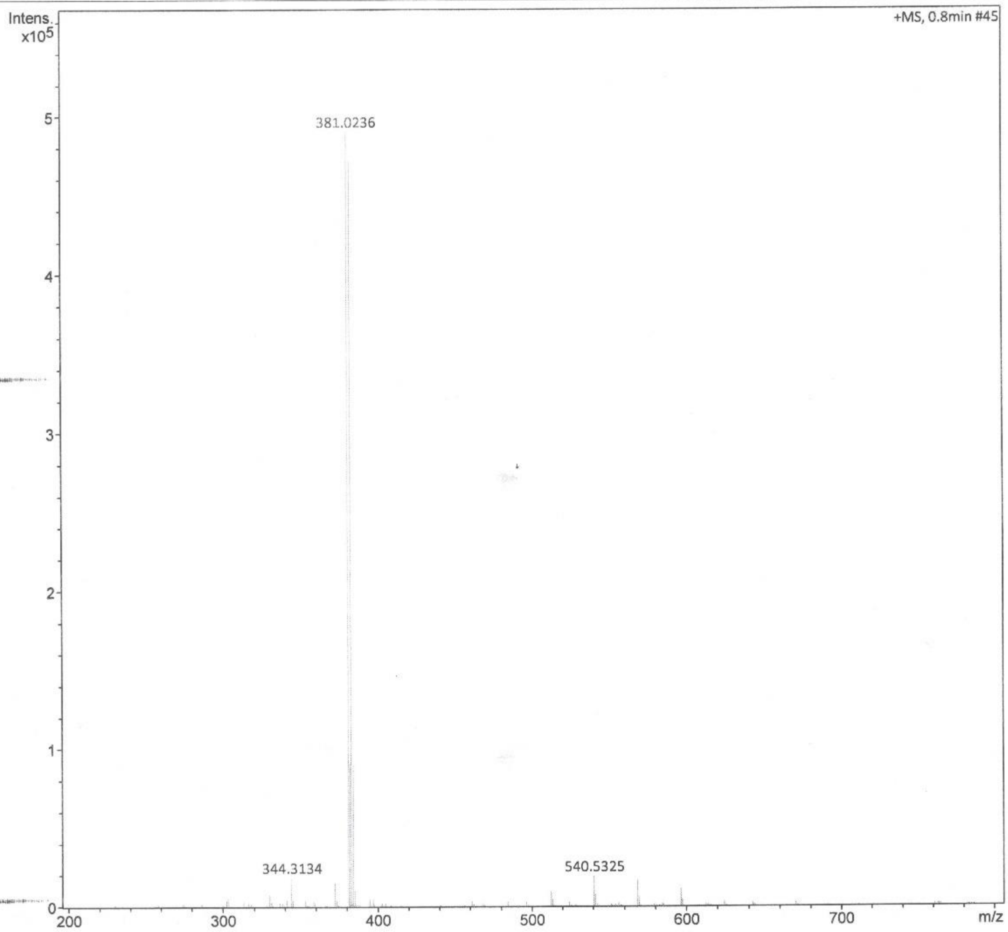
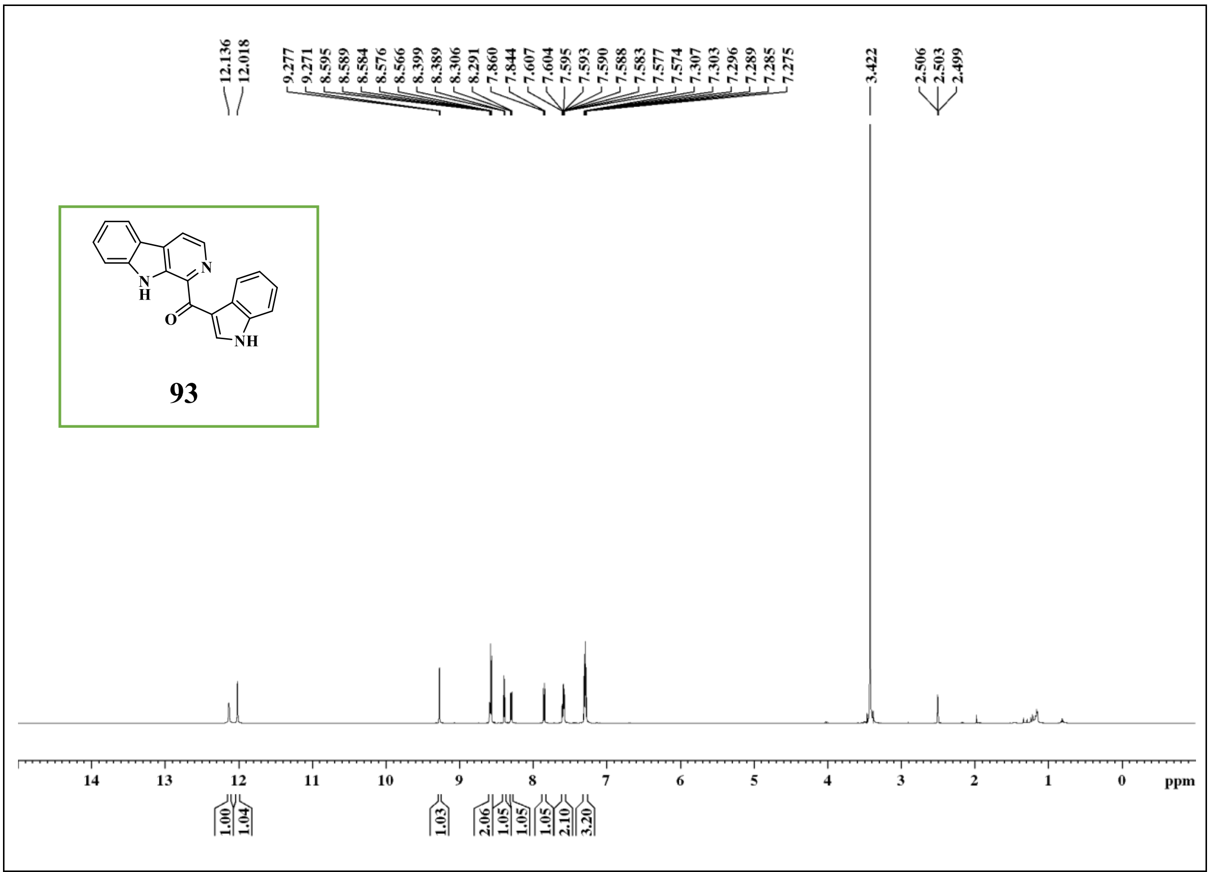
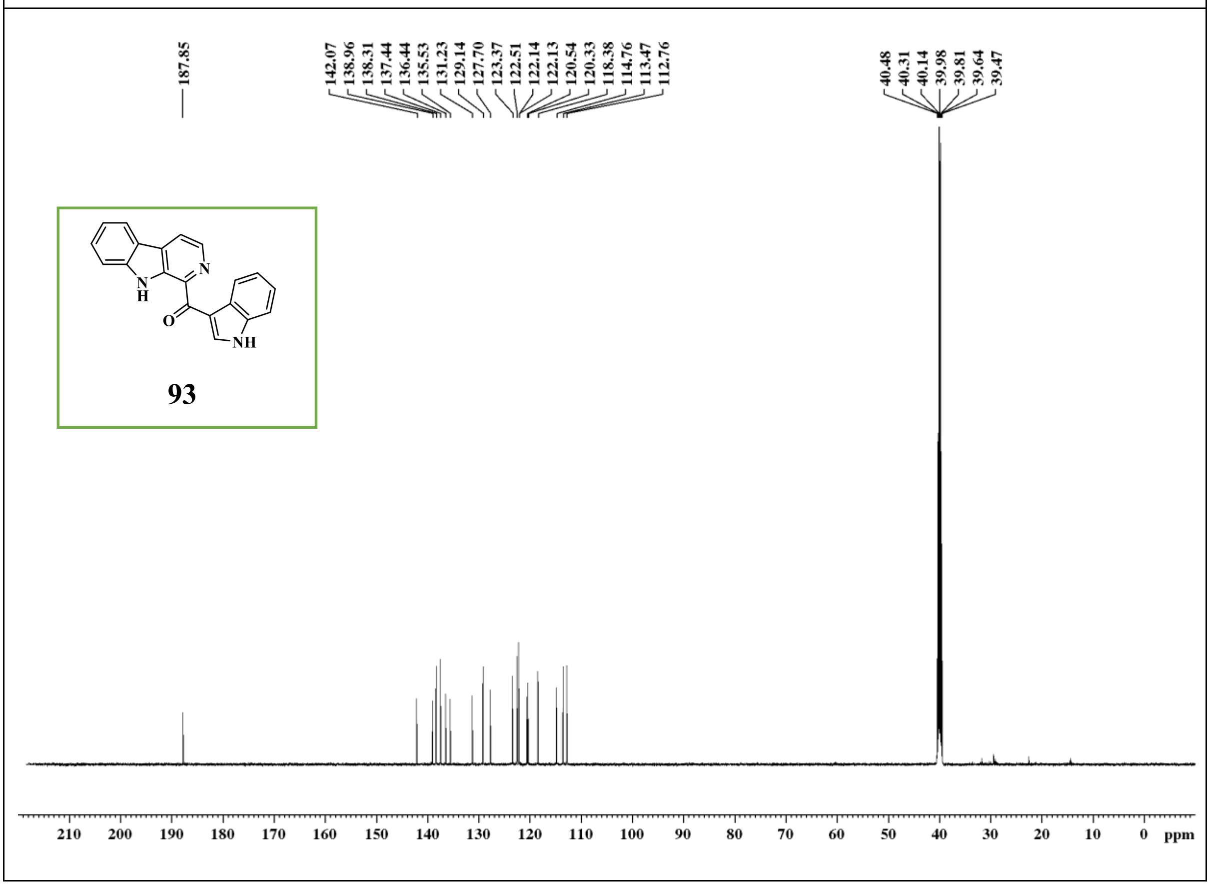


16.d
Bruker Compass DataAnalysis 4.2 printed: 11/22/2021 5:08:52 PM by: BDAL Page 1 of 1

[1]H and [13]C NMR Spectra of Compound **93**





HRMS of Compound 93

Display Report

Analysis Info

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Method	tune_low.m	Operator	BDAL
Sample Name	PY-BC-1	Instrument	maXis 255552.10138
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
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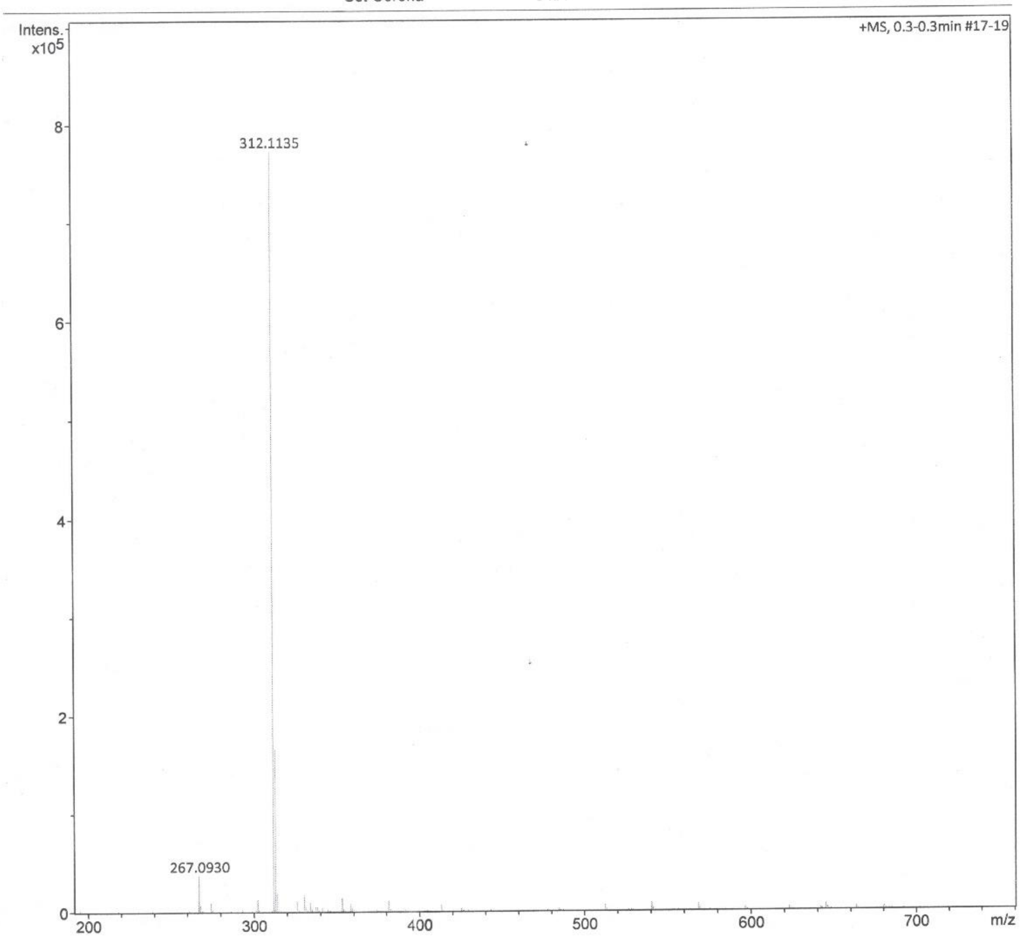
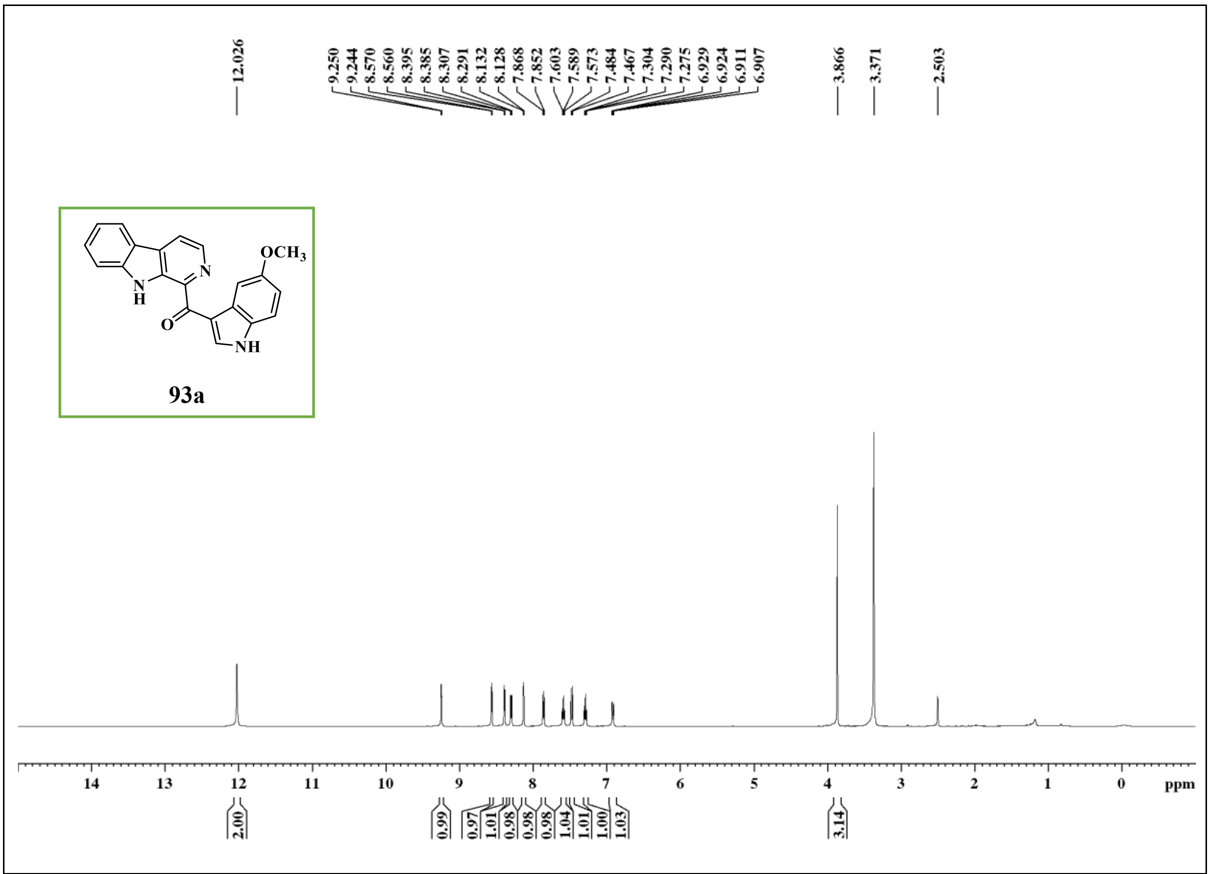
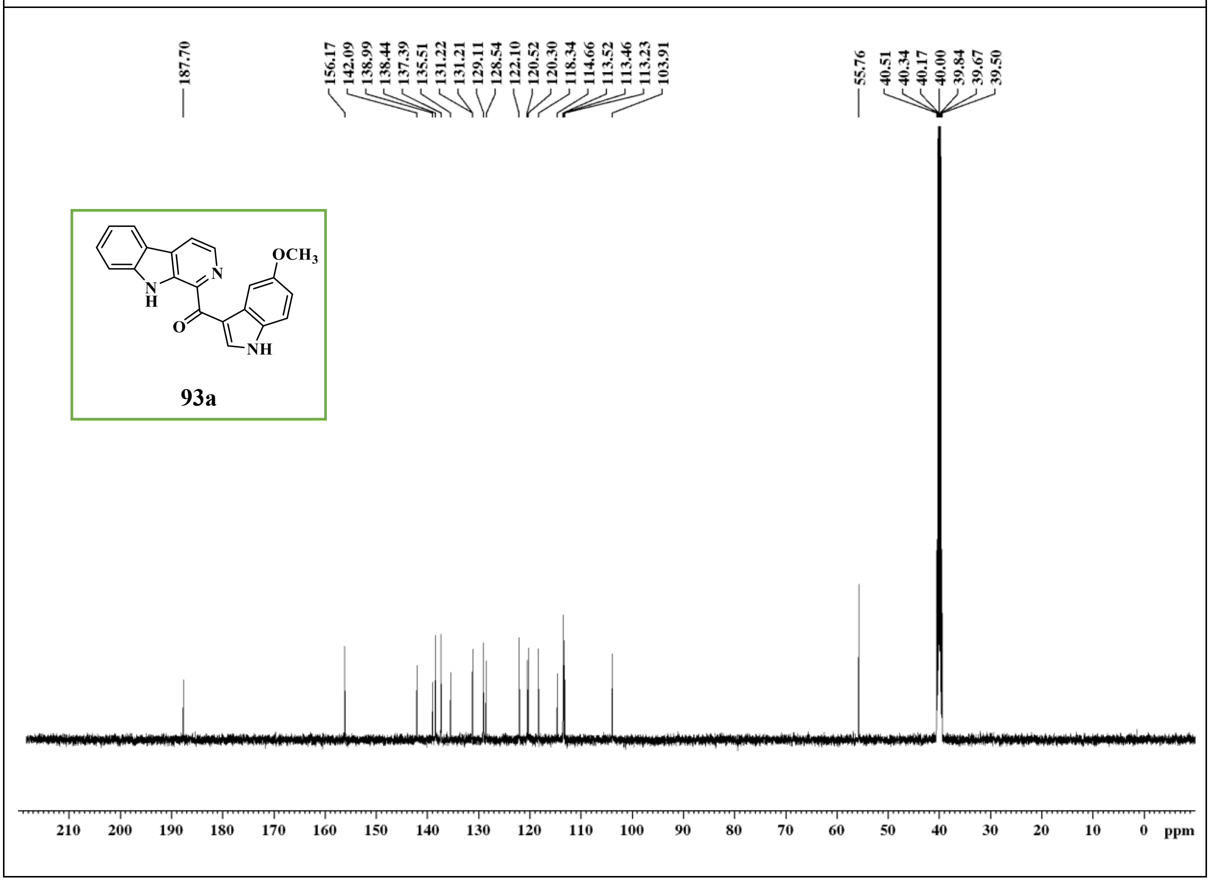


PY-BC-1.d

Bruker Compass DataAnalysis 4.2 printed: 10/12/2021 12:55:58 PM by: BDAL Page 1 of 1

^1H and ^{13}C NMR Spectra of Compound **93a**





HRMS of Compound 93a

Display Report

Analysis Info

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Method	tune_low.m	Operator	BDAL
Sample Name	18	Instrument	maXis 255552.10138
Comment			

Acquisition Parameter

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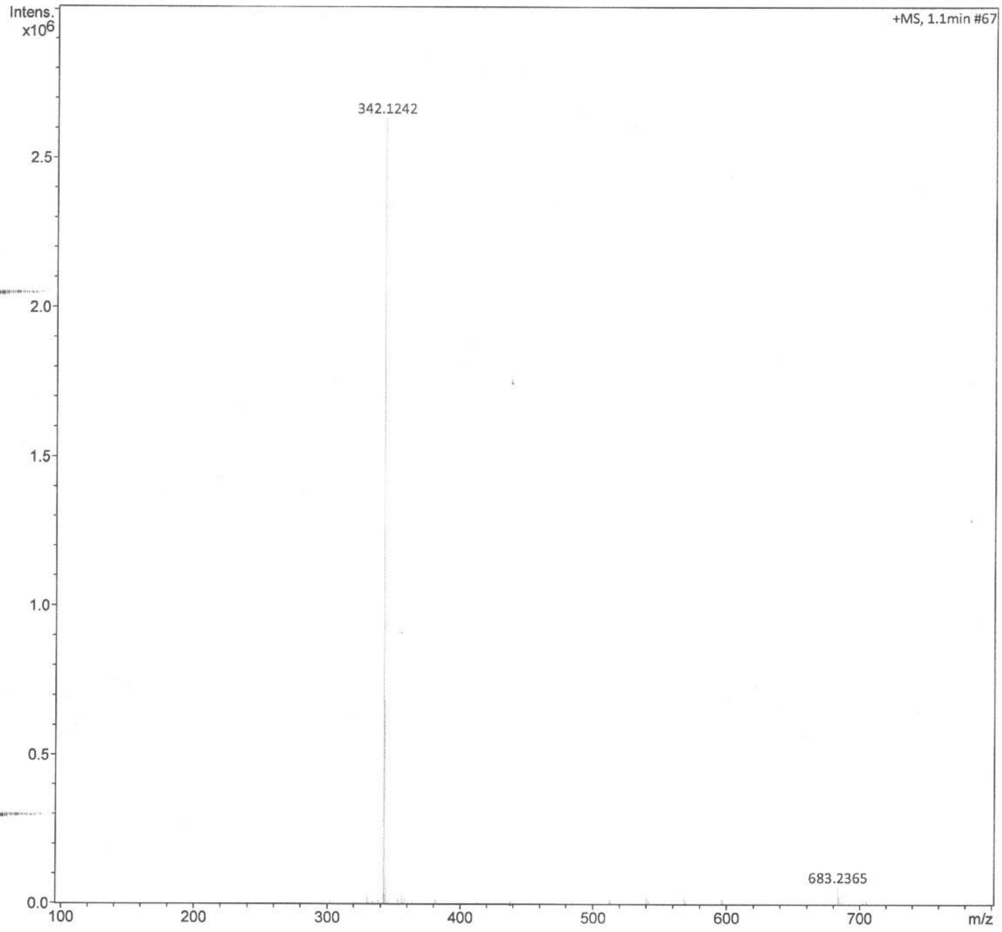
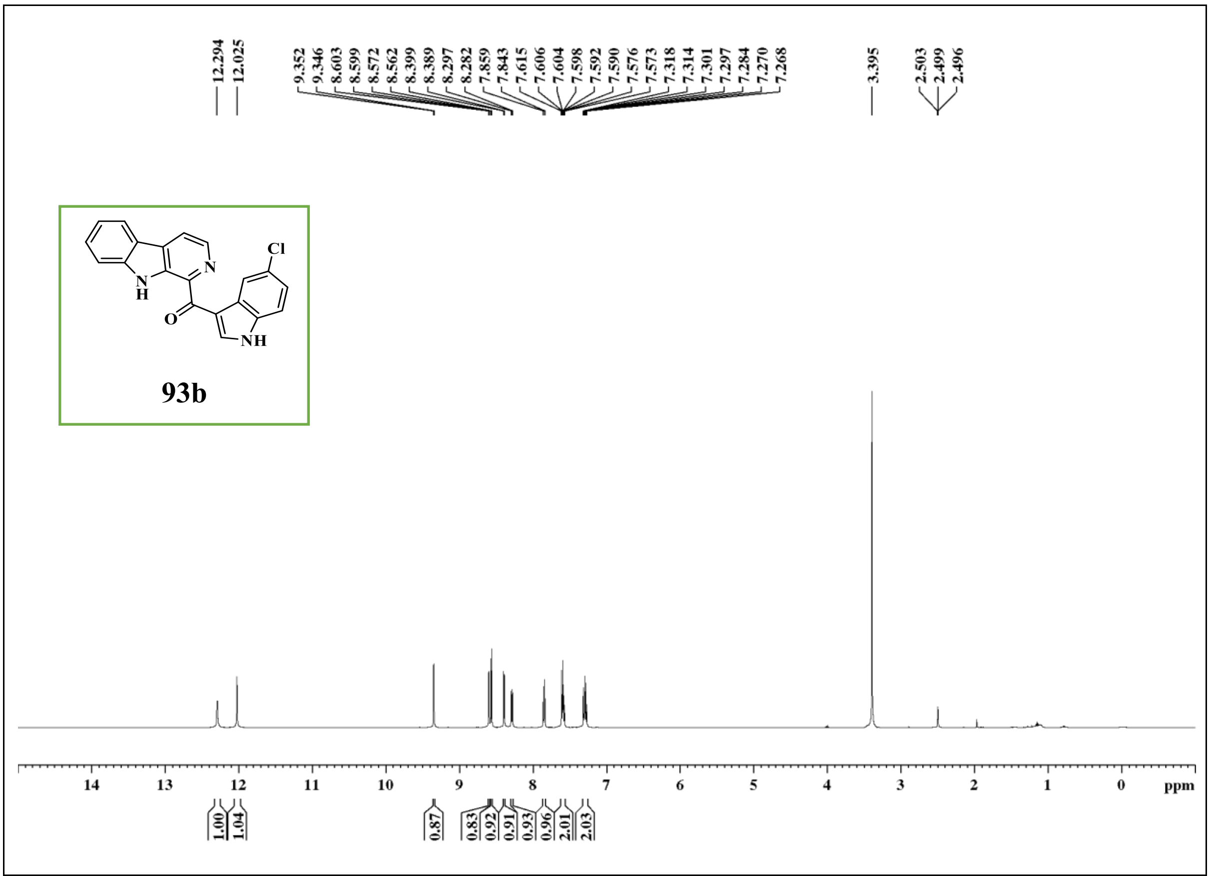
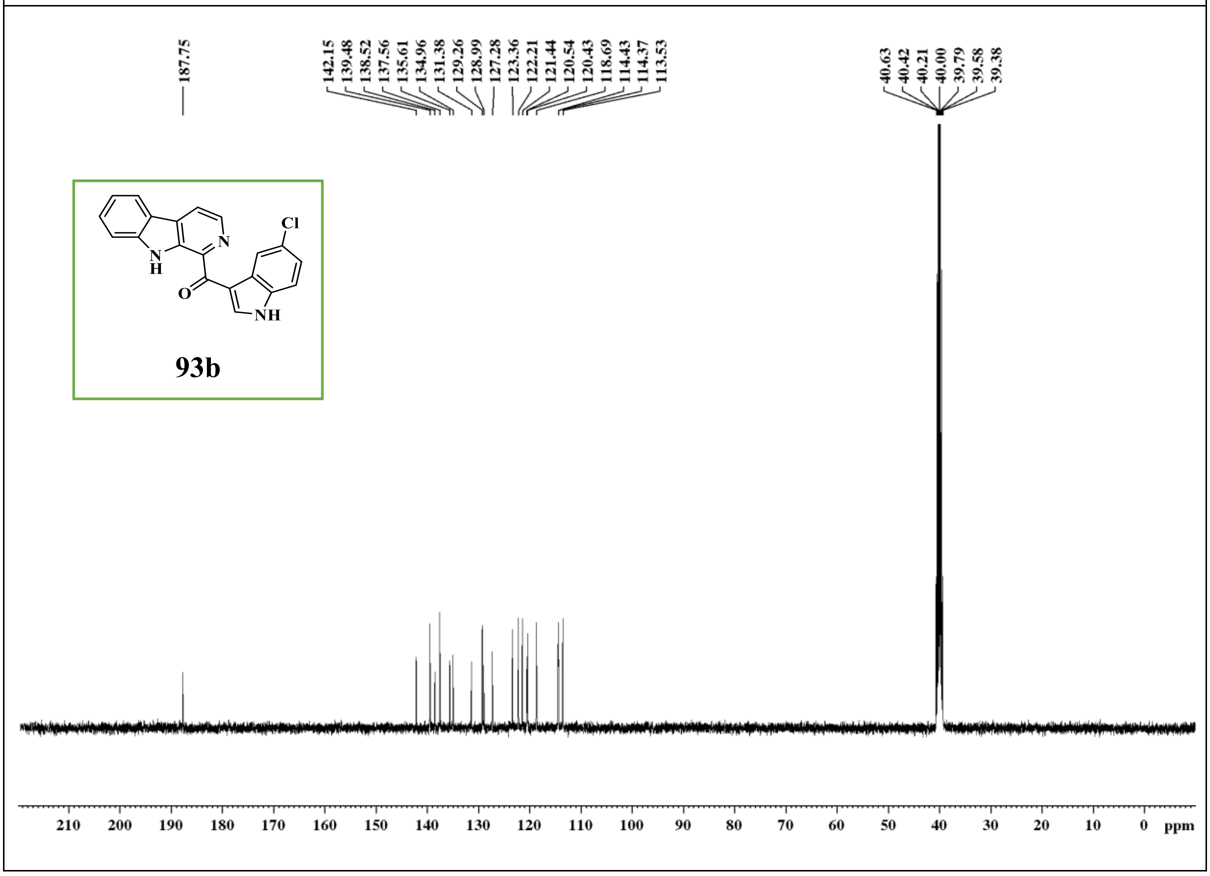


18.d

Bruker Compass DataAnalysis 4.2 printed: 11/24/2021 11:58:28 AM by: BDAL Page 1 of 1

[1]H and [13]C NMR Spectra of Compound **93b**





HRMS of Compound 93b

Display Report

Analysis Info

Analysis Name	D:\Data\2021-data\PROF.RN\NOV\20 R.d	Acquisition Date	11/24/2021 12:01:02 PM
Method	tune_low.m	Operator	BDAL
Sample Name	20 R	Instrument	maXis 255552.10138
Comment			

Acquisition Parameter

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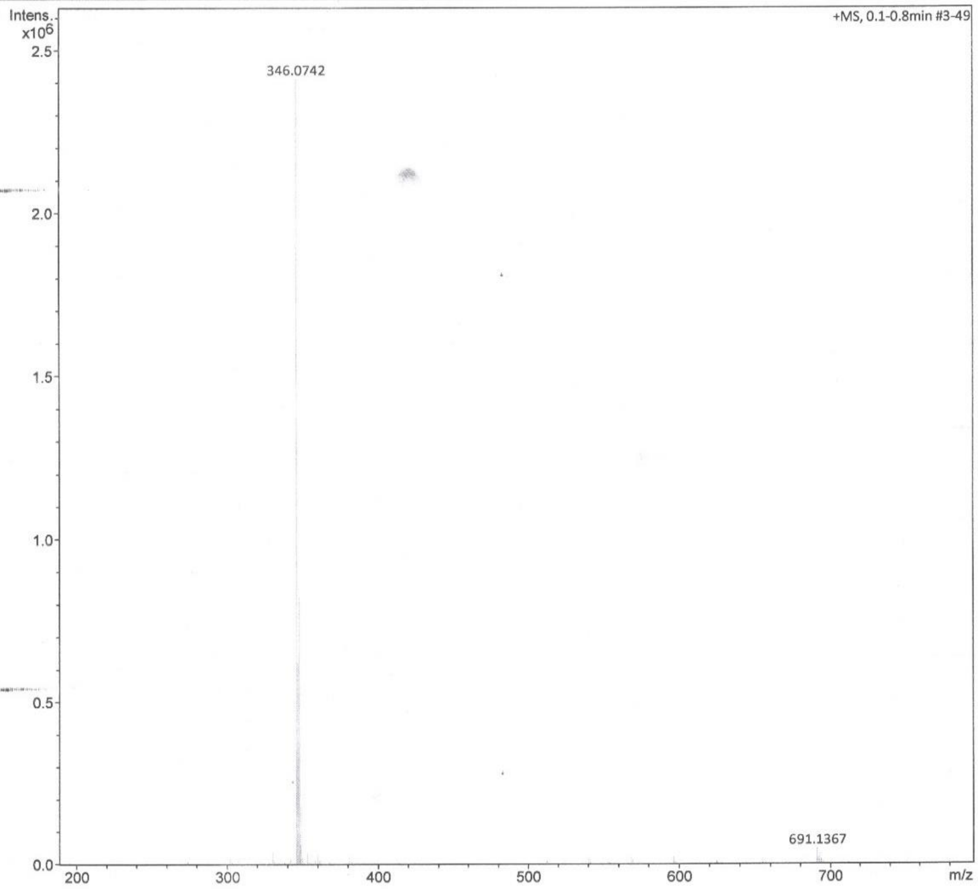
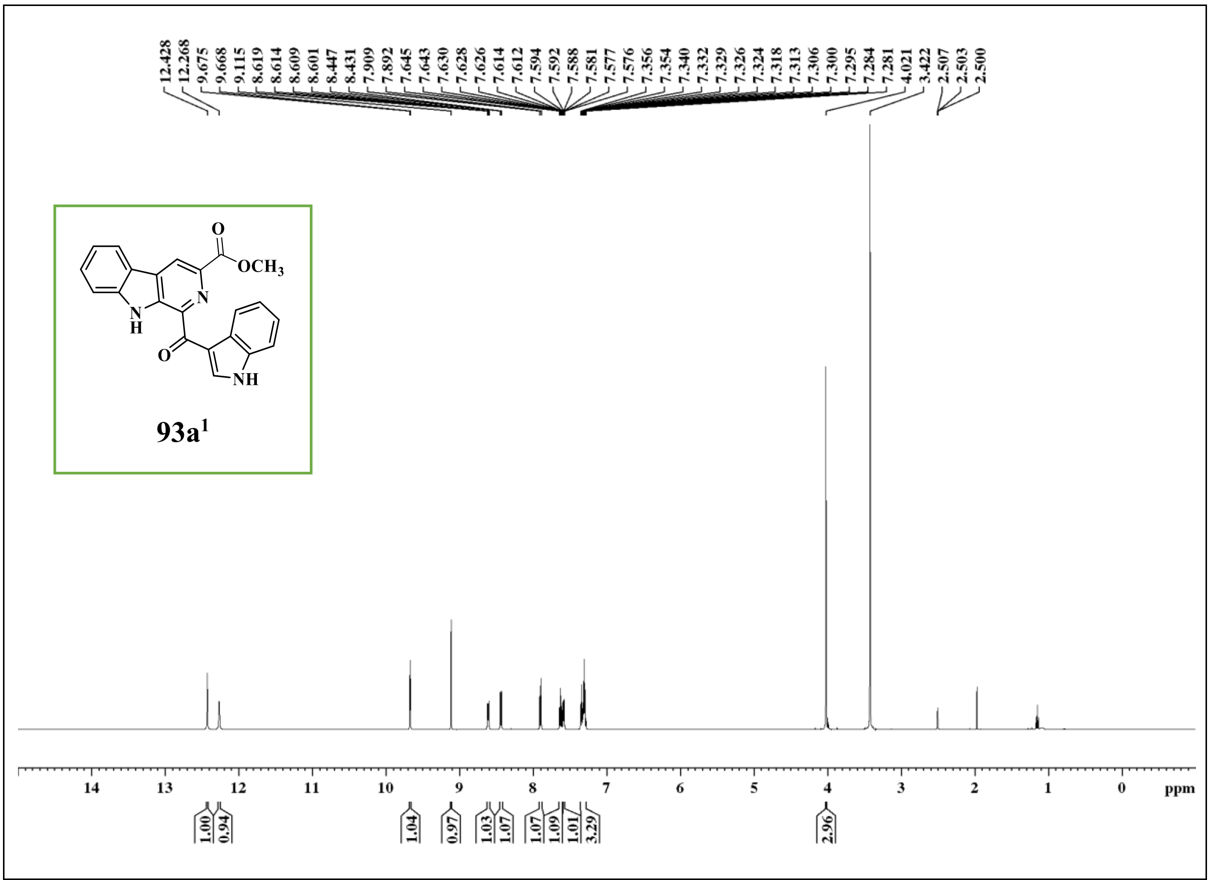
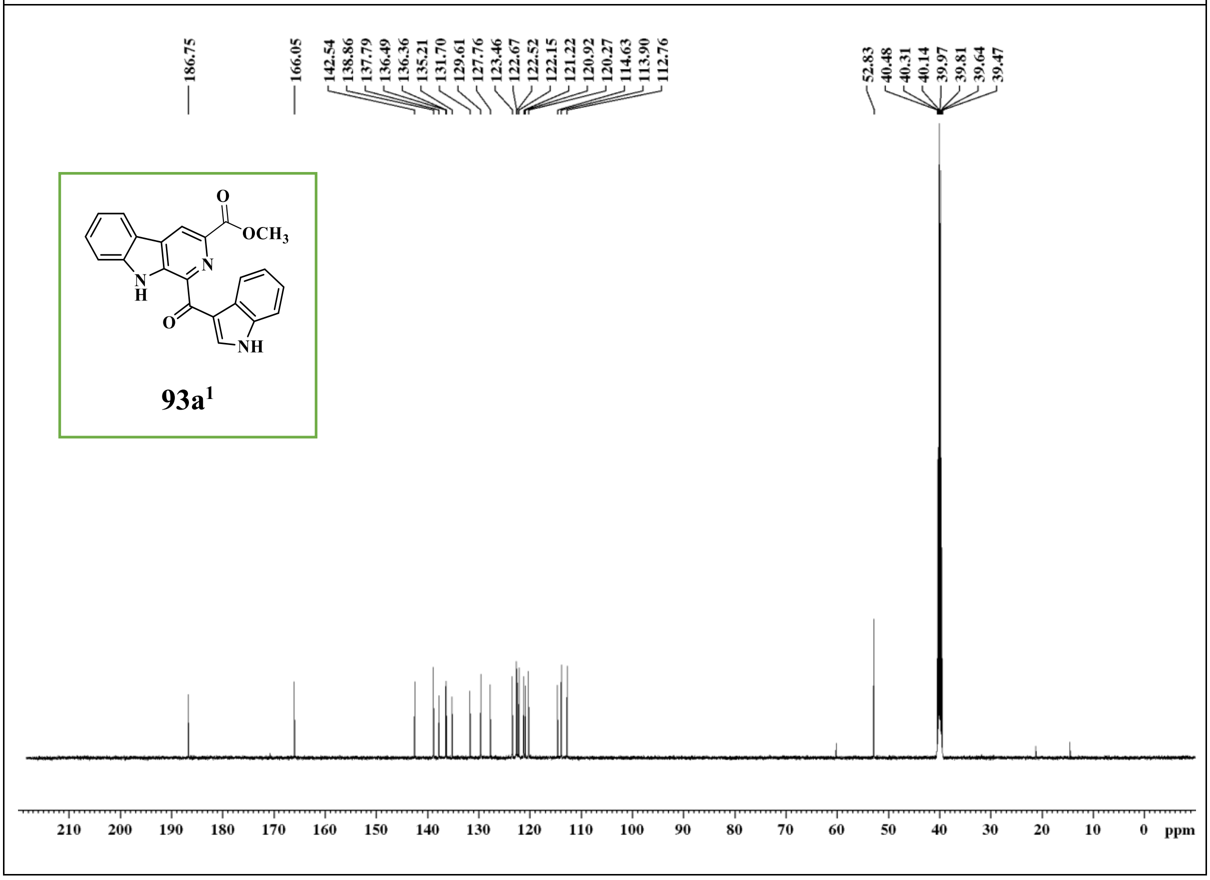


20 R.d

Bruker Compass DataAnalysis 4.2 printed: 11/24/2021 12:03:58 PM by: BDAL Page 1 of 1

^{1}H and ^{13}C NMR Spectra of Compound **93a[1]**





HRMS of Compound 93a[1]

Display Report

Analysis Info

Analysis Name D:\Data\2021-data\PROF.RN\oct\PY-BC-E2.d
Method tune_low.m
Sample Name PY-BC-E2
Comment

Acquisition Date 10/12/2021 1:08:26 PM
Operator BDAL
Instrument maXis 255552.10138

Acquisition Parameter

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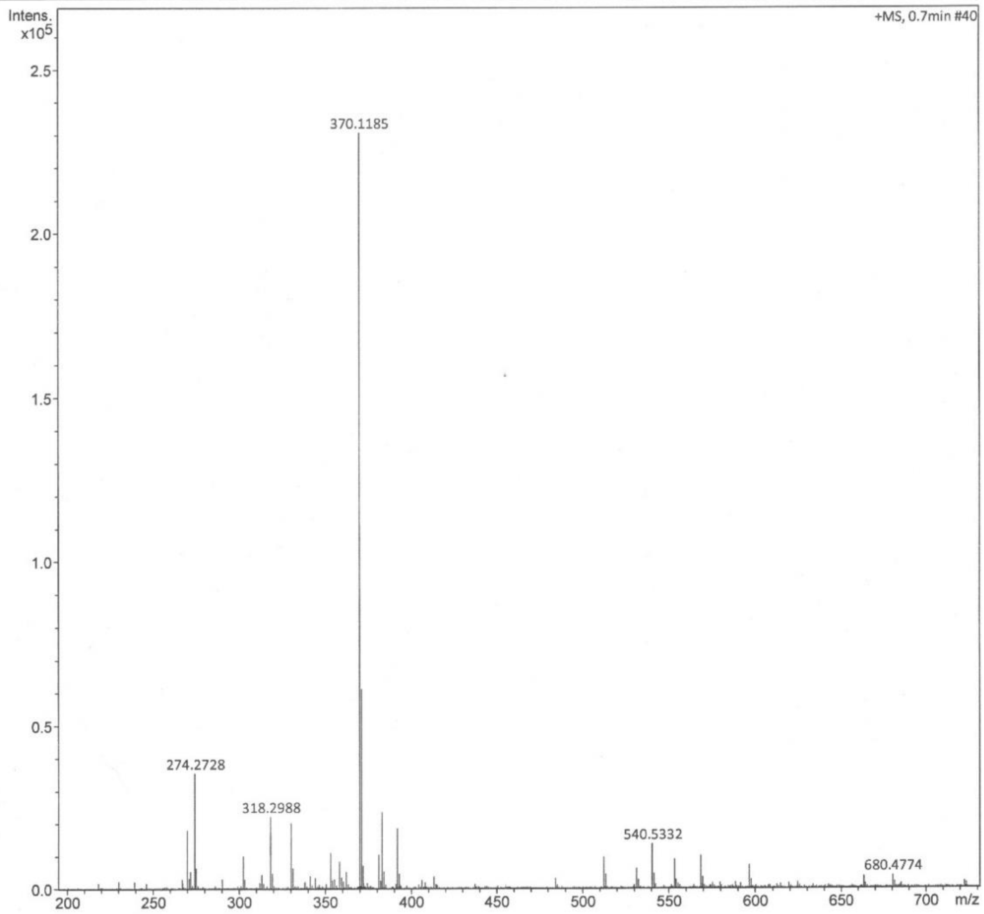
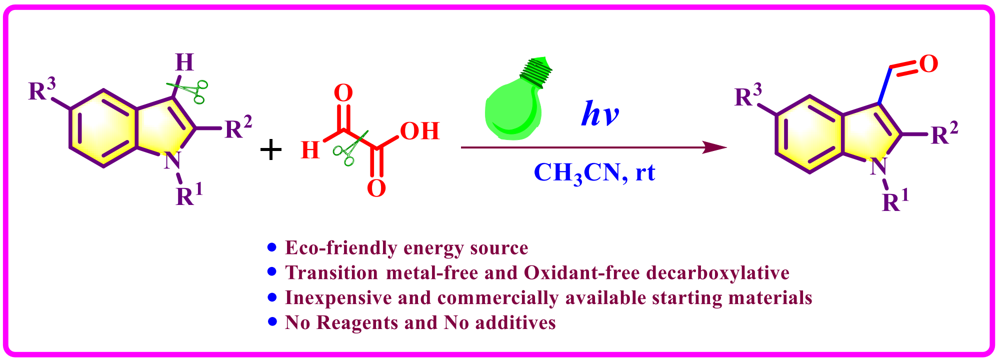
Scan End	1500 m/z	Set Charging Voltage	0 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



PY-BC-E2.d
Bruker Compass DataAnalysis 4.2 printed: 10/12/2021 1:10:36 PM by: BDAL Page 1 of 1

CHAPTER- *I (B)*

Photochemical Decarboxylative Formylation of Indoles with aq. Glyoxylic acid



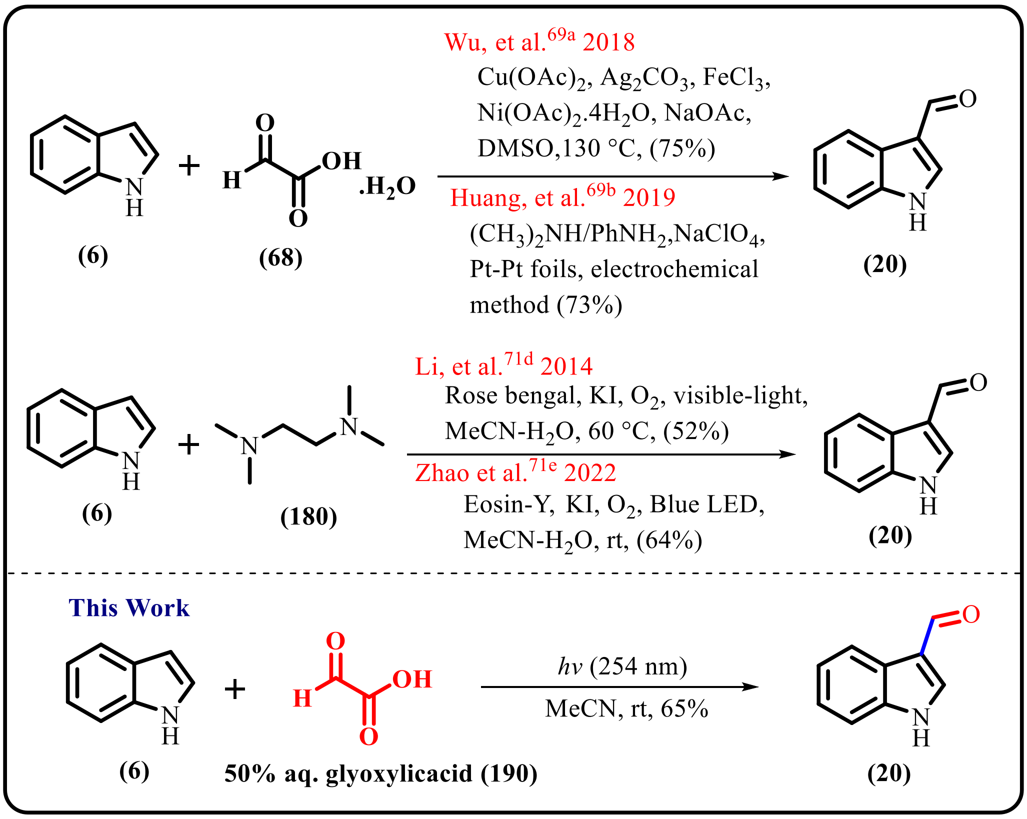
Abstract:

We reported a transition metal- and oxidant-free photochemical decarboxylative formylation of indoles was developed. This protocol enabled the direct C-H functionalization of indoles with 50% aq. glyoxylic acid solution as a formyl synthon under environmentally favourable conditions with good to moderate yields. This method would be attractive and alternative method to access biologically important molecules.

1.1.1 Introduction:

The aldehyde group is a ubiquitous functional group, and aldehydes are versatile intermediates, widely used in medicines, pesticides, chemical raw materials, and functional group interconversions; moreover, they are frequently used in syntheses of natural products and in drug discovery.[3c] Several formylation reactions[85] of aromatic or heteroaromatic compounds have been reported in recent decades.[2] Indole-3-carboxaldehyde (**20**) and its derivatives are key structures for the preparation of biologically active molecules, and are important generic materials that are usually synthesized by conventional methods such as the Vilsmeier–Haack,[67a] Riemer–Tiemann,[67b] Rieche,[67c] Duff,[67d] or other methods. However, these procedures suffer from one or more drawbacks, such as the use of non-ecofriendly reagents, the need for harsh reaction conditions (high temp, excess of strong bases and strong acids usage), or low selectivity.

Figure 1.1. Differences between previous reports and present approach for the synthesis of indole 3-carboxaldehyde:



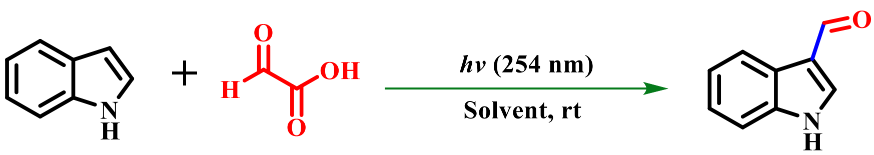
Recently, metal-catalyzed[74-75] or photo-mediated decarboxylative coupling reactions[76] have emerged and have attracted much attention due to their use of inexpensive carboxylic acids as starting materials. The use of carboxylic acids provides greater structural diversity and ease of handling, and the reactions proceed under neutral conditions with CO_2 as a byproduct.

Decarboxylative formylations of indoles have been reported with glyoxylic acid mono hydrate **68** as formyl equivalent that proceed under Ni -catalyzed[69a] (combinations of several metals with Ni were used) or electrochemical conditions.[69b] In another report, TMEDA **180** was used as a carbon source in the presence of photoredox catalysts to give moderate yields of the required products.[69c] These three methods involve the use of expensive metal catalysts,[73] electrochemistry, or metal-based photocatalysts[73f-g] (Figure **1.1**).

1.1.2 Results and discussion:

Here, we report a transition-metal-free and oxidant-free photochemical decarboxylative formylation of indoles with 50% aqueous glyoxylic acid **190** as a formyl synthon, which proceeds in good to moderate yields.

Table 2.1 Optimization of the reaction conditions (20) [a]



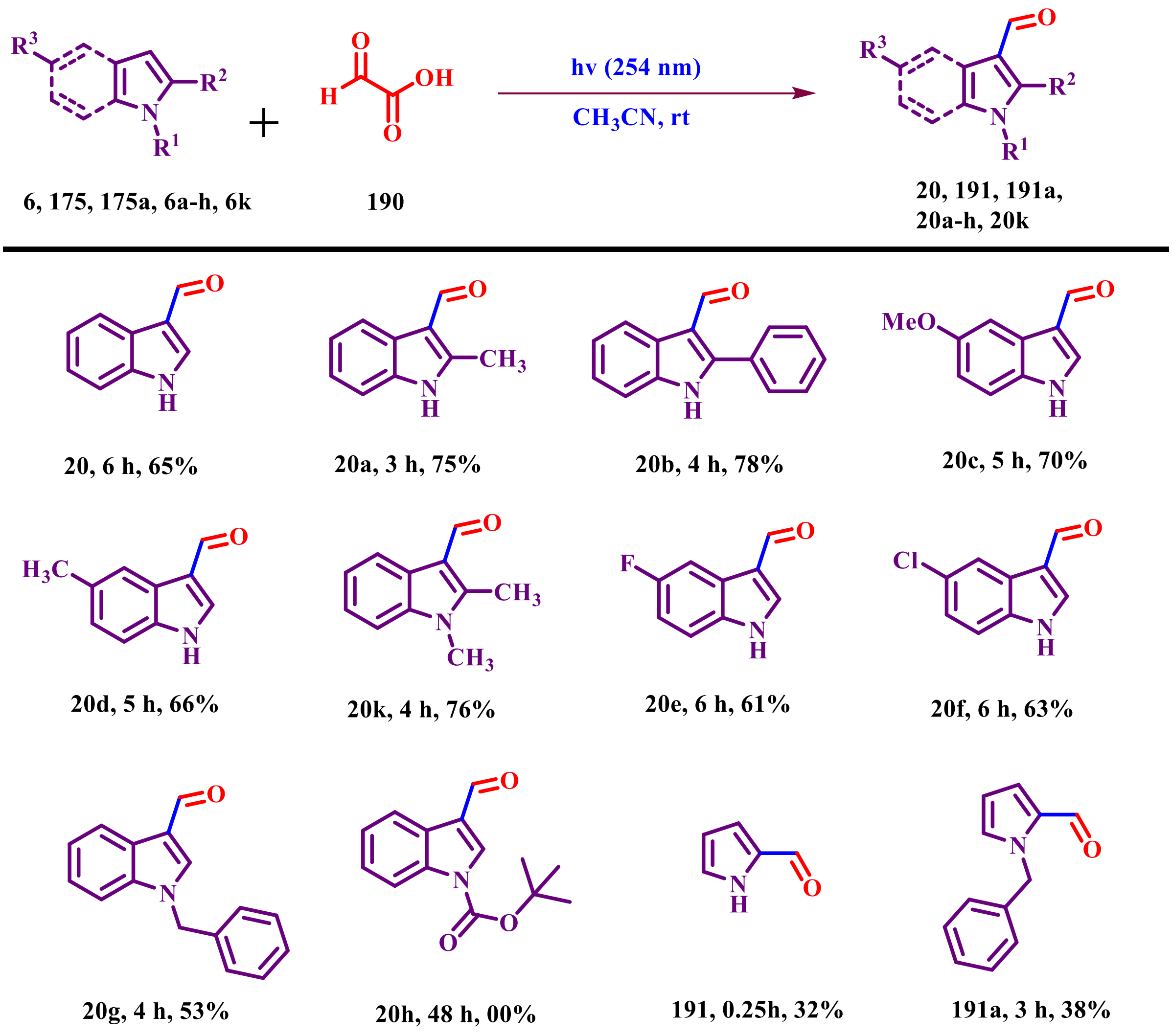
(6) **(190)** **(20)**

Entry	Base	Solvent	Time(h)	Yield (%)
1.	K_2CO_3	CH_3CN	24	26
2.	NaOH	CH_3CN	24	21
3.	-	EtOH	24	Trace
4.	-	DMSO	12	18
5.	-	CH_3CN	6	65
6.	-	Acetone	12	25

[a] Reaction conditions: indole (**20**, 0.25 mmol), 50% aq. glyoxylic acid (**190,** 0.51 mmol), solvent (6.0 mL), irradiation by eight 8 W 254 nm UV lamps, rt. Isolated yields after chromatography.

Initially, we attempted a formylation of indole with 50% aq. glyoxylic acid **190** under UV irradiation (λ = 254 nm) with K_2CO_3 as a base and acetonitrile as a solvent, affording 1*H*-indole-3-carboxaldehyde (**20**) in 26% yield (Table **2.1** in entry 1).The use of NaOH as a base decreased the yield to 21% (entry 2).We then examined various solvents (EtOH, DMSO, CH_3CN, and acetone) and we found that CH_3CN was the best solvent and that no base was required (entries 3–6).

Scheme 2.1. Substrate scope for the synthesis of indole-3-carboxaldehyde (20):

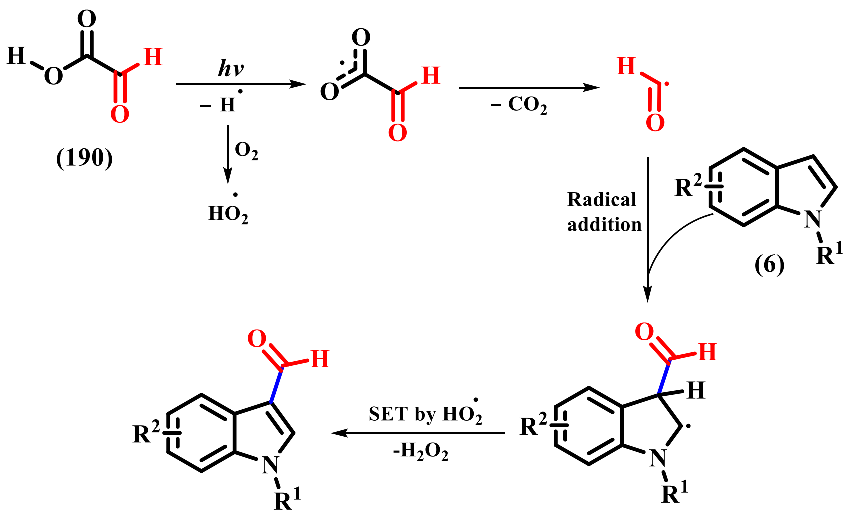


Reaction conditions: **6, 6a-h, 6k, 175, 175a** (1.0 equiv), 50% aqueous glyoxylic acid solution **190** (2 equiv), Acetonitrile (6.0 mL) using eight 8W 254 nm UV-lamps, room temperature.; Isolated yields after chromatography.

With the optimized reaction condition in hand, we carried out reactions of various substituted indoles **6a-h, 6k** with aq. glyoxylic acid **190** to afford the corresponding indole-3-carboxaldehydes **20a-h, 20k** in good to moderate yields of 53–78% (Scheme **2.1**), whereas the *N*-BOC-protected indole **6h** failed to give the corresponding product. With the same method, pyrrole (**175**) and *N*-benzylpyrrole (**175a**) were formylated to give **191** and **191a** in yields of 32 and 38%, respectively.

On the basis of reports available in the literature,[6e,7c,10c,11] we postulated the possible decarboxylative formylation mechanism shown in Scheme **2.2**

Scheme 2.2. Proposed mechanism:



1.1.3 Conclusion:

In conclusion, we have developed a photochemical decarboxylative formylation of indoles with aqueous glyoxylic acid as a formyl source.[13] Advantages of this method include its commercially available inexpensive starting materials; no transition metals, additives, or oxidants; the ease of handling of the reagents; and good to moderate yields of the products.

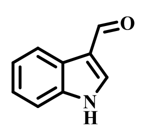
1.1.4 Experimental section:

All the reactions were observed and monitored by using precoated thin layer chromatography with ethyl acetate/hexane as solvent system. TLC plates either visualized under UV-light and/or iodine chamber or stained by dipping in 2,4-nitrophenylhydrazine TLC stain. Commercially available reagents were used in the reaction without any further purification. All compounds were characterized by analysis through TLC, melting point (if solid), ^{1}H NMR, ^{13}C NMR. The crude compounds were purified by column chromatography with silica gel (100–200 mesh) and eluted with ethyl acetate/hexane mixture to obtain pure products. ^{1}H and ^{13}C NMR spectra were recorded at Bruker 400 and 100 MHz, respectively, or at 500 MHz and 125 MHz, respectively. Chemical shifts are calculated in ppm units and the coupling constants (J) in Hz units. $CDCl_3$ and DMSO-d_6 were used as the NMR solvents and signal positions were measured, correlate to the signal for $CDCl_3$ (δ 7.28 ppm at ^{1}H NMR and δ 77.06 ppm at ^{13}C NMR) and DMSO-d_6 (δ 2.50 ppm at ^{1}H NMR and δ 39.92 ppm at ^{13}C NMR). NMR Data describes as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Melting points were determined by using a capillary melting point apparatus.

General procedure for formylation of indole:

A 10 mL quartz tube was charged with indole **6** (0.25 mmol, 1 equiv), 50% aq. glyoxylic acid **190** (0.51 mmol, 2 equiv), and CH_3CN (6.0 mL), and the solution was irradiated with eight 8 W 254 nm UV lamps in a photochemical reactor at rt for 6 h until the reaction was complete (TLC). The reaction was then quenched with H_2O (5 mL) and the mixture was extracted with EtOAc (3 × 5 mL). The extracts were dried (Na_2SO_4) and concentrated in a rotary evaporator, and the crude product was purified by column chromatography on silica gel with an ethyl acetate/hexane solvent mixture.

1*H*-Indole-3-carboxaldehyde (20)



20

Physical state: yellow solid

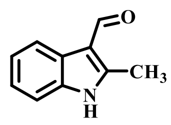
Yield: 24 mg (65 %)

M.P: 189-191 °C (Lit.[73a] 190-192 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.14 (br s, 1H), 9.95 (s, 1H), 8.28 (d, J = 3.1 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.28-7.21 (m, 2H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6): δ 185.4, 138.9, 137.5, 124.5, 123.9, 122.5, 121.3, 118.6, 112.8.

2-Methyl-1*H*-indole-3-carboxaldehyde (20a)



20a

Physical state: yellow solid

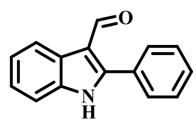
Yield: 27 mg (75 %)

M.P: 191-194 °C (Lit.[73h] 195-200 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.00 (br s, 1H), 10.09 (s, 1H), 8.09-8.07 (m, 1H), 7.42-7.41 (m, 1H), 7.22-7.16 (m, 2H), 2.71 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$): δ 184.7, 149.0, 135.8, 126.0, 123.0, 122.3, 120.4, 114.1, 111.8, 11.9.

2-Phenyl-1*H*-indole-3-carboxaldehyde (20b)



20b

Physical state: yellow solid

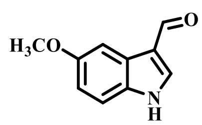
Yield: 26 mg (78 %)

M.P: 248-251 °C (Lit.[73a] 250-252 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.43 (br s, 1H), 9.98 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.80-7.78 (m, 2H), 7.62-7.58 (m, 3H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.32-7.28 (m, 1H), 7.27-7.24 (m, 1H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ 185.9, 149.5, 136.4, 130.3, 130.2, 130.2, 129.4, 126.2, 124.1, 122.9, 121.5, 113.9, 112.4.

5-Methoxy-1*H*-indole-3-carboxaldehyde (20c)



20c

Physical state: yellow solid

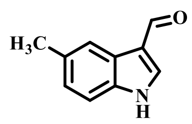
Yield: 24 mg (70 %)

M.P: 175-178 °C (Lit.[73a] 180-181 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.01 (br s, 1H), 9.89 (s, 1H), 8.20 (d, *J* = 3.1 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.78 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ 185.2, 156.1, 138.8, 132.2, 125.3, 118.5, 113.7, 113.6, 103.0, 55.7.

5-Methyl-1*H*-indole-3-carboxaldehyde (20d)



20d

Physical state: yellow solid

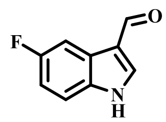
Yield: 24 mg (66 %)

M.P: 148-151 °C (Lit.[73a] 149-150 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.04 (br s, 1H), 9.90 (s, 1H), 8.22 (d, *J* = 3.1 Hz, 1H), 7.91 (d, *J* = 0.5 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.08 (dd, *J* = 8.3, 1.4 Hz, 1H), 2.40 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$): δ 185.3, 138.9, 135.8, 131.5, 125.3, 124.8, 121.0, 118.3, 112.5, 21.6.

5-Fluoro-1*H*-indole-3-carboxaldehyde (20e)



20e

Physical state: yellow solid

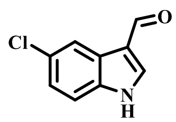
Yield: 22 mg (61 %)

M.P: 142-145 °C (Lit.[73a] 144-146 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.23 (br s, 1H), 9.92 (s, 1H), 8.35 (s, 1H), 7.76 (dd, *J* = 9.5, 2.6 Hz, 1H), 7.53 (dd, *J* = 8.8, 4.5 Hz, 1H), 7.14-7.10 (m, 1H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ 185.4, 159.1 (d, *J* = 233.8 Hz), 140.0, 134.0, 125.1 (d, *J* = 10.9 Hz), 118.5 (d, *J* = 4.4 Hz), 114.2 (d, *J* = 9.8 Hz), 112.0 (d, *J* = 25.7 Hz), 106.1 (d, *J* = 24.1 Hz).

5-Chloro-1*H*-indole-3-carboxaldehyde (20f)



20f

Physical state: yellow solid

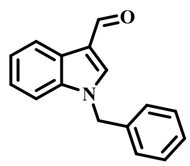
Yield: 22 mg (63 %)

M.P: 210-213 °C (Lit.[73a] 214-216 °C)

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 12.29 (br s, 1H), 9.93 (s, 1H), 8.35 (d, *J* = 3.0 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.27 (dd, *J* = 8.6, 2.1 Hz, 1H).

^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$): δ 185.6, 139.9, 135.9, 127.2, 125.7, 123.9, 120.3, 118.0, 114.6.

1-Benzyl-1*H*-indole-3-carboxaldehyde (20g)



20g

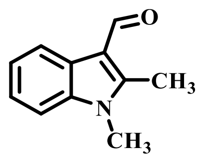
Physical state: yellow oil

Yield: 18 mg (53 %)

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.00 (s, 1H), 8.38-8.36 (m, 1H), 7.70 (s, 1H), 7.37-7.36 (m, 3H), 7.34-7.31 (m, 3H), 7.20-7.19 (m, 2H), 5.34 (s, 2H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 184.6, 138.6, 137.5, 135.3, 129.1, 128.4, 127.2, 125.5, 124.1, 123.0, 122.1, 118.5, 110.4, 50.9.

1,2-Dimethyl-1*H*-indole-3-carboxaldehyde (20k)



20k

Physical state: yellow solid

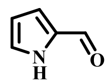
Yield: 26 mg (76 %)

M.P: 124-126 °C (Lit.[71e] 123.4-125.8°C)

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.11 (s, 1H), 8.25-8.24 (m, 1H), 7.27-7.25 (m, 3H), 3.64 (s, 3H), 2.62 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 184.0, 147.7, 136.9, 125.6, 123.0, 122.7, 120.8, 114.1, 109.1, 29.6, 10.5.

1*H*-Pyrrole-2-carboxaldehyde (191)



191

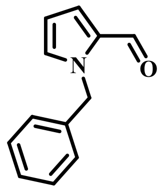
Physical state: viscous oil

Yield: 15 mg (32 %)

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.74 (br s, 1H), 9.50 (s, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 6.35-6.33 (m, 1H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 179.5, 132.8, 127.2, 122.1, 111.3.

1-Benzyl-1*H*-pyrrole-2-carboxaldehyde (191a)



191a

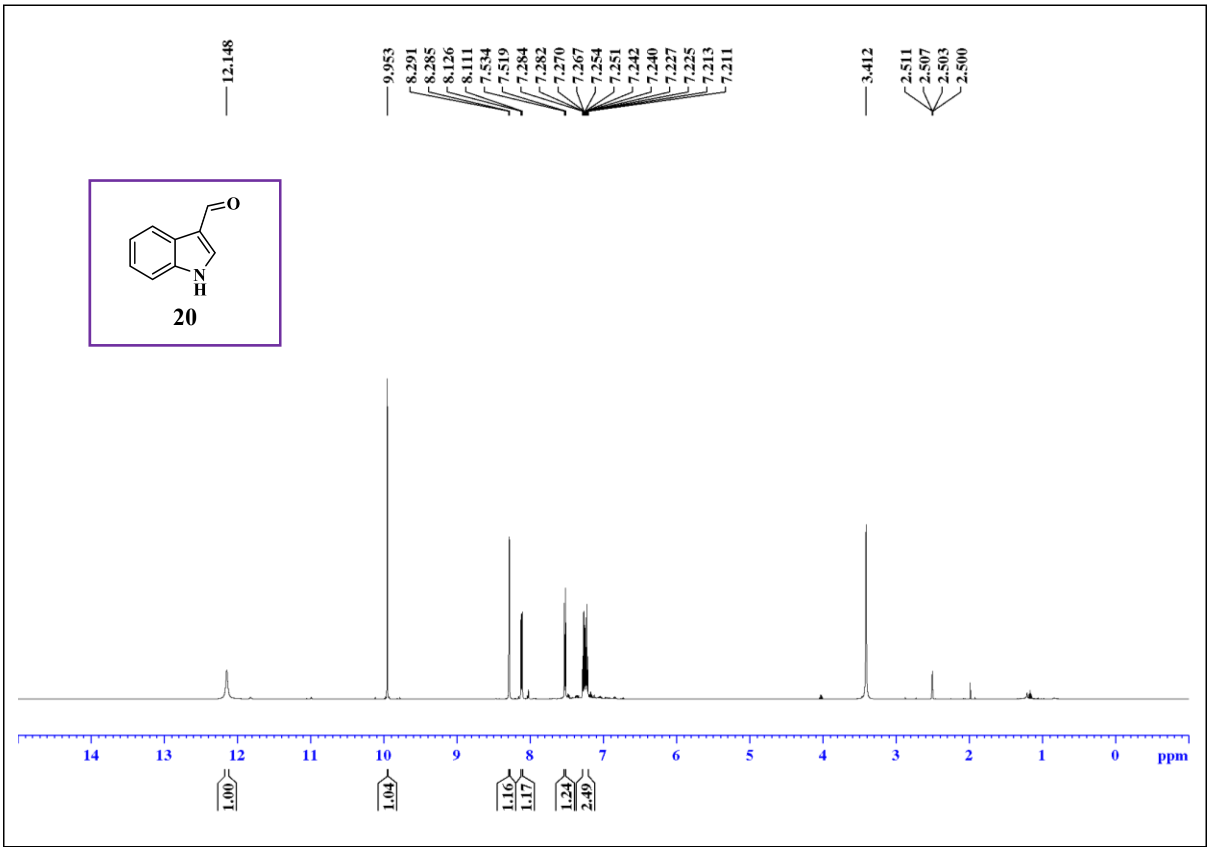
Physical state: viscous oil

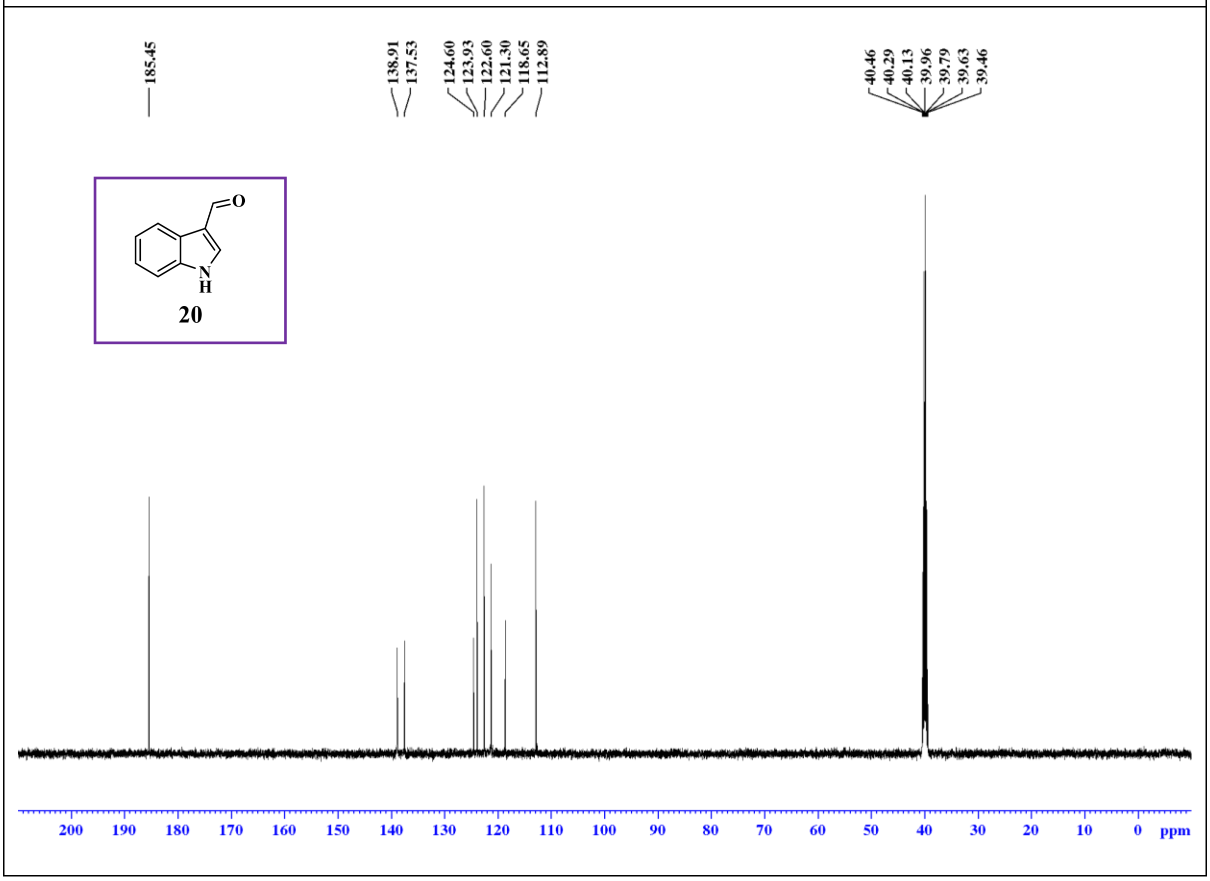
Yield: 13 mg (38 %)

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.35-7.32 (m, 2H). 7.30-7.29 (m, 1H), 7.19-7.17 (m, 2H), 7.00 (d, J = 3.5 Hz, 2H), 6.30 (t, J = 6.5, 3.2 Hz, 1H), 5.59 (s, 2H).

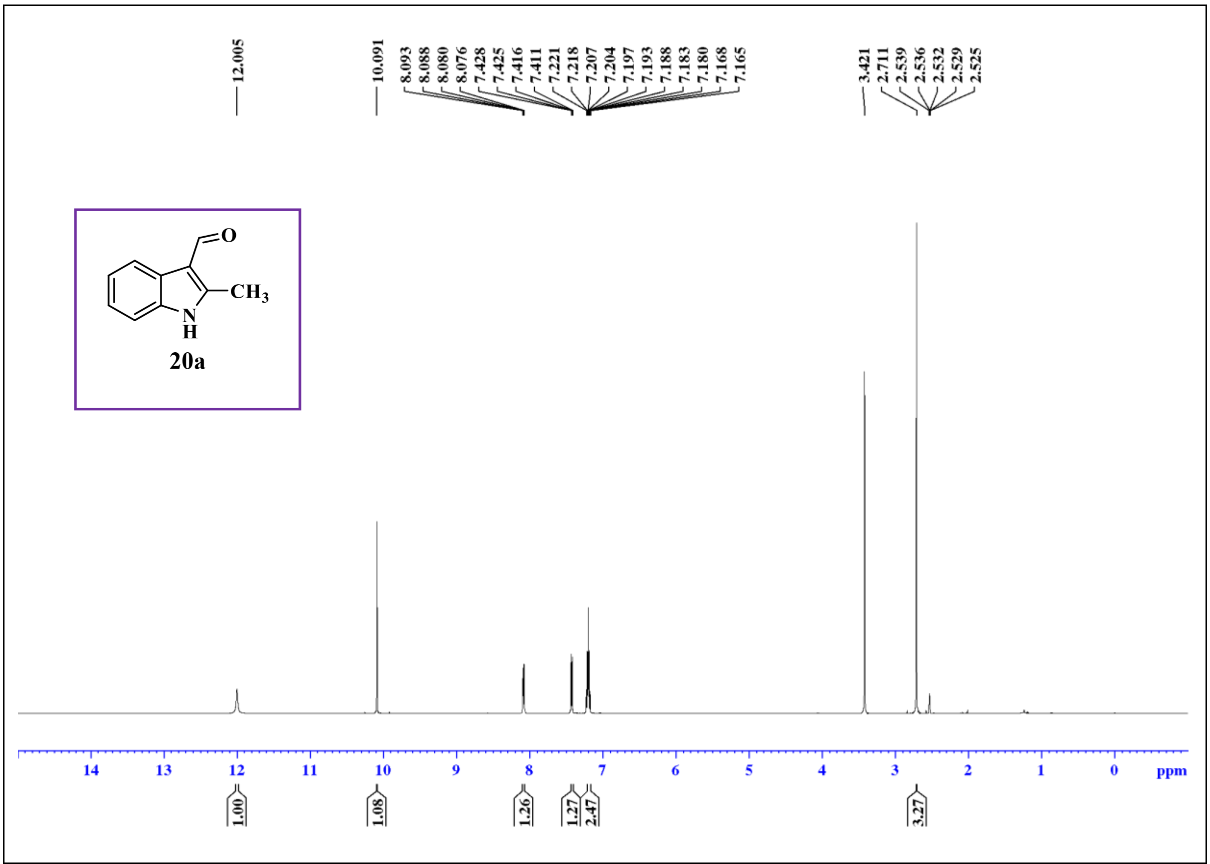
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 179.5, 137.5, 131.5, 131.4, 128.7, 127.7, 127.3, 124.8, 110.1, 51.9.

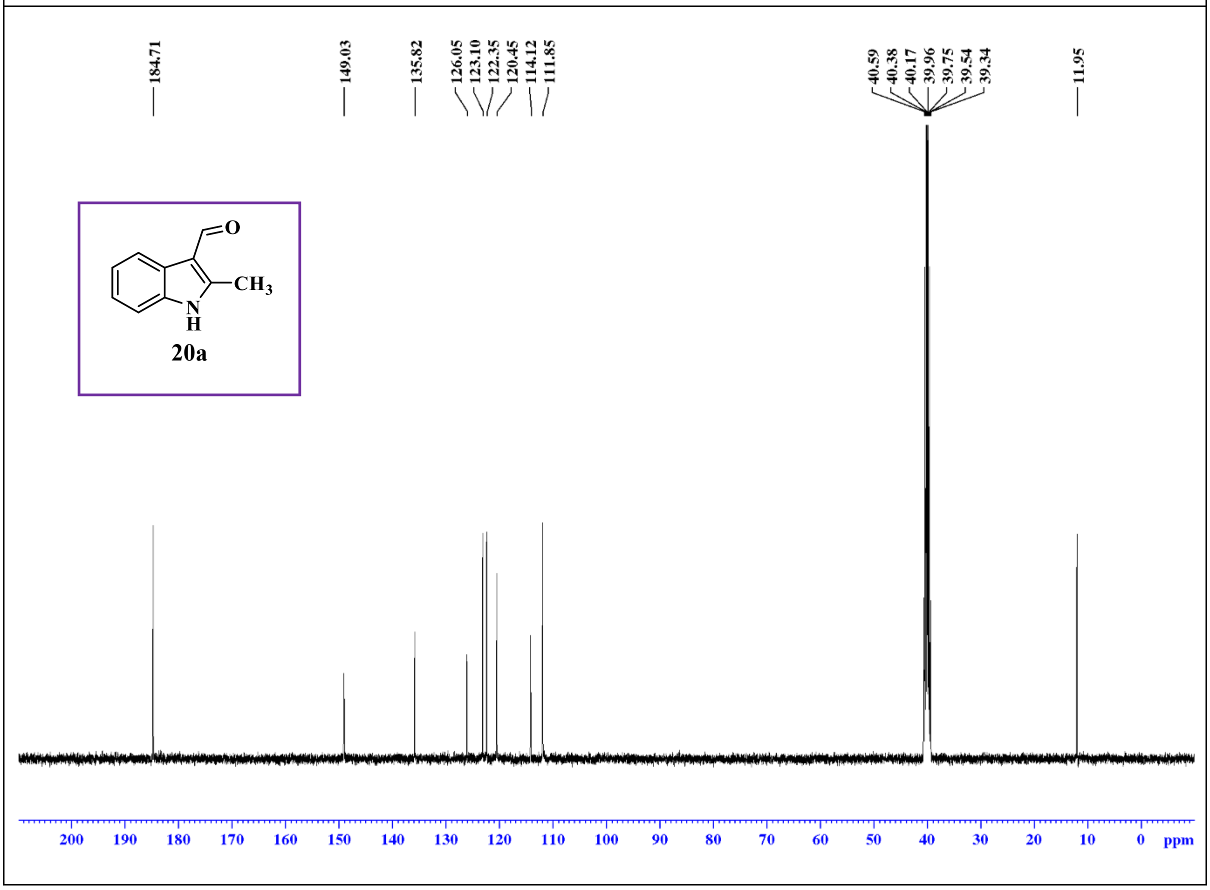
^1H and ^{13}C NMR Spectra of Compound **20**



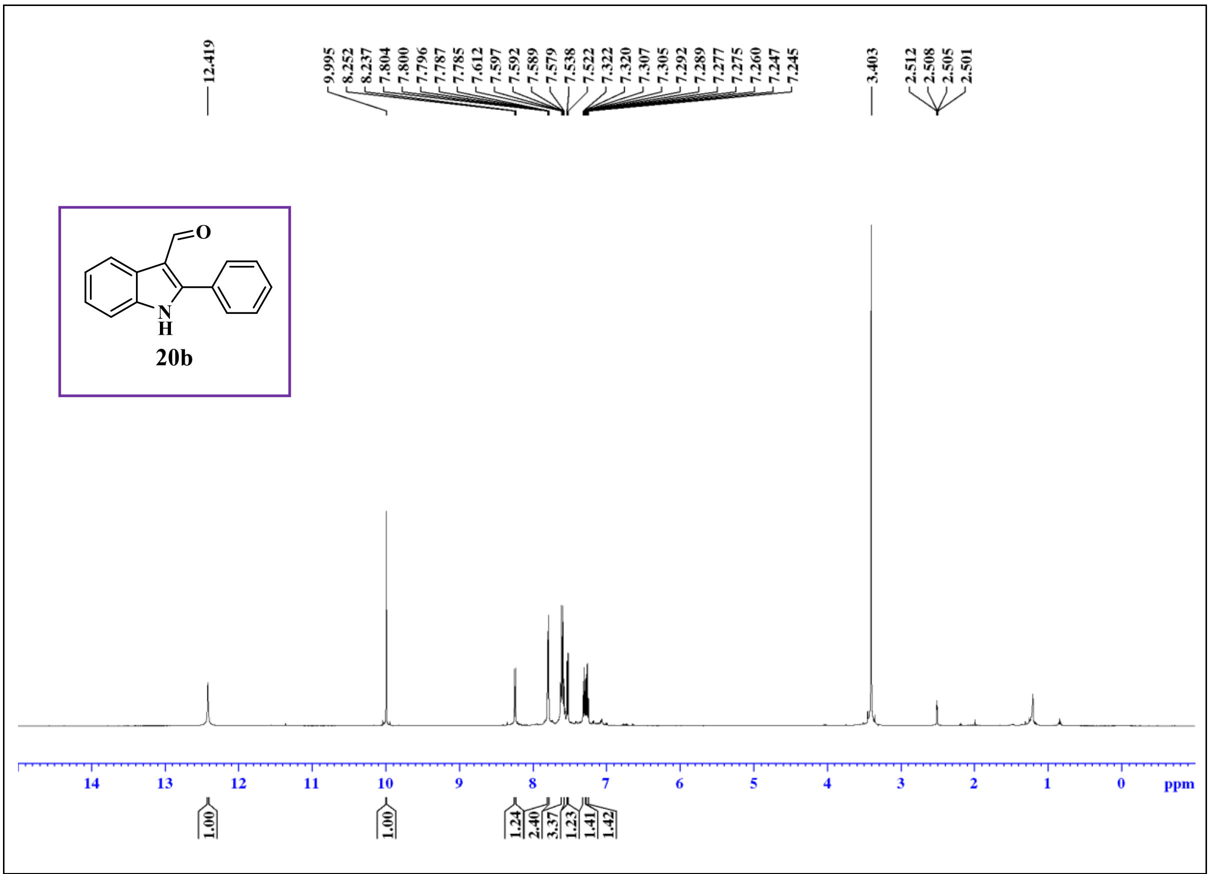


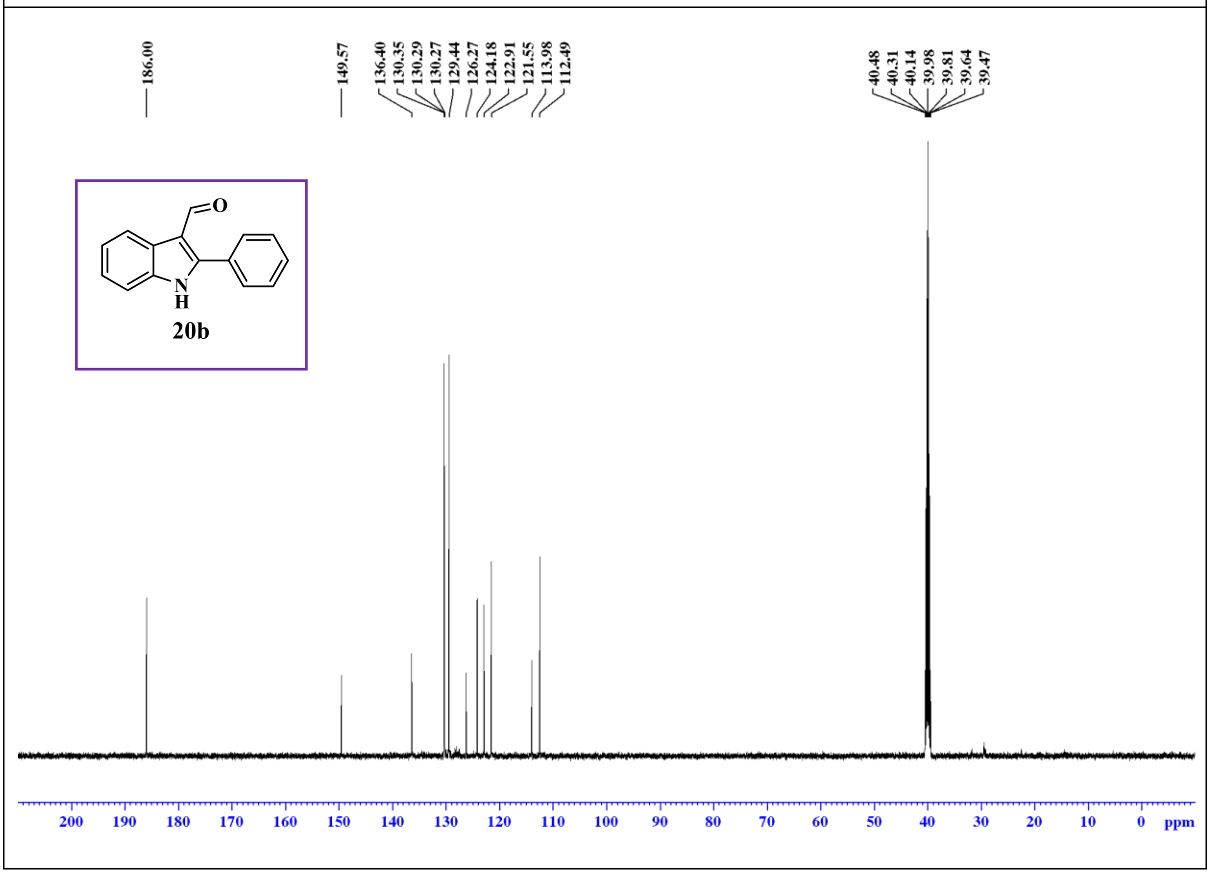
^1H and ^{13}C NMR Spectra of Compound **20a**



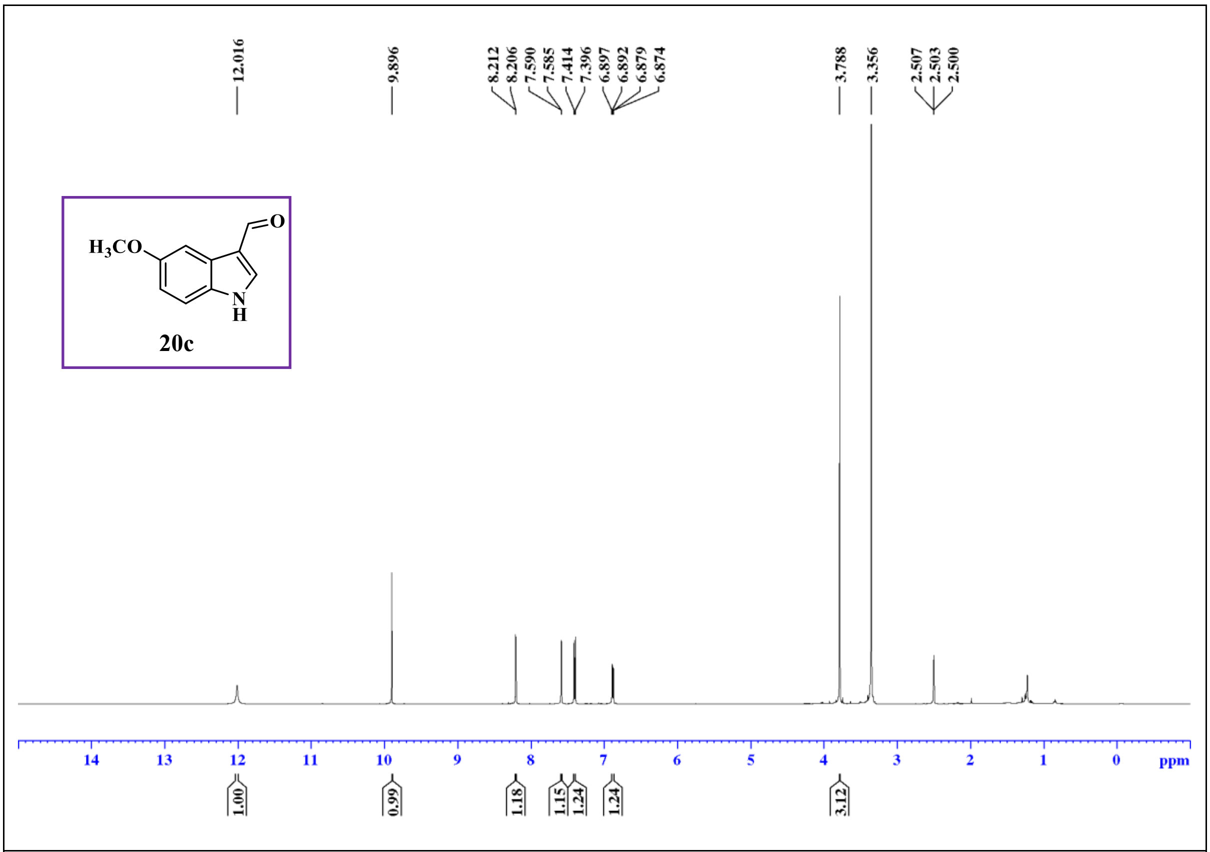


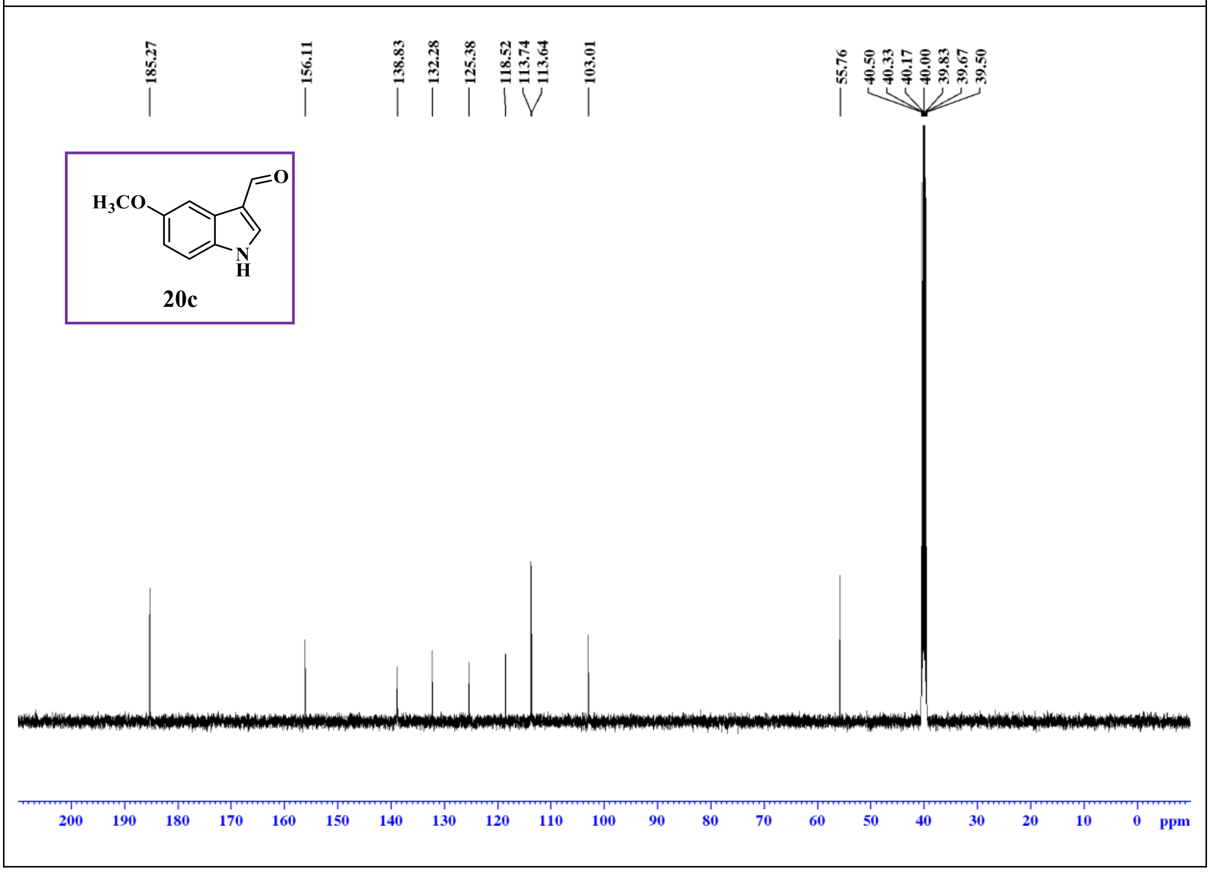
^{1}H and ^{13}C NMR Spectra of Compound **20b**



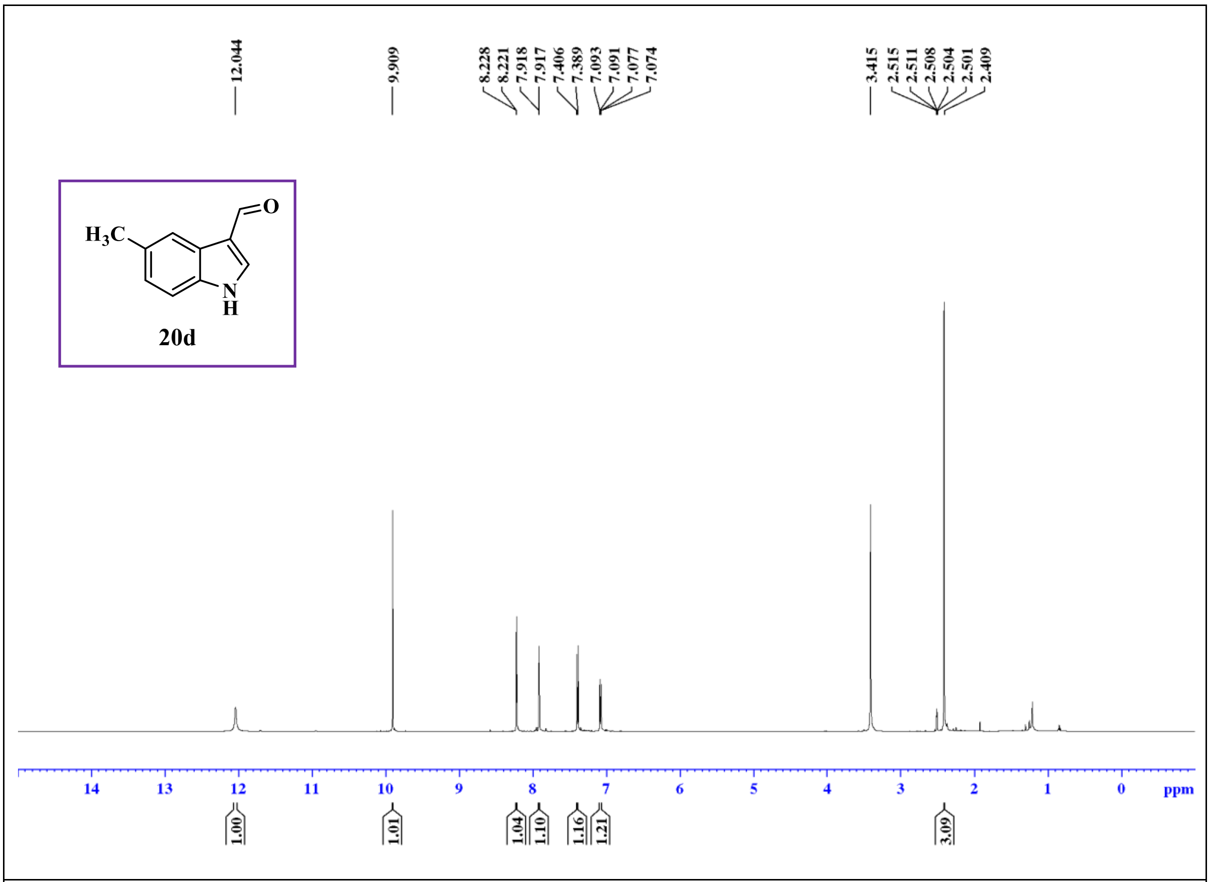


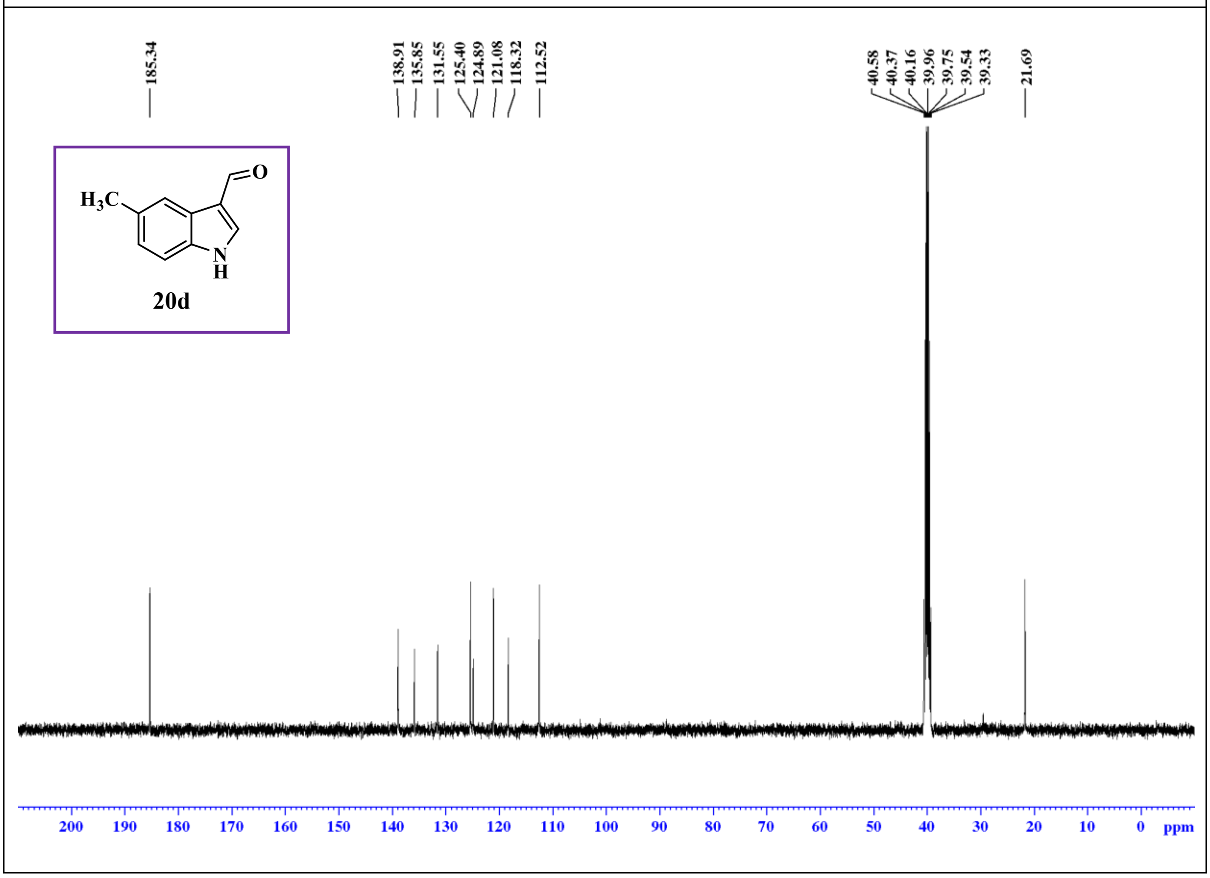
[1]H and [13]C NMR Spectra of Compound **20c**



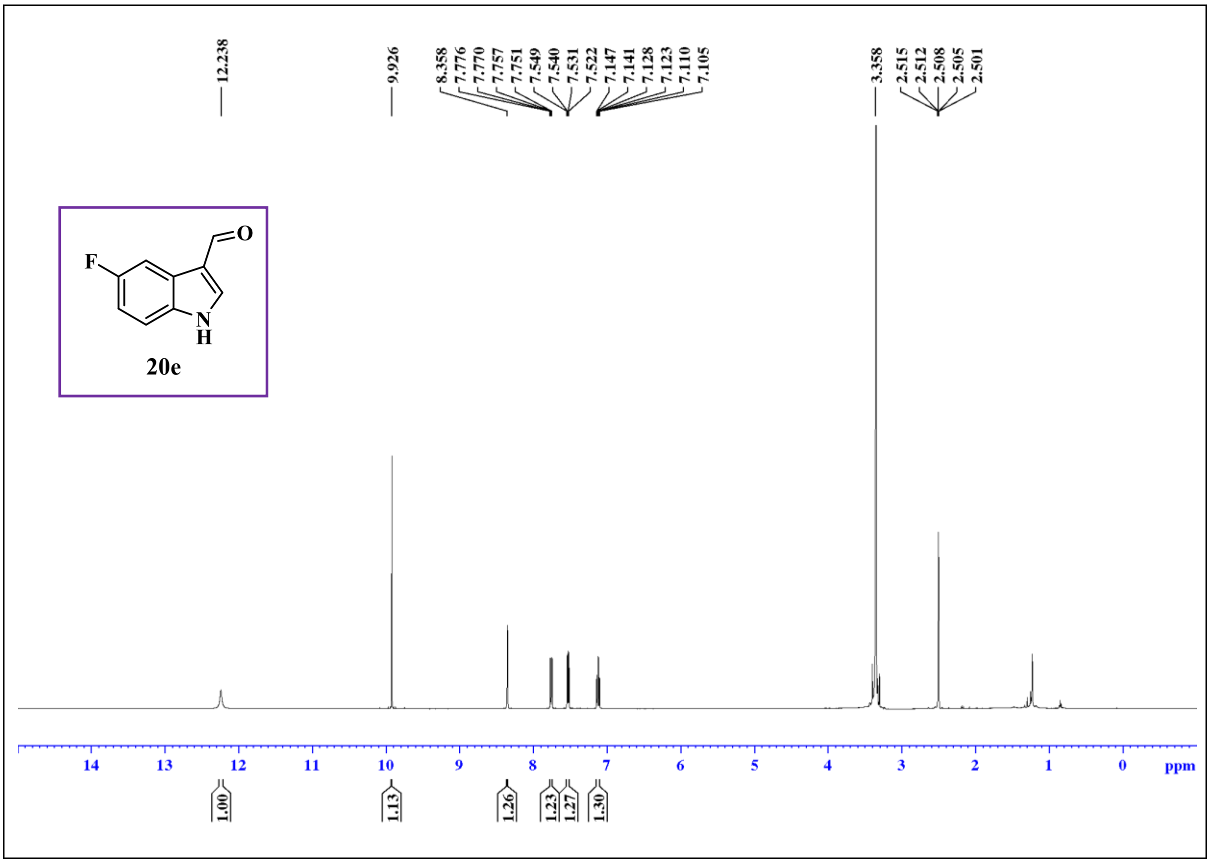


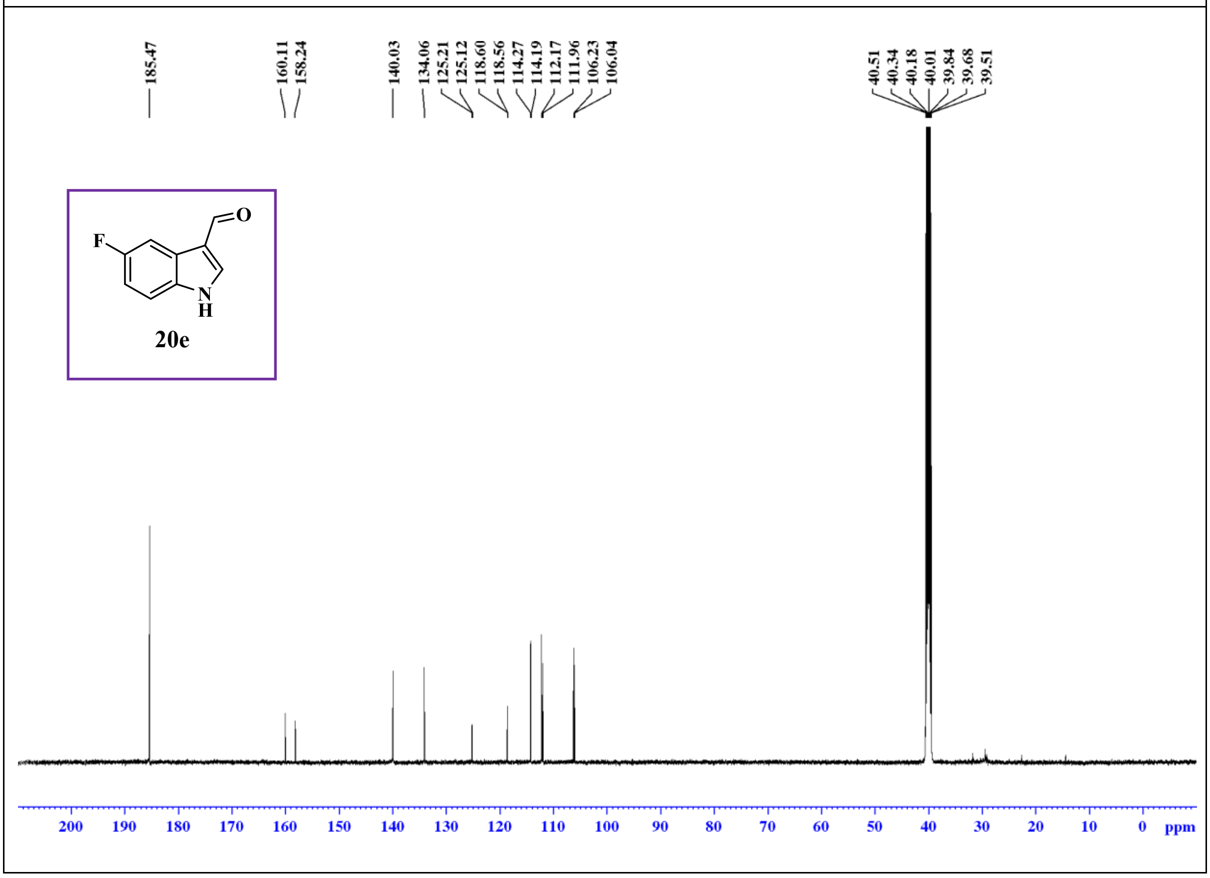
[1]H and [13]C NMR Spectra of Compound **20d**



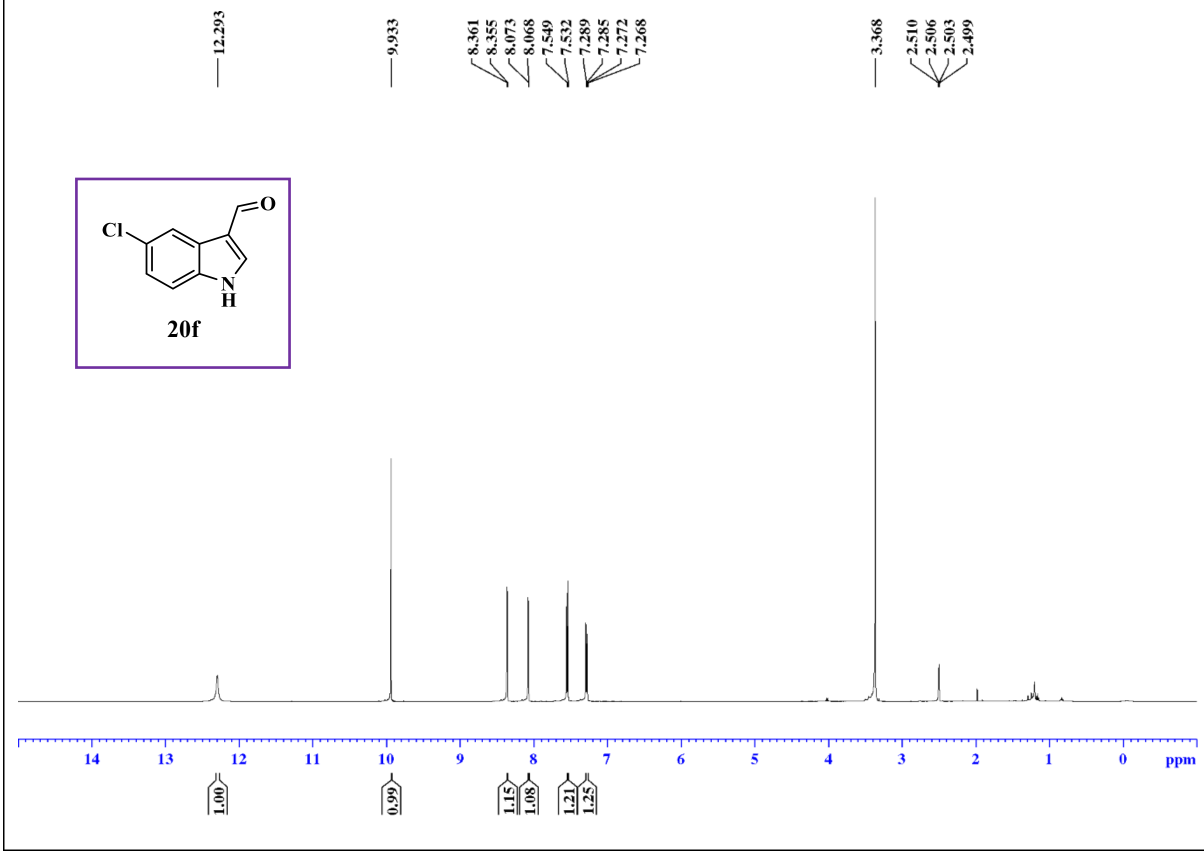


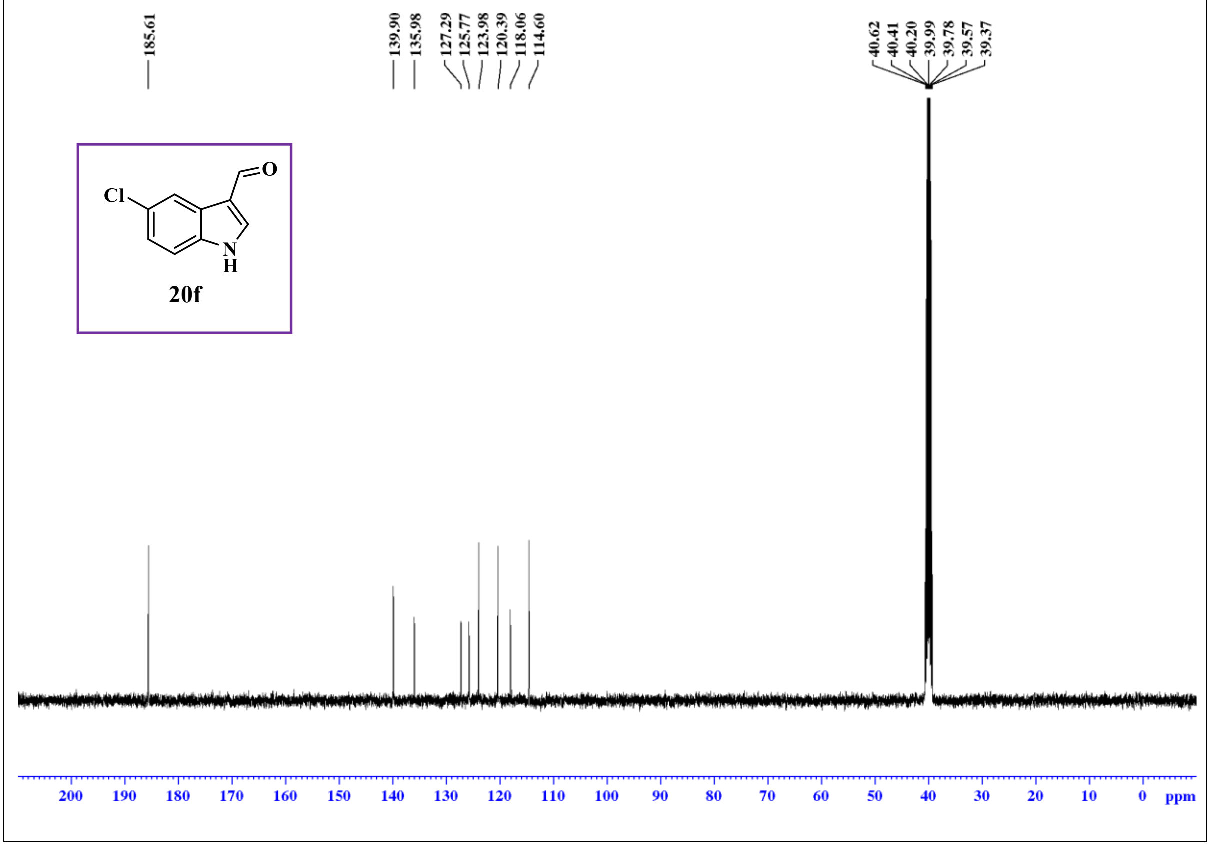
[1]H and [13]C NMR Spectra of Compound **20e**



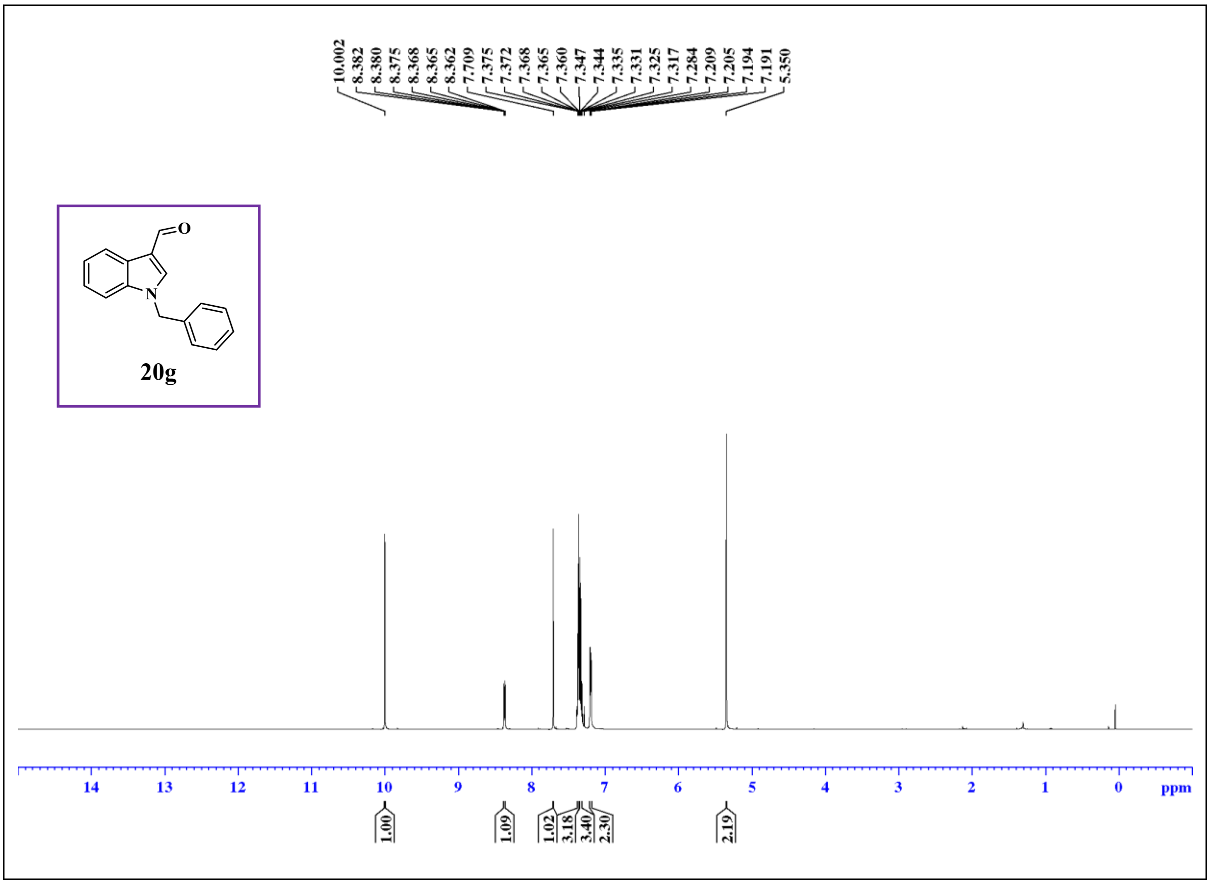


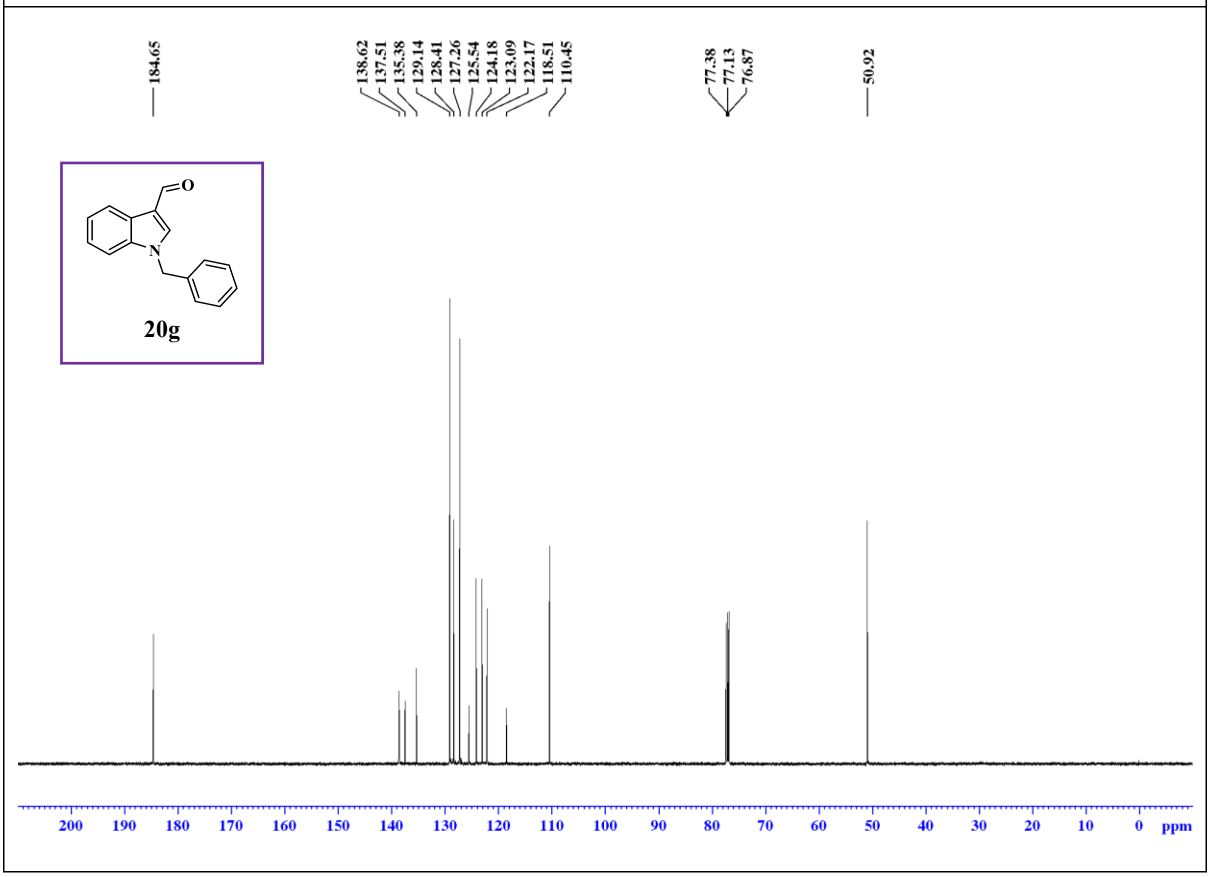
[1]H and [13]C NMR Spectra of Compound **20f**



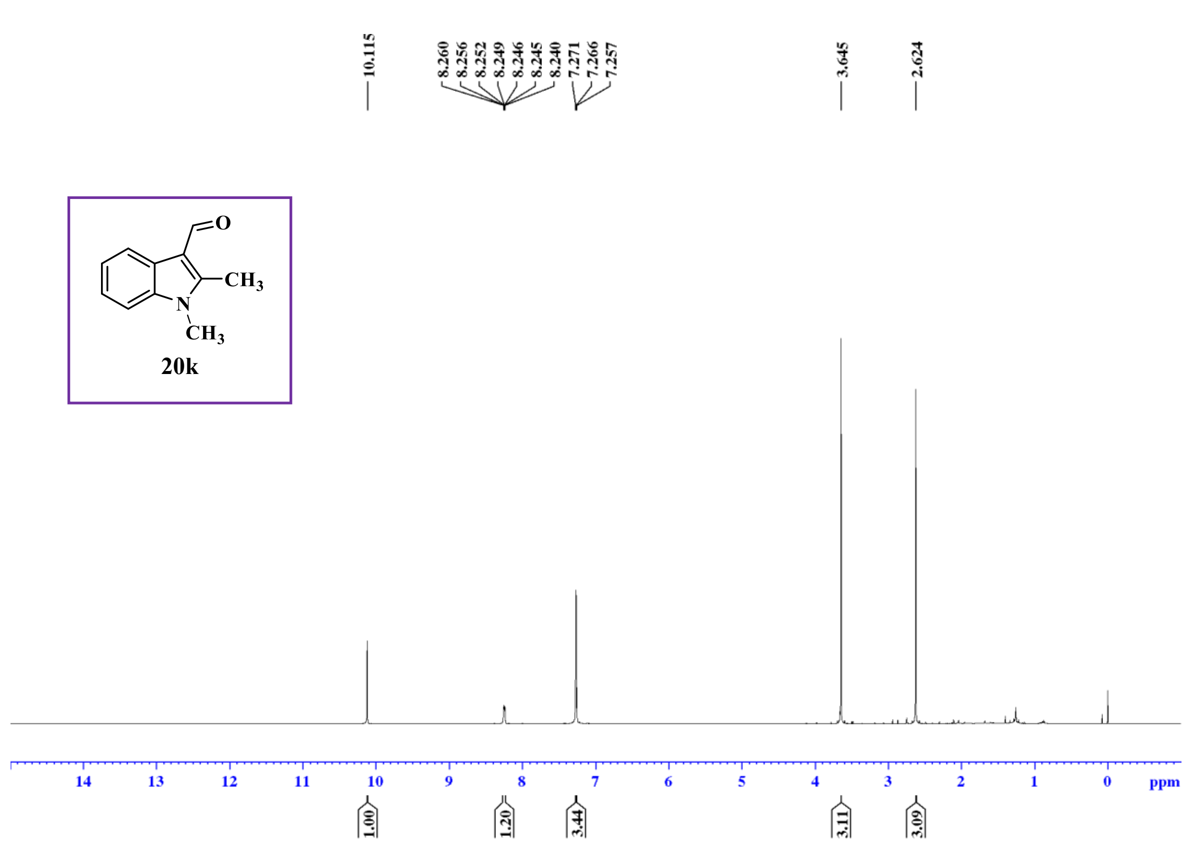


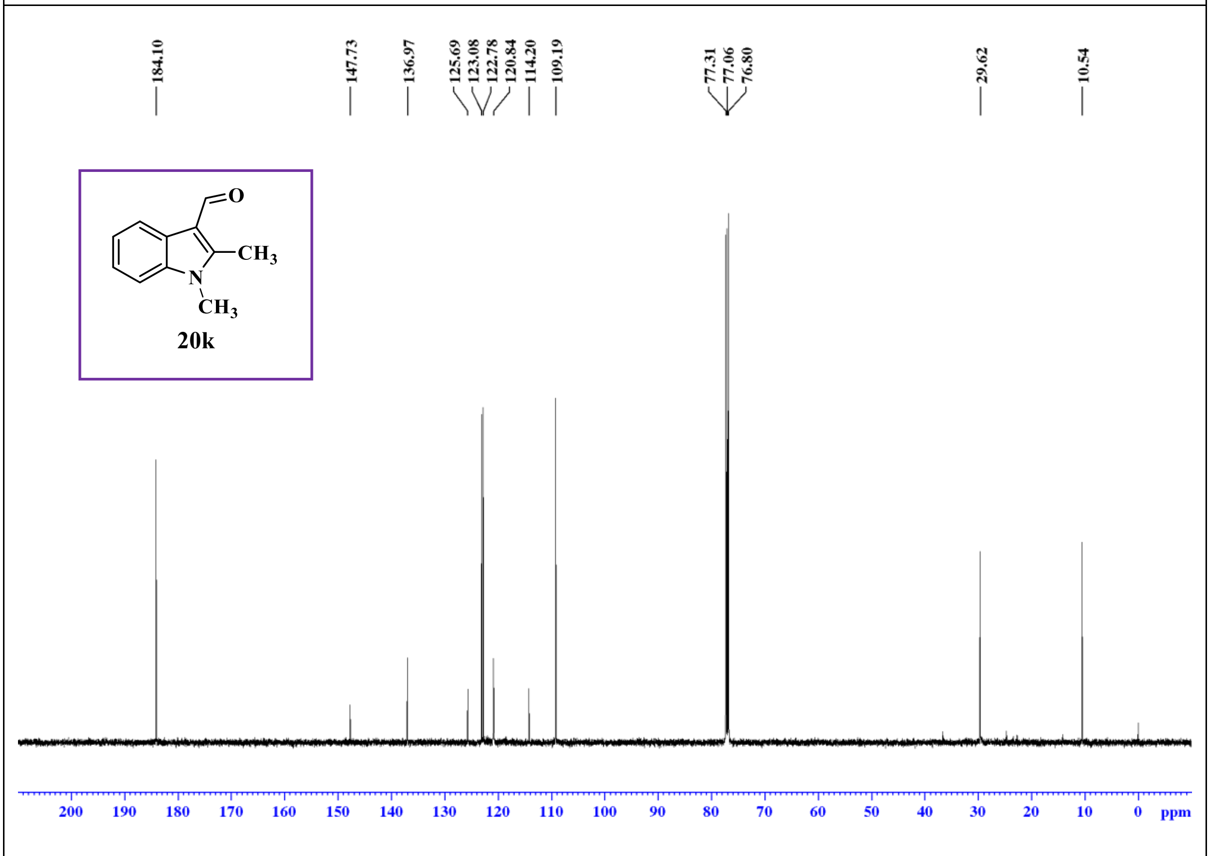
^{1}H and ^{13}C NMR Spectra of Compound **20g**



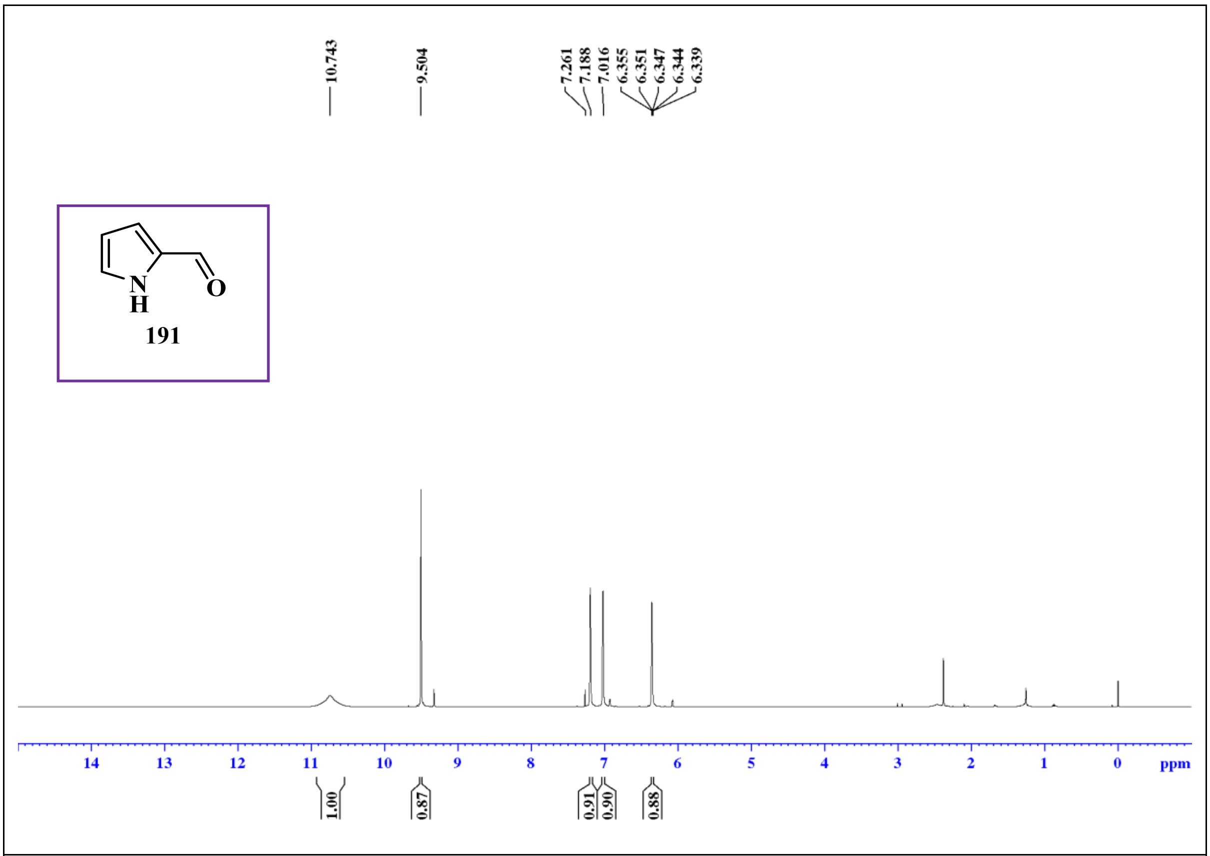


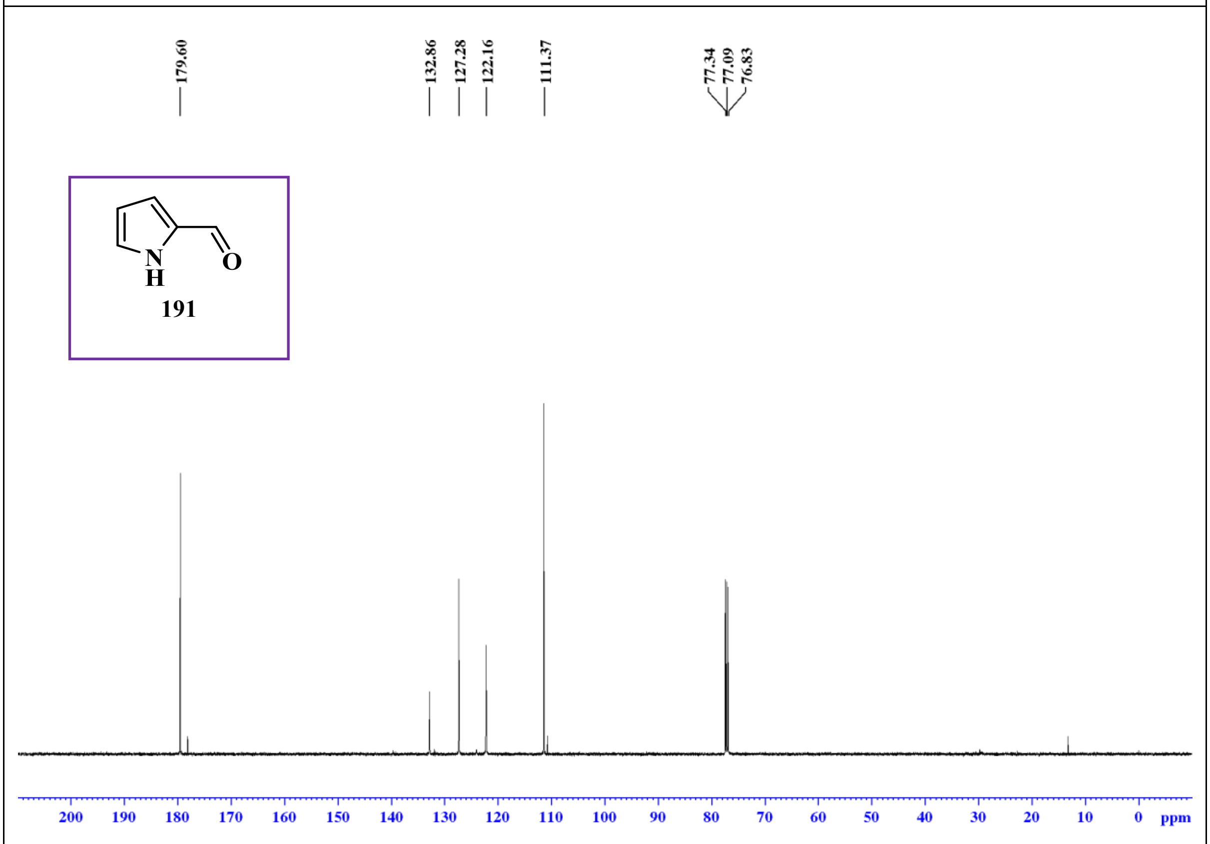
[1]H and [13]C NMR Spectra of Compound **20k**



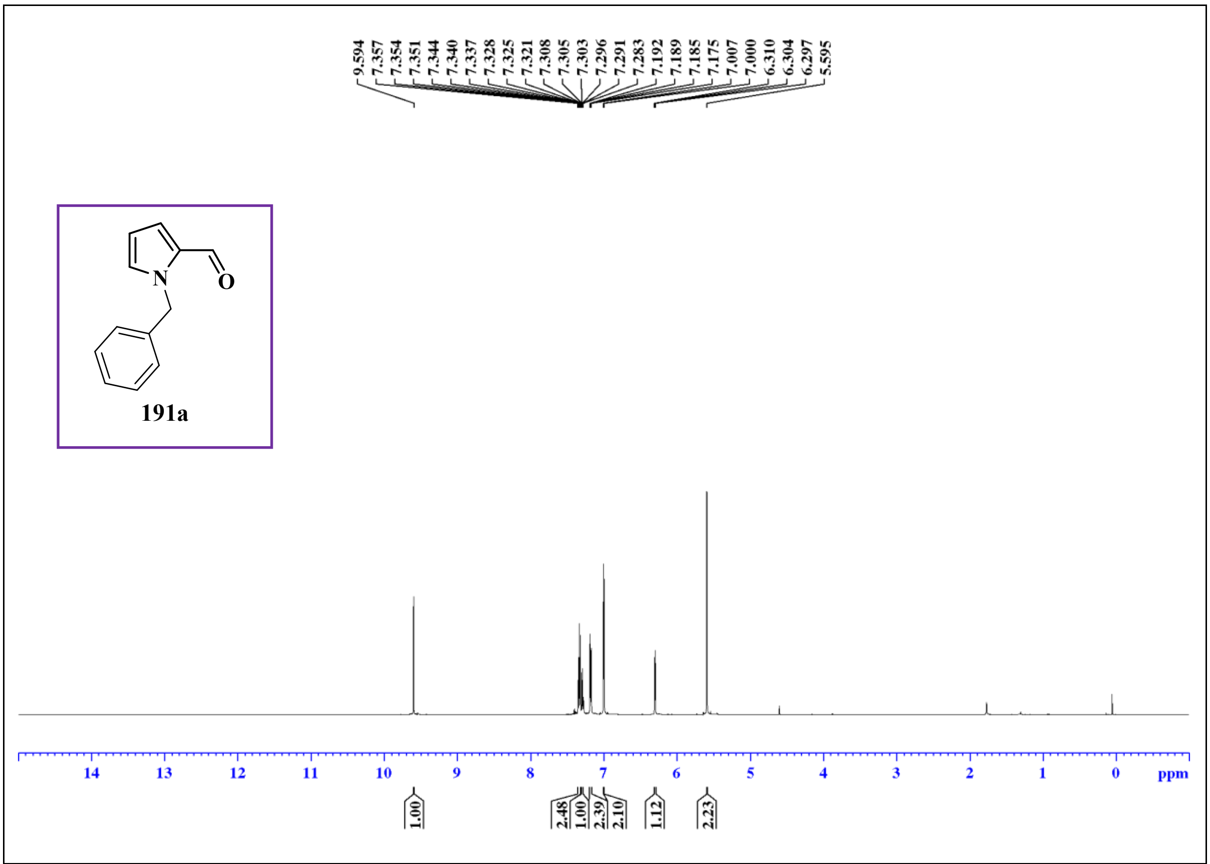


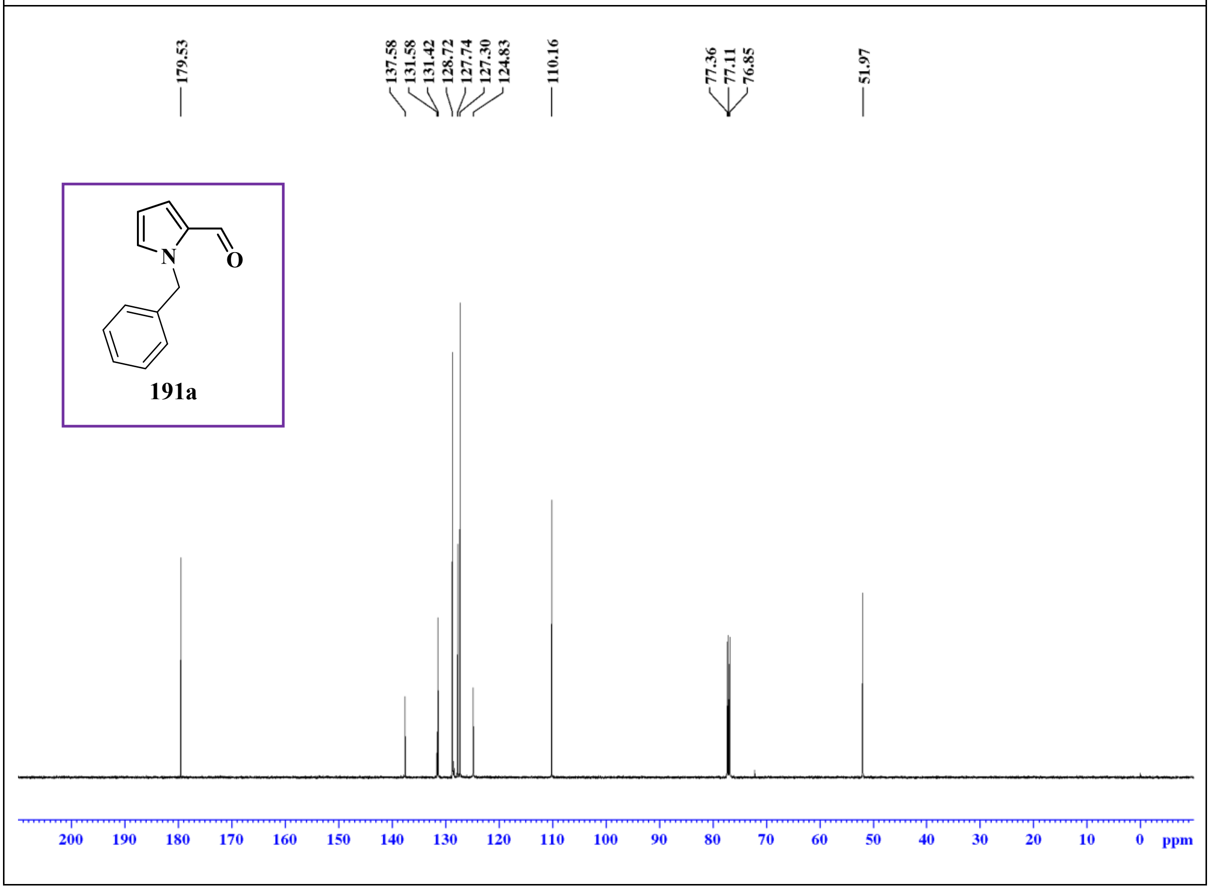
^{1}H and ^{13}C NMR Spectra of Compound **191**





[1]H and [13]C NMR Spectra of Compound **191a**





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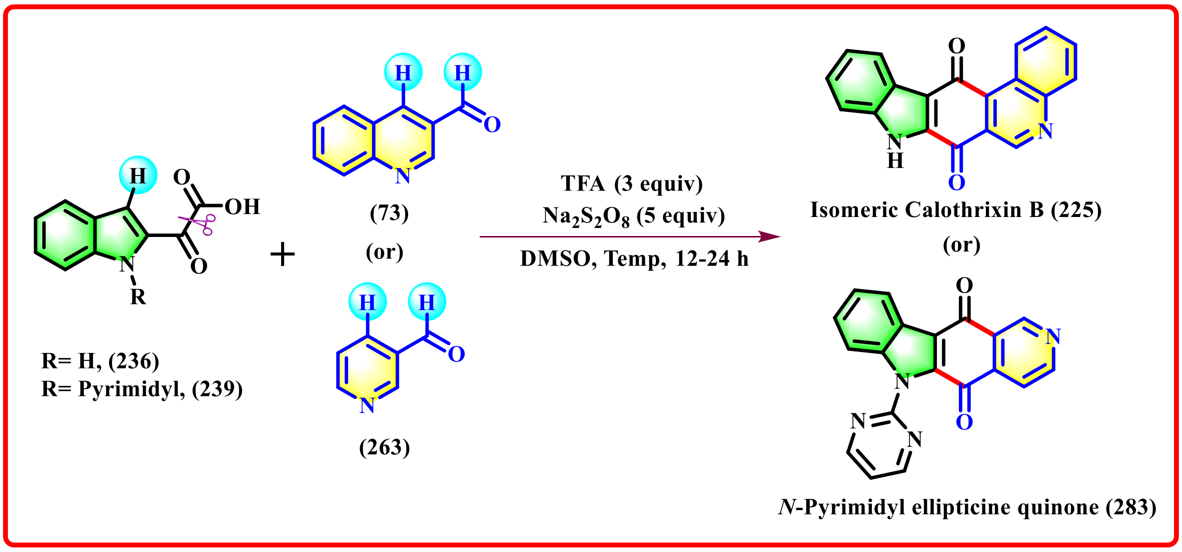
CHAPTER- *II*

Synthesis of isomeric Calothrixin B (7*H*-indolo[2,3-*j*] phenanthridine-7,13(8*H*)-dione) and *N*-Pyrimidyl Ellipticine quinone



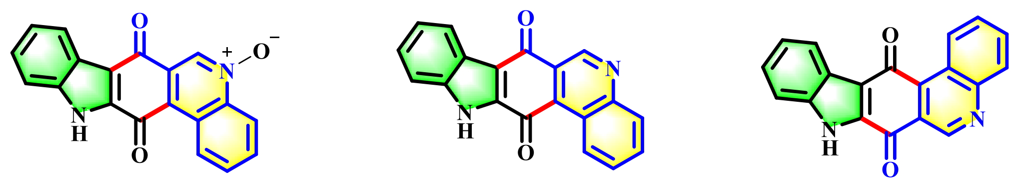
Abstract:

An efficient metal-free synthesis of isomeric calothrixin B and *N*-pyrimidyl ellipticine quinone involving decarboxylative cross-coupling method is reported. This methodology can able to construct carbazolequinone frame work in a single step with moderate to low yields.

2.1 Introduction:

Calothrixins are indolo[3,2-*j*]phenanthridine alkaloids. In 1999 Rickards and co-workers originally extracted[86] from *Calothrix* cyanobacteria. These pentacyclic quinone based alkaloids exhibits antiproliferative characteristics against many cancer cell lines and human DNA topoisomerase I poisoning activity are both displayed by chloroquinone-resistant variant of the malaria parasite Plasmodium falciparum. Calothrixin A and B (Figure **1.1**) are appealing targets for the total synthesis due to their unique structural characteristics and important biological activities.[87]

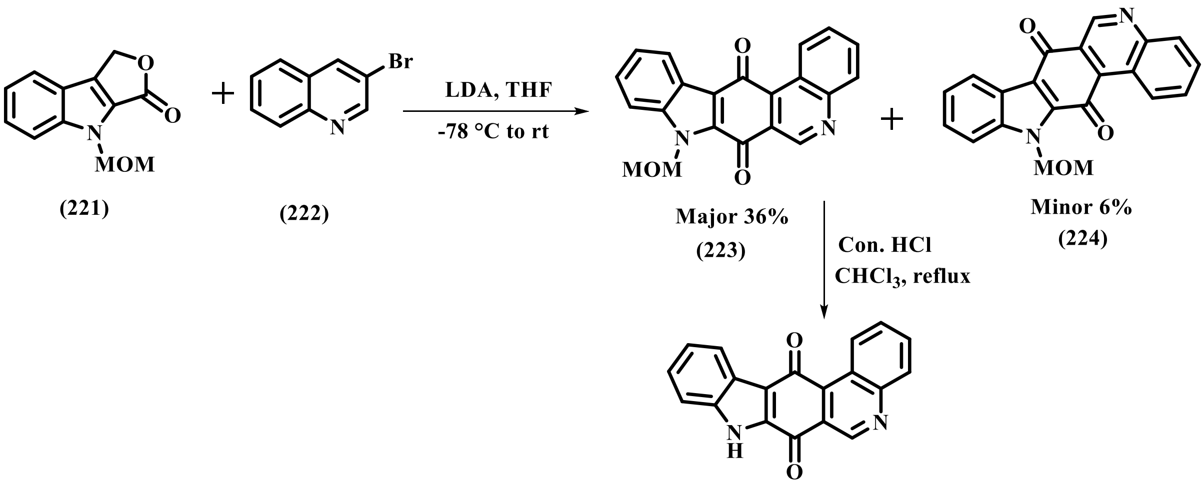
Figure 1.1 Structures of calothrixin A, B and isomeric calothrixin B



Calothrixin A	Calothrixin B	Isomeric Calothrixin B
7,13-dioxo-12,13-dihydro-7*H*-indolo[3,2-*j*] phenanthridine 5-oxide	7*H*-indolo[3,2-*j*]phenanthridine-7,13(12*H*)-dione	7*H*-indolo[2,3-*j*]phenanthridine-7,13(8*H*)-dione

Owing to their biological properties and fascinating structural features we targeted to achieve the synthesis of calothrixins with novel methodology, although several reports available,[88] during the synthesis of calothrixins we have identified an unprecedented indolo[2,3- *j*]phenanthridine frame work isomeric form of calothrioxin.

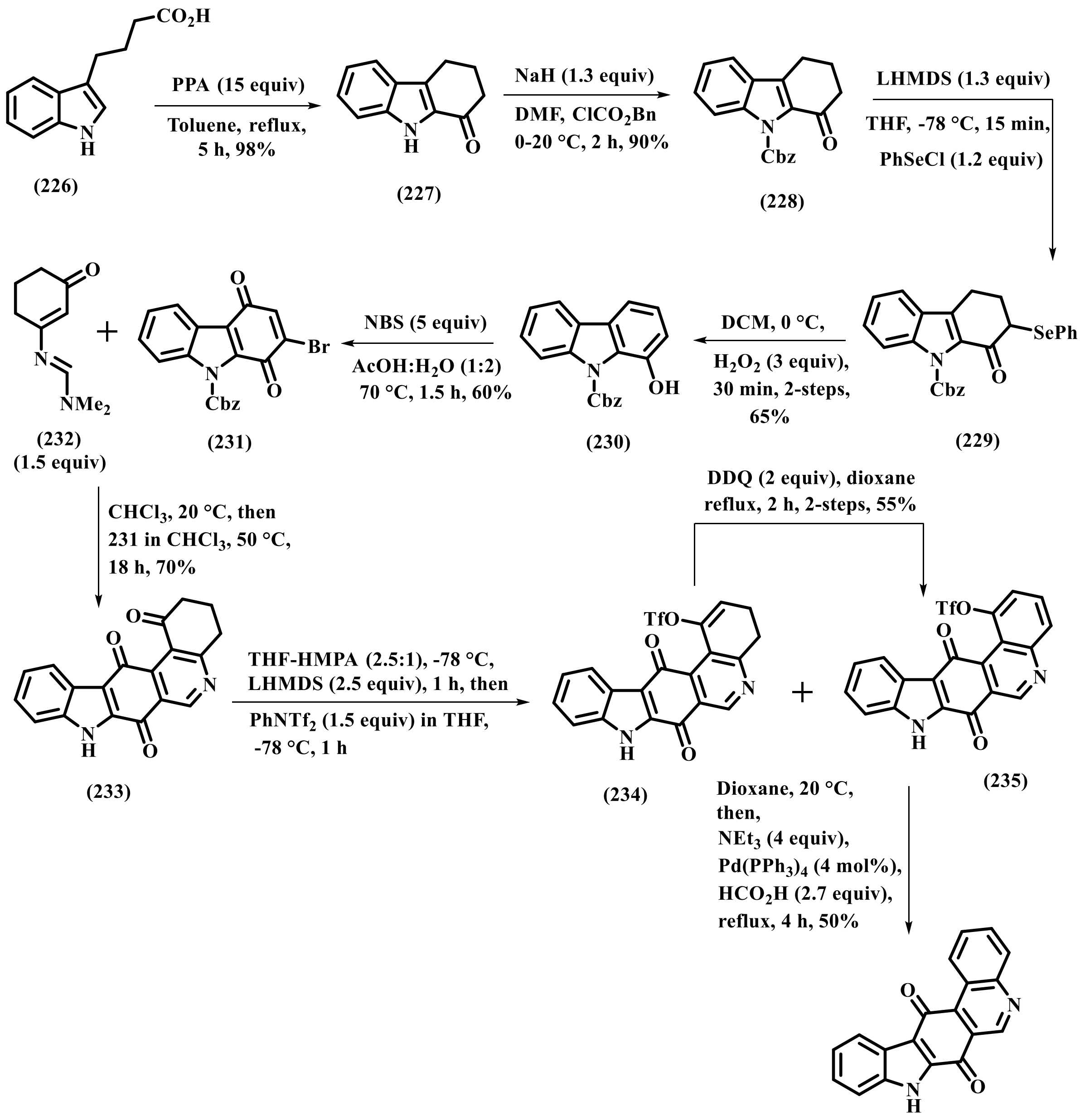
Previous reports on synthesis of isomeric calothrixin B



Isomeric calothrixin B (225)

Eq. 70. Mal *et al.* (2014)

In 2014 Mal *et al.* were reported[89] calothrixin B **75** and isomeric calothrixin B **225** involving addition, annulation, and subsequent elimination process by the reaction of *N*-MOM protected compound **221** with 3-bromoquinoline **222** in the presence of LDA at -78 °C in room temperature to obtain the mixture of compounds **223** (major) and **224** (minor) which are further deprotection to afford isomeric calothrixin **225** and calothrixin **75** (**Eq. 70**).



Isomeric calothrixin B (225)

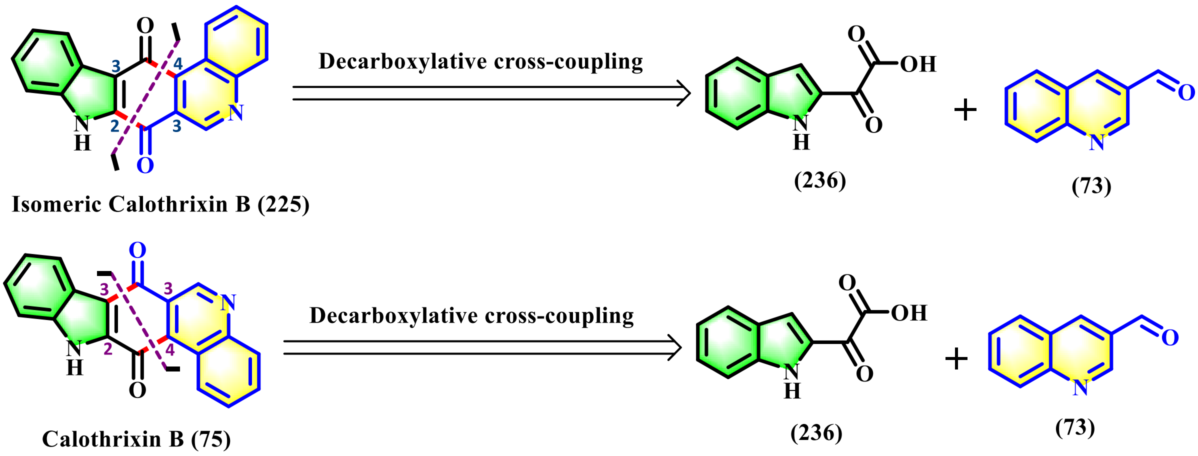
Eq. 71. Maingot *et al.* (2008)

Maingot *et al.* were developed[90] synthesis of isomeric calothrixin B **225** involving hetero Diels-Alder reaction to construct five-rings frame work by using new synthetic precursor 2-bromo-1*H*-carbazole-1,4(9*H*)-dione acts as dienophile with multistep sequence to obtain the corresponding indolo[2,3- *j*]phenanthridine alkaloid overall yield 5.5% in the year of 2008 (**Eq. 71**).

2.2 Results and discussion:

Metal-free decarboxylative cross-coupling reactions are emerged and important tool for the creation of C-C/C-X bond construction in various organic synthesis includes several naturally occurring alkaloids.

Figure 2.1 Retrosynthetic analysis



We outlined the retro synthesis of calothrixin B **75** in which the formation of quinone ring would be construct the disconnection between quinoline C-4 to indol-2-carbonyl to form indole-2-yl-quinoline skeleton by involving decarboxylative cross-coupling method then, indole C-3 with quinoline-3-carbonyl intramolecular cross-coupling to develop the indolo[3,2-*j*]phenanthridine core. During the progress of reaction, we found that indolo[2,3-*j*]phenanthridine system shown in Figure **2.1**

Table 2.1: Optimisation and synthesis of starting precursor 2-(1*H*-indol-2-yl)-2-oxoacetic acid (236)

Entry	Solvent	Temp (°C)	Time (h)	Yield 239 (%)
1.	Et_2O	rt	72	26
2.	-	70	24	31
3.	Dioxane	90	24	57
4.	Toluene	100	24	88

Reaction conditions: **238** (1 equiv), $(COCl)_2$ (15 equiv), Dry solvent

We have synthesized a staring material 2-(1*H*-indol-2-yl)-2-oxoacetic acid **236** (or) indole-2-ketoacid with modern route starting from *N*-pyrimidyl indole **238** reacts with oxalyl chloride. Previously in 2014 Mori *et al.*[91] were synthesized the same starting material by LDA mediated starting from indole with dimethyl oxalate.

We carried the reaction initially with ether solvent at room temperature 72 h observed indole-*N*-pyrimidyl-2-ketoacid (or) 2-oxo-2-(1-(pyrimidin-2-yl)-1*H*-indol-2-yl) acetic acid **239** with 26% yield mentioned **table 2.1** in entry **1**. Upon we tried the same reaction for yield improvement with neat condition and other solvents like dioxane and toluene at the mentioned reflux temperature and time in table **2.1** entrys **2-4** we found that, entry **4** mentioned with toluene solvent at 100 °C in 24 h to obtain the compound indole-*N*-pyrimidyl-2-ketoacid **239** with 88% yield, further deprotection with NaOMe in Dry. DMSO at 110 °C in 12 h time period to afford the compound indole-2-ketoacid **236** with good yields.

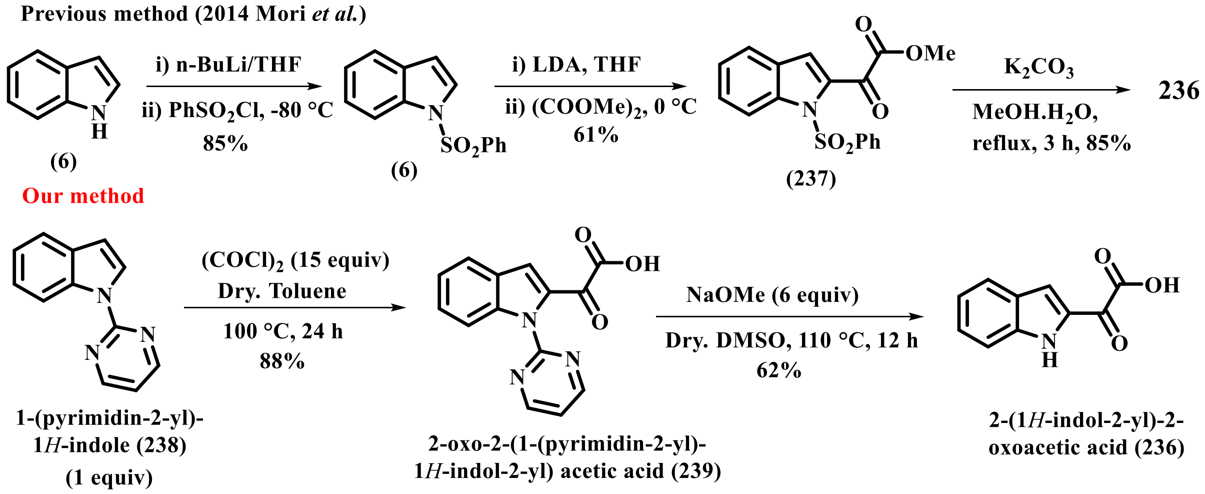
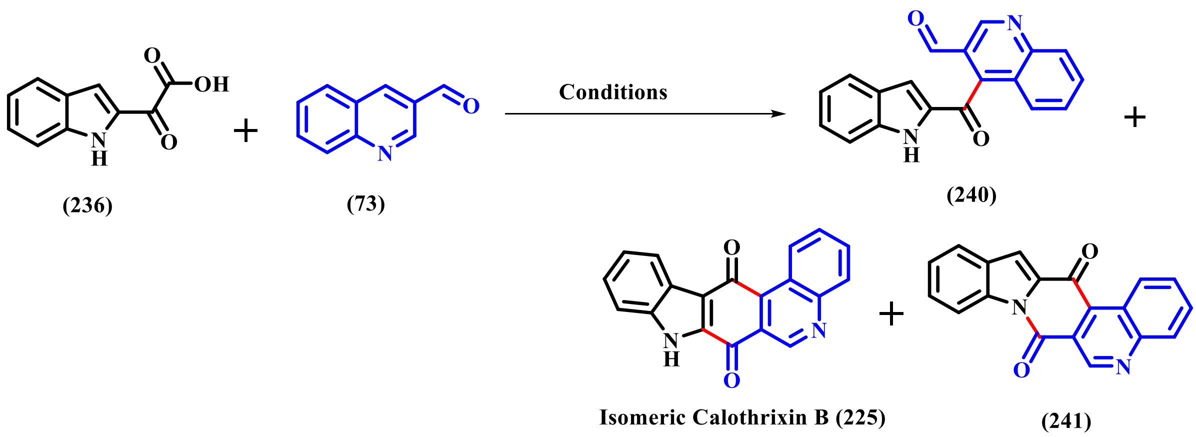


Table 2.2: Optimisation of the reaction condition

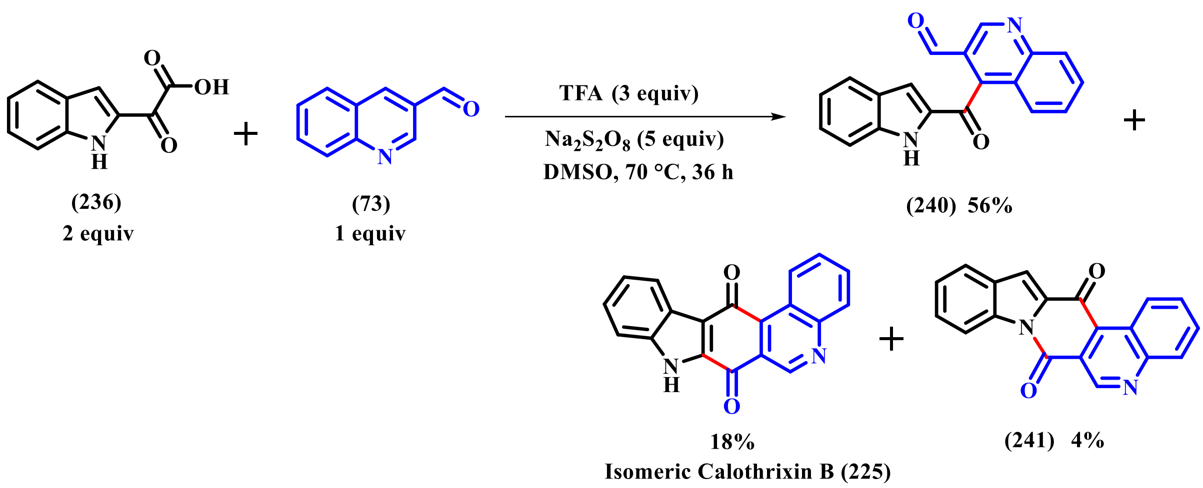


Entry	Oxidant (equiv)	Additive (equiv)	Solvent	T (°C)	Time (h)	Yield (%) [b]		
						240	241	225
1	$(NH_4)_2S_2O_8$ (3)	*p*-TSA (2)	CH_3CN	80	24	14	ND	ND
2	$(NH_4)_2S_2O_8$ (3)	*p*-TSA (2)	DCE	80	48	21	ND	5
3	$(NH_4)_2S_2O_8$ (5)	TFA (3)	DMSO	70	36	49	Trace	14
4	$K_2S_2O_8$ (5)	TFA (3)	DCE	80	48	23	ND	6
5	$K_2S_2O_8$ (5)	TFA (3)	DMSO	70	36	52	Trace	15
6	$Na_2S_2O_8$ (5)	*p*-TSA (2)	DMSO	70	36	55	3	15
7	$Na_2S_2O_8$ (5)	TFA (3)	DMSO	70	36	56	4	18
8	$Na_2S_2O_8$ (5)	TFA (3)	DMSO	110	12	41	6	38

[a] Reaction conditions: Quinoline-3-carboxaldehyde (**73**) (0.636 mmol, 1 equiv), Indole-2-ketoacid (**236**) (1.27 mmol, 2 equiv), Oxidant (3.18 mmol, 5 equiv), DMSO (2-3 mL), Temp (°C), Time (h). [b] Isolated yields after chromatography.

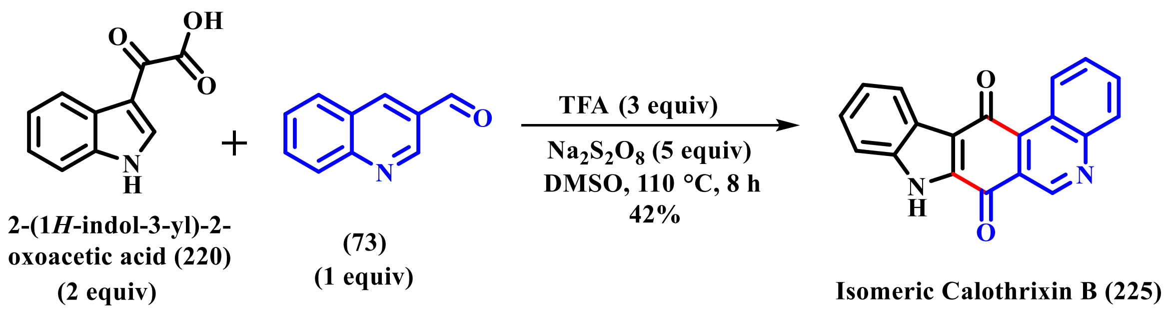
The optimisation of reaction condition we carried out with different oxidants ($M_2S_2O_8$; M= NH_4, Na or K) additives with various solvents (**Table 2.2**). From this we identified 5 equivalents of $Na_2S_2O_8$ Oxidant with 3 equivalents of additive TFA and DMSO was suitable solvent (**entry 7**), also we observed that if temperature enhances up to 110 °C with the same optimised condition entry **7** the compound isomeric calothrixin B **225** was increases (**entry 8**).

Scheme 2.1: Synthetic approach of isomeric calothrixin B {7*H*-Indolo[2,3-*j*] phenanthridine-7,13(8*H*)-dione} (225)



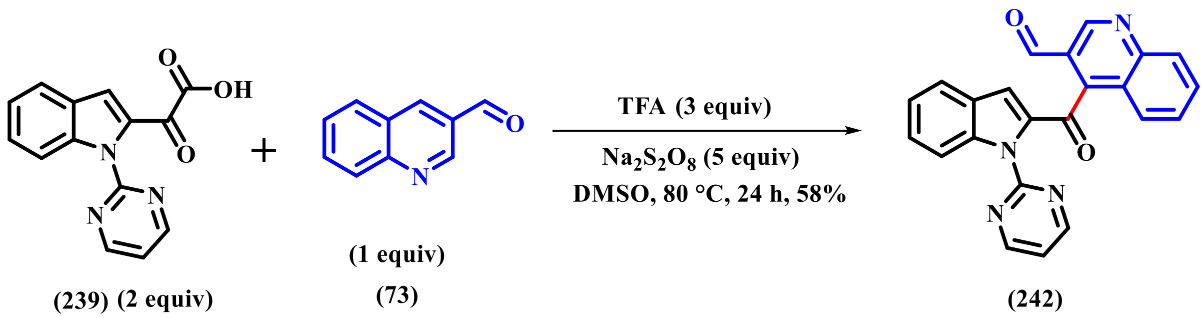
We attempted the reaction for synthesis of calothrixin B from the prepared starting material 2-(1*H*-indol-2-yl)-2-oxoacetic acid (**236**) treated with commercially available quinoline-3-carboxaldehyde (**73**) employing metal free decarboxylative coupling method in the presence of acid catalyzed, by using sodium persulfate as an oxidant with DMSO solvent at 70 °C in 36 h exclusively we observed in single step decarboxylative cross coupled product isomeric calothrixin B (**225**) in 18% along with compounds **240, 241** with 56%, 4% yields respectively (Scheme **2.1**).

Reaction 2.1 Synthesis of isomeric calothrixin B

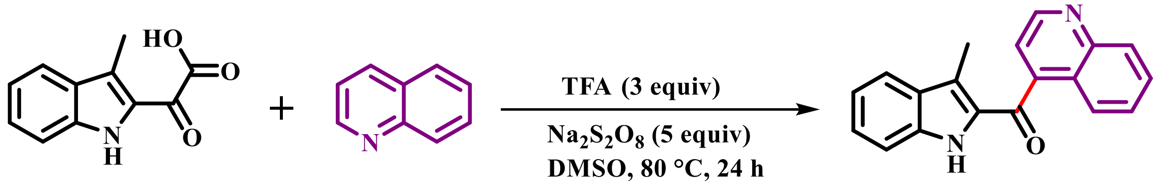


However, we aimed to synthesize the calothrixin B **75** from the retro synthetic route accordingly prepared starting materials exclusively we observed Isomeric calothrixin **225** employing decarboxylative cross-coupling method. Although we alter the starting material 2-(1*H*-indol-3-yl)-2-oxoacetic acid (**220**) reacts with quinoline-3-carboxaldehyde (**73**) involving decarboxylative cross-coupling strategy in the presence of acid catalyzed, using sodium persulfate as an oxidant with DMSO solvent at 110 °C in 8 h reaction period we found that, exclusive product isomeric calothrixin B (**225**) with 42% yield (Reaction **2.1**).

Reaction 2.2 Synthesis of compound 242



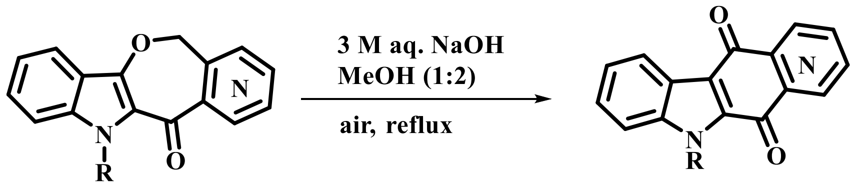
Reaction 2.3 Synthesis of compound 244



(2 equiv) (243) (1 equiv) (145) (244)

We are also attempted with other alternative approaches for calothrixin B shown in reaction **2.2** and **2.3** for the synthesis of calothrixin B **75** alkaloid. The compound **239** reacts with quinoline-3-carboxaldehyde **73** with the optimised reaction condition at 24 h involving decarboxylative cross-coupling method to obtain the corresponding cross-coupled product **242** with 58% yield (Reaction **2.2**). In the case of skatole-2-ketoacid **243** treated with quinoline **145** in the presence of optimised reaction condition at 24 h employing decarboxylative strategy to afford the compound **244** with 18% yield (Reaction **2.3**).

Previous reports on synthesis of ellipticine quinone alkaloid



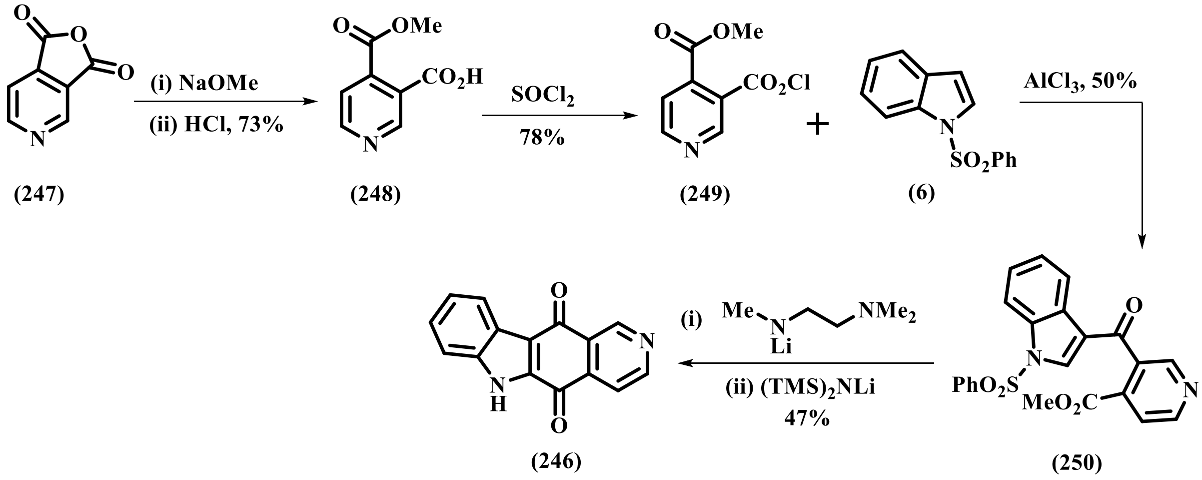
R = H, MOM, Me, Bn (245) R = H (246)

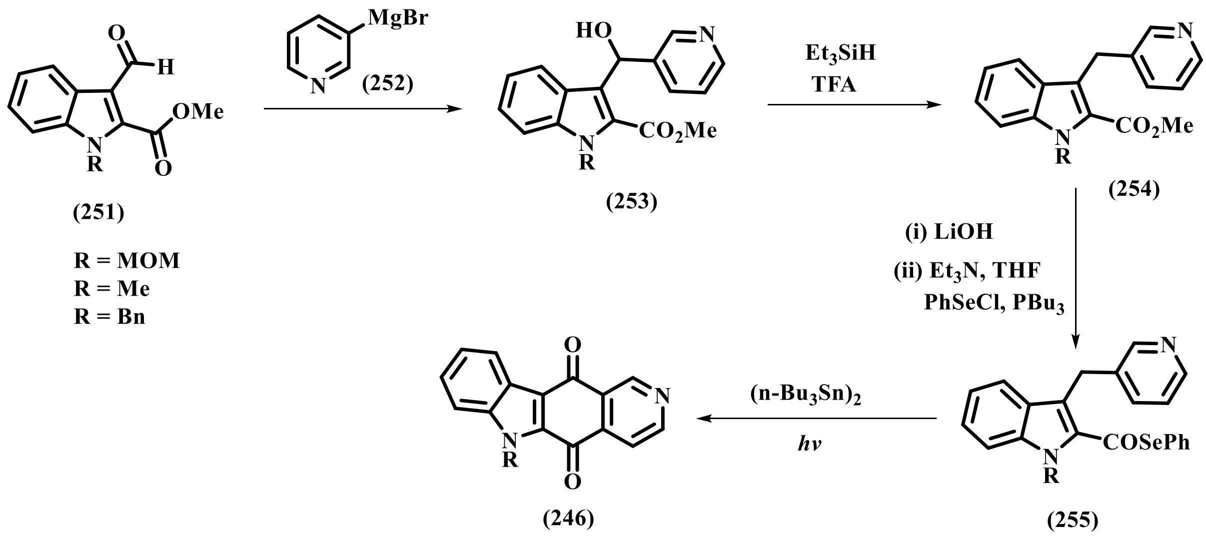
Eq. 72. Joule and co-workers (1979)

In 1979 Joule and co-workers[92] were first reported ellipticine quinone **246** and determined an important precursor in the synthesis of elliptcine alkaloids. By treating the compound pyrido-oxepino-indolone **245** with 3 M aq. NaOH in methanol presence of atmospheric air with refluxing condition to afford ellipticine quinone **246** includes other 3-isomeric form of ellipticine quinones (**Eq. 72**).

In 1985 Gribble *et al.* were synthesized[93] ellipticine quinone **246**, which was access to the synthesis of ellipticines. Pyridine-3,4-dicarboxylic anhydride **247** was transformed to monomethyl ester **248**, further this compound was converted to acid chloride **249** subsequently Friedel-Crafts acylation of *N*-sulfonyl indole **6** to give the compound **250** followed by Comin's methodology to afford the cyclized compound ellipticine quinone **246** (**Eq. 73**).

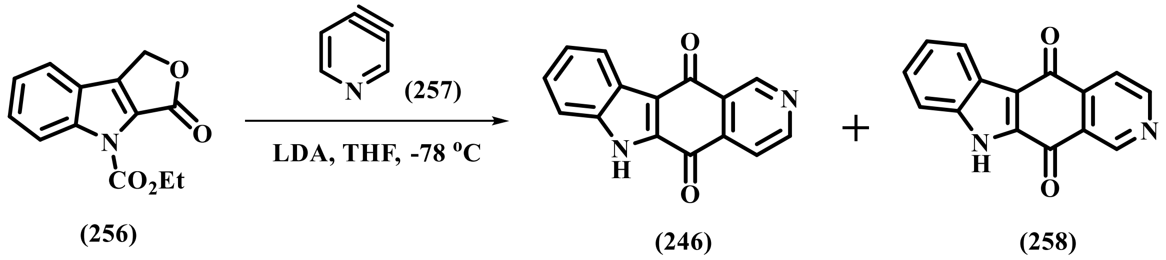
Eq. 73. Gribble *et al.* (1985)





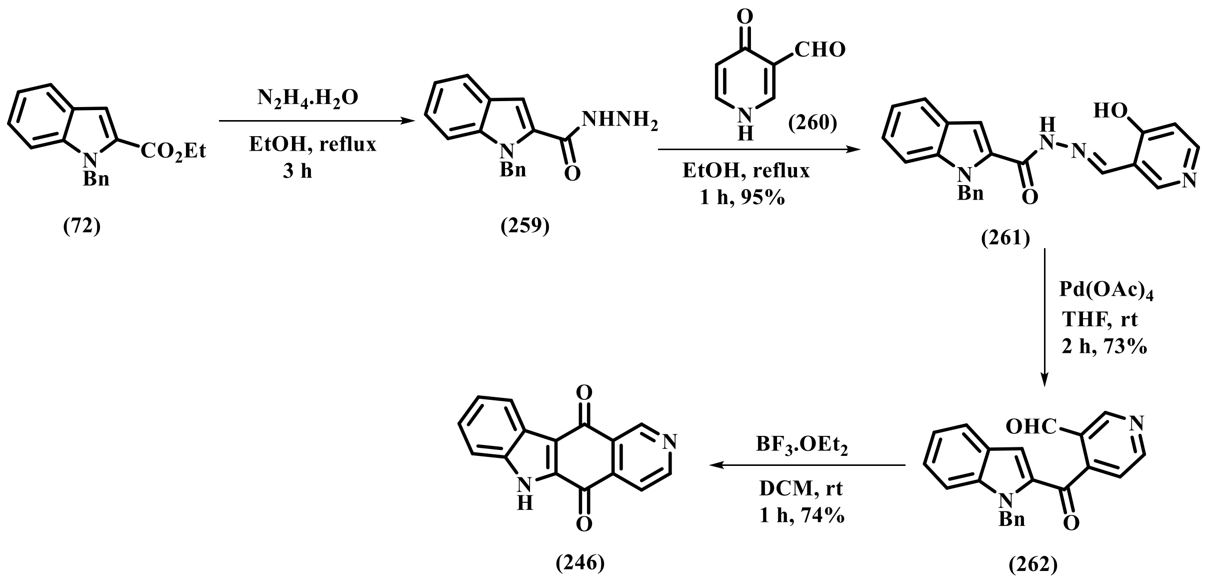
Eq. 74. Bennasar *et al.* (2005)

Bennesar *et al*. were described[94] radical cascade strategy for the synthesis of ellipticine quinones by the reaction of *N*-benzyl 2,3-disubstituted indole **251** reacts with 3-pyridylmagnesium bromide **252** to form alcoholic compound **253**, which was further converted to compound **254** by using triethyl silane subsequently hydrolysis of methyl ester then, treatment with phenyl selenium chloride to gave acyl selenide compound **255**. Further this compound **255** was transformed to cyclization as key step by irradiating in the presence of hexabutylditin to obtain the cyclized compound *N*-benzyl ellipticine quinone **246** in the year 2005. (**Eq. 74**).



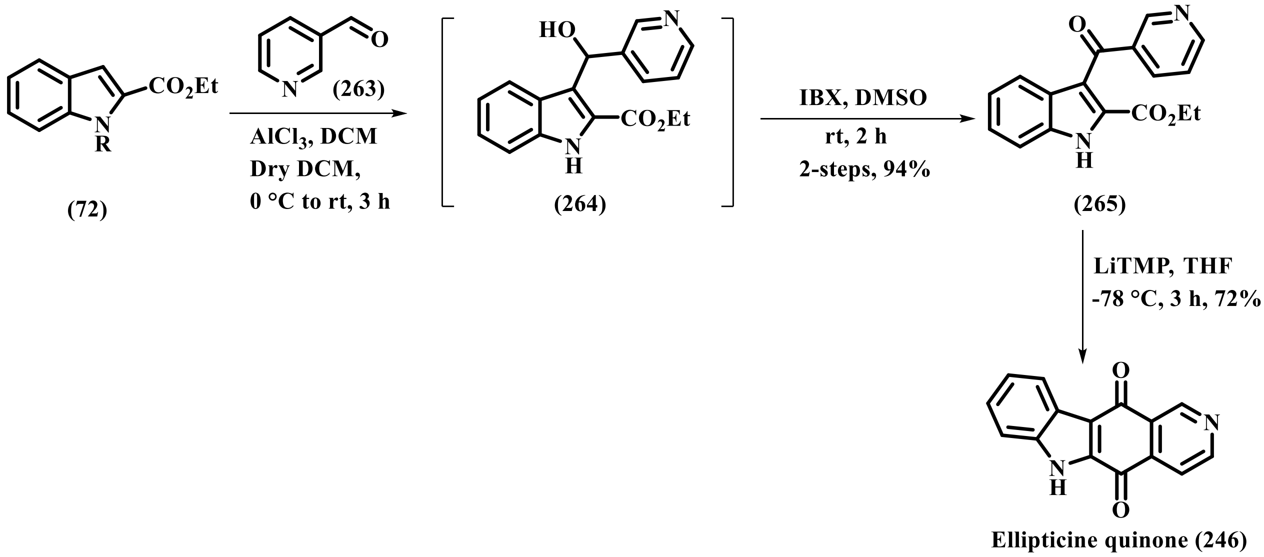
Eq. 75. Mal *et al.* (2007)

In 2007 Mal *et al.* were reported[95] an inseparable mixture of compounds ellipticine **246** and isoellipticine quinones **258** from *N*-Ethoxycarbonylindolofuranone **256** was treated with compound 3,4-pyridyne **257** which was in situ generated from 3-bromopyridine in the presence of LDA mediated involving [4+2] cyclo addition to obtain the mixture of compounds **246** and **258** (**Eq. 75**).



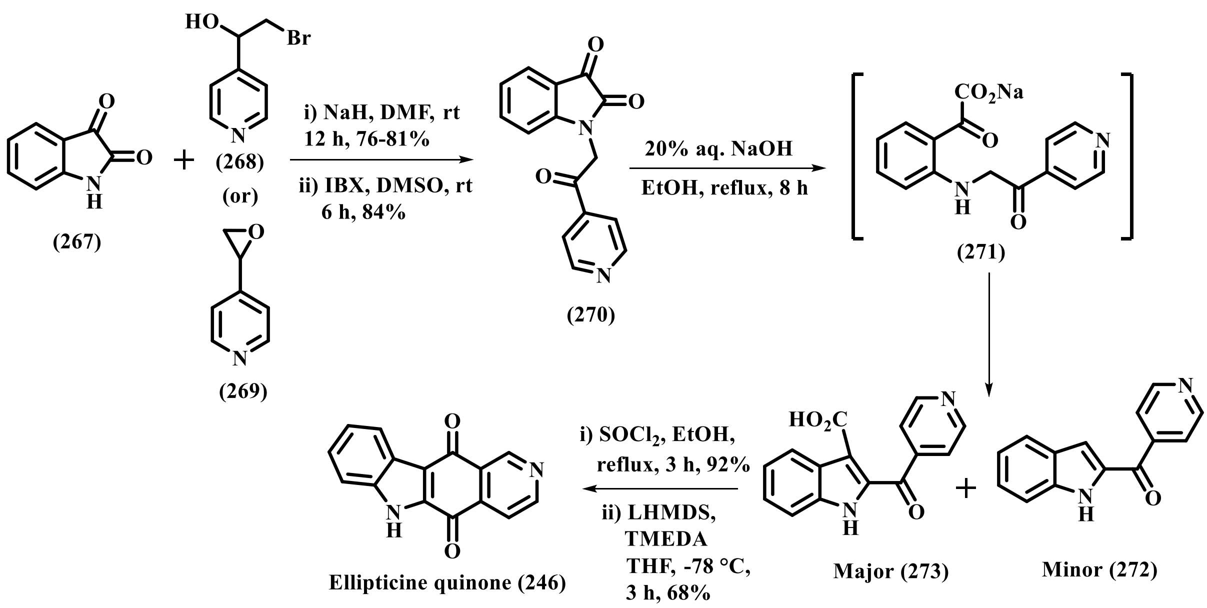
Eq. 76. Dethe and co-workers (2014)

In 2014 Dethe and co-workers[96] reported *N*-benzyl ellipticine quinone by the reaction of *N*-protected indole-2-ethyl ester **72** with hydrazine mono hydrate to form *N*-protected indolyl-hydrazide **259** further this compound **259** reacts with compound **260** to generate the respective hydrazone compound **261**, subsequently LTA-mediated oxidative rearrangement to obtain the compound ketoaldehyde **262** and cyclization using $BF_3.OEt_2$ to furnish the compound **246** (**Eq. 76**).



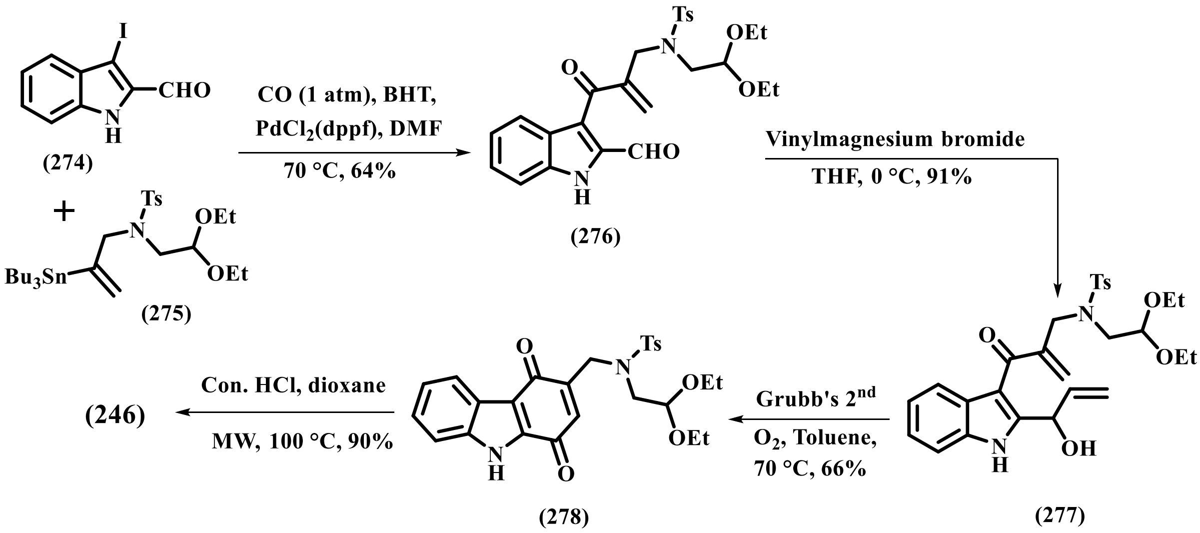
Eq. 77a. Ramkumar *et al.* (2014)

Ramkumar *et al.* were synthesized[35] ellipticine quinone **246** alkaloid from indole-2-ethyl ester treated with pyridine-3-carboxaldehyde **263** involving Friedel-Crafts hydroxy alkylation subsequently oxidation to gave the compound **265** and direct lithiation of this compound to obtain the cyclized compound ellipticine quinone **246** in 3-steps with overall 67.6% yield in the year 2014 (**Eq. 77a**).



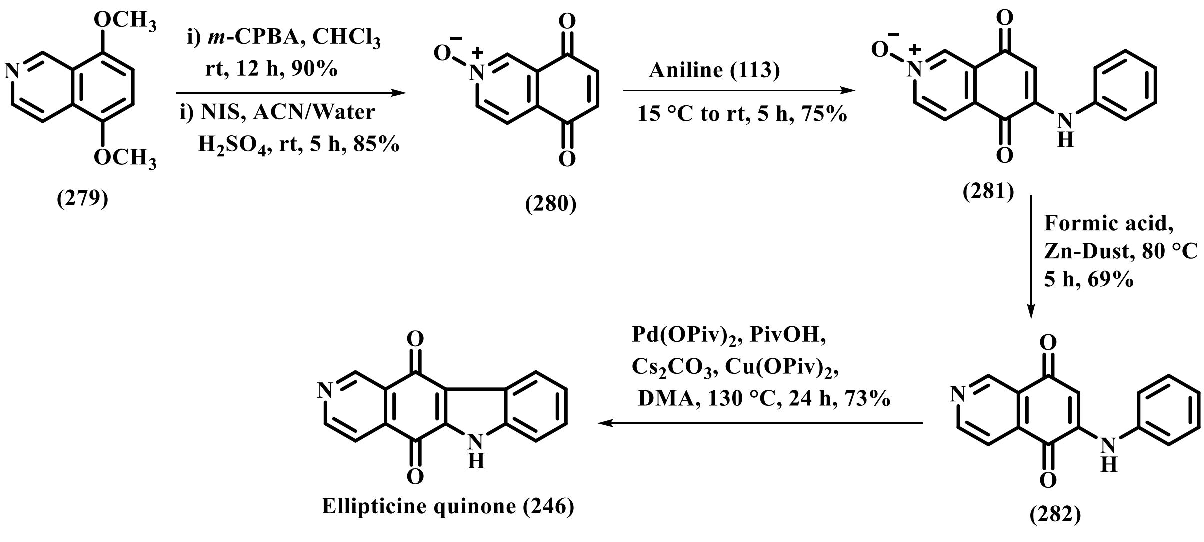
Eq. 77b. Nagarajan and co-workers (2014)

In 2014 Nagarajan and co-workers[97] the same group were reported ellipticine quinone **246** from isatin reacts with compound **268** or **269** to form *N*-alkylation compound **270** under treatment with aq. NaOH inducing reflux condition involving indoledione-indole rearrangement to gave the mixture of compounds **273** (major) and compound **272** (minor) subsequently direct ortho-lithiation of compound **273** to obtain the cyclic compound ellipticine quinone **246** (**Eq. 77b**).



Eq. 78. Nishiyama *et al.* (2017)

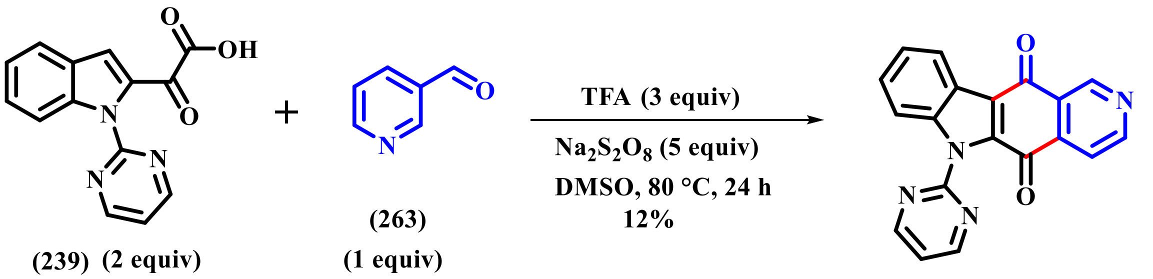
Nishiyama *et al.* was developed[98] for synthesis of compound **246** from 3-iodo indole-2-carboxaldehyde treated with compound **275** in the presence of Pd-mediated cross-coupling to form compound **276** and further treatment with vinylmagnesium bromide to gave corresponding alcohol compound **277** subsequently treated with grubbs catalyst involving ring closing metathesis followed by dehydrogenation with atmospheric oxygen to construct carbazole-1,4-quinone framework **278**. Furthermore, cyclization of compound **278** treat with 6M HCl in 1,4-dioxane presence of microwave irradiation at 100 °C to afford ellipticine quinone **246** in the year 2017 (**Eq. 78**).



Eq. 79. Miranda and co-workers (2022)

Recently, Miranda and co-workers[99] are developed for the synthesis of compound **246** from commercially available 2,5-dimethoxy isoquinoline **279** to convert isoquinoline-5,8-dione *N*-oxide **280**. They are first demonstrated nucleophilic attack on compound **280** regioselectivity C-6 position to gave the compound **281** subsequently intramolecular double C-H cross-coupling to afforded the compound ellipticine quinone **246** (**Eq. 79**).

Scheme 2.2: Synthetic approach of *N*-Pyrimidyl ellipticine quinone

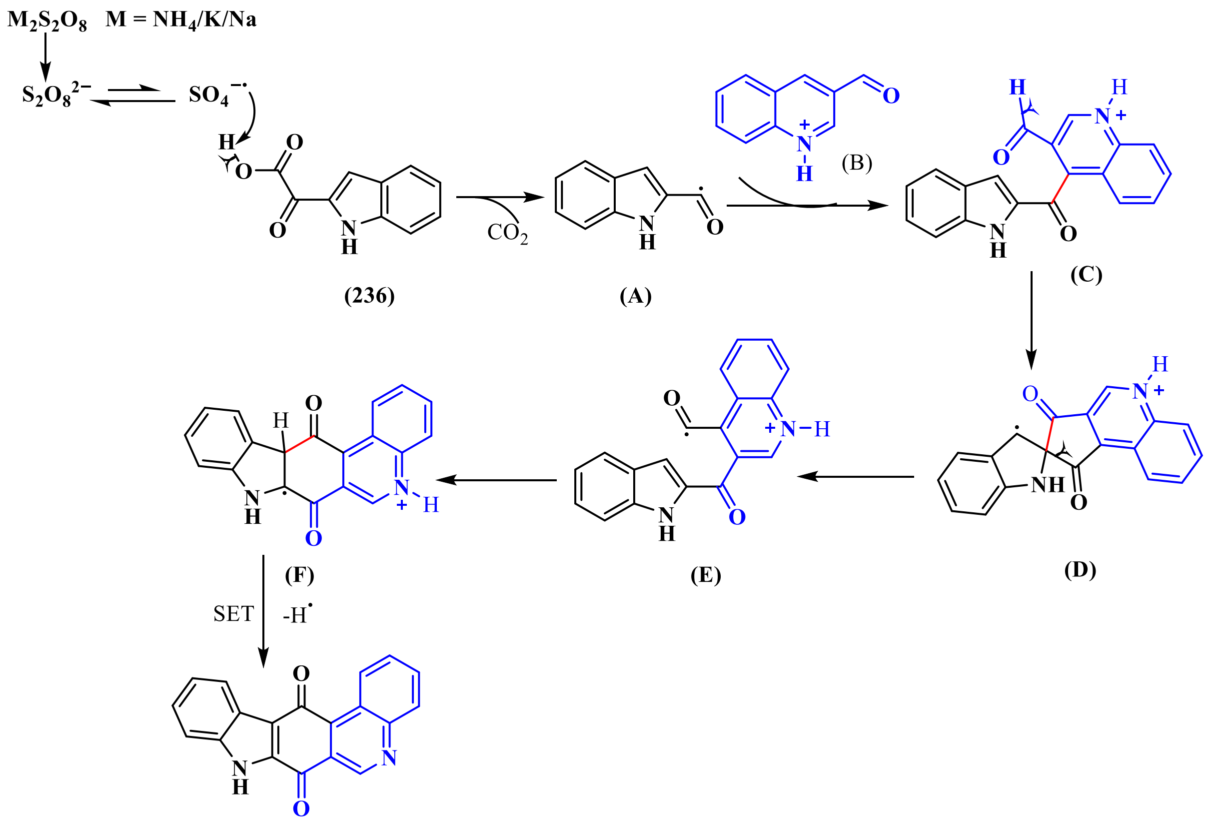


***N*-Pyrimidyl Ellipticine quinone (283)**

We have also synthesized *N*-pyrimidyl ellipticine quinone **283** alkaloid from the prepared compound **239** with commercially available starting material pyridine-3-carboxaldehyde **263** in the presence of acid-mediated sodium persulfate as an oxidant with DMSO solvent at 80 °C in 24 h undergoes metal free decarboxylative cross coupling to afforded the compound **283** with 12% yield. Further this compound can be easily deprotect the pyrimidyl group using NaOMe/NaOEt in DMSO to afford the ellipticine quinone (Scheme **2.2**)

Scheme 2.3: Plausible mechanism

We depicted mechanism initially oxidant dissociate to sulfate anion radical, readily abstract to the indole-2-keto attached acid hydrogen **236** undergoes decarboxylation to generate the respective indole-2-acyl radical (**A**) added to another reactive partner protonated quinoline-3-carboxaldehyde (**B**) to form indole-2-carbonyl-quinoline moiety (indole C2-quinoline C4 connection) (**C**) and further transformed to spiro cyclic compound (**D**) subsequently attains the aromaticity compound (**E**). Furthermore, compound **E** involves cyclization through quinoline-C3-acyl radical addition to indole-C3 position, and subsequent hydrogen radical abstraction by a sulfate radical anion or by a mechanism of single-electron transfer (SET) to obtain the corresponding carbazole quinone frame work (Scheme **2.3**).



Isomeric calothrixin B (225)

2.3 Conclusion:

We developed an enormous method for constructing indolo[2,3-*j*] phenanthridine frame work involving transition metal-free decarboxylative cross coupling methodology in single step. We aimed to synthesize calothrixin B **73**, unfortunately, we found that isomeric calothrixin B **225**, in addition we have also synthesized *N*-Pyrimidyl ellipticine quinone **283** by using decarboxylative cross-coupling strategy with 12% yield.

2.4 Experimental section:

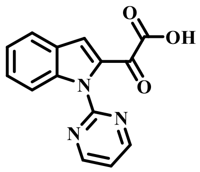
NMR spectra: DMSO-d_6 and $CDCl_3$ are used as the NMR solvents to record ^1H and ^{13}C NMR spectra were recorded at BRUKER-ADVANCE NMR analyser at 400 and 100 MHz or at 500 and 125 MHz respectively. Chemical shifts values were assigned with respect to TMS ($\delta = 0$) for ^1H NMR, and relative to NMR solvent residual peaks in $CDCl_3$ resonance ($\delta = 77.12$) and DMSO-d_6 ($\delta = 39.52$) for ^{13}C NMR. Data are presented as follows: chemical shifts, multiplicity (br s = broad singlet, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz) and integration. Melting points were determined by using a capillary melting point apparatus.

Mass spectral analysis: Shimadzu LCMS 2010A mass spectrometer was used. In all the cases EtOAc or DCM or MeOH were used to dissolve the compounds. HRMS were obtained from TOF and quadrupole mass analyzer types.

General procedure:

Quinoline-3-carboxaldehyde **73** (0.636 mmol. 1 equiv) was dissolved in DMSO (1 mL) in an Screw cap vial, and then slowly addition of TFA (1.90 mmol. 3 equiv) at 0 °C after 5 minutes added indole-2-ketoacid **236** (1.27 mmol. 2 equiv) in DMSO (1-2 mL) followed by Oxidant (3.18 mmol. 5 equiv). The resulting solution was stirred at temperature 70-110 °C for 12-36 h. After reaction was complete (TLC), the reaction was quenched with water (10 mL), the mixture was extracted with ethyl acetate (3×10 mL), and the combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated using a rotary evaporator. The crude product was further purified by column chromatography on silica gel with an ethyl acetate/hexane solvent mixture.

2-Oxo-2-(1-(pyrimidin-2-yl)-1*H*-indol-2-yl)acetic acid (239)



239

Physical state: Pale yellow solid

Yield: 120 mg (88 %)

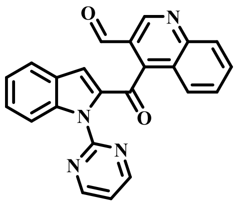
M.P: >250 °C

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 9.24 (s, 1H), 8.92 (d, *J* = 4.8 Hz, 2H), 8.73 (d, *J* = 8.2 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 4.8 Hz, 1H), 7.42-7.38 (m, 1H), 7.36-7.33 (m, 1H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ 188.3, 167.2, 159.5, 156.6, 136.4, 135.5, 128.2, 125.3, 124.3, 122.0, 119.2, 116.6, 116.0.

HRMS (ESI-TOF) Calcd for $C_{14}H_9N_3O_3$ $[M+H]^+$ 268.0717, found: 268.0715.

4-(1-(pyrimidin-2-yl)-1*H*-indole-2-carbonyl)quinoline-3-carboxaldehyde (242)



242

Physical state: brown solid

Yield: 139 mg (58 %)

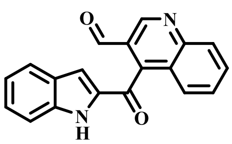
M.P: 243-245 °C

^{1}H NMR (500 MHz, CDCl$_3$): δ 10.30 (br s, 1H), 9.50 (s, 1H), 8.86-8.82 (m, 1H), 8.67 (d, *J* = 4.8 Hz, 2H), 8.28-8.24 (m, 3H), 7.96-7.94 (m, 1H), 7.90-7.87 (m, 1H), 7.60-7.57 (m, 1H), 7.53-7.51 (m, 2H), 7.17 (t, *J* = 4.8 Hz, 1H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 189.3, 189.2, 158.4, 156.6, 150.4, 150.0, 148.7, 136.2, 136.0, 132.9, 129.9, 128.5, 127.2, 127.0, 125.9, 124.9, 124.4, 124.3, 122.4, 121.2, 118.3, 116.6.

HRMS (ESI-TOF) Calcd for $C_{23}H_{14}N_4O_2$ $[M+H]^+$ 379.1190, found: 379.1190.

4-(1*H*-indole-2-carbonyl)quinoline-3-carboxaldehyde (240)



240

Physical state: brown solid

Yield: 107 mg (56 %)

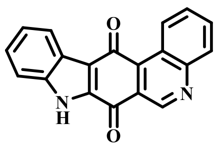
M.P: 248-250 °C

^{1}H NMR (500 MHz, DMSO-d_6): δ 12.25 (br s, 1H), 10.20 (br s, 1H), 9.42 (s, 1H), 8.23-8.20 (m, 1H), 7.99-7.95 (m, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.70-7.59 (m, 2H), 7.54-7.52 (m, 1H), 7.40-7.33 (m, 3H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 190.9, 187.8, 150.2, 150.0, 149.8, 137.5, 133.2, 133.2, 129.9, 129.0, 128.9, 127.3, 125.3, 124.5, 124.2, 123.2, 118.3, 113.1, 111.6.

HRMS (ESI-TOF) Calcd for $C_{19}H_{12}N_2O_2$ $[M+H]^+$ 301.0972, found: 301.0970.

7*H*-Indolo[2,3-*j*]phenanthridine-7,13(8*H*)-dione (225)



225

Physical state: Red solid

Yield: 35 mg (18 %)

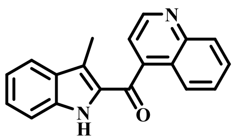
M.P: >250 °C (Lit.[89] >300 °C)

^{1}H NMR (500 MHz, DMSO-d_6): δ 13.15 (br s, 1H), 9.68 (d, J = 8.6 Hz, 1H), 9.53 (s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.94 (t, J = 7.4 Hz, 1H), 7.84 (t, J = 7.7 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 184.4, 178.1, 152.2, 147.3, 138.8, 135.9, 134.6, 132.3, 130.4, 130.2, 128.3, 127.6, 124.7, 124.5, 124.5, 123.5, 122.8, 119.0, 114.4.

HRMS (ESI-TOF) Calcd for $C_{19}H_{10}N_2O_2$ $[M+H]^+$ 299.0815, found: 299.0810.

(3-Methyl-1*H*-indol-2-yl)(quinolin-4-yl)methanone (244)



244

Physical state: yellow solid

Yield: 41 mg (18 %)

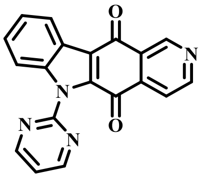
M.P: 136-138 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.31 (br s, 1H), 8.46-8.40 (m, 2H), 8.34 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.91-7.87 (m, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.75-7.71 (m, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.44-7.40 (m, 1H), 7.21-7.17 (m, 1H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 180.8, 156.0, 146.1, 137.6, 136.7, 131.5, 130.4, 129.9, 129.1, 128.7, 127.8, 127.8, 126.6, 125.4, 121.2, 120.4, 119.9, 112.4, 11.4.

HRMS (ESI-TOF) Calcd for $C_{19}H_{14}N_2O$ $[M+H]^+$ 287.1179, found: 287.1176.

6-(Pyrimidin-2-yl)-5*H*-pyrido[4,3-*b*]carbazole-5,11(6*H*)-dione (283)



283

Physical state: Red solid

Yield: 41 mg (18 %)

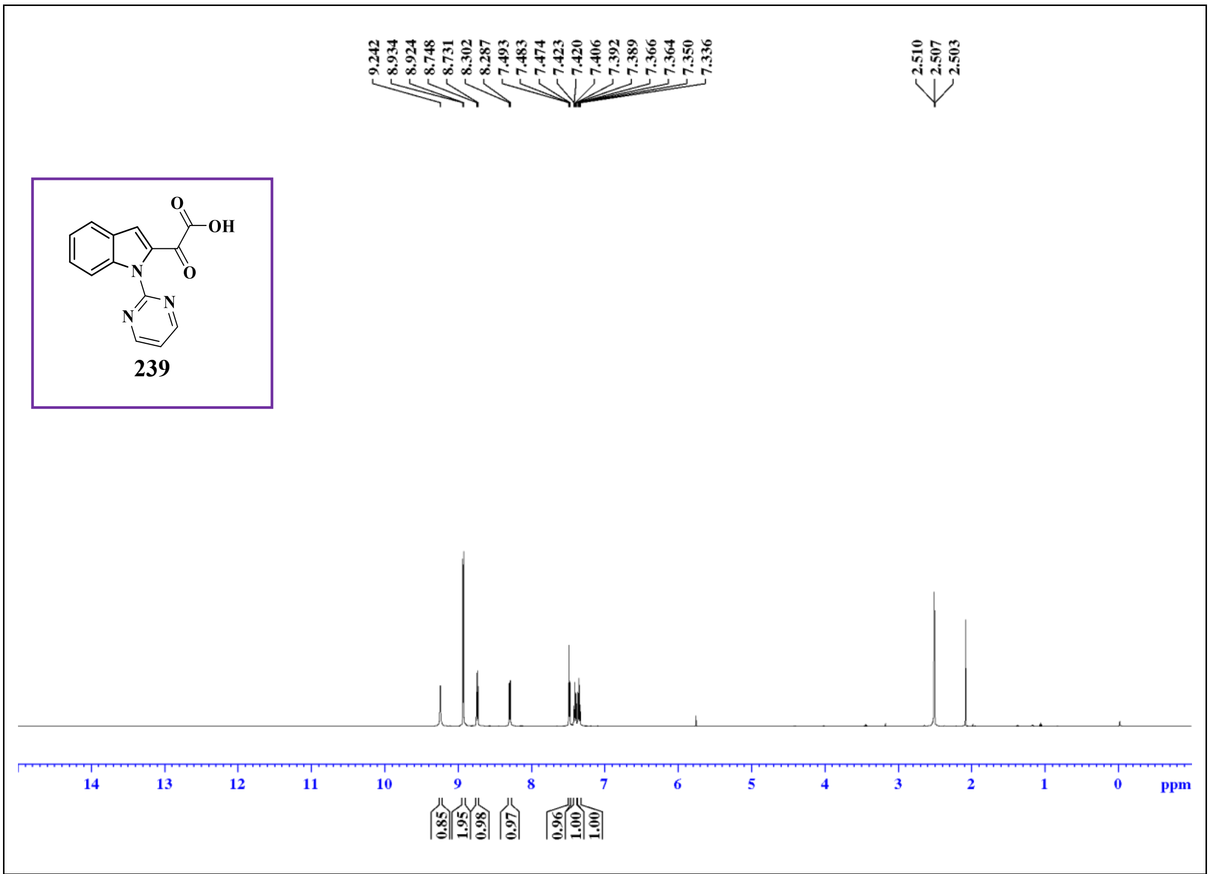
M.P: >250 °C

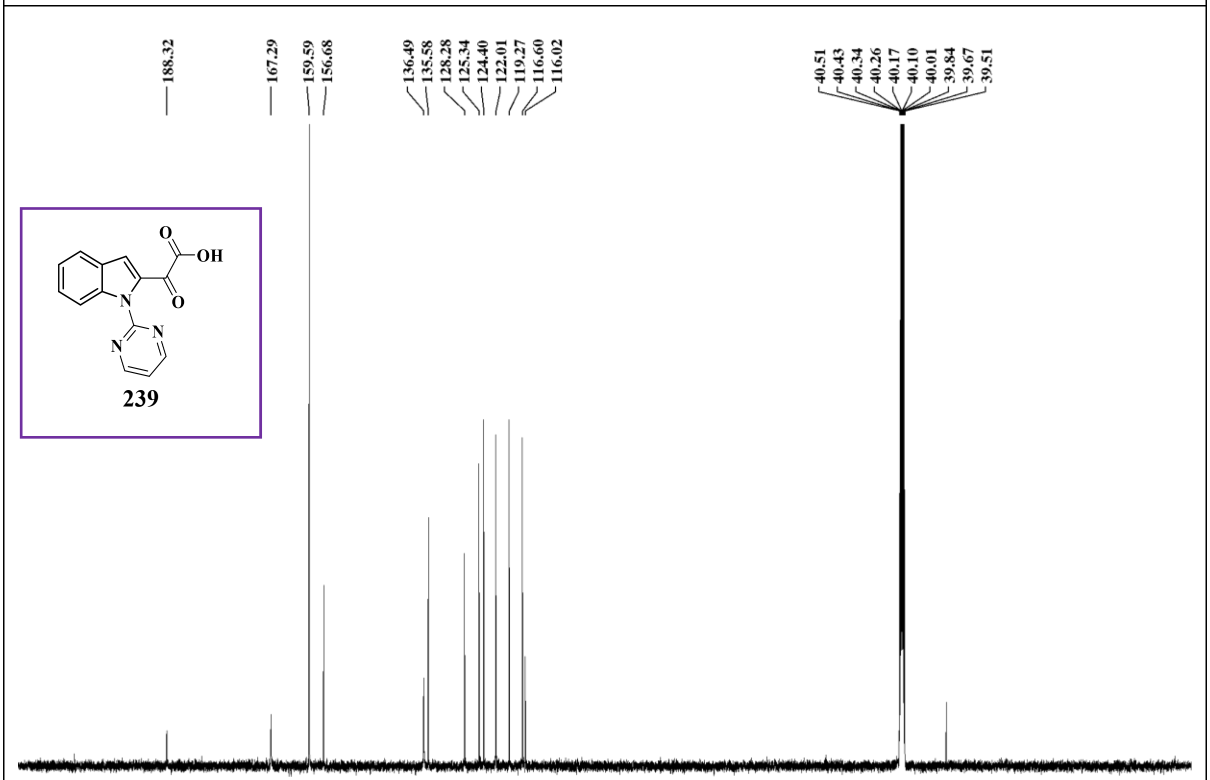
^{1}H NMR (500 MHz, CDCl$_3$): δ 9.32 (s, 1H), 8.97 (d, J = 4.9 Hz, 1H), 8.89 (d, J = 4.8 Hz, 2H), 8.43-8.41 (m, 1H), 7.97 (d, J = 4.9 Hz, 1H), 7.62-7.61 (m, 1H), 7.46-7.44 (m, 2H), 7.43 (t, J = 1.6 Hz, 1H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 180.3, 176.1, 159.0, 156.4, 155.3, 148.2, 139.7, 139.3, 135.9, 128.9, 126.7, 125.6, 123.8, 123.8, 121.6, 120.7, 118.8, 112.8.

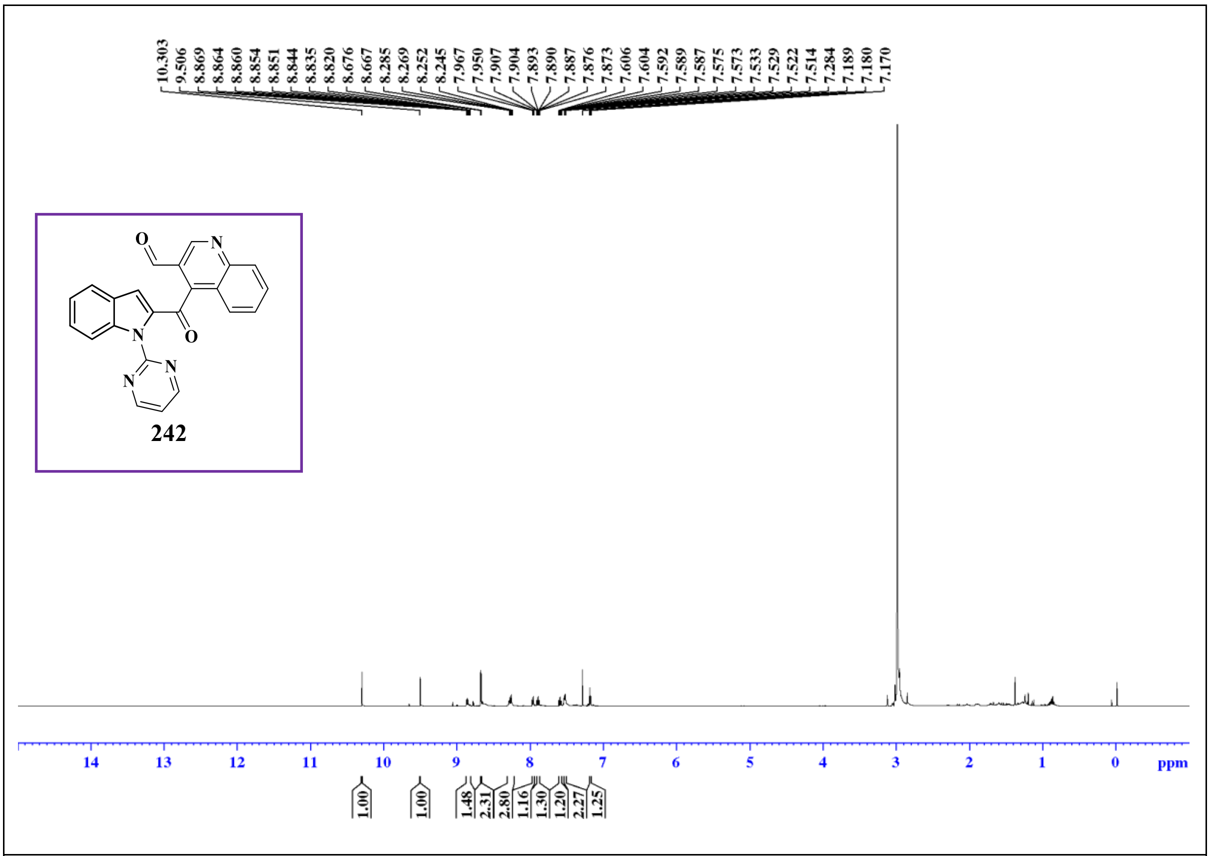
HRMS (ESI-TOF) Calcd for $C_{19}H_{10}N_4O_2$ [M+H]$^+$ 327.0877, found: 327.0877.

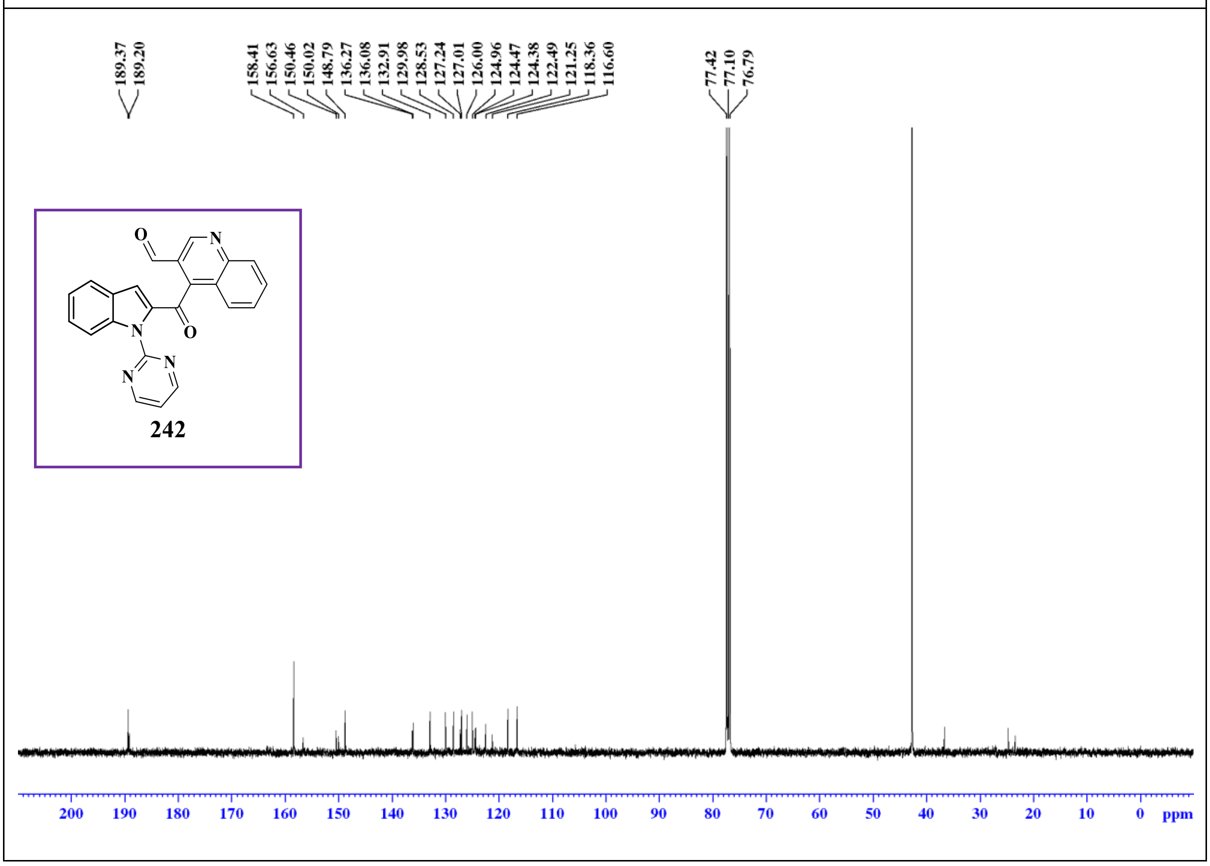
^{1}H and ^{13}C NMR Spectra of Compound **239**



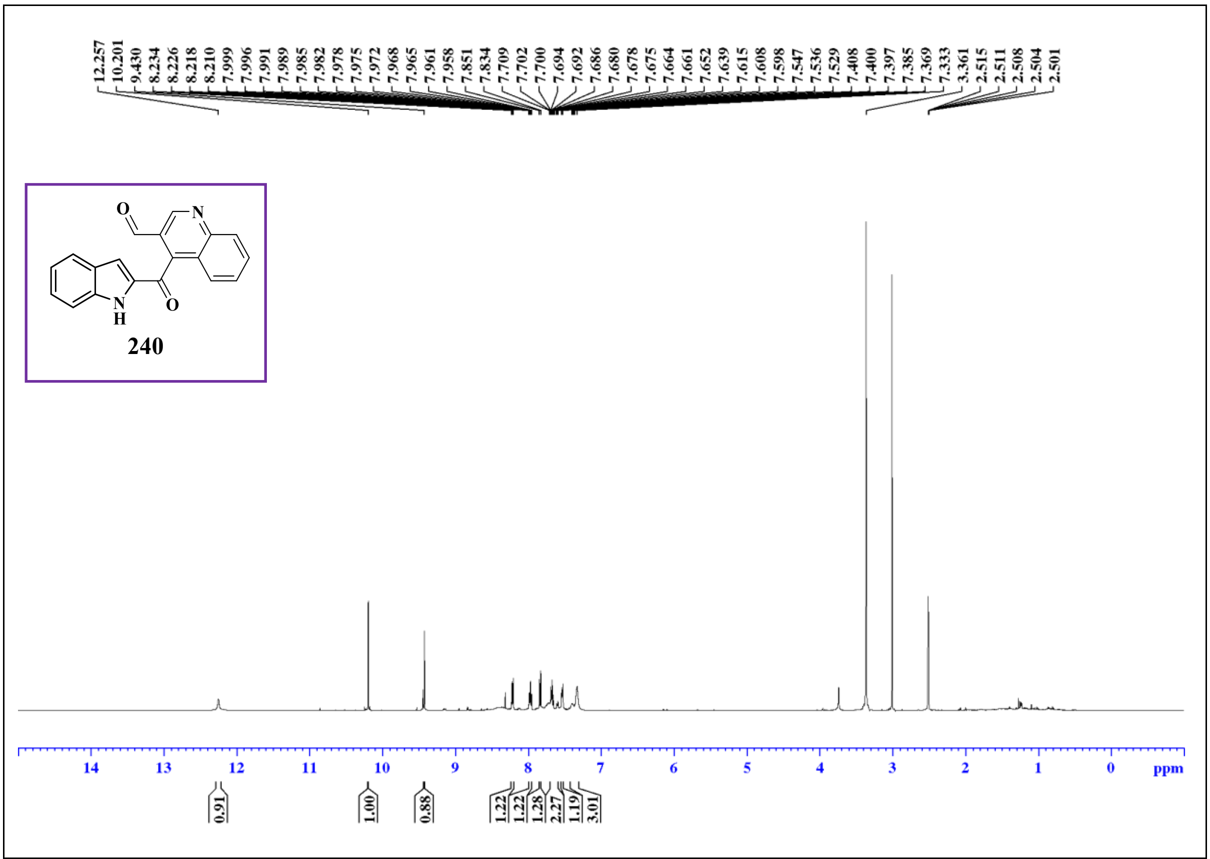


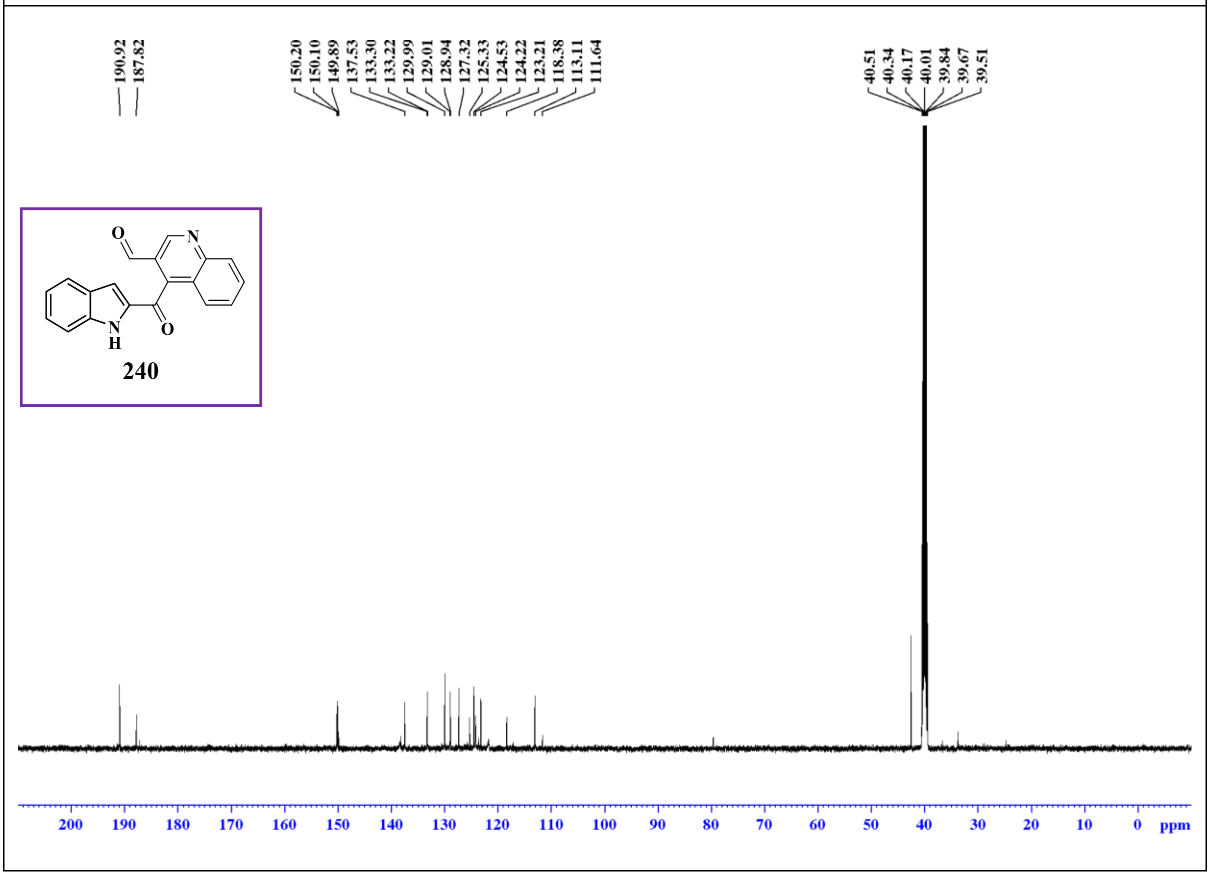
[1]H and [13]C NMR Spectra of Compound **242**



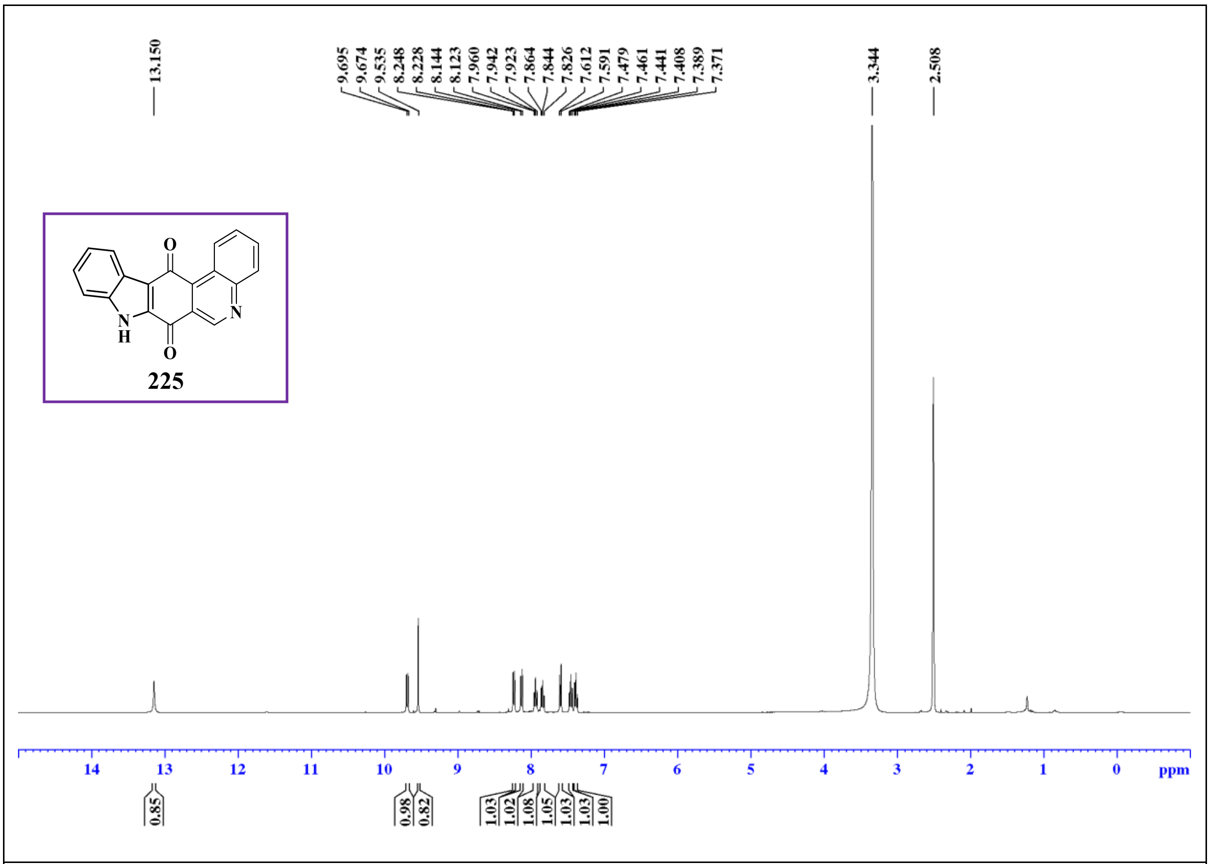


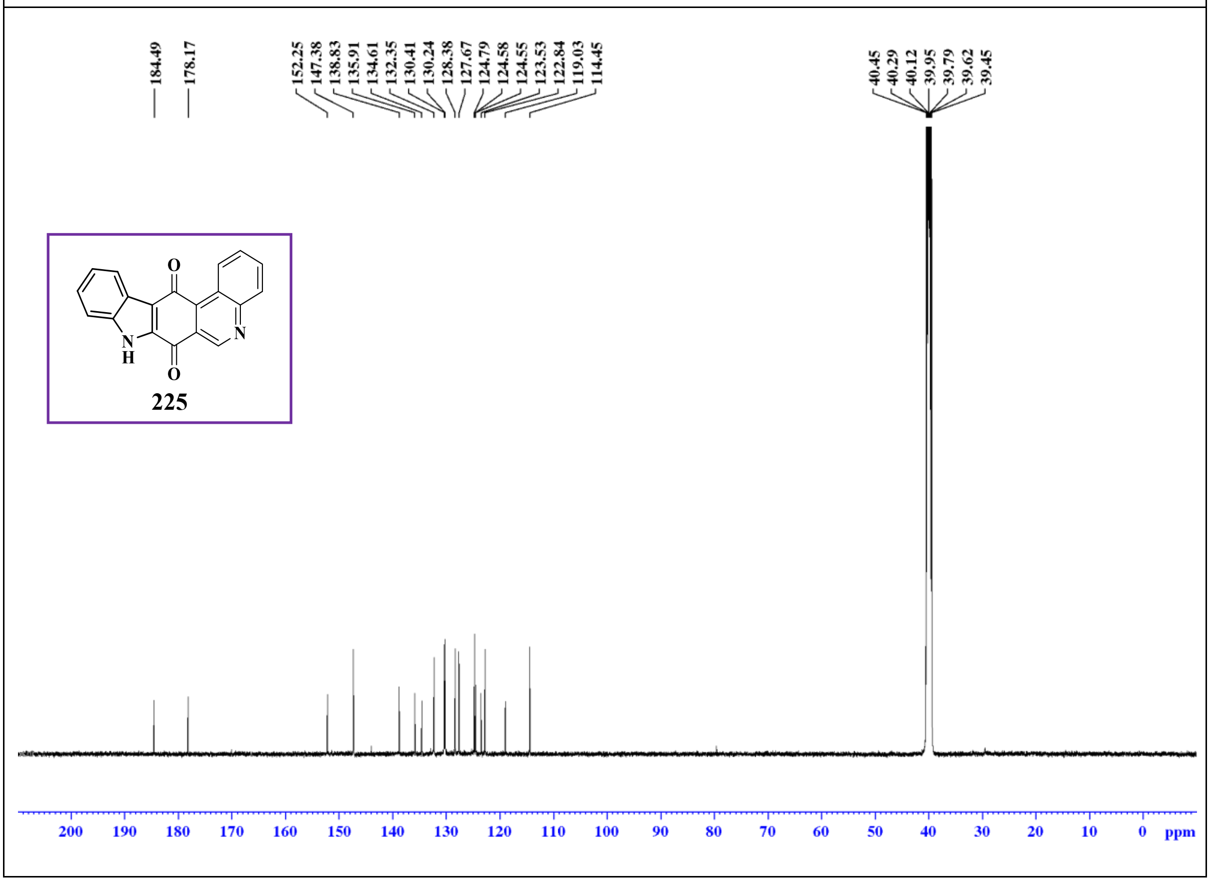
[1]H and [13]C NMR Spectra of Compound **240**



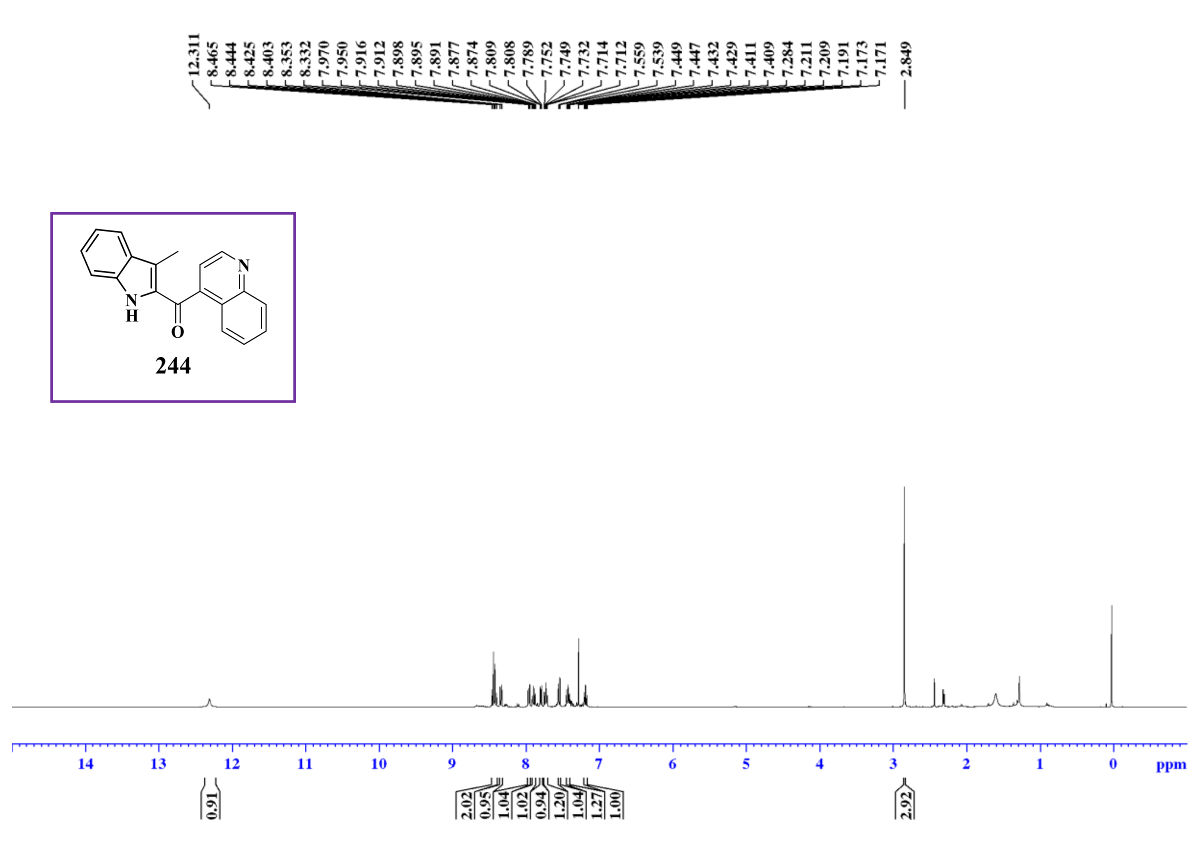


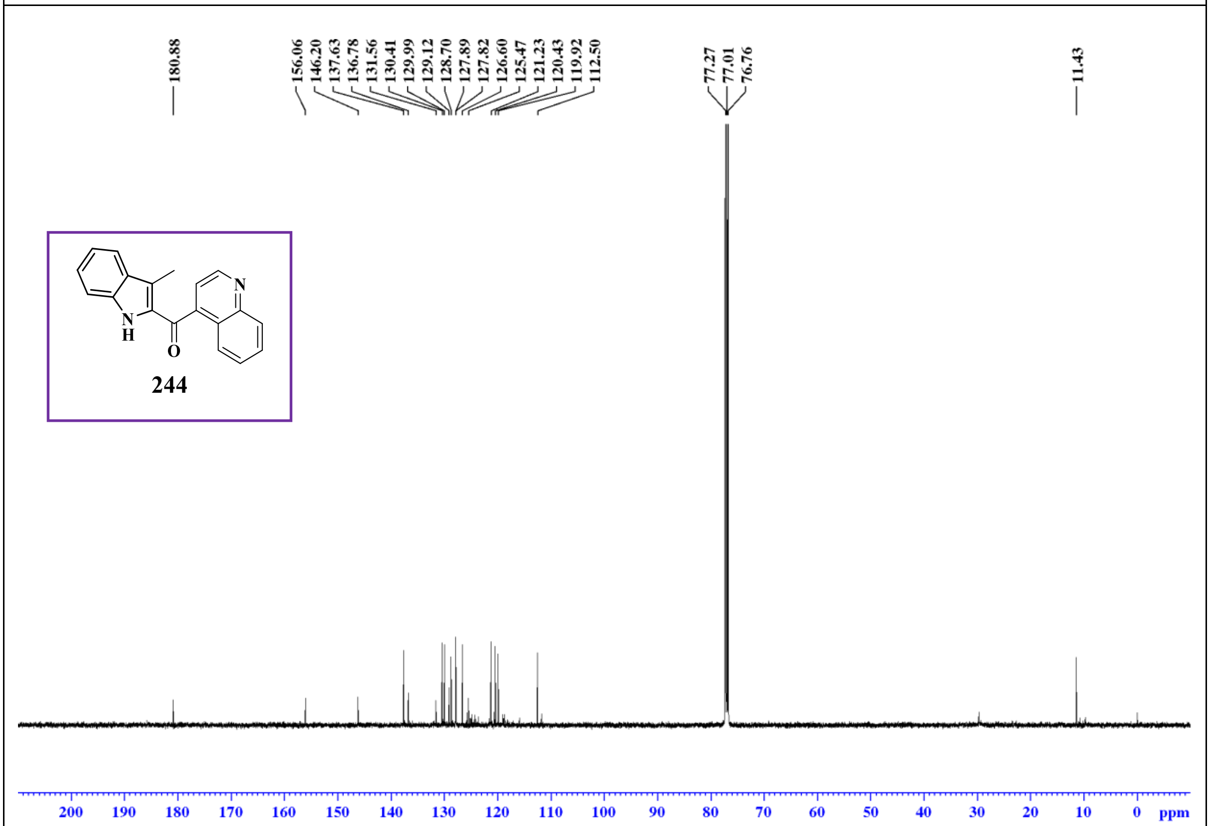
[1]H and [13]C NMR Spectra of Compound **225**



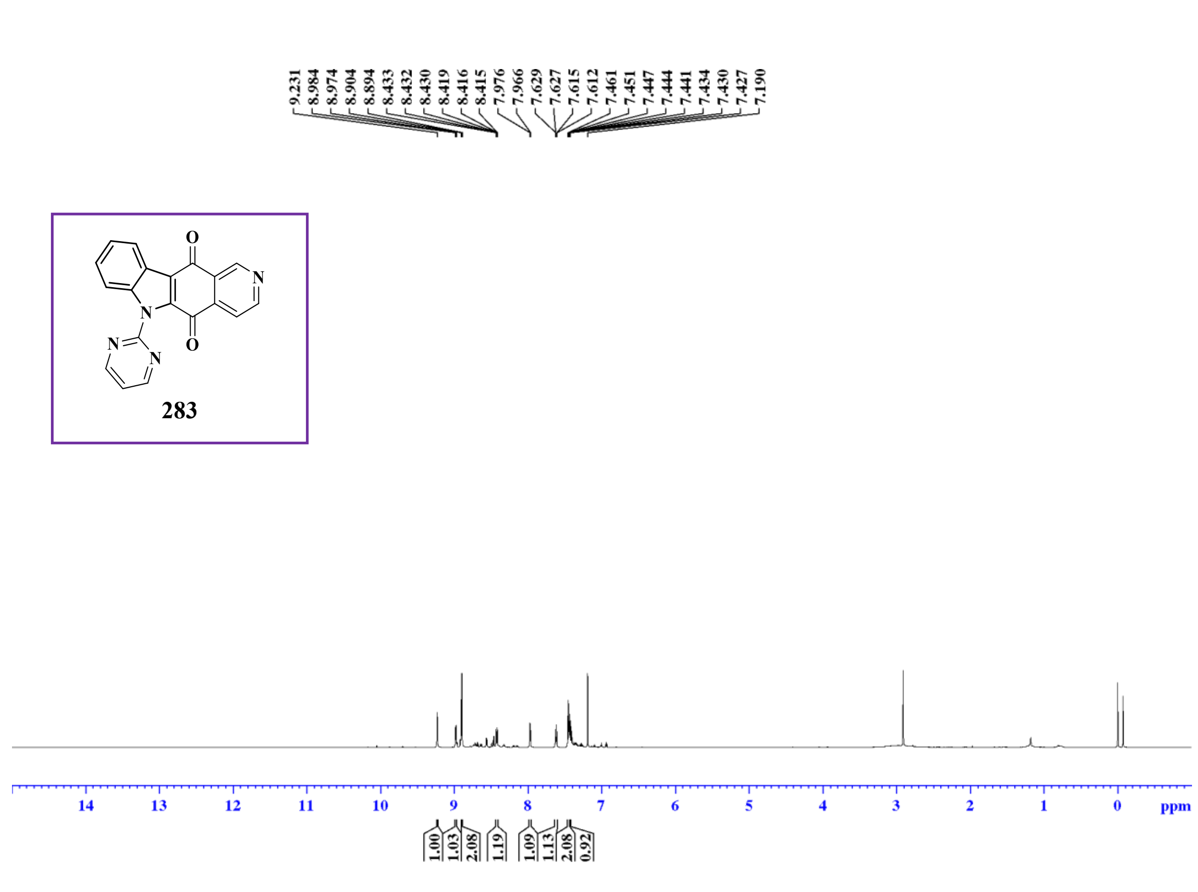


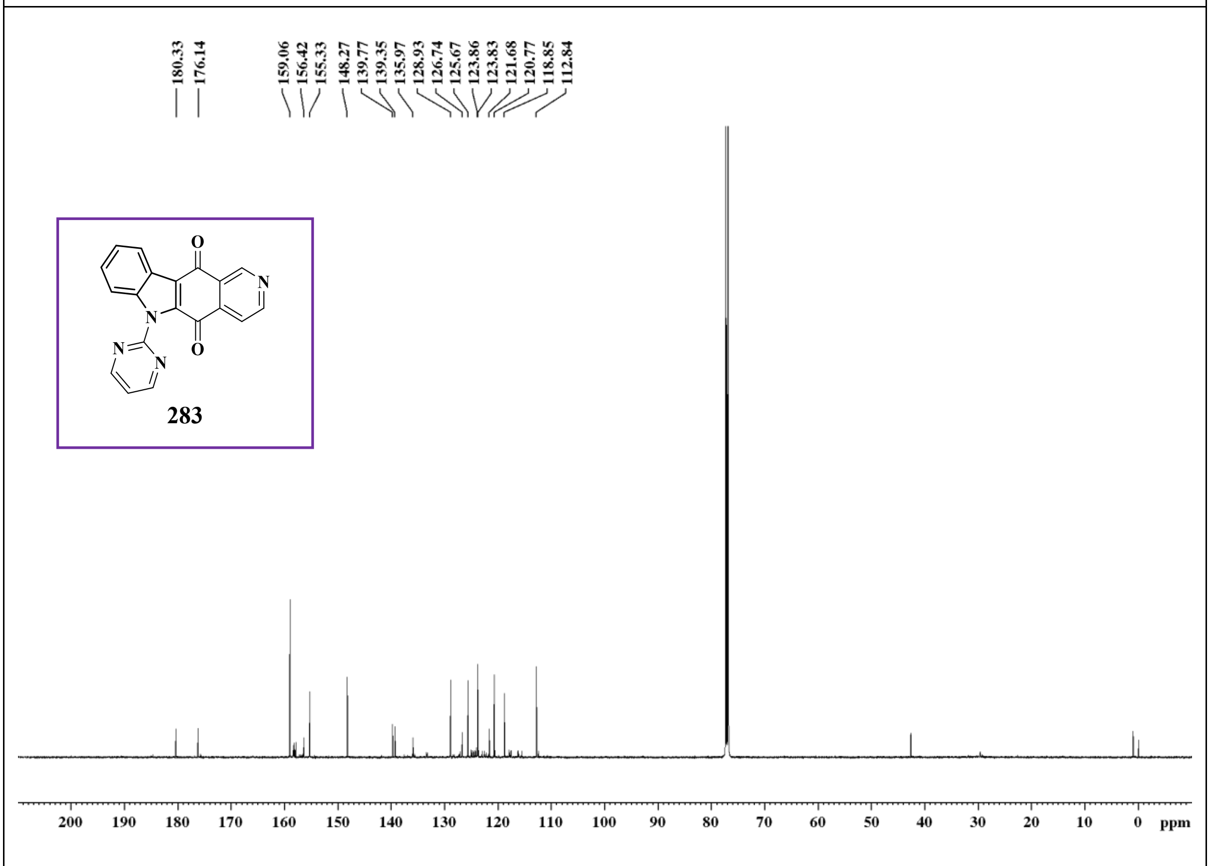
^{1}H and ^{13}C NMR Spectra of Compound **244**





^{1}H and ^{13}C NMR Spectra of Compound **283**





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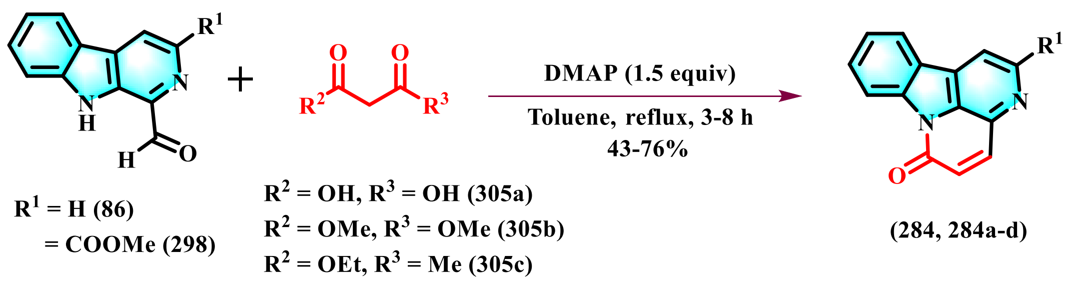
CHAPTER- *III*

Synthesis of Canthinone and its analogues through Knoevenagel condensation



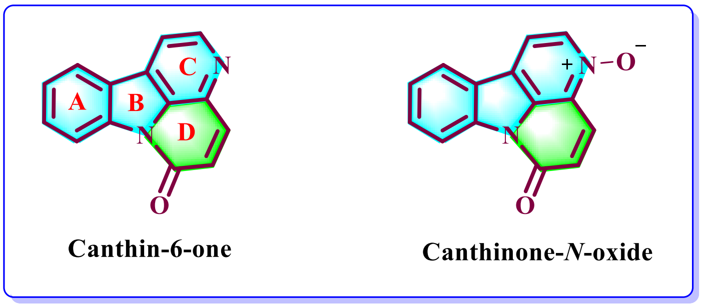
Abstract:

We have synthesized biologically active β-carboline alkaloid canthin-6-one and its analogues starting from β-carboline-1-carboxaldehyde treatment with commercially available starting precursors under the DMAP mediated condensation followed by cyclization in a single step with good to moderate yields.

3.1 Introduction:

Haynes *et al*. was first isolated[100] Canthin-6-one **284** from the Australian tree *Pentaceras australis* in the year 1952. Also found from the various plants families those are *Rutaceae*, *Malvaceae*, *Amaranthaceae*, *Simaroubaceae*, *Caryophyllaceae* and *Zygophyllaceae* marine organisms and recently isolated from fungi (Boletus curtisii *Berk*).[101] According to the literature search canthin-6-one **284** core was incorporated as inside the framework of more than 150 compounds, including pentacyclic analogues; since this type of alkaloids greater than sixty members are found from naturally occurring sources. It is a sub class of *β*-carboline contain alkaloid includes additional D-ring. It exhibits numerous potential therapeutic applications of canthine-6-one and its derivatives, such as antitumor, antiviral, antibacterial, antifungal, antiproliferative, anti-inflammatory, aphrodisiac, and antiparasitic agents, also uses in DNA screening, cancer chemoprevention, and so on.[101]

Figure 1.1 Structures of Canthin-6-one and Canthinone-*N*-oxide



Previous reports on synthesis of canthin-6-one alkaloids

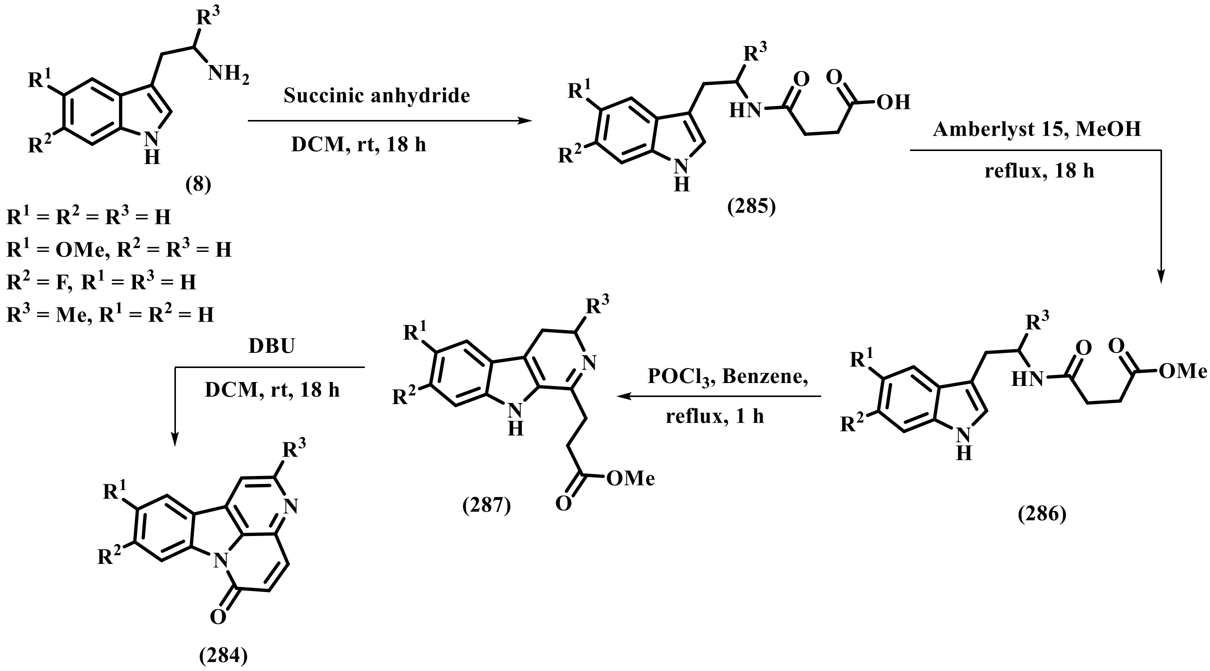
Canthinone alkaloids was synthesized with classical and non-classical methods have been reported by various groups from different starting precursors, are summarized below:

Classical routes:

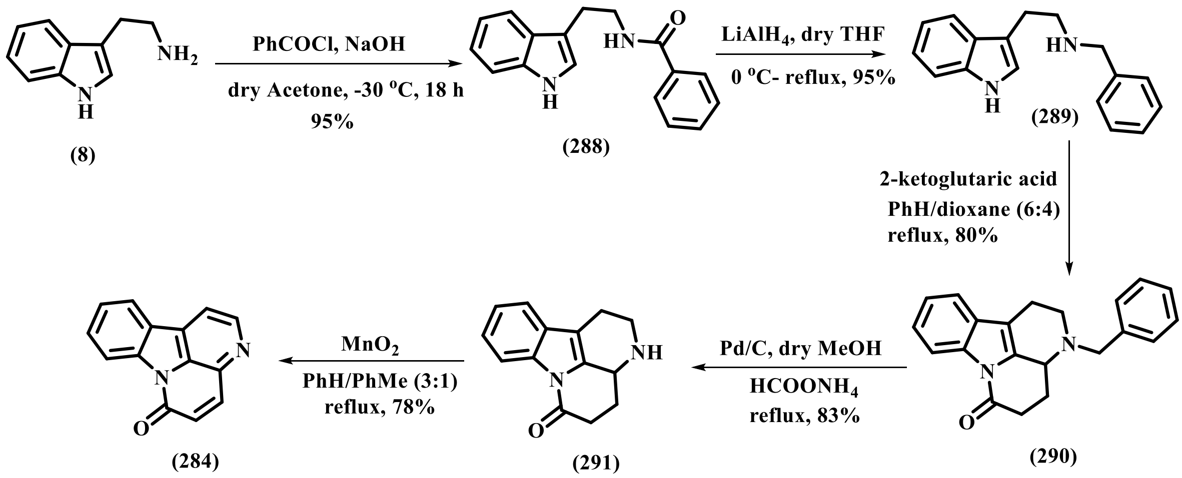
(A). Bischler-Napieralski method

Canthinone alkaloids were first reported[102a] in 1966 by Schmidt *et al.* involving Bischler-Napieralski reaction starting from tryptophan with succinic anhydride to afforded poor yield. In 2005 Soriano-Agaton *et al.* were reported[102b] canthinone and its analogues by the reaction of tryptamine **8** reacts with succinic anhydride to gave amide compound **285** subsequently esterification results compound **286** further involving Bischler-Napieralski cyclization followed by aromatization to afforded compound **284** within three to four steps overall 60% yield (**Eq. 80**) Erwan-Poupan and co-workers[102c] also synthesized canthinone in solution phase nanoparticle biosynthetically involving with the same Bischler-Napieralski cyclization method by the reaction with tryptamine **8** treated with succinic anhydride an overall 57% yield in the year 2013 (**Eq. 80**).

Eq. 80. Schmid *et al.* (1966), Soriano-Agaton *et al.* (2005) and Erwan Poupon and co-workers (2013)



(B). Pictet-Spengler method

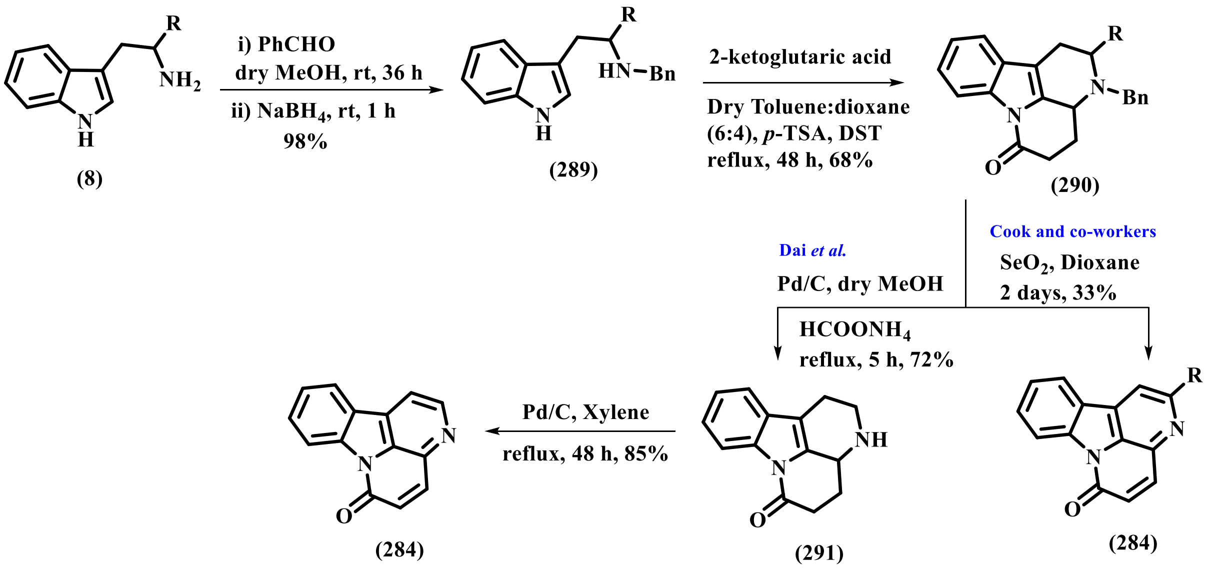


Eq. 81. Mitscher *et al.* (1975), Czerwinski *et al.* (2003)

In 1975 Mitscher *et al.* were synthesized[103a] canthin-6-one **284** alkaloids for the first time using the Pictet-Spengler method. Czerwinski *et al.* were reported[103b] an improved synthesis compound **284** starting from tryptamine **8** transformed to *N*-benzyl tryptamine **289** through the compound **288** undergoes reduction using $LiAlH_4$. Further compound **289** treated with 2-ketoglutaric acid undergoes Pictet-Spengler methodology gave cyclized compound **290** subsequently debenzylation by using catalytic transfer hydrogenation technique to afford the compound **291** followed by treatment with freshly prepared active MnO_2 for aromatization to obtain the corresponding *β*-carboline alkaloid canthin-6-one **284** with an overall 46.74% yield in the year 2003 (**Eq. 81**).

In 1983 Cook and co-workers[103c] reported canthin-6-one and its substituents from tryptamine and its substituents reacts with benzaldehyde and subsequent $NaBH_4$ reduction to form *N*-benzyl tryptamine **289** Further this compound **289** treated with 2-ketoglutaric acid involving Pictet-Spengler cyclization followed by aromatization and debenzylation to afford compound **284** with overall 26% yield (**Eq. 82**). Dai *et al.* synthesized[103d] canthin-6-one **284** starting from tryptamine **8** reacts with benzaldehyde and reduction with $NaBH_4$ to gave *N*-benzyl tryptamine **289** undergoes Pictet-Spengler methodology with 2-ketoglutaric acid to form compound **290**. The treatment of compound **290** with catalytic transfer hydrogenation and aromatization using Pd/C inducing reflux with xylene solvent to afford canthinone **284** an overall 42% yield in the year 2016 (**Eq. 82**).

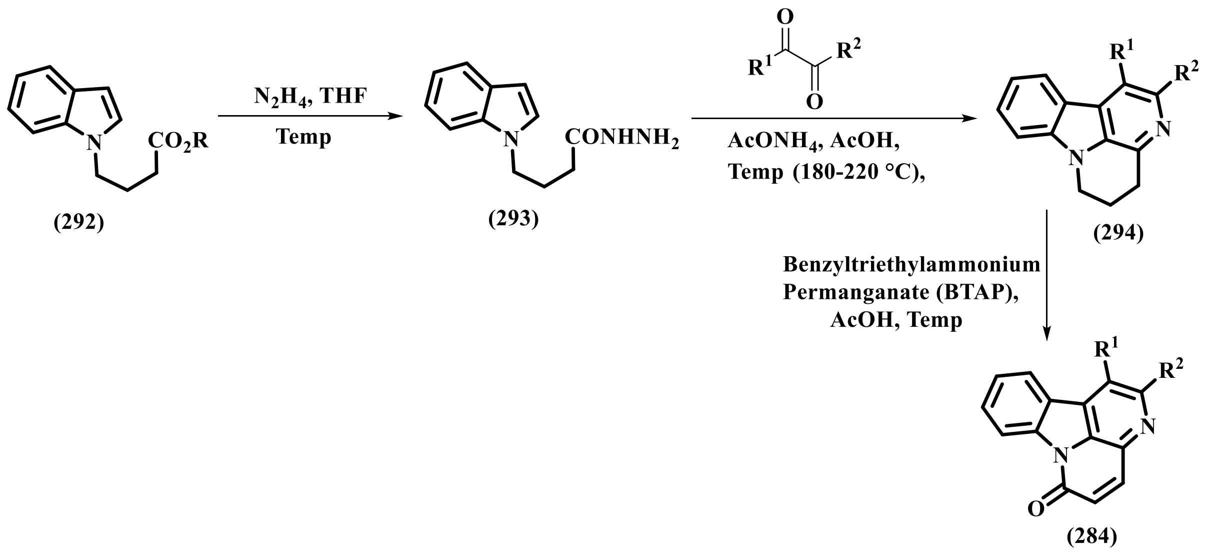
Eq. 82. Cook and co-workers (1983), Dai *et al.* (2016)



(C). Diels-Alder method

Snyder and his group described[104a-b] for synthesis of canthin-6-one **284** and its skeletons utilizing indole skeleton acts as dienophile character involving intramolecular inverse electron demand Diels-Alder reaction. Another group Lindsley *et al.* were also reported[104c] under the microwave-mediated involving the same Diels-Alder method for synthesis of canthin-6-one **284** and its analogues with an overall 48% yield in the year 2003 (**Eq. 83**).

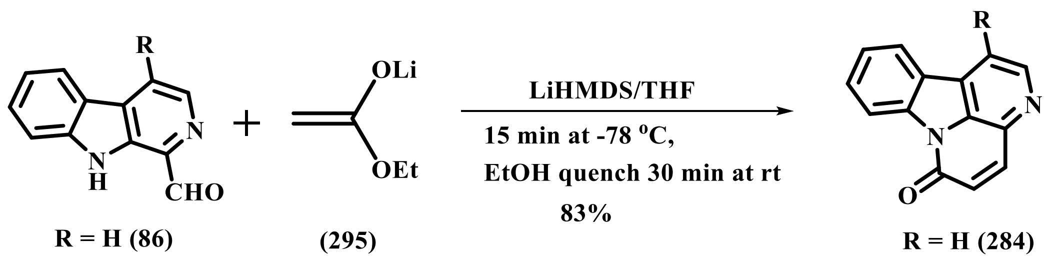
Eq. 83. Snyder and co-workers (1994 & 1992), Lindsley *et al.* (2003)



(D). Aldol method

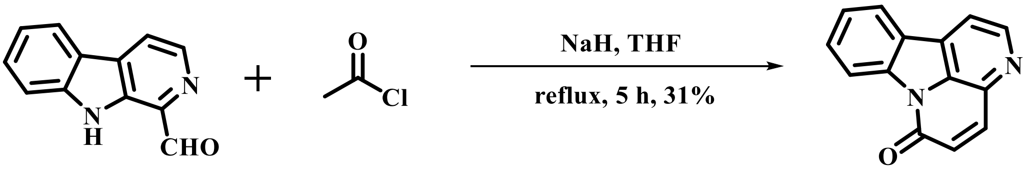
In 2005 Suzuki *et al.* were developed[105a] for synthesis of canthion-6-one **284** from β-carboline-1-carboxaldehyde **86** direct treatment with Li-enolate (ketene acetal) **295** in the presence of LHMDS mediated aldol condensation method to afforded compound **284** with 83% yield (**Eq. 84**).

Eq. 84. Suzuki *et al.* (2005)



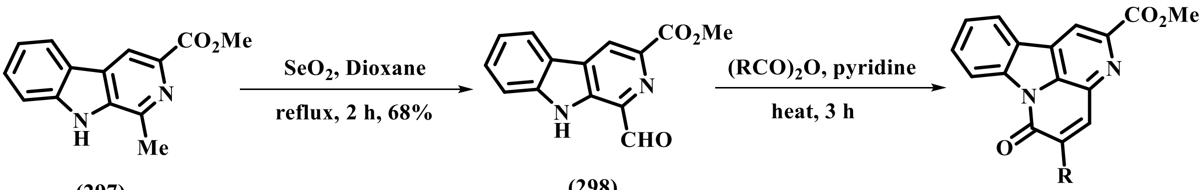
Takasu *et al.* were reported[105b] canthinone starting from β-carboline-1-carboxaldehyde **86** treated with acetyl chloride **296** under the base sodium hydride with refluxing the reaction mixture to obtain the corresponding aldol condensation followed by cyclization compound canthin-6-one **284** in single step with 31% yield in the year 2005 (**Eq. 85**).

Eq. 85. Takasu *et al.* (2005)



(86) (296) (284)

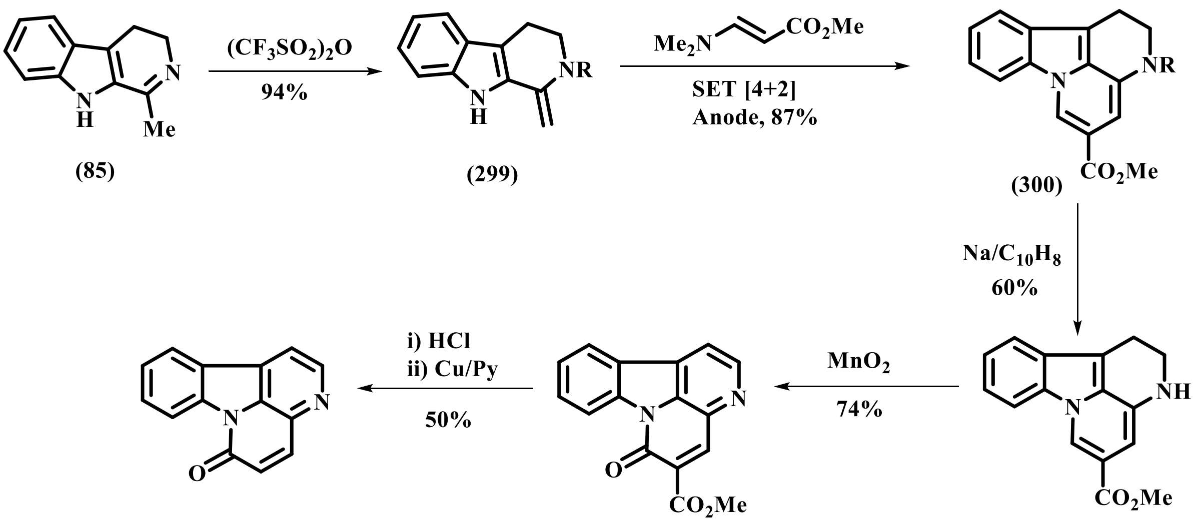
(E). Perkin reaction



(297) (298) (284) R = H, 72%
R = CH_3, 68%

Eq. 86. Giudice *et al.* (1990), Brahmbhatt *et al.* (2010)

Canthinone alkaloids was synthesized in 1990 by Giudice[106a] *et al.* and Brahmbhatt[106b] *et al.* in 2010 starting from 1-methyl *β*-carboline-3-methylester **297** treated with SeO_2 oxidation to forms aldehyde compound **298** further treatment with acetic anhydride involving Perkin reaction in the presence of pyridine inducing reflux to obtain the corresponding cyclized compound canthinone **284** with the overall yields 50% and 40% respectively (**Eq. 86**).



(85) (299) (300) (301) (284)

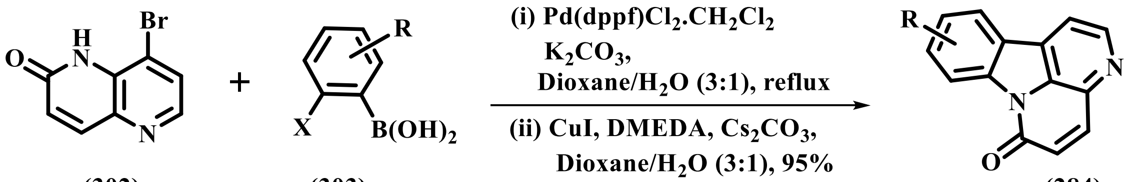
Eq. 87. Steckhan and co-workers (1999)

Steckhan and co-workers[107] developed for synthesis of canthin-6-one **284** by the reaction harmalan **85** single electron transfer (SET) induced radical cationic hetero [4+2] cycloaddition to forms compound **300** subsequently deprotection and aromatization with active MnO_2 followed by esterification and Cu-mediated decarboxylation to obtain in six-steps with overall 18% yield in the year 1999 (**Eq. 87**).

Modern methods:

In 2010 Gollner *et al.* were synthesized[108a] canthin-6-one and its analogues under the modern method to construct central pyrrole ring-B. This method undergoes Pd-catalyzed Suzuki-Miyaura C-C coupling subsequently Cu-catalyzed C-N coupling, which can be accomplished either sequentially or using a one-pot technique beginning with 8-bromo-1,5-naphthyridine **302** with excellent yields (**Eq. 88**).

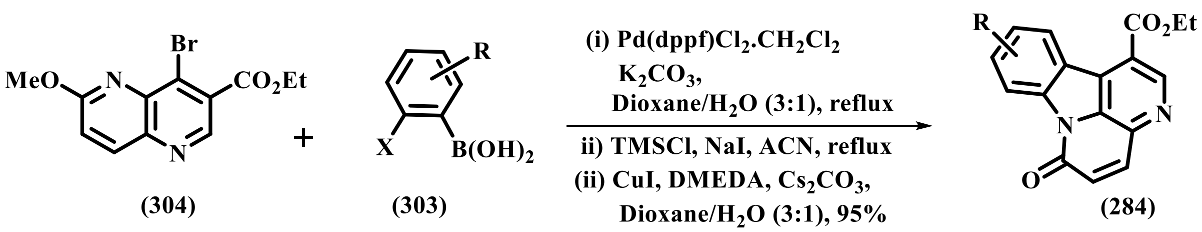
Eq. 88. Gollner *et al.* (2010)



(302) (303) (284)

Ioannidou *et al.* was reported[108b] canthin-6-one-1-ethylester within 3-step modern reaction that mainly focuses on formation of pyrrole ring-B through Pd-catalyzed Suzuki-Miyaura C-C coupling subsequently demethylation and Cu-catalyzed Buchwald C-N coupling which can be easily synthesized from 1,5-naphthyridine compound in the year 2011 (**Eq. 89**).

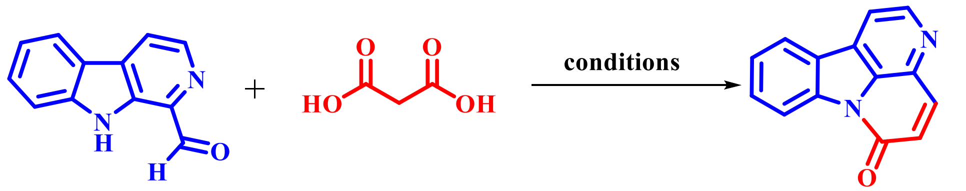
Eq. 89. Ioannidou *et al.* (2011)



(304) (303) (284)

3.2 Results and discussion:

Table 2.1: Optimisation for the synthesis of canthin-6-one alkaloid

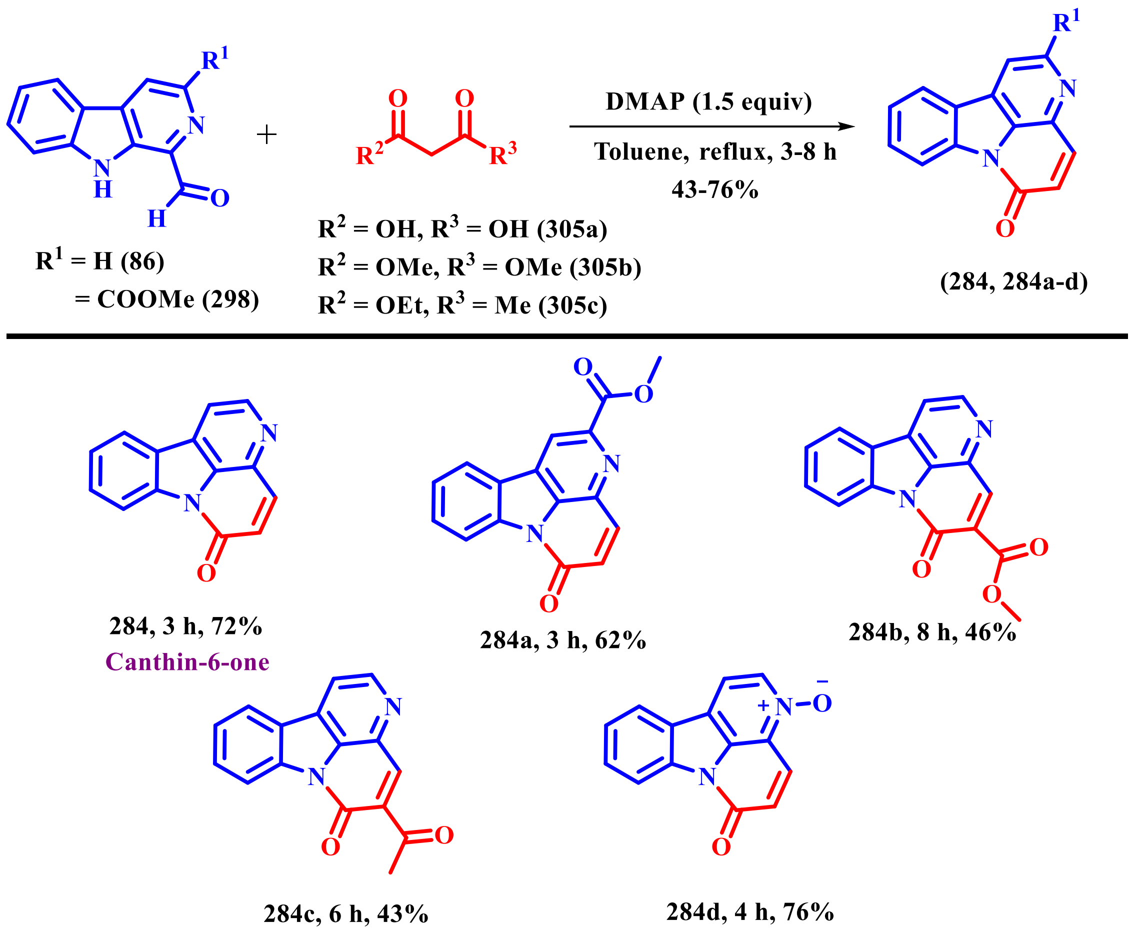


Entry	Base (1.5 equiv)	Solvent	Time (h)	Yield 284 (%)
1.	NEt_3	EtOH	12	26
2.	Piperidine	EtOH	12	32
3.	Pyridine	EtOH	12	41
4.	DMAP	EtOH	12	45
5.	DMAP	Toluene	3	72
6.	DBU	Toluene	6	64

Reaction conditions: β-carboline-1-carboxaldehyde **86** (0.25 mmol, 1.0 equiv), malonic acid **305a** (0.30 mmol, 1.2 equiv), Base, Solvent, reflux; [b] Isolated yields after chromatography.

The optimisation of the reaction condition for synthesis of canthin-6-one **284** alkaloid is shown in **Table 2.1** We carried out the reaction with different bases and the suitable solvents, initially we tried the reaction β-carboline-1-carbaoxldehyde **86** which was synthesized from the reported methods treated with malonic acid **305a** under the base triethylamine in EtOH at 12 h inducing reflux condition we observed condensation followed by cyclization product **284** in single step with 26% yield (**Table 2.1** in Entry **1**). Further we tried the reaction with other bases like piperidine, pyridine and dimethyl aminopyridine in EtOH solvent at 12 h under reflux condition (Entry's **2-4**) we observed that, the product was increases gradually with 32%, 41% and 45% yields respectively. Furthermore, we tried the reaction with DMAP as base in toluene solvent with the suitable reflux temperature in 3 h we obtained the condensation followed by cyclization product **284** with 72% yield (Entry **5**), with the same toluene solvent in the presence of DBU base we observed 64% yield (Entry **6**). With the optimisation study, we found entry **5** was the better optimised condition for the synthesis of canthi-6-one **284** alkaloid.

Scheme 2.1. Synthesis of canthin-6-one analogues



[a] Reaction conditions: *β*-carbolines-1-carboxaldehyde **86** or **298** (0.25 mmol, 1.0 equiv), **305a-c** (1.2 equiv), DMAP (0.38 mmol, 1.5 equiv), Toluene, reflux, 3-8 h, Isolated yields after chromatography.

The starting precursors *β*-carboline-1-carboxaldehydes (**86, 298**) are prepared as per the literature procedure. We have synthesized canthin-6-one and its derivatives, by the reaction of *β*-carboline-1-carboxaldehyde (**86**) treated with malonic acid (**305a**) in the presence of base mediated inducing reflux with toluene solvent undergoes condensation followed by cyclization to afforded canthi-6-one with 72% yield in single step. Upon this methodology was applied with the commercially available starting materials **305a-c** to afforded the condensation followed cyclized products (**284, 284a-d**) with moderate yields (**Scheme 2.1**).

3.3 Conclusion:

In conclusion, we have synthesized biologically active *β*-carboline alkaloid canthinone and its derivatives starting from kumujian C **86, 298** treatments with commercially available starting precursors **305a-c** under the base mediated involving condensation followed by cyclization to afforded in a single step with good to moderate yields.

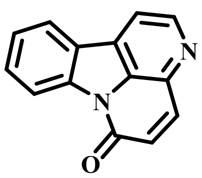
3.4 Experimental section:

NMR spectra: DMSO-d_6 and $CDCl_3$ are used as the NMR solvents to record ^1H and ^{13}C NMR spectra were recorded at BRUKER-ADVANCE NMR analyser at 400 and 100 MHz or at 500 and 125 MHz respectively. Chemical shifts values were assigned with respect to TMS (δ = 0) for ^1H NMR, and relative to NMR solvent residual peaks in $CDCl_3$ resonance (δ = 77.12) and DMSO-d_6 (δ = 39.52) for ^{13}C NMR. Data are presented as follows: chemical shifts, multiplicity (br s = broad singlet, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz) and integration. Melting points were determined by using a capillary melting point apparatus.

Mass spectral analysis: Shimadzu LCMS 2010A mass spectrometer was used. In all the cases EtOAc or DCM or MeOH were used to dissolve the compounds. HRMS were obtained from TOF and quadrupole mass analyzer types.

General procedure: *β*-Carboline-1-carboxaldehyde **86** (0.25 mmol, 1 equiv) and with compound **305a-c** (1.2 equiv) was dissolved in Toluene (2 mL) solvent in a screw cap vial, and then added DMAP (4-dimethyl aminopyridine) (0.38 mmol, 1.5 equiv). The resulting solution was stirred under reflux for 3-8 h. After reaction was complete (TLC monitor), the reaction was quenched with water (10 mL), and the mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers dried over anhydrous Na_2SO_4, and concentrated using a rotary evaporator. The crude product was further purified by column chromatography on silica gel using ethyl acetate/hexane.

6*H*-Indolo[3,2,1-*de*][1,5]naphthyridine-6-one (or) Canthin-6-one (284)



284

Physical state: Pale yellow solid

Yield: 0.040 g (72% Yield)

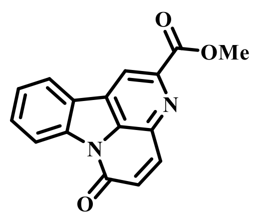
M.P: 161-163 °C (Lit.[103b] 161.2-162.9 °C)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.78 (d, *J* = 5.0 Hz, 1H), 8.60 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.98 (d, *J* = 9.8 Hz, 1H), 7.89 (d, *J* = 5.0 Hz, 1H), 7.68-7.64 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 9.7 Hz, 1H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 159.3, 145.7, 139.5, 136.3, 132.1, 130.6, 130.1, 128.8, 125.4, 124.4, 122.4, 117.2, 116.0.

HRMS (ESI-TOF) Calcd for $C_{14}H_8N_2O$ $[M+H]^+$ 221.0710, found: 221.0687.

Methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (284a)



284a

Physical state: Pale yellow solid

Yield: 0.043 g (62% Yield)

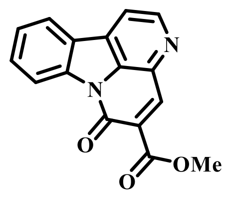
M.P: 248-250 °C (Lit.[103c] 249-250 °C)

^{1}H NMR (500 MHz, CDCl$_3$): δ 8.88 (s, 1H), 8.68 (d, *J* = 8.2 Hz, 1H), 8.19-8.16 (m, 2H), 7.78-7.75 (m, 1H), 7.60-7.57 (m, 2H), 7.05 (d, *J* = 9.8 Hz, 1H), 4.14 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 165.6, 159.3, 144.2, 139.8, 139.6, 135.7, 133.4, 131.4, 130.9, 129.9, 126.0, 124.1, 122.9, 118.5, 117.3, 53.3.

HRMS (ESI-TOF) Calcd for $C_{16}H_{10}N_2O_3$ $[M+H]^+$ 279.0764, found: 279.0767.

Methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-5-carboxylate (284b)



284b

Physical state: Pale yellow solid

Yield: 0.032 g (46% Yield)

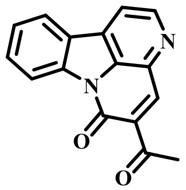
M.P: 186-188 °C (Lit.[107] 184 °C)

^{1}H NMR (500 MHz, CDCl$_3$): δ 8.87 (d, *J* = 4.9 Hz, 1H), 8.66 (s, 1H), 8.63 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.98 (d, *J* = 4.9 Hz, 1H), 7.70-7.66 (m, 1H), 7.52-7.49 (m, 1H), 4.04 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 164.5, 156.2, 146.8, 143.9, 139.4, 134.1, 133.2, 131.3, 130.3, 129.6, 126.0, 124.1, 122.8, 117.9, 117.5, 53.0.

HRMS (ESI-TOF) Calcd for $C_{16}H_{10}N_2O_3$ $[M+H]^+$ 279.0764, found: 279.0783.

5-Acetyl-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-6-one (284c)



284c

Physical state: Pale yellow solid

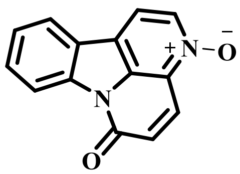
Yield: 0.024 g (43% Yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.93 (d, J = 4.8 Hz, 1H), 8.73 (d, J = 8.2 Hz, 1H), 8.68 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 4.8 Hz, 1H), 7.78-7.75 (m, 1H), 7.58 (t, J = 7.5 Hz, 1H), 2.86 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.1, 158.2, 147.0, 142.7, 139.6, 136.8, 134.6, 133.6, 131.3, 130.4, 126.1, 124.5, 122.9, 117.8, 117.5, 30.8.

HRMS (ESI-TOF) Calcd for $C_{16}H_{10}N_2O_2$ $[M+H]^+$ 263.0815, found: 263.0802.

6-Oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-3-oxide (or) Canthinone *N*-oxide (284d)



284d

Physical state: Pale yellow solid

Yield: 0.040 g (76% Yield)

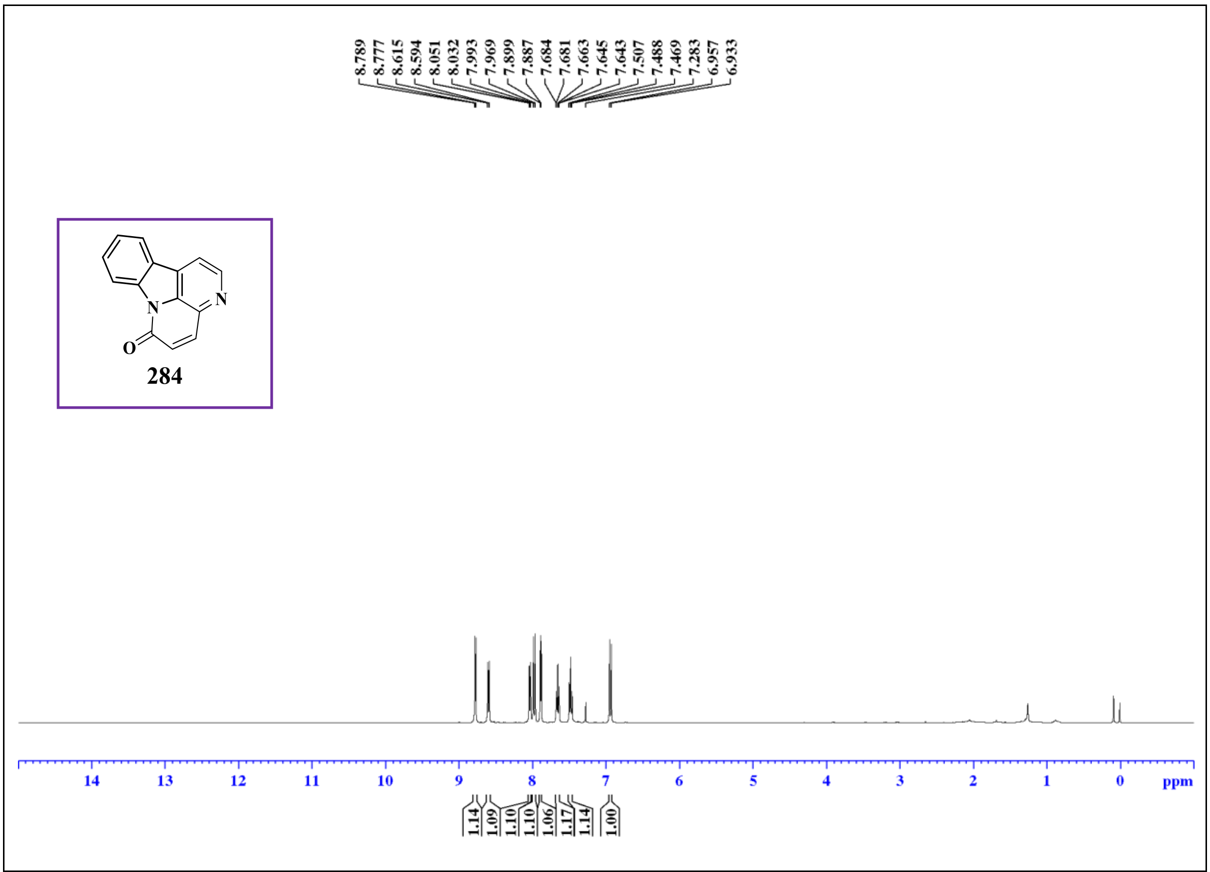
M.P: 243-245 °C (Lit.[103d] 243-245 °C)

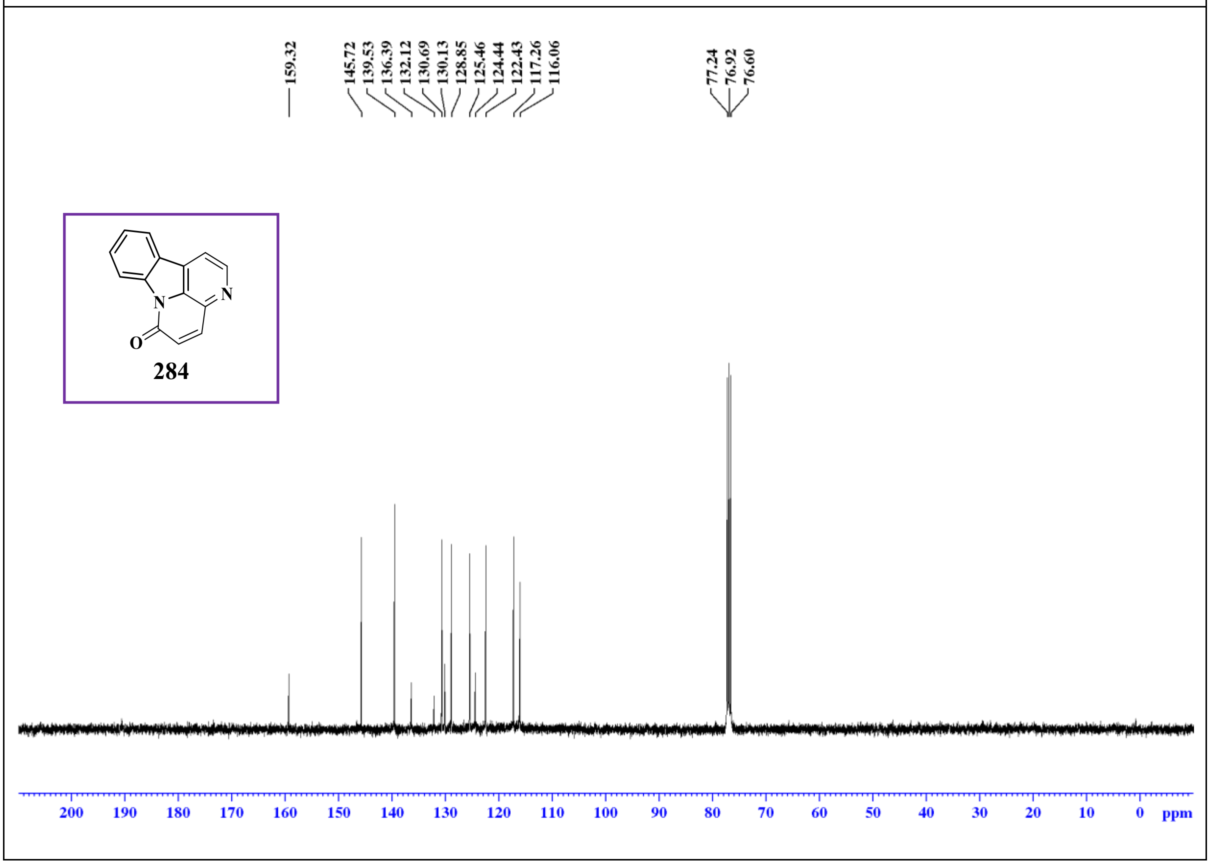
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, J = 5.0 Hz, 1H), 8.71 (d, J = 8.2 Hz, 1H), 8.16-8.14 (m, 1H), 8.06 (d, J = 9.8 Hz, 1H), 8.00 (d, J = 5.0 Hz, 1H), 7.76-7.72 (m, 1H), 7.58-7.54 (m, 1H), 7.02 (d, J = 9.8 Hz, 1H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.6, 145.9, 139.6, 139.5, 136.2, 132.1, 130.9, 130.4, 128.9, 125.7, 124.4, 122.7, 117.3, 116.4.

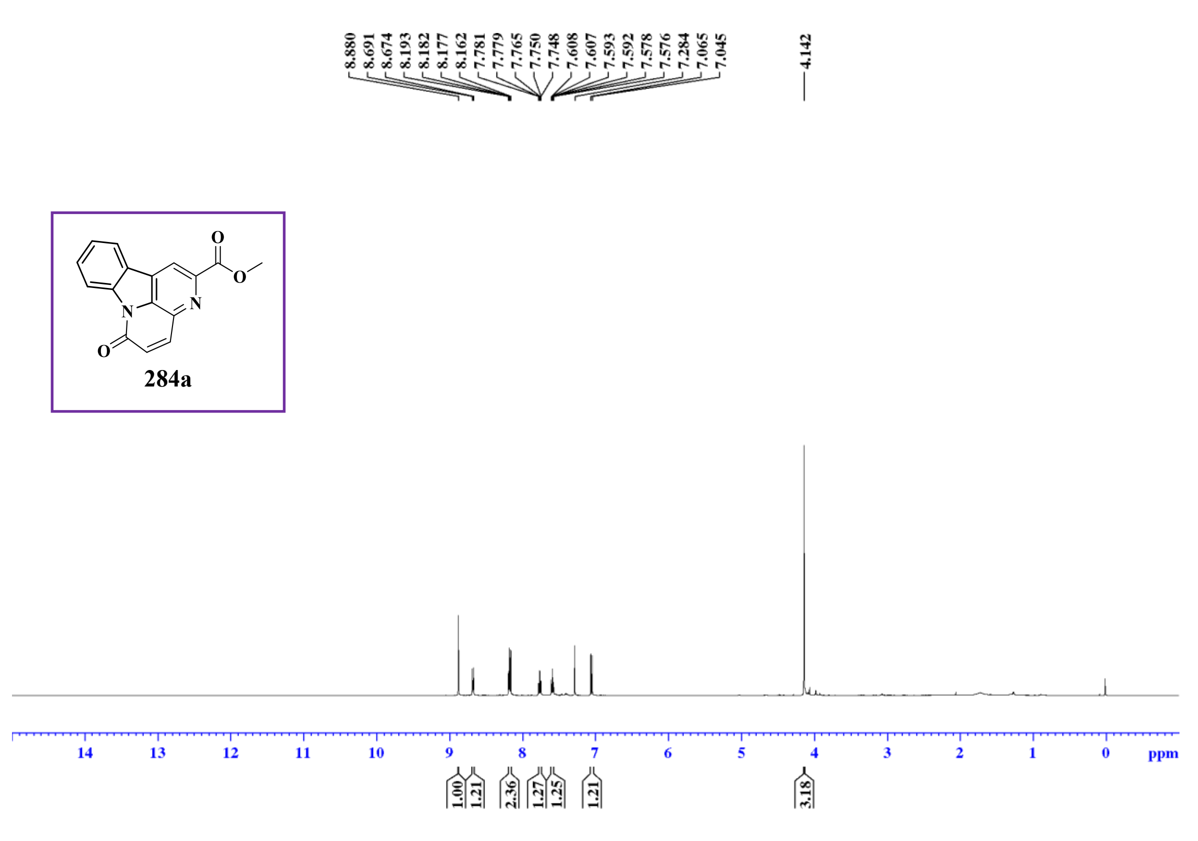
HRMS (ESI-TOF) Calcd for $C_{14}H_8N_2O_2$ $[M+H]^+$ 237.0659, found: 237.0659.

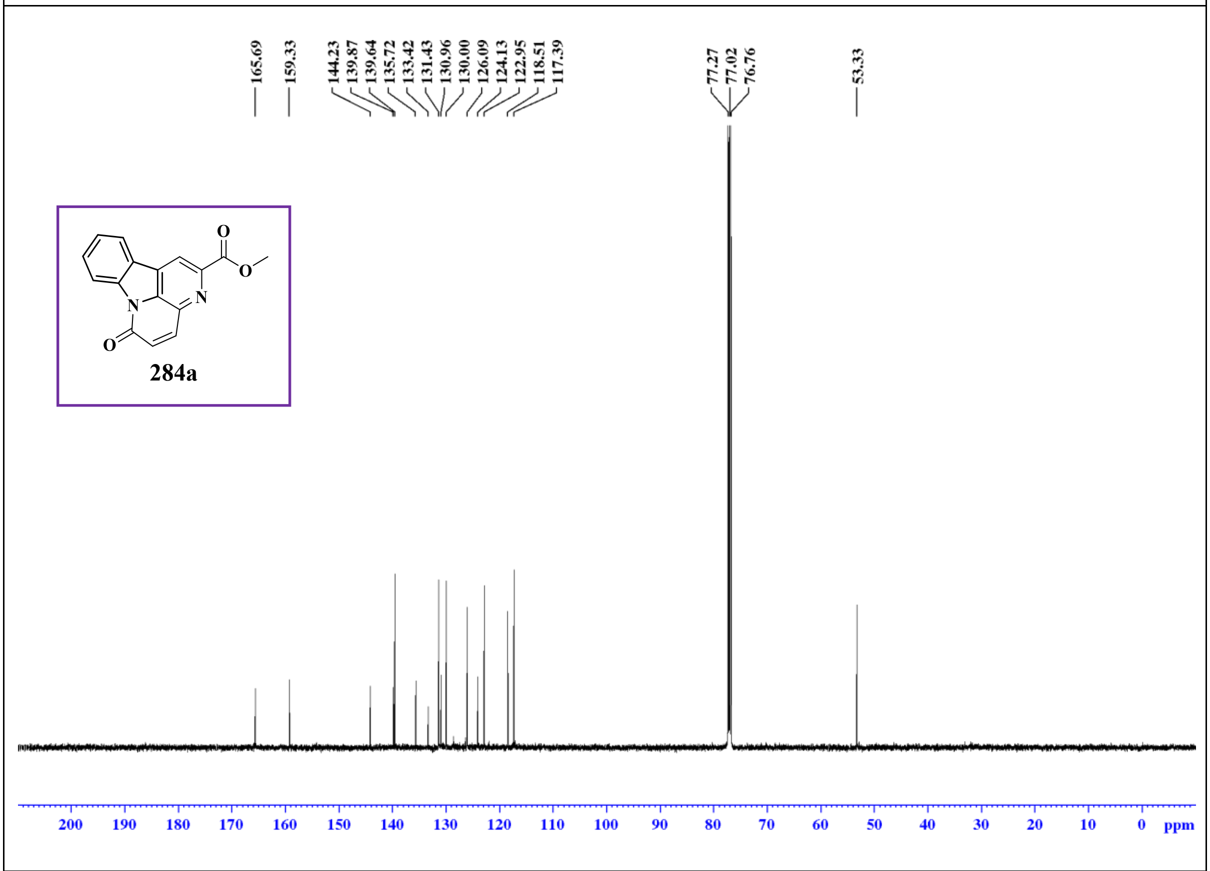
[1]H and [13]C NMR Spectra of Compound **284**



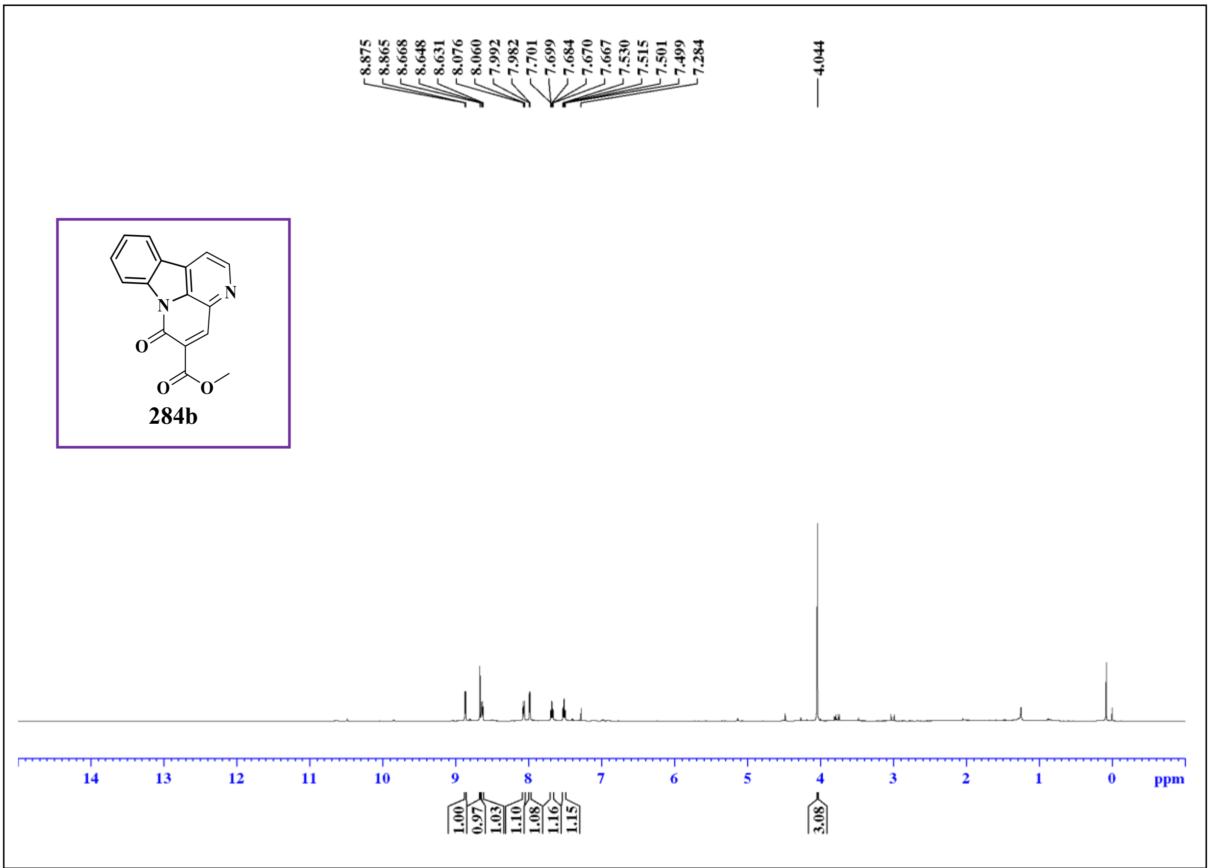


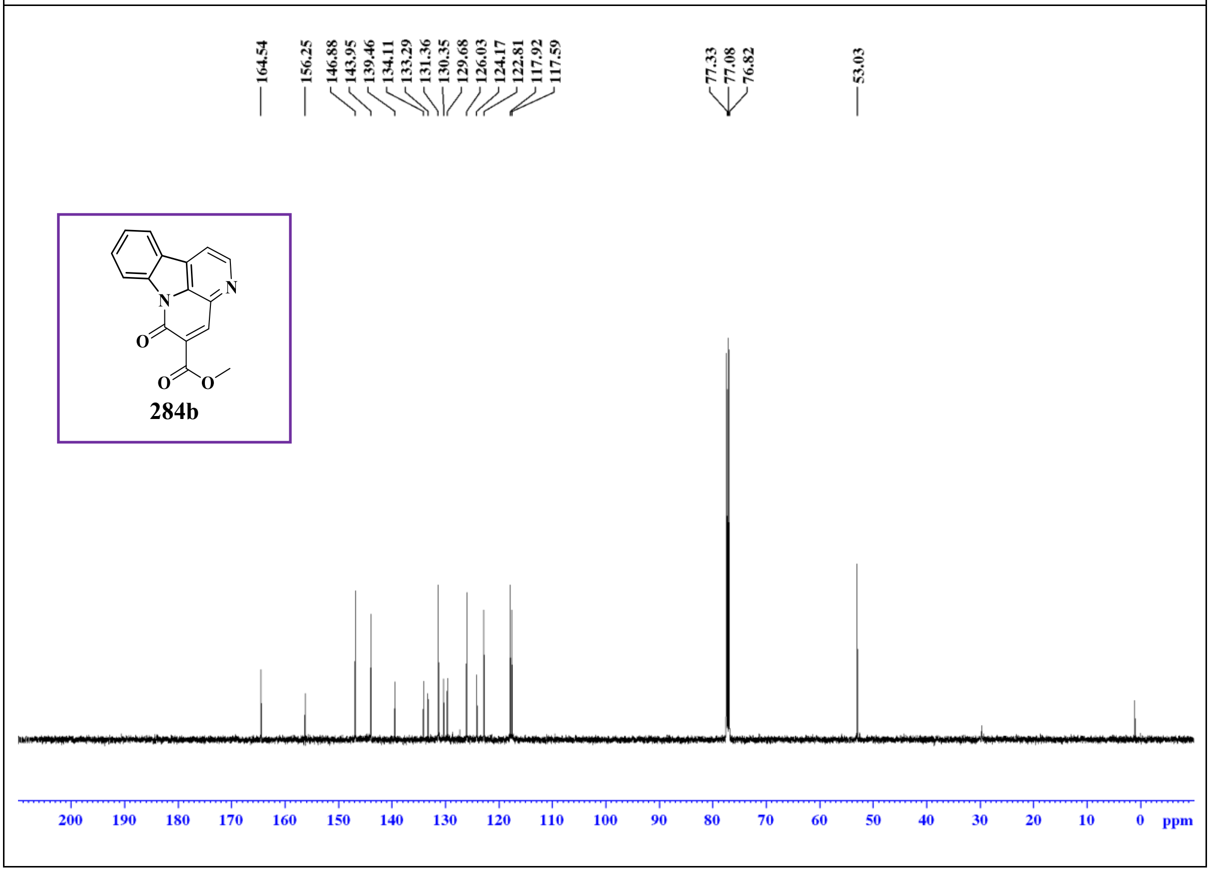
^{1}H and ^{13}C NMR Spectra of Compound **284a**



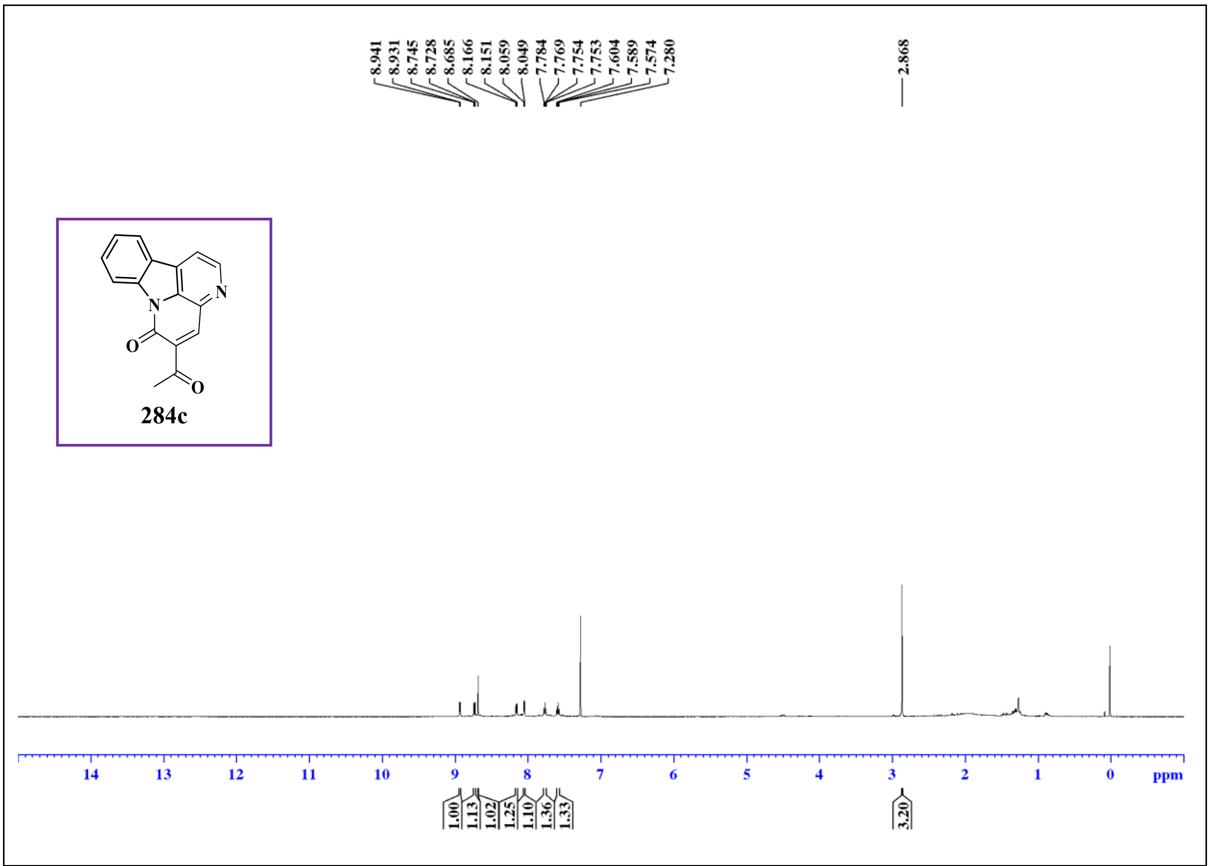


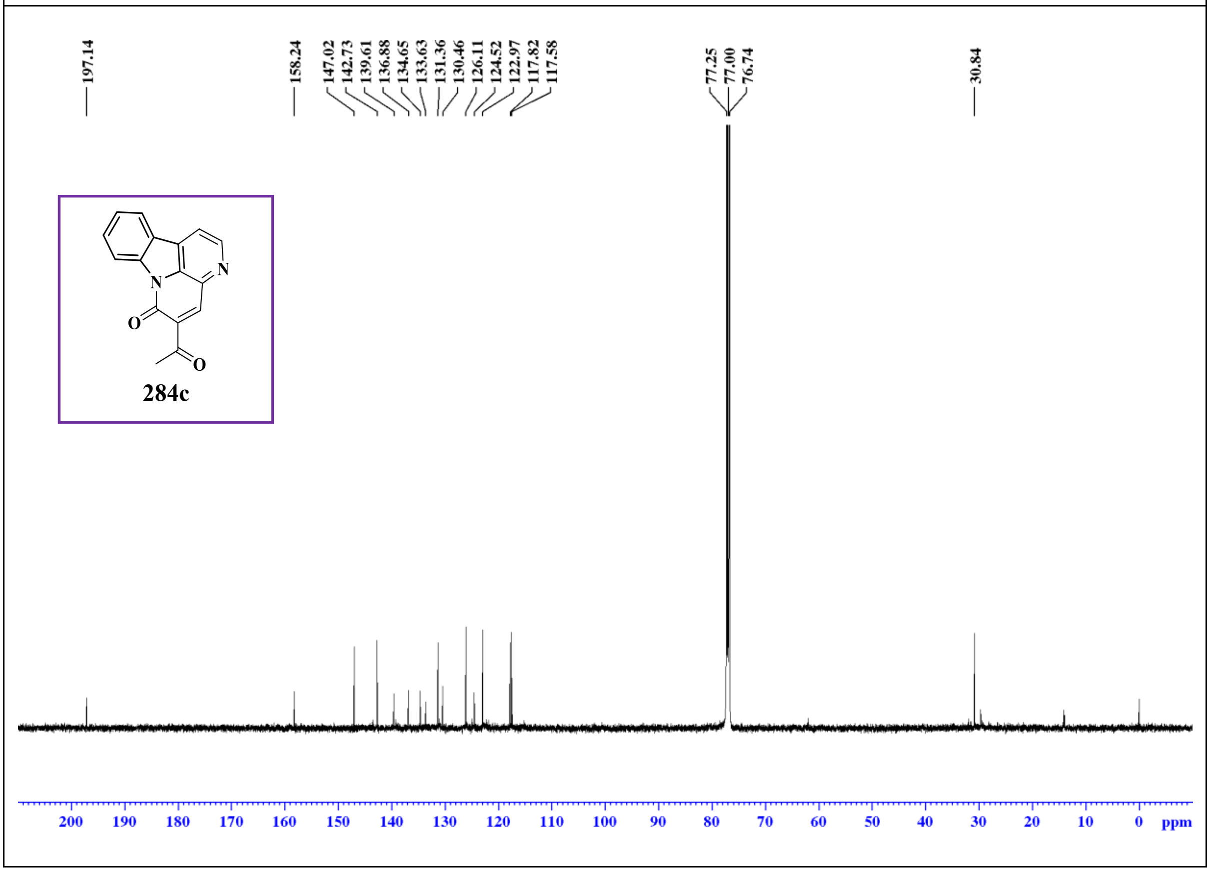
^1H and ^{13}C NMR Spectra of Compound **284b**



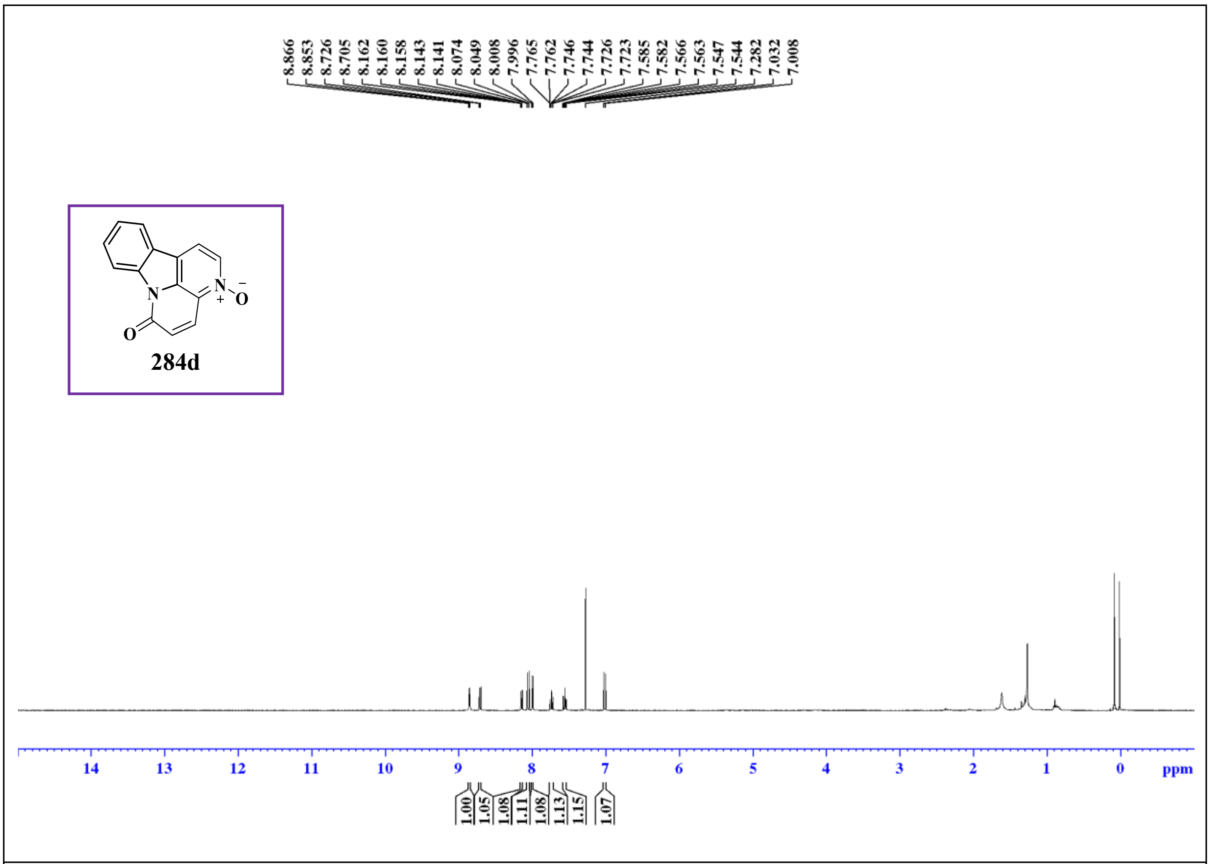


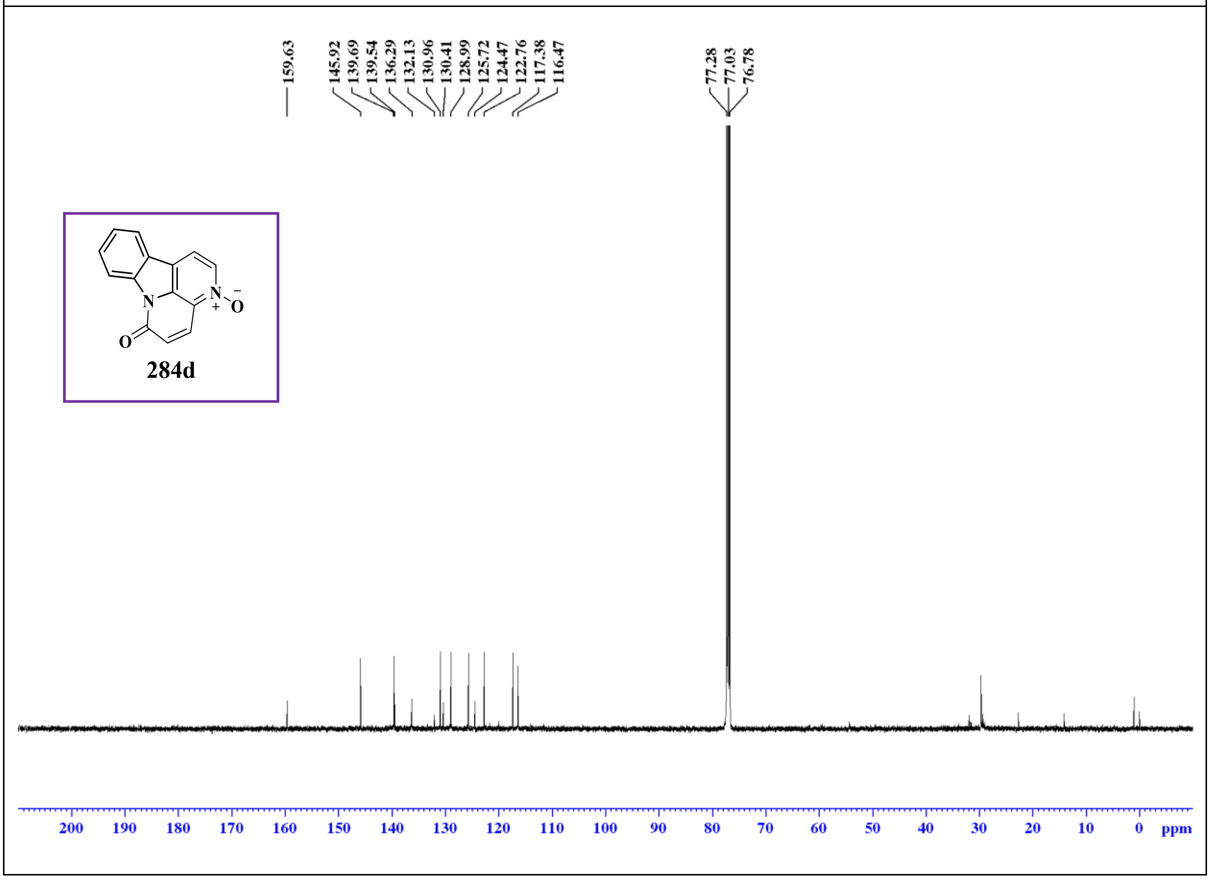
^{1}H and ^{13}C NMR Spectra of Compound **284c**





^{1}H and ^{13}C NMR Spectra of Compound **284d**





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CONCLUDING REMARKS

In this thesis we have developed transition metal-free decarboxylative formylation/acylation of indole-based alkaloids. We have successfully accomplished **Pityriacitrin**, **Isomeric calothrixin B**, ***N*-Pyrimidyl ellipticine quinone** and **Canthin-6-one** alkaloids.

Chapter-I (A): We have developed transition metal free direct decarboxylative cross coupling of α-oxo/ketoacids for formylation of indoles and acylation of β-carbolines with $(NH_4)_2S_2O_8$/DMSO. This reaction proceeds smoothly between ambient temperature and 40 °C under mild reaction conditions with commercially accessible starting precursors. This methodology was applied to the synthesis of biologically active natural product pityriacitrins and formal synthesis of eudistomins Y_1&Y_3, marinacarbolines A-D.

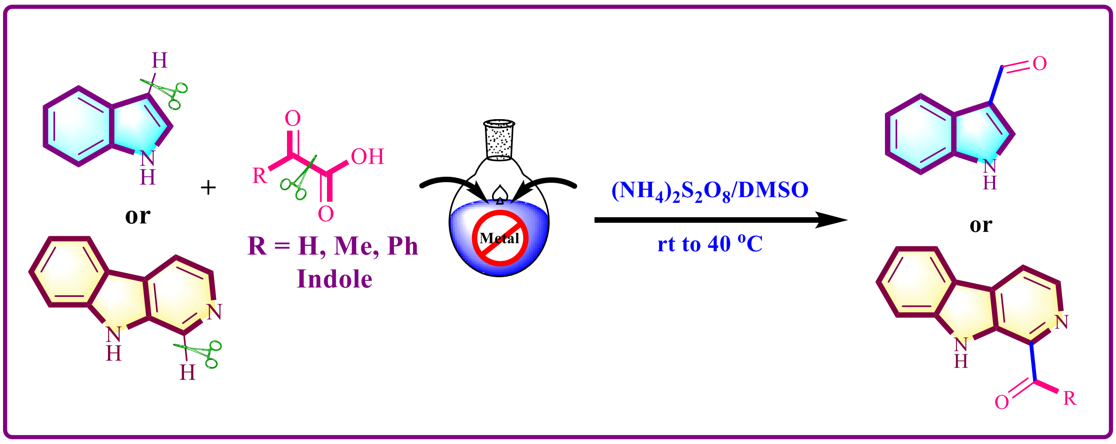
Chapter-I (B): We reported a transition metal- and oxidant-free Photochemical decarboxylative formylation of indoles was developed. This protocol enabled the direct C-H functionalization of indoles with 50% aq. Glyoxylic acid solution as a formyl synthon under environmentally favourable conditions with good to moderate yields. This method would be attractive and alternative method to access biologically important molecules.

Chapter-II: An efficient metal-free synthesis of isomeric calothrixin B and *N*-pyrimidyl ellipticine quinone involving decarboxylative cross-coupling method is reported. This methodology can able to construct carbazolequinone frame work in a single step with moderate to low yields.

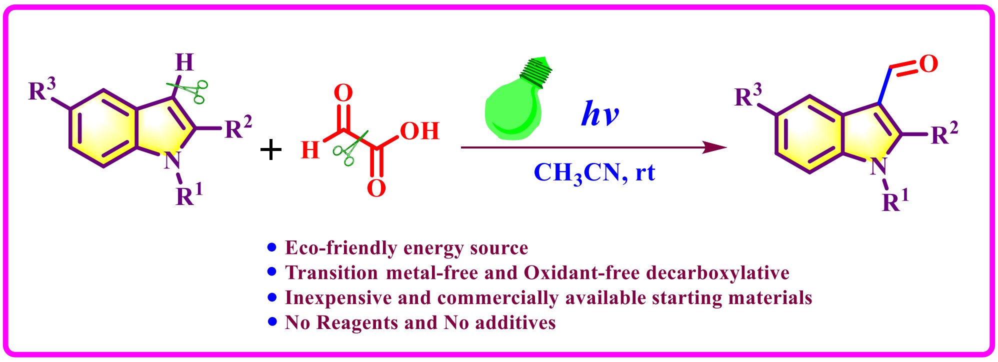
Chapter-III: We have synthesized biologically active β-carboline alkaloid canthin-6-one and its analogues starting from β-carboline-1-carboxaldehyde treatment with commercially available starting precursors under the DMAP mediated condensation followed by cyclization in a single step with good to moderate yields.

GRAPHICAL ABSTRACTS

Chapter I (A):



Chapter I (B):



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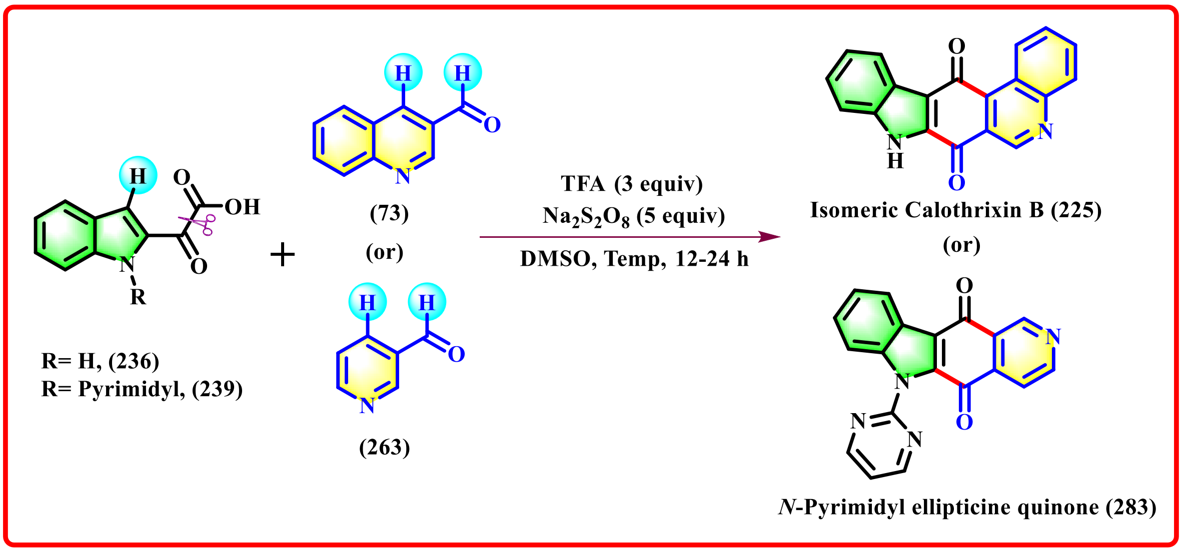
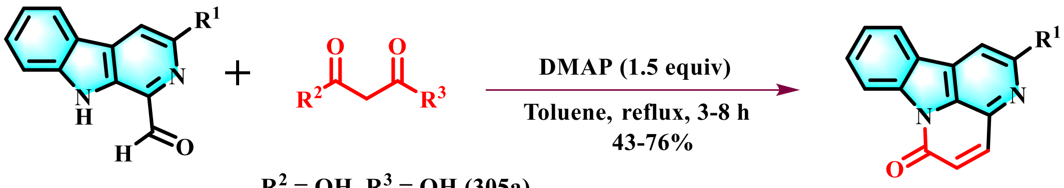


Chapter III:



R^1 = H (86)
= COOMe (298)

R^2 = OH, R^3 = OH (305a)
R^2 = OMe, R^3 = OMe (305b)
R^2 = OEt, R^3 = Me (305c)

(284, 284a-d)

Metal-free Decarboxylative Method for the Synthesis of Indole Alkaloids and Synthesis of Canthinones via Knoevenagel Condensation

by Votarikari Dinesh

N. Ravi Kumar

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