Synthesis of Hexahydrobenzo[*c*]phenanthridine and *β*-Carboline-1-one derivatives via Transition Metal Catalyzed C-H Bond Activation

by

GOPAL KRUSHNA DAS ADHIKARI

CHEM11201604017

National Institute of Science Education and Research,

Bhubaneswar, Odisha

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DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

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List of Publications

a. Published (* pertaining to thesis)

(1) ***G. K. D. Adhikari**; Rajesh Chebolu; P. C. Ravikumar. Regio- and Stereoselective Synthesis of the Core Structure of Hexahydrobenzo[*c*]phenanthridine Alkaloids via Redox-Neutral Cp*Rh(III)-Catalyzed C–H/N–H Annulation of Cyclic Alkenes with Benzamides. *ACS Omega*, **2020**, *5*, 24033-24044.

(2) ***G. K. D. Adhikari**; B. V. Pati; T. Nanda; P. Biswal; S. Banjare; P. C. Ravikumar. Co(II) Catalysed C-H/N-H Annulation of Cyclic Alkenes with Indole-2-Carboxamides at room temperature: A one step access to *β*-carboline-1-one derivatives. *J. Org. Chem.,* **2022**, *87*, 4438-4448.

(3) ***G. K. D. Adhikari**; B. V. Pati; S. R. Mohanty; N. Prusty; P. C. Ravikumar. Co(II) Catalyzed *C-H*/*N-H* Annulation of Cyclic Alkenes with Benzamides at room temperature: An access to the core skeleton of hexahydrobenzo[*c*]phenanthridine-type alkaloids. *Asian J. Org. Chem*. **2022**, doi.org/10.1002/ajoc.202200150.

(4) S. R. Mohanty; B. V. Pati; S. K. Banjare; **G. K. D. Adhikari**; P. C. Ravikumar. Redox-Neutral Cobalt(III)-Catalyzed C–H Activation/Annulation of *α,β*-Unsaturated Oxime Ether with Alkyne: One-Step Access to Multisubstituted Pyridine. *J. Org. Chem*. **2021**, *86*, 1074–1083.

(5) B. V. Pati; P. S. Sagara; A. Ghosh; **G. K. D. Adhikari**; P. C. Ravikumar. Ruthenium-Catalyzed Regioselective C(sp^2)–H Activation/Annulation of *N*-(7-Azaindole)amides with 1,3-Diynes Using *N*-Amino-7-azaindole as the *N*,*N*-Bidentate Directing Group. *J. Org. Chem*. **2021**, *86*, 9428–9443.

(6) S. K. Banjare[≠]; T. Nanda [≠]; B. V. Pati; **G. K. D. Adhikari**; J. Dutta; P. C. Ravikumar. Breaking the Trend: Insight into Unforeseen Reactivity of Alkynes in Cobalt-Catalyzed

Weak Chelation-Assisted Regioselective C(4)–H Functionalization of 3-Pivaloyl Indole. *ACS Catalysis* **2021**, *11*, 11579-11587. ≠ Equal Authors

(7) B. V. Pati; S. K. Banjare; **G. K. D. Adhikari**; T. Nanda; Ponneri C. Ravikumar. Rhodium-Catalyzed Selective C(sp^2)–H Activation/Annulation of *tert*-Butyl Benzoyloxycarbamates with 1,3-Diynes: A One Step Access to Alkynylated Isocoumarins and Bis-Isocoumarins**.** ***Org. Lett***. **2022**, *24*, 5651-5656.

b. Manuscript Communicated

(1) S. K. Banjare; S. Afreen; T. Nanda; **G. K. D. Adhikari**; N. Preeyanka; Ponneri C. Ravikumar. Cobalt catalysed decarbonylative ipso C-C bond functionalisation: Synthesis of Indole C-3 functionalized acyloins using 1,2-diketone.

(2) *__G. K. D. Adhikari__; S. R. Mohanty; S. K. Banjare; N. Prusty; G. Murmu; P. C. Ravikumar. Annulation of Indole-2-Carboxamides with Bicycloalkenes catalyzed by Ru(II) at room temperature: An easy access to β-carboline-1-one derivatives under mild conditions.

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Conferences

1. Progress Towards the Formal Total Synthesis of (+) Chelidonine Alkaloids. **G. K. D. Adhikari**; Rajesh Chebolu; P. C. Ravikumar. National Conference on Organic Synthesis (N-COS, 2020), Organised by P.G. Department of Organic Chemistry, Berhampur University, Odisha, during 02-03 March, 2020. (Poster Presentation)
2. Regio- and Stereoselective Synthesis of the Core Structure of Hexahydrobenzo[*c*]phenanthridine Alkaloids via Redox-Neutral Cp*Rh(III)-

Catalyzed C–H/N–H Annulation of Cyclic Alkenes with Benzamides. **G. K. D. Adhikari**; Rajesh Chebolu; P. C. Ravikumar. 27th CRSI-NSC Kolkata, four day symposium, held on 26th - 29th September, 2021. (Poster Presentation)

Gopalkrushna Das Adhikari

Gopal Krushna Das Adhikari

Dedicated to

My Family

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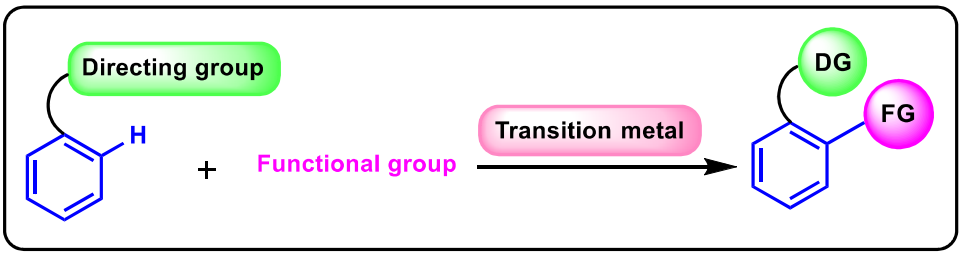
Gopal Krushna Das Adhikari

CONTENTS

SYNOPSIS

The thesis is divided into five chapters.

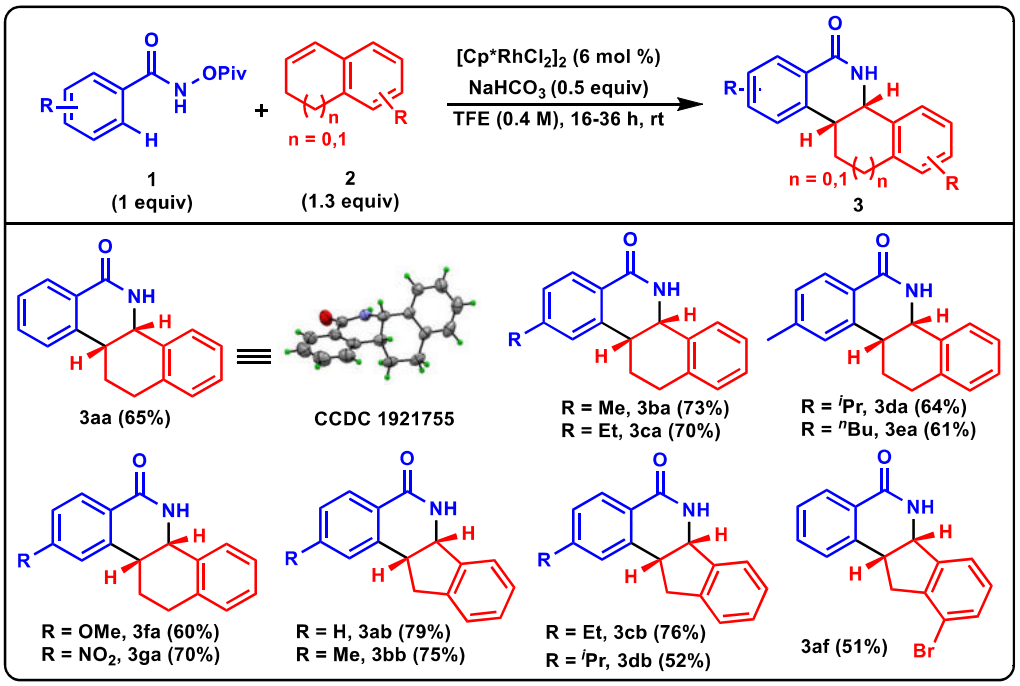
Chapter-1, is about the brief introduction of C-H activation reaction (**Scheme 1**).

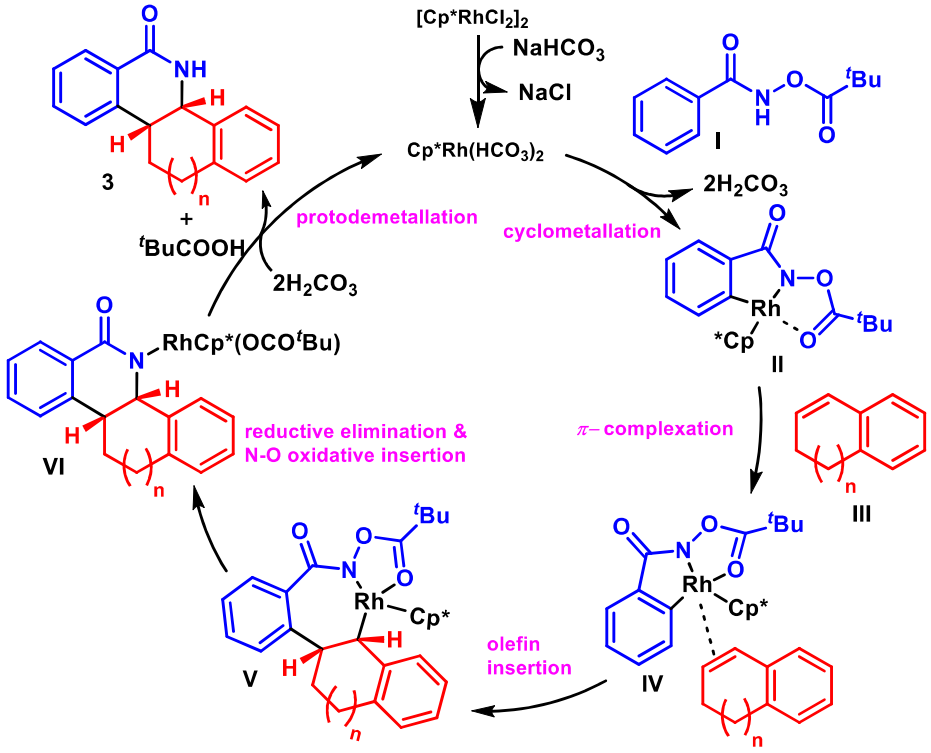


Scheme 1: Transition metal catalyzed C-H activation reaction

In Chapter-2, the Regio- and Stereoselective Synthesis of the Core Structure of Hexahydrobenzo[*c*]phenanthridine Alkaloids via Redox-Neutral Cp*Rh(III)-Catalyzed *C−H/N−H* Annulation of Cyclic Alkenes with Benzamides, is described (**Scheme 2**). The methodology is compatible for a wide range of functional groups and gives rise to a series of desired annulated products. The N-O bond acts as internal oxidant for the transformation. The mechanism goes through a cyclometallation, olefin insertion and protodemetallation steps.

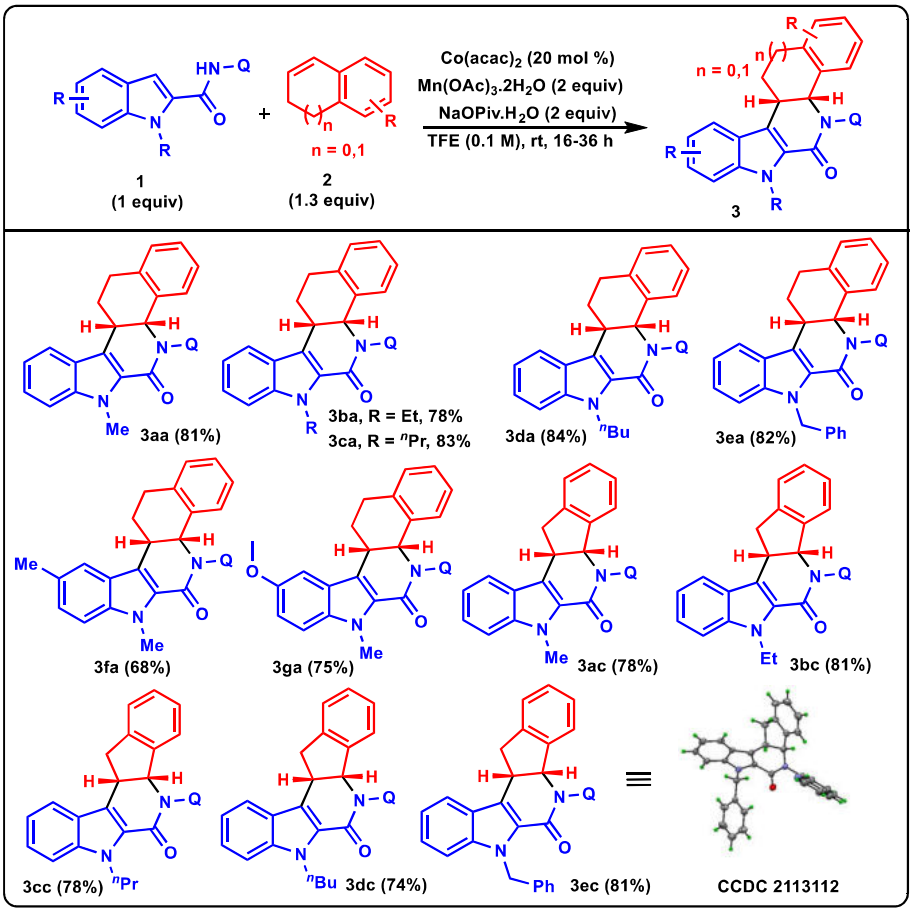
Scheme 2: Cp*Rh(III) Catalyzed Regio- and Stereoselective *C-H*/*N-H* Annulation of Substituted Benzamides with Dihydronaphthalenes and Indenes

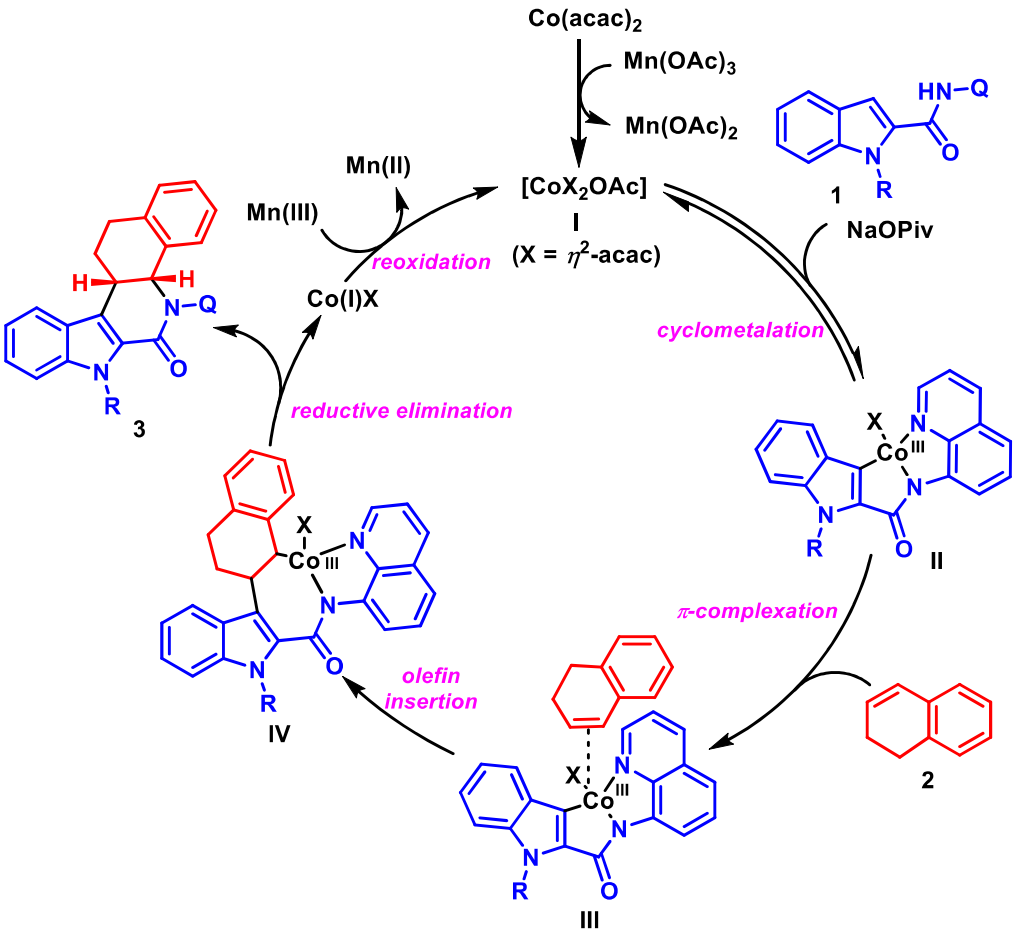




In Chapter-3, we described the Co(II)-Catalyzed *C-H/N-H* annulation of cyclic alkenes with indole-2-carboxamides at room temperature (**Scheme 3**). The methodology gives access to the core skeleton of *β*-carboline-1-one derivatives. The reaction tolerates a wide range of substituted indole-2-carboxamides and furnishes the desired annulated products. The 8-aminoquinoline group acts as directing group for the annulation reaction (**Scheme 3**). The mechanism of annulation reaction goes through cyclometallation followed by olefin insertion and reductive elimination steps.

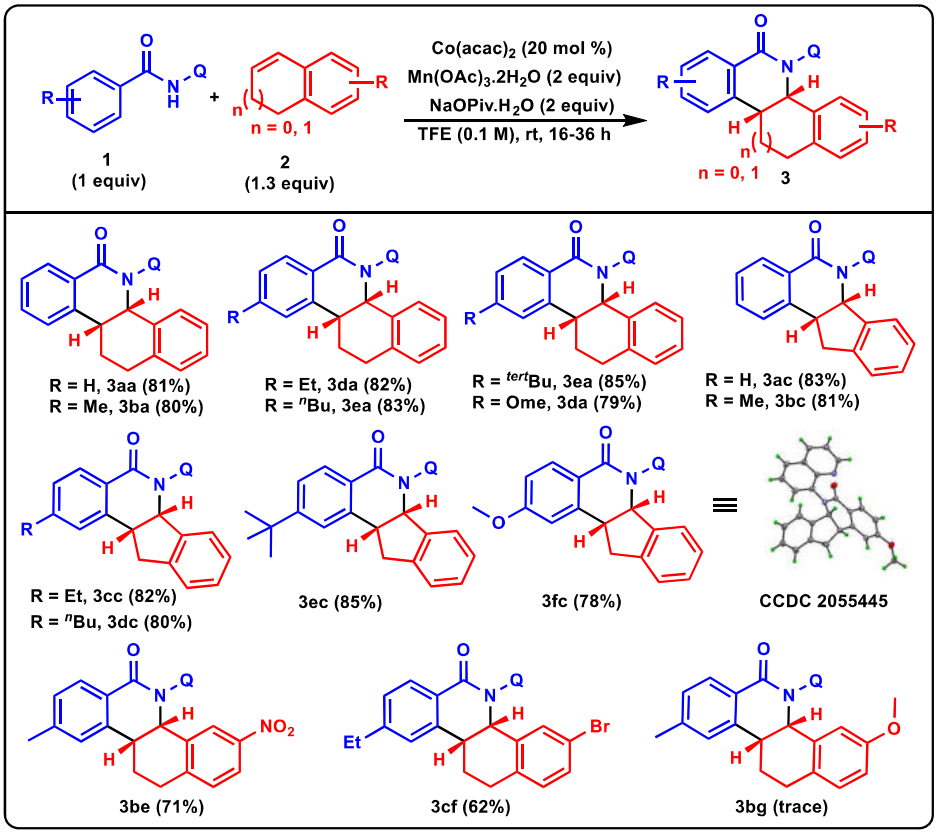
Scheme 3: Co(II) Catalyzed Regio- and Stereoselective *C-H/N-H* Annulation of Substituted Indole-2-Carboxamides with 1,2-Dihydronaphthalenes and Indenes.

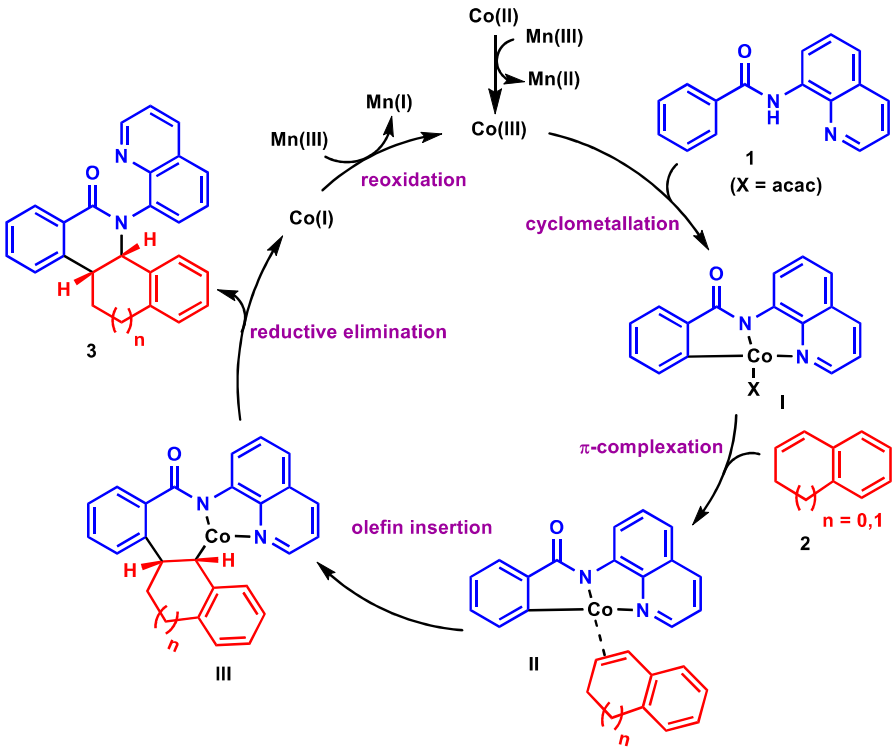




In Chapter 4, Co(II) catalyzed *C-H*/*N-H* annulation of cyclic alkenes with benzamides has been described at room temperature (**Scheme 4**). The reaction gives access to the core skeleton of hexahydrobenzo[*c*]phenanthridine-type alkaloids. A wide range of substituted benzamides and substituted coupling partners is compatible to the annulation reaction. The mechanism of the reaction goes through cyclometallation followed by olefin insertion and reductive elimination steps.

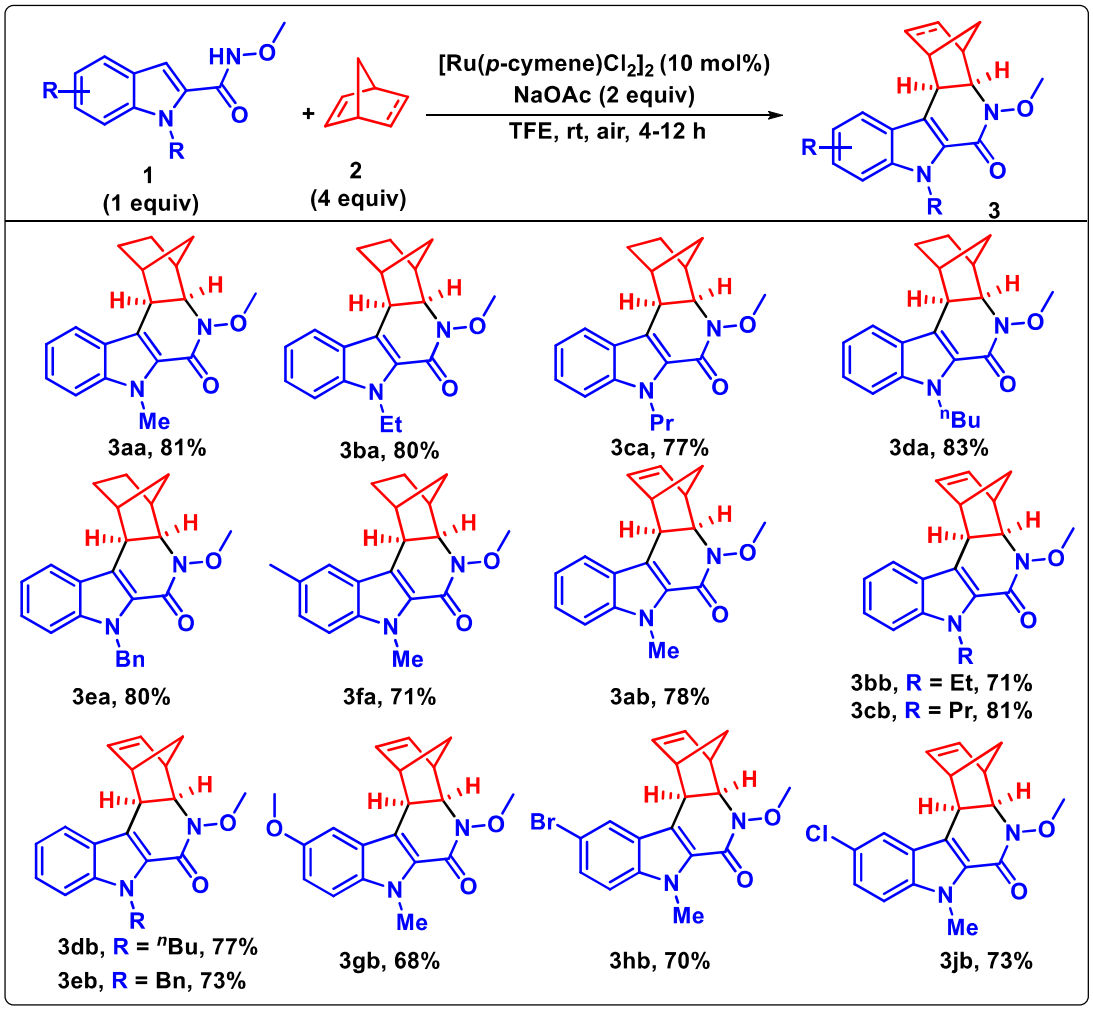
Scheme 4: Co(II) Catalyzed Regio- and Stereoselective *C-H*/*N-H* Annulation of Substituted Benzamides with Dihydronaphthalenes and Indenes

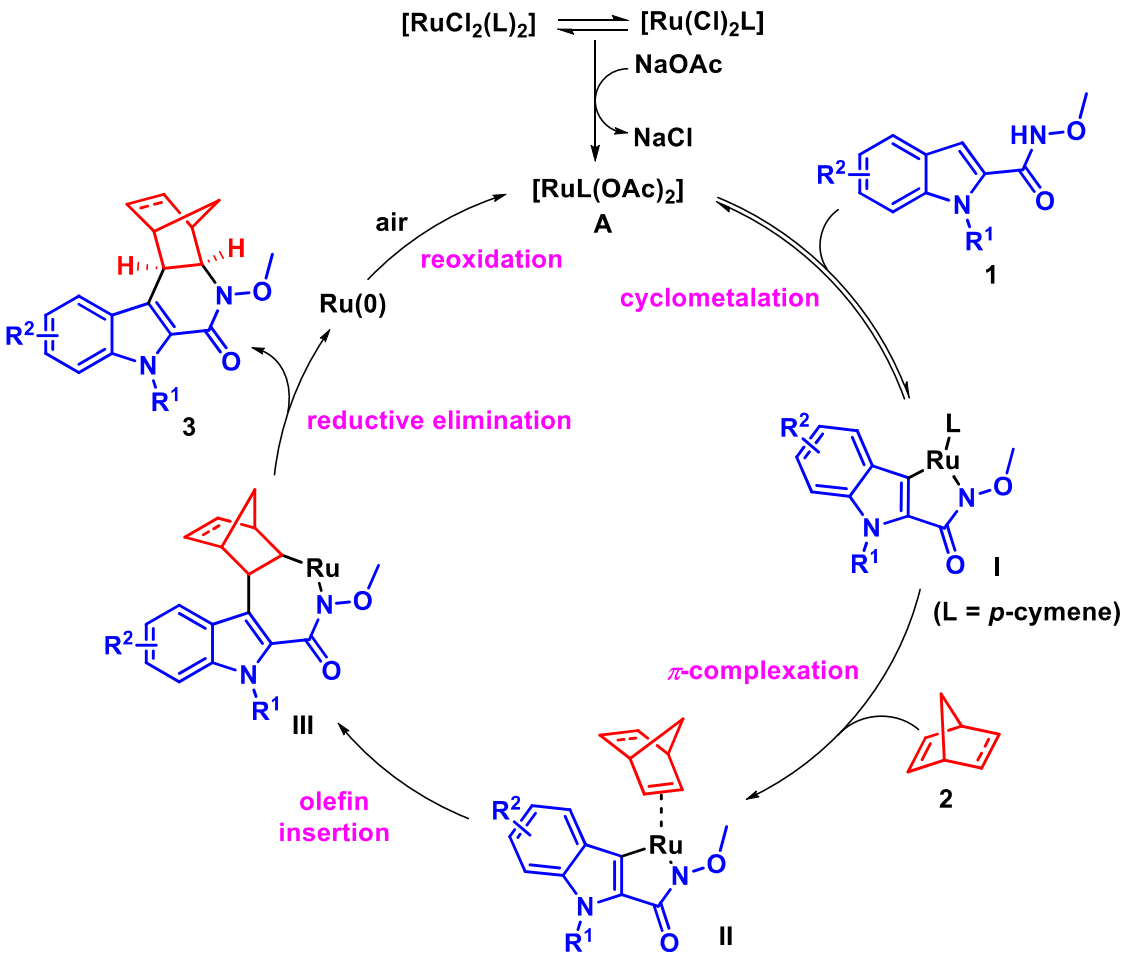




In Chapter 5, we described a Ru(II)-Catalyzed *C-H*/*N-H* annulation of bicycloalkenes with indole-2-carboxamides at room temperature (**Scheme 5**). The reaction gives access to the core skeleton of *β*-carboline-1-one derivatives. A wide range of substituted indole-2-carboxamides are compatible to the annulation reaction. The mechanism of reaction goes through cyclometallation followed by olefin insertion and reductive elimination steps.

Scheme 5: Ru(II)-Catalyzed Annulation of Substituted indole-2-carboxamides with 2-norbornene and 2,5-norbornadiene




[RuCl2(L)2]
[Ru(Cl)2L]
NaOAc
NaCl
[RuL(OAc)2]
A
air
reoxidation
Ru(0)
cyclometalation
1
3
reductive elimination
I
(L = p-cymene)
π-complexation
2
olefin
insertion
III
II

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List of Abbreviations

MeCN	Acetonitrile
BHT	Butylated Hydroxytoluene
^{t}BuOH	t*ert*-Butyl alcohol
^{t}Bu	tert-butyl
^{13}C NMR	Carbon nuclear magnetic resonance
$CDCl_3$	Chloroform-d
$CHCl_3$	Chloroform
Calcd	Calculated
CsOPiv	Cesium pivalate
CsOAc	Cesium acetate
Cs_2CO_3	Cesium carbonate
$Cu(OAc)_2$	Copper acetate
$Cu(OAc)_2.H_2O$	Copper acetate monohydrate
DCM	Dichloromethane
DCE	1,2-dichloroethane
DMF	Dimethylformamide
DG	Directing group
DIPEA	*N*, *N*-Diisopropylethylamine
EtOAc	Ethylacetate
EtOH	Ethanol
FG	Functional group
Fig.	Figure

HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HRMS	High resolution mass spectrometry
h	Hour
IR	Infrared
^{i}Pr	iso-propyl
KIE	Kinetic Isotope Effect
Li_2CO_3	Lithium carbonate
LiOAc	Lithium acetate
MeOH	Methanol
MHz	Megahertz
mg	Milligram
mmol	Millimole
mp	Melting point
mL	Milliliter
min.	Minute
$Mn(OAc)_3.2H_2O$	Manganese acetate dihydrate
NMR	Nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
ppm	Parts per million
KPF_6	Potassium hexafluorophosphate
KOAc	Potassium acetate
K_2CO_3	Potassium carbonate
$Pd(OAc)_2$	Palladium acetate
Ph	Phenyl

$AgSbF_6$	Silver hexafluoroantimonate
$AgBF_4$	Silver tetrafluoroborate
$NaOPiv.H_2O$	Sodium pivalate monohydrate
NaOAc	Sodium acetate
AgOAc	Silver acetate
Na_2CO_3	Sodium carbonate
Ag_2CO_3	Silver carbonate
$NaHCO_3$	Sodium bicarbonate
Ag_2O	Silver oxide
TM	Transition metal
TLC	Thin-layer chromatography
THF	Tetrahydrofuran
TFE	Trifluoroethanol
Et_3N	Triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
UV	Ultraviolet
$Zn(OAc)_2.2H_2O$	Zinc acetate dehydrate

Chapter 1

Introduction

Chapter 1

Introduction

1.1 INTRODUCTION TO C-H ACTIVATION

The C-C and C-N bonds are ubiquitous in almost all organic compounds. Therefore, designing of synthetic strategies for construction of these bonds is considered as one of the most important tasks in organic synthesis.[1] Since 18th century several classical methods such as Friedel-Crafts reaction, Grignard reaction, free radical reaction, and enolate chemistry have been developed.[2] In addition the palladium catalysed cross coupling reactions have also become very popular. The palladium catalysed cross coupling reactions is considered as a highly effective strategy for the construction of C-C and C-N bonds. The cross-coupling reaction of aryl halides with alkenes by using transition metal catalyst, is one of the most explored reaction for construction of C-C bonds.[3] Although the palladium catalysed cross-coupling reactions broadened the scope. However, it suffers from several drawbacks. The limitations are (a) the requirement of a prefunctionalized substrate for the cross coupling reactions. So, the preparation of these functionalized substrates requires extra steps and cost. So, it is not attractive from the step and cost economy point of view. This prefunctionalisation restricts the use of these methodology for the synthesis of natural products, due to the involvement of multiple steps. (b) generation of wasteful byproducts is another limitation associated with the cross-coupling reactions. Hence, the development of straightforward synthetic methods for the construction of C-C and C-N bonds using the C-H bonds as latent functional groups remained elusive for many decades.

In this regard, direct activation/functionalization of C-H bonds provided a streamlined approach for the construction of C-C and C-N bonds in an step and cost economic way (Fig-1.1). This C-H bond activation strategy has been at the center stage of the organic

synthesis for the last few decades by streamlining the organic synthesis by minimising the number of steps, thus redcuing the waste generation.[4] Thus, the direct C-H bond functionalization via C-H bond activation contributes towards green chemistry.

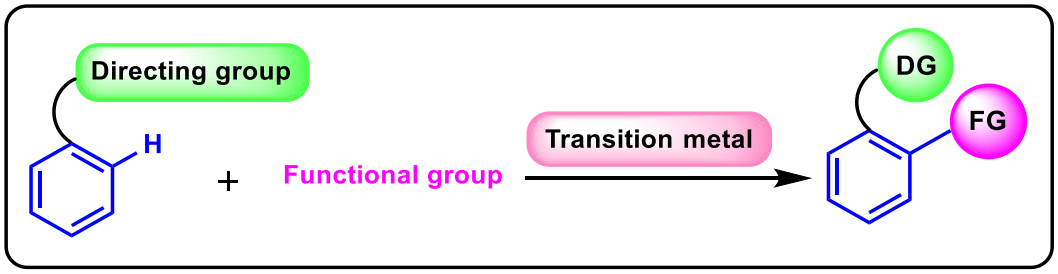

Figure-1.1: Transition metal catalyzed C-H activation reaction

1.2 DIFFERENT MECHANISM OF C-H ACTIVATION:

Depending on the substrate and metal catalyst used, the C-H activation reaction goes through six different mechanisms.[5] Each one of them is described below.[5,6]

(a) Oxidative Addition (OA):

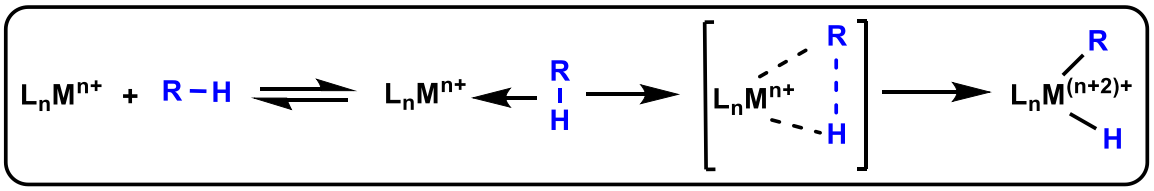

Figure-1.2: Oxidative addition

Such type of activation processes is generally observed in case of electron rich metal catalysts. A reactive organometallic species is formed by interaction of electron rich metal and inert C-H bond. Both coordination number and oxidation state of metal increases by two units.

(b) Electrophilic Aromatic Substitution (SEAR):

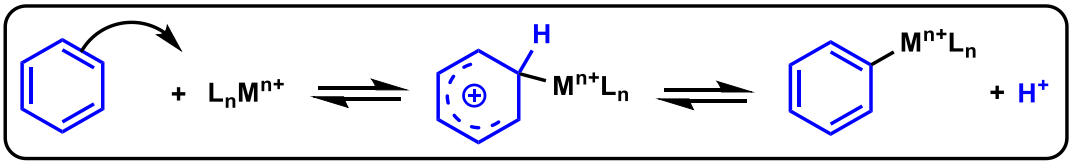

Figure-1.3: Electrophilic aromatic substitution

This type of process occurs between aromatic ring and transition metals. The transition metal catalyst acts as electrophile due to vacant *d*-orbital which subsequently undergoes electrophilic aromatic substitution with arenes. Finally a reactive organometallic species is formed as shown above. In this whole process the oxidation state of metal catalysts remains same.

(c) Sigma-bond metathesis:

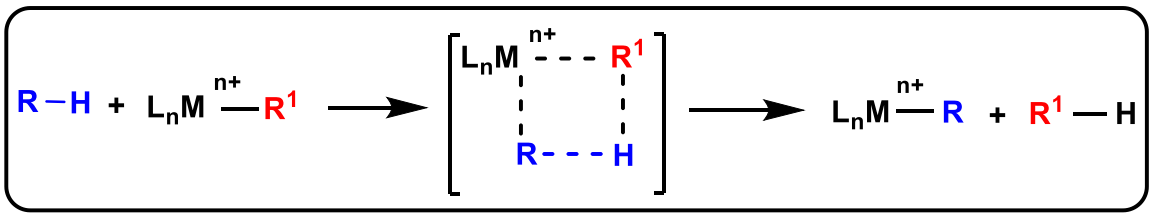

Figure-1.4: Sigma-bond metathesis

This type of mechanism proceeds through a four-membered transition state. A metathesis reaction occurs in the transition state and reactive organometallic species is formed. The oxidation state of metal remains unchanged in this process.

(d) Single electron transfer (SET):

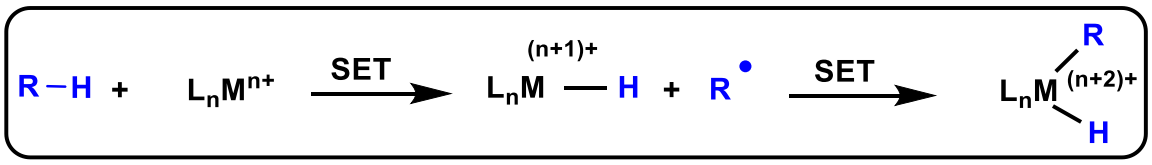

Figure-1.5: Single electron transfer

Such type of mechanism is observed with few first row transition metal catalysts (such as Ni, Cu, Mn, and Fe).[5d-g] A reactive organometallic species is formed by transfer of single electron and corresponding metal-carbon (M-C) bond is formed.

(e) Concerted Metalation Deprotonation (CMD):

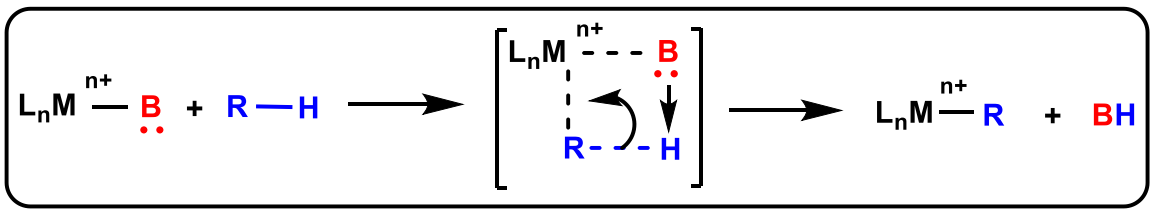

Figure-1.6: Concerted metalation deprotonation

It is observed with electron deficient arene in presence of a base. A metalation and deprotonation occurs in this process through a transition state and finally M-C bond is formed in a concerted manner.

(f) Base assisted intramolecular electrophilic substitution (BIES):

This type of mechanism is observed with electron rich aromatic rings. In this type of mechanism, the base attached with metal catalyst takes the proton and subsequently M-C bond is formed. This organometallic species is further functionalized to various useful derivatives.

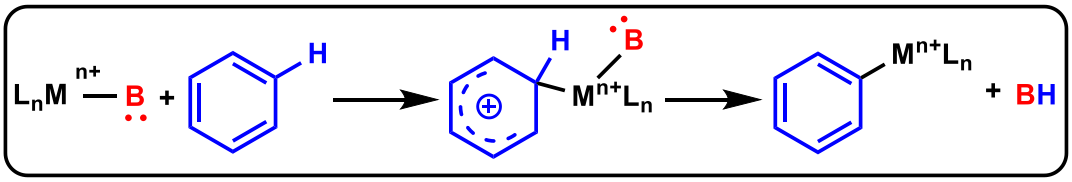

Figure-1.7: Base assisted intramolecular electrophilic substitution

1.3 EVOLUTION AND TYPES OF C-H ACTIVATION:

In the chelation assisted C-H activation reaction, various functional groups are used as a directing group (DG). In 20th century, an imine directed cobalt catalyzed C-H activation reaction followed by insertion of carbon monoxide was disclosed by Murahashi (Fig-1.8).[7] After this pioneering work of Murahashi several research groups have developed the use of various DG in C-H activation reaction.[8]

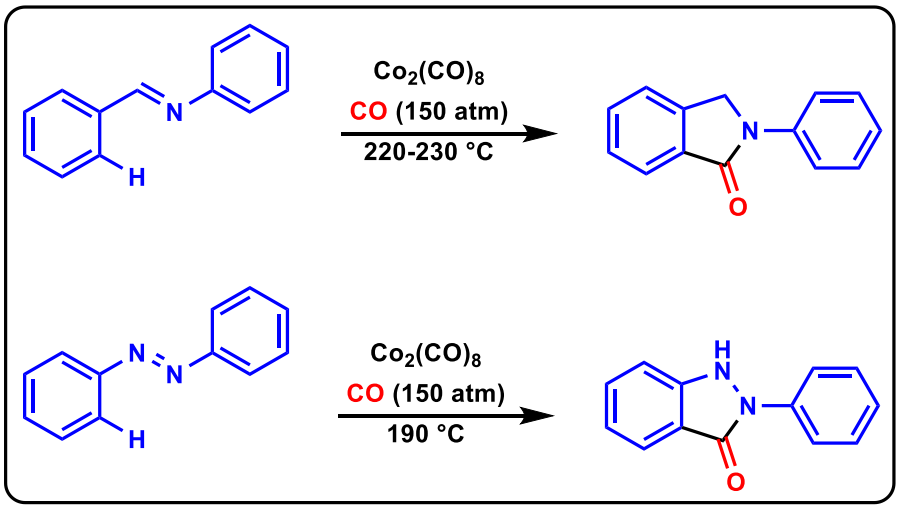

Figure-1.8: Evolution of directing group

The directing groups (DGs) have been classified broadly into two different types (monodentate and bidentate) depending on the number of coordination sites.[9]

(a) Monodentate directing group:

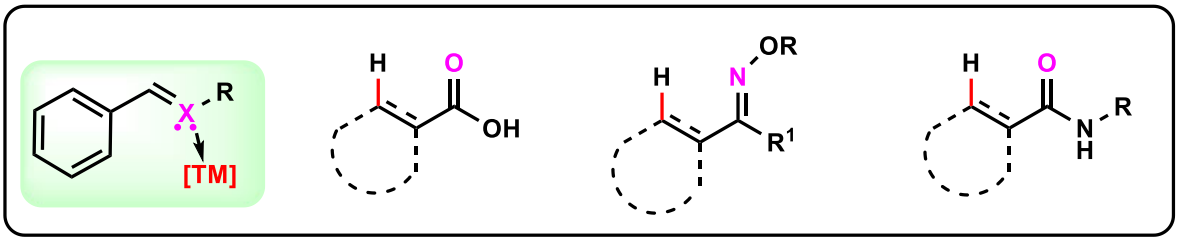

Figure-1.9: Monodentate directing group

This class of directing group possesses only one chelating atom. Functional groups like acids, imines and amides comes under this category. The transition metal chelates with the hetero atoms of the DG thereby forming a reactive metallacycle. This reactive metallacycle undergoes further reaction to furnish the corresponding product.

(b) Bidentate directing group:

This class of directing group possesses two chelating atoms. The directing group stabilises the metallacycle during the C-H activation process through extra coordination. Therefore, it governs the reactivity of intermediates to an certain extent. The metallacyclic intermediate further reacts with coupling partner to furnish the desired product.

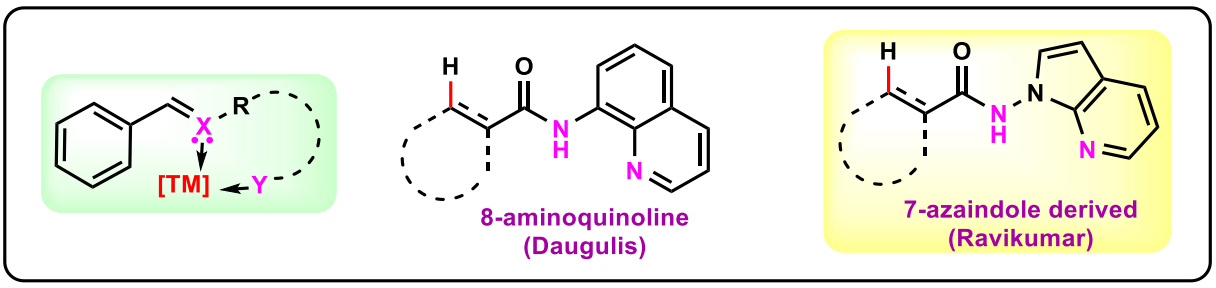

Figure-1.10: Bi-dentate directing group

1.4 NON-DIRECTED C-H ACTIVATION:

Generally carbocyclic and heterocyclic compounds are used as a substrate for non-directed C-H activation reaction. But this methodology leads to poor regio-selectivity. This

hypothesis can be understood from the below mentioned reaction.[10] A mixture of product is obtained with poor regioselectivity. To overcome the regioselectivity challenges, the directed C-H bond activation reaction is now being taken advantage of.

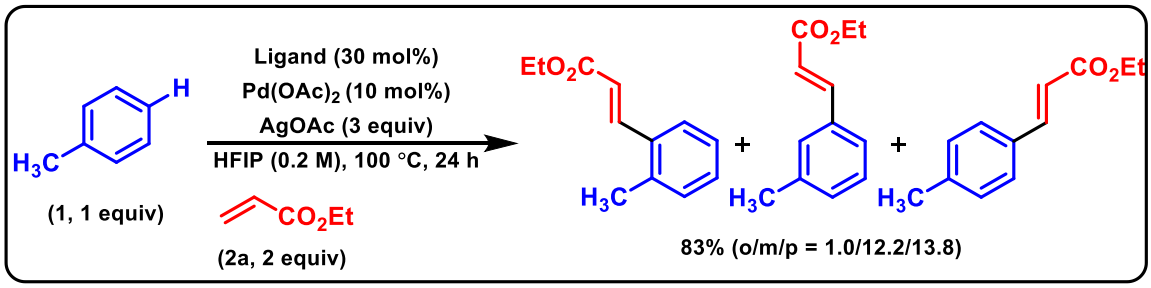

Figure-1.11: Non-directed C-H activation

1.5 DIRECTED C-H ACTIVATION:

The drawbacks associated with the non-directed C-H activation reaction is overcome by using a directing group.

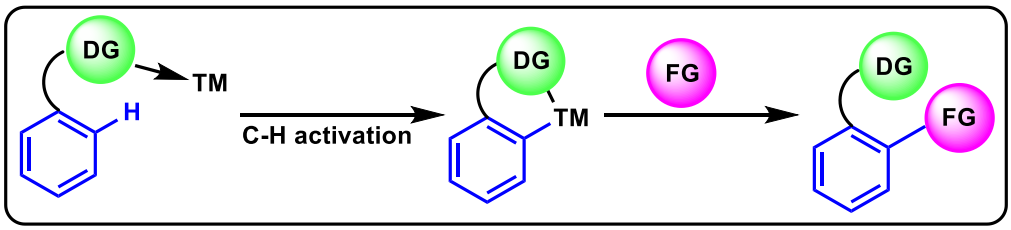

Figure-1.12: Directed C-H activation

The directing group chelates with the metal catalyst and subsequently activates a proximal C-H bond in the molecule (Fig-1.12). Therefore, a high regio-selectivity is obtained. By exploiting the directed C-H bond activation strategy a plethora of transformation have been documented in the last decade.[11,12] One of such typical example is given below (Fig-1.13).[13]

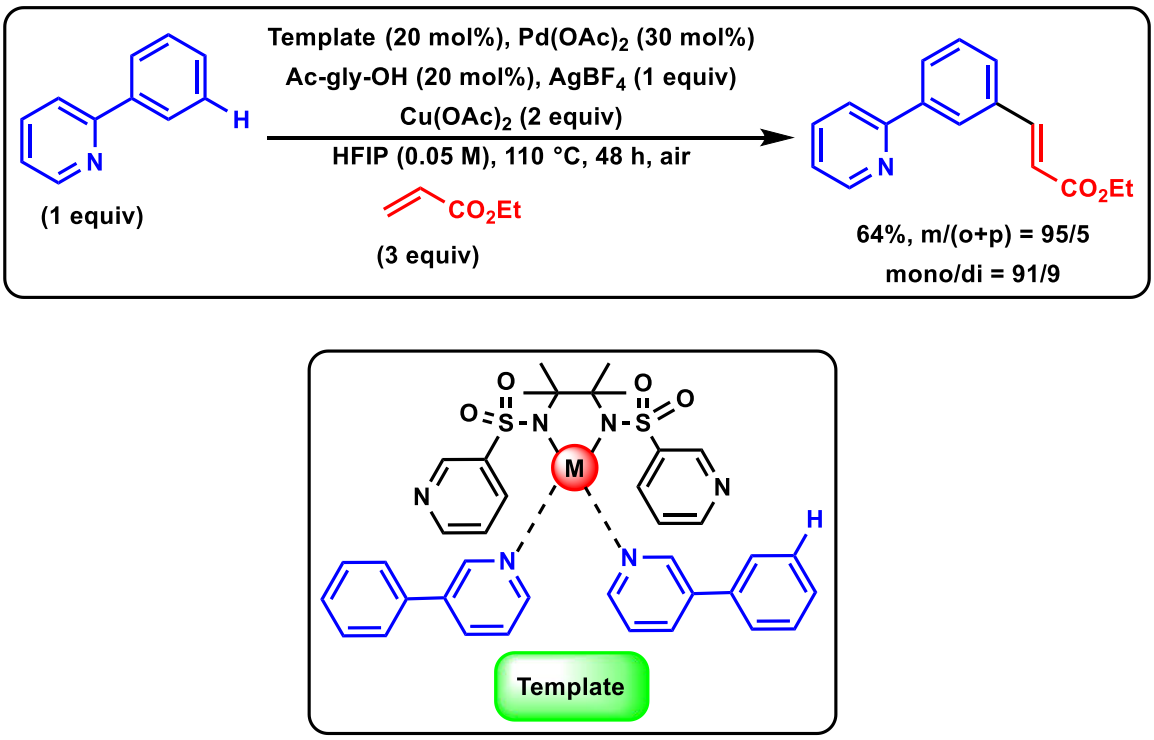

Figure-1.13: Example of Directed C-H activation

The template has been designed in such a way that, it chelates with metal and specifically activates the meta C-H bond of the phenyl pyridine. Finally, the olefinated product obtained with high meta-selectivity. Thus the directing group aided transition metal catalysed C-H bond activation is useful for the selective activation of a desired C-H bond in the presence of several other C-H bonds in the molecule.

1.6 REACTIVITY OF AMIDE WITH OLEFINS:

Duing the last couple of decades C-H bond activation strategy has emerged as an useful tool for the synthesis of medicinally important heterocycles and natural products. Among the various directed C-H activation reactions, alkenylation, alkylation and anuulation reaction has been studied extensively. In this regard transition metal catalyzed alkenylation reactions of benzamide with alkenes contributed significantly for C-C bond formation in organic synthesis.[14] Matsunaga reported the alkenylation of benzamide with ethyl acrylate

using Cp*Co(CO)I_2 catalyst and obtained the corresponding alkenylated product (Fig-1.14-a).[14a] Jeganmohan in 2016, revealed the olefination of benzamide with unactivated alkene using $Co(OAc)_2.4H_2O$ catalyst (Fig-1.14-b).[14b]

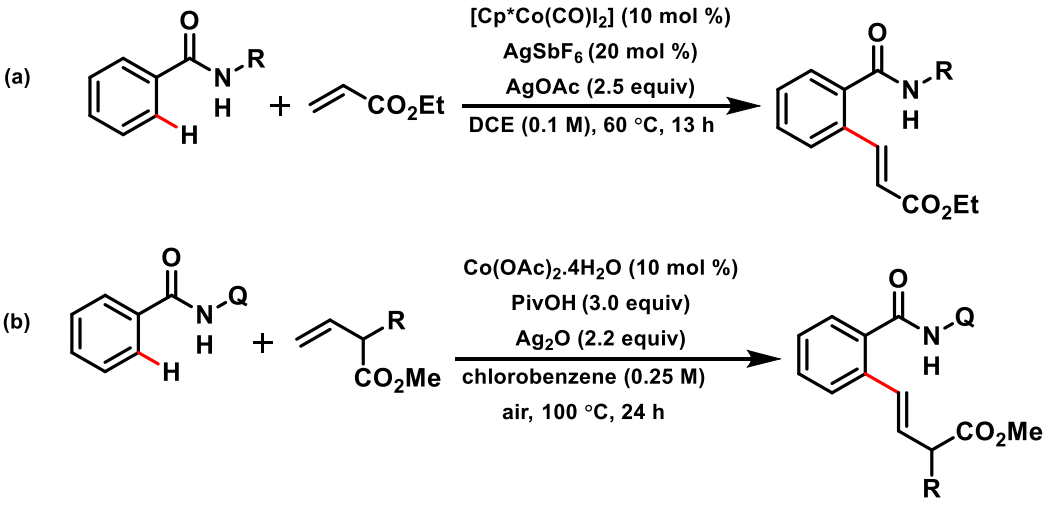

Figure-1.14: Alkenylation of benzamides with alkenes

Alkylation of benzamide has also been explored during last few decades.[15] Nakamura in 2011, disclosed the alkylation of a variety of alkenes with benzamide using cobalt-

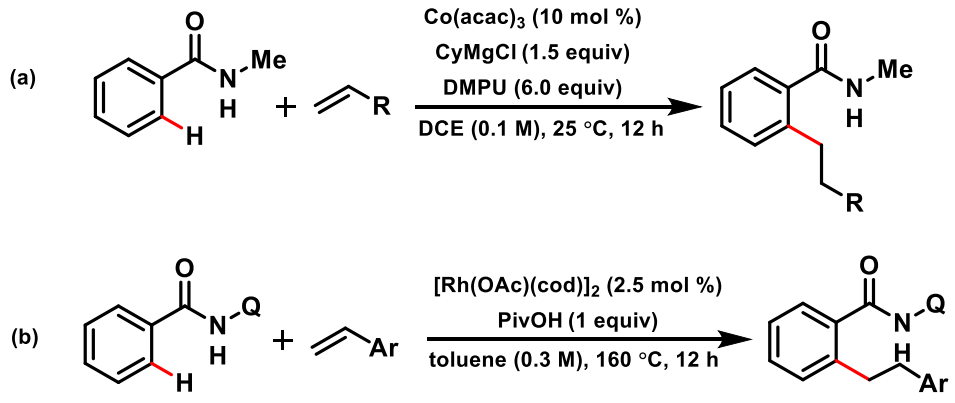

Figure-1.15: Alkylation of benzamides with alkenes

catalyzed C-H activation reaction (Fig-1.15-a).[15a] In 2015, Chatani reported the alkylation reaction of amides with styrene derivatives and obtained the alkylated product using rhodium catalyst (Fig-1.15-b).[15b]

However, the annulation reaction of benzamide with olefins is at the centre stage of C-H activation methodology. It can be attributed to its ability in affording the core skeleton of natural products and biologically active molecules in a single step.[16]

Zhai in 2018, reported a [4+1] annulation of maleimides with benzamides using cobalt-catalysis (Fig-1.16-a). The methodology provides spiro compound which gives access to the core skeletons of natural products.[16a] Waldmann reported the [4+1] annulation of styrene derivatives with benzamides and obtained the annulated products using $[RhCp^*Cl_2]_2$ catalyst (Fig-1.16-b).[16b] The transition metal catalysed annulation reactions have also been explored by various other groups because it gives access to many natural products (Fig-1.17).[17] Therefore, the multiple steps required to synthesize the natural products and drug molecules have been reduced significantly.

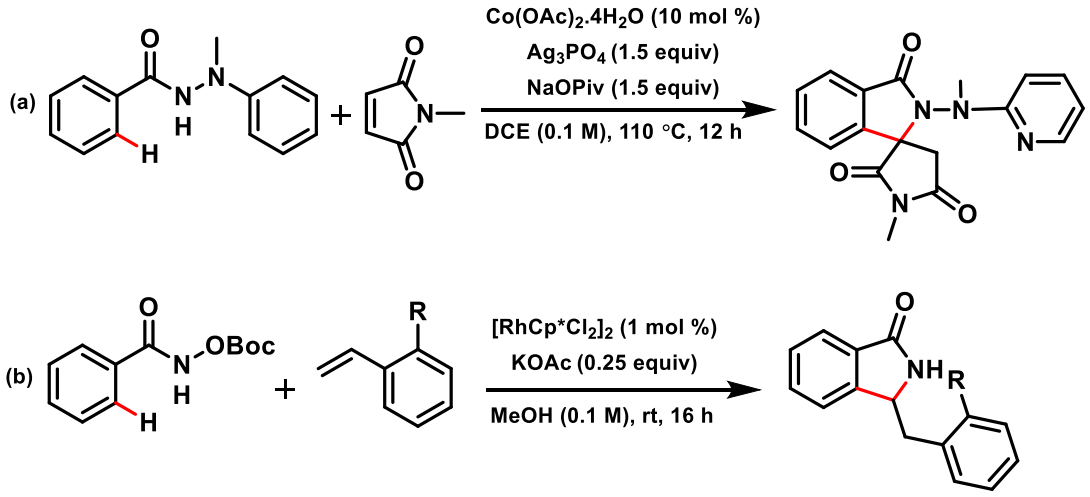

Figure-1.16: [4+1] Annulation of benzamides with alkenes

This important aspect of these methodology attracts chemists all over the world in organic synthesis.

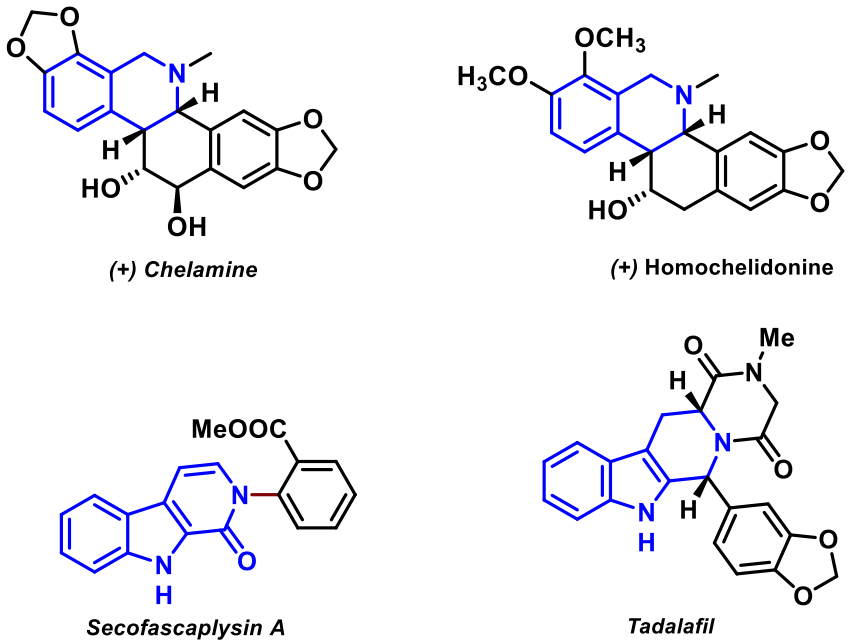

Figure-1.17: Access to core skeleton of natural products

The [4+2] annulation reaction also plays a major role in the arena of C-H activation reaction. Several important discovery have been disclosed by many groups in the last few decades.[18] Glorius in 2011, reported the annulation of olefins with benzamide and obtained the corresponding annulated product (Fig-1.18-a).[18a] The directing group in the substrate acts as internal oxidant for the transformation. In 2012, the annulation reaction of benzamide with allene was reported using rhodium catalyst. The corresponding annulated product is obtained by the assistance of pivaloyl group as a directing group. The weak N-O bond in the molecule works as a internal oxidant for the reaction (Fig-1.18-b).[18b]

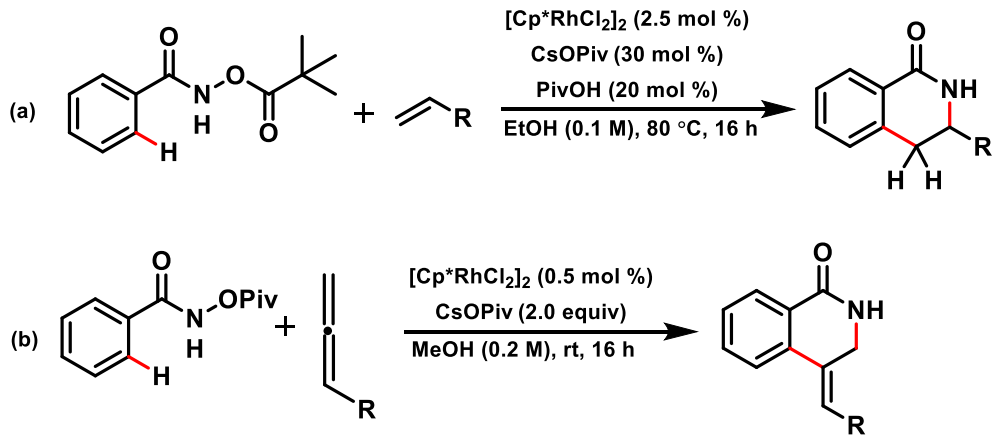

Figure-1.18: [4+2] Annulation of benzamides with alkenes

A general plausible catalytic cycle is depicted for transition metal-catalyzed directing group assisted annulation reaction of amides with olefins in Figure-1.19.[19] The metal catalyst activates the inert C-H bonds of substrate and forms a five membered metallacycle **I** .

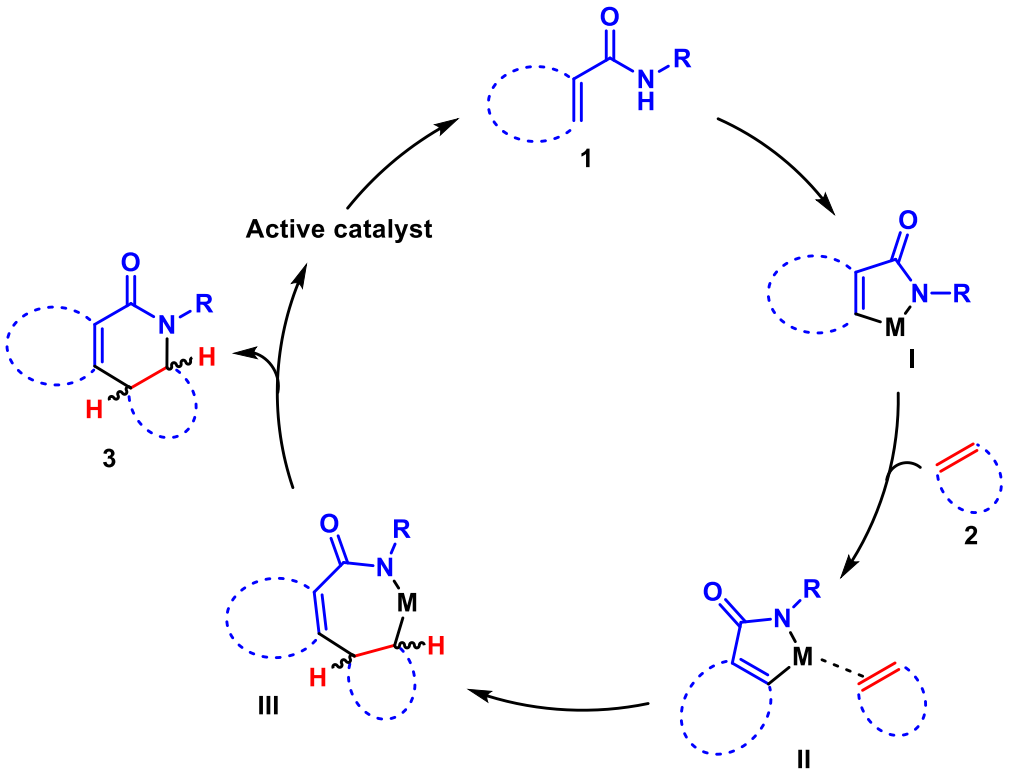

Figure-1.19: Proposed Mechanism for Annulation of Amides with Alkenes

In the subsequent step the olefin coordinates with intermediate **I** to form the intermediate **II** which then undergoes olefin insertion to give the intermediate **III.** Then the intermediate **III** undergoes reductive elimination forming the product **3** and subsequently the active catalyst is regenerated for the next catalytic cycle.

1.7 CONCLUSION:

In this chapter we briefly highlighted the importance of traditional reactions cross coupling reactions and its drawback for the construction of C-C and C-N bonds. Then we discussed about various pathways of C-H bond activation reactions. We have highlighted the advantages of directing group assisted C-H activation methodology. We also discussed about the different types of directing groups and its use for C-H activation reaction. In this context, various reactions such as alkenylation, alkylation and annulation reaction using directing group assisted C-H bond activation processes was documented. Finally we have concluded that annulation reactions through C-H activation is very useful for the synthesis of various natural product skeletons and bioactive molecules.

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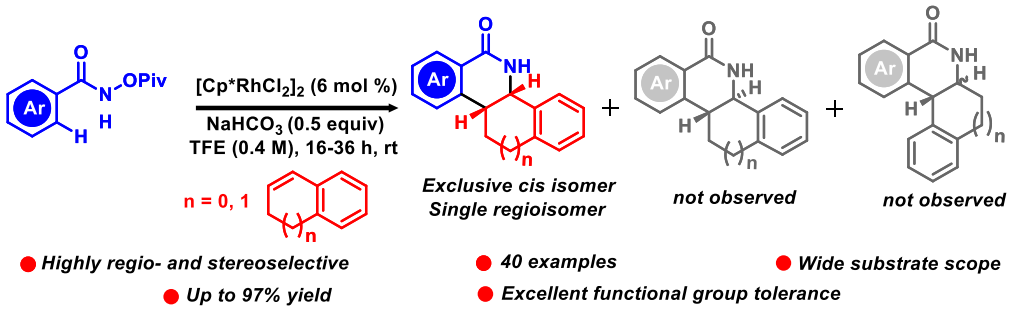
Chapter 2

Regio- and Stereoselective Synthesis of the Core Structure of Hexahydrobenzo[*c*]phenanthridine Alkaloids via Redox Neutral Cp*Rh(III)-Catalyzed C-H/N-H Annulation of Cyclic Alkenes with Benzamides

Chapter 2

Regio- and Stereoselective Synthesis of the Core Structure of Hexahydrobenzo[*c*]phenanthridine Alkaloids via Redox Neutral Cp*Rh(III)-Catalyzed C-H/N-H Annulation of Cyclic Alkenes with Benzamides



2.1 ABSTRACT: A highly stereo- and regioselective synthesis of the core skeleton of hexahydrobenzo[*c*]phenanthridine-type alkaloids is reported herein. A wide range of substrate scope, excellent functional group tolerance and good to excellent yields were observed. This reaction protocol gives a very concise and efficient access to the core skeleton of Chelidonine alkaloids as compared to the earlier approaches.

2.2 INTRODUCTION

Hexahydrobenzo[*c*]phenanthridine-type alkaloids (Figure 1) which are constituted by tetrahydroisoquinoline motif's are commonly present in papaverous plants which show wide range of biological activities such as antitumor, antinociceptive and antiserotoninergic effect.[1] Even though several synthetic approaches for this class of molecules are reported,[2] virtually all of them involved multiple steps to reach their core skeleton. Hence the

development of efficient and one-step synthetic protocol to access those structural scaffolds and their analogs are of immense interest.

Transition metal-catalyzed C-H bond activation reactions has taken the center stage of organic synthesis owing to its phenomenal advancements in recent years. It involves direct activation and functionalization of inert C-H bonds present in an organic molecule by taking advantage of the appropriate heteroatom/s as directing groups for transition metal catalysts.[3] Considering the advantages of directing group assisted C-H bond activations, there has been an intense focus in developing new approaches for the synthesis of complex organic scaffolds for medicinal[4] and material chemistry applications.[5] In this context, activation of aromatic *ortho* C-H bonds of benzamides and subsequent annulation with alkynes and olefins has remained an active area of research in recent years.

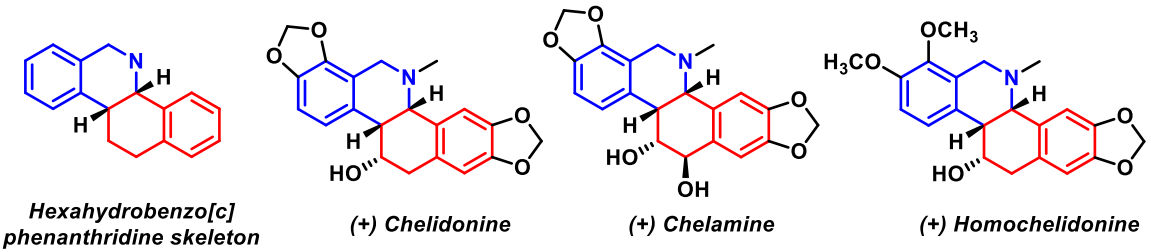
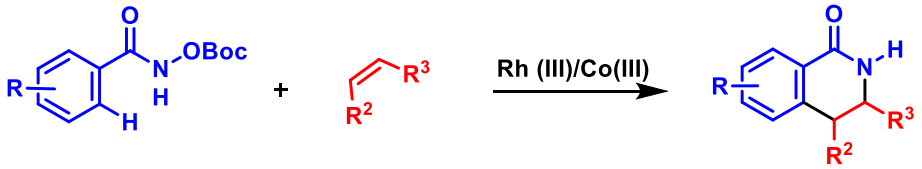


Figure 2.1 Examples of hexahydrobenzo[*c*]phenanthridine-type alkaloids.

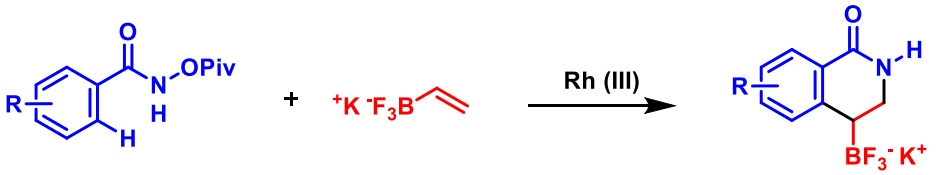
Several pioneering research groups such as You,[6] Liu,[7] Ackermann,[8] Zhu,[9] Fagnou[10] and others[11] have demonstrated the use of alkynes as coupling partner for *C-H/N-H* oxidative-annulation of amide derivatives. However, there are only a handful of reports on the use of alkene as a coupling partner. Cramer,[12] Rovis,[13] Perekalin[14] groups demonstrated the [4+2] annulation of amides with olefins, using Cp*Rh and its modified complex (scheme 1a). Molander[15] and Glorius[16] reported rhodium-catalyzed annulation of amides with vinyltrifluoroborates (scheme 1b) and conjugated olefins (scheme 1c) respectively. Also, cobalt- and ruthenium- catalyzed sp^2 C-H activation reaction of aminoquinolone and *N*-methoxy benzamides were reported by Daugulis[17] and Wang[18] groups.

Scheme 2.1 Previous work and our work

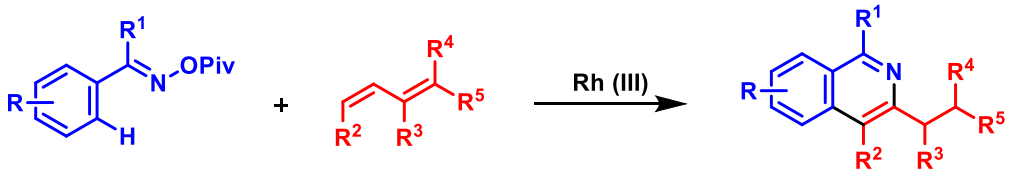
a. Annulation with Olefines[12-14]



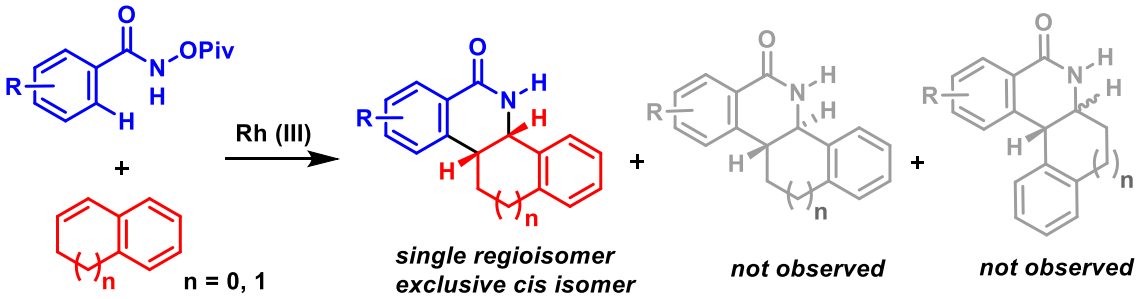
b. Annulation with Vinyltrifluoroboronates[17]



c. Annulation with 1,3-dienes[16b]



d. Highly regio- and stereoselective annulation with dihydronaphthalene and indene (Our Work)



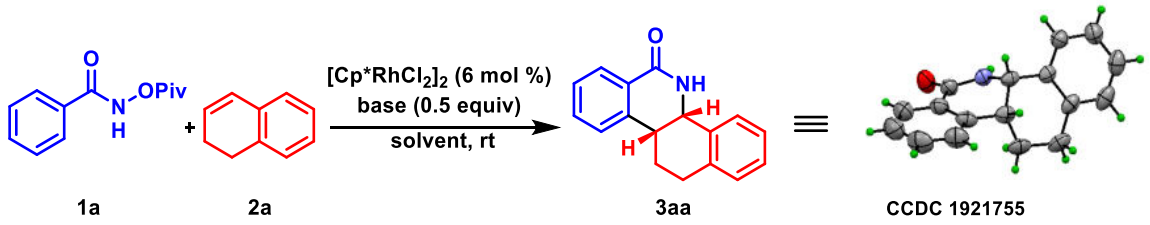
Herein, we report for the first time a rhodium (III)-catalyzed *C-H/N-H* annulation of amides with dihydronaphthalene to afford essential tetracyclic core of Chelidonine alkaloids in a highly regio- and stereoselective manner.

2.3 RESULTS AND DISCUSSION

To test our hypothesis, initially we attempted the annulation of *N*-(pivaloyloxy) benzamide **1a** with 1,2- dihydronaphthalene **2a** using $[Cp^*Rh(Cl_2)]_2$ as catalyst and cesium acetate as base in ethanol (table 2.1, entry 1). To our delight, we obtained the desired annulated product tetrahydrobenzo[*c*]phenanthridinone **3aa** but in only 25% yield. To improve the

yield of reaction, different reaction parameters such as additives, solvents were systematically screened. Since the reaction was partially successful in giving desired product in EtOH, other protic solvents such as MeOH and ^{t}BuOH were tried. However, the yield of **3aa** did not improve with those two protic solvents. While MeOH afforded 20%, ^{t}BuOH produced 11% yield of **3aa** (table 2.1, entries 2 and 3). It appeared that, the reaction is very sensitive to slight changes in the pKa of protic solvents. Therefore, we decided to check the influence

Table 2.1. Optimization of Reaction Conditions[a]



1a **2a** **3aa** **CCDC 1921755**

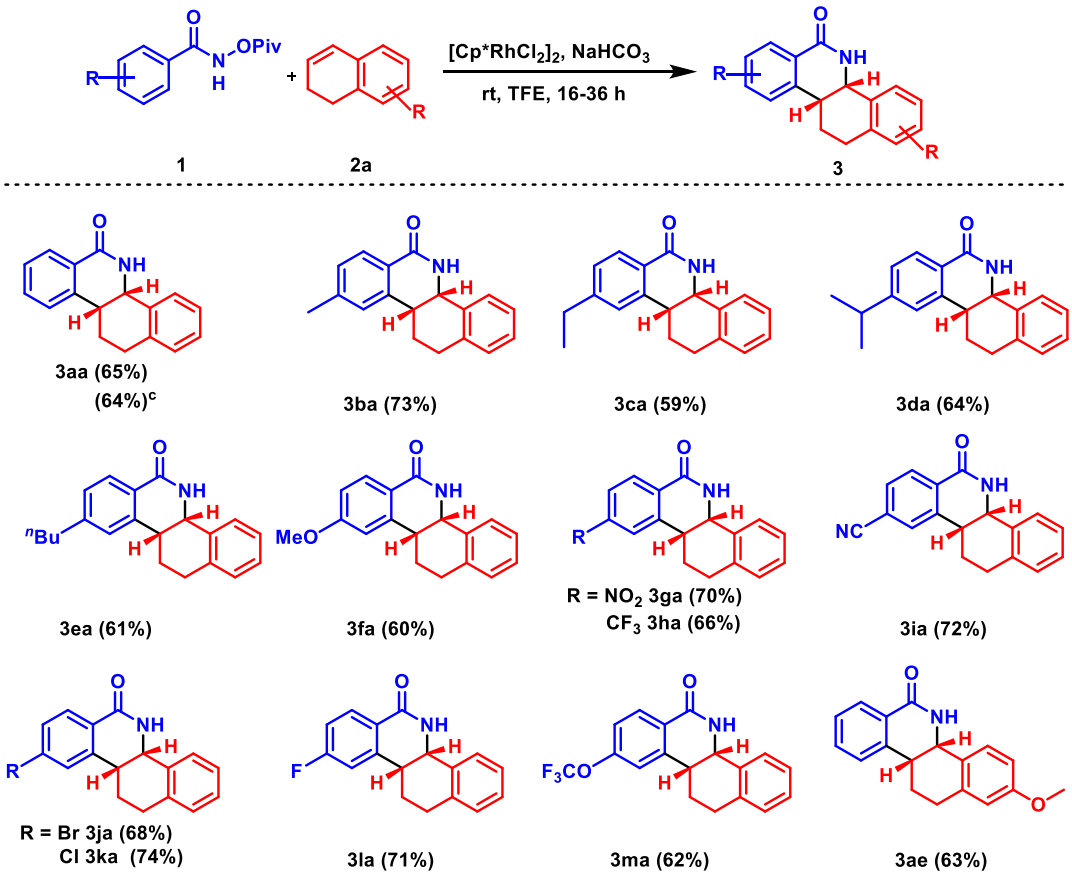
entry	base	solvent	time (h)	yield of **3aa** (%)[b]
1	CsOAc	EtOH	16	25
2	CsOAc	MeOH	16	20
3	CsOAc	^{t}BuOH	16	11
4	CsOAc	MeCN	24	2
5	CsOAc	DMF	16	3
6	CsOAc	DCE	24	10
7	CsOAc	HFIP	24	8
8	CsOAc	TFE	16	57
9	KOAc	TFE	16	63
10	NaOAc	TFE	16	69
11	LiOAc	TFE	30	20
12	Cs_2CO_3	TFE	30	70
13	K_2CO_3	TFE	24	67
14	Na_2CO_3	TFE	24	13
15	Li_2CO_3	TFE	36	11
16	**$NaHCO_3$**	**TFE**	**24**	**74**

[a]Reaction conditions:- *N*-(pivaloyloxy) benzamide **1a** (1 equiv, 0.04 mmol), 1,2-dihydronaphthalene **2a** (1.3 equiv, 0.06 mmol), $[Cp^*RhCl_2]_2$ (0.06 equiv, 0.003 mmol), base (0.5 equiv, 0.02 mmol), solvent (0.4 M, w.r.t. **1a**). [b]1,3,5-trimethoxy benzene has been used for ^{1}H NMR yield calculation.

of polar aprotic solvents such as CH_3CN, DMF on the reaction. However, the yield of **3aa** considerably decreased in CH_3CN and DMF (table 2.1, entries 4 and 5). As we did not observe any promising result with the solvents mentioned above, we tried the reaction with halogenated solvents such as 1,2-dichloroethane (DCE), hexafluoroisopropanol (HFIP), and 2,2,2-trifluoroethanol (TFE). Gratifyingly, substantial improvement in product yield (57%) was observed with TFE (table 2.1, entry 8). Intrigued by this result, we next turned our attention towards screening of various base additives with TFE as the optimized solvent. Initially, we examined the effect of various acetate bases such as KOAc, NaOAc and LiOAc. Although LiOAc failed to produce good yield of **3aa**, but KOAc and NaOAc were found to be effective in producing the desired annulated product **3aa** in 63% and 69% respectively (table 2.1, entries 9 and 10). For further Improvement of the product yield, we screened different carbonate bases such as $CsCO_3$, K_2CO_3, Na_2CO_3, Li_2CO_3 and $NaHCO_3$. Delightfully, $NaHCO_3$ produced best yield of **3aa** (74%, table 2.1, entry 16). On the contrary, Na_2CO_3 and Li_2CO_3 failed to improve the yield even after long reaction time giving **3aa** in only 13% and 11% respectively (table 2.1, entries 14, 15). Thus, the use of $NaHCO_3$ as base, TFE as solvent, with $[Cp^*Rh(Cl)_2]_2$ catalyst (entry 16) was found to be the best reaction condition, which produced the core skeleton of hexahydrobenzo[*c*]phenanthridine-type alkaloids at a very high level of regio- and stereoselectivity. The structure of the annulated product **3aa** was confirmed from single-crystal X-ray analysis (table 2.1). With the optimized reaction condition in hand, we examined the generality of this reaction with various electronically rich substrates such as alkyl- (**1b-1e**) and methoxy- **(1f)** substituted benzamides (scheme 2.2). With these electronically rich substrates, we obtained good yields (59-73%) of the annulated products

(**3ba-3fa**). Similarly, the reaction was found to be compatible with highly electron deficient benzamides affording the desired products (**3ga-3ia**) in good yields (66-72%).

Scheme 2.2 Cp*Rh(III) Catalyzed Regio- and Stereoselective *C-H*/*N-H* Annulation of Substituted Benzamides with Dihydronaphthalenes[a]

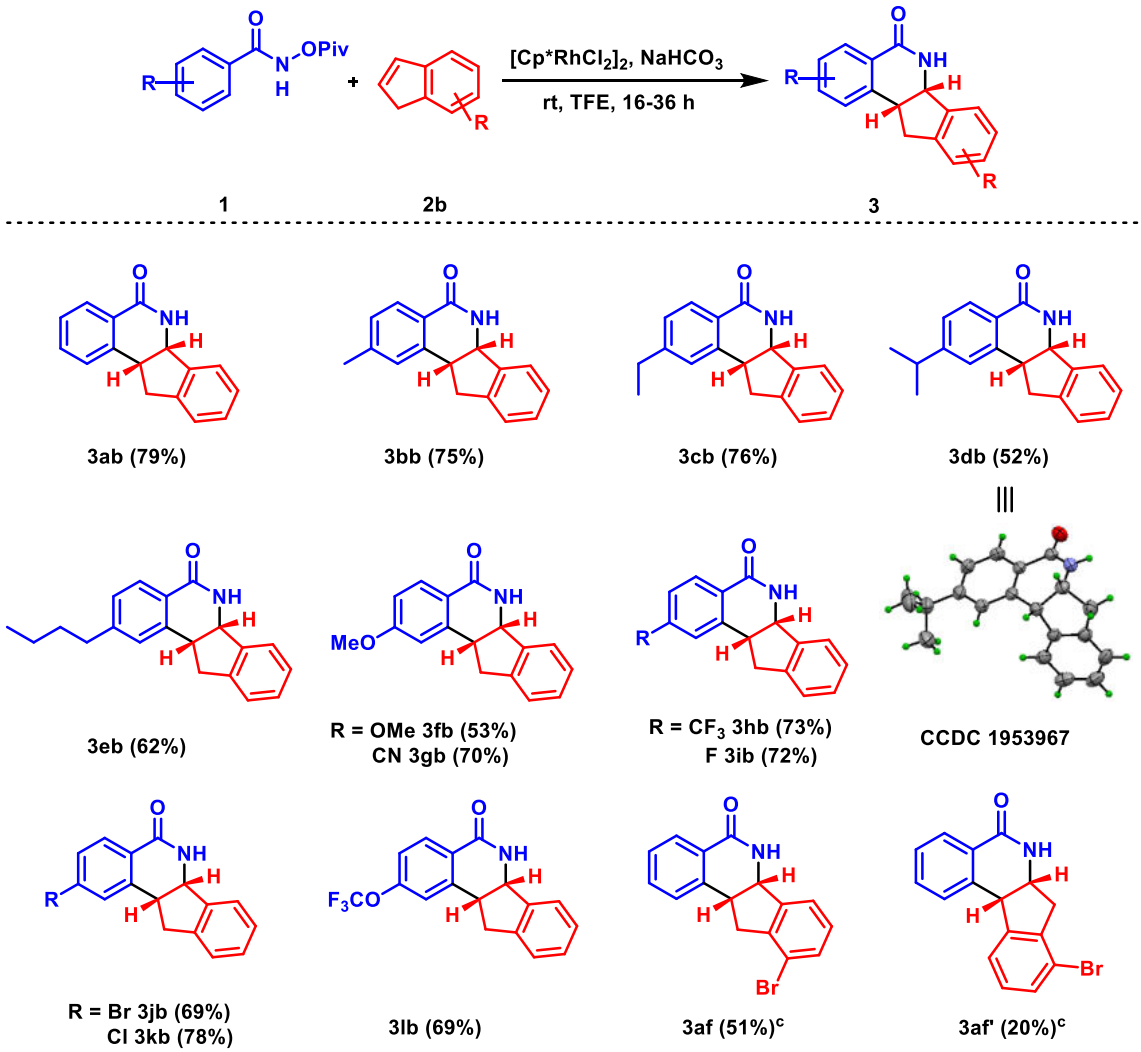


[a]In all cases, reactions were performed using **1** (1.0 equiv, 0.04 mmol), **2a** (1.3 equiv, 0.06 mmol), $[Cp^*RhCl_2]_2$ (0.06 equiv, 0.003 mmol), $NaHCO_3$ (0.5 equiv, 0.02 mmol) in 0.1 ml TFE under N_2 atmosphere. [b]All yields in parenthesis are isolated yield. [c]Compound **3aa** (159 mg, 64%) was prepared in one millimole scale.

Furthermore, the halo substituted benzamides (bromo-, chloro- and fluro-substituted) when subjected to the titled transformation, gave good yields (68-74%) of their respective annulated products (**3ja-3la**). Finally, trifluromethoxy-substituted benzamide (**1m**) was tested, which also resulted in good yield (62%) of the annulated product **3ma**. To check the effect of substituent on coupling partner, we performed one reaction with 7-methoxy-1,2-dihydronaphthalene (**2e**). Successfully, we got good amount of annulated product **3ae**

(63%). These results reveal that, the developed annulation protocol is facile for both electronically rich and electronically poor benzamides. To validate the synthetic utility of this protocol, we performed a reaction of **1a** with **2a** in 1mmol scale. Gratifyingly, we got 160 mg (64% yield) of isolated product **3aa**, which proves the generality of this methodology in higher scale.

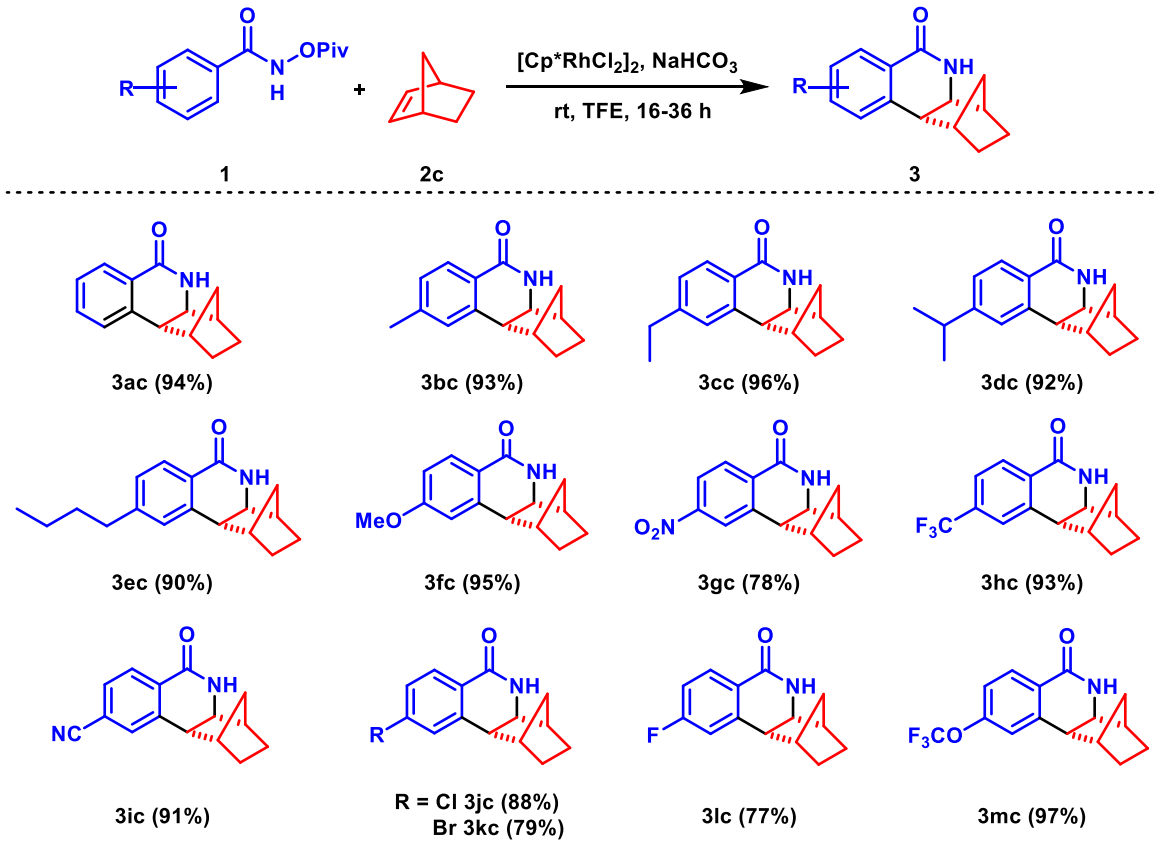
Scheme 2.3 Cp*Rh(III) Catalyzed Regio- and Stereoselective *C-H/N-H* Annulation of Substituted Benzamides with Indenes[a]



[a]In all cases, reactions were performed using **1** (1.0 equiv, 0.04 mmol), **2b** (1.3 equiv, 0.06 mmol), $[Cp^*RhCl_2]_2$ (0.06 equiv, 0.003 mmol), $NaHCO_3$ (0.5 equiv, 0.02 mmol) in 0.1 ml TFE under N_2 atmosphere. [b]All yields in parenthesis are isolated yield. [c]Compound **3af** (29 mg, 51%) and **3af'** (11 mg, 20%) were prepared in 0.18 mmol scale.

To further explore the scope of our developed methodology, we applied the optimized reaction condition with indene as the coupling partner (scheme 2.3). To our delight, we obtained 79% yield of annulated product **3ab**. Good yields of annulated products were obtained with electron-donating substrates such as methyl-, ethyl-, isopropyl-, n-butyl- and methoxy-substituted benzamides (**3bb-3fb**). Substrates with electron-withdrawing sub stituents such as cyano-, trifluoromethyl-, and fluoro- groups also worked well (**3gb-3ib**). As expected, halogenated substrates (bromo- and chloro-) also gave good yields of the desired products (**3jb, 3kb**). Finally, trifluoromethoxy-substituted benzamide also resulted in good yield (69%) of the annulated product **3lb**.

Scheme 2.4 Cp*Rh(III) Catalyzed Regio- and Stereoselective *C-H/N-H* Annulation of Substituted Benzamides with Norbornene[a]

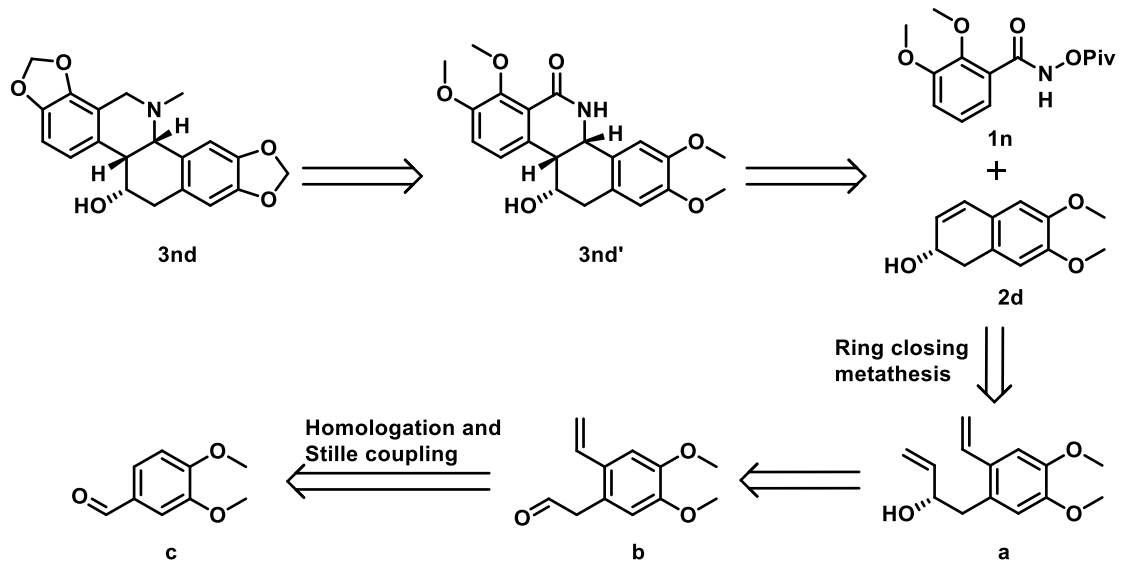


[a]In all cases, reactions were performed using **1** (1.0 equiv, 0.04 mmol), **2c** (1.3 equiv, 0.06 mmol), $[Cp^*RhCl_2]_2$ (0.06 equiv, 0.003 mmol), $NaHCO_3$ (0.5 equiv, 0.02 mmol) in 0.1 ml TFE under N_2 atmosphere. [b]All yields in parenthesis are isolated yield.

To prove the regioselectivity of this reaction over effect of substituent on coupling partner, we performed one reaction with 7-bromo-1*H*-indene (**2f**). Gratifyingly, we got major regioisomer **3af** in good yield (51%) over **3af'** (20%). This suggests that, the reaction is sensitive to steric bias. Overall it implies that, this method is quite general for indene system as well. After successful implementation of our methodology with dihydronaphthalene and indene, we tried annulation reaction with norbornene as coupling partner (scheme 2.4). Excellent yield (94%) of the annulated product **3ac** was obtained. Substrates bearing electron donating groups such as methyl-, ethyl-, isopropyl-, n-butyl- and methoxy- groups gave us good yields of products (**3bc-3fc**). Electron-withdrawing substituents such as nitro-, trifluoromethyl-, and cyano- groups also produced good to excellent yield (78-91%) of annulated products (**3gc-3ic**). Halo substituted benzamides (bromo-, chloro- and fluoro-) also gave good yields of annulated products (**3jc-3lc**). Finally, trifluoromethoxy-substituted benzamide produced excellent yield (97%) of annulated product **3mc**.

After successfully demonstrating the methodology for the regio- and stereo-selective

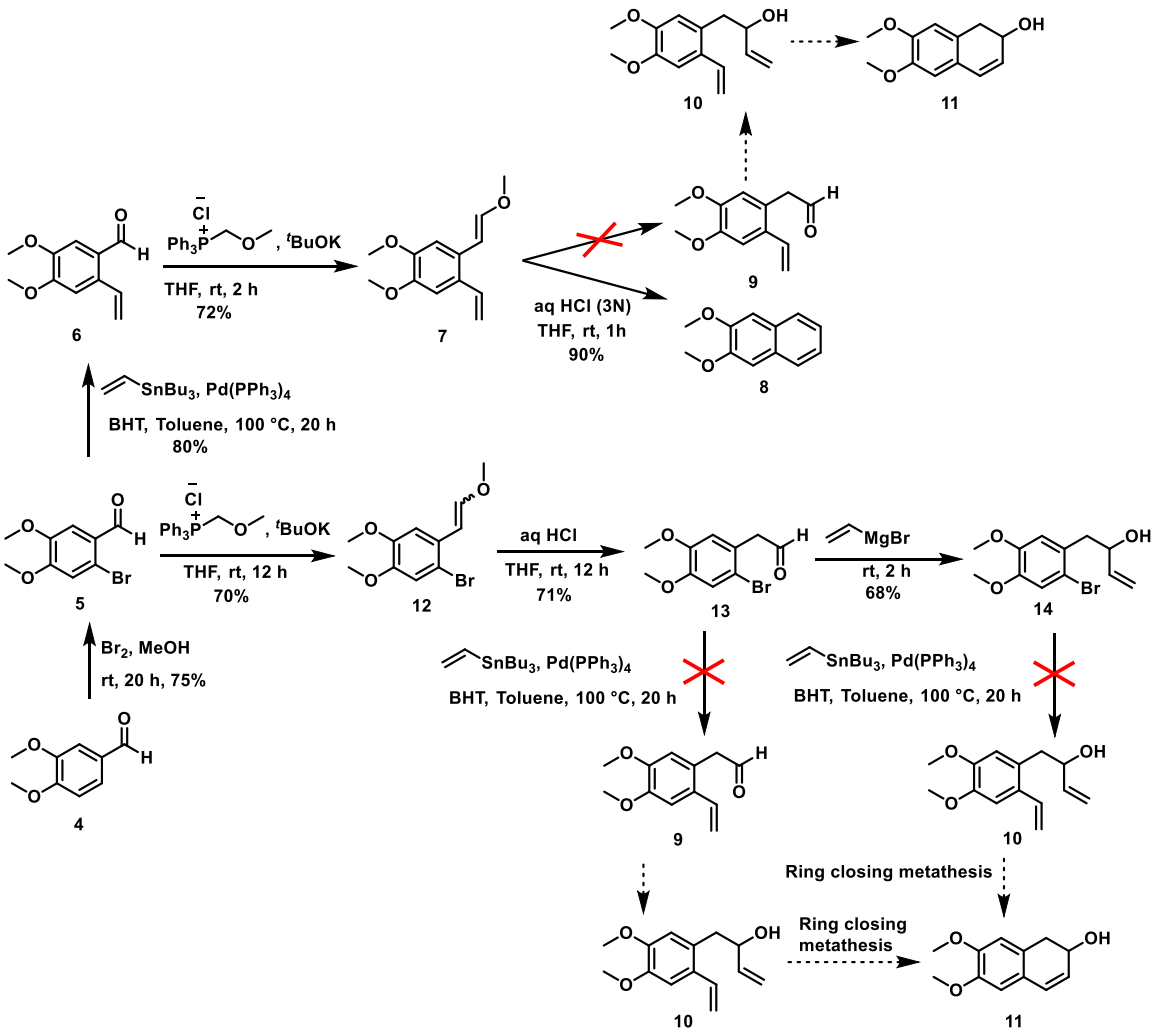
Scheme 2.5 Retrosynthetic Plan for the Synthesis of Chelidonine 3nd:



synthesis of hexahydrobenzo[*c*]phenanthiridine skeleton, we decided to attempt the total synthesis of Chelidonine alkaloid **3nd** (scheme 2.5). We envisioned that annulation of benzamide **1n** and 6,7-dimethoxy-1,2-dihydronapthalene-2-ol **2d** would give the advanced tetracyclic intermediate **3nd′** (scheme 2.5) with *cis* ring junction as required in the natural product.

We presumed that functional group maneuvering of tetracyclic intermediate **3nd′** would give the natural product Chelidonine **3nd** (scheme 2.5). We also thought that, the coupling partner 6,7-dimethoxy-1,2-dihydronapthalene-2-ol **2d** for the key annulation reaction, could be prepared from 3,4-dimethoxybenzaldehyde **c** via tin mediated vinylation of aromatic bromide and ring closing metathesis reactions. Accordingly, we performed bromination reaction of 3,4-dimethoxybenzaldehyde **4** (scheme 2.6) in methanol at room temperature. It gave us 2-bromo-4,5-dimethoxybenzaldehyde **5** (also available commercially) as colorless crystalline solid in 75% yield. Stille coupling of 2-bromo-4,5-dimethoxybenzaldehyde **5** with vinyltributylstanane and $Pd(PPh_3)_4$ gave 4,5-dimethoxy-2-vinylbenzaldehyde **6** as colourless liquid in 80% yield. Wittig olefination of the aldehyde **6** using potassium *tert*-butoxide and methoxymethyltriphenylphosphonium bromide in THF at room temperature gave us a mixture of (*Z*)-1,2-dimethoxy-4-(2-methoxyvinyl)-5-vinylbenzene and (*E*)-1,2-dimethoxy-4-(2-methoxyvinyl)-5-vinylbenzene **7** (*E*:*Z*;*1*:*1*) as a colorless liquid in 72% yield. The enol ether **7** was then subjected to acid catalyzed hydrolysis reaction. However, the reaction did not give us the expected homologated aldehyde **9,** instead we got aromatized product **8**. Formation of aromatic product **8** can be explained by the fact that, protonation of the electron rich olefin followed by the interception of carbocation by the pendant vinyl group leads to cyclization and aromatization. Several attempts to optimize this reaction with different acidic conditions did not give any fruitful result forcing us to search for alternative approaches. As the vinyl

Scheme 2.6 Synthetic Approach for the Synthesis of 6,7-Dimethoxy-1,2-dihydronapthalene-2-ol:

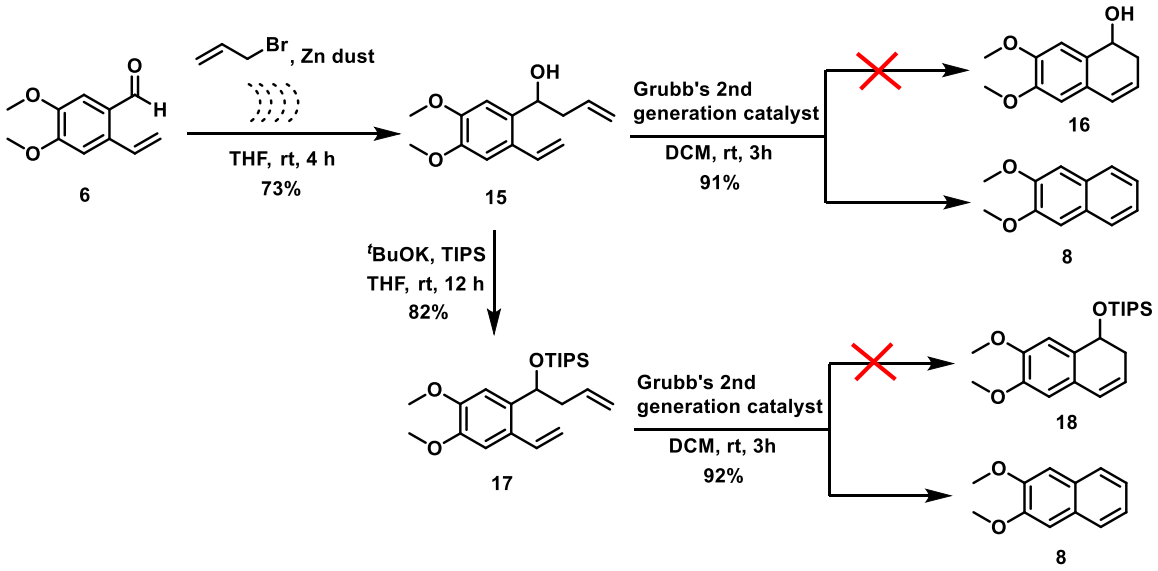


group was interfering with the acid catalysed hydrolysis step, we decided to install the vinyl group after the homologation step. Accordingly, treatment of 2-bromo-4,5-dimethoxybenzaldehyde **5** with methoxymethyltriphenyl phosphonium bromide and potassium *tert*-butoxide in THF at room temperature gave us a mixture of (*Z*)-1-bromo-4,5-dimethoxy-2-(2-methoxyvinyl)benzene and (*E*)-1-bromo-4,5-dimethoxy-2-(2-methoxyvinyl)benzene **12** (*E*:*Z*;*1*:*1*) in 70% yield. The *E*:*Z* mixture of enol ether **12** was then treated with aqueous hydrochloric acid. Gratifyingly, this time we got 2-(2-bromo-4,5-dimethoxyphenyl)acetaldehyde **13** as colourless liquid in 71% yield. The pure

compound **13** was then subjected to Stille coupling reaction using catalytic amount of $Pd(PPh_3)_4$ and vinyl tributylstanane. Surprisingly, even after several trials we could not obtain the vinylated product **9**. The TLC of this reaction was not very clean and presence of multiple spots indicated several side products. Silica gel chromatographic purification of the crude mixture did not yield any characterizable product. Therefore, we decided to postpone installation of vinyl group. Hence the pure compound **13** was subjected to Grignard reaction using vinyl magnesium bromide to obtain the allyl alcohol **14** in 68% yield. Left with limited options, we optimistically explored Stille's protocol on the tricky allyl alcohol **14**. Unfortunately, we could not get the desired product **10**. Having failed to synthesize the desired coupling partner 6,7-dimethoxy-1,2-dihydronapthalene-2-ol **11** through multiple approaches, we decided to adopt different coupling partner 6,7-dimethoxy-1,2-dihydronapthalene-1-ol **16** (scheme 2.7) which differs only in the position of hydroxy group.

Although the hydroxy group in coupling partner 6,7-dimethoxy-1,2-dihydronapthalene-1-

Scheme 2.7 Synthetic Approach for the Synthesis of 6,7-Dimethoxy-1,2-dihydronapthalene-1-ol:



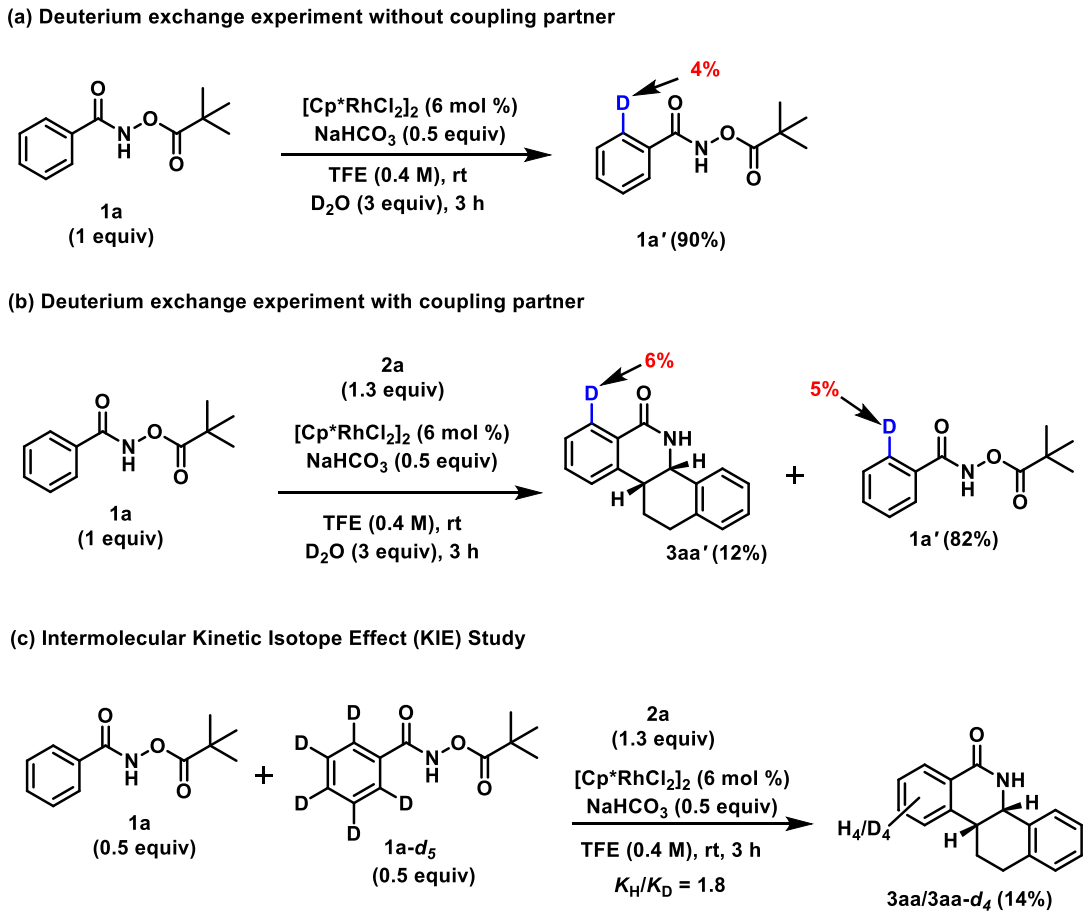
ol **16** is on the wrong carbon in comparision to natural product, we still thought of using it as coupling partner. As we could address this issue later through late stage functional group modification. Accordingly, we set ourselves to explore the synthesis of 6,7-dimethoxy-1,2-dihydronapthalene-1-ol **16**.

We planned a Barbier reaction on 4,5-dimethoxy-2-vinylbenzaldehyde **6**, accordingly the aldehyde **6** was sonicated at room temperature with allyl bromide and zinc dust in anhydro us THF. We obtained allyl alcohol **15** in good yield without any difficulty. The allyl alcohol **15** was then treated with Grubbs' catalyst to get the desired compound **16**. But unfortunately, we got aromatized product **8**. Even after several trial by lowering temperature, catalysts etc, we could not get favourable result. The aromatization process seems very rapid under these conditions. We then thought that protecting the hydroxy group of compound **15** with bulky protecting group such as triisopropylsilylether might solve the problem. Accordingly, the free hydroxy group in compound **15** was efficiently protected as its TIPS ether using triisopropylsilyl chloride (TIPSCl) and potassium *tert*-butoxide condition in anhydrous THF at room temperature. To our despair, even the TIPS protected compound **17** also underwent rapid aromatization with Grubbs' catalyst after ring closing metathesis. Even after several attempts by lowering temperature, varying concentration and varying catalyst loading, we did not observe any sign of improvement. Therefore, we decided not to pursue further with our total synthesis efforts.

In order to gain insights into the mechanism of this annulation pathway, deuterium labelling experiments were carried out. In the first case (scheme 2.8a), **1a** was subjected to standard reaction conditions in the absence of coupling partner **2a** and in the presence of 3 equiv of D_2O. Only 4% of deuterium incorporation at *ortho*-position was observed. Similarly, the reaction of **1a** with coupling partner **2a** (scheme 2.8b) in the presence of 3 equiv of D_2O

was conducted using standard reaction condition. Compound **1a′** and **3aa′** were isolated, and their deuterium incorporation at *ortho*-position was investigated by ^{1}H NMR study.

Scheme 2.8 Mechanistic Studies:

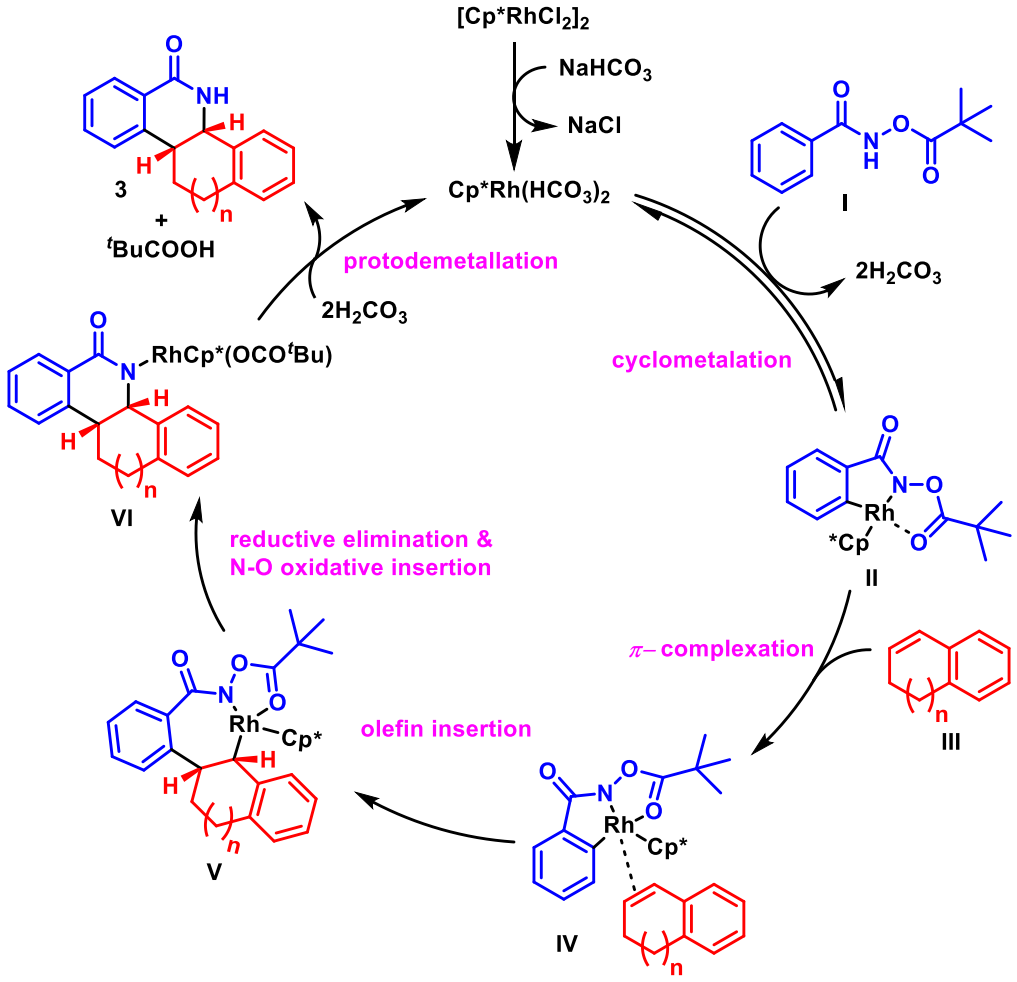


Only 5% and 6% of deuterium incorporation was observed in the case of **1a′** and **3aa′**, respectively (scheme 2.8b). Subsequently, an intermolecular kinetic isotope effect experiment was carried out between benzamide **1a** and isotopically labelled benzamide **1a-*d*$_5$** (Scheme 2.8c) that resulted a KIE (K_H/K_D) value of 1.8. These results reveals that, the reaction could be reversible for the C-H metalation step.[19]

Based on the above mechanistic findings and literature precedents,[20] a plausible catalytic cycle is proposed herein (scheme 2.9). The catalytic cycle starts from [Cp*Rh(HCO$_3$)$_2$], which gets coordinated to benzamide **I** with subsequent loss of H_2CO_3 through cyclometallation step and forms intermediate **II**. The intermediate **II** forms a π-complex

with the cyclic olefin **III** to produce intermediate **IV**, which undergoes the 1,2-olefin insertion process on carbon-rhodium bond and forms intermediate **V**. It is important to note

Scheme 2.9 Proposed Catalytic Cycle



here that the steric requirement of coupling partner prefers to orient benzene ring away from the substrate leading to high regioselectivity. Exclusive formation of *cis* stereoisomer in this step could be explained on the basis of favourable cation-π interaction between rhodium and benzenoid ring of dihydronaphthalene. As a result, the transition state leading to *cis* isomer could be of lower energy as compared to that of *trans* isomer. Further reductive elimination and *N-O* oxidative insertion would produce intermediate **VI**. Protodemetallation of intermediate **VI** gives the annulated product **3** along with the regeneration of the active catalyst.

2.4. CONCLUSION

In summary, we reported a redox-neutral Cp*Rh(III) catalyzed *C-H/N-H* annulation of *N*-(pivaloyloxy) benzamide with unexplored dihydronaphthalene and indene as the coupling partner in a highly stereo- and regioselective manner. The methodology provides an easy access to the core skeleton of hexahydrobenzo*c*]phenanthridine-type alkaloids and has applicability over a wide range of substrate. An attempted effort for the total synthesis of chelidonine alkaloid is also reported.

2.5 EXPERIMENTAL SECTION:

2.5.1 General Procedure for the Preparation of Annulated Products.

To an oven dried (100 °C) schlenk tube, cooled under N_2 atmosphere, was charged with *N*-(pivaloyloxy) benzamide **1** (0.04 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (0.03 mmol, 0.06 equiv), $NaHCO_3$ (0.02 mmol, 0.5 equiv), and anhydrous TFE (0.4 M). The reaction mixture was cooled to 0 °C, thereafter coupling partner (0.06 mmol, 1.3 equiv) was added in one shot. The sealed tube was tightened under positive pressure of N_2. The reaction mixture was stirred at room temperature for 16-36 hours (monitored by TLC). After complete consumption of starting materials, solvent was evaporated *in vaccuo* and the residue was purified by column chromatography to afford pure cyclized product **3** using EtOAc (Ethyl acetate)/Hexane as eluent.

2.5.2 General Procedure for the Preparation of Various Benzhydroxamic acid Derivatives.[21]

To the stirred solution of $NH_2OH.HCl$ (1 equiv, 17 mmol), Et_3N (3 equiv, 50 mmol), DMAP (0.05 equiv, 0.84 mmol), in DCM (0.062 M), was added solution of acid chloride (1 equiv, 17 mmol) in DCM (0.187 M) in a dropwise manner at room temperature. The reaction mixture was stirred at room temperature for 16-24 hours (TLC control). After complete consumption of starting material, DCM was evaporated *in vaccuo*. The crude

mixture was purified by silica gel column chromatography to get pure benzhydroxamic acid. All benzhydroxamic acid were prepared according to above mentioned procedure and the product was directly used for the next step.[21]

2.5.3 General Procedure for the Preparation of *N*-(pivaloyloxy) Benzamides.[22,16a]

All *N*-(pivaloyloxy) benzamides were prepared according to literature procedure with benzhydroxamic acid (1 equiv, 0.72 mmol), pivalic anhydride (0.8 equiv, 0.58 mmol), and anhydrous dichloromethane (0.3 M). Spectral data of *N*-(pivaloyloxy) benzamides **1a**,[22] **1b**,[16a] **1f**,[22,16a] **1g**,[22] **1h**,[22,16a] **1i**,[16a] **1j**,[22] **1l**,[22] **1m**[22] were matched with reported values; *N*-(pivaloyloxy) benzamides **1c**, **1d**, **1e**, **1k** were reported first time and their detailed data were given below.

Compound **5**,[23] **6**,[24] **8**,[25]**12**,[26] **13**,[27] **15**,[28] are reported earlier. Compound **7**, **14** and **17** are new compound, whose detailed preparation procedure were given below.

(*E*:*Z*;*1*:*1*)-1,2-dimethoxy-4-(2-methoxyvinyl)-5-vinylbenzene (7).

To the stirred solution of methoxy triphenylphosphoranilide (801 mg, 2.3 mmol, 3 equiv) in anhydrous THF (3 ml) was added potassium *tert*-butoxide (350 mg, 3.1 mmol, 4 equiv) under nitrogen atmosphere. The reaction mixture became deep red in colour, which indicates the formation of methoxy ylide. The deep red colour solution was heated to room temperature and stirred for 20 minute. Thereafter 4,5-dimethoxy-2-vinylbenzaldehyde **6** (150 mg, 0.8 mmol, 1 equiv) in anhydrous THF (2 ml) was added dropwisely to red colour solution of ylide at room temperature. The solution became brownish colour. The reaction mixture was stirred at room temperature for 12 hour. After completion of reaction as indicated by TLC, the reaction was quenched by saturated NH_4Cl. The combined organic layer was extracted by dichloromethane and dried over Na_2SO_4, and concentrated *in vaccuo*. The crude mixture was purified by column chromatography (5% EtOAc in Hexane) to afford pure colourless liquid **7** (124 mg, *Z*:*E*;*1*:*1*, 72%).

1-(2-bromo-4,5-dimethoxyphenyl)but-3-en-2-ol (14).

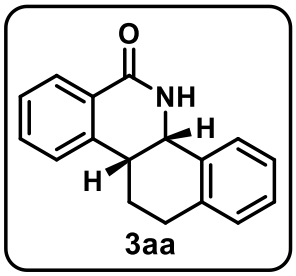
To the stirred solution of 2-(2-bromo-4,5-dimethoxyphenyl)acetaldehyde **13** (50 mg, 0.2 mmol, 1 equiv) in THF (1 ml) was added vinyl magnesium bromide (1 ml, 0.6 mmol, 3 equiv) at room temperature and stirred for 2 hour. Upon completion of starting material as confirmed from TLC, the reaction mixture was quenched by saturated NH_4Cl. The combined organic layer was extracted by dichloromethane and dried over Na_2SO_4, and concentrated *in vaccuo*. The crude mixture was purified by column chromatography (40% EtOAc in Hexane) to afford pure colourless liquid (38 mg, 68%).

{(1-(4,5-dimethoxy-2-vinylphenyl)but-3-en-1-yl)oxy}triisopropylsilane (17).

To the stirred solution of 1-(4,5-dimethoxy-2-vinylphenyl)but-3-en-1-ol **15** (30 mg, 0.1 mmol, 1 equiv) in anhydrous THF (1 ml) was added potassium *tert*-butoxide (36 mg, 0.3 mmol, 2.5 equiv) at ice cold temperature. The reaction mixture was heated to room temperature and stirred for 10 minute. Thereafter triisopropylsilyl chloride (30 mg, 0.1 mmol, 1.2 equiv) in anhydrous THF (2 ml) was added dropwisely at room temperature. The reaction mixture was stirred at room temperature for 12 hour. After completion of reaction as indicated by TLC, the reaction was quenched by saturated NH_4Cl. The combined organic layer was extracted by dichloromethane and dried over Na_2SO_4, and concentrated *in vaccuo*. The crude mixture was purified by column chromatography (5% EtOAc in Hexane) to afford pure colourless liquid **17** (41 mg, *Z*:*E*;*1*:*1*, 82%).

2.5.4 Experimental characterization data:

(4bS,10bR)-4b,10b,11,12-Tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3aa).

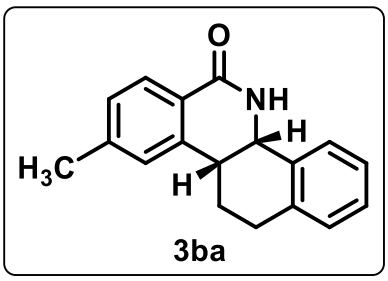


3aa

Physical State: Colourless solid; mp: 179-181 °C; yield: (44 mg, 65%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.2 Hz, 1H), 7.31–7.26 (m, 4H), 7.19 (d, J = 6.8 Hz, 1H), 5.84 (brs, 1H), 4.88 (d, J = 4.0 Hz, 1H), 3.09 (td, J = 12.8, 3.6 Hz, 1H), 2.98–2.94 (m, 2H), 2.25–2.14 (m, 1H), 1.87–1.84 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.8, 142.9, 136.5, 134.1, 132.8, 129.6, 128.9, 128.5, 128.1, 127.4, 127.3, 126.9, 52.0, 38.9, 29.1, 25.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}NO$: 250.1226; found: 250.1229. IR (KBr): 3052, 2985, 1604, 1475, 1260 cm $^{-1}$

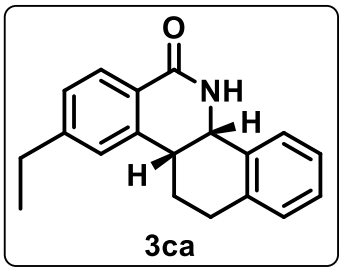
(4bS,10bR)-9-Methyl-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ba).

Physical State: Colourless solid; mp: 159-161 °C; yield: (16 mg, 73%). R_f: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 1H), 7.23–7.18 (m, 3H), 7.13 (t, J = 7.0 Hz, 2H), 7.05 (s, 1H), 5.51 (brs, 1H), 4.80 (d, J = 4.2 Hz, 1H), 2.97 (td, J = 12.6, 2.1 Hz, 1H), 2.90–2.88 (m, 2H), 2.34 (s, 3H), 2.15–2.09 (m, 1H), 1.79–1.76 (m, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 165.0, 143.4, 142.9, 136.5, 134.2, 129.6, 128.9, 128.5, 128.2, 128.1, 127.9, 126.9, 124.7, 52.1, 38.9, 29.1, 25.7, 21.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{18}NO$: 264.1383; found: 264.1391. IR (KBr): 3053, 2986, 1668, 1276, 1260 cm $^{-1}$



3ba

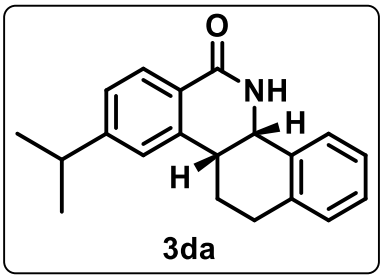
(4bS,10bR)-9-Ethyl-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ca).



3ca

Physical State: Colourless solid; mp: 194-196 °C; yield: (13 mg, 59%). *Rf*: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.04 (d, J = 7.7 Hz, 1H), 7.33–7.31 (m, 1H), 7.28–7.28 (m, 2H), 7.26–7.23 (m, 2H), 7.16 (s, 1H), 5.58 (s, 1H), 4.91 (d, J = 3.5 Hz, 1H), 3.09 (td, J = 12.6, 3.5 Hz, 1H), 3.01–2.99 (m, 2H), 2.74 (q, J = 7.7 Hz, 2H), 2.26–2.20 (m, 1H), 1.90–1.88 (m, 1H), 1.31 (t, J = 7.7 Hz, 3H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 165.1, 149.6, 143.0, 136.6, 134.2, 129.6, 128.9, 128.5, 128.2, 127.1, 126.9, 126.8, 125.0, 52.1, 39.0, 29.1, 29.0, 25.7, 15.2. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{20}NO$: 278.1539; found: 278.1540. IR (KBr): 3052, 2985, 2865, 1663, 1260, 896 cm $^{-1}$

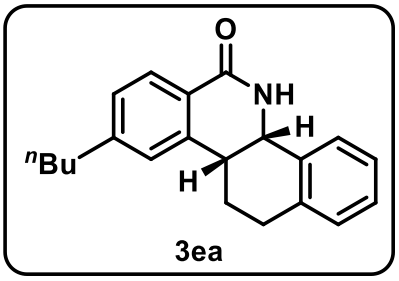
(4bS,10bR)-9-Isopropyl-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3da).



3da

Physical State: Colourless solid; mp: 197-199 °C; yield: (7 mg, 64%). *Rf*: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.0 Hz, 1H), 7.30–7.28 (m, 4H), 7.23 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 1.2 Hz, 1H), 5.71 (brs, 1H), 4.91 (d, J = 4.0 Hz, 1H), 3.13–3.07 (td, J = 12.8, 3.2 Hz, 1H), 3.03–2.96 (m, 3H), 2.29–2.18 (m, 1H), 1.92–1.86 (m, 1H), 1.31 (d, J = 6.8 Hz, 6H). ^{13}C{^{1}H} (100 MHz, $CDCl_3$): δ 165.0, 154.2, 143.0, 136.6, 134.3, 129.6, 128.9, 128.5, 128.2, 126.9, 125.6, 125.3, 125.1, 52.2, 39.1, 34.3, 29.2, 25.8, 23.8, 23.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{22}NO$: 292.1696; found: 292.1684. IR (KBr): 3054, 2986, 2871, 1664, 1260 cm $^{-1}$

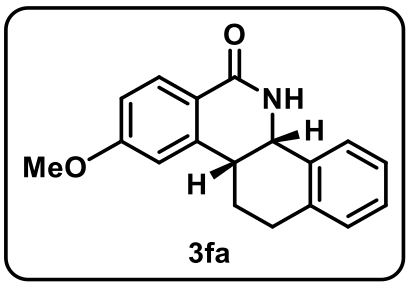
(4bS,10bR)-9-Butyl-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ea).



3ea

Physical State: Colourless solid; mp: 189-191 °C; yield: (13 mg, 61%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.0 Hz, 1H), 7.31–7.26 (m, 3H), 7.21 (d, J = 7.6, 2H), 7.13 (s, 1H), 5.71 (brs, 1H), 4.89 (d, J = 4.0 Hz, 1H), 3.07 (td, J = 20.0, 10.4 Hz, 1H), 2.99–2.95 (m, 2H), 2.67 (t, J = 8.0 Hz, 2H), 2.25–2.14 (m, 1H), 1.88–1.83 (m, 1H), 1.63 (quintet, J = 8.0 Hz, 2H), 1.38 (sextet, J = 7.6 Hz, 2H), 0.94 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ165.2, 148.6, 142.9, 136.5, 134.1, 129.6, 129.0, 128.5, 128.1, 127.6, 127.3, 126.9, 124.6, 52.2, 38.9, 35.8, 33.3, 29.1, 25.8, 22.4, 13.9. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{24}NO$: 306.1852; found: 306.1873. IR (KBr): 3053, 2986, 1663, 1420, 1265 cm $^{-1}$

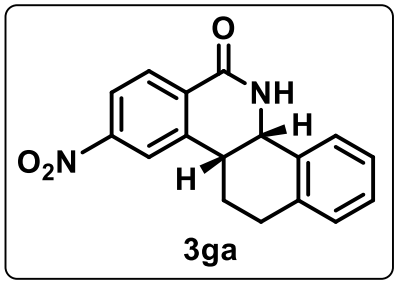
(4bS,10bR)-9-Methoxy-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3fa).



3fa

Physical State: Colourless solid; mp: 177-179 °C; yield: (13 mg, 60%). R_f: 0.30 (in 40% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.8 Hz, 1H), 7.32–7.25 (m, 3H), 7.21 (d, J = 6.8 Hz, 1H), 6.90 (dd, J = 8.4, 2.4 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 5.51 (brs, 1H), 4.88 (d, J = 4.0 Hz, 1H), 3.88 (s, 3H), 3.05 (td, J = 12.8, 3.2 Hz, 1H), 2.99–2.96 (m, 2H), 2.28–2.17 (m, 1H), 1.89–1.84 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.8, 163.1, 145.1, 136.5, 134.2, 130.3, 129.6, 128.9, 128.5, 126.9, 120.2, 112.8, 112.4, 55.4, 52.1, 39.3, 29.1, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{18}NO_2$: 280.1332; found: 280.1308. IR (KBr): 3053, 2986, 1604, 1260, 755 cm $^{-1}$

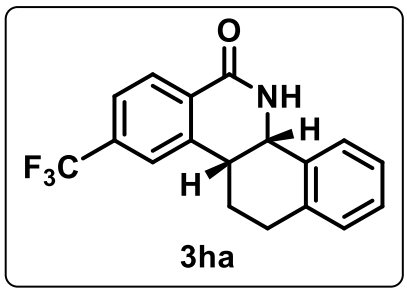
(4bS,10bR)-9-Nitro-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ga).



3ga

Physical State: Colourless solid; mp: 185-187 °C; yield: (15 mg, 70%). R_f: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 4.4 Hz, 1H), 8.22–8.21 (m, 2H), 7.34–7.27 (m, 3H), 7.23 (d, J = 4.4 Hz, 1H), 5.90 (brs, 1H), 4.95 (d, J = 1.6 Hz, 1H), 3.27 (td, J = 7.2, 2.0 Hz, 1H), 3.03–3.01 (m, 2H), 2.27–2.21 (m, 1H), 1.96–1.92 (m, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ162.7, 150.3, 144.4, 136.1, 133.1, 132.6, 129.7, 129.7, 129.0, 128.9, 127.2, 122.6, 122.3, 51.9, 38.9, 28.8, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{15}N_2O_3$: 295.1077; found: 295.1060. IR (KBr): 3052, 2986, 1675, 1531, 750 cm $^{-1}$

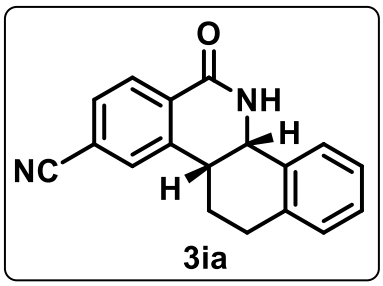
(4bS,10bR)-9-(Trifluoromethyl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ha).



3ha

Physical State: Colourless solid; mp: 169-171 °C; yield: (7 mg, 66%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.36–7.28 (m, 3H), 7.25 (d, J = 7.2 Hz, 1H), 5.83 (brs, 1H), 4.95 (d, J = 4.0 Hz, 1H), 3.21 (td, J = 12.8, 3.6 Hz, 1H), 3.04–3.01 (m, 2H), 2.31–2.20 (m, 1H), 1.95–1.91 (m,1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.4, 143.5, 136.3, 134.3 (q, J = 32.0 Hz), 133.5, 130.5, 129.7, 128.9, 128.82, 128.80, 127.1, 124.4 (q, J = 4.0 Hz), 124.2 (q, J = 3.0 Hz), 123.6 (q, J = 271.0 Hz) , 51.9, 38.9, 28.9, 25.6. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{18}H_{14}F_3NONa$: 340.0920; found: 340.0923. IR (KBr): 3053, 2985, 1674, 1274, 895, 740 cm $^{-1}$

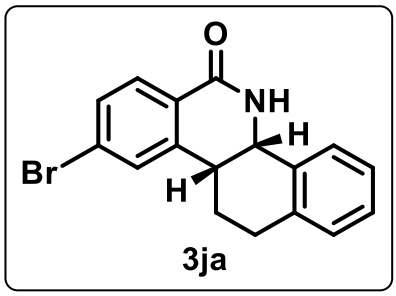
(4bS,10bR)-6-Oxo-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine-9- carbonit rile (3ia).



3ia

Physical State: Colourless solid; mp: 194-196 °C; yield: (8 mg, 72%). R_f: 0.35 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8.0 Hz, 1H), 7.68 (dd, J = 8.4, 1.2 Hz, 1H), 7.65 (s, 1H), 7.33–7.27 (m, 3H), 7.23 (d, J = 7.2 Hz, 1H), 5.77 (brs, 1H), 4.92 (d, J = 4.0 Hz, 1H), 3.18 (td, J = 12.8, 3.2 Hz, 1H), 3.01–2.99 (m, 2H), 2.28–2.17 (m, 1H), 1.91–1.86 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.9, 143.7, 136.2, 133.3, 131.3, 131.2, 131.0, 129.7, 129.0, 128.8, 127.2, 123.6, 118.0, 116.1, 51.8, 38.6, 28.8, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{15}N_2O$: 275.1179; found: 275.1178. IR (KBr): 3053, 2986, 2305, 1604, 1260, 905 cm $^{-1}$

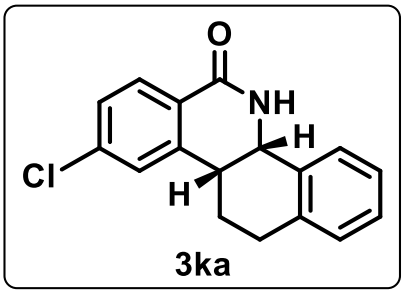
(4bS,10bR)-9-Bromo-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one(3ja*).*



3ja

Physical State: Colourless solid; mp: 175-177 °C; yield: (7 mg, 68%). R_f: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.96 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 7.49 (d, J = 1.4 Hz, 1H), 7.32–7.29 (m, 1H), 7.28–7.24 (m, 2H), 7.21 (d, J = 7.7 Hz, 1H), 5.65 (brs, 1H), 4.89 (d, J = 3.5 Hz, 1H), 3.08 (td, J = 12.6, 4.2 Hz, 1H), 2.97 (m, 2H), 2.24–2.18 (m, 1H), 1.89–1.86 (m, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 164.1, 144.7, 136.3, 133.7, 130.7, 130.4, 129.9, 129.6, 128.9, 128.7, 127.4, 127.0, 126.3, 52.0, 38.7, 28.9, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{15}BrNO$: 328.0332; found: 328.0318. IR (KBr): 3053, 2986, 1660, 1255, 895, 764 cm $^{-1}$

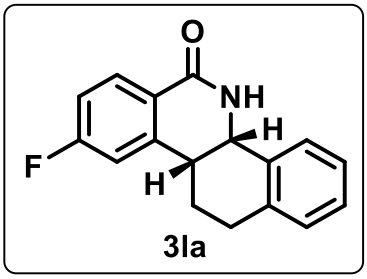
(4bS,10bR)-9-Chloro-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ka).



3ka

Physical State: Colourless solid; mp: 184-186 °C; yield: (8 mg, 74%). *Rf*: 0.50 (in 35% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 10.4, 8.4 Hz, 1H), 7.33–7.26 (m, 4H), 7.22 (d, J = 7.2 Hz, 1H), 5.58 (brs, 1H), 5.30 (DCM), 4.89 (d, J = 4.0 Hz, 1H), 3.08 (td, J = 12.4, 3.2 Hz, 1H), 3.00–2.96 (m, 2H), 2.24–2.17 (m, 1H), 1.91–1.85 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz,): δ 163.9, 144.6, 138.8, 136.3, 133.7, 129.8, 129.7, 128.9, 128.7, 127.8, 127.4, 127.0, 125.9, 52.0, 38.9, 28.9, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{15}NOCl$: 284.0837; found: 284.0834. IR (KBr): 3053, 2986, 1669, 1599, 1276, 898, 765 cm $^{-1}$

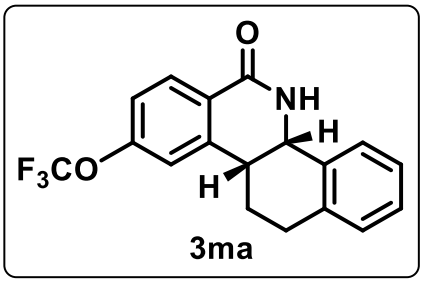
(4bS,10bR)-9-Fluoro-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3la).



3la

Physical State: Colourless solid; mp: 167-169 °C; yield: (8 mg, 71%). *Rf*: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (t, J = 6.8 Hz, 1H), 7.24-7.19 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 7.02-6.96 (m, 2H), 5.67 (brs, 1H), 4.84 (d, J = 4.0 Hz, 1H), 3.02 (td, J = 12.4, 3.6 Hz, 1H), 2.92–2.89 (m, 2H), 2.20–2.09 (m, 1H), 1.82–1.78 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4 (d, J = 266.0 Hz), 164.2, 145.8, 145.7, 136.3, 133.7, 131.0 (d, J = 10.0 Hz), 129.6, 128.9, 128.7, 127.0, 114.7 (d, J = 22.0 Hz), 114.1 (d, J = 22.0 Hz), 52.0, 39.0, 28.9, 25.5. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{15}FNO$: 268.1132; found: 268.1131. IR (KBr): 3053, 2985, 1665, 1265, 900, 749 cm $^{-1}$

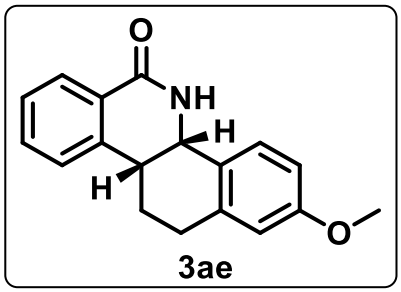
(4bS,10bR)-9-(Trifluoromethoxy)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ma).



3ma

Physical State: Colourless solid; mp: 188-190 °C; yield: (7 mg, 62%). R_f: 0.50 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.4 Hz, 1H), 7.33–7.26 (m, 3H), 7.22 (d, J = 7.3 Hz, 2H), 7.16 (s, 1H), 5.74 (brs, 1H), 4.92 (d, J = 4.4 Hz, 1H), 3.12 (td, J = 12.8, 4.0 Hz, 1H), 3.00–2.97 (m, 2H), 2.28–2.17 (m, 1H), 1.91–1.85 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.6, 152.2, 145.2, 136.3, 133.7, 130.5, 130.0, 128.9, 128.8, 127.1, 125.9, 120.3 (q, J = 257.0 Hz), 119.4, 119.0, 52.0, 39.0, 29.0, 25.6. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{18}H_{14}F_3NO_2Na$: 356.0869; found: 356.0873. IR (KBr): 3053, 2986, 1605, 1270, 770 cm $^{-1}$

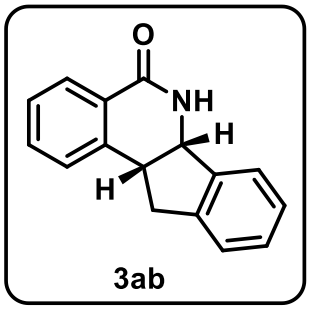
(4bS,10bR)-2-methoxy-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ae).



3ae

Physical State: Colourless solid; mp: 199-201 °C; yield: (47 mg, 63%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.81 (dd, J = 6.0, 2.4 Hz, 1H), 6.72 (s, 1H), 5 .62 (brs, 1H), 4.85 (d, J = 4.0 Hz, 1H), 3.81 (s, 3H), 3.08-3.05 (m, 1H), 2.97-2.93 (m, 2H), 2.24-2.13 (m, 1H), 1.86-1.82 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.8, 159.5, 143.0, 137.9, 132.7, 130.0, 128.7, 128.1, 127.4, 127.3, 126.5, 114.0, 113.1, 55.3, 51.6, 39.1, 29.4, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{18}NO_2$: 280.1332; found: 280.1343. IR (KBr): 3054, 2988, 1653, 898, 738 cm $^{-1}$

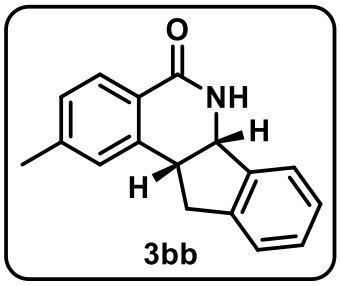
(6aS,11aR)-6,6a,11,11a-Tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3ab).



3ab

Physical State: Colourless solid; mp: 189-191 °C; yield: (8 mg, 79%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.07 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.0 Hz, 1H), 7.33–7.31 (m, 2H), 7.27 (d, J = 7.0 Hz, 1H), 7.24–7.19 (m, 3H), 5.83 (brs, 1H), 5.03 (d, J = 7.0 Hz, 1H), 3.67 (q, J = 7.7 Hz, 1H), 3.26 (dd, J = 15.4, 7.7 Hz, 1H), 3.10 (dd, J = 15.4, 9.1 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ164.1, 143.3, 142.4, 139.9, 132.5, 128.8, 128.4, 127.6, 127.40, 127.4, 126.6, 125.0, 123.9, 58.4, 42.4, 40.1. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{14}NO$: 236.1070; found: 236.1073. IR (KBr): 3052, 2987,1667, 1264 cm $^{-1}$

(6aS,11aR)-2-Methyl-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3bb).

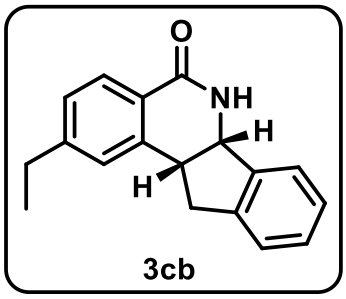


3bb

Physical State: Colourless solid; mp: 200-202 °C; yield: (8 mg, 75%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.95 (d, J = 7.6 Hz, 1H), 7.33–7.31 (m, 1H), 7.23–7.19 (m, 3H), 7.12 (d, J = 7.6 Hz, 1H), 7.07 (s, 1H), 5.79 (brs, 1H), 5.01 (d, J = 6.4 Hz, 1H), 3.62 (q, J = 8.0 Hz, 1H), 3.24 (dd, J = 15.6, 8.0 Hz, 1H), 3.08 (dd, J = 15.6, 9.2 Hz, 1H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.3, 143.3, 143.1, 142.5, 139.9, 128.7, 128.5, 128.25, 128.20, 127.3, 124.9, 123.9, 58.4, 42.4, 40.0, 21.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}NO$: 250.1226; found: 250.1214. IR (KBr): 3055, 2986, 1600, 1275, 1265 cm $^{-1}$

(6aS,11aR)-2-Ethyl-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3cb).

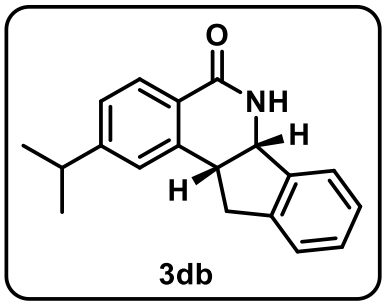
Physical State: Colourless solid; mp: 184-186 °C; yield: (8 mg, 76%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 6.8



3cb

Hz, 1H), 7.31–7.28 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 5.79 (brs, 1H), 5.09 (d, *J* = 6.4 Hz, 1H), 3.71 (q, *J* = 8.0 Hz, 1H), 3.33 (dd, 15.6, 8 Hz, 1H), 3.16 (dd, *J* = 15.6, 9.6 Hz, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 164.3, 149.5, 143.4, 142.4, 140.0, 128.8, 128.6, 127.4, 127.1, 127.0, 125.0, 123.9, 123.8, 58.5, 42.5, 40.1, 28.9, 15.2. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{18}NO$: 264.1383; found : 264.1389. IR (KBr): 3053, 2988, 2830, 1653, 1269, 895 cm^{-1}

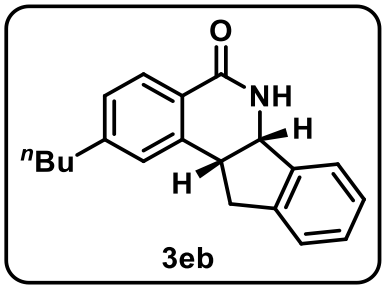
(6aS,11aR)-2-Isopropyl-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3db).



3db

Physical State: Colourless solid; mp: 201-203 °C; yield: (5 mg, 52%). *Rf*: 0.50 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.30–7.27 (m, 3H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 5.71 (brs, 1H), 5.30 (DCM), 4.68–4.66 (m, 1H), 4.36 (d, *J* = 5.2 Hz, 1H), 3.35 (dd, *J* = 16.4, 5.2 Hz, 1H), 3.06–2.99 (m, 1H), 2.94 (d, *J* = 15.6 Hz, 1H), 1.34 (d, *J* = 1.2 Hz, 3H), 1.33 (d, *J* = 1.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ165.1, 153.9, 142.3, 139.9, 137.6, 128.6, 127.5, 126.9, 126.3, 125.8, 125.0, 124.8, 124.2, 56.0, 47.4, 40.9, 34.3, 23.8, 23.8. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{20}NO$: 278.1539; found: 278.1550. IR (KBr): 3054, 2986, 1646, 1268 cm^{-1}

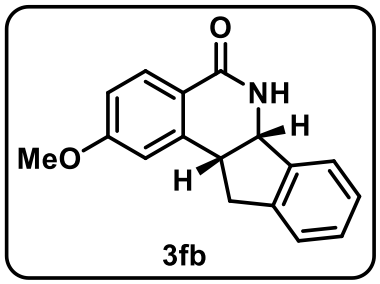
(6aS,11aR)-2-Butyl-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3eb). Physical State: Colourless solid; mp: 169-171 °C; yield: (6 mg, 62%). *Rf*: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 6.4



3eb

Hz, 1H), 7.31–7.27 (m, 3H), 7.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.14 (s, 1H), 5.86 (brs, 1H), 5.08 (d, *J* = 6.4 Hz, 1H), 3.70 (q, *J* = 8.0 Hz, 1H), 3.32 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.16 (dd, *J* = 15.6, 9.6 Hz, 1H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.63 (pentet, *J* = 7.6 Hz, 2H), 1.38 (sextet, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 164.4, 148.4, 143.3, 142.3, 139.9, 128.8, 128.5, 127.7, 127.6, 127.4, 125.0, 123.9, 123.5, 58.5, 42.4, 40.1, 35.7, 33.3, 22.4, 13.9. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{22}NO$: 292.1696; found: 292.1677. IR (KBr): 3060, 2985, 1663, 1422, 1268 cm^{-1}

(6aS,11aR)-2-Methoxy-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one(3fb).

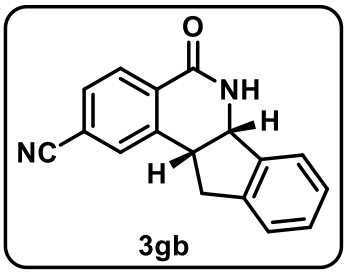


3fb

Physical State: Colourless solid; mp: 195-197 °C; yield: (6 mg, 53%). *R_f*: 0.30 (in 40% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 6.4 Hz, 1H), 7.24–7.19 (m, 3H), 6.84 (dd, *J* = 8.4, 2.0 Hz 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 5.96 (brs, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 3.64 (q, *J* = 8.0 Hz, 1H), 3.27 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.10 (dd, *J* = 16.0, 9.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1, 162.9, 143.2, 142.6, 142.0, 130.6, 128.7, 127.4, 125.0, 123.8, 119.3, 112.8, 112.7, 58.5, 55.4, 42.8, 40.0. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}NO_2$: 266.1176; found: 266.1185. IR (KBr): 3059, 2986, 1660, 1276, 750 cm^{-1}

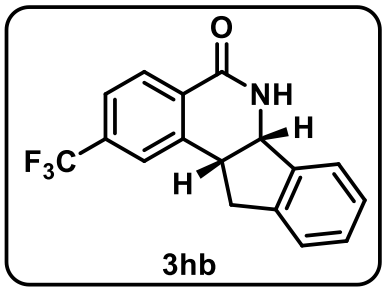
(6aS,11aR)-5-Oxo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinoline-2-carbonitrile (3gb).

Physical State: Colourless solid; mp: 203-206 °C; yield: (7 mg, 70%). *R_f*: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.6 Hz, 1H), 7.68–7.66 (m,



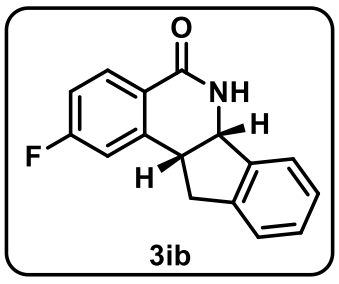
2H), 7.40 (d, *J* = 6.8 Hz, 1H), 7.52–7.30 (m, 3H), 5.94 (brs, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 3.78 (q, *J* = 7.6 Hz, 1H), 3.38 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.17 (dd, *J* = 15.6, 9.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 162.2, 143.5, 142.5, 141.6, 140.9, 131.5, 130.9, 130.3, 129.2, 129.2, 127.8, 125.1, 123.9, 118.0, 58.3, 41.8, 39.8. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$: 261.1022; found: 261.1026. IR (KBr): 3068, 2979, 2303, 1652, 1260, 900 cm^{-1}

(6aS,11aR)-2-(Trifluoromethyl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3hb).



Physical State: Colourless solid; mp: 199-201 °C; yield: (15 mg, 73%). *Rf*: 0.50 (in 30% EtOAc/Hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.33–7.29 (m, 3H), 5.99 (brs, 1H), 5.13 (d, *J* = 6.3 Hz, 1H), 3.80 (q, *J* = 7.7 Hz, 1H), 3.39 (dd, *J* = 15.4, 7.7 Hz, 1H), 3.18 (dd, *J* = 16.1, 9.8 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 162.8, 142.8, 141.9, 140.7, 134.1 (q, *J* = 31.5 Hz), 129.8, 129.2, 129.0, 127.6, 125.1, 124.7 (q, *J* = 5.2 Hz), 124.2 (q, *J* = 3.5 Hz), 123.9, 123.6 (q, *J* = 271.0 Hz), 58.4, 42.2, 39.9. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}F_3NO$: 304.0944; found: 304.0935. IR (KBr): 3056, 2983, 1670, 1264, 903, 742 cm^{-1}

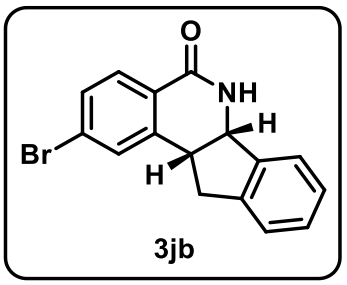
(6aS,11aR)-2-Fluoro-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3ib).



Physical State: Colourless solid; mp: 191-193 °C; yield: (8 mg, 72%). *Rf*: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.40 (d, *J* = 6.4 Hz, 1H), 7.32–7.28 (m, 3H), 7.09–7.02 (m, 2H), 5.95 (brs,

1H), 5.11 (d, *J* = 6.4 Hz, 1H), 3.73 (dd, *J* = 14.8, 8.0 Hz, 1H), 3.53 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.17 (dd, *J* = 15.6, 9.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 165.4 (d, *J* = 253.7 Hz), 163.5, 142.9 (d, *J* = 8.7 Hz), 142.7, 141.9, 131.4 (d, *J* = 8.7 Hz), 129.0, 127.6, 125.0, 124.0, 122.5, 114.8 (d, *J* = 21.0 Hz), 114.4 (d, *J* = 22.7 Hz), 58.5, 42.3, 39.8. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}FNO$: 254.0976; found: 254.0984. IR (KBr): 3051, 2986, 1668, 1275, 902, 756 cm^{-1}

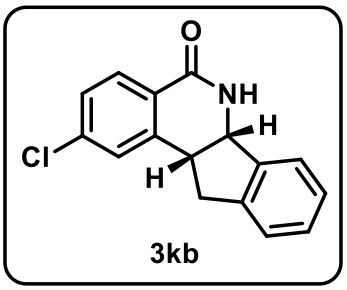
(6aS,11aR)-2-Bromo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3jb).



3jb

Physical State: Colourless solid; mp: 200-202 °C; yield: (7 mg, 69%). *Rf*: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.53–7.51 (m, 2H), 7.39 (d, *J* = 6.8 Hz, 1H), 7.32–7.27 (m, 3H), 5.83 (brs, 1H), 5.09 (d, *J* = 6.4 Hz, 1H), 3.71 (q, *J* = 7.2 Hz, 1H), 3.34 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.16 (dd, *J* = 15.6, 9.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 163.3, 142.8, 142.0, 141.8, 130.8, 130.6, 130.2, 128.9, 127.5, 127.3, 125.4, 125.0, 123.9, 58.4, 42.1, 39.9. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}BrNO$: 314.0175; found: 314.0172. IR (KBr): 3062, 2987, 1669, 1263, 890, 738 cm^{-1}

(6aS,11aR)-2-Chloro-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3kb).

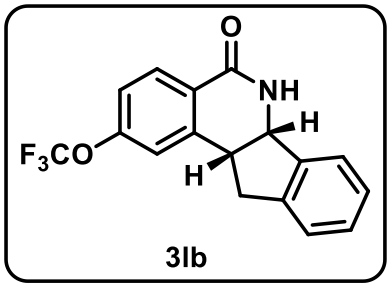


3kb

Physical State: Colourless solid; mp: 189-191 °C; yield: (8 mg, 78%). *Rf*: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.40–7.27 (m, 6H), 5.96 (brs, 1H), 5.09 (d, *J* = 6.4 Hz, 1H), 3.71 (q, *J* = 8.0 Hz, 1H), 3.34 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.16 (dd, *J* = 16.0, 9.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1, 141.5, 139.8, 139.3, 138.6, 130.1, 128.2, 127.9, 127.8, 127.2, 125.7,

125.2, 124.3, 55.9, 46.8, 40.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}ClNO$: 270.0680; found: 270.0672. IR (KBr): 3053, 2979, 1660, 1590, 1275, 890, 750 cm^{-1}

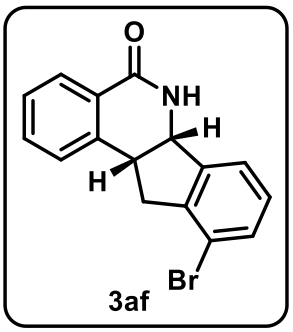
(6aS,11aR)-2-(Trifluoromethoxy)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3lb).



3lb

Physical State: Colourless solid; mp: 185-187 °C; yield: (14 mg, 69%). *Rf*: 0.50 (in 30% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8.8 Hz, 1H), 7.42–7.40 (m, 1H), 7.32–7.28 (m, 3H), 7.21 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 6.03 (brs, 1H), 5.12 (d, J = 6.4 Hz, 1H), 3.75 (q, J = 8.0 Hz, 1H), 3.36 (dd, J = 15.6, 7.6 Hz, 1H), 3.18 (dd, J = 16.0, 9.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.1, 152.10, 152.08, 142.5, 142.3, 142.1, 130.7, 128.8, 127.5, 125.1, 124.9, 124.1, 120.3 (q, J = 256.0 Hz), 119.2, 58.3, 42.0, 39.8. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{17}H_{12}F_3NO_2Na$: 342.0712; found: 342.0722. IR (KBr): 3050, 2985, 1630, 1275, 775 cm^{-1}

(6aS,11aR)-10-bromo-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3af).

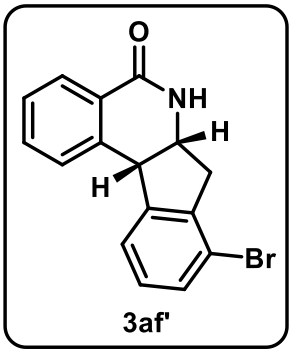


3af

Physical State: Colourless solid; mp: 199-201 °C; yield: (29 mg, 71%). *Rf*: 0.35 (in 30% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.2 Hz, 1H), 7.55-7.51(m, 1H), 7.45-7.34 (m, 4H), 7.15 (t, J = 7.6 Hz, 1H), 6.33 (brs, 1H), 5.18 (d, J = 6.8 Hz, 1H), 3.79 (q, J = 8.0 Hz, 1H), 3.43 (dd, J = 16.4, 8.0 Hz, 1H), 3.16 (dd, J = 16.4, 8.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1, 144.2, 143.5, 139.3, 132.7, 131.8, 129.2, 128.4, 127.6, 127.5, 126.5, 122.8, 120.1, 59.2, 41.2, 41.1. HRMS

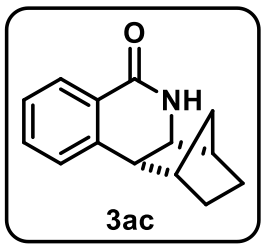
(ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}BrNO$: 314.0175; found: 314.0183. IR (KBr): 3053, 2986, 1604, 898, 751 cm^{-1}

(6aR,11bS)-8-bromo-6,6a,7,11b-tetrahydro-5*H*-indeno[2,1-*c*]isoquinolin-5-one (3af').



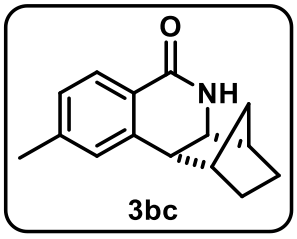
Physical State: Colourless solid; mp: 200-202 °C; yield: (11 mg, 20%). R_f: 0.35 (in 30% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, J = 7.6, 1.2 Hz, 1H), 7.62-7.57 (m, 1H), 7.46-7.31 (m, 2H), 7.36 (td, J = 7.6, 1.0 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.93-6.91 (m, 1H), 6.04 (brs, 1H), 4.68 (t, J = 5.2 Hz, 1H), 4.45 (d, J = 5.6, 1.2 Hz, 1H), 3.32 (dd, J = 16.8, 5.2 Hz, 1H), 3.06 (dd, J = 16.4, 1.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.7, 144.1, 140.5, 136.8, 132.6, 130.7, 128.8, 128.6, 128.2, 127.9, 127.1, 123.2, 120.4, 55.0, 48.1, 42.1. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}BrNO$: 314.0175; found: 314.0167. IR (KBr): 3059, 2986, 1653, 898, 778 cm^{-1}

(1S,4R,4aS,10bS)-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3ac).



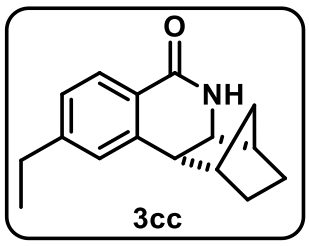
Physical State: Colourless solid; mp: 190-192 °C; yield: (9 mg, 94%). R_f: 0.30 (in 30% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.6 Hz, 1H), 7.46–7.42 (m, 1H), 7.29–7.20 (m, 2H), 7.02 (brs, 1H), 3.81 (d, J = 8.4 Hz, 1H), 3.10 (d, J = 8.8 Hz, 1H), 2.31 (s, 1H), 2.29 (s, 1H), 1.66–1.64 (m, 3H), 1.54–1.50 (m, 1H), 1.35–1.31 (m, 1H), 1.18–1.15 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.9, 140.3, 132.2, 128.3, 127.1, 126.2, 125.8, 58.1, 47.7, 46.0, 43.9, 32.3, 30.0, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{16}NO$: 214.1226; found: 214.1235. IR (KBr): 3052, 2987,1667, 1264 cm^{-1}

(1S,4R,4aS,10bS)-9-methyl-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3bc).



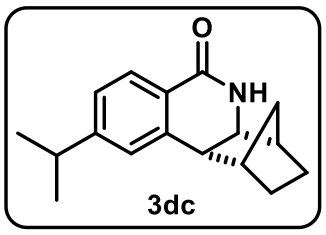
Physical State: Colourless solid; mp: 185-187 °C; yield: (18 mg, 93%). *Rf*: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 4.9 Hz, 1H), 7.02 (s, 1H), 6.69 (brs, 1H), 3.80 (d, J = 8.4 Hz, 1H), 3.07 (d, J = 9.1, 1H), 2.36 (s, 3H), 2.32 (s, 1H), 2.27 (s, 1H), 1.66–1.60 (m, 3H), 1.50 (t, J = 6.3, 1H), 1.34–1.31 (m, 1H), 1.17 (d, J = 10.5, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 164.2, 143.2, 140.3, 128.9, 127.4, 127.3, 122.6, 58.3, 47.7, 46.2, 44.0, 32.4, 30.0, 25.7, 21.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{18}NO$: 228.1383; found: 228.1381. IR (KBr): 3055, 2986, 1603, 1275, 1261 cm $^{-1}$

(1S,4R,4aS,10bS)-9-ethyl-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3cc).



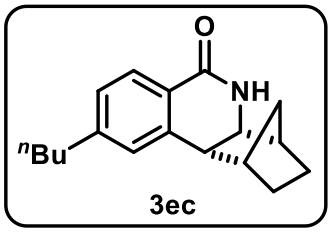
Physical State: Colourless solid; mp: 196-198 °C; yield: (18 mg, 96%). *Rf*: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.69 (brs, 1H), 3.78 (d, J = 8.8 Hz, 1H), 3.07 (d, J = 8.8 Hz, 1H), 2.65 (q, J = 7.6 Hz, 2H), 2.31 (s, 1H), 2.25 (s, 1H), 1.69–1.58 (m, 3H), 1.53–1.49 (m, 1H), 1.33–1.29 (m, 1H), 1.24 (t, J = 7.6 Hz, 3H), 1.16 (td, J = 10.4, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 164.2, 149.1, 140.4, 127.7, 127.4, 126.1, 123.3, 58.2, 47.7, 46.2, 44.1, 32.4, 30.0, 28.8, 25.6, 15.1. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}NO$: 242.1539; found: 242.1537. IR (KBr): 3052, 2980, 2830, 1660, 1265, 897 cm $^{-1}$

(1S,4R,4aS,10bS)-9-isopropyl-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3dc).



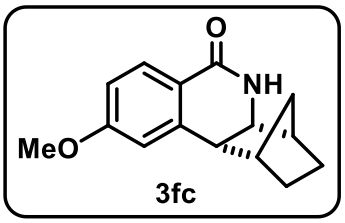
Physical State: Colourless solid; mp: 190-192 °C; yield: (19 mg, 92%). R_f: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 1H), 7.14 (dd, J = 8.0, 1.6 Hz, 1H), 7.05 (s, 1H), 6.45 (brs, 1H), 3.79 (d, J = 9.2 Hz, 1H), 3.09 (d, J = 9.2 Hz, 1H), 2.90 (heptet, J = 6.8 Hz, 1H), 2.32 (s, 1H), 2.24 (s, 1H), 1.67–1.59 (m, 3H), 1.55–1.50 (m, 1H), 1.34–1.30 (m, 1H), 1.26 (d, J = 0.8 Hz, 3H), 1.24 (d, J = 0.4 Hz, 3H), 1.71 (td, J = 10.8, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 164.1, 153.9, 140.4, 127.4, 126.3, 124.8, 123.1, 58.3, 47.8, 46.2, 44.2, 34.2, 32.4, 30.1, 25.6, 23.7, 23.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{22}NO$: 256.1696; found: 256.1695. IR (KBr): 3054, 2986, 2871, 1664, 1265 cm $^{-1}$

(1S,4R,4aS,10bS)-9-butyl-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3ec).



Physical State: Colourless solid; mp: 191-193 °C; yield: (19 mg, 90%). R_f: 0.30 (in 40% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 6.60 (brs, 1H), 3.79 (d, J = 8.8 Hz, 1H), 3.07 (d, J = 8.8 Hz, 1H), 2.61 (t, J = 8.0 Hz, 2H), 2.31 (s, 1H), 2.25 (s, 1H), 1.66–1.55 (m, 5H), 1.53–1.49 (m, 1H), 1.39–1.29 (m, 3H), 1.16 (d, J = 10.4 Hz, 1H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.1, 147.9, 140.3, 128.2, 127.3, 126.7, 123.1, 58.3, 47.7, 46.2, 44.1, 35.7, 33.2, 32.4, 30.0, 25.6, 22.3, 13.9. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{24}NO$: 270.1852; found: 270.1871. IR (KBr): 3060, 2985, 1663, 1422, 1268 cm $^{-1}$

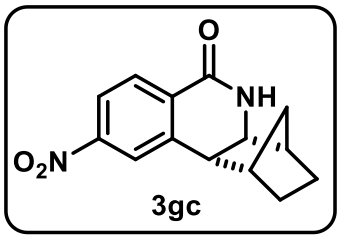
(1S,4R,4aS,10bS)-9-methoxy-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3fc).



3fc

Physical State: Colourless solid; mp: 199-201 °C; yield: (18 mg, 95%). *Rf*: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.8, 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.34 (brs, 1H), 3.84 (s, 3H), 3.78 (d, J = 8.8 Hz, 1H), 3.07 (d, J = 8.8 Hz, 1H), 2.33 (s, 1H), 2.24 (s, 1H), 1.67–1.61 (m, 3H), 1.53–1.49 (m, 1H), 1.33–1.29 (m, 1H), 1.17 (dd, J = 10.4, 0.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.9, 162.9, 142.5, 129.5, 118.3, 112.9, 112.4, 58.3, 55.3, 47.7, 46.2, 44.4, 32.5, 30.0, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$: 244.1332; found: 244.1334. IR (KBr): 3060, 2980, 1666, 1276,760 cm $^{-1}$

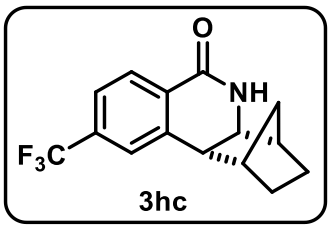
(1S,4R,4aS,10bS)-9-nitro-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3gc).



3gc

Physical State: Colourless solid; mp: 202-204 °C; yield: (15 mg, 78%). *Rf*: 0.30 (in 40% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.4 Hz, 1H), 8.11–8.08 (m, 2H), 6.42 (brs, 1H), 3.88 (d, J = 8.8 Hz, 1H), 3.22 (d, J = 8.8 Hz, 1H), 2.39 (s, 1H), 2.29 (s, 1H), 1.74–1.69 (m, 2H), 1.60 (t, J = 10.0 Hz, 2H), 1.40–1.36 (m, 1H), 1.26 (d, J = 10.8 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 161.7, 150.3, 142.1, 130.9, 129.1, 123.7, 121.2, 58.4, 48.0, 46.1, 44.1, 32.4, 29.9, 25.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1077; found: 259.1095. IR (KBr): 3062, 2979, 1656, 1530, 745 cm $^{-1}$

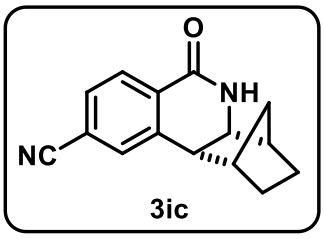
(1S,4R,4aS,10bS)-9-(trifluoromethyl)-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenan thridin-6(2*H*)-one (3hc).



3hc

Physical State: Colourless solid; mp: 201-203 °C; yield: (18 mg, 93%). *Rf*: 0.30 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 6.85 (brs, 1H), 3.85 (d, J = 8.8 Hz, 1H), 3.16 (d, J = 8.8 Hz, 1H), 2.34 (s,1H), 2.30 (s, 1H), 1.71–1.66 (m, 2H), 1.63–1.61 (m, 1H), 1.57–1.53 (m, 1H), 1.38–1.34 (m, 1H), 1.23 (td, J = 10.8, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 162.6, 141.1, 134.1 (q, J = 64.7 Hz), 128.6, 128.1, 125.5 (q, J = 3.5 Hz), 123.6 (q, J = 271.2 Hz), 123.1 (q, J = 3.5 Hz), 58.3, 47.9, 46.1, 44.0, 32.4, 30.0, 25.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{15}F_3NO$: 282.1100; found: 282.1118. IR (KBr): 3055, 2984, 1671, 1265, 904, 746 cm^{-1}

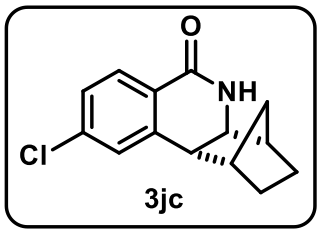
(1S,4R,4aS,10bS)-6-oxo-1,2,3,4,4a,5,6,10*b*-octahydro-1,4-methanophenanthridine-9-carbonitrile (3ic).



3ic

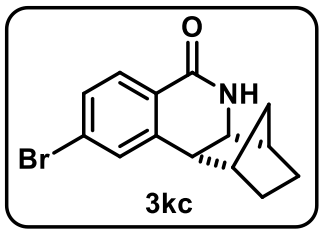
Physical State: Colourless solid; mp: 200-202 °C; yield: (17 mg, 91%). *Rf*: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 6.4 Hz, 2H), 7.04 (brs, 1H), 3.85 (d, J = 8.4 Hz, 1H), 3.13 (d, J = 8.8 Hz, 1H), 2.31 (s, 2H), 1.71–1.68 (m, 2H), 1.60–1.53 (m, 2H), 1.38–1.34 (m, 1H), 1.23 (d, J = 10.4 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 162.1, 141.4, 132.4, 129.7, 129.4, 128.1, 118.1, 115.9, 58.2, 48.0, 46.0, 43.6, 32.4, 29.9, 25.6. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{15}H_{14}N_2ONa$: 261.0998; found: 261.1008. IR (KBr): 3069, 2976, 2301, 1650, 1265, 900 cm^{-1}

(1S,4R,4aS,10bS)-9-chloro-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3jc).



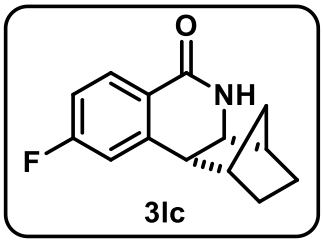
Physical State: Colourless solid; mp: 198-200 °C; yield: (17 mg, 88%). R_f: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H), 7.24–7.22 (m, 2H), 6.74 (brs, 1H), 3.81 (d, J = 8.4 Hz, 1H), 3.07 (d, J = 8.8 Hz, 1H), 2.32 (s, 1H), 2.26 (s, 1H), 1.68–1.60 (m, 3H), 1.52–1.48 (m, 1H), 1.34–1.30 (m, 1H), 1.19 (d, J = 10.8 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 163.2, 142.2, 138.5, 129.0, 128.3, 126.8, 124.4, 58.3, 47.7, 46.1, 43.9, 32.4, 29.9, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}ClNO$: 248.0837; found: 248.0830. IR (KBr): 3054, 2978, 1669, 1560,1274, 870, 780 cm $^{-1}$

(1S,4R,4aS,10bS)-9-bromo-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3kc).



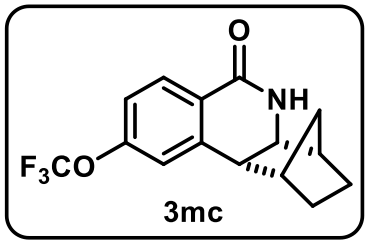
Physical State: Colourless solid; mp: 201-203 °C; yield: (17 mg, 88%). R_f: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.4 Hz, 1H), 7.41–7.39 (m, 2H), 6.62 (brs, 1H), 3.81 (d, J = 8.8 Hz, 1H), 3.08 (d, J = 8.8 Hz, 1H), 2.33 (s, 1H), 2.26 (s, 1H), 1.69–1.60 (m ,3H), 1.53–1.50 (m, 1H), 1.35–1.31 (m, 1H), 1.21 (d, J = 10.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.9, 142.3, 131.3, 129.8, 129.3, 127.1, 124.9, 58.5, 47.7, 46.3, 44.0, 32.4, 30.0, 25.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}BrNO$: 292.0332; found: 292.0337. IR (KBr): 3062, 2986, 1666, 1263, 895, 739 cm $^{-1}$

(1S,4R,4aS,10bS)-9-fluoro-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophenanthridin-6(2*H*)-one (3lc).



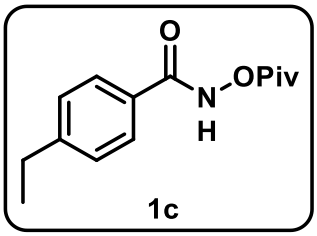
Physical State: Colourless solid; mp: 203-205 °C; yield: (15 mg, 77%). *Rf*: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 8.4, 6.0 Hz, 1H), 6.97–6.88 (m, 2H), 6.63 (brs, 1H), 3.82 (d, *J* = 8.8 Hz, 1H), 3.09 (d, *J* = 8.8 Hz, 1H), 2.31 (s, 1H), 2.27 (s, 1H), 1.68–1.61 (m, 3H), 1.53–1.49 (m, 1H), 1.34–1.30 (m, 1H), 1.20 (d, *J* = 10.4 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 165.3 (d, *J* = 252.0 Hz), 163.0, 143.3 (d, *J* = 8.7 Hz), 130.2 (d, *J* = 8.7 Hz), 122.3, 114.7 (d, *J* = 21.0 Hz), 113.9 (d, *J* = 21.0 Hz), 58.3, 47.7, 46.2, 44.3, 32.4, 29.9, 25.6. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{14}FNONa$: 254.0952; found: 254.0951. IR (KBr): 3052, 2986, 1665, 1276, 903, 758 cm $^{-1}$

(1S,4R,4aS,10bS)-9-(trifluoromethoxy)-1,3,4,4a,5,10*b*-hexahydro-1,4-methanophe nanthridin-6(2*H*)-one (3mc).



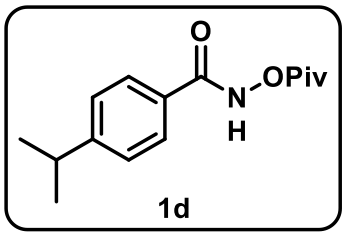
Physical State: Colourless solid; mp: 199-201 °C; yield: (18 mg, 97%). *Rf*: 0.50 (in 30% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H), 6.91 (brs, 1H), 3.82 (d, *J* = 8.8 Hz, 1H), 3.10 (d, *J* = 8.8 Hz, 1H), 2.30–2.28 (m, 2H), 1.69–1.61 (m, 3H), 1.54–1.50 (m, 1H), 1.35–1.31 (m, 1H), 1.22–1.19 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.8, 152.1 (q, *J* = 2.0 Hz), 142.8, 129.7, 124.4, 120.3 (q, *J* = 256.0 Hz), 119.9, 118.5, 58.3, 47.8, 46.1, 44.2, 32.4, 30.0, 25.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{15}F_3NO_2$: 298.1049; found: 298.1058. IR (KBr): 3056, 2985, 1635, 1273, 770 cm $^{-1}$

4-Ethyl-*N*-(pivaloyloxy)benzamide (1c).



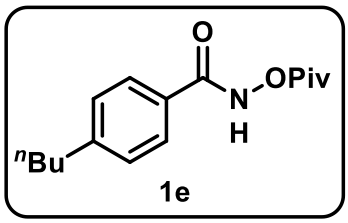
Physical State: Colourless solid; mp: 123-125 °C; yield: (106 mg, 70%). R_f: 0.60 (in 10% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (brs, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.6 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.26 (s, 9H), 1.15 (t, J = 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 177.0, 166.8, 149.4, 128.2, 128.1, 127.5, 38.4, 28.8, 27.0, 15.1. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{19}NO_3Na$: 272.1239; found: 272.1257. IR (KBr): 3006, 2985, 1635, 1447, 1273, 1007 cm $^{-1}$

4-Isopropyl-*N*-(pivaloyloxy)benzamide (1d).



Physical State: Colourless solid; mp: 130-132 °C; yield: (91 mg, 62%). R_f: 0.50 (in 10% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (brs, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 2.96 (septet, J = 6.8 Hz, 1H), 1.36 (s, 9H), 1.26 (d, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.1, 166.9, 154.2, 128.4, 127.6, 126.9, 38.4, 34.2, 27.0, 23.7. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{15}H_{21}NO_3Na$: 286.1424; found: 286.1414. IR (KBr): 3021, 2960, 1632, 1260, 1430, 1021 cm $^{-1}$

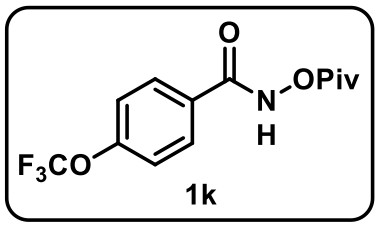
4-Butyl-*N*-(pivaloyloxy)benzamide (1e).



Physical State: Colourless solid; mp: 140-142 °C; yield: (106 mg, 74%). R_f: 0.40 (in 10% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (brs, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H), 1.59 (pentet, J = 8.0 Hz, 2H), 1.37-1.30 (m, 11H), 0.92 (t, J = 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.0, 166.8, 148.2, 128.7, 128.1, 127.5, 38.4, 35.6, 33.2, 27.0, 22.2, 13.8. HRMS

(ESI) m/z: $[M+Na]^+$ calcd for $C_{16}H_{23}NO_3Na$: 300.1570; found: 300.1572. IR (KBr): 3000, 2965, 1600, 1275, 1400, 1004 cm^{-1}

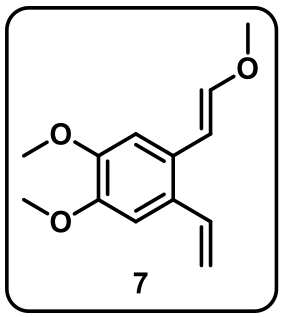
***N*-(Pivaloyloxy)-4-(trifluoromethoxy)benzamide (1k).**



Physical State: Colourless solid; mp: 133-135 °C; yield: (90 mg, 65%). R_f: 0.30 (in 10% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (brs, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.9, 165.4, 152.2, 129.4, 129.1, 120.6, 120.2 (q, J = 257.0 Hz), 38.4, 26.9. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}F_3NO_4Na$: 328.0767; found: 328.0761. IR (KBr): 3050, 2970, 1635, 1260, 1430, 1010 cm^{-1}

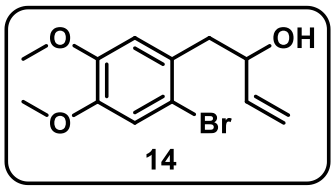
<u>Spectral data of starting materials used in total synthesis approach</u>:-

(E:Z;1:1)-1,2-dimethoxy-4-(2-methoxyvinyl)-5-vinylbenzene (7).



Colourless liquid; yield: (124 mg, 72%). R_f: 0.40 (in 5% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 6.99–6.93 (m, 3H), 6.90 (d, J = 10.8 Hz, 1H), 6.76 (d, J = 12.8 Hz, 1H), 6.73 (s, 1H), 6.13 (d, J = 7.2 Hz, 1H), 5.98 (d, J = 12.8 Hz, 1H), 5.56–5.49 (m, 2H), 5.39 (d, J = 7.2 Hz, 1H), 5.22 (dd, J = 2.8, 1.2 Hz, 1H), 5.19 (dd, J = 2.8, 1.2 Hz, 1H), 3.89 (s, 6H), 3.88 (s, 6H), 3.74 (s, 3H), 3.69 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.3, 148.9, 148.3, 147.7, 147.3, 146.9, 134.7, 134.6, 128.4, 127.9, 127.1, 126.2, 113.6, 113.4, 112.1, 109.1, 108.7, 108.4, 102.6, 102.1, 60.5, 56.5, 55.9, 55.84, 55.76, 55.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{17}O_3$: 221.1172; found: 221.1171.

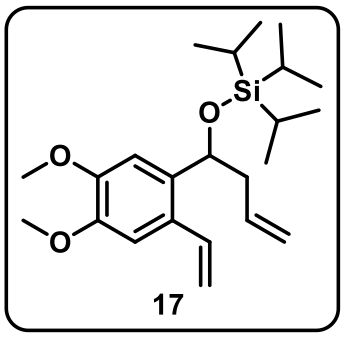
1-(2-bromo-4,5-dimethoxyphenyl)but-3-en-2-ol (14).



14

Colourless liquid; yield: (38 mg, 68%). *Rf*: 0.40 (in 5% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.78 (s, 1H), 6.00–5.92 (m, 1H), 5.27 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.14 (dt, *J* = 10.2, 1.2 Hz, 1H), 4.45–4.40 (m, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 2.97 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.83 (dd, *J* = 14.0, 8.4 Hz, 1H), 3.85 (brs, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.3, 148.2, 140.0, 129.3, 115.6, 116.0, 114.6, 114.4, 72.4, 56.1, 56.0, 43.3. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{12}H_{15}BrO_3$: 309.0097; found: 309.0071.

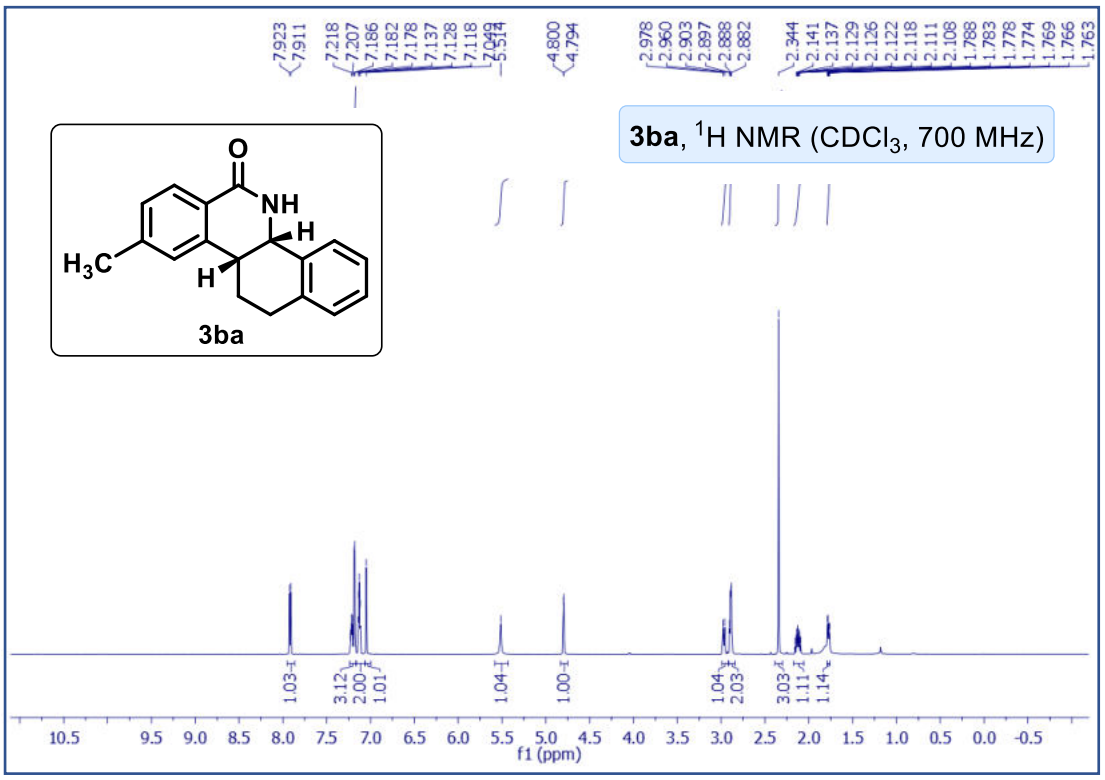
{(1-(4,5-dimethoxy-2-vinylphenyl)but-3-en-1-yl)oxy}triisopropylsilane (17).

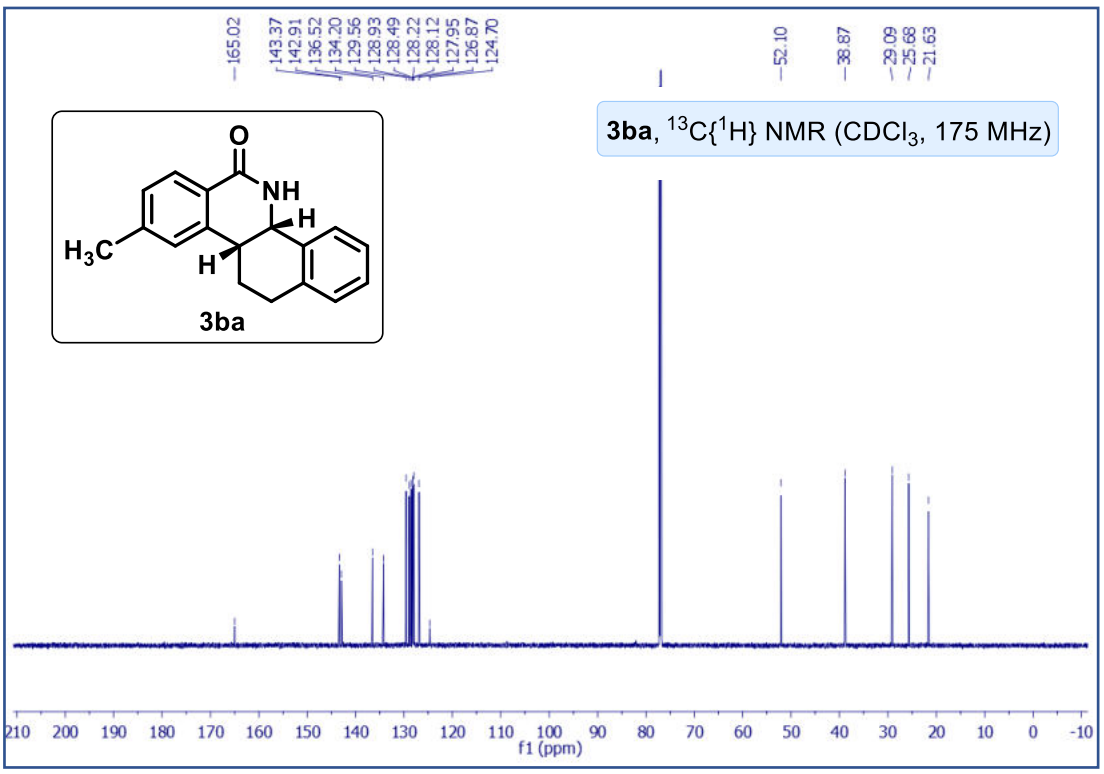


17

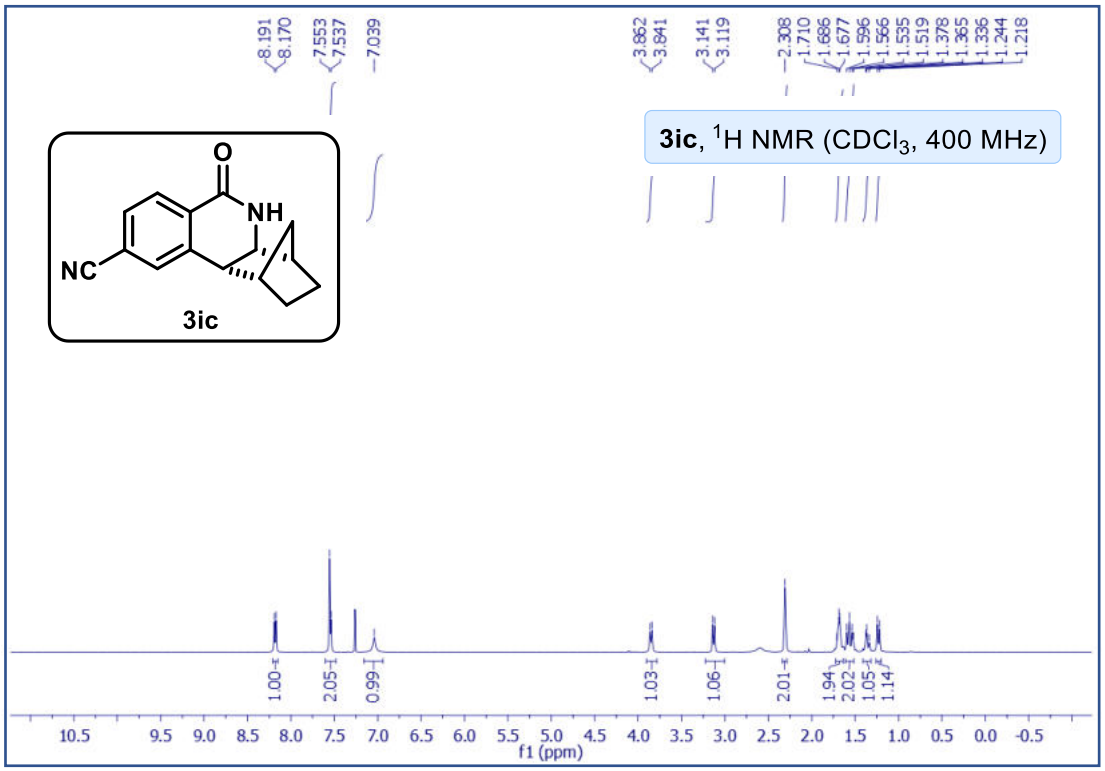
Colourless liquid; yield: 41 mg, 82%). *Rf*: 0.40 (in 5% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 6.96–6.89 (m, 2H), 5.78–5.68 (m, 1H), 5.50 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.20 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.14 (t, *J* = 6.0 Hz, 1H), 4.99–4.98 (m, 1H), 4.95 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.46 (t, *J* = 7.2 Hz, 2H), 1.06–1.01 (m, 3H), 1.10 (d, *J* = 18.8 Hz, 9H), 0.99 (d, *J* = 20.0 Hz, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.6, 147.7, 135.3, 134.6, 133.7, 126.8, 117.1, 114.0, 109.5, 107.9, 70.6, 55.7, 45.0, 18.0, 17.9, 12.3. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{38}O_3Si$: 413.2482; found: 413.2464.

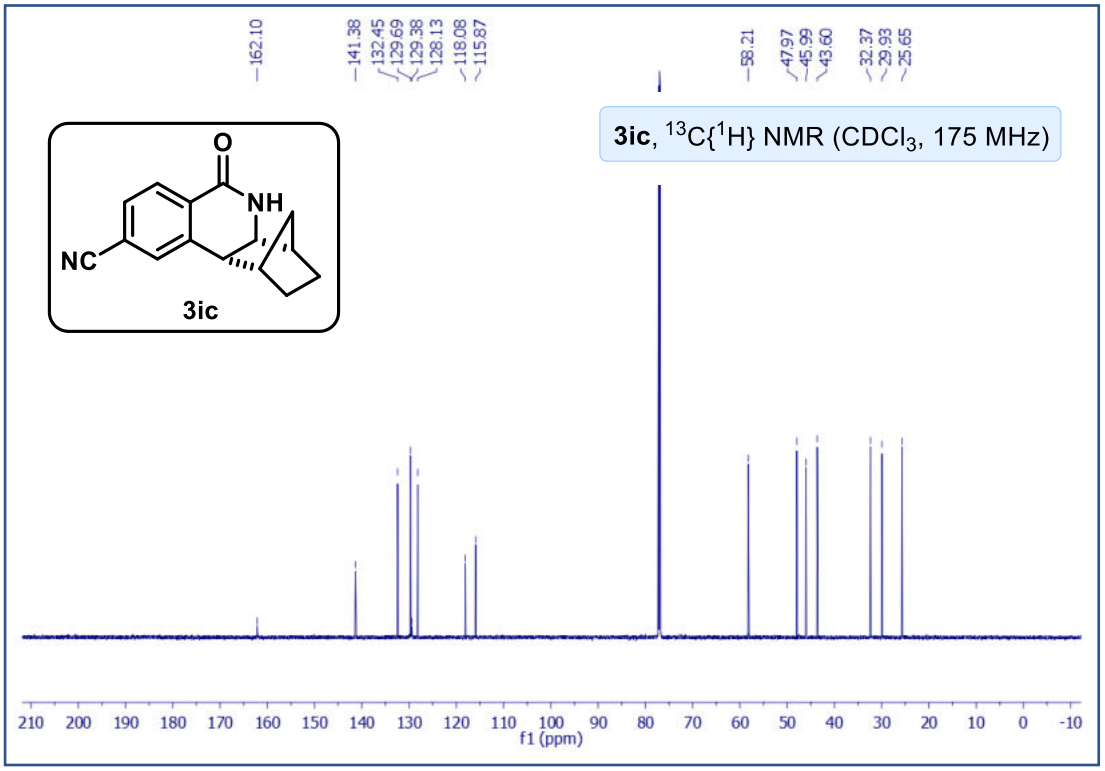
NMR spectra of (4bS,10bR)-9-Methyl-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ba).



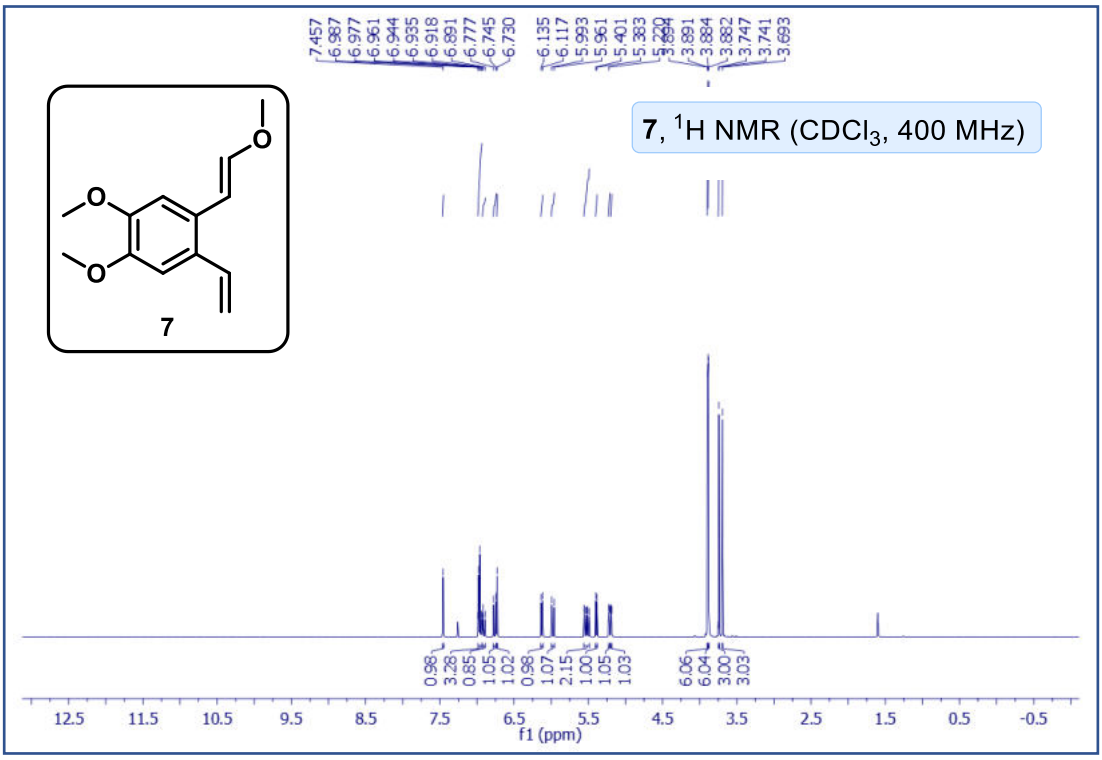


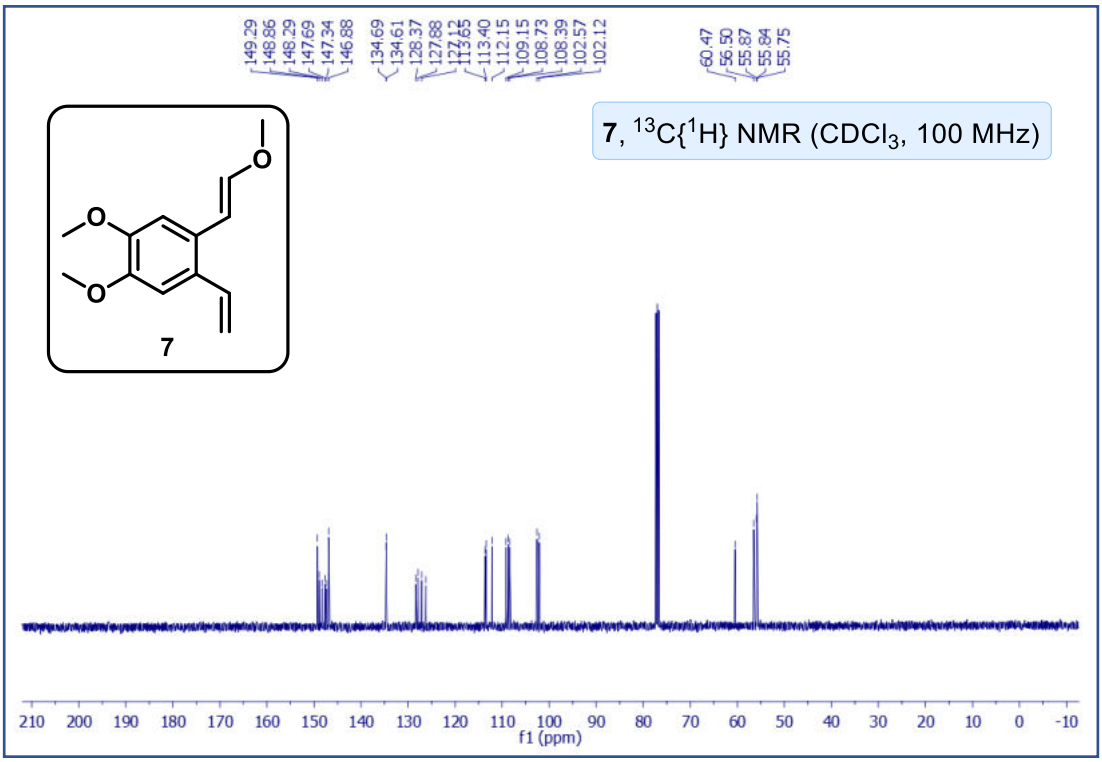
(1S,4R,4aS,10bS)-6-oxo-1,2,3,4,4a,5,6,10*b*-octahydro-1,4-methanophenanthridine-9-carbonitrile (3ic).



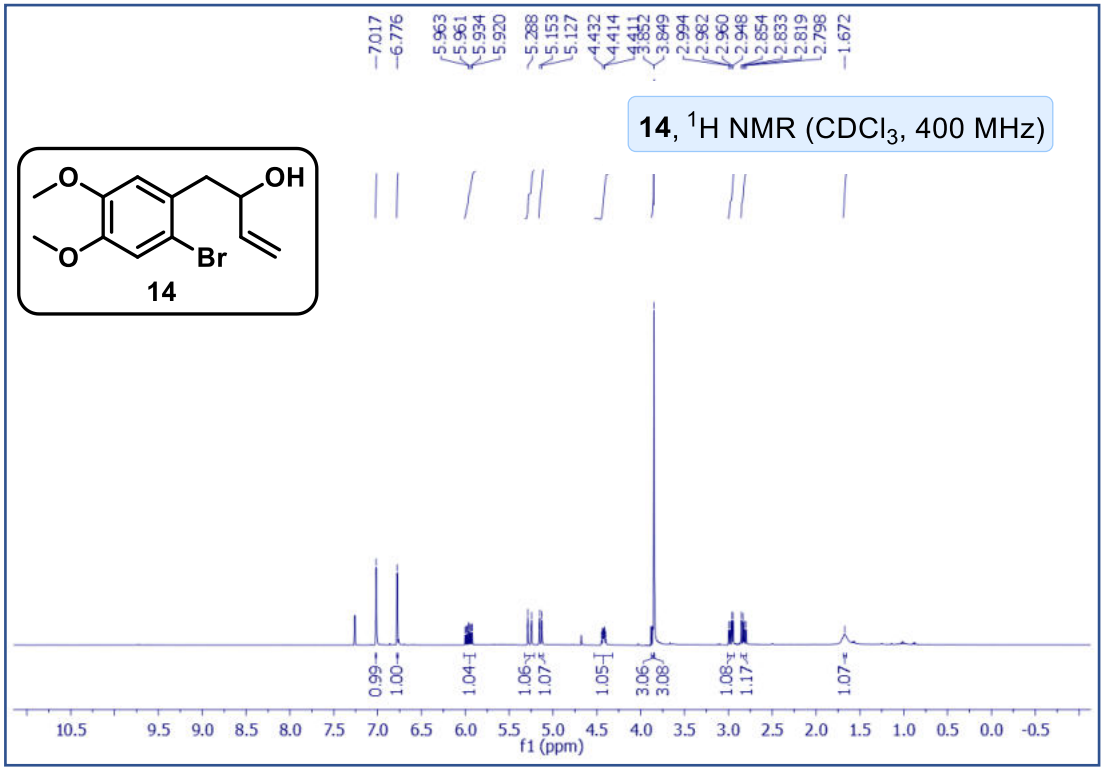


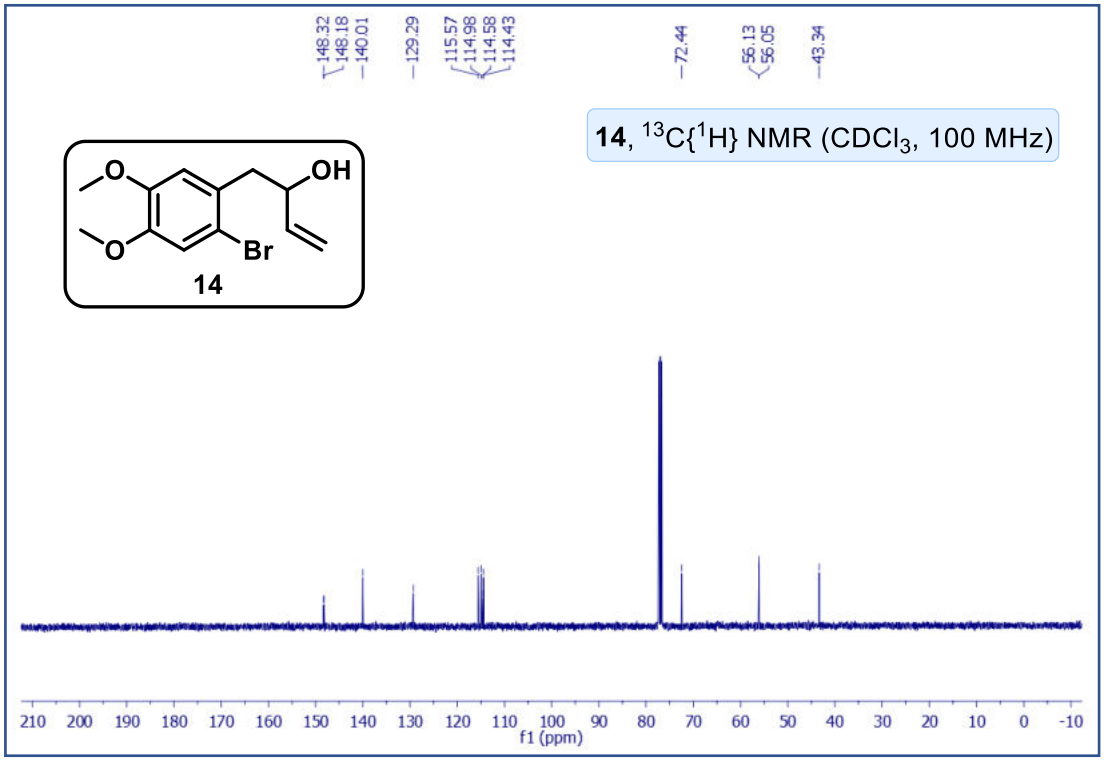
NMR spectra of (*E:Z, 1:1*)-1,2-dimethoxy-4-(2-methoxyvinyl)-5-vinylbenzene (7)



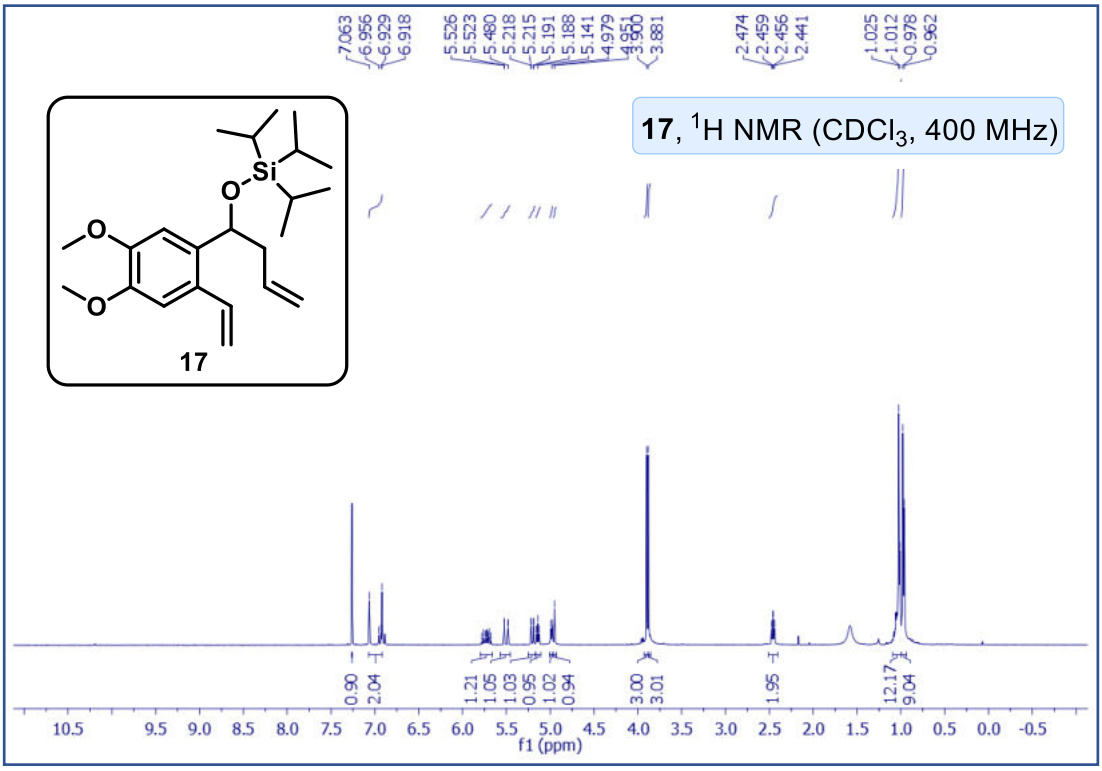


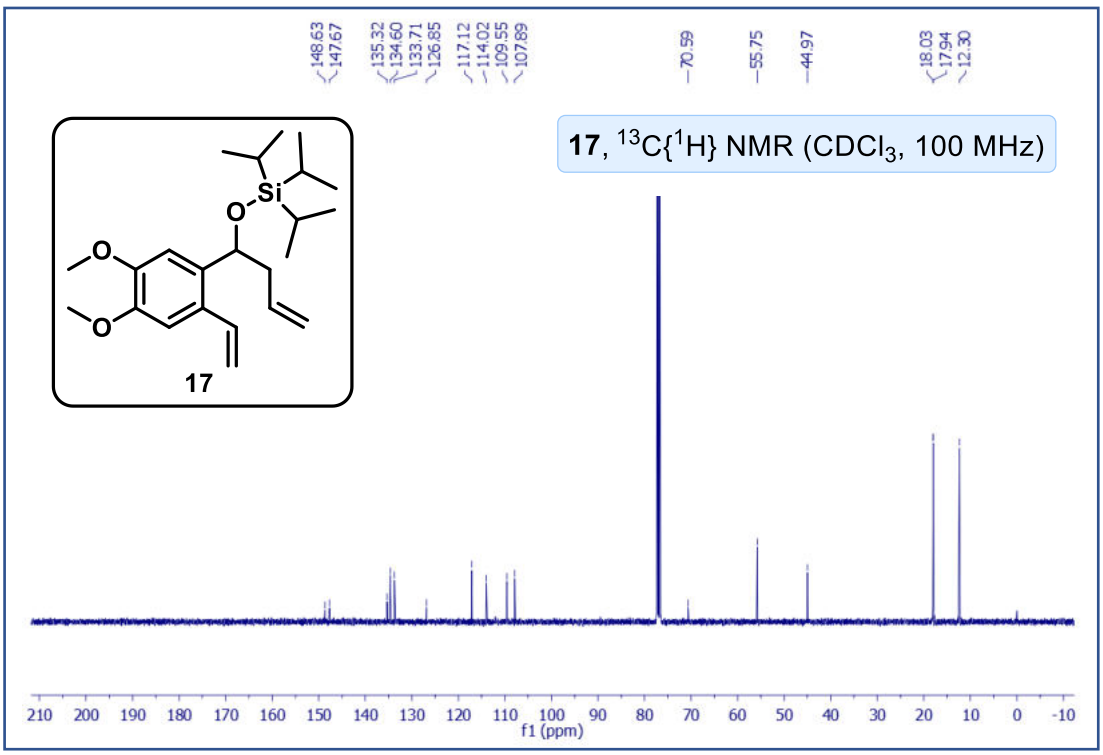
NMR spectra of 1-(2-bromo-4,5- dimethoxyphenyl)but-3-en-2-ol (14)



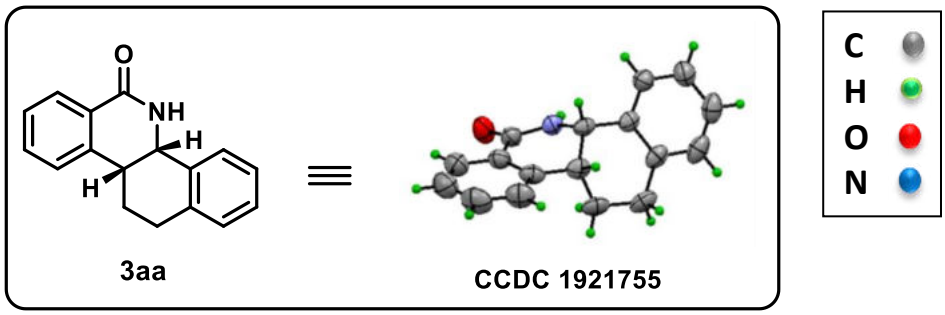


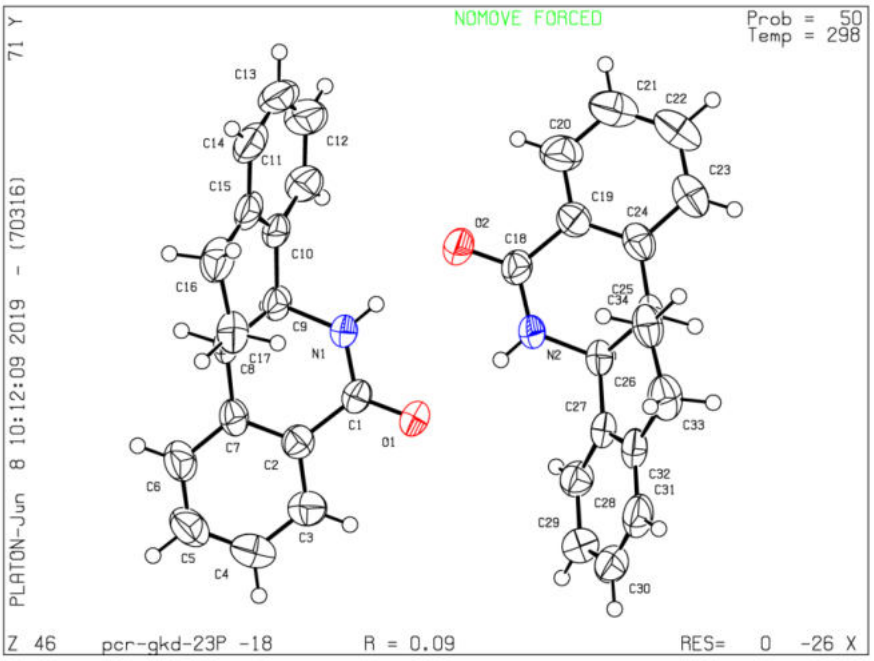
NMR spectra of {(1-(4,5-dimethoxy-2-vinylphenyl)but-3-en-1-yl)oxy}triisopropyl silane (17)





Crystal structure of 3aa





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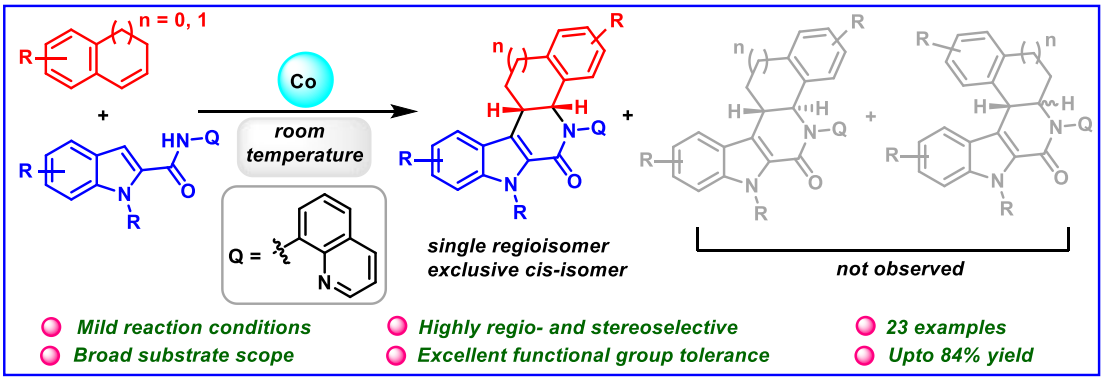
Chapter 3

Co(II)-Catalyzed *C-H*/*N-H* Annulation of Cyclic Alkenes with Indole-2-Carboxamides at room temperature: A one step access to β-carboline-1-one derivatives.

Chapter 3

Co(II)-Catalyzed *C-H*/*N-H* Annulation of Cyclic Alkenes with Indole-2-Carboxamides at room temperature: A one step access to *β*-carboline-1-one derivatives.



3.1 ABSTRACT: Herein, we report a cobalt catalyzed 8-aminoquinoline directed highly regio-and stereoselective C-H/N-H activation annulation of indole-2-carboxamides with 1,2-dihydronaphthalene for the synthesis of *β*-carboline-1-one derivatives at room temperature. A cheaper and commercially available cobalt catalyst has been used for this transformation. This reaction protocol tolerates a wide range of functional groups affording *β*-carboline-1-one derivatives in good yields. A reversible cyclometallation is found to be operative from initial mechanistic study.

3.2 INTRODUCTION

Indole moieties are not only widespread in numerous natural products but are also of considerable importance to pharmaceuticals and agrochemical industries. Hence, the functionalization of such heterocyclic moieties are of high interest to synthetic organic chemists. Polycyclic indole derivatives are found in many biological active molecules and natural products.[1] Among them, *β*-carboline-1-one derivatives (Figure 3.1) pertain to an

important class of polycyclic indole compounds owing to its wide application as an anticancer agent, and its use for the treatment of anxiety disorder, muscle spams and alzheimer's disease.[2]

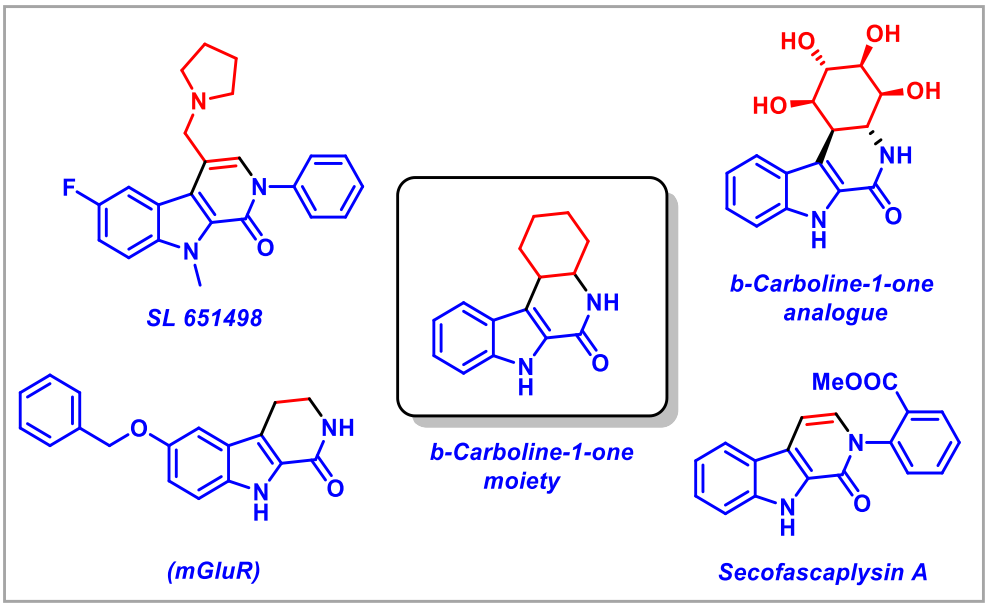


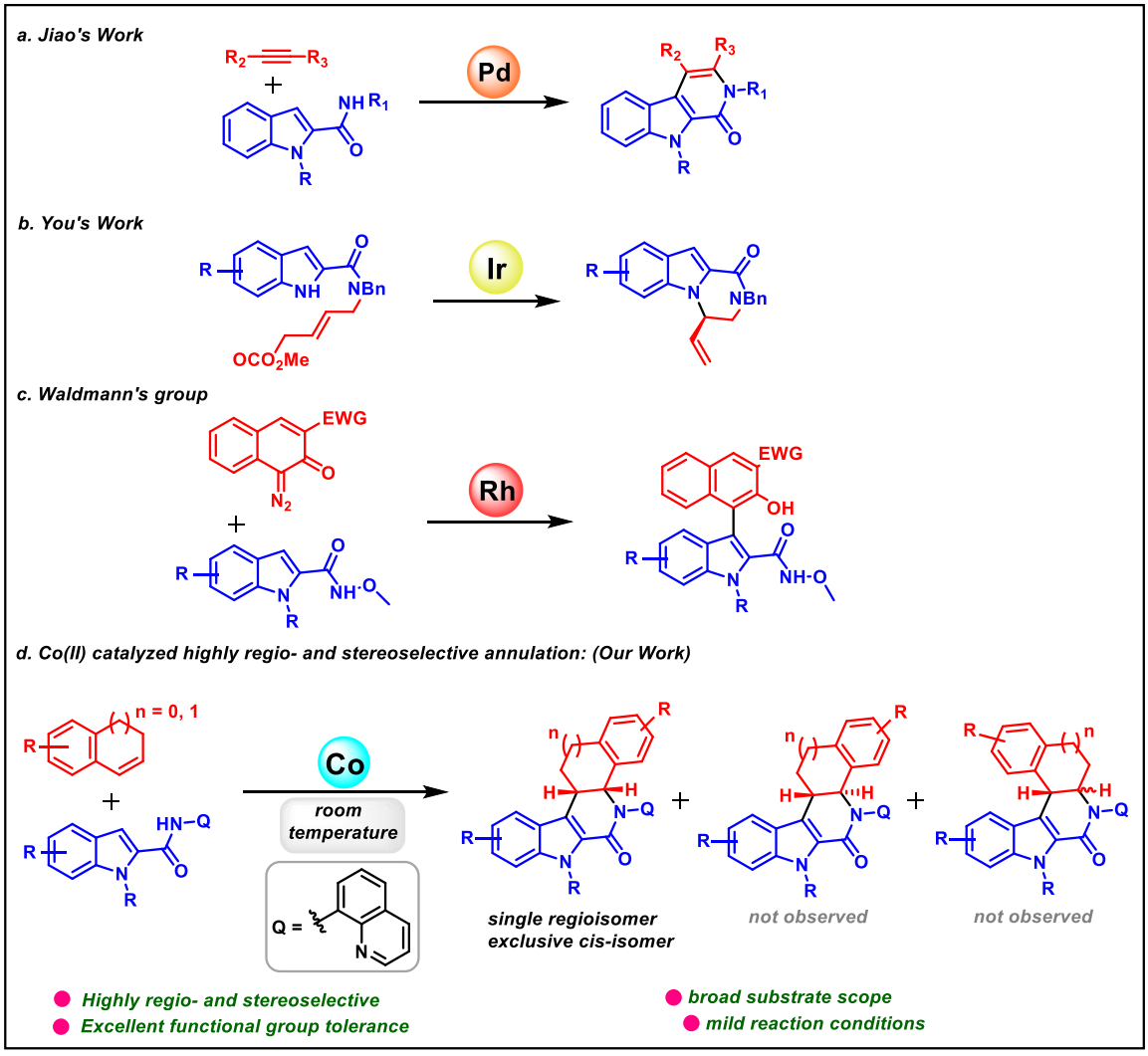
Figure 3.1. **Examples of *β*-carboline-1-one-type alkaloids.**

In this context, synthesis of *β*-carboline-1-one derivatives holds considerable interests in organic synthesis. In recent years, directing group assisted transition metal catalyzed selective C-H bond functionalization has emerged as a powerful tool in organic synthesis. It enables direct functionalization of C-H bonds making it possible, atom and step-economical synthesis of pharmacologically useful heterocycles.[3,4] This strategy also allows rapid synthesis of complex skeletons from simple starting materials.[5] Several indololactams have been successfully synthesized from indole amides using this strategy.[6] Jiao *et al*. in 2010 described the first synthesis of *β*- and γ-carbolinones via palladium catalyzed direct dehydrogenative annulation of indole-carboxamides with alkynes (Scheme-3.1a).[6a] In another report, You and co-workers reported the synthesis of indolopiperazinones from indoles via iridium catalyzed intramolecular enantioselective allylic amination reaction (Scheme-3.1b).[6b] Milburn group disclosed the Pd(II)-catalyzed cascade sequence for the

formation of polyheterocycles from from diene-tethered carboxamides.[6d,e] Antonchick and Waldmann developed the Rh-catalyzed enantioselective synthesis of five memberted ring atropisomers from direct functionalization of indole-2-carboxamide with 1-diazonaphthoquinones (Scheme-3.1c).[6f]

However, all these transformation have been achieved with expensive metal catalysts (Pd, Rh, Ir). The high cost of these metals restrict their application in industries. Hence, the use of cheaper and earth abundant alternatives which shows high catalytic efficiency and selectivity under mild reaction conditions is of high interest for sustainable synthesis.

Scheme 3.1 Previous work and our work



In this regard, harnessing the reactivity of first row transition metals is receiving much interest lately. It is attributed to their high earth crust abundance, low cost and scarce exploration. Recent years has seen an increase in the exploration of first row transition metals in C-H bond activation. Among the first row transition metals cobalt has emerged as one of the most successful metal for catalytic C-H bond activation due to its low cost and sustainability. Several research groups like Nakamura,[7a] Ackermann,[7b] Glorius,[7c] Daugulis,[7d] Kanai[7e] and others[7f-h] have explored the use of cheaper cobalt catalysts for C-H bond activation. Despite these major explorations, to the best of our knowledge, there is no report on the cobalt catalyzed stereoselective annulation of indole-2-carboxamide with 1,2-dihydronaphthalene to access *β*-carboline-1-one derivatives.

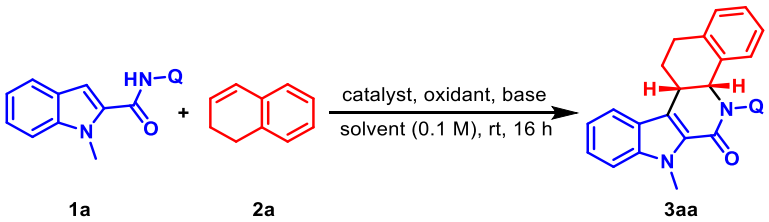
Perceiving the importance of C-H bond activation strategies involving cheaper cobalt catalysts (instead of Cp* catalysts) and the biological significance of *β*-carboline-1-one moiety, we envisaged that indole-2-amide assisted by an 8-aminoquinoline directing group can serve as a effective substrate for the stereoselective synthesis of *β*-carboline-1-one moiety. Herein, we report the first cobalt catalyzed C-H/N-H activation/annulation of indole-2-carboxamide with 1,2-dihydronaphthalene to access an array of distinct *β*-carboline-1-one derivatives. The important features of our strategy are (1) the use of earth abundant, low cost and commercially available cobalt catalyst, (2) use of lesser explored cyclic alkenes as coupling partners, (3) use of the combination of cyclic alkene and indole-2-carboxamide in C-H activation for the first time, (4) high stereoselectivity and (5) economic, one-step synthesis of complex *β*-carboline-1-one moiety.

3.3 RESULTS AND DISCUSSION:

To establish our methodology, we attempted to find optimal reaction conditions for the cobalt catalyzed stereoselective C(sp^2)-H activation/annulation of indole-2-carboxamide

with 1,2-dihydronaphtahlene. Accordingly, 1-methyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide **1a** and 1,2-dihydronaphthalene **2a** were chosen as the model substrates in the

Table 3.1. Optimization of Reaction Conditions[a]



1a **2a** **3aa**

entry	solvent	catalyst	oxidant	base	yield of **3aa** (%)[b]
1	DCE	$CoBr_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	nr
2	DCE	$Co(OAc)_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	5
3	DCE	$Co(acac)_3$	$Cu(OAc)_2$	$NaOPiv.H_2O$	nr
4	DCE	$Co(acac)_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	30
5	MeCN	$Co(acac)_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	30
6	MeOH	$Co(acac)_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	46
7	EtOH	$Co(acac)_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	45
8	DMF	$Co(acac)_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	40
9	TFE	$Co(acac)_2$	$Cu(OAc)_2$	$NaOPiv.H_2O$	62
10	TFE	$Co(acac)_2$	$Cu(OAc)_2.H_2O$	$NaOPiv.H_2O$	nr
11	TFE	$Co(acac)_2$	$Zn(OAc)_2.2H_2O$	$NaOPiv.H_2O$	nr
12	TFE	$Co(acac)_2$	$Mn(OAc)_2$	$NaOPiv.H_2O$	60
13	TFE	$Co(acac)_2$	$Mn(OAc)_3.2H_2O$	$NaOPiv.H_2O$	70
14	TFE	$Co(acac)_2$	Ag_2CO_3	$NaOPiv.H_2O$	55
15	TFE	$Co(acac)_2$	Ag_2O	$NaOPiv.H_2O$	59
16	**TFE**	**$Co(acac)_2$**	**$Mn(OAc)_3.2H_2O$**	**$NaOPiv.H_2O$**[c]	**81**
17	TFE	$Co(acac)_2$	$Mn(OAc)_3.2H_2O$	CsOPiv	40
18	TFE	$Co(acac)_2$	$Mn(OAc)_3.2H_2O$	Na_2CO_3	45
19	TFE	$Co(acac)_2$	$Mn(OAc)_3.2H_2O$	Li_2CO_3	39
20	TFE	$Co(acac)_2$	$Mn(OAc)_3.2H_2O$	Cs_2CO_3	30
21	TFE	$Co(acac)_2$	$Mn(OAc)_3.2H_2O$	––	31
22	TFE	––	$Mn(OAc)_3.2H_2O$	$NaOPiv.H_2O$	nr
23	other directing group instead of *N*-quinolyl				nr

[a]Reaction conditions:- 1-methyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide **1a** (1.0 equiv, 0.10 mmol), 1,2- dihydro naphthalene **2a** (1.3 equiv, 0.13 mmol), catalyst (0.2 equiv, 0.02 mmol), base (1.0 equiv, 0.10 mmol), oxidant (2.0 equiv, 0.20 mmol), TFE (0.1M, w.r.t. **1a**). [b]yields of **3aa** were calculated from isolated products. [c]base (2.0 equiv, 0.20 mmol). nr-no reaction.

presence of 20 mol % of cobalt catalyst. Initially, different cobalt catalyst were screened with $Cu(OAc)_2$ as oxidant, $NaOPiv.2H_2O$ as base in DCE solvent at room temperature (Table 3.1, entries 1-4). We were delighted to obtain the desired annulated product **3aa** in

5% and 30% yields with $Co(OAc)_2$ and $Co(acac)_2$ respectively (Table 3.1, entries 2 and 4).

With other cobalt catalysts such as $CoBr_2$ and $Co(acac)_3$, and we did not observe any product formation (Table 3.1, entries 1 and 3). With $Co(acac)_2$ as the optimized catalyst, we then screened various solvents for further improvement of the product yield. Other solvents such as MeCN, MeOH, EtOH, DMF and TFE produced the annulated product in 30%, 46%, 45%, 40% and 62% yields respectively (Table 3.1, entries 5-9).

Thus, a significant improvement in the yield was observed in the case of TFE. Intrigued by these results we next sought to investigate the effect of various oxidants on the outcome of the reaction. Various oxidants such as $Cu(OAc)_2.H_2O$, $Zn(OAc)_2.2H_2O$, $Mn(OAc)_2$, $Mn(OAc)_3.2H_2O$, Ag_2CO_3, and Ag_2O were screened (Table 3.1, entries 10-15). Gratifyingly, with $Mn(OAc)_3.2H_2O$ as oxidant 70% yield of the desired annulated product was isolated. But, other oxidants failed in improving the product yield.

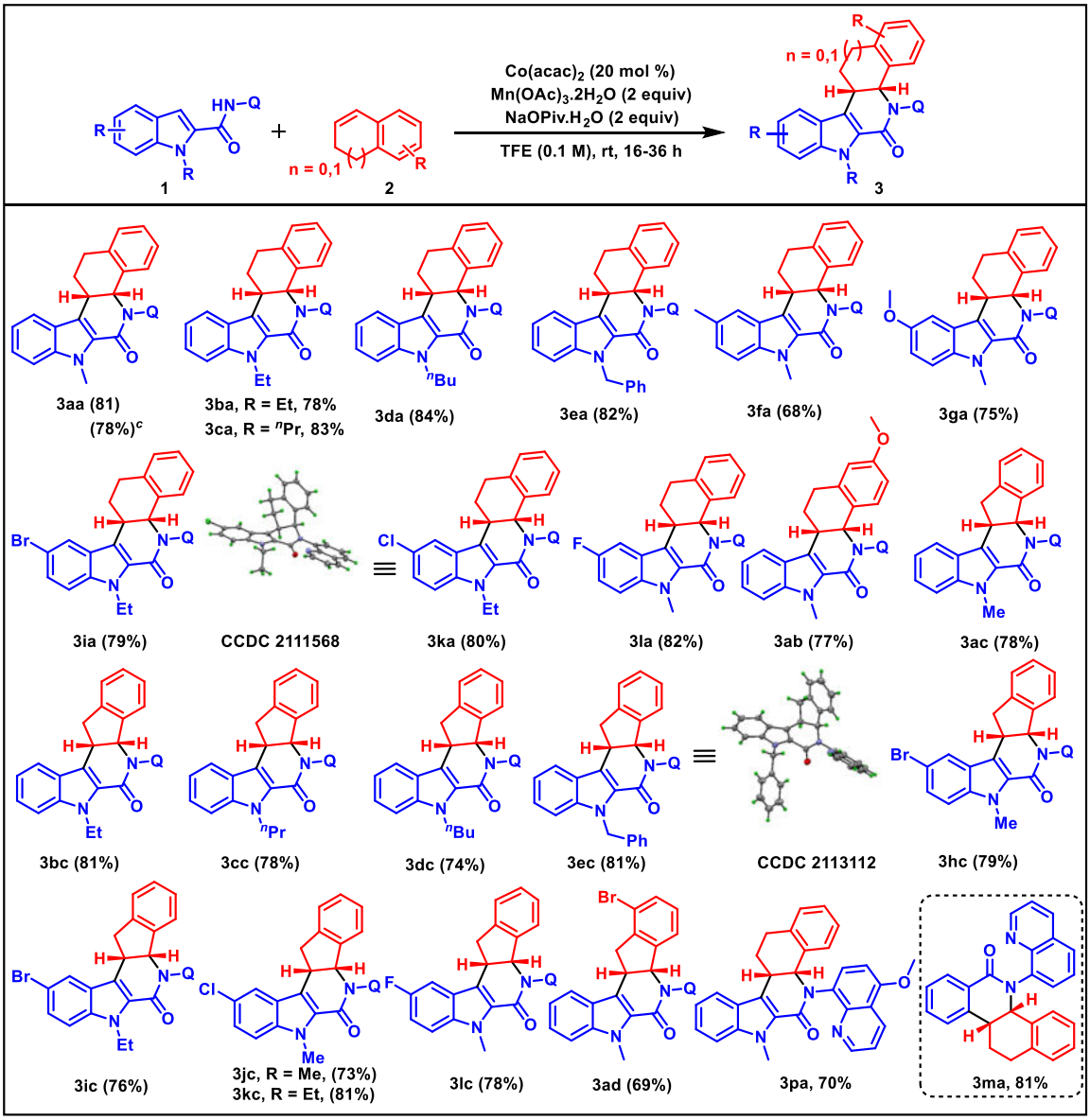
For further improvement of the product yield we increased the equivalence of the base used in the reaction. It is worthy to mention here that when 2.0 equivalents of $NaOPiv.H_2O$ was employed, the yield of **3aa** improved to 81% (Table 3.1, entry 16). However, an attempt to replace $NaOPiv.H_2O$ with CsOPiv had a deleterious effect on the reaction outcome affording the desired product in 40% yield (Table 3.1, entry 17). Again efforts to carry out the reaction with other carbonate bases was detrimental to the reaction yield (Table 3.1, entries 18-20). To check the influence of $NaOPiv.H_2O$ base and $Co(acac)_2$ catalyst we performed two control experiments. In the absence of $NaOPiv.H_2O$, 31% of **3aa** was obtained while without $Co(acac)_2$ catalyst no product was observed (Table 3.1, entries 21-22). Hence, the use of 20 mol % of $Co(acac)_2$ catalyst, 2.0 equivalent of $Mn(OAc)_3.2H_2O$ as oxidant along with 2.0 equivalent of $NaOPiv.H_2O$ as base in TFE (0.1 M) at room temperature gave the best yield of **3aa** (Table 3.1, entry 16). After establising the standard

reaction conditions, we screened one *N,S*-bidentate group such as 1-methyl-*N*-(2-(methylthio)phenyl)-1*H*-indole-2-carboxamide (**1n**) as substrate under standard reaction condition and we did not observe the annulated product. This reaction confirms that 8-aminoquinoline group serves as the best directing group for this reaction (Table 3.1, entry 23).

With the optimized reaction conditions in hand, we went on to check the generality of this stereoselective annulation of indole-2-carboxamide **1** with 1,2-dihydronaphthalene **2**. An array of substituted carboxamide **1** possessing a wide variety of functional groups, were explored (Scheme 3.2). Initially, we explored the scope of various *N*-protected indole-2-carboxamide substrates. Substrates bearing *N*-Me, *N*-Et, *N*-Pr, *N*-Bu, and *N*-Bn substituents delivered their corresponding desired pentacyclic product in 81%, 78%, 83%, 84% and 82% yields respectively (**3aa-3ea**).

After examining the scope with various *N*-substituted indole-2-carboxamide, we then checked the scope with various indole ring substituted carboxamides (**3fa-3la**). A variety of functional groups such as Me, OMe, F, Cl and Br were well tolerated in this Co-catalyzed protocol affording their corresponding pentacyclic annulated products in 68-82% yields. It is worth mentioning here that synthetically useful Br substituted indole-2-carboxamide reacted smoothly under the standard reaction condition. Hence, both electron rich and deficient carboxamides were facile under the reaction condition. We then extended the scope of this annulation strategy to substituted dihydronaphthalene. Pleasingly, 6-methoxy-1,2-dihydronaphthalene, **2b** reacted smoothly under the standard reaction condition and furnished the desired pentacyclic annulated product in 77% yield. To showcase the synthetic utility of this developed methodology a 1 mmol scale synthesis of **3aa** was carried out under the standard reaction condition (78% yield). The regio- and stereoselectivity of

Scheme 3.2. Co(II) Catalyzed Regio- and Stereoselective *C-H/N-H* Annulation of Substituted Benzamides with 1,2-Dihydronaphthalenes and Indenes[a]



[a]Reaction conditions:- **1** (1 equiv, 0.10 mmol), **2a** and 6-methoxy-1,2-dihydronaphthalene **2b, 2c** and **2d** (1.3 equiv, 0.13 mmol), $Co(acac)_2$ (0.2 equiv, 0.02 mmol), $NaOPiv.H_2O$ (2.0 equiv, 0.20 mmol), $Mn(OAc)_3.2H_2O$ (2.0 equiv, 0.20 mmol), TFE (0.1 M, w.r.t. **1a**). [b]All yields in parenthesis are isolated yields. [c]Compound **3aa** (335 mg, 78%) was prepared in 1 mmol scale.

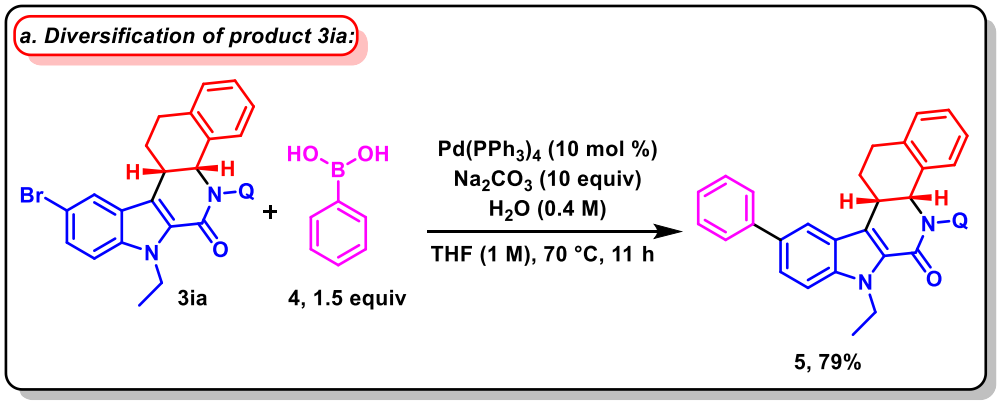
the annulated products was confirmed from single-crystal X-ray analysis of compound **3ka**.

To further extend the scope of our methodology, we investigated with indene **2c** as coupling partner (Scheme 3.2). To our delight, various substituted and *N*-protected indole-

2-carboxamides were found to be compatible under the standard reaction condition giving good yield of their annulated products (**3ac-3lc**, Scheme 3.2). The scope of the annulation reaction was further explored with substituted indene, 7-bromo-1*H*-indene (**2d**). Successfully, the desired annulated product **3ad** was obtained in 69% yield. Single crystal X-ray analysis of product **3ec** unambiguously confirmed the regio- and stereoselectivity. Substituent (-OMe) at the para-position of the directing group afforded the annulated product **3pa** in good yield (70% yield). Benzamide **1m** also gave the desired annulated product **3ma** in 81% yield.

We tried to remove the directing group in the annulated product,[7i] but we could not be able to succeed. Next, the synthetic diversification of the obtained pentacyclic annulated product was explored. The Suzuki-Miyaura coupling of **3ia** with phenyl boronic acid **4** successfully furnished the desired phenyl coupled product in 79% yield (Scheme 3.3).[8]

Scheme 3.3 Synthetic Applications

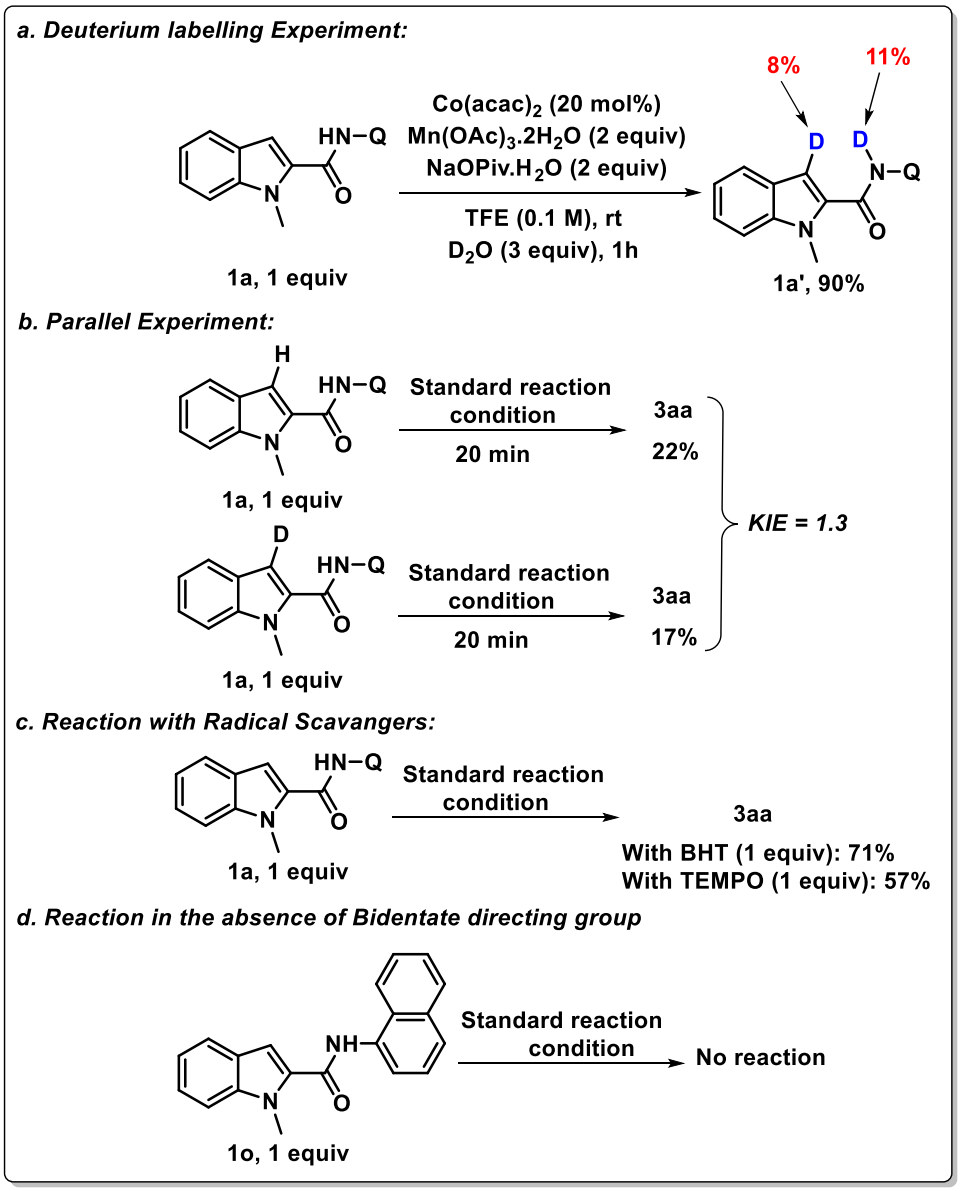


After successfully exploring the scope of diverse indole-2-carboxamides, we then carried out mechanistic study to understand the catalytic cycle. A deuterium labelling experiment of **1a** with D_2O in absence of coupling partner was carried out under the standard reaction conditions (Scheme 3.4a). The compound **1a**-[***d***] was isolated in 90% yield and the extent of deuterium incorporation was determined by ^{1}H NMR analysis. An 8% deuterium incorporation was observed at C3-position and 11% was observed for N/H proton.

Additionally, a KIE value of 1.3 obtained from the parallel experiments (Scheme 3.4b) suggest that the C-H activation step might not be involving in the rate determining step. Both the experiments indicate that the C-H metalation step is reversible.[9]

To understand the reaction pathway, a radical process experiment was conducted using radical scavengers such as 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and 3,5-di-tert-4-butylhydroxytoluene (BHT) (Scheme 3.4c). From these two reaction it was concluded that

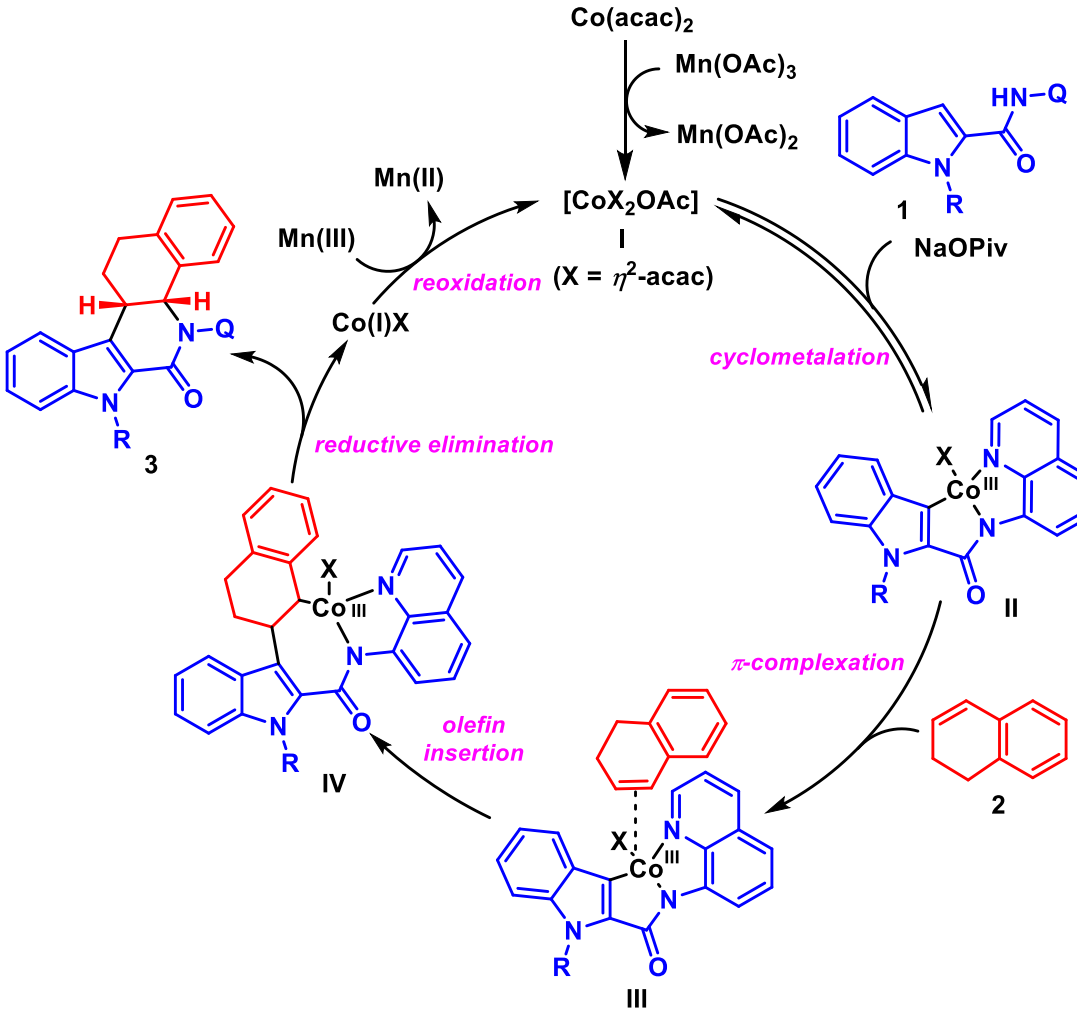
Scheme 3.4 Mechanistic Studies and Control Experiments



the reaction goes through ionic pathway. A control experiment was performed using monodentate directing group **1o** as substrate under standard reaction condition which failed to give desired product (Scheme 3.4d)**.** This suggests that a bidentate directing group is necessary for the annulation reaction.

Based on the above mechanistic details a mechanistic cycle was given below in **Scheme 3.5**. Initially, the catalytically active Co(III) species **I** is generated from Co(II) species by oxidation with $Mn(OAc)_3.2H_2O$. Cyclometalation of indole-2-carboxamide **1** with the active catalyst species **I** forms the intermediate **II**. Coordination of the cyclic alkene species **2** to the cobaltacyclic intermediate **II** delivers the intermediate **III**. Subsequently, the seven

Scheme 3.5. **Proposed Catalytic Cycle.**



membered cobaltacyclic intermediate **IV** is obtained by the 1,2-insertion of the coordinated cyclic olefin giving rise to intermediate **IV**. The formation of benzyl-Co species is preferred to the formation of alkyl-Co species, which leads to the high regio-selectivity in the product. Finally, reductive elimination from intermediate **IV** leads to the formation of product species **3** with the generation of the reduced Co(I) species. Afterwards, Co(I) is reoxidised to active catalytic species **I** to enter into the next catalytic cycle.

3.4 CONCLUSIONS

In summary, we reported the first cobalt catalyzed highly regio- and stereoselective C-H/N-H annulation of indole-2-amide with 1,2-dihydronaphathalene for the synthesis of core skeleton of *β*-carboline-1-one derivatives. The reaction works well at room temperature and exhibits a wide range of functional group tolerance. This protocol provides a one-step, economical and efficient synthesis of core skeleton of *β*-carboline-1-one derivatives. Synthetic diversification of the obtained annulated adducts have been carried out. The initial deuterium labelling experiment indicated the reversible cyclometallation to be operational.

3.5 EXPERIMENTAL SECTION:

3.5.1 General Procedure for the Preparation of Starting Materials.[10] All Indole-2-carboxamides were prepared from the corresponding acid (A)[11] according to literature procedure,[10] with indole-2-acid (1.2 equiv, 1.0 mmol), 8-aminoquinoline (1 equiv, 0.83 mmol), EDC.HCl (1.2 equiv, 1.0 mmol), HOBt (1.2 equiv, 1.0 mmol), DIPEA (2.5 equiv, 2.07 mmol) in anhydrous DMF (0.1 M). Characterization data of compounds **1a** and **1e** were matched with the reported literature.[10] Characterization data of all new compounds were listed below.

3.5.2 General Procedure for the Preparation of Annulated Products 3. To an oven dried Schlenk tube, cooled under N_2 atmosphere, was charged with Indole-2-carboxamides **1** (1

equiv, 0.10 mmol), $Co(acac)_2$ (0.2 equiv, 0.02 mmol), $NaOPiv.H_2O$ (2.0 equiv, 0.20 mmol), $Mn(OAc)_3.2H_2O$ (2.0 equiv, 0.20 mmol) in anhydrous TFE (0.1 M). Then the coupling partner **2** (1.3 equiv, 0.13 mmol) was added in one shot. The sealed tube was tightened under positive pressure of N_2. The reaction mixture was stirred at room temperature for 16-36 hours (monitored by TLC). After complete consumption of starting materials, excess solvent was evaporated in *vaccuo* and the crude residue was purified by column chromatography to afford pure cyclized product **3** using EtOAc (Ethyl acetate)/Hexane.

3.5.3 Procedure for the 1 mmol scale reaction.

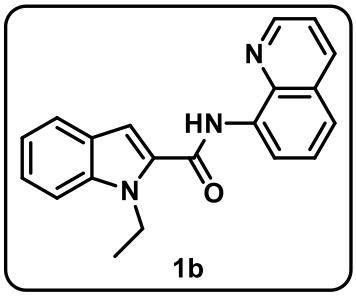
To an oven dried Schlenk tube, cooled under N_2 atmosphere, was charged with Indole-2-carboxamides **1a** (1 equiv, 1.0 mmol), $Co(acac)_2$ (0.2 equiv, 0.2 mmol), $NaOPiv.H_2O$ (2.0 equiv, 2.0 mmol), $Mn(OAc)_3.2H_2O$ (2.0 equiv, 2.0 mmol) in anhydrous TFE (0.1 M). Then the coupling partner **2a** (1.3 equiv, 1.3 mmol) was added. The sealed tube was tightened under positive pressure of N_2. The reaction mixture was stirred at room temperature for 16 h hours. Thereafter, excess solvent was evaporated in *vaccuo* and the crude residue was purified by column chromatography to afford pure cyclized product **3aa** (78% yield) using EtOAc (Ethyl acetate)/Hexane.

3.5.4 Procedure for the Preparation of Cross-coupled Product 5.[8]

A mixture of **3ia** (0.10 mmol, 1.00 equiv), phenylboronic acid 4 (1.5 equiv), Na_2CO_3 (10.00 equiv), and $Pd(PPh_3)_4$ (10.00 mol %) in THF (1.0 M) and H_2O (0.4 mL) was stirred at 70 °C in a preheated aluminum block for 11 h under N_2 atmosphere. The mixture was added with H_2O (10.00 mL) and extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/hexane) to afford product **5** in 79% yield.

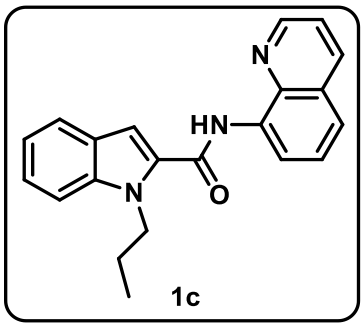
3.5.5 Experimental characterization data:

1-Ethyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1b):



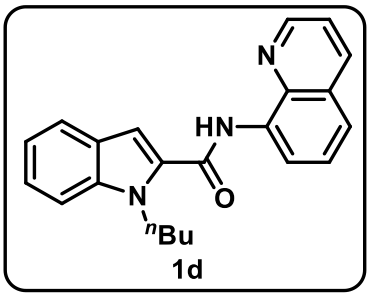
Physical State: Colourless solid; mp: 141-143 °C; yield: (246 mg, 78%). R_f: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.72 (brs, 1H), 8.88-8.86 (m, 2H), 8.17 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.49-7.45 (m, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.30-7.24 (m, 1H), 7.19 (t, J = 7.2 Hz, 1H), 4.72 (q, J = 7.2 Hz, 2H), 1.51 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.5, 148.3, 138.6, 138.4, 136.3, 134.7, 131.5, 128.0, 127.4, 126.3, 124.3, 122.2, 121.7, 121.5, 120.6, 116.2, 110.2, 105.2, 39.7, 15.8. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{20}H_{17}N_3ONa$: 338.1269; found: 338.1254. IR (KBr, cm^{-1}): 3052, 2980, 1672, 1368, 1050, 892, 701.

1-Propyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1c):



Physical State: Colourless solid; mp: 148-150 °C; yield: (263 mg, 80%). R_f: 0.40 (in 20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.72 (brs, 1H), 8.88-8.86 (m, 2H), 8.19 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.50-7.44 (m, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.30-7.25 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 4.65 (t, J = 7.2 Hz, 2H), 1.94 (sextet, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.6, 148.3, 138.8, 138.6, 136.3, 134.7, 131.9, 128.0, 127.4, 126.2, 124.2, 122.1, 121.7, 121.5, 120.5, 116.2, 110.5, 105.3, 46.2, 23.9, 11.4. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{21}H_{19}N_3ONa$: 352.1426; found: 352.1434. IR (KBr, cm^{-1}): 3053, 2986, 1630, 1362, 1051, 896, 705.

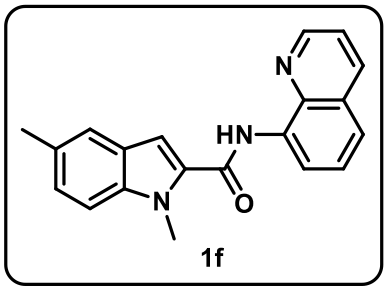
1-Butyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1d):



1d

Physical State: Colourless solid; mp: 142-144 °C; yield: (257 mg, 75%). R_f: 0.50 (in 20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.72 (brs, 1H), 8.88-8.87 (m, 2H), 8.19 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.50-7.44 (m, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.30-7.25 (m, 1H), 7.18 (t, J = 7.6 Hz, 1H), 4.68 (t, J = 7.2 Hz, 2H), 1.88 (quint, J = 7.6 Hz, 2H), 1.42 (sextet, J = 7.2 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.6, 148.3, 138.8, 138.6, 136.3, 134.8, 131.9, 128.0, 127.4, 126.2, 124.2, 122.1, 121.7, 121.5, 120.5, 116.2, 110.5, 105.3, 44.6, 32.8, 20.3, 13.9. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{21}N_3ONa$: 366.1582; found: 366.1563. IR (KBr, cm^{-1}): 3044, 2975, 1650, 1360, 1061, 926, 800, 747.

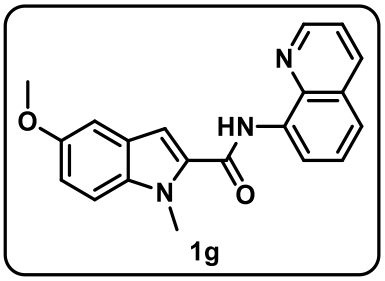
1,5-Dimethyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1f):



1f

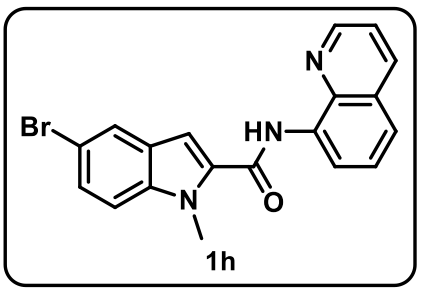
Physical State: Colourless solid; mp: 145-147 °C; yield: (246 mg, 78%). R_f: 0.50 (in 20% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.68 (s, 1H), 8.86-8.84 (m, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.52-7.49 (m, 2H), 7.45 (dd, J = 8.0, 4.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.24-7.20 (m, 1H), 7.18 (dd, J = 8.8, 1.6 Hz, 1H), 4.14 (s, 3H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.7, 148.3, 138.6, 138.0, 136.3, 134.7, 132.2, 129.9, 128.0, 127.3, 126.3, 121.7, 121.5, 121.4, 116.1 (2C), 109.8, 104.5, 31.7, 21.4. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{18}N_3O$: 316.1444; found: 316.1438. IR (KBr, cm^{-1}): 3046, 2975, 1660, 1360, 1060, 926, 800, 747.

5-Methoxy-1-methyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1g):



Physical State: Colourless solid; mp: 146-148 °C; yield: (258 mg, 78%). R_f: 0.40 (in 20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.68 (brs, 1H), 8.86 (d, J = 1.2 Hz, 1H), 8.85 (dd, J = 3.6, 1.6 Hz, 1H), 8.17 (dd, J = 8.4, 2.0 Hz, 1H), 7.60-7.56 (m, 1H), 7.52 (dd, J = 8.4, 1.6 Hz, 1H), 7.47 (dd, J = 8.4, 4.4 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.25-7.22 (m, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), 4.14 (s, 3H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.5, 154.7, 148.3, 138.5, 136.3, 135.0, 134.7, 132.4, 128.0, 127.3, 126.3, 121.7, 121.5, 116.1, 115.7, 111.1, 104.4, 102.3, 55.7, 31.8. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1399; found: 332.1392. IR (KBr, cm^{-1}): 3047, 2976, 1656, 1360, 1051, 926, 800, 746.

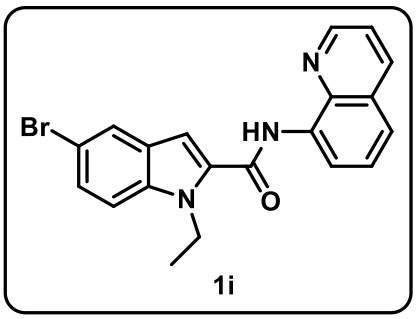
5-Bromo-1-methyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1h):



Physical State: Colourless solid; mp: 146-148 °C; yield: (281 mg, 74%). R_f: 0.60 (in 20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.69 (brs, 1H), 8.87-8.83 (m, 2H), 8.18 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 7.60-7.53 (m, 2H), 7.49 (dd, J = 8.0, 4.0 Hz, 1H), 7.43-7.41 (m, 1H), 7.30-7.26 (m, 1H), 7.19 (s, 1H), 4.13 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.1, 148.4, 138.5, 137.9, 136.4, 134.4, 133.2, 128.0, 127.6, 127.3, 127.2, 124.4, 121.8 (2C), 116.3, 113.7, 111.7, 104.1, 31.9. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{19}H_{14}BrN_3ONa$: 402.0212; found: 402.0234. IR (KBr, cm^{-1}): 3050, 2974, 1662, 1361, 1055, 925, 800, 745.

5-Bromo-1-ethyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1i):

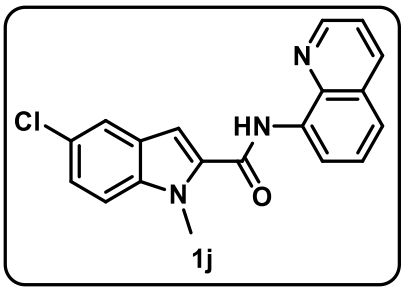
Physical State: Colourless solid; mp: 144-146 °C; yield: (295 mg, 75%). R_f: 0.40 (in 20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.70 (brs, 1H), 8.88-8.84 (m, 2H), 8.19-8.17 (m, 1H), 7.86 (s, 1H), 7.60-7.53 (m, 2H), 7.49 (dd, J = 8.4, 4.4 Hz, 1H), 7.43-7.41 (m, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.25-7.19 (m, 1H), 4.68 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.0, 148.4, 138.5, 136.9, 136.4, 134.5, 132.5, 128.0, 127.8, 127.3, 127.2, 124.5, 121.8, 121.8, 116.3, 113.6, 111.7, 104.3, 40.0, 15.8. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{17}BrN_3O$: 394.0550; found: 394.0544. IR (KBr, cm^{-1}): 3048, 2974, 1661, 1360, 1080, 925, 800, 743.



1i

5-Chloro-1-methyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1j):

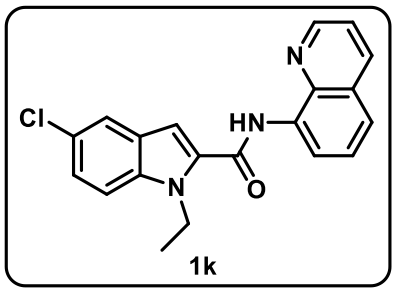
Physical State: Colourless solid; mp: 140-142 °C; yield: (224 mg, 67%). R_f: 0.50 (in 20% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.69 (brs, 1H), 8.88-8.87 (m, 1H), 8.85-8.83 (m, 1H), 8.20-8.18 (m, 1H), 7.69 (s, 1H), 7.60-7.53 (m, 2H), 7.50-7.48 (m, 1H), 7.35-7.28 (m, 2H), 7.26-7.20 (m, 1H), 4.14 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.2, 148.4, 138.5, 137.7, 136.4, 134.4, 133.4, 128.0, 127.3, 126.9, 126.2, 124.8, 121.8 (2C), 121.2, 116.3, 111.3, 104.2, 31.9. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O$: 336.0898; found: 336.0932. IR (KBr, cm^{-1}): 3052, 2975, 1665, 1360, 1076, 926, 800, 747.



1j

5-Chloro-1-ethyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1k):

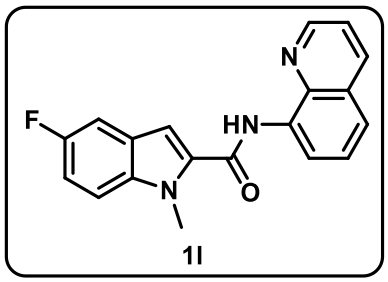
Physical State: Colourless solid; mp: 144-146 °C; yield: (244 mg, 70%). R_f: 0.50 (in 20% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.71 (s, 1H), 8.89-8.85 (m, 2H), 8.20 (dd,



1k

J = 8.4, 1.6 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.61-7.55 (m, 2H), 7.50 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.26-7.21 (m, 1H), 4.69 (q, *J* = 6.8 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): *δ* 160.0, 148.4, 138.5, 136.6, 136.4, 134.5, 132.7, 128.0, 127.3, 127.1, 126.1, 124.7, 121.76, 121.74, 121.3, 116.2, 111.3, 104.5, 40.0, 15.8. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{17}ClN_3O$: 350.1055; found: 350.1058. IR (KBr, cm^{-1}): 3049, 2974, 1667, 1360, 1054, 924, 804, 746.

5-Fluoro-1-methyl-*N*-(quinolin-8-yl)-1*H*-indole-2-carboxamide (1l):

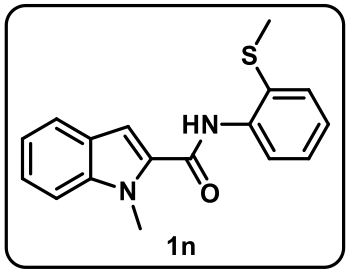


1l

Physical State: Colourless solid; mp: 147-149 °C; yield: (214 mg, 67%). R_f: 0.40 (in 20% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 10.70 (brs, 1H), 8.88-8.84 (m, 2H), 8.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.61-7.57 (m, 1H), 7.55 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.49 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.38-7.34 (m, 2H), 7.26-7.24 (m, 1H), 7.12 (td, *J* = 9.2, 2.8 Hz, 1H), 4.16 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): *δ* 160.3, 158.2 (d, *J* = 235.0 Hz), 148.4, 138.6, 136.4, 136.1, 134.5, 133.6, 128.0, 127.4, 126.2, 126.1, 121.8 (d, *J* = 4.0 Hz) 116.3, 113.3 (d, *J* = 26.0 Hz), 111.1 (d, *J* = 9.0 Hz), 106.3 (d, *J* = 23.0 Hz), 104.6 (d, *J* = 5.0 Hz), 31.9. $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 376 MHz): *δ* -123.31. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{19}H_{14}FN_3ONa$: 342.1013; found: 342.1009. IR (KBr, cm^{-1}): 3046, 2970, 1660, 1360, 1052, 924, 802, 749.

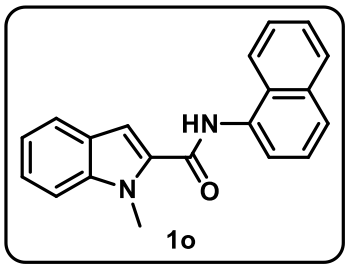
1-methyl-*N*-(2-(methylthio)phenyl)-1*H*-indole-2-carboxamide (1n):

Physical State: Colourless solid; mp: 158-160 °C; yield: (222 mg, 75%). R_f: 0.50 (in 10% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 9.23 (s, 1H), 8.48-8.46 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.55-7.53 (m, 1H), 7.42-7.40 (m, 1H), 7.37-7.33 (t, 2H), 7.19-7.16 (m, 1H), 7.11-7.07 (m, 2H), 4.12 (s, 3H), 2.41 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) *δ* 160.3,



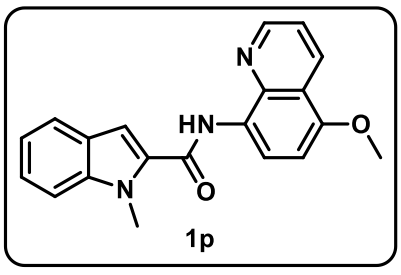
139.4, 138.6, 133.4, 131.8, 129.1, 125.9, 125.3, 124.5, 124.3, 122.0, 120.7, 120.1, 110.2, 104.6, 31.6, 19.2. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{17}H_{16}N_2SO$: 319.0876; found: 319.0891. IR (KBr, cm^{-1}): 3038, 2970, 1672, 1348, 1086, 916, 867.

1-methyl-*N*-(naphthalen-1-yl)-1*H*-indole-2-carboxamide (1o):



Physical State: Colourless solid; mp: 164-166 °C; yield: (210 mg, 70%). R_f: 0.50 (in 10% EtOAc/Hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.95-7.90 (m, 2H), 7.77-7.71 (m, 2H), 7.55-7.52 (m, 3H), 7.46-7.36 (m, 2H), 7.23-7.17 (m, 2H), 4.13 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 161.1, 139.4, 134.2, 132.0, 131.9, 128.9, 127.2, 126.5, 126.1, 126.0, 126.0, 125.8, 124.6, 122.0, 120.8, 120.8, 120.5, 110.3, 104.3, 31.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{17}N_2O$: 301.1335; Found: 301.1345. IR (KBr, cm^{-1}): 3038, 2970, 1651, 1349, 1080, 915, 771.

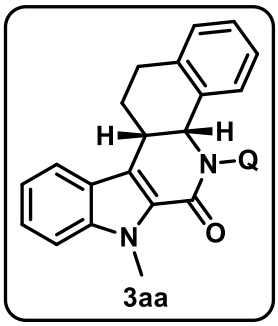
***N*-(5-methoxyquinolin-8-yl)-1-methyl-1*H*-indole-2-carboxamide (1p).**



Physical State: Colourless solid; mp: 150-152 °C; yield: (248 mg, 75%). R_f: 0.50 (in 20% EtOAc/Hexane). ^1H NMR (700 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.88-8.87 (m, 1H), 8.78 (d, J = 8.4 Hz, 1H), 8.61-8.60 (m, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.48-7.47 (m, 1H), 7.44-7.43 (m, 1H), 7.36 (t, J = 7.0 Hz, 1H), 7.26-7.25 (m, 1H), 7.19 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.18 (s, 3H), 4.02 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.4, 150.4, 148.8, 139.3, 139.3, 132.6, 131.3, 128.1, 126.2, 124.2, 122.0, 120.8, 120.6, 120.5, 116.4, 110.1,

104.6, 104.3, 55.8, 31.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{18}N_3O_2$: 332.1394; Found: 332.1391. IR (KBr, cm^{-1}): 3018, 2975, 1660, 1210, 1030.

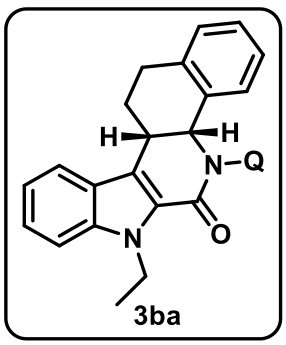
(4bR,11cS)-7-Methyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*] indolo[2,3-*c*]quinolin-6-one (3aa):



3aa

Physical State: Colourless solid; mp: 240-242 °C; yield: (35 mg, 81%). R_f: 0.40 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.98 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 8.0, 1.2 Hz, 1H), 7.44-7.36 (m, 3H), 7.29 (t, J = 7.6 Hz, 1H), 7.26-7.18 (m, 2H), 7.04 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.46 (t, J = 7.6 Hz, 1H), 6.26-6.24 (m, 1H), 5.76 (d, J = 2.8 Hz, 1H), 4.13 (s, 3H), 3.77 (dt, J = 10.8, 4.0 Hz, 1H), 3.17-3.10 (m, 1H), 3.05-2.96 (m, 1H), 2.67 (brs, 1H), 2.28-2.22 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 162.3, 150.5, 145.9, 139.6, 138.6, 136.9, 136.3, 133.9, 131.1, 130.5, 129.1, 128.7, 127.6, 127.5, 126.1, 126.0, 124.7, 124.5, 123.7, 123.6, 121.3, 120.2, 120.0, 110.4, 62.3, 33.0, 31.3, 28.5, 24.8. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{24}N_3O$: 430.1919; found: 430.1925. IR (KBr, cm^{-1})**:** 3048, 2986, 1652, 1457, 1275, 1056, 895, 764.

(4bR,11cS)-7-Ethyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*] indolo[2,3-*c*]quinolin-6-one (3ba):

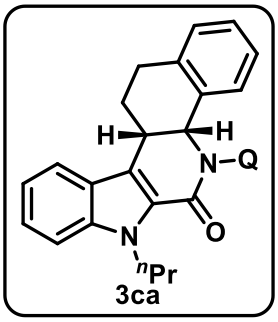


3ba

Physical State: Colourless solid; mp: 243-245 °C; yield: (34 mg, 78%). R_f: 0.30 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.95 (brs, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.45-7.34 (m, 3H), 7.26 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.3 Hz, 2H), 7.04 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.44 (t, J = 7.6 Hz, 1H), 6.18 (d, J = 6.4 Hz, 1H), 5.74 (brs, 1H), 4.69-4.59 (m, 2H), 3.73 (dt, J = 11.2, 3.6 Hz, 1H), 3.15-3.11 (m, 1H), 3.05-2.96 (m, 1H), 2.65

(brs, 1H), 2.56-2.22 (m, 1H), 1.42 (t, J = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 162.0, 150.4, 145.8, 138.5, 138.4, 136.8, 136.3, 133.8, 131.1, 130.5, 129.0, 128.6, 127.6, 127.4, 125.9, 125.5, 124.5, 124.5, 123.7 (2C), 121.3, 120.3, 119.8, 110.4, 62.1, 39.5, 32.9, 28.5, 24.7, 15.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{26}N_3O$: 444.2070; found: 444.2076. IR (KBr, cm^{-1}): 3054, 2986, 1646, 1421, 1274, 1060, 895, 749.

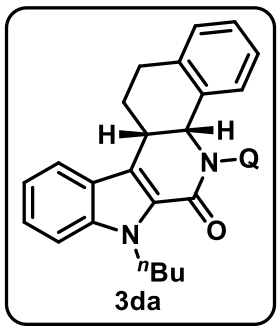
(4bR,11cS)-5-(Naphthalen-1-yl)-7-propyl-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*] indolo[2,3-*c*]quinolin-6-one (3ca):



Physical State: Colourless solid; mp: 240-242 °C; yield: (38 mg, 83%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (brs, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.45-7.39 (m, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.29-7.24 (m, 1H), 7.20-7.16 (m, 2H), 7.04 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.45 (t, J = 7.2 Hz, 1H), 6.17 (d, J = 6.8 Hz, 1H), 5.73 (brs, 1H), 4.62-4.50 (m, 2H), 3.74 (dt, J = 10.8, 3.6 Hz, 1H), 3.15-3.11 (m, 1H), 3.05-2.96 (m, 1H), 2.66 (brs, 1H), 2.26-2.22 (m, 1H), 1.87 (sextet, J = 7.2 Hz, 2H), 0.91 (t, J = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 162.2, 150.3, 145.8, 138.9, 138.7, 136.9, 136.3, 133.9, 131.1, 130.5, 129.1, 128.6, 127.6 (2C), 127.4, 126.0, 125.8, 124.5, 123.7, 121.3 (2C), 120.2, 119.8, 110.7, 62.2, 46.1, 32.9, 28.5, 24.7, 23.8, 11.4. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{28}N_3O$: 458.2232; found: 458.2218. IR (KBr, cm^{-1}): 3053, 2986, 1635, 1421, 1261, 1052, 895, 749.

(4b*R*,11c*S*)-7-Butyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*] indolo[2,3-*c*]quinolin-6-one (3da).

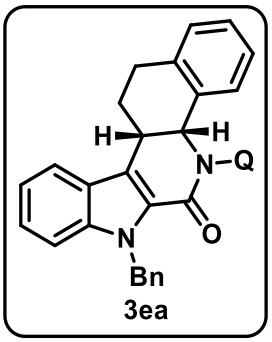
Physical State: Colourless solid; mp: 246-248 °C; yield: (39 mg, 84%). R_f: 0.50 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (brs, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.45-7.39 (m, 2H), 7.35 (t, J = 7.6 Hz,



3da

1H), 7.29-7.23 (m, 1H), 7.20-7.16 (m, 2H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.45 (t, *J* = 7.2 Hz, 1H), 6.18 (d, *J* = 7.2 Hz, 1H), 5.72 (d, *J* = 2.8 Hz, 1H), 4.66-4.53 (m, 2H), 3.74 (dt, *J* = 11.2, 3.6 Hz, 1H), 3.15-3.11 (m, 1H), 3.04-2.96 (m, 1H), 2.66 (brs, 1H), 2.26- 2.22 (m, 1H), 1.82 (quint, *J* = 7.6 Hz, 2H), 1.33 (sextet, *J* = 7.6 Hz, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): *δ* 162.1, 150.3, 145.8, 138.8, 138.7, 136.8, 136.3 (2C), 133.9, 131.1, 130.5, 129.1, 128.6, 127.6, 127.4 (2C), 126.0, 125.8, 124.4, 123.7, 121.3, 120.2, 119.8, 110.7, 62.2, 44.4, 32.9, 32.8, 28.5, 24.7, 20.2, 14.0. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{32}H_{30}N_3O$: 472.2389; found: 472.2384. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1421, 1261, 1046, 896, 749.

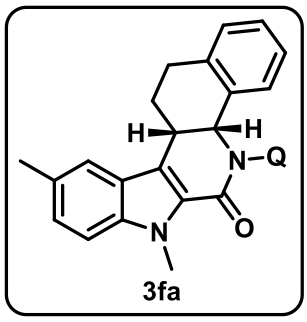
(4b*R*,11c*S*)-7-benzyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*] indolo[2,3-*c*]quinolin-6-one (3ea).



3ea

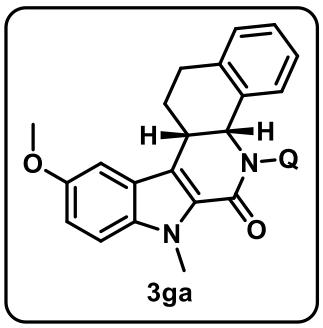
Physical State: Colourless solid; mp: 250-252 °C; yield: (41 mg, 82%). R_f: 0.50 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.93 (d, *J* = 3.2 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.41-7.37 (m, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.24 (brs, 1H), 7.22-7.20 (m, 4H), 7.19-7.12 (m, 3H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.49 (t, *J* = 7.6 Hz, 1H), 6.22 (d, *J* = 7.2 Hz, 1H), 6.01-6.00 (m, 1H), 5.83-5.79 (m, 1H), 5.74 (d, *J* = 3.2 Hz, 1H), 3.81 (dt, *J* = 10.8, 4.0 Hz, 1H), 3.18-3.11 (m, 1H), 3.05-3.00 (m, 1H), 2.71 (brs, 1H), 2.29-2.25 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): *δ* 162.3, 150.3, 145.6, 139.1, 138.7, 138.4, 136.9, 136.2, 134.1, 131.0, 130.4, 129.1, 128.7, 128.3, 127.6, 127.4, 127.1, 126.8, 126.0, 125.9, 124.8, 124.6, 124.2, 124.1, 121.3, 120.3, 120.2, 111.2, 62.4, 47.7, 33.0, 28.4, 24.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{35}H_{28}N_3O$: 506.2232; found: 506.2222. IR (KBr, cm^{-1}): 3052, 2985, 1638, 1420, 1271, 1053, 896, 746.

(4bR,11cS)-7,10-Dimethyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo [*h*]indolo[2,3-c]quinolin-6-one (3fa):



Physical State: Colourless solid; mp: 246-248 °C; yield: (30 mg, 68%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (brs, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.424-7.41 (m, 1H), 7.32-7.26 (m, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.44 (t, J = 7.6 Hz, 1H), 6.23 (d, J = 5.6 Hz, 1H), 5.74 (s, 1H), 4.10 (s, 3H), 3.70 (dt, J = 11.2, 3.2 Hz, 1H), 3.15-3.10 (m, 1H), 3.05-2.97 (m, 1H), 2.63 (brs, 1H), 2.50 (s, 3H), 2.25-2.19 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.4, 150.5, 146.0, 138.6, 138.1, 136.9, 136.3, 133.9, 131.1, 130.6, 129.2, 129.1, 128.6, 127.6, 127.5, 126.6, 126.0, 126.0, 124.5, 123.7, 123.2, 121.3, 119.5, 110.1, 62.2, 33.0, 31.3, 28.5, 24.8, 21.5. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{26}N_3O$: 444.2076; found: 444.2062. IR (KBr, cm^{-1}): 3050, 2986, 1638, 1420, 1271, 1047, 895, 744.

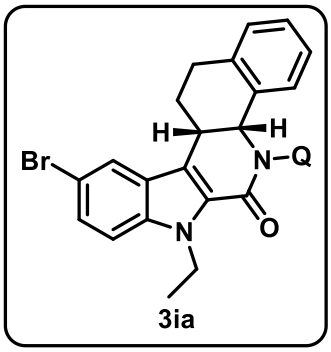
(4bR,11cS)-10-methoxy-7-methyl-5-(naphthalen-1-yl)4b,5,7,11c,12,13-hexahydro-6*H* -benzo[*h*]indolo[2,3-*c*]quinolin-6-one (3ga).



Physical State: Colourless solid; mp: 247-249 °C; yield: (34 mg, 75%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (brs, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.43-7.40 (m, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.29-7.25 (m, 1H), 7.19 (brs, 1H), 7.10 (s, 1H), 7.07-7.02 (m, 2H), 6.93 (t, J = 7.6 Hz, 1H), 6.44 (t, J = 7.2 Hz, 1H), 6.21 (d, J = 5.6 Hz, 1H), 5.75 (s, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.68 (dt, J = 10.8, 3.2 Hz, 1H), 3.16-3.12 (m, 1H), 3.06-3.00 (m, 1H), 2.64 (brs, 1H), 2.24-2.21 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.2, 154.3, 150.4, 146.0, 138.5, 136.8, 136.3, 135.1, 133.8, 131.1, 130.6, 129.0, 128.6, 127.6, 127.5,

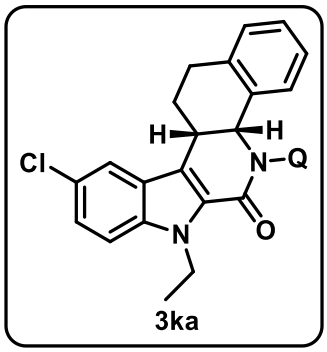
126.4, 126.0, 124.5, 123.6, 123.0, 121.3, 115.7, 111.3, 100.8, 62.2, 55.9, 32.9, 31.3, 28.5, 24.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{26}N_3O_2$: 460.2025; found: 460.2016. IR (KBr, cm^{-1}): 3053, 2986, 1636, 1421, 1264, 1058, 895, 748.

(4bR,11cS)-10-Bromo-7-ethyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*]indolo[2,3-*c*]quinolin-6-one (3ia).



Physical State: Colourless solid; mp: 250-252 °C; yield: (41 mg, 79%). R_f: 0.40 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.96 (brs, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.86 (brs, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.43-7.41 (m, 2H), 7.31 (d, J = 9.2 Hz, 1H), 7.29-7.24 (m, 1H), 7.18 (brs, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.95 (t, J = 7.2 Hz, 1H), 6.45 (t, J = 7.6 Hz, 1H), 6.18 (d, J = 6.8 Hz, 1H), 5.72 (brs, 1H), 4.66-4.56 (m, 2H), 3.67 (dt, J = 11.2, 3.6 Hz, 1H), 3.14-3.10 (m, 1H), 3.04-2.96 (m, 1H), 2.62 (brs, 1H), 2.23-2.20 (m, 1H), 1.40 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.6, 150.4, 145.7, 138.3, 137.0, 136.7, 136.3, 133.5, 131.0, 130.5, 129.1, 128.7, 127.7, 127.5, 127.4, 126.4, 126.0, 125.3, 124.5, 122.9, 122.7, 121.3, 113.0, 111.9, 62.1, 39.7, 32.8, 28.4, 24.6, 15.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{25}BrN_3O$: 522.1176; found: 522.1218. IR (KBr, cm^{-1}): 3053, 2987, 1634, 1421, 1275, 1060, 896, 763.

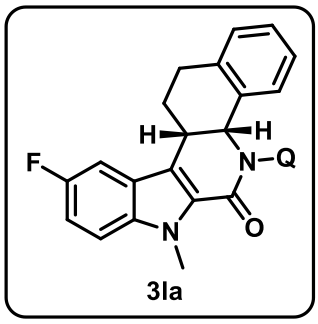
(4bR,11cS)-10-Chloro-7-ethyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*]indolo[2,3-*c*]quinolin-6-one (3ka).



Physical State: Colourless solid; mp: 250-252 °C; yield: (38 mg, 80%). R_f: 0.30 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.96 (d, J = 2.8 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 1.6 Hz, 1H), 7.67 (dd, J = 8.2, 1.2 Hz, 1H), 7.43 (dd, J = 8.2, 4.4 Hz, 1H), 7.38-7.36 (m, 1H), 7.30 (dd, J = 8.8, 2.0 Hz, 1H), 7.28-7.25 (m, 1H), 7.19 (brs, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz,

1H), 6.46 (t, *J* = 7.6 Hz, 1H), 6.20 (d, *J* = 7.6 Hz, 1H), 5.72 (d, *J* = 3.6 Hz, 1H), 4.67-4.57 (m, 2H), 3.70 (dt, *J* = 11.2, 3.6 Hz, 1H), 3.17-3.10 (m, 1H), 3.05-3.00 (m, 1H), 2.64 (brs, 1H), 2.26-2.20 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.7, 150.5, 145.7, 138.4, 136.8, 136.7, 136.4, 133.6, 131.1, 130.5, 129.1, 128.7, 127.7, 127.6, 126.6, 126.0, 125.5, 124.9, 124.6, 124.6, 123.0, 121.4, 119.6, 111.5, 62.1, 39.8, 32.8, 28.4, 24.6, 15.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{25}ClN_3O$: 478.1681; found: 478.1679. IR (KBr, cm^{-1}): 3052, 2985, 1638, 1420, 1271, 1050, 896, 742.

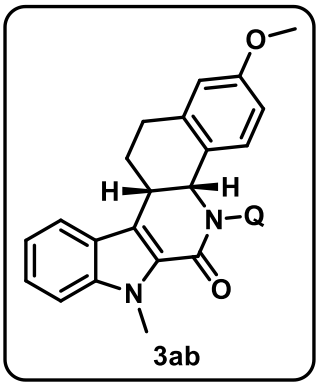
(4bR,11cS)-10-Fluoro-7-methyl-5-(naphthalen-1-yl) 4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*]indolo[2,3-*c*]quinolin-6-one (3la).



3la

Physical State: Colourless solid; mp: 243-245 °C; yield: (37 mg, 82%). R_f: 0.30 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.97 (brs, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.43-7.42 (m, 1H), 7.36-7.33 (m, 2H), 7.29 (t, *J* = 7.0 Hz, 1H), 7.25-7.20 (m, 1H), 7.13 (td, *J* = 9.1, 2.1 Hz, 1H), 7.03 (d, *J* = 5.6 Hz, 1H), 6.94 (t, *J* = 7.0 Hz, 1H), 6.47 (t, *J* = 7.0 Hz, 1H), 6.28 (brs, 1H), 5.74 (brs, 1H), 4.11 (s, 3H), 3.72 (d, *J* = 10.5 Hz, 1H), 3.14-3.10 (m, 1H), 3.02-3.00 (m, 1H), 2.63 (brs, 1H), 2.23-2.20 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz): δ 161.9, 157.9 (d, *J* = 234.5 Hz), 150.5, 145.8, 138.4, 136.8, 136.3, 136.2, 133.8, 131.0, 130.4, 129.1, 128.7, 127.7, 127.6, 127.4, 126.0, 124.6, 123.5 (d, *J* = 8.7 Hz), 123.2 (d, J = 5.2 Hz), 121.3, 113.5 (d, *J* = 26.2 Hz), 111.3 (d, *J* = 10.5 Hz), 104.6 (d, *J* = 22.7 Hz), 62.2, 32.9, 31.5, 28.4, 24.7. $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 376 MHz): δ -123.68. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{23}FN_3O$: 448.1820; found: 448.1830. IR (KBr, cm^{-1}): 3053, 2986, 1638, 1420, 1271, 1062, 896, 746.

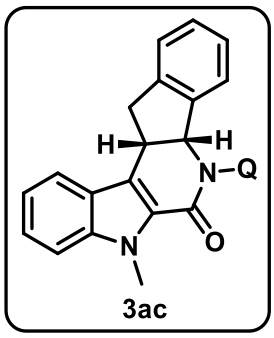
(4bR,11cS)-2-methoxy-7-methyl-5-(naphthalen-1-yl)-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*]indolo[2,3-*c*]quinolin-6-one (3ab).



3ab

Physical State: Colourless solid; mp: 244-246 °C; yield: (35 mg, 77%). R_f: 0.50 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (brs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.44-7.36 (m, 3H), 7.31-7.28 (m, 1H), 7.21-7.17 (m, 2H), 6.55 (brs, 1H), 6.06 (brs, 1H), 6.00-5.98 (m, 1H), 5.74 (brs, 1H), 4.13 (s, 3H), 3.68-3.64 (m, 1H), 3.62 (s, 3H), 3.12-3.07 (m, 1H), 3.04-2.95 (m, 1H), 2.60 (brs, 1H), 2.22-2.18 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.3, 158.8, 150.5, 146.0, 139.5, 138.6, 138.2, 136.3, 131.8, 131.8, 131.2, 129.1, 127.5, 126.1, 126.0, 124.6, 123.8, 123.6, 121.3, 120.2, 119.9, 112.9, 110.9, 110.4, 61.7, 55.0, 33.2, 31.2, 29.0, 24.7. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{26}N_3O_2$: 460.2025; found: 460.2016. IR (KBr, cm^{-1}): 3053, 2984, 1640, 1422, 1056, 1270, 890, 745.

(4bR,11cS)-7-Methyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6] pyrido[3,4-*b*]indol-6(5*H*)-one (3ac).

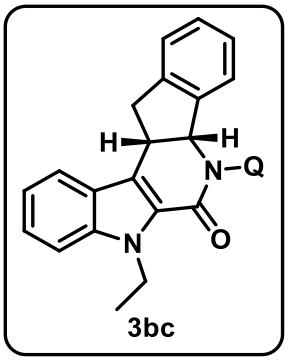


3ac

Physical State: Colourless solid; mp: 241-243 °C; yield: (32 mg, 78%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.96 (brs, 1H), 8.23 (brs, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.47-7.44 (m, 2H), 7.41-7.40 (m, 1H), 7.39-7.37 (m, 1H), 7.25-7.19 (m, 3H), 7.12 (brs, 1H), 6.81 (brs, 1H), 6.28 (d, J = 6.3 Hz, 1H), 6.05 (brs, 1H), 4.42-4.41 (m, 1H), 4.12 (s, 3H), 3.54-3.51 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 161.4, 150.6, 144.8, 143.1, 142.2, 139.6, 137.9, 136.4, 132.1, 129.6, 128.1, 127.8, 126.1, 125.8, 125.7, 125.1, 124.7, 124.5, 124.4, 121.4, 120.6, 120.4, 120.0, 110.4, 68.1, 38.8, 38.4, 31.4. HRMS (ESI) m/z: $[M+H]^+$ calcd for

$C_{28}H_{22}N_3O$: 416.1757; found: 416.1772. IR (KBr, cm^{-1}): 3050, 2983, 1662, 1422, 1261, 1076, 890, 746.

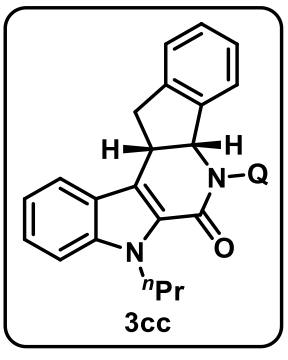
(4bR,11cS)-7-Ethyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6] pyrido[3,4-*b*]indol-6(5*H*)-one (3bc).



3bc

Physical State: Colourless solid; mp: 243-245 °C; yield: (35 mg, 81%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (brs, 1H), 8.22 (d, J = 6.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.47-7.42 (m, 3H), 7.37 (t, J = 7.6 Hz, 2H), 7.25-7.18 (m, 2H), 7.13 (brs, 1H), 6.82 (brs, 1H), 6.27 (d, J = 7.2 Hz, 1H), 6.03 (brs, 1H), 4.73-4.68 (m, 1H), 4.65-4.58 (m, 1H), 4.44-4.39 (m, 1H), 3.52 (d, J = 6.8 Hz, 2H), 1.39 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.0, 150.4, 144.9, 143.2, 142.3, 138.6, 138.2, 136.3, 132.0, 129.6, 128.0, 127.8, 126.0, 125.8, 125.6, 124.7, 124.7, 124.6, 124.5, 121.3, 120.6, 120.5, 119.9, 110.4. 68.2, 39.6, 38.8, 38.5, 15.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{24}N_3O$: 430.1914; found: 430.1925. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1456, 1275, 1059, 763, 749.

(4bR,11cS)-5-(Naphthalen-1-yl)-7-propyl-4b,7,11c,12 tetrahydroindeno[2',1':5,6] pyrido[3,4-*b*]indol-6(5*H*)-one (3cc).

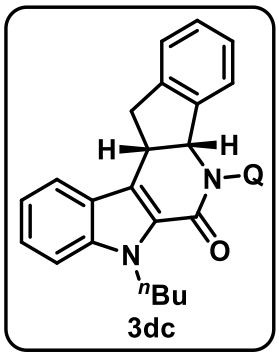


3cc

Physical State: Colourless solid; mp: 246-248 °C; yield: (34 mg, 78%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (brs, 1H), 8.21 (d, J = 6.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.45-7.41 (m, 3H), 7.35 (t, J = 8.0 Hz, 2H), 7.23-7.21 (m, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.11 (brs, 1H), 6.80 (brs, 1H), 6.23 (d, J = 7.2 Hz, 1H), 6.01 (brs, 1H), 4.61-4.50 (m, 2H), 4.41-4.36 (m, 1H), 3.51 (d, J = 6.8 Hz, 2H), 1.84 (sextet, J = 7.2 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100

MHz): δ 161.1, 150.5, 144.7, 143.2, 142.2, 138.9, 138.0, 136.4, 132.1, 129.6, 128.0, 127.8, 126.0, 125.8, 125.6, 124.8, 124.54, 124.46, 124.4, 121.3, 120.5, 120.4, 119.8, 110.7, 68.0, 46.2, 38.8, 38.4, 23.8, 11.4. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{26}N_3O$: 444.2070; found: 444.2093. IR (KBr, cm^{-1}): 3082, 2987, 1667, 1421, 1276, 1071, 895, 765.

(4bR,11cS)-7-Butyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6] pyrido[3,4-*b*]indol-6(5*H*)-one (3dc).

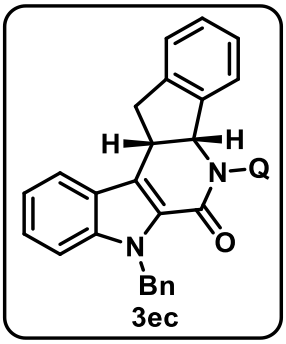


3dc

Physical State: Colourless solid; mp: 244-246 °C; yield: (34 mg, 74%). R_f: 0.40 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.93 (brs, 1H), 8.20 (d, J = 7.2 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.46-7.41 (m, 3H), 7.37-7.33 (m, 2H), 7.23-7.17 (m, 2H), 7.11 (brs, 1H), 6.80 (brs, 1H), 6.23 (d, J = 7.2 Hz, 1H), 6.00 (brs, 1H), 4.62-4.54 (m, 2H), 4.41-4.36 (m, 1H), 3.50 (d, J = 6.8 Hz, 2H), 1.80 (quint, J = 7.6 Hz, 2H), 1.37-1.30 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 161.1, 150.4, 144.7, 143.2, 142.3, 138.9, 138.1, 136.4, 132.1, 129.6, 128.0, 127.8, 126.0, 125.8, 125.6, 124.8, 124.5 (2C), 124.4, 121.4, 120.5, 120.4, 119.8, 110.7, 68.1, 44.6, 38.8, 38.4, 32.7, 20.2, 13.9. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{31}H_{28}N_3O$: 458.2227; found: 458.2252. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1456, 1275, 1046, 763, 749.

(4bR,11cS)-7-Benzyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6] pyrido[3,4-*b*]indol-6(5*H*)-one (3ec).

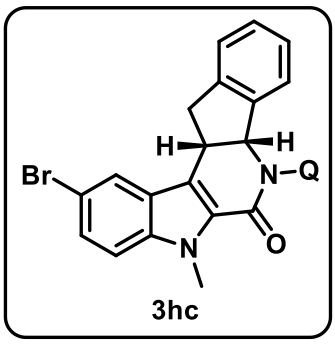
Physical State: Colourless solid; mp: 245-247 °C; yield: (40 mg, 81%). R_f: 0.30 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.92 (brs, 1H), 8.19 (d, J = 7.2 Hz, 1H), 7.79 (t, J = 7.6 Hz, 2H), 7.46-7.42 (m, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.31-7.27 (m, 1H), 7.25-7.20 (m, 2H), 7.18-7.13 (m, 7H), 6.83 (brs, 1H), 6.28 (d, J = 7.2 Hz, 1H), 5.99 (d, J = 15.6 Hz, 2H), 5.83 (d, J = 15.6 Hz, 1H), 4.46-4.41 (m, 1H), 3.54 (d, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$



NMR ($CDCl_3$, 100 MHz): δ 161.2, 150.4, 144.6, 143.1, 142.2, 139.2, 138.5, 138.0, 136.3, 132.0, 129.5, 128.3, 128.0, 127.8, 126.9, 126.8, 126.0, 125.8, 125.6, 125.0, 124.9, 124.8, 124.4, 121.3, 121.2, 120.4, 120.2, 111.2, 68.2, 47.8, 38.8, 38.5. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{34}H_{26}N_3O$: 492.2070; found: 492.2106. IR (KBr, cm^{-1}): 3040, 2987, 1635, 1456, 1275, 1070, 896, 763.

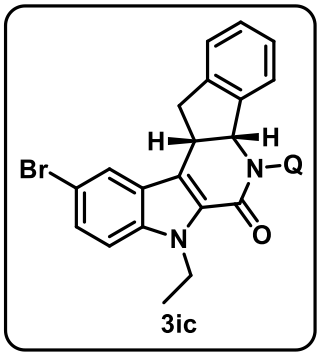
(4bR,11cS)-10-Bromo-7-methyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6]pyrido[3,4-*b*]indol-6(5*H*)-one (3hc).

Physical State: Colourless solid; mp: 247-249 °C; yield: (39 mg, 79%). R_f: 0.40 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.95 (brs, 1H), 8.23 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.83 (dd, J = 8.4, 1.2 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.45-7.42 (m, 2H), 7.39 (brs, 1H), 7.28-7.25 (m, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 6.4 Hz, 1H), 6.82 (brs, 1H), 6.30 (d, J = 7.6 Hz, 1H), 6.03 (brs, 1H), 4.38-4.33 (m, 1H), 4.08 (s, 3H), 3.54-3.49 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.9, 150.6, 142.8, 141.9, 138.2, 137.8, 136.5, 131.9, 129.6, 128.2, 128.0, 127.5, 126.1, 126.0 (2C), 125.9, 125.8, 125.7, 124.5, 122.8, 121.4, 119.8, 113.1, 111.9, 68.0, 38.6, 38.2, 31.5. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{21}BrN_3O$: 494.0863; found: 494.0855. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1456, 1275, 1046, 762, 746.



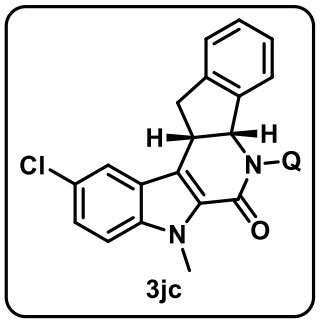
(4bR,11cS)-10-Bromo-7-ethyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6]pyrido[3,4-*b*]indol-6(5*H*)-one (3ic).

Physical State: Colourless solid; mp: 246-248 °C; yield: (39 mg, 76%). R_f: 0.40 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 400 MHz): δ ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (brs, 1H), 8.22 (d, J = 7.2 Hz, 1H), 7.89 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.49-7.41 (m, 3H), 7.37



(brs, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.24 (m, 1H), 7.13 (brs, 1H), 6.83 (brs, 1H), 6.30 (d, J = 7.2 Hz, 1H), 6.01 (brs, 1H), 4.69-4.64 (m, 1H), 4.60-4.54 (m, 1H), 4.36-4.34 (m, 1H), 3.50 (d, J = 6.4 Hz, 2H), 1.37 (t, J = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.6, 150.5, 144.8, 142.9, 142.0, 137.9, 137.2, 136.4, 131.9, 129.6, 128.1, 127.9, 127.4, 126.2, 126.0, 125.8, 125.7, 125.6, 124.5, 122.9, 121.4, 119.9, 113.0, 111.9, 68.1, 39.8, 38.6, 38.2, 15.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{23}BrN_3O$: 508.1019; found: 508.1047. IR (KBr, cm^{-1}): 3053, 2987, 1645, 1421, 1274, 1066, 896, 749.

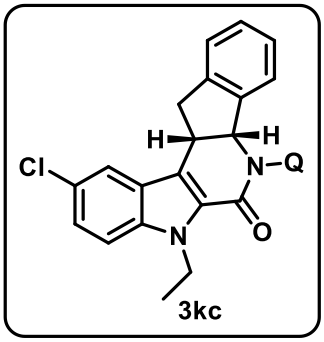
(4bR,11cS)-10-Chloro-7-methyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6]pyrido[3,4-*b*]indol-6(5*H*)-one (3jc).



Physical State: Colourless solid; mp: 248-250 °C; yield: (33 mg, 73%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.96 (brs, 1H), 8.23 (brs, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.73 (brs, 1H), 7.48-7.45 (m, 2H), 7.37 (brs, 1H), 7.32 (s, 2H), 7.25-7.23 (m, 1H), 7.13 (brs, 1H), 6.83 (brs, 1H), 6.31 (d, J = 7.7 Hz, 1H), 6.03 (brs, 1H), 4.36 (brs, 1H), 4.09 (s, 3H), 3.52-3.47 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz): δ 161.0, 150.6, 144.7, 142.8, 142.0, 137.9, 137.8, 136.5, 132.0, 129.6, 128.2, 128.0, 126.3, 126.0, 125.8, 125.7, 125.6, 125.2, 125.0, 124.5, 121.4, 119.9, 119.7, 111.5, 68.0, 38.6, 38.2, 31.5. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{21}ClN_3O$: 450.1368; found: 450.1372. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1421, 1275, 1063, 896, 763.

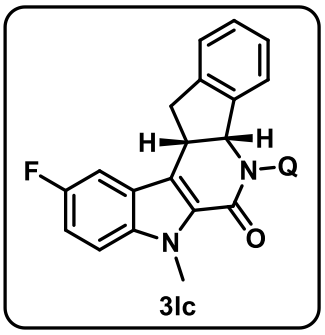
(4bR,11cS)-10-Chloro-7-ethyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6]pyrido[3,4-*b*]indol-6(5*H*)-one (3kc).

Physical State: Colourless solid; mp: 247-249 °C; yield: (37 mg, 81%). R_f: 0.50 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (brs, 1H), 8.22 (d, J = 6.8 Hz, 1H),



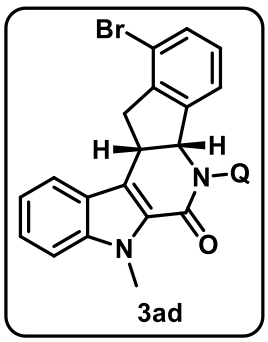
7.83 (d, *J* = 8.4 Hz, 1H), 7.73 (brs, 1H), 7.48-7.46 (m, 2H), 7.35-2.28 (m, 3H), 7.24-2.23 (m, 1H), 7.13 (brs, 1H), 6.83 (brs, 1H), 6.30 (d, *J* = 7.2 Hz, 1H), 6.01 (brs, 1H), 4.70-4.65 (m, 1H), 4.61-4.52 (m, 1H), 4.36-4.35 (m, 1H), 3.50 (d, *J* = 6.0 Hz, 2H), 1.37 (t, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.6, 150.5, 144.5, 142.8, 142.0, 137.7, 136.8, 136.5, 132.0, 129.6, 128.1, 127.9, 126.0, 125.7 (2C), 125.6, 125.5, 125.4, 125.0, 124.5, 121.4, 119.9, 119.7, 111.5, 68.0, 39.8, 38.5, 38.1, 15.6. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{23}ClN_3O$: 464.1524; found: 464.1526. IR (KBr, cm^{-1}): 3054, 2996, 1652, 1421, 1274, 1077, 896, 749.

(4bR,11cS)-10-Fluoro-7-methyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6]pyrido[3,4-*b*]indol-6(5*H*)-one (3lc).



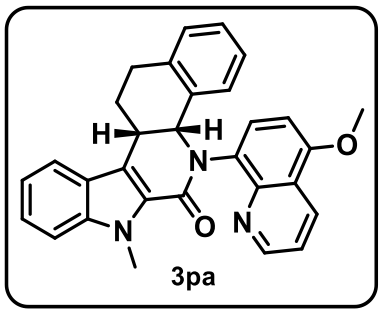
Physical State: Colourless solid; mp: 247-249 °C; yield: (34 mg, 78%). R_f: 0.40 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (brs, 1H), 8.22 (d, *J* = 6.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.48-7.44 (m, 2H), 7.40-7.38 (m, 2H), 7.31 (dd, *J* = 8.8, 4.0 Hz, 1H), 7.24-7.22 (m, 1H), 7.14-7.10 (m, 2H), 6.82 (brs, 1H), 6.31 (d, *J* = 7.2 Hz, 1H), 6.02 (brs, 1H), 4.37-4.35 (m, 1H), 4.09 (s, 3H), 3.48 (d, *J* = 6.4 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.0, 157.9 (d, *J* = 235.0 Hz), 150.5, 144.8, 142.9, 142.0, 138.0, 136.4 (d, *J* = 4.0 Hz), 131.8, 129.6, 128.1, 127.9, 126.6, 126.0, 125.75, 125.70, 124.5, 124.4, 124.3, 121.4, 120.2 (d, *J* = 5.0 Hz), 113.5 (d, *J* = 27.0 Hz), 111.3 (d, *J* = 10.0 Hz), 104.8 (d, *J* = 23.0 Hz), 68.2, 38.5, 38.3, 31.5. $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 376 MHz): δ -123.46. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{21}FN_3O$: 434.1663; found: 434.1660. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1421, 1275, 1070, 896, 749.

(4bR,11cS)-1-Bromo-7-methyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetrahydroindeno [2',1':5,6]pyrido[3,4-*b*]indol-6(5*H*)-one (3ad).



Physical State: Colourless solid; mp: 250-252 °C; yield: (34 mg, 69%). R_f: 0.30 (in 50% EtOAc/Hexane. ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.94 (brs, 1H), 8.23 (brs, 1H), 7.84-7.83 (m, 1 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.50 (brs, 1H), 7.44 (brs, 1H), 7.4-7.38 (m, 2H), 7.29-7.26 (m, 1H), 7.26-7.24 (m, 1H), 7.24-7.21 (m, 1H), 6.70 (brs, 1H), 6.26 (d, J = 7.0 Hz, 1H), 6.13 (brs, 1H), 4.46 (brs, 1H), 4.12 (s, 3H), 3.58 (dd, J = 8.8, 5.0 Hz, 1H), 3.52 (brs, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 161.2, 150.6, 144.7, 144.1, 143.4, 139.7, 137.7, 136.4, 132.0, 131.2, 129.6, 128.0, 127.5, 126.1, 125.0, 124.9, 124.6, 124.3, 121.5, 120.4, 120.2, 120.1, 119.8, 110.4, 68.9, 39.9, 37.5, 31.4. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{21}N_3OBr$: 494.0868; found: 494.0859. IR (KBr, cm^{-1}): 3050, 2985, 1638, 1420, 1271, 1066, 896, 746.

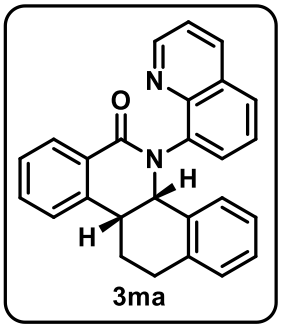
(4bR,11cS)-5-(5-methoxyquinolin-8-yl)-7-methyl-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*]indolo[2,3-*c*]quinolin-6-one (3pa).



Physical State: Colourless liquid; yield: (32 mg, 70%). R_f: 0.40 (in 30% EtOAc/Hexane). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.55 (s, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.42-7.36 (m, 3H), 7.19 (t, J = 7.7 Hz, 1H), 7.11-7.04 (m, 2H), 6.96 (s, 1H), 6.58 (s, 1H), 6.51 (t, J = 7.7 Hz, 1H), 6.31 (s, 1H), 5.73 (s, 1H), 4.12 (s, 3H), 3.92 (s, 3H), 3.76-3.74 (m, 1H), 3.13-3.10 (m, 1H), 3.03-2.98 (m, 1H), 2.60 (s, 1H), 2.23-2.21 (m, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 162.5, 154.5, 150.7, 150.7, 146.2, 139.5, 131.1, 130.9, 130.6, 128.6, 127.5 (2C), 126.2, 124.6, 124.6, 123.6, 123.6, 121.4, 120.4, 120.2, 119.9 (2C), 110.4, 103.5, 62.1, 55.7,

32.9, 31.2, 28.5, 24.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{26}N_3O_2$: 460.2020; Found: 460.2012. IR (KBr, cm^{-1}): 3038, 2987, 1651, 1421, 1240, 1069, 771.

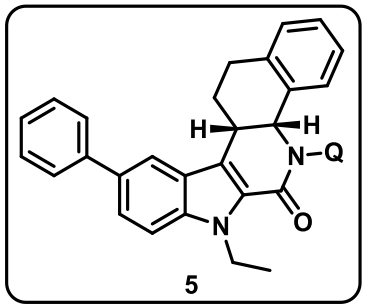
5-(Quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ma).



3ma

Physical State: Colourless solid; mp: 204-206 °C; yield: (30 mg, 81%). R_f: 0.40 (in 20% EtOAc/DCM). ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (brs, 1H), 8.20 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 8.4, 1.2 Hz, 1H), 7.54 (td, J = 7.2, 0.8 Hz, 1H), 7.43- 7.36 (m, 3H), 7.28-7.26 (m, 1H), 7.14 (brs, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.44 (t, J = 7.6 Hz, 1H), 6.15 (d, J = 6.4 Hz, 1H), 5.69 (s, 1H), 3.43 (dt, J = 11.6, 2.8 Hz, 1H), 3.14 (ddd, J = 17.2, 6.4, 2.0 Hz, 1H), 3.06-2.98 (m, 1H), 2.73 (s, 1H), 2.12-2.07 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.5, 150.4, 145.6, 143.0, 138.6, 136.2, 132.3 (2C), 130.7, 130.6, 129.2, 129.0, 128.7, 128.6, 127.8, 127.5, 127.2, 126.5, 125.9, 124.6, 124.5, 121.2, 59.8, 39.0, 28.3, 25.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O$: 377.1648; Found: 377.1651. IR (KBr, cm^{-1}): 3018, 2975, 1665, 1215, 1035.

(4bR,11cS)-7-ethyl-5-(naphthalen-1-yl)-10-phenyl-4b,5,7,11c,12,13-hexahydro-6*H*-benzo[*h*]indolo[2,3-*c*]quinolin-6-one (5).

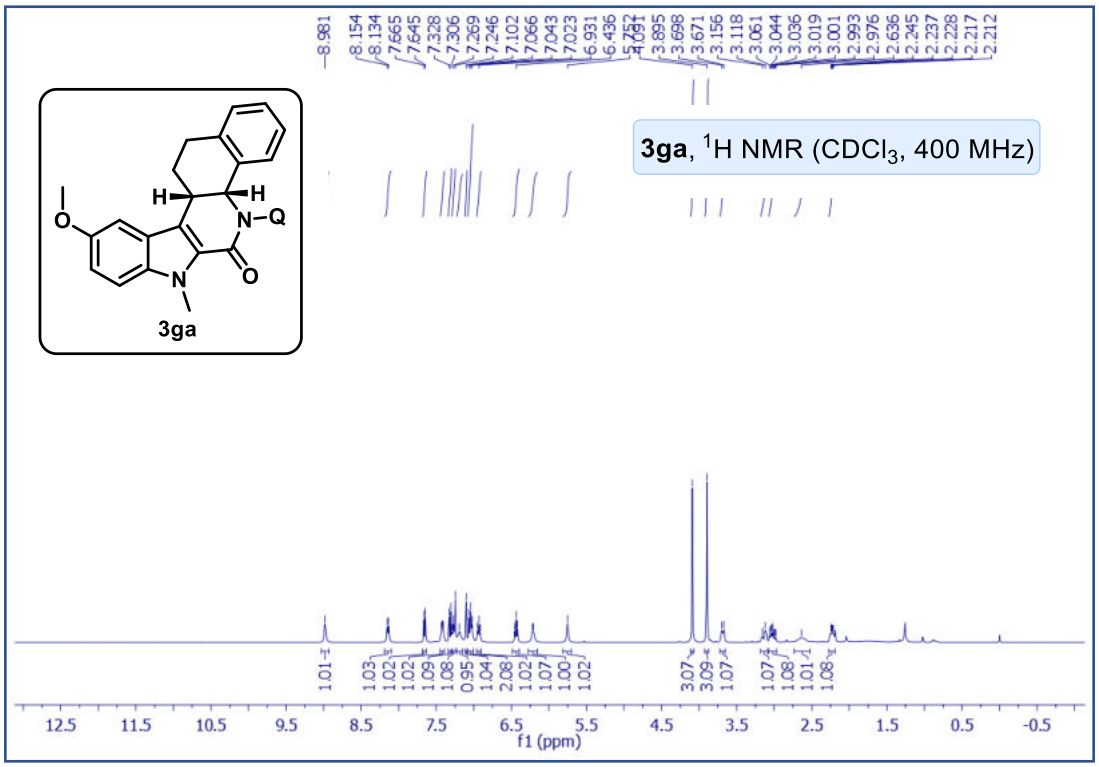


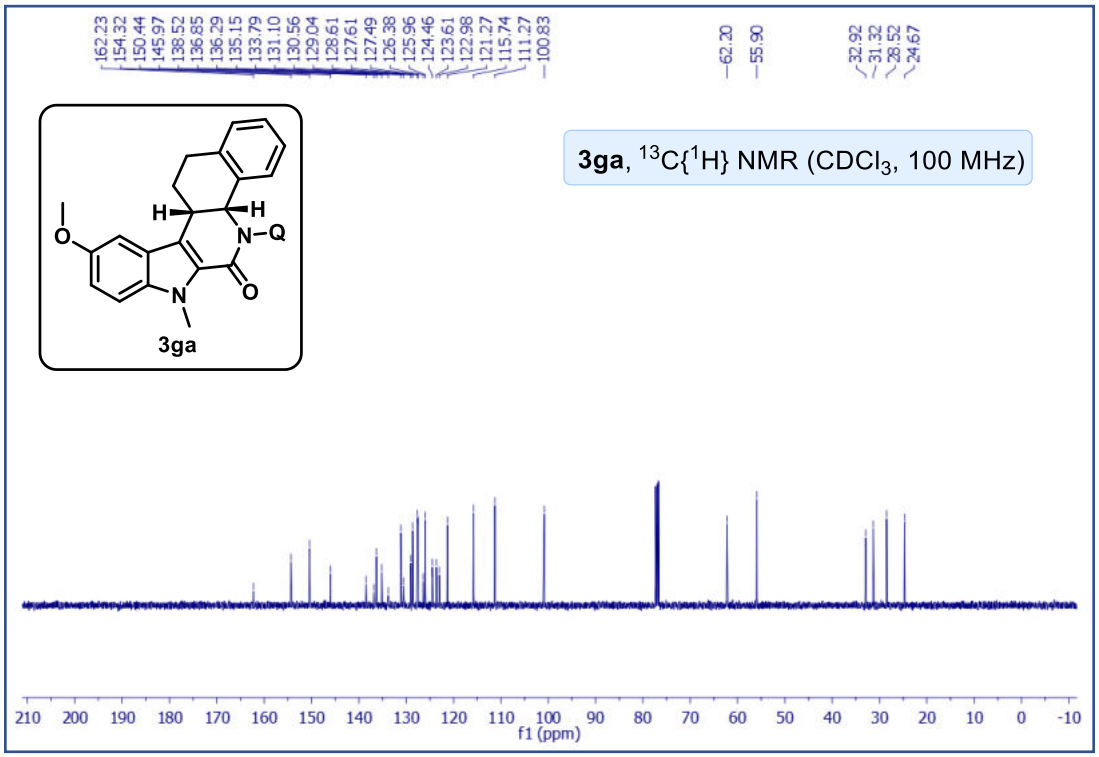
5

Physical State: Colourless solid; mp: 260-262 °C; yield: (41 mg, 79%). R_f: 0.50 (in 50% EtOAc/Hexane. ^1H NMR ($CDCl_3$, 700 MHz): δ 8.97 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.70-7.67 (m, 3H), 7.63 (dd, J = 8.4, 1.6 Hz, 1H), 7.53-7.50 (m, 1H), 7.48-7.42 (m, 2H), 7.35 (m, 1H), 7.30-7.26 (m, 2H), 7.19 (brs, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.96 (t, J = 6.8 Hz, 1H), 6.46 (t, J = 7.2 Hz, 1H), 6.18 (d, J = 5.6 Hz, 1H), 5.76 (d, J = 3.2 Hz, 1H), 4.73-4.63 (m, 2H), 3.79-3.75 (m, 1H), 3.19-3.13 (m, 1H), 3.08-2.99 (m, 1H), 2.69 (brs, 1H),

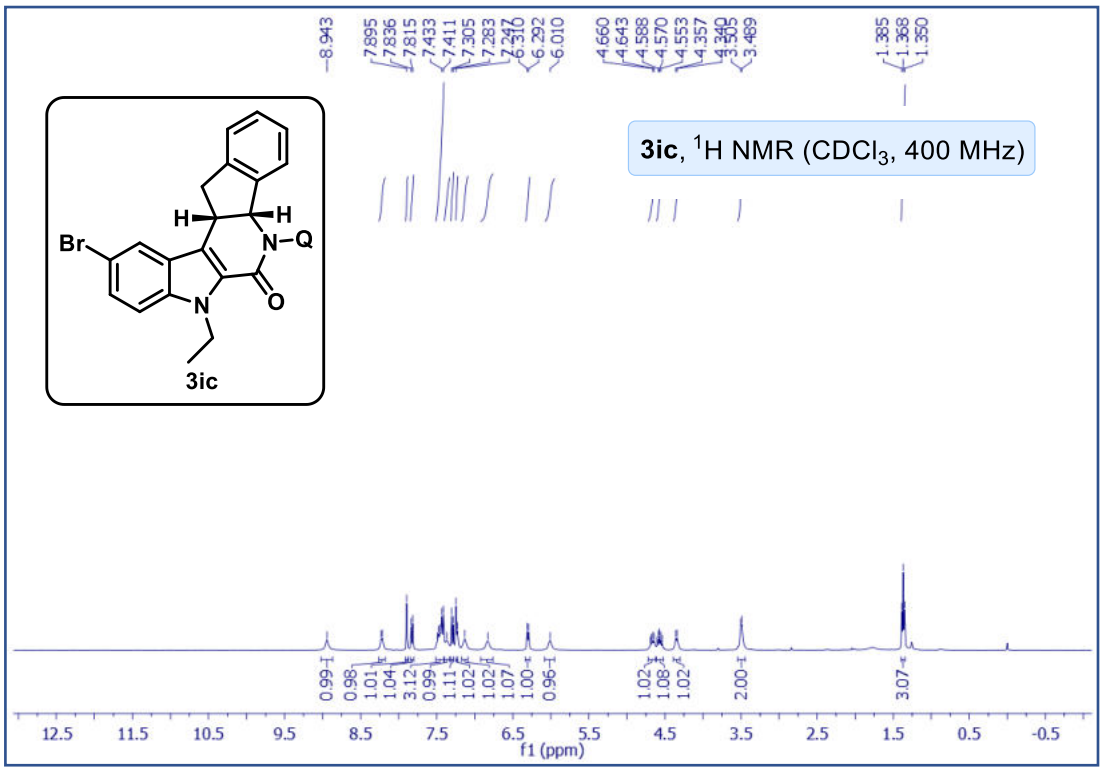
2.30-2.26 (m, 1H), 1.45 (t, J = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz): δ 162.0, 150.4, 145.9, 142.2, 138.6, 138.0, 136.9, 136.3, 133.8, 133.6, 131.1, 130.6, 129.1, 128.7, 128.7, 127.7, 127.5, 127.4, 126.6, 126.2, 126.0, 124.6, 124.5, 124.7, 124.1, 121.3, 118.6, 110.7, 62.2, 39.7, 33.0, 28.6, 24.7, 15.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{36}H_{30}N_3O$: 520.2389; Found: 520.2389. IR (KBr, cm^{-1}): 3053, 2986, 1640, 1420, 1271, 1050, 896, 745.

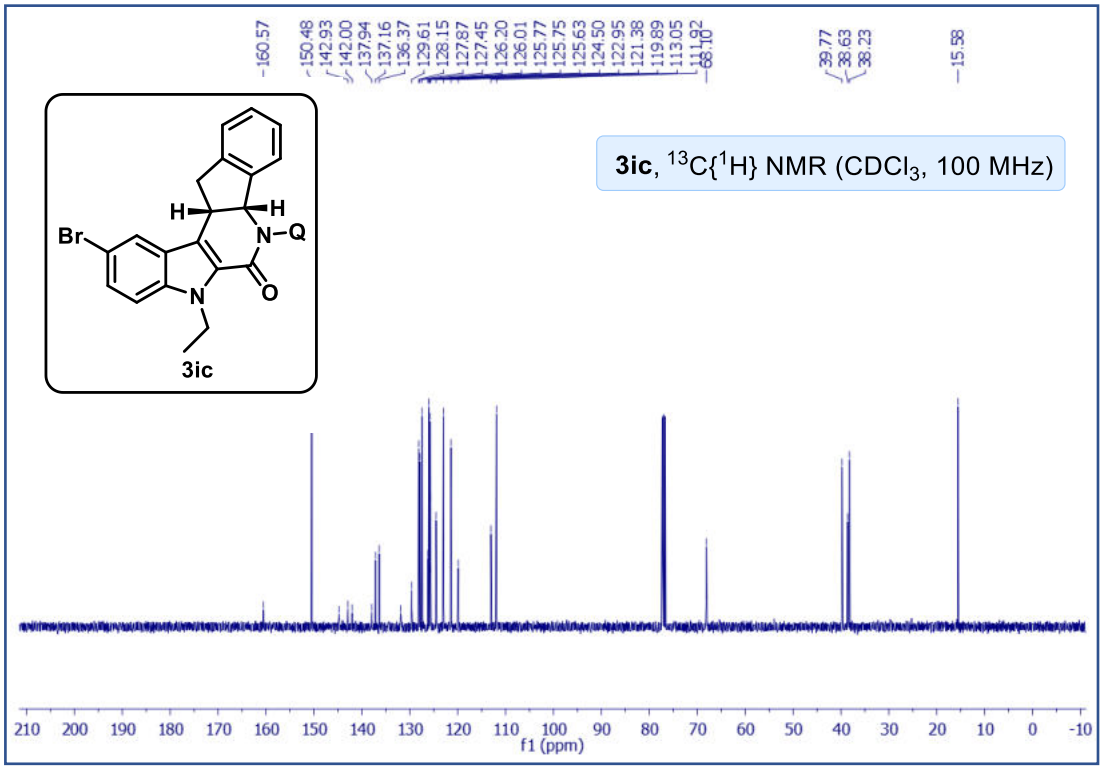
NMR spectra of (4b*R*,11c*S*)-10-methoxy-7-methyl-5-(naphthalen-1-yl) 4b,5,7,11c,12, 13-hexahydro-6*H*-benzo[*h*]indolo[2,3-*c*]quinolin-6-one (3ga).



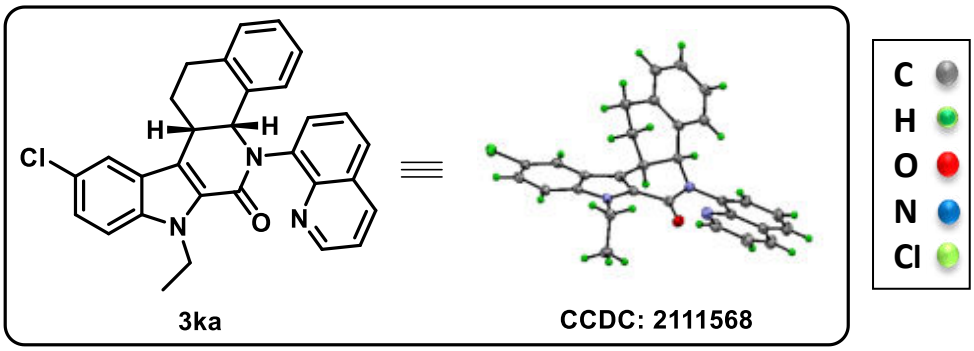


NMR spectra of (4bR,11cS)-10-Bromo-7-ethyl-5-(naphthalen-1-yl)-4b,7,11c,12-tetra hydroindeno[2',1':5,6]pyrido[3,4-*b*]indol-6(5*H*)-one (3ic).

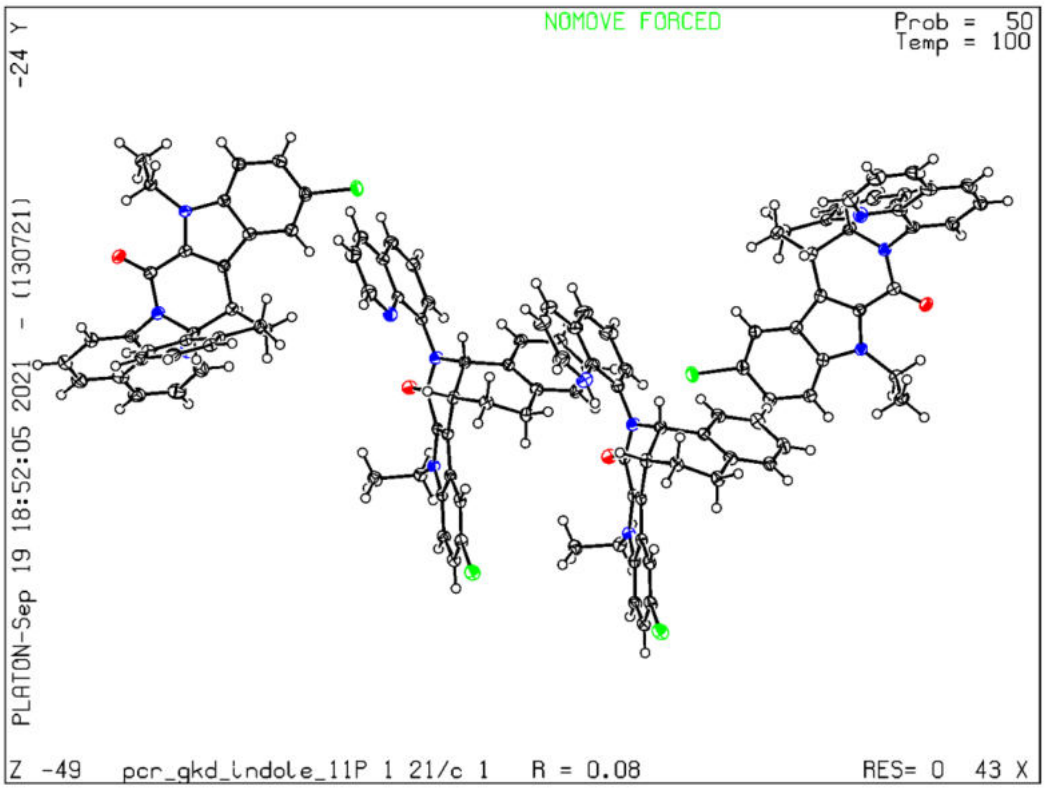




Crystal structure of 3ka



Datablock pcr_gkd_indole_1182 - ellipsoid plot



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Chapter 4

Co(II) Catalysed C-H/N-H Annulation of Cyclic Alkenes with Benzamides at Room Temperature; An Easy Access to the Core Skeleton of Hexahydrobenzo[*c*]phenanthridine type-Alkaloids.

Chapter 4

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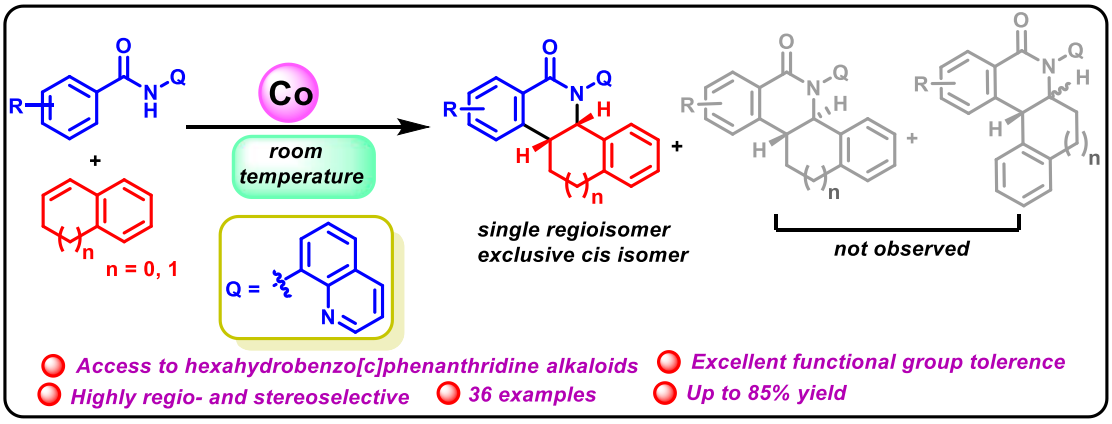


4.1 ABSTRACT: We report a highly regio- and stereoselective synthesis of the core skeleton of hexahydrobenzo[*c*]phenanthridine-type alkaloids at room temperature using $Co(acac)_2$. The reaction is compatible for a wide range of substrates and also provides good to excellent yield of products.

4.2 INTRODUCTION

Over the past few decades, directed C-H bond activation strategy has emerged as a powerful tool for the synthesis of natural products and medicinally important heterocycles.[1] Noble metals such as Rh, Ru, Ir and Pd has been widely explored in the realm of C-H bond activation reactions. Though these reaction protocols are very efficient, their high cost and low natural abundance are significant drawbacks.[2] Therefore, in recent years C-H activation reaction using first-row transition metals[3] have become more attractive on

account of its high natural abundance and low cost. Several groups like Hiyama,[4a] Piguel[4b] and many others[5] have described the use of first-row transition metal catalysts for the C-H activation reactions. Among the first-row transition metal catalysts cobalt is one of the most widely used transition metal for the C-H activation reactions due to its low cost and availability.[6]

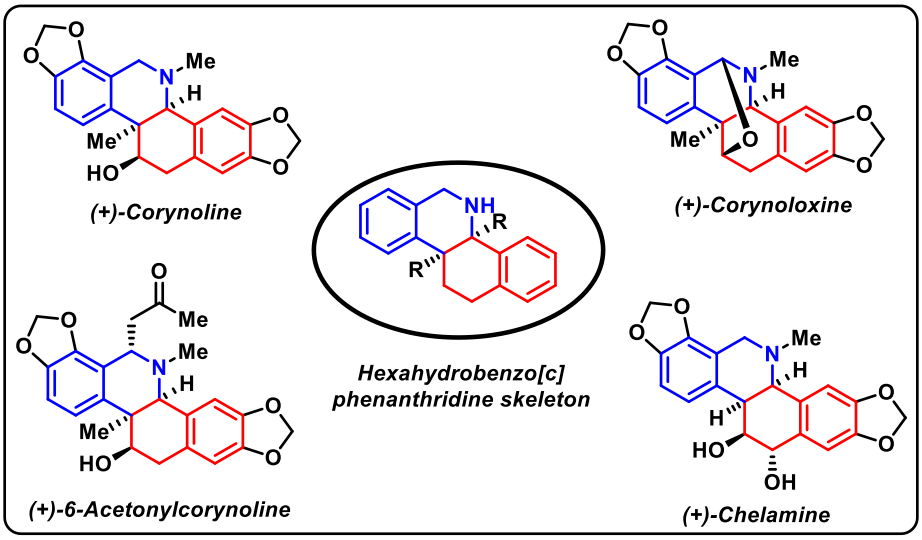


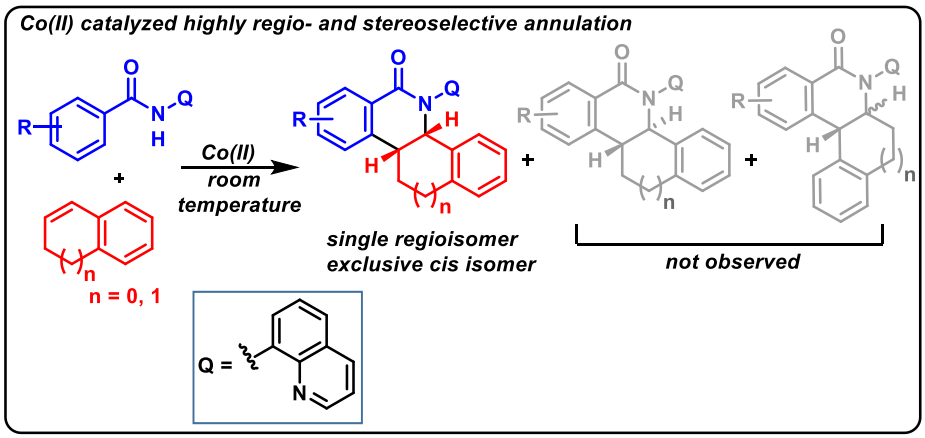
Figure 4.1. Examples of hexahydrobenzo[c]phenanthridine-type alkaloids.

Annulation of alkynes with benzamides has been well explored by many groups[7] but annulation reaction of alkenes is not much explored. Though there are few reports on the annulation of olefins with benzamides using C-H activation strategy, but they are mainly restricted to acyclic olefinic systems.[8]

Use of bicyclic olefinic systems has attracted our attention, because it can be used to synthesize hexahydrobenzo[*c*]phenanthridine type alkaloids which are widely prevalent in many natural products such as (+)-corynoline (+)-corynoloxine and (+)-chelamine etc (Figure 4.1).[9] Till now there is only one report[10] on the rhodium catalyzed synthesis of hexahydrobenzo[*c*]phenanthridine moiety by using bicyclic olefins.

It is worth noting that, the cis-stereochemistry of the ring junction is prevalent in all of the natural products (Figure 4.1).

Scheme 4.1. Synthesis of tetra/hexahydrobenzo[*c*]phenanthridine Core Structure

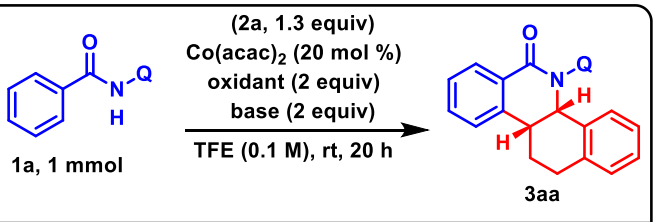


More interestingly, we observed high regio- and stereoselective annulation with cis-ring junction as present in the natural products (Scheme 4.1). In this regard, our methodology provides an easy access to the core skeleton of hexahydrobenzo[*c*]phenanthridine-type alkaloids. Herein, we report the annulation of *N*-(quinolin-8-yl) benzamide with dihydronaphthalenes and indenes by using a commercially available cobalt catalyst at room temperature. This reaction with readily available cobalt salts could be of great synthetic importance.

4.3 RESULTS AND DISCUSSION

As an extension of the communicated methodology[11] towards *β*-carboline-1-one derivatives; we investigated the versatility of substituted benzamides **1** bearing a wide array

Table 4.1 Optimisation of reaction condition.



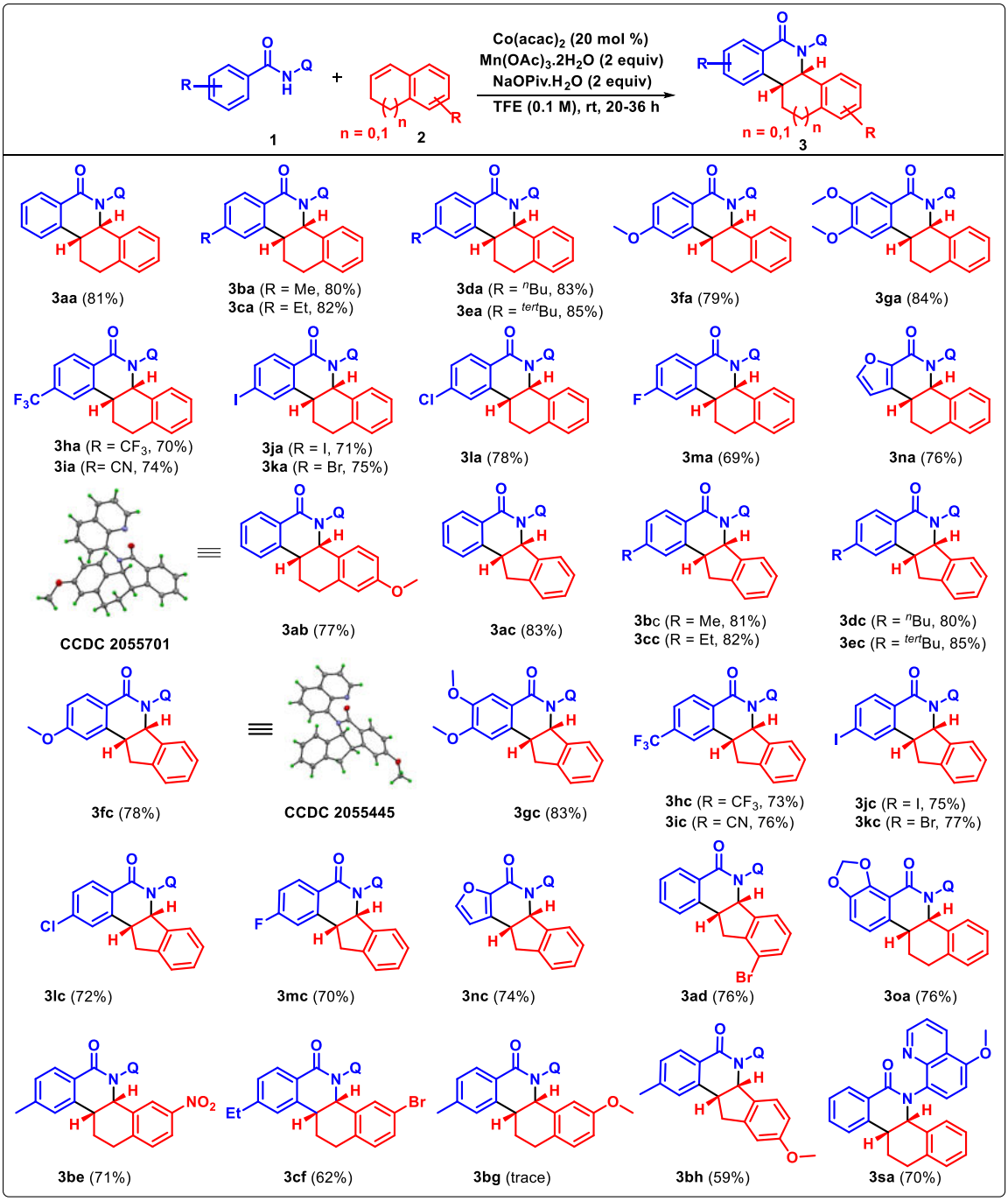
entry	oxidant	base	yield of 3aa (%)[b]
1	AgOAc	$NaOPiv.H_2O$	61
2	$Mn(OAc)_3.2H_2O$	NaOAc	66

[b]Yield of 3aa was determined by isolated yield.

of functional groups with dihydronapnthalene (**2a**) as coupling partner (Scheme 4.2). The optimised reaction condition was further screened with AgOAc as oxidant and in another reaction NaOAc as base, keeping other reaction parameters as constant (Table 4.1). We obtained 61% and 66% yield of the annulated product **3aa** respectively. Therefore, $Mn(OAc)_3.2H_2O$ was taken as oxidant and $NaOPiv.H_2O$ as base for the annulation reaction. Electron-rich and poor benzamides delivered good to excellent yields of the annulated products. The benzamides bearing electron-rich functional groups like methyl-, ethyl-, n-butyl-, tert-butyl- and methoxy- afforded their respective annulated products (**3aa-3fa**) in 79-85% yield. Di-substitued benzamide such as 3,4-dimethoxy-*N*-(quinolin-8-yl)benzamide **1g** furnished 84% yield of the annulated product **3ga** in highly regioselective manner. The benzamides containing electron-withdrawing groups such as trifluoromethyl- and cyano delivered their annulated product **3ha** and **3ia** in 70% and 74% respectively. It is noteworthy, that all halo-substituted benzamides (**1j, 1k, 1l, and 1m**) produced good to excellent yields (69-78%) of their annulated products (**3ja-3ma**). Our reaction protocol was also found to be amenable to heterocyclic amide **1n**, yielding 76% of the annulated product **3na**. To check the feasibility of the reaction with substituted dihydronaphthalene, we performed a reaction with 6-methoxy-1,2-dihydronaphthalene (**2b**). Gratifyingly, we observed 77% yield of the annulated product **3ab**. The regio- and stereoselectivity of the annulated products was confirmed from single-crystal X-ray analysis of compound **3ab**.

To further explore the substrate scope of our methodology, we tried annulation reaction of benzamide with indene (**2c**) as coupling partner and obtained the annulated product **3ac** in 83% yield (Scheme 4.2). Electron-rich substrates (**1b-1f**) gave good to excellent yields (78-85%) of their respective annulated products (**3bc-3fc**). Single crystal X-ray analysis of product **3fc** unambiguously confirmed the regio- and stereoselectivity.

Scheme 4.2. Co(II) Catalyzed Regio- and Stereoselective *C-H/N-H* Annulation of Substituted Benzamides with 1,2-Dihydronaphthalenes and Indenes.[a]



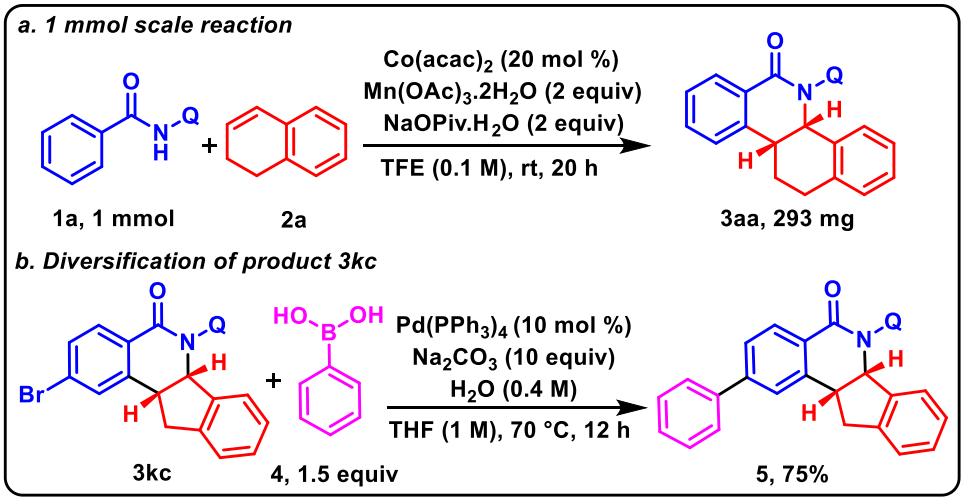
[a]Reaction conditions:- N-(quinolin-8-yl) benzamide **1** (1.0 equiv, 0.10 mmol), **2** (1.3 equiv, 0.13 mmol), $Co(acac)_2$ (0.2 equiv, 0.02 mmol), $NaOPiv.H_2O$ (2.0 equiv, 0.20 mmol), $Mn(OAc)_3.2H_2O$ (2.0 equiv, 0.20 mmol), TFE (0.1 M). [b]All yields in parenthesis are isolated yields.

Unsymmetrically substituted benzamide such as 3,4-dimethoxy-*N*-(quinolin-8-yl)benzamide **1g**, underwent annulation in highly regioselective manner furnishing 83% of the annulated product **3gc**. Benzamides with electron-deficient groups (trifluoromethyl- and cyano-) also resulted in good yields (73% and 76%) of their respective annulated product **3hc** and **3ic**.

Good to excellent yield (70-77%) was observed with halo-substituted benzamides as well (**3jc-3mc**). Furthermore, the heterocyclic amide **1n** was found to be viable under the standard condition yielding 74% of the annulated product **3nc**. The scope of the annulation reaction was further explored with substituted indene, 7-bromo-1*H*-indene (**2d**), the desired annulated product **3ad** was obtained in 76% yield. The reaction scope was tested with *ortho*-substituted benzamides (**1o-1r)**. Only benzamide **1o** gave the corresponding annulated product **3oa** in 76% yield. Whereas, other benzamides (**1p-1r)** failed to give the annulated product under the standard reaction condition. Substituted coupling partners (**2e-2h**) also furnished good yield of the annulated products in 59-71% yield, except **2g** which produced a trace amount of the annulated product **3bg**. The benzamide **1s** also produced the annulated product **3sa** in 70% yield.

The synthetic utility of this developed annulation protocol was showcased with a 1 mmol scale reaction between **1a** and **2a**, which furnished 293 mg (78%) of the annulated product **3aa** (Scheme 4.3a). The synthetic application of the annulated product was further explored. Accordingly, the Suzuki-Miyaura coupling[12] of **3kc** with phenyl boronic acid **4** was successfully carried to furnish the desired phenyl coupled product in 75% yield (Scheme 4.3b).

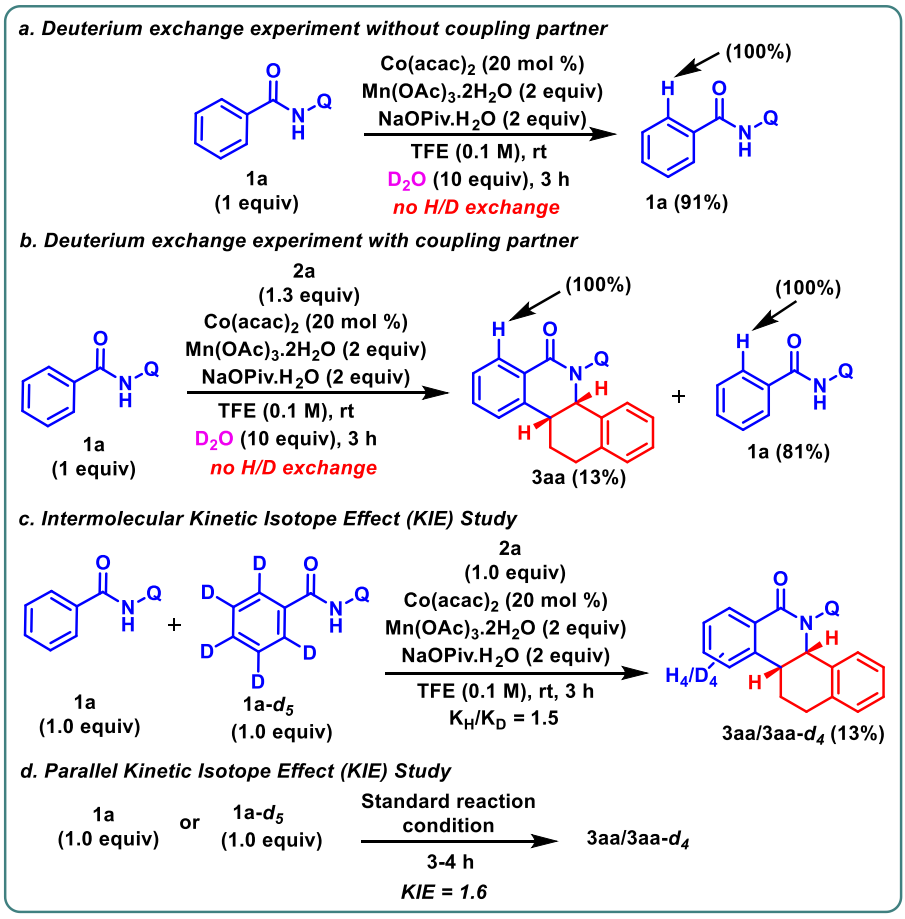
Scheme 4.3 Synthetic Application and 1 mmol scale reaction



The directing group in the annulated compound could not be removed with all possible methods,[13,14] including the modified substrate **3sa**.

To probe the mechanism of this annulation strategy, deuterium labelling and kinetic isotope

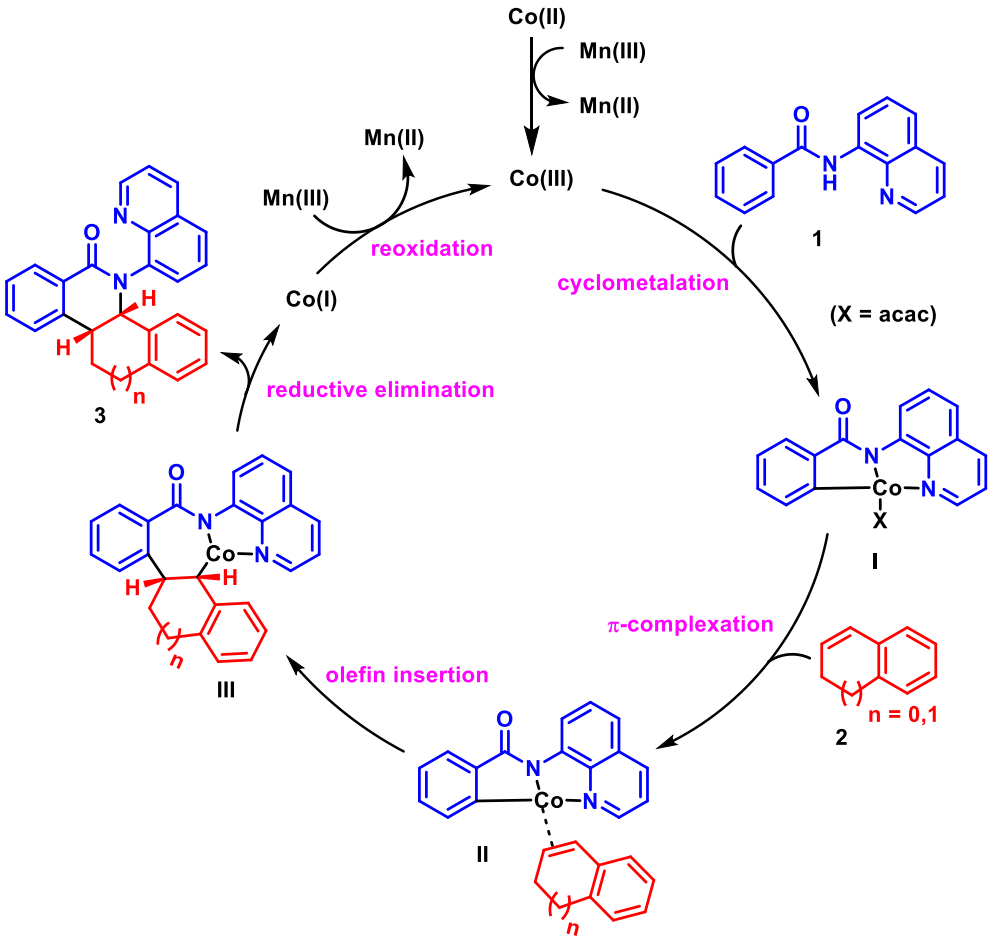
Scheme 4.4 Mechanistic Studies:



effect experiments were performed. Initially, we performed a deuterium labelling experiment of **1a** under standard reaction conditions in both the absence and the presence of coupling partner **2a** with 10 equiv of D_2O. In both the experiment, we did not observe any deuterium incorporation in the starting material **1a** and product **3aa** (Scheme 4.4a and 4.4b).

Next, an intermolecular kinetic isotope effect (KIE) and parallel KIE experiment was performed between benzamide **1a**/**1a-*d*$_5$** and **2a** (Scheme 4.4c and 4.4d). The KIE (kH/kD) value was found to be 1.5 and 1.6 for competitive and parallel experiment respectively. The obtained KIE value of 1.6 in the parallel experiment indicates that the C-H activation might be the turnover-limiting step.[15]

Scheme 4.5 Proposed Catalytic Cycle



Based on our mechanistic findings and literature reports[11,16] a possible catalytic cycle is proposed (Scheme 4.5). Initially Mn(III) oxidizes Co(II) to Co(III). Then the active catalyst undergoes cyclometallation to form intermediate **I**. The intermediate **I** forms intermediate **II**, through π-complexation with olefins. Subsequently, the intermediate **II** undergoes olefin insertion to produce intermediate **III**. Finally, reductive elimination of intermediate **III** leads to the product formation with the generation of Co(I), which after reoxidation regenerates active catalyst.

4.4 CONCLUSION:

In summary, we established a highly general, 8-aminoquinoline directed coupling of benzamides with bicyclic alkenes. The reaction works well at room temperature and also exhibits a wide range of functional group tolerance. Furthermore, our methodology provides an easy access to the core skeleton of hexahydrobenzo[*c*]phenanthridine-type alkaloids with high regio- and stereoselectivity

4.5 EXPERIMENTAL SECTION:

4.5.1 General Procedure for the Preparation of Starting Materials.[17-20]

All benzamides were prepared according to literature procedure with acid chloride (1.0 equiv, 1.0 mmol), 8-aminoquinoline (1.0 equiv, 1.0 mmol), triethylamine (1.1 equiv, 1.1 mmol) in anhydrous dichloromethane (0.7 M). Characterization data of compound **1a-1n** were matched to the reported values.

4.5.2 General Procedure for the Preparation of Annulated Products 3.

To an oven dried (100 °C) Schlenk tube, cooled under N_2 atmosphere, was charged with *N*-(quinolin-8-yl) benzamide **1** (1.0 equiv, 0.10 mmol), $Co(acac)_2$ (0.2 equiv, 0.02 mmol), $NaOPiv.H_2O$ (2.0 equiv, 0.20 mmol), $Mn(OAc)_3.2H_2O$ (2.0 equiv, 0.20 mmol) in anhydrous TFE (0.1 M). Then the coupling partner **2** (1.3 equiv, 0.13 mmol) was added in one shot. The sealed tube was tightened under positive pressure of N_2. The reaction mixture

was stirred at room temperature for 20-36 h (monitored by TLC). After complete consumption of starting materials, excess solvent was evaporated in *vaccuo* and the crude residue was purified by column chromatography to afford pure cyclized product **3** using EtOAc (Ethyl acetate)/Hexane or EtOAc/Dichloromethane (DCM) as eluent.

4.5.3 Procedure for the 1 mmol scale reaction.

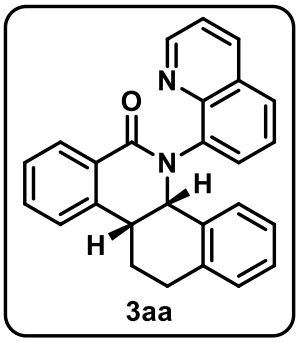
To an oven dried Schlenk tube, cooled under N_2 atmosphere, was charged with *N*-(quinolin-8-yl) benzamide **1a** (1.0 equiv, 1.0 mmol), $Co(acac)_2$ (0.2 equiv, 0.2 mmol), $NaOPiv.H_2O$ (2.0 equiv, 2.0 mmol), $Mn(OAc)_3.2H_2O$ (2.0 equiv, 2.0 mmol) in anhydrous TFE (0.1 M). Then the coupling partner **2a** (1.3 equiv, 1.3 mmol) was added in one shot. The sealed tube was tightened under positive pressure of N_2. The reaction mixture was stirred at room temperature for 20 h. Thereafter, excess solvent was evaporated in *vaccuo* and the crude residue was purified by column chromatography to afford pure cyclized product **3aa** (78% yield) using Ethyl acetate (EtOAc)/Hexane.

4.5.4 Procedure for the Preparation of Cross-coupled Product 5.[12]

A mixture of **3kc** (1.0 equiv, 0.10 mmol,), phenylboronic acid **4** (1.5 equiv), Na_2CO_3 (10.0 equiv), and $Pd(PPh_3)_4$ (10.00 mol %) in THF (1.0 M) and H_2O (0.4 mL) was stirred at 70 °C in a preheated aluminum block for 12 h under N_2 atmosphere. The mixture was added with H_2O (10.00 mL) and extracted with DCM. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/hexane) to afford product **5** in 75% yield.

4.5.5 Experimental characterization data:

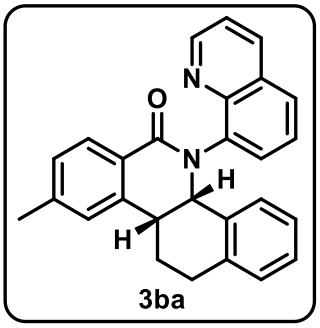
5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3aa)



3aa

Physical State: Colourless solid; mp 204-206 °C; yield: (30 mg, 81%). R_f: 0.40 (20% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (brs, 1H), 8.20 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 8.4, 1.2 Hz, 1H), 7.54 (td, J = 7.2, 0.8 Hz, 1H), 7.43- 7.36 (m, 3H), 7.28-7.26 (m, 1H), 7.14 (brs, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.44 (t, J = 7.6 Hz, 1H), 6.15 (d, J = 6.4 Hz, 1H), 5.69 (s, 1H), 3.43 (dt, J = 11.6, 2.8 Hz, 1H), 3.14 (ddd, J = 17.2, 6.4, 2.0 Hz, 1H), 3.06-2.98 (m, 1H), 2.73 (s, 1H), 2.12-2.07 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 150.4, 145.6, 143.0, 138.6, 136.2, 132.3 (2C), 130.7, 130.6, 129.2, 129.0, 128.7, 128.6, 127.8, 127.5, 127.2, 126.5, 125.9, 124.6, 124.5, 121.2, 59.8, 39.0, 28.3, 25.7. IR (KBr, cm^{-1}): 3018, 2975, 1665, 1215, 1035. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O$: 377.1648; Found: 377.1651.

9-methyl-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ba)

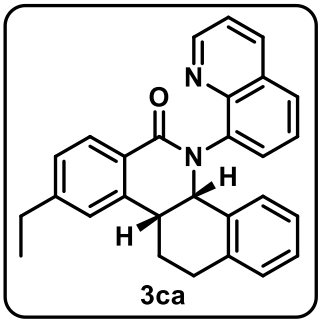


3ba

Physical State: Colourless solid; mp: 208-210 °C; yield: (31 mg, 80%). R_f: 0.40 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.64 (dd, J = 8.0, 0.8 Hz, 1H), 7.40-7.37 (m, 1H), 7.24-7.16 (m, 3H), 7.12 (s, 1H), 7.02 (d, J = 6.8 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 6.42 (t, J = 7.2 Hz, 1H), 6.12 (s, 1H), 5.67 (s, 1H), 3.35 (dt, J = 11.6, 3.2 Hz, 1H), 3.13 (ddd, J = 17.2, 6.4, 2.0 Hz, 1H), 3.04-2.96 (m, 1H), 2.71 (s, 1H), 2.44 (s, 3H), 2.09-2.04 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.6, 150.4, 145.6, 143.0, 142.8, 138.7, 136.2, 133.4, 130.8, 130.6, 129.2 (2C), 129.0, 128.7, 128.0, 127.8,

127.4, 127.0, 125.9, 124.5, 121.2, 59.8, 39.0, 28.3, 25.7, 21.7. IR (KBr, cm^{-1}): 3016, 2975, 1644, 1217, 1046. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O$: 391.1805; Found 391.1808.

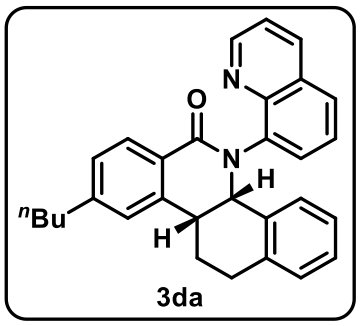
9-ethyl-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ca)



3ca

Physical State: Colourless solid; mp: 206-208 °C; yield: (33 mg, 82%). R_f: 0.30 (20% EtOAc/DCM). ^1H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.64 (dd, J = 8.4, 1.2 Hz, 1H), 7.38 (dd, J = 8.0, 4.0 Hz, 1H), 7.26-7.23 (m, 2H), 7.18 (s, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 6.42 (t, J = 7.2 Hz, 1H), 6.13 (d, J = 6.0 Hz, 1H), 5.68 (s, 1H), 3.37 (dt, J = 11.6, 3.2 Hz, 1H), 3.13 (ddd, J = 17.6, 6.8, 2.4 Hz, 1H), 3.05-2.96 (m, 1H), 2.74 (q, J = 7.6 Hz, 2H), 2.11-2.06 (m, 1H), 1.70 (s, 1H), 1.30 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 150.4, 149.0, 145.7, 143.1, 138.7, 136.3, 136.2, 133.4, 130.8, 130.7, 129.3, 129.0, 128.7, 127.7, 127.4, 126.8, 126.2, 125.9, 125.8, 124.5, 121.2, 59.8, 39.1, 29.0, 28.4, 25.8, 15.3. IR (KBr, cm^{-1}): 3018, 2975, 1638, 1220, 1046. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{25}N_2O$: 405.1961; Found 405.1959.

9-butyl-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3da)

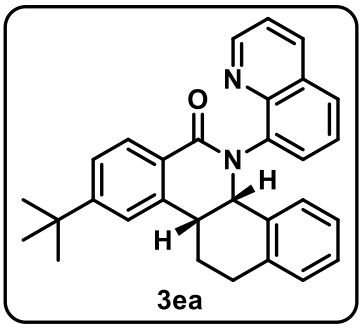


3da

Physical State: Colourless solid; mp: 204-206 °C; yield: (36 mg, 83%). R_f: 0.30 (40% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 1.2 Hz, 1H), 7.39 (dd, J = 8.0, 4.0 Hz, 1H), 7.27-7.25 (m, 1H), 7.22

(dd, *J* = 7.6, 1.2 Hz, 1H), 7.16 (s, 1H), 7.13 (brs, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.42 (t, *J* = 7.2 Hz, 1H), 6.13 (d, *J* = 6.4 Hz, 1H), 5.68 (s, 1H), 3.37 (dt, *J* = 11.6, 3.2 Hz, 1H), 3.13 (ddd, *J* = 17.2, 6.4, 2.4 Hz, 1H), 3.05-2.96 (m, 1H), 2.78 (s, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.10-2.04 (m, 1H), 1.66 (pentet, *J* = 7.2 Hz, 2H), 1.41 (sextet, *J* = 7.6 Hz, 2H), 0.96 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 150.4, 147.8, 145.7, 143.0, 138.7, 136.3, 136.2, 133.5, 130.8, 130.7, 129.2, 129.0, 128.7, 127.8, 127.4, 127.4, 126.4, 126.1, 125.9, 124.5, 121.2, 59.8, 39.1, 35.8, 33.4, 28.4, 25.8, 22.4, 13.9. IR (KBr, cm^{-1}): 3018, 2975, 1660, 1220, 1045. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{29}N_2O$: 433.2274; Found 433.2237.

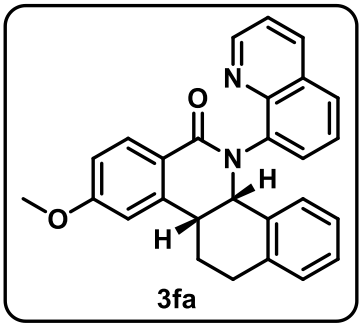
9-(*tert*-butyl)-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)- one (3ea)



3ea

Physical State: Colourless solid; mp: 206-208 °C; yield: (37 mg, 85%). R_f: 0.40 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.44 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.25-7.22 (m, 1H), 7.11 (s, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.41 (t, *J* = 7.6 Hz, 1H), 6.11 (d, *J* = 5.2 Hz, 1H), 5.69 (s, 1H), 3.38 (dt, *J* = 11.6, 3.2 Hz, 1H), 3.14 (ddd, *J* = 17.6, 6.8, 2.4 Hz, 1H), 3.07-2.98 (m, 1H), 2.75 (s, 1H), 2.11-2.04 (m, 1H), 1.39 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 155.9, 150.3, 145.5, 142.7, 138.5, 136.4 (2C), 133.4, 131.0, 130.7, 129.0, 128.9, 128.7, 127.8, 127.4, 126.0, 125.9, 124.5, 124.4, 123.3, 121.2, 59.8, 39.4, 35.1, 31.2, 28.4, 25.9. IR (KBr, cm^{-1}): 3017, 2969, 1650, 1213, 1040. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{29}N_2O$: 433.2274; Found 433.2258.

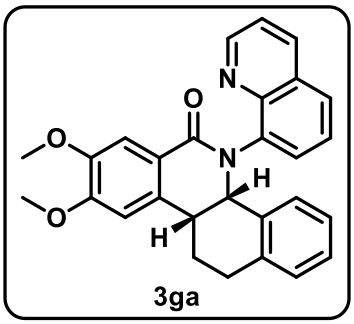
9-methoxy-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3fa)



3fa

Physical State: Colourless solid; mp: 210-212 °C; yield: (32 mg, 79%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, J = 2.0 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.0, 0.8 Hz, 1H), 7.37 (dd, J = 8.0, 4.0 Hz, 1H), 7.27-7.23 (m, 1H), 7.15 (brs, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.94-6.89 (m, 2H), 6.84 (d, J = 2.4 Hz, 1H), 6.47 (t, J = 7.6 Hz, 1H), 6.17 (d, J = 6.8 Hz, 1H), 5.71 (s, 1H), 3.88 (s, 3H), 3.38 (dt, J = 8.4, 3.6 Hz, 1H), 3.13 (ddd, J = 17.6, 6.8, 2.8 Hz, 1H), 3.04-2.95 (m, 1H), 2.74 (brs, 1H), 2.11-2.06 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.3, 162.8, 150.4, 145.7, 145.0, 138.8, 136.1, 133.5, 131.3 (2C), 130.8, 130.5, 129.0, 128.6, 127.7, 127.4, 125.9, 124.5, 121.5, 121.1, 112.5, 111.4, 59.8, 55.4, 39.3, 28.2, 25.6. IR (KBr, cm^{-1}): 3018, 2950, 1660, 1300, 1260, 1050. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_2$: 407.1754; Found 407.1759.

8,9-dimethoxy-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ga)

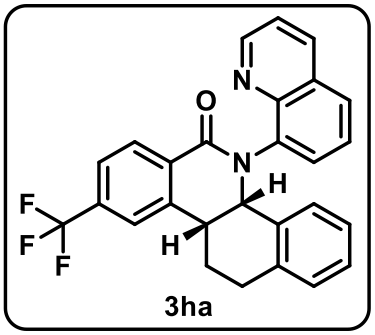


3ga

Physical State: Colourless solid; mp: 209-211 °C; yield: (37 mg, 84%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.40 (dd, J = 6.8, 3.6 Hz, 1H), 7.26-7.22 (m, 1H), 7.05-7.03 (m, 2H), 6.94 (t, J = 6.8 Hz, 1H), 6.81 (s, 1H), 6.42 (t, J = 7.6 Hz, 1H), 6.08 (d, J = 0.8 Hz, 1H), 5.68 (s, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.29 (dt, J = 11.6, 4.0 Hz, 1H), 3.14 (dd, J = 17.2, 5.2 Hz, 1H), 3.05-2.96 (m, 1H), 2.70 (s, 1H), 2.09-2.04 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 152.4, 150.4 (2C), 148.1, 145.7, 138.7, 136.9, 136.2, 133.3, 130.8 (2C), 128.9, 128.7, 127.8,

127.4, 125.9, 124.5, 121.2, 121.1, 111.2, 108.7, 60.0, 56.1, 56.0, 38.8, 28.4, 25.7. IR (KBr, cm^{-1}): 3018, 2960, 1665, 1300, 1260, 1045. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{25}N_2O_3$: 437.1860; Found 437.1843.

5-(quinolin-8-yl)-9-(trifluoromethyl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ha)

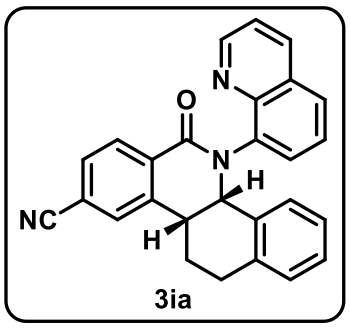


3ha

Physical State: Colourless solid; mp: 207-209 °C; yield: (31 mg, 70%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (d, J = 2.8 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 11.8, 5.0 Hz, 3H), 7.40 (dd, J = 8.2, 4.1 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 6.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.47 (t, J = 7.4 Hz, 1H), 6.21 (d, J = 7.2 Hz, 1H), 5.70 (d, J = 2.4 Hz, 1H), 3.54 (dt, J = 11.6, 3.6 Hz, 1H), 3.14 (ddd, J = 17.6, 8.0, 2.8 Hz, 1H), 3.06-3.00 (m, 1H), 2.76 (brs, 1H), 2.17-2.10 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.2, 150.5, 145.2, 143.6, 138.0, 136.4, 136.0, 133.8 (q, J = 32.0 Hz), 132.7, 131.7, 130.6, 130.5, 129.8, 129.0, 128.8, 128.1, 123.8 (q, J = 271.0 Hz), 127.8, 126.0, 124.7, 124.0 (q, J = 4.0 Hz), 123.6 (q, J = 4.0 Hz), 121.4, 59.7, 38.9, 28.0, 25.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9. IR (KBr, cm^{-1}): 3018, 2975, 1660, 1216, 1045, 789. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{20}F_3N_2O$: 445.1522; Found 445.1544.

6-oxo-5-(quinolin-8-yl)-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine-9-carbonitrile (3ia)

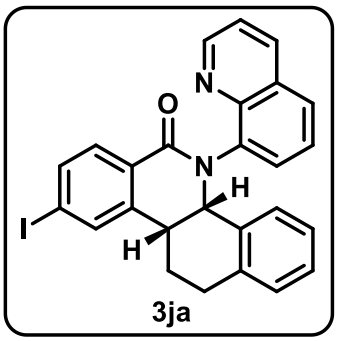
Physical State: Colourless solid; mp: 212-214 °C. yield: (30 mg, 74%); R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, J = 2.4 Hz, 1H), 8.29-8.27 (m, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.69–7.67 (m, 3H), 7.42 (dd, J = 8.4, 4.4 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.49 (t,



3ia

J = 7.6 Hz, 1H), 6.24 (d, *J* = 7.2 Hz, 1H), 5.67 (d, *J* = 2.0 Hz, 1H), 3.56 (dt, *J* = 8.4, 3.2 Hz, 1H), 3.14 (ddd, *J* = 17.6, 6.8, 3.2 Hz, 1H), 3.07–2.98 (m, 1H), 2.74 (brs, 1H), 2.15–2.10 (m, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7, 150.6, 145.1, 143.8, 138.0, 136.3, 135.9, 132.6, 132.5, 130.7, 130.5, 130.3, 130.0, 129.1, 128.8, 128.1, 127.9, 126.0, 124.9, 121.5, 118.4, 115.6, 59.7, 38.6, 27.8, 25.5. IR (KBr, cm^{-1}): 3018, 2975, 2252, 1665, 1220, 1046. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{20}N_3O$: 402.1601; Found 402.1615.

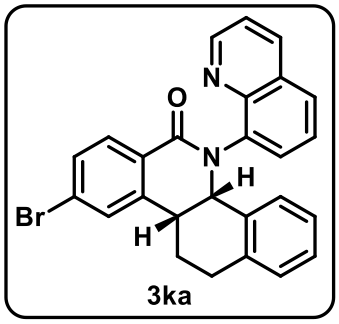
9-iodo-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ja)



3ja

Physical State: Colourless solid; mp: 216-218 °C; yield: (36 mg, 71%). R*f*: 0.40 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.91-7.88 (m, 1H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.28 (m, 1H), 7.15 (s, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 6.17 (d, *J* = 6.8 Hz, 1H), 5.66 (brs, 1H), 3.40 (dt, *J* = 11.6, 3.2 Hz, 1H), 3.13 (ddd, *J* = 17.6, 6.8, 2.8 Hz, 1H), 3.04-2.95 (m, 1H), 2.71 (s, 1H), 2.12-2.07 (m, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 150.4, 145.3, 144.7, 138.2, 136.5, 136.3, 136.0, 135.4, 133.0, 130.9, 130.7, 130.5, 129.0, 128.8, 128.1, 127.9, 127.67, 126.0, 124.7, 121.3, 99.6, 59.7, 38.6, 28.1, 25.6. IR (KBr, cm^{-1}): 3018, 2975, 1660, 1220, 1046, 781. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{20}IN_2O$: 503.0615; Found 503.0583.

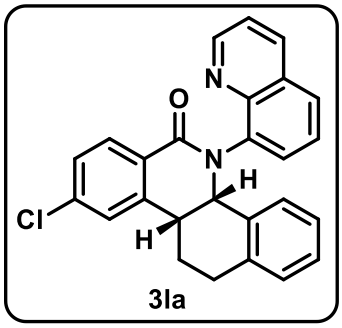
9-bromo-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ka)



3ka

Physical State: Colourless solid; mp: 214-216 °C; yield: (34 mg, 75%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.0, 0.8 Hz, 1H), 7.55-7.54 (m, 2H), 7.42 (dd, J = 7.6, 3.6 Hz, 1H), 7.29-7.26 (m, 1H), 7.15 (s, 1H), 7.04 (d, J = 6.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.46 (t, J = 7.2 Hz, 1H), 6.17 (d, J = 6.8 Hz, 1H), 5.67 (s, 1H), 3.44 (dt, J = 11.2, 4.0 Hz, 1H), 3.14 (ddd, J = 17.2, 6.4, 2.4 Hz, 1H), 3.02 (m, 1H), 2.72 (s, 1H), 2.14-2.08 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.8, 150.5, 145.4, 144.8, 138.3, 136.3, 136.1, 133.0, 131.0, 130.7 (2C), 130.5, 129.5, 129.1, 128.8, 128.0, 127.7, 127.6, 126.9, 126.0, 124.7, 121.3, 59.8, 38.8, 28.1, 25.6. IR (KBr, cm^{-1}): 3021, 2991, 1655, 1217, 1045, 750. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{20}BrN_2O$: 455.0754; Found 455.0743.

9-chloro-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3la)

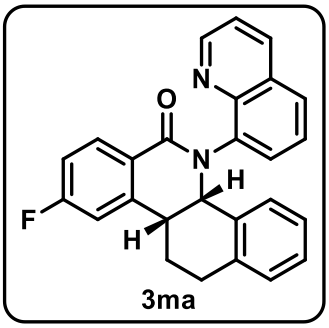


3la

Physical State: Colourless solid; mp: 212-214 °C; yield: (32 mg, 78%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, J = 2.4 Hz, 1H), 8.15-8.12 (m, 2H), 7.67 (dd, J = 8.4, 1.2 Hz, 1H), 7.41 (dd, J = 8.4, 4.4 Hz, 1H), 7.39-7.36 (m, 2H), 7.30-7.26 (m, 1H), 7.17 (brs, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.95 (t, J = 7.2 Hz, 1H), 6.46 (td, J = 7.2, 0.4 Hz, 1H), 6.19 (d, J = 7.2 Hz, 1H), 5.67 (d, J = 2.0 Hz, 1H), 3.45 (dd, J = 11.2, 3.2 Hz, 1H), 3.14 (ddd, J = 17.2, 6.8, 2.8 Hz, 1H), 3.05-2.96 (m, 1H), 2.73 (brs, 1H), 2.14-2.08 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.6, 150.5, 145.4, 144.6, 138.4, 138.3, 136.3, 136.1, 133.1, 130.9, 130.7, 130.5,

129.1, 128.8, 127.9, 127.7, 127.5, 127.2, 126.5, 125.9, 124.7, 121.3, 59.8, 38.9, 28.0, 25.5. IR (KBr, cm^{-1}): 3018, 2970, 1660, 1220, 1047, 911. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{20}ClN_2O$: 411.1259; Found 411.1227.

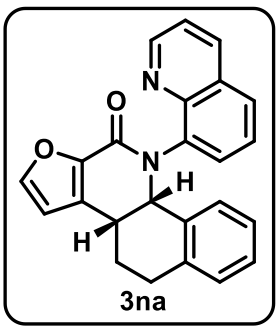
9-fluoro-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ma)



3ma

Physical State: Colourless solid; mp: 208-210 °C; yield: (27 mg, 69%). R_f: 0.30 (30% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.94 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 8.4, 6.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 8.4, 1.2 Hz, 1H), 7.40 (dd, J = 8.0, 4.0 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.19 (brs, 1H), 7.09-7.02 (m, 3H), 6.94 (t, J = 7.6 Hz, 1H), 6.46 (t, J = 7.2 Hz, 1H), 6.21 (d, J = 7.2 Hz, 1H), 5.68 (brs, 1H), 3.46 (dt, J = 8.0, 3.6 Hz, 1H), 3.17-3.10 (m, 1H), 3.05-2.96 (m, 1H), 2.73 (s, 1H), 2.14-2.07 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3 (d, J = 251.0 Hz), 164.6, 150.4, 145.8 (d, J = 9.0 Hz), 145.5, 138.5, 136.3, 136.1, 133.3, 132.1 (d, J = 9.0 Hz), 130.8, 130.4, 129.1, 128.7, 127.9, 127.6, 126.0, 125.1 (d, J = 3.0 Hz), 124.7, 121.3, 114.4 (d, J = 22.0 Hz), 113.1 (d, J = 22.0 Hz), 59.9, 39.1, 28.0, 25.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -107.1. IR (KBr, cm^{-1}): 3011, 2975, 1662, 1227, 1045, 926. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{20}FN_2O$: 395.1554; Found 395.1566.

10-(quinolin-8-yl)-3a,4,5,9b,10,11a-hexahydrobenzo[*h*]furo[2,3-*c*]quinolin-11(3b*H*)-one (3na)

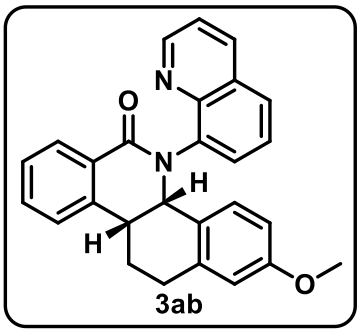


3na

Physical State: Colourless solid; mp: 212-214 °C; yield: (28 mg, 76%). R_f: 0.40 (20% EtOAc/DCM). ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, J = 4.0, 1.2 Hz, 1H), 8.15 (dd, J = 8.4, 1.2 Hz, 1H), 7.71-7.69 (m, 1H), 7.56 (d, J = 1.6 Hz, 1H), 7.51-7.49 (m, 1H), 7.42-7.36 (m, 2H), 7.02-6.96 (m, 2H), 6.67-6.64 (m, 2H), 6.53 (d, J =

1.6 Hz, 1H), 5.66 (d, *J* = 4.4 Hz, 1H), 3.77 (sextet, *J* = 4.0 Hz, 1H), 3.08-3.01 (m, 1H), 2.89-2.81 (m, 1H), 2.54-2.45 (m, 1H), 2.20-2.13 (m, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 158.3, 150.2, 146.3, 145.0, 143.4, 138.0, 136.4, 136.4, 134.5, 133.6, 130.8, 129.4, 129.2, 128.5, 127.5, 127.5, 125.9, 125.0, 121.2, 109.4, 62.5, 33.0, 27.4, 24.4. IR (KBr, cm^{-1}): 3018, 2975, 1665, 1216, 1046, 772. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{19}N_2O_2$: 367.1441; Found 367.1416.

2-methoxy-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ab)

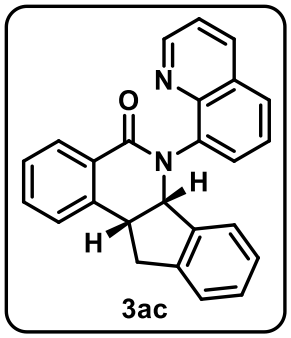


3ab

Physical State: Colourless solid; mp: 214-216 °C; yield: (31 mg, 77%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.37 (dt, *J* = 16.8, 7.2 Hz, 3H), 7.29-7.24 (m, 1H), 7.14 (s, 1H), 6.53 (s, 1H), 6.02 (td, *J* = 12.0, 1.6 Hz, 2H), 5.66 (s, 1H), 3.60 (s, 3H), 3.35 (dt, *J* = 11.6, 2.8 Hz, 1H), 3.08 (ddd, *J* = 15.6, 4.8, 1.6 Hz, 1H), 3.03-2.94 (m, 1H), 2.72 (s, 1H), 2.07-2.03 (m, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.5, 158.9, 150.3, 145.5, 143.1, 138.5, 137.6, 136.3, 132.2, 131.8, 130.9, 129.1, 129.0, 128.5, 127.5, 127.1, 126.5, 126.1, 125.6, 121.2, 112.9, 110.9, 59.2, 55.0, 39.4, 28.7, 25.7. IR (KBr, cm^{-1}): 3017, 2925, 1646, 1350, 1217, 1045, 771. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_2$: 407.1754; Found 407.1758.

6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3ac)

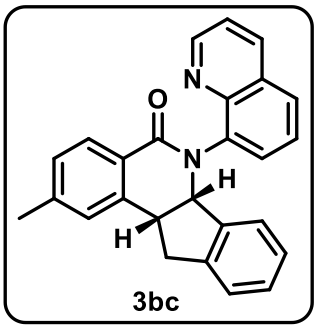
Physical State: Colourless solid; mp: 211-213 °C; yield: (30 mg, 83%). R_f: 0.40 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 8.21 (s, 1H), 7.78 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.54 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41 (m, 3H), 7.34 (brs, 1H), 7.26-7.24 (m, 1H), 7.12 (brs, 1H), 6.97 (brs, 1H), 6.71 (brs, 1H), 5.96-5.90 (m,



3ac

2H), 3.94 (q, *J* = 7.6 Hz, 1H), 3.41 (s, 1H), 3.33 (dd, *J* = 15.2, 7.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.3, 150.5, 144.5, 143.2, 142.0, 139.6, 137.6, 136.4, 132.2, 131.9, 129.3, 129.2, 128.1, 127.8, 127.4, 127.3, 127.2, 126.2, 125.9, 125.5, 124.2, 121.3, 65.1, 43.9, 40.2. IR (KBr, cm^{-1}): 3018, 2975, 1630, 1218, 1046. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{19}N_2O$: 363.1492; Found 363.1507.

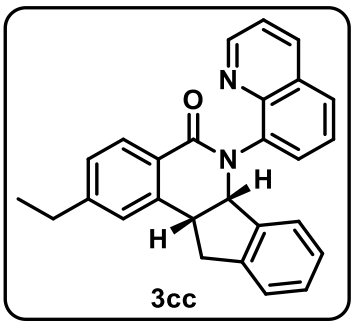
2-methyl-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3bc).



3bc

Physical State: Colourless solid; mp: 213-215 °C; yield: (30 mg, 81%). R_f: 0.40 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.22 (d, *J* = 4.8 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 7.25-7.21 (m, 3H), 7.12 (s, 1H), 6.96 (s, 1H), 6.72 (s, 1H), 5.93-5.90 (m, 2H), 3.89 (q, *J* = 7.2 Hz, 1H), 3.44-3.30 (m, 2H), 2.45 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 150.5, 144.6, 143.3, 142.7, 142.2, 139.6, 137.8, 136.4, 132.0, 129.3, 128.1 (2C), 127.9, 127.8, 126.2, 126.0, 125.5, 125.5, 124.8, 124.2, 121.3, 65.2, 44.0, 40.3, 21.6. IR (KBr, cm^{-1}): 3018, 2975, 1660, 1222, 1045. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O$: 377.1648; Found 377.1622.

2-ethyl-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3cc)

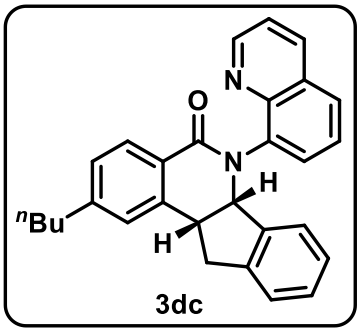


3cc

Physical State: Colourless solid; mp: 216-218 °C. yield: (32 mg, 82%). R_f: 0.30 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93-8.89 (m, 1H), 8.20 (d, *J* = 6.4 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.42 (brs, 1H), 7.34 (brs, 1H), 7.25-7.22 (m, 3H), 7.12 (brs, 1H), 6.96

(brs, 1H), 6.71 (brs, 1H), 5.93 (d, J = 15.2 Hz, 2H), 3.90 (q, J = 8.4 Hz, 1H), 3.43 (s, 1H), 3.34 (dd, J = 15.2, 7.6 Hz, 1H), 2.75 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 150.5, 148.9, 144.8, 143.5, 142.2, 139.7, 137.8, 136.3, 132.0, 129.4 (2C), 128.1, 127.8, 127.0, 126.7, 126.3, 126.0, 125.5, 125.1, 124.2, 121.2, 65.3, 44.1, 40.3, 29.0, 15.3. IR (KBr, cm^{-1}): 3016, 2974, 1662, 1218, 1040. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O$: 391.1805; Found 391.1822.

2-butyl-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3dc)

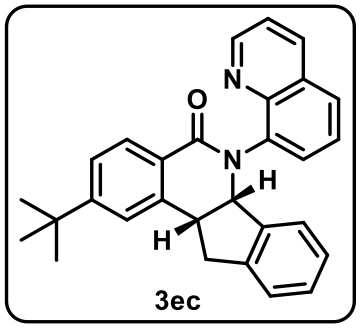


3dc

Physical State: Colourless solid; mp: 215-217 °C; yield: (33 mg, 80%). R_f: 0.40 (40% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.20 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.0, 0.8 Hz, 1H), 7.42 (s, 1H), 7.34 (s, 1H), 7.25-7.23 (m, 1H), 7.21-7.20 (m, J = 2H), 7.11 (s, 1H), 6.96 (s, 1H), 6.71 (s, 1H), 5.92 (dd, J = 18.8, 1.2 Hz, 2H), 3.90 (q, J = 8.0 Hz, 1H), 3.42 (s, 1H), 3.34 (dd, J = 15.2, 7.6 Hz, 1H), 2.71 (t, J = 7.6 Hz, 2H), 1.67 (pentet, J = 7.2 Hz, 2H), 1.42 (sextet, J = 7.2 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 150.5, 147.7, 144.8, 143.4, 142.2, 139.6, 137.9, 136.3, 132.0, 129.3, 128.1, 127.7, 127.5, 127.2, 126.2, 126.0 (2C), 125.5, 125.1, 124.2, 121.2, 65.2, 44.1, 40.3, 35.7, 33.4, 22.4, 13.9. IR (KBr, cm^{-1}): 3018, 2975, 1660, 1216, 1046. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{27}N_2O$: 419.2118; Found 419.2102.

2-(*tert*-butyl)-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3ec)

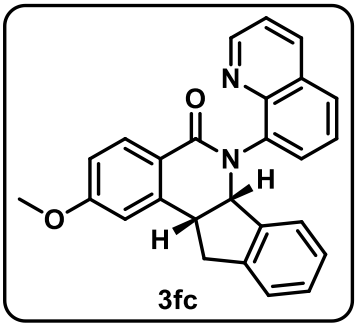
Physical State: Colourless solid; mp: 214-216 °C; yield: (35 mg, 85%). R_f: 0.30 (40% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.20 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 8.4, 0.8 Hz, 1H), 7.45 (dd, J = 8.0, 2.0 Hz, 1H), 7.42 (s, 1H), 7.39 (d,



3ec

J = 2.0 Hz, 1H), 7.33 (brs, 1H), 7.29-7.25 (m, 1H), 7.12 (brs, 1H), 6.94 (brs, 1H), 6.70 (brs, 1H), 5.96-5.88 (m, 2H), 3.91 (q, *J* = 8.4 Hz, 1H), 3.43 (brs, 1H), 3.36 (dd, *J* = 15.2, 7.6 Hz, 1H), 1.40 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 155.8, 150.4, 144.7, 143.5, 142.2, 139.3, 137.8, 136.3, 132.1, 129.3, 129.1, 128.1, 127.7, 126.3, 126.0, 125.5, 124.8, 124.5, 124.2, 124.1, 121.2, 65.3, 44.4, 40.5, 35.0, 31.2. IR (KBr, cm^{-1}): 3018, 2974, 1660, 1220, 1046. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{27}N_2O$: 419.2118; Found 419.2105.

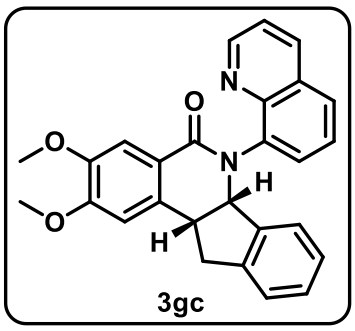
2-methoxy-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3fc).



3fc

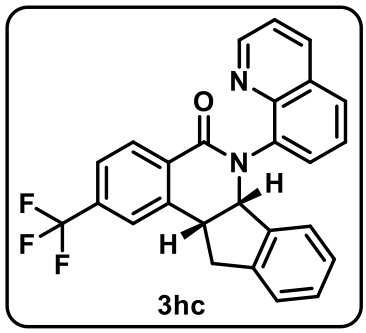
Physical State: Colourless solid; mp: 216-218 °C; yield: (30 mg, 78%). R*f*: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.28-7.27 (m, 2H), 7.12 (s, 2H), 6.95 (dd, *J* = 8.4, 2.4 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.72 (s, 1H), 5.97 (d, *J* = 6.4 Hz, 1H), 3.93 (s, 3H), 3.92-3.90 (m, 1H), 3.48 (s, 1H), 3.37 (dd, *J* = 15.2, 7.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.3, 162.8, 150.4, 144.8, 143.2, 142.2, 141.7, 137.9, 136.4, 132.1, 131.5, 129.4, 128.1, 127.7, 126.2, 126.0, 125.5, 124.2, 121.2, 120.4, 112.8, 112.3, 65.3, 55.4, 44.3, 40.2. IR (KBr, cm^{-1}): 3018, 2960, 1665, 1350, 1227, 1040, 794. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O_2$: 393.1598; Found 393.1611.

2,3-dimethoxy-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3gc)



Physical State: Colourless solid; mp: 214-216 °C; yield: (35 mg, 83%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.22 (brs, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.76 (brs, 1H), 7.44 (brs, 1H), 7.35 (brs, 1H), 7.29-7.26 (brs, 1H), 7.13 (brs, 1H), 6.96 (brs, 1H), 6.85 (brs, 1H), 6.73 (brs, 1H), 5.92 (brs, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 3.86 (q, J = 8.0 Hz, 1H), 3.38-3.32 (dd, J = 14.8, 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.4, 152.4, 150.5, 148.1, 144.7, 143.3, 142.1, 137.8, 136.4, 133.4, 132.0, 129.3, 128.1, 127.8, 126.2, 126.0, 125.5, 124.2, 121.2, 120.1, 111.2, 109.3, 65.4, 56.1, 56.0, 43.7, 40.3. IR (KBr, cm^{-1}): 3018, 2974, 1650, 1340, 1066, 912. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_3$: 423.1703; Found 423.1716.

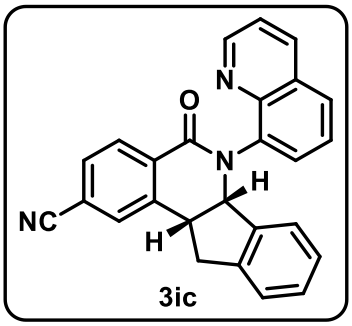
6-(quinolin-8-yl)-2-(trifluoromethyl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3hc)



Physical State: Colourless solid; mp: 210-212 °C; yield: (31 mg, 73%). R_f: 0.40 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.68-7.66 (m, 2H), 7.45 (s, 1H), 7.36 (s, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 6.97 (s, 1H), 6.75 (s, 1H), 5.97-5.94 (m, 2H), 4.00 (dd, J = 7.6 Hz, 1H), 3.43-3.41 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.0, 150.6, 144.4, 142.8, 141.5, 140.4, 137.3, 136.4, 133.8 (q, J = 32.0 Hz), 131.8, 130.6, 130.0, 129.4, 128.4, 128.1, 126.3, 126.0, 125.8, 124.4 (q, J = 4.0 Hz), 124.0 (q, J = 4.0 Hz), 124.3, 123.8 (q, J = 271.0 Hz), 121.4, 65.2, 43.7, 40.1. ^{19}F

NMR (376 MHz, $CDCl_3$): δ -62.8. IR (KBr, cm^{-1}): 3018, 2975, 1660, 1213, 1024, 786. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{17}F_3N_2ONa$: 453.1185; Found 453.1184.

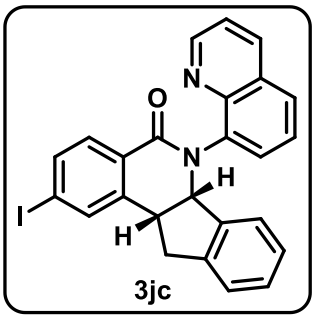
5-oxo-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinoline-2-carbonitrile (3ic)



3ic

Physical State: Colourless solid, m.p.: 213-215 °C. yield: (29 mg, 76%). R_f: 0.30 (40% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.68 (dd, J = 8.0, 1.2 Hz, 1H), 7.45 (brs, 1H), 7.38 (brs, 1H), 7.27-7.25 (brs, 1H), 7.15 (brs, 1H), 7.00 (s, 1H), 6.75 (s, 1H), 5.97 (brs, 2H), 3.98 (q, J = 6.8 Hz, 1H), 3.41-3.39 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.5, 150.6, 144.2, 142.5, 141.2, 140.7, 137.1, 136.4, 131.6, 131.3, 131.2, 130.7, 130.0, 129.3, 128.5, 128.2, 126.1, 125.9, 125.9, 124.3, 121.4, 118.2, 115.5, 65.1, 43.3, 39.9. IR (KBr, cm^{-1}): 3018, 2973, 2250, 1655, 1215, 909. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{18}N_3O$: 388.1444; Found 388.1463.

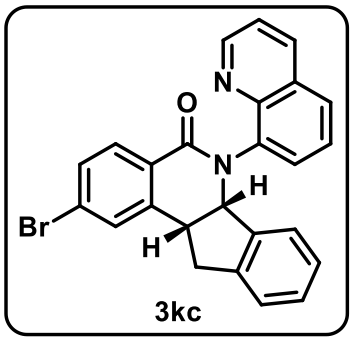
2-iodo-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3jc)



3jc

Physical State: Colourless solid; mp: 212-214 °C; yield: (37 mg, 75%). R_f: 0.40 (40% EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.22 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.81-7.53 (m, 3H), 7.44-7.26 (m, 4H), 7.13 (s, 2H), 6.96 (s, 1H), 6.73 (s, 1H), 5.93 (s, 1H), 3.88 (q, J = 8.0 Hz, 1H), 3.46-3.32 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.8, 150.5, 144.4, 142.9, 141.7, 141.5, 137.4, 137.4, 136.6, 136.3, 131.9, 131.0, 129.4, 128.3, 128.0, 127.1, 126.2, 126.0, 125.7, 124.3, 121.4, 99.6, 65.2, 43.4, 40.1. IR (KBr, cm^{-1}): 3018, 2975, 1640, 1227, 1046, 909. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{18}IN_2O$: 489.0458; Found 489.0424.

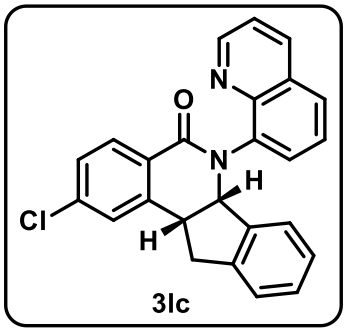
2-bromo-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3kc)



3kc

Physical State: Colourless solid; mp: 215-217 °C; yield: (34 mg, 77%). R_f: 0.30 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (brs, 1H), 8.21 (brs, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.79 (dd, J = 8.0, 0.8 Hz, 1H), 7.57-7.53 (m, 2H), 7.43 (s, 1H), 7.36 (s, 1H), 7.25 (s, 1H), 7.13 (s, 1H), 6.98 (s, 1H), 6.73 (s, 1H), 5.94 (s, 2H), 3.90 (q, J = 8.0 Hz, 1H), 3.42-3.32 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.6, 150.5, 144.4, 142.9, 141.7, 141.6, 137.4, 136.4, 131.8, 131.1, 130.6, 130.3, 129.4, 128.3, 128.0, 126.9, 126.5, 126.2, 126.0, 125.7, 124.3, 121.4, 65.3, 43.6, 40.1. IR (KBr, cm^{-1}): 3018, 2990, 1660, 1216, 1064, 910. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{18}BrN_2O$: 441.0597; Found 441. 0602.

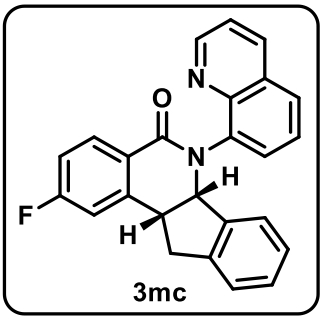
2-chloro-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3lc)



3lc

Physical State: Colourless solid; mp: 214-216 °C; yield: (28 mg, 72%). R_f: 0.30 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.23 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.41-7.37 (m, 3H), 7.27-7.25 (m, 1H), 7.14 (s, 1H), 6.98 (s, 1H), 6.74 (s, 1H), 5.94 (s, 2H), 3.91 (q, J = 8.0 Hz, 1H), 3.41-3.33 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.5, 150.6, 144.5, 142.9, 141.7, 141.4, 138.3, 137.5, 136.4, 131.9, 131.0, 129.4, 128.3, 128.0, 127.6, 127.3, 126.2, 126.1, 126.0, 125.7, 124.3, 121.4, 65.3, 43.7, 40.1. IR (KBr, cm^{-1}): 3018, 2975, 1643, 1215, 1044, 754. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{18}ClN_2O$: 397.1102; Found 397.1069.

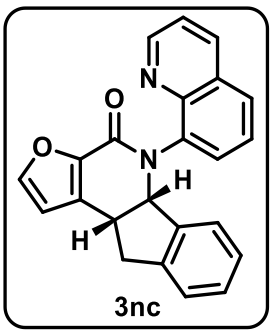
2-fluoro-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3mc)



3mc

Physical State: Colourless solid; mp: 211-213 °C; yield: (27 mg, 70%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, J = 1.6 Hz, 1H), 8.27-8.23 (m, 1H), 8.19 (d, J = 6.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.38 (m, 3H), 7.25-7.24 (m, 1H), 7.09-7.05 (m, 4H), 6.71 (s, 1H), 5.97 (d, J = 6.8 Hz, 1H), 3.92 (q, J = 8.0 Hz, 1H), 3.44 (s, 1H), 3.35 (dd, J = 14.8, 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.2 (d, J = 251.0 Hz), 163.5, 150.5, 144.5, 142.8, 142.5 (d, J = 8.0 Hz), 141.8, 137.6, 136.4, 132.2 (d, J = 9.0 Hz), 131.8, 129.4, 128.3, 127.9, 126.1, 126.0, 125.7, 124.3, 123.9, 121.3, 114.5 (d, J = 21.0 Hz), 113.9 (d, J = 22.0 Hz), 65.2, 43.9, 40.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -107.4. IR (KBr, cm^{-1}): 3018, 2975, 1648, 1215, 1046, 909. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{18}FN_2O$: 381.1398; Found 381.1424.

5-(quinolin-8-yl)-3a,5,5a,10,10a,10b-hexahydro-4*H*-furo[3,2-*d*]indeno[1,2-*b*]pyridin-4-one (3nc).

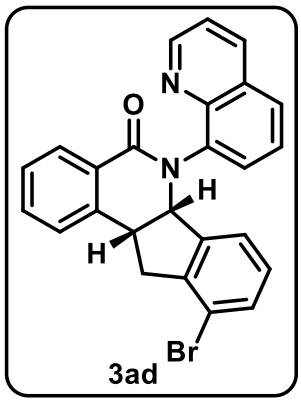


3nc

Physical State: Colourless solid; mp: 209-211 °C; yield: (26 mg, 74%). R_f: 0.40 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94-8.93 (m, 1H), 8.20 (dd, J = 8.4, 1.2 Hz, 1H), 7.84-7.82 (m, 1H), 7.78 (dd, J = 7.2, 0.8 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.4, 4.0 Hz, 1H), 7.21-7.19 (m, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.51 (d, J = 1.6 Hz, 1H), 5.92 (d, J = 6.8 Hz, 1H), 4.27 (sextet, J = 4.4 Hz, 1H), 3.36 (dd, J = 15.6, 7.2 Hz, 1H), 3.26 (dd, J = 15.2, 4.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.1, 150.3, 146.3, 144.2, 143.0, 142.1, 140.8, 137.6, 136.5, 131.4, 131.4, 129.6, 128.1, 127.8, 126.3, 126.0, 125.0, 124.6, 121.3, 109.9, 68.6, 38.4, 37.2. IR (KBr, cm^{-1}): 3018,

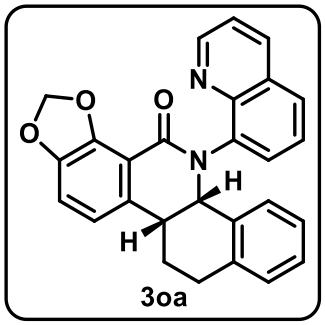
2900, 1665, 1211, 1020, 788. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{17}N_2O_2$: 353.1285; Found 353.1279.

10-bromo-2,3-dimethoxy-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3ad)



Physical State: Colourless solid; mp: 215-217 °C; yield: (33 mg, 76%). R_f: 0.30 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.26-8.21 (m, 2H), 7.80 (d, J = 7.6, 1.2 Hz, 1H), 7.57 (td, J = 10.7, 4.2 Hz, 1H), 7.43 (td, J = 6.8, 1.6 Hz, 4H), 7.26 (s, 1H), 7.08 (s, 1H), 6.60 (s, 1H), 6.05-5.90 (m, 2H), 3.99 (q, J = 14.0, 7.6 Hz, 1H), 3.46-3.39 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.1, 150.5, 144.6, 144.6, 143.8, 139.0, 137.6, 137.5, 136.4, 132.4, 132.0, 131.3 (2C), 129.3, 128.0, 127.4, 127.4, 127.4, 126.1, 125.0, 121.4, 119.3, 66.1, 42.9, 41.4. IR (KBr, cm^{-1}): 3018, 2975, 1650, 1213, 1046, 785. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{18}BrN_2O$: 441.0597; Found 441.0572.

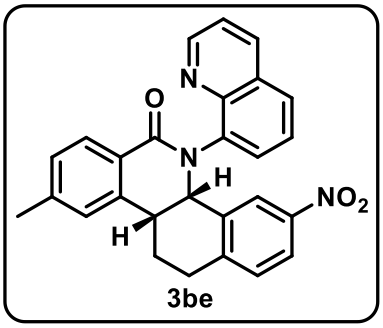
12-(quinolin-8-yl)-6,7,11b,12-tetrahydrobenzo[*c*][1,3]dioxolo[4,5-i]phenanthridin-13(5b*H*)-one (3oa)



Physical State: Colourless solid; mp: 209-211 °C; yield: (32 mg, 76%). R_f: 0.40 (30% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94-8.93 (m, 1H), 8.20 (dd, J = 8.4, 1.2 Hz, 1H), 7.84-7.82 (m, 1H), 7.78 (dd, J = 7.2, 0.8 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.4, 4.0 Hz, 1H), 7.21-7.19 (m, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.51 (d, J = 1.6 Hz, 1H), 5.92 (d, J = 6.8 Hz, 1H), 4.27 (sextet, J = 4.4 Hz, 1H), 3.36 (dd, J = 15.6, 7.2 Hz, 1H), 3.26 (dd, J = 15.2, 4.4 Hz, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 163.2, 150.4, 148.4, 147.9, 145.4, 138.2, 136.1, 133.6, 130.8, 130.3, 129.0, 128.7,

127.7, 127.4, 125.8, 124.6, 121.1, 118.7 (2C), 112.4, 111.2, 102.2, 60.2, 38.8, 27.9, 25.8 (2C). IR (KBr, cm^{-1}): 3053, 2986, 1650, 1266, 749. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{21}N_2O_3$: 421.1552; Found 421.1547.

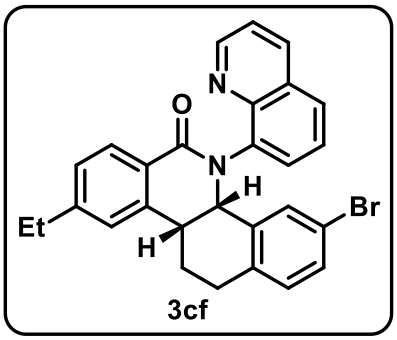
9-methyl-3-nitro-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3be)



3be

Physical State: Colourless solid; mp: 220-222 °C; yield: (31 mg, 71%). R*f*: 0.30 (50% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.76-7.74 (m, 1H), 7.67-7.65 (m, 1H), 7.45-7.43 (m, 1H), 7.31-7.29 (m, 1H), 7.25-7.23 (m, 2H), 7.19-7.13 (m, 3H), 5.77 (s, 1H), 3.49-3.46 (m, 1H), 3.26-3.18 (m, 1H), 3.09-3.01 (m, 1H), 2.80 (s, 1H), 2.46 (s, 3H), 2.19-2.14 (m, 1H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 165.3, 150.9, 145.4, 144.9, 143.1, 141.8, 138.1, 136.4, 130.8, 129.6, 129.4, 129.3, 128.4, 128.1, 127.0 (2C), 126.0, 125.8 (2C), 125.6, 122.4, 121.6, 59.3, 38.4, 28.5, 25.1, 21.7. IR (KBr, cm^{-1}): 3005, 2988, 1655, 1260, 751. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{22}N_3O_3$: 436.1661; Found 436.1658.

3-bromo-9-ethyl-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3cf)

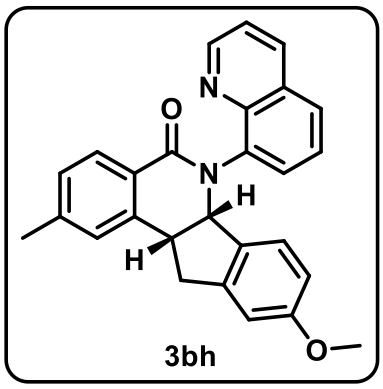


3cf

Physical State: Colourless solid; mp: 218-220 °C; yield: (30 mg, 62%). R*f*: 0.40 (50% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 8.4, 1.2 Hz, 1H), 7.42-7.39 (m, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.25-7.23 (m, 1H), 7.23-7.20 (m, 1H), 7.17-7.16 (m, 1H), 7.02-7.00 (m, 1H), 6.86-6.84 (m, 1H), 6.29 (s, 1H), 5.60 (s, 1H), 3.41-3.36 (m, 1H), 3.07-3.00 (m, 1H), 2.94-2.85 (m, 1H), 2.76-

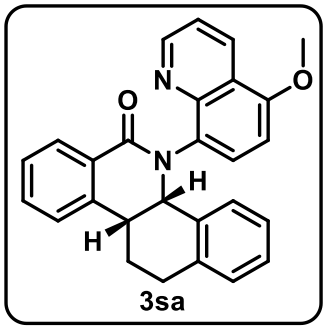
2.70 (m, 3H), 2.10-2.04 (m, 1H), 1.29 (t, J = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 150.5, 149.1, 145.5, 142.4, 138.3, 136.3, 135.6, 135.2, 133.3, 130.6, 130.6, 130.2, 129.3, 129.1, 127.8, 126.9, 126.1, 125.9, 125.8, 121.3, 117.9, 59.3, 38.7, 29.0, 27.8, 25.4, 15.3. IR (KBr, cm^{-1}): 3051, 2991, 1656, 1266, 750. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{24}BrN_2O$: 483.1072; Found 483.1083.

9-methoxy-2-methyl-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (3bh)



Physical State: Colourless solid; mp: 216-218 °C; yield: (24 mg, 59%). R_f: 0.40 (50% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.21-8.18 (m, 1H), 8.14-8.09 (m, 1H), 7.78-7.76 (m, 1H), 7.42-7.35 (m, 2H), 7.22-7.19 (m, 2H), 6.96-6.71 (m, 2H), 6.25-6.24 (m, 1H) 5.89-5.74 (m, 2H), 3.89-3.84 (m, 1H), 3.71 (s, 1H), 3.37-3.25 (m, 1H), 2.45 (s, 3H), 1.26 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 159.8, 150.5, 142.6, 139.6, 136.4, 132.2, 129.4, 129.0, 128.1, 128.0, 127.9, 127.7, 127.0, 126.1, 124.8, 121.5, 121.4, 121.2, 112.2, 111.5, 110.6, 109.4, 64.6, 55.2, 44.4, 40.6, 21.6. IR (KBr, cm^{-1}): 3053, 2988, 1654, 1274, 749. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_2$: 407.1760; Found 407.1748.

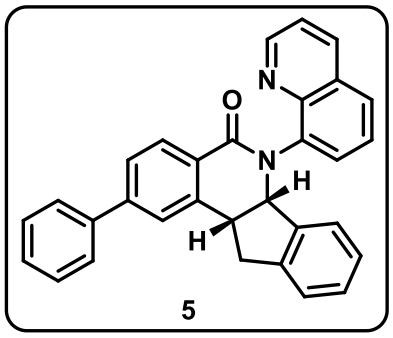
(5-methoxyquinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3sa)



Physical State: Colourless solid; mp: 222-224 °C; yield: (28.5 mg, 70%). R_f: 0.40 (50% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.52 (d, J = 7.6 Hz, 1H), 8.20-8.18 (m, 1H), 7.54-7.50 (m, 1H), 7.41-7.34 (m, 3H), 7.02-6.97 (m, 2H), 6.97-6.95 (m, 1H), 6.56-6.54 (m, 1H), 6.50-6.47 (m, 1H), 6.23

(d, J = 3.6 Hz, 1H), 5.66 (s, 1H), 3.91 (s, 3H), 3.43-3.40 (m, 1H), 3.15-3.09 (m, 1H), 3.05-2.97 (m, 1H), 2.69 (brs, 1H), 2.10-2.04 (m, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.7, 154.4, 150.6, 145.9, 143.0, 136.2, 133.7, 132.2, 131.0, 131.0, 130.7, 130.5, 129.2, 128.7, 128.6, 127.7, 127.1, 126.4, 124.7, 121.3, 120.3, 103.5, 59.6, 55.7, 39.0, 28.3, 25.7. IR (KBr, cm^{-1}): 3053, 2986, 1650, 1267, 747. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_2$: 407.1760; Found 407.1734.

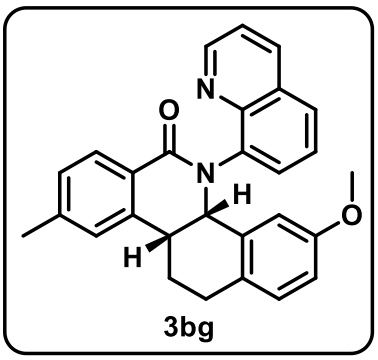
2-Phenyl-6-(quinolin-8-yl)-6,6a,11,11a-tetrahydro-5*H*-indeno[1,2-*c*]isoquinolin-5-one (5)



5

Physical State: Colourless solid; mp: 220-222 °C; yield: (33 mg, 75%). R_f: 0.30 (40% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (brs, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.24-8.22 (m, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.70-7.68 (m, 2H), 7.66-7.63 (m, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.43-7.40 (m, 2H), 7.37 (brs, 1H), 7.28 (brs, 1H), 7.14 (brs, 1H), 6.99 (brs, 1H), 6.73 (brs, 1H), 6.00-5.94 (m, 2H), 4.04-3.99 (m, 1H), 3.49 (brs, 1H), 3.43-3.37 (m, 1H). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 164.3, 150.6, 145.1, 144.7, 143.3, 142.2, 140.4, 140.1, 137.8, 136.4, 132.0, 129.9, 129.5, 128.9, 128.2, 128.0, 127.9, 127.3, 126.4, 126.3, 126.1, 126.1, 126.0, 125.6, 124.3, 121.3, 65.3, 44.2, 40.4. IR (KBr, cm^{-1}): 3053, 2986, 1654, 1274, 749. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{31}H_{23}N_2O$: 439.1805; Found: 439.1809.

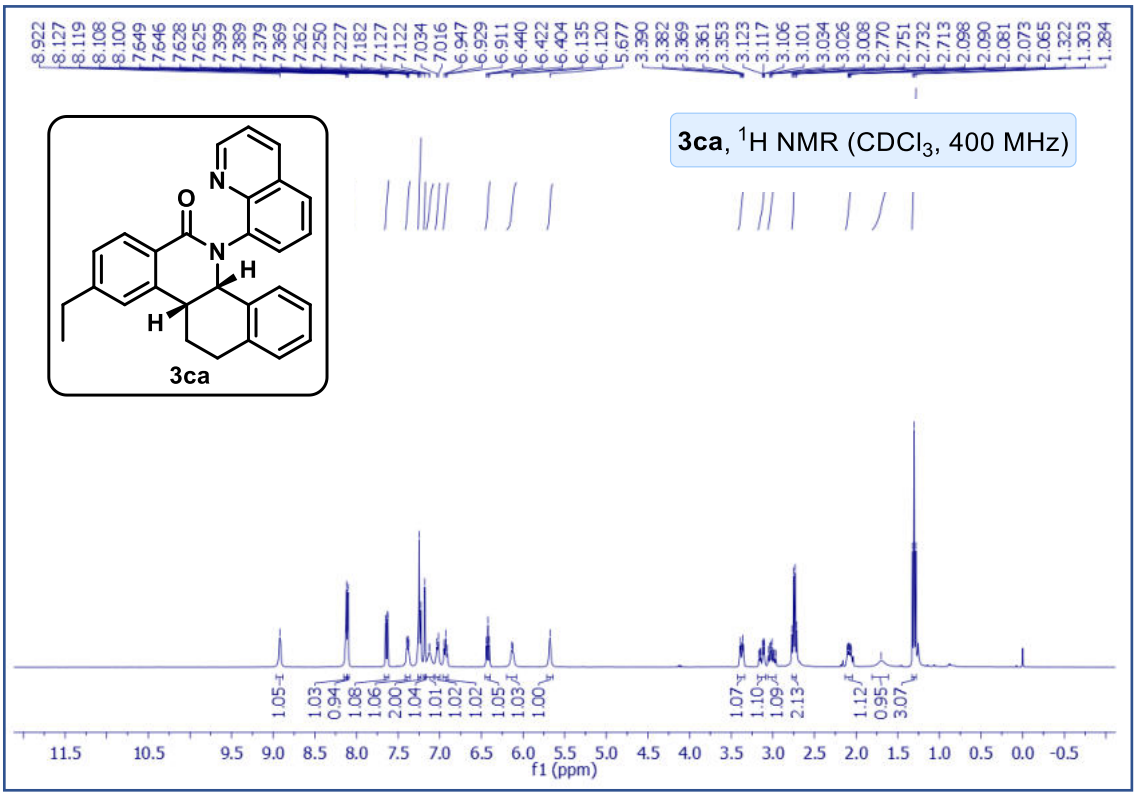
3-methoxy-9-methyl-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3bg)

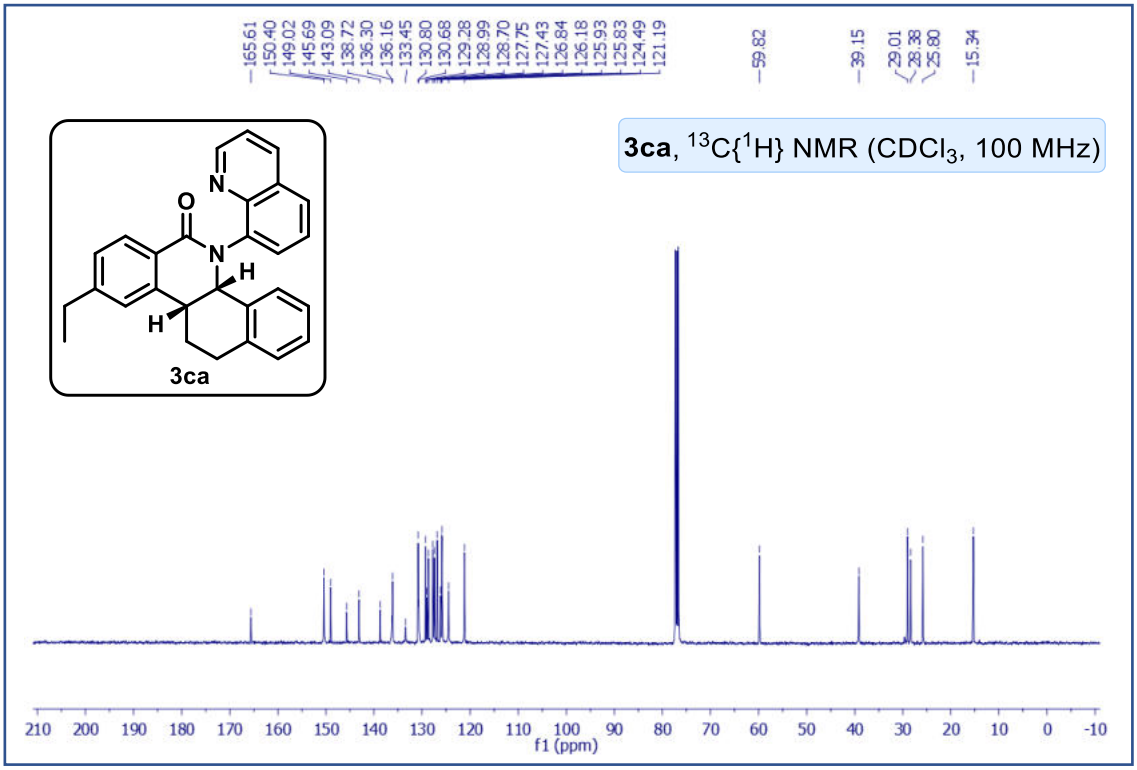


3bg

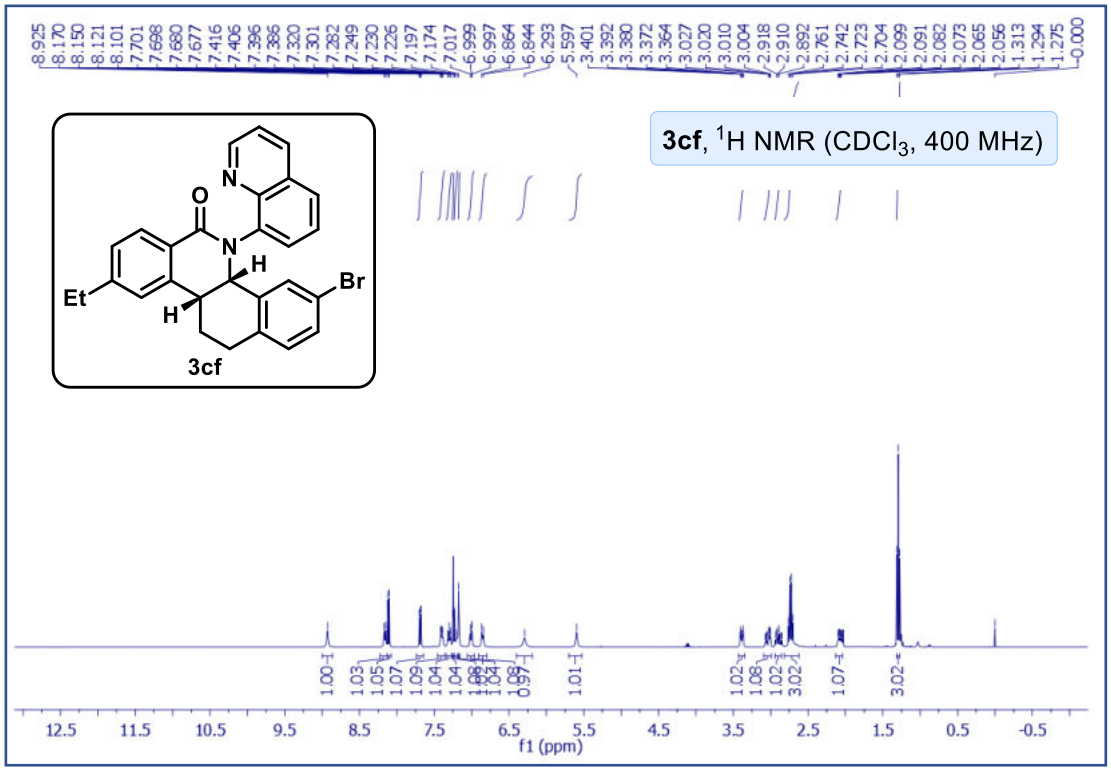
Trace amount was detected in HRMS. (HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{25}N_2O_2$: 421.1916; Found 421.1897.

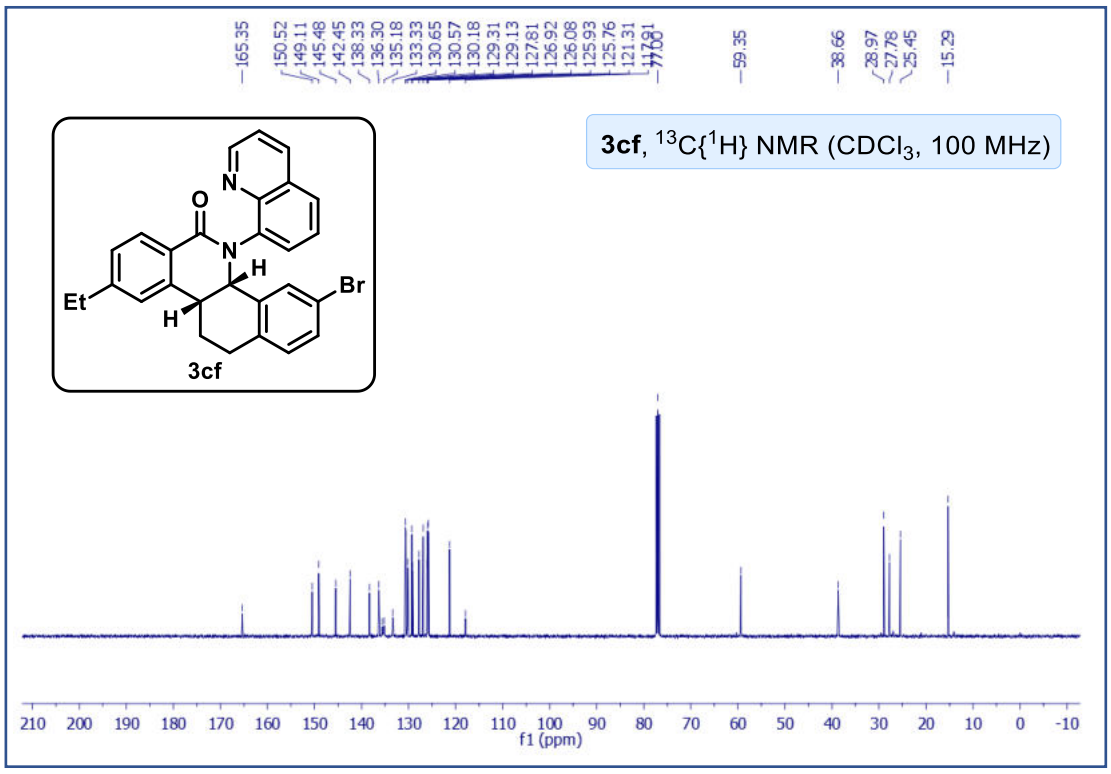
NMR spectra of 9-ethyl-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridin-6(5*H*)-one (3ca):



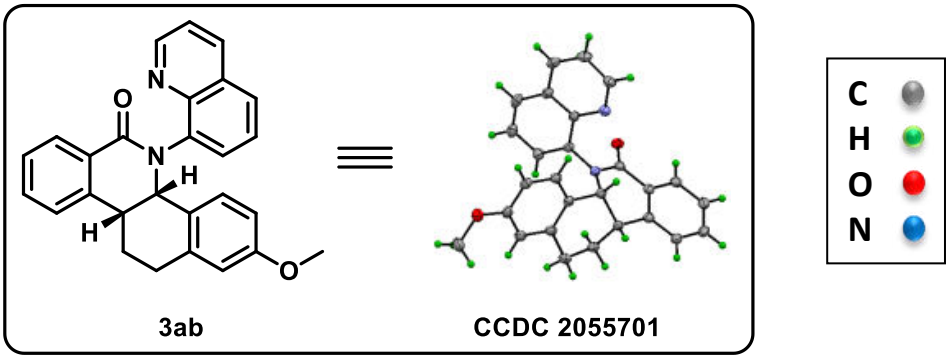


NMR spectra of 3-bromo-9-ethyl-5-(quinolin-8-yl)-4b,10b,11,12-tetrahydrobenzo[*c*] phenanthridin-6(5*H*)-one (3cf):

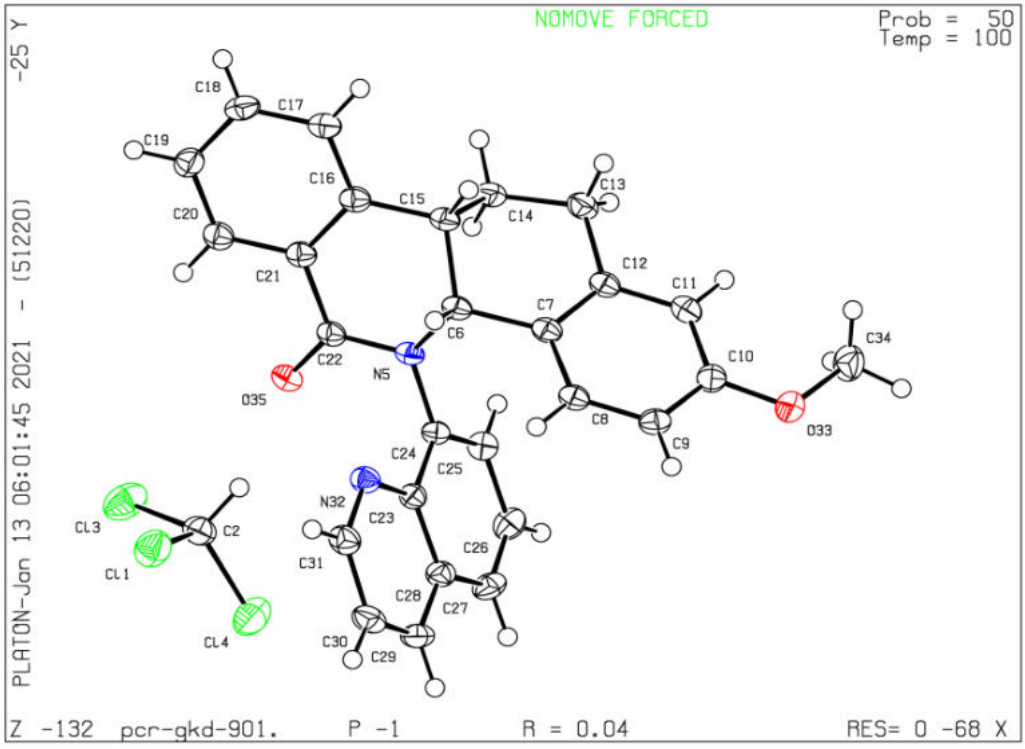




Crystal structure of 3ab



Datablock pcr_gkd_901. - ellipsoid plot



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Chapter 5

Annulation of Indole-2-Carboxamides with Bicycloalkenes catalyzed by Ru(II) at room temperature: An easy access to β-carboline-1-one derivatives under mild conditions

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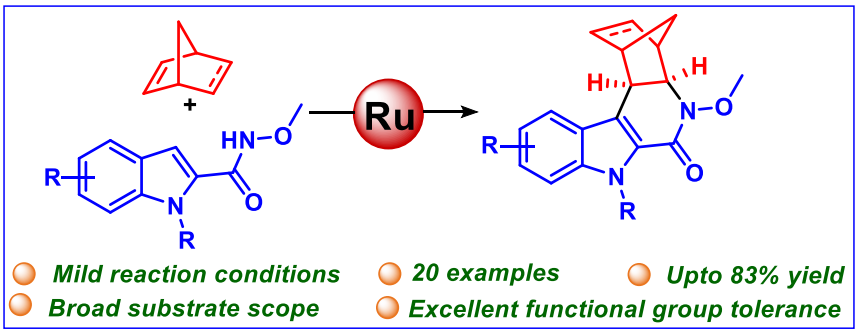
Annulation of Indole-2-Carboxamides with Bicycloalkenes catalyzed by Ru(II) at room temperature: An easy access to β-carboline-1-one derivatives under mild conditions



5.1 ABSTRACT: Herein, we report the annulaton of indole-2-carboxamides with bicycloalkenes, to synthesize β-carboline-1-one derivatives under mild condition. The commercially available ruthenium catalyst was used for the reaction. This reaction tolerates a wide range of functional groups, and affords good yield of β-carboline-1-one derivatives. A reversible cyclometalation pathway was found to be operative from the mechanistic study.

5.2 INTRODUCTION

Polycyclic indole scaffolds are prevalent in numerous natural products, and drugs.[1] Therefore, the synthesis of such heterocyclic moieties has immense importance in synthetic organic chemistry. Among the polycyclic indole compounds, β-carboline-1-one derivatives has significant importance due to its extensive use as an anticancer agent, and its application for the treatment of malaria, cancer, parkinson's and alzheimer's disease.[2]

Owing to its interesting biological properties, synthesis of *β*-carboline-1-one derivatives has attracted significant attention in recent years.

The C-H bond functionalization catalysed by transition metal has become a useful strategy[3,4] in recent years for the synthesis of complex heterocycles from readily available strating materials.[5] Many indololactams have been synthesized[6] using this approach. Notably, Jiao et al. reported the synthesis of carbolinones from indole-carboxamides using palladium catalysed annulation reaction with alkynes (Scheme-5.1a).[7] Cui et al. reported the synthesis of indolo fused N-heterocycles via rhodium catalysed cyclisation of indole-carboxamides with alkynes.[8] Zeng reported the formation of various indololactams from indole-carboxamides via cobalt catalyzed annulation reaction with alkynes.[9]

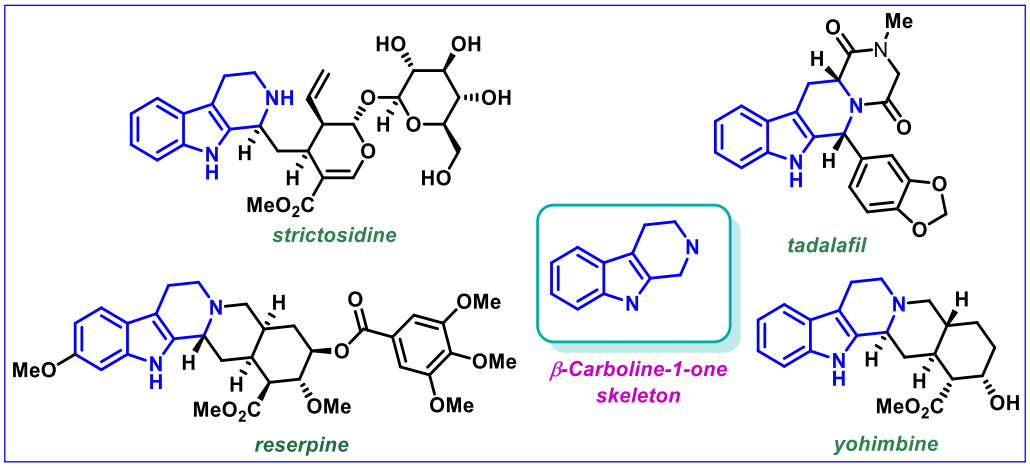


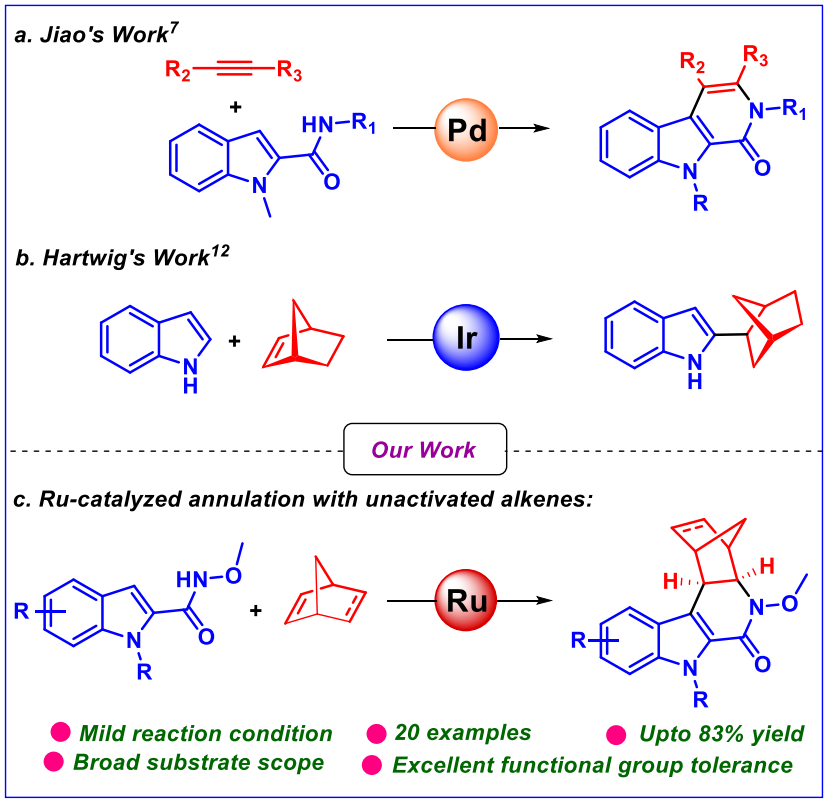
Figure 5.1 Alkaloids containing *β*-carboline-1-one moiety.

However, it is worthy to mention that, these reactions are reported with Pd, Ir, Co and Rh metal catalysts. However, these reactions has drawbacks such as use of expensive catalysts or high reaction temperature. Therefore, a mild condition that works at room temperature with a relatively less expensive ruthenium catalyst is desirable. In catalytic C-H activation processes, modification in the electronic and steric nature of substrate's or coupling

partners can lead to entirely different products.[10] This interesting feature of catalysis sets the platform to explore newer catalytic pathways by varying substrate, directing groups, and reagents, leading to variety of products.[11]

The use of bicycloalkenes on indole moiety has been less explored in the realm of transition metal catalysed C-H activation reaction and are restricted to only alkylation reaction (Scheme-5.1b).[12] Owing to the increasing importance of C-H bond activation reaction and the biological significance of *β*-carboline-1-one derivatives (Figure 5.1), here we developed the first ruthenium catalysed annulation reaction of indole-2-carboxamide with 2-norbornene **2a** and 2,5-norbornadiene **2b** to synthesize a variety of *β*-carboline-1-one

Scheme 5.1 Comparision with previous work



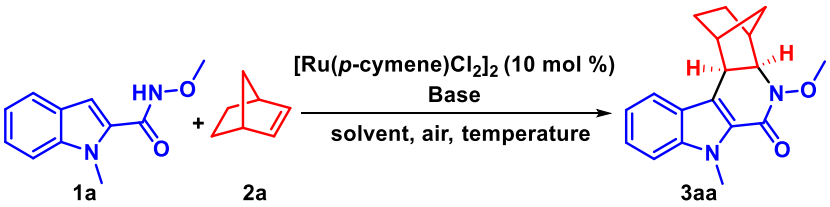
moieties (Scheme 5.1c). The important aspects of our reaction are (1) the commercially available ruthenium catalyst was used, (2) the bicycloalkenes has been used as coupling

partners which are underexplored, (3) the first report of annulation reaction of bicycloalkenes and substituted indole using C-H activation reaction in contrast to Hartwig's report,[12] (4) step and atom economic strategy for the efficient synthesis of complex *β*-carboline-1-one derivatives.

5.3 RESULTS AND DISCUSSIONS

We choosed indole-2-carboxamide **1a** and 2-norbornene **2a** as the model substrates for the ruthenium catalysed C-H/N-H annulation reaction.

Table 5.1. Screening of Reaction Conditions[a]



1a 2a 3aa

entry	solvent	catalyst	base	temp (°C)	yield of **3aa** (%)[b]
1	DCE	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	nr
2	MeCN	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	20
3	MeOH	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	35
4	HFIP	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	40
5	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	45
6	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	40[c]
7	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	42[d]
8	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	37[e]
9	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	60	39[f]
10	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	Na_2CO_3	60	45
11	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	Li_2CO_3	60	43
12	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	K_2CO_3	60	41
13	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	AgOAc	60	52
14	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	LiOAc	60	65
15	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	KOAc	60	73
16	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc	60	82
17	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc	40	80[g]
18	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc	90	75[h]
19	**TFE**	**$[Ru(p\text{-cymene})Cl_2]_2$**	**NaOAc**	rt	**81**[i]
20	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	—	rt	trace
21	TFE	—	NaOAc	rt	nr
22	TFE	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc	rt	4[j]

[a]Reaction conditions:- *N*-methoxy-1-methyl-1*H*-indole-2-carboxamide **1a** (1.0 equiv, 0.10 mmol), 2-Norbornene **2a** (4.0 equiv, 0.40 mmol), catalyst (0.1 equiv, 0.01 mmol), base (2.0 equiv, 0.20 mmol), TFE (0.1M) for 4 h at 60 °C, [b]yields of **3aa** were calculated from isolated products, [c-f]Additive (20 mol%) $AgSbF_6$, $AgBF_4$, KPF_6 and $Cu(OAc)_2$ respectively, [g]40°C, [h]90°C, [i]rt, [J]Degassed solvent, under Ar gas, NMR yield of **3aa** (calculated by taking 1,3,5-trimethoxybenzene as internal standard), nr-no reaction.

Initially various solvents were screened with $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst, CsOAc as base at 60°C (Table 5.1, entries 1-5). To our delight, we obtained the desired annulated product **3aa** in 45% yield with TFE as solvent (Table 5.1, entry 5). Using TFE as the optimized solvent, we screened different additives. Unfortunately, various additives like $AgSbF_6$, $AgBF_4$, KPF_6, $Cu(OAc)_2$ failed to improve the yield of the reaction (Table 5.1, entries 6-9). To further increase the yield of reaction, we decided to screen various carbonate bases. Different carbonate bases such as Na_2CO_3, Li_2CO_3 and K_2CO_3 were screened, which produced the annulated products in 45%, 43% and 41% yields respectively (Table 5.1, entries 10-12). Thus, we decided to screen various acetate bases (Table 5.1, entries 13-16). Gratifyingly, 82% of the annulated product was obtained with NaOAc as base (Table 5.1, entry 16). Encourged from these findings, we screened different temperatures for the annulation reaction (Table 5.1, entries 17-19). At room temperature, 81% of the corresponding annulated product was obtained (Table 5.1, entry 19). Finally, two control experiments were carried out to know the effect of catalyst and base. Without base, a trace amount of annulated product was obtained and in the absence of catalyst there was no reaction (Table 5.1, entries 20-21). To know the role of air in the reaction, a reaction was conducted under Ar atmosphere. The very low yield of the reaction suggests that the air is acting as oxidant for the reaction (Table 1, entry 22). Thus the use of [Ru(p-

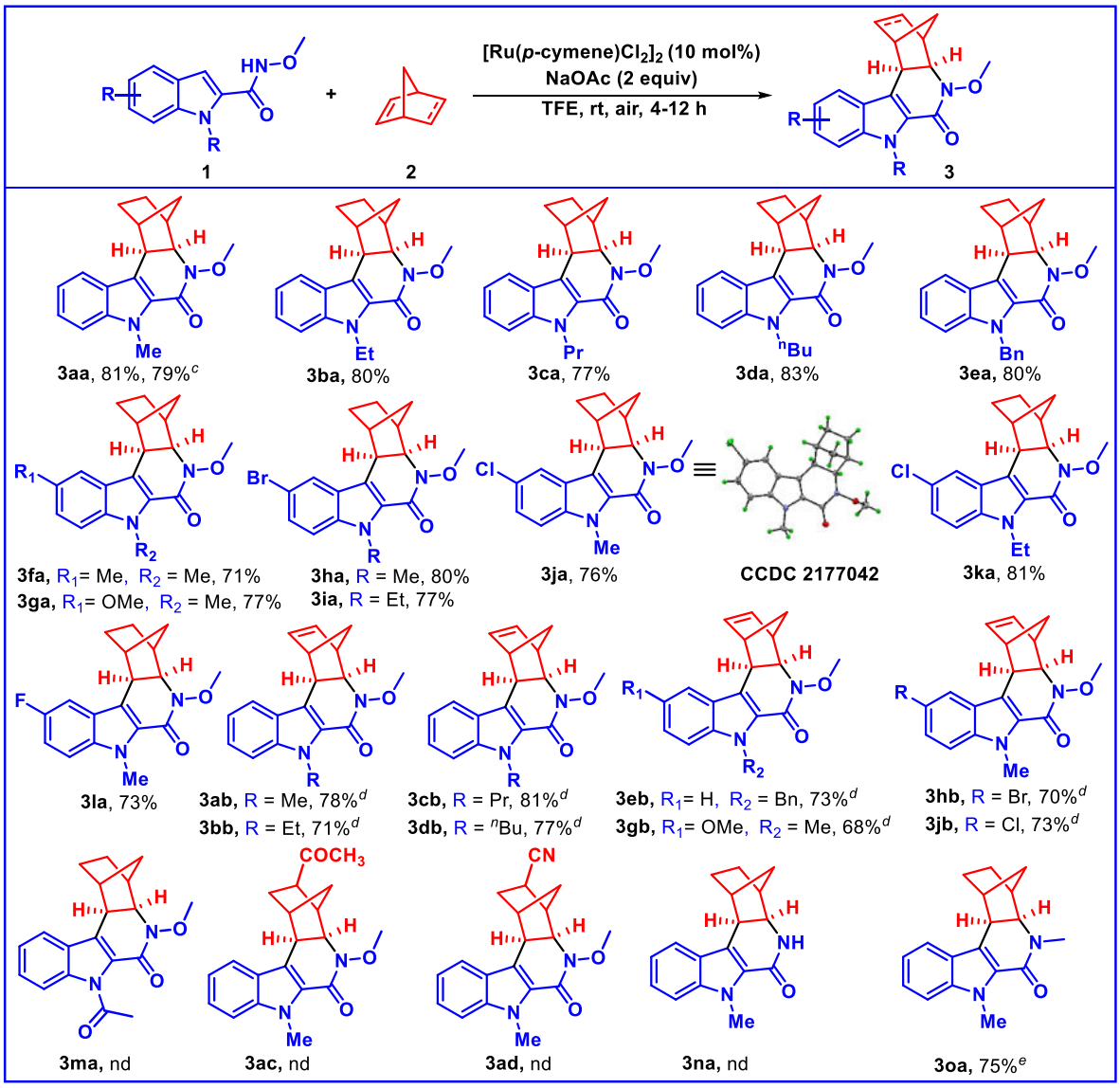
cymene)$Cl_2]_2$ as catalyst, NaOAc as base in TFE at room temperature was found to be the best reaction condition (Table 5.1, entry 19).

We investigated the generality of the annulation reaction with different *N*-protected indole-2-carboxamides such as *N*-ethyl, propyl, *n*-butyl, *n*-benzyl indole-2-carboxamides. In all cases good yields (77-83%) of the annulated product (**3aa-3ea**) were obtained (Scheme 5.2).

After screening of compatibility with different *N*-substituted indole-2-carboxamides, we tested the feasibility of reaction with substituted (substitution on benzene moiety) carboxamides. Electron donating groups such as methyl and methoxy substituents gave good yields of the products (**3fa, 3ga**). Halo group such as bromo and chloro substrates also gave good yields of the products (**3ha-3ja**). The stereochemistry and structure of the chloro substituted product **3ja** was unambiguously confirmed from single crystal X-ray analysis (CCDC 2177042). Electron deficient substrate such as fluoro substituted indole-2-carboxaminde also gave the product in good yield (**3la**). The synthetic usefulness of this reaction was further confirmed from a 1 mmol scale reaction of **1a** with **2a** using standard reaction condition, which furnished 79% yield of **3aa.**

The potential applications of this methodology was further explored with 2,5-norbornadiene **2b** (Scheme 5.2). Gratifyingly, different *N*-protected and substituted indole-2-carboxamides gave good yield of the corresponding annulated products (**3ab-3jb**, Scheme 5.2). The *N*-acetyl protected indole-2-carboxamide (1-acetyl-*N*-methoxy-1H-indole-2-carboxamide **1m**) did not furnish the desired annulated product under standard reaction condition. Thus it can be concluded that the annulated product is not obtained when *N*-protected group is a electron withdrawing group.

Scheme 5.2. Ru(II)-Catalyzed Annulation of Substituted indole-2-carboxamides with 2-norbornene and 2,5-norbornadiene [a, b]



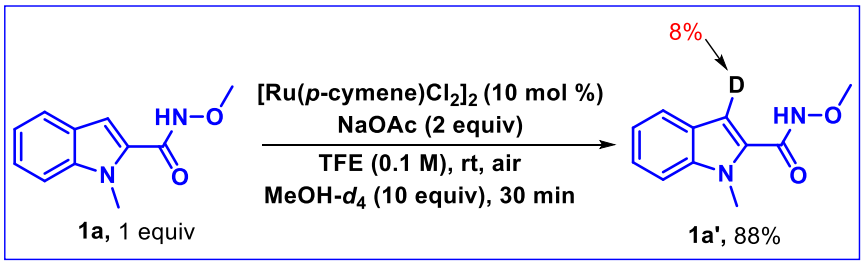
[a]Reaction conditions:- [a]Reaction conditions: **1** (1 equiv, 0.10 mmol), **2** (4.0 equiv, 0.40 mmol), [Ru(p-cymene)Cl_2]$_2$ (0.1 equiv, 0.01 mmol), NaOAc (2.0 equiv, 0.20 mmol), TFE (0.1 M), time = 4 h . [b]All yields in parenthesis are isolated yields. [c]Compound **3aa** (234 mg, 79%) was prepared in 1 mmol scale. [d]time = 12 h. nd - not detected, [e]60 °C.

After exploring 2-norbornene **2a** and 2,5-norbornadiene **2b** as coupling partner, we tried annulation reaction with substituted coupling partners. Different substituted coupling

partners like bicyclo[2.2.1]hept-5-en-2-yl)ethan-1-one **2c** and bicyclo[2.2.1]hept-5-ene-2-carbonitrile **2d** failed to furnish the desired annulated product. Finally, we tried different type of directing groups for the annulation reaction. With primary amide as directing group 1-methyl-1H-indole-2-carboxamide **1n**, the reaction did not produce the desired annulated product. Whereas, with secondary amide, *N*,1-dimethyl-1H-indole-2-carboxamide **1o** we observed 75% yield of the annulated product **3oa** (Scheme 5.2). This result clearly indicates the need for secondary amide as directing group for the annulation reaction.

After successful exploration of our methodology, we performed mechanistic investigation to have a insight into mechanistic cycle. The deuterium labelling of compound **1a** using D_2O in the absence of **2a** was performed (Scheme 5.3). A 8% deuterium incorporation was observed at C3 position of **1a.** This result suggests that, the C-H metalation step may be a reversible step.[13]

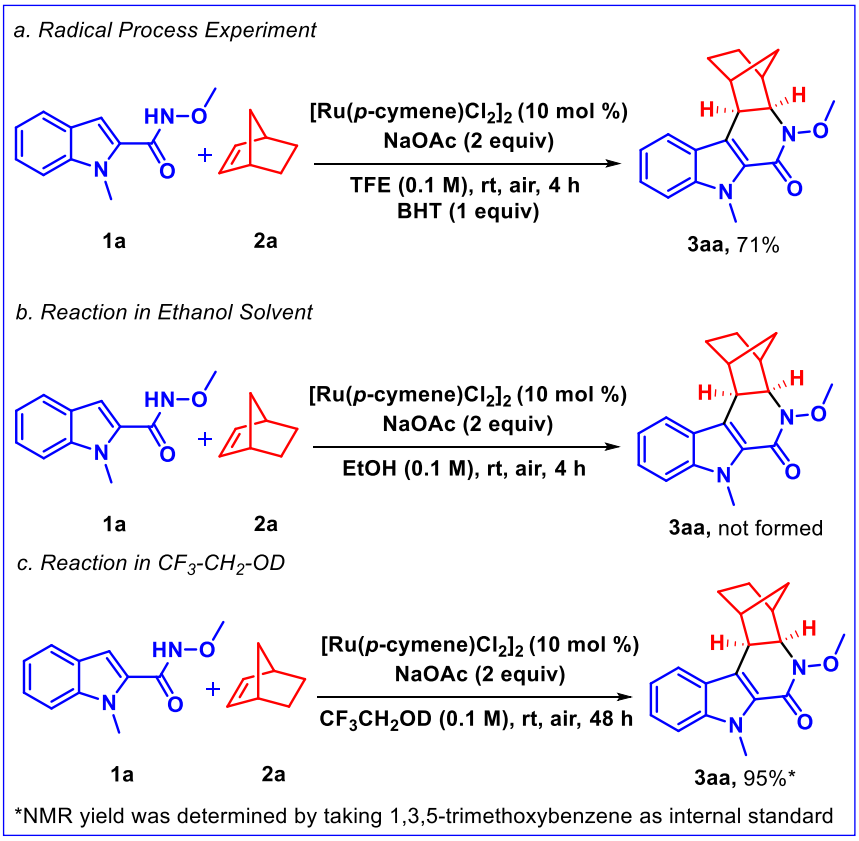
Scheme 5.3 Deuterium Exchange Experiment



To understand whether this reaction goes through radical mechanism, a radical quench experiment was performed using BHT as radical scavenger (Scheme 5.4a). But the yield of product **3aa** did not diminish significantly, and we got 71% yield of **3aa**, which indicates an ionic pathway for the reaction. To ascertain the critical role of TFE as an optimal solvent we set up two reactions, one with ethanol and the other one with CF_3CH_2OD as solvent

(Scheme 5.4b and 5.4c). The desired annulated product was not obtained in case of ethanol whereas with CF_3CH_2OD we obtained good yield (95% NMR yield) of the annulated product after prolonged time (48 hours). This result clearly justifies the need of TFE as optimal solvent.

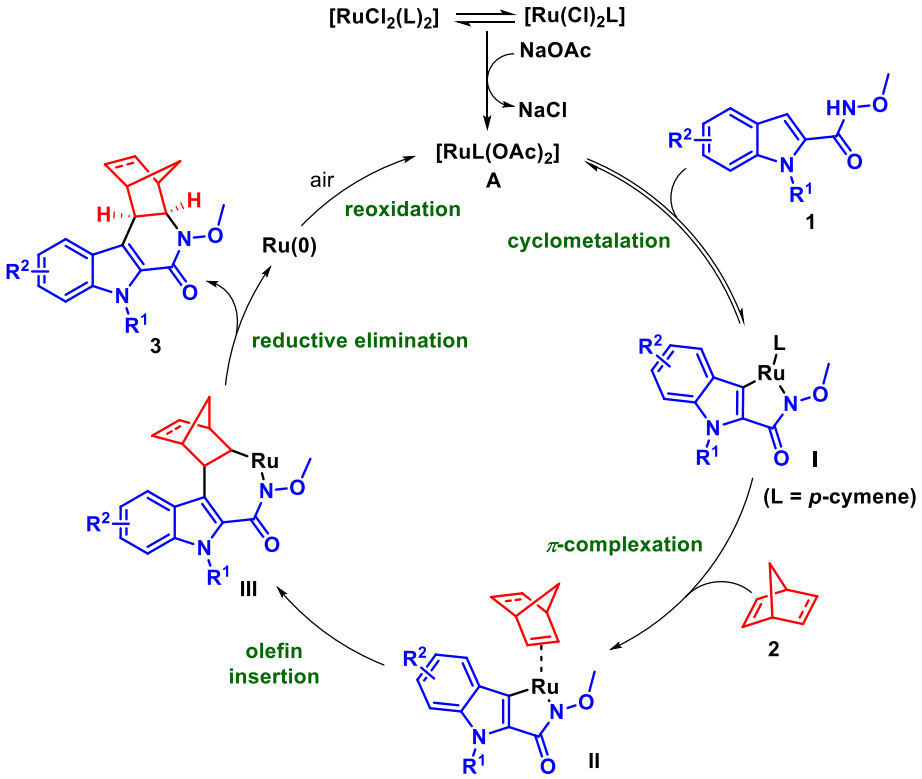
Scheme 5.4 Mechanistics Studies



A possible catalytic cycle was proposed in Scheme 5.5.[14, 15] Initially, a metallacyclic intermediate **I** is formed by the cyclometalation of indole-2-carboxamide **1** with the active catalyst **A**. Co-ordination of alkene with the intermediate **I** delivers the intermediate **II**. Subsequently it undergoes 1,2-insertion of olefin to produce intermediate **III**. The intermediate **III** undergoes reductive elimination to produce the annulated product **3** with the generation of reduced species Ru(0). Thereafter, Ru(0) is reoxidised to active catalytic

species **A** which enables catalytic cycle. To find the oxidant of the reaction, the reaction mixture was investigated using mass spectroscopy. A peak for norbornane was detected in LCMS and in GC analysis of the crude mixture (see page S3-S6 of Supporting Information). This result clearly indicates that, the bicycloalkenes acts as coupling partner as well as oxidant in the reaction.[15]

Scheme 5.5 Proposed Catalytic Cycle



Further, the reaction in argon atmosphere led to the formation of low yield (4%) of product 3, which suggests that the coupling partner, norbornene is acting as a minor oxidant. Therefore we can conclude that, the oxidation of Ru(0) to Ru(II) primarily occurs through oxygen in presence of air.[14]

5.4 CONCLUSIONS

In summary, we pursued the first ruthenium catalysed annulation reaction of indole-2-carboxamides and bicycloalkenes. The reaction sustains a variety of functional groups. This methodology offers a single step and economical synthesis of β-carboline-1-one moieties at room temperature. A deuterium labelling experiment suggests a reversible cyclometallation of the C-H activation step.

5.5 EXPERIMENTAL SECTION:[16]

All reactions were performed in sealed tubes. Chemicals were purchased from Alfa-aesar, Sigma-Aldrich, Spectrochem and were used without any purification. Using the recommended method from the book Armarego and Chai, 2003, Elsevier Science (USA), all solvents were purified. All compounds were purified by Column chromatography using distilled solvents and Avra Silica gel (100-200 mesh size). TLC was analysed by submersion in acidic *p*-anisaldehyde solution (PPA) and short wave (254 nm) UV light. The NMR spectras were recorded using Bruker AV-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) and Bruker 700 (^{1}H: 700 MHz, ^{13}C: 175 MHz). All NMR spectras were reported as δ in units of parts per million (ppm). ^{1}H chemical shifts were referenced in ppm with respect to residual $CHCl_3$ (7.26, singlet) and TMS (0.00) as per necessity. The chemical shifts for ^{13}C were referenced in ppm with respect to $CDCl_3$ (77.00 ppm, triplet). In parts per million (ppm) chemical shifts were documented and multiplicities were described as s (singlet), d (doublet), t (triplet), quint (quintet), q (quartet), m (multiplet), dt (doublet of triplet), td (triplet of doublet), brs (broad singlet). The coupling constants (*J*), were reported in Hertz

and integration were given. High Resolution Mass Spectrometry were recorded using Bruker micrOTOF Q- II.

5.5.1 General Procedure for the synthesis of Starting Materials.[17] All Indole-2-carboxamides were made from the corresponding acid chlorides (A), based on literature procedure,[17] with indole-2-carbonyl chloride (1.0 equiv, 1.0 mmol), *O*-Methylhydroxylamine hydrochloride (1.5 equiv, 1.5 mmol), triethyl amine (3.0 equiv, 3.0 mmol), DMAP (10.0 mmol%) in anhydrous DCM (0.25 M). Characterization data of compounds **1a, 1e, 1g, 1j** and **1l** were matched with the literature report.[17] Characterization data of new compounds were reported below.

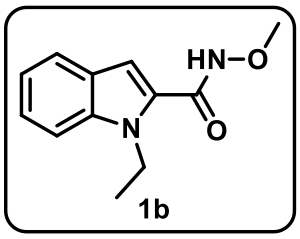
5.5.2 The General Method for making Annulated Products 3. The oven dried Schlenk tube, was filled with Indole-2-carboxamides **1** (1 equiv, 0.10 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.10 equiv, 0.01 mmol), NaOAc (2.0 equiv, 0.20 mmol), in anhydrous TFE (0.1 M). Thereafter, the coupling partner **2a**/**2b** (4.0 equiv, 0.40 mmol) was added under open atmosphere. The reaction mixture was stirred at room temperature for 4-12 hours (TLC control). After complete consumption of starting materials, the residual solvent was evaporated in *vaccuo* and the column chromatography was used to purify the crude residue which afforded the pure annulated product **3** using EtOAc/Hexane as eluent.

5.5.3 Reaction procedure for 1 mmol scale. The oven dried Schlenk tube, was filled with Indole-2-carboxamides **1a** (1 equiv, 1.0 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.10 equiv, 0.10 mmol), NaOAc (2.0 equiv, 2.0 mmol), in anhydrous TFE (0.1 M). Thereafter, the coupling partner **2a** (4.0 equiv, 4.0 mmol) was added under open atmosphere. The reaction mixture was stirred at room temperature for 4 hours. Excess solvent was evaporated in *vaccuo* following the complete consumption of starting materials and the crude residue was

purified by column chromatography which afforded the pure annulated product **3aa** (79%) using EtOAc/Hexane as eluent.

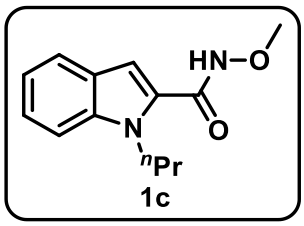
.5.5.4 Experimental characterization data:

1-ethyl-*N*-methoxy-1*H*-indole-2-carboxamide (1b):



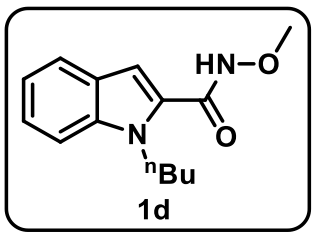
Physical State: colourless solid; mp: 140-142 °C; yield: (172 mg, 79%). R_f: 0.3 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.21 (brs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.85 (s, 1H), 4.53 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.8, 138.0, 127.6, 126.0, 124.3, 122.1, 120.5, 110.1, 104.8, 64.6, 39.5, 15.6. IR (KBr, cm^{-1}): 3053, 2991, 1635, 1275. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}N_2O_2$: 219.1134; Found: 219.1124.

***N*-methoxy-1-propyl-1*H*-indole-2-carboxamide (1c):**



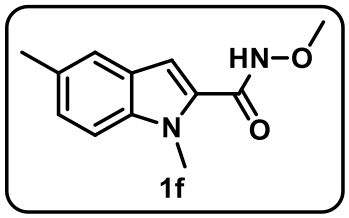
Physical State: colourless solid; mp: 136-138 °C; yield: (181 mg, 78%). R_f: 0.4 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.05 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.29-7.25 (m, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.82 (s, 1H), 4.46 (t, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.86-1.77 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.9, 138.5, 128.0, 125.9, 124.3, 122.0, 120.5, 110.4, 104.7, 64.7, 46.0, 23.7, 11.3. IR (KBr, cm^{-1}): 3053, 2984, 1652, 1275. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{16}N_2O_2Na$: 255.1104; Found: 255.1119.

1-butyl-*N*-methoxy-1*H*-indole-2-carboxamide (1d):



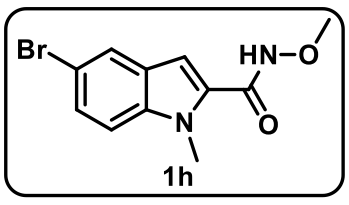
Physical State: colourless solid; mp: 118-120 °C; yield: (197 mg, 80%). R_f: 0.3 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.71 (s, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 7.0 Hz, 1H), 6.84 (s, 1H), 4.52 (t, J = 7.7 Hz, 2H), 3.91 (s, 3H), 1.79 (pentet, J = 7.7 Hz, 2H), 1.38-1.33 (m, 2H), 0.93 (t, J = 7.7 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 162.0, 138.5, 127.9, 126.0, 124.4, 122.1, 120.6, 110.5, 104.6, 64.8, 44.4, 32.6, 20.2, 13.8. IR (KBr, cm^{-1}): 3053, 2986, 1683, 1260. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{19}N_2O_2$: 247.1447; Found: 247.1439.

***N*-methoxy-1,5-dimethyl-1*H*-indole-2-carboxamide (1f)**:



Physical State: colourless solid; mp: 154-156 °C; yield: (168 mg, 77%). R_f: 0.3 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.73 (s, 1H), 7.39 (s, 1H), 7.28 (d, J = 9.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 162.1, 137.8, 130.0, 128.2, 126.5, 126.1, 121.3, 109.8, 103.9, 64.8, 31.5, 21.3. IR (KBr, cm^{-1}): 3053, 2986, 1640, 1264. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}N_2O_2$: 219.1134; Found: 219.1126.

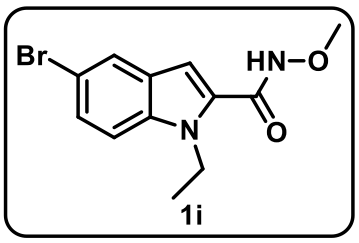
5-bromo-*N*-methoxy-1-methyl-1*H*-indole-2-carboxamide (1h):



Physical State: colourless solid; mp: 168-170 °C; yield: (232 mg, 82%). R_f: 0.4 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.74 (s, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.41 (dd,

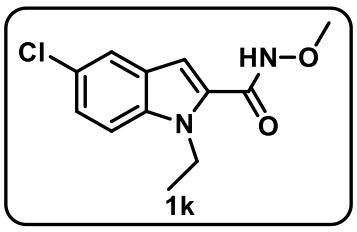
J = 9.1, 2.1 Hz, 1H), 7.27-7.26 (m, 1H), 6.77 (s, 1H), 4.01 (s, 3H), 3.91 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz): δ 161.5, 137.8, 129.4, 127.5, 127.4, 124.3, 113.9, 111.7, 103.7, 64.9, 31.6. IR (KBr, cm^{-1}): 3054, 2986, 1658, 1274, 749. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{11}H_{12}N_2O_2Br$: 283.0082; Found: 283.0073.

5-bromo-1-ethyl-*N*-methoxy-1*H*-indole-2-carboxamide (1i):



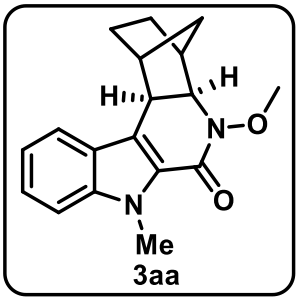
Physical State: colourless solid; mp: 161-163 °C; yield: (240 mg, 81%). R_f: 0.4 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 8.82 (s, 1H), 7.59-7.58 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.28-7.27 (m, 1H), 6.77 (s, 1H), 4.53 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz): δ 161.4, 136.4, 128.8, 126.9, 126.3, 124.9, 121.2, 111.3, 104.0, 64.8, 39.8, 15.6. IR (KBr, cm^{-1}): 3053, 2986, 1635, 1261, 752. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{14}N_2O_2Br$: 297.0239; Found: 297.0229.

5-chloro-1-ethyl-*N*-methoxy-1*H*-indole-2-carboxamide (1k):



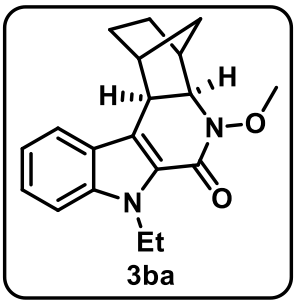
Physical State: colourless solid; mp: 168-170 °C; yield: (189 mg, 75%). R_f: 0.3 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.99 (s, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.40-7.37 (m, 1H), 7.26-7.25 (m, 1H), 6.76 (s, 1H), 4.51 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz): δ 161.3, 136.6, 128.7, 127.6, 127.3, 124.4, 113.7, 111.7, 103.9, 64.8, 39.8, 15.6. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1275, 763. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{14}N_2O_2Cl$: 253.0744; Found: 253.0744.

5-methoxy-7-methyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3aa):



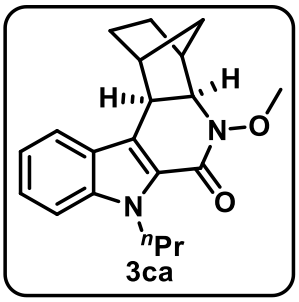
Physical State: colourless liquid; yield: (24 mg, 81%). R_f: 0.5 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.57 (d, J = 7.7 Hz, 1H), 7.36-7.35 (m, 1H), 7.34-7.32 (m, 1H), 7.14 (t, J = 7.0 Hz, 1H), 4.10 (s, 3H), 3.90 (s, 3H), 3.49 (d, J = 9.1 Hz, 1H), 2.77 (s, 1H), 2.60 (s, 1H), 1.71-1.67 (m, 3H), 1.56-1.55 (m, 2H), 1.35-1.33 (m, 1H), 1.23-1.21 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 157.8, 139.7, 124.5, 123.9, 123.0, 120.3, 120.0, 117.6, 110.3, 66.9, 61.9, 43.8, 41.7, 41.5, 33.2, 31.3, 29.2, 25.7. IR (KBr, cm^{-1}): 3053, 2986, 1652, 1275. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}N_2O_2Na$: 319.1417; Found: 319.1440.

7-ethyl-5-methoxy-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3ba):



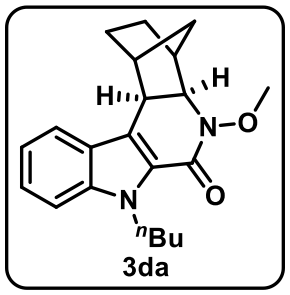
Physical State: colourless liquid; yield: (25 mg, 80%). R_f: 0.6 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.57 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.13 (t, J = 7.0 Hz, 1H), 4.69-4.59 (m, 2H), 4.10 (d, J = 9.1 Hz, 1H), 3.91 (s, 3H), 3.47 (d, J = 9.8 Hz, 1H), 2.77 (s, 1H), 2.60 (s, 1H), 1.71-1.66 (m, 3H), 1.57-1.54 (m, 1H), 1.39 (t, J = 7.0 Hz, 3H), 1.35-1.32 (m, 1H), 1.22-1.21 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 157.5, 138.6, 124.4, 124.1, 122.2, 120.3, 119.9, 117.8, 110.2, 67.0, 62.0, 43.8, 41.6, 41.5, 39.4, 33.2, 29.2, 25.7, 15.6. IR (KBr, cm^{-1}): 3053, 2984, 1635, 1275. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_2$: 311.1760; Found: 311.1750.

5-methoxy-7-propyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quino lin-6-one (3ca):



Physical State: Colourless liquid; yield: (25 mg, 77%). R_f: 0.60 (20% EtOAc/hexane). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.12 (t, J = 7.0 Hz, 1H), 4.59-4.51 (m, 2H), 4.09 (d, J = 9.8 Hz, 1H), 3.90 (s, 3H), 3.48 (d, J = 9.8 Hz, 1H), 2.76 (s, 1H), 2.60 (s, 1H), 1.85-1.81 (m, 2H), 1.70-1.65 (m, 3H), 1.57-1.54 (m, 1H), 1.35-1.32 (m, 1H), 1.22-1.20 (m, 1H), 0.92 (t, J = 7.7 Hz, 3H). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 157.6, 139.0, 124.4, 124.0, 122.7, 120.3, 119.8, 117.6, 110.6, 66.9, 61.9, 45.9, 43.8, 41.7, 41.5, 33.2, 29.1, 25.7, 23.7, 11.3. IR (KBr, cm^{-1}): 3053, 2984, 1634, 1275. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O_2$: 325.1911; Found: 325.1910.

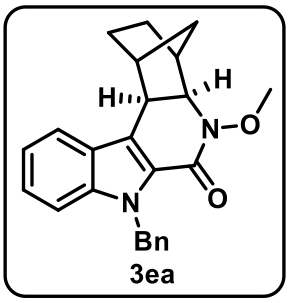
7-butyl-5-methoxy-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quino lin-6-one (3da):



Physical State: colourless liquid; yield: (28 mg, 83%). R_f: 0.5 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.57 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 7.0 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 4.63-4.54 (m, 2H), 4.09 (d, J = 9.1 Hz, 1H), 3.90 (s, 3H), 3.47 (d, J = 9.8 Hz, 1H), 2.77 (s, 1H), 2.60 (s, 1H), 1.78 (pentet, J = 7.7 Hz, 2H), 1.70-1.65 (m, 3H), 1.57-1.54 (m, 1H), 1.39-1.32 (m, 3H), 1.22-1.20 (m, 1H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 157.5, 139.0, 124.3, 124.0, 122.6, 120.3, 119.8, 117.7, 110.5, 66.9, 61.9, 44.3, 43.8, 41.7,

41.5, 33.2, 32.7, 29.1, 25.7, 20.1, 13.9. IR (KBr, cm^{-1}): 3052, 2955, 1667, 1267. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{27}N_2O_2$: 339.2073; Found: 339.2065.

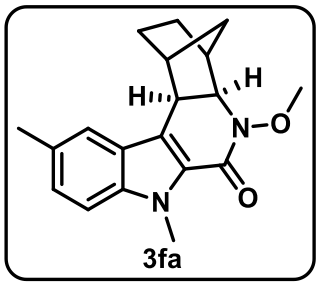
7-benzyl-5-methoxy-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3ea):



3ea

Physical State: colourless liquid; yield: (30 mg, 80%). R_f: 0.5 (20% EtOAc/Hexane). ^1H NMR ($CDCl_3$, 700 MHz): δ 7.58 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.26-7.22 (m, 2H), 7.22-7.21 (m, 1H), 7.17-7.16 (m, 3H), 7.12 (t, J = 7.7 Hz, 1H), 5.87 (s, 2H), 4.11 (d, J = 9.8 Hz, 1H), 3.88 (s, 3H), 3.50 (d, J = 9.8 Hz, 1H), 2.77 (s, 1H), 2.61 (s, 1H), 1.71-1.67 (m, 3H), 1.57-1.55 (m, 1H), 1.35-1.32 (m, 1H), 1.23-1.21 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 157.6, 139.3, 138.3, 128.4, 127.0, 126.8, 124.7, 124.2, 122.5, 120.3, 120.2, 118.2, 111.0, 66.9, 61.9, 47.7, 43.8, 41.7, 41.5, 33.2, 29.1, 25.7. IR (KBr, cm^{-1}): 3053, 2986, 1653, 1218. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{24}N_2O_2Na$: 395.1730; Found: 395.1752.

5-methoxy-7,10-dimethyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3fa):

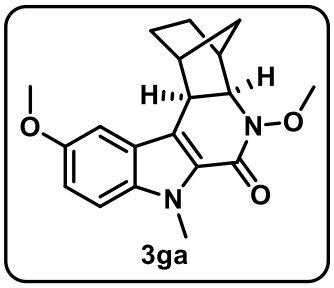


3fa

Physical State: colourless liquid; yield: (22 mg, 71%). R_f: 0.6 (20% EtOAc/Hexane). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (s, 1H), 7.24-7.22 (m, 1H), 7.16-7.13 (m, 1H), 4.09 (s, 1H), 4.06 (s, 3H), 3.90 (s, 3H), 3.43 (d, J = 9.6 Hz, 1H), 2.75 (s, 1H), 2.58 (s, 1H), 2.45 (s, 3H), 1.75-1.66 (m, 3H), 1.58-1.53 (m, 1H), 1.35-1.30 (m, 1H), 1.21-1.19 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 157.9, 138.2, 129.3, 126.4, 124.0, 122.9, 119.5, 117.0, 109.9, 66.9, 61.9, 43.7, 41.6, 41.5, 33.1, 31.3, 29.1, 25.7, 21.4. IR (KBr, cm^{-}

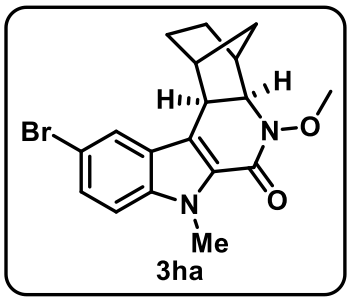
[1]): 3053, 2984, 1636, 1275. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_2$: 311.1760; Found: 311.1750.

5,10-dimethoxy-7-methyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*] quinolin-6-one (3ga):



Physical State: colourless liquid; yield: (25 mg, 77%). R_f: 0.6 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.25-7.24 (m, 1H), 7.00 (dd, J = 8.4, 2.1 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 4.08 (d, J = 8.4 Hz, 1H), 4.06 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.43 (d, J = 9.8 Hz, 1H), 2.76 (s, 1H), 2.57 (s, 1H), 1.71-1.67 (m, 3H), 1.57-1.55 (m, 1H), 1.35-1.32 (m, 1H), 1.22-1.21 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 157.7, 154.3, 135.2, 124.0, 123.3, 116.8, 115.4, 111.1, 101.0, 66.8, 61.9, 55.9, 43.4, 41.6, 41.4, 33.1, 31.3, 29.1, 25.7. IR (KBr, cm^{-1}): 3053, 2986, 1660, 1261, 748. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_3$: 327.1709; Found: 327.1699.

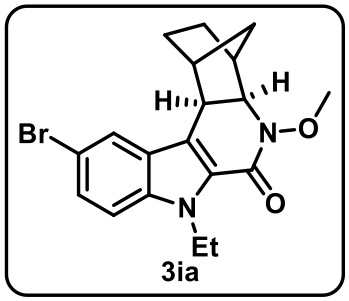
10-bromo-5-methoxy-7-methyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo [2,3-*c*]quinolin-6-one (3ha):



Physical State: colourless liquid; yield: (30 mg, 80%). R_f: 0.5 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.68 (d, J = 1.4 Hz, 1H), 7.38 (dd, J = 9.1, 1.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 4.09 (d, J = 9.8 Hz, 1H), 4.07 (s, 3H), 3.90 (s, 3H), 3.40 (d, J = 9.1 Hz, 1H), 2.77 (s, 1H), 2.54 (s, 1H), 1.71-1.68 (m, 2H), 1.56-1.54 (m, 1H), 1.35-1.32 (m, 1H), 1.23-1.22 (m, 1H), 0.89-0.83 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 157.3, 138.2, 127.3, 125.4, 123.9, 122.6, 116.8, 113.2, 111.8, 66.8, 61.9, 43.8, 41.6, 41.2, 33.1, 31.4, 29.1, 25.7. IR (KBr, cm^{-1}): 3053, 2984, 1635,

1275, 749. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}BrN_2O_2Na$: 397.0522; Found: 397.0530.

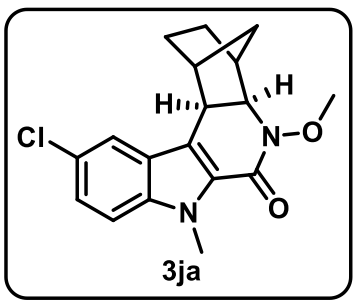
10-bromo-7-ethyl-5-methoxy-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo [2,3-*c*]quinolin-6-one (3ia):



3ia

Physical State: colourless solid; mp: 138-140 °C; yield: (30 mg, 77%). R_f: 0.5 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.52 (d, J = 2.1 Hz, 1H), 7.29-7.27 (m, 1H), 7.25-7.24 (m, 1H), 4.66- 4.56 (m, 2H), 4.09 (d, J = 9.1 Hz, 1H), 3.90 (s, 3H), 3.40 (d, J = 9.1 Hz, 1H), 2.77 (s, 1H), 2.54 (s, 1H), 1.71-1.70 (m, 2H), 1.65-1.64 (m, 1H), 1.56-1.53 (m, 1H), 1.37 (t, J = 7.0 Hz, 3H), 1.35-1.32 (m, 1H), 1.23-1.22 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 157.0, 136.9, 125.6, 124.9, 124.8, 123.3, 119.5, 117.1, 111.3, 66.9, 61.9, 43.7, 41.6, 41.2, 39.6, 33.1, 29.1, 25.6, 15.5. IR (KBr, cm^{-1}): 3053, 2987, 1635, 1275, 763. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}N_2O_2Br$: 389.0865; Found: 389.0851.

10-chloro-5-methoxy-7-methyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo [2,3-*c*]quinolin-6-one (3ja):

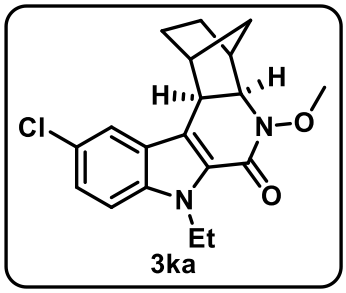


3ja

Physical State: colourless liquid; yield: (25 mg, 76%). R_f: 0.6 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.52 (s, 1H), 7.26-7.25 (m, 2H), 4.09 (d, J = 8.4 Hz, 1H), 4.07 (s, 3H), 3.90 (s, 3H), 3.40 (d, J = 9.1 Hz, 1H), 2.77 (s, 1H), 2.54 (s, 1H), 1.71-1.70 (m, 2H), 1.65-1.64 (m, 1H), 1.56-1.54 (m, 1H), 1.35-1.32 (m, 1H), 1.23-1.22 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): δ 157.3, 137.9, 125.7, 124.8, 124.7, 124.0, 119.4, 116.9, 111.4, 66.8, 61.9, 43.8, 41.6, 41.2, 33.1,

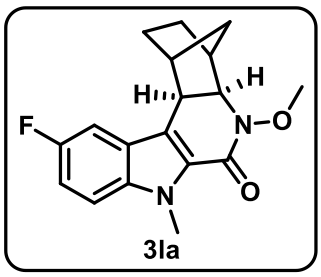
31.4, 29.1, 25.7. IR (KBr, cm^{-1}): 3053, 2986, 1640, 1260, 751. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{20}N_2O_2Cl$: 331.1213; Found: 331.1203.

10-chloro-7-ethyl-5-methoxy-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3ka):



Physical State: colourless solid; mp: 140-142 °C; yield: (28 mg, 81%). R_f: 0.5 (20% EtOAc/Hexane). ^1H NMR ($CDCl_3$, 700 MHz): δ 7.68 (s, 1H), 7.38-7.36 (m, 1H), 7.24 (d, J = 7.7 Hz, 1H), 4.65-4.56 (m, 2H), 4.09 (d, J = 9.1 Hz, 1H), 3.90 (s, 3H), 3.40 (d, J = 9.8 Hz, 1H), 2.77 (s, 1H), 2.54 (s, 1H), 1.71-1.68 (m, 2H), 1.65-1.63 (m, 1H), 1.56-1.54 (m, 1H), 1.37 (t, J = 7.0 Hz, 3H), 1.24-1.22 (m, 1H), 0.89-0.84 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 157.0, 137.1, 127.3, 125.6, 123.2, 122.7, 117.0, 113.0, 111.8, 66.9, 61.9, 43.8, 41.6, 41.3, 39.6, 33.1, 29.1, 25.7, 15.5. IR (KBr, cm^{-1}): 3053, 2986, 1633, 1261, 749. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}N_2O_2Cl$: 345.1370; Found: 345.1361.

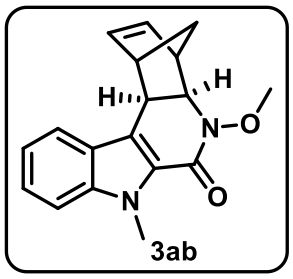
10-fluoro-5-methoxy-7-methyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo [2,3-*c*]quinolin-6-one (3la):



Physical State: colourless liquid; yield: (23 mg, 73%). R_f: 0.6 (20% EtOAc/Hexane). ^1H NMR ($CDCl_3$, 700 MHz): δ 7.28-7.26 (m, 1H), 7.19 (dd, J = 9.1, 2.1 Hz, 1H), 7.09-7.06 (m, 1H), 4.10 (s, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.41 (d, J = 9.1 Hz, 1H), 2.77 (s, 1H), 2.53 (s, 1H), 1.71-1.69 (m, 2H), 1.68-1.65 (m, 1H), 1.56-1.53 (m, 1H), 1.35-1.32 (m, 1H), 1.23-1.22 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 157.8 (d, J = 236.2 Hz), 157.4, 136.3, 124.3, 123.9 (d, J = 10.5 Hz), 117.2 (d, J = 5.2 Hz), 113.3 (d,

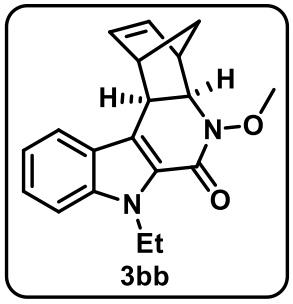
J = 26.2 Hz), 111.2 (d, *J* = 10.5 Hz), 104.6 (d, *J* = 24.5 Hz), 66.8, 61.9, 43.6, 41.6, 41.3, 33.1, 31.5, 29.2, 25.7. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -123.2. IR (KBr, cm^{-1}): 3053, 2984, 1634, 1275, 749. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{20}FN_2O_2$: 315.1503; Found: 315.1511.

5-methoxy-7-methyl-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3ab):



Physical State: colourless liquid; yield: (23 mg, 78%). R_f: 0.5 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.39-7.33 (m, 2H), 7.19-7.16 (m, 1H), 6.46-6.44 (m, 1H), 6.19-6.17 (m, 1H), 4.12 (s, 3H), 4.03 (d, *J* = 9.2 Hz, 1H), 3.93 (s, 3H), 3.48 (d, *J* = 9.6 Hz, 1H), 3.43 (s, 1H), 3.21 (s, 1H), 1.66-1.64 (m, 1H), 1.50-1.47 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.5, 139.6, 139.4, 134.7, 124.6, 123.8, 123.4, 120.2, 120.1, 117.5, 110.3, 62.6, 61.8, 49.0, 47.8, 43.5, 36.4, 31.2. IR (KBr, cm^{-1}): 3054, 2986, 1633, 1274. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{18}N_2O_2Na$: 317.1260; Found: 317.1265.

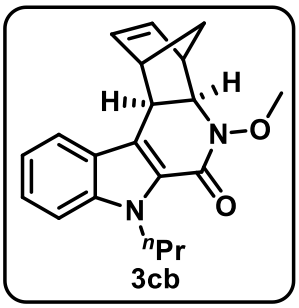
(4a*R*,11c*R*)-7-ethyl-5-methoxy-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3bb):



Physical State: colourless liquid; yield: (22 mg, 71%). R_f: 0.6 (20% EtOAc/Hexane) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.41-7.39 (m, 1H), 7.36-7.32 (m, 1H), 7.18-7.15 (m, 1H), 6.46-6.44 (m, 1H), 6.19-6.17 (m, 1H), 4.74-4.59 (m, 2H), 4.03 (d, *J* = 9.6 Hz, 1H), 3.93 (s, 3H), 3.47 (d, *J* = 9.2 Hz, 1H), 3.43 (s, 1H), 3.21 (s, 1H), 1.65 (s, 1H), 1.50-1.48 (m, 1H), 1.40 (t, *J* = 6.8 Hz, 3H).

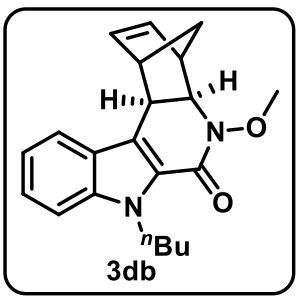
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.2, 139.4, 138.5, 134.7, 124.6, 124.0, 122.7, 120.3, 120.0, 117.7, 110.3, 62.7, 61.8, 49.0, 47.8, 43.5, 39.3, 36.5, 15.6. IR (KBr, cm^{-1}): 3054, 2986, 1633, 1274. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{20}N_2O_2Na$: 331.1417; Found: 331.1417.

5-methoxy-7-propyl-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3cb):



Physical State: colourless liquid; yield: (26 mg, 81%). R_f: 0.5 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, J = 8.0 Hz, 1H), 7.40-7.38 (m, 1H), 7.34-7.30 (m, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.46-6.44 (m, 1H), 6.19-6.17 (m, 1H), 4.65-4.52 (m, 2H), 4.03 (d, J = 9.2 Hz, 1H), 3.92 (s, 3H), 3.47 (d, J = 9.6 Hz, 1H), 3.43 (s, 1H), 3.22 (s, 1H), 1.88-1.79 (m, 2H), 1.63 (d, J = 9.6 Hz, 1H), 1.48 (d, J = 9.2 Hz, 1H), 0.93 (t, J = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.3, 139.3, 139.0, 134.8, 124.5, 124.0, 123.1, 120.3, 120.0, 117.6, 110.7, 62.6, 61.8, 49.0, 47.8, 45.8, 43.5, 36.5, 23.8, 11.3. IR (KBr, cm^{-1}): 3053, 2984, 1634, 1275. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2O_2Na$: 345.1573; Found: 345.1590.

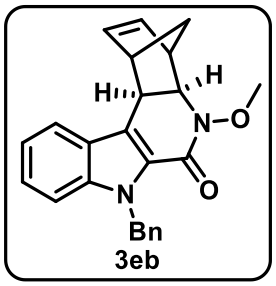
7-butyl-5-methoxy-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3db):



Physical State: colourless liquid; yield: (26 mg, 77%). R_f: 0.6 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J = 8.0 Hz, 1H), 7.40-7.38 (m, 1H), 7.35-7.31 (m, 1H), 7.16 (t, J = 6.4 Hz, 1H), 6.46-1.44 (m, 1H), 6.19-6.17 (m, 1H), 4.68-4.54 (m, 2H), 4.03 (d, J = 9.2 Hz, 1H), 3.92 (s, 3H), 3.47 (d, J = 9.6 Hz, 1H), 3.43 (s, 1H), 3.21 (s,

1H), 1.78 (pentet, *J* = 7.6 Hz, 2H), 1.66-1.64 (m, 1H), 1.49-1.47 (m, 1H), 1.42-1.33 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.3, 139.3, 138.9, 134.7, 124.5, 123.9, 123.0, 120.2, 120.0, 117.6, 110.6, 62.5, 61.7, 49.0, 47.8, 44.2, 43.5, 36.4, 32.7, 20.1, 13.9. IR (KBr, cm^{-1}): 3053, 2984, 1636, 1274. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{24}N_2O_2Na$: 359.1730; Found: 359.1723.

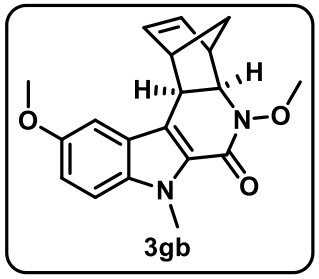
7-benzyl-5-methoxy-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3eb):



3eb

Physical State: colourless liquid; yield: (27 mg, 73%). R_f: 0.6 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.30-7.28 (m, 1H), 7.23-7.22 (m, 1H), 7.17-7.15 (m, 2H), 7.12-7.08 (m, 4H), 6.39-6.38 (m, 1H), 6.12-6.11 (m, 1H), 5.86-5.80 (m, 2H), 3.98-3.97 (m, 1H), 3.84 (s, 3H), 3.43-3.42 (m, 1H), 3.36 (s, 1H), 3.17 (s, 1H), 1.58-1.57 (m, 1H), 1.44-1.42 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175 MHz): δ 157.3, 139.3, 139.3, 138.3, 134.8, 128.5, 127.1, 126.9, 124.9, 124.2, 123.0, 120.4, 120.3, 118.2, 111.1, 62.7, 61.8, 49.0, 47.9, 47.6, 43.6, 36.5. IR (KBr, cm^{-1}): 3053, 2986, 1635, 1260. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{23}N_2O_2$: 371.1754; Found: 371.1760.

5,10-dimethoxy-7-methyl-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3gb):

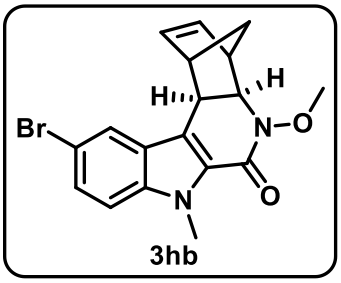


3gb

Physical State: colourless liquid; yield: (22 mg, 68%). R_f: 0.5 (20% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.28-7.27 (m, 1H), 7.03-7.01 (m, 2H), 6.46-7.45 (m, 1H), 6.19-6.18 (m, 1H), 4.09 (s, 3H), 4.02-4.01 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.43-3.42 (m, 2H), 3.19 (s, 1H), 1.65-1.64 (m, 1H), 1.50-1.49 (m, 1H). $^{13}C\{^{1}H\}$ NMR

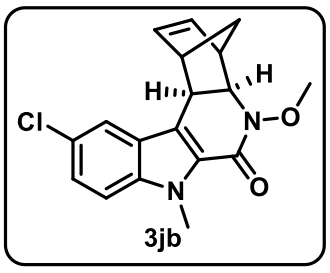
($CDCl_3$, 175 MHz): δ 157.5, 154.4, 139.3, 135.2, 134.8, 124.0, 123.8, 116.8, 115.6, 111.2, 101.0, 62.6, 61.8, 56.0, 48.6, 47.8, 43.5, 36.5, 31.3. IR (KBr, cm^{-1}): 3053, 2984, 1652, 1263, 766. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{20}N_2O_3Na$: 347.1366; Found: 347.1379.

10-bromo-5-methoxy-7-methyl-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3hb):



Physical State: colourless liquid; yield: (26 mg, 70%). R_f: 0.6 (20% EtOAc/Hexane). ^1H NMR ($CDCl_3$, 700 MHz): δ 7.78 (d, J = 1.4 Hz, 1H), 7.41 (dd, J = 8.1, 2.1 Hz, 1H), 7.25 (m, J = 8.1 Hz, 1H), 6.46-6.44 (m, 1H), 6.19-6.17 (m, 1H), 4.10 (s, 3H), 4.03-4.02 (m, 1H), 3.92 (s, 3H), 3.43 (s, 1H), 3.40-3.39 (m, 1H), 3.16 (s, 1H), 1.62-1.61 (m, 1H), 1.51-1.50 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 157.1, 139.3, 138.2, 134.8, 127.5, 125.4, 124.3, 122.6, 116.8, 113.3, 111.8, 62.6, 61.8, 49.0, 47.8, 43.4, 36.3, 31.4. IR (KBr, cm^{-1}): 3053, 2984, 1635, 1275, 764. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{17}BrN_2O_2Na$: 395.0366; Found: 395.0356.

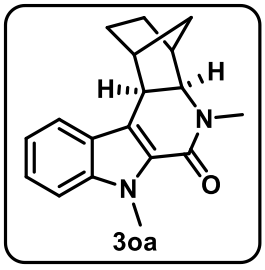
10-chloro-5-methoxy-7-methyl-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3jb):



Physical State: colourless liquid; yield: (24 mg, 73%). R_f: 0.5 (20% EtOAc/Hexane). ^1H NMR ($CDCl_3$, 700 MHz): δ 7.62 (s, 1H), 7.29 (s, 2H), 6.46-6.44 (m, 1H), 6.19-6.17 (m, 1H), 4.10 (s, 3H), 4.03-4.02 (m, 1H), 3.92 (s, 3H), 3.43 (s, 1H), 3.41-3.40 (m, 1H), 3.16 (s, 1H), 1.63-1.61 (m, 1H), 1.51-1.50 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 157.1, 139.3, 138.0, 134.8, 125.9, 125.0, 124.7, 124.5, 119.4, 116.9,

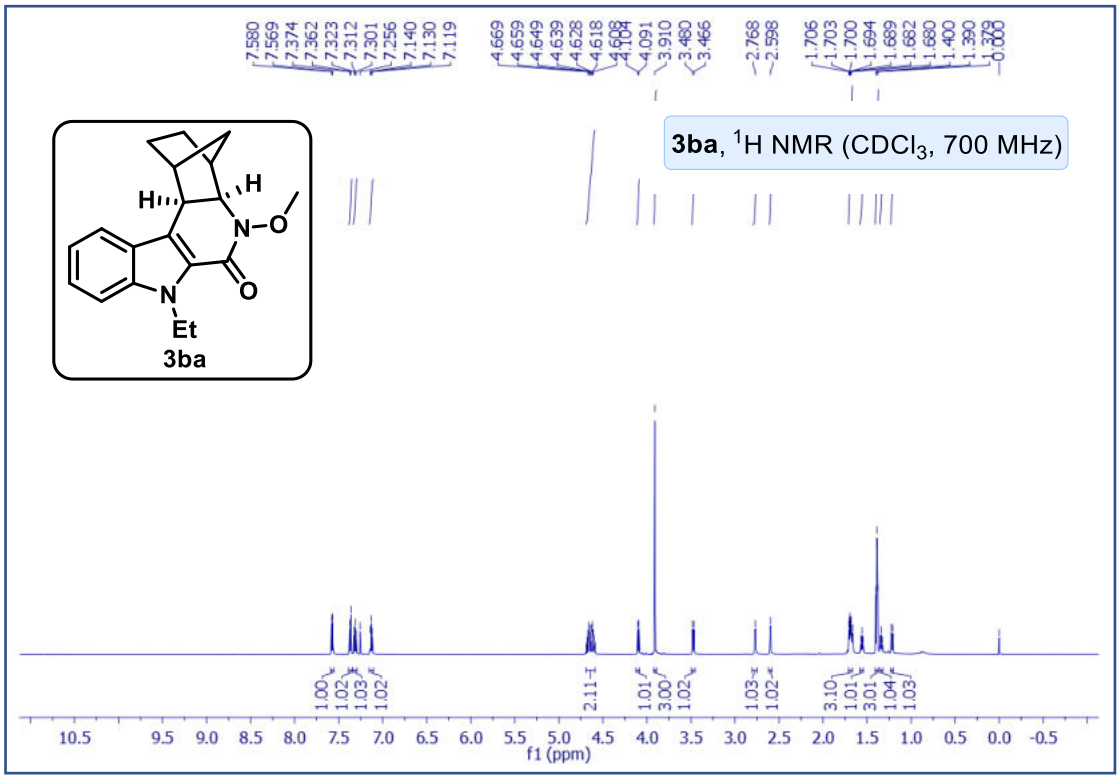
111.5, 62.6, 61.8, 49.0, 47.8, 43.4, 36.3, 31.4. IR (KBr, cm^{-1}): 3053, 2986, 1653, 1263, 766. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{17}ClN_2O_2Na$: 351.0871; Found: 351.0879.

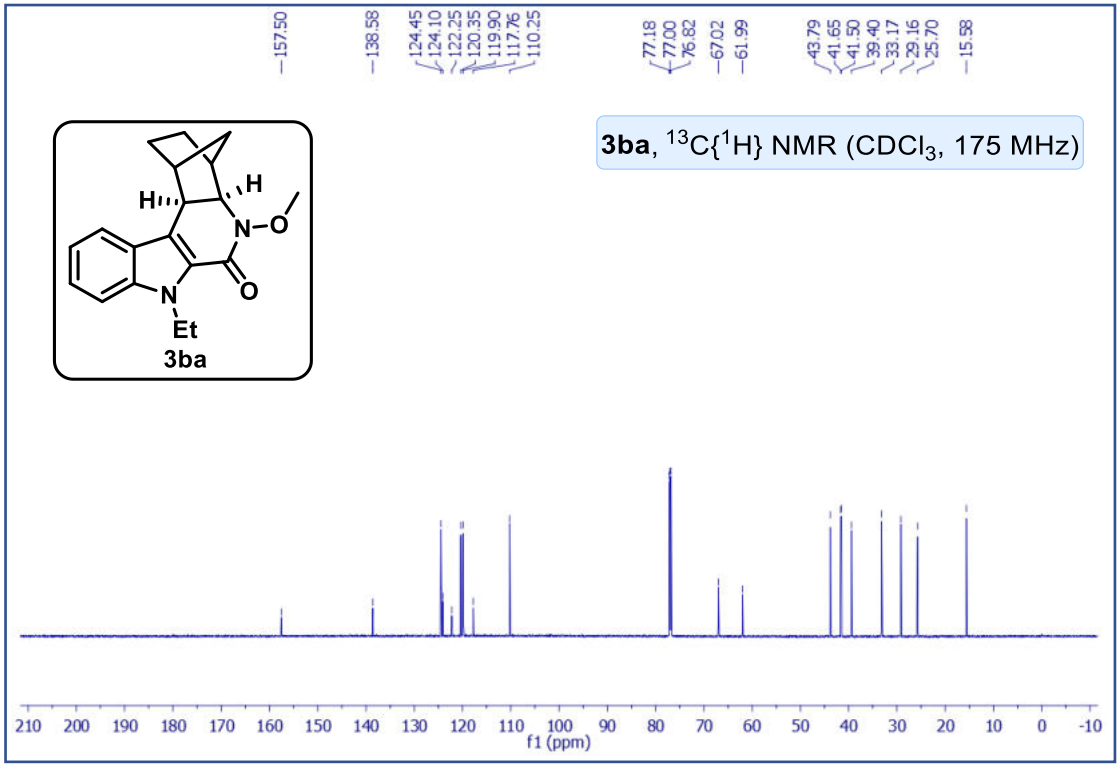
5,7-dimethyl-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-c]quinolin-6-one (3oa):



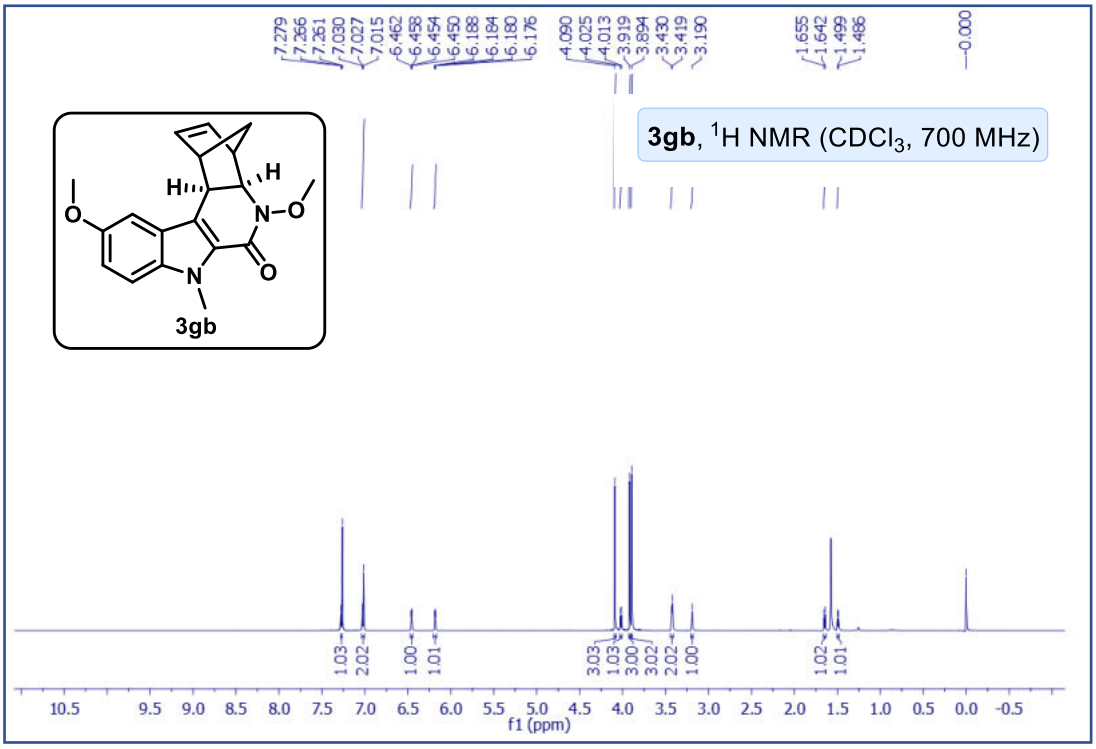
Physical State: colourless liquid; yield: (21 mg, 75%). R_f: 0.5 (30% EtOAc/Hexane). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, J = 7.6 Hz, 1H), 7.36-7.30 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 4.11 (s, 3H), 3.69 (d, J = 9.2 Hz, 1H), 3.46 (d, J = 9.6 Hz, 1H), 3.08 (s, 3H), 2.56 (d, J = 6.6 Hz, 2H), 1.68-1.62 (m, 3H), 1.55-1.54 (m, 1H), 1.32-1.29 (m, 1H), 1.59 (d, J = 10.8 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 160.0, 139.3, 124.3, 124.0, 123.99, 120.2, 119.7, 118.0, 110.2, 68.2, 43.8, 42.1, 40.8, 33.4, 33.0, 31.4, 28.8, 26.6. IR (KBr, cm^{-1}): 3053, 2986, 1653, 1263, 766. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O$: 281.1654; Found: 281.1680.

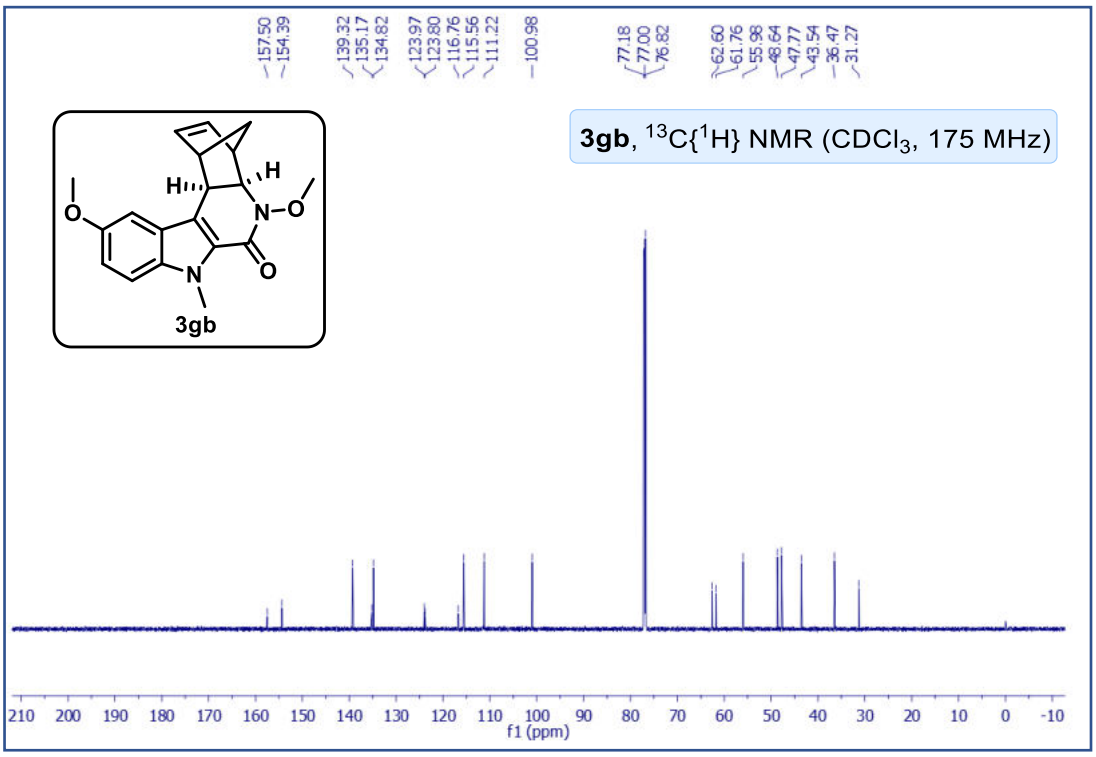
NMR spectra of 7-ethyl-5-methoxy-1,2,3,4,4a,5,7,11c-octahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3ba):



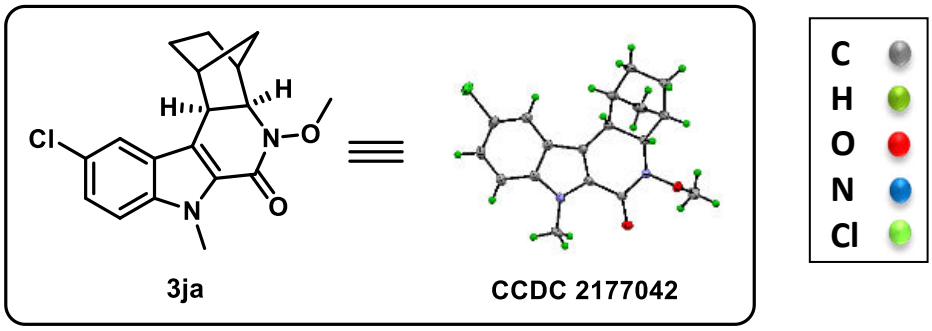


NMR spectra of 5,10-dimethoxy-7-methyl-1,4,4a,5,7,11c-hexahydro-6*H*-1,4-methanoindolo[2,3-*c*]quinolin-6-one (3gb):

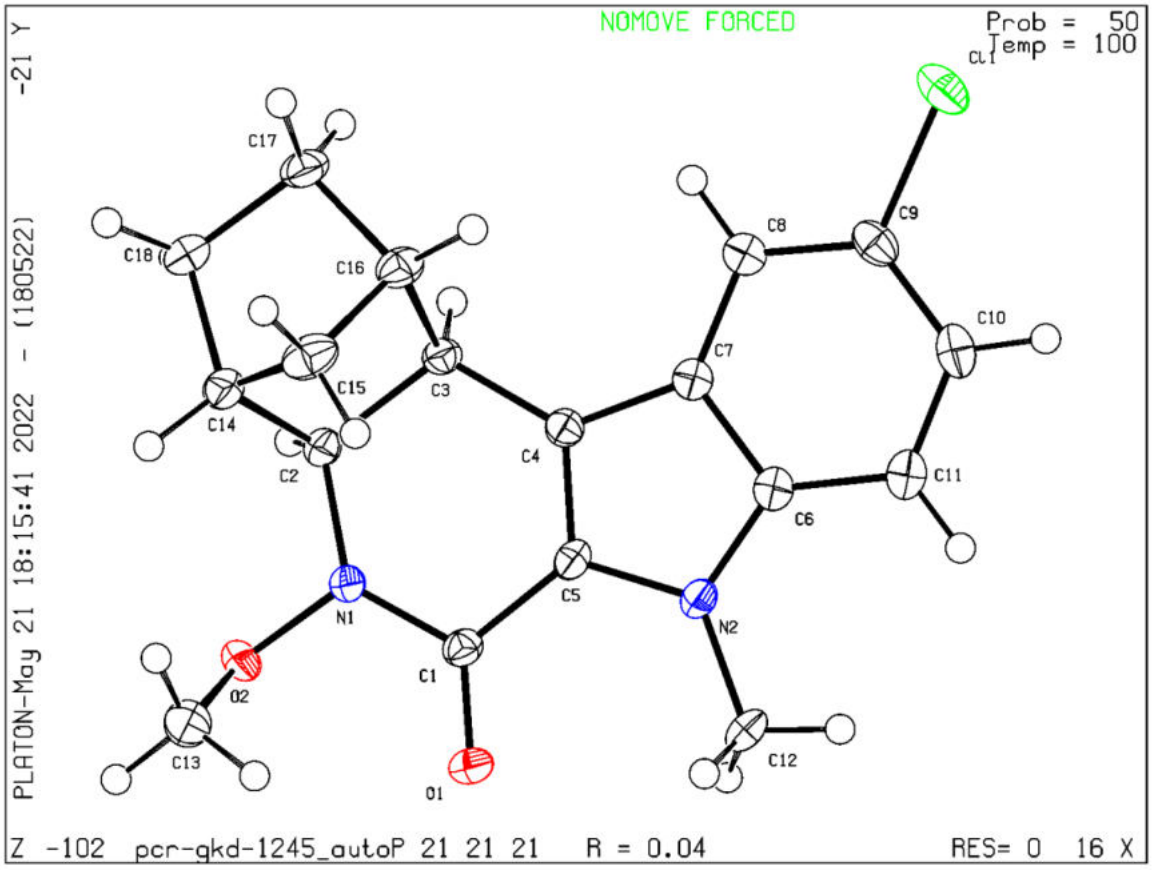




Crystal structure of 3ja



Datablock pcr-gkd-1245_auto - ellipsoid plot



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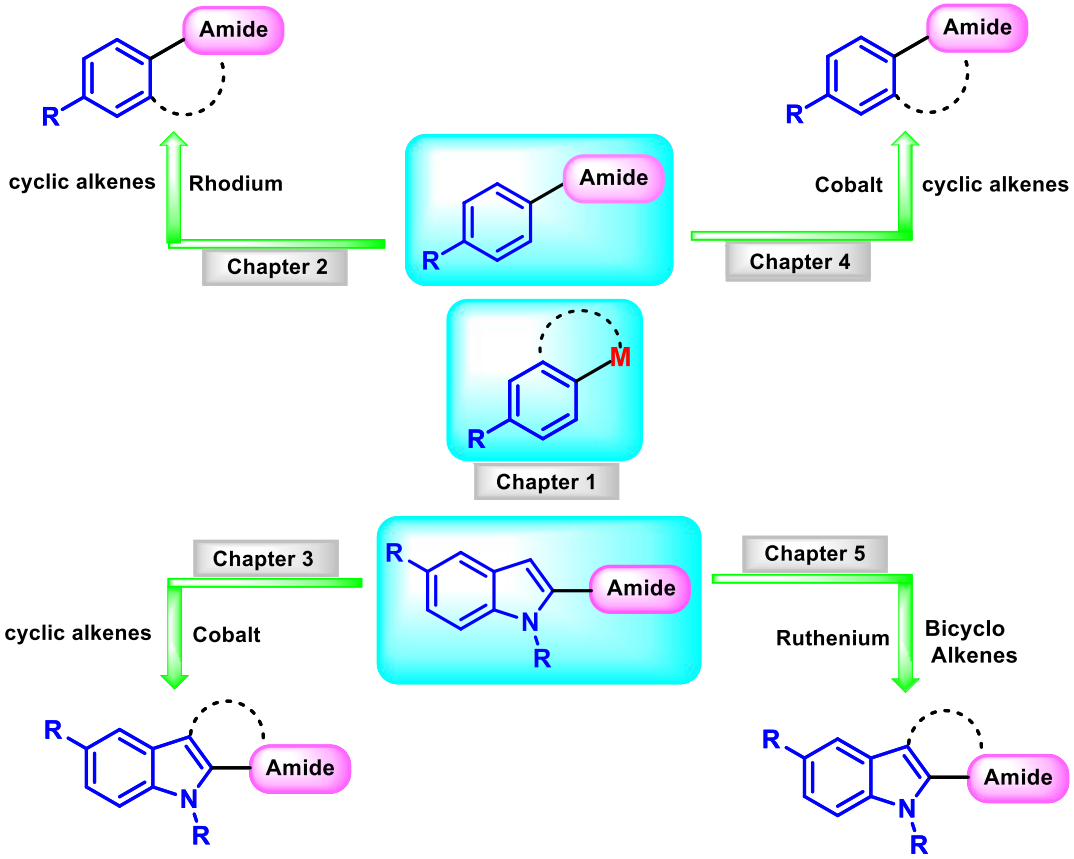
SUMMARY OF THE THESIS



About the Author

Gopal Krushna Das Adhikari, was born in the village of Badnafrai on 22nd February 1989. A village situated in the northern region of the state of Odisha. He completed his schooling from D.T.L.K. high school at Shyamanandipur situated near to his village. After that, he completed his intermediate and bachelor degree in science from R.I.H.S College at Bhograi. Then he did his MSc from Ravenshaw University and MPhil from Utkal University. He joined PhD under Prof. Ponneri C. Ravikumar in July 2016 at NISER. He submitted his PhD thesis on 13th June 2022.