SYNTHETIC STUDIES TOWARD PHEHARMINES A & B FROM PEGANUM HARMALA

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Abstract

This thesis describes the synthetic studies toward the alkaloid pheharmine A or B, isolated from the seeds of *Peganum harmala.* Pheharmine A and B possess a unique spirocyclic structure consisting of a β-carboline and phenylpropanoid motif.

56   pheharmine A   **57**


58   pheharmine B   **59**
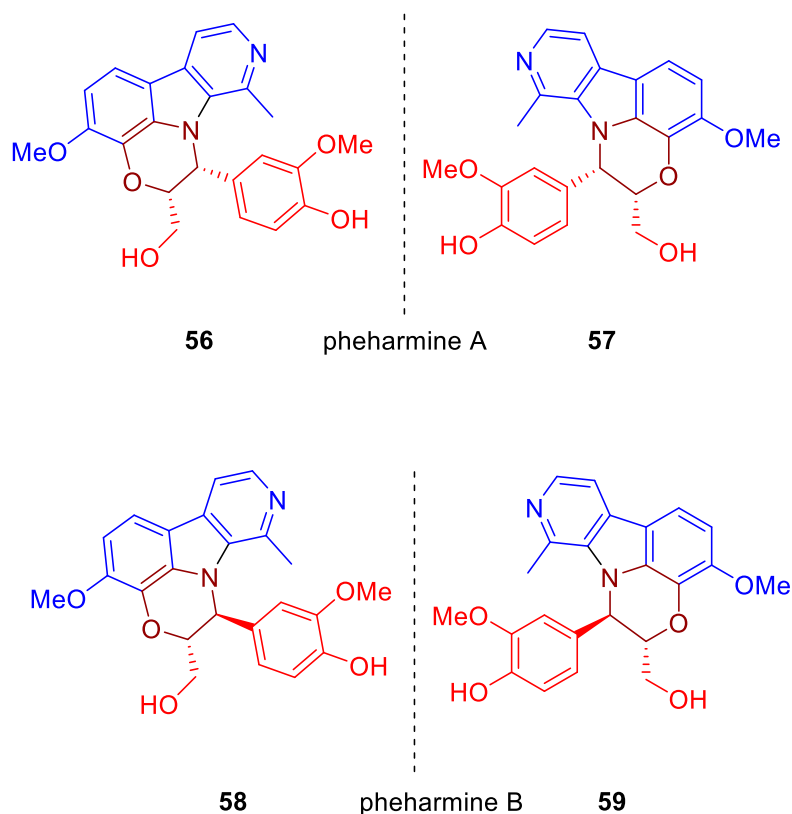
The first-generation approach focused on validating the initially proposed biosynthesis involving the Diels-Alder reaction between *o*-quinone imine (**61**) and coniferol dienes (**62** & **63**).The first task was to access suitable quantities of the β-carboline. However, upon subjecting *N*-pyrimidylcarboline (**73**) to C-H oxidation to give the key precursor (**60**) for the desired biomimetic Diels-Alder reaction, it was unsuccessful due to the presence C7-OMe group exerting steric congestion to neighboring the reactive site. The second-generation approach was a C-H borylation at the *N*-Boc tetrahydro-β-carboline (**101**) to give **102**. However, the reaction resulted was also no success due to the presence of C7-OMe in **101** decreased the acidity of C8-H and steric congestion. Thus, it can be concluded that installing OH or OMe at a later stage seems was not possible.
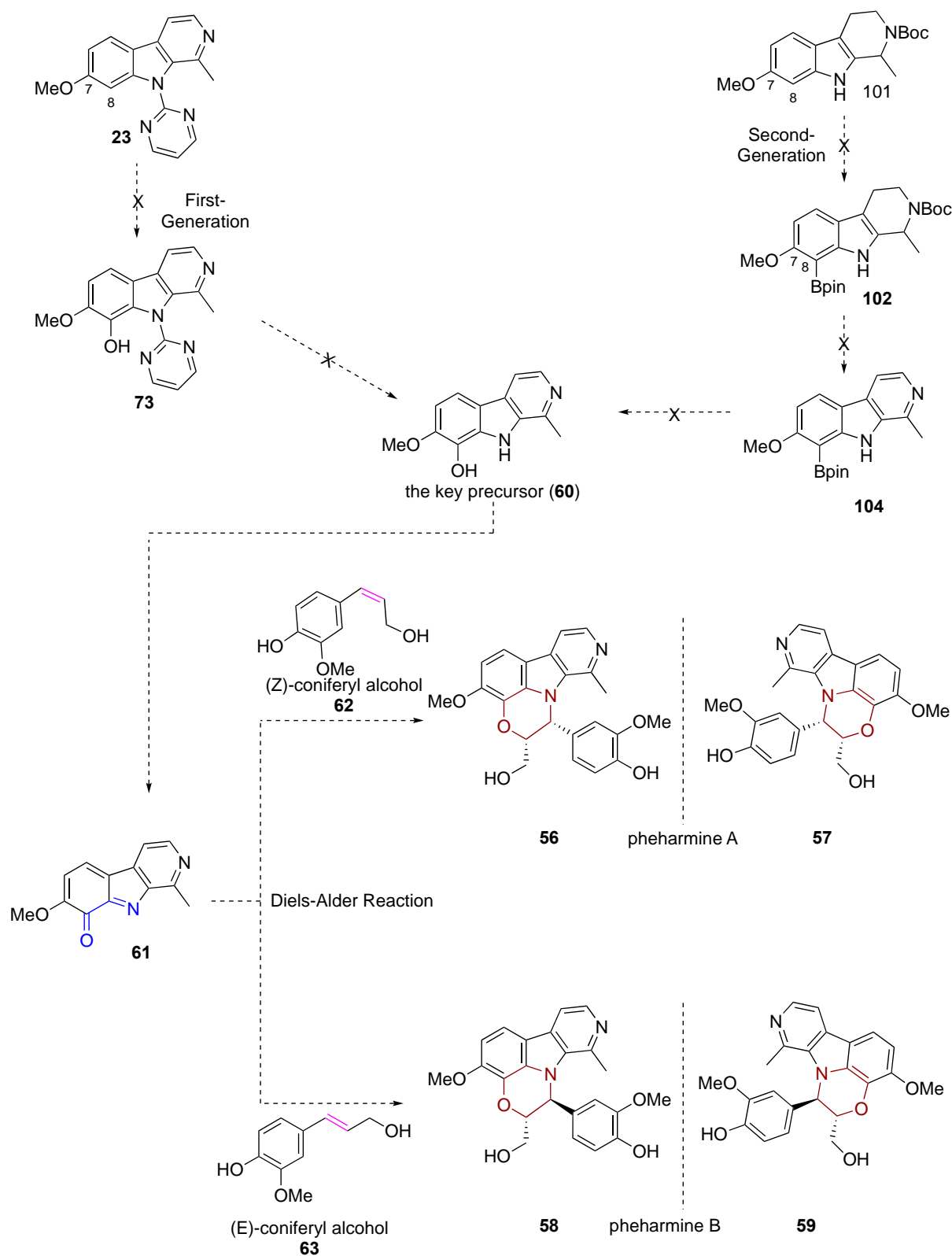
The third-generation approach focused on installing the OH at an early stage. However, the formylation of 6-methoxy-indol-7-ol (**114**) failed due to the presence of OH at the C7 position, possibly due to side reaction with the Vilsmeier Haack reagent. Thus, protecting the OH at the C7 *via* silylation and propylation was attempted, but these were unsuccessful. Time restrictions

prevented us from trialing different protecting groups in this reaction, only a few conditions were attempted.
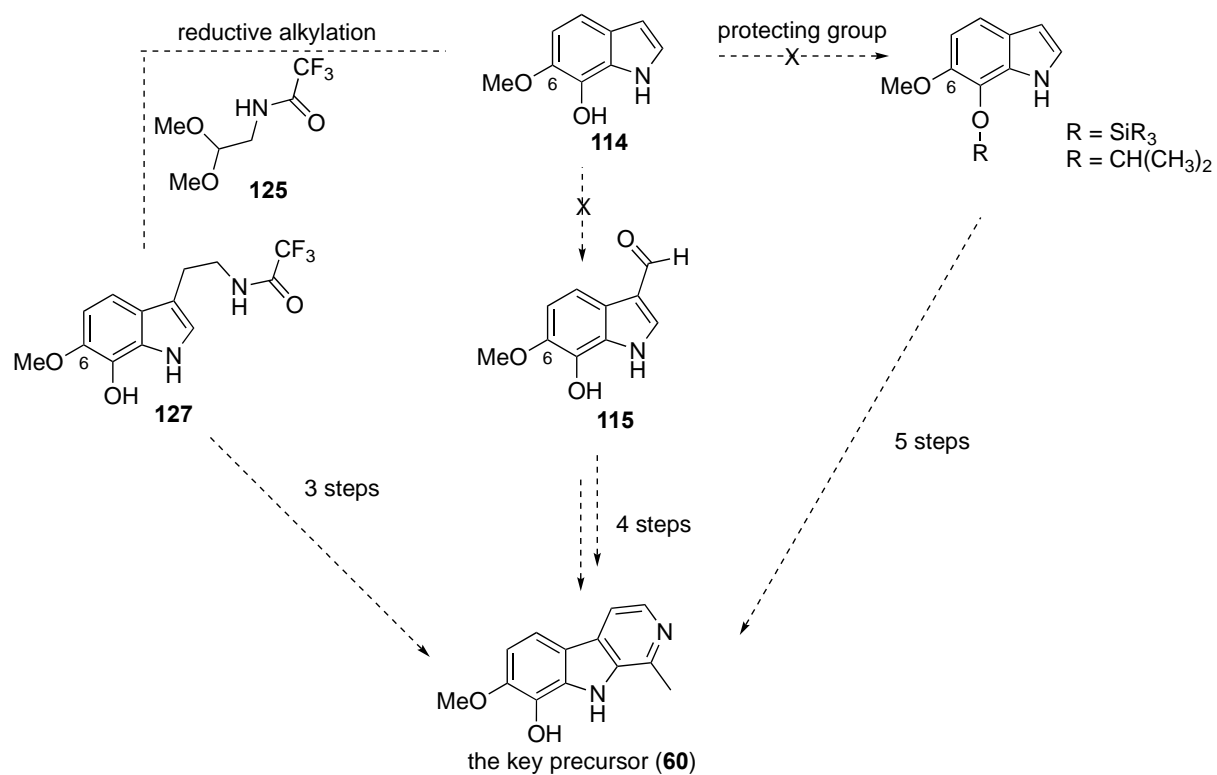
Alongside the formylation, the reductive alkylation of 6-methoxy-indol-7-ol (**114**) was attempted, but this was unsuccessful.

Acknowledgements

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growth but have also instilled in me a deep sense of gratitude. I am thankful for the opportunities provided and the belief shown in my potential to further my education.

Abbreviations

[O]	Oxidation
°C	Degrees Celsius
^{13}C	Carbon 13
^{1}H	Proton
Ac	Acetyl
Ar	Aromatic
approx.	Approximately
aq	Aqueous
B	Base
Bpin	Bis(pinacolato)diboron
Boc	Tert-butoxycarbonyl protecting group
C	Concentration; g 100 mL^{-1}
cat.	Catalyst
CCDC	Cambridge Crystallographic Data Centre
cm^{-1}	Wavenumber
Conc.	Concentration
COSY	Correlation spectroscopy
Cys	Cysteine
d	Doublet
dd	Doublet of doublets
DEPT	Distortionless Enhancement by Polarisation Transfer
DMC	Dimethyl carbonate
DMF	*N, N*-dimethylformamide
DMSO	Dimethyl sulfoxide
dq	Doublet of quartets
dt	Doublet of triplets
dtbpy	4,4´-Di-*tert*-butyl-2,2´-dipyridyl
E	Electrophile
equiv.	Equivalent(s)
Et	Ethyl
g	Gram(s)
h	Hour(s)

HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple-quantum correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation
Hydrog.	Hydrogenation
Hz	Hertz
IC50	Half maximal inhibitory concentration
*i*Pr	Isopropyl
IR	Infrared
J	NMR coupling constant (Hertz)
M	Molar/molecular ion
m	Multiplet
m-CPBA	m-Chloroperoxybenzoic acid
M.p.	Melting point
m/z	Mass to charge ratio
Me	Methyl
MHz	Megahertz
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
mol.	Molecular
mol L^{-1}	Moles per litre
mol%	Mole percent
mtbe	Methyl *tert*-butyl ether
nm	Nanometre(s)
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
*n*Pr	*n*-Propyl
Nu	Nucleophile
Ph	Phenyl
ppm	Parts per million
Py	Pyridine

q	Quartet
quant.	Quantitative
red.	Reductive amination
r.t.	Room temperature
SAc	Succinic acid
s	Singlet
sat.	Saturated
sep	Septet
t	Triplet
td	Triplet of doublets
tert	Tertiary
TFE	2,2,2-Trifluoroethanol
TBAI	Tetra-n-butylammonium iodide
THF	Tetrahydrofuran
THIQ	Tetrahydroquinoline
TLC	Thin layer chromatography
TOF	Time of flight
UV	Ultraviolet
wt	Weight
α	Alpha
β	Beta
γ	Gamma
δ	Delta/chemical shift
μM	Micromolar
v	Frequency
Å	Ångström

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Chapter One:

Introduction

1.1 <u>General Indole Introduction</u>

The indole is a heterocycle aromatic compound consisting of a π-excessive fused pyrrole and benzene ring.[1] Adolf von Baeyer was the first propose to propose the structure of an indole nucleus after synthesizing the compound during experiments involving indigo dyes;[2,3] isatin (**1**) was reduced in the presence of zinc dust to oxindole (**2**) and further to generate indole (**3**) (Scheme 1).[3] The accepted numbering and configuration convention of indole is shown in Figure 1.[1]
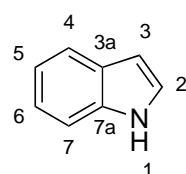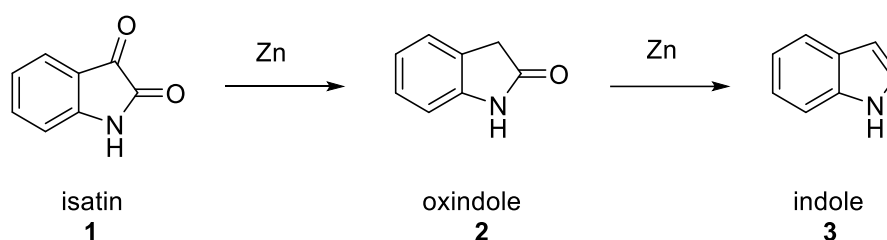

Figure 1. Indole with numbering convention.

Scheme 1. von Baeyer's seminal synthesis of indole from isatin.

1.1.1   Clinically-used Indole Alkaloids

Indole has been identified in many natural products and has isolated from a variety of sources.[1,4] These alkaloids have been shown to have many biological activities and some are used clinically.[1,4] Vincristine (**4**) and vincamine (**5**) and are members of the "*Vinca alkaloids*". Vincristine (**4**) is a potent inhibitor of tubulin polymerization, preventing chromosomes from separating during metaphase and inducing apoptosis in carcinogenic cells.[4] Vincamine (**5**) acts as a peripheral vasodilator that increases blood flow to the brain resulting in reducing the effects of aging.[4] Mitomycin C (**6**), one of the aziridine-containing chemotherapeutic agents that were isolated from various *Streptomyces* species, is used to treat breast, anal, and upper gastrointestinal cancers.[5] Physostigmine (**7**), found in the Calabar bean of tropical Africa, was used for the treatment of glaucoma, Alzheimer's disease, and hypotension *via* reversible cholinesterase inhibition.[6] Methysergide (**8**) is a 5-HT antagonist that specifically binds to

serotonin to prevent migraine attacks.[7] Reserpine (**9**) was first isolated in 1952 from the dried Indian snake root of *Rauwolfia serpentina.*[8] Reserpine is a drug that acts as a pharmacological agent that reduces neuronal and physiological activity in the central nervous system. It impedes the post-ganglionic nerve fiber in the synaptic gap, particularly hindering the excitatory neurotransmitter norepinephrine.[9] Pharmacological studies have shown that reserpine is a prominent target due to its significant antipyretic, antihypertensive properties and tranquilizing.[9, 10] Beyond its biological effects, reserpine serves as a hypnagogic for the central nervous system and is widely used in treating conditions such as melancholia and hypertension.[10-12]
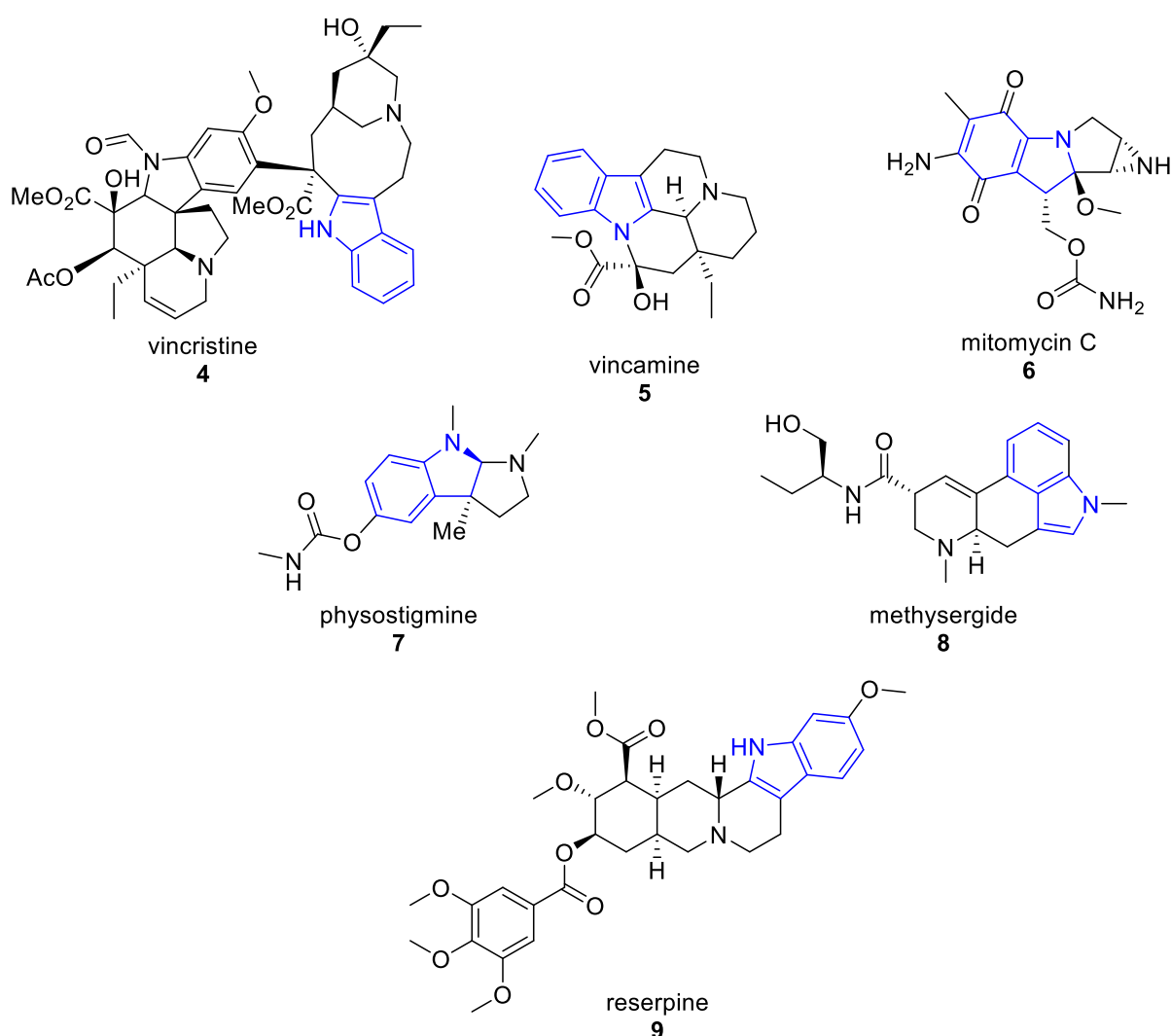

Figure 2. Examples of indole-containing natural products used as drugs. Indole heterocycles are highlighted in blue.

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1.1.2 Synthetic Drugs Containing the Indole Heterocycle

Due to its presence in biologically active alkaloids, the indole heterocycle plays a significant role in both approved synthetic drugs and those currently in clinical trials, it is recognized as a 'privileged scaffold' in the process of drug development.[1, 13-15] Zafirlukast (**10**) is a leukotriene receptor antagonist indicated for maintenance treatment of asthma, which inhibits the process of cysteinyl leukotrienes in the lungs, alleviating airway constriction and mucus build-up.[16] Indometacin (**11**) is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce swelling, pain, and fever. This drug interacts with cyclooxygenase enzymes, which is an important regulator in the inflammation pathway.[4] Arbidol (**12**) is an antiviral agent bearing a heavily substituted indole-core that is used to treat influenza in Russia and China.[17] Delavirdine (**13**) is a non-nucleoside reverse transcriptase inhibitor that was used as a combination therapy for HIV, which was approved in 1997. However, due to drug interactions and the risk of cross-resistance, delavirdine is rarely used and holds a place for second-line therapeutic agents instead.[18, 19] Oxypertine (**13**), an antipsychotic drug containing indole and phenylpiperazine motif, used to treat both anxiety and schizophrenia, acting in the central nervous system by decreasing the concentrations of catecholamine-based neurotransmitters while keeping serotonin concentration level untouched.[20, 21] Tropisetron (**14**) and ondansetron (**15**) are drugs used to treat chemotherapy-induced nausea and emesis *via* acting as serotonin receptor antagonists specifically targeting the 5-HT$_3$ subtype.[22, 23]
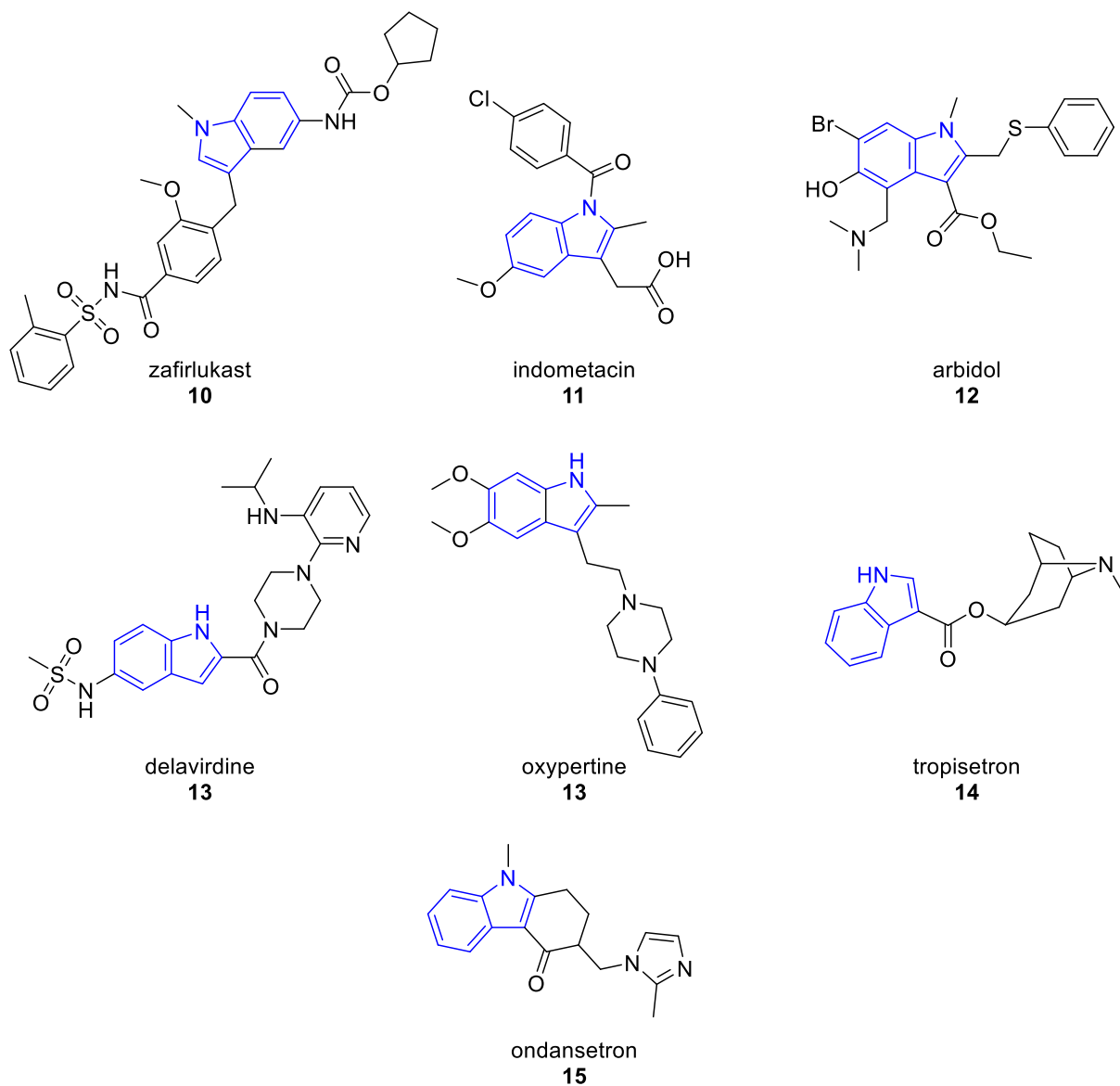
Figure 3. Examples of indole-containing, synthetic drugs. The core indole structure are highlighted in blue.

1.2 β-Carbolines

β-Carboline is from a class of indole alkaloids consisting of tricyclic, pyridine-fused indole framework (where the rings are identified as A, B, and C shown in Figure 4). They are classified according to the degree of saturation (unsaturated β-carbolines (**16**), fully saturated: 1,2,3,4-tetrahydro (**17**), partially saturated: 3,4-dihydro (**18**) and the position of N-atom in the "C"-ring as α-, β-, γ- or δ-carbolines shown in Figure 4.[24-26] However, this thesis will focus on the discussion of the 'simple' β-carbolines referred to as compounds consisting the tricyclic pyrido (3, 4-*b*) indole ring system (**16**).
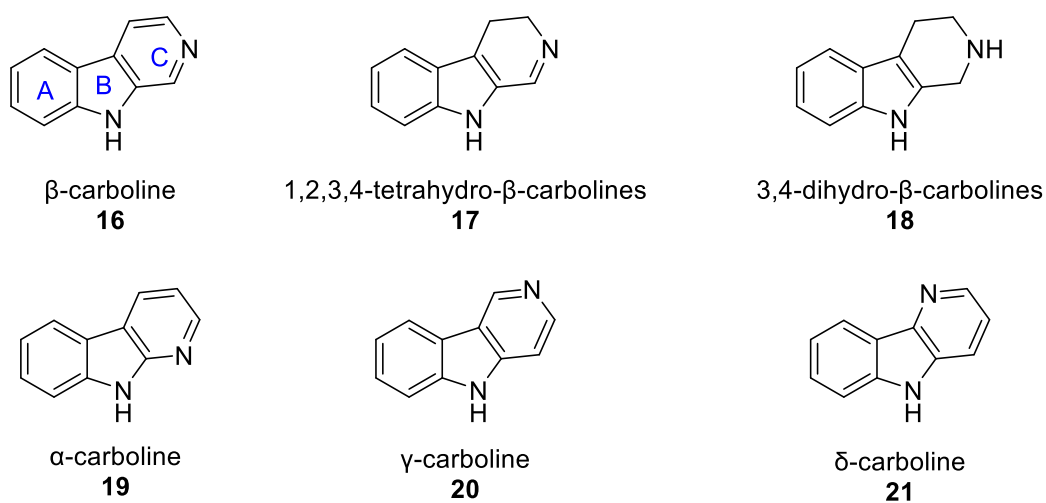

Figure 4. Structures and nomenclature of carbolines.

1.3 *Peganum harmala*

Peganum harmala L., a family member of Zygophyllaceae, is a perennial herb that was widely used in the semiarid land and deserts of Africa, Asia, and Mediterranean regions, as a traditional medicine for the treatment of swelling pain, malariam rheumatism, lumbago, hemiplegia, skin diseases, rheumatoid arthritis, cancers and other sickness.[27, 28] It holds a spiritual importance in certain cultures, and places such as Morocco and Turkey, the powdered seeds or fruits are kept in amulets, while in Iran they were burnt. Both practices were to demonstrate the purpose of warding off the "evil eyes."[29, 30] In addition, it is still believed that it has been used, and perhaps still currently used, as an entheogen – a substance that causes one to experience an awakening or enlightenment from a higher power – as ingestion of plant or its extracts is known to cause hallucinations.[31, 32]

Most commonly core structure found in *Peganum harmala L.,* is β-carboline alkaloids (Figure **5**). Harmine and harmaline isolated from *Peganum harmala L.,* are revealed to be potentially cytotoxic towards several tumor cell lines *in vitro* and also in a tumor model *in vivo,*[33, 34] *via* inhibition of DNA topoisomerases and disrupting DNA synthesis.[35-37] Furthermore, β-carboline extracted from the *P. harmala* also displayed potent activities, which is advantage in treating brain disorders including depression and Alzheimer's disease,[37-39] due to competitive and reversible inhibition against human monoamine oxidase (MAO-A) and inhibitory against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE).[38, 40-42] The extract from P. *harmala L.,* seeds contained alkaloids that demonstrate the strong binding activity with G-quadruplex and showed potent cytotoxic effects against HL-60, PC-3, and SGC 7901 cell lines, with IC_{50} values of 348, 10.59, and 11.53 μg/mL.[43] Furthermore, it provides many diverse bioactivities compounds.[27]

1.3.1 Norharman, Harmane, Harmine

Norharman (**16**), harmane (**22**), and harmine (**23**) have been isolated from the *Syrian Rue*, *Banisteriopsis caapi,* and *P.harmala* seed and roots.[44] These compounds can cross the blood-brain barrier, distributing throughout the brain.[45, 46] Indian tribes used to drink the hallucinogenic beverage Ayahuasca or yage which containing these substances.[47] They act as neuromodulators on the serotonin neurotransmitter system, producing neuroendocrine and behavioral effects found with serotoninergic involvement.[48, 49] These alkaloids inhibit monoamine oxidase (MAO) and serotonin uptake and bind to the GABA receptor, resulting in

several psychoactive effects.[50, 51] In a rodent study, harmine reduces cerebral infarct volume and neuronal cell death owing to the upregulation of glutamate transporter 1, which reduces excessive and neurotoxic glutamate levels.[52] It also selectively inhibits the action of DYRK1A protein kinase, a molecule specifically important for neurodevelopment[53, 54] and has been shown to support the survival of dopaminergic neurons in MPTP-treated mice.[55]
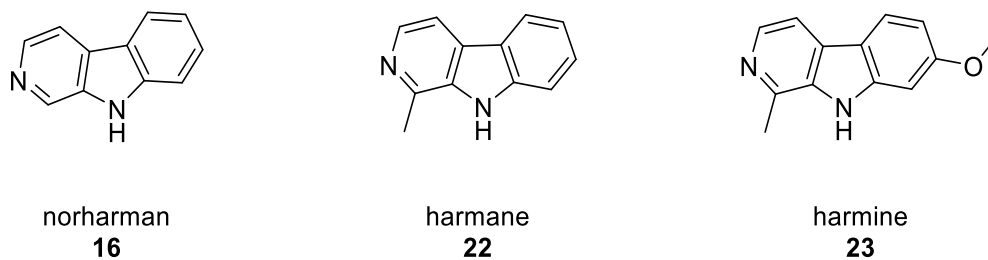

norharman
16

harmane
22

harmine
23

Figure 5. β-carbolines found in *Peganum Harmala*.

1.3.2 Peganumine A, B, C, D, E, F, G and H

Peganumine A, B, C, F, G, and H, were isolated from the *Peganum harmala's* seed and showed significant cytotoxic activity against leukemia cells HL-60, MCF-7, prostate cancer cells PC-3 and liver cancer HepG2 with IC_{50} values of 5.8, 38.5, 40.2, and 55.4 μM.[56] Peganumine B has inhibitory activity against both AChE and BChE with IC_{50} values of 0.25 ± 0.04 and 1.45 ± 0.34 μM, while the IC_{50} of ZR-75-1, MCF-7, SUM149 and SUM159 breast cancer cell line were larger than 20 μM.[57] Peganumine C was found to have selective inhibitory activity against AChE with an IC_{50} value of 14.38 ± 2.49 μM.[57] Peganumones A, B, and F have weak activity against the ZR-75-1 cell line with IC_{50} values of greater than 20 μM. Peganumine G and peganumine H demonstrated significant cytotoxicity against the ZR-75-1 cell line with IC_{50} values of 6.20 ± 2.71 and 2.43 ± 0.79 μM but weak activity against AChE and BChE with IC_{50} values of greater than 500 μM.[57] As for Peganumine F, it has demonstrated that it possesses weak activities against AChE and BChE (with IC_{50} values of greater than 500 μM) and the ZR-75-1 breast cancer cell line (with IC_{50} values of greater than 20 μM).[57]

Peganumine D, E and I do not contain the core β-carboline structure but these compounds are also isolated from the seeds of *P.harmala*. Peganumine D and (8*R*)-peganumine I, (8*S*)-Peganumine I has inhibitory activity against AChE with IC_{50} values of 5.71 ± 1.22, 24.58 ± 2.19, and 23.62 ± 1.08 μM. On the other hand, it has weak inhibitory activity against BChE with IC_{50} value of greater than 60 μM and no effects on breast cancer cell line. Peganumine E showed no effect in any of the biological assays that were tested.[57]
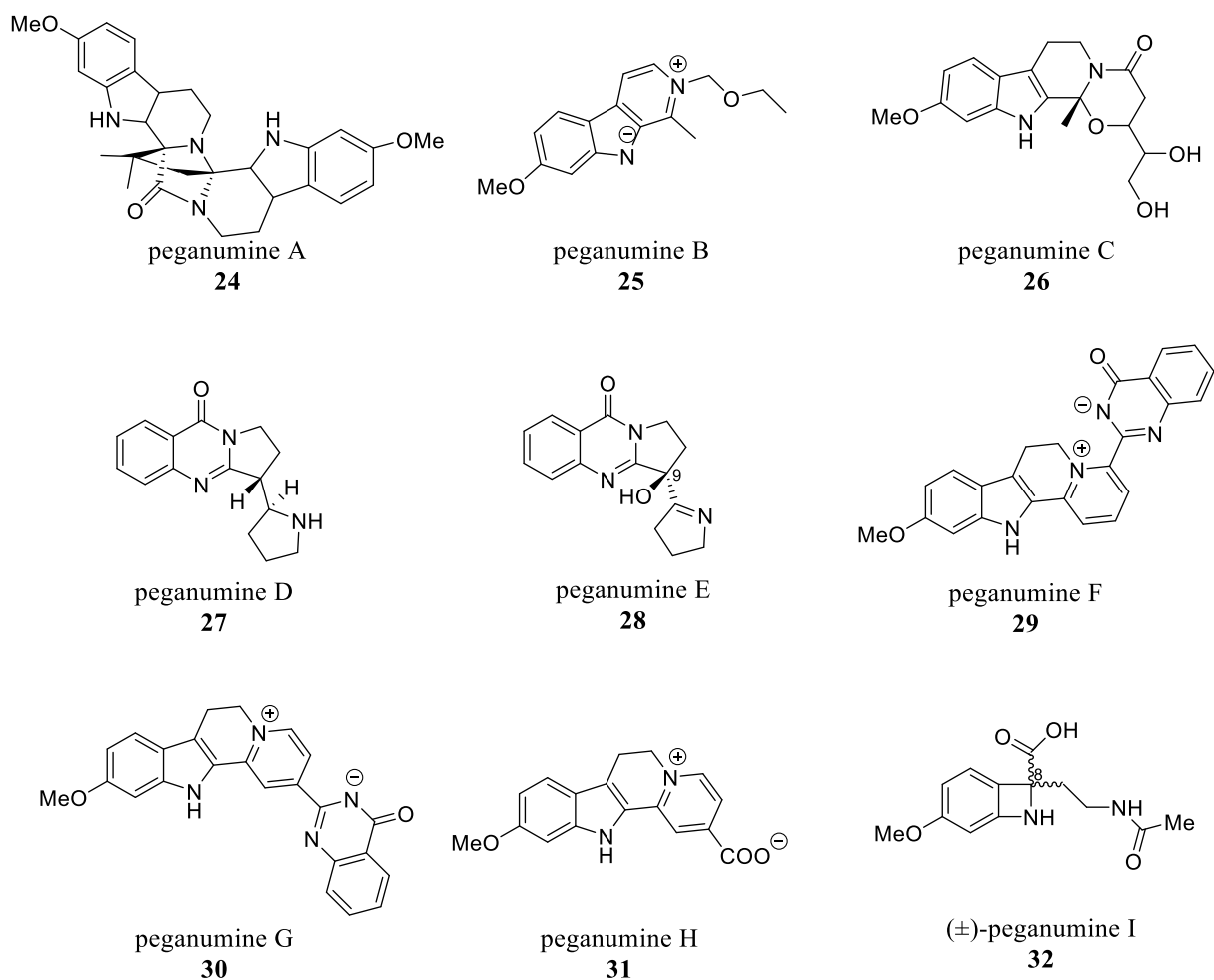
Figure 6. Peganumines that were extracted from the seeds of *Peganum harmala.*

1.3.3 Pegaharmols A & B

Two non-biaryl axially chiral β-carbolines-quinazoline dimers, pegaharmols A & B were isolated from the roots of *Peganum harmala* by Sheng and colleagues.[58] Pegaharmol A (**33**) was measured for its cytotoxic activities against four human cancer cell lines HL-60, A549, MDA-MD-231, and DU145. Pegaharmol A (**33**) only demonstrated moderate cytotoxicity against HL-60 and A549 cells with IC_{50} values of 39.02 and 55.69 μM. It did not exhibit any cytotoxic activity against MDA-MD-231 and DU145 cells with IC_{50} values of more than 100 μM.[58] On the other hand, the cytotoxicity of pegaharmol B (**34**) was not able to be examined due to low yield.[58]
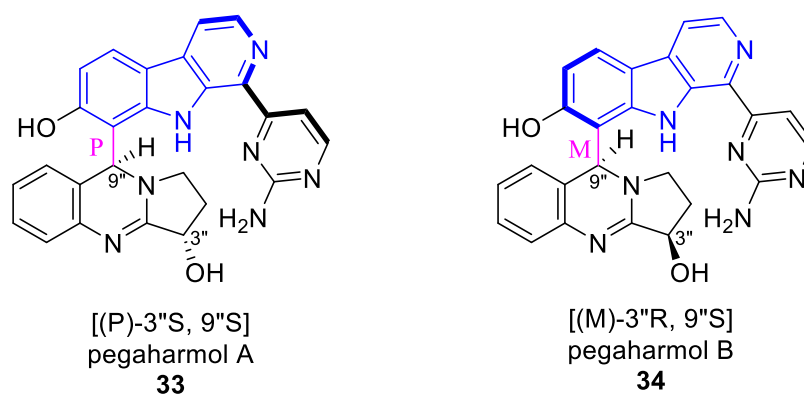
Figure 7. Pegaharmol A: β-carboline core structure highlighted in blue.

1.3.4 Pegaharmalines A & B

1.3.4.1 Isolation and assignment

Pegaharmalines A and B was isolated from the seed of *P. harmala.*[59] Inspection of the ^{1}H and ^{13}C NMR spectroscopic data indicated that pegaharmaline A (**35**) consisted of β-carboline and a vasicinone scaffold. Through HMBC correlations, Wang and colleagues were able to conclude the presence of a 7-methoxytetrahydro-β-carboline fragment and a 2',3'-dimethyl-substitued dehydrate-vasicinone fragment.[59] Pegaharmaline A (**35**) was reported to be chiral with an optical rotation of $[\alpha]_D^{20}$ −6.4 (*c* 0.11, MeOH) and NOESY correlations indicated the β-carboline moiety was roughly perpendicular to the vasicinone moiety. XRD analysis was unsuccessful due to the inability to grow the crystal, so the CD excitation chirality method was used instead to assign the absolute configuration of the $sp^2 – sp^3$ bond. They were able to determine that compound **35** has a (1*S*) configuration about the chiral center.[59]

Pegaharmaline B (**36**) was found to also contain a 7-methoxytetrahydro- β-carboline fragment. However, further analysis of the 2D NMR spectroscopic data showed the presence of disubstituted pyrrole and a quinazoline unit. The connectivity of these three units was determined using HMBC correlations.[59]
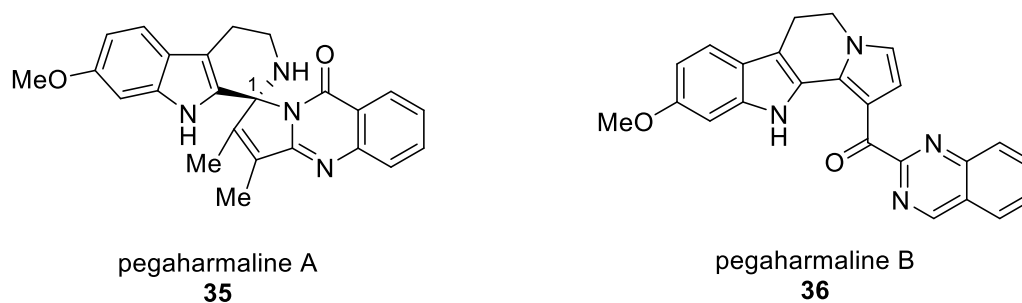
Figure 8. Assigned structures of pegaharmalines A and B.

1.3.4.2 Biological Activity

Pegaharmalines A (**35**) and B (**36**) were tested to determine the cytotoxicity activity. It was tested against five human cancer cell lines: HL-60, HepG-2, A549, PC-3, MCF-7.[59] Pegaharmaline A (**35**) demonstrated high toxicity against HL-60 cell line with IC_{50} values of 9.4 µM and only showed weak inhibitory effects against the rest of four cell lines. In addition to this, pegaharmaline B (**36**) showed similar results to (**35**), where it showed significant cytotoxicity activity against HL-60 cell lines with IC_{50} values of 13.6 µM but weak against the other four cell lines.[59]

1.3.5   Tryptamines

Serotonin (**37**) and 6-hydroxytryptamine (**38**) were isolated from *P. harmala* from calluses grown on auxin-deficient medium (Figure 9).[60, 61] 2-Acetyltryptamines have also been isolated from the seeds of *P*.harmala; 2-acetyl-3-(2-acetamidoethyl)-7-methoxyindole (**39**)[62], peganumaline F (**40**)[62] and pegaharmine E (**41**).[62, 63] Acetamide (**39**) showed no biological activity against SGC-7901, PC-3 and HL-60 cancer cell lines, while formamide F (**40**) and carbamate (**41**) has moderate activity against the HL-60 cancer cell line with IC_{50} values of 24.55 and 25.07 µM.[62]
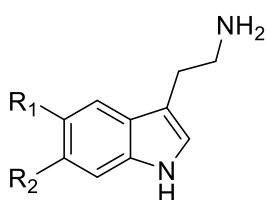
37 R^1 = OH, R^2 = H; serotonin
38 R^1 = H, R^2 = OH; 6-hydroxytryptamine
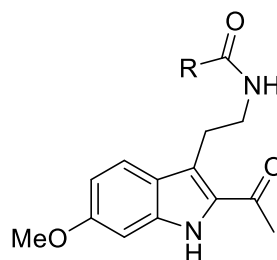
39 R = Me; 2-acetyl-3-(2-acetamidoethyl)-7-methoxyindole
40 R = H, peganumaline F
41 R = OMe, pegaharmline E

Figure 9. Tryptamines isolated from *P. harmala*.

1.3.6 Oxindoles

(±)-Peganumalines A-E (**42-46**) were isolated from the seeds of *P. harmala*. The absolute configurations of compounds **42-46** were established by comparing their experimentally obtained electronic circular dichroism (ECD) values.

(±)-Peganumaline A (**42**) was isolated as a racemate and was found to possess a rare 3,3'-bis-oxindole skeleton. HPLC separation with chiral stationary phase led to the enantiomers (-)-**42** and (+)-**42**; through the comparison of experimental and calculated ECD values, the absolute configurations were determined as (-)-(**42**) being (3*S*, 3'*S*) and (+)-(**42**) being (3R, 3'R).[62] (±)-Peganumaline B (**43**)'s ^{1}H and ^{13}C NMR spectroscopic data were similar to peganumaline A (**42**); however, based on mass spectroscopy it evidently showed that peganumaline B was a monomer of peganumaline A with a hydroxy group attached. HPLC separation with chiral stationary phase led to isolation of (-)-(**43**) and (+)-**43**; through comparing of experimental and calculated ECD values, the absolute configurations were determined to have the configurations of (3*R*) and (3*S*). The ^{1}H and ^{13}C NMR spectroscopic data of (±)-peganumaline C (**44**) and D (**45**) were like peganumaline B (**43**), but with different R^1 and R^2 groups (Figure 10). Following the same separation methods as peganumaline A and B, both peganumaline C and D have been found to be (3*R*) and (3*S*) respectively.[62]
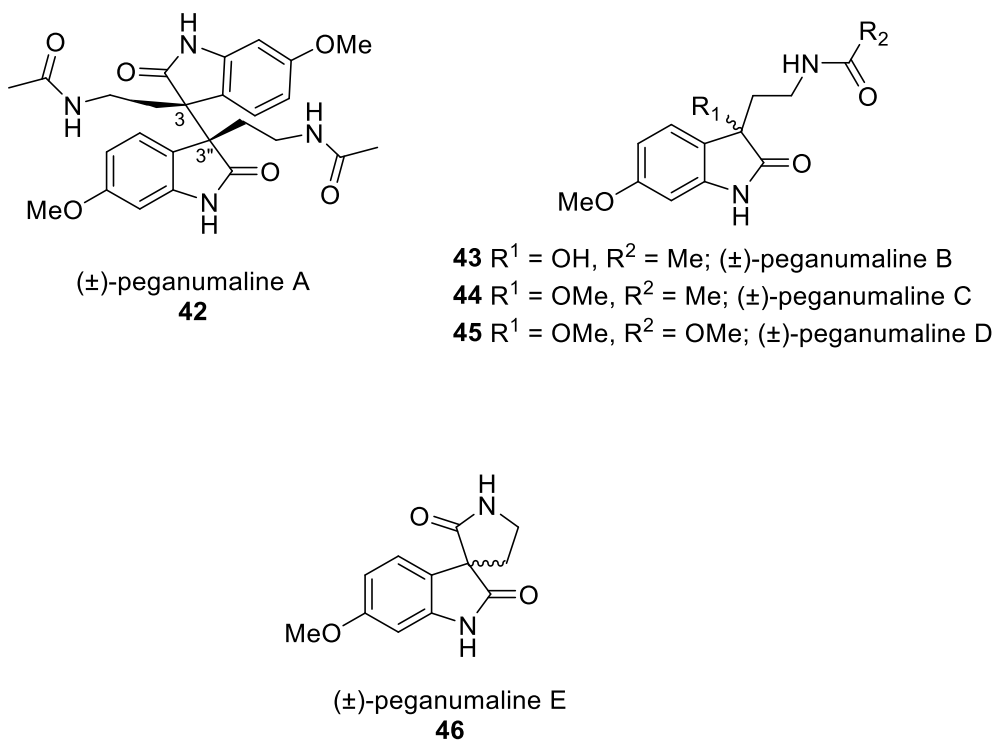
Figure 10. (±)-Peganumalines A-E isolated from seeds of *P. harmala.*

These oxindoles were tested for antiproliferative activities against HL-60, PC-3, and SGC-7901 cancer cell lines, only (±)-peganumaline B (**43**) showed moderate cytotoxicity against the HL-60 cell line (IC$_{50}$ of 21.54 µM). Meanwhile, the other alkaloids (**42**) and (**44-46**) showed only weak or no activity.[62]

1.3.7 Pyrroloquinazolines

Deoxyvasicine (**47**) has the core structure of pyrroloquinazoline alkaloid framework and was isolated from *P. harmala*. It was identified by comparing its properties with a synthetic compound prepared before its isolation as a natural product.[64] When isolated by Späth and Nikawitz, (-)-vasicine (**48**) was named peganine; however, a year later it was reported that peganine had the same physical and chemical properties as the known alkaloid vasicine, isolated from the plant *Adhatoda vasica* decades earlier.[65-67] Deoxyvasicinone (**49**) and (-)-vasicinone (**50**) are the oxidation of compounds **47** and **48**; respectively, and these compounds were already known when they were isolated.

Deoxyvasicine (**47**) and vasicine (**48**) were able to inhibit both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Compound **47** with IC$_{50}$ values of 2.37 ± 0.40 and 0.04 ± 0.01 µM and **48** with IC$_{50}$ values of 3.38 ± 0.03 and 0.10 ± 0.00 µM.[68] Furthermore, *in vitro* and *in vivo* studies, vasicine (**48**) and vasicinone (**50**) cause mild bronchodilation at low

concentrations, with **48** also causing bronchoconstriction at high concentrations.[69-71] Deoxyvasicine (**47**), vasicine (**48**), and vasicinone (**50**) all also have antitussive properties – all three reduced the coughing frequency of mice and guinea pigs significantly in induced coughing experiments.[71] In addition, the antitussive activities of all three at high doses (45 mg/kg) were comparable to that of codeine phosphate (30 mg/kg).[71]
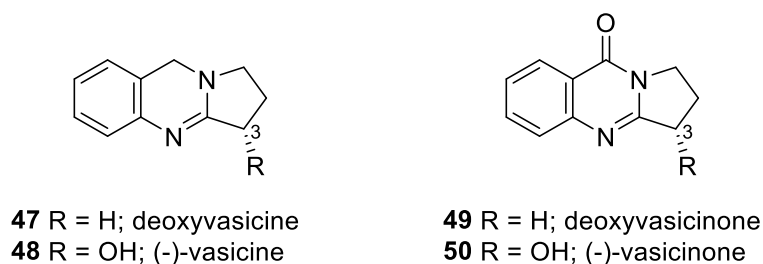

47 R = H; deoxyvasicine
48 R = OH; (-)-vasicine

49 R = H; deoxyvasicinone
50 R = OH; (-)-vasicinone

Figure 11. Pyrroloquinazolines isolated from *P. harmala*

Deoxypeganidine (**51**)[72], peganidine (**52**)[73], and peganol (**53**)[74] were all isolated from the leaves of *P. harmala* as racemates and all possess variations at the 3- and 9-position of the pyrroloquinazoline skeleton. No assignments of the absolute configurations were made, but the relative configuration of peganidine (**52**) was deduced by Okmanov and colleagues.[75] Through crystallization of its hydrochloride salt, they were able to determine substituents at C3 and C9 position were *cis* relative to the plane of the tricyclic core. When Telezhenetskaya and colleagues isolated peganol (**53**), it was clear it was an isomer of vasicine (**48**).[74] The presence of a C9-OH position confirmed upon oxidation with potassium permanganate to afford deoxyvasicinone (**49**). Pegamine (**54**) was also isolated from the leaves of *P. harmala,* it was recognised due to its mass spectrometry data containing many fragments in common with vasicinone (**50**), but characteristic features of the tricyclic skeleton were missing,[76] due to this it was eventually determined that the five-membered ring had opened, revealing a terminal hydroxy group. Similarly, 3,4-dihydroquinazoline-2-carboxylic acid (**55**) – isolated from the seeds of *P. harmala* through a bioassay-guided fractionation[68] – also does not possess the tricyclic structure the others in this group possess.
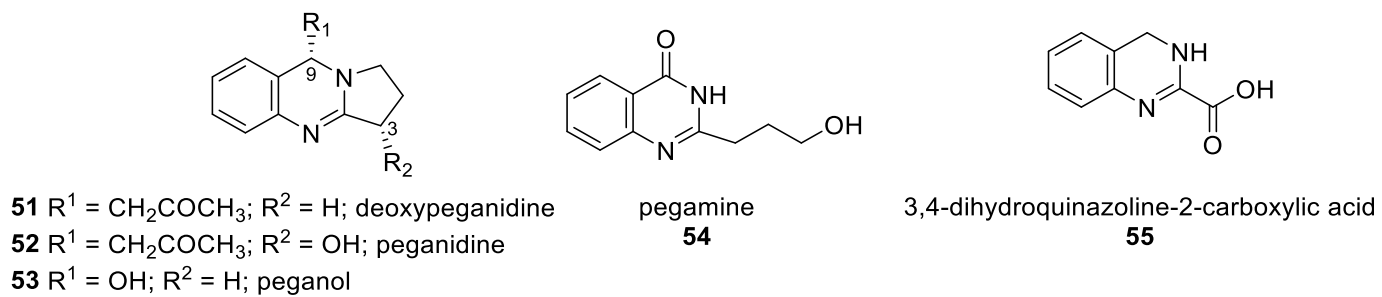
51 R^1 = CH$_2$COCH$_3$; R^2 = H; deoxypeganidine
52 R^1 = CH$_2$COCH$_3$; R^2 = OH; peganidine
53 R^1 = OH; R^2 = H; peganol

pegamine
54

3,4-dihydroquinazoline-2-carboxylic acid
55

Figure 12. Pyrroloquinazolines **51-55**.

peganol
53

KMnO$_4$

deoxyvasicinone
49
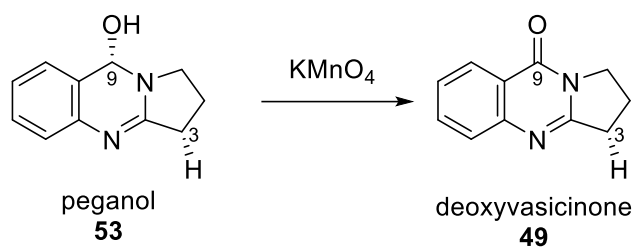
Scheme 2. Oxidation of peganol *via* potassium permanganate.

1.4 **Pheharmines A & B**

1.4.1 **Isolation and assignment**

Two pairs of structurally extraordinary alkaloids, (±)-pheharmines A-B (**56-59**) (Figure 13), were obtained from the root of *P. harmala*.[77] Inspection of ^{1}H and ^{13}C NMR spectroscopic data indicated that pheharmine A compromised of β-carboline and phenylpropanoid.[77] Through HMBC correlations, Sheng and colleagues were able to conclude the presence of 4-hydroxy-3-methoxyphenylpropranol fragments.[77] Furthermore, through NOESY correlations, they were able to determine that C-7' position (4-hydroxy-3-methoxyphenyl groups) and C-8' position (-CH$_2$OH-) were located on the same face. Pheharmine A (**56**) was reported to be chiral with an optical rotation of $[\alpha]_D^{20}$+ 41.7 (c 0.06, MeOH)), and the other (-)-pheharmine A (**57**) $[\alpha]_D^{20}$-50.8 (c 0.12, MeOH)).[77] ECD spectra of **56** and **57** shown the absolute configurations **56** and **57** having chiral centers assigned as 7'*R*, 8'*R* and 7'*S*, 8'*S*.

Inspection of ^{1}H and ^{13}C NMR spectroscopic data indicated that Pheharmine B has the same planar structure as that of pheharmine A. Furthermore, through NOESY correlations it has shown that 7', 8' position were *trans* configuration. Due to its specific rotation being zero, chiral HPLC resolution was performed, obtaining two compounds. Pheharmine B (**58**) was reported to be chiral with an optical rotation of $[\alpha]_D^{20}$– 26.1 (c 0.25, MeOH), and the other (+)-pheharmine B (**59**) $[\alpha]_D^{20}$+ 22.0 (c 0.23, MeOH).[77] Likewise, the ECD spectra of **58** and **59** were also mirrored. Their absolute configurations were explicitly defined as 7'*S*, 8'*R* and 7'*R*, 8'*S*.
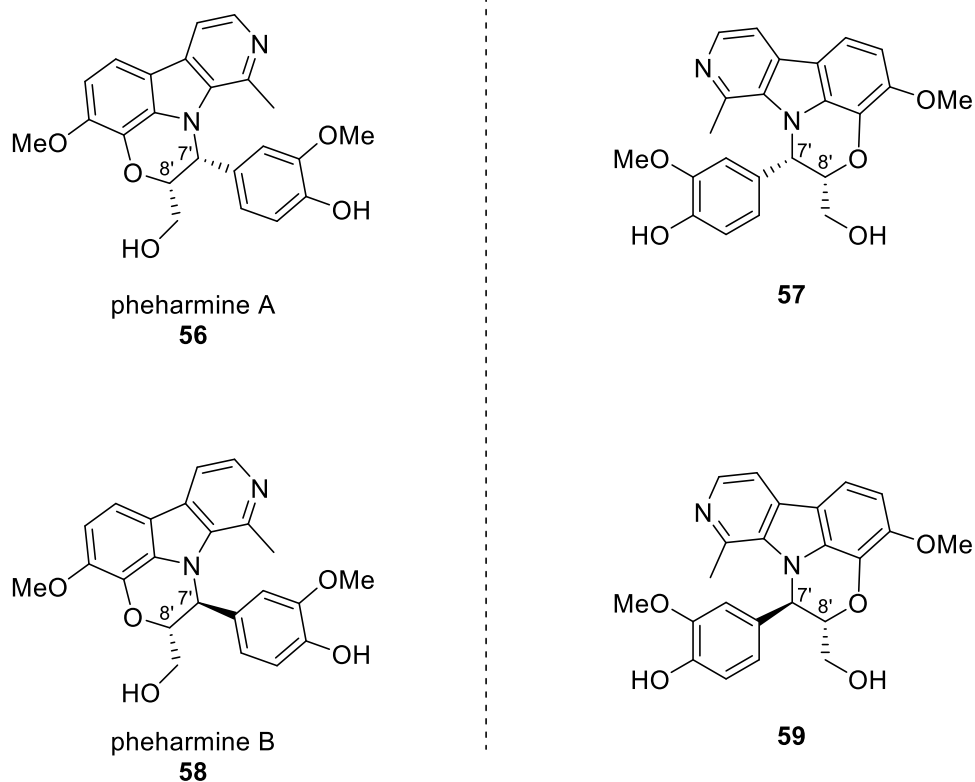
27

Figure 13. Chemical structures of pheharmines **56-59**.

1.4.2   Biological Activity

Pheharmines (**56-59**) were tested for their cytotoxicity against HL-60, HCT-116 (colon cancer), A549, and HepG2 cells. All the compounds showed moderate cytotoxic activities against HL-60 cells with an IC_{50} values of 26.1, 20.6, 15.7, and 38.0 μM), respectively. However, compound **57** has weak cytotoxicity against HCT-116 cells with an IC_{50} values of 59.97 μM, while the rest exhibited no cytotoxic activities with an IC_{50} greater than 100 μM. Furthermore, compounds **56-59** displayed no cytotoxic activities against A549 and HepG2 cell lines with an IC_{50} values of greater than 50 μM.[77]

1.4.3   Proposed biosynthesis

The proposed biosynthesis of pheharmine begins by oxidizing harmine (**23**) to give the intermediate (**60**) and (**61**), forming a Diels-alder reaction with the (*Z*)- or (*E*)-coniferyl alcohol (**62** or **63**) to give pheharmine (**56-59**) (Scheme 3).

28
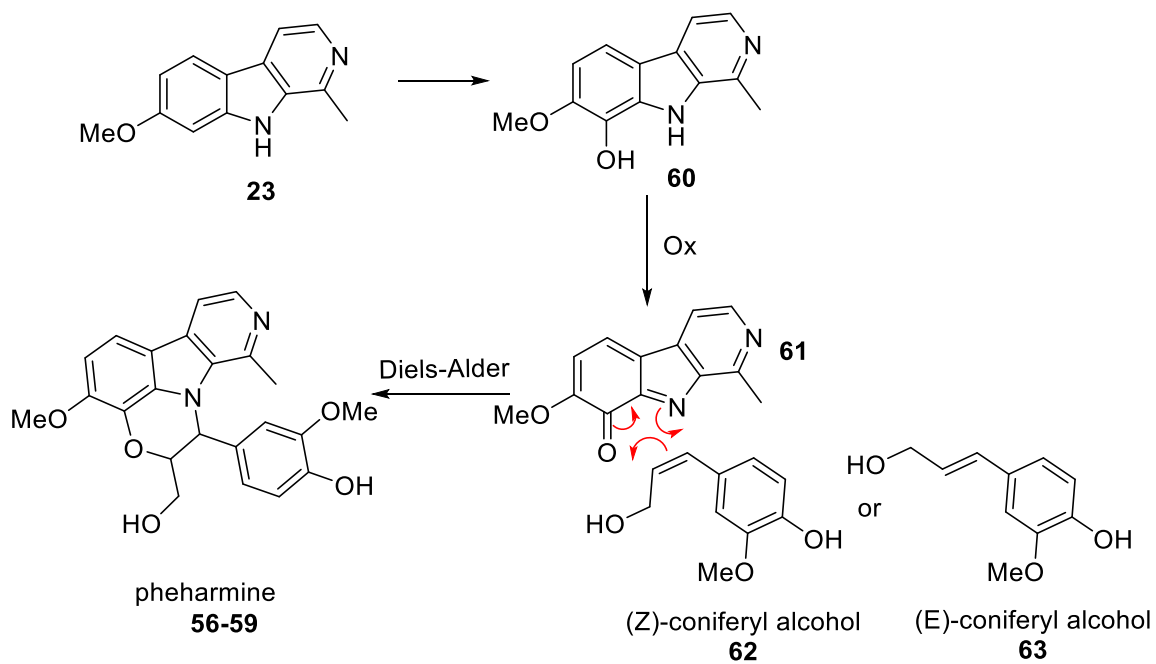
Scheme 3. Proposed biosynthesis pathway for pheharmine.

1.5 <u>Overall research objective</u>

The total synthesis of pheharmine would prove to be an interesting challenge owing to its unique scaffold. It is interesting to note that Sheng and colleagues have proposed hetero-Diels-Alder reactions occurring between diene (*o*-quinone imine) (**61**) and dienophile (**62** & **63**) as there is no precedent for this type of Diels-Alder reaction in nature. It is for this reason we pursued a biomimetic synthesis of pheharmine to validate the biosynthetic proposal.
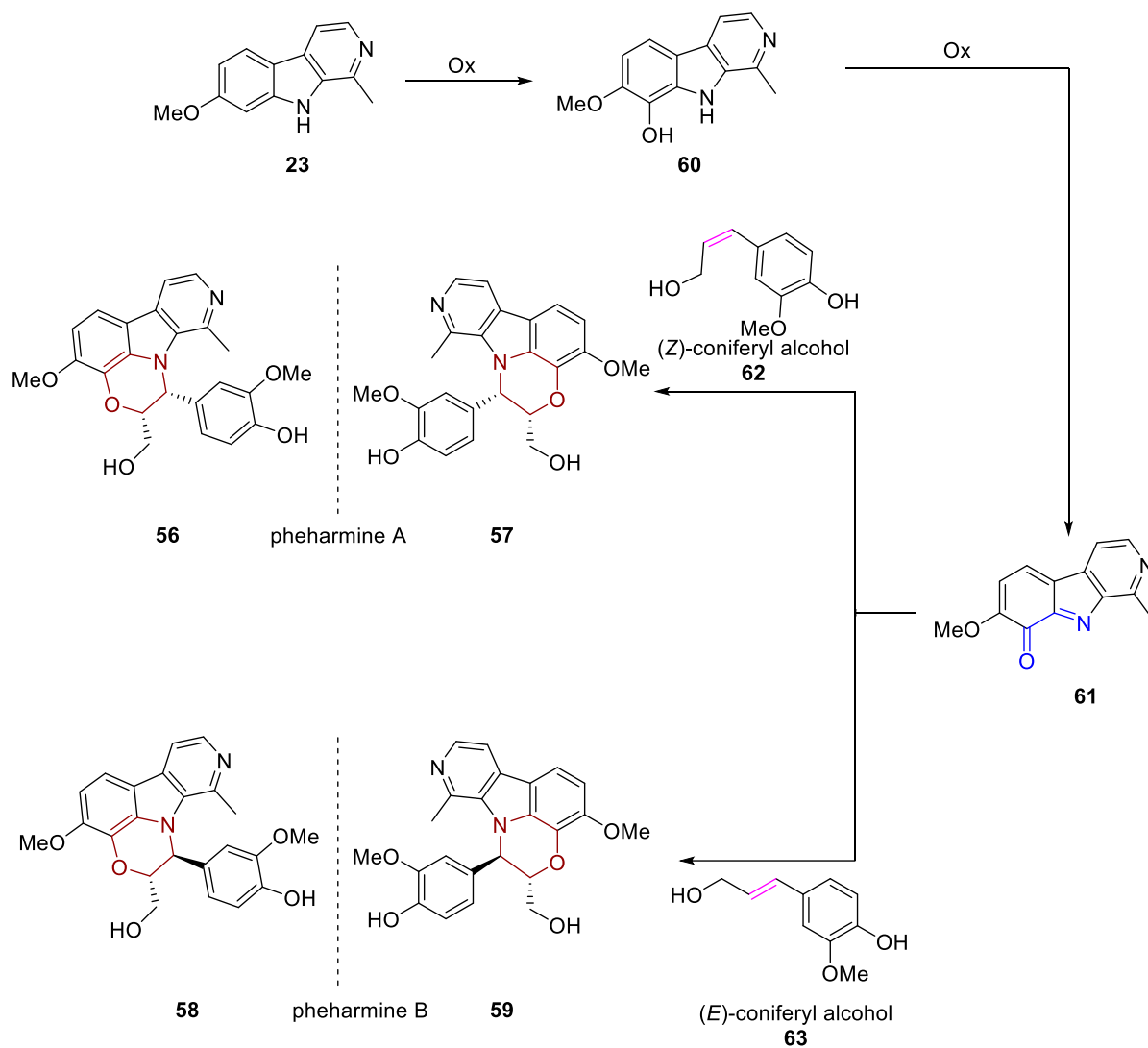

Scheme 4. Proposed synthesis of pheharmines.

Chapter Two:

**Discussion**

2.1 First approach to pheharmine

Formylation of commercially available 6-methoxyindole (**64**) will give carbaldehyde (**65**), that upon Henry reaction will deliver nitrolvinylindole **(66)**. Reduction of nitrovinylindole (**66**) will give tryptamine (**67**), which then react with ethanal (**68**) *via* Pictet-Spengler to form tetrahydro-β-carbolines (**69**). Oxidation of tetrahydro-β-carboline (**69**) will give harmine (**23**), upon addition of the directing group (**70-72**) gives the *N*-pyrimidylcarboline (**73**). From here, C-H oxidation onto the C-8 position will give 8-hydroxy-β-carboline (**74**). Removal of directing group to give **60**, then oxidation of **60** gives *o*-quinone imine (**61**), then upon can react (*Z*)- or (*E*)-coniferyl alcohol (**62** or **63**) to give pheharmines A or B (**56-59**).
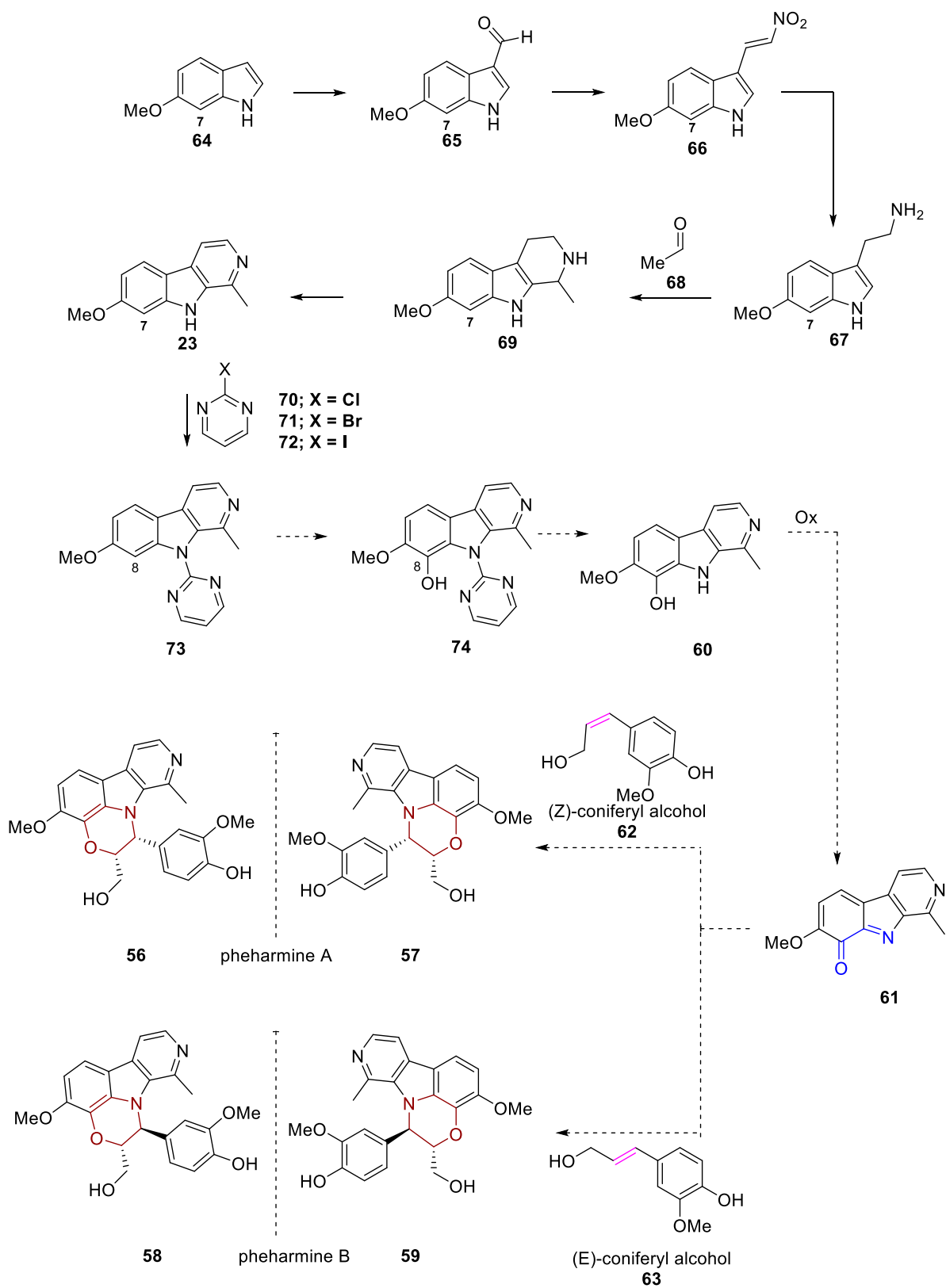
Scheme 5. First generation synthetic approach to pheharmines (**56-59**).

2.1.1 Vilsmeier reaction

Formylation of commercially available 6-methoxyindole (**64**) with phosphorus oxychloride in DMF gives indole-carbaldehyde (**65**) (Scheme 6).[78, 79] This Vilsmeier-Haack reaction (VH) consisted of two steps; the first part is formation of Vilsmeier reagent *via* POCl$_3$ reacting with DMF (Scheme 7), followed by the attack on indole. 6-Methoxyindole (**64**) can nucleophilically attack on the Vilsmeier reagent (iminium cation) to form intermediate (**76**), which then rapidly hydrolyzed during work up to give 6-methoxy-indole-carbaldehyde (**65**) (Scheme 7).[80]
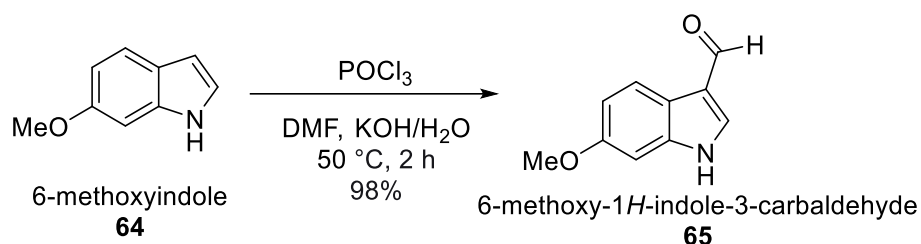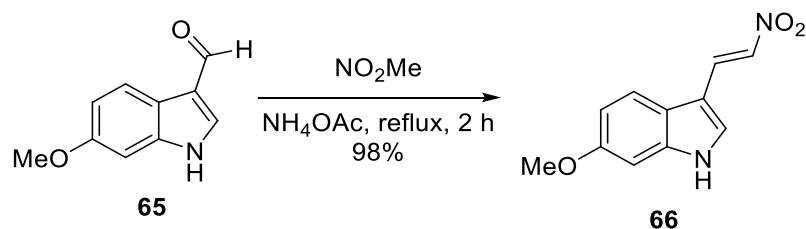

Scheme 6. Synthesis of indole carbaldehyde (**65**).
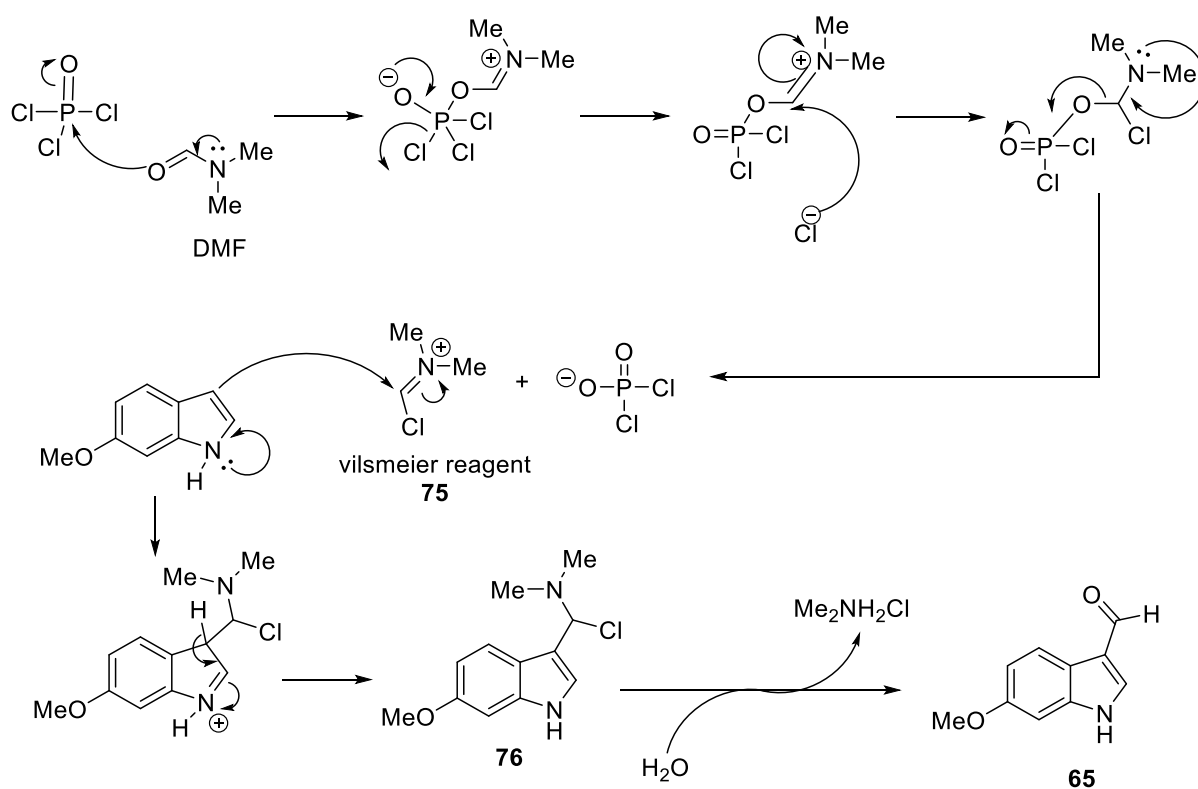
Scheme 7. Mechanism of Vilsmeier-Haack reaction synthesis of carbaldehyde (**65**).

2.1.2 Henry reaction

With the carbaldehyde (**65**) in hand. The carbaldehyde (**65**) was reacted with nitromethane and ammonium acetate to give 2-nitrovinylindole (**66**) (Scheme 8).[81] The Henry reaction is the formation of carbon-carbon bond reaction between nitroalkanes and aldehydes or ketone in the presence of base to form the β-nitro, which was discovered in 1985.[82]

Scheme 8. Synthesis of 6-methoxy-3-(2-nitrovinyl)indole (**66**).

In the presence of base, deprotonation of nitromethane forms the stabilized anion that undergoes nucleophilic attack onto indole carbaldehyde (**65**) resulting in formation of β-nitro alcohol compound (**77**). Dehydration forms the nitrovinylindole (**66**) (Scheme 9).
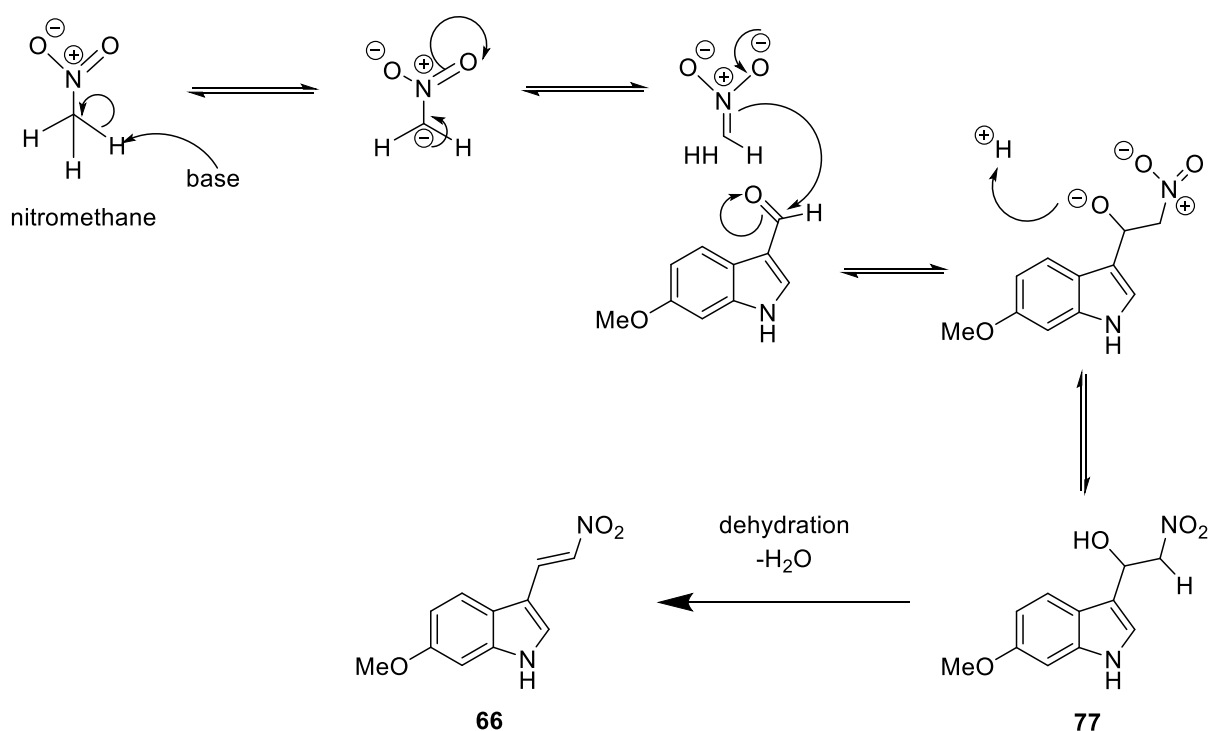
Scheme 9. Mechanism for the synthesis nitrovinylindole (**66**).

2.1.3 Synthesis of 6-methoxytryptamine (67) and 6-methoxytetrahydro-β-carboline (69)

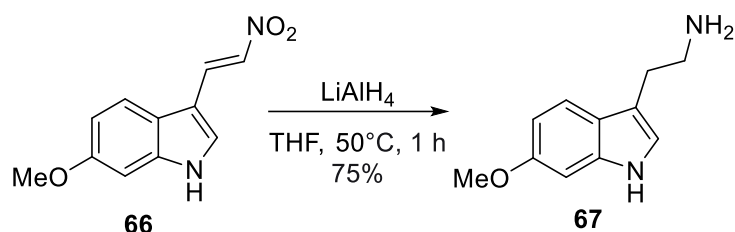Upon obtaining nitrovinylindole (**66**), reduction of **66** *via* lithium aluminum hydride in tetrahydrofuran (THF) resulted in the formation of 6-methoxytryptamine (**67**) (Scheme 10).[81]

Scheme 10. Synthesis of 6-methoxytryptamine (**67**).

With tryptamine (**67**) in hand, it underwent Pictet-Spengler reaction with ethanal in the presence of acid to form 7-methoxytetrahydro-β-carboline (**69**) (Scheme 11).
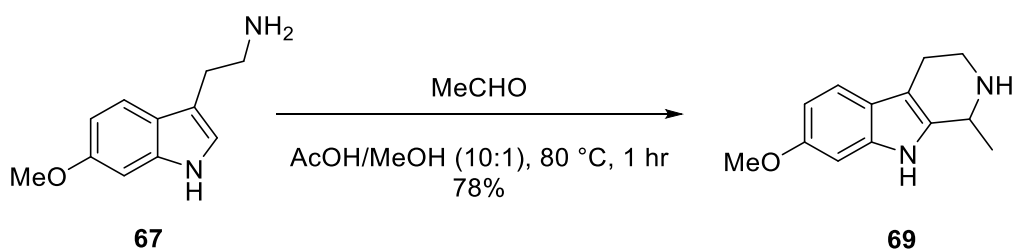
Scheme 11. Synthesis of 7-methoxytetrahydro-β-carboline (**69**).

2.1.3.1 Pictet-Spengler reaction

The Pictet-Spengler reaction is the condensation of a hetero arylethylamine with an aldehyde or ketone to form a range of nitrogen-containing heterocyclic structures such as β-carbolines, isoquinolines and azepines.[83-85] Established by Amé Pictet and Theodor Spengler, the cyclisation of phenethylamine (**78**) with dimethoxymethane to form tetrahydroisoquinoline (**79**) was published in 1911 (Scheme 12).[83] It was nearly 20 years later that the scope of the reaction was broadened to include tryptamine (**80**) as the amine component, which resulted a simple method for the synthesis of tetrahydro-β-carboline (**81**) (Scheme 12).
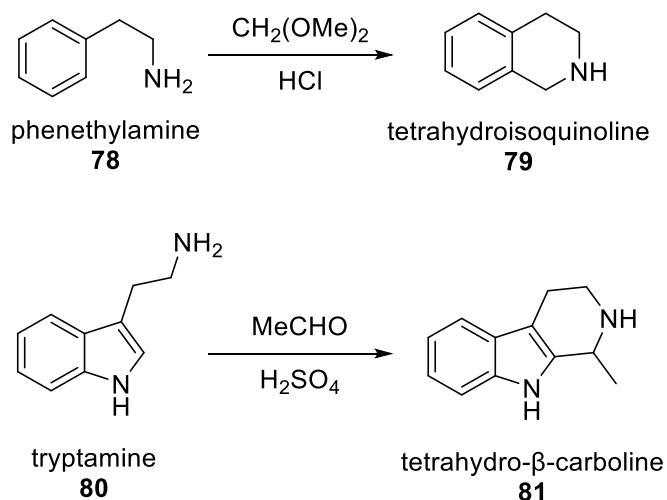
Scheme 12. The first Pictet-Spengler reactions forming the tetrahydroisoquinoline (**79**) and tetrahydro-β-carboline (**81**).

2.1.3.2 Mechanism

The mechanism of Pictet-Spengler reactions begins with 6-methoxytrytamine (**67**) attacking ethanal (**68**), upon dehydration gives the iminium ion (**82**) followed by nucleophilic attack of 6-methoxytryptamine (**67**) to form spiroindolenine intermediate (**83**). A 1,2-bond migration yields carbonium ion (**84**) and subsequent deprotonation affords the 7-methoxytetrahydro-β-carboline (**69**) (Scheme 13).
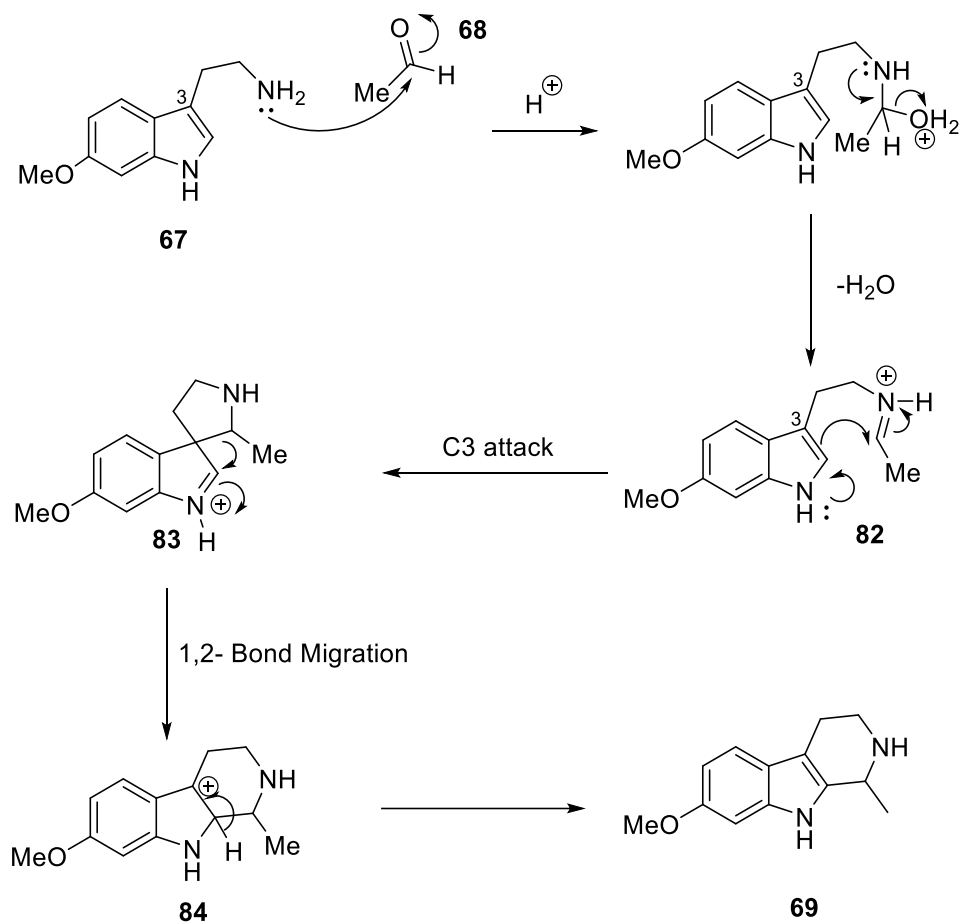
Scheme 13. Mechanism of the 7-methoxytetrahydro-β-carboline (**69**).

2.1.4   Synthesis of harmine (23)

Upon obtaining 7-methoxytetrahydro-β-carboline (**69**), the dehydrogenation step was the oxidation of **69** and results in the formation of harmine (**23**). However, the type of solvent and temperature played a role in the formation of harmine (**23**). Initially, 7-methoxytetrahydro-β-carboline (**69**) with Pd/C (50% w/w) in toluene was heated at reflux, but trace amount of products were formed after 24 h. In addition, the reaction was left further for another 24 h, which lead to degradation. However, using the same exact conditions but at a higher boiling point, with xylene as the solvent, under reflux for 24 h, resulted a higher yield of harmine with desirable quantity of harmine (**23**) in hand. With suitable quantities of harmine in hand, the C-H oxidation step was considered (Scheme 14).
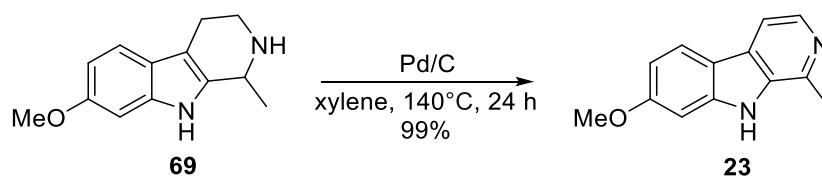
Scheme 14. Synthesis of harmine (**23**).

2.1.5 Synthesis of *N*-pyrimidylcarboline (73)

2.1.5.1 S$_N$Ar reaction
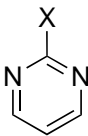
With harmine (**23**) in hand, the S$_N$Ar reaction could be attempted. Pyrimidine was used as the directing group as it has proved to be an efficient directing group for various metal catalysts.[86-90] As N-pyrimidyl group may facilitate the direct hydroxylation of C8-OH bond due to the presence of lone pair from N atom.[91] In this case, harmine (**23**) was deprotonated by various of bases generateing an anion that attacks the 2-halopyrimidine to give *N*-pyrimidylcarboline (**73**) (Scheme 15).
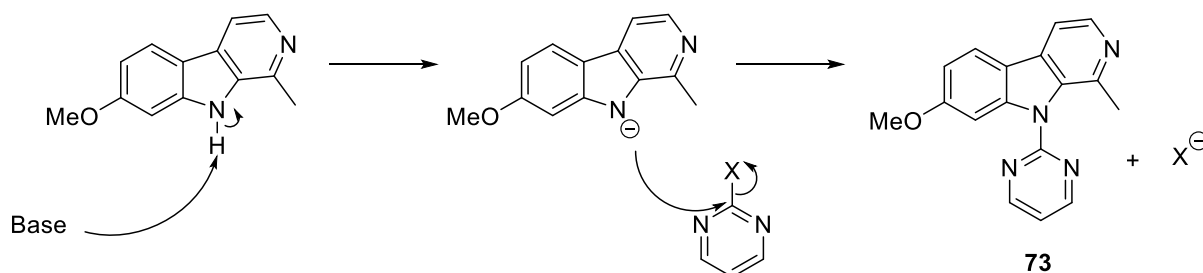
Scheme 15. S$_N$Ar mechanism for synthesis of *N*-pyrimidylcarboline (**73**).

N-pyrimidylcarboline (**73**) was prepared following a procedure published by Cao and colleagues.[92] NaH was used as the base, 2-chloropyrimidine as the electrophile and DMF or THF as the solvent was common; therefore, that became the starting point for the attempts shown in Table 1. Harmine (**23**) was deprotonated with NaH before addition of 2-chloropyrimidine and heated at reflux in DMF which resulted in degradation (entry 1). Adding THF solvent as 1:1 ratio to DMF and heating at reflux also resulted degradation (entry 2). Kwon and colleagues[93] have demonstrated that 2-iodopyrimidine gave higher yields than 2-bromo or 2-chloro pyrimidine. Thus, 2-iodo- and 2-bromo- pyrimidine groups were tried, with NaH as the base and heated at reflux lead to degradation (entries 3 and 5) and addition of THF solvent to DMF (1:1) but unsuccessful (entries 4 and 6). Changing the base to K$_2$CO$_3$ and Cs$_2$CO$_3$ and heated at reflux resulted in degradation (entries 7, 8 and 9).

39

Table 1. Attempted S$_N$Ar reaction between harmine (**23**) and 2-halopyrimidines.
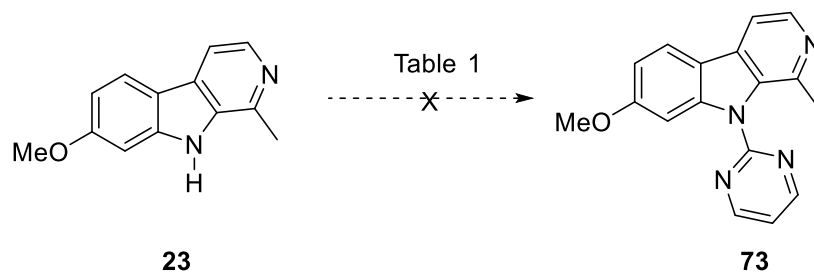
Entry	Base	X=	Solvent	Yields (%)
1	NaH	Cl	DMF	-
2	NaH	Cl	DMF:THF 1:1	-
3	NaH	Br	DMF	-
4	NaH	Br	DMF:THF 1:1	-
5	NaH	I	DMF	-
6	NaH	I	DMF:THF 1:1	-
7	K$_2$CO$_3$	Br	DMF	-

8	K$_2$CO$_3$	I	DMF	-
9	Cs$_2$CO$_3$	I	DMF	-

All reactions are carried out in a sealed tube. Reactions solvents thoroughly dried and degassed. All reactions were performed up to 140 ºC for 24 to 48 h unless specified.

2.1.5.2   Ullman-Goldberg reaction

After numerous unsuccessful S$_N$Ar attempts, the Ullman-Goldberg reaction was considered. The Ullman reaction is the formation of C-C bond through cross-coupling reactions with copper as the metal as the transition metal, which was first discovered in 1901.[94] About 30 years later, the Ullman-Goldberg reaction was discovered, which involves the reaction between aniline with an aryl halide with copper as catalyst.[95]
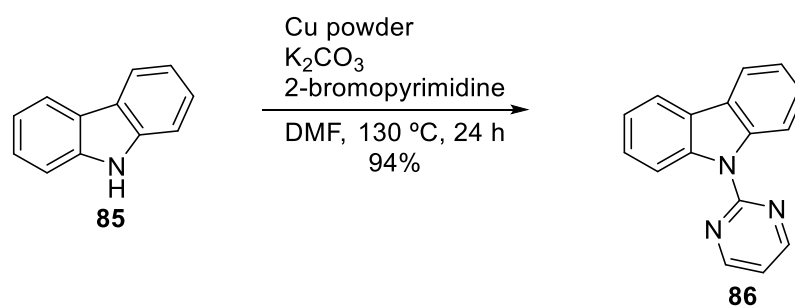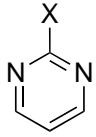
Scheme 16. Synthesis of *N*-pyrimidylcarbazole (**86**).

Jiang and colleagues[96] have demonstrated that carbazole (**85**) was able to undergo Ullman-Goldberg reaction with addition of 2-bromopyrimidine using copper, K$_2$CO$_3$ in DMF to give *N*-pyrimidylcarbzole (**86**) (Scheme 16). NaH, K$_2$CO$_3$ or Cs$_2$CO$_3$ as the base and dimethylformamide as the solvent was identified as common for Ullman reaction conditions;[92, 93, 97-99] therefore, that became the starting point for the attempts shown in Table 2. Degradation occurred when performing the reaction in K$_2$CO$_3$ in DMF with Cu as the metal catalyst and 2-bromopyprimidine, heated at 140 ºC (entry 1); changing the base to Cs$_2$CO$_3$ and the directing group to 2-chloropyrimdine and heated at 140 ºC also resulted in degradation of the starting material (entry 2). Afterward, addition of ligand (L-proline) was added, it has shown that having a ligand would stabilize and facilitating an increase in its concentration, which in turn increase rate of reaction of the copper intermediate.[100] So, L-proline was used as the ligand with NaH as base, CuI as metal catalyst, 2-chloropyrimidine as directing group (entry 3), which result in failure of the reaction; changing the base to K$_2$CO$_3$ and directing group to 2-

bromopyrimidine was also unsuccessful (entry 4). Changing the base to Cs_2CO_3 resulted in the formation of product (**73**) in trace amount. (entry 5). 2-Bromopyrimidine was swapped to 2-chloropyrimidine, and no product was formed (entry 6). L-Proline was removed to see if there were any changes to the reaction (entry 7); however, the results produced trace amounts. A last attempt was made to use 2-iodopyrimidine (entry 8), and this produced a surprising result with a high yield of novel product (**73**) being formed (97%).

Table 2. Ullman-Goldberg reaction of harmine (**23**) with 2-halopyrimidines.
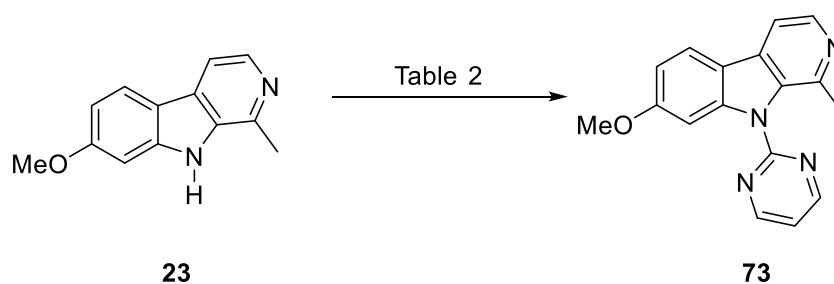
Entry	Base	Catalyst	Ligand	X=	Solvent	Yields (%)
1	K_2CO_3	CuI	-	Br	DMF	-
2	Cs_2CO_3	CuI	-	Cl	DMF	-
3	NaH	CuI	L-proline	Cl	DMF	-
4	K_2CO_3	CuI	L-proline	Br	DMF	-
5[a]	Cs_2CO_3	CuI	L-proline	Br	DMF	Trace amount

6	Cs$_2$CO$_3$	CuI	L-proline	Cl	DMF	-
7[a]	Cs$_2$CO$_3$	CuI	-	Br	DMF	Trace amount
8[b]	Cs$_2$CO$_3$	CuI	L-proline	I	DMF	97%

All reactions are carried out in a sealed tube. Reactions solvents thoroughly dried and degassed. All reactions were performed at 140 °C for 24 to 48 h unless specified. [a]Reaction was heated for 48 hours and [b]reaction was heated for 30 hours.

The mechanism for harmine underwent Ullman-Goldberg begins with deprotonation of harmine (**23**) followed by nucleophilic attacks toward CuI resulting iodine to leave from the metal. Oxidative addition of the intermediate **I** form the intermediate **II**. Lastly, reductive elimination gives the *N*-pyrimidylcarboline (**73**) (Scheme 17).
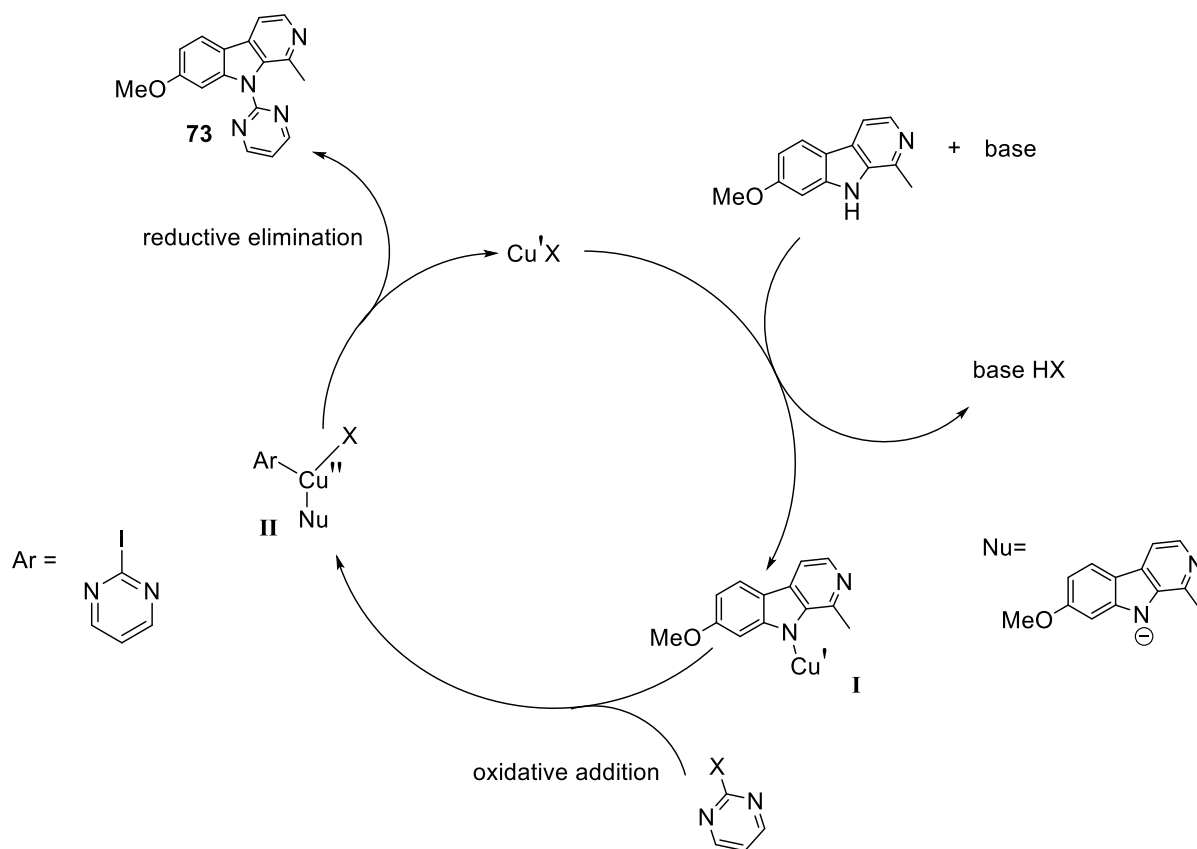
Scheme 17. Ullman-Goldberg reaction mechanism of C-H oxidation substrate harmine (**23**).

2.1.6 C-H Acetylation/hydroxylation of C-H oxidation substrates

2.1.6.1 Acetylation of *N*-pyrimidylcarboline (**73**)

After obtaining the desired *N*-pyrimidylcarboline (**73**), the C-H oxidation could be attempted. Gao and colleagues demonstrated that C-H oxidation on the C-7 position of *N*-pyrimidylcarboline (**87**) *via* Ullman-Goldberg reaction was possible (Scheme 18).[101] They were able to optimized the conditions using $Cu(OAc)_2.H_2O$ (0.5 eq) under air and dichloroethane (DCE) as the solvent, heating at 130 °C for 12 h to form 7-acetoxyindoline (**88**). (Scheme 18).
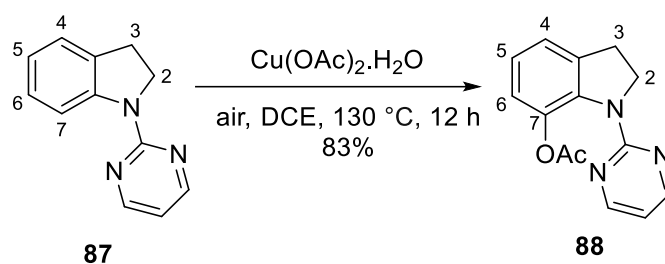

Scheme 18. C-H acetoxylation of *N*-pyrimidylindoline (**87**).

Using Gao and colleagues' conditions,[101] *N*-pyrimidylcarboline (**73**) and $Cu(OAc)_2.H_2O$ in DCE were heated at reflux leading to no reaction (Table 3, entry 1). A variety of different metal catalysts (Pd, Cu, Ru and Rh), oxidants and additives were being used.[90, 91, 101-105] Therefore, different conditions were being tested in this case. Addition of TBAI, Ag_2CO_3 and changing to DMF as the solvent and heated reflux resulted in degradation (entry 2). $AgBF_4$ was added and the solvent was changed back to DCE and heated at refluxed resulted degradation (entry 3). Changing to $Pd(OAc)_2$, *p*-TsOH and selectfluor in AcOH resulted in degradation (entry 4). No reaction occurred when changing to $PHI(OAc)_2$ and removal of p-TsOH in methanol (entry 5). Using the same conditions as entry 3 but changing the metal to $Pd(OAc)_2$ and heated at reflux also resulted in no reaction (entry 6). Changing the metal to ruthenium, $K_2S_2O_8$ and HBF_4 in dichloroethane : acetone (2:1) and heated at reflux resulted in degradation (entry 7). Lastly, using the same conditions as entry 3 but changing the metal to $[Ru(p-cymene)Cl_2]_2$ led to no reaction (entry 8).

Table 3. Attempted C-H oxidation on the C-8 position of the *N*-pyrimidylcarboline (**73**).

73

74; R = H
89; R = Ac
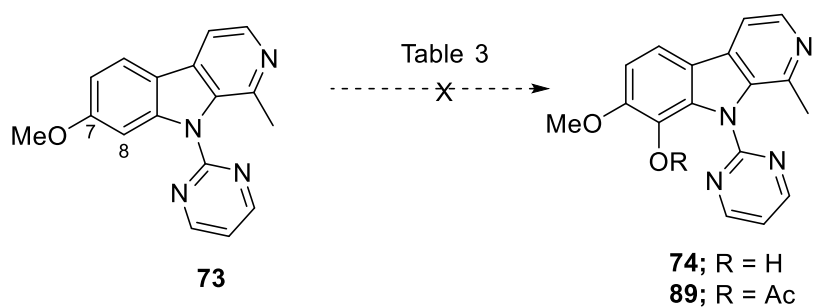
Entry	Catalyst (mol%)	Base (mol%)	Oxidiser (mol%)	Additive (mol%)	Solvent	Time	Yield (%)
1[a]	Cu(OAc)₂.H₂O (50)	-	-	-	DCE	90 h	NR
2	Cu(OAc)₂.H₂O (50)	Ag₂CO₃ (200)	-	TBAI (200)	DMF	60 h	-
3	Cu(OAc)₂.H₂O (50)	Ag₂CO₃ (200)	AgSBF₆ (20)	-	DCE	120 h	-
4	Pd(OAc) (10)	-	Selectfluor (200)	*p*-TsOH (200)	AcOH	48 h	-
5	Pd(OAc)₂ (10)	-	PhI(OAc)₂ (200)	-	MeOH	72 h	NR
6	Pd(OAc)₂	Ag₂CO₃ (200)	AgSBF₆ (20)	-	DCE	72 h	NR

7	[Ru(p-cymene)Cl$_2$]$_2$ (50)	-	K$_2$S$_2$O$_8$ (200)	HBF$_4$ (50)	DCE : Acetone (2 : 1)	48 h	-
8	[Ru(p-cymene)Cl$_2$]$_2$ (50)	Ag$_2$CO$_3$ (200)	AgSBF$_6$ (20)	-	DCE : AcOH(1 : 3)	24 h	NR

All reactions are carried out in a sealed tube. Reactions solvents thoroughly dried and degassed. All reactions were performed at refluxed unless specified. [a]Reaction was performed under air.

The failure of this reaction is possibly due to the C7-OMe group exerting steric congestion on the neighboring the reactive site,[106] which can be further confirmed in **section 2.1.6.2** and **2.1.6.3**. Indoline[101, 106-110] and carbazole[91, 111] that do not have substituents on the C6 position of indoline and C7 position of carbazole can undergo C-H oxidation on the C-7 and C-8 position (Scheme 19). On the other hand, a methoxy substituent on C6 position of indoline and C7 position of carbazole failed when trying to attempt C-H oxidation on the C-7 and C-8 position (Scheme 19) according to our model studies.
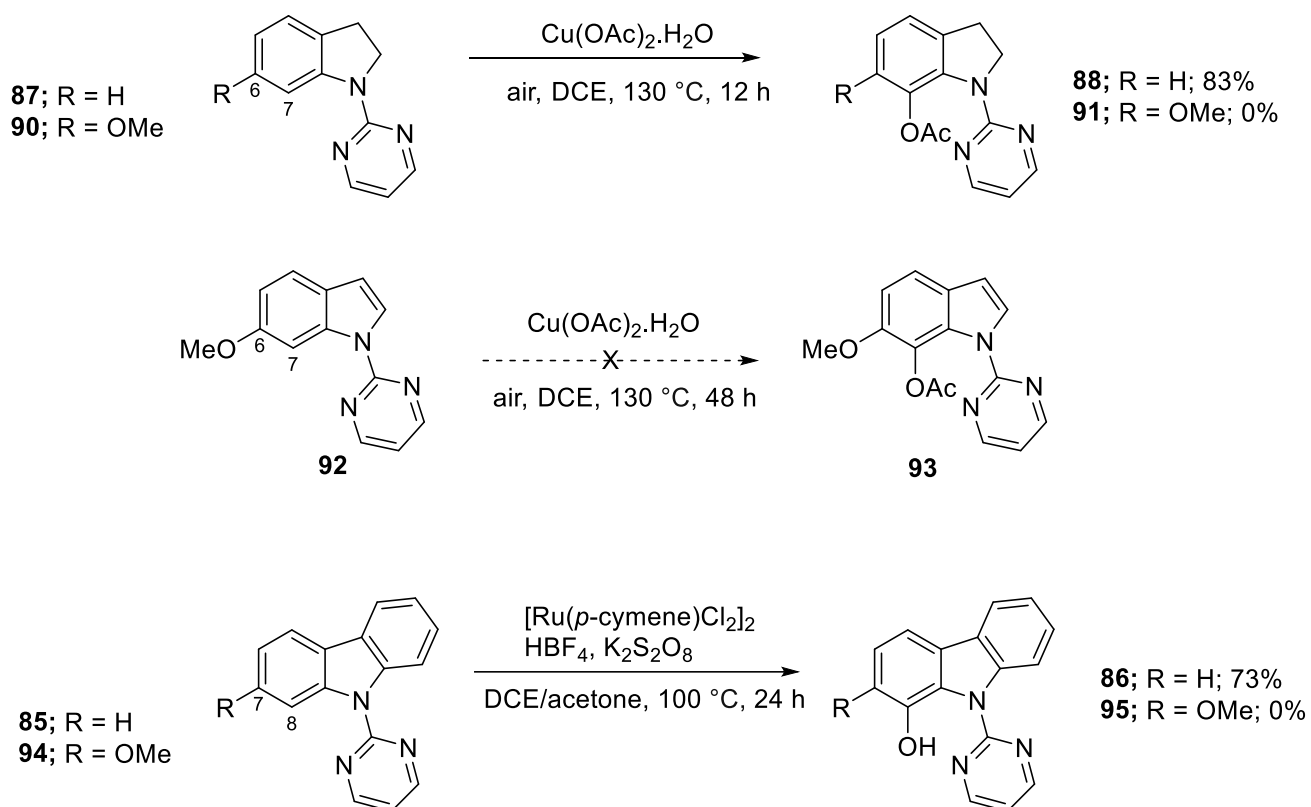
Scheme 19. C-H oxidation of *N*-pyrimidylindoline (**87** & **90**) , *N*-pyrimidylindole (**92**) and *N*-pyrimidycarbazole (**85** & **94**).

2.1.6.2 Synthesis of *N*-pyrimidylindoline (**91**)

Commercially available 6-methoxyindole (**64**) underwent reduction *via* sodium cyanoborohydride in neat acetic acid to give 6-methoxyindoline (**96**) as colourless oil. This was heated in the presence of 2-chloropyrimidine and dimethyl sulfoxide (DMSO) to form the novel *N*-pyrimylindoline (**91**) as a white solid. It then underwent the same reaction condition as Gao and colleagues,[101] however no products were formed but instead it gave *N*-pyrimidylindole (**92**) (10%) (Scheme 20). Gao and colleagues[101] have demonstrated that the substituent attached to the C-2,3,4 and 5 had no issues undergoing C-H oxidation. C6-Me were able to undergo C-H oxidation with 55% yield (Scheme 21).[101] However, large substituents such as methoxy or nitrogen dioxide would not be able to undergo C-H oxidation due to steric hindrance on the reactive site (Scheme 19 & 21).[106, 112]
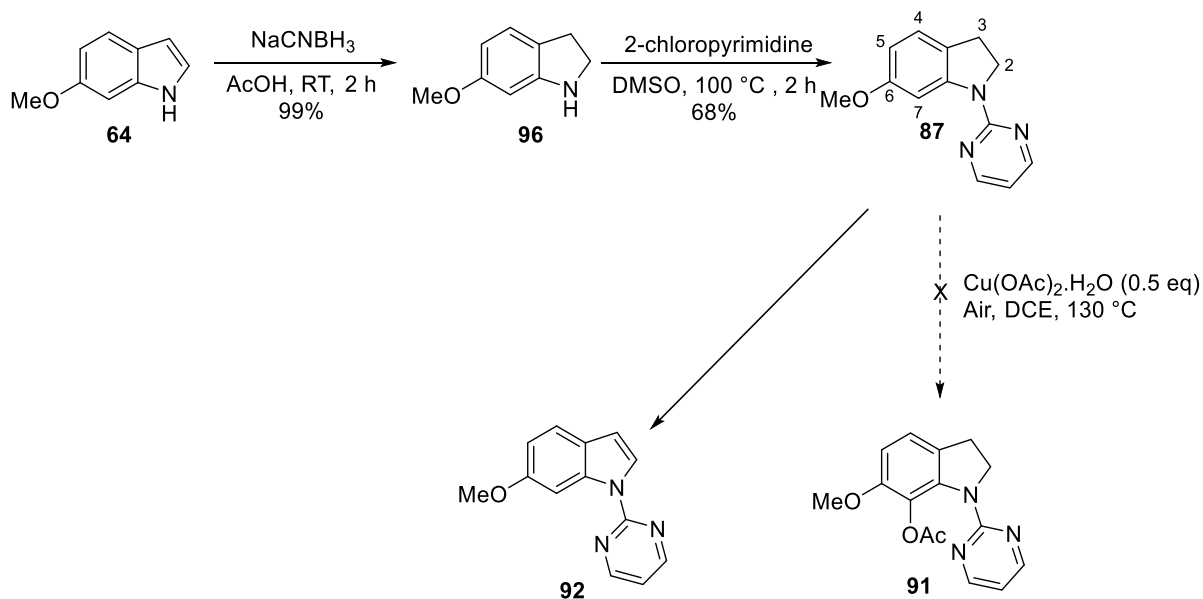
Scheme 20. *N*-pyrimidylindoline (**87**) does not undergo C-H oxidation on the C-7 position.
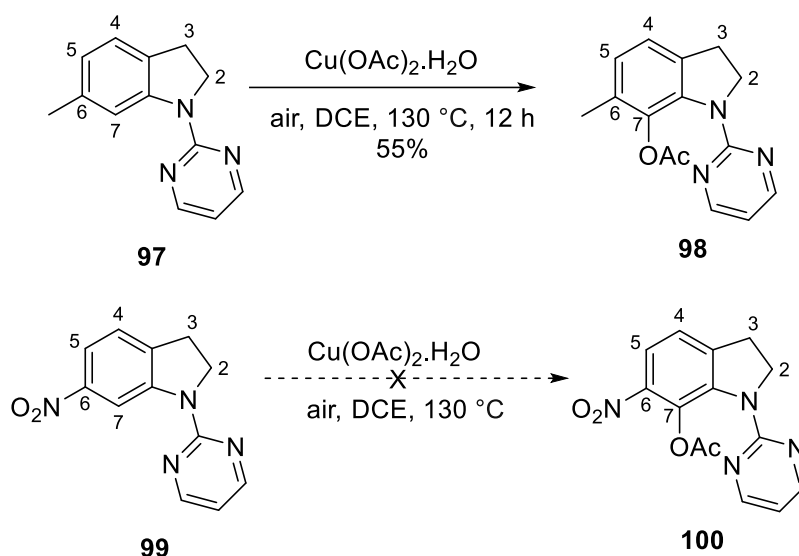
Scheme 21. C-H oxidation on 6-methyl-pyrimidylindoline (**97**) and 6-nitro-pyrimidylindoline (**99**).

2.1.6.3 Synthesis of *N*-pyrimidylindole (**92**)

Commercially available 6-methoxyindole (**64**) undergoes the addition of directing group *via* cesium carbonate, copper iodide, L-proline and 2-iodopyrimidine in DMF and heated at 140 °C give *N*-pyrimidylindole (**92**). It then undergoes the same reaction condition as Gao and colleagues.[101] As expected, no products formed because C6-OMe group has blocked the reactive site at the C7 location (Scheme 22).
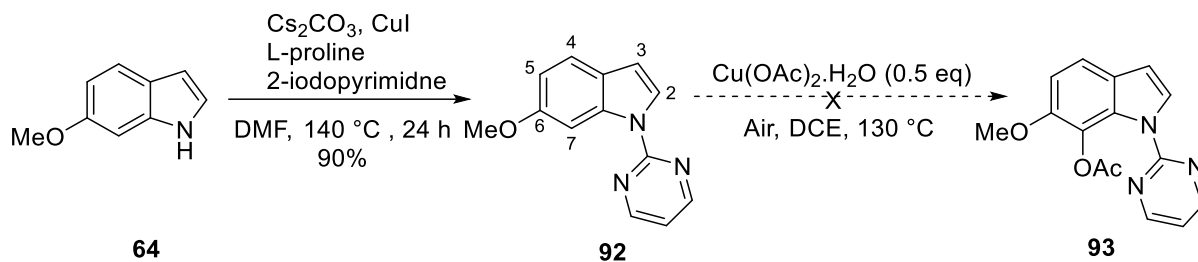
Scheme 22. *N*-pyrimidylindole (**64**) did not undergoes C-H oxidation on the C7 position.

2.2 Second Route

After many failed C-H oxidation attempts, an alternative route based on C-H borylation was considered. 7-Methoxytetrahydro-β-carboline (**69**) would undergoes Boc protection to give the **101**, that upon subjecting C-H borylation at C8 would give *N*-Boc 8-boryltetrahydro-β-carboline (**102**). Oxidative hydrolysis gave the *N*-Boc 8-hydroxytetrahydro-β-carboline (**103**) and deprotection of the Boc protecting group to give 8-hydroxytetrahydro-β-carboline (**104**). Oxidation of 8-hydroxytetrahydro-β-carboline gives 8-hydroxyharmine (**60**), then oxidation of **60** gives *o*-quinone imine (**61**), then upon can react (*Z*)- or (*E*)-coniferyl alcohol (**62** & **63**) to give pheharmines A or B (**56-59**) (Scheme 23).
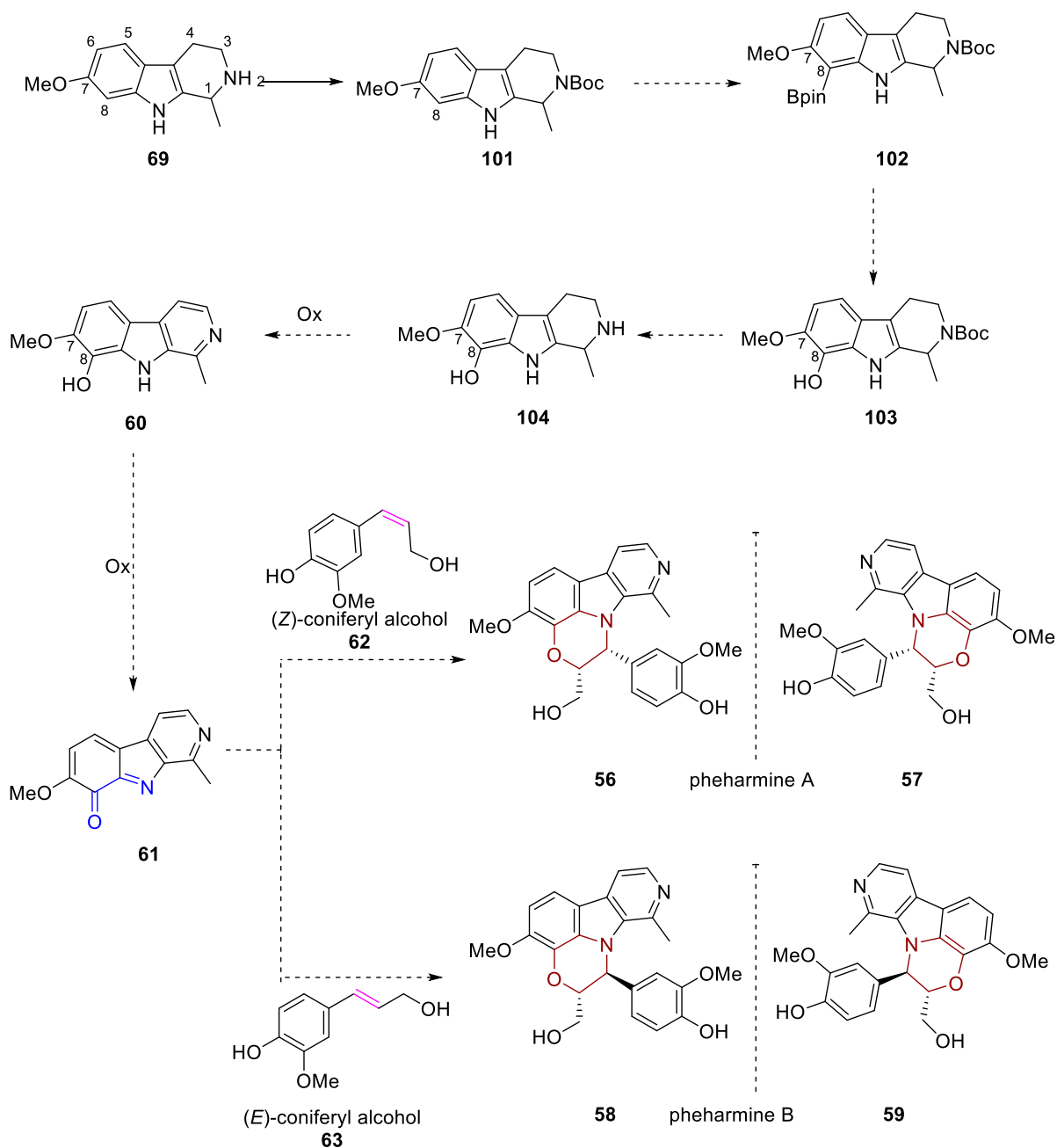
Scheme 23. Second generation synthetic approach to pheharmines (**56**-**59**).

2.2.1 Attempted C-H borylation of 101

7-Methoxytetrahydro-β-carboline (**69**) underwent smooth protection to give novel *N*-Boc tetrahydro-β-carboline (**101**) (Scheme 24).
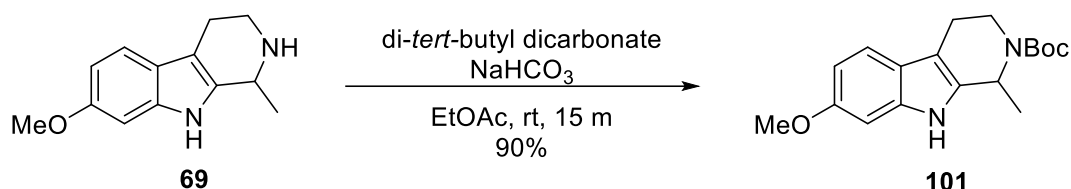
Scheme 24. Synthesis of *N*-Boc tetrahydro-β-carboline (**101**).

With *N*-Boc tetrahydro-β-carboline (**101**) in hand, it was subject to a range of C-H borylation conditions. Using [Ir(OMe)cod]$_2$ as the catalyst, dtbpy and B$_2$pin$_2$ in THF as the solvent was common;[113-116] therefore, that became the starting point for attempts shown in Table 4. Degradation occurred when using [Ir(OMe)cod]$_2$ with dtbpy, B$_2$pin$_2$ in THF (entry 1). Increasing the equivalents of the iridium metal, dtbpy and B$_2$pin$_2$ resulted in degradation (entry 2). Changing the ligand to Me$_4$Phen led to degradation (entry 3). No reaction occurred when changing to Phen (entry 4). Addition of HBpin also did nothing to the reaction (entry 5). Lastly, changing the solvent to DCE (entry 6) and 1,4-dioxane (entry 7) led to the degradation of both.

Table 4. Attempted C-H borylation of *N*-Boc tetrahydro-β-carboline (**101**).

Entry	Catalyst (mol%)	Ligand (mol%)	Reactant (mol%)	Temperature (°C)	Time (h)	Outcome
1	[Ir(OMe)cod]$_2$ (3)	Dtbpy (6)	B$_2$pin$_2$ (150)	140	72	Degradation
2	[Ir(OMe)cod]$_2$ (5)	Dtbpy (10)	B$_2$pin$_2$ (250)	140	72	Degradation
3	[Ir(OMe)cod]$_2$ (3)	Me$_4$Phen (6)	B$_2$pin$_2$ (150)	140	96	Degradation

4	[Ir(OMe)cod]$_2$ (5)	Phen (10)	B$_2$pin$_2$ (250)	120	72	No reaction
5[a]	[Ir(OMe)cod]$_2$ (5)	Phen (10)	B$_2$pin$_2$ (250)	120	72	No reaction
6[b]	[Ir(OMe)cod]$_2$ (5)	Phen (10)	B$_2$pin$_2$ (250)	120	48	Degradation
7c	[Ir(OMe)cod]$_2$ (5)	Phen (10)	B$_2$pin$_2$ (250)	120	48	Degradation

All reactions are carried out in a sealed tube in THF unless specified. Reactions solvents thoroughly dried and degassed. [a]HBpin (50% mol) was added into the reaction; [b]DCE was used as the solvent; [c]1,4-dioxane was used as the solvent.

Unfortunately, no borylation of *N*-Boc tetrahydro-β-carboline (**102**) was observed. In a detailed study,[113, 114] it was shown that steric factors have a large effect on C-H borylation, and that reaction occurs at the more acidic site. For example, trifluoromethyl quinone (**107**) undergoes a significant amount of C-H borylation at C5 compared to the methylquinoline analogue (**106**) (Scheme 25a).[113] In our case, the C7-OMe in **101** decreases the acidity of C8-H, thus not favoring the C-H borylation to occur at the C8 position. Furthermore, C7-OMe group exerts steric congestion that hinders the reaction. Our research group[116], demonstrated that the C-H borylation of *N*-Boc tetrahydrocarboline (**110**) was successful with a yield of 77% (Scheme 25b). However, in our case there is a C7-OMe that resulted in an unsuccessful reaction (Scheme 25b).
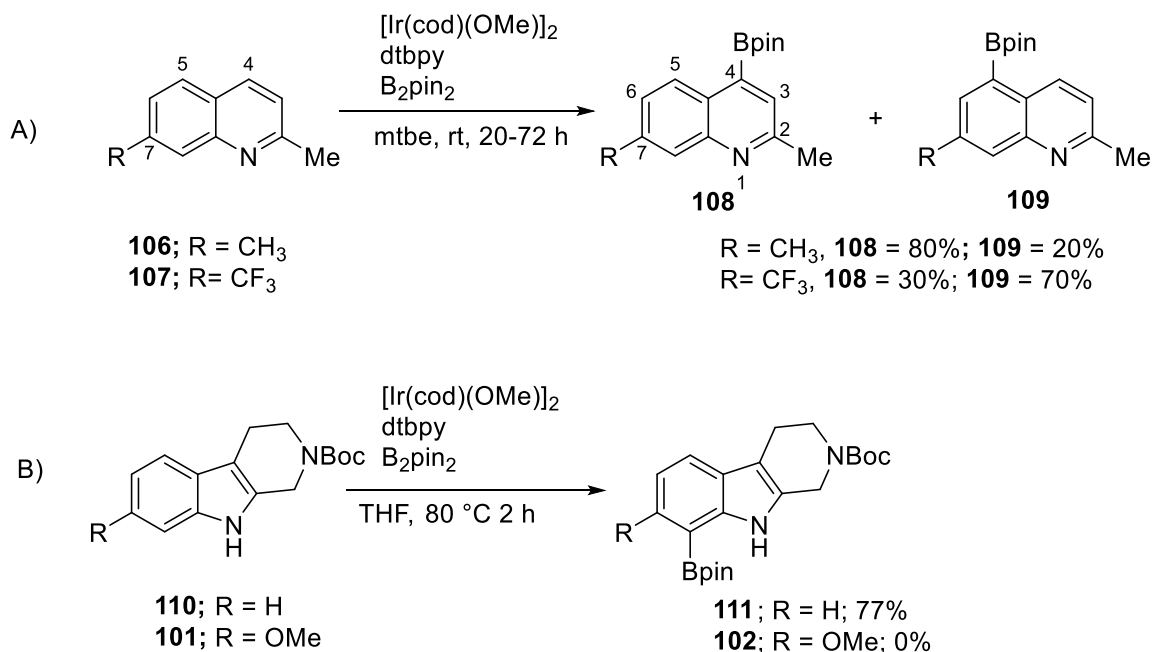
Scheme 25. A) Ir-catalysed C-H borylation of quinoline (**106** & **107**) achieved by Jay and colleagues;[113] B) C-H borylation of tetrahydro-β-carboline (**110**) achieved by our research group.[114]

2.3 Third Route

After unsuccessful C-H borylation, a third route was pursued based on early stage installation of the OH (Scheme 26). Acylation of commercially available 2,3-dimethoxyaniline (**112**) will give **113** that upon subjecting to 1,2-aryl arrangement to give 6-methoxy-indol-7-ol (**114**). Formylation of **114** will give 6-methoxy-indol-7-ol-3-carbaldehyde (**115**), that upon Henry reaction will deliver 7-hydroxy-nitrolvinylindole (**116**). Reduction of **116** will give 7-hydroxytryptamine (**117**), that upon Pictet-Spengler reaction with ethanal (**68**) form **104**. Dehydrogenation of 8-hydroxytetrahydro-β-carboline (**104**) to give 8-hydroxyharmine (**60**), the key precursor for the desired biomimetic Diels-Alder reaction.
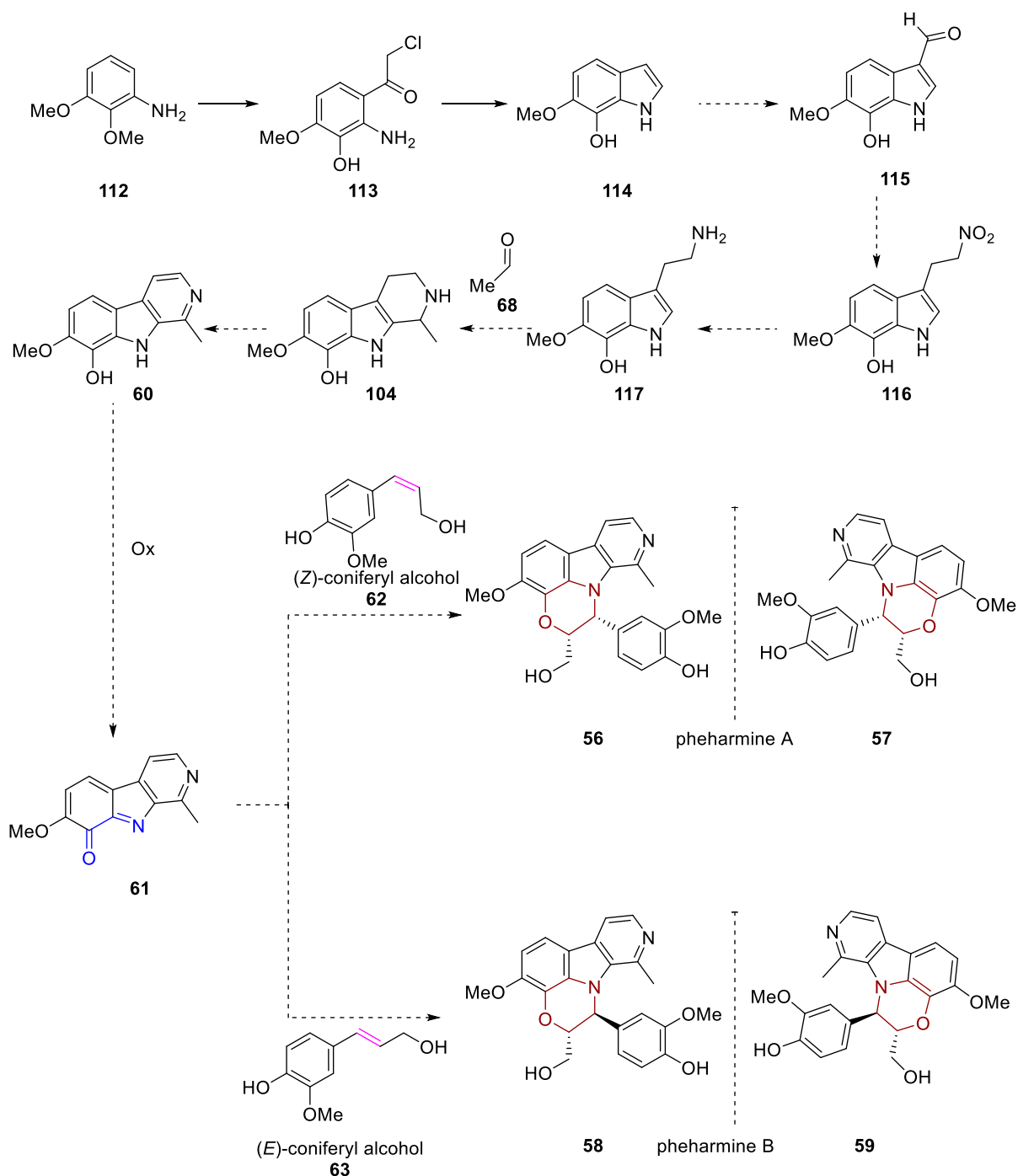
Scheme 26. Third generation synthetic approach to pheharmines (**56**-**59**).

2.3.1 Synthesis of 6-methoxy-indol-7-ol (114)

2.3.1.1 Sugasawa reaction

Discovered in 1978, The sugasawa reaction is a reliable means to selectively *ortho*-acylated aniline (Scheme 27).[117]
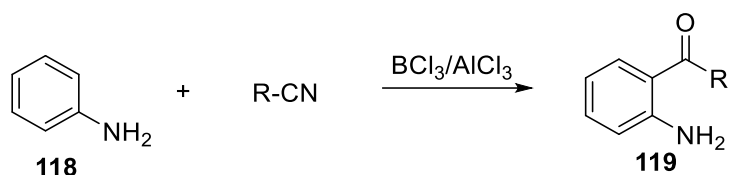
Scheme 27. Sugasawa reaction.

Commercially available 2,3-dimethoxyaniline (**112**) underwent Sugasawa reaction in the presence of excess boron trichloride and chloroacetonitrile in dichloroethane (DCE) gives acylated-aniline (**113**) (Table 5, entry 1). However, the reagents for Sugasawa reaction is quite harsh and expensive. Thus, a different condition was attempted. Decreasing the equivalents of BCl₃ to 1.3 equivalent gave **120** (entry 2). Changing to AlCl₃ give mixtures of **120** and **121** (entry 3). Addition of BCl₃ (110% mol) resulted in **120** (entry 4). Increasing the equivalents of BCl₃ to 2.0 and AlCl₃ to 4.0 gave **113** (entry 5).

Table 5. Sugasawa reaction of 2,3-dimethoxyaniline (**112**) with chloroacetonitrile.
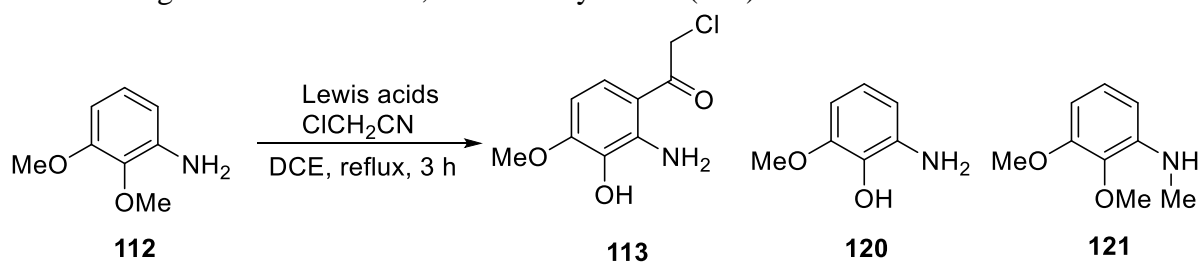
Entry	1 M BCl₃ (equivalent)	AlCl₃ (equivalent)	Temperature (°C)	Time (h)	Outcome
1	4.0	-	80	3	50%[a] (**113**)
2	1.3	-	80	3	30% (**120**)
3	-	1.3	80	1	27% (**120**) 34% (**121**)
4	1.1	1.3	80	3	30% (**120**)

| 5 | 2.0 | 4.0 | 80 | 3 | 58%[a] (**113**) |

All reactions are carried out in DCE. Reactions solvents thoroughly dried and degassed.
[a]Product were not separable, thus it was separate in the later step.

The mechanism of Sugasawa reaction begins with boron trichloride reacting with aniline to give Lewis acid-base complex **I**, followed by addition of chloroacetonitrile and aluminium trichloride causing $HAlCl_4$ to leave resulting in the key C-C bond formation between C6 and chloroacetonitrile to give **II**. Deprotonation results in the formation of **III** that upon addition of water gives acylated-aniline (**113**) (Scheme 28).
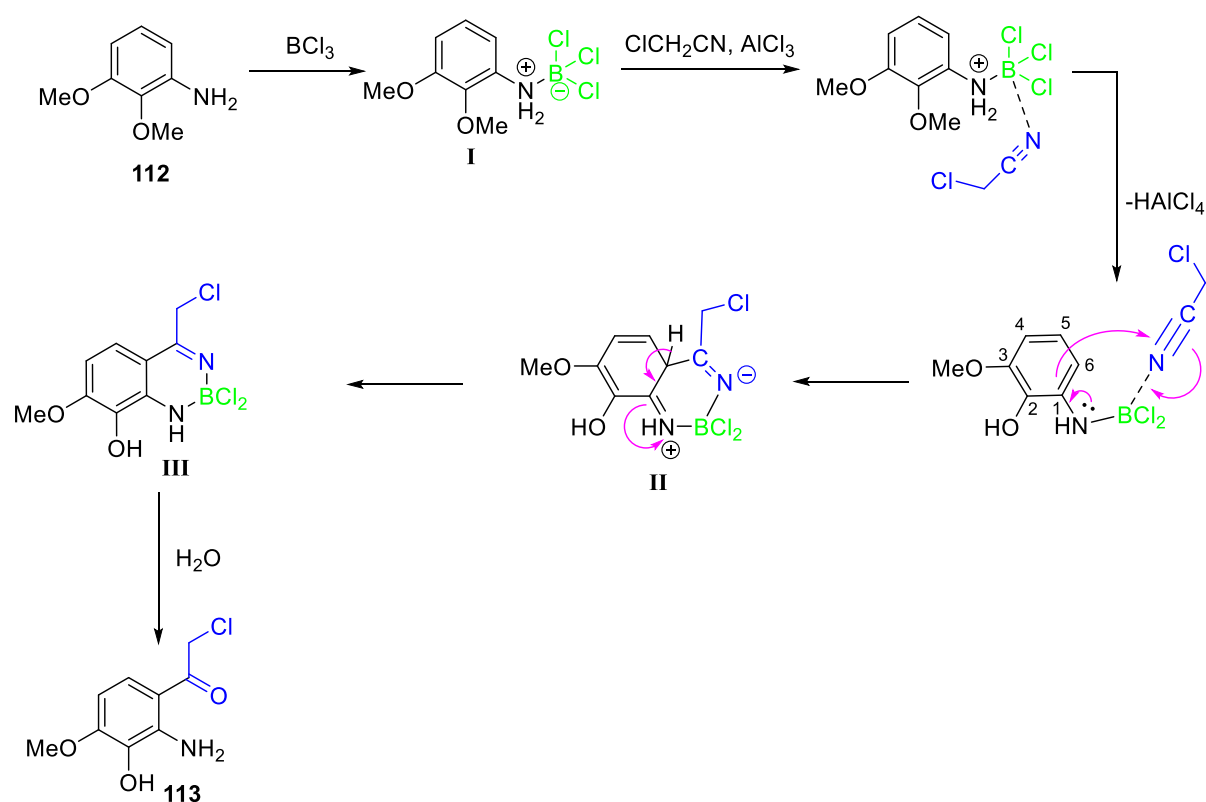
Scheme 28. Mechanism of the Sugasawa reaction for synthesis of acylated-aniline (**113**).

2.3.1.2   1,2-Aryl arrangement

With acylated-aniline (**113**) in hand, the next step was pursued. Acylated-aniline (**113**) underwent 1,2-aryl arrangement in the presence of sodium borohydride in 1,4-dioxane to give 6-methoxy-indol-7-ol (**114**) (Scheme 29).
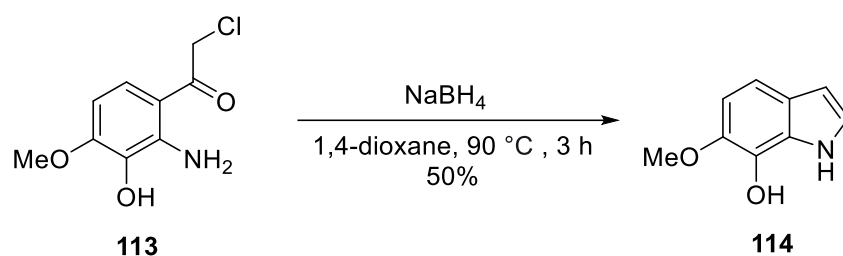
Scheme 29. Synthesis of 6-methoxy-indol-7-ol (**114**).

The mechanism of 1,2-aryl migration reactions begins with protonation of the carbonyl to form the intermediate **I**, followed by a facile [1,2]-aryl rearrangement to form ketone **II**,[118] ring-closure and dehydration to form 6-methoxy-indol-7-ol (**114**) (Scheme 30).

1,2-aryl migration
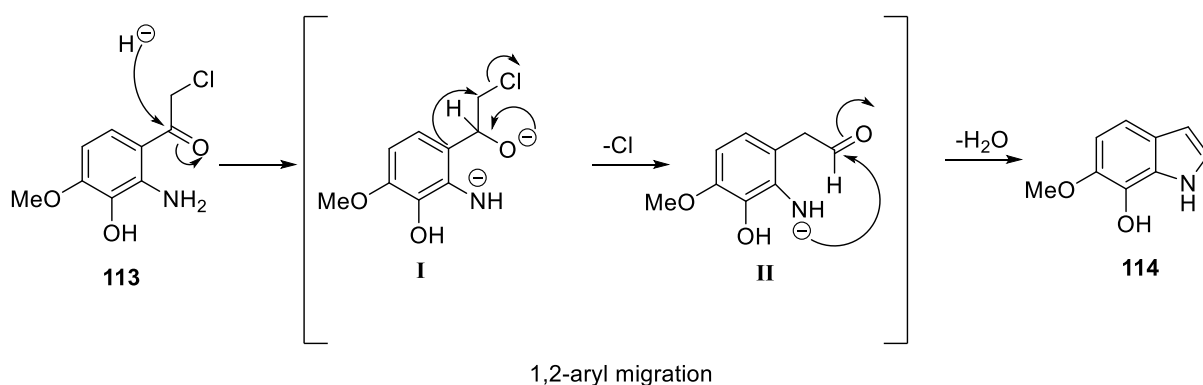
Scheme 30. Mechanism of the 6-methoxy-indol-7-ol (**114**).

2.3.2 Attempted formylation of 114

With 6-methoxy-indol-7-ol (**114**) in hand, it was subjected to Vilsmeier-Haack reaction. Using POCl$_3$ and DMF as the solvent was common;[78, 80] therefore, that became the starting point for attempts shown in Table 6. No reaction occurred when using POCl$_3$ and DMF (entry 1). The catalyst was allowed to stir for 1 h before 6-methoxy-indol-7-ol (**114**) was added leading to no reaction (entry 2). Increasing the temperature to 50 °C resulted in degradation (entry 3). Increasing the equivalents of POCl$_3$ led to degradation (entry 4). Decreasing the equivalents of POCl$_3$ and changing solvent to dimethyl sulfoxide (DMSO) resulted in degradation (entry 5).

Table 6. Attempted Vilsmeier-Haack reaction of 6-methoxy-indol-7-ol (**114**).
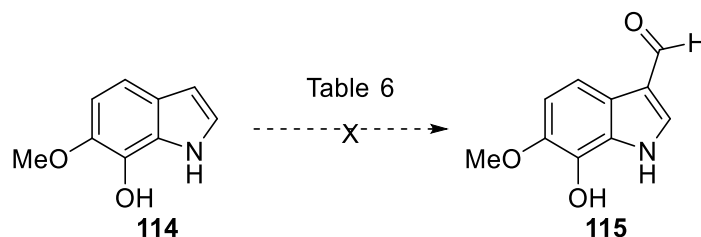
Entry	POCl$_3$ (equivalent)	Solvent	Temperature (°C)	Time (h)	Outcome
1	1.2	DMF	RT	20	NR
2[a]	1.2	DMF	RT	20	NR
3	1.2	DMF	50	3	Degradation
4	3.0	DMF	RT	2	Degradation
5	1.2	DMSO	50	3	Degradation

All reactions are carried out in a sealed tube in DMF unless specified. Reactions solvents thoroughly dried and degassed. [a]Reaction was to have the catalyst stirred for an hour then starting material was added.

Phillip and colleagues[119] demonstrated that 6,7-dimethoxyindole (**122**) underwent the Vilsmeier Haack reaction using POCl$_3$ and DMF to give 6,7-dimethoxy-indole-carbaldehyde (**123**) (Scheme 31). From this, we can conclude that OH at the C7 position prohibits the formylation from occurring, possibly due to side reaction with the Vilsmeier Haack reagent.
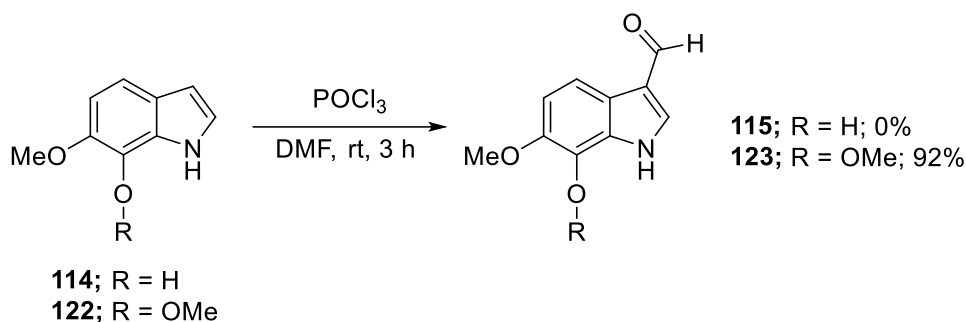
Scheme 31. Formylation of 6,7-dimethoxyindole (**122**) achieved by Phillip and colleagues[119] and attempted formylation of 6-methoxy-indol-7-ol (**114**).

2.3.3   Attempted reductive alkylation of 6-methoxy-indol-7-ol (114)

As we were unable to formylate 6-methoxy-indol-7-ol (**114**), a new strategy was employed. Our research group[120] demonstrated that subjecting 4,6-dibromoindole (**124**) to the acetal (**125**) in the presence of trifluoroacetic acid (TFA) and triethylsilane (Et$_3$SiH) gave 4,6-dibromotryptamine (**126**) (Scheme 32). So, the same conditions became the starting point for the attempt formylation of **114** shown in Table 7. No reaction occurred when using TFA and Et$_3$SiH in DCM (entry 1). Changing the solvent to DCE and heated at 140 ºC also led to no reaction (entry 2).
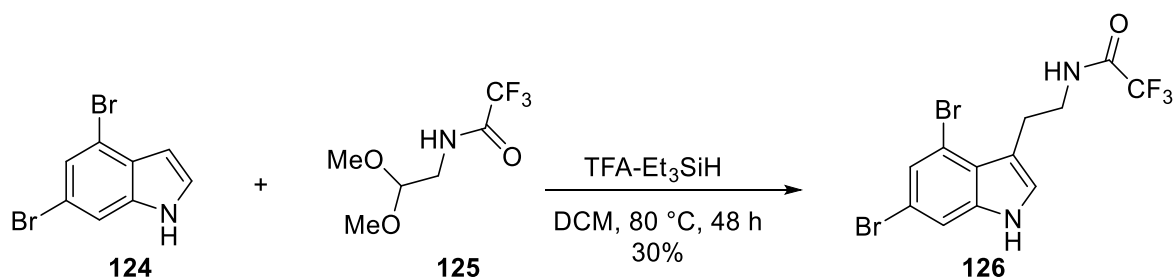
Scheme 32. Reductive alkylation of 4,6-dibromoindole (**124**) achieved by our research group.[120]

Table 7. Attempted reductive alkylation of 6-methoxy-indol-7-ol (**114**).
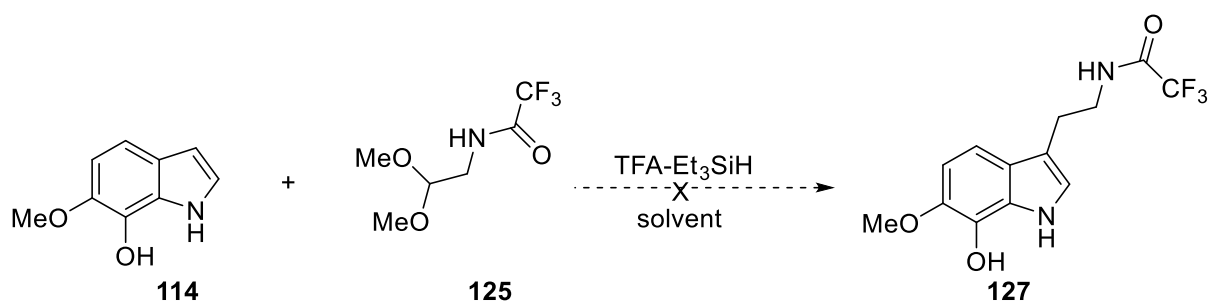
Entry	Solvent	Temperature (°C)	Time (h)	Outcome
1	DCM	80	72	NR
2	DCE	140	72	NR

All reactions are carried out in a sealed tube. Reactions solvents thoroughly dried and degassed.

Marika and colleagues demonstrated that subjecting C5 or C6 -OMe of indoles (**128** & **130**) to the acetal (**125**) in the presence of trifluoroacetic acid and triethylsilane in DCE as the solvent gave (**129**) and (**131**) (Scheme 33).[121] However, our research group showed that the 7-methoxyindole (**134**) gave an inseparable mixture of two products, tentatively identified by ^{1}H NMR spectroscopy of the crude reaction mixture as 4,6-dibromo-7-methoxy-indoline (**135**) and β-methoxytryptamine (**136**), the latter emanating from the initial alkylation product failing to undergo reduction (Scheme 34). So, we conducted a model study of 2-methyindole (**132**), where it was subjected to identical reductive alkylation conditions; in this instance, the desired 2-methyltryptamine (**133**) was formed (Scheme 33). This suggests that the C7-OH in **114** was preventing a successful outcome, as Karen and colleagues has demonstrated that C7-OMe prevents a successful outcome.[120] Currently, we lack a compelling explanation for this observation. However, it implies that synthesis of 7-hydroxytryptamines using this methodology may not be straightforward.

Scheme 33. Reductive alkylation of various substituents indole with acetal (**125**).
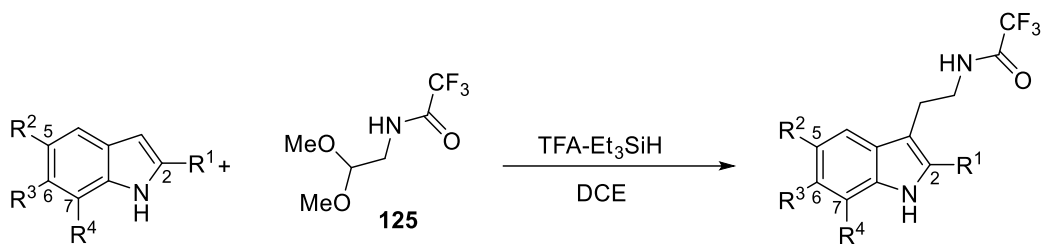
128; R^1 = Me; R^2 = OMe; R^3 = H; R^4 = H
130; R^1 = Ph; R^2 = H; R^3 = OMe; R^4 = H
132; R^1 = Me; R^2 = H; R^3 = H; R^4 = H
114; R^1 = H; R^2 = H; R^3 = OMe; R^4 = OH

129; R^1 = Me; R^2 = OMe; R^3 = H; R^4 = H; 63%
131; R^1 = Ph; R^2 = H; R^3 = OMe; R^4 = H; 43%
133; R^1 = Me; R^2 = H; R^3 = H; R^4 = H; 90%
127; R^1 = H; R^2 = H; R^3 = OMe; R^4 = OH; 0%
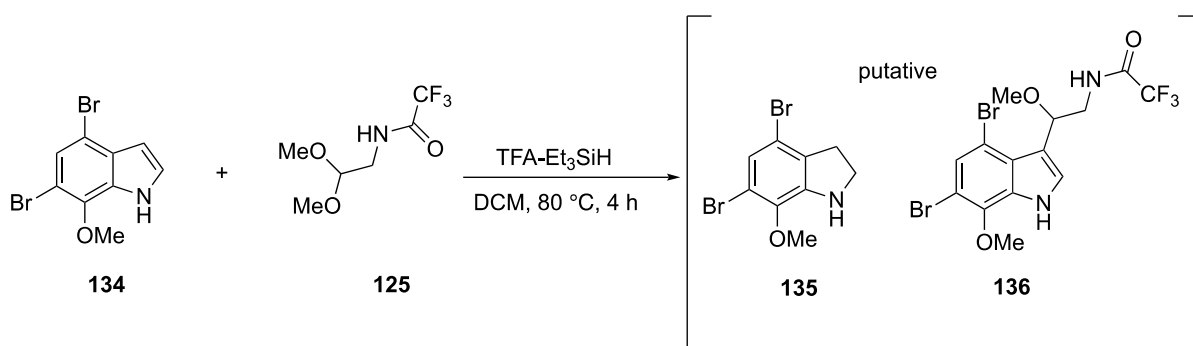
Scheme 34. Attempted reductive alkylation of **134** with acetal (**125**) achieved by our research group.[120]

2.3.4   Protecting the unprotected indole

2.3.4.1   Silylation of 6-methoxy-indol-7-ol (114)

As the unprotected indole did not work in the reactions described previously, a new strategy was employed. Exposing 6-methoxy-indol-7-ol (**114**) to silylation protects the C7-OH of **114** which protects the reactive sites interfering with the reaction. Thus, silylation of 6-methoxy-indol-7-ol (**114**) was attempted. Using imidazole as the organobase catalyzed and dichloromethane or dimethylformamide as the solvent was identified as common for the addition of silicon protecting group.[122-124] Therefore, Consequently, this approach served as the starting point for the attempts shown in Table 8. Addition of *tert*-butylchlorodimethylsilane and imidazole in dichloromethane and heated at 50 °C resulted in no reaction (entry 1). Changing the solvent to DMF and heated at 90 °C also had no reaction (entry 2). Changing the protecting group to chlorotriethylsilane and heated at 90 °C led to no reaction (entry 3).

Changing the protecting group to chlorotriisopropylsilane and heated at 90 °C resulted in degradation (entry 4).

Table 8. Attempted addition of Si-protecting group to 6-methoxy-indol-7-ol (**114**).
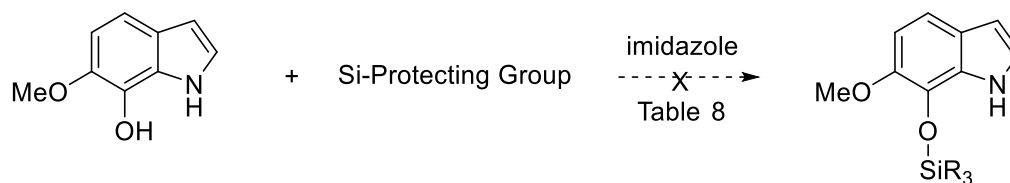
Entry	Protecting group	Solvent	Temperature (°C)	Time (h)	Outcome
1		DCM	50	72	No reaction
2		DMF	90	72	No reaction
3		DMF	90	72	No reaction
4		DMF	90	48	Degradation

All reactions are carried out in a sealed tube. Reactions solvents thoroughly dried and degassed.

Pearson and colleagues demonstrated that the addition *tert*-butylchlorodimethylsilane to 7-hydroxyindole (**137**) in the presence of imidazole as organobase catalyzed and DMF as the solvent gave **138** (Scheme 3t).[125] From this, we can conclude that OMe at the C6 position prohibits the protection from occurring, possibly due to the C6-OMe group exerting steric hindrance.
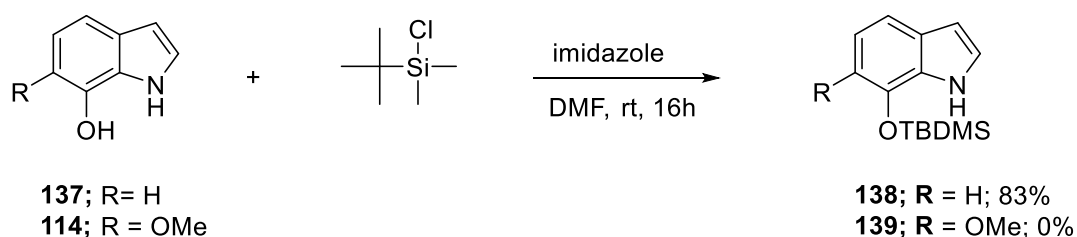
Scheme 35. Si-Protection to give 6-TBDMS-inidole (**137**) achieved by Pearson and colleagues[125] and attempted Si-protection of 6-methoxy-indol-7-ol (**114**).

2.3.4.2 Isopropylation of 6-methoxy-indol-7-ol (**114**)

After unsuccessful silylation, isopropylation was pursued as it is easier to selectively cleave isopropyl ethers compared to methyl due to the carbocation of isopropyl being more stable compared to methyl.[126] Using potassium carbonate as the base and acetone as the solvent was identified as common for the formation of isopropyl ethers.[127] Consequently, this approach served as the starting point for the attempts shown in Table 9. Addition of 2-bromopropane and potassium carbonate in acetone and heated at 50 °C resulted in no reaction (entry 1). Changing the solvent to DMF and heated at 100 °C led to degradation (entry 2).

Table 9. Attempted propylation of 6-methoxy-indol-7-ol (**114**)
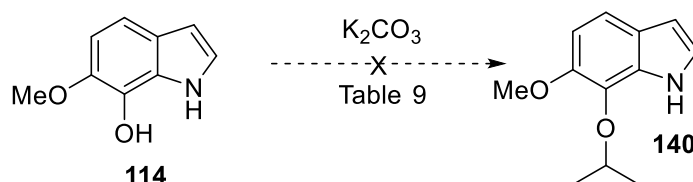
Entry	Protecting Group	Solvent	Temperature (°C)	Time (h)	Outcome
1	2-bromopropane	Acetone	50	72	NR
2	2-bromopropane	DMF	100	72	Degradation

All reactions are carried out in a sealed tube. Reactions solvents thoroughly dried and degassed.

Bringmann and colleagues demonstrated that the addition of 2-iodopropane to 8-hydroxycarbazole (**141**) in the presence of base and acetone as the solvent gave **142** (Scheme 36).[128] From this, we can conclude that OMe at the C6 position of **114** prohibits the protection from occurring, possibly due to the C6-OMe group exerting steric congestion.
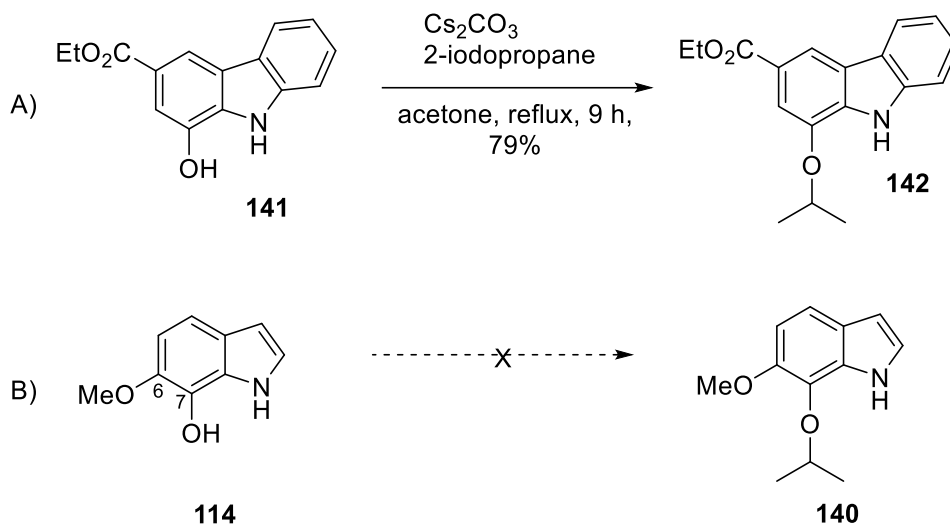

Scheme 36. A) Isoropylation of 7-hydroxycarbazole (**141**) achieved by Bringmann and colleagues;[128] B) Attempted isopropylation of 6-methoxy-indol-7-ol (**114**).

2.4   Conclusion

This thesis describes the synthetic of *P. harmala* derived alkaloid pheharmines (**56**-**59**), focused on validating the proposed biosynthesis by unusual hetero-Diels-Alder reactions occurring between diene (**61**) (*o*-quinone imine) and dienophiles (**62 or 63**) to give pheharmines (**56**-**59**) (Scheme 37). However, upon subjecting *N*-pyrimidylcarboline (**73**) to C-H oxidation the key precursor for the desired biomimetic Diels-Alder reaction, it was unsuccessful due to the presence C7-OMe group exerting steric congestion to neighboring the reactive site.
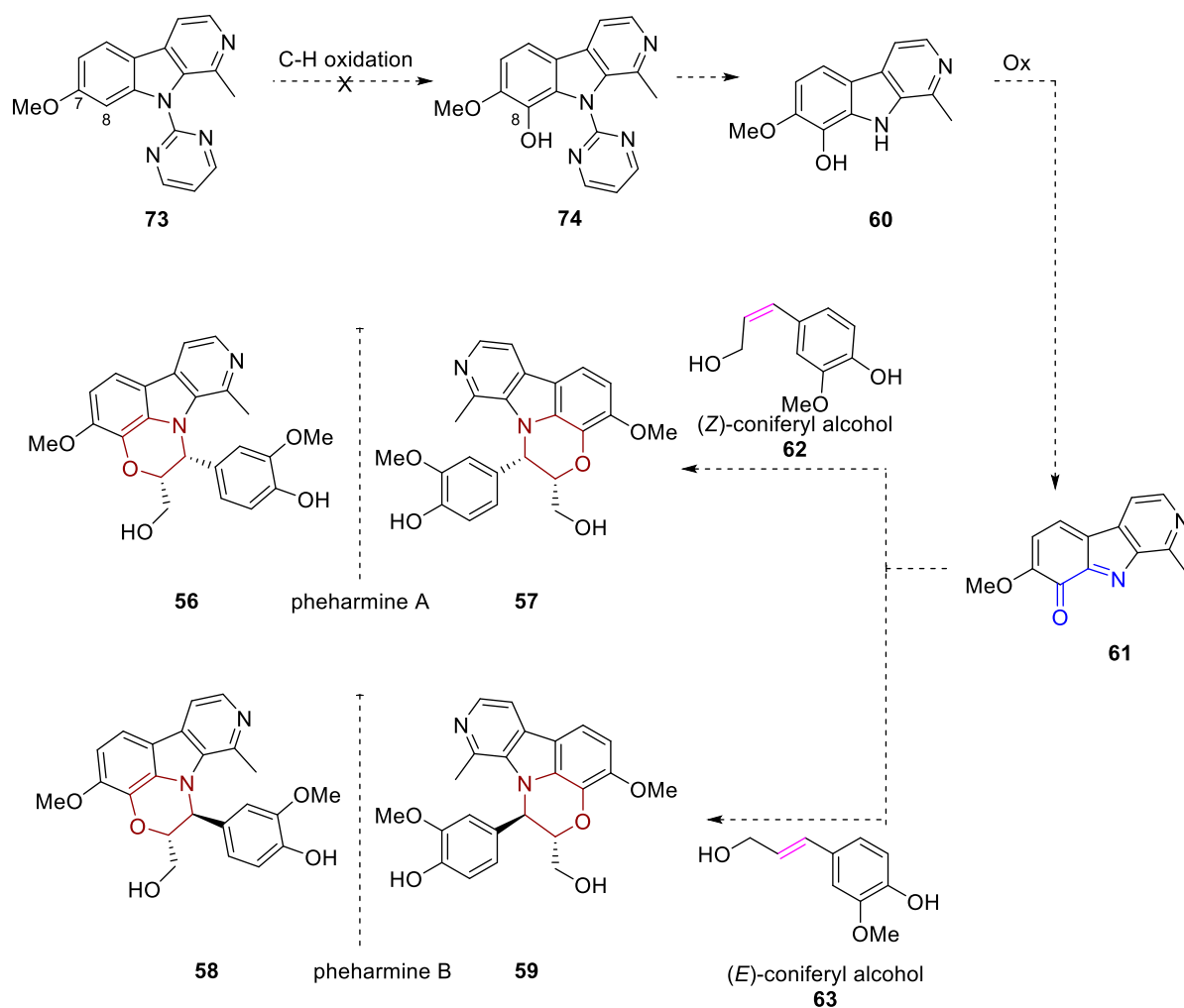
Scheme 37. Attempted C-H oxidation of **73** to achieve the precursor of pheharmine.

A second-generation approach attempted to C-H borylation of the *N*-Boc tetrahydro-β-carboline (**101**) (Scheme 38). However, the reaction failed because of the presence C7-OMe in **101**, which decreased the acidity of C8-H and increased steric congestion and that impacted the C-H borylation. Installing OH or OMe at a later stage was not possible in our hands.
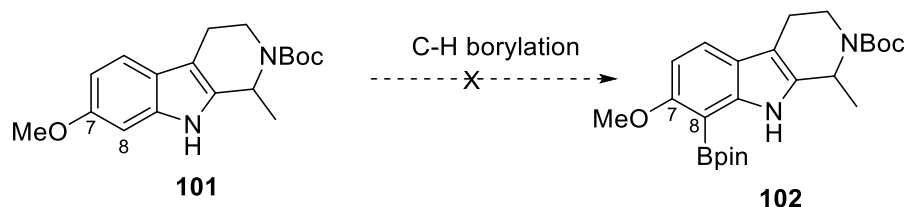
Scheme 38. Attempted C-H borylation on *N*-Boc tetrahydro-β-carboline (**101**)

A third-generation approach was to install the OH at an early stage of the synthesis. However, the formylation of 6-methoxy-indol-7-ol (**114**) failed due to the presence of OH at the C7 position prohibiting formylation to occur, possibly due to side reaction with the Vilsmeier Haack reagent (Scheme 39). Thus. A new strategy was employed by reductive alkylation of 6-methoxy-indol-7-ol (**114**) with acetal (**125**) in the presence of trifluoroacetic acid (TFA) and triethylsilane (Et₃SiH). However, the reaction was unsuccessful due to the C7-OH in **114** preventing a successful outcome. Currently, we lack a compelling explanation for this observation.
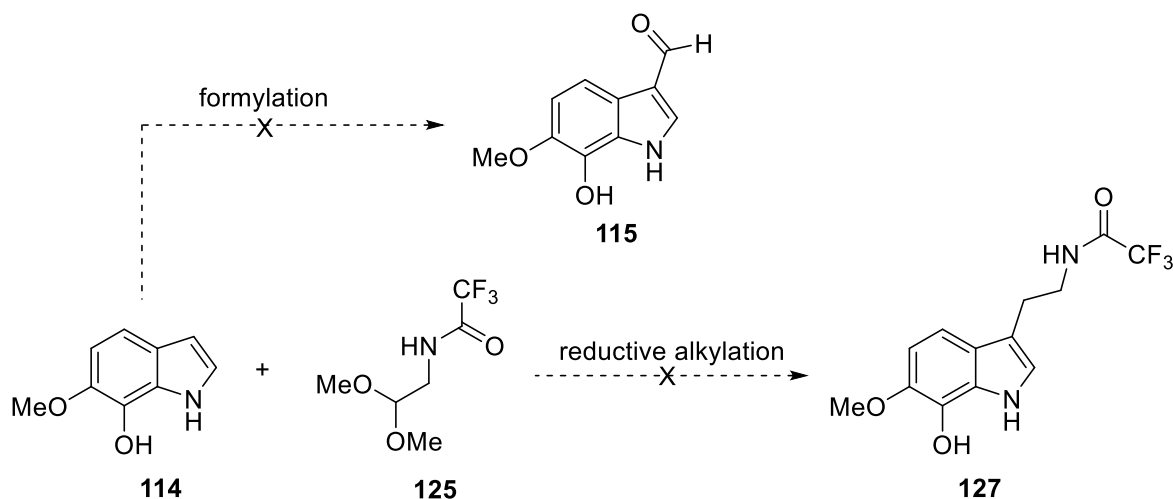
Scheme 39. Attempted formylation and reductive alkylation of 6-methoxy-indol-7-ol (**114**)

Unprotected OH of 6-methoxy-indol-7-ol (**114**) prohibited formylation from occurring. Thus, protection of OH was attempted *via* silylation and isopropylation. However, the presence of

C6-OMe of **114** prohibits the protection from occurring, due to the C6-OMe group exerting steric congestion neighboring the reactive site.
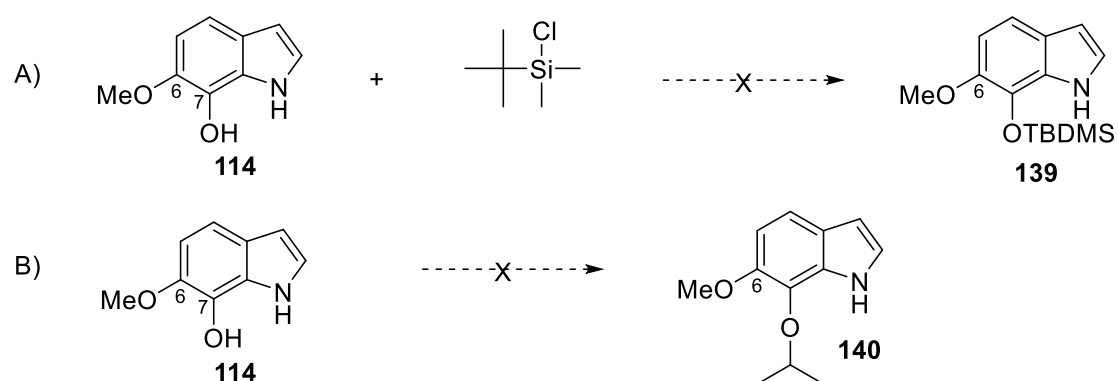
Scheme 40 Attempted a) silylation and b) isopropylation of C7-OH 6-methoxy-indol-7-ol (**114**).

Due to time restrictions, the Diels-Alder reaction was not able to be attempted as we were not able to obtain the key 8-hydroharmine (**60**) precursors.

2.5   Future work

Future work will focus on isopropylation of the C7-OH of 6-methoxy-indol-7-ol (**114**) with 2-iodopropane to give **140,** as this will likely work since iodine is a better leaving group than bromine as demonstrated in **Section 2.1.5.2**. Formylation of **140** will give isopropylcarbaldehyde (**143**), that upon Henry reaction will deliver isopropylnitrolvinylindole (**144**). Reduction of **144** will give isopropyltryptamine (**145**), that upon Pictet-Spengler reaction with ethanal (**68**) will form **146.** Dehydrogenation and selective dealkylation will give 8-hydroxyharmine (**60**), the key precursor for the desired biomimetic Diels-Alder reaction (Scheme 41).
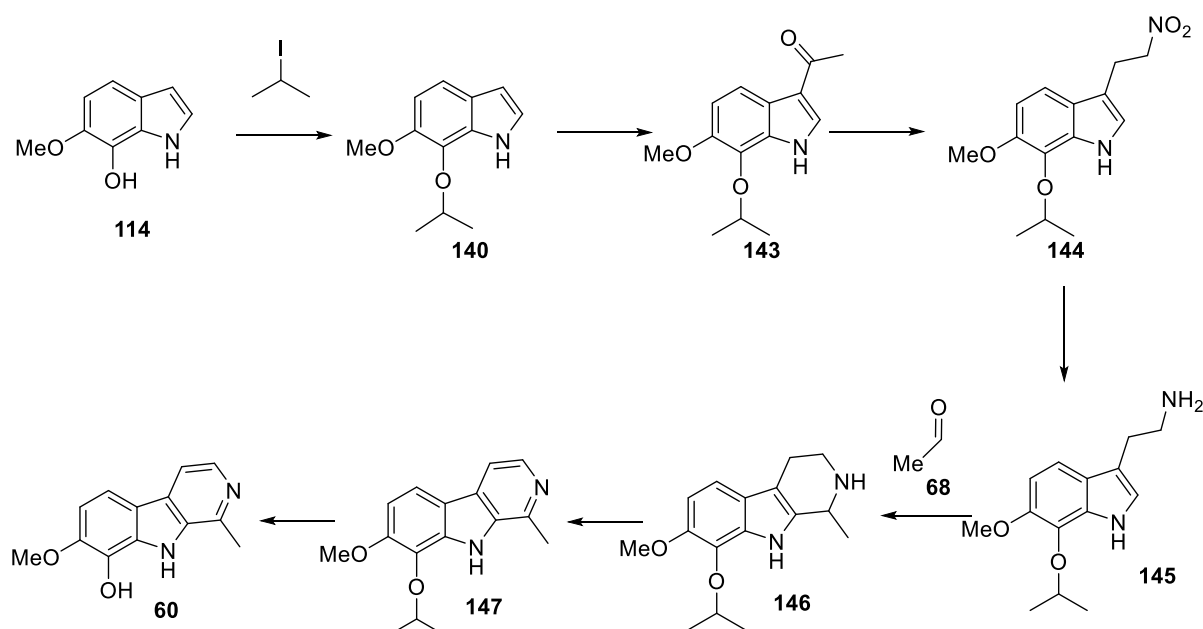
Scheme 41. Proposed pathway toward the key precursor 8-hydroxyharmine (**60**)

In the event of unsuccessful formylation of the protected-6-methoxy-indol-7-ol (**114**), another approach could be to perform C-H silylation onto the C7 position of the 6-methoxyindole (**64**), that upon oxidation would give 8-hydroxyharmine (**60**) (Scheme 42).
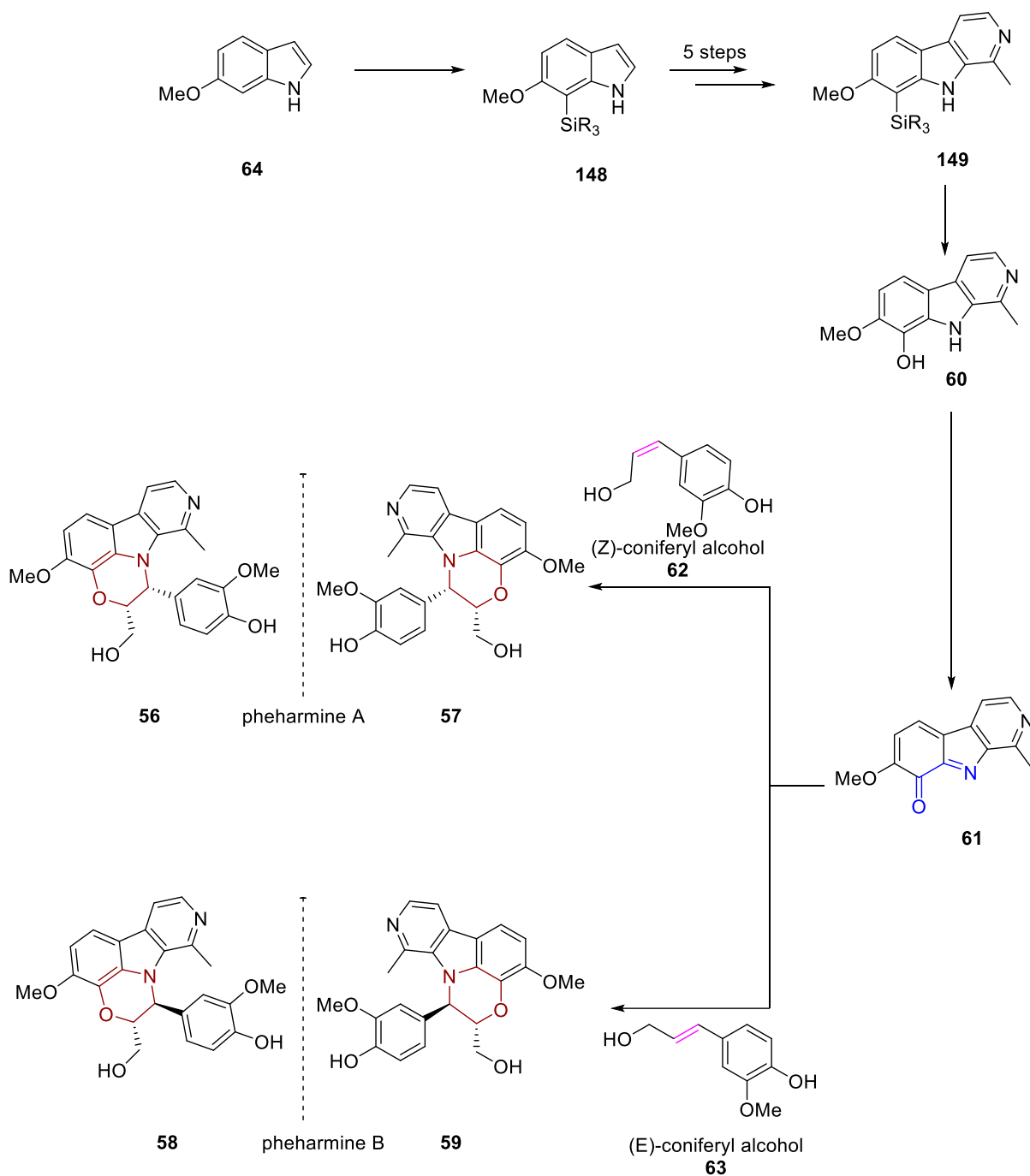
Scheme 42. Proposed pathway toward 8-hydroxyharmine (**60**) *via* C-Si as C-OH precursors.

Another alternative would be to perform a reductive alkylation with acetal (**125**) similar to **section 2.3.3** to give **151**, upon that reduction to give silyated-tryptamine (**152**), which can undergo Pictet-Spengler reaction to give **153**, upon that dehydrogenation of **153** to give **154**, oxidation of Si-protected-harmine (**154**) to give the key precursor 8-hydroxyharmine (**60**) for the desired biomimetic Diels-Alder reaction (Scheme 43).
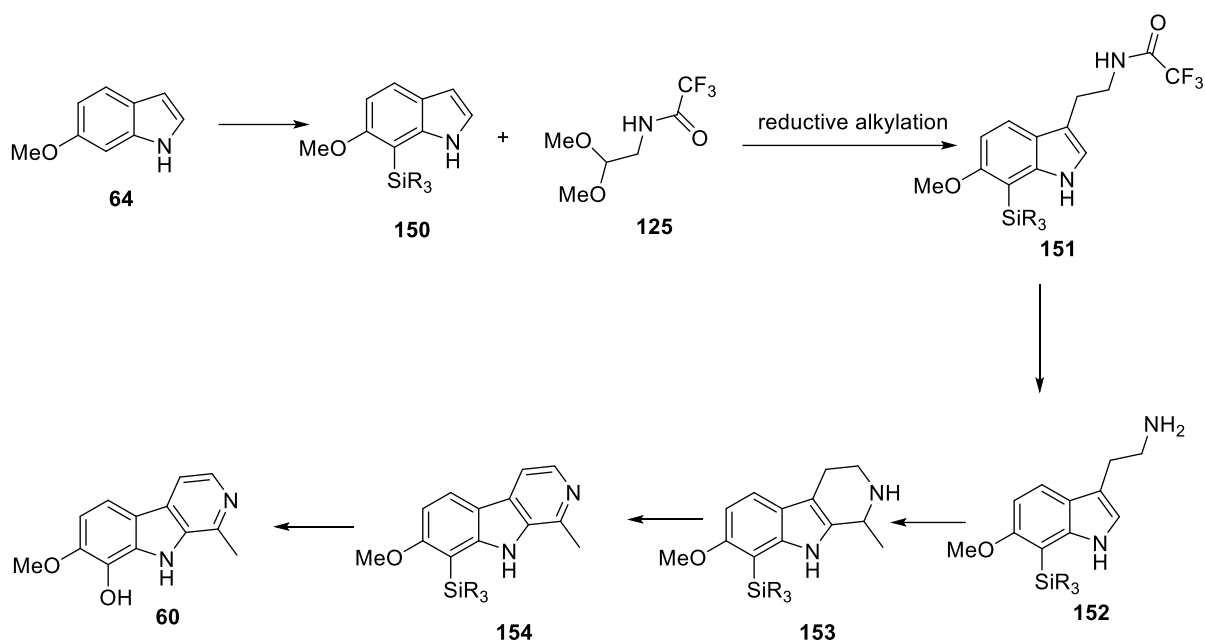
Scheme 43. Another proposed alternative route *via* reductive alkylation.

After obtaining *o*-quinone imine (**61**), then hetero-Diels-Alder reaction could be attempted would be to explore what conditions were used during the extraction of natural products – extraction of the crude alkaloids from the plant material was under both acidic conditions (acidifying with hydrochloric acid) and basic conditions (basifying with sodium hydroxide).

Chapter Three:

Experimental Procedures

General Experimental

Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were also supplied. Tetrahydrofuran, diethyl ether, acetonitrile, dichloromethane, toluene were dried using an LC technology Solutions Inc. SP-1 solvent purification system under an atmosphere of dry nitrogen. Ether refers to diethyl ether. All reactions were routinely carried out in an oven-dried glassware under a nitrogen atmosphere unless otherwise stated.

Low resolution mass spectra were recorded on a Bruker microOTOFQII *Bruker Daltonics, Bremen, Germany). Samples were diluted to 1-10 μg/mL and were introduced using either direct infusion at 180 μL/hr or *via* flow injection with a carrier flow at 0.1 mL/min (50/50 acetonitrile/water + 0.1% formic acid) into Esi source in positive mode. The capillary voltage was – 4500 V, employing dry gas of 99% N_2 at 180 °C, 5 L/min and nebulizer pressure 0.5 bar or infusion or 2 bar for flow injection. Sampling was averaged for 12 mins over a *m/z* range of 50 to 1000 amu. The mass was calibrated using an external calibrant of sodium formate clusters, from 90 to 975 amu, using an Enhanced Quadratic or Enhanced Cubic calibration mode fit. Spectra were processed using Compass Data Analysis Software (version 1.3 Bruker Dalronics, Bremen, Germany).

Pressurized (flash) colum chromatography was carried out with Kieselgel 60 0.063-0.200 mesh (Merck). Analytical thin layer chromatography was done by silica plates, and compounds were visualized at 254 and/or 360 nm ultraviolet irradiation, followed by staining with ethanolic vanillin, molybdenum, alkaline potassium permanganate solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima were expressed in wavenumbers (cm^{-1}). Melting points were recorded with an Electrothermal melting point apparatus.

NMR spectra were recorded on an NMR spectrometer machine operating at 400 MHz for ^{1}H nuclei and 125, 100 and 75 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) and ^{1}H NMR values were referenced to residual chloroform (δ 7.24 ppm), DMSO (δ 2.50 ppm) or methanol (δ 3.31 ppm) peaks. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triolet; q, quartet; m, multiplet), coupling constant (J in Hz) and assignment according to their position. The ^{13}C NMR values were referenced to the residual chloroform (δ 77.1 ppm), DMSO (δ 39.5 ppm) or methanol (δ

49.0 ppm). ^{13}C NMR values are reported as chemical shift δ and assignment according to their position. Assignments are made with the aid of DEPT 90, DEPT 125, COSY, NOESY, HSQC and HMBC experiments. All experiments were conducted at 298 K. Conventional NMR tubes (5 mm diameter, Norell) using a sample volume of 500 μL were used. High resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a micro TOF mass spectrometer. The reaction temperatures were measured using a surface sensor. GC-MS analyses were performed by means of Agilent 7890A GC-FID instrument equipped with Agilent DB-WAXETR 15 m x 250 μm x 0.25 μm column.

Experimental Procedures

6-Methoxy-1*H*-indole-3-carbaldehyde (**65**)
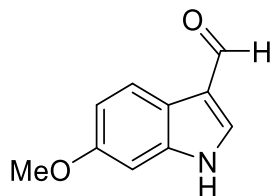
Phosphorous oxychloride (3.5 mL, 37.37 mmol) was added by dropwise to 6-methoxy-1*H*-indole (**64**) (5.0 g, 33.97 mmol) in DMF (45 mL) at 0 °C and the resulting mixture stirred at room temperature for 40 mins. The mixture then basified to pH 14 using 90 mL potassium hydroxide (20% w/w) and stirred for another 2 hours at 50 °C. A brown solid precipitation was be observed. Water (300 mL) and ethyl acetate (300 mL) were added and layers can be observed. The organic phase was washed further brine (2 x 300 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the *title compound* (5.8 g, 33.29 mmol, 98%) as a dark red/brown color. δ_H (400 MHz, $CDCl_3$) 11.91 (1 H, brs, NH), 9.86 (1 H, s, CHO), 8.15 (1 H, s, ArH), 7.94 (1 H, d, *J* 8.40, ArH), 6.99 (1 H, d, *J* 2.20, ArH), 6.86 (1 H, dd, *J* 8.86, 2.63, ArH), 3.79 (3 H, s, OMe). NMR data is consistent with that reported.[129]

6-Methoxy-3-(2-nitrovinyl)-1*H*-indole (**66**)
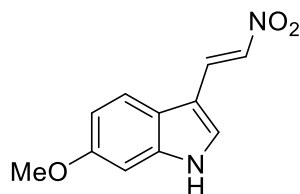
6-Methoxy-1*H*-indole-3-carbaldehyde (**65**) (1.74 g, 9.95 mmol) was added to ammonium acetate (1.25 g, 3.24 mmol) in nitromethane (34.8 mL) and heated at reflux for 30 mins. The resulting mixture was cooled to room temperature before removing nitromethane *in vacuo*. Purification by flash column chromatography on silica gel eluting with light petroleum – ethyl acetate (2:1 to 1:2) to gave *title compound* (2.06 g, 9.78 mmol, 98%) as a red solid. M.p 201.1 – 202.3 ºC; HRMS [ESI, (M + Na)$^+$] found 241.0583, [$C_{11}H_{10}N_2O_3$ + Na]$^+$ requires 241.0588; v_{max}/cm^{-1} (neat): 3273, 3115, 2922, 2843, 1609, 1465, 1293. δ_H (400 MHz, DMSO-d_6) 12.03 (1 H, brs, NH), 8.34 (1 H, d, *J* 13.36, CH), 8.12 (1 H, s, ArH), 7.95 (1 H, d, *J* 13.36, CH), 7.84 (1 H, d, *J* 8.71, ArH), 7.01 (1 H, d, *J* 2.28, ArH), 6.86 (1 H, dd, *J* 8.76, 2.32 , ArH), 3.80 (3 H, s,

OMe). δ_C (400 MHz, DMSO-d_6) 156.8 (C), 138.8 (C), 135.9 (CH), 134.7(CH), 130.8 (CH), 121.3 (CH), 118.4 (C), 111.4 (CH), 108.5 (C), 96.0 (CH), 55.2 (Me).

2-(6-Methoxy-1*H*-indol-3-yl)ethan-1-amine (**67**)
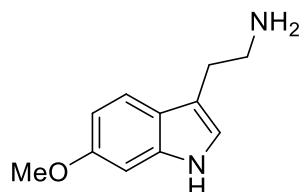
6-Methoxy-3-(2-nitrovinyl)-1*H*-indole (**66**) (398 mg, 1.82 mmol) in anhydrous THF (10.4 mL) was added to LiAlH$_4$ in THF (2.0 M, 4.6 mL) dropwise and heated at 40 °C for to 75 mins. The mixture was allowed to cool to room temperature then cooled further to 0 °C. Excess LiAlH$_4$ was quenched with water at 0 °C and the mixture filtered over Na$_2$SO$_4$, and washed with ethyl acetate. The filtrate was concentrated *in vacuo.* The crude product was purified by flash chromatography using (DCM : MeOH: NH$_3$ = 15 : 1 : 0.1 − 5 : 1 : 0.1) to obtain the *title compound* (260 mg, 1.37 mmol, 75%) as dark brown oil. δ_H (400 MHz, CDCl$_3$) 7.90 (1 H, brs, NH), 7.47 (1 H, d, *J* 8.72, ArH), 6.92 (1 H, d, *J* 1.86, ArH), 6.86 (1 H, d, *J* 2.20, ArH), 6.79 (1 H, dd, *J* 8.64 & 2.28, ArH), 3.85 (3 H, s, Me), 3.02 (2 H, t, *J* 6.60, CH$_2$), 2.87 (2 H, t, *J* 6.62, CH$_2$). NMR data is consistent with that reported.[130]

7-Methoxy-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**69**)
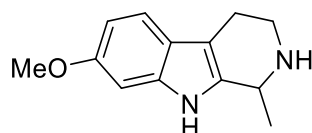
2-(6-Methoxy-1*H*-indol-3-yl)ethan-1-amine (**67**) (400 mg, 2.10 mmol) and MeCHO (0.186 mL, 2.52 mmol) was added into a shared solution of AcOH/MeOH (10:1). The mixture was heated to 80 °C for 1 hour, then cooled to room temperature. NH$_3$.H$_2$O was added until the pH reached 9-10 and, the whole extracted with DCM (15 mL). The organic phase was washed with brine (2 x 20 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography on silica gel eluting with dichloromethane : methanol : ammonia (5: 1 : 0.1) provided the *title compound* (**69**) (355 mg, 1.64 mmol, 78%) as a light brown solid. δ_H (400 MHz, CDCl$_3$) 7.61 (1 H, brs, NH), 7.35 (1 H, d, *J* 8.56, ArH), 6.85 (1 H, d *J* 2.16, ArH), 6.77 (1 H, dd *J* 8.56, 2.36, ArH), 4.17–4.19 (1 H, m, CHCH$_3$), 3.84 (3 H, s, OMe), 3.37-3.33 (1 H,

m, CH$_2$CH$_2$), 3.07-3.00 (1 H, m, CH$_2$CH$_2$), 2.74-2.67 (2 H, m, CH$_2$CH$_2$), 1.65 (1 H, brs, NH), 1.44 (3 H, d *J* 6.74, Me). NMR data is consistent with that reported.[81]

7-Methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (**23**)
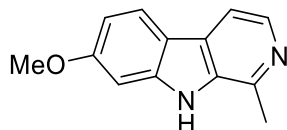
7-methoxy-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**69**) (200   mg, 0.93 mmol) and Pd/C (100 mg, 50% w/w) in xylene (8 mL) was heated at 140 °C for 24 hours and cooled to room temperature. The mixture was filtered through a bed of celite and the cake washed with methanol (3 x 30 mL), and the filtrate concentrated *in vacuo.* Purification by flash column chromatography on silica gel eluting with DCM : MeOH (10 : 1 to 5 : 1) provided the *title compound* (200 mg, 0.96 mmol, 99%) as a sandy-brown solid. δ$_H$ (400 MHz, CDCl$_3$) 8.32 (1 H, d, *J* 5.32, ArH), 8.13 (1 H, brs, NH), 7.96 (1 H, d, *J* 8.72, ArH), 7.71 (1 H, d, *J* 5.28, ArH), 6.97 (1 H, d, *J* 2.20, ArH), 6.91 (1 H, dd *J* 8.71 & 2.40, ArH), 3.92 (3 H, s, OMe), 2.80 (3 H, s, Me). NMR data is consistent with that reported.[131]

7-Methoxy-1-methyl-9-(pyrimidin-2-yl)-9*H*-pyrido[3,4-*b*]indole (**73**)
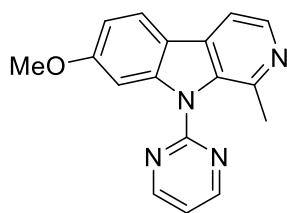
7-Methoxy-1-methyl-9H-pyrido[3,4-*b*]indole (**23**) (200 mg, 0.93 mmol) and cesium carbonate (614.03 mg, 1.88 mmol) in dry DMF (8 mL) stirred for 1 hour. Copper iodide (17.90 mg, 0.09 mmol), L-proline (21.70 mg, 0.19 mmol) was added into the mixture. Lastly, 2-iodopyrimidine (388 mg, 1.88 mmol) was then added to the mixture and heated under at 130 °C for 48 hours. The reaction mixture was allowed to cool to room temperature before poured in ethyl acetate (50 mL) and water (50 mL) and washed with brine (3 x 50 mL) and dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude material was purified through a plug of silica using EtOAc : MeOH (10:1) to afford the *title compound* (265 mg, 0.91 mmol. 97%) as orange/yellow solid. M.P 133–136 °C. HRMS [ESI, (M + H)$^+$] found 291.1240 [C$_{17}$H$_{14}$N$_4$O + H]$^+$ requires

291.1235; v_{max}/cm^{-1} (neat): 3710, 3681, 2923, 2827, 1630, 1561, 1273. δ_H (400 MHz, CD$_3$OD) 8.98 (2 H, d, J 4.90, ArH), 8.28 (1 H, d, J 5.30, ArH), 8.02 (1 H, d, J 8.63, ArH), 7.86 (1 H, d, J 5.30, ArH), 7.55 (1 H, d, J 2.20, ArH), 7.48 (1 H, t, J 4.90, ArH), 6.98 (1 H, dd J 8.63, 2.20, ArH), 3.85 (3 H, s, OMe), 2.34 (3 H, s, Me); δ_C (400 MHz, CD$_3$OD) 163.2 (C), 160.6 (C), 160.3 (2 X CH), 159.0 (C), 145.1 (C), 144.9 (C), 141.3 (CH), 134.0 (C), 123.4 (CH), 117.6 (C), 113.2 (CH), 112.7 (CH), 97.6 (CH), 56.1 (OMe), 23.9 (Me).

1-(7-Methoxy-1-methyl-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)-2,2-dimethylpropan-1-one (**101**)
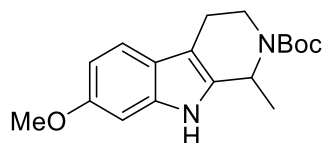
7-Methoxy-1-methyl-9H-pyrido[3,4-b]indole (**69**) (200 mg, 0.93 mmol) in ethyl acetate (3.8 mL) was added. Saturated aqueous sodium bicarbonate (1.9 mL) was added, followed by Boc$_2$ (241 mg, 1.10 mmol). The mixture was stirred at room temp for 15 mins and was extracted AcOEt (3 x 50 mL) and the combined organic phases were washed with water (2 x 20 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo.* Purification by flash column chromatography on silica gel eluting with petroleum ether : ethyl acetate (3 : 1) provided the *title compound* (248 mg, 0.83 mmol, 90%) as a clear liquid oil. HRMS [ESI, (M + K)$^+$] found 339.1469 [C$_{18}$H$_{24}$N$_2$O$_2$ + K]$^+$ requires 339.1464; v_{max}/cm^{-1} (neat): 3284, 2976, 1660, 1419, 1326, 1156. δ_H (400 MHz, CD$_3$OD) 7.23 (1 H, d, J 8.56, ArH), 6.83 (1 H, d, J 2.16, ArH), 6.64 (1 H, dd, J 8.58, 2.18, ArH), 5.18 (1 H, brs, CH), 4.29 (1 H, brs, CH$_2$), 3.78 (3 H, s, OMe), 3.12 (1 H, brs, CH$_2$), 2.71-2.68 (2 H, m, CH$_2$), 1.49 (9 H, s, 3 x Me), 1.45 (3 H, d, J 6.64, Me). δ_C (400 MHz, CD$_3$OD) 157.5 (C), 156.5 (CH), 138.7 (CH), 135.1 (CH), 122.6 (C), 119.2 (CH), 109.5 (CH), 108.1 (CH), 95.8 (CH), 56.0 (CH$_3$), 39.3 (CH$_2$), 22.5 (CH$_2$), 19.6 (CH$_3$).

6-Methoxyindoline (**96**)
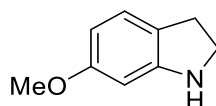
Sodium cyanoborohydride (853.9 mg, 13.59 mmol) was added by portion to 6-methoxy-1*H*-indole (**64**) (1000 mg, 6.79 mmol) in AcOH (20 mL). The mixture stirred at room temperature

for 2 hours and poured into 500 mL of 2 M sodium hydroxide and extracted with chloroform. The combined organic layers were washed with brine (2 x 30 mL), dried over Mg_2SO_4 and concentrated *in vacuo* to result the *title compound* (1002.8 mg, 6.72 mmol, 99%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 6.99 (1 H, d, *J* 2.83, ArH), 6.27-6.24 (2 H, m, ArH), 3.75 (3 H, s, OMe), 3.56 (2 H, t, *J* 7.46, CH_2), 2.96 (2 H, t, *J* 7.46, CH_2). NMR data is consistent with that reported.[132]

6-Methoxy-1-(pyrimidin-2-yl)indoline (**90**)
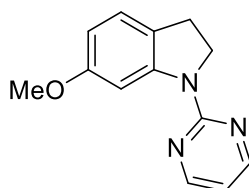
2-Chloropyrimidine was added to 6-methoxyindoline (**64**) (500 mg, 3.35 mmol) in DMSO (10 mL) at room temperature. The mixture was heated at 100 °C for 3 hours. Upon cooling to room temperature, water (3 x 20 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by plug of column chromatography (using 5% ethyl acetate : pet ether) to give the *title compound* (518 mg, 2.28 mmol, 68%) as colourless solid. MP. 58–64 °C. HRMS [ESI, (M + H)$^+$] found 228.1131 [$C_{13}H_{14}N_3O$ + H]$^+$ requires 228.1136 ; v_{max}/cm^{-1} (neat): 2956, 1578, 1458, 1282. δ_H (400 MHz, $CDCl_3$) 8.49 (2 H, d, *J* 4.92, ArH), 8.13 (1 H, d, *J* 2.48, ArH), 7.08 (1 H, d, *J* 2.20, ArH), 6.69 (1 H, t, *J* 4.90, ArH), 6.49 (1 H, dd, *J* 8.26, 2.46, ArH), 4.24 (2 H, t, *J* 8.56, CH_2), 3.84 (3 H, s, OMe), 3.13 (2 H, t, *J* 8.55, CH_2). δ_C (400 MHz, $CDCl_3$) 159.5 (C), 159.3 (C), 157.5 (CH_2), 144.8 (C), 124.4 (C), 111.5 (CH), 106.4 (CH), 102.7 (CH), 55.6 (OMe), 49.6 (CH_2), 26.5 (CH_2).

6-Methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**92**)
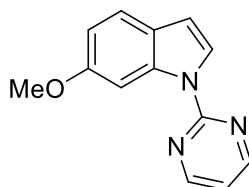
Catalyst was first prepared by combining [Ru(p-cymene)Cl_2]$_2$ (6.74 mg, 0.011 mmol), $AgSBF_6$ (15.12 mg, 0.044 mmol), Ag_2CO_3 (121.33 mg, 0.44 mmol) in DCM (1.5 mL) and the mixture was stirred for 1 min. The catalyst mixture was then added into the 6-methoxy-1-(pyrimidin-

2-yl)indoline (50 mg, 0.22 mmol) in DCM (1.5 mL) and lastly AcOH (0.1 mL) was added. The mixture was then stirred heated at 100 °C for 24 hours. The reaction was cooled to room temperature and filtered over celite pad washed with ethyl acetate (10 mL) and concentrated *in vacuo*. Purification by flash column chromatography on silica gel eluting with petroleum ether : ethyl acetate (10:1) to afford the *title compound* (5 mg, 0.018 mmol, 8%) as dark brown liquid. δ_H (400 MHz, CDCl$_3$) 8.69 (2 H, d, *J* 4.96, ArH), 8.45 (1 H, d, *J* 2.44, ArH), 8.17 (1 H, d, *J* 3.80, ArH), 7.48 (1 H, d, *J* 8.56, ArH), 7.03 (1 H, t, *J* 4.92, ArH), 6.90 (1 H, dd, *J* 8.48, 2.48, ArH), 6.63 (1 H, d, *J* 3.36, ArH), 3.93 (3 H, s, OMe). NMR data is consistent with that reported.[133]

2,3-Dimethoxy-*N*-methylaniline (**121**)
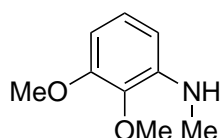
Aluminium trichloride (283 mg, 2.12 mmol) was added into the 2,3-dimethoxyaniline (**122**) (250 mg, 1.63 mmol) in DCE (2.5 mL) at 0 °C. Chloroacetonitrile (0.14 mL, 1.96 mmol) was added. The mixture was heated at refluxed for 1 hour and allowed to cool to room temperature before dropping to 0 °C. Phosphate buffer (18 g/L NaH$_2$PO4, 72 g/L NaHPO$_4$) was slowly added to the mixture and extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with the phosphate buffer (2 x 30 mL), brine (2 x 30 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified through a plug of silica gel with ethyl acetate/cyclohexane (1 : 4) to give the *title compound* (85 mg, 0.61 mmol, 34%) as a brown oil. δ_H (400 MHz, CDCl$_3$) 6.97 (1 H, t, *J* 7.35, ArH), 6.36-6.33 (2 H, m, ArH), 3.86 (3 H, s, OMe), 3.82 (3 H, s, OMe), 2.86 (3 H, s, Me). NMR data is consistent with that reported.[134]

1-(2-Amino-3-hydroxy-4-methoxyphenyl)-2-chloroethan-1-one (**113**)
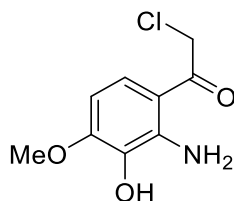
2,3-Dimethoxyaniline (**122**) (1.0 g, 6.5 mmol) in DCE (10 mL) was added dropwise to 1 M BCl$_3$ in DCM (13 mL, 13 mmol) and AlCl$_3$ (3.5 g, 26 mmol) at 0 °C. Subsequently, chloroacetonitrile (8 mL, 8.5 mmol) was added. The mixture was heated at refluxed for 2 hours and ice-cold phosphate buffer (18 g/L NaH$_2$PO4, 72g/L NaHPO$_4$) was slowly added to the mixture and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with phosphate buffer (2 x 100 mL), brine (2 x 100 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified through a plug of silica gel with ethyl acetate/pet ether (3:7) to give the *title compound* (815.8 mg, 3.77 mmol, 58%) as yellow/orange solid. δ$_H$ (400 MHz, CDCl$_3$) 12.20 (1 H, brs, NH), 7.24 (1 H, d, *J* 8.64, ArH), 6.31 (1 H, d, *J* 9.20, ArH), 5.38 (1 H, brs, OH), 4.61 (2 H, s, CH$_2$), 3.92 (3 H, s, OMe). NMR data is consistent with that reported.[135]

6-Methoxy-1*H*-indol-7-ol (**114**)
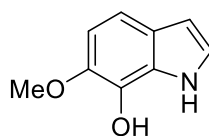
NaBH$_4$ (52.6 mg, 1.39 mmol) was added to crude 1-(2-amino-3-hydroxy-4-methoxyphenyl)-2-chloroethan-1-one (**113**) (200.0 mg, 0.93 mmol) in dioxane (10 mL) and water (1 mL) at 0 °C. The mixture was heated at 90 °C for 3 hours and then cooled to room temperature and concentrated *in vacuo*. 1 M HCL (100 mL) was added and the mixture was extracted with DCM. The aqueous layer was separated and extracted with DCM. The combined organic phases were washed with 1M HCl (2 x 50 mL), brine (2 x 30 mL), dried over sodium sulfate and concentrated *in vacuo* to give the *title compound* (69.8 mg, 0.47 mmol, 50%) as yellow oil. δ$_H$ (400 MHz, CDCl$_3$) 8.24 (1 H, brs, NH), 7.14 (2 H, m, ArH), 6.84 (1 H, d, *J* 8.52, ArH), 6.47 (1 H, m, ArH), 5.68 (1 H, brs, OH), 3.93 (3 H, s, OMe). NMR data is consistent with that reported.[135]

2,2,2-Trifluoro-*N*-(2-(2-methyl-1*H*-indol-3-yl)ethyl)acetamide (**133**)
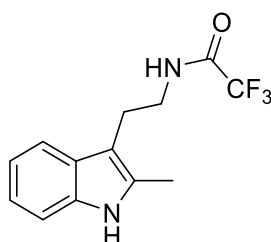
2-Methyl-1*H*-indole (80 mg, 0.61 mmol) and acetal (**125**) (137 mg, 0.67 mmol) in DCM (1 mL) was added to a solution of TFA (0.26 mL, 3.1 mmol) and Et$_3$SiH (0.3 mL, 1.86 mmol in DCM (1 mL) that was stirred at room temperature for 10 minutes. The mixture was stirred for 3 hours. The mixture was allowed to cool to room temperature and cooled down to 0 °C before NaHCO$_3$ (25 mL) was added and extracted with DCM (3 x 25 mL). The organic phase mixture was washed with NaHCO$_3$ (25 mL), brine (2 x 25 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by a plug of silica gel with ethyl acetate/pet ether (10:1) to give *title compound* (148 mg, 0.55 mmol, 90%) as yellow solid. δ$_H$ (400 MHz, CDCl$_3$) 8.04 (1 H, brs, NH), 7.46 (1 H, d, *J* 7.6, ArH), 7.27 – 7.23 (1 H, m, ArH), 7.15 – 7.07 (2 H, m, ArH), 6.51 (1 H, brs, NH), 3.58 (2 H, q, *J* 6.50, CH$_2$), 2.96 (1 H, t, *J* 6.74, CH$_2$), 2.33 (3 H, s, Me). NMR data is consistent with that reported.[136]

Chapter Four:

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