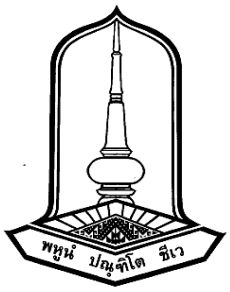

# SYNTHESIS OF INDOLE DERIVATIVES HAVING THIOSEMICARBAZONE, 1,4-DIHYDROPYRIDINE AND IMIDAZOLE FRAMEWORKS

**SUKANYA TONGKHAN**

**A dissertation submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Chemistry atMahasarakham University**

**October 2015**



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**October 2015**

The examining committee has unanimously approved this dissertation, submitted by Miss. Sukanya Tongkhan, as a partial fulfillment of the requirements for the Doctor of Philosophy degree in Chemistry at Mahasarakham University.

Examining Committee

| | |
|---|---|
| S. Saikrasun | |
| (Assoc. Prof. Sunan Saikrasun, Ph.D.) | Chairman (Faculty graduate committee) |
| U. Sakee | |
| (Assoc. Prof. Uthai Sakee, Ph.D.) | Committee (Advisor) |
| S. Kr. | |
| (Senee Kruanetr, Ph.D.) | Committee (Co-advisor) |
| Widchaya Radchatawedchakoon | |
| (Widchaya Radchatawedchakoon, Ph.D.) | Committee (Co-advisor) |
| W. Siriangkhawut | |
| (Watsaka Siriangkhawut, Ph.D.) | Committee (Faculty graduate committee) |
| Chanokbhorn Phaosiri | |
| (Asst. Prof. Chanokbhorn Phaosiri, Ph.D.) | Committee (External expert) |

Mahasarakham University has granted approval to accept this dissertation as a partial fulfillment of the requirements for the Doctor of Philosophy degree in Chemistry.

| | |
|---|---|
| Wichian Magtoon | P Terdtoon |
| (Prof. Wichian Magtoon, Ph.D.) | (Prof. Pradit Terdtoon, Ph.D.) |
| Dean of the Faculty of Science | Dean of Graduate School |
| | October 13, 2015 |

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Sukanya Tongkhan

**ชื่อเรื่อง** การสังเคราะห์อนุพันธ์ของอินโดลที่มีส่วนของไทโอเซมิคาร์บาโซน 1,4-ไดไฮโดรไพริดีน และ อิมิดาโซล
**ผู้วิจัย** นางสาว สุกัญญา ทองขัน
**ปริญญา** ปรัชญาดุษฎีบัณฑิต **สาขาวิชา** เคมี
**กรรมการควบคุม** รองศาสตราจารย์ ดร.อุทัย สาขี
อาจารย์ ดร.วิชญ รัชตเวชกุล
อาจารย์ ดร.เสนีย์ เครือเนตร
**มหาวิทยาลัย** มหาวิทยาลัยมหาสารคาม **ปีที่พิมพ์** 2558

## บทคัดย่อ

สารตั้งต้นอินโดลที่ไม่มีหมู่แทนที่ในตำแหน่งที่ 3 ได้มาจากการสังเคราะห์แบบฟิชเชอร์ระหว่างอนุพันธ์ของอะซีโตฟีโนน และฟีนิลไฮดราซีน และได้มาจากการปิดวงแบบออกซิเดชันของ เอ็น-เอริลอิมีนที่เร่งปฏิกิริยาด้วยด้วย Pd/Cu

อนุพันธ์ของ 3-ฟอร์มิลอินโดลได้มาโดยการเติมหมู่ฟอร์มิลที่มาจากเฮกซะเมทิลลีนเตตระเอมีน (HMTA) และซีริคแอมโมเนียมไนเตรทที่อยู่บนซิลิกาเจล (CAN–$SiO_2$) การใช้รีเอเจนต์ที่อยู่บนของแข็งในปริมาณที่เป็นตัวเร่งปฏิกิริยานี้สามารถใช้ได้กับอินโดลที่มีหมู่แทนที่หลายชนิด ด้วยร้อยละผลิตภัณฑ์ที่สูง ผลิตภัณฑ์ 3-ฟอร์มิลอินโดลนี้ได้นำไปทำปฏิกิริยาต่างๆ ให้อินโดลที่มีหมู่แทนที่ในตำแหน่งที่สาม

3-ฟอร์มิล อินโดลทำปฏิกิริยากับไธโอเซมิคาร์บาไซด์ให้ไธโอเซมิคาร์บาโซนซึ่งได้นำไปทำปฏิกิริยาต่อกับ มาเลอิก แอนไฮไดด์ ให้อนุพันธ์อินโดลิล 4-ออกโซ-3*H*-ไธเอโซลิดีน อะซีติกแอซิด ในร้อยละผลิตภัณฑ์ปานกลางด้วยกระบวนการแบบขั้นตอนเดียว

ปฏิกิริยาของ 3-ฟอร์มิลอินโดลกับ 1,10-ฟีแนนโทรลีน-5,6-ไอโอน หรือ 2,2′-ไดไฮดรอกซีเบนซิลที่มีแอมโมเนียมอะซีเตทเกิดอนุพันธ์อิมิดาโซลในร้อยละผลิตภัณฑ์ปานกลางถึงสูง

ในศึกษาปฏิกิริยาสี่องค์ประกอบของ 3-ฟอร์มิลอินโดล ไดมีโดน มาโลโนไนไตรล์ และแอมโมเนียมอะซีเตทเพื่อให้ได้อนุพันธ์ 1,4-ไดไฮโดรไพริดีน พบว่าไม่พบผลิตภัณฑ์ตามที่ต้องการได้

**คำสำคัญ:** อินโดล; 3-ฟอร์มิลอินโดล; อินโดล-3-คาร์บอกซาลดีไฮด์; ไธโอเซมิคาร์บาโซน; ไธเอโซลิดิโนน; อิมิดาโซล; 1,4-ไดไฮโดรไพริดีน

**TITLE** Synthesis of indole derivatives having thiosemicarbazone, 1,4- dihydropyridine and imidazole frameworks
**CANDIDATE** Miss Sukanya Tongkhan
**DEGREE** Doctor of Philosophy degree in Chemistry
**ADVISORS** Assoc. Prof. Uthai Sakee, Ph.D.
Widchaya Radchatawedchakoon, Ph.D.
Senee Kruanetr, Ph.D.
**UNIVERSITY** Mahasarakham University **YEAR** 2015

## ABSTRACT

The starting materials, 3-unsubstituted indole derivatives were obtained *via* Fischer synthesis between acetophenone derivatives and phenyl hydrazine and Pd/Cu-catalyzed oxidative cyclization of *N*-aryl imine.

3-Formyl indole derivatives were achieved by formylating species generated from hexamethylenetetramine (HMTA) and silica-supported ceric ammonium nitrate (CAN–$SiO_2$). The use of a catalytic amount of this solid-supported reagent was found to be compatible with a range of substituents on the indoles with generating good yields. The 3-formyl indole products were subjected to different reactions affording the 3-substituted indoles.

3-Formyl indoles reacted with thiosemicarbazide to give thiosamicarbazone which were subjected to react with maleic anhydride to give indolyl 4-oxo-3*H*-5–thiazolidine acetic acid derivatives in moderate yield in a one pot process.

The reaction of 3-formyl indoles with 1,10-phenanthroline-5,6-dione or 2,2′-dihydroxybenzil in the presence of ammonium acetate provided imidazole derivatives in moderate to good yield.

The four-component reaction of 3-formyl indole, dimedone, malononitrile and ammonium acetate have evaluated to give the corresponding 1,4-dihydropyridine derivatives. It was found that the desired product was not obtained.

**Keywords:** Indole; 3-Formylindole; Indole-3-carboxaldehyde; Thiosemicarbazone; Thiazolidinone; Imidazole; 1,4-Dihydropyridine

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# LIST OF SCHEMES

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | Acetyl |
| ASA | Alumina sulfuric acid |
| BINAP | 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl |
| [BMIm]$BF_4$ | 1-Butyl-3-methylimidazolium tetrafluoroborate |
| Bu | Butyl |
| CAN | Ceric ammonium nitrate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DCC | *N*,*N*'-Dicyclohexylcarbodiimide |
| DMEDA | *N*,*N'*-Dimethylethylenediamine |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| [Dsim]$HSO_4$ | 1,3-disulfonic acid imidazolium hydrogen sulfate |
| $E^+$ | Electrophile |
| Et | Ethyl |
| H | Hour |
| HMPA | Hexamethylphosphoramide |
| HMTA | Hexamethylenetetramine |
| HOMO | Highest occupied molecular orbital |
| HRMS | High resolution mass spectra |
| LDA | Lithium diisopropylamide |
| LSD | Lysergic acid diethylmide |
| Me | Methyl |
| MW | Microwave irradiation |
| MS 4Aº | Molecular Sieves 4Aº |
| NBS | *N*-Bromosuccinimide |
| PivOH | Pivalic acid or Dimethylpropanoic acid |
| PPA | Polyphosphoric acid |
| *p*-TsOH | Para toluenesulfonic acid |
| rt | Room temperature |

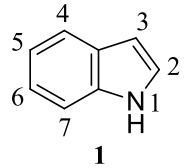
| | |
|---|---|
| SSA | Silica sulfuric acid |
| TBAF | Tetra-n-butylammonium fluoride |
| TBHP | *tert*-Butyl hydroperoxide |
| TBPB | *tert*-Butyl Peroxybenzoate |
| TEBAC | Triethylbenzylammonium chloride |
| TEMPO | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMEDA | Tetramethylethylenediamine |
| TMS | Trimethylsilyl |
| Ts | Tosyl |
| ))) | Sonication |
| $^{1}$H NMR | Proton nuclear magnetic resonance |
| $^{13}$C NMR | Carbon 13 nuclear magnetic resonance |

# CHAPTER 1

# INTRODUCTION

## 1.1 Introduction to indole

Indole ring (1) is a benzopyrrole in which the benzene and pyrrole ring fused through the 2, 3-positions of a five-membered nitrogen-containing pyrrole ring [1]. Analogs based on indole are significant players in a diverse array of markets such as dyes, plastics, agriculture, vitamin supplements, flavor enhancers, perfumery and especially drugs [2]. The significant biological indole nucleus could be obtained from natural and synthetic molecules. Naturally, indole ring system is a core structure of tryptophan that is an essential amino acid and as such a constituent of most protein. It also serves as a biosynthetic precursor for a wide variety of tryptamine- and indole-containing secondary metabolites [3]. Therefore, natural indoles were found in a hugely diverse array of biologically significant compounds, from simple derivatives such as the neurotransmitter serotonin (2), anticancer agent vinblastine (3) and mitomycin C (4) and the antihypertensive alkaloid reserpine (5) (Figure 1.2). Moreover, indole derivatives have a topic of considerable research interest and continue to capture synthetic organic chemist at the fore as pharmacologically active lead compound for drug development. A number of important synthetic drugs contain an indole motif, including sumatriptan (6) and rizatriptan (7) which used for the treatment of migraine, tadalafil (8), is a drug for the treatment of pulmonary arterial hypertension, and fluvastatin (9), treat for hypercholesterolemia and prevent cardiovascular disease (Figure 1.3) [4].




**1**

**Figure 1.1** Structure of indole.

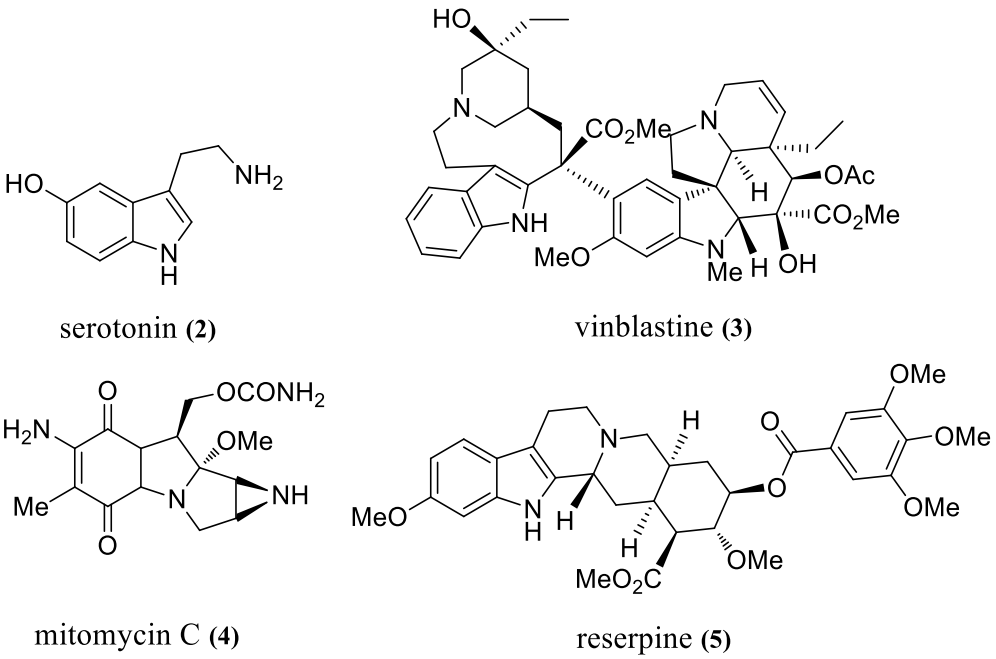



**Figure 1.2** Natural compounds containing an indole moiety.

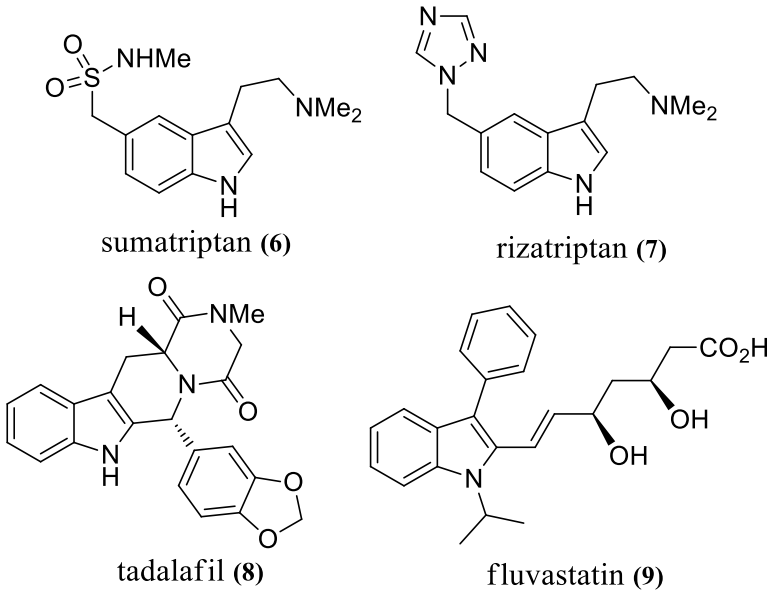



**Figure 1.3** Synthetic drugs containing an indole moiety.

At present, many indole ring-containing marketed drug molecules including natural and unnatural compounds which were widely used in clinical pharmacology and therapy of cancer, leukemia, heart failure, hypertension, depression and psychosis (Table 1.1) [5].

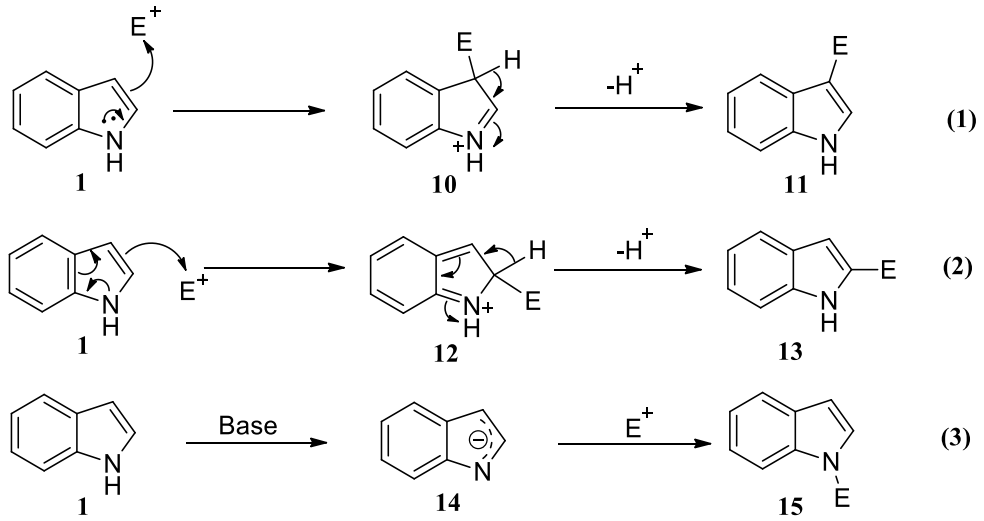
**Table 1.1** Indole ring containing important marketed drug molecules [5].

| Drug | Application | Drug | Application |
|---|---|---|---|
| Vincristine | Anticancer | Reserpine | Antihypertensive |
| Vinblastine | Anticancer | Peridopril | Antihypertensive |
| Vinorelbine | Anticancer | Pindolol | Antihypertensive |
| Vindesine | Anticancer | Indomethacin | Anti-inflammatory |
| Mitraphylline | Anticancer | Zafirlukast | Anti-Asthmatic |
| Cediranib | Anticancer | Panobinostat | Anti-leukamic |
| Apaziquone | Anticancer | Oxypertine | Antipsychotic |
| Tropisetron | Antiemetic | Vincamine | Vasodilator |
| Doleasetron | Antiemetic | Arbidol | Antiviral |
| Delavirdine | Anti-HIV | Yohimbine | Sexual Disorder |
| Atevirdine | Anti-HIV | Bucindolol | β-Blockers |
| Pericine | Opioid agonist | Roxindole | Schizophrenia |
| Mitragynine | Opioid agonist | Oglufanide | Immunomodulatory |
| Indalpine | Antidepressant | Pravadoline | Analgesic |
| Siramesine | Antidepressant | Bufotenidine | Toxin |
| Binedaline | Antidepressant | Proamanullin | Toxin |
| Amedalin | Antidepressant | | |

## 1.2 Fundamental reactivity of indole

Indole is one of the most fascinating compounds and its chemistry had been studied for a century. Since the pyrroles part of indole nucleus is electron rich, nucleophilic reactivity of the 1-3 positions plays the major part of indole chemistry. A basic feature that accounts for this large diffusion in the literature is the spectacular

nucleophilicity of the indolyl core, which is commonly dispatched through the C(3)-position of the pyrrolyl ring (Scheme 1.1, eqn (1)). Moreover, electrophilic replacement at the C(2)-position can occur only if the pyrrole core is electronically isolated (Scheme 1.1, eqn (2)). Finally, hydrogen atom replacement at the N(1)-position allows N-substitution only when the N–H proton of indoles is removed to generate a strong charged nucleophile (Figure 1.1, eqn (3)) [6].




**Scheme 1.1** Electrophilic attacks to indole ring.

### 1.3 3-Formylindole derivatives

3-Formylindoles and their derivatives are important and widely used building blocking of the preparation of biologically active natural products and drugs. For example, 3-formylindoles have been used as a starting materials for the synthesis of cryptosanguinolentine [7], homofascaplysin C [8], FR-9004823 [9], dramacidin [10-12], edudistomin U [13] and indole alkaloids [14-20]. 3-Formylindoles are not only key intermediates for the preparation of biologically active molecules and indole alkaloids but also important precursors for the synthesis of a variety of indole derivatives because they have many active sites to achieve in difference reactions. Their carbonyl groups can facilely undergo C–C and C–N coupling reactions, oxidations and reductions [21].

Moreover, 2-phenylindole-3-carboxaldehydes proved to exert an antimitotic activity in human breast cancer cells by inhibition of tubulin polymerization (Figure 1.4) [22].

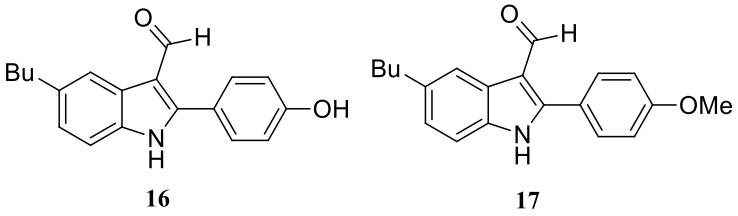



**Figure 1.4** Examples of 2-phenylindole-3-carboxaldehyde derivative with anticancer activity.

Furthermore, several modifications on the 3-formyl group were carried out in order to overcome the in-vivo instability of the aldehyde functional group. These modifications included the formation of oximes, methylamine, propanedinitriles, hydrazones, imidazole, thiosemicarbazone and other derivatives that proved to possess high stability and good antimitotic activity, which show in figure 1.5 [22, 23].

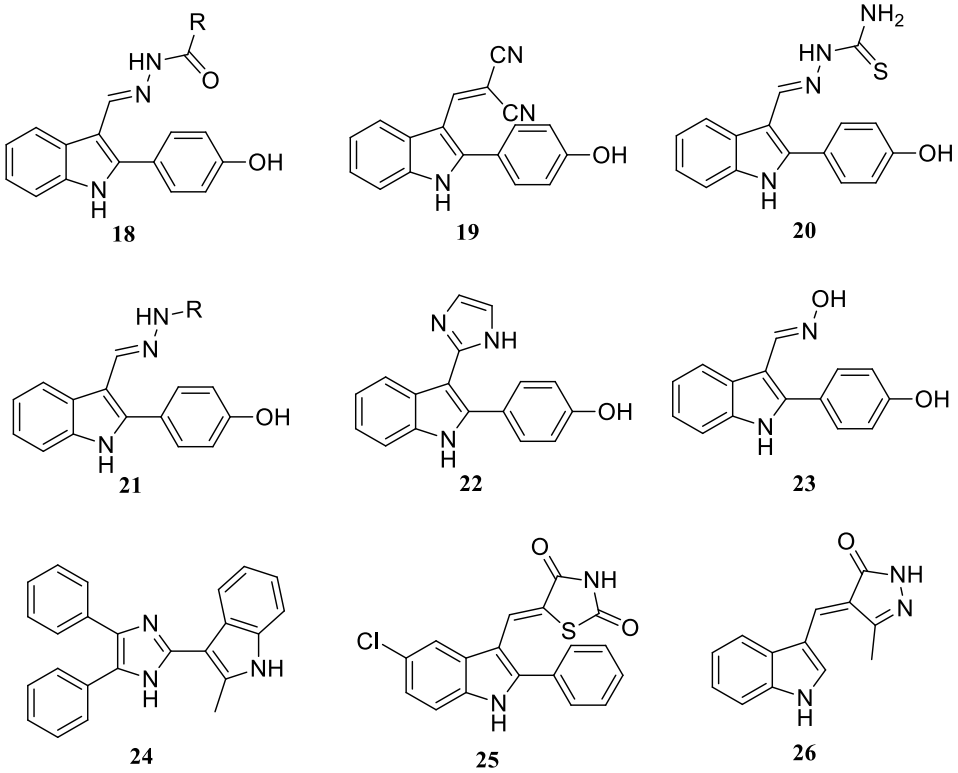



**Figure 1.5** Examples of bioactive compounds from 3-formylindole derivatives.

## 1.4 Thiosemicarbazone

Thiosemicarbazones basically are schift bases and are obtained by condensation of an aldehyde or ketone with thiosemicarbazide. They are broadly classified as mono-thiosemicarbazones (27) and bis-thiosemicarbazones (28 and 29) (Figure 1.3) which are an important compounds with in numerous biological applications as antifungal, antiviral, antibacterial and anticancer agents (Figure 1.7) [24].

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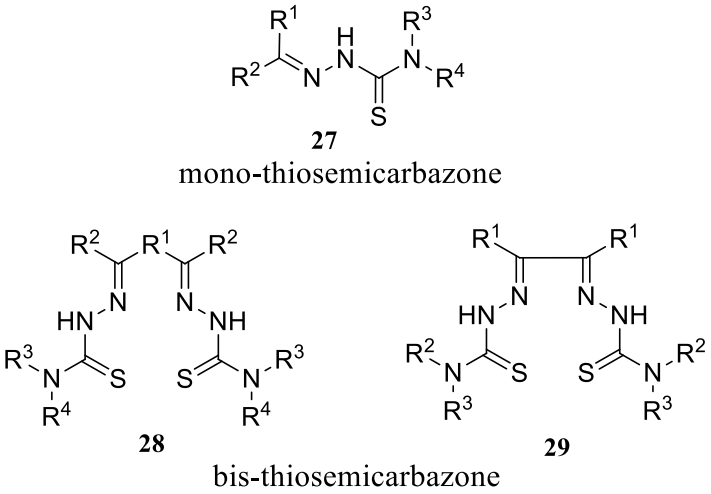



**Figure 1.6** Structure of mono-thiosemicarbazones and bis-thiosemicarbazones.

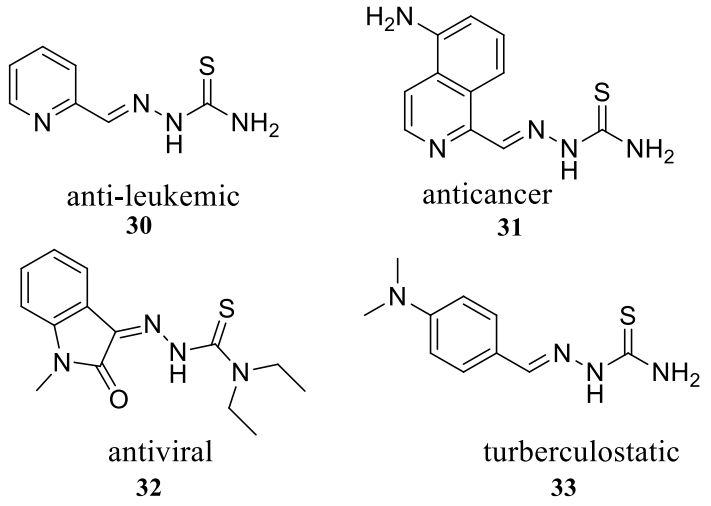



**Figure 1.7** Representative bioactive thiosemicarbazones.

The presence of amide, imine and thione groups makes thiosemicarbazones to constitute an important class of donor ligands via nitrogen and sulphur atom. Studies on the coordination chemistry of thiosemicarbazone ligands of different types are therefore of considerable importance [24, 25]. Recently, thiosemicarbazone metal complexes show significant biological activity such as Cu-ASTM (34) which is an orally bioavailable, blood-brain barrier permeable complex that specifically inhibits the action of peroxynitrite on Cu, Zn superoxide dismutase (SOD1) and subsequent nitration of cellular proteins, GSK3b inhibition complex **35** and antifungal activity against tin complex **36** (Figure 1.8) [26, 27].

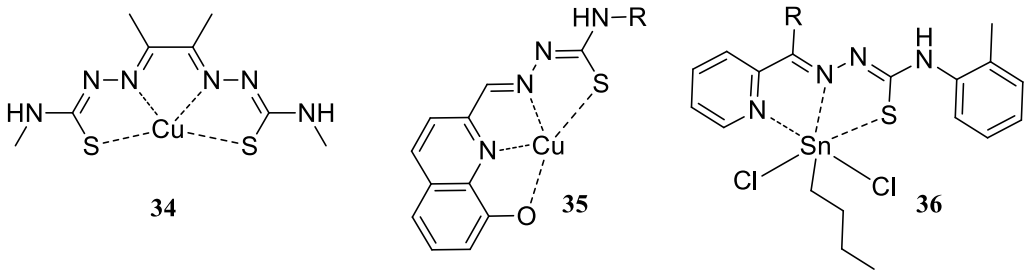



**Figure 1.8** Significant biological activities of thiosemicarbazone metal complexes.

In addition, thiosemicarbazones and their thiosemicarbazone metal complexes are receiving a growing interest since their properties are relevant to a wide range of chemical sensors including anion sensors and cation sensors [28], especially fluoride detection [29-38]. Furthermore a urea derivatives also had been studied in other receptor, such as carboxylate [39-43] and cobalt [44].

### 1.5 Thiazolidinone

The structure of 4-Thiazolidinone (37) is a five membered ring containing a carbonyl group at 4- position substituent and sulfur atom and nitrogen atom in 1 and 3 position respectively. Thiazolidinones, which belong to an important group of heterocyclic compound, have been extensively explored for their application in the field of medicine [45].

4-Thiazolidinones are always being an attraction point for researchers because of its efficiency towards various pharmacological usages such as antibacterial and antifungal activity (38), anti-*Toxoplasma gondii* (39), antiviral/anti-HIV activity (40), antidiabetic activity (41) and anticonvulsant and antidepressant activity (42) which show in figure 1.9 [46].

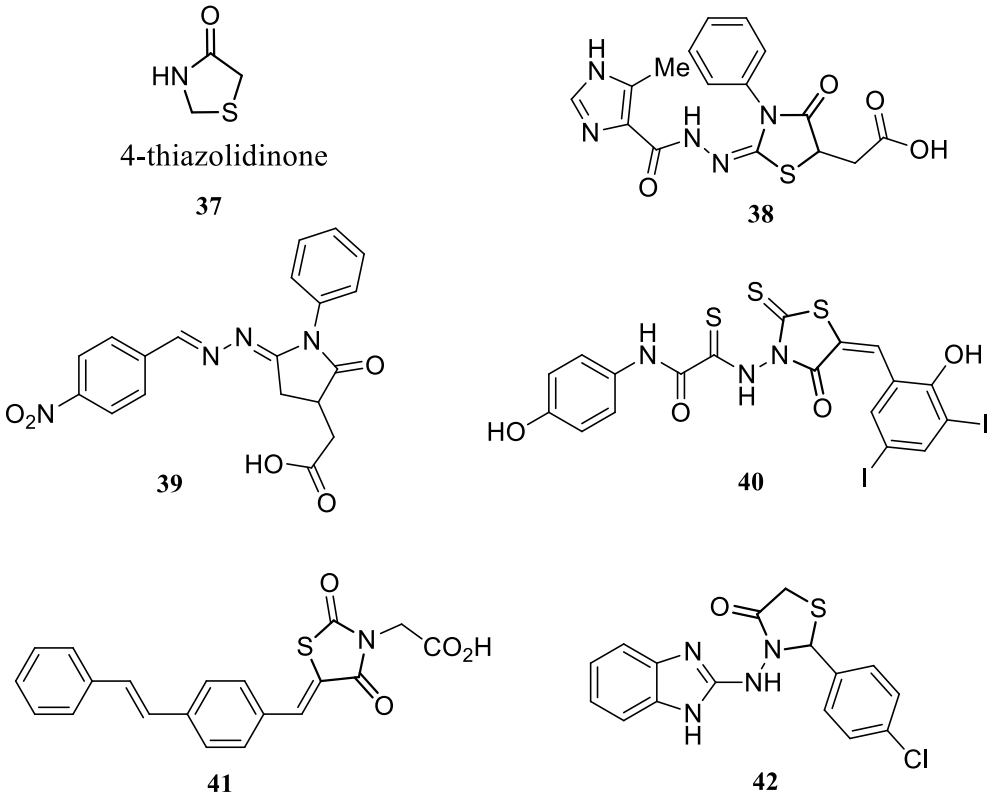



**Figure 1.9** Bioactive compounds of 4-thiazolidinone.

## 1.6 Imidazole

Imidazole (43) is a heterocyclic aromatic organic compound with aromaticity in completely conjugated monocyclic systems requires a planar array of atoms with $4n+2\pi$ electrons. Imidazole is an important biological building block being present in the amino acid histidine and is also a component of the biogenic amine histamine [47, 48].

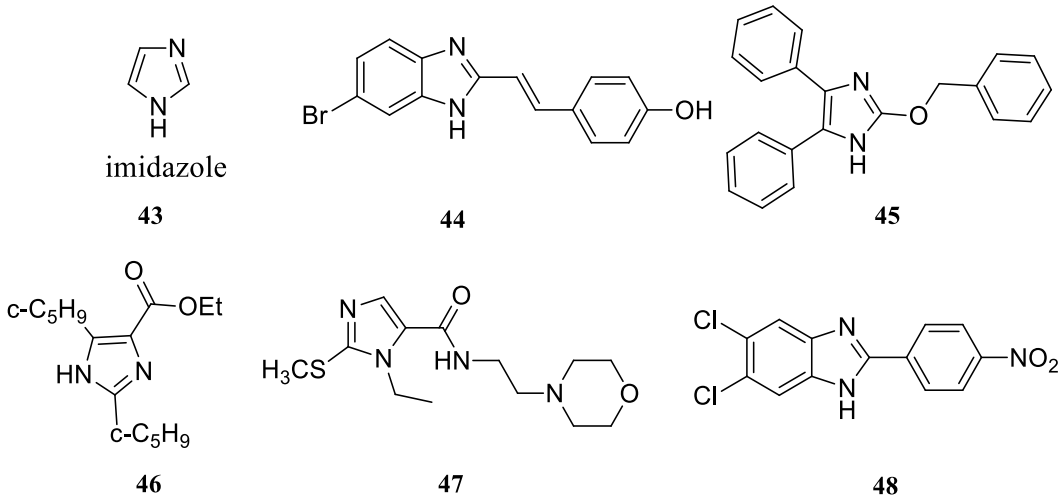
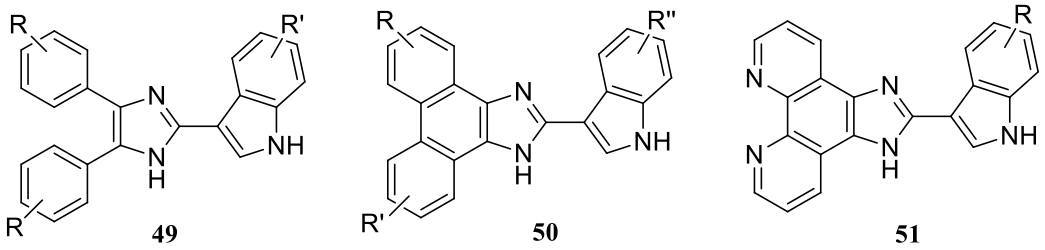



**Figure 1.10** Structure imidazole and bioactive imidazole derivatives.

Moreover, this ring system is present in important biological building blocks, such as anti-fungal and anti-bacterial activity (44), anti-inflammatory activity and analgesic activity (45), anti-tubercular activity (46), anti-depressant activity (47), viral activity (48) and especially anti-cancer activity (Figure 1.2) [49]. There are a lot of aryl imidazoles having indolyl have been registered a patent as anti-cancer agents (Figure 1.13) [50, 51].




R = H, R' = 5-Br
R = 4-F, R' = 2-Me
R = 4-F, R' = 5-Br
R = 4-OMe R' = 2-Me
R = 4-OMe R' = 5-Br

R = R' = H, R" = 5-CN
R = R' = H, R" = Ph
R = R' = H, R" = 5-F
R = R' = H, R" = $NO_2$
R = R' = $3NO_2$, R" = 5-Br
R = R' = $3NO_2$, R" = H
R = 3-$CO_2$H, R' = H, R" = 5-Br

R = H
R = 5-Br
R = 2-Me
R = 5-F
R = Ph
R = 2-Cl
R = 2-Me, 5-Cl
R = 2-Me, 5-OMe
R = 2-Me, 5-F
R = 2-Me, 5-OH

**Figure 1.11** Aryl imidazoles having indolyl as anti-cancer agents.

### 1.7 1,4-Dihydropyridine

1,4-Dihydropyridine **52** is a molecule based upon pyridine as a parent that consist of semi-saturated with two substituents replacing one double bond [52]. 1,4-Dihydropyridine derivatives are particularly well known in pharmacology as L-type calcium channel blockers inhibits which used in the treatment of hypertension. The example of L-type calcium channel blockers containing 1,4-dihydropyridine (53-56) show in figure 1.5 [53].

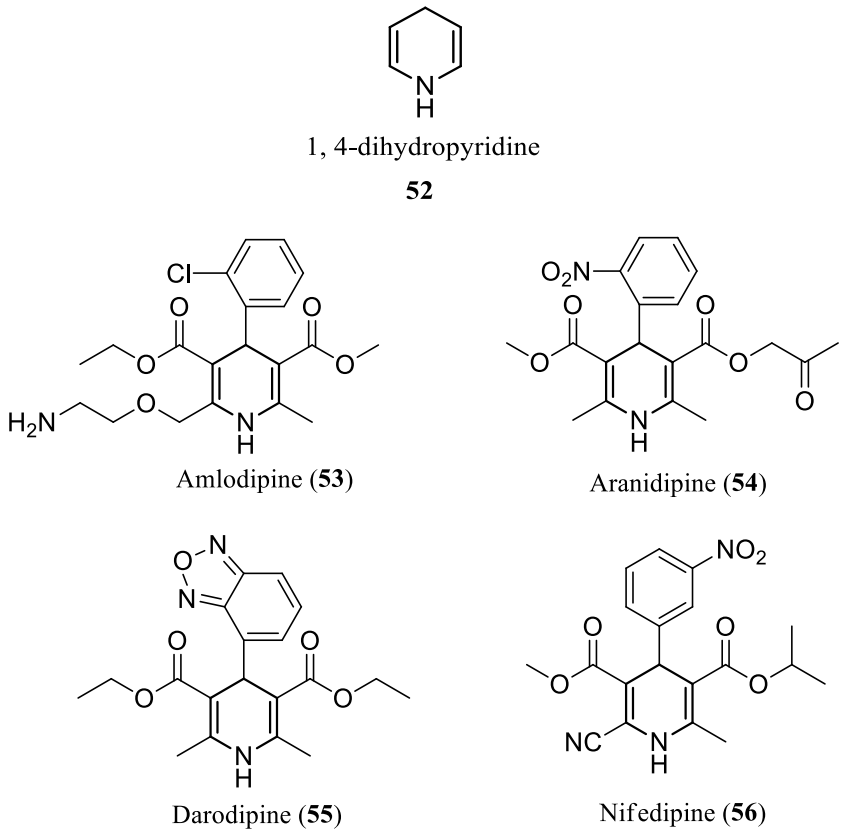



**Figure 1.12** Structure of 1,4-dihydropyridine and L-type calcium channel blockers containing 1,4-dihydropyridine.

Moreover, 1,4-dihydropyridine derivatives exhibit other pharmacological activities such as antitubercular activity (57), antimicrobial activity (58), anticancer activity (59-60) cardiovascular activity (61) which show in figure 1.1 [52].

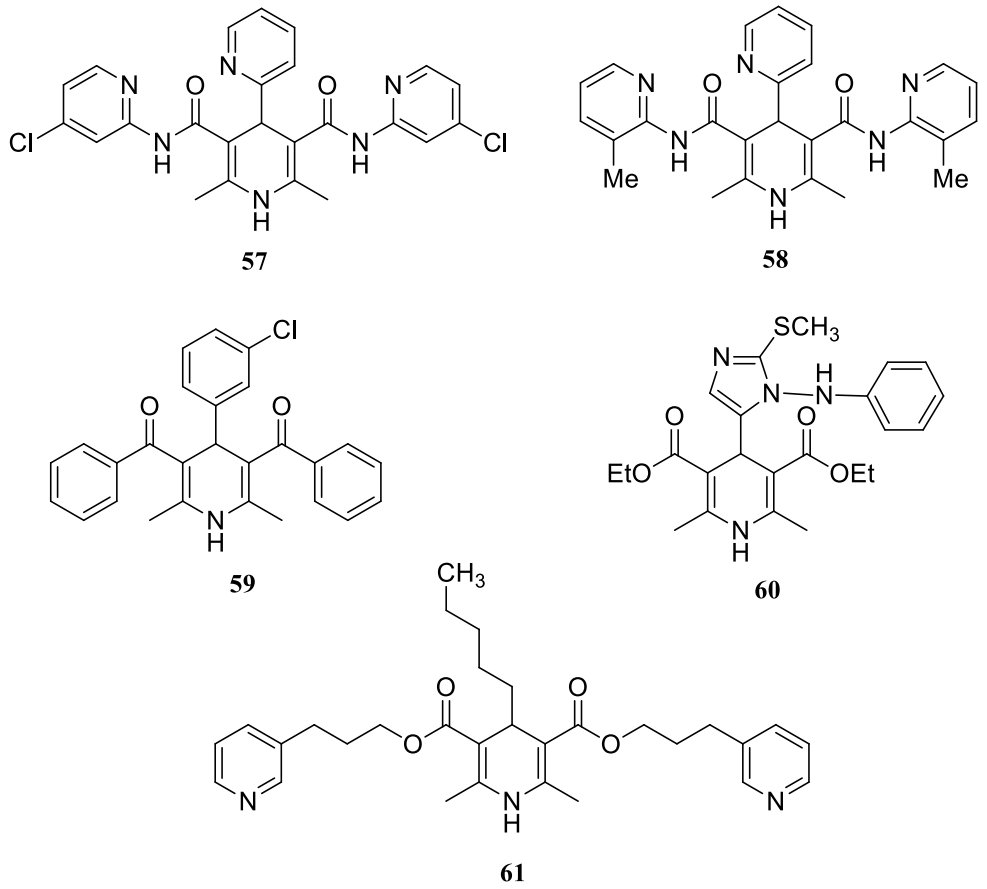



**Figure 1.13** Biological compounds of 1,4-dihydropyridine derivatives.

From widely differing pharmaceutical and biological properties of indole, thiosemicarbazome, thiazolidinone, imidazole and 1,4-dihydropyridine, they were an interesting compound to design new active compound. A principle to improve communication and awareness of this emerging field within the drug discovery community was proposed by Morphy and Rankovic in the term “designed multiple ligands (DMLs)” as a generic phrase to describe compounds that are rationally designed to modulate multiple targets of relevance to a disease, with the overall goal of enhancing efficacy and/or improving safety [54]. To obtain novel DMLs, a design strategy is usually applied in which distinct pharmacophores of different drugs are combined in the same structure to afford hybrid molecules. In principle, each pharmacophore of new drugs should retain the ability to interact with its specific site on the target and consequently to produce specific pharmacological responses that taken together should slow or block the disease process [55]. The most common strategy was

to start with a single molecule that, in most cases, had good activity at one of the targets of interest and at least some minimal activity at the other target. The design strategy started with two compounds, one of which bound with high selectively to one of the targets and the other with high selectively to the other target [56]. In this research, indole will be used as a core structure which will be merging with thiosemicarbazone, thiazolidinone, imidazole and 1,4-dihydropyridine through 3-formylindole.

**1.8 Objectives of the research**

The objectives of this research can be summarized as follows:

1.8.1 To synthesize indole derivatives from commercial anilines or phenyl hydrazine and ketones.

1.8.2 To develop a method for formylation reaction of indole.

1.8.3 To synthesize indole derivatives containing thiosemicarbazone, thiazolidinone, 1,4-dihydropyridine and 2,4,5-trisubstituted imidazole from 3-formylindole.

**1.9 Expected results obtain from the research**

New method for formylation reaction of indole and synthesized novel indole derivatives containing thiosemicarbarzone, thiazolidinone, 1,4-dihydropyridine and imidazole framework could be discovered.

**1.10 Scope of the research**

1.10.1 Aniline or phenyl hydrazine and acetophenone derivatives were used to synthesize indole derivatives.

1.10.2 The new condition for formylation reaction of indole was developed by cerium (IV) supported on silica gel.

1.10.3 Indole thiosemicarbazone, thiazolidinone, 1,4-dihydropyridine and imidazole derivatives were synthesized from 3-formyl indole.

# CHAPTER 2

# LITERATURE REVIEWS

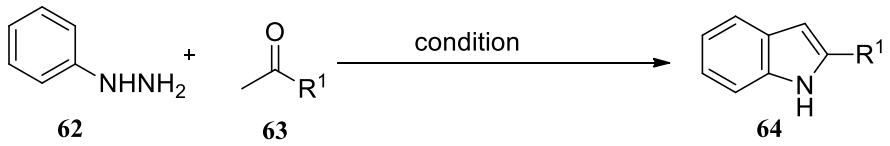
## 2.1 Synthesis of 3-unsubstituted indole

Indoles are usually prepared from non-heterocyclic precursors by cyclisation reactions on suitably substituted benzenes, monosubstituted- and ortho substituted benzene. They can also be prepared from pyrroles by construction of the homocyclic aromatic ring and intramolecular Diels-Alder cyclisation. The construction of indole ring in some reaction gave substituted indole product on N1, C2, C3 or phenyl ring. In this research, a synthesis of indole was scoped on 3-unsubstituted indoles which easily undergo on electrophilic aromatic substitution such as formylation and can be prepared by commercial available starting material, aniline and phenyl hydrazine.

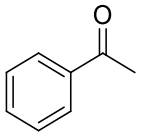
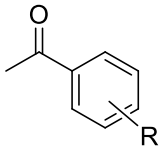
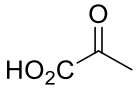
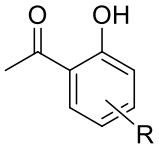
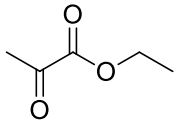
2.1.1 3-unsubstituted indole from phenyl hydrazine derivatives

Fischer indole synthesis is a classical reaction for synthesis of indole from phenylhydrazine and ketone that had been reported in 1886 which involve a condensation of phenylhydrazine (62) and ketone (63) to generate hydrazone. Then the hydrazone undergoes 3,3-sigmatropic rearrangement and cyclocondensation (Scheme 2.1) in acidic condition. [57, 58]. There are a numerous methods have been developed which show in table 1.1.

**Table 2.1** Fischer indole syntheses with different conditions.

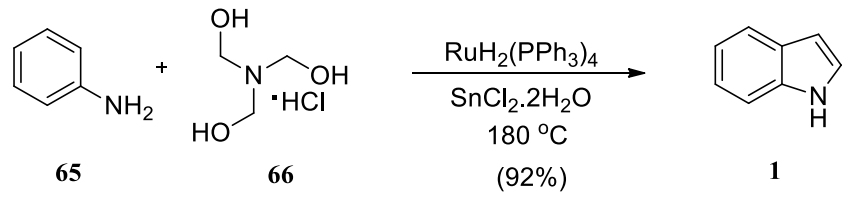



**62** **63** **64**

| Entry | Ketone (63) | condition | Ref. |
|---|---|---|---|
| 1 |  | PPA (76%) | [59] |
| 2 |  R = H, 4-Cl, 4-$NO_2$, 4-$CH_3$ | Clay, MeOH (88-92%) | [60] |
| 3 |  | $Zncl_2$, $PCl_5$ (71-88%) | [61] |
| 4 |  | EtOH, $H_2SO_4$ (49-92%) | [62] |
| 5 |  | p-TsOH, toluene, reflux | [63] |

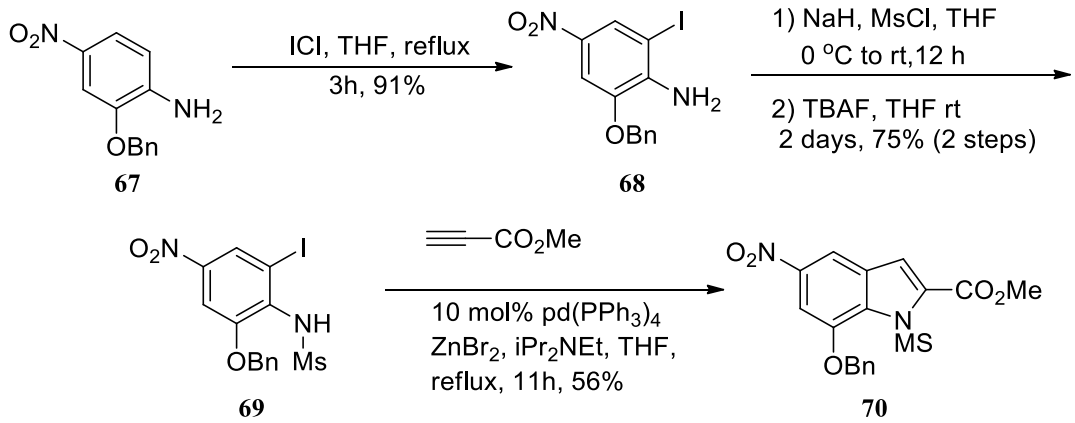
2.1.2 3-Unsubstituted indole by aniline derivatives

Indole (1) could be synthesized from aniline (65) and alkanol ammonium chloride (66) in the presence of a ruthenium catalyst and $SnCl_2.2H_2O$ in aqueous medium in good yield (Scheme 2.1) [64].



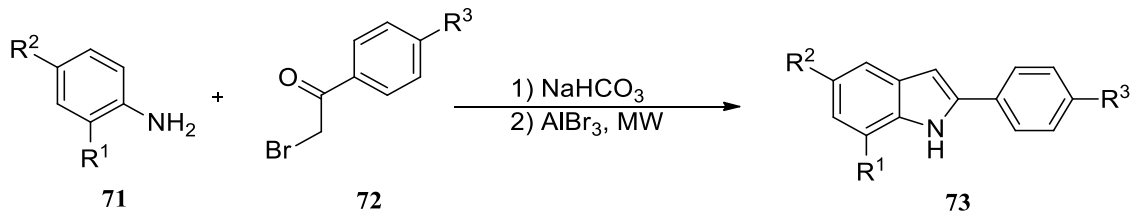

**Scheme 2.1** Reaction of aniline and alkanolammonium chloride in indole synthesis.

The sequential coupling and cyclization reactions between aryl iodide (68) and methyl propiolate were investigated. Firstly, iodination of aniline (67) by ICI gave an iodinated product 68, followed by coupling and cyclization reaction with methyl propiolate employing Negishi's reaction conditions. The electron-withdrawing groups on the aromatic ring are essential for producing the methyl indole-2-carboxylate derivatives (70) (Scheme 2.2) [65].



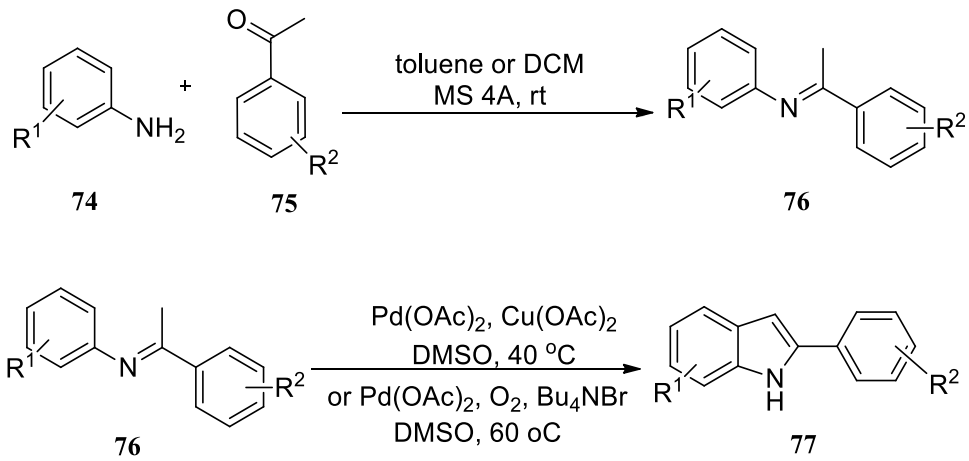

**Scheme 2.2** The sequential coupling and cyclization reactions between aryl iodide (61) and methyl propiolate.

The solid-state reaction between anilines (71) and phenacyl bromides (72) in the presence of an equimolecular amount of sodium bicarbonate gives *N*-phenacylanilines. Microwave irradiation of mixtures of these compounds with anilinium bromides at 540 W for 45–60 s provides a mild, general, and environmentally friendly method for the synthesis of 2-arylindoles (73) [66, 67].



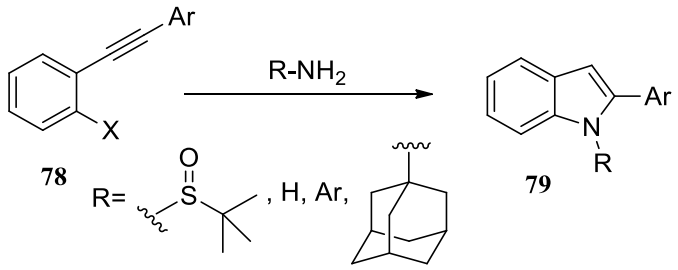

**Scheme 2.3** Reaction of anilines and phenacyl bromides.

In 2012, Wei and coworker have been developed oxidative cyclization of *N*-aryl immine (76) by palladium catalyst to relate 3-unsubstutited indole products (77) (Scheme 2.9). The *N*-aryl imine was easily prepared from condensation reaction of readily available anilines (74) and acetophenone derivatives (75) [68].




**Scheme 2.4** Pd-catalyzed oxidative cyclization of *N*-aryl imines.

In addition, many research about an intermolecular *N*-arylation and an intramolecular hydroamination of 2-alkynylhaloarene (78) has been reported to provide 3-unsubstituted indole products (79). This reaction could be carried out by Palladium catalyst [67, 69-71] and Nickel catalyst [72].




**Scheme 2.5** Intermolecular *N*-arylation and an intramolecular hydroamination of 2-alkynylhaloarene.

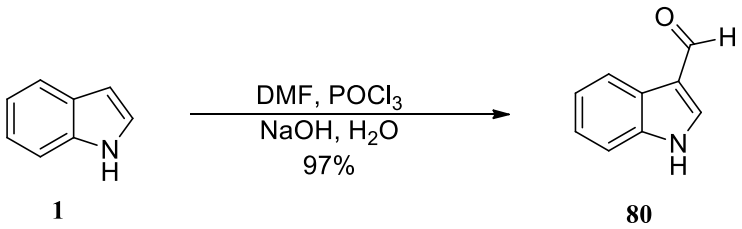
## 2.2 C-Formylation reaction of indole

A number of synthetic methods have been reported in the literature for a formylation of aromatic compound with various reagents. Traditionally, the Vilsmeier–Haack reagent (e.g. $POCl_3$ + DMF) [73-75], Duff reaction [74], Gattermann–Koch reaction [76-79], and Reimer–Tiemann reaction [80] are also powerful methods leading to formylated products. Recent year, other formyl source had been report to achieve in formylated aromatic compound (benzene ring) such as carbon monoxide (CO), carbon dioxide ($CO_2$), formic acid, metalcarbonyl materials and isocyanides [81]. Electron rich property and resonance effect of N1 made C3 of indole more reactive to electrophilic attack than benzene. Thus indoles are quite easily undergone in formylation reaction. Some traditional formylations can be achieved in this reaction.

### 2.2.1 Vilsmeier–Haack reaction

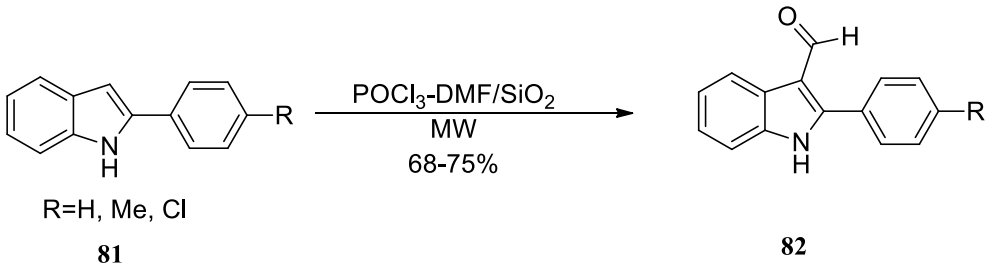
Vilsmeier–Haack reaction is a well-known reaction to formylate indole. This reaction was achieved by using a mixture of phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF) (Scheme 2.6) to generate a substituted chloroiminium ion followed by undergo electrophilic substitution on C3 indole ring. By means of some

simplifications in the procedure, a 97% yield of very pure 3-formyl indole product has now been obtained [73-75, 82].




**Scheme 2.6** Formylation reaction of indole by DMF/$POCl_3$.

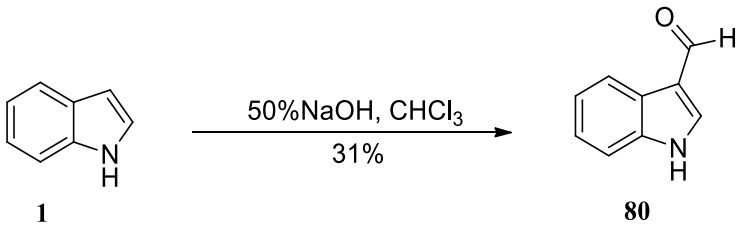
Moreover, In 2000 Paul and coworker have been developed $POCl_3$-DMF over silica gel for the synthesis of 2-aryl-3-formyl indoles using solvent-free conditions under microwave irradiation comparison with thermal heating (Scheme 2.7). The results showed the microwave irradiation in solvent-free condition provide an excellent methodology [83].




**Scheme 2.7** Formylation reaction of indole by DMF/$POCl_3$ supported on siliga gel.

2.2.2 Reimer–Tiemann reaction

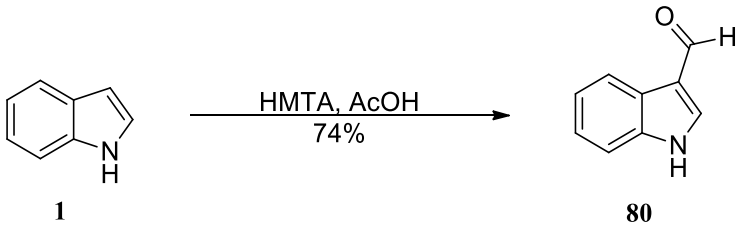
The Reimer–Tiemann reaction is originally used for the preparation of phenolic aldehydes by the action of chloroform on phenol in alkaline medium. This reaction was applied to many compounds including indole (Scheme 2.8) [80].




**Scheme 2.8** Reimer–Tiemann reaction.

2.2.3 Duff reaction

The original method for formation of aromatic aldehyde was discovered by Duff with hexamethyltetraamine (HMTA) as a formyl source in acidic media at reflux temperature. This condition has been developed to formylate C-3 in indole ring to give indole aldehyde (Scheme 2.9) in good yield [74].

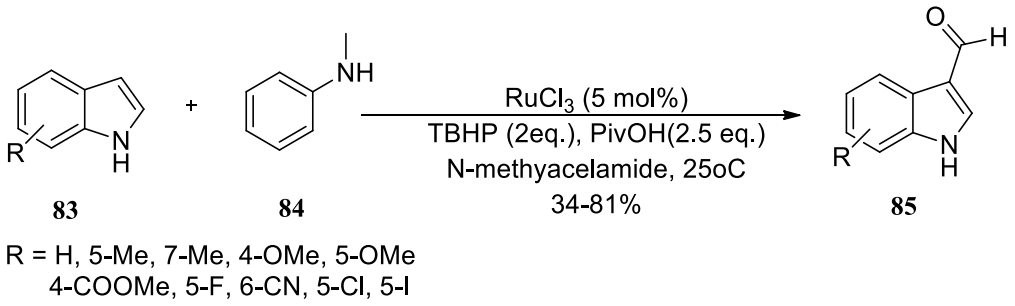



**Scheme 2.9** The formylation reaction of indole by Duff reaction.

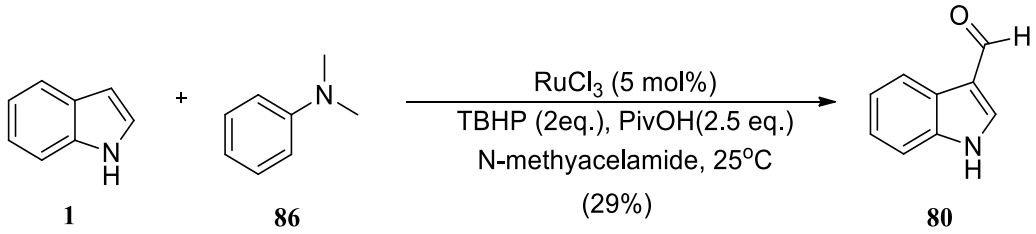
2.2.4 *N*-methyl amine as a formyl source

Recent year a formylation of indole was developed with *N*-methyl amine such as *N*-methyl aniline, *N,N′*-dimethyl aniline, tetramethylethylenediamine, *N*,*N*-dimethylbenzylamine and *N,N′*-dimethylethylenediamine.

In 2011 Wu and coworker first report the formylation of free (N-H) indole by using *N*-methyl aniline as a carbonyl sources with rhodium (Ru) catalyst and *tert*-butly hydrogentperoxide as an oxidant in water at room temperature. This process provided desired products in moderated to good yield (34-81%) (Scheme2.10). Moreover, other amines were investigated for this reaction. The results show that *N*,*N*-dimethylaniline also afforded 3-formyl indole product in 29% (Scheme 2.11) [84].

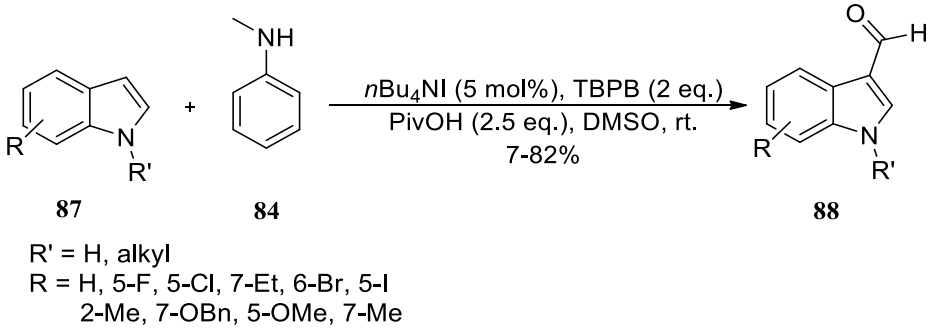



**Scheme 2.10** The formylation reaction of indole by using rhodium catalyst.



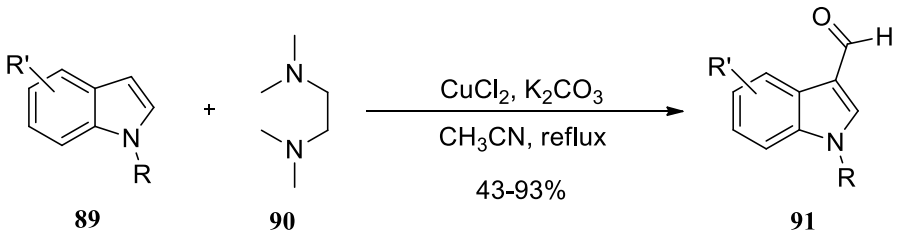

**Scheme 2.11** The formylation reaction of indole by using rhodium catalyst with various amines.

In 2012, tetrabutylammoniuniodide (*n*Bu$_4$NI)-catalyzed C3-formylation of free (N-H) indole and *N*-substituted indole with *N*-methyl aniline had been reported to give indole products in yield 7-82% (Scheme 2.12) [85].




**Scheme 2.12** The formylation reaction of indole by using *n*Bu$_4$NI catalyst.

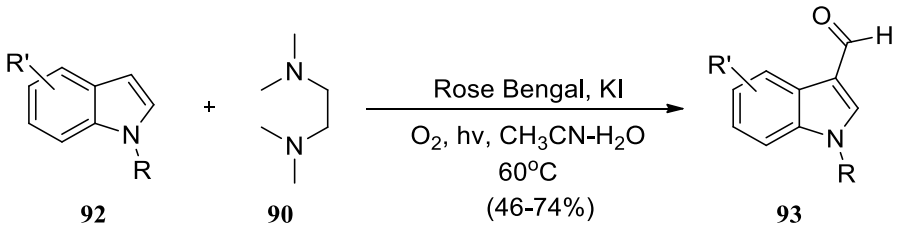
Tetramethylethylenediamine (TMEDA) (90) was studied to be carbonyl source for formylation of *N*-substituted indole in 2010 by using Cu (II)-catalyzed in acetonitrile ($CH_3CN$) under refluxing condition to provide 3-formylindole in excellent yield (Scheme 2.13) [86].




R = H, Me, Et, PMB, Bn
R' = H, 5-OMe, 5-Cl, 5-CN, 2-Me, 4- Me, 7-Me

**Scheme 2.13** The formylation reaction of indole by copper catalyst.

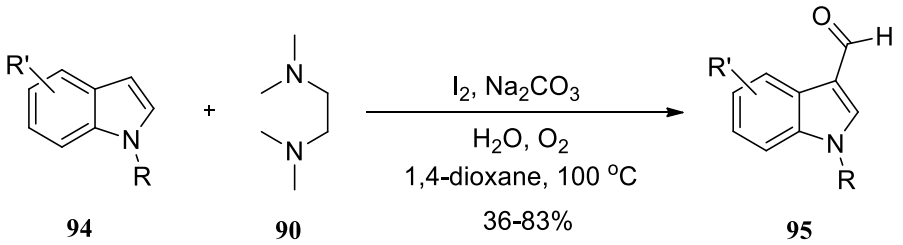
In 2014, an aerobic visible-light-promoted *N*-substituted indole C-3 formylation reaction catalyzed by Rose Bengal has been reported. This transition-metal-free process employs molecular oxygen as the terminal oxidant and uses tetramethylethylenediamine (TMEDA) (90) as the one-carbon source through C−N bond cleavage (Scheme 2.14). The reaction provided product from *N*-substituted indole in modest yield (46-74%) [87].




**Scheme 2.14** The formylation reaction of indole by rose bengal.

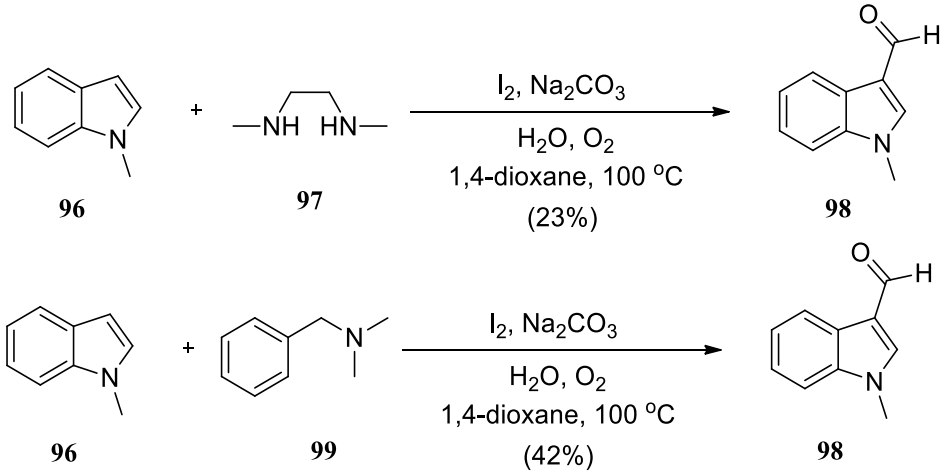
In the same year, An $I_2$-promoted 3-formylation of free (N–H) and *N*-substituted indoles with tetramethylethylenediamine (TMEDA) (90) and $H_2O$ as the carbonyl source in the presence of sodium carbonate ($Na_2CO_3$) under aerobic conditions

was achieved (Scheme 2.15) and provided desired 3-formylindole products in moderate to excellent yields (39-83%). Some other amines or amides were subjected to this reaction. As show in scheme 2.54, *N*,*N*-dimethylbenzylamine (99) and *N*,*N*′-dimethylethylenediamine (97) provided 3-formyl indole product (98) in 42 and 23% respectively (Scheme 2.16) [21].



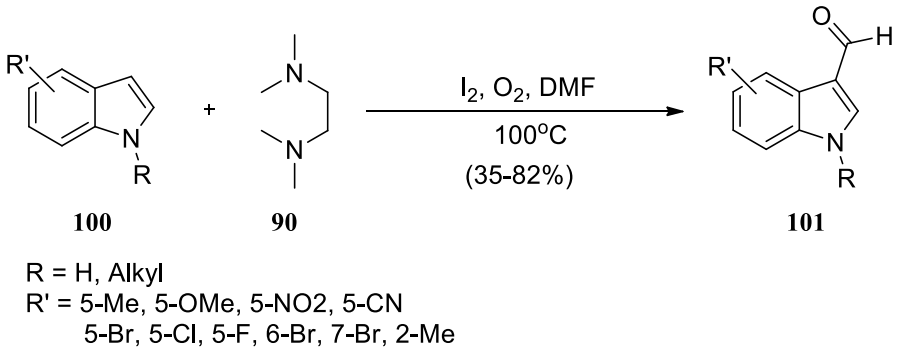

R = H, Me
R = H, 5-Me, 6-Me, 5-F, 5-Cl
5-Br, 5-$NO_2$, 5-CHO, 5-CN
2-Me, 2-Ph,

**Scheme 2.15** The formylation reaction of indole by iodine catalyst.




**Scheme 2.16** The formylation reaction of indole by iodine catalyst with various *N*-methyl amines.

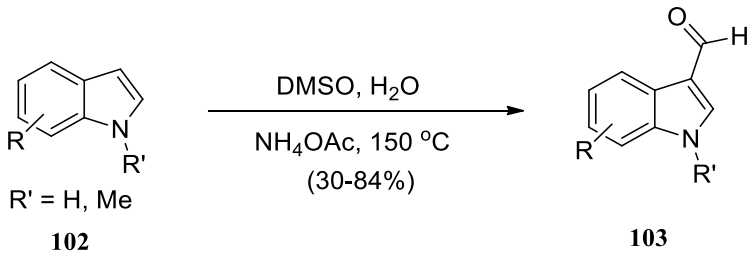
Then Lu and coworker also reported iodine-catalyzed C3-formylation of free (N–H) and *N*-substituted indoles via C-N bond cleavage of tetramethylethylenediamine (TMEDA) (90) under $O_2$ atmosphere in DMSO (Scheme 2.17). A wide range of 3-formylindoles were obtained in moderate to good yields (35-82%) [88].




**Scheme 2.17** The formylation reaction of indole by iodine catalyst.

2.2.5 Dimethyl sulfoxide (DMSO) as a formyl source

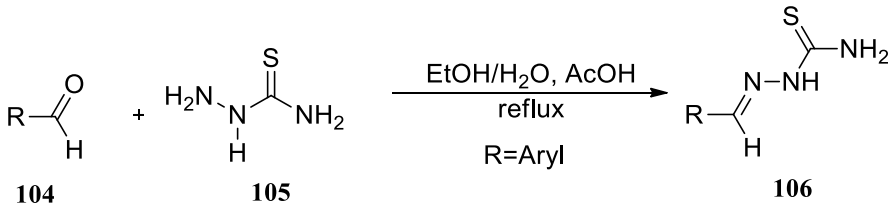
In 2013, Fei and coworker reported the ammonium acetate ($NH_4OAc$)-promoted formylation of indoles by DMSO and $H_2O$ via Pummerer reaction under nearly neutral conditions (Scheme 2.18). This procedure was applied to free (N–H) and *N*-substituted indoles to afford 3-formyl indole in modest to good results (30-84%) [89].




**Scheme 2.18** The ammonium-promoted formylation of indoles by DMSO and $H_2O$.

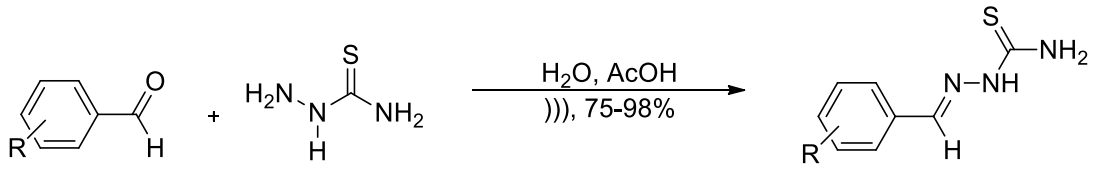
## 2.3 Synthesis of thiosemicarbazone

Thiosemicarbazone derivatives were prepared by condensation of aldehyde with thiosemicarbazide in $EtOH/H_2O$ as the solvent and acetic acid as a catalyst under refluxing condition (Scheme 2.19) [90]. Moreover, this reaction has been achieved by using acetic acid as a catalyst under ultrasound irradiation in aqueous medium (Scheme 2.20) [91].




**104** **105** **106**

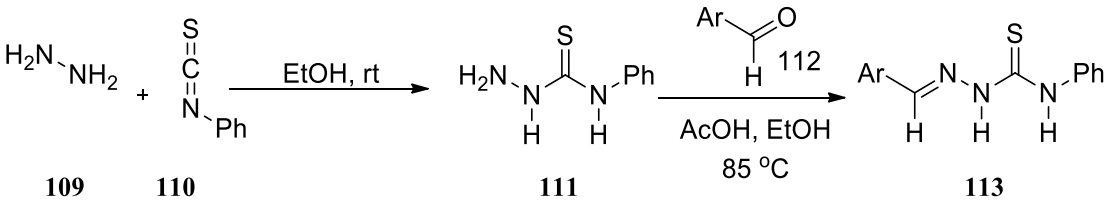
**Scheme 2.19** Thiosemicarbazone synthesis.




**107** **105** **108**

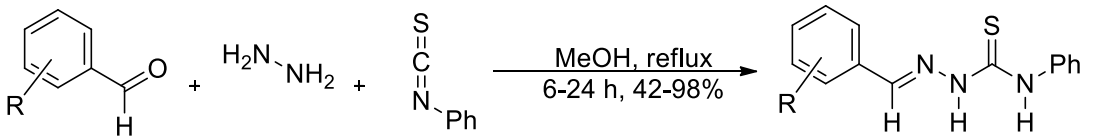
**Scheme 2.20** Thiosemicarbazone synthesis in aqueous medium.

In addition, thiosemicarbazone (113) can be prepared in two steps. The first step, a reaction of isothiocyanate (110) and hydrazine (109) generated 4-phenyl thiosemicarbazide (111). Then a condensation of thiosemicarbazide (111) and various aldehydes (112) in the presence of few drop of acetic acid in ethanol at 85 $^{\circ}$C gave thiosemicarbazone product (113) [92]. In 2009, Cunha *et al.* reported multicomponent reaction of aldehyde, hydrazine and phenyl iosthiocyanate in methanol under refluxing condition (Scheme 2.22) [93].




**109** **110** **111** **113**

**Scheme 2.21** Two steps for synthesis of thiosemicarbazone.



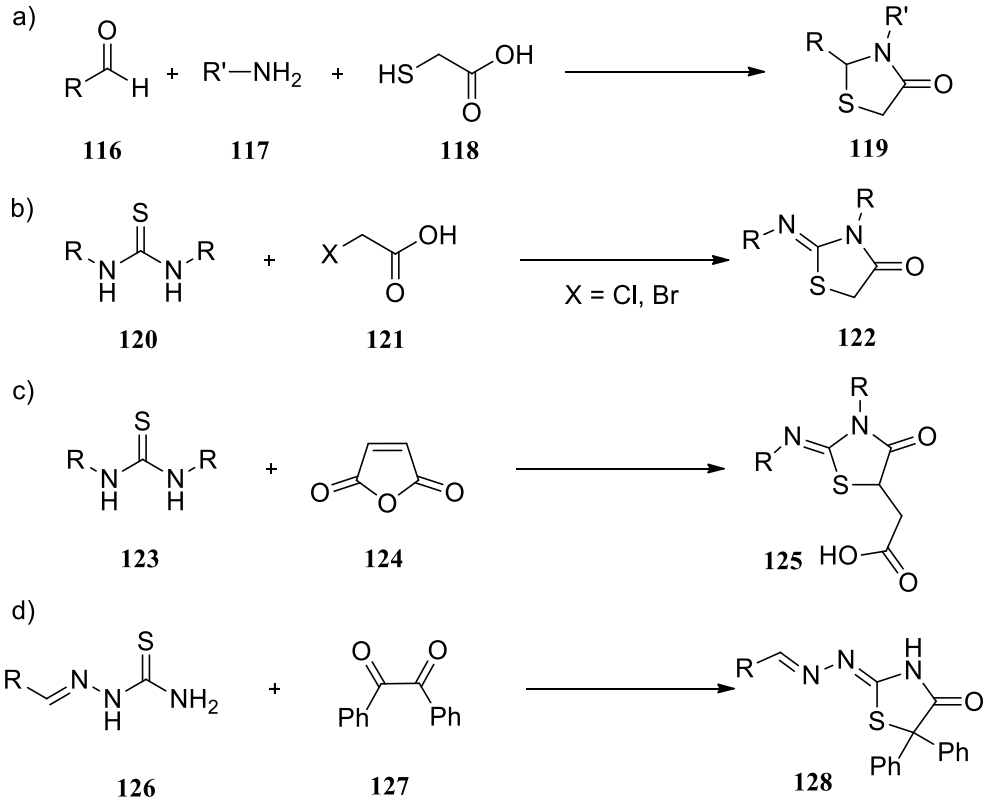

**114** **109** **110** **115**

R=2-OH, 2-OMe, 4-OMe
4-$NO_2$, 5-Cl, 3-OMe-4-OH,
3-OH-4-OMe

**Scheme 2.22** Three components reaction for synthesis of thiosemicarbazone.

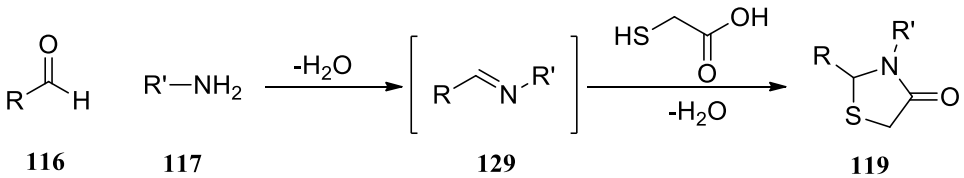
## 2.4 Synthesis of thiazolidinone

Several methods for the synthesis of 4-thiazolidinones are widely reported in the literature. The classical synthesis was reported via a one-pot three-component condensation or a two-step process (Scheme 2.23, a). In addition, thiazolidinone derivertives had been reported by a substitution reaction of 1,2-dielectrophile such as α-haloacetic acid derivative (Scheme 2.23, b), maleic anhydride (Scheme 2.23, c) and benzil (Scheme 2.23, d) with thiourea derivative.




**Scheme 2.23** Synthetic route for synthesis of 4-thiazolidinone.

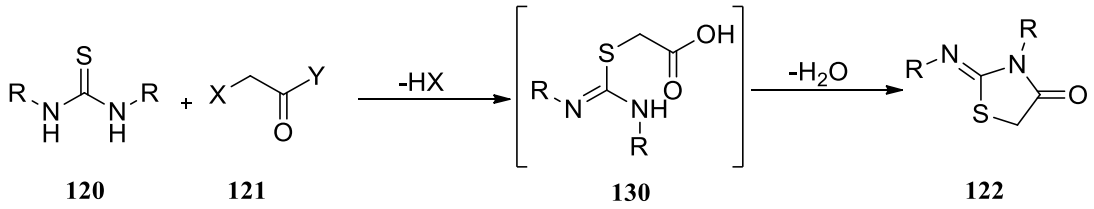
The classical thiazolidinone synthesis was achieved from three-component reaction of aldehyde amine and mercaptoacetic acid in aprotic solvent and catalyst (Scheme 2.24). The reactions begin by a condensation of aldehyde (116) and amine (117) to form an imine (129), which attacks by sulfur nucleophile of mercaptoacetic acid. Finally intramolecular cyclization on carboxylic acid group to dehydration gives 4-thiazolidinone product [94-99].




**Reaction conditions:** DCC, THF
toluene, Dean-Star
THF, reflux
$ZnCl_2$, DMF, reflux

**Scheme 2.24** Synthesis of 4-thiazolidinone via three-component reaction.

A reaction of thiourea derivertives (120) and $\alpha$-haloacetic acid derivatives (121) was reported in various conditions (Scheme 2.25) to synthesize 4-thiazolidinone (122). The reaction starts with substitution reaction by sulfur nucleophile on $\alpha$-carbon followed by intramolecular cyclization with nitrogen on carbonyl group [92, 100-105].




**X = Cl, Br**

**Reaction conditions:** dioxane, 90 $^{o}$C, (X=Cl, Y=OH)

$NEt_3$, $CHCl_3$, rt (X=Cl, Y=Cl)

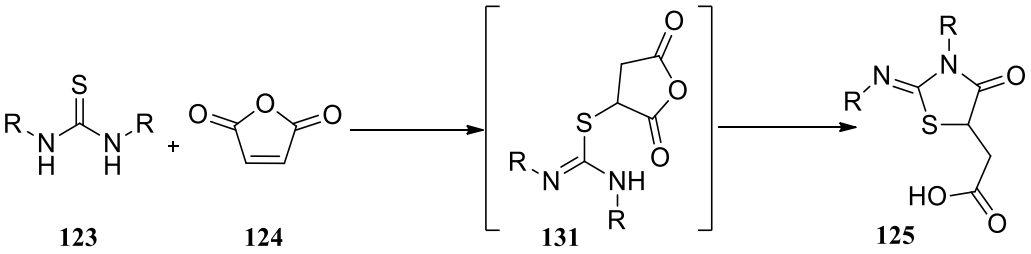
EtOH, reflux (X=Cl, Y=OEt)

$NEt_3$, EtOH, reflux (X=Cl, Y=OMe)

NaOAc, EtOH, reflux (X=Br, Y=OEt)

**Scheme 2.25** Synthesis of 4-thiazolidinone from the reaction of thiourea and $\alpha$-haloacetic acid derivative.

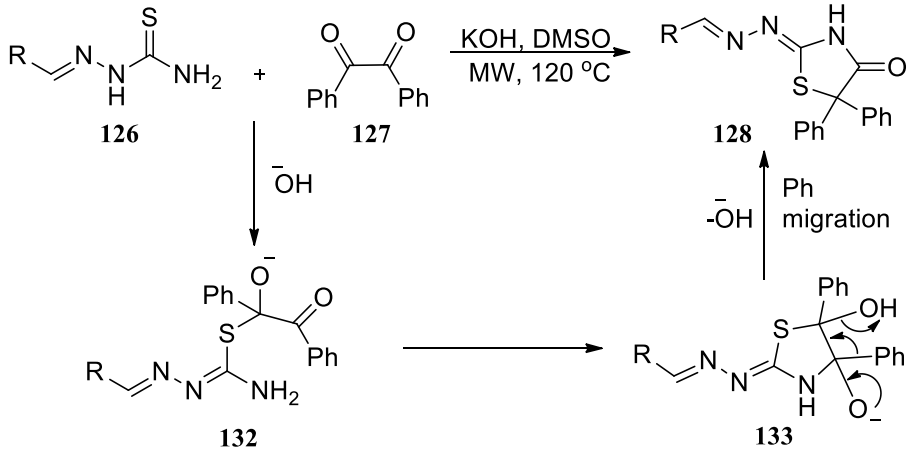
In 1939, M'Lean and Wilson first reported the reaction between thiosemicarbazones (123) and maleic anhydride (124) in benzene or toluene under reflux condition to generate 4-oxo-5-thiazolidineacetic acids (125) [106]. This reaction was achieved via Michael addition of maleic anhydride (124) with sulfur nucleophile and intramolecular cyclization (ring opening of succinic anhydride ring) by nitrogen attraction. Recent year, this reaction was developed with some catalyst which shows in Scheme 2.26 [90, 107-109].




**Reaction conditions:** benzene or toluene, reflux
toluene/DMF, reflux
Dean-Stark, toluene/DMF, reflux
acetone, reflux
10 mmol% TsOH, toluene/DMF, reflux or MW

**Scheme 2.26** Synthesis of 4-thiazolidinone from the reaction of thiourea derivertive and maleic anhydride.

Furthermore, Saiz *et al.* reported the reaction of thiosemicarbazone (126) with benzil (127) as the electrophile in basic condition under microwave irradiation to give 2-hydrazolyl-5,5-diphenyl-4-thiazolidinone (128). They proposed the mechanism by nucleophilic attack to diketone by sulfur and nitrogen followed by a phenyl group migration (Scheme 2.27) [90].



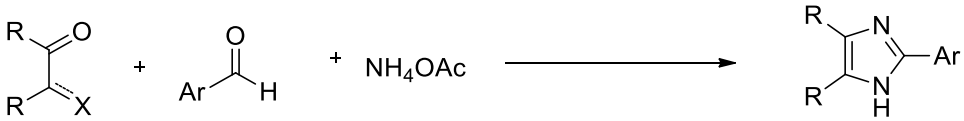

**Scheme 2.27** Synthesis of 4-thiazolidinone from the reaction of thiosemicarbazone and benzil.

## 2.5 Synthesis of imidazole

Several methods have been reported in the literature for the synthesis of imidazoles and some of those recently developed have wide application.

Cyclocondensation of a 1,2-diarylethanedione or keto-oximes or *α*-hydroxy ketone, an aryl aldehyde, ammonium acetate or ammonia in refluxing under different conditions are a well-established procedure for the preparation of 2,4,5-triaryl-1*H*-imidazoles. The reaction was achieved via condensation reaction as a key step. Cyclocondensation of a 1,2-diarylethanedione (145), an aryl aldehyde (146), ammonium acetate or ammonia in difference conditions are a well-established procedure for the preparation of 2,4,5-triaryl-1*H*-imidazoles (147) as show in Table 2.5.

**Table 2.2** Reaction of 1,2-diarylethanedione or keto-oximes or *α*-hydroxy ketone, an aryl aldehyde, ammonium acetate or ammonia with different conditions.




**134** **135** **136**

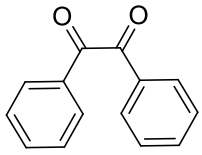
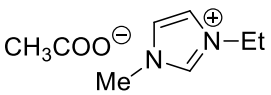
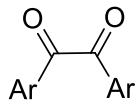
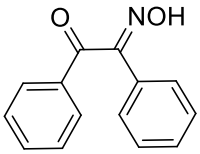
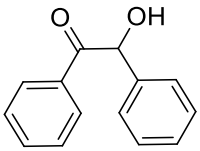
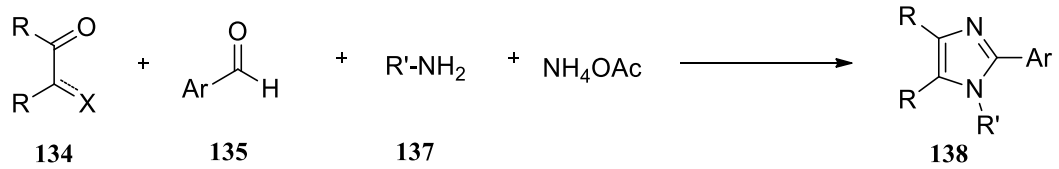
| Entry | Ketone | Condition | Ref. |
|---|---|---|---|
| 1 |  **134a** | SSA, reflux | [110] |
| | | $CuCl_2.2H_2O$, MW | [111] |
| | | $Y(TFA)_3$, neat, 100ºC | [112] |
| | | AcOH, reflux | [113] |
| | | DABCO, *t*-BuOH, 60-65 ºC | [114] |
| | |  EtOH, ))), rt | [115] |

**Table 2.2** (Continued)

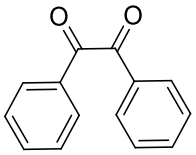
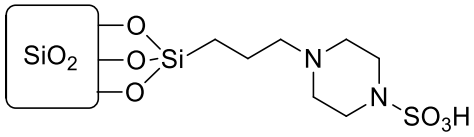
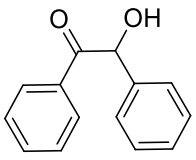
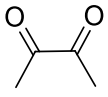
| Entry | Ketone | Condition | Ref. |
|---|---|---|---|
| 2 |  **134b** | 10 mol% $InCl_3.3H_2O$, MeOH, rt<br>15 mol% L-Proline, MeOH, 60$^oC$<br>$InF_3$, solvent-free, 60 $^oC$ | [116]<br>[117]<br>[118] |
| 3 |  **134c** | SSA, reflux | [110] |
| 4 |  **134d** | SSA, reflux | [110] |

1,2,4,5-tetraaryl-1*H*-imidazoles (149) were synthesized by condensation of 1,2-diarylethanedione or *α*-hydroxy ketone (145), an aryl aldehyde (146), amine (148) and ammonium acetate under various conditions which summarized in table 2.6.

**Table 2.3** Reaction of 1,2-diarylethanedione or $\alpha$-hydroxy ketone, an aryl aldehyde, amine and ammonium acetate with different conditions.

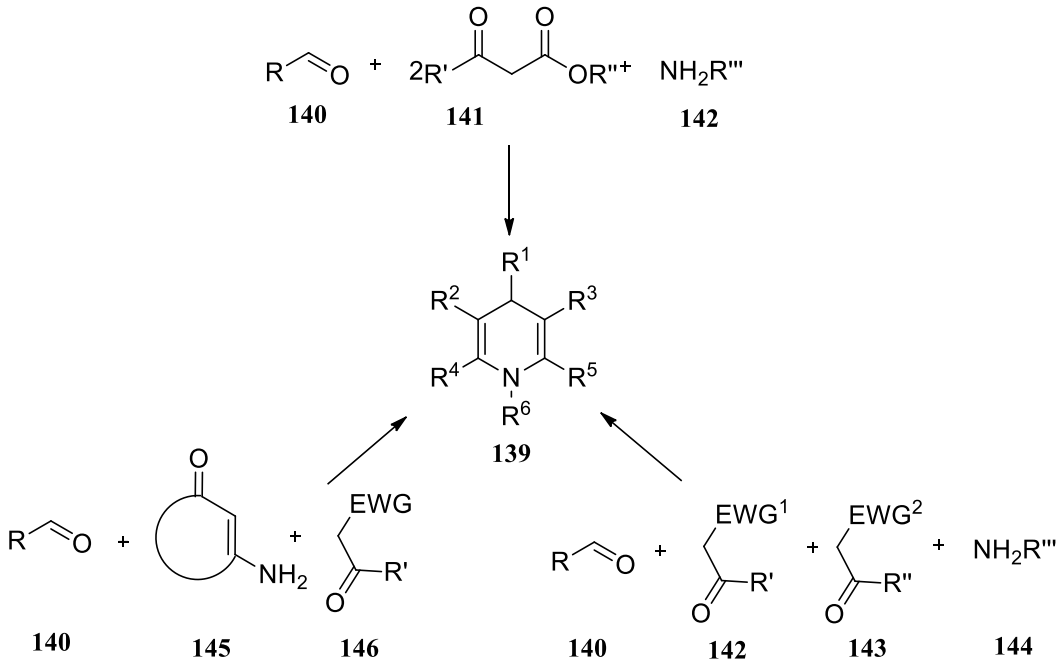



**134** **135** **137** **138**

| Entry | Ketone | Condition | Ref. |
|---|---|---|---|
| 1 |  **134a** | 37% $BF_3.SiO_2$, solvent-free, 140$^oC$ | [119] |
| 2 | | $HClO_4/SiO_2$, Neat, 140 $^oC$ | [120] |
| 3 | | $K_5CoW_{12}O_{40}.3H_2O$, MW or Classical heating | [121] |
| 4 | | $Cu(NO_3)_2$-Zeolite | [122] |
| 5 | |  Solvent-free, 140 $^oC$ | [123] |
| 6 | | [Dsim]$HSO_4$ (1 mol%), solvent-free, 90 $^oC$ | [124] |
| 7 | | Nanocrystalline $MgAl_3O_2$, EtOH, ))) | [125] |
| 8 |  **134d** | $K_5CoW_{12}O_{40}.3H_2O$, MW or Classical heating | [121] |
| 9 | | $Cu(NO_3)_2$-Zeolite | [122] |
| 10 |  **134e** | EtOH, reflux | [126] |

## 2.6 Synthesis of 1,4-dihydropyridine

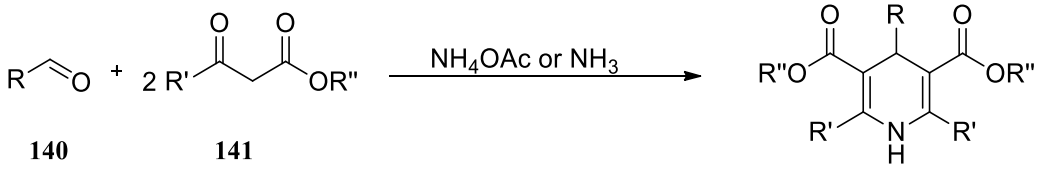
Synthesis of 1,4-dihydropyridines was first reported by Hantzsch (Table 2.2, entry 1,) by refluxing of aldehyde, *β*-ketoester and ammonium salts (Such as $NH_4OAc$) in ethanol [127]. In 1986, Katritzky *et al.* reported the mechanism of the hantzsch 1, 4-dihydropyridine synthesis [128]. The reaction can be visualized as proceeding through a Knoevenagel Condensation product as a key intermediate. There are many methods for synthesis of 1,4-dihydropyridine. Mostly reactions involve multicomponent reaction of aldehyde, 2 molecule of *α*-keto nucleophile and amine or ammonia (Scheme 2.28).



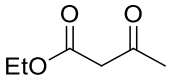
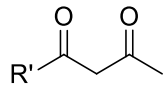
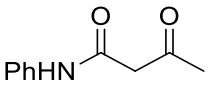

**Scheme 2.28** Synthetic route for synthesis of 1,4-dihydropyridine.

In addition various methods have been proposed to develop Hantzsch reaction for the synthesis of 1,4-dihydropyridine which are summarized in Table 2.2.

**Table 2.4** Reaction of aldehyde, *β*-ketoester and ammonia or ammonium salts with different conditions.

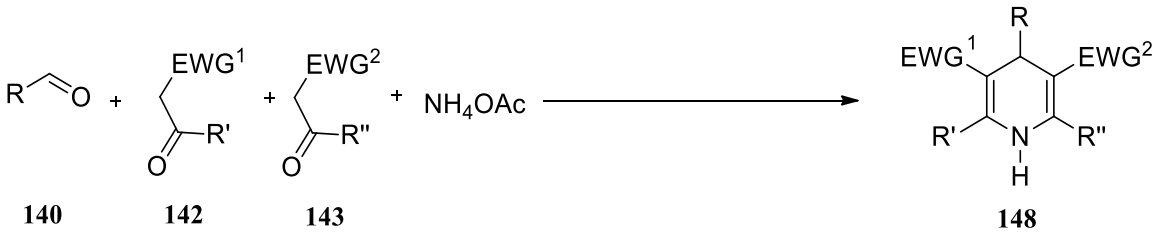



**140** **141** **147**

| Entry | 1,3-Diketone | Condition | Ref. |
|---|---|---|---|
| 1 |  | $NH_4OAc$, EtOH, reflux | [127] |
| | **141a** | $NH_4OAc$, Solvent-free, ((( | [129] |
| | | $NH_4OAc$, ASA, MeOH, rt, Grinding | [130] |
| 2 |  R'= alkyl | $NH_4OAc$, TMSCl/NaI, $CH_3CN$, rt | [131] |
| | **141b** | $NH_4OAc$, MgO nanotube, $CH_3CN$, reflux | [132] |
| | | Liq. $NH_3$, $H_2O$ | [133] |
| | | $NH_3$, aq.EtOH (1:1)/hυ | [134] |
| 3 |  **141c** | $NH_4OAc$, $Ba(NO_3)_2$, rt | [135] |

Moreover other pronucleophiles were studied in synthesis of 1,4-dihydropyridine such as 5,5-dimethyl-cyclohexane-1,3-dione (142b), cyclohexane-1,3-dione cyclohexane-1,3-dione (143a), Indan-1,3-dione (143b), 2,2-Dimethyl-[1,3]dioxane-4,6-dione (1142c), malononitrile (142d) and terminal alkyne (143c) by using Brønsted or Lewis acid in various condition which shows in Table 2.3.

**Table 2.5** Reaction of aldehyde, nucleophiles and amine or ammonium salts with different conditions in the synthesis of 1,4-dihydropyridine.




**140** **142** **143** **148**

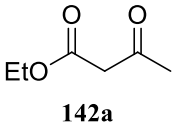
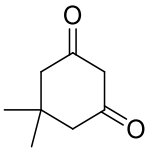
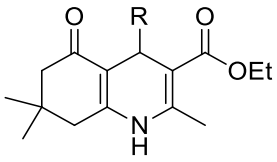
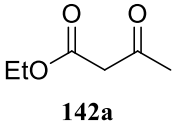
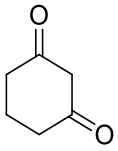
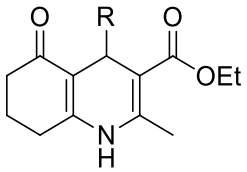
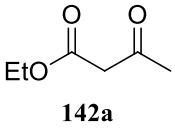
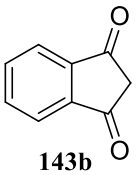
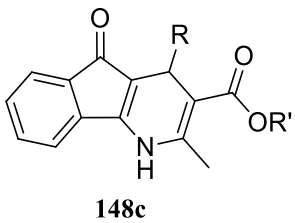
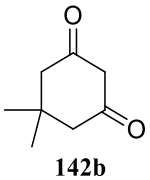
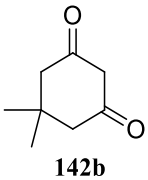
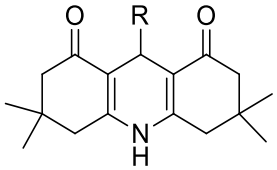
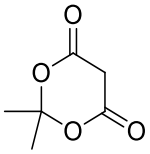
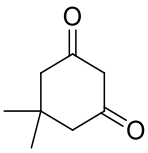
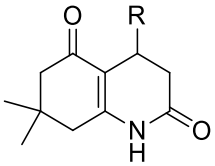
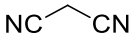
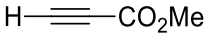
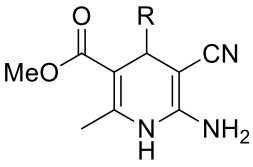
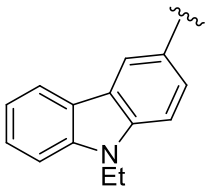
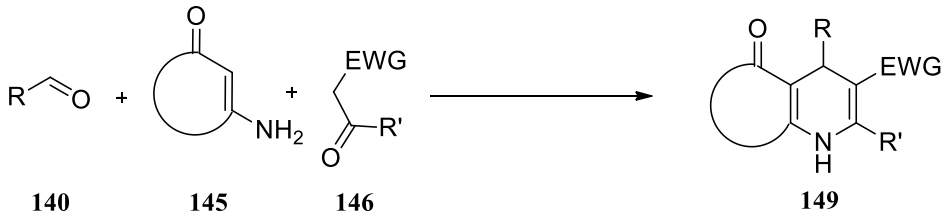
| Entry | Nu1 | Nu2 | Product | Condition |
|---|---|---|---|---|
| 1 |  **142a** |  **142b** |  **148a** | rt, Grinding [130]<br>$Yb(OTf)_3$, EtOH, rt [136]<br>ASA, MeOH, 70 $^oC$ [137] |
| 2 |  **142a** |  **143a** |  **148b** | $I_2$, rt [138] |
| 3 |  **142a** |  **143b** |  **148c** | Grinding, rt, solvent-free [139] |
| 4 |  **142b** |  **142b** |  **148d** | Glycol, MW [140] |

**Table 2.5** (Continued)

| Entry | Nu1 | Nu2 | Product | Condition |
|---|---|---|---|---|
| 5 |  **142c** |  **142b** |  **148e** | EtOH, MW [141] |
| 6 |  **142d** |  **143c** |  **148d** | $R\text{-}NH_2$, $InCl_3$, 70 $^oC$, MW<br>R=  <br>[142] |

Furthermore many enamines (145) such as 2,6-diamino-3*H*-pyrimidin-4-one (145a), 6-Amino-1,3-dimethyl-1 *H*-pyrimidine-2,4-dione (145b), naphthalen-2-ylamine (145c), 3-amino-5,5-dimethyl-cyclohex-2-enone (145d), 4-methoxy-aniline (145e) and 4-amino-pent-3-en-2-one (145f) were used as a nucleophile for ammomia-free reaction in the synthesis of 1,4-dihydropyridine which reacted with aldehyde (140) and other nucleophile (146). Various conditions had been reported which are summarized in Table 2.4.

**Table 2.6** Reaction of aldehyde, enamine, nucleophile with different conditions in the synthesis of 1,4-dihydropyridine.




**140** **145** **146** **149**

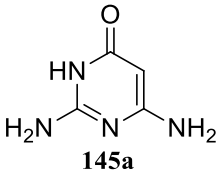
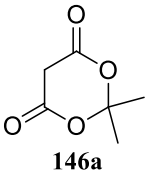
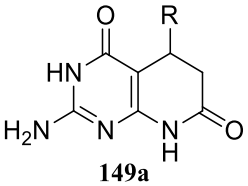
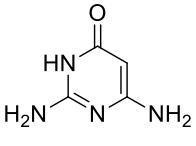
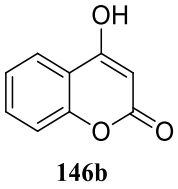
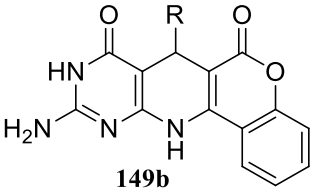
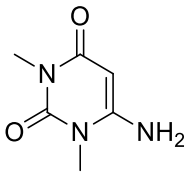
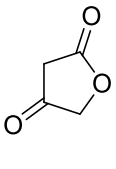
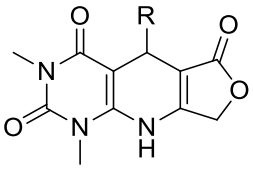
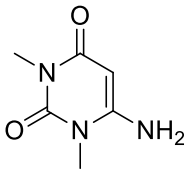
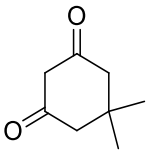
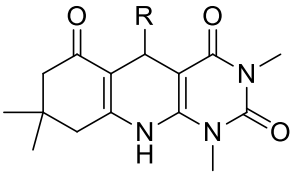
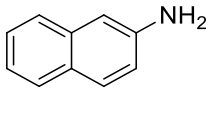
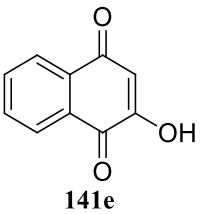
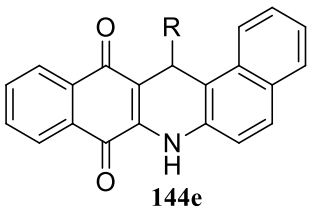
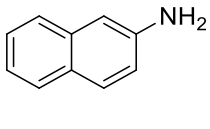
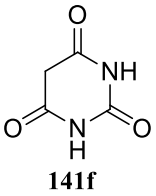
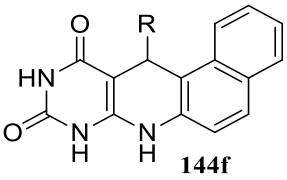
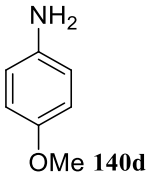
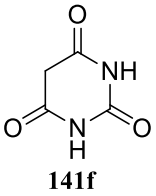
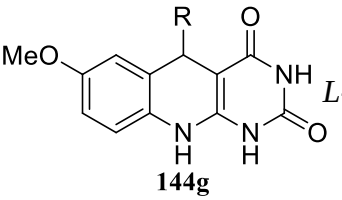
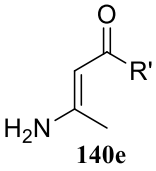
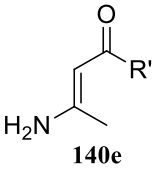
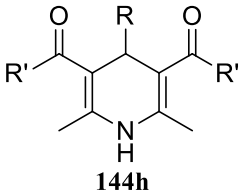
| Entry | Nu1 | Nu2 | Product | Condition |
|---|---|---|---|---|
| 1 |  **145a** |  **146a** |  **149a** | $H_2O$, TEBAC (4 mol%), 90 $^oC$ [143] |
| 2 |  **145a** |  **146b** |  **149b** | DMF, 140 $^oC$, MW [144] |
| 3 |  **145b** |  **146c** |  **149c** | $H_2O$, 90 $^oC$ [145] |
| 4 |  **145b** |  **146d** |  **149d** | *p*-TSA (20 mol%), $H_2O$, 90 $^oC$ [146] |

**Table 2.6** (Continue)

| Entry | Nu1 | Nu2 | Product | Condition |
|---|---|---|---|---|
| 5 |  **140c** |  **141e** |  **144e** | [BMIm]$BF_4$, rt [145] |
| 6 |  **140c** |  **141f** |  **144f** | $H_2O$, $I_2$ (5 mol%), rt [147] |
| 7 |  **140d** |  **141f** |  **144g** | *L*-Proline (20 mol%), $H_2O$ [148] |
| 8 |  **140e** |  **140e** |  **144h** | TMSCl/NaI, $CH_3CN$, rt [131] |

# CHAPTER 3

# MATERIALS AND METHODS

## 3.1 Materials

### 3.1.1 Instrumentation

Nuclear magnetic resonance ($^{1}$H-NMR and $^{13}$C-NMR) spectra were recorded at 400 MHz on Varian Mercury Plus 400 spectrometer at Department of Chemistry, Khon Kaen University and Bruker AVANCE 400 spectrometer at Ramkhamhaeng University. Deuterochloroform ($CDCl_3$) and dimethyl sulfoxide-$d_6$ (DMSO-$d_6$) were used as a solvent. Chemical shifts are in parts per million ($\delta$, ppm) relative to tetramethylsilane ($\delta$ 0.00 ppm). Coupling constants ($J$) were reported in Hertz (Hz). Splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; dd, double doublet.

High resolution mass spectra (HRMS) were measured on Bruker Daltonics, microTOF at Department of Chemistry, Mahidol University.

The infrared (IR) spectra were recorded on a FTIR Perkin-Elmar Spectrum 1 spectrophotometer. IR spectra were recorded either as KBr platelet at the Central Instrumentation Unit, Faculty of science, Mahasarakham University.

### 3.1.2 Chromatographic systems

Thin layer chromatography (TLC) on aluminum sheets with silica gel 60 F254 was used routinely for monitoring reaction process. Flash column chromatography was used for purification some of products reaction using a glass columns dry-packed with silica gels (40-60 mesh) according to the method of W. Clark Still [149].

### 3.1.3 Chemicals and reagents

All chemicals and reagents which were used in this work are listed in Table 3.1

**Table 3.1** List of chemicals used in this work.

| Chemicals | Formula | Grade | Company |
|---|---|---|---|
| Acetic acid | $C_2H_4O_2$ | AR | LAB SCAN |
| Acetonitrile | $C_2H_3N$ | HPLC | CARLO ERBA |
| Acetophenone | $C_8H_8O$ | AR | MAY&BAKER |
| Aluminiumtrichloride | $AlCl_3$ | AR | Carlo Erba |
| Amberist 15 | - | - | Merck |
| Ammonuim acetate | $NH_4OAc$ | AR | UNILAB |
| Ammonuim hydroxide | $NH_4OH$ | AR | UNILAB |
| Aniline | $C_6H_7N$ | AR | Fluka |
| Benzil | $C_{14}H_{10}O_2$ | AR | ACROS |
| Ceric ammonium nitrate (CAN) | $Ce(NO_3)_6(NH_4)_2$ | AR | ACROS |
| Copper(II)acetate | $Cu(OAc)_2$ | AR | UNILAB |
| Dichloromethane | $CH_2Cl_2$ | Commercial | Italmar |
| Dimethylformamide (DMF) | $C_2H_7NO$ | HPLC | Fluka |
| Dimethylsulfoxide (DMSO) | $C_2H6SO$ | HPLC | LAB-SCAN |
| 5,5-Dimethyl-cyclohexane-1,3-dione | $C_8H_{12}O_2$ | AR | ACROS |
| Ethanol | $C_2H_5OH$ | HPLC | LAB-SCAN |
| Ethyl acetate | $C_4H8O_2$ | Commercial | Italmar |
| Hexane | $C_6H_{14}$ | Commercial | Italmar |
| 2-Hydroxybenzaldehyde | $C_7H_6O_2$ | AR | ACROS |
| Indole | $C_8H_7N$ | AR | ACROS |
| Iodine | $I_2$ | AR | ACROS |
| Iron(III)chloride | $FeCl_3$ | AR | UNILAB |
| L-proline | $C_5H_9NO_2$ | AR | Fluka |
| Maleic anhydride | $C_4H_2O_3$ | AR | Fluka |
| Malononitrile | $C_3H_2N_2$ | AR | ACROS |
| Methanol | $CH_4O$ | HPLC | CARLO ERBA |
| 4-methoxyacetophenone | $C_9H_{10}O_2$ | AR | ACROS |

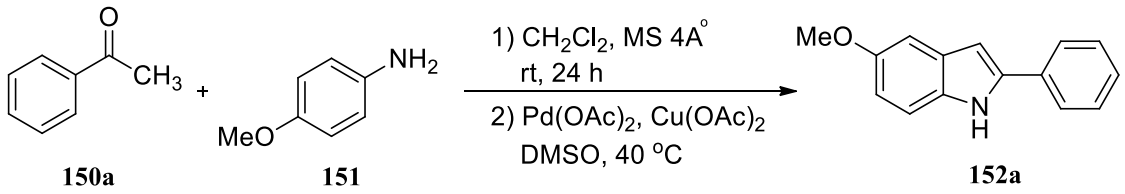
**Table 3.1** (Continued).

| Chemicals | Formula | Grade | Company |
|---|---|---|---|
| 4-methylacetophenone | $C_9H_{10}O_2$ | AR | ACROS |
| 4-methoxyindole | $C_9H_9NO$ | AR | ACROS |
| 5-methoxyindole | $C_9H_9NO$ | AR | ACROS |
| 6-methoxyindole | $C_9H_9NO$ | AR | ACROS |
| 7-methoxyindole | $C_9H_9NO$ | AR | ACROS |
| *N,N´*-dimethylaniline | $C_8H_{11}N$ | AR | Fluka |
| Nitric acid | $HNO_3$ | AR | CARLO ERBA |
| Palladium(II)acetate | $Pd(OAc)_2$ | AR | ACROS |
| 9,10-Phenanthrenequinone | $C_{14}H_8O_2$ | AR | ACROS |
| Phenyl hydrazine | $C_6H_8N2$ | AR | ACROS |
| Potassiumbromide | KBr | AR | UNILAB |
| Potassiumcyanide | KCN | AR | UNILAB |
| Silica gel | $SiO_2$ | - | Merck |
| Sodium hydroxide | NaOH | AR | UNILAB |
| Sulphuric acid | $H_2SO_4$ | AR | UNILAB |
| Tetramethylethylenediamine (TMEDA) | $C_6H_{16}N_2$ | AR | Fluka |
| Thiamine hydrochloride | $C_{12}H_{17}N_4OS.HCl$ | AR | ACROS |
| Thiosemicarbazide | $CH_5N_3S$ | AR | ACROS |
| *p*-toluenesulfonic acid | $C_7H_8O_3S$ | AR | MERCK |
| Toluene | $C_6H_5CH_3$ | HPLC | CARLO ERBA |
| Triethylamine | $C_6H_{15}N$ | AR | ACROS |
| Trifluoracetic acid | $C_2HO_2F_3$ | AR | ACROS |

## 3.2 Methods

### 3.2.1 Synthesis of indole derivertives

#### 3.2.1.1 Synthesis of 5-methoxy-2-phenyl-1*H*-indole (152a)




**150a** **151** **152a**

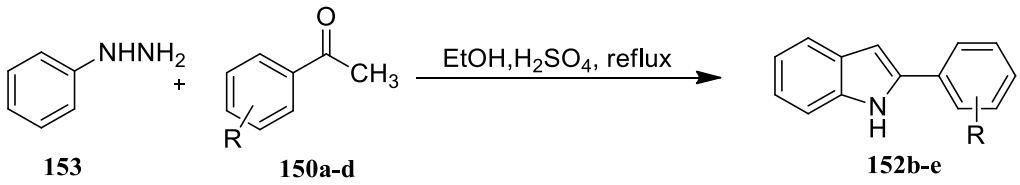
A mixture of acetophenone (150a) (0.12 mL. 1.0 mmol, 1.0 equiv.) and 4-methoxy aniline (151) (147.8 mg, 1.2 mmol, 1.2 equiv.) and 4Aº molecular sieve (200 mg) and $CH_2Cl_2$ (3 mL) was stirred at room temperature for 24 h. The reaction mixture was filtrated and evaporated to release crude imine then $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 10 mol%), $Cu(OAc)_2$ (544.9 mg, 3.0 mmol, 3.0 equiv.) and DMSO (5 mL) were added. The mixture reaction was refluxed under $N_2$ atmosphere for 12 h. The mixture was then allowed to cool down to room temperature, 5 mL of EtOAc was added, followed by filtration through a pad of silica gel. The filtrate was washed with water (3×10 mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give crude residue. This material was purified by flash chromatography (silica gel, 1:8 EtOAc/Hexane) to afford 152a (129.5 mg, 58%); as a yellowish white powder which was identified by comparison of their physical data with those reported in the literature [68]. Spectral data for 152a were presented below.

mp 161-163 ºC

IR (KBr) ($cm^{-1}$): 1180, 1254, 1292, 1349, 1459, 1498, 1552, 2834, 2970, 3012, 3060

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.85 (s, 3H, $OCH_3$), 6.74 (s, $J$ = 8.80 Hz, 1H, ArH), 6.84 (d, $J$ = 8.80 Hz, 1H, ArH), 7.07 (s, 1H, ArH), 7.24-7.31 (m, 2H, ArH), 7.42 (t, $J$ = 7.40 Hz, 2H, ArH), 7.63 (d, $J$ = 7.60 Hz, 2H, ArH), 8.20 (br s, 1H, NH)

3.2.1.2 Synthesis of indole derivatives from Fisher reaction

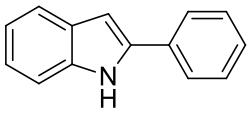



**153** **150a-d** **152b-e**

General procedure A: One-pot indole synthesis

The solution of phenylhydrazine (153) (0.99 mL, 10.0 mmol, 1.0 equiv.) and acetophenone derivative (150) (10.0 mmol, 1.0 equiv.) was refluxed in EtOH (5 mL) for 4 h. The solution was cooled to room temperature then added $H_2SO_4$ (5 mL). The reaction mixture was refluxed for 4 h and then poured into ice water; precipitate was collected by filtration, dried and crystallized from methanol to give 2-substituted indole (152a-d).

2-phenyl-1*H*-indole (152b)




**152b**

Synthesized by general procedure A from phenylhydrazine (153) (0.99 mL, 10.0 mmol, 1.0 equiv.) and acetophenone (150a) (1.20 mL, 10.0 mmol, 1.0 equiv.) in EtOH (5 mL) and conc. $H_2SO_4$ (5 mL) to give 152b (1.85 g, 96%) as a yellowish white powder which was crystallized from methanol. The product was identified by comparison of their physical data with those reported in the literature [68]. Spectral data for 152b were presented below.

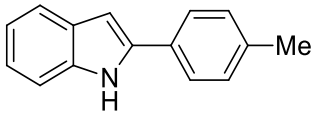
mp 166-167 ºC

IR (KBr) ($cm^{-1}$): 1300, 1349, 1457, 1509, 1541, 3051

$^1$H NMR (400 MHz, $CDCl_3$+3 drops DMSO-$d_6$): $\delta$ 6.74 (s, 1H, ArH), 7.00 (t, $J$ = 7.20 Hz, 1H, ArH), 7.08 (t, $J$ = 7.60 Hz, 1H, ArH), 7.22 (t, $J$ = 7.20 Hz, 1H, ArH), 7.34 (d, $J$ = 8.00 Hz, 1H, ArH), 7.36 (d, $J$ = 8.00 Hz, 2H, ArH), 7.53 (d, $J$ = 7.60 Hz, 1H, ArH), 7.69 (d, $J$ = 8.00 Hz, 2H, ArH), 10.06 (s, 1H, NH)

$^{13}$C MNR (100 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 98.98, 111.02, 119.56, 120.14, 121.65, 125.09 (2), 127.19, 128.62 (2), 128.88, 132.41, 136.96, 137.80

2-(4-methlyphenyl)-1*H*-indole (152c)




**152c**

Synthesized by general procedure A from phenylhydrazine (153) (0.99 mL, 10.0 mmol, 1.0 equiv.) and 4-methylacetophenone (150c) (1.34 g, 10 mmol, 1.0 equiv.) in EtOH (5 mL) and conc. $H_2SO_4$ (5 mL) to give 152c (1.76 g, 85%) as a yellowish white powder which was crystallized from methanol. The product was identified by comparison of their physical data with those reported in the literature [150]. Spectral data for 152c were presented below.

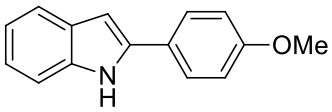
mp 212-213 ºC

IR (KBr) ($cm^{-1}$): 1117, 1237, 1297, 1348, 1427, 1455, 1505, 1545, 2915, 3049

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.31 (s, 3H, $CH_3$), 6.70 (d, $J$ = 1.20 Hz, 1H, ArH), 7.04 (t, $J$ = 7.60 Hz, 1H, ArH), 7.10 (t, $J$ = 6.80 Hz, 1H, ArH), 7.16 (d, $J$ = 8.00 Hz, 2H, ArH), 7.30 (d, $J$ = 7.60 Hz, 1H, ArH), 7.47 (d, $J$ = 8.00 Hz, 2H, ArH), 7.54 (d, $J$ = 7.60 Hz, 1H, ArH), 8.22 (s, 1H, NH)

$^{13}$C MNR (100 MHz, $CDCl_3$): $\delta$ 21.21, 99.38, 110.79, 120.17, 120.50, 122.10, 122.66, 125.05, 125.86, 128.97, 129.56, 129.69, 136.69, 137.62, 138.04

2-(4-methoxyphenyl)-1*H*-indole (152d)




**152d**

Synthesized by general procedure A from phenylhydrazine (153) (0.99 mL, 10.0 mmol, 1.0 equiv.) and 4-methoxyacetophenone (150b) (1.50 g, 10 mmol, 1.0 equiv.) in EtOH (5 mL) and conc. $H_2SO_4$ (5 mL) to give 152d (1.76 g, 79%) as a yellowish white powder which was crystallized from methanol. The product was identified by comparison of their physical data with those reported in the literature [151]. Spectral data for 152d were presented below.

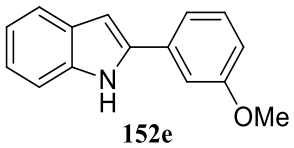
mp 220-221 ºC

IR (KBr) ($cm^{-1}$): 1182, 1252, 1289, 1348, 1432, 1457, 1501, 1543, 2837, 2966, 3005, 3054

$^1$H NMR (400 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 3.76 (s, 3H, $OCH_3$), 6.58 (s, 1H, ArH), 6.87 (d, $J$ = 8.80 Hz, 2H, ArH), 6.93 (t, $J$ = 6.80 Hz, 1H, ArH), 7.00 (t, $J$ = 7.20 Hz, 1H, ArH), 7.32 (d, $J$ = 7.60 Hz, 1H, ArH), 7.45 (d, $J$ = 7.60 Hz, 1H, ArH), 7.64 (d, $J$ = 8.80 Hz, 2H, ArH), 10.62 (s, 1H, NH)

$^{13}$C MNR (100 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 54.76, 97.12, 110.60, 113.68, 118.93, 119.34, 120.70, 124.94, 126.08, 128.65, 136.58, 137.65, 158.51

2-(3-methoxyphenyl)-1*H*-indole (152e)




**152e**

Synthesized by general procedure A from phenylhydrazine (153) (0.99 mL, 10.0 mmol, 1.0 equiv.) and 3-methoxylacetophenone (150d) (1.37 mL, 10 mmol, 1.0 equiv.) in EtOH (5 mL) and conc. $H_2SO_4$ (5 mL) to give 152e (1.65 g, 74%) as a yellowish white powder which was crystallized from methanol. The product was identified by comparison of their physical data with those reported in the literature [152]. Spectral data for 152e were presented below.

mp 130.5-132.5 ºC

IR (KBr) ($cm^{-1}$): 1169, 1219, 1263, 1303, 1348, 1434, 1458, 1542, 1597, 2836, 2939, 2967, 3010, 3048

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.91 (s, 3H, $CH_3$), 6.86 (s, 1H, ArH), 6.91 (dd, $J$ = 8.20, 1.60 Hz, 1H, ArH), 7.16 (t, $J$ = 7.60 Hz, 1H, ArH), 7.22-7.29 (m, 3H, ArH), 7.38 (d, $J$ = 8.00 Hz, 1H, ArH), 7.43 (d, $J$ = 8.00 Hz, 1H, ArH), 7.67 (d, $J$ = 7.60 Hz, 1H, ArH), 8.38 (s, 1H, NH)

$^{13}$C MNR (100 MHz, $CDCl_3$): $\delta$ 55.33, 100.18, 110.89, 110.95, 113.08, 117.62, 120.25, 120.66, 122.39, 129.14, 130.05, 133.73, 136.73, 137.72, 160.06

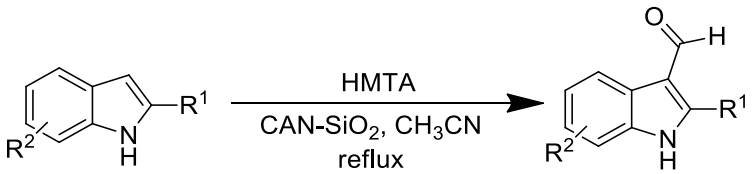
3.2.2 Synthesis of 3-formylindole derivatives

3.2.2.1 Preparation of 10% ceric ammonium nitrate on silica gel (10% CAN-$SiO_2$)

A solution of CAN (1.01 g) in $H_2O$ (2.0 mL) was added dropwise to silica gel 60 (9.01 g, Merck Kieselgel 60, particle size 0.063–0.200 mm, 70–230 mesh) under stirring followed by evaporation under reduced pressure at 60 $^oC$ for 4 h. A dry yellowish powder was collected and stored in a well-sealed bottle. Other loading ratios of CAN–$SiO_2$ were prepared by the same method (9.51 g silica gel and 0.51 g CAN for 5% CAN–$SiO_2$, 8.51 g silica gel and 1.51 g CAN for 15% CAN–$SiO_2$).

3.2.2.2 Synthesis of 3-formylindole derivertievs

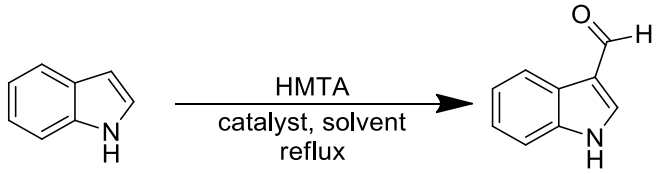
General procedure B: CAN–$SiO_2$ catalyzed a formylation of indole




**152a-j** **154a-j**

A mixture of indole (152) (1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol CAN, 10 mol%) was refluxed in $CH_3CN$ (5.0 mL). After the reaction was complete, the mixture was evaporated to give a crude residue of CAN–$SiO_2$ and product. The crude residue was washed with EtOAc (5×10 mL) and dried to leave a crude product that was purified by short flash column chromatography (EtOAc/hexane) to provide formylindole product 154.

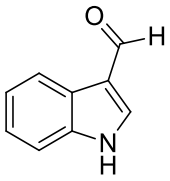
General procedure C: Formylation of indole




**1** **154a**

A mixture of indole (1) (1.0 mmol, 1.0 equiv.), HMTA (280.3 mg, 2.0 mmol, 2.0 equiv.) and catalyst (0.01 mmol, 10 mol%) was refluxed in solvent (5.0 mL). Catalysts and solvents show in table 4.2 and 4.3. After the reaction was complete, the mixture was evaporated to give a crude residue of a product. The crude residue purified by short flash column chromatography to provide 3-formylindole product 154a.

1*H*-indole-3-carbaldehyde (154a)




**154a**

Synthesized by general procedure B from indole (1) (117.2 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 20 h. Crude product was purified by short flash column chromatography (1:2 EtOAc/hexane) on silica gel to provide 154a (117.58 mg, 81%) as a cream powder which was identified by comparison of their physical data with those reported in the literature [84]. Spectral data for 154a were presented below.

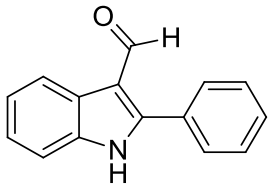
mp 195-197 ºC

IR (KBr) ($cm^{-1}$): 1521, 1575, 1636, 2930, 3170

$^1$H NMR (400 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 7.21 (m, 2H, ArH), 7.36 (d, $J$ = 4.80 Hz, 1H, ArH), 7.78 (s, 1H, ArH), 8.17 (d, $J$ = 4.80 Hz, 1H, ArH), 9.87 (s, 1H, CHO)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 111.81, 118.79, 121.37, 122.61, 123.89, 124.39, 136.76, 137.06, 185.60

2-phenyl-1*H*-indole-3-carbaldehyde (154b)



**154b**

Synthesized by general procedure B from 2-phenyl-1*H*-indole (152b) (193.3 mg, 1.0 mmol), HMTA (350.0 mg, 2.5 mmol), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 12 h. Crude product was purified by short flash column chromatography (1:3 EtOAc/hexane) on silica gel to provide 154b (194.7 mg, 88%) as a cream powder which was identified by comparison of their physical data with those reported in the literature [83]. Spectral data for 154b were presented below.

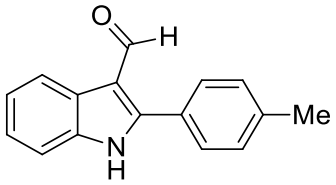
mp 241-242 ºC

IR (KBr) ($cm^{-1}$): 1578, 1627, 2927, 3136

$^1$H NMR (400 MHz, $CDCl_3$+4 drops DMSO-$d_6$): $\delta$ 7.15-7.21(m, 2H, ArH), 7.40-7.48 (m, 4H, ArH), 7.61(t, 2H, ArH), 8.25 (t, 1H, ArH), 9.95 (s, 1H, CHO), 11.71 (br s, 1H, NH)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 111.13, 113.47, 120.87, 121.79, 122.97, 125.34, 128.04, 128.93, 129.17, 129.59, 130.22, 135.48, 148.92, 185.61

2-(4-methylphenyl)-1*H*-indole-3-carbaldehyde (154c)




**154c**

Synthesized by general procedure B from 2-(4-methylphenyl)-1*H*-indole (152c) (207.3 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 12 h. Crude product was purified by short flash column chromatography (1:3 EtOAc/hexane) on silica gel to provide 154c (164.7 mg, 70%) as a cream powder which was identified by comparison of their physical data with those reported in the literature [83]. Spectral data for 154c were presented below.

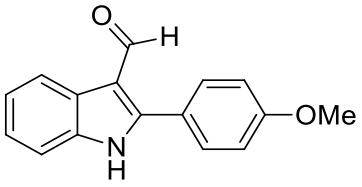
mp 202-204 ºC

IR (KBr) ($cm^{-1}$): 1579, 1624, 3145

$^1$H NMR (400 MHz, $CDCl_3$ + 5 drops DMSO-$d_6$): $\delta$ 2.37 (s, 3H, $CH_3$), 7.17-7.21 (m, 2H, ArH), 7.26 (d, $J$ = 7.84 Hz, 2H, ArH), 7.39-7.41 (m, 1H, ArH), 7.50 (d, $J$ = 7.96 Hz, 2H, ArH), 9.96 (s, 1H, CHO), 11.50 (s, 1H, NH)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 5 drops DMSO-$d_6$): $\delta$ 20.83, 111.23, 113.62, 121.15, 122.02, 123.14, 125.68, 126.94, 128.65, 129.00, 129.26, 135.66, 139.38, 149.46, 186.07

2-(4-methoxylphenyl)-1*H*-indole-3-carbaldehyde (154d)




**154d**

Synthesized by general procedure B from 2-(4-methoxylphenyl)-1*H*-indole (152d) (223.3 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 12 h. Crude product was purified by short flash column chromatography (1:3 EtOAc/hexane) on silica gel to provide 154d (195.9 mg, 78%) as a cream powder which was identified by comparison of their physical data with those reported in the literature [153]. Spectral data for 154d were presented below.

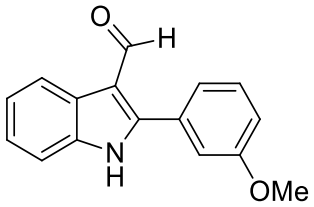
mp 204-205 ºC

IR (KBr) ($cm^{-1}$): 1628, 3175

$^1$H NMR (400 MHz, $CDCl_3$ + 5 drops DMSO-$d_6$): $\delta$ 3.80 (s, 3H, $CH_3$), 6.97 (d, $J$ = 8.65 Hz, 2H, ArH), 7.15-7.19 (m, 2H, ArH), 7.38 (t, 1H, ArH), 7.55 (d, $J$ = 8.66 Hz, 2H, ArH), 8.23 (d, $J$ = 7.59 Hz, 1H, ArH), 9.93 (s, 1H, CHO), 11.54 (s, 1H, NH)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 5 drops DMSO-$d_6$): $\delta$ 54.91, 111.17, 113.36, 113.78, 121.00, 121.94, 122.13, 123.02, 125.72, 130.70, 135.62, 145.30, 160.33, 185.82

2-(3-methoxylphenyl)-1*H*-indole-3-carbaldehyde (154e)




**154e**

Synthesized by general procedure B from 2-(3-methoxylphenyl)-1*H*-indole (152e) (223.3 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 12 h. Crude product was purified by short flash column chromatography (1:3 EtOAc/hexane) on silica gel to provide 154e (201.3 mg, 81%) as a cream powder. Spectral data for 154e were presented below.

mp 196-197 ºC

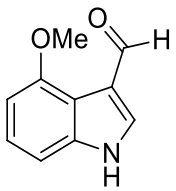
IR (KBr) ($cm^{-1}$): 3175, 1628, 1453, 1370, 1239, 1166

$^1$H NMR (400 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 3.80 (s, 3H, $CH_3$), 7.19 (dd, $J$ = 2.66, 8.27 Hz, 1H, ArH), 7.35 (d, $J$ = 8.13 Hz, 1H, ArH), 7.39 (m, 1H, ArH), 8.25 (d, $J$ = 7.28 Hz, 1H, ArH), 9.99 (s, 1H, CHO), 11.68 (br s, 1H, NH)

$^{13}$C MNR (100 MHz) ($CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 54.9, 111.3, 113.8, 114.7, 114.9, 121.2, 121.9, 122.1, 123.3, 125.6, 129.4, 131.1, 135.7, 148.9, 159.2, 185.9

HRMS: m/z calcd for $C_{16}H_{13}NO_2Na$ $[M+Na]^+$ :274.0844 ; Found: 274.0858

4-methoxy-1*H*-indole-3-carbaldehyde (154f)




**154f**

Synthesized by general procedure B from 4-methoxy-1*H*-indole (152f) (147.2 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 9 h. A crude product was purified by short flash column chromatography (1:2 EtOAc/hexane) on silica gel to provide 154f (113.87 mg, 65%) as a cream powder which was identified by comparison of their physical data with those reported in the literature [84]. Spectral data for 154f were presented below.

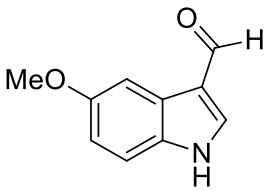
mp 105-106 ºC

IR (KBr) ($cm^{-1}$): 1515, 1586, 1648, 2964, 3213

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.98 (s, 3H, $CH_3$), 6.70 (d, $J$ = 7.82 Hz, 1H, ArH), 7.08 (d, $J$ = 8.15 Hz, 1H, ArH), 7.18 (t, 2H, ArH), 7.90 (d, $J$ = 2.74 Hz, 1H, ArH), 9.68 (br s, 1H, NH), 10.47 (s, 1H, CHO)

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 55.34, 102.47, 105.31, 116.06, 119.37, 123.51, 124.25, 128.64, 137.77, 154.46

5-methoxy-1*H*-indole-3-carbaldehyde (154g)




**154g**

Synthesized by general procedure B from 5-methoxy-1*H*-indole (152g) (147.2 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol. 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 15 h. Crude product was purified by short flash column chromatography (1:2 EtOAc/hexane) on silica gel to provide 154g (105.1 mg, 60%) as a cream powder which was identified by comparison of their physical data with those reported in the literature [84]. Spectral data for 154g were presented below.

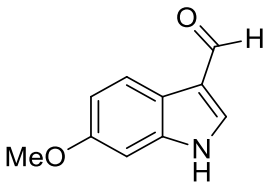
mp 175-176 ºC

IR (KBr) ($cm^{-1}$): 1524, 1640, 2947, 3184

$^1$H NMR (400 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 3.77 (s, 3H, $CH_3$), 6.80 (dd, $J$ = 8.75, 1.90 Hz, 1H, ArH), 7.26 (d, $J$ = 8.80 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.72 (d, $J$ = 2.95 Hz, 1H, ArH), 9.86 (s, 1H, CHO), 11.35 (br s,1H, NH)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 55.14, 102.45, 112.37, 113.46, 118.18, 124.70, 131.60, 136.42, 155.64

6-methoxy-1*H*-indole-3-carbaldehyde (154h)




**154h**

Synthesized by general procedure B from 6-methoxy-1*H*-indole (152h) (147.2 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.), and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 6 h. Crude product was purified by short flash column chromatography (1:2 EtOAc/hexane) on silica gel to provide 154h (122.62 mg, 70%) as a brown powder which was identified by comparison of their physical data with those reported in the literature [84]. Spectral data for 154h were presented below.

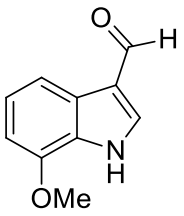
mp 182-183 ºC

IR (KBr) ($cm^{-1}$): 1528, 1582, 1638, 3191

$^1$H NMR (400 MHz, $CDCl_3$ + 5 drops DMSO-$d_6$): $\delta$ 3.75 (s, 3H, $CH_3$), 6.78 (dd, $J$ = 5.47, 3.49 Hz, 1H, ArH), 6.86 (d, $J$ = 1.74 Hz, 1H, ArH), 7.71 (t, 1H, ArH), 7.96 (m, 1H, ArH), 9.82 (s, 1H, CHO), 11.40 (br s,1H, NH)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 5 drops DMSO-$d_6$): $\delta$ 54.63, 94.71, 111.06, 117.58, 117.98, 121.09, 135.54, 137.45, 156.39

7-methoxy-1*H*-indole-3-carbaldehyde (154i)




**154i**

Synthesized by general procedure B from 7-methoxy-1*H*-indole (152i) (147.2 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.) and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 12 h. Crude product was purified by short flash column chromatography (1:2 EtOAc/hexane) on silica gel to provide 154i (134.9 mg, 77%) as a cream powder which was identified by comparison of their physical data with those reported in the literature [154]. Spectral data for 154i were presented below.

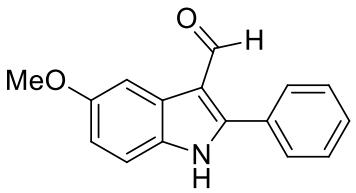
mp 156-158 ºC

IR (KBr) ($cm^{-1}$): 1506, 1622, 2940, 3176

$^1$H NMR (400 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 3.90 (s, 3H, $CH_3$), 6.70 (d, $J$ = 7.84 Hz, 1H, ArH), 7.15 (t, $J$ = 7.92 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.78 (d, $J$ = 7.98 Hz, 1H, ArH), 9.90 (s, 1H, CHO)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 55.36, 104.11, 113.94, 119.37, 123.45, 125.85, 127.19, 135.42, 146.07, 185.68

5-methoxy-2-phenyl-1*H*-indole-3-carbaldehyde (154j)




**154j**

Synthesized by general procedure B from 5-methoxy-2-phenyl-1*H*-indole (152a) (223.3 mg, 1.0 mmol, 1.0 equiv.), HMTA (350.0 mg, 2.5 mmol, 2.5 equiv.) and 10%CAN–$SiO_2$ (548.2 mg, 0.01 mmol of CAN, 10 mol%) in $CH_3CN$ (5.0 mL) with reaction time 12 h. A crude product was purified by short flash column chromatography (1:3 EtOAc/hexane) to provide 154j (223.64 mg, 89%) as a cream powder. Spectral data for 154j were presented below.

mp 250-251 ºC.

IR (KBr) ($cm^{-1}$): 3129, 2982, 1624, 1468, 1368, 1259, 1213

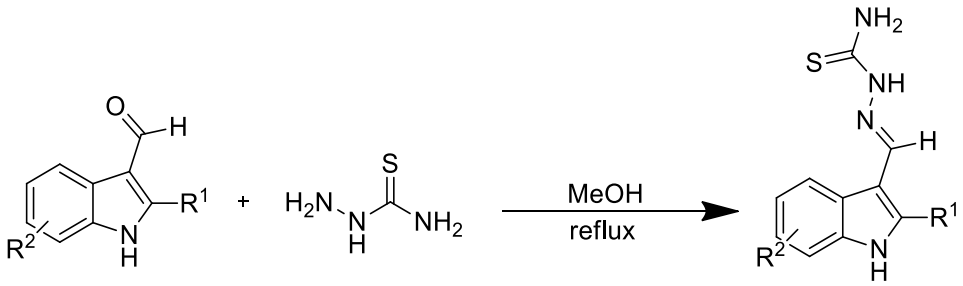
$^1$H NMR (400 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 3.79 (s, 3H, $CH_3$), 6.80 (dd, $J$ = 2.21, 8.97 Hz, 1H, ArH), 7.22 (d, $J$ = 8.75 Hz, 1H, ArH), 7.45 (m, 3H, ArH), 7.59 (d, $J$ = 6.2 Hz, 2H, ArH), 7.73 (s, 1H, ArH), 9.91 (s, 1H, CHO), 11.82 (br s, 1H, NH)

$^{13}$C NMR (400 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 55.1, 102.7, 112.2, 113.2, 113.6, 126.4, 128.3, 129.1, 129.9, 130.6, 149.1, 155.75, 185.7

HRMS: m/z calcd for $C_{16}H_{13}NO_2Na$ $[M+Na]^+$ :274.0844 ;Found: 274.0834

3.2.3 Synthesis of indole derivatives having thiosemicarbazone

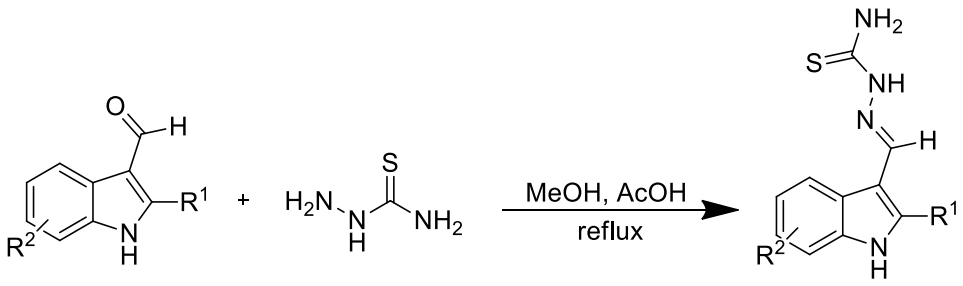
General procedure D: Synthesis of indole derivatives using thiosemicarbazide




**154a-e** **155** **156a-e**

A mixture of 3-formyl indole (154) (1.0 mmol, 1.0 equiv.) and thiosemicarbazide (155) (1.0 mmol, 1.0 equiv.) was refluxed in methanol (5 mL) until completion of the reaction. The reaction mixture was cooled to room temperature; a product was precipitated. The precipitate was filtrated and purified by crystallization by methanol to provide 156.

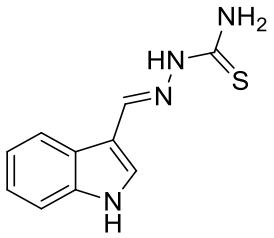
General procedure E: Synthesis of indole derivatives using thiosemicarbazide and acetic acid as a catalyst.




**154a-e** **155** **156a-e**

A mixture of indole-3-carbaldehyde 154 (1.0 mmol, 1.0 equiv.), thiosemicarbazide 155 (1.1 mmol, 1.1 equiv.) and 2 drops of acetic acid was refluxed in methanol (5 mL) for 24 hour. The reaction mixture was cooled to room temperature; a product was precipitated. The precipitate was filtrated and purified by recrystallization by methanol to provide 156.

1*H*-indole-3-carbaldehyde thiosemicarbazone (156a)




**156a**

Synthesized by general procedure D from 1*H*-indole-3-carbaldehyde (154a) (145.1 mg, 1.0 mmol, 1.0 equiv.) and thiosemicarbazide (155) (91.2 mg, 1.0 mmol, 1.0 equiv.) in 5 mL methanol with reaction time 12 h to provide 156a (187.72 mg, 86%) as a yellowish white powder. The product was identified by comparison of their physical data with those reported in the literature [155]. Spectral data for 156a were presented below.

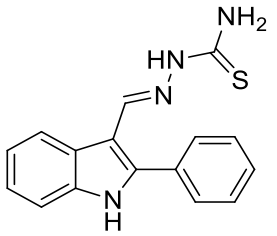
mp 221-222 ºC)

IR (KBr) ($cm^{-1}$): 1114, 1251, 1365, 1446, 1546, 1613, 3039, 3231, 3315, 3448

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.12 (t, 1H, ArH), 7.18 (t, 1H, ArH), 7.40 (t, 2H, ArH), 7.79 (s, 1H, NH), 7.98 (s, 1H, NH), 8.19 (d, $J$ = 7.65 Hz, 1H, ArH), 8.29 (s, 1H, NH), 11.14 (s, 1H, NH), 11.57 (s, 1H, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 111.08, 111.70, 120.55, 122.00, 122.56, 123.94, 130.85, 137.00, 140.77, 176.54

2-phenyl-1*H*-indole-3-carbaldehyde thiosemicarbazone (156b)



**156b**

Synthesized by general procedure D from a mixture of 2-phenyl-1*H*-indole-3-carbaldehyde (154b) (221.3 mg, 1.0 mmol, 1.0 equiv.) and thiosemicarbazide (155) (91.2 mg, 1.0 mmol, 1.0 equiv.) in methanol (5 mL) with reaction time 24 h. The reaction progress was monitored by thin layer chromatography that the reaction did not complete.

Synthesized by general procedure E from a mixture of 2-phenyl-1*H*-indole-3-carbaldehyde (154b) (221.3 mg, 1.0 mmol, 1.0 equiv.), thiosemicarbazide (155) (100.3 mg, 1.1 mmol, 1.1 equiv.) and 2 drops of acetic acid in methanol (5 mL) with reaction time 24 h to provide 156b (250.2 mg, 85%) as a yellow powder. The product was identified by comparison of their physical data with those reported in the literature [156]. Spectral data for 156b were presented below.

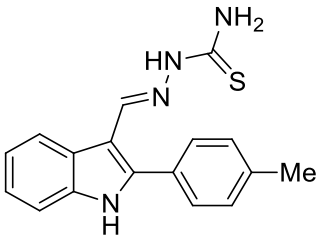
mp 180-182 ºC

IR (KBr) ($cm^{-1}$): 1097, 1276, 1358, 1454, 1530, 1584, 3153, 3242, 3398

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.15 (t, 1H, ArH), 7.23 (t, 1H, ArH), 7.37 (s, 1H, NH), 7.43 (d, $J$ = 8.00 Hz, 1H, ArH), 7.47 (t, 1H, ArH), 7.54 (t, 2H, ArH), 7.63 (d, $J$ = 8.00 Hz, 2H, ArH), 8.04 (s, 1H, NH), 8.32 (d, $J$ = 7.60 Hz, 1H, ArH), 8.50 (d, $J$ = 3.20 Hz, 1H, NH), 11.16 (s, 1H, NH), 11.88 (s, 1H, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 107.73, 111.88, 121.47, 123.12, 123.51, 125.64, 129.20, 129.33, 129.71, 131.41, 136.93, 141.84, 142.66, 176.96

2-(4-methylphenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156c)




**156c**

Synthesized by general procedure D from a mixture of 2-(4-methylphenyl)-phenyl-1*H*-indole-3-carbaldehyde (154c) (235.3 mg, 1.0 mmol, 1.0 equiv.) and thiosemicarbazide (155) (91.2 mg, 1.0 mmol, 1.0 equiv.) in methanol (5 mL) with reaction time 24 h. The reaction progress was monitored by thin layer chromatography that the reaction did not complete.

Synthesized by general procedure E from a mixture of 2-(4-methylphenyl)-phenyl-1*H*-indole-3-carbaldehyde (154c) (235.3 mg, 1.0 mmol, 1.0 equiv.), thiosemicarbazide (155) (100.3 mg, 1.1 mmol, 1.1 equiv.) and 2 drops of acetic acid in methanol (5 mL) with reaction time 24 h to provide 156c (255.97 mg, 83%) as a yellowish white powder. The product was identified by comparison of their physical data with those reported in the literature [156]. Spectral data for 156c were presented below.

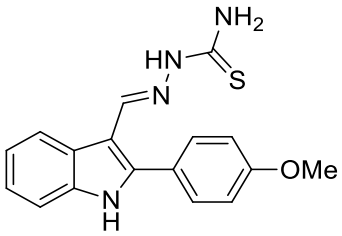
mp 239-240 ºC

IR (KBr) ($cm^{-1}$): 1098, 1279, 1357, 1455, 1534, 1590, 2959, 3022, 3126, 3233, 3397

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.39 (s, 3H, $CH_3$), 7.14 (t, 1H, ArH), 7.21 (t, 1H, ArH), 7.36 (d, $J$ = 7.20 Hz, 2H, ArH), 7.37 (s, 1H, NH), 7.41 (d, $J$ = 8.00 Hz, 1H, ArH), 7.52 (d, $J$ = 7.60 Hz, 2H, ArH), 8.04 (s, 1H, NH), 8.31 (d, $J$ = 8.00 Hz, 1H, ArH), 8.49 (s, 1H, NH), 11.15 (s, 1H, NH), 11.82 (s, 1H, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 21.33, 107.65, 111.81, 121.41, 123.00, 123.37, 125.69, 128.56, 129.56, 129.90, 136.88, 138.84, 141.99, 142.85, 176.92

2-(4-methoxylphenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156d)




**156d**

Synthesized by general procedure D from a mixture of 2-(4-methoxyphenyl)-phenyl-1*H*-indole-3-carbaldehyde (154d) (251.3 mg, 1.0 mmol, 1.0 equiv.) and thiosemicarbazide (155) (91.2 mg, 1.0 mmol, 1.0 equiv.) in methanol (5 mL) with reaction time 24 h. The reaction progress was monitored by thin layer chromatography that the reaction did not complete.

Synthesized by general procedure E from a mixture of 2-(4-methoxyphenyl)-phenyl-1*H*-indole-3-carbaldehyde (154d) (251.3 mg, 1.0 mmol, 1.0 equiv.), thiosemicarbazide (155) (100.3 mg, 1.1 mmol, 1.1 equiv.) and 2 drops of acetic acid in methanol (5 mL) with reaction time 24 h to provide 156d (259.52 mg, 80%) as a yellow powder which was identified by comparison of their physical data with those reported in the literature [157]. Spectral data for 156d were presented below.

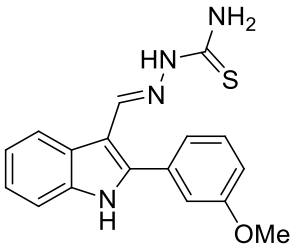
mp 171-173 ºC

IR (KBr) ($cm^{-1}$): 1029, 1096, 1177, 1257, 1357, 1456, 1532, 1595, 3024, 3135, 3246, 3404

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.83 (s, 3H, $OCH_3$), 7.12 (d, $J$ = 8.40 Hz, 2H, ArH), 7.13 (t, 1H, ArH), 7.20 (t, 1H, ArH), 7.34 (s, 1H, NH), 7.40 (d, $J$ = 7.6 Hz, 1H, ArH), 7.56 (d, $J$ = 8.40 Hz, 2H, ArH), 8.02 (s, 1H,NH), 8.29 (d, $J$ = 7.6 Hz, 1H, ArH), 8.46 (s, 1H, NH), 11.14 (s, 1H, NH), 11.79 (s, 1H, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.83, 107.27, 111.71, 114.82, 121.35, 122.87, 123.22, 123.74, 125.73, 131.02, 136.80, 142.08, 142.85, 160.23, 176.85

2-(3-methoxylphenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156e)




**156e**

Synthesized by general procedure D from a mixture of 2-(3-methoxyphenyl)-phenyl-1*H*-indole-3-carbaldehyde (154e) (251.3 mg, 1.0 mmol, 1.0 equiv.) and thiosemicarbazide (155) (91.2 mg, 1.0 mmol, 1.0 equiv.) in methanol (5 mL) with reaction time 24 h. The reaction progress was monitored by thin layer chromatography that the reaction did not complete.

Synthesized by general procedure E from a mixture of 2-(3-methoxyphenyl)-phenyl-1*H*-indole-3-carbaldehyde (154e) (251.3 mg, 1.0 mmol, 1.0 equiv.), thiosemicarbazide (155) (100.3 mg, 1.1 mmol, 1.1 equiv.) and 2 drops of acetic acid in methanol (5 mL) with reaction time 12 h to provide 156e (240.06 mg, 74%) as a yellowish white powder. Spectral data for 156e were presented below.

mp 221-222 ºC

IR (KBr) ($cm^{-1}$): 1039, 1090, 1166, 1219, 1283, 1354, 1455, 1533, 1586, 2955, 3017, 3124, 3230, 3404

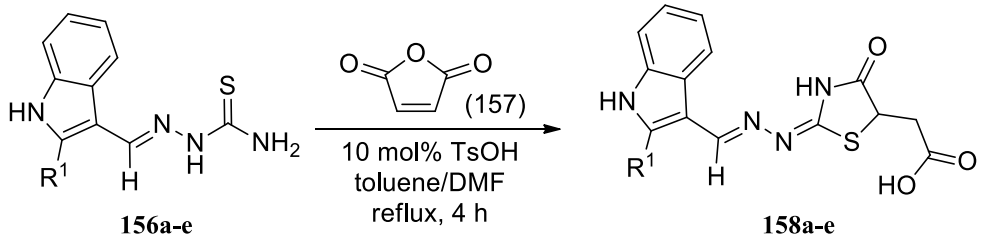
$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.87 (s, 3H, $OCH_3$), 7.06 (dd, $J$ = 8.00, 2.00 Hz, 1H, ArH), 7.13-7.25 (m, 4H, ArH), 7.37 (s, 1H, NH), 7.42-7.49 (m, 2H, ArH), 8.06 (s, 1H, NH), 8.33 (d, $J$ = 7.60 Hz, 1H, ArH), 8.52 (s, 1H, NH), 11.23 (s, 1H, NH), 11.88 (s, 1H, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.73, 108.04, 111.87, 114.81, 115.10, 121.48, 121.99, 123.13, 123.54, 125.63, 130.45, 132.67, 136.87, 141.73, 142.43, 159.59, 176.99

HRMS: m/z calcd for $C_{17}H_{16}N_4OS$ $[M+H]^+$: 325.1123; Found: 325.1124

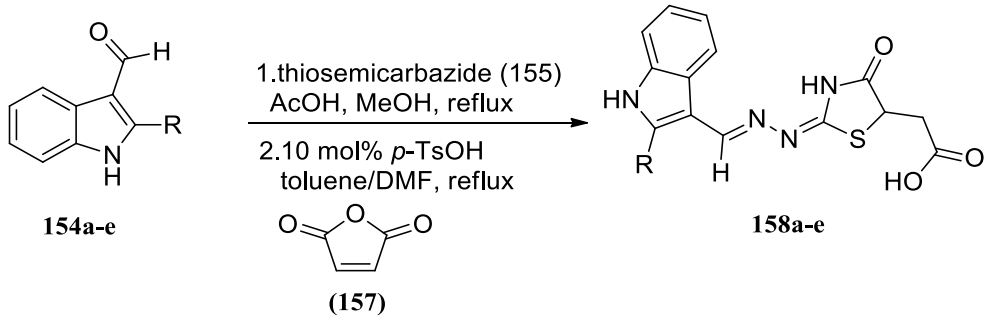
3.2.4 Synthesis of indole derivatives having thiazolidinone

General procedure F: Synthesis of thiazolidinone from thiosemicarbazone and maleic anhydride




A mixture of indole-3-carbaldehyde thiosemicarbazone (156) (0.50 mmol, 1 equiv.), maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) was refluxed in 1:10 DMF/toluene or 1:5 DMF/toluene (3 mL) for 4 h. The reaction mixture was evaporated and precipitated in water (20 mL) to give a solid product which was filtrated and purified by crystallization from EtOAc to provide 158.

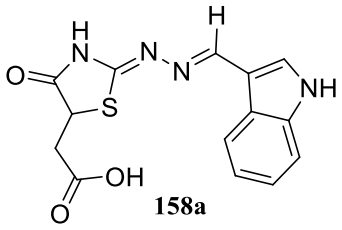
General procedure G: One-pot synthesis of thiazolidinone




A mixture of 3-formyl indole (154) (0.50 mmol, 1.0 equiv.), thiosemicarbazide (155) (50.5 mg, 0.55 mmol, 1.1 equiv.) and 1 drop of acetic acid was refluxed in methanol (2.5 mL) for 24 h. Then the reaction mixture was evaporated to afford a crude thiosemicarbazone. The crude material so obtained was taken directly to the next step without further purification. Maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) were added to a solution of the crude thiosemicarbazone in 1:10 DMF/toluene or 1:5 DMF/toluene (3 mL) and refluxed

until the completion of the reaction. The reaction mixture was evaporated and precipitated in water (20 mL) to give a solid product which was filtrated and purified by flash column chromatography (silica gel) to provide 158.

2-[[(indol-3-yl)methylene]hydrazono]-4-oxo-5-thiazolidineacetic acid (158a)




**158a**

Synthesized by general procedure F from 1*H*-indole-3-carbaldehyde thiosemicarbazone (156a) (109.1 mg, 0.50 mmol, 1.0 equiv.), maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:10 DMF/toluene (3 mL) to provide 158a (142.4 mg, 90%) as a brown powder.

Synthesized by general procedure G from 1*H*-indole-3-carbaldehyde (154a) (72.5 mg, 0.5 mmol), thiosemicarbazide (155) (50.5 mg, 0.55 mmol, 1.1 equiv.) in methanol (5 mL) to generate a crude thiosemicarbazone which was continuously reacted with maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:10 DMF/toluene (3 mL) to afford a crude 149a. The crude product was purified by flash column chromatography (silica gel, 1:1 EtOAc/hexane) to afford 158a (121.8 mg, 77%) which was identified by comparison of their physical data with those reported in the literature [158]. Spectral data for 158a were presented below.

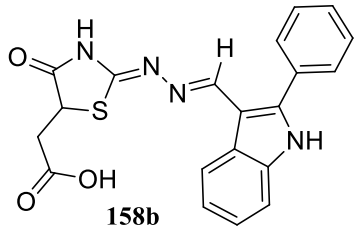
mp 262-264 ºC

IR (KBr) ($cm^{-1}$): 1209, 1281, 1394, 1590, 1699, 2940, 3032, 3287

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.89 (dd, $J$ = 17.20, 8.80 Hz, 1H, $CH_2$), 3.01 (dd, $J$ =17.20, 4.00 Hz, 1H, $CH_2$), 4.33 (dd, $J$ = 17.20, 8.80 Hz, 1H, CH), 7.14-7.22 (m, 2H, ArH), 7.44 (d, $J$ = 2.8 Hz, 1H, ArH), 8.16 (d, $J$ = 7.20 Hz, 1H, ArH), 8.53 (s, 1H, OH), 11.65 (s, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 37.26, 43.94, 112.39, 112.44, 121.25, 122.39, 123.24, 124.92, 132.24, 137.58, 152.98, 160.56, 172.18, 176.06

2-[[(2-phenyl indol-3-yl)methylene]hydrazono]-4-oxo-5-thiazolidine acetic acid (158b)



**158b**

Synthesized by general procedure F from 2-phenyl-1*H*-indole-3-carbaldehyde thiosemicarbazone (156b) (147.2 mg, 0.50 mmol, 1.0 equiv.), maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to provide 158b (164.8 mg, 84%) as a yellowish brown powder.

Synthesized by general procedure G from 2-phenyl-1*H*-indole-3-carbaldehyde (154b) (110.63 mg, 0.50 mmol, 1.0 equiv.), thiosemicarbazide (155) (50.5 mg, 0.55 mmol, 1.1 equiv.) in methanol (5 mL) to generate a crude thiosemicarbazone which was continuously reacted with maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to afford a crude 158b. The crude product was purified by flash column chromatography (silica gel, 1:1 EtOAc/hexane) to afford 158b (137.4 mg, 70%).

mp 246-249 ºC

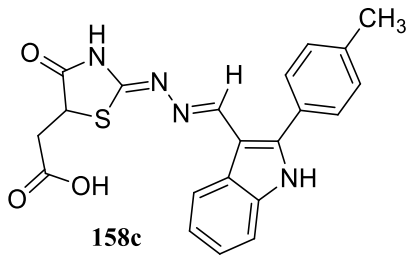
IR (KBr) ($cm^{-1}$): 1217, 1279, 1392, 1581, 1696, 2938, 3057, 3292

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.89 (dd, $J$ = 17.40, 8.40 Hz, 1H, $CH_2$), 3.04 (dd, $J$ = 17.40, 3.60 Hz, 1H, $CH_2$), 4.37 (dd, $J$ = 8.40, 3.60 Hz, 1H, CH), 6.62 (s, 1H, NH), 7.18-7.27 (m, 2H, ArH), 7.46 (d, $J$ = 8.00 Hz, 1H, ArH), 7.51 (d, $J$ = 7.60 Hz, 1H, ArH), 7.57 (d, $J$ = 7.60 Hz, 1H, ArH), 7.58 (d, $J$ = 7.20 Hz, 1H, ArH), 7.65 (d, $J$ = 7.60 Hz, 2H, ArH), 8.29 (d, $J$ = 7.60 Hz, 1H, ArH), 8.54 (s, 1H, OH), 12.01 (s, 1H, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 37.31, 44.11, 108.54, 112.14, 121.61, 122.71, 123.60, 126.24, 129.40, 129.67, 131.38, 134.45, 136.98, 143.27, 152.66, 160.93, 166.47, 172.18, 176.03

HRMS: m/z calcd for $C_{20}H_{16}N_4O_3S$ $[M+H]^+$: 393.1021; Found: 393.1020

2-[[(2-(4-methyl)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-5-thiazolidin acetic acid (158c)



**158c**

Synthesized by general procedure F from 2-(4-methylphenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156c) (154.2 mg, 0.50 mmol, 1.0 equiv.), maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to provide 158c (168.7 mg, 83%) as an orange-brown powder.

Synthesized by general procedure G from 2-(4-methylphenyl)-1*H*-indole-3-carbaldehyde (154c) (117.64 mg, 0.50 mmol, 1.0 equiv.), thiosemicarbazide (155) (50.5 mg, 0.55 mmol, 1.1 equiv.) in methanol (5 mL) to generate a crude thiosemicarbazone which was continuously reacted with maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to afford a crude 158c. The crude product was purified by flash column chromatography (silica gel, 1:1 EtOAc/hexane) to afford 158c (136.2 mg, 67%).

mp 198-200 ºC

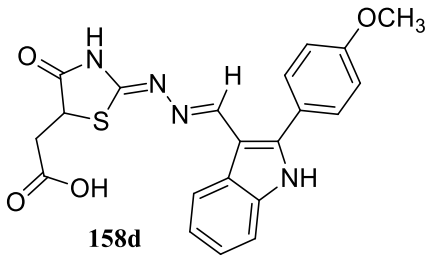
IR (KBr) ($cm^{-1}$): 1249, 1376, 1457, 1623, 1719, 2931, 3236, 3414

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.38 (s, 3H, $CH_3$), 2.91 (dd, $J$ = 17.40, 8.80 Hz, 1H, $CH_2$), 3.04 (dd, $J$ = 17.40, 3.60 Hz, 1H, $CH_2$), 4.36 (dd, $J$ = 8.80, 3.60 Hz, 1H, CH), 7.17-7.25 (m, 2H, ArH), 7.38 (d, $J$ = 8.40 Hz, 2H, ArH), 7.45 (d, $J$ = 8.00 Hz, 1H, ArH), 7.53 (d, $J$ = 8.00 Hz, 2H, ArH), 8.27 (d, $J$ = 7.20 Hz, ArH), 8.54 (s, 1H, OH), 11.94 (s, 1H, CNH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 37.31, 44.10, 108.27, 112.06, 121.54, 122.64, 123.47, 126.29, 128.52, 129.51, 129.99, 136.92, 139.08, 143.42, 152.76, 172.18, 176.02

HRMS: m/z calcd for $C_{21}H_{18}N_4O_3S$ $[M+H]^+$: 407.1178; Found: 407.1178

2-[[(2-(4-methoxy)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-5-thiazolidineacetic acid (158d)



**158d**

Synthesized by general procedure F from 2-(4-methoxyphenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156d) (162.2 mg, 0.50 mmol, 1.0 equiv.), maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to provide 158d (185.9 mg, 88%) as an orange-brown powder.

Synthesized by general procedure G from 154d (125.6 mg, 0.50 mmol, 1.0 equiv.), thiosemicarbazide (155) (50.5 mg, 0.55 mmol, 1.1 equiv.) in methanol (5 mL) to generate crude thiosemicarbazone which was continuously reacted with maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to afford a crude 158d. The crude product was purified by flash column chromatography (silica gel, 1:1 EtOAc/hexane) to afford 158d (143.6 mg, 68%).

mp 208-211 ºC

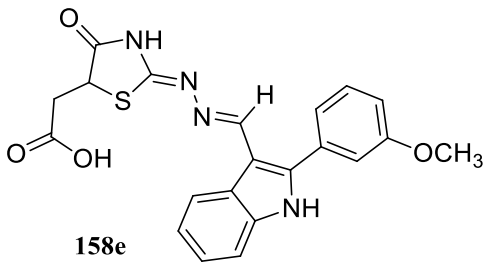
IR (KBr) ($cm^{-1}$): 1180, 1249, 1458, 1499, 1623, 1708, 3412

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.91 (dd, $J$ = 17.40, 8.00 Hz, 1H, $CH_2$), 3.04 (dd, $J$ = 17.40, 4.00 Hz, 1H, $CH_2$), 3.83 (s, 3H, $OCH_3$), 4.36 (dd, $J$ = 8.00, 4.00 Hz, 1H, CH), 7.14 (d, $J$ = 8.80 Hz, 2H, ArH), 7.16-7.24 (m, 2H, ArH), 7.43 (d, $J$ = 7.60 Hz, 1H, ArH), 7.58 (d, $J$ = 8.40 Hz, 2H, ArH), 8.25 (d, $J$ = 7.60 Hz, 1H, ArH), 8.52 (s, 1H, OH), 11.90 (s, 1H, CHN)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 37.33, 44.09, 55.81, 107.94, 111.96, 114.93 (2), 121.47, 122.53, 123.33, 123.66, 126.35, 130.98 (2), 136.86, 143.43, 152.86, 160.37, 172.16, 176.00

HRMS: m/z calcd for $C_{21}H_{18}N_4O_4S$ $[M+H]^+$: 423.1127; Found: 423.1128

2-[[(2-(3-methoxy)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-5-thiazolidineacetic acid (158e)



**158e**

Synthesized by general procedure F from 2-(3-methoxyphenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156e) (162.2 mg, 0.50 mmol, 1.0 equiv.), maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to provide 158e (188.0 mg, 89%) as a yellowish brown powder.

Synthesized by general procedure G from 2-(3-methoxyphenyl)-1*H*-indole-3-carbaldehyde (154e) (125.6 mg, 0.50 mmol, 1.0 equiv.), thiosemicarbazide (155) (50.5 mg, 0.55 mmol, 1.1 equiv.) in methanol (5 mL) to generate a crude thiosemicarbazone which was continuously reacted with maleic anhydride (157) (73.6 mg, 0.75 mmol, 1.5 equiv.) and *p*-TsOH (9.5 mg, 0.05 mmol, 10 mol%) in 1:5 DMF/toluene (3 mL) to afford a crude 158e. The crude product was purified by flash column chromatography (silica gel, 1:1 EtOAc/hexane) to afford 158e (137.3 mg, 65%).

mp 180-184 ºC

IR (KBr) ($cm^{-1}$): 1238, 1459, 1624, 1705, 3412

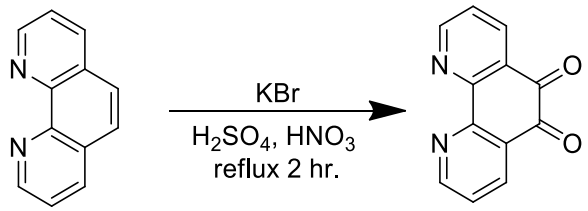
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.91 (dd, $J$ = 17.4, 8.8 Hz, 1H, $CH_2$), 3.04 (d, $J$ = 17.4 Hz, 1H, $CH_2$), 3.84 (s, 3H, $OCH_3$), 4.37 (d, $J$ = 4.40 Hz, 1H, CH), 7.08 (d, $J$ = 8.00 Hz, 1H, ArH), 7.19-7.27 (m, 4H, ArH), 7.45-7.51 (m, 2H, ArH), 8.29 (d, $J$ = 7.60 Hz, 1H, ArH), 8.58 (s, 1H, OH), 12.00 (s, 1H, CHN)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 37.33, 44.15, 55.80, 108.64, 112.13, 114.94, 115.07, 121.62, 122.07, 122.73, 123.65, 126.24, 130.56, 132.62, 136.91, 142.97, 152.64, 159.97, 172.19, 176.08

HRMS: m/z calcd for $C_{21}H_{18}N_4O_4S$ $[M+H]^+$: 423.1127; Found: 423.1128

3.2.5 Synthesis of indole derivatives having imidazoles

3.2.5.1 Synthesis of 1,10-phenanthroline-5,6-dione (160)




**159** **160**

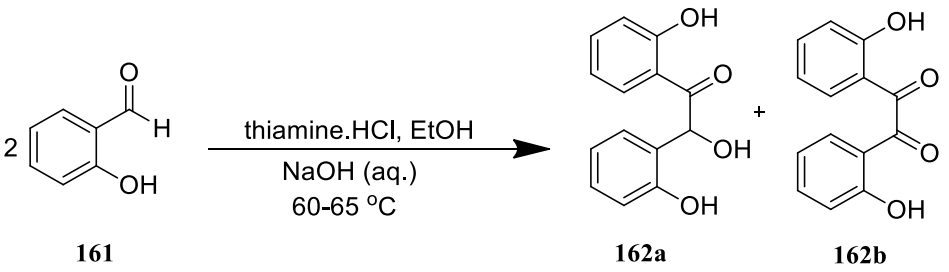
A cooled solution of $H_2SO_4$ (10 mL) and $HNO_3$ (5 mL) was dropped to a cooled mixture of potassium bromide (KBr) (1.487 g, 13.85 mmol, 5 equiv) and 1,10-phenanthroline (159) (500 mg, 2.77 mmol) in ice bath. The reaction mixture was refluxed for 2 h in sand bath. Then the hot solution was poured into crude ice (200 mL). The precipitate was filtrated by suction pump and washed with distillation water to give 151 (337.7 mg, 58%) as an orange yellow powder which was identified by comparison of their physical data with those reported in the literature [159]. Spectral data for 160 were presented below.

mp decomposed at 340 ºC

IR (KBr) ($cm^{-1}$): 1121, 1241, 1292, 1429, 1457, 1524, 1575, 1605, 1701, 3087, 3234

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.99 (dd, $J$ = 8.00 Hz, 1.20, 2H, ArH), 8.72 (dd, $J$ = 8.00 Hz, 1.60, 2H, ArH), 9.08 (d, $J$ = 3.60 Hz, 2H, ArH)

3.2.5.2 Synthesis of 2,2′-dihydroxy benzoin (162a) and 2,2′-dihydroxy benzil (162b)




**161** **162a** **162b**

A solution of thiamine.HCl (168.6 mg, 0.5 mmol, 5 mol%) in $H_2O$ (0.5 mL) cooled in ice bath and then added absolute ethanol (2 mL). The cool solution of thiamine.HCl was neutralized with 3 M NaOH (0.32 mL) in ice bath; the colorless solutions changed to yellow solution when drop NaOH into the solution and turn to colorless again in 20 minute at room temperature. 2-Hydroxy benzaldehyde (161) (1.06 mL, 10 mmol) was added to the solution and heated at 60-65 ºC for 24 h. The reaction mixture was evaporated to eliminate EtOH and 2-hydroxy benzaldehyde (161). The aqueous solution was extracted by dichloromethane, dried over anhydrous $NaSO_4$ and evaporated to give a crude product. The crude product was purified by flash column chromatography (1:9, EtOAc/hexane and 1:4 EtOAc/Hexane) on silica gel to afford 1562b (clear yellow needle, 72.7 mg, 6%) and 162a (yellow powder, 244.2 mg, 20%) which were identified by comparison of their physical data with those reported in the literature [160]. Spectral data for 162a and 162b were presented below.

2,2′-dihydroxy benzoin (162a)

mp 147-148 ºC

IR (KBr) ($cm^{-1}$): 1163, 1292, 1364, 1457, 1497, 1645, 3350

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.70 (s, 1H, OH), 6.26 (s, 1H, CH), 6.66-6.73 (m, 2H, ArH), 6.80 (d, 1H, $J$ = 8.40 Hz, ArH), 6.85 (d, $J$ = 8.00 Hz, 1H, ArH), 7.02 (d, $J$ = 8.00 Hz, 1H, ArH), 7.07 (d, $J$ = 8.00 Hz, 1H, ArH), 7.31 (t, $J$ = 7.60 Hz, 1H, ArH), 7.77 (d, $J$ = 8.00 Hz, 1H, ArH), 9.08 (s, 1H, OH), 11.78 (s, 1H, OH)

2,2′-dihydroxy benzil (162b)

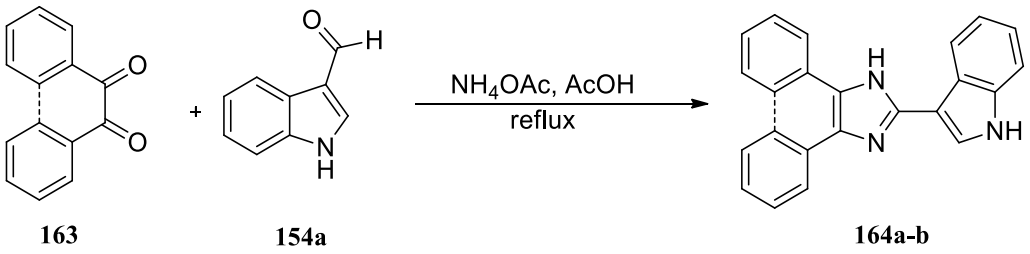
mp 156-158 ºC

IR (KBr) ($cm^{-1}$): 1148, 1201, 1274, 1322, 1399, 1483, 1626, 3147, 3147, 3414

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.92 (t, $J$ = 8.00 Hz, 2H, ArH), 7.10 (d, $J$ = 8.40 Hz, 2H, ArH), 7.48 (dd, $J$ = 8.00 Hz, 1.20, 2H, ArH), 7.59 (t, $J$ = 8.00 Hz, 2H, ArH), 11.29 (s, 2H, OH)

3.2.5.3 Synthesis of imidazole derivatives

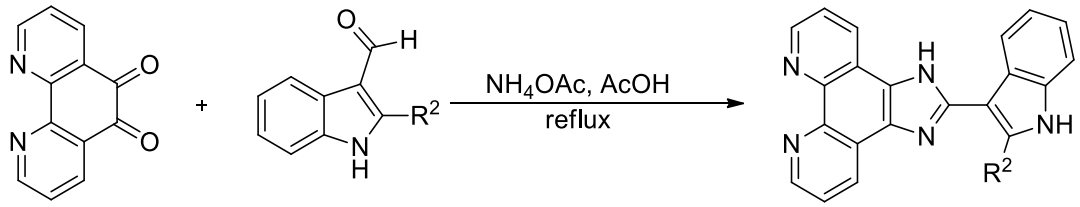
General procedure H: Synthesis of imidazole derivatives




**163** **154a** **164a-b**

A mixture of 3-formylindole (154) (72.5 mg, 0.5 mmol, 1.0 equiv.), benzoin (163a) or benzil (163b) or phenanthrenequinone (163c) (0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in glacial acetic acid (3 mL) was refluxed until the completion of the reaction. The reaction mixture was cooled and poured to ice water (~150 mL); a solid product was precipitated. Then the precipitated product was filtrated, washed with water and dried to provide a crude product. The crude product was purified by flash column chromatography on silica gel to afford 164.

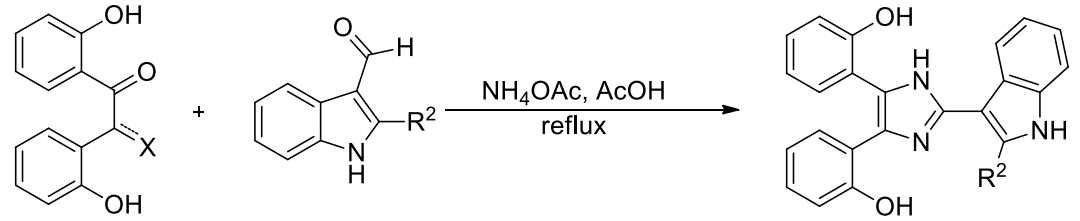
General procedure I: Synthesis of imidazole derivatives with 1,10-phenanthroline-5,6-dione and 3-formyl indole




**160** **154a-e** **165a-e**

A mixture of 3-formylindole (154) (0.5 mmol, equiv.), crude 1,10-phenanthroline-5,6-dione (160) (105.1 mg, 0.5 mmol, 1 equiv.) and ammonium acetate ($NH_4OAc$) (385 mg, 5 mmol, 10.0 equiv.) was refluxed in glacial acetic acid (3.0 mL). After the reaction was completed, the reaction mixture was poured to crude ice (~150 mL). The aqueous solution was neutralized with saturated aqueous solution of $Na_2CO_3$ then the precipitated product was filtrated, washed with water and dried to provide crude product. The crude product was washed with refluxing in dichloromethane (5 mL) 10 minute for 3 times to remove unreacted starting materials and give pure product 165.

General procedure J: Synthesis of imidazole derivatives with 2,2′-dihydroxy benzil/benzoin and 3-formyl indole

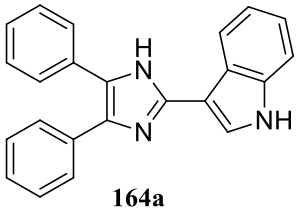



**162a: X = OH**
**162b: X = O** **154a-e** **166a-e**

A mixture of 3-formyl indole (154) (0.25 mmol, 1.0 equiv.), 2,2′-dihydroxy benzil (162b) or benzoin (162a) (0.28 mmol, 1.1 equiv.) and ammonium acetate (19.3 mg, 2.5 mmol, 10.0 equiv.) was refluxed in glacial acetic acid (1.5 mL) for 4 hour. After the reaction was completed, the reaction mixture was cooled and poured to crude ice (~70 mL). Then the precipitated product was filtrated, washed with water and

dried to provide a crude product. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) on silica gel to give 166.

2-indolyl-4,5-diphenyl-1*H*-imidazole (164a)




**164a**

Synthesized by general procedure H from 3-formylindole (154a) (72.5 mg, 0.5 mmol, 1.0 equiv.), benzoin (163a) (106.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (3 mL) for 8 h. The crude product was purified by flash column chromatography (1:2 EtOAc/Hexane) on silica gel to give 164a (129.1 mg, 77%) as a white powder which was identified by comparison of their physical data with those reported in the literature [161]. Spectral data for 164a were presented below.

Synthesized by general procedure H from 3-formylindole (154a) (72.5 mg, 0.5 mmol, 1.0 equiv.), benzil (163b) (105.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (3 mL) for 6 h. The crude product was purified by flash column chromatography (1:2 EtOAc/Hexane) on silica gel to give 164a (137.5 mg, 82%) as a white powder which was identified by comparison of their physical data with those reported in the literature [161]. Spectral data for 164a were presented below.

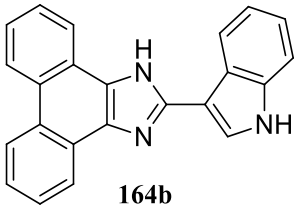
mp 158-160 ºC

IR (KBr) ($cm^{-1}$): 1182, 1338, 1453, 1507, 1603, 1696, 3053

$^{1}$H NMR (400 MHz, $CDCl_3$ + 10 drops DMSO-$d_6$): $\delta$ 7.06-7.12 (m, 2H, ArH), 7.17 (s, 2H, ArH), 7.25 (s, 4H, ArH), 7.34 (d, $J$ = 8.00 Hz, 1H, ArH), 7.56-7.60 (m, 4H, ArH), 7.84 (s, 1H, ArH), 8.42 (d, $J$ = 8.00 Hz, 1H, ArH), 10.71 (d, $J$ = 9.6 Hz, 1H, NH)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 10 drops DMSO-$d_6$): $\delta$ 106.29, 110.46, 118.86, 120.67, 120.93, 122.81, 124.36, 125.66, 126.84, 127.25, 135.53, 143.08

2-Indolyl imidazo[4,5-d] phenanthrene (164b)




**164b**

Synthesized by general procedure H from 3-formylindole (154a) (72.5 mg, 0.5 mmol, 1.0 equiv.), phenanthrenequinone (163c) (104.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (3 mL) for 6 h. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) on silica gel to give 164b (87%) as a white powder which was identified by comparison of their physical data with those reported in the literature [162]. Spectral data for 164b were presented below.

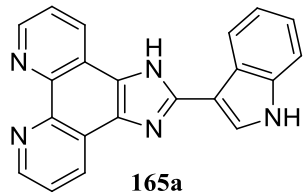
mp 188-190 ºC

IR (KBr) ($cm^{-1}$): 1127, 1240, 1363, 1395, 1420, 1456, 1577, 1618, 1653, 1700, 3144

$^{1}H$ NMR (400 MHz, $CDCl_3$ + 6 drops DMSO-$d_6$): $\delta$ 7.19 (m, 2H, ArH), 7.39 (d, $J$ = 7.60 Hz, 1H, ArH), 7.50 (t, $J$ = 8.00 Hz, 2H, ArH), 7.58 (t, $J$ = 8.00 Hz, 2H, ArH), 8.01 (d, $J$ = 2.00 Hz, 1H, ArH), 8.55 (s, 2H, ArH), 8.59 (d, $J$ = 7.60 Hz, 1H, ArH), 8.65 (d, $J$ = 8.40 Hz, 2H, ArH), 10.46 (s, 1H, NH), 10.55 (s, 1H, NH)

$^{13}C$ NMR (100 MHz, $CDCl_3$ + 6 drops DMSO-$d_6$): $\delta$ 107.17, 111.16, 119.95, 121.23, 121.66, 121.89, 122.94, 124.01, 124.66, 125.12, 126.16, 127.21, 136.24, 147.04

2-Indolyl imidazo[4,5-d]phenanthroline (165a)



**165a**

Synthesized by general procedure I from 3-formylindole (154a) (72.5 mg, 0.5 mmol, 1.0 equiv.), crude 1,10-phenanthroline-5,6-dione (160) (105.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (3 mL) for 3 h. The reaction provided 165a (75.5 mg, 45%) as a yellowish brown powder which was identified by comparison of their physical data with those reported in the literature [51]. Spectral data for 165a were presented below.

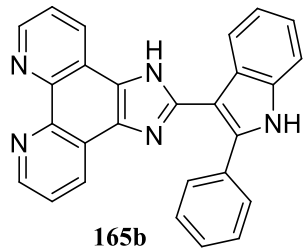
mp >360 ºC

IR (KBr) ($cm^{-1}$): 1127, 1356, 1457, 1560, 1577, 1620, 1653, 1700, 3245

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.19-7.24 (m, 2H, ArH), 7.48 (t, $J$ = 4.80 Hz, 1H, ArH), 7.77 (dd, $J$ = 8.00 , 4.80 Hz, 2H, ArH), 8.74 (t, $J$ = 4.80 Hz, 1H, ArH), 8.92-8.95 (m, 4H, ArH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 108.41, 112.26, 112.50, 120.47, 122.23, 122.52, 123.46, 125.66, 125.87, 129.97, 132.00, 136.97, 143.29, 147.22, 150.96, 155.29

2-(2-phenyl indolyl)-1*H*-imidazo[4,5-d]phenanthroline (165b)



**165b**

Synthesized by general procedure I from 2-phenyl-1*H*-indole-3-carbaldehyde (154b) (105.1 mg, 0.5 mmol, 1.0 equiv.), crude 1,10-phenanthroline-5,6-dione (160) (105.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (3 mL) for 3 h. The reaction provided 165b (102.9 mg, 50%) as a yellowish brown powder which was identified by comparison of their physical data with those reported in the literature [163]. Spectral data for 165b were presented below.

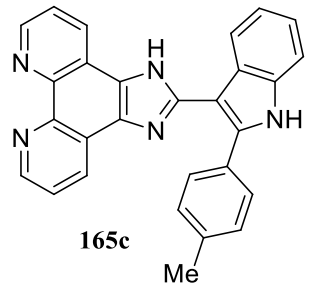
mp 284-286 ºC

IR (KBr) ($cm^{-1}$): 1130, 1459, 1510, 1560, 1653, 1700

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.14 (t, $J$ = 7.20 Hz, 1H, ArH), 7.22 (t, $J$ = 7.20 Hz, 1H, ArH), 7 .33 (d, $J$ = 7.20 Hz, 2H, ArH), 7.39 (t, $J$ = 7.60 Hz, 2H, ArH), 7.53 (d, $J$ = 8.40 Hz, 1H, ArH), 7.73-7.80 (m, 5H, ArH), 8.86 (d, $J$ = 7.60 Hz, 2H, ArH), 8.99 (d, $J$ = 4.00 Hz, 2H, ArH), 12.03 (s, 1H, NH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 104.02, 112.11, 120.21, 120.76, 123.04, 123.70, 128.45, 128.69, 128.86, 129.04, 130.03, 130.12, 132.12, 136.43, 137.80, 141.57, 143.68, 143.82, 147.79, 147.98, 148.08

2-(2-(4-methyl phenyl)-1*H*-indolyl) imidazo[4,5-d]phenanthroline (165c)




**165c**

Synthesized by general procedure I from 2-(4-methyl phenyl)-1*H*-indole-3-carbaldehyde (154a) (117.6 mg, 0.5 mmol, 1.0 equiv.), crude 1,10-phenanthroline-5,6-dione (160) (105.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (3 mL) for 3 h. The reaction provided 165c (112.7 mg, 53%) as a yellowish brown powder. Spectral data for 165c were presented below.

mp 306-308 ºC

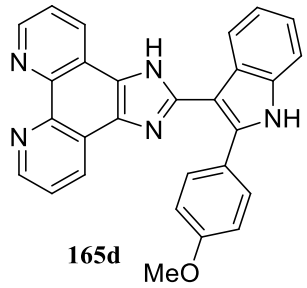
IR (KBr) ($cm^{-1}$): 1134, 1350, 1457, 1508, 1565, 1617, 1653, 1700

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.27 (s, 3H, $CH_3$), 7.13 (t, $J$ = 7.20 Hz, 1H, ArH), 7.18-7.24 (m, 3H, ArH), 7.51 (d, $J$ = 8.40 Hz, 2H, ArH), 7.63 (d, $J$ = 8.00 Hz, 2H, ArH), 7.77 (d, $J$ = 7.60 Hz, 3H, ArH), 8.85 (s, 2H, ArH), 8.99 (d, $J$ = 2.80 Hz, 2H, ArH), 11.92 (s, 1H, NH)

$^{13}$C NMR (100 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta$ 21.26, 111.99, 120.11, 120.66, 122.84, 123.66, 128.30, 128.96, 129.31, 129.61, 130.06, 136.33, 137.87, 138.15, 143.69, 147.93

HRMS: m/z calcd for $C_{28}H_{19}N_5$ $[M+H]^+$: 426.1713; Found: 426.1713

2-(2-(4-methoxy phenyl)-1*H*-indolyl) imidazo[4,5-d]phenanthroline (165d)




**165d**

Synthesized by general procedure I from 2-(4-methoxy phenyl)-1*H*-indole-3-carbaldehyde (154d) (125.6 mg, 0.5 mmol, 1.0 equiv.), crude 1,10-phenanthroline-5,6-dione (160) (105.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid. The reaction provided 165d (112.6 mg, 51%) as a yellowish brown powder. Spectral data for 165d were presented below.

mp 258-260 ºC

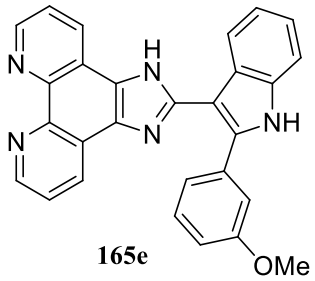
IR (KBr) ($cm^{-1}$): 1252, 1458, 1508, 1541, 1559, 1617, 1700

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.73 (s, 3H, $OCH_3$), 6.97 (d, $J$ = 8.80 Hz, 2H, ArH), 7.13 (t, $J$ = 7.60 Hz. 1H, ArH), 7.22 (t, $J$ = 7.60 Hz, 1H, ArH), 7.51 (d, $J$ = 8.40 Hz, 1H, ArH), 7.69 (d, $J$ = 8.40 Hz, 2H, ArH), 7.77 (d, $J$ = 8.00 Hz, 1H, ArH), 7.84 (dd, $J$ = 8.00, 4.00 Hz, 2H, ArH), 8.92 (d, $J$ = 8.00 Hz, 2H, ArH), 9.00 (d, $J$ = 4.00 Hz, 2H, ArH), 11.88 (s, 1H, NH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.66, 102.79, 111.94, 114.56, 119.93, 120.69, 122.73, 124.03, 124.45, 128.92, 129.82, 130.90, 136.26, 138.07, 142.49, 147.58, 148.20, 159.85

HRMS: m/z calcd for $C_{28}H_{19}N_5O$ $[M+H]^+$: 442.1662; Found: 442.1664

2-(2-(3-methoxy phenyl)-1*H*-indolyl) imidazo[4,5-d]phenanthroline (165e)




**165e**

Synthesized by general procedure I from 2-(3-methoxy phenyl)-1*H*-indole-3-carbaldehyde (154e) (125.6 mg, 0.5 mmol, 1.0 equiv.), crude 1,10-phenanthroline-5,6-dione (160) (105.1 mg, 0.5 mmol, 1.0 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid. The reaction provided 165e (108.2 mg, 49%) as a brown powder. Spectral data for 165e were presented below.

mp 276-279 ºC

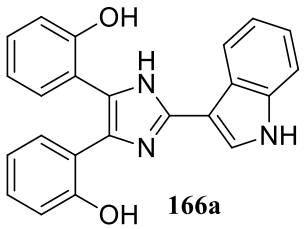
IR (KBr) ($cm^{-1}$): 1227, 1458, 1508, 1569, 1653, 1700

$^{1}H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.64 (s, 3H, $OCH_3$), 6.88 (d, $J$ = 7.60 Hz, 1H, ArH), 7.14 (t, $J$ = 7.60 Hz, 1H, ArH), 7.22-7.29 (m, 3H, ArH), 7.53 (d, $J$ = 8.40 Hz, 2H, ArH), 7.76-7.78 (m, 3H, ArH), 8.87 (s, 2H, ArH), 8.99 (d, $J$ = 2.8 Hz, 2H, ArH), 12.01 (s, 1H, NH)

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.43, 104.30, 112.08, 113.60, 114.67, 120.23, 120.59, 120.78, 123.12, 123.69, 128.97, 130.03, 130.13, 133.36, 136.31, 137.45, 143.73, 147.76, 147.98, 159.72

HRMS: m/z calcd for $C_{28}H_{19}N_5O$ $[M+H]^+$: 442.1662; Found: 442.1666

2-indol-3-yl-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166a)




**166a**

Synthesized by general procedure J from 1*H*-indole-3-carbaldehyde (154a) (36.3 mg, 0.25 mmol, 1.0 equiv.), 2,2′-dihydroxy benzoin (162a) (65.9 mg, 0.28 mmol, 1.1 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (1.5 mL) for 24 h. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) to afford 166a (2.8 mg, 3%).

Synthesized by general procedure J from 1*H*-indole-3-carbaldehyde (154a) (36.3 mg, 0.25 mmol), 2,2′-dihydroxy benzil (162b) (65.5 mg, 0.28 mmol, 1.1 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10 equiv.) in acetic acid (1.5 mL) for 4 h. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) on silica gel to afford 166a (65.2 mg, 71%) as a white powder. Spectral data for 166a were presented below.

mp 214-216 ºC

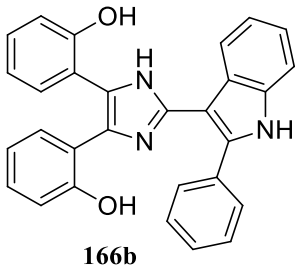
IR (KBr) ($cm^{-1}$): 1248, 1395, 1456, 1511, 1696

$^{1}$H NMR (400 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 6.67 (t, $J$ = 7.20 Hz, 2H, ArH), 6.90 (d, $J$ = 7.20 Hz, 2H, ArH), 7.05-7.11 (m, 4H, ArH), 7.24 (d, $J$ = 7.20 Hz, 2H, ArH), 7.30 (d, $J$ = 6.60 Hz, 1H, ArH), 7.73 (s, 1H, ArH), 8.19 (s, 1H, ArH), 9.95 (s, 1H, OH)

$^{13}$C MNR (100 MHz, $CDCl_3$ + 3 drops DMSO-$d_6$): $\delta$ 106.26, 111.69, 116.62, 118.53, 119.12, 120.52, 120.64, 122.29, 124.10, 124.80, 128.76, 136.53, 141.44, 155.88

HRMS: m/z calcd for $C_{23}H_{17}N_3O_2$ $[M+H]^+$: 368.1399; Found: 368.1399

2-(2-phenyl indolyl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166b)




**166b**

Synthesized by general procedure J from 2-phenyl-1*H*-indole-3-carbaldehyde (154b) (52.6 mg, 0.25 mmol, 1.0 equiv.), 2,2′-dihydroxy benzil (162b) (65.5 mg, 0.25 mmol, 1.1 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (1.5 mL) for 4 h. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) on silica gel to afford 166b (72.1 mg, 65%) as a green-cream powder. Spectral data for 166b were presented below.

mp 145-147 ºC

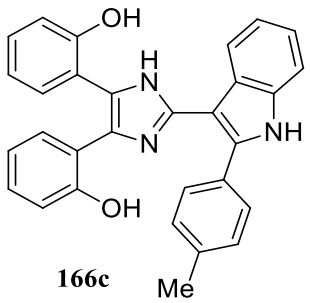
IR (KBr) ($cm^{-1}$): 1246, 1395, 1457, 1517, 1580, 1618, 1653, 1700

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.56 (s, 1H, ArH), 6.70-6.97 (m, 4H, ArH), 7.11-7.36 (m, 5H,ArH), 7.38-7.50 (m, 4H, ArH), 7.65 (d, $J$ = 8.00 Hz, 2H, ArH), 7.73 (d, t, $J$ = 8.00 Hz, 1H, ArH), 9.75 (br s, 1H, OH), 11.82 (s, 1H, OH), 12.45 (br s, 1H, NH), 13.13 (br s, 1H, NH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 102.91, 112.06, 118.90, 119.88, 120.60, 122.88, 128.27, 128.42, 128.56, 129.05, 132.26, 136.39, 137.17, 139.37, 156.49

HRMS: m/z calcd for $C_{29}H_{23}N_3O_2$ $[M+H]^+$: 444.1712; Found: 444.1716

2-(2-(4-methyl phenyl) indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166c)




**166c**

Synthesized by general procedure J from 2-(4-methyl phenyl)-1*H*-indole-3-carbaldehyde (154c) (55.3 mg, 0.25 mmol, 1.0 equiv.), 2,2′-dihydroxy benzil (162b) (65.5 mg, 0.28 mmol, 1.1 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (1.5 mL) for 4 h. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) on silica gel to afford 166c (83.5 mg, 73%) as a cream powder. Spectral data for 166c were presented below.

mp 144-147 ºC

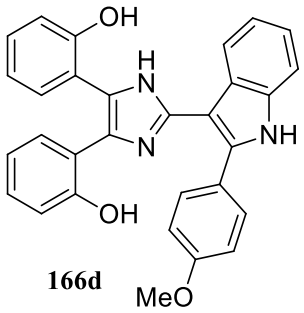
IR (KBr) ($cm^{-1}$): 1245, 1394, 1457, 1508, 1583, 1696, 2925

$^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.33 (s, 3H, $CH_3$), 6.80 (s, 2H, ArH), 6.99 (d, $J$ = 8.00 Hz, 2H, ArH), 7.18-7.32 (m, 8H, ArH), 7.32 (d, $J$ = 4.80 Hz, 1H, ArH), 7.42 (d, $J$ = 7.60 Hz, 2H, ArH), 8.18 (d, $J$ = 5.60 Hz, 1H, ArH), 8.42 (s, 1H, OH)

$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.29, 102.56, 111.10, 116.86, 117.34, 119.98, 120.73, 121.61, 123.33, 126.97, 128.47, 128.57, 129.58, 130.13, 135.80, 136.80, 139.65, 139.63, 141.49, 155.00

HRMS: m/z calcd for $C_{30}H_{23}N_3O_2$ $[M+H]^+$: 458.1869; Found: 458.1868

2-(2-(4-methoxy phenyl) indolyl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166d)




**166d**

Synthesized by general procedure J from 2-(4-methoxy phenyl)-1*H*-indole-3-carbaldehyde (154d) (58.8 mg, 0.25 mmol, 1.0 equiv.), 2,2′-dihydroxy benzil (160b) (65.5 mg, 0.28 mmol, 1.1 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (1.5 mL) for 4 h. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) on silica gel to afford 166d (84.1 mg, 71%) as a cream powder. Spectral data for 166d were presented below.

mp 171-174 ºC

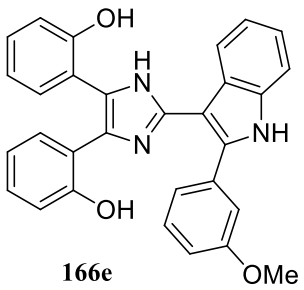
IR (KBr) ($cm^{-1}$): 1181, 1249, 1395, 1457, 1507, 1579, 1653, 1700, 2930

$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.79 (s, 3H, $OCH_3$), 6.53 (s, 1H, ArH), 6.70-6.78 (m, 2H, ArH), 6.88-7.03 (m, 6H, ArH), 7.08-7.28 (m, 6H, ArH), 7.45 (d, $J$ = 8.40 Hz, 1H, ArH), 7.58 (d, $J$ = 8.80 Hz, 2H, ArH), 7.69 (d, $J$ = 7.60 Hz, 1H, ArH), 9.72 (br s, 1H, OH), 11.70 (s, 1H, OH), 12.38 (br s, 1H, NH), 13.21 (br s, 1H, NH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.71, 101.98, 111.86, 114.57, 114.93, 116.46, 117.00, 118.92, 119.13, 119.60, 120.47, 122.52, 124.63, 126.36, 128.44, 129.69, 130.48, 136.21, 137.24, 139.54, 143.46, 155.87, 156.01, 156.35, 156.64, 159.70

HRMS: m/z calcd for $C_{30}H_{23}N_3O_3$ $[M+H]^+$: 474.1818; Found: 474.1819

2-(2-(3-methoxy phenyl) indolyl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166e)




**166e**

Synthesized by general procedure J from 2-(3-methoxy phenyl)-1*H*-indole-3-carbaldehyde (154e) (58.8 mg, 0.25 mmol, 1.0 equiv.), 2,2′-dihydroxy benzil (162b) (65.5 mg, 0.28 mmol, 1.1 equiv.) and ammonium acetate (385.0 mg, 5.0 mmol, 10.0 equiv.) in acetic acid (1.5 mL) for 4 h. The crude product was purified by flash column chromatography (1:3 EtOAc/Hexane) on silica gel to afford 166e (88.8 mg, 75%) as a green-cream powder. Spectral data for 166e were presented below.

mp 138-140 ºC

IR (KBr) ($cm^{-1}$): 1245, 1395, 1459, 1517, 1580, 1696, 2929

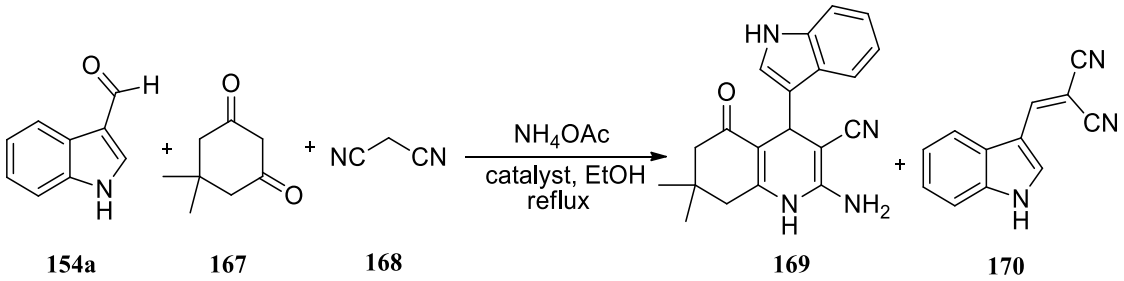
$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.74 (s, 3H, $OCH_3$), 6.55 (s, 1H, ArH), 6.80-6.98 (m, 5H, ArH), 7.13 (t, $J$ = 7.60 Hz, 2H, ArH), 7.17-7.23 (m, 5H, ArH), 7.36 (t, $J$ = 7.60 Hz, 1H, ArH), 7.49 (d, $J$ = 8.00 Hz, 1H, ArH), 7.71 (d, $J$ = 7.60 Hz, 1H, ArH), 9.73 (br s, 1H, OH), 11.83 (s, 1H, OH), 12.48 (br s, 1H, NH), 13.16 (br s, 1H, NH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.47, 103.09, 112.06, 113.26, 114.70, 118.89, 119.85, 120.63, 120.65, 122.97, 128.40, 130.14, 133.46, 136.30, 136.95, 139.28, 156.49, 159.76

HRMS: m/z calcd for $C_{30}H_{23}N_3O_3$ $[M+H]^+$: 474.1818; Found: 474.1814

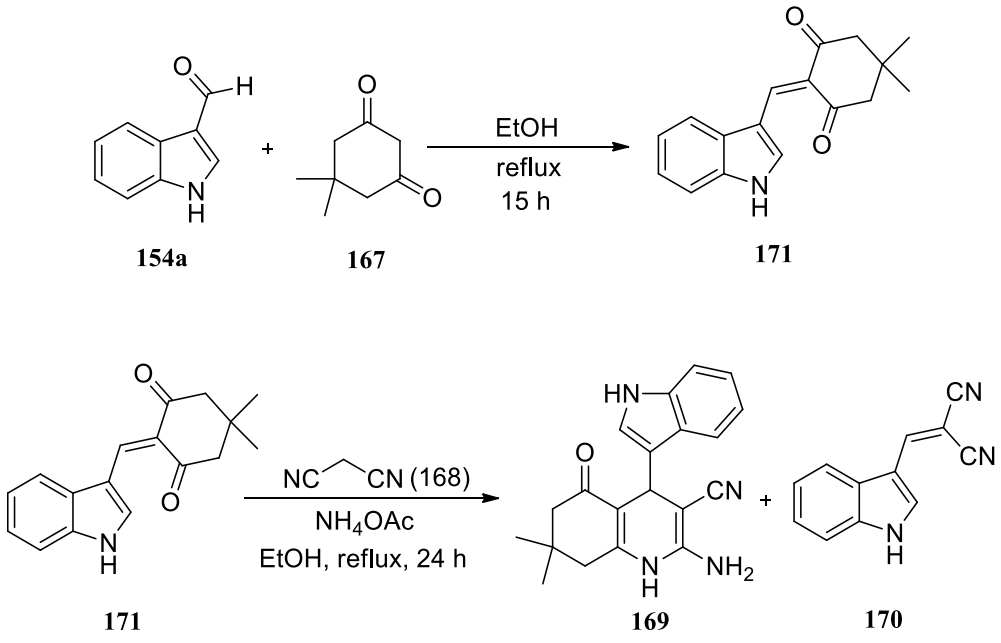
3.2.6 Synthesis of indole derivatives having 1,4-dihydropyridine

3.2.6.1 One-pot synthesis of 1,4-dihydropyridine




A mixture of 3-formyl indole (154a) (14.5 mg, 0.1 mmol, 1.0 equiv.), dimedone (167) (14.0 mg, 0.1 mmol, 1.0 equiv.), ammonium acetate (15.4 mg, 0.2 mmol, 2.0 equiv.) and malononitrile (168) (5.6 µL, 0.1 mmol, 1.0 equiv.) was refluxed in ethanol in the presence of 10 mol% of catalyst (Table 4.10). The reaction progress was monitored by thin layer chromatography.

3.2.6.2 Sequential synthesis of 1,4-dihydropyridine




A mixture of 3-formyl indole (154a) (72.5 mg, 0.5 mmol, 1.0 equiv.) and dimedone (168) (70.0 mg, 0.5 mmol, 1.0 equiv.) was refluxed in ethanol (2.5 mL) for 15 h. The solvent was evaporated to give crude product which was crystallized from

methanol to afford 171 (104.3 mg, 78%). The mixture of 171 (66.83 mg, 0.25 mmol, 1.0 equiv.), malononitrile (14 µL, 0.25 mmol, 1.0 equiv.) and ammonium acetate (38.5 mg, 0.5 mmol, 2.0 equiv.) was refluxed in ethanol (1.5 mL) under reflux temperature for 24 h. The reaction mixture was evaporated to give crude product and purified by flash column chromatography (1:3 EtOAc/Haxane) to afford 170 (40.6 mg, 84%) as a yellow solid which was identified by comparison of their physical data with those reported in the literature [164]. Spectral data for 170 were presented below.

mp 221-223 ºC

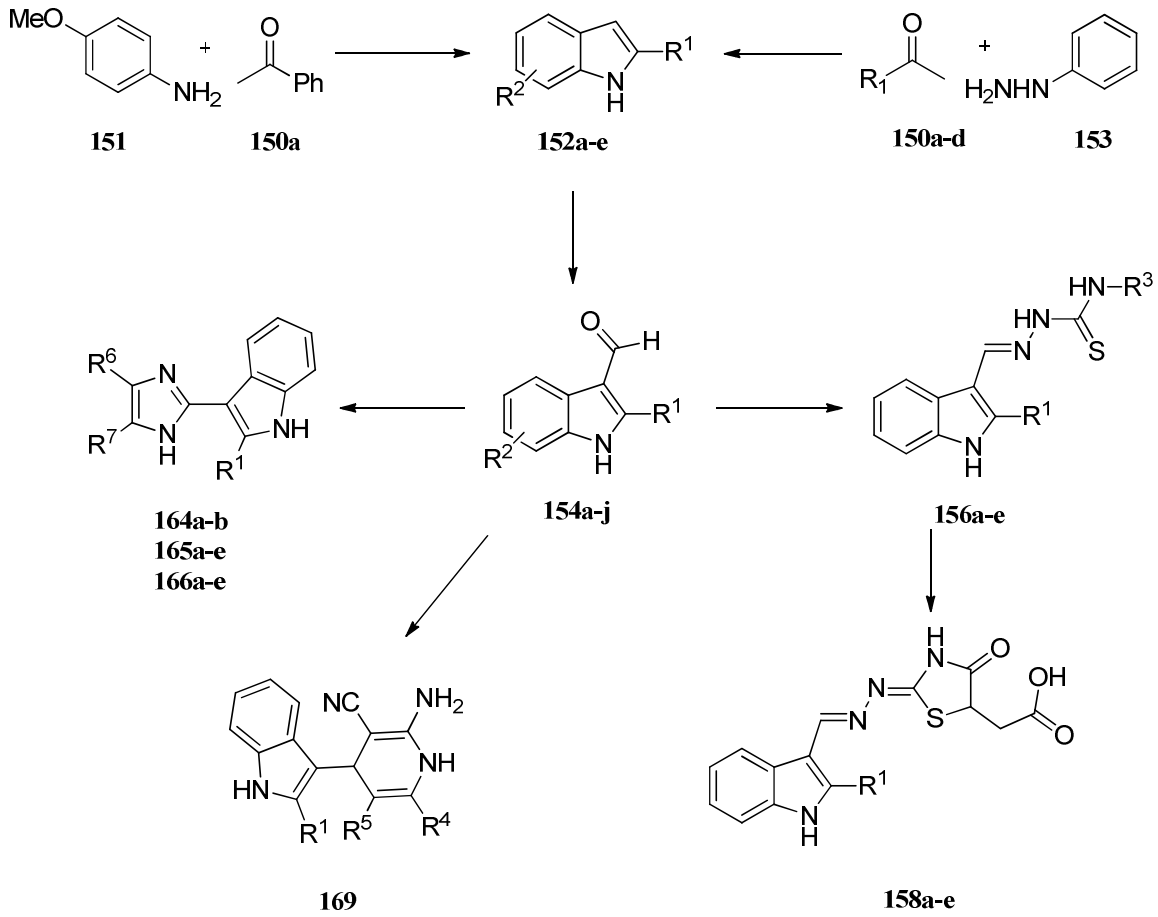
IR (KBr) ($cm^{-1}$): 1112, 1249, 1523, 1579, 3177

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.27 (m, 2H, ArH), 7.55 (d, $J$ = 7.60 Hz, 1H, ArH), 8.01 (d, $J$ = 7.60 Hz, 1H, ArH), 8.49 (s, 1H, C=CH), 8.65 (s, 1H, ArH)

# CHAPTER 4

# RESULTS AND DISCUSSION

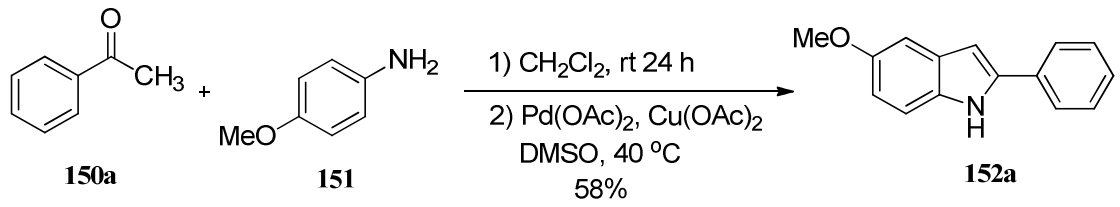
In this thesis the results compose of synthesis of indole from acetophenone derivatives and aniline or phenylhydrazine, a formylation of indole, synthesis of thiosemicarbazone, thiazolidinone, 1,4-dihydropyridine and imidazole. The synthesis of indole derivatives is shown in scheme 4.1.




**Scheme 4.1** A straightforward route for synthesis of indole derivatives having thiosemicarbazone, thiazolidinone, 1,4-dihydropyridine and imidazole.

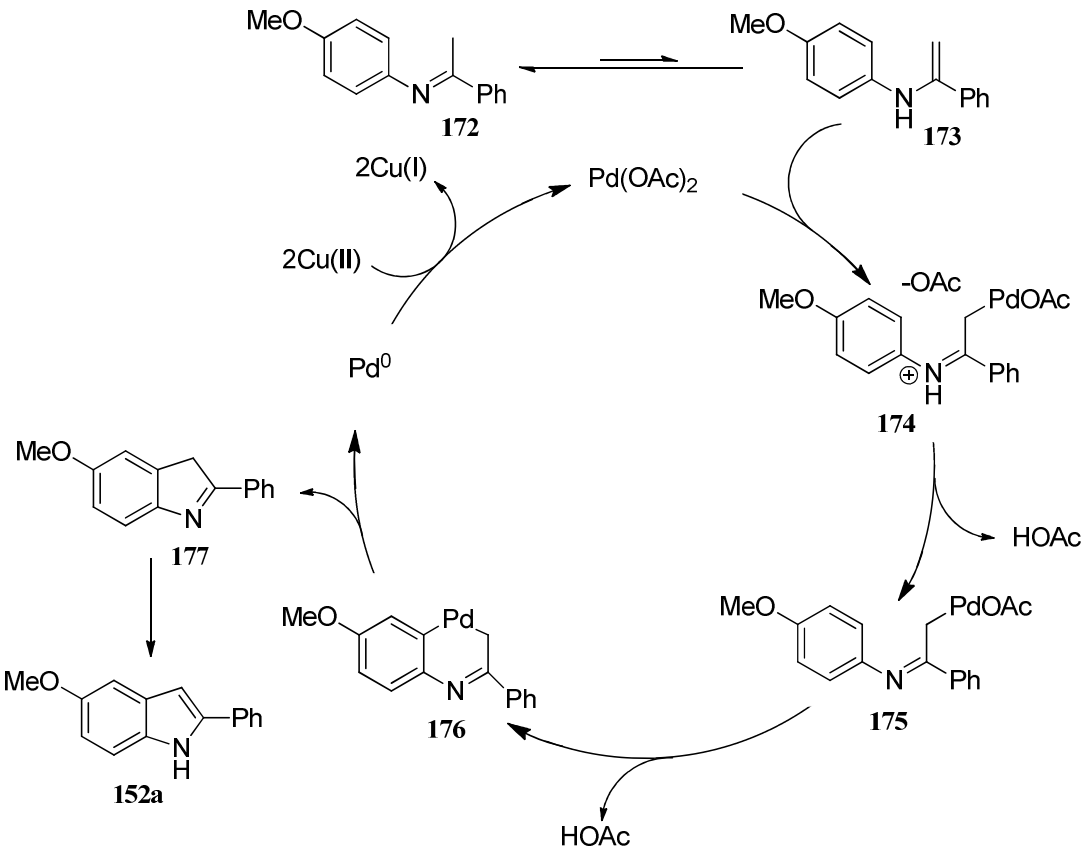
**4.1 Synthesis of indole derivertives**

Work initial synthesized 2-phenyl-5-methoxy-1*H*-indole (152a) by palladium (II)-catalyzed, copper (II)-mediated oxidative cyclisation of an imine, from condensation reaction of *N*-aryl enamine derived from acetophenone and aniline to give the corresponding indole (152a) in 58% (Scheme 4.1). The palladium (II)-catalyzed oxidative cyclization of *N*-aryl imine to indole involves palladation of *N*-aryl enamines (172) formed *via* imine-enamine tautomerization. A possible catalytic cycle [68] involves a Pd(II)/Pd(0) redox process. Enamine 173 would be attacked by $Pd(OAc)_2$, followed by elimination of acetic acid (AcOH) to provide a palladated imine (175). The intermediate 175 would then undergo intermolecular aromatic C-H palladation to give palladacycle 176. Subsequent reductive elimination affords indole and Pd(0) which is oxidized back to Pd(II) with $Cu(OAc)_2$. However, this method remains unpractical for the synthesis of 2-phenyl indole due to the results from the formation of 2-phenyl indole in modest yield. Moreover, there are still some problems with carefully controlled reaction conditions (e.g., exclusion of air and moisture) and cost of transition-metal catalysts.




**150a** **151** **152a**

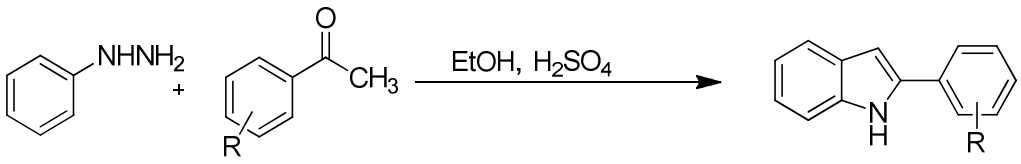
**Scheme 4.2** Synthesis of indole derivatives by palladium-catalyzed oxidative cyclization of *N*-aryl imine.



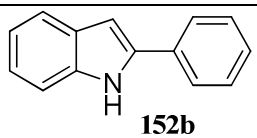
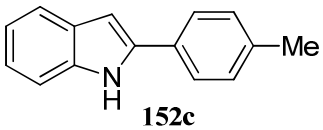
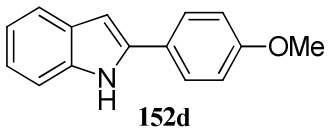
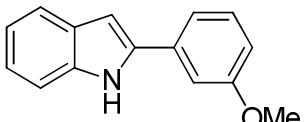

**Scheme 4.3** Possible catalytic cycle of palladium-catalyzed oxidative cyclization of *N*-aryl imine from acetophenone and aniline.

The other indole derivatives were synthesized by Fischer indole synthesis reaction. The raction was accomplished by condensation of acetophenone derivertive and phenyl hydrazine in ethanol under refluxing condition for 4 hour to form hydrazone intermediate. The intermediate underwent 3,3-sigmatropic rearrangement and cyclization in acidic solution under refluxing condition to give 2-phenyl indole derivative (152b-e) in high yield (74-96%) (Table 4.1).

**Table 4.1** Fisher indole synthesis of acetophenone and phenyl hydrazine [a]




**153** **150a-d** **152b-e**

| Entry | Product | Yield (%)[b] |
|---|---|---|
| 1 |  **152b** | 96 |
| 2 |  **152c** | 79 |
| 3 |  **152d** | 85 |
| 4 |  **152e** | 74 |

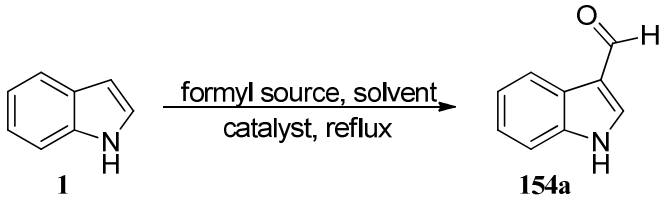
[a] Reaction condition: acetophenone (10 mmol), phenyl hydrazine (10 mmol), EtOH 5 mL, $H_2SO_4$ 5 mL reflux; [b] Crude yield.

### 4.2 Synthesis of 3-formyl indole derivertives

The study was initiated by carrying out the formylation of indole with hexamethylenetetramine (HMTA) by screening a variety of catalysts ($SiO_2$, CAN and CAN-$SiO_2$) in $CH_3CN$ under refluxing condition. The results from the optimization studies are summarized in Table 4.2. It was found that catalysts including $SiO_2$ and CAN are either ineffective or less effective than CAN-$SiO_2$ (Table 4.2, entries 2-6). The effect of solvent on the reaction efficiency was also observed (entries 7-10). Among the tested solvents, $CH_3CN$ gave the best result (Table 4.2, entry 1). Other formyl sources

such as TMEDA and *N*-methyl aniline were investigated for this reaction. However, the desired 3-formyl indole was not observed.

**Table 4.2** Formylation of indole in various reaction conditions [a].

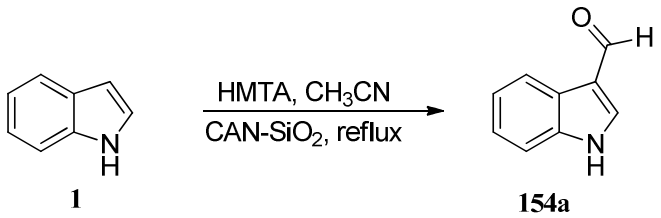



**1** **154a**

| Entry | Catalyst | Formyl source | Solvent | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $SiO_2$ | HMTA | $CH_3CN$ | 24 | trace |
| 2 | CAN-$SiO_2$ [c] | HMTA | $CH_3CN$ | 22 | 81 |
| 3 | $AlCl_3$ | HMTA | $CH_3CN$ | 24 | 19 |
| 4 | $FeCl_3$ | HMTA | $CH_3CN$ | 24 | 36 |
| 5 | $FeCl_3$-$SiO_2$ | HMTA | $CH_3CN$ | 22 | 59 |
| 6 | CAN | HMTA | $CH_3CN$ | 7 | 29 |
| 7 | Amberlyst-15 | HMTA | $CH_3CN$ | 24 | 10 |
| 8 | - | HMTA | $CH_3COOH$ | 3 | 24 |
| 9 | - | HMTA | TFA | 3 | decompose |
| 10 | CAN-$SiO_2$ [c] | HMTA | MeOH | 7 | 10 |
| 11 | CAN-$SiO_2$ [c] | HMTA | EtOH | 4 | 20 |
| 12 | CAN-$SiO_2$ [c] | HMTA | DMF | 24 | 58 |
| 13 | CAN-$SiO_2$ [c] | HMTA | THF | 24 | trace |
| 14[d] | CAN-$SiO_2$ [c] | HMTA | $CH_3CN$ | 22 | ND |
| 15 | CAN-$SiO_2$ [c] | TMEDA | $CH_3CN$ | 24 | ND |
| 16 | CAN-$SiO_2$ [c] | *N*,*N*-dimethyl aniline | $CH_3CN$ | 24 | ND |

[a] Reaction condition: indole (1 mmol), Formyl source (2 mmol), catalyst (10 mol%), solvent 5 mL.; [b] Isolated yields. ; [c] 10 % (by weight) of CAN; [d] A reaction was carried out at room temperature.; ND = No detected

**Table 4.3** Evaluation of catalytic activity of ceric ammonium nitrate on silica gel ($CAN\text{-}SiO_2$) in the formylation of indole [a].




**1** **154a**

| Entry | %wt | CAN (%mol)[c] | HMTA (eq.) | Time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 10% $CAN\text{-}SiO_2$ | 5 | 2 | 26 | 63 |
| 2 | 10% $CAN\text{-}SiO_2$ | 10 | 2 | 22 | 81 |
| 3 | 10% $CAN\text{-}SiO_2$ | 15 | 2 | 22 | 81 |
| 4 | 5% $CAN\text{-}SiO_2$ | 5 | 2 | 22 | 57 |
| 5 | 15% $CAN\text{-}SiO_2$ | 15 | 2 | 20 | 78 |
| 6 | 5% $CAN\text{-}SiO_2$ | 10 | 2 | 22 | 81 |
| 7 | 15% $CAN\text{-}SiO_2$ | 10 | 2 | 20 | 73 |
| 8 | 10% $CAN\text{-}SiO_2$ | 10 | 1.5 | 22 | 79 |
| 9 | 10% $CAN\text{-}SiO_2$ | 10 | 2.5 | 20 | 87 |
| 10 | 10% $CAN\text{-}SiO_2$ | 10 | 3 | 20 | 88 |

[a] Reaction condition: indole (1 mmol), HMTA, catalyst , $CH_3CN$ 5 mL, reflux ; [b] Isolated yields. ; [c] Amount of CAN in reaction.

Moreover, to check the effectiveness of the catalyst, the reaction was carried out in the presence of various amounts of catalyst in $CH_3CN$ (Table 4.3). The results show no improvable product from different loading ratios and amounts of CAN-$SiO_2$. Equivalences of HMTA were studied (Table 4.3, entries 8-10). Among various amounts of HMTA, the 3-formyl indole product increased with using HMTA 2.5 and 3.0 equiv., 87% and 88% respectively.

**Table 4.4** Formylation of indole derivatives.[a]

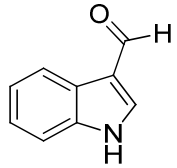
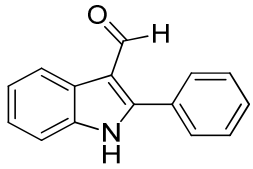
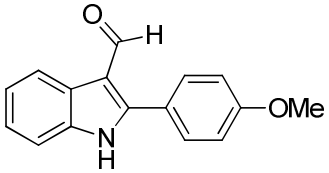
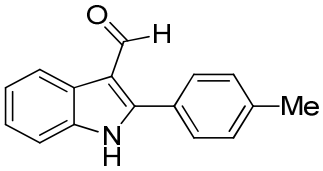
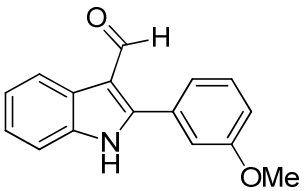
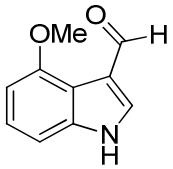
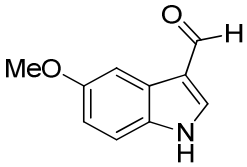
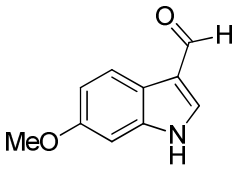
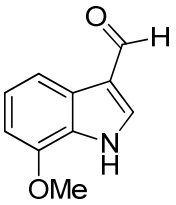
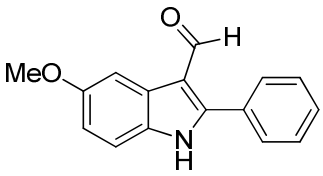
| Entry | Product | Time (h) | Yield (%) [b] |
|---|---|---|---|
| 1 |  **154a** | 20 | 87 |
| 2 |  **154b** | 12 | 88 |
| 3 |  **154c** | 12 | 78 |
| 4 |  **154d** | 12 | 70 |
| 5 |  **154e** | 12 | 81 |

**Table 4.4** (Continued)

| Entry | Product | Time (h) | Yield (%) [b] |
|---|---|---|---|
| 6 |  **154f** | 9 | 65 |
| 7 |  **154g** | 15 | 60 |
| 8 |  **154h** | 6 | 70 |
| 9 |  **154i** | 12 | 77 |
| 10 |  **154j** | 12 | 89 |

[a] Reaction condition: indole derivative (1 mmol), HMTA (2.5 mmol), 10% w/w CAN-$SiO_2$ (10 mol% CAN in reaction), $CH_3CN$ 5 mL, reflux.; [b] Isolated yields.

With the optimized reaction conditions in hand, we next explored the substrate scope using CAN-$SiO_2$ as the catalyst. The CAN-$SiO_2$ catalyzed C3-selective formylation of free N-H indoles was compatible with a range of substituents on the benzene and pyrrole ring of indole, and generated the corresponding products with reasonable to good yields (Table 4.4, entries 1-10). In addition, giving the reusability of

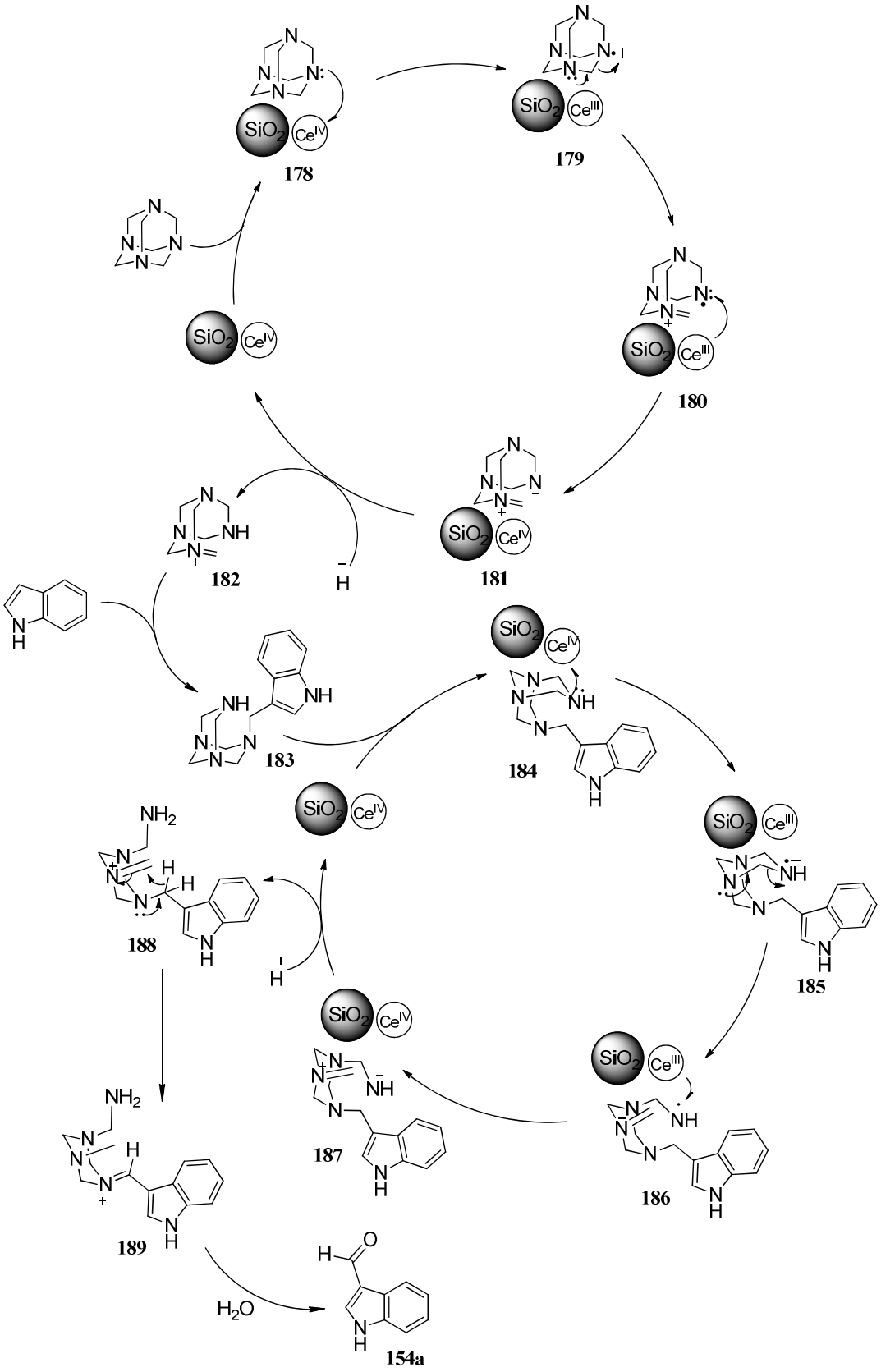
the catalyst was also studied after filtration, washing with EtOAc and drying. The results of the recycling show that the catalyst can be recycled once (87 and 81% yield, respectively, Table 4.5).

**Table 4.5** The catalytic activity of CAN-$SiO_2$ in the formylation with indole [a].

| Entry | No. of cycles | Time (hour) | Yield (%)[b] |
|---|---|---|---|
| 1 | 1 | 20 | 87 |
| 2 | 2 | 22 | 81 |
| 3 | 3 | 24 | 68 |
| 4 | 4 | 24 | 65 |

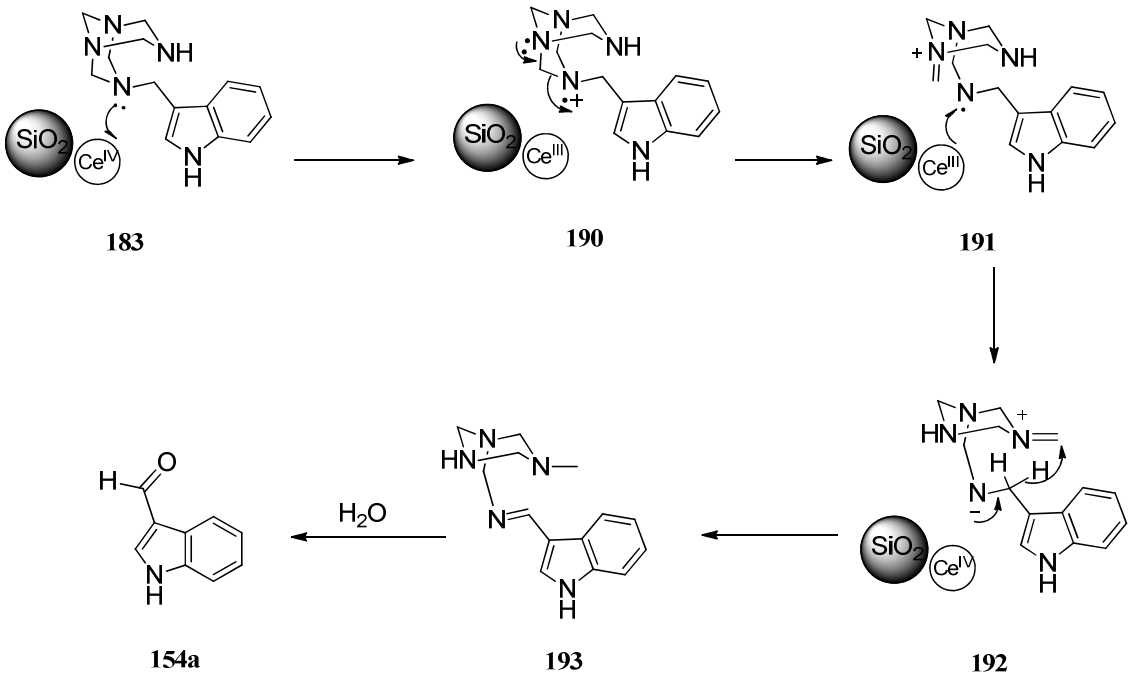
[a] Reaction conditions: indole (1 mmol), HMTA (2.5 equiv), 10% CAN–$SiO_2$ (10 mol % of CAN in the reaction), $CH_3CN$ (5 mL), reflux.; [b] Isolated yield.

The adsorption of HMTA on to the silica gel impregnated with CAN could bring the substrates and the catalyst into close proximity [165]. This facilitates the electron transfer process between CAN and the substrates. The use of silica gel as a support could also increase the effective surface area and constrain both the substrate and the reactant in pores thus decreasing the entropy of activation for electron transfer [166, 167]. We propose a mechanism in Scheme 4.4 for the formylation of indole using CAN-$SiO_2$. HMTA was adsorbed on CAN-$SiO_2$ to afford 178. The proximity of HMTA to CAN in 178 results in a favorable entropy of activation and, consequently, a rate enhancement of the reaction. Oxidation of HMTA in 178 gives the corresponding radical cation in 179, while reduction of Ce(IV) to Ce(III) takes place. The radical cation then undergoes fragmentation to give an iminuim cation and an amine radical as shown in 180. The reduction of the amine radical 180 to amine anion 181 allows regeneration of Ce(IV) from Ce(III). Meanwhile, protonation of the amine anion 181 give an imminium ion 182 and allows regeneration of CAN-$SiO_2$. The nucleophilic aromatic substitution of indole with iminium 182 generates 183.




**Scheme 4.4** Proposed mechanism for CAN-$SiO_2$-catalyzed a formylation of indole.

Removal of the amine groups from 183 with CAN-$SiO_2$ could produce through a similar mechanism. The first step involves the oxidation of the secondary amine in 184 after coordination to CAN-$SiO_2$. The resultant radical cation in 185 could then undergo a ring-opening reaction to give 186. Regeneration of Ce(IV)-$SiO_2$ from Ce(III)-$SiO_2$ during reduction of the amine radical in 186 affords the amine anion 187. Protonation of 187 then gives the primary amine 188. Intermediate 188 undergoes a 1,5-hydrogen shift to give iminium ion 189, followed by hydrolysis to give the 3-formylindole (154a). In addition, the other plausible mechanism is given in scheme 4.3 which involve a removal of the amine groups from 183 via 1,7-hydrogen shift.

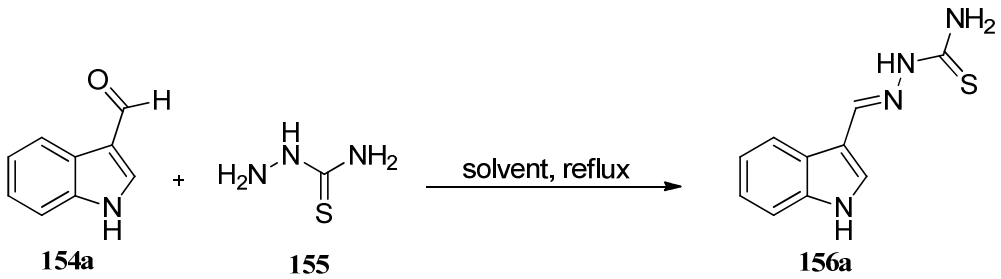



**Scheme 4.5** The other plausible mechanism for removal of the amine groups from 183 with CAN-$SiO_2$ by 1,7-hydrogen shift.

### 4.3 Synthesis of indole derivatives having thiosemicarbazone

Thiosemicarbazone derivatives (156a-e) were synthesized from condensation of 1*H*-indole-3-carbaldehyde derivatives (154a-e) with thiosemicabazide (155) by refluxing in alcoholic solvent or water. The effect of solvents was studied. The results show that methanol give the best result (Table 4.6, entry 1). However, condensation of thiosemicarbazide and 2-phenyl 3-caboxadehyde indoles (154b-e) did not complete by refluxing in methanol; thiosemicarbazone products cannot be separated. Thus the reaction was carried out in the presence of acetic acid. The results show an improvement in the conversion and product yield (Table 4.7, entries 2-5).

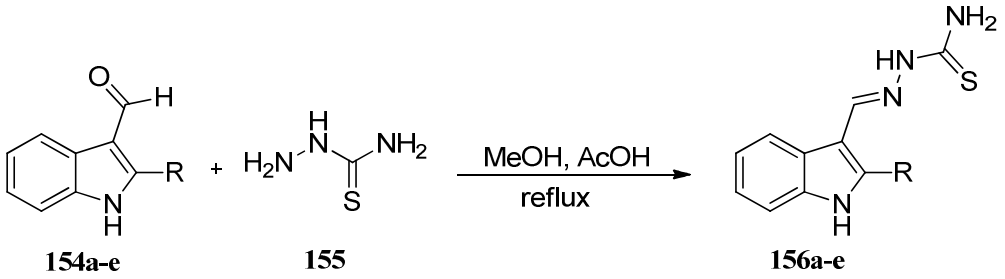
**Table 4.6** Optimization of solvent in the condensation reaction of thiosemicarbazide and 1*H*-indole-3-carbaldehyde [a].




| Entry | Solvent | Time (hour) | Yield (%) [b] |
|---|---|---|---|
| 1 | MeOH | 12 | 86 |
| 2 | EtOH | 12 | 84 |
| 3 | $H_2O$ | 24 | 56 |

[a] Reaction condition: 1*H*-indole-3-carbaldehyde (1 mmol) and thiosemicarbazide (1 mmol) was refluxed in methanol (5 mL).; [b] Yields were obtained from crystallization.

**Table 4.7** Synthesis of thiosemicarbazone [a]




**154a-e** **155** **156a-e**

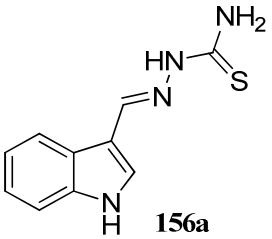
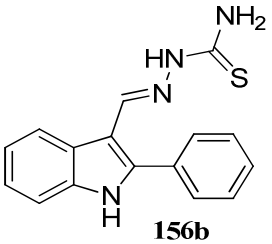
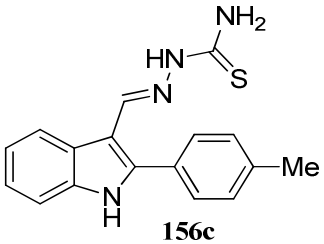
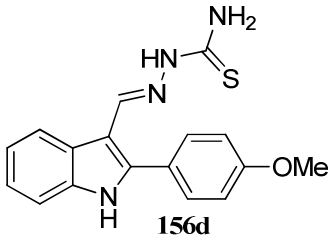
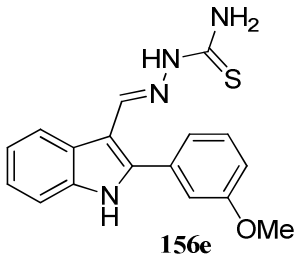
| Entry | Product | Time (hour) | Yield (%)[c] |
|---|---|---|---|
| 1 [b] |  **156a** | 12 | 86 |
| 2 |  **156b** | 24 | 85 |
| 3 |  **156c** | 24 | 83 |
| 4 |  **156d** | 24 | 80 |

**Table 4.7** (Continued)

| Entry | Product | Time (hour) | Yield (%) |
|---|---|---|---|
| 5 |  **156e** | 24 | 74 |

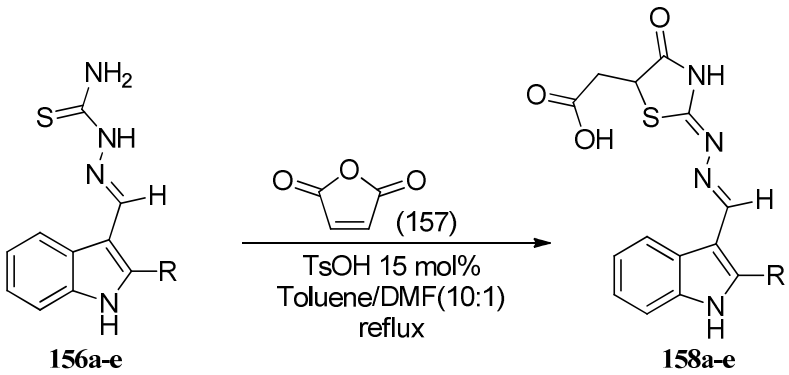
[a] Reaction condition: 3-formyl indole (1 mmol) and thisemicarbazide (1.1 mmol) was refluxed in methanol (5 mL) and 2 drops of acetic acid.; [b] 3-formyl indole (1 mmol) and thisemicarbazide (1 mmol) was refluxed in methanol (5 mL).; [c] Yields were obtained from crystallization.

### 4.4 Synthesis of indole derivatives having thiazolidinone

The synthesis of the indole derivatives having thiazolidinone was carried out using the same methodology previously reported by Saiz and coworker [90]. Thia-Michael addition reaction of the indolyl thiosemicarbazone (156a-e) and maleic anhydride using *p*-TsOH as a catalyst under refluxing for 4 h provided thiazolidinone product (158a-e) with high yield (Table 4.8).

Furthermore, the one pot syntheses of indole derivatives having thiazolidinone from 3-formyl indole (154a-e) have been performed. Condensation of 3-formylindole and thiosemicarbazide afford a crude thiosemicarbazone. The crude material was directly taken to the next step without further purification which underwent thia-Michael addition reaction with maleic anhydride in present of *p*-TsOH in the mixture of toluene and DMF. The results show that the desired thiazolidinone products were obtained in modest yield (65-77%) (Table 4.9).

**Table 4.8** Synthesis of thiazolidinone derivatives [a].



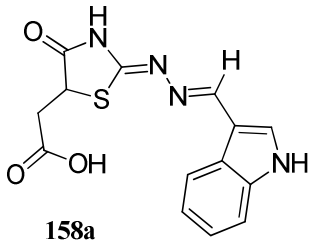
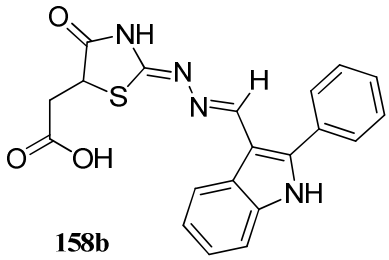
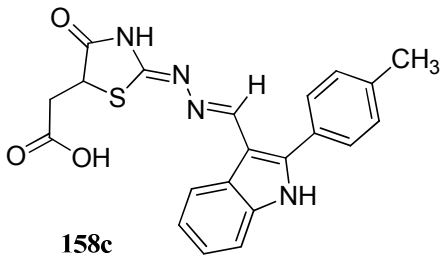
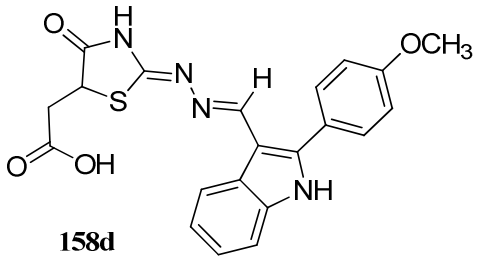
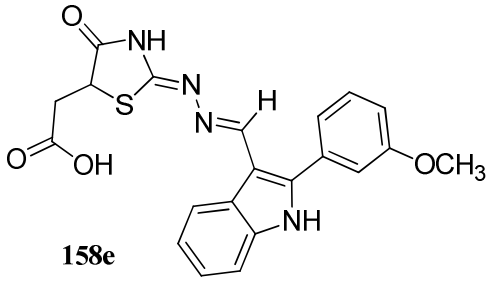
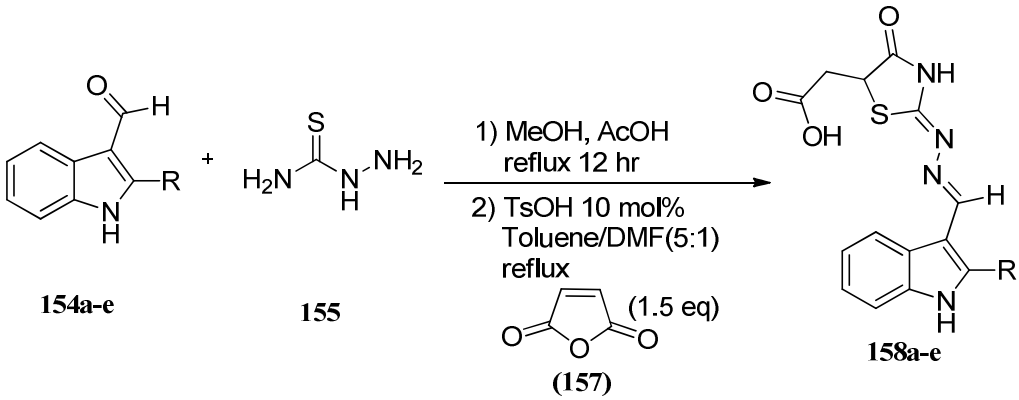

| Entry | Product | Time (hour) | Yield (%)[c] |
|---|---|---|---|
| 1 [b] |  **158a** | 4 | 90 |
| 2 |  **158b** | 4 | 84 |
| 3 |  **158c** | 4 | 83 |
| 4 |  **158d** | 4 | 88 |

**Table 4.8** (Continued)

| Entry | Product | Time (hour) | Yield (%)[c] |
|---|---|---|---|
| 5 |  **158e** | 4 | 89 |

[a] Reaction condition: thiosemicarbazone (0.50 mmol), maleic anhydride (0.75 mmol) and *p*-toluene sulphonic acic (10 mol%) was refluxed in Toluene/DMF (5:1) (3 mL).; [b] Used Toluene/DMF (10:1)**;** [c]Isolated yield

**Table 4.9** One pot synthesis of thiazolidinone derivatives [a]




**154a-e** **155** **(157)** **158a-e**

| Entry | R | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | H | 6 | 77 |
| 2 | Ph | 8 | 70 |
| 3 | 4-Me Ph | 8 | 67 |
| 4 | 4-OMe Ph | 8 | 68 |
| 5 | 3-OMe Ph | 8 | 65 |

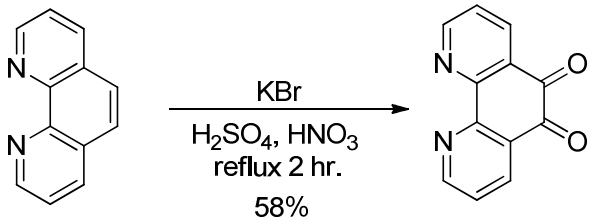
[a] Reaction condition was followed general procedure G.; [b]Isolated yield

## 4.5 Synthesis of indole derivative having imidazole

4.5.1 Preparation of 1, 2-diketone

4.5.1.1 Synthesis of 1,10-phenanthroline-5,6-dione (160)

1,10-phenanthroline-5,6-dione (160) was synthesized by oxidation reaction of 1,10-phenanthroline (159) in mixture of sulphuric acid and nitric acid with the presence potassium bromide at refluxed temperature (Scheme 4.6).




**159** **160**

**Scheme 4.6** Oxidation of 1,10-phenanthroline to 1,10-phenanthroline-5,6-dione.

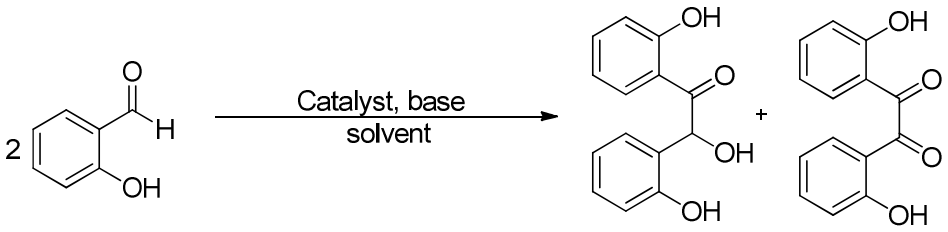
4.5.1.2 Synthesis of 2,2′-dihydroxy benzoin (162a) and 2,2′-dihydroxy benzil (162b)

Synthesis of 2,2′-dihydroxy benzoin (162a) was investigated by condensation of two molecules of 2-hydroxy benzaldehyde (162) using potassium cyanide and thiamine as a catalyst (Table 4.10). The results showed that 2-hydroxy benzaldehyde was decomposed by potassium cyanide as a catalyst. 2,2′-Dihydroxy benzoin (162a) and 2,2′-dihydroxy benzil (162b) were obtained by using thiamine catalyst. Generally addition of the cyanide ion to the aldehyde carbonyl forms a stable cyanohydrin, Mandelonitrile (194). Mandelonitrile loses a proton from C-1 carbon giving a carban ion (195, 196). This carbanion, in turn, functions as a nucleophile and attacks a second molecule of benzaldehyde producing benzoin (Scheme 4.7). However, a strong electron-donating group in the 2-position of the phenyl ring makes the difficult loss of the proton from the cyanohydrin. (Table 4.10, entry 1-4) [168].

The reaction mechanism of vitamin thiamine catalyst (Scheme 4.8) is similar to cyanide catalyst. However the deprotonated intermediate 202 and 203 are more stable than 195 and 196. Thus, the vitamin thiamine catalyst archived in the

benzoin condensation of 2-hydroxy benzaldehyde. The effect of a strong electron-donating group in the 2-position (hydroxyl group) still influences benzoin condensation providing the benzoin product in low yield. The reaction gives a minor product by air oxidation as 2,2′-dihydroxy benzil (162b) (Table 4.10, entry 5) [168].

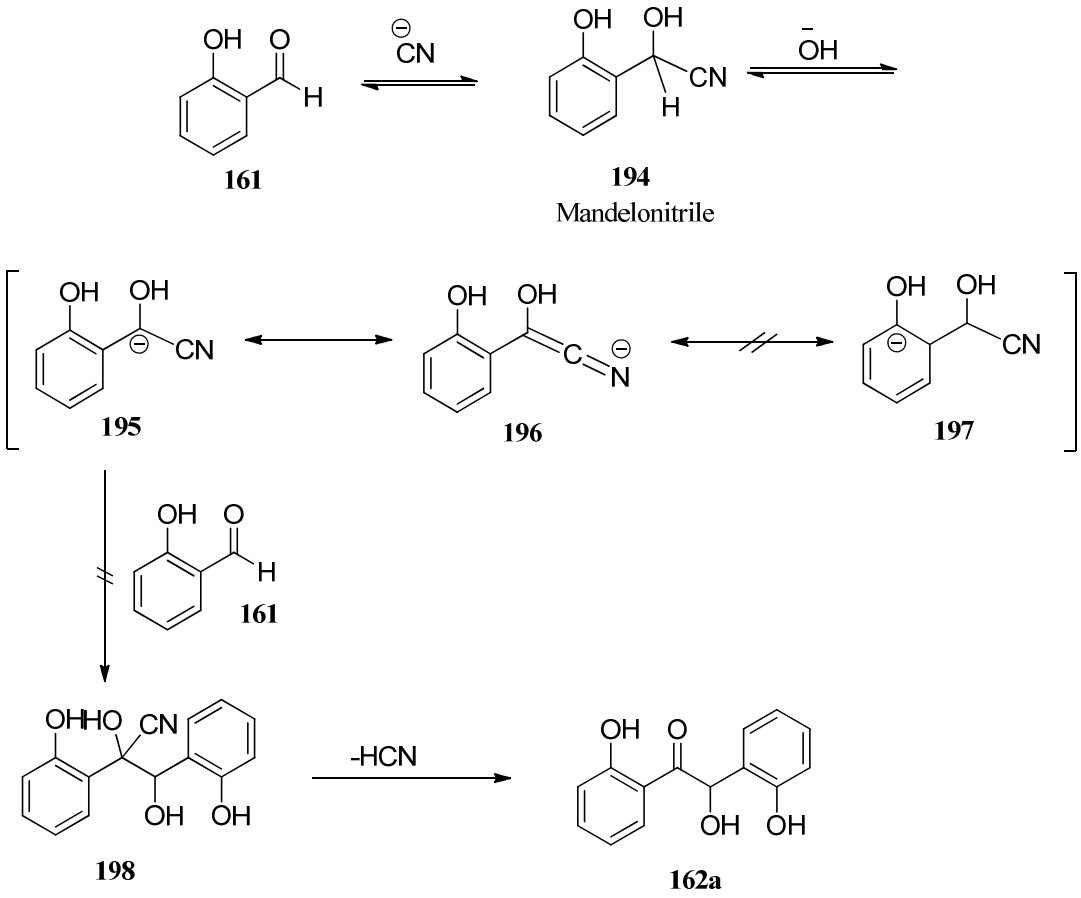
**Table 4.10** Optimization for synthesis of 2,2′-dihydroxy benzoin and 2,2′-dihydroxy benzil [a].



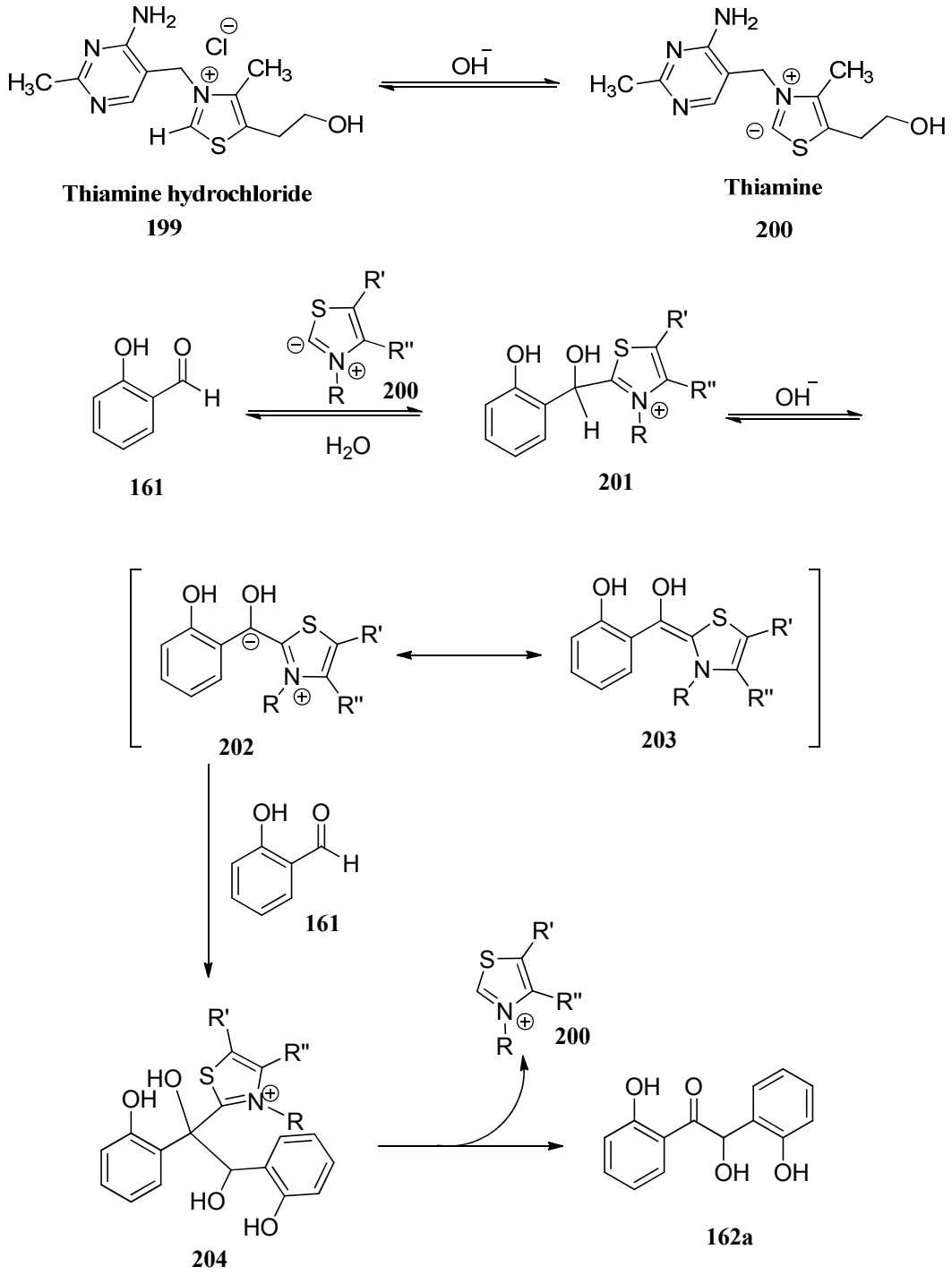

**161** **162a** **162b**

| Entry | Solvent | Catalyst (5 mol%) | Base (10 mol%) | Temp. | Product (%)[b] | |
|---|---|---|---|---|---|---|
| | | | | | 162a | 162b |
| 1 | EtOH | KCN | - | reflux | decompose | |
| 2 | $H_2O$ | KCN | - | reflux | decompose | |
| 3 | EtOH/$H_2O$ (4:1) | KCN | - | reflux | decompose | |
| 4 | EtOH/$H_2O$ (4:1) | KCN | NaOH | reflux | decompose | |
| 5 | EtOH/$H_2O$ (4:1) | thiamine.HCl | NaOH | 60-65°C | 20 | 6 |
| 6 | DMSO | thiamine.HCl | $NEt_3$ | 60-65°C | No reaction | |
| 7 | DMSO/$H_2O$ (4:1) | thiamine.HCl | $NEt_3$ | 60-65°C | No reaction | |
| 8 | EtOH/$H_2O$ (4:1) | thiamine.HCl | KOH | 60-65°C | No reaction | |

[a] Reaction condition: 2-hydroxy benzaldehyde (10 mmol), catalyst and base was stirred in solvent 2.5 mL.; [b]Isolated yield




**Scheme 4.7** The reaction mechanism of benzoin condensation by cyanide ion catalyst.




**Scheme 4.8** The reaction mechanism of benzoin condensation by thiamine catalyst.

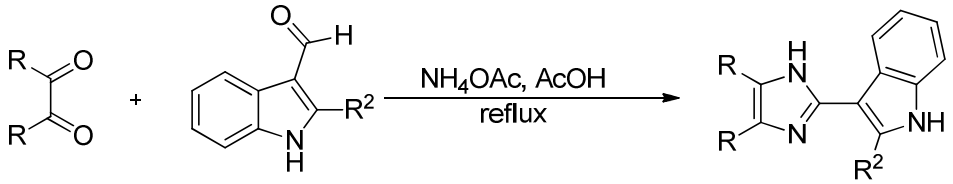
4.5.2 Synthesis of imidazole derivatives

Firstly, a three components reaction of 3-formyl indole, ammomiun acetate and commercial available benzil (163a) or benzoin (163b) in glacial acetic acid under refluxing condition was investigated (Table 4.11, entry 1 and 2). The results show that high yield of the 2,4,5-trisubstituted imidazole products were obtained.

Next, the synthetic 1,10-phenanthroline-5,6-dione (160) was applied to this reaction. The product was found as measured from thin layer chromatography at baseline (1:2 EtOAc/hexane and 100% MeOH). The high polar product could not be separated with column chromatography. Thus the crude product was purified by washing by hot dichloromethane giving pure product in moderate yield (45-53%) (Table 4.11, entries 3-7).

In addition a 2,2´-dihydroxy benzoin (162a) and 2,2'-dihydroxy benzil (162b) were investigated for synthesis of imidazole derivatives. The same imidazole product was expected to obtain from 162a and 162b (Table 4.11, entries 8-9). However, 2-hydroxy substituted on phenyl ring of 2,2´-dihydroxy benzoin (162a) reduce electrophilicity of the $\alpha$-hydroxy ketone to give imidazole product in a low yield (3%) (Table 4.11, entry 8). However, the use of 2,2´-dihydroxy benzil (162b) give the product with high yield (65-75%) (Table 4.11, entries 9-13).

**Table 4.11** Synthesis of imidazole derivertives [a].




**160**
**162a-b**
**163a-c**

**154a-e**

**164a-b**
**165a-e**
**166a-e**

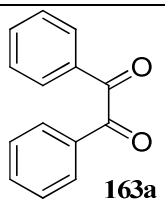
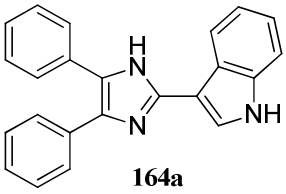
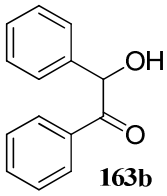
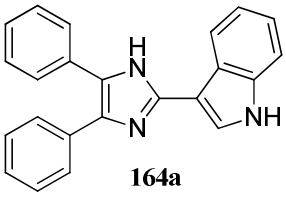
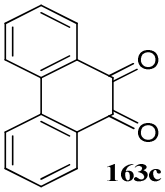
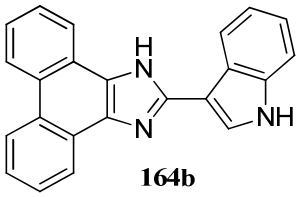
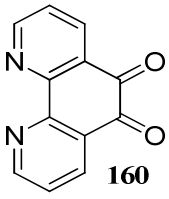
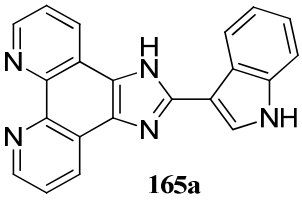
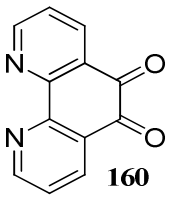
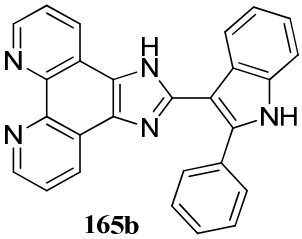
| Entry | 1,2-diketone | Product | Time (h) | Yield (%)[c] |
|---|---|---|---|---|
| 1 |  **163a** |  **164a** | 6 | 82 |
| 1 |  **163b** |  **164a** | 8 | 77 |
| 2 |  **163c** |  **164b** | 6 | 87 |
| 3 |  **160** |  **165a** | 3 | 45 |
| 4 |  **160** |  **165b** | 3 | 50 |

**Table 4.11** (Continued)

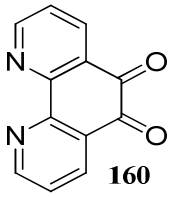
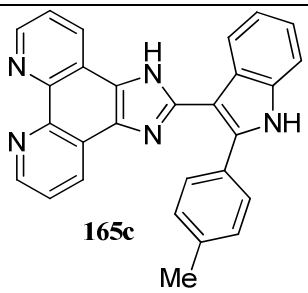
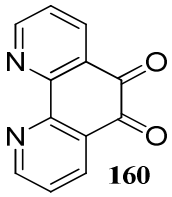
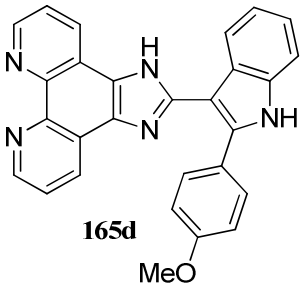
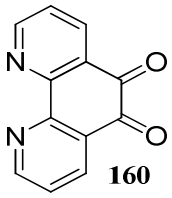
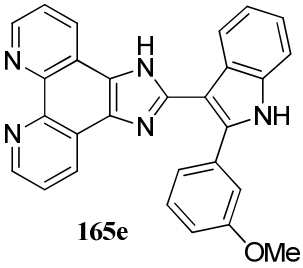
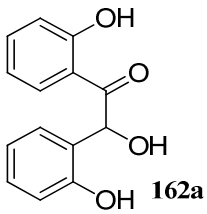
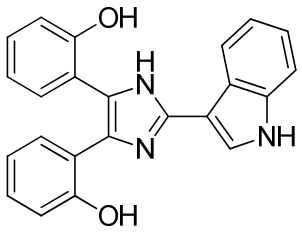
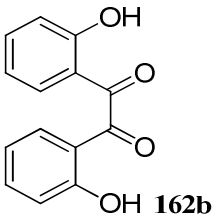
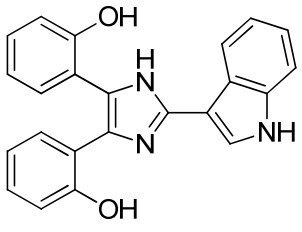
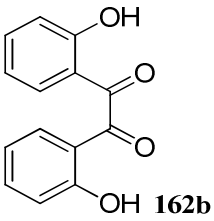
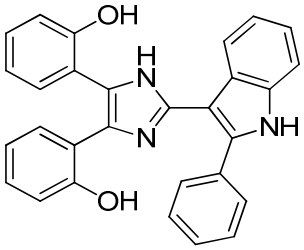
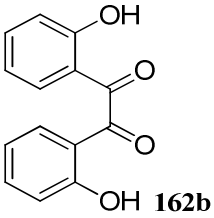
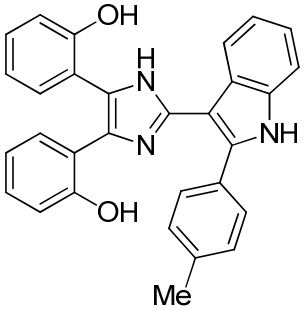
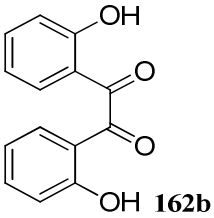
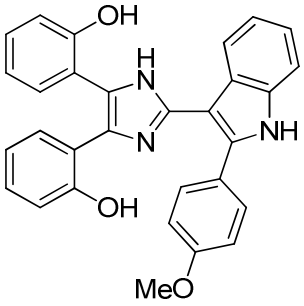
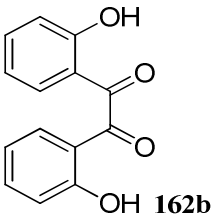
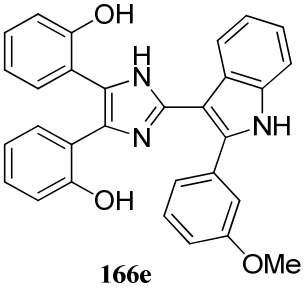
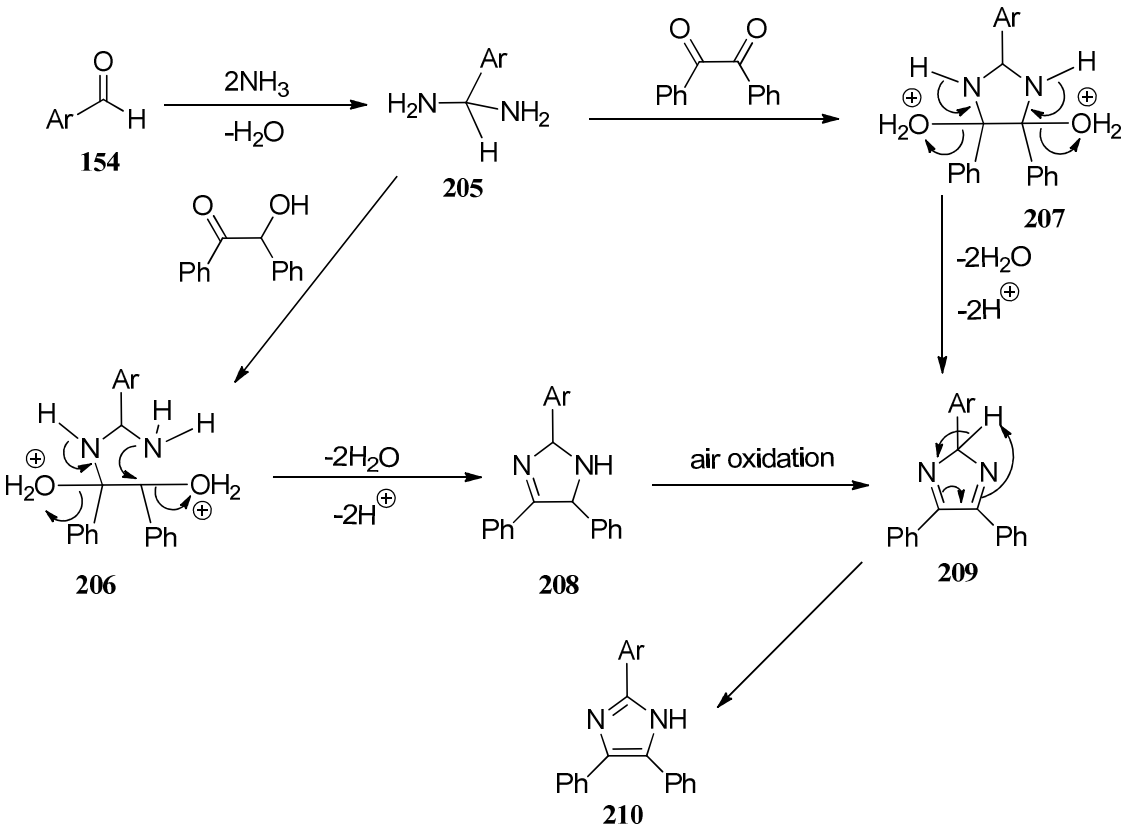
| Entry | 1,2-diketone | Product | Time (h) | Yield (%)[c] |
|---|---|---|---|---|
| 5 |  **160** |  **165c** | 3 | 53 |
| 6 |  **160** |  **165d** | 3 | 51 |
| 7 |  **160** |  **165e** | 3 | 49 |
| 8[b] |  **162a** |  **166a** | 24 | 3 |
| 9[b] |  **162b** |  **166a** | 4 | 71 |

**Table 4.11** (Continued)

| Entry | 1,2-diketone | Product | Time (hour) | Yield (%)[c] |
|---|---|---|---|---|
| 10[b] |  **162b** |  **166b** | 4 | 65 |
| 11[b] |  **162b** |  **166c** | 4 | 73 |
| 12[b] |  **162b** |  **166d** | 4 | 71 |
| 13[b] |  **162b** |  **166e** | 4 | 75 |

[a] Reaction condition: a mixture of 3-formyl indole (0.5 mmol), benzil or benzoin (0.5 mmol) and ammonium acetate (5.0 mmol) was refluxed in AcOH 2.5 mL.; [b] Reaction condition: a mixture of 3-formyl indole(0.25 mmol), benzil or benzoin (0.28 mmol) and ammonium acetate (2.5 mmol) was refluxed in AcOH 1.5 mL.; [c]Isolated yield

The reaction mechanism of a syntheszed imidazole derivative by three component reaction of aldehyde, 1,2-diketone or α-hydroxyketone and ammonium acetate involves condensation reaction. The reaction mechanism starts with the addition of ammonia to carbonyl of aldehyde (154), followed by substitution of hydroxyl group by ammonia to generate diamino intermediate (205). The 205 intermediate undergoes condensation with 1,2-diketone or α-hydroxyketone to form intermediates 206 and 207. Dehydration of intermediates 206 and 207 provides intermediates 208 and 209 respectively. The intermediate 208 is transformed to intermediate 209 by air oxidation. Finally, the tautomerization of 209 affords 2,4,5-triaryl-1*H*-imidazoles 210 [169].

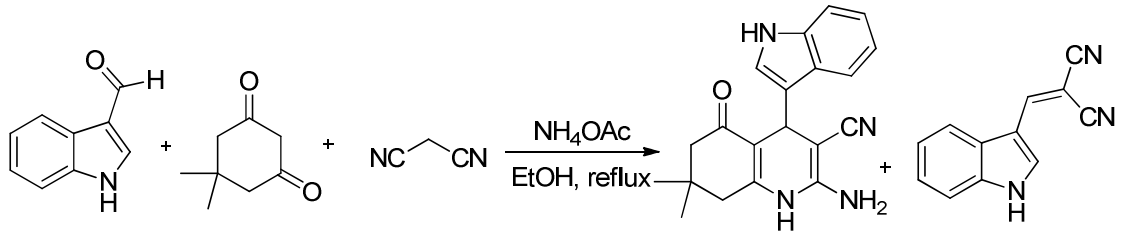



**Scheme 4.9** Reaction mechanism of a synthesis imidazole derivative by three component reaction of aldehyde, 1,2-diketone or α-hydroxyketone and ammonium acetate.

**4.6 Synthesis of indole derivative having 1,4-dihydropyridine**

Synthesis of 1,4-dihydropyridine was investigated by one-pot reaction of 1*H*-indole-3-carbaldehyde (154a), 5,5-dimethylcyclohexane-1,3-dione (167), malononitrile (168) and ammonium acetate in various catalyst (such as free-catalyst, CAN, $I_2$, TsOH and L-proline) in ethanol under refluxing condition is in Table 4.12. Unfortunately, the designed 1,4-dihydropyridine product (169) was not obtained. Only Knoevenagel product (170), from the reaction of malononitrile (168) and 1*H*-indole-3-carbaldehyde (154a), was formed. Furthermore, the sequential reaction was studied by the reaction of 1*H*-indole-3-carbaldehyde (154a) with 5,5-dimethylcyclohexane-1,3-dione (167) to generate the Knoevenagel product (171). Then the *α,β*-unsaturated compound (171) was continuously reacted with malononitrile and ammonium acetate under reflux temperature in ethanol. However, the result showed that the designed product 169 did not formed. Based on reaction mechanism, 1,4-dihydropyridine come from intermediate 171. However, N(1)-position of indole is a driving force for elimination of dimidone (167) from intermediate 211 to yield 170 (Figure 4.11) [128].

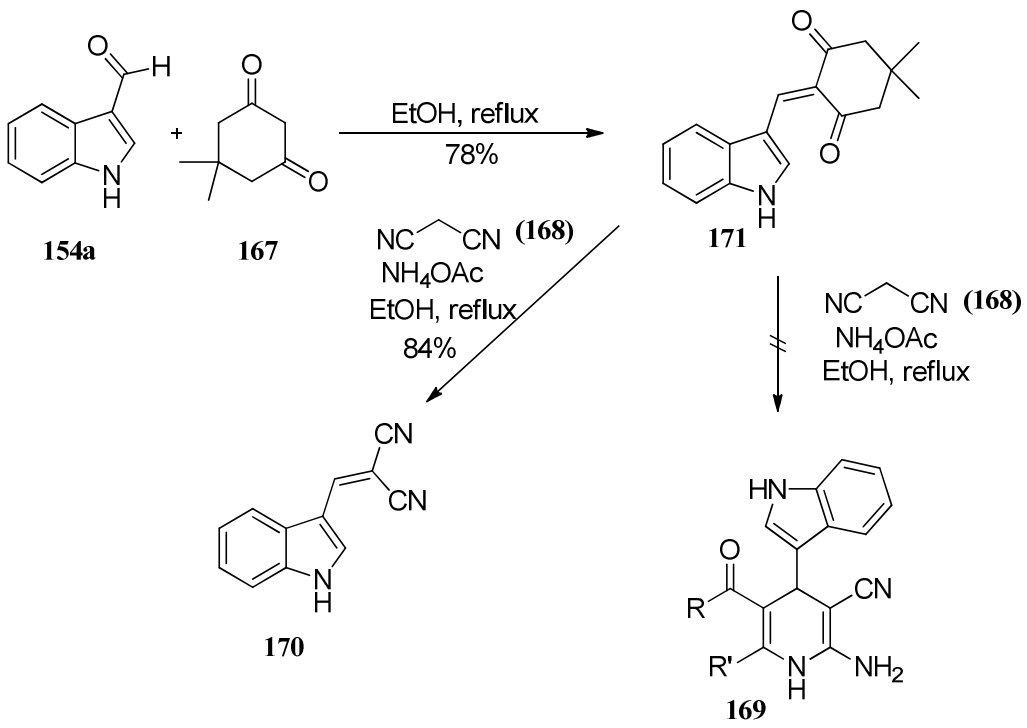
**Table 4.12** Synthesis of 1,4-dihydropyridine by four components reaction of 1*H*-indole-3-carbaldehyde, 5,5-dimethylcyclohexane-1,3-dione, malononitrile and ammonium acetate [a]



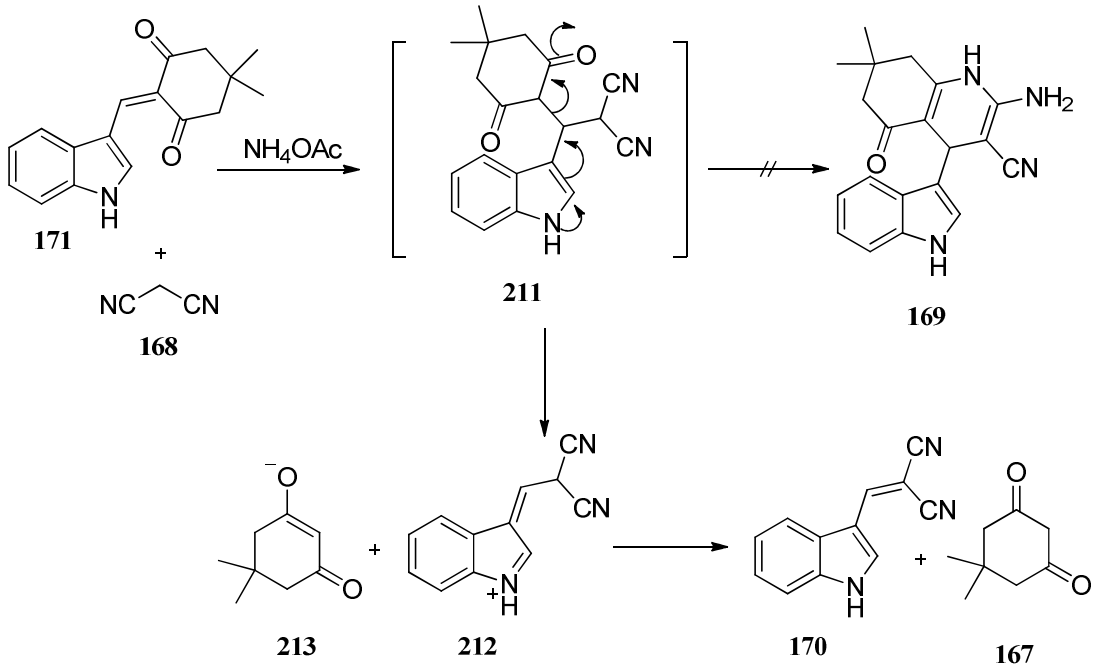

**154a** **167** **168** **169** **170**

| Entry | Condition | Time (hour) | Product[b] | |
|---|---|---|---|---|
| | | | 169 | 170 |
| 1 | $NH_4OAc$, EtOH | 24 | ND | / |
| 2 | $NH_4OAc$, 10 mol% CAN, EtOH | 24 | ND | / |
| 3 | $NH_4OAc$, 10 mol% $I_2$, EtOH | 24 | ND | / |
| 4 | $NH_4OAc$, 10 mol% TsOH, EtOH | 24 | ND | / |
| 5 | $NH_4OAc$, 10 mol% L-proline, EtOH | 24 | ND | / |
| 6 | $NH_3$ (aq.), EtOH | 24 | ND | / |

[a] Reaction condition: a mixture of 1*H*-indole-3-carbaldehyde, (0.1 mmol), 5,5-dimethylcyclohexane-1,3-dione (0.1 mmol), malononitrile (0.1 mmol) and ammonium acetate (0.2 mmol) wae reflux in EtOH.; [b] Monitored by Thin layer chromatography (TLC).; ND=Not Detected; / = Detected by TLC (254 nm)




**Scheme 4.10** Sequential synthesis of 1,4-dihydropyridine.




**Scheme 4.11** The proposed mechanism of the formation of 170 by the reaction between 171 and malononitrile.

# CHAPTER 5

# CONCLUSION

The synthesis of indole derivatives was investigated using Pd/Cu-catalyzed oxidative cyclization of *N*-aryl imine and Fischer reaction from phenylhydrazone and acetophenone. The indole product was obtained in modest yield. Whereas Fischer method gave 3-unsubstituted indoles in high yield (74-96%) from a commercial available staring material and reagent.

The formylation of a variety of indoles was achieved with new method using the formylating species generated from HMTA and CAN–$SiO_2$. The formylation of free (N–H) indoles proceeded smoothly giving the corresponding aldehydes with good yields (60-89%). The reaction was useful for the synthesis of highly functionalized indoles.

The synthesis of indole derivatives having thiosemicarbazone derivatives were carried out by the condensation of thiosemicarbazide and 3-formyl indole using few drops of acetic acid in good yield (74-86%). The thiosemicarbazones were treated with maleic anhydride in mixture of toluene and DMF in present of *p*-TsOH at reflux temperature to yield 4-oxo-3*H*-5–thiazolidine acetic acid product in high yield. Moreover, 4-oxo-3*H*-5–thiazolidine acetic acid can be prepared from one-pot reaction of thiosemicarbazide, 3-formyl indole and maleic anhydride in modest yield (65-77%).

The preparation of indole derivatives containing imidazole motif were achieved by the cyclocondensation of 1,10-phenanthroline-5,6-dione or 2,2′-dihydroxybenzil, 3-formyl indole and ammonium acetate in acetic acid under refluxing condition to provide desired product in moderate to good yield (45-87%).

Finally, the synthtesis of 1,4-dihydropyridine derivative was investigated by the reaction of 3-formyl indole, dimedone, malononitrile and ammonium acetate in various conditions. The designed product could not obtain.

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# REFERENCES


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# APPENDICES

# Appendix A

# Spectral data of indole derivatives

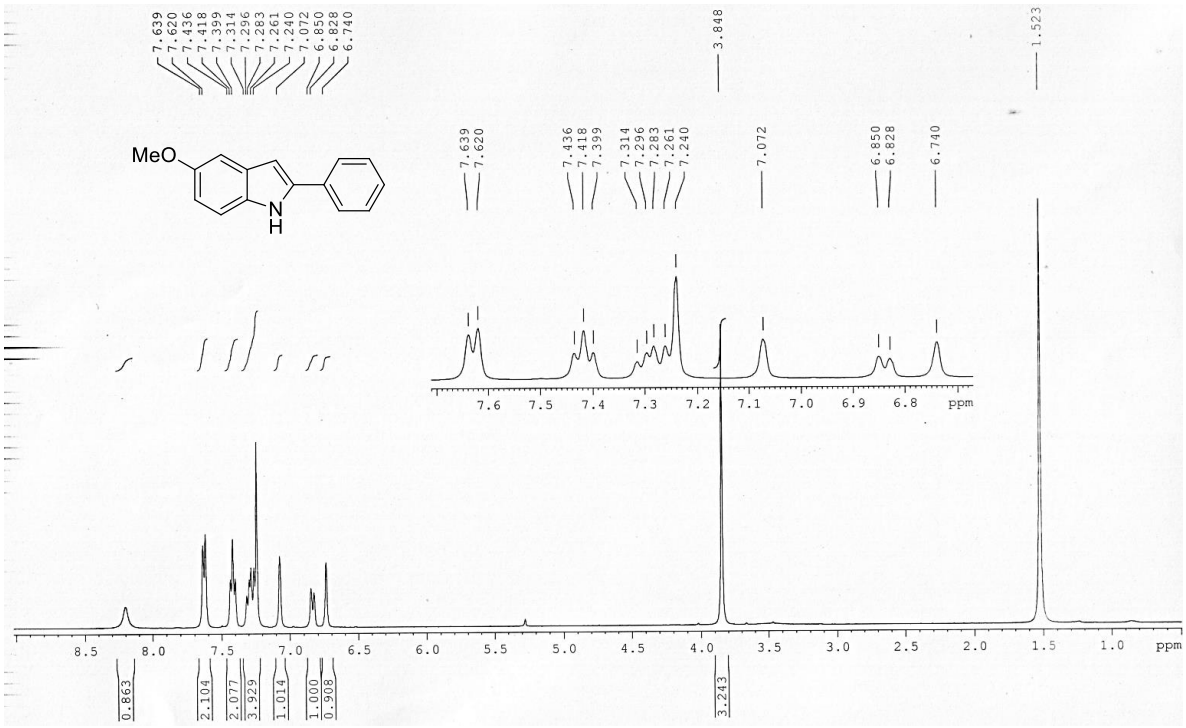


**Figure A1** $^{1}$H-NMR spectrum of 5-methoxy-2-phenyl-1*H*-indole (152a).

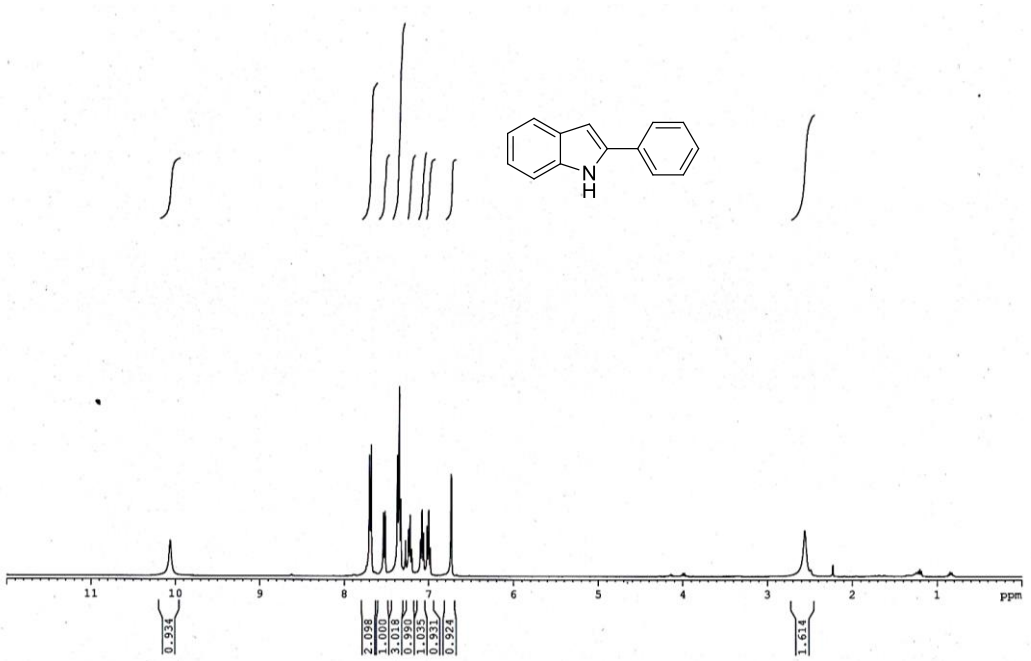


**Figure A2** $^{1}$H-NMR spectrum of 2-phenyl-1*H*-indole (152b).

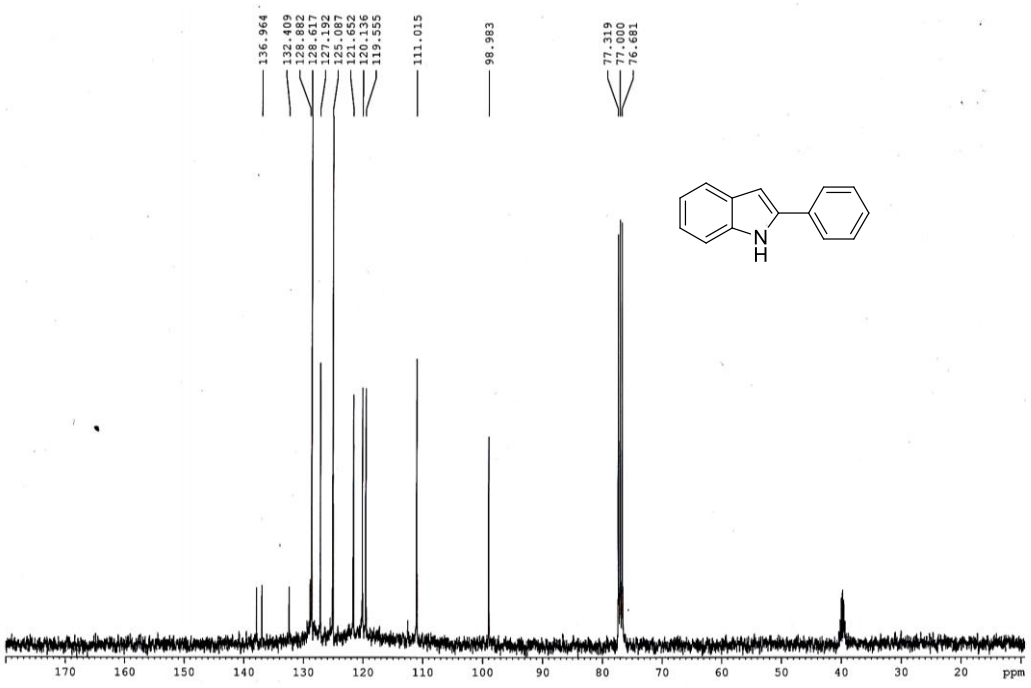


**Figure A3** $^{13}$C-NMR spectrum of 2-phenyl-1*H*-indole (152b).

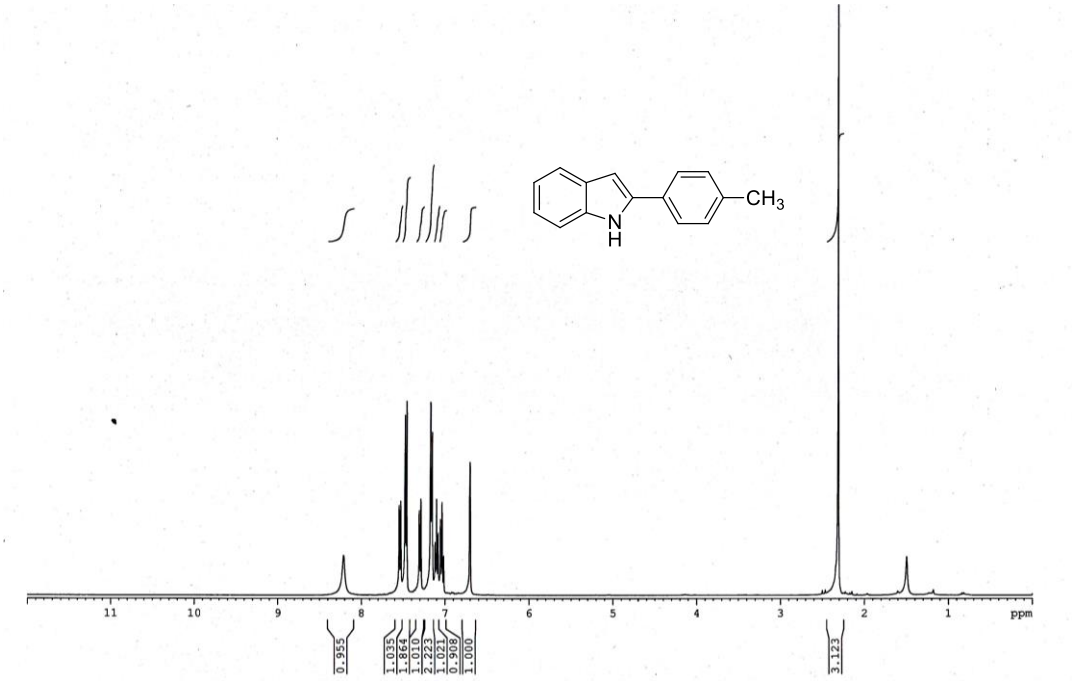


**Figure A4** $^{1}$H-NMR spectrum of 1*H*-2-(4-methyl phenyl) indole (152c).

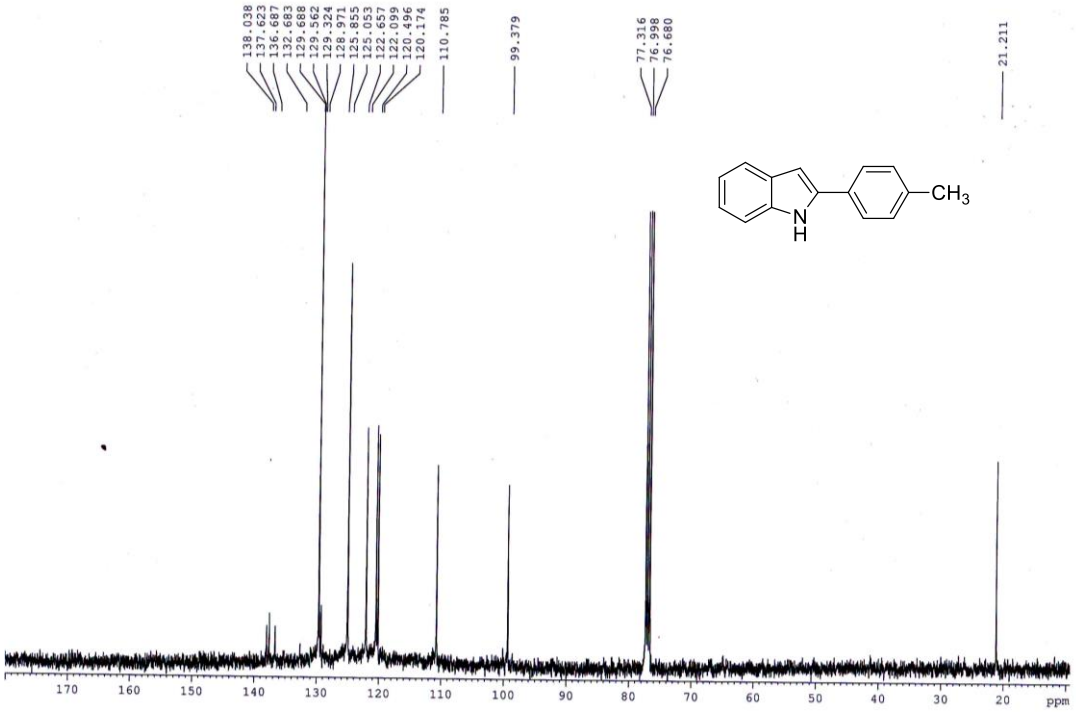


**Figure A5** $^{13}$C-NMR spectrum of 1*H*-2-(4-methyl phenyl) indole (152c).

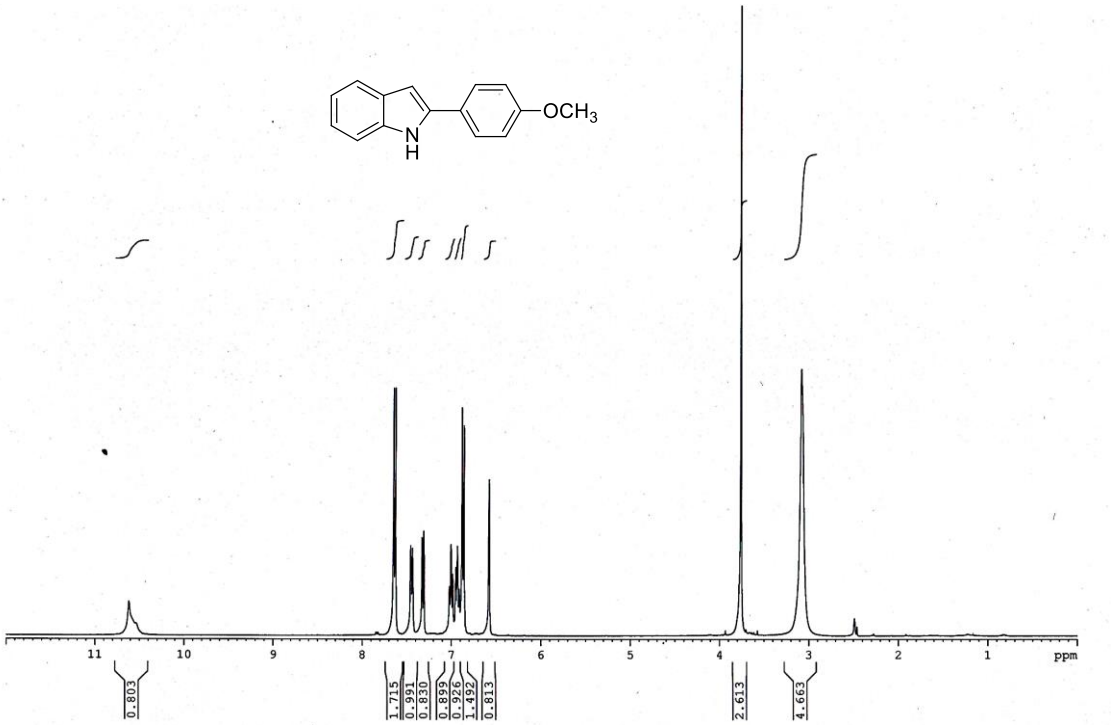


**Figure A6** $^{1}$H-NMR spectrum of 2-(4-methoxy phenyl)-1*H*-indole (152d).

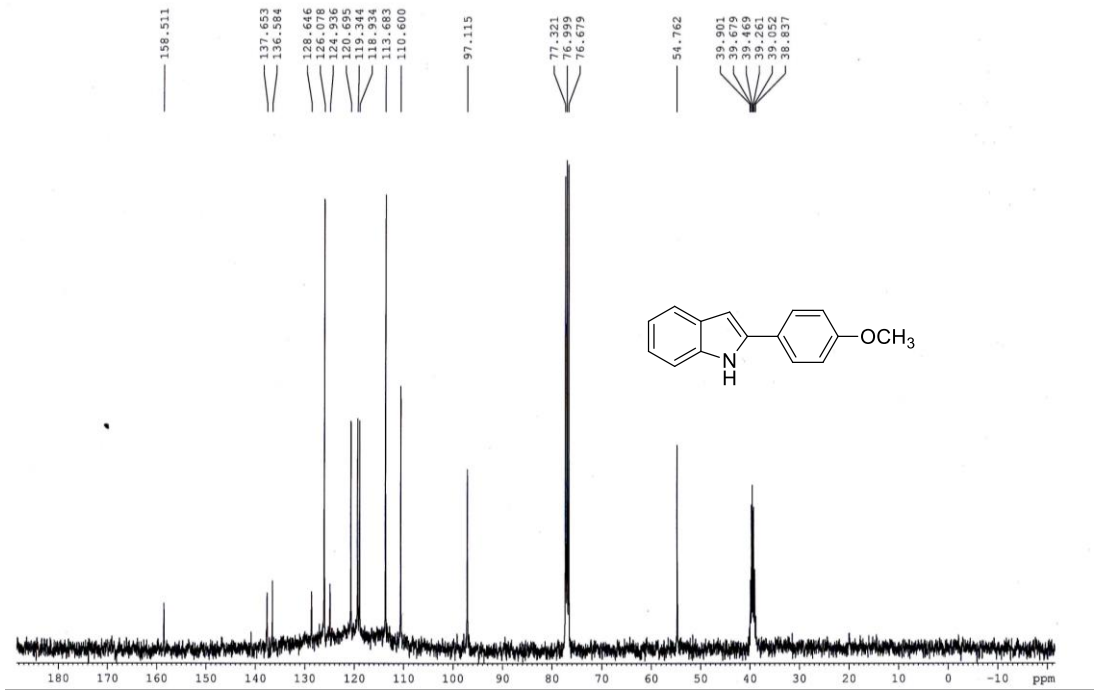


**Figure A7** $^{13}$C-NMR spectrum of 2-(4-methoxy phenyl)-1*H*-indole (152d).

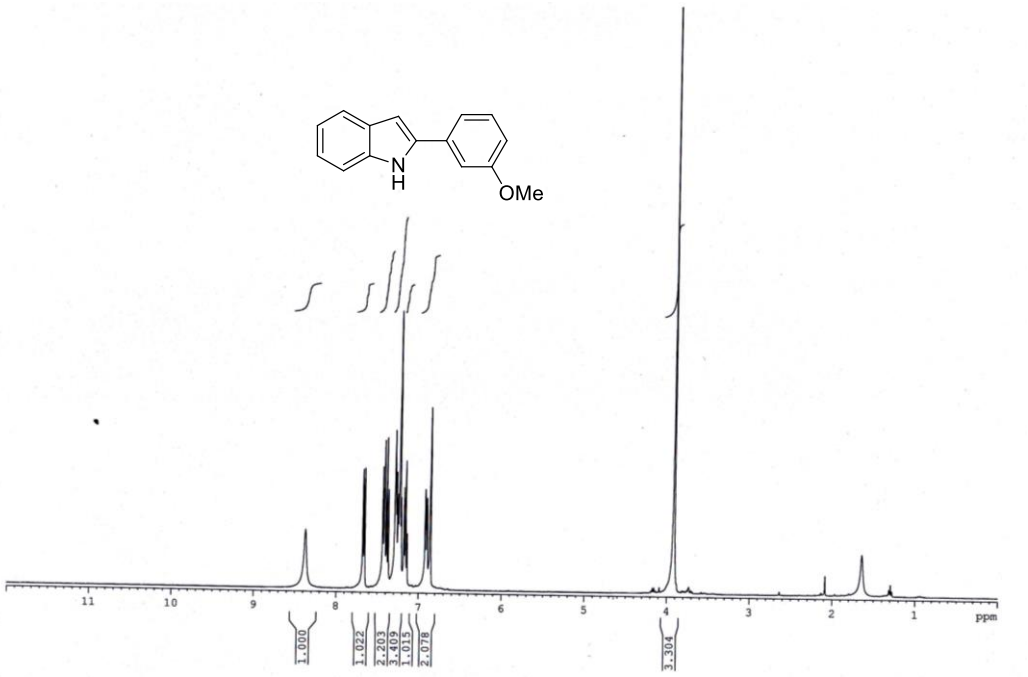


**Figure A8** $^{1}$H-NMR spectrum of 2-(3-methoxyphenyl)-1*H*-indole (152e).

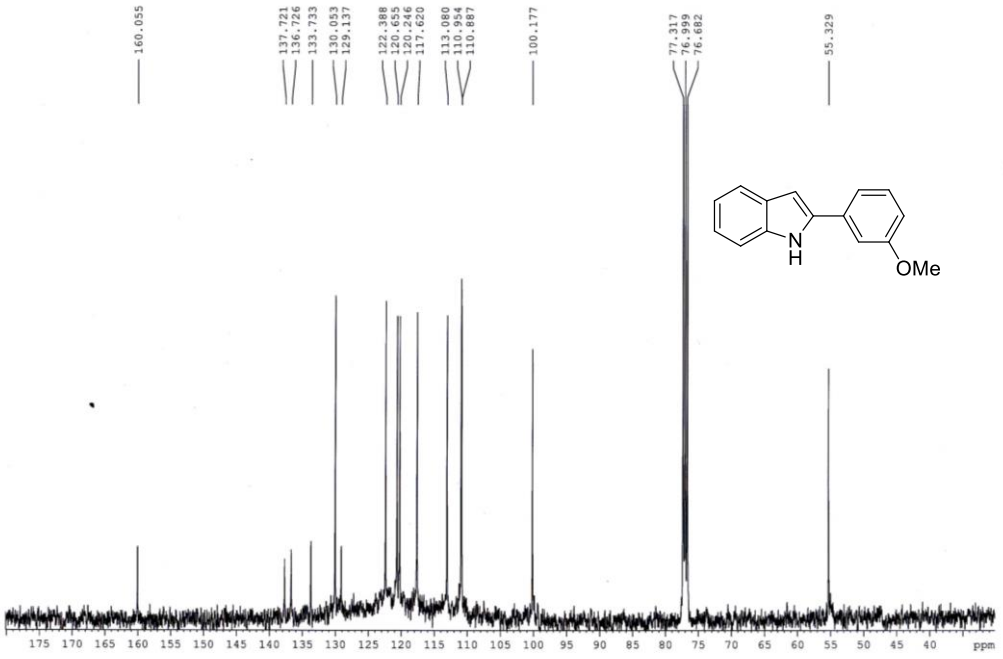


**Figure A9** $^{13}$C-NMR spectrum of 2-(3-methoxyphenyl)-1*H*-indole (152e).

# Appendix B

# Spectral data of 3-formyl indole derivatives

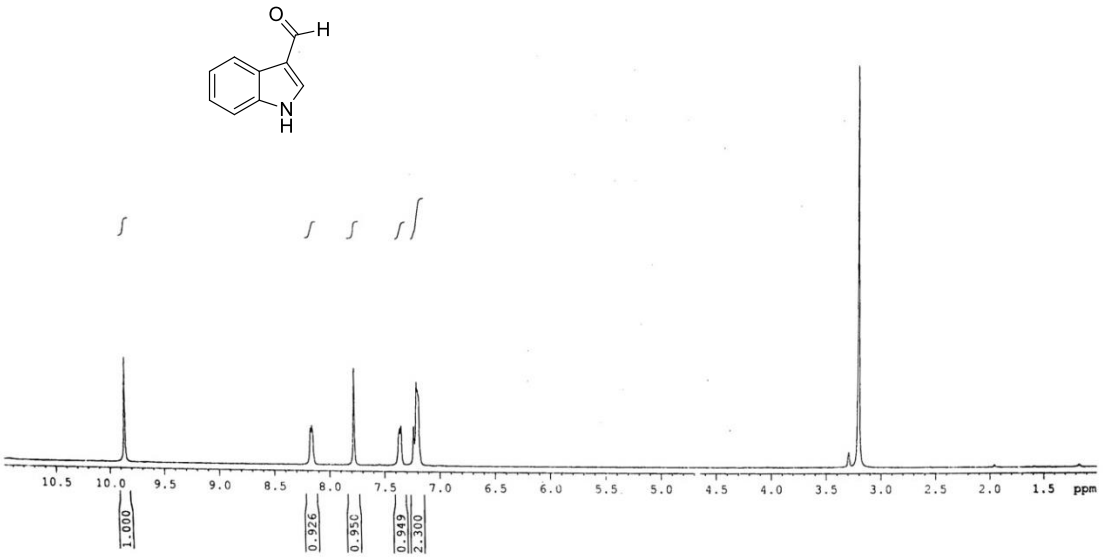


**Figure B1** $^{1}$H-NMR spectrum of 1*H*-indole-3-carbaldehyde (154a).

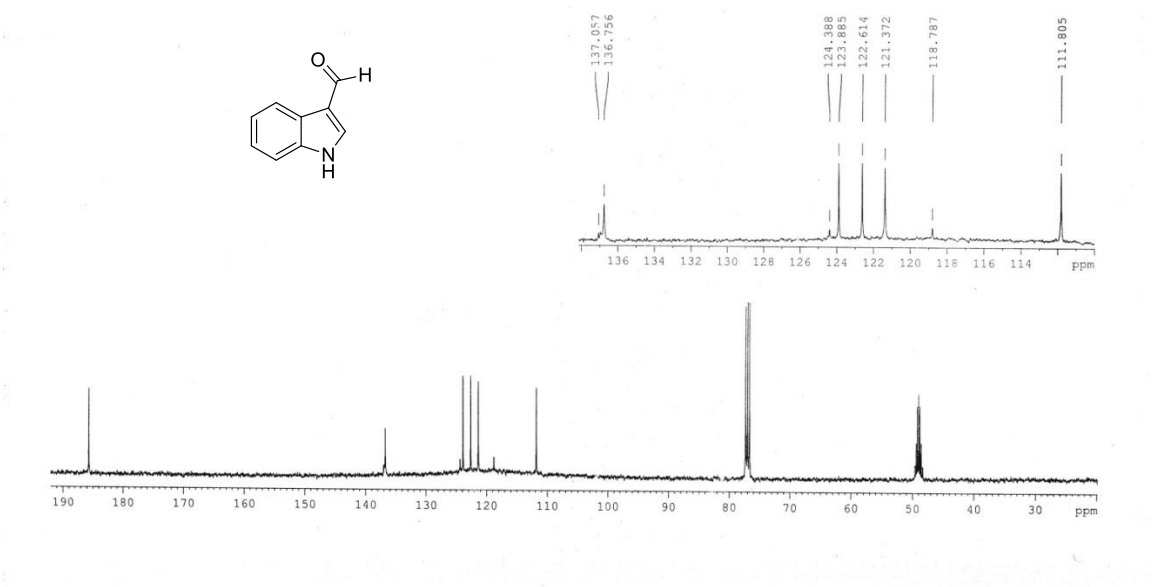


**Figure B2** $^{13}$C-NMR spectrum of 1*H* -indole-3-carbaldehyde (154a).

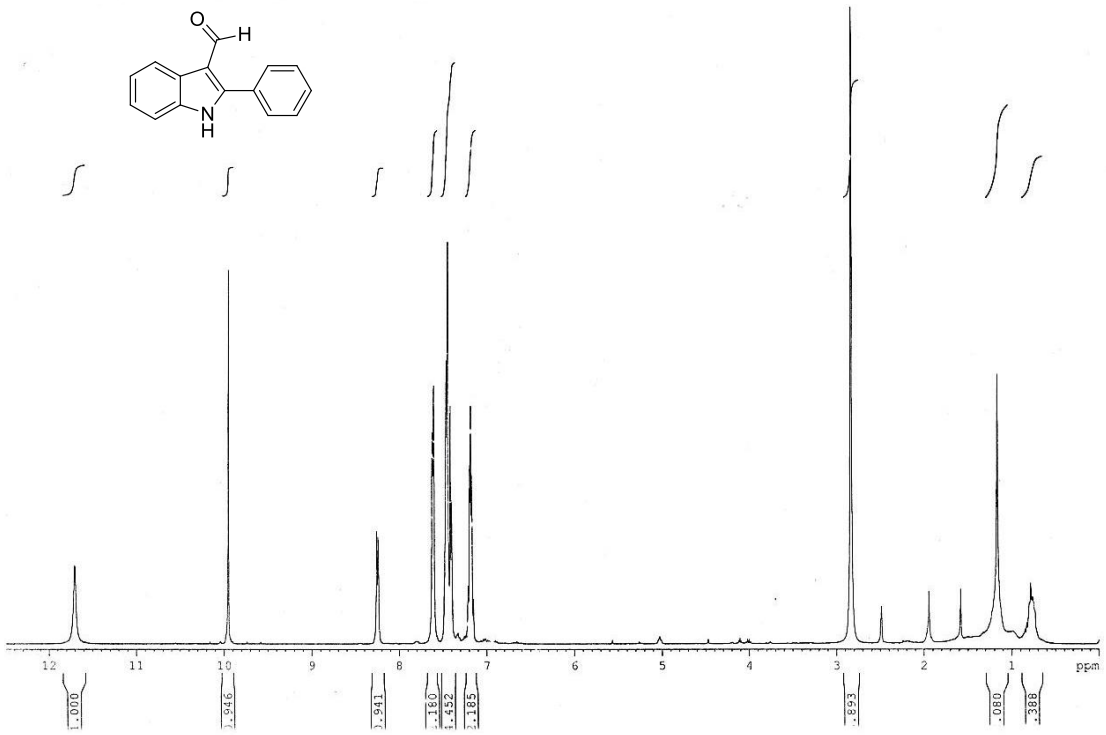


**Figure B3** $^{1}$H-NMR spectrum of 2-phenyl-1*H*-indole-3-carbaldehyde (154b).

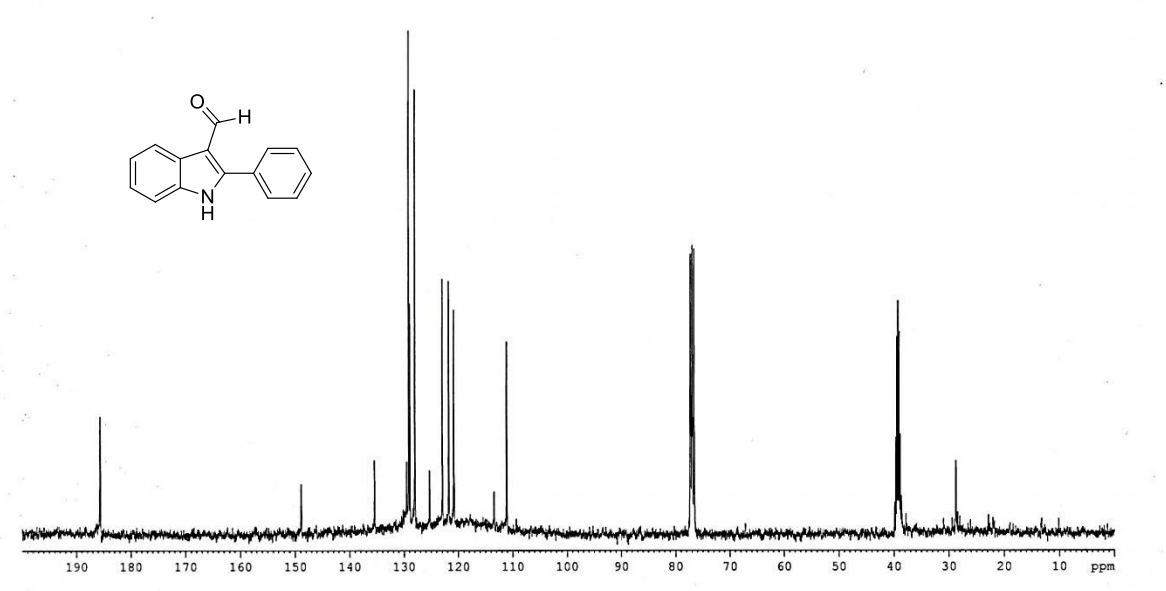


**Figure B4** $^{13}$C-NMR spectrum of 2-phenyl-1*H*-indole-3-carbaldehyde (154b).

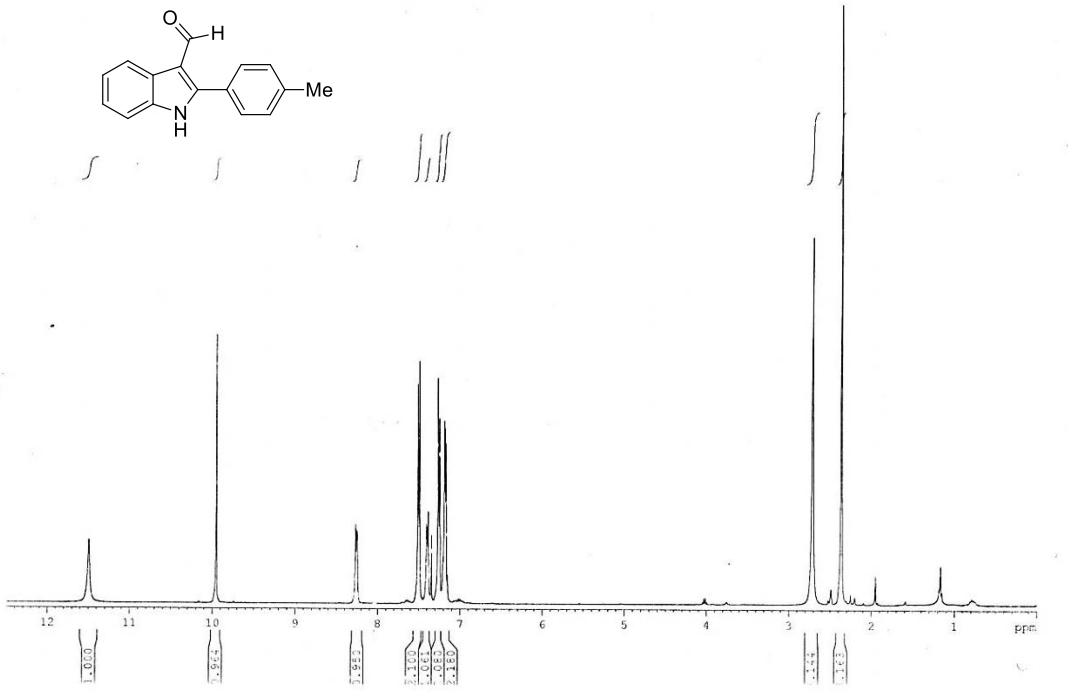


**Figure B5** $^{1}$H-NMR spectrum of 2-(4-methyl phenyl)-1*H*-indole-3-carbaldehyde (154c).

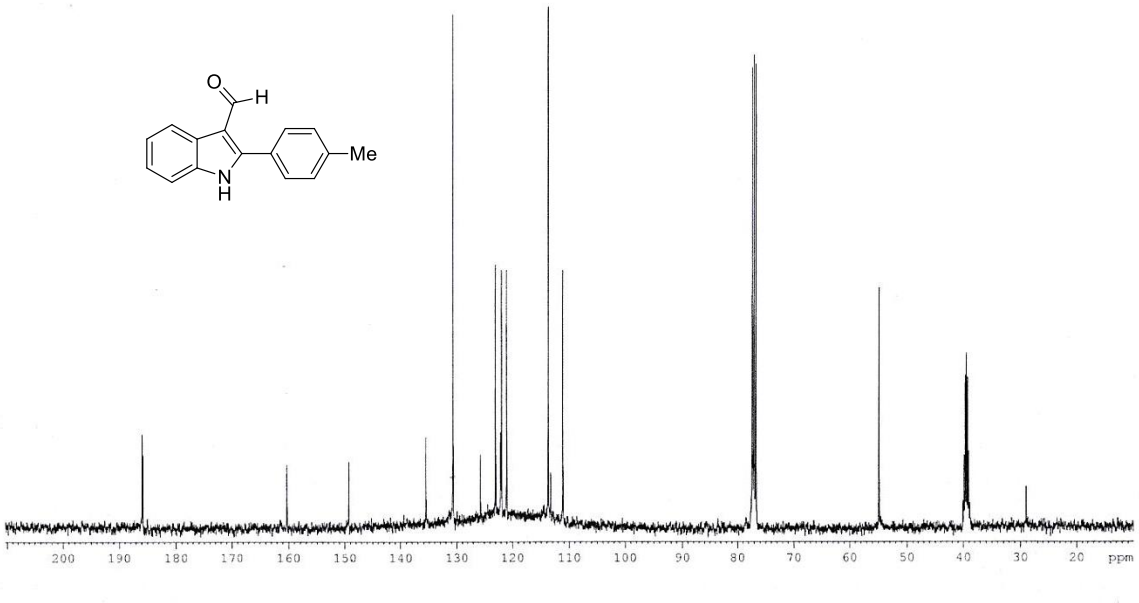


**Figure B6** $^{13}$C-NMR spectrum of 2-(4-methyl phenyl)-1*H*-indole-3-carbaldehyde (154c).

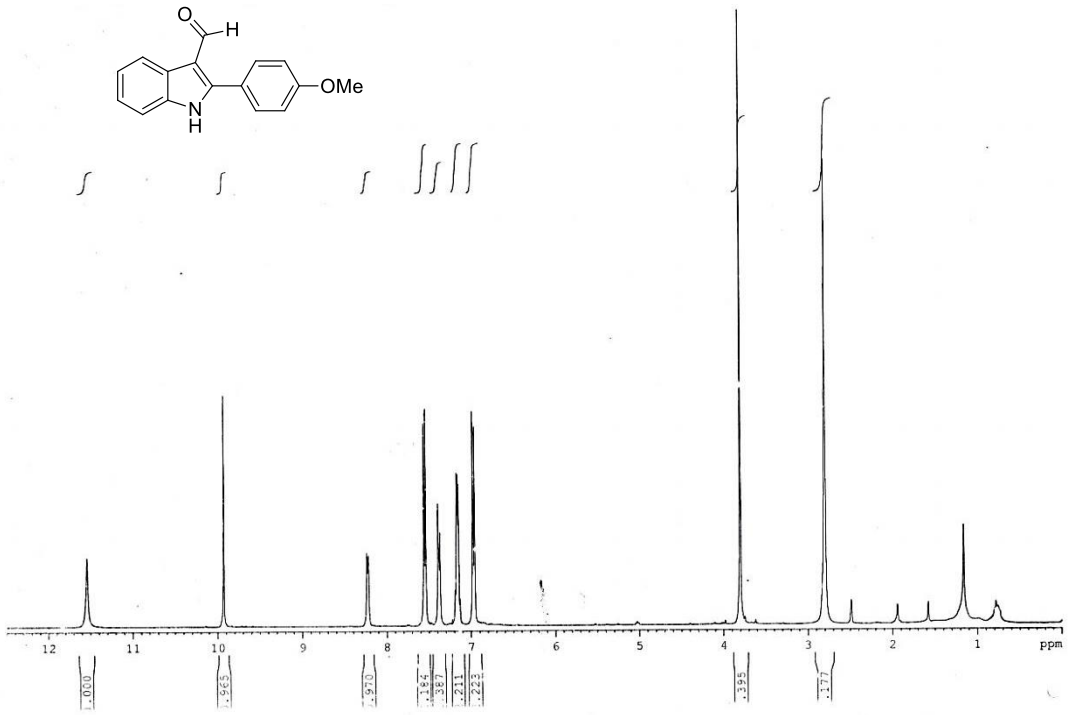


**Figure B7** $^{1}$H-NMR spectrum of 2-(4-methoxy phenyl)-1*H*-indole-3-carbaldehyde (154d).

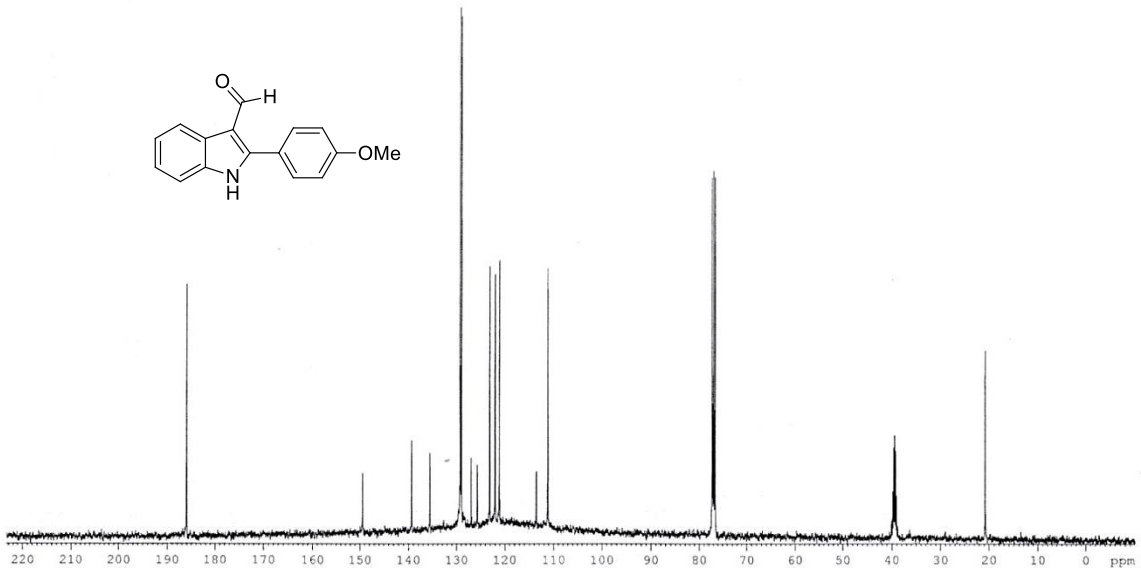


**Figure B8** $^{13}$C-NMR spectrum of 2-(4-methoxy phenyl)-1*H*-indole-3-carbaldehyde (154d).

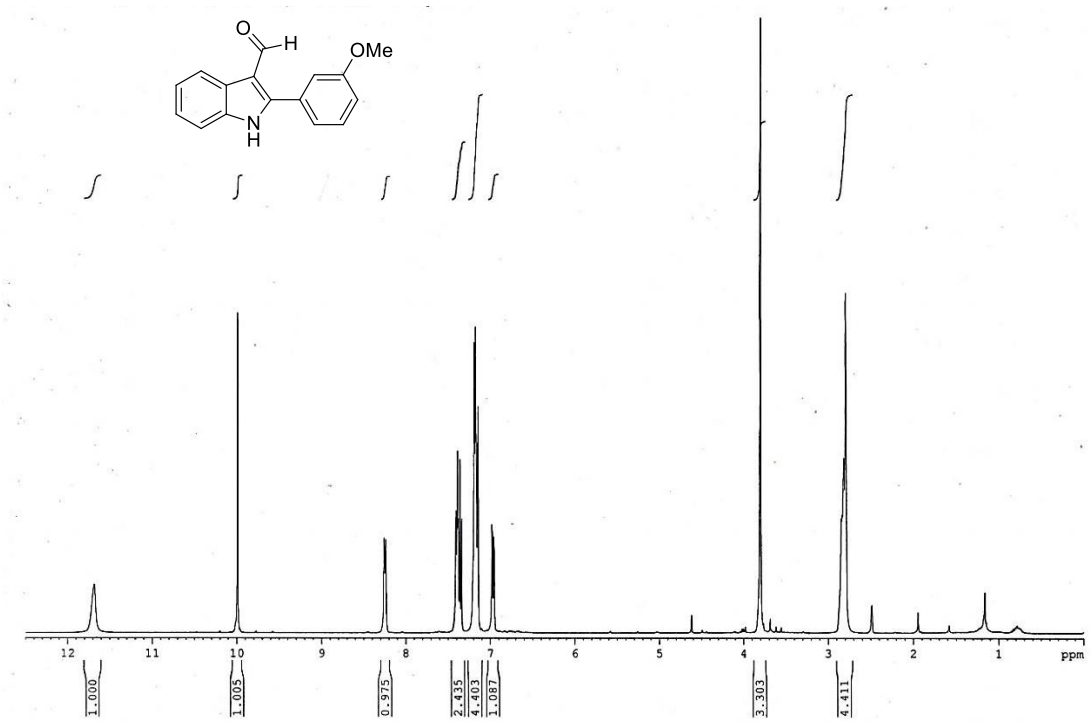


**Figure B9** $^{1}$H-NMR spectrum of 2-(3-Methoxy phenyl)-1*H*-indole-3-carbaldehyde (154e).

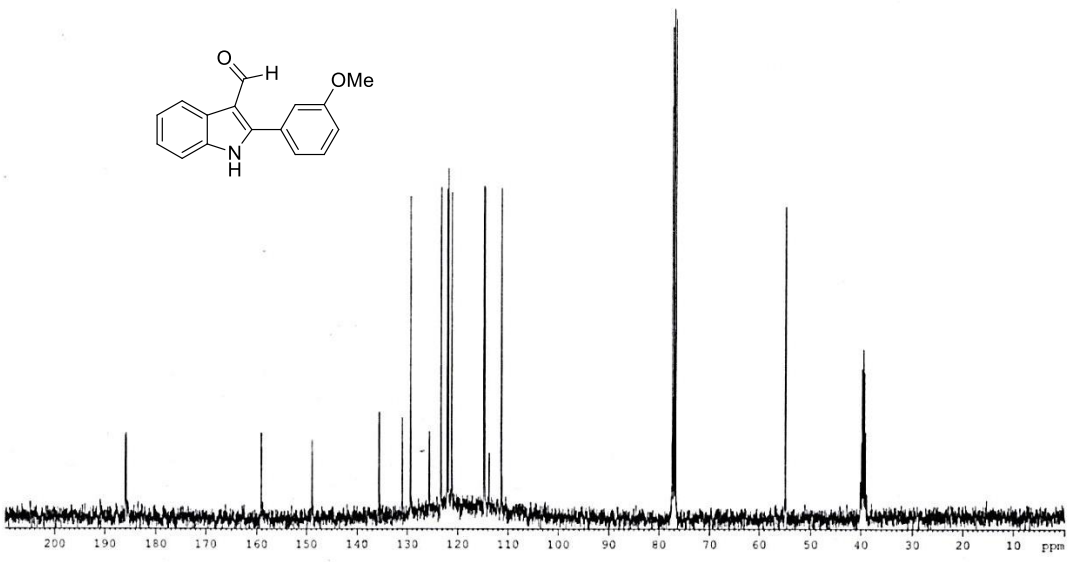


**Figure B10** $^{13}$C-NMR spectrum of 2-(3-Methoxy phenyl)-1*H*-indole-3-carbaldehyde (154e).

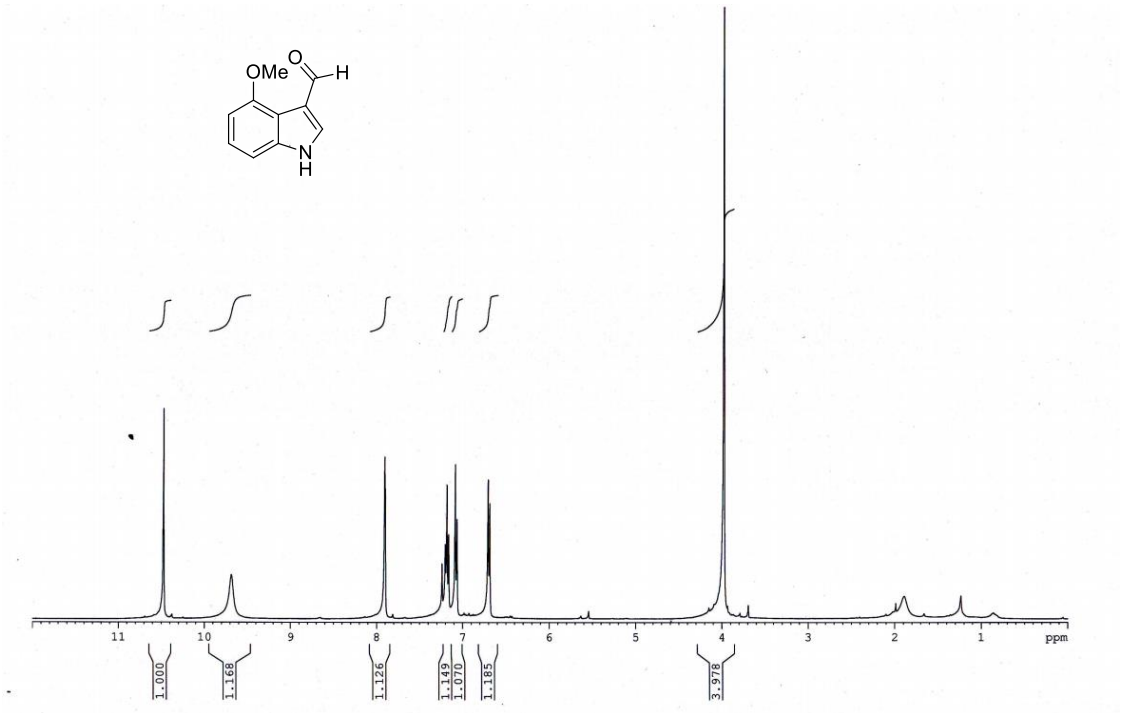


**Figure B11** $^{1}$H-NMR spectrum of 4-methoxy-1*H*-indole-3-carbaldehyde (154f).

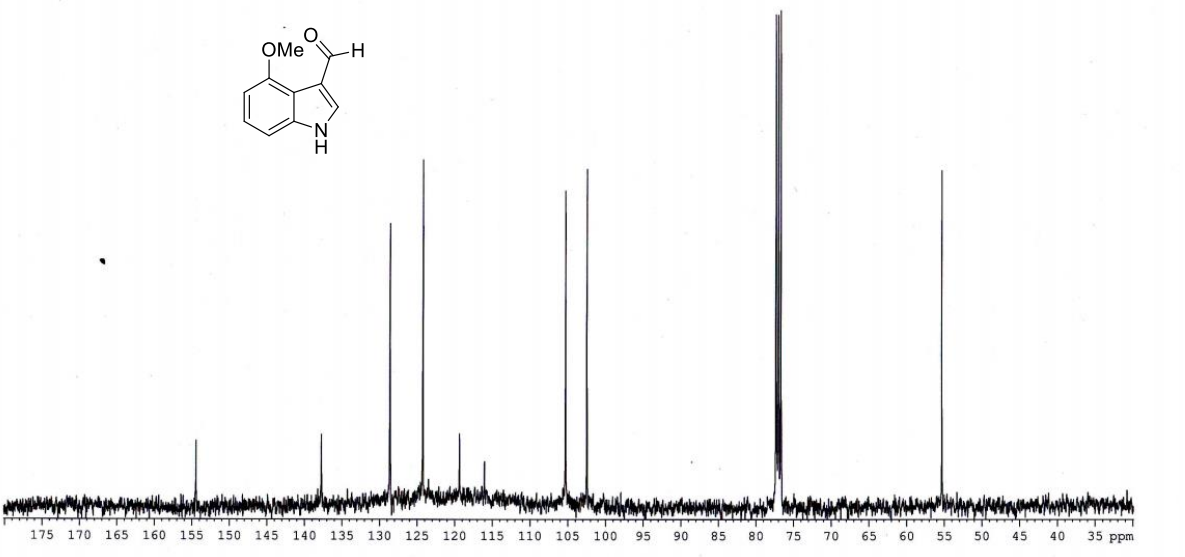


**Figure B12** $^{13}$C-NMR spectrum of 4-methoxy-1*H*-indole-3-carbaldehyde (154f).

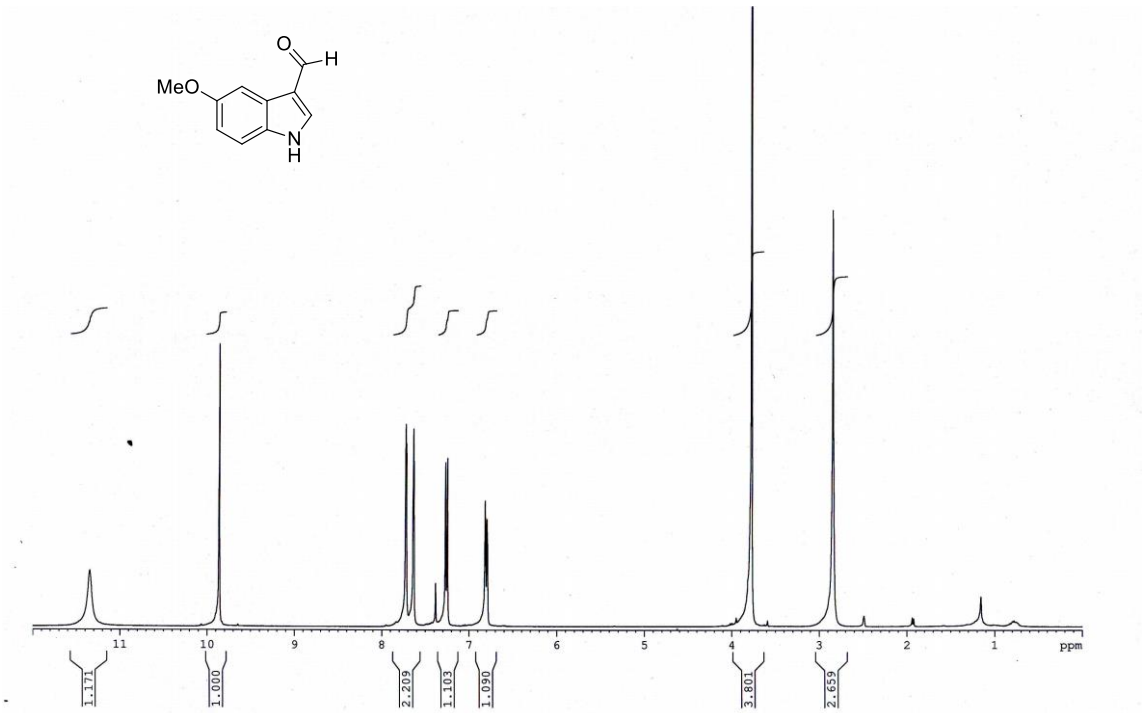


**Figure B13** $^{1}$H-NMR spectrum of 5-methoxy-1*H*-indole-3-carbaldehyde (154g).

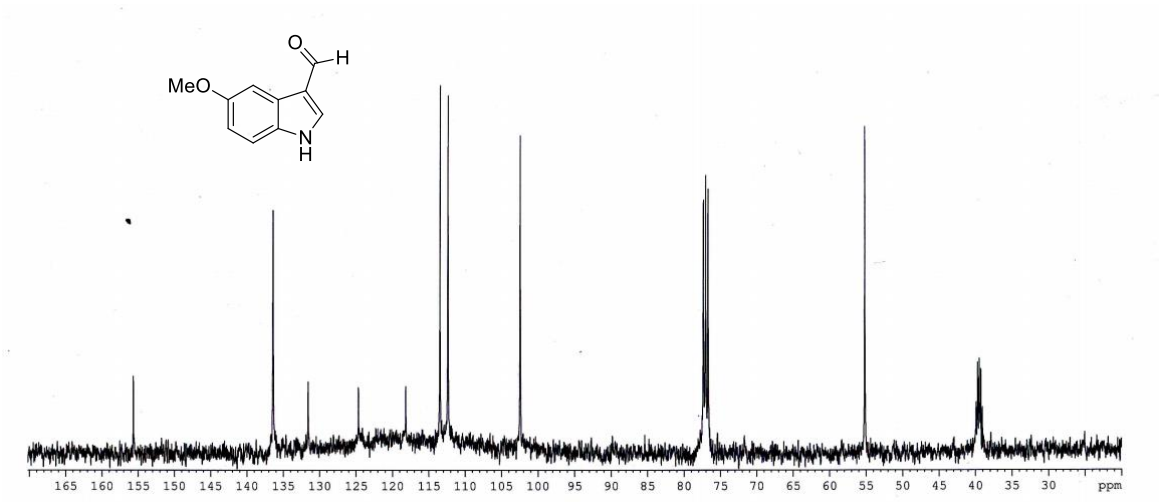


**Figure B14** $^{13}$C-NMR spectrum of 5-methoxy-1*H*-indole-3-carbaldehyde (154g).

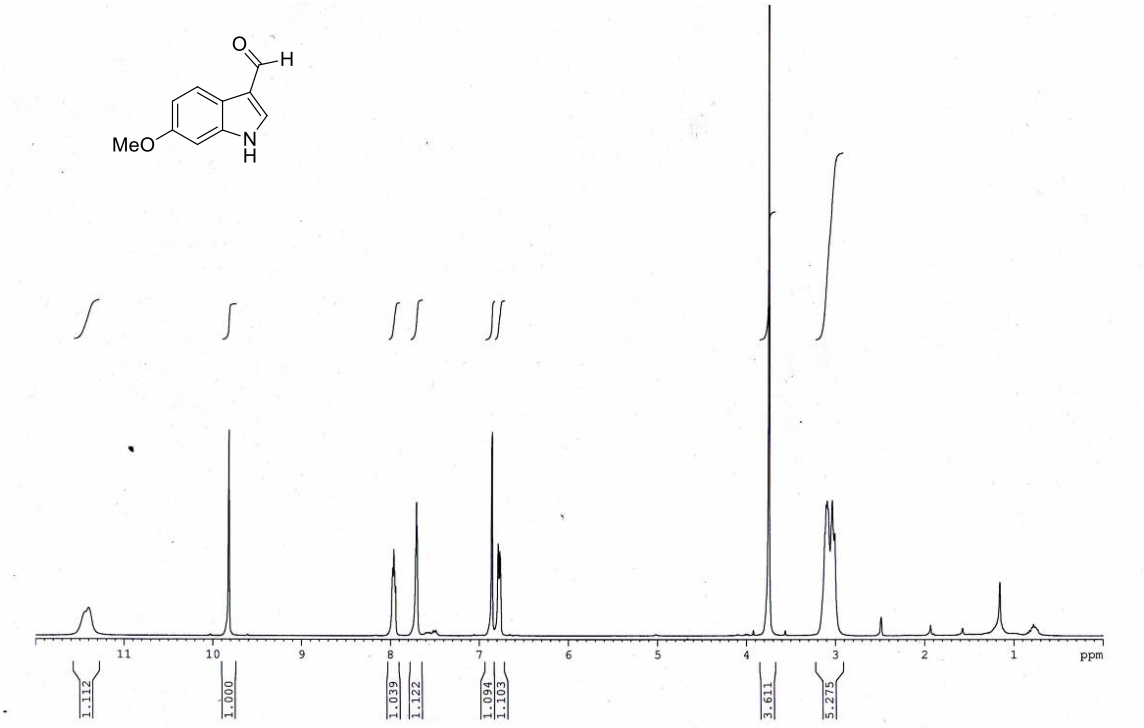


**Figure B15** $^{1}$H-NMR spectrum of 6-methoxy-1*H*-indole-3-carbaldehyde (154h).

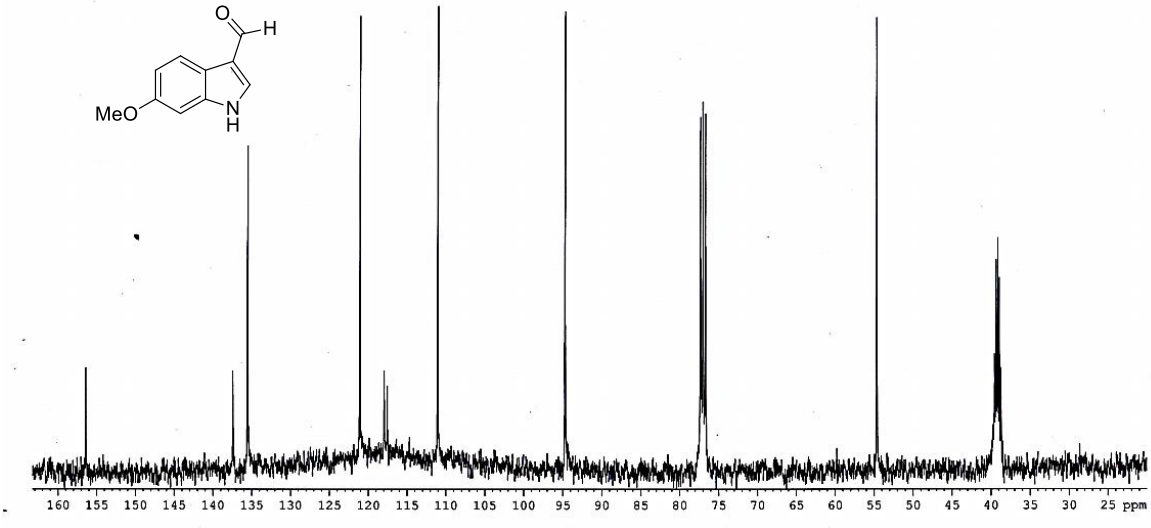


**Figure B16** $^{13}$C-NMR spectrum of 6-methoxy-1*H*-indole-3-carbaldehyde (154h).

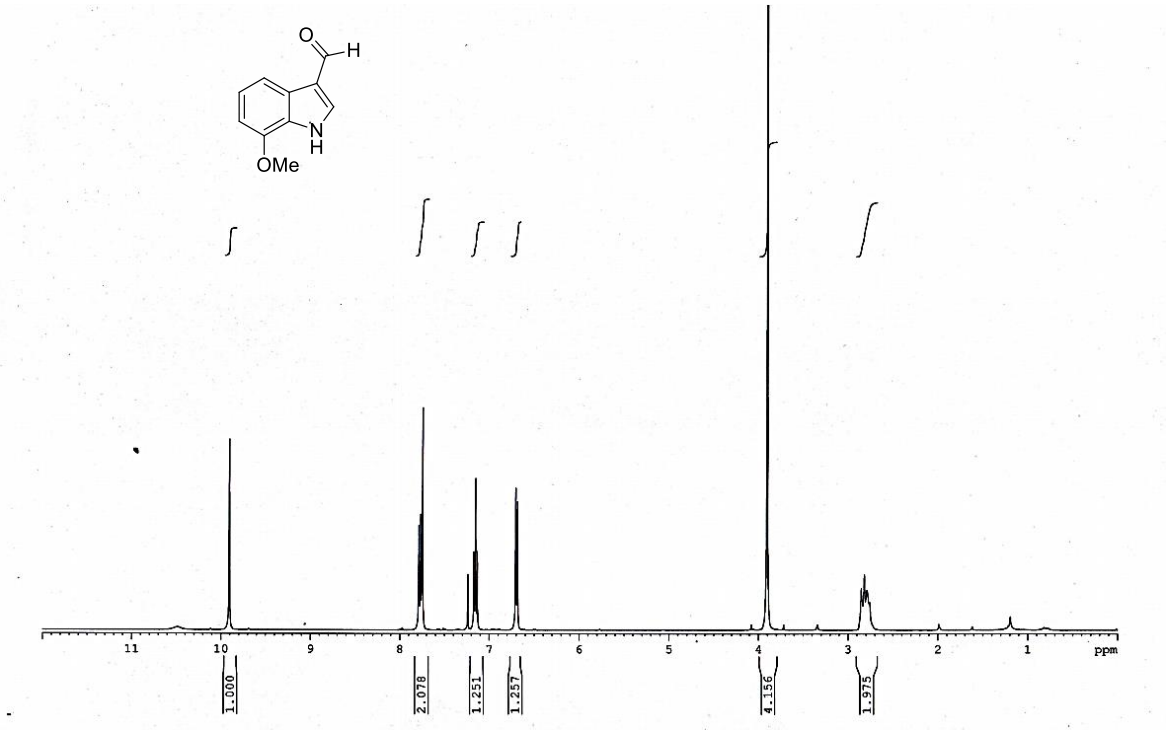


**Figure B17** $^{1}$H-NMR spectrum of 7-methoxy-1*H*-indole-3-carbaldehyde (154i).

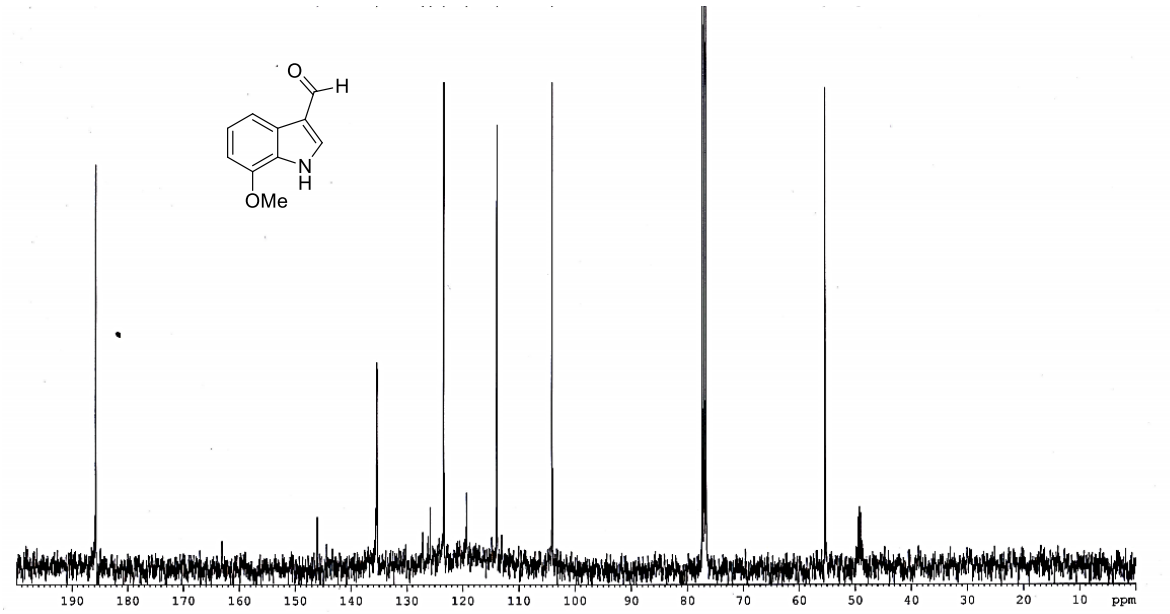


**Figure B18** $^{13}$C-NMR spectrum of 7-methoxy-1*H*-indole-3-carbaldehyde (154i).

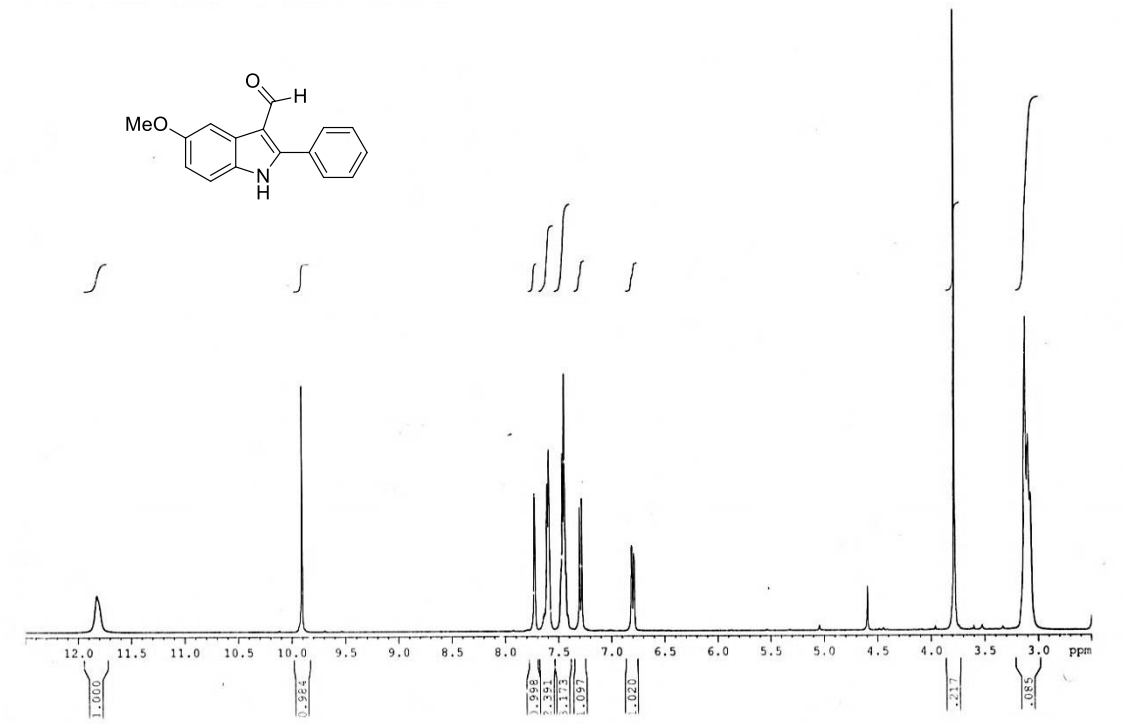


**Figure B19** $^{1}$H-NMR spectrum of 5-methoxy-2-phenyl-1*H*-indole-3-carbaldehyde (154j).

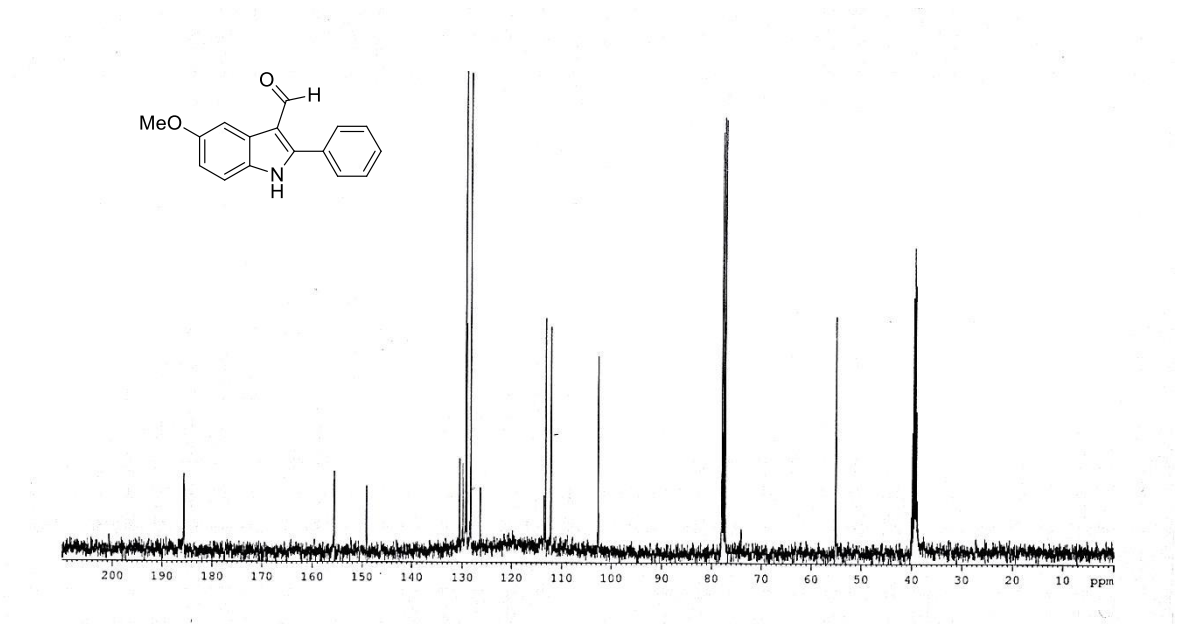


**Figure B20** $^{13}$C-NMR spectrum of 5-methoxy-2-phenyl-1*H*-indole-3-carbaldehyde (154j).

# Appendix C

# Spectral data of thiosemicarbazone derivatives

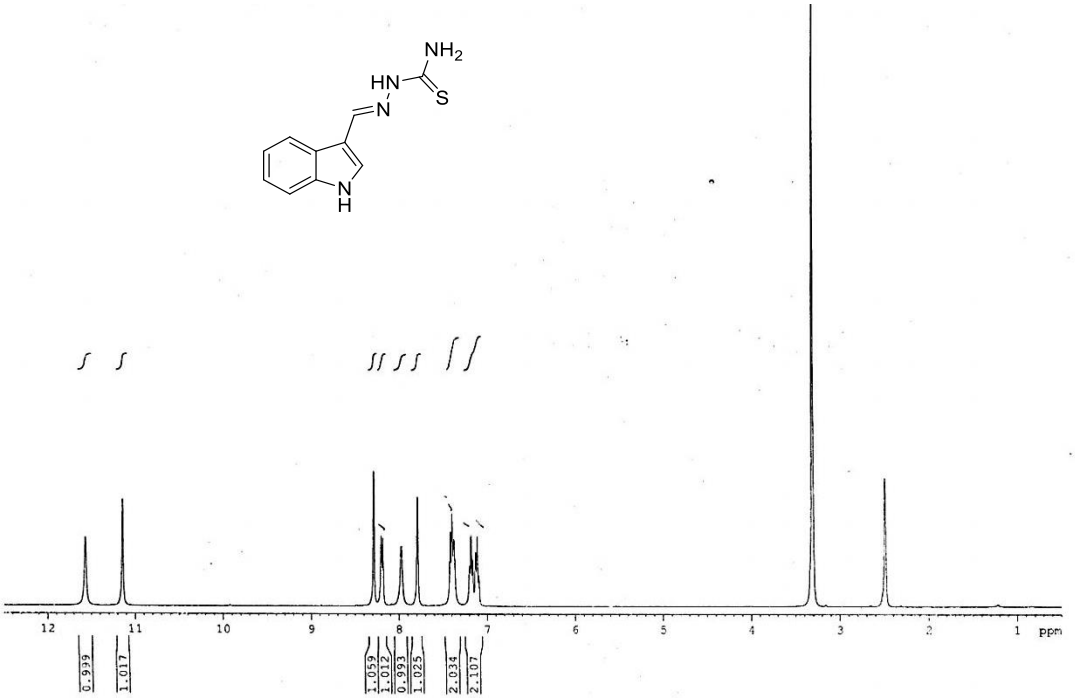


**Figure C1** $^{1}$H-NMR spectrum of 1*H*-indole-3-carbaldehyde thiosemicarbazone (156a).

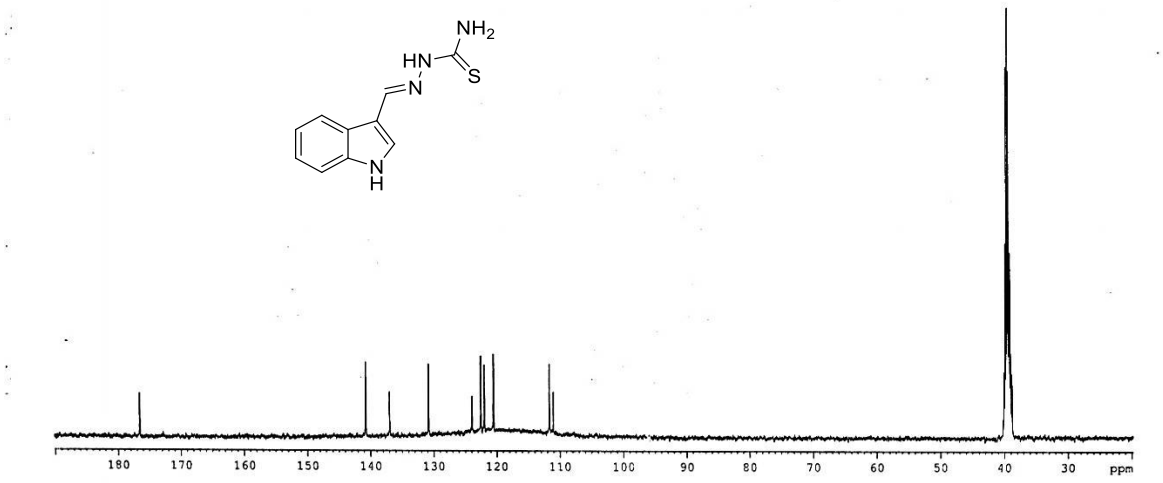


**Figure C2** $^{13}$C-NMR spectrum of 1*H*-indole-3-carbaldehyde thiosemicarbazone (156a).

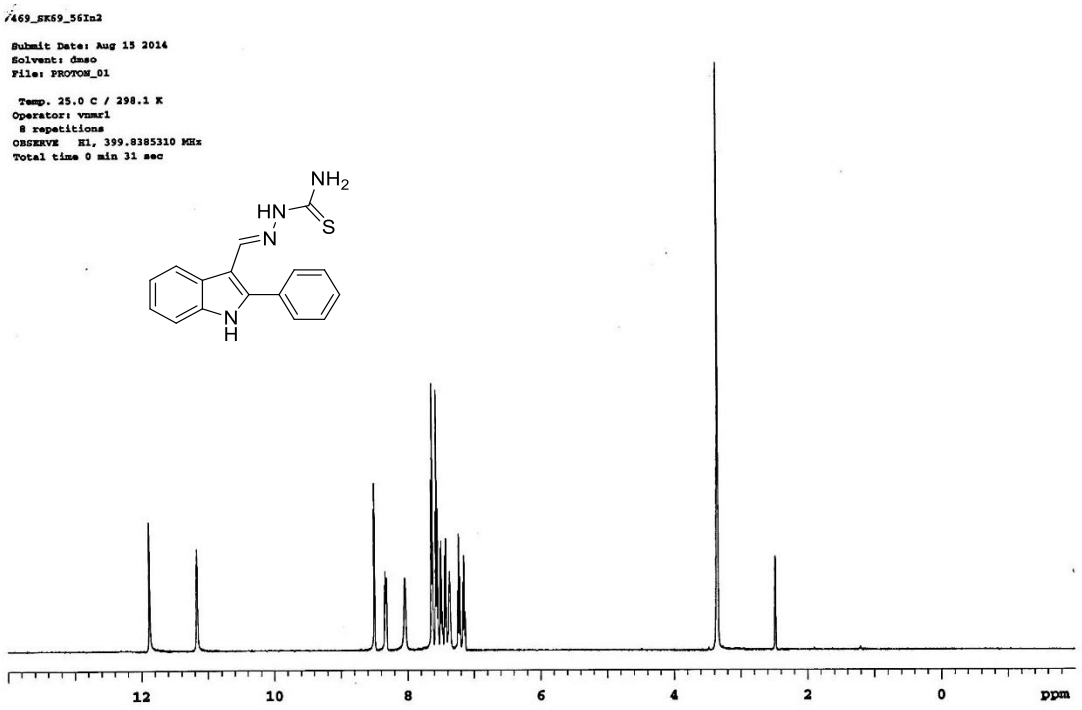


**Figure C3** $^{1}$H-NMR spectrum of 2-phenyl-1*H*-indole-3-carbaldehyde thiosemicarbazone (156b).

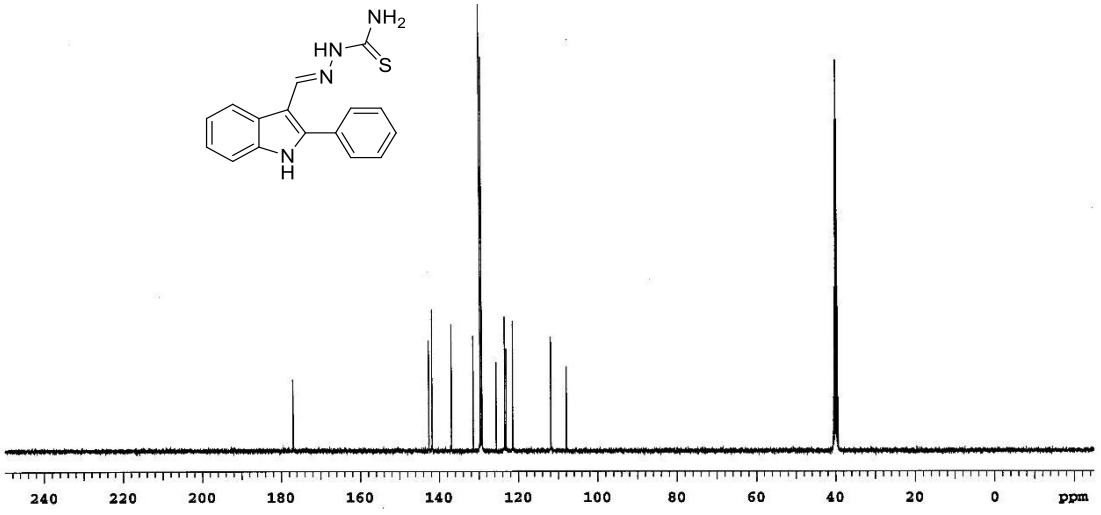


**Figure C4** $^{13}$C-NMR spectrum of 2-phenyl-1*H*-indole-3-carbaldehyde thiosemicarbazone (156b).

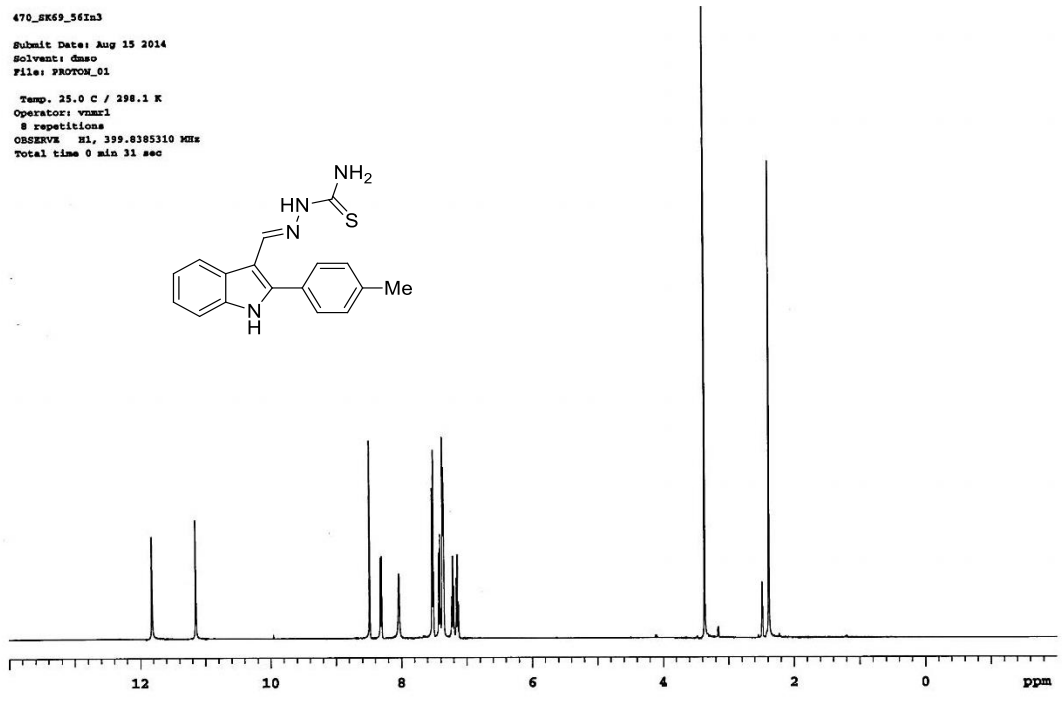


**Figure C5** $^{1}$H-NMR spectrum of 2-(4-methyl phenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156c).

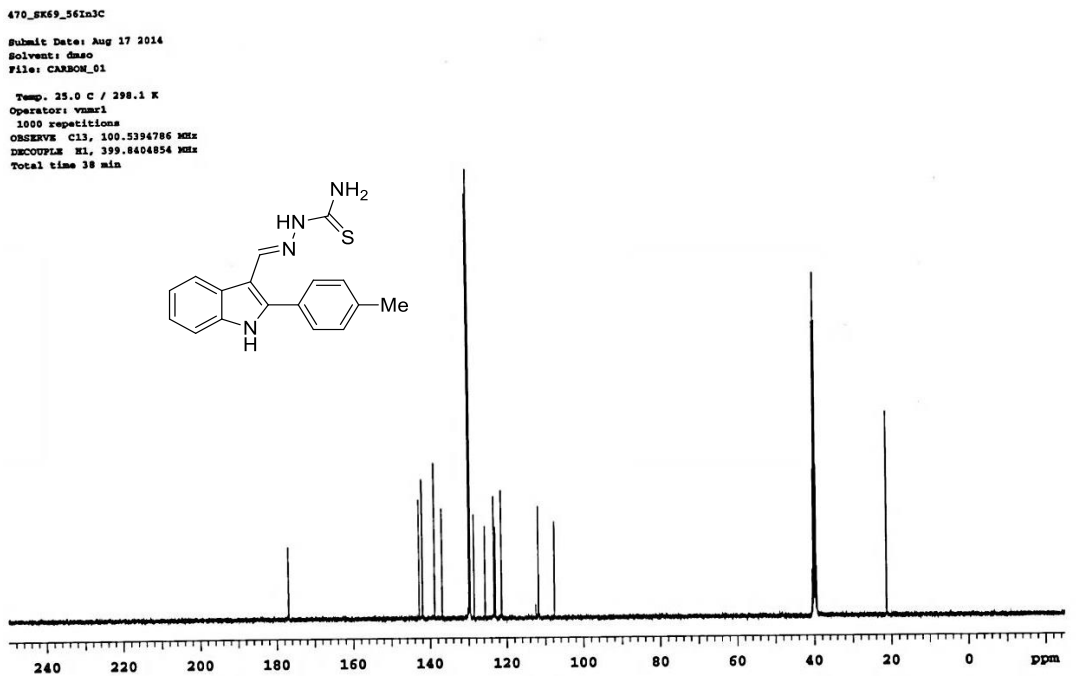


**Figure C6** $^{13}$C-NMR spectrum of 2-(4-methyl phenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156c).

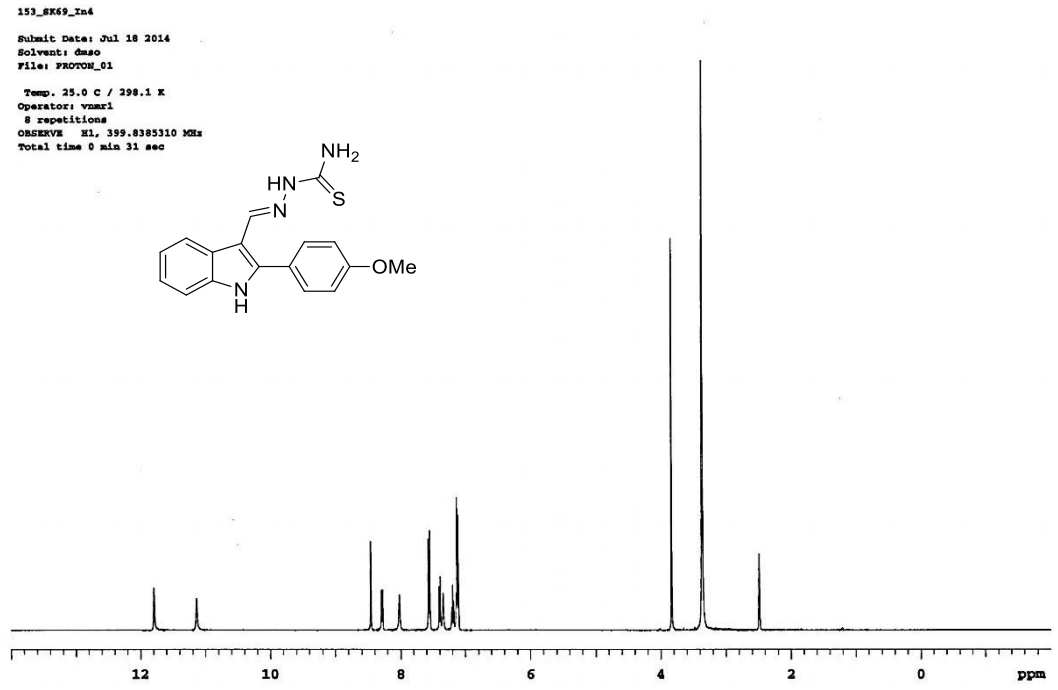


**Figure C7** $^{1}$H-NMR spectrum of 2-(4-methoxy phenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156d).

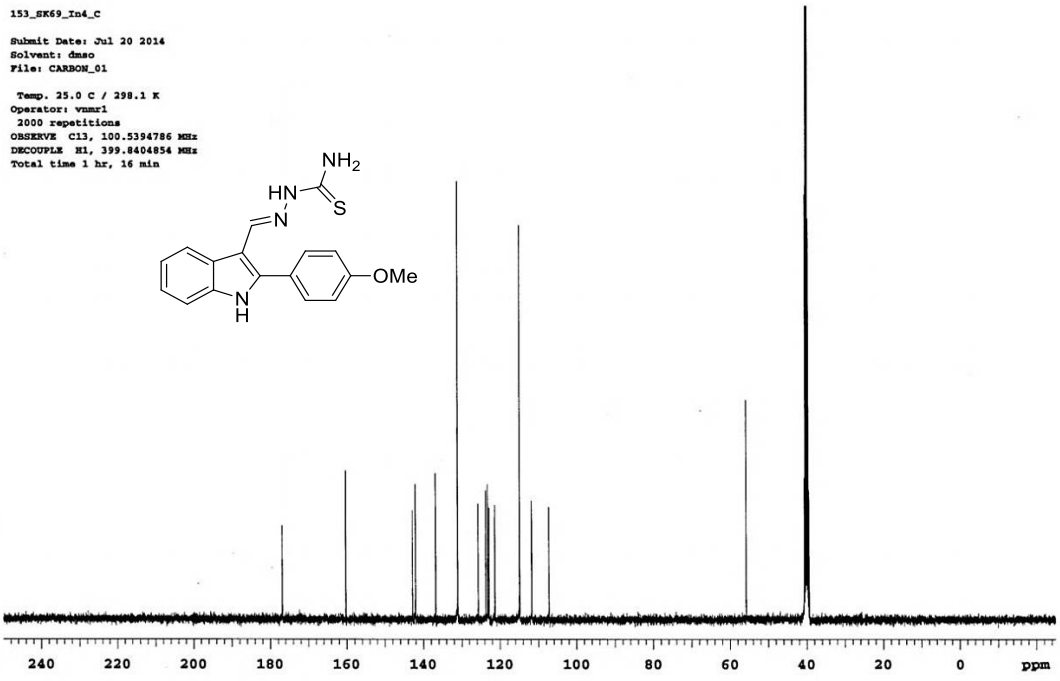


**Figure C8** $^{13}$C-NMR spectrum of 2-(4-methoxy phenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156d).

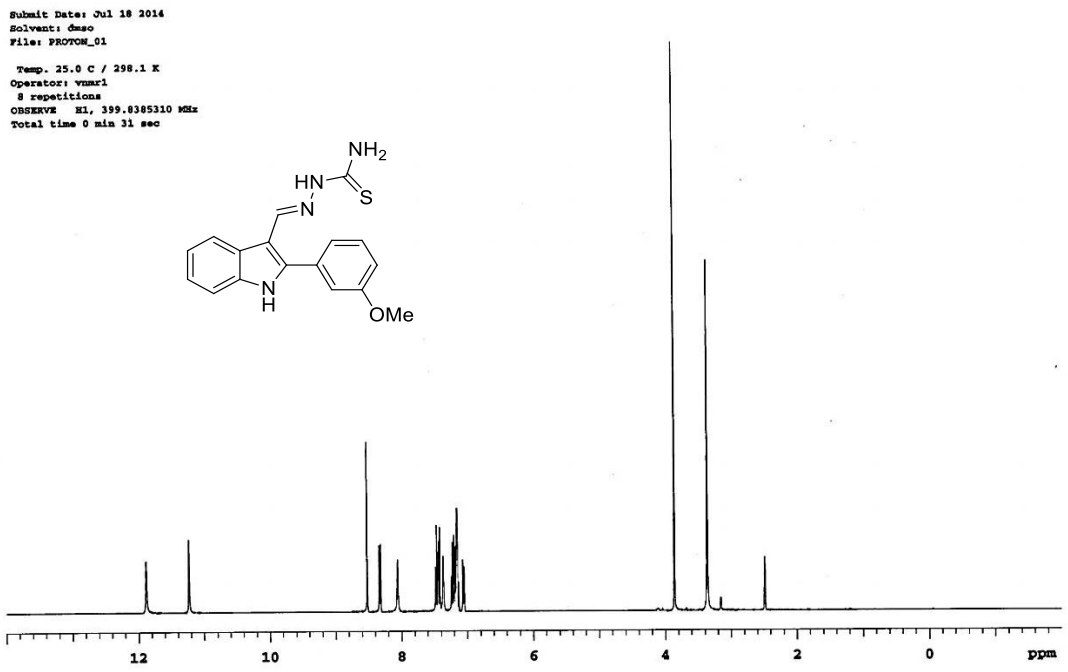


**Figure C9** $^{1}$H-NMR spectrum of 2-(3-methoxy phenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156e).

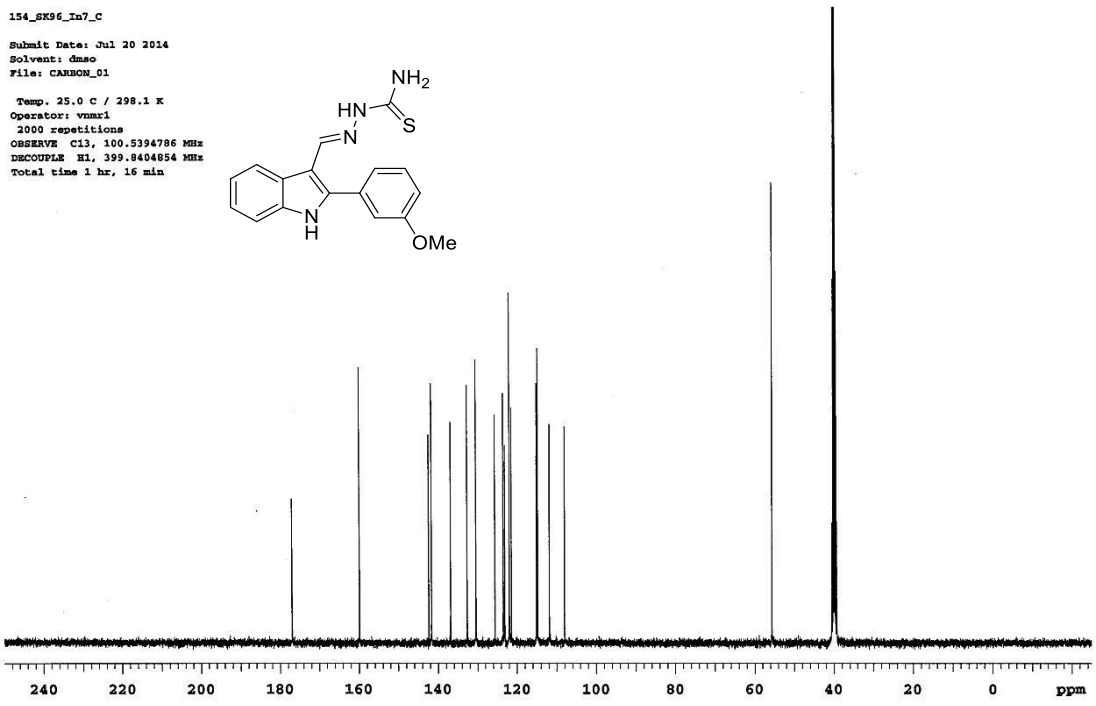


**Figure C10** $^{13}$C-NMR spectrum of 2-(3-methoxy phenyl)-1*H*-indole-3-carbaldehyde thiosemicarbazone (156e).

# Appendix D

# Spectral data of thiazolidinone derivatives

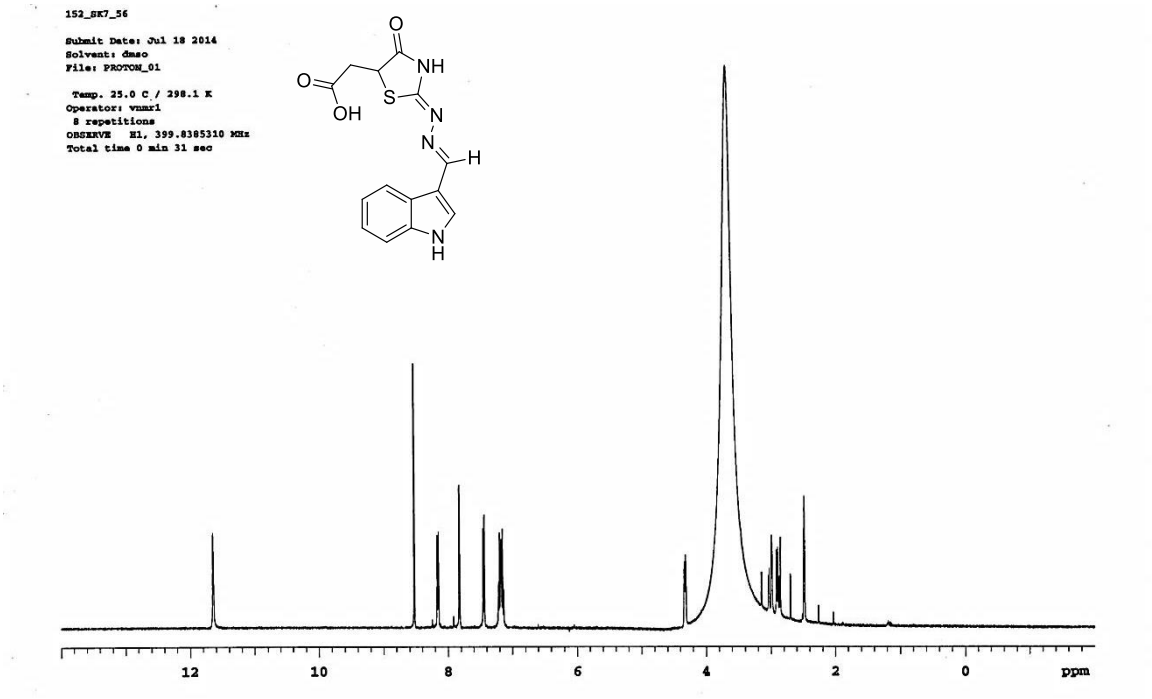


**Figure D1** $^{1}$H-NMR spectrum of 2-[[(indol-3-yl)methylene]hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158a).

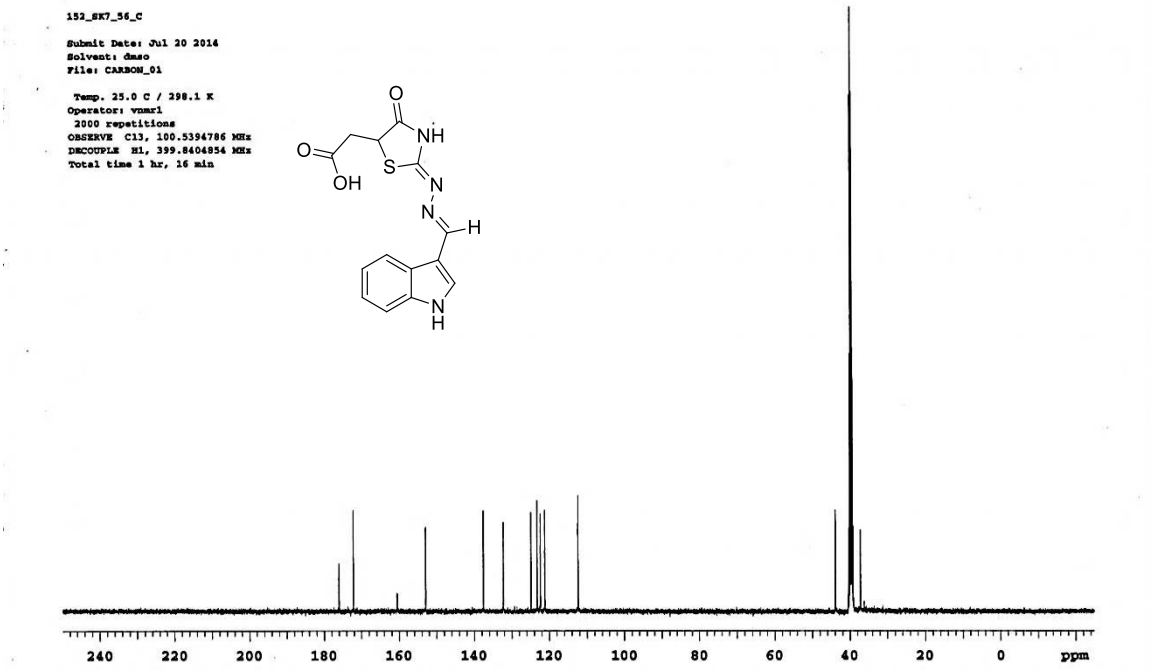


**Figure D2** $^{13}$C-NMR spectrum of 2-[[(indol-3-yl)methylene]hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158a).

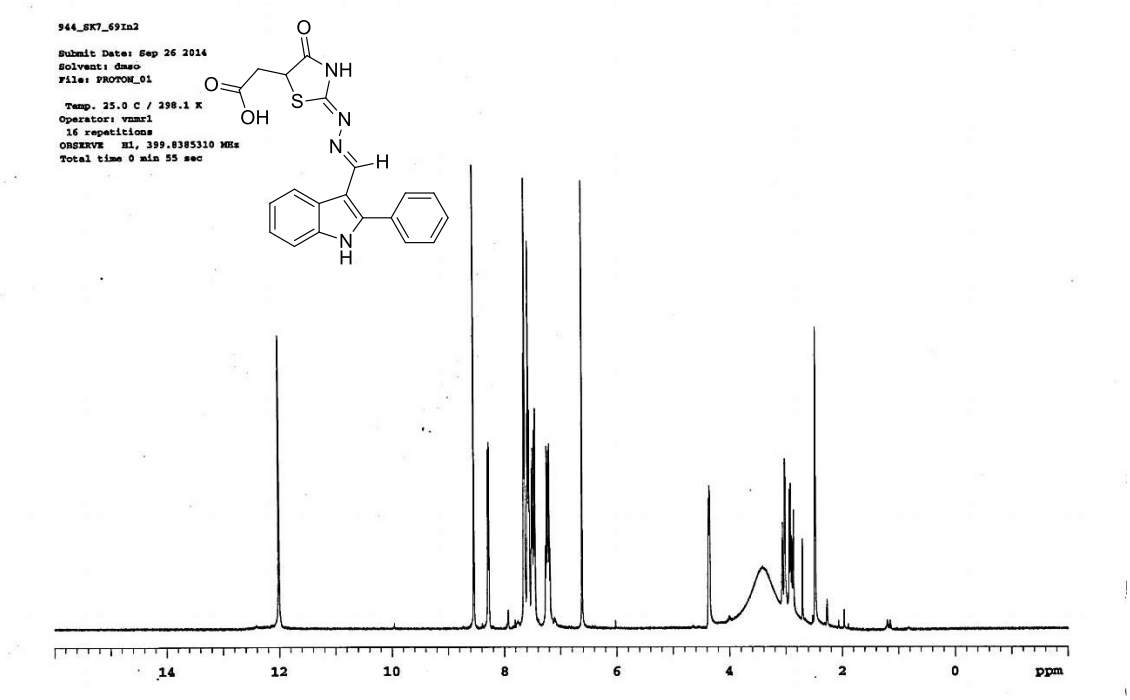


**Figure D3** $^{1}$H-NMR spectrum of 2-[[(2-phenyl indol-3-yl)methylene]hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158b).

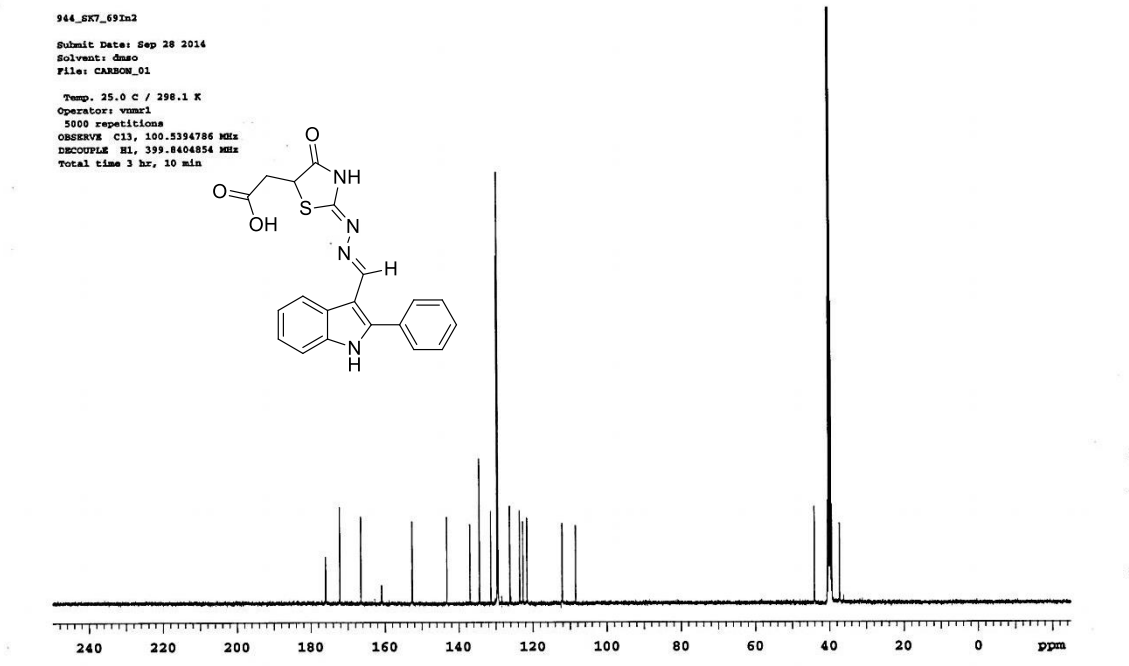


**Figure D4** $^{13}$C-NMR spectrum of 2-[[(2-phenyl indol-3-yl)methylene]hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158b).

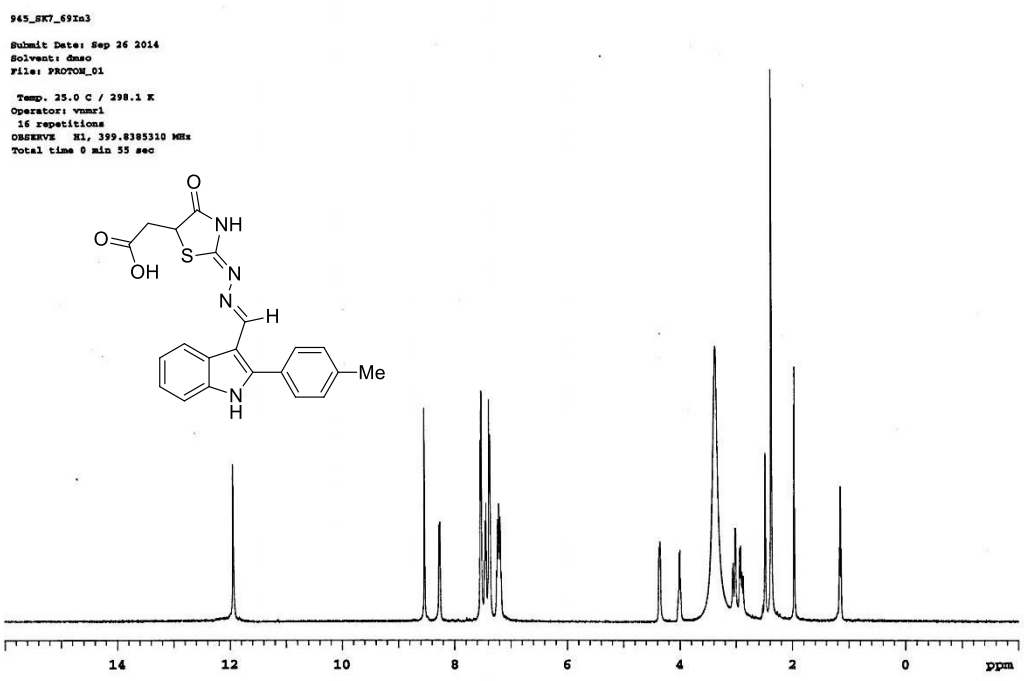


**Figure D5** $^{1}$H-NMR spectrum of 2-[[(2-(4-methyl)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158c).

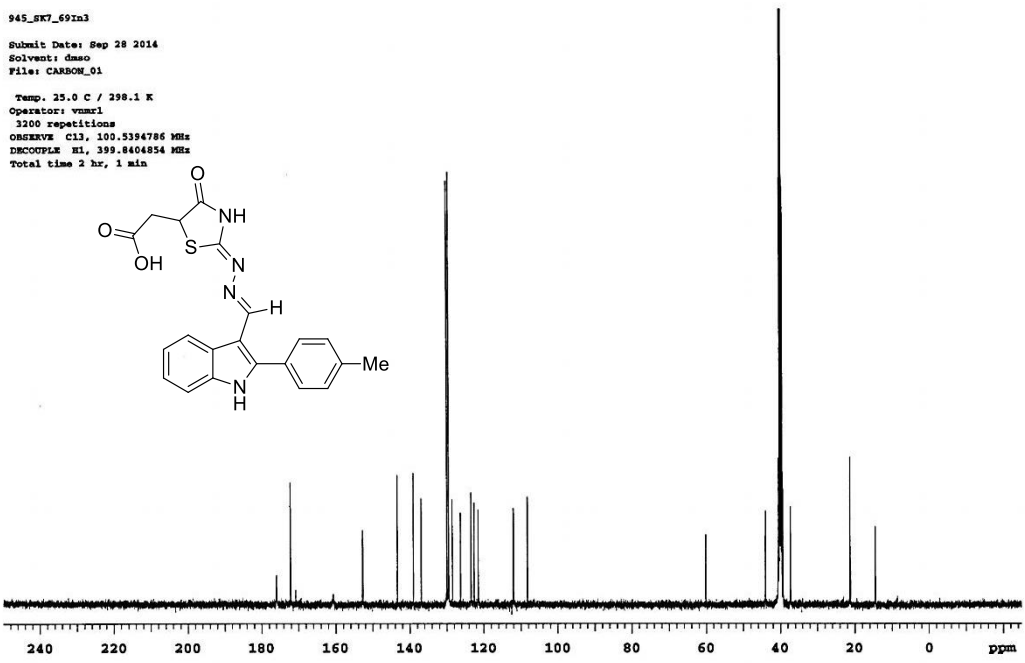


**Figure D6** $^{13}$C-NMR spectrum of 2-[[(2-(4-methyl)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158c).

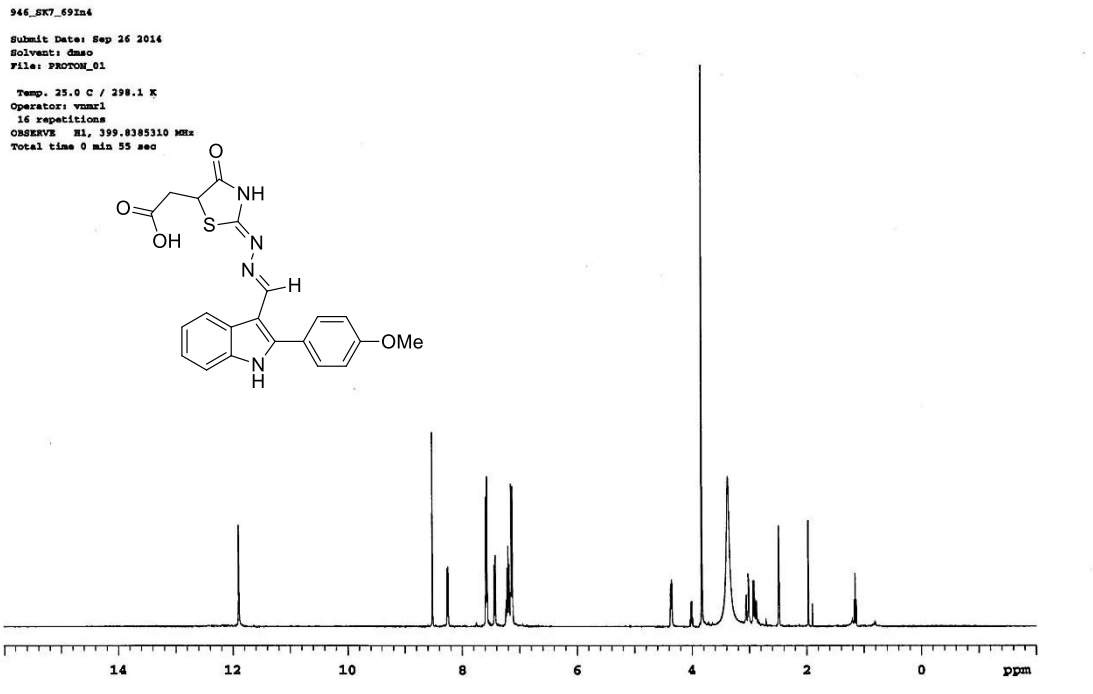


**Figure D7** $^{1}$H-NMR spectrum of 2-[[(2-(4-methoxy)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158d).

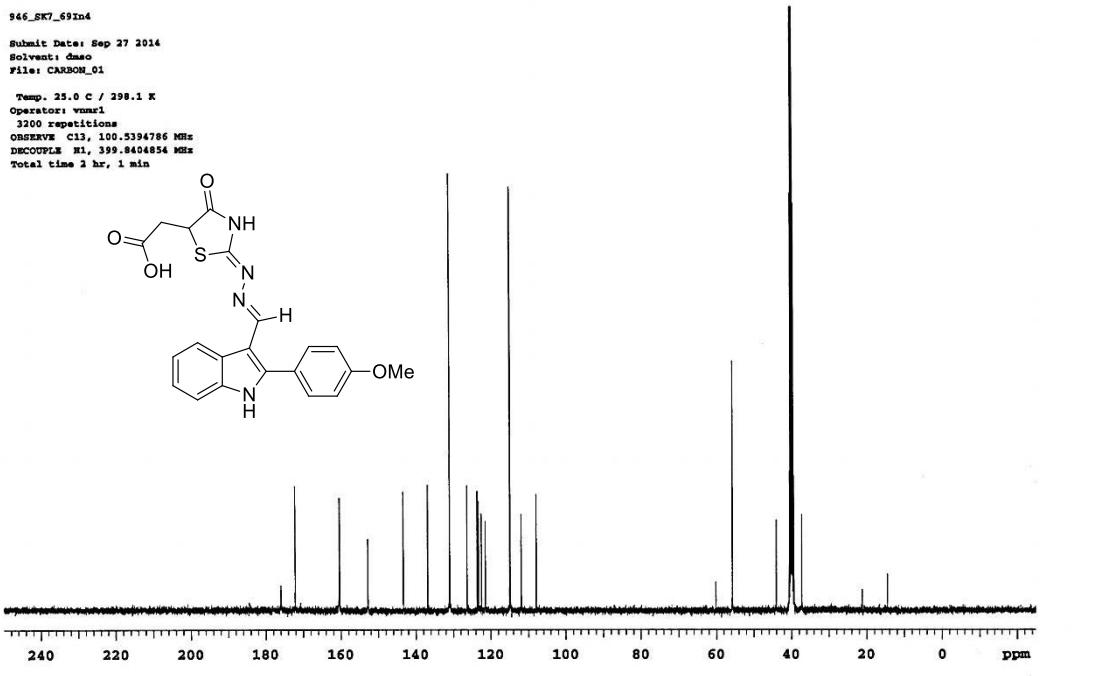


**Figure D8** $^{13}$C-NMR spectrum of 2-[[(2-(4-methoxy)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158d).

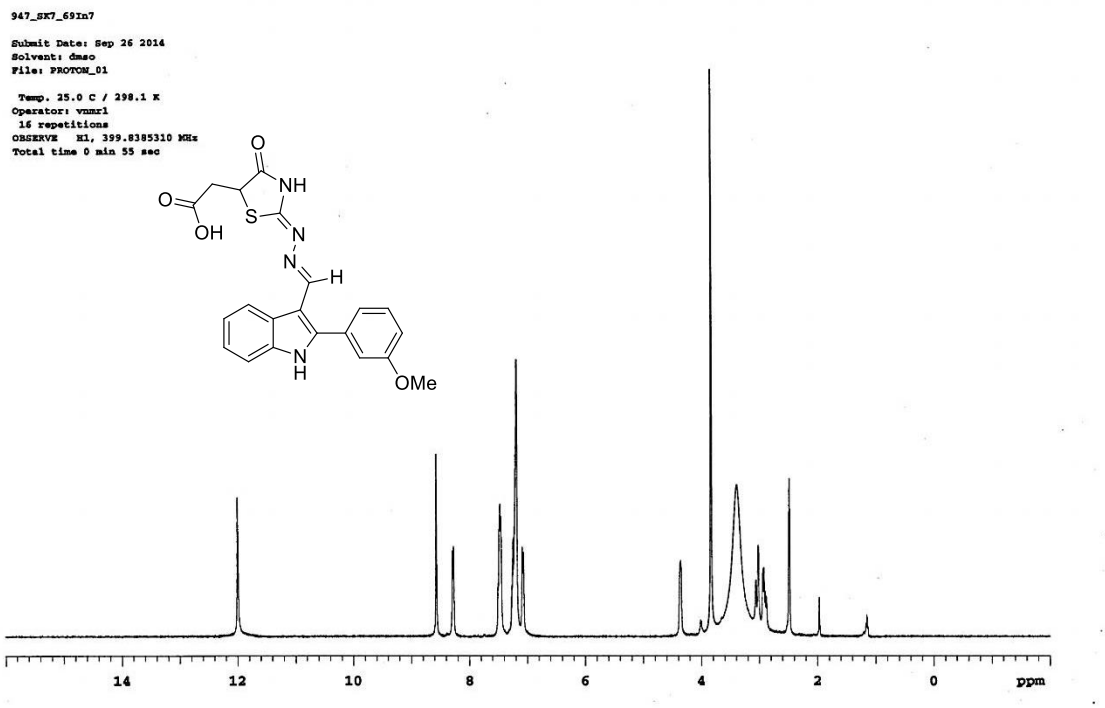


**Figure D9** $^{1}$H-NMR spectrum of 2-[[(2-(3-methoxy)phenyl)indol-3-yl) methylene] hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158e).

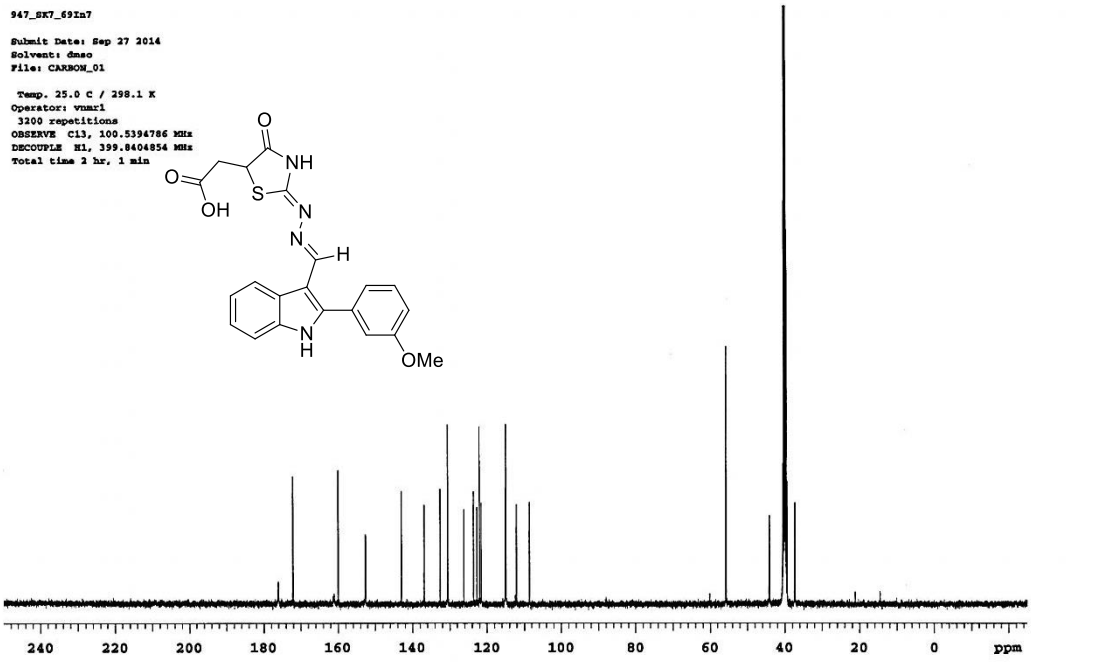


**Figure D10** $^{13}$C-NMR spectrum of 2-[[(2-(3-methoxy)phenyl indol-3-yl)methylene] hydrazono]-4-oxo-3*H*-5-thiazolidineacetic acid (158e).

# Appendix E

## Spectral data of imidazole derivatives

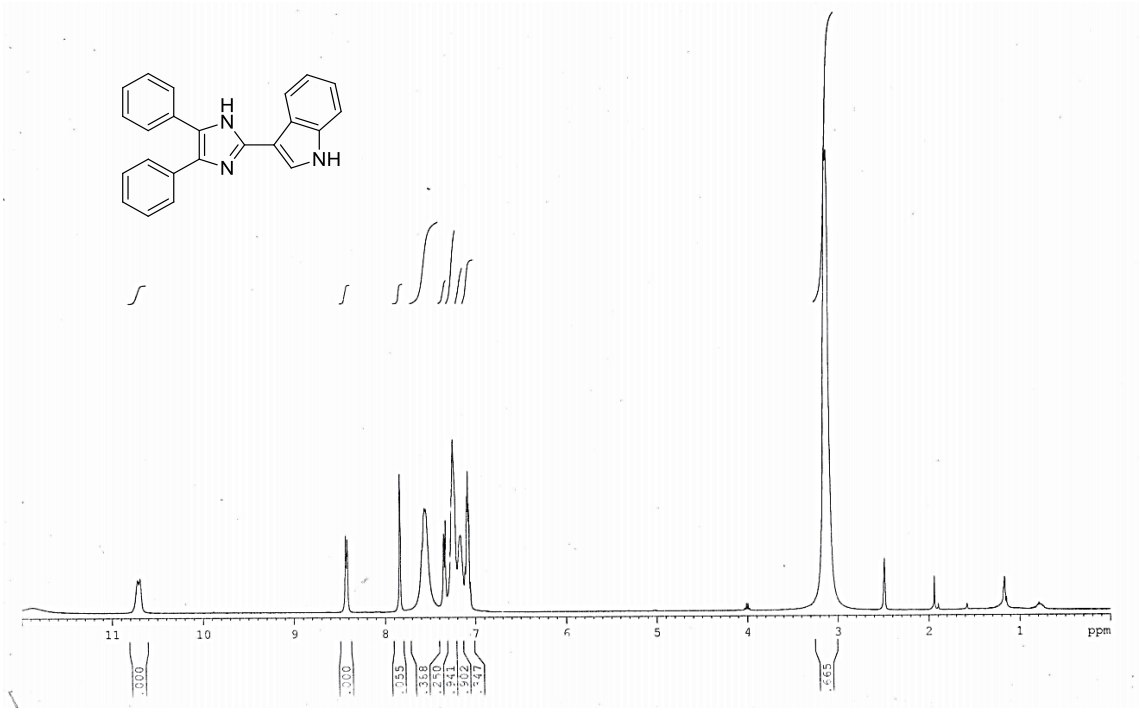


**Figure E1** $^{1}$H-NMR spectrum of 2-(indol-3-yl)-4,5-diphenyl imidazole (164a).

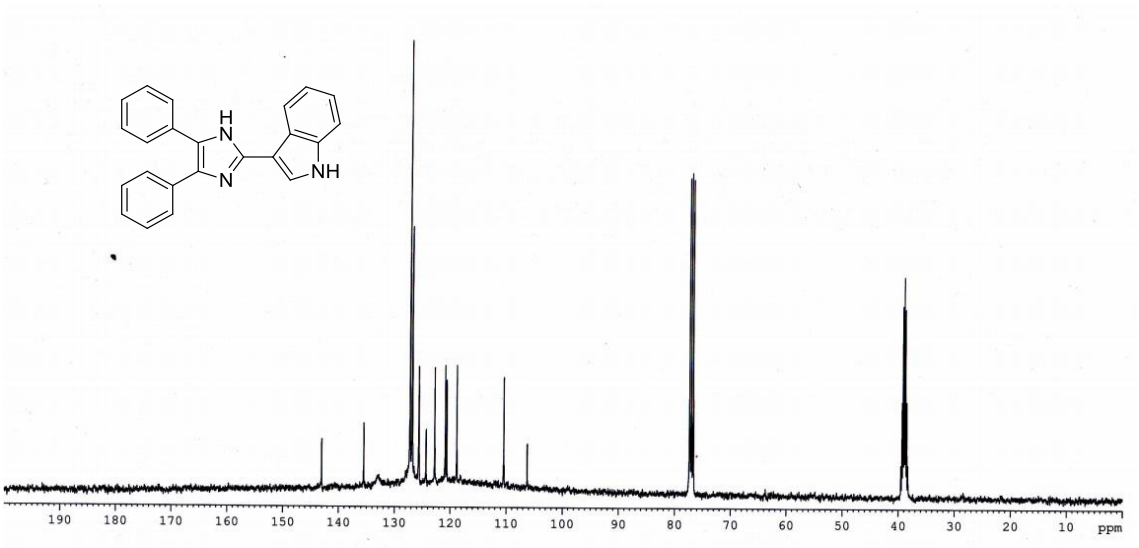


**Figure E2** $^{13}$C-NMR spectrum of 2-(indol-3-yl)-4,5-diphenyl imidazole (164a).

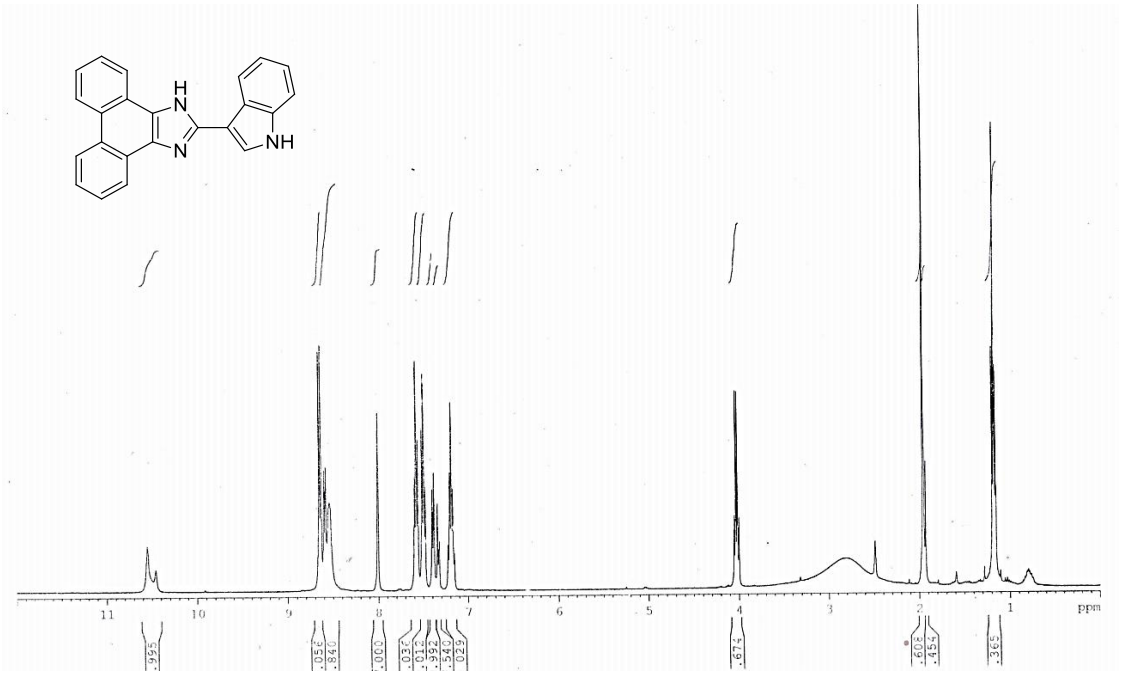


**Figure E3** $^{1}$H-NMR spectrum of 2-(indol-3-yl) imidazo[4,5-*d*] phenanthrene (164b).

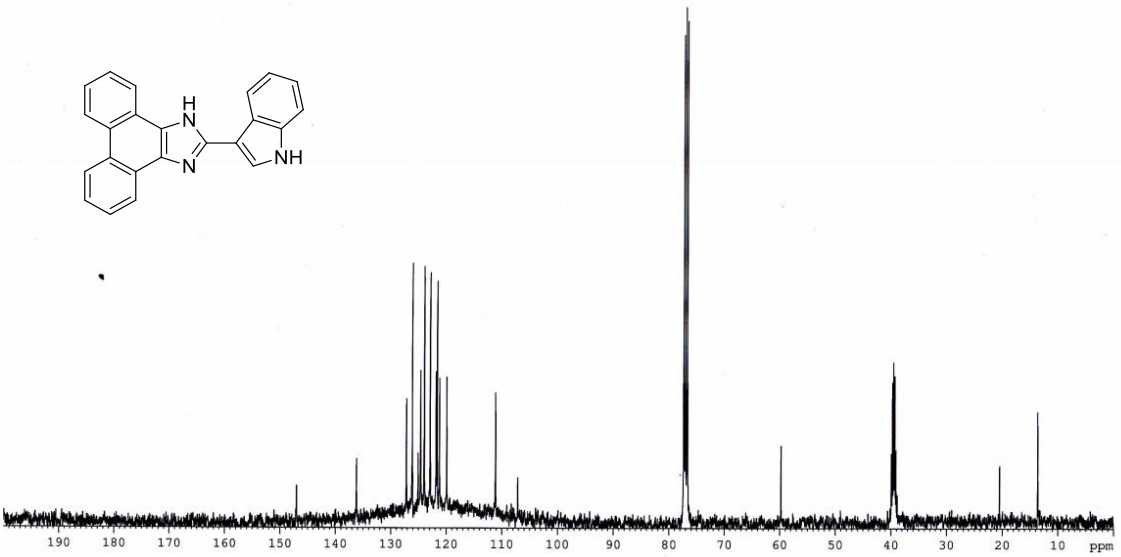


**Figure E4** $^{13}$C-NMR spectrum of 2-(indol-3-yl) imidazo[4,5-*d*] phenanthrene (164b).

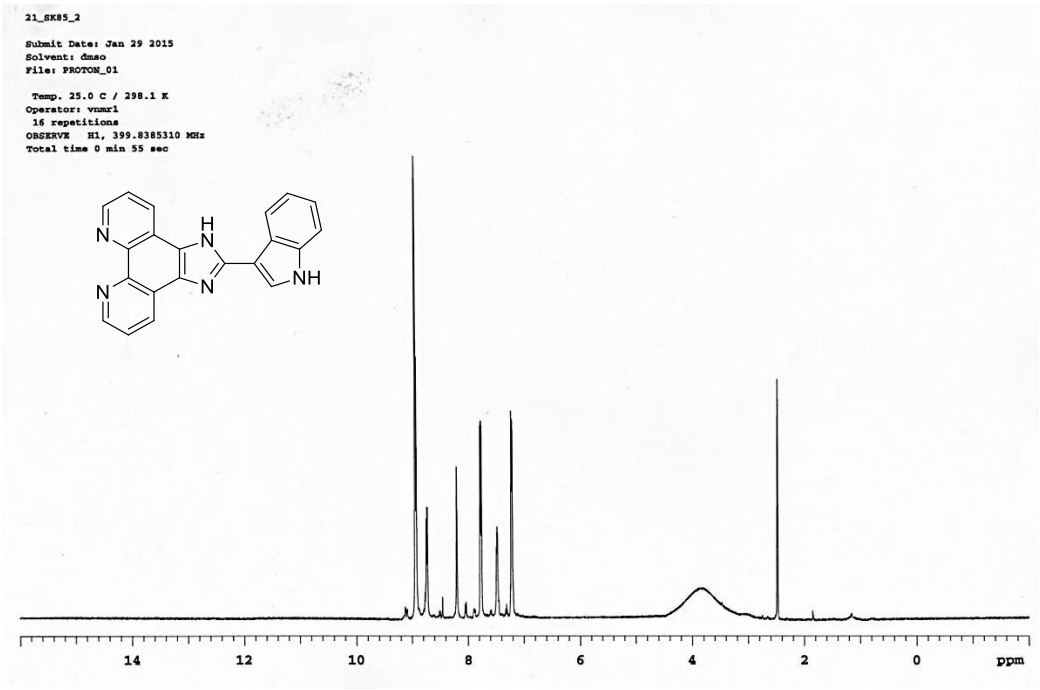


**Figure E5** $^{1}$H-NMR spectrum of 2-(indol-3-yl) imidazo[4,5-*d*]phenanthroline (165a).

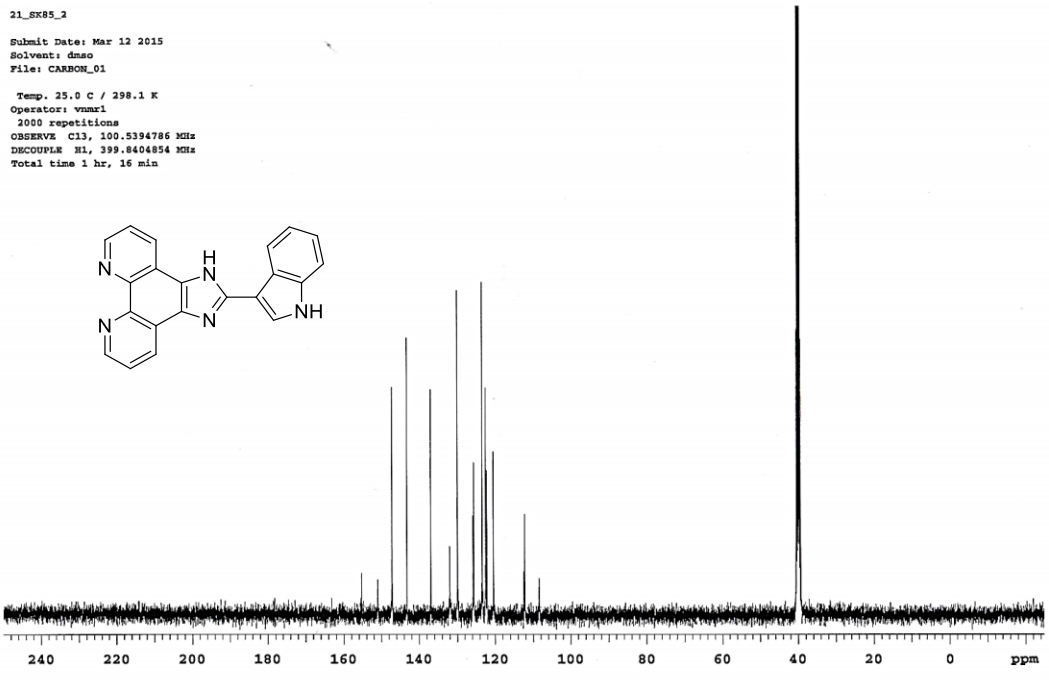


**Figure E6** $^{13}$C-NMR spectrum of 2-(indol-3-yl) imidazo[4,5-*d*]phenanthroline (165a).

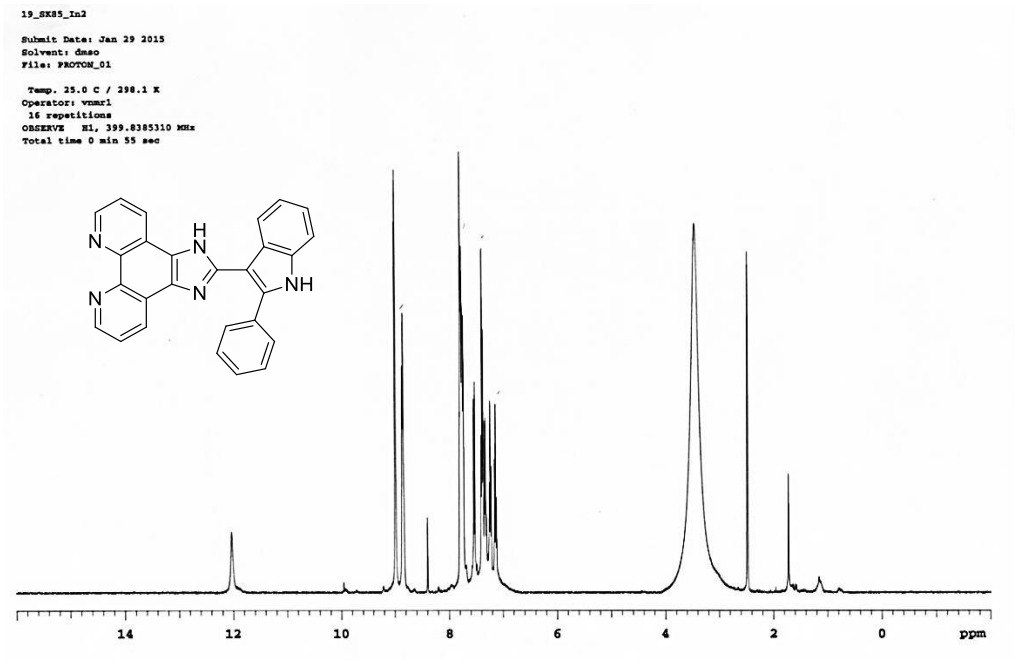


**Figure E7** $^{1}$H-NMR spectrum of 2-(2-phenylindol-3-yl) imidazo[4,5-*d*]phenanthroline (165b).

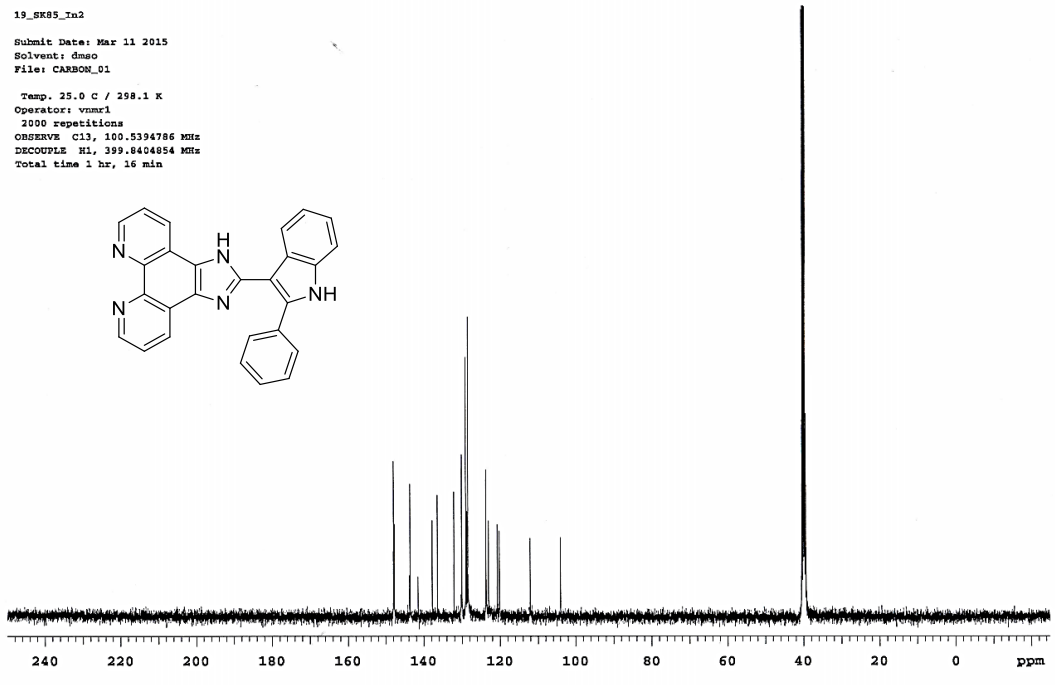


**Figure E8** $^{13}$C-NMR spectrum of 2-(2-phenyl indol-3-yl)imidazo[4,5-*d*]phenanthroline (165b).

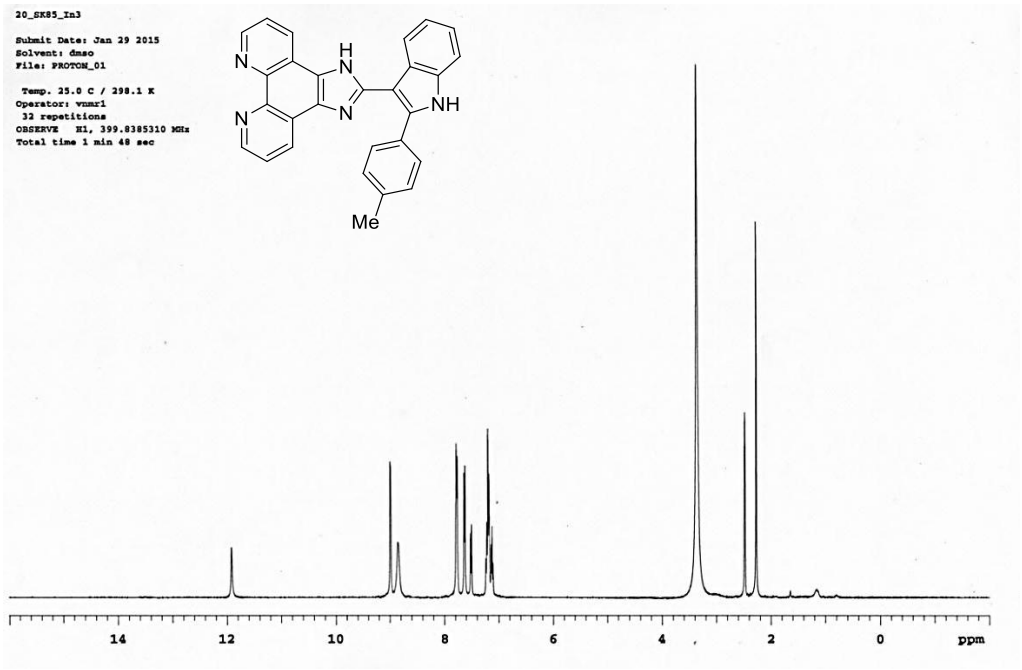


**Figure E9** $^{1}$H-NMR spectrum of 2-(2-(4-methyl phenyl)-indol-3-yl) imidazo[4,5-*d*] phenanthroline (165c).

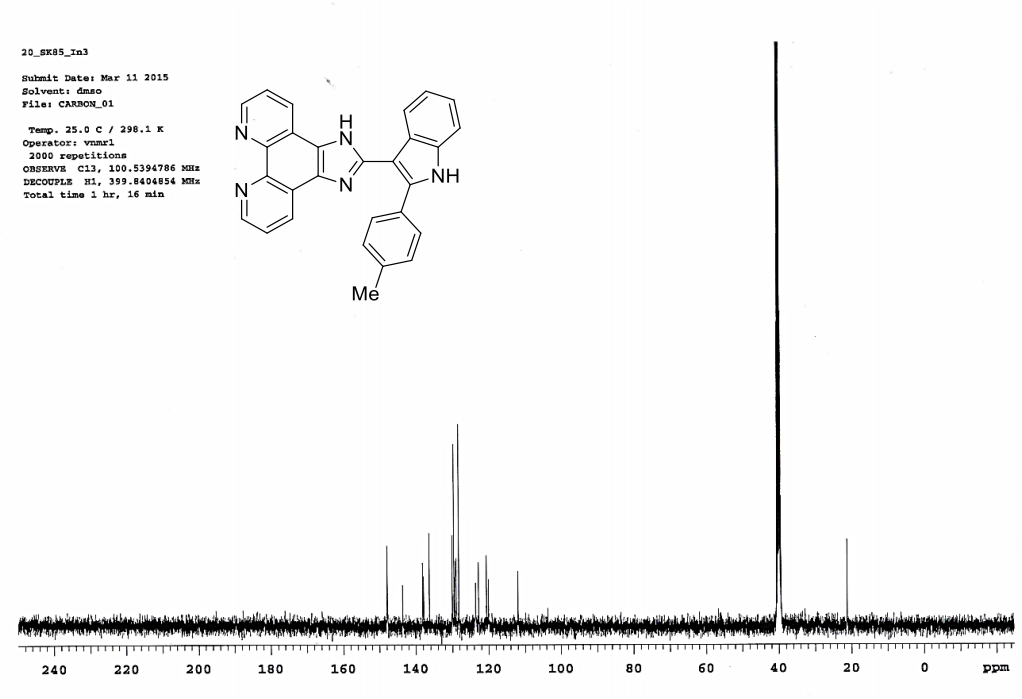


**Figure E10** $^{13}$C-NMR spectrum of 2-(2-(4-methyl phenyl)-indol-3-yl) imidazo[4,5-*d*] phenanthroline (165c).

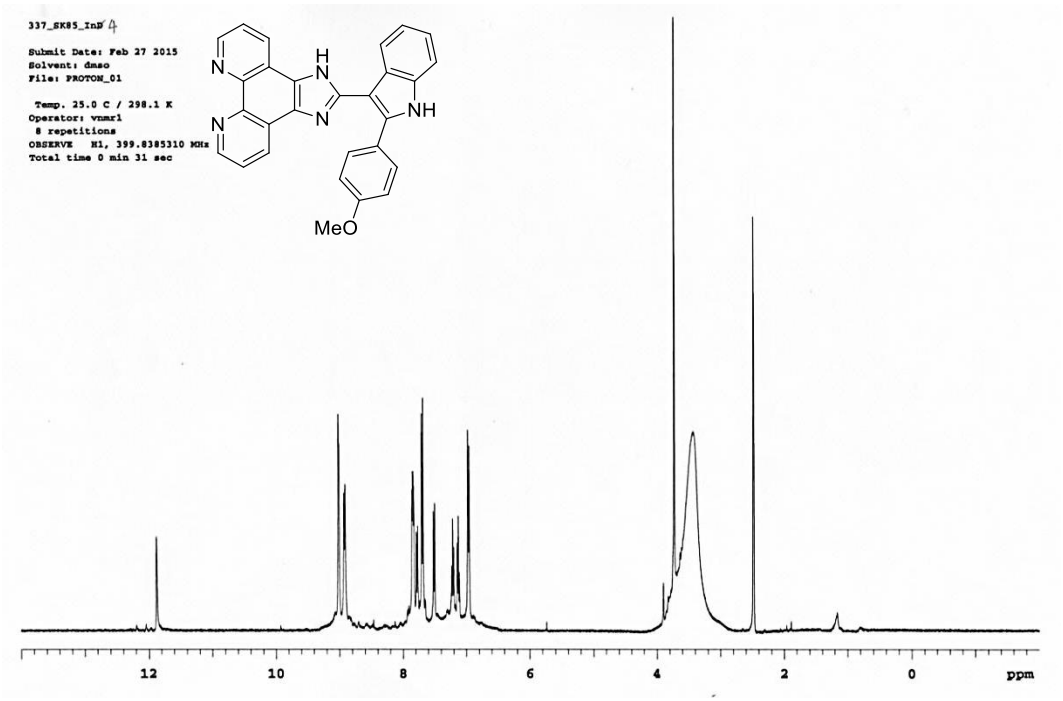


**Figure E11** $^{1}$H-NMR spectrum of 2-(2-(4-methoxy phenyl)-indolyl) imidazo[4,5-*d*] phenanthroline (165d).

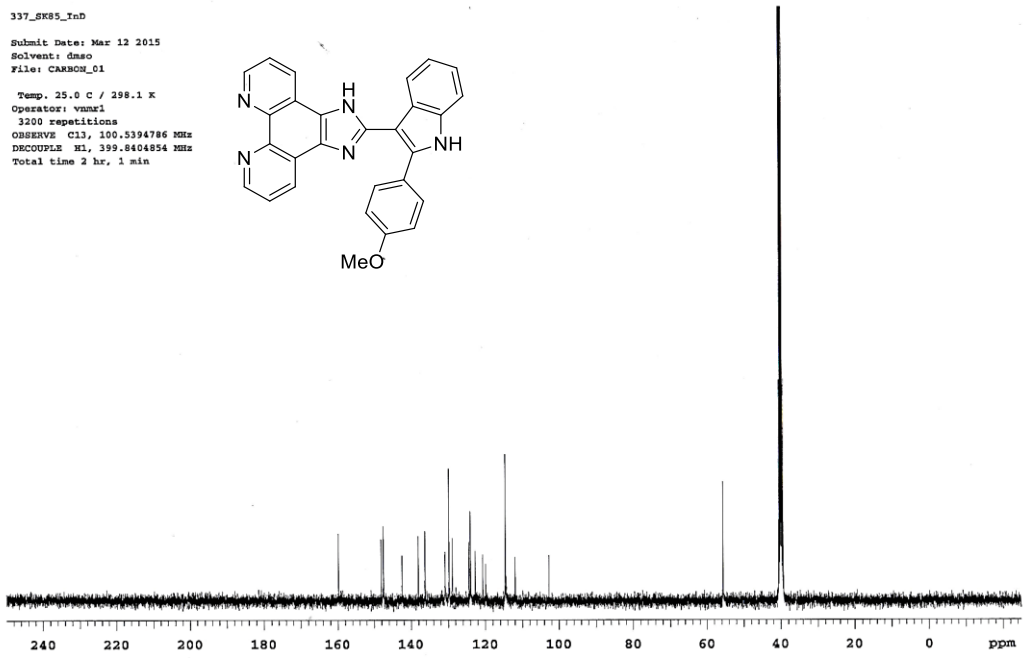


**Figure E12** $^{13}$C-NMR spectrum of 2-(2-(4-methoxy phenyl)-indol-3-yl) imidazo[4,5-*d*] phenanthroline (165d).

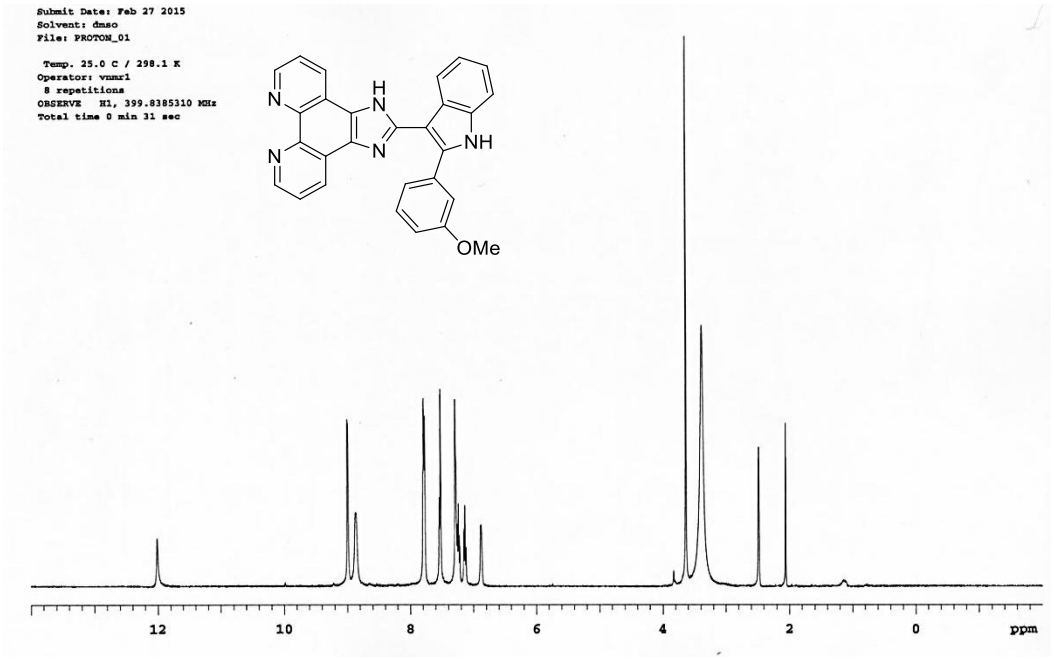


**Figure E13** $^{1}$H-NMR spectrum of 2-(2-(3-methoxy phenyl)-indol-3-yl) imidazo[4,5-*d*]phenanthroline (165e).

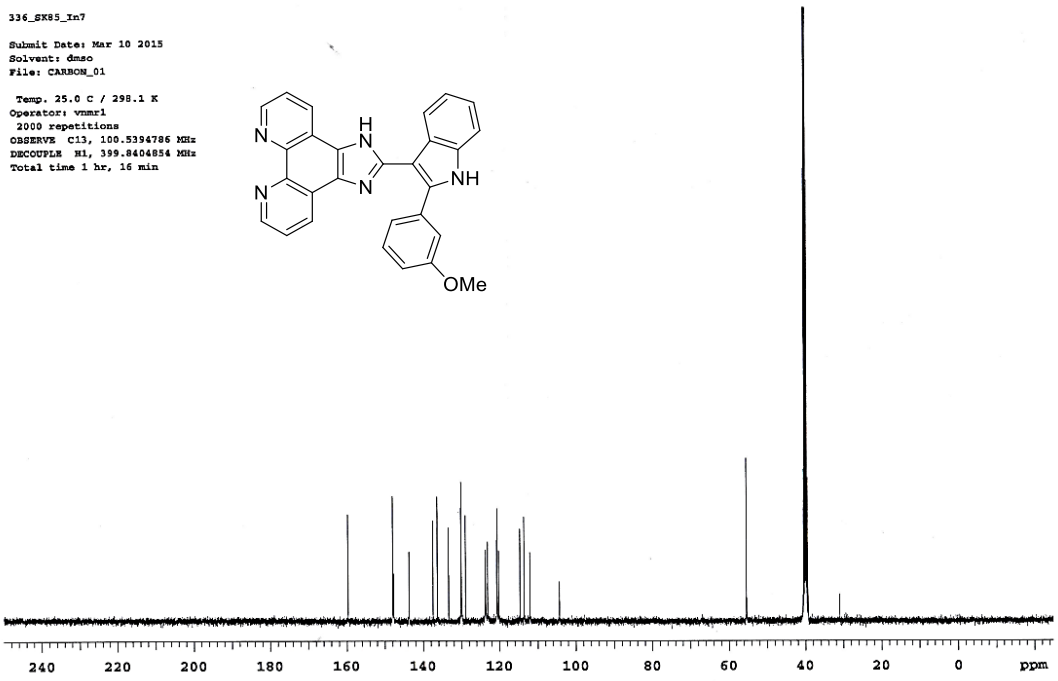


**Figure E14** $^{13}$C-NMR spectrum of 2-(2-(3-methoxy phenyl)-indol-3-yl) imidazo[4,5-*d*]phenanthroline (165e).

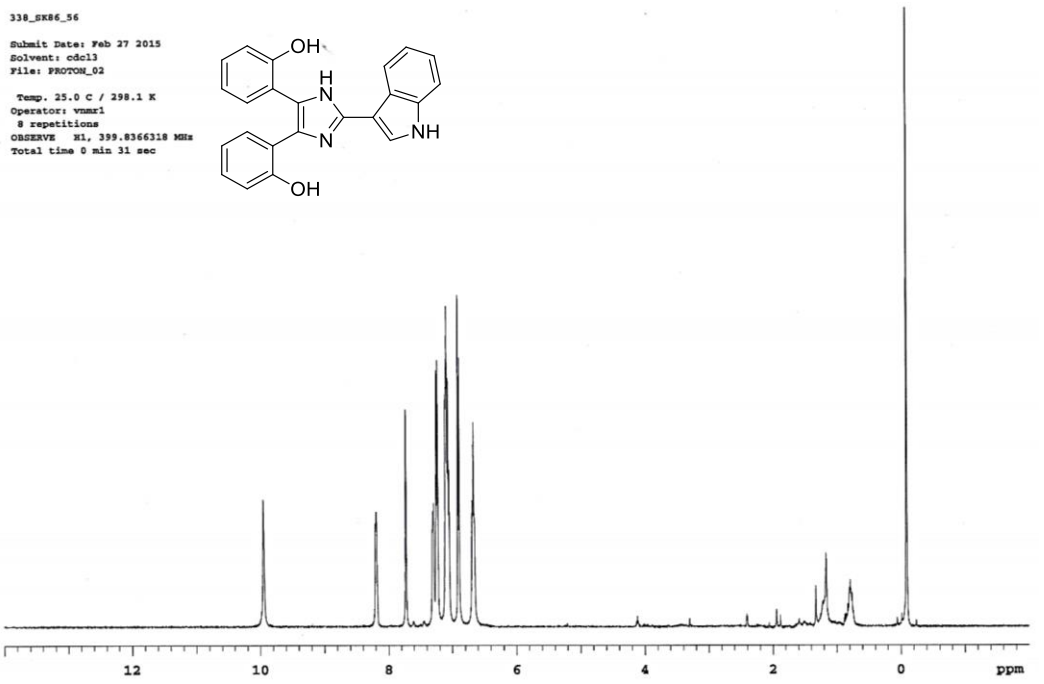


**Figure E15** $^{1}$H-NMR spectrum of 2-(indol-3-yl)-4,5-di(2-hydroxyphenyl)-1*H*-imidazole (166a).

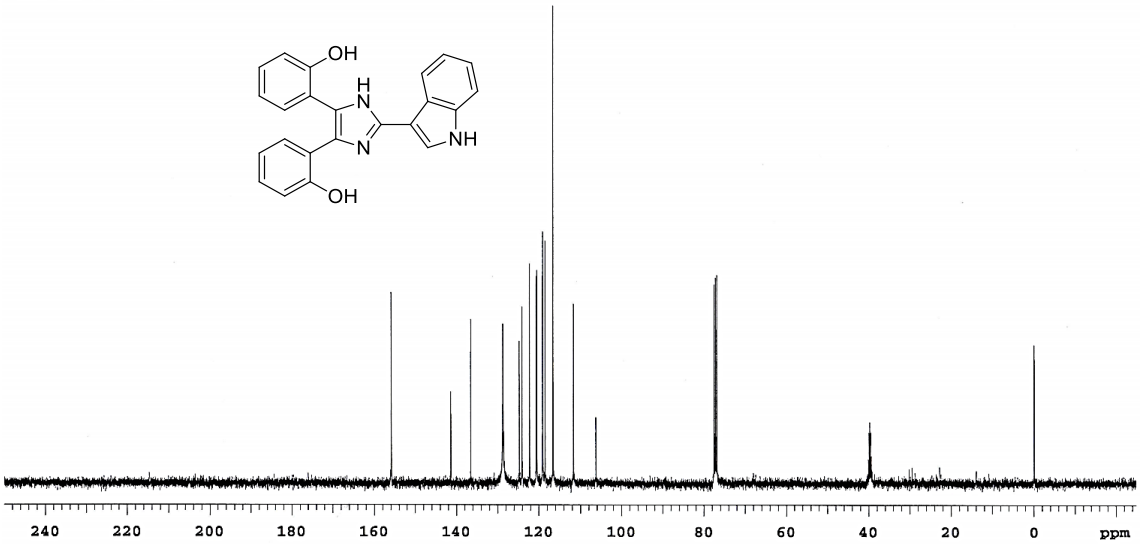


**Figure E16** $^{13}$C-NMR spectrum of 2-(indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166a).

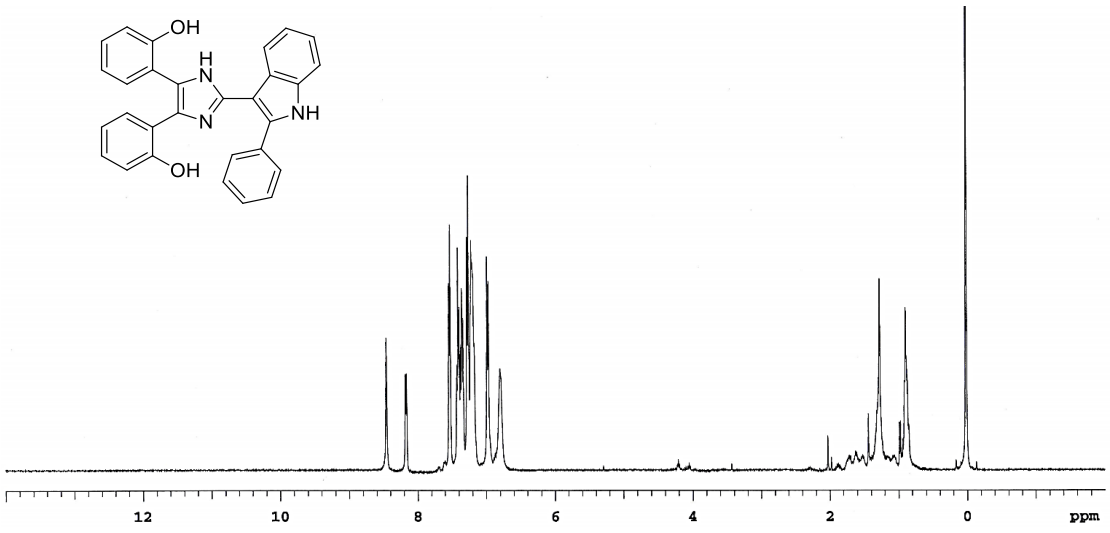


**Figure E17** $^{1}$H-NMR spectrum of 2-(2-phenyl indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166b).

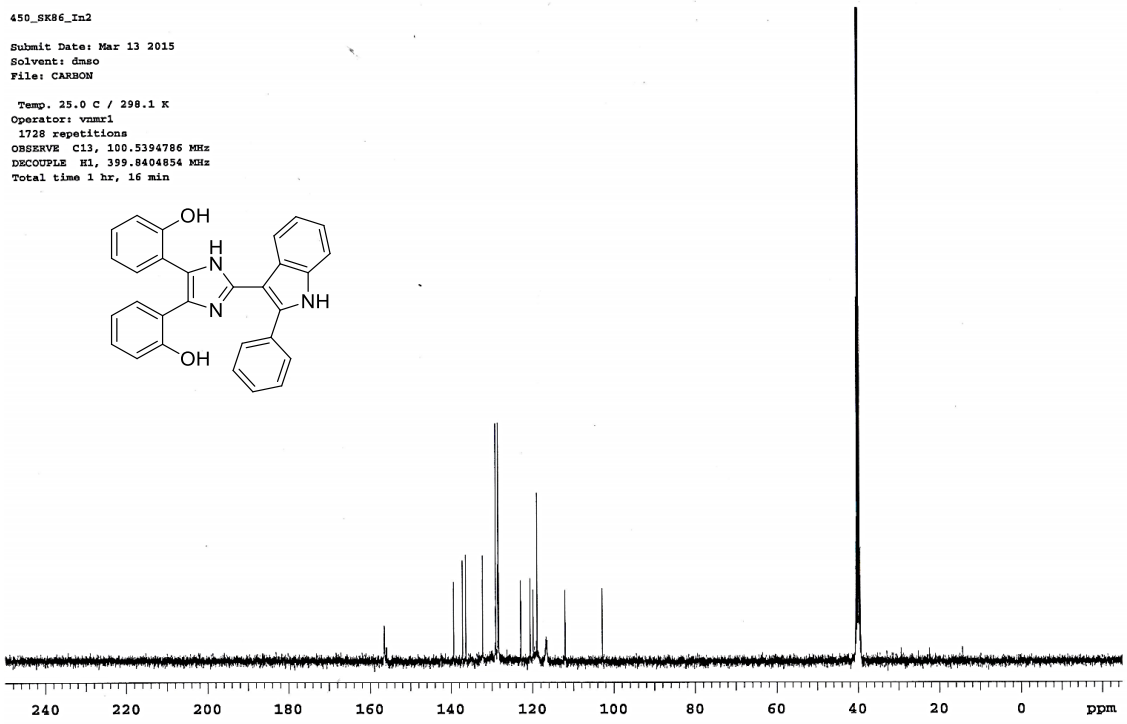


**Figure E18** $^{13}$C-NMR spectrum of 2-(2-phenyl indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166b).

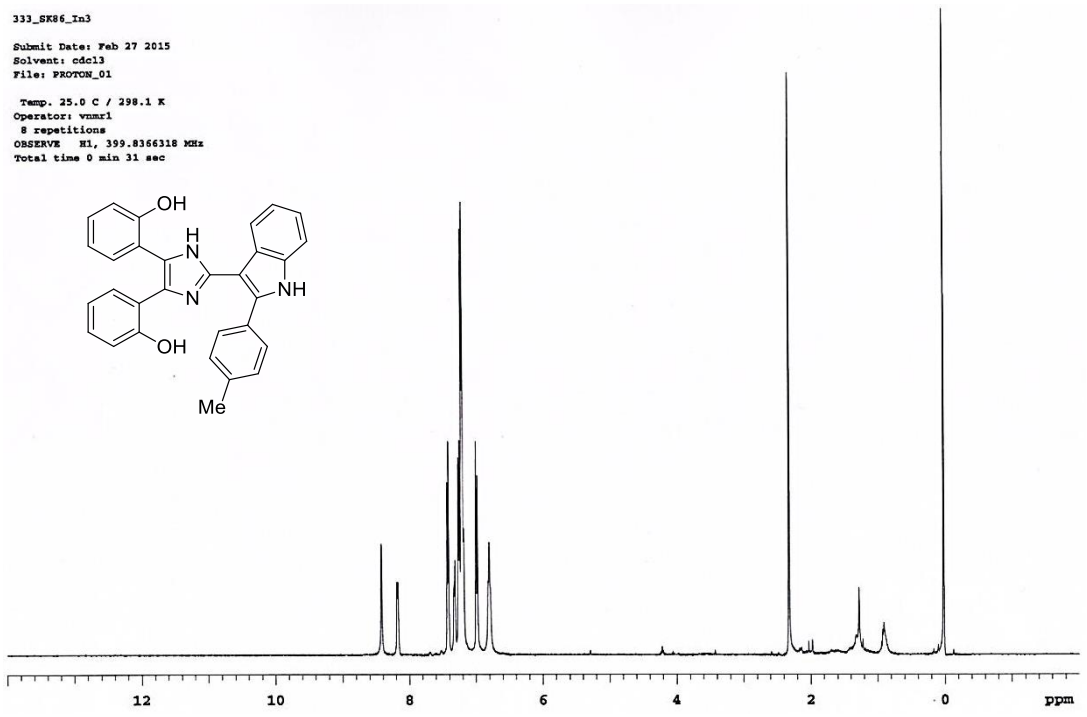


**Figure E19** $^{1}$H-NMR spectrum of 2-(2-(4-methyl phenyl) indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166c).

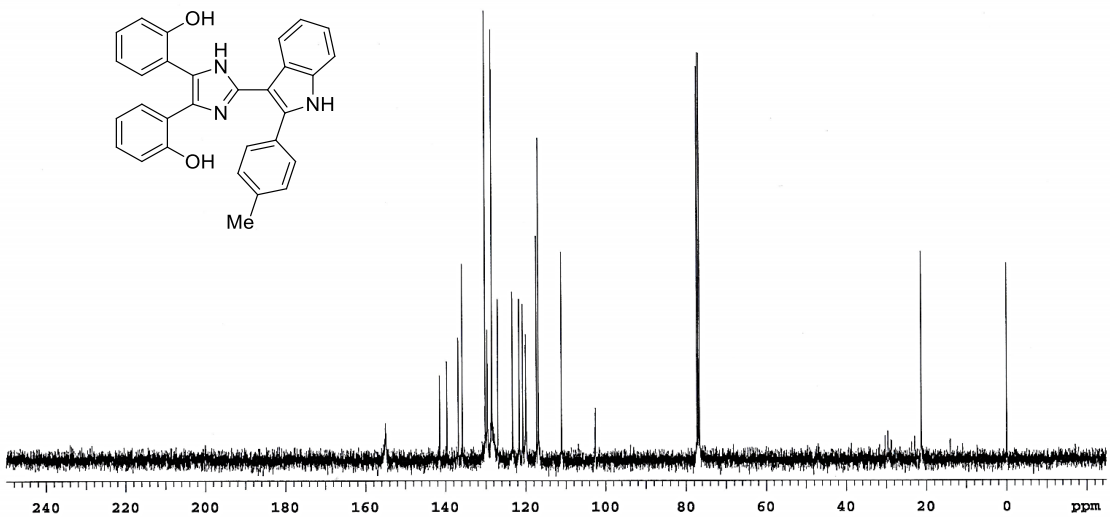


**Figure E20** $^{13}$C-NMR spectrum of 2-(2-(4-methyl phenyl) indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166c).

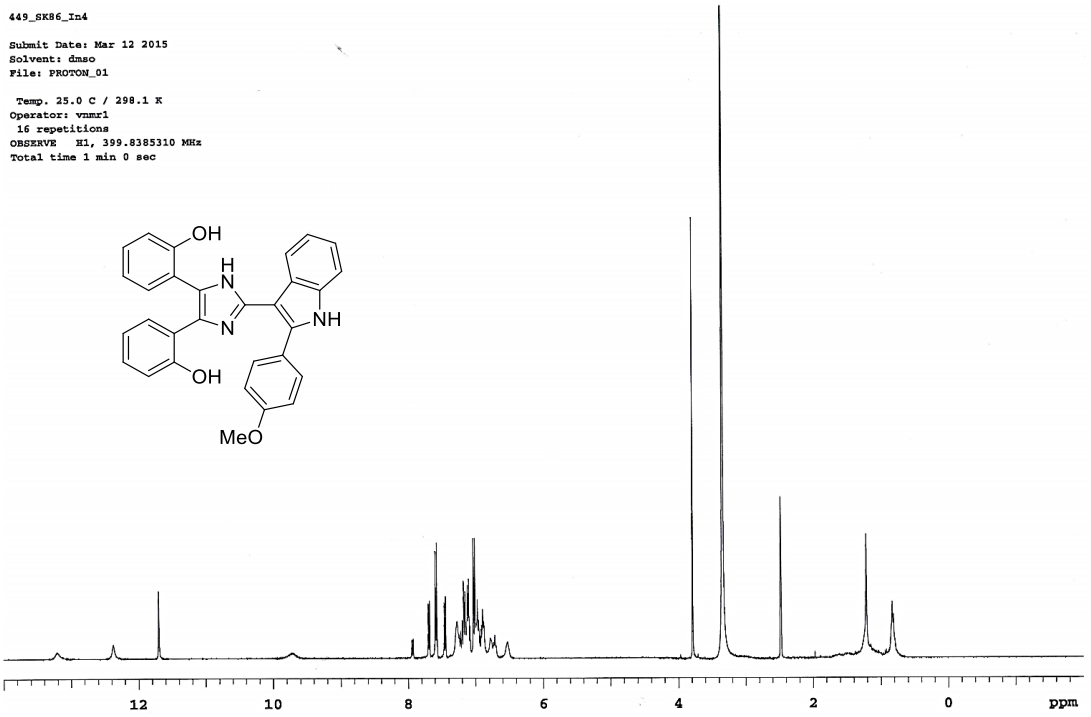


**Figure E21** $^{1}$H-NMR spectrum of 2-(2-(4-methoxy phenyl) indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166d).

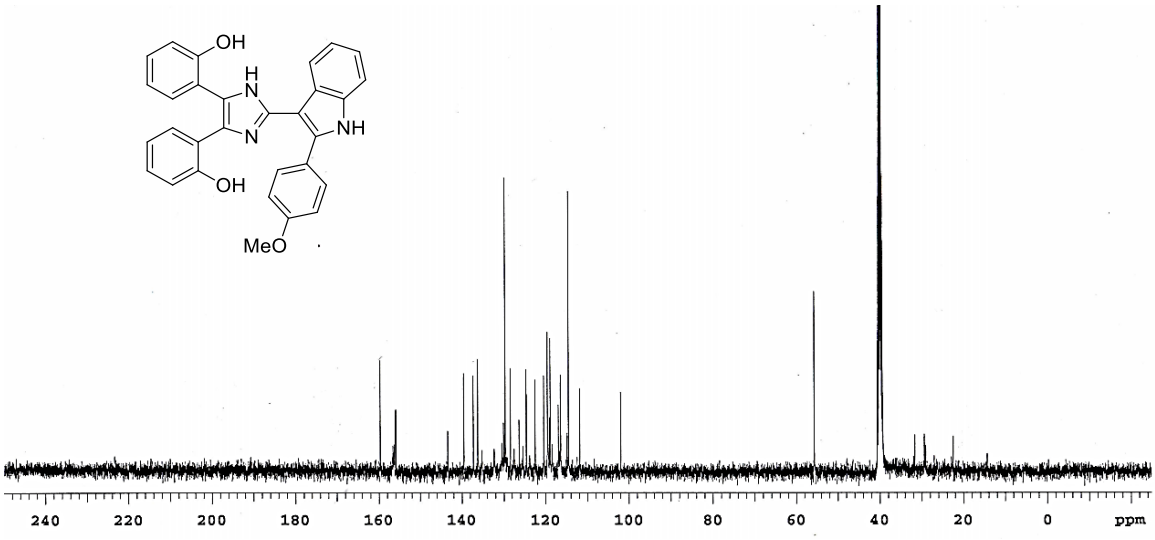


**Figure E22** $^{13}$C-NMR spectrum of 2-(2-(4-methoxy phenyl) indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166d).

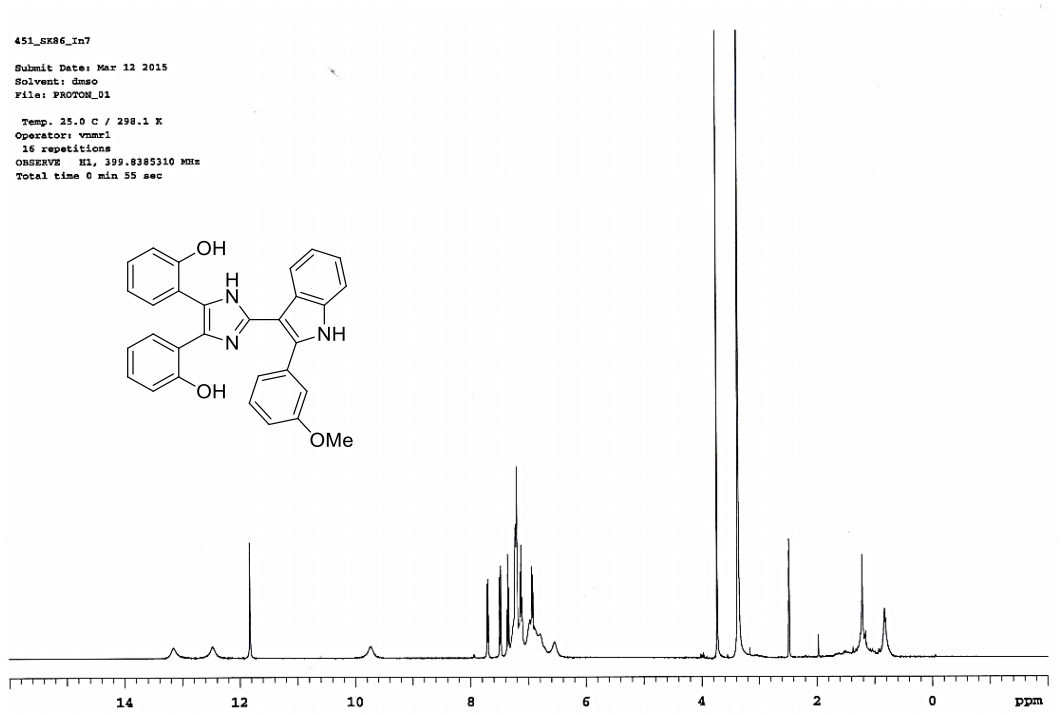


**Figure E23** $^{1}$H-NMR spectrum of 2-(2-(3-methoxy phenyl) indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166e).

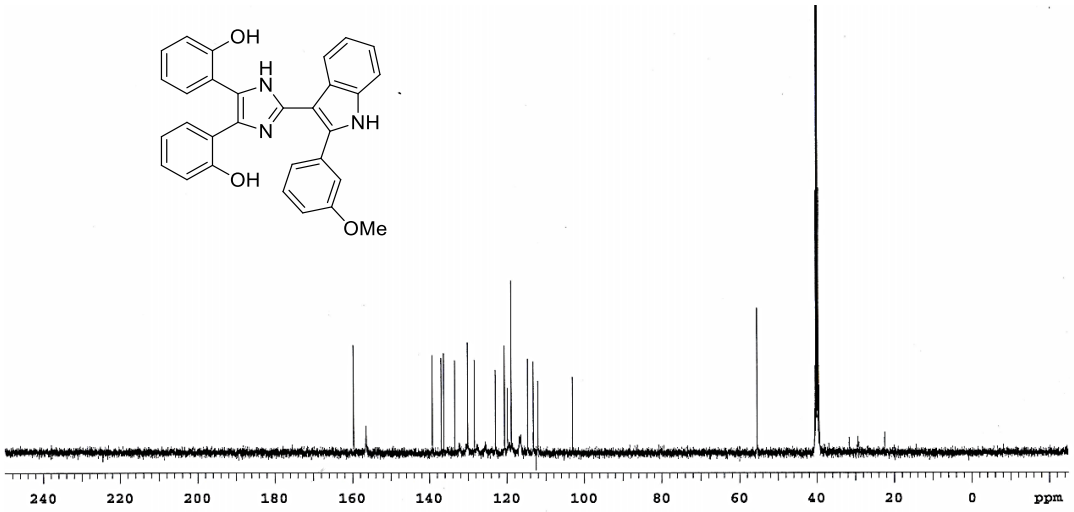


**Figure E24** $^{13}$C-NMR spectrum of 2-(2-(3-methoxy phenyl) indol-3-yl)-4,5-di(2-hydroxy phenyl)-1*H*-imidazole (166e).

# Appendix F

## Spectral data of 1,10-phenanthroline-5,6-dione 2,2´-dihydroxy benzoin, and 2,2´-dihydroxy benzil

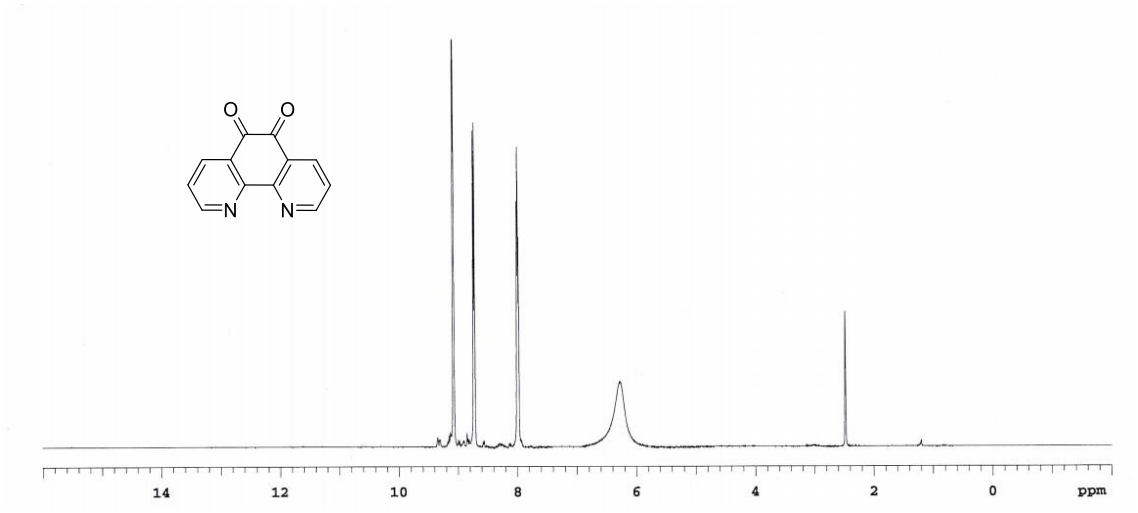


**Figure F1** $^{1}$H-NMR spectrum of 1,10-phenanthroline-5,6-dione (160).

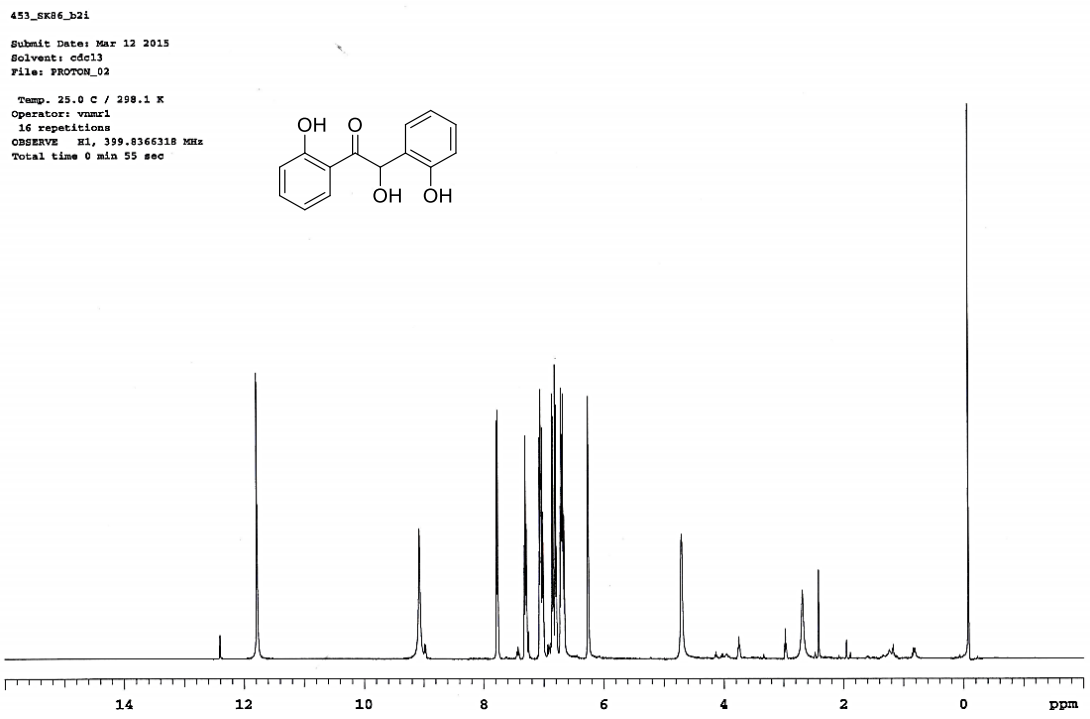


**Figure F2** $^{1}$H-NMR spectrum of 2,2′-dihydroxy benzoin (162a).

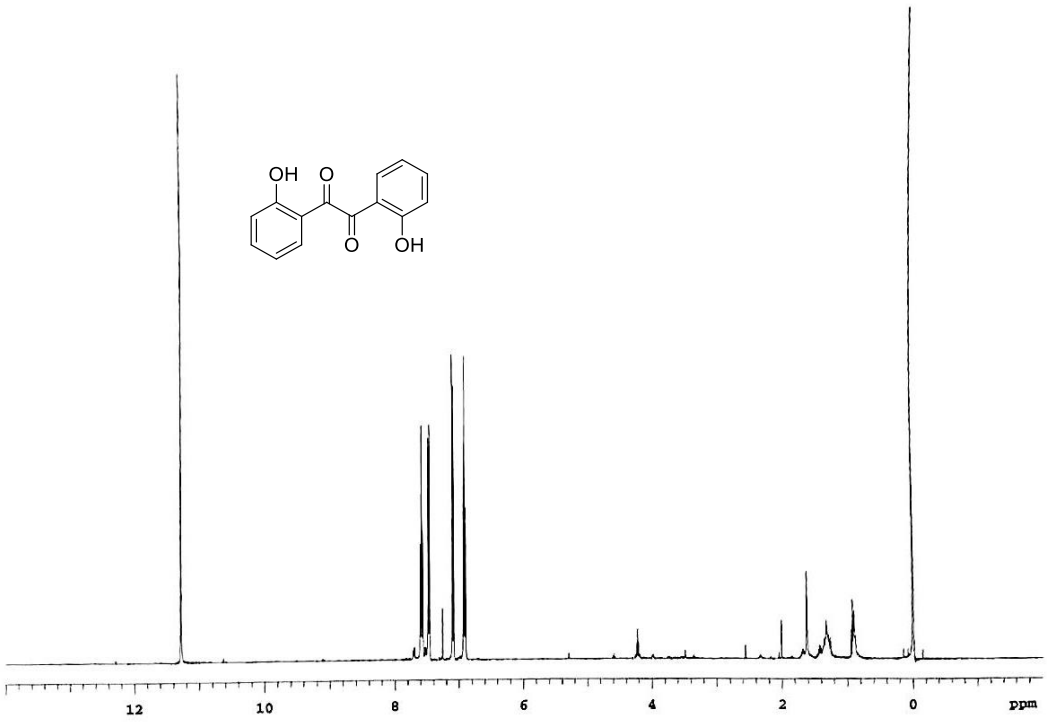


**Figure F3** $^{1}$H-NMR spectrum of 2,2′-dihydroxy benzil (162b).

# Appendix G

## Spectral data of 2-((1*H*-indol-3-yl)methylene)malononitrile

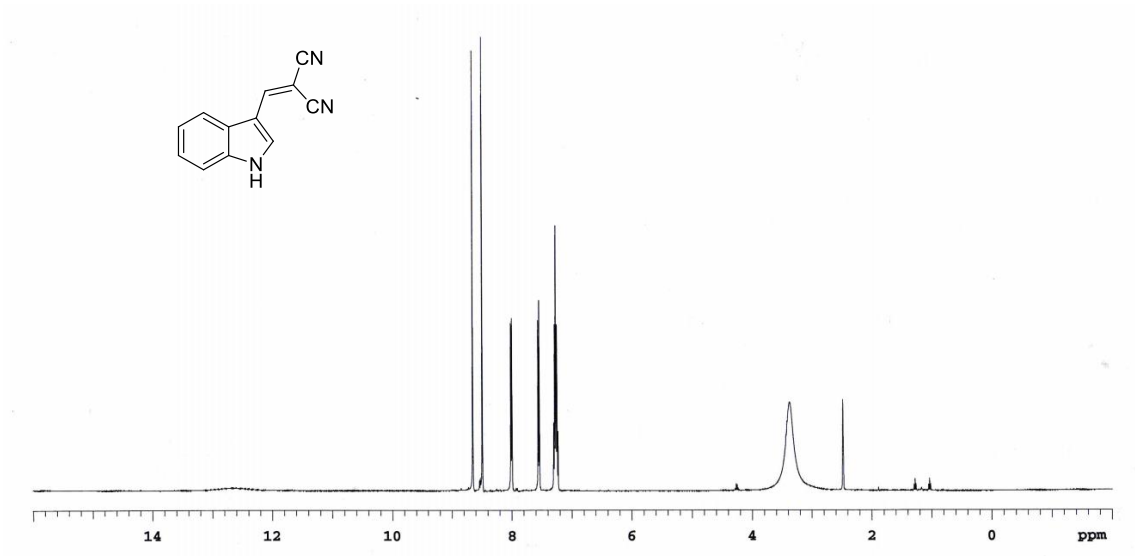


**Figure G1** $^{1}$H-NMR spectrum of 2-((1*H*-indol-3-yl)methylene)malononitrile (170).

# BIOGRAPHY

# BIOGRAPHY

| | |
|---|---|
| **Name** | Miss Sukanya Tongkhan |
| **Date of birth** | September 21, 1987 |
| **Place of birth** | Maha Sarakham, Thailand |
| **Institutions attended** | |
| 2010 | Bachelor of Science degree in Chemistry, Mahasarakham University, Thailand |
| 2015 | Doctor of Philosophy in Chemistry, Mahasarakham University, Thailand |
| **Contact address** | 32 Moo 16, Tambon Khamrieng, Ampher Kantarawichai, Maha Sarakham Province, 44150 |
| **Research grants & awards** | Human Resource Development in Science Project (Science Achievement Scholarship of Thailand; SAST) |

**Research output**

[1] Tongkhan S, Radchatawedchakoon W, Kruanetr S, Sakee U., Silica-supported ceric ammonium nitrate catalyzed chemoselective formylation of indoles. Tetrahedron Letters 2014; 55[29]; 3909-3912

[2] Tongkhan S, Radchatawedchakoon W, Kruanetr S, Sakee U., Silica-supported ceric ammonium nitrate catalyzed chemoselective formylation of indoles. Proceeding of the 3rd Science Achievement Scholarship of Thailand (SAST). 23th-25th July 2014, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani, Thailand (Oral presentation).

[3] Tongkhan S, Radchatawedchakoon W, Kruanetr S, Sakee U., "Synthesis of 2-[[2(prop-2-ynyloxy)phenylmethylene]hydrazono]-4-oxo-5-thiazolidineacetic acid as chromogenic and fluorescent anion sensors". Proceeding of the Pure and Applied Chemistry International Conference (PACCON). 8th-10th January 2014, Centara Hotel and Convention Centre, Khon Kaen, Thailand. (Poster presentation).

[4] Tongkhan S, Radchatawedchakoon W, Sakee U., "Synthesis of 1*H*-indole 3-thiosemicarbazone" Journal of Science and Technology Mahasarakham University 2013; 9[0]; 637-647