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SYNTHESIS OF CANNABIMIMETIC INDOLES CONTAINING NON-CARBONYL BIOISOSTERES

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A Thesis Submitted in Partial Fulfillment of the Requirements
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ฐากูร โล่ห์สิริวัฒน์: การสังเคราะห์สารกลุ่มแคนนาบิมิเมติกอินโดลที่มีนอนคาร์บอนิลไบโอไอโซสเทียร์ (SYNTHESIS OF CANNABIMIMETIC INDOLES CONTAINING NON-CARBONYL BIOISOSTERES) อ. ที่ปรึกษาวิทยานิพนธ์หลัก : ผศ. ดร. วรินทร ชวศิริ, 96 หน้า.

พัฒนาการสังเคราะห์สารกลุ่มแคนนาบิมิเมติกอินโดลใหม่ด้วยวิธีวันพอท โดยไม่ต้องอาศัยเครื่องมือพิเศษหรือสารเคมีหายาก และพบว่าสามารถควบคุมปริมาณของผลิตภัณฑ์ข้างเคียงที่เกิดขึ้นในปฏิกิริยาให้เกิดน้อยลงได้โดยการผ่านก๊าซไนโตรเจนตลอดการทำปฏิกิริยา ผลิตภัณฑ์ที่ได้มีปริมาณเป็นที่น่าพอใจ โดยได้สูงสุดถึงร้อยละ 88

นอกจากนั้นยังทำการสังเคราะห์สารประกอบกลุ่มแคนนาบิมิเมติกอินโดลชนิดใหม่ โดยการแทนที่หมู่ฟังก์ชันคาร์บอนิลในโครงสร้างของแคนนาบิมิเมติกอินโดลด้วยหมู่ฟังก์ชันอื่น สำหรับหมู่ฟังก์ชันไทโอคาร์บอนิล ไทออล เอ็กโซ-เมทิลีน และคาร์บินอล ทำการศึกษาวิธีสังเคราะห์โดยใช้แคนนาบิมิเมติกอินโดลที่สังเคราะห์ด้วยวิธีการวันพอทเป็นสารตั้งต้น และศึกษาวิธีการสังเคราะห์อนุพันธ์ที่มีหมู่อัลคิล ซัลฟินิล และซัลโฟนิลจากอินโดล

ภาควิชา เคมี ลายมือชื่อนิสิต .....

สาขาวิชา เคมี ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก .....

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TAKUL LOSIRIWAT: SYNTHESIS OF CANNABIMIMETIC INDOLES CONTAINING NON-CARBONYL BIOISOSTERES. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 96 pp.

A new one-pot synthetic methodology of cannabimimetic indole is developed. Neither special apparatus nor exotic reagent is required for the reaction. The polymeric by-products from the reaction are suppressed by continuous nitrogen flow. Yield of the reaction are satisfactory up to 86 percent.

Several novel cannabimimetic indoles analogs which the carbonyl group is replaced by other bioisosteres are also synthesized. The synthetic methodology of thiocarbonyl, thiol, *exo*-methylene and carbinol analogs starting from one-pot ketone product is investigated. The synthesis of other analogs including alkyl, sulfenyl and sulfonyl from indole is also investigated.

Department: Chemistry . Student's Signature .....
Field of Study : Chemistry . Advisor's Signature .....
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CONTENTS

CHAPTER **page**

CHAPTER **page**

LIST OF TABLES

LIST OF FIGURES

Figure **page**

LIST OF ABBREVIATIONS

Ar	aryl group
br	broad signal
b.p.	boiling point
CB1	cannabinoid receptor type I
CB2	cannabinoid receptor type II
CHO	Chinese hamster ovary
COX	cyclooxygenase
DCE	1,2-dichloroethane
DCM	dichloromethane
d	doublet
dd	double doublets
DMF	*N*,*N*-dimethylformamide
eq	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
hCB	human cannabinoid receptor
hex	hexane
hr	hour(s)
Hz	Hertz
LR	Lawesson's Reagent
m	multiplet
Me	methyl
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
nm	nanometer
NMR	nuclear magnetic resonance
Ph	phenyl

ppm	part per million
PS	phosphorus sulfides
q	quartet
QSAR	quantitative structure-activity relationship
quant	quantitative yield
R , R', R''	alkyl group
R_f	retention factor
rt	room temperature (25 ^{o}C)
s	singlet
SAR	structure-activity relationship
S_EAr	electrophilic aromatic substitution
S_NAr	nucleophilic aromatic substitution
t	triplet
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	toluenesulfonyl
UV	ultraviolet
#	entry
%	percent
δ^+	partial positive charge
δ^-	partial negative charge
^{o}C	degree of Celcius

CHAPTER I

INTRODUCTION

1.1 Introduction to Cannabinoids

The medicinal use of the cannabinoids can be traced back to the ancient time, dating back to over thousands of years. In the Chinese culture as an anesthetic, the use of alcoholic extract of cannabis (麻沸散) as an anesthetic was described by Hua Tuo (华佗), the Chinese expertise in surgery and anesthesia[1]. There are also records regarding the use of cannabinoids for their medical properties throughout the human history along with different regions and cultures, including ancient Egypt[2], India[3], Europe[4] and the Middle East[5] civilizations.

Cannabinoids possess several pharmacological profiles. The effectiveness of the cannabinoid-class compounds was evaluated, which primarily involved in the case of chronic pain management like arthritis[6]. The suppression of pain by the cannabinoids also have an advantage over other potent painkillers like opioids, as the density of the specific receptors is low or absent in the medulla oblongata[7], part of the brain that involves the major role in respiration control, cannabinoids generally do not over-suppress the respiratory system.

The neuroprotective properties of cannabinoids are also studied in the treatment or the prolongation of the onset of neurological-related diseases such as Alzheimer's syndrome[8] Parkinson's syndrome[9,10] Tourette's syndrome[11,12] attention-deficit hyperactivity (ADHD) syndrome[13]. It has also been used to treat diseases stemming from neurodegeneration like multiple sclerosis (MS)[14] amyothophic lateral sclerosis (ALS)[15] pruritus[16] sleep apnea[17] and dystonia[18].

Cannabinoids also posses antitumor activity both *in vitro* and *in vivo* which affects different cancerogenic cell lines consisting of brain tumor, breast tumor, lung tumor, skin tumor and leukemia[19-21].

Other medicinal uses of cannabinoids include the treatment of oesteophorosis[22] and hypertension[23]. The antimicrobial activity is also present against methicillin-resistant *Staphylococcus aureus* (MRSA)[24] and hepatitis C virus[25].

1.2 The Cannabinoid Ligands

As there are discrepancies between the structures of the cannabinoids, they can be classified into groups regarding their chemical structures or their sources.

1.2.1 Phytocannabinoids

The phytocannabinoids are the first group of cannabinoids discovered from the extract of the plant *Cannabis sativa* in 1964[26]. The structure of the phytocannabinoids contains the aromatic part fused with a monoterpene unit in various positions. The aromatic moieties are derived from the structure of olivetol, or other lesser number of carbon side chain phenolic compounds counterpart.

It was held that the cannabinoids are present only within the plant in *Cannabaceae* family. Nevertheless, the class of compounds are then found present in some liverwort of the *Radula* genus[27-28]. The first phytocannabinoid isolated was cannabinol (CBN), whereas the major active components are Δ^9-tetrahydrocannabinol (THC), along with the non-psychoactive cannabidiol (CBD) and other components in the class of cannabinochromene (CBC), canabigerol (CBG), cannabicyclol (CBL) , cannabicitran (CBT), cannabifurans (CBF) and several cannabinoid acids.

The similarities between each structural type are illustrated in Figure 1.1, which clearly hints on the similar biosynthetic pathway.

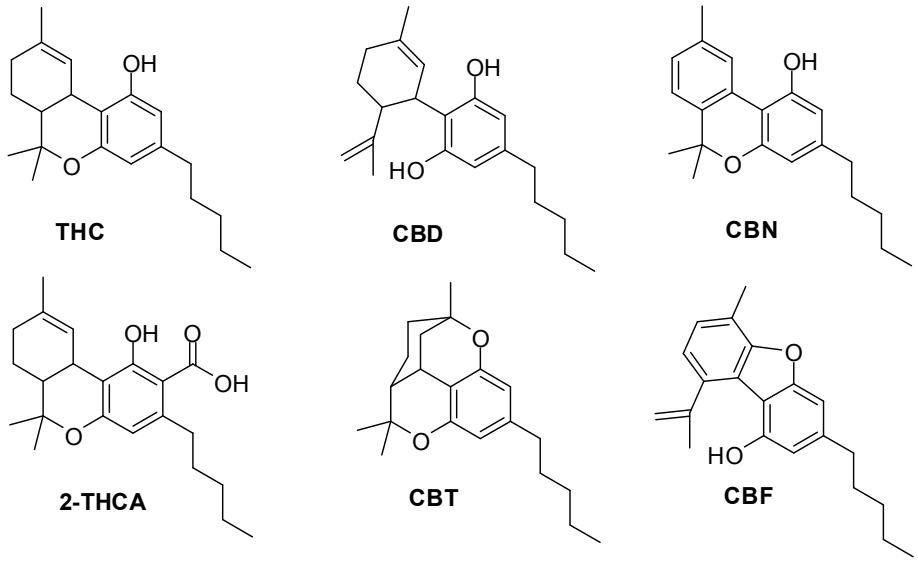


Figure 1.1 Selected Examples of Naturally Occuring Phytocannabinoids

There are also several synthetic and semi-synthetic analogs bearing the resemblance of structures to this class of compound. Some of which becomes a standard ligand in the binding assay of cannabinoid-class compounds, such as CP-55940 (Pfizer®)[29]. HU-210 and HU-308[30] are other examples of potent synthetic cannabinoids which based on the structure of the phytocannabinoids.

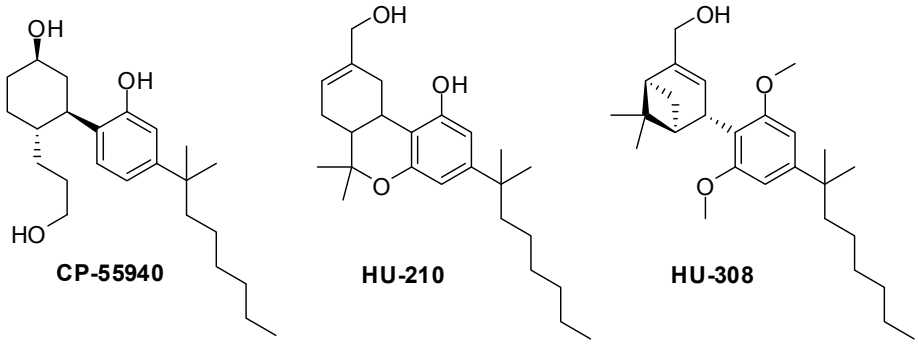


Figure 1.2 Selected Examples of Synthetic Analogs of Phytocannabinoids

1.2.2 Endocannabinoids

The discovery and the psychoactivity of phytocannabinoids have lead to the search for the specific receptors and ligands of the cannabinoids in the body. The first endocannabinoid was isolated from porcine brain[31]. The structure of

endocannabinoids consist of the part of polyunsaturated fatty acid and the hydrophilic head group. At least one unsaturation must be present in the fatty acid part in order to retain the activity. The polar head group can be varied to several analogs. The most prevalent endocannabinoids are the hydroxyl-amide derivative, anandamide (AEA); and the glyceryl derivative, 2-AG. Paracetamol (acetaminophen), a common over-the-counter analgesic and antipyretic, exerts its activity *via* its metabolite (AM404), which acts as an inhibitor for natural endocannabinoids anandamide.[32-33]

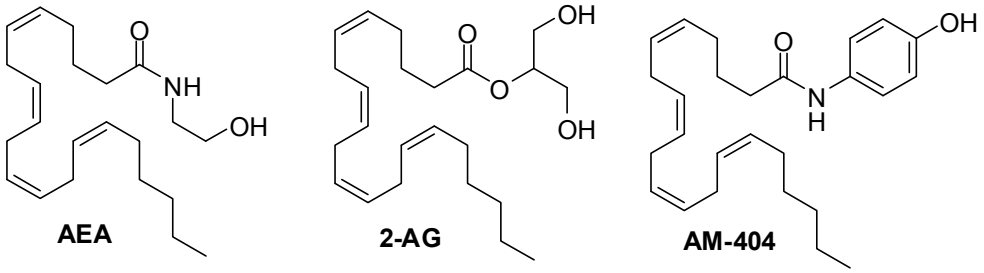


Figure 1.3 Selected Examples of Endocannabinoids and a Derivative

1.2.3 Cannabimimetic Indoles

In contrast with the other group of cannabinoids, the cannabimimetic indoles are not found in nature, and all compounds of this class are obtained by synthesis. The general structure consists of two aromatic parts linked with a carbonyl bridge and one alkyl chain. Indole can be replaced with pyrole, phenylpyrrole, 2-methylindole or other aromatic moieties[34-35]. Pravadoline[36] (WIN-48098) is the first cannabimimetic indoles discovered. Some of the potent derivative like WIN-55212-2[37] is still utilized as a standard of cannabinoids binding assay. Some of the derivatives have much simplified structure while retain the high activity like JWH-018.

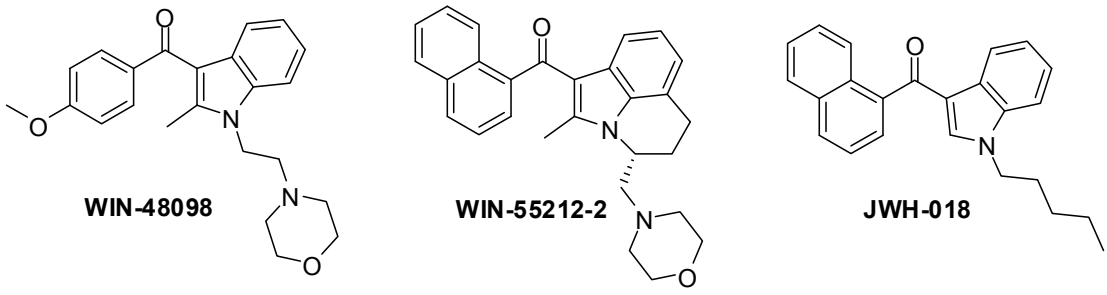


Figure 1.4 Selected Examples of Cannabimimetic Indoles

1.3 The Cannabinoid Receptors

The cannabinoid receptors are responsible for both the psychotomimetic and somatic effects of the cannabinoid compounds. Cannabinoid receptors are G-protein coupled receptors (GPCRs) located throughout the body as their primary role is important to the functionality of communication between neurons, or between neuron and other cells. Acting as a response signal, the endocannabinoids are synthesized upon activation from the lipid bilayer of the post-synaptic neuron, then sending back through the synapse to the pre-synaptic neuron. The retrograding signal is an important feedback in maintaining the neurotransmitter firing rate from the pre-synaptic neuron.

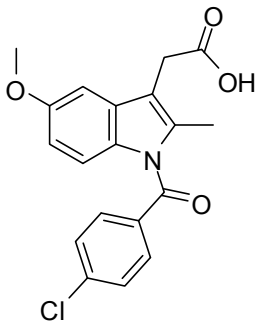
Currently two types of cannabinoid receptors have been identified; namely CB1 and CB2 according to the order of discoveries. CB1 and CB2 receptors differ in their distribution location. CB1 receptors are primarily present in the central nervous system, being the most abundant receptor in the brain, brain stems and neurons[38]. They are also found in hepatic cells and fat cells, which they control the anabolism and metabolism of lipid[39]. CB2 receptors, on the other hand, are primarily found in the immune-system related tissues or cells like T-cell and B-cell. They also modulate the keratin production in hair and nails[40].

Different sequence of amino acid present in cannabinoid receptors affects the binding region pocket size, thus fine-tuning of the receptor affinity of two subtypes can be accomplished by modifying the molecular structure. There are also evidences of undiscovered cannabinoid receptor types as some compound exerts cannabinoid activity but do not bind to both CB1 and CB2[41-42].

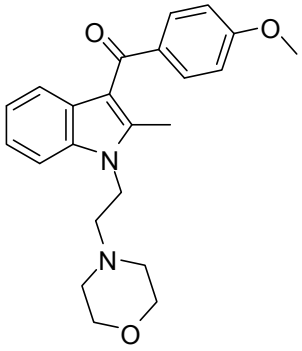
The docking study of cannabinoids cannot be done directly as there have been no successful attempts crystallizing CB1 nor CB2 receptors for x-ray crystallography[43]. All studies involved the use of homologous model from bovine rhodopsin receptor, which bear structural similarity to the CB1 receptor.

1.4 The Development of Cannabimimetic Indoles

The first cannabimimetic indole was discovered in 1991 in the synthesis of new COX-2 inhibitors where less gastrointestinal disturbance was aimed[44]. The structure is closely related to other COX-2 inhibitors like indometacin.



Indometacin

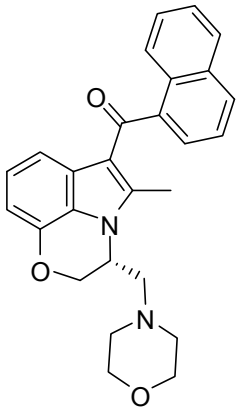


Pravadoline

However the analgesic effect was prominent, as the dosage needed for analgesia was roughly ten times lower than the effective dose of other analogs and could not be explained using the mechanism of COX-2 inhibition alone. The introduction of a strong opioid antagonist like Naloxone did not block the analgesic effect[36]. Pravadoline was then found to suppress the pain by agonizing at CB1 receptor.

In 1992, D'Ambra[45] *et al* studied the structure-activity relationship of cannabimimetic indoles by substituting the acyl group with other ring substituent. It was found that bicyclic aryl system like naphthyl provided high affinity in binding comparing to the monocyclic counterpart, like phenyl. The alkylmorpholine chain was also rigidified by forming a ring to test the effect of stereocenter, and the optimum number of carbon between indole and morpholine was found to be two.

WIN 55212-2, a compound from this study, is potent cannabinoid full agonists used for research in CB receptor binding and in prevention of memory impairment from the accumulation of amyloid-β proteins in Alzheimer's diseases patients.



WIN 55,212-2

Shim *et al* performed a computational study[46] (QSAR – CoMFA study) while retaining the optimal two carbon spacer between the indole and the amino group. The morpholino group was also replaced by various amines, either open chain or ring, and shifting the position of nitrogen within the ring. In this study, the amino group was overlayed onto phenol group as hydrogen bond acceptor, whereas the hydrophobic aroyl group was aligned with the hydrophobic alkyl chain of the phytocannabinoids. The result shows this alignment gave moderate correlation trends.

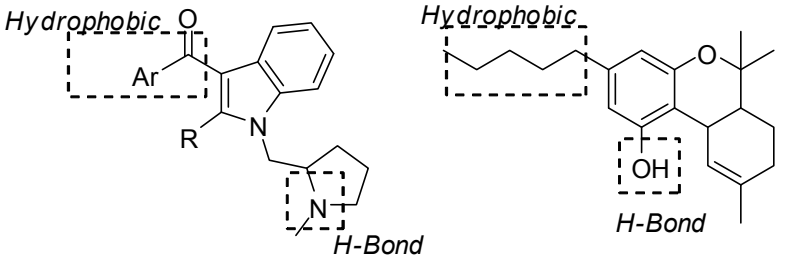


Figure 1.5 Alignment Proposed in the Study of Shim *et al*

In 1994, Huffman *et al* provided a different perspective on binding mode[47]. As it was found that compounds absence of amino group entirely, having straight chain alkyls, have comparably high affinity toward the receptor. With this alignment the carbonyl group would act as a hydrogen bond acceptor like phenolic hydroxyl in phytocannabinoids, whereas two aromatic rings provide π-stacking interactions, and the alkyl groups in both structure, fitted together.

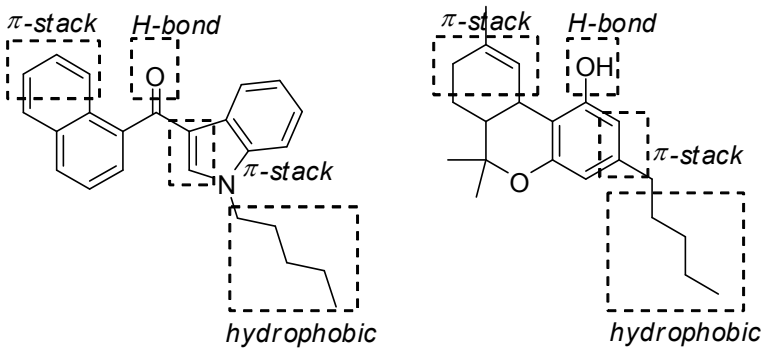


Figure 1.6 Alignment Proposed by Huffman

Cannabimimetic indoles can be aligned to two possible lowest-energy conformations, namely *s-cis* and *s-trans*. These conformations have low energy barrier and can interconvert. As for general cannabimimetic indoles, the lowest energy conformation is *s-trans*; however, substituting the hydrogen in indolic-2-position with a methyl group switches the lowest energy conformation to *s-cis* due to the steric requirement of the methyl group. Despite having a large different in the conformation, the 2-methyl compounds only showed slight diminished activity comparing to 2-hydrogen ones. To rule out whether they change their conformation in binding, or they bind to the receptor of different regions, compounds with rigid structure was synthesized by Reggio in 1998[48]. The conformational rigidity was accomplished by the replacement of indole with indene, which they provided two distinct different compounds.

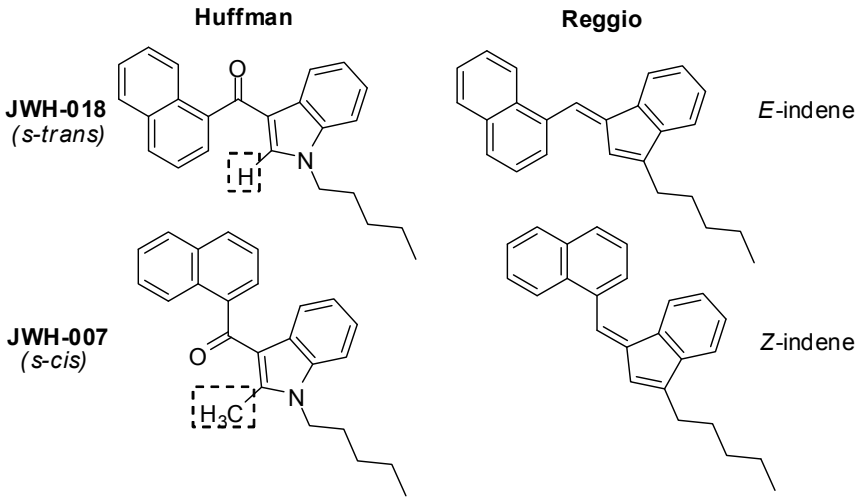


Figure 1.7 Conformational Comparisons Between Cannabimimetic Indoles and Indenes

However, the carbonyl group is absent in the structure of cannabimimetic indenes. By comparison, the alkene is a very weak hydrogen bond acceptor comparing to carbonyl. So, the importance of the carbonyl group was challenged by Huffman again in 2003[49]. The compound with carbonyl group replaced with methylene bridge still exerts moderate cannabimimetic activity. It is noted that the angle between two aromatic planes of these analogs differed from both the *s-cis* and *s-trans* conformations in the carbonyl analogs, pointing the aromatic ring toward other directions, yet they still possess the activity.

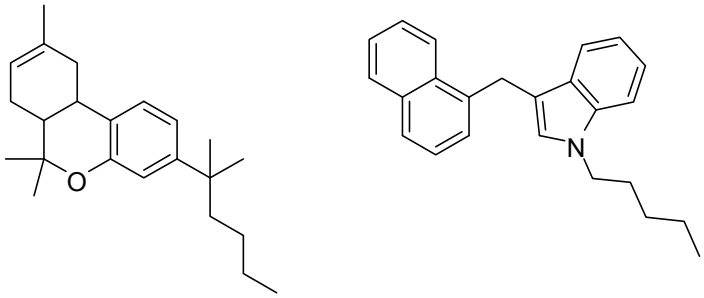


Figure 1.8 Cannabinoids Lacking a Hydrogen Bond Acceptor

The lack of hydrogen bonding capability while retained some of the activity among these methylene analogs suggest a slightly different binding modes between the phytocannabinoids and cannabimimetic indoles. In case of phytocannabinoids, removal or blocking this hydrogen bond acceptor abolish almost all activity[50]. This strongly suggests that the main binding interactions between the receptors and cannabimimetic indoles are greatly contributed by the hydrophobic alkyl region and π-stacking interaction regions. Hydrogen bonding only partially contributes toward the affinity. Thus, replacement of the carbonyl group with other bioisosteres would provide a new class of cannabinoids for further research. The differences in hydrogen bonding capability and stereoelectronic demand among these compounds could make these compounds a useful ‘molecular probe’ for studying the exact structure of the cannabinoid receptors.

1.5 Goal of Research

The objective of this research is to establish the methods and conditions to synthesize cannabimimetic indole analogs, in which the carbonyl functionality is replaced by other functional groups. The variation would result in cannabimetic indoles with non-carbonyl bioisosteres those can be used for the further activity assay.

CHAPTER II

EXPERIMENTAL

2.1 NMR Data Acquisitions

The ^{1}H NMR spectra was measured in deuterated chloroform ($CDCl_3$) using Varian™ nuclear magnetic resonance spectrometer, model Mercury Plus 400, which operated at 399.84 MHz for ^{1}H nuclei.

2.2 NMR Data Processing

The obtained NMR data was processed by Fourier transform using *Mestrelab Research - MestReNova* version 6.0.2-5475. Chemical shifts are assigned using solvent residual protons. Peak integral ranges are manually set.

2.3 TLC

Thin layer chromatography was performed on pre-coated silica gel plates (Merck Keisergel 60). Short-wavelength UV (254 nm) and iodine are used for spots detection.

2.4 TLC Data Processing

TLC plate was scanned using HP Scanjet G3110 at 600 dpi as uncompressed 24-bit bitmap (BMP) image, and was processed using *Scion Image* Alpha 4.0.3.2. Spots visibility are enhanced by converting the RGB image to 8-bit colors, then

applied appropriate color table on the LUT, followed by Enhance Contrast function. 2D TLC plots are obtained using Plot Profile function.

2.5 Column Chromatography

Column chromatography was carried out on silica gel (Merck Kieselgel 60, 70-230 mesh). Conventional air pumps might be used to speed up to separation.

2.6 Chemicals

Solvents used in this research were dried prior to use by standard methods unless those which were reagent grades. Chemicals used in this research were purchased from Fluka™, TCI™ or Sigma-Aldrich™ unless otherwise stated, and were used without further purification.

2.7 Preparation of Haloalkanes

2.7.1 Preparation of Reagents

Hexabromoacetone

Anhydrous sodium acetate (7 g) was added to glacial acetic acid. The slurry was heated to 60^{o}C, and then 1.5 mL was then added, followed by dropwise addition of liquid bromine (5 mL) with stirring. The mixture was then heated to 95^{o}C for 2 hour. After cooling to room temperature, 100 mL of cold water was added to precipitate the product. Recrystallization using hexane gave the pure product.

2.7.2 Preparation of Chloroalkanes

To the solution of triphenylphosphine (3 eq) in dichloromethane, an appropriate alcohol was added, followed by careful addition of hexachloroacetone (2 eq). The resulting mixture was then heated at 60^{o}C for 30 minute then the resulting chloroalkane was distilled and collected.

2.7.3 Preparation of Bromoalkanes

To the solution of triphenylphosphine (3 eq) in appropriate alcohol, hexabromoacetone (1.25 eq) were carefully added. After the exothermic reaction has ceased, the resulting bromoalkanes was then distilled.

2.7.4 Preparation of Iodoalkanes

To an excess of saturated solution of sodium iodide in acetone, chloroalkane or bromoalkane was added at once, heated to 45^{o}C for 1 hour then left at room temperature for 3 days. The resulting solution was then filtered, and the organic layer was evaporated to give the corresponding iodoalkane.

2.8 *N*-Alkylation of Indole

2.8.1 General Procedure

Method A (NaH – DMF/THF)

Solution of indole (1 eq) in DMF/THF (1:2) in nitrogen atomosphere was cooled to 0^{o}C using an ice bath. Sodium hydride (1.2 eq) was carefully added, then stir for 30 min. Haloalkane (1.2 eq) was then added dropwise. Then stir at room temperature as followed by TLC and quenched by adding methanol. The resulting mixture was concentrated *in vacuo* and separate using column chromatography. (Hexane/EtOAc 5:1 to 9:1)

Method B (NaOH – DMF/THF)

Sodium hydroxide pellets (5 eq) was added to indolic (1 eq) DMF/THF (1:2) solution, then reflux at 65^{o}C under nitrogen atmosphere for 1 hour. Haloalkane (1.2 eq) was then added to the refluxing solution. Maintain the temperature at 50^{o}C for an appropriate time then quenched by adding water. The product was then extracted 3 times using dichloromethane. The combined fraction was then purified by column chromatography.

Method C (KOH – EtOH)

Potassium hydroxide pellets (10 eq) was dissolved in ethanol, followed by indole (1 eq) and haloalkane (1.5 eq) in nitrogen atmosphere. The mixture was heated to boiling, then evaporated *in vacuo*. The crude was then purified using column chromatography.

Method D (K_2CO_3 – DCM)

A two-phase mixture containing water, dichloromethane, indole (1 eq), haloalkane (1.2 eq), potassium carbonate (5 eq) and tetrabutylammonium chloride (0.2 eq) was stirred at room temperature for an appropriate time. The organic phase was collected, concentrated and purified using column chromatography.

2.9 3-Acylation of Indole

2.9.1 Preparation of Reagents

1-Bromonaphthalene

Naphthalene (1 eq) was refluxed in 1,2-dichloroethane with gentle boiling, liquid bromine (1.3 eq) was slowly charged into the mixture. Reflux for additional 8 hours, then solid sodium hydroxide was added to destroy the formed acid. The crude was extracted with dichloromethane and purified using column chromatography. (Hexane/EtOAc 3:1)

1-Naphthonitrile

To 1-bromonaphthalene (1 eq) in wet DMF solution, NaCN (3 eq) and CuCN (0.1 eq) was added. The solution was heated to 120^{o}C for 4 hours. Water was then added and extracted with portions of dichloromethane. The combined portion was then evaporated and used for the next step without further purification.

Naphthalene-1-carboxylic acid

To 1-naphthonitrile (1 eq) in THF/water mixture (5:1), KOH was added and reflux for 4 hours. Then, the mixture was acidified and the product was extracted out using dichloromethane, giving pale white solid upon evaporation.

Thionyl Chloride

The crude yellow thionyl chloride was redistilled and collected the fraction at 74.6^{o}C to obtain colorless liquid.

Naphthalene-1-carbonyl Chloride

Naphthalene-1-carboxylic acid (1 eq) was added to excess $SOCl_2$, and reflux at 80^{o}C for 2 hours. Excess thionyl chloride was distilled off. Toluene was then added and distilled off (2 times) to remove remaining thionyl chloride. The resulting yellow liquid was used immediately after the preparation.

2.9.2 Synthesis of 3-(1-Naphthoyl)-1*H*-indole

Mixture of Naphthalene-1-carbonyl chloride, indole and Lewis acid was stirred at appropriate temperature under general Friedel-Craft's reaction condition.

2.9.3 Effect of Lewis Acids

Lewis acids for the reaction was chosen among: $AlCl_3$, $InCl_3$, $FeCl_3$, $Fe(acac)_3$ $TiCl_4$, $BF_3.Et_2O$ and $ZnCl_2$. The amount was varied from 1 eq to 4 eq.

2.9.4 Effect of Reaction Time

The reaction was monitored by TLC at different times by using peak areas.

2.9.5 Effect of Solvents

Solvent for each reaction was chosen among: dichloromethane, 1,2-dichloroethane, chloroform and n-hexane.

2.9.6 Effect from Order of Addition

Due to the differences of yields which had been noted during experiments, the orders seemed to play a major role so the test was conducted.

Method A

Indole and Lewis acid was dissolved in dichloromethane and $AlCl_3$ was slowly added.

Method B

Indole was dissolved in dichloromethane, and $AlCl_3$ was added to give a stable yellow precipitate, then Lewis acid was added dropwise.

2.10 One-Pot Synthesis of Cannabimimetic Indoles

Indole (1 eq) was dissolved in dichloromethane under flowing nitrogen atmosphere with continuous ventilation. Anhydrous $AlCl_3$ was added in small portions and stir for 30 minutes. To the resulting light yellow mixture, 1-naphthoyl chloride was then added dropwise at 0^oC with vigorous stirring. Make sure that the generated HCl gas has sufficient nitrogen flush throughout the reaction. After the addition was completed, the reaction mixtures was brought to room temperature and stirred at an appropriate time or at reflux, indicated by TLC, then quenched with H_2O/THF (1:2) mixture.

Concentrated NaOH solution was then carefully added and brought back to reflux for 30 min. Excess THF was evaporated under reduced pressure resulting in

insoluble heavy precipitation. The basic solution was then discarded, rinsed with water several times then decanted to give red-brown solid.

A pre-chilled mixture of MeOH/H_2O (85:15) was added to the red-brown solid and stir vigorously, then the orange-red liquid was carefully rinsed off. Repeat until the red coloration disappeared. The resulting white or off-white solid was evaporated to dryness *in vacuo*.

A mixed DMF/THF (2:3) solvent was added to the same flask under inert atmosphere, NaH (1.2 eq) was then added and stirred for 30 minute. Haloalkane (1.2 eq) was added and the mixture was stirred at room temperature for 15 minute. MeOH was carefully added to quench the reaction, then concentrated *in vacuo* and purified by column chromatography.

2.11 The Carbinol Analogs

2.11.1 Preparation of Reagents

(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanone (Ketone)

These carbonyl analogs were prepared using the above mentioned one-pot synthesis of cannabimimetic indoles.

Magnesium

Magnesium wire was sanded with no.0 sandpaper until it gave metallic luster. It was then quickly washed in 0.1M HCl solution, then rinsed with water and dried with adsorbent paper.

Methylmagnesium Iodide

To the freshly dried diethyl ether, Magnesium wire and iodomethane were added, along with a catalytic iodine crystal. After the reaction, the resulting methyl Grignard solution was used without further purification.

Cerium (III) Chloride

Cerium(IV) ammonium nitrate was mixed with boiling HCl/NaCl solution until orange color disappeared. The resulting liquor was fractional crystallized giving cerium(III) chloride heptahydrate. The hydrated salt was then reflux with thionyl chloride for 3 hours to give the anhydrous salt, then decanted in desiccators to obtain white cerium(III) chloride.

Acetylene

Water was slowly dripped onto commercial grade calcium carbide, with a gas tube leading the crude gas to sulfuric acid trap and then to distilled water trap.

Copper(I) Acetylide

30% Ammonium hydroxide was added to 5 M $CuSO_4$ solution until deep blue complex was formed. Then acetylene gas was bubbled through this solution for 20 minutes or until the gas ceased. This resulted in red precipitation of the product. It was stored under water-ammonia solution prior to use.

Silver(I) Acetylide – Silver(I) Nitrate

$AgNO_3$ was dissolved in dilute nitric acid, then bubbled with acetylene gas. The resulting white precipitate was collected, protected from light.

2.11.2 The Stability Test

The carbinol analogs showed instability as they decomposed to dark colorations. So it had been tested for stability in various organic solvent, either in the dark or with exposure to light.

2.11.3 (1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanol

Method A (Borohydride)

To a solution of the ketone (1 eq) in MeOH/THF (1:1) mixture in ice bath, $NaBH_4$ (4 eq) was added, then the solution was left to room temperature and heated to

a reflux for 15 min. The solution was then extracted using EtOAc, concentrated then purified by chromatographic means.

Method B (Acid)

To a dichloromethane solution of indole (1eq), 1-naphthaldehyde (1 eq) is added, followed by *p*-TsOH (0.1 eq) The mixture was stirred at room temperature for 1 hour and fine white precipitates are then collected.

2.11.4 1-(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)ethanol

Method A (Grignard)

To a solution of the ketone (1eq) in diethyl ether, an excess of methylmagnesium iodide was added. After 10 min of stirring the solution was then quenched by carefully adding isopropyl alcohol. The crude mixture was concentrated and separated using column chromatography.

Method B (Grignard + Cerium)

Using similar procedure to Method A, but with cerium(III) chloride added to the mixture prior to the addition of methyl Grignard.

2.11.5 1-(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)prop-2-yn-1-ol

Method A (Acetylene)

Acetylene was bubbled to the THF solution containing the ketone (1 eq) and potassium hydroxide (1.5eq). The resulting black crude was collected.

Method B (Metal Acetylides)

To the solution of the ketone in DMSO was added either copper(I) acetylide, silver(I) acetylide-nitrate double salt, or monosodium acetylide ethylenediamine complex. The reaction was then stirred for 2 hours then quenched with water. The crude was then collected.

2.12 The Ether Analogs

2.12.1 1-Alkyl-3-(methoxy(naphthalen-1-yl)alkyl)-1*H*-indole

Method A (Sodium Metal)

Sodium metal was cut into small pieces, then added to the ethereal solution of crude (1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanol (alcohol) in inert atmosphere. After the evolution of hydrogen ceased, excess sodium was physically removed and iodomethane was added to the solution. The resulting mixture is concentrated and collected.

Method B (Sodium Hydride)

(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanol (alcohol) was dissolved in DMF/THF (1:2) mixture. Sodium hydride (2 eq) was then added and stirred for 15 min, followed by iodomethane. The reaction was stirred for 1 hours, concentrated and collected.

2.13 The Thiocarbonyl Analogs

2.13.1 Preparation of Reagents

Red Phosphorus

Matchbox strikers were removed from the boxes and cut to small pieces, then soaked in acetone for 1 day. The binder, paper, glass powder and carbon black were filtered and discarded. The remaining filtrate was evaporated to give crude red phosphorus.

Phosphorus Sulfides

Red phosphorus and sulfur powder were mixed in a glass tube, and flushed with nitrogen, then heated cautiously using a torch (approx. 350^{o}C). The resulting

greenish-dark solid was kept away from air and moisture, and was used without more purifying steps.

2.13.2 (1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethione

Method A (Phosphorus Sulfides)

Phosphorus sulfides (excess) and ketone (1 eq) was added to organic solvent and stirred at reflux. The resulting mixture was quenched with water, then purified using thin layer chromatography Hexane/EtOAc (1:3 to 1:6).

Method B (Lawesson's Reagent)

Ketone (1 eq) was dissolved in organic solvent, followed by Lawesson's Reagent (1.1 eq). The solution was heated to reflux for 4 hours. The resulting red solution was concentrated and purified using thin layer chromatography.

2.13.3 The Stability Test

Since thioketones often decomposes slowly upon storage, the stability tests were conducted by boiling the thioketone analogs in various solvent, either with the presence or absence of light and/or air. The (de)composition were then followed using ^{1}H NMR

2.14 The Thiol Analogs

2.14.1 (1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethiol

To a solution of the thioketone (1 eq) in MeOH/THF (1:1) mixture in ice bath, $NaBH_4$ (2.5 eq) was added, and then the solution was left to room temperature until hydrogen gas bubbling ceased, iced water was subsequently added to quench the reaction. Extracted 2 times using EtOAc. The resulting solid was collected.

2.15 The *exo*-Methylene Analogs

2.15.1 Preparation of Reagents

Methyltriphenylphosphonium Iodide

Triphenylphosphine (1 eq) was dissolved in benzene or toluene followed by iodomethane (2 eq). The reaction was settled for 6 hours to give white crystalline solid of the phosphonium salt.

Sodium Ethoxide

Small pieces of sodium metal was then carefully added to anhydrous methanol to give the alkoxide.

2.15.2 1-Alkyl-3-(1-(naphthalen-1-yl)vinyl)-1*H*-indole

Method A (Wittig)

The ketone (1 eq) and methyltriphenylphosphonium iodide were dissolved THF, followed by either sodium metal, sodium hydride, sodium ethoxide or potassium *t*-butoxide (1.5 eq) as a base. The reaction was then refluxed for 3 hours, then concentrated and collected.

Method B (Tebbe)

The ketone (1 eq) was dissolved in toluene, followed by a dropwise addition of Tebbe's reagent (1.5 eq) and triethylamine (1.5 eq). It was stirred at room temp for 1 hour then brought to a reflux for additional 2 hours, then quenched by adding water-methanol mixture, extracted using dichloromethane, concentrated *in vacuo* and collected.

2.16 The Alkyl Analogs

2.16.1 Preparation of Reagents

1-(1-hydroxoethyl)naphthalene

To the solution of 1-acetonaphthone (1 eq) in methanol at room temperature, $NaBH_4$ (2 eq) was added slowly and stirred for 1 hour, then quenched with water. The resulting mixture was extracted with dichloromethane and evaporated to give the pure product.

1-(1-chloroethyl)naphthalene

1-(1-hydroxoethyl)naphthalene (1 eq) was charged into the flask of thionyl chloride (excess). After the exothermic reaction, it was refluxed for 30 more min, then excess thionyl chloride is distilled off.

1-(2-hydroxopropan-2-yl)naphthalene

Methylmagnesium iodide was charged into a nitrogen-filled tube, followed by dropwise addition of 1-acetonaphthone. The reaction was quenched with methanol and extracted with toluene to give the tertiary alcohol.

1-(2-chloropropan-2-yl)naphthalene

1-(2-hydroxopropan-2-yl)naphthalene was reacted with thionyl chloride similar to previous reaction.

2.16.2 1-Alkyl-3-(1-(naphthalen-1-yl)ethyl)-1*H*-indole

Method A (Alcohol)

1-(1-hydroxoethyl)naphthalene (1.2 eq) and indole (1 eq) was dissolved in ethanol then acid was then added and stir for an appropriate time. The reaction was then washed with water to remove excess acid, collected and purify by column chromatography.

Method B (Chloroalkane)

Anhydrous $AlCl_3$ (0.1 eq) was added to indole (1 eq) solution in dichloromethane, after the yellow precipitate formed, 1-(1-chlroethyl)naphthalene was slowly added. The resulting green crude was collected and purified by column chromatography.

2.16.3 1-Alkyl-3-(2-(naphthalen-1-yl)propan-2-yl)-1*H*-indole

Synthesized either by *Method A* or *Method B*, using 1-(2-hydroxopropan-2-yl)naphthalene and 1-(2-chloropropan-2-yl)naphthalene for each method respectively

2.16.4 Effects of Brønsted Acids

Brønsted acids for *Method A* were chosen among sulfuric acid, *p*-toluenesulfonic acid, 10-camphorsulfonic acid, boric acid and sulfamic acid.

2.17 The Sulfenyl Analogs

2.17.1 Preparation of Reagents

Thiophenol, *p*-Thiocresol and 1-Thionaphthol

Method A (Sandmeyer)

Aniline, 4-methylaniline or 1-naphthylamine (1 eq) was diazotized using solution of sodium nitrite (2 eq) in 2M hydrochloric acid at 0^oC. Sodium hydrogen sulfide (1.2 eq) is added. The resulting precipitate was collected.

Method B (Phosphine)

Phenylsulfonyl chloride, *p*-toluenesulfonyl chloride or 1-napthalenesulfonyl chloride (1 eq) was reacted with triphenylphosphine (3 eq). The resulting mixture was separated using column chromatography.

2.17.2 1-Alkyl-3-(phenylthio)-1*H*-indole

Indole (1 eq) and thiophenol (1.5 eq) was dissolved in methanol. Iodine (0.2 eq) was then added. The resulting brown solution was shaken periodically and was

kept in darkness at room temperature for 1 day. The precipitate formed was filtered and discarded. The resulting liquid was then evaporated and purified using column chromatography.

2.17.3 1-Alkyl-3-(4-methylphen-1-ylthio)-1*H*-indole

Using the same protocol as described for 1-alkyl-3-(phenylthio)-1*H*-indole, with *p*-thiocresol as a reagent.

2.17.4 1-Alkyl-3-(naphthalen-1-ylthio)-1*H*-indole

Using the same protocol as described for 1-alkyl-3-(phenylthio)-1*H*-indole, with 1-thionaphthol as reagent.

2.18 The Sulfonyl Analog

2.18.1 Preparation of Reagents

Naphthalen-1-sulfonic Acid

Naphthalene (1 eq) was melted in water bath (90^{o}C), concentrated sulfuric acid (1.4 eq) is slowly added, with careful stirring. The reaction progress was checked by TLC. The product was then quenched and extracted from remaining naphthalene with sodium hydroxide solution and re-acidified to give white crystals of the sulfonic acid.

Naphthalen-1-sulfonyl Chloride

Naphthalene-1-sulfonic acid was added to thionyl chloride (excess) along with catalytic amount of DMF. Reflux at 80^{o}C for 5 hours. Excess thionyl chloride was distilled over and the product was recrystalized using hot hexane/THF mixture to give white solid of the sulfonyl chloride.

Sodium Bentonite

Bentonite (10g) was obtained from commercial pet-litter sand, listed bentonite as only ingredients. It was then pulverized and washed extensively with large amount of distilled water by stirring overnight and decanted. The washed bentonite (9.4g) was then basified by stirring in 5M NaOH solution for 1 day. It was then re-washed with distilled water and dried to give sodium bentonite (8.8g)

Iron-Pillared Bentonite

Sodium Bentonite was submerged into 3M iron(III) chloride solution and stirred overnight. The iron solution was then decanted and the bentonite are washed with water and dried. Then, it was packed into metal can and calcined at 400^{o}C

Aluminum-Pillared Bentonite

Using similar method to iron-pillared bentonite, but use 5M aluminum(III) chloride solution instead.

2.18.2 1-Alkyl-3-(phenylsulfonyl)-1*H*-indole

Method A (Oxone)

To 1-alkyl-3-(phenylthio)-1*H*-indole (sulfenyl) (1eq) solution in dichloromethane, Oxone^{TM} (2.5 eq) was added. The solution was stirred at room temperature for 3 hours and filtered. The solution was crystallized to give the sulfone as white solid.

Method B (Grignard)

To a newly prepared methylmagnesium iodide (1.2 eq) in flask sealed with nitrogen atmosphere, indolic THF solution (1 eq) was then added, yielding precipitate of indolylmagnesium iodide. Then phenylsulfonyl chloride is added dropwise to the solution. The resulting thick oil was collected.

Method C (Friedel-Crafts)

To the solution of indole (1 eq) in dichloromethane, either anhydrous $AlCl_3$, $FeCl_3$, $BiCl_3$ or $InCl_3$ was subsequently added. Phenylsulfonyl chloride (1.5 eq) was then added and the mixture was brought to a reflux for 6 hours. Quenched with water, then extracted using dichloromethane, concentrated and separated using column chromatography.

Method D (Bentonite)

Bentonites were added to dichloromethane solution of indole (1 eq) in catalytic amount (10% w/w) followed by phenylsulfonyl chloride (1.5 eq). The mixture was then refluxed for 6 hours, filtered and collected.

2.18.3 1-Alkyl-3-(4-tolylsulfonyl)-1*H*-indole

Synthesized in similar fashion to 1-alkyl-3-(phenylsulfonyl)-1*H*-indole *Method C*, using toluenesulfonyl chloride as reagent.

2.18.4 1-Alkyl-3-(naphthalen-1-ylsulfonyl)-1*H*-indole

Synthesized in similar fashion to 1-alkyl-3-(phenylsulfonyl)-1*H*-indole *Method C*, using 1-naphthalenesulfonyl chloride as reagent.

CHAPTER III

RESULTS AND DISCUSSION

3.1 Preparation of Haloalkanes

An active cannabinoid requires the hydrophobic side chain in their structure according to the structure-activity relationship. In case of cannabimimetic indoles, a simple aliphatic alkyl chain ranging from 3-5 carbon atoms gives the promising binding efficacy[47], thus the use of haloalkanes are nearly inevitable due to their simplicity. Although straight-chain haloalkanes are commercially available, their chemistry and preparations are still of interests.

Table 3.1 Preparation of Haloalkanes

Entry	ROH	Product	Isolated Yield (%)	Boiling Point (^oC)	Ref. Boiling Point (^oC)[51]
1	C_3H_7OH	C_3H_7Cl	33	45	46.7
2	C_3H_7OH	C_3H_7Br	45	71	71.0
3	C_3H_7OH	C_3H_7I	95	103	102.5
4	C_4H_9OH	C_4H_9Cl	41	78	79.0
5	C_4H_9OH	C_4H_9Br	33	102	101.4
6	C_4H_9OH	C_4H_9I	92	128	130
7	$C_5H_{11}OH$	$C_5H_{11}Cl$	65	106	107
8	$C_6H_{13}OH$	$C_6H_{13}Cl$	59	129	135

Using Taboonpong and Chavasiri's method[52], the hexachloroacetone was found to instantaneously react when adding to the solution of triphenylphosphine in alcohol. (Entry 1,4,7 and 8). The crude mixture also turned into dark solid clump, so the resulting chloroalkane was distilled out. The first fraction collected at 39.5^{o}C was discarded (dichloromethane). The second fraction was the haloalkane product, which each was collected at its boiling point. Distillation was stopped after the second fraction ceased.

In case of bromination (Entry 2 and 5), the reaction was performed at much smaller scale, but the black-brown coloration still formed and the bromoalkanes need to be distilled out.

Both distilled chloroalkanes and bromoalkanes prepared by this method smells strongly of hydrohalic acids, so resulting fraction was shaken with $NaHCO_3$ solution to remove the extra acid. The ^{1}H NMR sampling of the haloalkanes shows the pure product.

Unlike chloroalkanes and bromoalkanes, the iodo- counterpart cannot be prepared using similar manner as the analogous iodinating agent are either too unstable (hexaiodoacetone, triiodoacetamide) or too low reactivity (iodoform), so the iodoalkane counterpart was prepared using *Finkelstein reaction*[53], which uses the principle of halogen exchange via S_N2 pathway:

$$RX + Y^{\ominus} \rightleftharpoons RY + X^{\ominus}$$

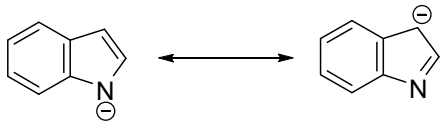
Owing to the solubility of sodium iodide in acetone, and not sodium chloride or bromide, the equilibrium strongly shifts to the product side. The reaction was found to work well with all haloalkanes studied.

$$RX\,(acetone) + NaI\,(acetone) \longrightarrow RI\,(acetone) + NaX(s)$$

The product after evaporated contains a trace amount of free iodine from aerial oxidation of iodide ion in solution, this can be removed by shaking with freshly prepared sodium thiosulfate solution.

3.2 *N*-Alkylation of Indole

The *N*-alkylindoles are important chemicals required for later experiments, so they were synthesized using standard base-promoted reaction. In this reaction, indole was deprotonated to an indolyl anion, which has a stabilizing resonance structures as shown:



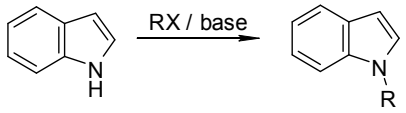
indol-1-yl indol-3-yl

Figure 3.1 Predominant Resonance Structures of Indolyl Anion

The regioselectivity of this reaction can be controlled using a proper counter ion of the base. Using a 'hard' counter ions like Na^+ or K^+ exclusively give the 1-alkylated product, while a 'softer' counter ions like Mg^{2+} or Ca^{2+} tend to give 3-alkylated products[54].

As there are several methods of *N*-alkylation, the experiments were carried off to investigate the practical advantages and disadvantages of each methods.

Table 3.2 *N*-Alkylation of Indoles



Entry	RX	Method	Reaction Time (min)	Isolated Yield (%)
1	CH_3I	A	5	99
2	CH_3I	B	240	65
3	CH_3I	C	30	27
4	CH_3I	D	60	81
5	C_3H_7Cl	A	240	85
6	C_3H_7Br	A	150	95
7	C_3H_7I	A	45	93
8	C_4H_9Cl	A	150	82
9	C_4H_9Br	A	60	89
10	C_4H_9Br	B	480	51
11	C_4H_9Br	D	120	70
12	$C_5H_{11}Br$	A	60	96
13	$C_5H_{11}Br$	B	480	75
14	$C_5H_{11}Br$	D	120	52
15	$C_5H_{11}Br$ + KI (10% mol)	D	90	64

The reaction with NaH *(Method A)*, undoubtedly, was the fastest and highest yielding due to the strong basicity of hydride ion. The resulting 1-indolylsodium can even be separated out as white solid. According to TLC checkups, the reaction was done before the mixture reached room temperature (30^{o}C) after taken off the ice bath.

By changing to weaker base like hydroxide *(Method B)* the reaction proceeded much slower as NaOH has low solubility in DMF and the reaction occurred only at

the surface. Heat was needed to be applied to drive the reaction. The reaction gave worse yields comparing to hydride, but were still acceptable. Oxygen must be flushed off completely as this method tends to give indigo from oxidation of indolyl anion, which in turn renders the product green, then blue.

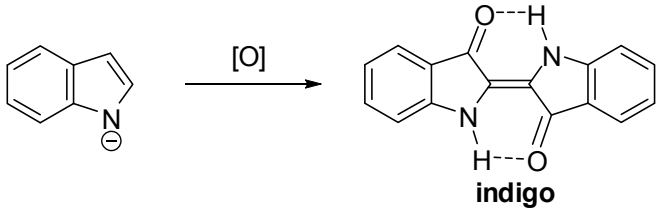


Figure 3.2 Formation of Indigo by Aerial Oxidation

By using ethanolic KOH *(Method C)*, it was found that this method gave not so good yield, and most of the indole were left unreacted, and some was oxidized.

The last method, in entry 4, 11 and 14 *(Method D)* used carbonate, which is weakest base comparing to others used in the reaction. However, the yield was satisfactory, although not comparable to the hydride method. This method also provides an advantage of easiness in work-ups, and used the most benign reagents. Tetrabutylammonium ion seems to play a crucial role as a phase transfer catalyst in this reaction. Another independent reaction was tested without the addition of tetrabutylammonium chloride and was found to give virtually no yield.

In case of *Method A* and *Method D*, the work-up is easy and need no more purification. However by using *Method B* and *Method C*, a chromatographic separation is needed. An air pump to facilitate the flow is recommended to use with this separation as indole is reactive with the acidic silanol group present in silica yielding red by-products, and an electron-rich alkylindoles are even more reactive toward this.

There is a note that using *Method B*, the product obtained has a strong and numb fecal-like smell which lingered for hours, whereas *N*-alkylindoles are almost odorless, this might be owing to the 3-alkylated product which forms in small amount.

The 3-alkylated indoles have similar structure to skatole, which occurred naturally and gives feces the stench odors[55]. The product prepared from this method also seemed to attract some insects. However, even if these existed, the concentration must be low that they did not show their signal on ^{1}H NMR at all.

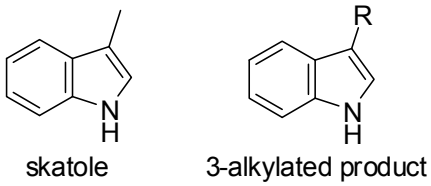


Figure 3.3 Structural Comparison Between Skatole and 3-Alkylindoles

The effect of leaving groups on haloalkanes can be noted from the reaction time before completion as indicated by TLC. The iodide counterpart provided the faster reaction time, as can be seen by comparing entry 6 and 7. Methyl iodide (entry 1) reacted the fastest. It is noted that by adding KI (entry 15) to other alkyl halides in the reaction involving *Method D* accelerated the reaction. This can be explained by halogen exchange between other halides and iodide *in situ*.

The *N*-alkylindoles are characterized using ^{1}H NMR as the broad N<u>H</u> peak ought to disappear from the product. (Appearing at 8.10 ppm). Protons on alkyl group adjacent to nitrogen atom shows the triplet splitting pattern at 4.12 ppm, which can be used to distinguish the product from haloalkanes used as reactant. All aromatic protons do not change their chemical shifts much despite the attached alkyl group.

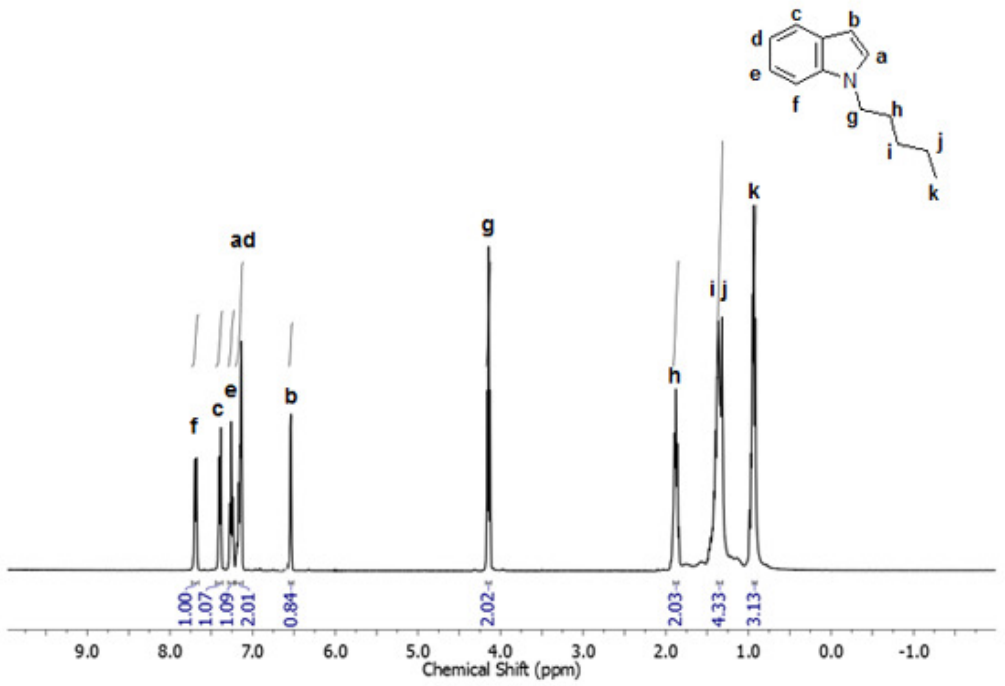


Figure 3.4 ^{1}H NMR Spectrum of N-pentylindole

***N*-methylindole** ^{1}H NMR ($CDCl_3$):

(aromatic) 7.71 (d, 1H), 7.41 (d, 1H), 7.24 (t, 1H), 7.15-7.20 (m, 2H), 6.55 (m, 1H)

(aliphatic) 3.90 (s, 1H)

***N*-ethylindole** ^{1}H NMR ($CDCl_3$):

(aromatic) 7.71 (d, 1H), 7.41 (d, 1H), 7.24 (t, 1H), 7.15-7.20 (m, 2H), 6.52 (m, 1H)

(aliphatic) 4.22 (q, 2H), 1.75 (t, 3H)

***N*-propylindole** ^{1}H NMR ($CDCl_3$):

(aromatic) 7.71 (d, 1H), 7.40 (d, 1H), 7.22 (t, 1H), 7.15-7.20 (m, 2H), 6.53 (m, 1H)

(aliphatic) 4.15 (t, 2H), 1.88 (m, 2H), 1.30 (t, 3H)

***N*-butylindole** ^{1}H NMR ($CDCl_3$):

(aromatic) 7.71 (d, 1H), 7.38 (d, 1H), 7.22 (t, 1H), 7.15-7.20 (m, 2H), 6.53 (m, 1H)

(aliphatic) 4.15 (t, 2H), 1.88 (m, 2H), 1.25-1.5 (m, 2H), 0.97 (t, 3H)

***N*-pentylindole** ^{1}H NMR ($CDCl_3$):

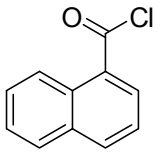
(aromatic) 7.71 (d, 1H), 7.40 (d, 1H), 7.23 (t, 1H), 7.15-7.20 (m, 2H), 6.55 (m, 1H)

(aliphatic) 4.20 (t, 2H), 1.87 (m, 2H), 1.25-1.5 (m, 4H), 0.97 (t, 3H)

***N*-hexylindole** ^{1}H NMR ($CDCl_3$):
(aromatic) 7.71 (d, 1H), 7.38 (d, 1H), 7.22 (t, 1H), 7.15-7.20 (m, 2H), 6.55 (m, 1H)
(aliphatic) 4.17 (t, 2H), 1.88 (m, 2H), 1.25-1.5 (m, 6H), 0.97 (t, 3H)

Although all newly prepared *N*-alkylindoles are colorless, these compounds generate highly-colored decomposition product readily upon exposure to air at room temperature. *N*-butylindole and *N*-pentylindole were found to discolor within few hours of standing in open air (from colorless to green, then red, then dark brown). Thus, these compounds must be kept airtight until the time of use.

3.3 Synthesis of Naphthalene-1-carbonyl Chloride



Bicyclic system with π-bonds such as naphthalene moiety provides a structure for cannabimimetic indoles as interacting part (*via* π-stacking interaction in the receptor) and are the most used group in the study of cannabimimetic indole for the previous SAR exploration. So the acid chloride of naphthalene is investigated.

The direct bromination with liquid bromine gives several products, which one of them contained the desired 1-bromonaphthalene. It was found that temperature plays a crucial role in determining the outcome of this reaction. Reacting at low temperature (80^oC) gives mainly 1-bromonaphthalene, while reacting at higher temperature gives more 2-bromonaphthalene. This shows the effect of kinetics *versus* thermodynamics in determining the outcome of the reaction. (31% yield)

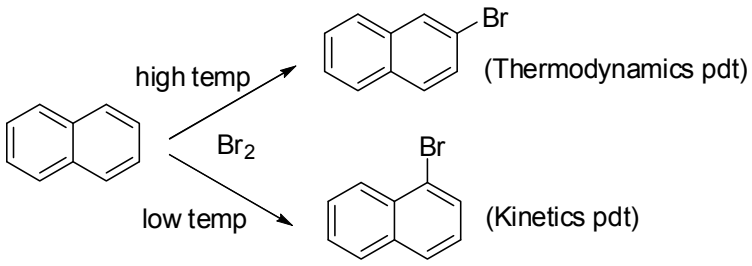


Figure 3.5 Thermodynamics and Kinetics Products from Napthalene Bromination Reaction

The separated 1-bromonaphthalene is then reacted with cyanide ion, which provides the nucleophile for nucleophilic aromatic substitution (S_NAr) reaction. Catalytic amount of CuCN (1-5% w/w) improves the reaction time from 12 hours to 4 hours which may accounts from the ability of copper in attracting bromine as ligand, as compared to sodium. (50% yield)

The nitrile was then separated and hydrolysed in strong basic solution. THF/water mixture was chosen because the ability to solute both the nitrile and KOH used. After the reaction, the naphthalenecarboxylate anion in the aqueous phase is re-acidified and crystalised out as white crystal. (92% yield)

The ^{1}H NMR shows signal of alpha proton of 7-position of naphthalene-1-carboxylic acid at 9.10 ppm. Protons in the *ortho*- and *para*- position to the carboxylic group were upfielded to 8.43 ppm and 8.11 ppm respectively. Proton signal from the carboxylic group could not be observed due to hydrogen-deuterium exchange with the used solvent. Other aromatic protons are found in the range of 7.5 – 8.0 ppm. The observed spectrum is in agreement with reference compound.

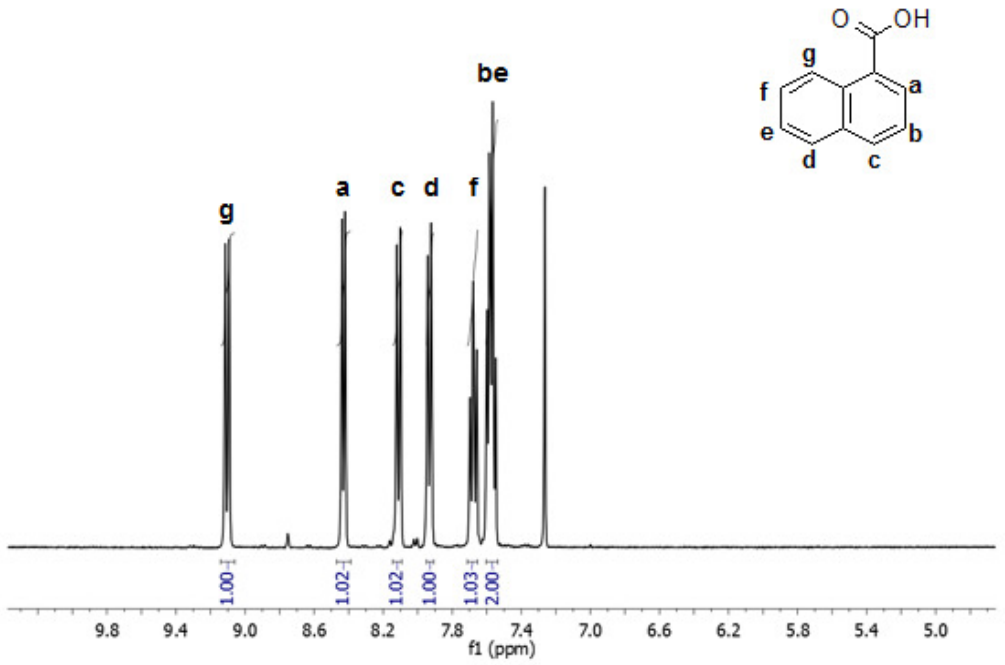


Figure 3.6 ^{1}H NMR Spectrum of Naphthalene-1-Carboxylic Acid

Naphthalene-1-Carboxylic Acid ^{1}H NMR ($CDCl_3$):
9.10 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.93 (d, 1H), 7.68 (t, 1H), 7.54-7.60 (m, 2H)

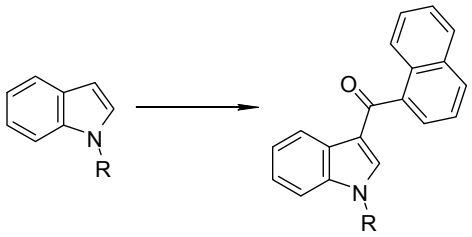
The carboxylic does not dissolve in $SOCl_2$ at room temperature, but reacts at approximately 65^{o}C to form the acid chloride as pale yellow oil. The removal of excess thionyl chloride was needed, as remaining traces of thionyl chloride would react violently with indole at the used temperature forming green gum.

3.4 3-Acylation of Indole

The acylation reaction needs a regioselectivity control more than the alkylation, as the result from counter ions seemed to give more differed products in this case. Indolylsodium, though easily prepared as described was not suitable for this reaction as Na^{+} favors the 1-position. A Grignard would deprotonate indole to give indolylmagnesium halide, which favors the 3-position. However there is a report that reaction is not quite yield-effective, even when transmetallated to indolylzinc[54,56].

On the other hand, Friedel-Crafts reaction is one of the most extensively used reactions to introduce the acyl group onto the aromatic moiety. However, the reaction on indole gives unimpressive yield due to the by-product formed. As indole is an acid-sensitive moiety, it captures H^+ released from Friedel-Crafts reaction forming the indolium cation, which in turn leads to polymeric by-products.

Table 3.3 3-Acylation of Indoles



Entry	Solvent	Lewis Acid		Time (hr)[a]	Isolated Yield (%)
		Type	Amount (eq)		
1	DCM	$AlCl_3$	2.2	0.5	41
2	DCM	$InCl_3$	0.2	4	50
3	DCM	$FeCl_3$	2.5	12	15
4	DCM	$Fe(acac)_3$	2.5	12	trace[b]
5	DCM	$FeCl_3$	2.5	72	21
6	DCM	$TiCl_4$	2.2	0.5	28
7	DCM	$BF_3.Et_2O$	2.0	0.5	20
8	DCM	$ZnCl_2$	2.0	6	0
9	DCM	$ZnCl_2$/pyridine	2.0[c]	6	15
10	DCM	$InCl_3$	1.0	2	62
11	DCE	$InCl_3$	1.0	2	43
12	DCE	$AlCl_3$	2.2	0.5	39
13	hexane	$AlCl_3$	2.2	12	0
14	chloroform	$AlCl_3$	2.2	1	36
15[d]	DCM	$AlCl_3$	2.2	0.5	66
16[e]	DCM	$AlCl_3$	2.2	0.5	19
17[d,e]	DCM	$AlCl_3$	2.2	0.5	32

a) stopped upon completion or no further change as indicated by TLCs *b)* not isolated

c) as $Zn(py)_2Cl_2$ complex. *d)* without inert atmosphere *e)* using *N*-pentylindole instead of plain indole

Comparing between each Lewis acid (entry 1-7), it was found that $AlCl_3$ and $InCl_3$ resulted in notably higher yield comparing to the other acids tested. In this case, $AlCl_3$ reacted stoichiometrically with the reactants, one part reacted with the acid chloride forming the acylium ion intermediate, and the other formed indole-aluminum complex[54,57] which acts as a synthon for indolyl anion. $InCl_3$, on the other hand, was found to react catalytically as can be seen from the amount used (entry 2). It also offers an easy work-up by washing with water.

Despite the report that $InBr_3$ can be used with higher yield[58], the chloro-counterpart was failed to reproduce the result. Addition of more $InCl_3$ to the reaction raised the yield (entry 10 and 11), but not so notably comparing to the extra amount of catalyst needed.

Iron salts reacted very slowly and reflux is needed after the addition. The yield was not good. In the case of acetylacetone complex (entry 4) there was no product at all which indicates the absence of Lewis acid center in the structure of $Fe(acac)_3$. The yield was similar in case of $TiCl_4$ and $BF_3.Et_2O$.

With $ZnCl_2$, the salt did not dissolve at all thus giving no yield, however by an addition of pyridine to form a $Zn(py)_2Cl_2$ complex which had some solubility in the reaction mixture, some of the acylated indole was formed. (entry 9)

Although $AlCl_3$ is avoided in former synthesis of cannabimetic indoles owing to the acidity destroying indole, it is still a promising reagent as it overcomes the yield from other metals. There are also published researches on successfully using $AlCl_3$ on indole with either side product suppressed by nitromethane[59] or involve the use of ionic liquids[60-61]. $AlCl_3$ also has an advantage on the workup step due to its amphotericity, as it can be removed either by using acid (as aluminum(III); Al^{3+}) or base (as tetrahydroxoaluminate(III); $Al(OH)_4^-$), unlike Fe salt which becomes insoluble hydroxides upon quenching.

According to entry 16 and 17 the *N*-alkylindole suffers oligomerization more than plain indole (entry 1). Despite having the alkyl groups, which is activating group and, in theory, should facilitate the reaction progress. The *N*-alkylindoles are so electron rich as they accept protons readily and become an indolium ion, which is unreactive toward the Friedel-Crafts reaction.

The reaction was tracked using TLC and reaction times were optimized. It is found that leaving the reaction for too long indeed lower the yield as the naphthoyl moiety started to become polymerized. Solvent had not much effect on this reaction (entry 1, 12 and 14) except for that in hexane (entry 13) the reaction did not proceed at all, this might be due to the solubility of the reactants, along with the dipole moment of the solvent used. Hexane is too nonpolar to stabilize a charge of the acylium ion.

As observed during experimentation, order of addition played an important role in this reaction (entry 1 *versus* 15 and 16 *versus* 17) as both methods gave the crude which looked the same (brown-red). But after separation, *Method A* gave comparably low yield comparing to *Method B*. The red coloration seemed to mask other colors which then made judging by plain eyes impossible. Computer-enhanced TLCs (Figure 3.7) of the crude using both methods agree with this result, which clearly shows the difference in proportions between each spot. Product peaks are marked with X's.

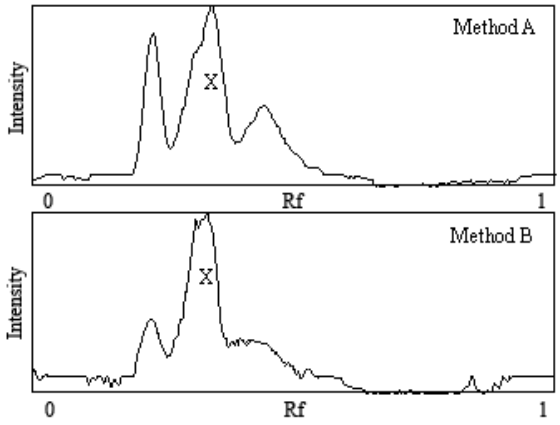


Figure 3.7 TLC Comparison of Indole Acylation with Method A and Method B

Moreover, a similar reaction set-up with open air gave somewhat better yield comparing to ones under nitrogen atmosphere (entry 15 and 17). This unusual phenomenon could be explained from the reaction itself. The *Friedel-Crafts*-type reaction gives of hydrohalic acid fumes after the reaction. In a sealed, nitrogen filled atmosphere, the acidic fumes accumulated and chewed up the unreacted indoles, which lowered the yield by polymerizing them to red sticky solid. By opening the reaction vessel to air, these acid fumes could escape out of the reaction, thus enhancing the yield somewhat.

The ^{1}H NMR spectra can be identified by the disappearance of the peak of a proton attached to 3- position of indole (at average 6.5 ppm), which confirms the position of the acyl group. The spectra also shows the downfield shifts on all over indole ring of the 3-acylindole comparing with indole. This is attributed from the effect of electron withdrawing property of the acyl (naphthoyl) group on the indole. The spectra also show the most downfield proton at naphthalene alpha position at 8.19 ppm and 8.52 ppm. In case of the reaction with plain indole, the present of broad NH peak indicates the regioselectivity of the acylation to the 3-position.

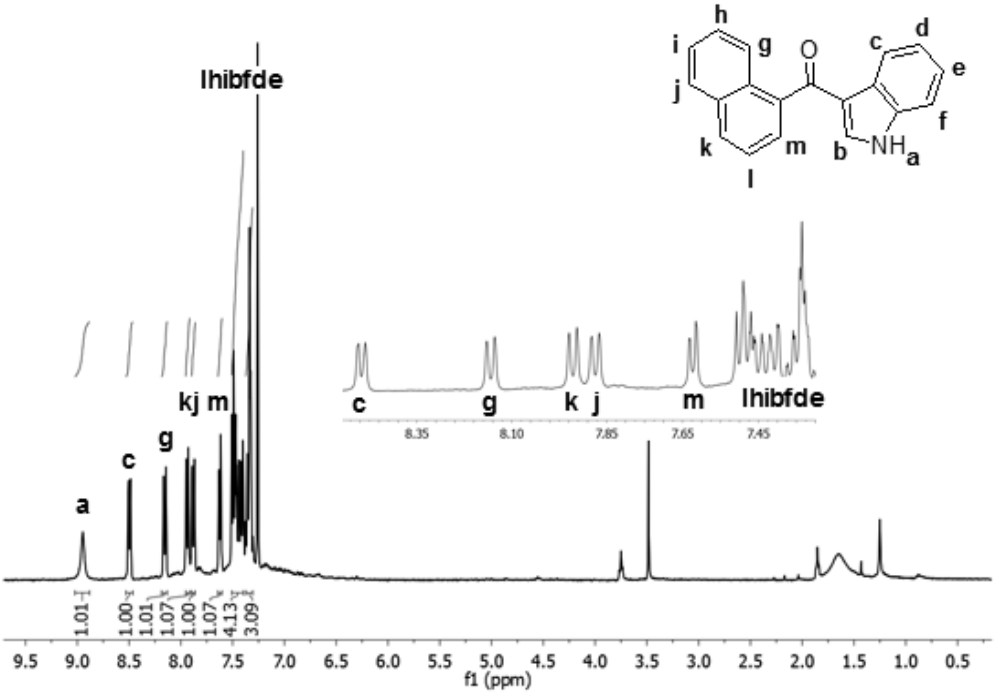


Figure 3.8 ^{1}H NMR Spectrum of 3-(1-Naphthoyl)indole

3-(1-Naphthoyl)indole ^{1}H NMR ($CDCl_3$):
8.97 (br, NH, 1H), 8.45 (m, 1H), 8.15 (m, 1H), 7.93 (d, 1H), 7.87 (d, 1H), 7.62 (dd, 1H), 7.30-7.56 (m, overlapped, 7H)

3.5 One Pot Synthesis of Cannabimimetic Indoles

Cannabimimetic indoles carry both the *N*-alkyl and 3-acyl in their structure. From the data obtained from prior experiments, the one-pot method on the synthesis of cannabimimetic indole was investigated.

There are two main routes toward the cannabimimetic indoles, with the switching order between the alkylation and acylation, which can be explained below:

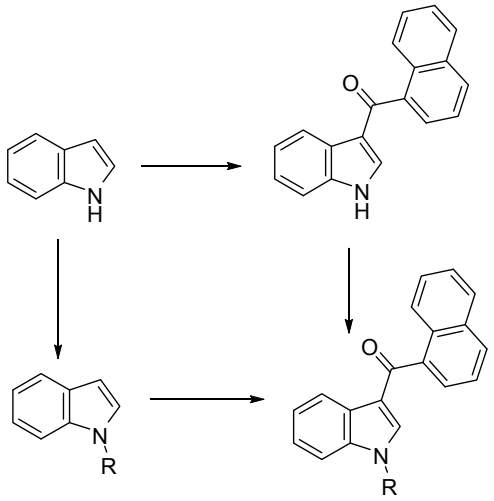


Figure 3.9 Cannabimimetic Indoles Synthetic Pathway

As *N*-alkylindoles tends to give oligomeric product as previously described, the pathway chosen was to 3-acylate first, followed by 1-alkylate. This is a good strategy as the electron withdrawing acyl group would render indolic NH to become more acidic, thus easier for base to deprotonate during the alkylation step, while avoiding the previously low-yielded conditions.

A method was then applied using prior observations to optimize the one-pot synthesis reaction of these cannabimimetic indoles, by continuously flowing nitrogen into the reaction as described in Chapter II, to help vent the acidic fume away from the reaction vessel. Although judging by visual appearance, the red-brown color intensity was not different, but according to TLC tests. This method effectively improved the final yield of the acylated products.

Some parts of red by-products were found to be washable with methanol, so individual tests were conducted to find the most suitable solvent, which dissolves a lot of red impurities but not as much 3-naphthoylindole. It was found that pre-chilled methanol/water mixture (85:15) at 0^{o}C is an effective washer. A repeated washing was done on crude 3-naphthoylindole using this mixture. The color then changed from red to brown to beige to off-white.

Iodine was applied to TLC plates in order to enhance the visibility of spots. Computer-processed TLC data also clearly indicates the disappearance of some red-colored by-products peaks, while retaining the desired product.

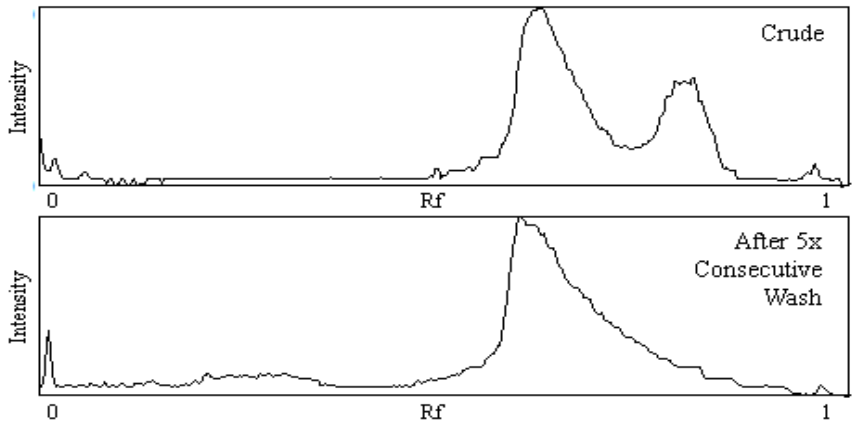
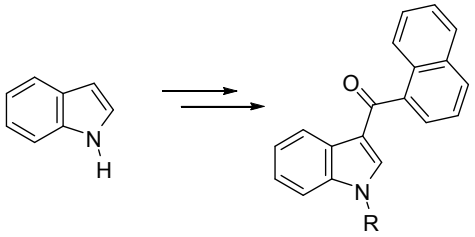


Figure 3.10 TLC Comparison between Crude and Washed Product

Alkylation can then be done smoothly using either *Method A* or *Method D*, which completes faster than on indole itself. The crude product can be recrystalized, but it is not necessarily as the ^{1}H NMR shows an acceptable purity to be used in further synthesis.

Table 3.4 One-pot Synthesis of Cannabimimetic Indole.



R	Isolated Yield (%)
CH_3	86
C_2H_5	84
C_3H_7	79
C_4H_9	63
C_5H_{11}	65
C_6H_{13}	53

All the cannabimimetic indoles (bearing this carbonyl group) have relatively the same chemical shifts on aromatic protons, varying only on the alkyl groups. The observed range of chemical shifts are in agreement with the reference[47].

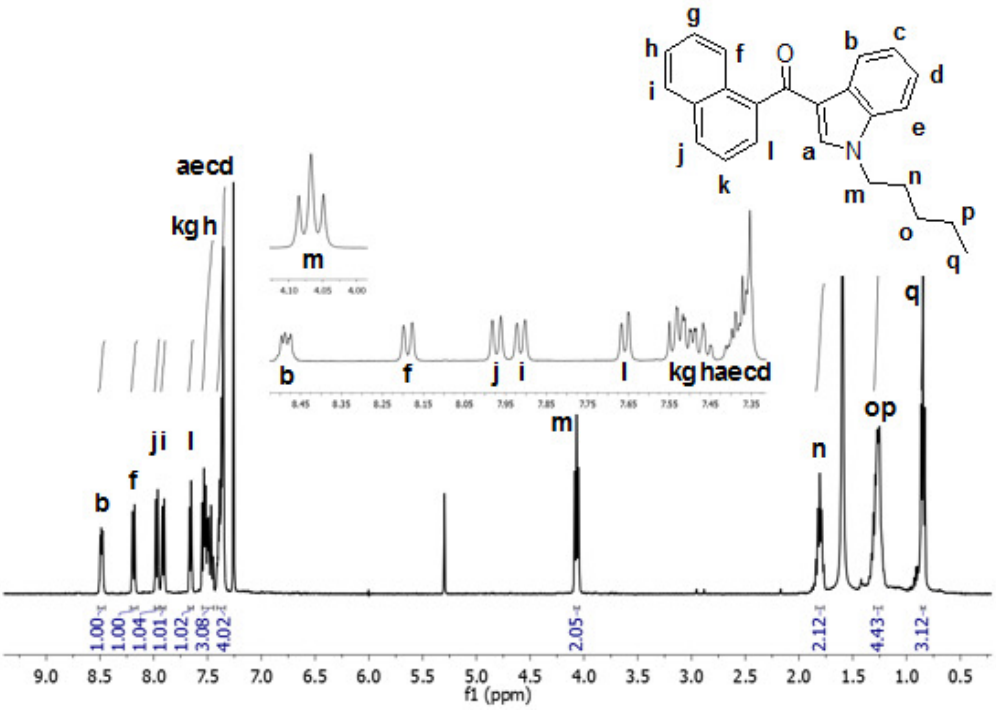


Figure 3.11 ^{1}H NMR Spectrum of Naphthalen-1-yl(1-pentyl-1H-indol-3-yl)methanone

Naphthalen-1-yl(1-methyl-1H-indol-3-yl)methanone ^{1}H NMR ($CDCl_3$):

(aromatic) 8.45 (m, 1H), 8.17 (d, 1H), 7.95 (d, 1H), 7.91 (d, 1H), 7.64 (dd, 1H), 7.43-7.56 (m, overlapped, 3H), 7.33-7.42 (m, overlapped, 4H)

(aliphatic) 3.78 (s, 3H)

Naphthalen-1-yl(1-ethyl-1H-indol-3-yl)methanone ^{1}H NMR ($CDCl_3$):

(aromatic) 8.45 (m, 1H), 8.19 (d, 1H), 7.95 (d, 1H), 7.92 (d, 1H), 7.64 (dd, 1H), 7.43-7.56 (m, overlapped, 3H), 7.33-7.42 (m, overlapped, 4H)

(aliphatic) 4.12 (q, 2H), 1.81 (t, 3H)

Naphthalen-1-yl(1-propyl-1H-indol-3-yl)methanone ^{1}H NMR ($CDCl_3$):

(aromatic) 8.47 (m, 1H), 8.17 (d, 1H), 7.96 (d, 1H), 7.91 (d, 1H), 7.64 (dd, 1H), 7.43-7.56 (m, overlapped, 3H), 7.33-7.42 (m, overlapped, 4H)

(aliphatic) 4.05 (t, 2H), 1.77 (m, 3H), 0.91 (t, 3H)

Naphthalen-1-yl(1-butyl-1H-indol-3-yl)methanone ^{1}H NMR ($CDCl_3$):

(aromatic) 8.45 (m, 1H), 8.19 (d, 1H), 7.95 (d, 1H), 7.92 (d, 1H), 7.64 (dd, 1H), 7.43-7.56 (m, overlapped, 3H), 7.33-7.42 (m, overlapped, 4H)

(aliphatic) 4.05 (t, 2H), 1.74 (m, 2H), 1.23 (m, 2H), 0.92 (t, 3H)

Naphthalen-1-yl(1-pentyl-1H-indol-3-yl)methanone ^{1}H NMR ($CDCl_3$):

(aromatic) 8.48 (m, 1H), 8.19 (d, 1H), 7.97 (d, 1H), 7.91 (d, 1H), 7.66 (dd, 1H), 7.43-7.56 (m, overlapped, 3H), 7.33-7.42 (m, overlapped, 4H)

(aliphatic) 4.05 (t, 2H), 1.74 (m, 2H), 1.26 (m, overlapped, 4H), 0.86-0.91 (m, 3H)

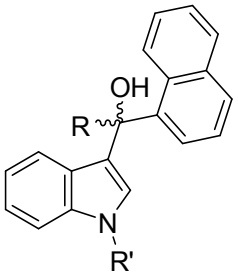
Naphthalen-1-yl(1-hexyl-1H-indol-3-yl)methanone ^{1}H NMR ($CDCl_3$):

(aromatic) 8.45 (m, 1H), 8.17 (d, 1H), 7.95 (d, 1H), 7.92 (d, 1H), 7.64 (dd, 1H), 7.43-7.56 (m, overlapped, 3H), 7.33-7.42 (m, overlapped, 4H)

(aliphatic) 4.05 (t, 2H), 1.74 (m, 2H), 1.22-1.32 (m, overlapped, 6H), 0.86-0.91 (m, 3H)

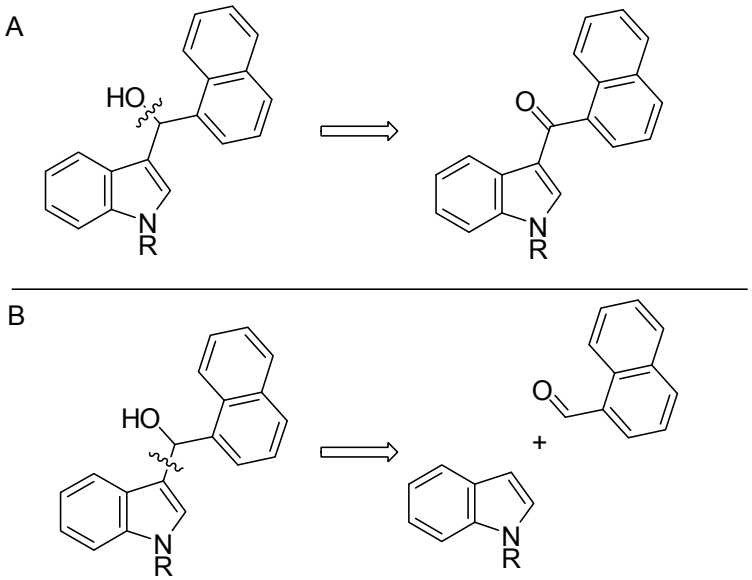
3.6 The Carbinol Analogs

In the carbinol analogs, the sp^2 ketone bridge was replaced with a sp^3 center, which alters the angle between two arene systems (indole and naphthalene), while retaining the capability of hydrogen bonding acceptors. The R group attached to the benzylic position should also bend the angle between the two arene systems depending on its steric demand. The hydroxyl group present in the molecule also contributes to polarity changes, which also played an important role in drug absorption and distribution.



Retrosynthetic pathway:

(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanol



With *Method A*, the ketone was reduced using conventional $NaBH_4$ as reductant. The reaction proceeded sluggishly to give the mixture of reactants and products and it was found that this reaction never went to completion, terminating at roughly 50% conversion. The excess addition of $NaBH_4$ (up to 20 eq), changing the solvent or bringing the mixture to the reflux gave no difference. The same condition was tested on smaller molecule (acetophenone and benzophenone) which gave the corresponding alcohol (1-phenylethanol and diphenylmethanol, respectively) rapidly in quantitative or near quantitative yield. This might be attributed to the hindrance of the bicyclic aryl groups.

TLC indicates a new product with different R_f value, which can be noticed with ease, as the product spot turns to bright pink color within few tens minute. However, if the crude mixture was purified using column chromatography, it was observed that the separated product decomposed rapidly within the range of few minutes changing from colorless to lime-green, then to purple. But storing the crude without separation lengthens the lifetime extensively. The crude ^1H NMR spectra shows two sets of compound, one being the starting material (ketone) and another is comparably shifted up-field. (alcohol). Integrals can be easily calculated from alpha proton of alkyl chain attached to nitrogen as there is 0.12 ppm difference in chemical shifts between the two, which is also used to see the conversion. The difference comes from the electronic configuration between the two. The ketone analogs have an electron withdrawing group on the ring, while the carbinol analogs are electron-donating.

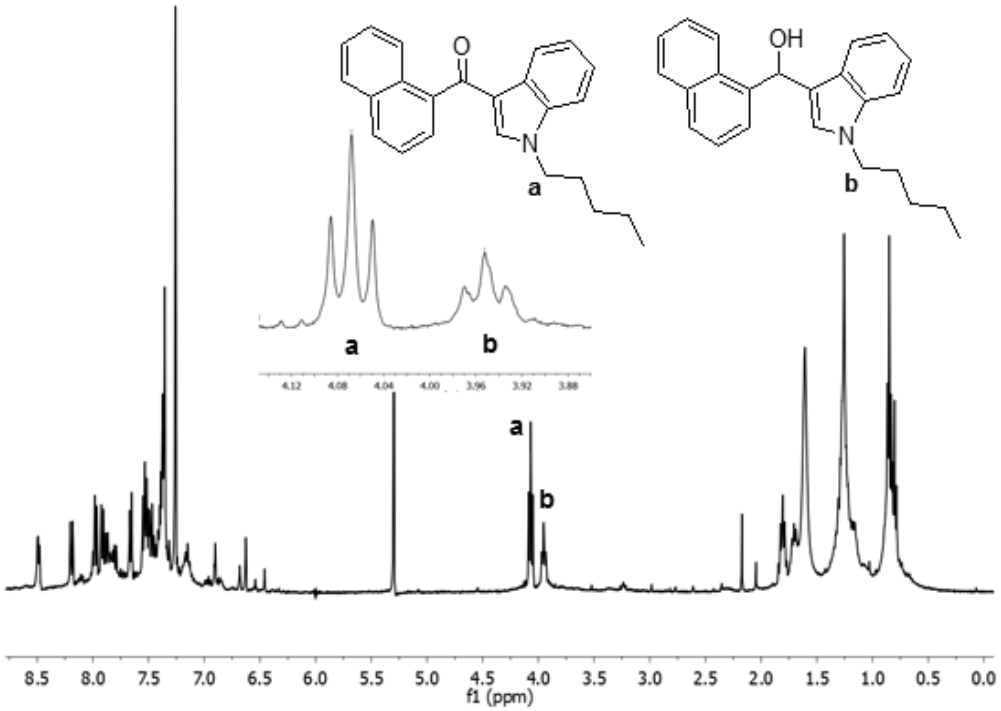


Figure 3.12 ^{1}H NMR Spectrum of Crude Carbinol Analog

The decomposition was tracked using ^{1}H NMR by comparing the mentioned alpha proton to observe the proportion between the alcohol and ketone. It was also found that the alcohol slowly converted back to ketone upon exposure to atmospheric oxygen. All carbinol analogs changed to violet-red rapidly upon exposure to silica, alumina, glass and even haloalkanes; would bring up a reasonable guess that the carbinol analog accepts H^{+} (or activates by Lewis acids) easily, and eliminate water forming a stable carbocation in the double benzylic position, which is stabilized by both of the aryl groups.

Method B involves the use of aromatic alhehyde and a Brønsted acid. The planned reaction is described as follow:

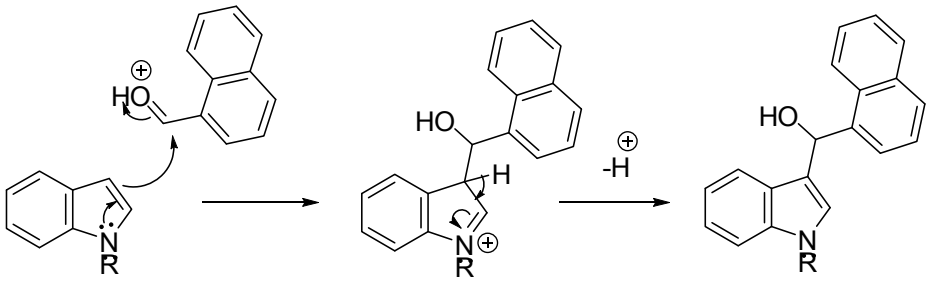


Figure 3.13 Condensation of Indole and Aldehyde Catalyzed by Acid

Interestingly, the reaction formed some heavy precipitate rapidly from dichloromethane after ten minutes of stirring at room temperature. So the collected precipitate was investigated and was found not to be the product. The ^{1}H NMR of this precipitate is shown below:

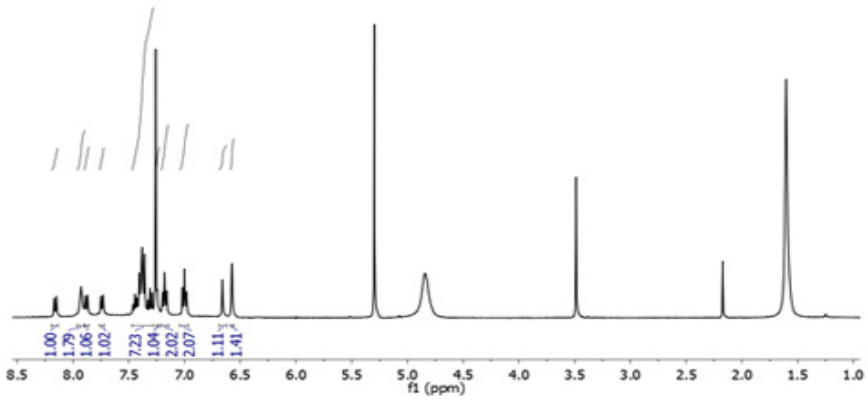


Figure 3.14 ^{1}H NMR Spectrum of the Precipitate

According to ^{1}H NMR, a broad singlet signal at 7.90 ppm showing that the indolic N<u>H</u> was still present, unsubstituded, along with the absence of 3-H indolic peak. Moreover, the alpha proton of naphthalene system, which could be easily noted at 8.18 and 7.75 ppm was found to be “too small” comparing to the indole ring which gave merely twice the peak area. The structure was predicted to contain two indoles moiety per one naphthalene moiety.

Other experiments were conducted to confirm the structure, by alkylation of the compound and re-checked the ^{1}H NMR to compare the integral of protons from each part (naphthalene, indole, alkyl). The resulting peaks confirmed the structure as bis(indolyl)naphthylmethane.

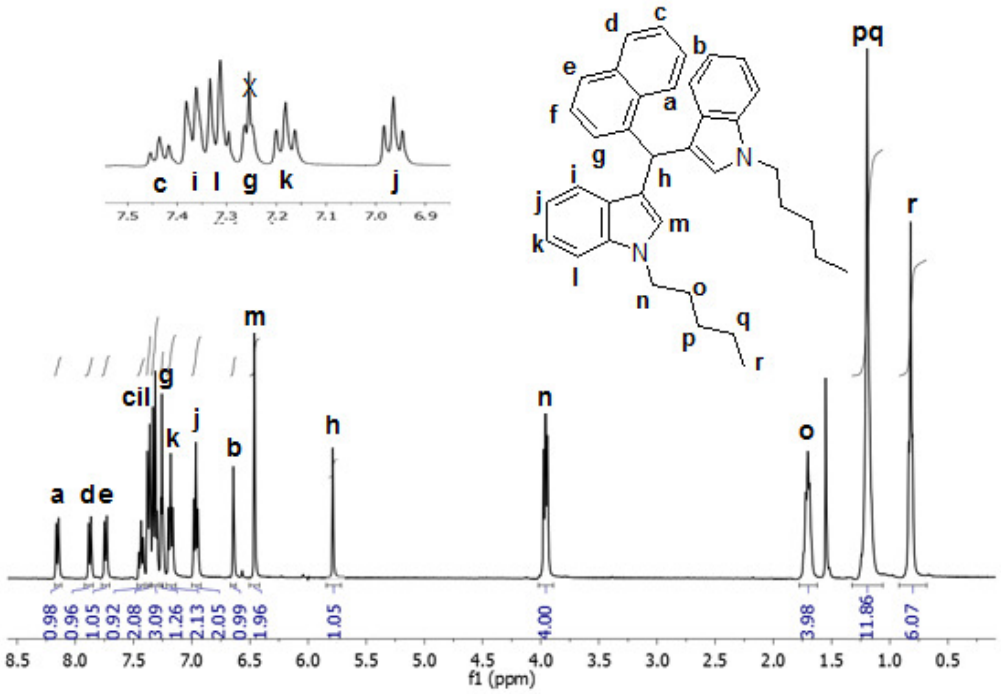


Figure 3.15 ^{1}H NMR Spectrum of *N,N*'-dipentylbis(indolyl)naphthylmethane

bis(indolyl)naphthylmethane ^{1}H NMR ($CDCl_3$):

(aromatic) 8.16 (d, 1H), 7.92 (br, NH, 1H), 7.88 (d, 1H), 7.74 (d, 1H), 7.44 (t, 1H), 7.37 (d, 2H), 7.28-7.34 (m, 3H), 7.25 (d, 1H), 7.18 (d, 2H), 6.96 (t, 2H), 6.64 (s, 1H), 6.46 (s, 2H)

(aliphatic) 5.56 (s, 1H)

***N,N*'-dipentylbis(indolyl)naphthylmethane** ^{1}H NMR ($CDCl_3$):

(aromatic) 8.16 (d, 1H), 7.88 (d, 1H), 7.74 (d, 1H), 7.44 (t, 1H), 7.37 (d, 2H), 7.28-7.34 (m, 3H), 7.25 (d, 1H), 7.18 (d, 2H), 6.96 (t, 2H), 6.64 (s, 1H), 6.46 (s, 2H)

(aliphatic) 5.58 (s, 1H), 3.95 (t, 4H), 1.70 (t, 4H), 1.20 (m, 12H), 0.82 (t, 6H)

***N,N*'-dihexylbis(indolyl)naphthylmethane** ^{1}H NMR ($CDCl_3$):

(aromatic) 8.16 (d, 1H), 7.88 (d, 1H), 7.74 (d, 1H), 7.44 (t, 1H), 7.38 (d, 2H), 7.28-7.34 (m, 3H), 7.25 (d, 1H), 7.18 (d, 2H), 6.95 (t, 2H), 6.64 (s, 1H), 6.46 (s, 2H)

(aliphatic) 5.57 (s, 1H), 3.95 (t, 4H), 1.71 (t, 4H), 1.20 (m, 14H), 0.82 (t, 6H)

Table 3.5 Formation of bis(indolyl)naphthylmethane

	Indole	**1-naphthaldehyde**	**Isolated**
R	**Amount (eq)**	**Amount (eq)**	**Yield (%)**[a]
H	1	1	92
H	1	2	90
H	1	5	94
H	1	10	92
H	1	20	95
C_5H_{11}	2	1	quant
C_6H_{13}	2	1	99

a) calculation based on indole

Trying to control the reaction to give the desired product, the ratio between indole and 1-naphthaldehyde was investigated, varying the ratio of indole and 1-naphthaldehyde to 1:2, 1:5, 1:10, 1:20 but it was found that this reaction gave exclusively the bis(indolyl)naphthylmethane product, where the remaining aldehydes were left over. This can be explained by two reasons.

First, because of the insolubility of product in dichloromethane, the precipitate crashed out thus driving the reaction forward to give the insoluble bis(indolyl)naphthylmethane product.

Second, as the reaction progressed in acidic media, the desired carbinol product would be protonated, to a double benzylic stabilized carbocation as described before. This carbocation have the structure of an vinylogous amide, which furthermore stabilizes this carbocation in the form of azafulvenium-like ion.

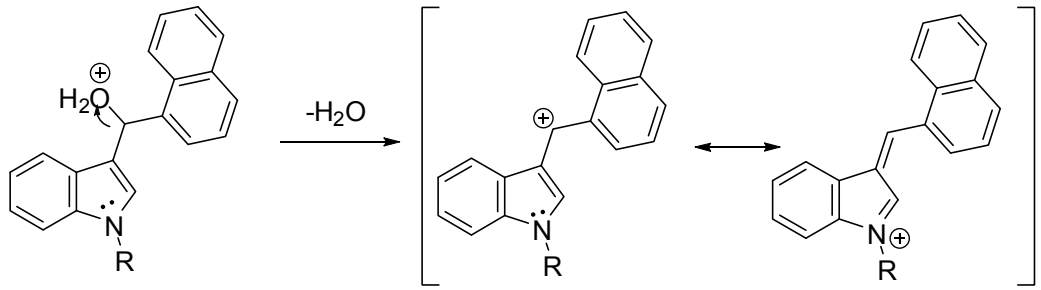


Figure 3.16 Formation of Stabilized Carbocation

The stabilized carbocation reacted with another indole molecule, which acted as a nucleophile, to form the bis(indolyl)naphthylmethane as product.

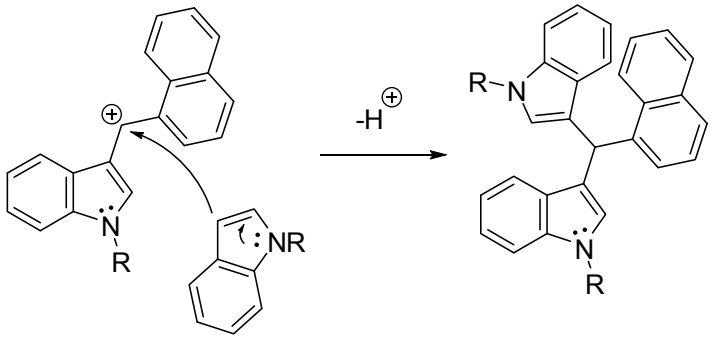
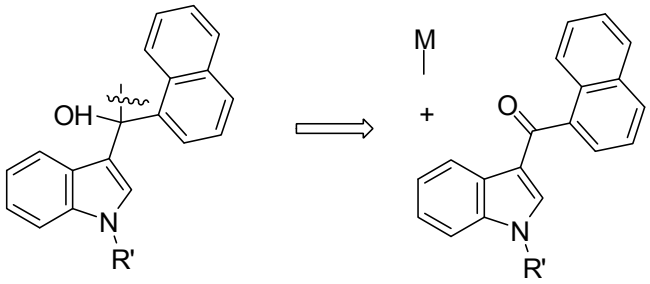


Figure 3.17 Secondary Indole Attack

This condition applies in case of both *N*-substituted and *N*-unsubstitued indole in similar manner. The yield in all case was high to quantitative.

Retrosynthetic Pathway:

1-(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)ethanol



From retrosynthetic point of view, this molecule could be prepared from reacting an organometallic (carbanion-like) with the ketone analog. So the experiment was carried out.

Grignard reagent was found to be very hard to initiate as several attempts had failed. Iodomethane was chosen in place of bromomethane as of ease of usage (liquid *versus* gas). Iodine crystal was sometimes helpful in initiating the reaction.

The reaction was rapid as it seemed to be complete instantly after the addition. After quenching, the crude gave a new spot which got stained by iodine in different color. The product in case of *N*-methyl and *N*-ethyl substituted indoles crystallized from the crude readily upon evaporation, while the longer *N*-alkyl chains tended to turn into oil.

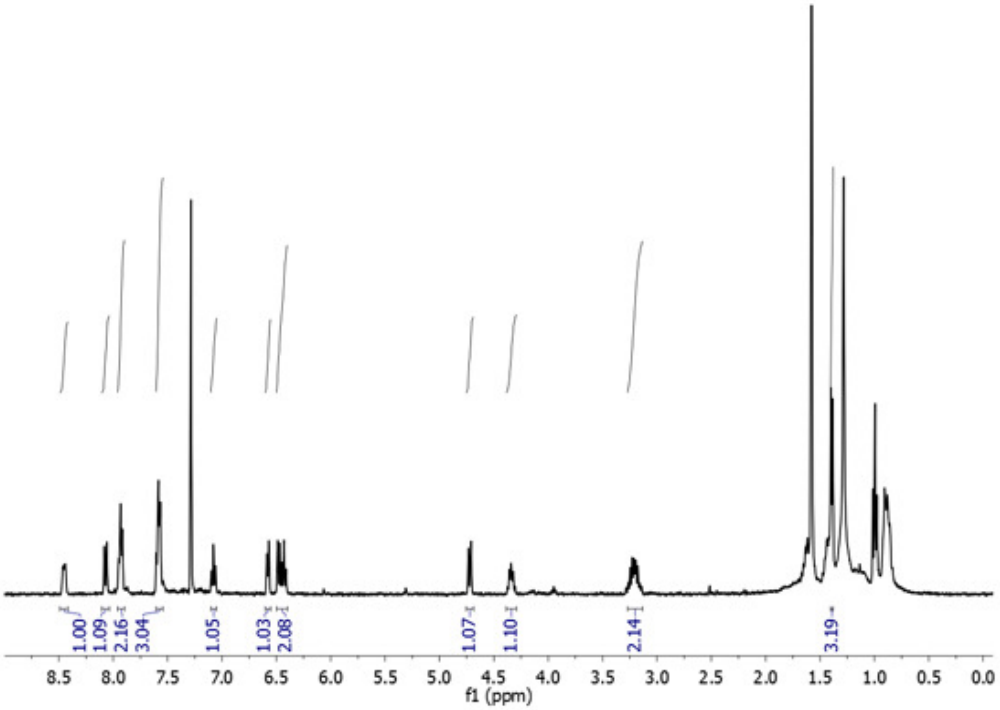


Figure 3.18 1H NMR Spectrum of Grignard-reagent Reaction Product

The ^{1}H NMR shows an interesting result, as the splitting pattern does not match the desired product. And unlike previous alcohol analog, this product does not seem to change color or decompose upon contacting to acids, and can be separated

readily using silica column. This does not agree with the previous explanations on the decomposition, as of being a pre-tertiary carbocationic center, it should even be more reactive.

To assist in interpreting the result, COSY experiment was then conducted to see the connected structures, combined with the ^{1}H NMR data, the structure could be described as having 2-methylindoline core as in 1-alkyl-3-(1-naphthoyl)-2-methylindoline.

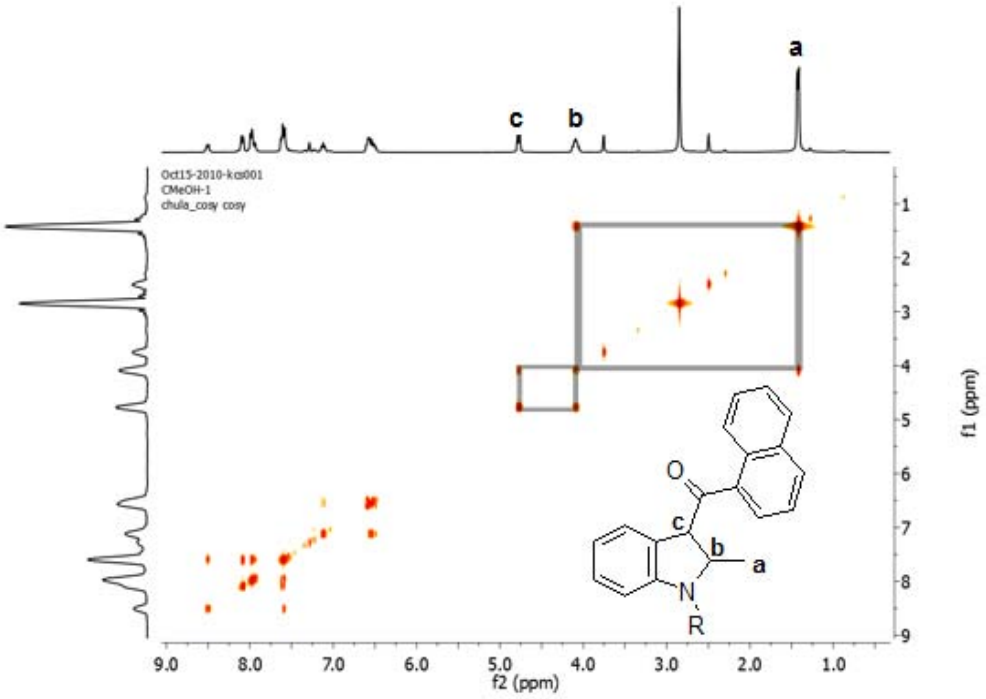


Figure 3.19 COSY Spectrum of
1-Methyl-3-(1-naphthoyl)-2-methylindoline

The results were unexpected, since Grignard reagents are strong nucleophiles and should readily attack the carbonyl functionality to a tertiary alcohol. Despite all of this, the Grignard reagent seemed to add its methyl at the 2-indolic position. The only product obtained was Michael-like 1,4-addition product. The reason might be due to the transition state, since the cannabimimetic indoles (ketone) are known to have 2 stable conformations, namely *s-cis* and *s-trans*, with low energy barrier between these conformations. In normal conditions, the cannabimimetic indole prefers *s-trans*

conformation. In contrast, the bond might get flipped to *s-cis* conformation during the Grignard reaction as this geometry can form a preferred six-membered ring transition state. The purposed mechanism is explained in Figure 3.20.

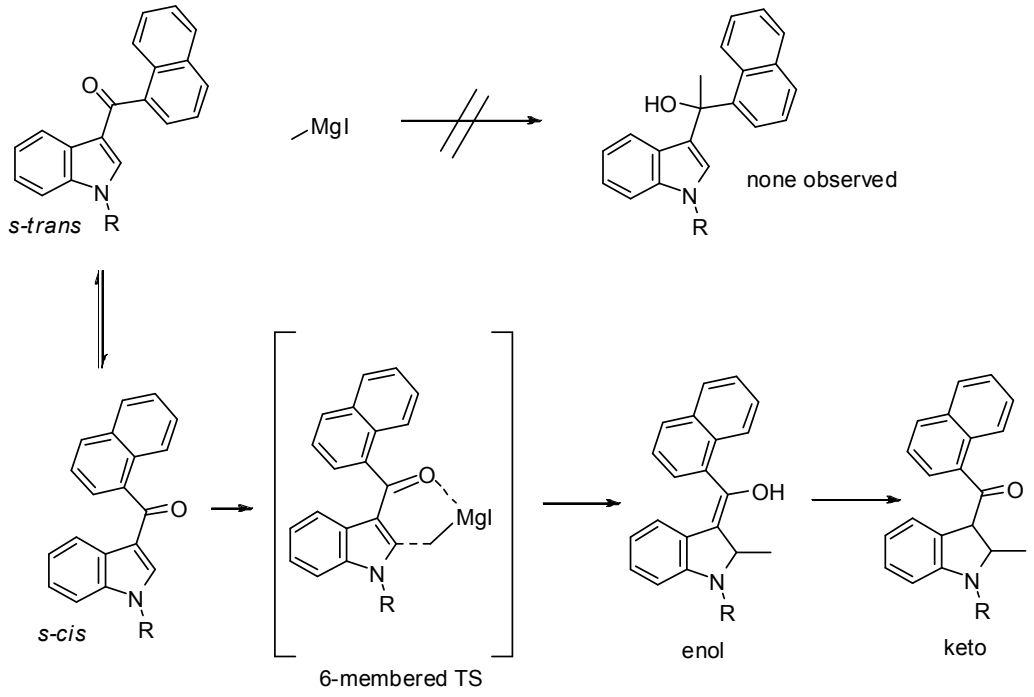
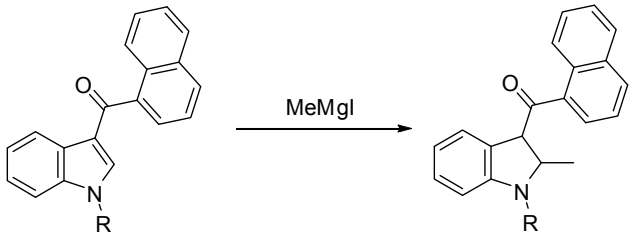


Figure 3.20 Formation of 2-Methylindoline Analogs in Grignard Condition

Cerium(III) chloride is known promote the regioselectivity of the reaction, by coordinating ketonic oxygen rendering the ketone more acidic. The salt is prepared by reduction of the common oxidant, cerium(IV) ammonium nitrate, with boiling chloride solutions. This gives off chlorine gas and $CeCl_3.nH_2O$, which can be dehydrated using $SOCl_2$.

Table 3.6 Formation of 2-methylindoline Analogs



Entry	R	CeCl3 (%mol)	Isolated Yield (%)
1	H	-	0
2	CH_3	-	quant
3	CH_3	10	quant
3	C_5H_{11}	-	95
4	C_6H_{13}	-	97

According to entry 1, an NH unsubstituted indole did not undergo such reaction, this could be explained by the acidity of NH which would get deprotonated in the Grignard condition forming a stabilized indolyl anion, thus stopping the reaction. All other *N*-alkyl group gave the methylindoline analog in high to quantitative yield within 10 minutes of reaction. This can be attributed to the reactivity of the methyl Grignard. Cerium chloride, however, was found not to help in directing the position to favor a 1,2-attack in this reaction, as the methylindoline can still be isolated in quantitative yield (entry 3).

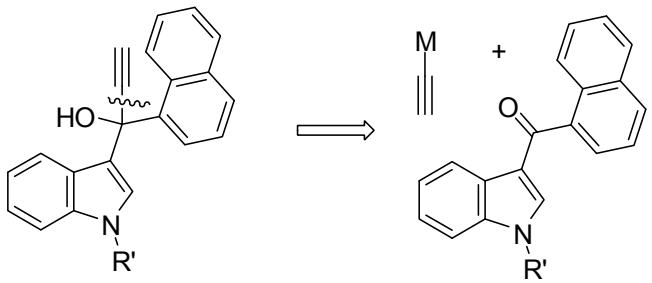
These 2-methylindolines may still possess the cannabinoid activity due to the similar 3D structures despite the missing p-orbitals which may affect the strength of π-stacking interaction inside the cannabinoid receptors. The 2-methyl analogs are well tolerated and show moderate activity in the indole core. As no methylindoline analogs have been tested for the activity yet, these can be used as excellent probes in studying the receptor affinity on whether the π-interaction on indole ring had contributed much

in receptor binding or not, by comparing the value from the known 2-methylindole compounds to these new 2-methylindoline compounds.

1-Methyl-3-(1-naphthoyl)-2-methylindoline ^{1}H NMR ($CDCl_3$):
(aromatic) 8.45 (m, 1H), 8.07 (d, 1H), 7.90-7.96 (m, 2H), 7.54-7.62 (m, 3H), 7.08 (t, 1H), 6.57 (d, 1H), 6.38-6.50 (m, 2H)
(aliphatic) 4.72 (d, 1H), 4.34 (m, 1H), 3.11-3.30 (m, 2H), 1.39 (d, 3H), 1.28 (s, 3H)
1-Pentyl-3-(1-naphthoyl)-2-methylindoline ^{1}H NMR ($CDCl_3$):
(aromatic) 8.45 (m, 1H), 8.08 (d, 1H), 7.90-7.96 (m, 2H), 7.54-7.60 (m, 3H), 7.08 (t, 1H), 6.57 (d, 1H), 6.38-6.50 (m, 2H)
(aliphatic) 4.72 (d, 1H), 4.34 (m, 1H), 3.93 (t, 2H), 3.11-3.30 (m, 2H), 1.58 (m, 2H), 1.39 (d, 3H), 1.28 (s, 3H), 1.23 (m, 4H), 0.83 (t, 3H)
1-Hexyl-3-(1-naphthoyl)-2-methylindoline ^{1}H NMR ($CDCl_3$):
(aromatic) 8.46 (m, 1H), 8.08 (d, 1H), 7.90-7.96 (m, 2H), 7.54-7.60 (m, 3H), 7.08 (t, 1H), 6.57 (d, 1H), 6.38-6.50 (m, 2H)
(aliphatic) 4.72 (d, 1H), 4.34 (m, 1H), 3.94 (t, 2H), 3.11-3.30 (m, 2H), 1.58 (m, 2H), 1.38 (d, 3H), 1.28 (s, 3H), 1.23 (m, 6H), 0.83 (t, 3H)

Retrosynthetic Pathway:
1-(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)prop-2-yn-1-ol

The retrosynthetic routes entailed the use of acetylide synthon, which can be described as:



The acetylide anion was prepared *via* different means, *Method A* seemed to be the direct method involving the use of calcium carbide and water, which they

produced acetylene gas. The commercial calcium carbide also emitted a small amount of hydrogen sulfide, phosphine and diphosphine, which could be removed by passing the crude acetylene gas through sulfuric acid trap, then water trap before leading them into the reaction[62].

Method B forms the acetylide salts of silver and copper, with different preparation between those compounds. Both silver and copper salt are primary explosive, which must be handled with care. The silver counterpart can be prepared from an acidic $AgNO_3$ solution. This will form the more stable double-salt of $Ag_2C.AgNO_3$ that can be more easily handled than the single acetylide salt which explodes on contact. However, this seems to be short-lived as they decompose from white to grey solid within a day. On the other hand, the copper salt can be prepared from the basic solution of ammonia, which then strongly precipitates the product due to the insolubility in this media.

The attempts to react the acetylide anion with the ketonic carbon have failed, as although new products can be detected using TLC, they then decomposed rapidly to green, then to black sticky tar with mixed composition. This green-black tar stuck onto silica surface and could not be easily eluted by organic solvents (dichloromethane, ethyl acetate, methanol, ether) and no product was obtained. There were some few reactants left in all of these reactions.

The ease in decomposition can be attributed to the sensitivity to acids in the same manner as other carbinol analogs, but these ones seemed to be the most reactive, as the position is double-benzylic, propargilic and tertiary center. The carbocation, if formed, should be greatly stabilized by this, thus longetivity gives rise to polymerization by attacking onto other reactive aromatic moieties (such as naphthalene ring) by S_EAr mechanism, or by cationic polymerization at alkyne part, or both.

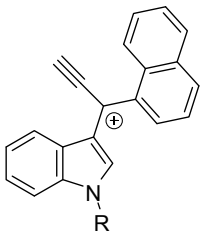
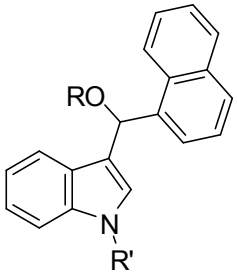


Figure 3.21 Proposed Structure of Carbocation Formed

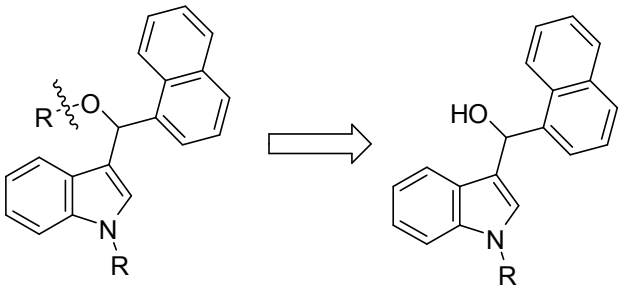
3.7 The Ether Analogs

Like the alcohol counterpart, ether functional group retains the capability of hydrogen bond acceptor of the molecule, but the polarity would decrease drastically in comparison with the alcohol.

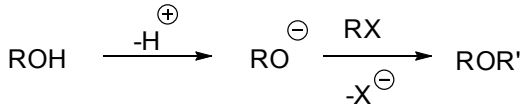


Retrosynthetic Pathway:

3-(alkoxy(naphthalen-1-yl)methyl)-1-alkyl-1H-indole



This involves the use of conditions of *Williamson ether synthesis*. The mechanism can be described as deprotonation of the alcohol to an alkoxide, followed by the attack with alkyl halide to yield the ether as the following equation:



As the carbinol analogs are unstable toward separations and storage, the ether analogs were directly synthesized from the crude of alcohol analog, in which they contained both alcohol and the unreacted indole. However the conversion could also be traced back regarding the different of chemical shifts of alpha protons on alkyl chain, and the newly added alkoxy protons which shows the different ratios.

Method A involved the use of sodium metal in place of potassium metal in the original Williamson ether synthesis. The reactivity of sodium toward this alcohol was surprisingly low. This could be attributed to the oxide or hydroxide coating on the surface of metallic sodium during the reaction, unlike potassium used in the original synthesis. The use of sodium amalgam is discouraged as it requires the use of mercury which is one of the accumulated biotoxins. So, the ethereal solution was replaced by higher boiling point ether like dioxane (b.p. 110^{o}C) and heat was applied to melt the sodium metal, as liquid sodium (m.p. 98^{o}C) always have a "fresh" surface. The reaction was quenched after the addition of iodomethane.

The resulting product displayed a strong smell reminiscent of hot fusel, which was not present within the starting material; the distinctive smell might be a hint of the ether compound. Along with the alcohol analogs, these ether analogs degraded upon exposure to acidic conditions and could not be isolated to pure form. This can be explained using the analogous manner involving the alkoxonium ion as leaving group in place of the hydroxonium.

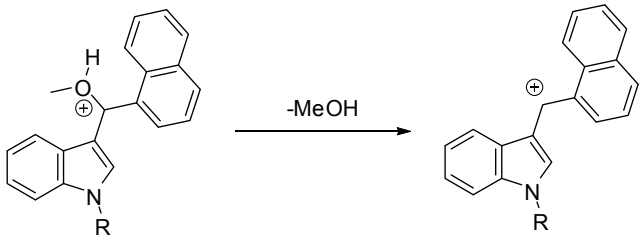
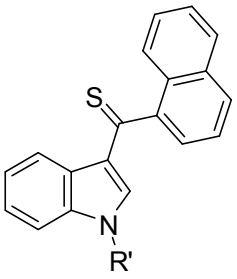


Figure 3.22 Elimination of Alcohol

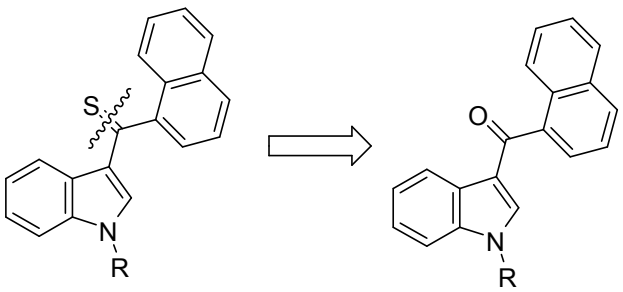
3.8 The Thiocarbonyl Analogs

Thiocarbonyl functional group are thought to have the activity at the binding site, as the overall molecular geometry resemble one of the ketone analogs. Interestingly, there are some distinctive differences between the two; sulfur has larger effective radius comparing to oxygen, thus the angle between two aromatic planes would get more highly distorted. Also, as sulfur possess the *d* orbital, the polarity of C=S bond becomes higher than of those the C=O bond due to resonance stabilization, which may have effect on the binding activity. Owing to the lower electronegativity, the sulfur atom also toned down the strength of possible hydrogen-bonding interaction in the receptor comparing to oxygen atom.



Retrosynthetic Pathway:

(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethione

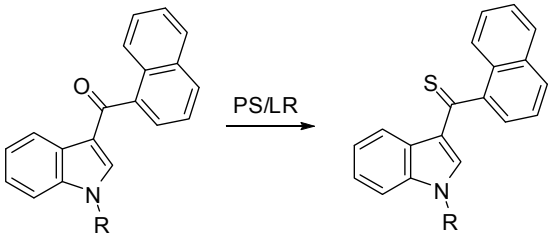


The carbonyl functional group can be convert to a thiocarbonyl, with the use of either P_4S_{10}[63] or Lawesson's Reagent[64]. To compare the versatility of these, both methods were experimented.

Red phosphorus can be obtained from matchbox striker as described in Chapter II, the resulting red phosphorus was use as is, combining with sulfur then heated. The reaction evolves considerable amount of heat and gas. The smell of phosphine and hydrogen sulfide was prominent and must be vented out. This resulted in mixed sulfides of phosphorus after the reaction tube was cooled.

The ketone was then reacted with either prepared phosphorus sulfides or Lawesson's reagent.

Table 3.7 Thionation of Cannabimimetic Indoles



Entry	R	PS / LR[a]	Amount(eq)	Solvent	Isolated Yield (%)
1	H	PS	excess	benzene	0
2	H	LR	1.2	benzene	-[b]
3	CH_3	PS	excess	benzene	25
4	CH_3	LR	1.2	benzene	85
5	C_2H_5	LR	1.2	benzene	88
6	C_3H_7	LR	1.2	benzene	73
7	C_4H_9	LR	1.2	benzene	70
8	C_5H_{11}	LR	1.2	benzene	68
9	C_5H_{11}	LR	1.2	toluene	67

a) Phosphorus sulfides / Lawesson's Reagent *b)* not isolated

Lawesson's Reagent was found to be superior to phosphorus sulfides, this can be accounted for the unreactive form of phosphorus sulfides, since pyrolysis of red phosphorus with sulfur do not selectively yielded P_4S_{10}, and thus the activity of reagent is reduced. Reacting with *N*-unsubstituted indole failed to give any product, whereas the *N*-methyl gave some (entry 1 and 3).

Arylthioketones are often highly colored due to the electronic transition from n to π* orbital, for example as in the case of thiobenzophenone bearing deep blue color. The observation of color could be primarily be used to trace the formation of the thioketone product. In this case, the thioketone products were found to have a deep red color, which can be observed after refluxing the ketone with Lawesson's Reagent for a while.

The mechanism of the transformation of ketone functional group to thioketone by Lawesson's Reagent started with de-dimerization of Lawesson's Reagent to its reactive species, which then formed a 4-membered thioxaphosphetane intermediate *via* a [2+2] dipolar cycloaddition mechanism, then underwent another retro[2+2] cycloaddition which cleaves the thioxaphosphetane ring to the thioketone product. The affinity for oxygen of phosphorus promotes the ring cleavage to the thioketone direction.

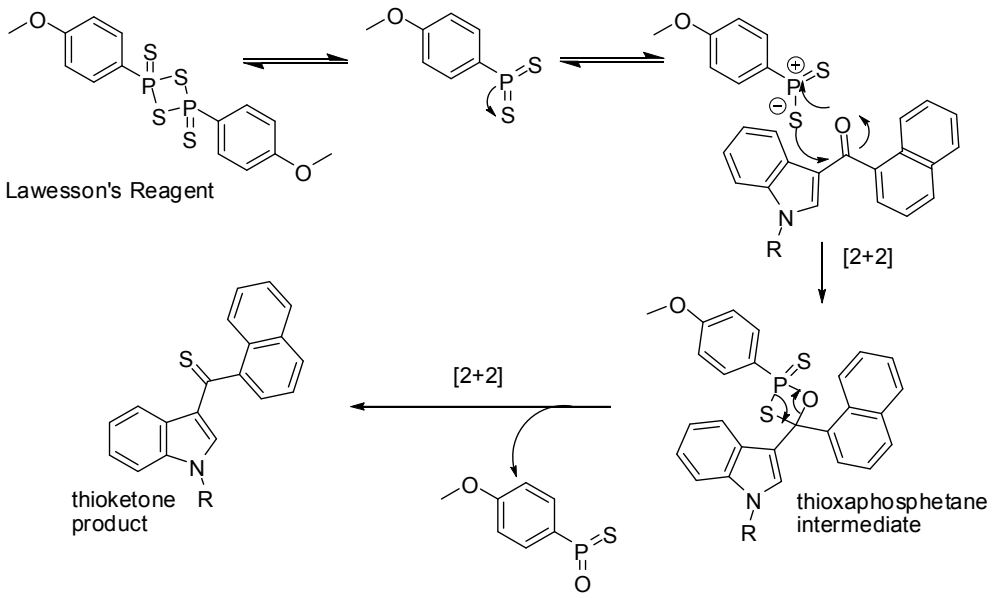


Figure 3.23 Mechanism Involved in Thionation Using Lawesson's Reagent

For later syntheses, toluene was substituted for benzene due to its lower carcinogenicity (entry 9), the yield was indifferent to the case of benzene.

As the crude products from these reaction produced very strong smell of sulfur compounds, the separation using column chromatography was avoided due to the spreading of the stench. Preparative TLC plates were then used to overcome this problem. In the case of *N*-unsubstituted indole (entry 2) the product was not isolated as the R_f was in the same range with other products from the reaction in all tested solvent system. The propagation of the product during separation can be observed easily as a red band.

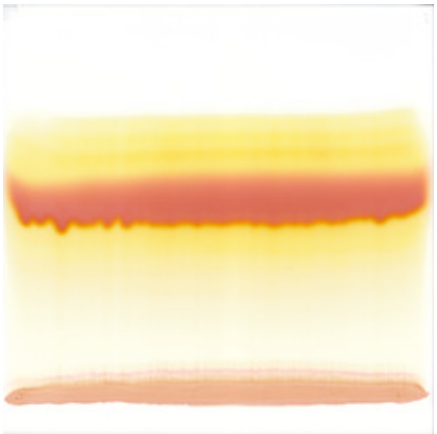


Figure 3.24 TLC Showing Red-colored Band of Thioketone Product

^{1}H NMR spectra of these compounds show distinctive differences in chemical shifts, which can be noted from the alpha protons of naphthalene ring, which is located at 7.92 ppm and 7.85 ppm, comparing to the ketone analog, in which they appear at 8.45 ppm and 8.18 ppm respectively. The differences in the shifts can also be noted at from the proton on alkyl group on nitrogen. In this case, they showed a lower chemical shift of 3.95 ppm comparing to 4.05 ppm of the parent compound.

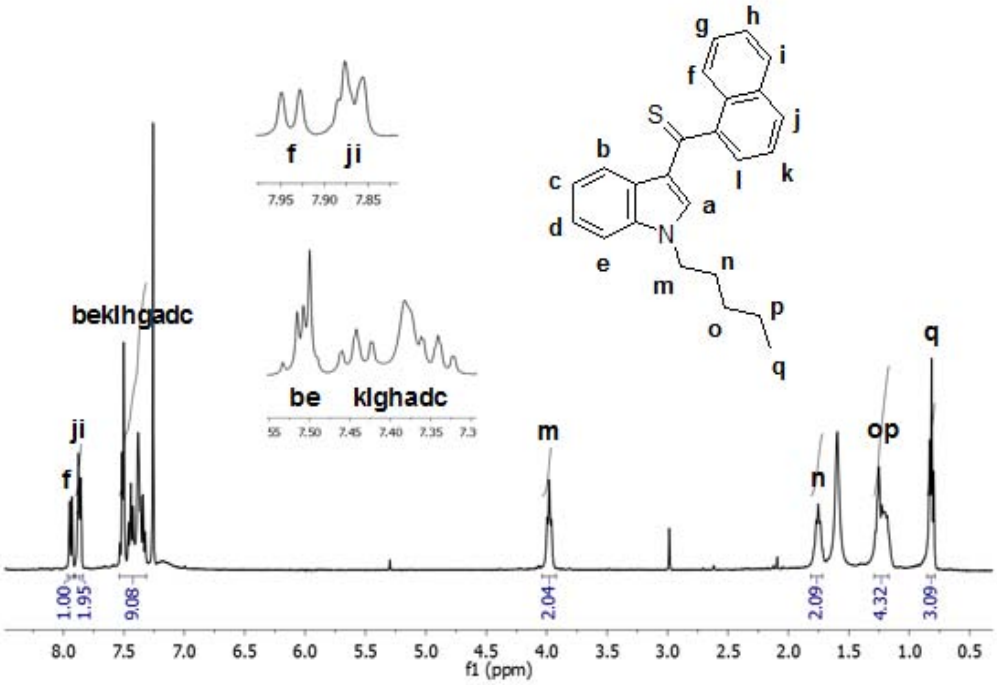


Figure 3.25 ^{1}H NMR Spectrum of
(1-Pentyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethione

(1-Propyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethione ^{1}H NMR ($CDCl_3$):
(aromatic) 7.92 (d, 2H), 7.87 (d, overlapped, 1H), 7.86 (d, overlapped, 1H), 7.33-7.50 (m, overlapped, 9H)
(aliphatic) 3.95 (t, 2H), 1.75 (t, 2H), 1.29 (t, 3H)
(1-Butyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethione ^{1}H NMR ($CDCl_3$):
(aromatic) 7.93 (d, 2H), 7.86 (d, overlapped, 1H), 7.85 (d, overlapped, 1H), 7.30-7.53 (m, overlapped, 9H)
(aliphatic) 3.97 (t, 2H), 1.78 (t, 2H), 1.23 (m, 2H), 0.81 (t, 3H)

(1-Pentyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethione ^{1}H NMR ($CDCl_3$):
(aromatic) 7.92 (d, 2H), 7.86 (d, overlapped, 1H), 7.85 (d, overlapped, 1H), 7.30-7.53 (m, overlapped, 9H)
(aliphatic) 3.95 (t, 2H), 1.75 (t, 2H), 1.23 (m, 4H), 0.81 (t, 3H)

As thioketones are known to degrade gradually in normal condition back to ketone and sulfur, the synthesized compounds are tested for their stability. Each test was done by dissolving the thioketones in various organic solvents, then exposed the solution either to air, oxygen gas, heat, UV irradiation or the combination of those stated, then their ^{1}H NMR scans were compared. The result was surprising as it was found that these thioketones survived those conditions and only degraded to the ketone counterpart in very small amount. The decomposition is shown in the spectrum below:

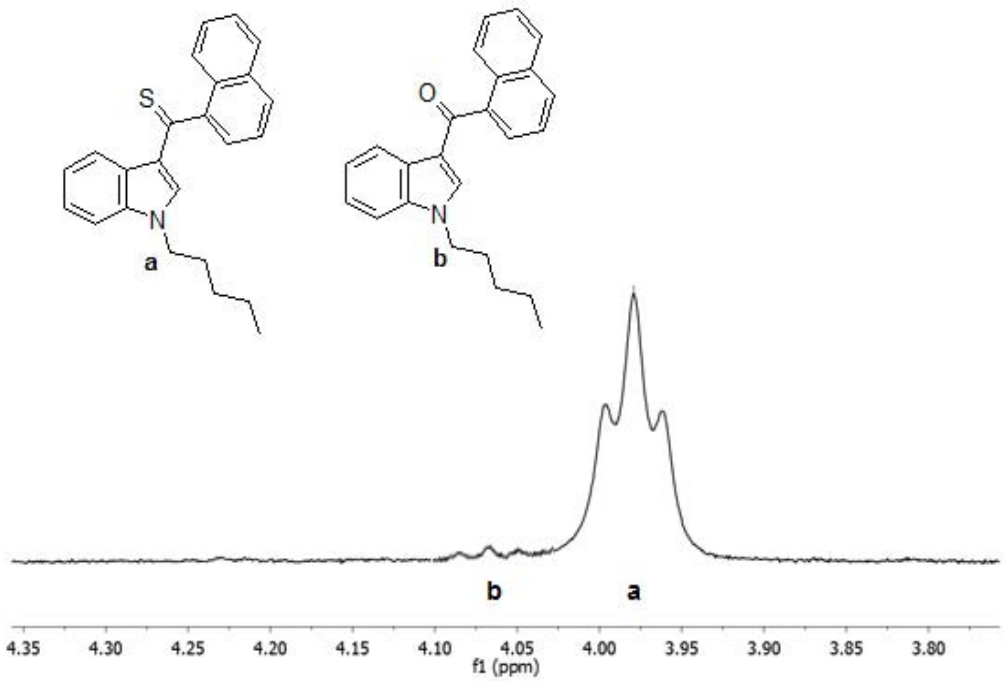


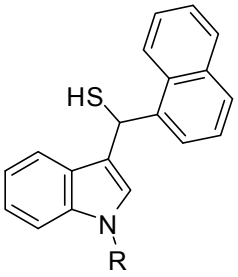
Figure 3.26 ^{1}H NMR Showing the Decomposition of Thioketone to Ketone

An interesting behavior of these compounds was also observed, as they produced light yellow color in low concentration, in the solution of halogenated solvent (tested on dichloromethane, chloroform and dichloroethane). But as the

concentration rose, the color of the solution changed from light yellow to red without any transition into orange shade.

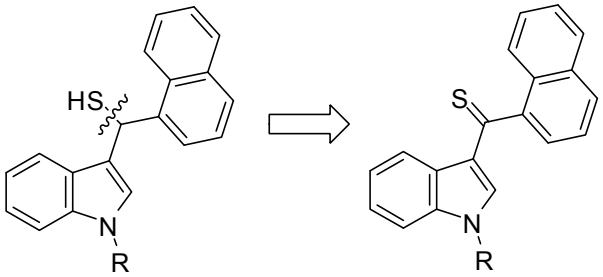
3.9 The Thiol Analogs

Thiol analogs are the hybrid between the alcohol and sulfur containing counterpart. The molecular geometry of thiol analog is similar to those of alcohol. However, as thiol is one of the biological reactive functional group as can be found in sulfur-containg protein, and its affinity for some metal center. Thiols are also known to form disulfide upon oxidation under certain conditions. So, the thiol analogs are interesting to study in that they might possess unpredicted activity.



Retrosynthetic Pathway:

(1-Alkyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanethiol



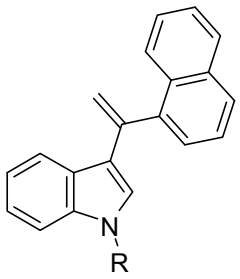
In the reaction, the thioketone that was synthesized beforehand was used. Conventional borohydride method was used. The reaction is analogous to the reduction of ketone to alcohol. However, the resulting products could not be isolated as they decomposed rapidly to red coloration upon quenching the reaction.

The thiol product is predicted to decompose in similar manner to the alcohol analog, forming the stabilized carbocation as previously described. In this case, hydrogen sulfide was eliminated from the molecule. The smell of hydrogen sulfide can be detected throughout the experiment after the step of quenching.

As similar decomposition of both alcohol and thiol product is prominent, the synthesis was not continued to other *N*-alkyl analogs in both case, as the products are predicted a similar decomposition fate.

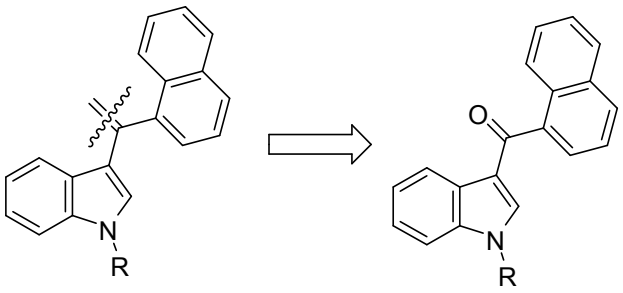
3.10 The *exo*-Methylene Analogs

Compound in this class would provide the structure needed to check for the contribution of H-bond in receptor binding. Comparing with the parent ketone compound, these exo-methylenes provide similar conformation between two planes. Despite of those similarities; the hydrogen bonding capability of the molecule would get reduced dramatically. This was a result of swapping the methylene group which is a poor hydrogen bond acceptor into the place of the oxygen group, which is the good hydrogen bond acceptor. Polarity of the molecule is also decreased as well.



Retrosynthetic Pathway:

1-Alkyl-3-(1-(naphthalen-1-yl)vinyl)-1*H*-indole



Method A involves the pathway of Wittig reaction[65-66], whereas the carbonyl functionality is exchanged to alkene. The mechanism of this reaction involves the formation of phosphorus ylide, which reacts with the carbonyl group *via* [2+2] dipolar cycloaddition to form an oxaphosphetane intermediate, which then cleaves to give the alkene product. The mechanism of the proposed reaction is shown in Figure 3.27.

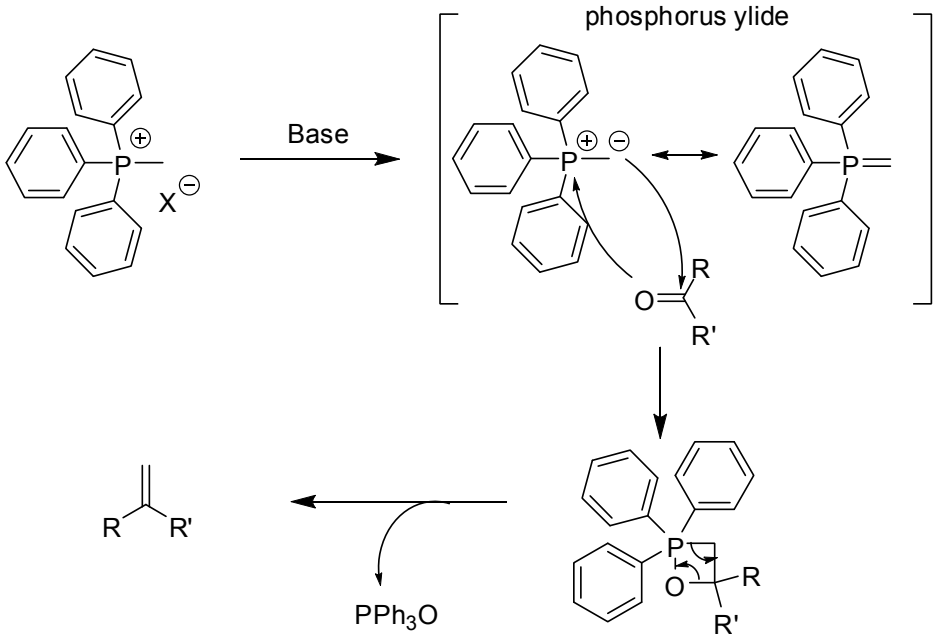


Figure 3.27 Mechanism Involved in Methylenation *via* Wittig Reaction

According to target molecule, the desired alkene only contains one carbon atom, so the corresponding phosphonium salt, methyltriphenylphosphonium iodide, is prepared. The mixture of triphenylphosphine and excess methyl iodide in aromatic, nonpolar solvent like benzene or toluene produced needle-like crystal after settled undisturbed at room temperature. The crystallization process started at roughly 3 hours after the addition of all components. No more crystals were observed forming after 6 hour so the crystallization was stopped. The resulting methyltriphenylphosphonium iodide salt was then washed several times with either benzene or toluene to remove the remaining organic impurities.

^{1}H NMR spectra of the salt indicates a distinctive methyl peak at 3.14 ppm, whereas the aromatic part is displayed in the range of 7.65 ppm to 7.83 ppm, which the correct ratio regarding to the structure, so no further purification is done for this prepared reagent.

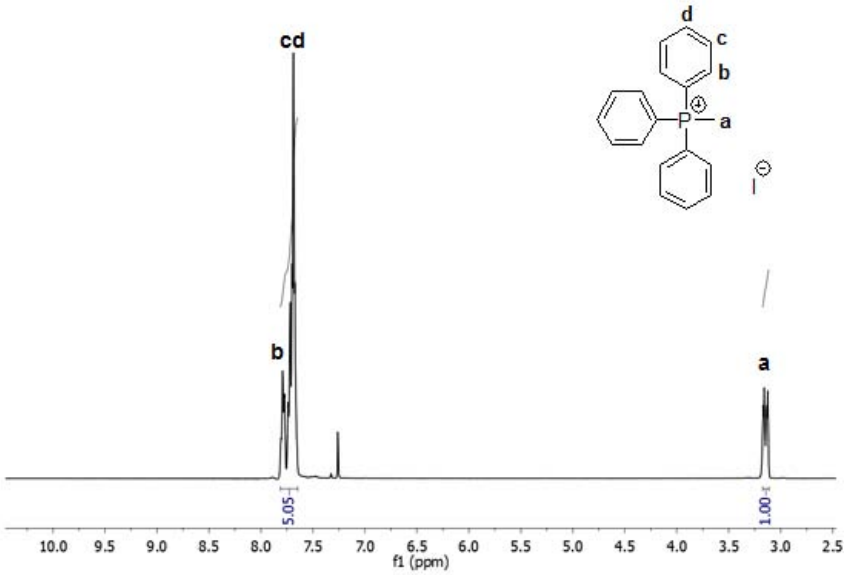


Figure 3.28 ^{1}H NMR Spectrum of Methyltriphenylphosphonium Iodide

Method B, on the other hand, involves the use of Tebbe's Reagent[67] which is Schröck carbene equivalence. Tebbe's Reagent is widely used in the transformation of carbonyl group to methylene, especially in the case where Wittig reaction does not give desirable yield or reactivity. Tebbe's Reagent itself does not react with carbonyl compound, but upon treating with Lewis base like pyridine or triethylamine, the

reactive Schröck carbene is produced. The affinity for oxygen of titanium would result in reaction with the ketone to oxatitanacyclobutane intermediate, in similar way to Wittig's, which then cleaves to get the desired *exo*-methylene compound. The mechanism is shown below:

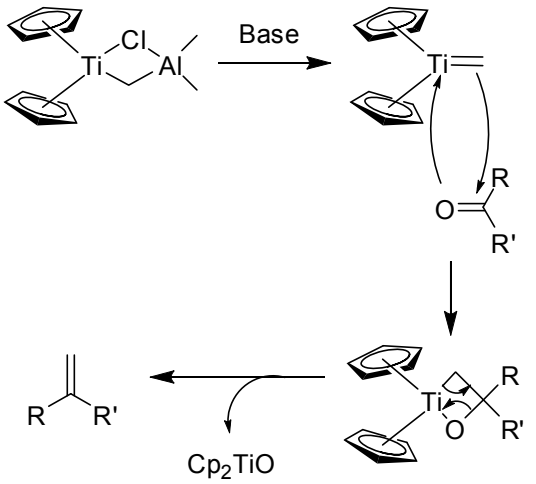
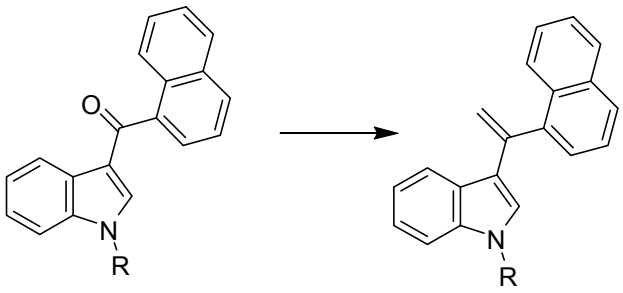


Figure 3.29 Mechanism Involved in Methylenation Using Tebbe's Reagent

Table 3.8 Methylenation of Cannabimimetic Indoles



Entry	R	Method	Base	Isolated Yield (%)
1	H	A	^{t}BuOK	0
2	H	B	Et_3N	0
3	CH_3	A	Na	0
4	CH_3	A	NaH	0
5	CH_3	A	NaOMe	0
6	CH_3	A	^{t}BuOK	0

7	CH_3	B	Et_3N	0
8	benzophenone[a]	A	^tBuOK	91
9	benzophenone[a]	B	Et_3N	quant

a) control

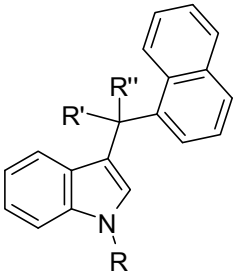
Surprisingly, it was found that the parent ketone was unreactive toward both conditions. Entry 1 and 2 was predicted in prior to give low or no product due to NH deprotonation. The experiment confirmed this postulate as insoluble sodium salt of indole was found precipitating during the addition. In the case of Wittig's reaction condition, the base was also varied to see the effect since solubility of the base sometimes affected the reaction outcome. Unfortunately, no conditions were found to obtain the product. Tebbe's reagent, although offering higher reactivity due to the oxophilicity of titanium, still failed to result in formation of the product. Increasing either the reaction time or temperature made no change as indicated by TLC. ^{1}H NMR spectra of the crude products showed either mixture of starting ketone with triphenylphosphine (and its oxide) or starting ketone with Tebbe's reagent.

Comparison reactions were then set up to check the viability of methylenation by these reagents, by substituting the starting ketone with benzophenone, another diarylketone with simpler structure. It was found that Wittig's reaction gave high yield (entry 8) while Tebbe's reagent resulted in quantitative conversion of the reactant (entry 9). The resulting alkene displayed a sharp signal of the methylene protons at 5.45 ppm.

The unreactivity toward *N*-alkylindoles were unexpected, in spite of the high yielding control (entry 8 and 9). This could be explained using the effect of steric hindrance, whereas the two aryl moieties are too sterically crowded for the reaction to take place. (naphthalene and *N*-alkylindole *versus* two phenyls)

3.11 The Alkyl Analogs

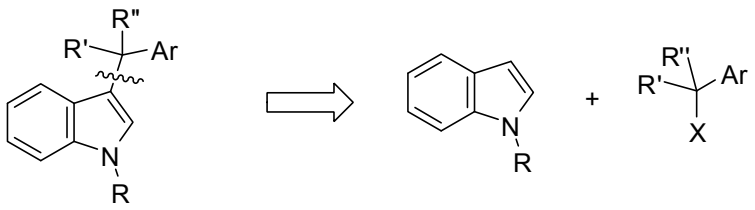
The alkyl as linking groups between two aromatic planes provided a structures those the aromatic planes are bended in different angles. The only published alkyl-bridge analog was methylene (-CH_2-), which has some activity at the cannabinoid receptor despite the vast different between the angle comparing to the parent ketone compound. Alkyl group in this position prevents the possible hydrogen bonding interaction at this site. So these analogs are useful in verifying the importance of hydrogen bonding interaction whether it contributes much or not.



Retrosynthetic Pathway:

1-Alkyl-3-(1-(naphthalen-1-yl)ethyl)-1*H*-indole *and*

1-Alkyl-3-(2-(naphthalen-1-yl)propan-2-yl)-1*H*-indole



As can be seen from the provided retrosynthesis, both *Method A* and *Method B* involve the attack of indole, which acts as a nucleophile, on the secondary or tertiary carbocation center. *Method A* generates the carbocation by protonating the alcohol, whereas *Method B* generates the carbocation *via* Friedel-Crafts condition.

The alcohol required in *Method A* can be prepared by reduction of 1-acetonaphthone at room temperature with sodium borohydride, which gave nearly quantitative yield. This resulting alcohol was subsequently used to prepare the

haloalkane for *Method B* by reacting with thionyl chloride, resulting in conversion in near quantitative yield. The ^{1}H NMR spectra shows the distinctive differences in chemical shifts between the alcohol and the chloroalkane, as shown below:

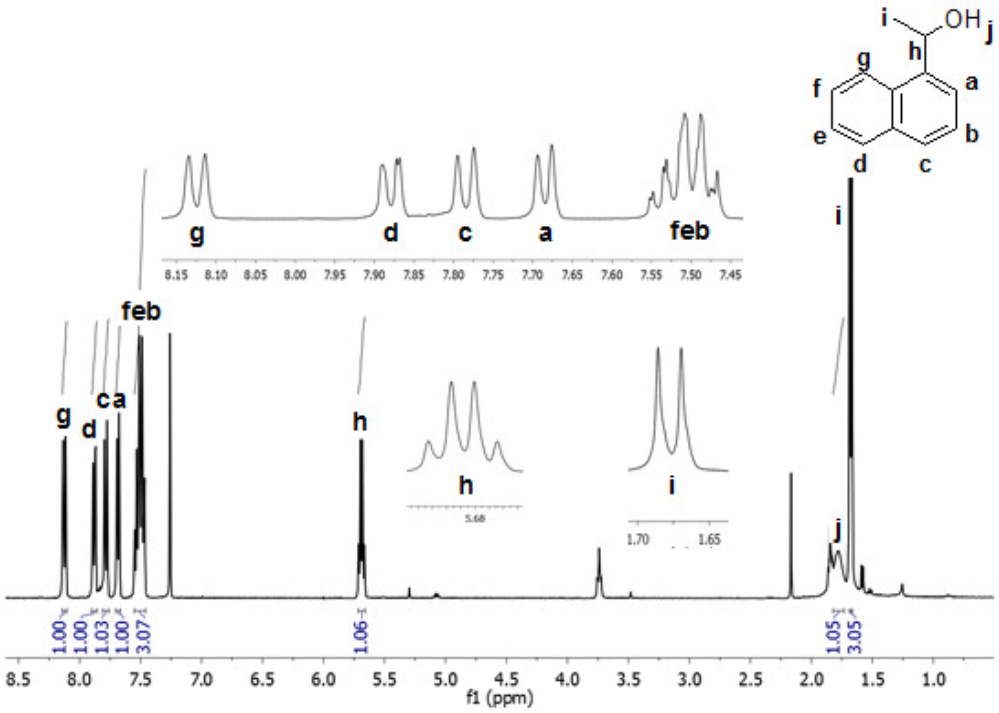


Figure 3.30 ^{1}H NMR Spectrum of 1-(Naphthalen-1-yl)ethanol

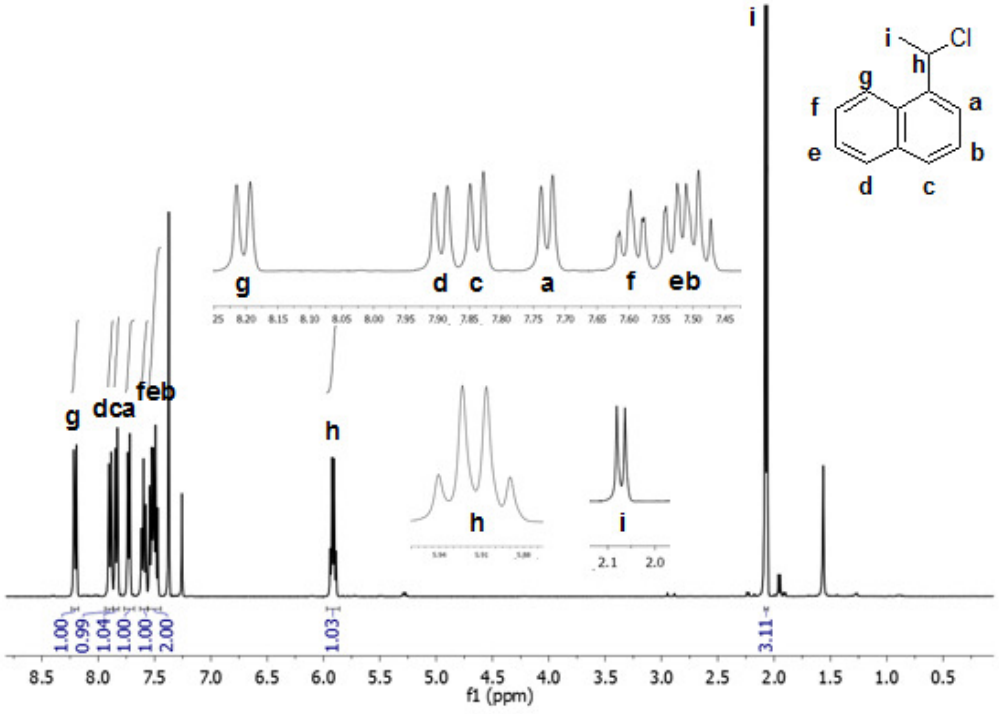


Figure 3.31 ^{1}H NMR Spectrum of 1-(1-Chloroethyl)naphthalene

1-(Naphthalen-1-yl)ethanol ^{1}H NMR ($CDCl_3$):

(aromatic) 8.12 (d, 1H), 7.88 (dd, 1H), 7.78 (d, 1H), 7.68 (d, 1H), 7.45-7.55 (m, overlapped, 3H)

(aliphatic) 5.69 (q, 1H), 1.78 (br, OH, 1H), 1.68 (d, 3H)

1-(1-Chloroethyl)naphthalene ^{1}H NMR ($CDCl_3$):

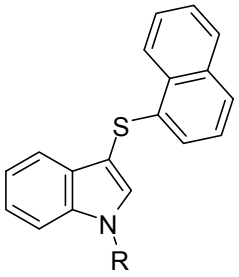
(aromatic) 8.20 (d, 1H), 7.89 (d, 1H), 7.83 (d, 1H), 7.73 (d, 1H), 7.60 (dt, 1H), 7.45-7.54 (m, overlapped, 2H)

(aliphatic) 5.91 (q, 1H), 2.07 (d, 3H)

Despite the conditions, no product was obtained using both methods. With *Method A*, the different choice of acid determines one of the two end results. Boric acid and 10-camphorsulfonic did not result in any reaction, even after stirring overnight or applying heat, whereas stronger acids like *p*-toluenesulfonic results in red oligomeric indole products after some few hours. Sulfuric acid, even in small amount, yielded the oligomeric by-products instantly. *Method B*, on the other hand, gives rise to instant polymeric product in Friedel-Crafts condition. As the newly introduced group onto indole ring is activating (an alkyl group), the resulting alkylindoles would be more prone to acidic attack, resulting in overalkylation and polymerization. The resulting gum barely eluted at all in TLC check with different mobile phases.

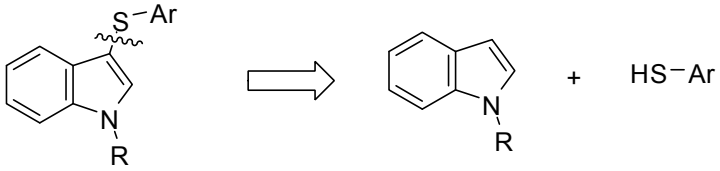
3.12 The Sulfenyl Analogs

The sulfenyl analogs provide the structural difference comparing to cannabimimetic indoles. Unlike other cannabimimetic indoles whereas linker between the aromatic planes is carbon, in this case the linking atom is sulfur. By replacing the carbonyl group with sulfur, the proximity between lone pair electrons capability of forming a hydrogen bonding interaction would change, thus resulting in alteration in receptor binding affinity. The sulfenyl group also renders both aromatic ring more electron-rich.



Retrosynthetic Pathway:

1-Alkyl-3-(arylthio)-1*H*-indole



Regarding to the retrosynthesis, the corresponding thiols (being thiophenol, *p*-thiocresol and 1-thionaphthol) were prepared either by diazotization of the corresponding aniline, followed by a nucleophilic attack with SH^- ion, or by reducing the corresponding sulfonyl chloride with triphenylphosphine[68].

With *Method A*, the thiols are obtained in low yield as most formed thiol got further oxidized into disulfide compound, which precipitated from the reaction. Whereas *Method B* provides more practical synthesis, as the reducing properties of triphenylphosphine might help prevent the formed thiol from aerial oxidation. It was found that triphenylphosphine reacted aggressively toward the sulfonyl chloride solution. The resulting thiols cannot be purified from the crude mixture using conventional acid/base extraction, as in basic solution, the deprotonated form of thiol is very reactive toward oxidation, thus resulting in precipitation of the disulfide instead. So, chromatographic separation using a column is unavoidable.

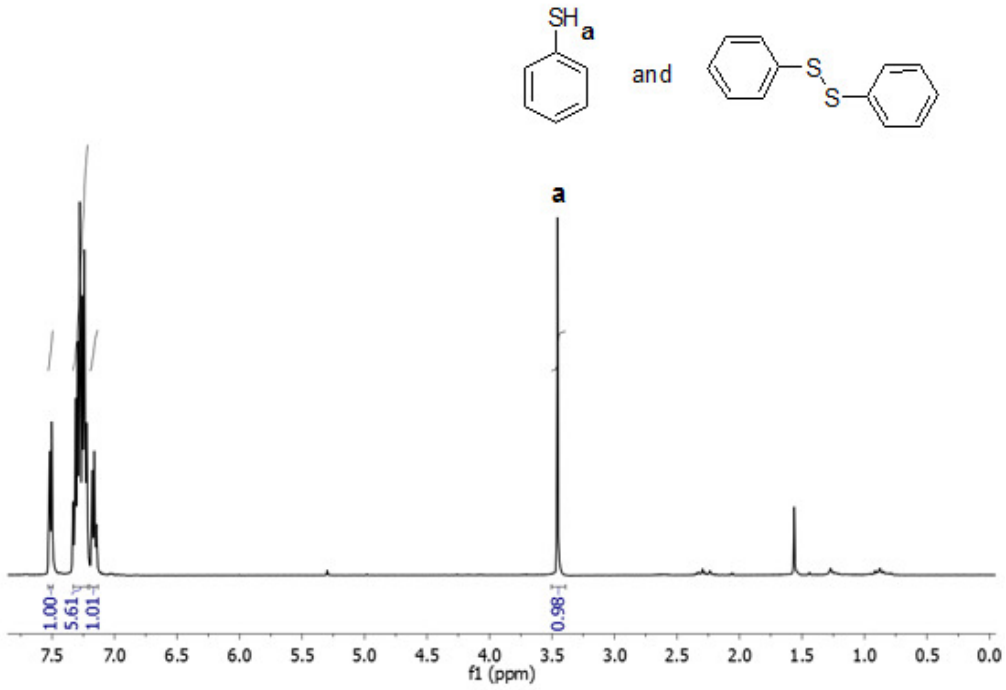


Figure 3.32 ^{1}H NMR Spectrum of Crude 1-Thionaphthol

Thiophenol ^{1}H NMR ($CDCl_3$):

6.97-7.44 (m, overlapped, 5H), 3.47 (s, S<u>H</u>, 1H)

4-Thiocresol ^{1}H NMR ($CDCl_3$):

7.31 (d, overlapped, 2H), 7.08 (d, overlapped, 2H), 3.45 (s, S<u>H</u>, 1H), 2.31 (s, 3H)

1-Thionaphthol ^{1}H NMR ($CDCl_3$):

8.10 (m, overlapped, 2H), 7.88 (d, 1H), 7.37-7.52 (m, overlapped, 3H), 7.22 (d, 1H), 3.46 (s, S<u>H</u>, 1H)

Thiols condensed with indole selectively at 3-position. The reaction involves elemental iodine, which acted as a Lewis acid activating the thiol group. The mechanism of the reaction is proposed as in Figure 3.33.

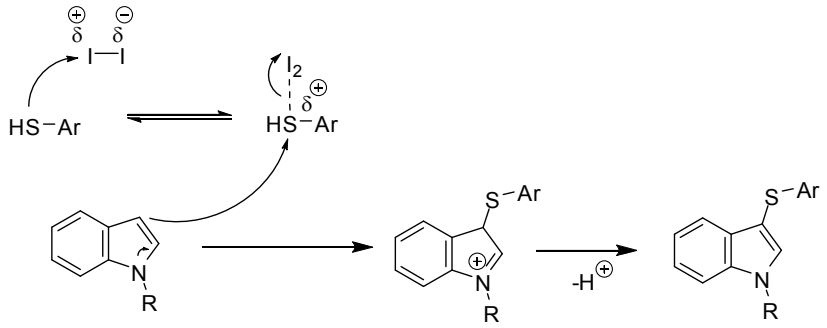
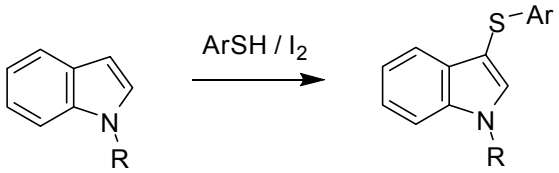


Figure 3.33 Mechanism Involved in Iodine-catalyzed Sulfenylation

Table 3.9 Sulfenylation of Indoles



Entry	R	Ar	Isolated Yield (%)
1	H	phenyl	24
2	Me	phenyl	27
3	H	1-(4-methylphenyl)	31
4	H	1-naphthyl	25
5	H	phenyl	0[a]

a) triphenylphosphine not isolated from crude thiol

3-sulfur-substitued indoles can be synthesized in moderate yield, unlike the 3-oxygen-substitued counterparts which are often unstable. The result showed that substitution at nitrogen has marginally low effect on the outcome (entry 1 and 2), whereas similar yield range was obtained from other arylthiol used.

The main factor which reduced the yield might still be the oxidation. Due to the observation, there was a competiting reaction between the condensation of thiol onto indole, or the oxidation of thiol to disulfide. The former is driven by the electron-

rich nature of indole, whereas the latter is driven by precipitate formation which drives the equilibrium.

As the separation of thiol from the crude mixture was quite tedious owing to the smell, the unseparated crude containing the thiol, the disulfide and the remaining triphenylphosphine was used in entry 5. Albeit the thiols can be detected, it was found that no product is formed after the addition of iodine, even after 3 days of reaction. This might be attributed from the adduct formation between triphenylphosphine, acted as Lewis base, and iodine which acts as Lewis acid. So the prior purification of thiol was a needed step.

The synthesized sulfenyl analogs are either colorless or very lightly yellow. Leaving these compounds as solution in halogenated solvent such as chloroform or dichloromethane resulted in color change to light grey, then brown. Unlike visual color change, the ^{1}H NMR was not affected. Phenyl and tolyl analogs are known compounds and their spectra are in agreement with the reference[69]. The ^{1}H NMR of naphthyl counterpart is displayed in Figure 3.34.

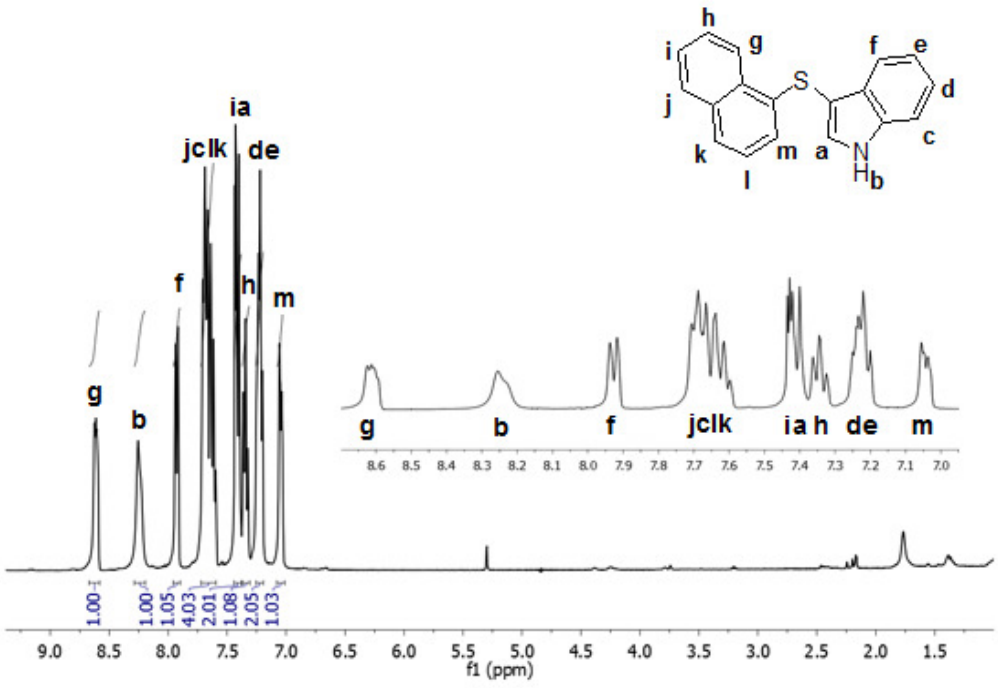


Figure 3.34 ^{1}H NMR Spectrum of 3-(1-naphthylthio)-1*H*-indole

3-(phenylthio)-1*H*-indole ^{1}H NMR ($CDCl_3$):

8.20 (br, NH, 1H), 7.33-7.62 (m, 1H), 7.22-7.30 (m, 1H), 6.80-7.20 (m, overlapped, 8H)

3-(4-methylphenylthio)-1*H*-indole ^{1}H NMR ($CDCl_3$):

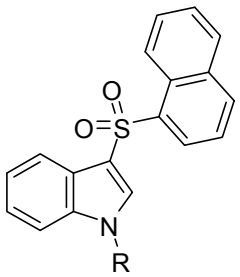
8.20 (br, NH, 1H), 7.44-7.55 (m, 1H), 7.22-7.30 (m, 1H), 7.01-7.16 (m, overlapped, 5H), 6.83-6.96 (m, 4H), 2.26 (s, 1H)

3-(1-naphthylthio)-1*H*-indole ^{1}H NMR ($CDCl_3$):

8.62 (t, 1H), 8.25 (br, NH, 1H), 7.93 (d, 1H), 7.57-7.76 (m, overlapped, 4H), 7.43 (s, overlapped, 1H), 7.42 (t, overlapped, 1H), 7.34 (t, 1H), 7.22 (m, overlapped, 2H), 7.06 (m, 1H)

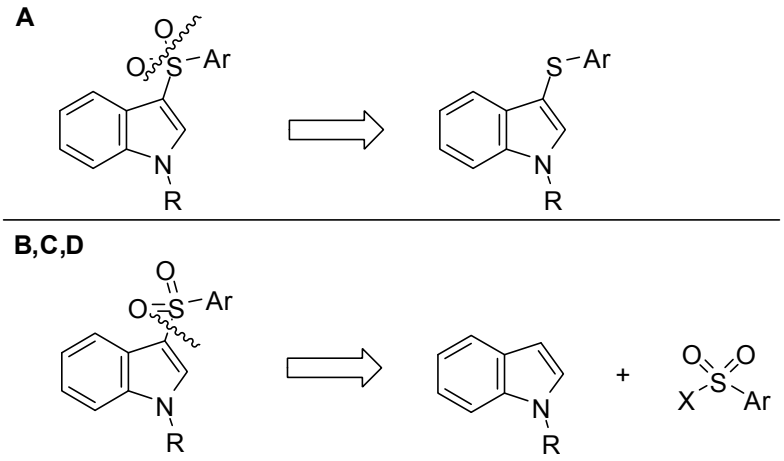
3.13 The Sulfonyl Analogs

Analogs containing the sulfonyl groups are useful molecular probes to study the significance of distance between the two arene systems within the cannabimimetic indole, as per larger atomic radii of sulfur versus carbon. This group bears much resemblance to the carbonyl counterpart. Both of them are electron-withdrawing group, and both groups are able to interact as hydrogen bond acceptor.



Retrosynthetic Pathway:

1-Alkyl-3-(arylsulfonyl)-1*H*-indole



There are several routes toward the sulfonyl analogs. The first route is direct oxidation of the sulfur atom in the corresponding sulfenyl analogs. The second route involves the use of Grignard reagent to form an indole-grignard, in which the stabilization at 3-position of "soft" magnesium counterion should provide the regioselectivity for the 3-attack by the following mechanism:

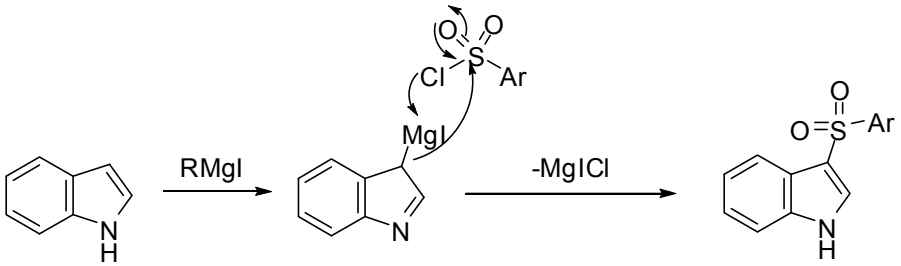


Figure 3.35 Proposed Mechanism for Sulfonylation of Indole Using Grignard Reagent

Other methods are performed in Friedel-Craft fashion[58]. It is known that Friedel-Crafts sulfonylation requires harsher condition comparing to the analogous acylation. In most case, higher temperature, longer reaction time and more reactants are needed.

As can be seen from the retrosynthetic route, the corresponding sulfonyl chlorides are needed. Whereas some which are commercially available as common reagents, like phenylsulfonyl chloride and toluenesulfonyl chloride; 1-naphthalene sulfonyl chloride was prepared from the common reagent, naphthalene. The

sulfonation of naphthalene went well, resulting majorly in the desired 1-naphthalenesulfonic acid products. The minor 2-sulfonic and 1,4-disulfonic counterpart can be removed after careful crystallization of the sulfonic acid as the sodium salt. The resulting sulfonic acid was converted to sulfonyl chloride with $SOCl_2$ with traces of DMF acting as a catalyst[70]. It was also found that without DMF, the reaction did not proceed at all, and all sulfonic acid can be recovered.

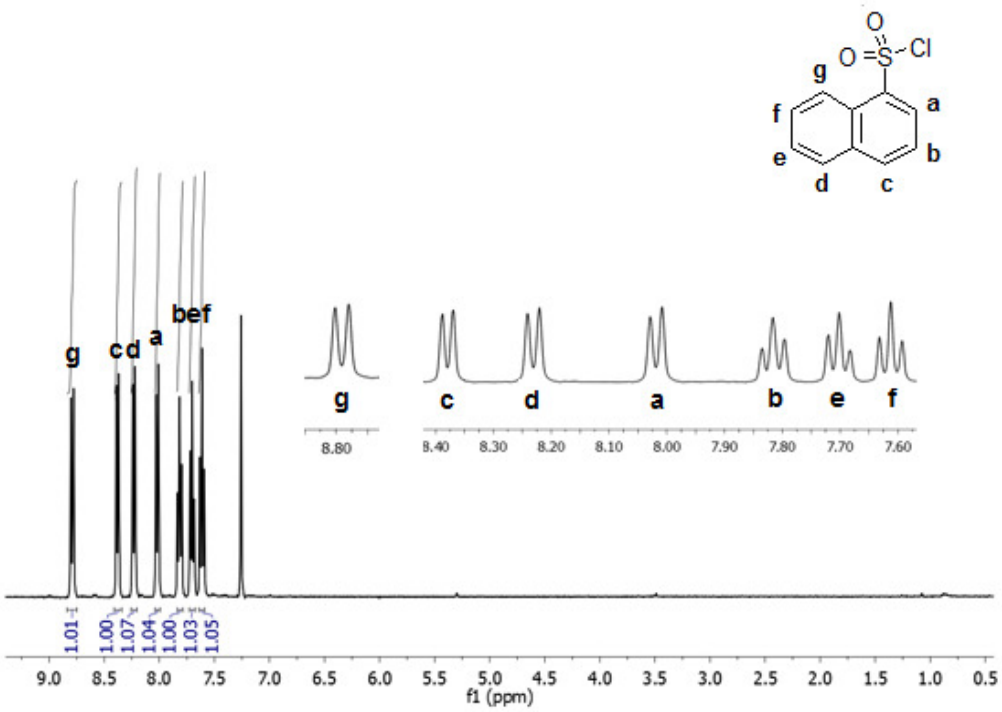
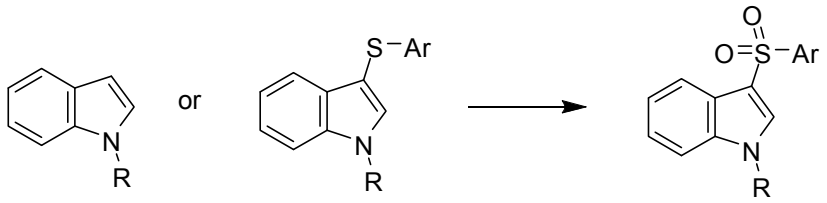


Figure 3.36 ^{1}H NMR Spectrum of Naphthalene-1-sulfonyl Chloride

Naphthalene-1-sulfonyl Chloride ^{1}H NMR ($CDCl_3$):
8.79 (d, 1H), 8.38 (d, 1H), 8.23 (d, 1H), 8.02 (d,1 H), 7.82 (t, 1H), 7.70 (t, 1H), 7.61 (t, 1H)

Heterogeneous Lewis acid catalyst have been reported to catalyze sulfonylation onto indole[71], so the preparation of this solid-phase catalyst is also studied.

Table 3.10 Sulfonylation of Indoles



Entry	R	Ar	Method	Lewis Acid[a]	Isolated Yield (%)
1	H	phenyl	A	-	quant
2	H	phenyl	B	-	0 (26[b])
3	H	phenyl	C	$FeCl_3$	37
4	H	phenyl	D	Fe-bentonite	20
5	H	phenyl	D	Al-bentonite	9
6	Me	phenyl	A	-	quant
7	Me	phenyl	B	-	0
8	H	1-(4-methylphenyl)	C	$FeCl_3$	35
9	H	1-naphthyl	C	$FeCl_3$	trace[c]
10	H	phenyl	C	$AlCl_3$	-[c]
11	H	phenyl	C	$InCl_3$	33
12	H	phenyl	C	$BiCl_3$	6

a) for *Method C* or *Method D* only *b)* 3-chloroindole *c)* not isolated

According to the result, it is clearly shown that *Method A* looks promising since it give the quantitative yield (entry 1 and 6). The oxidation of the sulfenyl analog underwent smoothly and cleanly to give the sulfonyl product. However, to use this method, the sulfenyl compounds are needed, whereas they cannot be synthesize in high yield as of yet.

With *Method B*, the *N*-methyl counterpart cannot undergo any reaction as predicted as deprotonation with Grignard is hard to occur without N<u>H</u> proton (entry 7). Unexpectedly, the *N*-unsubstituted indole failed to yield any sulfonyl products too.

It was found that there was an unknown competiting reaction which gives 3-chloroindole as the product instead. In this case, the sulfonyl chloride acted as a chlorinating agent, which is uncommon. The proposed mechanism for the formation of 3-chloroindole is described below:

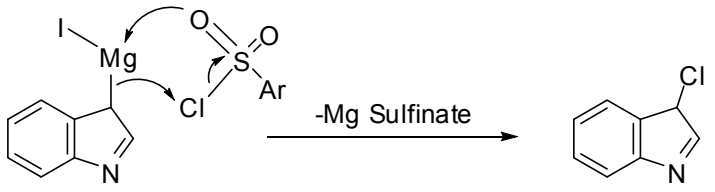


Figure 3.39 Proposed Mechanism for the Formation of 3-Chloroindole

As predicted, the activity of homogeneous catalyst (entry 3) was higher than that of heterogeneous catalyst (entry 4). Both aluminum-pillared bentonite and iron-pillared bentonite also aggregate with the sticky indole gum forming the solid that was hard to work up with. Combining with the multi-step preparation of the pillared clay, and the lower yield range, the heterogeneous catalysts were not further explored.

Unlike the case of acylation, the reaction using $AlCl_3$ underwent sluggishly, as at low temperature no reaction could be observe at all, whereas higher temperature leads to sticky tars. The product can be identified by TLC checkups, but the ratio were small comparing to by-products which forms in large amount, so the product was not isolated (entry 10). $FeCl_3$ was found to be more effective in this case (entry 3) and remain the choice for this reaction except in the case of naphthylsulfonyl (entry 9). It was noted that this sulfonylation reaction never went to completion after tracking with TLC, so the reaction was stopped after 6 hours. By comparison, $InCl_3$ gave yield in the same range (entry 11). $BiCl_3$ was discouraged to use despite the moderately high conversion to product that was observed in TLC. This is due to the voluminous solid which occurs at the work-up step. These oxo-chloro bismuth precipitate has porous consistency and trapped the mother liquer from the reaction, whereas several extraction of this voluminous precipitate with organic solvents was not as effective (entry 6).

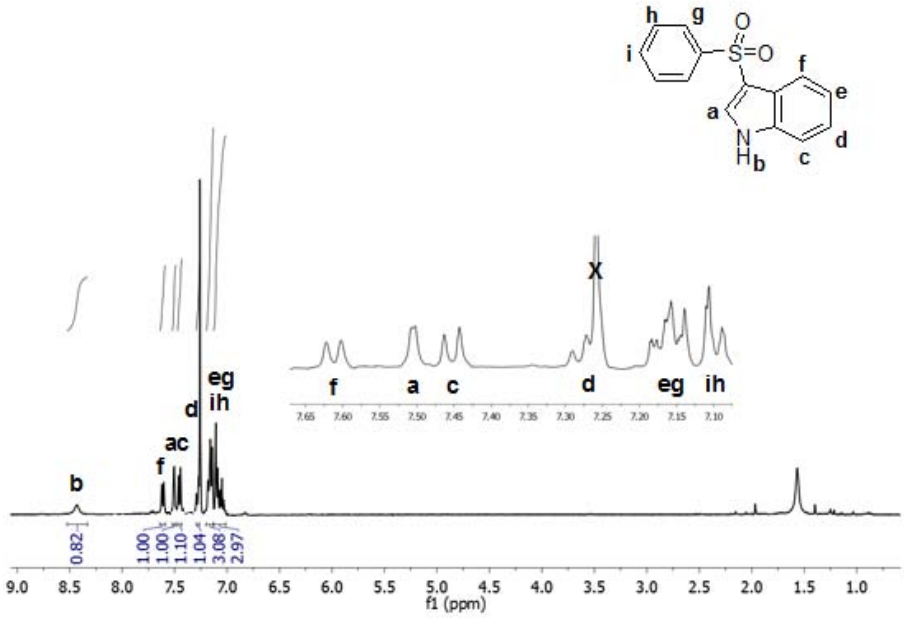


Figure 3.37 ^{1}H NMR Spectrum of 3-(phenylsulfonyl)-1*H*-indole

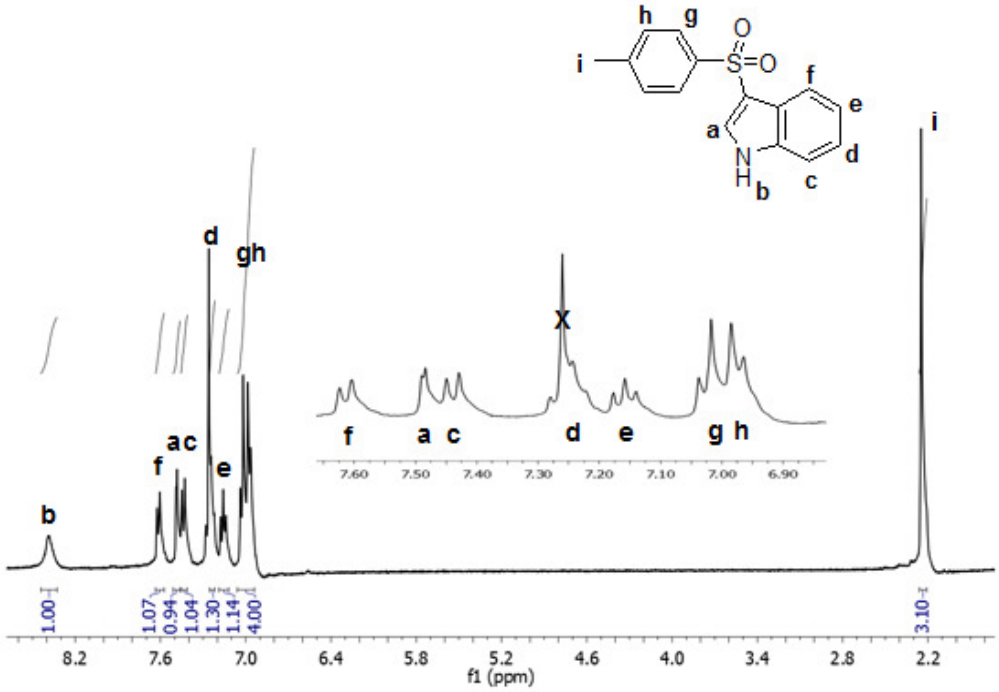


Figure 3.38 ^{1}H NMR Spectrum of 3-(4-methylphenyl-1-sulfonyl)-1*H*-indole

3-(phenylsulfonyl)-1*H*-indole ^{1}H NMR ($CDCl_3$):
8.43 (br, NH, 1H), 7.61 (d, 1H), 7.50 (d, 1H), 7.45 (d, 1H), 7.27 (t, 1H), 7.17 (t, 1H), 7.16 (m, overlapped, 2H), 7.03-7.18 (m, overlapped, 3H)
3-(4-methylphenyl-1-sulfonyl)-1*H*-indole ^{1}H NMR ($CDCl_3$):
8.39 (br, NH, 1H), 7.61 (d, 1H), 7.49 (d, 1H), 7.44 (d, 1H), 7.24 (t, 1H), 7.16 (t, 1H), 6.91-7.05 (m, overlapped, 4H), 2.25 (s, 3H)

Compounds of this class can be recrystallized easily from dichloromethane to a colorless needle-like crystal. Storing in solution discolors a little to light grey, but no change in ^{1}H NMR was observed.

CHAPTER IV

CONCLUSION

This research focuses on the synthesis of cannabimimetic indoles with various functional groups in the structures. There is an improvement to the synthesis of the known carbonyl analog, whereas the uses of expensive reagents are avoided. By continually flushing nitrogen throuout the reaction, combining with the wash as stated previously; the acylation of indole could be synthesized by conventional $AlCl_3$ with lower amount of by-products formed comparing to conventional methods.

The carbonyl analogs can be synthesized in newly developed one-pot condition as described. No needs of exotic reagents or apparatus are required. With this method, the given yields are satisfactory, ranging from 53 to 86 percent.

In the cases of non-carbonyl analogs, thiocarbonyls can be effectively prepared from the carbonyl analogs with Lawesson's Reagent, giving the yield up to 88 percent. Sulfenyl analogs can be prepared by condensation of indole with thiols, catalyzed by iodine. This method gives the moderate yield in the range of 25 to 31 percent. Sulfonyl analogs can either be prepared from sulfenyl analogs by oxidation which gives nearly quantitative yield, or by Friedel-Craft sulfonylation. In the latter case, homogeneous catalysts were found to give better yield comparing to heterogeneous catalyst. The yields are ranging around 30 percent.

Some analogs suffer decomposition during reaction and/or separation, such as the carbinol analogs and thiol analogs. The Alkyl analogs cannot be synthesized using the studied methods. This is due to steric hindrance of the structure in the case of *exo*-methylene analogs. On the other hand, oligomerization in acidic media disrupts the

formation of the other alkyls. In these cases, further improvements of the methodology are required.

Computer-enhanced TLC images are found to be very useful in determining the spots on TLC with similar R_f value. Also, it can be used to estimate the change in ratio between each substances in the crude mixture.

Proposal for Future Work

Cannabimimetic indoles with non-carbonyl bioisosteres are subject to be tested for the binding affinity at human CB1 and CB2 receptors. The standard assay involves the detection in displacement of standard radioligand; such as radiolabelled-CP-55940, onto the hCB1 and hCB2 receptors implanted in cloned CHO cells.

The determination of K_i can then be correlated with the currently known SAR of the cannabimimetic indoles. By comparing the actual angle between the arene systems of the molecules with the known cannabinoid receptors structures, the model for human CB1 and CB2 receptors can be improved. Either, QSAR can be done to quantify the relationship between the angle and binding efficacy. The extended understanding of the structure of cannabinoid receptors could advocate to the development of new pharmaceuticals.

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