Synthesis and Pharmacology of N-alkyl-3-(halo-naphthoyl)indoles

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SYNTHESIS AND PHARMACOLOGY OF N-ALKYL-3-(HALONAPHTHOYL)INDOLES

A Dissertation
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy
Chemistry

by
Valerie J. Smith
August 2008

Accepted by:
Dr. John W. Huffman, Committee Chair
Dr. R. Karl Dieter
Dr. Dennis W. Smith, Jr.
Dr. William T. Pennington
ABSTRACT

The medicinal values of marijuana have often been overshadowed due to the psychotropic, “recreational” effects it brings about in a user. For hundreds of years the therapeutic uses of cannabis sativa were appreciated, but the inability to control the dosage of the main constituent, and therefore the psychotropic effects, rendered the drug a liability. The elucidation of the structure of this main psychoactive constituent, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) by Gaoni and Mechoulam in 1964 opened the door to the discovery of a vast array of knowledge about cannabinoids. From the multiple classes of cannabinoids and the ways these compounds interact with the body to the design and synthesis of new cannabinoids based on structure-activity relationships (SAR), the scientific studies into the medicinal effects of marijuana have flourished. There are two main goals of the research presented in this dissertation: To design new cannabinoids that have the potential to become pharmaceutical products with therapeutic effects parallel to $\Delta^9$-THC while minimizing the psychoactive effects and to better understand the interactions that these cannabimimetic analogs have with the cannabinoid receptors. This dissertation pursues these goals through the syntheses of two series of cannabimimetic indoles possessing electron-withdrawing substituents and one series of indoles possessing an electron-donating substituent.

Halogenated compounds were the primary focus of the series of indoles possessing electron-withdrawing substituents. These compounds were designed to be selective for the CB$_2$ receptor while also maintaining an affinity for the receptor. Series
of both $N$-alkyl-3-(4-halo-1-naphthoyl)indoles and $N$-alkyl-3-(8-halo-1-naphthoyl)indoles have been synthesized. These compounds show good affinities for the CB$_2$ receptor and some also have selectivity for CB$_2$.

Huffman, et.al. had previously synthesized four series of $N$-alkyl-3-(methoxy-1-naphthoyl)indoles which showed either affinity or selectivity for the CB$_2$ receptor depending on the location of the alkoxy group on the naphthoyl ring. A series of $N$-alkyl-3-(6-methoxy-2-naphthoyl)indoles was synthesized and found to lack any substantial affinity or selectivity for the receptors.
ACKNOWLEDGMENTS

First and foremost, I would like to extend my deepest gratitude to my advisor, Dr. John W. Huffman. The guidance, patience and encouragement I have received from him over the course of my graduate career has been invaluable.

I would also like to thank Dr. R. Karl Dieter, Dr. Dennis W. Smith, Jr. and Dr. William T. Pennington for their support and assistance in writing this dissertation.

I am grateful to the research groups of Dr. Billy Martin and Dr. Jenny L. Wiley at Virginia Commonwealth University for the pharmacology data presented in this dissertation.

I would like to recognize the members of the Huffman research group, past and present. Special thanks goes to Dr. Karla-Sue Marriott and Dr. Alicia Thompson not only for the guidance and patience they have given me but for their friendship throughout the past five years.

The course of my education has been influenced by many people over the years. My deepest thanks goes out to all of the chemistry professors I have had during my undergraduate and graduate careers at both Wheeling Jesuit University and Clemson University. If not for a very special teacher and the passion that he conveyed to a young classroom, my interest in chemistry may never have been discovered. The initial exposure and solid understanding of chemistry that he set forth has allowed me to achieve the many successes I have had throughout my chemistry career. My most sincere thanks
goes out to Mr. Vincent Thornburg for sparking the passion that has led me to where I now am.

To my family and all of my friends, this dissertation would not have been possible without your strength and support. It is through all of you that I know I am able to achieve anything. A special thanks goes to my parents, Francis and Vicki Jo Smith, for their love, tolerance and support while I have been molding myself into the woman I am today.
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<tr>
<td>AAI</td>
<td>aminoalkylindole</td>
</tr>
<tr>
<td>AEA</td>
<td>anadamide</td>
</tr>
<tr>
<td>AlCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>aluminum chloride</td>
</tr>
<tr>
<td>AMP</td>
<td>adenosine monophosphate</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine 5'-triphosphate</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CBD</td>
<td>cannabidiol</td>
</tr>
<tr>
<td>CBG</td>
<td>cannabigerol</td>
</tr>
<tr>
<td>CBN</td>
<td>cannabinol</td>
</tr>
<tr>
<td>CDC&lt;sub&gt;3&lt;/sub&gt;</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CHO</td>
<td>Chinese hamster ovary</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>D&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>deuterium oxide</td>
</tr>
<tr>
<td>DCDMH</td>
<td>1,3-dichloro-5,5-dimethylhydantoin</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DMH</td>
<td>1,1-dimethylheptyl</td>
</tr>
<tr>
<td>DMH</td>
<td>5,5-dimethylhydantoin</td>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<td>EtAlCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ethylaluminum dichloride</td>
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<td>Et&lt;sub&gt;2&lt;/sub&gt;AlCl</td>
<td>diethylaluminum chloride</td>
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<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>GC/MS</td>
<td>gas chromatograph / mass spectrometry</td>
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<tr>
<td>GDP</td>
<td>guanosine diphosphate</td>
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<td>GPCR</td>
<td>G-protein coupled receptor</td>
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<td>GTP</td>
<td>guanosine triphosphate</td>
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<td>HHC</td>
<td>(-)-9-nor-9β-hydroxy-hexahydrocannabinol</td>
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<td>mouse vas deferens</td>
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<td>NMR</td>
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<td>dp</td>
<td>doublet of pentets</td>
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<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<tr>
<td>N-Ts-pyrrole</td>
<td>N-\textit{p}-toluenesulfonylp{	extit{y}}rrole</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>RI</td>
<td>ring immobility</td>
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<tr>
<td>RT</td>
<td>rectal temperature</td>
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CHAPTER ONE
INTRODUCTION

The initial usage of marijuana, or *Cannabis Sativa L.*, named by Carl Linnaeus in 1753, dates back possibly 10,000 years to ancient Chinese culture. To these people, cannabis was a necessity, not as a psychoactive substance, but rather as a source of fiber. The thick stalks of the plant were turned into fabric, or hemp, and used for making such items as clothing, rope, baskets and fishing nets. It is believed that not until the twenty-eighth century BC that the medicinal properties of the cannabis plant were introduced to the people by the emperor Shen-Nung. While this early culture was not unaware of the psychedelic effects of cannabis, they looked upon them as a negative influence until the first century AD when Taoism, and its interest in magic and alchemy, was at its height.\(^1\)

Until the 19\(^{th}\) century, when cannabis began receiving serious attention as a result of its medicinal properties, the main uses of the plant remained both as a source of recreation and a source of fiber. When the Irish physician William Brooke O’Shaughnessy returned to England from a professorship at the Medical College of Calcutta in India, he introduced the western world to the medicinal uses of marijuana. The news of his findings spread to America, where up until that time the American settlers primary use of this crop was the fabrication of hemp. In 1854 the U.S. Dispensatory listed cannabis among the nation’s medicines.\(^{1,2}\)

In the 1920’s and 1930’s the use of marijuana as a recreational drug began to rise among migrant workers and members of lower socioeconomic groups. Following in the
footsteps of anti-opium laws, which were directed at Chinese immigrants, and prohibition, which was an attack upon the unsupported theory that the working class was becoming lazy from demon rum, the regulation and eventual outlawing of cannabis was aimed at the rising Mexican population. The media successfully encouraged this “reefer racism” among the public and it ultimately ended with the passage of the Marijuana Tax Law of 1937. This law still permitted the use of cannabis stalks for hemp and the seeds for bird feed but outlawed the recreational possession of marijuana and put heavy regulations on the medicinal use, study and prescription of the drug.\textsuperscript{1} Marijuana has since been cited in many additional narcotic laws and is today classified as a Schedule I Controlled Substance under the Comprehensive Drug Abuse Prevention and Control Act of 1970. A Schedule I substance is defined as having a high abuse potential, no medical use in the United States, and lacks accepted safety data for use under medical supervision.\textsuperscript{3}

The elucidation of the structure of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC, \textbf{1}, Figure 1), the main psychoactive component of marijuana, by Gaoni and Mechoulum in 1964, was instrumental in the development of the therapeutic uses of medicinal marijuana and other cannabinoids that are employed today.\textsuperscript{4} The medicinal attributes of THC, which is found in the flowering buds and upper leaves of the female plant, include, but are not limited to, analgesic, anti-convulsive, anti-inflammatory, antipyretic, antiemetic and appetite stimulant effects. Patients who suffer from multiple sclerosis, cancer patients undergoing chemotherapy, those who suffer from glaucoma, and people who have succumbed to anorexia nervosa due to HIV/AIDS are amongst those experiencing the relief of
symptoms by using marijuana. However, the drawback of using cannabis as a medicinal agent is the psychotropic effects. These effects include feelings of euphoria, or the “high” that recreational users experience, a distorted perception of time, a decrease in attention as well as short term memory problems.

![Figure 1. Structure of Δ⁹-THC and the IUPAC dibenzopyran numbering system.](image)

Since the structure of Δ⁹-THC was resolved, thousands of cannabinoids have been synthesized and investigated. However there are currently only four cannabinoids commercially available on the global market. Of these, two have been sanctioned for use in the United States by the Food and Drug Administration (FDA). The first cannabinoid endorsed for medical use was dronabinol (1). Approved in 1992, dronabinol is synthetic Δ⁹-THC, marketed under the name Marinol®, as an antiemetic for cancer patients as well as an appetite stimulant for those who suffer from anorexia associated with HIV and AIDS. Nabilone (2, Figure 2), the racemate is marketed as Cesamet®, was approved in 2006 for use as an antiemetic for cancer patients undergoing chemotherapy.
oromucosal spray Sativex®️, available for prescription in Canada and the United Kingdom, is a mixture of Δ⁹-THC (1) and cannabidiol (3, Figure 2) which is prescribed to alleviate neuropathic pain associated with multiple sclerosis. The European Union approved the marketing of the cannabinoid receptor antagonist rimonabant (4, Figure 2), or Acomplia®, in 2006 as an anti-obesity drug.

**Figure 2.** Structures of pharmaceutical cannabinoids.

Over the decades following the structure elucidation of Δ⁹-THC many advances were made in the area of medicinal marijuana. It was found that over 60 types of
cannabinoids are naturally occurring in cannabis, a cannabinoid being classically defined as any terpenophenol classified as a C$_{21}$ compound typical of and present in *Cannabis sativa* L., their carboxylic acids, analogs and transformation products. Of the over 60 naturally occurring cannabinoids found in marijuana, ∆$_9$-THC and cannabinol (CBN, Figure 3) are the most abundant. Other cannabinoids found in *cannabis sativa* include, but are not limited to, ∆$_8$-THC (6, Figure 3), cannabidiol (CBD, 3) and cannabigerol (CBG, 7, Figure 3). Many of the naturally occurring cannabinoids, including CBN, CBD and CBG, do not have psychotropic effects. Today, the term cannabinoid refers to any compound that interacts with either cannabinoid receptor, exhibiting pharmacology similar to that of ∆$_9$-THC.

To date thousands of cannabinoids have been synthesized, but they are all placed into one of five general classes of cannabinoids: classical, non-classical, aminoalkylindoles, endocannabinoids, or diaryl pyrazoles. Once the structure of ∆$_9$-THC was identified there was debate over whether the numbering should be based on the monoterpenoid substructure or the IUPAC recommendation based on the ABC dibenzopyran system (ABC - 1). Use of the former was popular in Europe, which led to some confusion since THC was ∆$_1$-THC under the terpenoid numbering system, but ∆$_9$-THC using the IUPAC system.
Today classical cannabinoids are those compounds closely structurally related to the native plant constituents through the ABC tricyclic substructure and are numbered based on the IUPAC numbering system. There is not a structural feature of Δ⁹-THC that has not been altered to better understand the reactivity of cannabinoids. Studies showed that the three locations of greatest interest were the C-1 phenolic hydroxyl, the C-3 alkyl side chain and the moieties surrounding the C-9 carbon. First, it was determined that the C-3 side chain retained activity when it consisted of between three to eight carbons and that addition of either 1,1- or 1,2-dimethyl groups on the chain increased potency. Stereochemistry of the 1,2-dimethyl substituents in this position did not seem to change the binding affinities. The lengthening and branching of the chain to 1,1-dimethylheptyl (DMH) seemed to increase the receptor affinity of many cannabinoids. The C-1

**Figure 3.** Naturally occurring cannabinoids.
The hydroxyl group of the A-ring was believed to be necessary for CB₁ binding due to interaction through hydrogen bonding with the receptor. Substitution of this phenolic moiety has shown that phenol ethers have less binding affinity than Δ⁹-THC while phenol esters are active in vivo. Replacement of the hydroxyl with either an amine or thiol has given mixed results. The dimethyl groups on C-6 of the B-ring have been altered but have been found to have a less pronounced effect than altering the C-3 side chain. It has been found that the methyl functionality at C-9 is not a requirement for activity. Synthesis of 11-OH-THC (8, Figure 4), HU 210 (9, Figure 4), and other analogs having alternative substitutions at this position, have been found to display a high affinity for the receptor. It is also known that the olefin of the Δ⁹ or Δ⁸ position is not a necessity, stemming from the synthesis of HHC (10, Figure 4).
Figure 4. Some synthetic classical cannabinoids.

The altering of these various substituents on ∆⁹-THC has led to the suggestion that a three point interaction of the ligand with the receptor is essential for cannabinoid selectivity. This hypothesis was based on structure-activity relationship (SAR) studies, which have been verified through the synthesis of a number of additional traditional cannabinoids. The three features found necessary for biological activity include the C-1 phenol group, which is essential for hydrogen bonding interactions with the receptor, the C-3 side chain of the A-ring because of its hydrophobic interactions with the receptor and the placement of a moiety on the C-9 carbon atom of the C-ring (Figure 5).¹⁴
Compounds that exhibit structural features required for analgesia and lack the B-ring of the tricyclic benzopyran nucleus of classical cannabinoids are referred to as nonclassical cannabinoids. The development of these AC bicyclic terpenoids by Pfizer in the mid-1980s as a series of non-opioid analgesics was based on the observation that the pyran nucleus and its geminal dimethyl groups on the C-6 carbon were not necessary for activity. Altering the A-ring C-3 side chain, addition of a side chain at C-4 of the C-ring and synthesizing a series with the C-ring ranging from cyclopentyl to cyclooctyl led to the optimization of this series with the discovery of CP 55,940 (Figure 6). The synthesis of a variety of the nonclassical cannabinoids, the most common derivations being an AC or an AB bicyclic ring system, supports the hypothesis of three sites for receptor recognition.

In 1991, a group at Sterling-Winthrop found that pravadoline, an indole based nonsteroidal anti-inflammatory drug (NSAID), showed cannabimimetic activity. This discovery ultimately led to the development of a series of cannabimimetic indoles classified as aminoalkylindoles (AAI’s). These AAIs are in general characterized by the
presence of an aroyl moiety at C-3 of the indole nucleus and an alkyl side chain on the indole nitrogen. (12, Figure 6). While many hypotheses have been made regarding a correlation of the SAR for classical and nonclassical cannabinoids with AAIs, it has been found that this class interacts with the receptors in a different manner than classical and nonclassical cannabinoids.17

A class of endogenous cannabinoids, which occur naturally in mammalian tissue, was discovered by Mechoulam and co-workers in 1992. These endocannabinoids are derivatives of arachidonic acid and are characterized by their long chain, polyunsaturated fatty acid structure. The first two major endocannabinoids, isolated from porcine brain, are arachidonylethanolamide, or anandamide (AEA), so named because the term ananda comes from the Sanskrit word for inner bliss, and 2-arachidonylglycerol (13, Figure 6). Since their discovery, many endocannabinoids have been synthesized or isolated. SAR of endocannabinoids have led to the conclusions that typically they contain 18 to 22 carbon atoms and that 3 to 4 double bonds are required for CB₁ binding to occur.18,19

In 1994, the Sanofi group reported the discovery of diaryl pyrazole cannabinoid antagonists. The most notable of these antagonists is SR141716A (Rimonabant, 13, Figure 6). These compounds have affinity for the cannabinoid receptors but do not activate the intracellular signaling system typically initiated upon binding of G-protein coupled receptors. Note that Acomplia® is prescribed to overcome obesity when typically one associates marijuana with appetite stimulation.11,20
Figure 6. Examples of non-traditional (11), AAI (12), endogenous (13), and diarylpyrazole (14) cannabinoid ligands.

In 1988, the first cannabinoid receptor, CB$_1$, was structurally identified by Devane and co-workers and the nature of the structure-activity relationships (SAR) of cannabinoids could begin to be understood. This receptor is primarily located in the central nervous system and parts of the brain that affect such activities as body movement, coordination and short term memory. In 1993, the discovery of a second
cannabinoid receptor, CB$_2$, located in the spleen and affecting the immunological, or peripheral system, aroused more questions about receptor-ligand interactions.$^{22}$

Cannabinoid receptors are known to be members of the family of G-protein coupled receptors (GPCR). The commonly shared structural characteristics of GPCR’s are an extracellular $N$-terminus and an intracellular $C$-terminus connected through seven transmembrane (TM) $\alpha$-helical loops, which are made up of amino acids. Hydrophilic amino acids face the interior of the protein while hydrophobic amino acids face the exterior. The CB$_1$ receptor was isolated in mouse brain in 1990 and then finally in human brain by Gerard and co-workers in 1991.$^{23-24}$ The structure of GPCR’s is based upon the structure of rhodopsin. These $G$ proteins exist in a heterotrimer form ($\alpha\beta\gamma$) and possess tightly bound guanosine diphosphate (GDP) in the inactive state. Guanosine diphosphate (GDP) is the product of dephosphorylation of GTP (guanosine-5’-triphosphahte) through GTPase. Upon interaction with a receptor agonist, a conformational change of the receptor confers sufficient energy to the system such that GDP dissociates. In the absence of the guanine nucleotides, the receptor-hormone-$G$ protein intermediate complex exhibits a relatively high affinity for the agonist. The receptor is activated upon binding of GTP to this complex. The affinity of the agonist ligand for the receptor is then decreased, and the G-protein dissociates from the receptor and separates into $\alpha$ and $\beta\gamma$ subunits. The GTP bound $\alpha$ subunit now interacts with adenylate cyclase and inhibits its enzymatic activity, causing a decrease in the conversion of ATP to cyclic AMP (cAMP). The activated protein also interacts with target ion channels by opening potassium channels and closing calcium channels.$^{25}$ Dissociation of the ligand from the receptor
along with hydrolysis of the GTP on the α subunit allows the system to perpetually respond to altered concentrations of hormone\textsuperscript{21} (Figure 7).

\textbf{Figure 7.} Interaction of a G-protein coupled receptor (GPCR).

Since the mapping of the CB\textsubscript{1} receptor (Figure 8), many breakthroughs have been made in the determination of key points of ligand-receptor interaction. Cannabinoid ligands interact with intracellular G-proteins to inhibit adenylate cyclase. The inhibition of this secondary messenger leads to a decrease in cyclic AMP production resulting in the CNS effects that cannabinoids produce in humans and animals.\textsuperscript{14} Transmutagenic studies have been carried out on the CB\textsubscript{1} receptor in order to identify possible sites of interaction. The binding of a cannabinoid changes the conformation of transmembrane helix-7 (TM7), which in turn is believed to alter residues in the C-terminus. It is believed that the
altering of the C-terminus initiates G-protein activation. It has also been found through chimera studies that in some way Asp_{163} on TM2 as well as peptides on the third intracellular loop (C3) play a role in G-protein activation. Another factor showing involvement of the C3 loop on G-protein activation are interactions between TM3 and TM6. TM6 has a pro-kink allowing for the possibility that movement in that helix could be facilitated by a ligand binding. Both Barnett-Norris and Shim and colleagues proposed that the hydrophobic alkyl side chains of cannabinoid agonists act as triggers to move TM6. This motion alters the conformation of the C-terminal side of the C3 loop.\(^\text{27}\) It has also been found in studies performed using CP-55,940 that Lys_{192} on TM3 may be a hydrogen bonding donor to the phenolic oxygen in traditional and non-traditional cannabinoids.\(^\text{28}\)

To date the detailed structure of the CB\(_2\) receptor remains elusive. It is known that the CB\(_2\) receptor has 44% sequence identity with the CB\(_1\) receptor and 68% identity in the TM regions associated with ligand-receptor recognition.\(^\text{22}\) Chimeric data on Lys_{192}, known to be involved in CB\(_1\) binding, indicates that AAI’s, which have a binding preference for CB\(_2\), do not bind to CB\(_1\) in the same manner as other classes of cannabinoids.\(^\text{28}\) Ligands found to show an affinity for the CB\(_2\) receptor include AAI’s and structures lacking the A-ring phenolic hydroxyl or possessing hydroxymethyl groups at that position. Huffman and co-workers have found evidence based on AAIs that aromatic stacking may be involved in receptor bonding with CB\(_2\).\(^\text{29}\)
Interactions with the CB₁ and CB₂ receptors can be measured both *in vivo* and *in vitro*. It can be determined if there is possible cannabimimetic activity based on animal behavioral studies. These tests focus on the prediction of cannabis-like activity through drug discrimination and other *in vivo* procedures. Data from *in vivo* bioassays is quantified and reported as an ED₅₀ value. An ED₅₀ value is the dose that produces a response equal to half of the maximum response. These are determined by plotting the dose-response relationship, a simple X-Y graph, of the logarithm of the dose versus the intensity of the response. This results in a sigmoidal curve indicating the threshold dose along with the dose necessary for maximal response. These behavioral results have
been correlated with CB$_1$ receptor affinity. *In vitro* affinity (K$_i$) has been plotted against *in vivo* potency (ED$_{50}$) using linear-regression analysis of log-log data. It has been shown that compounds displaying a high receptor affinity also display behavioral results in mice. The two common bioassays for *in vivo* measurement are drug discrimination and a series of tests referred to as the mouse tetrad.

In the drug discrimination test, an animal is put into a cage and taught that it must press a lever to receive a food reward. Once this is accomplished, the mouse is injected with Δ$^9$-THC and learns that only one lever will release food. The mouse is then injected with a vehicle drug and the opposing lever gives the food reward. Finally, the possible cannabinoid ligand is injected and physiological effects can be noted by observing which lever the mouse associates with the food reward. This model has been indicative of compounds that would produce cannabimimetic psychoactivity in humans.

More commonly used for *in vivo* studies is the mouse tetrad bioassay. Developed in the mid-1980s by Billy Martin and colleagues, this methodology is preferred because of the nominal expenses and short time duration that this series of four tests requires. The series of four behavioral tests, that when put together are capable of determining cannabis-like activity, include the measurement of spontaneous activity (SA), analgesia by means of tail flick (TF), hypothermia via rectal temperature (RT) and catalepsy using ring immobility (RI). Carried out in one group of mice, these tests are performed at 5, 20, 60 and 90 minutes, respectively, after initial injection of the cannabinoid.

*In vitro* assays, which quantify CB$_1$ and CB$_2$ activity through radiolabelled ligands, include [$^{35}$S]GTPγS binding and competitive binding assays. Also,
autoradiography, using the radiolabelled ligand $[^{35}\text{S}]\text{GTP}_{\gamma}S$ (Figure 9) has provided an effective method for exploring the brain regional distribution of CB$_1$ receptor activated G-proteins.$^{32}$ These receptors are now known to reside mainly in the basal ganglia, cerebellum, hippocampus and cerebral cortex, which explains the psychological and physiological effects cannabinoids have on the CNS. It is also known that agonist promoted binding of $[^{35}\text{S}]\text{GTP}_{\gamma}S$ evaluates the interactions between G-proteins and GPCR’s. Unlike its GTP analog, $[^{35}\text{S}]\text{GTP}_{\gamma}S$ is poorly hydrolyzed due to the phosphorothioate group. When present, this radioligand competes with GTP for the G$_{\alpha}$-GTP binding site and forms the quasi-irreversible G$_{\alpha}$-GTP$_{\gamma}S$ complex, whose half-life is prolonged (Figure 10). From this, the agonist rates of GDP and $[^{35}\text{S}]\text{GTP}_{\gamma}S$ exchange can be compared and the degree of G protein activation is determined. The amount of $[^{35}\text{S}]\text{GTP}_{\gamma}S$ displaced provides a quantitative measure of the affinity and the efficacy of a compound. These qualities are then used to determine if a cannabinoid is an agonist, antagonist or partial agonist. The efficacy, which is the ability of a drug to induce a biological response in a receptor, should not be confused with the affinity of a drug to bind to a receptor. Generally an agonist has a high affinity as well as a high efficacy and an antagonist has affinity but lacks efficacy. An agonist can also have a high efficacy, producing maximal response, while having low affinity for the receptor. Alternatively, an agonist of low efficacy, which cannot activate the receptor to the same degree, may occupy a large part of the receptor, or have a high affinity. A drug categorized as a partial agonist falls into the latter category.$^{35,36}$
Figure 9. Structure of $^{35}$S\text{GTP}$\gamma$S showing the phosphorothioate group.

Figure 10. Interaction of $^{35}$S\text{GTP}$\gamma$S with a G Protein.

A second method for determining cannabimimetic activity in vitro employs the use of competitive binding assays. These bioassays measure the displacement of [$^3$H]CP-55,940 or [$^3$H]WIN-55,212-2, as described by Compton and co-workers. Comparison of these in vitro values with findings from previous in vivo studies reinforced the validity
of this procedure. This assay employs either rat brain membrane preparations for
determining CB\textsubscript{1} activity or chinese hamster ovary (CHO) transfected cell lines if
determining CB\textsubscript{2} activity.\textsuperscript{37} The appropriate cells are added to solutions containing a
known quantity of radioligand followed by varying concentrations of the cannabinoid
analog. The amount of radioactivity present is quantified using liquid scintillation
spectrometry.\textsuperscript{32} The amount of displacement, or IC\textsubscript{50} value, is obtained by non-linear
regression of the log of the concentration-percent displacement data. This value is used to
determine the K\textsubscript{i} value, or inhibition constant, through the application of the Cheng-
Prusoff equation (Figure 11).\textsuperscript{38} This equation applies the concentration of radioligand,
[^3L], the known dissociation constant of the radioligand from the receptor, K\textsubscript{d}, and the
IC\textsubscript{50} value, or the concentration of the cannabinoid analog that displaces fifty-percent of
the radioligand, as obtained from the binding assay. All studies are performed in triplicate
and reported results are representative of the combined data of three to six independent
experiments.

\begin{equation}
K_i = \frac{IC_{50}}{1 + \frac{[^3L]}{K_d}}
\end{equation}

\textbf{Figure 11.} Cheng-Prusoff Equation.\textsuperscript{38}

The affinity of a cannabinoid for either the CB\textsubscript{1} or CB\textsubscript{2} receptors is reported as a
K\textsubscript{i} value. A high affinity ligand will have a low K\textsubscript{i} value for one or both of these
receptors. When one receptor has a much higher affinity than the other, this cannabinoid
is said to selective for that receptor. This selectivity helps in understanding the SAR of certain compounds with the receptors and assists in the design of future cannabinoids. The $K_i$ values for some aforementioned cannabinoids are shown in Table 1, along with the $CB_1$ and/or $CB_2$ selectivity of each.

Table 1. $K_i$ values of common cannabinoids.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_i CB_1$ (nM)</th>
<th>$K_i CB_2$ (nM)</th>
<th>$CB_1$ selectivity</th>
<th>$CB_2$ selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta^2$-THC (1)</td>
<td>40.7 ± 2.0$^a$</td>
<td>36.4 ± 10$^a$</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>$\Delta^8$-THC (6)</td>
<td>47.6 ± 2.4$^b$</td>
<td>39.3 ± 2.0$^b$</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Cannabidiol, CBN (5)</td>
<td>308 ± 40$^a$</td>
<td>96.3 ± 14.4$^a$</td>
<td>0.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Cannabidiol, CBD (3)</td>
<td>4350 ± 390$^a$</td>
<td>2860 ± 1230$^a$</td>
<td>0.7</td>
<td>1.5</td>
</tr>
<tr>
<td>HU-210 (9)</td>
<td>0.73 ± 0.11$^a$</td>
<td>0.22 ± 0.18$^a$</td>
<td>0.3</td>
<td>3.3</td>
</tr>
<tr>
<td>SR141716A (14)</td>
<td>12.3 ± 3.1$^a$</td>
<td>702 ± 62$^a$</td>
<td>57</td>
<td>0.01</td>
</tr>
<tr>
<td>CP-55,940 (11)</td>
<td>0.58 ± 0.07$^a$</td>
<td>0.69 ± 0.02$^a$</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>AEA (13)</td>
<td>89 ± 10$^a$</td>
<td>371 ± 102$^a$</td>
<td>4.2</td>
<td>0.2</td>
</tr>
<tr>
<td>WIN-55,212-2 (12)</td>
<td>1.9 ± 0.1$^a$</td>
<td>0.28 ± 0.16$^a$</td>
<td>0.1</td>
<td>6.8</td>
</tr>
</tbody>
</table>

$^a$ Ref. 37. $^b$ Ref. 39.

The focus of this dissertation is the synthesis of $CB_2$ selective ligands. This research is derived from investigations into the SAR of aminoalkylindoles (AAIs). Modification and distribution of various substituents on the indole and naphthoyl moieties of AAIs has led to the design of many new $CB_2$ selective ligands.

Studies into AAIs began in 1991 when Sterling-Winthrop was designing a new series of nonsteroidal anti-inflammatory drugs (NSAIDs). Of these NSAIDs, Pravadoline (15, Figure 12) was found to inhibit contractions of mouse vas deferens. The inhibition of
mouse vas deferens (MVD) is known to be due to effects caused by CB$_1$ receptor interactions.$^{17,40}$ The inhibition of MVD activity has been associated with the inhibition of adenylate cyclase as well as the inhibition of prostaglandin synthetase activity.$^{41}$ The finding that this drug had cannabimimetic activity led to the design of a series of indole based cannabinoids, the most potent of which is WIN-55,212-2 (12). These AAIs display a higher affinity for the CB$_2$ receptor, thus making them the focus of many new investigations. Huffman and co-workers initiated studies using the program PCModel to describe a common pharmacophore between Δ$_9$-THC and this new class of cannabinoids.$^{42}$ It was found that the aroyl moiety of the AAIs align with the Δ$_9$ olefin of Δ$_9$-THC, the carbonyl of AAIs align with the phenolic C-1 hydroxyl and the aminoalkylindole on the indole nitrogen align with the C-3 side chain of classical cannabinoids (Figure 13).

![Figure 12. Structure of the NSAID pravadoline.](image-url)
In addition to the alignment predicted above, it was believed by Eissenstat that a small substituent, or none, was required at the C-2 of the indole.\textsuperscript{43} Based on this pharmacophore, a series of 2-methyl-N-alkyl-3-(1-naphthoyl)indoles was designed.\textsuperscript{42} The replacement of the morpholino group emanated from the assumption that since the C-3 alkyl side chain of $\Delta^9$-THC aligned with this group, the replacement of the amine substituent with an alkyl chain would retain its cannabimimetic activity. The synthesis of a series of 2-methyl-N-alkyl-3-(1-naphthoyl)indoles (16, Figure 14) with the alkyl chain ranging from one to seven carbons was initiated and the results can be seen in Table 2.

Figure 13. PCModel comparison of $\Delta^9$-THC and WIN-55,212-2.
Figure 14. General structure of 2-methyl-N-alkyl-3-(1-naphthoyl)indole.

Table 2. Effects of replacing the aminoalkyl side chain with an alkyl chain.

<table>
<thead>
<tr>
<th>compound</th>
<th>R</th>
<th>$K_i$, CB$_1$ (nM)</th>
<th>$K_i$, CB$_2$ (nM)</th>
<th>CB$_2$ selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-042</td>
<td>methyl</td>
<td>&gt;10,000$^c$</td>
<td>5050 ± 192$^c$</td>
<td>-</td>
</tr>
<tr>
<td>JWH-043</td>
<td>ethyl</td>
<td>1180 ± 44.0$^c$</td>
<td>964 ± 242$^c$</td>
<td>1.2</td>
</tr>
<tr>
<td>JWH-015</td>
<td>n-propyl</td>
<td>336 ± 36.0$^c$</td>
<td>13.8 ± 4.6$^c$</td>
<td>24</td>
</tr>
<tr>
<td>JWH-016</td>
<td>n-butyl</td>
<td>22.0 ± 1.5$^c$</td>
<td>4.3 ± 1.6$^c$</td>
<td>5.1</td>
</tr>
<tr>
<td>JWH-007</td>
<td>n-pentyl</td>
<td>9.5 ± 4.5$^c$</td>
<td>2.9 ± 2.6$^c$</td>
<td>3.3</td>
</tr>
<tr>
<td>JWH-004</td>
<td>n-hexyl</td>
<td>48.0 ± 13.0$^c$</td>
<td>4.0 ± 1.5$^c$</td>
<td>12</td>
</tr>
<tr>
<td>JWH-009</td>
<td>n-heptyl</td>
<td>311 ± 106$^c$</td>
<td>141 ± 14.5$^c$</td>
<td>2.2</td>
</tr>
</tbody>
</table>

$^c$ Ref. 44.

The $K_i$ values for the $N$-alkyl-2-methyl-3-(1-naphthoyl)indole series shown above show that an alkyl chain ranging from three to six carbons have affinity for the cannabinoid receptors.$^{44}$ It should be noted however that it is the propyl and pentyl chains
that display affinity as well as a selectivity for the CB\textsubscript{2} receptor. The affinities of chain lengths below propyl and above hexyl are greatly attenuated.

Since affinity for the receptors was maintained by replacement of the aminoalkyl chain with an alkyl chain, studies began into the altering of other sites of these \textit{N}-alkyl-3-(1-naphthoyl)indoles. Analysis of the 2-methyl substituent of the indole resulted the findings that while the removal of the methyl group maintained and in some cases accentuated receptor binding, elongation of the methyl substituent reduced or terminated all affinity.\textsuperscript{17, 40, 45}

The aromatic functionality of the AAI pharmacophore is typically a naphthyl ring, a phenyl or substituted phenyl substituent usually attenuates receptor affinity. The aryl moiety was proven to be essential for activity; when it was replaced with an acyl substituent the compounds had virtually no affinity. This supported the hypothesis that aromaticity was playing a vital role in receptor interactions.\textsuperscript{42}

The remaining piece of the predicted pharmacophore to be altered was the carbonyl. The alignment of the carbonyl with the phenolic hydroxyl of traditional cannabinoids implied that this site was involved in hydrogen bonding interactions with the receptors. Reduction of the carbonyl group to a methylene gave compounds that retain receptor affinity, thus reinforcing the conclusion that AAIs do not interact via hydrogen bonding while supporting the aromatic stacking hypothesis.\textsuperscript{46}

The details of the interaction of AAIs with the CB\textsubscript{1} and CB\textsubscript{2} receptors remain enigmatic. Showalter performed initial approaches to establishing SAR for the peripheral receptor by determining and compiling CB\textsubscript{2} \textit{K}_i data for known AAIs.\textsuperscript{37} It was found that
these cannabinoids had selectivity for this receptor. Mutation studies done on the CB₁ receptor have verified that this class of cannabinoids does not interact in the same manner as classical, nonclassical and endogenous cannabinoids. The replacement on CB₁ of Lys₁⁹² with an alanine by Song and Bonner corroborated the previously stated finding.²⁸ This mutation attenuated the affinity of classical and nonclassical cannabinoids while only slightly affecting the potency of WIN-55,212-2. It has been hypothesized that AAIs may interact with the receptors via aromatic stacking.²⁸ Both Reggio⁴⁷ and Huffman²⁹ have done studies, which show that hydrogen bonding is not a factor in AAI ligand-receptor interactions. This was accomplished through the synthesis of series of compounds incapable of hydrogen bonding. While these naphthylideneindenes (17, Figure 15) and the indolynaphthymethane JWH-175 (18, Figure 15) showed affinity for the CB₁ receptor there was still speculation that hydrogen bonding could occur involving the indole nitrogen. To eliminate any doubt, Huffman synthesized the indene JWH-176 (19, Figure 15), a hydrocarbon, and found that it too retained an affinity for the CB₁ receptor, thus providing compelling evidence against a ligand-receptor hydrogen bonding interaction (Table 3). Studies supporting aromatic stacking have also been reported by Reggio and colleagues.⁴⁷ There are two transmembrane regions of the CB₁ receptor that contain clusters of aromatic amino acids. Docking studies that the Reggio group performed showed that on TM5 there is a tryptophan that may interact with the indole ring system, a phenylalanine that possibly interacts with one ring of the naphthoyl system and a tyrosine on TM3 believed to interact with the second naphthoyl ring. This evidence is further supported by the decreased potency of the pyrrole derivatives, having one less
aromatic ring than their indole analogs.\textsuperscript{46,47} A series of 3-(1-naphthoyl)-N-pentylpyrroles with aromatic substituents placed at the C-2 of the pyrrole nucleus showed moderate to high affinities for the receptors.\textsuperscript{48} The findings from this series, which increased possible aromatic interactions by the addition of another aromatic moiety, reinforced the theory of aromatic stacking between the ligand and the receptor.

![Image of molecules](image.png)

**Figure 15.** AAIs synthesized to disprove H-bonding with cannabinoid receptors.

<table>
<thead>
<tr>
<th>compound</th>
<th>$K_i$, CB\textsubscript{1} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-175 (18)</td>
<td>22 ± 2.0\textsuperscript{d}</td>
</tr>
<tr>
<td>JWH-176 (19)</td>
<td>26 ± 4.0\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{d} Ref. 29.

**Table 3.** $K_i$ values for AAIs lacking the carbonyl moiety.
When Reggio developed indene 17 it was not only to study the effects of the carbonyl group, but to study the bioactive conformations of these AAIIs. The E and Z indene isomers serve as good rigid analogs of the S-cis and S-trans AAI conformations. Ultimately, it was determined that when the C-2 position of the indole is unsubstituted, the principal conformation is the S-trans, in which the C-3 aryl is proximate to C-2 (Figure 16). However, when there is a methyl group at the C-2 position, the preferred conformation is S-cis, which places the C-3 aryl near C-4 of the indole nucleus (Figure 17). It is believed that the reason for these preferred conformations is to avoid steric bulk in the plane of the indole ring system so allowing the cannabinoids to interact with the receptors via aromatic stacking.47
Figure 16. Conformations of $N$-alkyl-3-(1-naphthoyl)indoles.

Figure 17. Conformations of 2-methyl-$N$-alkyl-3-(1-naphthoyl)indoles.
Many AAIs have been synthesized with various substituents on the naphthoyl ring. To summarize, addition of these groups reveals that frequently the placement of alkyl and alkoxy substituents on the two, four, six, and seven positions of the naphthoyl ring has shown increased CB\textsubscript{2} affinity relative to their unsubstituted analogs\textsuperscript{44,49,50}.

Based on the significant receptor affinities and the observed CB\textsubscript{2} selectivity of aminoalkylindoles such as WIN-55,212-2 (12, Figure 6, Table 1) and JWH-015 (Figure 14, Table 2), and the increased affinities of the naphthalene substituted analogs, the synthesis of a series of halogen substituted compounds was proposed. The research in this dissertation focuses on the synthesis and pharmacology of these 4’-halo and 8’-halo-naphthoylindoles.
Many $N$-alkyl-3-(1-naphthoyl)indoles have been synthesized with electron-donating substituents, namely alkyl and alkoxy groups, on the naphthoyl ring. These compounds show increased CB$_2$ affinity relative to their unsubstituted analogs. However, no compounds have been previously synthesized in this series which have electron-withdrawing substituents. For this reason it was decided to design a series of $N$-alkyl-3-(halo-naphthoyl)indoles. The primary focus of the research in this dissertation has been in the area of cannabimimetic indoles possessing halogen substituents on a 3-(1-naphthoyl) substituent. An initial retrosynthetic pathway to $N$-alkyl-3-(4-halo-1-naphthoyl)indoles and their 2-methyl analogs was designed (Figure 18). This synthesis involved the coupling of a naphthoyl halide with an alkyl indole via the Okauchi modification of the Friedel-Crafts reaction.$^{51}$ The required starting materials for this pathway were not commercially available, therefore the first priority was to synthesize the precursor compounds.
Figure 18. Retrosynthetic pathway to N-alkyl-3-(4-halo-1-naphthoyl)indoles and the 2-methyl analogs.

Alkyl Indoles

Alkylation of indole and its 2-methyl analog was performed using KOH and DMSO along with the appropriate alkyl halide (Figure 19). This S_N2 reaction involves deprotonation of the indole followed by nucleophilic attack on the primary alkyl halide, displacing the halide leaving group. This reaction gave yields of 88-98%, the by-product being the 1,3-dialkyl indole. Purification of the indoles was performed by one of two methods: vacuum distillation at 200 °C using a Kugelrohr or column chromatography.
\[ R' = \text{H, CH}_3 \]
\[ RX = n\text{-C}_3\text{H}_7\text{I} = n\text{-C}_5\text{H}_{11}\text{Br} \]

**Figure 19.** Preparation of alkyl indoles.

**Table 4.** Yields of alkyl indoles.

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>n-C\textsubscript{5}H\textsubscript{11}</td>
<td>H</td>
<td>98</td>
</tr>
<tr>
<td>21</td>
<td>n-C\textsubscript{5}H\textsubscript{11}</td>
<td>CH\textsubscript{3}</td>
<td>97</td>
</tr>
<tr>
<td>22</td>
<td>n-C\textsubscript{3}H\textsubscript{7}</td>
<td>H</td>
<td>90</td>
</tr>
<tr>
<td>23</td>
<td>n-C\textsubscript{3}H\textsubscript{7}</td>
<td>CH\textsubscript{3}</td>
<td>88</td>
</tr>
</tbody>
</table>

**4-halo-1-naphthoic acids**

All 4-halo-1-naphthoic acids, with the exception of 4-fluoro-1-naphthoic acid which is commercially available, were to be synthesized from the corresponding 1-halonaphthalenes. Initially, the proposed synthetic pathway involved electrophilic aromatic substitution of the 1-halonaphthalene using \( N,N \)-diphenylcarbamyl chloride and aluminum chloride to produce the 4-halo-1-naphthalamide.\textsuperscript{52} Base hydrolysis of the
amide using KOH and diethylene glycol would subsequently yield the 4-halo-1-naphthoic acid (Figure 20).

\[
\begin{align*}
\text{X} & \quad (\text{Ph})_2\text{NCOCl, AlCl}_3 & \quad \text{DCE} & \quad \text{reflux, 6 h} & \quad \text{X} \\
\text{X} & \quad \text{O} & \quad \text{N} & \quad \text{Ph} \\
\text{X} & \quad \text{O} & \quad \text{OH} \\
\text{X} & \quad \text{= Br, Cl, I}
\end{align*}
\]

**Figure 20.** Initially proposed synthetic pathway for 4-halo-1-naphthoic acids.

The first attempts at this synthesis were carried out using 1-bromonaphthalene. Acylation was achieved using \(N,N\)-diphenylcarbamyl chloride and anhydrous aluminum chloride in 1,2-dichloroethane (DCE), successfully resulting in 4-bromo-1-naphthalamide in 40% yield. The \(N,N\)-diphenylamide functionality is very stable and sterically hindered, so the conditions employed by Cason and co-workers were believed necessary.\(^{53}\) Several attempts to obtain the desired carboxylic acid using KOH and diethylene glycol were unsuccessful. Spectral data indicated that starting material was recovered, so an alternative route was sought and the overall scheme is shown in Figure 21.
Figure 21. Second proposed synthesis of 4-halo-1-naphthoic acids.

The first step in the alternate route (Figure 21) employed the Friedel-Crafts acylation of the 1-halonaphthalenes using anhydrous aluminum chloride and acetyl chloride. The solvents and reaction times differed for each halide (Figure 22), but the same chemistry was behind the product formation. While some 2-acylation product was observed, acylation occurred primarily in the 4- position and provided the desired product, 4-acetyl-1-halonaphthalene in 55-84% yield, after purification by column chromatography.
Oxidation of 4-acetyl-1-halonaphthalene to the corresponding carboxylic acid was achieved through the pyridinium salt via application of the King modification of the Haloform reaction, followed by hydrolysis using NaOH. Since the purification of carboxylic acids can be difficult and can result in a significant loss of yield, purification was effected by refluxing the crude acid in methanol and sulfuric acid. This gave the corresponding methyl 4-halo-1-naphthoate. After purification of the methyl ester, base hydrolysis was carried out in KOH and water to provide the 4-halo-1-naphthoic acids in acceptable yields.

Figure 22. Friedel-Crafts conditions and yields for each halide.
### Table 5. Yields for 4-acetyl-1-halonaphthoates.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>Br</td>
<td>58</td>
</tr>
<tr>
<td>28</td>
<td>Cl</td>
<td>63</td>
</tr>
<tr>
<td>29</td>
<td>I</td>
<td>56</td>
</tr>
</tbody>
</table>

### Table 6. Yields for 4-halo-1-naphthoic acids.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Br</td>
<td>73</td>
</tr>
<tr>
<td>31</td>
<td>Cl</td>
<td>88</td>
</tr>
<tr>
<td>32</td>
<td>I</td>
<td>86</td>
</tr>
</tbody>
</table>
The proposed subsequent steps for the target compounds were to prepare the naphthoyl chloride from the carboxylic acid, then activate the C-3 of the indole ring using the conditions described by Okauchi and co-workers to achieve acylation at the C-3 position. The mild Lewis acid dimethylaluminum chloride was to be used to achieve this (Figure 23).

**Figure 23.** Okauchi modification of the Friedel-Crafts reaction.
4-Bromo-1-naphthoic acid (30) was refluxed with thionyl chloride to provide the corresponding acyl chloride. Subsequent treatment of the indole 20 in dimethylaluminum chloride and dichloromethane with the acid chloride was expected to afford the desired product 39. Unfortunately this reaction proceeded only to give back starting materials. Subsequent attempts employing the use of various Lewis acids including ethylaluminum dichloride and diethylaluminum chloride were performed. These efforts proved futile in initial trials using both 4-bromo-1-naphthoic acid (30) and 4-chloro-1-naphthoic acid (31). Again, an alternative route was explored for successful coupling to arrive at the desired compounds.

A previously used method by former Huffman group member Dong Dai was employed.\textsuperscript{42} This procedure involved treating indole or 2-methylindole with methylmagnesium bromide in anhydrous diethyl ether. Treatment of the indolyl anion with the appropriate naphthoyl chloride ideally would provide the corresponding 3-(4-halo-1-naphthoyl)indoles. N-Alkylation of the indole was to be carried out as previously discussed and would yield the target compound (Figure 24). Unfortunately, this procedure was known to give low yields and the intermediate 3-naphthoylindoles are difficult to purify.
Accordingly, indole was stirred at 0 °C in anhydrous diethyl ether followed by addition of methymagnesium bromide. A temperature of 0 °C was maintained throughout the addition of the 4-bromo-1-naphthoyl chloride and was kept at that temperature for four hours thereafter. Successful coupling resulted in a 76% yield of 3-(4-bromo-1-naphthoyl)indole. The target compounds were acquired following N-alkylation in KOH and DMSO. Target compounds 37-40 were prepared in this manner. This procedure also proved successful for the synthesis of the N-alkyl-3-(4-chloro-1-naphthoyl)indole series and the 2-methyl analogs (41-44).

**Figure 24.** Alternative coupling using the Grignard Reagent MeMgBr.
Table 7. Yields of 3-(4-halo-naphthoyl)indoles and the 2-methyl analogs.

![Diagram of 3-(4-halo-naphthoyl)indoles and the 2-methyl analogs]

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>X</th>
<th>R′</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>Br</td>
<td>H</td>
<td>76</td>
</tr>
<tr>
<td>34</td>
<td>Br</td>
<td>CH₃</td>
<td>44</td>
</tr>
<tr>
<td>35</td>
<td>Cl</td>
<td>H</td>
<td>35</td>
</tr>
<tr>
<td>36</td>
<td>Cl</td>
<td>CH₃</td>
<td>36</td>
</tr>
</tbody>
</table>

Repeatedly low yields of the intermediates 34-36 were burdensome and reversion to the Okauchi procedure was attempted for the acylation using 4-iodo-1-naphthoic acid and 4-fluoro-1-naphthoic acid. Attempts to synthesize target compounds 45-48 and 49-52 proved successful and the desired products were formed in yields of 7-52%.
Table 8. Yields of $N$-alkyl-3-(4-halo-1-naphthoyl)indoles and the 2-methyl analogs synthesized via Figure 24.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>X</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>Br</td>
<td>$n$-$C_3H_7$</td>
<td>H</td>
<td>12</td>
</tr>
<tr>
<td>38</td>
<td>Br</td>
<td>$n$-$C_3H_7$</td>
<td>CH$_3$</td>
<td>50</td>
</tr>
<tr>
<td>39</td>
<td>Br</td>
<td>$n$-$C_5H_{11}$</td>
<td>H</td>
<td>18</td>
</tr>
<tr>
<td>40</td>
<td>Br</td>
<td>$n$-$C_5H_{11}$</td>
<td>CH$_3$</td>
<td>10</td>
</tr>
<tr>
<td>41</td>
<td>Cl</td>
<td>$n$-$C_3H_7$</td>
<td>H</td>
<td>15</td>
</tr>
<tr>
<td>42</td>
<td>Cl</td>
<td>$n$-$C_3H_7$</td>
<td>CH$_3$</td>
<td>46</td>
</tr>
<tr>
<td>43</td>
<td>Cl</td>
<td>$n$-$C_5H_{11}$</td>
<td>H</td>
<td>48</td>
</tr>
<tr>
<td>44</td>
<td>Cl</td>
<td>$n$-$C_5H_{11}$</td>
<td>CH$_3$</td>
<td>31</td>
</tr>
</tbody>
</table>

$^a$Yields are unoptimized and are representative of the one time alkylation of 3-(4-halo-1-naphthoyl)indoles.
Table 9. Yields of N-alkyl-3-(4-halo-1-naphthoyl)indoles and the 2-methyl analogs synthesized via the Okauchi Method (Figure 23).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>X</th>
<th>R</th>
<th>R'</th>
<th>Yields (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>I</td>
<td>n-C₃H₇</td>
<td>H</td>
<td>7</td>
</tr>
<tr>
<td>46</td>
<td>I</td>
<td>n-C₃H₇</td>
<td>CH₃</td>
<td>13</td>
</tr>
<tr>
<td>47</td>
<td>I</td>
<td>n-C₅H₁₁</td>
<td>H</td>
<td>15</td>
</tr>
<tr>
<td>48</td>
<td>I</td>
<td>n-C₅H₁₁</td>
<td>CH₃</td>
<td>27</td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>n-C₃H₇</td>
<td>H</td>
<td>52</td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>n-C₃H₇</td>
<td>CH₃</td>
<td>56</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>n-C₅H₁₁</td>
<td>H</td>
<td>10</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>n-C₅H₁₁</td>
<td>CH₃</td>
<td>15</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields are unoptimized and are representative of a one time Okauchi coupling.
Table 10. Pharmacology results for N-alkyl-3-(4-bromo-1-naphthoyl)indole series and the 2-methyl analogs.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R’</th>
<th>$K_i^{a}/CB_1^{b}$ (nM)</th>
<th>$K_i^{a}/CB_2^{c}$ (nM)</th>
<th>CB$_2$ selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-386 (37)</td>
<td>n-C$_3$H$_7$</td>
<td>H</td>
<td>161 ± 16</td>
<td>27 ± 1.6</td>
<td>6</td>
</tr>
<tr>
<td>JWH-395 (38)</td>
<td>n-C$_3$H$_7$</td>
<td>CH$_3$</td>
<td>373 ± 43</td>
<td>31 ± 2</td>
<td>12</td>
</tr>
<tr>
<td>JWH-387 (39)</td>
<td>n-C$<em>5$H$</em>{11}$</td>
<td>H</td>
<td>1.19 ± 0.06</td>
<td>1.10 ± 0.13</td>
<td>1</td>
</tr>
<tr>
<td>JWH-394 (40)</td>
<td>n-C$<em>5$H$</em>{11}$</td>
<td>CH$_3$</td>
<td>14 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>5</td>
</tr>
</tbody>
</table>

$K_i$ data was acquired by Dr. Billy Martin and Dr. Jenny Wiley of Virginia Commonwealth University.

$^a$Data from displacement of [³H]CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean.

$^b$Receptor affinity determined using rat brain homogenate.

$^c$Receptor affinity determined using membranes from CHO-K1 cells transfected with the human CB$_2$ cannabinoid receptor.
Table 11. Pharmacology and GTPγS results for \( N \)-alkyl-3-(4-chloro-1-naphthoyl)indole series and the 2-methyl analogs.

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R'</th>
<th>( K_i^{a,b} / CB_1 ) (nM)</th>
<th>( K_i / CB_2 ) (nM)</th>
<th>CB2 selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-400 (41)</td>
<td>( n-C_3H_7 )</td>
<td>H</td>
<td>93 ± 8</td>
<td>44 ± 0.4</td>
<td>2</td>
</tr>
<tr>
<td>JWH-399 (42)</td>
<td>( n-C_3H_7 )</td>
<td>CH₃</td>
<td>187 ± 16</td>
<td>22 ± 1</td>
<td>9</td>
</tr>
<tr>
<td>JWH-398 (43)</td>
<td>( n-C_5H_{11} )</td>
<td>H</td>
<td>2.3 ± 0.1</td>
<td>2.8 ± 0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>JWH-397 (44)</td>
<td>( n-C_5H_{11} )</td>
<td>CH₃</td>
<td>8.9 ± 0.3</td>
<td>2.3 ± 0.02</td>
<td>4</td>
</tr>
</tbody>
</table>

\( K_i \) and GTP\( \gamma \)S data were acquired by Dr. Billy Martin and Dr. Jenny Wiley of Virginia Commonwealth University.

\(^a\)Data from displacement of \( [\text{H}] \)CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean.

\(^b\)Receptor affinity determined using rat brain homogenate.

\(^c\)Receptor affinity determined using membranes from CHO-K1 cells transfected with the human CB₂ cannabinoid receptor.

<table>
<thead>
<tr>
<th>GTPγS CB₂ (^c)</th>
<th>Compound no.</th>
<th>EC(_{50}) (nM)</th>
<th>( E_{\text{max}} ) (%)</th>
<th>( E_{\text{max}} ) vs CP-55,940</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JWH-397 (44)</td>
<td>0.74 ± 0.01</td>
<td>63.2 ± 4.1</td>
<td>0.51 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>JWH-399 (42)</td>
<td>6.58 ± 0.11</td>
<td>97.8 ± 35.6</td>
<td>0.79 ± 0.28</td>
</tr>
<tr>
<td></td>
<td>JWH-400 (41)</td>
<td>9.46 ± 2.94</td>
<td>100.3 ± 2.7</td>
<td>0.81 ± 0.02</td>
</tr>
</tbody>
</table>
Table 12. Pharmacology results for N-alkyl-3-(4-iodo-1-naphthoyl)indole series and the 2-methyl analogs

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R'</th>
<th>$K_i^{a/CB_1}$ (nM)</th>
<th>$K_i^{a/CB_2}$ (nM)</th>
<th>CB_2 selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-423 (45)</td>
<td>n-C_3H_7</td>
<td>H</td>
<td>140 ± 10</td>
<td>6.6 ± 0.2</td>
<td>21</td>
</tr>
<tr>
<td>JWH-422 (46)</td>
<td>n-C_3H_7</td>
<td>CH_3</td>
<td>501 ± 48</td>
<td>20 ± 0.4</td>
<td>25</td>
</tr>
<tr>
<td>JWH-421 (47)</td>
<td>n-C_5H_11</td>
<td>H</td>
<td>2.5 ± 0.2</td>
<td>1.3 ± 0.02</td>
<td>2</td>
</tr>
<tr>
<td>JWH-420 (48)</td>
<td>n-C_5H_11</td>
<td>CH_3</td>
<td>14 ± 1</td>
<td>2.1 ± 0.1</td>
<td>7</td>
</tr>
</tbody>
</table>

$K_i$ data was acquired by Dr. Billy Martin and Dr. Jenny Wiley of Virginia Commonwealth University.

aData from displacement of $[^3]$H]CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean.

bReceptor affinity determined using rat brain homogenate.

cReceptor affinity determined using membranes from CHO-K1 cells transfected with the human CB_2 cannabinoid receptor.
Table 13. Pharmacology results for N-alkyl-3-(4-fluoro-1-naphthoyl)indole series and the 2-methyl analogs

\[
\begin{align*}
\text{K}_i \text{ data was acquired by Dr. Billy Martin and Dr. Jenny Wiley of Virginia Commonwealth University.} \\
\text{a} \text{Data from displacement of [}^3\text{H}]\text{CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean.} \\
\text{b} \text{Receptor affinity determined using rat brain homogenate.} \\
\text{c} \text{Receptor affinity determined using membranes from CHO-K1 cells transfected with the human CB}_2 \text{ cannabinoid receptor.}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R’</th>
<th>(K_i^{a/\text{CB}_1}) (nM)</th>
<th>(K_i^{a/\text{CB}_2}) (nM)</th>
<th>\text{CB}_2 selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-414 (49)</td>
<td>(n\text{-C}_3\text{H}_7)</td>
<td>H</td>
<td>240 ± 7</td>
<td>33 ± 2</td>
<td>7</td>
</tr>
<tr>
<td>JWH-415 (50)</td>
<td>(n\text{-C}_3\text{H}_7)</td>
<td>(\text{CH}_3)</td>
<td>530 ± 37</td>
<td>38 ± 1</td>
<td>14</td>
</tr>
<tr>
<td>JWH-412 (51)</td>
<td>(n\text{-C}<em>5\text{H}</em>{11})</td>
<td>(\text{H})</td>
<td>7.2 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>2</td>
</tr>
<tr>
<td>JWH-413 (52)</td>
<td>(n\text{-C}<em>5\text{H}</em>{11})</td>
<td>(\text{CH}_3)</td>
<td>14 ± 0.7</td>
<td>2.2 ± 0.2</td>
<td>6</td>
</tr>
</tbody>
</table>
The CB$_1$ and CB$_2$ receptor affinities of the 4-bromo, 4-chloro-, 4-iodo and 4-fluoro indole derivatives 37-40, 41-44, 45-48 and 49-52 are presented in Table 10, 11, 12 and 13, respectively. Table 11 also provides CB$_2$ GTP$\gamma$S binding data for three of the four 4-chloro analogs.

Data for the N-alkyl-3-(4-bromo-1-naphthoyl)indole series and the 2-methyl analogs (37-40) provided some interesting findings. While all compounds exhibited from good to high affinity for the CB$_2$ receptor, both 37 and 38, the 2$H$- and C-2 methyl propyl derivatives, displayed 6- and 12-fold selectivity for CB$_2$. The pentyl analogs 39 and 40 have very high affinity for the CB$_2$ receptor as well as the CB$_1$ receptor. Even though this high affinity ($K_i = 1.2$ nM/ CB$_1$ and $K_i = 1.1$ nM/ CB$_2$ for 39; $K_i = 14$ nM/ CB$_1$ and $K_i = 3$ nM/ CB$_2$ for 40) is desirable, when the affinity is high for both receptors the compound is considered ineffective. The propyl analogs have decent affinity for the CB$_2$ receptor, although not as high their pentyl analogs, but they are better CB$_2$ selective ligands.

In the N-alkyl-3-(4-chloro-1-naphthoyl)indole series, and their 2-methyl analogs, (41-44) the propyl compounds are again the more CB$_2$ selective of the group. The 2-methyl propyl compound 42 has 9-fold selectivity for the CB$_2$ receptor with $K_i$ values of 187 nM and 22 nM at CB$_1$ and CB$_2$, respectively. The 2$H$- pentyl derivative 43 actually displays a slight preference for the CB$_1$ receptor but overall both pentyl derivatives have high affinity for both cannabinoid receptors.

GTP$\gamma$S data was determined for the 4-chloro compounds (41, 42 and 44). The EC$_{50}$ and E$_{max}$ values determine the potency and efficacy of a compound. Each of these
compounds was found to initiate a response in the CB$_2$ G-coupled protein receptor (GPCR) at low nanomolar concentrations, indicating that they are agonists.

The propyl derivatives of the $N$-alkyl-3-(4-iodo-1-naphthoyl)indole series and its 2-methyl analogs (45-48) show the highest CB$_2$ selectivity of the entire 4-halo series. $K_i$ values for 45, the 2H-analog, are 140 nM for CB$_1$ and 6.6 nM for CB$_2$ while the 2-methyl analog has $K_i$ values of 501 nM at CB$_1$ and 20 nM at CB$_2$. These equate to 21- and 25-fold selectivities for CB$_2$ as well as having good CB$_2$ affinities. The pentyl derivatives display high affinity for both receptors with 48, the C-2 substituted compound, having selectivity for CB$_2$.

Compounds 49-52, the $N$-alkyl-3-(4-fluoro-1-naphthoyl)indole series and its 2-methyl analogs, continue the trends seen in the previously discussed series. The propyl analogs 49 and 50 display high selectivities for the CB$_2$ receptor. It was determined that the pentyl compounds continue to have a very high affinity for both CB$_1$ and CB$_2$, ultimately rendering them devoid of any pertinent cannabimimetic interest.

In general, the $N$-alkyl-3-(4-halo-1-naphthoyl)indole series of cannabinoids display high affinity as well as some selectivity for the CB$_2$ receptor. The propyl analogs have CB$_2$ selectivities of up to 25-fold and maintain an affinity for CB$_2$ ranging from 20-40 nM, except for 45 which has the highest affinity, 6.6 nM, of all the propyl compounds. It is also observed that within the propyl compounds, the C-2 substituted analogs display higher selectivities than the pentyl analogs. In the pentyl series, all 2H-derivatives have very high affinity for both CB$_1$ and CB$_2$ receptors, and therefore have no selectivity. The 2-methyl analogs, while having very high affinities for both receptors, do show
selectivity for the CB$_2$ receptor over their 2$H$- analogs. The N-propyl 4-iodo series stands apart from the other halogens, displaying high CB$_2$ selectivity of 21- and 25-fold as well as high CB$_2$ affinity.

**$N$-alkyl-3-(8-halo-1-naphthoyl)indoles**

Based on the pharmacology data for the 4-halo series of cannabimimetic indoles that indicated several examples of compounds with selectivity for the CB$_2$ receptor it was decided to synthesize another series of halo indoles. A literature search provided procedures for the synthesis of 8-bromo-1-naphthoic acid and 8-iodo-1-naphthoic acid. As reported by Bailey and co-workers these carboxylic acids could be produced through a simple two step pathway in relatively high yields.$^{58}$

The selective mercury-mediated decarboxylation of an aromatic anhydride, specifically 1,8-naphthalic anhydride, to give the mono-acid and carbon dioxide is known as the Pesci reaction.$^{59}$ Numerous studies on the mechanism of this reaction have been carried out, however the exact mechanism remains unclear.$^{60-65}$ The naphthalic anhydride is hydrolyzed to the dicarboxylate anion followed by treatment with mercury (II) oxide (HgO) in acetic acid and water, to give *in situ* generation of mercuric acetate [Hg(OAc)$_2$]. The mercury species subsequently displaces one of the carboxylate groups, releasing CO$_2$. This results in formation of the 8-hydroxymercuri-1-naphthoic anhydride.
intermediate. Acidic hydrolysis then releases mercury as a salt yielding the arene mono-acid (Figure 25).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Hg} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\begin{align*}
i) \quad \text{NaOH, H}_2\text{O} & \quad \text{ii) HgO, AcOH/H}_2\text{O (3:1)} \\
& \quad \text{conc. HCl}
\end{align*}

**Figure 25.** The Pesci reaction.

Treatment of 1,8-naphthalic anhydride with NaOH followed by mercuric acetate in acetic acid and water prompted mercury-mediated decarboxylation of the anhydride. Two days at reflux in acetic acid resulted in formation of the highly stable 8-hydroxymercuri-1-naphthoic anhydride (53, Figure 26) in 96% yield. Halogenation of this organo-mercurio intermediate, as shown in Figure 26, was carried out and provided a series of 8-halo-1-naphthoic acids.

Intermediate 53 was stirred at 0 °C in aqueous acetic acid followed by addition of bromine and aqueous sodium bromide. Bromination was initiated via the tribromide anion, Br$_3$. Nucleophilic attack of 8-hydroxymercuri-1-naphthoic anhydride (53) by bromide resulted in a bromo-mercuri intermediate. This intermediate underwent nucleophilic substitution by bromine leading to the desired 8-bromo-1-naphthoic acid (54) in 87% yield with no further purification necessary along with mercury (II) bromide.
8-Iodo-1-naphthoic acid was synthesized in a similar manner after 15 hours of reflux following the addition of iodine and aqueous potassium iodide to 53. Iodine is poorly soluble in water, however, in the presence of iodide salts solubility is increased by the formation of tri-iodide anion, I$_3^-$, which promotes iodination in the same way as the tribromide anion.$^{67,70,71}$ The solution was filtered and to the filtrate was added sodium thiosulfate and water, which reduces any remaining iodine to iodide. The filtrate was acidified and acid 55 was filtered out of the solution in 52% yield (Figure 26).

![Synthesis of 8-halo-1-naphthoic acids](image)

**Figure 26.** Synthesis of 8-halo-1-naphthoic acids.
A procedure for making 8-chloro-1-naphthoic acid was described by Whitmire and co-workers \(^72\) (Figure 27). However, this procedure employed the use of chlorine gas and alternate routes of chlorination were investigated. Initial attempts to synthesize the desired carboxylic acid involved generation of \(\text{Cl}_2(\text{g})\) \textit{in situ} using 6M HCl and dilute sodium hypochlorite (Figure 28).\(^73\) A vial containing bleach was placed into a 60mL syringe and the 6M HCl was drawn through the needle. Upon shaking the syringe, the solution reacted and a yellow gas was immediately formed. This gas was then injected into the organo-mercurio solution at 0 °C and then slowly heated to 100 °C. Confirmation of the addition of chlorine to the aromatic system was difficult due to the crude spectroscopic data, so purification through the methyl ester was initiated. The identity of the methyl ester, once purified, could then be verified by NMR spectroscopy and GC/MS. Compounds containing chlorine have a distinct mass spectrometry signature. An M+2 peak is observed with an intensity ratio of M:M+2 of 3:1.\(^74\) Esterification was attempted using methanol and sulfuric acid. The methyl ester was isolated and the spectroscopic data indicated that the chlorination reaction had failed. The resulting product was the unsubstituted methyl-1-naphthoate.

![Figure 27. Whitmire synthesis of 8-chloro-1-naphthoic acid.](image-url)
\[ \text{NaOCl}_{(aq)} + 2\text{HCl}_{(aq)} \rightarrow \text{Cl}_2(g) + \text{NaCl}_{(aq)} + \text{H}_2\text{O} \]

**Figure 28.** Generation of chlorine gas *in situ.*

Modifications of Whitmire’s procedure were attempted and a second chlorinating agent, *N*-chlorosuccinimide (56, Figure 29, NCS), was employed. The strength of the nitrogen-chlorine bond in NCS makes it difficult to break, thus this is the rate-determining step, or a first order reaction.\(^{75}\) It is also reported that in aqueous acidic solutions in the presence of chloride ion, NCS produces a steady but small concentration of \(\text{Cl}_2(g)\) along with succinimide.\(^{76}\) Unlike elemental halogens where only half of the halogen is consumed, NCS allows for consumption of all of the halogen species.\(^{77}\) Ring chlorination of aromatic compounds with NCS proceeds by electrophilic substitution.\(^{77,78}\) Unfortunately this reagent also proved to be unsuccessful and 1-naphthoic acid was obtained along with recovered organo-mercurio starting material.

![Figure 29. Chlorinating agents used.](image)

Using NCS in an alternate synthetic pathway was the next approach. The procedure previously employed by Rule and co-workers\(^ {79}\) was combined with the above
procedure designed by Bailey\textsuperscript{58} for the formation of 54. Reagents were adjusted and an aqueous solution of sodium chloride and NCS were used in place of aqueous sodium bromide and molecular bromine. Attempts to methylate the crude acid using methanol and sulfuric acid proved unsuccessful. A new esterification method involving refluxing the carboxylic acid in thionyl chloride followed by removal of the thionyl chloride \textit{in vacuo} and treatment of the remaining gum with anhydrous methanol was performed.\textsuperscript{80} Although only yields of 2-3\% were obtained, enough of the methyl ester was formed to show by GC/MS that the addition of chlorine was not successful.

A 1:1 ratio of chlorinating agent to 53 was being used. Since this was a first-order reaction and NCS allows for use of all the available chlorine, it is known that raising the equivalents of NCS would have no effect on the rate of the reaction. Therefore, an alternate chlorinating agent was pursued. Chlorination employing the use of 1,3-dichloro-5,5-dimethyl hydantoin (57, Figure 29, DCDMH) proceeds in the same manner as NCS.\textsuperscript{77}

During the Pesci reaction, the addition of the HgO solution to the hydrolyzed dicarboxylate salt results in a dense white precipitate. It was believed that inefficient stirring of this solution may have been hindering efficient mixing of the reagents and the substrate. The following approach incorporated the use of a stir plate with sufficient power to maintain constant stirring of the dense solution.

DCDMH was used in the Bailey\textsuperscript{58} procedure, with vigorous stirring, followed by dissolution of the mercuri-chloro intermediate in 12M NaOH. Filtration of the undesired mercury salts and acidification of the filtrate using concentrated HCl resulted in the formation of a white precipitate. This precipitate, which is soluble in water, is believed to
be 5,5-dimethylhydantoin (DMH). Extraction of the filtrate with dichloromethane gave the desired 8-chloro-1-naphthoic acid (58, Figure 30). To verify this, the methyl ester was to be synthesized. It was found however that esterification of 1-naphthoic acid derivatives with substituents in the C-8 position would not undergo esterification using methanol and sulfuric acid. The addition of a substituent in the C-8 position caused steric hindrance of the carboxyl moiety. The lone reported methylating agent to esterify one of these carboxyl derivatives was diazomethane. The hazards associated with the preparation of diazomethane led to the safer solution of using trimethylsilyl diazomethane (TMSD). The methylation of 58 was successfully performed in a medium of TMSD and methanol, the mechanism of which can be seen in Figure 31. The addition of the chlorine was supported by the spectral data. Proton nuclear magnetic resonance (1H NMR) indicated six rather than seven aromatic hydrogens as well as splitting patterns associated with substitution in the 1 and 8 positions and GC/MS showed an M peak at 220 as well as an M+2 peak at 222 in a 3:1 ratio.
Figure 30. Successful synthesis and esterification of 8-chloro-1-naphthoic acid.
Carboxylic acids 54, 55 and 58 were converted to their corresponding acid chlorides using thionyl chloride and then coupled with the appropriate $N$-alkylindoles via the previously employed Okauchi method of acylation using dimethylaluminum chloride.

Figure 31. Mechanism of esterification using TMSD.
Yields of 11-64% of the corresponding N-alkyl-3-(8-halo-1-naphthoyl)indoles (60-67) were achieved after column chromatography.

\[
\begin{align*}
\text{X} & \quad \text{O} & \quad \text{X} \\
\text{H} & \quad \text{Cl} & \\
\text{SOCl}_2 & \quad \text{reflux}, \ 2 \ h & \\
\text{8-halo-1-naphthoyl chloride} & \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & = n-C_3H_7 \\
& = n-C_5H_{11} \\
\text{R'} & = H, \ CH_3 \\
\text{X} & = \text{Br}, \ I \\
\end{align*}
\]

**Figure 32.** Okauchi coupling of N-alkyl-3-(8-halo-1-naphthoyl)indoles and the 2-methyl analogs
Table 14. Yields of N-alkyl-3-(8-halo-1-naphthoyl)indoles and the 2-methyl analogs.

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>X</th>
<th>R</th>
<th>R’</th>
<th>Yields (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>Br</td>
<td>$n$-C$_3$H$_7$</td>
<td>H</td>
<td>48</td>
</tr>
<tr>
<td>61</td>
<td>Br</td>
<td>$n$-C$_3$H$_7$</td>
<td>CH$_3$</td>
<td>16</td>
</tr>
<tr>
<td>62</td>
<td>Br</td>
<td>$n$-C$<em>5$H$</em>{11}$</td>
<td>H</td>
<td>78</td>
</tr>
<tr>
<td>63</td>
<td>Br</td>
<td>$n$-C$<em>5$H$</em>{11}$</td>
<td>CH$_3$</td>
<td>15</td>
</tr>
<tr>
<td>64</td>
<td>I</td>
<td>$n$-C$_3$H$_7$</td>
<td>H</td>
<td>21</td>
</tr>
<tr>
<td>65</td>
<td>I</td>
<td>$n$-C$_3$H$_7$</td>
<td>CH$_3$</td>
<td>35</td>
</tr>
<tr>
<td>66</td>
<td>I</td>
<td>$n$-C$<em>5$H$</em>{11}$</td>
<td>H</td>
<td>11</td>
</tr>
<tr>
<td>67</td>
<td>I</td>
<td>$n$-C$<em>5$H$</em>{11}$</td>
<td>CH$_3$</td>
<td>64</td>
</tr>
</tbody>
</table>

$^a$Yields are unoptimized and are representative of a one time Okauchi coupling.
Table 15. Pharmacology results for N-alkyl-3-(8-bromo-1-naphthoyl)indole series and the 2-methyl analogs

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R’</th>
<th>Kᵢᵃ/CB₁ᵇ (nM)</th>
<th>Kᵢᵃ/CB₂ᶜ (nM)</th>
<th>CB₂ selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-428 (60)</td>
<td>n-C₃H₇</td>
<td>H</td>
<td>&gt;10,000</td>
<td>192 ± 14</td>
<td>&gt;52</td>
</tr>
<tr>
<td>JWH-429 (61)</td>
<td>n-C₃H₇</td>
<td>CH₃</td>
<td>&gt;10,000</td>
<td>278 ± 69</td>
<td>&gt;36</td>
</tr>
<tr>
<td>JWH-424 (62)</td>
<td>n-C₅H₁₁</td>
<td>H</td>
<td>21 ± 3.4</td>
<td>5.4 ± 0.2</td>
<td>4</td>
</tr>
<tr>
<td>JWH-425 (63)</td>
<td>n-C₅H₁₁</td>
<td>CH₃</td>
<td>54 ± 11</td>
<td>9.97 ± 0.4</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Kᵢ data was acquired by Dr. Billy Martin and Dr. Jenny Wiley of Virginia Commonwealth University.

ᵃData from displacement of [³H]CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean.

ᵇReceptor affinity determined using rat brain homogenate.

ᶜReceptor affinity determined using membranes from CHO-K1 cells transfected with the human CB₂ cannabinoid receptor.
Table 16. Pharmacology results for N-alkyl-3-(8-iodo-1-naphthoyl)indole series and the 2-methyl analogs

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R’</th>
<th>$K_i^{a}/CB_1^{b}$ (nM)</th>
<th>$K_i^{a}/CB_2^{c}$ (nM)</th>
<th>CB$_2$ selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-419 (64)</td>
<td>$n$-C$_3$H$_7$</td>
<td>H</td>
<td>2960 ± 240</td>
<td>152 ± 33</td>
<td>19</td>
</tr>
<tr>
<td>JWH-418 (65)</td>
<td>$n$-C$_3$H$_7$</td>
<td>CH$_3$</td>
<td>4290 ± 440</td>
<td>536 ± 66</td>
<td>8</td>
</tr>
<tr>
<td>JWH-416 (66)</td>
<td>$n$-C$<em>5$H$</em>{11}$</td>
<td>H</td>
<td>73 ± 10</td>
<td>3.3 ± 0.1</td>
<td>22</td>
</tr>
<tr>
<td>JWH-417 (67)</td>
<td>$n$-C$<em>5$H$</em>{11}$</td>
<td>CH$_3$</td>
<td>522 ± 58</td>
<td>13 ± 0.2</td>
<td>40</td>
</tr>
</tbody>
</table>

$K_i$ data was acquired by Dr. Billy Martin and Dr. Jenny Wiley of Virginia Commonwealth University.

$^a$Data from displacement of [3$^3$H]CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean.

$^b$Receptor affinity determined using rat brain homogenate.

$^c$Receptor affinity determined using membranes from CHO-K1 cells transfected with the human CB$_2$ cannabinoid receptor.
The CB₁ and CB₂ receptor affinities of the 8-bromo and 8-iodo indole derivatives 60-63 and 64-67 are presented in Tables 15 and 16, respectively. Both the N-alkyl-3-(8-halo-1-naphthoyl)indole series and their 2-methyl analogs provided some intriguing findings.

N-propyl-3-(8-bromo-1-naphthoyl)indole and the 2-methyl analog displayed no affinity for the CB₁ receptor. They did however have very modest affinities for the CB₂ receptor (Kᵢ = 192 nM for 60 and Kᵢ = 278 nM for 61). This moderate affinity for CB₂, combined with total lack of affinity for CB₁, ultimately gives a 52- and 36-fold selectivity for the CB₂ receptor. The pentyl analogs 62 and 63 have selectivity for the CB₂ receptor, however, the high affinities that the 2H- and C-2 methyl derivatives display for both receptors provides an undesirable combination.

The N-alkyl-3-(8-iodo-1-naphthoyl)indoles and their 2-methyl analogs provided some unexpected results. All compounds in this series have high selectivity for CB₂. The propyl series, like the 8-bromo series, has little affinity for the CB₁ receptor. The 2H-analog displays 19-fold selectivity for the CB₂ receptor, while the 2-methyl analog has lower affinity resulting in an 8-fold preference for CB₂. The pentyl series, on the other hand, exhibits not only high affinity for the CB₂ receptor, but high selectivity. The 2H-derivative (66) was found to have Kᵢ at CB₁ of 73 nM and Kᵢ at CB₂ of 3.3 nM. The 2-methyl derivative, 67, has Kᵢ at the CB₁ receptor of 522 nM and Kᵢ at CB₂ of 13 nM. This equates to 22- and 40-fold selectivity for the pentyl analogs, respectively. Note that the 8-iodo series reverses the trends previously seen in the 4- and 8-halo compounds.
In summary, placement of a halogen in the C-8 position of the naphthoyl ring leads to an increase in CB$_2$ selectivity as well as to a decrease in CB$_1$ affinity. In the propyl derivatives, it is now the unsubstituted C-2 analog that displays higher CB$_2$ selectivity relative to its 2-methyl analog. The N-pentyl-3-(8-bromo-1-naphthoyl)indoles continue to show higher selectivity for the 2-methyl substituted derivative over its unsubstituted analog. However, the N-pentyl-3-(8-iodo-1-naphthoyl)indoles display a much higher selectivity than their propyl counterparts while maintaining the trend previously seen with the 2-methyl cannabinoid having higher selectivity than its 2$H$-derivative. It is worth mentioning that the iodo substituted compounds (45-48 and 64-67) demonstrate CB$_2$ affinity and selectivity that is much greater than the other halogen substituted cannabimimetic indoles, particularly JWH-417 (67).

$N$-alkyl-3-(6-methoxy-2-naphthoyl)indoles

Over the years, many derivatives of the $N$-alkyl-3-(1-naphthoyl)indole series have been synthesized. The addition of alkyl and alkoxy substituents to various positions of the naphthoyl ring has been investigated.$^{49}$ A wide range of affinities for the CB$_1$ receptor and affinity along with selectivity for CB$_2$ has been observed. This is true particularly in the methoxy series of analogs. Receptor affinities have been determined for four different methoxy series, in which the group has been located on the C-2, C-4, C-6 and C-7 positions of the naphthoyl ring. It was found that in the 7-methoxy series and the 4-
methoxy series, no selectivity was observed, but both had an affinity for each receptor. The 2-methoxy derivatives display CB$_2$ selectivity ranging from 22 to 53-fold while compounds in the 6-methoxy series have selectivities of 17, 23 and 333-fold as well as high affinity for the CB$_2$ receptor. In the N-alkyl-3-(6-methoxy-1-naphthoyl)indole series the pentyl compounds have high affinities for the CB$_1$ receptor as well as selectivity for the CB$_2$ receptor. The propyl compounds also display high selectivity for the CB$_2$ receptor over the CB$_1$ receptor. While the 2H indole with an N-propyl substituent has 17-fold selectivity for the CB$_2$ receptor, the 2-methyl analog has not only a high affinity for the CB$_2$ receptor but has 333-fold selectivity. Based upon the selectivity of the 3-(6-methoxy-1-naphthoyl)indoles the synthesis of a series of N-alkyl-3-(6-methoxy-2-naphthoyl)indoles was initiated. The proposed synthetic approach is outlined in Figure 33.
Figure 33. Synthetic pathway for N-alkyl-3-(6-methoxy-2-naphthoyl)indoles

Table 17. Yields of N-alkyl-3-(6-methoxy-2-naphthoyl)indoles

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>n-C₃H₇</td>
<td>H</td>
<td>4</td>
</tr>
<tr>
<td>70</td>
<td>n-C₃H₇</td>
<td>CH₃</td>
<td>37</td>
</tr>
<tr>
<td>71</td>
<td>n-C₅H₁₁</td>
<td>H</td>
<td>59</td>
</tr>
<tr>
<td>72</td>
<td>n-C₅H₁₁</td>
<td>CH₃</td>
<td>11</td>
</tr>
</tbody>
</table>

^aYields are unoptimized and are representative of a one time Okauchi coupling.

6-Methoxy-2-naphthoic acid is commercially available and the synthesis of this series of cannabimimetic indoles employed the Okauchi method previously discussed. The use of dimethylaluminum chloride to activate the C-3 of the indole ring coupled with
the 6-methoxy-2-naphthoyl chloride (68) resulted in the target $N$-alkyl-3-(6-methoxy-2-naphthoyl)indole compounds.
Table 18. Pharmacology results for \( N \)-alkyl-3-(6-methoxy-2-naphthoyl)indole series and the 2-methyl analogs

![Chemical structure of compound](image)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R</th>
<th>R'</th>
<th>( K_{i}^{a}/CB_{1}^{b} ) (nM)</th>
<th>( K_{i}^{a}/CB_{2}^{c} ) (nM)</th>
<th>CB2 selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-411 (69)</td>
<td>( n-C_{3}H_{7} )</td>
<td>H</td>
<td>2036 ± 203</td>
<td>561 ± 54</td>
<td>4</td>
</tr>
<tr>
<td>JWH-410 (70)</td>
<td>( n-C_{3}H_{7} )</td>
<td>CH₃</td>
<td>2682 ± 397</td>
<td>322 ± 46</td>
<td>8</td>
</tr>
<tr>
<td>JWH-408 (71)</td>
<td>( n-C_{5}H_{11} )</td>
<td>H</td>
<td>190 ± 12</td>
<td>91 ± 3.4</td>
<td>2</td>
</tr>
<tr>
<td>JWH-409 (72)</td>
<td>( n-C_{5}H_{11} )</td>
<td>CH₃</td>
<td>746 ± 77</td>
<td>232 ± 21</td>
<td>3</td>
</tr>
</tbody>
</table>

\( K_{i} \) data was acquired by Dr. Billy Martin and Dr. Jenny Wiley of Virginia Commonwealth University.

\( a \) Data from displacement of \(^{3}\text{H}\)CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean.

\( b \) Receptor affinity determined using rat brain homogenate.

\( c \) Receptor affinity determined using membranes from CHO-K1 cells transfected with the human CB\(_2\) cannabinoid receptor.
Pharmacological data for the \( N \)-alkyl-3-(6-methoxy-2-naphthoyl)indoles were considerably different from those of the corresponding 1-naphthoyl analogs. Unlike the 6-methoxy-1-naphthoyl derivatives, this series displayed no significant affinity for either the CB\(_1\) or CB\(_2\) receptor nor was there selectivity for either receptor. The \( \text{2H-} \) and \( \text{2-methyl-} \)N-propyl compounds \( 69 \) and \( 70 \), display 4- and 8-fold selectivity for the CB\(_2\) receptor but exhibit little affinity (\( K_i = 561 \) nM for \( 69 \) and \( K_i = 322 \) nM for \( 70 \)). The pentyl series displays moderate CB\(_2\) affinity but lacks any significant selectivity for the receptor.

**Electron-withdrawing nitro substituents**

The studies presented in this dissertation of electron-withdrawing halogen substituents on \( N \)-alkyl-3-(1-naphthoyl)indoles and their affinity for the cannabinoid receptors has shown that relative to their unsubstituted analogs, either significant affinity or selectivity for the CB\(_2\) receptor is observed. These findings led to an inquiry into how other electron-withdrawing substituents would affect receptor interactions. For this reason it was determined that a series of cannabimimetic naphthoylindoles possessing a nitro substituent should be synthesized.

Previous studies conducted by Hongfeng Deng of the Makriyannis group showed that addition of a nitro group to \( N \)-alkyl-3-(1-benzoyl)indole derivatives showed increased affinity for CB\(_2\) relative to unsubstituted analogs.\(^{83}\)
Initially the study by Deng involved nitration of AM679 (73) to AM1202 (74). These compounds can be seen in Figure 34, nitration being achieved using fuming nitric acid and concentrated sulfuric acid. While AM679 had selectivity for CB₁, the addition of the nitro substituent led to a more than 15-fold increase for the CB₂ receptor in AM1202 (Table 19). Based on this observation, another series of nitro analogs was designed. Pharmacology for some of the series can be seen in Table 20.

![Figure 34. N-pentyl-3-(2-iodo-1-benzoyl)indole, AM 679 and its nitro analog, AM1202.](image)

### Table 19. Pharmacology for AM679 (73) and AM1202 (74).³

<table>
<thead>
<tr>
<th>Compound</th>
<th>(K_i^{\text{a}}/\text{CB}_1) (nM)</th>
<th>(K_i^{\text{a}}/\text{CB}_2) (nM)</th>
<th>(\text{CB}_2) selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM679 (73)</td>
<td>13.5</td>
<td>49.5</td>
<td>0.3</td>
</tr>
<tr>
<td>AM1202 (74)</td>
<td>98.9</td>
<td>22.9</td>
<td>4</td>
</tr>
</tbody>
</table>

³Data from displacement of \(^3\text{H}\)CP-55,940 in at least three independent experiments run in duplicate and expressed as the mean of three values with standard error of mean. Receptor affinity determined using rat brain homogenate. Receptor affinity determined using membranes from CHO-K1 cells transfected with the human CB₂ cannabinoid receptor.
No nitro compounds were synthesized that were devoid of a halogen substituent. Reasoning for this is that the Makriyannis group is interested in developing covalent affinity radioprobes, which are used to label the cannabinoid receptors, allowing studies of receptor-ligand interactions. The iodo compound AM661 (Table 20) displayed high affinity for both CB₁ and CB₂ receptors. Also, the iodo substituent allowed the compound to be radioactively labeled. Therefore, it was decided that this compound would be a good lead structure for the synthesis of additional cannabimimetic indoles. The replacement of the N-pentyl chain on the indole with an (N-methyl-2-piperidinyl)methyl group creates a chiral center on the cannabinoid. This is of interest because it has been found that when the enantiomers are separated, one racemate has a higher binding affinity than the other, thus affecting the selectivity profile. Proposed research to be carried out in the Huffman laboratory has interest in the investigation of cannabimimetic indoles with one electron-withdrawing substituent on the naphthoyl ring, in this case a nitro group.
Table 20. $K_i$ values for 1-($N$-methyl-2-piperidinyl)methyl-3-(2-iodobenzoyl)indole derivatives with nitro substituents.

<table>
<thead>
<tr>
<th>Deng Compounds</th>
<th>R$_5$</th>
<th>R$_2$</th>
<th>R$_6$</th>
<th>$K_i$/CB$_1$ (nM)</th>
<th>$K_i$/CB$_2$ (nM)</th>
<th>CB$_2$ selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM2233</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>3.4</td>
<td>7.6</td>
<td>0.4</td>
</tr>
<tr>
<td>AM1241</td>
<td>NO$_2$</td>
<td>H</td>
<td>H</td>
<td>548.4</td>
<td>1.6</td>
<td>343</td>
</tr>
<tr>
<td>AM661</td>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>33.6</td>
<td>33.9</td>
<td>1</td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>NO$_2$</td>
<td>CH$_3$</td>
<td>H</td>
<td>2133</td>
<td>41.8</td>
<td>51</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>H</td>
<td>CH$_3$</td>
<td>NO$_2$</td>
<td>40</td>
<td>80</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Over the course of this study three nitro-naphthoic acids were synthesized. Initial attempts were focused on the formation of 4-nitro-1-naphthoic acid. The retrosynthetic pathway can be seen in Figure 35.
Figure 35. Retrosynthetic pathway for the synthesis of 4-nitro-1-naphthoic acid

5-nitroacenaphthene (75) was synthesized by the nitration of acenaphthene. The substrate was dissolved in acetic acid, which was followed by the slow addition of nitric acid. When the addition was finished, the solution was immediately poured over ice and a yellow precipitate (75) was filtered out in 88% yield.\textsuperscript{84} Oxidation of 75 was carried out using potassium dichromate in acetic acid at 100 °C for 3.5 h.\textsuperscript{85} The reaction mixture was then poured over ice and 4-nitro-1,8-naphthalic anhydride (76) precipitated as an orange solid in yields of up to 63% (Figure 36). Comparison of the synthetic 4-nitro-1,8-naphthalic anhydride (76) with commercially available 4-nitro-1,8-naphthalic anhydride revealed that they are identical.
Transformation of 76 to 4-nitro-1-naphthoic acid (78) was to proceed via the Pesci reaction (Figure 25), just as in the syntheses of the 8-halo-1-naphthoic acids, however difficulties were encountered. The overall procedure of mercury mediated decarboxylation again involved stirring 4-nitro-1,8-naphthalic anhydride (76) in a sodium hydroxide solution, followed by neutralization of the excess base with acetic acid. Mercuric acetate in water was then added and the solution was refluxed for 50 h. Filtering this solution led to anhydro-4-nitro-8-hydroxymercuri-1-naphthoic acid (77), a highly stable, insoluble mercury intermediate. This compound was then refluxed in 1 M HCl for 2 h. Ideally, 4-nitro-1-naphthoic acid (78) would be the product of this reaction. However, it was determined by infrared spectroscopy that no acid was formed. Only trace amounts of product were soluble in organic solvents indicating that the organo-mercuri intermediate had not been recovered. This procedure was repeated using 0.58 M, 0.65 M, and 2.5 M solutions of sodium hydroxide. Following the mercuration, reflux was carried out in 1 M HCl. Occasionally a water soluble salt was formed, however attempts to further acidify this salt, which was formed in an acidic medium, did not result in the precipitation of product. Overall, these reactions resulted in no
identifiable product, let alone the desired acid. Since an insoluble intermediate was being formed, the concentration of HCl used in the acid hydrolysis of 77 was altered. Concentrations of 0.65 M, 1.0 M, 2.0 M, and concentrated HCl were employed under the conditions of each of the previous synthetic attempts. Again, no formation of the desired product was observed.

Rather than using mercuric acetate, a solution of mercury (II) oxide in acetic acid and water was utilized to create the mercuric acetate in situ. Attempts were made using both red and yellow mercury (II) oxide, for which no chemical difference has been reported in the literature. Ultimately, this procedure did not produce the desired 4-nitro-1-naphthoic acid.

An additional aspect of the reaction that may have been the problem was the solubility of various salts in this reaction medium. Rather than using sodium hydroxide, potassium hydroxide was used to initiate decarboxylation. This was followed by addition of yellow mercury oxide in acetic acid and water. After 96 h at reflux, the solid was filtered, and dried. This reaction is thermally driven and reaction times of 48 to 96 h have been previously reported, as well as the need for temperatures of up to 200 °C when a nitro substituent is present. The solid was refluxed in concentrated HCl for 6 h, the suspension filtered and then dried. The crude product was recrystallized from glacial acetic acid. Spectral data verified that 4-nitro-1-naphthoic acid (78) had been synthesized. The optimized synthetic pathway can be seen in Figure 37. The formation of 78 was further verified by the synthesis of methyl-4-nitro-1-naphthoate (79) using methanol and sulfuric acid.
Figure 37. Synthesis of 4-nitro-1-naphthoic acid (78) from 4-nitro-1,8-naphthalic anhydride (76).

While the investigation into the formation of 78 was being undertaken, the synthesis of 8-nitro-1-naphthoic acid and 5-nitro-1-naphthoic acid was accomplished. It is known that electrophilic attack on naphthalenes with deactivating *meta*-directing groups is expected to take place in the 5- and 8-positions of the naphthalene ring. This is because the electron withdrawing substituent is more effective in deactivating the ring on which it is situated than the adjacent ring. This leads to attack at the two remaining 1-positions of the naphthalene. 1-Naphthaldehyde was nitrated using fuming nitric acid, acetic acid and sulfuric acid. This led to the formation of 8- (80) and 5-nitro-1-naphthaldehydes (81). Purification of the aldehydes was achieved using column
chromatography and it was found that these compounds formed in a 2:1 ratio, respectively. The successful oxidation of $\text{80}$ and $\text{81}$ was accomplished using freshly prepared Jones Reagent and distilled acetone. This procedure gave 8-nitro-1-naphthoic acid ($\text{82}$) and 5-nitro-1-naphthoic acid ($\text{83}$) in about 60% yield. These acids could be used without further purification. (Figure 38).

![Synthesis of 5- and 8-nitro-1-naphthoic acids.](image)

**Figure 38.** Synthesis of 5- and 8-nitro-1-naphthoic acids.

After the successful synthesis of carboxylic acids $\text{78}$, $\text{82}$ and $\text{83}$, the next step was to attempt coupling with an alkylindole. Initial attempts using 8-nitro-1-naphthoic acid ($\text{82}$) employed the Okauchi procedure. The acid chloride was prepared and added to a stirring solution of $N$-pentyllindole ($\text{20}$) in dichloromethane and dimethylaluminum
chloride (Me₂AlCl). Multiple Okauchi syntheses employing various N-alkylindoles were attempted with no success for either 82 or 83. The use of different Lewis acids was also enlisted. Ethylaluminum dichloride (EtAlCl₂) and diethylaluminum chloride (Et₂AlCl) did not give the desired product and it was suspected that the aluminum may form a complex with the nitro substituent. Possible evidence to refute this interaction was due to the fact that the Makriyannis group was able to successfully couple indoles with nitrobenzoyl halides employing aluminum chloride (AlCl₃). If such an interaction was indeed playing a role in the inability of the coupling to proceed smoothly, it would be necessary to employ the use of a metal that would not interact with the substituent. Ottoni and co-workers⁹⁰ reported the successful use of tin (IV) chloride (SnCl₄) in the activation of the 3-position of the indole ring, therefore the synthesis was attempted utilizing this Lewis acid. Ultimately, no coupling of the indole with 8-nitro-1-naphthoyl chloride was observed. Synthesis was also attempted employing AlCl₃. Procedures using this Lewis acid were performed under both the Okauchi modification of Friedel-Crafts acylation as well as traditional Friedel-Crafts conditions.⁹¹ All efforts to couple both 5-nitro-1-naphthoic acid (83) and 8-nitro-1-naphthoic acid (82) proved futile.

The synthesis of 4-nitro-1-naphthoic acid (78) was more efficient than the synthesis of the 5- (83) and 8-nitro-1-naphthoic acids (82), therefore, after the initial attempts of Okauchi coupling failed using acid 78 a synthesis of 3-(4-nitro-1-naphthoyl)indole was designed (Figure 39). This process involved formation of indolylmagnesium bromide by stirring indole and methylmagnesium bromide (MeMgBr) in dichloromethane at 0 °C followed by addition of the 4-nitro-1-naphthoyl chloride (84).
This coupling has proven difficult but trace amounts of 3-(4-nitro-1-naphthoyl)indole (85) have been successfully obtained when the reaction was run at 0 °C for 4 h. Minute amounts of 2-methyl-3-(4-nitro-1-naphthoyl)indole (86) have also been isolated under the same conditions.

Figure 39. Synthesis of 3-(4-nitro-1-naphthoyl)indole and the 2-methyl analog.

Due to the difficulty in producing moderate yields of the unsubstituted 85 and 86 analogs the project was dropped. Further attempts to synthesize the target N-alkyl-3-(4-nitro-1-naphthoyl)indoles were not undertaken.
Reinvestigation of the Friedel-Crafts acylation of N-p-toluenesulfonypyrrole

Several years ago a series of cannabimimetic N-alkyl-3-(1-naphthoyl)pyrroles was synthesized by Julia Lainton of the Huffman group. These were investigated to further provide evidence for binding of AAIs to the cannabinoid receptors via aromatic stacking. Friedel-Crafts acylation conditions were employed for the final coupling of the pyrrole derivatives and 1-naphthoyl chloride catalyzed by the strong Lewis acid aluminum chloride ($\text{AlCl}_3$). These standard Friedel-Crafts conditions involve the addition of the substrate to a stirring solution of aluminum chloride and the acyl halide.

Although it has been known for many years that electrophilic substitution reactions of pyrrole and its substituted derivatives occur predominantly at the 2-position, it has also been found that placement of a bulky substituent on the nitrogen provided mainly acylation in the 3-position under Friedel-Crafts conditions. This was believed to be primarily due to steric hindrance at the pyrrole 2-position. However, the regioselectivity has been found to differ when using weaker Lewis acids. While $\text{AlCl}_3$ provides regioselective acylation at the 3-position, Kakushima and co-workers found that weaker Lewis acids such as ethylaluminum dichloride ($\text{EtAlCl}_2$) and diethylaluminum chloride ($\text{Et}_2\text{AlCl}$) regioselectively acylate the 2-position of the pyrrole.

The Huffman group continually uses the modified Okauchi procedure of the Friedel-Crafts acylation. This method has been employed for the synthesis of many 3-acylindoles and involves stirring the substrate with the catalyst for approximately 30 minutes prior to addition of the acyl halide. Using this method, Padgett found that
with Et₂AlCl, only the 2-isomer was obtained, but when AlCl₃ was used, a 9:1 ratio of the 3-isomer to the 2-isomer was obtained unlike when Lainton had carried out this procedure finding that under typical Friedel-Crafts conditions with AlCl₃, an equal mixture of the 2- and 3-isomers was obtained.⁹²,¹⁰¹

Overall, the findings of the Huffman group, using N-p-toluenesulfonylpyrrole (87, Figure 40, N-Ts-pyrrole) as the substrate, showed that when using more than 1.0 equivalents of AlCl₃ under typical Friedel-Crafts conditions, in both dichloromethane (DCM) and 1,2-dichloroethane (DCE) the predominant product (>88%) was the 3-acylated (86, Figure 40) isomer. Reducing the amount of catalyst to 1.0 equivalents and 0.9 equivalents showed an increase to 15-32% of 2-isomer (89, Figure 40) attained, respectively.⁹²

Further investigations into the effect of the Lewis acid were performed utilizing the Okauchi method of acylation. N-Ts-pyrrole (Figure 40) was used in concentrations of 0.075M and 0.221M in both DCM and DCE. The findings are summarized as follows: When using AlCl₃ the 3-isomer was the main product, however when EtAlCl₂ was used as catalyst the ratio of 2- to 3-isomer greatly increased and the 2-isomer became the predominant product. The use of Et₂AlCl led to almost exclusively to the 2-isomer along with recovered starting material.¹⁰²
The reinvestigation into the effects of the use of AlCl$_3$ in the Okauchi method involved acylation using 1-naphthoyl chloride, acetyl chloride and acetic anhydride. Whether 1.0, 1.2, 1.5 or 2.0 equivalents of AlCl$_3$ were used, all led to the 3-isomer as the major product. When 0.9 equivalents of AlCl$_3$ were used, the ratio of 2- to 3-isomer was increased, but the 3-isomer was still the predominant product.$^{102,103}$

As previously stated, pyrroles normally undergo electrophilic substitution at the 2-position.$^{92}$ It was originally considered that acylation in the 3-position may occur via initial substitution at the 2-position followed by rearrangement to the C-3 carbon, as this has been observed in substituted pyrroles in acidic medium.$^{104-106}$ However, Kakushima and co-workers established that this was not a logical mechanism based on the observation that 2-acetyl-$N$-benzenesulfonylpyrrole formed a stable complex with AlCl$_3$ and could be recovered unchanged after aqueous work-up.$^{98}$ Similarly, the Huffman
group recovered both 2-(1-naphthoyl)-N-p-toluenesulfonylpyrrole and the 3-isomer unchanged after stirring with AlCl$_3$ in DCM for 2 h.$^{102}$

![Figure 41. Synthesis of N-p-toluenesulfonylpyrrole.](image)

In early studies of the acylation of indoles in the 3-position using the Okauchi method, Paul Szklennik of the Huffman group obtained evidence that the Okauchi procedure involves an intermediate organoaluminum complex between the indole and the Lewis acid.$^{100}$ Ottoni and co-workers had found that organotin intermediates formed when employing the Okauchi procedure were insoluble in DCM unless nitromethane was added to the reaction mixture.$^{90}$ The organoaluminum counterparts however, are found to be soluble in DCM.$^{100}$

Kakushima reported that $N$-benzenesulfonylpyrrole and AlCl$_3$ in DCE remains heterogenous and that there is no evidence of complex formation by $^1$H NMR and UV.$^{99}$ However, it was found that a mixture of $N$-Ts-pyrrole and 0.9 equivalents of AlCl$_3$ in DCE is a homogenous solution and $N$-benzenesulfonylpyrrole behaved similarly.
Attempts to acquire a $^1$H NMR of the homogenous solution run in DCE-$d_4$ proved difficult so it was found necessary to prepare the sample in a dry, inert atmosphere.$^{102}$

The $^1$H NMR spectra that was obtained from the stirring of $N$-Ts-pyrrole and 0.9 equivalents of AlCl$_3$ in DCE-$d_4$ was not well resolved (Figure 43), but it clearly showed the loss of signals at $\delta$6.29 and $\delta$7.17 which correspond to the C-3 and C-2 protons of $N$-Ts-pyrrole (Figure 42). It was also noted that the doublets assigned to the phenyl ring at $\delta$7.30 and $\delta$7.74 were no longer present. The most prominent doublets in the spectra appear at $\delta$7.80 and $\delta$7.83, however the bulk of aromatic protons appear as a wide multiplet and no reasonable integration was possible. The absence of $N$-Ts-pyrrole signals in Figure 43 cannot be attributed to a shift of the spectrum. In addition to the aromatic methyl peak at $\delta$2.36 there was now a second peak at $\delta$2.46 (Figure 43). A $^{13}$C NMR could not be taken because of the rapid decomposition of the sample. When the $N$-Ts-pyrrole and AlCl$_3$ in DCE was quenched with water, starting material was recovered. Quenching of a solution of $N$-Ts-pyrrole and AlCl$_3$ with D$_2$O showed deuterium incorporation at the C-2 and C-3 positions while quenching the reaction in either EtAlCl$_2$ or Et$_2$AlCl with D$_2$O showed no deuterium incorporation by $^1$H NMR.$^{107}$
Figure 42. $^1$H NMR spectrum of $N$-$p$-toluenesulfonylpyrrole (87) in DCE-$d_4$.\textsuperscript{103}

Figure 43. $^1$H NMR spectrum of $N$-$p$-toluenesulfonylpyrrole (87) and AlCl$_3$ in DCE-$d_4$.\textsuperscript{103}
This evidence indicates that the mechanism of acylation of $N$-Ts-pyrrole using AlCl$_3$ differs from that employing the use of weaker Lewis acids. Changes in the $^1$H NMR spectrum, the deuterium quenching results and the homogeneity of the reaction using AlCl$_3$ implies that the mechanism of this reaction is probably similar to that of the Okauchi and Ottoni acylation procedure.$^{51, 90}$ A possible mechanism for formation of the 2- and 3-isomers is shown in Figure 43.

Figure 44. Proposed mechanism of the acylation of $N$-$p$-toluenesulfonylpyrrole using AlCl$_3$.\textsuperscript{102}
As shown in Figure 43, the reaction of $N$-Ts-pyrrole with AlCl$_3$ leads reversibly to a mixture of the 2- and 3-organoaluminum intermediates. This occurs through either cation 90 or 91. Reaction of species 92 with the aroyl chloride leads to the corresponding 3-arylopyrrole 88. Similarly, reaction of 93 with an aroyl chloride will lead to the 2-arylopyrrole 89. Although the suggested mechanistic pathway ideally provides both regioisomers, it is believed that the acylation of the 2-position occurs at a much slower rate of reaction due to steric effects that are not a problem when acylation occurs at the unencumbered C-3 position. It is also hypothesized that there is a direct electronic interaction of the electrophilic aluminum atom of the 2-isomer with an oxygen of the sulfonyl group, forming a five-membered structure (94). This interaction would stabilize the organoaluminum intermediate and decrease the rate of reaction with the aroyl chloride.\textsuperscript{102}

Evidence to support the mechanistic hypotheses put forward in this study has been established. In the Okauchi procedure, the organoaluminum intermediates 92 and 93 are formed prior to addition of the acyl halide, therefore when using 0.9 equivalents of AlCl$_3$ there is no competing reaction for the Lewis acid between the aroyl chloride and the substrate. However, under normal Friedel-Crafts conditions where the acyl halide is stirred with the Lewis acid prior to addition of the substrate, $N$-Ts-pyrrole, it is hypothesized that a reversible complex in which the AlCl$_3$ is coordinated to the carbonyl oxygen of the acyl halide exists.\textsuperscript{108-111} The substrate must then either compete with the aroyl chloride for AlCl$_3$ or the aluminum-oxygen complex itself becomes the Lewis acid, resulting in compounds 88 and 89.
Weaker Lewis acids are less regioselective and presumably do not involve an organometallic pyrrole derivative. It has been found that under typical Friedel-Crafts conditions, a polarized AlCl$_3$–acyl halide complex is formed with no NMR indication of an acylium ion.\textsuperscript{109} Also, the degree of Lewis acid induced polarization of this complex decreased with the inductively withdrawing effect of the α-halogens of the Lewis acid and that the rate of acylation decreased when there were electron withdrawing substituents on the acyl halide.

It has been suggested that aromatic substitution reactions may proceed via a single transition state; strongly electrophilic reagents providing early transition states resembling a π-complex, or a reactant-like transition state, while less electrophilic reagents provide product-like transition states similar to a resonance stabilized σ-complex, or Wheland intermediates.\textsuperscript{112-115} The application of the Hammond postulate to these considerations predicts that in the electrophilic substitution reactions of pyrroles electrophilic species such as AlCl$_3$ will react at the 3-position, having a higher activation energy, while electrophilic species such as Et$_2$AlCl will attack at the 2-position, producing the resonance stabilized, energetically favored, 3-carbocation.\textsuperscript{102} The Merck group carried out studies, the findings of which supported this theory, using CNDO/2 calculations. These studies found that the 3-cation was significantly more stable than the 2-cation. This conclusion is also supported by classical valence bond theory.\textsuperscript{97}

Ultimately, the reinvestigation of the mechanism of Friedel-Crafts acylation of $N$-$p$-toluenesulfonylpyrrole led to the hypothesis that there are two distinct mechanistic pathways dependent on the order of addition of reactants. The regioselective acylation of
\( N-p \)-toluenesulfonylpyrrole, when stirred with \( \text{AlCl}_3 \) prior to acyl halide addition, is not a Friedel-Crafts acylation, but the reaction of an organoaluminum intermediate with an acyl chloride. Acylations employing weaker Lewis acids proceed via a normal Friedel-Crafts reaction through a polarized complex between the Lewis acid and the acylating agent. The nature of the acylating agent and the strength of the Lewis acid determine the electrophilicity of this complex while the regiochemistry is determined by the transition state leading to the 2- or 3-carbocation.
CHAPTER THREE

CONCLUSIONS

This dissertation focuses on the syntheses and pharmacology of three series of cannabimimetic indoles: (4-halonaphthoyl)indoles, (8-halonaphthoyl)indoles and (6-methoxy-2-naphthoyl)indoles. These compounds were designed to investigate structure-activity relationships at the cannabinoid receptors and possibly to lead to the discovery of additional selective ligands for the CB$_2$ receptor.

The two series of halogen analogs were designed as possible selective ligands for the CB$_2$ receptor. The $N$-alkyl-3-(4-halo-1-napththoyl)indoles and their 2-methyl analogs were synthesized in one of two ways: By coupling a 4-halo-1-naphthoyl chloride with indole or 2-methyl indole followed by $N$-alkylation of the indole or by a modified Friedel-Crafts reaction employing the use of dimethylaluminum chloride to form an organoaluminum $N$-alkylindole intermediate to be coupled with a 4-halo-1-naphthoyl chloride. The 4-halo-1-naphthoic acids were prepared by Friedel-Crafts acetylation of the corresponding 1-halonaphthalenes. The King modification of the haloform reaction followed by base hydrolysis gave the crude 4-halo-1-naphthoic acids which were purified through their methyl esters. Saponification of the esters led to the desired 4-halo-1-naphthoic acids. None of these halogenated compounds are devoid of CB$_2$ affinity and some have CB$_2$ selectivity. This is especially true in the 4-iodo series which has high affinity as well as selectivity for the CB$_2$ receptor.

The analogous $N$-alkyl-3-(8-halo-1-naphththoyl)indoles and their 2-methyl analogs were synthesized through a modification of the Pesci reaction. The mercury-mediated
decarboxylation of 1,8-naphthalic anhydride led to a highly stable organomercurio intermediate which upon halogenation gave the desired 8-halo-1-naphthoic acids. The coupling of an 8-halo-1-naphthoic acid via its acid chloride with an N-alkylindole was successfully carried out using the Okauchi modification of the Friedel-Crafts reaction. Each halogen series displays affinity for the CB$_2$ receptor and in some cases selectivity is also displayed. As in the 4-halo series, the 8-iodo compounds have relatively high selectivity for CB$_2$.

In the realm of studying the effects of the location of the methoxy substituent on the naphthoyl ring a series of N-alkyl-3-(6-methoxy-2-naphthoyl)indoles was synthesized. The Okauchi coupling of an N-alkylindole with 6-methoxy-2-naphthoyl chloride, prepared from the commercially available 6-methoxy-2-naphthoic acid, led to the desired N-alkyl-3-(6-methoxy-2-naphthoyl)indoles. However, these compounds have no significant affinity for either receptor.

A reinvestigation into the acylation of N-$p$-toluenesulfonylpyrrole with AlCl$_3$ led to the following conclusions. When using AlCl$_3$ the acylation appears to proceed via reaction of an organoaluminum intermediate with the acyl chloride. Acylations using weaker Lewis acids proceed by a normal Friedel–Crafts reaction through a polarized complex formed from the acylating agent and the Lewis acid. The electrophilicity of this complex is determined by a combination of the nature of the acylating agent and the strength of the Lewis acid. In these reactions the regiochemistry is determined by the character of the transition state leading to the intermediate carbocation. With highly reactive electrophiles, a reactant-like transition state will favor the 3-substituted product,
while less reactive electrophiles will provide a product-like transition state that resembles the more stable cation resulting from attack at C-2.
CHAPTER FOUR
EXPERIMENTAL

All $^1$H and $^{13}$C NMR spectra were determined on a 300 MHz Bruker Fourier Transform Spectrometer or a 500 MHz Bruker Fourier Transform Spectrometer. The solvent was deuterated chloroform (CDCl$_3$) unless otherwise stated. $^1$H chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS, $\delta = 0.00$ ppm) as an internal standard. $^{13}$C chemical shifts are reported in ppm relative to TMS using the central CDCl$_3$ peak (t, $\delta = 77.0$ ppm) as an internal standard. Coupling constants are reported in Hertz (Hz).

GC/MS analyses were performed on a Hewlett-Packard 5890A capillary gas chromatograph/mass spectrometer at 70 eV or a Shimadzu QP2010 capillary gas chromatograph/mass spectrometer at 1.01 kV. Mass spectra data are reported as mass/charge, with intensity as a percentage of the base peak.

High-resolution mass spectrometry data were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois.

Melting points were determined using a Fisher-Johns apparatus and are uncorrected.

Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone; dichloromethane and pyridine were distilled from calcium hydride; acetone was distilled from potassium permanganate and then dried over calcium carbonate.
Chemicals were used as received from Sigma-Aldrich, Alfa-Aesar, and Fisher Scientific unless otherwise stated. All new compounds were homogenous to TLC and $^{13}$C NMR.

Column chromatography was carried out on Sorbent Technologies silica gel (32 – 63 μm) using the indicated solvents as eluents. TLC was carried out using the indicated solvents.
N-pentylindole (20).

To a stirred solution of 5.00 g (42.7 mmol) of indole in 10 mL of DMSO was added 10.8 g (192 mmol) of crushed KOH. Addition of 12.9 g (85.4 mmol) of 1-bromopentane was followed by stirring at ambient temperature for 1.5 h under N₂. The reaction was quenched with water and the product was extracted with 3 portions of dichloromethane. The organic layer was dried (MgSO₄) and concentrated in vacuo. Kugelrohr distillation at 200 °C under 19 in. Hg gave 8.15 g (98%) of N-pentylindole as a green oil: ¹H NMR (300 MHz, CDCl₃) δ 1.08 (t, J = 6 Hz, 3H), 1.44-1.58 (m, 4H), 1.99 (q, J = 6 Hz, 2H), 4.24 (t, J = 6 Hz, 2H), 6.68 (d, J = 3 Hz, 1H), 7.24 (d, J = 3 Hz, 1H), 7.30 (t, J = 6 Hz, 1H), 7.40 (t, J = 6 Hz, 1H), 7.53 (d, J = 9 Hz, 1H), 7.85 (d, J = 9 Hz, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 14.2, 22.5, 29.3, 30.1, 46.5, 101.0, 109.6, 119.3, 121.1, 121.5, 128.0, 128.8, 136.1; GC/MS (EI) m/z (rel intensity) 187 (91), 172 (5), 158 (8), 144 (4), 130 (100), 117 (14), 103 (17), 89 (11), 77 (18), 63 (4), 51 (2).
2-Methyl-N-pentyldione (21).

To a stirred solution of 5.00 g (38.1 mmol) of 2-methylindole in 10 mL of DMSO was added 9.6 g (171.5 mmol) of crushed KOH. Addition of 11.5 g (76.2 mmol) of 1-bromopentane was followed by stirring at ambient temperature for 1.5 h under N₂. The reaction was quenched with water and the product was extracted with 3 portions of dichloromethane. The organic layer was dried (MgSO₄) and concentrated in vacuo. Kugelrohr distillation at 200 °C under 19 in. Hg gave 7.93 g (97%) of 2-methyl-N-pentyldione as a brown oil: ¹H NMR (300 MHz, CDCl₃) δ 1.41 (t, J = 6 Hz, 3H), 1.75-1.85 (m, 4H), 2.15 (q, J = 6 Hz, 2H), 2.82 (s, 3H), 4.37 (t, J = 7.5 Hz, 2H), 6.74 (s, 1H), 7.60 – 7.68 (m, 2H), 7.73 (d, J = 9 Hz, 1H), 8.87 (d, J = 9 Hz, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.1, 14.5, 23.0, 29.6, 30.4, 43.5, 100.4, 109.5, 119.6, 120.1, 120.8, 128.7, 136.6, 137.2; GC/MS (EI) m/z (rel intensity) 201(99), 186 (27), 172 (4), 158 (4), 144 (100), 130 (29), 115 (24), 103 (12), 91 (9), 77 (15), 63 (4), 51 (3).
N-propylindole (22).

To a stirred solution of 5.00 g (42.7 mmol) of indole in 10 mL of DMSO was added 10.8 g (192 mmol) of crushed KOH. Addition of 14.5 g (85.4 mmol) of 1-iodopropane was followed by stirring at ambient temperature for 1.5 h under N\textsubscript{2}. The reaction was quenched with water and the product was extracted with 3 portions of dichloromethane. The organic layer was dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo}. Kugelrohr distillation at 200 °C under 19 in. Hg gave 7.54 g (90%) of N-propylindole as a yellow oil: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 1.19 (t, J = 6 Hz, 3H), 2.10 (sextet, J = 6 Hz, 2H), 4.28 (t, J = 6 Hz, 2H), 6.82 (d, J = 3 Hz, 1H), 7.33 (d, J = 3 Hz, 1H), 7.45 (t, J = 6 Hz, 1H), 7.54 (t, J = 6 Hz, 1H), 7.64 (d, J = 6 Hz, 1H), 7.99 (d, J = 9 Hz, 1H); \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}) δ 11.8, 23.8, 48.2, 101.1, 109.7, 119.5, 121.3, 121.6, 128.2, 129.0, 136.3; GC/MS (EI) m/z (rel intensity) 159 (95), 130 (100), 117 (11), 103 (22), 89 (20), 77(24), 63 (8), 51 (4).
2-Methyl-N-propylindole (23).

To a stirred solution of 5.00 g (38.1 mmol) 2-methylindole in 10 mL of DMSO was added 9.6 g (171.5 mmol) of crushed KOH. Addition of 12.9 g (76.2 mmol) of 1-iodopropane was followed by stirring at ambient temperature for 1.5 h under N₂. The reaction was quenched with water and the product was extracted with 3 portions of dichloromethane. The organic layer was dried (MgSO₄) and concentrated in vacuo. Kugelrohr distillation at 200 °C under 19 in. Hg gave 7.49 g (88%) 2-methyl-N-propylindole as a red oil: ¹H NMR (300 MHz, CDCl₃) δ 1.32 (t, J = 6 Hz, 3H), 2.09 – 2.20 (m, 2H), 2.78 (s, 3H), 4.32 (t, J = 6 Hz, 2H), 6.70 (s, 1H), 7.53 – 7.63 (m, 2H), 7.68 (d, J = 6 Hz, 1H), 8.02 (d, J = 6 Hz, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 11.9, 13.1, 23.8, 45.0, 100.3, 109.5, 119.6, 120.1, 120.7, 128.6, 136.8, 137.2; GC/MS (EI) m/z (rel intensity) 173 (91), 144 (100), 130 (18), 115 (18), 103 (11), 89 (6), 77 (13), 63 (4), 51 (4).
1-Acetyl-4-bromo-naphthalene (24) (VJS-066).

To a stirred solution of 1.00 g (4.8 mmol) of 1-bromonaphthalene in 15 mL of carbon disulfide at 0 °C in a flame-dried flask under N₂ was added 0.42 g (5.3 mmol) of acetyl chloride. This solution was stirred at 0 °C for 10 min and 0.84 g (6.3 mmol) of AlCl₃ was added. The reaction was stirred at 0 °C for 3 days followed by 2 days of stirring at ambient temperature. The reaction mixture was then poured over ice and concentrated HCl, extracted with ether and washed with NaHCO₃ and brine. After drying (MgSO₄) the solution was concentrated in vacuo and purified by column chromatography (95:5. petroleum ether: ether) to give 0.75 g (62%) of 1-acetyl-4-bromo-naphthalene as a brown oil: ¹H NMR (300 MHz, CDCl₃) δ 2.74 (s, 3H), 7.65-7.69 (m, 2H), 7.74 (d, J = 6 Hz, 1H), 7.83 (d, J = 6 Hz, 1H), 8.32-8.35 (m, 1H), 8.72-8.75 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 30.1, 126.4, 127.5, 127.8, 128.2, 128.4, 128.7, 128.7, 131.2, 132.3, 135.2, 201.0; GC/MS (EI) m/z (rel intensity) 248 (46), 233 (100), 205 (44), 169 (2), 140 (4), 126 (83), 99 (6), 84 (10), 76 (10), 63 (25), 50 (4). The data agree in all respects with those reported in the literature.¹¹⁶
Methyl-4-bromo-1-naphthoate (27) (VJS-070).

To a solution of 0.52 g (2.09 mmol) of 1-acetyl-4-bromonaphthalene in 5 mL of freshly distilled pyridine in a flame-dried round bottom flask under N₂ was added 0.58 g (2.29 mmol) of I₂ dissolved in 10 mL of freshly distilled pyridine. This mixture was refluxed for 30 min and allowed to cool to ambient temperature. The solution was diluted with ether until a brown precipitate formed. The precipitate was filtered off, suspended in 25 mL of 6 M aqueous NaOH and heated at reflux for 2 h. Upon cooling the solution was acidified with 10% HCl and the crude 4-bromo-1-naphthoic acid was extracted with ether and washed with brine. After drying (MgSO₄) the ethereal solution was concentrated in vacuo. The product was dissolved in 20 mL of MeOH to which 4 mL of concentrated H₂SO₄ was cautiously added. This solution was heated at reflux for 2 h. After cooling to ambient temperature the crude product was extracted into ether, the ethereal solution was washed with brine and dried (MgSO₄). The solution was concentrated in vacuo and purified by column chromatography (95:5 petroleum ether: ether) to give 0.55g (57.3%) of methyl 4-bromo-1-naphthoate as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 4.00 (s,
3H), 7.63 (p, J = 8.4 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.96 (d, J = 8.0 Hz, 1H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 52.3, 126.3, 126.9, 127.6, 127.7, 128.5, 128.8, 128.9, 130.1, 132.1, 132.4, 167.4; GC/MS (El) \(m/z\) (rel intensity) 264 (65), 249 (2), 233 (98), 295 (35), 170 (4), 153 (2), 126 (100), 99 (6), 87 (4), 74 (12), 63 (21), 50 (6).

4-Bromo-1-naphthoic acid (30) (VJS-077).

To a round bottom flask containing 0.50 g (1.9 mmol) of methyl-4-bromo-1-naphthoate was added 3.5 g (60 mmol) of crushed KOH in 25 mL of H\(_2\)O. The solution was refluxed overnight and acidified by the dropwise addition of concentrated HCl. The mixture acid was extracted with ether and dried (MgSO\(_4\)). Concentration in vacuo gave 0.35 g (73%) of 4-bromo-1-naphthoic acid as a white solid: m.p. 215-217 °C (lit m.p. \(^{117}\) 217-219 °C); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.74-7.77 (m, 2H), 8.00 (q, J = 9, 12 Hz, 2H), 8.25-8.28
(m, 1H), 8.90-8.93 (m, 1H), 13.3 (br s, 1H); $^{13}$C NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 63.4, 126.7, 127.5, 127.5, 128.6, 129.0, 129.9, 130.5, 131.8, 132.3, 168.6.

1-Acetyl-4-chloro-naphthalene (25) (VJS-083).

To a solution of 0.15 g (1.9 mmol) of acetyl chloride in 8 mL of freshly distilled dichloromethane in a flame-dried round bottom flask under N$_2$ was added 0.26 g (2.0 mmol) of AlCl$_3$. This mixture was stirred at ambient temperature for 5 min and 0.28 g (1.72 mmol) of 1-chloronaphthalene was added dropwise over 10 min. The mixture was heated to 40 °C and stirred for 1 h, poured over a mixture of ice and concentrated HCl. The product was extracted into ether, washed with brine and dried over MgSO$_4$. The solution was concentrated in vacuo to give 0.56 g (84%) of 1-acetyl-4-chloro-naphthalene as a yellow oil, which was used without further purification: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.58 (s, 3 H), 7.33 (d, $J$ = 7.8 Hz, 1 H), 7.48-7.55 (m, 2 H), 7.57 (d, $J$ = 7.8 Hz, 1 H), 8.16 (d, $J$ = 7.8, 1 H), 8.72 (d, $J$ = 7.2, 1 H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 29.8, 124.5, 124.7, 126.4, 127.4, 128.4, 128.6, 130.9, 131.2, 134.1, 136.6, 200.5; GC/MS (EI) m/z (rel
intensity) 204 (69), 189 (100), 161 (75), 126 (54), 99 (7), 84 (6), 75 (11), 63 (19), 50 (3).
The data agree in all respects with those reported in the literature.\textsuperscript{116}

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**Methyl-4-chloro-1-naphthoate (28) (VJS-084).**

To a solution of 2.44 g (11.9 mmol) of 1-acetyl-4-chloronaphthalene in 5 mL of freshly
distilled pyridine in a flame-dried round bottom flask under N\textsubscript{2} was added 3.33 g (13.1
mmol) of I\textsubscript{2} dissolved in 15 mL of freshly distilled pyridine. This mixture was refluxed
for 40 m and allowed to cool to ambient temperature. The solution was diluted with ether
until a brown precipitate formed. The precipitate was filtered off, suspended in 12 mL of
6M aqueous NaOH and heated at reflux for 2 h. Upon cooling the solution was acidified
with 10\% HCl and the crude 4-chloro-1-naphthoic acid was extracted with ether and
washed with brine. After drying (MgSO\textsubscript{4}) the ethereal solution was concentrated \textit{in vacuo}. The product was dissolved in 25 mL of MeOH to which 5 mL of concentrated
H\textsubscript{2}SO\textsubscript{4} was cautiously added. This solution was heated at reflux for 3 h. After cooling to
ambient temperature the crude product was extracted into ether, the ethereal solution was
washed with brine and dried (MgSO₄). The solution was concentrated in vacuo to give 1.66 g (63%) of methyl 4-chloro-1-naphthoate as a brown oil, which was used without further purification: ¹H NMR (300 MHz, CDCl₃) δ 3.90 (s, 3 H), 7.38 (d, J = 7.8, 1 H), 7.45-7.56 (m, 2H), 7.87 (d, J = 8.1, 1 H), 8.18 (d, J = 8.4, 1 H), 8.93 (d, J = 8.1, 1 H); ¹³C NMR (75.5 MHz, CDCl₃) δ 52.1, 124.6, 124.9, 125.8, 126.2, 127.1, 128.3, 129.9, 130.7, 132.3, 137.2, 166.9; GC/MS (EI) m/z (rel intensity) 220 (61), 205 (2), 189 (100), 161 (48), 126 (42), 99 (5), 94 (2), 75 (8), 63 (16), 50 (3).

4-Chloro-1-naphthoic acid (31) (VJS-086).

A solution of 0.25 g (1.1 mmol) of 4-chloro-1-methylnaphthoate and 2.10 g (37.4 mmol) of KOH in 20 mL of H₂O were refluxed 12 h under N₂. The reaction was cooled to ambient temperature and acidified with concentrated HCl. The product was extracted with ether and dried (MgSO₄). The organic phase was concentrated in vacuo to give 0.267 g (88%) of 4-chloro-1-naphthoic acid as an off-white solid: m.p. 223-224 °C (lit
m.p.\textsuperscript{117} 220-221 °C; \textsuperscript{1}H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.74-7.81 (m, 3H), 8.11 (d, $J = 6$ Hz, 1H), 8.28-8.31 (m, 1H), 8.93-8.97 (m, 1H), 13.8 (br s, 1H); \textsuperscript{13}C NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 124.7, 126.1, 126.7, 127.9, 128.3, 129.0, 130.4, 130.6, 132.3, 135.7, 168.5.

\textbf{1-Acetyl-4-iodo-1-naphthalene (26) (VJS-248)}.

To a stirred solution of 2.00 g (15.4 mmol) of AlCl$_3$ in 10 mL of freshly distilled dichloromethane in a flame-dried flask under Ar at 0 °C was added dropwise 1.0 g (13.0 mmol) of acetyl chloride. This mixture was stirred at 0 °C for 10 min and 3.0 g (11.2 mmol) of 1-iodonaphthalene was added dropwise over 10 min. The reaction was stirred at 0 °C for 3 days followed by stirring at ambient temperature for 2 days. The reaction mixture was poured over ice and concentrated HCl, extracted into ether and dried (MgSO$_4$). The solvent was removed \textit{in vacuo} and the crude product was purified using column chromatography (petroleum ether: ether, 7:3) to give 1.9 g (55%) of 1-acetyl-4-iodonaphthalene as a brown oil: \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 2.71 (s, 3H), 7.49 (d, $J = 7.8$ Hz, 1H), 7.58-7.64 (m, 2H), 8.08 (d, $J = 7.5$ Hz, 1H), 8.13-8.17 (m, 1H), 8.63-8.66 (m, 1H); \textsuperscript{13}C NMR (75.5 MHz, CDCl$_3$) $\delta$ 30.2, 106.1, 126.5, 128.2, 128.6, 128.8, 130.4,
132.8, 134.6, 136.2, 136.3, 201.3; GC/MS (EI) m/z (rel intensity) 296 (70), 281 (100), 253 (27), 169 (2), 154 (4), 141 (4), 126 (89), 100 (4), 87 (3), 76 (13), 63 (7), 50 (6).

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Methyl-4-iodo-1-naphthoate (29) (VJS-251).

To a solution of 2.0 g (6.75 mmol) of 1-acetyl-4-iodonaphthalene in 15 mL of freshly distilled pyridine in a flame-dried round bottom flask under N₂ was added 1.9 g (7.43 mmol) of I₂ dissolved in 20 mL of freshly distilled pyridine. This mixture was refluxed for 40 min and allowed to cool to ambient temperature. The solution was diluted with ether until a brown precipitate formed. The precipitate was filtered off, suspended in 40 mL of 6 M aqueous NaOH and heated at reflux for 2.5 h. Upon cooling the solution was acidified with 10% HCl and the crude 4-bromo-1-naphthoic acid was extracted into ether. The ether extracts were washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude product was dissolved in 60 mL of MeOH to which 12 mL of concentrated H₂SO₄ was cautiously added. This solution was heated at reflux for 2 h., cooled to ambient temperature and extracted with ether. The ethereal solution was washed with
brine, dried (MgSO₄) and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether: ether, 7:3) to give 1.2g (56%) of methyl 4-iodo-1-naphthoate as a brown oil: \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 4.03 (s, 3H), 7.63-7.69 (m, 2H), 7.83 (d, \(J = 7.5\) Hz, 1H), 8.17 (d, \(J = 7.5\) Hz, 1H), 8.21 (d, \(J = 8.0\) Hz, 2H); \(^{13}\)C NMR (125.77 MHz, CDCl₃) \(\delta\) 52.4, 125.8, 126.2, 126.4, 127.8, 128.1, 128.5, 130.3, 133.0, 133.4, 136.5, 167.6; GC/MS (EI) \(m/z\) (rel intensity) 312 (100), 281 (84), 253 (22), 170 (8), 153 (5), 126 (76), 99 (4), 87 (3), 76 (9), 63 (7), 50 (4).

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**4-Iodo-1-naphthoic acid (32) (VJS-253).**

To a round bottom flask containing 1.1 g (3.5 mmol) of methyl-4-iodo-1-naphthoate was added 2.0 g (35 mmol) of crushed KOH in 50 mL of H₂O. The solution was refluxed overnight and then acidified by the dropwise addition of concentrated HCl. The mixture was extracted with ether and dried (MgSO₄). Concentration in vacuo gave 0.90g (86%) of 4-iodo-1-naphthoic acid as a white solid: m.p. 209 °C (lit. m.p. \(^{118}\) 213 °C); \(^1\)H NMR (500
MHz, DMSO-$d_6$) $\delta$ 7.72-7.74 (m, 2H), 7.84 (d, $J = 8$ Hz, 1H), 8.14 (dd, $J = 3$, 6.5 Hz, 1H), 8.27 (d, $J = 7.5$ Hz, 1H), 8.84 (dd, $J = 3$, 6.5 Hz, 1H), 13.35 (br s, 1H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$) $\delta$ 106.1, 126.0, 126.8, 128.8, 128.9, 130.7, 131.5, 132.8, 134.4, 137.2, 168.8.

3-(4-Bromo-1-naphthoyl)indole (33) (VJS-173).

To a solution of 0.54 mL (1.71 mmol) of MeMgBr [3.17 M in diethyl ether] in 1 mL of dry ether was added, at 0 °C under Ar, a solution of 0.14 g (1.2 mmol) of indole in dry ether. The mixture was stirred at 0 °C for 1 h. A solution of freshly prepared 4-bromo-1-naphthoyl chloride in 3 mL of dry ether was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.27 g (1.07 mmol) of 4-bromo-1-naphthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The
acid chloride and indole mixture was stirred at ambient temperature for 4 h. After this
time the reaction was quenched with NH₄Cl, the organic phase was extracted with ether
and dried (MgSO₄). Concentration in vacuo followed by column chromatography
(petroleum ether;ether, 2:1) gave 0.29 g (76%) of 3-(4-bromo-1-naphthoyl)indole as a
brown solid: ¹H NMR (300 MHz, DMSO-d₆) δ 7.27-7.33 (m ,2H), 7.53-7.57 (m, 1H),
7.59-7.64 (m, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.75-7.80 (m, 1H), 7.98 (d, J = 7.5 Hz, 1H),
8.07 (d, J = 8.1 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.37-8.34 (m, 1H), 12.18 (br, 1H); ¹³C
NMR (75.5MHz, DMSO-d₆) δ 113.0, 117.6, 121.9, 122.8, 123.9, 124.0, 126.2, 126.6
(br), 127.3, 128.2, 128.6, 129.7, 131.8, 131.9, 137.5, 137.7, 139.4.

2-Methyl-3-(4-bromo-1-naphthoyl)indole (34) (VJS-190).

The title compound was prepared using the procedure VJS-173. To a solution of 0.42 mL
(1.27 mmol) of EtMgBr [3.0M in diethyl ether] in 1 mL of dry ether was added, at 0 °C
under Ar, a solution of 0.12 g (0.88 mmol) of 2-methylindole in dry ether. The mixture
was stirred at 0 °C for 45 min. Freshly prepared 4-bromo-1-naphthoyl chloride, from 0.20
g (0.80 mmol) of 4-bromo-1-naphthoic acid in 3 mL of thionyl chloride, was dissolved in dry ether and added dropwise via syringe and stirred at ambient temperature for 4 h. After this time the reaction was quenched with NH₄Cl and the organic phase was extracted with ethyl acetate. After sitting at ambient temperature for 15 min the solid precipitate was filtered to give 0.13 g (44%) of 2-methyl-3-(4-bromo-1-naphthoyl)indole as a yellow oil: ¹H NMR (500 MHz, DMSO- d₆) δ 2.76 (s, 3H), 6.99 (d, J = 8.0 Hz, 2H), 7.38-7.50 (m, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.84-7.86 (m, 2H), 8.03 (d, J = 8.0 Hz, 1H), 8.36-8.38 (m, 1H), 12.09 (br, 1H); ¹³C NMR (75.5 MHz, DMSO-d₆) δ 15.8, 111.7, 114.0, 120.5, 122.6, 122.8, 125.0, 125.1, 126.0, 126.5, 128.1, 128.5, 129.0, 131.5, 131.7, 132.1, 135.9, 142.4, 148.7, 188.4.

3-(4-Chloro-1-naphthoyl)indole (35) (VJS- 201).

A solution of 0.48 mL (1.45 mmol) of EtMgBr [3.0M in diethyl ether] was added with stirring to 3 mL of dry ether at 0 °C under Ar and stirred until it became cloudy white. A solution of 0.12 g (1.06 mmol) of indole in 2 mL of dry ether was then added and the
resulting mixture was stirred at 0 °C for 30 min followed by stirring at ambient temperature for 30 min. A solution of freshly prepared 4-chloro-1-naphthoyl chloride in 3 mL of dry ether was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.20 g (0.97 mmol) of chloro-1-naphthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at ambient temperature for 4 h, quenched with NH₄Cl and extracted with ether. The ethereal solution was allowed to stand at ambient temperature for 20 min upon which time a precipitate was filtered out to give 0.11 g (38%) of 3-(4-chloro-1-naphthoyl)indole as a cream colored solid: ^1^H NMR (300 MHz, DMSO-d₆) δ 7.27-7.31 (m, 2H), 7.52-7.55 (m, 1H), 7.61-7.71 (m, 2H), 7.74-7.76 (m, 2H), 7.80 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 8.29-8.33 (m, 2H), 12.25 (br s, 1H); ^13^C NMR (75.5 MHz, DMSO-d₆) δ 112.9, 117.5, 121.9, 122.8, 123.8, 124.5, 126.0, 126.3, 126.6, 128.2, 128.4, 130.5, 131.8, 132.5, 137.5, 137.7, 138.7, 190.8.
2-Methyl-3-(4-chloro-1-naphthoyl)indole (36) (VJS-204).

The title compound was prepared using the procedure VJS-201. A solution of 0.29 mL (0.87 mmol) of EtMgBr [3.0M in diethyl ether] was added with stirring to 3 mL of dry ether at 0 °C under Ar until it became cloudy white. A solution of 0.08 g (0.64 mmol) of 2-methylindole in 2 mL of dry ether was then added and the resulting mixture was stirred at 0 °C for 30 min followed by stirring at ambient temperature for 30 min. Freshly prepared 4-chloro-1-naphthoyl chloride, from 0.12 g (0.58 mmol) of 4-chloro-1-naphthoic acid, was dissolved in dry ether and added via syringe. The reaction was stirred at ambient temperature for 4 h, quenched with NH₄Cl and extracted with ether. The ethereal solution was allowed to stand at ambient temperature for 20 min upon which time a precipitate was filtered out giving 0.12 g (62%) of 2-methyl-3-(4-chloro-1-naphthoyl)indole as a cream colored solid: \( ^1H \text{NMR} (300 \text{ MHz, DMSO-}d_6) \delta 6.95 (t, J = 7.2 \text{ Hz, 1H}), 7.08 (t, J = 7.5 \text{ Hz, 1H}), 7.26 (d, J = 7.5 \text{ Hz, 1H}), 7.39 (d, J = 7.8 \text{ Hz, 1H}), 7.46-7.69 (m, 5H), 7.76 (d, J = 7.5 \text{ Hz, 2H}), 7.87 (d, J = 8.4 \text{ Hz, 1H}), 8.25 (d, J = 8.4 \text{ Hz, 1H}), 11.1 (br s, 1H); ^{13}C \text{NMR} (75.5 \text{ MHz, DMSO-}d_6) \delta 14.7, 112.0, 114.0, 120.5, 122.0, \ldots \)
122.6, 124.5, 125.1, 126.0, 126.5, 127.4, 128.3, 128.4, 130.5, 131.2, 132.1, 135.5, 140.7, 146.7, 191.3.

**N-Pentyl-3-(4-bromo-1-naphthoyl)indole (39) (JWH-387).**

**Method A (VJS-178):** To a solution of 0.10 g (0.28 mmol) of 3-(4-bromo-1-naphthoyl)indole in 5 mL of DMSO was added 0.07 g (1.3 mmol) of crushed KOH and 0.09 g (0.57 mmol) of 1-bromopentane. After heating at 80 °C for 12 h the reaction was poured into ice and water, extracted with ethyl acetate, dried (MgSO₄) and concentrated _in vacuo_. Purification by column chromatography (petroleum ether: ether, 8:2) gave 0.022 g (18%) of _N_-pentyl-3-(4-bromo-1-naphthoyl)indole as an orange oil:

**Method B (VJS-569):** Dimethylaluminum chloride (0.60 mL, 1M in hexanes, 0.60 mmol) was added to a solution of 0.08 g (0.44 mmol) of _N_-pentylindole in 5 mL of dry dichloromethane under Ar and the mixture was stirred for 1 h at 0 °C. A solution of
freshly prepared 4-bromo-1-naphthoyl chloride in 3 mL of dry dichloromethane was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.10 g (0.40 mmol) of 4-bromo-1-naphthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at ambient temperature for 4 h. The reaction mixture was quenched with water and extracted with dichloromethane. The organic extract was washed with water, dried (MgSO₄) and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether: ethyl acetate, 9:1) to give 0.09 g (53%) of N-pentyl-3-(4-bromo-1-naphthoyl)indole as an orange oil:

\[ ^1\text{H NMR} \ (300 \text{ MHz, CDCl}_3) \delta 0.87 \ (t, \ J = 6.6 \text{ Hz,} \ 3\text{H}), 1.25-1.31 \ (m, \ 4\text{H}), 1.80-1.85 \ (m, \ 2\text{H}), 4.09 \ (t, \ J = 7.2 \text{ Hz,} \ 2\text{H}), 7.28 \ (s, \ 1\text{H}), 7.35-7.41 \ (m, \ 4\text{H}), 7.50-7.56 \ (m, \ 1\text{H}), 7.63-7.68 \ (m, \ 1\text{H}), 7.87 \ (d, \ J = 7.5 \text{ Hz,} \ 1\text{H}), 8.20 \ (d, \ J = 8.4 \text{ Hz,} \ 1\text{H}), 8.36 \ (d, \ J = 8.4 \text{ Hz,} \ 1\text{H}), 8.48-8.51 \ (m, \ 1\text{H}); \]

\[ ^{13}\text{C NMR} \ (75.5 \text{ MHz, CDCl}_3) \delta 13.9, 22.2, 28.9, 29.48, 47.2, 110.1, 117.4, 122.9, 123.0, 123.8, 124.8, 125.8, 126.5, 126.9, 127.4, 127.5, 127.8, 128.8, 132.0, 132.2, 137.1, 137.9, 139.1, 191.0; \]

GC/MS (EI) \( m/z \) (rel intensity) 419 (64), 402 (31), 362 (42), 340 (11), 334 (61), 283 (9), 269 (13), 254 (16), 245 (11), 233 (16), 214 (100), 207 (16), 186 (7), 170 (2), 154 (2), 144 (59), 126 (36), 116 (18), 102 (5), 89 (7), 76 (2), 63 (2), 50 (1); HRMS (EI⁺) \( m/z \) calcd for C₂₄H₂₂BrNO: 419.0885; found: 419.0086.
2-Methyl-\(N\)-pentyl-3-(4-bromo-1-naphthoyl) (40) (JWH-394).

**Method A** (VJS-195): A solution of 0.12 g (0.33 mmol) of 2-methyl-3-(4-bromo-1-naphthoyl)indole and 0.08 g (1.48 mmol) of crushed KOH in 5 mL of DMSO was stirred at ambient temperature for 1 h. To this mixture was added 0.10 g (0.66 mmol) of 1-bromopentane and stirring at ambient temperature was continued for 4 h. The reaction was quenched with water and extracted with ethyl acetate. After being dried (\(\text{MgSO}_4\)) and concentrated *in vacuo* the product was purified by column chromatography (petroleum ether: ether, 8:2) to give 0.014 g (10%) of 2-methyl-\(N\)-pentyl-3-(4-bromo-1-naphthoyl)indole as a green oil:

**Method B** (VJS-573): The title compound was prepared using the procedure VJS-569. From 0.11 g (0.57 mmol) of 2-methyl-\(N\)-pentylindole and 0.13 g (0.52 mmol) of 4-bromo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ethyl acetate, 7:3) 0.16 g (73%) of 2-methyl-\(N\)-pentyl-3-(4-bromo-1-naphthoyl)indole as a green oil:
1H NMR (500 MHz, CDCl$_3$) $\delta$ 0.96 (t, $J$ = 7.0 Hz, 3H), 1.39-1.42 (m, 4H), 1.83 (p, $J$ = 7.3 Hz, 2H), 2.55 (s, 3H), 4.15 (t, $J$ = 7.8 Hz, 2H), 7.05 (t, $J$ = 7.3 Hz, 1H), 7.19-7.24 (m, 2H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.44 (d, $J$ = 7.5 Hz, 1H), 7.52 (t, $J$ = 8.3 Hz, 1H), 7.65 (t, $J$ = 8.0 Hz, 1H), 7.86 (d, $J$ = 7.5 Hz, 1H), 8.16 (d, $J$ = 8.0 Hz, 1H), 8.39 (d, $J$ = 8.5 Hz, 1H);

13C NMR (125.77 MHz, CDCl$_3$) $\delta$ 12.7, 14.0, 22.4, 29.1, 29.4, 43.4, 109.6, 114.7, 121.1, 122.1, 122.4, 124.8, 125.8, 126.2, 127.0, 127.5, 127.7, 127.8, 129.3, 131.6, 132.3, 136.1, 140.7, 145.9, 192.3; GC/MS (EI) $m/z$ (rel intensity) 433 (100), 418 (93), 404 (7), 377 (31), 354 (98), 348 (27), 312 (9), 298 (40), 283 (18), 269 (22), 254 (42), 233 (80), 213 (15), 207 (47), 177 (14), 158 (64), 149 (42), 126 (71), 115 (19), 103 (13), 89 (4), 77 (9), 63 (2), 55 (4), 50 (2); HRMS (EI$^+$) $m/z$ calcd for C$_{25}$H$_{24}$BrNO: 433.1041; found: 433.1041.

2-Methyl-N-propyl-3-(4-bromo-1-naphthoyl)indole (38) (JWH-395).

Method A (VJS-200): The title compound was prepared using the procedure VJS-195. From 0.22 g (0.60 mmol) of 2-methyl-N-propyl-3-(4-bromo-1-naphthoyl)indole and 0.15
g (2.72 mmol) of crushed KOH in 5 mL of DMSO followed by addition of 0.21 g (1.21 mmol) of 1-iodopropane to give after column chromatography (petroleum ether: ether, 7:3) 0.12 g (50%) of 2-methyl-N-propyl-3-(4-bromo-1-naphthoyl)indole as a green solid: m.p. 51-53 °C:

Method B (VJS-562): The title compound was prepared using the procedure VJS-569. From 0.08 g (0.48 mmol) of 2-methyl-N-propylindole and 0.11 g (0.45 mmol) of 4-bromo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ethyl acetate, 8:2) 0.11 g (60%) of 2-methyl-N-propyl-3-(4-bromo-1-naphthoyl)indole as a green oil:

$^1$H NMR (300 MHz, CDCl$_3$) δ 1.02 (t, $J = 7.5$ Hz, 3H), 1.85 (sextet, $J = 7.5$ Hz, 2H), 2.54 (s, 3H), 4.11 (t, $J = 7.5$ Hz, 2H), 7.04 (t, $J = 7.2$ Hz, 1H), 7.14-7.24 (m, 2H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.51 (t, $J = 7.2$ Hz, 1H), 7.64 (t, $J = 7.2$ Hz, 1H), 7.76 (d, $J = 7.5$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 8.38 (d, $J = 8.4$ Hz, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 11.5, 12.7, 22.9, 44.9, 109.7, 114.7, 121.1, 122.1, 122.4, 124.8, 125.8, 126.2, 126.9, 127.5, 127.7, 127.8, 129.3, 131.6, 132.3, 136.2, 140.7, 146.0, 192.3; GC/MS (EI) m/z (rel intensity) 405 (82), 390 (31), 376 (4), 348 (22), 326 (100), 309(24), 296 (11), 283 (18), 269 (18), 254 (18), 235 (29), 213 (11), 200 (69), 158 (49), 149 (27), 126 (53), 103 (11), 89 (4), 77 (9), 63 (2), 50 (2); HRMS (ES$^+$) m/z calcd for C$_{23}$H$_{20}$BrNO: 405.0728; found: 405.0721.
N-Propyl-3-(4-bromo-1-naphthoyl)indole (37) (JWH-386).

**Method A** (VJS-174): The title compound was prepared using the procedure VJS-195. From 0.30 g (0.86 mmol) of N-propyl-3-(4-bromo-1-naphthoyl)indole and 0.22 g (3.8 mmol) of crushed KOH in 5 mL of DMSO followed by addition of 0.31 g (1.8 mmol) of 1-iodopropane was obtained after column chromatography (petroleum ether: ether, 9:1) 0.040 g (12%) of N-propyl-3-(4-bromo-1-naphthoyl)indole as a white solid: m.p. 186-188 °C;

**Method B** (VJS-574): The title compound was prepared using the procedure VJS-569. From 0.07 g (0.44 mmol) of N-propylindole and 0.10 g (0.40 mmol) of 4-bromo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ethyl acetate, 9:1) 0.12 g (72%) of N-propyl-3-(4-bromo-1-naphthoyl)indole as a yellow solid: m.p. 186-187 °C:
\[^1\text{H}\text{ NMR}\ (300 \text{ MHz, DMSO-d}_6)\ \delta \ 0.77 \ (t, \ J = 7.2 \text{ Hz, 3H}), 1.72 \ (\text{sextet, } J = 7.2 \text{ Hz, 2H}),\]

4.15 (t, \( J = 6.9 \text{ Hz, 2H}), 7.32-7.36 \ (m, 2H), 7.58-7.66 \ (m, 3H), 7.74 \ (m, 1H), 7.83 \ (s, 1H), 8.03 \ (t, J = 9 \text{ Hz, 2H}), 8.27 \ (d, J = 8.4 \text{ Hz, 1H}), 8.32-8.35 \ (m, 1H);\]

\[^{13}\text{C}\text{ NMR}\ (75.5 \text{ MHz, DMSO-d}_6)\ \delta \ 11.4, 23.2, 48.1, 111.6, 116.4, 122.2, 123.1, 123.9, 124.0, 126.6, 126.7, 127.2, 128.2, 128.6, 129.8, 131.8, 131.8, 137.4, 139.3, 140.4, 162.3, 190.4;\]

\[\text{GC/MS (EI)} m/z \ (\text{rel intensity}) \ 391 \ (64), 376 \ (22), 364 \ (23), 348 \ (3), 334 \ (3), 312 \ (6), 281 \ (23), 269 \ (12), 254 \ (5), 240 \ (5), 207 \ (100), 186 \ (67), 156 \ (5), 144 \ (33), 126 \ (25), 115 \ (10), 96 \ (12), 73 \ (15), 59 \ (1);\]

\[\text{HRMS (EI\textsuperscript{+}) } m/z \text{ caled for } C_{22}H_{18}BrNO: 391.0572; \text{ found: 391.0590.}\]

\[\text{2-Methyl-N-pentyl-3-(4-chloro-1-naphthoyl)indole (44) (JWH-397) (VJS-206).}\]

A solution of 0.15 g (0.47 mmol) of 2-methyl-3-(4-chloro-1-naphthoyl)indole and 0.12 g (2.1 mmol) of crushed KOH in 5 mL of DMSO was stirred at ambient temperature for 1 h. To this mixture was added 0.14 g (0.94 mmol) of 1-bromopentane and stirring at ambient temperature was continued for 6 h. The reaction was quenched with \( H_2O \) and the product
was extracted with ethyl acetate. After being dried (MgSO₄) and concentrated in vacuo
the product was purified by column chromatography (petroleum ether:ether, 8:2)
resulting in 0.05 g (31%) of 2-methyl-N-pentyl-3-(4-chloro-1-naphthoyl)indole as a
yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 0.97 (t, J = 6.9 Hz, 3H), 1.37-1.42 (m, 4H),
1.80-1.85 (m, 2H), 2.55 (s, 3H), 4.15 (t, J = 7.5 Hz, 2H), 7.01-7.06 (m, 1H), 7.16-7.24
(m, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.2 Hz, 2H), 7.63-7.68 (m, 2H), 8.17 (d, J =
8.4 Hz, 1H), 8.41 (d, J = 8.7 Hz, 1H); ¹³C NMR (75.5MHz, CDCl₃) δ 12.7, 14.0, 22.4,
29.1, 29.3, 43.4, 109.6, 114.7, 121.1, 122.1, 122.4, 124.7, 125.5, 126.2, 127.0, 127.4,
127.7, 131.1, 131.6, 133.7, 136.1, 139.9, 145.9, 192.4; GC/MS (EI) m/z (rel intensity)
389 (100), 374 (81), 354 (43), 332 (30), 304 (27), 269 (9), 154 (13), 228 (32), 189 (88),
172 (7), 161 (39), 149 (9), 126 (22), 103 (7), 77 (5), 55 (3); HRMS (ES⁺) m/z calc’d for
C₂₅H₂₄ClNO: 389.1546; found: 389.1541.
**N-Pentyl-3-(4-chloro-1-naphthoyl)indole (43) (JWH-398) (VJS-216).**

The title compound was prepared using the procedure VJS-206. From 0.10 g (0.33 mmol) of 3-(4-chloro-1-naphthoyl)indole and 0.08 g (1.5 mmol) of crushed KOH in 5 mL of DMSO followed by addition of 0.10 g (0.65 mmol) of 1-bromopentane there was obtained after column chromatography (petroleum ether:ether, 9:1) 0.06 g (48%) of **N-pentyl-3-(4-chloro-1-naphthoyl)indole** as a brown oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.87 (t, $J$ = 6.8 Hz, 3H), 1.28-1.34 (m, 4H), 1.82-1.86 (m, 2H), 4.09 (t, $J$ = 7.0 Hz, 2H), 7.37 (s, 1H), 7.39-7.42 (m, 3H), 7.56 (t, $J$ = 7.5 Hz, 1H), 7.59 (d, $J$ = 7.5 Hz, 1H), 7.65-7.68 (m, 2H), 8.25 (d, $J$ = 8.5 Hz, 1H), 8.40 (d, $J$ = 8.5 Hz, 1H), 8.51-8.53 (m, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 13.9, 22.2, 28.9, 29.5, 47.3, 110.1, 117.4, 122.9, 123.0, 123.8, 124.6, 125.0, 125.6, 126.5, 126.9, 127.5, 127.6, 131.0, 132.0, 133.8, 137.1, 138.0, 138.4, 191.0; GC/MS (EI) $m/z$ (rel intensity) 375 (100), 358 (51), 340 (11), 318 (75), 304 (17), 290 (8), 254 (12), 214 (86), 201 (18), 189 (28), 161 (24), 144 (49), 126 (19), 116 (16), 89 (6), 55 (3); HRMS (ES$^+$) $m/z$ calcd for C$_{24}$H$_{22}$ClNO: 375.1390; found: 375.1383
2-Methyl-N-propyl-3-(4-chloro-1-naphthoyl)indole (42) (JWH-399) (VJS-219).

The title compound was prepared using procedure VJS-206. From 0.12 g (0.37 mmol) of 2-methyl-3-(4-chloro-1-naphthoyl)indole and 0.09 g (1.69 mmol) of crushed KOH in 5 mL of DMSO followed by addition of 0.13 g (0.75 mmol) of 1-iodopropane there was obtained after column chromatography (petroleum ether:ether; 1:1) 0.06 g (46%) of 2-methyl-N-propyl-3-(4-chloro-1-naphthoyl)indole as a brown oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.02 (t, $J$ = 7.2 Hz, 3H), 1.86 (sextet, $J$ = 7.5 Hz, 2H), 2.54 (s, 3H), 4.13 (t, $J$ = 7.2 Hz, 2H), 7.03 (t, $J$ = 7.2 Hz, 1H), 7.16-7.23 (m, 2H), 7.35 (d, $J$ = 8.4 Hz, 1H), 7.52 (t, $J$ = 7.5 Hz, 2H), 7.63-7.68 (m, 2H), 8.17 (d, $J$ = 8.4 Hz, 1H), 8.41 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 11.5, 12.7, 22.9, 44.9, 109.6, 114.7, 121.1, 122.1, 122.4, 124.7, 125.5, 126.1, 126.9, 127.5, 127.7, 131.1, 131.6, 133.7, 136.2, 139.8, 145.9, 192.4; GC/MS (EI) $m/z$ (rel intensity) 361 (100), 346 (26), 326 (56), 304 (29), 283 (7), 269 (8), 254 (11), 200 (38), 189 (35), 158 (31), 149 (6), 126 (19), 103 (8), 89 (3), 77 (5), 63 (2), 50 (1); HRMS (ES$^+$) $m/z$ calcd for C$_{23}$H$_{26}$ClNO: 361.1233; found: 361.1232.
N-Propyl-3-(4-chloro-1-naphthoyl)indole (41) (JWH-400) (VJS-214).

Method A (VJS-214): The title compound was prepared using procedure VJS-206. From 0.16 g (0.52 mmol) of 3-(4-chloro-1-naphthoyl)indole and 0.13 g (2.35 mmol) of crushed KOH in 5 mL of DMSO followed by addition of 0.18 g (1.05 mmol) of 1-iodpropane was filtered 0.03 g (15%) of N-propyl-3-(4-chloro-1-naphthoyl)indole as a white solid:

Method B (VJS-575): Dimethylaluminum chloride (1.10 mL, 1M in hexanes, 1.1 mmol) was added to a solution of 0.13 g (0.80 mmol) of N-propylindole in 5 mL of dry dichloromethane under Ar and the mixture was stirred for 1 h at 0 °C. A solution of freshly prepared 4-chloro-1-naphthoyl chloride in 3 mL of dry dichloromethane was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.15 g (0.73 mmol) of 4-chloro-1-napthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at ambient
temperature for 4 h. The reaction mixture was quenched with water and extracted with dichloromethane. The organic extract was washed with water, dried (MgSO₄) and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether: ethyl acetate, 7:3) to give 0.04 g (15%) of N-propyl-3-(4-bromo-1-naphthoyl)indole as a tan solid: m.p. 194-195 °C.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 0.79 (t, \(J = 7.3\) Hz, 3H), 1.73 (sextet, \(J = 7.3\) Hz, 2H), 4.17 (t, \(J = 7.0\) Hz, 2H), 7.33-7.36 (m, 2H), 7.63-7.69 (m, 3H), 7.76 (t, \(J = 7.5\) Hz, 1H), 7.83-8.84 (m, 2H), 8.07 (d, \(J = 8.0\) Hz, 1H), 8.33 (t, \(J = 8.5\) Hz, 2H); \(^{13}\)C NMR (125.77 MHz, DMSO-\(d_6\)) 11.4, 23.2, 48.2, 111.6, 116.4, 122.2, 123.1, 123.9, 124.5, 126.1, 126.3, 126.5, 126.8, 128.3, 128.4, 130.6, 131.8, 132.5, 137.4, 138.7, 140.4, 190.4; GC/MS (EI) m/z (rel intensity) 347 (96), 330 (41), 318 (54), 304 (15), 281 (17), 269 (16), 254 (13), 241 (11), 226 (3), 207 (22), 186 (100), 161 (22), 144 (63), 126 (26), 116 (28), 102 (4), 89 (13), 73 (22), 57 (4), 51 (2); HRMS (EI\(^+\)) calcd for C\(_{22}\)H\(_{18}\)ClNO: 347.1077; found: 347.0927.
Dimethylaluminum chloride (0.73 mL, 1M in hexanes, 0.73 mmol) was added to a solution of 0.13 g (0.67 mmol) of N-pentylindole in 5 mL of dry dichloromethane under Ar and the mixture was stirred for 1 h at 0 °C. A solution of freshly prepared 4-iodo-1-naphthoyl chloride in 3 mL of dry dichloromethane was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.20 g (0.67 mmol) of 4-iodo-1-naphthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at ambient temperature overnight. The reaction mixture was quenched with water and extracted with ether. The ethereal solution was washed with water, dried (MgSO\(_4\)) and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether: ether, 1:1) to give 0.047 g (15%) of N-pentyl-3-(4-iodo-1-naphthoyl)indole as a peach colored oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.89 (t, \(J = 7.5\) Hz, 3H), 1.30-1.36 (m, 4H), 1.83-1.86 (m, 2H), 4.08
(t, J = 7.5 Hz, 2H), 7.35 (s, 1H), 7.36-7.42 (m, 4H), 7.51 (t, J = 8 Hz, 1H), 7.62 (t, J = 8 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 7 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.48-8.50 (m, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 13.9, 22.2, 28.9, 29.5, 47.3, 101.9, 110.1, 117.5, 122.9, 123.0, 123.8, 126.3, 126.7, 126.9, 127.6, 128.2, 131.4, 132.5, 134.5, 136.4, 137.1, 138.0, 140.1, 191.0; GC/MS (EI) m/z (rel intensity) 467 (33), 450 (14), 410 (21), 380 (2), 340 (7), 324 (1), 281 (36), 240 (15), 214 (100), 191 (8), 170 (5), 144 (53), 126 (43), 89 (9), 73 (5), 55 (3); HRMS (ES$^+$) m/z calcd for C$_{24}$H$_{22}$INO: 468.0824; found: 468.0811.

![Chemical structure](image)

2-Methyl-N-pentyl-3-(4-iodo-1-naphthoyl)indole (48) (JWH-420) (VJS-255).

The title compound was prepared using the procedure VJS-254. From 0.10 g (0.50 mmol) of 2-methyl-N-pentylindole and 0.15 g (0.50 mmol) of 4-iodo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 7:3) 0.065 g (27%) of 2-methyl-N-pentyl-3-(4-iodo-1-naphthoyl)indole as a brown oil: $^1$H NMR (500 MHz, CDCl$_3$) δ 0.95 (t, J = 6.8 Hz, 3H), 1.39-1.42 (m, 4H), 1.81-1.84 (m, 2H), 2.55 (s, 3H), 2.57-2.65 (m, 2H), 2.71-2.78 (m, 2H), 2.81-2.90 (m, 2H), 3.09-3.30 (m, 2H), 3.46-3.57 (m, 2H), 3.76-3.85 (m, 2H), 4.18-4.27 (m, 2H), 4.39-4.48 (m, 2H), 5.29-5.38 (m, 1H), 5.89-5.98 (m, 1H), 6.09-6.18 (m, 1H), 6.29-6.38 (m, 1H), 6.49-6.58 (m, 1H), 6.69-6.78 (m, 1H), 6.89-6.98 (m, 1H), 7.09-7.18 (m, 1H), 7.29-7.38 (m, 1H), 7.49-7.58 (m, 1H), 7.69-7.78 (m, 1H), 7.89-7.98 (m, 1H), 8.09-8.18 (m, 1H), 8.29-8.38 (m, 1H), 8.49-8.58 (m, 1H), 8.69-8.78 (m, 1H), 8.89-8.98 (m, 1H), 9.09-9.18 (m, 1H), 9.29-9.38 (m, 1H), 9.49-9.58 (m, 1H).
4.15 (t, \( J = 7.5 \) Hz, 2H), 7.05 (t, \( J = 7.5 \) Hz, 1H), 7.19 (d, \( J = 8 \) Hz, 1H), 7.22 (t, \( J = 7.5 \) Hz, 1H), 7.28-7.29 (m, 1H), 7.35 (d, \( J = 8 \) Hz, 1H), 7.50 (t, \( J = 7.5 \) Hz, 1H), 7.62 (t, \( J = 8 \) Hz, 1H), 8.08 (d, \( J = 8.5 \) Hz, 1H), 8.17 (d, \( J = 7.5 \) Hz, 1H), 8.23 (d, \( J = 8.5 \) Hz, 1H); \(^{13}\)C NMR (125.77 MHz, CDCl\(_3\)) \( \delta \) 12.7, 13.9, 22.4, 29.1, 29.3, 43.4, 101.7, 109.6, 114.7, 121.1, 122.2, 122.4, 126.2, 126.3, 126.9, 127.7, 128.1, 131.0, 132.6, 134.6, 136.1, 136.9, 141.6, 145.9, 192.3; GC/MS (EI) \( m/z \) (rel intensity) 481 (100), 466 (62), 425 (17), 396 (12), 354 (48), 337 (7), 312 (2), 298 (17), 281 (41), 269 (8), 254 (16), 228 (30), 213 (9), 177 (7), 158 (27), 126 (46), 115 (6), 103 (4), 77 (3), 63 (1), 50 (1); HRMS (ES\(^{+}\)) \( m/z \) calcd for \( \text{C}_{25}\text{H}_{24}\text{IN} \) 482.0981; found: 482.0987.

2-methyl-N-propyl-3-(4-iodo-1-naphthoyl)indole (46) (JWH-422) (VJS-256).

The title compound was prepared using procedure VJS-254. From 0.12 g (0.67 mmol) of 2-methyl-N-propylindole and 0.20 g (0.67 mmol) of 4-iodo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 7:3) 0.039 g (13%) of 2-
methyl-<i>N</i>-propyl-3-(4-iodo-1-naphthoyl)indole as a green oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.03 (t, <i>J</i> = 7.5 Hz, 3H), 1.86 (sextet, <i>J</i> = 7.5 Hz, 2H), 2.55 (s, 3H), 4.14 (t, <i>J</i> = 7.5 Hz, 2H), 7.04 (t, <i>J</i> = 8 Hz, 1H), 7.18 (d, <i>J</i> = 8 Hz, 1H), 7.21 (t, <i>J</i> = 7.5 Hz, 1H), 7.28 (d, <i>J</i> = 7.5 Hz, 1H), 7.35 (d, <i>J</i> = 8.5 Hz, 1H), 7.49 (t, <i>J</i> = 7.8 Hz, 1H), 7.62 (t, <i>J</i> = 7.8 Hz, 1H), 8.07 (d, <i>J</i> = 8.5 Hz, 1H), 8.17 (d, <i>J</i> = 7 Hz, 1H), 8.23 (d, <i>J</i> = 8.5 Hz, 1H); <sup>13</sup>C NMR (125.77 MHz, CDCl<sub>3</sub>) δ 11.5, 12.7, 22.9, 44.9, 101.7, 109.6, 114.7, 121.1, 122.1, 122.4, 126.1, 126.3, 126.9, 127.7, 128.1, 131.0, 132.5, 134.6, 136.2, 136.9, 141.6, 145.9, 192.3; GC/MS (EI) m/z (rel intensity) 453 (100), 436 (15), 424 (5), 410 (2), 396 (14), 326 (58), 309 (10), 296 (7), 281 (18), 269 (8), 254 (12), 200 (36), 158 (25), 149 (17), 126 (35), 115 (6), 103 (6), 77 (4), 63 (2), 50 (1); HRMS (ES<sup>+</sup>) m/z calcd for C<sub>23</sub>H<sub>20</sub>INO: 454.0668; found: 454.0665.

**<i>N</i>-propyl-3-(4-iodo-1-naphthoyl)indole (45) (JWH-423) (VJS-257).**

The title compound was prepared using procedure VJS-254. From 0.11 g (0.70 mmol) of <i>N</i>-propylindole and 0.21 g (0.70 mmol) of 4-iodo-1-naphthoic acid there was obtained
after column chromatography (petroleum ether:ethyl acetate, 9:1) 0.022 g (7%) of N-propyl-3-(4-iodo-1-naphthoyl)indole as a pale cream powder: m.p. 160-161 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.79 (t, $J = 7$ Hz, 3H), 1.72-1.76 (m, 2H), 4.17 (t, $J = 7$ Hz, 2H), 7.33-7.35 (m, 2H), 7.43 (d, $J = 7$ Hz, 1H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.64 (d, $J = 7$ Hz, 1H), 7.71 (t, $J = 7.5$ Hz, 1H), 7.81 (s, 1H), 7.98 (d, $J = 8$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 8.28 (d, $J = 7.5$ Hz, 1H), 8.32 (d, $J = 6.5$ Hz, 1H); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 11.3, 23.1, 48.9, 101.9, 110.1, 117.5, 122.9, 123.0, 123.8, 126.3, 126.7, 126.9, 127.6, 128.2, 131.4, 132.5, 134.5, 136.4, 137.1, 138.0, 140.1, 191.0; GC/MS (EI) $m/z$ (rel intensity) 439 (100), 422 (37), 410 (40), 396 (5), 382 (3), 312 (9), 293 (12), 269 (10), 254 (11), 240 (8), 213 (6), 186 (83), 156 (4), 144 (41), 126 (31), 116 (18), 102 (3), 89 (6), 76 (3), 62 (2), 50 (1); HRMS (ES$^+$) $m/z$ calcd for C$_{22}$H$_{18}$INO: 440.0511; found: 440.0526.
$N$-pentyl-3-(4-fluoro-1-naphthoyl)indole (51) (JWH-412) (VJS-233).

Dimethylaluminum chloride (0.60 mL, 1 M in hexanes, 0.60 mmol) was added to a solution of 0.07 g (0.38 mmol) of $N$-pentyindole in 5 mL of dry dichloromethane under Ar and the mixture was stirred for 30 min at 0 °C. A solution of freshly prepared 4-fluoro-1-naphthoyl chloride in 3 mL of dry dichloromethane was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.11 g (0.58 mmol) of 4-fluoro-1-naphthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. This acid chloride and indole mixture was stirred at ambient temperature overnight. The reaction was quenched with water and extracted with ether. The ethereal solution was washed with water and 1 M KOH, dried (MgSO$_4$) and the solvent was removed in vacuo to give the crude product, which was purified by column chromatography (petroleum ether: ether, 7:3) to give 0.021 g (10%) of $N$-pentyln-3-(4-fluoro-1-naphthoyl)indole as a brown oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.89 (t, $J$ = 7
Hz, 3H), 1.28-1.35 (m, 4H), 1.85 (p, J = 7 Hz, 2H), 4.11 (t, J = 7 Hz, 2H), 7.22 (dd, J = 8, 10 Hz, 1H), 7.38-7.40 (m, 3H), 7.42-7.43 (m, 1H), 7.56 (t, J = 7 Hz, 1H), 7.61 (t, J = 7 Hz, 1H), 7.66 (dd, J = 5.5, 8 Hz, 1H), 8.21 (d, J = 8 Hz, 1H), 8.28 (d, J = 8.5 Hz, 1H), 8.48-8.50 (m, 1H); $^{13}$C NMR (125.77 MHz, CDCl$_3$) δ 13.9, 22.2, 28.9, 29.5, 47.2, 108.1, 108.3, 110.0, 117.5, 120.6, 120.7, 122.9, 122.9, 123.7, 126.0, 126.4, 126.7, 127.0, 127.8, 132.6, 137.1, 137.7, 191.0; GC/MS (EI) m/z (rel intensity) 359 (50), 343 (22), 327 (2), 302 (54), 281 (26), 259 (8), 244 (2), 222 (24), 207 (100), 191 (9), 173 (36), 145 (34), 125 (9), 96 (8), 73 (32), 55 (1); HRMS (ES$^+$) m/z calcd for C$_{24}$H$_{22}$FNO: 359.1685; found: 359.1679.

2-Methyl-N-pentyl-3-(4-fluoro-1-naphthoyl)indole (52) (JWH-413) (VJS-235).

The title compound was prepared using the procedure VJS-233. From 0.10 g (0.48 mmol) of 2-methyl-N-pentylindole and 0.14 g (0.74 mmol) of 4-fluoro-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 9:1) 0.022 g (12%) of 2-methyl-N-pentyl-3-(4-fluoro-1-naphthoyl)indole as a green oil: $^1$H NMR (500 MHz,
CDCl\textsubscript{3} δ 0.95 (t, J = 7 Hz, 3H), 1.41-1.42 (m, 4H), 1.81-1.85 (m, 2H), 2.56 (s, 3H), 4.16 (t, J = 7.5 Hz, 2H), 7.03 (d, J = 8 Hz, 1H), 7.15-7.22 (m, 4H), 7.34 (d, J = 8.5 Hz, 1H), 7.54-7.60 (m, 3H), 8.22 (d, J = 9 Hz, 1H); \textsuperscript{13}C NMR (125.77 MHz, CDCl\textsubscript{3}) δ 12.6, 13.9, 22.4, 29.1, 29.4, 43.4, 108.6, 108.8, 109.5, 114.9, 120.7, 120.7, 121.1, 121.9, 122.2, 123.9, 124.1, 125.7, 126.6, 126.7, 127.1, 127.9, 136.1, 145.5, 192.4; GC/MS (EI) m/z (rel intensity) 373 (74), 358 (45), 341 (9), 316 (44), 300 (10), 281 (35), 259 (8), 228 (12), 207 (49), 173 (100), 145 (55), 125 (11), 103 (4), 73 (59), 55 (2); HRMS (ES\textsuperscript{+}) m/z calcd for C\textsubscript{25}H\textsubscript{24}FNO: 373.1842; found: 373.1850.

\begin{center}
\includegraphics[width=0.5\textwidth]{2-methyl-N-propyl-3-(4-fluoro-1-naphthoyl)indole.png}
\end{center}

2-methyl-N-propyl-3-(4-fluoro-1-naphthoyl)indole (50) (JWH-415) (VJS-239).

The title compound was prepared using procedure VJS-233. From 0.08 g (0.45 mmol) of 2-methyl-N-propylindole and 0.13 g (0.68 mmol) of 4-fluoro-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 8:2) 0.89 g (56%) of 2-methyl-N-propyl-3-(4-fluoro-1-naphthoyl)indole as a yellow oil: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 0.98 (t, J = 7.5 Hz, 3H), 1.82 (sextet, J = 7.5 Hz, 2H), 2.51 (s, 3H), 4.09 (t, J =
7.5 Hz, 2H), 6.99 (t, J = 7.5 Hz, 1H), 7.16 (q, J = 8.3 Hz, 3H), 7.31 (d, J = 8.3 Hz, 1H),
7.50 (t, J = 7.4 Hz, 1H), 7.53-7.56 (m, 2H), 8.17-8.20 (m, 2H); $^{13}$C NMR (125.77 MHz,
CDCl$_3$) δ 11.5, 12.6, 23.0, 44.9, 108.7, 108.8, 109.6, 114.9, 120.7, 120.8, 121.1, 121.9,
122.3, 125.7, 126.7, 126.7, 127.1, 127.9, 136.1, 136.5, 145.6, 190.5; GC/MS (EI) m/z (rel
intensity) 345 (100), 328 (34), 303 (14), 288 (47), 272 (10), 233 (7), 200 (37), 173 (73),
145 (51), 125 (9), 103 (7), 77 (4), 51 (2); HRMS (ES$^+$) m/z calcd for C$_{23}$H$_{20}$FNO:
345.1529; found: 345.1531.

$N$-propyl-3-(4-fluoro-1-naphthoyl)indole (49) (JWH-414) (VJS-238).

The title compound was prepared using procedure VJS-233. From 0.07 g (0.44 mmol) of
$N$-propylindole and 0.12 g (0.63 mmol) of 4-fluoro-1-naphthoic acid there was obtained
after column chromatography (petroleum ether: ether, 8:2) 0.076 g (52%) of $N$-propyl-3-
(4-fluoro-1-naphthoyl)indole as a tan solid: m.p. 166–167 °C; $^1$H NMR (500 MHz, 
CDCl$_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.87 (sextet, J = 7.3 Hz, 2H), 4.09 (t, J = 7 Hz, 2H),
7.21 (t, J = 8.8 Hz, 1H), 7.40-7.43 (m, 4H), 7.57 (t, J = 7Hz, 1H), 7.62 (t, J = 7 Hz, 1H),

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7.66 (t, J = 6.5 Hz, 1H), 8.22 (d, J = 8 Hz, 1H), 8.29 (d, J = 8 Hz, 1H), 8.51-8.53 (m, 1H); ¹³C NMR (125.77 MHz, CDCl₃) δ 11.3, 23.1, 48.8, 108.1, 108.3, 110.1, 117.5, 120.7, 120.7, 122.9, 122.9, 123.7, 126.0, 126.4, 126.4, 126.7, 127.0, 127.8, 137.1, 137.8, 191.1; GC/MS (EI) m/z (rel intensity) 331 (100), 302 (66), 274 (12), 259 (9), 231 (7), 207 (23), 186 (95), 165 (3), 144 (47), 116 (22), 89 (8), 63 (2); HRMS (ES⁺) m/z calcd for C₂₂H₁₈FNO: 331.1372; found: 331.1367.

Anhydro-8-(hydroxymercuri)-1-naphthoic acid (53) (VJS-240).

To 7.0 g (0.18 mol) of NaOH in 300 mL of water was added 10.0 g (0.05 mol) of 1,8-naphthalic anhydride and the suspension was refluxed until dissolution occurred. The excess NaOH was neutralized with 5 mL of acetic acid and 16.1 g (0.05 mol) of mercuric acetate and 50 mL of water were added in one portion. The slurry was refluxed for 30 min and 9 mL of acetic acid was added to ensure evolution of CO₂. The reaction was refluxed for 48 h, cooled and filtered to give 18.0 g (96%) of anhydro-8-hydroxymercuri-1-naphthoic acid as a cream colored solid, which was used without further purification.
8-Bromo-1-naphthoic acid (54) (VJS-258).

To a stirring mixture of 3.9 mL (67 mmol) of acetic acid and 0.40 mL (22.2 mmol) of H₂O was added 1.0 g (2.70 mmol) of anhydro-8-hydroxymercuri-1-naphthoic acid and the suspension was stirred at 0 °C for 10 min. A solution of 0.89 g (8.66 mmol) of NaBr in 3.2 mL of water and 0.43 g (2.70 mmol) of bromine were added sequentially and the reaction was slowly heated to 100 °C. After cooling to ambient temperature the mixture was poured into ice and 0.57 g (84%) of 8-bromo-1-naphthoic acid was filtered out as a cream colored solid: m.p. 173-174 °C (lit. m.p. 174-175 °C); ¹H NMR (500 MHz, DMSO-d₆) δ 7.49 (t, J = 7.8 Hz, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.68 (d, J = 7.0 Hz, 1H), 7.96 (d, J = 7.3 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 13.32 (s, 1H); ¹³C NMR (125.77 MHz, DMSO-d₆) δ 119.3, 126.3, 127.6, 128.0, 128.3, 129.4, 131.2, 133.6, 133.9, 135.7, 171.3.
Dimethylaluminum chloride (0.90 mL, 1M in hexanes, 0.90 mmol) was added to a solution of 0.12 g (0.66 mmol) of N-pentylindole in 5 mL of dry dichloromethane under Ar and the mixture was stirred for 1 h at 0 °C. A solution of freshly prepared 8-bromo-1-naphthoyl chloride in 3 mL of dry dichloromethane was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.15 g (0.60 mmol) of 8-bromo-1-naphthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at ambient temperature overnight. The reaction mixture was quenched with water and extracted with dichloromethane. The organic extract was washed with water, dried (MgSO₄) and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether:ethyl acetate, 7:3) to give 0.20 g (78%) of N-pentyl-3-(8-bromo-1-naphthoyl)indole as a brown
oil: GC/MS (EI) m/z (rel intensity) 421 (3), 340 (100), 270 (58), 254 (5), 235 (1), 214 (5), 144 (5), 126 (7), 89 (1), 74 (1), 55 (1); HRMS (ES\textsuperscript{+}) m/z calcd for C\textsubscript{24}H\textsubscript{22}BrNO: 420.0963; found: 420.0959.

Ambient Temperature: \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 0.86 (t, \(J = 7.0\) Hz, 3H), 1.22-1.32 (m, 4H), 1.77-1.81 (m, 2H), 4.00-4.02 (m, 2H), 7.19-7.29 (m, 1H), 7.31-7.43 (m, 4H), 7.53 (t, \(J = 7.5\) Hz, 1H), 7.62 (d, \(J = 7.0\) Hz, 1H), 7.80 (d, \(J = 8.5\) Hz, 1H), 7.96 (d, \(J = 8.0\) Hz, 1H); \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}) \(\delta\) 14.0, 22.2, 28.8, 29.4, 47.1, 110.1, 119.3, 120.2, 122.7, 122.8, 123.5, 125.4, 126.7, 126.9, 128.1, 128.7, 129.5, 130.4, 133.1, 136.0, 137.1, 137.3, 140.1, 192.3.

At 35 °C: \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 0.78 (t, \(J = 7.0\) Hz, 3H), 2.18 (dp, \(J = 7.5, 36.5\) Hz, 4H), 1.69-1.71 (m, 2H), 4.12-4.22 (m, 2H), 7.26 (t, \(J = 7.5\) Hz, 1H), 7.32 (t, \(J = 7.8\) Hz, 1H), 7.49 (t, \(J = 7.8\) Hz, 1H), 7.56 (s, 1H), 7.60 (d, \(J = 8.0\) Hz, 2H), 7.67 (t, \(J = 8.0\) Hz, 1H), 7.87 (d, \(J = 7.5\) Hz, 1H), 8.12 (d, \(J = 8.0\) Hz, 1H), 8.16 (d, \(J = 8.0\) Hz, 1H).

At 50 °C: \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 0.79 (t, \(J = 7.3\) Hz, 3H), 1.19 (dp, \(J = 7.5, 36.5\) Hz, 4H), 1.72 (p, \(J = 7.5\) Hz, 2H), 4.17-4.19 (m, 2H), 7.26 (t, \(J = 7.5\) Hz, 1H), 7.31 (t, \(J = 7.5\) Hz, 1H), 7.49 (t, \(J = 7.8\) Hz, 1H), 7.55 (s, 1H), 7.58-7.61 (m, 2H), 7.67 (t, \(J = 7.0\) Hz, 1H), 7.87 (d, \(J = 7.5\) Hz, 1H), 8.11 (d, \(J = 8.0\) Hz, 1H), 8.15 (d, \(J = 8.0\) Hz, 1H), 8.19 (br s, \(\frac{1}{2}H\)).
At 75 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.80 (t, $J = 7.0$ Hz, 3H), 1.17-1.28 (m, 4H), 1.74 (t, $J = 7.3$ Hz, 2H), 4.18 (t, $J = 7.0$ Hz, 2H), 7.26 (t, $J = 7.3$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 7.51 (s, 1H), 7.57-7.61 (m, 2H), 7.66 (t, $J = 7.8$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H), 8.10 (d, $J = 8.0$ Hz, 1H), 8.14-8.17 (m, 2H).

![Chemical Structure](image)

2-Methyl-N-pentyl-3-(8-bromo-1-naphthoyl)indole (63) (JWH-425) (VJS-260).

The title compound was prepared using the procedure VJS-259. From 0.13 g (0.66 mmol) of 2-methyl-N-pentylindole and 0.15 g (0.60 mmol) of 8-bromo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ethyl acetate, 9:1) 0.04 g (15%) of 2-methyl-N-pentyl-3-(8-bromo-1-naphthoyl)indole as a brown oil: GC/MS (EI) $m/z$ (rel intensity) 433 (6), 354 (78), 284 (100), 269 (28), 254 (13), 233 (5), 213 (7), 177 (3), 158 (5), 126 (9), 115 (3), 103 (1), 89 (1), 77 (1), 55 (1); HRMS (ES$^+$) $m/z$ calcd for C$_{25}$H$_{24}$BrNO: 434.1120; found: 434.1128.
Ambient Temperature: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.83-0.88 (m, 3H), 1.25-1.34 (m, 4H), 1.64-1.77 (m, 2H), 2.91 (s, ½H), 4.21-4.27 (m, 2H), 5.89 (br s, ½H), 6.67 (br s, ½H), 7.04 (br s, ½H), 7.27 (br s, 1H), 7.48-7.52 (m, 2 ½H), 7.65 (t, J = 7.5 Hz, 1H), 7.86-7.91 (m, 1H), 8.13-8.17 (m, 1 ½H), 8.41 (br s, ½H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$) $\delta$ 12.7, 14.0, 22.4, 29.1, 29.4, 43.4, 109.7, 120.1, 121.4, 121.7, 122.7, 125.9, 126.6, 127.4, 127.5, 128.6, 130.1, 132.9, 133.4, 135.4, 136.1, 142.2, 144.3, 146.0, 193.5.

At 35 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.86 (br s, 3H), 1.24-1.34 (m, 4H), 1.67-1.78 (m, 2H), 2.92 (br s, ½H), 4.16-4.27 (m, 2H), 5.93 (br s, ½H), 6.68 (br s, ½H), 7.04 (br s, ½H), 7.27 (br s, ¾H), 7.46-7.53 (m, 3H), 7.65 (t, J = 7.8 Hz, 1H), 7.88 (br s, 1H), 8.12-8.17 (m, 2H), 8.44 (br s, ¼H).

At 50 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.86 (br s, 3H), 1.32 (br s, 4H), 2.92 (br s, 1H), 4.22 (br s, 2H), 7.10-7.30 (m, 1½H), 7.46-7.52 (m, 3H), 7.65 (t, J = 7.8 Hz, 1H), 7.87-7.88 (m, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.44 (br s, ¼H).

At 75 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.87 (t, J = 6.8 Hz, 3H), 1.33-1.34 (m, 4H), 1.72-1.74 (m, 2H), 4.21 (t, J = 7.0 Hz, 2H), 7.15 (br s, 1H), 7.46-7.50 (m, 3H), 7.65 (t, J = 7.8 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H).

At 100 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.88 (t, J = 7.0 Hz, 3H), 1.34-1.36 (m, 4H), 1.75 (p, J = 7.0 Hz, 2H), 4.22 (t, J = 7.5 Hz, 2H), 6.45 (br s, 1H), 7.15 (t, J = 7.3
Hz, 1H), 7.47 (q, $J = 7.3$ Hz, 3H), 7.64 (t, $J = 7.8$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H), 8.09 (d, $J = 8.0$ Hz, 1H), 8.13 (d, $J = 7.0$ Hz, 1H).

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\text{N-Propyl-3-(8-bromo-1-naphthoyl)indole (60) (JWH-428) (VJS-262).}
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The title compound was prepared using the procedure VJS-259. From 0.08 g (0.53 mmol) of N-propylindole and 0.12 g (0.48 mmol) of 8-bromo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ethyl acetate, 8:2) 0.09 g (48%) of N-propyl-3-(8-bromo-1-naphthoyl)indole as an orange solid: m.p. 101-102 °C; GC/MS (EI) $m/z$ (rel intensity) 391 (10), 312 (100), 296 (2), 282 (19), 270 (99), 254 (26), 241 (25), 226 (10), 213 (15), 207 (6), 186 (31), 156 (16), 144 (42), 126 (38), 116 (29), 101 (7), 89 (14), 75 (6), 63 (4), 50 (1); HRMS (ES$^+$) $m/z$ calcd for C$_{22}$H$_{18}$BrNO: 392.0650; found: 392.0637.

Ambient Temperature: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.74 (t, $J = 7.0$ Hz, 3H), 1.71 (q, $J = 7.0$ Hz, 2H), 4.14-4.18 (m, 2H), 7.27-7.33 (m, 2H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.61
(t, J = 7.0 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.88 (d, J = 7.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$) δ 11.3, 23.1, 48.0, 111.4, 118.3, 119.6, 122.1, 122.7, 123.5, 126.2, 126.8, 127.4, 128.4, 129.1, 129.5, 130.7, 133.5, 136.1, 137.3, 139.0, 140.0, 191.5.

At 35 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.77 (t, J = 7.5 Hz, 3H), 1.72 (q, J = 7.0 Hz, 2H), 4.15-4.17 (m, 2H), 7.26-7.32 (m, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.60-7.62 (m, 3H), 7.66 (t, J = 7.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 9.5 Hz, 1H).

At 50 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.78 (t, J = 7.5 Hz, 3H), 1.74 (q, J = 7.0 Hz, 2H), 4.16 (br s, 2H), 7.26 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.56 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H).

At 75 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.81 (t, J = 7.5 Hz, 3H), 1.76 (sextet, J = 7.0 Hz, 2H), 4.15 (t, J = 7.0 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.59 (t, J = 8.5 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.13-8.17 (m, 2H).

At 100 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.82 (t, J = 7.3 Hz, 3H), 1.78 (sextet, J = 7.3 Hz, 2H), 4.15 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H),
7.45 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 7.0 Hz, 1H),
7.65 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.13 (t, J = 7.8
Hz, 2H).

2-Methyl-N-propyl-3-(8-bromo-1-naphthoyl)indole (61) (JWH-429) (VJS-261).

The title compound was prepared using the procedure VJS-259. From 0.13 g (0.66 mmol)
of 2-methyl-N-propylindole and 0.15 g (0.60 mmol) of 8-bromo-1-napthoic acid there
was obtained after column chromatography (petroleum ether: ethyl acetate, 8:2) 0.04 g
(16%) of 2-methyl-N-propyl-3-(8-bromo-1-naphthoyl)indole as a green oil: GC/MS (EI)
m/z (rel intensity) 405 (10), 326 (100), 311 (1), 284 (79), 269 (31), 254 (16), 226 (4), 200
(9), 158 (9), 142 (2), 126 (13), 103 (3), 77 (2), 51 (1); HRMS (ES+) m/z calcd for
C_{23}H_{20}BrNO: 406.0807; found: 406.0788.

Ambient Temperature: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.81-0.90 (m, 3H), 1.65-1.76
(m, 2H), 2.89 (s, 1½H), 4.23-4.24 (m, 2H), 6.63-6.66 (m, ½H), 7.01-7.03 (m, ½H), 7.26-
7.27 (m, ½H), 7.43-7.54 (m, 2½H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.83-7.91 (m, 1H), 8.11-8.17 (m, 2H), 8.39 (br s, ½H); $^{13}$C NMR (75.5 MHz, DMSO-$d_6$) δ 11.5, 14.3, 23.0, 44.7, 109.5, 120.0, 120.2, 121.4, 121.6, 122.7, 125.9, 126.6, 127.4, 127.7, 128.6, 129.2, 130.16, 132.9, 136.1, 142.2, 144.4, 146.0, 193.5.

At 35 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.81-0.90 (m, 3H), 1.65-1.76 (m, 2H), 2.89 (s, 1½H), 4.23-4.24 (m, 2H), 6.63-6.66 (m, ½H), 7.01-7.03 (m, ½H), 7.26-7.27 (m, ½H), 7.43-7.50 (m, 2½H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.85 (br s, 1H), 8.11 (d, $J = 8.0$ Hz, 1H), 8.14-8.15 (m, 1H), 8.39 (br s, ½H).

At 50 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.87 (br s, 3H), 1.73 (br s, 2H), 2.89 (br s, 2½H), 4.18 (br s, 2H), 7.44 (t, $J = 7.0$ H, 1H), 7.47-7.51 (m, 2H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.84-7.86 (m, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 8.14 (d, $J = 8.0$ Hz, 1H).

At 75 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.88 (t, $J = 7.5$ Hz, 3H), 1.75 (sextet, $J = 7.3$ Hz, 2H), 4.17 (t, $J = 7.0$ Hz, 2H), 7.13 (br s, 1H), 7.43-7.49 (m, 3H), 7.63 (t, $J = 7.8$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H).

At 100 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.89 (t, $J = 7.5$ Hz, 3H), 1.76 (sextet, $J = 7.3$ Hz, 2H), 2.89 (br s, 3H), 4.17 (t, $J = 7.0$ Hz, 2H), 6.92 (br s, 1H), 7.13 (t, $J = 7.5$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 3H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 8.07 (d, $J = 8.0$ Hz, 1H), 8.12 (d, $J = 8.5$ Hz, 1H).
8-Iodo-1-naphthoic acid (55) (VJS-243).

To a round bottom flask containing 5.00 g (13.5 mmol) of anhydro-8-(hydroxymercuri)-1-naphthoic acid was added 9.63 g (58.0 mmol) of potassium iodide in 47 mL of H₂O. After dissolution, 3.42 g (13.5 mmol) of iodine was added and the reaction mixture was refluxed for 15 h. The solution was cooled to ambient temperature and a brown precipitate was filtered out. The addition of 1.62 g (10 mmol) of sodium thiosulfate in 9 mL of H₂O to the filtrate destroyed excess iodine and the solution was acidified by the dropwise addition of concentrated HCl. The crude acid was filtered, dissolved in hot acetone and concentrated *in vacuo*. Recrystallization with chloroform gave 2.1 g (52%) of 8-iodo-1-naphthoic acid as a white solid: m.p. 155-156 °C (lit m.p. 164-165°C); $^1$H NMR (500 MHz, CDCl₃) $\delta$ 7.23 (t, $J = 7.8$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.93 (d, $J = 7.5$ Hz, 2H), 8.27 (d, $J = 7.5$ Hz, 1H), 12.63 (br s, 1H); $^{13}$C NMR (125.77 MHz, CDCl₃) $\delta$ 93.1, 125.1, 127.5, 129.5, 129.6, 131.4, 132.6, 133.5, 135.4, 141.9, 175.5.
Dimethylaluminum chloride (0.79 mL, 1 M in hexanes, 0.79 mmol) was added to a solution of 0.10 g (0.57 mmol) of N-pentylindole in 5 mL of dry dichloromethane under Ar and the mixture was stirred for 10 min at 0 °C then ambient temperature for 1h. A solution of freshly prepared 8-iodo-1-naphthoyl chloride in 3 mL of dry dichloromethane was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.23 g (0.77 mmol) of 8-iodo-1-naphthoic acid under Ar. The mixture was refluxed for 2 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at ambient temperature overnight. The reaction mixture was quenched with water and extracted with ether. The ethereal solution was washed with water, dried (MgSO₄) and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether: ether, 1:1) to give 0.040 g (11%) of N-pentyl-3-(8-iodo-1-naphthoyl)indole as a yellow oil: GC/MS (EI) m/z (rel intensity) 341 (100), 324
(48), 284 (86), 256 (16), 241 (16), 214 (85), 186 (4), 167 (22), 144 (48), 127 (70), 101 (7), 77 (9), 51 (2); HRMS (EI⁺) calcd for C₂₄H₂₂INO: 467.0747; found: 467.0742.

Ambient Temperature: ¹H NMR (500 MHz, DMSO-d₆) δ 0.88 (t, J = 7.0 Hz, 3H), 1.26-1.32 (m, 4H), 1.81-1.83 (m, 2H), 4.04-4.14 (m, 2H), 7.20 (t, J = 7.0 Hz, 1H), 7.38-7.43 (m, 2½H), 7.54 (t, J = 7.0 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 8.22 (d, J = 7.5 Hz, 1H); ¹³C NMR (125.77 MHz, CDCl₃) δ 13.9, 22.2, 28.8, 29.4, 47.1, 93.2, 109.9, 122.7, 123.0, 123.5, 125.1, 126.9, 127.0, 127.3, 128.5, 129.1, 129.5, 130.9, 132.0, 132.2, 135.7, 137.1, 141.6, 191.6.

At 50°C: ¹H NMR (500 MHz, DMSO-d₆) δ 0.88 (t, J = 7.0 Hz, 3H), 1.26-1.32 (m, 4H), 1.81-1.83 (m, 2H), 4.04 (s, 2H), 7.17 (t, J = 7.0 Hz, 1H), 7.22 (br s, ½H), 7.38-7.43 (m, 2.5H), 7.54 (t, J = 7.0 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 8.22 (d, J = 7.5 Hz, 1H), 8.45 (br s, ½H).

At 75°C: ¹H NMR (500 MHz, DMSO-d₆) δ 0.88 (t, J = 6.0 Hz, 3H), 1.21-1.28 (m, 4H), 1.74-1.76 (m, 2H), 4.19 (t, J = 7.0 Hz, 2H), 7.25-7.33 (m, 3H), 7.51 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.62-7.63 (m, 2H), 8.08-8.12 (m, 2H), 8.23 (d, J = 7.0 Hz, 2H).
2-Methyl-N-pentyl-3-(8-iodo-1-naphthoyl)indole (67) (JWH-417) (VJS-246).

The title compound was prepared using the procedure VJS-244. From 0.17 g (0.84 mmol) of 2-methyl-N-pentylindole and 0.25 g (0.84 mmol) of 8-iodo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 1:1) 0.25 g (64%) of 2-methyl-N-pentyl-3-(8-iodo-1-naphthoyl)indole as a brown oil: GC/MS (EI) m/z (rel intensity) 481 (3), 354 (70), 339 (9), 324 (1), 310 (1), 296 (7), 284 (100), 269 (45), 254 (28), 240 (9), 226 (8), 213 (12), 189 (3), 177 (6), 148 (12), 126 (19), 113 (3), 89 (1), 77 (2), 55 (1); HRMS (ES⁺) m/z calcd for C₂₅H₂₄INO: 482.0981; found: 482.0961.

Ambient Temperature: ¹H NMR (500 MHz, DMSO-d₆) δ 0.84-0.89 (m, 3H), 1.24-1.36 (m, 4H), 1.65-1.84 (m, 2H), 2.91 (s, 1½ H), 4.17-4.28 (m, 2H), 5.99-6.01 (m, ½H), 6.69-6.71 (m, ½H), 7.03-7.06 (m,½ H), 7.28-7.31 (m, 2H), 7.45-7.48 (m, 1H), 7.52-7.61 (m, 2H), 8.13-8.26 (m, 3H), 8.43 (br s, ½H); ¹³C NMR (125.77 MHz, DMSO-d₆) δ 13.0, 14.3, 22.3, 28.8, 29.4, 43.1, 93.8, 110.7, 119.7, 121.5, 122.0, 122.6, 123.0, 126.4, 127.9, 130.0, 131.1, 131.6, 135.8, 136.2, 141.7, 144.0, 146.3, 191.8.
At 35 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.88 (br s, 3H), 1.24-1.35 (m, 4H), 1.74-1.92 (m, 2H), 2.92 (br s, 1½H), 4.18-4.28 (m, 2H), 5.99-6.01 (m, ½H), 6.69-6.71 (m, ½H), 7.03-7.06 (m,½ H), 7.30 (t, $J$ = 7.5 Hz, 2H), 7.47-7.54 (m, 2H), 7.60 (t, $J$ = 8.0 Hz, 1H), 8.10-8.17 (m, 2H), 8.23 (br s, 1H), 8.44 (br s, ½H).

At 50 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.88 (s, 3H), 1.34 (s, 4H), 1.73 (s, 2H), 3.21 (s, 3H), 4.23 (br s, 2H), 7.29 (t, $J$ = 7.5 Hz, 1H), 7.47 (d, $J$ = 7.0 Hz, 1H), 7.52 (d, $J$ = 10.0 Hz, 1H), 7.60 (t, $J$ = 8.0 Hz, 1H), 8.11 (t, $J$ = 9.0 Hz, 2H), 8.22-8.24 (m, 1H).

At 75 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.35-1.39 (m, 4H), 1.75 (t, $J$ = 7.5 Hz, 2H), 3.07 (br s, 3H), 4.23 (t, $J$ = 7.5 Hz, 2H), 7.16 (br s, 1H), 7.28 (t, $J$ = 8.0 Hz, 1H), 7.47 (d, $J$ = 7.0 Hz, 1H), 7.50 (d, $J$ = 8.5 Hz, 1H), 7.60 (t, $J$ = 7.5 Hz, 1H), 8.10 (t, $J$ = 9.0 Hz, 2H), 8.22 (d, $J$ = 7.5 Hz, 1H).

At 100 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.89 (t, $J$ = 7.0 Hz, 3H), 1.36-1.38 (m, 4H), 1.77 (p, $J$ = 7.5 Hz, 2H), 2.93 (br s, 2½H), 4.23 (t, $J$ = 7.5 Hz, 2H), 6.96 (br s, 1H), 7.15 (t, $J$ = 7.5 Hz, 1H), 7.27 (t, $J$ = 7.5 Hz, 1H), 7.48-7.49 (m, 2H), 7.60 ($J$ = 7.5 Hz, 1H), 8.09 (t, $J$ = 9.0 Hz, 1H), 8.23 (d, $J$ = 7.5 Hz, 1H).
2-Methyl-N-propyl-3-(8-iodo-1-naphthoyl)indole (65) (JWH-418) (VJS-249).

The title compound was prepared using the procedure VJS-244. From 0.14 g (0.84 mmol) of 2-methyl-N-propylindole and 0.36 g (1.2 mmol) of 8-iodo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 3:7) 0.13 g (35%) of 2-methyl-N-propyl-3-(8-iodo-1-naphthoyl)indole as a brown oil: GC/MS (EI) $m/z$ (rel intensity) 453 (6), 326 (100), 312 (6), 296 (11), 284 (95), 269 (54), 254 (31), 241 (8), 226 (8), 207 (40), 191 (4), 163 (10), 148 (14), 127 (21), 106 (5), 89 (6), 77 (4), 63 (3), 51 (4); HRMS (ES$^+$) $m/z$ calcd for $C_{23}H_{20}INO$: 454.0668; found: 454.0662

Ambient Temperature: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.87-0.95 (m, 3H), 1.70-1.86 (m, 2H), 2.91 (s, 1½H), 4.16-4.27 (m, 2H), 5.99-6.00 (m, ½H), 6.69-6.72 (m, ½H), 7.03-7.06 (m, ½H), 7.28-7.31 (m, 1½H), 7.44-7.46 (m, 1H), 7.54-7.62 (m, 2H), 8.12-8.15 (m, 2H), 8.20-8.28 (m, 1H), 8.42 (br s, ½H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$) $\delta$ 11.5, 13.0, 23.0, 44.9, 92.9, 109.3, 109.7, 116.0, 120.5, 121.4, 121.7, 122.7, 125.7, 127.1, 128.0, 129.5, 130.7, 132.0, 135.9, 141.4, 143.8, 146.2, 192.8.
At 50 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.93 (s, 3H), 1.76 (br s, 2H), 3.21 (s, 3H), 4.22 (br s, 2H), 7.26 (br s, 1H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.47 (d, $J = 7.0$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 1H), 7.61 (t, $J = 7.5$ Hz, 1H), 8.12 (t, $J = 9.0$ Hz, 2H), 8.23-8.24 (m, 1H).

At 75 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.94 (t, $J = 7.5$ Hz, 3H), 1.78 (sextet, $J = 7.5$ Hz, 2H), 3.06 (br s, 3H), 4.22 (t, $J = 7.0$ Hz, 2H), 7.15 (br s, 1H), 7.29 (t, $J = 7.5$ Hz, 1H), 7.47 (d, $J = 7.0$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.61 (t, $J = 7.5$ Hz, 1H), 8.11 (t, $J = 9.5$ Hz, 2H), 8.23 (d, $J = 7.0$ Hz, 1H).

At 100 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.94 (t, $J = 7.5$ Hz, 3H), 1.80 (sextet, $J = 7.5$ Hz, 2H), 2.93 (br s, 3H), 4.22 (t, $J = 7.5$ Hz, 2H), 6.95 (br s, 1H), 7.15 (t, $J = 8.0$ Hz, 1H), 7.28 (t, $J = 8.0$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 2H), 7.60 (t, $J = 7.5$ Hz, 1H), 8.09 (t, $J = 9.0$ Hz, 2H), 8.23 (d, $J = 7.5$ Hz, 1H).
**N-Propyl-3-(8-iodo-1-naphthoyl)indole (64) (JWH-419) (VJS-250).**

The title compound was prepared using the procedure VJS-244. From 0.11 g (0.69 mmol) of *N*-propylindole and 0.31 g (1.0 mmol) of 8-iodo-1-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 1:1) 0.064 g (21%) of *N*-propyl-3-(8-iodo-1-naphthoyl)indole as a brown oil: GC/MS (EI) *m/z* (rel intensity) 439 (2), 312 (100), 282 (17), 270 (63), 254 (13), 240 (14), 226 (6), 207 (23), 186 (5), 156 (3), 144 (11), 126 (13), 113 (5), 101 (3), 89 (3), 75 (3), 63 (3), 51 (1); HRMS (ES\(^+\)) *m/z* calcd for C\(_{22}\)H\(_{18}\)INO: 440.0511; found: 440.0491.

Ambient Temperature: \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 0.78 (t, \(J = 7.5\) Hz, 3H), 1.73 (q, \(J = 7.0\) Hz, 2H), 4.15-4.22 (m, 2H), 7.28-7.33 (m, 3H), 7.62-7.65 (m, 3½H), 8.11-8.14 (m, 2H), 8.23 (d, \(J = 7.0\) Hz, 1H); \(^13\)C NMR (125.77 MHz, DMSO-\(d_6\)) \(\delta\) 11.3, 23.1, 48.0, 94.1, 111.3, 119.3, 122.3, 122.3, 122.7, 123.5, 125.9, 126.9, 127.8, 128.7, 130.0, 131.2, 131.9, 135.8, 137.3, 141.8, 141.9, 190.9.
At 50 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.80 (t, $J = 7.5$ Hz, 3H), 1.75 (sextet, $J = 7.0$ Hz, 2H), 4.18 (br s, 2H), 7.26-7.33 (m, 3 H), 7.60-7.65 (m, 4H), 8.10-8.13 (m, 2H), 8.24 (d, $J = 7.5$ Hz, 1H).

At 75 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.82 (t, $J = 7.5$ Hz, 3H), 1.77 (sextet, $J = 7.0$ Hz, 2H), 4.17 (t, $J = 7.0$ Hz, 2H), 7.27-7.32 (m, 3H), 7.54 (s, 1H), 7.58-7.60 (m, 1H), 7.62-7.63 (m, 2H), 8.09-8.12 (m, 2H), 8.23-8.24 (m, 2H).

At 100 °C: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.84 (t, $J = 7.5$ Hz, 3H), 1.79 (sextet, $J = 7.5$ Hz, 2H), 4.16 (t, $J = 7.0$ Hz, 2H), 7.26-7.31 (m, 3H), 7.50 (s, 1H), 7.57 (d, $J = 8.5$ Hz, 1H), 7.61-7.63 (m, 2H), 8.08-8.11 (m, 2H), 8.19 (d, $J = 8.0$ Hz, 1H), 8.23 (d, $J = 7.5$ Hz, 1H).

8-Chloro-1-naphthoic acid (58).

**Method A (VJS-533)** To a stirring solution of 1.2 mL (20.2 mmol) of glacial acetic acid and 0.12 mL (6.7 mmol) of H$_2$O at 0 °C was added 0.18 g (0.48 mmol) of anhydro-8-hydroxymercuri-1-naphthoic acid. Vigorous stirring at 0 °C for 15 min was followed by
the addition of 0.19 g (0.33 mmol) of NaCl in 0.61 mL of H₂O and 0.09 g (0.48 mmol) of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) over a period of 30 min. The resultant dense, white precipitate was slowly heated to 100 °C and left at that temperature for 12 h. The solution was cooled to ambient temperature and poured into ice. A pale yellow precipitate was filtered out. This precipitate was dissolved in hot 12M NaOH and the solution was filtered to remove HgCl₂. The filtrate was acidified by the dropwise addition of concentrated HCl and extracted with dichloromethane. After drying (MgSO₄) and concentration in vacuo, 0.04 g (36%) of crude 8-chloro-1-naphthoic acid remained as a white solid.

Method B (VJS-580) To a round bottom flask containing 0.15 g (0.68 mmol) of methyl-8-chloro-1-naphthoate was added 0.38 g (6.8 mmol) of crushed KOH in 10 mL of H₂O. The solution was refluxed overnight and then acidified by the dropwise addition of concentrated HCl. The mixture was extracted with ether and dried (MgSO₄). Concentration in vacuo gave 0.12 g (88%) of 8-chloro-1-naphthoic acid as a white solid: m.p. 168-169 °C (lit. m.p. 171–171.5 °C); ¹H NMR (300 MHz, CDCl₃) δ 7.49 (t, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 13.25 (br s, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 125.3, 126.6, 127.0, 127.9, 128.2, 129.3, 129.8, 130.3, 131.5, 135.4, 176.3.
Methyl-8-chloro-1-naphthoate (59) (VJS-539).

Trimethylsilyldiazomethane (0.25 mL, 2 M in ether, 0.51 mmol) was added to a suspension of 0.07 g (0.34 mmol) of crude 8-chloro-1-naphthoic acid in 6 mL of MeOH and the solution was heated at reflux for 1.5 h. After being cooled to ambient temperature the reaction mixture was quenched with H₂O and extracted with dichloromethane. The organic phase was washed with water, dried (MgSO₄), and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether: ether, 8:2) to give 0.03 g (36%) of methyl-8-chloro-1-naphthoate as a peach colored oil: 

\[ \delta \] H NMR (500 MHz, CDCl₃) δ 4.01 (s, 3H), 7.41 (t, \( J = 7.5 \) Hz, 1H), 7.50 (t, \( J = 7.5 \) Hz, 1H), 7.62 (d, \( J = 7.0 \) Hz, 2H), 7.78 (d, \( J = 8.0 \) Hz, 1H), 7.91 (d, \( J = 8.5 \) Hz, 1H); ¹³C NMR (125.77 MHz, CDCl₃) δ 52.8, 125.4, 126.4, 127.1, 127.8, 128.0, 129.0, 130.0, 130.6, 131.0, 135.3, 171.2; GC/MS (EI) \( m/z \) (rel intensity) 220 (33), 205 (2), 185 (100), 170 (66), 161 (61), 142 (2), 126 (64), 99 (13), 95 (9), 75 (17), 63 (28), 50 (5).
N-pentyl-3-(6-methoxy-2-naphthoyl)indole (71) (JWH-408) (VJS-226).

Dimethylaluminum chloride (0.90 mL, 1 M in hexanes, 0.90 mmol) was added to a solution of 0.12 g (0.63 mmol) of N-pentylindole in 5 mL of dry dichloromethane under Ar and the mixture was stirred for 1 h at 0 °C. A solution of freshly prepared 6-methoxy-2-naphthoyl chloride in 3 mL of dry dichloromethane was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.12 g (0.59 mmol) of 6-methoxy-2-naphthoic acid under Ar. The mixture was refluxed for 1.5 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at ambient temperature for 6 h. The reaction mixture was quenched with water and extracted with ether. The ethereal solution was washed with water, dried (MgSO₄) and the solvent was removed in vacuo to give the crude product, which was purified by column chromatography (petroleum ether: ether, 7:3) to give 0.13 g (59%) of N-pentyl-3-(6-methoxy-2-naphthoyl)indole as a brown oil: ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, J = 6.6 Hz, 3H), 1.34-1.36 (m, 4H), 1.85-1.91
(m, 2H), 3.97 (s, 3H), 4.16 (t, $J = 7.0$ Hz, 2H), 7.24-7.26 (m, 2H), 7.36-7.44 (m, 3H), 7.66 (s, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.96 (d, $J = 8.4$ Hz, 1H), 8.28 (s, 1H), 8.49-8.51 (m, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 14.0, 22.3, 29.0, 29.6, 47.1, 55.4, 105.8, 110.0, 115.8, 119.6, 122.5, 122.8, 123.5, 126.3, 127.0, 127.5, 127.9, 129.4, 130.6, 136.2, 136.3, 136.8, 136.9, 159.1, 190.7; GC/MS (EI) $m/z$ (rel intensity) 371 (100), 354 (4), 314 (30), 272 (3), 214 (32), 185 (10), 157 (5), 144 (9), 128 (3), 114 (4), 102 (2), 89 (2), 55 (2); HRMS (ES$^+$) $m/z$ calcd for C$_{25}$H$_{25}$NO$_2$: 371.1885; found: 371.1880.

2-Methyl-N-pentyl-3-(6-methoxy-2-naphthoyl)indole (72) (JWH-409) (VJS-230).

The title compound was prepared using procedure VJS-226. From 0.14 g (0.70 mmol) of 2-methyl-N-pentylindole and 0.12 g (0.60 mmol) of 6-methoxy-2-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 6:4) 0.026 g (11%) of 2-methyl-N-pentyl-3-(6-methoxy-2-naphthoyl)indole as an orange solid: mp 134-135 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 0.96 (t, $J = 6.6$ Hz, 3H), 1.41-1.43 (m, 4H), 1.85-1.86 (m,
2H), 2.66 (s, 3H), 3.98 (s, 3H), 4.18 (t, $J = 7.5$ Hz, 2H), 7.07 (t, $J = 7.8$ Hz, 1H), 7.18-7.24 (m, 3H), 7.36 (t, $J = 8.1$ Hz, 2H), 7.81 (t, $J = 8.7$ Hz, 2H), 7.90 (d, $J = 8.0$ Hz, 1H), 8.26 (s, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 12.5, 14.0, 22.4, 29.2, 29.5, 43.5, 55.4, 105.8, 109.5, 113.9, 119.4, 121.0, 121.2, 121.8, 126.6, 126.7, 127.3, 128.0, 130.3, 130.8, 135.9, 136.5, 136.6, 144.0, 159.2, 192.7; GC/MS (EI) $m/z$ (rel intensity) 385 (100), 370 (25), 342 (7), 328 (28), 315 (7), 281 (11), 270 (3), 254 (4), 228 (11), 207 (46), 185 (57), 158 (26), 142 (11), 128 (6), 114 (8), 96 (5), 73 (8), 55 (5); HRMS (ES$^+$) $m/z$ calcd for C$_{26}$H$_{27}$NO$_2$: 385.2042; found: 385.2028

2-Methyl-N-propyl-3-(6-methoxy-2-naphthoyl)indole (70) (JWH-410) (VJS-231).

The title compound was prepared using procedure VJS-226. From 0.12 g (0.69 mmol) of 2-methyl-N-propylindole and 0.12 g (0.58 mmol) of 6-methoxy-2-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 7:3) 0.076 g (37%) of 2-methyl-N-propyl-3-(6-methoxy-2-naphthoyl)indole as a brown oil: $^1$H NMR (300
MHz, CDCl$_3$) $\delta$ 1.05 (t, $J = 7.5$ Hz, 3H), 1.91 (sextet, $J = 7.5$ Hz, 2H), 2.66 (s, 3H), 3.98 (s, 3H), 4.16 (t, $J = 7.5$ Hz, 2H), 7.04 (t, $J = 7.2$ Hz, 1H), 7.18-7.24 (m, 3H), 7.36 (t, $J = 8.1$ Hz, 2H), 7.78-7.84 (m, 2H), 7.91 (d, $J = 8.4$ Hz, 1H), 8.26 (s, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 11.5, 12.5, 23.1, 44.9, 55.4, 105.8, 109.5, 113.9, 119.4, 121.0, 121.3, 121.9, 126.6, 126.8, 127.3, 128.0, 130.3, 130.9, 136.0, 136.5, 136.6, 144.1, 159.2, 192.7; GC/MS (El) m/z (rel intensity) 356 (100), 340 (22), 328 (8), 315 (7), 300 (2), 286 (2), 270 (2), 254 (2), 242 (4), 200 (17), 185 (29), 179 (2), 158 (28), 142 (11), 130 (8), 114 (8), 103 (4), 88 (2), 77 (3), 63 (1), 50 (1); HRMS (ES$^+$) m/z calcd for C$_{24}$H$_{23}$NO$_2$: 357.1729; found: 357.1727

\[ N\text{-Propyl-3-(6-methoxy-2-naphthoyl)indole (69) (JWH-411) (VJS-232).} \]

The title compound was prepared using procedure VJS-226. From 0.23 g (1.4 mmol) of N-propylindole and 0.26 g (1.3 mmol) of 6-methoxy-2-naphthoic acid there was obtained after column chromatography (petroleum ether: ether, 8:2) 0.016 g (4%) of N-propyl-3-(6-methoxy-2-naphthoyl)indole as a white solid: m.p. 139-141 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$...
To a flamed dried round bottom flask, under Ar containing 20.1 mL (346 mmol) of glacial acetic acid 14.0 mL (333 mmol) of fuming nitric acid was slowly added followed by the dropwise addition of 1.0 g (0.64 mmol) of 1-naphthaldehyde. The solution turned from red to golden yellow over the course of the addition. After the slow addition of 0.68 mL (1.28 mmol) of H$_2$SO$_4$ the reaction mixture was stirred at ambient temperature for 1
The solution was poured into ice and extracted with ether. The ethereal solution was dried (MgSO$_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether: ether, 7:3) to give 0.39 g (30%) of 5-nitro-1-naphthaldehyde as a yellow solid: m.p. 135-137 °C (lit. m.p.$^{119}$ 136-137 °C); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.80 (t, $J = 8.3$ Hz, 1H), 7.92 (t, $J = 7.8$ Hz, 1H), 8.15 (d, $J = 6.5$ Hz, 1H), 8.30 (d, $J = 7.5$ Hz, 1H), 8.79 (d, $J = 9.0$ Hz, 1H), 9.67 (d, $J = 8.5$ Hz, 1H), 10.42 (s, 1H); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 124.3, 125.3, 127.5, 128.2, 129.6, 131.1, 131.3, 131.4, 137.8, 147.1, 193.1; GC/MS (EI) $m/z$ (rel intensity) 201 (100), 184 (5), 172 (16), 154 (25), 145 (16), 127 (98), 115 (93), 101 (39), 89 (12), 77 (47), 63 (23), 51 (21).

Further elution with the same solvent system (petroleum ether: ether, 7:3) gave 0.77 g (60%) of 8-nitro-1-naphthaldehyde as a yellow solid: m.p. 120-121 °C (lit. m.p.$^{119}$ 123-124 °C); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.66 (t, $J = 8.0$ Hz, 1H), 7.76 (t, $J = 7.8$ Hz, 1H), 8.12-8.18 (m, 4H), 10.15 (s, 1H); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 120.7, 125.5, 125.9, 126.6, 132.8, 133.9, 134.2, 134.9, 135.0, 147.9, 190.0; GC/MS (EI) $m/z$ (rel intensity) 201 (100), 184 (5), 172 (16), 154 (25), 145 (16), 127 (98), 115 (93), 101 (39), 89 (12), 77 (47), 63 (23), 51 (21).
5-Nitro-1-naphthoic acid (83) (VJS-443).

To a flask containing 3.0 mL of distilled acetone was added 0.12 g (0.60 mmol) of 5-nitro-1-naphthaldehyde. Slight heat was applied to the reaction vessel followed by 1.5 mL aliquots of freshly prepared Jones Reagent until the precipitation of a green salt occurred. The reaction mixture was stirred for 6 h and quenched with water, the chromium salts were filtered out and the filtrate was extracted with dichloromethane. The organic layer was dried (MgSO₄) and removal of the solvent in vacuo gave 0.07 g (57%) of 5-nitro-1-naphthoic acid as a white solid: m.p. 239-240 °C (lit. m.p. 239 °C); ¹H NMR (500 MHz, DMSO-d₆) δ 7.82-7.88 (m, 2H), 8.29 (d, J = 7.0 Hz, 1H), 8.33 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 9.0 Hz, 1H), 9.19 (d, J = 8.5 Hz, 1H), 13.59 (br s, 1H); ¹³C NMR (125.77 MHz, DMSO-d₆) δ 124.1, 124.9, 126.9, 126.9, 128.9, 129.5, 131.3, 131.6, 132.0, 168.6.
8-Nitro-1-naphthoic acid (83) (VJS-452).

The title compound was prepared using procedure VJS-443. From 0.22 g (1.10 mmol) of 8-nitro-1-naphthaldehyde was obtained 0.14 g (60%) of 8-nitro-1-naphthoic acid as a white solid: m.p. 210-211 °C (lit. m.p. 210-215 °C); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.75 (q, $J$ = 7.5 Hz, 2H), 8.12 (d, $J$ = 7.0 Hz, 1H), 8.24 (d, $J$ = 7.5 Hz, 1H), 8.29 (d, $J$ = 8.0 Hz, 1H), 8.38 (d, $J$ = 8.5 Hz, 1H), 13.43 (br s, 1H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$) $\delta$ 121.3, 125.6, 126.0, 127.3, 129.1, 131.5, 132.5, 134.8, 135.0, 147.7, 168.7.

5-Nitroacenaphthene (75) (VJS-301).

To a suspension of 0.20 g (1.3 mmol) of acenaphthene and 1.6 mL (27.4 mmol) of acetic acid which had been stirring at ambient temperature for 15 min, 0.25 mL (5.6 mmol) of
nitric acid was added dropwise over 15 min. A yellow precipitate formed and after cooling in an ice bath 0.23 g (88%) of 5-nitroacenaphthene was filtered off as a yellow solid: m.p. 98-99 °C (lit m.p. 84-100-101 °C); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.46-3.49 (m, 2H), 3.51-3.53 (m, 2H), 7.36 (d, $J$ = 7.5 Hz, 1H), 7.47 (d, $J$ = 7.0 Hz, 1H), 7.74 (dd, $J$ = 8.5 Hz, 1H), 8.52 (d, $J$ = 7.5 Hz, 1H), 8.59 (d, $J$ = 8.5 Hz, 1H); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 30.6, 30.6, 118.0, 120.2, 121.3, 124.4, 127.8, 131.7, 132.0, 140.2, 146.6, 155.8; GC/MS (EI) $m/z$ (rel intensity) 199 (78), 183 (6), 169 (25), 152 (100), 141 (27), 126 (8), 115 (20), 102 (3), 87 (4), 76 (14), 63 (12), 51 (6).

![4-Nitro-1,8-naphthalic anhydride](image)

4-Nitro-1,8-naphthalic anhydride (76) (VJS-305).

To a solution of 0.12 g (0.60 mmol) of 5-nitroacenaphthene in 1.7 mL (29 mmol) of acetic acid was slowly added 0.71 g (2.4 mmol) of K$_2$Cr$_2$O$_7$ The mixture was heated at 100 °C for 3 h, cooled to ambient temperature and poured into ice. The product was extracted using dichloromethane, dried (MgSO$_4$) and concentrated in vacuo to give 0.092 g (63%) of 4-nitro-1,8-naphthalic anhydride as an orange solid: m.p. 226-227 °C (lit
m.p.\textsuperscript{85} 226-229 °C; \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) δ 8.13 (t, \textit{J} = 8.3 Hz, 1H), 8.57 (d, \textit{J} = 8.0 Hz, 1H), 8.64 (d, \textit{J} = 8.0 Hz, 1H), 8.67 (d, \textit{J} = 7.5 Hz, 1H), 8.76 (d, \textit{J} = 8.5 Hz, 1H); \textsuperscript{13}C NMR (125.77 MHz, DMSO-\textit{d}_6) δ 120.5, 123.3, 124.5, 124.8, 130.3, 130.8, 131.1, 131.6, 133.7, 150.0, 159.9, 160.5.

![Structure of 4-Nitro-1-naphthoic acid](image)

**4-Nitro-1-naphthoic acid (78).**

**Method A** (VJS-535): To a solution of 0.35 g (6.2 mmol) of KOH in 9.3 mL of water was added 0.50 g (2.1 mmol) of 4-nitro-1,8-naphthalic anhydride. Vigorous stirring for 1.5 h resulted in a homogeneous brown solution. A solution of freshly prepared mercuric acetate from 0.45 g (2.06 mmol) of yellow mercury oxide in 0.37 mL of acetic acid and 1.2 mL of water was added dropwise to the reaction mixture. After addition of the mercuric acetate a dense, tan colored precipitate formed. The reaction was heated at reflux for 96 h, cooled to ambient temperature and filtered. The resultant organo-mercuri intermediate was refluxed in concentrated HCl for 6 h, cooled to ambient temperature, filtered and washed with water to give crude 4-nitro-1-naphthoic acid as a tan solid.
Recrystallization from glacial acetic acid gave 0.37 g (82%) of 4-nitro-1-naphthoic acid as a tan solid:

**Method B (VJS-541):** To a round bottom flask containing 0.08 g (0.35 mmol) of methyl-4-nitro-1-naphthoate was added 0.19 g (3.5 mmol) of crushed KOH in 0.6 mL of water. The solution was refluxed overnight, acidified by the dropwise addition of concentrated HCl extracted with ether and dried (MgSO$_4$). Concentration in vacuo gave 0.04 g (50%) of 4-nitro-1-naphthoic acid as a tan solid: m.p. 220-221 °C (lit. m.p. 62 219–220 °C); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.83-7.86 (m, 2H), 8.17 (d, $J = 8.0$ Hz, 1H), 8.25-8.28 (m, 2H), 8.82-8.84 (m, 1H), 13.87 (br s, 1H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$) $\delta$ 122.5, 122.9, 124.6, 126.6, 128.1, 129.3, 129.9, 131.6, 134.4, 149.2, 168.1.

![4-nitro-1-naphthoic acid](image)

**Methyl-4-nitro-1-naphthoate (79) (VJS-536).**

To a solution of 5 mL of MeOH and 1 mL of H$_2$SO$_4$ was added 0.40 g (1.84 mmol) of 4-nitro-1-naphthoic acid. The reaction mixture was heated at reflux overnight. The solution

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was cooled to ambient temperature, quenched with water and extracted with dichloromethane. The organic phase was washed with NaHCO₃, dried (MgSO₄) and concentration in vacuo. The crude product was purified by column chromatography (petroleum ether: ethyl acetate, 7:3) to give 0.06g (14%) of methyl 4-nitro-1-naphthoate as a reddish orange oil: ¹H NMR (500 MHz, CDCl₃) δ 4.08 (s, 3H), 7.74-7.79 (m, 2H), 8.09 (d, J = 7.5 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.40-8.43 (m, 1H), 8.90-8.92 (m, 1H); ¹³C NMR (125.77 MHz, CDCl₃) δ 52.9, 121.4, 123.0, 125.1, 126.3, 127.9, 128.9, 129.3, 132.2, 132.7, 149.7, 166.7; GC/MS (EI) m/z (rel intensity) 231 (78), 216 (4), 200 (29), 186 (9), 170 (27), 154 (27), 142 (33), 126 (100), 114 (56), 102 (15), 87 (10), 76 (22), 59 (34), 50 (11).

3-(4-Nitro-1-naphthoyl)indole (85) (VJS-542).

To a solution of 0.26 mL (0.78 mmol) of MeMgBr [3.17M in diethyl ether] in 2.5 mL of dry THF was added, at 0 °C under Ar, a solution of 0.06 g (0.52 mmol) of indole in dry
THF. The mixture was stirred at 0 °C for 1 h. A solution of freshly prepared 4-nitro-1-naphthoyl chloride in 3 mL of dry THF was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.11 g (0.52 mmol) of 4-nitro-1-naphthoic acid under Ar. The mixture was refluxed for 3 hrs, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at 0 °C for 4 h. After this time the reaction was quenched with NH₄Cl, the organic phase extracted with ethyl acetate and dried (MgSO₄). Concentration in vacuo followed by column chromatography (petroleum ether;ethyl acetate, 7:3) resulted in 0.02 g (10%) of 3-(4-nitro-1-naphthoyl)indole as a yellow solid: m.p. 235-236 °C; ¹H NMR (500 MHz, DMSO-­d₆) δ 7.31-7.33 (m, 2H), 7.54-7.55 (m, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.78-7.79 (m, 1H), 7.84-7.87 (m, 2H), 8.07 (d, J = 8.5 Hz, 1H), 8.32-8.33 (m, 1H), 8.39 (t, J = 9.2 Hz, 2H), 12.24 (s, 1H); ¹³C NMR (125.77 MHz, DMSO-­d₆) δ 113.0, 117.3, 121.9, 123.0, 123.5, 124.1, 124.4, 124.9, 126.0, 126.7, 128.7, 130.1, 131.4, 137.5, 138.3, 144.8, 147.3, 190.1.
2-Methyl-3-(4-nitro-1-naphthoyl)indole (86) (VJS-549).

To a solution of 0.26 mL (0.78 mmol) of MeMgBr [3.17M in diethyl ether] in 2.5 mL of dry THF was added, at 0 °C under Ar, a solution of 0.07 g (0.55 mmol) of 2-methylindole in dry THF. The mixture was stirred at 0 °C for 1 h. A solution of freshly prepared 4-nitro-1-naphthoyl chloride in 3 mL of dry THF was added dropwise via syringe. The acid chloride was prepared by the addition of 3 mL (41 mmol) of thionyl chloride to 0.12 g (0.55 mmol) of 4-nitro-1-naphthoic acid under Ar. The mixture was refluxed for 3 h, cooled to ambient temperature, and the thionyl chloride was removed in vacuo to give the acid chloride, which was added to the indole mixture without further purification. The acid chloride and indole mixture was stirred at 0 °C for 4 h. After this time the reaction was quenched with NH₄Cl, the organic phase extracted with ethyl acetate and dried (MgSO₄). Concentration in vacuo followed by column chromatography (petroleum ether;ethyl acetate, 7:3) resulted in 0.01 g (7%) of 2-methyl-3-(4-nitro-1-naphthoyl)indole as a yellow solid: m.p. 165-166 °C; ¹H NMR (500 MHz, DMSO-d₆) δ
2.41 (s, 3H), 6.73 (t, $J = 7.5$ Hz, 1H), 6.80 (t, $J = 7.5$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.95 (t, $J = 7.3$ Hz, 1H), 7.23 (dd, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.73-7.75 (m, 2H), 10.89 (s, 1H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$) δ 14.4, 113.0, 117.3, 121.9, 123.0, 123.0, 123.5, 124.1, 124.4, 124.9, 126.0, 126.7, 128.7, 130.1, 131.4, 137.5, 138.3, 144.8, 147.3, 190.1.

\[ \text{N-Benzenesulfonyl pyrrole (VJS-454).} \]

To a solution of 0.5 g (7.45 mmol) of pyrrole in 3.0 mL of THF was added 1.45 g (8.20 mmol) of benzenesulfonyl chloride. The mixture was cooled to 0 °C before the addition of 0.43 g (10.8 mmol) of NaH (60% in mineral oil). The mixture was stirred at ambient temperature for 16 h and quenched with ice water. The organic product was extracted with ether and mixed with an equivalent volume of 2M NaOH. The mixture was stirred for 2 h. The ether layer was extracted, washed with water and dried (MgSO$_4$). Concentration in vacuo gave 0.19 g (12%) of N-benzenesulfonyl pyrrole as a grey oil.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.27 (t, $J = 2.5$ Hz, 2H) 7.16 (t, $J = 2.3$ Hz, 2H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.52-7.55 (m, 1H), 7.83 (d, $J = 7.5$ Hz, 2H); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 113.7, 120.8, 126.8, 129.4, 133.9, 139.1; GC/MS (EI) m/z (rel intensity) 207 (83), 141 (55), 115 (14), 104 (1), 97 (3), 77 (100), 67 (7), 51 (36).

$N$-$p$-Toluenesulfonfyl pyrrole (87) (VJS-410).

The title compound was prepared using the procedure VJS-454. From 2.0 g (29.8 mmol) of pyrrole and 6.25 g (32.8 mmol) of $N$-$p$-toluenesulfonfyl pyrrole in 23 mL of THF there was obtained after recrystallization from isopropanol 5.15 g (78%) of $N$-$p$-toluenesulfonfyl pyrrole as an off-white solid: m.p. 103-104 °C (lit. m.p. 99-103 °C); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.42 (s, 3H), 6.31 (t, $J = 2.3$ Hz, 2H), 7.18 (t, $J = 2.3$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.76 (d, $J = 8.5$ Hz, 2H); $^{13}$C NMR (125.77 MHz, CDCl$_3$) $\delta$ 21.6, 113.5, 120.7, 126.8, 130.0, 136.2, 145.0; GC/MS (EI) m/z (rel intensity) 221 (33), 155 (29), 128 (2), 115 (2), 91 (100), 77 (1), 65 (23), 51 (2).
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