Synthesis Of A Novel Family Of Amide Derivatives Of Podocarpic Acid

2004

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SYNTHESIS OF A NOVEL FAMILY OF AMIDE DERIVATIVES OF PODOCARPIC ACID

by

DAO NGUYEN
B.S. Hochiminh City University, 1987

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in the Department of Chemistry in the College of Arts and Sciences at the University of Central Florida Orlando, Florida

Fall Term
2004
ABSTRACT

As a class, amides are of great interest in biological studies and pharmaceutical applications. In this work, podocarpic acid, a natural tricyclic diterpene, derived from Podocarpus species, has been employed to form a novel family of amide derivatives which will later be studied for their potential as new drug leads.

Novel amide derivatives of podocarpic acid were synthesized from podocarpic acid in three steps. The first step involved methylation with dimethylsulfate to form methyl-O-methylpodocarpate. This step was followed by iodination with iodine to give iodomethyl-O-methylpodocarpate. Finally amidation with various aliphatic amides using a copper catalyst yielded four amide derivatives of podocarpic acid. However, iodo-methyl-O-methylpodocapate did not react with aromatic amides. This is perhaps because of the reduction in electrophilicity of an aromatic amide versus an aliphatic amides.

Thus this research had led to the discovery of a method that is selective for the synthesis of aliphatic amide derivatives of podocarpic acid. Furthermore, five novel derivatives of podocarpic acid have been synthesized. Therefore a small library of novel compounds has been synthesized by utilizing selective methodology, that are now available for future examination of their anticancer and anti-tuberculosis properties.
ACKNOWLEDGEMENTS

I would like to thank the Chemistry Department at the University of Central Florida for their support relative to providing laboratory space and supplies. Special thanks to Dr. Clausen and Dr. Hampton who have served as members of my committee. I wish to express my deepest appreciation to my adviser and the chair of my committee, Dr. Miles, for his guidance and constantly helpful on this research.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>Degree Celcius</td>
</tr>
<tr>
<td>$^{13}$C-NMR</td>
<td>13-Carbon Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>Deuterated Chloroform</td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>Chloroform</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Chemical Shift</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Fig</td>
<td>Figure</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>$^1$H-NMR</td>
<td>Proton Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>hr</td>
<td>Hour</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>M$^+$</td>
<td>Molecular Ion</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliters</td>
</tr>
<tr>
<td>m.p</td>
<td>Melting Point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectroscopy</td>
</tr>
</tbody>
</table>
NCI  National Cancer Institute
NIAID  National Institute for Allergies and Infections Diseases
ppm  Parts per Million
r.a.  Relative Abundance
s  Singlet
TMS  Tetramethylsilane
1. INTRODUCTION

1.1. The Goal of This Research

The ultimate goal of this research is to use podocarpic acid as a template to prepare a library of novel amide derivatives of podocarpic acid. Podocarpic acid derivatives are known to possess biological activity as well as many compounds with amide functionalities. Therefore, the premise of this work is that the synthesis of amide derivatives of podocarpic acid will provide a library of compounds that will be evaluated by the NCI against 60 human cancer cell lines. Also these novel compounds will be evaluated by NIAID for their activity against tuberculosis.

1.2. Natural Products and Bioactive Agents

Natural products, such as herbs and plants, have been used for thousands of years as traditional medicine in the treatment of diseases and cancers\(^{(1)}\). Natural products from plants, fungi, and bacteria contain valuable agents for study as new drug leads that could lead to new pharmaceutical agents for HIV, malaria, fungal, viral, infections, and inflammation\(^{(2)}\). In the analysis of data on prescription drugs dispensed in United States from 1959 to 1980, twenty five percent were active principles from higher plants\(^{(3)}\). According to the annual report on medicinal chemistry in the period from 1983 to 1994, 60% to 75% of the prescription drugs are derived either from a natural origin or a synthetic derivative of a compound of natural origin\(^{(4)}\). Also
approximately 60% of all drugs now in clinical trials for the multiplicity of cancers are either natural products or derived from natural products. Thus compounds produced by "Mother Nature" are still in the forefront of cancer chemotherapeutics as sources of active compounds. Natural products have the advantage that much larger doses of the prescription drugs can be administered since they are less toxic and have less advert effects when applied to the human body.

There is a huge of supply of unexploited natural products with demonstrated biological activity. Many of these compounds are known for their anticancer activity\(^5\). As an example, Taxol (1) or Paclitaxel is a complex diterpene amide derived from the Pacific yew tree Taxus brevifolia\(^6\) which was collected in Washington State as a part of a random collection program by the U.S. Department of Agriculture for the National Cancer Institute. The structure is showed in Figure 1 and a photograph of the yew tree from which it was extracted is shown in Figure 2.

![Diagram of Taxol (1)](image)

Figure 1: Structure of Taxol (1)
It is interesting to note that Taxol has a large variety of functional groups including one amide moiety.

![Figure 2: Taxus Brevifolia](image)

1.3. The Role of Anticancer Drug

Cancer has been a major cause of death in the 21\textsuperscript{st} century. Anticancer drugs or antineoplastic drugs have been used to treat malignancies or the growths of cancerous cells in the body. Cancer forms when cells multiply uncontrollably and abnormally. By definition, cancer is the uncontrolled growth of cells with loss of differentiation which upon metastasis spreads to other tissues and organs. As the result, cancer can be life threatening to the body and must be treated. Cancer chemotherapy is a method which applies a drug or combination of drugs to the body to treat cancerous cells. Anticancer drugs act by interfering with the cycle of cancerous cell growth or the process of their reproduction. There are many classes of anticancer drugs used in cancer treatment. The treatment selected by medical personnel depends upon the type of cancer.
John Boik, the author of the book *Natural Compounds in Cancer Therapy*\(^{(7)}\), stated that in general there are seven strategies for cancer inhibition as follows:

1. Reduce genetic instability
2. Inhibit abnormal expression of genes
3. Inhibit abnormal signal transduction
4. Encourage normal cell-to-cell communication
5. Inhibit tumor angiogenesis
6. Inhibit invasion and metastasis
7. Increase the immune response

Some anticancer drugs will directly inhibit cancer cells which causes cell death or just stop proliferating because of molecular target interactions. In the contrast, other drugs inhibit cancer cell progression indirectly by inducing changes in the local environments which are unfavorable to angiogenesis, invasion, or metastasis.

Since breast cancer is commonly stimulated by sex hormones or estrogens, this kind of cancer is treated with anticancer drugs that inactivate estrogens or limit the amount of estrogens in the body. The drugs block steroid hormone action and this anti-hormonal effect stops cancer cell replication by alteration of the local hormonal supplies. For example, tamoxifen is an antiestrogen drug because it is inhibits of estrogen action that is required to reduce the level of bio-available of estradiol which is necessary for breast cancer cell to growth. For the same reason the newest approach to angiogenesis therapy is to inhibit the formation of blood vessels which feed the tumor and contribute to the tumor growth.
1.4. Amines and Amides as Biological Active Agents

Many nitrogen containing compounds that occur in nature are amines. Because of the natural occurrence and the basicity of amines these compounds are called alkaloids. Many alkaloids such as morphine \( \text{2} \), the structure of which is shown in Figure 3, from \textit{Papaver somniferum} (Figure 4) have demonstrated important biological activity\(^\text{(8)}\). Morphine is well known and widely used as an analgesics drug.

![Figure 3: Structure of Morphine (2)](image)

![Figure 4: \textit{Papaver Somniferum}](image)
Amines possess enhanced biological activity because of the lone pair of electrons on nitrogen which make these compounds basic and nucleophilic. Since a wide variety of amides are known to have high biological activity and are useful as pharmaceuticals, one can also conclude that it is possible that the amide functionality is important. Simple aromatic amides such as acetanilide (3), acetaminophen or Tylenol (4), phenacetin (5), benzamide (6), and salicylamide (7) are analgesics and antipyretic drugs. Their structures are shown in Figure 5 below:

Figure 5: Structure of Some Important Pharmaceuticals That Are Aromatic Amides
There are many reports of amides being utilized such as antifungal and antiinflammatory agents\(^9\), or for the treatment of blood diseases\(^{10}\). For example Nazumamide A (9), a thrombin-inhibiting linear tetrapeptide, isolated from a marine sponge *Theonella* species (Figure 6).

![Figure 6: Structure of Nazumamide (9)](image)

Compounds containing the amide functionality have also been used to prevent and treat thrombo-embolic illness\(^{11}\); obesity, anorexia, mental disorders, and diseases associated with the melanocortin receptors.\(^{12}\) They also have used to reduce or prevent the formation of UV-induced skin cancer\(^{13}\) and to kill cancer cells in human patients\(^{14}\).

1.5. Podocarpic Acid

Podocarpic acid (10) as shown in Figure \(7^{(15),(16),(17)}\) is a natural conifer resin acid that was first isolated by Oudemans in 1873\(^{18}\) from *Podocarpus cupressinu* (Figure 8). It also
extracted from the “kahikatea” tree *Podocarpus dacrydioides* (Figure 9), and from the “rimu” tree *Dacrydium cupressinum* as shown (Figure 10).

![Structure of Podocarpic Acid](image)

**Figure 7:** Structure of Podocarpic Acid (10)

![Podocarpus Cupressinus](image)

**Figure 8:** *Podocarpus Cupressinus*
Figure 9: *Podocarpus Dacrydioides*

Figure 10: *Dacrydium Cupressinum*

These forest trees are endemic to New Zealand and Java which are geographically shown in Figure 11:
Podocarpic acid was extracted by methanol from the heartwood of the podocarpus species. Podocarpic acid has been used in pharmaceutical\(^\text{19}\) and other industries for variety of products such as soaps, adhesives, and paints\(^\text{20}\). Podocarpic acid is a very stable white solid material with a melting point of \(195^0\text{C}\). It contains two functionalities which are a carboxylic acid and a phenol. It is also a natural diterpenoid with tricyclic framework structure of phenanthrene. The carboxylic acid moiety (11) is relative unreactive\(^\text{21,22}\) because of the steric hindrance due to the diaxial interaction with the C-10 methyl group as shown below in Figure 12.

![Figure 11: Global Map Distribution of *Podocarpus* Species (■)](image)

![Figure 12: Conformation of Podocarpic Acid (11)](image)
1.6. Previous Studies of Biological Active Agents from Podocarpic Acid Derivatives

Podocarpic acid and its derivatives date back to 1948 as source of oestrogenic activity\textsuperscript{(23)}. Podocarpinol (12) as shown in Figure 13 below is an example of one derivative that demonstrates this type of activity.

![Figure 13: Structure of Podocarpinol (12)](image)

Podocarpic acid has also been utilized since 1950 in the synthesis of antiinflammatory and antiviral agents as well as other derivatives\textsuperscript{(24), (25), (26)}. Also, a variety of novel compounds\textsuperscript{(27)} containing the lactones and lactams (cyclic amides) have been synthesized from podocarpic acid. Two examples of compounds synthesized from podocarpic acid are nimbiol\textsuperscript{(28)} (13) and (+)-winterin\textsuperscript{(29)} (14), respectively (Figure 14 and 15).
In 1982, Hayashi et. al, synthesized of biologically active dilactone (15) from podocarpic acid\textsuperscript{(30)}. The structure of hydroxynagilactone is shown in Figure 16 below:
In 1984, Parish and Miles investigated the antitumor activity of podocarpic acid derivatives. The compound methyl-6α-bromo-7-oxo-O-methylpodocarpate (16) which is shown in Figure 17 demonstrated the highest level of activity.

Figure 16: Structure of Hydroxynagilactone (15)

Figure 17: Structure of Compound (16)
This compound demonstrated activity against human epidermoid carcinoma of the nasopharynx in vitro. Furthermore, in 1987, Parish et al synthesized several podocarpic acid derivatives\(^{(32)}\) with fungistatic activity. The most potent of these derivatives is 11,13-dinitropodocarpic acid (17) whose structure is shown in Figure 18 below:

![Structure of Compound (17)](image)

Figure 18: Structure of Compound (17)

Recently, as the result of these works on podocarpic acid derivatives above, in 1997, Eli Lily and Company was launched serious studies on many other new derivatives from podocarpic acid for treatment of viral infections with many patents\(^{(33), (34), (35)}\). The active compounds include isopropyl-O-methylpodocarpate (18) and methyl-O-6-en-7-oxo-methylpodocarpate (19), respectively (Figure 19 and 20).
In 1998, methyl-O-methylpodocarpate (20) (Figure 21) was reported to have antiviral properties. This compound inhibited multicycle replication in protein synthesis of influenza A/Kawasaki virus\textsuperscript{(36)}.
In 2003, Adams et al., prepared podocarpic derivative (21) (Figure 22) which were used as LXR agonists for treating dyslipidemic conditions such as depressed levels of HDL cholesterol\(^{37}\).
2. RESULTS AND DISCUSSION

The goal of this work was to synthesize a series of amide derivatives of podocarpic acid at C-13 of the aromatic ring (as outlined in Scheme 1) with R being hydrogen, an alkyl group, a vinyl group, or an aryl group.

![Scheme 1: Synthesis of Amide Derivatives from Podocarpic Acid](image)

As mention previously, amides are of interest in organic synthesis because of the potential for application in pharmaceutical industry. It is known that aromatic amides can be prepared from aryl halides\(^{(38)}\). The literature contains a reference to the reaction of aryl halides by using copper catalyst. Some a hundred year ago Ullmann discovered the coupling of aryl bromide to form biaryl in 1903\(^{(39)}\). At the same time in 1906, Goldberg studied the reaction
N-arylation of acetanilide on aryl bromide utilizing a copper catalyst\(^{(40)}\). However, these reactions required high temperature such as at 200° C, an aprotic solvent, and a large amounts of catalyst. Also the yields were modest and the separations were difficult.

Recently, palladium catalyst were used in many applications\(^{(41)},(42)\) for yield optimization. However the high cost of palladium catalysts and phosphine ligands made the industrial application uneconomical \(^{(43)}\). As the result, the search for an inexpensive copper catalysts for the reaction of coupling of aryl halide and amide was conducted\(^{(44)},(45)\). One advantage in comparison with palladium catalysts in that copper can be used under many different conditions such as high moisture and oxygen content such as we find it under normal atmosphere conditions. The postulate for this work was if the reaction of 13-iodomethyl-O-methylpodocarpate with an amide was successful that a general method for preparing amides derivatives of the aromatic system (phenolic) of podocarpic acid could be developed and could be applied to other iodides or halides as well. Since copper catalyst is more versatile than palladium catalyst, the decision was made to utilize copper in an attempt to synthesize the novel amide derivative of podocarpic acid.

The first step in this process was to methylate podocarpic acid utilizing dimethylsulfate by known methods\(^{(46)}\) to form methyl-O-methylpodocarpate \((23)\) as shown in Scheme 2:
Scheme 2: Formation of Methyl-O-Methylpodocarpate

Compound (23) formed (m.p. 127°C) in 82 % yield and was identical to methyl-O-methylpodocarpate by comparison of the m.p., IR, NMR, and MS spectrum with an authentic sample.

Methyl-O-methylpodocarpate (23) was then reacted with iodine to form novel compound 24 in 95 % yield as shown in Scheme 3.

Scheme 3: Formation of 13-Iodomethyl-O-Methylpodocarpate 24
In this reaction, mercury (II) acetate was used to form a precipitate of mercury (II) iodide and shift the balance of equation (1) to right:

\[
2C_{19}H_{26}O_3 + 2I_2 + Hg(AcO)_2 \leftrightarrow 2C_{19}H_{25}IO_3 + HgI_2(s) + 2AcOH
\]  

(1)

Equation 1: Reaction of Methyl-O-Methylpodocarpate with Iodine

Compound 24 had a m.p. of 149\(^0\)C. The IR, \(^1\)H-NMR, \(^{13}\)C-NMR, and HRMS spectra of compound 24 are shown in Figure 23, 24, 25, and 26, respectively.

Transmittance, %.

![Infrared Spectrum](image)

Figure 23: Infrared Spectrum of Compound 24
The IR spectrum of compound 24 displayed strong absorptions at 600 and 750 cm\(^{-1}\) for a C-I bond and an absorption for a carbonyl was present at 1720 cm\(^{-1}\). Absorptions were present for an aromatic ring at 1600, 1500, and 1450 cm\(^{-1}\). There was also a strong absorption at 1200 cm\(^{-1}\) for a C-O bond which is present in the ether and ester moieties.

Figure 24: \(^1\)H-NMR Spectrum of Compound 24
Examination of the $^1$H-NMR spectrum of compound 24 (Figure 24) in CDCl$_3$ showed the absenced of a aromatic ring proton in comparison with methyl-O-methylpodocarpate (23). Compound 24 showed two singlets at δ 6.65 (1H) and δ 7.45 ppm (1H). (the peak at δ 7.25 ppm is due to the solvent CDCl$_3$ in relative to chemical shift δ of TMS at 0 ppm). The signals at δ 3.85 (s, 3H) and 3.95 ppm (s, 3H) could be assigned to the two methoxy groups while the remaining protons had chemical shift values that were identical with those in the spectrum of compound (23).

![13C-NMR Spectrum of Compound 24](image)

Figure 25: $^{13}$C-NMR Spectrum of Compound 24
The $^{13}$C-NMR spectrum (Figure 25) showed a significant downfield shift for the aromatic C-13 carbon from 131 to 140 ppm. This downfield shift is consistent with the presence of iodine at the C-13 position in the aromatic ring.

<table>
<thead>
<tr>
<th>Relative Abundance, %</th>
<th>M$^+$</th>
</tr>
</thead>
</table>

![Figure 26: HRMS Spectrum of Compound 24](image)

The HRMS spectrum from University of Nebraska shows the molecular ion M$^+$ at m/z 428.0844 as the base peak for formula C$_{19}$H$_{25}$IO$_3$. Figure 27 showed the fragmentation of compound 24. The peak at m/z 381.0361 is represented as [M-47]$^+$ and consistent with the lost of a methoxy group and a methyl group. The peak at m/z 353.0405 is represented as [M-75]$^+$ and is due to the lost of a carboxyl group and a methyl group. Further fragmentation gave a peak at m/z 226.1359 and peaks at m/z 172.0886 and 115.0553. The peak at m/z 286.9927 is represented by [M-141]$^+$ which is the lost of an iodine atom and a methyl group.
Figure 27: Possible Fragmentations of Compound 24
The IR, MS, and NMR evidence are consistent with the structure of compound 24 (13-iodomethyl-O-methylpodocarpate) as shown in Figure 28.

![Structure of Compound 24](image)

Figure 28: Structure of Compound 24

Compound 24 was then reacted with a variety of aliphatic and aromatic amides (as given in Table 1) in attempt to form an amide at the C-13 aromatic position according to the reaction illustrated in Scheme 4.

<table>
<thead>
<tr>
<th>Amide</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formamide</td>
<td>H-CO-NH₂</td>
</tr>
<tr>
<td>Acetamide</td>
<td>CH₃-CO-NH₂</td>
</tr>
<tr>
<td>Propionamide</td>
<td>CH₃-CH₂-CO-NH₂</td>
</tr>
<tr>
<td>Butyramide</td>
<td>CH₃-CH₂-CH₂-CO-NH₂</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>H₂C=CH-CO-NH₂</td>
</tr>
<tr>
<td>Benzamide</td>
<td>C₆H₅-CO-NH₂</td>
</tr>
<tr>
<td>Salicylamide</td>
<td>o-HO-C₆H₄-CO-NH₂</td>
</tr>
</tbody>
</table>
Scheme 4: General Reaction for Formation of Amide Derivatives of Podocarpic Acid

Table 2: Attempts to Synthesis of Amides \( P \) with Various R Groups

<table>
<thead>
<tr>
<th>R</th>
<th>-H</th>
<th>-CH(_3)</th>
<th>-C(_2)H(_5)</th>
<th>n-C(_3)H(_7)</th>
<th>-CH=CH(_2)</th>
<th>-C(_6)H(_5)</th>
<th>o-HO-C(_6)H(_4)-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound ( P )</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>30</td>
<td>31</td>
</tr>
</tbody>
</table>

The general reaction involved mixing 1 molar equivalent of compound 24 with 1.5 molar equivalent of the corresponding amide, 0.1 molar equivalent of copper catalyst, 0.2 molar equivalent of N,N’-dimethylethylenediamine, and 2.5 molar equivalent of potassium carbonate in dioxane at 100\(^0\)C in 24 hours. When the reaction mixture was allowed to cool, a precipitate was obtained by vacuum filtration. Open column chromatography was then performed with 100 mesh silicagel in order to purify the reaction product. The structure of each product was elucidated by IR, \(^1\)H-NMR, \(^{13}\)C-NMR, and HRMS spectroscopy as described in the following text.
The reaction with formamide formed the new compound 25 (80 % yield) with a m.p. of 145\(^0\)C. The IR, \(^1\)H-NMR, \(^{13}\)C-NMR, and MS spectra of compound 25 are shown in Figures 29, 30, 32 and 33, respectively.

Transmittance, %

![Infrared Spectrum of Compound 25](image)

Figure 29: Infrared Spectrum of Compound 25

The IR spectrum of compound 25 showed one absorption at 3400 cm\(^{-1}\) which is consistent with a secondary amide. The strong absorption at 1720-1700 cm\(^{-1}\) can be assigned to carbonyl groups of the ester and the amide. Absorptions for the aromatic ring were present at 1600, 1500, and 1450 cm\(^{-1}\). A strong absorption was also present at 1200 cm\(^{-1}\) for a C-O bond of the ether and the ester.
Figure 30: $^1$H-NMR Spectrum of Compound 25
The $^1$H-NMR spectrum of compound 25 (Figure 30) shows two additional protons in comparison with the $^1$H-NMR spectrum of compound 24. They were assigned as shown in Figure 31 and Table 3.

![Chemical Structure of Compound 25](image)

**Figure 31: Proton Assignments of Compound 25**

**Table 3: Proton Assignments of Compound 25**

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift $\delta$, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_A$</td>
<td>6.80</td>
</tr>
<tr>
<td>$H_B$</td>
<td>7.85</td>
</tr>
<tr>
<td>$H_C$</td>
<td>8.02</td>
</tr>
<tr>
<td>$H_D$</td>
<td>8.42</td>
</tr>
</tbody>
</table>
The $^{13}$C-NMR spectrum of compound 25 displayed a new peak at 160 ppm which is consistent with the carbonyl carbon of an amide. The chemical shift of the aromatic carbons of compound 25 were more downfield in comparison with compound 24. There were a total of 8 carbons with a chemical shift lower than 100 ppm for carbons of the aromatic ring and carbonyl groups. The
spectrum gives a total of 20 signals that is consistent with the 20 non equivalent carbons found in compound \( \text{25} \).

<table>
<thead>
<tr>
<th>Relative Abundance, %</th>
<th>( M^+ )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>345.1927</td>
</tr>
<tr>
<td>90%</td>
<td>344.1868</td>
</tr>
<tr>
<td>80%</td>
<td>343.0254</td>
</tr>
<tr>
<td>70%</td>
<td>342.2639</td>
</tr>
<tr>
<td>60%</td>
<td>344.3977</td>
</tr>
<tr>
<td>50%</td>
<td>345.4962</td>
</tr>
<tr>
<td>40%</td>
<td>345.6938</td>
</tr>
<tr>
<td>30%</td>
<td>347.2017</td>
</tr>
<tr>
<td>20%</td>
<td>348.0000</td>
</tr>
</tbody>
</table>

Figure 33: HRMS Spectrum of Compound \( \text{25} \)

The HRMS spectrum of compound \( \text{25} \) shows a molecular ion m/z 345.1927 for a molecular formula of \( \text{C}_{20}\text{H}_{27}\text{NO}_{4} \).
The mass spectrum of compound 25 displayed a $[M+1]^+$ peak at m/z 346.2. The peak at m/z 302.1 is represented as the methyl-O-methylpodocarpate ion as the result of the cleavage of N-C bond. Further fragmentation gave the base peak at m/z 154.1 represented as $[M-191]^+$ (Figure 35).
Therefore compound 25 is consistent with the structural assignment of 13-formamidomethyl-O-methylpodocarpate (Figure 36).
Figure 36: Structure of Compound 25

Compound 26 was formed in 90% yield and gave a m.p. of 147°C. The IR, $^1$H-NMR, $^{13}$C-NMR, and HRMS spectra of compound 26 are shown in Figures 37, 38, 40, and 41, respectively.

Figure 37: Infrared Spectrum of Compound 26

The IR spectrum of 26 displayed a strong absorption at 3400 cm$^{-1}$ which is consistent with a secondary amide. The absorption 1680 cm$^{-1}$ could be assigned to the amide.
Figure 38: $^1$H-NMR Spectrum of Compound 26
The $^1$H-NMR spectrum of compound 26 shows one additional proton in comparison with compound 24. Three singlets at $\delta$ 6.70 (1H), 7.60 (1H), and 8.00 (1H) were assigned to the three protons $H_A$, $H_B$, and $H_C$ respectively (Figure 36). The signals for the methoxy groups at $\delta$ 3.85 (3H) and 3.95 (3H) were relatively unchanged, but there was an additional a singlet at $\delta$ 2.20 ppm which could be assigned to the protons of the acetyl group.

![Figure 39: Proton Assignments of Compound 26](image)

$H_A = 6.70$ ppm  
$H_B = 7.60$ ppm  
$H_C = 8.00$ ppm

The $^{13}$C-NMR spectrum of compound 26 in comparison with compound 24 is shown in Fig. 40.

![$^{13}$C-NMR Spectrum of Compound 24](image)
The $^{13}$C-NMR spectrum of compound 26 showed a new signal for the amide carbon at 168 ppm. Among the of 21 signals, there were 8 at a lower field than 100 ppm. These can be assigned to the aromatic carbons, the ester carbon, and the amide carbon.

Relative Abundance, %

![HRMS Spectrum of Compound 26](image1)

**Figure 41: HRMS Spectrum of Compound 26**
The HRMS spectrum of compound 26 showed a molecular ion at m/z 359.2096 which was consistent with a molecular formula of C$_{21}$H$_{29}$NO$_4$. The mass spectrum of compound 26 (Figure 42) was displayed as [M+1]$^+$ peak at m/z 360.2. The peak at m/z 302.1 is represented as methyl-O-methylpodocarpate ion as the result of the cleavage of N-C bond. Further fragmentation gave the base peak at m/z 154.1 or [M-205]$^+$ as shown in Figure 43, respectively.

![Mass Spectrum of Compound 26](image)

Figure 42: Mass Spectrum of Compound 26
Therefore, the compound 26 can be assigned as 13-acetamidomethyl-O-methylpodocarpate (Figure 44).
Compound 27 was formed in 82% yield and gave a m.p. of 149°C. The IR, $^1$H-NMR, $^{13}$C-NMR, and MS spectra are shown in Figures 45, 46, 48, and 49, respectively.

Figure 44: Structure of Compound 26

Figure 45: Infrared Spectrum of Compound 27
The infrared spectrum of compound 27 showed a significant absorption at 3400 cm\(^{-1}\) for the presence of a secondary amide. There was an absorption at 1680 cm\(^{-1}\) for the amide carbonyl and one at 1720 cm\(^{-1}\) for the ester carbonyl. Absorptions for the aromatic ring were presented at 1600, 1540, and 1400 cm\(^{-1}\). Absorption for the C-O bond in the ether and ester were present at 1220 cm\(^{-1}\).

Figure 46: \(^1\)H-NMR Spectrum of Compound 27
The $^1$H-NMR of compound $27$ shows 3 singlets at $\delta$ 6.70 (1H), 7.62 (1H), and 8.02 (1H) for three proton $H_A$, $H_B$, and $H_C$ respectively as shown in Figure 47. The protons for the methoxy groups appeared at $\delta$ 3.85 (s, 3H) and 3.95 (s, 3H). The protons for the ethyl group appeared at $\delta$ 2.4 ppm for the methylene group and gave a signal at $\delta$ 1.1 (3H) for the methyl group.

![Figure 47: Proton Assignments of Compound $27$](image)

The $^{13}$C-NMR spectrum of compound $27$ in comparison with compound $24$ is shown in Fig. 48.

![$^{13}$C-NMR Spectrum of Compound $24$](image)
Investigation the $^{13}$C-NMR spectrum of compound 27 displayed a new signal at 172 ppm that could be assigned as an amide. For structure of compound 27 there were eight carbons with the chemical shift downfield from $\delta$ 100 ppm with a total of 22 carbons.

Examination HRMS of compound 27 (Figure 49) shows the molecular ion at m/z 373.2264 which was consistent with a molecular formula of C$_{22}$H$_{31}$NO$_4$.

Relative Abundance,
The mass spectrum of compound 27 was displayed a [M+1]$^+$ peak at m/z 374.2 (Figure 50). The peak at m/z 302.1 represented the methyl-O-methylpodocarpate ion and is a result of the cleavage of N-C bond. Further fragmentation gave the base peak at m/z 154 or [M-219]$^+$ as shown in figure 51 below:

**Figure 50: Mass Spectrum of Compound 27**
Therefore, the compound 27 can be assigned as 13-propionamidomethyl-O-methylpodocarpate (Figure 52).
Compound 28 was synthesized in 85% yield and gave a m.p. of 150°C. The IR, $^1$H-NMR, $^{13}$C-NMR, and MS spectra are shown in figures 53, 54, 56, and 57, respectively.

Figure 52: Structure of Compound 27

Figure 53: Infrared Spectrum of Compound 28
The spectrum of compound 28 displayed a strong absorption at 3400 cm\(^{-1}\) for a secondary amide. The absorption for an amide carbonyl was present at 1680 cm\(^{-1}\) while an absorption for the carbonyl of ester was present at 1720 cm\(^{-1}\). Absorptions for an aromatic ring were present at 1600, 1500, and 1470 cm\(^{-1}\) while there was an absorption for the C-O bond at 1220 cm\(^{-1}\).

Figure 54: \(^1\text{H-NMR Spectrum of Compound 28}\)
The $^1$H-NMR spectrum of compound 28 showed three singlets at $\delta$ 6.62 (1H), 7.82 (1H), and 8.00 (1H) for the protons $H_A$, $H_B$, and $H_C$ (figure 53). The protons of methoxy groups were present at $\delta$ 3.85 (3H) and 3.95 ppm (3H). The protons for the propyl group appeared at $\delta$ 2.20, 1.90, and 1.60 ppm.

![Proton Assignments of Compound 28](image)

Figure 55: Proton Assignments of Compound 28

The $^{13}$C-NMR spectrum of compound 28 in comparison with compound 24 is shown in Fig. 56.
The $^{13}$C-NMR of compound 28 gave a signal at 171.5 ppm for the amide carbon. For the structure of compound 28, there were 8 carbons with the chemical shift downfield from $\delta$ 100 ppm with a total of 23 signals. New signals at $\delta$ 14 and 19.5 ppm which can be assigned to methyl and methylene groups of the propyl group.

The HRMS spectrum of compound 28 (figure 56) showed a molecular ion at m/z 387.2411 which was consistent with a molecular formula of C$_{23}$H$_{33}$NO$_4$.

Relative Abundance, %
The mass spectrum of compound 28 was displayed as \([M+1]^+\) peak at m/z 388.3. The peak at m/z 302.1 can be assigned to the methyl-O-methylpodocarpate ion as the result of the cleavage of N-C bond. Further fragmentation gave the base peak at m/z 154.1 as represented by \([M-233]^+\) as shown in figure 59.
Figure 59: Possible Fragmentations of Compound 28

Therefore, the structure of compound 28 can be assigned as 13-butyramidomethyl-O-methylpodocarpate (Figure 60).
Attempts to synthesize aromatic (using benzamide and salicylamide) and vinyl (using acrylamide) derivatives of compound 24 gave no significant yields.

In the summary the reaction of 13-iodomethyl-O-methylpodocarpate with aliphatic amides to form amide derivatives of podocarpic acid were in yields between 80 and 90% has been developed. In the contrast, reaction of 13-iodomethyl-O-methylpodocarpate with vinyl amide or aromatic amides were not successful because little or no product could be isolated. Perhaps this is due the reduction of the electrophilicity of the reactant amide because of the conjugation of the carbonyl of amide with double bond or aromatic ring as the results illustrated in table 4. Thus, this reaction seems to be selective for aliphatic amides.

In short, five new compounds have been synthesized. These compounds have been submitted to the NCI and NIAID for testing against 60 human cell lines. Thus the potential exists that this work might result in a new drug lead for cancer treatment.
Table 4: Yields of the Amidation Reaction of Compound 24 and Various Amides

<table>
<thead>
<tr>
<th>Amide H$_2$N-CO-R</th>
<th>R</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formamide</td>
<td>-H</td>
<td>80</td>
</tr>
<tr>
<td>Acetamide</td>
<td>-CH$_3$</td>
<td>90</td>
</tr>
<tr>
<td>Propionamide</td>
<td>-CH$_2$-CH$_3$</td>
<td>82</td>
</tr>
<tr>
<td>Butyramide</td>
<td>-CH$_2$-CH$_2$-CH$_3$</td>
<td>85</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>-CH=CH$_2$</td>
<td>No significant yield</td>
</tr>
<tr>
<td>Benzamide</td>
<td>-C$_6$H$_5$</td>
<td>No significant yield</td>
</tr>
<tr>
<td>Salicylamide</td>
<td>o-HO-C$_6$H$_4$-</td>
<td>No significant yield</td>
</tr>
</tbody>
</table>

Thus, one novel iodo-derivative and four amide derivatives of methyl-O-methylpodocarpate have been synthesized. Also a general methodology has been developed for the formation of aliphatic amide derivatives of aromatic systems such those found in podocarpic acid. This method involves amidation reaction at 100°C in 24 hours with a molar equivalent of 1 to 1.5 mole of aryl iodide to amide in basic medium in the present of copper iodide catalyst. A small library of novel compound included one new iodo-derivative and four novel amides derived from podocarpic acid which will be tested for the biological active against cancer and tuberculosis.
3. EXPERIMENTAL

General Experimental Procedures

The following instruments were used to obtain physical data: melting points were read on a MEL-TEMP apparatus, IR spectra were recorded on a Perkin Elmer Spectrum One spectrometer in CHCl₃, ¹H and ¹³C NMR spectra were obtained on a Varian Mercury 300 MHz spectrometer, and HRMS spectra were performed on Finnigan spectrometer from University of Nebraska Mass Spectrometry Center. Silicagel (Selecto Scientific, 63-200 mesh) was used for open column chromatography.

3.1. Preparation of Methyl-O-Methylpodocarpate (23)

50 g of crude podocarpic acid was weighed in a 300 mL beaker and 50 g of ice was added into it. Then 50 mL of methanol was added to the beaker. This mixture was stirred then added 24 g pellets of sodium hydroxide. The solution was continually stirred to dissolve completely the podocarpic acid and sodium hydroxide, then it was cooled to 15°C in an ice bath. 42.5 mL of dimethyl sulfate was added into this solution in a period of 1 hour⁴⁷. At the end this period, this solution solidified. This mixture was stirred for an addition of 30 minutes then added 100 mL water then it was filtered. The solid was dissolved in 100 mL water then filtered and dried to obtain 45g a white solid. This solid was recrystallized to obtain 20 g of methyl-O-
methylpodocarpate with m.p. of 125°C. Yield 82%. IR (Perkin Elmer Spectrometer, CHCl₃): 3000, 2950, 2900, 2860, 1720, 1600, 1540, 1490, 1460, 1400, 1360, 1300, 1240, 1200, 1190, 1150, 1060, 1020950, 760, 740 cm⁻¹. ¹H-NMR (Mercury 300 MHz): 6.95 (d), 6.8 (s), 6.65 (d), 3.85 (s), 3.65 (s), 2.8 (m), 2.25 (m), 1.95 (m), 1.6 (m), 1.5 (m), 1.4 (m), 1.22 (m), 1,2 (s), 1.15 (m), 1.05 (m), 1.00 (s) ppm. ¹³C-NMR (Mercury 300 MHz): 178, 158, 150, 130, 128, 114, 112, 56, 52, 51, 44, 39.5, 38, 31, 28, 25, 22.5, 20.5, 20 ppm. MS: 302(44), 287(6), 228(16), 227(100), 173(6), 170(23), 147(10), 121(6), 91(4).

3.2. Preparation of 13-Iodomethyl-O-Methylpodocarpate

3.025 g of methyl-O-methylpodocarpate was weighed and transferred into a 500 mL volumetric flask, then it dissolved in 60 mL of acetic acid. In a separated beaker, 2 g of mercury (II) acetate was weighed and dissolved in 60 mL of acetic acid, then this content was added into the flask above. This solution was heated to 70°C and stirred for 15 minutes. A solution of iodine was prepared by dissolving of 7.614 g of iodine in 240 mL of warm acetic acid. This iodine solution was then added dropwise in a period of 45 minutes into the flask while the temperature maintained at 70°C during this period. At the end of this period, the solution was stirred for an addition 1 hour then cooled the flask to 15°C in an ice bath, the solution was filtrated and the filtrate was added into 500 mL of cold water in a 1L beaker. The resulting precipitate was filtered to yield 3 g of product. The product was recrystallized from acetone to obtain 2 g of pure product with m.p.149°C, yield 95%. IR (Perkin Elmer Spectrometer, CHCl₃): 3000, 2940, 2850, 2400, 1720, 1600, 1495, 1470, 1440, 1390, 1350, 1300, 1250, 1200, 1150, 1050, 950, 900, 800, 750, 650 cm⁻¹. ¹H-NMR (Mercury 300 MHz): 7.45 (s), 6.65 (s), 3.95 (s),
3.85 (s), 2.70 (m), 2.20 (m), 1.95(m), 1.6 (m), 1.5 (m), 1.25 (s), 1.15 (m), 1.02 (s), 0.95 (m) ppm.

$^{13}$C-NMR (Mercury 300 MHz): 178, 156, 150, 140, 131, 108, 83, 56.5, 52.5, 52, 44, 39, 38.5, 32, 31.5, 29.5, 23, 21, 20 ppm. HRMS (Finnigan Spectrometer): 428(100), 413(8), 381(3), 368(3), 353(77), 313(4), 287(6), 272(6), 227(15), 211(4), 172(6), 140(5), 129(8), 115(6), 101(3), 91(2).

3.3. Preparation of Acetamide

50g of ammonium acetate was weighed and transferred into a 300 mL volumetric flask to which 60 mL of acetic acid was added. The flask was heated and refluxed for 4 hours$^{49}$. At the end of this period, the liquid inside the flask was distilled and collected the boiling fractions at 220°C and above to obtain 25g of crude acetamide, yield 66%. The product was recrystallized in acetone to yield 15g acetamide with m.p.75°C (literature m.p. 79°C$^{50}$). IR (Perkin Elmer Spectrometer, CHCl$_3$): 3680, 3510, 3480, 3410, 3350, 3190, 3000, 2940, 2900, 2860, 2390, 1675, 1615, 1470, 1405, 1380, 1280, 1240, 1210, 1095, 1050, 1030, 980, 895, 780, 760, 680, 580 cm$^{-1}$. $^1$H-NMR (Mercury 300 MHz): 2.3 (s), 5.8(s), 6.2(s) ppm. $^{13}$C-NMR (Mercury 300 MHz): 20, 172 ppm.

3.4. Preparation of 13-Formamidomethyl-O-Methylpodocarpate

0.1 g of copper (I) iodide was weighed into a 100 mL volumetric flask to which, then 3.46 g of potassium carbonate was added. This was followed by the addition of 0.34 g of formamide and 0.1 g of N,N"-dimethylethlenediamine. In a separate beaker, 2.15 g of 13-iodomethyl-O-methylpodocarpate was weighed and dissolved in 10 mL of dioxane. The content inside the beaker was poured into the flask and a magnetic stirring bar was added into this solution. The mixture was stirred and a condenser was connected. The mixture was heated at
100\(^{0}\)C for 24 hrs. The reaction mixture was allowed to cool. The precipitate formed and filtered. The precipitate was washed with 100 mL of ethylacetate. The filtrate was evaporated under vacuum to obtain a 2 g of a solid. This product was purified on 63-200 mesh silicagel column to obtain 0.2 g of 13-formamidomethyl-O-methylpodocarpate with m.p.145\(^{0}\)C. Yield 80%. IR (Perkin Elmer Spectrometer, CHCl\(_3\)): 3680, 3620, 3410, 3010, 2960, 2920, 2400, 1700, 1640, 1620, 1520, 1480, 1460, 1420, 1260, 1220, 1150, 1080, 1050, 990, 950, 790, 750, 680, 650, 480 cm\(^{-1}\). \(^{1}\)H-NMR (Mercury 300 MHz): 8.42 (s), 8.02(s), 7.80 (s), 6.80 (m), 3.95 (s), 3.85 (s), 2.80(m), 2.30 (m), 1.95 (m), 1.65 (m), 1.60 (m), 1.40 (m), 1.30 (s), 1.20 (s) ppm. \(^{13}\)C-NMR (Mercury 300 MHz): 178, 160, 147, 145, 128, 124.5, 120.5, 117.5, 56, 53, 53, 44.5, 40, 39, 38, 32, 29, 23, 21.5, 20 ppm. HRMS (Finnigan Spectrometer): 346(48), 345(12), 302(82), 300(43), 219(24), 154(100).

3.5. Preparation of 13-Acetamidomethyl-O-Methylpodocarpate

0.1 g of copper (I) iodide was weighed in a 100 mL volumetric flask to which 3.46 g of potassium carbonate was added. 0.45 g of acetamide and 0.1 g of N,N'-dimethylethylenediamine were added into the flask. These components were dissolved in 5 mL of dioxane. In a separate beaker, 2.15 g of 13-iodomethyl-O-methylpodocarpate was weighed and dissolved in 5 mL dioxane. The solution inside the beaker was then added into the flask and connected with a condenser. The flask was stirred and heated at 100\(^{0}\)C during a period of 24 hours. The mixture was cooled to room temperature and 20 mL of ethylacetate was added. The resulting precipitate was filtered and washed several times with 100 mL of ethylacetate. The filtrate was evaporated under vacuum to obtain 1.8 g of a solid powder (90% yield). This solid was purified by chromatography on 63-200 mesh silicagel column to obtain 0.3 g of 13-acetamidomethyl-O-
methylpodocarpate with m.p.147°C. IR (Perkin Elmer Spectrometer, CHCl₃): 3660, 3400, 2990, 2940, 2820, 1710, 1680, 1600, 1580, 1520, 1470, 1450, 1400, 1340, 1300, 1260, 1240, 1220, 1180, 1140, 1070, 1020, 980, 890, 840, 780, 760, 680, 580 cm⁻¹. ¹H-NMR (Mercury 300 MHz): 8.00 (s), 7.65 (s), 6.70 (s), 3.95 (s), 3.85 (s), 2.80 (m), 2.20 (m), 1.95 (m), 1.65 (m), 1.50 (m), 1.35 (m), 1.22 (s), 1.05 (m), 1.00 (s) ppm. ¹³C-NMR (Mercury 300 MHz): 178, 168, 146.5, 144, 128, 125.5, 120, 107, 56, 53, 44, 40, 39.5, 39, 32, 29, 25, 24, 22, 20.5 ppm. HRMS(Finnigan Spectrometer): 360(22), 302(24), 284(90), 219(10), 242(100), 154(100).

3.6. Preparation of 13-Propionamidomethyl-O-Methylpodocarpate

0.1 g of copper (I) iodide was weighed in a 100 mL volumetric flask to which 3.46 g of potassium carbonate was added. 0.55 g of propionamide and 0.1 g of N,N'-dimethylethylenediamine were added into the flask. These components were dissolved in 5 mL of dioxane. In a separate beaker, 2.15 g of 13-iodomethyl-O-methylpodocarpate was weighed and dissolved in 5 mL dioxane. The solution inside the beaker was then added into the flask and connected with a condenser. The flask was stirred and heated at 100°C during a period of 24 hours. The mixture was cooled to room temperature and 20 mL of ethylacetate was added. The resulting precipitate was filtered and washed several times with 100 mL of ethylacetate. The filtrate was evaporated under vacuum to obtain 2 g of a solid powder in 82 % yield. This solid was purified by chromatography on 63-200 mesh silicagel column to obtain 0.2 g of 13-propionamidomethyl-O-methylpodocarpate with m.p.149°C. IR (Perkin Elmer Spectrometer, CHCl₃): 3660, 3400, 3010, 2960, 2890, 2850, 2380, 1720, 1680, 1610, 1595, 1520, 1490, 1470, 1350, 1290, 1260, 1220, 1130, 1070, 1020, 980, 895, 850, 780, 760, 680, 590, 500 cm⁻¹. ¹H-NMR (Mercury 300 MHz): 8.02 (s), 7.65 (s), 6.65 (s), 3.95 (s), 3.85 (s), 2.80 (s), 2.35 (s), 2.20
(m), 1.95 (m), 1.75 (m), 1.60 (m), 1.50 (m), 1.30 (s), 1.20 (s), 1.05 (s) ppm. $^{13}$C-NMR (Mercury 300 MHz): 178.2, 172, 146, 143.6, 128, 125.8, 120, 107.8, 56, 54, 52, 44, 40, 38.6, 38, 32, 31.6, 28.8, 23.6, 21.8, 20, 10 ppm. HRMS (Finnigan Spectrometer): 374(42), 358(5), 350(8), 302(56), 300(30), 219(18), 154(100).

3.7. Preparation of 13-Butyramidomethyl-O-Methylpodocarpate

0.1 g of copper (I) iodide was weighed in a 100 mL volumetric flask to which 3.46 g of potassium carbonate was added. 0.66 g of butyramide and 0.1 g of N,N'-dimethyleneethylenediamine were added into the flask. These components were dissolved in 5 mL of dioxane. In a separate beaker, 2.15 g of 13-iodomethyl-O-methylpodocarpate was weighed and dissolved in 5 mL dioxane. The solution inside the beaker was then added into the flask and connected with a condenser. The flask was stirred and heated at $100^\circ C$ during a period of 24 hours. The mixture was cooled to room temperature and 20 mL of ethylacetate was added. The resulting precipitate was filtered and washed several times with 100 mL of ethylacetate. The filtrate was evaporated under vacuum to obtain 2.15 g of a solid powder in 85% yield. This solid was purified by chromatography on 63-200 mesh silicagel column to obtain 0.3 g of 13-butyramidomethyl-O-methylpodocarpate with m.p.150$^\circ C$. IR (Perkin Elmer Spectrometer, CHCl$_3$): 3640, 3395, 3010, 2960, 2870, 2820, 2380, 1710, 1680, 1600, 1590, 1510, 1480, 1460, 1410, 1380, 1300, 1260, 1210, 1140, 1080, 1040, 940, 880, 820, 790, 740, 685 cm$^{-1}$. $^1$H-NMR (Mercury 300MHz): 8.00 (s), 7.62 (s), 6.65 (s), 3.92 (s), 3.82 (s), 2.80 (m), 2.22 (m), 2.15 (m), 1.95 (m), 1.60 (m), 1.50 (m), 1.30 (m), 1.20 (s), 1.00 (m) ppm. $^{13}$C-NMR (Mercury 300 MHz): 178, 171.5, 146.5, 143.2, 128, 126, 120, 107, 56, 53, 52, 44, 40.5, 40, 38.8, 38, 32, 29, 23, 22, 20.5, 19.5, 14 ppm. HRMS (Finnigan Spectrometer): 388(30), 302(35), 219(10), 154(100).

0.1 g of copper (I) iodide was weighed in a 100 mL volumetric flask to which 3.46 g of potassium carbonate was added. 0.54 g of acryltamide and 0.1 g of N,N'-dimylethlenediamine were added into the flask. These components were dissolved in 5 mL of dioxane. In a separate beaker, 2.15 g of 13-iodomethyl-O-methylpodocarpate was weighed and dissolved in 5 mL dioxane. The solution inside the beaker was then added into the flask and connected with a condenser. The flask was stirred and heated at 100°C during a period of 24 hours. The mixture was cooled to room temperature and 20 mL of ethylacetate was added. A solid precipitate was formed at the bottle of the flask. The resulting precipitate was filtered and washed several times with 100 mL of ethylacetate. The filtrate was evaporated under vacuum. However, no significant yield of the desired product could be isolated.


0.1 g of copper (I) iodide was weighed in a 100 mL volumetric flask to which 3.46 g of potassium carbonate was added. 0.91 g of benzamide and 0.1 g of N,N'-dimylethlenediamine were added into the flask. These components were dissolved in 5 mL of dioxane. In a separate beaker, 2.15 g of 13-iodomethyl-O-methylpodocarpate was weighed and dissolved in 5 mL dioxane. The solution inside the beaker was then added into the flask and connected with a condenser. The flask was stirred and heated at 100°C during a period of 24 hours. The mixture was cooled to room temperature and 20 mL of ethylacetate was added. The resulting precipitate was filtered and washed several times with 100 mL of ethylacetate. However, no significant amount of the desired product could be isolated.
3.10. Attempted Preparation of 13-Salicylamidomethyl-O-Methylpodocarpate

0.1 g of copper (I) iodide was weighed in a 100 mL volumetric flask to which 3.46 g of potassium carbonate was added. 1.03 g of acetamide and 0.1 g of N,N'-dimethylene diamine were added into the flask. These components were dissolved in 5 mL of dioxane. In a separate beaker, 2.15 g of 13-iodomethyl-O-methylpodocarpate was weighed and dissolved in 5 mL dioxane. The solution inside the beaker was then added into the flask and connected with a condenser. The flask was stirred and heated at 100°C during a period of 24 hours. The mixture was cooled to room temperature and 20 mL of ethylacetate was added. The resulting precipitate was filtered and washed several times with 100 mL of ethylacetate. The filtrate was evaporated under vacuum to obtain a solid powder. However, no significant amount of the desired product could be isolated from this powder.
REFERENCES


10. Miles, Howard D., Nguyen, Chi L., Miles, David H. Utilization of Natural Products for


