Phidianidines are a class of compound that has been extracted from the sea mollusk *Phidianis militaris*. These compounds have been shown to exhibit a variety of useful properties such as antihistamine effects, anti-cancer activity, agonism of the µ-opioid receptor and neuroprotection. The biological activities are thought to be caused by the 1,2,4-oxadiazole ring found within the molecule. The goal of this project is to synthesize analogues of phidianidine that contain a 1,2,3-triazole instead of the 1,2,4-oxadiazole ring using a method that will allow for other regions of the molecule to be changed. This will help to elucidate the role of the 1,2,4-oxadiazole ring in biological activity as well as probe if the 1,2,3-triazole analogue can provide significant improvement to any activities.

**Introduction**

Marine organisms have been proven a rich source for bioactive molecules over the last 50 years. Many of the marine natural products discovered belong to a class of compounds called alkaloids. Alkaloids are produced widely by both terrestrial and marine organisms and evolved as a defense mechanism. For this reason alkaloids are often cytotoxic. A subset of alkaloids, indole alkaloids, are important compounds in the field of drug discovery that commonly possess neurological activity. One such group of indole alkaloids are the phidianidines, which were isolated by Gavagnin in 2011 from the sea mollusk *Phidianis militaris*. Phidianidines A and B (Figure 1), which differ based on the presence of a bromide, possess a unique 1,2,4-oxadizole ring and biological properties.

The phidianidines have a range of interesting bioactivity such as antimalarial, HIV and neurological activity. Phidianidine A binds to the chemokine receptor CXCR4. CXCR4 is an important target in the field of pharmacology due to its involvement in HIV progression, tumor development and metastasis, and rheumatoid arthritis. Phidianidine A was shown to bind to CXCR4 moderately with hopes of improving its activity. Additionally, the phidianidines have interesting applications in neurological disorders. They function as a selective inhibitor of the dopamine transporter and a selective ligand of the µ-opioid receptor. Selectivity among opioid receptors is important because the δ- and κ-opioid receptors are linked to addiction, while the µ-opioid receptor is responsible for the analgesic effects. Other projects investigated the neuroprotective activities of phidianidine derivatives, and found that 4-substituted phidianidine derivatives offer significant protection against hydrogen peroxide and oxygen-glucose deprivation in vitro which can impact the onset and progression of neurodegenerative diseases like Alzheimer’s. Given these several important biological activities, synthesis of phidianidine analogues are essential to understanding and improving its functions.

Phidianidines are composed of three distinct regions, an indole, a 1,2,4-oxadiazole ring, and an aminoalkylguanidine chain. The bioactivity is mainly thought to be a result of the 1,2,4-oxadiazole ring, and phidianidine is the first isolated natural product to contain this structure. Previous synthesis of the phidianidines used a hydroxyguanidine linker with a protected nitrogen and ethyl indole-3-acetate to form the 1,2,4-oxadiazole ring. This has limited the ability of groups to explore the affect of structural changes to the 1,2,4-oxadiazole and indole on the biological activity. We hope to develop an approach to phidianidine analogues that addresses this limitation.

The overall goal of this project is to synthesize a 1,2,3-triazole analogue of the phidianidines (Figure 2) via cyclization of an azido-group with a 3-propargyl indole. This approach will allow for the impact of changes to the 1,2,4-oxadiazole ring and indole on the molecule’s biological activity to be determined. The identification of cyclization conditions to be used for the synthesis of the 1,2,3-triazole analogues is reported herein.

**Chemistry**

In the reaction scheme, indole was reacted with propargyl bromide to produce 3-propargyl indole (Scheme 1). This reaction was successfully realized with a variety of indoles (Table 1). To determine the optimum conditions for the synthesis of the 1,2,3-triazole heterocycle,
commercially available benzyl azide was used as a model (Scheme 2). Treatment of the alkyne and azide under standard cycloaddition conditions gave poor results\(^\text{15}\) (Table 2, entry 1). No product was isolated though this could be due to difficulties in purification. In order to improve the yield, the equivalents of the reactants were doubled and the temperature increased to 60 °C. This provided moderate increases to yield in some cases, however the yield was still around 30% (Table 2, entries 2-4). The temperature and equivalents were increased again (80 °C, 4 equiv.) however the yield decreased to 8% (Table 2, entry 5). It was hypothesized that the low yields were caused by oxidation of the Cu (I) catalyst by O\(_2\); gas within the solvent. The solvent was degassed with bubbling N\(_2\); this led to the heterocycle being successfully synthesized in 59% yield (Table 2, entry 6). The cyclization was also tested with various indoles with less success (Table 2, entries 7-10). Using benzyl azide for the reaction allowed for reaction conditions to be developed, but provided a truncated analogue of the natural product missing the guanidine functionality. Work is currently underway to identify more general cyclization conditions and to construct the azide needed to synthesize the full analogue.

### Table 2. Optimization of the cycloaddition reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Benzyl Azide equiv.</th>
<th>Sodium Ascorbate equiv.</th>
<th>CuSO(_4) equiv.</th>
<th>Temp</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1.1</td>
<td>0.45</td>
<td>0.15</td>
<td>RT</td>
<td>------</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>2.2</td>
<td>0.9</td>
<td>0.3</td>
<td>60°C</td>
<td>31%</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>2.2</td>
<td>0.9</td>
<td>0.3</td>
<td>60°C</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>2.2</td>
<td>0.9</td>
<td>0.3</td>
<td>60°C</td>
<td>8%</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4.4</td>
<td>1.8</td>
<td>0.6</td>
<td>80°C</td>
<td>28%</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>1.1</td>
<td>0.45</td>
<td>0.15</td>
<td>RT</td>
<td>59%</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>2.2</td>
<td>0.9</td>
<td>0.3</td>
<td>60°C</td>
<td>8%</td>
</tr>
<tr>
<td>8</td>
<td>6-bromo</td>
<td>1.1</td>
<td>0.45</td>
<td>0.15</td>
<td>RT</td>
<td>17%</td>
</tr>
<tr>
<td>9</td>
<td>7-methyl</td>
<td>1.1</td>
<td>0.45</td>
<td>0.15</td>
<td>RT</td>
<td>25%</td>
</tr>
<tr>
<td>10</td>
<td>2-methyl</td>
<td>1.1</td>
<td>0.45</td>
<td>0.15</td>
<td>RT</td>
<td>14%</td>
</tr>
</tbody>
</table>
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Notes and References

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