A Fisher Indole Synthesis Approach to Phidianidine Analogues

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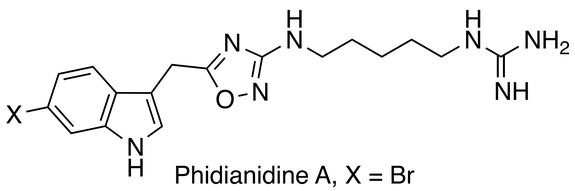
Introduction

Phidianidines A & B are natural products which are isolated from a shell-less mollusk, *Phidiana militaris*. These molecules are comprised of a 1,2,4-oxadiazole ring flanked by an indole ring and an aminoalkylguanadio group.



Phidianidine A, X = Br
Phidianidine B, X = H

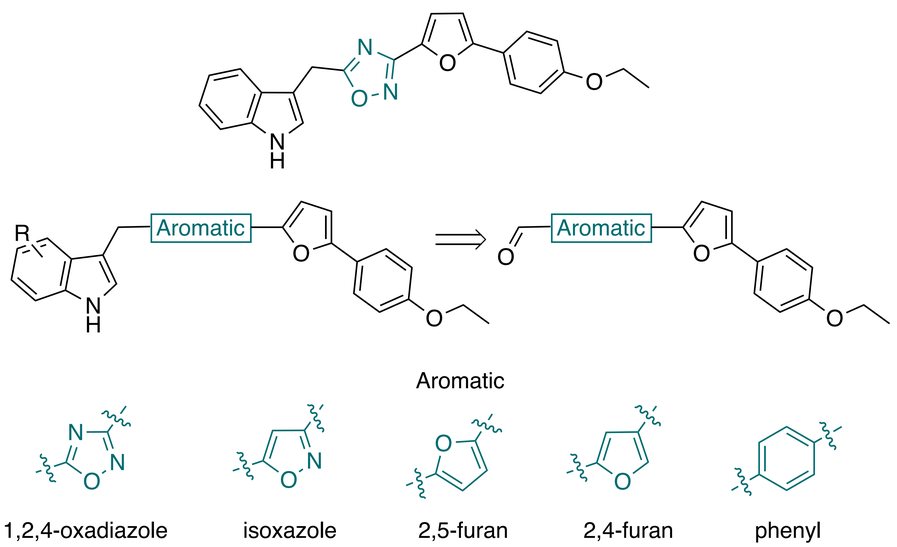
Researchers were originally drawn to the compound for its similarities to quisqualic acid which has been shown to have agonistic effects against group I metabotropic glutamate receptors. The similarities between these compounds are mainly due to the structure of the 1,2,4-oxadiazole ring, as these two compounds are one of the few known compounds to naturally produce these rings.

Despite their structural similarities, upon testing, phidianidines compounds have exhibited striking pharmacological behavior such as neutralizing reactive oxygen species and acting as an agonist for the μ-opioid receptor. The μ-opioid receptor regulates the body's response to pain stimulus and is known to bind strong pain-relieving compounds like hydrocodone, codeine, and illegal substances like heroin.

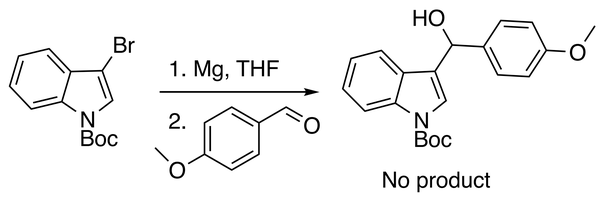
It has been shown that when the phidianidine indole is brominated it has significantly more biological activity than if the indole is hydrogenated. This relationship, while naturally occurring, raises the question: "Could different substitutions cause a more active phiainidine, thus allowing the compound to have either a smaller dosage or be a more effective treatment?"

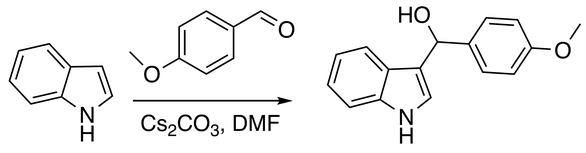
The purpose of this research is to develop a synthetic route that allows for substitutions on the indole ring and the central aromatic ring. Specifically, the focus is on a route using Fischer Indole synthesis methodology. This approach will allow us to make compounds with variations around the indole ring that will then be tested to determine their biological activity.

Proposed Research



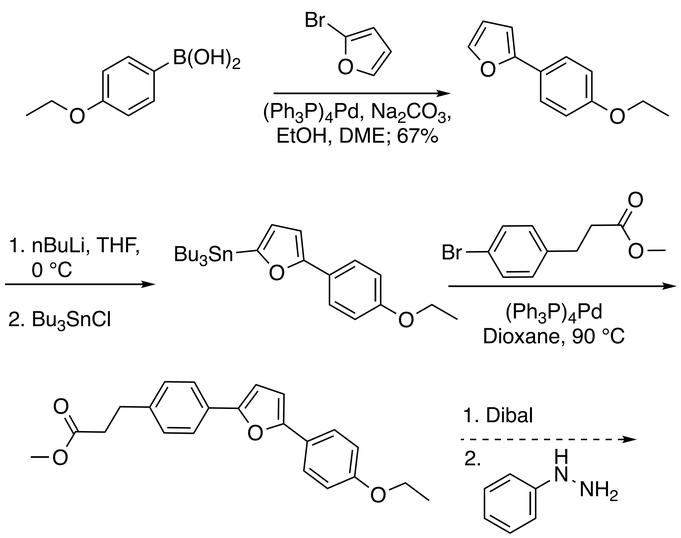
Addition to Model Aldehydes

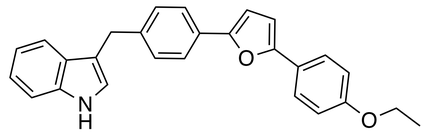




Temperature	Result
Room Temperature	No Alcohol
100 °C	Alcohol by IR

Current Approach





Conclusion

The addition of indole to model aldehydes worked, but created a product that could not be successfully reduced to the goal molecule. In the future, we hope to use the Fisher Indole synthesis approach to avoid this issue and to synthesize phidianidine analogs that vary the substituents of indoles to determine the impact on biological activity.

Acknowledgements

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