Synthesis of Novel Temozolomide-Fatty Acid Imide Hybrid Compounds for the Chemotherapeutic Treatment of Glioblastoma Multiforme

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Abstract

Glioblastoma multiforme is an aggressive form of brain cancer that originates from glial cells, which make up the supportive tissue surrounding neurons. Temozolomide (TMZ) is the current chemotherapeutic drug administered to treat glioblastoma as it works to inhibit the growth of the cancer cells. This research study focuses on developing a method for synthesizing novel hybrid compounds that combines TMZ with various fatty acids known to have anticancer properties, forming a series of imide compounds with potential chemotherapeutic effects. Once the novel hybrid compounds are successfully synthesized, they will be tested for their anticancer properties on glioblastoma cells.

Introduction

Several studies have focused on developing more potent chemotherapeutic drugs from novel hybrid compounds to treat glioblastoma. The aim for this project is to successfully synthesize potential chemotherapeutic drugs known as novel temozolomide-fatty acid imide hybrid compounds. Temozolomide (TMZ) is currently being used in chemotherapy, along with radiation, to treat glioblastoma. However, glioblastoma cells have developed a resistance to TMZ. Combining TMZ with other compounds known to have anticancer properties is hypothesized to overcome this resistance. An experiment done by Maor *et al.* (2018) tested the effect of physically combining TMZ with various fatty acids, which have been studied previously for anticancer activity. TMZ and fatty acids were found to have antagonistic effects toward each other, inhibiting their respective anticancer properties. Chemically combining the two compounds may produce different results and have some cooperative anticancer effect on glioblastoma cells. In addition to the individual anticancer properties of TMZ and fatty acids, the formation of the novel hybrid compound will produce an imide, which is a functional group known to have a variety of biological properties, including anticancer activity, and may also contribute to the efficacy of the compounds.

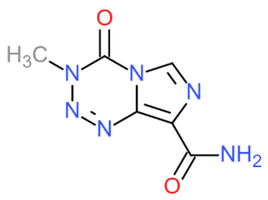

Figure 1. Structure of Temozolomide

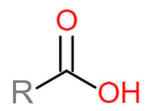

Figure 2. General Structure of Fatty Acids

Methodology

A method for synthesizing an imide from a primary amide must be developed first to ensure that the reaction combining TMZ with a fatty acid will be successful. The current method being tested uses 4-methoxybenzamide (primary amide) and valeryl chloride (fatty acid chain). The method is essentially organized into three steps:

1) Reaction
2) Isolation/Purification
3) Analysis/Identification

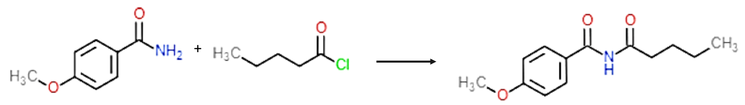

Figure 3. Reaction between 4-methoxybenzamide (left) and valeryl chloride (middle) to form a novel imide hybrid compound (right).

Once a method is developed, TMZ will be combined with various fatty acid chains to produce a series of novel hybrid compounds that can be tested on glioblastoma cells.

Results

A total of eight products have been synthesized so far. Based on the NMR results in Figure 4, the desired product is present, however it is not pure. It is possible that there may still be some of the starting materials (4-methoxybenzamide and valeryl chloride) that did not undergo the reaction.

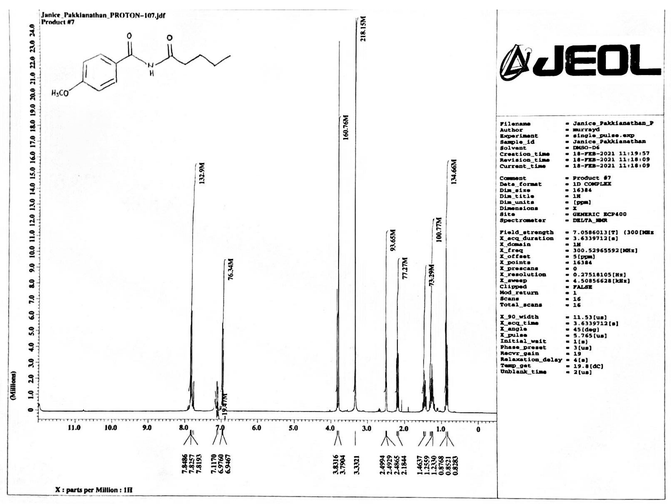

Figure 4. NMR spectrum results for Product #7

Conclusion

Although there are no compounds that have been successfully synthesized yet, we still have a contribution to the development of a method for imide synthesis from a primary amide. There are elements in the tested methods that have shown promise and others that have not. Scientists can use the information in future research to consider what may or may not work well in their own experiments.

Future Work

- Optimize methodology for producing an imide from a primary amide.
- Synthesize the novel Temozolomide-fatty acid imide hybrid compounds.
- Test compounds on glioblastoma cells.

Literature Cited

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