

Inhibition of Fatty Acid Synthase for Prostate Cancer

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Purpose

To synthesize new FAS TE inhibitors in the hope that they would be an effective new treatment for prostate cancer.

Background

All cells in the body rely on fatty acids to control necessary cellular functions such as blood pressure, immune response, and blood clotting. Normal cells use the fatty acids found in food consumed by the body, however cancer cells are entirely dependent upon fatty acid biosynthesis to grow. As a result of this dependence, fatty acid synthase (FAS, the enzyme responsible for fatty acid biosynthesis) is overexpressed in cancer cells. If FAS is prevented from signaling fatty acid biosynthesis by inhibition, then cancer cells undergo apoptosis. Orlistat, an over the counter weight loss drug, is the only known inhibitor of the thioesterase domain of FAS (FAS TE). When injected into mice, orlistat has potent anti-cancer effects in a model of prostate cancer. However, orlistat is not absorbed orally, so novel FAS TE inhibitors are of great interest as new treatments for prostate cancer.

Research Design

24 different analogs of fatty acid chains were made in order to find an optimal FAS TE inhibitor. The focus was on creating fatty acid chains with differing heterocyclic rings and chain lengths as summarized in Figure 1. The heterocyclic rings increase electrophilicity of the ketone functional group, which will then undergo attack by the active site serine residue of FAS TE, thereby reversibly inhibiting the enzyme. Chains with fewer carbons are shorter and tend to not bind as well to the enzyme, while chains with more carbons are longer and bind better. The synthesis of inhibitors with unsaturated and saturated fatty acid chains was also involved. Double bonds in unsaturated fatty acid chains are prospectively better for binding to FAS because the double bonds restrict the rotation of the fatty acid chains.

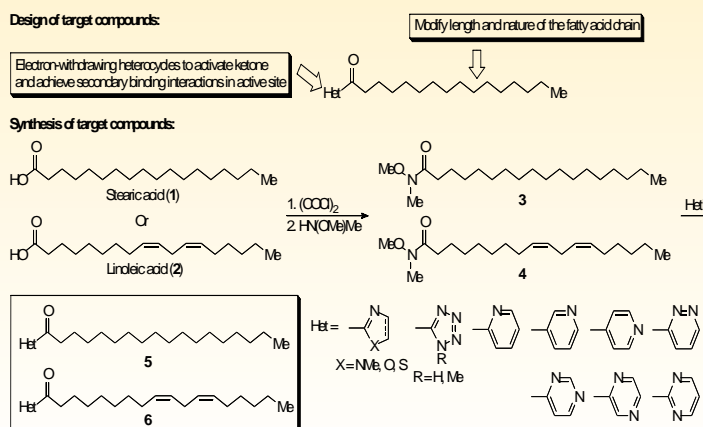
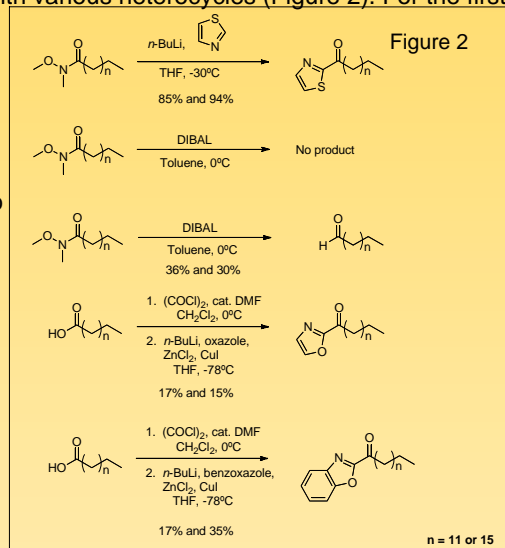


Figure 1. Design and synthesis of fatty acid synthase thioesterase (FAS TE) inhibitors.

Method

The fatty acid derivatives that I worked on were stearic acid and myristic acid. For each of the reactions, Weinreb amides of the derivatives were needed, which are easily made by converting the carboxylic acid of the long chain to the Weinreb amide. The Weinreb amides of these acids were already completed when I arrived in the laboratory, so I focused on the reactions of the Weinreb amides with various heterocycles (Figure 2). For the first reaction, *n*-Butyllithium and thiazole were reacted with the myristic acid and stearic acid Weinreb amides to produce a myristic and stearic chain with a thiazole ending. The second reaction was a reduction reaction using the common reducing reagent diisobutylaluminum hydride (DIBAL) with the myristic acid and stearic acid Weinreb amides.



The reaction did not work at the temperature it was set at, so it was repeated as the third reaction at -78°C to produce an aldehyde of the myristic and stearic acids. In the fourth reaction, the carboxylic myristic and stearic acids were reacted with dimethylformamide (DMF) and oxalyl chloride to form the acid chlorides. *n*-Butyllithium, oxazole, a solution of zinc chloride, and a solution of copper iodide were then added to produce a myristic and stearic chain with an oxazole ending. The fifth reaction was the same as the fourth, except benzoxazole was used instead of oxazole to produce a myristic and stearic chain with an oxazole ending.

Yield

For the first reaction the yield of the myristic acid reaction was 85%, and the yield of the stearic acid reaction was 94%. The second reaction yielded no product, but when set at a different temperature, the third reaction yielded 36% of the myristic acid reaction and 30% of the stearic acid reaction. The yield of the fourth reaction was 17% for the myristic acid reaction, and 15% for the stearic acid reaction. For the fifth reaction, the yield of the myristic acid reaction was 17%, and the yield of the stearic acid reaction was 35%.

Conclusion

Several potential FAS TE inhibitors have been synthesized and are currently being tested for inhibition of FAS TE and cytotoxicity against prostate cancer cells

Acknowledgment

The research was funded by a grant from the Undergraduate Research Opportunity Program.



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