The Synthesis of Potential Anti-Fungal Compounds

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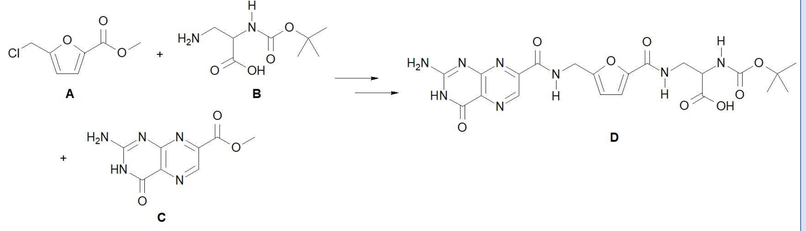
Abstract

Fungal infections are very common throughout the world, but there is a lack of effective anti-fungal drugs. Potential anti-fungal drugs (e.g., D) are being developed to inhibit Methionine Synthase; an enzyme responsible for making the essential amino acid methionine. Previous investigations have shown that compounds containing the Pterin group demonstrated potential anti-fungal activity; however, it is challenging to synthesize these compounds because of low solubility and low overall yield. To combat these issues, work is being conducted on adding the Pterin group at the end of the synthesis thereby bypassing the low solubility issue and improving the yield. So far, the Boc Amine group (B) has been added to the starting material (A). Work is being done now in scaling up the (AB) reaction and eventually adding the Pterin group (C).



Background

Even though fungal infections are a common health risk, there is a lack of effective drugs in the world to treat them. As the fungi mutates and becomes more resistant against existing drugs, the desire for new and effective anti-fungal drugs is high. Dr. Pruet's research group is investigating new compounds that inhibit Methionine Synthase (MetSyn), which is an enzyme that converts homocysteine in methionine using a substituted folate molecule.

The structure of fungal MetSyn contains two adjacent active sites, but in the human form the active sites are far apart. It is therefore possible to design a synthetic compound that will bind to the fungi MetSyn and not the human MetSyn (Figure 1).

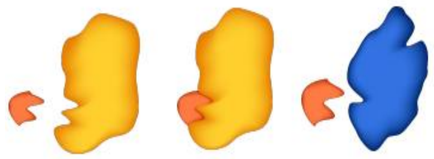


Figure 1. The orange MetSyn is the fungi form, and the blue is the human form.

Dr. Pruet and his research group examined several potential anti-fugal compounds containing a Pterin group; however, it proved difficult to make in the original synthetic route because of the Pterin group's low solubility and the route's low yield. This posed a question of whether it would be easier to add the Pterin group in the last step of the synthesis and therefore avoid the low solubility issue and improve the yield.

Results and Discussions

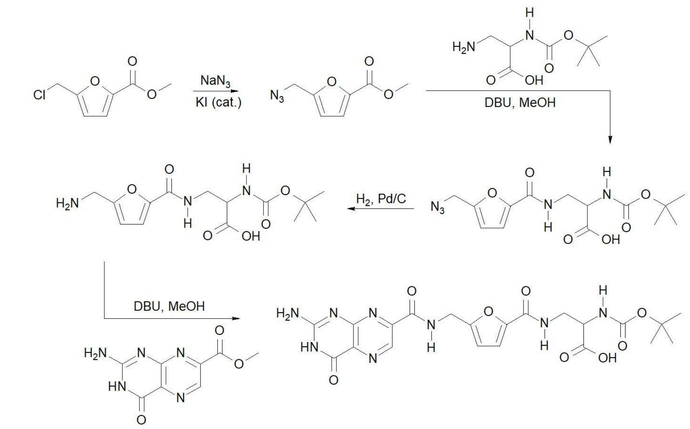


Figure 2. New proposed synthetic route of a potential anti-fungal compound. In this route the Boc Amine is added in the second step and the Pterin group is added in the fourth step.

The first step of this new proposed synthesis proved to be an easy and affective reaction. Problems arose in the second step (DBU amidation) of the synthesis due to formation of multiple products which lowered the yield and made isolation of the desired product more difficult. Many different reaction conditions and solvents were tried, but multiple products were formed (the multiple peaks present in top spectrum in Figure 3).

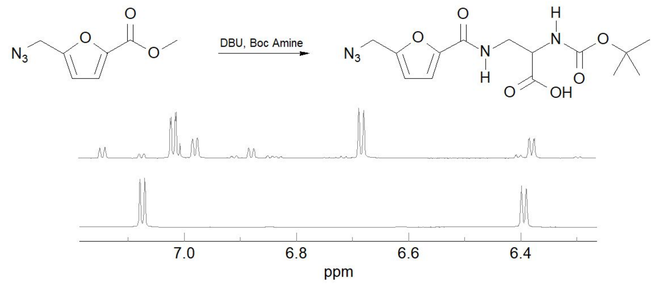


Figure 3. ^{1}H NMR of failed DBU amidation. The bottom spectrum is of starting material and the top spectrum is of the products.

The DBU amidation was proving to be nonviable so it was decided to try a different synthetic route to get to the Boc Amine amidation product. The new route proceeds through an acyl chloride intermediate product which is much more reactive than the original ester. This should make the amidation step occur in better yield.

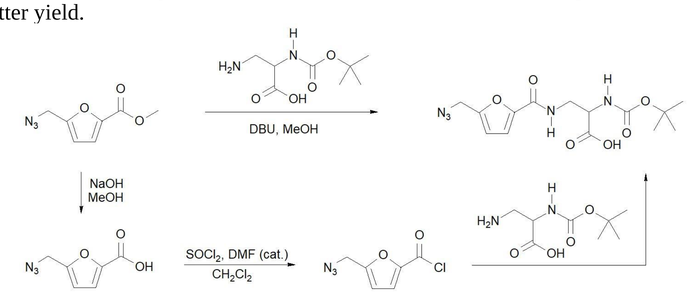


Figure 4. Top step is the original synthetic route, and the bottom three steps are the new synthetic route. Every other step in the synthesis is remaining the same.

Via ^{1}H NMR it was determined that the amidation step from the acid chloride produced two products. They were separated via column chromatography and the minor product came off first in less polar solvents. This minor product was the carboxylic acid derivative. The minor product formed because of small amounts of water was getting into the reaction even though the solvents/reagents had previously been dried over molecular sieves, the glassware was dried in an oven prior to use, and the reaction was performed under nitrogen.

The second product to come off in more polar solvents was the desired amidation product. The product's structure was confirmed by ^{1}H NMR (Figure 5). In the 6.4-7.4 ppm range there is only one set of peaks indicating the other byproducts were successfully removed.

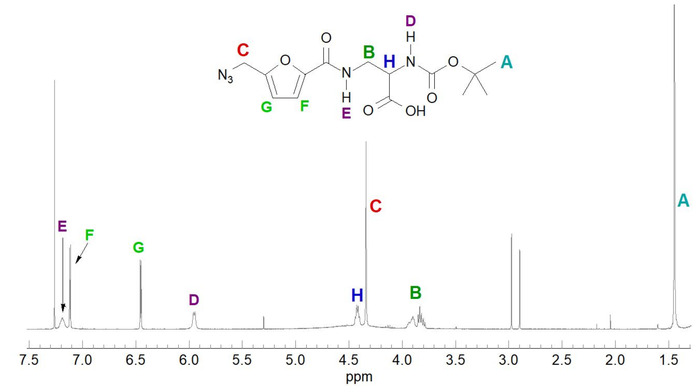


Figure 5. ^{1}H NMR spectra of the pure Boc Amine amidation product

When the amidation step was scaled up the carboxylic acid derivative formed instead of the desired amidation product. This result indicated too much water was getting into the reaction. To solve the water issue, the solvents/reagents were dried more thoroughly (distillation, in some cases from CaH_2). This method of drying the reagents was affective and the amidation product was formed in better yields.

Future Work

- Scale up the amidation step
- Continue with the synthesis
- Find an alternative intermediate that is less susceptible to water

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