Synthesis of Agonist AR437735 and Inverse Agonist AR437948 and Assessment of their Bioactivity to GPR119 for Treatment of Type II Diabetes

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Abstract

Type II Diabetes is one of the leading causes of death in the United States and is categorized by high blood glucose levels, insulin deficiencies, and inhibition.[1] Located in the pancreas and intestine, there is a receptor called G-Protein Receptor 119 (GPR119) that was noted for having an important effect on insulin secretion.[2] Previous studies found that when the receptor is activated, insulin secretion was upregulated which is vital for type II diabetes treatment.[3] It has been reported that compound AR437735 is a GPR119 agonist and its counterpart, AR437948, acts as a possible inverse agonist. After synthesizing these two compounds, their bioactivities to the receptor will be tested and observed to determine how their binding effects the two leucine residues on the receptor.[5] According to Dr. Kotsikorou's research group, the alterations to the GPR119 caused by the binding of the agonist and inverse agonist should affect the ligands on the receptor which in turn affects the drug bindings, and to confirm this the synthesized compounds were sent to another research lab to test its bioactivity. The synthesis of AR437735 was confirmed with an overall 93% yield and 97% purity and its counterpart AR437948 is currently in progress. All compounds synthesized in this project are to be characterized by nuclear magnetic resonance (NMR) proton spectroscopy and submitted to Dr. Dean's research group for bioactivity testing.

Introduction

Figure 1: Dock of agonist and inverse agonist onto GPR119

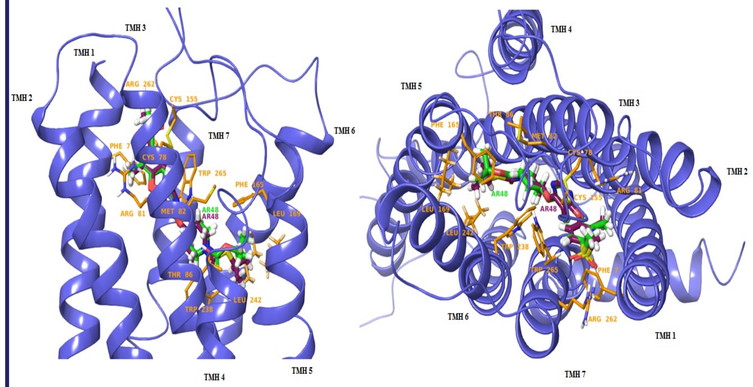
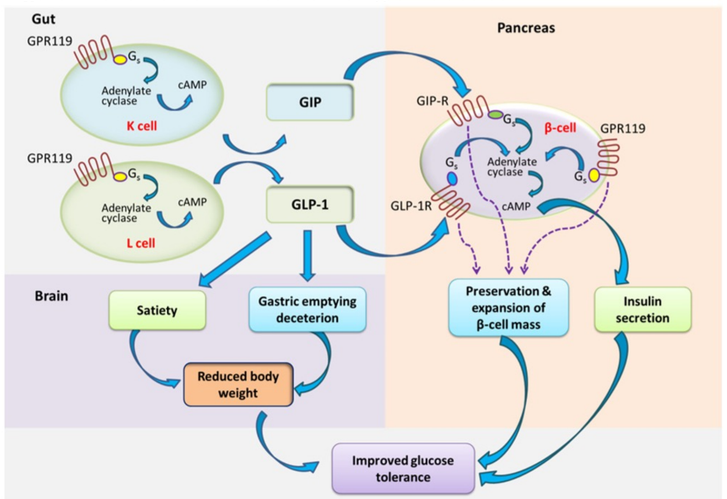
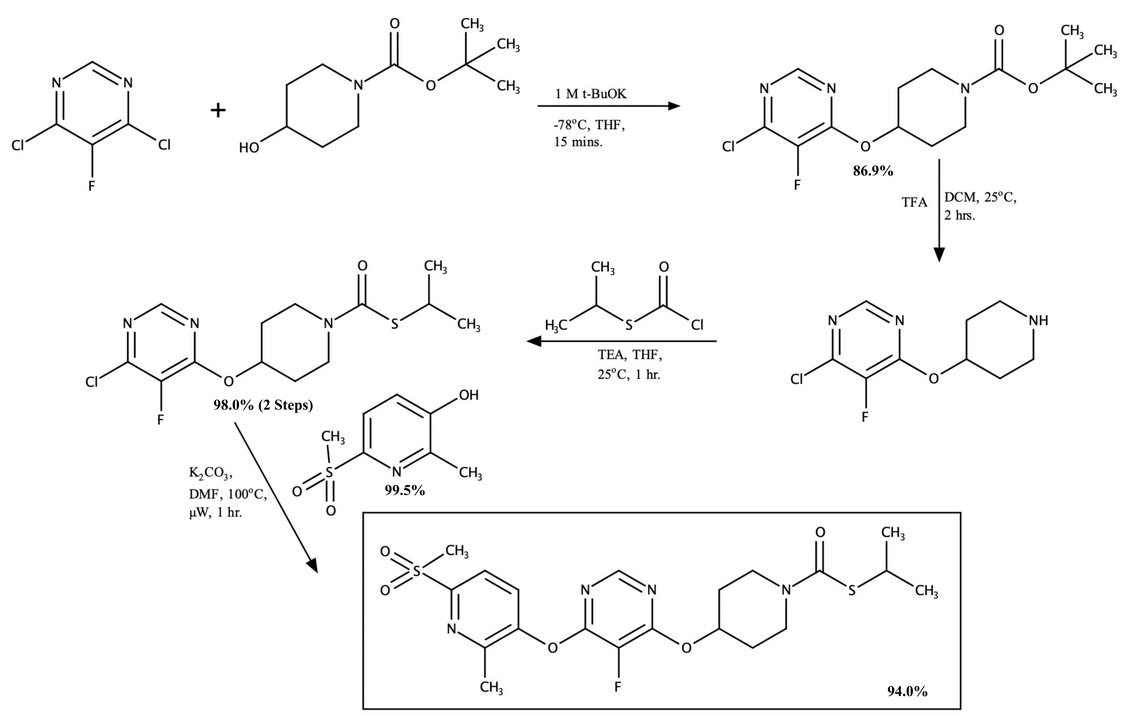


Figure 2: Overview of the treatment of type II diabetes[4]

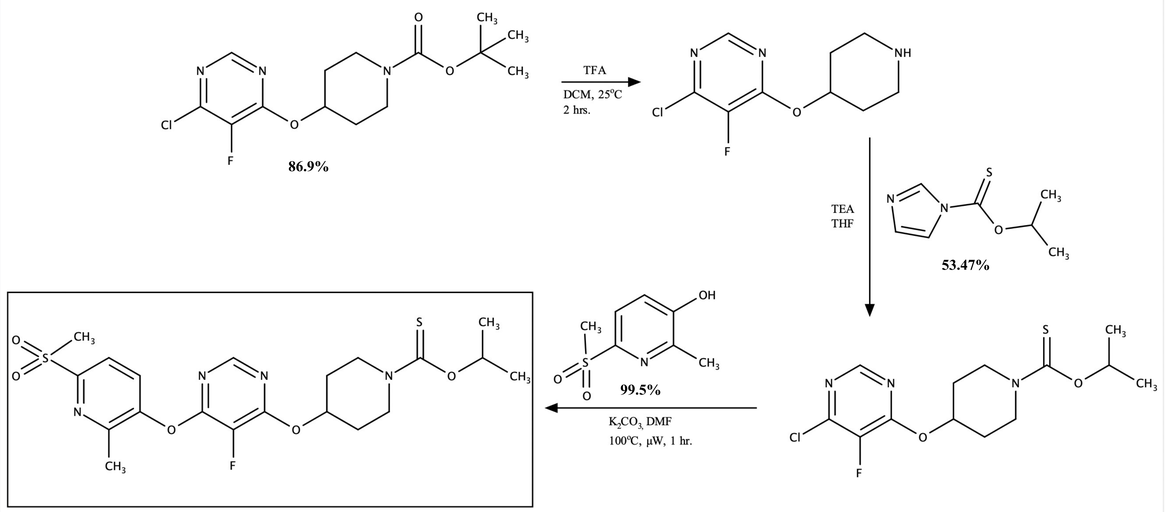


Results

Synthesis of agonist AR437735:



Synthesis of inverse agonist AR437948:



Discussion

AR437735:

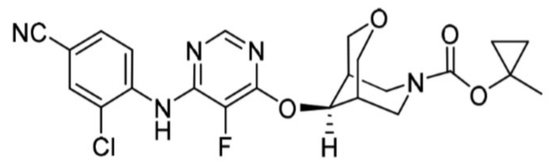
- Step one was the synthesis of tert-butyl 4-(6-chloro-5-fluoropyrimidin-4-yloxy)piperidine-1-carboxylate.
- Step two is a deprotection of N-BOC. The deprotection will prepare the compound for the addition of S-isopropyl chlorothioformate.
- The deprotection of N-Boc was initially difficult due to the use of 4N HCl in Dioxane. The acid was later replaced with TFA for deprotection.
- Synthesis of agonist AR437735 was achieved with an overall 79.2%.
- The purity of title compound AR437735 was 97%.
- Synthesis of inverse agonist is similar to agonist synthesis. Both procedures follow the exact same step, but use different compounds as an attachment for the right side of the structure.

AR437948:

- For the second step in synthesizing AR437948, propanol and 1,1—carbonyl diimidazole was replaced with isopropanol and 1,1'-thiocarbonyldiimidazole to form the attachment.
- Both title compounds require the synthesis of the sulfonyl pyridine compound.
- According to theoretical calculations, hydrogen bond acceptor groups on both terminals of both compounds are critical for ligand binding at the GPR119 receptor.
- The conversion of the sulfonyl substituent on the pyridine ring to smaller hydrogen bond accepting substituent should yield greater efficiency.
- All compounds were characterized using NMR.

Future Work

- Synthesis of inverse agonist title compound and modification of pharmacophore to identify structural activities and binding relationship between analogs of AR234153 and GPR119



AR234153

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References

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