Chemical Synthesis of Astatine Labelled ASCT2 Inhibitor Analogue (HA01) as a Radiotherapeutic Agent for Theranostics

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Background

Glutamine is an amino acid that is utilized by cancer cells as a source of energy to replicate and spread. It is the most abundant amino acid in plasma. Glutamine is able to enter the cells through the amino acid transporter ASCT2 (Neutral amino acid transporter B(0)). V-9302 is a known competitive inhibitor of ASCT2 and is capable of killing cancer cells *in vitro* and *in vivo.* However, there have been limitations to the usage of V-9302 due to toxicity *in vivo* and its modest potency.

While there are many possibilities to enhance its efficacy such as substitution with larger π-electron rich aromatics or optimizing its pharmacophore, we chose to explore the possibility of creating a radiotherapeutic drug.

Recent studies have found that alpha emitting radiotherapies have proven to have promising results in clinical settings. Astatine-211 (^{211}At) being an alpha particle emitter of interest. This leads us to an interest in an ^{211}At labeled ASCT2 inhibitor analogue.

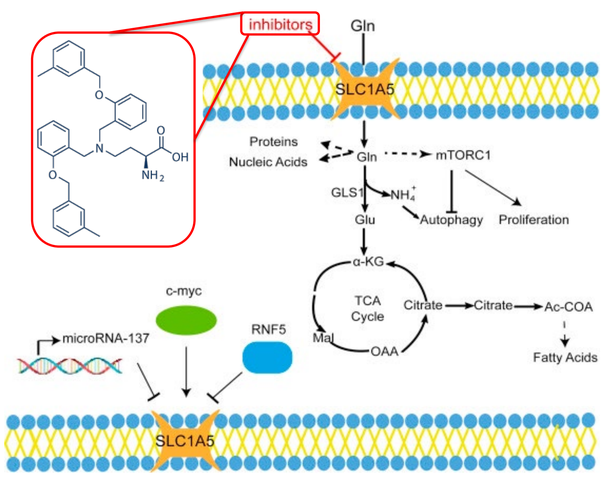


Figure 1. Inhibition of ASCT2 (encoded by SLC1A5 gene) by V-9302.[1]

Objective

Synthesize a V-9302 analogue with equal or greater affinity towards ASCT2 than V-9302 that can be used for radiolabeling with ^{211}At for radiotherapy *in vivo*.

Methods

The analogue was synthesized using standard organic synthetic procedures (ether synthesis, reductive amination, “click”-reaction and deprotection). The intermediates were isolated by normal phase silica column (10-50% Ethyl acetate in hexane gradient) and the final products were purified by reverse phase (C-18) HPLC (10-95% acetonitrile in water gradient over 35 min).

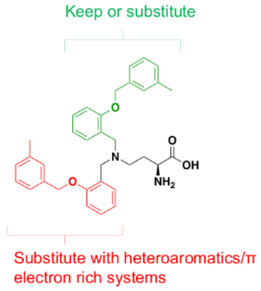
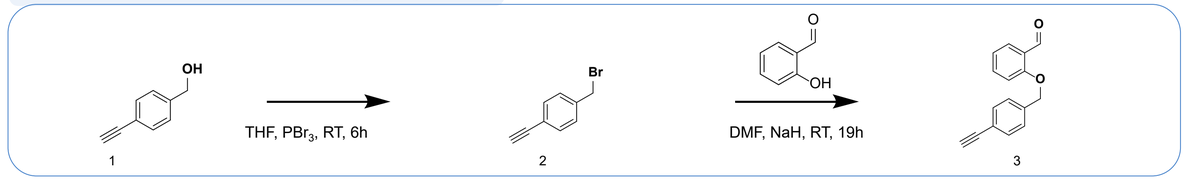


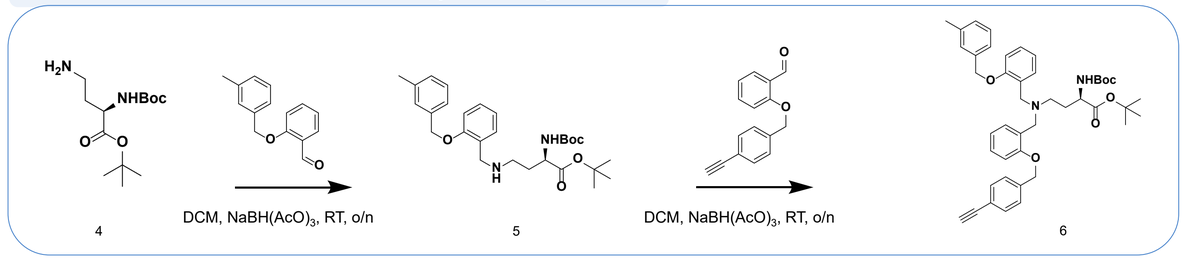
Figure 2. Possibilities for changes and substitutions in V-9302.

Results

PHASE ONE – Sidechain synthesis



PHASE TWO – Condensation with pharmacophore



PHASE THREE – Conjugation with radionuclide binding ligand

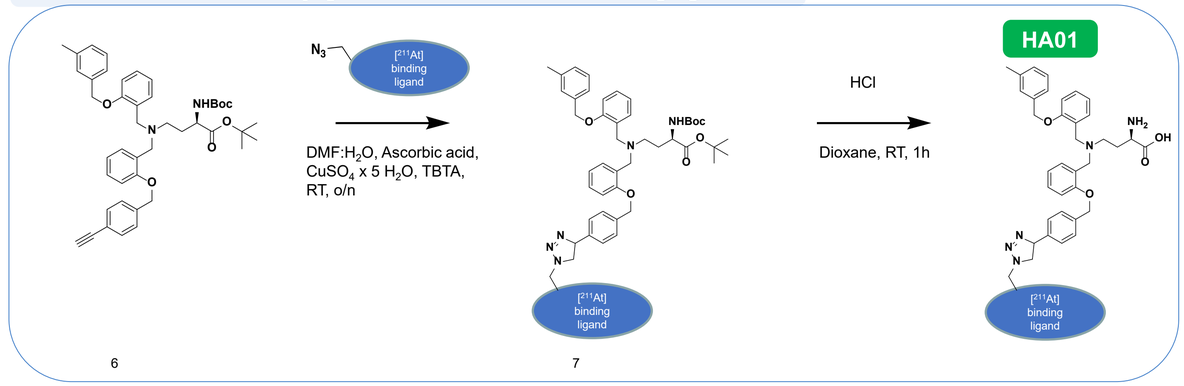


Figure 3. Synthesis of V-9302 analogue, HA01 ligand.

Conclusions

We successfully synthesized HA01 in six steps. HA01’s efficacy as an ASCT2 inhibitor must now be tested through a DARTS (Drug affinity responsive target stability) assay. Assuming this assay is successful - meaning the analogue properly binds to ASCT2 - HA01 will be radiolabeled with an astatine ion to be used for radiotherapy. To prepare for this, an astatine ion will be attached to the location marked by the blue circle below and then tested in a mouse model.

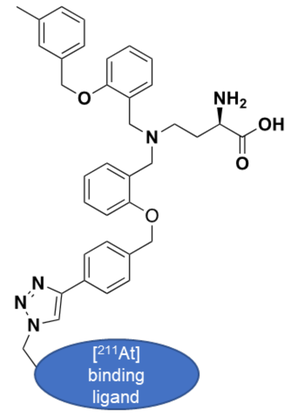


Figure 4. HA01 ligand. Blue ellipses represents astatine binding site.

References

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