JURA
Journal of Undergraduate Research in Alberta
UNIVERSITY OF CALGARY

THE SYNTHESIS OF ABIRATERONE O- β-D GLUCURONIDE FOR USE IN CLINICAL TRIALS AS A REFERENCE STANDARD

Mohit Vohra
Sussex Research Laboratories, Ottawa Ontario
mvohra@ucalgary.ca

INTRODUCTION

Abiraterone is an active pharmaceutical ingredient (API) that is used for the treatment of hormone-resistant prostate cancers [1]. Due to the action of the human xenobiotic metabolism, Abiraterone undergoes various chemical modifications to form the phase II metabolite, Abiraterone-O- β-D- glucuronide [2]. This process occurs due to the highly soluble nature of glucuronides and their ability to act as effective agents in drug excretion. As a consequence, Abiraterone-O- β-D- glucuronide normally presents itself in urine and is thus essential for toxicological testing and an analysis of the pharmacological activity of Abiraterone [2]. However, in order to confirm the identity of Abiraterone-O- β-D- glucuronide and quantify the amount metabolised within the body via liquid chromatography-mass spectrophotometry (LC-MS) based assays and nuclear magnetic resonance (NMR) requires a reference standard that completely resembles the native form of the metabolite.

METHODS

The first step entails the protection of the hydroxyl moieties on a methyl glucuronate molecule via pivaloyl chloride. This is followed by the selective deprotection of the C1 hydroxyl group and the addition of an imidate moiety to form and activate a glucuronyl donor. The next stage involves the coupling of this glucuronyl donor with Abiraterone in the presence of boron trifluoride etherate to synthesize the final intermediate. Abiraterone-O- β-D- glucuronide is produced via deprotection of the remaining hydroxyl groups in tetrabutylammonium hydroxide. The final product is isolated through column chromatography.

RESULTS

A total of 137mg of Abiraterone-O- β-D- glucuronide was produced which corresponds to an overall yield of 26%. LC-MS analysis as shown in Figure 1 reveals a final purity of >98%. NMR results were consistent with the structure of the final compound.

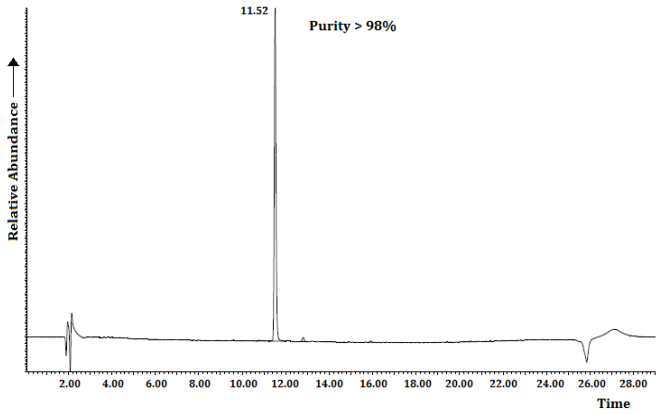

Figure 1. Liquid chromatography-mass spectrophotometry (LCMS) analysis of the Abiraterone-O- β-D- glucuronide. The graphs y-axis denotes relative abundance and the x-axis denotes retention time. The graph shows a single distinct peak representing the final compound with no intruding impurity peaks. Overall, the final compounds purity is >98%.

DISCUSSION AND CONCLUSIONS

This research shows that pure synthetic Abiraterone-O- β-D- glucuronide can be successfully synthesized and used as a reference standard for clinical trials.

REFERENCES

1. De Bono JS, et al. *N Engl J Med*. **364**(21):1995–2005, 2011.

2. Atzrodt J, et al. *ARKIVOC*. **2012**(3):257–78, 2012.