

## THE SYNTHESIS OF ABIRATERONE O- $\beta$ -D GLUCURONIDE FOR USE IN CLINICAL TRIALS AS A REFERENCE STANDARD

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### INTRODUCTION

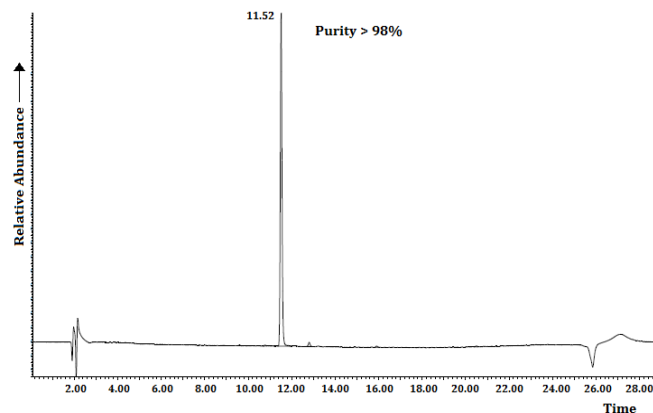
Abiraterone is an active pharmaceutical ingredient (API) that is used for the treatment of hormone-resistant prostate cancers [1]. Due to the action of the human xenobiotic metabolism, Abiraterone undergoes various chemical modifications to form the phase II metabolite, Abiraterone-O-  $\beta$ -D- glucuronide [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-  $\beta$ -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-  $\beta$ -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-  $\beta$ -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-  $\beta$ -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-  $\beta$ -D- glucuronide. The graph's 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 compound's purity is >98%.

### DISCUSSION AND CONCLUSIONS

This research shows that pure synthetic Abiraterone-O-  $\beta$ -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.