THE SYNTHESIS OF ABIRATERONE O-β-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-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.

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