Determining the Absolute Configuration of the alpha-Carbon in JNJ-A (a GPR40 Superagonist) by NMR Spectroscopy

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GPR40 is an emerging target for Type II Diabetes (T2D) therapeutics, representing a unique mechanism of action for treatment of this disease. It is a G-protein-coupled receptor that mediates both fatty acid-induced glucose-stimulated insulin secretion from pancreatic beta cells and incretin release from enteroendocrine cells of the small intestine.

A GPR40 superagonist (JNJ-A) was recently discovered at Janssen.[1] The carboxylic acid headgroup common to most synthetic GPR40 agonists may cause idiosyncratic toxicities, including drug-induced-liver-injury (DILI). With a methyl group and a fluorine atom substituted at the α-C of the carboxylic acid group, this compound is not only highly efficacious in lowering glucose and body weight in rodent models of T2D but also has a low DILI risk due to its stable acyl glucuronide metabolite. However, the epimer, JNJ-B, was about 30-fold less potent in the *in vitro* assays.

Synthesis yielded a racemic mixture, after which JNJ-A and JNJ-B were separated by chiral HPLC. The objective of the present work is to determine the absolute configuration of the alpha-carbon, given the definitive *S*-configuration of the beta-carbon.

Single-crystal X-ray diffraction remains the gold standard for determination of the absolute configuration of a molecule. However, obtaining high quality monocrystals is often a significant challenge. Additionally, the magnitude of the resonant scattering is usually very weak for crystals of compounds that do not contain an element heavier than oxygen. In such cases NMR spectroscopy can provide a convenient and reliable alternative to single-crystal x-ray crystallography. Computational studies may also provide insights in these challenging cases.

Reference： 1. Hui Huang, *et. al. ACS Med. Chem. Lett.*, **2019**, *10 (1)*, pp 16-21