How Glycosylation May Improve the Physicochemical Properties of Cannabinoids

Introduction

Whereas hydroxylation, methylation, fluorination etc. are in the mainstream of medicinal chemistry and ADMET thinking, attaching carbohydrates to improve molecules is considered rather more exotic or not at all (despite an abundance of examples of natural molecules that gain, alter or lose activity by glycosylation or de-glycosylation).

Even if this is considered, glycoside chemistry is difficult. Chemical glycosylation is not in itself straightforward, and since many interesting molecules have more than one or even many side groups (-OH, -COOH, -NH, -SH) which may be glycosylated, all the other groups but the one in question need to be chemically blocked, a very tedious process.

Using small molecule glycosyltransferase enzymes almost any given molecule (with appropriate side groups) can be glycosylated, most often regio-specifically (thus abolishing the need for side group blocking), in many cases even stereo-specifically and, if needed, with a number of different sugars (glucose, galactose, xylose, glucuronic acid, rhamnose etc.).

Cannabinoid glycosides: In vitro production of a new class of cannabinoids with improved physicochemical properties
Janee' M. Hardman, Robert T. Brooke, Brandon J. Zipp
bioRxiv 104349; doi: https://doi.org/10.1101/104349

Hydroxylation and glycosylation of Δ9-tetrahydrocannabinol by *Catharanthus roseus* cell suspension culture, Biocatalysis and Biotransformation
Muhammad Tayyab Akhtar, NAtali Rianika Mustafa & Robert Verpoorte (2015) , 33:5-6, 279-286, DOI: 10.3109/10242422.2016.1151006

Cannabinoids

So-called "cannabinoid" molecules are now being pursued as new treatment options in diverse medical fields such as neurology, gastroenterology, pain management, and oncology.

However, cannabinoids as they come from the *Cannabis sativa* plant are extremely hydrophobic (hard to dissolve in water) and therefore they have bad ADME properties. Further, they are generally unstable molecules, making the formulation design limited in scope.

Hardman J. et al. recently demonstrated that the UGT76G1 enzyme from *Stevia rebaudiana* has strong glucosyltransferase activity towards a broad range of phytocannabinoids, e.g. cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ 9-THC), as well as some human endocannabinoids. Additionally, Os03g0702000p, a glycosyltransferase from *Oryza sativa*, was able to transfer secondary glucose residues onto cannabinoid monoglycosides previously established by UGT76G1. This new class of cannabinoid-glycosides has been named as "cannabosides". Of particular interest, the addition of one glucose decreased the Δ9-THC ClogP value from 7.2 to 5.7, and the addition of the second further reduced ClogP to 4.3. Apart from the improved water solubility, glycosylated molecule have shown modified distribution and pharmacokinetic properties as well as the ability to be used as prodrugs. In general, cannabosides have the potential to enable administration of cannabinoids via the well-tolerated oral administration.

In a different type of study **Akhtar M et al.** showed that Δ9-THC can be converted into a more polar derivative by culturing it in a *Catharanthus roseus* cell suspension. The Δ9-THC molecule was rapidly absorbed by the *C. roseus* cells and bio-transformed into a new glycosylated derivative. The authors conclude that cultured *C. roseus* cells have the potential for large scale production of novel, improved cannabinoids.

The Gly-It glycosylation platform contains enzymes from a vast and very biodiverse spectrum of natural sources, and therefore has the potential to excel in this space.

What is the Gly-it platform?

The Gly-it platform is a library of 380 diverse "Family 1" UDP-glucose dependent glycosyltransferase enzymes (UGTs) plus associated screening, analytical and lab scale production protocols ("Family 1" denotes glycosyltransferases that will glycosylate small molecules).

All the enzymes in Gly-it are found in plants (which have diverse UGTs to work with the diverse range of small molecules that occur in plants or their environment). The library contains enzymes from all known Family 1 UGT sub-families and sub-sub-families and from a wide set of evolutionarily diverse plants.

The majority of the enzymes will be able to add glucose to small molecule substrates with relevant functional groups. Some enzymes will work with other sugars (such as xylose, rhamnose, galactose or glucuronic acid). We can advise you on the best path for specific sugars.

We realize that this may be your first step in determining if Gly-it technology will be able to help you in your current project. We are happy to assist you in determining if Gly-It is the right fit.

To discuss, or for more help, just get in touch.
We would like to make sure Gly-it is a proper fit for your current goals.

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