GLY-KIT

Improving Small Molecules

Introduction

Whereas hydroxylation, methylation, fluorination etc. is 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 or even many "glycolysable" side groups (-OH, -COOH, -NH, -SH), 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.).

Improve Activity via Glycosylation

Doxorubicin

Mürdter *et al*. demonstrated better efficacy of the anti-cancer drug DOXORUBICIN (DOX) by attaching by glycosylation glucuronic acid (GLUC) to the molecule. Doxorubicin has serious side effects, e.g. cardiac toxicity, at certain concentrations and can therefore only be applied in concentrations not always adequate. This is the case for e.g. certain lung tumors, a problem augmented by the natural tendency of lung cancer tissue to take up less DOX than normal tissue. But the DOX-GLUC prodrug was shown to be taken up in lung cancer tissue at 7-fold increased rate, very likely due to cancer cells expressing high levels of glucuronidase that can cleave off GLUC from DOX-GLY, thus accomplishing improved localized delivery of DOX.
https://cancerres.aacrjournals.org/content/57/12/2440.short

Morphine

Frances *et al*. demonstrated that morphine-6-glucuronide is a 45-60x more potent analgesic than morphine itself in animal models. Furthermore, morphine-6-glucuronide induced a longer lasting analgesic effect compared to morphine.
https://europepmc.org/abstract/med/2154808

Glycosylation provides remarkable opportunities for improving characteristics, use and production of small molecules that are not currently being taken advantage of. River Stone has significant proprietary knowledge as well as a collection of diverse enzymes that have the potential to help our customers doing just that.

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What is Gly-Kit

The Gly-Kit 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-Kit 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 kit contains enzymes from all known Family 1 UGT sub-families and sub-sub-families and from a huge 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-Kit will be able to help you in your current project. We are happy to assist you in determining if Gly-Kit is the right fit.

To discuss your order, or for more help, just get in touch. We would like to make sure Gly-Kit is a proper fit for your current goals. Once we connect and assure Gly-kit is the right fit, we will send you pricing options. Email us directly at sales@rstbio.com

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