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Drug Designing: Open Access

ISSN: 2169-0138

Commentary

Recent Advancement in Glycorandomization

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DESCRIPTION

Glycorandomization is a drug discovery and development technological platform that uses sugars to allow for the fast diversification of bioactive small compounds, drug leads, and/or licensed medications. Originally developed as a simple method for manipulating carbohydrate substitutions of naturally occurring glycosides to yield differentially glycosylated natural product libraries, glycorandomization applications have expanded to include both small molecules (drug leads and approved drugs) and macromolecules. Glycorandomization, also known as 'glycodiversification,' has resulted in the identification of novel glycoside analogues with improved potency, selectivity, and/or ADMET relative to the parent molecule. Glycorandomization applications have expanded to include both small molecules (drug leads and approved drugs) and macromolecules [1]. It was originally developed as a simple method for manipulating carbohydrate substitutions of naturally occurring glycosides to yield differentially glycosylated natural product libraries (proteins). Glycorandomization, also known as 'glycodiversification,' has led to the discovery of new glycoside analogues with higher potency, selectivity, and/or ADMET than the original molecule.

Chemical glycosylation is the standard method for attaching sugars to natural materials, medicines, or drug leads. This traditional method often needs additional protection/deprotection steps in addition to the main anomeric activation/coupling reaction, which might result in a mixture of anomers depending on the glycosyl donor/acceptor combination. Unlike traditional chemical glycosylation, glycorandomization procedures are divergent and do not require sugar/aglycon protection/deprotection or sugar anomeric activation. Some of the glycodiversification methods include:

In-vitro glycorandomization (IVG)

Chemoenzymatic glycorandomization is a three-enzyme process that involves activating natural or unnatural sugars with promiscuous anomeric kinases and Ntfs to synthesise nucleotide diphosphosugar (NDP-sugar) libraries, then conjoining these activated sugar libraries to natural products aglycone substrates with promiscuous Gtfs. This method has several advantages over traditional glycosylation methods: it is a fast, single-pot method that is flexible and selective (region and stereo-selective coupling of sugars to natural product aglycones); because it is an enzymatic method, it can be used for *in-vivo* synthesis and thus has applications for scale production. The first platform for chemo enzymatic glycorandomization was based on a set of two highly permissive sugar activation enzymes (a sugar anomeric kinase and sugar-1-phosphate nucleotidyltransferase) that provided sugar nucleotide libraries as donors for these promiscuous glycosyltransferases, where the permissivity of the corresponding sugar kinase and nucleotide shows[2]. Enzymatic glycorandomization combines the chemical synthesis of unique sugar precursors' limitless flexibility with the endogenous or engineered substrate promiscuity of enzymes that activate (sugar kinases and nucleotidylyltransferases) and attach (glycosyltransferases) these carbohydrates to various natural product aglycones.

Neoglycorandomization

Natural products and smallmolecule-based pharmaceuticals are connected to alkoxyamine and glycosylated variably using a variety of natural and synthesised reducing sugars in neoglycorandomization. It entails the creation of a glycosidic bond between a reducing sugar library and a secondary alkoxylamine-aglycone. Neoglycorandomization is a chemo selective glycodiversification . This reaction uses an oxy-iminium intermediate to produce the closed ring neoglycoside, which is more thermodynamically advantageous. The neoglycosylation reaction is compatible with a wide range of saccharide and aglycon functionality, and the anomeric stereospecificity of neoglycosides is determined by thermodynamics. Neoglycorandomization is based on the production of "neoglycosides" through the chemoselective creation of glycosidic linkages between reducing sugars and a secondary alkoxylamine-containing aglycon. Neoglycorandomization is a versatile approach that is adaptable to a wide range of solvent conditions, aglycone/sugar diversity, alkoxyamine handling variations, and high throughput synthesis platforms. This flexibility of

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Received: 28-Apr-2022, Manuscript No. DDO-22-17726; **Editor assigned:** 02-May-2022, PreQC No. DDO-22-17726 (PQ); **Reviewed:** 16-May-2022, QC No. DDO-22-17726; **Revised:** 23-May-2022,Manuscript No. DDO-22-17726 (R); **Published:** 30-May-2022, DOI: 10.35248/ 2169-0138.22.11.212

Citation: Faust A (2022) Recent Advancement in Glycorandomization. Drug Des.11:212

neoglycorandomization, together with the capacity to insert alternative reactive handles and the tremendous combinatorial potential of carbohydrates, allows for almost limitless access to novel structurally and functionally diverse libraries. In addition, biological testing of neoglycosides and neoglycorandomized libraries revealed that this technique can improve solubility, potency, PK, PD, and efficacy, as well as change the parent compound's fundamental mode of action in some circumstances [3].

In-vivo glycorandomization

In-vivo glycorandomization consists of pathway engineering and bioconversion. It follows three steps are: A sugar library is fed to a natural product-producing host (e.g. Streptomyces) that has been engineered to produce anomeric kinase and Ntf, with the host providing aglycone and Gtf; The non-producing host (e.g., *S. lividans* or *E. coli*) is given a library of natural product aglycones and sugars to express Ntf, Gtf, and anomeric kinase; aglycones are supplied to a bacterial host that has been genetically modified to express Gtf, with endogenous NDP-sugar serving as a glycosyl donor[4].

CONCLUSION

Glycorandomization is a promising method for glycosylation of natural products for drug discovery and development. It's a flexible technique when it comes to sugar/aglycone substrates, and it can lead to the creation of vast glycorandomized libraries with a variety of sugars, reactive handles, and aglycones. Glycorandomization could also encourage natural product diversity by specific enzyme and/or chemical catalysed reactions such as alkylation, halogenation, acylation, oxidation, sulfation, and/or phosphorylation, among others.

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