SUGAR CONJUGATES OF DRUG MOLECULES

(OPPORTUNITIES & CHALLENGES)

JRF GLOBAL
Pharma Solutions

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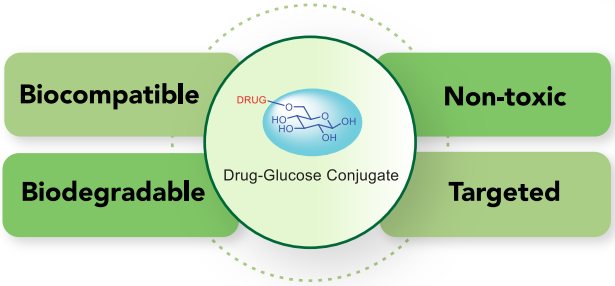
Synthetic organic chemist with 15+ years of experience that encompasses small molecule library synthesis, NCE`s, Route scouting, Process innovation & development. Extensively worked on synthesis of unknown impurities & metabolites with complete characterization. Associated with JRF for the past 2 years & 8 months leading a team of synthetic and analytical chemists.

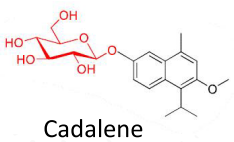


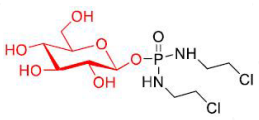
Introduction

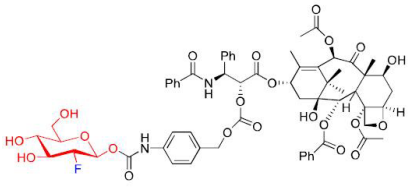
Sugar-conjugated molecules are fundamental materials of biological systems. They are involved in energy metabolism, signal transductions[1], and even work as anti-viral & bacterial. Conjugated drugs were developed with a variety of biological activities in disease treatment and diagnosis. Advantages include high solubility in water, low toxicity, and high biocompatibility providing promising leads for drug design and development.

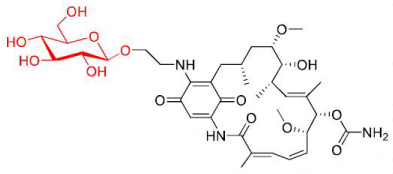
Cancer Treatment

The use of drug glucose conjugates in anti-cancer drug development has been proven to improve both selectivity and activity. Thanks to the Warburg effect!!![2]. Cancerous tissues consume large amounts of glucose compared to normal tissue and have high rates of aerobic glycolysis. This mechanism of overexpression of glucose transporters in tumour cells provides a new strategy for improving the selectivity of chemotherapy drugs by conjugating them to sugars.[3]
Over a period, various glucose conjugates have been synthesized for several therapeutic areas which were found to be showing superior activities when compared with their non-sugar drug counterpart.[4,5]


Cadalene


Glufosfamide


Paclitaxel


Geldanamycin

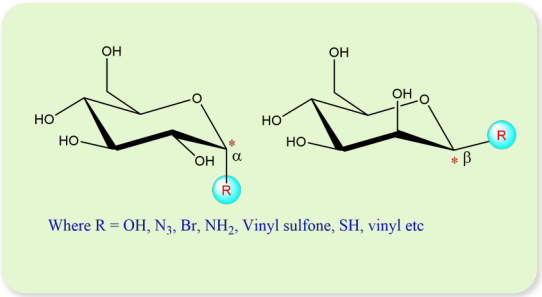
In glycose conjugation, not only D-glucose but other sugars can also be used, e.g., D-galactose, D-mannose, L-arabinose, D-ribose, or D-fucose. The type of sugar may be important which depends upon the binding modes in biochemical systems.

Synthesis

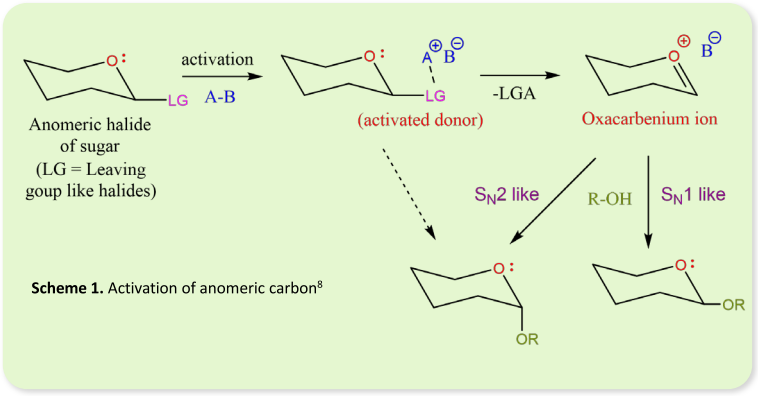
The chemical synthesis of sugar conjugate is always associated with great challenge because of,

1. The inherent regioselectivity and stereoselectivity issues
2. Lack of a general protocol to construct glycosides efficiently.
3. Reactive pre-functionalized monosaccharides are not commercially available or available at a high price.
4. Multi-step protecting/-deprotecting procedures.

There are five hydroxyl groups in D-glucose, which offer various possibilities to attach a drug molecule and the position of substitution influences the biological properties to a greater extent.[6]



Drug molecules can be conjugated preferentially to the anomeric position of sugars due to the special reactivity of the C1 hydroxy group aided by ring oxygen. The process becomes more complicated when a specific position apart from anomeric carbon is targeted. Strategies that precisely activate or protect the reactive centers are very important.[7] From the side of the drug molecule, O-glycosylation (oxygen of drug molecule) is mostly encountered, however, N, S, and C atoms in drug molecules can also undergo glycosylations.

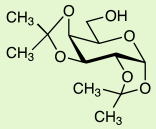


Scheme 1. Activation of anomeric carbon[8]

In general, a time-tested approach is the one using anomeric halides of sugars as donors and silver or mercury salts as promotors. While anomeric halides provide good selectivity, access to these substrates is very strenuous[7].

Innovative approaches have been developed for controlling anomeric selectivity by introducing steric or conformational constraints[9a,b]. Apart from classical ideas, new methods like Staudinger ligation, azide-alkyne cycloaddition reactions, thiol-ene reactions, metathesis reactions, Suzuki-Miyaura reactions, vinyl sulfone reactions, and vinyl sulfoxide conjugations are also reported.[10]

Commercially available, partially protected isopropylidene derivatives of sugars provide a good option for selectively targeting a specific position.[11]



1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose.

Inspiringly, enzymes promote glycosylation flawlessly in biological systems. While chemoenzymatic methods seem to be promising, enzyme availability, substrate specificity, and scalability interfere with the feasibility.

Linker based approaches using isoxazoles and isooxazoline's have received much attention in recent years. The demand for a generalized approach unlocked many avenues for exploration mostly based on a trial-and-error approach. Versatile experience in glycochemistry particularly in drug-conjugates plays a vital role in predicting the plausible approach for a given substrate.

The organic synthesis team at JRF has extensive experience in the synthesis of sugar conjugates of various drugs and metabolites. Each molecule is synthesised using a novel approach from which we gained extensive knowledge about the reactivity & selectivity patterns. A talented pool of scientists supported by advanced analytical facilities is complementary to our success.

Elected References

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