The synthesis of gliflozins

KEYWORDS: Gliflozins, diabetes 2, glucose transporters, silane reductions.

Abstract

Some of the general approaches to the key steps in the synthesis of gliflozins, a class of glucose transporters, are discussed. In particular, the glycosidation step for the introduction of the key aryl moiety onto the glucose and the reduction steps are presented.

INTRODUCTION

Gliflozins constitute a class of compounds that is useful as sodium glucose co-transporter-2 (SGLT2) inhibitors. The gliflozins have shown particular expediency in the treatment of diabetes 2. They accomplish this through blocking of sodium glucose transport proteins, which, in turn, inhibit the kidneys from resorbing glucose back into the blood stream. The excess, non-resorbed glucose is then eliminated with the urine with the net result being a dosage-regulated glucose level. It has been shown that a key feature of the gliflozins is their ability to distinguish between the inhibition of the SGLT1 transporter, a low-capacity, high-affinity transporter that is expressed in the gut, heart and kidney, and the SGLT2 transporter, a high-capacity, low-affinity transporter expressed mostly in the kidney. It is estimated that by the year 2025 nearly 400 million people will suffer from diabetes 2 (1). Due in large part to this growing population of diabetes sufferers, considerable efforts have been and continue to be taken in the gliflozin approach towards addressing the diabetes 2 affliction. A significant part of these efforts has centered on various derivatives of the gliflozin class, represented by the general structure 1. (Figure 1a) An excellent review of the structure activity relationship and some of the history of this class of drugs has appeared (2). This mini-review will look at some of the general approaches to the synthesis of the gliflozins with an emphasis on the glycosidation and the key reduction steps.

As early as the 19th century phlorizin 2 was isolated and shown to inhibit both SGLT1 and SGLT2 and, thus, promote urinary excretion of glucose. Unfortunately, being a hemiacetal structure, phlorizin is subject to hydrolysis to phloretin 3 and glucose thus excluding it as a candidate for oral administration as the SGLT inhibitory activity of the phloretin is significantly reduced (3). (Figure 1b) Nevertheless, this led to investigations of structurally similar, more hydrolytically stable derivatives of phlorizin as SGLT2 inhibitors (4,5).

Figure 1a. General structure of typical Gliflozin.

Figure 1b. Phloretin decomposition.

Figure 1c. Structures of five approved Gliflozins.

The general structures of the gliflozins have in common a glucose sugar to which is attached an aromatic group in the β-position at the anomeric carbon 1. It will be noted that in addition to the glucose sugar moiety and the β-isomeric aryl substituent the aryl group is composed of a diarylmethylene structure. The differences in the structures are not large, vis the similarities in the structures of dapagliflozin, empagliflozin and ertugliflozin as well as those of canagliflozin and ipragliflozin.

Five of the gliflozins have now been approved for prescribed use. These are dapagliflozin 4, Fanxica or Fonica, (Bristol Myers-Squibb/AstraZeneca), canagliflozin 5, Invokana, (Janssen Pharmaceuticals), ipragliflozin 6, Suglat, (Allessta Pharmaceuticals), empagliflozin 7, Jardiance, (Boehringer-Ingehelm/Eli Lilly) and ertugliflozin 8, Sitaglipton, (Pfizer/Merck) (Figure 1c).

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SYNTHESIS OF GLIFLOZINS

The synthetic approaches to the gliflozins essentially consist of three general steps: 1) construction of the aryl substituent, 2) introduction of the aryl moiety onto the sugar or glucosylation of the aryl substituent, and 3) deprotection and modification of the arylated anomeric center of the sugar to the final desired product.

Synthesis of the aryl group

The synthetic approach to the gliflozins first involves the construction of the aryl substituent with a suitable handle to allow its attachment to the sugar. There are two classical entries into the diarylmethylene units, namely, reaction of an organometallic reagent with an aldehyde to give the diaryl carbinal or a Friedel-Crafts acylation to provide a diaryl ketone. Both of these intermediates would then be followed by a reduction of the functionalized carbon to the requisite methylene. The former of these is exemplified in a synthetic route to 12 wherein aldehyde 9 was reacted with the Grignard reagent 10 to form the diarylmethanol 11, which was then reduced with triethylsilane to the diarylmethane 12 (6). It is worth noting that organosilanes have been shown to be excellent reagents for the reduction of benzylic alcohols to the corresponding alkanes (7,8) (Figure 2a).

A similar approach was employed in procuring the aryl substrate in a synthesis of ipragliflozin (9) (Figure 2b).

In an alternate approach to the diarylcarbinol precursor to the diarylmethylene moiety Fürstner and Krause showed that the rhodium trichloride-catalyzed coupling of an aryl boronic acid with an aldehyde leads to the diaryl carbinal intermediates in high yields (10). Two of the 16 examples reported involved the preparation of an aryl bromide, indicating that the reaction can be carried out without competing aryl-aryl, Suzuki-type cross-coupling taking place. The resulting brominated diarylmethane could be converted to an organometallic reagent for reaction with the gluconolactone leading to a gliflozin (Figure 2c).

Alternatively, a Friedel-Crafts acylation/reduction sequence can be used as was employed in the preparation of 14 via the formation and reduction of intermediate 13, in a synthesis of dapagliflozin, 4. In this approach the acid chloride required for the Friedel Crafts acylation is prepared in-situ and reacted directly with ethylphenyl ether to give the required 4-acylated derivative (11). The direct organosilane reduction of ketone carbonyls, especially acetophenone derivatives, to a methylene group is well documented (12) (Figure 2d).

Reduction of the carbonyl functionality to the methylene can be accomplished in a number of ways, but it has been shown that the reduction of aryl ketones to the corresponding methylenes can be conveniently done with an organosilane and an acid catalyst. The reduction of benzyl alcohols or aryl ketones to the corresponding methylene group is a particularly efficient process due in large part to the enhanced stability of the benzyl cationic intermediate. In a related case triethylsilane, and with greatly improved selectivity and the avoidance of a hazardous intermediate, tetramethyldisiloxane, TMDS, have been used in the reduction of an acetophenone derivative in the synthesis of the key intermediate 15 in a synthesis of ziprasidone, a Pfizer anti-psychotic drug (13). In this case the use of TMDS resulted in the avoidance of the hazardous chloromethyl ketone intermediate as well as the partially- and over-reduced by-products. Pentamethyldisiloxane and dimethylethoxysilane were less selective than TMDS for this process. Common catalysts for these organosilane reductions are trifluoroacetic acid or boron trifluoride etherate among others. The yields for these reductions are typically high and offer a facile isolation of the final product (Figure 3a).

Addition of the aryl group to the glucose

The second aspect in the synthesis of the gliflozins is that of glucosylation of the aryl moiety with the final stereochemistry being that wherein the aryl group occupies a β-position. One early approach to the gliflozins is illustrated for the synthesis of 17 as a general entry into the C1-aryl glucosonides.
The tribenzyl glycal \(23\) was converted to the gliflozin structures in a couple of ways. One of these is via the corresponding epoxide \(24\), which serves to place the 3-hydroxyl group on the sugar as well as provide a route for the introduction of the aryl unit \(22\). Reaction of \(24\) with 2-lithiofuran leads to the \(\beta\)-substituted benzyl-protected glucose \(25\). On the other hand reaction of the epoxide with the corresponding zinc reagent \(26\) results in the introduction of the aryl group in the \(\alpha\)-position. This is based on the earlier work of Halcomb and Danishefsky \(23\) (Figure 5a).

The di-tert-butylsilylene-protected dihydropyran \(27\) was subjected to a Stille cross-coupling reaction with an aryl sulfonyl chloride to show that this approach will work to introduce an aryl group to the sugar. Introduction of the requisite 3-hydroxyl group in the \(\alpha\)-position was then accomplished via hydroboration/oxidation to provide the \(\beta\)-arylated sugar derivative \(29\) \(24\) (Figure 5b).

Finally, the tetramethyldisiloxane, TMDS, silane reducing agent has been employed in the successful reduction of a hemiketal to the corresponding furan derivative as shown in the reduction of the protected precursor to canagliflozin, which is based on some earlier work by Kraus and coworkers who demonstrated the silane reduction of sugar hemiketals \(17-20\).

A highly stereoselective introduction of the aryl moiety can be accomplished via the cross-coupling of an aryl zinc reagent, using the well-developed organozinc chemistry of Knochel and co-workers, with the bromo-functionalized glucose \(21\) \(21\). Thus, zinc reagent \(21\) was reacted with bromopyran \(22\) to introduce the aryl group in the \(\beta\)-position assisted by the neighboring group participation of the pivaloyl group. Other ester protecting groups for the hydroxyls on the sugar also worked, but the pivalate protection was shown to be preferred for reasons of selectivity and yield. Deprotection led to dapagliflozin \(4\) (Figure 4b).

Gong and Gagné have shown that the reaction of arylic reagents with suitably-protected glucosyl bromides under Ni(0) catalysis results in the C1-arylated glucoside with good \(\beta\)-selectivity \(25\) (Figure 5c).

Figure 3b. Lithium reagent approach to arylation of glucose derivative.

Figure 4a. Lithium reagent - silane reduction approach to arylation of glucose derivative.

Figure 4b. Zinc cross-coupling approach to Dapagliflozin.

Figure 5a. Epoxide approach to arylation of glucose.

Figure 5b. Stille cross-coupling approach to Gliflozins.

Figure 6. Silyl enol ether reduction to canagliflozin.
CONCLUSIONS

A number of gliflozins has now been approved for prescription use in the dosage control of diabetes 2. The most general and flexible synthetic approaches to this class of drugs are outlined herein and follow a similar three-step sequence of preparation of the appropriate aryl substituent, attachment of the aryl moiety to a protected glucose followed by deprotection and modification of the anomeric center of the arylated glucose. The use of the gluconolactone intermediate does have the disadvantage of carrying out an oxidation step to the lactone and a subsequent reduction step, usually carried out with an organosilane.

REFERENCES AND NOTES


Nanoparticles that deliver oligonucleotide drugs into cells

Therapeutic oligonucleotide analogs represent a new and promising family of drugs that act on nucleic acid targets such as RNA or DNA; however, their effectiveness has been limited due to difficulty crossing the cell membrane. A new delivery approach based on cell-penetrating peptide nanoparticles can efficiently transport charge-neutral oligonucleotide analogs into cells, as reported in Nucleic Acid Therapeutics, a peer-reviewed journal from Mary Ann Liebert, Inc., publishers.

In the article, “Peptide Nanoparticle Delivery of Charge-Neutral Splice-Switching Morpholino Oligonucleotides,” Peter Järver and coauthors, Cambridge Biomedical Campus (U.K.), Karolinska University Hospital (Huddinge, Sweden), Stockholm University (Sweden), Alexandria University (Egypt), and University of Oxford (U.K.), note that while delivery systems exist to facilitate cell entry of negatively charged oligonucleotide drugs, these approaches are not effective for charge-neutral oligonucleotide analogs. The authors describe lipid-functionalized peptides that form a complex with charge-neutral morpholino oligonucleotides, enabling them to cross into cells and retain their biological activity.

“The exploitation of phosphorodiamidate morpholinos represents an exciting approach to treating a number of therapeutic targets,” says Executive Editor Graham C. Parker, PhD, The Carman and Ann Adams Department of Pediatrics, Wayne State University School of Medicine, Children’s Hospital of Michigan, Detroit, MI. “This paper suggests an intriguing but practical approach to solving the lack of a convenient non-covalent delivery system.”

Nucleic Acid Therapeutics journal