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ABSTRACT

The ability of 2-deoxy-d-glucose (2-DG) to interfere with d-glucose metabolism demonstrates that nutrient and energy deprivation is an efficient tool to suppress SARS CoV-2 cell growth and survival. Acting as a d-glucose mimic, 2-DG inhibits glycolysis due to formation and intracellular accumulation of 2-deoxy-d-glucose-6-phosphate (2-DG6P), inhibiting the function of hexokinase and glucose-6-phosphate isomerase, and inducing cell death. In addition to glycolysis inhibition, other molecular processes are also affected by 2-DG. Attempts to improve 2-DG’s drug-like properties, its role as a potential adjuvant for other chemotherapeutics, and novel 2-DG analogues as promising new anti-covid agents are discussed in this review.
INTRODUCTION:
Preamble: Acting as a d-glucose mimic, 2-DG inhibits glycolysis due to formation and intracellular accumulation of 2-deoxy-d-glucose-6-phosphate (2-DG6P), inhibiting the function of hexokinase and glucose-6-phosphate isomerase, and inducing cell death.

2-Deoxy-d-glucose [CAS: 54-17-6] is a glucose molecule which has the 2-hydroxyl group replaced by hydrogen, so that it cannot undergo further glycolysis. As such, it acts to competitively inhibit the production of glucose-6-phosphate from glucose at the phosphoglucoisomerase level (step 2 of glycolysis). In most cells, glucose hexokinase phosphorylates 2-deoxyglucose, trapping the product 2-deoxyglucose-6-phosphate intracellularly (with exception of liver and kidney); thus, labelled forms of 2-deoxyglucose serve as a good marker for tissue glucose uptake and hexokinase activity. Many cancers have elevated glucose uptake and hexokinase levels. 2-Deoxyglucose labelled with tritium or carbon-14 has been a popular ligand for laboratory research in animal models, where distribution is assessed by tissue-slicing followed by autoradiography, sometimes in tandem with either conventional or electron microscopy.
IUPAC: \((4R,5S,6R)-6-(\text{hydroxymethyl})\text{oxane-2,4,5-triol}
\)

**Other names:** 2-Deoxyglucose, 2-Deoxy-d-mannose, 2-Deoxy-d-arabino-hexose, 2-DG

**Chemical formula:** \(\text{C}_6\text{H}_{12}\text{O}_5\)

**Molar mass:** 164.16 g/mol,

**Melting point:** 142 to 144°C (288 to 291°F; 415 to 417 K)

2-DG is uptaken by the glucose transporters of the cell. Therefore, cells with higher glucose uptake, for example tumor cells, have also a higher uptake of 2-DG. Since 2-DG hampers cell growth, its use as a tumor therapeutic has been suggested, and in fact, 2-DG is in clinical trials.\(^{[1-3]}\) A recent clinical trial showed 2-DG can be tolerated at a dose of 63 mg/kg/day, however the observed cardiac side-effects (prolongation of the Q-T interval) at this dose and the fact that a majority of patients' (66%) cancer progressed casts doubt on the feasibility of this reagent for further clinical use.\(^{[4]}\) However, it is not completely clear how 2-DG inhibits cell growth. The fact that glycolysis is inhibited by 2-DG, seems not to be sufficient to explain why 2-DG treated cells stop growing.\(^{[5]}\) Because of its structural similarity to mannose, 2DG has the potential to inhibit N-glycosylation in mammalian cells and other systems, and as such induces ER stress and the Unfolded Protein Response (UPR) pathway.\(^{[6-8]}\)

Clinicians have noted that 2-DG is metabolised in the pentose phosphate pathway in red blood cells at least, although the significance of this for other cell types and for cancer treatment in general is unclear.

**Figure-3: Hexokinase pathway**

Work on the ketogenic diet as a treatment for epilepsy have investigated the role of glycolysis in the disease. 2-Deoxyglucose has been proposed by Garriga-Canut et al. as a mimic for the ketogenic diet, and shows great promise as a new anti-epileptic drug.\(^{[9,10]}\) The authors suggest that 2-DG works, in part, by increasing the expression of Brain-derived neurotrophic factor (BDNF), Nerve growth factor...
(NGF), Arc (protein) (ARC), and Basic fibroblast growth factor (FGF2).\textsuperscript{11} Such uses are complicated by the fact that 2-deoxyglucose does have some toxicity. A study found that by combining the sugar 2-deoxy-D-glucose (2-DG) with fenofibrate, a compound that has been safely used in humans for more than 40 years to lower cholesterol and triglycerides, an entire tumor could effectively be targeted without the use of toxic chemotherapy.\textsuperscript{12,13} 2-DG has been used as a targeted optical imaging agent for fluorescent \textit{in-vivo} imaging.\textsuperscript{14,15} In clinical medical imaging (PET scanning), fluorodeoxyglucose is used, where one of the 2-hydrogens of 2-deoxy-D-glucose is replaced with the positron-emitting isotope fluorine-18, which emits paired gamma rays, allowing distribution of the tracer to be imaged by external gamma camera(s). This is increasingly done in tandem with a CT function which is part of the same PET/CT machine, to allow better localization of small-volume tissue glucose-uptake differences. On May 8, 2021, the Drugs Controller General of India approved an anti-COVID oral drug, developed by DRDO, for emergency use as adjunct therapy in moderate to severe coronavirus patients based on this compound. The drug comes in powder form in sachet, which is taken orally by dissolving it in water. Clinical trial results have shown that 2-DG helps in faster recovery of hospitalised patients and reduces supplemental oxygen dependence.\textsuperscript{16} Resistance to 2-DG has been reported in HeLa cells and in yeast; in the latter, it involves the detoxification of a metabolite derived from 2-DG (2DG-6-phosphate) by a phosphatase.\textsuperscript{8,17,18} Despite the existence of such a phosphatase in human (named HDHD1A) However it is unclear whether it contributes to the resistance of human cells to 2DG or affects FDG-based imaging. The present invention provides a process for the synthesis of 2-deoxy-D-glucose comprising haloalkoxylation of R-D-Glucal wherein R is selected from H and 3, 4, 6-tri-O-benzyl, to obtain alkyl 2-deoxy-2-halo-R-α/β-D-glucopyranoside, converting alkyl 2-deoxy-2-halo-R-α/β-D-glucopyranoside by reduction to alkyl 2-deoxy-α/β-D-glucopyranoside, hydrolysing alkyl 2-deoxy-α/β-D-glucopyranoside to 2-deoxy-D-glucose.\textsuperscript{19}

\textbf{Scheme of synthesis:}\n
The preferred synthetic reactions and conditions for each individual steps of the above process are set forth below. The reaction scheme for the reactions involved in the process of the invention are also given below:

\textbf{Innovative approach:} The present invention relates to a process for the synthesis of 2-deoxy-D-glucose.

\textbf{Background:} 2-deoxy-D-glucose is useful in control of respiratory infections and for application as an antiviral agent for treatment of human genital herpes. Prior art for preparation of 2-deoxy-D-glucose while operable, tend to be expensive and time consuming.

\textbf{Objects:} The main object of the present invention is to provide a process for the synthesis of 2-deoxy-D-glucose resulting in good yield and with good purity. Another object of the invention is to provide an economical process for the synthesis of 2-deoxy-D-glucose.
Summary: A process that would produce 2-deoxy-D-glucose economically and with desired purity, is a welcome contribution to the art. This invention fulfils this need efficiently.

Accordingly, the present invention relates to a process for the synthesis of 2-deoxy-D-glucose comprising haloalkoxylation of R-D-glucal wherein R is selected from H and 3,4,6-tri-O-benzyl, to obtain alkyl 2-deoxy-2-halo-R-α/β-D-glucopyranoside,

converting alkyl 2-deoxy-2-halo-R-α/β-D-gluco/mannopyranoside by reduction to alkyl 2-deoxy-α/β-D-glucopyranoside, hydrolysing alkyl 2-deoxy-α/β-D-glucopyranoside to 2-deoxy-D-glucose.[20-25]

In one embodiment of the invention, the alkyl 2-deoxy-α/β-D-glucopyranoside is obtained by (a) haloalkoxylation 3,4,6, tri-O-benzyl-D-glucal to alkyl 2-deoxy-2-halo-3,4,6-tri-O-benzyl-α/β-D-glucopyranoside,

(b) subjecting alkyl 2-deoxy-2-halo-3,4,6-tri-O-benzyl-α/β-D-gluco/mannopyranoside to reductive dehalogenation and debenzylation to obtain alkyl 2-deoxy-α/β-D-glucopyranoside.

In another embodiment of the invention, in step (a) haloalkoxylation of 3,4,6-tri-O-benzyl-D-glucal is carried out by reaction with a haloalkoxylation agent selected from a N-halosuccinimide and a N-haloacetamide, and alcohol.

In another embodiment of the invention, alkyl 2-deoxy-α/β-D-glucopyranoside is obtained by (a) haloalkoxylation D-glucal to alkyl 2-deoxy-2-halo-α/β-D-glucopyranoside;

(b) subjecting alkyl 2-deoxy-2-halo-α/β-D-gluco/mannopyranoside to reductive dehalogenation and hydrogenation to obtain alkyl 2-deoxy-α/β-D-glucopyranoside.

Converting 3,4,6-tri-O-benzyl-D-glucal (I) to alkyl 2-deoxy-2-halo-3,4,6-tri-O-benzyl-α/β-D-glucopyranoside (II).

Figure-5: Serological culture of SARS-CoV-2 with 2-DG
CONCLUSION:
With the country battling the second wave of Covid-19 infections, The Drugs Controller General of India (DCGI) on Saturday [8th May 2021] approved a drug developed by the DRDO for emergency use. The drug: 2-deoxy-D-glucose (2-DG) - has been approved as an adjunct therapy in moderate to severe cases of coronavirus. Clinical trial results have shown that this molecule helps in faster recovery of hospitalized patients and reduces supplemental oxygen dependence, an official of the Defence Research and Development Organisation (DRDO) was quoted as saying. According to the official statement, "clinical trial results have shown that this molecule helps in faster recovery of hospitalised patients and reduces supplemental oxygen dependence." "Higher proportion of patients treated with 2-DG showed RT-PCR negative conversion in COVID patients. The drug will be of immense benefit to the people suffering from Covid-19," the statement goes on to say. The 2-DG drug, which comes in powder form in sachets, has to be taken orally by dissolving it in water. It accumulates in the virus infected cells and prevents virus growth by stopping viral synthesis and energy production," said the official statement by the Government of India. The DRDO says that the 2-deoxy-D-glucose (2-DG) drug can easily be produced and made available in plenty in the country since it is a generic molecule and analogue of glucose.

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