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C-Glucopyranosyl heterocycles in antidiabetic research—The potential of glycogen phosphorylase inhibitors

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Diabetes mellitus (DM) is a frequent cause of death and disability all over the world mainly due to its long term complications. Epidemic spread of the non-insulin-dependent (type 2) DM, representing more than 90 % of the diagnosed cases, induced extensive efforts in academia and industry to find new therapies. Several fields of antidiabetic research are based on carbohydrate derivatives which are also used in current clinical practice such as inhibitors of intestinal α-glucosidases and renal sodium dependent glucose cotransporters. C-Glycosyl compounds are monosaccharide derivatives wherein the anomeric centre of a sugar ring is attached to a carbon substituent. They are present in Nature and also represent a subclass of synthetic glycomimetics with multiple biological effects. Such molecules are valuable tools in deciphering the biological roles of natural sugars, and also serve as leads for new drugs. Glycogen phosphorylase (GP), the main regulatory enzyme of glycogen metabolism, has become a validated target in searching new therapies for type 2 DM. Inhibition of the liver isoform of GP may directly act on hepatic glucose production, hence on blood glucose levels. During our work, several C-glucopyranosyl heterocycles emerged as potent inhibitors of GP. Presented will be the design principles, synthetic challenges, results of enzyme kinetic, crystallographic, computational and physiological studies related to such inhibitors as well as the interplay of all of these investigations in producing potentially antidiabetic new sugar derivatives. In addition, other mechanisms of antidiabetic action and other possible uses of GP inhibitors, e. g. in anticancer therapy will also be highlighted.

Biography

Laszlo Somsak studied and obtained his PhD at the University of Debrecen where at present he is the head of the Department of Organic Chemistry. His research is directed to synthetic carbohydrate chemistry by working out new methodologies toward glycomimetic compounds such as glycoenzyme inhibitors of potential biological and therapeutical utilization.

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