STEREOSELECTIVE SYNTHESIS OF CARBOHYDRATE-FUSED ISOCHROMANS BY OXA-PICTET-SPENGLER REACTION AS POTENTIAL INHIBITORS OF SGLT-2 AND GLYCOGEN PHOSPHORYLASE

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Diabetes mellitus (DM) is a chronic multireasonal metabolic disorder associated with high morbidity and mortality, and its incidence is increasing despite available treatments [1]. The search for antidiabetic compounds with an optimal pharmacological profile, despite the challenges, has led to safer, more effective oral therapies. C-aryl glucoside SGLT2 inhibitors (gliflozins), featuring an aryl or heteroaryl aglycone, represent a promising advancement in diabetes treatment [2]. Additionally, inhibition of glycogen phosphorylase, a key liver enzyme regulating blood glucose levels, has become a validated target for the treatment of type 2 diabetes [3]. Our research aims to synthesize novel gliflozin analog molecules as potential inhibitors of SGLT2 and glycogen phosphorylase by conducting oxa-Pictet-Spengler reaction in which aromatic alcohol derivatives were reacted with sugar aldehydes starting from enantiopure chiral alcohol derivatives, and commercially available monosaccharides (Fig 1). The effect of the reaction conditions, the protecting groups and the configuration of the starting materials were studied on the yield and the stereochemical outcome of the reaction. It was found that the amount and the type of the applied acid catalyst, the configuration of the alcohol, and the sugar (glucose, galactose) aldehyde influence the stereochemistry of the cyclization. Preliminary studies indicate that some of our synthesized compounds exhibit moderate activity as glycogen phosphorylase inhibitors, while their potential as SGLT-2 inhibitors is currently under investigation, highlighting their dual therapeutic promise in diabetes management.

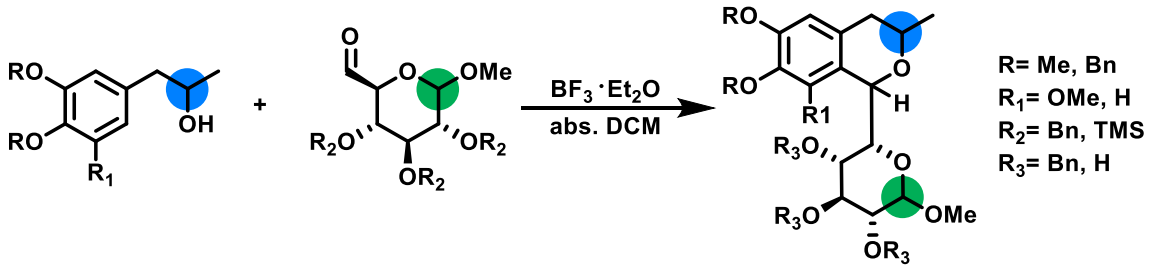

Figure 1. Synthesis of isochroman-sugar hybrids with benyzl and silyl protecting groups

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