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Computer-aided design of glucokinase activators

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Abstract

Glucokinase (GK), also termed as hexokinase IV, is a unique isoform of the hexokinase enzymes. It catalyzes the phosphorylation of glucose to glucose-6-phosphate. GK plays an important role in the control of whole-body glucose homeostasis by enhancing glucose stimulated insulin release from the pancreatic β-cells and promoting glycogen synthesis in the liver. Compounds that activate GK have been shown to increase hepatic glucose uptake and reduce hyperglycemia in multiple animal models of T2D. Multiple glucokinase activators (GKAs) have been evaluated in the clinic for the treatment of T2D.

However, despite the promising efficacy of this mechanism, there has been significant attrition in the clinical development of glucokinase activators, driven by narrow therapeutic windows against hypoglycemia as well as concerns around durability and chemotype-specific safety issues. These issues with early activators have fostered investigations into structurally diverse second generation activators with different biochemical profile to reduce hypoglycemia risk.

Unlike traditional medicinal chemistry binding affinity optimization, enzymatic biochemical profile (K_m and V_{max}) has been proved to be extremely hard to SAR. In the talk, we will present a computational model that enabled us prospectively design GKAs with desired biochemical profiles that demonstrated reduced hypoglycemia risk.