Novel, Highly Potent Systemic Glucokinase Activators for the Treatment of Type II Diabetes Mellitus

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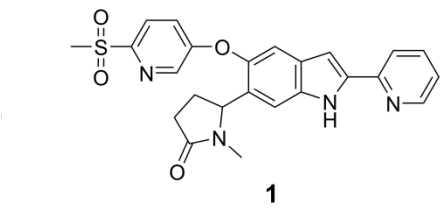
Abstract

Glucokinase (GK, hexokinase IV) is a unique hexokinase that plays a central role in mammalian glucose homeostasis. Glucose phosphorylation by GK in the pancreatic β-cell is the rate-limiting step that controls glucose-stimulated insulin secretion. Similarly, GK-mediated glucose phosphorylation in hepatocytes plays a major role in increasing hepatic glucose uptake and metabolism and possibly lowering hepatic glucose output. Small molecule GK activators (GKAs) have been identified that increase enzyme activity by binding to an allosteric site. GKAs offer a novel approach for the treatment of Type 2 Diabetes Mellitus (T2DM) and as such have garnered much attention. We now report the design, synthesis, and biological evaluation of a novel series of 2,5,6-trisubstituted indole derivatives that act as highly potent GKAs. Among them, Compound **1** was found to possess high *in vitro* potency, excellent physicochemical properties, and good pharmacokinetic profile in rodents. Oral administration of Compound **1** at doses as low as 0.03 mg/kg led to robust blood glucose lowering efficacy in 3 week high fat diet-fed mice.



1

hGK EC50 (@2.5 mM glucose) = 3.7 nM; Max activity = 784%

hGK EC50 (@10 mM glucose) = 2.4 nM; Max activity = 193%