Discovery of N-Heteroaryl Phenylacetamides as Glucokinase Activators for the Treatment of Type 2 Diabetes

Glucokinase (GK) is a glycolytic enzyme that catalyzes the oxidative phosphorylation of hexoses by ATP. Studies of glucokinase-linked genetically-modified mice and mutations in humans have illustrated the important roles played by glucokinase in whole-body glucose homeostasis, and suggest that the use of pharmacological agents that augment glucokinase activity could represent a viable treatment strategy in patients with type 2 diabetes. In the mid-1990s, high throughput screening of 120,000 small molecules of the Roche compound library identified a lead molecule that stimulated GK directly. The optimization effort of this newly discovered GK activator (GKA) molecule resulted in the discovery of piragliatin which was the first GK activator to reach the clinic advanced to phase II human trials but then shelved due to transient mild elevation of liver enzymes in a small percentage of patients because of metabolite cycling. The successful resolution of metabolite cycling resulted in the development of RO4597014 as a backup molecule to piragliatin. In the clinic, no evidence of metabolic cycling was seen in contrast to observations from the previous clinical GKA piragliatin.

References:


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