

Discovery of Glycogen Phosphorylase Inhibitors for the Treatment of Type 2 Diabetes

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The break down of glycogen to glucose in the liver is mediated by the enzyme glycogen phosphorylase (GP). Inhibition of GP should result in a decrease in hepatic glucose production and is therefore a target for treating type 2 diabetes. After screening for GP inhibitors, X-ray crystallography was used to optimize inhibitors that bind to the AMP site of GP. The medicinal chemistry leading to compounds with low nano-molar potency for the inhibition of human liver GP as well as the biology of these inhibitors will be presented.