Researchers at the University of South Florida have derived small molecules capable of increasing glucose uptake when bound to sortilin.

Diabetes Mellitus is a chronic disease associated with high levels of blood glucose. Diabetics have difficulties regulating their blood sugar, obesity, and insulin production. Insulin resistance, inability for glucose transport by insulin, is a key hallmark of type 2 diabetes mellitus. Without medication, insulin is continuously produced by the pancreas which can be detrimental to diabetics. Regulation of blood glucose levels in mammals is achieved by translocation of fat and muscle specific transporter-Glut4 to the plasma membrane. Sortilin, a major component of the Glut4 containing vesicles in adipocytes, plays an essential role in the development of the insulin responsive transport system in cultured adipocytes and muscle cells. Glut4 is often times mis-localized in diabetic patients, and more than 80% of diabetic patients are obese or overweight. It has been shown that decreasing sortilin inhibits insulin-induced glucose transport and biogenesis of insulin-responsive compartment. Obese diabetic humans have decreased sortilin expression which contributes to defects in glucose transport. This invention addresses the challenges of regulating glucose levels in obese diabetics via stabilizing sortilin and increase glucose transport in adipocytes.

The inventors identified various scaffolds of small molecules with the ability to dock at a site within sortilin to promote the increase of glucose uptake. These scaffolds include norbornene anhydride amino acid adducts, phenyl-amide-acids of benzyl substituted glutaric acids, and 2-substituted 3-oxo-1,2,3,4-tetrahydro-2-quinoxalines. The compounds are identified by their ability to suitably bind to a region of the sortilin protein with high affinity and thereby mediate the interaction of sortilin with various protein molecules or other natural substrates. Compounds of three scaffolds, according to embodiments of the invention, are observed to bind to sortilin both in vivo and in silico. These sortilin ligands increase can be employed in compositions to increase uptake of glucose for the treatment of diabetic patients.

**ADVANTAGES:**
- Increase glucose uptake
- Treat diabetic patients
- Address obesity in diabetics

**Control Glucose Transport in Obese Diabetics**

**Scaffolds for Sortilin binding:** Norbornene anhydride amino acid adducts Phenyl-amide-acids of benzyl substituted glutaric acids 2-substituted 3-oxo-1,2,3,4-tetrahydro-2-quinoxalines

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