**Summary:**

Twenty one thiazolidin-4-one derivatives were synthesized, purified by chromatographic and non-chromatographic methods. These were characterized through physical constants like melting point, various spectral and chromatographic techniques like, UV scan, IR spectra, NMR spectra, TLC, and LC-MS methods.

Since the aim of the study was to evaluate the antidiabetic and hypolipidemic activities of the thiazolidin-4-ones, four compounds were tested using the streptozotocin + nicotinamide induced type-2 diabetes in mouse. All of them reversed the hyperglycemia. Among them, two compounds also reduced the glucose intolerance in an OGTT.

All the synthesized 21 thiazolidin-4-ones were tested in an *in vitro* glucose uptake assay using isolated rat diaphragm. Three compounds showed significant enhancement of glucose uptake by isolated rat diaphragm in presence and absence of insulin. This suggested the potential of these compounds in attenuation of hyperglycemia through enhancement of glucose uptake by peripheral tissue and sensitization of tissue for insulin.

In high carbohydrate diet (HCD)-induced insulin resistance mice model, three thiazolidin-4-ones were selected and evaluated. All tested compounds attenuated hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia, and glucose intolerance. However, these compounds did not show any effect on hypoadiponectinemia. However, two thiazolidin-4-ones were able to enhance the leptin levels. In HCD model the disturbed liver antioxidants milieu was corrected by all three compounds. Thus, these results showed their anti-oxidant potential to attenuate oxidative stress in diabetes.

Further, the histopathological investigation of liver, pancreas, and white adipose tissue revealed no difference in liver architecture among the treatment groups. The test compounds reduced the size of adipocytes. However, hyperplasia was observed in islets of Langerhans in the groups treated with test compounds.

Study reports the potential of thiazolidin-4-ones against metabolic disorders through modulation of the multiple mechanisms, which correct the state of insulin resistance and development of type-2 diabetes.