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Novel 1,3,5-triazine-thiazole (TT-31) derivative exert protective action against diabetes induced nephropathy in rat via inhibition of DPP-4

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Objectives: The inhibition of Dipeptidyl peptidase IV (DPP-4) enzyme causes stimulation of insulin secretion via preventing the degradation of incretins. Thus, agents attenuating DPP-4 have a profound role in controlling type-2 diabetes. These agents cause reduction of glucose independent of kidney function without causing hypoglycemia in diseased kidneys undergoing dialysis. Therefore, the present study was intended to develop a novel series of 1,3,5-triazine-thiazole derivatives as potent DPP-4 inhibitors and its effect was also investigated on diabetic nephropathy in rat.

Methods: The compounds were tested for DPP-4 inhibition via ELISA based assay kit. The compounds were also analyzed via docking study with 3D crystal structure of DPP-4 to identify critical interactions vital for bioactivity. The most potent analogue was further tested for its protective action against streptozotocin (STZ)-induced diabetic nephropathy (DN) in Wistar rats. The test compound (TT-31) was administered orally in graded doses to the animals and observed for changes in various biochemical, molecular, and histological parameters after induction of DN.

Results: In DPP-4 inhibitory assay, compound 5c was identified as most potent analogues with IC_{50} = 1.04 µM and showed to interact with Glu205, Arg358, Arg669 in docking study. In Wistar rats, TT-31 causes dose-dependent improvement of serum and urine biochemistry (urine creatinine, uric acid, albumin, and BUN) in STZ-treated rats. As compared to diabetes group, the TT-31 causes reduction in preprandial and postprandial glucose levels with significant increase in creatinine clearance and reduction of renal oxido-nitrosative stress in STZ induced diabetes in dose-dependent manner.

Conclusions: Taken altogether, it has been summarized that, compound TT-31 showed protective effect against diabetes induced nephropathy in rats via inhibition of DPP-4.