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Novel 1,3,5-triazine-thiazole derivatives exert protective action against diabetes induced nephropathy in experimental animal 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 profound role in controlling type-2 diabetes. These agents cause reduction of glucose independent of kidney function without causing hypoglycemia in diseased kidney undergoing dialysis. Therefore, the present study was intended to develop novel series of 1,3,5-triazine-thiazole derivatives as potent DPP-4 inhibitor and its effect on diabetic nephropathy in experimental animal.

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 was administered orally in graded doses (5mg/kg, 10mg/kg and 15mg/kg) 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, 5c causes dose-depended improvement of serum and urine biochemistry (urine creatinine, uric acid, albumin, and BUN) in STZ-treated rats. As compared to diabetes group, the 5c causes reduction in preprandial and postprandial glucose levels together with significant increase in creatinine clearance and reduction of renal oxidonitrosative stress in STZ induced diabetes in dose-dependant manner.

Conclusions: Taken altogether, it has been summarized that, compound 5c showed protective effect against diabetes induced nephropathy in experimental animal via inhibition of DPP-4.