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Novel Imeglimine derivatives exert protective action against diabetes induced nephropathy in experimental animal via inhibition of DPP-4

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Objectives: Dipeptidyl peptidase-4 (DPP-4) inhibitors are increasingly used in the treatment of Type-2 diabetes patients with chronic kidney disease but also on patients with end-stage kidney disease on dialysis. These inhibitors provide similar glucose-lowering effect independent of the kidney function either diseased or normal and reduce the levels of glycated albumin without causing hypoglycemia in altered kidney function undergoing dialysis. Studies have also shown that, DPP-4inhb exert kidney-protective effect via reducing the incidence of albuminuria. Thus, in the present study, we wish to explore a novel series of Imeglimine (1,3,5-triazine) 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 7e was identified as most potent analogues with $IC_{50} = 3.24 \mu M$. Compound 7e interacted with Arg358, Arg669, Glu205 as confirmed via docking study. In Wistar rats, 7e causes dose-dependent modulation of STZ-induced alterations in serum and urine biochemistry (urine creatinine, uric acid, albumin, and BUN). It also significantly enhanced creatinine clearance rate together with decline in STZ induced increase in renal oxidonitrosative stress at the maximum test dose of 15mg/kg.

Conclusions: The results of present investigation suggest that treatment with 7e exert protective action against STZ-induced DN possibly via the inhibition of DPP-4.