Abstract

Diabetes mellitus is a chronic progressive metabolic disorder that has profound consequences for individuals, families, and society. To date, main available oral antidiabetic medications target either insulin resistance (metformin, glitazones), or insulin deficiency (sulfonylureas, glinides), but leading to shortfalls in medication. Advancement in modern oral hypoglycemic agents may be encouraged with or in place of traditional therapies. The lower risk for hypoglycemic events as compared with other insulinotropic or insulin-sensitizing agents make DPP-4 inhibitors very promising candidates for a more physiological treatment of type-2 diabetes. Only some DPP-4 inhibitors are currently used for the treatment of type 2 diabetes (T2DM) and various inhibitors currently undergoing animal and human testing. A number of catalytically active DPPs distinct from DPP-4 (DPP II, FAP, DPP-8, and DPP-9) have been described that is associated with side-effect and toxicity. To discover potent and selective and safer drugs in a shorter time frame and with reduced cost it requires using an innovative approach for designing novel inhibitors**.**

To design of novel DPP-4 inhibitors ligand based and structure based screening approaches were applied. An analog based design study was performed using HQSAR, pharmacophore modeling and 3D-QSAR to designing potential lead compounds. For exploration of substrate like and non substrate like novel peptidomimatic inhibitors, systematic pharmacophore based screening protocol was used to screen commercial databases and hits were screened out which were further optimized and designed new lead compounds. These novel lead compounds were synthesized and evaluate for DPP-4 inhibitory activity.

In-vitro activity assay identified compound SA01, SB08, SC03, SD03 and SD10 are the more comparable active as with respect to the standard drugs which were further subjected to determine invivo hypoglycemic activity. The in vivo studies showed that the compounds exhibited significant reduction in serum glucose level compared to diabetic control. Thus, Peptidomimetic based derivatives as potent, selective and acting DPP-4 inhibitors for an effective treatment of T2DM. Future optimization of derivatives can lead to the discovery of new potent compounds.