Summary and Conclusion

As many clinical studies have shown, the DPP-4 inhibitors are a very promising approach for the treatment of T2DM. Treatment with DPP-4 inhibitors proved to be beneficial in achieving good glycaemic control without side effect of existing therapies when they were employed either as monotherapy or as a combined therapy with other antidiabetic agents. Furthermore, animal studies have indicated that theseagents prolong β-cell survival which offers the theoretical chance of slowing the progression to T2DM. Up to date there are more than 20 different DPP-4 inhibitors developed for various therapeutic interests-mainly type II diabetes. Among currently developed oral DPP-4 inhibitors, vildagliptin (LAF237), sitagliptin (MK-0431) and saxagliptin (BMS-477118) Linaglaptin (BI-1356) from Novartis, Merck & Co., and BMS, and BI and Eli Lilly and Company respectively are marketed around the world. DPP-4 is a key regulator of incretin hormones, but the functions of other group members e.g. QPP, DPP-8, DPP-9 are unknown. A number of DPP-4 inhibitors have been described, all have good potency and stability and safety profile. However, the specificity and length of action of individual inhibitors is clearly important, since high doses of DPP-4 inhibitors have been shown to exert toxic effects via inhibition of DPP8/DPP9. To avoid poor ADME problems, increasing efforts is now being made to consider ADME parameters in the early phases of lead optimization and short term toxicity models to extrapolate toxic side-effects. Here, we summarized the currently available diverse, potent and selective DPP-4 inhibitors along with inhibitors related to other DPP enzymes.

To improve the potency as well as selectivity and stability its require to optimize lead molecules by rational way. Structure-based lead optimization is a powerful approach to the selection of lead compounds with potential for drug development. Therefore modification in chemical structure as per requirement of binding site by lead optimization technique provide better molecule. The information provided in this manuscript can be useful to prospective researchers and medicinal chemist to exploit new scaffold which may also lead to the discovery of other possible DPP-4 inhibitors, which could add to the successful treatment of diabetes.

An analog based design study was performed using HQSAR, pharmacophore modeling and 3D-QSAR to designing potential lead compounds. From the atomic contribution maps obtained

using the HQSAR model, it was revealed that ortho or pera electro-withdrawing substituent's on the phenyl ring at S2 site contributed to the inhibition activity. According to this study, in order to obtain selective DPP-4 inhibitors compared to the isozymes, the interaction of the inhibitors with the S2 site and S1 site in DPP-4 should be carefully considered. Dpp-4 Selectivity of designed molecules with respect to DPP-2, DPP-8, and DPP-9 were predicted using developed HQSAR models**.**

The pharmacophore model described represents the contribution to the rational design of peptidomometic Dpp-4 inhibitors. This pharmacophore contained one hydrophobic regions, one positive ionizable region, one aromatic region and two hydrogen bond acceptor region. The successful explanation of structure activity relationshipsproves the efficiency of pharmacophore model to screen identify and predicted the activity of unknown molecules. These pharmacophore models were used to identified pharmacophore sites and predict the activity of designed molecules. Systematic pharmacophore based screening protocol was used to screen commercial databases. Hits retrieved were passed progressively through filters like predicted activity, fitness score, Lipinski screen and docking scores. The survived hits were further visually analyzed which shows that all hits contain same threefold of piperazinum ring which can be replaced the azabicyclo ring in existing lead which may increase the potency of DPP-4 inhibitors.

The previously reported pharmacophore model, HQSAR selectivity models and a 'lead-like' screening hit inspired the development of a series of piperazine-constrained DPP-4 inhibitors. A novel series of DPP-4 inhibitors with excellent potency and selectivity over DPP-2, DPP-8 and DPP-9 has been discovered by *in silico* method. These novel piperazine derivatives were designed, synthesized and evaluate for DPP-4 inhibitory activity. Invitro activity results identified that compound SA01; SB08 and SC03 are comparable active as with respect to the standard drugs which were further subjected to determine hypoglycemic activity. The in vivo studies revealed that compounds SA01; SB08 and SC03 reduced significant blood glucose level as compared to standard sitagliptin. The docking results and predicted activities were in accordance with the biological activity data. Thus, peptidomimetic based cyanopyrrolidine derivatives as potent, selective and long acting DPP-4 inhibitors for an effective treatment of T2DM. Future, optimization of piperazine derivatives can lead to the discovery of new potent compounds.

Recent studies sitaglaptindrugs widely used to treat Type 2 diabetes may have unintended effects on the pancreas that couldlead to a form of low-grade pancreatitis in some patients and a greater risk of pancreatic cancer inlong-term users. In this research, we summarize the available data in this field and optimization of experimental results through molecular modeling techniques of DPP-4 inhibitors in humans.Extensive structure–activity relationship (SAR) studiesaround the left side phenyl ring and the right side triazolopiperazinemoiety in the β-aminoamide series provided various close analogs of sitagliptin.

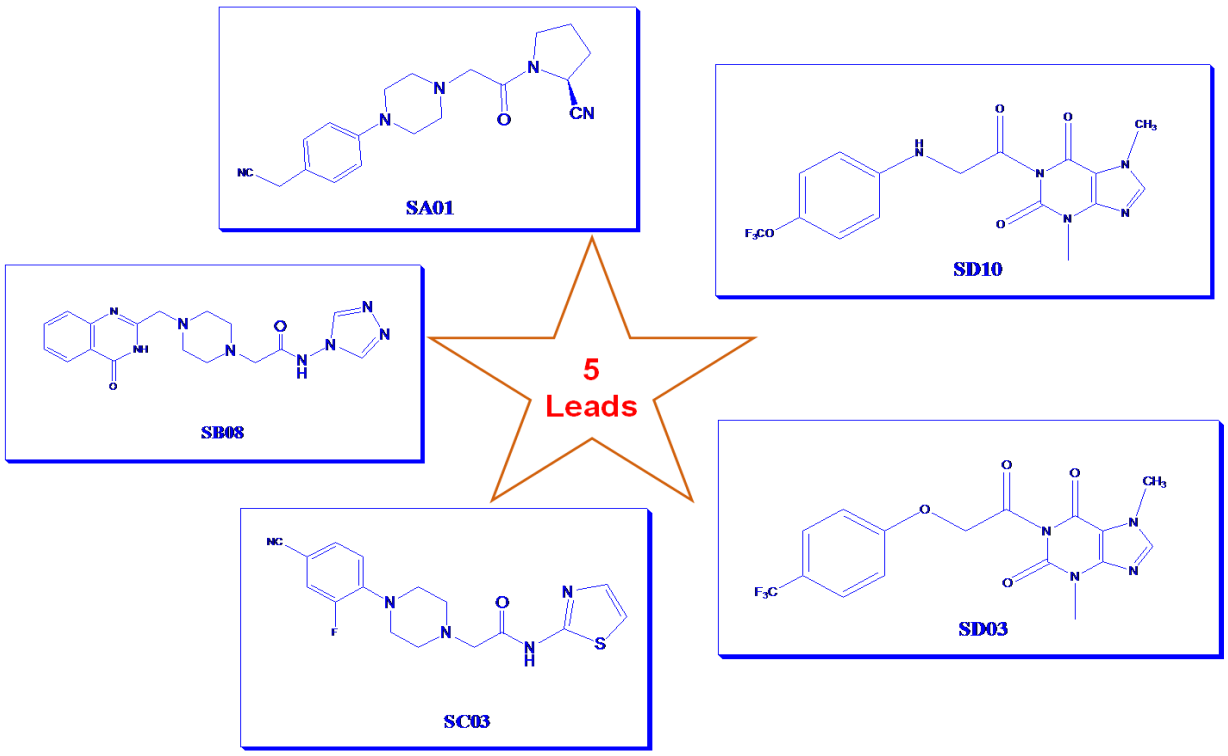
Combine ligand and structure based strategies provide great insight of structural requirement of DPP-4 inhibitors as compile to fit into target structure. Herein described are pharmacophore development with atom-based 3D-QSAR analysis and virtual screening of previouslyreported sitaglaptin inhibitors in order to get insight into their structural features responsible for high affinity. The best pharmacophore model generated consisted of four features AHHRR: a hydrogen bond acceptor (A), two hydrophobic groups (H) and two aromatic ring (R).The statisticallysignificant 3D-QSAR model with $r^2$of 0.93 and $q^2$of 0.82 wasdeveloped using PHASE and analyzed in order to understand thetrends of these molecules for their DPP-4 inhibitory activity. Theinfluence of electron withdrawing, hydrogen-bond donor, negative/positive ionic, aromaticity and hydrophobic groups was analyzed and discussedusing the 3D-QSAR PHASE hypotheses. 3D-QSAR as well as screened hits provide clues for possible structural modifications and willbe of interest and significance for the strategic design of morepotent molecules in the DPP-4 inhibitors as anti diabetic agent. Invitro activity assay identified compound SD03 and SD10 are the more comparable active as with respect to the standard drugs.

The finallySA01 SB08, SC03, SD03 and SD10 compound posses' comparative invitro activity, physicochemical and pharmacokinetic properties as compared to benchmark compounds of DPP-4 inhibitors. These compounds were further subjected to determine invivo hypoglycemic activity. The in vivo studies showed that the active metabolite had a very high inhibitory potency with respect to DPP-4. 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. The peptidomimetic inhibitors exhibited significant lowering of blood glucose levels in STZ diabetic rats. Diabetic rats treated with inhibitors

exhibited significant ($p<0.001$) reduction in serum insulin and glycated hemoglobin levels when compared to diabetic control. A marked decrease in triglycerides, total cholesterol has been observed in diabetic rats treated with inhibitors which show the possibility of inhibitors in interring with cholesterol metabolism.The elevation of serum creatinine related to renal dysfunction in diabetic hyperglycemia was improved significantly. Animals treated with inhibitors caused statistically significant reduction in the activity of SGOT, SGPT and total protein level when compared with diabetic control and standard which signifies the role of compounds in overcoming the hepatic damage caused by diabetes.

Future Prospect

DPP-4 inhibitors are a novel class of oral antidiabetic drugs. The overall understanding to date with DPP-4 inhibition is that they are orally active, safe and highly tolerable agents with a minimal risk of producing hypoglycemia. Compounds SA01, SB08, SC03, SD03 and SD10 representative of each series posses overall good binding affinity towards DPP-4 enzyme which results into hypoglacemic activity with no increased risk of adverse events.



The structure activity relationships of substrate like inhibitor reveal that electron-deficient 4-arylpiperazine scaffold is desirable for improved potency. Further different alkyl or aryl substitution which increases the lipophlicity on piperazine ring may be superior lead to increase the potency and pharmacokinetic properties. A second generation of compounds involving changes in the core piperazine ring by hetroaromaticpiperazine like imidazopiperazine may improve the potency and metabolic stability of the compounds.

The structure activity relationships of non substrate like inhibitor reveal that the xanthine structure may be favorable for designing potent DPP-4 inhibitors. Further optimization of xanthine ring with different aryl and hetro aryl ring at N-2 position may be increase the potency and efficacy. Target compound SD10 containing trifloromethoxy group, in particular, showed comparatively good inhibitory activity. Such studies helps in further lead optimization by substituting more electronegative groups. Modification in amino and ether liker chain may provide the scope of further optimization.

Therefore, both series of compounds could be served as useful clues for developing next generation of antidiabetes medicines via inhibiting DPP-4 activity.The information provided in this study can be useful to prospective researchers and medicinal chemist to exploit new scaffold which may also lead to the discovery of other possible DPP-4 inhibitors, which could add to the successful treatment of diabetes.