SUMMARY

Diabetes mellitus is considered to be a main threat to human health on account of development of many severe complications and protein tyrosine phosphatase 1B (PTP 1B) emerged as a molecular level legitimate approach for the management of type 2 diabetes mellitus. Thiazolidinediones (TZDs), a representative of PPAR-γ agonists, are oral insulin-sensitizing agents available clinically for the management of diabetes but suffered from serious side effects.

Initially, QSAR studies were performed on series of PTP 1B inhibitors bearing 2,4-TZD scaffold in order to find out structural features essentials for optimal inhibitory activity. Based on literature survey and QSAR study, three different series of 2,4-TZD scaffold bearing biphenyl arylidene, cinnamylidene and Pioglitazone were designed. In order to get further insight into structure activity relationship (SAR) various other substituents were also incorporated at ‘N-3’ of TZD skeleton. Docking studies were performed in order to determine the exact mode of binding of above designed compounds against PTP 1B. The docking studies of various biphenyl derivatives revealed that all the molecules bind at the active site of PTP 1B. Although their substituents interacted with different amino acid residues in the active site, core structure in all molecules exhibited similar hydrophobic interactions. TZD ring bearing multiple functionalities has been also involved in binding interactions. As compared to biphenyl derivatives interactions with cinnamylidene and Pioglitazone derivatives were limited but presence of a selective substituent like methyl benzoic acid resulted in compound binding selectively to catalytic active site pocket and could behave as potent inhibitor of PTP 1B. The above designed compounds were synthesized and all synthesized compounds TRB-1001 to TRB-1028 were characterized using spectral techniques such as IR, NMR and Mass.

All the synthesized compounds TRB-1001 to TRB-1028 were evaluated in vitro for their inhibitory activity using PTP 1B assay kit. Among various series, compounds TRB-1014, TRB-1024 and TRB-1028 bearing phosphotyrosine mimetic domain as predicted by docking studies emerged as the most potent having activity in low micromolar range. All the compounds were also evaluated in vivo for their antihyperglycemic activity using streptozotocin-nicotinamide
induced diabetic mice model. Most of the compounds showed good to better antihyperglycemic activity while compound TRB-1014 exhibited most potent antihyperglycemic activity. Simultaneously, a marginal increase in the body weight observed with synthesized compounds as compared to Pioglitazone can be attributed to inhibition of PTP 1B, which has a major role in obesity. Histopathology studies further indicated that administration of most active compounds protect pancreatic β-cells against diabetes induced changes.

For further structural optimization 3D-QSAR study was performed using SOMFA on all newly synthesized compounds i.e. TRB-1001 to TRB-1028. To incorporate essential structural features, all the compounds were included in the model derivation process. QSAR results indicated that incorporation of bulky substituent as well as functionalities bearing phosphotyrosine mimic domain along with substituted biphenyls bearing electropositive substituents could result in compound with optimal inhibitory activity. Presence of carbonyl group next to ether linkage of Pioglitazone derivatives could be another approach to achieve selectivity against PTP 1B.

Three independent 3D-QSAR studies were also performed on different series of inhibitors and the outcome of the studies provided additional information in terms of structural features essential for improved spectrum of inhibitory activity.