ABSTRACT

ADAMs are type I integral membrane proteins and several members of this family have been involved in the ectodomain shedding of membrane proteins. Since elevated levels of aggrecanase are associated with inflammatory diseases, such as arthritis. The development of small-molecule inhibitors emerged as an important pharmaceutical target during the last decade. ADAMTS1, ADAMTS4, ADAMTS5, ADAM10 and ADAM12 plays major role in degradation of aggrecan. As these enzymes play a major role in mediating or accompanying diverse array of pathologies, this work has been focused on identification of novel specific ADAM inhibitors against these five ADAM subtypes.

The binding of ligand with aggrecanases can be influenced by Zn$^{2+}$ ions, therefore a study was conducted to check the binding mode in the presence and absence of zinc using Docking and Molecular dynamics simulation. Results suggest that the absence of zinc decreases the binding affinity of ADAMTS4 and ADAMTS5 with its inhibitor.

For, ADAMTS1 study, Known ligands for ADAMTS1 was less for ligand based pharmacophore modelling, therefore Structure based Pharmacophore modelling and virtual screening approach was carried to screen Zinc natural and Synthetic compounds. pharmacophore ADR was used as query for screening. For, ADAMTS4, High throughput Virtual Screening, Ligand based and Structure based Pharmacophore Modelling was performed. In Ligand based Pharmacophore modeling, Model AHHRR had the best survival score. The Receptor-Ligand Pharmacophore method, three features pharamacophore AAR was used for screening. S1’ loop specific binding was also performed for the short listed candidates. For, ADAMTS5, High throughput Virtual Screening, Ligand based and Structure based Pharmacophore Modelling was performed. In Ligand based Pharmacophore modeling, Model AARRR.4144 had the best survival score. The Receptor-Ligand Pharmacophore method, ARN was selected as the pharmacophore and screened against Zinc database. ADAM12 does not have crystal structure therefore Homology based 3D model was developed and validated using SAVES server and Molecular Dynamics. Structure based Pharmacophore modelling and virtual screening approach was carried for ADAM12. NDR was selected as the pharmacophore for screening database. ADAM10 does not have crystal structure therefore Homology model was build and validated using SAVES server and Molecular Dynamics. Structure based Pharmacophore modelling and virtual screening approach was
carried for ADAM10. NDR was selected as the pharmacophore for screening database. All the short listed candidates were checked for ADME property, which was in acceptable range and Molecular Dynamics was done to check the stability of the Protein-Ligand complex.

In vitro validation was done for ADAMTS4 short listed candidates from Duke’s database. Chebulinic acid, epicatechin, mangeferin, L-dopa and Quercitin had the best XP Glide score > 8 kcal/mol was used in in vitro studies.

Using different approaches can be more efficient way in identification of potent hits that can bind to various bioactive conformations available in the active site of ADAM proteins. Therefore, the short listed leads can be more potent in targeting ADAM. Thus these compounds of novel scaffolds provide valuable leads for further optimization as potent ADAMs inhibitors.