Discovery of potential inhibitors for STAT3: Ligand based 3D pharmacophore, Virtual Screening and Molecular Docking Studies

KAVIARASAN LAKSHMANAN[1], Selvaraj Ayyamperumal[1], Jemmy christy[2], and Gowramma Byran[1]

[1]JSS College of Pharmacy Ooty
[2]Sathyambama Institute of Science and Technology

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Abstract

Background: A tremendous research on signal transducer and activator of transcription (STAT3) pertaining to cancer. It regulated the gene expressions like normal cellular process includes differentiation, cell development, proliferation, survival, maturation and immune perform. There are many drugs are clinically approved derivatives are used as STAT3 for cancer therapy suffer from many limitations related to stability and toxicity. Experiment: In order to envisage structurally diverse novel chemical entity as STAT3 poison with better efficacy, Ligand-based-pharmacophore model was developed using 3D QSAR pharmacophore generation (HypoGen algorithm) methodology in Discovery studio 4.1 clients. The chemical features of 48 different derivatives were taken as the training set. The selected pharmacophore model Hypo1 was further validated by 15 test set molecules and used as a query model for further screening of 1,45,000 drug-like molecules from SPECS databases. These molecules were subjected to several assessments such as Lipinski rule of 5, verber's rule and SMART filtration. The molecule obtained after filtration was further scrutinized by molecular docking analysis on the active site of STAT3 crystal structure. Result: 19 potential inhibitory molecules have been selected by analysing the binding interaction and Ligand- Pharmacophore mapping with the validated pharmacophore model. These 19 hits are further subjected to TOPKAT program for toxicity assessment. These 19 hit molecules can be utilized for designing future class of potential STAT3 inhibitor. Conclusion: From the result of all of these studies compounds Specs 1, Specs 9, Specs 13, Specs 17, Specs 28 and Specs 37 was finalised for further studies.

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