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Ligand based and e-pharmacophore modeling, 3D-QSAR and hierarchical virtual screening to identify dual inhibitors of spleen tyrosine kinase (Syk) and Janus kinase 3 (JAK3)

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Among various kinase family members, Syk (spleen tyrosine kinase) and JAK3 (Janus kinase 3) have emerged as key players in immune cell signaling. Both the kinases have been implicated in autoimmune disorders such as rheumatoid arthritis, psoriasis etc. In last few years several Syk and JAK3 inhibitors have been reported in literature to reach later phases in the clinical trials. Fostamatinib (R788), an orally available Syk inhibitor is now in Phase III for RA. The major milestone for the use of kinase inhibitors for autoimmune disorders is the recent FDA approval of tofacitinib a JAK3 inhibitor. PRT062070, a novel dual inhibitor of Syk and JAK3 entered clinical trials announced by Portola Pharmaceuticals. In the light of above, Syk and JAK3 dual inhibitors can offer scientific and rational treatment for complex autoimmune disorders. In the present study, LBPM were developed for Syk and JAK3 using diverse Syk and JAK3 inhibitors. The best models for Syk (ADPR.14) and JAK3 (AADH.54) were selected on the basis of highest value of Q²test. The selected models were then modified manually on the basis of e-pharmacophore models generated for highest active and clinical trial inhibitors for both Syk and JAK3. The modified pharmacophores for Syk (APDRR.14) and JAK3 (AAHDR.54) were validated and employed for screening of Asinex database followed by docking based screening. The hits with pharmacophoric features and essential docking interactions for both enzymes were further employed for pharmacokinetic properties and MM-GBSA energy calculation. The systematic ligand and structure based modelling strategies lead to nine hits as dual inhibitors of Syk and JAK3. Among them top two hits were validated by molecular dynamics. Thus these dual inhibitors can be further explored as therapeutics for autoimmune disorders.

Biography

Maninder Kaur is pursuing her PhD from Punjabi University Patiala in the Department of Pharmaceutical Sciences and Drug Research. She has been awarded Gold Medal in MPharmacy in Pharmaceutical Chemistry from the same university. She has published more than 25 papers in reputed international journals.

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