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Quantitative Structure Activity Relationships and Molecular Docking Studies of P56 LCK Inhibitors

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Lymphocyte specific protein tyrosine kinase (LCK) is a member of the Src family of non-receptor protein tyrosine kinases, expressed primarily in T-lymphocytes and natural killer cells. LCK is essential for T-cell development and function. It is constitutively associated with the cytoplasmic portions of the CD4 and CD8 surface receptors and plays a key role in T-cell antigen receptor (TCR) linked signal transduction pathways. Inhibitors of LCK may have potential thereputic ability in the treatment of auto immune diseases such as coxsackievirus B3-mediated heart diseases, rheumatoid arthritis, multiple sclerosis, lupus, as well as inflammatory diseases, prevention of solid organ transplantation and allergic diseases.

Three dimensional quantitative structure - activity relationship (3D-QSAR) models were developed for 67 molecules of 2-amino-benzothiazole-6-anilide derivatives against lymphocyte-specific protein tyrosine kinase (P56 LCK). The molecular field analysis (MFA) and receptor surface analysis (RSA) modules of Cerius2 software was employed for studies and the predictive ability of the 3D-QSAR model was validated by 15 test set molecules. The presence of bulky groups at the meta position of anilide group gave a negative effect on activity of the molecule. The presence electrostatic groups on aliphatic chain or heterocyclic rings at the 4th position of pyridine and 6th position of pyrimidine ring is strongly favored both in RSA and MFA. MFA model with r^2 value of 0.83, cross validated r^2 value of 0.764 and RSA model with r^2 value of 0.796, cross validated r^2 value of 0.706 were developed.

Structure-based investigations using molecular docking simulation by GOLD software were performed with crystal structure of P56 LCK (PDB code: 1QPC) and fitness scores were compared with experimental activities. The correlation between experimental activities and GOLD predicted fitness scores was 0.56. The results help to understand the nature of substitutions at the 2-amino and 6-anilide positions. Therefore providing new guidelines for the novel inhibitor design with molecular docking and 3D-QSAR methods can be useful to accelerate the drug discovery process.