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A Quantitative Structure-Activity Relationship Study, Compound Development, Pharmacophore Feature, and Molecular Docking of Pyrazolo-[3,4-d]-Pyrimidine Derivatives as Mer Tyrosine Kinase Inhibitor

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Abstract: Objective: Mer Tyrosine Kinase is ectopically expressed in T and Bcells of Acute Lymphoblastic Leukemia(ALL) patient, but is not expressed in normal human T and B cells at any stage of its development. Therefore Mer Tyrosine Kinase can be a treatment target ALL with a good selectivity. Phosphorylation inhibition of Mer receptor by signal transduction inhibitor decreases cell proliferation and increases apoptosis, there by suppressing the development of leukemia cells. Pirazolo-[3,4-*d*]-pyrimidines are a new generation of drugs that act as inhibitors of Mer tyrosine kinase. The purposes of the present research are to determine descriptors that influence the inhibitory activity on Mer receptor tyrosine kinase, to determine the ligands pharmacopores features and receptors which play important roles i nligand-receptors binding and to study model and free energy value of pirazolo-[3,4-d]-pyrimidines with Mer interactions. **Methods**: Modeling and optimization geometry was carried out using HyperChem® software. Molecules structure were geometrically optimized using Ab initio method. Predictors values were computed using MOE® and statistical calculationsof QSARequations was carried out using SPSS®. The selected equation was determined by the best statistical criteria, such as r^2, Pearson correlations, and q^2 *Leave One Out* validation. Determination of pharmacophores features used optimized model structure using 'Pharmacophore Query ditor' in the MOE software. The study Molecular docking used 'Simulations Dock' where the scoring values were calculated using the London dG approach. **Conclusion:** The most important descriptors were mr, vol_vdw, ASA_H, log S and LUMOenergy. Ligands pharmacophores features were composed of a proton donor, a proton acceptor, one cations and proton donors, and aromatic. Distance (6.92 Å) between cation and proton donors features with aromatic group play importantrole as Mer inhibitors. Receptor pharmocophore features were composed of a proton acceptor (Met 674), three proton donors (Pro 672, Arg727 and Asn728) and one anion (Asp 678), which is important in the binding with ligand features pharmacopore. All of pirazolo-[3,4-d]-pyrimidines derivates had good docking score where as compound 40 had the best scoring -12.7584 kcal/mol.

Keywords : acute lymphoblastic leukemia, pyrazolo-[3,4-*d*]-pyrimidine, Mer, QSAR, pharmacophore features.

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