Three-Dimensional Quantitative Structure-Activity Relationship Analysis of a Set of *Pneumocystis Crainii* Dihydrofolate Reductase Inhibitors Using A Pharmacophore Generation Approach

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Pneumocystis carinii pneumonia (PCP) is one of the premier causes of morbidity and mortality in patients with acquired immunodeficiency syndrome (AIDS) and also affects patients with other immune disorders.[1] Trimetrexate (TMQ) and piritrexim (PTX) are potent lipophilic inhibitors of *Pneumocystis carinii* Dihydrofolate reductase enzyme (pcDHFR), but inhibit mammalian DHFR to a greater extent. Thus, there is great interest in developing potent and selective inhibitors of pcDHFR. Pharmacophore based methods provide a way of establishing a structure–activity relationship for a series of known active ligands. A ligand-based pharmacophore model using Catalyst HypoGen algorithm was developed for set of 2,4-diaminoquinazolines[2] and pyrimidine analogues[3] as pcDHFR inhibitors with an aim to obtain rational hypothetical image of the primary chemical features responsible for activity and this pharmacophore model was used as an in silico screening tool to retrieve novel and potential inhibitors against pcDHFR from various databases. The best pharmacophore model for selective pcDHFR inhibitors (Hypo-1) was obtained through a Cat-Scramble validation process. The best pharmacophore model (Hypo-1) for pcDHFR inhibitors are shown in Fig. 1, consisting of one hydrogen bond acceptor lipid (HBAl), three hydrophobic (HY) and one ring aromatic (RA) features, as well as two exclude volume with highest correlation coefficient (0.94), cost difference (45.1), low RMS (0.72), as well as it shows a high goodness of fit and predictive factor. Hydrophobic interactions are essential for ligand pharmacophore interaction. Highly active compounds share up to three hydrophobic features that allow the ligand to occupy large areas of the predominantly hydrophobic binding pocket. Pharmacophore models have been validated toward a test set containing 8 molecules. To further evaluate the model external test set comprising of known pcDHFR inhibitors were mapped on to developed pharmacophoric model which also showed five point mapping and estimated values in close range to actual values. The models were used for screening chemical data base. This resulted in identification of one druggable structurally diverse potent lead compounds. The results of our study will act as a valuable tool for retrieving potent compounds with desired biological activities and designing novel selective pcDHFR inhibitors.