Designing Hypothesis of Some 2,4-disubstituted-phenoxy acetic acid derivatives as a CRTH2 Receptor Antagonist: A QSAR Approach

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In pursuit of better CRTh2 receptor antagonist agents, 2D-QSAR, 3D- QSAR studies were performed on a series of 2,4-disubstituted-phenoxy acetic acid derivatives. The purpose of the present study was to investigate the physico-chemical parameters of phenoxy acetic acid derivatives responsible for the CRTh2 antagonist activity, to explore the correlation between them. All of the Molecular Modeling studies, reported herein were performed using Win CAChe 6.1 and VLifeMDS, the calculated descriptors for 2D QSAR were related to topological, thermodynamic, spatial, and electronic and we report a novel three-dimensional QSAR approach, kNN-MFA, developed based on principles of the k-nearest neighbor method .Stepwise multiple linear regression analysis was performed to derive QSAR models which were further evaluated for statistical significance and predictive power by internal and external validation.

The best QSAR model was selected, having correlation coefficient R = 0.904, standard error of estimation SEE = 0.456 and cross validated squared correlation coefficient Q2 = 0.739. The predictive ability of the selected model was also confirmed by leave one out cross validation and by leave 33% out Q2 = 688. The QSAR model indicates that the descriptors (logP, SI3, LM, and DVZ). play an important role for the CRTh2 receptor antagonist activities.

The kNN-MFA approach was used to generate models by all three different methods and predict the activity of test molecules through each of these models. The Q2, pred_r2, Vn and k value of kNN-MFA with SW, SA & GA were (0.8392, 0.7059, 2/2) (0.6725, 0.6716, 2/4) and (0.6832, 0.6716, 2/4) SW kNN-MFA method have better q2 (0.8392) and pred_r2 (0.7059) than other two methods, model validation correctly predicts activity 83.9% and 70.5% for the training and test set respectively. It uses 2 steric descriptors with 2 k nearest neighbor to evaluate activity of new molecule.