vLife
adding value to life

Case study: Pharmaceutical

Anti-cancer : AKT1 QSAR model development

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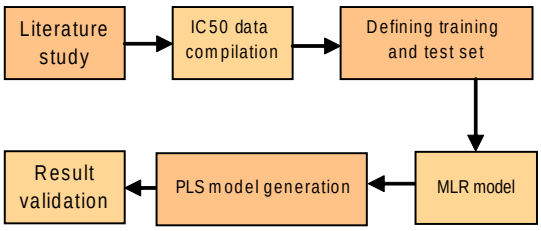
Customer type

A discovery research company

Software modules

VLife Engine

QSARPlus



Application

NCE design

Techniques

Regression

QSAR modeling

Background:

Akt1 (PKBα) is one of the three isoforms of Akt, also known as protein kinase B (PKB). It has been recognized to be responsible for a wide range of proliferative and antiapoptotic processes in many human tumors. Data indicate that PKBα is a central player in tumorigenesis and a potential target for cancer intervention. Consequently the development of molecules capable of blocking PKB activity is a valuable route for anticancer drug discovery. Here we demonstrate the use of PLS and MLR regression methods as well as k- Nearest Neighbor method of model building to understand the structural/ feature requirements for Akt inhibition thus paving way to the design of novel and potent Akt inhibitors.

Design challenge:

The chemical classes of collected Akt1 inhibitors are quite diverse. Generation of quantitative structure activity relationship models using simple 2D descriptors had been a challenge due to the discreetness of the data points.

Project work:

The IC50 affinity data of 266 compounds were collected ranging in activity from 0.16 to 126000 nM. Optimal training set (comprising of 217 molecules) and test set (comprising of 48 molecules) were generated using sphere exclusiona lgorithm.

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VLifeMDS

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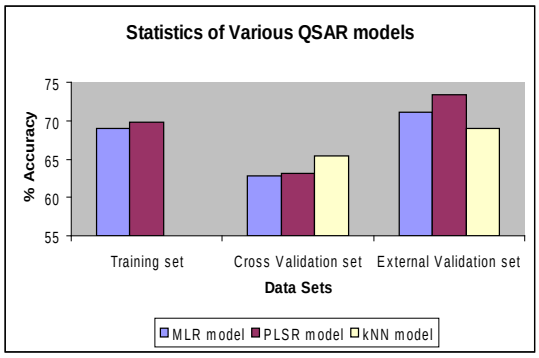
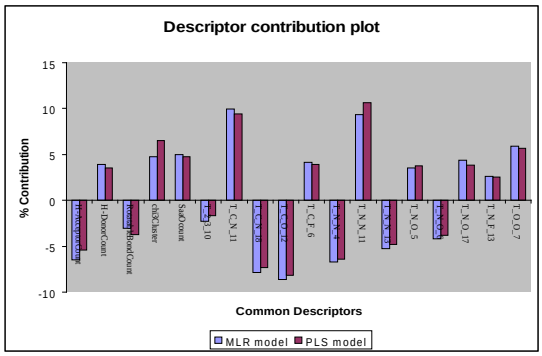


Graph 1: Plot showing percentage accuracy with respect to predictions of various models



Graph 2: Plot of percentage contribution of the descriptors common in both MLR and PLS regression models towards Akt1 inhibitory activity.

A total of 343 descriptors calculated using VLifeMDS software, which included various physicochemical descriptors, Baumann alignment independent topological descriptors and MMFF atom type count descriptors were used for model building with MLR, PLS and kNN methods.

Result analysis:

The models obtained were of optimal statistical significance from the same training data set and having more or less similar prediction statistics, as shown in graph 1, explaining the prediction statistics of various QSAR models. This provides confidence on the selected set of descriptors in various models. Graph 2 shows the comparison of contribution (%) of descriptors common in MLR and PLS regression models. F- test of these models was 22. 98 (for MLR model) and 68.79 (for PLS model), which is much more than the F- test probability value of 1.64 and 1.62. These results give reasonable confidence in the prediction ability of the model with the prediction probability being above 0.005 of the F-test.

Several descriptors contributing to the model provided vital clues for design of novel compounds having Akt1 activity in nM range. The developed models were also utilized for screening of compound databases.

A robust screen was developed using above models for finding Akt1 inhibitors by VLife.

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