vLife
adding value to life

Case study: Pharmaceutical

Anti-cancer : Classification model development

Avantika Agrawal, Dr. Subhash Ajmani

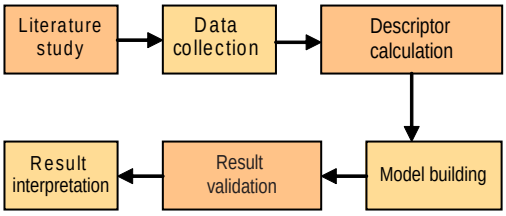
Customer type

A leading discovery research company

Software modules

VLife Engine

QSARPlus



Application

Data classification

Techniques

kNN

Background:

Among the approaches under investigation for the treatment of Cancer, Akt (or protein kinase B (PKB)) inhibition has recently generated considerable attention as anticancer target. It has been found to be responsible for a wide range of proliferative and anti-apoptotic processes in many human tumors like breast cancer, human prostate, ovarian carcinomas etc. Akt is a subfamily consisting of Akt1 (PKBα), Akt2 (PKBβ), and Akt3 (PKBγ). Each of these are composed of a kinase domain, an N-terminal pleckstrin homology (PH) domain and a short carboxy terminal tail region.

Design challenge:

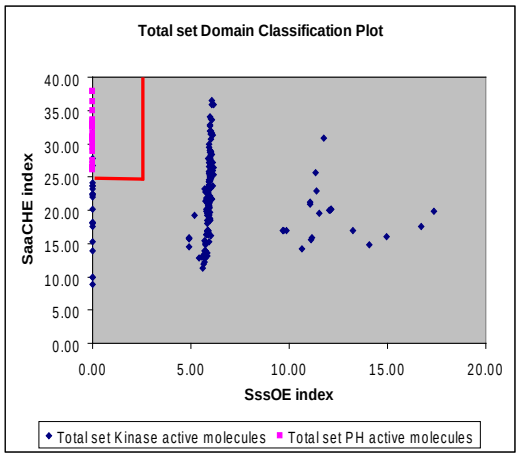
There are lot of issues for existing Akt1 inhibitors towards selectivity against various other kinases, which is mainly due to acting on kinase catalytic domain as compared to PH domain. So it was thought worthwhile to develop a discriminant model to predict binding domain of a new molecule. The developed discriminant model may be helpful in shortlisting the molecules on the basis of their predicted AKT1 binding domain.

VLife Sciences Technologies Pvt. Ltd.
Pride Purple Coronet, 1st Floor,
Baner Road, Pune - 411 045, India

Phone: +91 20 2729 1590
Web: www.vlifesciences.com
E-mail: products@vlifesciences.com

VLifeMDS

Case study: Pharmaceutical



Graph 1: Akt domain classification plot

Project work:

Akt1 data of 267 molecules, reported to have activity against PH or kinase domain was compiled. Binary response was considered to generate the discriminant model with 212 molecules (including 21 PH-domain and 191 kinase domain active molecules) in the training set and 54 molecules (including 13 PH- domain and 41 kinase domain active molecules) in the validation set. Training and test set were selected by sphere-exclusion method. Topological and electro-topological descriptors were evaluated. k Nearest Neighbor (kNN) classification method in VLifeMDS was used to generate the model.

Result analysis:

A kNN model with 2 nearest neighbors with 100% classification predict-ability was obtained. Kinase and PH domain classification plot with respect to the two important descriptors SssOE index and SaaCHE index is shown in graph 1. It can be seen that with these descriptors the model is able to classify all the kinase and PH domain molecules (PH domain molecules pink points within the red rectangular line). Both q2 = 1.0 and r2 = 1.0 for the model indicate utility of above method. Thus the model is able to discriminate the overall dataset correctly with respect to the two classes (i.e. kinase or PH domain). This model was further utilized to screen molecules to identify their binding mode.

Reliable method was suggested for domain specific activity of Akt inhibitors by VLife.

VLife Sciences Technologies Pvt. Ltd.
Pride Purple Coronet, 1st Floor,
Baner Road, Pune - 411 045, India

Phone: +91 20 2729 1590
Web: www.vlifesciences.com
E-mail: products@vlifesciences.com