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Research Article

QSAR - Based Molecular Signatures of Lantadenes Underlying Anticancer Potency Against A549 Cell Lines

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Abstract

Traditional drug discovery methods have a basis in trial-and-error. In contrary, rational drug design approaches attempt to modulate specific structural features with the hope for a better therapeutic value. Typically, the quantitative structure activity relationship (QSAR) is one of the most widely used molecular modelling technique. Lantadenes are bioactive compounds derived from the *Lantana camara* showing anticancer potentials. But so far, no 2D and 3D-QSAR studies have been reported. Utilizing the advantage of this technique, in the present study, two and three-dimensional QSAR of lantadene derivatives have been developed for anticancer activity against A549 cell lines. The regression coefficient (r^2), internal cross-validation regression coefficient (q^2) and external cross-validation regression coefficient ($pred\_r^2$) of derived QSAR models were 0.87, 0.81 and 0.82 respectively. Furthermore, in order to highlight the key structural controlling regions and different active and inactive sites, field points-based descriptors were used to develop a 3D-QSAR model by aligning known active compounds on to identified pharmacophore template. The derived LOO validated PLS regression QSAR model showed acceptable r^2 0.81% and q^2 0.78%. Hence, this method suggests the key structural features/ consideration in designing of lantadenes as potential anticancer agents.

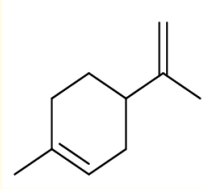
Keywords: Lantadene; Anticancer; NF-kB; QSAR

Abbreviations

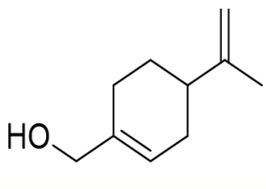
NF-Kb: Nuclear Factor kappa-beta; MS: Manual Selection; RS: Random Selection; SE: Sphere Exclusion Method; QSAR: Quantitative Structure Activity Relationship

Introduction

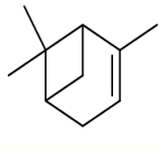
Natural products offer unexplored intricate molecular frameworks for the development of chemical leads and innovative drugs [1-3]. Terpenoids are one of the most diverse and most extensively investigated family of natural products and serve as an important source for medicinal treatments [4-5]. These metabolites shown in figure 1 have been reported to possess activity against malaria, infectious diseases, inflammation and cancer [6-8]. Some of the metabolites like Lantadenes from the weed *Lantana camara* have been known with potent cytotoxic activity against a number of cancer cell lines and showed anti-antitumor potential [9-11].



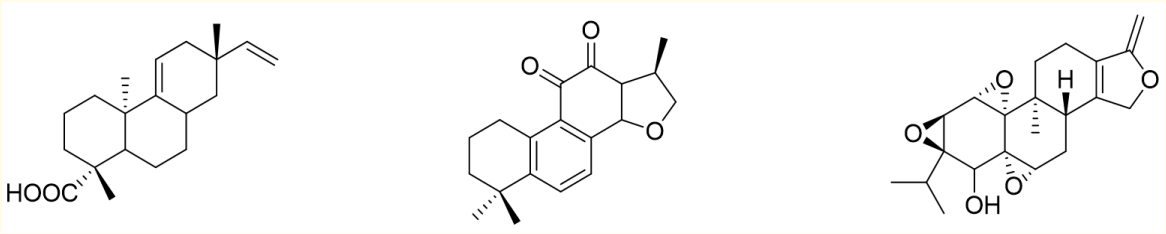
Limonene



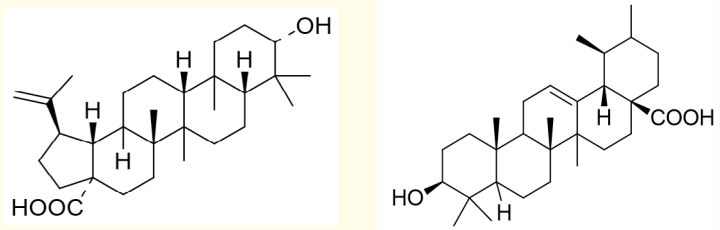
Perillyl alcohol



alpha-Pinene



Acantholic acid **Tanshinone IIA** **Triptolide**



Betulic acid **Ursolic acid**

Figure 1: Chemical structure representation of biological active terpenoids.

A number of mechanisms have been proposed for their activity but, majority of them have been found to have the nuclear factor kappa-beta (NF-κB) signalling pathway [12-13]. Since NF-κB as shown in figure 2 [14] was first shown to serve as a molecular lynchpin that links persistent infections and chronic inflammation to increase cancer risk, the young field of inflammation and cancer have now become of age, and inflammation has been recognized by the broad cancer research community as a hallmark and cause of cancer [15-17].

Presently, advances in areas such as 'organ on a chip' technologies and artificial intelligence are extensively providing the bases for more widespread application of semi-autonomous or even fully autonomous processes that help to rationalize the development of molecules with nature inspired physicochemical properties in identifying and optimizing hit to lead in drug discovery [18-19]. The benefits of automation include: diminished measurement errors and reduced material consumption by the application of standardized procedures with robotic support; shortened synthesize-and-test cycle times [20-21].

Quantitative structure–activity/property relationship (QSAR/QSPR) models characterize the associations among molecular descriptors (numerical representations derived from the underlying molecular structure) that represent information related to the

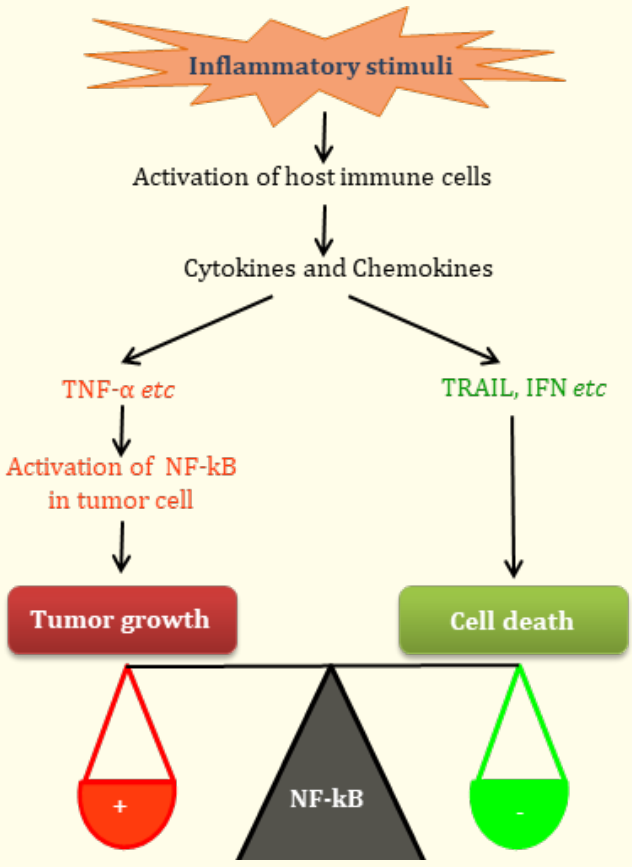


Figure 2: Role of NF-κB in tumor growth [15].

structure of chemical compounds and a target physicochemical or biological property under study [22-23]. These models play a central role in drug identification or optimization of drugs, because they allow a preliminary *in silico* evaluation of crucial properties related to the activity, selectivity, and toxicity of candidate molecules. In this way, important savings in terms of money and time can be achieved during the drug discovery projects and therefore be more efficient [24-25].

Innumerable articles are available on the diverse biological activities of the natural and the semi synthetic lantadene derivatives, but papers indicating the key regulatory features controlling the anticancer activity are very rare. In this context, it is aimed to analyse 2D and 3D QSAR structural requirements by performing QSAR studies on a data set of lantadene derivatives as NF-kB inhibitors against A549 Cell Lines. The model deduced from these investigations provides underlying structural requirements, steric and electrostatic influences and good predictive ability, which could aid new NF-kB inhibitors prior to their synthesis.

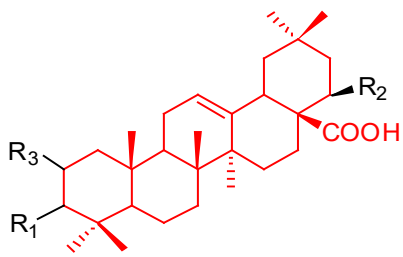
Materials and Methods

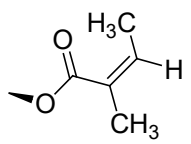
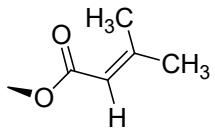
All molecular modelling studies 2D and 3D QSAR were performed using the Molecular Design Suite (V Life MDS 4.6.07082017 software package, from Pune, India) on an HP Pentium IV 2.80 GHz Processor/ Microsoft Win XP Home Edition system [26]. The structures of all compounds were sketched in Chem sketch version 12.0. The 2D structures were transformed into 3D structures using the converter module of V Life software followed by their energy minimization, which was performed in two steps. The first step was energy minimization using Merck molecular force field method with molecular mechanics-2 (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/mol Å and in the second step, minimized MM2 (dynamics) compounds were subjected to re-optimization through the Molecular Orbital Package method (MOPAC) until the RMS gradient attained a value smaller than 0.0001 kcal/mol Å24. Conformers for all the structures were generated and low energy conformer for each compound was selected for further studies [27-28].

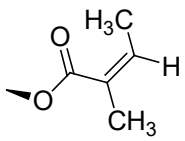
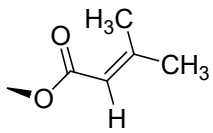
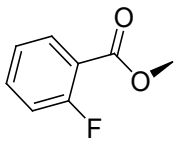
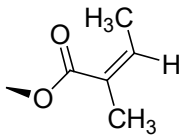
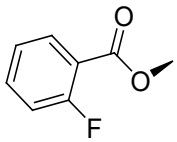
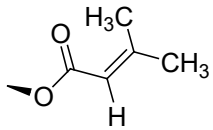
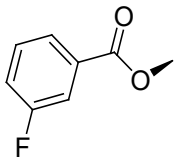
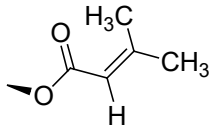
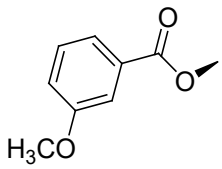
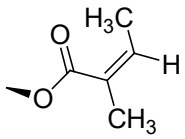
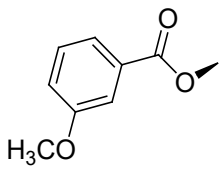
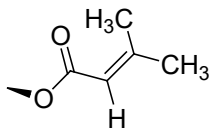
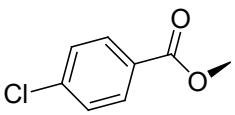
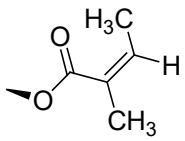
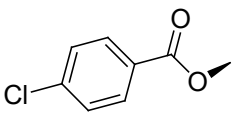
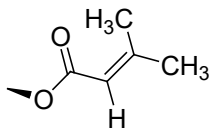
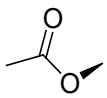
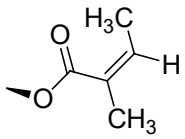
2D - QSAR study

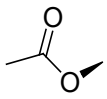
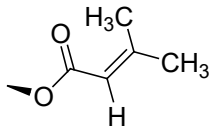
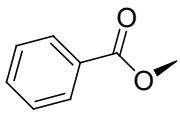
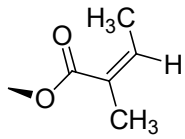
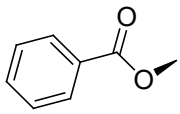
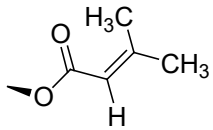
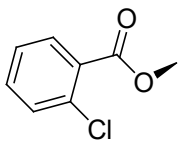
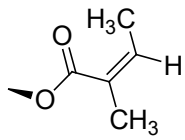
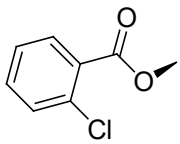
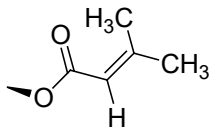
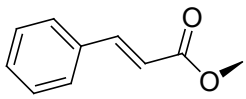
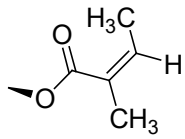
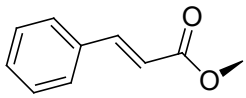
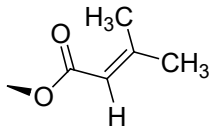
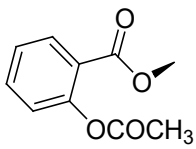
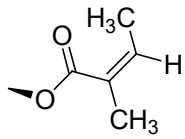
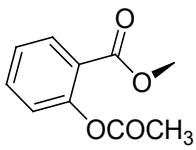
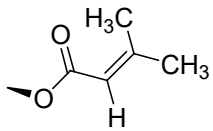
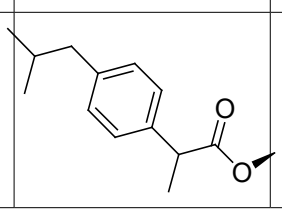
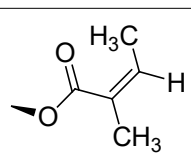
Dataset and molecular modelling

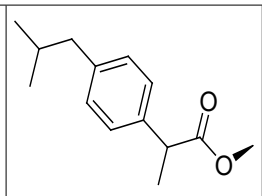
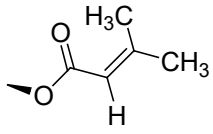
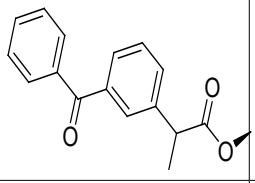
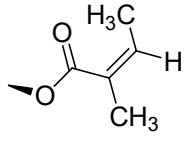
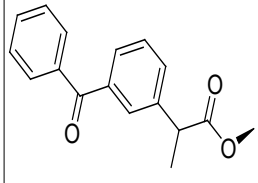
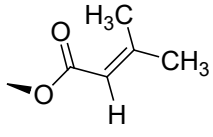
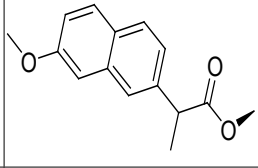
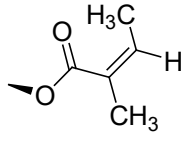
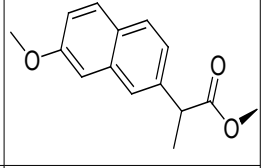
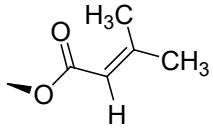
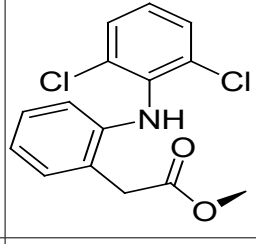
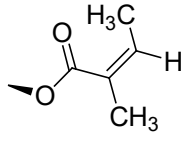
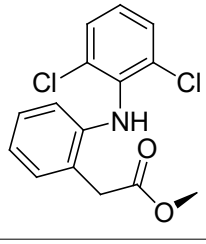
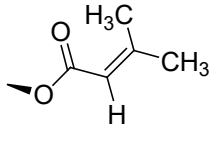
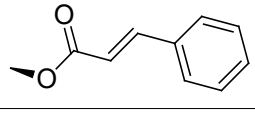
We had chosen Manu Sharma and co-workers data [8,11,23,29], on lantadene derivatives as antitumors, wherein the activity was expressed as IC_{50} and is defined as the half maximal inhibitory concentration (IC_{50}), a measure of the effectiveness of lantadene derivatives against A549 cell lines. *In vitro* effective concentrations of the molecules were converted into logarithm units (corresponding pEC_{50} values) shown in table 1 and used as dependent variables for the QSAR calculations.



Compound	R1	R2	R3	pIC_{50}	Predicted IC_{50}	Training/ Test/ Validation set
1	=O		H	2.84	5.96	Training set
2	=O		H	1.19	5.96	Test set

3	-OH		H	0.79	6.48	Validation set
4	-OH		H	0.43	5.87	Training set
5			H	2.04	5.96	Test set
6			H	1.96	5.99	Training set
7			H	6.86	5.74	Training set
8			H	1.84	6.12	Training set
9			H	0.98	5.49	Training set
10			H	1.32	5.60	Test set
11			H	1.12	6.04	Training set
12			H	5.42	5.84	Validation set

13			H	4.90	6.49	Training set
14			H	7.36	5.82	Training set
15			H	7.20	5.87	Training set
16			H	6.80	5.30	Test set
17			H	6.52	6.06	Training set
18			H	0.12	5.21	Test set
19			H	0.08	6.17	Training set
20			H	0.77	6.39	Training set
21			H	1.10	6.15	Training set
22			H	0.75	6.23	Training set

23			H	1.13	5.87	Training set
24			H	1.31	5.9	Validation set
25			H	1.23	6.4	Test set
26			H	0.90	5.85	Training set
27			H	0.91	5.42	Training set
28			H	0.15	5.34	Training set
29			H	0.42	5.57	Training set
30	=O		H	3.64	5.60	Training set

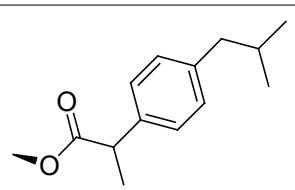
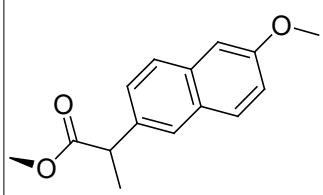
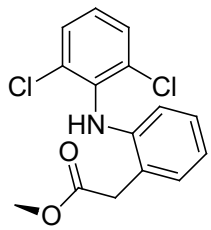
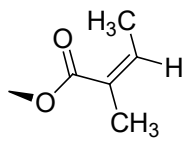
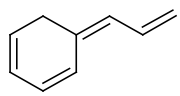
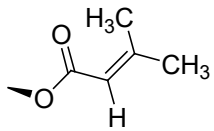
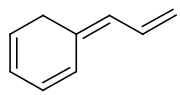
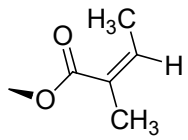
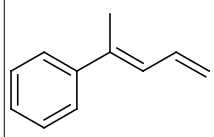
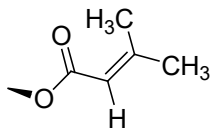
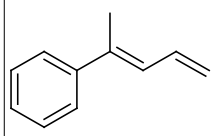
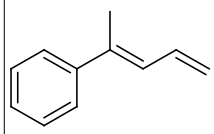
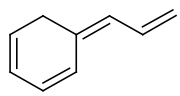
31	=O		H	2.95	6.03	Training set
32	=O		H	3.45	5.75	Test set
33	=O		H	1.65	6.51	Validation set
34	=O			0.48	5.89	Training set
35	=O			0.54	5.15	Training set
36	=O			2.31	5.78	Test set
37	=O			9.36	5.49	Training set
38	=O	-OH		2.08	6.43	Validation set
39	-OCH3	-OH	H	2.25	5.72	Training set
40	=O	-OH		2.80	5.36	Training set

Table 1: The selected series of lantadene derivatives for 2D and 3D QSAR studies.

Prior to the QSAR model development, selected experimental dataset of 40 compounds was divided into two sets using various methods such as Manual selection method (MS), Random selection method (RS) and Sphere exclusion method (SE). Twenty-seven (27) molecules were chosen based on the activity variation to represent the quantitative model (training set), 8 molecules as test set, and rest of the 5 molecules were kept for internal validation of the proposed models. A Uni-Column statistic for training and test set were generated to check correctness of selection criteria of trainings and test set molecules shown in table 1. Additionally, leave one- out protocol was performed on the training set for internal validation by automatic software for the obtained models.

Descriptor calculations

According to Deschini and Consonni, "The molecular descriptor is the final result of a logic and mathematical procedure, which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment" [30]. A large number of theoretical 2D individual descriptors such as molecular weight, volume, XlogP; physiochemical parameters such as estate numbers, estate contributions, polar surface area, element count, dipole moment, hydrophobicity XlogpA, hydrophobicity, SlogpA; topological etc have been computed. The correlation matrix was applied to select the predominant descriptors influencing the antitumor activity of the analogues taking each descriptor as independent variables and IC50 as dependent variable. A total of 220 descriptors were calculated by QSAR tool module within VLife Sciences Molecular Design Suite. The descriptors having the same value or almost same value or highly correlated with other descriptors were removed initially, applying invariable column selection, as they do not contribute to the QSAR. The reduced set of 137 descriptors were then treated by stepwise variable selection (SW), genetic algorithm (GA), simulated annealing (SA) with statistical methods including Multiple linear regression (MLR), Principal component regression (PCR), Partial least squares (PLS) and kNN (k-Nearest Neighbor method) for further reduction of non-significant descriptors.

Statistical analysis and validation

Innumerable 2D - QSAR models were generated using MLR, PCR, PLS and kNN based regression/ algorithm using various variable selection method including SW, GA, SA. Descriptors showing highest correlation with biological activity were selected for generation of the QSAR model. For getting reliable results, parameters were set such that the regression equation should generate number of independent variables (descriptors) 5 times less than that of compounds or molecules. The program computes the best model on the basis of regression coefficient (r^2) indicating the variance in the observed activity values; internal cross-validation regression coefficient (q^2) a relative measure of quality of fit; external cross-validation regression coefficient (pred_r^2) reflecting the external predictive power and Fischer's value F-test represents F-ratio between the variance of calculated and observed activity.

The calculated value of F-test in comparison with tabulated value of F-test shows the level of statistical significance (99.99%) of the QSAR model. Whereas low standard error of pred_r^2, q^2, and r^2 reflects the absolute quality of fitness of the model [30-32]. The generated QSAR models were validated for predictive ability inside the model using cross validation (leave-one-out, LOO) for q^2 and external validation, a more robust alternative method by dividing the data into training set and test set and calculating pred_r^2. The statistical significance of selected 2D - QSAR model was further supported by the 'fitness plot' obtained, namely a plot of observed versus predicted activity of training and test set compounds that provided an idea about how well the model was trained and how well it predicted the activity of the external test set. The contribution chart for the significant model gave the percentage contribution of the descriptors used in deriving the model [31].

3D - QSAR study

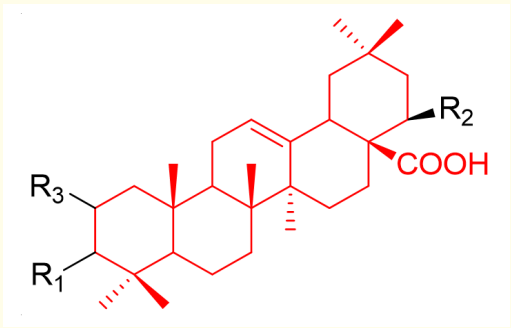
Data set and molecular modelling

The total set of compounds was divided into subsets such as training: test: Internal validation set: 27:8:5 using the same methods as previously described in the 2D-QSAR models' development. Multiple conformation of each molecule was generated using the Monte Carlo conformation search method. It is a random search method for finding the conformations of molecules, which uses the metropolis condition to accept or discard generated conformers. Nine thousand, eight hundred and twenty-nine (9829) descriptors were produced and prior to model development descriptors having zero values or same values were removed and finally 9746 descriptors for all the compounds were used for the further studies.

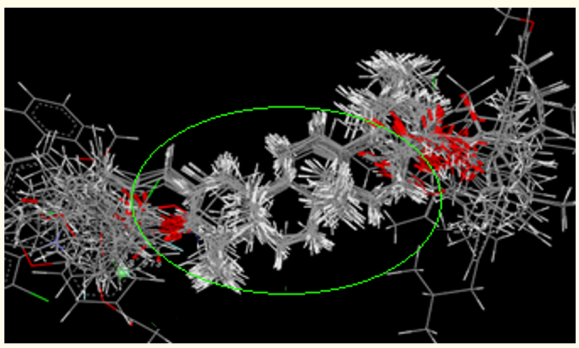
Molecular alignment

The 3D - QSAR method define descriptors by calculating the different molecular properties at the intersection points of a 3D frame. Molecular alignment is a crucial step in the ligand-based 3D-QSAR modelling method to obtain meaningful results. All molecules in the data set were aligned by template-based method, where a template structure is defined and used as a basis for

alignment of a set of molecules. Template is built by considering common sub-structures in the series as shown in figure 3.



(a)



(b)

Figure 3: (a) Template structure; (b) 3D view of aligned lantadene derivatives on template.

Further, highly bioactive energetically stable conformation in the series is chosen as a reference molecule on which other molecules were aligned.

Descriptor calculations and model evaluation

Using Tripos force field and Gasteiger and Marsili charge type electrostatic, steric and hydrophobic field descriptors were calculated. The dielectric constant was set to 1.0, considering the distance-dependent dielectric function. Probe setting was carbon atom with charge 1.0. This resulted in the calculation of descriptors for each electrostatic, steric, and hydrophobic for all the compounds. QSAR analysis was performed after removal of all the invariable columns, as they do not contribute to the QSAR. Developed quantitative models were evaluated using the following statistical measures: number of observations (molecules) in the training set, regression coefficient (r^2), internal cross-validation regression coefficient (q^2), number of k-nearest neighbour, pred_r^2 se, cross-validated r^2, pred_r^2, q^2_se, standard error of cross-validation. The low standard error of pred_r^2 se and q^2_se shows absolute quality of fitness of the model. Finally, q^2 and pred_r^2 values were used as deciding factors in selecting the optimal models.

Results and Discussion

2D QSAR

Literature has indicated promising role of lantadene derivatives against the as anticancer agents, but no reports have been found structural features/ considerations responsible for the activity. Therefore, to investigate the potentials of these derivatives, QSAR studies were performed using molecular QSAR approach. Several statistically significant 2D - QSAR models (MPR, PLS, PCR, kNN) were generated using various variable selection methods resulting in three best models. Wherein, equation/ models 1 - 3 indicating the relation between biological activity and descriptors, fitness; contribution and contour plots are shown in the figure 4a and 4d.

Obtained equation 1 using SW-F, kNN approach indicated an activity–descriptors relationship with internal (q^2) and external (pred_r^2) predictive ability as 59% and 67% respectively. Descriptors- Z comp Dipole, XK Most Hydrophobic, Hydrophilic Distance, 1Path Count, SdOcount, SA Most Hydrophobic, Hydrophilic Distance showed positive contribution toward the anticancer activity.

Predicted log IC_{50} = +0.0141 (Zcomp Dipole)-0.1598 (XK Most Hydrophobic Hydrophilic Distance) +0.0715 (1PathCount) +0.7501 (SdOcount) +0.3134 (SA Most Hydrophobic Hydrophilic Distance) … **Model/Equation 1**

where, descriptor signifies the followingx

- **ZcompDipole**: Z component of the dipole moment.
- **XK Most Hydrophobic Hydrophilic Distance**: Distance between most hydrophobic and hydrophilic point on the vdW surface.
- **1PathCount**: Total number of fragments of first order (bonds) in a compound.
- **SdOcount:** Total number of oxygens connected with one double bond.
- **SA Most Hydrophobic Hydrophilic Distance:** Distance between most hydrophobic and hydrophilic point on the vdW surface.

To improve the external predictivity of the model, kNN analysis was performed on given data set. Model with internal (q^2) and external (pred_r^2) predictive ability of 73% and 68% respectively, indicated very small increase in the pred_r^2. The model showed that

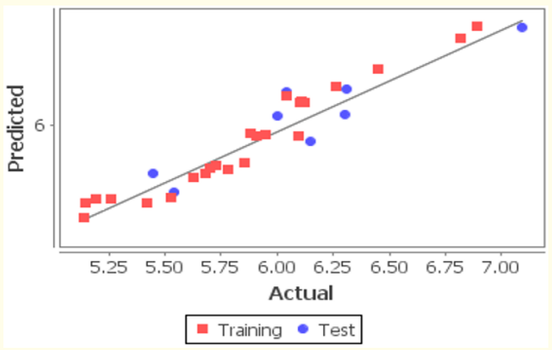
descriptors (SsCH3count, Fluorines Count, Quadrupole3, k2alpha, Dipole Moment) were highly correlated with the biological activity.

Predicted log IC_{50} = + 0.0137 (SsCH3count), +0.0421 (Fluorines Count), -0.1650 (Quadrupole3)-0.6831 (k2alpha), -0.1836 (Dipole Moment) ……. **Model/Equation 2**

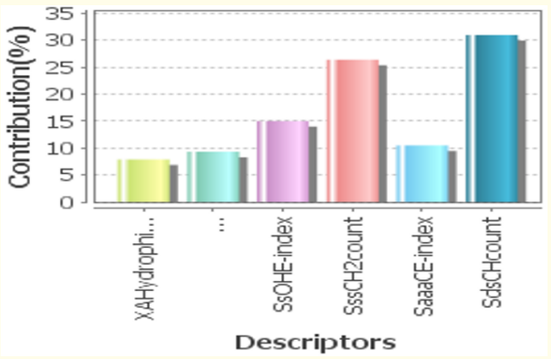
where, descriptor signifies the following

- **SsCH3count:** Total number of –CH3 group connected with single bond.
- **Fluorines Count:** Number of fluorine atoms in a compound.
- **Quadrupole3:** Magnitude of third tensor of quadrupole moments.
- **k2alpha:** Second alpha modified shape index.
- **Dipole Moment:** Dipole moment calculated from the partial charges of the molecule.

Highly statistically significant model 3 was obtained using SW-PLS approach wherein descriptors (XA Hydrophilic Area, H-Acceptor Count, SsOHE-index, SssCH2, SaaaCH-index, SdsCHcount) showed good correlation with biological activity with r^2 = 0.87 and q^2 = 0.81%. The low standard error of r^2_se = 0.1421 demonstrated the accuracy of the model. The model was found to be statistically significant, with F test value 26.528. Good internal predictive power of the model has been indicated LOO based validation approach gave high q^2 = 0.81% and low q^2_se = 0.1623. However, a high q^2 value does not necessarily give a suitable representation of the real predictive power of the model for ligands, thus an external validation was also carried out in the present study. Parameter with high pred_r^2 = 0.82% and low pred_r^2se =1.7431, confirmed the predictive power of the model. The fitness, contributions (positive and negative) aggregate of each of the descriptors has been provided in figure 4a and 4b. Further, a radar plot representing the closeness between the actual and predicted activity of training and test set compounds has also been summarized in figure 4c and 4d.



4(a)



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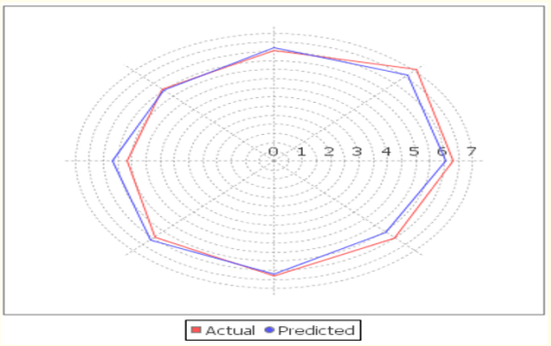
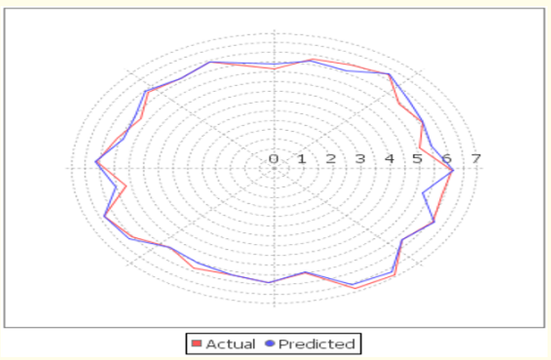


4(c)



4(d)

Figure 4: (a) Fitness plot of training and test set molecules; (b) Contribution plot of various descriptors; (c) Radar plot showing overlapping of actual and predicted activity of test set (d) Radar plot showing overlapping of actual and predicted activity of training set by SW-PLS method.

Predicted log IC_{50} = 0.0141 (XA Hydrophilic Area) + 0.1598 (H-Acceptor Count) + 0.0715 (SsOHE-index) +0.7501 (SssCH2) + 0.3134 (SaaaCH-index) + 0.5794 (SdsCHcount)……. **Model/Equation 3**

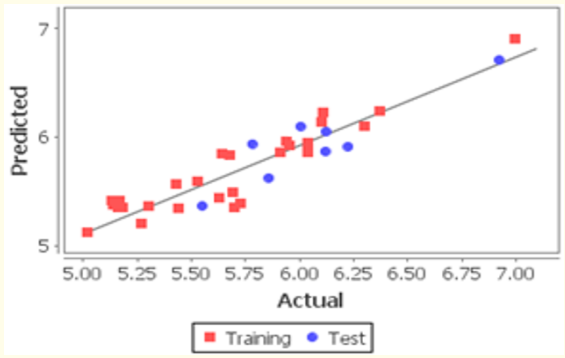
where, descriptor signifies the following

- **XA Hydrophilic Area:** vdW surface descriptor showing hydrophilic surface area.
- **H-Acceptor Count:** Number of hydrogen bond acceptor atoms.

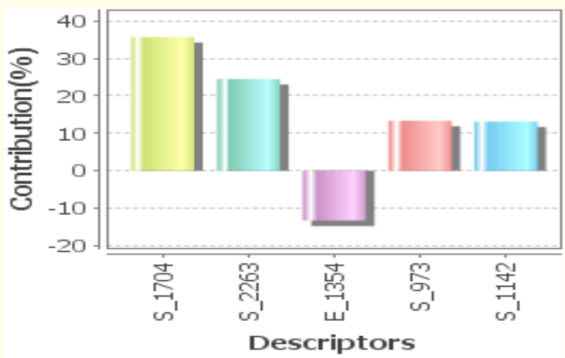
- **SsOHE-index:** Electro topological state indices for number of –OH group connected with one single bond.
- **SssCH2:** Total number of –CH2 group connected with two single bonds.
- **SaaaCH-index:** Electro topological state indices for number of carbon atom connected with three aromatic bonds.
- **SdsCHcount:** Total number of –CH group connected with one double and one single bond.

3D QSAR

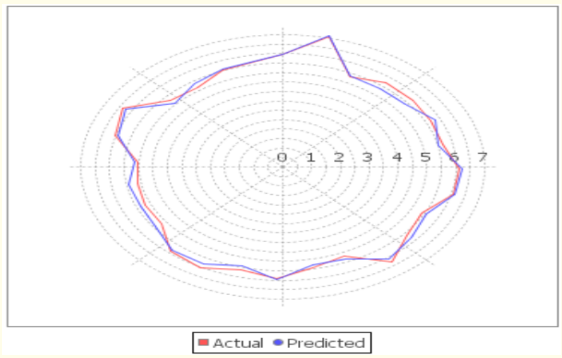
Abundant 3D-QSAR models were generated using SW, SA and GA variable selection method, of which the corresponding best models are reported herein. Model indicating the relation between biological activity and molecular field analysis (MFA) include the electrostatic (E), steric (S) and hydrophobic (H) fields being represented by blue, green and red ball respectively along with their range (negative/ positive) to indicate their importance for biological activity. Furthermore, fitness; contribution and contour plots are reported in the figure 5.



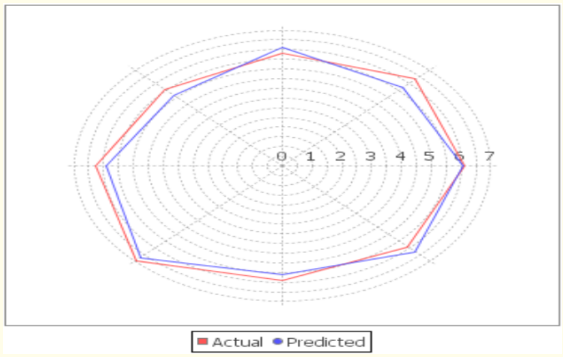
(a)



(b)



(c)



(d)

Figure 5: (a) Fitness plot of training and test set molecules; (b) Contribution plot of various descriptors. (c) Radar plot showing overlapping of actual and predicted activity of test set (d) Radar plot showing overlapping of actual and predicted activity of training set by SW-F-MLR method.

The statistical results generated with SA using kNN methodology, relies on a simple distance learning approach, whereby an unknown member is classified according to the majority of its k-nearest neighbours in the training set. The nearness is measured by an appropriate distance metric. This method was found to be statistically significant, especially with respect to the internal predictive ability ($q^2 = 0.75$) of the model. But, at the same time external predictive ability pred r2 was found to 0.59%. The generated points in SA-kNN method are H_1703 (1.2566 1.4877), H_2513 (2513 0.7244 0.8252) E_431 (-0.1879 0.0191), S_2652 (-0.7305 -0.5825) and S_1157 (11.2481 30.0000) indicating the significance and requirement of hydrophobic, electrostatic and steric features for anticancer potential along with the ranges in parenthesis. Further attempts were made to improve these statistical parameters.

Model developed by SW-kNN method where, SW- forward variable selection algorithm, search procedure begins with developing a trial model step by step with a single independent variable. To each step; independent variables are added one at a time, examining the fit of the model by using the kNN cross-validation procedure. Improved internal and external predictive powers have been indicated with high q^2 and pred_r^2, 0.76% and 0.63% respectively. Generated model indicated the importance of electronic {E_3069 (0.1144 0.4666), E_1342 (-2.2298 -1.3803), E_233 (-0.0031 -0.0026), E_64 (30.0000 30.0000)} and steric S_1704 (-1.0402 -0.5816) groups required for optimum anticancer activity.

Model generated by SW-F-MLR, was found to be statistically most significant among the all developed models, especially with respect to the regression coefficient (r^2 = 0. 81), which depicted the accuracy of the model. Further, reliability and accuracy of the model has been indicated by cross-validated q^2 value i,e. 0. 78%. Statistical significance of the model was finally confirmed by the high value of observed F-test (34.30) against the calculated F-test value of 24. Contour plots for test set and training set also showed a good overlap to actual and predictive value.

The generated points contribution shown in figure 6 are S_1704 (0.0375 (± 0.0044), S_2263 (0.0210 (± 0.0035), S_973 (0.0116 (± 0.0039) S_1142 (0.0434 (± 0.0151) and E_1354 (- 0.0259 (± 0.0094) for steric and electrostatic field interactions respectively and the relative contribution indicates that steric field is more predominant.

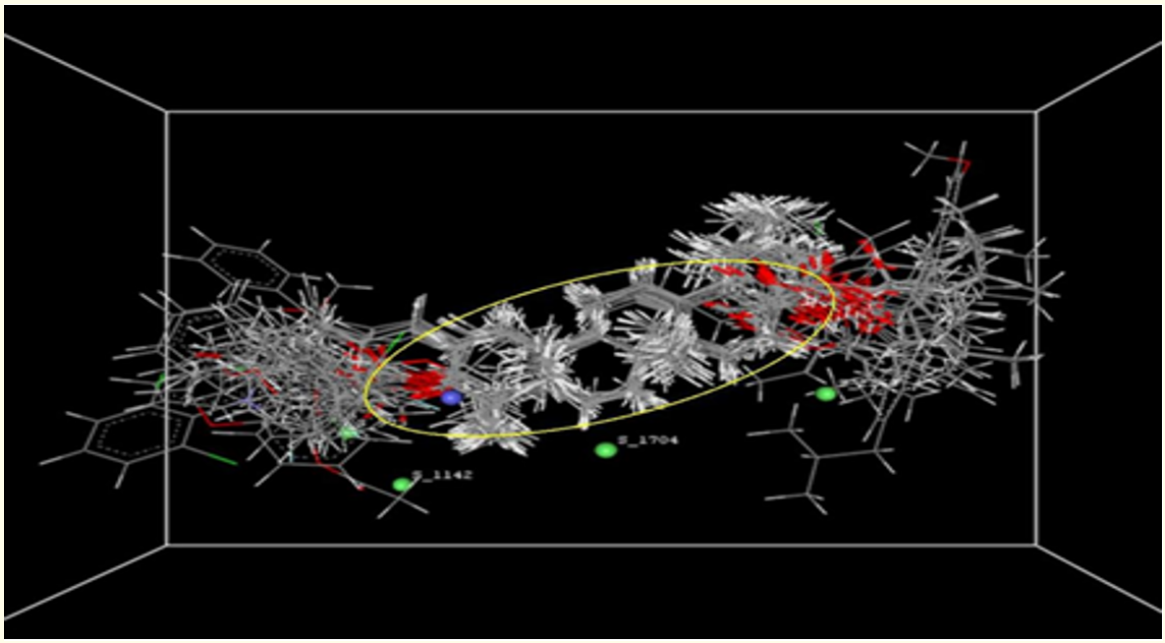


Figure 6: Stereoview of the molecular rectangular field grid generated around the superposed molecular units of lantadene derivatives using SW-F-MLR model.

It is evident that the predicted activities of all the compounds in the test set are in good agreement with their corresponding experimental activities and optimal fit as shown in table 1. Contribution plots with green coloured ball near ring A and D/E with positive contribution revealed the bulky groups are favourable at the respective regions. Further insights into the contribution plot with presence of blue coloured ball led to the conclusion that not only steric properties but also electronegative effect guides the activity, and electron releasing group would decrease the activity, in contrast to electron withdrawing group that resulted into increased activity as exemplified by choro substituted lantadene esters.

Design of lantadene pharmacophore

The quest for high target potency should not be pursued blindly, without an understanding of its relevance to efficacy and efficiency. The strategy used in this study may provide understanding in

designing novel and promising lantadene derivatives as anticancer agents. The findings of 2D and 3D QSAR studies summarised and shown in figure 7, indicated the overall substitution pattern required around the lantadene pharmacophore.

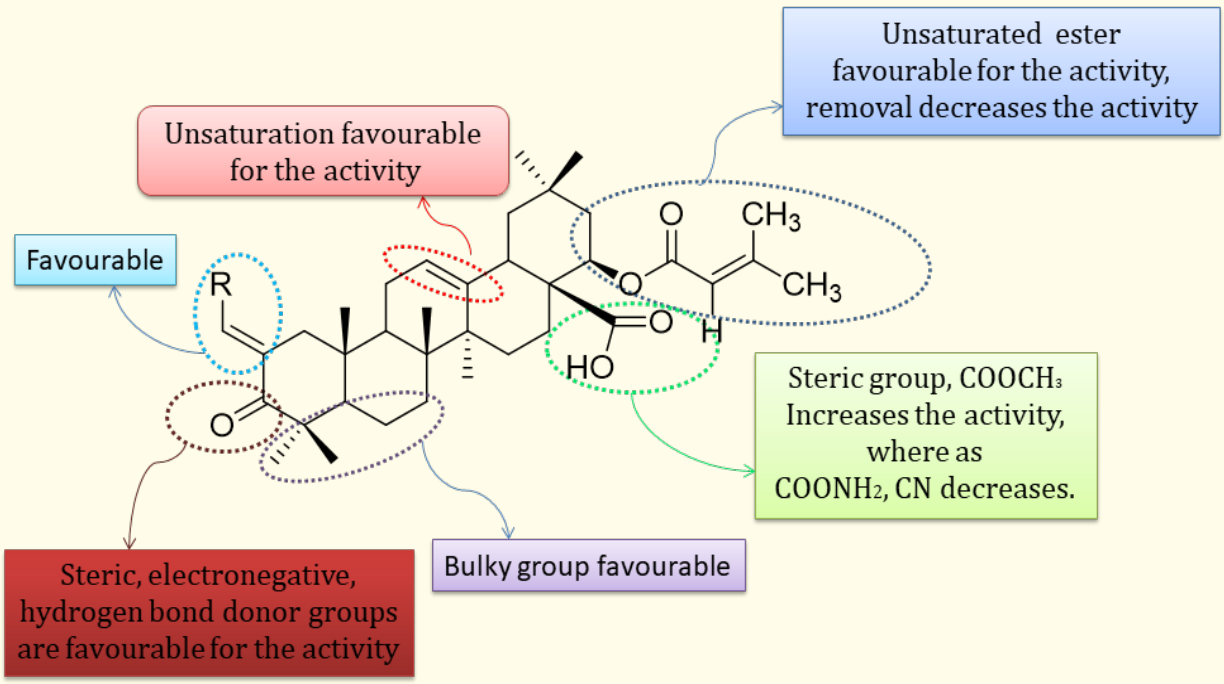


Figure 7: Pharmacophoric requirement around lantadene derivative.

Designed scaffold forms a basis for future synthesis of the designed analogues with promising biological activity.

Conclusion

In conclusion we expect our findings validated this divulged molecular representation for hit to lead findings.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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