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**Research Article**

# QSAR MODEL FOR IDENTIFY NEW ACTIVE MOLECULE AGAINST HUMAN PHASPHOLIPASE $A_2$ ENZYME

Irfan N, Jothilingam. S, Ramesh Kumar. N,
Department of pharmaceutical chemistry, C l baid Metha College of pharmacy,
Jyothi nagar, Thorapakkam
Chennai-96, TamilNadu, India.

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**Corresponding author's email:* nirfanahamed1985@live.com

## ABSTRACT

The present research work deals with identification of biologically active molecule against human phaspholipase $A_2$ enzyme with the help of QSAR model. Phospholipase $A_2$ is an enzyme which hydrolyzes the sn-2 position of certain cellular phospholipids. The liberated lysophospholipid and arachidonic acid are precursors in the biosynthesis of various biologically active products. As human pancreatic $PLA_2$ is present high level in the blood of patients are the responsible for several pathological conditions like septic shock, pancreatities, trauma, bronchial asthma, gout and other diseases. The potent $PLA_2$ inhibitors have been suggested to be useful drugs. This QSAR model created based on the 23 physicochemical parameters of 79 indene and indole molecules. The genetic function approximation (GFA) method performs a search over the space of possible QSAR models using lack of fit (LOF) scores to estimate the fitness of each model. These models lead to the discovery of predictive QSAR equations. The correlation coefficient value of this equation was found to be 0.968. With this equation we can easily find the novel biologically active compound against several pathological conditions.

**Key words:** QSAR model, Phospholipase $A_2$, Anti-inflammatory

## INTRODUCTION

Phospholipase $A_2$ is an enzyme which hydrolyzes the sn-2 position of certain cellular phospholipids. The liberated Lysophospholipid and Arachidonic acid are precursors in the biosynthesis of various biologically active products. As human pancreatic $PLA_2$ is present high level in the blood of patients are responsible for several pathological conditions. The potent $PLA_2$ inhibitors have been suggested to be useful drugs.

The present study was to create QSAR model based on 23 physicochemical parameters of 79 indene and indole molecules. This model will help the medicinal chemist to target efforts on Analogues which should have improved activity and thus cut down the number of Analogues which have to be made. If an analogue is discovered which does not fit the equation, it implies that some other feature is important and provides a lead for further development.

**MATERIALS AND METHODS**

Present experimental studies carried out using the tools

**Accelrys software**

Discovery studio is a complete modeling and simulations environment for life science researchers. Discovery Studio is a single, easy-to-use, graphical interface for powerful drug design and protein modeling research. Discovery Studio 2.1 combines established gold-standard applications such as Catalyst, Modeler, and CHARMm that have years of proven results and utilizes cutting-edge science to address the drug discovery challenges of today. Discovery Studio 2.1 is built on the Pipeline Pilot open operating platform to seamlessly integrate protein modeling, pharmacophore analysis, virtual screening, and third-party applications

**Preparation of molecular system:**

**Macro molecule (protein 1db4) preparation:**

For this QSAR studies, the protein 1DB4 load from RCSB protein data bank (www.rcsb.org/pdb/) and apply the force field .Force field refers to the functional form parameter sets which are used to find out potential energy of a system. It includes parameter which is obtained through experimental works and quantum mechanics calculations.

All molecules in a molecule in a mechanical system are made up of a number of components. Covalently bonded atoms takes into consideration several parameters such as bond length , bond angle , dihedral angles etc., similarly there exists non bonded interactions such as vanderwaals interactions , electrostatic interactions . Thus the total potential energy of the system is calculated as follows E1= [E bond + E angle + E torsion + E vandervaals + E electronic] this summation when given is an explicit form, represents force field, evaluating the potential of a system.

**Minimization:**

The minimizer uses algorithm to identify the geometrics of the molecule corresponding to the minimum points on the potential surface energy. The minimum reduced the unwanted forces which are present in the molecule and lower the energy level of the molecule. There are

many algorithms available in the minimization process. Some of the minimization methods used in the smart minimizer is steepest decent method, conjugate gradient method, Newton raphson method and quasi Newton method. From the DS protocols select the minimization and run .the following figure shows the minimized protein with fixed constraint .than save the minimized protein for further studies.

**Preparation of bio active molecules:**

The 111 bio active compounds are collected from the journals with the activity range 0.005 to >50 μM.

1 One molecule was drawn with basic scaffold and the other molecules were constructed with one drawn earlier as the reference model. 2. Drawn compounds are typed with charmm force field. 3. The typed molecule is subjected to the energy minimization using smart minimizer. Minimize a series of ligand poses using CHARMm. 4. Minimized molecule is saved with .sd and .mol2 extension for further study. Following table shows the 2d structure of the molecule and activity

**Basic requirement in QSAR studies**

1. All analogue belong congeneric series 2. All analogues exert same mechanisms of actions. 3. All analogue bind in a comparable manner. 4. Effect of isosteric replacement can be predicted 5. Binding affinity correlated to interaction energies 6. Biological activities correlated to binding activity

**To set up a Calculate Molecular Properties protocol:**

1. Load the QSAR and apply the force field on molecules and Calculate Molecular Properties protocol from the Protocols Explorer. The parameters display in the Parameters Explorer.

2. On the Parameters Explorer, click in the cell for the Input Ligands parameter and click the button to specify the ligand source on the Specify Ligands dialog. On the dialog, select all ligands from a Table Browser, a 3D Window, or a file.

3. Select the properties to calculate by clicking the button in a cell for the Molecular Properties, Semi empirical QM descriptors, or Density Functional QM descriptors, and follow the instructions in the popup dialog window. The Create genetic function approximation can build a Create genetic function approximation model for a dependent property using the selected molecular descriptors.

**To set up a Create genetic function approximation Model protocol**

1. Load the QSAR | Create genetic function approximation Model protocol from the Protocols Explorer. The

parameters display in the Parameters Explorer.

2. On the Parameters Explorer, click in the cell for the Input Ligands parameter and click the button to specify the ligand source on the Specify Ligands dialog. On the dialog, select all ligands from a Table Browser, a 3D Window, or a file.

3. Set the desired model name using the Model Name parameter. Once created, this model will appear under the other category of the Molecular Properties parameter in the Calculate Molecular Properties protocol and can be used to compute the property for future ligands. 4. Set the initial equation length and remaining parameters as desired. Parameters presented in red are required.

**QSAR:**

In the present study quantitative structure activity relationship studies were carried out on phospholipasea2 inhibitors in order to design selective and potential inhibitors. QSAR models were developed using 1D and 2D-descriptors using discovery studio software. QSAR attempts to model the activity of a series of compounds using measured or computed properties of the compounds. In the equation the term N means the number of data points, $r^2$ which is the square of the correlation coefficient which describing the binding of the compounds to the QSAR model. XV $r^2$, a squared correlation coefficient generated during a validation procedure using the equation XV $r^2$ = (SD PRESS)/SD SD means the sum of squared deviations of the dependent variable values from their mean the predicted sum of squares (PRESS), the sum of overall compounds of the squared differences between the actual and the predicted values for the dependent variables. The PRESS value is computed during a validation procedure for the entire training set. The larger the PRESS value the more reliable is the equation. XV $r^2$ is usually smaller than the overall $r^2$ for a QSAR equation. It is used as a diagnostic tool to evaluate the predicted power of an equation generated using the multiple leaner regression method. GFA work by generating random populations of solution to a problem, scoring the relative quality of the solution , and caring forward the most fit solutions or analogues(generated through mutation and crossover)of other solutions to iteratively generated(and finally converge on)new, more fit solution. In this study GFA analysis was done with following parameters.

- Population size
- Initial equation length
- Final equation length
- Number of generation

Root strap $r^2$ correlation coefficient calculated during the validation procedure.

79 compounds were included in the training set to generate the primitive QSAR model covering the widest data range of $IC_{50}$ values 0.005 to 50.01 μM. The predictive characters of QSAR were further assessed using test molecules. To judge the predictive ability of the QSAR model for new drug candidates the $IC_{50}$ values for the test and training set were evaluated.

**GFA parameters**

| | |
|---|---|
| Number of rows in model | 79 |
| Population | 100 |
| Maximum generation | 50000 |
| Initial terms per equation | 20 |
| Scoring function | Friedman LOF |
| Mutation probability | 0.1 |

## RESULT AND DISCUSSION

The GFA method performs a search over the space of possible QSAR models using lack of fit (LOF) scores to estimate the fitness of each model. These models lead to the discovery of predictive QSAR equations.

GFA equation = 4.7849 + 0.00716121 * −In−Situ Starting Energy − 2.0176 * Activ + 0.10343 * Dipole_Mag_Propgen_VAMP − 0.610585 * Local_polarity_Propgen_VAMP + 0.26681 * Mean_Polarizability_VAMP + 0.633171 * Num_H_Acceptors − 0.149947 * Num_RotatableBonds − 0.000507116 * Octupole_XYY_VAMP + 0.0647933 * RIJestateSumHal_Propgen_VAMP + 8.73998e−05 * −In−Situ Final Energy * −In−Situ Final Energy + 5.40146e−05 * ESP_point_count__3_Propgen_VAMP * ESP_point_count__3_Propgen_VAMP + 17.3371 * Molecular_FractionalPolarSurfaceArea * Molecular_FractionalPolarSurfaceArea − 7.29063e−07 * No._of_surface_points_with_−ve_ESP_Propgen_VAMP * No._of_surface_points_with_−ve_ESP_Propgen_VAMP + 86.4313 * QsumHal_Propgen_VAMP * QsumHal_Propgen_VAMP − 0.000148821 * Quadrupole_YY_VAMP * Quadrupole_YY_VAMP − 2.65319e−07 * Total_Energy_VAMP * Total_Energy_VAMP + 13.6832 * Activ * Covalent_hydrogen_bond_acidity_Propgen_VAMP − 0.000694297 * Activ * No._of_surface_points_with_+ve_ESP_Pr

opgen_VAMP + 1.85589e−06 * DMol3_Mol_ID * Electronic_Energy_VAMP + 0.0165753 * Num_AromaticRings * RIJestateSumO_Propgen_VAMP

From the above equation, the positive values are the reference for the presence of specific group at that point and increase the activity of molecule and the negative values indicate the presence of ionic group which reduce the activity.

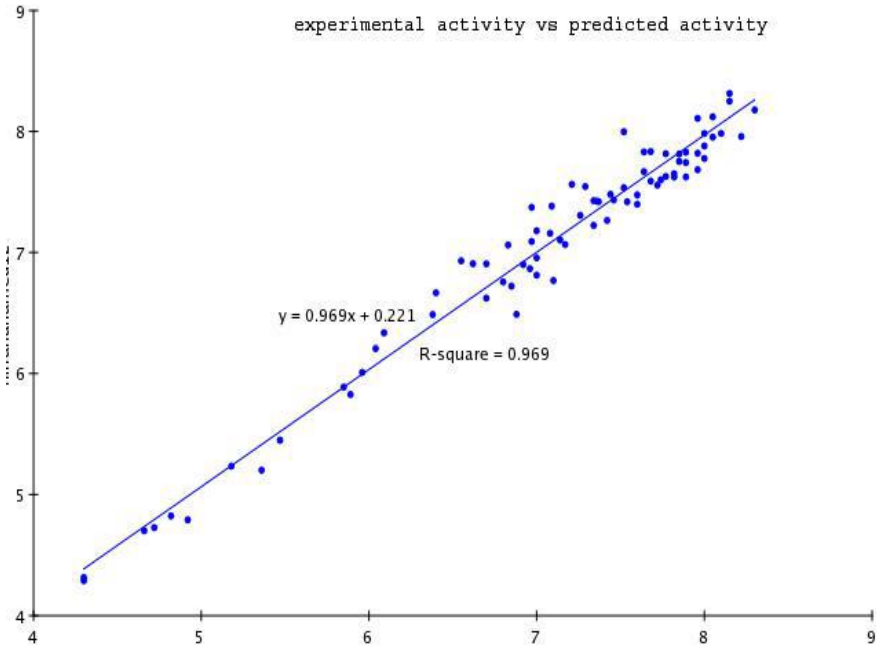
**The validation statistics for the model**

| | |
|---|---|
| Fridman LOF | 0.323 |
| R-squared | 0.968 |
| adjusted R-squared | 0.957 |
| cross validated R-squared | 0.941 |
| lack of fit points | 58 |
| error for non-significant LOF | 0.176 |
| significance of regression F value | 89.789 |

**Experimental and predicted values of Training set compounds using GFA**

| Molecule Name | Activity | GFA Predicted Value | Molecule Name | Activity | GFA Predicted Value | Molecule Name | Activity | GFA Predicted Value |
|---|---|---|---|---|---|---|---|---|
| 1 | 7.89 | 7.829 | 26 | 7.96 | 7.82 | 28xii | 7.21 | 7.563 |
| 10 | 6.97 | 7.091 | 12d | 4.72 | 4.727 | 28xiii | 7.77 | 7.628 |
| 11 | 8 | 7.983 | 15b | 7.85 | 7.813 | 28xix | 8 | 7.88 |
| 12 | 7.14 | 7.103 | 15c | 7.82 | 7.651 | 28xl | 4.3 | 4.315 |
| 13 | 8.05 | 7.953 | 15e | 7.89 | 7.624 | 28xv | 5.18 | 5.235 |
| 14 | 6.88 | 6.489 | 15g | 7.52 | 7.998 | 28xvi | 7.29 | 7.545 |
| 16 | 6.09 | 6.336 | 27ii | 7.77 | 7.816 | 28xviii | 7.96 | 8.108 |
| 17 | 7.09 | 7.383 | 28i | 8.1 | 7.984 | 28xx | 7.68 | 7.59 |
| 18 | 6.97 | 7.373 | 28ii | 8.22 | 7.958 | 28xxi | 7.44 | 7.481 |
| 19 | 7.89 | 7.743 | 28iv | 8.05 | 8.121 | 28xxii | 7.6 | 7.476 |
| 20 | 8.15 | 8.314 | 28ix | 7.68 | 7.834 | 28xxiii | 6.92 | 6.9 |
| 21 | 6.96 | 6.866 | 28v | 8.3 | 8.178 | 28xxix | 7.85 | 7.752 |
| 23 | 7 | 6.813 | 28viii | 7.74 | 7.6 | 28xxv | 7.34 | 7.428 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 24 | 7.96 | 7.684 | 28x | 7.72 | 7.556 | 28xxvii | 8 | 7.777 |
| 25 | 6.83 | 7.062 | 28xi | 7.64 | 7.831 | 28xxviii | 7.54 | 7.419 |
| 28xxx | 7.37 | 7.42 | 43d | 5.47 | 5.449 | 49h | 7.36 | 7.424 |
| 28xxxi | 7.46 | 7.434 | 43e | 5.85 | 5.888 | 50b | 7.52 | 7.535 |
| 28xxxii | 7 | 7.179 | 43f | 5.89 | 5.827 | 51a | 4.3 | 4.288 |
| 28xxxiii | 6.55 | 6.931 | 43g | 6.62 | 6.907 | 65a | 6.04 | 6.206 |
| 28xxxv | 7.42 | 7.265 | 48b | 4.66 | 4.701 | 65b | 6.38 | 6.487 |
| 28xxxvii | 7.64 | 7.668 | 49b | 8.15 | 8.25 | 65c | 6.8 | 6.757 |
| 28xxxviii | 7.82 | 7.623 | 49c | 7.34 | 7.224 | 65d | 7 | 6.956 |
| 43a | 6.7 | 6.906 | 49d | 7.08 | 7.158 | 67a | 4.82 | 4.823 |
| 43b | 5.36 | 5.201 | 49e | 7.26 | 7.307 | 67b | 4.92 | 4.791 |
| 43c | 6.85 | 6.722 | 49g | 7.1 | 6.768 | 6b | 5.96 | 6.009 |




**Graph 1: Correlation between experimental and predicted activities by QSAR equation using GFA method**

## CONCLUSION

The result generated from QSAR equation using GFA method, the values observed $r^2$ and XV $r^2$ are in specific range and there is a good correlation between experimental and GFA predicted activity. Good correlation is observed between the experimental $IC_{50}$ and computational predicted $IC_{50}$ values. It has been

suggested as since the predictive ability of equations is good, they can be used to develop new analogs.

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