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Research Article

3-Dimensional QSAR and molecular docking studies of a series of indole analogues as inhibitors of human non-pancreatic secretory phospholipase A_2

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ABSTRACT

Background: Design and development of new drugs is simplified and made more cost-effective because of the advances in the concepts of Quantitative Structure-Activity Relationship (QSAR) studies. A methodology of QSAR studies is one of the approaches to the rational drug design.
Methods: 3-Dimensional QSAR studies were performed on a series of indole analogues as inhibitors of human non-pancreatic secretory phospholipaseA_2 (PLA_2) by using Scigress explorer software suite. Docking studies of these compounds were also performed to understand the interactions with amino acid residues of PLA_2 protein.
Results: The multiple linear regression analysis was used to correlate the physicochemical descriptors with the PLA_2 inhibitory activity of 20 training set of compounds and the best QSAR model was developed. The best model was validated using leave-one-out method and found to be statistically significant, with coefficient of determination (r^2) of 0.788. This model was further used to predict the PLA_2 inhibitory activity of 12 test set of compounds. Docking analysis revealed that most of the compounds formed H-bond interactions with amino acid residues of PLA_2 protein (PDB ID: 1DB4). Predicted pIC_{50} value of one of the test compounds was 7.454 and it showed H-bond interactions with Asp48, Cys44, His27, Gly29 and Gly31 residues.
Conclusion: The present study shall help in rational drug design and synthesis of new selective PLA_2 inhibitors with predetermined affinity and activity and provides valuable information for the understanding of interactions between PLA_2 and the novel indole analogue compounds.

Keywords: QSAR, multiple linear regression, physicochemical descriptors, docking, PLA_2, Scigress explorer, Molegro Virtual Docker

INTRODUCTION

PLA_2 are ubiquitous enzymes that hydrolyse the *sn*-2-acyl bond of cell membrane phospholipids and lipoproteins and yield free fatty acids and lysophospholipids, precursors of various proinflammatory lipid mediators, including leukotrienes, prostaglandins and platelet-activating factor.[1] Mammalian PLA_2 are subdivided into two major families: low molecular mass secretory enzymes ($sPLA_2$) consisting of four types (I, II, V, and X), and high molecular mass cytosolic PLA_2 existing as two types (IV or $cPLA_2$ and VI or $iPLA_2$).[2,3]

$sPLA_2$-IIA is highly expressed in several types of mammalian cells and tissues, and this enzyme acts as a critical modulator of cytokine-mediated synovial inflammatory diseases,[4] rheumatoid arthritis[5,6] and neoplastic disease.[7] This group of enzymes has been reported to release arachidonic acid in some systems and

may provide the substrate for both cyclooxygenase (COX) and 5-lipoxygenase (5-LO) product formation in mouse bone marrow-derived mast cells.[8] Elevated levels of $sPLA_2$ have been reported in various body fluids from humans with several inflammatory conditions, including systemic inflammatory response syndrome encompassing sepsis and multiple organ trauma,[9] acute pancreatitis[10] and inflammatory bowel disease.[11,12]

The role of $sPLA_2$ in various inflammatory conditions will be determined only when potent, specific inhibitors of $sPLA_2$ are developed and evaluated in the clinic. As a step toward achieving this goal, we performed Quantitative Structure-Activity Relationship (QSAR) analysis to study the human non-pancreatic $sPLA_2$ inhibitory activity of a series of indole analogues. The present study was aimed at rationalizing the substituent variations of these analogues to provide insight for the future endeavours.

QSAR is a type of analysis where some measures of chemical properties are correlated with biological activity to derive a mathematical illustration of the underlying Structure Activity Relationship (SAR).[13] QSAR studies are unquestionably of great importance in modern chemistry and biochemistry. To get an insight into the SAR we need molecular descriptors that can effectively characterize molecular size, molecular branching or the variations in molecular shapes, and can influence the structure and its activities.[14]

Design and development of new drugs is simplified and made more cost-effective because of the advances in the concepts of QSAR studies. A methodology of QSAR studies is one of the approaches to the rational drug design.[15] The introduction of Hansch model, in early 1960, enabled chemists to describe the structure activity relationships in quantitative terms and check those using statistical methods.[16] QSAR are statistically derived models that can be used to predict the biological activity of untested compounds from their molecular structures.[17,18] This concept helps to understand the role of physicochemical descriptors of compounds in determining the biological activity and in estimating the characteristics of the new and potent compounds, without the chemical synthesis of the compounds.[16]

Docking various ligands to the protein of interest followed by scoring to determine the affinity of binding and to reveal the strength of interaction has also become increasingly important in the context of drug discovery.[19] Thus, the objective of the present work was to develop various QSAR models by Multiple Linear Regression (MLR) methods and to use the best QSAR model for the prediction of $sPLA_2$ inhibitory activity of newly designed compounds by using Scigress explorer software suite. We also performed the molecular docking of the newly designed compounds against $sPLA_2$ protein, 1DB4 (PDB ID) with bound ligand [3-(1-Benzyl-3-carbamoylmethyl-2-methyl-1H-indol-5-yloxy)-propyl-]-phosphonic acid (8IN) extracted from Protein Data Bank (PDB), by utilizing fast, exhaustive docking software Molegro Virtual Docker.[20]

METHODS

Data set for 3D QSAR

The first step in developing QSAR equations was to compile a list of compounds for which the experimentally determined inhibitory activity was known. The data set was divided into training set for model generation, and a test set for model validation, containing 20 and 12 compounds respectively. The human non-pancreatic $sPLA_2$ inhibitory activity data (IC_{50}) and chemical structures of indole analogues for training set were retrieved from PubChem database.[21,22] The biological activity (IC_{50}) of the molecules were converted to their corresponding pIC_{50} values,[23] and used as dependent variables in the QSAR calculations (Table 1).

Table 1: Data set used in the generation of the QSAR models (Training set). IC_{50} values were converted to their corresponding pIC_{50} values.

Compound	PubChem ID	IC_{50} (µM)	pIC_{50} (µM)
1	CID 10503444	6.13	5.212
2	CID 10623151	0.04	7.397
3	CID 10815003	0.022	7.657
4	CID 10504075	0.266	6.575
5	CID 44365370	0.015	7.823
6	CID 10694479	0.074	7.130
7	CID 10743057	0.04	7.397
8	CID 10644791	0.203	6.692
9	CID 10766584	0.016	7.795
10	CID 24860461	0.12	6.920
11	CID 10688272	38.1	4.419
12	CID 10615829	0.26	6.585
13	CID 10568884	11.13	4.953
14	CID 10550162	1.27	5.896
15	CID 10157472	0.189	6.723
16	CID 3710	0.152	6.818
17	CID 44365008	0.654	6.184
18	CID 10710393	2.05	5.688
19	CID 10666583	0.527	6.278
20	CID 10620653	1.15	5.939

*Source: PubChem database

Chemical structure construction and optimization

The molecules were drawn using chemical drawing software 'ACD/ChemSketch',[24] and 3D optimization of molecules was done by 'ACD/3D viewer'.[25] Structures of the training set and test set compounds are illustrated in Figure 1 and 2 respectively. The molecules were first optimized to their lowest energy state using Merck

Molecular Force Field-3 (MMFF3) method,[26] using Scigress explorer software suite. To avoid the local stable conformations of the compounds, geometry optimization was run many times with different starting points of each molecule, and conformation with the lowest energy was considered for the calculation of the molecule descriptors.

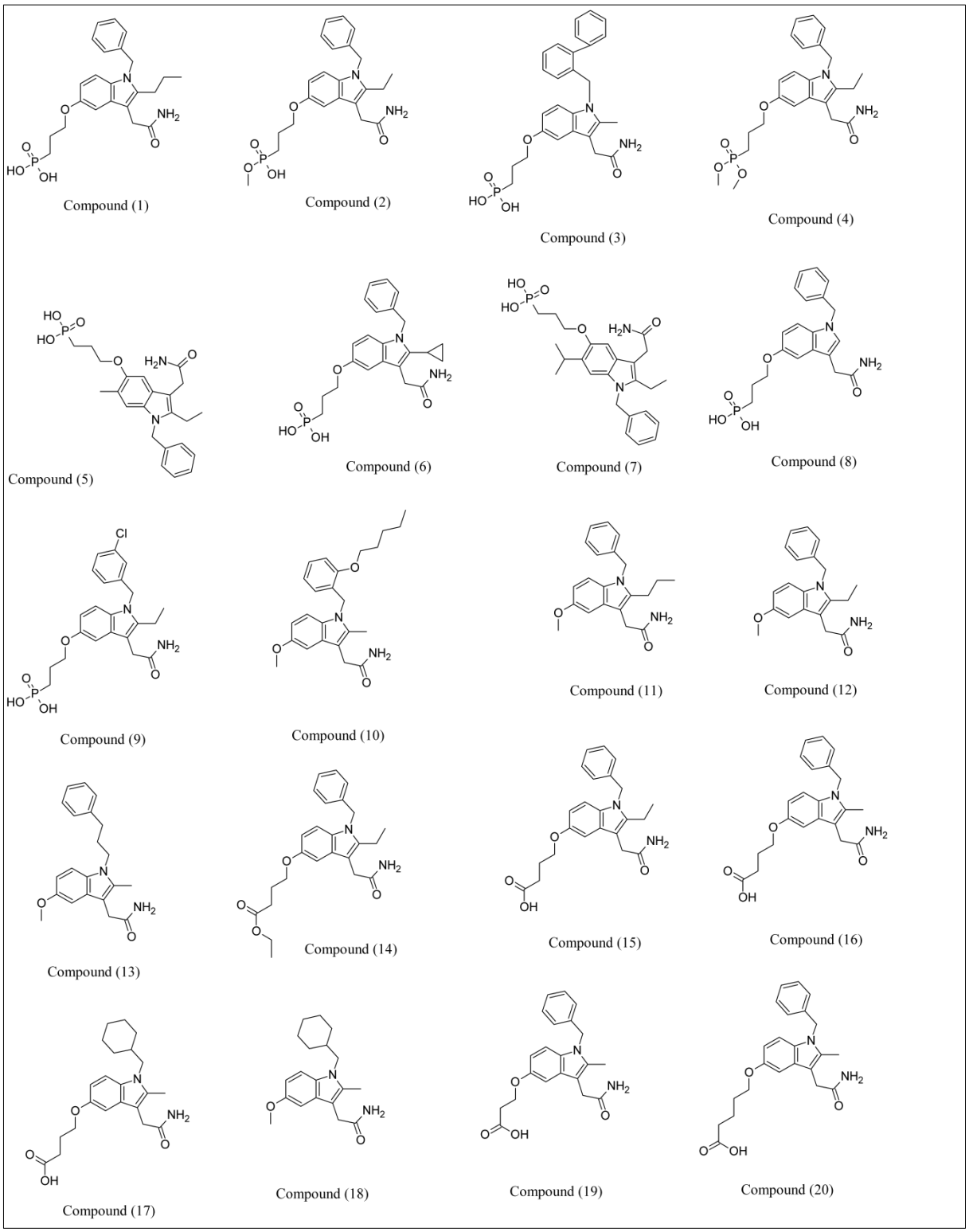

Figure 1: Structures of 20 training set of compounds used for QSAR analysis.

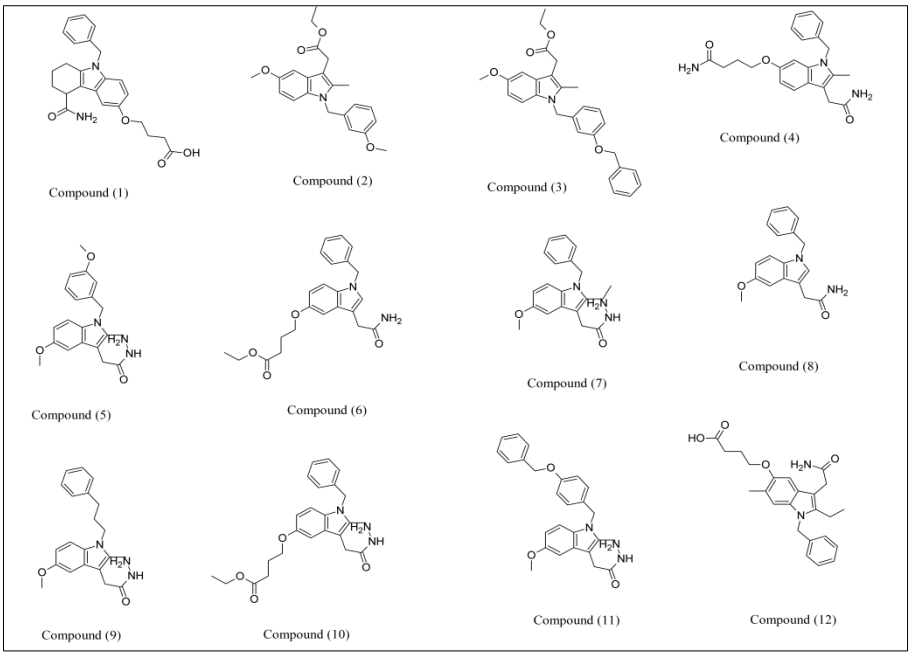

Figure 2: Structures of 12 test set of compounds.

Calculation of physicochemical descriptors

The structure of a molecule is expressed quantitatively in terms of its physicochemical descriptors, which are lipophilic, electronic and steric in nature. The aligned molecules were selected for calculation of the descriptors after inserting the biological activity as a dependent variable and the descriptors generated were selected as independent variables. List of physicochemical descriptors used in this study are summarised in Table 2.

Table 2: List of physicochemical descriptors selected for this study.

Abbreviation	Full name	Description
SE	Steric energy	The steric energy of a molecule is the sum of the molecular mechanics potential energies calculated for the bonds, bond angles, dihedral angles, non-bonded atoms and so forth.
HF	Heat of formation	The energy released or used when a molecule was formed from elements in their standard states
LOG P	Log p	The octanol-water partition coefficient
HOMO	HOMO energy	The energy required to remove an electron from the highest occupied molecular orbital (HOMO)
POL	Polarizability	The molecule's average alpha polarizability
SASA	Solvent accessible surface area	The molecular surface area accessible to a solvent molecule
DP	Dipole moment	It can be defined as the product of magnitude of charge and distance of separation between the charge
TE	Total energy	The total energy contained in an object was identified with its mass, and energy (like mass)
IP	Ionization potential	The energy per unit charge needed to remove an electron from a given kind of atom or molecule to an infinite distance
MR	Molecular refractivity	It is measure of the total polarizability of a mole of a substance and was dependent on the temperature, the index of refraction and the pressure
^{1}X	Connectivity index (order 1)	It is the information in any molecular formula or model regarding the order in which the constituent atoms of the molecule were linked, irrespective of the nature of the linkage.
EA	Experimental activity	A measured activity such as therapeutic activity or catalytic activity

Development and validation of QSAR models

The QSAR studies were carried out to correlate physicochemical descriptors of 20 derivatives from the training set with their $sPLA_2$ inhibitory activity. The physicochemical descriptors were taken as the independent variables and the human non-pancreatic $sPLA_2$ inhibitory activity was taken as the dependent variable. Various QSAR models were developed by correlating more than one (stepwise MLR analysis implemented in Scigress explorer's "Project Leader" program) physicochemical descriptors at a time, with $sPLA_2$ inhibitory activity of the compounds. Validation parameter, predictive r^2 (r^2 pred) was calculated for evaluating the predictive capacity of the models. The models were then cross-validated by the 'leave one out' scheme,[27] where a model was built with n-1 compounds and the n^{th} compound was predicted. Each compound was left out of the model derivation and predicted in turn. An indication of the performance of the model was obtained from the cross-validated r^2_{CV} (or predictive q^2) coefficient which is defined as:

$$q^2 = (SD\text{-}PRESS/SD)$$

Where, SD is the sum of squares deviation for each activity from the mean. PRESS (or predictive sum-of-squares) is the sum of the squared difference between the actual and that of the predicted values when the compound is omitted from the fitting process. Cross-validation coefficient q^2 is considered as an indicator of the predictive performance and stability of a model. For a reliable model, the square of cross-validation coefficient q^2 should be ≥ 0.5.[28] The $sPLA_2$ inhibitory activity of 20 compounds in the training set and 12 compounds in the test set was predicted using the best QSAR model (Equation 1). For further validation of the accuracy of the predicted values by the best QSAR model, the experimental human non-pancreatic $sPLA_2$ inhibitory activity of the 20 training set of compounds was correlated with their predicted $sPLA_2$ inhibitory activity.

Graphical analysis

Graphical analysis was performed using Scigress explorer's plotting facilities to display molecules that were outliers in the database. Through scatter plot there was evaluation of regression in the graph. By plotting the actual activities along X-axis versus the predicted activities along Y-axis, the predicted ability of the model was assessed. From the regression line it was easy to predict the number of molecules lie on and away from regression line.

Receptor X-ray structure

The 3D coordinates of the crystal structure of human non-pancreatic $sPLA_2$ in complex with [3-(1-Benzyl-3-carbamoylmethyl-2-methyl-1H- indol-5-yloxy)-propyl-]-phosphonic acid (8IN) (PDB code: 1DB4) extracted from the protein data bank (www.rcsb.org/) was selected as the receptor model for docking experiments.

Docking analysis

We used the template docking available in Molegro Virtual Docker software and evaluated MolDock, Rerank and protein-ligand interaction scores from MolDock and MolDock [GRID] options. Template docking is based on extracting the chemical properties like the pharmacophore elements of a ligand bound in the active site and using that information for docking structurally similar analogues. We used the default settings, including a grid resolution of 0.30 Å for grid generation and a 15 Å radius from the template as the binding site. We used the MolDock optimizer as a search algorithm, and the number of runs was set to 10. A population size of 50, maximum iteration of 2000, scaling factor of 0.50, crossover rate of 0.90 and a variation based termination scheme for parameter settings were used. The maximum number of poses was set to a default value of 5.

RESULTS

Physicochemical descriptors listed in Table 2 were calculated for the training set of molecules using the Scigress explorer's "Project Leader" program. Human non-pancreatic $sPLA_2$ inhibitory activity (experimental activity) of all the training compounds was added manually in the data set and was correlated with the different physicochemical descriptors by stepwise MLR analysis and QSAR models were generated. The best model (equation 1) was validated using leave-one-out method and found to be statistically significant, with coefficient of determination (r^2 pred) of 0.788 and cross-validated r^2CV (or predictive q^2) coefficient of 0.692.

Table 3: Predicted activity values of 10 test set of compounds calculated from the best QSAR model (equation 1).

Test compound	Predicted activity from model 1
Compound (1)	7.253
Compound (2)	6.42
Compound (3)	7.146
Compound (4)	6.305
Compound (5)	6.296
Compound (6)	7.261
Compound (7)	6.447
Compound (8)	7.152
Compound (9)	6.645
Compound (10)	7.359
Compound (11)	7.107
Compound (12)	7.454

Equation 1 (Model 1): M = 0.0768873*SE - 0.693698*HF - 0.501317*HOMO - 0.327067*POL + 0.0459367*SASA - 0.0589168*DP + 0.13583*TE - 3.30125*IP - 0.0262338*MR + 1.69878*1X + 35.1266 r2CV=0.692724 r2=0.788791

Equation 1 was considered as the best model to predict the activities of 12 test set of compounds (Table 3).

In order to validate our results we correlated the predicted activities of 20 molecules of the training set using the model expressed by equation 1 and compared with the experimental values. Predicted and the experimental activities were very close to each other evidenced by low values of residual activity (difference between experimentally observed activity and QSAR predicted activity) (Table 4).

Table 4: Values of actual, predicted & residual activities of 20 training set of compounds.

Compound	Actual activity	Predicted activity	Residual activity
Compound (1)	5.212	5.46	-0.248
Compound (2)	7.397	7.303	0.094
Compound (3)	7.657	7.515	0.142
Compound (4)	6.575	7.349	-0.774
Compound (5)	7.823	7.372	0.451
Compound (6)	7.130	7.478	-0.348
Compound (7)	7.397	7.442	-0.045
Compound (8)	6.692	6.486	0.206
Compound (9)	7.795	7.497	0.298
Compound (10)	6.920	7.154	-0.234
Compound (11)	4.419	7.155	-2.736
Compound (12)	6.585	6.646	-0.061
Compound (13)	4.953	7.13	-2.177
Compound (14)	5.896	5.855	0.041
Compound (15)	6.723	6.518	0.205
Compound (16)	6.818	6.945	-0.127
Compound (17)	6.184	6.631	-0.447
Compound (18)	5.688	5.558	0.13
Compound (19)	6.278	6.062	0.216
Compound (20)	5.939	6.233	-0.294

*Predicted and the experimental activities closely matches as evidenced by low values of residual activity (difference between experimentally observed activity and QSAR predicted activity)

The graph between predicted and experimental activity of training set compounds by using model 1 is illustrated in Figure 3. Through this scatter plot, the compounds aligned on and around the regression line showed good correlation level between the predicted and experimental activity and compounds which were deviated from the regression line showed low correlation level between the predicted and experimental activity of training set of compounds. Variations in residual activity of training set of compounds are illustrated in Figure 4.

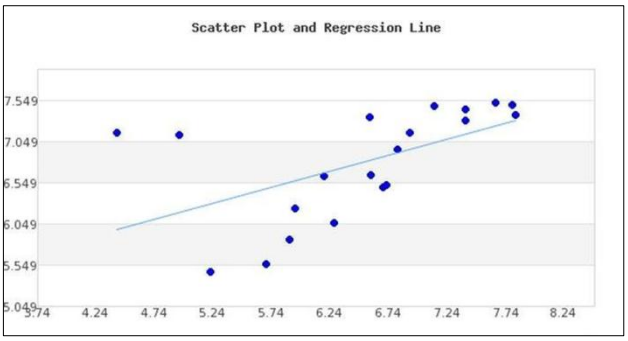

Figure 3: Graph between predicted (vertical axis) and experimental activity (horizontal axis) of training set of compounds by using equation 1. Compounds 1, 2, 3, 7, 8, 10, 12, 13, 14, 15, 16, 18 & 19 were aligned on and around the regression line showing good correlation between predicted and experimental activity.

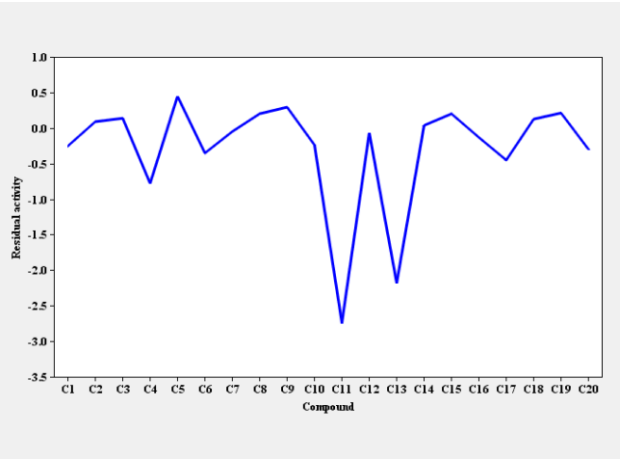

Figure 4: Graphical illustration of variation in residual activity (difference between actual and predicted activity) of 20 training set of compounds.

Before the docking experiments, the protocol was validated. 1DB4 (PDB ID) bound ligand [3-(1-Benzyl-3-carbamoylmethyl-2-methyl-1H-indol-5-yloxy)-propyl-]-phosphonic acid (8IN) was docked into the binding pocket of $sPLA_2$ protein to obtain the docked pose and the RMSD (Root Mean Square Deviation) of all atoms between these two conformations indicating that the parameters for docking simulation were good in reproducing the X-ray crystal structure. Therefore, indole analogues (12 test set of molecules) were docked into the binding pocket of $sPLA_2$ protein. 1DB4 co-crystallized ligand resulted in MolDock score of -177.358 kcal/mol. Therefore, any molecule from the dataset which shows a score lower than -177.358 kcal/mol would be regarded as ligand with higher binding affinity and would act as inhibitor against $sPLA_2$ protein. Our approach identified three compounds from the test set of molecules with better energy scores than the 1DB4 bound co-crystallized ligand. The docked energies (Moldock score) and H-bond interaction data of the three best compounds from the 12 test set of molecules are given in Table 5.

Table 5: Interaction parameters of 1DB4 with the three best test set of compounds and co-crystallized [3-(1-Benzyl-3-carbamoylmethyl-2-methyl-1H- indol-5-yloxy)-propyl-]-phosphonic acid (8IN) (Reference ligand).

Compound	MolDock score (kcal/mol)	Rerank score	H-Bond
Compound (12)	-183.162	-140.491	-4.44321
Compound (10)	-180.432	-135.669	-7.7549
Compound (6)	-178.368	-125.119	-5.91827
Reference ligand	-177.358	-135.4	-7.89931

*H-Bond stands for Hydrogen Bond interaction score, Compound (12), in particular, showed high binding affinity with MolDock score (binding score) of -183.162kcal/mol against 1DB4 (PDB ID) in docking analysis

Out of 12 test set of molecules, the best one was molecule 12th with predicted pIC_{50} value of 7.454 and binding energy score of -183.162 kcal/mol This compound was docked within the binding pocket of $sPLA_2$ protein (PDB ID: 1DB4) forming H-bond interactions with Asp48, Cys44, His27, Gly29 and Gly31 residues. Interaction parameters of $sPLA_2$ with the best compound are illustrated in Figures 5.

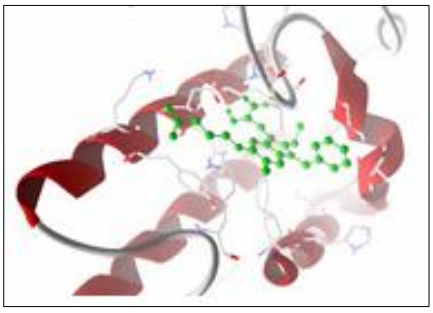

Figure 5: Docked pose of test compound 12th with PLA_2 protein (PDB id: 1DB4). The ligand was docked deeply within the binding pocket region forming hydrogen bond interactions with Asp48, Cys44, His27, Gly29 and Gly31. (Image generated using Molegro Virtual Docker software).

DISCUSSION

Finding novel compounds at starting points for lead optimization is a major challenge in drug discovery. The number of methods and softwares which use the QSAR and docking approaches are increasing at a rapid pace. It has been clearly demonstrated that the approach utilized in this study was successful in finding novel $sPLA_2$ inhibitors from the data set developed by computational methods. The model generated from various physicochemical descriptors corresponds to the essential structural features of indole analogues and found to have significant correlation [coefficient of determination (r^2) of 0.788] with $sPLA_2$ inhibiting activity. Substituted indole analogues designed by using computational approaches also showed good interactions with $sPLA_2$ protein. Compound (12), in particular, showed high binding affinity with MolDock score of -183.162 kcal/mol against 1DB4 (PDB ID) in docking analysis and predicted pIC50 value of 7.454 in QSAR analysis. The ligand was docked deeply within the binding pocket region forming hydrogen bond interactions with Asp48, Cys44, His27, Gly29 and Gly31. This study shall help in rational drug design and synthesis of new selective $sPLA_2$ inhibitors with predetermined affinity and activity and provides valuable information for the understanding of interactions between $sPLA_2$ and the novel compounds and might pave the way towards discovery of novel $sPLA_2$ inhibitors. The physicochemical descriptors used in QSAR analysis in this study were important in further lead optimization of the substituted indole derivatives.

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Conflict of interest: None declared
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