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3D-QSAR, design, docking and *in silico* ADME studies of indole-glyoxylamides and indolyl oxoacetamides as potential pancreatic lipase inhibitors

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The versatility of indole heterocyclic led to the understanding of their structural requirements to develop new potential derivatives. The indole derivatives estimated to be active against pancreatic lipase have been chosen to develop 3D-QSAR field and atom-based models, validated using the Schrodinger suite. Designing of new agents through QSAR based predictions and performing docking on these compounds helped in defining the binding pattern and pharmacophoric features like π–π stacking interactions, hydrogen bonding, and π-cation interactions with the amino acid residues. The protein-ligand complex displayed good binding energies. In silico ADMET properties have been generated using the Quick-prop module of the Schrodinger suite. The 3D-QSAR model is found to be statistically significant and evaluated using various parameters like R^2, R^2CV, stability, F-value, P-value, RMSE, Q^2, and Pearson-r by PLS factor of 4. The field fractions and contour maps along with their visualizations have helped in inferring the essential nature and type of substituent that should be incorporated for a compound to display potent pancreatic lipase inhibitory activity. These deductions and evaluations of the synthesized compounds through the generation of models could be further utilized for designing new molecules rationally.

Keywords: 3D-QSAR, Field based, Atom based, Indole glyoxylamide, Indolyl oxoacetamides, Pancreatic lipase inhibition, Anti-obesity

Obesity is characterized by an excess of fat deposition inside the body. The major cause of fat deposition in the body is initiated via a cascade of mechanisms that convert these fats into small molecules which are then stored inside the adipose tissue. The human diet consists of 90% of exogenous fats known to be triglycerides that cannot be absorbed without any hydrolysis. The hydrolysis of these fats is carried out by the digestive lipases that are present inside the body.[1,2] The overall contribution of pancreatic lipase in the hydrolysis of dietary fats makes it an attractive target to study on. The pancreatic lipase does not function individually but requires co-lipase (a pancreatic protein) because of the presence of amphiphiles.

Inhibition of pancreatic lipase is one of the widely studied mechanisms for the synthesis of new anti-obesity agents[6]. The original class of anti-obesity agents consisted of centrally acting agents like, phenylethylamine, an amphetamine that acted on the neural pathways and imparted major side effects like dizziness, insomnia, dry mouth, and in higher severe cases were even prone to show cardiovascular side effects resulted in the withdrawal of centrally acting agents from the market[7]. Recently, Indole glyoxylamide and Indolyl oxoacetamides derivatives have been reported as potent and selective pancreatic lipase inhibitors. These compounds shared a basic skeleton, 2-(1H-indol-3-yl)-2-oxo-N-phenylacetamide, that has been selected to perform 3D-QSAR research in this paper[9,10].

The quantitative structure-activity relationship (QSAR) approaches have been denoted as a powerful tool for the prediction of activity in drug design. The 3D-QSAR is a broad term that correlates the macroscopic target properties with atom-based properties derived using spatial representations of the molecule[11]. It is a tool in modern drug design that utilizes techniques like CoMFA (comparative molecular field analysis) and CoMSIA (comparative molecular similarity analysis) to understand the drug-receptor interactions. The literature survey confirms that computational techniques provide a solid medium in designing novel and potent inhibitors via revealing the mechanism and interactions between drug and receptor[12].

In the present work, 3D-field based QSAR and Atom-based QSAR models were generated and were validated using parameters like R^2, Q^2, R, F, RMSE, and Pearson-r values along with the ADMET properties. The indole glyoxylamide and indolyl oxoacetamides are novel PL inhibitors that displayed good activity in comparison with the standard drug and were potent enough to exhibit the results in the inhibition assay performed. The lead optimization of the compounds can be done via studying steric, electrostatic, hydrophobic, H-bond acceptor, and H-bond donor in 3D-Space. The data generated from these models will help in designing new compounds with an approach of rational designing with more active and selective PL inhibition.

Experimental Details

Selection of ligand for developing the 3D-QSAR model

The indole glyoxylamide and indolyl oxoacetamides shared a similar skeleton and were chosen from the literature. The structure of these compounds was computed using a 2D-sketcher of the Schrodinger Suite 2020[13].

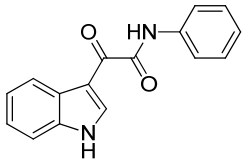
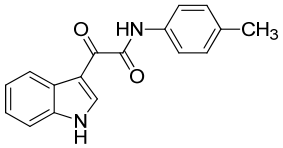
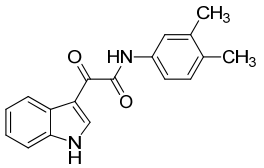
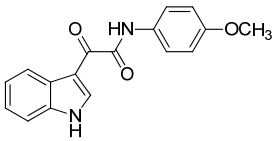
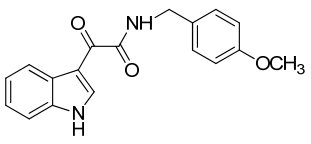
Data set for Field and Atom based 3D-QSAR model

The data set altogether comprised of 30 molecules for field and atom-based studies. They were subjected for ligand preparation and were further optimized via default set parameters at pH of 7 (neutral), after which they were incorporated for alignment. Subsequently, the compounds were subjected to the development of the model through distributing them partially and randomly into training and test set. This random distribution is carried out at the ratio of 70:30%. Thus, 70% of the compounds go into a training set and the remaining 30% into a test set according to the module.

3D-QSAR

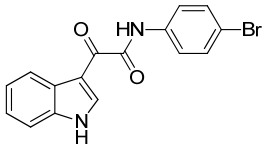
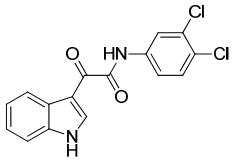
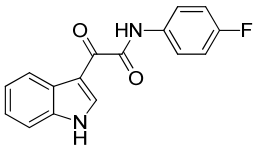
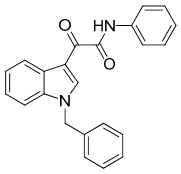
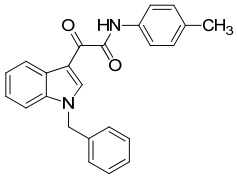
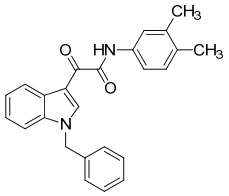
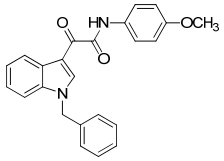
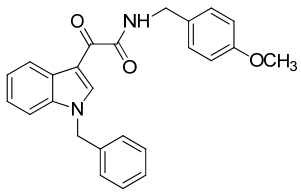
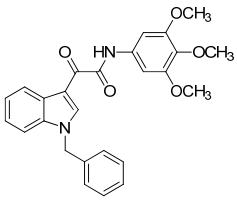
The *in vitro* inhibitory activity (IC_{50}) value of the compounds selected was converted into pIC_{50} ($-logIC_{50}$) value (Table 1). The pIC_{50} values have significance as they are used as a dependent variable for the evaluations of CoMFA and CoMSIA models[14,15]. Initially, the ligands were superimposed using ligand alignment property from the maestro suite (Fig. S1, Supplementary Information). Once the alignment was done, the QSAR model generation was initiated, and the ligands were distributed randomly into training and test set in the ratio of 70:30%. According to the ratio, from

Table 1 — Ligands with their IC50 (μM) and pIC50 (μM) values

No. of ligand	Ligand	IC_{50} (μM)	pIC_{50} (μM)
1		27.49 ± 1.68	4.560
2		26.13 ± 0.92	4.582
3		26.07 ± 1.14	4.583
4		23.72 ± 0.67	4.624
5		17.39 ± 0.53	4.759

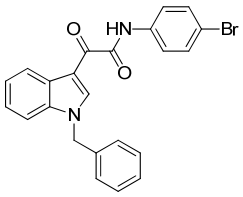
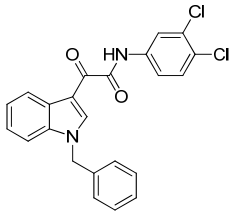
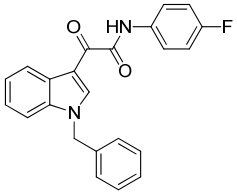
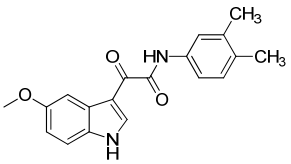
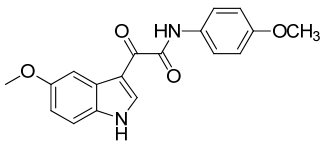
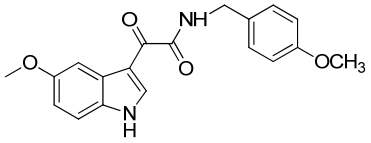
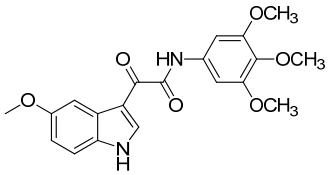
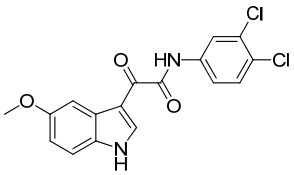
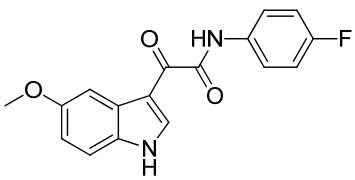
(*Contd.*)

Table 1 — Ligands with their IC50 (μM) and pIC50 (μM) values (*Contd*.)

No. of ligand	Ligand	IC_{50} (μM)	pIC_{50} (μM)
7		43.36 ± 1.67	4.362
8		44.27 ± 1.21	4.353
9		47.62 ± 1.48	4.322
10		18.24 ± 0.74	4.738
11		12.9 ± 0.58	4.889
12		10.62 ± 0.66	4.973
13		10.86 ± 0.71	4.964
14		5.83 ± 0.64	5.234
15		4.92 ± 0.29	5.308

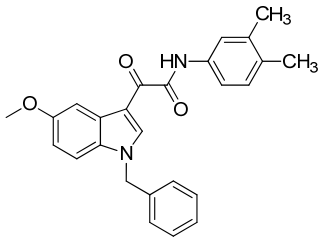
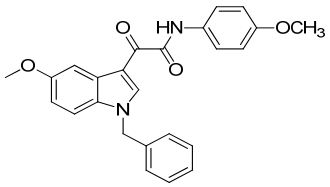
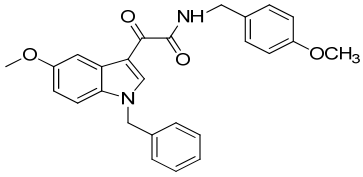
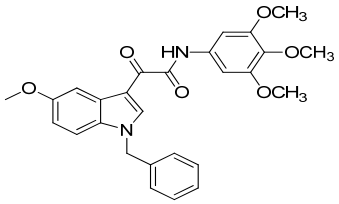
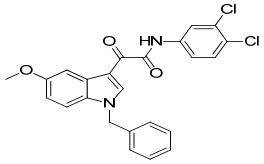
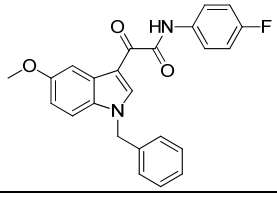
(*Contd*.)

Table 1 — Ligands with their IC50 (μM) and pIC50 (μM) values (*Contd*.)

No. of ligand	Ligand	IC_{50} (μM)	pIC_{50} (μM)
16		25.76 ± 0.97	4.589
17		26.72 ± 0.79	4.573
18		24.18 ± 0.86	4.616
19		18.26 ± 0.58	4.738
20		18.12 ± 0.43	4.741
21		17.93 ± 0.39	4.746
22		16.38 ± 0.26	4.785
23		34.62 ± 0.94	4.460
24		37.83 ± 0.98	4.422

(*Contd*.)

Table 1 — Ligands with their IC50 (μM) and pIC50 (μM) values (*Contd*.)

No. of ligand	Ligand	IC_{50} (μM)	pIC_{50} (μM)
25		9.14 ± 0.69	5.039
26		6.28 ± 0.24	5.202
27		5.12 ± 0.38	5.290
28		4.53 ± 0.47	5.343
29		23.21 ± 0.93	4.634
30		19.48 ± 0.76	4.710

30 compounds 21 were allotted into the training set and the remaining 9 compounds were allotted under the test set. After the distribution, the model was built based on the PLS factor that was decided through several compounds placed under the training set divided by 5. The final model was built on the PLS factor of 4 for the atom as well as field based QSAR with the grid space of 1 Å unit. The field style for the field-based QSAR model was Gaussian that comprises five features like Gaussian steric, Gaussian electrostatic, Gaussian hydrophobic, Gaussian H-bond acceptor, and H-bond donor. The atom-based comprises field fractions of H-donor, Hydrophobic/non-polar, and Electron withdrawing features.

ADMET

The QikProp module facilitated the prediction of QSAR based ADME properties. The standard values were compared with the generated values and helped in defining the significance of the overall study.

Designing new analogues based on 3D-QSAR data and their docking studies

The compounds were designed based on result generated through QSAR models and were

characterized by docking studies. The binding site was the one where the inhibitor was already incorporated under the co-crystallized structure of the protein. Glide Xtra precision docking method was used to get the best docking poses and the ligand with the best confirmation was ranked by Glide Gscore[16].

Results and Discussion

3D-QSAR model

The 3D-QSAR models were generated according to the QSAR statistics. The predicted models were built and thoroughly validated according to the parameters and set of rules. The statistics comprised SD (Standard deviation), R^2, R^2CV, R^2Scramble, Stability, F-value, P-value, RMSE, Q^2-value, and lastly Pearson-r value. According to the parameters and rules the standard deviation value should be as less as possible. The R^2 value is considered predictive only when its nearest to 1.0 and R^2CV (Cross validatory correlation coefficient) determines whether the QSAR model built is truly correlated or not. The values in R^2CV are generated employing LOO (Leave one out) method, it removes one ligand from the training set and generates the model and correlation coefficient. It is considered that the value of R^2CV should not change by the removal of one compound from the data set and it must be closest or comparable with the values of R^2. Mostly, Q^2 (Q-squared) is analogous with the R^2 values but is for the test set instead of the training set and it should always be above 0.5 and nearest to 1. The R^2 scramble is a correlation coefficient for the scramble data set and should be far less than the R^2 value. They play a very significant role and suggest scrambling of structural data with biological data. It also affects the model predictions, and the value of the scramble set should be less than the R^2 value as this imparts significance to the model and confirms its predictive ability along with its statistical and biological significance. The F-value also referred to as analysis of variance can be as much as possible. The P-value demonstrates the statistical significance (trueness) of the null hypothesis and should be as less as possible. Root mean square error (RMSE) is for test set the value of which should be nearest to zero for a model to be well predictive. The Pearson-r is an important parameter that imposes a correlation between predicted and observed activity for test set compounds. If the values are close to 1 the graph of actual vs. predicted activities is less scattered[17,18].

Field Based 3D-QSAR model for PL-inhibitors

The field based QSAR model is generated to study the compounds more thoroughly structurally. It helps in inferring the structural requirement utilizing lead optimization and aligning the ligand and predicting their steric, hydrophobic, and electrostatic values to deduce whether the compounds will be biologically active or inactive. The structure was made using a 2D-sketcher of Schrödinger suite and was then subjected for ligand preparation. These 3D-structures were then aligned for the generation of the model. The aligned structures were selected from the properties along with their pIC_{50} values and the model generation was initiated (Table 1). After which the randomized training set was assigned in the ratio of 70:30% and the QSAR statistics table was built. The statistical parameters which were obtained indicated that the model generated was well predicted and imparts significance to the study. The total compounds were 30 out of which 21 go in the training set and the remaining 9 were in the test set. The leave one out method was adopted for assessment of the parameters of the model (Table 2). The R^2CV (cross validation) value was obtained as 0.7483. The R^2 value for the regression was 0.9327 along with the stability value of 0.877. The p-value of 3.57e-09 suggested a greater degree of confidence. The reliability of the model was confirmed by 9 compounds incorporated in the test set. The RMSE value was 0.11, Q^2 of 0.8456 which was closest to the R^2 value, and the Pearson-r value was 0.9462. These best parameters were selected based on the R^2 value which was highest and nearest to one that confirmed the robustness of the model (Table 3). The PLS (partial least square) factor was kept at 4 and generated best-predicted activity values (Table S1 & Fig. 1).

Table 2 — PLS based QSAR statistical parameters

Factors	SD	R^2	R^2 CV	R^2 Scramble	Stability	F	P	RMSE	Q^2	Pearson-r
1	0.1624	0.7150	0.5815	0.2016	0.968	47.7	1.39e-06	0.14	0.7441	0.8688
2	0.1231	0.8448	0.6852	0.2980	0.949	49.0	5.24e-08	0.09	0.8996	0.9621
3	0.0931	0.9161	0.7069	0.3670	0.795	61.9	2.34e-09	0.15	0.6829	0.9202
4	0.0860	0.9327	0.7482	0.4466	0.877	55.4	3.57e-09	0.11	0.8456	0.9462

Contour maps analysis of 3D-field based QSAR

The contour maps were analysed based on Gaussian factors of field based QSAR. These factors include Gaussian steric, electrostatic, hydrophobic, H-bond acceptor, and H-bond donor visualization which illustrates the significance of substituent attached to the compounds and its overall effect seen on the activity of the compound. Thus, these visualizations help in deducing the activity variation caused due to various substitutions. The favourable positions for substitutions on these molecules were at N-1 and C-5 of indole nucleus and Aryl (ring) substitution. These positions were evaluated using contour map generation. All the compounds were subjected for the visualization out of which compounds showing highest and least IC_{50} values are taken into consideration.

Table 3 — Parameters of best QSAR model

Training Set	Test Set
PLS = 4	N_{test} = 9
$N_{training}$ = 21	Q^2 = 0.8456
R^2 = 0.9327	RMSE =0.11
SD = 0.0860	Pearson-r = 0.9462
R^2CV = 0.7482	
F = 55.4	
p = 3.57e-09	
Stability = 0.877	

$N_{training}$ = number of molecules in the training set, N_{test} = number of molecules in the test set, R^2 = Correlation coefficient of observed and predicted activities in the training set, SD = Standard deviation, R^2CV = leave one out validation, F = Analysis of variance, *p* = statistical significance value, Q^2 = test set value, RMSE = Root mean square error, Pearson-r = Correlation coefficient of observed and predicted activities in the test set.

Gaussian steric

Ligand no. 15 displayed the highest IC50 value of 4.92 and its steric maps revealed a large green contour near the N-1 position revealing the position to be highly favoured for the substitution of bulkier groups. Thus, all the other ligands with the N-1 substitution displayed higher activity than the ligands with no substituents i.e., ligand no. 9. The yellow contour over the aryl ring reveals the region where bulky groups are not favoured (Fig. 2).

Gaussian electrostatic

The electrostatic contour maps of ligand no. 28 (IC_{50} = 4.530) revealed that electropositive substitution (ring activating groups) at aryl ring is important for the lipase inhibition activity while the red contour revealed that electronegative substitutions at benzyl ring-substituted on N-1 of indole will be

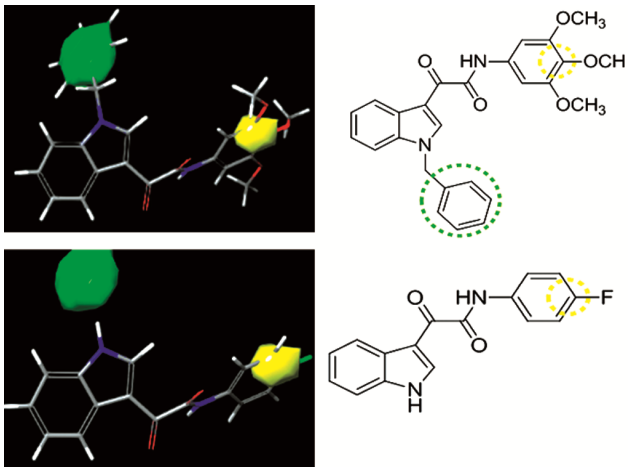


Fig. 2 — Gaussian steric factor – A comparativeanalysis between ligand no. 15 (upper panel) and ligand no. 9 (lower panel)

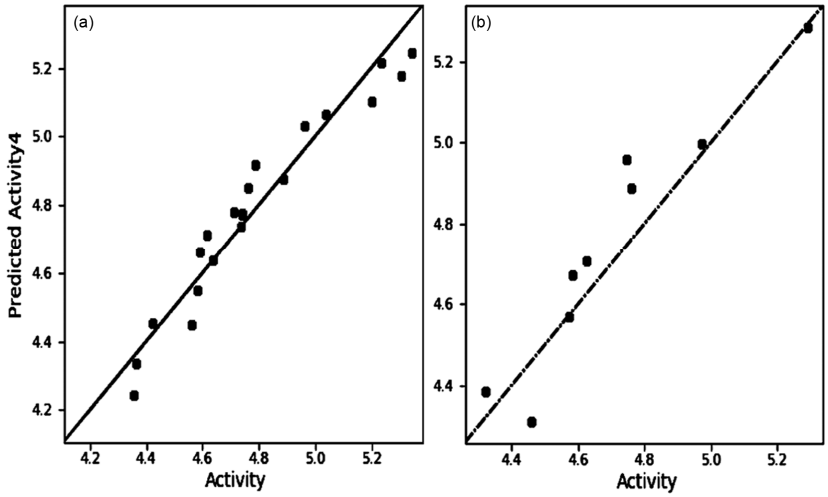


Fig. 1 — Field based 3D-QSAR scatter plot based on predicted activity vs. activity- (a) Training set and (b) Test set

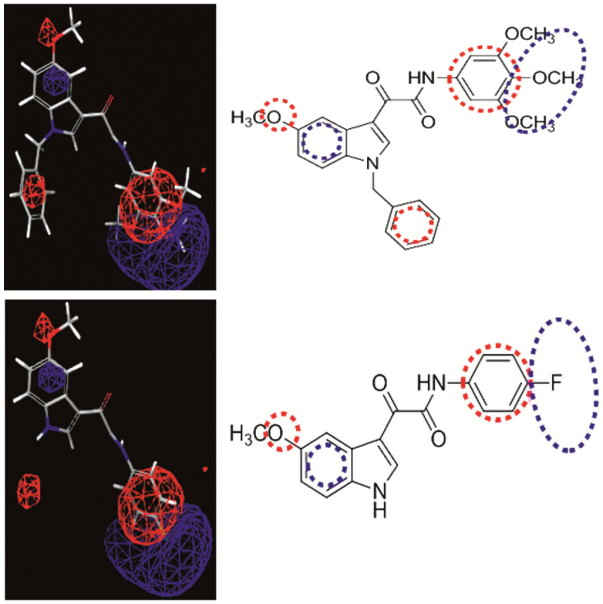


Fig. 3 — Gaussian electrostatic factor - A comparative analysis between ligand no. 28 (upper panel) and ligand no. 24 (lower panel)

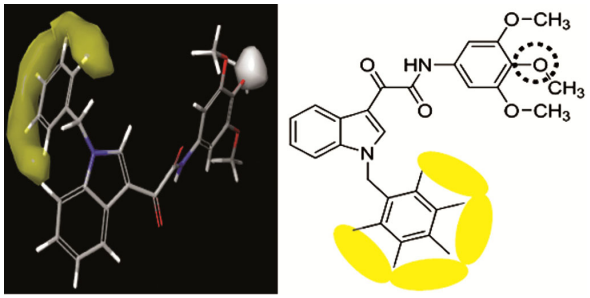


Fig. 4 — Hydrophobicity/Non-polar factor of ligand no. 15

favourable for activity. On the other hand, ligand no. 24 which does not have any substitution at N-1 and contained electronegative substitution at aryl ring had IC_{50} of 37.830 which shows its poor activity (Fig. 3).

Hydrophobicity/Non-polar

The hydrophobicity contour maps of ligand no.15, clearly depicted in yellow colour that extended hydrophobic substitution at N-1 is good for activity and further hydrophobic substitutions at this benzyl ring will favour the activity (Fig. 4).

H-bond Acceptor

For the H-bond acceptor property, the red and magenta colour regions of the contour maps display the H-bond acceptor groups favourability and unfavorability, respectively. For ligand no.28 the red colour over the methoxy substitution shows that these are unfavourable as H-bond acceptors, while magenta colour favours the H-bond acceptor groups (Fig. 5).

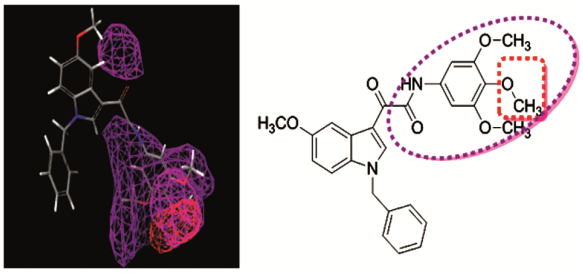


Fig. 5 — H-bond Acceptor factor of ligand no. 28

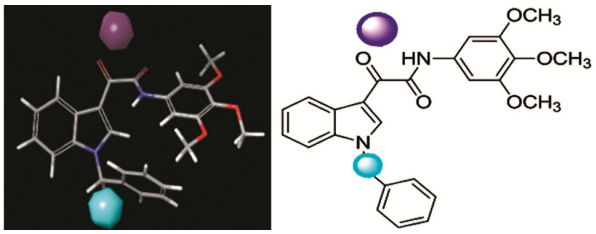


Fig. 6 — H-bond Donor factor of ligand no. 15

H-bond Donor

The H-bond donor contour maps of ligand no.15 depict the cyan to be good for H-donating groups and purple to be unfavourable. Thus, the H-donor group at N-1 of indole favours the activity (Fig. 6).

Atom Based model for PL-inhibitors

The atom based QSAR model is generated to study the structural requirements that are necessary for the inhibition of pancreatic lipase enzymes. It helps in inferring these requirements using lead optimization, aligning the ligand, and predicting their hydrogen bond donor, hydrophobic/non-polar, and electron-withdrawing field fractions. Initially, the structure was made by 2D-sketcher of Schrodinger suite and was subjected for ligand preparation. These 3D structures were aligned for the generation of an atom-based model. The molecule in the training and test set was assigned by the ratio of 70:30%. Those molecules which were distributed in the training and test set of the Field-based QSAR model were similarly assigned for the atom-based QSAR model. The generated statistical parameters added significance to the model as it was well predicted. Out of the 30 compounds, 21 were incorporated in the training and the remaining 9 were incorporated under the test set. The statistical parameters were assigned based on the leave one out method (Table 4). The R^2CV (cross validation) value was obtained as 0.7194. The R^2 value for the regression was 0.9186 along with the stability value of 0.876. The p-value of 1.61e-08 suggested a greater degree of confidence. The reliability of the model was confirmed by 9 compounds incorporated in the test

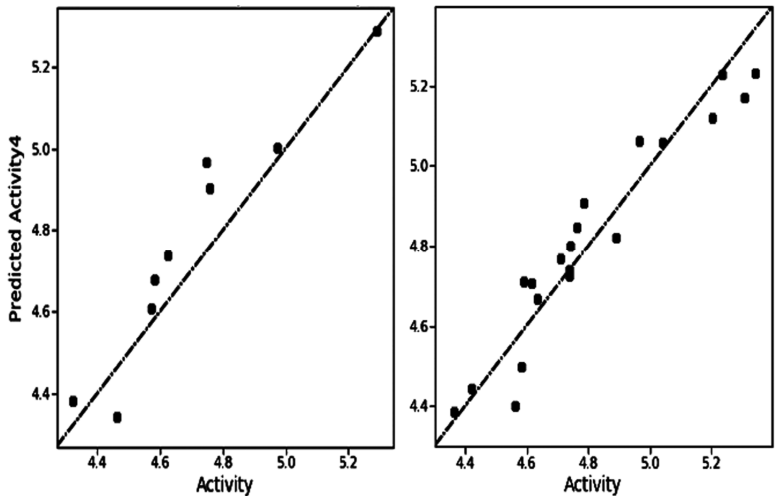


Fig. 7 — Atom based 3D-QSAR scatter plot based on predicted activity vs. activity- (a) Test set and (b) Training set

Table 4 — PLS-based QSAR statistical parameters

Factors	SD	R^2	R^2 CV	R^2 Scramble	Stability	F	P	RMSE	Q^2	Pearson-r
1	0.1600	0.7233	0.5623	0.2469	0.952	49.7	1.04e-06	0.13	0.7588	0.8766
2	0.1318	0.8221	0.6181	0.3538	0.927	41.6	1.79e-07	0.10	0.8698	0.9412
3	0.1077	0.8877	0.6506	0.4494	0.772	44.8	2.75e-08	0.17	0.6014	0.9066
4	0.0946	0.9186	0.7194	0.4984	0.876	45.1	1.61e-08	0.11	0.8360	0.9499

Table 5 — Parameters of best QSAR model

TRAINING SET	TEST SET
PLS = 4	N_{test}= 9
$N_{training}$ = 21	Q^2 = 0.8360
R^2 = 0.9186	RMSE =0.11
SD = 0.0946	Pearson-r = 0.9499
R^2CV = 0.9186	
F = 45.1	
p = 1.61e-08	
Stability = 0.876	

$N_{training}$ = number of molecules in the training set, N_{test} = number of molecules in the test set, R^2 = Correlation coefficient of observed and predicted activities in the training set, SD = Standard deviation, R^2CV = leave one out validation, F = Analysis of variance, *p* = statistical significance value, Q^2 = test set value, RMSE = Root mean square error, Pearson-r = Correlation coefficient of observed and predicted activities in the test set

set. The RMSE value was 0.11, Q^2 was 0.8360 which was closest to the R^2 value, and the Pearson-r value was 0.9499. These best parameters were selected based on the R^2 value which was highest and nearest to one that confirmed the robustness of the model (Table 5). The PLS (partial least square) factor was kept 4 that presumed and generated the best-predicted values (Table S2 & Fig. 7).

Contour maps analyses of Atom based QSAR model

The contour maps generated through atom based QSAR visualization are a great tool to study the structural requirements and the type of substituent suitable at the given positions. The maps are either blue or red colour cubes, the blue colour cubes are associated with substituent that will show increased activity, and red colour cubes are associated with substituent that will decrease the activity. The field fractions that were monitored in the atom-based model are hydrogen bond donor, hydrophobic/non-polar, and electron-withdrawing properties. These all were represented with blue and red cubes over the substituent that implicated their overall activities.

H-bond donor

The nitrogen of the amide group is a good hydrogen bond donor and will increase the overall activity. The methylene group of the extended hydrophobic substitution at N-1 of indole is less favourable as an H-bond donor and may decrease the activity. The N-1 hydrogen of the indole ring as observed in ligand no. 9 is an unfavourable H-donor group because the hydrogen is not readily available for the substitution. As observed in field-based results if extended hydrophobicgroups are incorporated at N-1 on which H-donating groups are substituted will be more favourable for the lipase inhibition activity (Fig. 8).

Hydrophobic/Non-polar substitution

In the ligand no. 28 hydrophobic group that is substituted at N-1 (Benzyl ring) and C-5(Methoxy) of

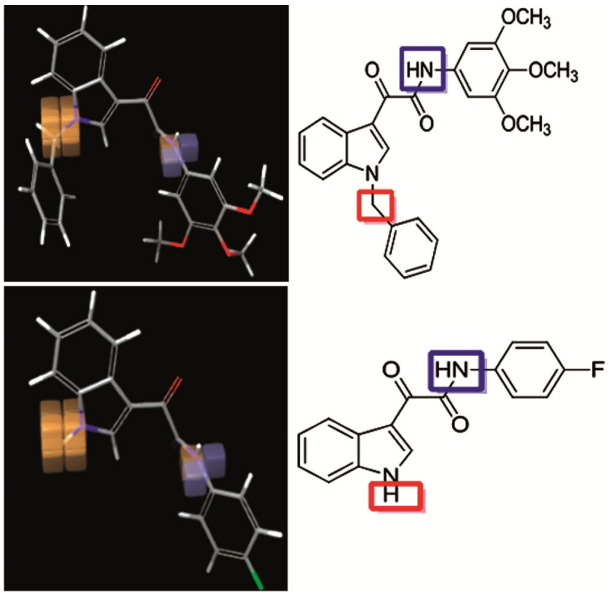


Fig. 8 — H-bond donor - A comparative analysis between ligand no. 15 (upper panel) and ligand no. 9 (lower panel)

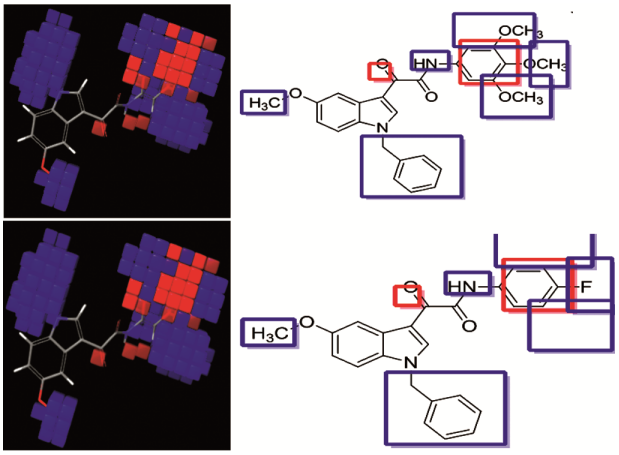


Fig. 9 — Hydrophobic/Non-polar substitution - A comparative analysis between ligand no. 15 (upper panel) and ligand no. 9 (lower panel)

indole ring will increase the overall activity of the compound. From the contour maps generated on the 3,4,5-trimethoxyphenyl ring substitutions, the blue contour maps were seen over the methoxy group that indicates increased activity. Ligand no. 24 also displays the same favourable and unfavourable regions for the substitutions previously observed in ligand no 28 (Fig. 9).

Electron-withdrawing substitution

In ligand no.15 and 28, the observed contour maps in blue colour reveal that the oxygen of methoxy groups at C-5 and Aryl ring favours the electron-withdrawing effect (Fig. 10).

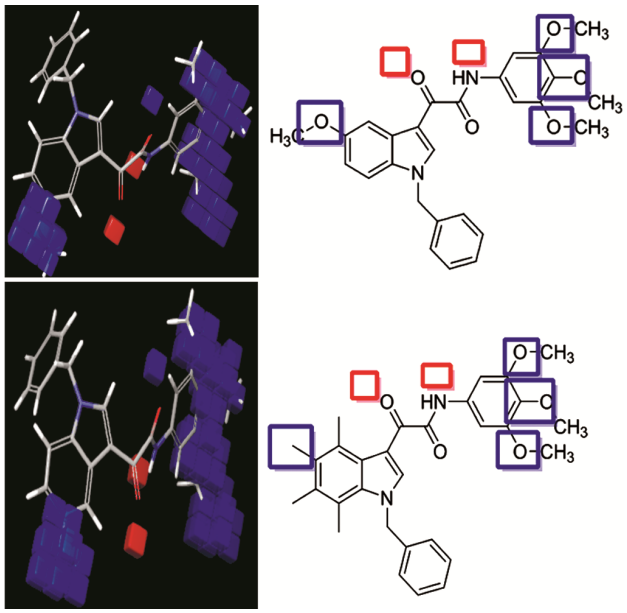


Fig. 10 — Hydrophobic/Non-polar substitution - A comparative analysis between ligand no. 15 (upper panel) and ligand no. 28 (lower panel)

ADMET Properties of 3D-QSAR model

The ADMET properties were calculated using the QikProp program running in normal mode. This program generates descriptors that are physically relevant and uses these to perform ADMET predictions. The pharmacokinetic profiles of the compounds were assessed using the ADME-compliance score by using #stars. These #stars parameters indicated the number of descriptors computed and which fall outside the optimum range in comparison to 95% of known compounds[19]. The recommended range of stars in the results generated falls in between 0-5 standard range[20]. The CNS activity predicted values fall perfectly under the -2 to +2 scale. Other important parameters like SASA, FOSA, FISA, PISA, and WPSA are various components of SASA and are denoted in Å and these predicted components have their range of scale. The range lies between 300.0-1000.0 for SASA, 0.0-750.0 for FOSA, 7.0-330.0 for FISA, 0.0-450.0 for PISA and 0.0-175.0 for WPSA. As per the observed values from the Tables S3-S5, they are in the given range of the recommended values. The volume usually describes the total solvent accessible volume in cubic angstrom and should be under the 500.0-2000.0 range. The donor HB and acceptor HB are average values that are taken under a certain range of configurations thus can be non-integer and should be under the recommended range of 0.0-6.0 and 2.0-20.0,

respectively. Globularity is always considered 1 for a spherical molecule and the given recommended range is 0.75-0.95 and the observed predicted values were 0.8 more or less. The prediction of various logarithmic parameters like polarizability (13.0-70.0), octanol/gas (8.0-35.0), water/gas (4.0-45.0), octanol/water (-2.0-6.5), HERG (concern below -5), Caco-2 (<25 poor and >500 great), BB (-3.0-1.2), MDCK (<25 poor and >500 great), K_P (-8.0 - -1.0) and K_{HSA} (-1.5 – 1.5) all were seen under the recommended ranges. The table also display predicted human oral absorption (1,2,3: low, medium, high), percent human oral absorption (>80% is high and <25 is poor), van der Waals surface area of amide oxygen atoms (7.0-200.0), Lipinski's rule of five are set of rules that determines whether a compound is drug-like or not. If a compound satisfies the sets of rules, it is drug-like (maximum is 4). Rule of three is another such set of rules that predict whether the compound would be orally available or not (preferable range: maximum of 3) and Jm value demonstrate predicted maximum transdermal rate[21].

Designing of new analogues based on the generated 3D-QSAR model

The new analogues were designed based on SAR (structure-activity relationship) studies and contour map visualizations done after QSAR model generation. These new agents were designed by incorporating sets of substituent according to their nature and by studying the contour maps thoroughly for the best results. The docking of these newly designed molecules was initiated by drawing these structures on 2D-sketcher, by doing ligand preparation at PH 7.0 on LigPrep followed by protein preparation of the receptor with the PDB ID: 1LPB, Generation of the grid, and docking the compound in the XP (extra precision) of the maestro suite. The compounds show good docking score and glide energy that confirmed its binding with the receptor pocket (Fig. 11). These agents displayed interactions with the chosen amino acids important for a compound to interact to display lipase activity (Table 6). Thus, all these results generated indicate that further synthesis of these agents will facilitate

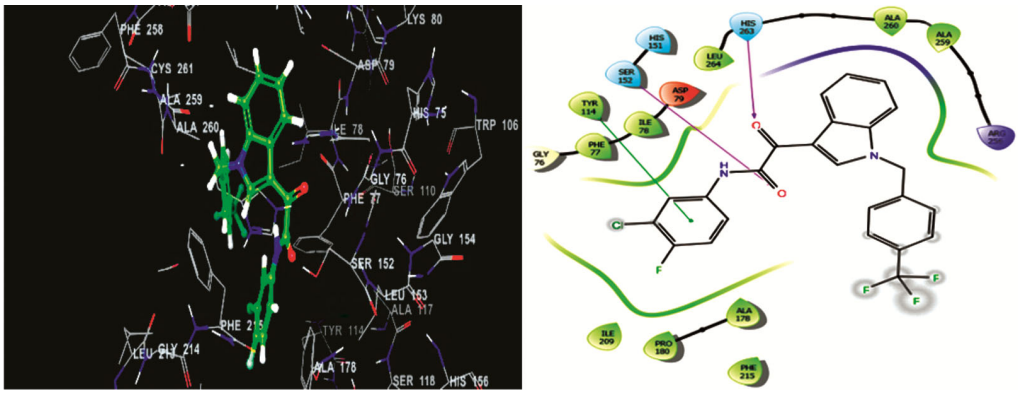
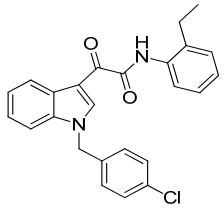
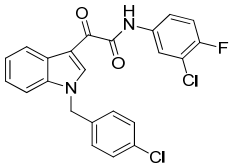


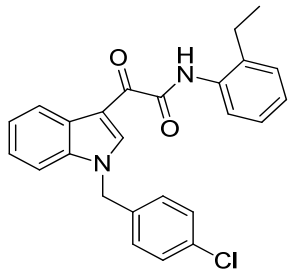
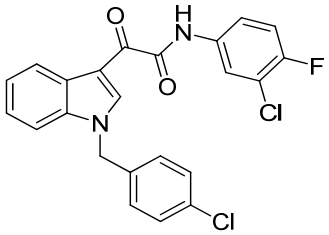
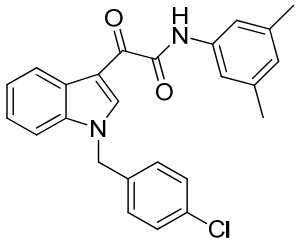
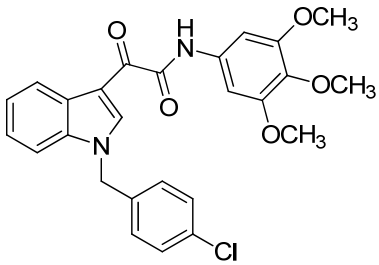
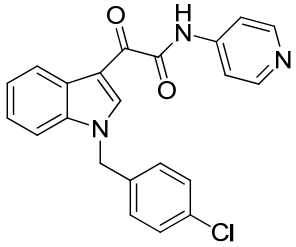
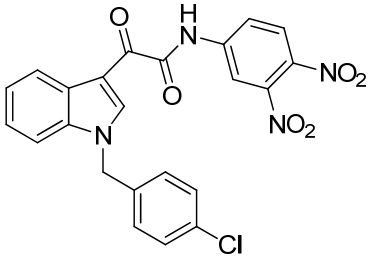
Fig. 11 — Docking interactions of ligand no. 8

Table 6 — Docking results of the designed compounds

Sl. No.	Ligand	Interactions				Docking G-Score
		H-bond	H-bond interaction	π–π	π-cation	
1		2.28,1.93	PHE77, SER152	TYR114, PHE215	--	-8.370
2		2.35, 2.03, 2.14	HIS263, SER152, PHE77	PHE77, TYR114	ARG256	-8.466

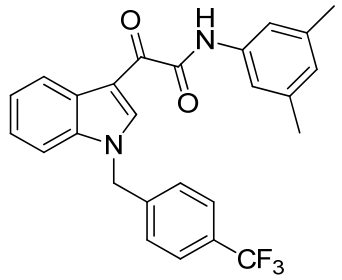
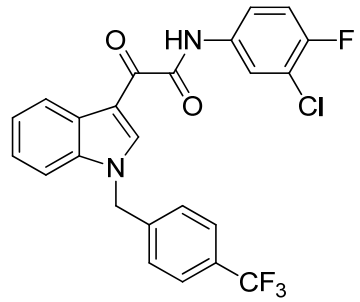
(*Contd.*)

Table 6 — Docking results of the designed compounds

Sl. No.	Ligand	Interactions				Docking G-Score
		H-bond	H-bond interaction	π–π	π-cation	
1		2.28,1.93	PHE77, SER152	TYR114, PHE215	--	-8.370
2		2.35, 2.03, 2.14	HIS263, SER152, PHE77	PHE77, TYR114	ARG256	-8.466
3		2.02	SER152	TYR114	HIS263	-6.365
4		2.24	HIS263	PHE77	--	-8.084
5		2.00	PHE77	TYR114	HIS263, ARG256	-6.588
6		1.81, 2.65	HIS263, PHE77	PHE77, HIS263, TYR114	--	-6.811

(*Contd.*)

Table 6 — Docking results of the designed compounds

Sl. No.	Ligand	Interactions				Docking G-Score
		H-bond	H-bond interaction	π–π	π-cation	
7		--	--	HIS151	HIS263	-6.731
8		2.09, 2.30	SER152, PHE77	TYR114, PHE215	--	-8.914

compounds with similar pharmacophore to be a potential target as a pancreatic lipase inhibitor.

Conclusion

The 3D-field based, and atom based QSAR models for indole glyoxylamide and indolyl oxoacetamides were found to be robust and well predictive for pancreatic lipase inhibitory activity. Overall parameters of the QSAR model like R^2, R^2CV, Stability, F, RMSE, etc. helped in the validation of the model along with contour maps generation that depicted visualizations very well. These visualizations helped in designing new molecules with favourable substitutions responsible for lipase inhibition and displayed a good glide Gscore that confirmed binding of the ligand with the receptor pocket. This docking simulation will help in synthesizing newly designed molecules. The ADMET properties of compounds taken for the QSAR model along with compounds that were designed and docked was generated to understand the behaviour of the molecules. The results revealed detailed structural insights of novel indole derivatives as pancreatic lipase inhibitors which could be a guide for rational designing of such agents that will possess lipase inhibitory activity.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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