Ind. J. Pharm. Edu. Res., 2027; 1-7.
https://www.ijper.org

Original Article

Structure-Based and Ligand-Based Computational Investigation of 2-Aryl Carbamoyl-Phenoxyacetic Acid Derivatives as Potential Aldose Reductase Inhibitors

Saurabh Kumar Gupta[1], Amit Verma[2], Rakhi Mishra[3,*]

[1]Rameshwaram Institute of Technology and Management, Lucknow
[2]School of Pharmacy, Chandigarh University (Unnao Campus), Unnao
[3]Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida

ABSTRACT

Introduction: Aldose reductase (ALR2) is an important therapeutic target associated with diabetic complications. This study investigates 2-aryl carbamoyl-phenoxyacetic acid derivatives as potential aldose reductase inhibitors (ARIs) using an integrated computational approach to identify structural features associated with inhibitory activity and propose novel derivatives for further investigation. **Materials and Methods:** We divided the compounds into training and test sets for quantitative structure–activity relationship (QSAR) analysis. Two-dimensional QSAR (2D-QSAR) analysis was performed using multiple linear regression (MLR), while three-dimensional QSAR analysis was carried out using k-nearest neighbour molecular field analysis (kNN-MFA). The pIC_{50} values were used as the dependent variable. Pharmacophore-guided analysis was subsequently employed to design a library of 30 compounds, followed by molecular docking against human aldose reductase (PDB ID: 1US0). **Results:** The 2D-QSAR model showed satisfactory statistical performance, with r^2 = 0.7567, q^2 = 0.8471, and pred_r^2 = 0.7736. Randomisation testing supported the statistical significance of the model. The kNN-MFA analysis identified important electrostatic and steric field contributions (q^2 = 0.8367, pred_r^2 = 0.7649). These findings were used to guide the design of the proposed compound library. Molecular docking computationally prioritised compounds S3, S11, S18, S27, S28, and S29 based on their predicted binding scores and interactions with active-site residues. Discussion: The QSAR analyses indicated that electrostatic and steric substitution patterns may contribute to aldose reductase inhibitory activity. The docking analysis provided insights into the predicted binding modes of the designed compounds; however, these computational results do not establish biological activity or experimentally validate the QSAR models. **Conclusion:** The integrated 2D-QSAR, 3D-QSAR, pharmacophore, and molecular docking approach identified structural features associated with the predicted aldose reductase inhibitory activity of 2-aryl carbamoyl-phenoxyacetic acid derivatives and prioritised compounds for further investigation. Experimental synthesis and in-vitro aldose reductase inhibition studies, including IC_{50} determination, are required to confirm the predicted activity. The present study did not evaluate comparative selectivity against aldehyde reductase (ALR1), which remains an important area for future investigation.

Keywords: Aldose Reductase Inhibitors, Complications, Diabetes Mellitus, Molecular Field Analysis, QSAR Analysis

Correspondence:
Dr. Rakhi Mishra
Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida 7906833682
Email: rakhi.misra84@rediffmail.com

www.ijper.org

INTRODUCTION

Amidst the sweeping landscape of healthcare, Diabetes mellitus emerges as a formidable adversary, inflicting a cascade of debilitating complications such as blindness, renal failure, neuropathy, limb amputation, myocardial infarction, and stroke. This silent menace quietly affects approximately 17 million lives in the United States, exacting a staggering annual toll of over 100 billion dollars. These alarming statistics underscore the urgency of understanding and combating the underlying causes.[1] Numerous clinical studies, including the monumental Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have shown a stark correlation between the development and progression of these complications and elevated blood glucose levels in patients with both type I and type II diabetes. This revelation forms the crux of our battle against the pernicious effects of diabetes.[2–5]

DOI: 10.5530/ijper.20270567

Copyright Information :
Copyright Author (s) 2027 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

In the quest for effective solutions, aldose reductase inhibitors (ARIs) present a tantalising opportunity. While many potent ARIs have been unearthed, their journey to global implementation has been fraught with obstacles. Challenges stemming from inadequacies in therapeutic indices have deterred their widespread acceptance.[6] The spectre of toxicity, often exacerbated by poor selectivity for aldehyde reductase (ALR1), has cast a shadow over these promising candidates. ALR1, a pivotal player in this process, converts highly reactive 2-oxoaldehydes, such as 3-deoxyglucosone and methylglyoxal, into their nonreactive, innocuous alcohol counterparts. These notorious aldehydes, born from the degradation of glucose and fructose, drive protein cross-linking and form advanced glycation end products (AGEs). In the crucible of prolonged hyperglycaemia, these aldehydes flourish, sowing the seeds of chronic diabetic complications and hastened ageing.

As members of the aldo-keto reductase superfamily, aldehyde reductase (ALR1) and aldose reductase (ALR2) share substantial structural similarity. Subtle amino acid changes in the C-terminal loop, a vital section of the protein that lines the active site cleft, dictate diverse substrate and inhibitor specificities. The relentless pursuit of innovation and endeavours to design novel, potent, and highly selective ARIs have borne fruit. A new class of compounds has emerged, marked by a core template of 2-arylcarbamoyl-phenoxyacetic acid.[7,8] This ingenious design incorporates an intramolecular hydrogen bond, orchestrating the alignment of the acetic acid moiety and aromatic side chain, the linchpins of the pharmacophore, in the precise orientation needed for optimal binding affinity.

Quantitative Structure-Activity Relationship (QSAR) and Structure-Based Drug Design (SBDD) are essential computational methodologies that have significantly transformed new-compound development, resulting in substantial savings in time and financial resources. SBDD serves as a strategic framework, utilising high-resolution three-dimensional structures of biological targets, primarily proteins, acquired through X-ray crystallography or cryo-electron microscopy (cryo-EM).[9] Visualising how a potential drug molecule fits within a target's binding pocket enables medicinal chemists to rationally design novel compounds that optimise interactions. This method turns random screening into targeted engineering, enabling the strategic design of effective, selective inhibitors from the start and minimising the number of compounds needed for synthesis and testing. Additionally, QSAR offers a robust predictive framework. By applying statistical models, the study establishes a correlation between the chemical structures of various compounds and their biological activity.[10] Identifying molecular features (descriptors) that influence potency allows QSAR models to predict the activity of novel, untested virtual compounds. This enables researchers to prioritise the most promising candidates for synthesis, filtering out those likely to be inactive or poorly optimised before laboratory work begins. Integrating these methods is significant. SBDD establishes the structural framework for design, whereas QSAR provides a quantitative approach to improve and predict the efficacy of those designs. This integrated computational strategy mitigates risks in the early phases of drug discovery, expediting the development of viable clinical candidates and improving time and cost efficiency.[11] The present work is an effort to design novel aldose reductase inhibitors through QSAR and SBDD approaches, which may offer hope for the effective treatment of these debilitating conditions that develop as an aftermath of diabetes complications.

MATERIALS AND METHODS

QSAR analysis was carried out by VLife Molecular Design Suite (VLife MDS supplied by VLife Science Technologies, Pune, India).

Collection of datasets

Initially, 59 (2-aryl carbamoyl-phenoxy)-acetic acid derivatives were collected from the reported literature. Seven compounds were excluded due to incomplete or inconsistent biological activity/structural information. Thus, 52 compounds with reliable and comparable IC_{50} data were retained for QSAR analysis and divided into 34 training and 18 test compounds. The IC_{50} values were converted into pIC_{50} values ($-\log IC_{50}$, M) for QSAR modelling. We used the sphere-exclusion method to divide the compounds into training and test sets while maintaining chemical diversity. The selected dissimilarity threshold was chosen to provide adequate structural diversity between the training and test sets while retaining sufficient compounds for model development. The applicability domain (AD) of the developed QSAR models was evaluated using a Williams plot, in which standardised residuals were plotted against leverage values. Compounds falling outside the defined leverage limit or standardised residual limits were considered potential outliers and were examined for their reliability within the model domain. This analysis was also used to determine whether the designed compounds fall within the reliable chemical space of the developed QSAR model. The V Life Engine was used to generate the 2D structures, which were converted to 3D counterparts via V Life MDS. We then performed energy minimisation using the molecular mechanics force field (MMFF) with default parameters in V Life MDS.

In a comprehensive 2D-QSAR investigation to elucidate the structural features governing the potency of (2-aryl carbamoyl-phenoxy)-acetic acid derivatives, we employed a rigorous computational workflow. The study began by calculating 1064 molecular descriptors, then filtering out invariable ones. The dataset was then partitioned into training, test, and validation sets using the sphere exclusion method, and model applicability was validated by ensuring test-set values fell within the training-set range. For model generation, we used multiple regression

www.ijper.org

techniques, including multiple linear regression (MLR), partial least squares, and principal component regression. A stepwise variable selection method was applied within the MLR framework to construct the final 2D-QSAR model, the fitness and predictive capability of which were rigorously evaluated using a suite of statistical parameters (r^2, q^2, F-test, etc.). This thorough process ensured the development of a reliable and robust model for predictive activity assessment.

A robust 3D-QSAR analysis was conducted using the k-nearest neighbour molecular field analysis (kNN-MFA) approach to elucidate the critical steric and electrostatic fields governing biological activity. The compounds were aligned using a common structural template based on the conserved 2-aryl carbamoyl-phenoxyacetic acid scaffold. The aligned molecules were subjected to conformational optimisation before generation of a common rectangular grid for calculation of steric and electrostatic field descriptors. The kNN-MFA calculations employed a methyl probe with a +1 charge, a dielectric constant of 1.0, and Gasteiger–Marsili partial charges. We maintained the grid dimensions, grid spacing, and field cutoff values used for model generation and report them to ensure reproducibility. We considered the selected alignment biologically relevant because it preserves the common pharmacophoric arrangement of the investigated derivatives and is consistent with the binding orientation considered for aldose reductase. Electrostatic and steric descriptors were computed using a dielectric constant of 1.0 and Gasteiger-Marsili charges, resulting in an initial pool of 2080 descriptors which were subsequently filtered to remove invariant columns. For model development, a dataset of 34 training and 18 test set compounds was selected via the sphere exclusion method, with uni-column statistics confirming the test set's appropriateness. The kNN-MFA model itself was constructed using a stepwise forward-backward variable selection method, employing distance-based weighted averaging with a defined range of nearest neighbors. The model's predictive robustness and statistical significance were rigorously validated against stringent criteria, including q^2 and pred_r^2 values exceeding 0.6, supported by a comprehensive suite of statistical parameters.[12]

Based on results from both 2D and 3D QSAR analyses, we designed a library of 30 compounds with the essential features required for activity. The designed compounds were subjected to docking studies to ascertain the binding characteristics with the target protein 1US0, a human aldose reductase protein.[13] The designed compounds were docked using Glide. The Glide software is a module available in the Schrodinger software. Docking studies involve analysing favourable ligand binding poses in the receptor's active site. Docking results are reported as amino acid residue interactions with the ligand and docking energies. The designed molecules, which were drawn in ChemDraw, were imported in the Schrodinger software and were minimised by the LigPrep module using the default parameters [14]. The protein used for the docking studies was human aldose reductase (PDB ID 1US0), downloaded from the Protein Data Bank. The protein had a resolution of 0.66 Å. We prepared the protein using the Protein Preparation Wizard with default parameters. All the heteroatoms were removed during the final preparation, except for the important water molecules HOH 2061, 2062, and 2131, which also showed interactions with the co-crystallised ligand. The active site was defined using the co-crystallised inhibitor IDD594 by the Receptor grid generation module using the default parameters, which was used to dock the ligands using the XP mode of Glide. The Results and Discussion section summarises and analyses the docking results.

Table 1: Univariate statistics results for the 2D-QSAR model.

	Average	Max	Min	StdDev	Sum
Activity (Training set)	7.4326	9.0695	5.6021	0.6902	115.3187
Activity (Test set)	7.5621	8.5586	6.0487	0.9864	30.2970

RESULTS AND DISCUSSION

The aim of the study was to identify key structural features interacting with the aldose reductase enzyme to help predict the binding mechanisms of (2-aryl carbamoyl-phenoxy)-acetic acid derivatives. While 2D QSAR highlighted the importance of 2D descriptors, 3D QSAR examined substituents' electrostatic and steric effects.

This study investigates the efficacy of (2-aryl carbamoyl-phenoxy)-acetic acid derivatives using detailed 2D-QSAR analyses. A total of 52 derivatives were selected and categorised into two groups: a training set of 34 compounds and a test set of 18 compounds. Univariate statistical analysis (Table 1) validated the dataset and revealed a coherent alignment between the two sets. The maximum values of the test set were lower than those of the training set, whereas the minimum values were higher than the corresponding minima of the training set, suggesting an appropriate data distribution. The test set values were interpolated within the range established by the training set, and the standard deviation values corroborated this internal consistency. Systematic selection and validation of training and test sets ensure statistical robustness and reliability, providing a solid foundation for developing and interpreting predictive QSAR models.

www.ijper.org

Table 2: MLR model summary of the generated 2D QSAR model

Statistical parameters	2D QSAR
N (training/test)	34
Degree of freedom	29
r^2 (squared correlation coefficient)	0.7567
q^2 (internal predictive ability)	0.8471
F test	22.5506
r^2_se (correlation coefficient standard error)	0.5262
q^2_se (internal predictive ability standard error)	0.5548
pred_r^2 (external predictive ability)	0.7736
pred_r^2se (standard error)	0.3777

QSAR model analysis and validation

Data sets were analysed to generate the best 2D QSAR equation using different model-building methods (multiple linear regression, principal component regression) coupled with a stepwise variable selection method. Statistically, the best significant model obtained through the multiple linear regression (MLR) method is given in Equation (1):

The Multiple Linear Regression (MLR) model developed for 2D-QSAR analysis demonstrates high precision, robustness, and predictive capability. The squared correlation coefficient (r^2) explains 75% of the variance among the 34 compounds, indicating excellent model fitting, while the internal predictive ability (q^2) of approximately 84% and external predictability (pred_r^2) of around 77% highlight its strong predictive performance. The F-test validates the statistical significance of the model at nearly 99.99%, and the Z-score derived from randomisation tests confirms model reliability with a confidence level of 99.9%, affirming its non-random character (Table 2-3).

The r^2 value of 0.7567, with an r^2 standard error of 0.5262, supports the model's accuracy and consistency. The fitness plot (Figure 1) illustrates a strong correlation between observed and predicted biological activities, with most data points closely aligned along the regression line, underscoring the model's predictive precision for both training and test sets. Complementarily, a radar plot (Figure 2) visually represents the proximity between actual (blue) and predicted (red) activities, demonstrating high alignment and coherence between empirical and predicted values.

The high r^2 value further signifies substantial agreement between experimental and computational data, reflecting the reliability of the established model. Equation (1) highlights the relationship between physicochemical and alignment-independent 2D descriptors, with four descriptors—T_2_N_0, T_N_O_5, T_F_F_6, and SddssS(sulfate)count—emerging as key contributors to inhibitory activity (Figure 3). Among these, T_2_N_0, representing the count of double-bonded atoms, exhibits a positive contribution of 42%, suggesting an enhancing effect on activity; T_N_O_5, describing the distance between nitrogen and oxygen atoms, shows a negative contribution of -25%; T_F_F_6, related to fluorine–fluorine interactions, contributes -17%; and SddssS(sulfate)count, representing sulfate bonding patterns, contributes -15% (Figure 3).

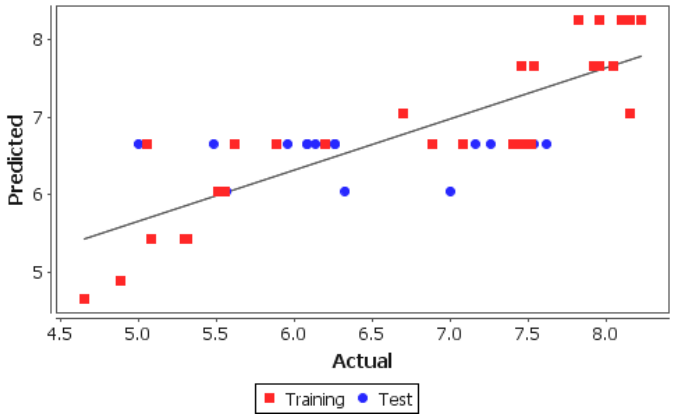


Figure 1: Fitness plot of observed vs. predictive activity of selected dataset.

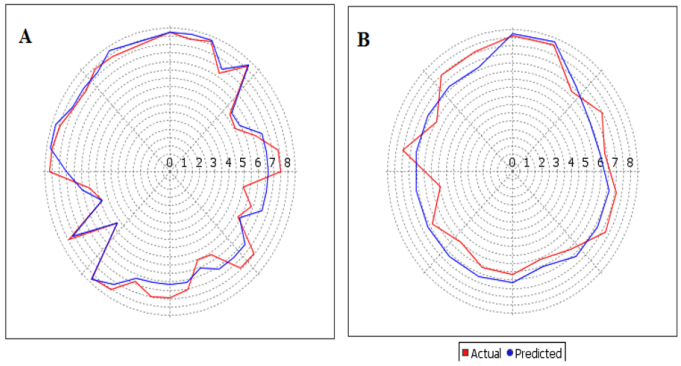


Figure 2: Radar plots depicted the actual and predicted activities of (A) the Training set (B) the Test set

These descriptors collectively elucidate the structural and electronic influences governing molecular activity, revealing crucial correlations between substitution patterns and biological potency. The experimental and predicted activities of selected compounds reflect a coherent integration of empirical and computational findings.

3D QSAR Studies

Using k-nearest neighbour molecular field analysis (kNN-MFA), the compounds were partitioned into training and test sets through the sphere exclusion method with a dissimilarity threshold of 4.0. Validation through uni-column statistical analysis (Table 4) confirmed the appropriate selection and alignment of activity ranges between the two sets. This

www.ijper.org

Table 3: Randomisation test results of the generated 2D QSAR model

Dep variable	Z Score r^2	Z Score q^2	Best Rand r^2	Best Rand q^2	Alpha Rand r^2	Alpha Rand q^2	Z Score Pred r^2	Best Rand Pred r^2	Alpha Rand Pred r^2
pIC_{50}	9.9431	10.018	0.3444	0.0892	0.000	0.000	1.6199	0.381	0.1000

Table 4: Uni-column statistics results for the 3D-QSAR model.

	Average	Max	Min	Std Dev	Sum
Activity (Training set)	7.3235	8.0020	5.8012	0.4246	118.3254
Activity (Test set)	7.6245	7.8232	6.2427	0.864	29.3572

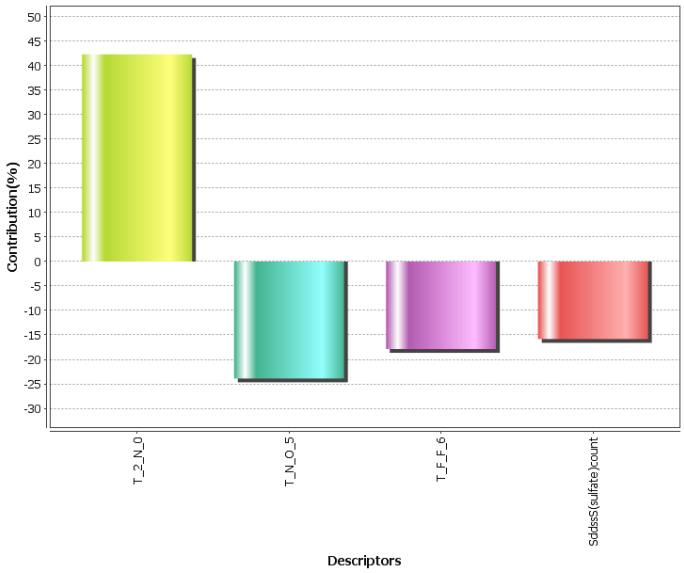


Figure 3: 2D Descriptors contribution plot

consistency indicates that the data sets were accurately chosen within the prescribed activity limits for effective model training and testing.

The kNN-MFA model was implemented in combination with simulated annealing (SA), genetic algorithm (GA), and stepwise (SW) variable selection techniques, following the generation of a standard rectangular grid around the molecules and the computation of steric and electrostatic energy fields using a methyl probe with a +1 charge. Among the approaches, the model derived from stepwise variable selection performed best, indicating that electrostatic interaction (E_904) and steric interactions (S_965, S_8, S_434, S_749, S_478, S_291, S_758, S_303, and S_838) significantly influence the determination of biological activity. Additional statistical parameters and descriptor details are provided in Table 5.

The developed kNN-MFA model exhibits strong statistical validation and predictive reliability. The model achieved an internal validation coefficient (q^2) of 0.8367 and an external validation coefficient (pred_r^2) of 0.7649, accurately predicting

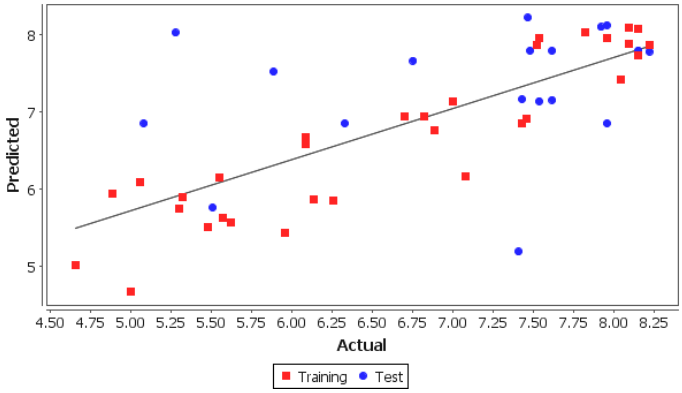


Figure 4: Fitness plot of observed vs. predictive activity of selected dataset (3D QSAR).

biological activity in the training and test sets with approximately 83% and 76% precision, respectively. The standard internal validation error (q^2_se) of 0.4712 further reflects the model's precision and its capacity to capture subtle variations in activity. Employing a forward–backward stepwise variable selection method, the model demonstrates remarkable robustness and stability across multiple statistical parameters. The experimental and predicted activities, along with the corresponding residuals reveal a close alignment between observed and computed values that reinforces the model's predictive efficiency. The fitness plot (Figure 4) illustrates the relationship between observed and predicted activities, highlighting minimal deviation and showcasing the model's accuracy and reliability. Complementing this, the radar plot (Figure 5) visually represents the proximity between actual (blue) and predicted (red) activities, effectively capturing both the convergence and divergence patterns, thereby emphasising the model's proficiency in accurately predicting biological responses.

Pharmacophore Exploration

In the strategic evaluation of molecular fields, the model systematically identifies key steric and electrostatic descriptors distributed across a uniform grid encompassing the studied compounds. These descriptors encode critical field values that underpin understanding of molecular interactions and guide the rational design of novel ligands. Figure 6 illustrates the spatial distribution and magnitude of electrostatic fields within the kNN-MFA model, providing a visual framework for interpreting activity-related regions. Analysis of these electrostatic landscapes reveals that positive potential regions correspond to enhanced biological activity, suggesting the

www.ijper.org

incorporation of less electronegative substituents at these positions, while negative potential regions favour the introduction of more electronegative groups to augment activity. This interpretative framework underscores the model's capacity to translate electrostatic and steric field information into meaningful design strategies, thereby enabling the conceptualization of new molecules with optimised pharmacophoric features. Ultimately, this balance between electronegativity and molecular potential provides valuable insight for directing future ligand design toward improved potency and specificity.

Interpretation of 3D QSAR studies and pharmacophore identification

The descriptors that get selected in an obtained model are the field points either of steric or electrostatic nature at different locations in a common grid around the set of compounds. The field values of the selected descriptors are utilised for new ligand design. Figure 6 shows the position and ranges of the corresponding electrostatic fields in the kNN MFA model provides the information for the design of new molecules. Positive range of electrostatic field descriptors suggests that positive electrostatic potential is favourable for increase in the activity, and as consequences, a less electronegative substituent group is preferred in that region while negative range of electrostatic field descriptor indicates that negative electrostatic potential is favourable for increase in activity, and consequently, a more electronegative substituent group is preferred in that region.[15]

Based on the range guidelines and the developed kNN-MFA field plots, one electrostatic field descriptor (E_904) exhibited predominantly positive potential values, indicating that a decrease in the electronegativity of the substituent on the phenoxy ring is favourable for enhancing biological activity. In contrast, nine steric field descriptors displayed regions of both negative and positive steric potential. The negative steric regions suggest that smaller or less bulky substituents are preferred to improve activity, whereas the positive steric regions indicate that bulkier substituents may contribute favourably to increased activity.[16] These observations were instrumental in identifying the key pharmacophoric features essential for the design of novel and more potent aldose reductase inhibitors.[17] Thus, integrating insights from both 2D descriptor analysis and 3D-QSAR modelling provides a comprehensive understanding of the structural requirements governing enhanced inhibitory activity. The structural requirements as developed through our studies have been summarised in figure (Figure 7) below.

Generation of library

The 30-member compound library was designed using the structural requirements identified from the 2D-QSAR and kNN-MFA analyses. The electrostatic field descriptor E_904 indicated that reduced electronegativity of the substituent on the phenoxy ring was favourable for activity, whereas the steric field descriptors indicated regions where smaller or bulkier substituents could be considered. These steric and electrostatic field requirements, together with the common pharmacophoric features identified from the QSAR analyses, were used as the design criteria for selecting substituent patterns in the proposed compounds. The structures have been given in Table 7 along with their chemical data in Table 8.

We performed docking studies on the designed compounds using PDB ID 1US0, a human aldose reductase protein. Table 9 summarises the docking scores and interacting residues.

The designed compounds showed variations in molecular weight, aromatic atoms, rotatable bonds, and hydrogen-bonding characteristics (Table 8). These residues, along with the docking energies, were used to predict the most active compounds. The compound S3 was found to have the most common amino acid interaction (14) as well as the lowest binding energy (-12.16 kcal/mol) followed by compound S11 and S29 with 10 and -12.13 kcal/mol and -11.84 kcal/mol as the number of common interactions each and binding energy, respectively. The compounds S18, S27 and S28 all showed 11 common interactions each with -10. 91, -11.08, and -10.96 kcal/mol as binding energies. All other compounds had either few common interactions with low binding energies or many common interactions with high binding energies. Based on the docking scores and observed interactions, compounds S3, S11, S18, S27, S28, and S29 were computationally prioritised for further investigation. These findings represent docking-based prioritisation and do not establish biological activity. Experimental synthesis, followed by in vitro aldose reductase inhibition and IC_{50} determination, is required for confirmation. These filtered compounds may be used for further synthesis to elucidate other outcomes. The 3D and 2D poses of the top compounds (S3 and S11) are given in Figure 8.

CONCLUSIONS

The present study investigated 2-aryl carbamoyl-phenoxyacetic acid derivatives using integrated 2D- and 3D-QSAR approaches to identify structural features associated with aldose reductase inhibition. The kNN-MFA analysis highlighted important steric and electrostatic field contributions that supported the computational design of new derivatives. Docking analysis computationally prioritised S3, S11, S18, S27, S28, and S29 based on their predicted binding scores and interactions with active-site residues. However, these findings represent computational predictions and do not establish biological activity or therapeutic

www.ijper.org

efficacy. Experimental confirmation requires synthesis of the prioritised compounds followed by in vitro aldose reductase inhibition assays and IC_{50} determination. However, the present study did not computationally evaluate the selectivity of the designed compounds toward ALR2 over ALR1, which requires dedicated comparative studies. Future studies should include comparative ALR1/ALR2 docking and in vitro selectivity assays to establish the selectivity profile of the prioritised compounds. This research represents a meaningful step toward developing new ARIs, potentially improving treatment options for diabetes-related complications.

AUTHORS' CONTRIBUTION

All authors contributed to the manuscript's conceptualisation, literature review, and writing.

CONFLICT OF INTEREST

None

FUNDING

None

ACKNOWLEDGEMENT

None

ABBREVIATIONS

AR - Aldose Reductase; ARI - Aldose Reductase Inhibitor; CADD - Computer-Aided Drug Design; QSAR - Quantitative Structure–Activity Relationship; 2D-QSAR - Two-Dimensional Quantitative Structure–Activity Relationship; 3D-QSAR - Three-Dimensional Quantitative Structure–Activity Relationship; MLR - Multiple Linear Regression; PLS - Partial Least Squares; PCR - Principal Component Regression; kNN - k-Nearest Neighbour; kNN-MFA - k-Nearest Neighbour Molecular Field Analysis; MFA - Molecular Field Analysis; IC_{50} - Half-Maximal Inhibitory Concentration; pIC_{50} - Negative Logarithm of IC_{50}; PDB - Protein Data Bank; MMFF - Merck Molecular Force Field; MMFF94 - Merck Molecular Force Field 94; VLife MDS - VLife Molecular Design Suite; Gasteiger–Marsili - Gasteiger–Marsili Partial Charge Method; XP - Extra Precision; Glide XP - Glide Extra Precision; ADME - Absorption, Distribution, Metabolism and Excretion; PES - Potential Energy Surface; SD - Standard Deviation; RMSE - Root Mean Square Error; r^2 - Squared Correlation Coefficient; q^2 - Cross-Validated Squared Correlation Coefficient; pred_r^2 - Predictive Squared Correlation Coefficient; E - Electrostatic Field Descriptor; S - Steric Field Descriptor; nM - Nanomolar; µM - Micromolar; M - Molar; H-bond - Hydrogen Bond; H_2O - Water; SAR - Structure–Activity Relationship; R^2 - Coefficient of Determination.

REFERENCES

1. Rogers DG. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. Clin Pediatr (Phila). 1994;33(6):378. doi:10.1097/00132586-199406000-00052
2. Quattrini L, La Motta C. Aldose reductase inhibitors: 2013-present. Expert Opin Ther Pat. 2019;29(3):199-213. doi:10.1080/13543776.2019.1582646
3. Tomlinson DR, Stevens EJ, Diemel LT. Aldose reductase inhibitors and their potential for the treatment of diabetic complications. Trends Pharmacol Sci. 1994;15(8):293-7. doi:10.1016/0165-6147(94)90010-8
4. Tomlinson DR, Willars GB, Carrington AL. Aldose reductase inhibitors and diabetic complications. Pharmacol Ther. 1992;54(2):151-94. doi:10.1016/0163-7258(92)90031-T
5. Turner R, Holman RR, Cull CA, Stratton IM, Matthews DR, Frighi V, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53. doi:10.1016/S0140-6736(98)07019-6
6. Pawar V, Lokwani D, Bhandari S, Mitra D, Sabde S, Bothara K, et al. Design of potential reverse transcriptase inhibitor containing isatin nucleus using molecular modeling studies. Bioorg Med Chem. 2010;18(9):3198-211. doi:10.1016/j.bmc.2010.03.030
7. Barski OA, Tipparaju SM, Bhatnagar A. The aldo-keto reductase superfamily and its role in drug metabolism and detoxification. Drug Metab Rev. 2008;40(4):553-624. doi:10.1080/03602530802431439
8. Díaz-Viraqué F, Chiribao ML, Paes-Vieira L, Machado MR, Faral-Tello P, Tomasina R, et al. New insights into the role of the *Trypanosoma cruzi* aldo-keto reductase TcAKR. Pathogens. 2023;12(1):85. doi:10.3390/pathogens12010085
9. Bastikar V, Bastikar A, Gupta P. Quantitative structure-activity relationship-based computational approaches. In: Computational approaches for novel therapeutic and diagnostic designing to mitigate SARS-CoV2 infection: revolutionary strategies to combat pandemics. Elsevier; 2022. p. 191-205. doi:10.1016/B978-0-323-91172-6.00001-7
10. Cai Z, Zafferani M, Akande OM, Hargrove AE. Quantitative structure-activity relationship (QSAR) study predicts small-molecule binding to RNA structure. J Med Chem. 2022;65(10):7262-77. doi:10.1021/acs.jmedchem.2c00254
11. Azad I, Khan T, Ahmad N, Khan AR, Akhter Y. Updates on drug designing approach through computational strategies: a review. Future Sci OA. 2023;9(2):FSO862. doi:10.2144/fsoa-2022-0085
12. Leemans E, Mahasenan KV, Kumarasiri M, Spink E, Ding D, O'Daniel PI, et al. Three-dimensional QSAR analysis and design of new 1,2,4-oxadiazole antibacterials. Bioorg Med Chem Lett. 2016;26(3):1011-5. doi:10.1016/j.bmcl.2015.12.041
13. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015;20(7):13384-421. doi:10.3390/molecules200713384
14. Ma Z, Ajibade A, Zou X. Docking strategies for predicting protein-ligand interactions and their application to structure-based drug design. Commun Inf Syst. 2024;24(2):199-230. doi:10.4310/CIS.241021221101
15. Kumar S, Kumar N, Sharma CS, Mishra SS. Molecular insights of 1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole as CRF-1 receptor antagonists: combined QSAR, Glide docking, molecular dynamics, and in-silico ADME studies. Iran J Pharm Res. 2021;20(1):22-34. doi:10.22037/ijpr.2020.113746.14464
16. Prasanna S, Doerksen R. Topological polar surface area: a useful descriptor in 2D-QSAR. Curr Med Chem. 2009;16(1):21-41. doi:10.2174/092986709787002817
17. Bakal RL, Jawarkar RD, Manwar JV, Jaiswal MS, Ghosh A, Gandhi A, et al. Identification of potent aldose reductase inhibitors as antidiabetic (anti-hyperglycemic) agents using QSAR based virtual screening, molecular docking, MD simulation and MMGBSA approaches. Saudi Pharm J. 2022;30(5):693-710. doi:10.1016/j.jsps.2022.04.003

Cite this article: Gupta SK, Verma A, Mishra R. Structure-Based and Ligand-Based Computational Investigation of 2-Aryl Carbamoyl-Phenoxyacetic Acid Derivatives as Potential Aldose Reductase Inhibitors. Indian J of Pharmaceutical Education and Research. 2027;1-7.

www.ijper.org