Insights into the structural requirements of triazole derivatives as promising DPP IV inhibitors: computational investigations

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\textbf{ABSTRACT}

Diabetes is one of the leading causes of death globally as per World Health Organization 2019. To cope up with side effects of current diabetes therapy, researchers have found several novel targets for the treatment of diabetes. Currently, dipeptidyl peptidase IV (DPP IV) has emerged as a target in modulating the diabetes physiology. In the present work, various 3D-Quantitative structure activity relationship (QSAR) techniques namely comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis, topomer CoMFA and molecular hologram QSAR are used to explore the structural requirements of triazole derivatives as DPP IV inhibitors. Different models generated by 3D QSAR studies had acceptable statistical values for further prediction of molecules. From the contour maps of QSAR results, important structural features are deduced. Substitutions on N1 and N2 of triazole ring with H-bond donor group enhances the biological activity. Aliphatic side chain, less bulky group, H-bond donor group and \(-\text{COOH}\) group on N3 of triazole ring are vital for the DPP IV inhibition. Moreover, electron withdrawing side chain on the triazole ring improves the biological activity. Further, novel triazole derivatives were designed and docking results of these compounds proved the efficiency of the developed 3D QSAR model. In future, results of this study may provide promising DPP IV inhibitors for the treatment of diabetes.

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\textbf{1. Introduction}

Type 2 diabetes is the metabolic disease caused by deficiency of insulin due to pancreatic \(\beta\)-cell dysfunction or resistance of insulin in target organs (Sagar et al., 2015). Being the ninth leading cause of death in 2019, diabetes places huge pressure on individual and overwhelming cost to global health economies (Chatterjee et al., 2017; World Health Organization, 2019). According to International Federation of Diabetes (IDF), \(\sim463\) million adults were living with diabetes in 2019 and this figure will rise to 700 million by 2045 (Saedi et al., 2019). Currently available antidiabetic agents cause hypoglycaemia which is the major barrier in optimizing glucose lowering therapy.

Dipeptidyl-peptidase IV is a serine type protease enzyme, widely distributed in various body tissues such as intestine, spleen, adrenal glands, kidney, placenta, lymphocytes and endothelial cells. The incretin hormones namely glucagon-like...
peptide-1 (GLP-1) and gastric inhibitory polypeptide are the substrates of dipeptidyl peptidase IV (DPP IV) (Kshirsagar et al., 2011; Sagar et al., 2015). DPP IV inhibitors induce glucose-dependent insulin secretion and stabilize endogenous GLP-1. DPP IV inhibition results in the improvement of glucose tolerance and increases levels of circulating active GLP-1. Currently available insulinotropic agents release insulin in glucose-independent manner and thereby cause hypoglycemia as a major side effect (Green et al., 2006; Shah et al., 2020). Currently available DPP IV inhibitors are called as ‘Gliptins’ namely Sitagliptin, Vildagliptin, Alogliptin, and so on. These drugs are associated with several side effects, i.e. hypersensitivity, pancreatitis, skin reactions and nasopharyngitis (Shah et al., 2020). Therefore, this novel class of therapeutic is still under the development stage for its potential use as antidiabetic agents. Efforts are ongoing to design and synthesize more potent DPP IV inhibitors.

Quantitative structure activity relationship (QSAR) can provide basic information which helps in designing more active and safe drugs and it also predicts biological activity based on their chemical structures. Hence, in the present study, 51 triazole derivatives were selected for comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA), topomer CoMFA and molecular hologram QSAR (HQSAR) studies for designing novel DPP IV inhibitors (Caballer, 2010; Cramer, 2003; da Silva et al., 2004; Wang et al., 2016). On the one hand, CoMFA model was generated using steric and electrostatic field while on the other different combinations of steric, electrostatic, hydrophobic, donor and acceptor parameters were optimized and used for generation of the best CoMSIA model. Based on the counter maps of CoMFA and CoMSIA models, structurally favourable and unfavourable regions were identified from the most active compound of the series. Furthermore, topomer CoMFA and HQSAR analysis suggested many fragments responsible for the biological activity. These studies provide an insight on positive and negative contributions of each fragment.

2. Materials and methods

2.1. Molecular structure construction

The structure of 51 compounds, collected from the literature (Dastjerdi et al., 2020; Deng et al., 2017; Kim et al., 2005; Li et al., 2016; Narasimha et al., 2020) were drawn by sketch function of SYBYL-X-2.1 software. All the molecules were optimized by Gasteiger-Huckel charges. Further, energy minimization and conformational search were performed using Powell method and Tripos force field with energy convergence criterion of 0.005 kcal/mol Å (Clark et al., 1989). Maximum iteration was set to 100 to obtain stable conformation. Other parameters were taken as default value of SYBYL-X-2.1.

2.2. Data set, molecular alignment and selection of training and test set

A total of 51 triazole derivatives and their biological activities were retrieved from the literature. The chemical structure and biological activity of all the compounds are depicted in Table 1. Fifty-one minimized structures were aligned together by least-squares fitting of five atoms using common functional moiety 1,3-triazole. The core structure used for the alignment is shown in Figure 1. Out of 51 compounds, 8 compounds have 1,2,4-triazole ring structure and rest 43 compounds have 1,2,3-triazole ring structure. Due to this structural variation, eight structures were eliminated after alignment. All the aligned structures are shown in Figure 2. IC50 values were converted into pIC50 for construction of the QSAR models. Compounds were randomly selected as training and test set. Even after random selection, training set and test set comprised of compounds with low, moderate and high activity values. Out of 43 compounds, 35 compounds were taken as training set and rest 8 compounds were taken as test set which were then used to validate the predictive ability of the generated model.

2.3. CoMFA and CoMSIA field descriptors

3D-lattice was generated on the aligned molecules of the series and steric and electrostatic fields of CoMFA were calculated by Equations 1 (Lennard-Jones) and 2 (Coulomb potentials), respectively (Chhatbar et al., 2019).

\[ E_{vdW} = \sum_n (A_i r_j - 12 - C_i r_j^{-6}) \]  \hspace{1cm} (1) \hfill \\

\[ E_C = \sum_{i=1}^{n} \left( \frac{q_i q_j}{r_{ij}} \right) \]  \hspace{1cm} (2)

Here, \( E_{vdW} \) van der Waals energy; \( A_i \) and \( C_i \) are constants, \( r_{ij} \) = distance between atom \( i \) of the molecule and the grid point \( j \) where probe atom is located, \( E_C \) coulomb energy; \( q_i \) partial charge of atom \( i \) of the molecule; \( q_j \) charge of the probe atom; \( D \) dielectric constant.

2.4. Development of significant CoMFA and CoMSIA models

Aligned molecules were placed on a 3D cubic lattice with a grid spacing of 2.0 Å. CoMFA and CoMSIA fields were calculated for each compound in a dataset at every grid point using a sp3-hybridized carbon probe with a charge of +1.0. The electrostatic and steric fields of CoMFA were based on Columbic and Lennard-Jones potentials, respectively, with the cut-off energy of 30 kcal/mol (Chavda & Bhatt, 2019; Tong et al., 2020). Similar standard settings were used to calculate various CoMSIA fields; steric, electrostatic, hydrogen bond donor, hydrogen bond acceptor and hydrophobic using Gaussian function (Klebe, 1998). Finally, 3D-QSAR models were generated by quantifying the relationship between independent variables (CoMFA/CoMSIA fields) and dependent variable (pIC50 values) of compounds using partial least square (PLS) analysis (Buolamwini & Assefa, 2002).

2.5. Topomer CoMFA modelling

Topomer CoMFA is a 3D-QSAR method based on translocation technology (topomer) defined by Cramer (Cramer, 2003) in which molecules are proposed as a collection of fragments. Fragments are helpful in generating CoMFA...
Table 1. List of structures used in QSAR studies.

| No. | Structure | IC$_{50}$ (nM) | pIC$_{50}$ | Role |
|-----|-----------|----------------|------------|------|
| 1a  | ![Structure 1a](image1) | 87.41 | 7.60 | test |
| 1b  | ![Structure 1b](image2) | 67.98 | 7.17 | training |
| 1c  | ![Structure 1c](image3) | 16.34 | 7.79 | test |
| 1d  | ![Structure 1d](image4) | 29.87 | 7.52 | test |
| 1e  | ![Structure 1e](image5) | 14.75 | 7.83 | training |
| 1f  | ![Structure 1f](image6) | 6.75 | 8.17 | training |
| 1g  | ![Structure 1g](image7) | 6.57 | 8.18 | training |
| 1h  | ![Structure 1h](image8) | 125 | 6.90 | training |
| No. | Structure | IC<sub>50</sub> (nM) | pIC<sub>50</sub> | Role |
|-----|-----------|---------------------|----------------|------|
| 1i  | ![Structure](image1.png) | 104 | 6.98 | training |
| 1j  | ![Structure](image2.png) | 102 | 6.99 | test |
| 1k  | ![Structure](image3.png) | 2000 | 5.70 | training |
| 1l  | ![Structure](image4.png) | 925 | 6.03 | training |
| 1m  | ![Structure](image5.png) | 1470 | 5.83 | test |
| 1n  | ![Structure](image6.png) | 1351 | 5.87 | training |
| 1o  | ![Structure](image7.png) | 2208 | 5.66 | training |

(continued)
Table 1. Continued.

| No. | Structure | IC<sub>50</sub> (nM) | pIC<sub>50</sub> | Role |
|-----|-----------|----------------------|-----------------|------|
| 1p  | ![Structure](image1.png) | 12.45               | 7.90            | training |
| 1q  | ![Structure](image2.png) | 84.72               | 7.07            | training |
| 1r  | ![Structure](image3.png) | 175.23              | 6.76            | training |
| 1s  | ![Structure](image4.png) | 205.34              | 6.69            | training |
| 1t  | ![Structure](image5.png) | 182.48              | 6.74            | training |
| 1u  | ![Structure](image6.png) | 194.81              | 6.71            | training |

(continued)
| No. | Structure | $\text{IC}_{50}$ (nM) | $\text{pIC}_{50}$ | Role   |
|-----|-----------|----------------------|------------------|--------|
| 1v  | ![Structure](image1) | 165.32 | 6.78 | training |
| 1w  | ![Structure](image2) | 118.31 | 6.93 | training |
| 1x  | ![Structure](image3) | 28.62 | 7.54 | training |
| 1y  | ![Structure](image4) | 80.43 | 7.09 | test    |
| 1z  | ![Structure](image5) | 132.72 | 6.88 | training |
| 2a  | ![Structure](image6) | 455  | 6.34 | eliminated |
| 2b  | ![Structure](image7) | 231  | 6.64 | eliminated |
| No. | Structure                        | IC$_{50}$ (nM) | pIC$_{50}$ | Role   |
|-----|----------------------------------|----------------|------------|--------|
| 2c  | ![Structure 2c](image)           | 128            | 6.89       | eliminated |
| 2d  | ![Structure 2d](image)           | 27             | 7.57       | eliminated |
| 2e  | ![Structure 2e](image)           | 18             | 7.74       | eliminated |
| 2f  | ![Structure 2f](image)           | 68             | 7.17       | eliminated |
| 2g  | ![Structure 2g](image)           | 71             | 7.15       | eliminated |
| 2h  | ![Structure 2h](image)           | 103            | 6.99       | eliminated |
| 2i  | ![Structure 2i](image)           | 185.24         | 6.73       | training |
| 2j  | ![Structure 2j](image)           | 64.05          | 7.19       | training |

(continued)
| No. | Structure | \( \text{IC}_{50} \) (nM) | \( \text{pIC}_{50} \) | Role |
|-----|-----------|-----------------|-----------------|------|
| 2k  | ![Structure](image1) | 135.45 | 6.87 | training |
| 2l  | ![Structure](image2) | 243.67 | 6.61 | test |
| 2m  | ![Structure](image3) | 168.63 | 6.77 | training |
| 2n  | ![Structure](image4) | 219.42 | 6.66 | training |
| 2o  | ![Structure](image5) | 88.53 | 7.05 | training |

(continued)
Table 1. Continued.

| No. | Structure | IC<sub>50</sub> (nM) | pIC<sub>50</sub> | Role   |
|-----|-----------|----------------------|-----------------|--------|
| 2p  | ![Structure 2p](image1.png) | 345.32 | 6.46 | training |
| 2q  | ![Structure 2q](image2.png) | 172.53 | 6.76 | training |
| 2r  | ![Structure 2r](image3.png) | 65.63 | 7.18 | training |
| 2s  | ![Structure 2s](image4.png) | 84.72 | 7.07 | test   |
| 2t  | ![Structure 2t](image5.png) | 12.45 | 7.90 | training |
| 2u  | ![Structure 2u](image6.png) | 64.31 | 7.19 | training |
model using PLS analysis. Based on that, various steric and electrostatic properties of each fragment can be calculated.

The most important step of this method is the choice of splitting modes or the identification of the R group (Kumar & Tiwari, 2015). Fragmentation pattern of R1 and R2 substitution for all molecules of the dataset in topomer CoMFA analysis is represented in Figure 3. The predictive accuracy of the topomer CoMFA models and the reliability of contour maps depend on fragmentation step. The standard topomer 3D model was automatically built for each fragment. The carbon SP3 probe is used to calculate the interaction energy between solids and electrons (Cramer et al., 2008). Space and electrostatic descriptors are used as independent variables, and pIC50 values as dependent variable.

In topomer CoMFA, 35 molecules of triazole derivatives were divided into 2 fragments (Figure 3). In addition, molecule with the highest inhibitory activity was selected as the template molecule. After that, the remaining molecules were automatically separated according to the cutting method of the template molecule. The fragments were adjusted according to empirical rules to generate a 3D-QSAR model.

### 2.6. HQSAR

Training set molecules were used for the generation of all possible fragments and these fragmented structures were encoded in the form of bins of the hologram through the hashing algorithm. To generate predictive HQSAR models, hologram-generated bins were correlated with the biological activity. For generation of the hologram, several parameters were considered viz. atomic number (A), bond type (B), atomic connection (C), hydrogen bond donor/acceptor (DA), hydrogen (H) and chirality (Ch) (Sridhar et al., 2011). In current work, five different fragments namely bond type (B), atomic connection (C), hydrogen-bond donor/acceptor (DA), hydrogen (H) and chirality (Ch) were selected for the HQSAR

| No. | Structure | IC50 (nM) | pIC50 | Role |
|-----|-----------|-----------|-------|------|
| 2w  | ![Structure](image1) | 71.62     | 7.14  | training |
| 2x  | ![Structure](image2) | 9.56      | 8.02  | training |
| 2y  | ![Structure](image3) | 105.56    | 6.98  | training |
model generation. All the important structural features were analysed for the generation of the best model. Fragments were created by breaking input molecules and the value of minimum (M) and maximum (N) number of fragments were checked. Hologram length was kept in the range 50–500. Fragment collision was reduced by selecting the value of L as prime numbers. Default L values i.e. 53, 59, 61, 71, 83, 97, 151, 199, 257, 307, 353 and 401 were selected (Abdizadeh et al., 2020). Further, PLS analysis can be employed to correlate the biological activity with hologram descriptors for designing of novel drug candidates (Seel et al., 1999).

### 2.7. PLS analysis

PLS regression analysis was performed for CoMFA, CoMSIA and HQSAR studies. The calculated descriptors of CoMFA, CoMSIA and HQSAR models were used as independent variables and DPP IV inhibition activity (pIC50) as the dependent variable. Various statistical parameters i.e. $q^2$, $r^2$, $r^2_{\text{pred}}$ and $r^2_{\text{bs}}$ were determined in PLS analysis (Baroni et al., 1993). The internal validation of CoMFA and CoMSIA models was done using $q^2$ value [Leave-One-Out (LOO) cross-validation correlation coefficient]. $q^2$ value provides an idea about predictive ability of CoMFA and CoMSIA models with reduced dataset of molecules (Verma et al., 2010). During the PLS analysis, one molecule from the data set was excluded and then after a model was generated. Afterwards, the activity prediction of the excluded molecule was done using this generated model. This procedure was continued for $n$ number of times until all the compounds had been excluded. $q^2$ value was obtained as an outcome of this work, which provided robustness and predictive ability of the CoMFA and CoMSIA models. Moreover, $r^2$ value (person’s correlation coefficient) gives an idea about the relationship between the actual activity and the predicted activity. A graph of actual activity versus predicted activity gives $r^2$ value. The $r^2$ predicted ($r^2_{\text{pred}}$) value was used for validation of CoMFA and CoMSIA model. Training set molecules were used for model building and the generated model was used for prediction of activity of test set molecules. The $r^2$ value indicates how well the model predicted the activity of external test set molecules (Politi et al., 2009). This $r^2_{\text{pred}}$ value is quite similar to the $q^2$ value. Further, $r^2_{\text{bs}}$ (100 cycles bootstrap analysis) was performed to assess the quality of generated model. LOO cross-validated coefficient ($q^2$) and predicted correlation coefficient ($r^2_{\text{pred}}$) must be greater than 0.5 to validate the quality of 3D-QSAR model. The formula for calculation of $q^2$ and $r^2_{\text{pred}}$ is given in Equations (3) and (4), respectively (Murugesan et al., 2009).

\[
q^2 = 1 - \frac{\sum (Y_{\text{pred}} - Y_{\text{obs}})^2}{\sum (Y_{\text{obs}} - Y_{\text{mean}})^2}
\]

\[
r^2_{\text{pred}} = 1 - \frac{\sum_{i=1}^{n} (Y_{\text{obs}} - Y_{\text{test}})^2}{\sum_{i=1}^{n} (Y_{\text{obs}} - Y_{\text{training}})^2}
\]

Here, $Y_{\text{pred}}$ = predicted value, $Y_{\text{obs}}$ = experimental value, $Y_{\text{mean}}$ = average activity value of entire dataset, $Y_{\text{test}}$ = test set activity value and $Y_{\text{training}}$ = training set activity value.

### 2.8. Molecular docking (MD) and molecular dynamics simulations (MS)

To validate the contour maps of CoMFA and CoMSIA, molecular docking study was carried out using DPP enzyme structure and active compounds 1g and 2x. For molecular docking studies, the three-dimensional crystal structure of human DPP-IV enzyme (PDB ID: 4A5S) was retrieved from the protein data bank. Inhibitor (6-[(3s)-3-Aminopiperidin-1-yl]-5-benzyl-4-oxo-3-(quinolin-4-ylmethyl)-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile) complexed with an enzyme was removed for pre-processing of protein structure. Water molecules were
also removed from the protein and hydrogen atoms were added. Further, charges were assigned for protein (AMBER7FF99) and ligand (Gasteiger added). Further, charges were assigned for protein q and ligand (Gasteiger added). Further, charges were assigned for protein q and ligand (Gasteiger added).

Table 2. Statistical parameters of CoMFA and CoMSIA models by PLS analysis.

| Description | CoMFA | CoMSIA | Topomer COMFA |
|-------------|-------|---------|---------------|
| $q^2$       | 0.784 | 0.958   | 0.503         |
| $r^2_{ncv}$ | 0.831 | 0.974   | 0.755         |
| $r^2_{cv}$  | 0.787 | 0.957   | --            |
| $r^2_{bs}$  | 0.855 | 0.978   | --            |
| ONC         | 4     | 10      | 3             |
| $F$         | 78.495 | 171.703 | 31.924        |
| SEE         | 0.268 | 0.113   | 0.330         |
| $r^2_{pred}$ | 0.549 | 0.72    | 0.645         |

$q^2$ is the Leave-One-Out (LOO) validation coefficient; $r^2_{ncv}$ non-cross-validated coefficient; $r^2_{cv}$ cross-validated coefficient; $r^2_{bs}$ correlation coefficient after 100 runs of bootstrapping; ONC optimal number of components determined by PLS–LOO cross-validation; SEE standard error of estimate for 100 runs of bootstrapping; $r^2_{pred}$ predictive correlation coefficient; $F$-test value.

3. Results and discussion

3.1. CoMFA and CoMSIA results

Generated CoMFA and CoMSIA models were validated using statistical results in terms of $q^2$, $r^2_{ncv}$, $r^2_{cv}$, $r^2_{bs}$, $F$ and SEE. The values for $q^2$, $r^2_{ncv}$, $r^2_{cv}$, $r^2_{bs}$, $F$ and SEE of CoMFA model was found to be 0.784, 0.831, 0.787, 0.855, 78.495 and 0.268, respectively (Table 2). The values for $q^2$, $r^2_{ncv}$, $r^2_{cv}$, $r^2_{bs}$, $F$ and SEE of CoMSIA model was 0.958, 0.974, 0.957, 0.978, 171.703 and 0.113, respectively (Table 2). From the 43 molecules, 8 molecules were removed from the data set which acted as external test molecules and their activity were predicted with the help of the generated CoMFA and CoMSIA models. The value of $r^2_{pred}$ is 0.549 and 0.72, respectively, for CoMFA and CoMSIA models. These values are more than 0.5 and thus they validate the predictive capability of the generated models. Regression summary (ligand-based) of CoMSIA models is shown in Table 3 in which the highlighted model was taken for further analysis. Model (S + E + H + D + A) was taken for further analysis as it showed better $r^2$ value with minimum standard error (0.113) and good $F$ value (171.703). Model (S + E + D + A) showed better $r^2$ value but when compared with model (S + E + H + D + A), it showed higher SEE (0.171) and lower $F$ value (87.63). The experimental and predicted $pIC_{50}$ with residual values of CoMFA and CoMSIA are shown in Tables 4 and 5, and graphically presented in Figures 4 and 5. Linear correlation between experimental and predicted $pIC_{50}$ of CoMFA and CoMSIA model for training and test set molecules is shown by blue and orange colour, respectively, with their correlation equations. The residual values of all the molecules were found near zero in training set however, two molecules namely 1h and 1i showed high residual values. This abnormal behaviour can be attributed to the heterogeneous behaviour of the molecules with activity ranges from 6 to 2208 nM.

3.2. Topomer CoMFA

In topomer CoMFA analysis, the cross-validated coefficient ($q^2$) and non-cross-validated coefficient ($r^2$) were found to be 0.812 and 0.966, respectively. It is universally accepted that if the cross-validated $q^2 > 0.5$ and non-cross-validated $r^2 > 0.6$ in analysis consequence, generated model has good predictive ability. Experimental and predicted $pIC_{50}$ with residual values as well as their fragment contribution are shown in Tables 6 and 7, and graphically presented in Figure 6. Correlation between the experimental and predicted activities of training set molecules in topomer CoMFA model is shown by blue line with $R^2$ value of 0.78. Similarly, correlation between the experimental and predicted activities of
test set molecules in topomer CoMFA model is showed by orange line with $R^2$ value of 0.65 (Figure 6).

### 3.3. HQSAR

HQSAR study was performed using different combinations of parameters like atomic number (A), bond type (B), atomic connection (C), hydrogen bond donor/acceptor (DA), hydrogen (H) and chirality (Ch) in which, minimum four and maximum seven atom counts were taken for statistically better HQSAR model (Table 8). The results suggested that the parameters such as bond type (B), atomic connection (C), hydrogen-bond donor/acceptor (DA), hydrogen (H) and chirality (Ch) were important for a model generation. Among 15 generated models, model 13 was selected for further improvement of $q^2$, and for this purpose, the fragment size of 1–10 was explored (Table 9). A significant difference was observed in the statistical parameters as shown in Table 9 where $q^2$ and $r^2$ values were found to be 0.753 and 0.845, respectively. The experimental and predicted pIC$_{50}$ with residual values of HQSAR are shown in Tables 4 and 5, and pictorial presentation is given in Figure 7. Linear correlation between the experimental and predicted activities of training and test set molecules of HQSAR model is shown by blue and orange colour, respectively, with their regression equation and $r^2$ values.

### 3.4. Contribution maps of 3D-QSAR analysis

Steric and electrostatic contour maps of the active compounds 1g (IC$_{50} = 6.57$ nM) and 2x (IC$_{50} = 9.56$ nM) were chosen as representative molecules for visualization of contour maps. CoMFA steric contour map of compound 1g is shown in Figure 8(a). Green contour indicates favourable region for bulky substitutions whereas, yellow contour indicates unfavourable region for bulky substituents. Presence of bulky group at triazole ring and at para position of phenyl ring is beneficial for higher activity as shown by green contour. Bulky group is disfavoured at triazole ring and at para position of phenyl ring.

![Figure 4. Linear correlation plot of experimental pIC$_{50}$ versus predicted pIC$_{50}$ of training set and test set molecules in CoMFA model.](image)

![Figure 5. Linear correlation plot of experimental pIC$_{50}$ versus predicted pIC$_{50}$ of training set and test set molecules in CoMSIA model.](image)
Table 6. The experimental and predicted pIC\textsubscript{50} of training set with residual values of topomer CoMFA model.

| No. | Exp. | Pred. | Residual | \( R_1 \) | \( R_2 \) |
|-----|------|-------|----------|----------|----------|
| 1b  | 7.17 | 7.09  | −0.08    | −0.35    | 0.58     |
| 1e  | 7.83 | 7.47  | −0.36    | −0.1     | 0.7      |
| 1f  | 8.17 | 7.69  | −0.48    | −0.1     | 0.93     |
| 1g  | 8.18 | 7.85  | −0.33    | −0.1     | 1.08     |
| 1h  | 6.9  | 7.63  | 0.73     | −0.1     | 0.86     |
| 1i  | 6.98 | 7.64  | 0.66     | −0.1     | 0.88     |
| 1k  | 5.7  | 5.8   | 0.1      | −0.1     | −0.96    |
| 1l  | 6.03 | 5.73  | −0.3     | −0.1     | −1.03    |
| 1n  | 5.87 | 5.7   | −0.17    | −0.1     | −1.06    |
| 1o  | 5.66 | 5.74  | 0.08     | −0.1     | −1.02    |
| 1p  | 7.9  | 7.28  | −0.62    | 0.12     | 0.29     |
| 1q  | 7.07 | 7.14  | 0.07     | −0.02    | 0.29     |
| 1r  | 6.76 | 7.17  | 0.41     | 0.01     | 0.29     |
| 1s  | 6.69 | 6.69  | 0        | −0.17    | 0.29     |
| 1t  | 6.74 | 6.8   | 0.06     | −0.36    | 0.29     |
| 1u  | 6.71 | 6.76  | 0.05     | −0.4     | 0.29     |
| 1v  | 6.78 | 6.76  | −0.02    | −0.4     | 0.29     |
| 1w  | 6.91 | 7.14  | 0.21     | −0.02    | 0.29     |
| 1x  | 7.54 | 7.23  | −0.31    | 0.07     | 0.29     |
| 1y  | 6.86 | 6.87  | −0.11    | −0.39    | 0.29     |

Exp., experimental value; Pred., predicted value.

Table 7. The experimental and predicted pIC\textsubscript{50} of test set with residual values of topomer CoMFA model.

| No. | Exp. | Pred. | Residual | \( R_1 \) | \( R_2 \) |
|-----|------|-------|----------|----------|----------|
| 1a  | 6.97 | 7.06  | 0.09     | −0.45    | 0.56     |
| 1c  | 6.99 | 7.19  | 0.2      | −0.45    | 0.58     |
| 1d  | 7.1  | 7.52  | 0.42     | −0.35    | 0.58     |
| 1j  | 7.53 | 6.99  | −0.54    | −0.1     | 0.77     |
| 1m  | 5.71 | 5.83  | 0.12     | −0.1     | −1.05    |
| 1y  | 6.95 | 7.09  | 0.14     | −0.2     | 0.29     |
| 2l  | 7    | 6.61  | −0.39    | −0.34    | 0.48     |
| 2s  | 7.32 | 7.07  | −0.25    | −0.02    | 0.48     |

Exp., = experimental value; Pred., predicted value.

Contour. Low biological activity is observed for compound 1k (IC\textsubscript{50} 2000 nM) because no substitution is present on para position of phenyl ring. CoMFA electrostatic contour map of compound 1g is represented in Figure 8b. Red colour region is favourable for electron withdrawing group while blue colour region is favourable for electron donating group. Presence of electron withdrawing group is favourable at meta- and para-position of phenyl ring and on –NH linkage as shown in red contour while electron donating group is favourable at ortho- position of phenyl ring (blue contour).

Decrease in the potency of compounds 1l, 1m, 1n and 1o is observed due to the presence of electron donating groups on phenyl ring like p-methyl, p-chloro, p-bromo and p-flouro, respectively.

Table 8. Summary of HQSAR statistical parameters for various fragment size (4–7).

| Model no. | Fragment distribution | \( N \) | \( q^2 \text{st}\) | Stder\text{st} | \( r^2 \text{st} \) | SEE | BHL |
|-----------|----------------------|--------|-----------------|--------------|-------------|-----|-----|
| 1         | A/B/C                | 3      | 0.661           | 0.354        | 0.797       | 0.274 | 257 |
| 2         | A/B/H                | 6      | 0.564           | 0.422        | 0.899       | 0.203 | 307 |
| 3         | A/B/CH               | 4      | 0.696           | 0.341        | 0.817       | 0.264 | 353 |
| 4         | A/B/DA               | 4      | 0.713           | 0.331        | 0.822       | 0.261 | 71  |
| 5         | A/C/D                | 4      | 0.735           | 0.318        | 0.83        | 0.255 | 71  |
| 6         | B/C/H                | 3      | 0.686           | 0.34          | 0.806       | 0.268 | 353 |
| 7         | B/C/CH               | 3      | 0.686           | 0.34          | 0.806       | 0.268 | 353 |
| 8         | A/B/CH/CH            | 3      | 0.658           | 0.355        | 0.79        | 0.279 | 257 |
| 9         | A/B/CH/CH            | 3      | 0.504           | 0.435        | 0.778       | 0.291 | 353 |
| 10        | A/B/CH/CH/DA         | 3      | 0.768           | 0.308        | 0.891       | 0.211 | 257 |
| 11        | B/CH/DA              | 4      | 0.753           | 0.307        | 0.845       | 0.243 | 307 |
| 12        | B/C/CH/CH            | 3      | 0.686           | 0.34          | 0.806       | 0.268 | 353 |
| 13        | B/C/CH/CH/DA         | 3      | 0.753           | 0.307        | 0.845       | 0.243 | 307 |
| 14        | C/CH/DA              | 4      | 0.671           | 0.354        | 0.812       | 0.268 | 353 |
| 15        | A/B/C/CH/CH/DA       | 5      | 0.638           | 0.378        | 0.851       | 0.243 | 199 |

Note: Highlighted (bold font) model was further used for analysis.
| a | Best cross-validated \( q^2 \) (Leave-One-Out). |
| b | Cross-validated standard error. |
| c | Non-cross-validated \( r^2 \). |
| d | Best hologram length. A (atom), B (bond), C (connections), DA (donor/acceptor), Ch (chirality), H (hydrogens). |

CoMFA steric contour map of compound 2x is represented in Figure 8c. Substitution on triazole ring with bulky group decreases the activity as seen in the case of compound 2k (4-flouro phenyl, IC\textsubscript{50} 135.45 nM), 2l (2,4-diflouro phenyl, IC\textsubscript{50} = 243.67 nM), 2m (3-chloro phenyl, IC\textsubscript{50} = 168.63 nM), 2n (2-methoxy phenyl, IC\textsubscript{50} = 219.42 nM) and 2o (3-methoxy phenyl, IC\textsubscript{50} = 88.53 nM). Substitution on –COOH group with more bulk increases the activity as per steric CoMFA model but compounds 2u and 2y does not impart much effect on the activity because
chain length between triazole ring and terminal –COOH group is responsible in this case. Increase in aliphatic side chain length imparts electron-donating effects which ultimately increases the biological activity as shown in Figure 8(d). Interestingly, the presence of phenyl ring between triazole ring and terminal –COOH group does not increase the biological activity (compounds 2s, 2t and 2w) though it contains electron donating feature. The reason for decrement in the activity may be due to the presence of bulkiness which is not sterically favourable as shown in Figure 8(c).

CoMSIA contour maps of compound 1g are shown in Figure 9(a–e). CoMSIA steric contour map is presented in Figure 9(a). Green contour is favourable at para- position of phenyl ring while yellow contour is favourable at ortho- and meta- position of phenyl ring same as CoMFA results. CoMSIA electrostatic contour map is given in Figure 9(b). Electron donating substitution is favourable at para- position of phenyl ring, –NH linkage and near triazole ring while electron withdrawing group is favourable at the place of phenyl ring. CoMSIA hydrophobic contour map is represented in Figure 9(c), in which hydrophobic group like phenyl ring shows better activity with favourable yellow colour whereas, substitution on phenyl ring with hydrophilic group is beneficial for higher activity as shown in grey contour. CoMSIA hydrogen-bond donor contour map is shown in Figure 9(d). The presence of hydrogen-bond donor group at –NH linkage (cyan colour) and substitution on triazole ring without hydrogen-bond donor group are beneficial (purple colour). Hydrogen-bond acceptor contour map is shown in Figure 9(e). Magenta contour map over phenyl and N1-triazole indicates favourable hydrogen-bond acceptor groups while red contour map over –NH linkage and N2 and N3 triazole indicate unfavourable hydrogen-bond acceptor groups. CoMSIA contour maps of compound 2x are incorporated in the supplementary material Figure S1.

The contour maps of topomer CoMFA were generated on R1 and R2 fragments as shown in Figure 10(a–d). The steric contour maps of R1 and R2 fragment are represented in Figure 10(a,c) in which green colour indicates favourable region for sterically bulky group while yellow colour indicates unfavourable region for sterically bulky group. The electrostatic contour map for R1 and R2 fragments are represented in Figure 10(b,d) in which blue colour indicates favourable donating group while red colour indicates favourable withdrawing group.

HQSAR contribution maps of most active compound 1g and least active compound 1k are shown in Figure 11(a,b), respectively. In HQSAR contribution maps, role of individual atom on biological activity was shown by different colours.
Green or yellow colour shows maximum contribution on biological activity while white colour indicates intermediate effects on biological activity. Red or orange colour indicates negative effect on biological activity. Ring nitrogen of triazoles and –NH linkage show the maximum contribution to the biological activity which is represented in Figure 11(a). Imide linkage (\(\equiv\text{NH}\)) and unsubstituted phenyl ring at meta and para position show negative contribution on biological activity as shown in Figure 11(b).

### 3.5. Molecular docking (MD) and molecular dynamics simulations (MS)

Molecular docking and molecular dynamics were performed by using the potent compounds 1g and 2x to evaluate the CoMFA and CoMSIA contour maps. This study was performed with compound 1g, 2x and protein (PDB: 4a5s) to obtain the most stable conformation of these two compounds. Simulation of protein structure was carried out considering potential energy, kinetic energy and temperature up to 0–10,000 fs as shown in Figure 12(a–c), respectively. Compound 1g formed a stable conformer with DPP IV enzyme when stimulated up to 10,000 fs with reference to KE (\(\sim 2441.958\) kJ/mol), PE (\(\sim 2093.596\) kJ/mol) and temperature (\(\sim 300\) K). Results of KE, PE and temperature of the compound 2x is incorporated in the supplementary material Figure S2. For validation of CoMFA and CoMSIA contour maps, molecular docking of compound 1g and 2x was performed. Based on the CoMFA and CoMSIA results of compound 1g (Figures 8(a) and 9(c)), phenyl ring substitution is highly beneficial for the activity, which is again validated through \(\pi\)-\(\pi\) stacking interaction of phenyl ring with TYR666 (Figure 13). Triazole ring is also involved in the \(\pi\)-\(\pi\) stacking interaction with Phe357. As per Figure 9(d,e), the presence of hydrogen bond donor group at\(\sim\text{NH}\) linkage and \(N_2, N_3\) triazole increases the activity. These results are also validated through the H-bond interaction of\(\sim\text{NH}\) linkage with Glu206 and \(N_2, N_3\) triazole with Arg669 (Figure 13). Docking results of compound 2x is given in the supplementary material Figure S3.

Overall, the outcome of the present work is highlighted in Figure 14. Combined outcome of all these studies suggested that the presence of electron withdrawing group and H-bond donor groups are desirable on side chain of triazole ring. Instead of phenyl substitution, aliphatic substitution on ring nitrogen (\(R_3\) in Figure 14) is beneficial. Further substitution on ring nitrogen with carboxylic acid side chain shows increment in the activity but the chain length between triazole ring and terminal carboxylic acid is critical for the
Figure 10. Topomer CoMFA contour maps of fragment R1 and R2. (a) Topomer steric contour maps for R1 fragments, (b) topomer electrostatic contour maps for R1 fragments, (c) topomer steric contour maps for R2 fragments and (d) topomer electrostatic contour maps for R2 fragments.

Figure 11. Atom contribution map of compounds 1g and 1k from HQSAR model: (a) for compound 1g and (b) for compound 1k. Green or yellow colour, positive contribution; grey or white colour, intermediate contribution and red or yellow colour, negative contribution.

Figure 12. Molecular dynamics study of compound 1g with DPP IV enzyme (PDB ID: 4A5S). (a) Plot of time versus kinetic energy (KE), (b) plot of time versus potential energy (PE) and (c) plot of time versus temperature.
biological activity and even less bulky group substitution is favorable at this site. H-bond donor substitution on ring nitrogen is desirable (R1 and R2 in Figure 14). Presence of nitrogen at X is not necessary for the inhibition activity. Substitutions with bulky and electron withdrawing groups are beneficial for the activity (R5 in Figure 14).

3.6. Design of novel DPP IV inhibitors using developed models

Based on the combined outcome of QSAR results, novel molecules were designed and their activities were predicted (pIC50) with respect to the active compounds in QSAR series (compound 1g and 2x). Different substitutions were tried on the triazole core moiety using the outcome of 3D QSAR studies. The predictive activity (pIC50) of newly designed compounds is incorporated in Table 10. These pIC50 values were predicted from the most reliable CoMSIA (S + E + H + D + A) model with better external test validation parameter ($r^2_{pred} = 0.72$) when compared with the CoMFA model. These newly designed triazole derivatives were found to exhibit encouraging results. Compound 5 shows interactions with DPP IV enzyme same as that of the compound 1g. Compound 5 interacts with Arg358 by forming hydrogen bond with $\text{–COOH}$ group. Moreover, $\text{–NH}$ and $\text{–NH}_2$ functionality are responsible for H-bonding interactions with Glu206 and Arg669. Phenyl ring is involved in the pi–pi stacking interaction with Tyr662 and Tyr666 as

Figure 13. Molecular docking interactions of compound 1g and compound 5. (a) Interactions of compound 1g with DPP IV enzyme (PDB ID: 4A5S) after MD stimulation, (b) interactions of newly designed compound 5 with DPP IV enzyme after MD stimulation (pi–pi stacking interactions are represented by green lines; H-bonding interactions are given by pink lines).

Figure 14. Combined outcome of all the 3D QSAR studies.
Table 10. Predicted activity and total score of newly designed molecules.

| Sr. no. | Compound | Predicted pIC$_{50}$ (CoMSIA) | Total score$^a$ |
|---------|----------|-------------------------------|---------------|
| 1       | ![Compound 1](image1) | 8.19 | 7.34 |
| 2       | ![Compound 2](image2) | 8.21 | 7.62 |
| 3       | ![Compound 3](image3) | 8.19 | 7.93 |
| 4       | ![Compound 4](image4) | 8.22 | 8.28 |
| 5       | ![Compound 5](image5) | 8.30 | 8.55 |
| 6       | ![Compound 6](image6) | 8.26 | 8.40 |
| 1g      | ![Compound 1g](image7) | 8.18 | 8.13 |
| 2x      | ![Compound 2x](image8) | 8.02 | 8.01 |

$^a$Total score is expressed in $-\log_{10}(K_d)$ units to represent binding affinities.
shown in Figure 13(b). The outcome of docking results proved that these 3D QSAR methods are very useful for designing novel DPP IV inhibitors.

4. Conclusion

DPP IV inhibitors are promising therapeutics for the treatment of diabetes. In ligand-based drug design approach, 3D QSAR study plays a vital role in designing of novel compounds. In order to find potent DPP IV inhibitors, 3D QSAR studies were performed on several triazole derivatives obtained from the literature data. A total of 43 triazole derivatives were used for CoMFA, CoMSIA, topomer CoMFA and HQSAR studies. In CoMFA study, statistical validation parameters like $q^2$, $r^2_{ncv}$, $r^2_{cv}$, $r^2_{bs}$ and $r^2_{pred}$ values were found to be 0.784, 0.831, 0.787, 0.855 and 0.549, respectively. Similarly, in CoMSIA study, $q^2$, $r^2_{ncv}$, $r^2_{cv}$, $r^2_{bs}$ and $r^2_{pred}$ values were obtained as 0.958, 0.974, 0.957, 0.978 and 0.72, respectively. Results of topomer CoMFA showed $q^2$ value of 0.503, $r^2_{ncv}$ value of 0.755 and $r^2_{pred}$ value of 0.645. In HQSAR analysis, statistical values were found for $q^2$ as 0.753, $r^2$ as 0.845 and $r^2_{pred}$ as 0.677 with 307 as best hologram length (BHL). Moreover, contour maps of these studies were utilized to gain an insight on structural features responsible for the biological activity. Based on the summary of 3D QSAR results, it was found that no bulk is desirable on the triazole ring scaffold. Triazole ring ‘N’ with COOH group and aliphatic side chain are highly acceptable features for DPP IV inhibition. Moreover, imide linkage does not impart any change in DPP IV inhibitory activity. These 3D QSAR results were validated through molecular docking and dynamics studies. The newly designed DPP IV inhibitors showed noteworthy results in docking studies which proved the efficiency of QSAR results. These novel compounds could be explored for experimental validation through in vitro and in vivo studies for DPP IV inhibition.

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