QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIP (QSAR) AND MOLECULAR DOCKING ANALYSIS OF THE INHIBITORY ACTIVITIES OFBENZOFURAN/BENZOTHIOPHENE BIPHENYLS DERIVATIVES ON PROTEIN TYROSINE PHOSPHATASE 1B

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Abstract: A quantitative structure–activity relationship (QSAR) was performed to analyze inhibitory activities of 42 Benzofuran/Benzothiophene Biphenyls derivatives using multiple linear regressions (MLR). A suitable set of molecular descriptors were calculated to represent the molecular structures of compounds, such as constitutional, topological, geometrical, electrostatic and quantum-chemical descriptors. The important descriptors were selected with the aid of the genetic function algorithm (GFA) method. The root mean square errors (RMSE) of the training set, and the test set for genetic algorithm- multiple linear regression (GA–MLR) model were calculated to be 0.1072 and 0.3880, the square of correlation coefficients (R^2) were obtained as 0.952 and 0.942, respectively and Molecular docking study showed that,Benzofuran/Benzothiophene Biphenyls derivatives leads to stronger interaction with PTP1B when compared to the diabetic drug Glibenclamide due to low binding energy (-7.7, -8.1,and -7.9 compared to -7.5). Results showed that the predictive ability of the model was satisfactory, and it can be used for designing similar group of PTP1B enzyme inhibitors.

Keywords: QSAR, GFA, protein tyrosine phosphates 1B (PTP1B)

Introduction

Protein tyrosine phosphatases (PTPs) constitute a large family of enzymes that are crucial modulators of tyrosine phosphorylation-dependent cellular events, such as growth, proliferation and differentiation, metabolism, immune response, cell-cell adhesion, and cell-matrix contacts (Fischer *et al.*, 1991; Tonks, 2006). The deregulation of PTP activity contributes to the pathogenesis of several human diseases, including cancer, diabetes, and immune disorders (Tonks, 2006). Protein-tyrosine phosphatase 1B (PTP1B), a member of the PTP superfamily, has emerged as the best-validated drug target for therapeutic development (Zhang and Lee, 2003). PTP1B is localized to the cytoplasmic face of the endoplasmic reticulum and is expressed ubiquitously, including in classically insulin-targeted tissues, such as liver, muscle, and fat (Tonks, 2003). PTP1B plays an important role in down-regulating insulin signaling cascades via tyrosine dephosphorylation of the insulin receptor, which renders it inactive, or dephosphorylation of insulin receptor substrates 1 and 2, which inhibits their interactions with downstream signaling molecules. PTP1B also negatively regulates the leptin signaling pathway by dephosphorylating Janus kinase 2 (JAK2), a phosphorylated tyrosine kinase, in the hypothalamus. This decreases food intake and increases energy expenditure (Asante-Appiah and Kennedy, 2003; Zabolotny*et al.*, 2002; Bence*et al.*, 2006; Koren and Fantus, 2007).

World Health Organization (WHO) reported that, the number of adults with diabetes has quadrupled in the past 25 years, from 108 million in 1980 to 422 million in 2014. This adds up to a global prevalence of 8.5% in 2014 vs. 4.7% in 1980. 90-95% of these individual have type II diabetes (WHO, 2016). Type II diabetes is a progressive disease characterized by insulin resistance in peripheral tissues and/or impaired insulin secretion by the pancreas. The resultant high blood glucose level generally leads to several serious complications. At the molecular level, the mechanism of insulin resistance in type II diabetes appears to involve defects in post-receptor signal transduction (Montalibet and Kennedy, 2005; Youngren and Goldfine, 1997). Increased incidence of type II diabetes mellitus and obesity has elevated the medical need for new agents to treat these disease states. Resistance to the hormones insulin and leptin are hallmarks of both type II diabetes and obesity. Drugs that can ameliorate this resistance should be effective in treating type II diabetes and possibly obesity. Protein tyrosine phosphatase 1B (PTP1B) is thought to function as a negative regulator of insulin and leptin signal transduction.

Quantitative structure–activity relationship (QSAR) approach is very useful for the prediction of biological activities, especially in drug design. This approach is based on the assumption that variations in the properties of the compounds can be correlated with changes in their molecular characteristics (Kamlendra*et al.*, 2015). Molecular docking is used to study how a ligand interacts with its biological target and to confirm the conclusions of QSAR studies. Therefore, the QSAR and docking techniques are valuable molecular modelling tools for drug design (Sharma *et al.*, 2014; Bhadoriya*et al.*, 2013; Bhadoriya*et al.*, 2012; Jain *et al.*, 2012).

This study was performed to analyze the inhibitory effects of certain experimentally known compounds on human recombinant PTP1B enzyme, their interaction details and effectiveness. In this study we have used human recombinant PTP1B enzyme 3D structure as receptor against a dataset of Benzofuran/Benzothiophene Biphenyls derivatives. Binding site of human recombinant PTP1B enzyme was identified and insilico analysis was carried out via performing docking studies of human recombinant PTP1B enzyme structures with Benzofuran/Benzothiophene Biphenyls derivatives and diabetic drug Glibenclamide and to compare the results.

Material and Methods

Data collection and splitting

In this study, a Data set of 42 molecules was collected from published literature (Vats *et al.*, 2005). The chemical structures and the biological response (IC_{50}) of these 42 molecules are presented in Fig. 1 and Table 1. The IC_{50} values were converted into its logarithmic scale $pIC_{50} = -\log(IC_{50})$, to reduce the skewness of the data set, which was then used for successive QSAR analysis as the response variable. The entire set of compounds was divided into two subsets: training set (70%) consisting of 29 molecules were used to build the actual models, and test set (30%) consisting of 13 molecules not found in the training set, which was used to validate the models once they were built.

Software and hardware

The following software packages were utilized in this research: ChemDraw Ultra 12.0, Cambridge Soft Corp. (www.cambridgesoft.Corn), USA;Materials Studio (Version 8), Accelrys Inc. (www.accelrys.-com), USA;Spartan'14 (version1.1.2), California, USA, PaDEL Descriptor(Yap,2011)(http://www.yapcwsoft.com/dd/padeldescriptor/), Accelerys Discovery Studio Visualiser 2016 Client Ligplus and AutoDock 4.2. (Anitha*et al.*, 2013) with MGL tools (http://mgltools.scripps.edu/downloads)installed on a Dell personal computer (PC) equipped with 8GBRAM capacity, processor intel CORE ™i5, hard disc capacity of 1000GB and CPU@ 2.20GHz2.20GHz running on 64-bit Operating System.

Molecular descriptor calculation

All of the molecules were drawn using ChemDrawsoftware and were imported into Spartan'14 to create the three dimensional (3D) structure and was pre-optimized using the MM+ molecular mechanics force field. Then a more precise optimization were performed with the density functional theory (DFT) level using Becke's three-parameter Lee-Yang-Parr hybrid functional (B3LYP) in combination with the 6-311G* basis set (Malamas*et al.*, 2000; Becke, 1993). Descriptors were calculated using the Spartan'14 andPaDEL Descriptor software package version 2.18 (Lee *et al.*, 1988) which include: constitutional, topological, geometrical, electrostatic, charged partial surface area, quantum-chemical, molecular orbital and thermodynamic descriptors.

Statistical analysis

The correlation analysis was performed by the statistical and modeling software Material Studio where the PIC_{50} was used as dependent variable and the computed descriptors as independent variable. The descriptors with higher correlation to pIC_{50} and lower inter-correlation were selected to carry out the GFA regression analysis to establish the optimal QSAR equations. The statistical significance of the generated models were assessed based on Friedman's Lack of Fit (LOF) score (Ravinchandran*et al*., 2011) Table 3 show the summary of the generated models and model 1 was selected as best model based on the lowest LOF score.

Model validation

The performance of external validation was characterized by the determination coefficient (R^2), root mean standard error (*RMSE*) and external explained variance (R^2_{ext}), which are defined as follows (Schüürmann*et al*., 2008):

$$R^2 = 1 - \frac{\sum(Y_{obs} - Y_{pred})^2}{\sum(Y_{obs} - \bar{Y}_{training})^2} \quad 1$$

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(Y_{obs} - Y_{pred})^2}{n}} \quad 2$$

$$R^2_{ext} = 1 - \frac{\sum(Y_{obs(Test)} - Y_{pred(Test)})^2}{\sum(Y_{obs(Test)} - \bar{Y}_{training})^2} \quad 3$$

WhereY_{obs}; Y_{pred}; $\bar{Y}_{training}$ are observed activity values, predicted activity values and the mean observed activity values of the samples in the training set, respectively. n is the total number of samples in the training set, $Y_{obs(Test)}$, $Y_{pred(Test)}$, $\bar{Y}_{training}$are observed activity values, predicted activity values and the mean observed activity values of the samples in the test set, respectively.

Docking studies

Ligand structure preparation

Ligand 2D structures were drawn using ChemDraw Ultra 7.0 (ChemOffice 2002). Chem3D Ultra 7.0 was used to convert 2D structure into 3D and the energy minimized using semi empirical AM1 method. Minimize energy to minimum RMS gradient of 0.100 was set in each iteration. All the ligand structures were then saved in PDBQT file format, for input into AutoDock version 4.2 (Ruth and Garrett, 2006).

Protein structure preparation

For the molecular docking study, protein structure was obtained from the Brookhaven protein data bank; the DPPIV structure PDB ID was 3zv2. The co crystallized ligand (PF2) in the DPP-IV structure was removed. The macromolecule was checked for polar hydrogens, partial atomic Kollman charges were assigned, and then atomic solvation parameters were allotted. Torsion bonds of the inhibitors were selected and defined. Secondly, the three dimensional grid box was created by Auto Grid algorithm to evaluate the binding energies on the macromolecule coordinates. The grid maps representing the intact ligand in the actual docking target site were calculated with Auto Grid. The structures were then saved in PDBQT file format, for input into AutoDock version 4.2. The results of the Autodock tools were viewed in the Accelerys Discovery Studio Visualiser 2016 Client and Ligplus (Ruth and Garrett, 2006).

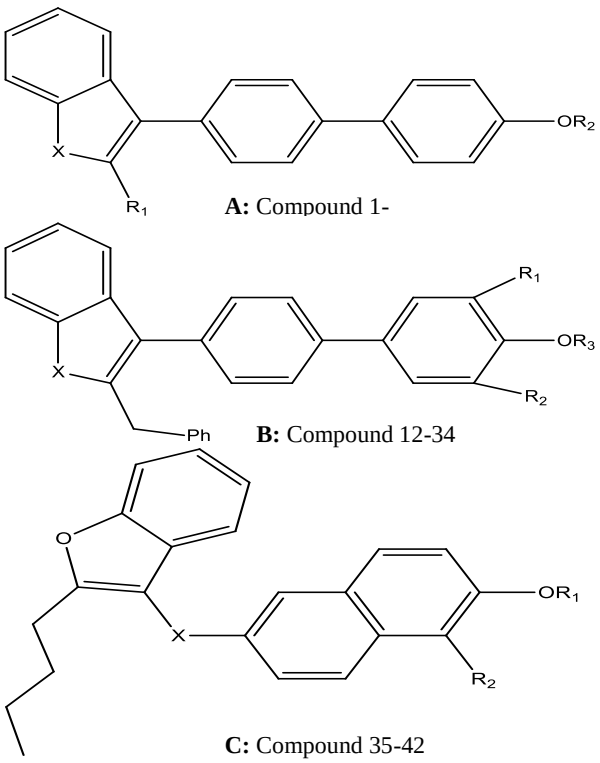

Fig. 1: Parent structure of the Benzofuran/Benzothiophene Biphenyls derivatives

Table 1: The Benzofuran/Benzothiophene Biphenyls derivatives with their activities

Cpd No	R_1	R_2	X	pIC_{50}
1[b]	butyl	H	O	0.130
2[a]	benzyl	H	O	0.0362
3[a]	benzoyl	H	O	0.130
4[a]	butyl	H	S	0.154
5[a]	4-OH benzyl	H	S	-0.033
6[a]	benzyl	CH_2Ph-4-COOH	O	0.443
7[a]	2,4-di-OH-benzyl	H	S	0.236
8[b]	butyl	CH_2COOH	O	-0.340
9[a]	butyl	$CH(CH_2Ph)COOH$	O	0.356
10[a]	benzyl	$CH(CH_2Ph)COOH$	O	0.568
11[a]	2,4-di-OH-benzyl	$CH(CH_2Ph)COOH$	S	1.070

Cpd No	R_1	R_2	R_3	X	pIC_{50}
12[a]	Br	H	H	S	-0.029
13[b]	Br	Br	H	S	0.346
14[a]	I	I	H	S	0.283
15[a]	Br	H	CH_2COOH	S	0.443
16[a]	Br	Br	CH_2COOH	S	1.000
17[a]	4-OCH_3-Ph	H	CH_2COOH	S	1.096
18[a]	4-OC_2H_5-Ph	H	CH_2COOH	S	1.283
19[a]	2,3-di-OCH_3-Ph	H	CH_2COOH	S	1.148
20[a]	3,4,5-tri-OCH_3-Ph	H	CH_2COOH	S	1.000
21[b]	4-OCH_3-Ph	Br	CH_2COOH	S	1.537
22[b]	2,4-di-OCH_3-Ph	Br	CH_2COOH	S	1.327
23[a]	3-OCH_3-Ph	3-OMe-Ph	CH_2COOH	S	1.602
24[b]	4-OCH_3-Ph	4-OMe-Ph	CH_2COOH	S	1.602
25[a]	Br	H	$CH_2CH_2CH_2COOH$	S	0.769
26[a]	Br	Br	$CH[(CH_2)_5CH_3]COOH$	O	1.638
27[b]	Cyclopentyl	H	CH_2COOH	O	0.769
28[a]	$NHCH_2CH_2COOH$	H	CH_2CH_2Ph	O	0.853
29[b]	$NHCOCH_2CH_2COOH$	H	H	O	0.036
30[a]	NHCOCH=CHCOOH	H	H	O	0.337
31[a]	Ph	H	CH_2COOH	S	1.00
32[b]	3-OCH_3-Ph	Br	CH_2COOH	S	1.552
33[a]	Br	Br	$CH[(CH_2)_3CH_3]COOH$	O	1.283
34[a]	$NHCH_2COOH$	H	CH_2CH_2Ph	O	1.086

Cpd No	R_1	R_2	X	pIC_{50}
35[a]	H	H	CH(OH)	-0.041
36[a]	H	Br	CH(OH)	0.318
37[a]	H	Br	CH_2	0.481
38[b]	H	I	CH_2	0.420
39[b]	CH_2COOH	Br	CH_2	-0.146
40[b]	$CH(CH_2Ph)COOH$	Br	CH_2	0.431
41[b]	$CH(CH_2Ph)COOH$	Br	CO	-0.079
42[a]	$CH(CH_2Ph)COOH$	I	CH_2	0.494

[a]Training set; [b]Test set

Results and Discussion

A QSAR analysis was performed to explore the structure – activity relationship of different 42 benzofuran/benzothiophene derivatives acting as PTP1B inhibitors. Five QSAR models were built using GFA algorithm, but only the best model (Model 1) was selected and reported due to small value of Friedman's Lack of fit **(**LOF), high value of R^2. The Description of the descriptors used in the QSAR optimization model are shown in Table 2. Table 3 show the Summary of generated GFA equations and Fig. 2 is the graph of calculated pIC_{50} against the experimental values for the training and test sets. The R^2 value of the QSAR model was 0.9522, indicating a high goodness-of-fit of the model. Q^2_{LOO} of the QSAR was as high as 0.9151, implying good robustness of the model. The differences between R^2 and Q^2_{LOO} (0.0371) did not exceed 0.3, indicating no over-fitting in the model (Golbraikh and Tropsha, 2002). As shown in Fig. 2, the predicted pIC_{50} values were consistent with the observed values for both the validation and training sets. The model revealedacceptable predictability with R^2_{pred}= 0.672, *RMSE*= 0.1072. In summary, the developed QSAR model showed satisfactory performance.

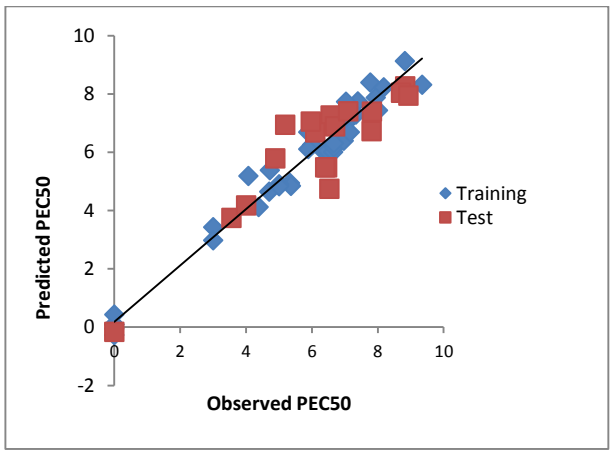

Fig. 2: The calculated pIC_{50} against the experimental values for the training and test sets

Molecular docking studies were carried out against human recombinant PTP1B enzyme (target). All the compounds were found to strongly inhibit by completely occupying the active sites of the target protein. The docking of diabetic drug Glibenclamide and compound 10, 21 and 34 into active site of PTP1B (Figs. 3, 4, 5, and 6) was carried out using

Autodocktool 4.2 and ligplus. The final docking score in Kcal/mol for each docking experiment was calculated and represented in Table 4 alongside with Binding residue, Hydrogen bond and its distance (A˚) and all inhibitors showed low energy values as indicated in Table 4.

From docking of diabetic drug Glibenclamide (Fig. 3) into active site of PTP1B, we observed four Hydrogen bonds with protein amino acid residues that are Arg45, Tyr46, Asn44 and compound 10 (Fig. 4) with four H - bond with the protein amino acid residues that are Arg112, Thr177, Gln127 and compound 21 (Fig. 5) with four H - bond with the protein amino acid residues that are Arg112, Trp179, Thr177 and compound 34 (Fig. 6) with four H - bond with the protein amino acid residues that are Arg221, Ile219, Gln266, Gly183.

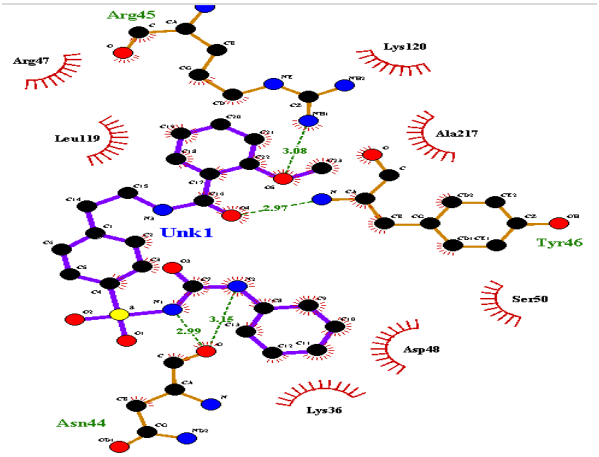

Fig. 3: Docking views of Glibenclamide (ligand) in the binding site of Protein Tyrosine Phosphates 1B (PTP1B). (A) Green dotted line shows H-bonds between Glibenclamide and basic groups. Carbon is colored in grey, oxygen red and nitrogen blue

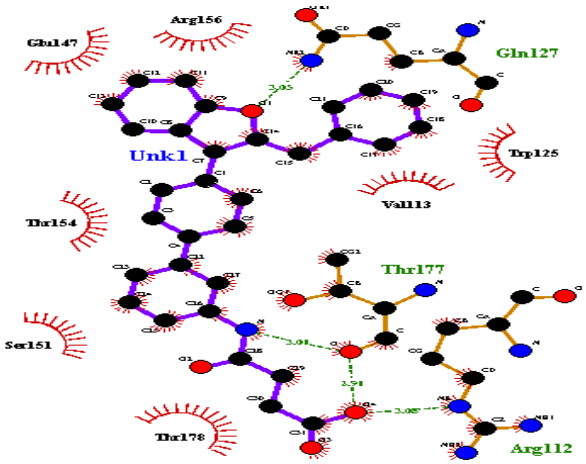

Fig. 4: Docking views of compound 10 in the binding site of Protein Tyrosine Phosphates 1B (PTP1B). (A) Green dotted line shows H-bonds between compound 10 and basic groups. Carbon is colored in grey, oxygen red and nitrogen blue

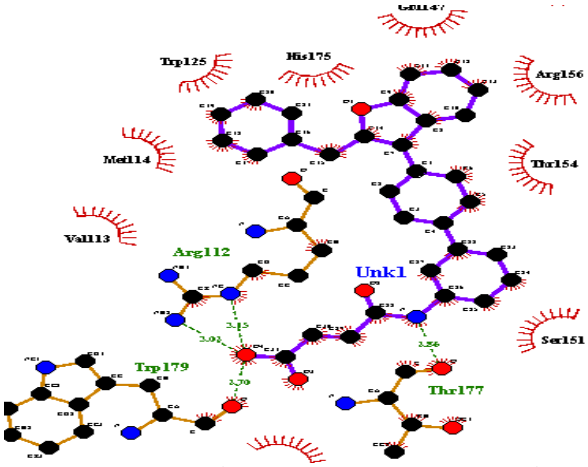

Fig. 5: Docking views of compound 21 in the binding site of Protein Tyrosine Phosphates 1B (PTP1B). (A) Green dotted line shows H-bonds between compound 21 and basic groups. Carbon is colored in grey, oxygen red and nitrogen blue

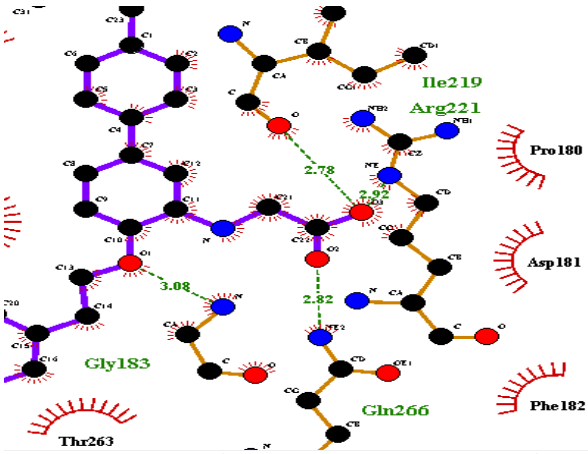

Fig. 6: Docking views of compound 34 in the binding site of Protein Tyrosine Phosphates 1B (PTP1B). (A) Green dotted line shows H-bonds between compound 34 and basic groups. Carbon is colored in grey, oxygen red and nitrogen blue.

Strong inhibitor binding is reflected by the frequency of hydrogen bonds as shown in Table 4 and Figs. 3 – 6. These Compounds each made four hydrogen bonds with target residues. It was observed that, Arg was the most frequently occurring residue in hydrogen bonding. The details of hydrogen bonds formed by the compounds with binding residues, atoms involved in the bonds and distance are given in Table 4.

Model 1

PIC50= -14.750 +0.00047 ATSC6v +0.6933 VE1_Dzs +3.51507SpMax2_Bhv +0.04512 RDF30u +0.05 RDF45m

N=29, LOF = 0.0652, R^2 = 0.9522, R^2_{adj}= 0.9418, Q^2_{LOO}=0.9151, RMSE = 0.1072, R^2_{pred}= 0.672

Table 2: Description of the descriptors

Descriptor Class	Descriptor	Description	Class
Autocorrelation Descriptor	ATSC6v	Centered Broto-Moreau autocorrelation - lag 6 / weighted by van der Waals volumes	2D
Barysz Matrix Descriptor	VE1_Dzs	Coefficient sum of the last eigenvector from Barysz matrix / weighted by I-state	2D
Burden Modified Eigenvalues Descriptor	SpMax2_Bhv	Largest absolute eigenvalue of Burden modified matrix - n 2 / weighted by relative van der Waals volumes	2D
RDF Descriptor	RDF30u	Radial distribution function - 030 / unweighted	3D
RDF Descriptor	RDF45m	Radial distribution function - 045 / weighted by relative mass	3D

Table 3: Summary of generated GFA equations

	Equation 1	Equation 2	Equation 3	Equation 4	Equation 5
Friedman LOF	0.065197	0.066082	0.068838	0.07316	0.074364
R-squared	0.952183	0.951534	0.949513	0.946343	0.94546
Adjusted R-squared	0.941788	0.940998	0.938537	0.934678	0.933603
Cross validated R-squared	0.91512	0.91929	0.906545	0.911388	0.918112
Significant Regression	Yes	Yes	Yes	Yes	Yes
Significance-of-regression F-value	91.60047	90.31209	86.51206	81.12958	79.74166
Critical SOR F-value (95%)	2.663088	2.663088	2.663088	2.663088	2.663088
Replicate points	0	0	0	0	0
Computed experimental error	0	0	0	0	0
Lack-of-fit points	23	23	23	23	23
Min expt. error for non-significant LOF (95%)	0.097212	0.097869	0.099889	0.102977	0.103821

Table 4: Atoms of the compounds and target protein residues involved in making hydrogen bonds and bond distance

Compound	Binding Affinity (Kcal/mol)	Binding residue	Hydrogen bond	Distance (A°)
Glibenclamide	-7.5	Arg45	O–HN	3.08
		Tyr46	O–HN	2.97
		Asn44	NH–O	3.15
			NH–O	2.99
10	-7.7	Arg112	O–HN	3.08
		Thr177	NH–O	3.01
			O–O	2.91
		Gln127	O–HN	3.05
21	-8.1	Arg112	O–HN	3.15
			O–HN	3.02
		Trp179	O–O	2.70
		Thr177	NH–O	2.86
34	-7.9	Arg221	O–HN	2.92
		Ile219	O–O	2.78
		Gln266	O–HN	2.82
		Gly183	O–HN	3.08

Conclusion

In conclusion, QSAR analysis on a series of benzofuran/benzothiphene biphenyls with PTP1B inhibitory activity expressed as pIC_{50} (μM) against human recombinant PTP1B enzyme was performed using robust statistical technique GFA, coupled with the use of combination of different classes of descriptors. The generated equations were analyzed for their statistical significance and predictive ability by using test set of 13 molecules that were not used in model generation. GFA handled the physico-chemical descriptors effectively in the generation of QSAR models with significant statistical terms including external predictivity. Equation 1 was selected as representative equation to explain the variance in the biological activity for present series of PTP1B inhibitors. This equation explains about 95% (R^2 = 0.952) variance in the biological activity. The variables in the equation reveal that electronic, spatial and structural descriptors contribute significantly for the biological activity of PTP1B inhibitors. Molecular docking study supported that the antidiabetes compounds reported by Vats *et al.* (2005) prove their in silico inhibitory activity on human recombinant PTP1B enzyme that can be used in the treatment of type II diabetes and some other diseases. Inhibition of the active site residues with high activity, strong binding and low energy values showed that these compounds can be used in drug design against certain diseases that can somehow be linked to the protein PTP1B.

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