Original Article

Pharmacoinformatic Studies on 4-Thiazolyl-phenoxy Tail Containing Indanyl Acetic Acid Derivatives as PPAR-Pan Agonists as Potent Anti-Diabetic Agent

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ABSTRACT

Aim: The increasing incidences of type 2 diabetes mellitus, represents a considerable public health problem and characterized by loss in sensitivity of tissues to insulin which can be restored by activation of Peroxisome Proliferator-Activated Receptors (PPARs). The present work takes in consideration for the development of PPAR agonists, which can activate PPARs and is expected to lower LDL cholesterol and triglycerides, raise HDL cholesterol and normalize hyperglycaemia. **Materials and Methods:** Quantitative Structure-Activity Relationship (QSAR) study is performed by means of Multiple Linear Regression (MLR) analysis on a set of indanyl acetic acid derivatives followed by ADMET prediction and Docking Studies. **Results:** A good correlation is found by regression analysis between the observed and predicted activities as evident by their R^2 (0.81), Q^2 (0.81) and R^2 pred (0.86) for PPARα and R^2 (0.66), Q^2 (0.66) and R^2 pred (0.90) for PPARδ and R^2 (0.82), Q^2 (0.77) and R^2 pred (0.58) for PPARγ respectively. Molecular docking of the ligands qualifying all the Drug Likeness properties to the proteins PPARα (PDB ID: 3ET1), PPARδ (PDB ID: 3ET2) and PPARγ (PDB ID: 3ET3) with FlexX score -11.98, -9.69 and -21.48 respectively followed by core hoping. **Conclusion:** Docking studies revealed that hydrogen-bonding interactions are crucial for the binding of ligands with the target. Core replacement of the best-docked conformations of the selected ligand is performed in order to obtain more potent and novel ligands.

Key words: Quantitative structure-activity relationship, Multiple Linear Regression, Molecular docking, Drug Likeness, Hydrogen-bonding interaction.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is an important public health problem, one of four priority Non-Communicable Diseases (NCDs) targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades.[1,2] Worldwide, almost 0.422 billion grown-ups are existing with T2DM in 2014, as compared to 0.108 billion in 1980.[3] The overall occurrence (age-standardized) of T2DM has approximately doubled since 1980, escalating from 4.7% towards 8.5% in 2014 in the population of adult.[4,5] India has been termed as the "Diabetes capital of the world" as it is leading the world with the biggest number of diabetic subjects.[6]

There are currently various curative treatment available and therapy is reliant on the use of existing anti-diabetic drugs having their own long term toxic effects.[7] Therefore it is crucial for identifying such molecules which are effective and possessing least side effects. Several authors have been studied PPAR as a potential target to treat these diseases.[8] The Peroxisome Proliferator-Activated Receptors (PPARs) are categorized under the nuclear receptor superfamily are transcription factors activated by ligands.[9,10] PPARs have three subtypes namely PPARα, PPARβ/δ and PPARγ and they divulge a usual impact

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on target cells as their actions are restricted to specific tissue types.[11-13] All three receptors are important regulators in multiple physiological pathways, such as glucose homeostasis, fatty acid metabolism, inflammation and cellular differentiation.[14,15] Activation of PPARs improves the condition of insulin resistance and therefore PPARs became a primary target in the treatment of type 2 diabetes.[16] Derivatives of indanyl acetic acid are synthetic ligands which exhibit unique PPAR agonistic activities.[17] Structure and ligand-based approaches have been successfully employed in the development of new drugs.[18]

The computational methods in drug discovery collectively termed pharmacoinformatics includes Structure-Activity Relationship,[19] virtual screening,[20] molecular docking[21] and ADMET prediction[22] have proven their pivotal role in the pharmaceutical industry for lead identification and optimization. Several research groups worldwide identified PPAR agonists using pharmacoinformatics approaches for potential application for the treatment of T2DM. In the present study, these pharmacoinformatic techniques are used to identify important features necessary for a compound to behave as an activator of PPAR-α, PPAR-γ and PPAR-δ/β receptors.[10,23]

MATERIALS AND METHODS

Dataset

A set comprising of 69 indanyl acetic acid compounds bearing substituted phenyl tail groups, 4-heteroaryl-substituted aryl tail groups and thiazolylphenyl groups is taken from the available literature and used in the present study.[17] The selected compounds for the data set shared the same assay i.e. FRET assay procedure with significant variations in their structures and potency profiles. The half-maximal effective concentration of the compounds included in data set, with EC_{50} values varying from 47 to 10000 nM, 0.58 to 2230 nM and 12 to 10000 nM for PPARα, δ and γ subtypes respectively which are converted into molar values. These are then converted into pEC_{50} values using the formula given below.

$$pEC_{50} = -\log10\ [EC_{50}]$$

The structures of ligands are generated using the Chem Draw Ultra 7.0 software package.[24] The energy minimization is performed for each ligand using the Chem3Dultra software. The X-ray crystal structure of the PPAR receptor is obtained from the Protein Data Bank (PDB ID: 3ET1, 3ET2 and 3ET3).[25,26] The active site coordinates of the co-crystallized ligand are used for molecular docking studies to calculate the docking scores using FlexX algorithms.[27] The FlexX program is used for docking of the receptor with the ligands qualifying all the drug-likeness filters like Lipinski's rule, Ghose filter, veber rules as well as a Quantitative Estimate of Drug-likeness (QED) calculated using DruLiTo software.[28]

Multiple Linear Regression

MLR analysis is a method for establishing the relationship between a single dependent variable and collection of independent variables (or predictors).[29,30] It relies on the assumption that the variation in molecular properties of compounds can be related to changes in their structural/physicochemical properties.[31] The optimized structures are used for all subsequent calculations. The EC_{50} data on indanyl acetic acid derivatives (Table 1) are grabbed from the literature.[17] the dataset is randomly divided into a training set for creating QSAR models and a test set for the validation of the excellence of the models. All compounds in the test set contain the Biological Activity (BA) within the maximum and minimum value range of the BA of training set compounds.

Physicochemical properties of Active Compounds

Bad pharmacokinetic properties are one of the major cause for cessation of the generation of drug candidates. The drug detrition is a significant issue at clinical stages of drug development due to insufficient pharmacokinetics and pharmacodynamics examination. Numerous physicochemical properties like drug-like properties and toxicity of all the compounds in the dataset are evaluated employing the open source tools such as DruLiTo.[28]

Molecular Docking

The three-dimensional crystal structures of three selected molecular targets involved in the regulation of glucose homeostasis are obtained from PDB.[25] The receptors are prepared by removal of heteroatoms such as water, ions and addition of polar hydrogens using the FlexX software.[27] The active site is defined as including all atoms within a 6.5 A° radius of the co-crystallized ligand. The docking scores (FlexX-Score) of the ligands are computed from the FlexX docked ligand-receptor complexes. Docking studies are performed for 100 generations and the energetically favorable conformations are analyzed. One complex structure for every ligand is selected as the best fit based on the orientations of ligand and its score is added to the molecular spreadsheet.

Fragment-Based Drug Design

The ReCore module developed by BioSolveIT is a useful suite for Fragment-Based Drug Design (FBDD).[32]

Table 1: Biological Activity (pEC_{50}) and Structure of Indanyl Acetic Acid derivatives.

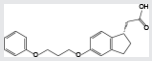
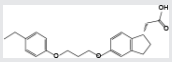
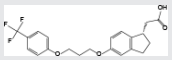
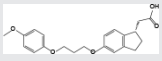
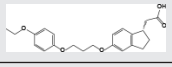
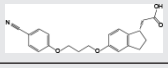
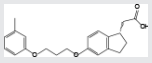
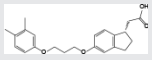
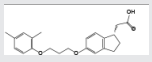
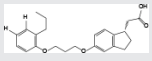
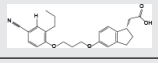
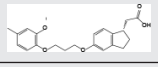
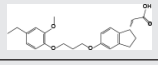
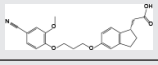
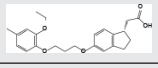
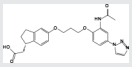
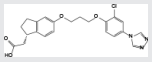
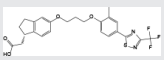
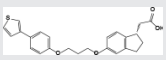
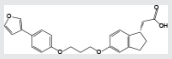
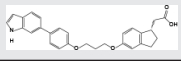
S.No.	Structure	PPAR-α		PPAR-δ		PPAR-γ	
		Actual	Predicted	Actual	Predicted	Actual	Predicted
C1		5.00	4.91	7.36	7.98	5.00	5.56
C2		5.70	5.28	8.05	8.34	5.21	5.53
C3		5.79*	5.31	8.38	8.37	5.25	5.41
C4		5.17	4.84	7.89	8.45	5.99	5.74
C5		5.00	5.01	8.17	8.14	5.52	5.62
C6		5.00	5.30	8.18*	8.18	6.03	5.70
C7		5.24	4.99	8.14	7.65	6.20*	5.50
C8		5.00	5.01	7.25	7.94	5.10	5.27
C9		5.00	5.13	7.17	7.73	5.00	5.45
C10		5.03	5.13	8.34	7.90	5.66	5.77
C11		5.00	5.49	8.62	8.09	5.82	6.20
C12		5.94	5.90	8.80	8.14	6.52*	6.63
C13		5.40	5.58	7.60	7.79	6.24	6.34
C14		5.00	5.12	8.12*	8.07	5.78	5.76
C15		6.16	5.39	8.57	8.31	5.78	6.01
C16		5.13	5.10	7.85	7.65	6.16	5.93
C17		5.00	5.42	8.66	8.01	5.91	5.85
C18		5.00	5.32	7.96	8.03	6.26*	6.30
C19		5.04	4.88	6.44	6.81	5.25	5.84
C20		5.16	5.20	5.65	5.68	5.06	5.94
C21		6.28*	6.31	8.47	8.23	6.80	6.69
C22		5.00	5.48	8.23*	8.61	6.19	6.33
C23		5.49	5.32	8.42	8.61	5.39	5.90
C24		5.18	5.05	8.82	8.71	6.13	6.00

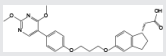
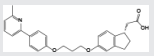
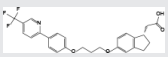
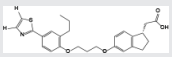
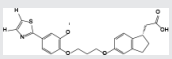
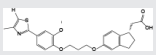
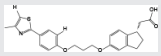
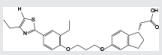
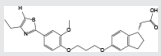
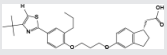
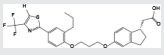
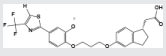
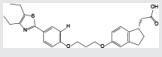
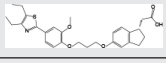
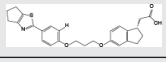
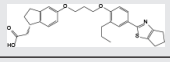
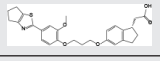
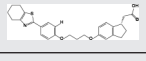
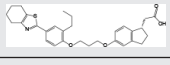
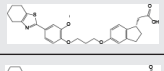
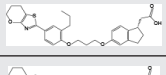
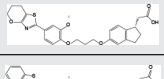
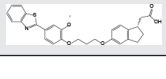
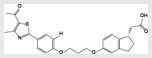
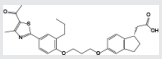
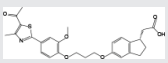
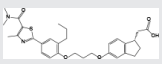
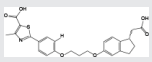
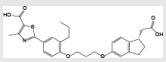
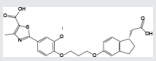
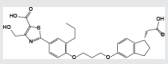
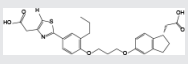
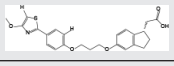
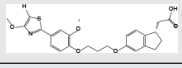
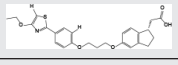
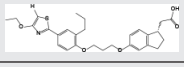
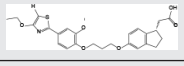
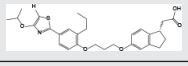
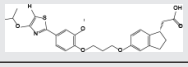
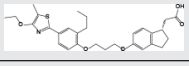
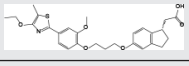
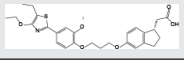
Table 1: Cont'd.							
S.No.	Structure	PPAR-α		PPAR-δ		PPAR-γ	
		Actual	Predicted	Actual	Predicted	Actual	Predicted
C25		5.77	5.34	8.64	8.43	6.26*	6.10
C26		5.00	5.45	7.37	8.32	6.31	6.47
C27		5.14	5.33	7.96	8.46	6.01	6.12
C28		5.00	5.13	8.25	8.07	6.52	6.69
C29		5.28	5.47	8.66	8.62	6.26	6.12
C30		5.54	5.75	9.02	8.86	5.75	6.23
C31		6.96	6.45	8.80*	8.25	7.32	7.05
C32		6.59	5.97	9.24	8.38	6.43*	6.55
C33		6.57	6.09	8.57	8.43	6.02	6.57
C34		5.89*	5.98	8.36	8.50	6.06	6.13
C35		6.83	6.63	7.96	8.43	7.35	7.17
C36		6.60	6.35	8.60	8.39	7.19	6.80
C37		7.06	6.92	7.96	8.37	7.75	7.74
C38		6.71	6.87	8.48	8.52	7.26	7.41
C39		6.36	6.39	8.54*	8.68	6.48*	6.70
C40		5.90	6.58	8.54	8.62	6.55	6.83
C41		7.08	6.68	8.40	8.56	7.48	7.31
C42		6.95	6.60	8.89	8.73	5.92	6.82
C43		6.48	7.18	8.46	8.51	7.03	7.75
C44		7.28*	6.71	8.39	8.68	6.94	7.28
C45		6.41	6.80	8.66*	8.75	6.53	7.10
C46		7.37	7.39	8.72	8.55	7.92*	8.00
C47		7.36	6.91	8.48	8.72	7.08	7.52
C48		7.00	7.21	8.40	8.65	7.38	7.63
C49		6.48	6.73	8.89	8.89	6.74	6.83
C50		6.28	6.21	8.28	8.67	6.67	6.87

Table 1: Cont'd.							
S.No.	Structure	PPAR-α		PPAR-δ		PPAR-γ	
		Actual	Predicted	Actual	Predicted	Actual	Predicted
C51		5.60	6.16	8.16	8.22	6.32	6.72
C52		6.76	6.75	7.75	8.12	7.77	7.80
C53		6.25	6.27	8.47	8.13	7.31*	7.02
C54		6.85*	6.85	8.36	8.09	7.70	8.12
C55		5.00	5.04	6.66*	7.97	6.51	5.86
C56		5.77	5.62	7.34	7.67	6.62	7.00
C57		5.00	5.14	7.55	7.88	6.00	6.31
C58		5.19	5.19	7.92	7.65	6.05	6.34
C59		5.61	5.74	8.34	8.20	7.57*	7.09
C60		5.24	5.97	8.89	8.64	6.52	6.47
C61		6.12	6.08	8.52	8.41	7.16	6.84
C62		7.00	6.27	8.92	8.54	6.12	6.46
C63		6.98*	6.86	8.70*	8.30	7.39	7.45
C64		5.87	6.38	8.47	8.55	6.04	6.80
C65		7.33	6.96	8.64	8.48	7.35	7.71
C66		6.75	6.48	8.52	8.52	7.36*	7.02
C67		7.22	6.92	8.50	8.28	7.47	7.55
C68		6.82	6.44	8.22	8.46	6.75	6.90
C69		6.28	6.71	8.27	8.50	6.44	7.13

*test set compounds

This module alters hit ligands by replacing their core. 3D Fragments are generated to replace the core using a vector-based scheme and the resulting structures are scored using the FlexX docking program.[33,34] Recore offers constructive hopping of scaffold, replacement of 3D core and linking and merging of the fragment. ReCore delivers back a rank-sorted list of fragments within seconds (depending on the complexity of the query). The hit fragments are sorted according to how well they comply with the query using a multi-dimensional Euclidean distance.

RESULTS AND DISCUSSION

The substituted indanyl acetic acid derivatives reportedly exhibit strong agonistic activities against PPARs. In the current study, we examined only the agonistic activities

against PPARs using 2DQSAR studies, specifically MLR and molecular docking scores.

MLR Analysis

The MLR models are derived for a dataset of 69 PPAR activators. The statistical parameters associated with the MLR analysis of PPARα, PPARβ/δ and PPARγ, represented by respective model I, II and III are listed in Table 2. The prediction ability of models is determined using a set of test compounds not included in the model generation. The values of experimental and predicted activities of all models are depicted in Table 1. The graphs of actual activity versus predicted activity of the training set and test set for all models are illustrated in Figure 1.

$$pEC_{50} = 3.439 + 1.024 \times chi1v\text{-}.520 \times a\_don\text{-}.661 \times SMR\text{-}.015 \times PEOE\_VSA2\_A$$

Model 1 represents the MLR equation for PPAR-α agonists which shows chi1v as the important feature contributing positively to the activity. The a_don (Number of hydrogen bond donor atoms) and SMR (Molecular refractivity) descriptors dominate in explaining the variation in activity as evidenced by the final QSAR equation. The model also reveals the importance of PEOE_VSA2 (Partial Equalization of Orbital Electronegativity) descriptor contributing towards the BA.

$$pEC_{50} = -2.770 - 2.014 \times a\_nCl + 0.233 \times dipoleY - 0.031 \times vsa\_pol + 2.157 \times VDistEq - 16.323 \times GCUT\_SMR\_1$$

Model 2 represents the MLR equation for PPAR-δ agonists in which negative value of the coefficients of a_ncl (Number of chlorine atoms), vsa_pol (Approximation to the sum of VDW surface areas (Å^2) of polar atoms) and GCUT_SMR_1 (atomic contribution to molar refractivity) descriptors reveals that increase in a_ncl, vas_pol and GCUT_SMR_1 value also increases the activity of the molecule. A positive value of the dipole (coefficient of dipole) and VDistEq (sum of the distance matrix entries) indicates that it has a positive impact on the biological activity of the ligands.

$$pEC_{50} = -373455.688 + .013 \times vol - 0.636 \times lip\_don + 127961.965 \times BCUT\_SMR\_3 - 10.619 \times BCUT\_SLOGP\_1 - .009 \times PEOE\_VSA1$$

Model 3 represents the MLR equation for PPAR-γ agonists which reveals that vol (van der Waals volume) and BCUT_SMR_3 (atomic contribution to molar refractivity) descriptors positively affects the activity of ligands while the negative value of lip_don (The number of OH and NH atoms) and BCUT_SLOGP_1 (atomic contribution to logP) descriptor indicates that increase in lip_don and BCUT_SLOGP_1 is responsible for an increase in the activity of the molecule.

ADMET Prediction

Distinct pharmacokinetic characteristics of the compounds considered for the study are subjected to ADME predictions by DruLiTo. The compounds are assessed for their fundamental parameters of Lipinski's rule of 5 and furthermore various pharmacokinetic properties.[35] Table 3 shows the results obtained from

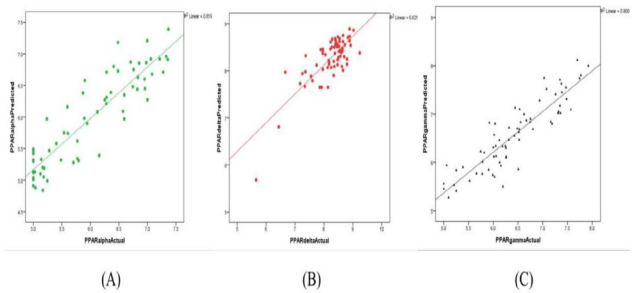


Figure 1: Scatter Plot between Actual and Predicted Activity (pEC50) of (A) PPAR-α (B) PPAR-δ and (C) PPAR-γ agonists

Table 2: Statistical Parameters Associated with the MLR analysis and docking studies.

	PPARα / Model 1	PPARδ / Model 2	PPARγ / Model 3
MLR Analysis			
nTr (No. of comp. in training set)	63	59	61
nTs (No. of comp. in the test set)	6	10	8
R^2 (Correlation Coefficient)	0.81	0.66	0.82
R^2 *pred* (Predicted Correlation Coefficient)	0.86	0.90	0.58
Q2 (Cross validated Correlation Coefficient)	0.81	0.66	0.77
See (Standard Error of Estimation)	0.35	0.36	0.34
Sp	0.32	0.17	0.15
Docking Analysis (FlexX Score)			
C5	-11.16	-17.93	-12.08
C7	-12.17	-12.81	-18.86
C16	-11.98	-9.69	-21.48
C18	-9.65	-15.61	-15.07
Natural Ligand	-19.83	-22.54	-23.92
Zinc03584559 (Obtained from Recore)	-21.76	-18.51	-31.09

Table 3: ADME properties of all compounds.

Sr. No.	MW	logp	Alogp	HBA	HBD	TPSA	AMR	nRB	nAtom	nAcidic Group	RC	nRigidB	nArom
C1	304.99	5.35	-0.77	2.00	0.00	35.53	39.46	8.00	25.00	0.00	3.00	18.00	2.00
C2	328.99	6.24	-0.46	2.00	0.00	35.53	49.81	9.00	27.00	0.00	3.00	19.00	2.00
C3	373.98	6.26	0.33	2.00	0.00	35.53	45.90	9.00	29.00	0.00	3.00	21.00	2.00
C4	389.98	5.95	1.32	2.00	0.00	44.76	47.89	10.00	30.00	0.00	3.00	21.00	2.00
C5	332.98	4.70	-0.82	2.00	0.00	44.76	46.78	9.00	27.00	0.00	3.00	19.00	2.00
C6	344.98	5.12	-0.57	2.00	0.00	44.76	51.07	10.00	28.00	0.00	3.00	19.00	2.00
C7	330.99	4.49	-0.73	3.00	0.00	59.32	45.66	8.00	27.00	0.00	3.00	20.00	2.00
C8	316.99	5.68	-0.12	2.00	0.00	35.53	44.96	8.00	26.00	0.00	3.00	19.00	2.00
C9	328.99	6.00	0.52	2.00	0.00	35.53	50.47	8.00	27.00	0.00	3.00	20.00	2.00
C10	328.99	5.79	0.52	2.00	0.00	35.53	50.47	8.00	27.00	0.00	3.00	20.00	2.00
C11	340.99	6.60	-0.94	2.00	0.00	35.53	53.14	10.00	28.00	0.00	3.00	19.00	2.00
C12	409.98	7.51	0.16	2.00	0.00	35.53	59.57	11.00	32.00	0.00	3.00	22.00	2.00
C13	366.99	5.74	-0.91	3.00	0.00	59.32	59.34	10.00	30.00	0.00	3.00	21.00	2.00
C14	344.98	5.02	-0.18	2.00	0.00	44.76	52.28	9.00	28.00	0.00	3.00	20.00	2.00
C15	356.98	5.59	-0.51	2.00	0.00	44.76	57.13	10.00	29.00	0.00	3.00	20.00	2.00
C16	358.99	4.05	-0.78	3.00	0.00	68.55	52.98	9.00	29.00	0.00	3.00	21.00	2.00
C17	356.98	5.44	0.08	2.00	0.00	44.76	56.57	10.00	29.00	0.00	3.00	20.00	2.00
C18	371.00	4.41	-0.75	5.00	0.00	66.24	42.36	9.00	30.00	0.00	4.00	23.00	3.00
C19	424.99	3.65	-1.38	7.00	0.00	83.31	55.23	11.00	34.00	0.00	4.00	25.00	3.00
C20	405.97	4.90	-0.01	5.00	0.00	66.24	47.98	9.00	31.00	0.00	4.00	24.00	3.00
C21	469.96	6.60	1.57	4.00	0.00	89.55	59.19	10.00	35.00	0.00	4.00	27.00	3.00
C22	384.96	6.43	-0.18	2.00	0.00	63.77	47.26	9.00	30.00	0.00	4.00	23.00	3.00
C23	368.98	5.33	-0.92	2.00	0.00	48.67	41.08	9.00	30.00	0.00	4.00	23.00	3.00
C24	416.00	6.97	-1.19	3.00	1.00	51.32	42.76	9.00	35.00	0.00	5.00	28.00	4.00
C25	378.99	5.60	-1.19	3.00	0.00	48.42	42.76	9.00	31.00	0.00	4.00	24.00	3.00
C26	406.99	5.15	-1.24	3.00	0.00	57.65	50.08	10.00	33.00	0.00	4.00	25.00	3.00
C27	380.99	4.78	-0.77	4.00	0.00	61.31	39.46	9.00	31.00	0.00	4.00	24.00	3.00
C28	448.98	5.62	-0.87	4.00	0.00	79.77	54.09	11.00	36.00	0.00	4.00	26.00	3.00
C29	390.99	6.48	-0.75	3.00	0.00	48.42	48.50	9.00	32.00	0.00	4.00	25.00	3.00
C30	447.99	7.10	-0.09	3.00	0.00	48.42	49.20	10.00	35.00	0.00	4.00	27.00	3.00
C31	422.96	6.67	-0.35	3.00	0.00	76.66	60.93	11.00	33.00	0.00	4.00	24.00	3.00
C32	414.96	4.97	-0.23	3.00	0.00	85.89	54.57	10.00	32.00	0.00	4.00	24.00	3.00
C33	426.96	5.47	0.21	3.00	0.00	85.89	60.30	10.00	33.00	0.00	4.00	25.00	3.00
C34	398.96	5.91	0.26	3.00	0.00	76.66	52.99	9.00	31.00	0.00	4.00	24.00	3.00
C35	434.96	6.95	-0.11	3.00	0.00	76.66	66.42	11.00	34.00	0.00	4.00	25.00	3.00
C36	438.96	5.83	-0.46	3.00	0.00	85.89	63.38	11.00	34.00	0.00	4.00	25.00	3.00
C37	470.96	8.21	1.21	3.00	0.00	76.66	80.06	12.00	37.00	0.00	4.00	27.00	3.00
C38	491.96	8.17	0.75	3.00	0.00	76.66	67.37	12.00	37.00	0.00	4.00	27.00	3.00
C39	483.95	6.47	0.87	3.00	0.00	85.89	61.01	11.00	36.00	0.00	4.00	27.00	3.00
C40	434.96	6.74	-0.65	3.00	0.00	76.66	64.88	11.00	34.00	0.00	4.00	25.00	3.00
C41	462.96	6.30	-0.70	3.00	0.00	85.89	72.19	12.00	36.00	0.00	4.00	26.00	3.00
C42	422.96	6.04	0.05	3.00	0.00	76.66	59.07	9.00	33.00	0.00	5.00	27.00	3.00
C43	458.96	7.29	-0.13	3.00	0.00	76.66	72.75	11.00	36.00	0.00	5.00	28.00	3.00
C44	450.96	5.60	0.00	3.00	0.00	85.89	66.39	10.00	35.00	0.00	5.00	28.00	3.00
C45	450.96	5.60	0.00	3.00	0.00	85.89	66.39	10.00	35.00	0.00	5.00	28.00	3.00

Table 3: Cont'd.													
Sr. No.	MW	logp	Alogp	HBA	HBD	TPSA	AMR	nRB	nAtom	nAcidic Group	RC	nRigidB	nArom
C46	470.96	7.65	-0.42	3.00	0.00	76.66	75.66	11.00	37.00	0.00	5.00	29.00	3.00
C47	462.96	5.96	-0.29	3.00	0.00	85.89	69.30	10.00	36.00	0.00	5.00	29.00	3.00
C48	474.96	6.92	-0.53	3.00	0.00	85.89	74.63	11.00	37.00	0.00	5.00	29.00	3.00
C49	466.95	5.22	-0.40	3.00	0.00	95.12	68.27	10.00	36.00	0.00	5.00	29.00	3.00
C50	462.96	6.39	-0.23	3.00	0.00	85.89	54.57	10.00	36.00	0.00	5.00	29.00	4.00
C51	438.96	5.42	0.01	4.00	0.00	93.73	63.76	10.00	34.00	0.00	4.00	26.00	3.00
C52	474.96	6.67	-0.16	4.00	0.00	93.73	77.43	12.00	37.00	0.00	4.00	27.00	3.00
C53	466.95	4.97	-0.04	4.00	0.00	102.90	71.07	11.00	36.00	0.00	4.00	27.00	3.00
C54	500.96	6.33	-0.34	5.00	0.00	96.97	85.50	13.00	39.00	0.00	4.00	28.00	3.00
C55	442.95	5.15	0.02	5.00	0.00	93.73	60.21	10.00	34.00	0.00	4.00	26.00	3.00
C56	478.95	6.40	-0.15	5.00	0.00	93.73	73.88	12.00	37.00	0.00	4.00	27.00	3.00
C57	470.95	4.71	-0.03	5.00	0.00	102.90	67.52	11.00	36.00	0.00	4.00	27.00	3.00
C58	494.95	5.27	-1.04	6.00	0.00	93.73	75.43	13.00	38.00	0.00	4.00	27.00	3.00
C59	478.95	6.28	-0.56	5.00	0.00	93.73	72.70	13.00	37.00	0.00	4.00	26.00	3.00
C60	414.96	5.47	-0.23	3.00	0.00	85.89	54.57	10.00	32.00	0.00	4.00	24.00	3.00
C61	442.95	5.03	-0.28	3.00	0.00	95.12	61.89	11.00	34.00	0.00	4.00	25.00	3.00
C62	426.96	5.90	0.02	3.00	0.00	85.89	58.87	11.00	33.00	0.00	4.00	24.00	3.00
C63	462.96	7.15	-0.15	3.00	0.00	85.89	72.54	13.00	36.00	0.00	4.00	25.00	3.00
C64	454.95	5.45	-0.03	3.00	0.00	95.12	66.18	12.00	35.00	0.00	4.00	25.00	3.00
C65	474.96	7.61	-0.45	3.00	0.00	85.89	77.75	13.00	37.00	0.00	4.00	26.00	3.00
C66	466.95	5.91	-0.33	3.00	0.00	95.12	71.39	12.00	36.00	0.00	4.00	26.00	3.00
C67	474.96	7.26	0.29	3.00	0.00	85.89	78.27	13.00	37.00	0.00	4.00	26.00	3.00
C68	466.95	5.56	0.41	3.00	0.00	95.12	71.91	12.00	36.00	0.00	4.00	26.00	3.00
C69	478.95	5.92	-0.27	3.00	0.00	95.12	74.99	13.00	37.00	0.00	4.00	26.00	3.00
ZINC03584559	441.10	3.18	-0.40	6.00	1.00	91.59	82.38	5.00	49.00	0.00	5.00	30.00	2.00

DruLiTo with their permissible range. In general, an orally dynamic compound ought not to have more than 2 infringement of the Lipinski rule. The dynamic test compounds in the present study are not found disregarding the most extreme permissible limits of Lipinski rule and in this way demonstrating their drug likeliness properties. The ideal estimations of the descriptors, rotatable bonds and polar surface area likewise have an extraordinary impact on the oral bioavailability of the drug atoms. The important parameters with their permissible ranges are delineated in Table 3. The compounds C5, C7, C16 and C18 qualifying all the ADME filters are further used for docking Analysis.

Molecular Docking

PPARα: The compounds qualifying all the ADME filters are further used for docking Analysis using FlexX software. All four compounds are docked for its binding interactions in the active site of (PDB 3ET1) protein. The binding pocket consisted of TYR464, TYR314, HIS440, PHE273, GLN277, CYS276, ILE354, SER280, etc. residues in the targeted protein as shown in Figure 2. For the interaction between ligands and receptor, the presence of a hydrogen bonding feature is found very crucial which is also observed in the QSAR studies. Residue TYR464 and TYR314 are found to show favorable interaction, including HB acceptor and HB donor with the best conformers. The TYR464 and TYR314 residues in receptor binding pocket interacts with the oxygen atom of the carboxyl group of conformers of compounds C5, C7, C16 and C18 with FlexX score -11.16, -12.17, -11.98 and -9.65 respectively.

PPARδ: The minimum binding energy indicates that the PPARδ receptor (PDB 3ET2) is successfully docked with indanyl acetic acid derivative is shown in Table 2. The possible binding modes of indanyl acetic acid derivative at PPARδ active sites have been shown in Figure 2. PPARδ protein residues TYR437, HIS287, HIS413, CYS249, PHE246, LEU433, etc. formed active site in the protein. Residue TYR437, HIS413 and HIS287 found to form H-bond with the ligand molecules. Ligand showed relatively good binding affinity as

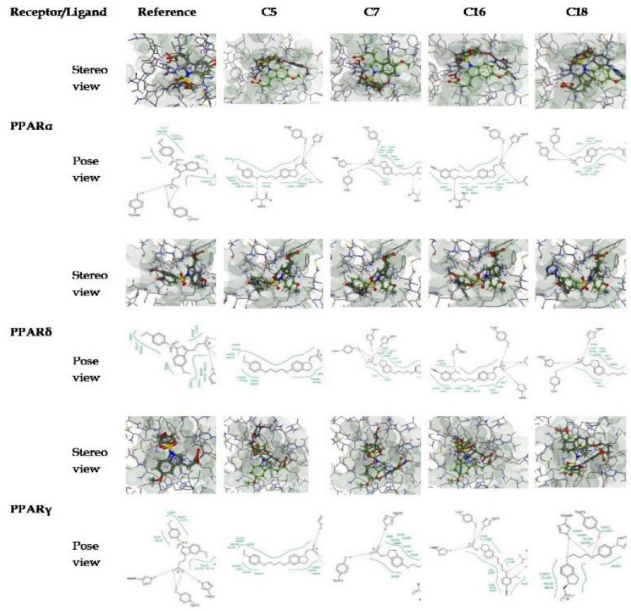


Figure 2: Molecular Docking between PPARα (PDB 3ET1), PPARδ (PDB 3ET2) and PPARγ (PDB 3ET3) receptors with natural ligand and Compound C5, C7, C16 and C18.

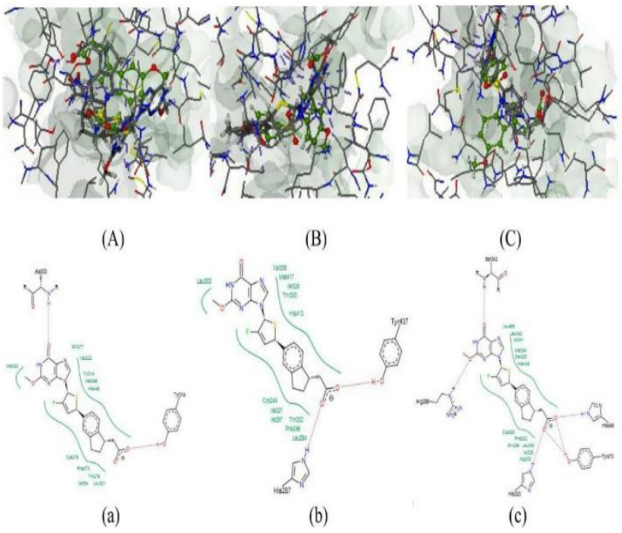


Figure 3: Molecular interaction between PPARα, PPARδ and PPARγ receptors with modified compound ZINC03584559 obtained from Recore analysis. A, B and C showing stereo-view and a, b and c showing pose view of interaction between PPARα, PPARδ and PPARγ receptors with novel compound (modified ZINC03584559) respectively.

compared to the natural ligand as standard which showed minimum binding energy shown in Table 2.

PPARγ: To further observe the interactions, the compounds are docked for its binding interactions with the active site of (PDB 3ET3) protein. To calculate the docked scores of the agonist structures against PPARγ, the molecular docking program FlexX is employed. In the current study, 100 conformational binding modes are generated for each ligand at the active site and the number of HB interactions are observed. The docked conformation of compounds revealed that the compound interacted with the binding pocket residues (TYR473, HIS449, HIS323, ARG288, CYS285, etc.) of receptor through several favorable interactions such as HB donor and acceptor with residue TYR473, HIS449 and HIS323 respectively as shown in Figure 2. The binding affinity of ligands is shown in Table 2.

Fragment-Based Drug Design using Recore

The ReCore module is used to modify the best docked hit C16 compounds by replacing their core. Fragments utilized to replace the chemical scaffold are generated in 3D, to cut and replace the fragment, a vector based scheme is used. To score the resulting structures the FlexX docking program is used. The starting hit compound is altered with linker fragments that possess similar functional groups; The new fragment is grafted onto the starting fragment by overlapping. As a result, various compounds obtained out of which the best-scored compound is analyzed using FlexX. It is interesting to note that compound containing ZINC03584559[36] in core exhibited better scores than the natural ligand and the other docked highly active compounds as shown in Table 2. The binding poses for the interaction are shown in Figure 3.

CONCLUSION

The combined computational approaches are applied to give insight into the structural basis and activation mechanism for a series of indanyl acetic acid derivatives as anti-diabetic agents. QSAR modeling is performed to provide a structural framework for understanding the structure-activity relationship of these compounds. The 2D-QSAR generated models exhibited good predictive power, correlation and satisfactory agreement between theory and experiment. Further, ADME predictions are performed for the set of compounds followed by molecular docking studies to generate possible binding poses for these compounds to PPARs. Conclusively, the hits obtained on virtual screening of the zinc database using RECORE module have provided new chemical starting points for design and development of novel PPAR targeting agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **NCD:** Non-Communicable Diseases; **PPAR:** Peroxisome Proliferator-Activated Receptor; **QED:** Quantitative Estimate of Drug Likeness; **QSAR:** Quantitative Structure-Activity Relationship; **MLR:** Multiple Linear Regression; **BA:** Biological Activity; **FBDD:** Fragment-Based Drug Design; **ADME:** Absorption, Distribution, Metabolism and Excretion.

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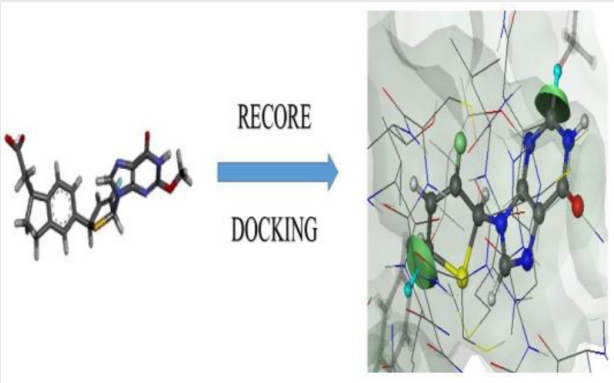
PICTORIAL ABSTRACT



SUMMARY

Diabetes is one of the largest global health emergencies of the 21st century. There are currently various curative treatment available and therapy is reliant on the use of existing anti-diabetic drugs having their own long term toxic effects. Therefore it is crucial for identifying such molecules which are effective and possessing least side effects. Improvement in drug design has become a successively important step and field of interest within healthcare. This article provides an overview and application of potential methods for the enhancement in agonistic activity of PPAR activators and design of novel ligands possessing anti-diabetic characteristics.

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Ms. Neha Verma is Ph.D Research Scholar with research interest in computer aided drug design. She is vigorously involved in researches of molecular docking, molecular dynamics simulation and next generation sequencing. Passionate Investigator of molecular modelling and drug design. The data of the paper are parts of the Ph.D thesis submitted in MANIT, Bhopal supervised by Professor Chouhan.

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